RAS INHIBITORS

Background

The vast majority of small molecule drugs act by binding a functionally important pocket on a target protein, thereby modulating the activity of that protein. For example, cholesterol-lowering drugs known as statins bind the enzyme active site of HMG-CoA reductase, thus preventing the enzyme from engaging with its substrates. The fact that many such drug/target interacting pairs are known may have misled some into believing that a small molecule modulator could be discovered for most, if not all, proteins provided a reasonable amount of time, effort, and resources. This is far from the case. Current estimates are that only about 10% of all human proteins are targetable by small molecules. Bojadzic and Buchwald, Curr Top Med Chem 18: 674-699 (2019). The other 90% are currently considered refractory or intractable toward above-mentioned small molecule drug discovery. Such targets are commonly referred to as “undruggable.” These undruggable targets include a vast and largely untapped reservoir of medically important human proteins. Thus, there exists a great deal of interest in discovering new molecular modalities capable of modulating the function of such undruggable targets.

It has been well established in literature that Ras proteins (K-Ras, H-Ras, and N-Ras) play an essential role in various human cancers and are therefore appropriate targets for anticancer therapy. Indeed, mutations in Ras proteins account for approximately 30% of all human cancers in the United States, many of which are fatal. Dysregulation of Ras proteins by activating mutations, overexpression or upstream activation is common in human tumors, and activating mutations in Ras are frequently found in human cancer. For example, activating mutations at codon 12 in Ras proteins function by inhibiting both GTPase-activating protein (GAP)-dependent and intrinsic hydrolysis rates of GTP, significantly skewing the population of Ras mutant proteins to the “on” (GTP-bound) state (Ras(ON)), leading to oncogenic MAPK signaling. Notably, Ras exhibits a picomolar affinity for GTP, enabling Ras to be activated even in the presence of low concentrations of this nucleotide. Mutations at codons 13 (e.g., G13C) and 61 (e.g., Q61K) of Ras are also responsible for oncogenic activity in some cancers.

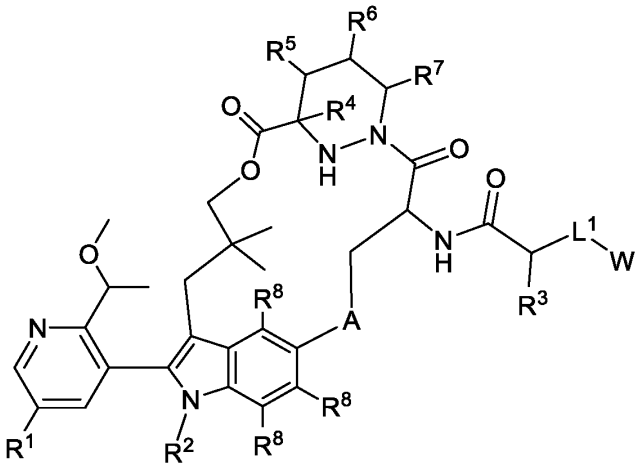
Despite extensive drug discovery efforts against Ras during the last several decades, only two agents targeting the K-Ras G12C mutant have been approved in the U.S. (sotorasib and adagrasib). Additional efforts are needed to uncover additional medicines for cancers driven by the various Ras mutations.

Summary

Provided herein are Ras inhibitors and compounds useful for studying Ras inhibition. The approach described herein entails formation of a high affinity three-component complex, or conjugate, between a synthetic ligand and two intracellular proteins which do not interact under normal physiological conditions: the target protein of interest (e.g., Ras), and a widely expressed cytosolic chaperone (presenter protein) in the cell (e.g., cyclophilin A). More specifically, in some embodiments, the inhibitors of Ras described herein induce a new binding pocket in Ras by driving formation of a high affinity tri-complex, or conjugate, between the Ras protein and the widely expressed cytosolic chaperone, cyclophilin A (CYPA). Without being bound by theory, the inventors believe that one way the inhibitory effect on Ras is effected by compounds of the invention and the complexes, or conjugates, they form is

by steric occlusion of the interaction site between Ras and downstream effector molecules, such as RAF and PI3K, which are required for propagating the oncogenic signal.

As such, in some embodiments, the disclosure features a compound of structural Formula I:



Formula I

or pharmaceutically acceptable salt thereof, wherein A is optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 6-membered heteroarylene;

L^1 is absent or a linker;

W is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl. optionally substituted 3 to 10-membered heterocycloalkyl, optionally substituted 3 to 10-membered cycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 to 10-membered heteroaryl, $C(O)OR^t$, $C(O)R^t$, optionally substituted acetamido, optionally substituted sulfonyl, or an optionally substituted cross-linking group comprising a vinyl ketone, a vinyl sulfone, an ynone, an alkynyl sulfone, or a sulfonyl halide;

R^t is hydrogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl;

R^1 is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 15-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl;

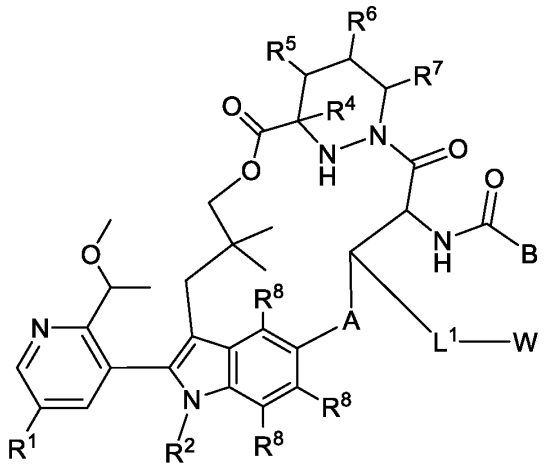
R^2 is optionally substituted C_1-C_6 alkyl or optionally substituted C_1-C_6 heteroalkyl;

R^3 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_3 heteroalkyl, optionally substituted C_3-C_6 cycloalkyl, or optionally substituted 3 to 6-membered heterocycloalkyl;

each of R^4, R^5, R^6, and R^7 is hydrogen; or R^4 and R^6 are hydrogen and R^5 and R^7 combine, together with the atoms to which they are attached, to form an optionally substituted four-membered cycloalkyl; or R^5 and R^7 are hydrogen and R^4 and R^6 combine, together with the atoms to which they are attached, to form an optionally substituted four-membered cycloalkyl; and

each R^8 is, independently, hydrogen or halo.

In some embodiments, the disclosure features a compound of structural Formula II:



Formula II

or pharmaceutically acceptable salt thereof, wherein A is optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 6-membered heteroarylene;

B is optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6-membered aryl, or optionally substituted 5 to 6-membered heteroaryl;

L^1 is absent or a linker;

W is optionally substituted 3 to 10-membered heterocycloalkyl, optionally substituted 3 to 10-membered cycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 to 6-membered heteroaryl, optionally substituted acetamido, or an optionally substituted cross-linking group comprising a vinyl ketone, a vinyl sulfone, an ynone, an alkynyl sulfone, or a sulfonyl halide;

R^1 is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 15-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl;

R^2 is optionally substituted C_1-C_6 alkyl or optionally substituted C_1-C_6 heteroalkyl;

R^3 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_3 heteroalkyl, or optionally substituted 3 to 6-membered heterocycloalkyl;

each of R^4, R^5, R^6, and R^7 is hydrogen; or R^4 and R^6 are hydrogen and R^5 and R^7 combine, together with the atoms to which they are attached, to form an optionally substituted four-membered cycloalkyl; or R^5 and R^7 are hydrogen and R^4 and R^6 combine, together with the atoms to which they are attached, to form an optionally substituted four-membered cycloalkyl; and

each R^8 is, independently, hydrogen or halo.

In some embodiments, one or more compounds of WO 2021/091982 is excluded from any embodiment herein. In some embodiments, one or more compounds of WO 2021/091967 is excluded from any embodiment herein. In some embodiments, one or more compounds of WO 2021/091956 is

excluded from any embodiment herein. In some embodiments, one or more compounds of WO 2022/060836 is excluded from any embodiment herein. In some embodiments, one or more compounds of WO 2022/235864 is excluded from any embodiment herein. In some embodiments, one or more compounds of WO 2022/235870 is excluded from any embodiment herein. In some embodiments, one or more compounds of WO 2022/060253 is excluded from any embodiment herein. In some embodiments, one or more compounds of WO 2023/133543 is excluded from any embodiment herein. In some embodiments, one or more compounds of WO 2023/240263 is excluded from any embodiment herein. The disclosure of each of these publications is incorporated herein by reference.

Also provided are pharmaceutical compositions comprising a compound of Formula I or Formula II, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. Also provided are pharmaceutical compositions comprising a compound of Table 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

Also provided is a method of treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof.

In some embodiments, a method is provided of treating a Ras protein-related disorder in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof.

Further provided is a method of inhibiting a Ras protein in a cell, the method comprising contacting the cell with an effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof.

It is specifically contemplated that any limitation discussed with respect to one embodiment of the invention may apply to any other embodiment of the invention. Furthermore, any compound or composition of the invention may be used in any method of the invention, and any method of the invention may be used to produce or to utilize any compound or composition of the invention.

Definitions and Chemical Terms

In this application, unless otherwise clear from context, (i) the term “a” means “one or more”; (ii) the term "or" is used to mean "and/or" unless explicitly indicated to refer to alternatives only or the alternative are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and "and/or"; (iii) the terms “comprising” and “including” are understood to encompass itemized components or steps whether presented by themselves or together with one or more additional components or steps; and (iv) where ranges are provided, endpoints are included.

As used herein, the term “about” is used to indicate that a value includes the standard deviation of error for the device or method being employed to determine the value. In certain embodiments, the term “about” refers to a range of values that fall within 25%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or less in either direction (greater than or less than) of a stated value, unless otherwise stated or otherwise evident from the context (e.g., where such number would exceed 100% of a possible value).

As used herein, the term “adjacent” in the context of describing adjacent atoms refers to bivalent atoms that are directly connected by a covalent bond.

A “compound of the present invention” and similar terms as used herein, whether explicitly noted or not, refers to Ras inhibitors described herein, including compounds of Formula I and subformulae thereof, for example, a compound of Table 1, as well as salts (e.g., pharmaceutically acceptable salts), solvates, hydrates, stereoisomers (including atropisomers), and tautomers thereof.

The term “wild-type” refers to an entity having a structure or activity as found in nature in a “normal” (as contrasted with mutant, diseased, altered, etc.) state or context. Those of ordinary skill in the art will appreciate that wild-type genes and polypeptides often exist in multiple different forms (e.g., alleles).

Those skilled in the art will appreciate that certain compounds described herein can exist in one or more different isomeric (e.g., stereoisomers, geometric isomers, atropisomers, tautomers) or isotopic (e.g., in which one or more atoms has been substituted with a different isotope of the atom, such as hydrogen substituted for deuterium) forms. Unless otherwise indicated or clear from context, a depicted structure can be understood to represent any such isomeric or isotopic form, individually or in combination.

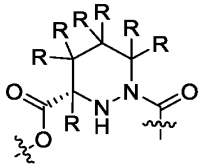
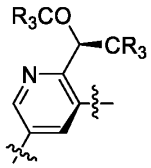
Compounds described herein can be asymmetric (e.g., having one or more stereocenters). All stereoisomers, such as enantiomers and diastereomers, are intended unless otherwise indicated. Compounds of the present disclosure that contain asymmetrically substituted carbon atoms can be isolated in optically active or racemic forms. Methods on how to prepare optically active forms from optically active starting materials are known in the art, such as by resolution of racemic mixtures or by stereoselective synthesis. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present disclosure. Cis and trans geometric isomers of the compounds of the present disclosure are described and may be isolated as a mixture of isomers or as separated isomeric forms.

In some embodiments, one or more compounds depicted herein may exist in different tautomeric forms. As will be clear from context, unless explicitly excluded, references to such compounds encompass all such tautomeric forms. In some embodiments, tautomeric forms result from the swapping of a single bond with an adjacent double bond and the concomitant migration of a proton. In certain embodiments, a tautomeric form may be a prototropic tautomer, which is an isomeric protonation states having the same empirical formula and total charge as a reference form. Examples of moieties with prototropic tautomeric forms are ketone – enol pairs, amide – imidic acid pairs, lactam – lactim pairs, amide – imidic acid pairs, enamine – imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, such as, 1H- and 3H-imidazole, 1H-, 2H- and 4H-1,2,4-triazole, 1H- and 2H- isoindole, and 1H- and 2H-pyrazole. In some embodiments, tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution. In certain embodiments, tautomeric forms result from acetal interconversion.

Unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. Exemplary isotopes that can be incorporated into compounds of the present invention include isotopes of hydrogen, carbon, nitrogen,

oxygen, phosphorus, sulfur, fluorine, chlorine, and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{32}P, ^{33}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I and ^{125}I. Isotopically labeled compounds (e.g., those labeled with ^{3}H and ^{14}C) can be useful in compound or substrate tissue distribution assays. Tritiated (i.e., ^{3}H) and carbon-14 (i.e., ^{14}C) isotopes can be useful 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). In some embodiments, one or more hydrogen atoms are replaced by ^{2}H or ^{3}H, or one or more carbon atoms are replaced by ^{13}C- or ^{14}C-enriched carbon. Positron emitting isotopes such as ^{15}O, ^{13}N, ^{11}C, and ^{18}F are useful for positron emission tomography (PET) studies to examine substrate receptor occupancy. Preparations of isotopically labelled compounds are known to those of skill in the art. For example, isotopically labeled compounds can generally be prepared by following procedures analogous to those disclosed for compounds of the present invention described herein, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

Non-limiting examples of moieties that may contain one or more deuterium substitutions in compounds of the present invention, where any position "R" may be deuterium (D), include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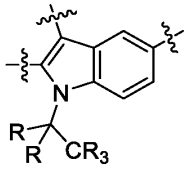
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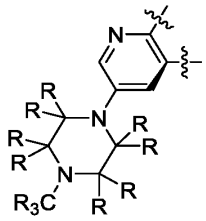
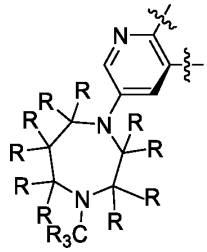
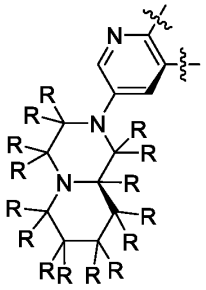
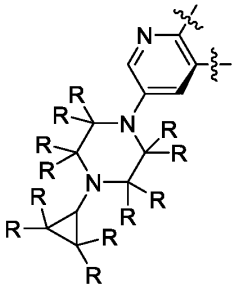
Additional examples include moieties such as




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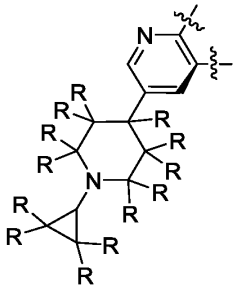
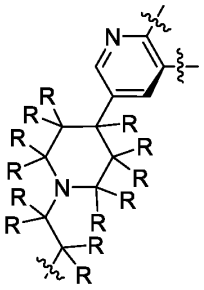
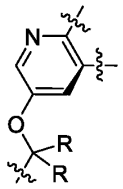
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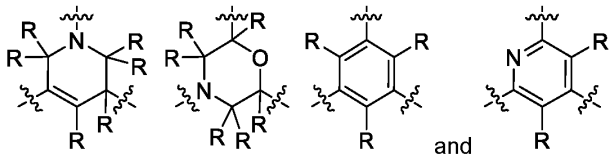
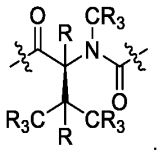
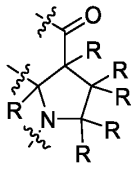
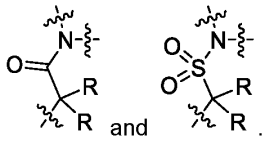
deuteration of similar moieties, e.g., in compounds of Formula I and subformulae thereof). Moreover,

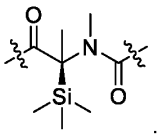
deuteration of available positions in any A moiety of compounds of the Formulas described herein is also contemplated, such as

 and . Further, deuterium substitution may also take place in compounds of the present invention at the linker position, such as

. Further, deuterium substitution may also take place in compounds of the present invention at the linker position, such as .

Further, deuterium substitution may also take place in compounds of the present invention at the linker position, such as  and .

In a further embodiment, silylation substitution is also contemplated, such as in the linker as follows:

.

As is known in the art, many chemical entities can adopt a variety of different solid forms such as, for example, amorphous forms or crystalline forms (e.g., polymorphs, hydrates, solvate). In some embodiments, compounds of the present invention may be utilized in any such form, including in any solid form. In some embodiments, compounds described or depicted herein may be provided or utilized in hydrate or solvate form.

At various places in the present specification, substituents of compounds of the present disclosure are disclosed in groups or in ranges. It is specifically intended that the present disclosure include each and every individual subcombination of the members of such groups and ranges. For example, the term "C_1-C_6 alkyl" is specifically intended to individually disclose methyl, ethyl, C_3 alkyl, C_4 alkyl, C_5 alkyl, and C_6 alkyl. Furthermore, where a compound includes a plurality of positions at which substituents are disclosed in groups or in ranges, unless otherwise indicated, the present disclosure is intended to cover individual compounds and groups of compounds (e.g., genera and subgenera) containing each and every individual subcombination of members at each position.

The term “optionally substituted X” (e.g., “optionally substituted alkyl”) is intended to be equivalent to “X, wherein X is optionally substituted” (e.g., “alkyl, wherein said alkyl is optionally substituted”). It is not intended to mean that the feature “X” (e.g., alkyl) *per se* is optional. As described herein, certain compounds of interest may contain one or more “optionally substituted” moieties. In general, the term “substituted”, whether preceded by the term “optionally” or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent, e.g., any of the substituents or groups described herein. Unless otherwise indicated, an “optionally substituted” group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. For example, in the term “optionally substituted C_1-C_6 alkyl-C_2-C_9 heteroaryl,” the alkyl portion, the heteroaryl portion, or both, may be optionally substituted. Combinations of substituents envisioned by the present disclosure are preferably those that result in the formation of stable or chemically feasible compounds. The term “stable”, as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein.

Suitable monovalent substituents on a substitutable carbon atom of an “optionally substituted” group may be, independently, deuterium; halogen; oxo; $-(CH_2)_{0-4}R^\circ$; $-(CH_2)_{0-4}OR^\circ$; $-O(CH_2)_{0-4}R^\circ$; $-O-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}CH(OR^\circ)_2$; $-(CH_2)_{0-4}SR^\circ$; $-(CH_2)_{0-4}Ph$, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}Ph$ which may be substituted with R°; $-CH=CHPh$, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}$-pyridyl which may be substituted with R°; 4- to 8-membered saturated or unsaturated heterocycloalkyl (e.g., pyridyl); 3- to 8- membered saturated or unsaturated cycloalkyl (e.g., cyclopropyl, cyclobutyl, or cyclopentyl); 3- to 10- membered saturated or unsaturated cycloalkyl; $-NO_2$; $-CN$; $-N_3$; $-(CH_2)_{0-4}N(R^\circ)_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)R^\circ$; $-N(R^\circ)C(S)R^\circ$; $-(CH_2)_{0-4}N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)C(S)NR^\circ_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)OR^\circ$; $N(R^\circ)N(R^\circ)C(O)R^\circ$; $-N(R^\circ)N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)N(R^\circ)C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)R^\circ$; $-C(S)R^\circ$; $-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}$-$C(O)$-$N(R^\circ)_2$; $-(CH_2)_{0-4}$-$C(O)$-$N(R^\circ)$-$S(O)_2$-R°; $-C(NCN)NR^\circ_2$; $-(CH_2)_{0-4}C(O)SR^\circ$; $-(CH_2)_{0-4}C(O)OSiR^\circ_3$; $-(CH_2)_{0-4}OC(O)R^\circ$; $-OC(O)(CH_2)_{0-4}SR^\circ$; $-SC(S)SR^\circ$; $-(CH_2)_{0-4}SC(O)R^\circ$; $-(CH_2)_{0-4}C(O)NR^\circ_2$; $-C(S)NR^\circ_2$; $-C(S)SR^\circ$; $-(CH_2)_{0-4}OC(O)NR^\circ_2$; $-C(O)N(OR^\circ)R^\circ$; $-C(O)C(O)R^\circ$; $-C(O)CH_2C(O)R^\circ$; $-C(NOR^\circ)R^\circ$; $-(CH_2)_{0-4}SSR^\circ$; $-(CH_2)_{0-4}S(O)_2R^\circ$; $-(CH_2)_{0-4}S(O)_2OR^\circ$; $-(CH_2)_{0-4}OS(O)_2R^\circ$; $-S(O)_2NR^\circ_2$; $-(CH_2)_{0-4}S(O)R^\circ$; $-N(R^\circ)S(O)_2NR^\circ_2$; $-N(R^\circ)S(O)_2R^\circ$; $-N(OR^\circ)R^\circ$; $-C(NOR^\circ)NR^\circ_2$; $-C(NH)NR^\circ_2$; $-P(O)_2R^\circ$; $-P(O)R^\circ_2$; $-P(O)(OR^\circ)_2$; $-OP(O)R^\circ_2$; $-OP(O)(OR^\circ)_2$; $-OP(O)(OR^\circ)R^\circ$; $-SiR^\circ_3$; $-(C_{1-4}$ straight or branched alkylene$)O-N(R^\circ)_2$; or $-(C_{1-4}$ straight or branched alkylene$)C(O)O-N(R^\circ)_2$, wherein each R° may be substituted as defined below and is independently hydrogen, $-C_{1-6}$ aliphatic,C_{2-6} alkenyl, C_{2-6} alkynyl, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, $-CH_2$-(5- to 6-membered heteroaryl ring), $-CH_2$-(5- to 10-membered heteroaryl ring), 3- to 15-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms as ring members independently selected from nitrogen, oxygen, sulfur, SO or SO_2, or a 3- to 6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of

R°, taken together with their intervening atom(s), form a 3- to 12-membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which may be substituted as defined below.

Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), may be, independently, halogen, $-(CH_2)_{0-2}R^{\bullet}$, $-(haloR^{\bullet})$, $-(CH_2)_{0-2}OH$, $-(CH_2)_{0-2}OR^{\bullet}$, $-(CH_2)_{0-2}CH(OR^{\bullet})_2$; $-O(haloR^{\bullet})$, -CN, $-N_3$, $-(CH_2)_{0-2}C(O)R^{\bullet}$, $-(CH_2)_{0-2}C(O)OH$, $-(CH_2)_{0-2}C(O)OR^{\bullet}$, $-(CH_2)_{0-2}SR^{\bullet}$, $-(CH_2)_{0-2}SH$, $-(CH_2)_{0-2}NH_2$, $-(CH_2)_{0-2}NHR^{\bullet}$, $-(CH_2)_{0-2}NR^{\bullet}_2$, $-NO_2$, $-SiR^{\bullet}_3$, $-OSiR^{\bullet}_3$, $-C(O)SR^{\bullet}$, $-(C_{1-4}$ straight or branched alkylene)$C(O)OR^{\bullet}$, C_{2-6} alkenyl, C_{2-6} alkynyl, oxo, or $-SSR^{\bullet}$ wherein each $R^{\bullet}$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently selected from C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, a 3- to 10-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, sulfur, SO, or SO_2, or a 5- to 6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents on a saturated carbon atom of R° include =O and =S.

Suitable divalent substituents on a saturated carbon atom of an "optionally substituted" group include the following: =O, =S, $=NNR^*_2$, $=NNHC(O)R^*$, $=NNHC(O)OR^*$, $=NNHS(O)_2R^*$, $=NR^*$, $=NOR^*$, $-O(C(R^*_2))_{2-3}O-$, or $-S(C(R^*_2))_{2-3}S-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, a 3- to 10-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur or an unsubstituted 5- to 6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents that are bound to vicinal substitutable carbons of an "optionally substituted" group include: $-O(CR^*_2)_{2-3}O-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5- to 6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

Suitable substituents on the aliphatic group of R^* include halogen, $-R^{\bullet}$, $-(haloR^{\bullet})$, -OH, $-OR^{\bullet}$, $-O(haloR^{\bullet})$, -CN, -C(O)OH, $-C(O)OR^{\bullet}$, $-NH_2$, $-NHR^{\bullet}$, $-NR^{\bullet}_2$, C_{2-6} alkenyl, C_{2-6} alkynyl, or $-NO_2$, wherein each $R^{\bullet}$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, a 3- to 10-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5- to 6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

Suitable substituents on a substitutable nitrogen of an "optionally substituted" group include $-R^{\dagger}$, $-NR^{\dagger}_2$, $-C(O)R^{\dagger}$, $-C(O)OR^{\dagger}$, $-C(O)C(O)R^{\dagger}$, $-C(O)CH_2C(O)R^{\dagger}$, $-S(O)_2R^{\dagger}$, $-S(O)_2NR^{\dagger}_2$, $-C(S)NR^{\dagger}_2$, $-C(NH)NR^{\dagger}_2$, or $-N(R^{\dagger})S(O)_2R^{\dagger}$; wherein each $R^{\dagger}$ is independently hydrogen, C_{1-6} aliphatic which may be substituted as defined below, unsubstituted -OPh, a 3- to 10-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an unsubstituted 3- to 6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two

independent occurrences of $R^{\dagger}$, taken together with their intervening atom(s) form an unsubstituted 3- to 12-membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

Suitable substituents on an aliphatic group of $R^{\dagger}$ are independently halogen, $-R^{\bullet}$, -(halo$R^{\bullet}$), -OH, $-OR^{\bullet}$, -O(halo$R^{\bullet}$), -CN, -C(O)OH, $-C(O)OR^{\bullet}$, $-NH_2$, $-NHR^{\bullet}$, $-NR^{\bullet}_2$, C_{2-6} alkenyl, C_{2-6} alkynyl, or $-NO_2$, wherein each $R^{\bullet}$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, a 3- to 10-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5- to 6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents on a saturated carbon atom of $R^{\dagger}$ include =O and =S.

The term "acetyl," as used herein, refers to the group $-C(O)CH_3$.

The term "alkoxy," as used herein, refers to a $-O-C_1-C_{20}$ alkyl group, wherein the alkoxy group is attached to the remainder of the compound through an oxygen atom.

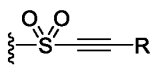
The term "alkyl," as used herein, refers to a saturated, straight or branched monovalent hydrocarbon group containing from 1 to 20 (e.g., from 1 to 10 or from 1 to 6) carbons. In some embodiments, an alkyl group is unbranched (i.e., is linear); in some embodiments, an alkyl group is branched. Alkyl groups are exemplified by, but not limited to, methyl, ethyl, *n*- and *iso*-propyl, *n*-, *sec*-, *iso*- and *tert*-butyl, and neopentyl.

The term "alkylene," as used herein, represents a saturated divalent hydrocarbon group derived from a straight or branched chain saturated hydrocarbon by the removal of two hydrogen atoms, and is exemplified by methylene, ethylene, isopropylene, and the like. The term "C_x-C_y alkylene" represents alkylene groups having between x and y carbons. Exemplary values for x are 1, 2, 3, 4, 5, and 6, and exemplary values for y are 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, or 20 (e.g., C_1-C_6, C_1-C_{10}, C_2-C_{20}, C_2-C_6, C_2-C_{10}, or C_2-C_{20} alkylene). In some embodiments, the alkylene can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein.

The term "alkenyl," as used herein, represents monovalent straight or branched chain groups of, unless otherwise specified, from 2 to 20 carbons (e.g., from 2 to 6 or from 2 to 10 carbons) containing one or more carbon-carbon double bonds and is exemplified by ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, and 2-butenyl. Alkenyls include both cis and trans isomers. The term "alkenylene," as used herein, represents a divalent straight or branched chain groups of, unless otherwise specified, from 2 to 20 carbons (e.g., from 2 to 6 or from 2 to 10 carbons) containing one or more carbon-carbon double bonds.

The term "alkynyl," as used herein, represents monovalent straight or branched chain groups from 2 to 20 carbon atoms (e.g., from 2 to 4, from 2 to 6, or from 2 to 10 carbons) containing a carbon-carbon triple bond and is exemplified by ethynyl, and 1-propynyl.

The term "alkynyl sulfone," as used herein, represents a group comprising the structure



, wherein R is any chemically feasible substituent described herein.

The term "amino," as used herein, represents $-N(R^{\dagger})_2$, e.g., $-NH_2$ and $-N(CH_3)_2$.

The term “aminoalkyl,” as used herein, represents an alkyl moiety substituted on one or more carbon atoms with one or more amino moieties.

The term “amino acid,” as described herein, refers to a molecule having a side chain, an amino group, and an acid group (e.g., -CO_2H or -SO_3H), wherein the amino acid is attached to the parent molecular group by the side chain, amino group, or acid group (e.g., the side chain). As used herein, the term “amino acid” in its broadest sense, refers to any compound or substance that can be incorporated into a polypeptide chain, e.g., through formation of one or more peptide bonds. In some embodiments, an amino acid has the general structure H_2N-C(H)(R)-COOH. In some embodiments, an amino acid is a naturally-occurring amino acid. In some embodiments, an amino acid is a synthetic amino acid; in some embodiments, an amino acid is a D-amino acid; in some embodiments, an amino acid is an L-amino acid. “Standard amino acid” refers to any of the twenty standard L-amino acids commonly found in naturally occurring peptides. Exemplary amino acids include alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, optionally substituted hydroxylnorvaline, isoleucine, leucine, lysine, methionine, norvaline, ornithine, phenylalanine, proline, pyrrolysine, selenocysteine, serine, taurine, threonine, tryptophan, tyrosine, and valine.

The term “aryl,” as used herein, represents a monovalent monocyclic, bicyclic, or multicyclic ring system formed by carbon atoms, wherein the ring attached to the pendant group is aromatic. Examples of aryl groups are phenyl, naphthyl, phenanthrenyl, and anthracenyl. An aryl ring can be attached to its pendant group at any heteroatom or carbon ring atom that results in a stable structure and any of the ring atoms can be optionally substituted unless otherwise specified.

The term “C_0,” as used herein, represents a bond. For example, part of the term -N(C(O)-(C_0-C_5 alkylene-H)- includes -N(C(O)-(C_0 alkylene-H)-, which is also represented by -N(C(O)-H)-.

The terms “carbocyclic” and “carbocyclyl,” as used herein, refer to a monovalent, optionally substituted C_3-C_{12} monocyclic, bicyclic, or tricyclic ring structure, which may be bridged, fused or spirocyclic, in which all the rings are formed by carbon atoms and at least one ring is non-aromatic. Carbocyclic structures include cycloalkyl, cycloalkenyl, and cycloalkynyl groups. Examples of carbocyclyl groups are cyclohexyl, cyclohexenyl, cyclooctynyl, 1,2-dihydronaphthyl, 1,2,3,4-tetrahydronaphthyl, fluorenyl, indenyl, indanyl, decalinyl, and the like. A carbocyclic ring can be attached to its pendant group at any ring atom that results in a stable structure and any of the ring atoms can be optionally substituted unless otherwise specified.

The term “carbonyl,” as used herein, represents a C(O) group, which can also be represented as C=O.

The term “carboxyl,” as used herein, means -CO_2H, (C=O)(OH), COOH, or C(O)OH or the unprotonated counterparts.

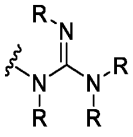
The term “cyano,” as used herein, represents a -CN group.

The term “cycloalkyl,” as used herein, represents a monovalent saturated cyclic hydrocarbon group, which may be bridged, fused or spirocyclic having from three to eight ring carbons, unless otherwise specified, and is exemplified by cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cycloheptyl.

The term “cycloalkenyl,” as used herein, represents a monovalent, non-aromatic, saturated cyclic hydrocarbon group, which may be bridged, fused or spirocyclic having from three to eight ring carbons, unless otherwise specified, and containing one or more carbon-carbon double bonds.

The term “diastereomer,” as used herein, means stereoisomers that are not mirror images of one another and are non-superimposable on one another.

The term “enantiomer,” as used herein, means each individual optically active form of a compound of the invention, having an optical purity or enantiomeric excess (as determined by methods standard in the art) of at least 80% (i.e., at least 90% of one enantiomer and at most 10% of the other enantiomer), preferably at least 90% and more preferably at least 98%.

The term “guanidinyl,” refers to a group having the structure: , wherein each R is, independently, any chemically feasible substituent described herein.

The term “guanidinoalkyl alkyl,” as used herein, represents an alkyl moiety substituted on one or more carbon atoms with one or more guanidinyl moieties.

The term “haloacetyl,” as used herein, refers to an acetyl group wherein at least one of the hydrogens has been replaced by a halogen.

The term “haloalkyl,” as used herein, represents an alkyl moiety substituted on one or more carbon atoms with one or more of the same of different halogen moieties.

The term “halogen,” as used herein, represents a halogen selected from bromine, chlorine, iodine, or fluorine.

The term "heteroalkyl,” as used herein, refers to an "alkyl" group, as defined herein, in which at least one carbon atom has been replaced with a heteroatom (e.g., an O, N, or S atom). The heteroatom may appear in the middle or at the end of the radical.

The term “heteroaryl,” as used herein, represents a monovalent, monocyclic, or polycyclic ring structure that contains at least one fully aromatic ring: i.e., they contain $4n+2$ pi electrons within the monocyclic or polycyclic ring system and contains at least one ring heteroatom selected from N, O, or S in that aromatic ring. Exemplary unsubstituted heteroaryl groups are of 1 to 12 (e.g., 1 to 11, 1 to 10, 1 to 9, 2 to 12, 2 to 11, 2 to 10, or 2 to 9) carbons. The term “heteroaryl” includes bicyclic, tricyclic, and tetracyclic groups in which any of the above heteroaromatic rings is fused to one or more, aryl or carbocyclic rings, e.g., a phenyl ring, or a cyclohexane ring. Examples of heteroaryl groups include, but are not limited to, pyridyl, pyrazolyl, benzooxazolyl, benzoimidazolyl, benzothiazolyl, imidazolyl, thiazolyl, quinolinyl, tetrahydroquinolinyl, and 4-azaindolyl. A heteroaryl ring can be attached to its pendant group at any ring atom that results in a stable structure and any of the ring atoms can be optionally substituted unless otherwise specified. In some embodiments, the heteroaryl is substituted with 1, 2, 3, or 4 substituents groups.

The term “heterocycloalkyl,” as used herein, represents a monovalent monocyclic, bicyclic, or polycyclic ring system, which may be bridged, fused or spirocyclic, wherein at least one ring is non-aromatic and wherein the non-aromatic ring contains one, two, three, or four heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur. The 5-membered ring has zero to two

double bonds, and the 6- and 7-membered rings have zero to three double bonds. Exemplary unsubstituted heterocycloalkyl groups are of 1 to 12 (e.g., 1 to 11, 1 to 10, 1 to 9, 2 to 12, 2 to 11, 2 to 10, or 2 to 9) carbons. The term "heterocycloalkyl" also represents a heterocyclic compound having a bridged multicyclic structure in which one or more carbons or heteroatoms bridges two non-adjacent members of a monocyclic ring, e.g., a quinuclidinyl group. The term "heterocycloalkyl" includes bicyclic, tricyclic, and tetracyclic groups in which any of the above heterocyclic rings is fused to one or more aromatic, carbocyclic, heteroaromatic, or heterocyclic rings, e.g., an aryl ring, a cyclohexane ring, a cyclohexene ring, a cyclopentane ring, a cyclopentene ring, a pyridine ring, or a pyrrolidine ring. Examples of heterocycloalkyl groups are pyrrolidinyl, piperidinyl, 1,2,3,4-tetrahydroquinolinyl, decahydroquinolinyl, dihydropyrrolopyridine, and decahydronapthyridinyl. A heterocycloalkyl ring can be attached to its pendant group at any ring atom that results in a stable structure and any of the ring atoms can be optionally substituted unless otherwise specified.

The term "hydroxy," as used herein, represents a -OH group.

The term "hydroxyalkyl," as used herein, represents an alkyl moiety substituted on one or more carbon atoms with one or more -OH moieties.

The term "isomer," as used herein, means any tautomer, stereoisomer, atropisomer, enantiomer, or diastereomer of any compound of the invention. It is recognized that the compounds of the invention can have one or more chiral centers or double bonds and, therefore, exist as stereoisomers, such as double-bond isomers (i.e., geometric E/Z isomers) or diastereomers (e.g., enantiomers (i.e., (+) or (-)) or cis/trans isomers). According to the invention, the chemical structures depicted herein, and therefore the compounds of the invention, encompass all the corresponding stereoisomers, that is, both the stereomerically pure form (e.g., geometrically pure, enantiomerically pure, or diastereomerically pure) and enantiomeric and stereoisomeric mixtures, e.g., racemates. Enantiomeric and stereoisomeric mixtures of compounds of the invention can typically be resolved into their component enantiomers or stereoisomers by well-known methods, such as chiral-phase gas chromatography, chiral-phase high performance liquid chromatography, crystallizing the compound as a chiral salt complex, or crystallizing the compound in a chiral solvent. Enantiomers and stereoisomers can also be obtained from stereomerically or enantiomerically pure intermediates, reagents, and catalysts by well-known asymmetric synthetic methods.

As used herein, the term "linker" refers to a divalent organic moiety connecting a first moiety (e.g., one portion of a macrocycle) to a second moiety (e.g., a second portion of the same macrocycle). In some embodiments, the linker results in a compound capable of achieving an IC50 of 1 μM or less in the Ras-RAF disruption assay (or Ras-RAF binding assay) protocol provided here:

The purpose of this biochemical assay is to measure the ability of test compounds to facilitate ternary complex formation between a nucleotide-loaded Ras isoform and cyclophilin A; the resulting ternary complex disrupts binding to a $BRAF^{RBD}$ construct, inhibiting Ras signaling through a RAF effector.

In assay buffer containing 25 mM HEPES pH 7.3, 0.002% Tween20, 0.1% BSA, 100 mM NaCl and 5 mM $MgCl_2$, tagless cyclophilin A, His6-K-Ras-GMPPNP (or other Ras variant), and GST-$BRAF^{RBD}$ are combined in a 384-well assay plate at final concentrations of 25 μM, 12.5 nM

and 50 nM, respectively. Compound is present in plate wells as a 10-point 3-fold dilution series starting at a final concentration of 30 μM. After incubation at 25°C for 3 hours, a mixture of Anti-His Eu-W1024 and anti-GST allophycocyanin is then added to assay sample wells at final concentrations of 10 nM and 50 nM, respectively, and the reaction incubated for an additional 1.5 hours. TR-FRET signal is read on a microplate reader (Ex 320 nm, Em 665/615 nm). Compounds that facilitate disruption of a Ras:RAF complex are identified as those eliciting a decrease in the TR-FRET ratio relative to DMSO control wells.

This assay may be used to assess selectivity as well. In some embodiments, a compound of the present invention is selective for one or more particular Ras mutants over other Ras mutants or wild-type compared to what is known in the art. For example, a compound of the present invention may be more selective for NRAS having a mutation at Q61 (e.g., Q61H, Q61K, Q61L, or Q61R) versus wild-type NRAS. In some embodiments, a compound of the present invention may be more selective for KRAS having a mutation at Q61 (e.g., Q61H) versus wild-type KRAS.

In some embodiments, the linker comprises 20 or fewer linear atoms. In some embodiments, the linker comprises 15 or fewer linear atoms. In some embodiments, the linker comprises 10 or fewer linear atoms. In some embodiments, the linker has a molecular weight of under 500 g/mol. In some embodiments, the linker has a molecular weight of under 400 g/mol. In some embodiments, the linker has a molecular weight of under 300 g/mol. In some embodiments, the linker has a molecular weight of under 200 g/mol. In some embodiments, the linker has a molecular weight of under 100 g/mol. In some embodiments, the linker has a molecular weight of under 50 g/mol.

As used herein, a “monovalent organic moiety” is less than 500 kDa. In some embodiments, a “monovalent organic moiety” is less than 400 kDa. In some embodiments, a “monovalent organic moiety” is less than 300 kDa. In some embodiments, a “monovalent organic moiety” is less than 200 kDa. In some embodiments, a “monovalent organic moiety” is less than 100 kDa. In some embodiments, a “monovalent organic moiety” is less than 50 kDa. In some embodiments, a “monovalent organic moiety” is less than 25 kDa. In some embodiments, a “monovalent organic moiety” is less than 20 kDa. In some embodiments, a “monovalent organic moiety” is less than 15 kDa. In some embodiments, a “monovalent organic moiety” is less than 10 kDa. In some embodiments, a “monovalent organic moiety” is less than 1 kDa. In some embodiments, a “monovalent organic moiety” is less than 500 g/mol. In some embodiments, a “monovalent organic moiety” ranges between 500 g/mol and 500 kDa.

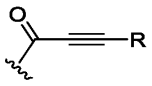
The term “stereoisomer,” as used herein, refers to all possible different isomeric as well as conformational forms which a compound may possess (e.g., a compound of any formula described herein), in particular all possible stereochemically and conformationally isomeric forms, all diastereomers, enantiomers or conformers of the basic molecular structure, including atropisomers. Some compounds of the present invention may exist in different tautomeric forms, all of the latter being included within the scope of the present invention.

The term “sulfonyl,” as used herein, represents an -$S(O)_2$- group.

The term “thiocarbonyl,” as used herein, refers to a -C(S)- group.

The term “vinyl ketone,” as used herein, refers to a group comprising a carbonyl group directly connected to a carbon-carbon double bond.

The term "vinyl sulfone," as used herein, refers to a group comprising a sulfonyl group directed connected to a carbon-carbon double bond.

The term "ynone," as used herein, refers to a group comprising the structure , wherein R is any chemically feasible substituent described herein.

Those of ordinary skill in the art, reading the present disclosure, will appreciate that certain compounds described herein may be provided or utilized in any of a variety of forms such as, for example, salt forms, protected forms, pro-drug forms, ester forms, isomeric forms (e.g., optical or structural isomers), isotopic forms, etc. In some embodiments, reference to a particular compound may relate to a specific form of that compound. In some embodiments, reference to a particular compound may relate to that compound in any form. In some embodiments, for example, a preparation of a single stereoisomer of a compound may be considered to be a different form of the compound than a racemic mixture of the compound; a particular salt of a compound may be considered to be a different form from another salt form of the compound; a preparation containing one conformational isomer ((Z) or (E)) of a double bond may be considered to be a different form from one containing the other conformational isomer ((E) or (Z)) of the double bond; a preparation in which one or more atoms is a different isotope than is present in a reference preparation may be considered to be a different form.

Detailed Description

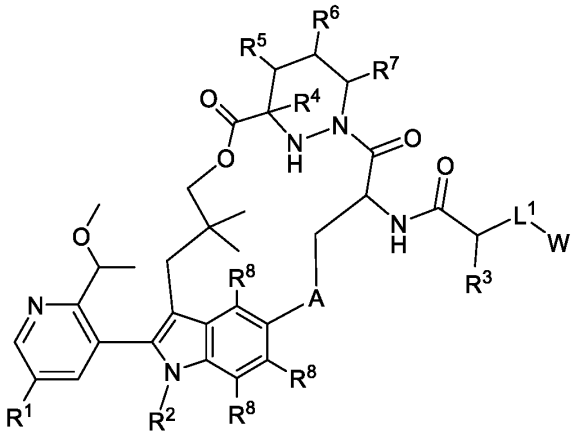
Compounds

Provided herein are Ras inhibitors. The approach described herein entails formation of a high affinity three-component complex, or conjugate, between a synthetic ligand and two intracellular proteins which do not interact under normal physiological conditions: the target protein of interest (e.g., Ras), and a widely expressed cytosolic chaperone (presenter protein) in the cell (e.g., cyclophilin A). More specifically, in some embodiments, the inhibitors of Ras described herein induce a new binding pocket in Ras by driving formation of a high affinity tri-complex, or conjugate, between the Ras protein and the widely expressed cytosolic chaperone, cyclophilin A (CYPA). Without being bound by theory, the inventors believe that one way the inhibitory effect on Ras is effected by compounds of the invention and the complexes, or conjugates, they form is by steric occlusion of the interaction site between Ras and downstream effector molecules, such as RAF, which are required for propagating the oncogenic signal.

Without being bound by theory, the inventors postulate that non-covalent interactions of a compound of the present invention with Ras and the chaperone protein (e.g., cyclophilin A) contribute to the inhibition of Ras activity. For example, van der Waals, hydrophobic, hydrophilic and hydrogen bond interactions, and combinations thereof, may contribute to the ability of the compounds of the present invention to form complexes and act as Ras inhibitors.

Accordingly, a variety of Ras proteins may be inhibited by a compound of the present invention (e.g., K-Ras, N-Ras, H-Ras, and mutants thereof at position 61, such as K-Ras Q61K, N-Ras Q61H, N-Ras Q61K, N-Ras Q61R, or N-Ras Q61L, or a combination thereof).

Accordingly, provided herein is a compound having the structure of Formula I:



Formula I

or pharmaceutically acceptable salt thereof, wherein A is optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 6-membered heteroarylene;

L^1 is absent or a linker;

W is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl. optionally substituted 3 to 10-membered heterocycloalkyl, optionally substituted 3 to 10-membered cycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 to 10-membered heteroaryl, $C(O)OR^t$, $C(O)R^t$, optionally substituted acetamido, optionally substituted sulfonyl, or an optionally substituted cross-linking group comprising a vinyl ketone, a vinyl sulfone, an ynone, an alkynyl sulfone, or a sulfonyl halide;

R^t is hydrogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl;

R^1 is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 15-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl;

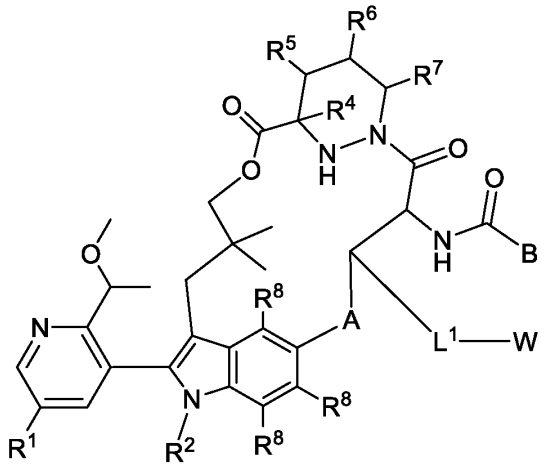
R^2 is optionally substituted C_1-C_6 alkyl or optionally substituted C_1-C_6 heteroalkyl;

R^3 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_3 heteroalkyl, optionally substituted C_3-C_6 cycloalkyl, or optionally substituted 3 to 6-membered heterocycloalkyl;

each of R^4, R^5, R^6, and R^7 is hydrogen; or R^4 and R^6 are hydrogen and R^5 and R^7 combine, together with the atoms to which they are attached, to form an optionally substituted four-membered cycloalkyl; or R^5 and R^7 are hydrogen and R^4 and R^6 combine, together with the atoms to which they are attached, to form an optionally substituted four-membered cycloalkyl; and

each R^8 is, independently, hydrogen or halo.

In some embodiments, provided herein is a compound having the structure of Formula II:



Formula II

or pharmaceutically acceptable salt thereof, wherein A is optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 6-membered heteroarylene;

B is optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6-membered aryl, or optionally substituted 5 to 6-membered heteroaryl;

L^1 is absent or a linker;

W is optionally substituted 3 to 10-membered heterocycloalkyl, optionally substituted 3 to 10-membered cycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 to 6-membered heteroaryl, optionally substituted acetamido, or an optionally substituted cross-linking group comprising a vinyl ketone, a vinyl sulfone, an ynone, an alkynyl sulfone, or a sulfonyl halide;

R^1 is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 15-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl;

R^2 is optionally substituted C_1-C_6 alkyl or optionally substituted C_1-C_6 heteroalkyl;

R^3 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_3 heteroalkyl, or optionally substituted 3 to 6-membered heterocycloalkyl;

each of R^4, R^5, R^6, and R^7 is hydrogen; or R^4 and R^6 are hydrogen and R^5 and R^7 combine, together with the atoms to which they are attached, to form an optionally substituted four-membered cycloalkyl; or R^5 and R^7 are hydrogen and R^4 and R^6 combine, together with the atoms to which they are attached, to form an optionally substituted four-membered cycloalkyl; and

each R^8 is, independently, hydrogen or halo.

In some embodiments, the linker L^1 is the structure of Formula III:

A^1-$(B^1)_f$-$(C^1)_g$-$(B^2)_h$-(D^1)-$(B^3)_i$-$(C^2)_j$-$(B^4)_k$–A^2

Formula III,

wherein A^1 is a bond to the linker; A^2 is a bond to W; B^1, B^2, B^3, and B^4 each, independently, is selected from optionally substituted C_1-C_2 alkylene, optionally substituted C_1-C_3 heteroalkylene, O, S, and NR^N; each R^N is, independently, hydrogen, optionally substituted C_1–C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, optionally substituted 3 to 14-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted C_1-C_7 heteroalkyl; C^1 and C^2 are each, independently, selected from carbonyl, thiocarbonyl, sulphonyl, or phosphoryl; f, g, h, i, j, and k are each, independently, 0 or 1; and D^1 is optionally substituted C_1-C_{10} alkylene, optionally substituted C_2-C_{10} alkenylene, optionally substituted C_2-C_{10} alkynylene, optionally substituted 3 to 14-membered heterocycloalkylene, optionally substituted 5 to 10-membered heteroarylene, optionally substituted 3 to 8-membered cycloalkylene, optionally substituted 6 to 10-membered arylene, optionally substituted C_2-C_{10} polyethylene glycolene, or optionally substituted C_1-C_{10} heteroalkylene, or a chemical bond linking A^1-$(B^1)_f$-$(C^1)_g$-$(B^2)_h$- to -$(B^3)_i$-$(C^2)_j$-$(B^4)_k$–A^2.

In some embodiments of linkers of Formula III, f is 0. In some embodiments, f is 1. In some embodiments, g is 0. In some embodiments, g is 1. In some embodiments, h is 0. In some embodiments, h is 1. In some embodiments, i is 0. In some embodiments, i is 1. In some embodiments, j is 0. In some embodiments, j is 1. In some embodiments, k is 0. In some embodiments, k is 1.

In some embodiments, of linkers of Formula III, B^1 is optionally substituted C_1-C_2 alkylene. In some embodiments, B^1 is optionally substituted C_1-C_3 heteroalkylene. In some embodiments, B^1 is O. In some embodiments, B^1 is S. In some embodiments, B^1 is NR^N.

In some embodiments, of linkers of Formula III, B^2 is optionally substituted C_1-C_2 alkylene. In some embodiments, B^2 is optionally substituted C_1-C_3 heteroalkylene. In some embodiments, B^2 is O. In some embodiments, B^2 is S. In some embodiments, B^2 is NR^N.

In some embodiments, of linkers of Formula III, B^3 is optionally substituted C_1-C_2 alkylene. In some embodiments, B^3 is optionally substituted C_1-C_3 heteroalkylene. In some embodiments, B^3 is O. In some embodiments, B^3 is S. In some embodiments, B^3 is NR^N.

In some embodiments, of linkers of Formula III, B^4 is optionally substituted C_1-C_2 alkylene. In some embodiments, B^4 is optionally substituted C_1-C_3 heteroalkylene. In some embodiments, B^4 is O. In some embodiments, B^4 is S. In some embodiments, B^4 is NR^N.

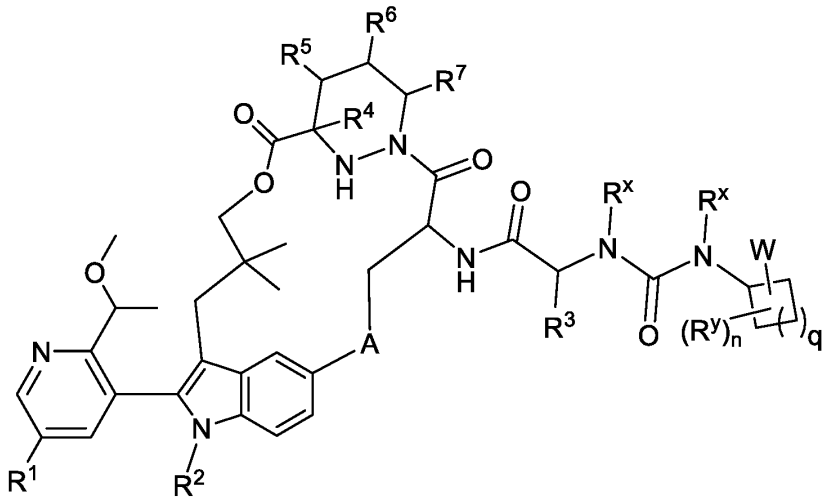
In some embodiments, of linkers of Formula III, C^1 is carbonyl. In some embodiments, C^1 is thiocarbonyl. In some embodiments, C^1 is sulphonyl. In some embodiments, C^1 is phosphoryl.

In some embodiments, of linkers of Formula III, C^2 is carbonyl. In some embodiments, C^2 is thiocarbonyl. In some embodiments, C^2 is sulphonyl. In some embodiments, C^2 is phosphoryl.

In some embodiments of linker of Formula III, D^1 is optionally substituted C_1-C_{10} alkylene. In some embodiments, D^1 is optionally substituted C_2-C_{10} alkenylene. In some embodiments, D^1 is optionally substituted C_2-C_{10} alkynylene. In some embodiments, D^1 is optionally substituted 3 to 14-membered heterocycloalkylene. In some embodiments, D^1 is optionally substituted 5 to 10-membered heteroarylene. In some embodiments, D^1 is optionally substituted 3 to 8-membered cycloalkylene. In some embodiments, D^1 is optionally substituted 6 to 10-membered arylene. In some embodiments, D^1 is

optionally substituted C_2-C_{10} polyethylene glycolene. In some embodiments, D^1 is optionally substituted C_1-C_{10} heteroalkylene. In some embodiments, D^1 is a chemical bond linking A^1-$(B^1)_f$-$(C^1)_g$-$(B^2)_h$- to -$(B^3)_i$-$(C^2)_j$-$(B^4)_k$–A^2.

In some embodiments, a compound of the present invention is a compound of Formula Ia:



Formula Ia

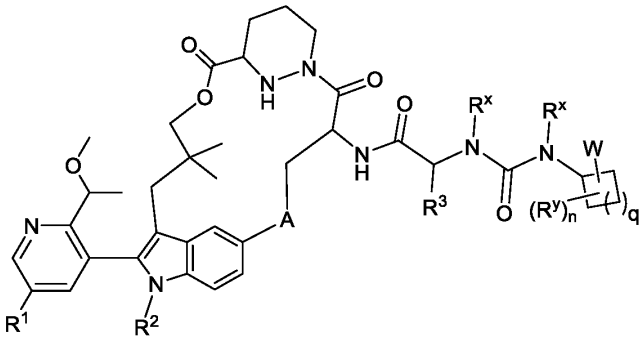
or pharmaceutically acceptable salt thereof, wherein R^x is optionally substituted C_1–C_4 alkyl;

each R^y, if present, is independently optionally substituted C_1–C_4 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, optionally substituted 3 to 14-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl, or halogen;

q is 0, 1, or 2; and

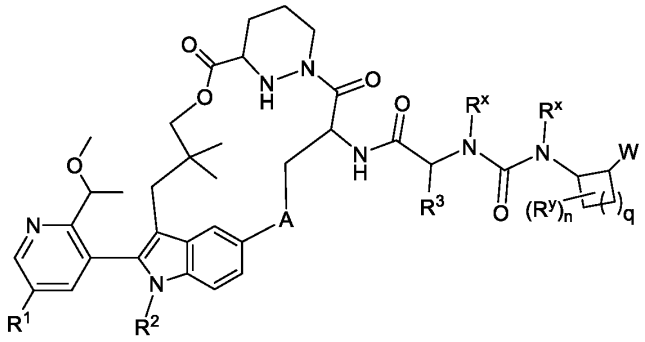
n is 0, 1, or 2.

In some embodiments, a compound of Formula Ia has the structure of Formula Ia-1:



or pharmaceutically acceptable salt thereof.

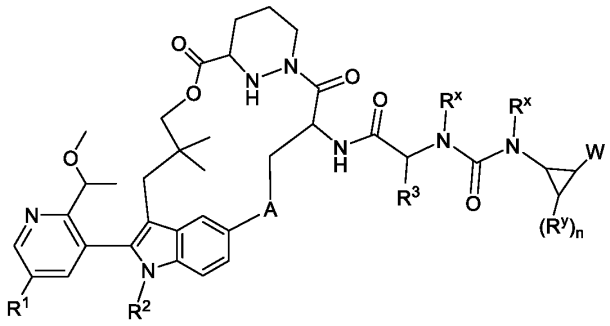
In some embodiments, a compound of Formula Ia has the structure of Formula Ia-2:



Formula Ia-2

or pharmaceutically acceptable salt thereof.

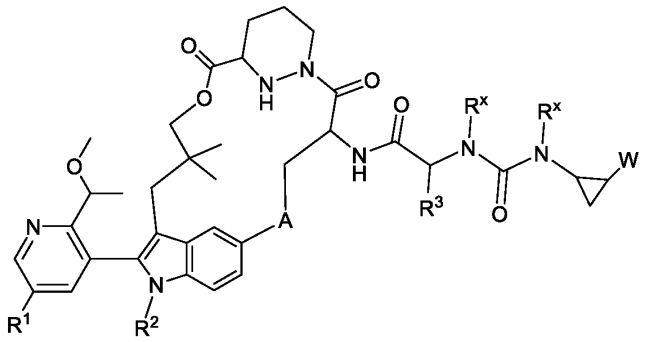
In some embodiments, a compound of Formula Ia has the structure of Formula Ia-3:



Formula Ia-3

or pharmaceutically acceptable salt thereof.

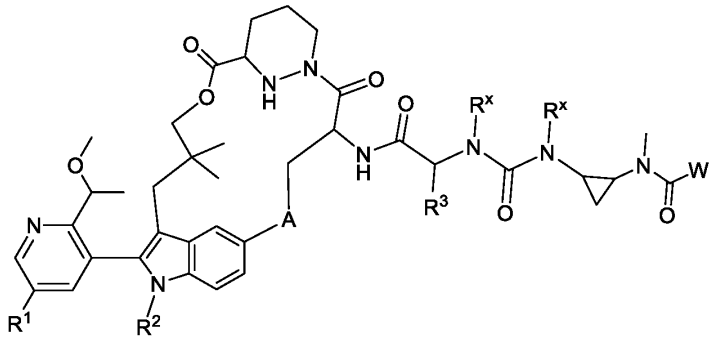
In some embodiments, a compound of Formula Ia has the structure of Formula Ia-4:



Formula Ia-4

or pharmaceutically acceptable salt thereof.

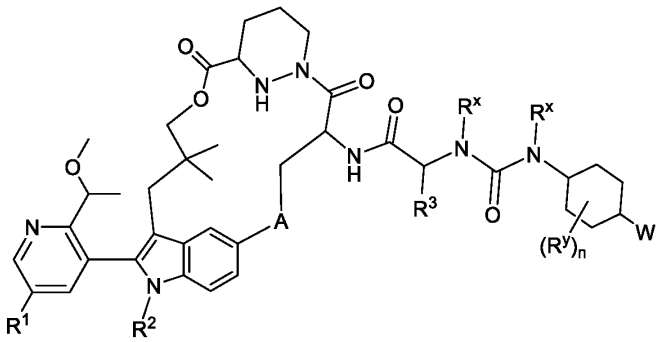
In some embodiments, a compound of Formula Ia has the structure of Formula Ia-5:



Formula Ia-5

or pharmaceutically acceptable salt thereof.

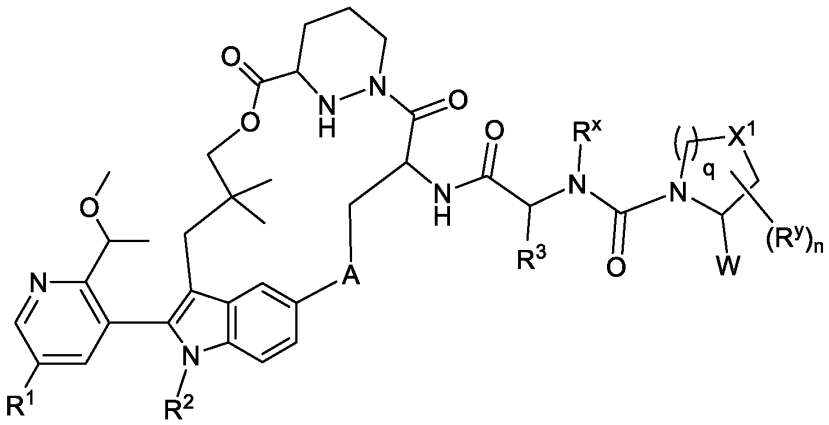
In some embodiments, a compound of Formula Ia has the structure of Formula Ia-6:



Formula Ia-6

or pharmaceutically acceptable salt thereof.

In some embodiments, a compound of the present invention has the structure of Formula Ib:



Formula Ib

or a pharmaceutically acceptable salt thereof, wherein R^x is optionally substituted C_1-C_4 alkyl; each R^y, if present, is independently optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, optionally substituted 3 to 14-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl,

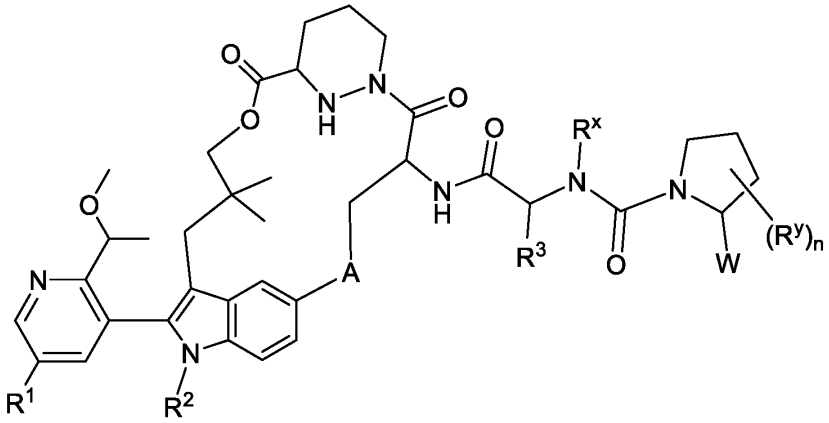
optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl, or halogen;

X^1 is CH_2, O, or NH;

n is 0, 1, or 2; and

q is 0, 1, or 2.

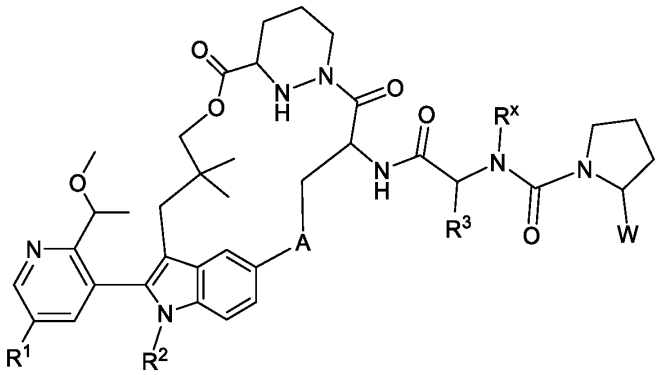
In some embodiments, a compound of Formula Ib has the structure of Formula Ib-1:



Formula Ib-1

or a pharmaceutically acceptable salt thereof.

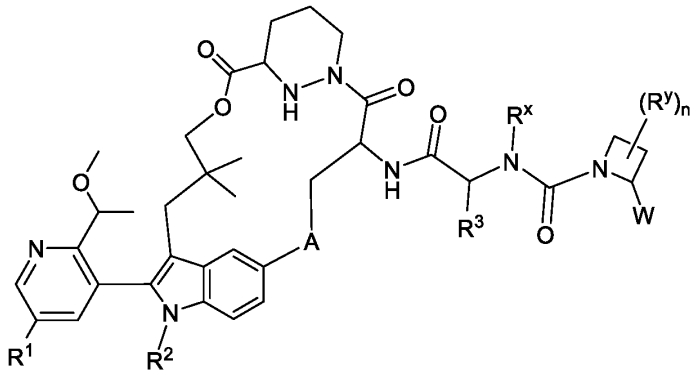
In some embodiments, a compound of Formula Ib has the structure of Formula Ib-2:



Formula Ib-2

or a pharmaceutically acceptable salt thereof.

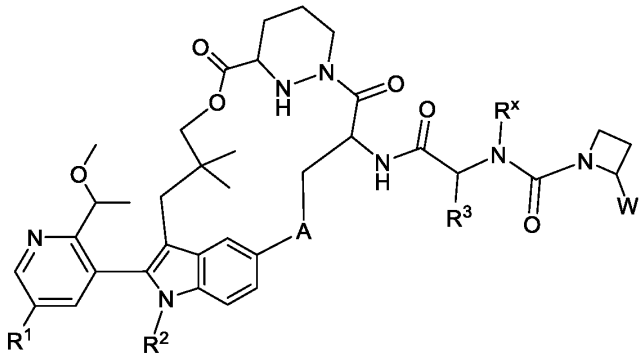
In some embodiments, a compound of Formula Ib has the structure of Formula Ib-3:



Formula Ib-3

or a pharmaceutically acceptable salt thereof.

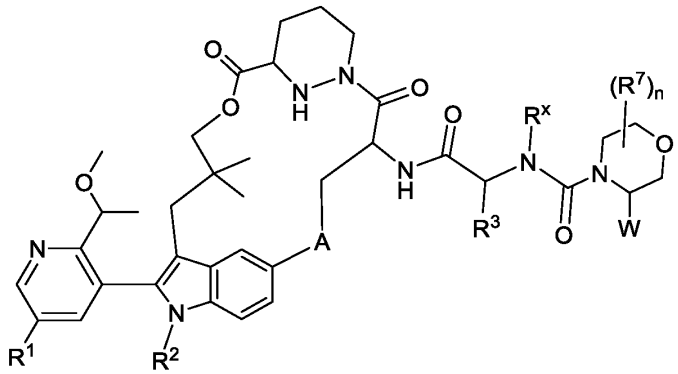
In some embodiments, a compound of Formula Ib has the structure of Formula Ib-4:



Formula Ib-4

or a pharmaceutically acceptable salt thereof.

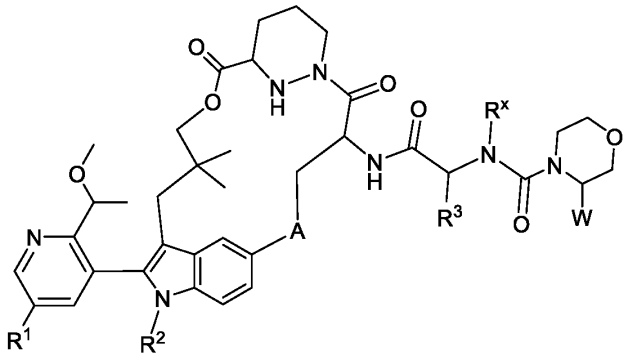
In some embodiments, a compound of Formula Ib has the structure of Formula Ib-5:



Formula Ib-5

or a pharmaceutically acceptable salt thereof.

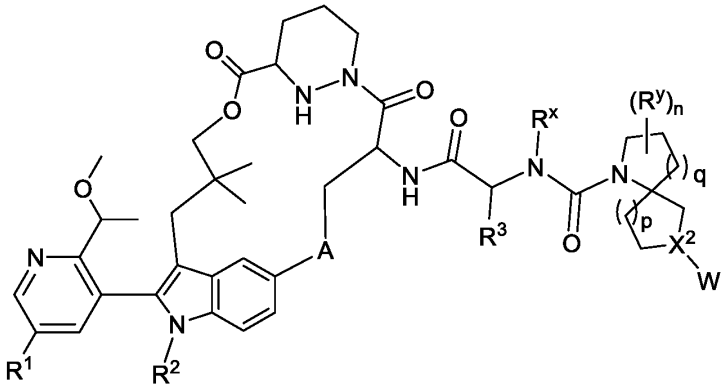
In some embodiments, a compound of Formula Ib has the structure of Formula Ib-6:



Formula Ib-6

or a pharmaceutically acceptable salt thereof.

In some embodiments, a compound of the present invention has the structure of Formula Ic:



Formula Ic

or a pharmaceutically acceptable salt thereof, wherein R^x is optionally substituted C_1-C_4 alkyl; each R^y, if present, is independently optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, optionally substituted 3 to 14-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl, or halogen;

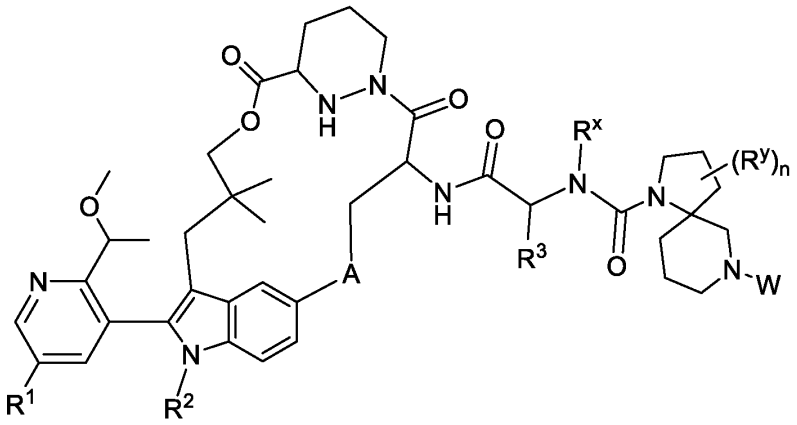
X^2 is CH or N;

n is 0, 1, or 2;

q is 0, 1, or 2; and

p is 0, 1, or 2.

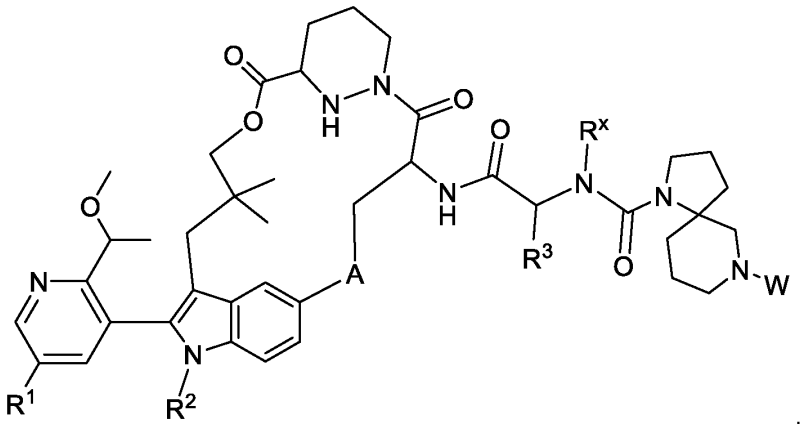
In some embodiments, a compound of Formula Ic has the structure of Formula Ic-1:



Formula Ic-1

or a pharmaceutically acceptable salt thereof.

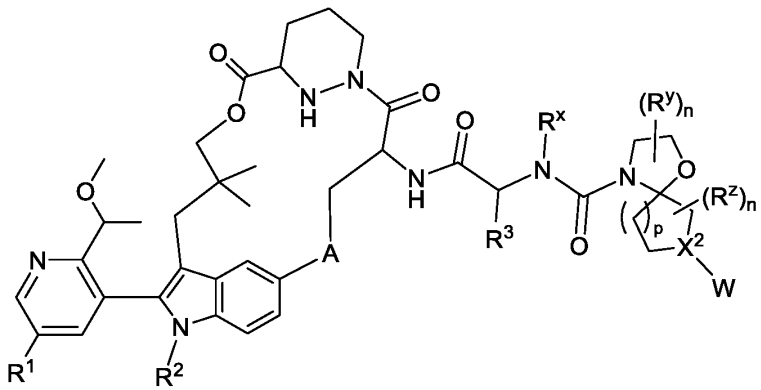
In some embodiments, a compound of Formula Ic has the structure of Formula Ic-2:



Formula Ic-2

or a pharmaceutically acceptable salt thereof.

In some embodiments, a compound of the present invention has the structure of Formula Id:



Formula Id

or a pharmaceutically acceptable salt thereof, wherein R^x is optionally substituted C_1-C_4 alkyl;

each R^y, if present, is independently optionally substituted C_1–C_4 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, optionally substituted 3 to 14-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl, or halogen;

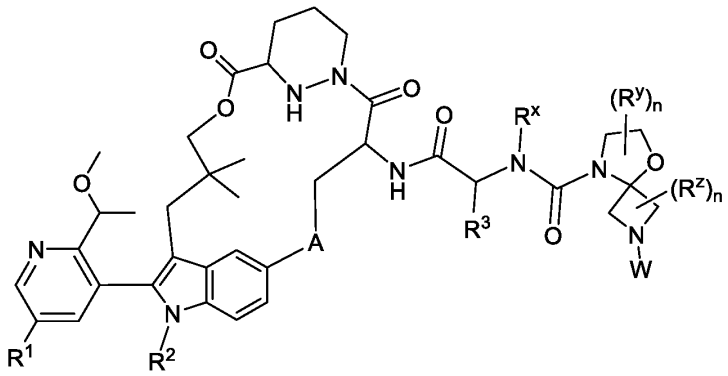
each R^z, if present, is independently optionally substituted C_1–C_4 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, optionally substituted 3 to 14-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl, or halogen;

X^2 is CH or N;

each n is, independently, 0, 1, or 2; and

p is 0, 1, or 2.

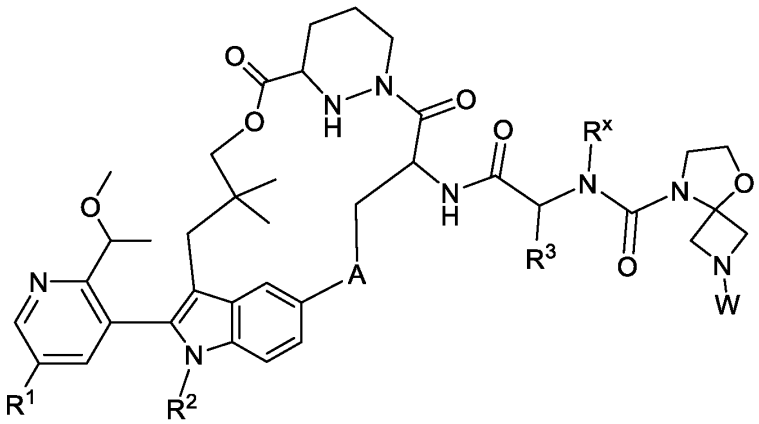
In some embodiments, a compound of Formula Id has the structure of Formula Id-1:



Formula Id-1

or a pharmaceutically acceptable salt thereof.

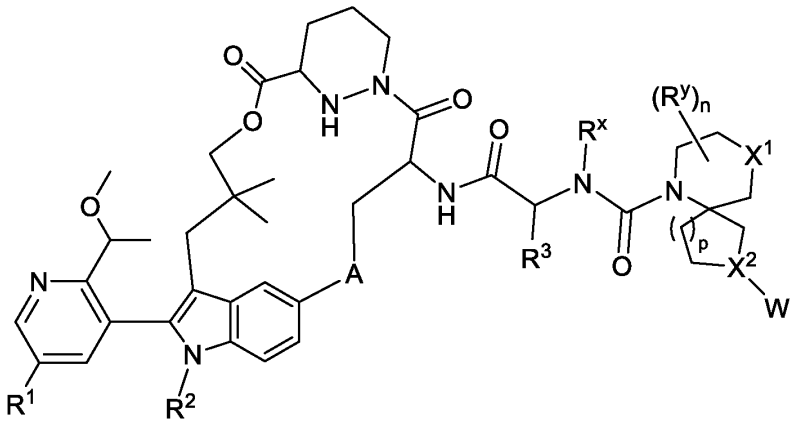
In some embodiments, a compound of Formula Id has the structure of Formula Id-2:



Formula Id-2

or a pharmaceutically acceptable salt thereof.

In some embodiments, a compound of the present invention has the structure of Formula Ie:



Formula Ie

or a pharmaceutically acceptable salt thereof, wherein R^x is optionally substituted C_1-C_4 alkyl;

each R^y, if present, is independently optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, optionally substituted 3 to 14-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl, or halogen;

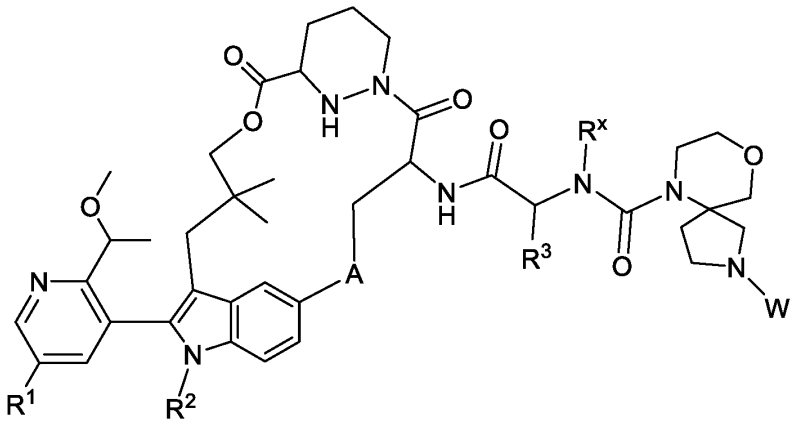
X^1 is CH_2, O, or NH;

X^2 is CH or N;

n is 0, 1, or 2; and

p is 0, 1, or 2.

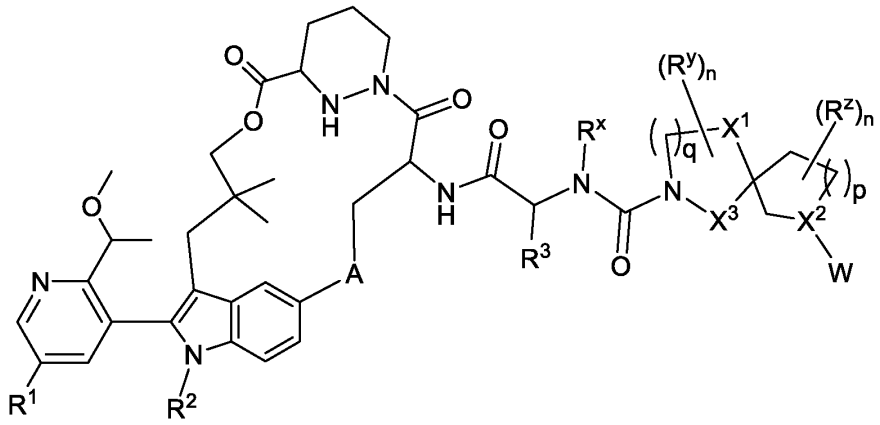
In some embodiments, a compound of Formula Ie has the structure of Formula Ie-1:



Formula Ie-1

or a pharmaceutically acceptable salt thereof.

In some embodiments, a compound of the present invention has the structure of Formula If:



Formula If

or a pharmaceutically acceptable salt thereof, wherein R^x is optionally substituted C_1-C_4 alkyl;

each R^y, if present, is independently optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, optionally substituted 3 to 14-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl, or halogen;

each R^z, if present, is independently optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, optionally substituted 3 to 14-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl, or halogen;

X^1 is CH_2, O, or NH;

X^2 is CH or N;

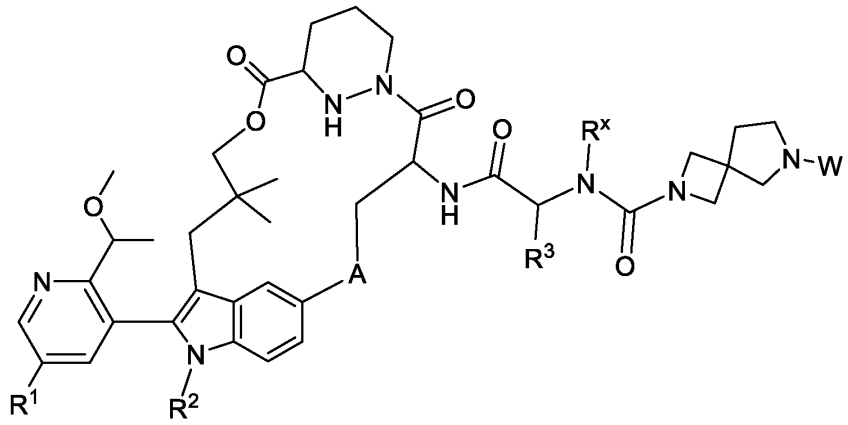
X^3 is CH_2, carbonyl, or NH;

each n is, independently, 0, 1, or 2;

q is 0, 1, or 2; and

p is 0, 1, or 2.

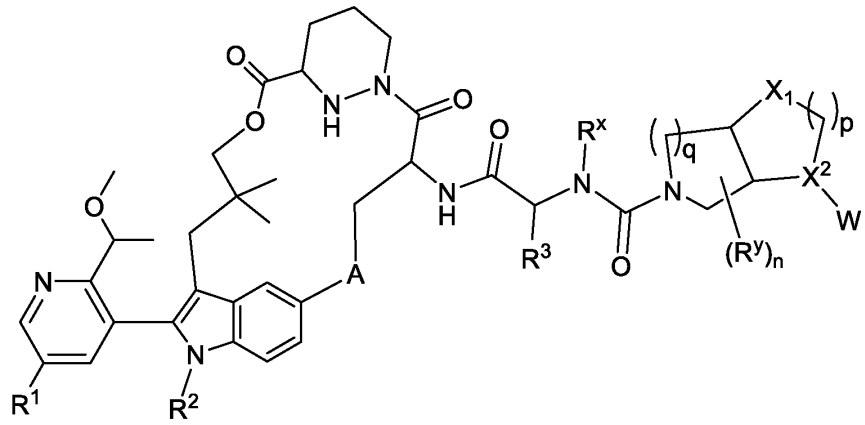
In some embodiments, a compound of Formula If has the structure of Formula If-1:



Formula If-1

or a pharmaceutically acceptable salt thereof.

In some embodiments, a compound of the present invention has the structure of Formula Ig:



Formula Ig

or a pharmaceutically acceptable salt thereof, wherein R^x is optionally substituted C_1-C_4 alkyl;

each R^y, if present, is independently optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, optionally substituted 3 to 14-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl, or halogen;

X^1 is CH_2, O, S, or NH;

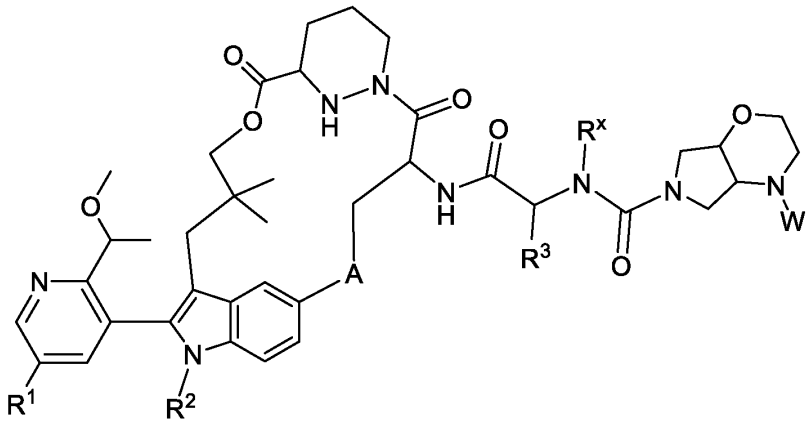
X^2 is CH or N;

n is 0, 1, or 2;

q is 0, 1, or 2; and

p is 0, 1, or 2.

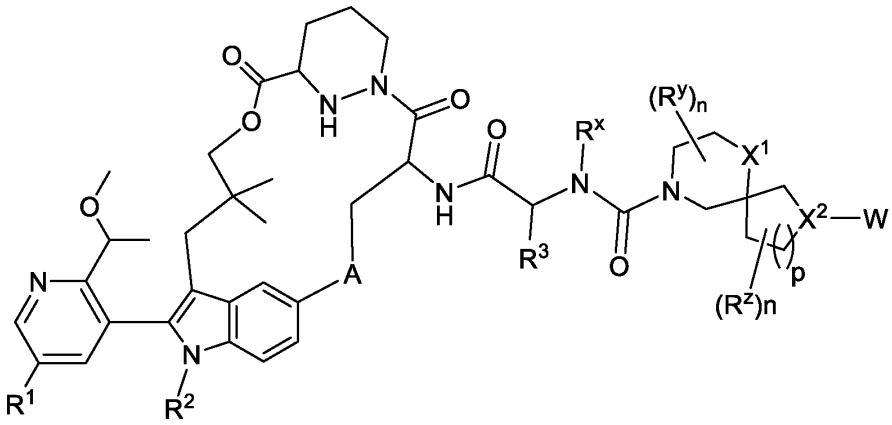
In some embodiments, a compound of Formula Ig has the structure of Formula Ig-1:



Formula Ig-1

or a pharmaceutically acceptable salt thereof.

In some embodiments, a compound of the present invention has the structure of Formula Ih:



Formula Ih

or a pharmaceutically acceptable salt thereof, wherein R^x is optionally substituted C_1-C_4 alkyl;

each R^y, if present, is independently optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, optionally substituted 3 to 14-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl, or halogen;

each R^z, if present, is independently optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, optionally substituted 3 to 14-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl, or halogen;

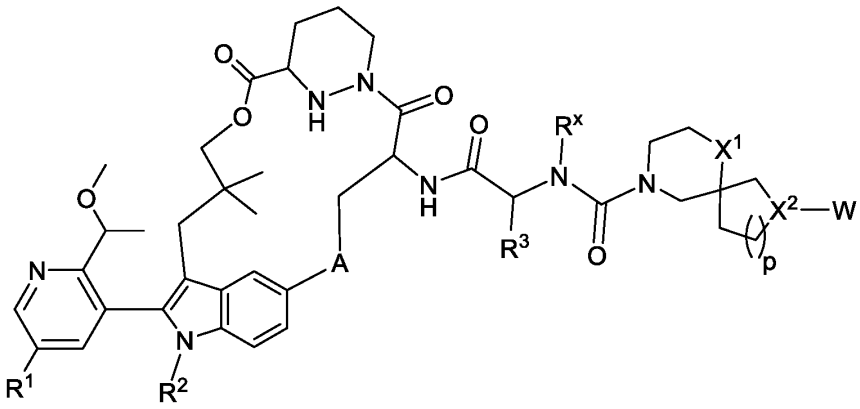
X^1 is CH_2, O, or NH;

X^2 is CH or N;

each n is, independently, 0, 1, or 2; and

p is 0, 1, or 2.

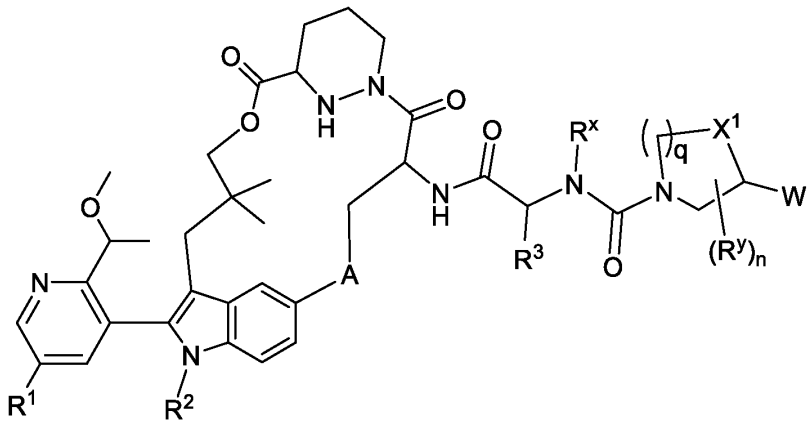
In some embodiments, a compound of Formula Ih has the structure of Formula Ih-1:



Formula Ih-1

or a pharmaceutically acceptable salt thereof.

In some embodiments, a compound of the present invention has the structure of Formula Ii:



Formula Ii

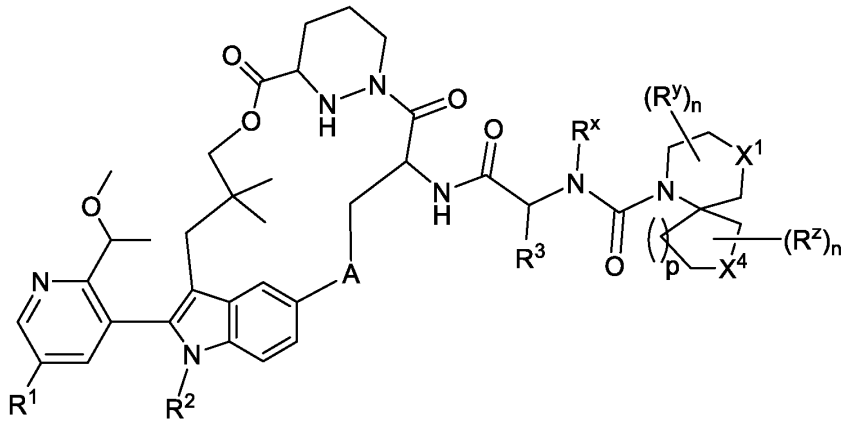
or a pharmaceutically acceptable salt thereof, wherein R^x is optionally substituted C_1-C_4 alkyl; each R^y, if present, is independently optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, optionally substituted 3 to 14-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl, or halogen;

X^1 is CH_2, O, or NH;

n is 0, 1, or 2; and

q is 0, 1, or 2.

In some embodiments, a compound of the present invention has the structure of Formula Ij:



Formula Ij

or a pharmaceutically acceptable salt thereof, wherein R^x is optionally substituted C_1-C_4 alkyl;

each R^y, if present, is independently optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, optionally substituted 3 to 14-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl, or halogen;

each R^z, if present, is independently optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, optionally substituted 3 to 14-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl, or halogen;

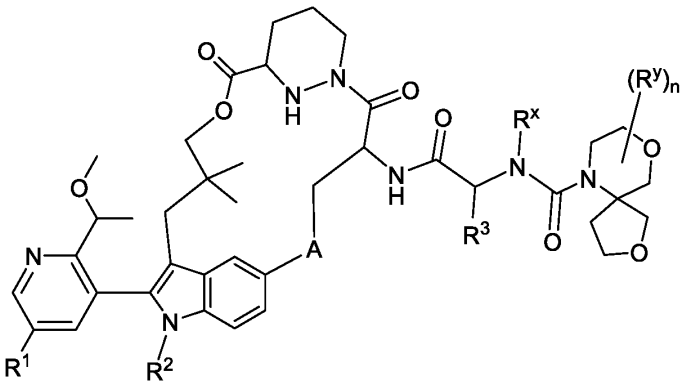
X^1 is CH_2, O, or NH;

X^4 is CH_2, NH, O, S, or sulfonyl;

each n is, independently, 0, 1, or 2; and

q is 0, 1, or 2.

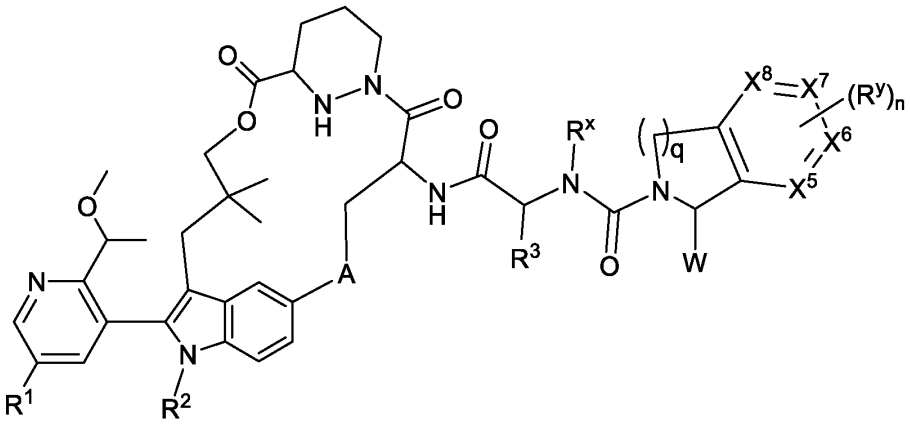
In some embodiments, a compound of Formula Ij has the structure of Formula Ij-1:



Formula Ij-1

or a pharmaceutically acceptable salt thereof.

In some embodiments, a compound of the present invention has the structure of Formula Ik:



Formula Ik

or a pharmaceutically acceptable salt thereof, wherein R^x is optionally substituted C_1–C_4 alkyl;

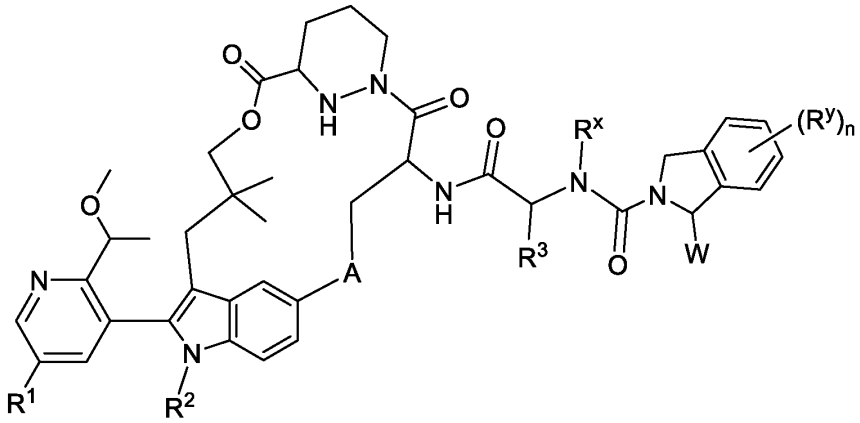
each R^y, if present, is independently optionally substituted C_1–C_4 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, optionally substituted 3 to 14-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl, or halogen;

X^5, X^6 , X^7, and X^8 are, independently, CH, N, or S;

n is 0, 1, or 2; and

q is 0, 1, or 2.

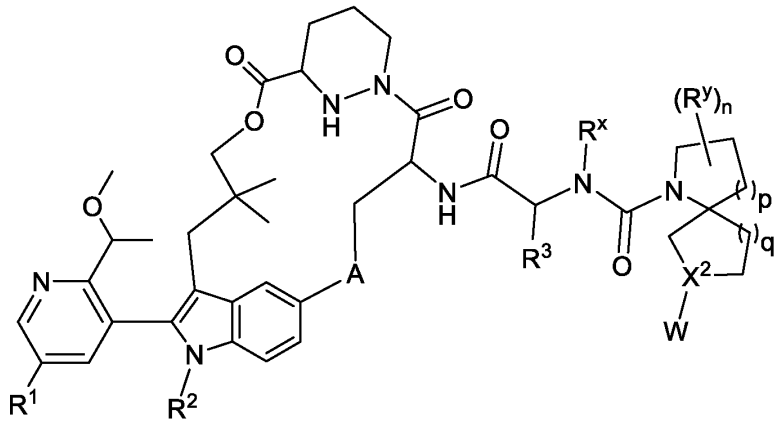
In some embodiments, a compound of Formula Ik has the structure of Formula Ik-1:



Formula Ik-1

or a pharmaceutically acceptable salt thereof.

In some embodiments, a compound of the present invention has the structure of Formula Im:



Formula Im

or a pharmaceutically acceptable salt thereof, wherein R^x is optionally substituted C_1-C_4 alkyl;

each R^y, if present, is independently optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, optionally substituted 3 to 14-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl, or halogen;

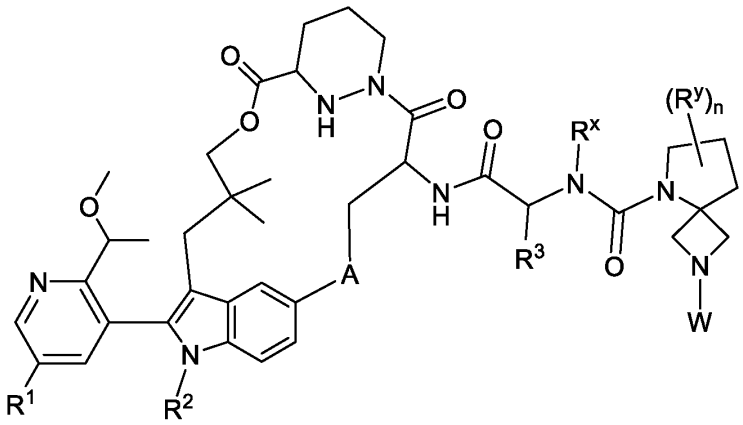
X^2 is CH or N;

n is 0, 1, or 2;

q is 0, 1, or 2; and

p is 0, 1, or 2.

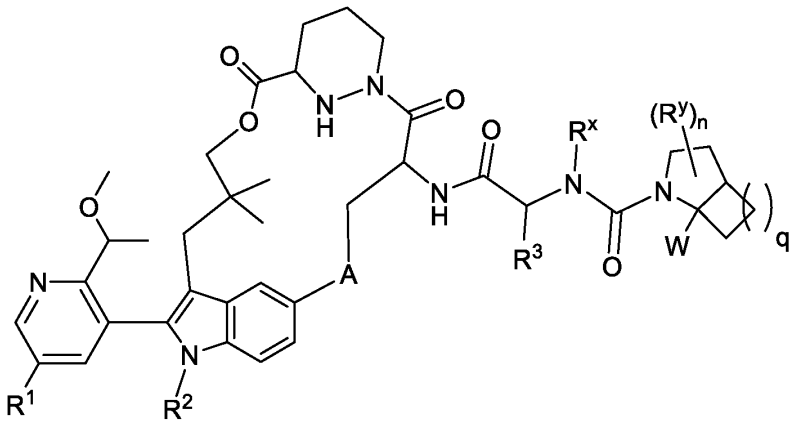
In some embodiments, a compound of Formula Im has the structure of Formula Im-1:



Formula Im-1

or a pharmaceutically acceptable salt thereof.

In some embodiments, a compound of the present invention has the structure of Formula In:



Formula In

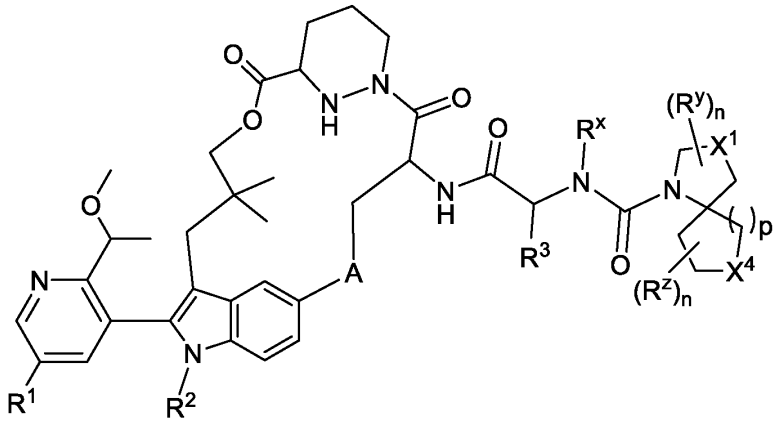
or a pharmaceutically acceptable salt thereof, wherein R^x is optionally substituted C_1-C_4 alkyl;

each R^y, if present, is independently optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, optionally substituted 3 to 14-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl, or halogen;

n is 0, 1, or 2; and

q is 0, 1, or 2.

In some embodiments, a compound of the present invention has the structure of Formula Io:



Formula Io

or a pharmaceutically acceptable salt thereof, wherein R^x is optionally substituted C_1-C_4 alkyl;

each R^y, if present, is independently optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, optionally substituted 3 to 14-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl, or halogen;

each R^z, if present, is independently optionally substituted C_1–C_4 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, optionally substituted 3 to 14-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl, or halogen;

X^1 is CH_2, O, or NH;

X^4 is CH_2, NH, O, S, or sulfonyl;

each n is, independently, 0, 1, or 2; and

p is 0, 1, or 2.

In some embodiments of compounds of the present invention, R^X is C^1-C^4 alkyl. In some embodiments, R^X is methyl.

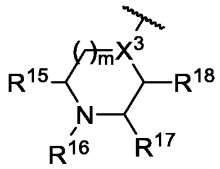
In some embodiments of compounds of the present invention R^y, is optionally substituted C_1–C_4 alkyl. In some embodiments, R^y is optionally substituted C_1-C_6 heteroalkyl. In some embodiments, R^y is optionally substituted C_2-C_4 alkenyl. In some embodiments, R^y is optionally substituted C_2-C_4 alkynyl. In some embodiments, R^y is optionally substituted 3 to 14-membered cycloalkyl. In some embodiments, R^y is optionally substituted 3 to 14-membered heterocycloalkyl. In some embodiments, R^y is optionally substituted 6 to 10-membered aryl. In some embodiments, R^y is optionally substituted 5 to 10-membered heteroaryl. In some embodiments, R^y is halogen (e.g., fluoro).

In some embodiments of compounds of the present invention, each of R^4, R^5, R^6, and R^7 are hydrogen.

In some embodiments of compounds of the present invention R^4 and R^6 are hydrogen and R^5 and R^7 combine, together with the atoms to which they are attached, to form an optionally substituted four-membered cycloalkyl.

In some embodiments of compounds of the present invention, R^1 is hydrogen.

In some embodiments of compounds of the present invention, R^1 is optionally substituted 3- to 6-membered heterocycloalkyl. In some embodiments, R^1 is



wherein X^3 is N or CH;

m is 1 or 2;

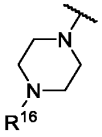
R^{15}, R^{16}, R^{17}, and R^{18} are each independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl; or

R^{16} and R^{17} combine with the atoms to which they are attached to form an optionally substituted 3 to 8-membered heterocycloalkyl; or

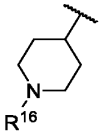
R^{17} and R^{18} combine with the atoms to which they are attached to form an optionally substituted 3 to 8-membered heterocycloalkyl; or

R^{17} and R^{15} combine with the atoms to which they are attached to form an optionally substituted 4 to 8-membered heterocycloalkyl.

In some embodiments of compounds of the present invention, R^1 is

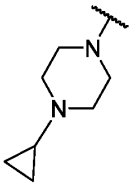


In some embodiments of compounds of the present invention, R^1 is



In some embodiments, R^{16} is methyl. In some embodiments, R^{16} is cyclopropyl.

In some embodiments, R^1 is:

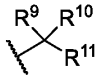


In some embodiments, W is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl. optionally substituted 3 to 10-membered heterocycloalkyl, optionally substituted 3 to 10-membered cycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5- to 10-membered heteroaryl, $C(O)OR^t$, $C(O)R^t$, optionally substituted acetamido, or optionally substituted sulfonyl.

In some embodiments of compounds of the present invention, W is optionally substituted 3 to 10-membered heterocycloalkyl. In some embodiments, W is 3- to 10-membered heterocycloalkyl. In some embodiments, W is 5- to 7-membered heterocycloalkyl.

In some embodiments, W is optionally substituted 3- to 10-membered cycloalkyl. In some embodiments, W is 3- to 10-membered cycloalkyl. In some embodiments, W is 5- to 7-membered cycloalkyl.

In some embodiments, W is optionally substituted C_1-C_6 alkyl. In some embodiments, W is C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of 5- or 6-membered heteroaryl, 5- or 6- membered cycloalkyl, C_1-C_3 alkyl, 5- or 6- membered heterocycloalkyl. In some embodiments, W is:



wherein R^9 and R^{10} are each, independently, hydrogen, hydroxyl, or C_1-C_3 alkyl, and

R^{11} is cyano, 5- or 6-membered heteroaryl, 6-membered aryl, or 5- or 6-membered heterocycloalkyl.

In some embodiments, W is optionally substituted 6-membered aryl. In some embodiments, W is phenyl.

In some embodiments, W is optionally substituted 5- to 10-membered heteroaryl. In some embodiments, W is optionally substituted 5- or 6-membered heteroaryl. In some embodiments, W is 5-membered heteroaryl. In some embodiments, W is 6-membered heteroaryl. In some embodiments, W is pyridyl.

In some embodiments, W is $C(O)OR^t$ or $C(O)R^t$. In some embodiments, R^t is hydrogen. In some embodiments, R^t is optionally substituted C_1-C_6 alkyl.

In some embodiments, W is an optionally substituted cross-linking group comprising a vinyl ketone, a vinyl sulfone, an ynone, an alkynyl sulfone, or a sulfonyl halide.

In some embodiments, W is an optionally substituted cross-linking group comprising a vinyl ketone.

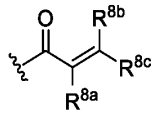
In some embodiments, W is an optionally substituted cross-linking group comprising a vinyl sulfone.

In some embodiments, W is an optionally substituted cross-linking group comprising an ynone.

In some embodiments, W is an optionally substituted cross-linking group comprising an alkynyl sulfone.

In some embodiments, W is an optionally substituted cross-linking group comprising a sulfonyl halide.

In some embodiments, W is a vinyl ketone having the structure of Formula IVa:

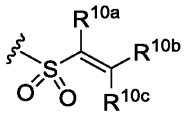


Formula IVa,

wherein R^{8a}, R^{8b}, and R^{8c} are, independently, hydrogen, -CN, halogen, or -C_1-C_3 alkyl optionally substituted with one or more substituents independently selected from -OH, -O-C_1-C_3 alkyl, -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, or a 4 to 7-membered saturated heterocycloalkyl.

In some embodiments, R^{8a}, R^{8b}, and R^{8c} are each independently selected from hydrogen and C_1-C_3 alkyl.

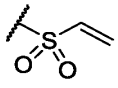
In some embodiments, W is a vinyl sulfone having the structure of Formula IVc:



Formula IVc,

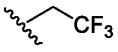
wherein R^{10a}, R^{10b}, and R^{10c} are each, independently, hydrogen, -CN, or -C_1-C_3 alkyl optionally substituted with one or more substituents independently selected from -OH, -O-C_1-C_3 alkyl, -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, or a 4 to 7-membered saturated heterocycloalkyl.

In some embodiments, R^{10a}, R^{10b}, and R^{10c} are each, independently, hydrogen or -C_1-C_3 alkyl.

In some embodiments, W has the structure of .

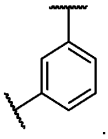
In some embodiments of compounds of the present invention, R^2 is optionally substituted C_1-C_6 alkyl.

In some embodiments, R^2 is:

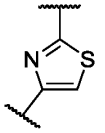
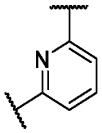
 or .

In some embodiments of compounds of the present invention, R^3 is optionally substituted C_1-C_6 alkyl. In some embodiments, R^3 is: .

In some embodiments of compounds of the present invention, A is optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 6-membered heteroarylene. In some embodiments, A is optionally substituted 6-membered arylene, or optionally substituted 5- to 6-membered heteroarylene. In some embodiments, A is optionally substituted 6-membered arylene. In some embodiments, A is

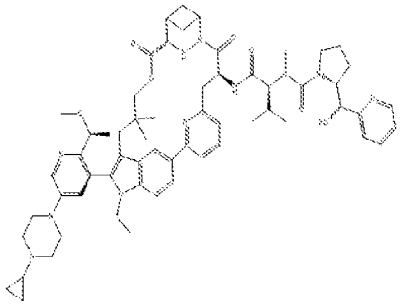
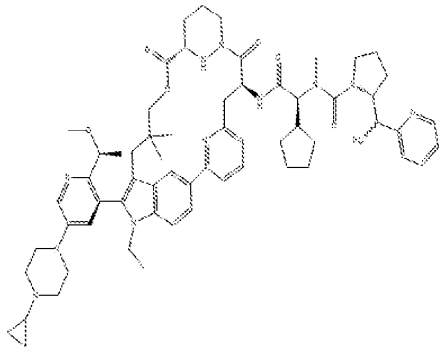
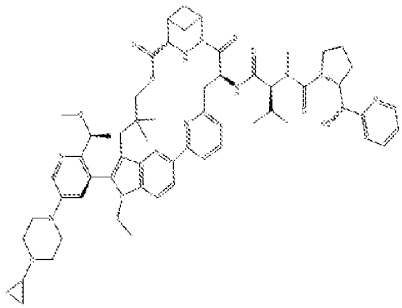
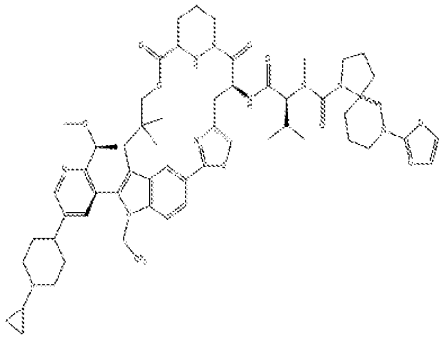
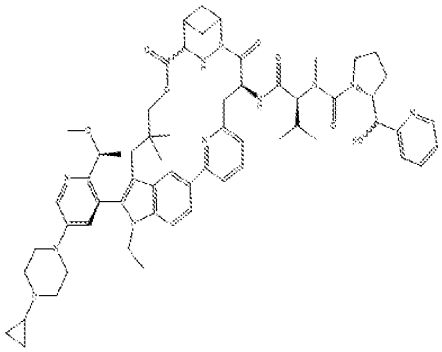
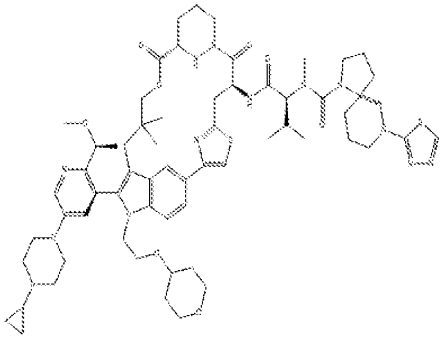
.

In some embodiments, A is optionally substituted 5- or 6-membered heteroarylene. In some embodiments, A is:

 or .

In some embodiments, a compound of the present invention is selected from Table 1, or a pharmaceutically acceptable salt or stereoisomer thereof. In some embodiments, a compound of the present invention is selected from Table 1, or a pharmaceutically acceptable salt or atropisomer thereof.

Table 1. Certain Compounds of the Present Invention

Ex#	Structure	Ex#	Structure
A1		A4	
A2		A5	
A3		A6	

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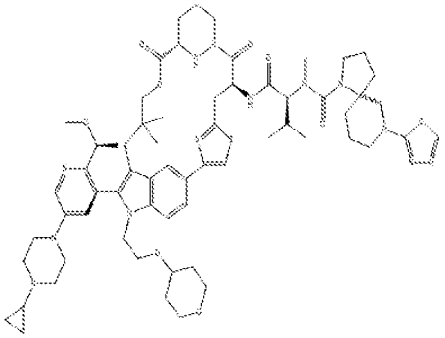
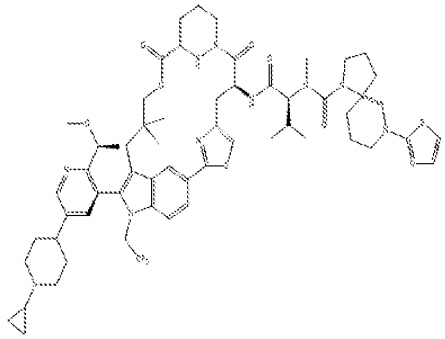
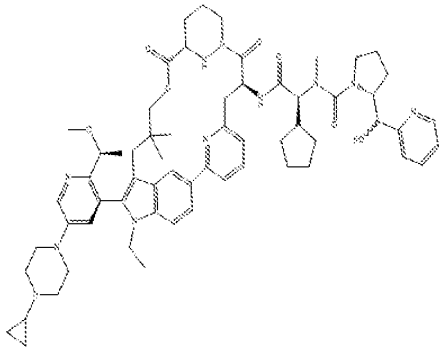
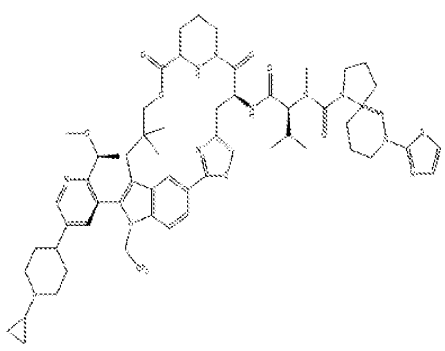
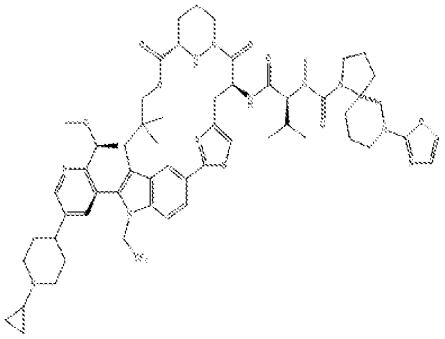
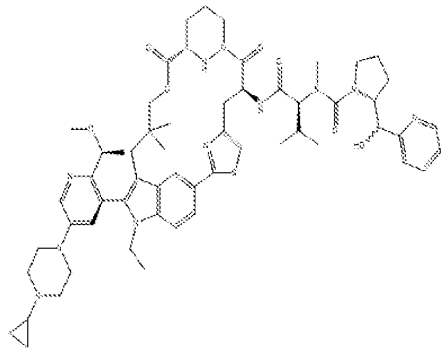
A7		A10	
A8		A11	
A9		A12	

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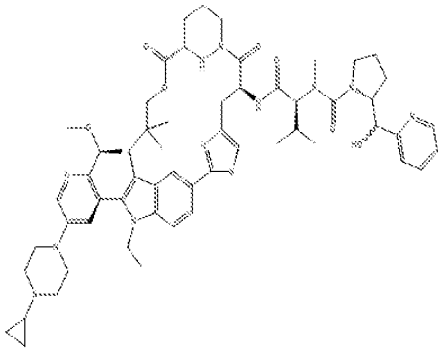
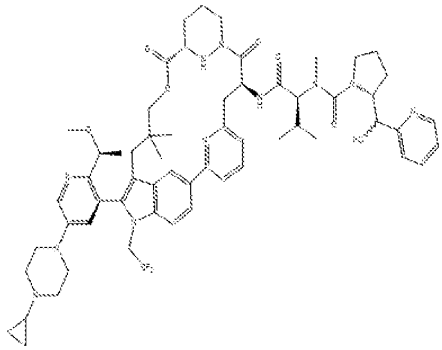
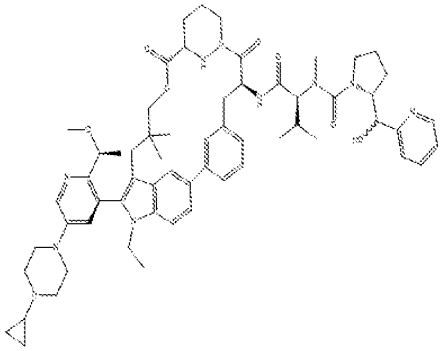
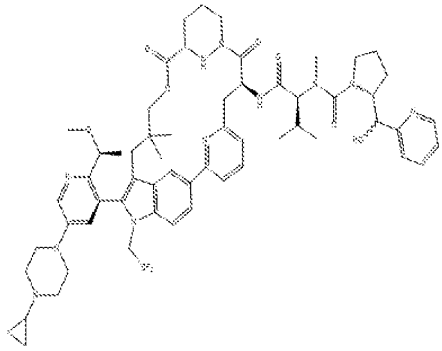
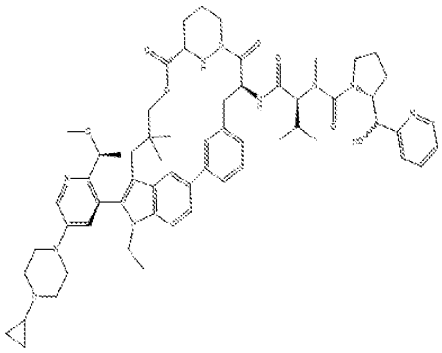
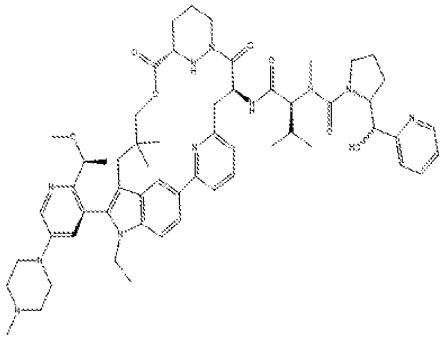
A13		A16	
A14		A17	
A15		A18	

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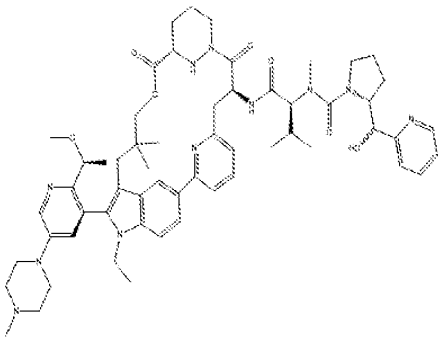
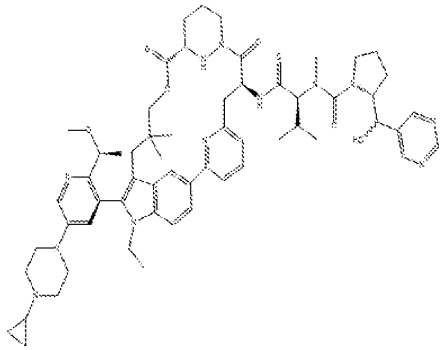
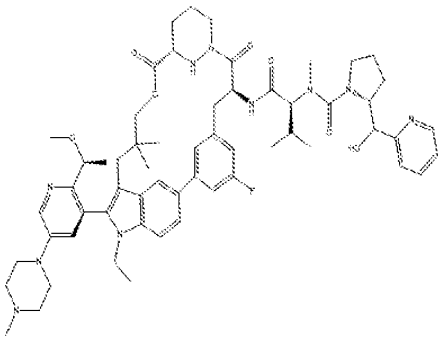
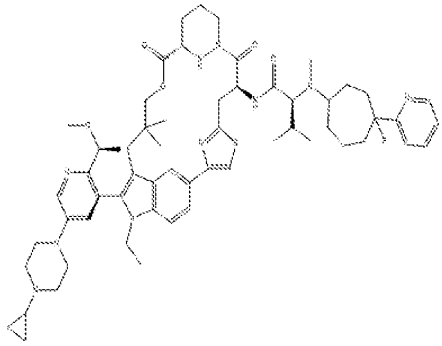
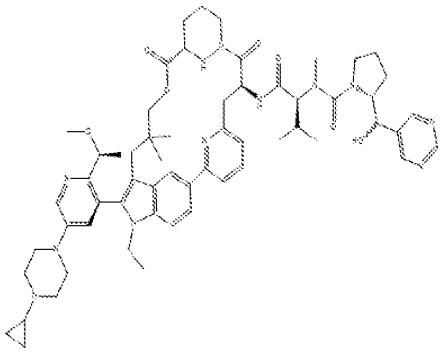
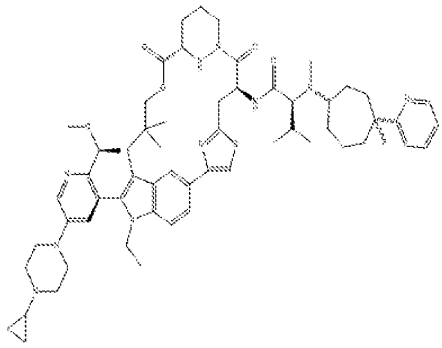
A19		A22	
A20		A23	
A21		A24	

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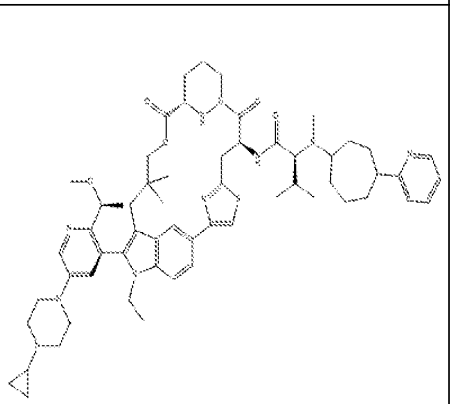
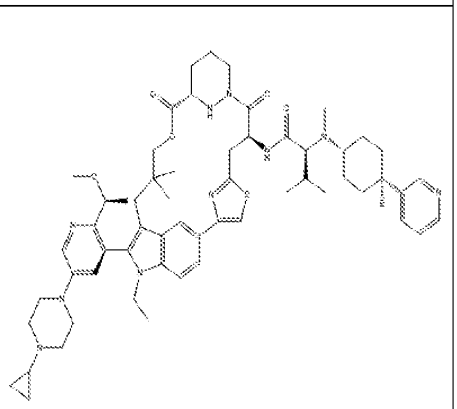
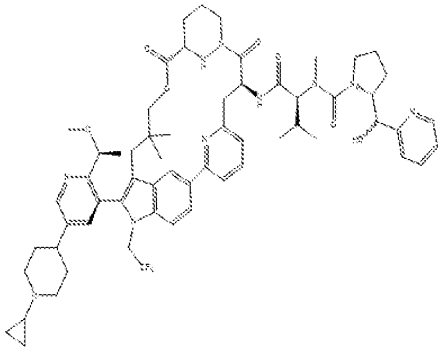
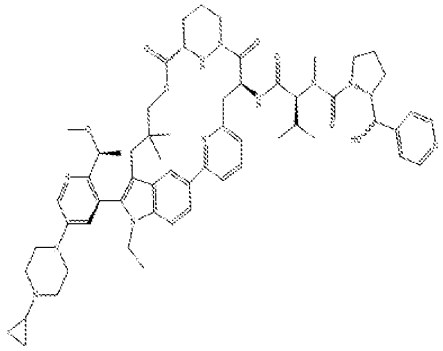
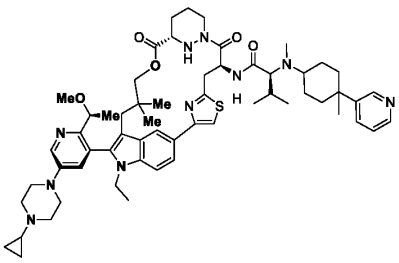
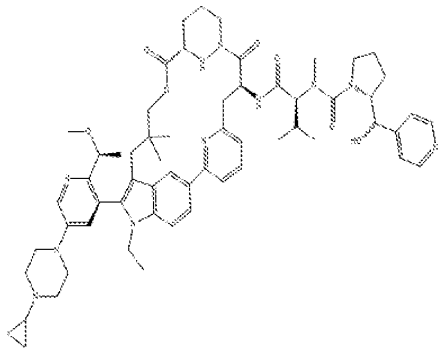
A25		A28	
A26		A29	
A27		A30	

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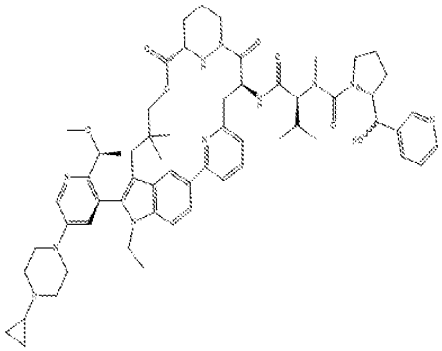
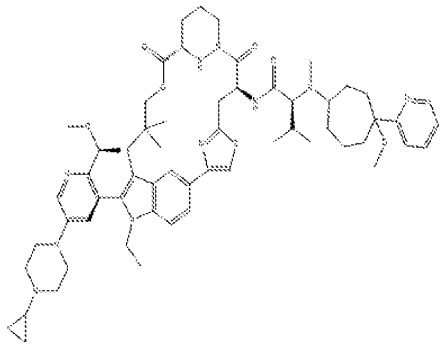
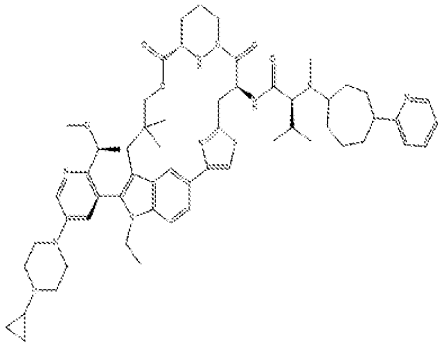
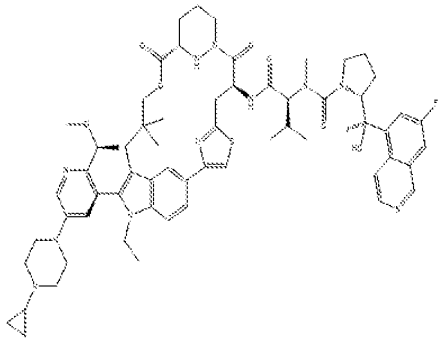
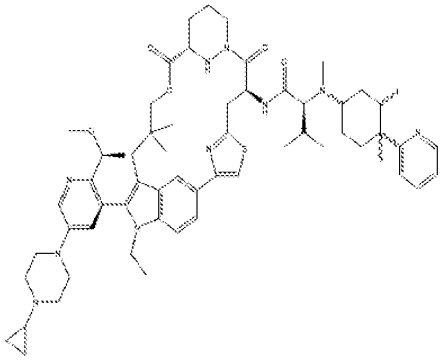
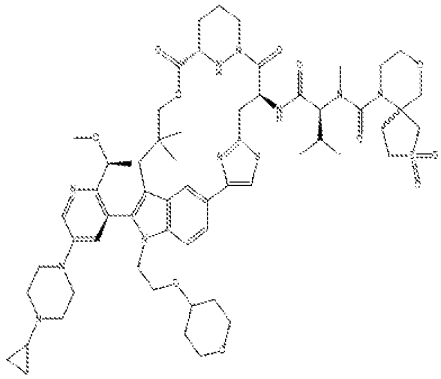
A31		A34	
A32		A35	
A33		A36	

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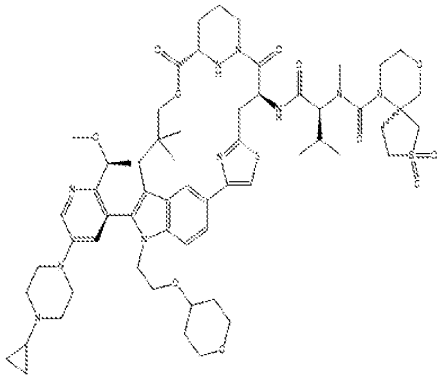
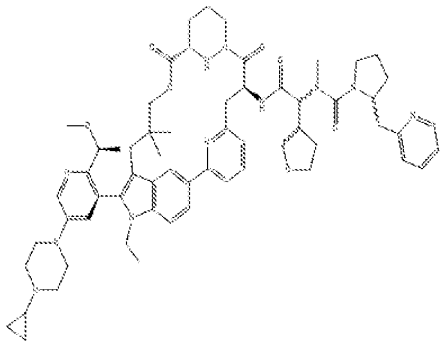
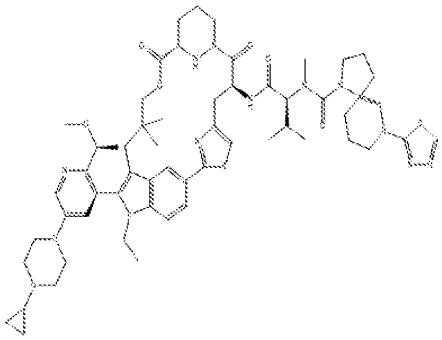
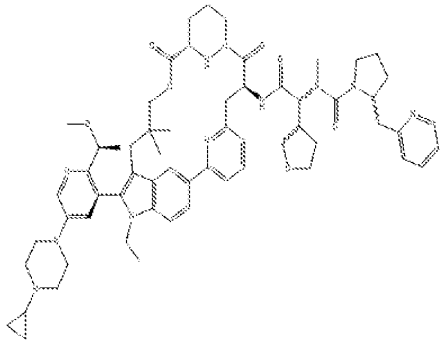
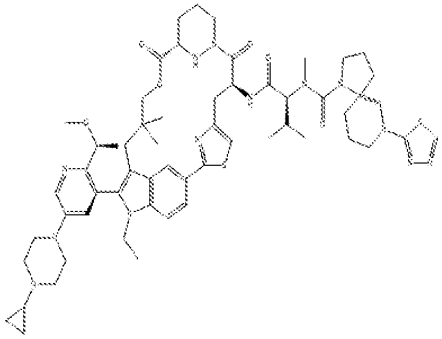
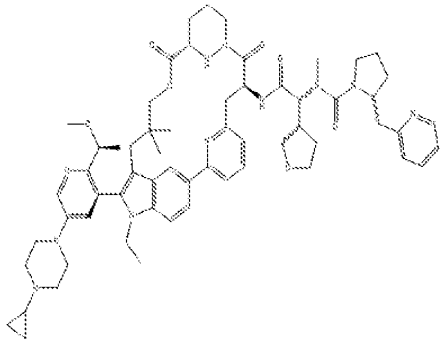
A37		A40	
A38		A41	
A39		A42	

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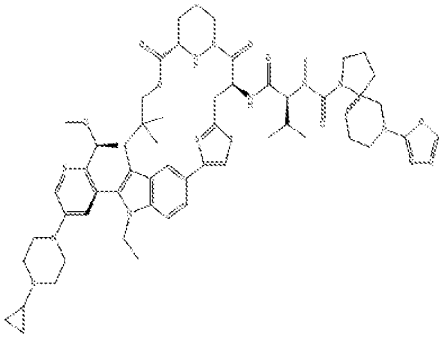
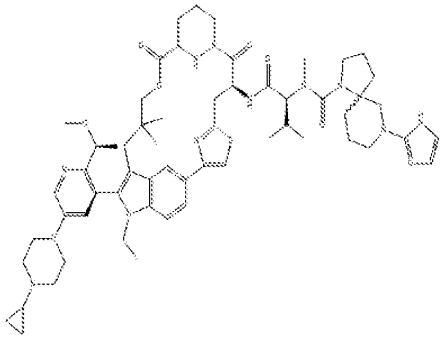
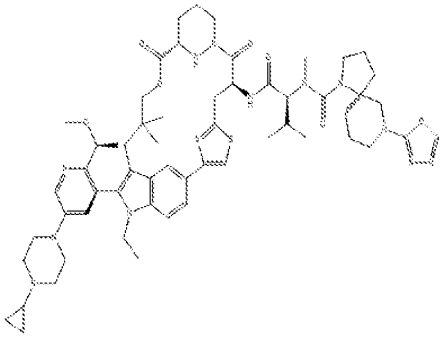
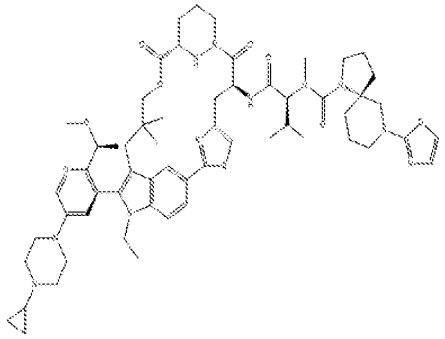
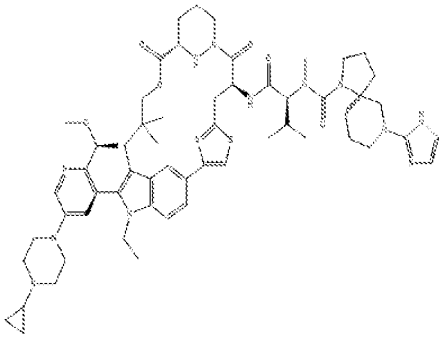
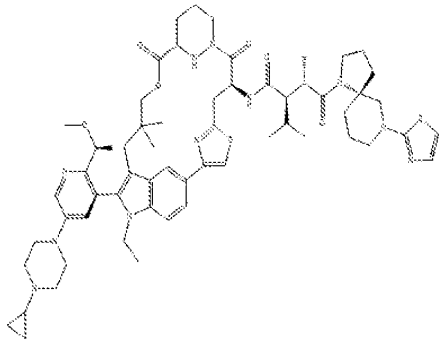
A43		A46	
A44		A47	
A45		A48	

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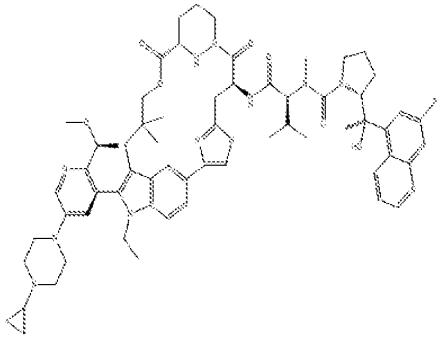
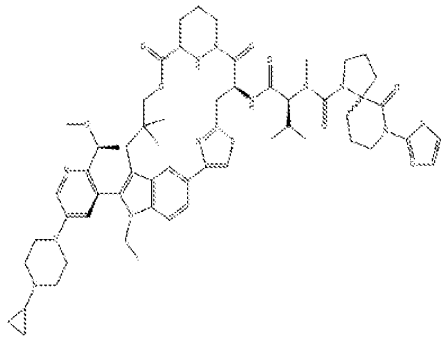
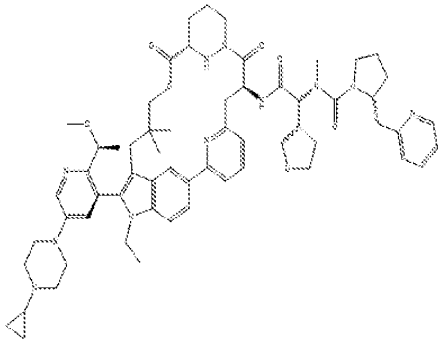
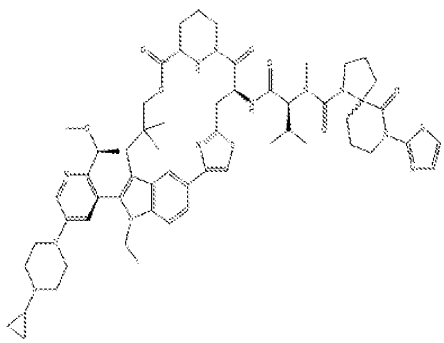
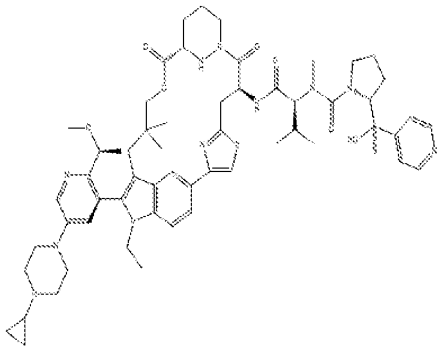
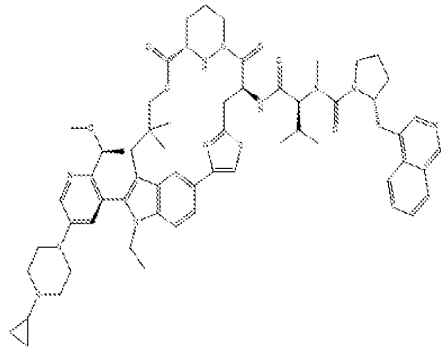
A49		A52	
A50		A53	
A51		A54	

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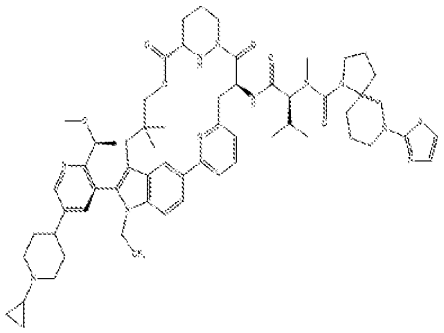
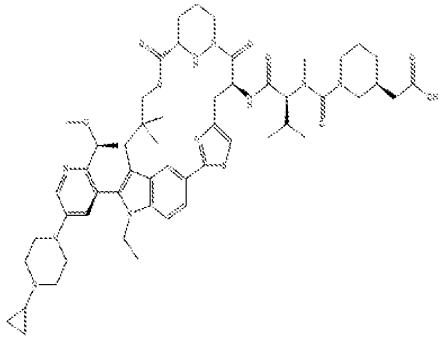
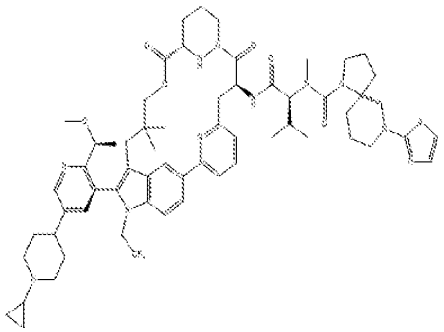
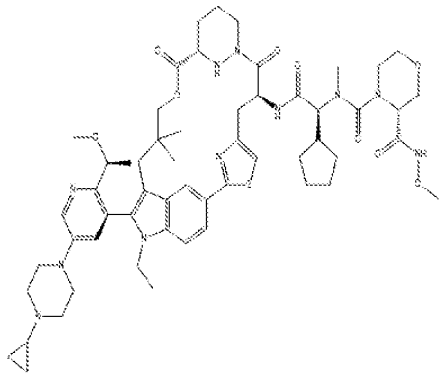
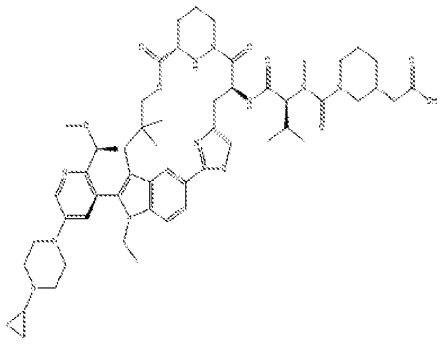
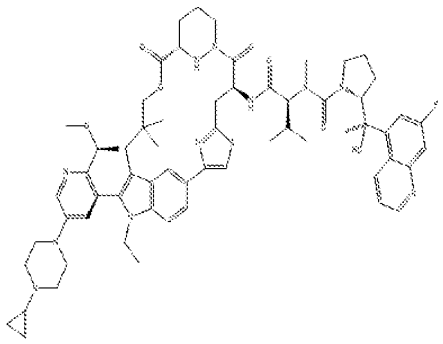
A55		A58	
A56		A59	
A57		A60	

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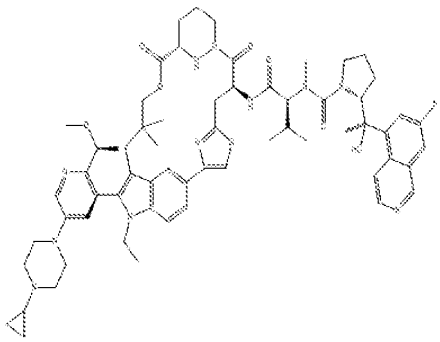
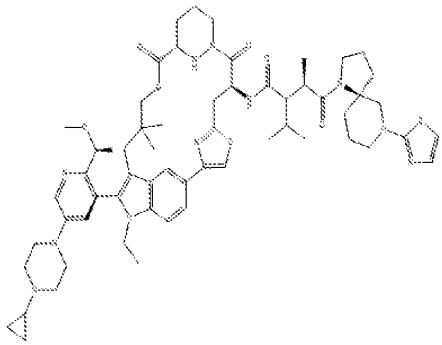
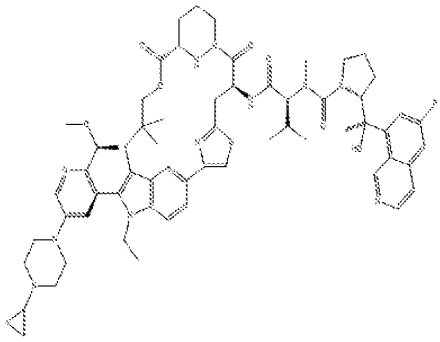
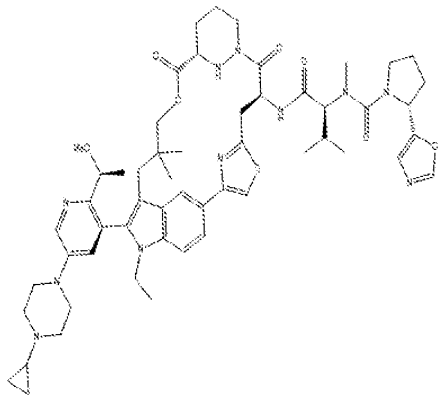
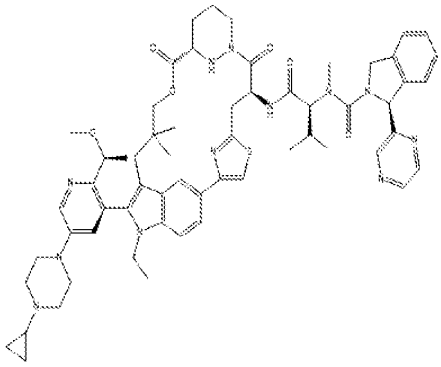
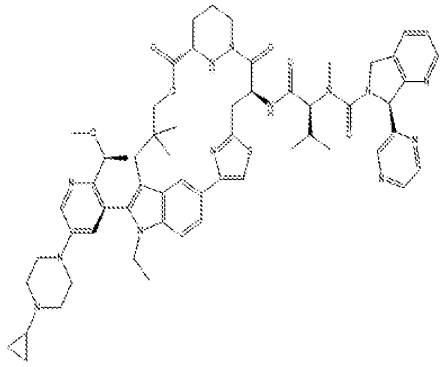
A61		A64	
A62		A65	
A63		A66	

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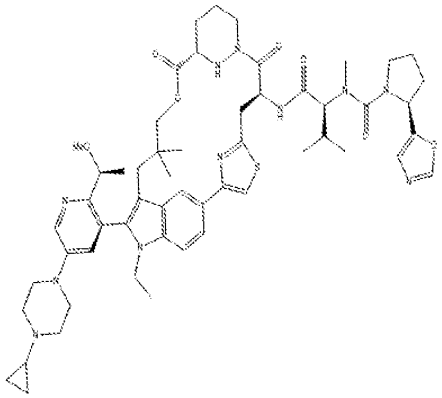
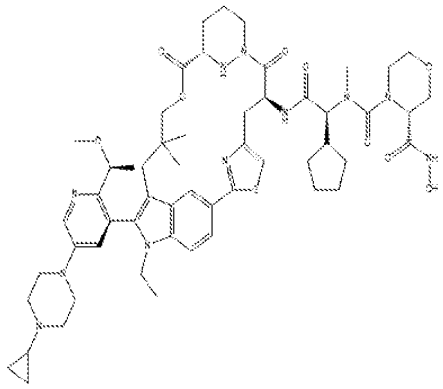
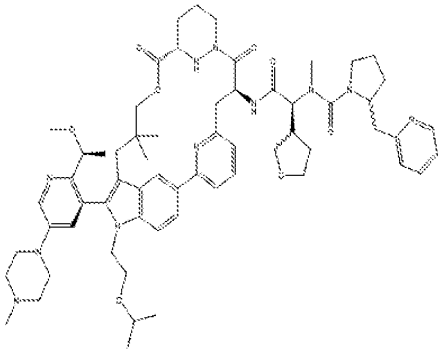
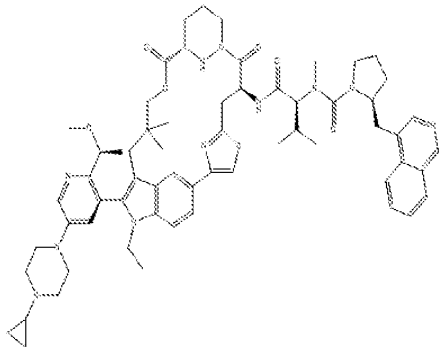
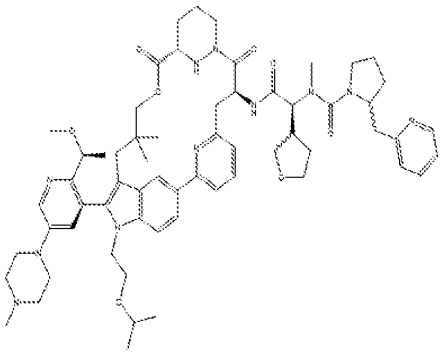
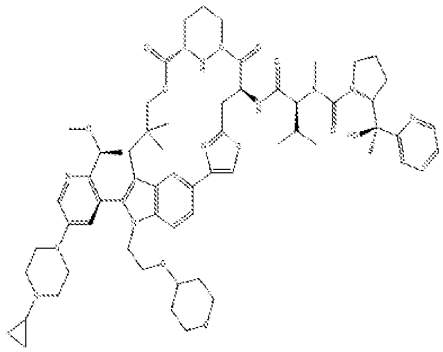
A67		A70	
A68		A71	
A69		A72	

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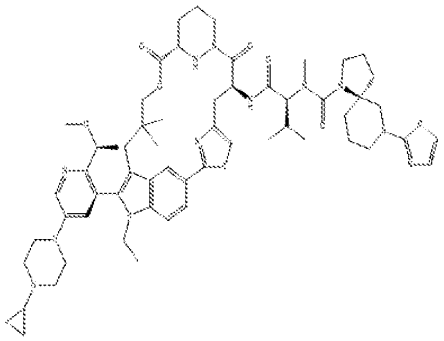
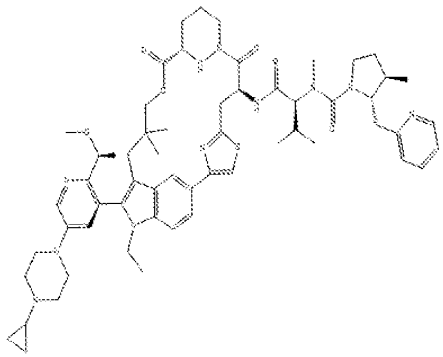
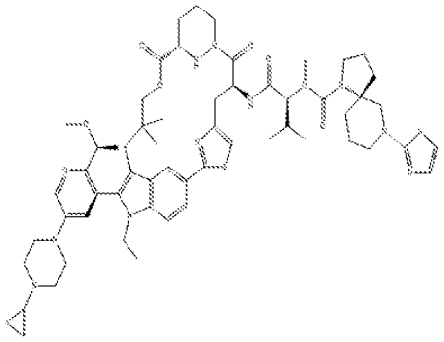
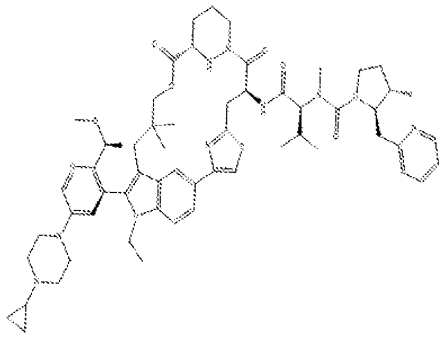
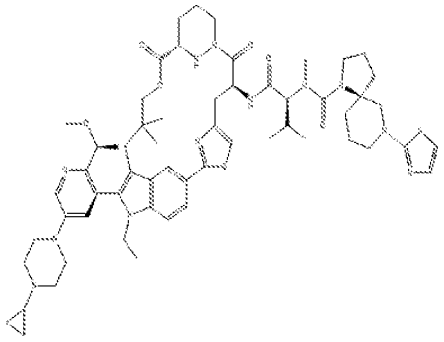
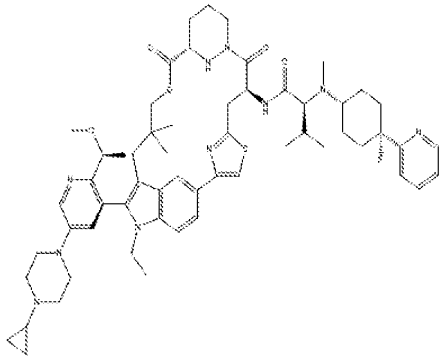
A73		A76	
A74		A77	
A75		A78	

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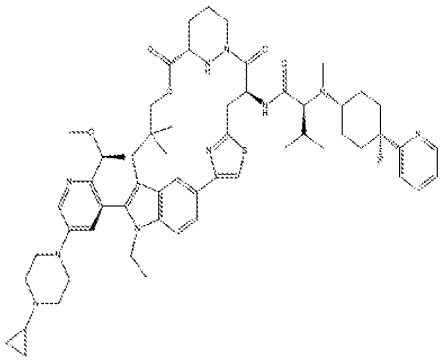
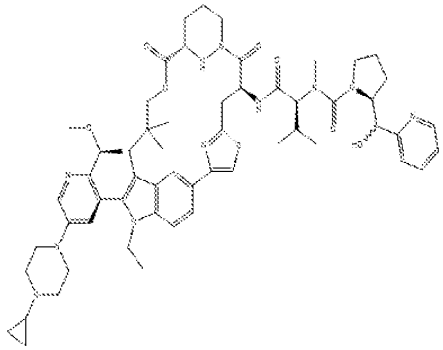
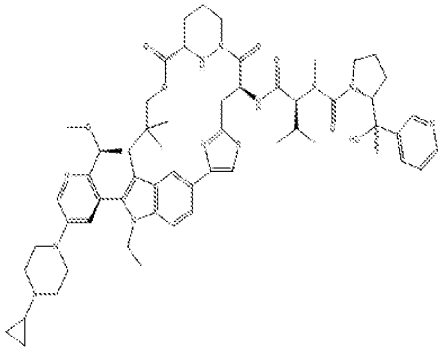
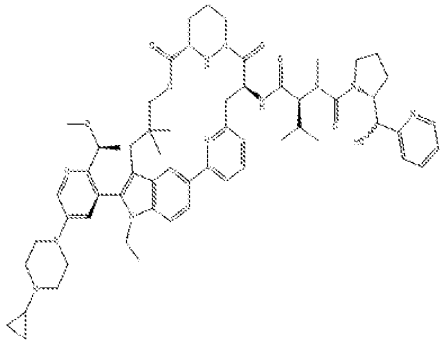
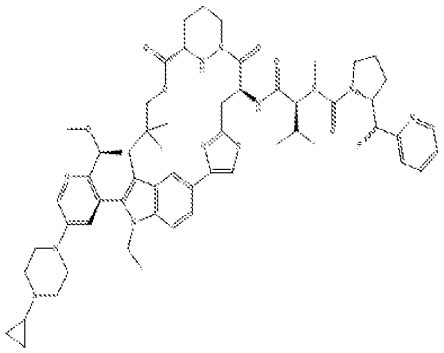
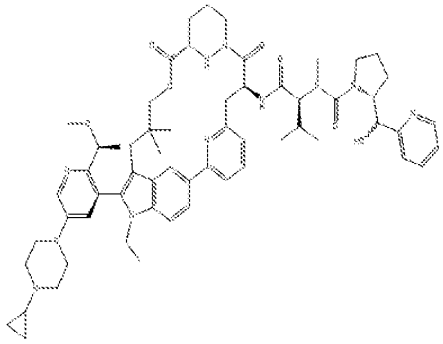
A79		A82	
A80		A83	
A81		A84	

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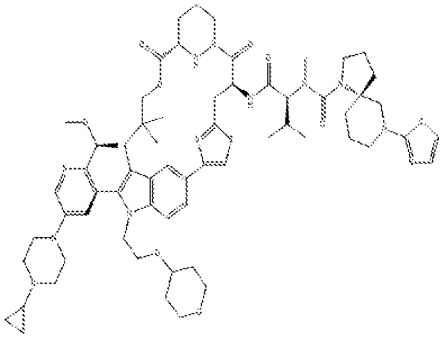
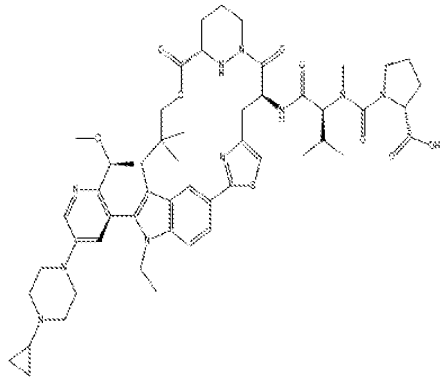
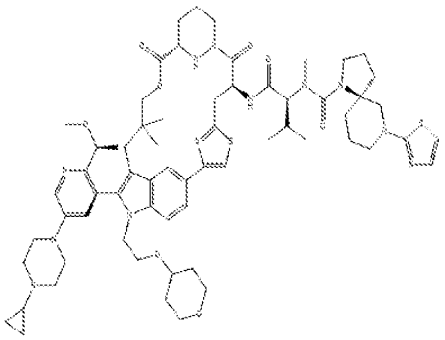
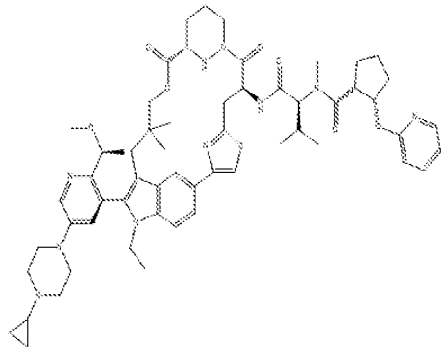
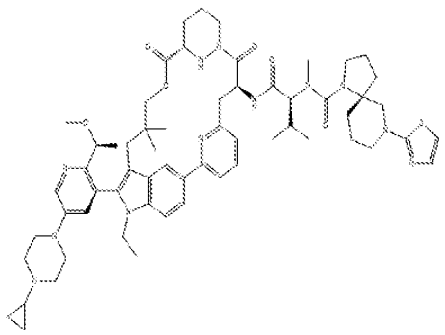
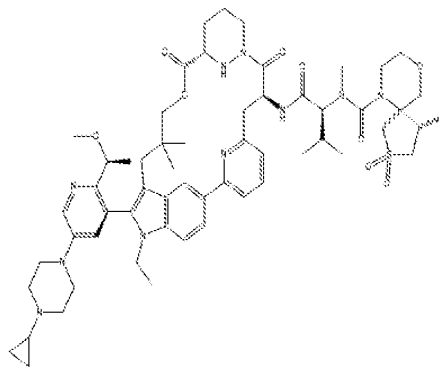
A85		A88	
A86		A89	
A87		A90	

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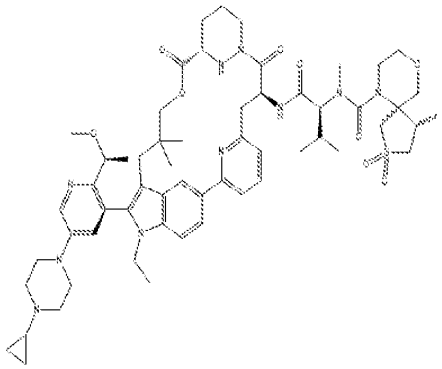
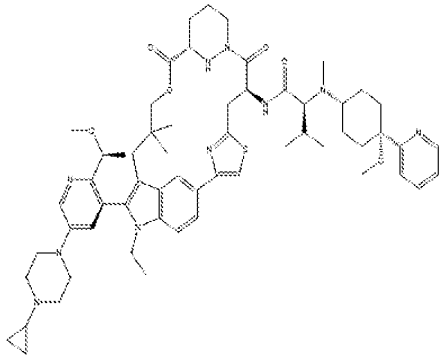
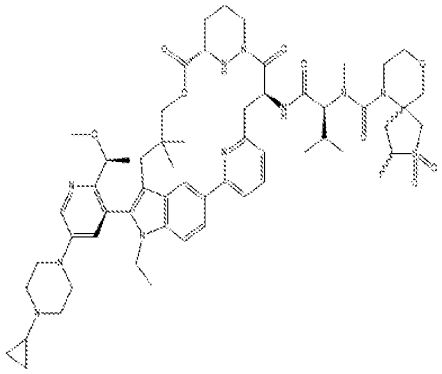
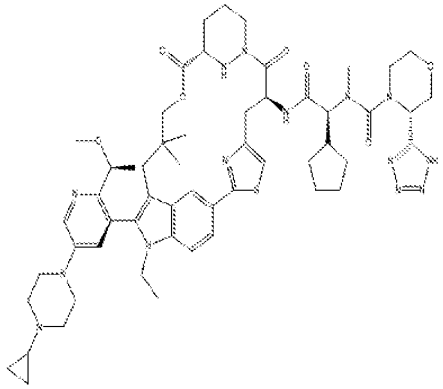
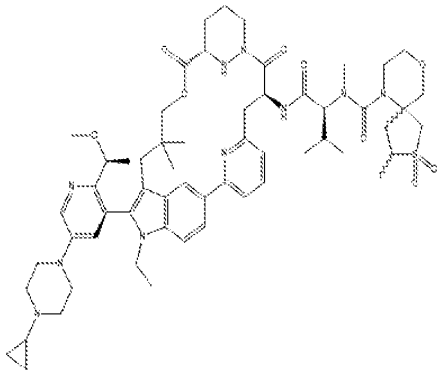
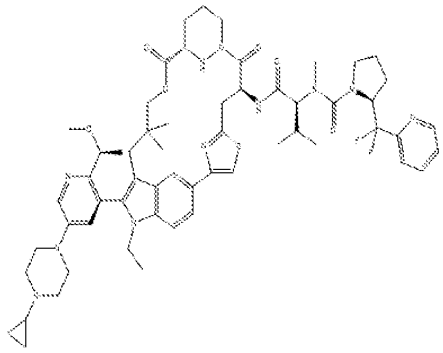
A91		A94	
A92		A95	
A93		A96	

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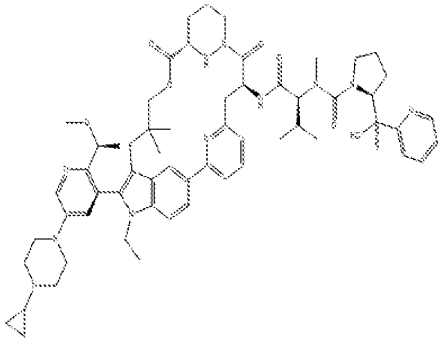
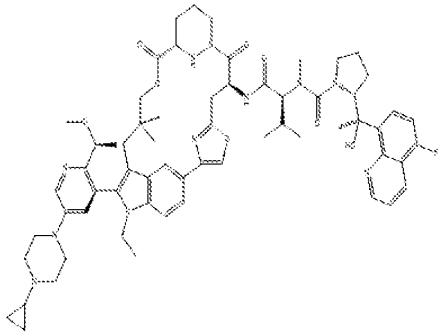
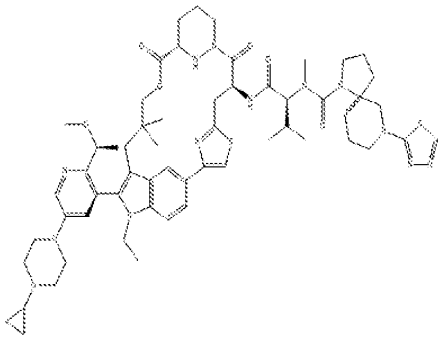
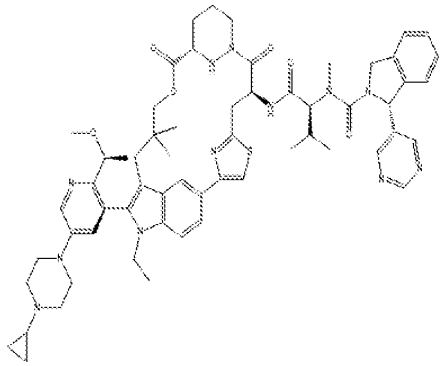
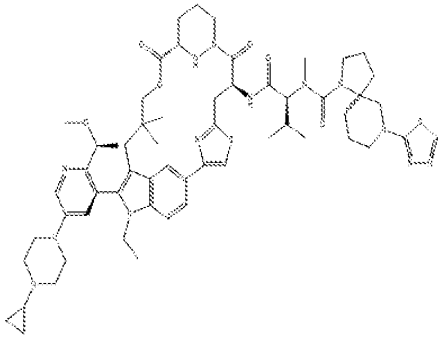
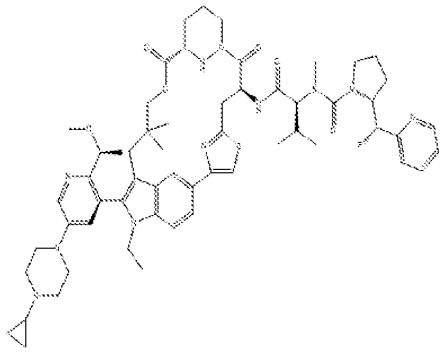
A97		A100	
A98		A101	
A99		A102	

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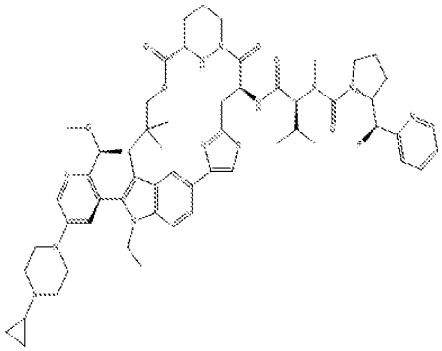
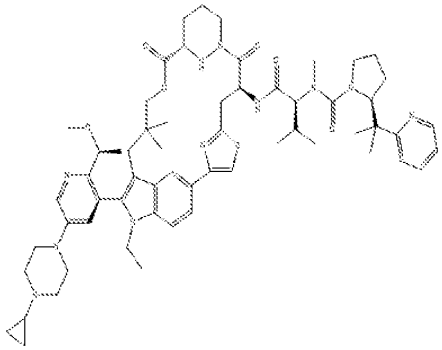
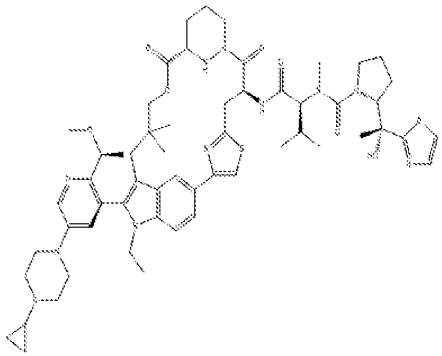
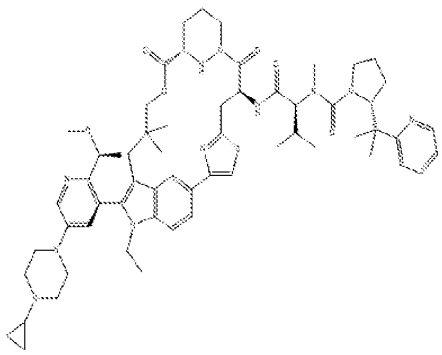
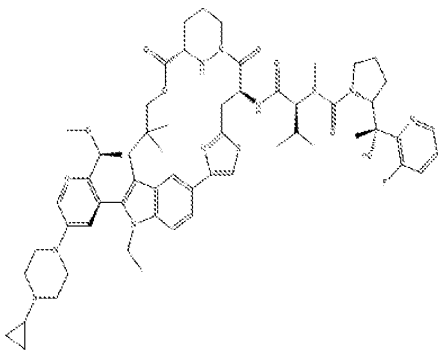
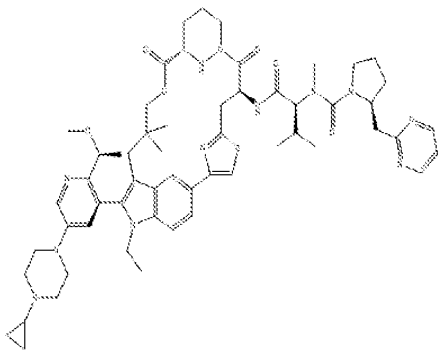
A103		A106	
A104		A107	
A105		A108	

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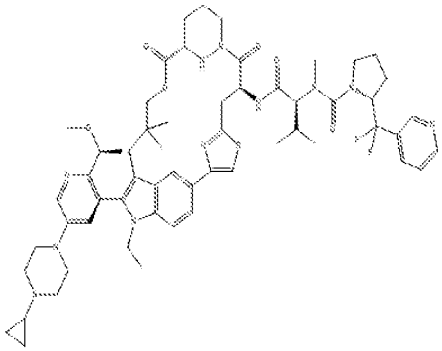
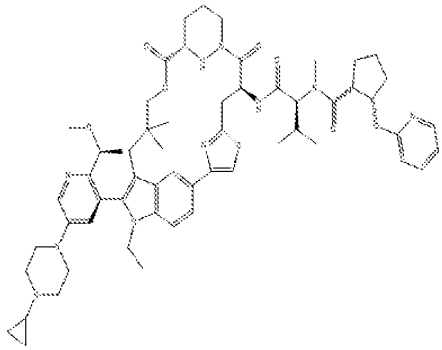
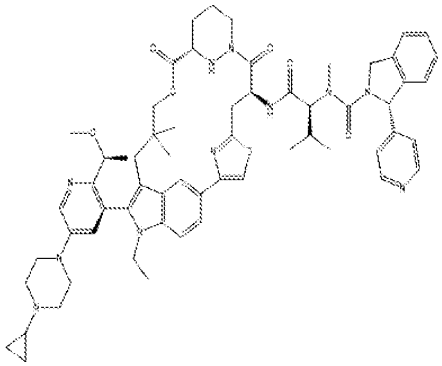
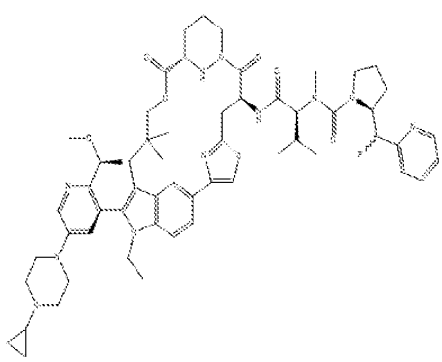
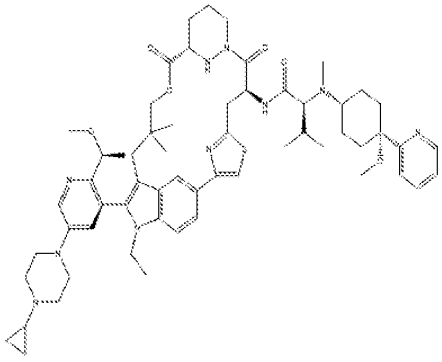
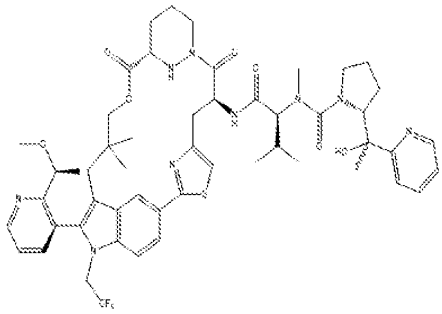
A109		A112	
A110		A113	
A111		A114	

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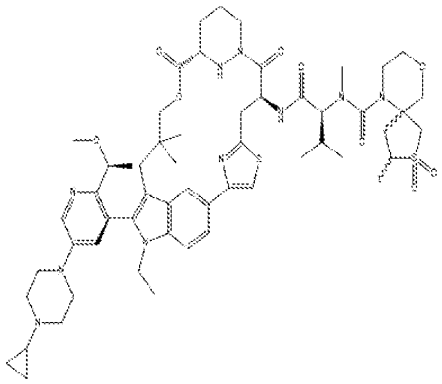
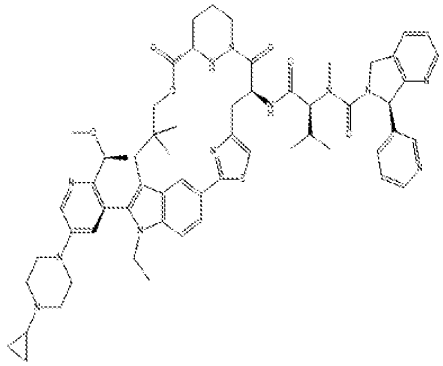
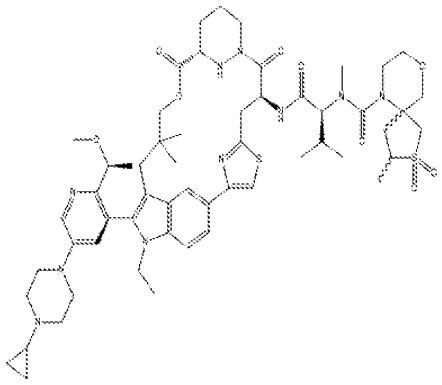
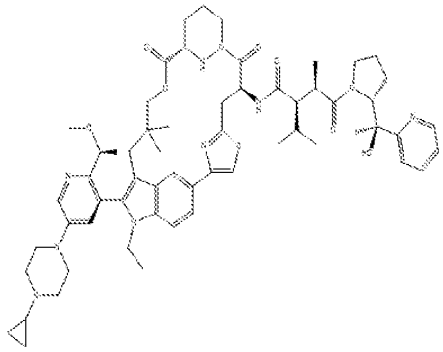
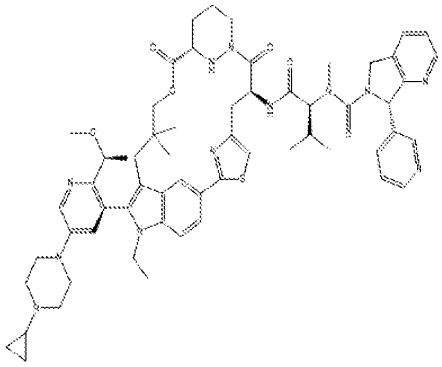
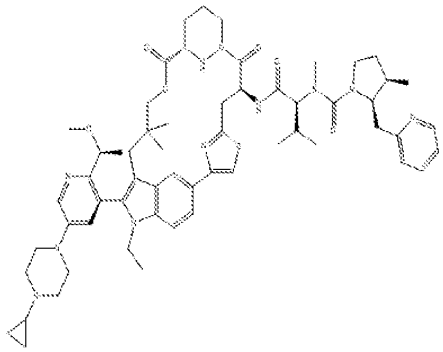
A115		A118	
A116		A119	
A117		A120	

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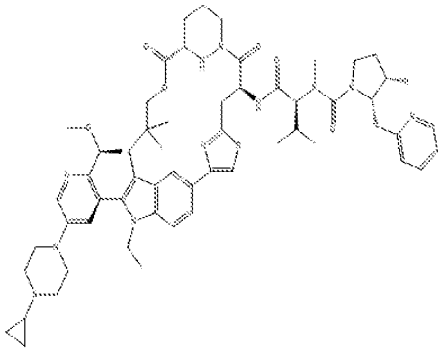
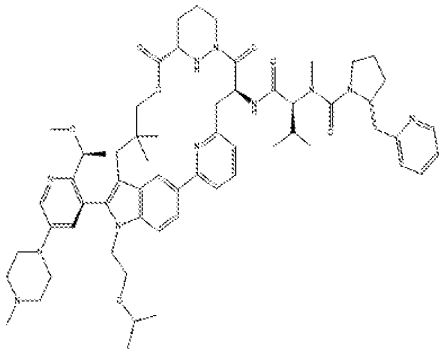
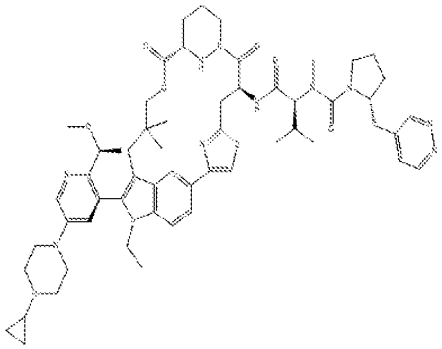
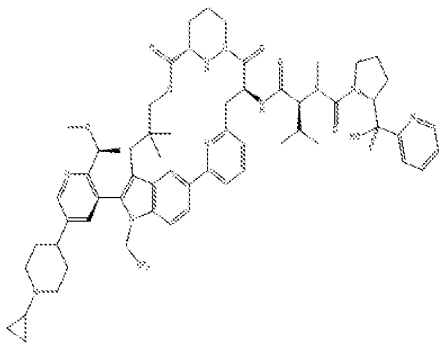
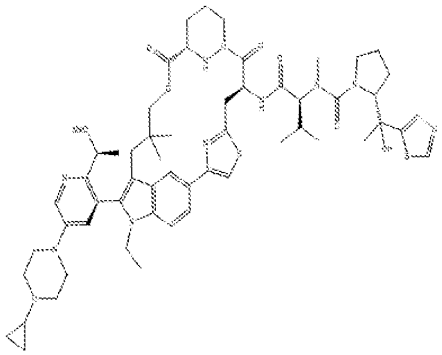
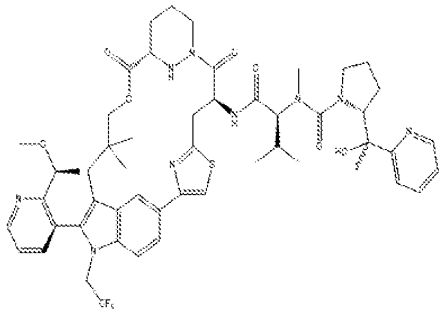
A121		A124	
A122		A125	
A123		A126	

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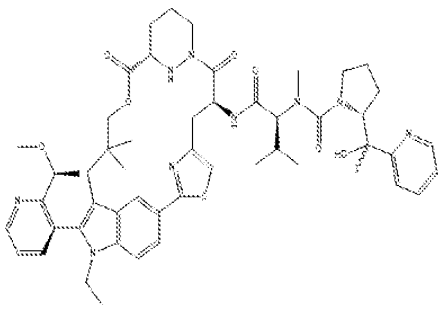
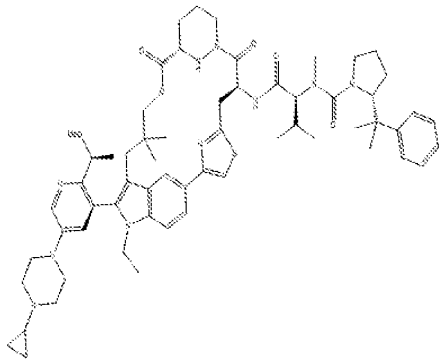
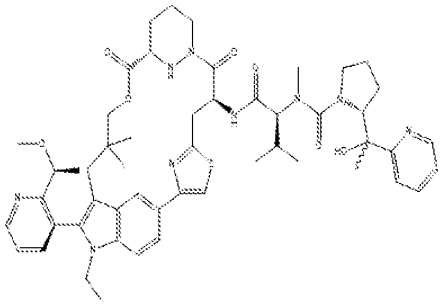
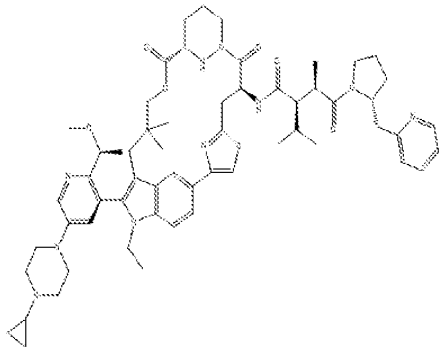
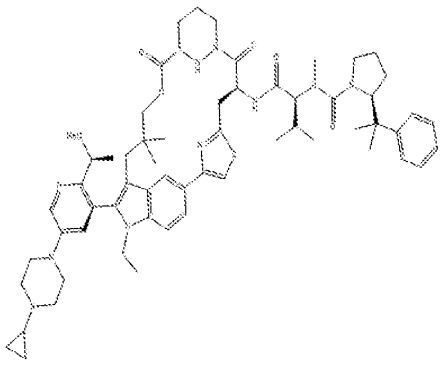
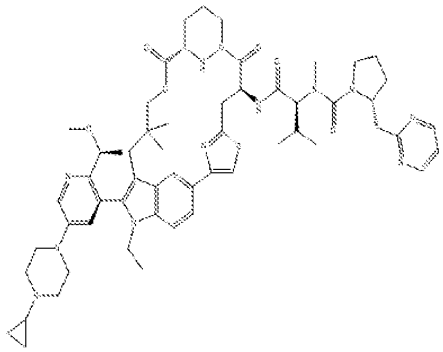
A127		A130	
A128		A131	
A129		A132	

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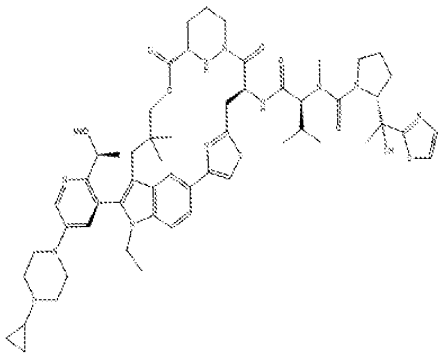
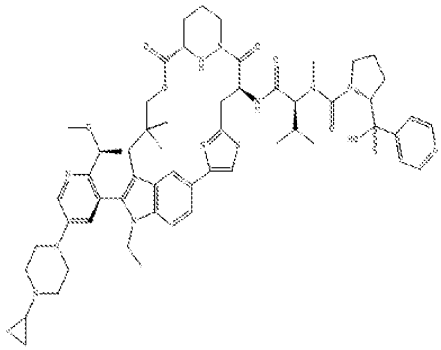
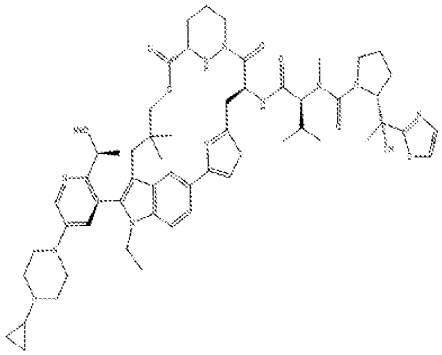
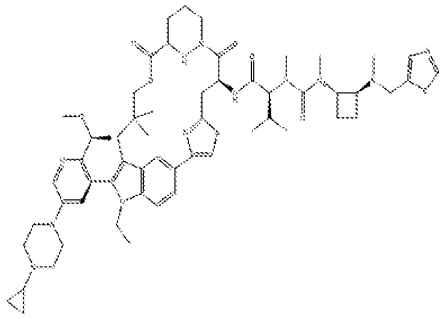
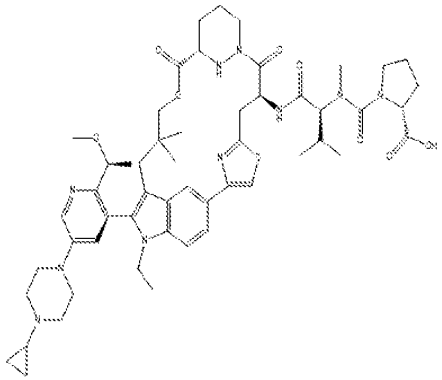
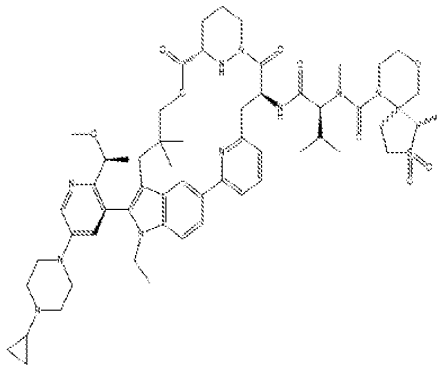
A133		A136	
A134		A137	
A135		A138	

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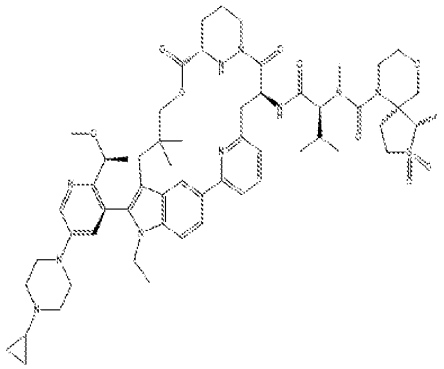
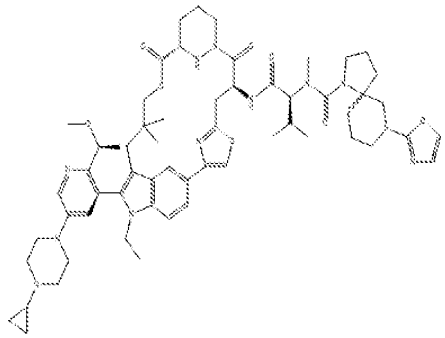
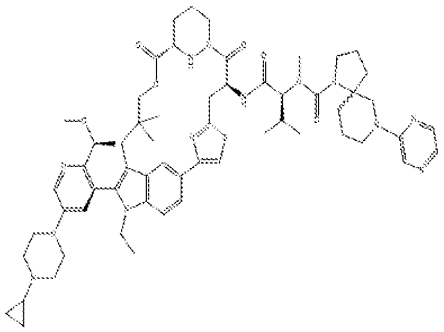
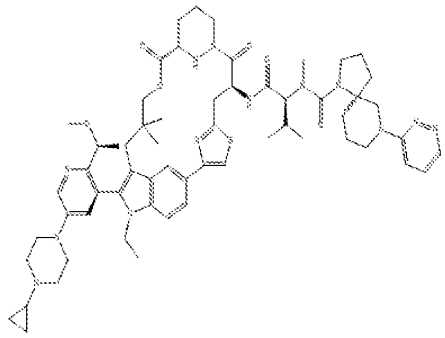
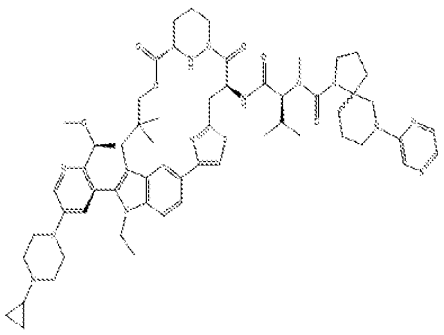
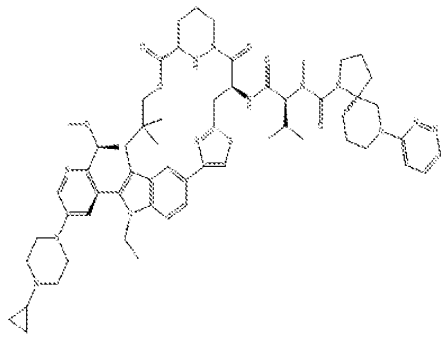
A139		A142	
A140		A143	
A141		A144	

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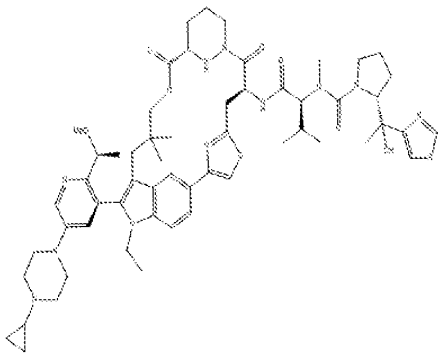
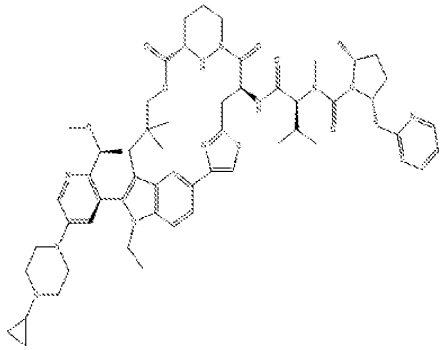
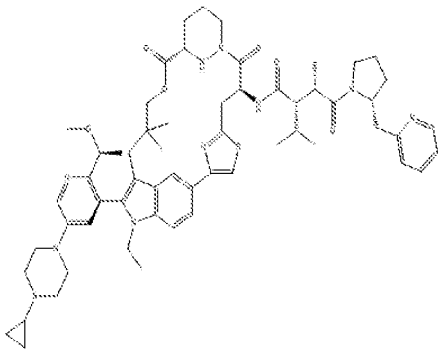
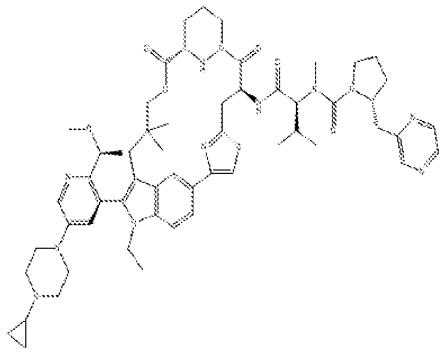
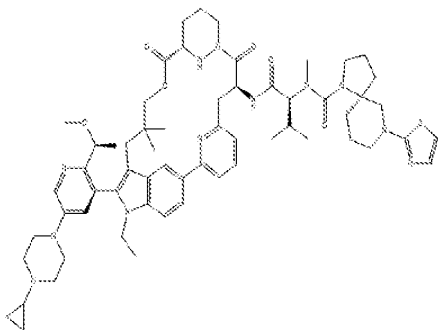
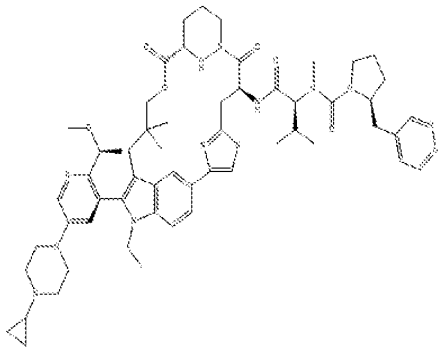
A145		A148	
A146		A149	
A147		A150	

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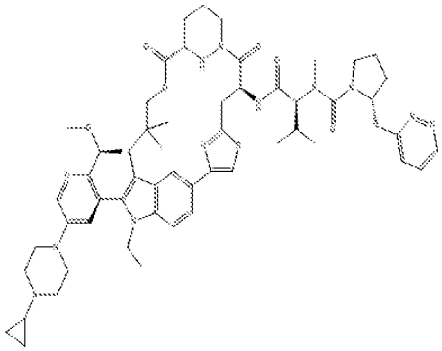
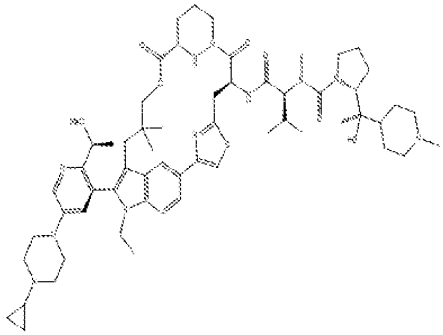
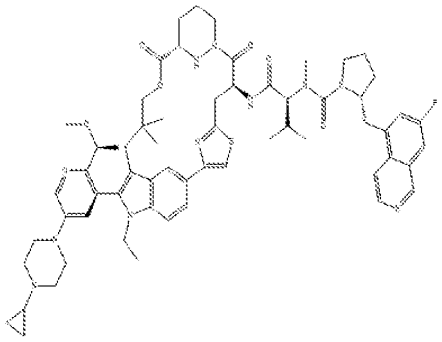
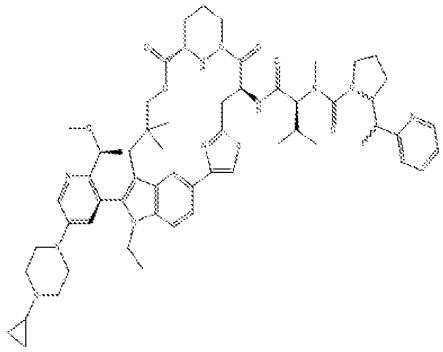
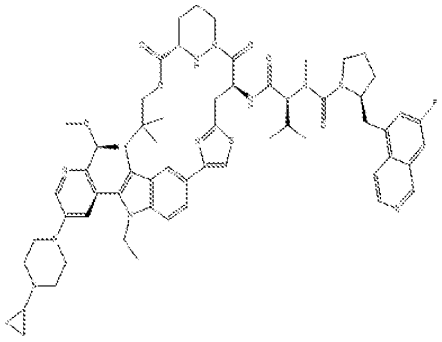
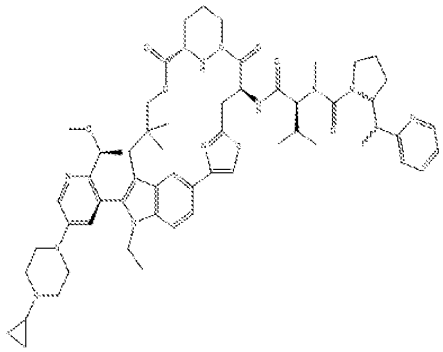
A151		A154	
A152		A155	
A153		A156	

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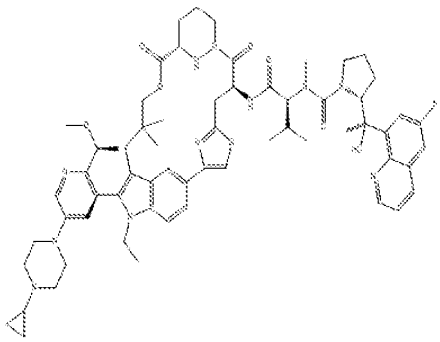
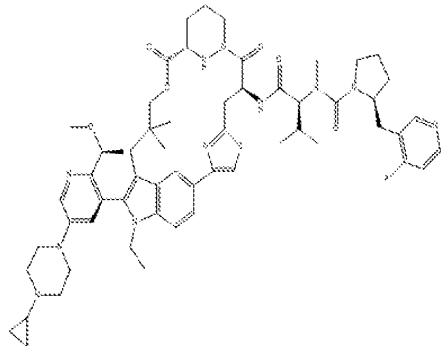
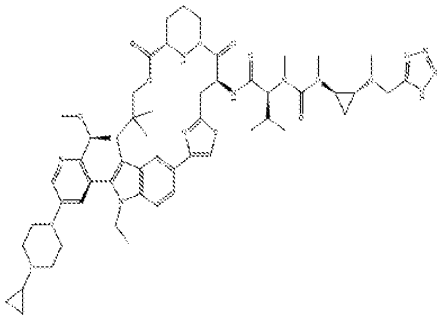
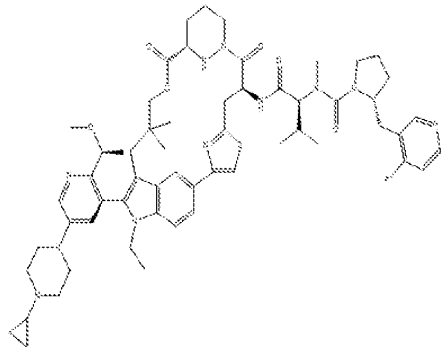
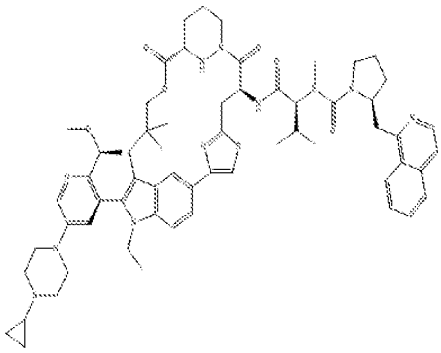
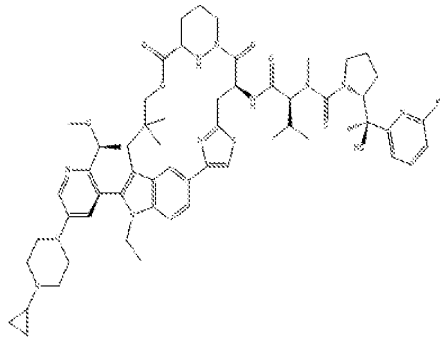
A157		A160	
A158		A161	
A159		A162	

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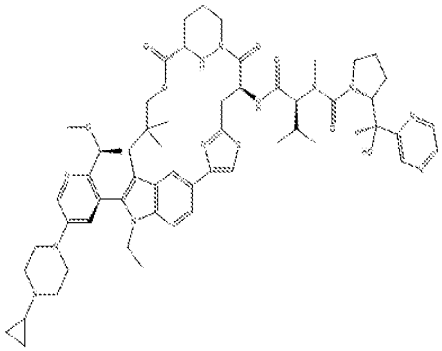
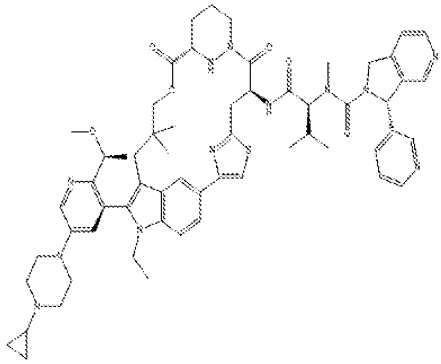
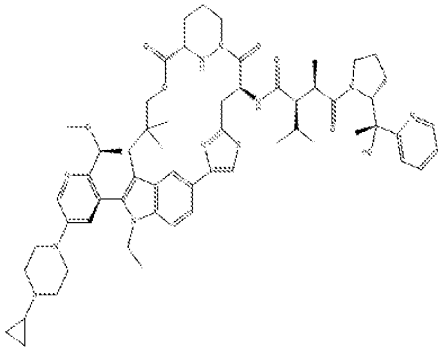
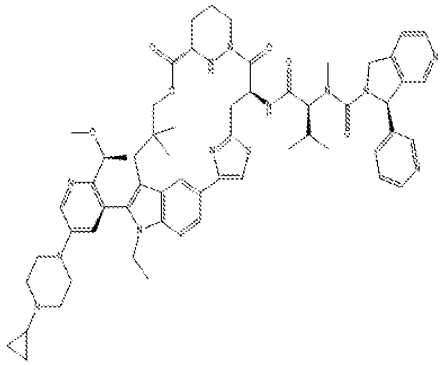
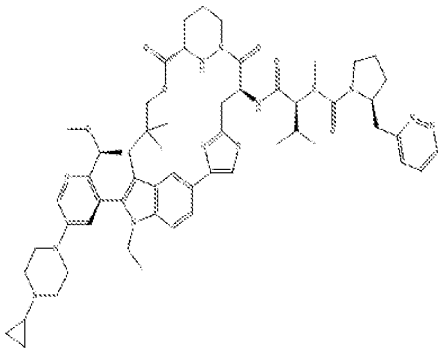
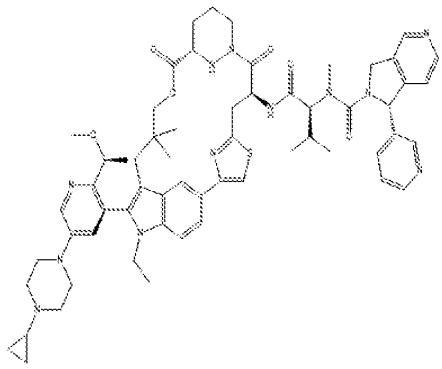
A163		A166	
A164		A167	
A165		A168	

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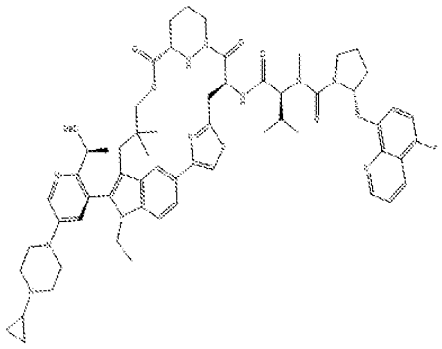
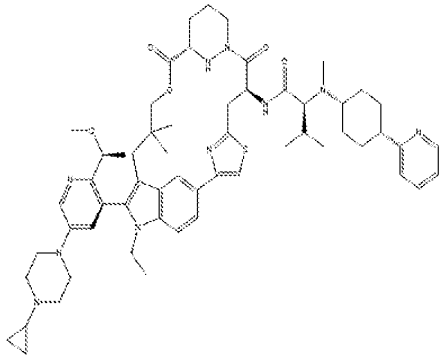
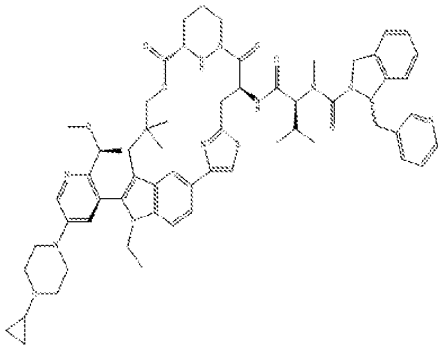
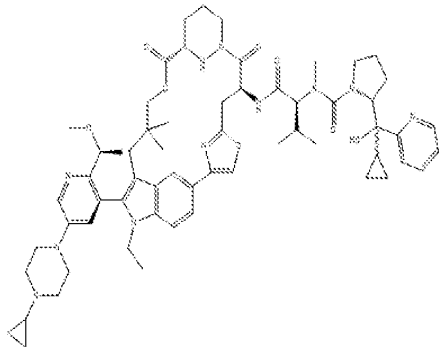
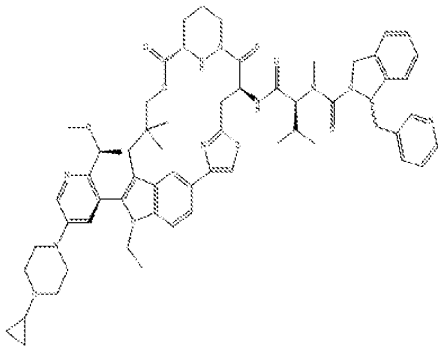
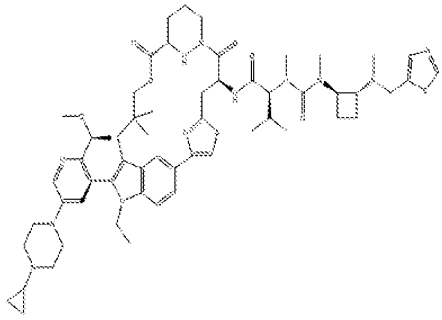
A169		A172	
A170		A173	
A171		A174	

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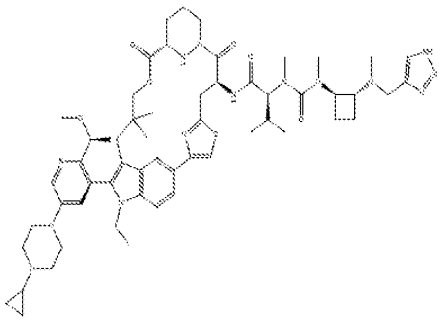
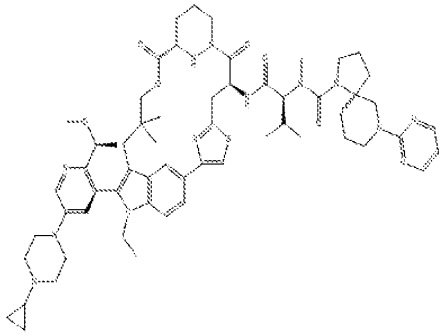
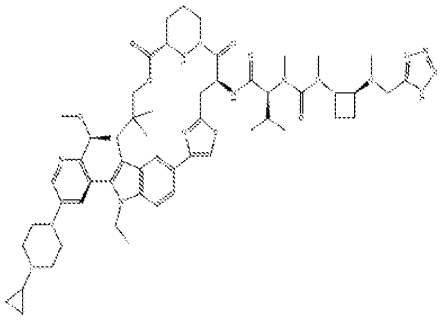
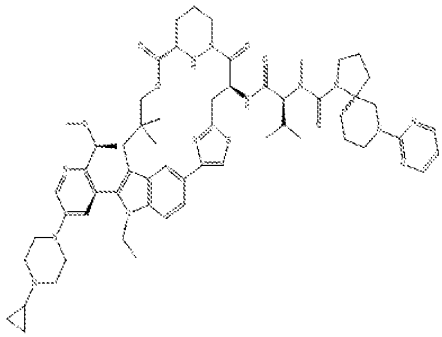
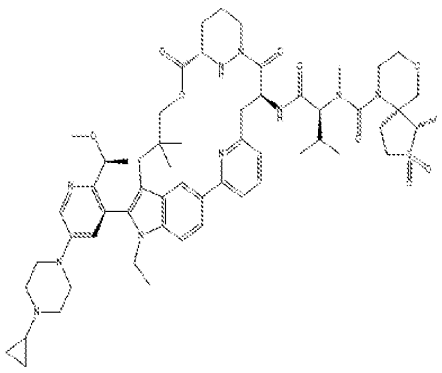
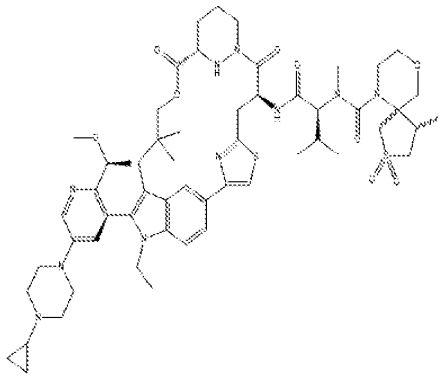
A175		A178	
A176		A179	
A177		A180	

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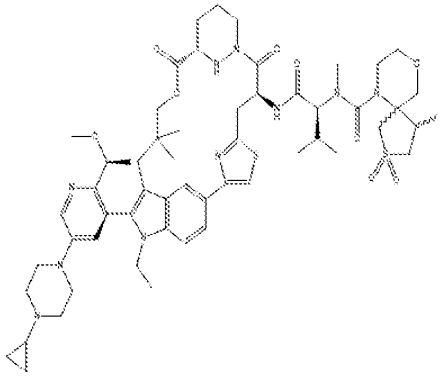
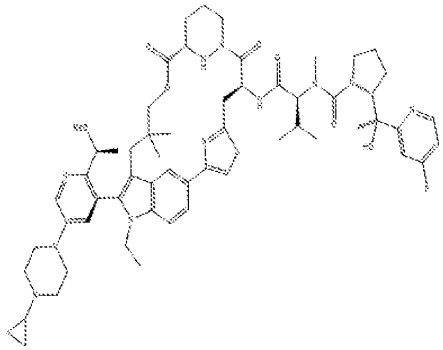
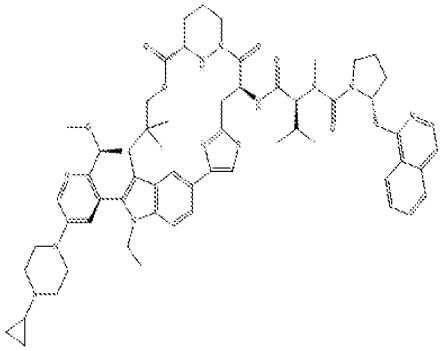
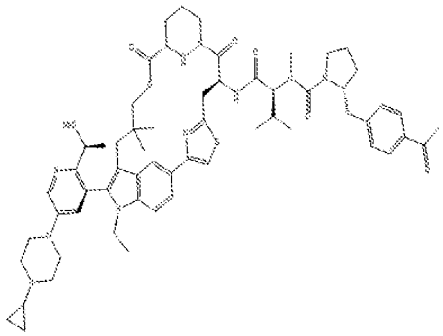
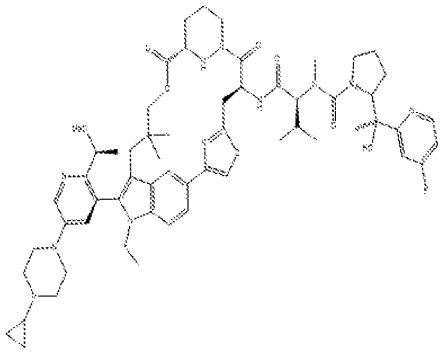
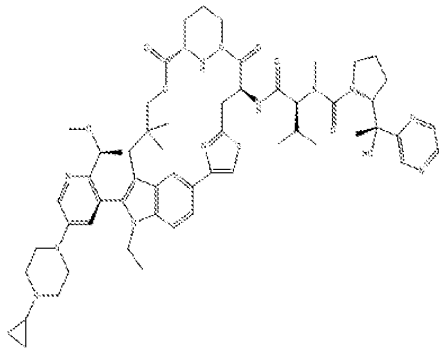
A181		A184	
A182		A185	
A183		A186	

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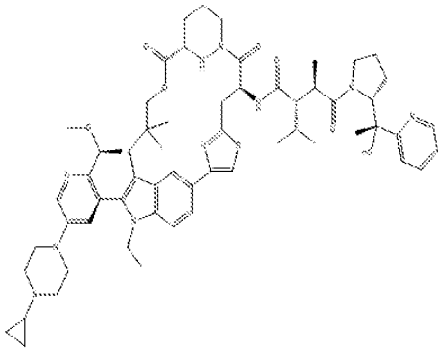
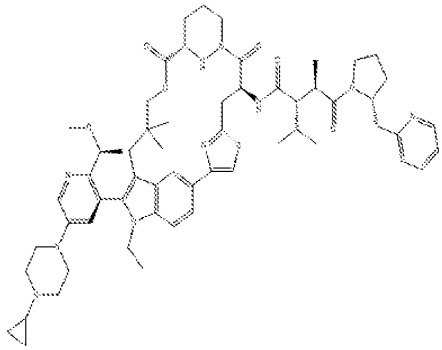
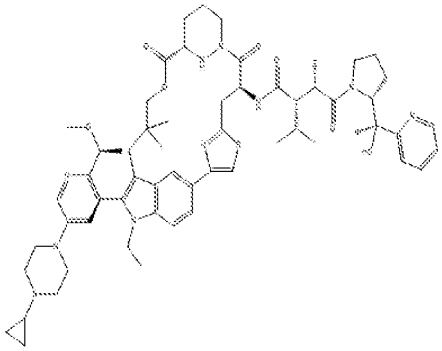
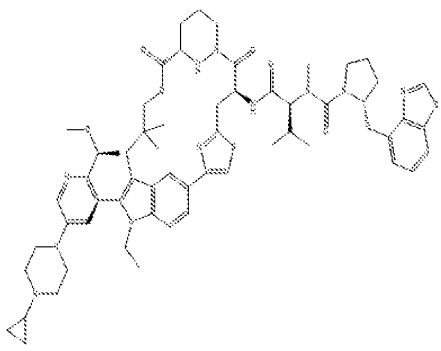
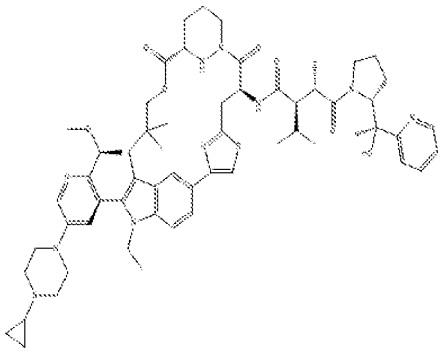
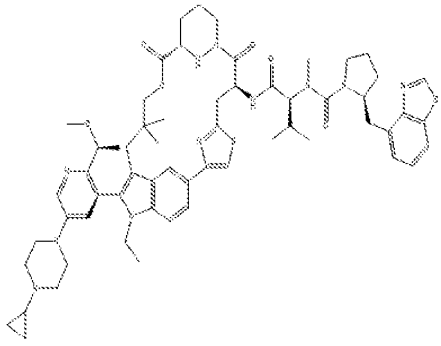
A187		A190	
A188		A191	
A189		A192	

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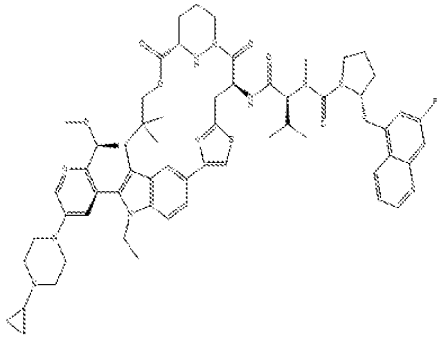
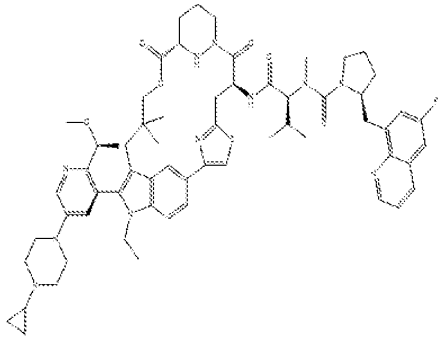
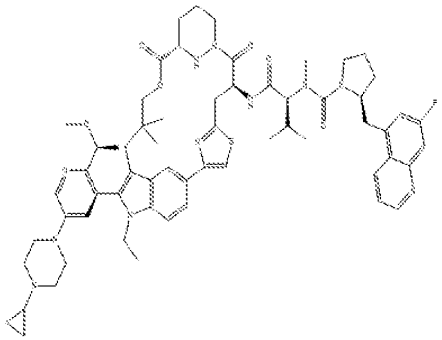
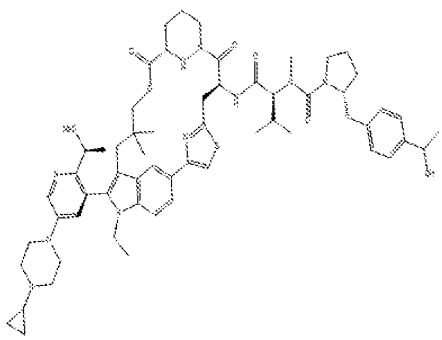
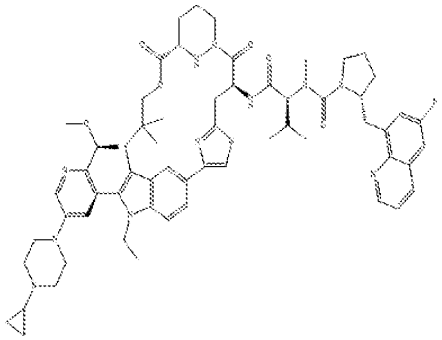
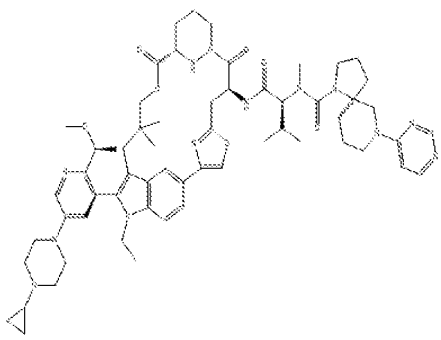
A193		A196	
A194		A197	
A195		A198	

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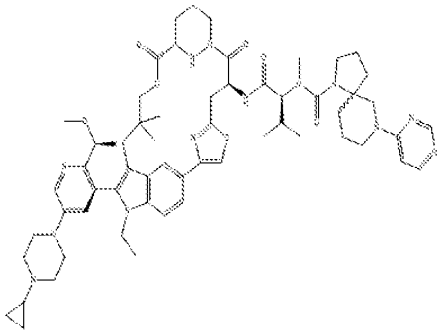
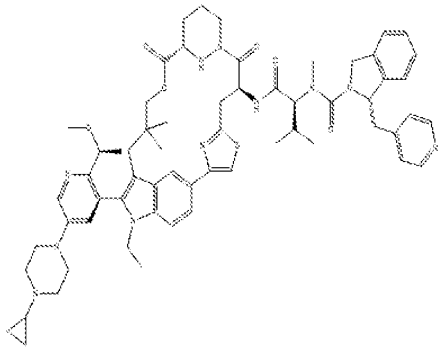
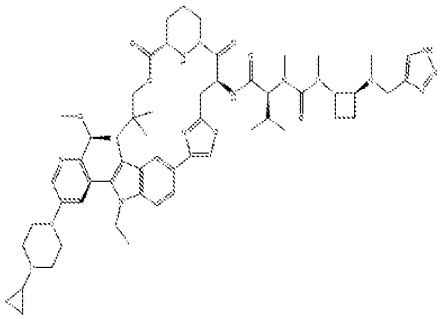
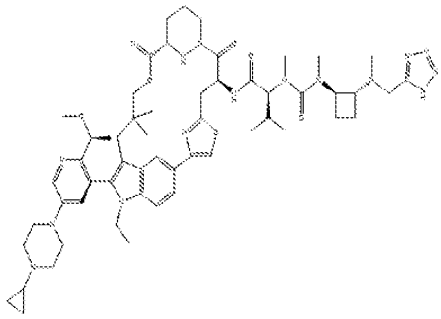
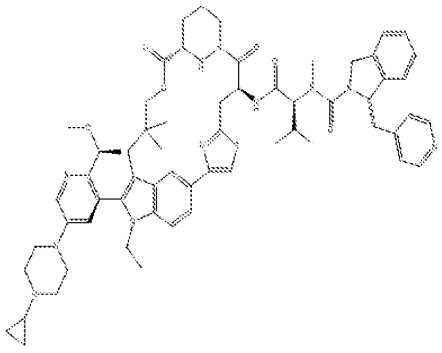
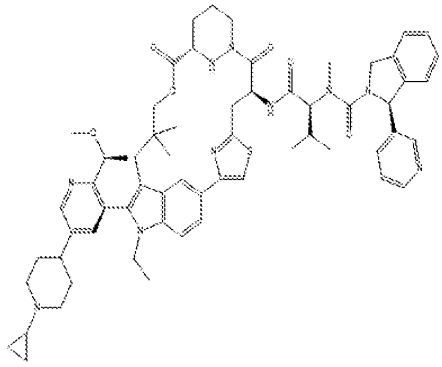
A199		A202	
A200		A203	
A201		A204	

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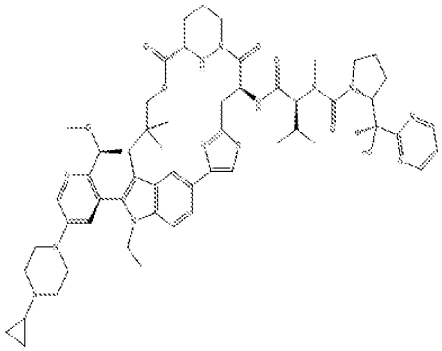
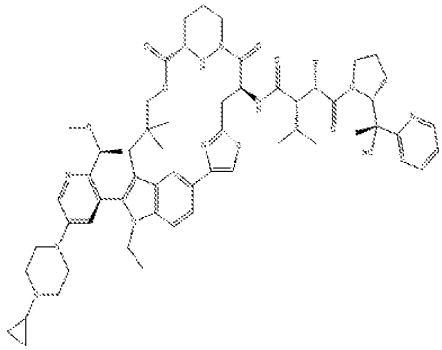
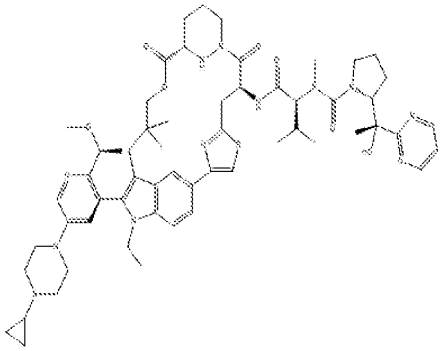
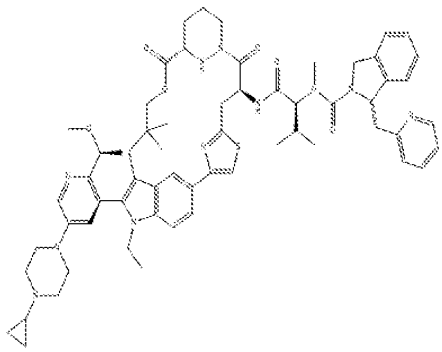
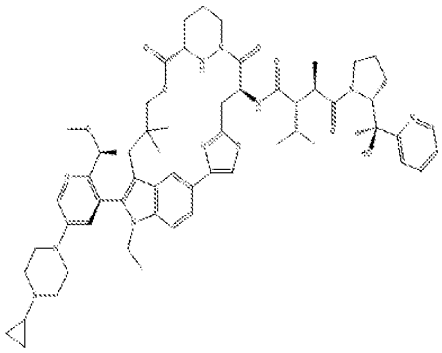
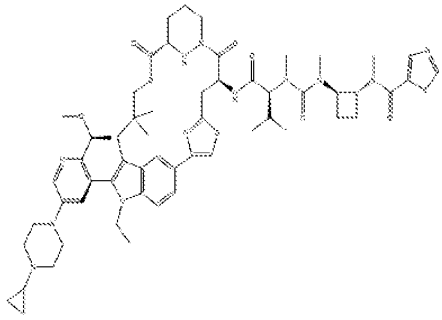
A205		A208	
A206		A209	
A207		A210	

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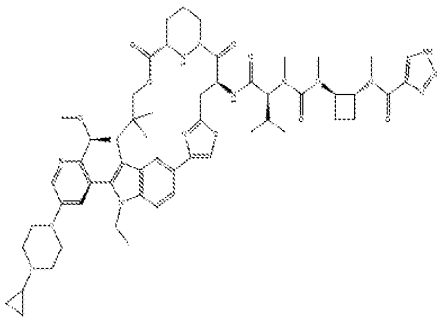
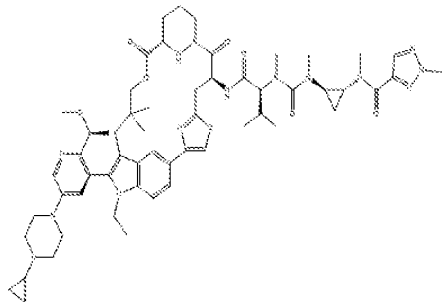
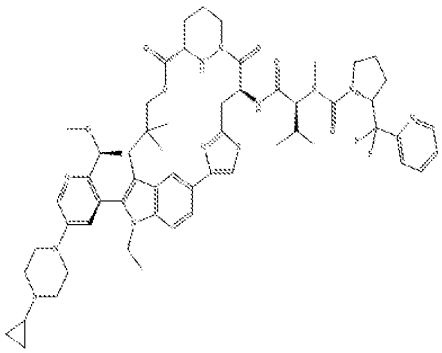
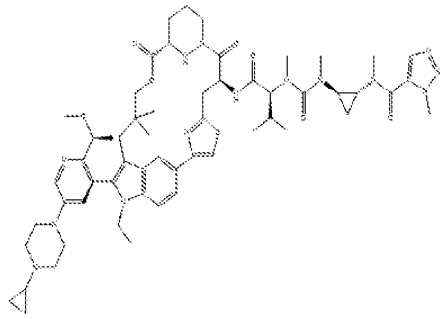
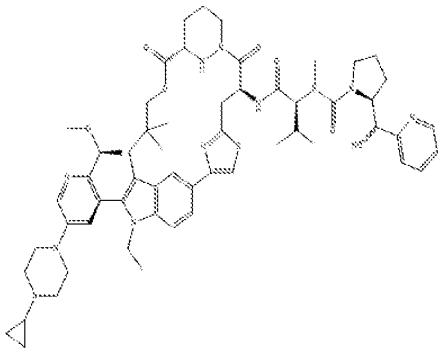
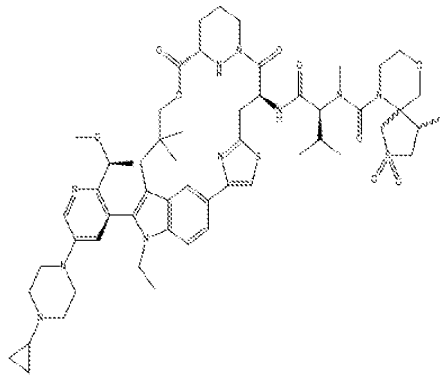
A211		A214	
A212		A215	
A213		A216	

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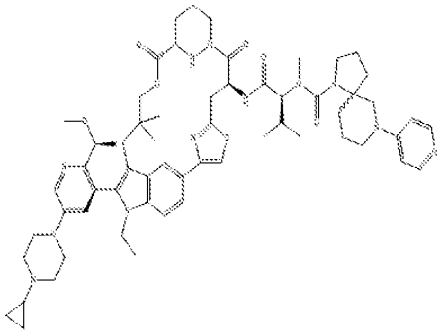
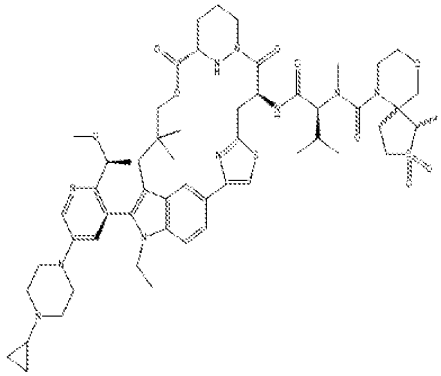
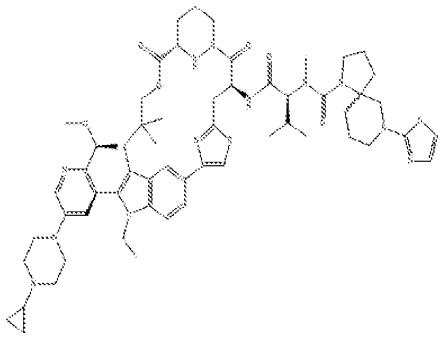
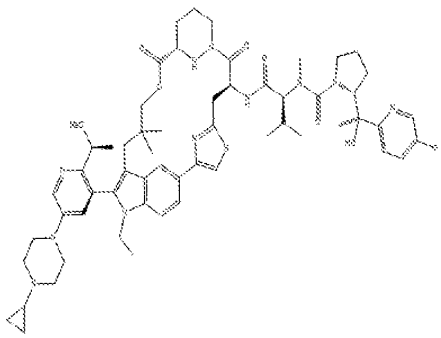
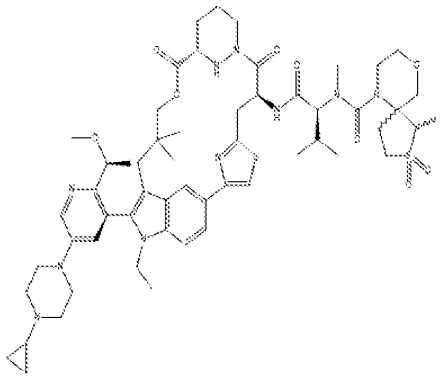
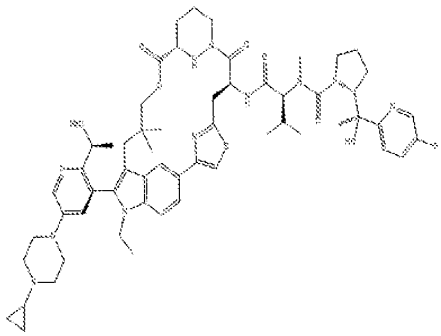
A217		A220	
A218		A221	
A219		A222	

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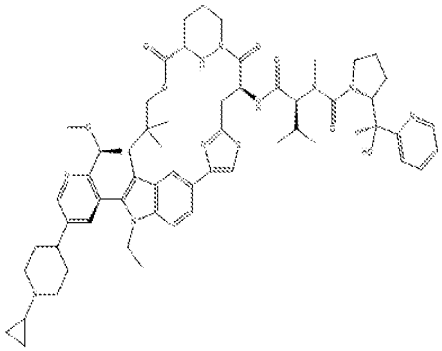
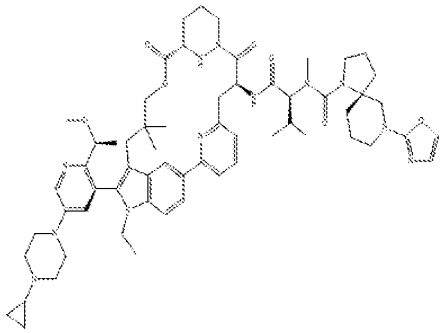
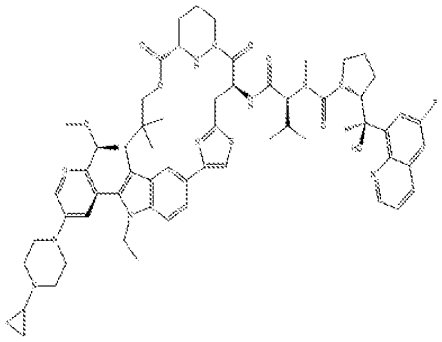
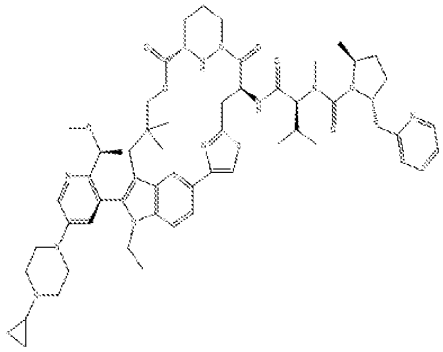
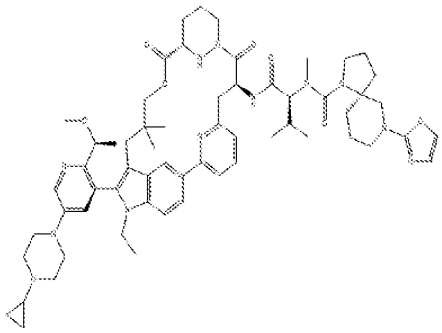
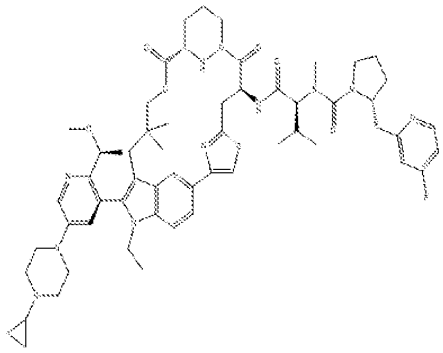
A223		A226	
A224		A227	
A225		A228	

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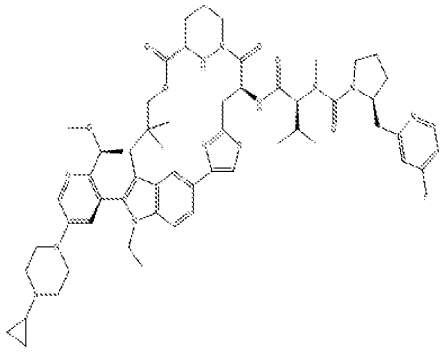
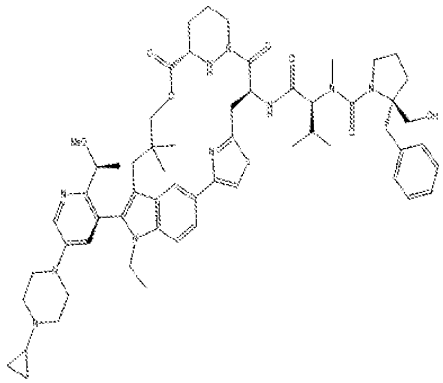
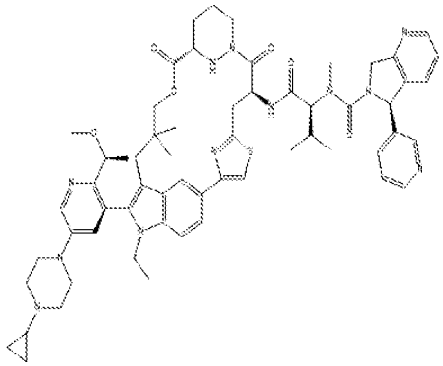
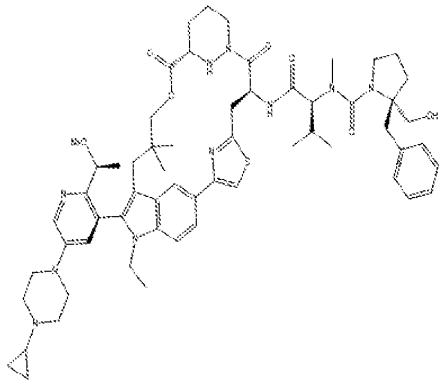
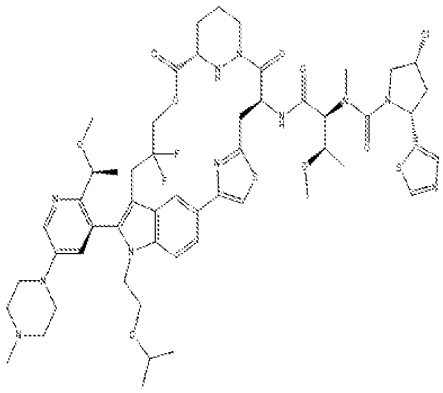
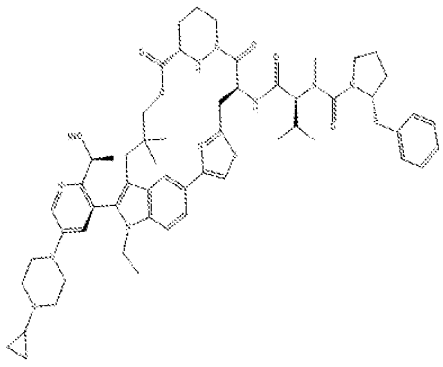
A229		A232	
A230		A233	
A231		A234	

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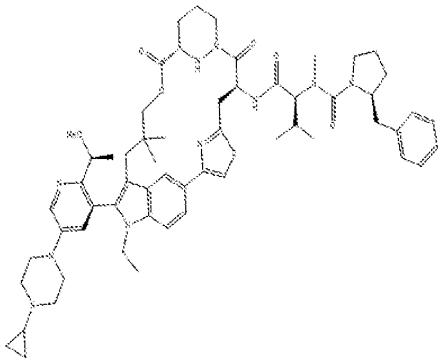
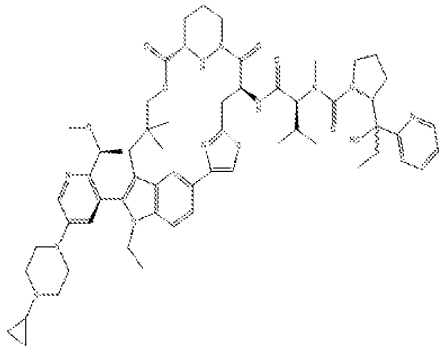
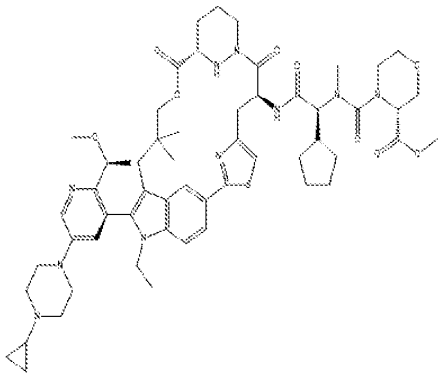
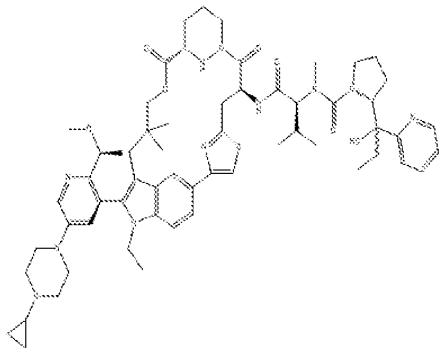
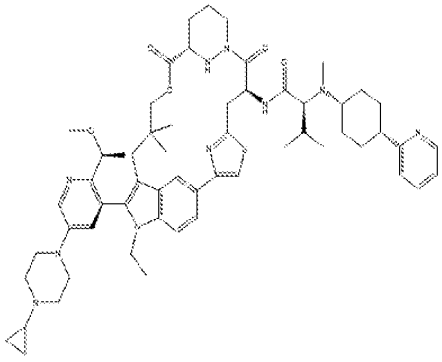
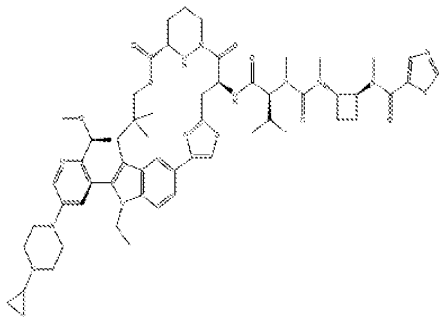
A235		A238	
A236		A239	
A237		A240	

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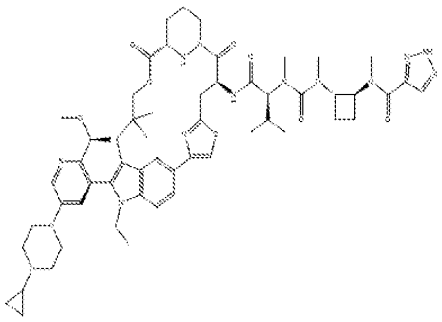
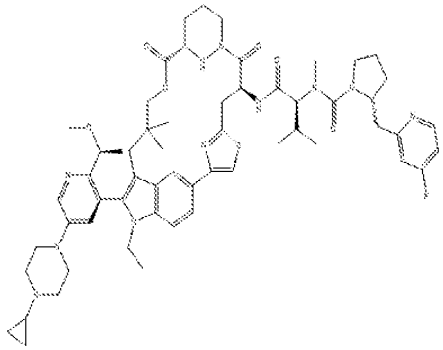
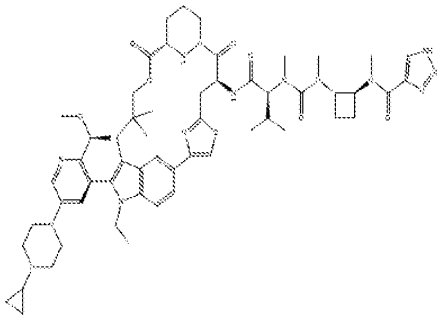
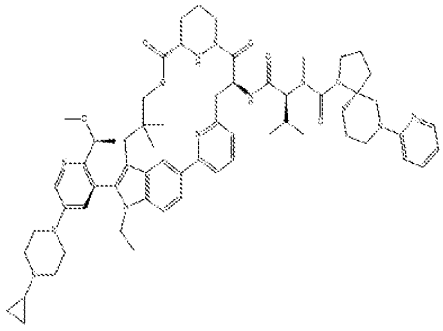
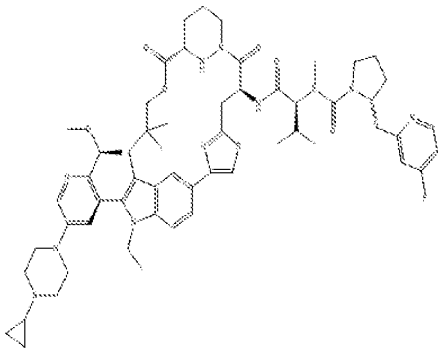
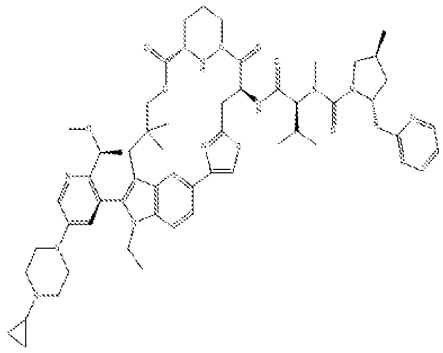
A241		A244	
A242		A245	
A243		A246	

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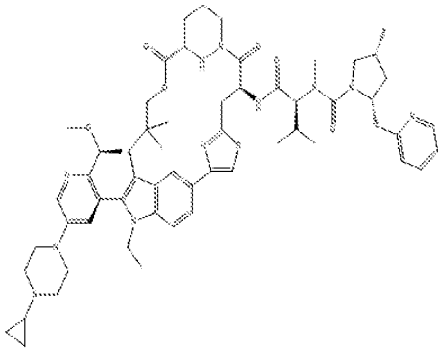
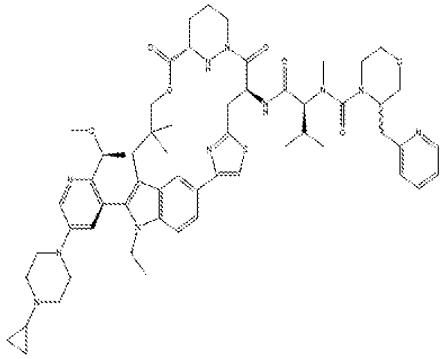
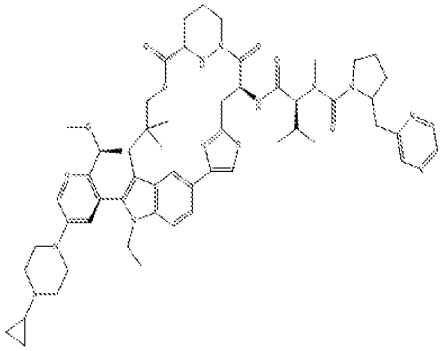
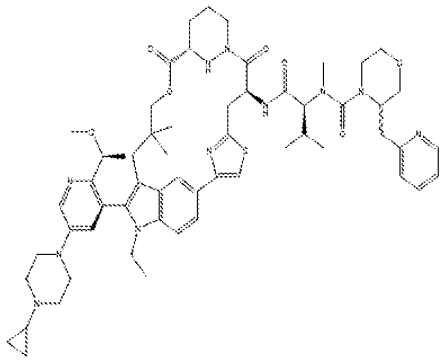
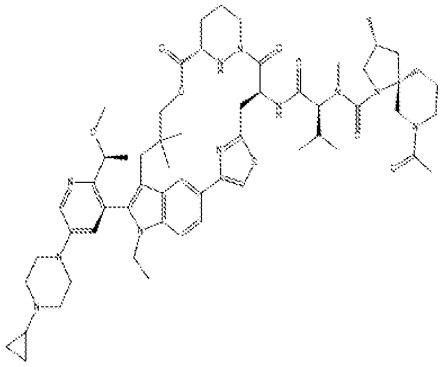
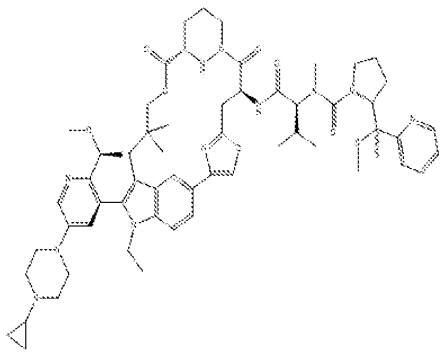
A247		A250	
A248		A251	
A249		A252	

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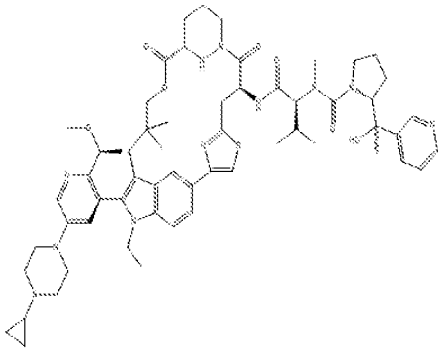
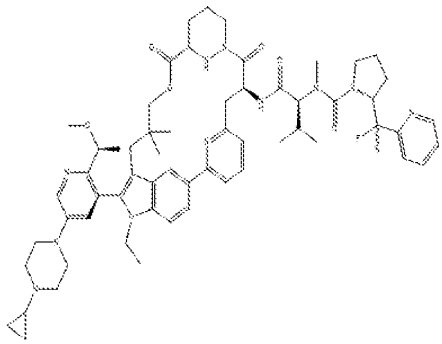
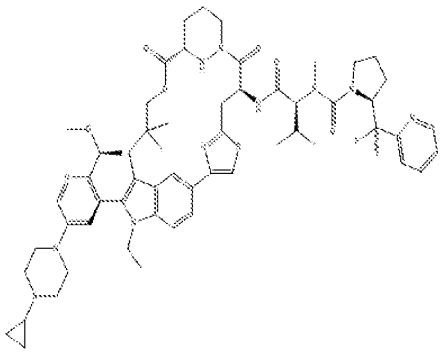
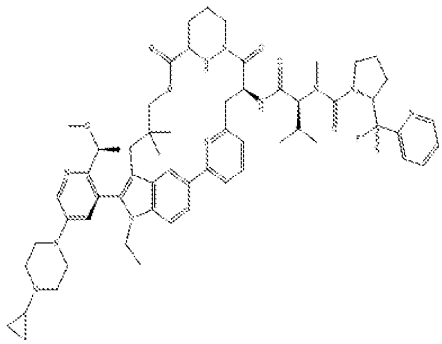
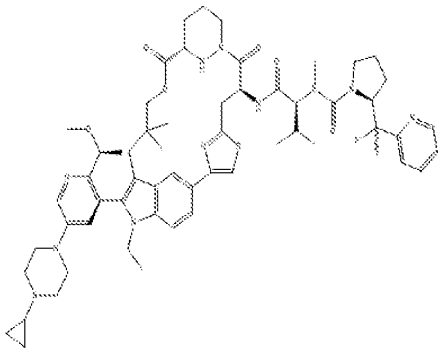
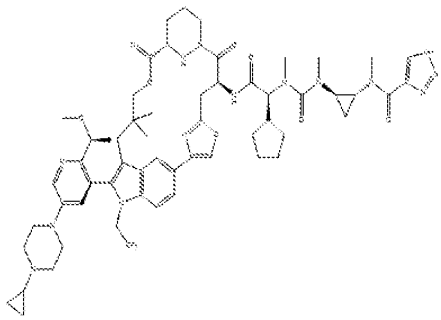
A253		A256	
A254		A257	
A255		A258	

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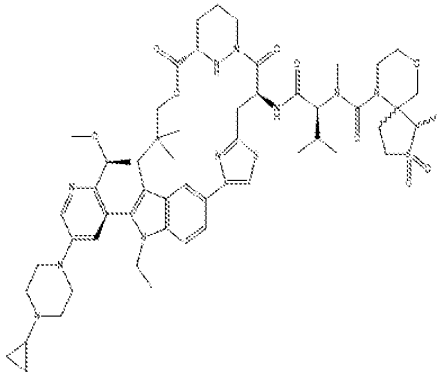
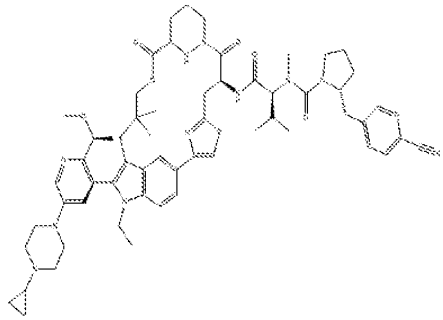
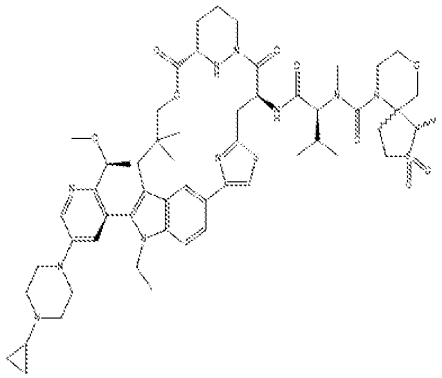
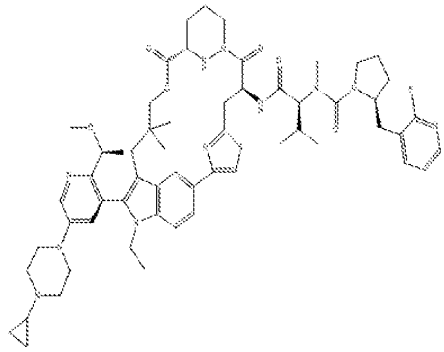
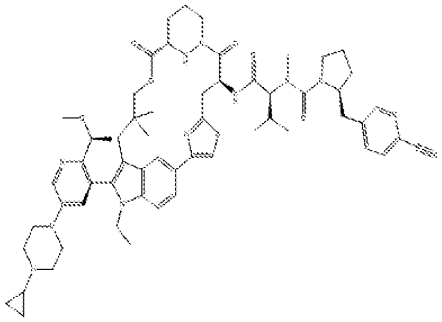
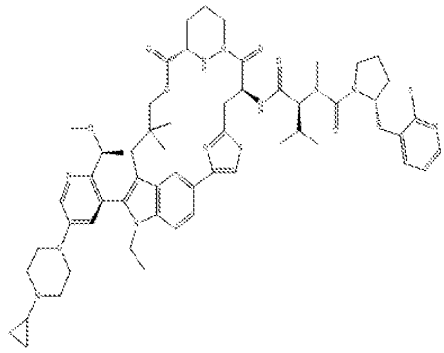
A259		A262	
A260		A263	
A261		A264	

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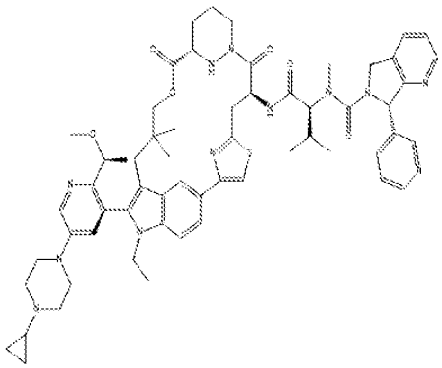
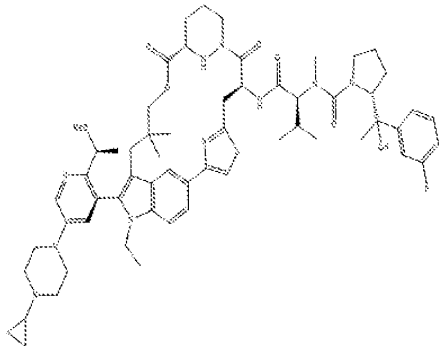
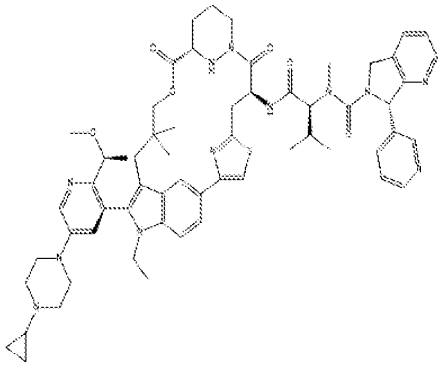
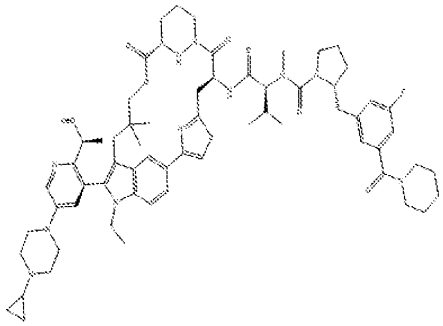
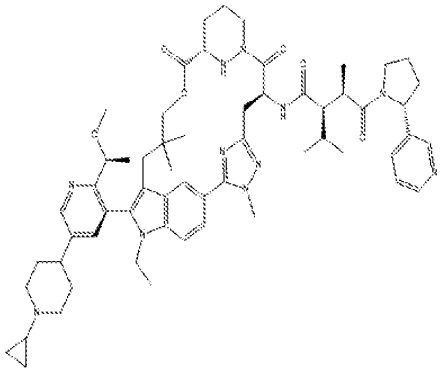
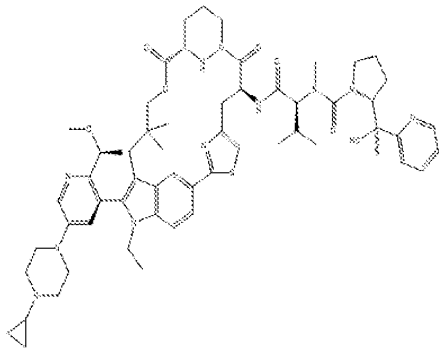
A265		A268	
A266		A269	
A267		A270	

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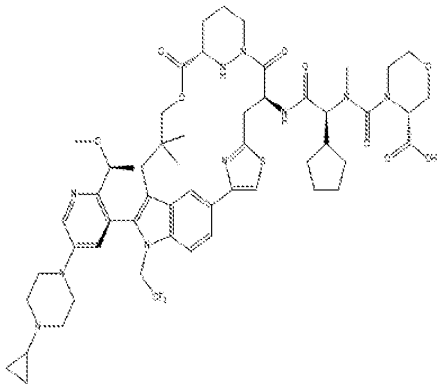
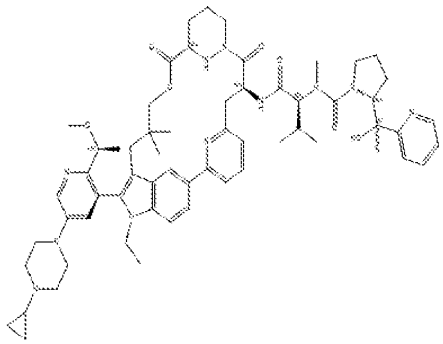
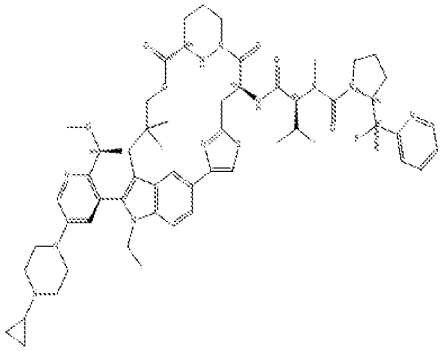
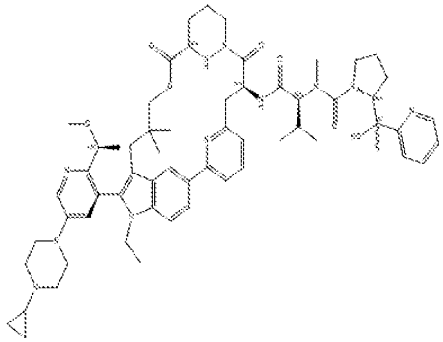
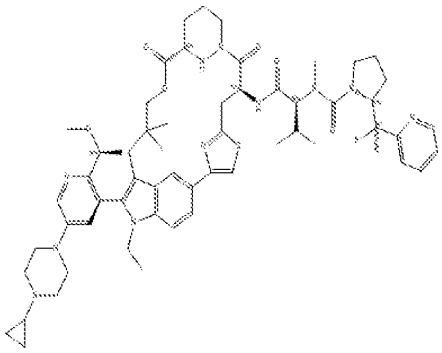
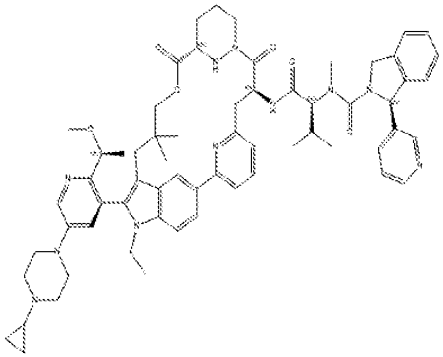
A271		A274	
A272		A275	
A273		A276	

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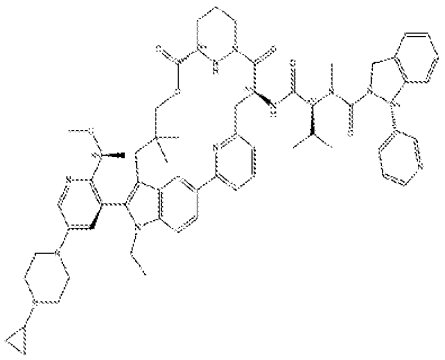
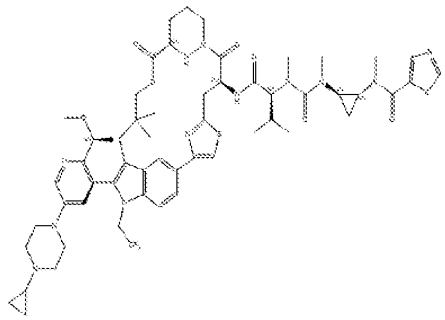
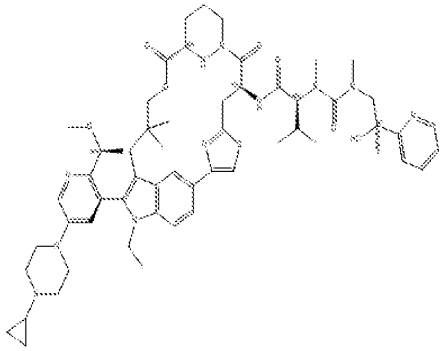
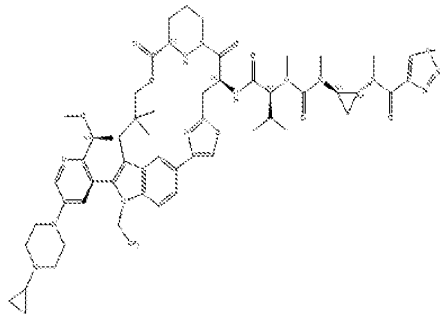
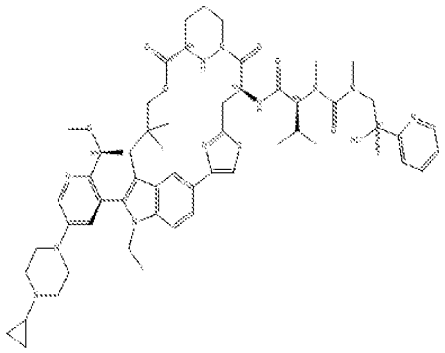
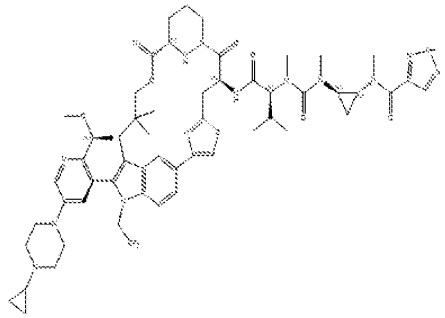
A277		A280	
A278		A281	
A279		A282	

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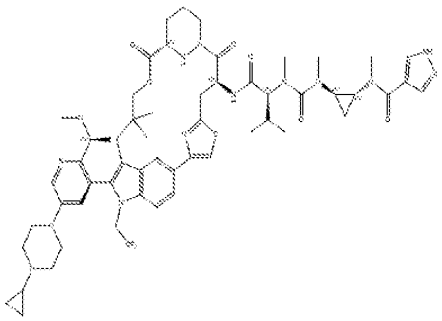
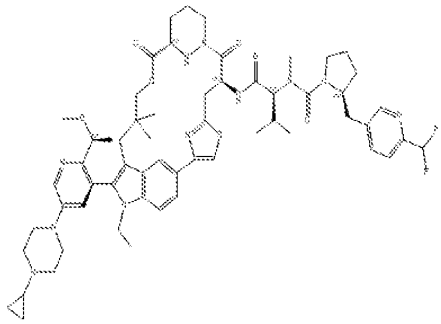
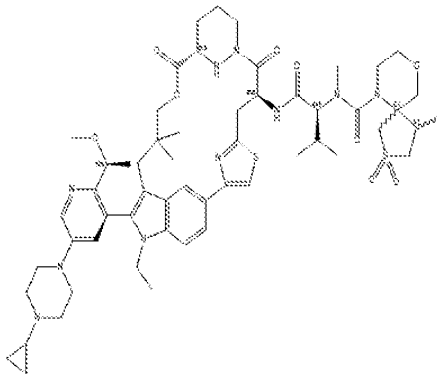
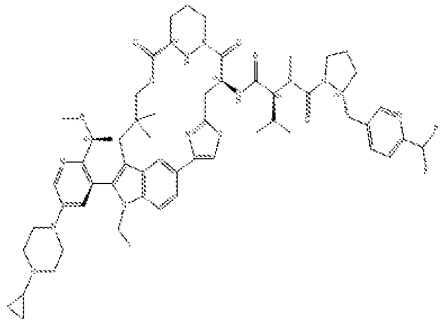
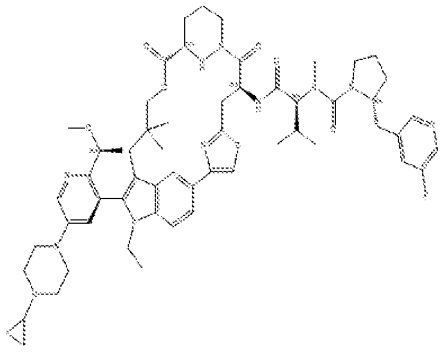
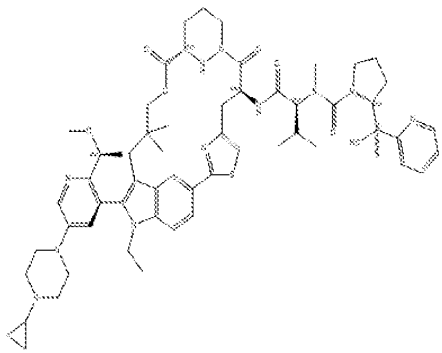
A283		A286	
A284		A287	
A285		A288	

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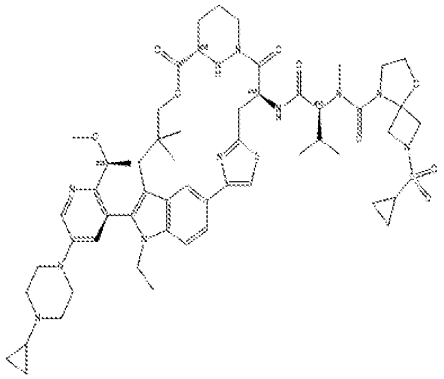
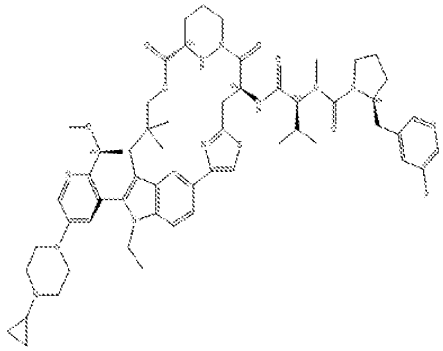
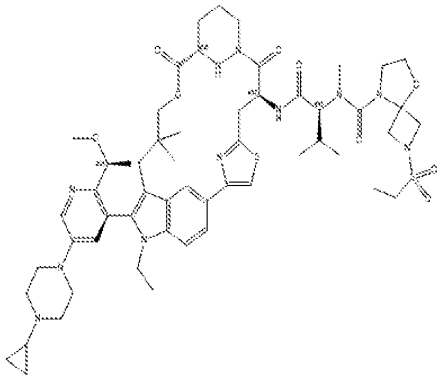
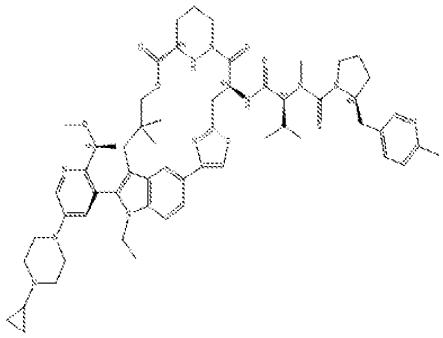
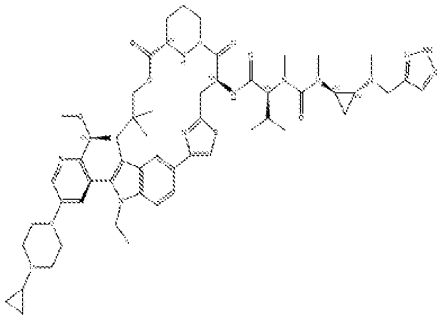
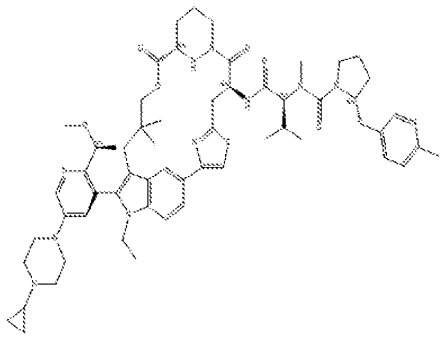
A289		A292	
A290		A293	
A291		A294	

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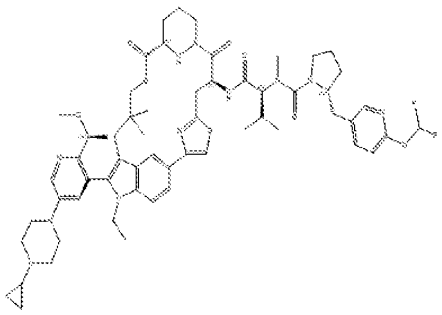
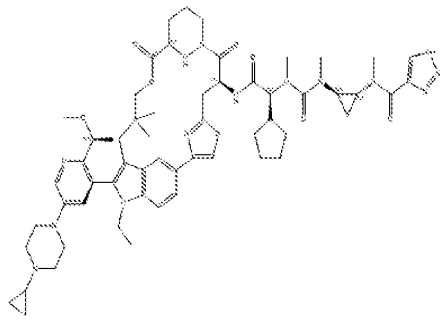
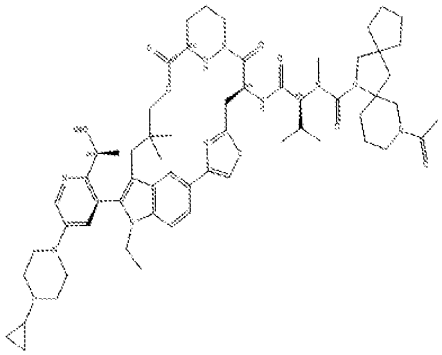
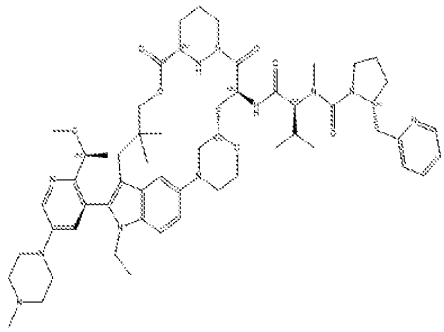
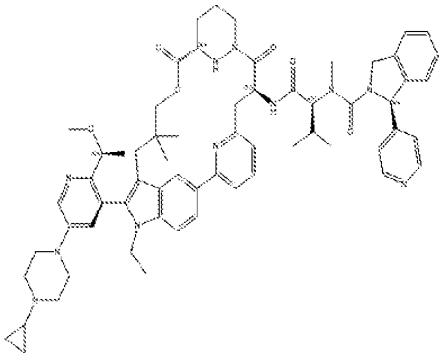
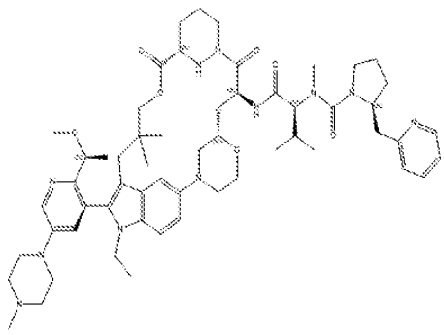
A295		A298	
A296		A299	
A297		A300	

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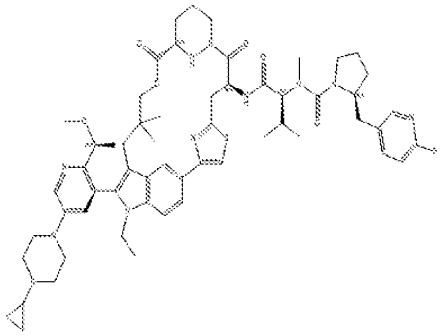
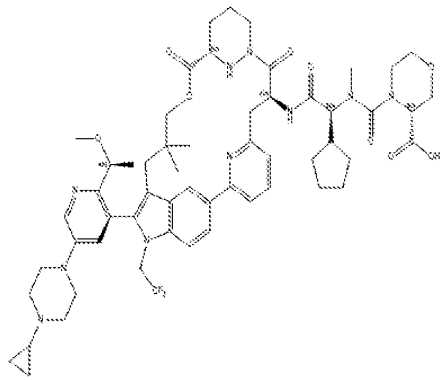
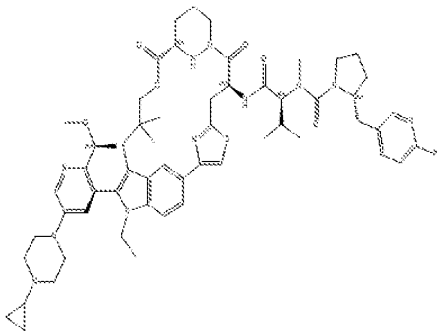
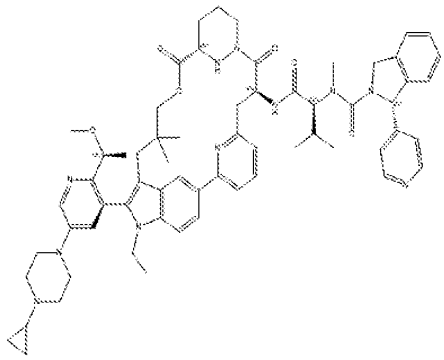
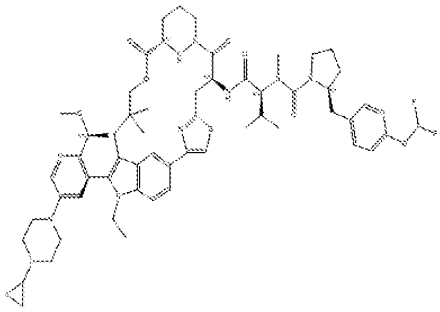
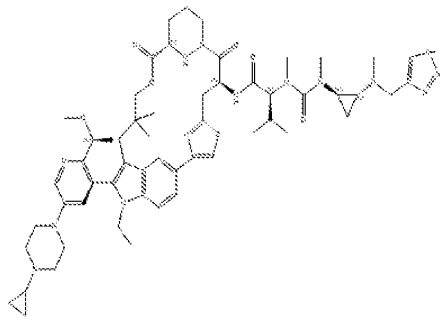
A301		A304	
A302		A305	
A303		A306	

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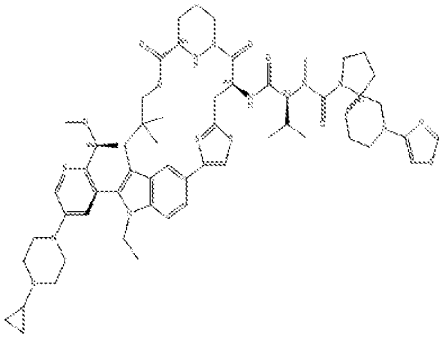
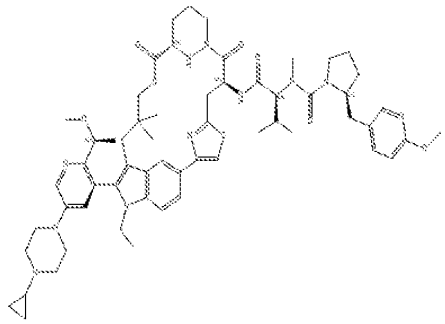
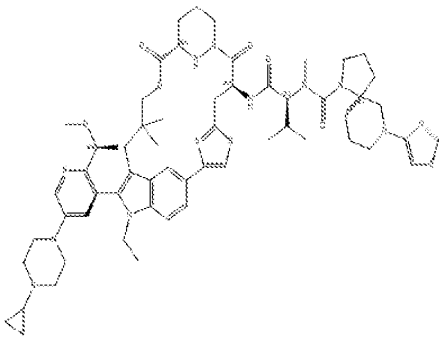
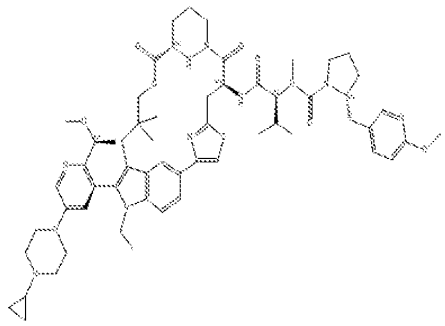
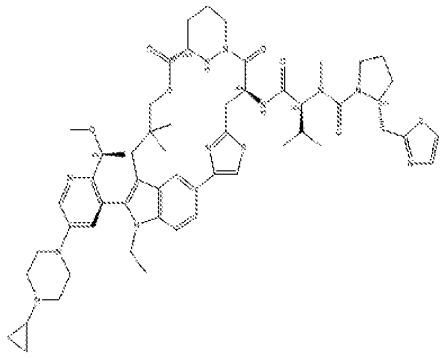
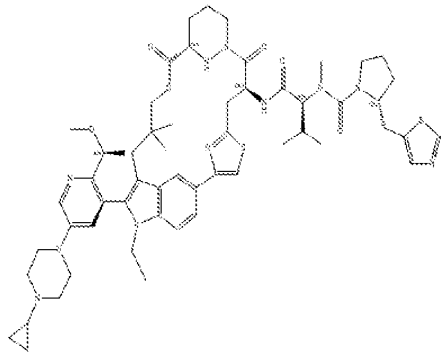
A307		A310	
A308		A311	
A309		A312	

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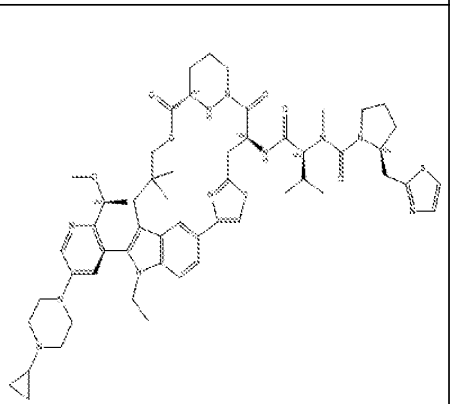
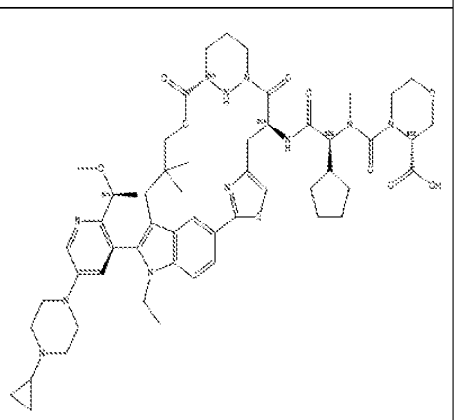
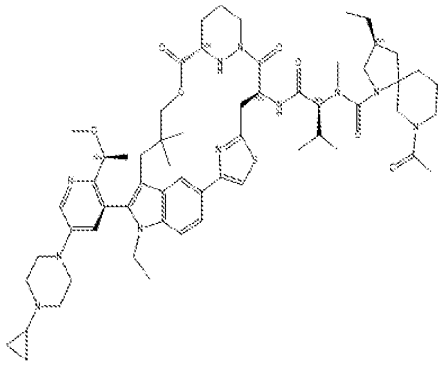
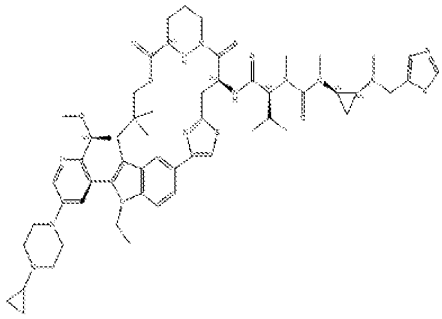
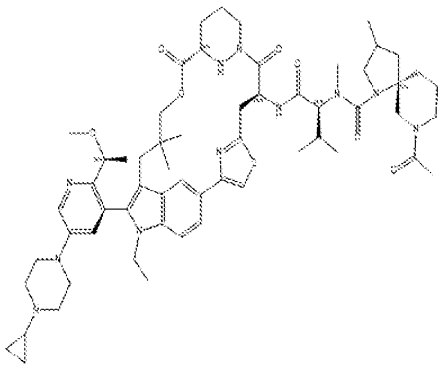
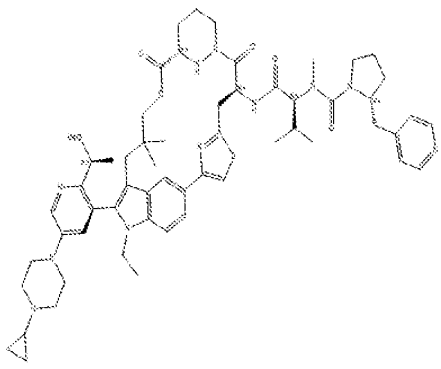
A313		A316	
A314		A317	
A315		A318	

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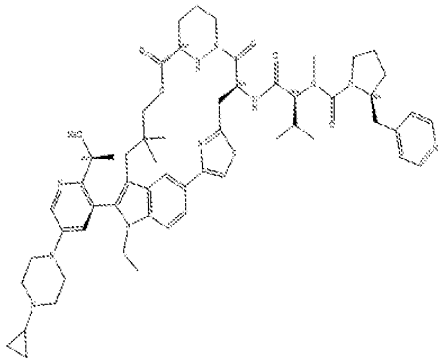
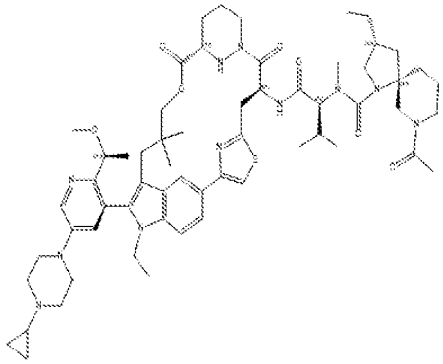
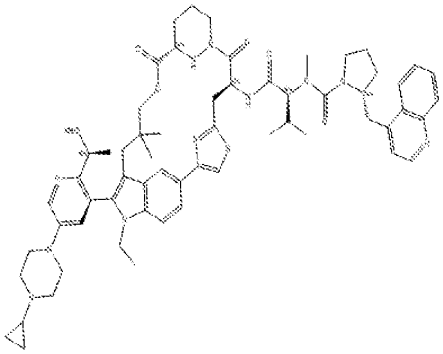
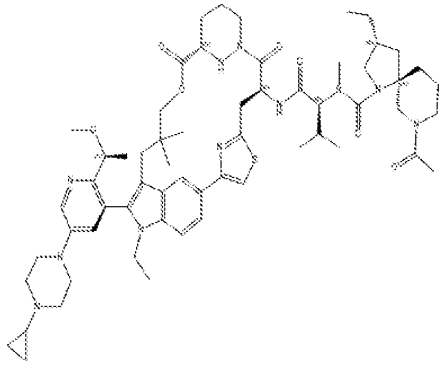
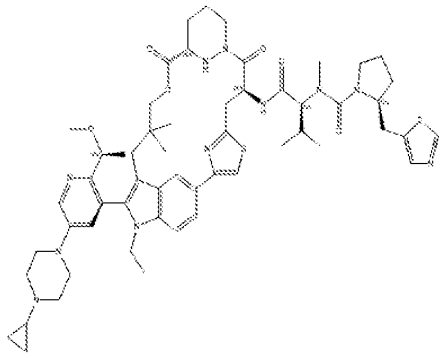
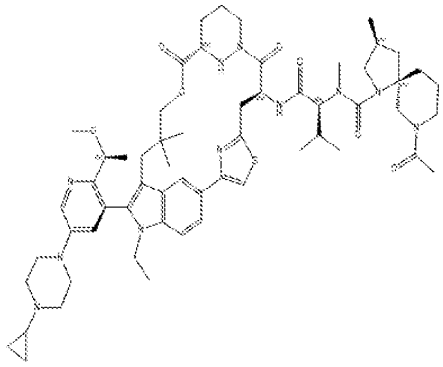
A319		A322	
A320		A323	
A321		A324	

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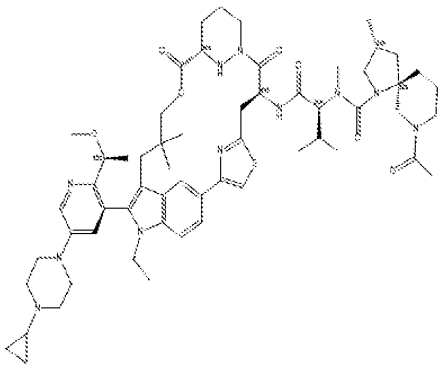
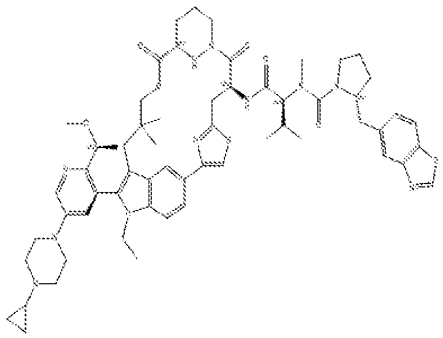
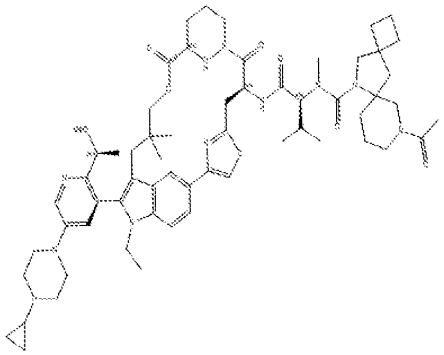
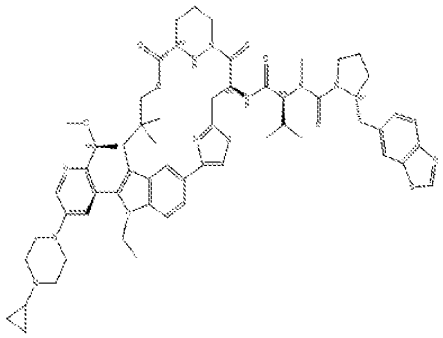
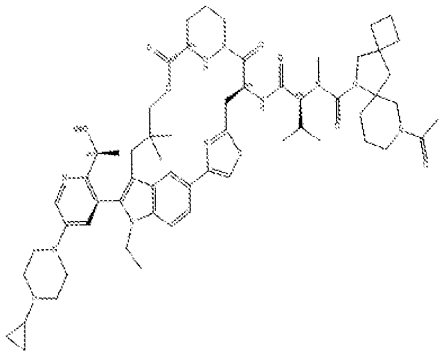
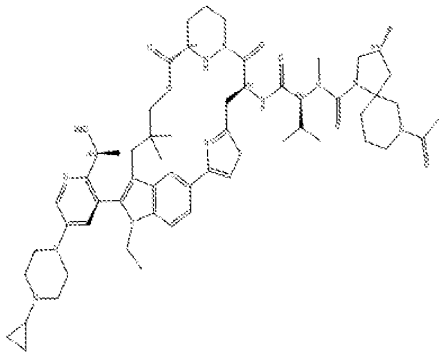
A325		A328	
A326		A329	
A327		A330	

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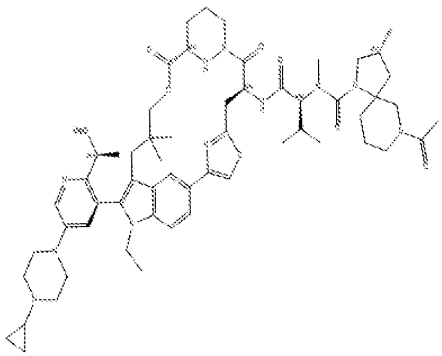
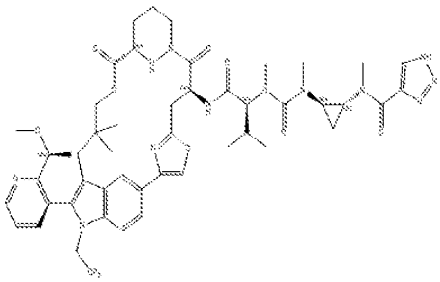
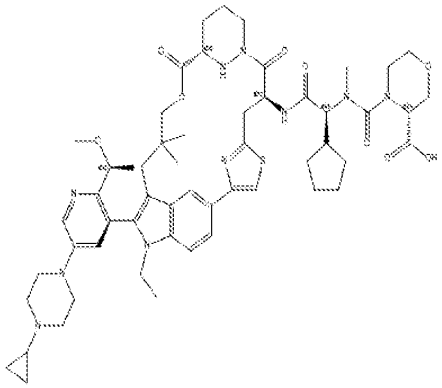
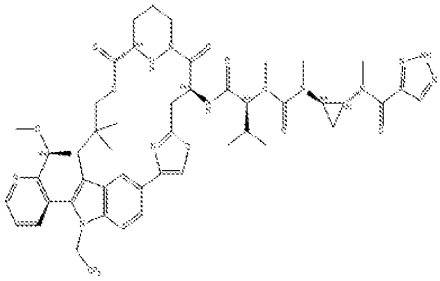
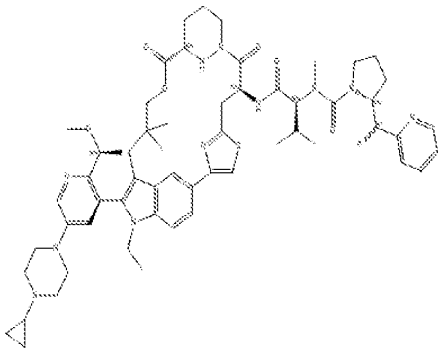
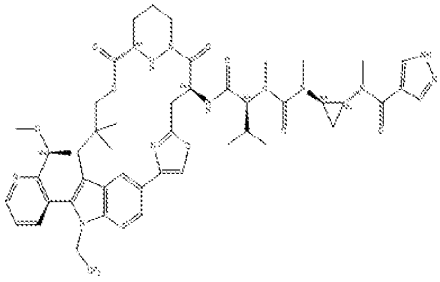
A331		A334	
A332		A335	
A333		A336	

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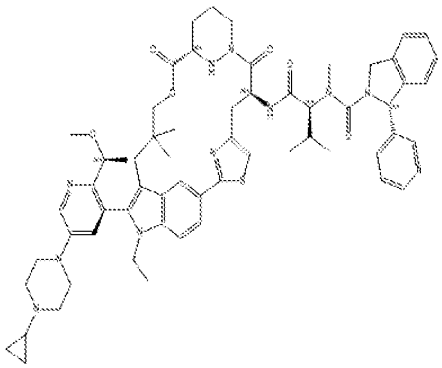
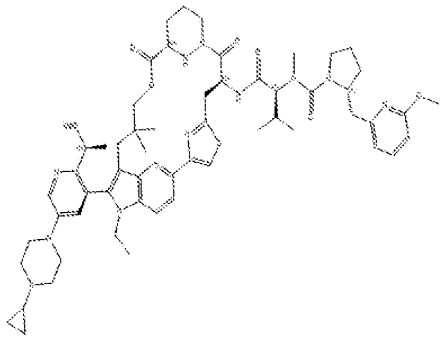
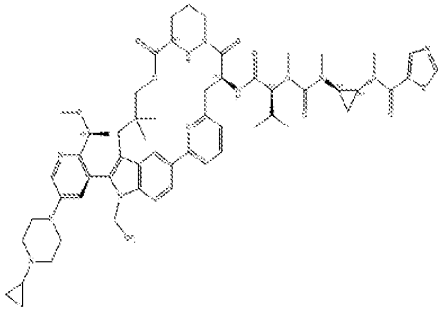
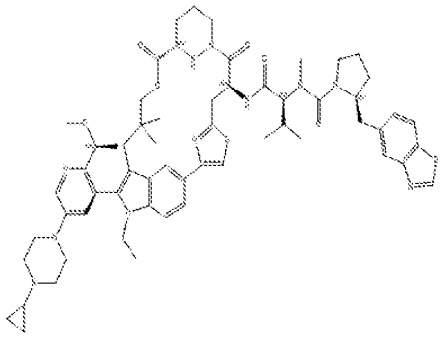
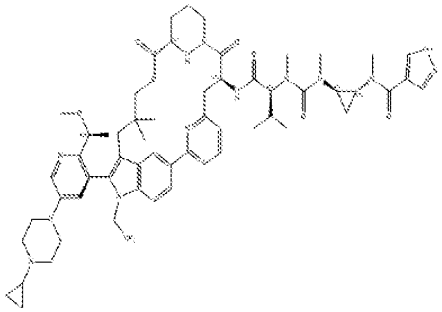
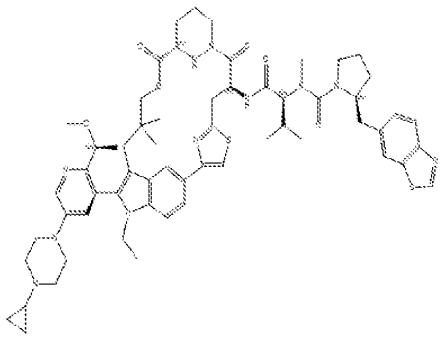
A337		A340	
A338		A341	
A339		A342	

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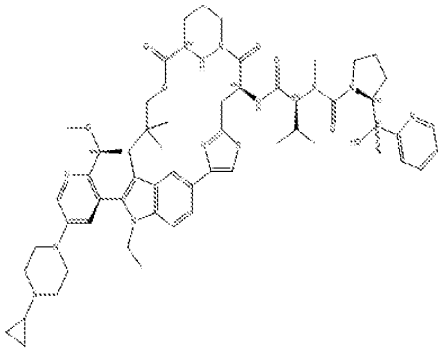
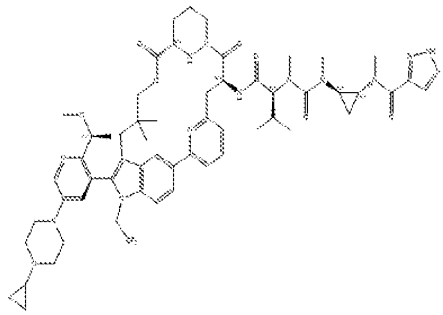
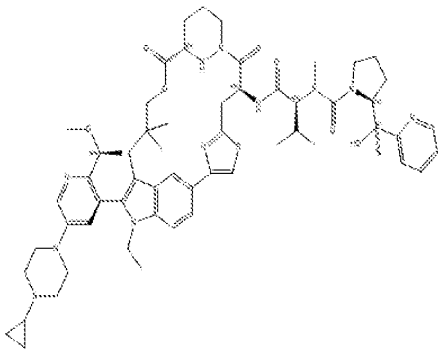
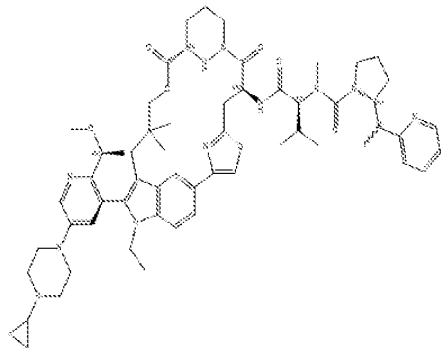
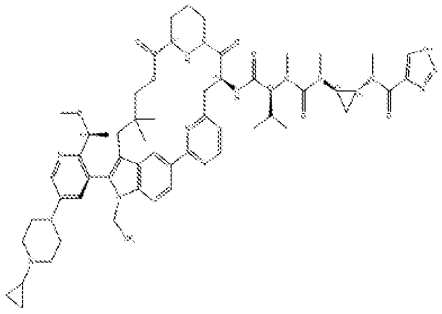
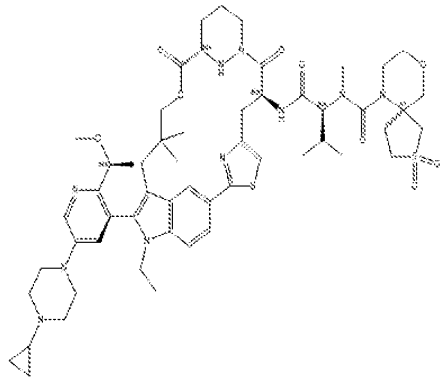
A343		A346	
A344		A347	
A345		A348	

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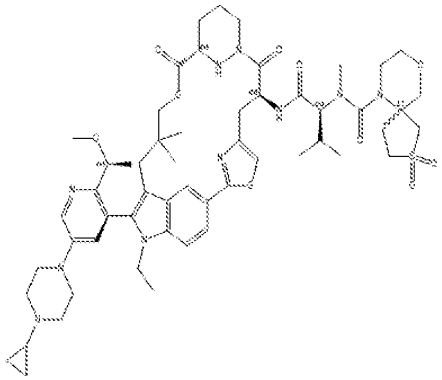
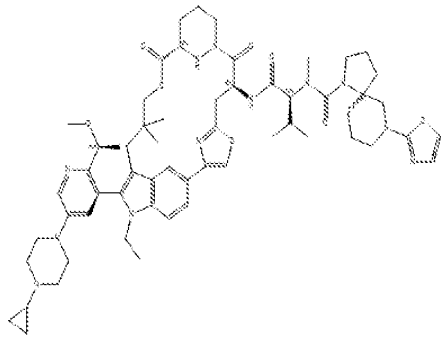
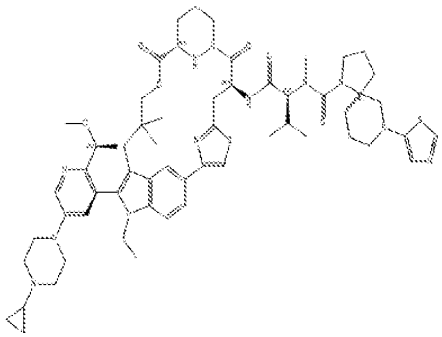
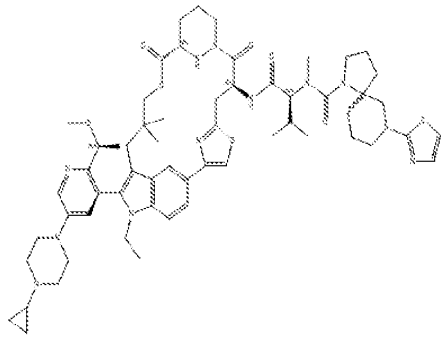
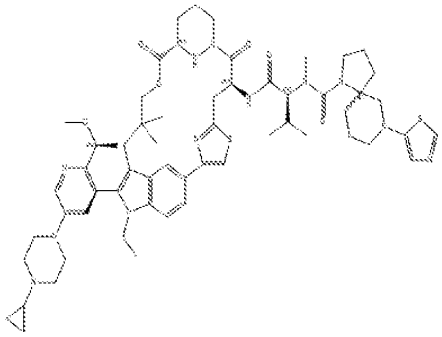
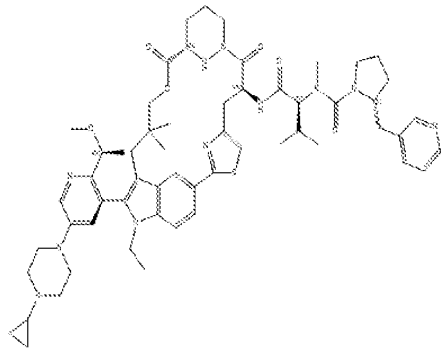
A349		A352	
A350		A353	
A351		A354	

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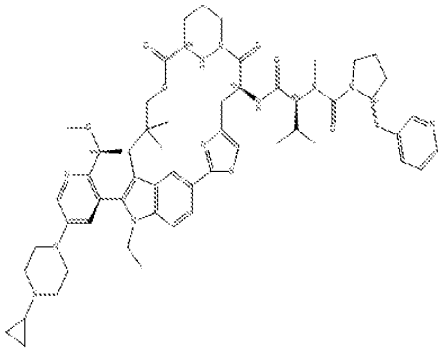
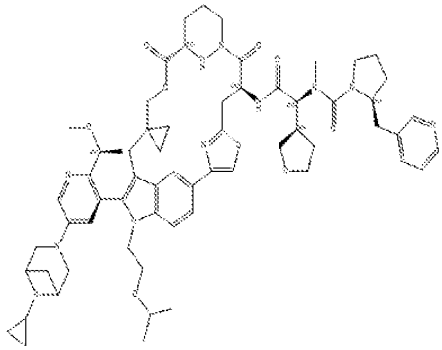
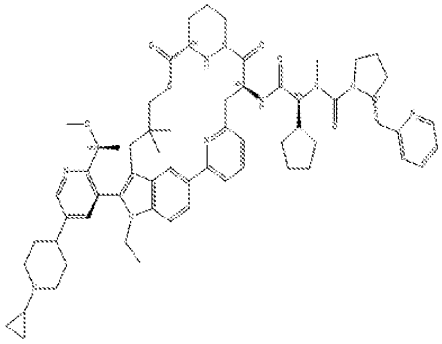
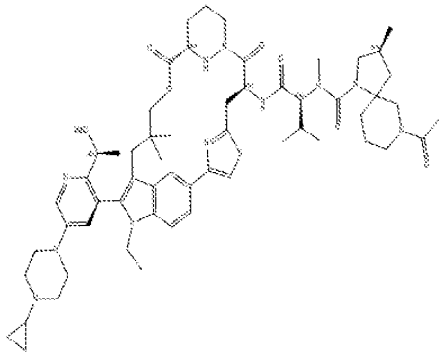
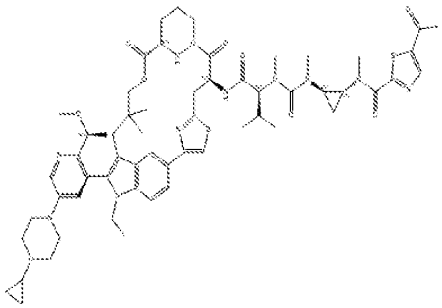
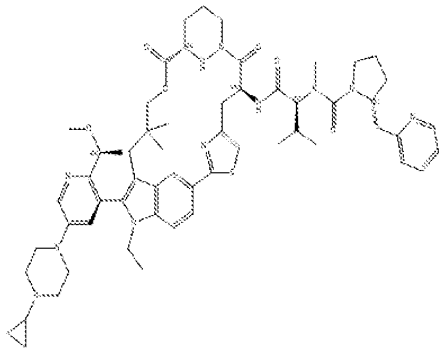
A355		A358	
A356		A359	
A357		A360	

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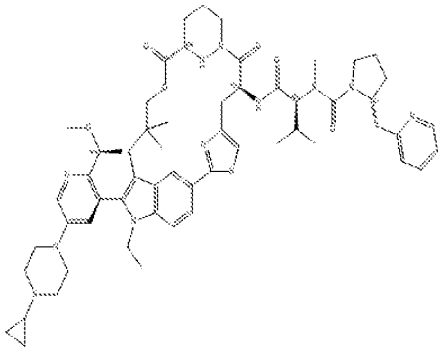
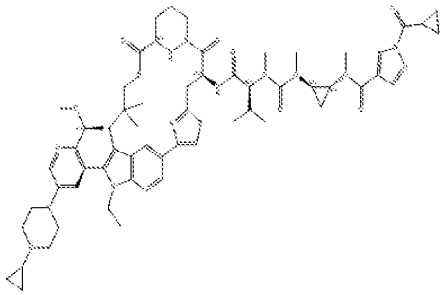
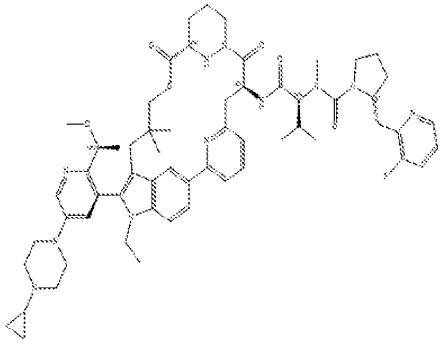
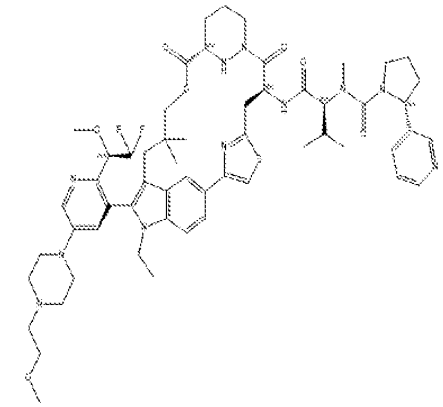
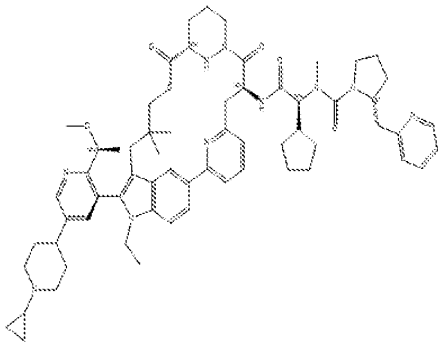
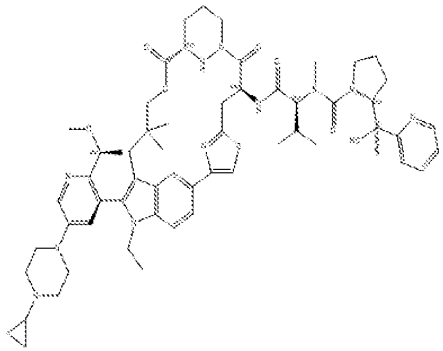
A361		A364	
A362		A365	
A363		A366	

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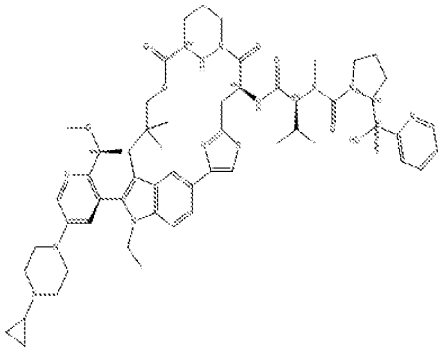
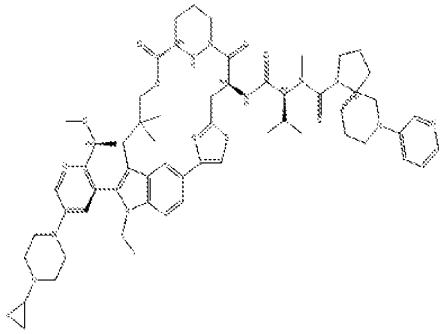
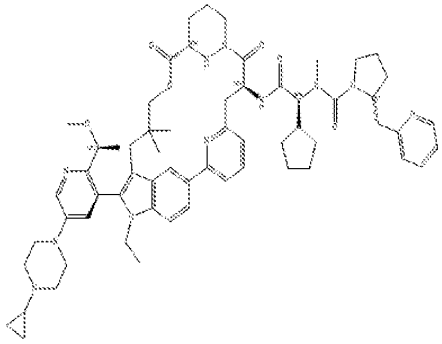
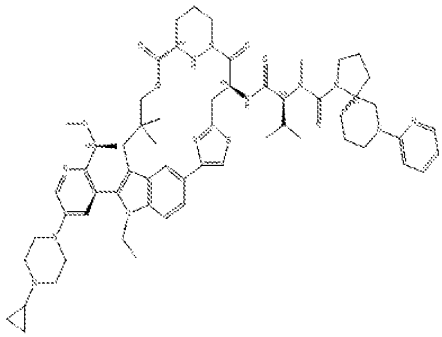
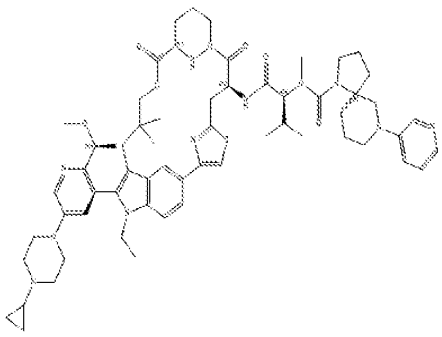
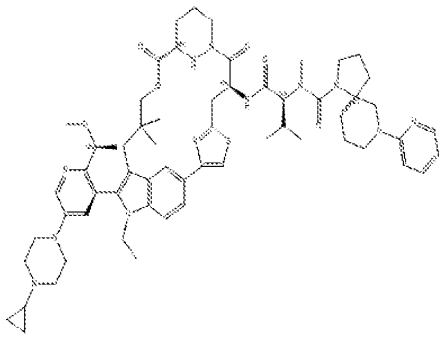
A367		A370	
A368		A371	
A369		A372	

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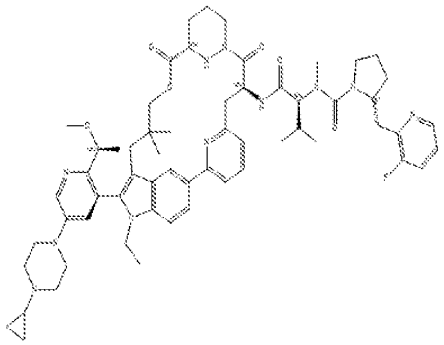
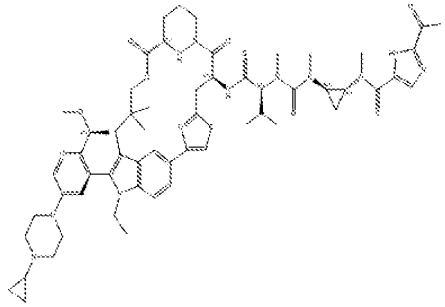
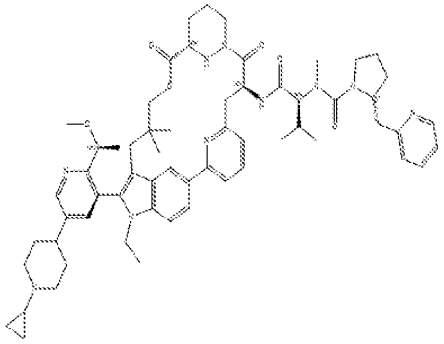
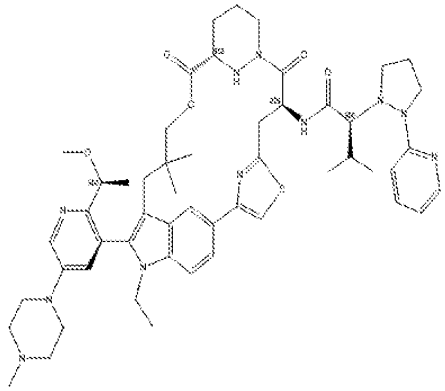
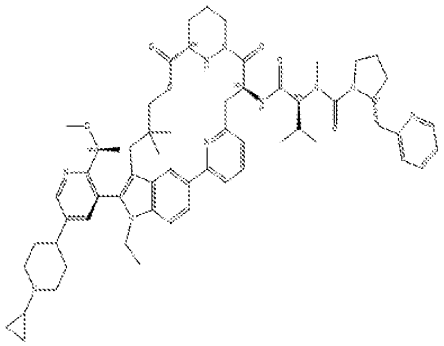
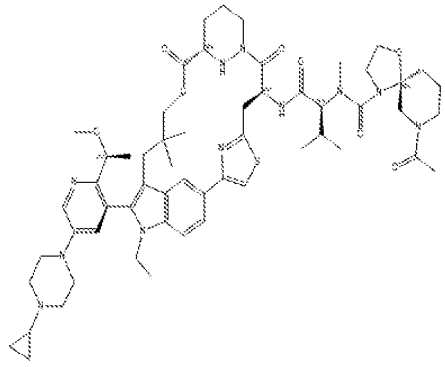
A373		A376	
A374		A377	
A375		A378	

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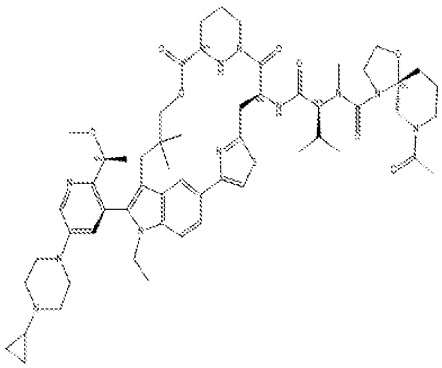
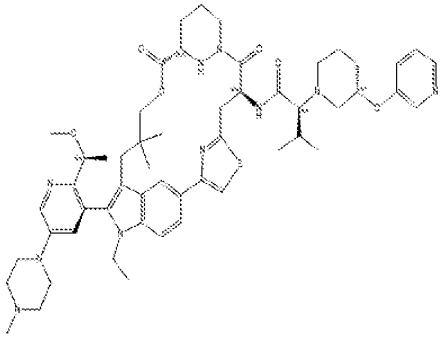
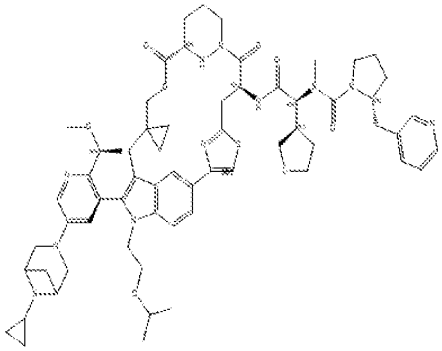
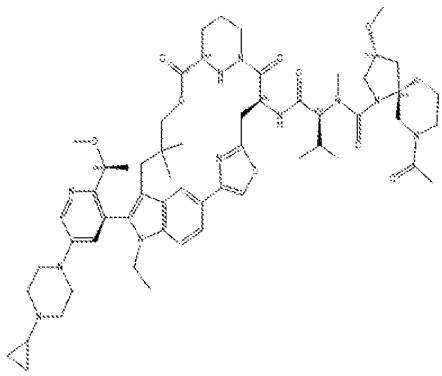
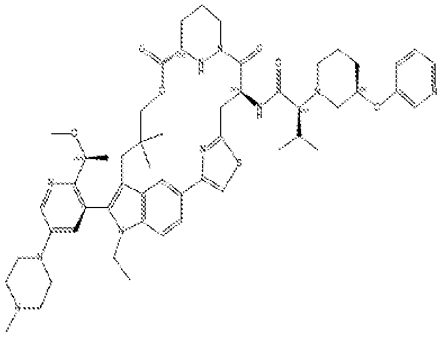
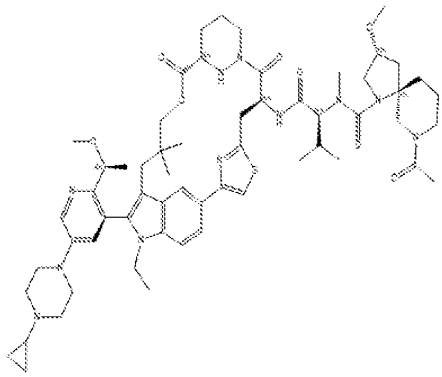
A379		A382	
A380		A383	
A381		A384	

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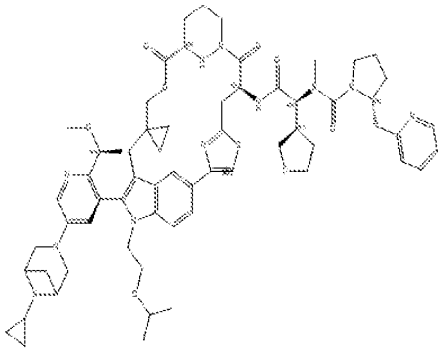
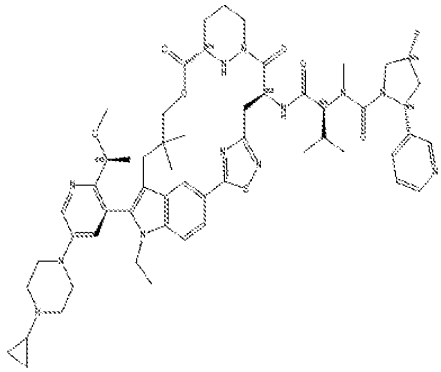
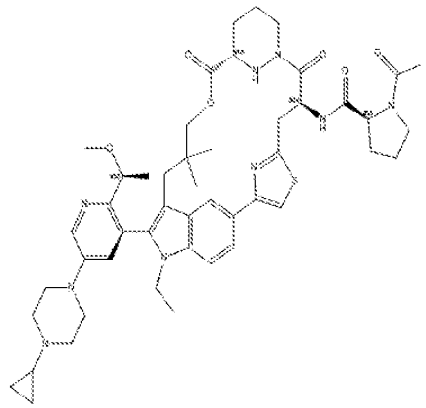
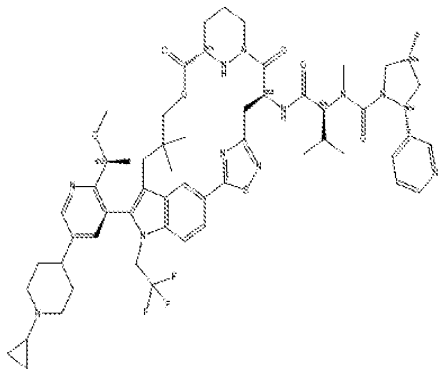
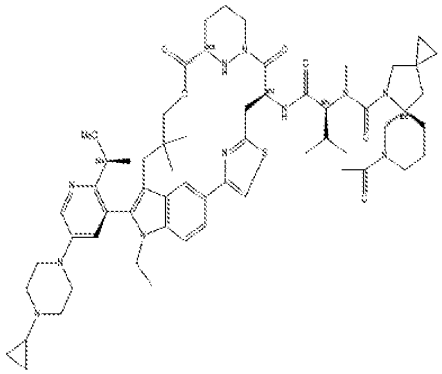
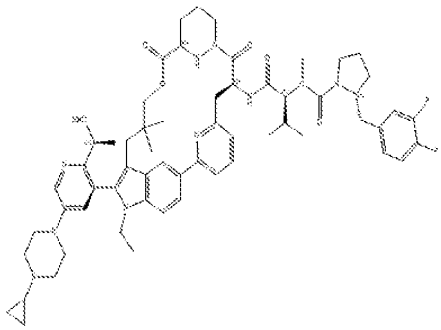
A385		A388	
A386		A389	
A387		A390	

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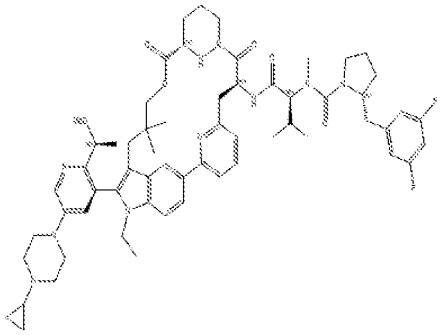
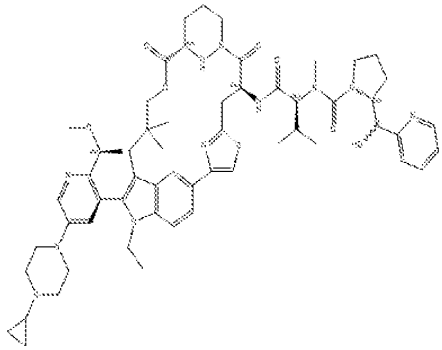
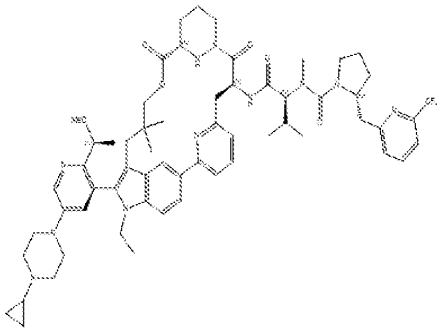
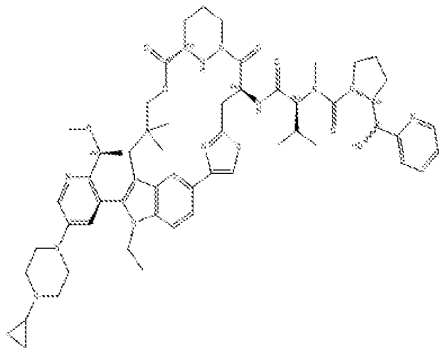
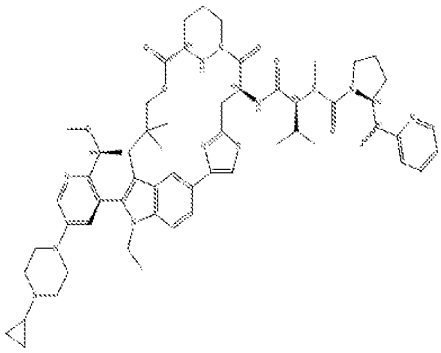
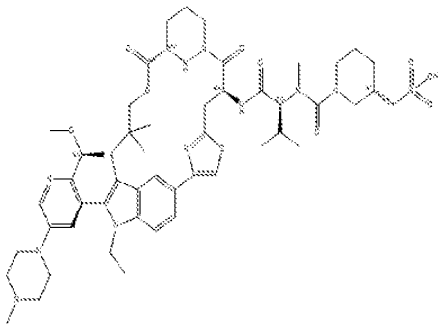
A391		A394	
A392		A395	
A393		A396	

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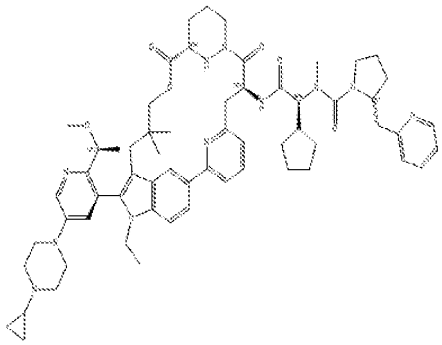
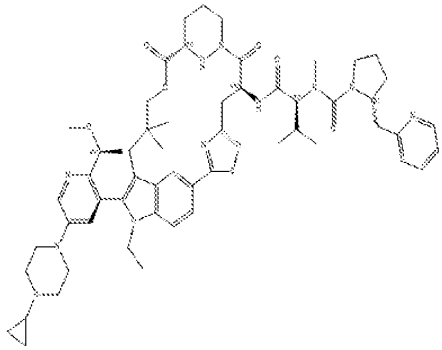
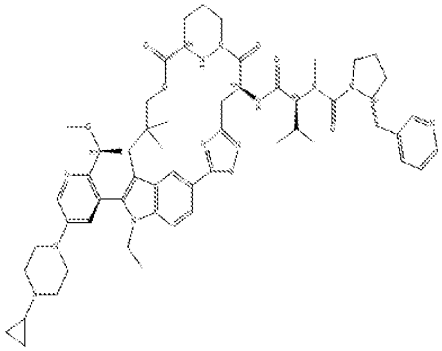
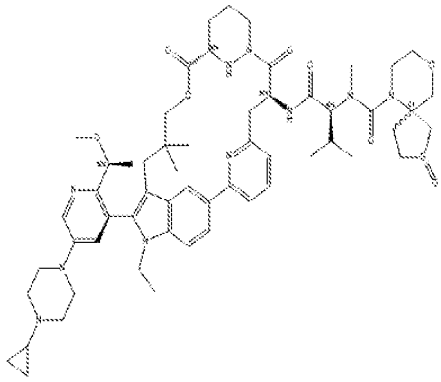
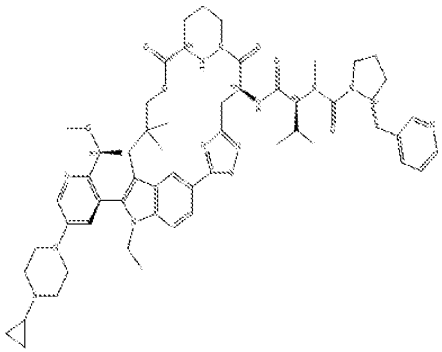
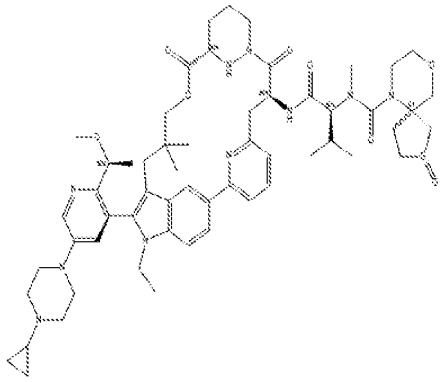
A397		A400	
A398		A401	
A399		A402	

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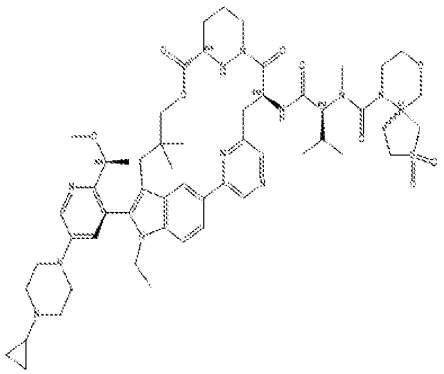
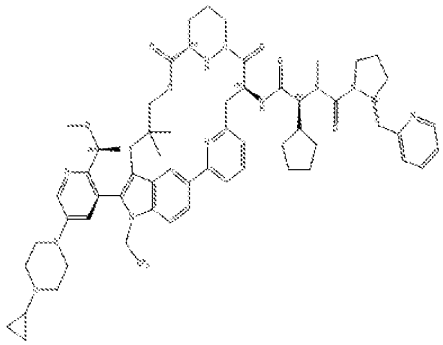
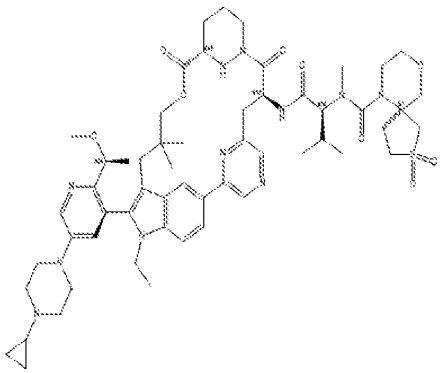
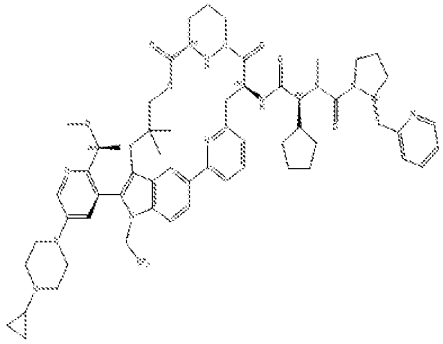
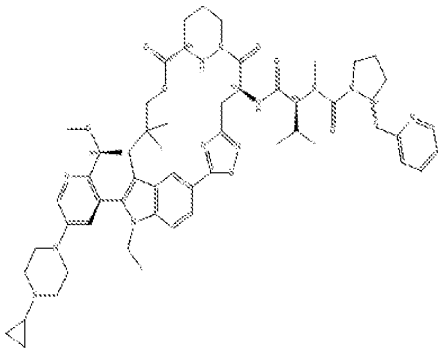
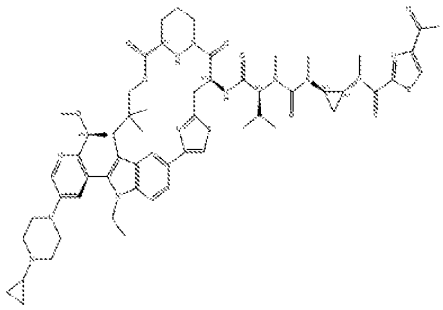
A403		A406	
A404		A407	
A405		A408	

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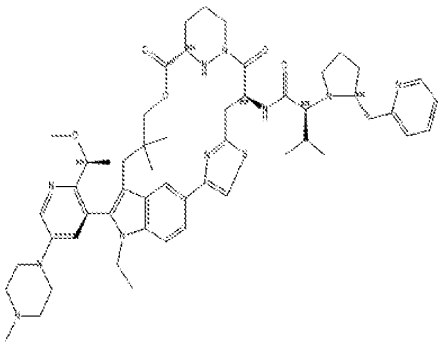
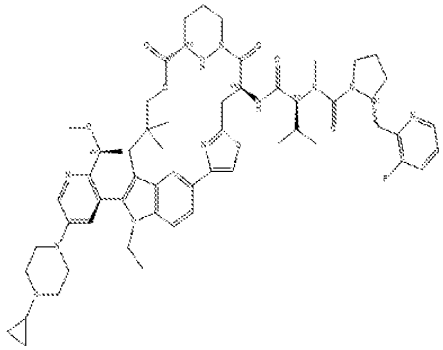
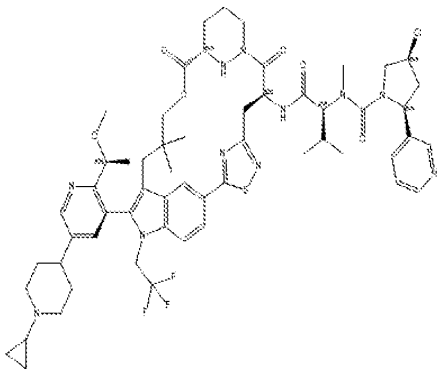
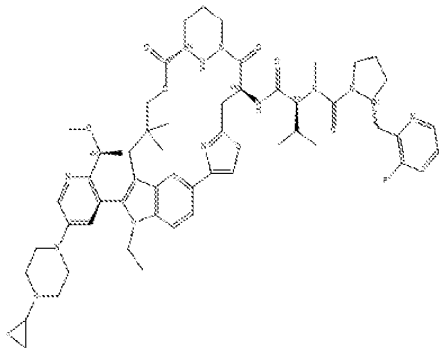
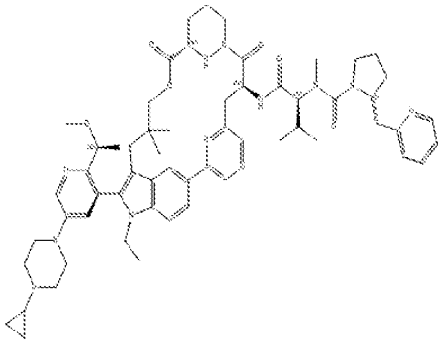
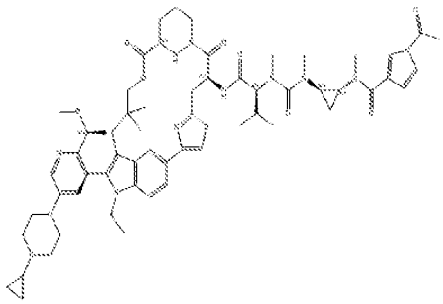
A409		A412	
A410		A413	
A411		A414	

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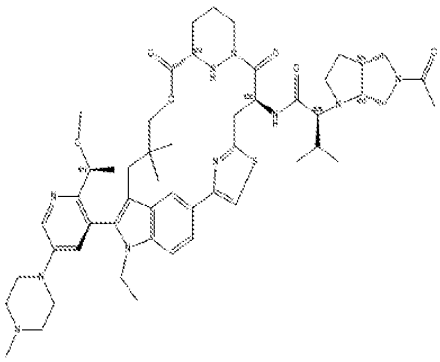
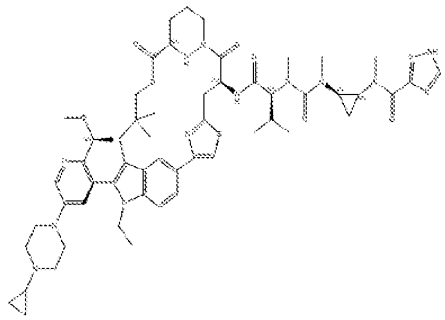
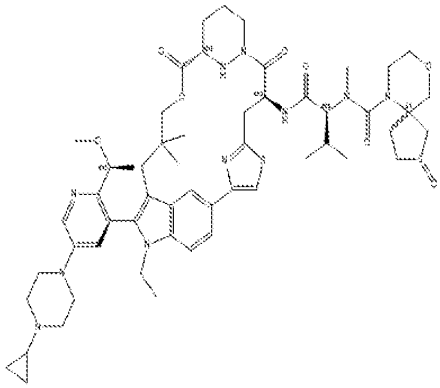
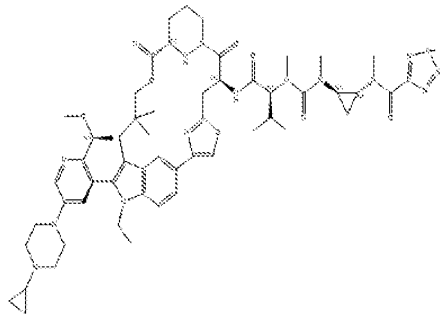
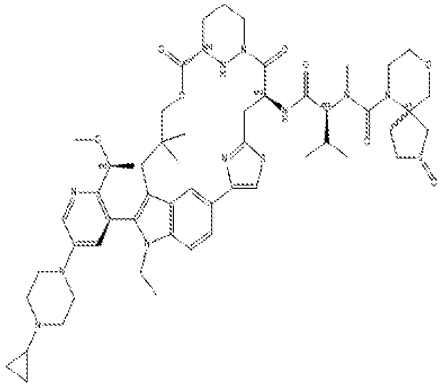
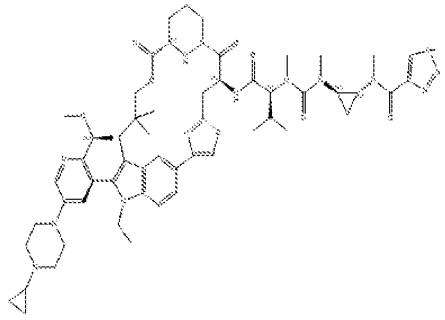
A415		A418	
A416		A419	
A417		A420	

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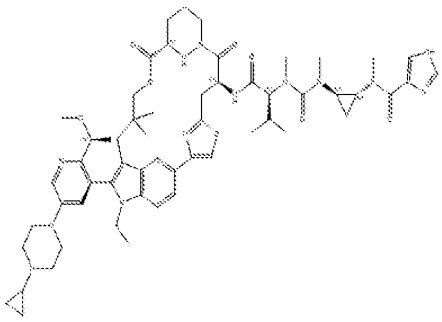
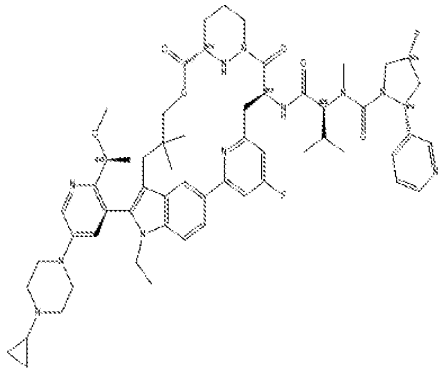
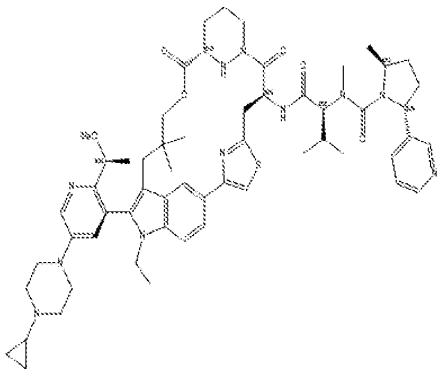
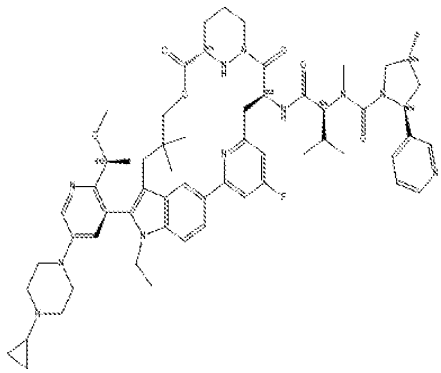
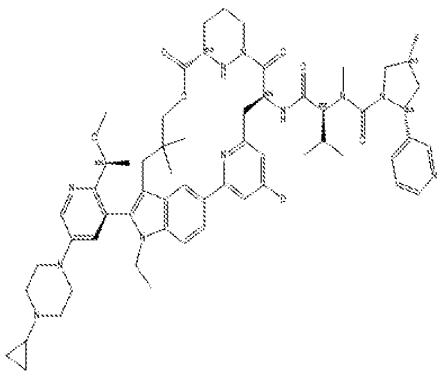
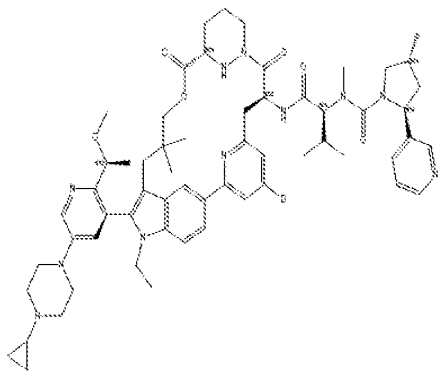
A421		A424	
A422		A425	
A423		A426	

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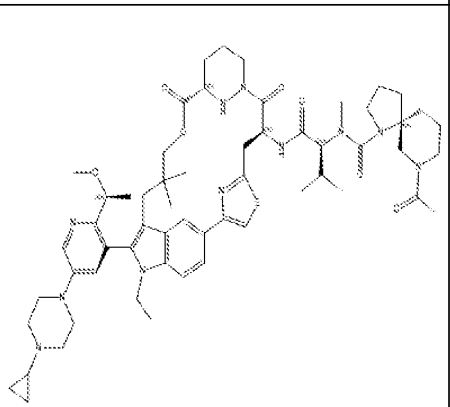
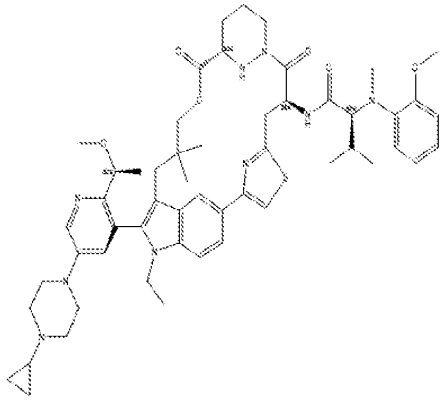
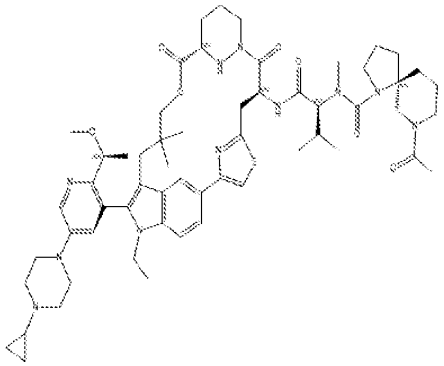
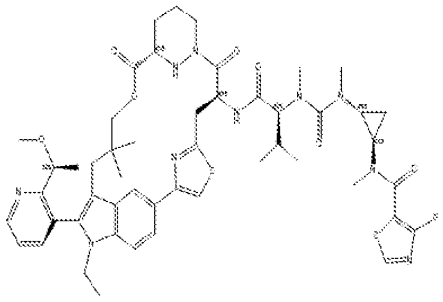
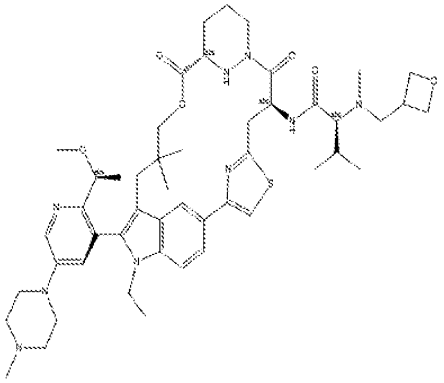
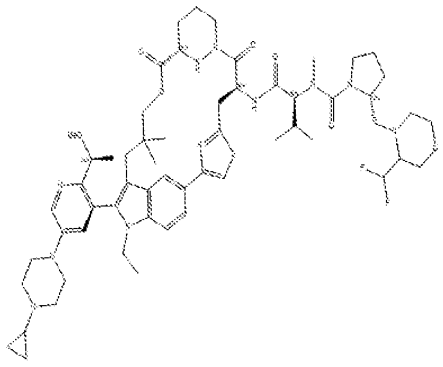
A427		A430	
A428		A431	
A429		A432	

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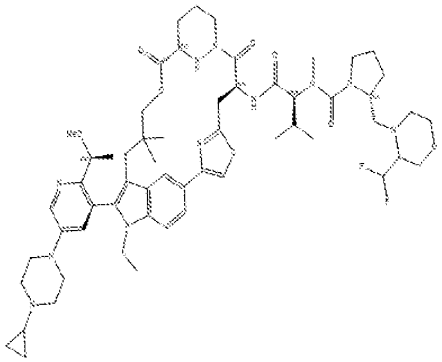
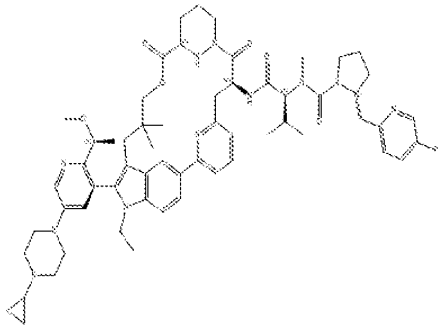
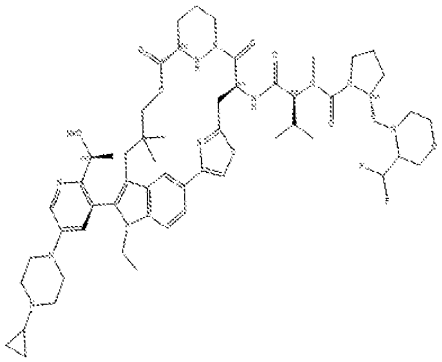
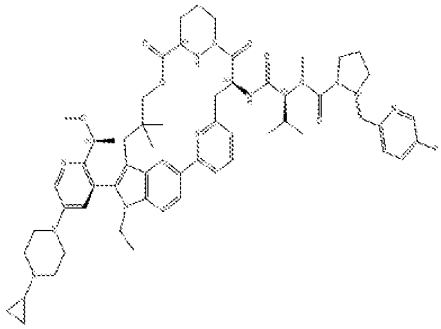
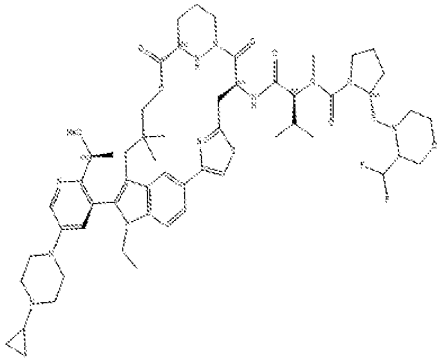
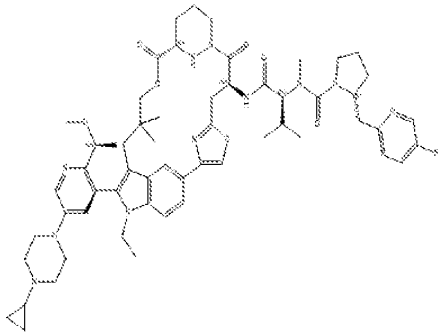
A433		A436	
A434		A437	
A435		A438	

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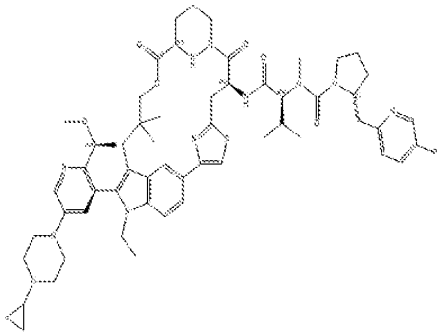
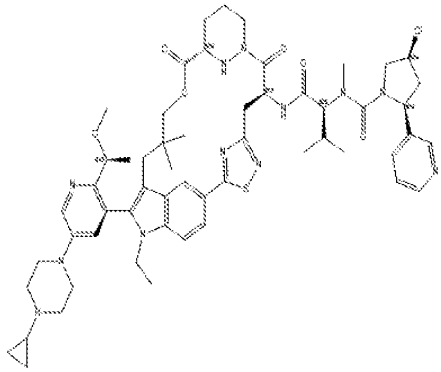
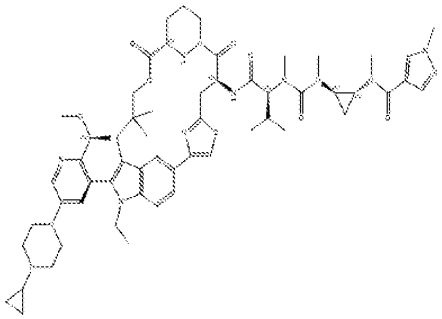
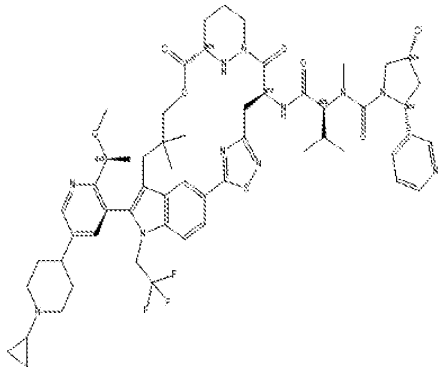
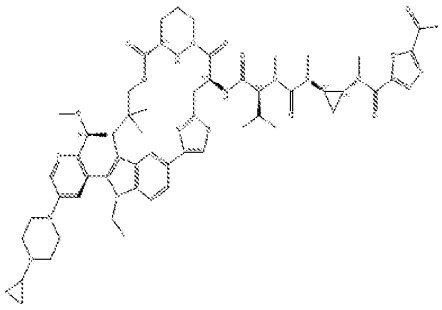
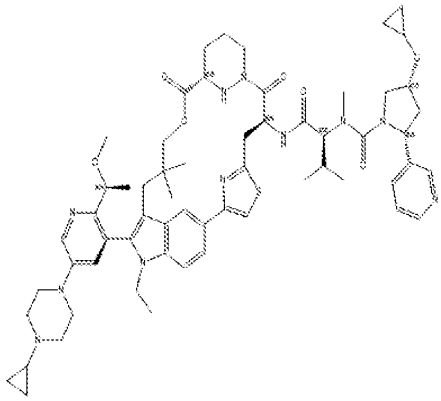
A439		A442	
A440		A443	
A441		A444	

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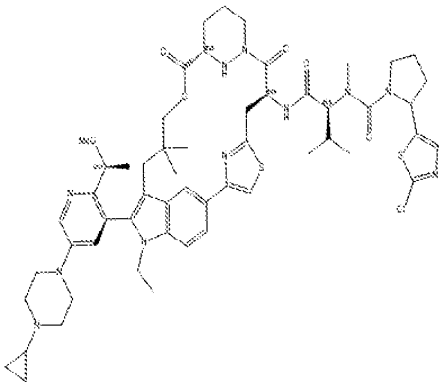
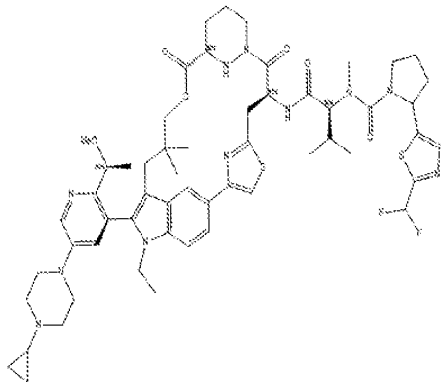
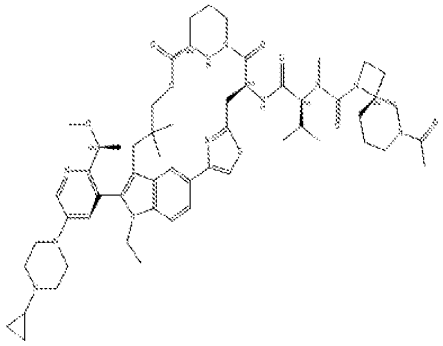
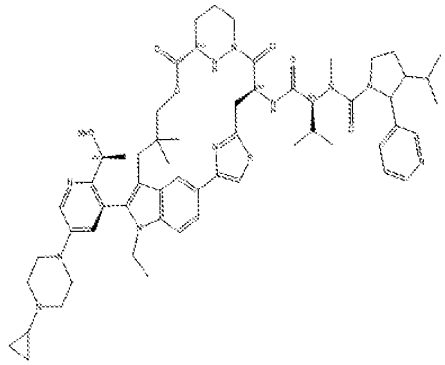
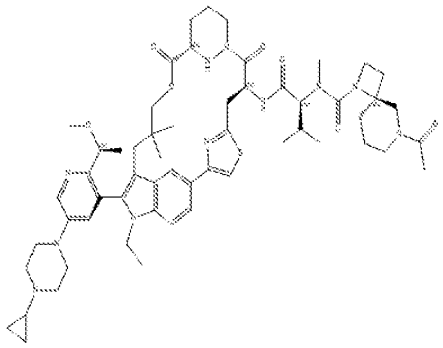
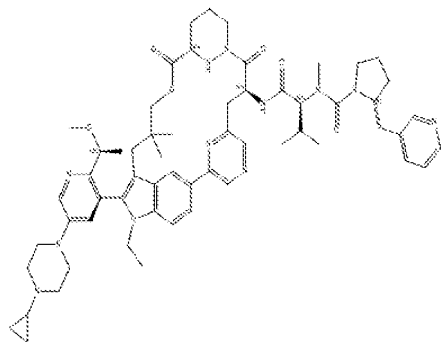
A445		A448	
A446		A449	
A447		A450	

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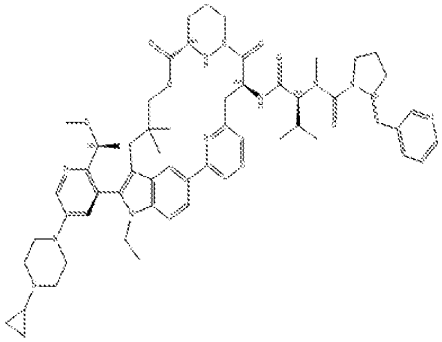
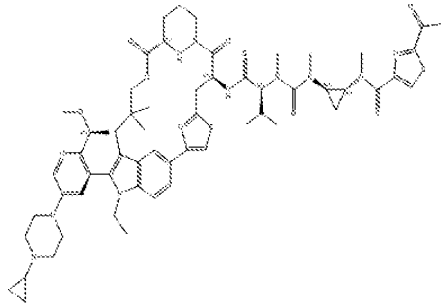
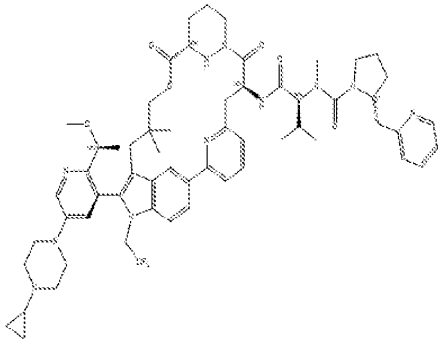
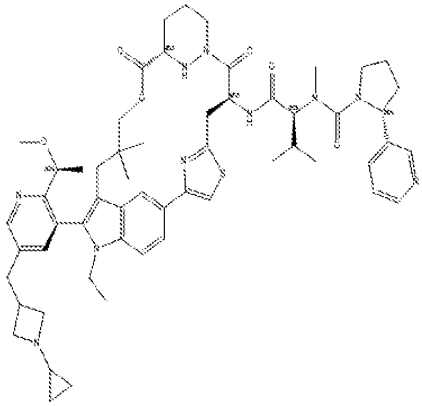
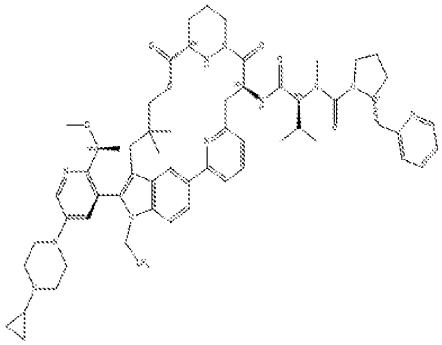
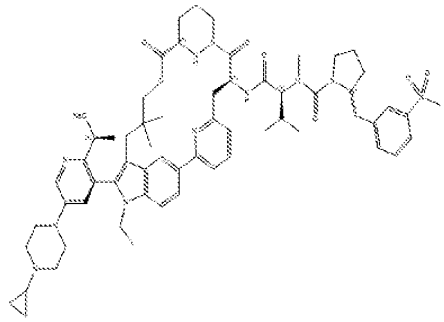
A451		A454	
A452		A455	
A453		A456	

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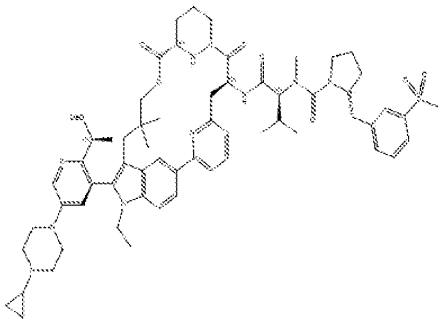
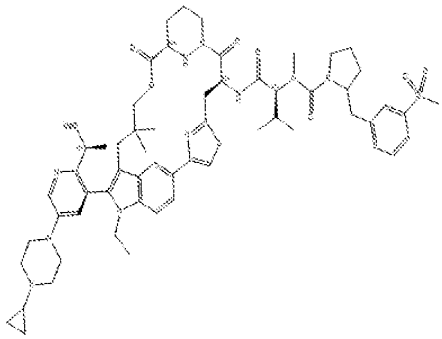
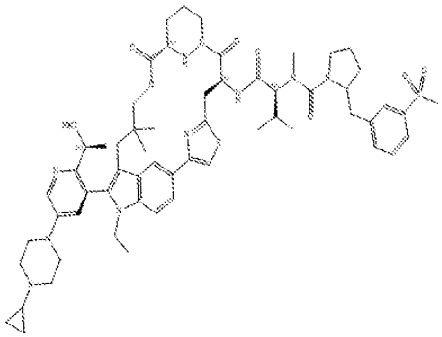
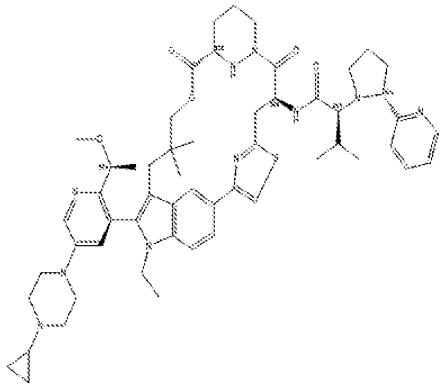
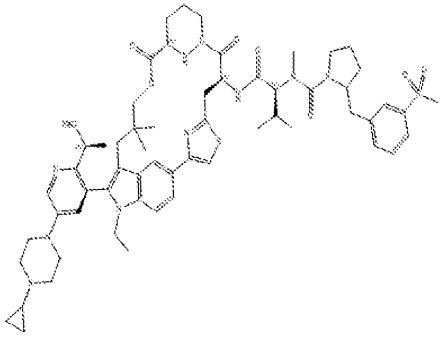
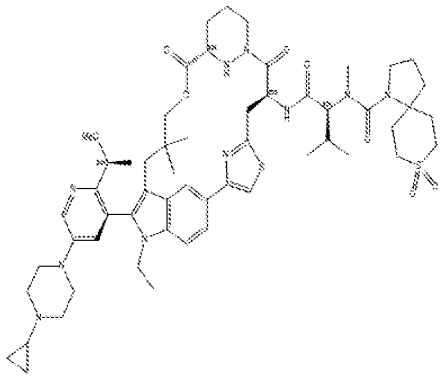
A457		A460	
A458		A461	
A459		A462	

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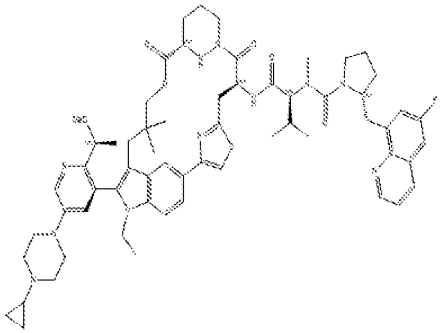
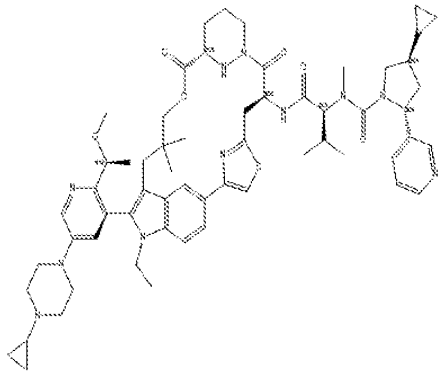
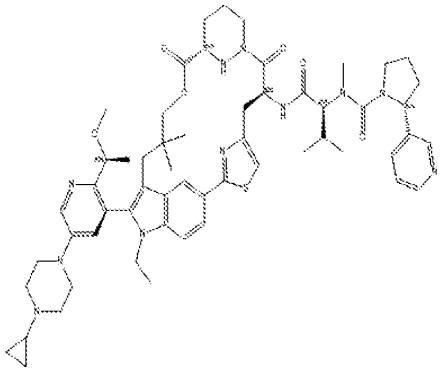
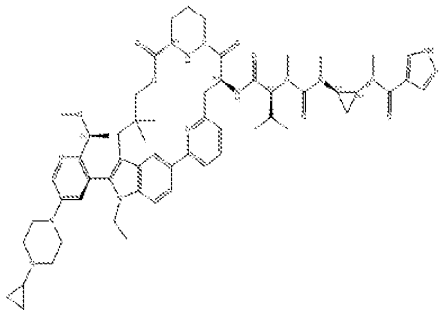
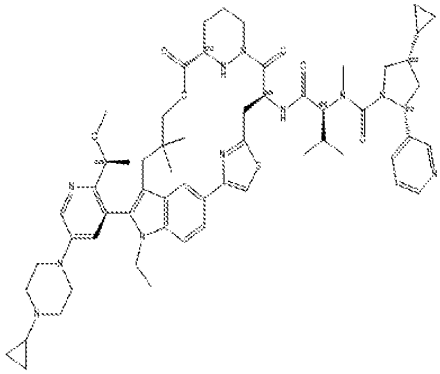
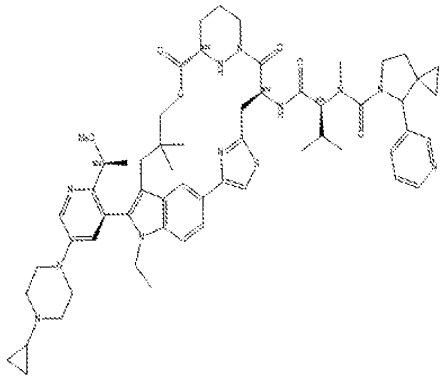
A463		A466	
A464		A467	
A465		A468	

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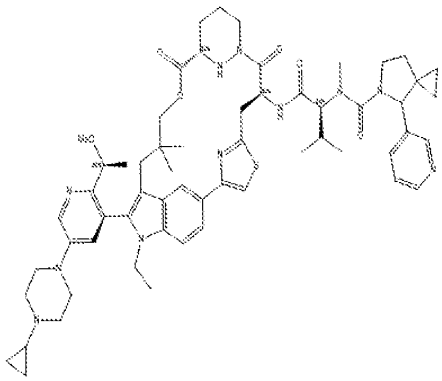
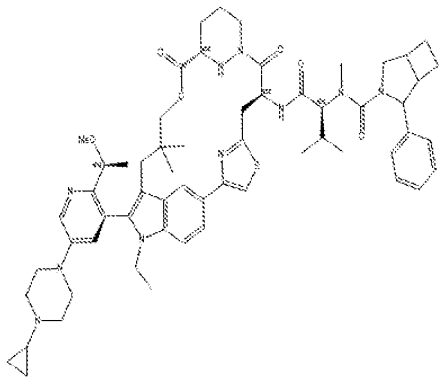
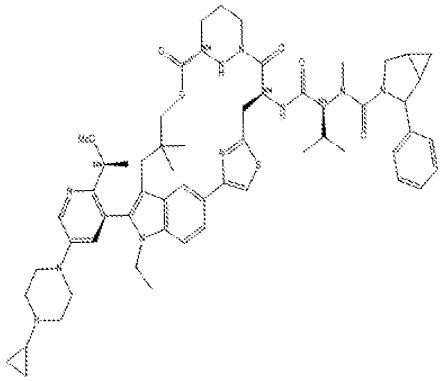
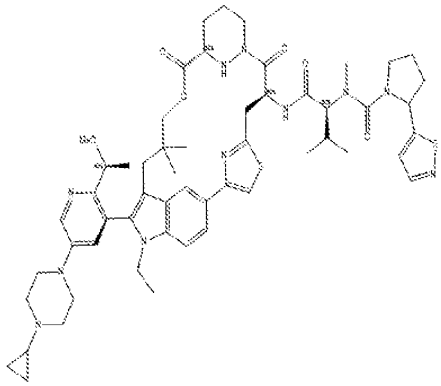
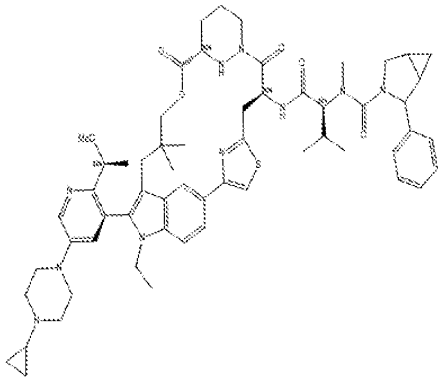
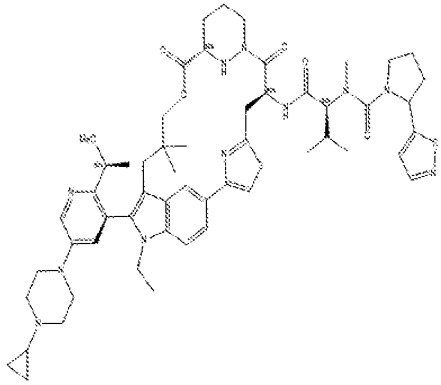
A469		A472	
A470		A473	
A471		A474	

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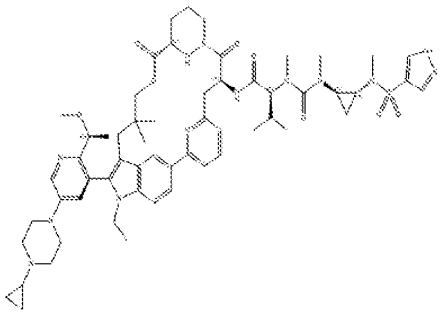
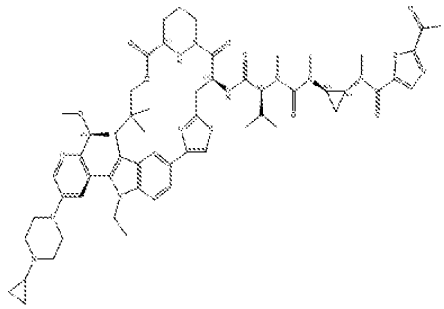
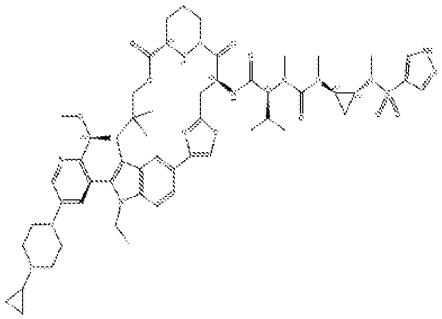
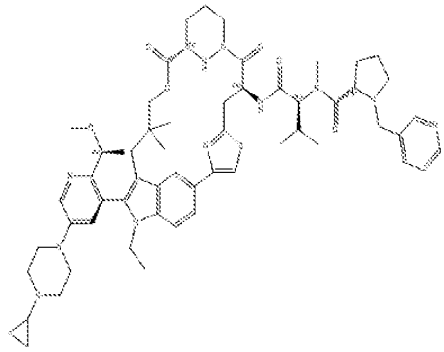
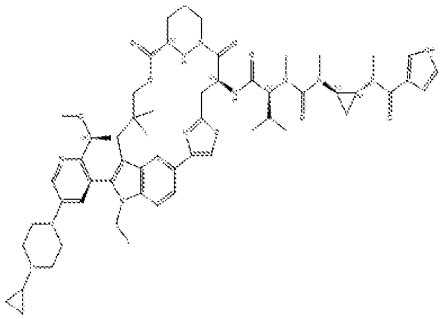
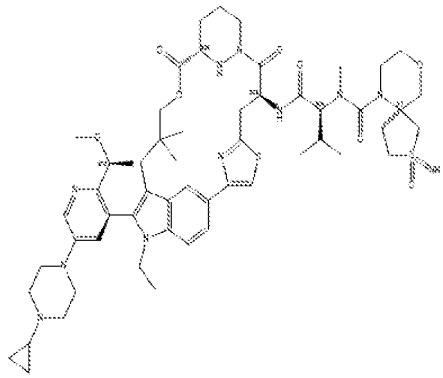
A475		A478	
A476		A479	
A477		A480	

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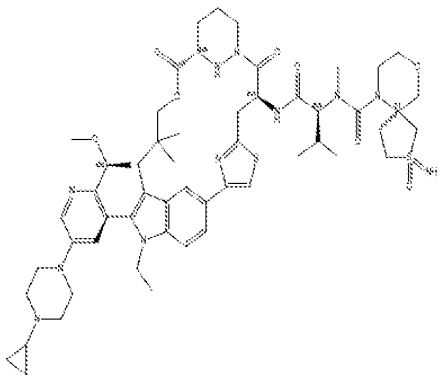
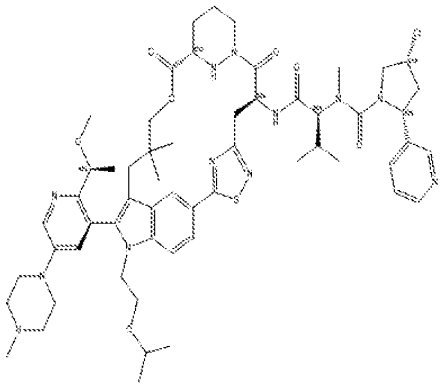
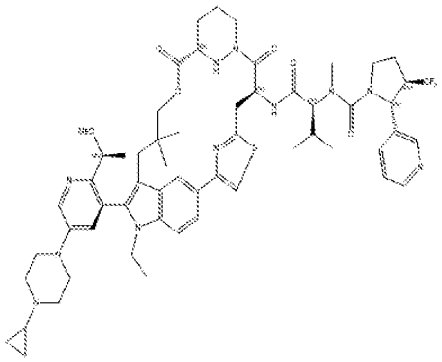
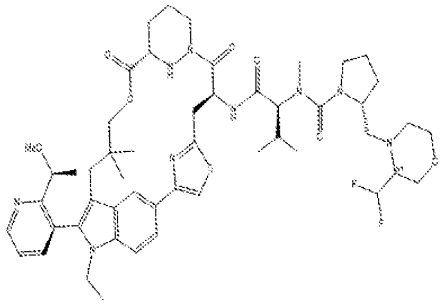
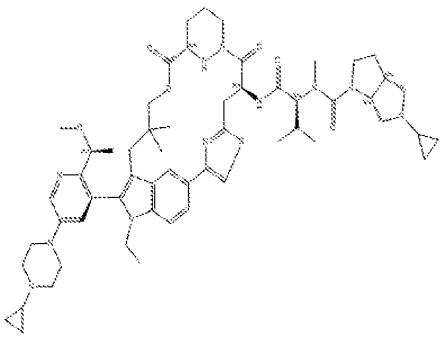
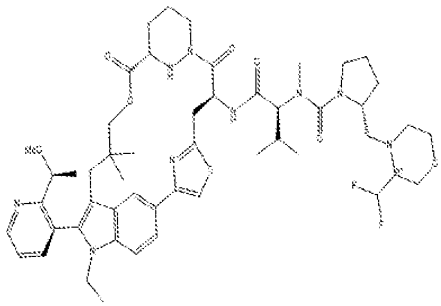
A481		A484	
A482		A485	
A483		A486	

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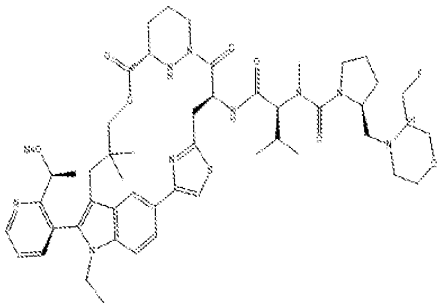
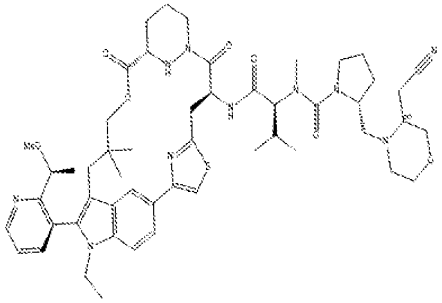
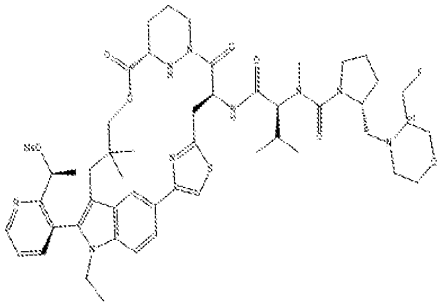
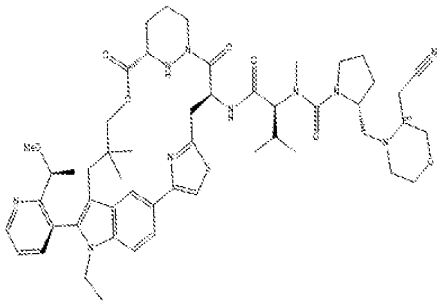
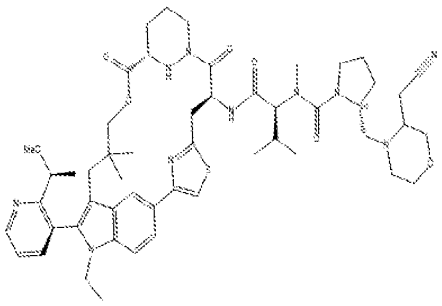
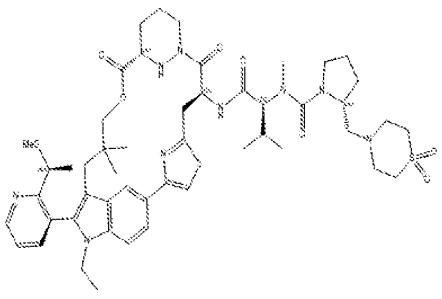
A487		A490	
A488		A491	
A489		A492	

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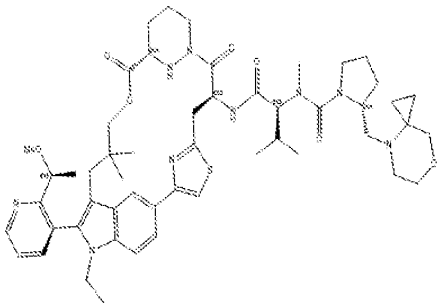
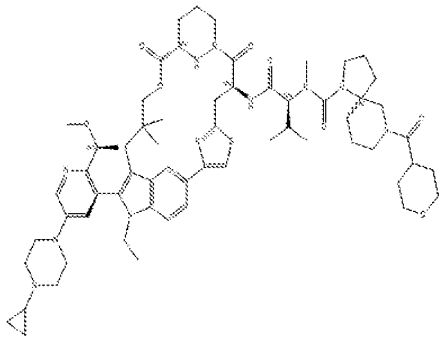
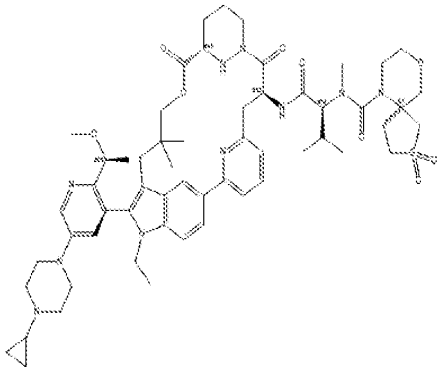
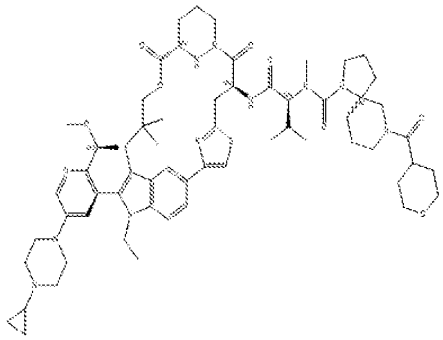
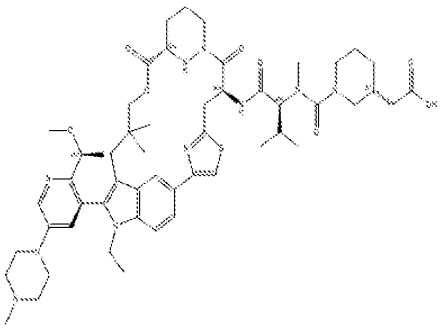
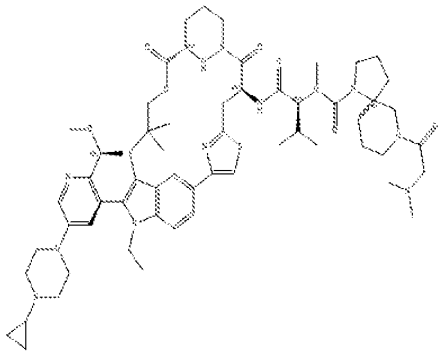
A493		A496	
A494		A497	
A495		A498	

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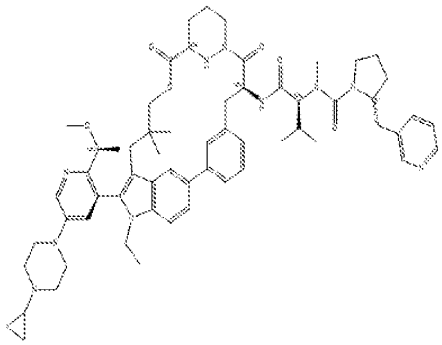
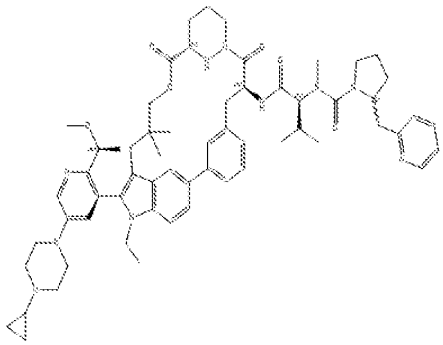
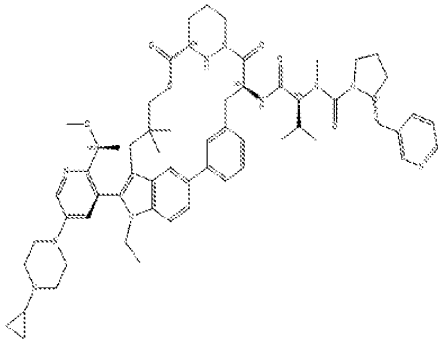
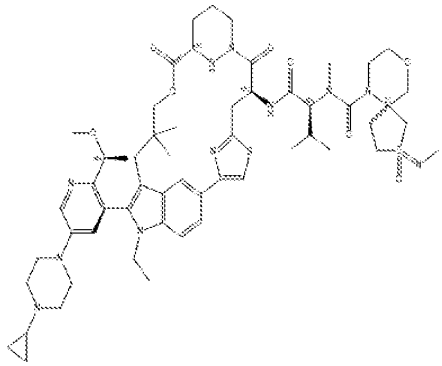
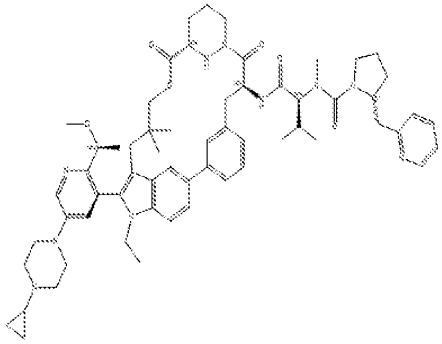
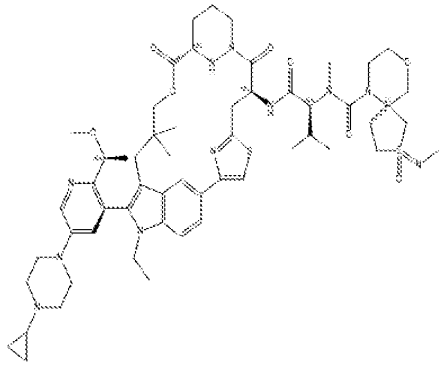
A499		A502	
A500		A503	
A501		A504	

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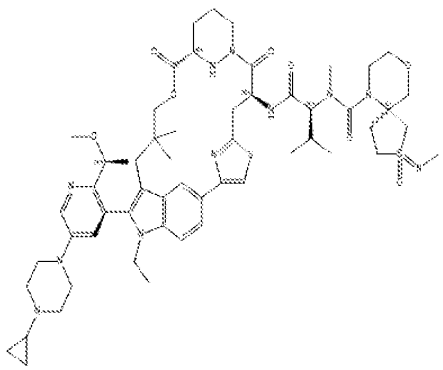
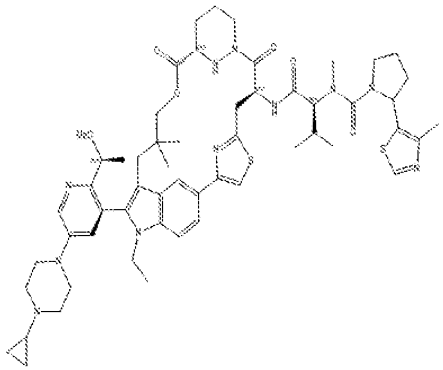
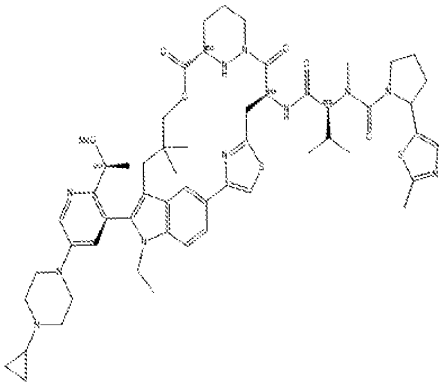
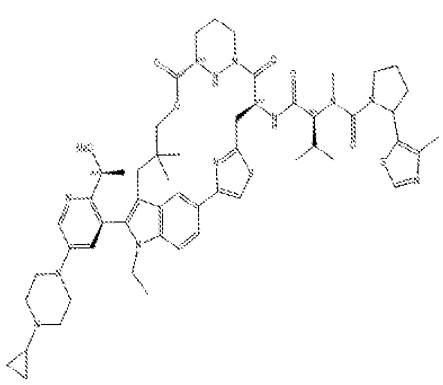
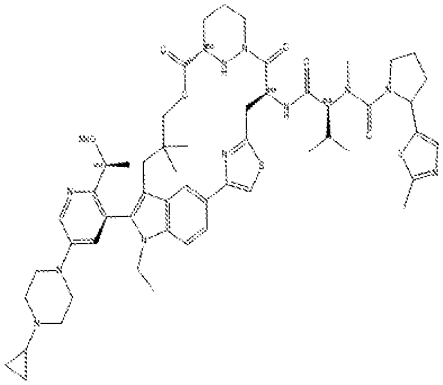
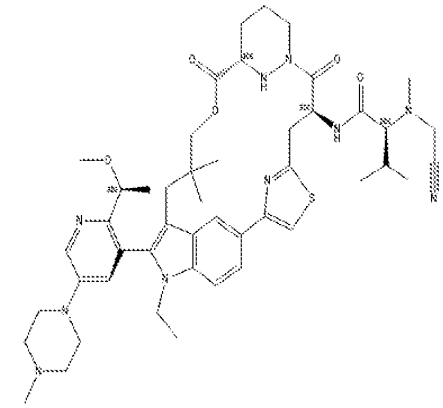
A505		A508	
A506		A509	
A507		A510	

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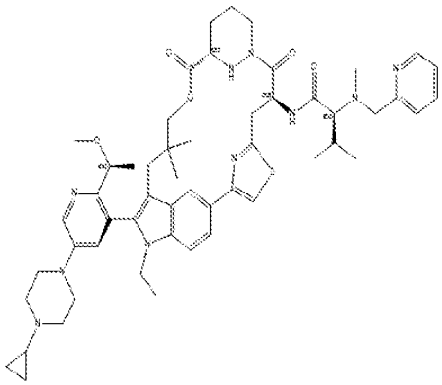
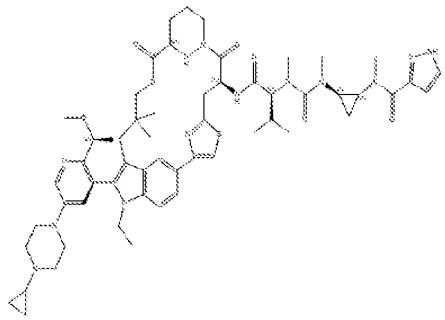
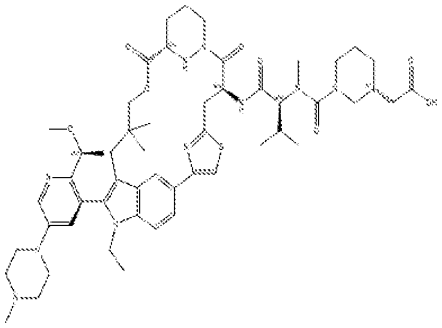
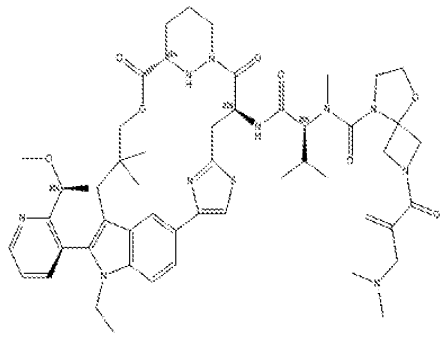
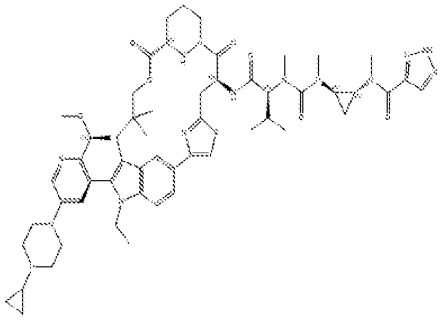
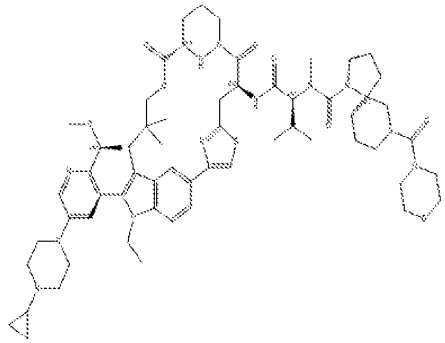
A511		A514	
A512		A515	
A513		A516	

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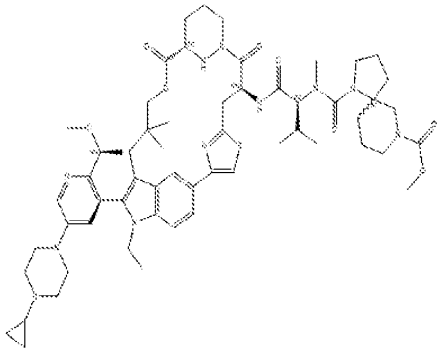
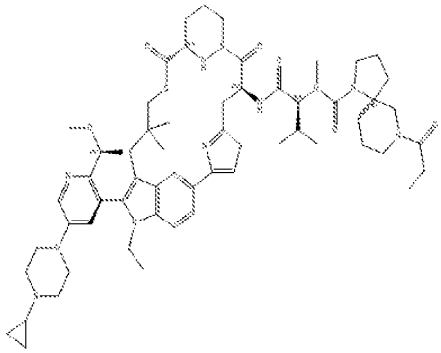
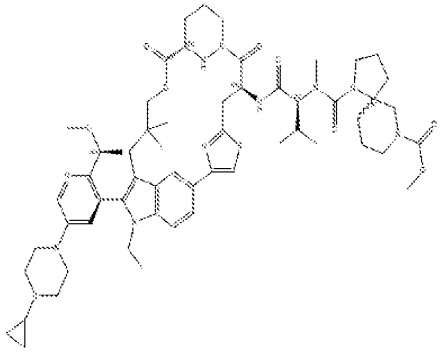
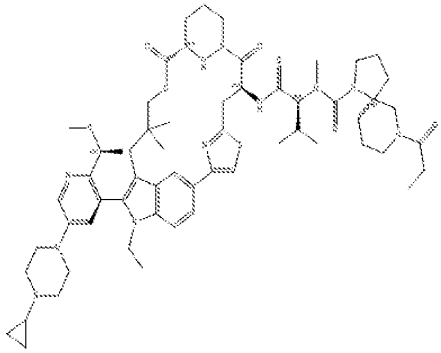
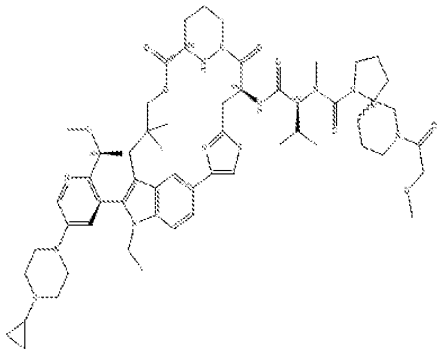
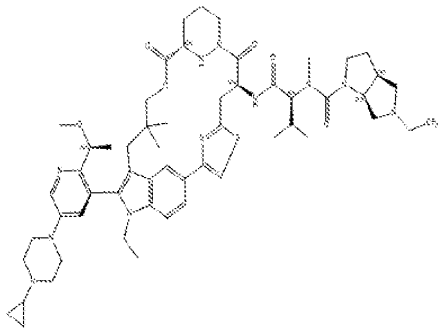
A517		A520	
A518		A521	
A519		A522	

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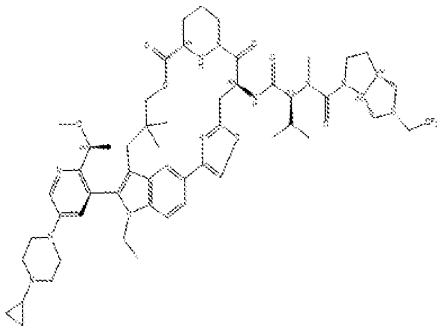
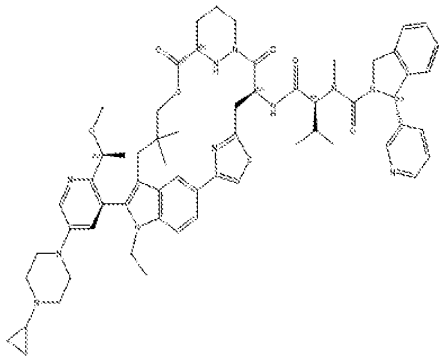
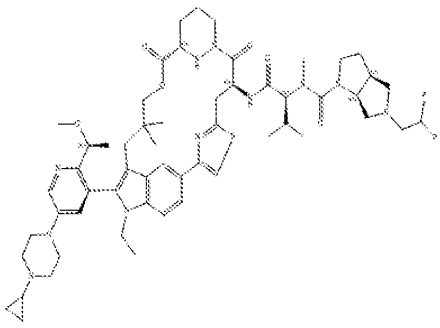
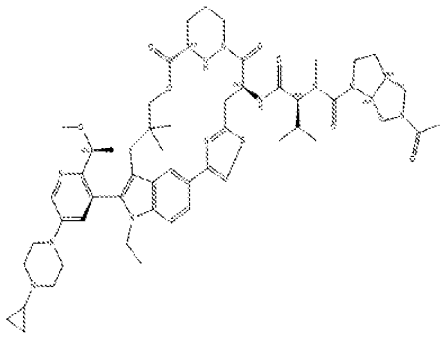
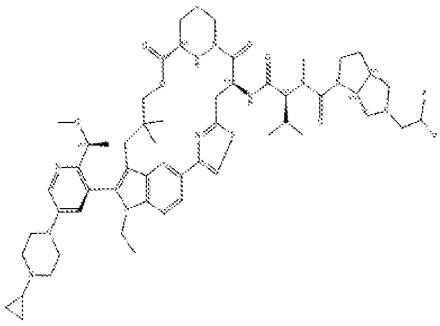
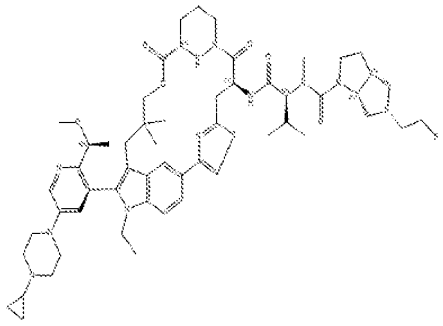
A523		A526	
A524		A527	
A525		A528	

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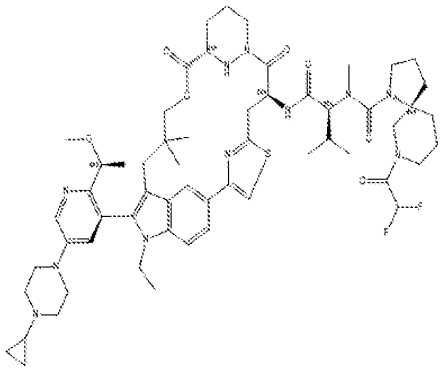
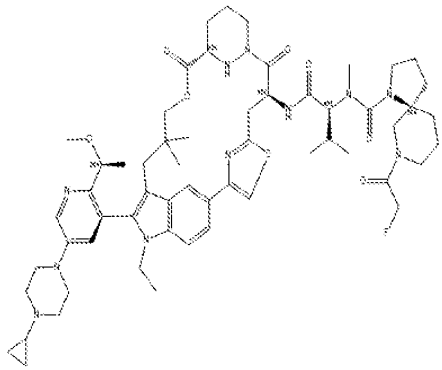
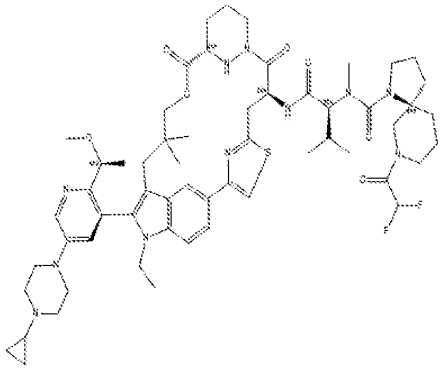
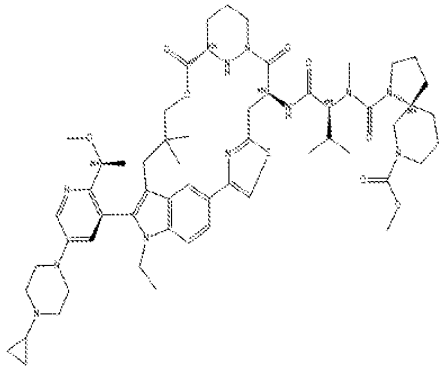
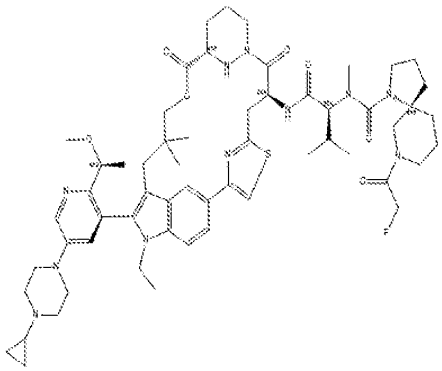
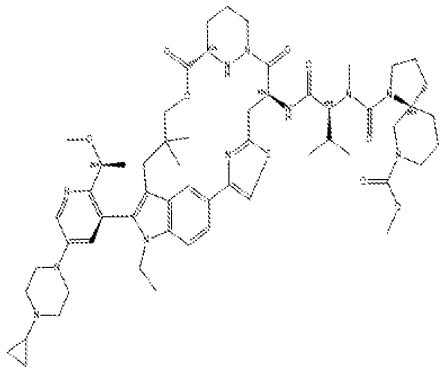
A529		A532	
A530		A533	
A531		A534	

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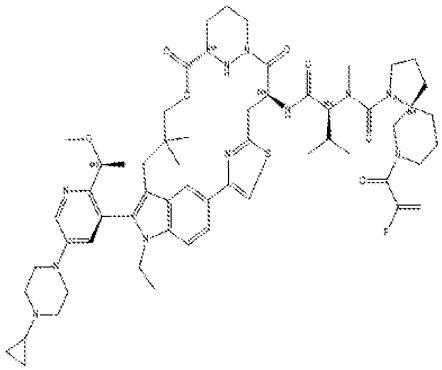
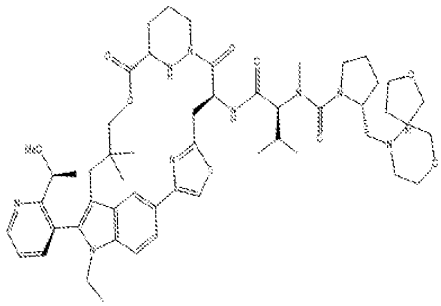
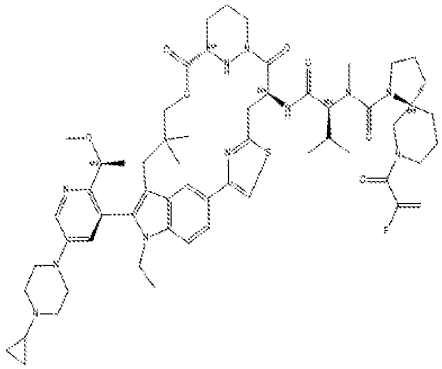
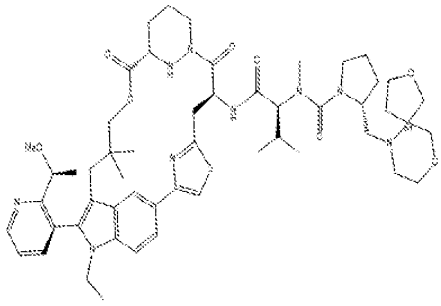
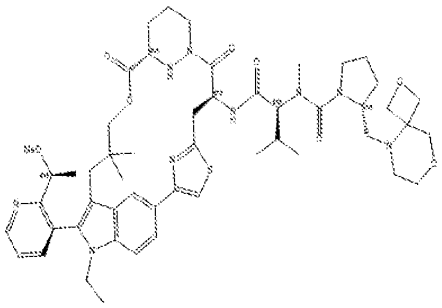
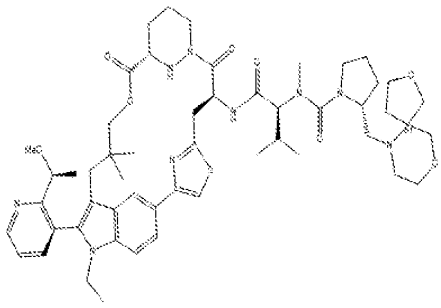
A535		A538	
A536		A539	
A537		A540	

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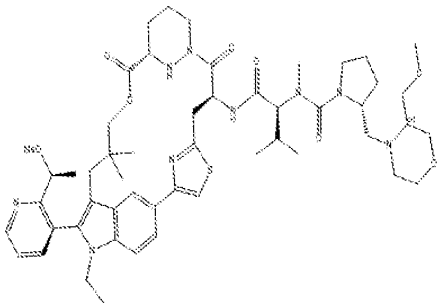
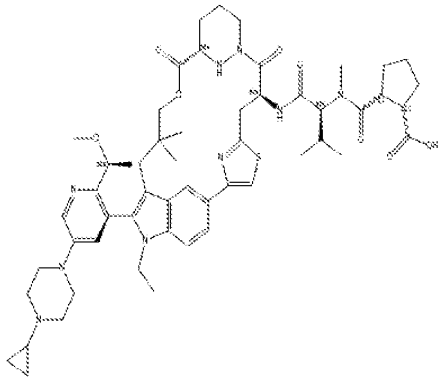
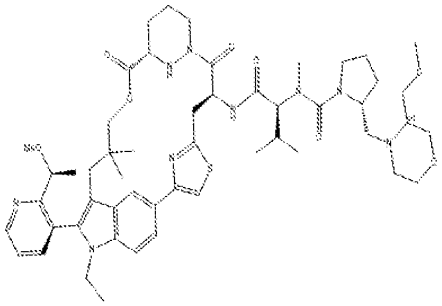
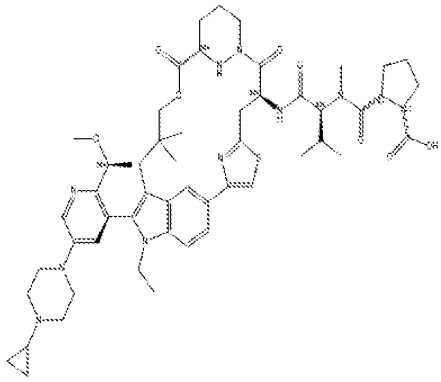
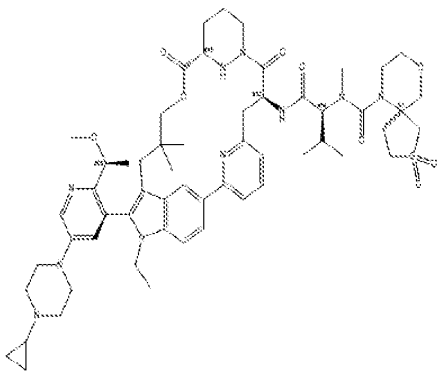
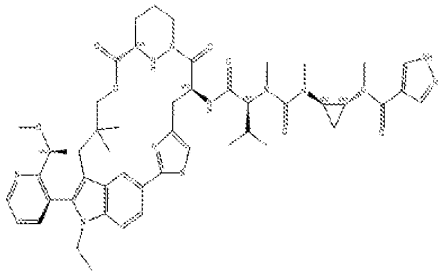
A541		A544	
A542		A545	
A543		A546	

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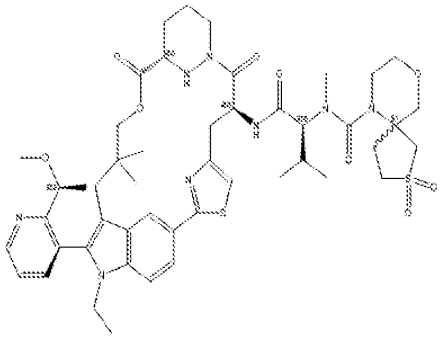
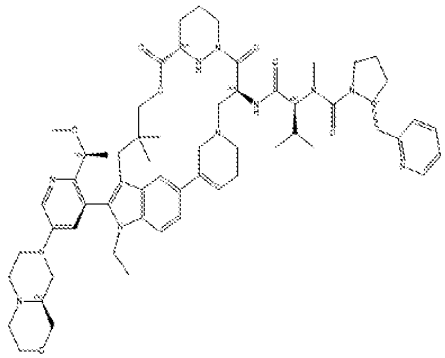
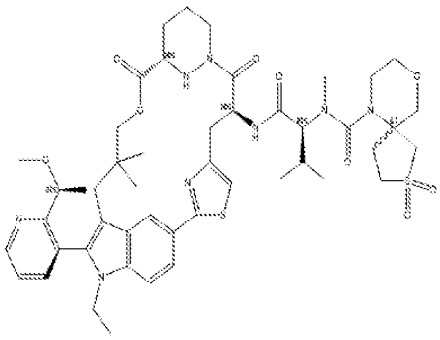
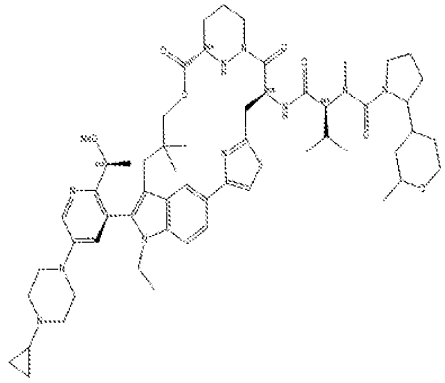
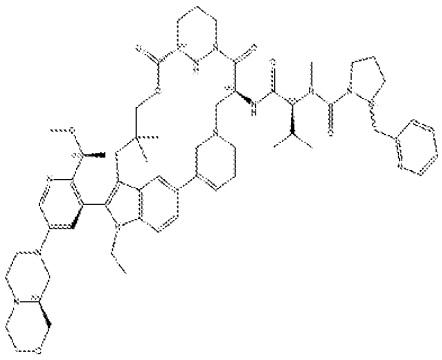
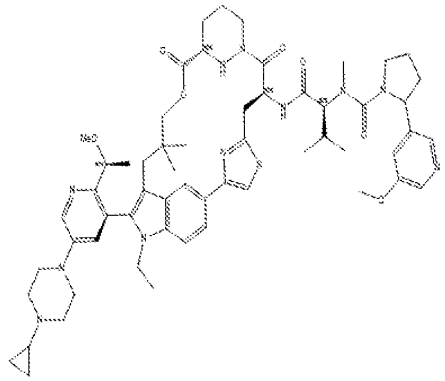
A547		A550	
A548		A551	
A549		A552	

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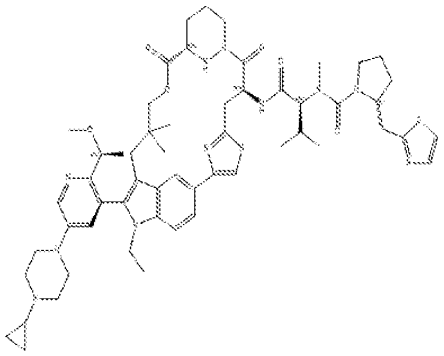
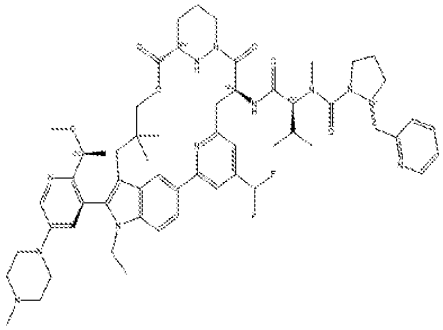
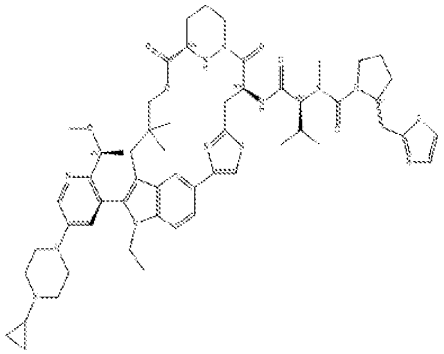
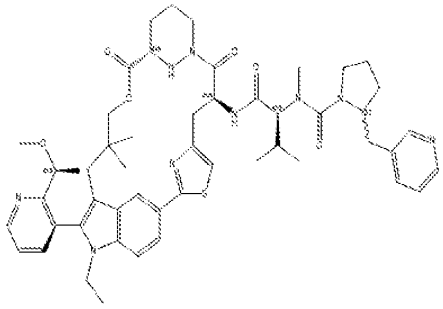
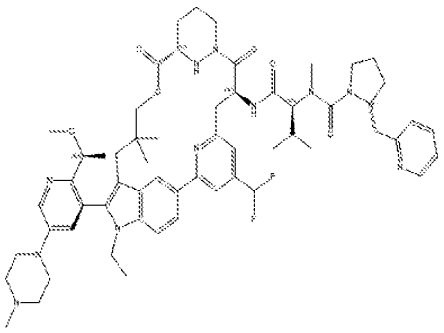
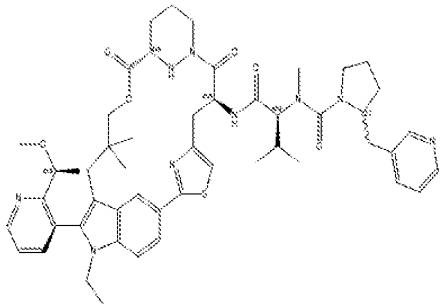
A553		A556	
A554		A557	
A555		A558	

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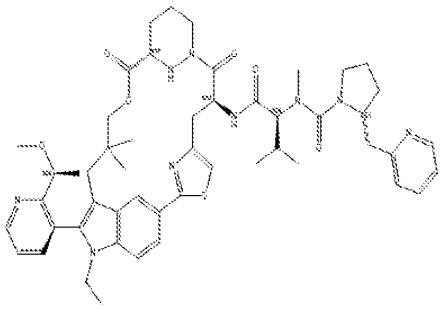
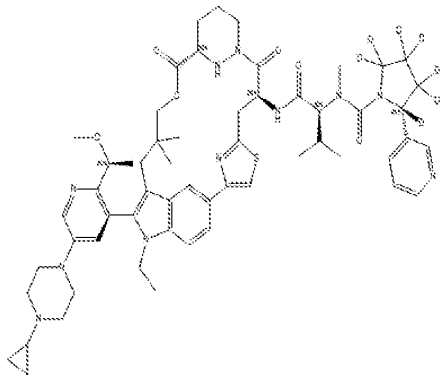
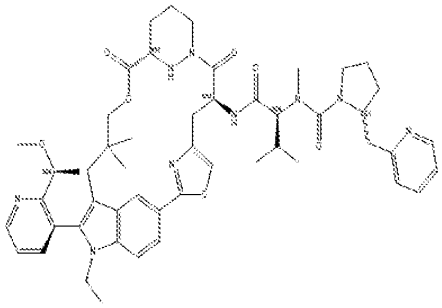
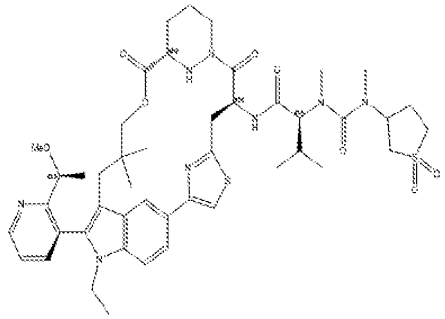
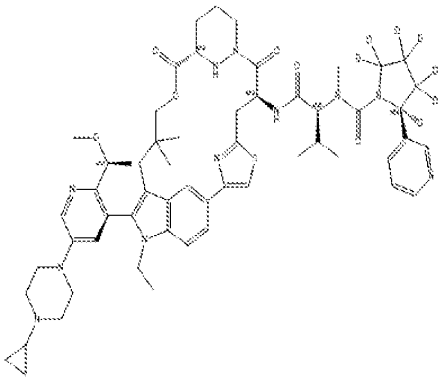
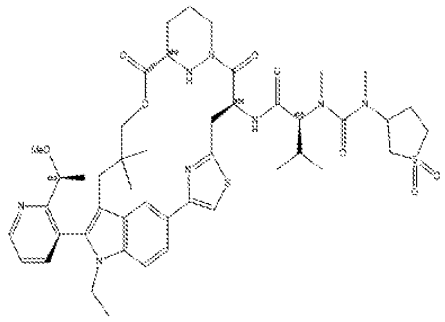
A559		A562	
A560		A563	
A561		A564	

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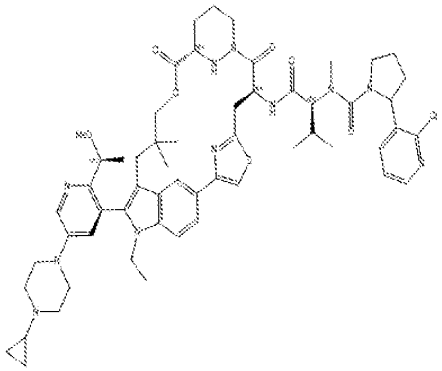
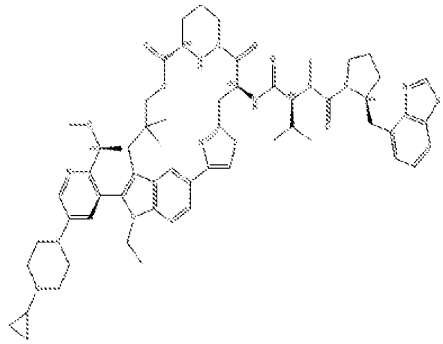
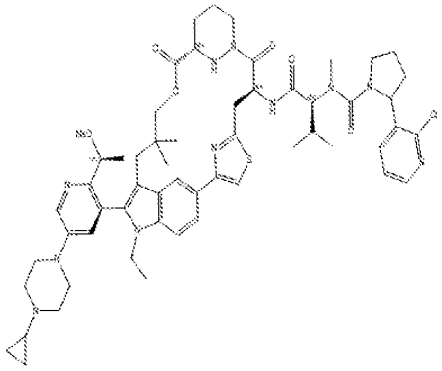
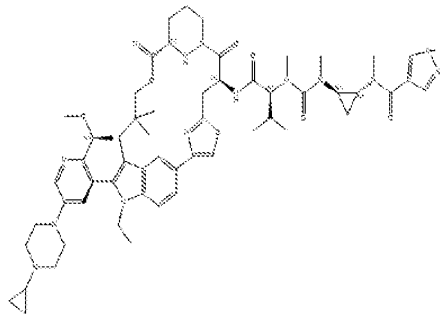
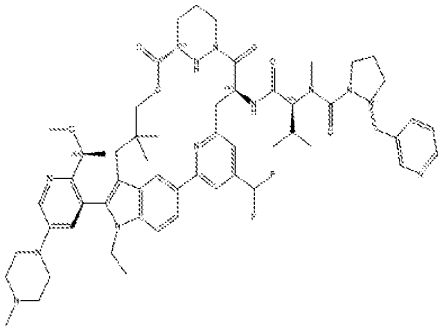
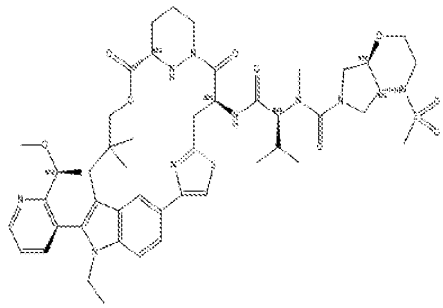
A565		A568	
A566		A569	
A567		A570	

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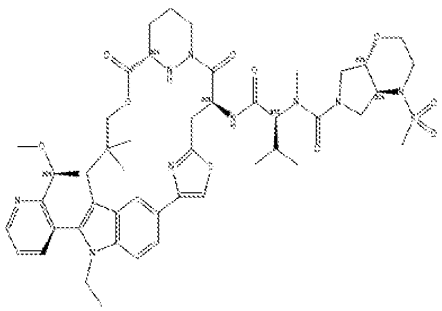
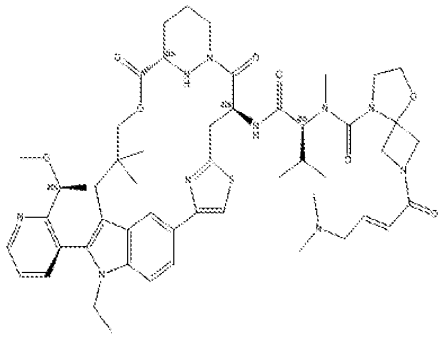
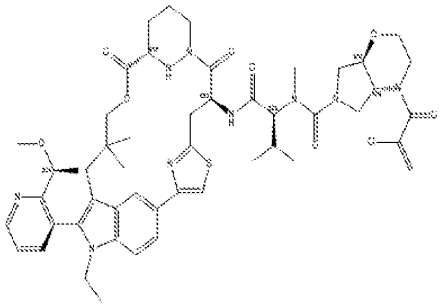
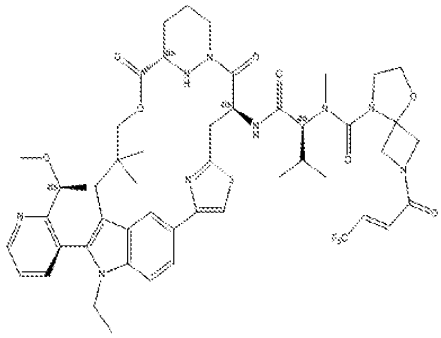
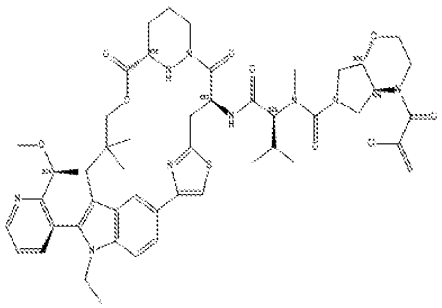
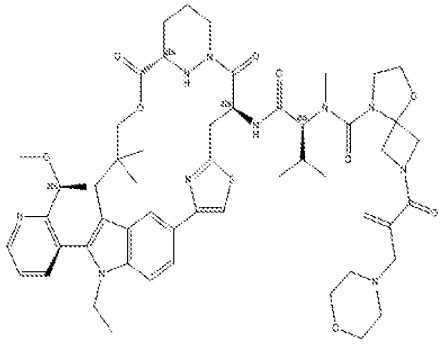
A571		A574	
A572		A575	
A573		A576	

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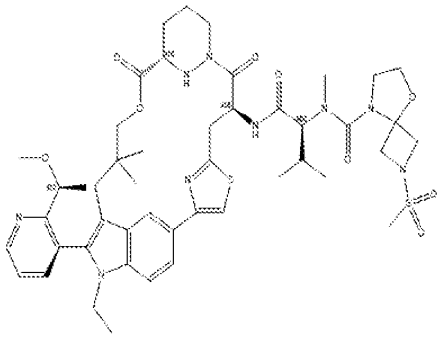
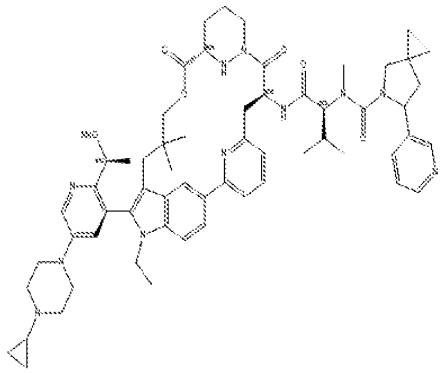
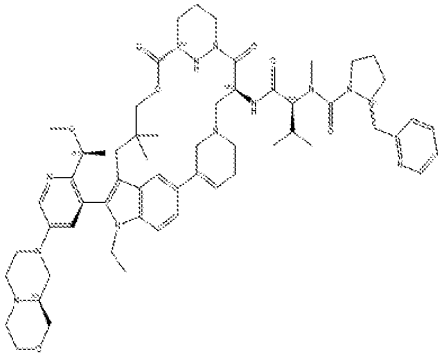
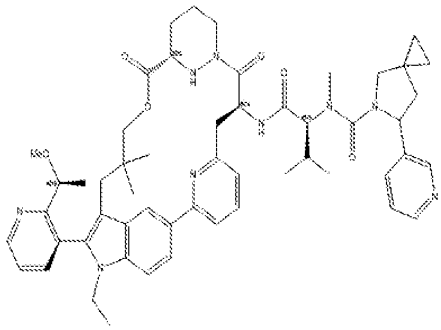
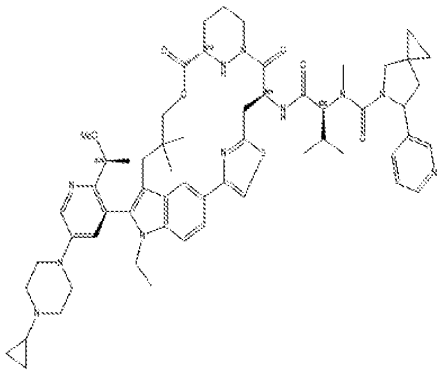
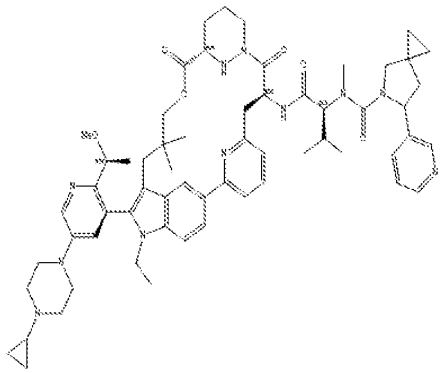
A577		A580	
A578		A581	
A579		A582	

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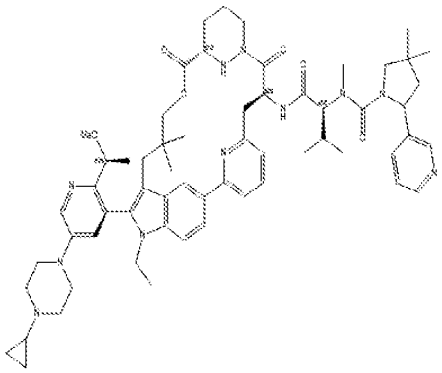
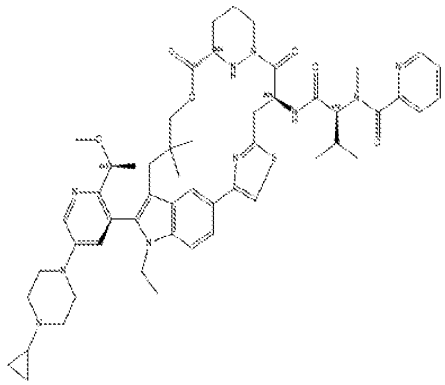
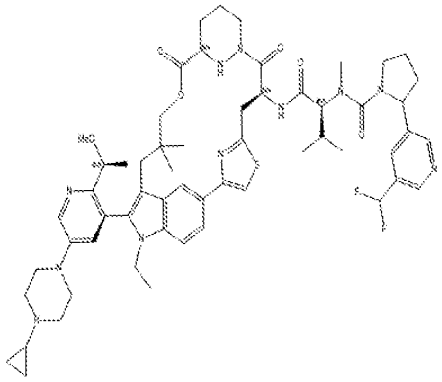
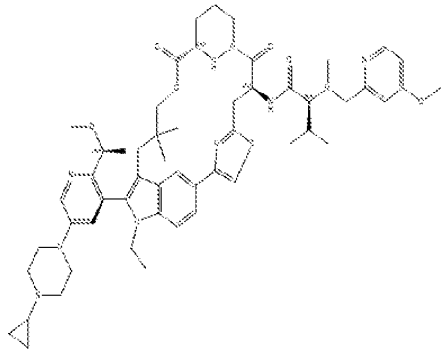
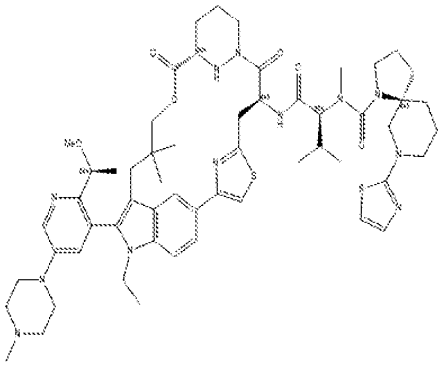
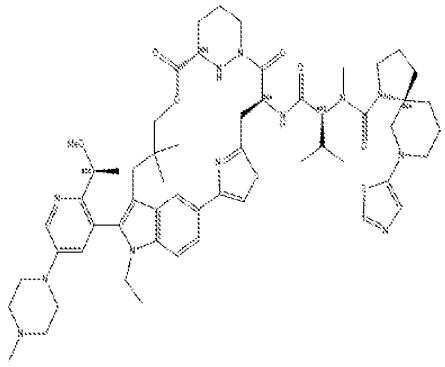
A583		A586	
A584		A587	
A585		A588	

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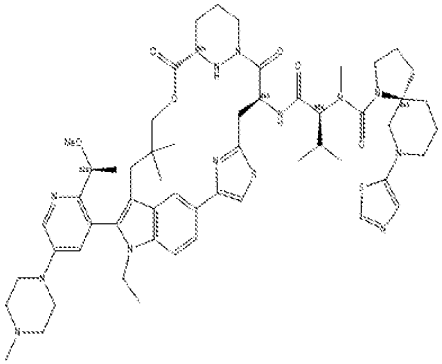
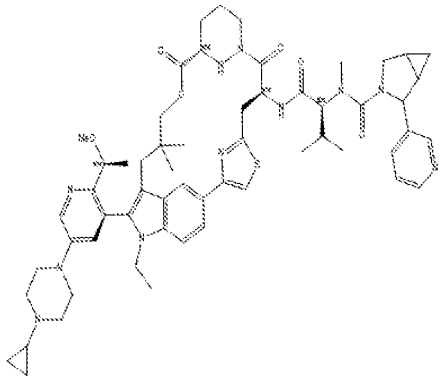
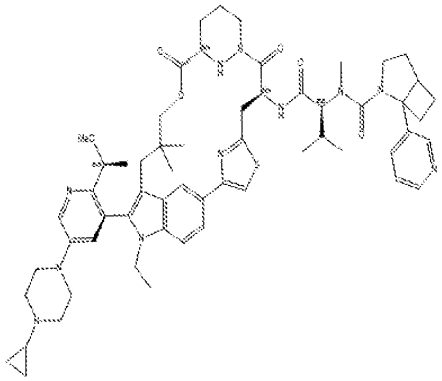
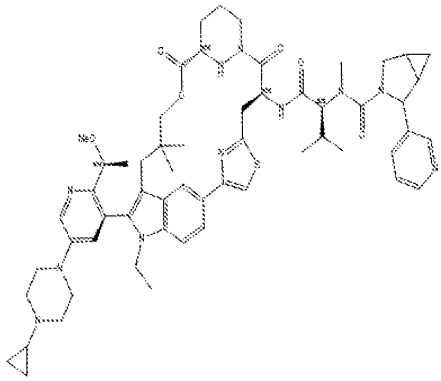
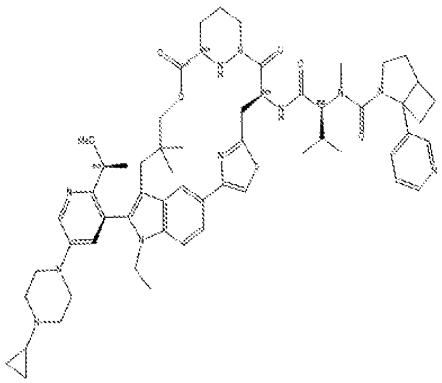
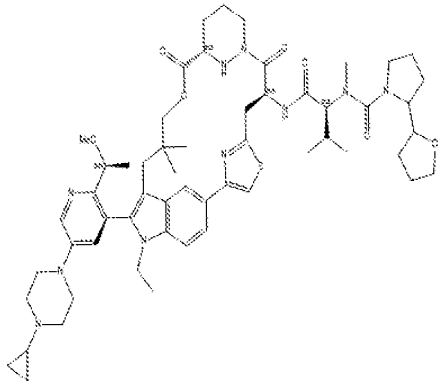
A589		A592	
A590		A593	
A591		A594	

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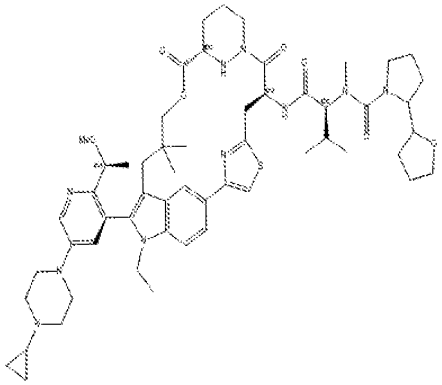
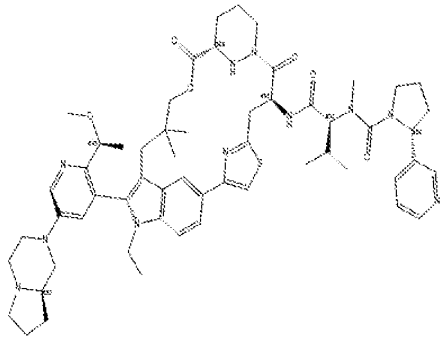
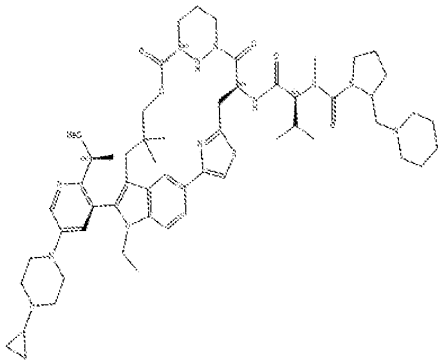
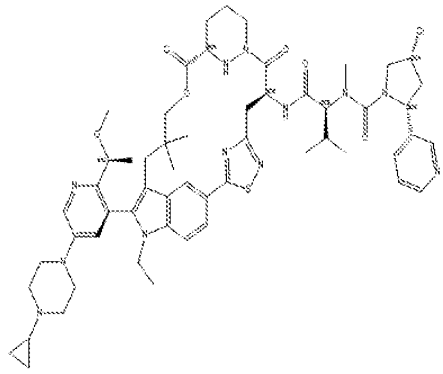
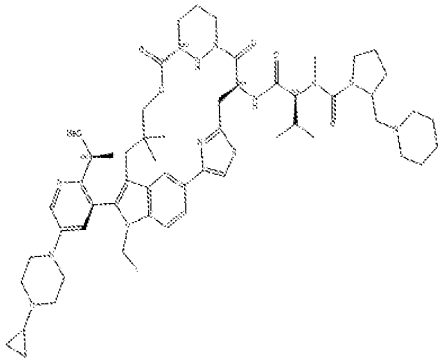
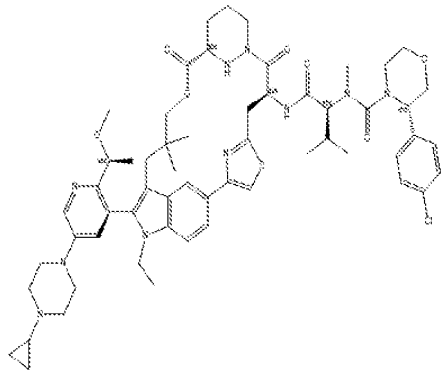
A595		A598	
A596		A599	
A597		A600	

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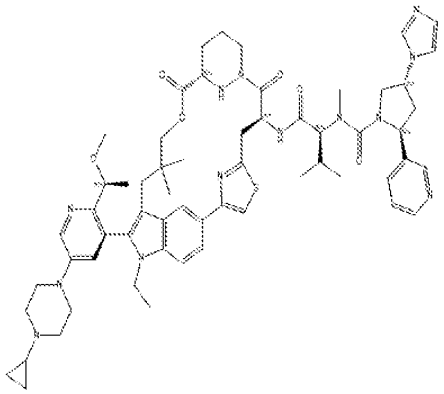
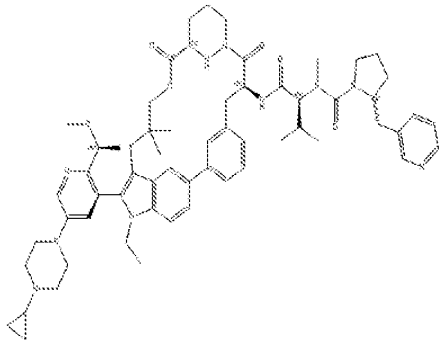
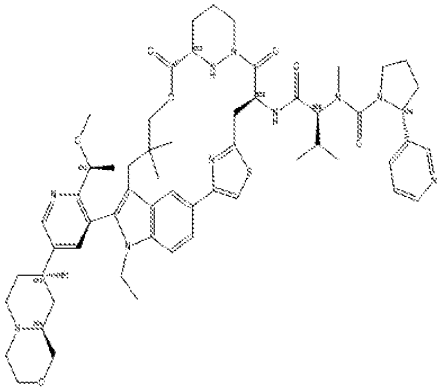
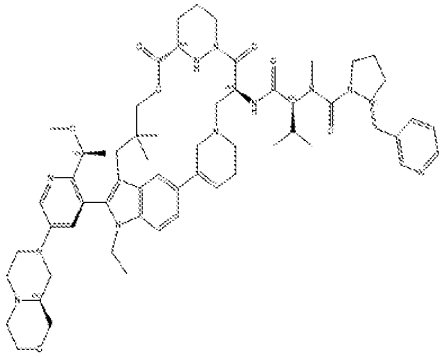
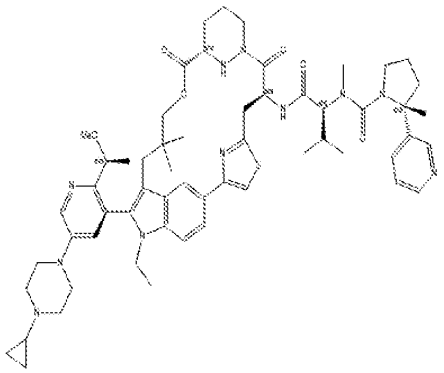
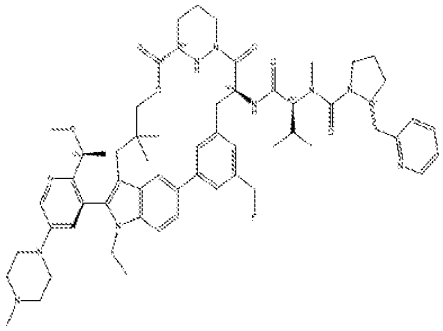
A601		A604	
A602		A605	
A603		A606	

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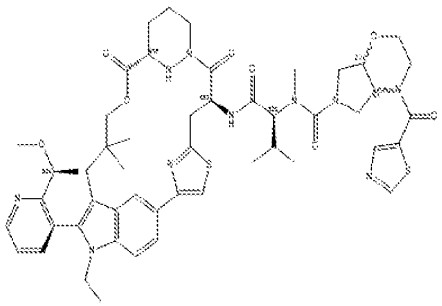
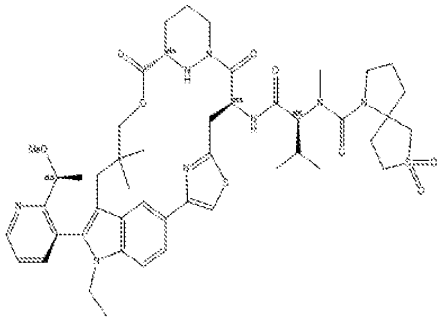
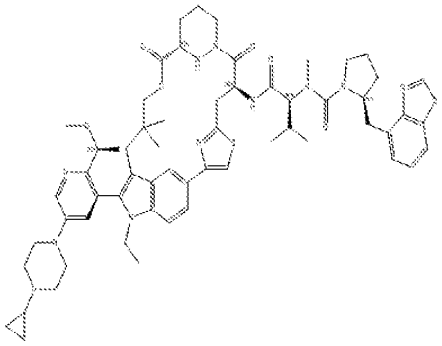
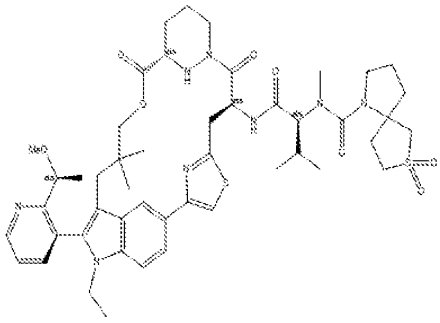
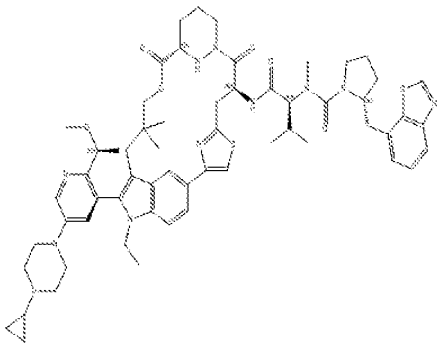
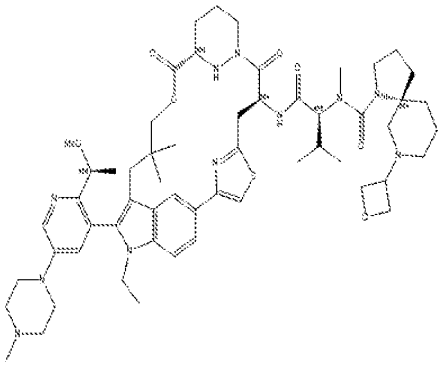
A607		A610	
A608		A611	
A609		A612	

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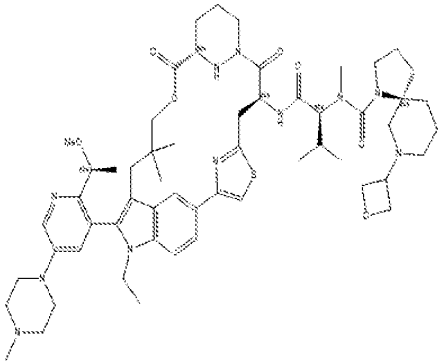
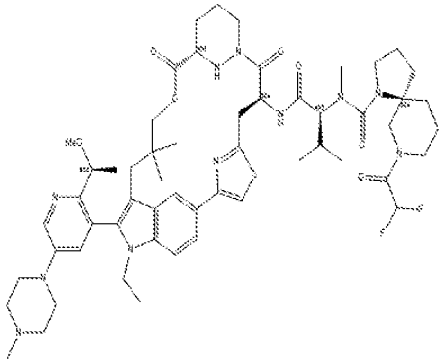
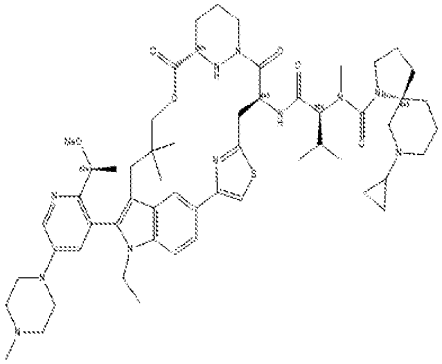
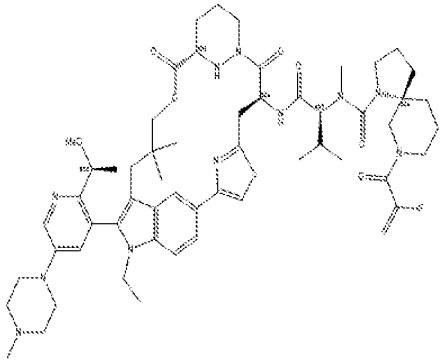
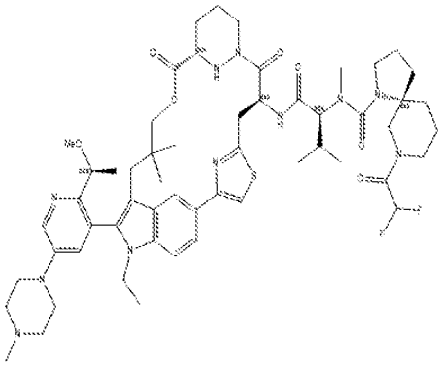
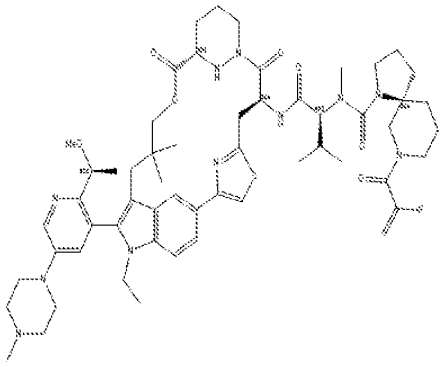
A613		A616	
A614		A617	
A615		A618	

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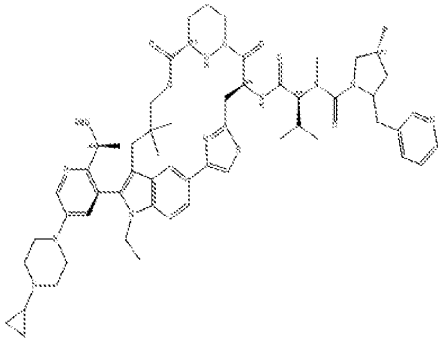
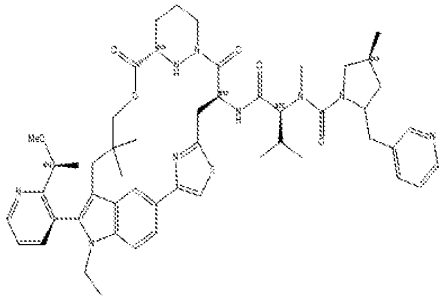
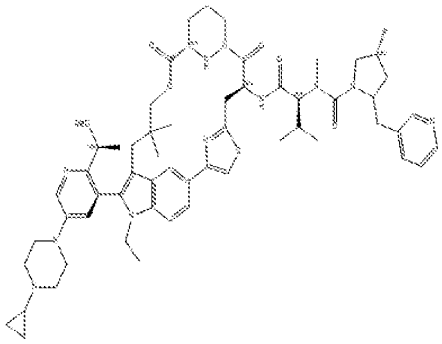
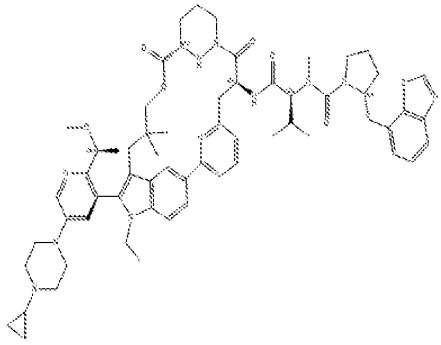
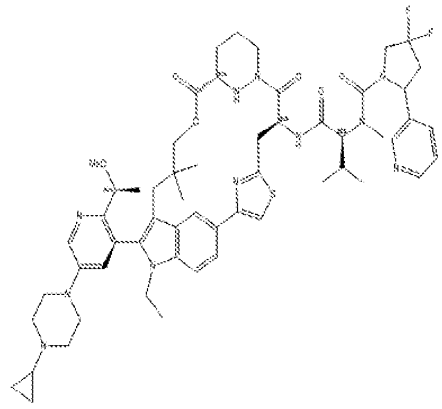
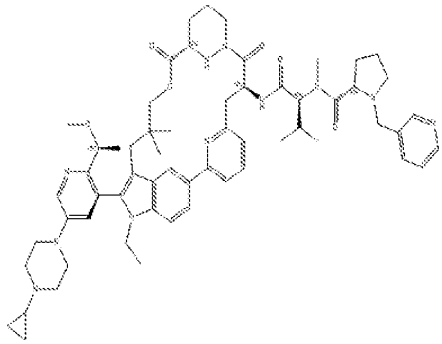
A619		A622	
A620		A623	
A621		A624	

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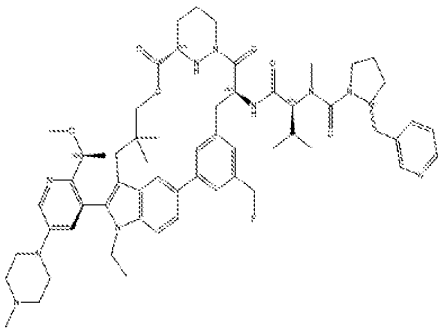
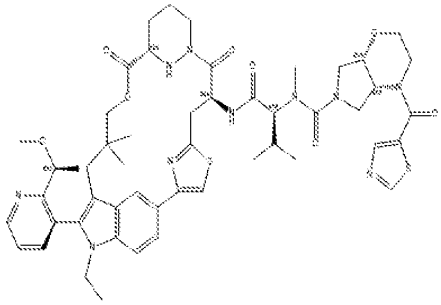
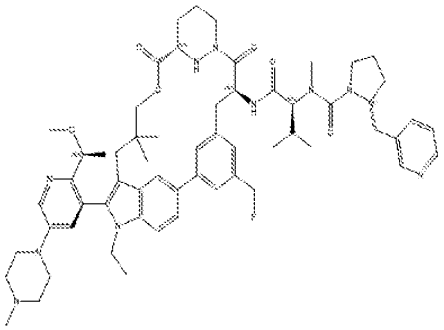
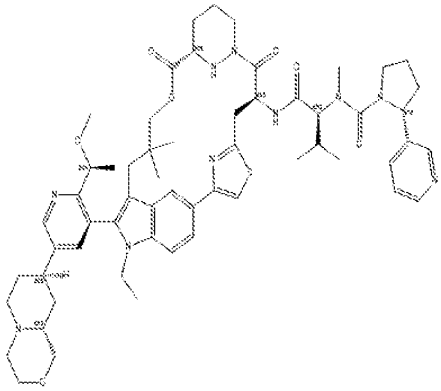
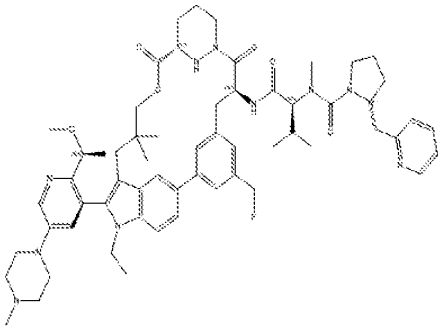
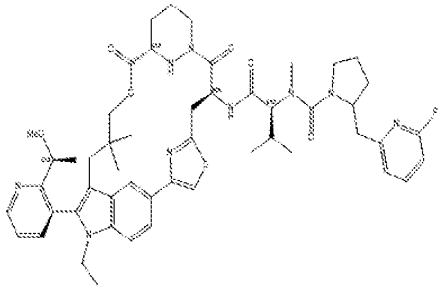
A625		A628	
A626		A629	
A627		A630	

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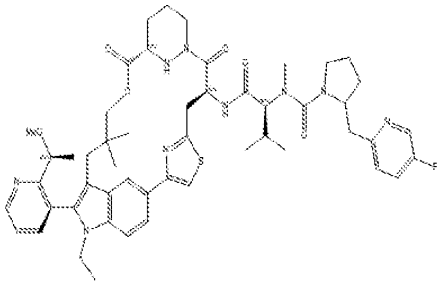
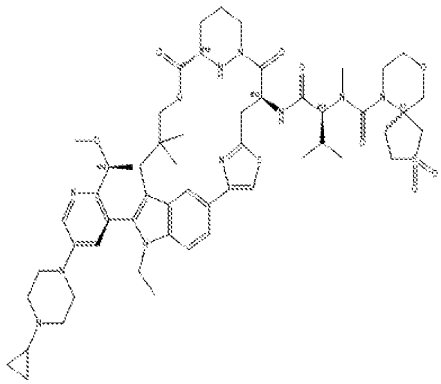
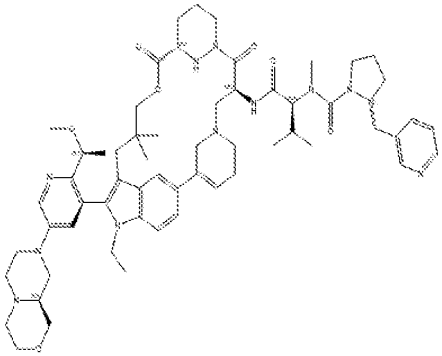
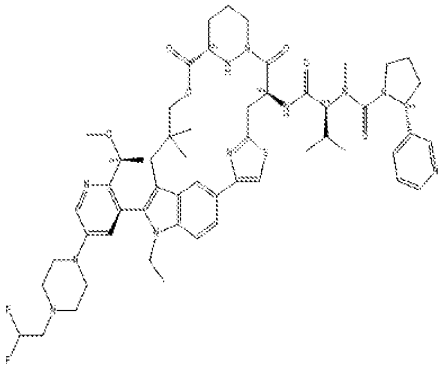
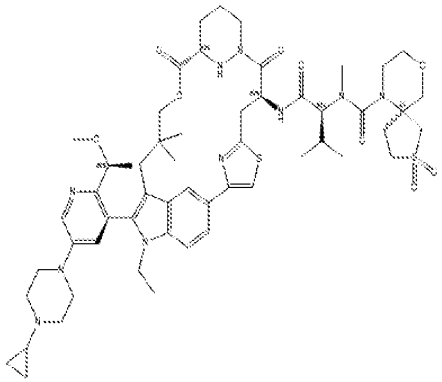
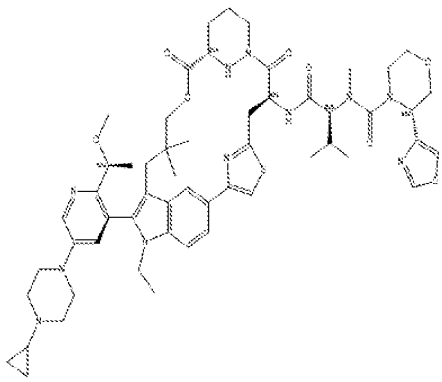
A631		A634	
A632		A635	
A633		A636	

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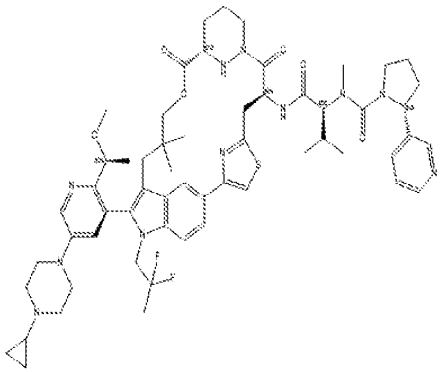
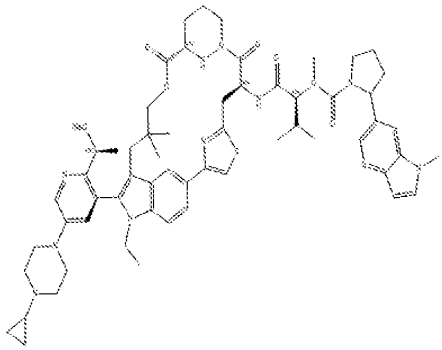
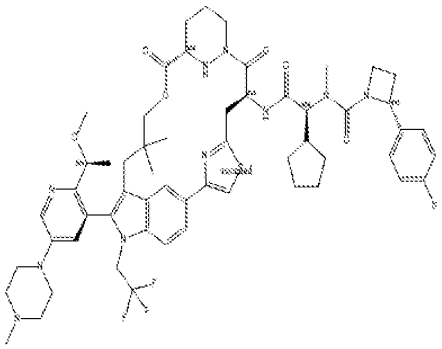
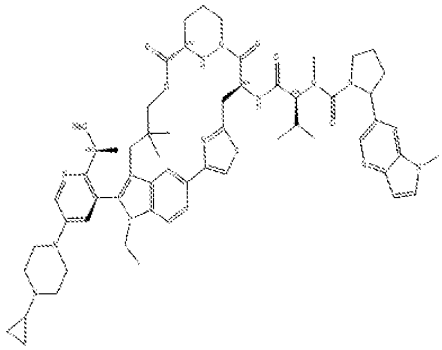
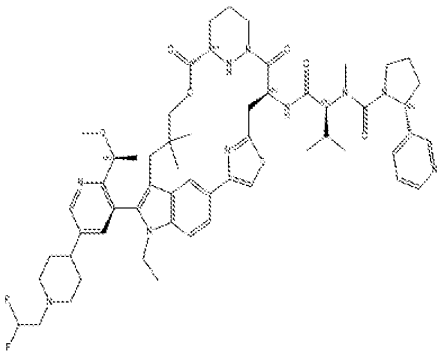
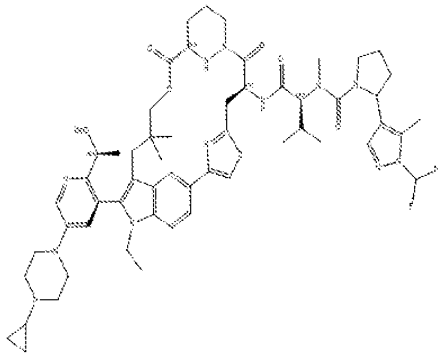
A637		A640	
A638		A641	
A639		A642	

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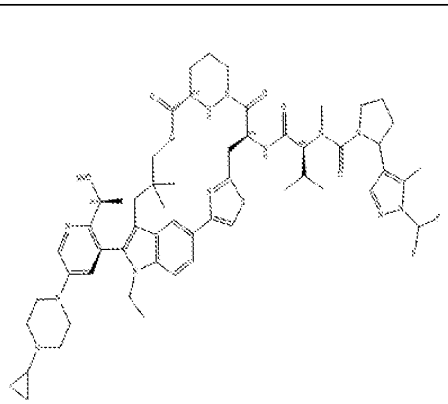
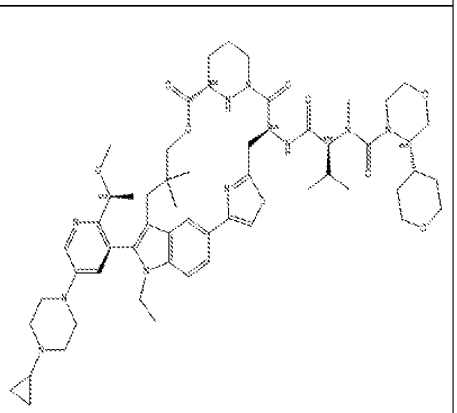
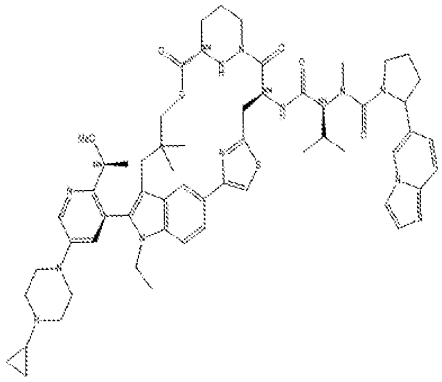
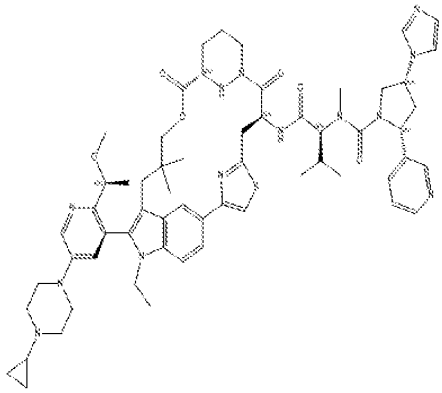
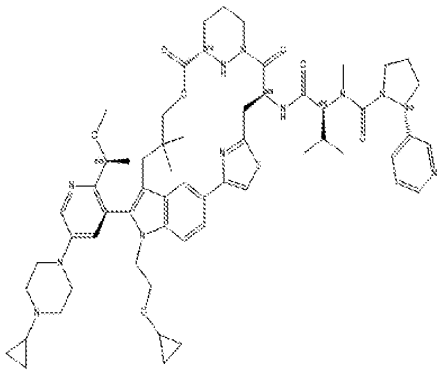
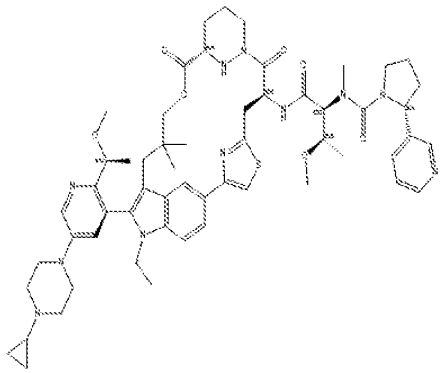
A643		A646	
A644		A647	
A645		A648	

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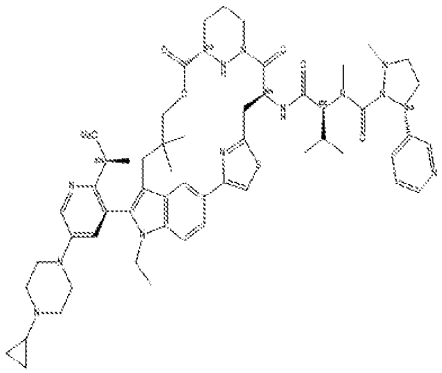
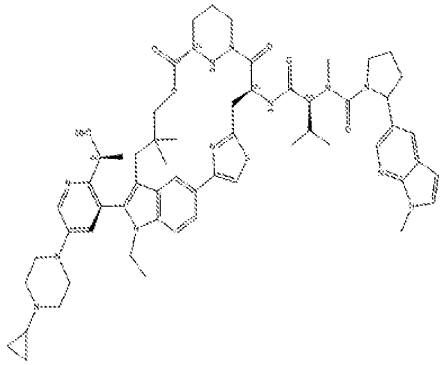
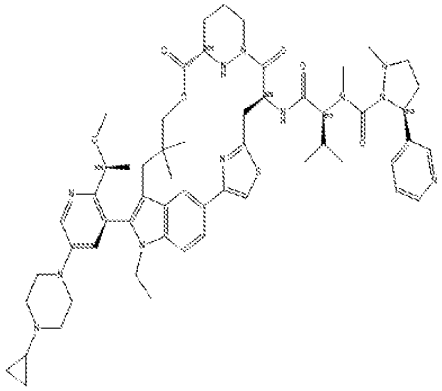
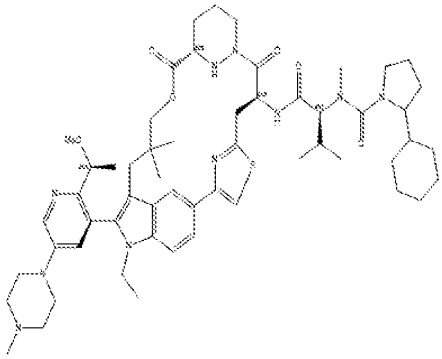
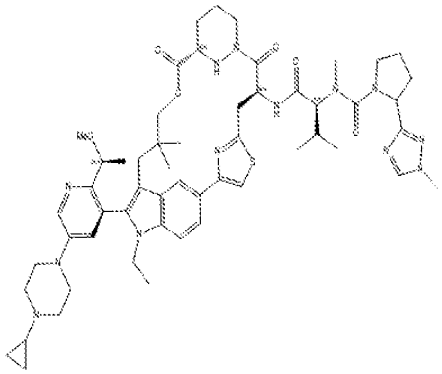
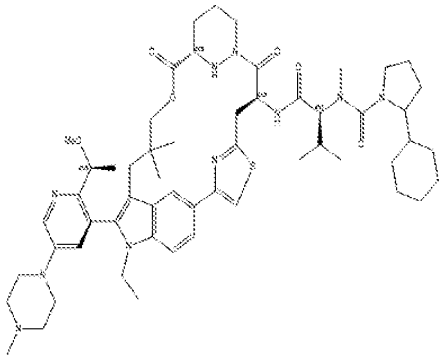
A649		A652	
A650		A653	
A651		A654	

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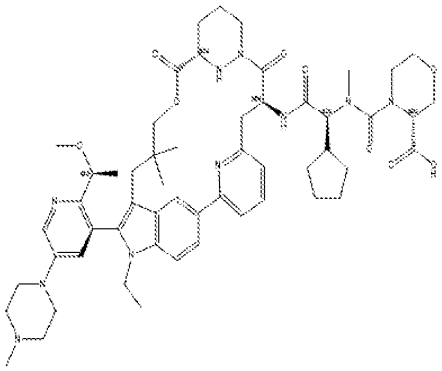
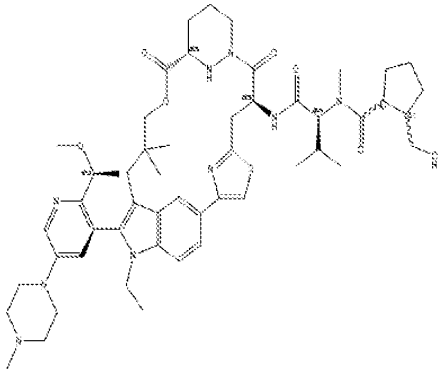
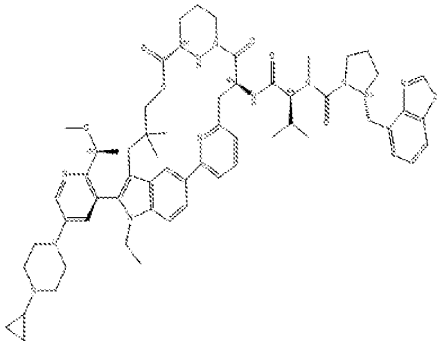
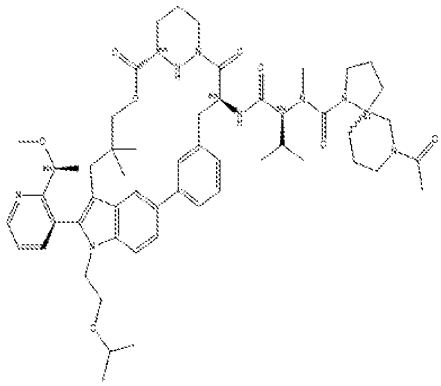
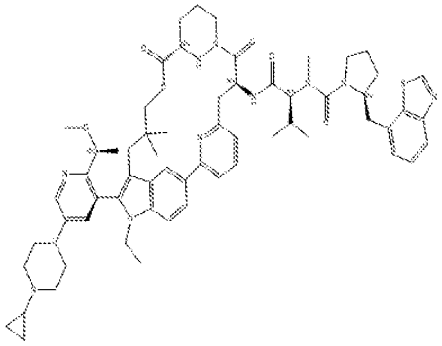
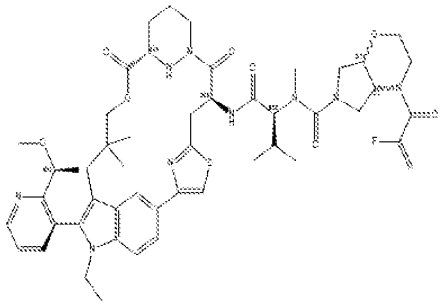
A655		A658	
A656		A659	
A657		A660	

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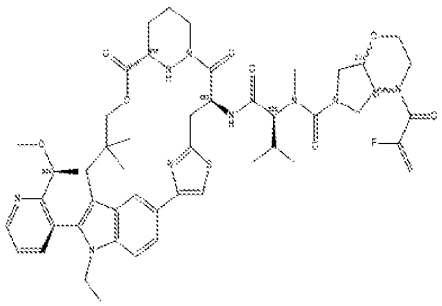
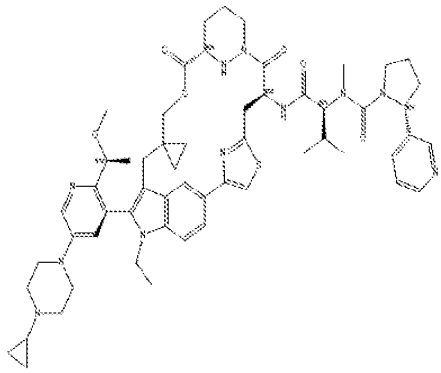
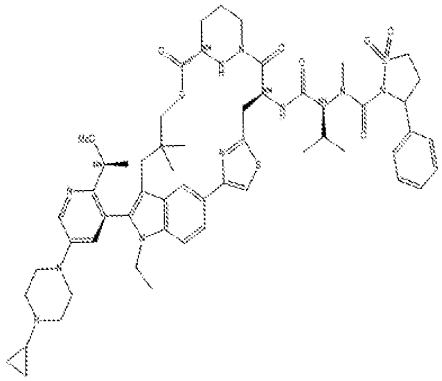
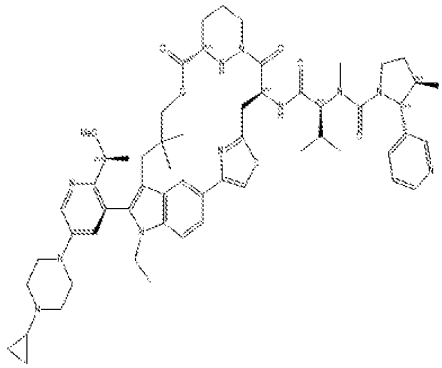
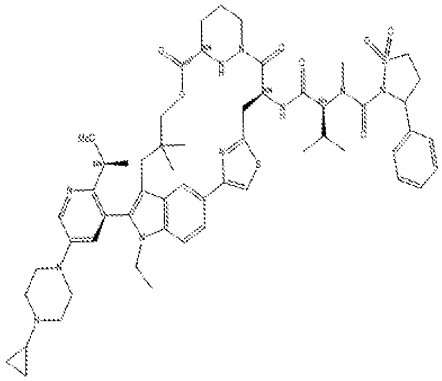
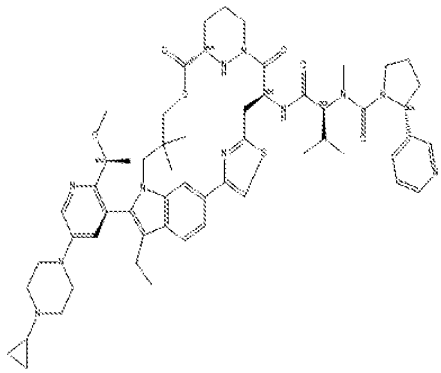
A661		A664	
A662		A665	
A663		A666	

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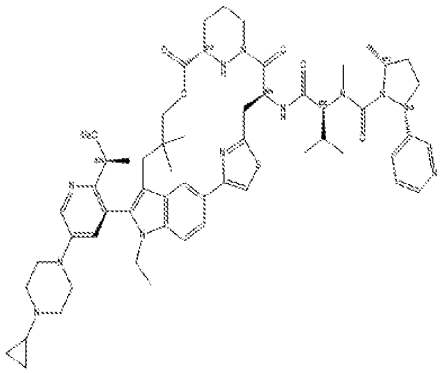
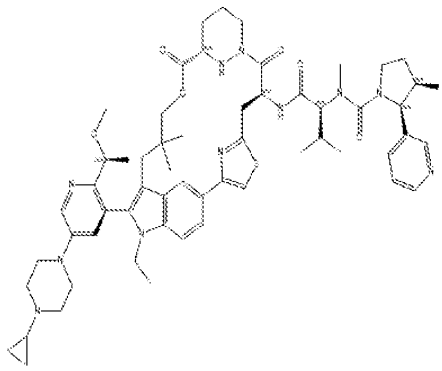
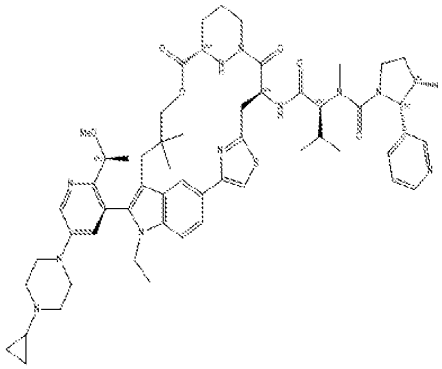
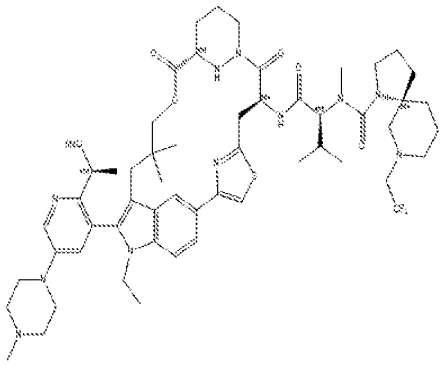
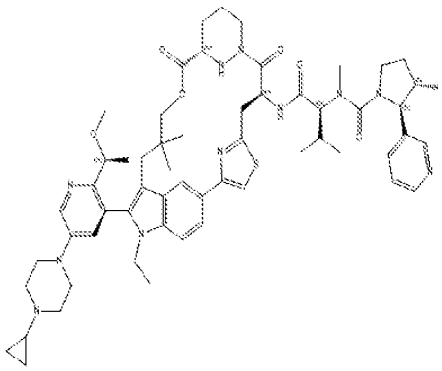
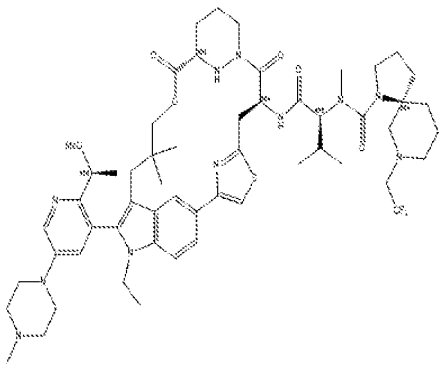
A667		A670	
A668		A671	
A669		A672	

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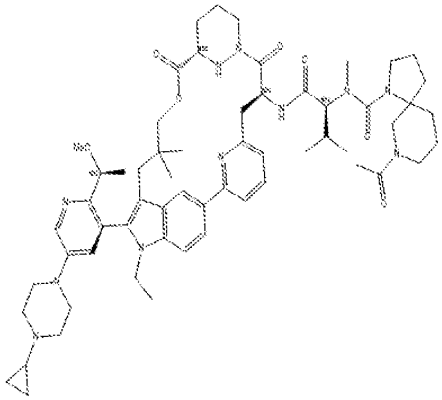
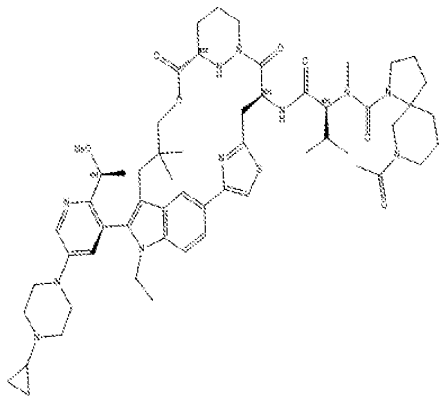
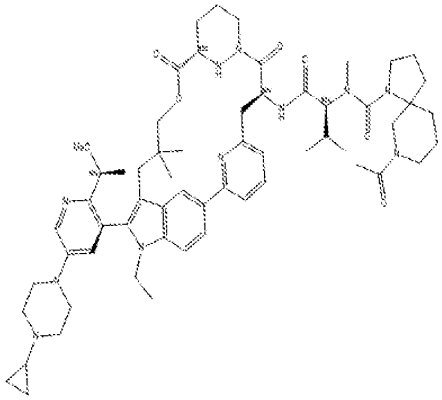
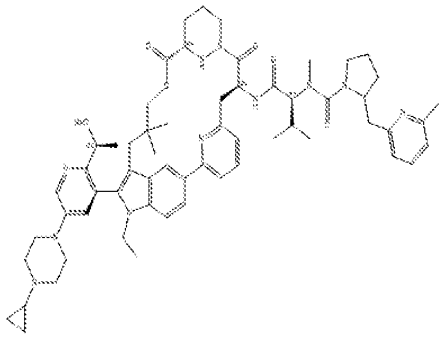
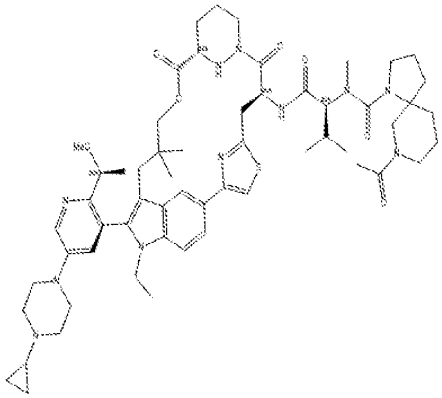
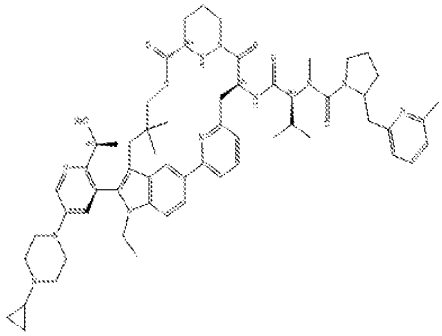
A673		A676	
A674		A677	
A675		A678	

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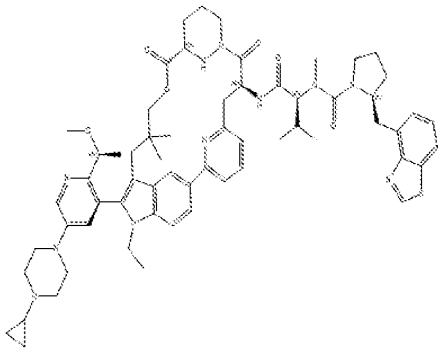
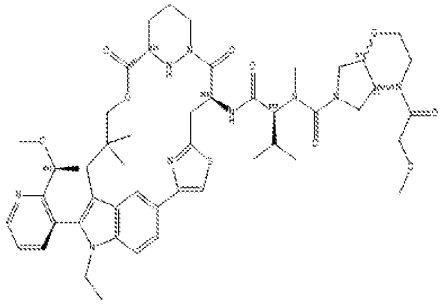
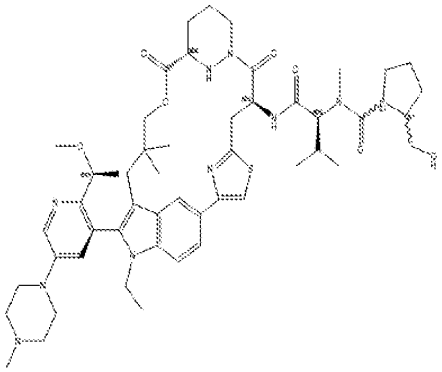
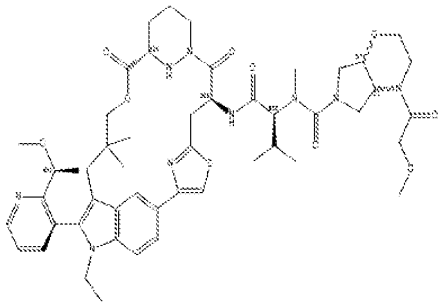
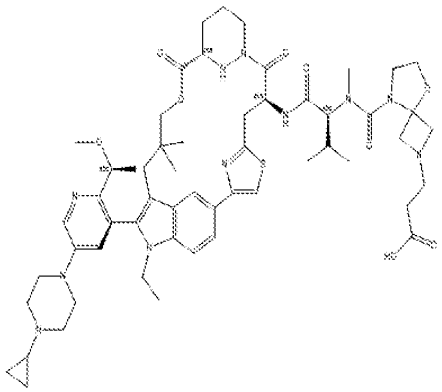
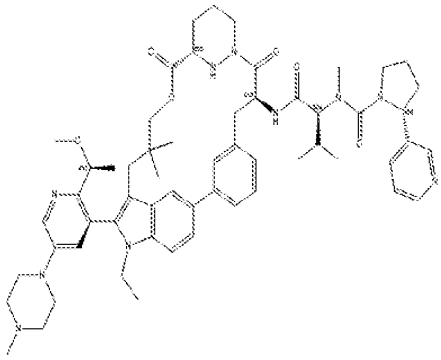
A679		A682	
A680		A683	
A681		A684	

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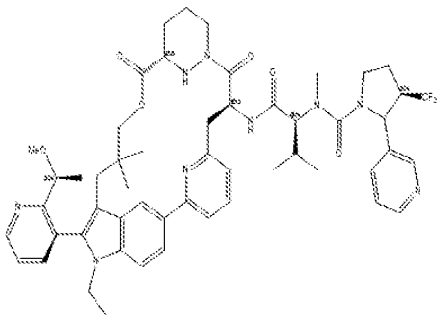
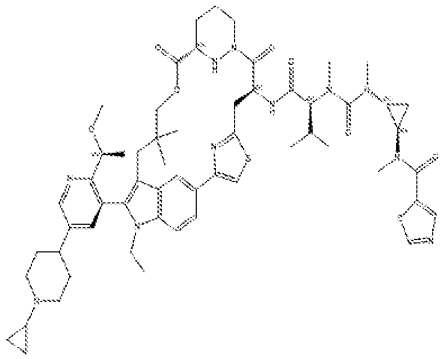
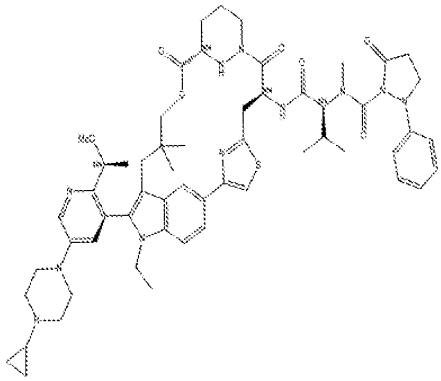
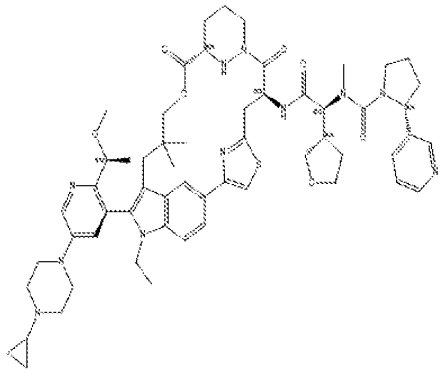
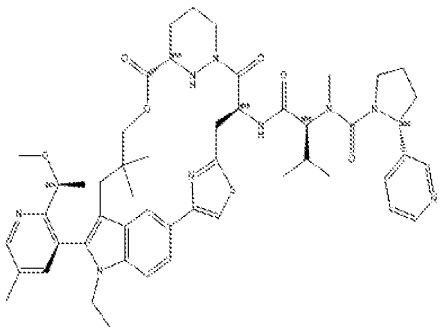
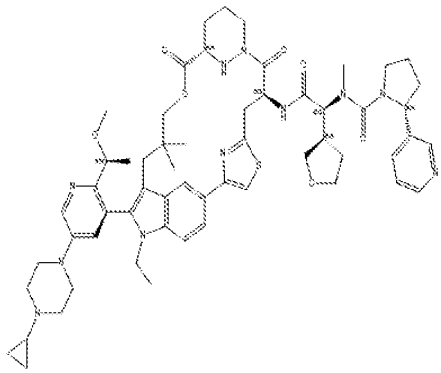
A685		A688	
A686		A689	
A687		A690	

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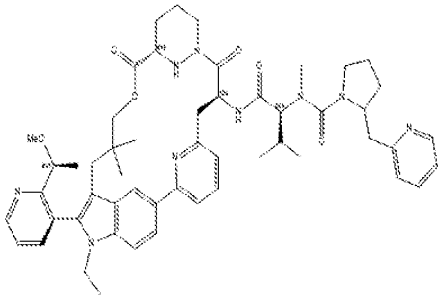
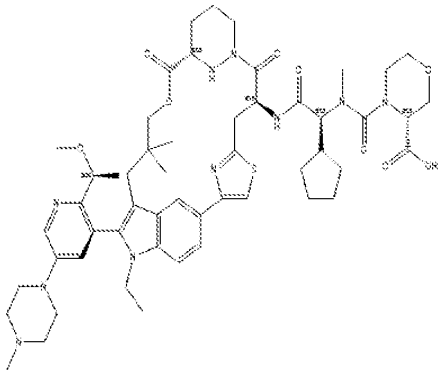
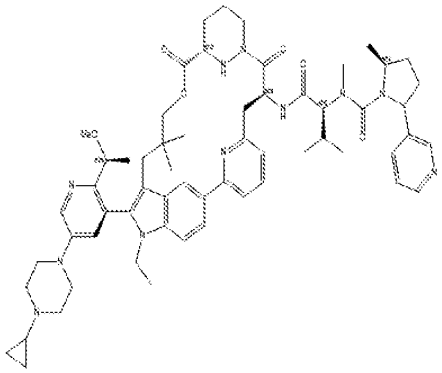
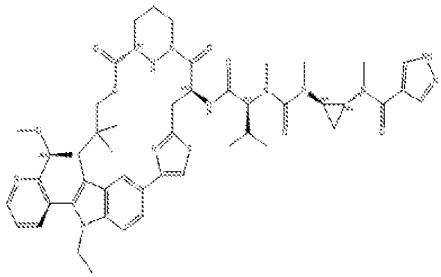
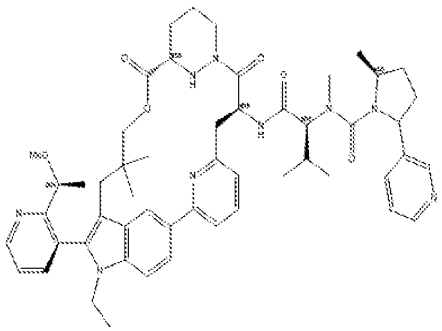
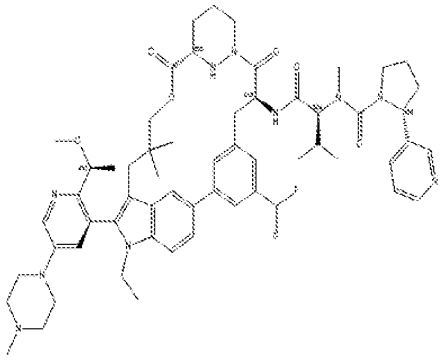
A691		A694	
A692		A695	
A693		A696	

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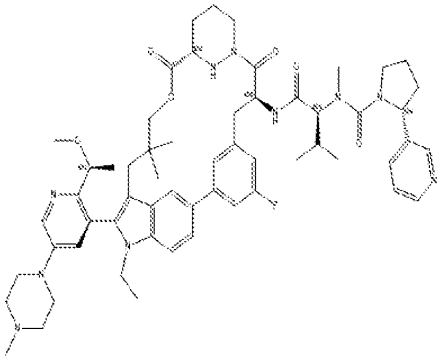
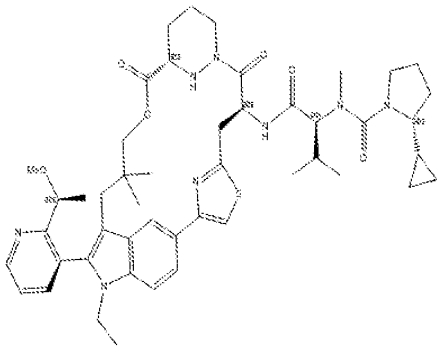
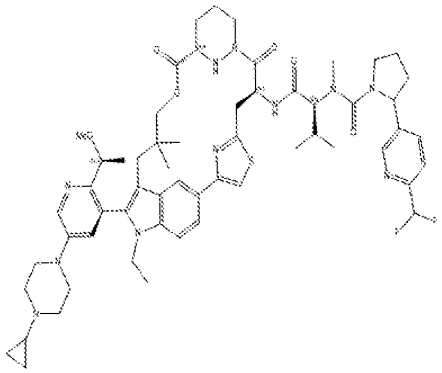
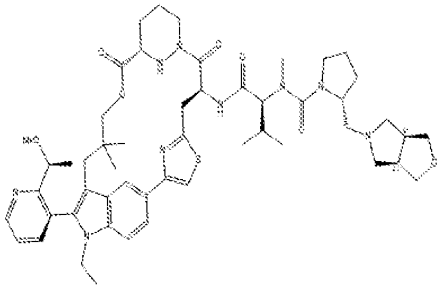
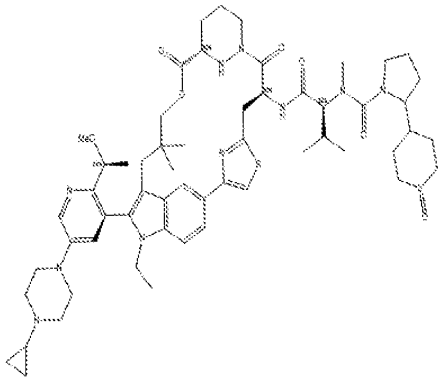
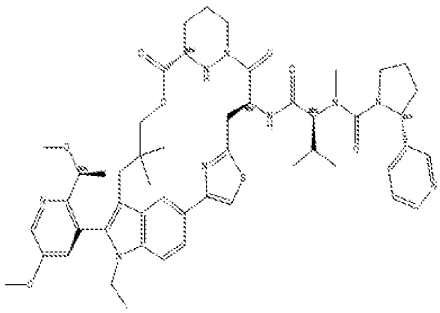
A697		A700	
A698		A701	
A699		A702	

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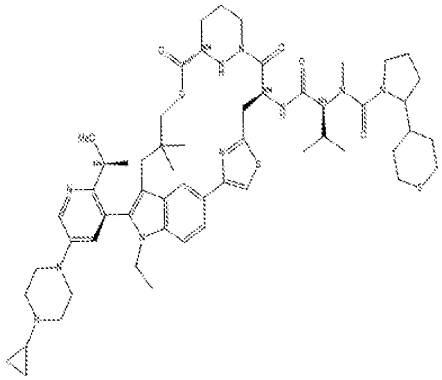
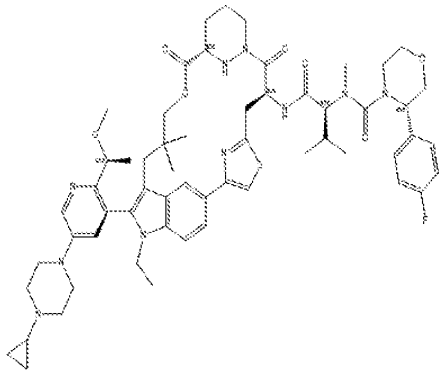
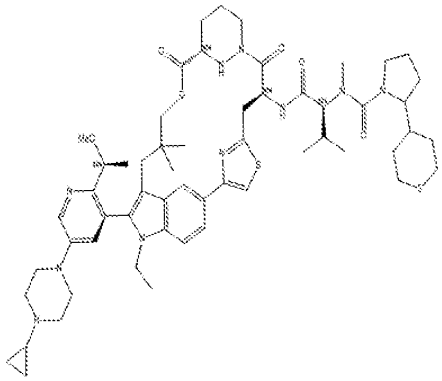
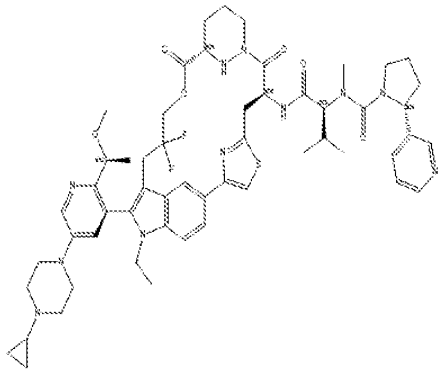
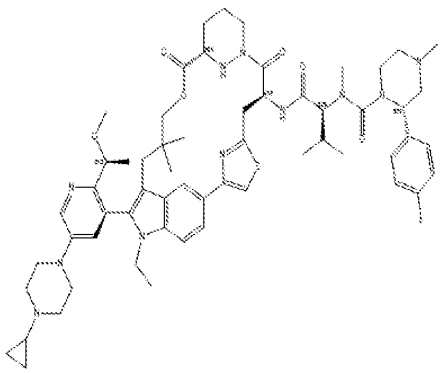
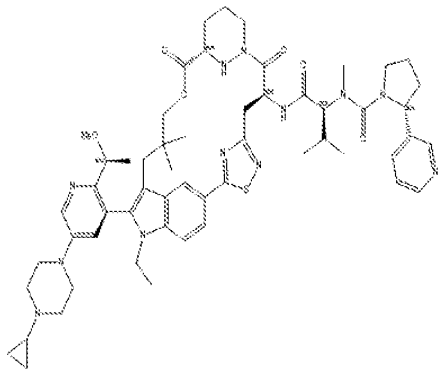
A703		A706	
A704		A707	
A705		A708	

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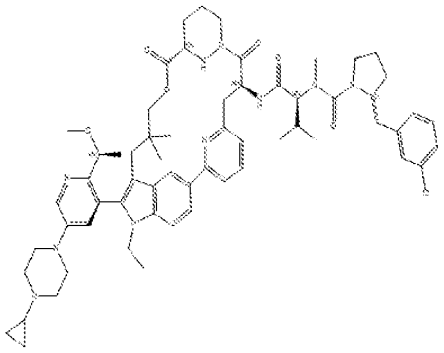
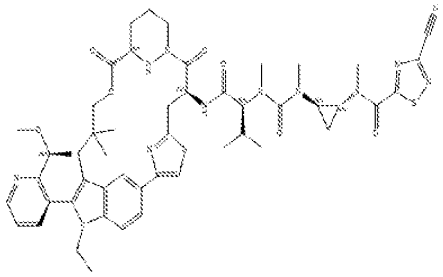
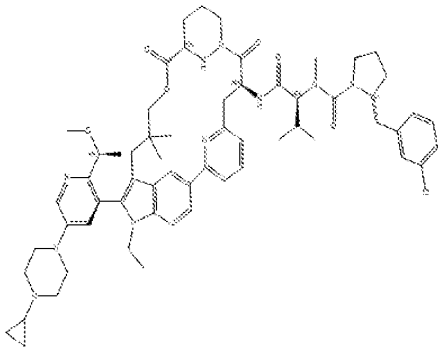
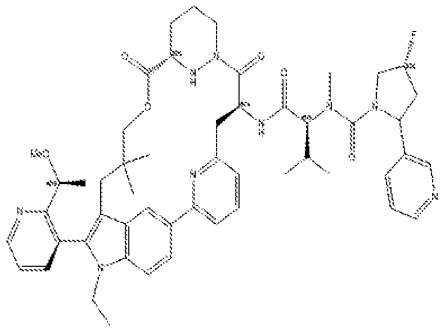
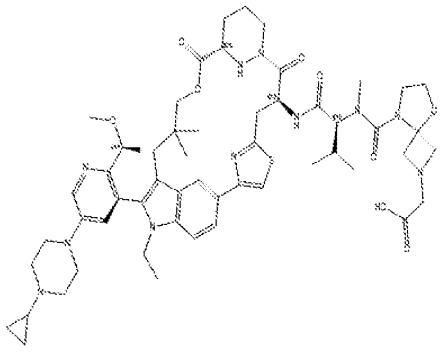
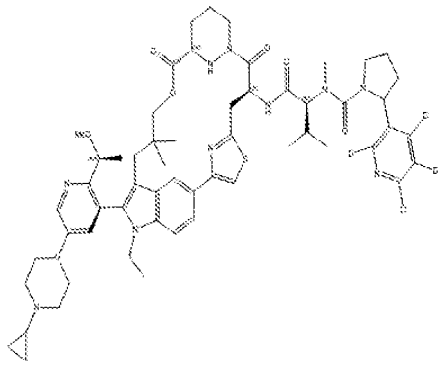
A709		A712	
A710		A713	
A711		A714	

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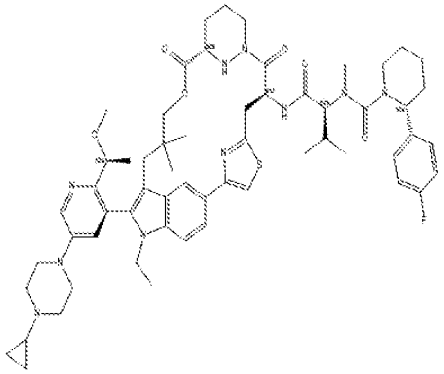
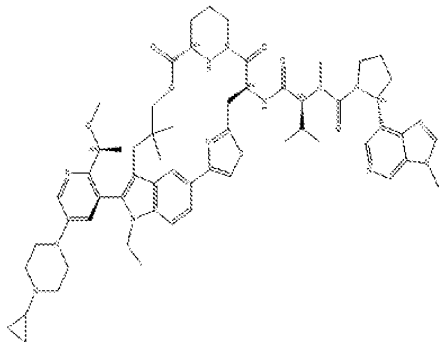
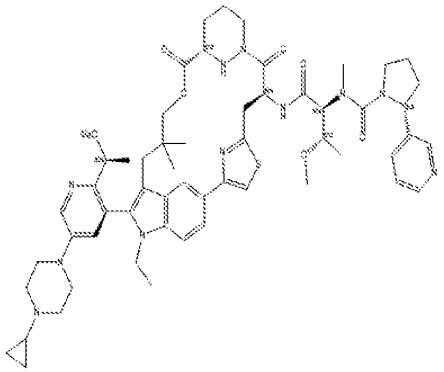
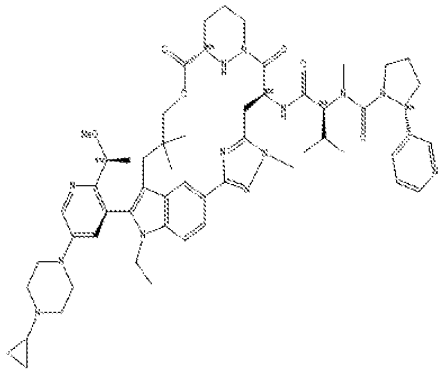
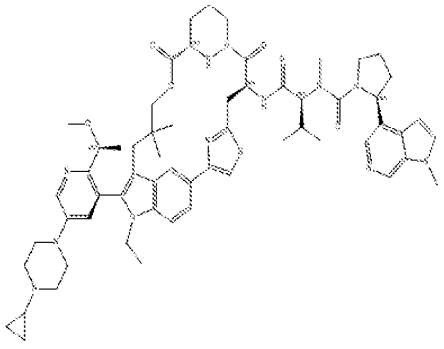
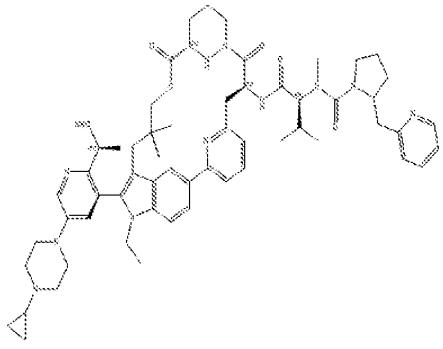
A715		A718	
A716		A719	
A717		A720	

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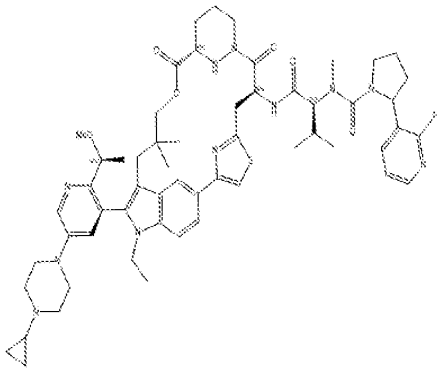
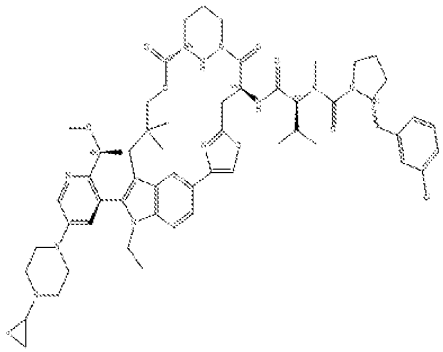
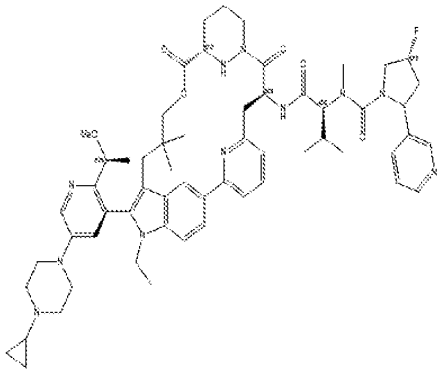
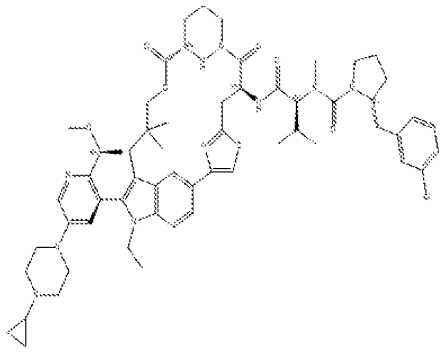
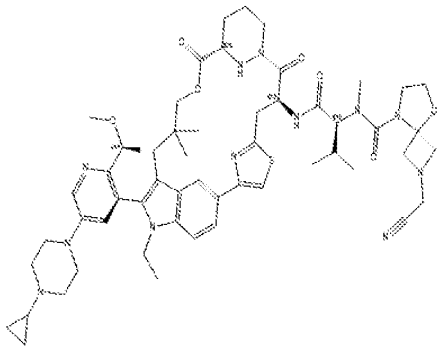
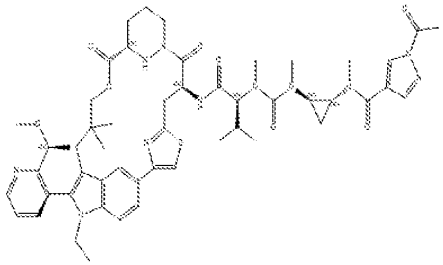
A721		A724	
A722		A725	
A723		A726	

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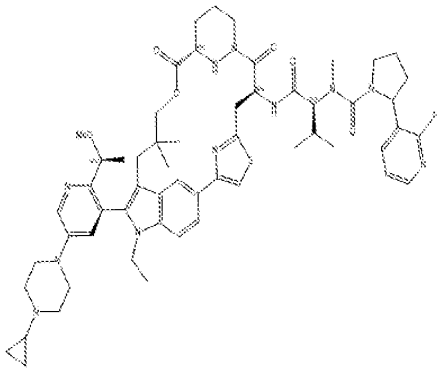
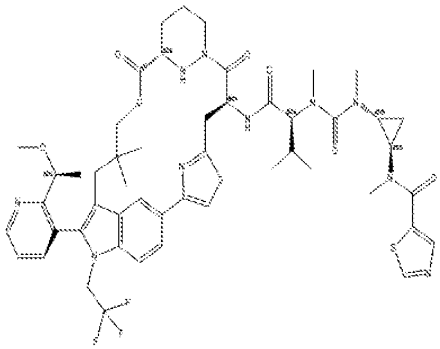
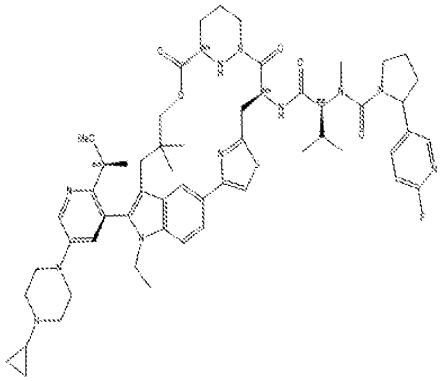
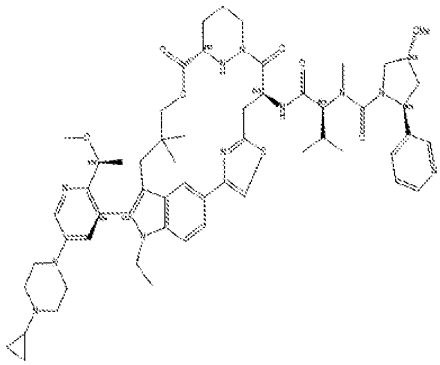
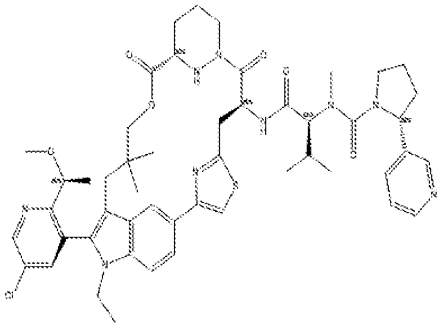
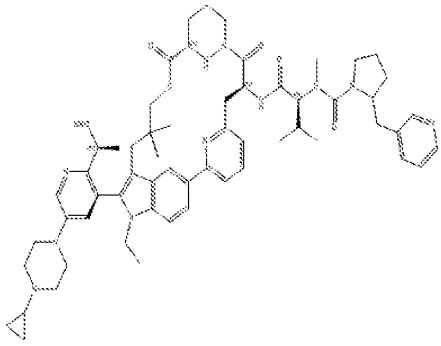
A727		A730	
A728		A731	
A729		A732	

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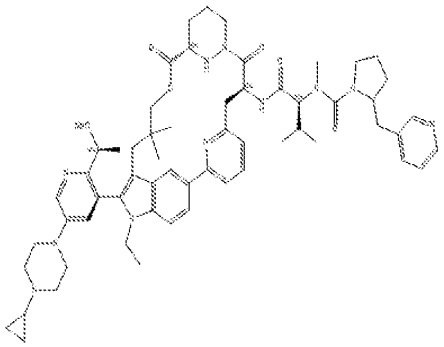
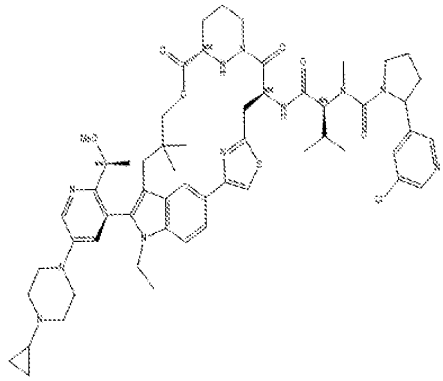
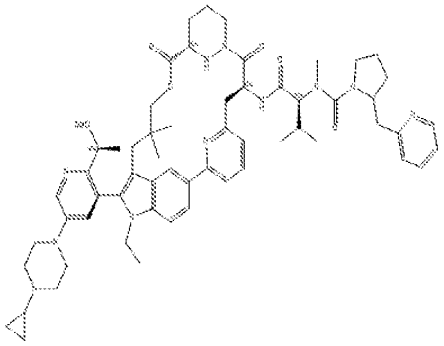
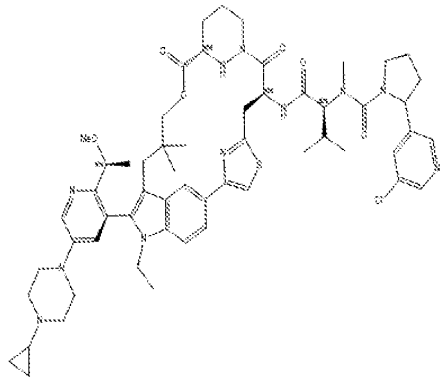
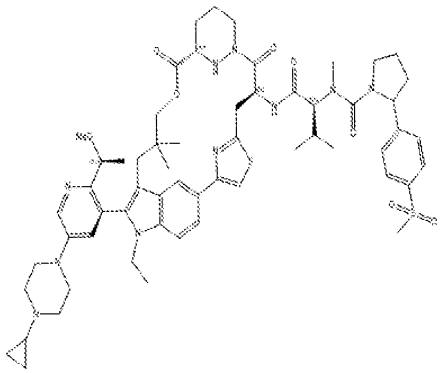
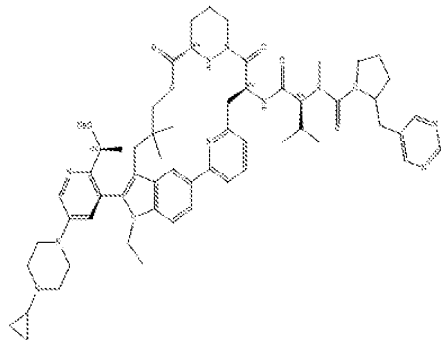
A733		A736	
A734		A737	
A735		A738	

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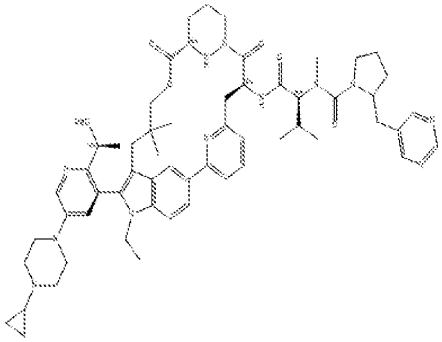
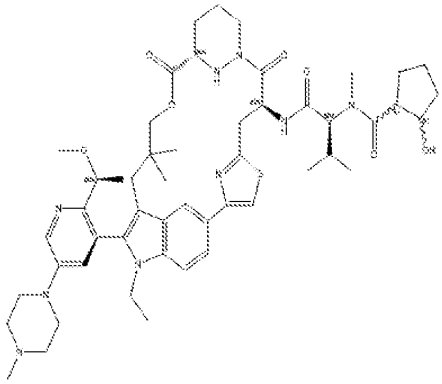
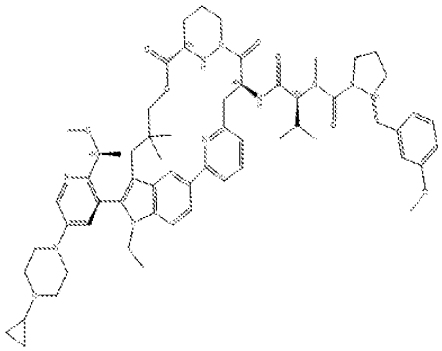
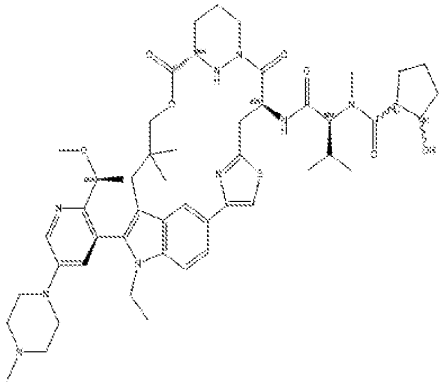
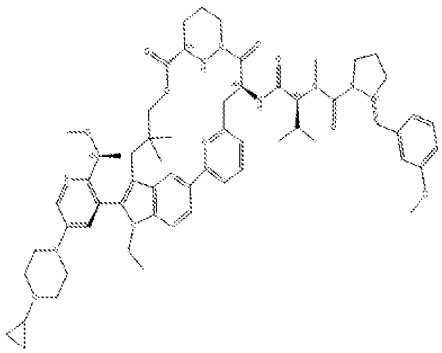
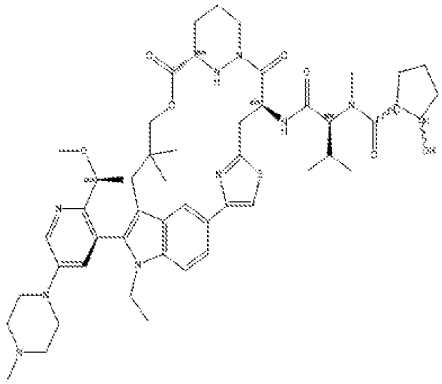
A739		A742	
A740		A743	
A741		A744	

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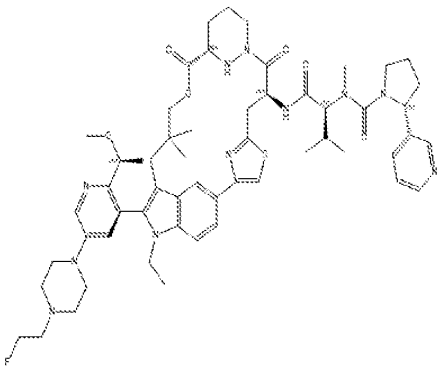
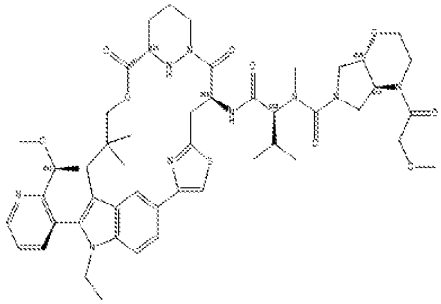
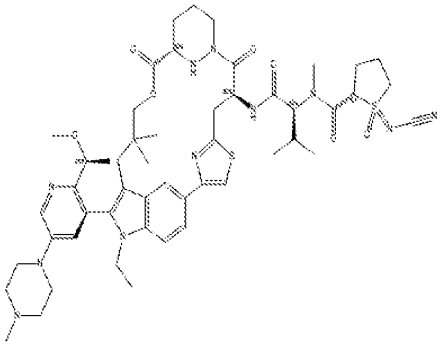
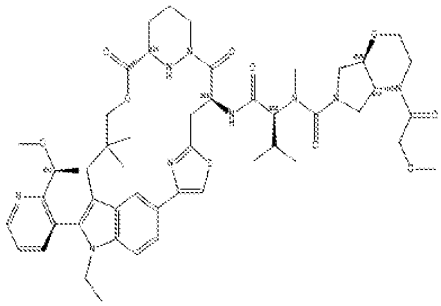
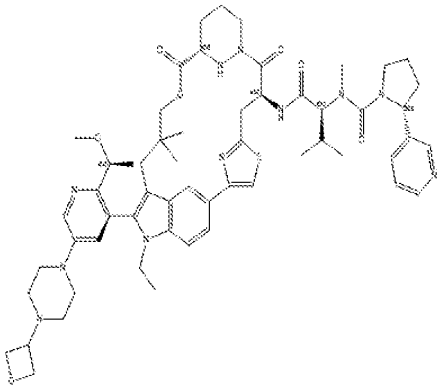
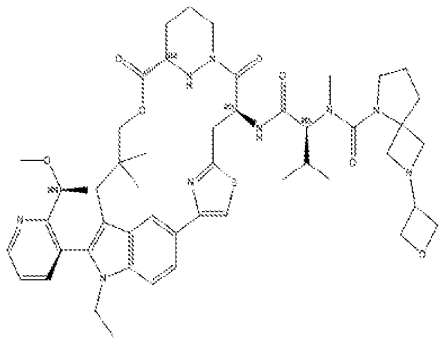
A745		A748	
A746		A749	
A747		A750	

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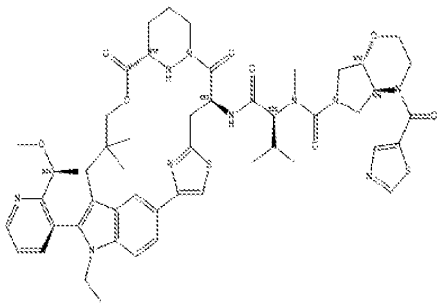
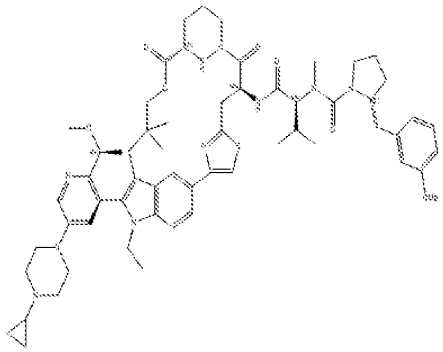
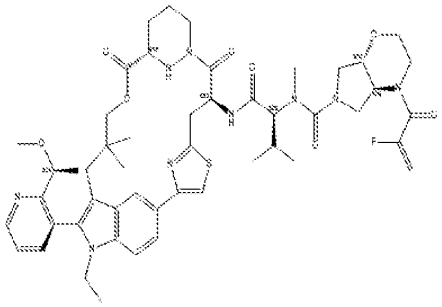
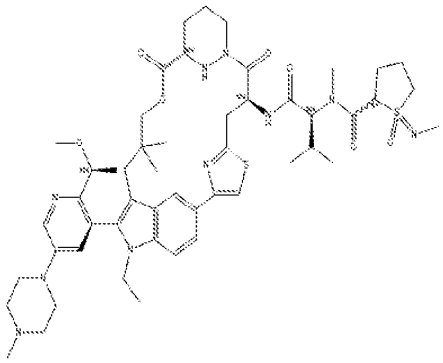
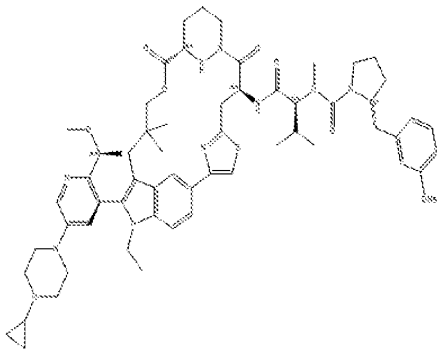
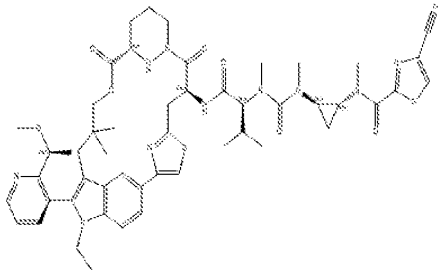
A751		A754	
A752		A755	
A753		A756	

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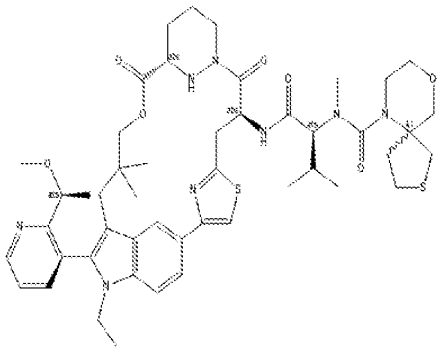
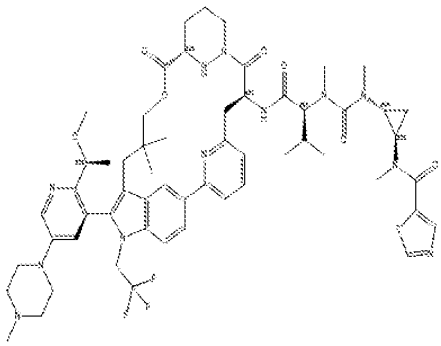
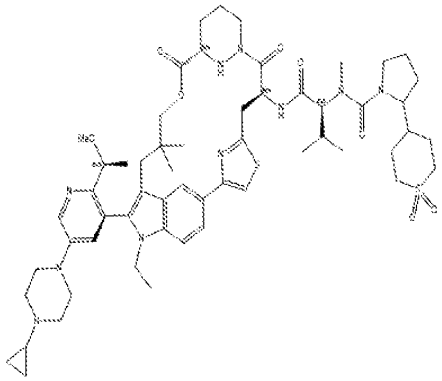
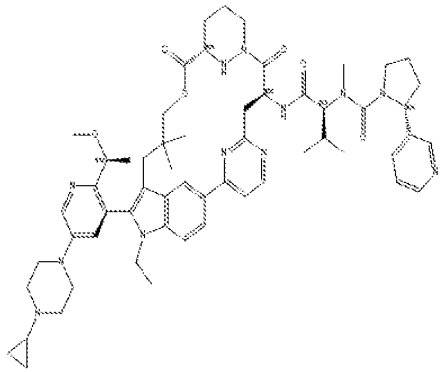
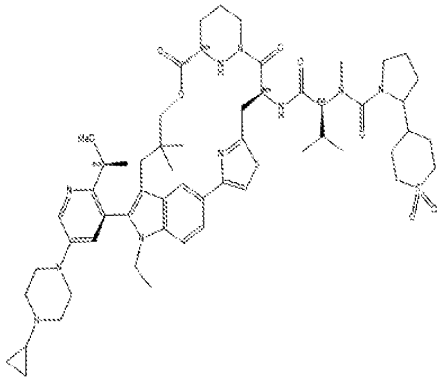
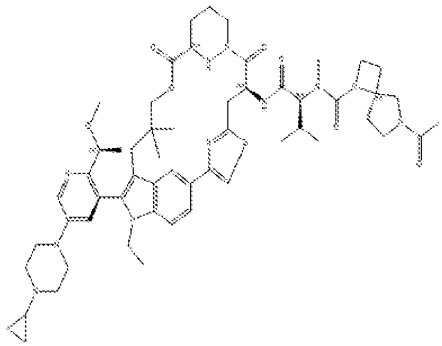
A757		A760	
A758		A761	
A759		A762	

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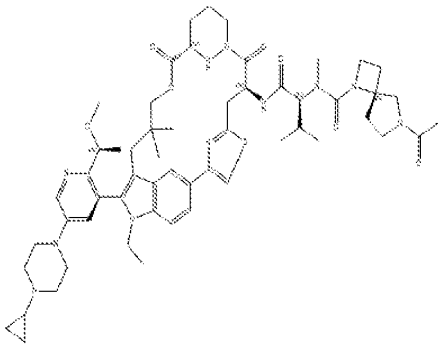
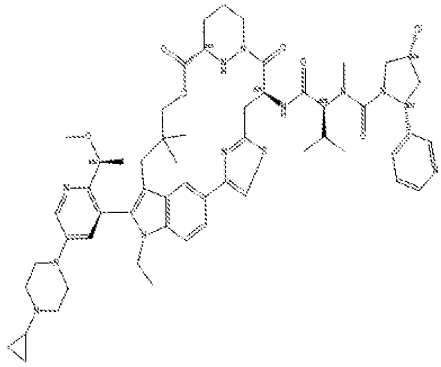
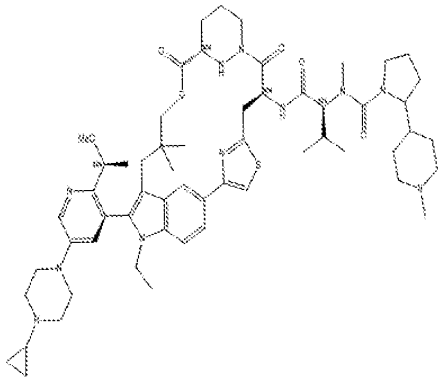
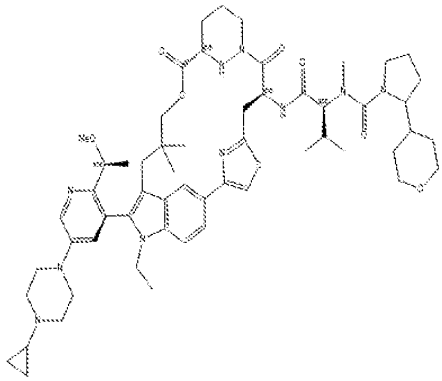
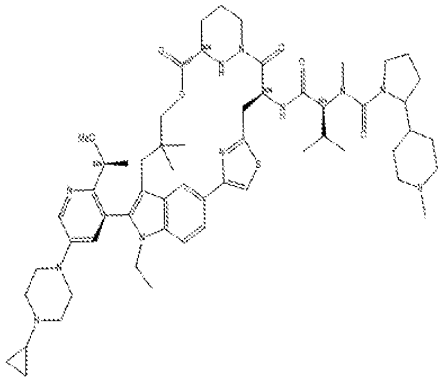
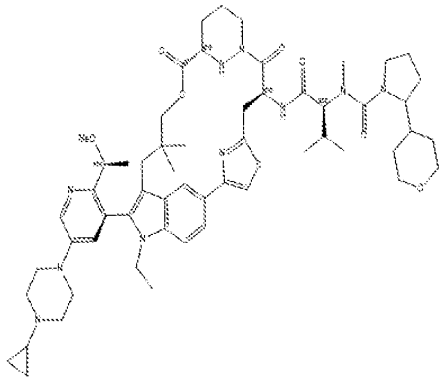
A763		A766	
A764		A767	
A765		A768	

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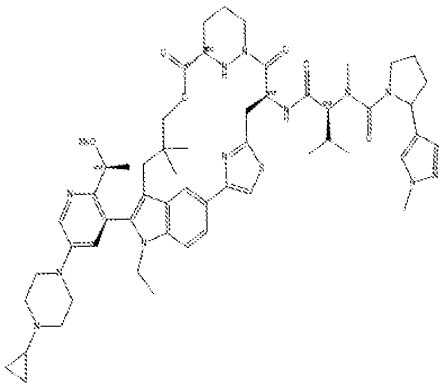
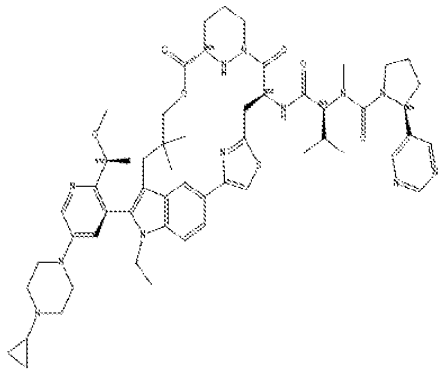
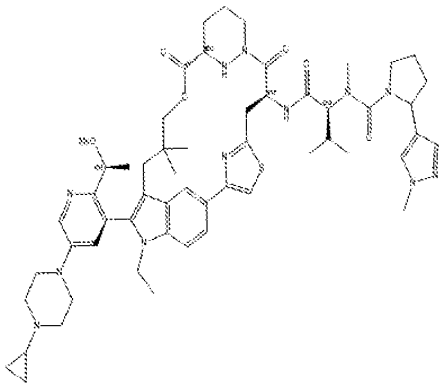
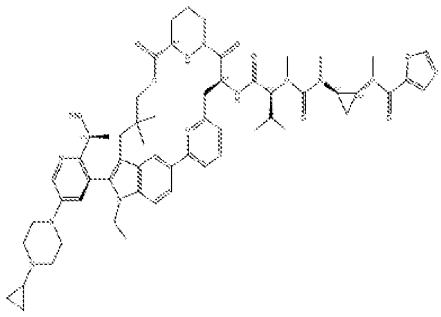
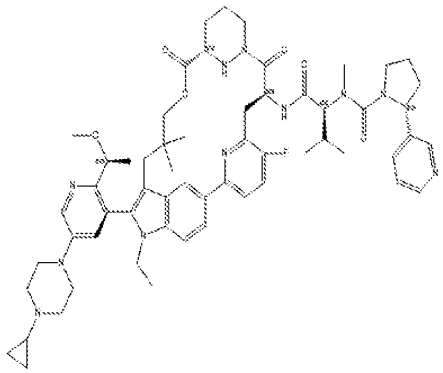
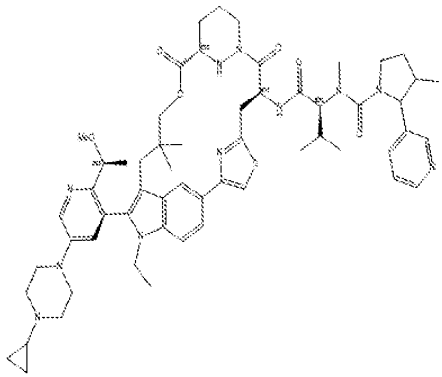
A769		A772	
A770		A773	
A771		A774	

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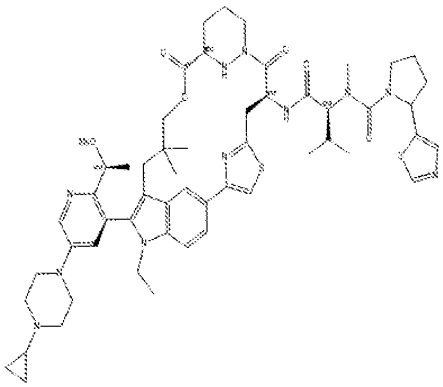
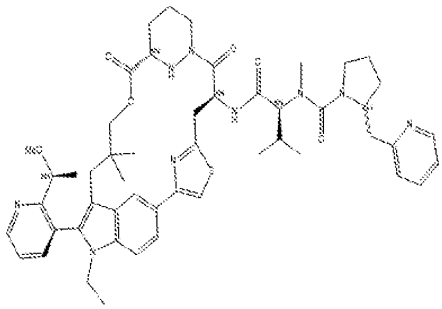
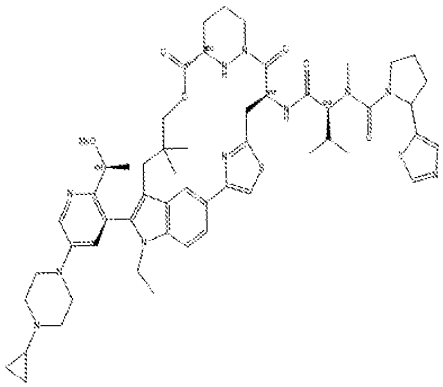
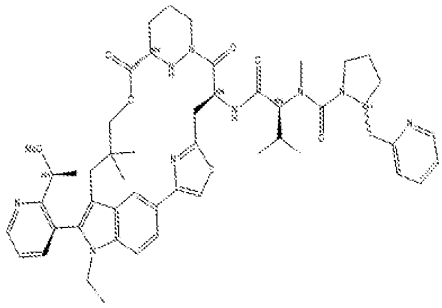
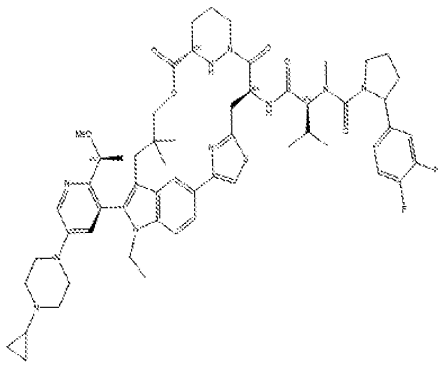
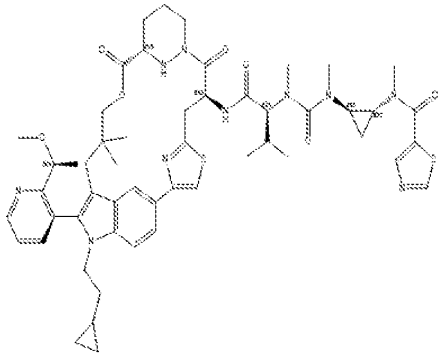
A775		A778	
A776		A779	
A777		A780	

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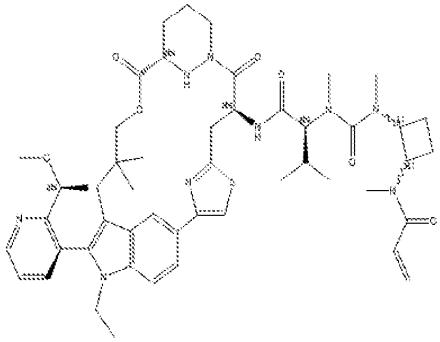
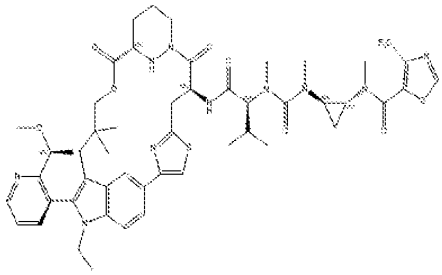
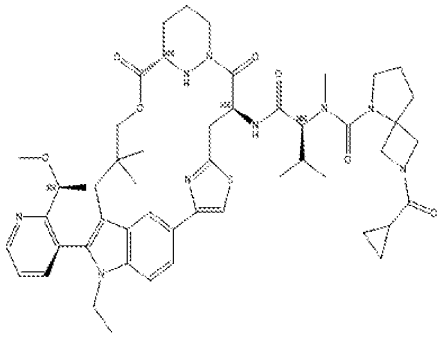
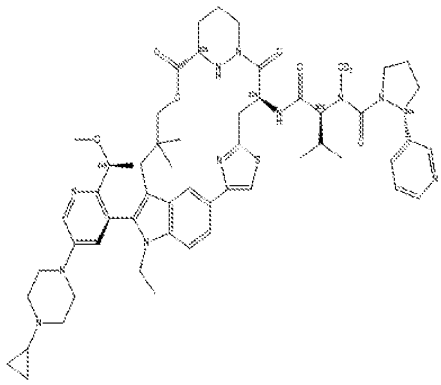
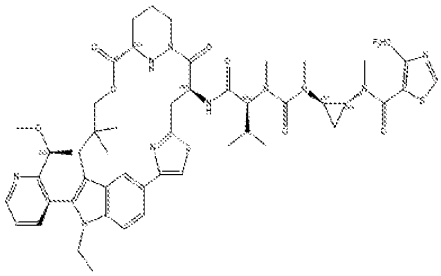
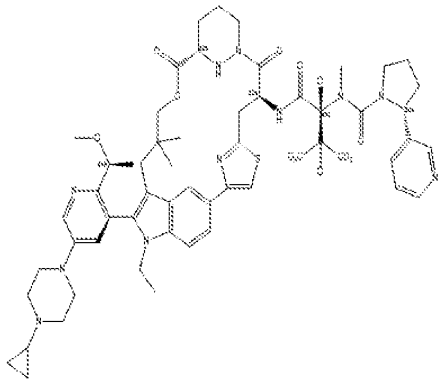
A781		A784	
A782		A785	
A783		A786	

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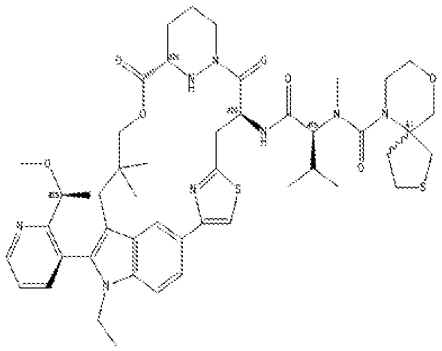
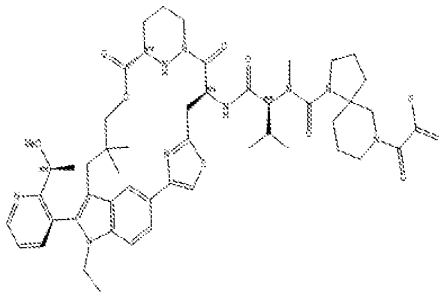
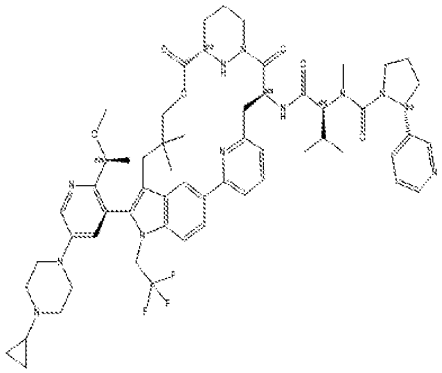
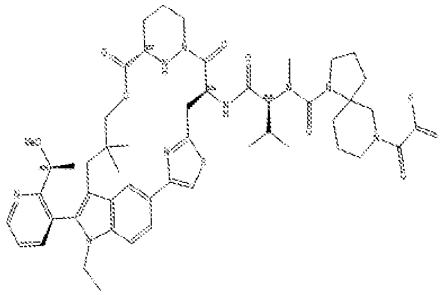
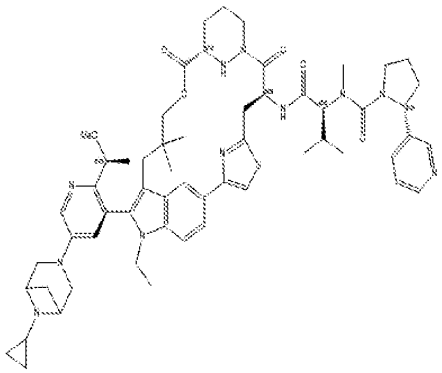
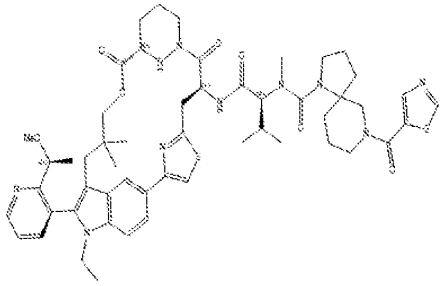
A787		A790	
A788		A791	
A789		A792	

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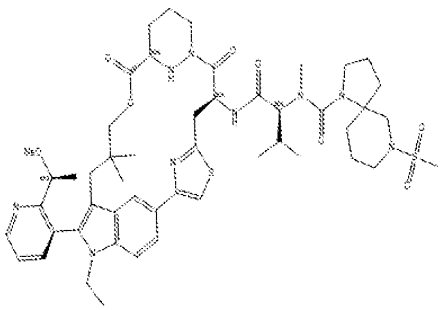
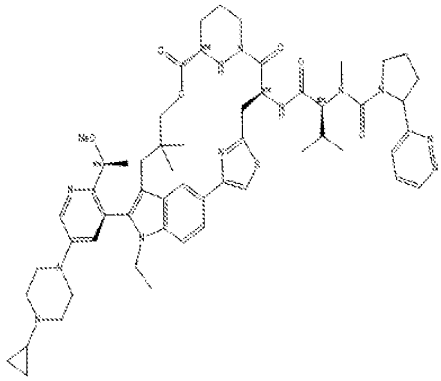
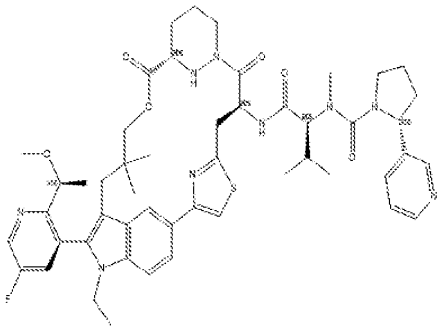
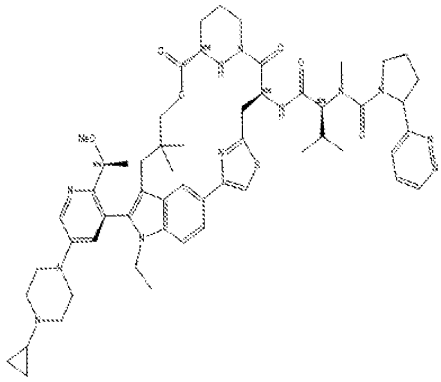
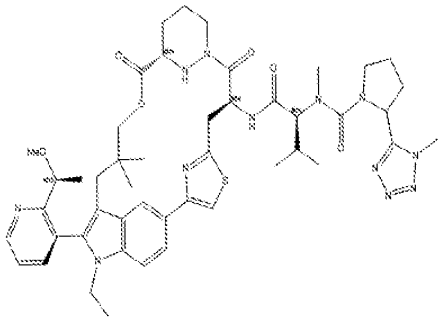
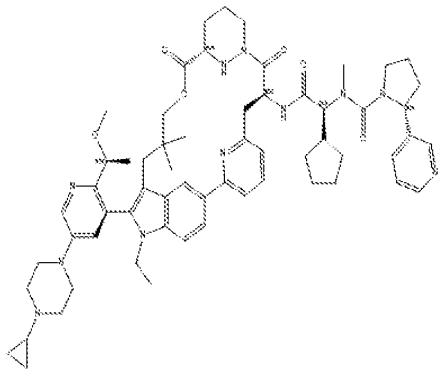
A793		A796	
A794		A797	
A795		A798	

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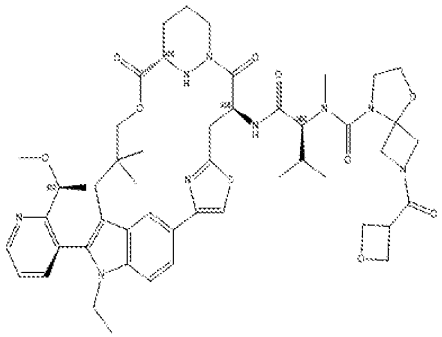
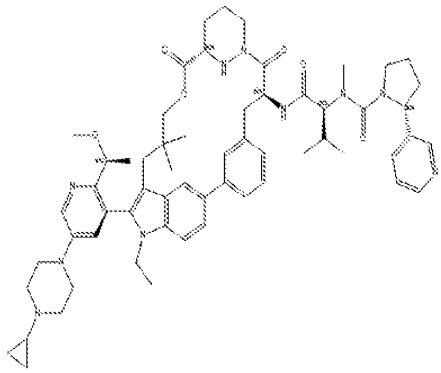
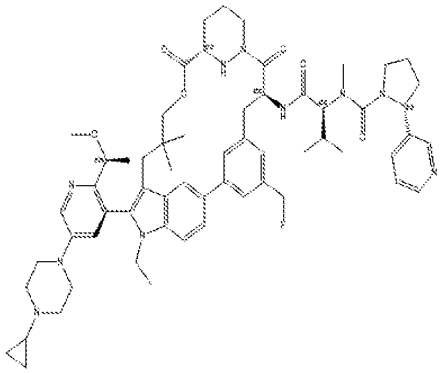
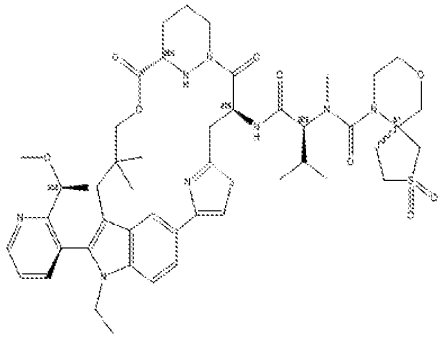
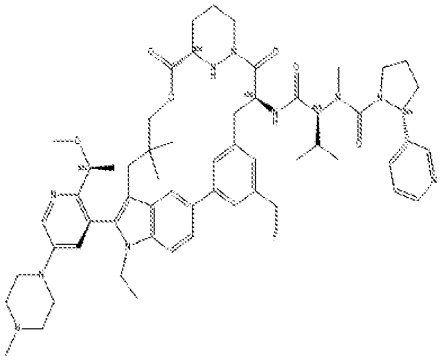
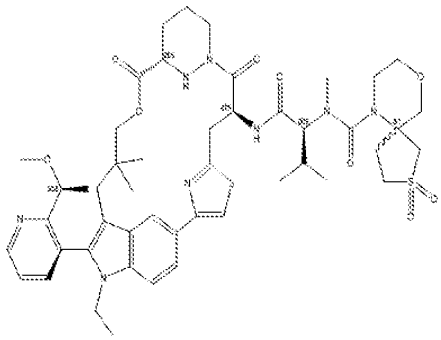
A799		A802	
A800		A803	
A801		A804	

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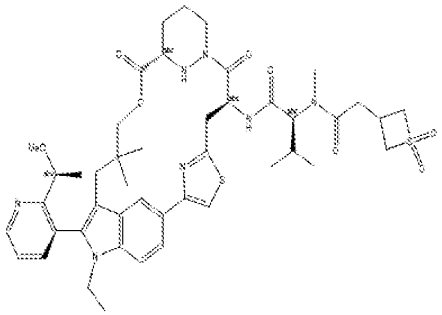
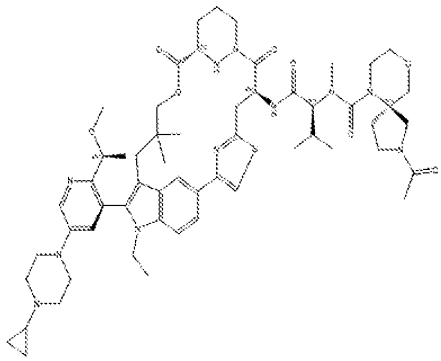
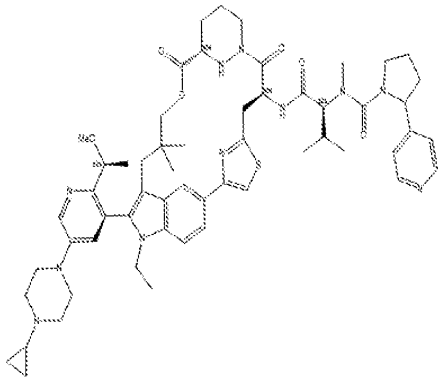
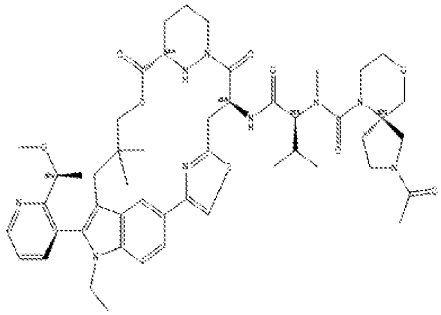
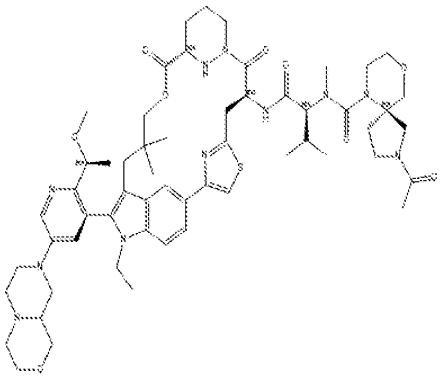
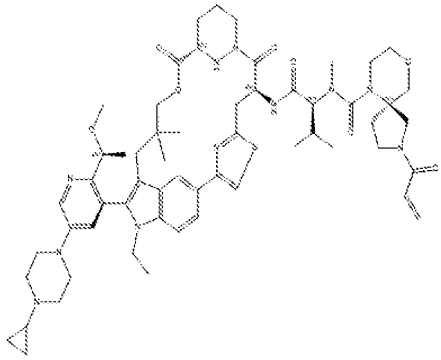
A805		A808	
A806		A809	
A807		A810	

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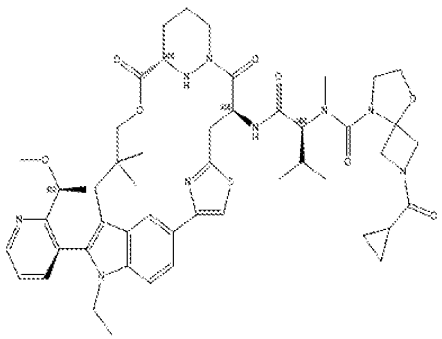
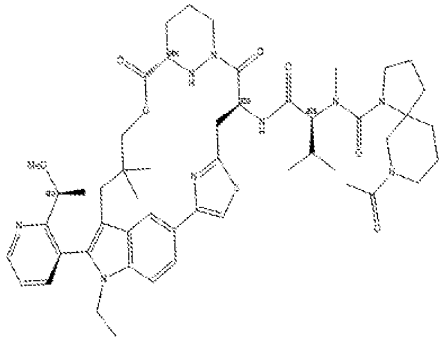
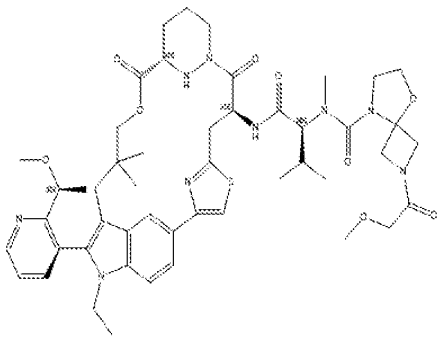
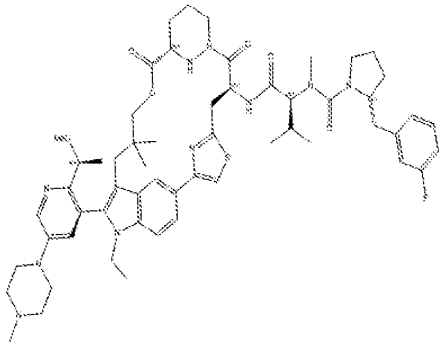
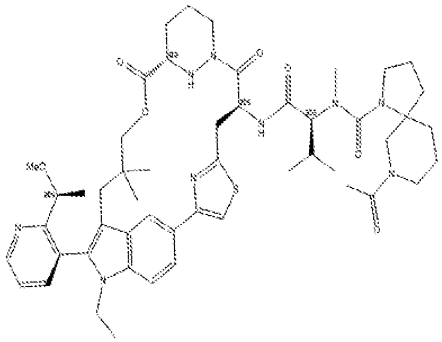
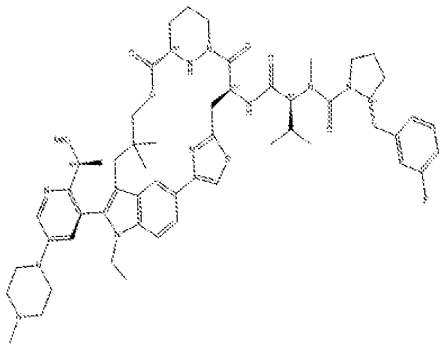
A811		A814	
A812		A815	
A813		A816	

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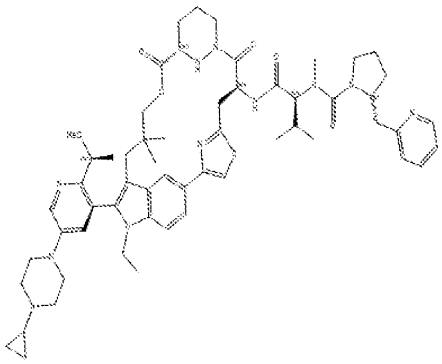
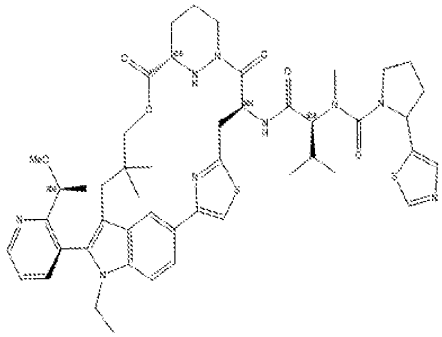
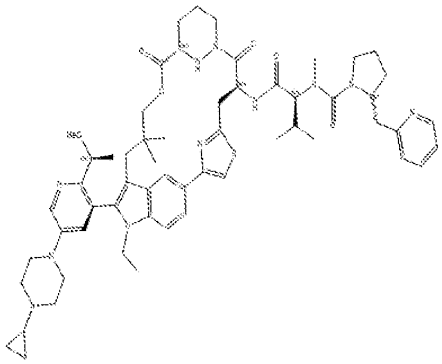
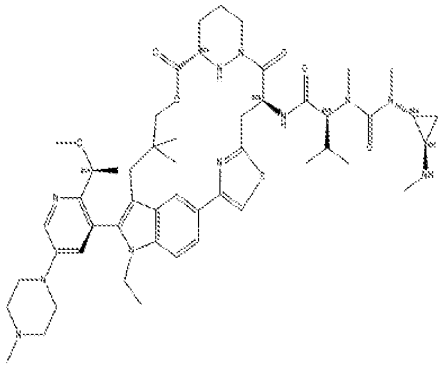
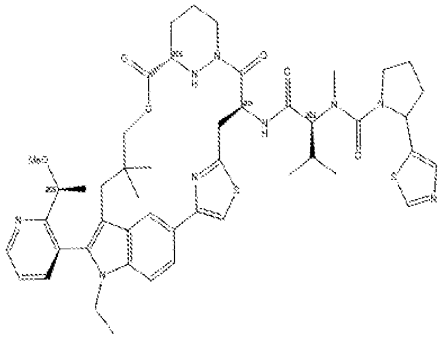
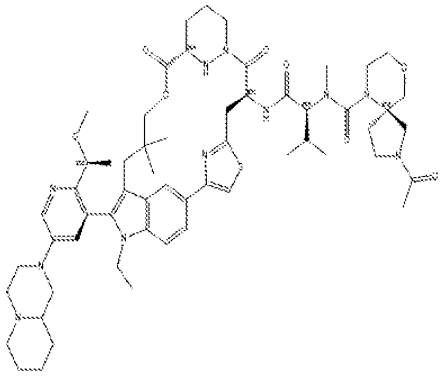
A817		A820	
A818		A821	
A819		A822	

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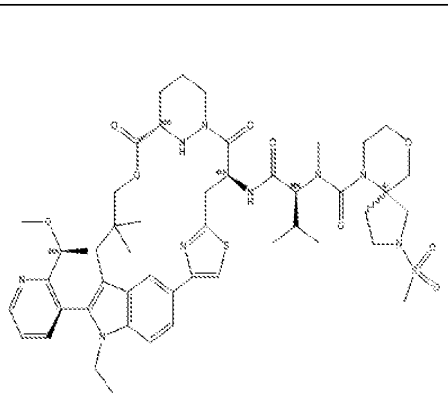
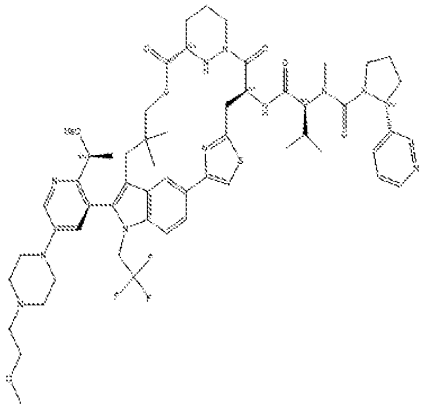
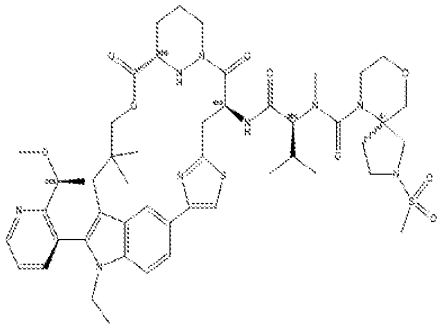
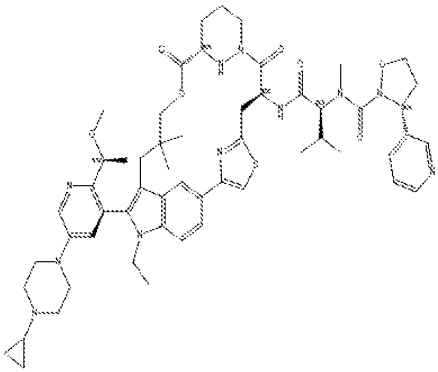
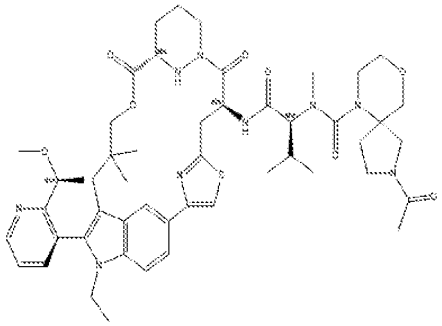
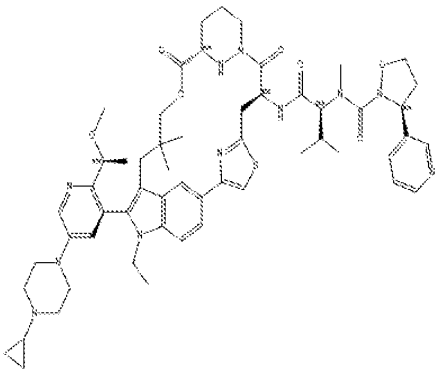
A823		A826	
A824		A827	
A825		A828	

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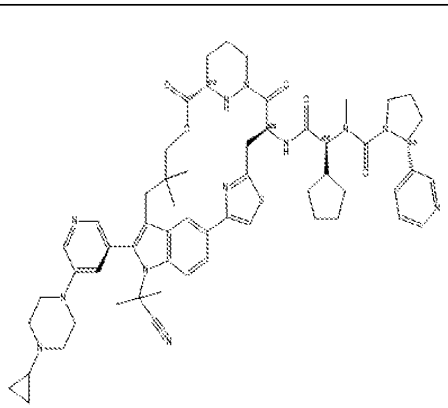
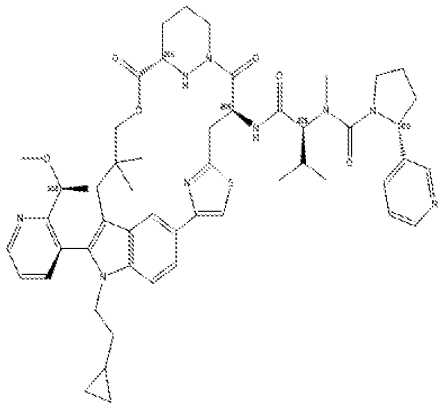
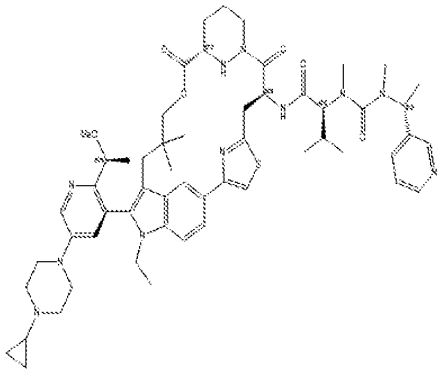
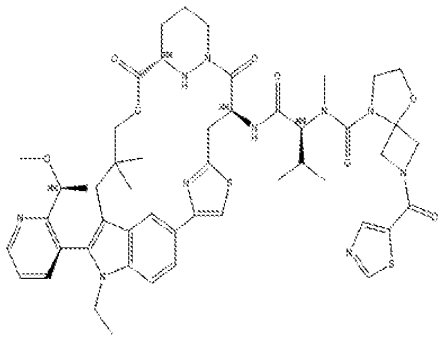
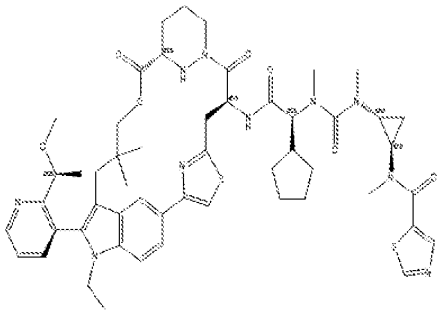
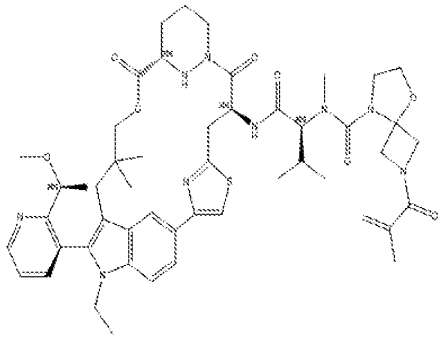
A829		A832	
A830		A833	
A831		A834	

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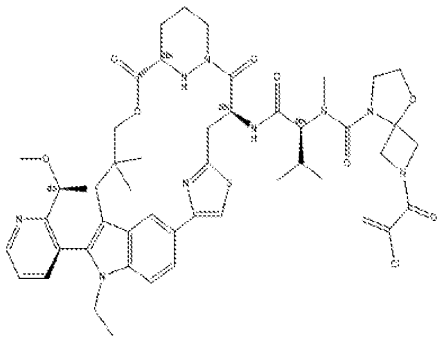
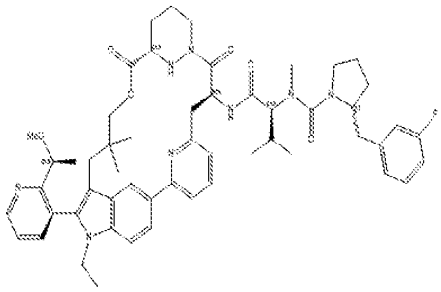
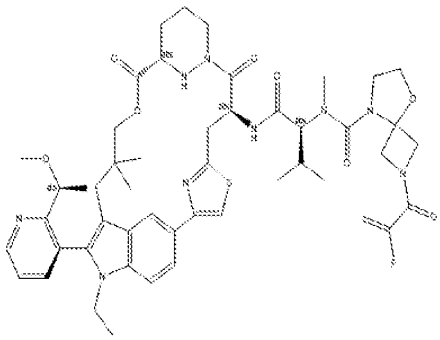
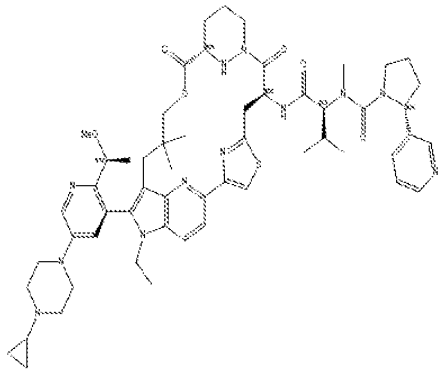
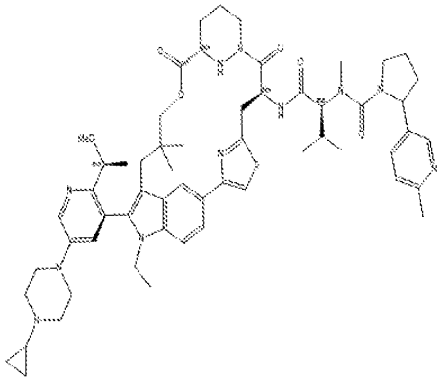
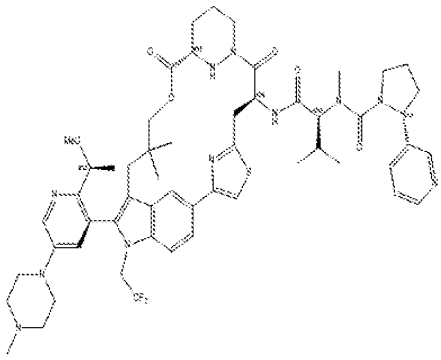
A835		A838	
A836		A839	
A837		A840	

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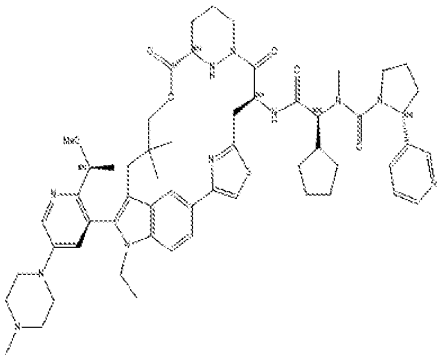
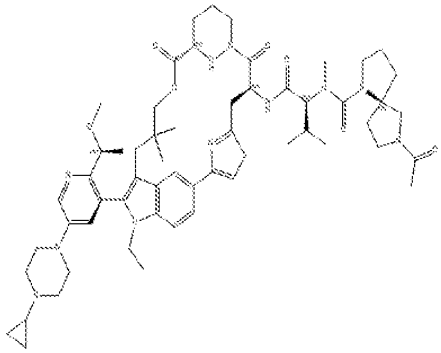
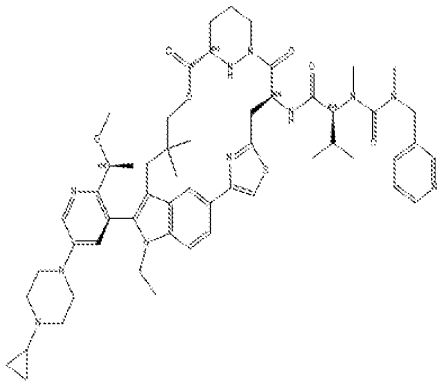
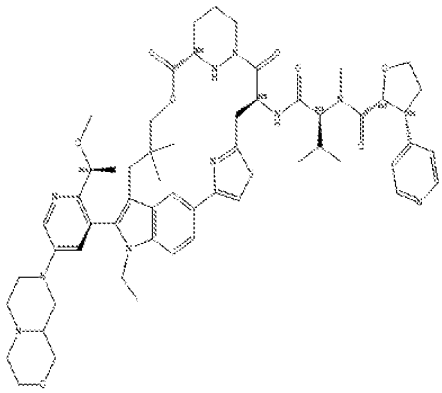
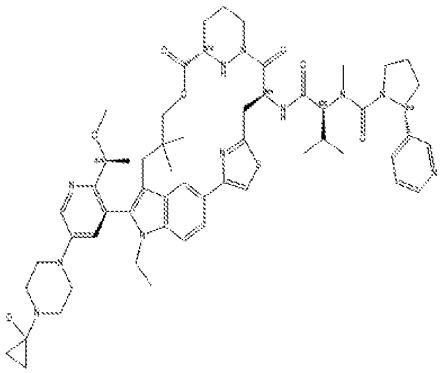
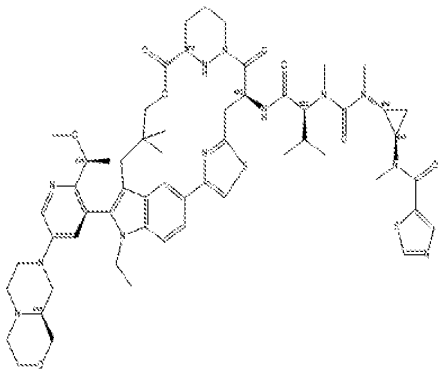
A841		A844	
A842		A845	
A843		A846	

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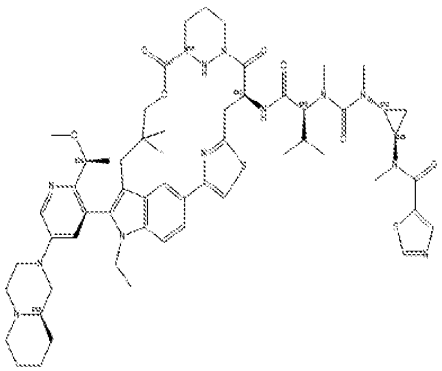
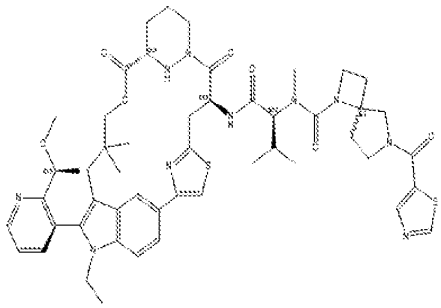
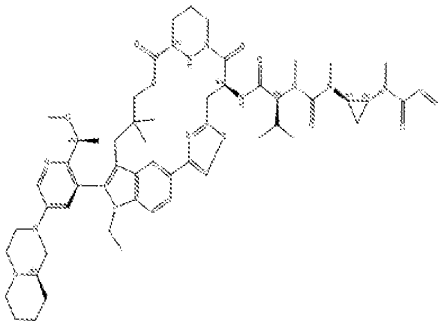
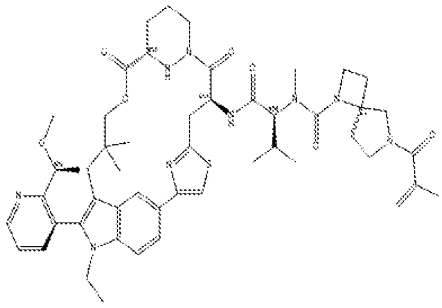
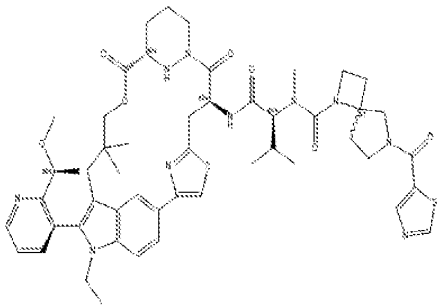
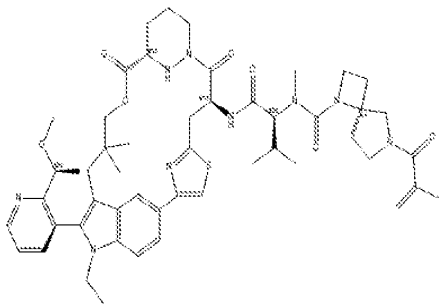
A847		A850	
A848		A851	
A849		A852	

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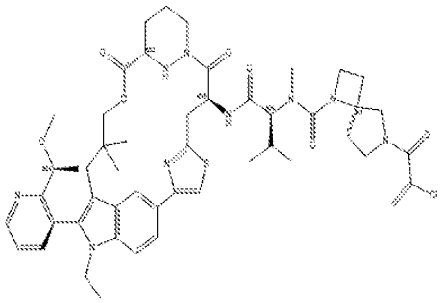
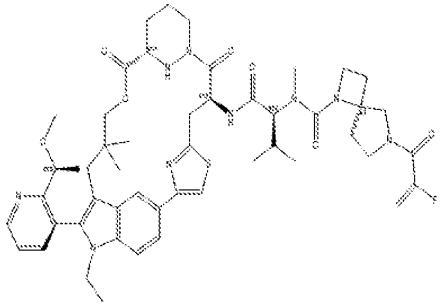
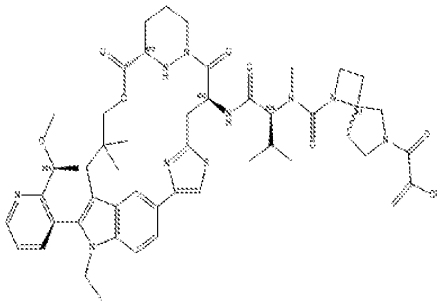
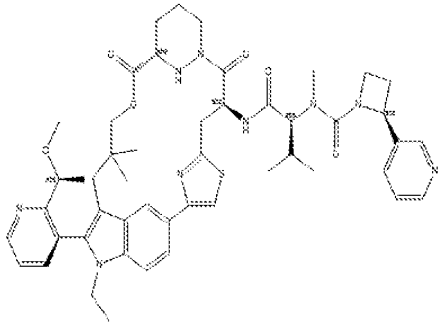
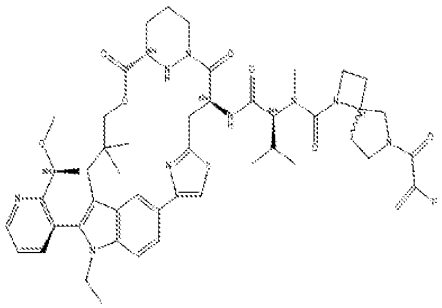
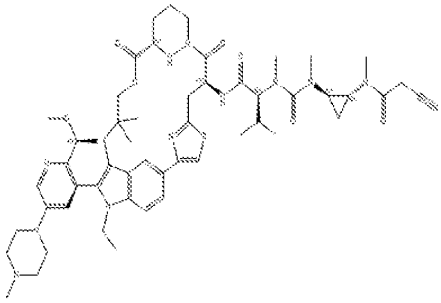
A853		A856	
A854		A857	
A855		A858	

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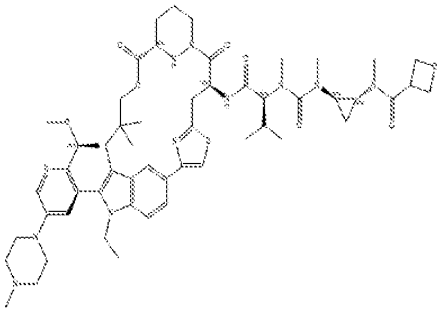
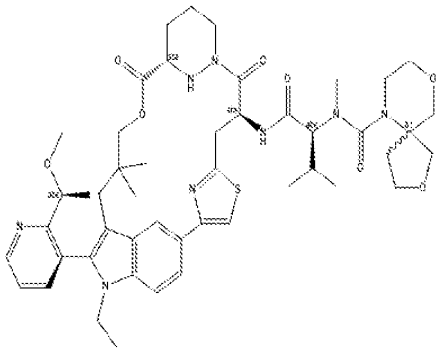
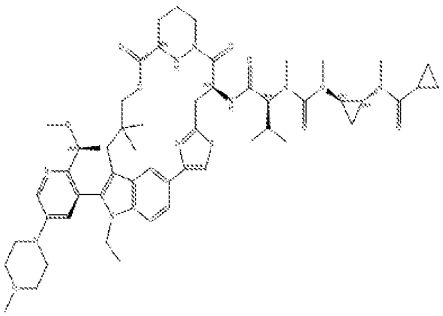
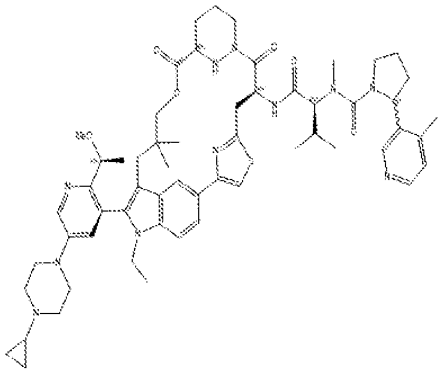
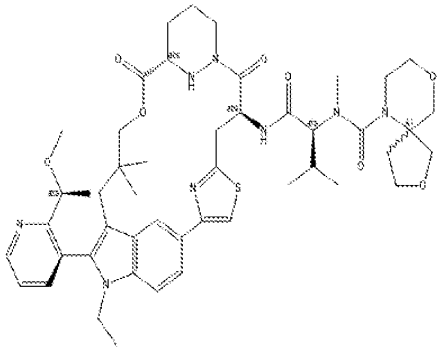
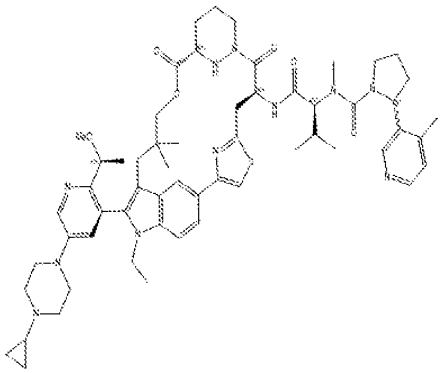
A859		A862	
A860		A863	
A861		A864	

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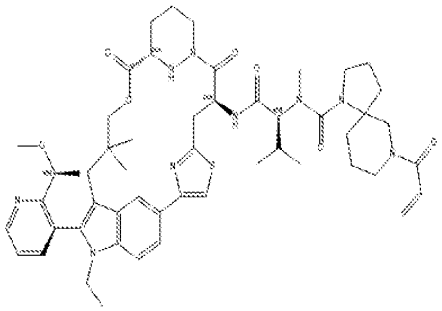
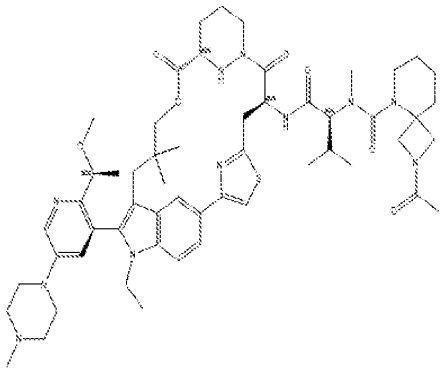
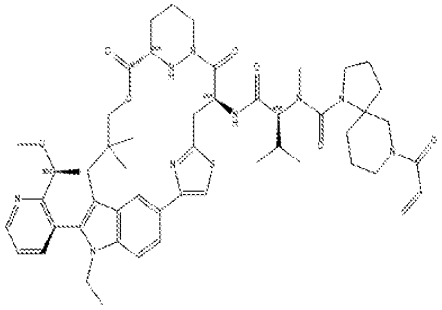
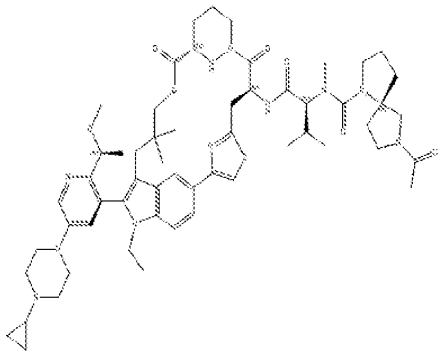
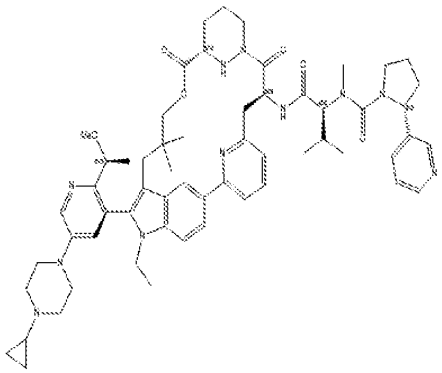
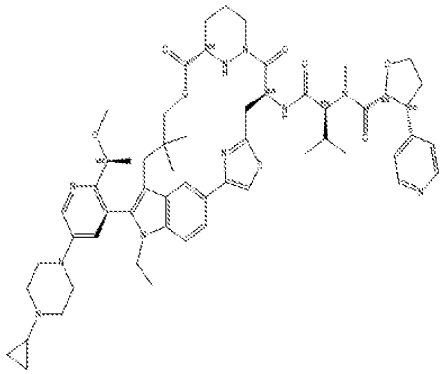
A865		A868	
A866		A869	
A867		A870	

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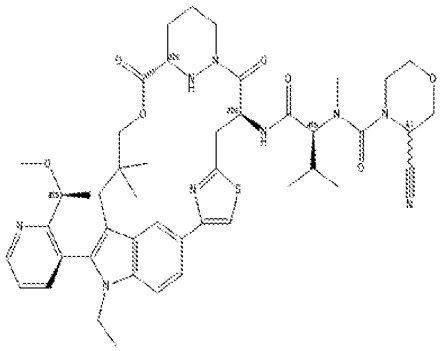
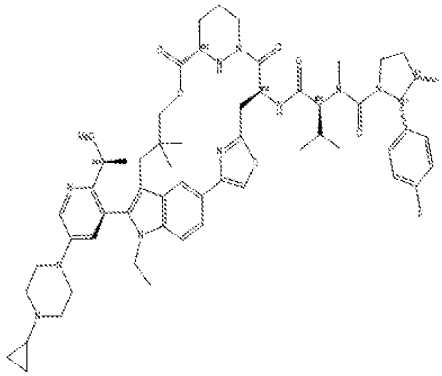
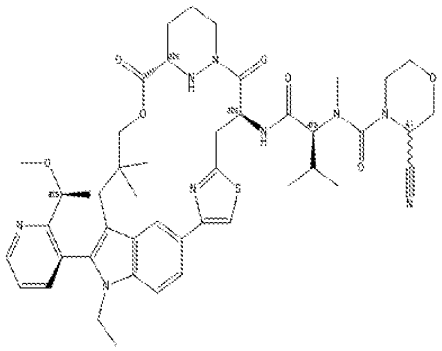
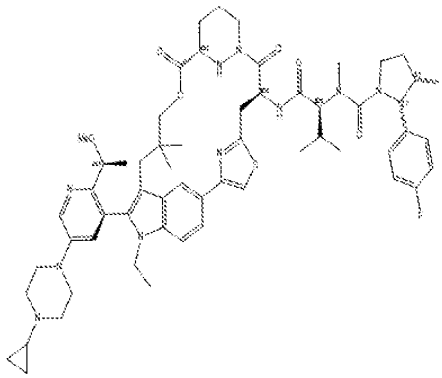
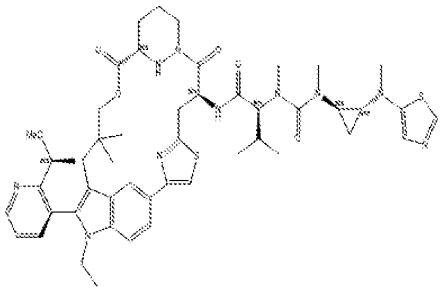
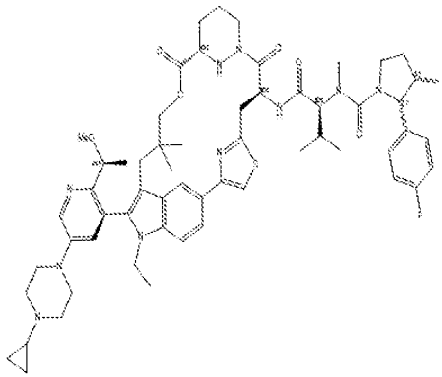
A871		A874	
A872		A875	
A873		A876	

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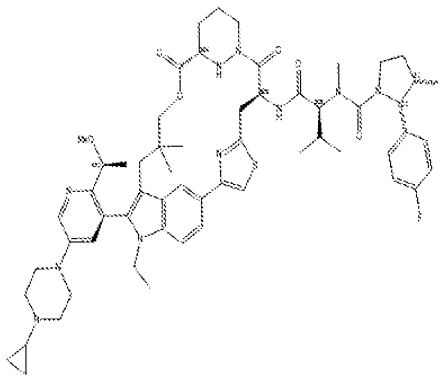
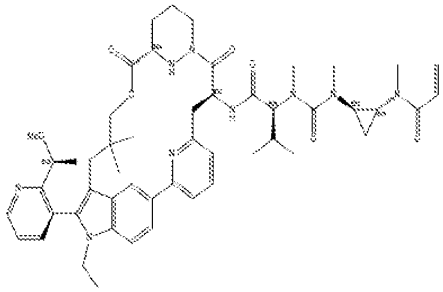
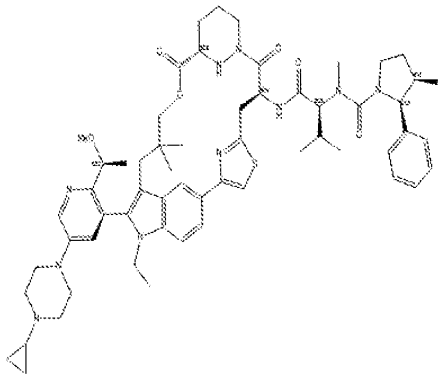
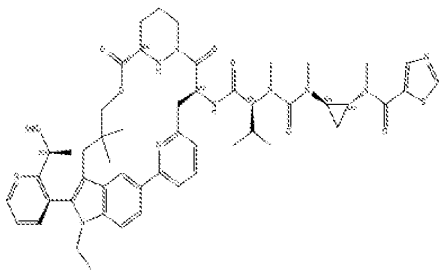
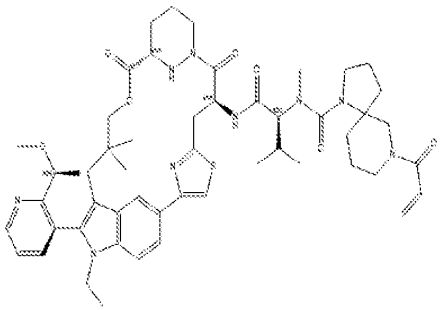
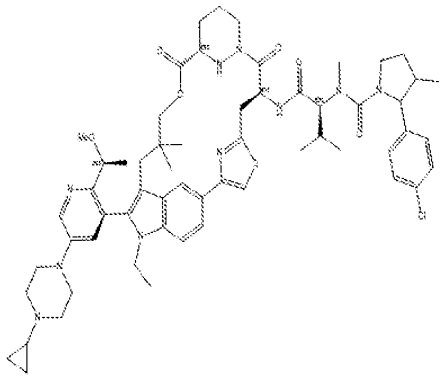
A877		A880	
A878		A881	
A879		A882	

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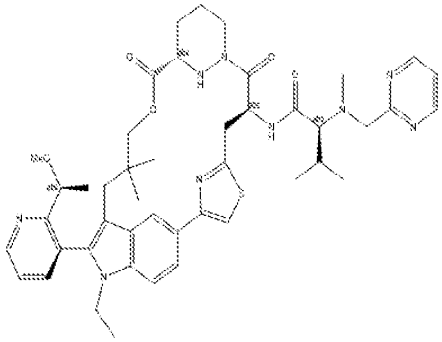
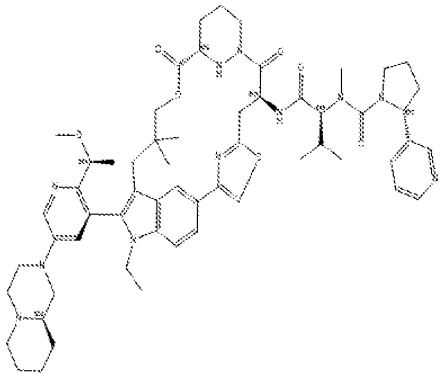
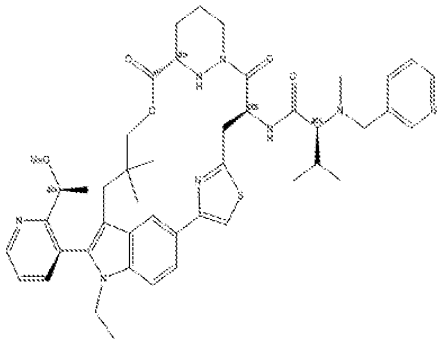
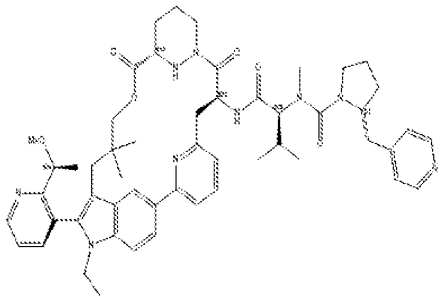
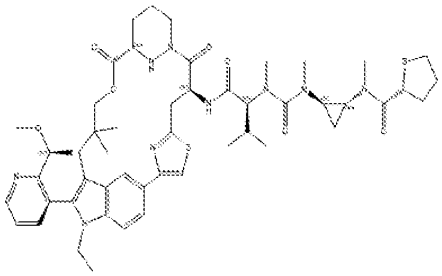
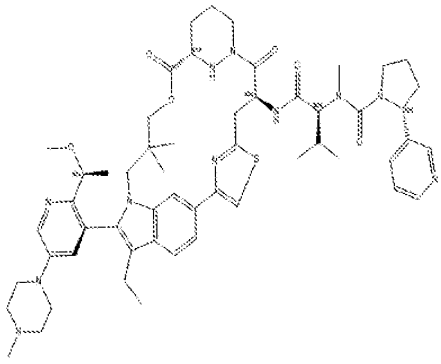
A883		A886	
A884		A887	
A885		A888	

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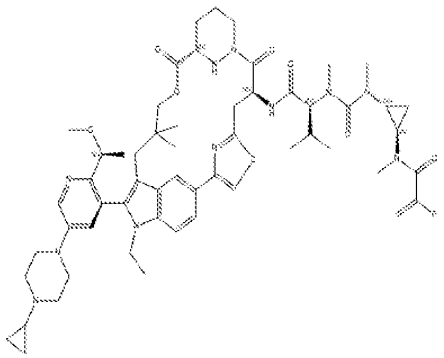
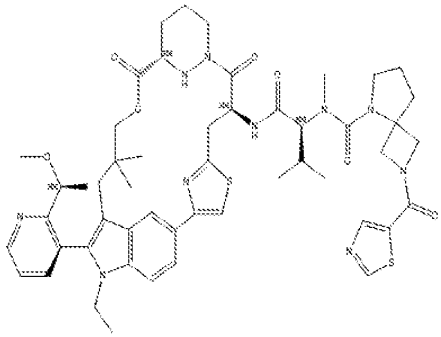
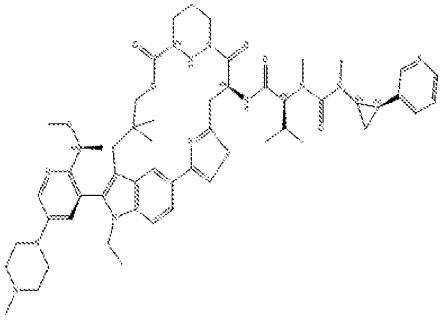
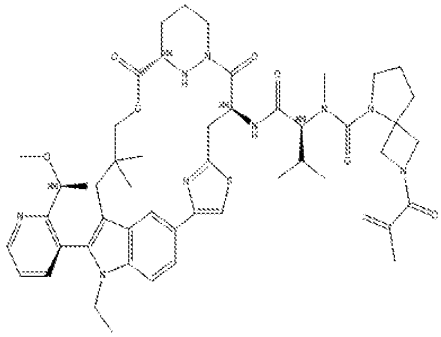
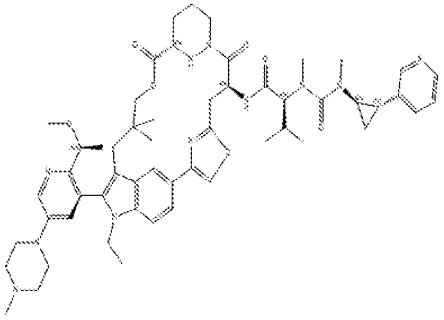
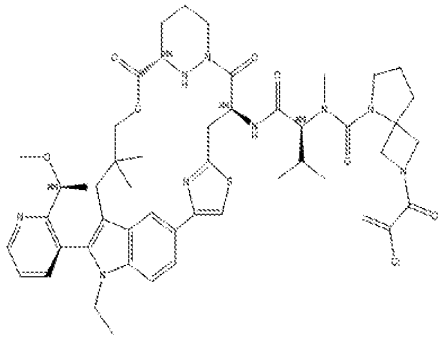
A889		A892	
A890		A893	
A891		A894	

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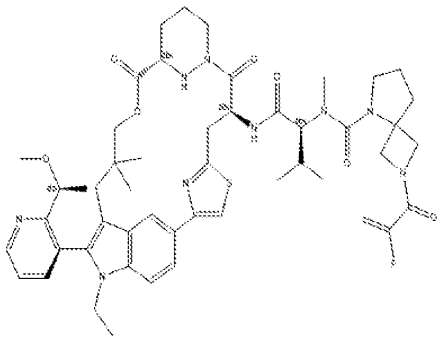
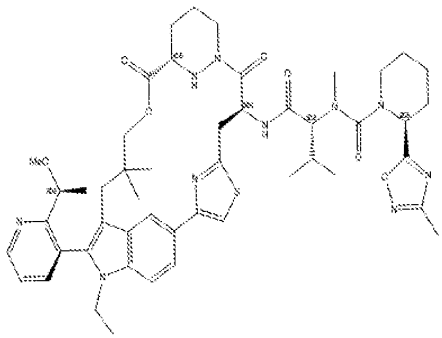
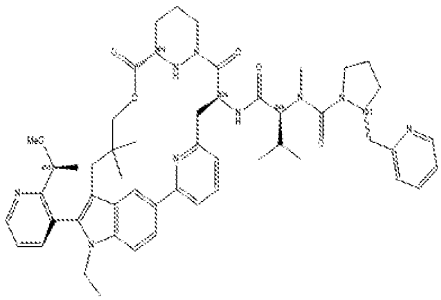
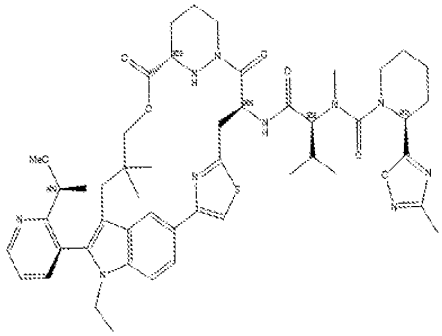
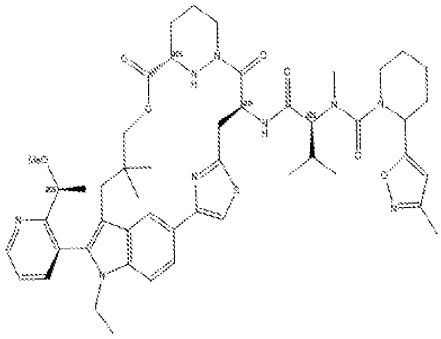
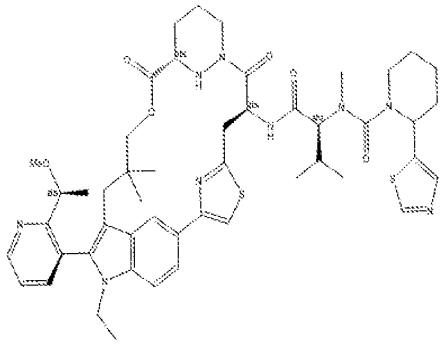
A895		A898	
A896		A899	
A897		A900	

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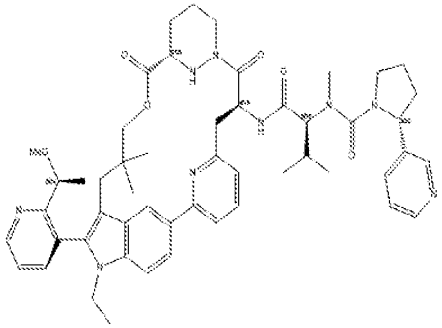
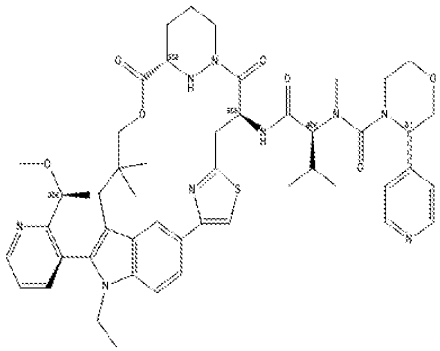
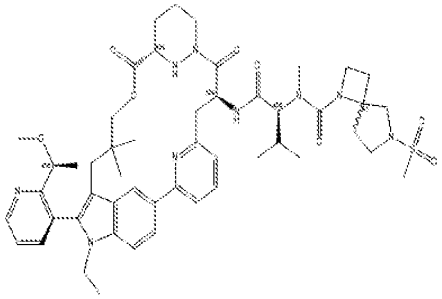
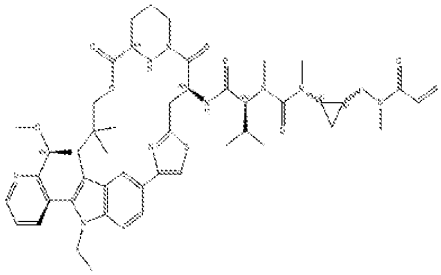
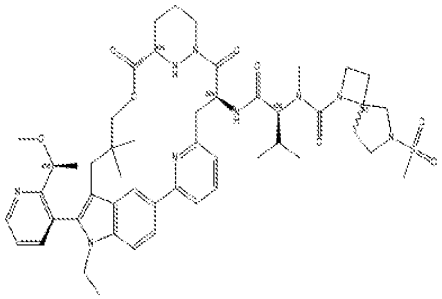
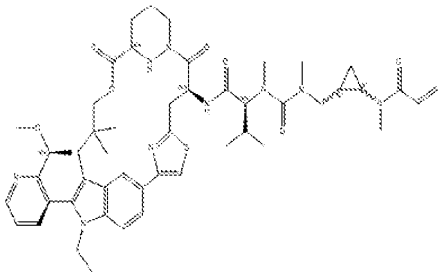
A901		A904	
A902		A905	
A903		A906	

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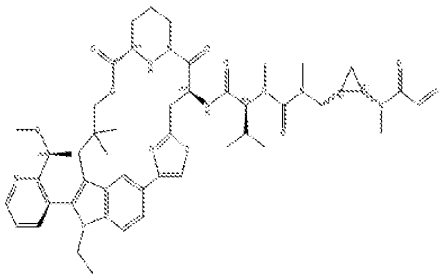
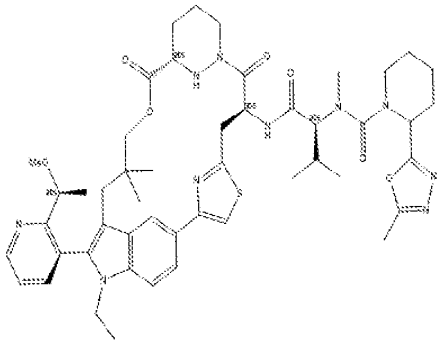
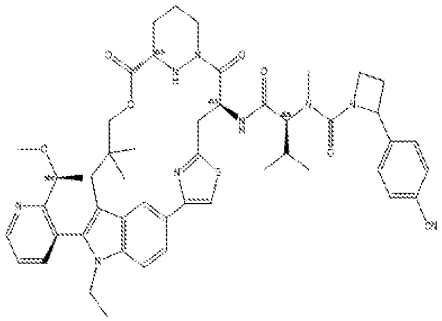
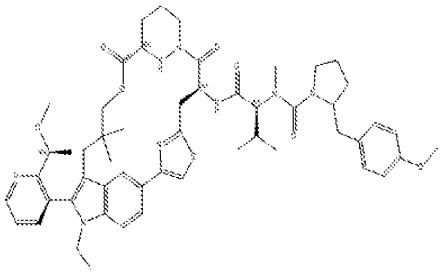
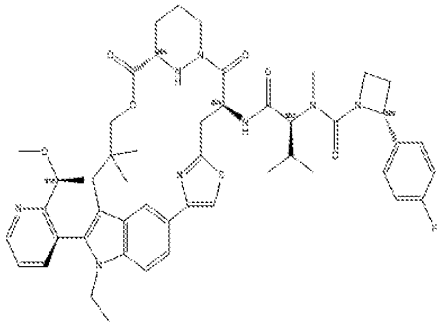
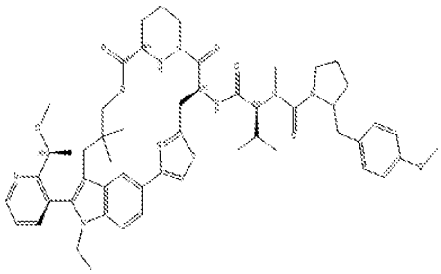
A907		A910	
A908		A911	
A909		A912	

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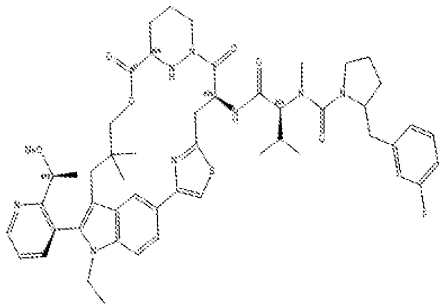
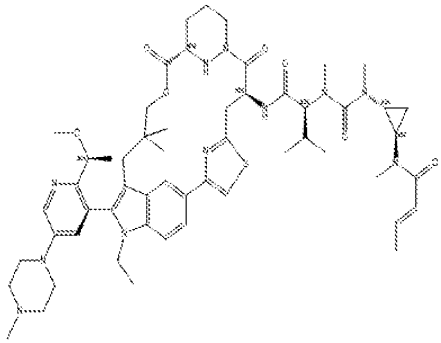
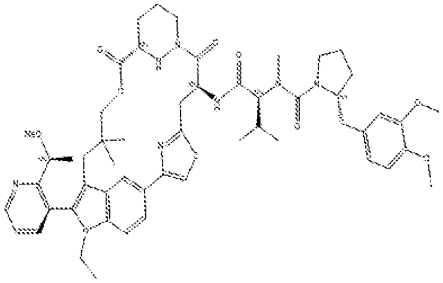
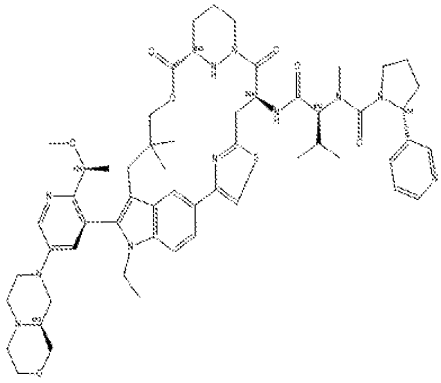
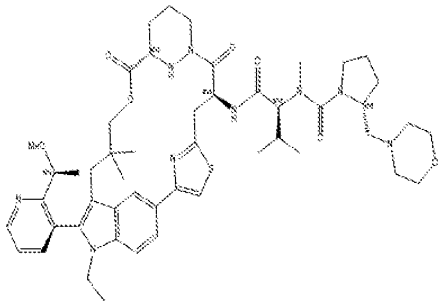
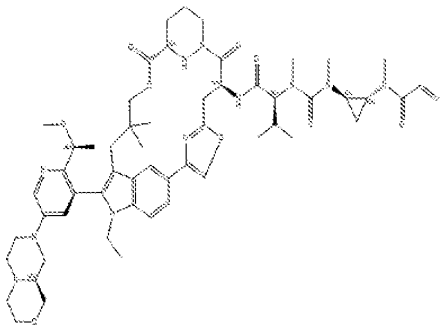
A913		A916	
A914		A917	
A915		A918	

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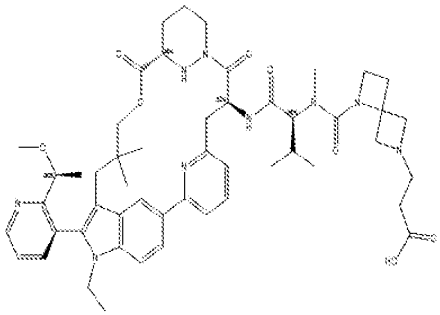
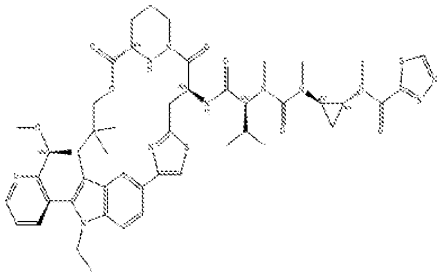
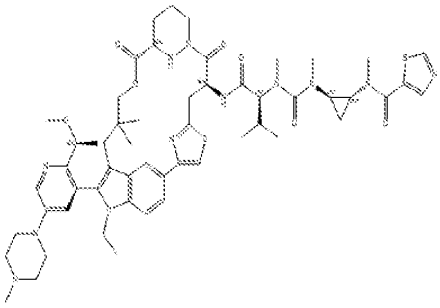
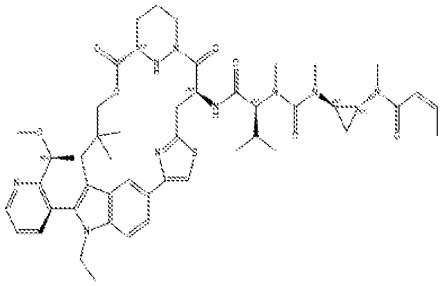
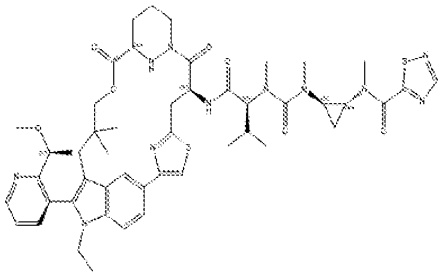
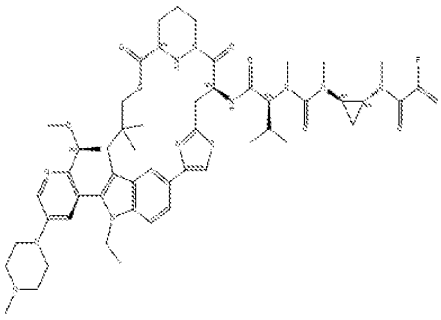
A919		A922	
A920		A923	
A921		A924	

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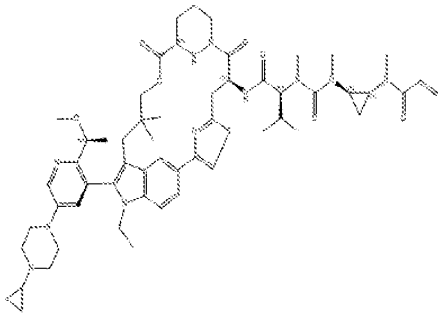
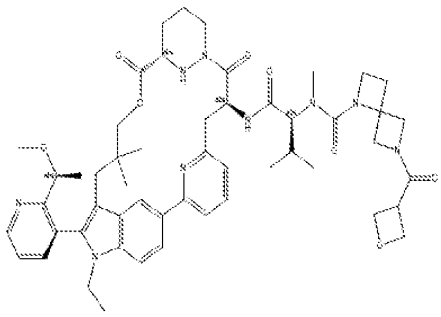
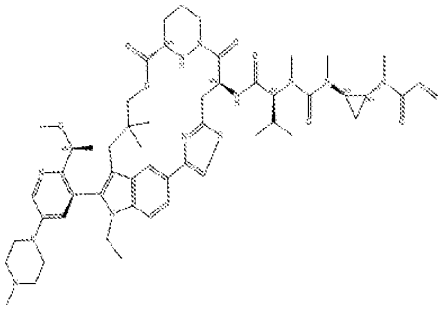
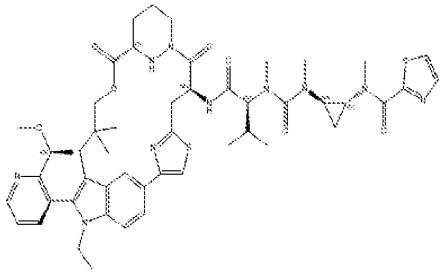
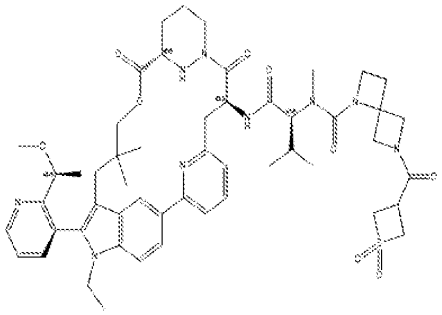
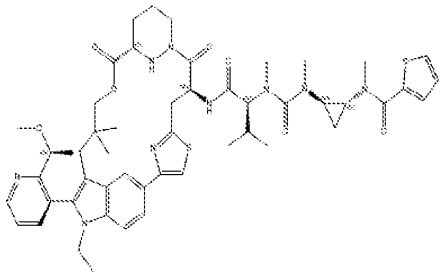
A925		A928	
A926		A929	
A927		A930	

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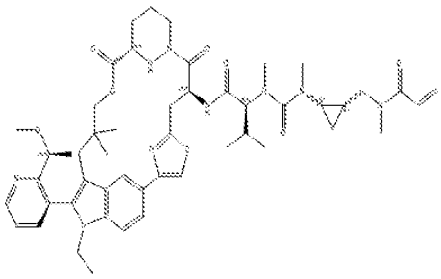
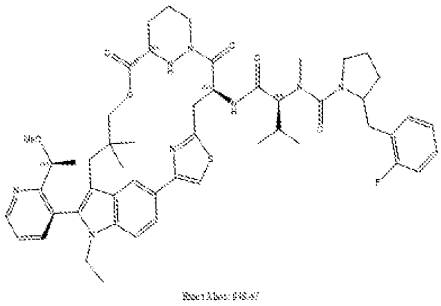
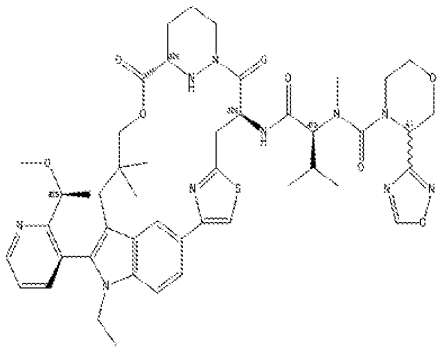
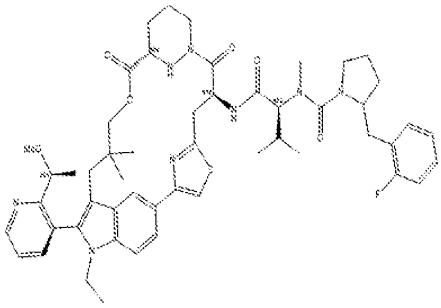
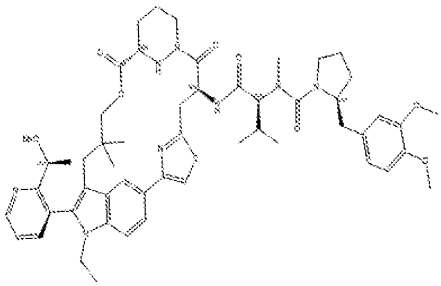
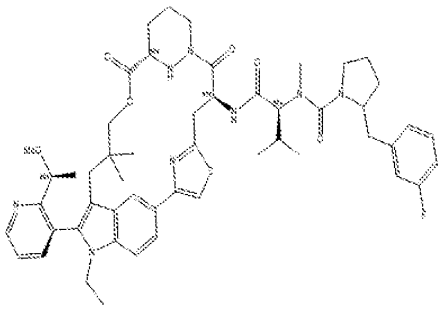
A931		A934	
A932		A935	
A933		A936	

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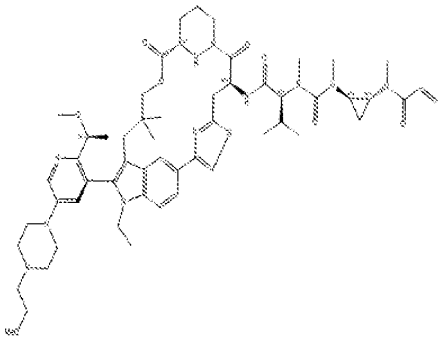
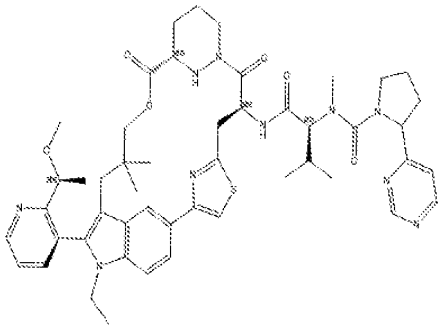
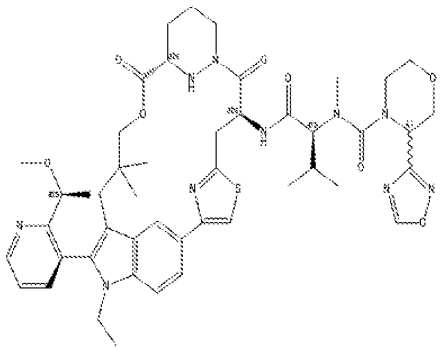
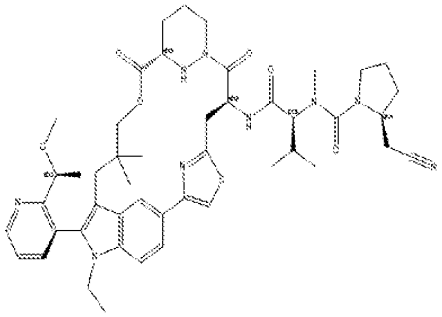
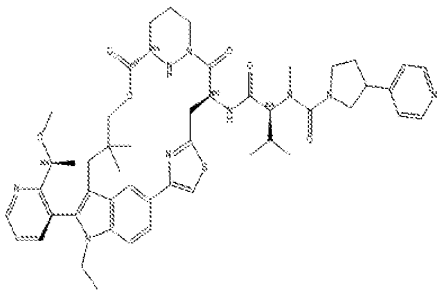
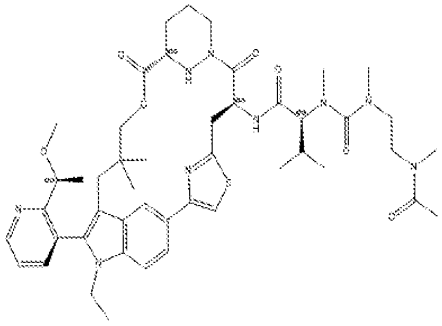
A937		A940	
A938		A941	
A939		A942	

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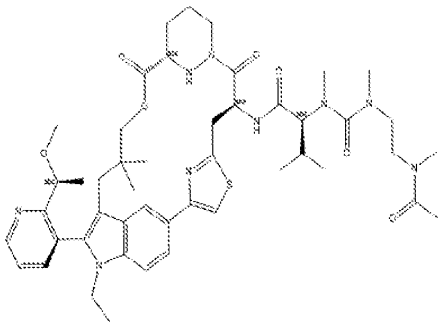
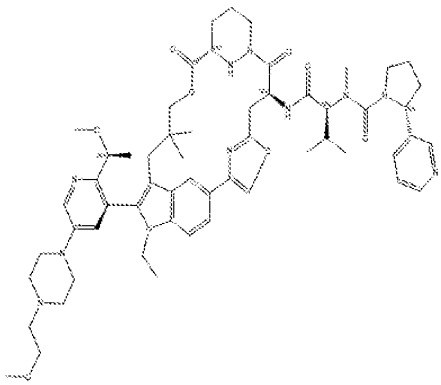
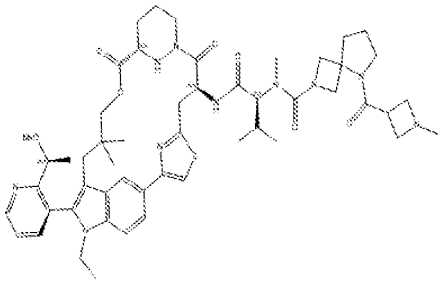
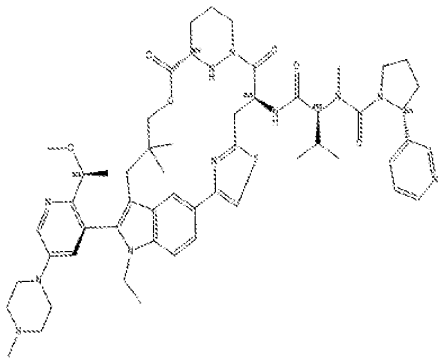
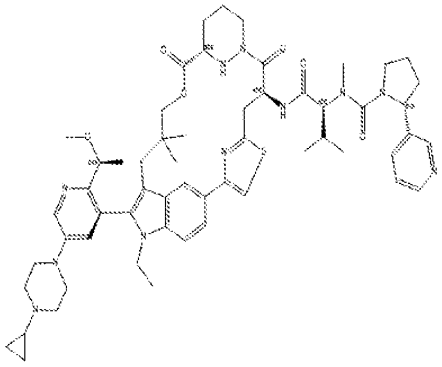
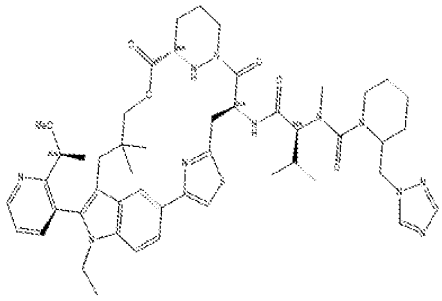
A943		A946	
A944		A947	
A945		A948	

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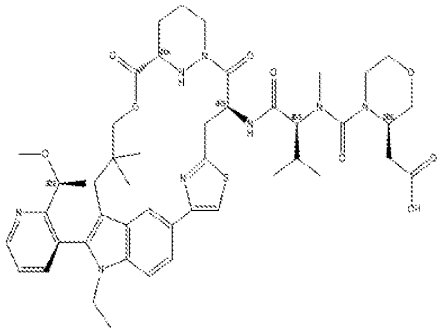
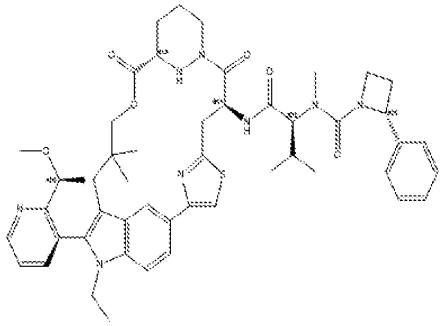
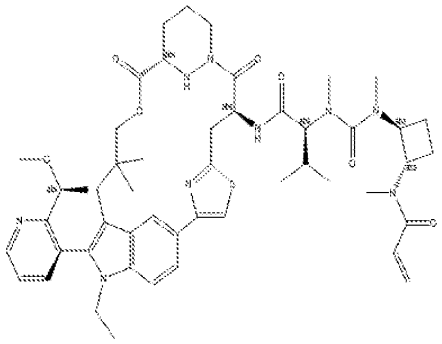
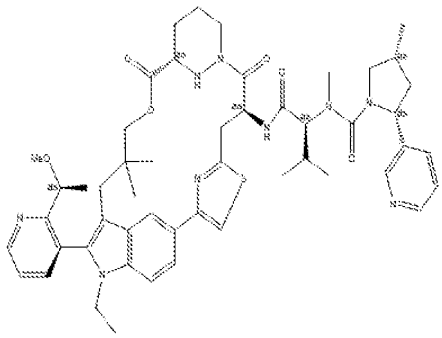
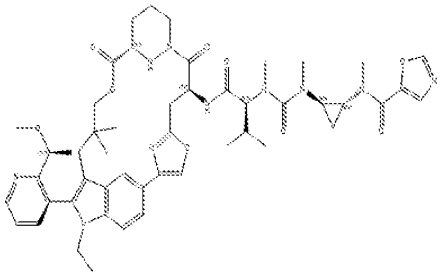
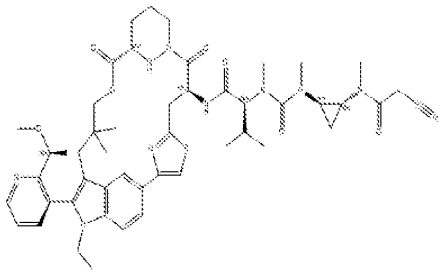
A949		A952	
A950		A953	
A951		A954	

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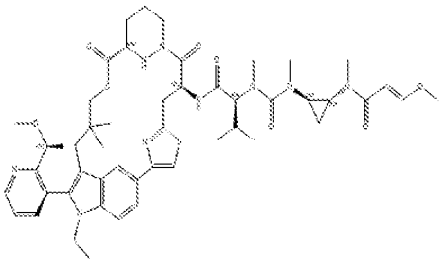
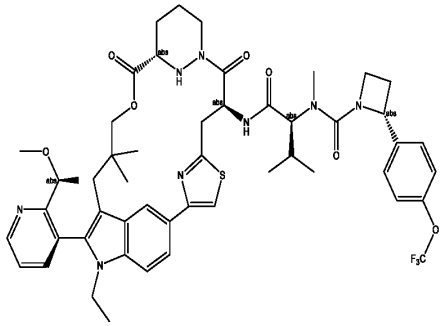
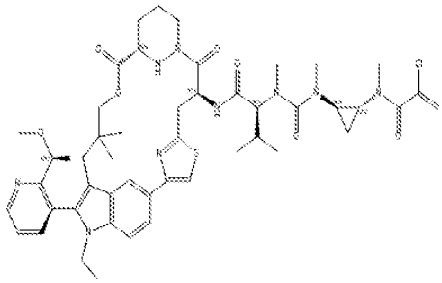
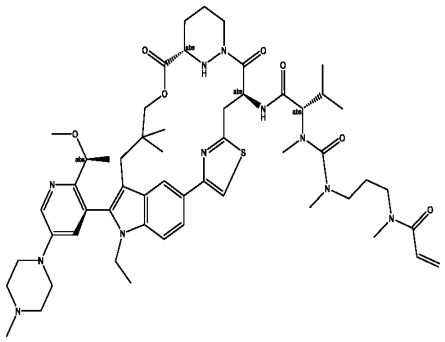
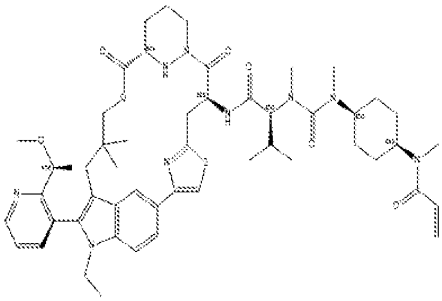
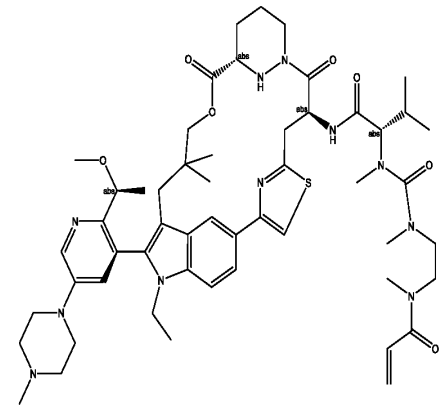
A955		A958	
A956		A959	
A957		A960	

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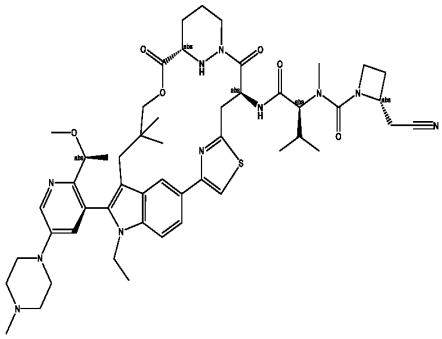
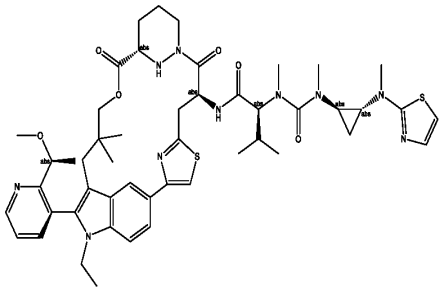
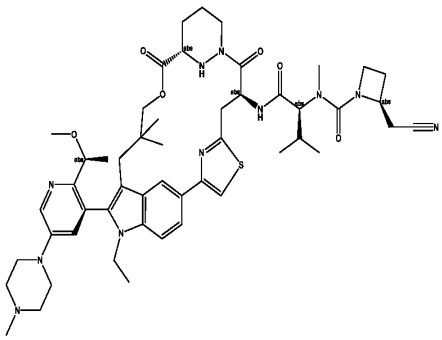
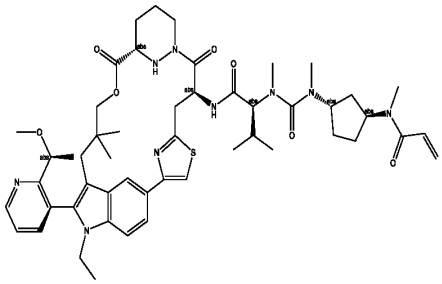
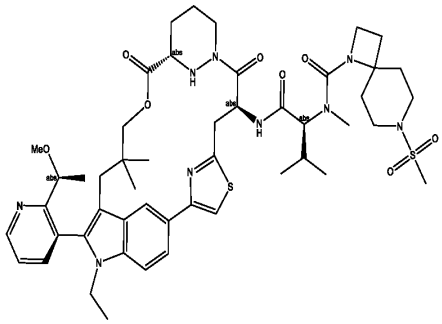
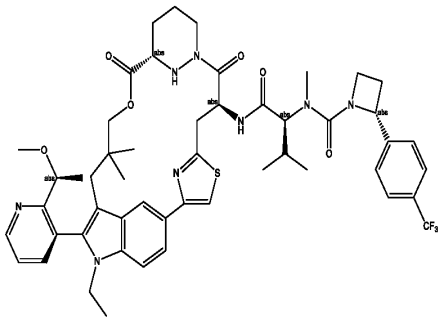
A961		A964	
A962		A965	
A963		A966	

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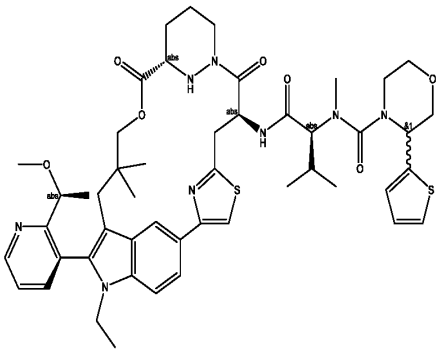
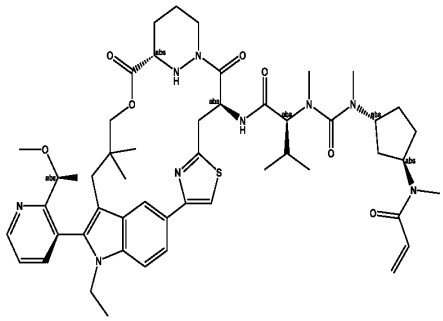
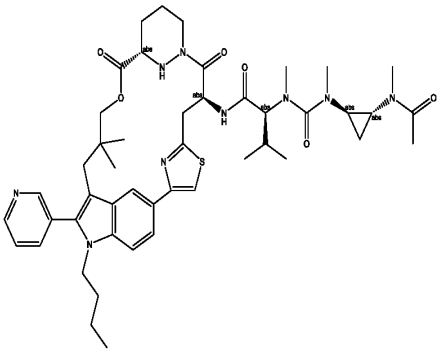
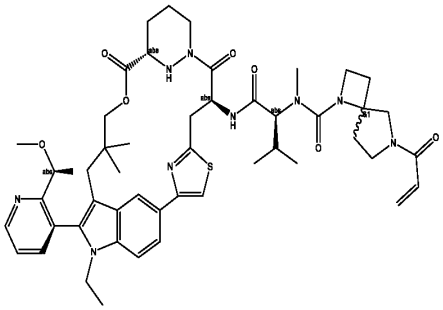
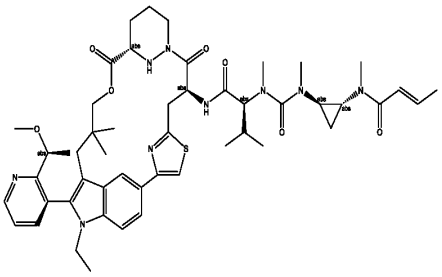
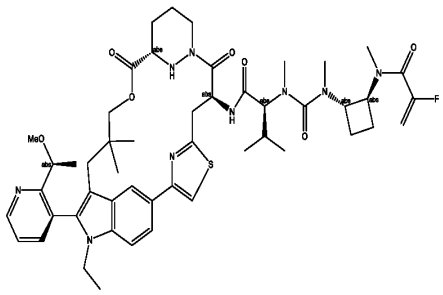
A967		A970	
A968		A971	
A969		A972	

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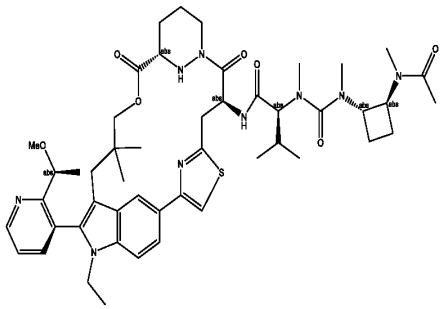
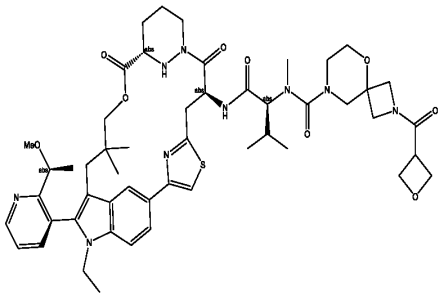
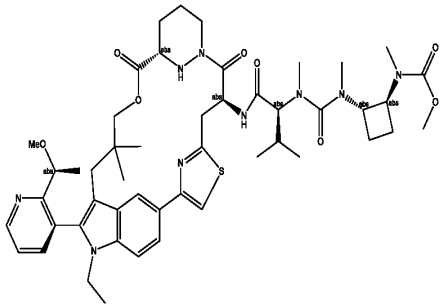
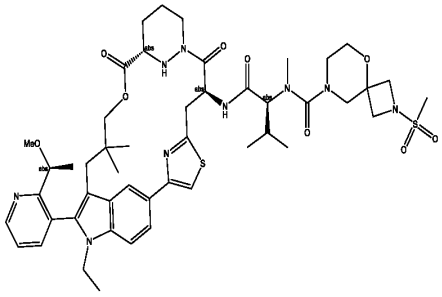
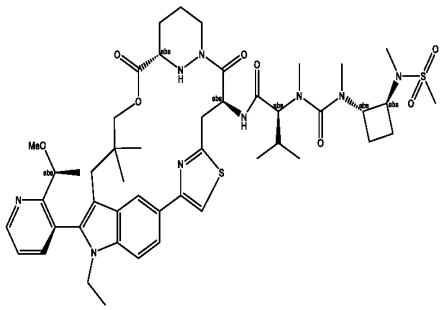
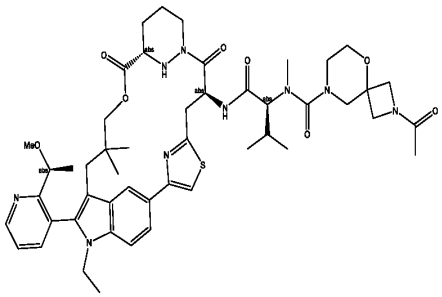
A973		A976	
A974		A977	
A975		A978	

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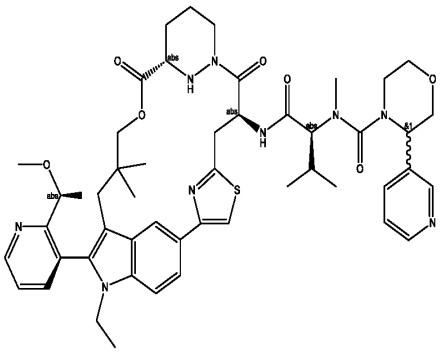
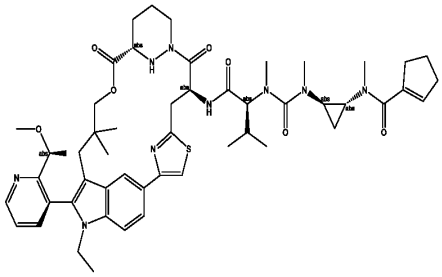
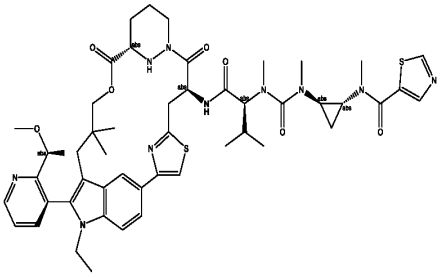
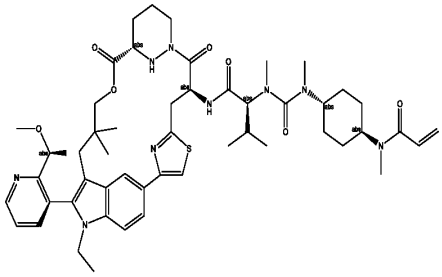
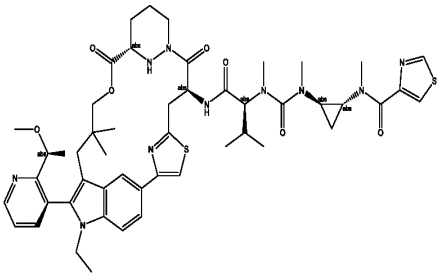
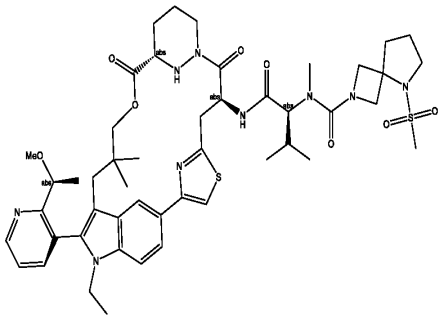
A979		A982	
A980		A983	
A981		A984	

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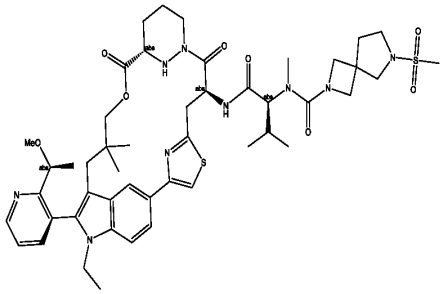
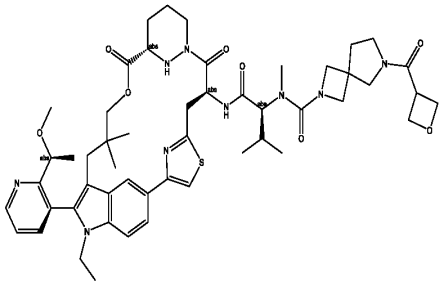
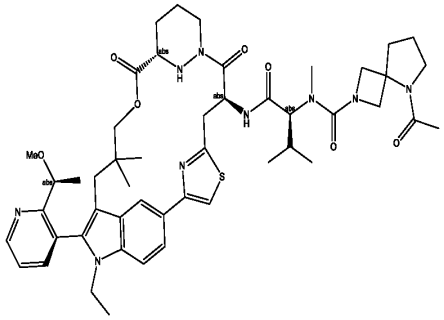
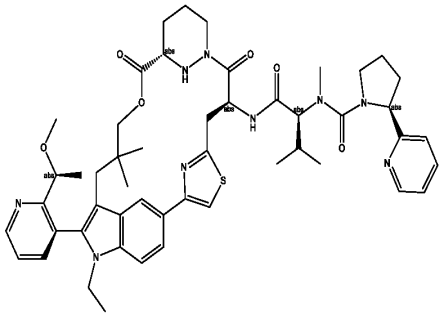
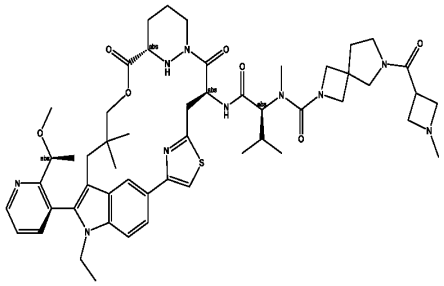
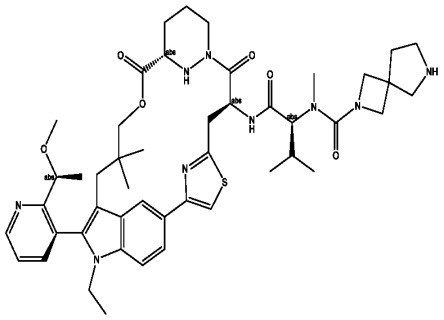
A985		A988	
A986		A989	
A987		A990	

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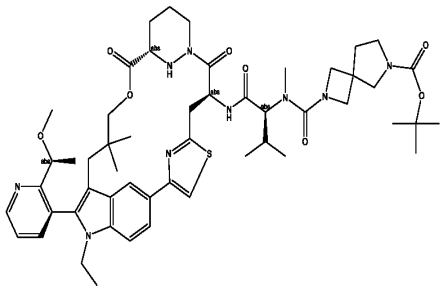
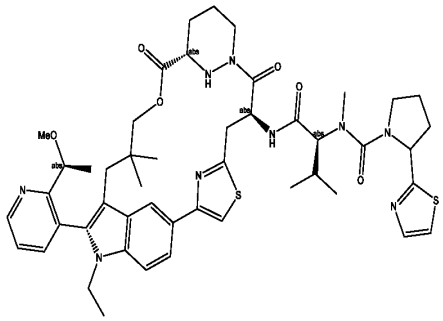
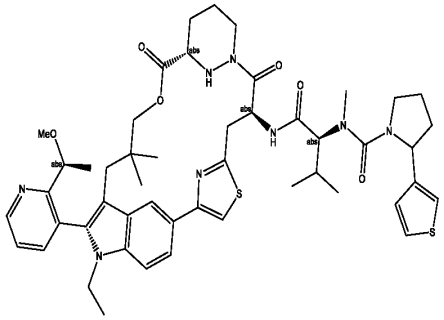
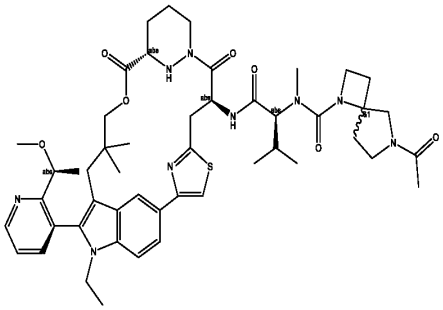
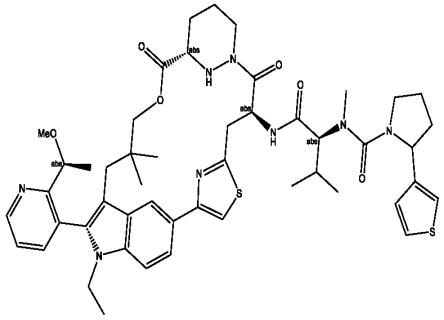
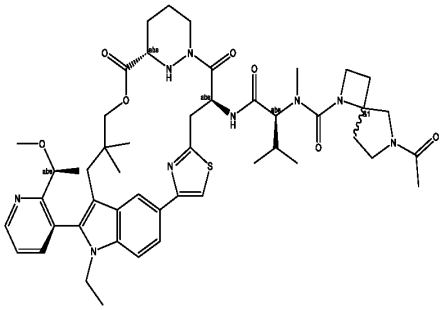
A991		A994	
A992		A995	
A993		A996	

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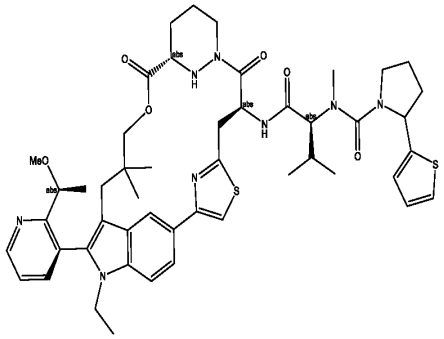
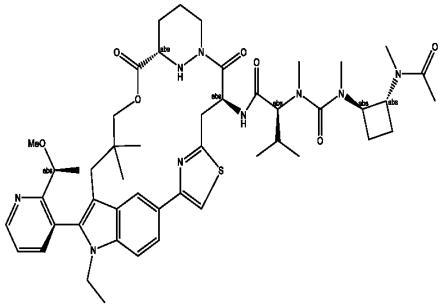
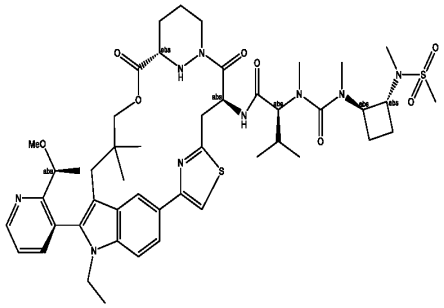
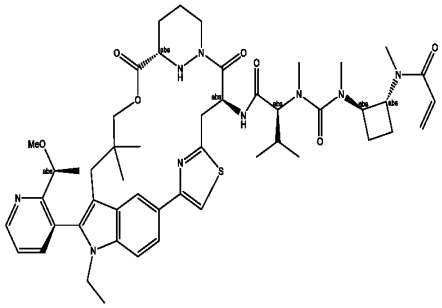
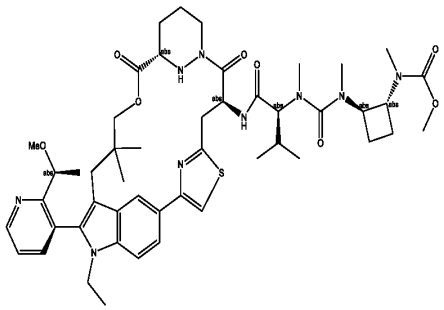
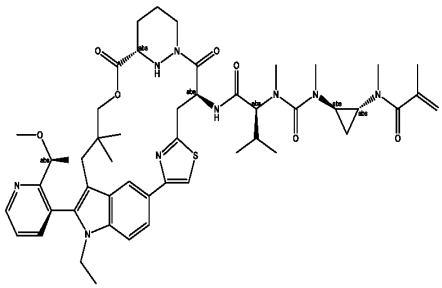
A997		A1000	
A998		A1001	
A999		A1002	

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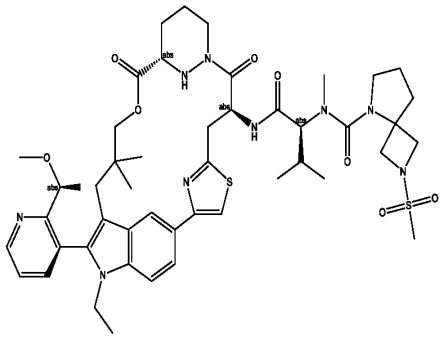
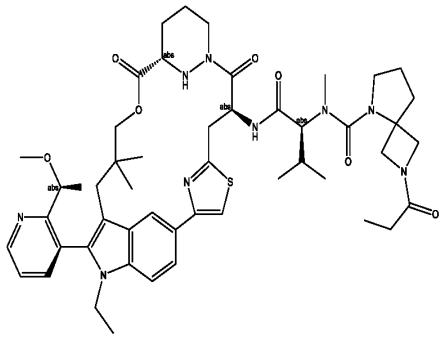
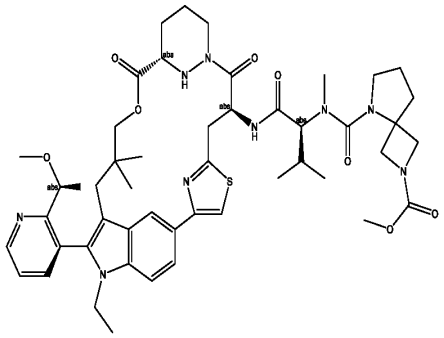
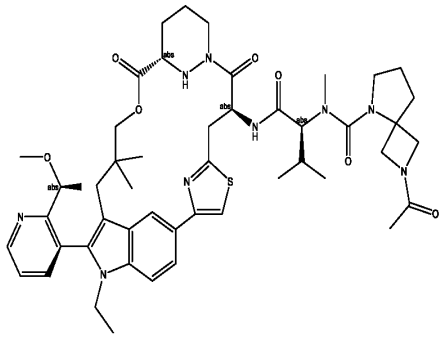
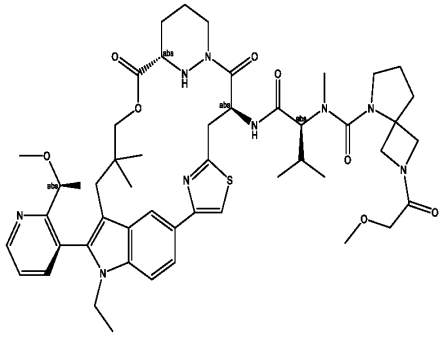
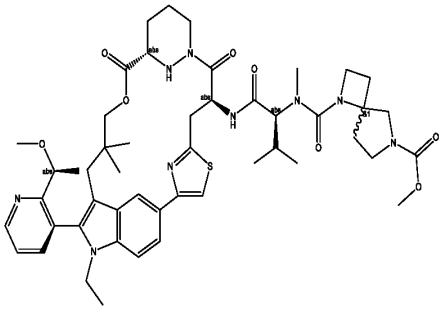
A1003		A1006	
A1004		A1007	
A1005		A1008	

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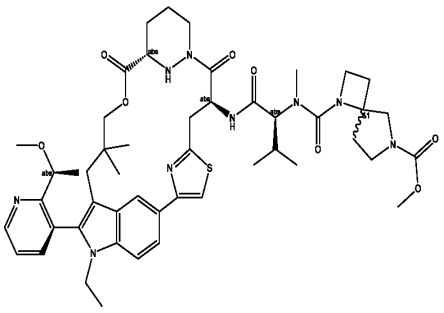
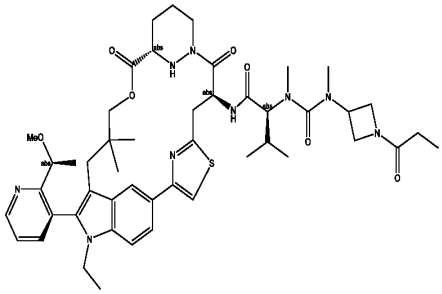
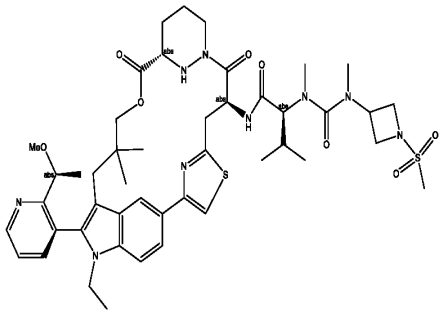
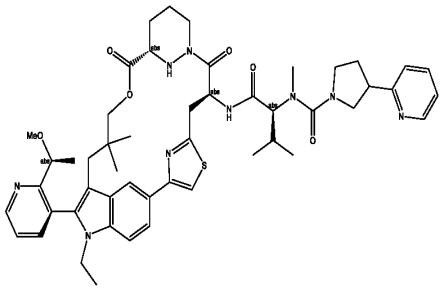
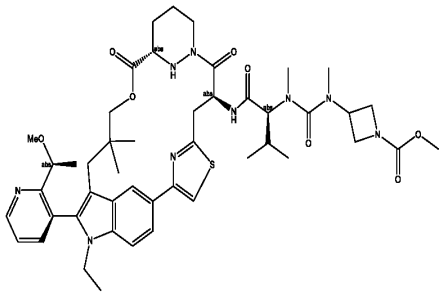
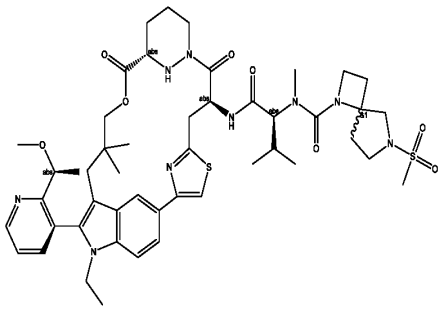
A1009		A1012	
A1010		A1013	
A1011		A1014	

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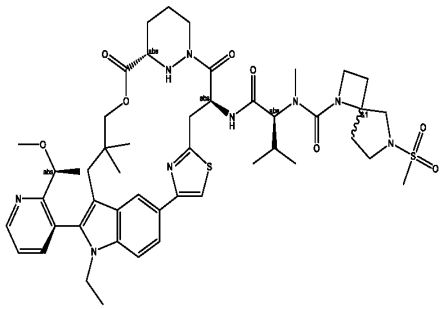
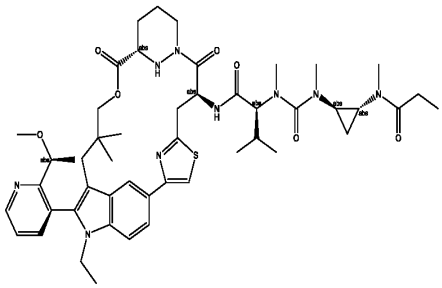
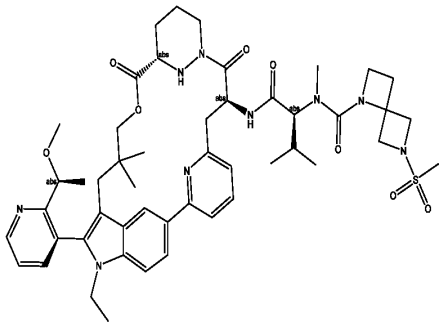
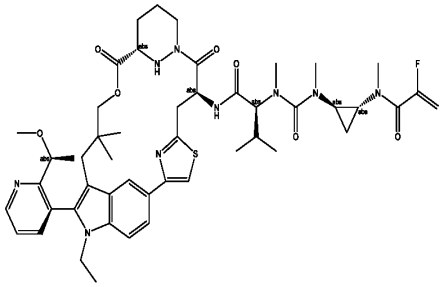
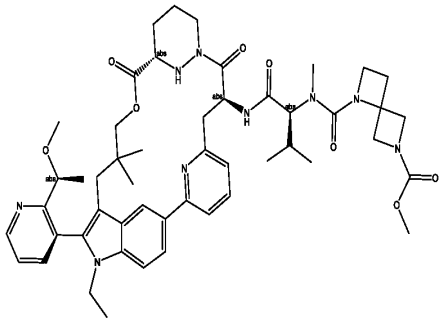
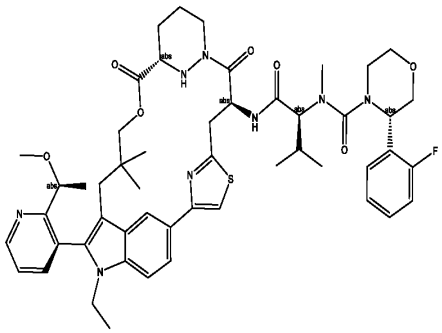
A1015		A1018	
A1016		A1019	
A1017		A1020	

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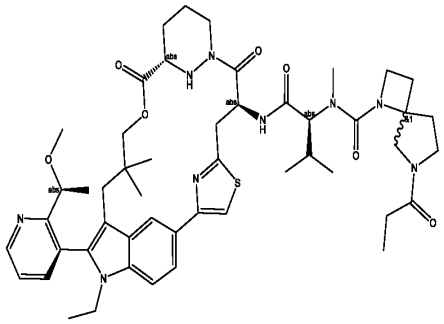
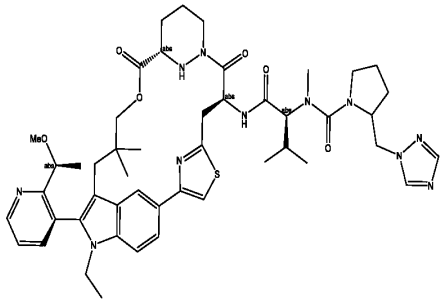
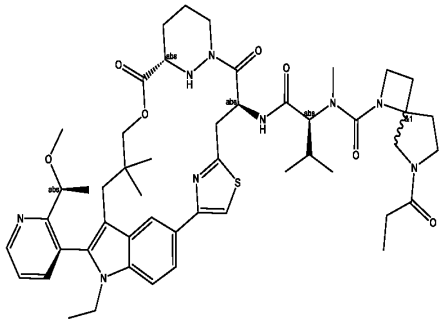
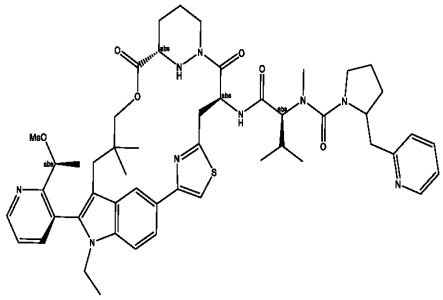
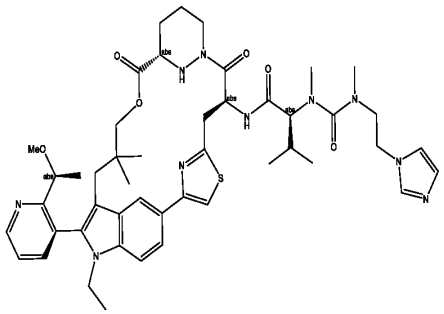
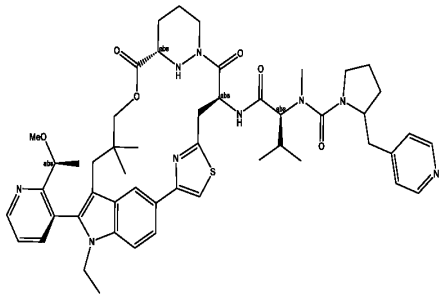
A1021		A1024	
A1022		A1025	
A1023		A1026	

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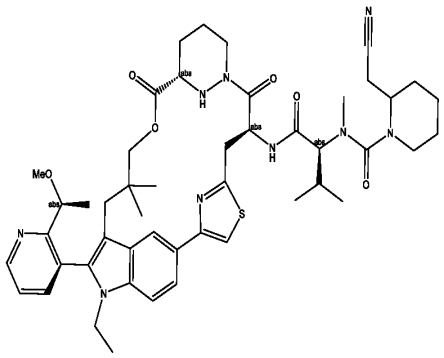
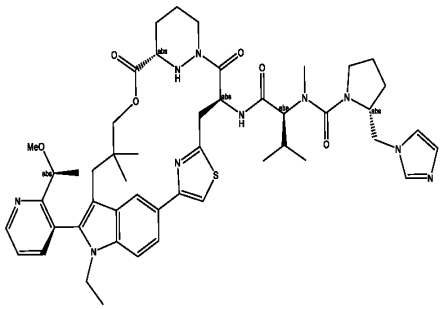
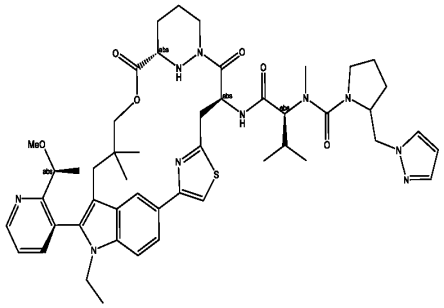
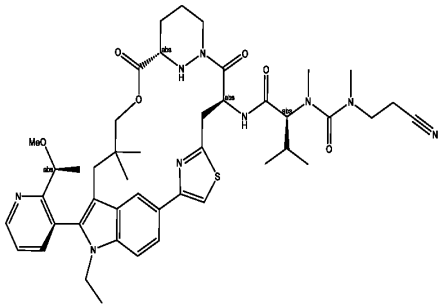
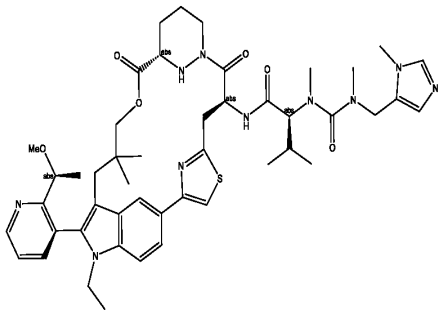
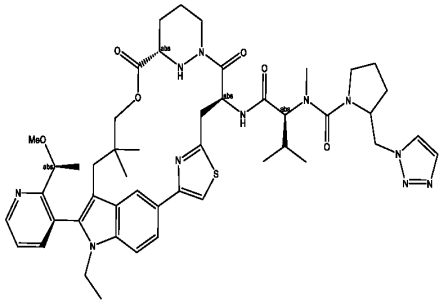
A1027		A1030	
A1028		A1031	
A1029		A1032	

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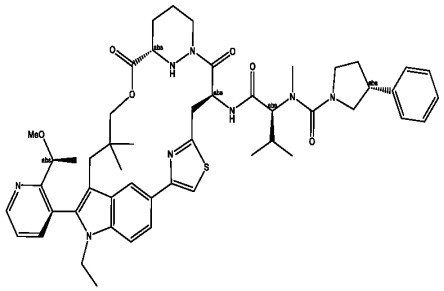
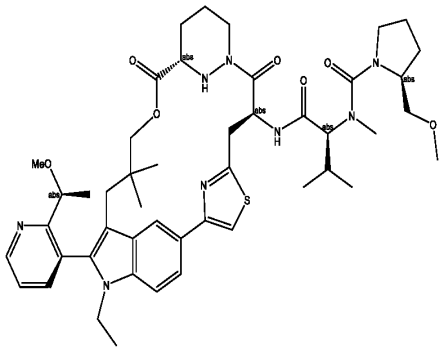
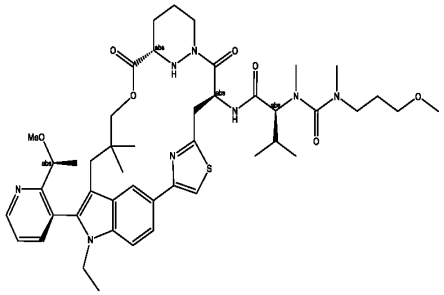
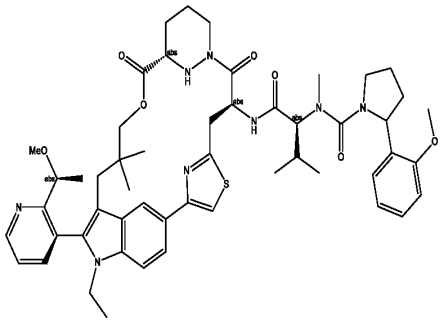
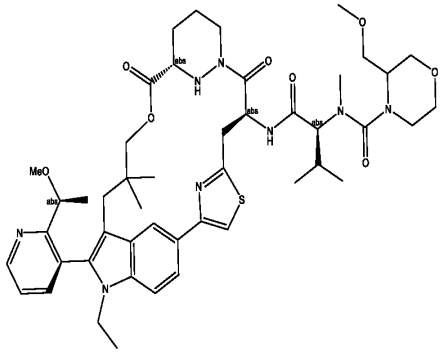
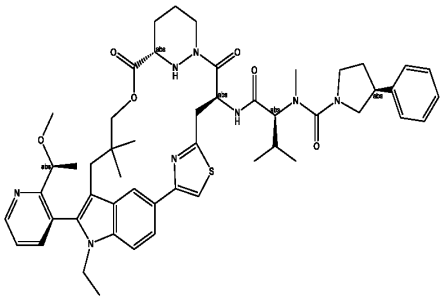
A1033		A1036	
A1034		A1037	
A1035		A1038	

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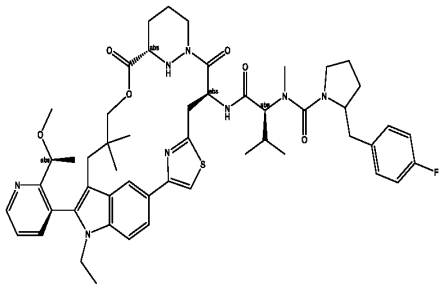
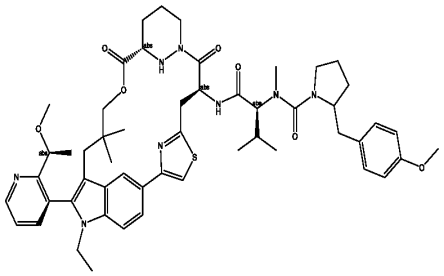
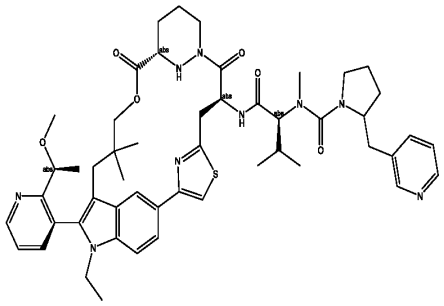
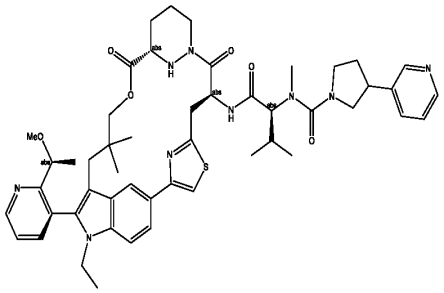
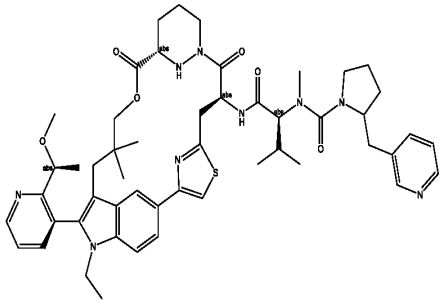
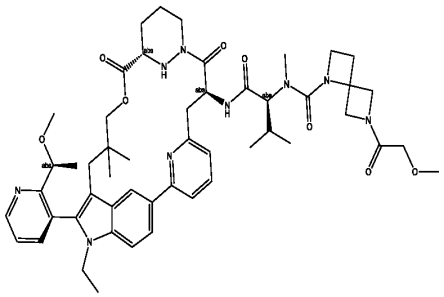
A1039		A1042	
A1040		A1043	
A1041		A1044	

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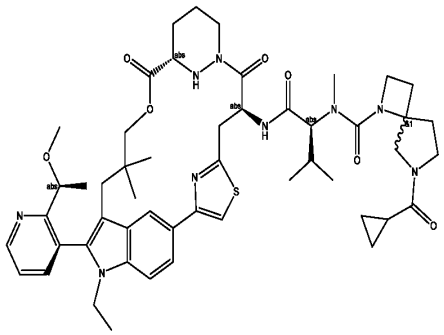
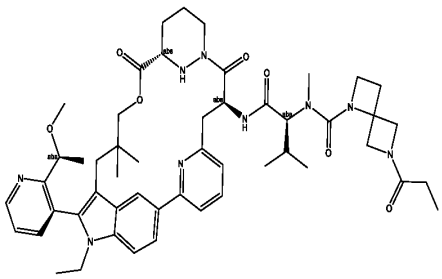
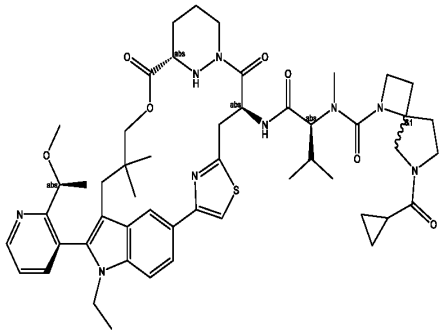
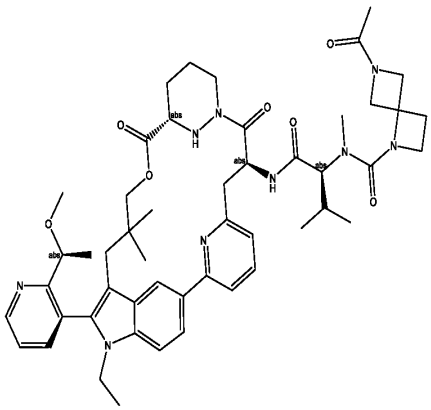
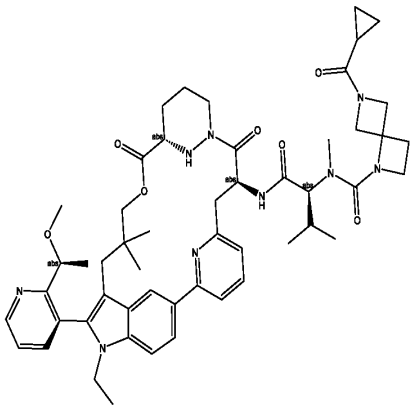
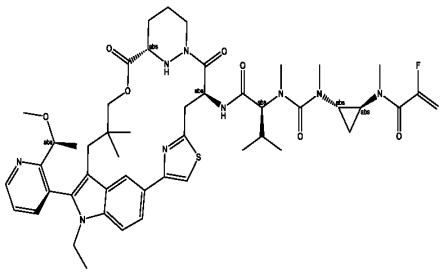
A1045		A1048	
A1046		A1049	
A1047		A1050	

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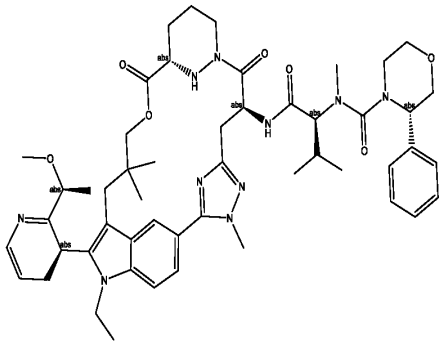
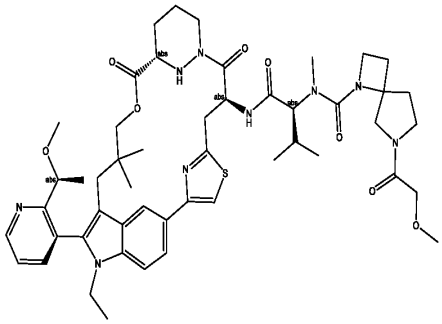
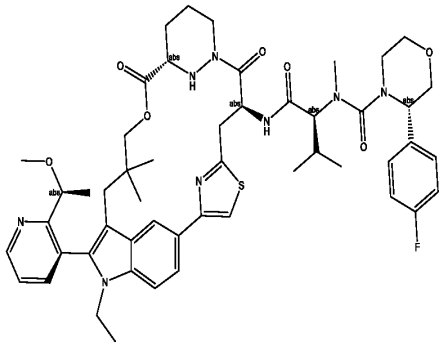
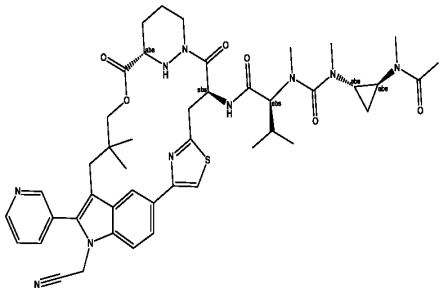
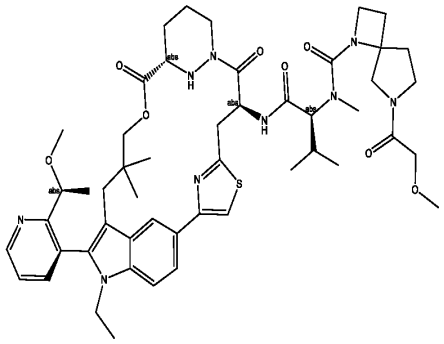
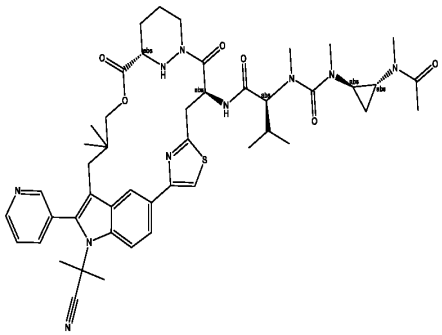
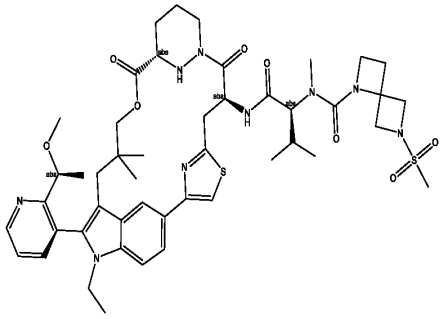
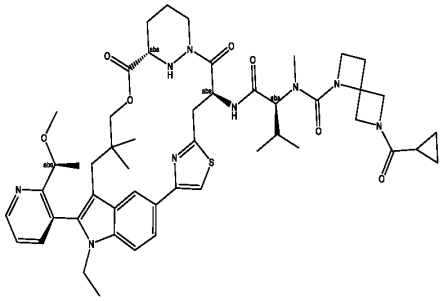
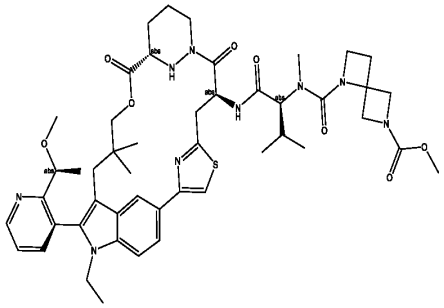
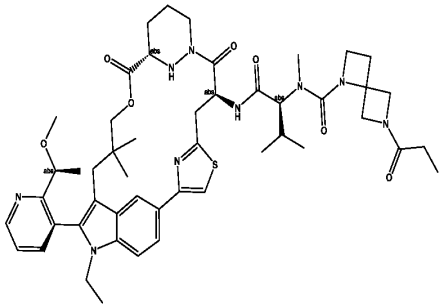
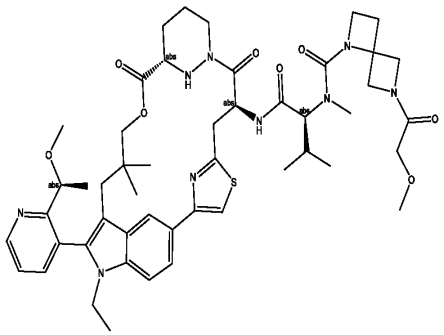
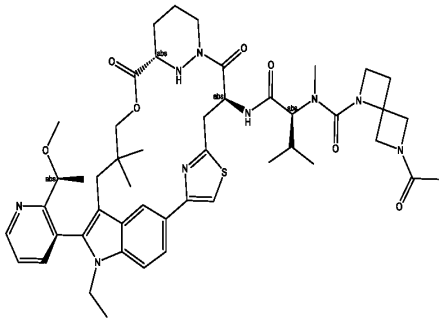
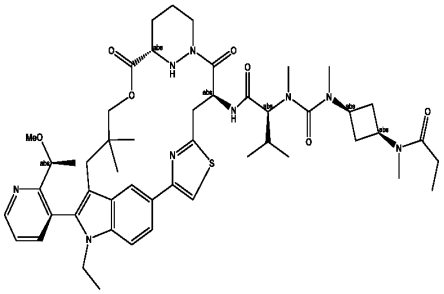
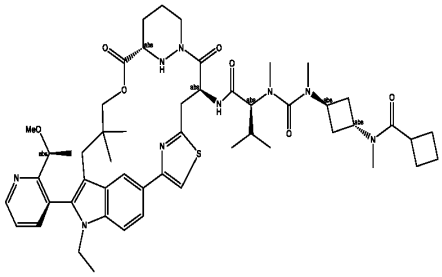
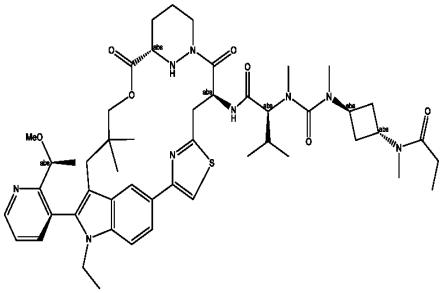
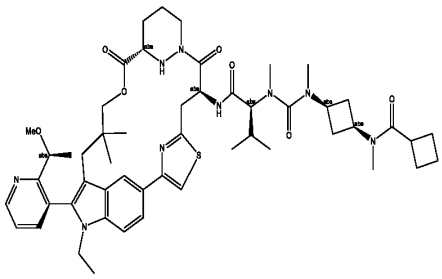
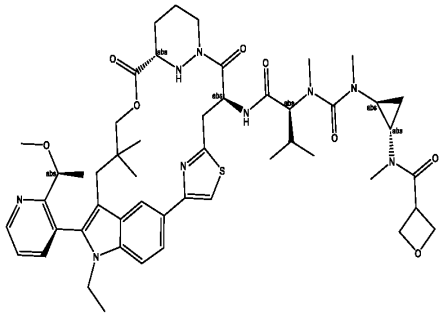
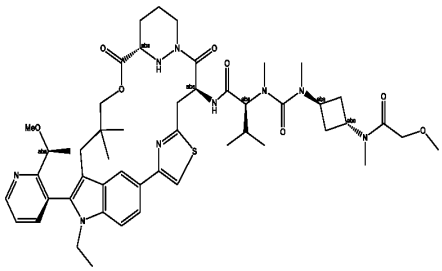
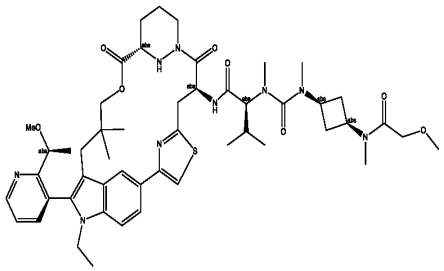
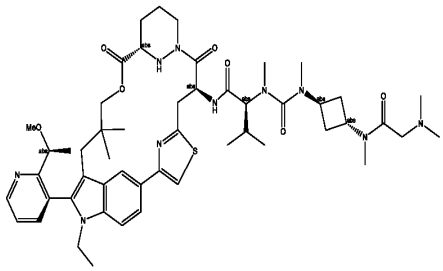
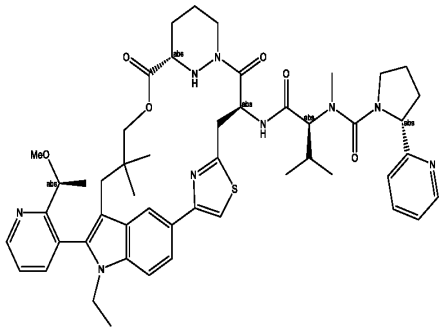
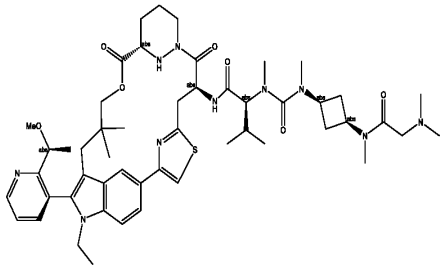
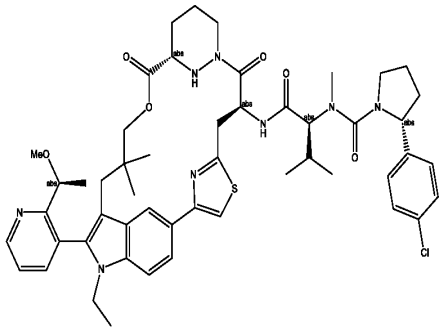
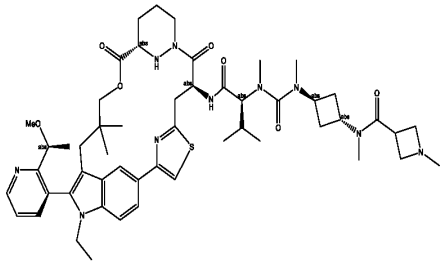
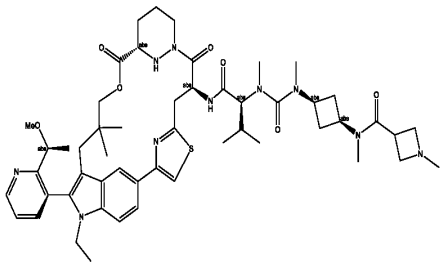
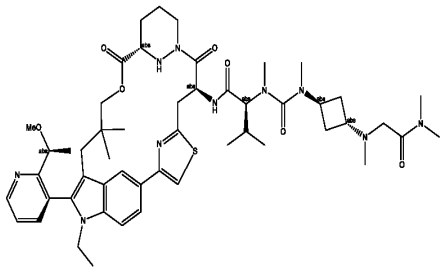
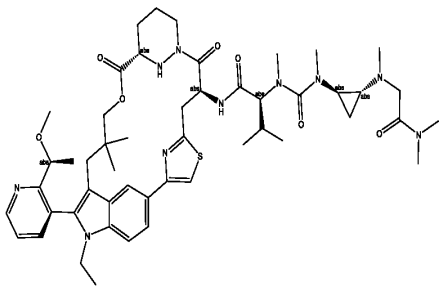
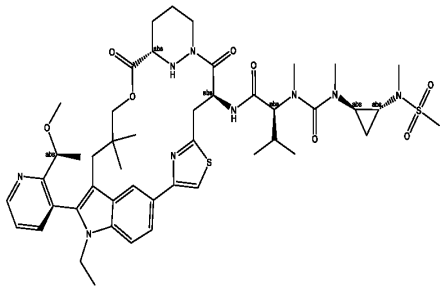
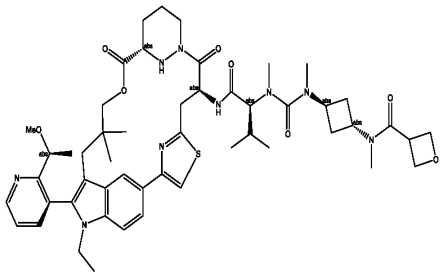
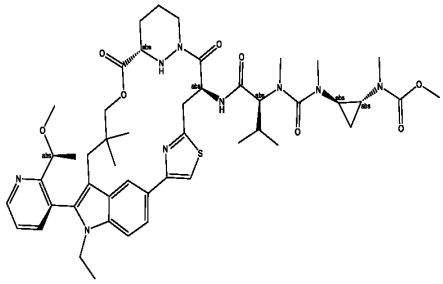
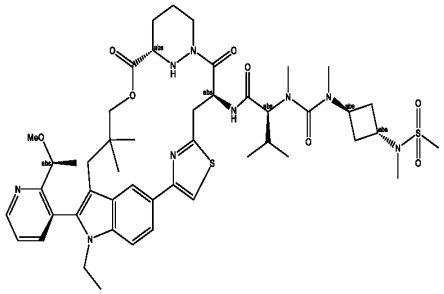
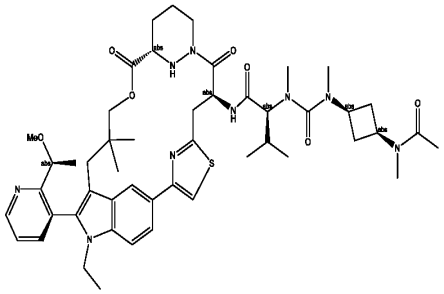
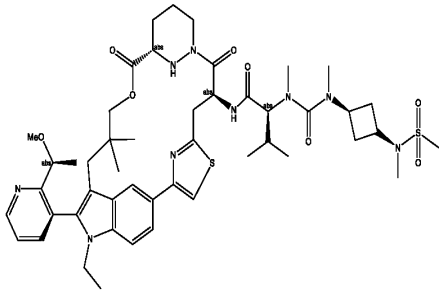
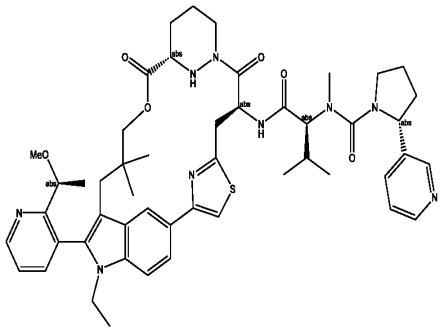
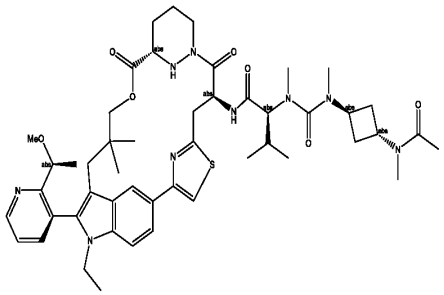
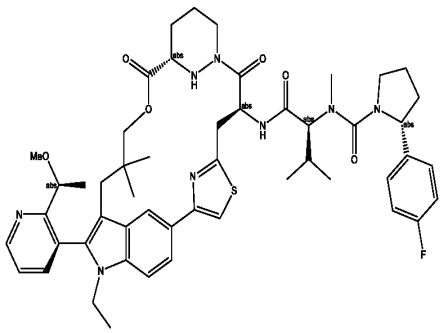
A1051		A1054	
A1052		A1055	
A1053		A1056	

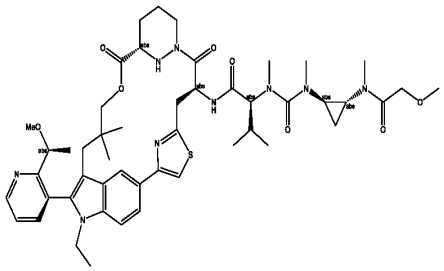
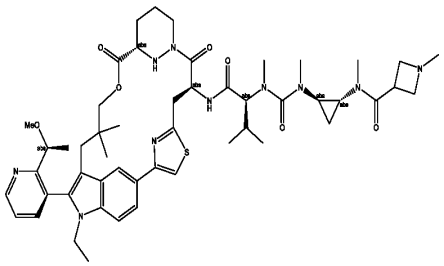
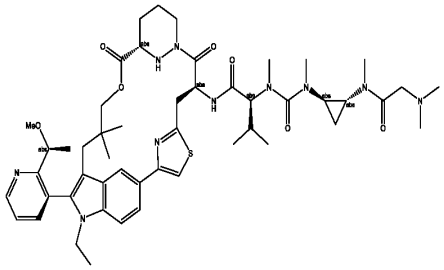
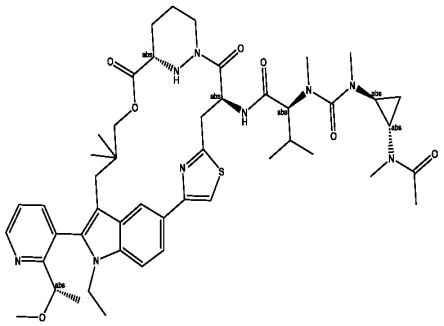
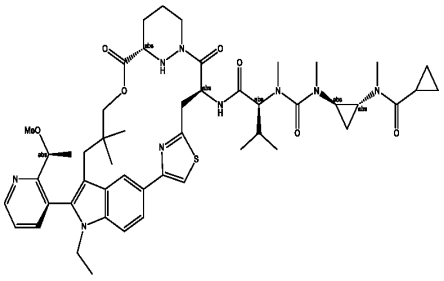
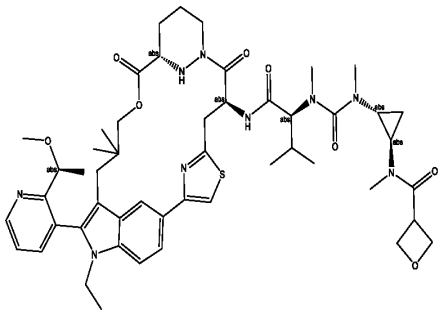
Ex#	Structure	Ex#	Structure
A1057		A1060	
A1058		A1061	
A1059		A1062	

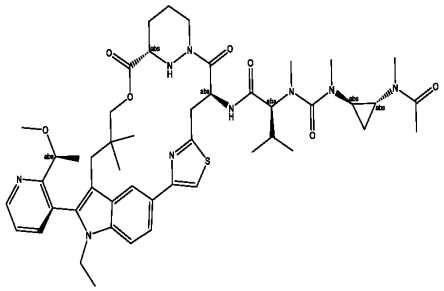
Ex#	Structure	Ex#	Structure
A1063		A1066	
A1064		A1067	
A1065		A1068	

Ex#	Structure	Ex#	Structure
A1069		A1072	
A1070		A1073	
A1071		A1074	

Ex#	Structure	Ex#	Structure
A1075		A1078	
A1076		A1079	
A1077		A1080	

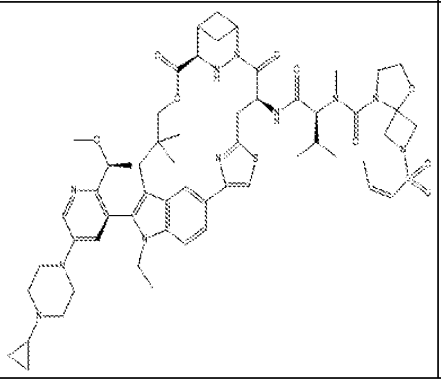
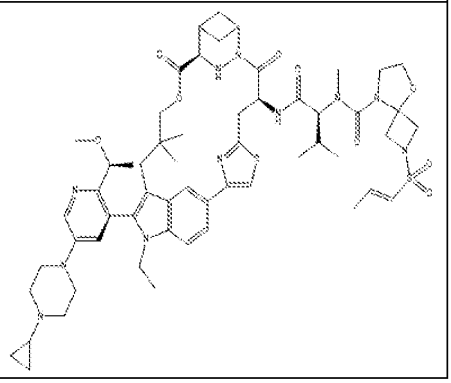
Ex#	Structure	Ex#	Structure
A1081		A1084	
A1082		A1085	
A1083		A1086	

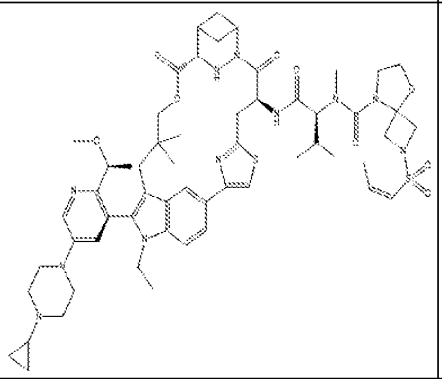
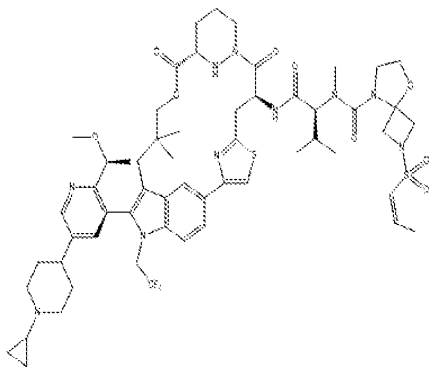
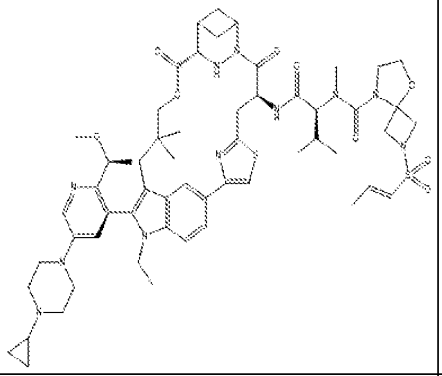
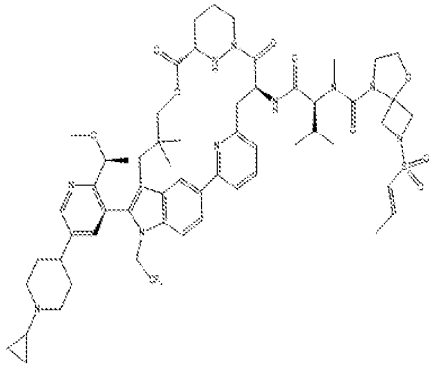
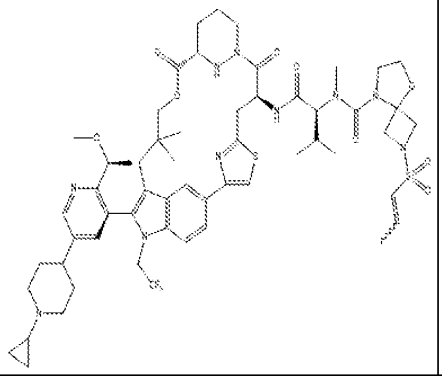
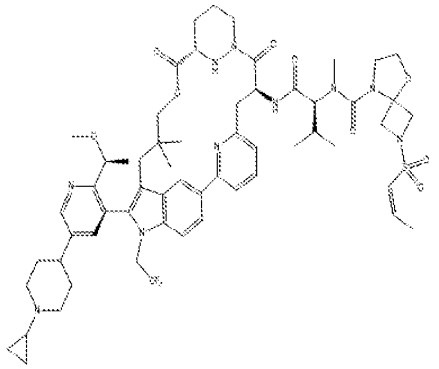
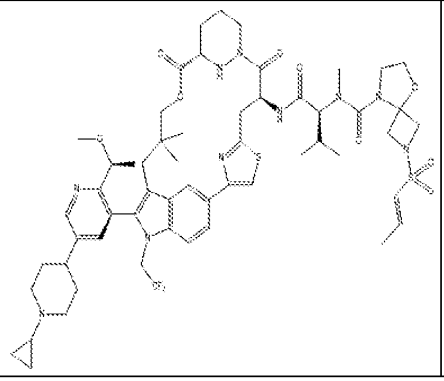
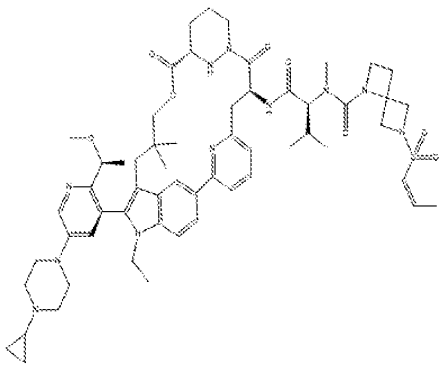
Ex#	Structure	Ex#	Structure
A1087		A1090	
A1088		A1091	
A1089		A1092	

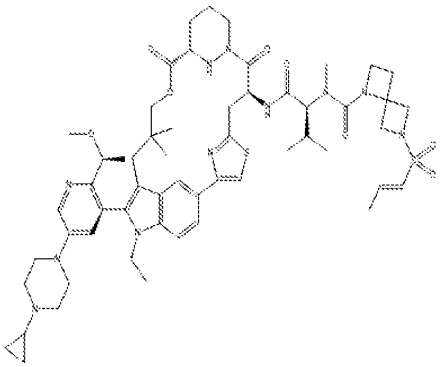
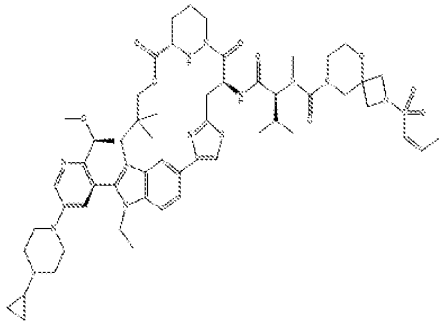
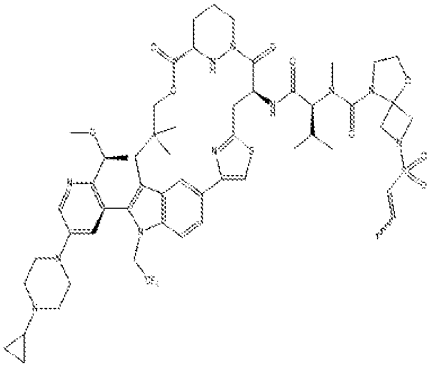
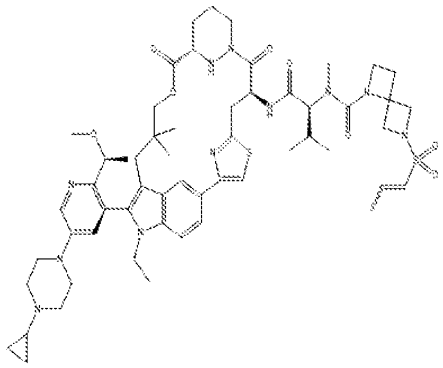
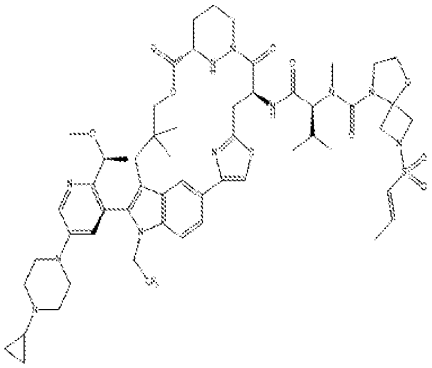
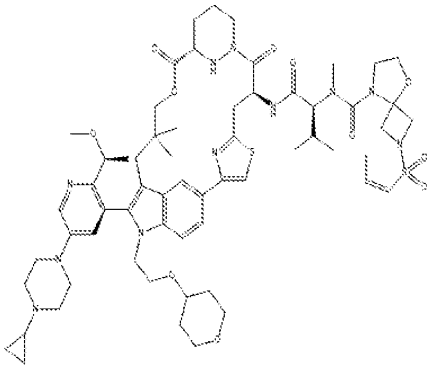
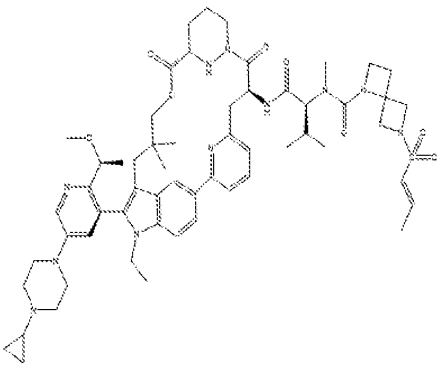
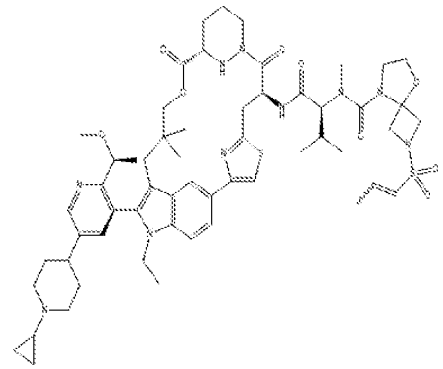
Ex#	Structure
A1093	

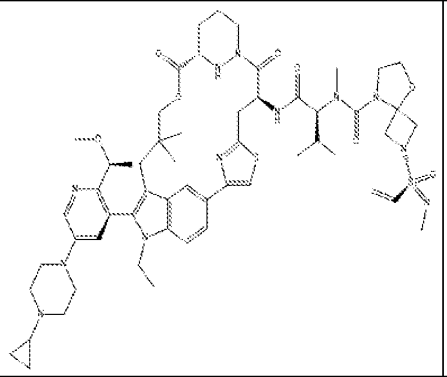
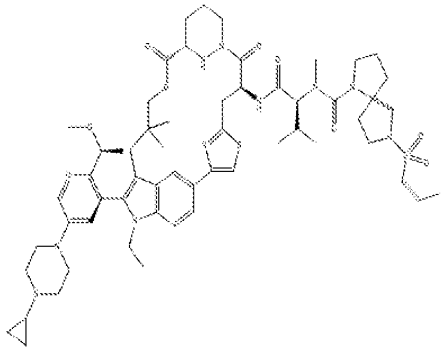
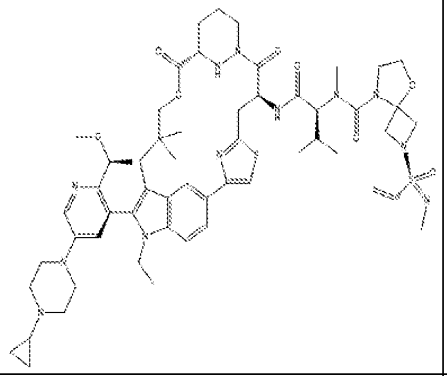
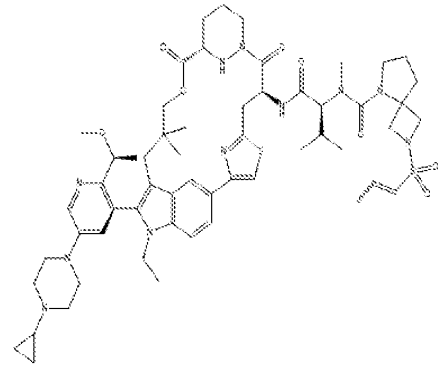
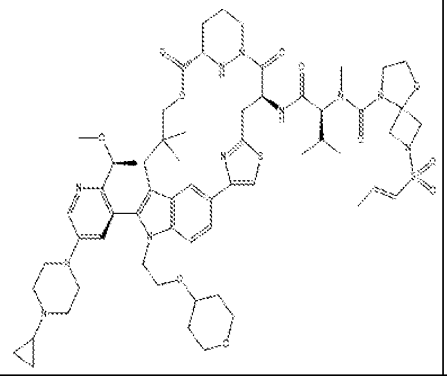
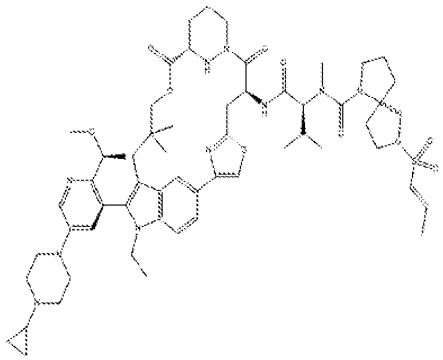
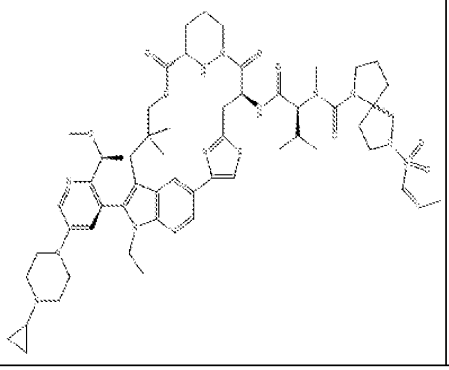
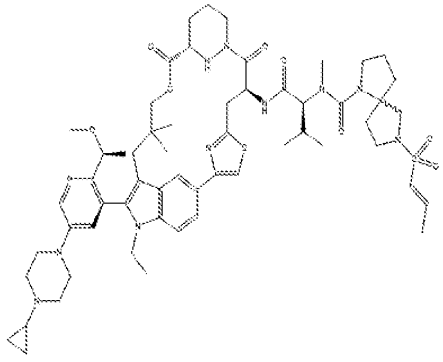
In some embodiments, a compound of the present invention is selected from Table 2, or a pharmaceutically acceptable salt or stereoisomer thereof. In some embodiments, a compound of the present invention is selected from Table 2, or a pharmaceutically acceptable salt or atropisomer thereof.

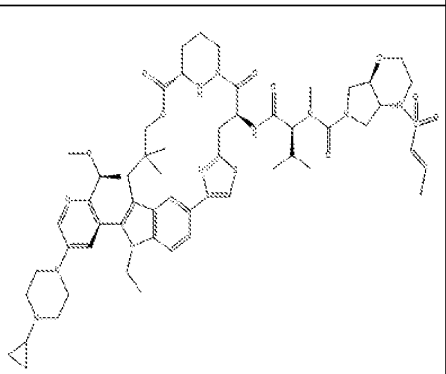
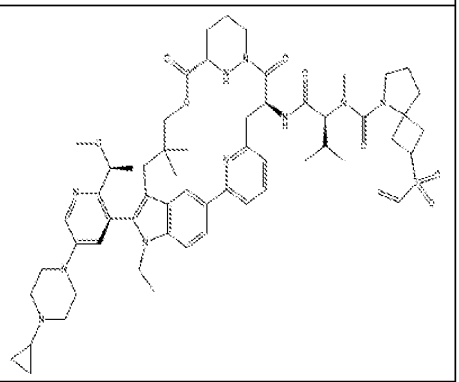
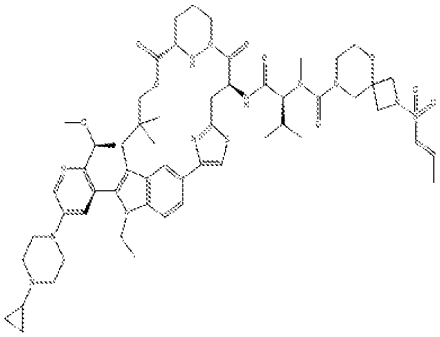
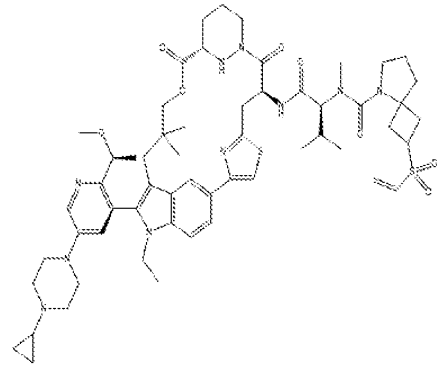
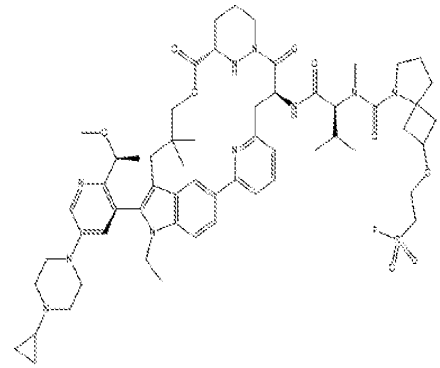
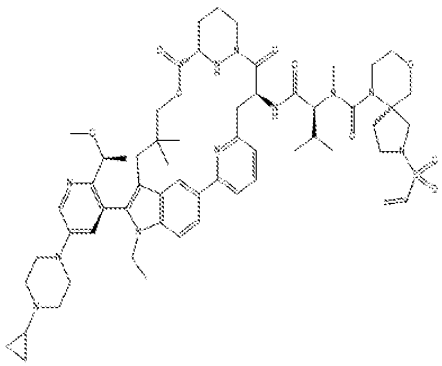
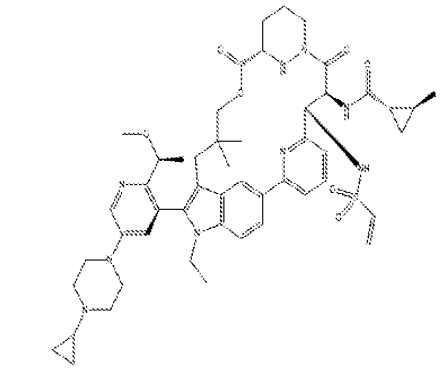
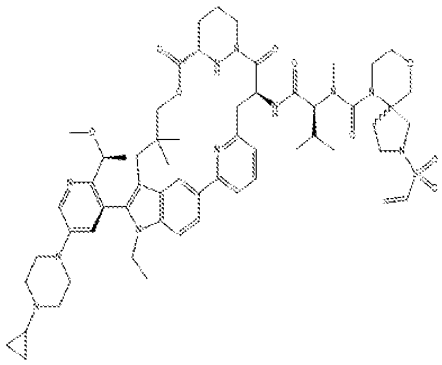
Table 2. Certain Compounds of the Present Invention

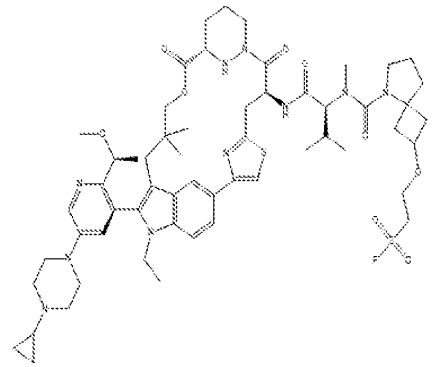
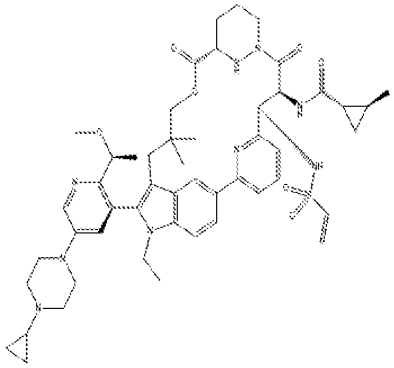
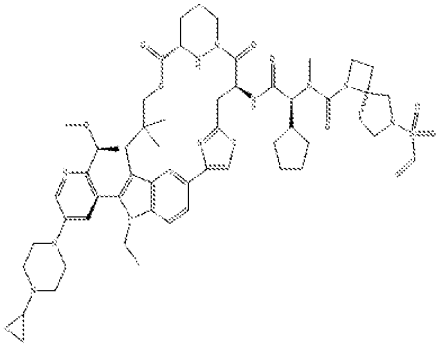
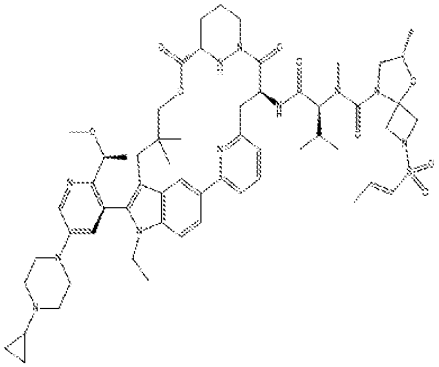
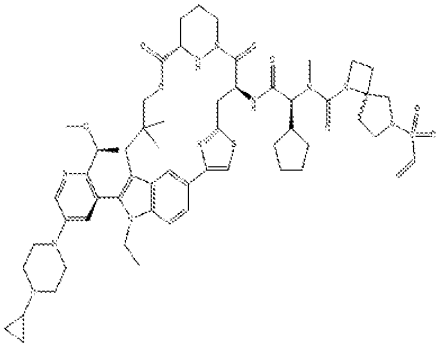
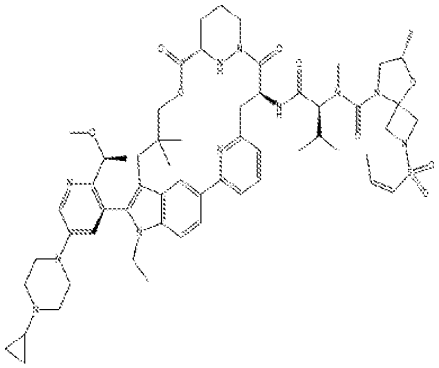
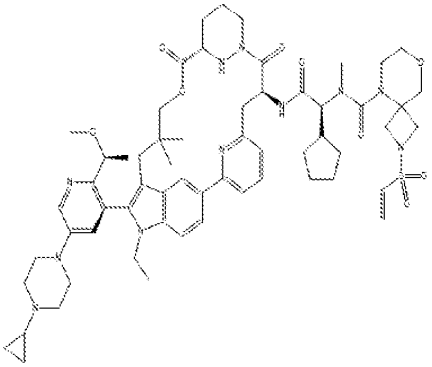
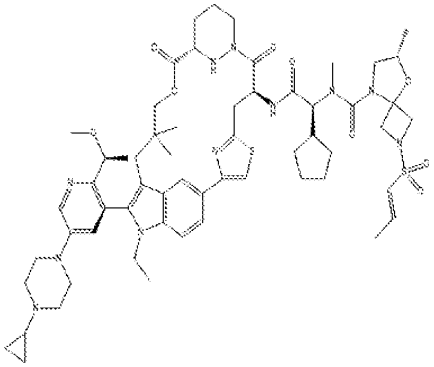
Ex#	Structure	Ex#	Structure
B1		B2	

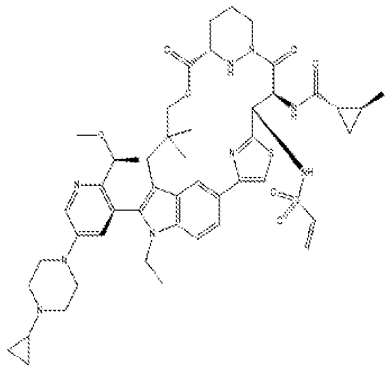
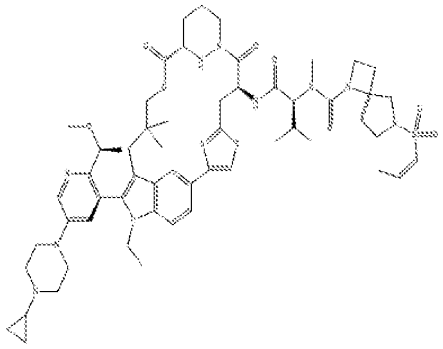
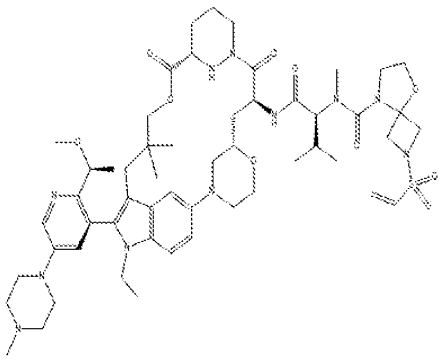
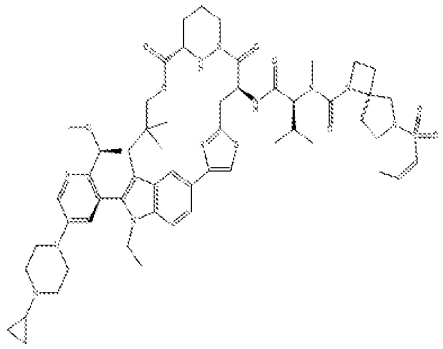
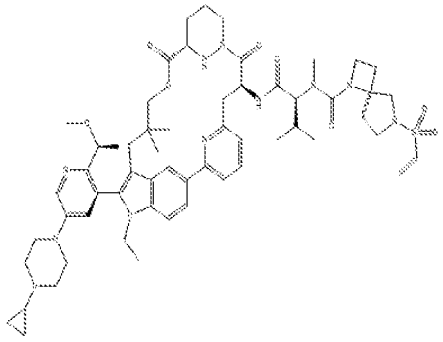
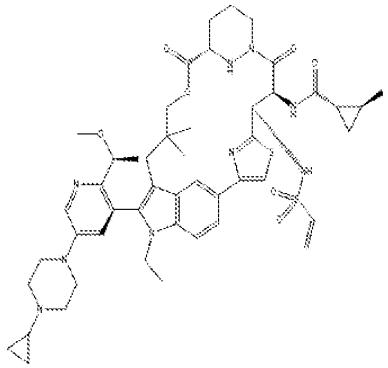
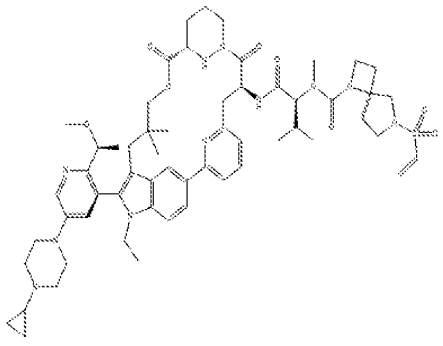
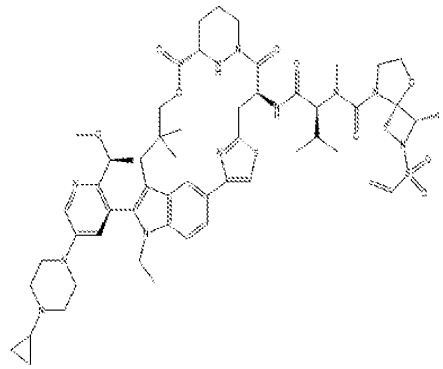
Ex#	Structure	Ex#	Structure
B3		B7	
B4		B8	
B5		B9	
B6		B10	

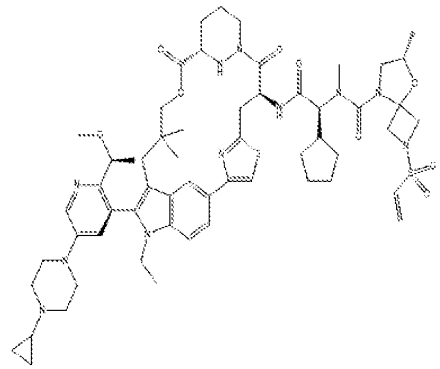
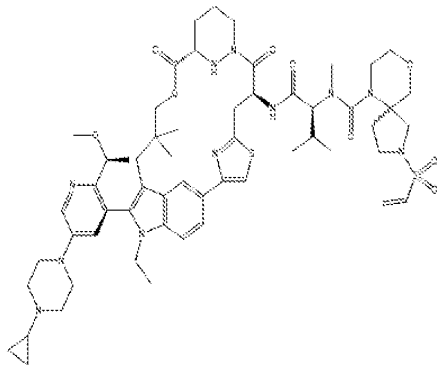
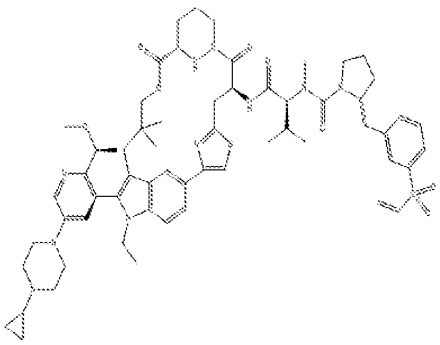
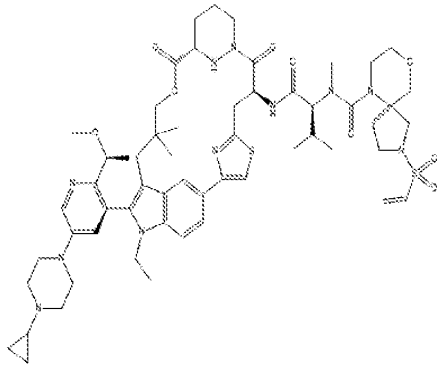
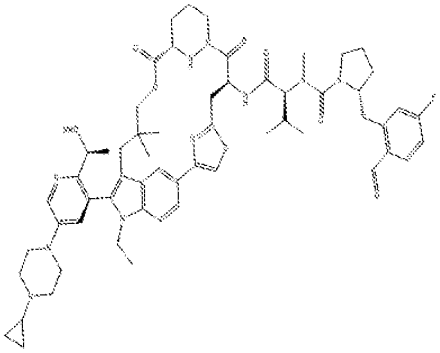
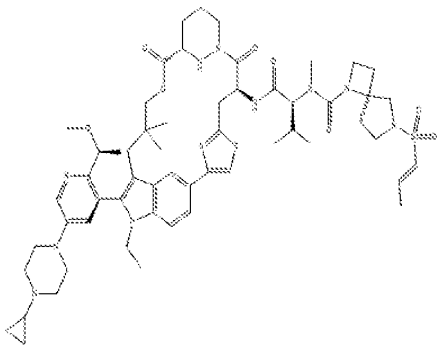
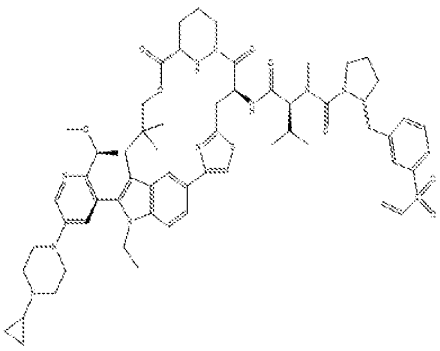
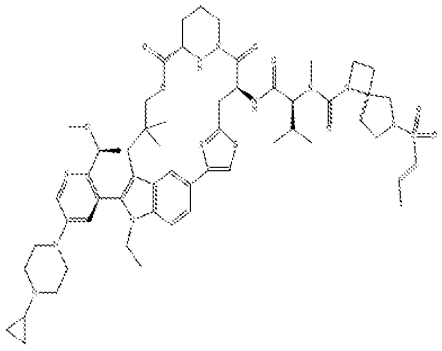
Ex#	Structure	Ex#	Structure
B11		B15	
B12		B16	
B13		B17	
B14		B18	

Ex#	Structure	Ex#	Structure
B19		B23	
B20		B24	
B21		B25	
B22		B26	

Ex#	Structure	Ex#	Structure
B27		B31	
B28		B32	
B29		B33	
B30		B34	

Ex#	Structure	Ex#	Structure
B35		B39	
B36		B40	
B37		B41	
B38		B42	

Ex#	Structure	Ex#	Structure
B43		B47	
B44		B48	
B45		B49	
B46		B50	

Ex#	Structure	Ex#	Structure
B51		B55	
B52		B56	
B53		B57	
B54		B58	

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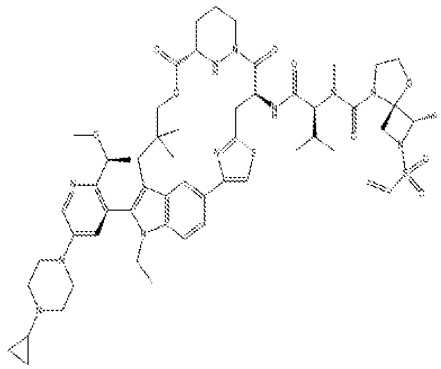
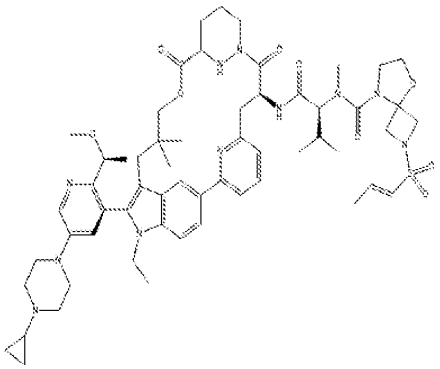
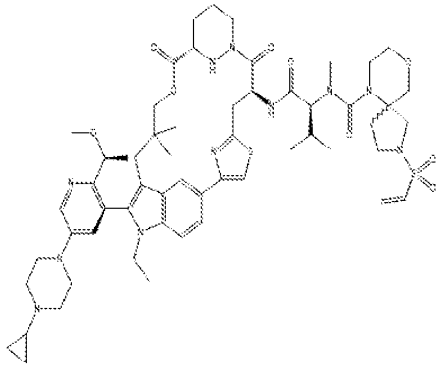
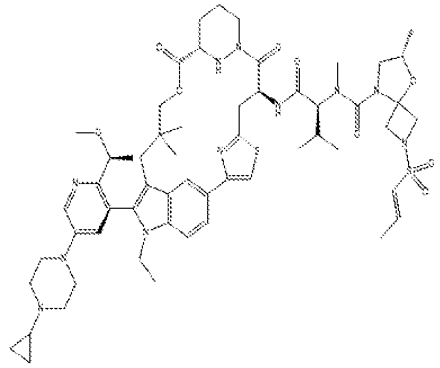
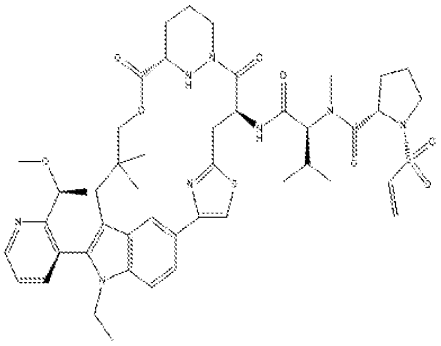
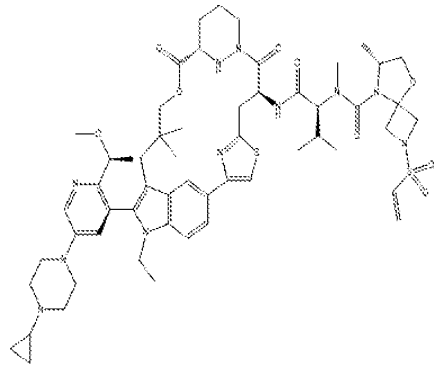
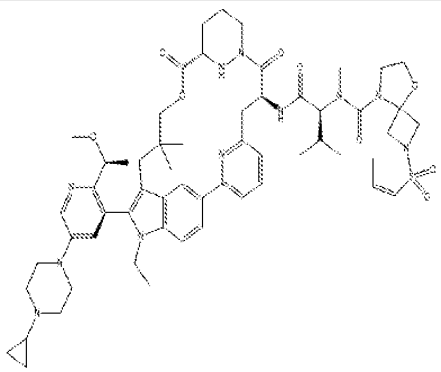
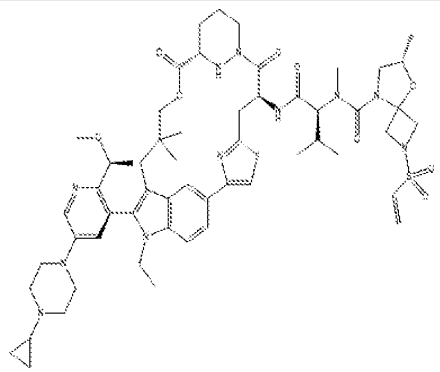
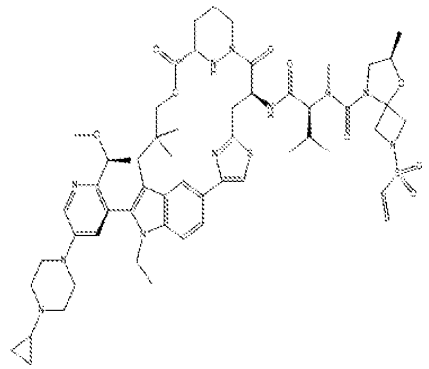
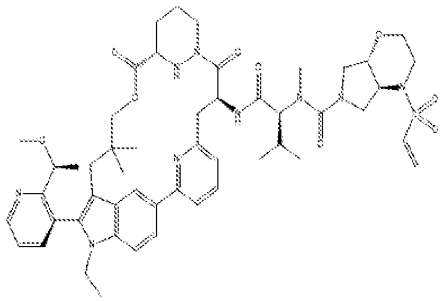
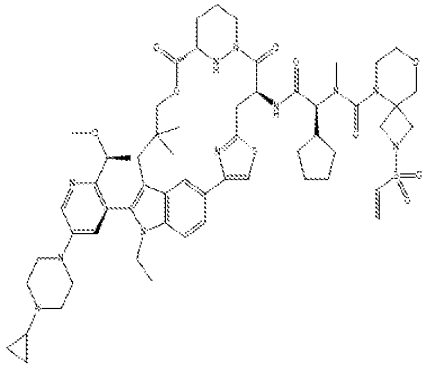
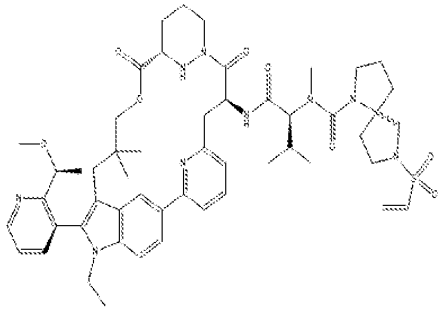
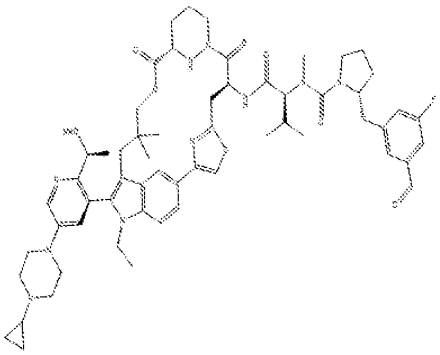
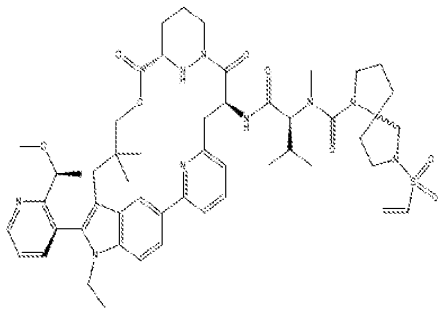
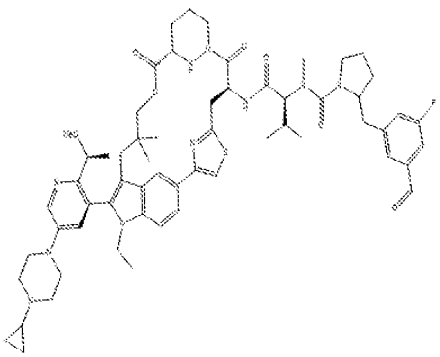
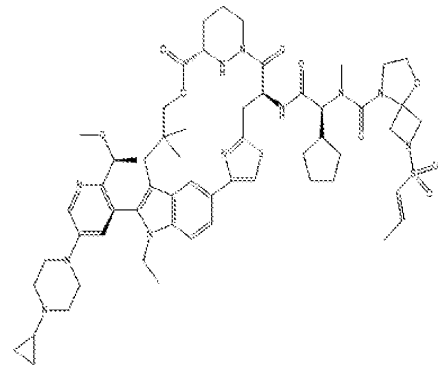
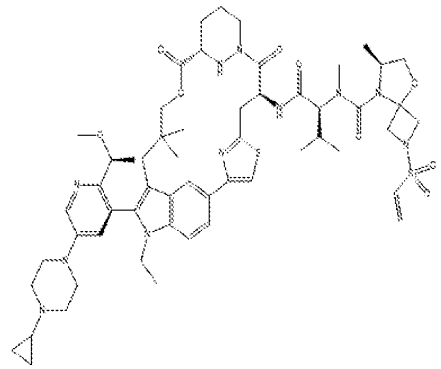
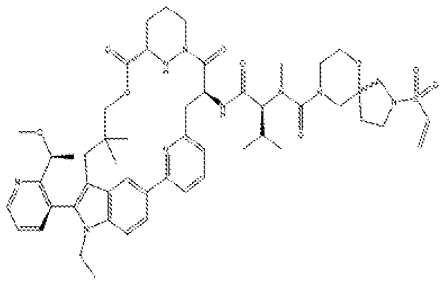
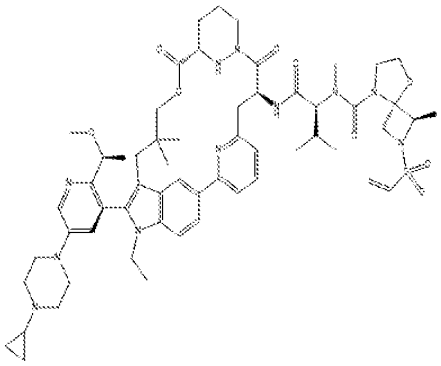
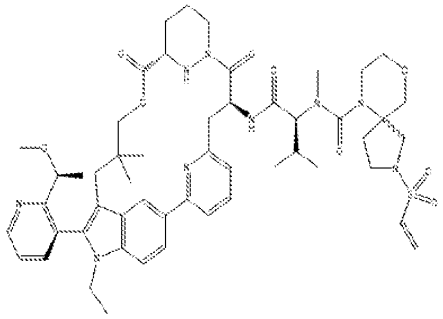
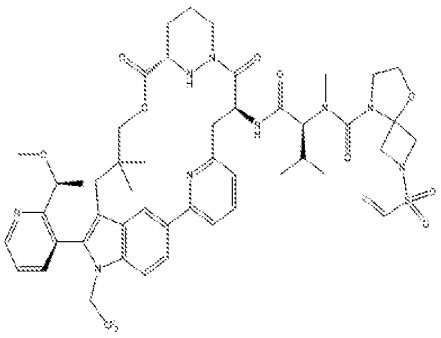
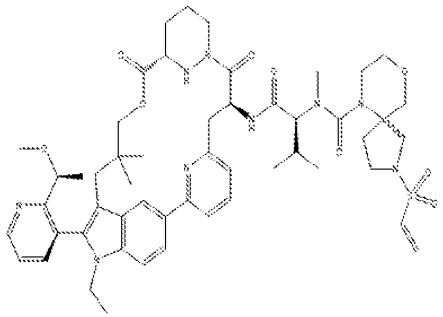
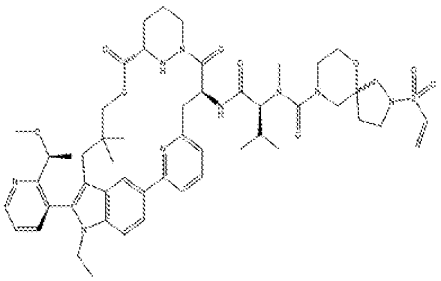
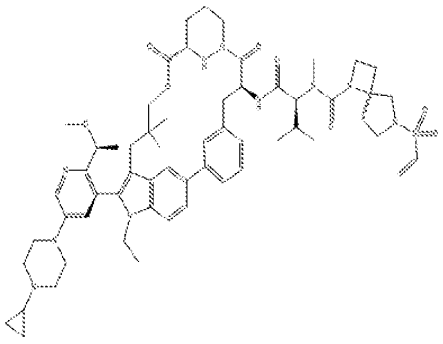
B59		B63	
B60		B64	
B61		B65	
B62		B66	

Ex#	Structure	Ex#	Structure
B67		B71	
B68		B72	
B69		B73	
B70		B74	

Ex#	Structure	Ex#	Structure
B75		B79	
B76		B80	
B77		B81	
B78		B82	

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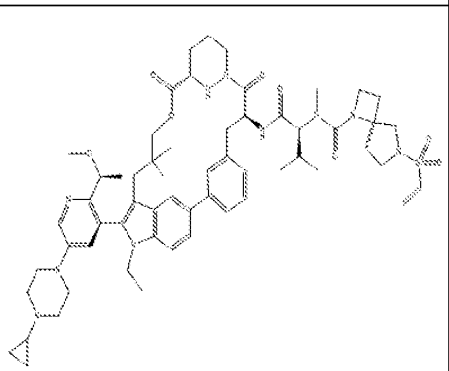
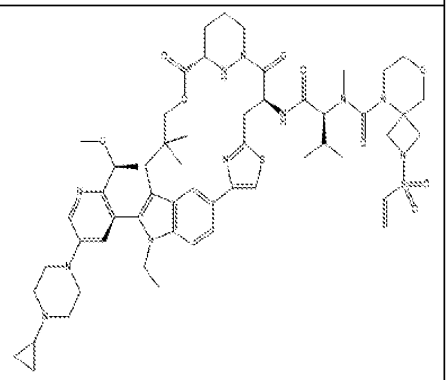
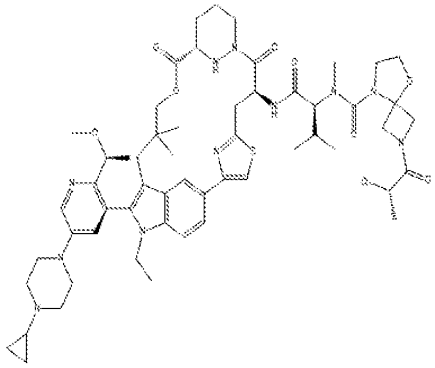
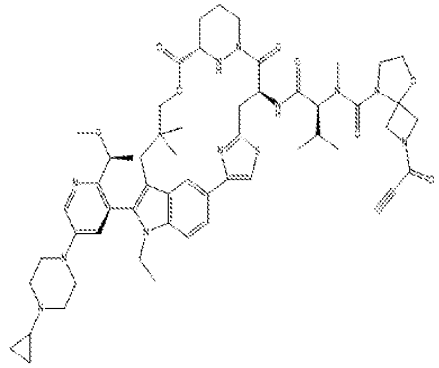
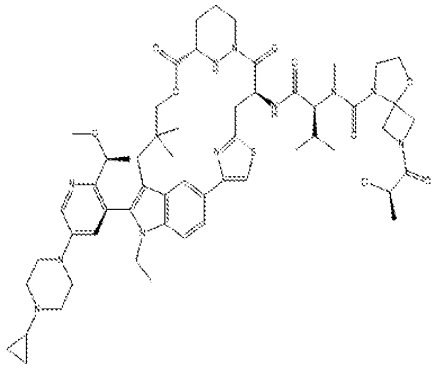
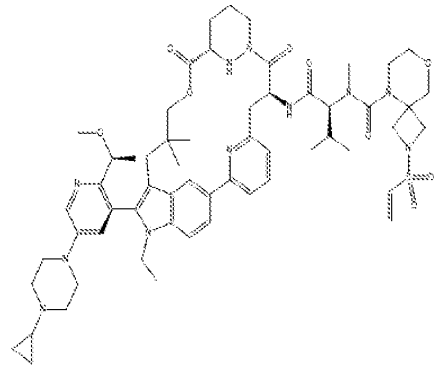
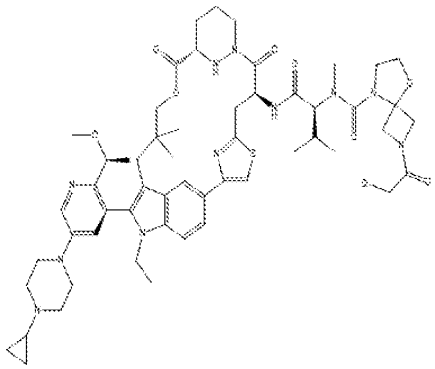
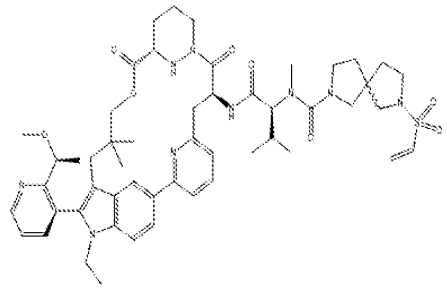
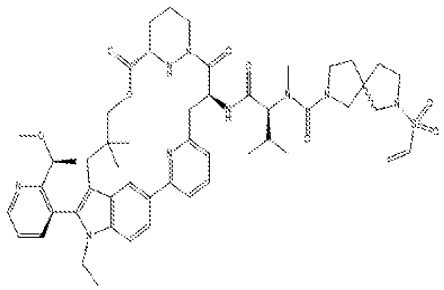
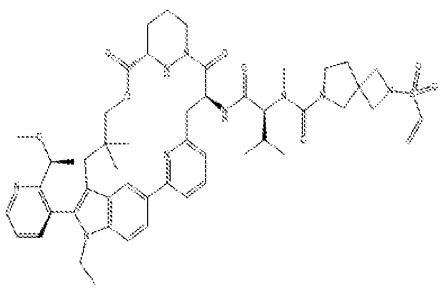
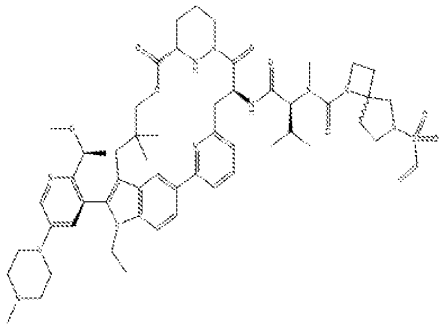
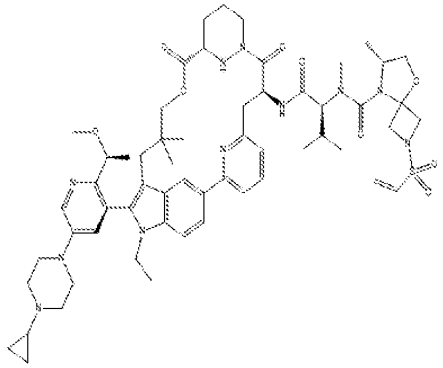
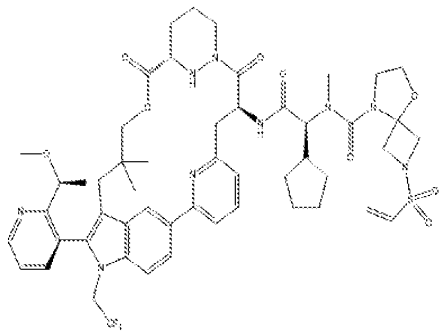
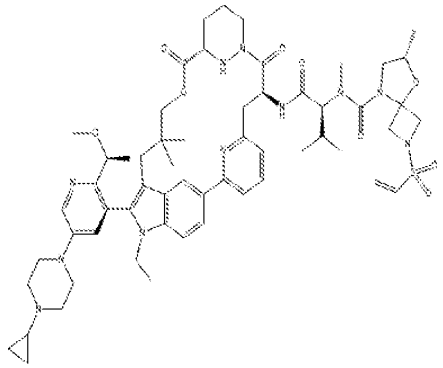
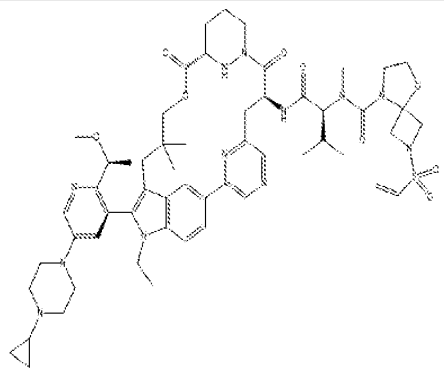
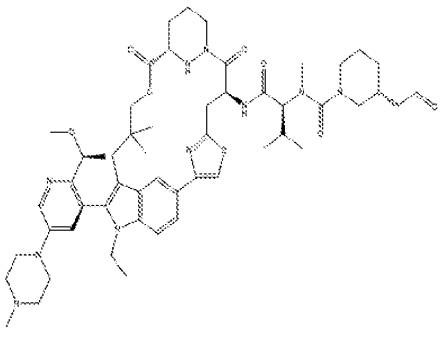
B83		B87	
B84		B88	
B85		B89	
B86		B90	

Ex#	Structure	Ex#	Structure
B91		B95	
B92		B96	
B93		B97	
B94		B98	

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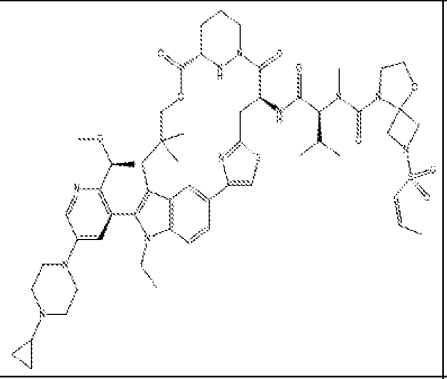
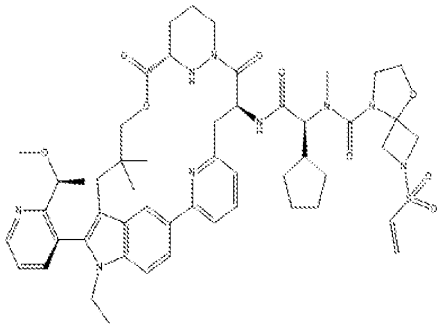
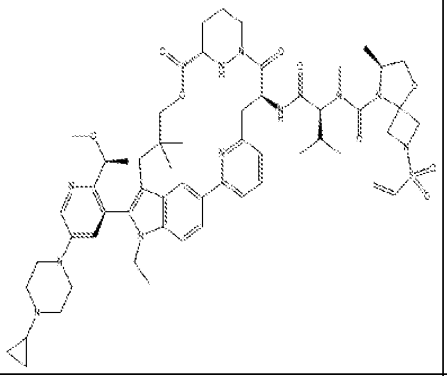
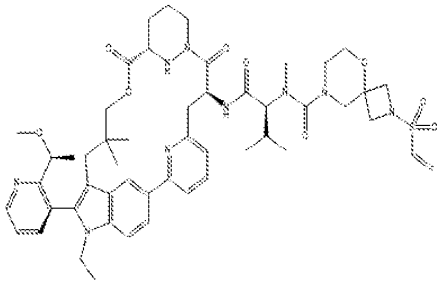
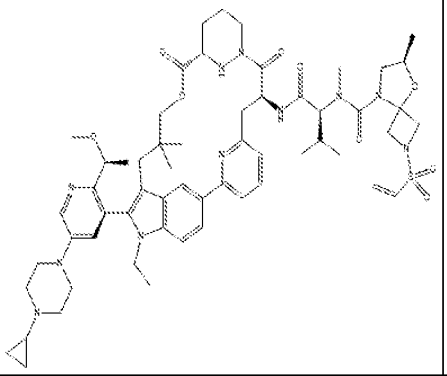
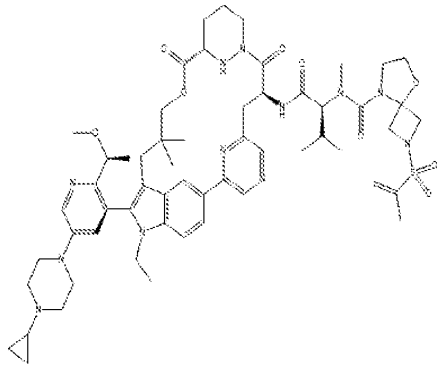
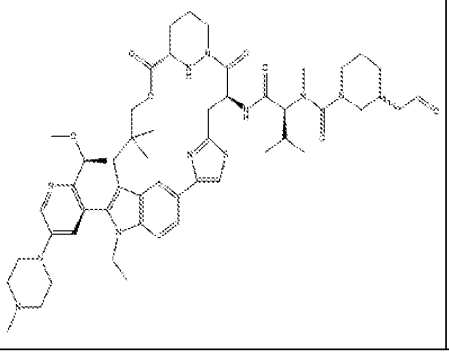
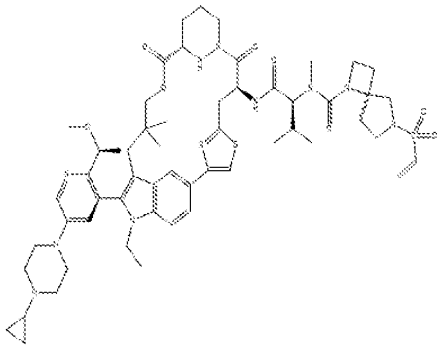
B99		B103	
B100		B104	
B101		B105	
B102		B106	

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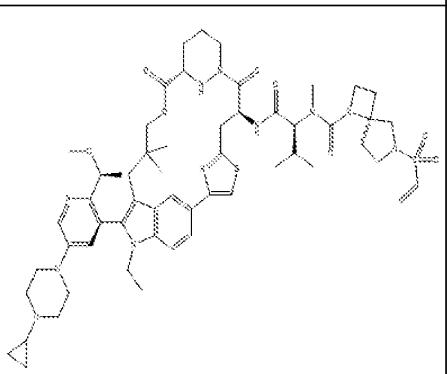
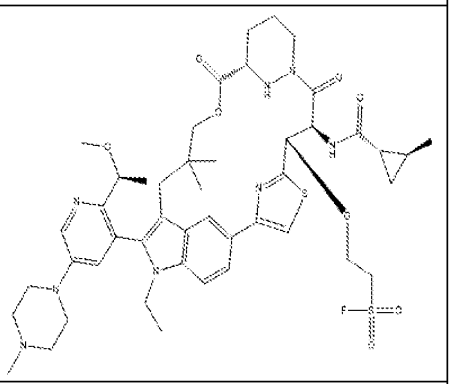
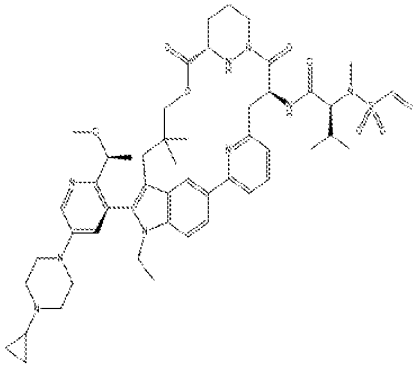
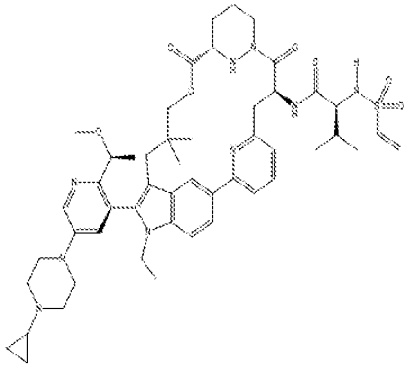
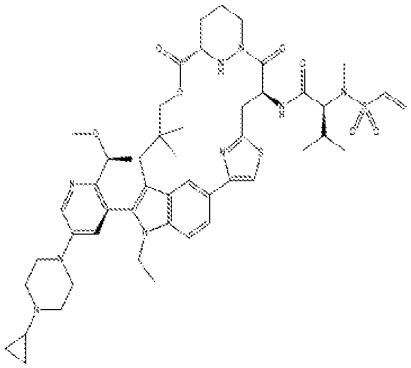
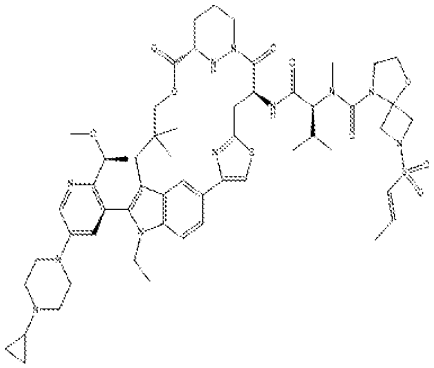
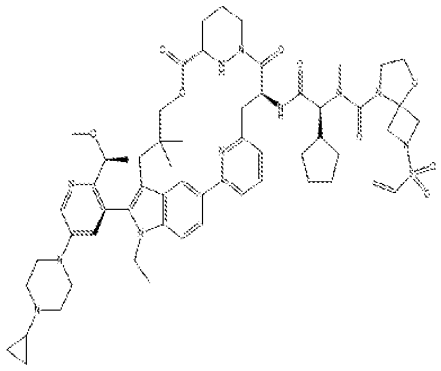
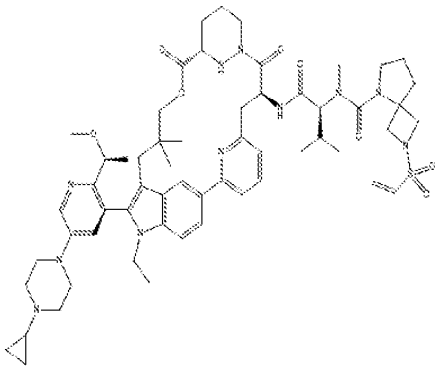
B107		B111	
B108		B112	
B109		B113	
B110		B114	

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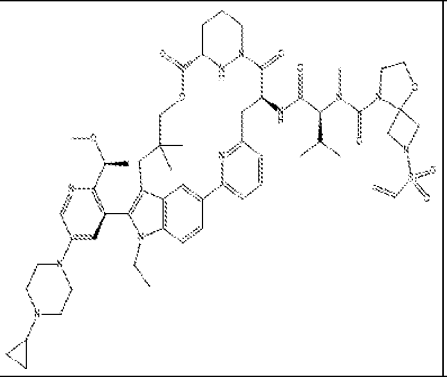
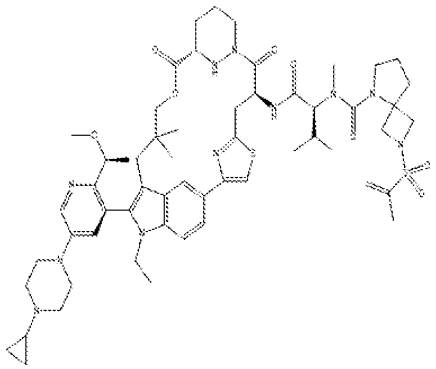
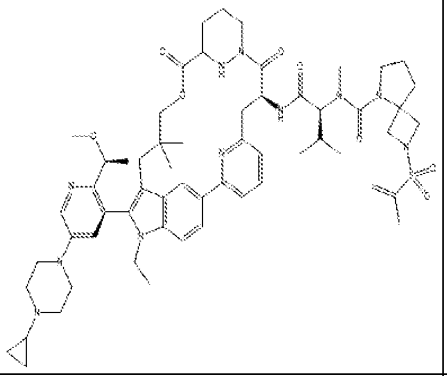
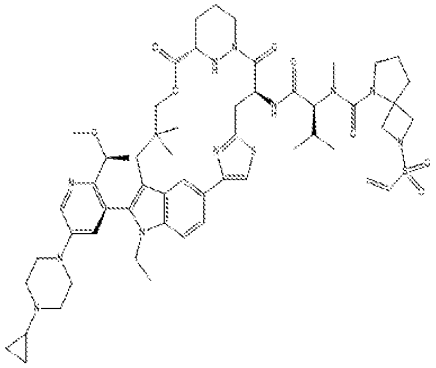
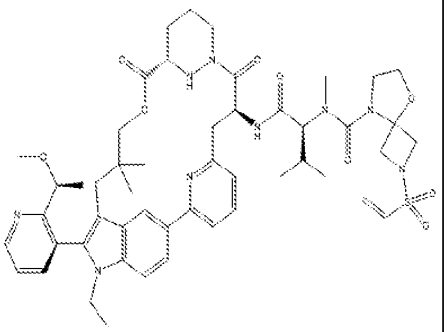
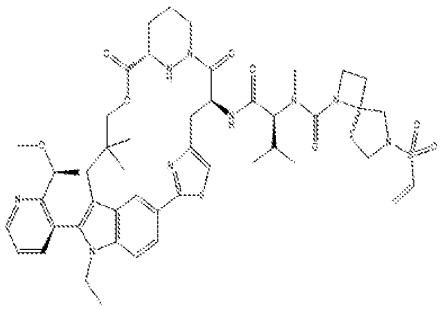
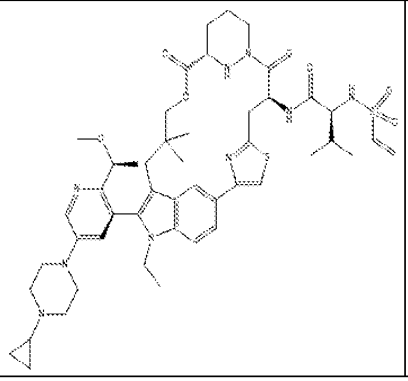
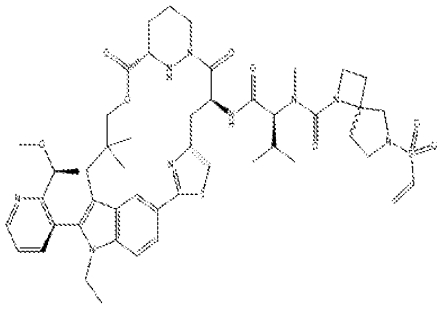
B115		B119	
B116		B120	
B117		B121	
B118		B122	

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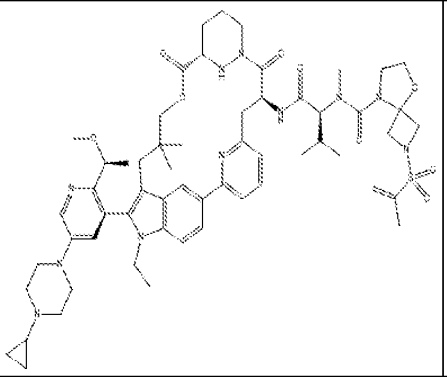
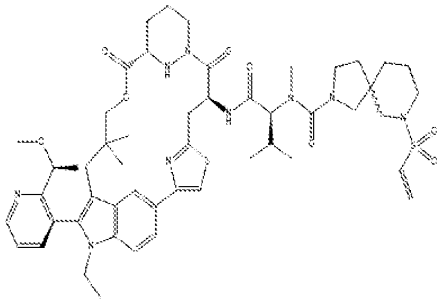
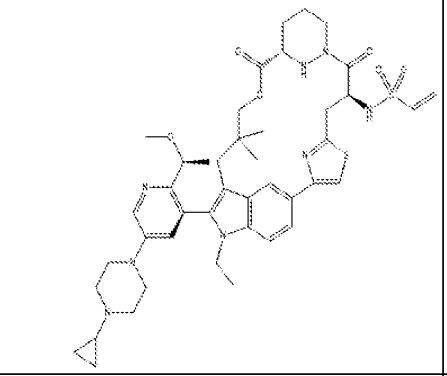
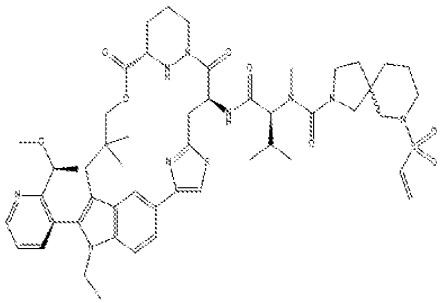
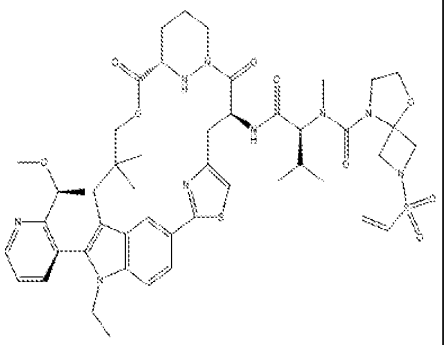
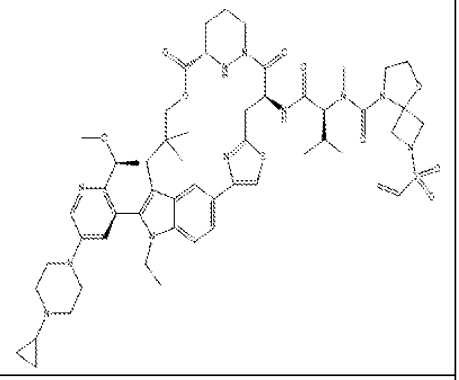
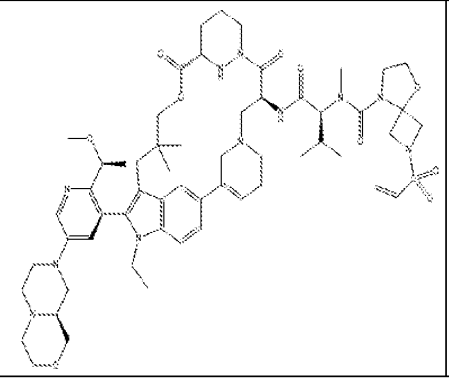
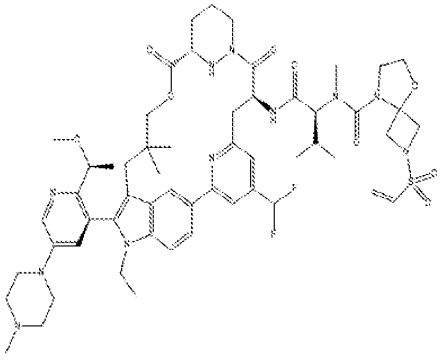
B123		B127	
B124		B128	
B125		B129	
B126		B130	

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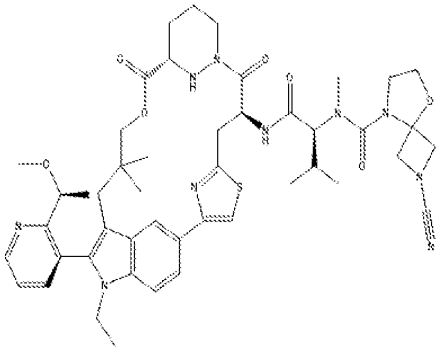
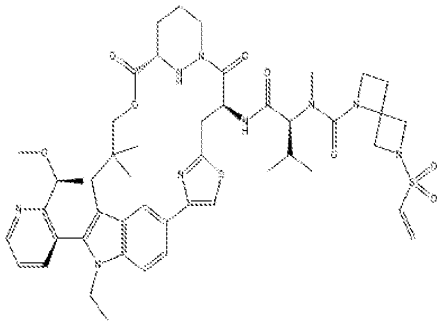
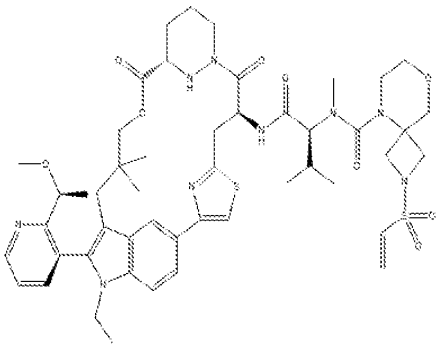
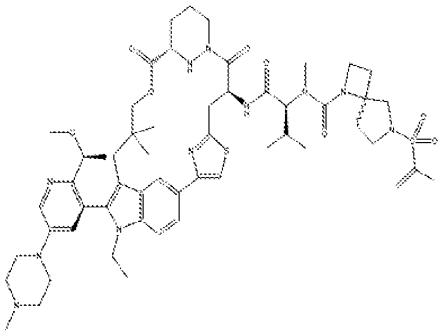
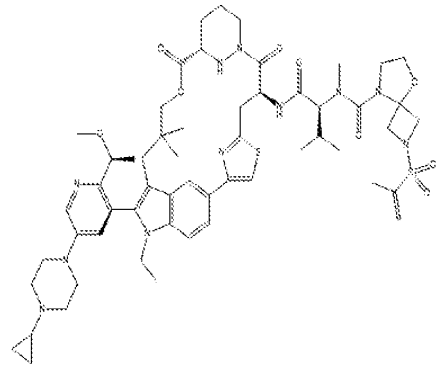
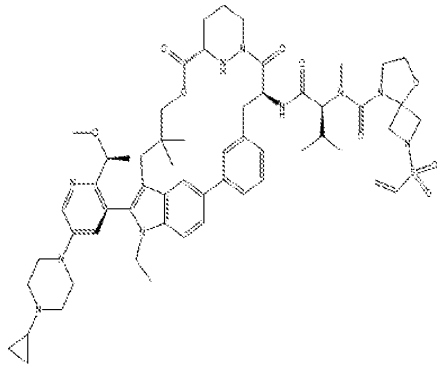
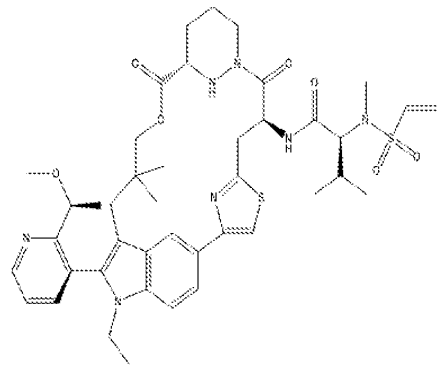
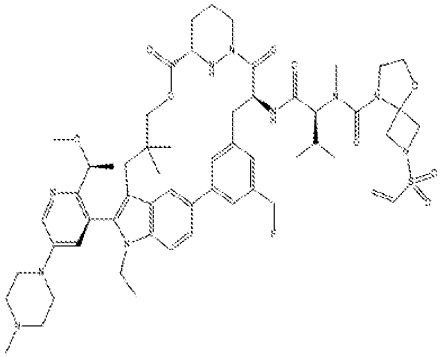
B131		B135	
B132		B136	
B133		B137	
B134		B138	

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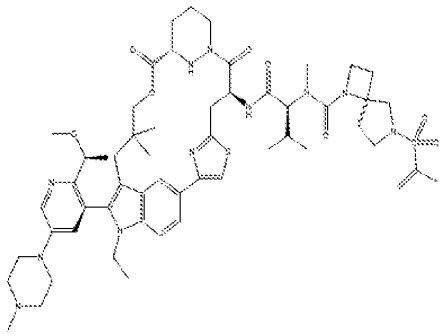
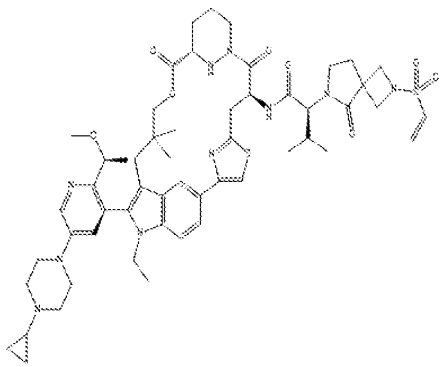
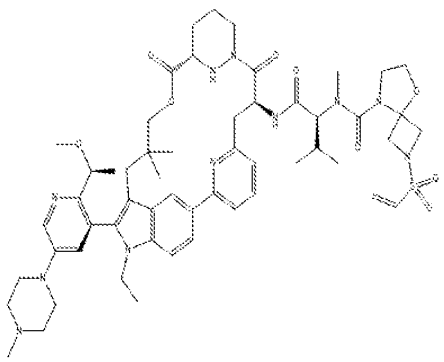
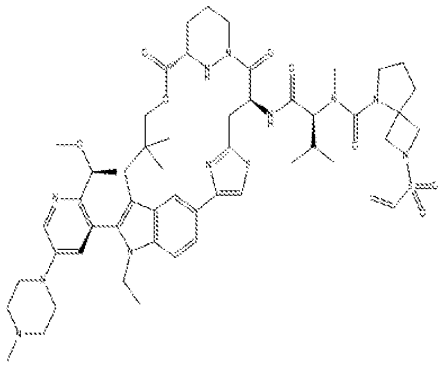
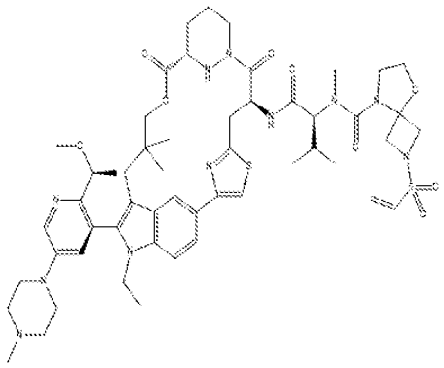
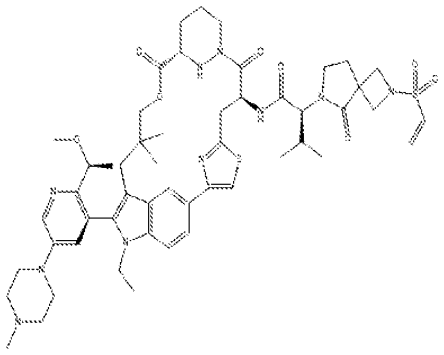
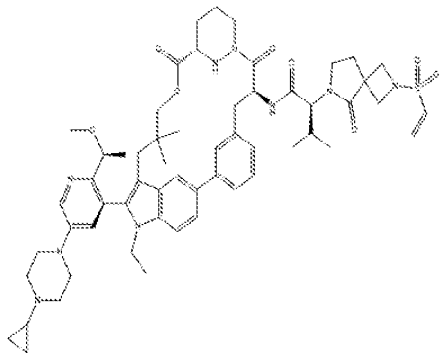
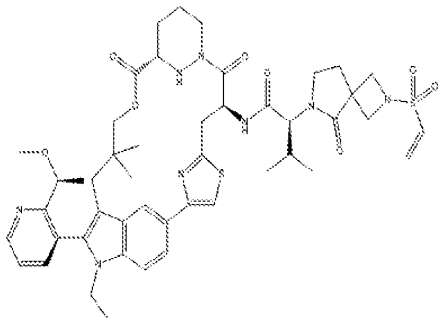
B139		B143	
B140		B144	
B141		B145	
B142		B146	

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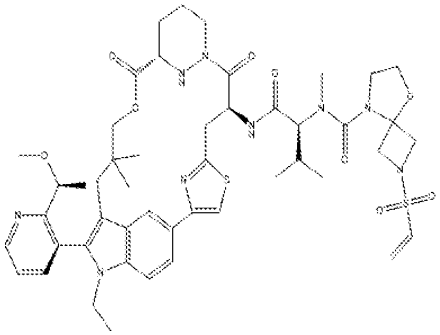
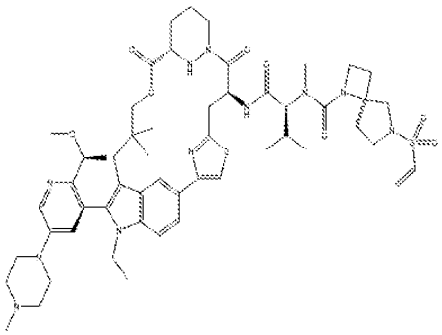
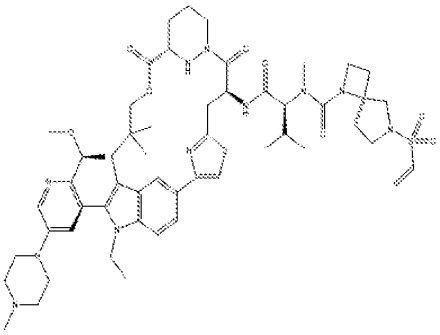
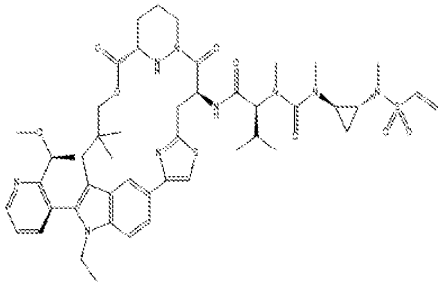
B147		B149	
B148		B150	

In some embodiments, a compound of the present invention is selective for one or more particular Ras mutants over other Ras mutants or wild-type compared to what is known in the art. Methods of measuring such selectivity are known in the art, such as the Ras-Raf binding assay, a protocol for which is provided above. Accordingly, in some embodiments, compounds of the present invention are selective for Ras having a mutation at Q61 (e.g., Q61H, Q61K, Q61L, or Q61R) over other Ras mutants or over wild-type, or combinations thereof. In some embodiments, compounds of the present invention are selective for N-Ras having a mutation at Q61 (e.g., Q61H, Q61K, Q61L, or Q61R) over other Ras mutants or over wild-type, or combinations thereof.

In some embodiments, compounds of the present invention exhibit an IC50 value of less than 1 μM for $NRAS^{Q61K}$ in the Ras-Raf binding assay described above. In some embodiments, compounds of the present invention exhibit an IC50 value of less than 1 μM for $NRAS^{Q61H}$ in the Ras-Raf binding assay described above. In some embodiments, compounds of the present invention exhibit an IC50 value of less than 1 μM for $NRAS^{Q61L}$ in the Ras-Raf binding assay described above. In some embodiments, compounds of the present invention exhibit an IC50 value of less than 1 μM for $NRAS^{Q61R}$ in the Ras-Raf binding assay described above. In some embodiments, compounds of the present invention exhibit an IC50 value of less than 1 μM for $KRAS^{Q61K}$ in the Ras-Raf binding assay described above.

In some embodiments, a compound of the present invention is or acts as a prodrug, such as with respect to administration to a cell or to a subject in need thereof.

Also provided are pharmaceutical compositions comprising a compound of the present invention, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

Compounds of the present invention are also adaptable for uses in antibody-drug conjugates as well as degrader applications.

Further provided is a method of treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof. The cancer may, for example, be pancreatic cancer, colorectal cancer, non-small cell lung cancer, acute myeloid leukemia, multiple myeloma, thyroid gland adenocarcinoma, a myelodysplastic syndrome, or squamous cell lung carcinoma. Other Ras mutations are described herein.

Further provided is a method of treating a Ras protein-related disorder in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof.

Further provided is a method of inhibiting a Ras protein in a cell, the method comprising contacting the cell with an effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof. For example, the Ras protein is K-Ras Q61K, N-Ras Q61H, N-Ras Q61K, N-Ras Q61L, or N-Ras Q61R. Other Ras proteins are described herein. The cell may be a cancer cell, such as a pancreatic cancer cell, a colorectal cancer cell, a lung cancer (e.g., non-small cell lung cancer cell), an acute myeloid leukemia cell, a multiple myeloma cell, a thyroid gland adenocarcinoma cell, a myelodysplastic syndrome cell, a melanoma cell, or a squamous cell lung carcinoma cell. Other cancer types are described herein. The cell may be in vivo or in vitro.

With respect to compounds of the present invention, one stereoisomer may exhibit better inhibition than another stereoisomer. For example, one atropisomer may exhibit inhibition, whereas the other atropisomer may exhibit little or no inhibition.

In some embodiments, a method or use described herein further comprises administering an additional anti-cancer therapy. In some embodiments, the additional anti-cancer therapy is a HER2 inhibitor, an EGFR inhibitor, a second Ras inhibitor, a SHP2 inhibitor, a SOS1 inhibitor, a Raf inhibitor, a MEK inhibitor, an ERK inhibitor, a PI3K inhibitor, a PTEN inhibitor, an AKT inhibitor, an mTORC1 inhibitor, a BRAF inhibitor, a PD-L1 inhibitor, a PD-1 inhibitor, a CDK4/6 inhibitor, or a combination thereof. In some embodiments, the additional anticancer therapy is a SHP2 inhibitor. Other additional anti-cancer therapies are described herein.

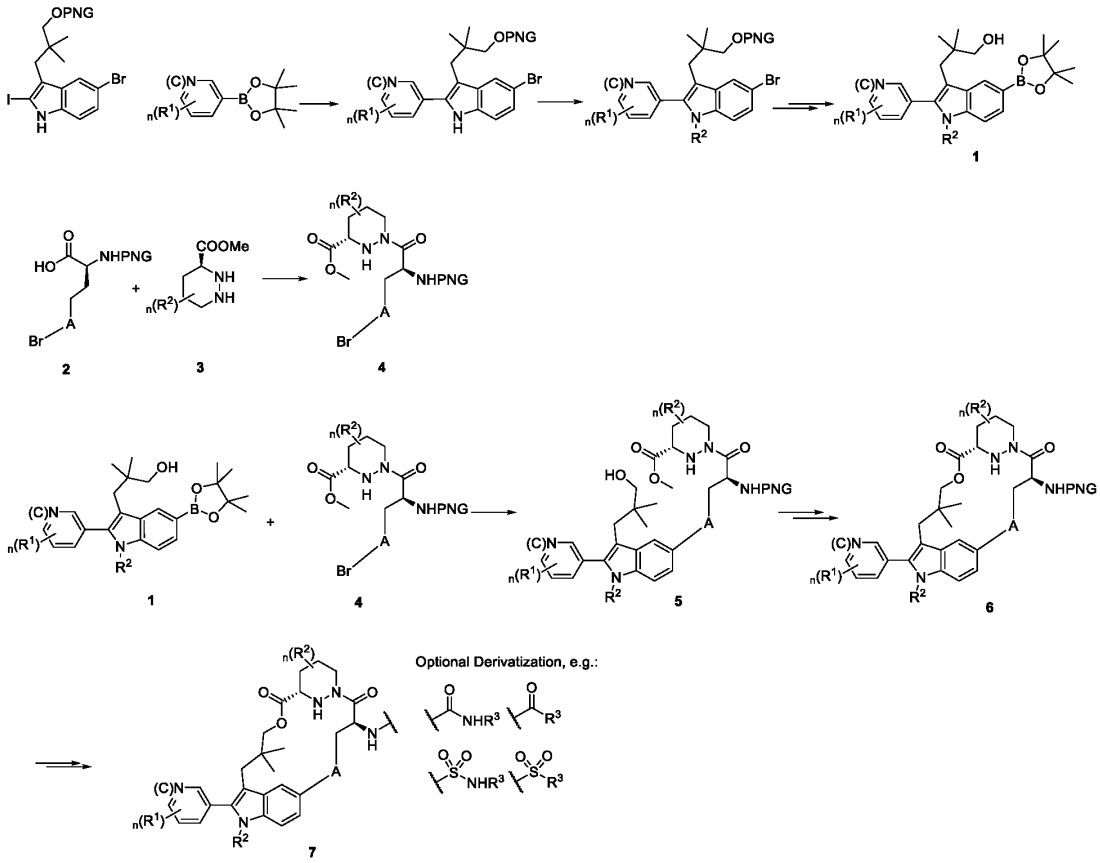
Methods of Synthesis

The compounds described herein may be made from commercially available starting materials or synthesized using known organic, inorganic, or enzymatic processes.

The compounds of the present invention can be prepared in a number of ways well known to those skilled in the art of organic synthesis. By way of example, compounds of the present invention can be synthesized using the methods described in the Scheme below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. As a further example, synthetic methods described in WO 2020/132597, WO 2021/091982, WO

2021/091967, WO 2021/091956, WO 2022/060836, WO 2022/235864, WO 2022/235870, WO 2023/060253, and WO 2023/133543, the disclosure of each of which is incorporated herein by reference, may be useful in preparing compounds of the invention. These methods include but are not limited to those methods described in the Schemes below.

Scheme 1. General synthesis of macrocyclic esters



A general synthesis of macrocyclic esters is outlined in Scheme 1. An appropriately substituted indolyl boronic ester (**1**) can be prepared in four steps starting from protected 3-(5-bromo-2-iodo-1H-indol-3-yl)-2,2-dimethylpropan-1-ol and appropriately substituted boronic acid, including palladium mediated coupling, alkylation, de-protection, and palladium mediated borylation reactions.

Methyl (*S*)-hexahydropyridazine-3-carboxylate analogs (**3**) can be prepared by a variety of methods highlighted below.

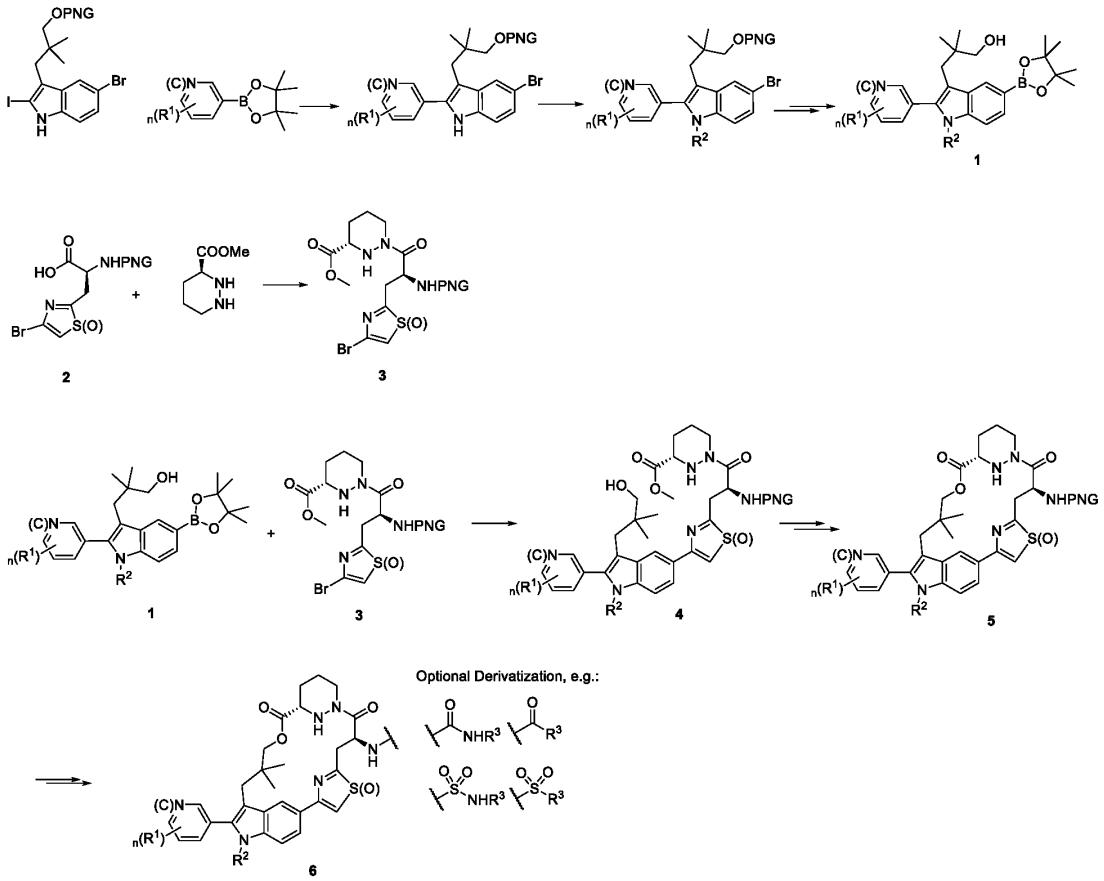
Methyl-amino-3-(4-bromothiazol-2-yl)propanoyl)hexahydropyridazine-3-carboxylate (**4**) can be prepared via coupling of (S)-2-amino-3-(4-bromothiazol-2-yl)propanoic acid (**2**) with methyl (*S*)-hexahydropyridazine-3-carboxylate derivative (**3**).

The final macrocyclic esters can be made by coupling of methyl-amino-3-(4-bromothiazol-2-yl)propanoyl)hexahydropyridazine-3-carboxylate (**4**) and an appropriately substituted indolyl boronic ester (**1**) in the presence of Pd catalyst followed by hydrolysis and macrolactonization steps to result in an appropriately protected macrocyclic intermediate (**5**). Deprotection and coupling with an appropriately

substituted carboxylic acid (or other coupling partner) results in a macrocyclic product. Additional deprotection or functionalization steps could be required to produce a final compound (**6**).

Further, with respect to Scheme 1, the thiazole may be replaced with an alternative optionally substituted 5 to 6-membered heteroarylene, an optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene (e.g., morpholino), or optionally substituted 6-membered arylene (e.g., phenyl).

Scheme 2. General synthesis of macrocyclic esters



A further general synthesis of macrocyclic esters is outlined in Scheme 2. An appropriately substituted indolyl boronic ester (**1**) can be prepared in four steps starting from protected 3-(5-bromo-2-iodo-1H-indol-3-yl)-2,2-dimethylpropan-1-ol and appropriately substituted boronic acid, including palladium mediated coupling, alkylation, de-protection, and palladium mediated borylation reactions.

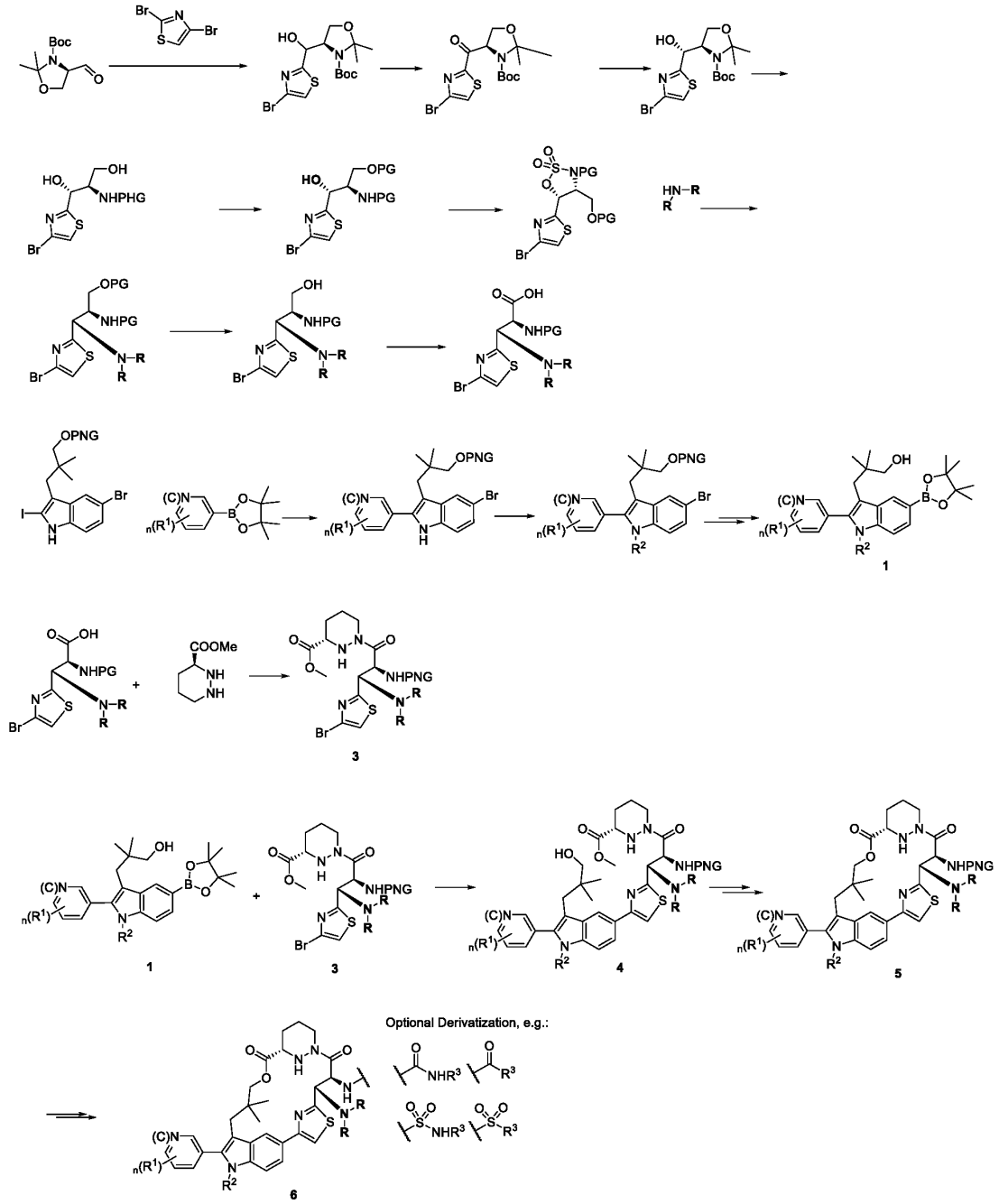
Methyl-amino-3-(4-bromothiazol-2-yl)propanoyl)hexahydropyridazine-3-carboxylate (**3**) can be prepared via coupling of (S)-2-amino-3-(4-bromothiazol-2-yl)propanoic acid (**2**) with methyl (*S*)-hexahydropyridazine-3-carboxylate (**3**).

The final macrocyclic esters can be made by coupling of methyl-amino-3-(4-bromothiazol-2-yl)propanoyl)hexahydropyridazine-3-carboxylate (**3**) and an appropriately substituted indolyl boronic ester (**1**) in the presence of Pd catalyst followed by hydrolysis and macrolactonization steps to result in an

appropriately protected macrocyclic intermediate (**4**). Deprotection and coupling with an appropriately substituted carboxylic acid (or other coupling partner) results in a macrocyclic product. Additional deprotection or functionalization steps could be required to produce a final compound (**6**).

Further, with respect to Scheme 1, the thiazole may be replaced with an alternative optionally substituted 5 to 6-membered heteroarylene, an optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene (e.g., morpholino), or optionally substituted 6-membered arylene (e.g., phenyl).

Scheme 3. Alternative General Synthesis of Macrocyclic Esters



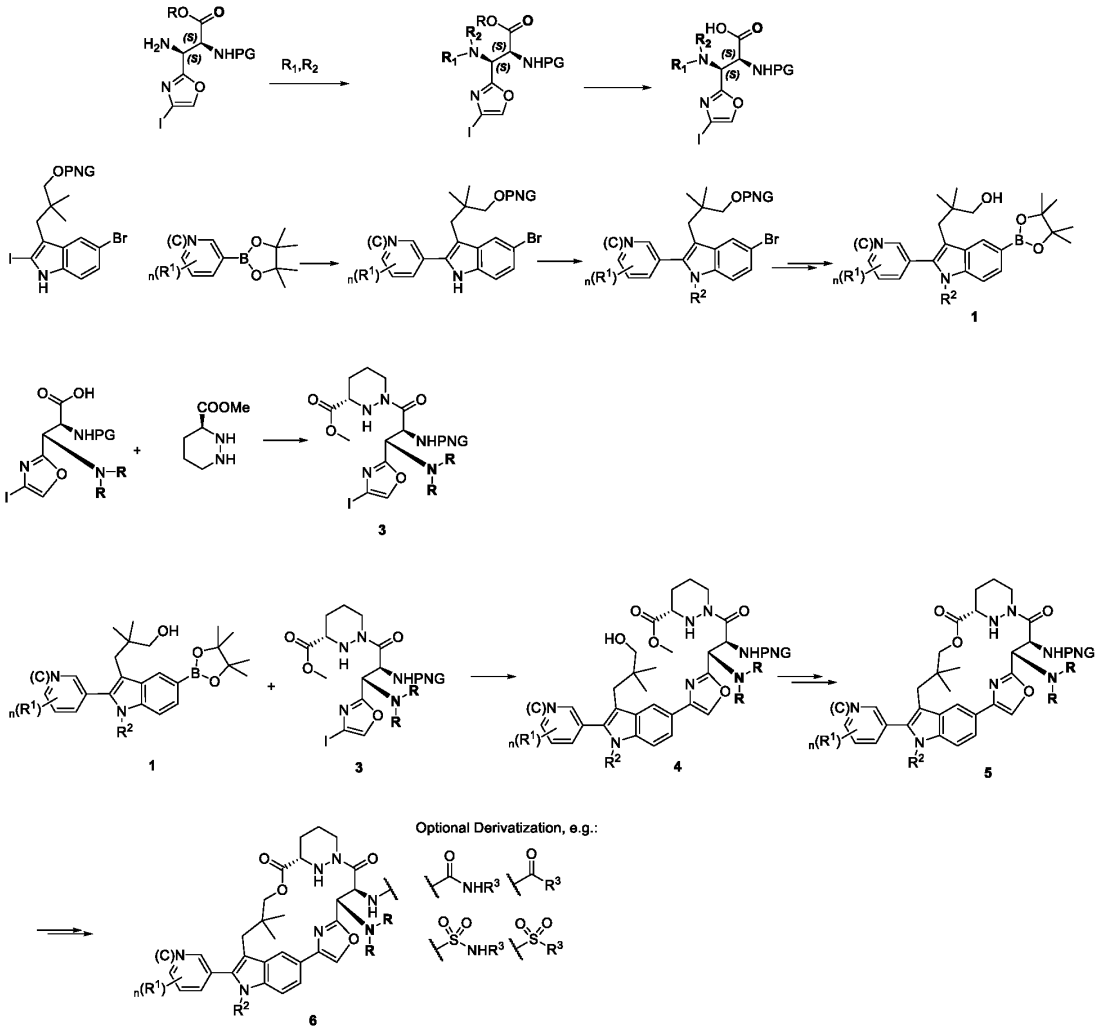
A further general synthesis of macrocyclic esters is outlined in Scheme 3. An appropriately substituted indolyl boronic ester (**1**) can be prepared as described in Schemes 1 and 2.

Amino-substituted (S)-2-amino-3-(4-bromothiazol-2-yl)propanoic acid can be prepared from 2,4-dibromothiazole as shown in Scheme 3, above.

Amino-substituted methyl-amino-3-(4-bromothiazol-2-yl)propanoyl)hexahydropyridazine-3-carboxylate (**3**) can be prepared via coupling of amino-substituted (S)-2-amino-3-(4-bromothiazol-2-yl)propanoic acid with methyl (*S*)-hexahydropyridazine-3-carboxylate.

The final macrocyclic esters can be prepared in the manner described in Schemes 1 and 2.

Scheme 4. Alternative General Synthesis of Macrocyclic Esters



Oxazole-containing compounds can be prepared in an analogous method as shown in Schemes 1-3 but with diamino-substituted iodo-oxazole (**3**). This compound can be prepared as shown in Scheme 4, above.

The final macrocyclic esters can be prepared in the manner described in Schemes 1 and 2.

Pharmaceutical Compositions and Methods of Use

The compounds with which the invention is concerned are Ras inhibitors and are useful in the treatment of cancer. Accordingly, one embodiment of the present invention provides pharmaceutical

compositions containing a compound of the invention or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, as well as methods of using the compounds of the invention to prepare such compositions.

As used herein, the term “pharmaceutical composition” refers to a compound, such as a compound of the present invention, or a pharmaceutically acceptable salt thereof, formulated together with a pharmaceutically acceptable excipient.

In some embodiments, a compound is present in a pharmaceutical composition in unit dose amount appropriate for administration in a therapeutic regimen that shows a statistically significant probability of achieving a predetermined therapeutic effect when administered to a relevant population. In some embodiments, pharmaceutical compositions may be specially formulated for administration in solid or liquid form, including those adapted for the following: oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, e.g., those targeted for buccal, sublingual, and systemic absorption, boluses, powders, granules, pastes for application to the tongue; parenteral administration, for example, by subcutaneous, intramuscular, intravenous or epidural injection as, for example, a sterile solution or suspension, or sustained-release formulation; topical application, for example, as a cream, ointment, or a controlled-release patch or spray applied to the skin, lungs, or oral cavity; intravaginally or intrarectally, for example, as a pessary, cream, or foam; sublingually; ocularly; transdermally; or nasally, pulmonary, and to other mucosal surfaces.

A “pharmaceutically acceptable excipient,” as used herein, refers to any inactive ingredient (for example, a vehicle capable of suspending or dissolving the active compound) having the properties of being nontoxic and non-inflammatory in a subject. Typical excipients include, for example: antiadherents, antioxidants, binders, coatings, compression aids, disintegrants, dyes (colors), emollients, emulsifiers, fillers (diluents), film formers or coatings, flavors, fragrances, glidants (flow enhancers), lubricants, preservatives, printing inks, sorbents, suspensing or dispersing agents, sweeteners, or waters of hydration. Excipients include, but are not limited to: butylated optionally substituted hydroxyltoluene (BHT), calcium carbonate, calcium phosphate (dibasic), calcium stearate, croscarmellose, crosslinked polyvinyl pyrrolidone, citric acid, crospovidone, cysteine, ethylcellulose, gelatin, optionally substituted hydroxylpropyl cellulose, optionally substituted hydroxylpropyl methylcellulose, lactose, magnesium stearate, maltitol, mannitol, methionine, methylcellulose, methyl paraben, microcrystalline cellulose, polyethylene glycol, polyvinyl pyrrolidone, povidone, pregelatinized starch, propyl paraben, retinyl palmitate, shellac, silicon dioxide, sodium carboxymethyl cellulose, sodium citrate, sodium starch glycolate, sorbitol, starch (corn), stearic acid, stearic acid, sucrose, talc, titanium dioxide, vitamin A, vitamin E, vitamin C, and xylitol. Those of ordinary skill in the art are familiar with a variety of agents and materials useful as excipients. See, e.g., e.g., Ansel, et al., Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems. Philadelphia: Lippincott, Williams & Wilkins, 2004; Gennaro, et al., Remington: The Science and Practice of Pharmacy. Philadelphia: Lippincott, Williams & Wilkins, 2000; and Rowe, Handbook of Pharmaceutical Excipients. Chicago, Pharmaceutical Press, 2005. In some embodiments, a composition includes at least two different pharmaceutically acceptable excipients.

Compounds described herein, whether expressly stated or not, may be provided or utilized in salt form, e.g., a pharmaceutically acceptable salt form, unless expressly stated to the contrary. The term

"pharmaceutically acceptable salt," as use herein, refers to those salts of the compounds described herein that are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and other animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, pharmaceutically acceptable salts are described in: Berge et al., *J. Pharmaceutical Sciences* 66:1-19, 1977 and in *Pharmaceutical Salts: Properties, Selection, and Use*, (Eds. P.H. Stahl and C.G. Wermuth), Wiley-VCH, 2008. The salts can be prepared in situ during the final isolation and purification of the compounds described herein or separately by reacting the free base group with a suitable organic acid.

The compounds of the invention may have ionizable groups so as to be capable of preparation as pharmaceutically acceptable salts. These salts may be acid addition salts involving inorganic or organic acids or the salts may, in the case of acidic forms of the compounds of the invention, be prepared from inorganic or organic bases. In some embodiments, the compounds are prepared or used as pharmaceutically acceptable salts prepared as addition products of pharmaceutically acceptable acids or bases. Suitable pharmaceutically acceptable acids and bases are well-known in the art, such as hydrochloric, sulfuric, hydrobromic, acetic, lactic, citric, or tartaric acids for forming acid addition salts, and potassium hydroxide, sodium hydroxide, ammonium hydroxide, caffeine, various amines, and the like for forming basic salts. Methods for preparation of the appropriate salts are well-established in the art.

Representative acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, hydrobromide, hydrochloride, hydroiodide, 2-optionally substituted hydroxyl-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate, undecanoate, valerate salts and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium and the like, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like.

As used herein, the term "subject" refers to any member of the animal kingdom. In some embodiments, "subject" refers to humans, at any stage of development. In some embodiments, "subject" refers to a human patient. In some embodiments, "subject" refers to non-human animals. In some embodiments, the non-human animal is a mammal (e.g., a rodent, a mouse, a rat, a rabbit, a monkey, a dog, a cat, a sheep, cattle, a primate, or a pig). In some embodiments, subjects include, but are not limited to, mammals, birds, reptiles, amphibians, fish, or worms. In some embodiments, a subject may be a transgenic animal, genetically-engineered animal, or a clone.

As used herein, the term "dosage form" refers to a physically discrete unit of a compound (e.g., a compound of the present invention) for administration to a subject. Each unit contains a predetermined quantity of compound. In some embodiments, such quantity is a unit dosage amount (or a whole fraction

thereof) appropriate for administration in accordance with a dosing regimen that has been determined to correlate with a desired or beneficial outcome when administered to a relevant population (i.e., with a therapeutic dosing regimen). Those of ordinary skill in the art appreciate that the total amount of a therapeutic composition or compound administered to a particular subject is determined by one or more attending physicians and may involve administration of multiple dosage forms.

As used herein, the term “dosing regimen” refers to a set of unit doses (typically more than one) that are administered individually to a subject, typically separated by periods of time. In some embodiments, a given therapeutic compound (e.g., a compound of the present invention) has a recommended dosing regimen, which may involve one or more doses. In some embodiments, a dosing regimen comprises a plurality of doses each of which are separated from one another by a time period of the same length; in some embodiments, a dosing regimen comprises a plurality of doses and at least two different time periods separating individual doses. In some embodiments, all doses within a dosing regimen are of the same unit dose amount. In some embodiments, different doses within a dosing regimen are of different amounts. In some embodiments, a dosing regimen comprises a first dose in a first dose amount, followed by one or more additional doses in a second dose amount different from the first dose amount. In some embodiments, a dosing regimen comprises a first dose in a first dose amount, followed by one or more additional doses in a second dose amount same as the first dose amount. In some embodiments, a dosing regimen is correlated with a desired or beneficial outcome when administered across a relevant population (i.e., is a therapeutic dosing regimen).

A “therapeutic regimen” refers to a dosing regimen whose administration across a relevant population is correlated with a desired or beneficial therapeutic outcome.

The term “treatment” (also “treat” or “treating”), in its broadest sense, refers to any administration of a substance (e.g., a compound of the present invention) that partially or completely alleviates, ameliorates, relieves, inhibits, delays onset of, reduces severity of, or reduces incidence of one or more symptoms, features, or causes of a particular disease, disorder, or condition. In some embodiments, such treatment may be administered to a subject who does not exhibit signs of the relevant disease, disorder, or condition or of a subject who exhibits only early signs of the disease, disorder, or condition. Alternatively, or additionally, in some embodiments, treatment may be administered to a subject who exhibits one or more established signs of the relevant disease, disorder, or condition. In some embodiments, treatment may be of a subject who has been diagnosed as suffering from the relevant disease, disorder, or condition. In some embodiments, treatment may be of a subject known to have one or more susceptibility factors that are statistically correlated with increased risk of development of the relevant disease, disorder, or condition.

The term “therapeutically effective amount” means an amount that is sufficient, when administered to a population suffering from or susceptible to a disease, disorder, or condition in accordance with a therapeutic dosing regimen, to treat the disease, disorder, or condition. In some embodiments, a therapeutically effective amount is one that reduces the incidence or severity of, or delays onset of, one or more symptoms of the disease, disorder, or condition. Those of ordinary skill in the art will appreciate that the term “therapeutically effective amount” does not in fact require successful treatment be achieved in a particular individual. Rather, a therapeutically effective amount may be that

amount that provides a particular desired pharmacological response in a significant number of subjects when administered to patients in need of such treatment. It is specifically understood that particular subjects may, in fact, be "refractory" to a "therapeutically effective amount." In some embodiments, reference to a therapeutically effective amount may be a reference to an amount as measured in one or more specific tissues (e.g., a tissue affected by the disease, disorder, or condition) or fluids (e.g., blood, saliva, serum, sweat, tears, urine). Those of ordinary skill in the art will appreciate that, in some embodiments, a therapeutically effective amount may be formulated or administered in a single dose. In some embodiments, a therapeutically effective amount may be formulated or administered in a plurality of doses, for example, as part of a dosing regimen.

For use as treatment of subjects, the compounds of the invention, or a pharmaceutically acceptable salt thereof, can be formulated as pharmaceutical or veterinary compositions. Depending on the subject to be treated, the mode of administration, and the type of treatment desired, e.g., prevention, prophylaxis, or therapy, the compounds, or a pharmaceutically acceptable salt thereof, are formulated in ways consonant with these parameters. A summary of such techniques may be found in *Remington: The Science and Practice of Pharmacy*, *21st Edition*, Lippincott Williams & Wilkins, (2005); and *Encyclopedia of Pharmaceutical Technology*, eds. J. Swarbrick and J. C. Boylan, 1988-1999, Marcel Dekker, New York, each of which is incorporated herein by reference.

Compositions can be prepared according to conventional mixing, granulating, or coating methods, respectively, and the present pharmaceutical compositions can contain from about 0.1% to about 99%, from about 5% to about 90%, or from about 1% to about 20% of a compound of the present invention, or pharmaceutically acceptable salt thereof, by weight or volume. In some embodiments, compounds, or a pharmaceutically acceptable salt thereof, described herein may be present in amounts totaling 1-95% by weight of the total weight of a composition, such as a pharmaceutical composition.

The composition may be provided in a dosage form that is suitable for intraarticular, oral, parenteral (e.g., intravenous, intramuscular), rectal, cutaneous, subcutaneous, topical, transdermal, sublingual, nasal, vaginal, intravesicular, intraurethral, intrathecal, epidural, aural, or ocular administration, or by injection, inhalation, or direct contact with the nasal, genitourinary, reproductive, or oral mucosa. Thus, the pharmaceutical composition may be in the form of, e.g., tablets, capsules, pills, powders, granulates, suspensions, emulsions, solutions, gels including hydrogels, pastes, ointments, creams, plasters, drenches, osmotic delivery devices, suppositories, enemas, injectables, implants, sprays, preparations suitable for iontophoretic delivery, or aerosols. The compositions may be formulated according to conventional pharmaceutical practice.

As used herein, the term "administration" refers to the administration of a composition (e.g., a compound, or a preparation that includes a compound as described herein) to a subject or system. Administration to an animal subject (e.g., to a human) may be by any appropriate route. For example, in some embodiments, administration may be bronchial (including by bronchial instillation), buccal, enteral, intradermal, intra-arterial, intradermal, intragastric, intramedullary, intramuscular, intranasal, intraperitoneal, intrathecal, intravenous, intraventricular, mucosal, nasal, oral, rectal, subcutaneous, sublingual, topical, tracheal (including by intratracheal instillation), transdermal, vaginal, or vitreal.

Formulations may be prepared in a manner suitable for systemic administration or topical or local administration. Systemic formulations include those designed for injection (e.g., intramuscular, intravenous, or subcutaneous injection) or may be prepared for transdermal, transmucosal, or oral administration. A formulation will generally include a diluent as well as, in some cases, adjuvants, buffers, preservatives and the like. Compounds, or a pharmaceutically acceptable salt thereof, can be administered also in liposomal compositions or as microemulsions.

For injection, formulations can be prepared in conventional forms as liquid solutions or suspensions or as solid forms suitable for solution or suspension in liquid prior to injection or as emulsions. Suitable excipients include, for example, water, saline, dextrose, glycerol and the like. Such compositions may also contain amounts of nontoxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like, such as, for example, sodium acetate, sorbitan monolaurate, and so forth.

Various sustained release systems for drugs have also been devised. See, for example, U.S. Patent No. 5,624,677.

Systemic administration may also include relatively noninvasive methods such as the use of suppositories, transdermal patches, transmucosal delivery and intranasal administration. Oral administration is also suitable for compounds of the invention, or a pharmaceutically acceptable salt thereof. Suitable forms include syrups, capsules, and tablets, as is understood in the art.

Each compound, or a pharmaceutically acceptable salt thereof, as described herein, may be formulated in a variety of ways that are known in the art. For example, the first and second agents of the combination therapy may be formulated together or separately. Other modalities of combination therapy are described herein.

The individually or separately formulated agents can be packaged together as a kit. Non-limiting examples include, but are not limited to, kits that contain, e.g., two pills, a pill and a powder, a suppository and a liquid in a vial, two topical creams, etc. The kit can include optional components that aid in the administration of the unit dose to subjects, such as vials for reconstituting powder forms, syringes for injection, customized IV delivery systems, inhalers, etc. Additionally, the unit dose kit can contain instructions for preparation and administration of the compositions. The kit may be manufactured as a single use unit dose for one subject, multiple uses for a particular subject (at a constant dose or in which the individual compounds, or a pharmaceutically acceptable salt thereof, may vary in potency as therapy progresses); or the kit may contain multiple doses suitable for administration to multiple subjects (“bulk packaging”). The kit components may be assembled in cartons, blister packs, bottles, tubes, and the like.

Formulations for oral use include tablets containing the active ingredient(s) in a mixture with non-toxic pharmaceutically acceptable excipients. These excipients may be, for example, inert diluents or fillers (e.g., sucrose, sorbitol, sugar, mannitol, microcrystalline cellulose, starches including potato starch, calcium carbonate, sodium chloride, lactose, calcium phosphate, calcium sulfate, or sodium phosphate); granulating and disintegrating agents (e.g., cellulose derivatives including microcrystalline cellulose, starches including potato starch, croscarmellose sodium, alginates, or alginic acid); binding agents (e.g., sucrose, glucose, sorbitol, acacia, alginic acid, sodium alginate, gelatin, starch, pregelatinized starch, microcrystalline cellulose, magnesium aluminum silicate, carboxymethylcellulose sodium,

methylcellulose, optionally substituted hydroxylpropyl methylcellulose, ethylcellulose, polyvinylpyrrolidone, or polyethylene glycol); and lubricating agents, glidants, and antiadhesives (e.g., magnesium stearate, zinc stearate, stearic acid, silicas, hydrogenated vegetable oils, or talc). Other pharmaceutically acceptable excipients can be colorants, flavoring agents, plasticizers, humectants, buffering agents, and the like.

Two or more compounds may be mixed together in a tablet, capsule, or other vehicle, or may be partitioned. In one example, the first compound is contained on the inside of the tablet, and the second compound is on the outside, such that a substantial portion of the second compound is released prior to the release of the first compound.

Formulations for oral use may also be provided as chewable tablets, or as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent (e.g., potato starch, lactose, microcrystalline cellulose, calcium carbonate, calcium phosphate or kaolin), or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin, or olive oil. Powders, granulates, and pellets may be prepared using the ingredients mentioned above under tablets and capsules in a conventional manner using, e.g., a mixer, a fluid bed apparatus or a spray drying equipment.

Dissolution or diffusion-controlled release can be achieved by appropriate coating of a tablet, capsule, pellet, or granulate formulation of compounds, or by incorporating the compound, or a pharmaceutically acceptable salt thereof, into an appropriate matrix. A controlled release coating may include one or more of the coating substances mentioned above or, e.g., shellac, beeswax, glycowax, castor wax, carnauba wax, stearyl alcohol, glyceryl monostearate, glyceryl distearate, glycerol palmitostearate, ethylcellulose, acrylic resins, dl-polylactic acid, cellulose acetate butyrate, polyvinyl chloride, polyvinyl acetate, vinyl pyrrolidone, polyethylene, polymethacrylate, methylmethacrylate, 2-optionally substituted hydroxylmethacrylate, methacrylate hydrogels, 1,3 butylene glycol, ethylene glycol methacrylate, or polyethylene glycols. In a controlled release matrix formulation, the matrix material may also include, e.g., hydrated methylcellulose, carnauba wax and stearyl alcohol, carbopol 934, silicone, glyceryl tristearate, methyl acrylate-methyl methacrylate, polyvinyl chloride, polyethylene, or halogenated fluorocarbon.

The liquid forms in which the compounds, or a pharmaceutically acceptable salt thereof, and compositions of the present invention can be incorporated for administration orally include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

Generally, when administered to a human, the oral dosage of any of the compounds of the invention, or a pharmaceutically acceptable salt thereof, will depend on the nature of the compound, and can readily be determined by one skilled in the art. A dosage may be, for example, about 0.001 mg to about 2000 mg per day, about 1 mg to about 1000 mg per day, about 5 mg to about 500 mg per day, about 100 mg to about 1500 mg per day, about 500 mg to about 1500 mg per day, about 500 mg to about 2000 mg per day, or any range derivable therein.

In some embodiments, the pharmaceutical composition may further comprise an additional compound having antiproliferative activity. Depending on the mode of administration, compounds, or a pharmaceutically acceptable salt thereof, will be formulated into suitable compositions to permit facile delivery. Each compound, or a pharmaceutically acceptable salt thereof, of a combination therapy may be formulated in a variety of ways that are known in the art. For example, the first and second agents of the combination therapy may be formulated together or separately. Desirably, the first and second agents are formulated together for the simultaneous or near simultaneous administration of the agents.

It will be appreciated that the compounds and pharmaceutical compositions of the present invention can be formulated and employed in combination therapies, that is, the compounds and pharmaceutical compositions can be formulated with or administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. The particular combination of therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics or procedures and the desired therapeutic effect to be achieved. It will also be appreciated that the therapies employed may achieve a desired effect for the same disorder, or they may achieve different effects (e.g., control of any adverse effects).

Administration of each drug in a combination therapy, as described herein, can, independently, be one to four times daily for one day to one year, and may even be for the life of the subject. Chronic, long-term administration may be indicated.

Methods of Use

In some embodiments, the invention discloses a method of treating a disease or disorder that is characterized by aberrant Ras activity due to a Ras mutant. In some embodiments, the disease or disorder is a cancer.

Accordingly, also provided is a method of treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising such a compound or salt. In some embodiments, the cancer is colorectal cancer, non-small cell lung cancer, small-cell lung cancer, pancreatic cancer, appendiceal cancer, melanoma, acute myeloid leukemia, small bowel cancer, ampullary cancer, germ cell cancer, cervical cancer, cancer of unknown primary origin, endometrial cancer, esophagogastric cancer, GI neuroendocrine cancer, ovarian cancer, sex cord stromal tumor cancer, hepatobiliary cancer, or bladder cancer. In some embodiments, the cancer is appendiceal, endometrial or melanoma. Also provided is a method of treating a Ras protein-related disorder in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising such a compound or salt.

In some embodiments, the compounds of the present invention or pharmaceutically acceptable salts thereof, pharmaceutical compositions comprising such compounds or salts, and methods provided herein may be used for the treatment of a wide variety of cancers including tumors such as lung, prostate, breast, brain, skin, cervical carcinomas, testicular carcinomas, etc. More particularly, cancers that may be treated by the compounds or salts thereof, pharmaceutical compositions comprising such compounds or

salts, and methods of the invention include, but are not limited to tumor types such as astrocytic, breast, cervical, colorectal, endometrial, esophageal, gastric, head and neck, hepatocellular, laryngeal, lung, oral, ovarian, prostate, and thyroid carcinomas and sarcomas. Other cancers include, for example:

Cardiac, for example: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma, and teratoma;

Lung, for example: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma;

Gastrointestinal, for example: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma);

Genitourinary tract, for example: kidney (adenocarcinoma, Wilm's tumor (nephroblastoma), lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma);

Liver, for example: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma;

Biliary tract, for example: gall bladder carcinoma, ampullary carcinoma, cholangiocarcinoma;

Bone, for example: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma, and giant cell tumors;

Nervous system, for example: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, neurofibromatosis type 1, meningioma, glioma, sarcoma);

Gynecological, for example: uterus (endometrial carcinoma, uterine carcinoma, uterine corpus endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma);

Hematologic, for example: blood (myeloid leukemia (acute and chronic), acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases (e.g., myelofibrosis and myeloproliferative neoplasms), multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma (malignant lymphoma);

Skin, for example: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and

Adrenal glands, for example: neuroblastoma.

In some embodiments, the Ras protein is wild type (Ras^{WT}). Accordingly, in some embodiments, a compound of the present invention is employed in a method of treating a patient having a cancer comprising a Ras^{WT} (e.g., K-Ras^{WT}, H-Ras^{WT} or N-Ras^{WT}). In some embodiments, the Ras protein is Ras amplification (e.g., K-Ras^{amp}). Accordingly, in some embodiments, a compound of the present invention is employed in a method of treating a patient having a cancer comprising a Ras^{amp} (K-Ras^{amp}, H-Ras^{amp} or N-Ras^{amp}). In some embodiments, the cancer comprises a Ras mutation, such as a Ras mutation described herein. In some embodiments, a mutation is selected from: K-Ras Q61K, N-Ras Q61R, N-Ras Q61K, N-Ras Q61L, or N-Ras Q61H, or combinations thereof.

Methods of detecting Ras mutations are known in the art. Such means include, but are not limited to direct sequencing, and utilization of a high-sensitivity diagnostic assay (with CE-IVD mark), e.g., as described in Domagala, et al., Pol J Pathol 3: 145-164 (2012), incorporated herein by reference in its entirety, including TheraScreen PCR; AmoyDx; PNAClamp; RealQuality; EntroGen; LightMix; StripAssay; Hybcell plexA; Devyser; Surveyor; Cobas; and TheraScreen Pyro. See, also, e.g., WO 2020/106640.

Also provided is a method of inhibiting a Ras protein in a cell, the method comprising contacting the cell with an effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof. A method of inhibiting RAF-Ras binding, the method comprising contacting the cell with an effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof, is also provided. The cell may be a cancer cell. The cancer cell may be of any type of cancer described herein. The cell may be in vivo or in vitro.

Combination Therapy

The methods of the invention may include a compound of the present invention used alone or in combination with one or more additional therapies (e.g., non-drug treatments or therapeutic agents). The dosages of one or more of the additional therapies (e.g., non-drug treatments or therapeutic agents) may be reduced from standard dosages when administered alone. For example, doses may be determined empirically from drug combinations and permutations or may be deduced by isobolographic analysis (e.g., Black et al., Neurology 65:S3-S6 (2005)).

A compound of the present invention may be administered before, after, or concurrently with one or more of such additional therapies. When combined, dosages of a compound of the invention and dosages of the one or more additional therapies (e.g., non-drug treatment or therapeutic agent) provide a therapeutic effect (e.g., synergistic or additive therapeutic effect). A compound of the present invention and an additional therapy, such as an anti-cancer agent, may be administered together, such as in a

unitary pharmaceutical composition, or separately and, when administered separately, this may occur simultaneously or sequentially. Such sequential administration may be close or remote in time.

In certain embodiments, compositions of the disclosure comprise a compound of the present invention and one additional therapeutic agent. In certain embodiments, compositions of the disclosure comprise a compound of the present invention and two additional therapeutic agents. In certain embodiments, compositions of the disclosure comprise a compound of the present invention and three additional therapeutic agents. In certain embodiments, compositions of the disclosure comprise a compound of the present invention and four or more additional therapeutic agents.

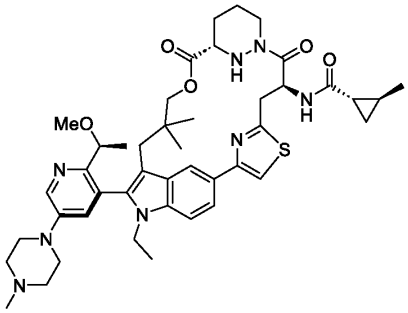
Also provided are pharmaceutical compositions including the combinations, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. Compositions comprising a combination of therapeutic agents may be used in methods of modulating RAS (e.g., in a subject or in a cell) and in methods of treating RAS related diseases and disorders (e.g., cancer), as described herein. The present disclosure provides, inter alia, compositions, methods, and kits for treating or preventing a RAS related disease or disorder.

Exemplary agents that may be used in combination with a compound of the present invention are described below. All references herein are incorporated by reference for the agents described, including compound or molecular structures disclosed therein, whether explicitly stated as such or not.

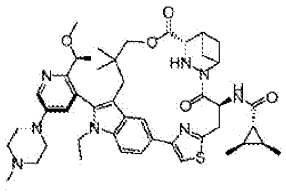
a) RAS(ON) Inhibitors

Compositions and methods of the present disclosure may include a compound of the present invention plus a RAS(ON) inhibitor. In some embodiments, the RAS(ON) inhibitor is RMC-6236, RMC-7977, RMC-6291, RMC-4998, RMC-9805, RMC-044, RMC-5127, GFH547, ERAS-0015 or compound 6A of WO 2024067857. Exemplary RAS(ON) inhibitors useful in combinations according to the present disclosure can be found in any one of the following patent applications: WO 2024206858, WO 2024169914, WO 202453208, WO 2024206858, WO 2024149819, WO 2024104364, WO 2024067857, WO 2024060966, WO 2024017859, WO 2024102421, WO 2024008834, WO 2024008610, WO 2023232776, WO 2023240263, WO 2023086341, WO 2023208005, WO 2023133543, WO 2023060253, WO 2023025832, WO 2023015559, WO 2023060253, WO 2022235870, WO 2022235864, WO 2022060836, WO 2021091982, WO 2021091967, WO 2021091956, WO 2020132597, CN 117903169, CN 117720556, CN 117720555, CN 117720554, CN 117534687, CN 117534685, CN 117534684, PCT/US2024/030993, PCT/US2024/023272, and PCT/US2024/023208, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein.

In some embodiments, the RAS(ON) inhibitor is the multi-selective inhibitor RMC-6236



In some embodiments, a RAS(ON) multi-selective inhibitor is compound 6A of WO 2024067857



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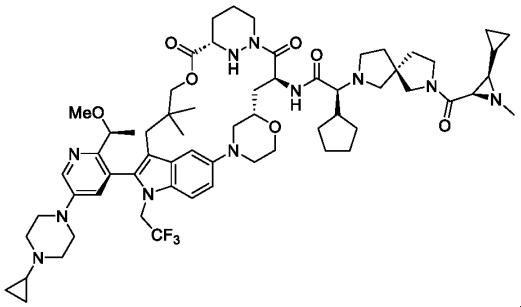
Some embodiments of combinations comprising a compound of the present invention include a composition comprising a RAS(ON) mutant-selective inhibitor. In some embodiments, the RAS(ON) mutant-selective inhibitor is a RAS(ON) G12C-selective inhibitor. In some embodiments, the RAS(ON) mutant-selective inhibitor is a RAS(ON) G12D-selective inhibitor. In some embodiments, the RAS(ON) mutant-selective inhibitor is a RAS(ON) G13C-selective inhibitor. In some embodiments, the RAS(ON) mutant-selective inhibitor is a RAS(ON) Q61H-selective inhibitor. In some embodiments, the RAS(ON) mutant-selective inhibitor is a RAS(ON) G13D-selective inhibitor. In some embodiments, the RAS(ON) mutant-selective inhibitor is a RAS(ON) G12R-selective inhibitor.

In some embodiments, the RAS(ON) mutant-selective inhibitor useful according to the present disclosure is RMC-9805, a G12D mutant-selective inhibitor



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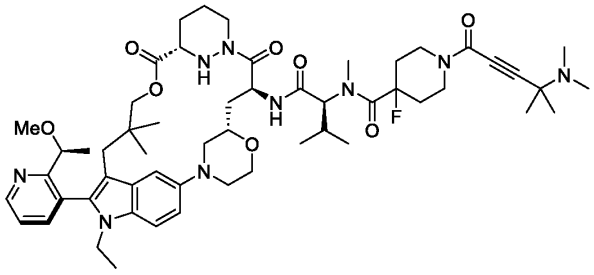
In some embodiments, the RAS(ON) mutant-selective inhibitor is the RAS(ON) G12C-selective



tri-complex inhibitor, RMC-6291 (Schulze et. al., Science. 2023 Aug 18; 381(6659): 794–799).

In some embodiments, the combination therapy comprising a compound of the present invention may include one or more RAS(ON) inhibitors, for example, a compound of the present invention plus one or more RAS(ON) multi-selective inhibitors and/or one or more RAS(ON) mutant-selective inhibitors.

b) RAS/MAPK Inhibitors

Compositions and methods described herein may include a compound of the present invention in combination with one or more RAS/MAPK pathway inhibitors. The RAS/MAPK pathway is a signal

transduction cascade downstream of various cell surface growth factor receptors in which activation of RAS (and its various isoforms and allotypes) is a central event that drives a variety of cellular effector events that determine the proliferation, activation, differentiation, mobilization, and other functional properties of the cell. SHP2 conveys positive signals from growth factor receptors to the RAS activation/deactivation cycle, which is modulated by guanine nucleotide exchange factors (GEFs, such as SOS1) that load GTP onto RAS to produce functionally active GTP-bound RAS as well as GTP-accelerating proteins (GAPs, such as NF1) that facilitate termination of the signals by conversion of GTP to GDP. GTP-bound RAS produced by this cycle conveys essential positive signals to a series of serine/threonine kinases including RAF and MAP kinases, from which emanate additional signals to various cellular effector functions. In some embodiments, a therapeutic agent that may be combined with a RAS(ON) inhibitor is an inhibitor of the MAP kinase (MAPK) pathway (or "MAPK pathway inhibitor"). MAPK pathway inhibitors include, but are not limited to, one or more MAPK pathway inhibitors described in Cancers (Basel) 2015 Sep; 7(3): 1758–1784. For example, the MAPK inhibitor may be selected from one or more of trametinib, binimetinib, selumetinib, cobimetinib, LErafAON (NeoPharm), ISIS 5132; vemurafenib, pimasertib, TAK733, RO4987655 (CH4987655); CI-1040; PD-0325901; CH5126766; MAP855; AZD6244; refametinib (RDEA 119/BAY 86-9766); GDC-0973/XL581; AZD8330 (ARRY-424704/ARRY-704); RO5126766 (Roche, described in PLoS One. 2014 Nov 25;9(11)); and GSK1120212 (or JTP-74057, described in Clin Cancer Res. 2011 Mar 1;17(5):989-1000). The MAPK pathway inhibitor may be PLX8394, LXH254, GDC-5573, or LY3009120. A MAPK pathway inhibitor may be a PI3Kα:RAS breaker, such as BBO-10203.

i) RAS(OFF) inhibitors and RAS(OFF) degraders

Compositions and methods described herein may include a compound of the present invention in combination with one or more RAS(OFF) inhibitors. Numerous mutant-selective and pan-KRAS inhibitors have been disclosed and are known in the art. A RAS(OFF) inhibitor may be administered or formulated in combination with a RAS(ON) inhibitor described herein. RAS(OFF) inhibitors are designed to inhibit RAS activity by targeting different regions of the RAS protein in its inactive state (GDP bound state), preventing its activation and downstream signaling.

In some embodiments, a RAS(OFF) inhibitor is a KRAS(OFF) inhibitor that has a molecular weight of under 700 Da. The term "KRAS(OFF) inhibitor" refers to any RAS(OFF) inhibitor that binds to KRAS in its GDP-bound "OFF" position. In some embodiments, the KRAS(OFF) inhibitor is specific for a *KRAS*^{G12C} mutation. KRAS^{G12C}(OFF) inhibitors use a covalent binding group that allows them to selectively target the KRAS^{G12C} mutant protein, and many such inhibitors comprise a pyrimidine core. KRAS^{G12C}(OFF) inhibitors all target the same cysteine residue in the KRAS^{G12C} mutant protein, leading to a conformational change that locks the protein in an inactive state. KRAS^{G12C}(OFF) inhibitors include, but are not limited to, adagrasib (MRTX849), divarasib (RG6330/GDC-6036), fulzerasib (IBI351/GFH925), garsorasib (D-1553), glecirasib (JAB-21822), olomorasib (LY3537982), opnurasib (JDQ443), sotorasib (AMG 510), ARS-853, ARS-1620, BI 1823911, BPI-421286, D3S-001, GEC255, HBI-2438, HS-10370, JAB-21000, JAB-21822, JMKX001899, JNJ-74699157 (ARS-3248), MK-1084, YL-15293, BBO-8520, and FMC-376. In some embodiments, the KRAS(OFF) inhibitor is selected from AMG 510 and MRTX849. In some embodiments, the KRAS(OFF) inhibitor is sotorasib (AMG 510). In some embodiments, the

KRAS(OFF) inhibitor is adagrasib (MRTX849). In some embodiments, the KRAS(OFF) inhibitor is divarasib (GDC-6036). In some embodiments, the KRAS(OFF) inhibitor is selected from BPI-421286, JNJ-74699157 (ARS-3248), LY3537982, MRTX1257, ARS853, ARS1620, or GDC-6036.

In some embodiments, a KRAS(OFF) inhibitor is specific for a $KRAS^{G12D}$ mutation. Many $KRAS^{G12D}$(OFF) inhibitors have been developed using $KRAS^{G12C}$(OFF) inhibitors as a starting point, thus sharing the backbone of G12C inhibitors in combination with other chemical moieties such as piperazine-based compounds. Non-limiting examples of $KRAS^{G12D}$(OFF) inhibitors include ASP3082, BPI-501836, ERAS-4693, ERAS-5024, HBW-012-D, HBW-012-E, HRS-4642, JAB-22000, KD-8, TSN1611, LY3962673, MRTX282, MRTX1133, Q2a, SHR1127, TH-Z827, TH-Z835, TSN1611, VRTX153, DN022150, GDC-7035, AZD0022, GFH375 (VS-7375), INCB161734, QTX3046, TSN1611, and TH-Z835.

In some embodiments, the small molecule RAS(OFF) inhibitor is specific for a $KRAS^{G12V}$ mutation, such as JAB-23000 or QTX3544. In some embodiments, the small molecule RAS(OFF) inhibitor is specific for a $KRAS^{G13D}$ mutation. In some embodiments, the small molecule RAS(OFF) inhibitor is a pan-KRAS(OFF) inhibitor, such as A2A-03, ABREV01, ABT-200, ADT-030, ADT-1004, AN9025, BBP-454, BGB-53038, BI-2865, BI 3706674, ERAS-4, ERAS-254, ERAS-4001, HB-700 (G12X+G13D), JAB-23400, OC211, PF-07934040, QTX3034, RSC-1255, YL-17231, ZG2001, BI-2493, or PF-07985045. In some embodiments, the Ras inhibitor is JAB-23400. In some embodiments, the Ras inhibitor is BI-2852. In some embodiments, the Ras inhibitor targets both the ON and OFF states of Ras, such as BBO-11818, JAB-23E73, JAB-23425, JAB-23E73, BBO-8520, FMC-376, GFH375 (VS-7375), INCB161734, QTX3046, TSN1611, or TH-Z835.

In some embodiments, reference to the term RAS(OFF) inhibitor includes any such RAS(OFF) inhibitor disclosed in any one of the following patent applications: WO 2024206766, WO 2024206747, WO 2024197503, WO 2024193698, WO 2024192424, WO 2024179546, WO 2024178313, WO 2024178304, WO 2024173842, WO 2024167922, WO 2024160225, WO 2024159471, WO 2024159470, WO 2024158778, WO 2024158242, WO 2024153119, WO 2024153116, WO 2024138486, WO 2024138206, WO 2024138052, WO 2024131829, WO 2024125642, WO 2024125600, WO 2024123913, WO 2024123102, WO 2024120433, WO 2024120419, WO 2024119277, WO 2024118926, WO 2024109233, WO 2024112654, WO 2024104453, WO 2024104425, WO 2024107686, WO 2024104453, WO 2024103010, WO 2024097559, WO 2024091409, WO 2024088273, WO 2024085661, WO 2024083258, WO 2024083256, WO 2024083246, WO 2024083168, WO 2024078555, WO 2024076674, WO 2024076672, WO 2024076670, WO 2024067714, WO 2024067575, WO 2024064335, WO 2024063578, WO 2024063576, WO 2024061370, WO 2024061333, WO 2024061267, WO 2024056063, WO 2024055112, WO 2024054926, WO 2024054647, WO 2024054625, WO 2024051763, WO 2024051721, WO 2024050742, WO 2024050640, WO 2024046406, WO 2024046370, WO 2024045066, WO 2024044667, WO 2024044649, WO 2024044334, WO 2024041621, WO 2024041606, WO 2024041589, WO 2024041573, WO 2024040131, WO 2024040109, WO 2024040080, WO 2024036270, WO 2024034657, WO 2024034593, WO 2024034591, WO 2024034123, WO 2024032747, WO 2024032704, WO 2024032703, WO 2024032702, WO 2024031088, WO 2024030647, WO 2024030633, WO 2024029613, WO 2024022507, WO 2024022444, WO 2024020159, WO 2024019103, WO 2024017859, WO 2024017392, WO 2024015731, WO 2024015262, WO 2024012456, WO 2024009191,

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2021248090, WO 2021248083, WO 2021248082, WO 2021248079, WO 2021248055, WO 2021245051, WO 2021244603, WO 2021239058, WO 2021231526, WO 2021228161, WO 2021219090, WO 2021219090, WO 2021219072, WO 2021218939, WO 2021217019, WO 2021216770, WO 2021215545, WO 2021215544, WO 2021211864, WO 2021190467, WO 2021185233, WO 2021180181, WO 2021175199, 2021173923, WO 2021169990, WO 2021169963, WO 2021168193, WO 2021158071, WO 2021155716, WO 2021152149, WO 2021150613, WO 2021147967, WO 2021147965, WO 2021143693, WO 2021142252, WO 2021141628, WO 2021139748, WO 2021139678, WO 2021129824, WO 2021129820, WO 2021127404, WO 2021126816, WO 2021126799, WO 2021124222, WO 2021121371, WO 2021121367, WO 2021121330, WO 2021113595, WO 2021107160, WO 2021106231, WO 2021088458, WO 2021086833, WO 2021085653, WO 2021081212, WO 2021058018, WO 2021057832, WO 2021055728, WO 2021031952, WO 2021027911, WO 2021023247, WO 2020259513, WO 2020259432, WO 2020234103, WO 2020233592, WO 2020216190, WO 2020178282, WO 2020146613, WO 2020118066, WO 2020113071, WO 2020106647, WO 2020102730, WO 2020101736, WO 2020097537, WO 2020086739, WO 2020081282, WO 2020050890, WO 2020047192, WO 2020035031, WO 2020028706, WO 2019241157, WO 2019232419, WO 2019217691, WO 2019217307, WO 2019215203, WO 2019213526, WO 2019213516, WO 2019155399, WO 2019150305, WO 2019110751, WO 2019099524, WO 2019051291, WO 2018218070, WO 2018218071, WO 2018218069, WO 2018217651, WO 2018206539, WO 2018143315, WO 2018140600, WO 2018140599, WO 2018140598, WO 2018140514, WO 2018140513, WO 2018140512, WO 2018119183, WO 2018112420, WO 2018068017, WO 2018064510, WO 2017201161, WO 2017172979, WO 2017100546, WO 2017087528, WO 2017058807, WO 2017058805, WO 2017058728, WO 2017058902, WO 2017058792, WO 2017058768, WO 2017058915, WO 2017015562, WO 2016168540, WO 2016164675, WO 2016049568, WO 2016049524, WO 2015054572, WO 2014152588, WO 2014143659, WO 2013155223, KR 20240101190, KR 20240101189, KR 20240041720, KR 20240041719, CN 118666870, CN 118666869, CN 118580238, CN 118307563, CN 118221700, CN 118221699, CN 118221698, CN 118221685, CN 118126064, CN 118078802, CN 118078801, CN 118005656, CN 117986263, CN 117986263, CN 117946135, CN 117924327, CN 117903117, CN 117800990, CN 117800989, CN 117800976, CN 117736226, CN 117683051, CN 117645627, CN 117624194, CN 117624190, CN 117586280, CN 117486901, CN 117466917, CN 117462688, CN 117362315, CN 117327102, CN 117327094, CN 117327074, CN 117285590, CN 117263959, CN 117247382, CN 117186095, CN 117164605, CN 116969977, CN 116925075, CN 116891489, CN 116731045, CN 116731044, CN 116554208, CN 116514846, CN 116478184, CN 116478141, CN 116410145, CN 116375742, CN 116354988, CN 116332948, CN 116332938, CN 116327956, CN 116262759, CN 116217592, CN 116199703, CN 116162099, CN 116143806, CN 116143805, CN 116120315, CN 116102559, CN 115960105, CN 115894520, CN 115872979, CN 115850267, CN 115785199, CN 115785124, CN 115724842, CN 115724842, CN 115721720, CN 115716840, CN 115703775, CN 115611923, CN 115611898, CN 115583937, CN 115572278, CN 115557949, CN 115521312, CN 115504976, CN 115490709, CN 115466272, CN 115433183, CN 115433179, CN 115403575, CN 115385938, CN 115385937, CN 115385912, CN 115381786, CN 115368383, CN 115368382, CN 115368381, CN 115353506, CN 115322158, CN 115304623, CN 115304602, CN 115197245, CN 115181106, CN 114989195, CN

114989166, CN 114989147, CN 114920741, CN 114920739, CN 114907387, CN 114874234, CN 114874201, CN 114716436, CN 114716435, CN 114685532, CN 114685460, CN 114591319, CN 114539293, CN 114539286, CN 114539246, CN 114437107, CN 114437084, CN 114409653, CN 114380827, CN 114195804, CN 114195788, CN 114437107, CN 114409653, CN 114380827, CN 114195804, CN 114057776, CN 114057744, CN 114057743, CN 113999226, CN 113980032, CN 113980014, CN 113960193, CN 113929676, CN 113754653, CN 113683616, CN 113563323, CN 113527299, CN 113527294, CN 113527293, CN 113493440, CN 113429405, CN 113321654, CN 113248521, CN 113087700, CN 113024544, CN 113004269, CN 112920183, CN 112778284, CN 112390818, CN 112390788, CN 112300196, CN 112300194, CN 112300173, CN 112225734, CN 112142735, CN 112110918, CN 112094269, CN 112047937, CN 109574871, US2024270736, or EP 4389751, each of which is incorporated herein by reference in its entirety, including the RAS compound structures disclosed therein which are specifically incorporated herein by reference.

In some embodiments, reference to the term RAS(OFF) inhibitor refers to a pan-KRAS inhibitor, such as selected from one disclosed in any of the following: WO 2024206766, WO 2024206747, WO 2024192424, WO 2024178313, WO 2024178304, WO 2024173842, WO 2024153180, WO 2024119277, WO 2024120433, WO 2024115890, WO 2024112654, WO 2024104453, WO 2024104425, WO 2024107686, WO 2024104453, WO 2024103010, WO 2024085661, WO 2024083246, WO 2024083168, WO 2024067575, WO 2024064335, WO 2024063578, WO 2024063576, WO 2024051852, WO 2024051763, WO 2024046370, WO 2024044667, WO 2024041621, WO 2024041606, WO 2024041589, WO 2024040131, WO 2024040109, WO 2024032747, WO 2024032704, WO 2024032703, WO 2024032702, WO 2024031088, WO 2024030647, WO 2024030633, WO 2024015262, WO 2024009191, WO 2024008068, WO 2024002373, WO 2023287896, WO 2023274324, WO 2023246914, WO 2023246777, WO 2023230190, WO 2023215802, WO 2023215801, WO 2023197984, WO 2023190748, WO 2023183585, WO 2023179703, WO 2023173017, WO 2023173016, WO 2023173014, WO 2023172737, WO 2023154766, WO 2023143352, WO 2023143312, WO 2023138589, WO 2023133183, WO 2023122662, WO 2023114733, WO 2023099624, WO 2023099623, WO 2023099612, WO 2023099608, WO 2023099592, WO 2023097227, WO 2023064857, WO 2023056421, WO 2023049697, WO 2023046135, WO 2023039240, WO 2023034290, WO 2023020523, WO 2023020521, WO 2023020519, WO 2023020518, WO 2023001123, WO 2022271823, WO 2022261210, WO 2022258974, WO 2022256459, WO 2022250170, WO 2022248885, WO 2022228543, WO 2022216762, WO 2022072783, WO 2016161361, KR 20240101190, KR 20240101189, KR 20240041720, KR 20240041719, CN 118221700, CN 118126064, CN 117924327, CN 117946135, CN 117800990, CN 117800989, CN 117683051, CN 117486901, CN 117263959, CN 116969977, or CN 116332948, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein. In some embodiments, the combination therapy comprising a compound of the present invention may include one or more additional RAS inhibitors, for example, a pan-KRAS inhibitor. In some embodiments, combination comprising a pan-KRAS inhibitor therapy comprises ERAS-4001. In some embodiments, the pan-KRAS inhibitor, is a pan-KRAS inhibitor in a patent application filed in the name of Medshine Discovery, Inc. In some embodiments, combination comprising a pan-KRAS inhibitor therapy

includes BGB-53038, BBO-11818, YL-17231, QTX3034, ABT-200, ADT-1004, AN9025, OC211, JAB-23425, BI-2865, BI-2493, ABREV01, A2A-03, or PF-07934040.

In any embodiment employing a RAS(OFF) inhibitor herein, a RAS(OFF) degrader targeting the OFF state of RAS may be employed. These degraders are known in the art. RAS degraders may be found, for example, in one or more of the following applications: WO 2024199266, WO 2024188281, WO 2024/159164, WO 2024/152247, WO 2024/149214, WO 2024131777, WO 2024120424, WO 2024119278, WO 2024118966, WO 2024118960, WO 2024083258, WO 2024083256, WO 2024055112, WO 2024054625, WO 2024050742, WO 2024044334, WO 2024040080, WO 2024034657, WO 2024034593, WO 2024034591, WO 2024034123, WO 2024029613, WO 2024020159, WO 2024019103, WO 2024017392, WO 2023215906, WO 2023185864, WO 2023171781, WO 2023141570, WO 2023138524, WO 2023130012, WO 2023116934, WO 2023099620, WO 2023081476, WO 2023077441, WO 2022260482, CN 118725012, CN 118496502, CN 118496300, CN 118126040, or CN 115785199, each of which is incorporated herein by reference in its entirety.

In some embodiments, the RAS(OFF) inhibitor is a peptide-based inhibitor. Peptide-based RAS(OFF) inhibitors have been developed that target specific regions of the RAS protein, such as the Switch II region or the RAS-effector interface. Non-limiting examples include the K-Ras-binding peptide (Krpep-2d), the Ras inhibitory peptide (RasIn) and LUNA18 (NCT05012618). Peptide-based RAS(OFF) inhibitors are a class of compounds that target the RAS protein by disrupting its interaction with its downstream effectors or other signaling proteins. These inhibitors are typically designed to mimic the binding motifs of RAS-interacting proteins or other RAS effectors, such as RAF or PI3K. By binding to RAS at the same site as these effectors, peptide-based inhibitors can effectively compete with these proteins and prevent the activation of downstream signaling pathways. See, e.g., WO 2024176153, WO 2024101402, WO 2024101386, WO 2023214576, WO 2023140329, WO 2022234853, WO 2022234852, WO 2022234851, and WO 2022234639, each of which is incorporated herein by reference in its entirety.

Peptide-based RAS(OFF) inhibitors can be further classified into two main categories: those that target the RAS-effector interface, and those that target other regions of the RAS protein. Peptide-based inhibitors that target the RAS-effector interface are designed to bind to the switch regions of RAS that are critical for its interaction with downstream effectors, such as RAF or PI3K. These inhibitors typically contain amino acid residues that are similar to those found in the binding motifs of RAS-interacting proteins or effectors and are often designed to form hydrogen bonds or other interactions with key residues on the surface of RAS.

Peptide-based RAS(OFF) inhibitors that target other regions of the RAS protein are typically designed to disrupt other interactions that are critical for the activation or signaling of RAS. For example, some peptide-based inhibitors are designed to bind to the hypervariable region of RAS, which is thought to play a role in membrane localization and anchoring of the protein. By binding to this region, peptide-based inhibitors can prevent the proper localization of RAS to the plasma membrane, which is necessary for its activation and signaling.

Several common motifs have been identified as important for the binding of RAS-interacting proteins and effectors and are often used in the design of peptide-based inhibitors. One example is the RAF-binding domain (RBD), which is found in many RAS-interacting proteins and is important for the

interaction of RAS with downstream effectors such as RAF. The RBD contains a conserved amino acid sequence (Arg-Xaa-Arg) that is critical for binding to RAS, and this motif has been incorporated into several peptide-based inhibitors designed to disrupt the RAS-RAF interaction. Another example is the RAS-binding domain (RBD) of PI3K, which is important for the interaction of RAS with this downstream effector. The RBD of PI3K contains several conserved amino acid residues (such as Arg-Arg-Trp) that are critical for binding to RAS, and these motifs have been used in the design of peptide-based inhibitors that target the RAS-PI3K interaction. Other common motifs used in peptide-based RAS(OFF) inhibitors include the Ras-binding domain (RBD) of other RAS-interacting proteins such as RalGDS and SOS, as well as sequences that mimic the structure of the switch regions of RAS itself. These motifs are typically used to optimize the binding affinity and selectivity of the inhibitor for the desired target protein or interaction.

In some embodiments, the RAS(OFF) inhibitor is an antibody or antigenic binding peptide specific for RAS(OFF). Antibodies have been developed that bind to specific regions of the RAS protein, such as the Switch II region or the RAS-effector interface. For example, some antibodies have been developed that target the switch regions of RAS proteins, which are critical for the activation of these proteins and their interaction with downstream effectors. Binding of these antibodies to the switch regions can prevent the conformational changes required for RAS activation and downstream signaling. Another approach involves the use of antibodies that target RAS-interacting proteins or downstream effectors, such as RAF or PI3K. Binding of these antibodies to their target proteins can disrupt the RAS-dependent signaling pathways and inhibit the growth and survival of cancer cells. Additionally, some antibodies have been developed that can induce the internalization and degradation of RAS proteins, leading to their depletion and inhibition of downstream signaling. For example, some antibodies have been developed that recognize the unique structure of mutant RAS proteins and target them for degradation via the ubiquitin-proteasome pathway. Non-limiting examples of KRAS(OFF)-specific inhibitory antibodies include anti-p21ser, and K27 (DARPin) (see, e.g., Khan et al, Biochim Biophys Acta Mol Cell Res. 2020 Feb;1867(2):118570). See also WO 2024136608 and WO 2024111590, each of which is incorporated herein by reference in its entirety.

Antibody-drug conjugates may also be constructed using RAS inhibitors, such as WO 2024189481, which is incorporated herein by reference in its entirety, including the compound structures disclosed therein.

ii) SOS1 inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more SOS1 inhibitors. A SOS1 inhibitor may be administered or formulated in combination with compound of the present invention and/or any additional therapeutic agent described herein. In some embodiments, a SOS1 inhibitor is one or more of RMC-5845, RMC-4948, RMC-0331, BI-1701963, BI-3406, SDR5, MRTX-0902, ZG2001, and BAY-293. In some embodiments, reference to the term SOS1 inhibitor includes any such SOS1 inhibitor disclosed in any one of the following patent applications: WO 2023109929, WO 2023059597, WO 2023029833, WO 2023041049, WO 2023022497, WO 2022157629, WO 2022184116, WO 2022170952, WO 2022170917, WO 2022171184, WO 2022170802, WO 2022161461, WO 2022121813, WO 2022028506, WO

2022139304, WO 2021228028, WO 2019122129, CN 115215847, CN 115028644, CN 114685488, CN 111393519, CN 115677702, and CN 115806560 each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

iii) SHP inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more SHP inhibitors. A SHP inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. In some embodiments, the SHP inhibitor is an inhibitor of SHP1. In some embodiments, the SHP inhibitor is an inhibitor of SHP2. In some embodiments, the SHP1 inhibitor is SB8091 or SB6299 aka DA-4511. In some embodiments, a SHP2 inhibitor is one or more of SHP099, TNO155, RMC-4550, RMC-4630, JAB-3068, JAB-3312, RLY-1971, ERAS-601, SH3809, PF-07284892, or BBP-398. In some embodiments, reference to the term SHP2 inhibitor includes any such SHP2 inhibitor disclosed in any one of the following patent applications: WO 2023282702, WO 2023280283, WO 2023280237, WO 2023018155, WO 2023011513, WO 2022271966, WO 2022271964, WO 2022271911, WO 2022259157, WO 2022242767, WO 2022241975, WO 2022237676, WO 2022237367, WO 2022237178, WO 2022235822, WO 20222084008, WO 2022135568, WO 2022063190, WO 2022043865, WO 2022042331, WO 2022033430, WO 2022017444, WO 2022007869, WO 2021259077, WO 2021249449, WO 2021249057, WO 2021244659, WO 2021218755, WO 2021176072, WO 2021171261, WO 2021149817, WO 2021148010, WO 2021147879, WO 2021143823, WO 2021143701, WO 2021143680, WO 2021281752, WO 2021121397, WO 2021119525, WO 2021115286, WO 2021110796, WO 2021088945, WO 2021073439, WO 2021061706, WO 2021061515, WO 2021043077, WO 2021033153, WO 2021028362, WO 2021033153, WO 2021028362, WO 2021018287, WO 2020259679, WO 2020249079, WO 2020210384, WO 2020201991, WO 2020181283, WO 2020177653, WO 2020165734, WO 2020165733, WO 2020165732, WO 2020156243, WO 2020156242, WO 2020108590, WO 2020104635, WO 2020094104, WO 2020094018, WO 2020081848, WO 2020073949, WO 2020073945, WO 2020072656, WO 2020065453, WO 2020065452, WO 2020063760, WO 2020061103, WO 2020061101, WO 2020033828, WO 2020033286, WO 2020022323, WO 2019233810, WO 2019213318, WO 2019183367, WO 2019183364, WO 2019182960, WO 2019167000, WO 2019165073, WO 2019158019, WO 2019152454, WO 2019051469, WO 2019051084, WO 2018218133, WO 2018172984, WO 2018160731, WO 2018136265, WO 2018136264, WO 2018130928, WO 2018129402, WO 2018081091, WO 2018057884, WO 2018013597, WO 2017216706, WO 2017211303, WO 2017210134, WO 2017156397, WO 2017100279, WO 2017079723, WO 2017078499, WO 2016203406, WO 2016203405, WO 2016203404, WO 2016196591, WO 2016191328, WO 2015107495, WO 2015107494, WO 2015107493, WO 2014176488, WO 2014113584, CN 115677661, CN 115677660, CN 115611869, CN 115521305, CN 115490697, CN 115466273, CN 115394612, CN 115304613, CN 115304612, CN 115300513, CN 115197225, CN 114957162, CN 114920759, CN 114716448, CN 114671879, CN 114539223, CN 114524772, CN 114213417, CN 114195799, CN 114163457, CN 113896710, CN 113248521, CN 113248449, CN 113135924, CN 113024508, CN 112920131, CN 112823796, CN 112409334, CN 112402385, CN 112174935, 111848599, CN 111704611, CN

111393459, CN 111265529, CN 110143949, CN 108113848, US 11179397, US 11044675, US 11034705, US 11033547, US 11001561, US 10988466, US 10954243, US 10934302, or US 10858359, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

iv) MEK inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more MEK inhibitors. A MEK inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. In some embodiments, a MEK inhibitor is one or more of pimasertib, IMM-1-104, selumetinib, cobimetinib (Cotellic®), trametinib (Mekinist®), and binimetinib (Mektovi®). In some embodiments, a MEK inhibitor targets a MEK mutation that is a Class I MEK1 mutation selected from D67N; P124L; P124S; and L177V. In some embodiments, the MEK mutation is a Class II MEK1 mutation selected from ΔE51-Q58; ΔF53-Q58; E203K; L177M; C121S; F53L; K57E; Q56P; and K57N. In some embodiments, reference to the term MEK inhibitor includes any such MEK inhibitor disclosed in any one of the following patent applications: WO 2022221866, WO 2022125941, WO 2022208391, WO 2022015736, WO 2022177557, WO 2021018866, WO 2021069486, WO 2021142144, WO 2021168283, WO 2021234097, WO 2019076947, WO 2018233696, WO 2016188472, WO 2014063024, WO 2013019906, WO 2011047238, WO 2007044515, US 2023032403, and CN 115813930, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

v) RAF inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more RAF inhibitors. A RAF inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. In some embodiments, a RAF inhibitor is VS-6766 or BTDX-4933. In some embodiments, a RAF inhibitor is a BRAF inhibitor. BRAF inhibitors that may be used in combination with a compound of the present invention include, for example, Vs6766, IK-595, vemurafenib, dabrafenib, and encorafenib. BRAF may comprise a Class 3 BRAF mutation. In some embodiments, the Class 3 BRAF mutation is selected from one or more of the following amino acid substitutions in human BRAF: D287H; P367R; V459L; G466V; G466E; G466A; S467L; G469E; N581S; N581I; D594N; D594G; D594A; D594H; F595L; G596D; G596R and A762E. In some embodiments, reference to the term RAF inhibitor includes any such RAF inhibitor disclosed in any one of the following patent applications: WO 2023076991, WO 2022226626, WO 2022226261, WO 2019084459, WO 2018203219, WO 201851306, WO 2017212442, WO 2015075483, WO 2013134243, WO 2013134298, WO 2011047238, WO 2011025965, WO 2011025947, WO 2011025951, WO 2011025940, WO 2011025938, WO 2010065893, WO 2009016460, WO 2009130015, WO 2009111278, WO 2009111279, WO 2008028141, and WO 2006024834, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

vi) ERK inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more ERK inhibitors. An ERK inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. In some embodiments, an ERK inhibitor is an ERK1/2 inhibitor, such as ERAS-007. In some embodiments, an ERK inhibitor is an ERK 5 inhibitor. In some embodiments, an ERK inhibitor is one or more of ASTX-029 or I-75. In some embodiments, reference to the term ERK inhibitor includes any such ERK inhibitor disclosed in any one of the following patent applications: WO 2023076305, WO 2022259222, WO 2022221547, WO 2021110169, WO 2021110168, WO 2021252316, WO 2020102686, WO 2020228817, WO 2020107987, WO 2019233456, WO 2019233457, WO 2016025561, WO 2016192063, WO 2016106029, WO 2016106009, WO 2015051341, WO 2014124230, WO 2014052563, WO 2011041152, WO 200910550, WO 2008153858, CN 114315837, CN 115057860, CN 107973783, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

vii) MAPK inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more Mitogen-Activated Protein Kinase (MAPK) inhibitors. A MAPK inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. In some embodiments, a MAPK inhibitor is a p38MAPK inhibitor or a MAP3K8 inhibitor. In some embodiments, the MAPK inhibitor is one or more of Tilpisertib (GS-4875) and neflamapidmod (VX-745). In some embodiments, reference to the term MAPK inhibitor includes any such MAPK inhibitor disclosed in any one of the following patent applications: WO 2016029263, CN 114767674, CN 115850179, and CN 1743006, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

In some embodiments, a therapeutic agent that may be combined with a compound of the present invention is an inhibitor of MAP2K4. A non-limiting example of a MAP2K4 inhibitor useful according to the disclosure is HRX-0233.

c) Kinase Inhibitors

Compositions and methods described herein may include a compound of the present invention in combination with one or more kinase inhibitors. Tyrosine kinases and serine/threonine kinases play a crucial role in various cellular processes such as cell signaling, growth, and differentiation. Kinase inhibitors known in the art have been developed as a treatment for various types of cancer in addition to therapies for conditions such as neurodegenerative diseases, autoimmune disorders, and inflammation.

i) PKA inhibitors

In some embodiments, compositions and methods described herein may include one or more Protein Kinase A (PKA) inhibitors. A PKA inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. In some embodiments, a PKA inhibitor is H89. In some embodiments, reference to the term PKA inhibitor includes any such PKA inhibitor disclosed in any one of the following patent applications: CN 106620678 and CN

114632155, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

ii) FAK inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more Focal Adhesion Kinase (FAK) inhibitors. A FAK inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. In some embodiments, a FAK inhibitor is one or more of BI853520, defactinib, GSK2256098, PF-00562271, and VS-4718. In some embodiments, reference to the term FAK inhibitor includes any such FAK inhibitor disclosed in any one of the following patent applications: WO 2022152315, WO 2021098679, WO 2020135442, WO 2020191448, WO 2012022408, WO 2013134353, WO 2012110774, WO 2010062578, CN 111072571, and KR 101691536, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

iii) ROCK inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more Rho-associated, coiled-coil containing protein kinase (ROCK) inhibitors. A ROCK inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. In some embodiments, a ROCK inhibitor is GSK269962A. In some embodiments, reference to the term ROCK inhibitor includes any such ROCK inhibitor disclosed in any one of the following patent applications: WO 2023051753, WO 2022237892, WO 2022012409, WO 2021093795, WO 2021214200, WO 2020177292, WO 202011751, WO 2019014304, WO 2019179525, WO 2019089868, WO 2019014300, WO 2018108156, WO 2018009627, WO 2018009625, WO 2018009622, WO 2017123860, WO 2017205709, WO 2016112236, WO 2014068035, WO 2013030367, WO 2012146724, WO 2012067965, WO 2011107608, CN 108129453, CN 108191821, CN 110917352, CN 108558823, CN 108047193, CN 107973777, CN 108047197, CN 108129448, CN 115869304, and GB202214708, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

iv) MSK1 inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more Mitogen- and stress-activated kinase (MSK1) inhibitors. A MSK1 inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. In some embodiments, a MSK1 inhibitor is one or more of SB-747651A, SB 747651A, Ro 320432, CGP 57380, GSK2830371, SR1664, LY-3214996, PFI-4, MSC-2363318A, and AS601245.

v) RSK inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more ribosomal S6 kinase (RSK) inhibitors. A RSK1 inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. In some embodiments, a RSK inhibitor is one or

more of BI-D1870, LJH685, SL0101-1, FMK, BRD7389, BIX 02565, LJI308, LJI308-S, LJI308-1, and LJH685-S. In some embodiments, a RSK inhibitor is PMD-026. In some embodiments, reference to the term RSK inhibitor includes any such RSK inhibitor disclosed in any one of the following patent applications: WO 2021249558, WO 2020165646, WO 2017141116, and CN 113801139, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

vi) ALK inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more Anaplastic Lymphoma Kinase (ALK) inhibitors. An ALK inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. In some embodiments, an ALK inhibitor is one or more of Crizotinib (Xalkori), Ceritinib (Zykadia), Alectinib (Alecensa), Brigatinib (Alunbrig), Lorlatinib (Lorbrena), Ensartinib (X-396), TAE684, ASP3026, TPX-0131, LDK378 (Ceritinib analog), CEP-37440; 4SC-203, TL-398, PLB1003, TSR-011, CT-707, TPX-0005, and AP26113. Additional examples of ALK kinase inhibitors are described in examples 3-39 of WO 2005016894. In some embodiments, reference to the term ALK inhibitor includes any such ALK inhibitor disclosed in any one of the following patent applications: WO 2019142095, WO 2019179482, WO 2018130928, WO 2018127184, WO 2017101803, WO 2016192132, WO 2014100431, WO 2012082972, CN 111138492, CN 110526914, CN 109836415, CN 105801603, CN 107987056, and CN 105878248, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

d) Receptor tyrosine kinase inhibitors

Compositions and methods described herein may include a compound of the present invention in combination with one or more receptor tyrosine kinase inhibitors. A receptor tyrosine kinase (RTK) inhibitor is a type of molecule (e.g., small molecule, antibody, and nucleic acid) that binds to and blocks the activity of receptor tyrosine kinases or their ligands. RTKs are proteins found on the surface of cells that play a critical role in cell signaling and growth and have been developed as therapeutics for a range of diseases, including cancer, diabetes, and autoimmune disorders. In some embodiments, a therapeutic agent may be a pan-RTK inhibitor, such as afatinib.

i) EGFR inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more EGFR inhibitors. An EGFR inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. EGFR inhibitors include, but are not limited to, small molecule antagonists, antibody inhibitors, or specific antisense nucleotide or siRNA. Useful antibody inhibitors of EGFR include cetuximab (Erbitux®), panitumumab (Vectibix®), zalutumumab, nimotuzumab, and matuzumab. Further antibody-based EGFR inhibitors include any anti-EGFR antibody or antibody fragment that can partially or completely block EGFR activation by its natural ligand. Non-limiting examples of antibody-based EGFR inhibitors include those described in Modjtahedi et al., Br. J. Cancer 1993, 67:247-253; Teramoto et al., Cancer 1996, 77:639-645; Goldstein et al., Clin. Cancer Res. 1995,

1:1311-1318; Huang et al., 1999, Cancer Res. 15:59(8):1935-40; and Yang et al., Cancer Res.1999, 59:1236-1243. The EGFR inhibitor can be monoclonal antibody Mab E7.6.3 (Yang, 1999 supra), or Mab C225 (ATCC Accession No. HB-8508), or an antibody or antibody fragment having the binding specificity thereof.

Small molecule antagonists of EGFR include gefitinib (Iressa®), lazertinib, erlotinib (Tarceva®), and lapatinib (TykerB®). See, e.g., Yan et al., Pharmacogenetics and Pharmacogenomics In Oncology Therapeutic Antibody Development, BioTechniques 2005, 39(4):565-8; and Paez et al., EGFR Mutations In Lung Cancer Correlation With Clinical Response To Gefitinib Therapy, Science 2004, 304(5676):1497-500. In some embodiments, the EGFR inhibitor is osimertinib (Tagrisso®). In some embodiments, an EGFR inhibitor is one or more of cetuximab, gefitinib (Iressa™), erlotinib (Tarceva™), and afatinib (Gilotrif™). Additional non-limiting examples of small molecule EGFR inhibitors include any of the EGFR inhibitors described in Traxler et al., Exp. Opin. Ther. Patents 1998, 8(12):1599-1625. An EGFR inhibitor may be ERAS-801. In some embodiments, an EGFR inhibitor is an ERBB inhibitor. In humans, the ERBB family contains HER1 (EGFR, ERBB1), HER2 (NEU, ERBB2), HER3 (ERBB3), and HER (ERBB4). In some embodiments, the EGFR inhibitor may be bosutinib, crizotinib, dasatinib, erlotinib, gefitinib, lapatinib, pazopanib, ruxolitinib, sunitinib, vemurafenib, abrocitinib, asciminib, futibatinib, ibrutinib, imatinib, pacritinib, or sorafenib. In some embodiments, reference to the term EGFR inhibitor includes any such EGFR inhibitor disclosed in any one of the following patent applications: WO 2023041071, WO 2023049312, WO 2023020600, WO 2023284747, WO 2022206797, WO 2022258977, WO 2022033416, WO 2022033410, WO 2022105908, WO 2022100641, WO 2022014639, WO 2022007841, WO 2021018009, WO 2021057882, WO 2021252661, WO 2021018003, WO 2021073498, WO 2021238827, WO 2020254547, WO 2020216371, WO 2020147838, WO 2020207483, WO 2020254572, WO 2020001350, WO 2021001351, WO 2019164948, WO 2019218958, WO 2019046775, WO 2019015655, WO 2018121758, WO 2018218963, WO 2017220007, WO 2017205459, WO 2017161937, WO 2016192609, WO 199633980, WO 199630347, WO 199730034, WO 199730044, WO 199738994, WO 199749688, WO 199802434, WO 199738983, WO 199519774, WO 199519970, WO 199713771, WO 199802437, WO 199802438, WO 199732881, WO 199833798, WO 199732880, WO 199732880, WO 199702266, WO 199727199, WO 199807726, WO 1997/34895, WO 199631510, WO 199814449, WO 199814450, WO 199814451, WO 199509847, WO 199719065, WO 199817662, WO 199935146, WO 199935132, WO 199907701, WO 199220642, DE 19629652, EP 682027, EP 837063, EP 0787772, EP 0520722, EP 0566226, CN 115960018, CN 110283162, CN 114044774, CN 111973601, CN 111973602, and CN 113896744, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

ii) HER2 inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more HER2 inhibitors. A HER2 inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. In some embodiments, an HER2 inhibitor is one or more of tucatinib, rastuzumab (Herceptin™), pertuzumab (Perjeta™), lapatinib (Tykerb™), ado-trastuzumab emtansine (Kadcyla), and neratinib (Nerlynx). Non-limiting examples of HER2 inhibitors include monoclonal

antibodies such as trastuzumab (Herceptin®) and pertuzumab (Perjeta™); small molecule tyrosine kinase inhibitors such as gefitinib (Iressa®), erlotinib (Tarceva®), pilitinib, CP-654577, CP-724714, canertinib (CI 1033), HKI-272, lapatinib (GW-572016; Tykerb®), PKI-166, AEE788, BMS-599626, HKI-357, BIBW 2992, ARRY-334543, and JNJ-26483327. In some embodiments, reference to the term HER2 inhibitor includes any such HER2 inhibitor disclosed in any one of the following patent applications: WO 2021156178, WO 2021156180, WO 2021213800, WO 2021088987, WO 2013561183, and WO 2013056108, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

iii) MET inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more MET inhibitors. A MET inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. In some embodiments, a MET inhibitor is one or more of Crizotinib (Xalkori™), Cabozantinib (Cometriq, Cabometyx®), Capmatinib (Tabrecta™), Tepotinib (Tepmetko™), Savolitinib (Volitinib™), Onartuzumab (MetMab™), Foretinib (GSK1363089), MGCD-265 (amuvatinib), SU11274, and SU5416. In some embodiments, reference to the term MET inhibitor includes any such MET inhibitor disclosed in any one of the following patent applications: WO 2022226168, WO 2021222045, WO 2020047184, WO 2020015744, WO 2020244654, WO 2020156453, WO 2019206268, WO 2018077227, WO 2017012539, WO 2016015653, WO 2016012963, WO 2012015677, WO 2011162835, WO 2010089507, WO 2009091374, WO 2009056692, WO 2008051547, WO 2007130468, US 2012237524, CN 103497177, CN 107311983, CN 107382968, CN 110218191, and TW201331206, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

iv) AXL inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more AXL inhibitors. An AXL inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. AXL is a receptor tyrosine kinase that belongs to the TAM family of receptors, which also includes TYRO3 and MERTK. In some embodiments, an AXL inhibitor is one or more of bemcentib, BGB324, R428, SGI-7079, TP-0903, BMS-777607, UNC2025, and TP-0903. In some embodiments, reference to the term AXL inhibitor includes any such AXL inhibitor disclosed in any one of the following patent applications: WO 2023045816, WO 2022237843, WO 2022246179, WO 2021012717, WO 2021088787, WO 2021067772, WO 2021239133, WO 2021204713, WO 2020238802, WO 2019039525, WO 2019101178, WO 2019074116, WO 2017146236, WO 2016097918, WO 2015012298, WO 2010005876, WO 2010083465, CN 115073367, and JP 2022171109, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

v) IGFR inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more insulin-like growth factor receptor 1 (IGF-1R)

inhibitors. An IGFR inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. IGFR inhibitors have been developed to target the IGFR receptor, which plays a critical role in cancer progression and metastasis. In some embodiments, an IGFR inhibitor is one or more of linsitinib, AXL1717, OSI-906 (Linsitinib), BMS-754807, BI 836845, AZ12253801, PQIP (Pyrrolo[1,2-a]quinoxaline), and NVP-AEW541. In some embodiments, reference to the term IGFR inhibitor includes any such IGFR inhibitor disclosed in any one of the following patent applications: WO 2022115946, WO 2022217923, WO 2021203861, WO 2021246413, WO 2020116398, WO 2019046600, WO 2018195250, WO 2018221521, WO 2018204872, WO 2017072196, WO 2016173682, WO 2015162291, WO 2015162292, WO 2010066868, WO 2006069202, and CN 112125916, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

vi) RET inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more Rearranged during transfection (RET) inhibitors. An RET inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. RET plays a critical role in various cellular processes, including cell growth, differentiation, survival, and migration. RET is activated by binding of its ligands, such as glial cell line-derived neurotrophic factor (GDNF) family ligands, which leads to the activation of downstream signaling pathways that promote these cellular processes. In some embodiments, a RET inhibitor is one or more of pralsetinib, selpercatinib (LOXO-292), BLU-667, RXDX-105, TPX-0046, GSK3179106, molidustat (BAY 85-3934), and RPI-1 (Retrophin). In some embodiments, reference to the term RET inhibitor includes any such RET inhibitor disclosed in any one of the following patent applications: WO 2021211380, WO 2021057963, WO 2021043209, WO 2021222017, WO 2020035065, WO 2020114487, WO 2020200314, WO 2020200316, WO 2020114494, WO 2018071447, WO 2018213329, WO 2017079140, WO 2014050781, CN 113943285, CN 113683610, CN 113683611, CN 113620944, CN 113620945, CN 113527291, CN 113527292, CN 113527290, CN 113135896, CN 111057075, CN 111233899, and CN 111362923, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

vii) ROS1 inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more c-ros oncogene 1 (ROS1) inhibitors. A ROS1 inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. ROS1 is a receptor tyrosine kinase that belongs to the insulin receptor family and plays a role in various cellular processes, including cell growth, differentiation, survival, and migration. In some embodiments, a ROS1 inhibitor is one or more of taletrectinib, DS-6051b, TPX-0131, GZD824, and PF-06463922. In some embodiments, reference to the term ROS1 inhibitor includes any such ROS1 inhibitor disclosed in any one of the following patent applications: WO 2021098703, WO 2020024825, and US 2017079972, each of which is incorporated

herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

viii) PDGFR inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more platelet-derived growth factor receptor (PDGFR) inhibitors. A PDGFR inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. PDGFR is a family of receptor tyrosine kinases that consists of two members, PDGFRα and PDGFRβ. They are activated by binding to their ligands, such as platelet-derived growth factor (PDGF), which leads to the activation of downstream signaling pathways that promote cell growth, proliferation, and survival. In some embodiments, a PDGFR inhibitor is one or more of CP-673451, imatinib, nintedanib (Ofev™), sunitinib (Sutent™), pazopanib (Votrient™), regorafenib (Stivarga™), and dasatinib (Sprycel™).

ix) FGF inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with fibroblast growth factor (FGF) inhibitors. An FGF inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. FGFRs are a family of receptor tyrosine kinases that consists of four members, FGFR1-4. FGFRs are activated by binding to their ligands, fibroblast growth factors (FGFs), which leads to the activation of downstream signaling pathways that promote cell growth, differentiation, and survival. In some embodiments, the FGFR inhibitor is an inhibitor of FGFR2. In some embodiments, the FGFR inhibitor is an inhibitor of FGFR4. In some embodiments, an FGFR inhibitor is one or more of futibatinib (TAK-659), erdafitinib (Balversa™), infigratinib (Truseltiq™), Debio 1347, and rogaratinib (BAY 1163877). In some embodiments, reference to the term FGFR inhibitor includes any such FGFR inhibitor disclosed in any one of the following patent applications: WO 2022033472, WO 2022152274, WO 2022166469, WO 2022206939, WO 2021037219, WO 2021089005, WO 2021113462, WO 2020185532, WO 2019213544, WO 2020164603, WO 2019154364, WO 2019034076, WO 2019213506, WO 2019223766, WO 2018028438, WO 2018153373, WO 2018121650, WO 2018010514, WO 2017028816, WO 2017118438, WO 2016134320, WO 2015008844, WO 2014172644, WO 2014007951, WO 2013179033, WO 2013087578, WO 2012047699, CN 105906630, CN 115869315, CN 115141176, CN 115043832, and CN 115028634, each of which is incorporated herein by reference in its entirety. In some embodiments, the FGF pathway inhibitor targets an FGF ligand. Such FGF pathway inhibitors include FGF ligand traps and antibodies. Non-limiting examples include, FP-1039, an FGF ligand trap consisting of the extracellular domain of FGFR1 fused to the Fc portion of human IgG1, designed to sequester FGF ligands and inhibit FGF signaling, and MFGR1877S, a monoclonal antibody targeting FGF ligands, designed to block FGF-mediated signaling, including the compound structures disclosed therein which are specifically incorporated herein by reference.

x) VEGF inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more vascular endothelial growth factor (VEGF) signaling inhibitors. VEGF (vascular endothelial growth factor) signaling inhibitors are a class of drugs

that target the signaling pathway mediated by VEGF and its receptors. VEGF plays a critical role in angiogenesis, the process of forming new blood vessels from existing ones, and it is overexpressed in many types of cancer, making it an attractive target for cancer therapy. A VEGF inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. In some embodiments, the VEGF inhibitor is an antibody or antigen binding regions that specifically bind VEGF (e.g., bevacizumab), or soluble VEGF receptors or a ligand binding region thereof) such as VEGF-TRAP™, and anti-VEGF receptor agents (e.g., antibodies or antigen binding regions that specifically bind thereto). In some embodiments, the VEGF inhibitor is one or more of bevacizumab, aflibercept, ramucirumab, sorafenib, sunitinib, and pazopanib.

e) PI3K/mTOR pathway inhibitors

Compositions and methods described herein may include a compound of the present invention in combination with one or more inhibitors of the PI3K-AKT-TOR signaling pathway. The PI3K-AKT-mTOR signaling pathway is a critical intracellular pathway that regulates a wide range of cellular processes including cell growth, proliferation, metabolism, and survival. The pathway is initiated when growth factors, such as insulin or IGF-1, bind to cell surface receptors and activate phosphoinositide 3-kinase (PI3K). Activated PI3K then phosphorylates phosphatidylinositol 4,5-bisphosphate (PIP2) to produce phosphatidylinositol 3,4,5-trisphosphate (PIP3), which in turn activates AKT. Activated AKT then phosphorylates a variety of downstream targets including the tuberous sclerosis complex (TSC1/TSC2), leading to the activation of mTOR (mammalian target of rapamycin) complex 1 (mTORC1). Activated mTORC1 promotes protein synthesis and cell growth by phosphorylating key regulators of translation initiation such as S6 kinase (S6K) and eukaryotic initiation factor 4E-binding protein 1 (4E-BP1).

i) PI3K inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more PI3K inhibitors. A PI3K inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. PI3K inhibitors include, but are not limited to, wortmannin; 17-hydroxywortmannin analogs described in WO 2006044453; 4-[2-(1H-Indazol-4-yl)-6-[[4-(methylsulfonyl)piperazin-1-yl]methyl]thieno[3,2-d]pyrimidin-4-yl]morpholine (also known as pictilisib or GDC-0941 and described in WO 2009036082 and WO 2009055730); 2-methyl-2-[4-[3-methyl-2-oxo-8-(quinolin-3-yl)-2,3-dihydroimidazo[4,5-c]quinolin-1-yl]phenyl]propionitrile (also known as BEZ 235 or NVP-BEZ 235, and described in WO 2006122806); (S)-1-(4-((2-(2-aminopyrimidin-5-yl)-7-methyl-4-morpholinothieno[3,2-d]pyrimidin-6-yl)methyl)piperazin-1-yl)-2-hydroxypropan-1-one (described in WO 2008070740); LY294002 (2-(4-morpholinyl)-8-phenyl-4H-l-benzopyran-4-one (available from Axon Medchem); PI 103 hydrochloride (3-[4-(4-morpholinylpyrido-[3',2':4,5]furo[3,2-d]pyrimidin-2-yl] phenol hydrochloride (available from Axon Medchem); PIK 75 (2-methyl-5-nitro-2-[(6-bromoimidazo[1,2-a]pyridin-3-yl)methylene]-1-methylhydrazide-benzenesulfonic acid, monohydrochloride) (available from Axon Medchem); PIK 90 (N-(7,8-dimethoxy-2,3-dihydro-imidazo[l,2-c]quinazolin-5-yl)-nicotinamide (available from Axon Medchem); AS-252424 (5-[l-[5-(4-fluoro-2-hydroxy-phenyl)-furan-2-yl]-meth-(Z)-ylidene]-thiazolidine-2,4-dione (available from Axon Medchem); TGX-221 (7-methyl-2-(4-morpholinyl)-9-[1-(phenylamino)ethyl]-4H-pyrido-[1,2-a]pyrirnidin-4-one (available from Axon Medchem); XL-765; and XL-

147. Other PI3K inhibitors include demethoxyviridin, perifosine, CAL101, PX-866, BEZ235, SF1126, INK1117, IPI-145, BKM120, XL147, XL765, Palomid 529, GSK1059615, ZSTK474, PWT33597, IC87114, TGI 00-115, CAL263, PI-103, GNE-477, CUDC-907, and AEZS-136. In some embodiments, the PI3K inhibitor is alpelisib or copanlisib.

ii) AKT inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more AKT inhibitors. An AKT inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. AKT inhibitors include, but are not limited to, ipatasertib, GSK-2141795, Akt-1-1 (inhibits Aktl) (Barnett et al., Biochem. J. 2005, 385(Pt. 2): 399-408); Akt-1-1,2 (inhibits Akl and 2) (Barnett et al., Biochem. J. 2005, 385(Pt. 2): 399-408); API-59CJ-Ome (e.g., Jin et al., Br. J. Cancer 2004, 91:1808-12); 1-H-imidazo[4,5-c]pyridinyl compounds (e.g., WO 2005011700); indole-3-carbinol and derivatives thereof (e.g., U.S. Pat. No. 6,656,963; Sarkar and Li J Nutr. 2004, 134(12 Suppl):3493S-3498S); perifosine (e.g., interferes with Akt membrane localization; Dasmahapatra et al. Clin. Cancer Res. 2004, 10(15):5242-52); phosphatidylinositol ether lipid analogues (e.g., Gills and Dennis Expert. Opin. Investig. Drugs 2004, 13:787-97); and triciribine (TCN or API-2 or NCI identifier: NSC 154020; Yang et al., Cancer Res. 2004, 64:4394-9). The PI3K/AKT inhibitor may include, but is not limited to, one or more PI3K/AKT inhibitors described in Cancers (Basel) 2015 Sep; 7(3): 1758–1784. For example, the PI3K/AKT inhibitor may be selected from one or more of NVP-BEZ235; BGT226; XL765/SAR245409; SF1126; GDC-0980; PI-103; PF-04691502; PKI-587; and GSK2126458.

iii) mTOR inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more mTOR inhibitors. A mTOR inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. mTOR inhibitors include, but are not limited to, ATP-competitive mTORC1/mTORC2 inhibitors, e.g., PI-103, PP242, PP30; Torin 1; FKBP12 enhancers; 4H-1-benzopyran-4-one derivatives; and rapamycin (also known as sirolimus) and derivatives thereof, including: temsirolimus (Torisel®); everolimus (Afinitor®; WO 199409010); ridaforolimus (also known as deforolimus or AP23573); rapalogs, e.g., as disclosed in WO 199802441 and WO 200114387, e.g. AP23464 and AP23841; 40-(2-hydroxyethyl)rapamycin; 40-[3-hydroxy(hydroxymethyl)methylpropanoate]-rapamycin (also known as CC1779); 40-epi-(tetrazolyt)-rapamycin (also called ABT578); 32-deoxorapamycin; 16-pentynyloxy-32(S)-dihydrorapanycin; derivatives disclosed in WO 2005005434; derivatives disclosed in U.S. Patent Nos. 5,258,389, 5,118,677, 5,118,678, 5,100,883, 5,151,413, 5,120,842, and 5,256,790, and in WO 1994090101, WO 199205179, WO 1993111130, WO 199402136, WO 199402485, WO 199514023, WO 199402136, WO 199516691, WO 199641807, WO 199641807, and WO 2018204416; and phosphorus-containing rapamycin derivatives (e.g., WO 2005016252). In some embodiments, the mTOR inhibitor is a bisteric inhibitor (see, e.g., WO 2018204416, WO 2019212990 and WO 2019212991), such as RMC-5552.

iv) MNK inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more mitogen-activated protein kinase-interacting kinase (MNK) inhibitors. A MNK inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. MNK proteins are activated downstream of the mitogen-activated protein kinase (MAPK) signaling pathway, which plays a critical role in the regulation of cellular proliferation, differentiation, and survival. MNKs phosphorylate eIF4E, a key component of the eukaryotic translation initiation complex, which enhances the translation of specific mRNAs, including those encoding proteins involved in cell cycle regulation and oncogenesis. In some embodiments, a MNK inhibitor is one or more tomivosertib (eFT508), CGP57380, and SEL201. In some embodiments, reference to the term MNK inhibitor includes any such MNK inhibitor disclosed in any one of the following patent applications: WO 2021098691, WO 2020108619, WO 2020086713, WO 2018152117, WO 2018228275, WO 2015200481, and CN 115583942, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

v) eIF4 inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more eukaryotic initiation factor 4A (eIF4A) inhibitors. An eIF4A inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. eIF4A is a critical component of the eukaryotic translation initiation complex, where it functions as an RNA helicase to unwind the secondary structure of mRNA and facilitate ribosome binding. eIF4A is required for the translation of many cancer-associated genes, making it an attractive therapeutic target for cancer treatment. In some embodiments, an eIF4A inhibitor is one or more zotatifin (eFT226), silvestrol, pateamine A, and rocaglates. In some embodiments, reference to the term eIF4A inhibitor includes any such eIF4A inhibitor disclosed in any one of the following patent applications: WO 2023034813, WO 2021195128, and WO 2017091585, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

In some embodiments, compositions and methods described herein may include one or more eukaryotic initiation factor 4G (eIF4G) inhibitors. An eIF4G inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. eIF4G family includes several proteins that are involved in the initiation of protein translation. eIF4G serves as a scaffold for other proteins, including eIF4E and eIF4A, to form the eIF4F complex, which is responsible for binding to the 5' cap of mRNA and unwinding the secondary structure of the mRNA to allow ribosomal scanning and translation initiation. In some embodiments, an eIF4G inhibitor is one or more pateamine A, and hippuristanol.

f) DNA Damage Response Inhibitors

Compositions and methods described herein may include a compound of the present invention in combination with one or more DNA damage response (DDR) inhibitors. The DDR pathway is a critical cellular pathway that is activated in response to DNA damage and is essential for maintaining genomic stability, thereby preventing the development of cancer. However, cancer cells often have defects in the

DDR pathway, which makes them more sensitive to DDR inhibitors. DDR inhibitors have shown promise in preclinical studies as potential cancer therapeutics, particularly in combination with other agents.

i) Wee1 inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more Wee1 inhibitors. Wee1 is a kinase that plays a critical role in regulating the cell cycle by inhibiting the activity of cyclin-dependent kinases (CDKs) and preventing the progression of cells through the G2/M checkpoint. Wee1 is overexpressed in several cancer types and has been implicated in tumor growth and survival. In some embodiments, a Wee1 inhibitor is one or more of imp7068, adavosertib, azenosertib or ZNL-02-096. In some embodiments, reference to the term Wee1 inhibitor includes any such Wee1 inhibitor disclosed in any one of the following patent applications: WO 2022011391, WO 2022247641, WO 2021043152, WO 2020221358, WO 2020083404, WO 2020192581, WO 2019085933, WO 2018133829, WO 2015115355, WO 2015183776, WO 2014085216, and CN 114831993, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

ii) CHK inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more checkpoint kinase (CHK) inhibitors. A CHK inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. CHK1 kinase is a critical regulator of the cell cycle and the DNA damage response pathway. In some embodiments, the CHK inhibitor is a CHK1 inhibitor. In some embodiments, a CHK inhibitor is a CHK2 inhibitor. In some embodiments, a CHK1 inhibitor is one or more BBI-355, rabusertib, LY2606368, GDC-0575, and MK-8776. In some embodiments, reference to the term CHK1 inhibitor includes any such CHK1 inhibitor disclosed in any one of the following patent applications: WO 2021113661, WO 2021104461, WO 2019012030, WO 2010118390, WO 2008067027, WO 2002070494, and TW202126818, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

iii) ATM inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more ataxia telangiectasia mutated (ATM) inhibitors. An ATM inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. ATM plays a role in regulating the replication stress response and maintaining genomic stability. In some embodiments, an ATM inhibitor is one or more M4076, AZD0156, KU-60019, and VE-821. In some embodiments, reference to the term ATM inhibitor includes any such ATM inhibitor disclosed in any one of the following patent applications: WO 2021197339, WO 2021098734, WO 2021260580, WO 2007026157, WO 2006085067, and US 2016113935, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

iv) ATR inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more ataxia telangiectasia and Rad3-related (ATR) inhibitors. An ATR inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. In some embodiments, an ATR inhibitor is one or more ceralaertib, VE-821, RP-350, AZ20, VX-970, abd110, VX-803, and BAY 1895344. In some embodiments, reference to the term ATR inhibitor includes any such ATR inhibitor disclosed in any one of the following patent applications: WO 2023016529, WO 2022237875, WO 2022268025, WO 2021012049, WO 2021023272, WO 2021260579, WO 2021228758, WO 2019050889, WO 2019154365, WO 2019133711, WO 2017059357, WO 2013049859, WO 2007046426, WO 2007015632, and CN 113797341, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

v) PARP inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more Poly(ADP-ribose) polymerase (PARP) inhibitors. A PARP inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. There are 17 PARP (aka tankyrase) family members that have been identified. PARP enzymes play a critical role in DNA damage repair, particularly in the repair of single-strand DNA breaks. PARP inhibitors block the activity of PARP enzymes, leading to the accumulation of DNA damage and ultimately cell death. In some embodiments, a PARP inhibitor is one or more Olaparib, rucaparib, niraparib, and veliparib (ABT-888). In some embodiments, reference to the term PARP inhibitor includes any such PARP inhibitor disclosed in any one of the following patent applications: WO 2023051812, WO 2023051807, WO 2023051716, WO 2023278592, WO 2022228387, WO 2022022664, WO 2022000946, WO 2022222921, WO 2021163530, WO 2020122034, WO 2020239097, WO 2020142583, WO 2020156577, WO 2020098774, WO 2020196712, WO 2019200382, WO 2018125961, WO 2018205938, WO 2018192576, WO 2018218025, WO 2017032289, WO 2017177838, WO 2017029601, WO 2017088723, WO 2016155655, WO 2015154630, WO 2013097225, WO 2012130166, WO 2011006794, WO 2009046205, WO 2009063244, WO 2008084261, WO 2007138351, WO 2006110816, WO 2005053662, WO 2005012524, CN 113698356, CN 113603647, CN 115073544, CN 108938634, CN 104887680, CN 110343088, CN 108976236, and CN 107629071, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

vi) DNA-PK inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more DNA-dependent protein kinase (DNA-PK) inhibitors. An DNA-PK inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. DNA-dependent protein kinase (DNA-PK) is a serine/threonine protein kinase that plays a crucial role in DNA repair and maintenance of genome stability. In some embodiments, a DNA-PK inhibitor is one or more NU7441,

AZD7648, VX-984, M3814, and CC-115. In some embodiments, reference to the term DNA-PK inhibitor includes any such DNA-PK inhibitor disclosed in any one of the following patent applications: WO 2022187965, WO 2021197159, WO 2021260583, WO 2021204111, WO 2021104277, WO 2021098813, WO 2021022078, WO 2020259613, WO 2019143678, WO 2019143675, WO 2019201283, WO 2015058031, WO 2014159690, WO 2012028233, WO 2009010761, WO 2006032869, WO 2006109084, CN 112574179, CN 112300132, and CN 112300126, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

g) Cell Cycle Inhibitors

Compositions and methods described herein may include a compound of the present invention in combination with one or more cell cycle inhibitors. Cell cycle inhibitors target specific proteins involved in regulating the cell cycle, which is the process by which a cell divides and replicates its DNA. Non-limiting examples cell cycle proteins include cyclin-dependent kinase (CDK), aurora kinase, and polo-like kinase (PLK). CDKs are a family of kinases that are involved in regulating the cell cycle. CDK inhibitors block the activity of these kinases, leading to cell cycle arrest and/or apoptosis. Aurora kinases are a family of serine/threonine kinases that play a critical role in regulating mitosis. Aurora kinase inhibitors block the activity of these kinases, leading to mitotic arrest and cell death. PLKs are a family of serine/threonine kinases that are involved in regulating multiple stages of the cell cycle. PLK inhibitors block the activity of these kinases, leading to cell cycle arrest and/or apoptosis.

i) CDK inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more CDK inhibitors. A CDK inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. Cyclin-dependent kinases are a family of protein kinases that regulate cell division and proliferation. Cell cycle progression is controlled by cyclins and their associated cyclin-dependent kinases, such as CDK1, CDK2, CDK3, CDK4 and CDK6, while other CDKs such as CDK7, CDK8 and CDK9 are critical to transcription. CDK binding to cyclins forms heterodimeric complexes that phosphorylate their substrates on serine and threonine residues, which in turn initiates events required for cell-cycle transcription and progression. In some embodiments, a CDK inhibitor is a CDK2 inhibitor. In some embodiments, a CDK inhibitor is a CDK4/6 inhibitor. In some embodiments, a CDK inhibitor is a CDK7 inhibitor. In some embodiments, a CDK inhibitor is a CDK9 inhibitor. In some embodiments, a CDK inhibitor is one or more palbociclib, ribociclib, abemaciclib, and trilaciclib. In some embodiments, a CDK inhibitor is one or more of tagtociclib (PF-07104091), seliciclib, voruciclib P1446A-05, BLU-222, dinaciclib, AT-7519, RGB286638, and AZD4573.

In some embodiments, reference to the term CDK inhibitor includes any such CDK inhibitor disclosed in any one of the following patent applications: WO 2022166793, WO 2022187611, WO 2022130304, WO 2021227906, WO 2021057867, WO 2020207260, WO 2020138370, WO 2020125513, WO 2020148635, WO 2020215156, WO 2020052627, WO 2017177837, WO 2017162215, WO 2017177836, WO 2016193939, WO 2016014904, WO 2016015598, WO 2016015605, WO 2015181737, WO 2012061156 A1, WO 2012038411, WO 2010020675, WO 2010125004, WO 2007139732, WO

2006024945, CN 114478529, CN 108794496, CN 105294737, CN 107652284, KR 20180106188, and US 2017152269, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

ii) Aurora kinase inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more aurora kinase inhibitors. An aurora kinase inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. Aurora kinases are a family of serine/threonine kinases that play a critical role in regulating cell division and maintaining genomic stability. The Aurora kinase family consists of three members: Aurora A, Aurora B, and Aurora C. In some embodiments, an aurora kinase inhibitor is one or more palbociclib, ribociclib, and abemaciclib. In some embodiments, an aurora kinase inhibitor is one or more of alisertib, danusertib, barasertib, and MLN8237. In some embodiments, reference to the term aurora kinase inhibitor includes any such aurora kinase inhibitor disclosed in any one of the following patent applications: WO 2021110009, WO 2021008338, WO 2020112514, WO 2019129234, WO 2016077161, WO 2013143466, WO 2011103089, WO 2010081881, WO 2010133794, WO 2009134658, WO 2008001886, WO 2007095124, WO 2007003596, WO 2006129064, CN 114276227, CN 108078991, CN 106543155, CN 104211692, and CN 104098551, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

iii) PLK inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more polo-like kinase (PLK) inhibitors. A PLK inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. PLKs are a family of serine/threonine kinases that play a crucial role in regulating cell division, DNA damage response, mitotic progression, and consists of four members: PLK1, PLK2, PLK3, and PLK4. In some embodiments, a PLK inhibitor is one or more of volasertib, onvansertib, BI 2536, and GSK461364. In some embodiments, reference to the term PLK inhibitor includes any such PLK inhibitor disclosed in any one of the following patent applications: WO 2011012534, WO 2010065134, WO 2009130453, WO 2009042806, WO 2004043936, WO 2007030361, WO 2006021547, CN 115804777, and EP 2325185, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

iv) Kinesin superfamily of microtubule motor protein inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more Kinesin spindle protein (KSP) inhibitors. In some embodiments, compositions described herein may include one or more Kinesin family (KIF) inhibitors. In some embodiments, a KSP inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. KSP and KIF are a subset of the kinesin superfamily of microtubule motor proteins. KSP, also known as Eg5, is a member of the kinesin superfamily of motor proteins that plays a critical role in mitotic spindle formation and cell

division. KSP inhibitors selectively target rapidly dividing cancer cells by disrupting spindle formation and inducing mitotic arrest. In some embodiments, a KSP inhibitor is one or more of SB743921, monastrol, S-Trityl-L-cysteine (STLC), and filanesib (ARRY-520). In some embodiments, a KIF inhibitor is an inhibitor of a Kinesin-8 family microtubule motor protein. In some embodiments, the kinesin-8 family protein is KIF18A. In some embodiments, a KIF inhibitor is one or more of AMG650, BTB-1, K03861, and SJ000291942. In some embodiments, reference to the term kinesin superfamily of microtubule motor protein inhibitor includes any such kinesin superfamily of microtubule motor protein inhibitor disclosed in any one of the following patent applications: WO 2015114854, WO 2015114855, WO 2010084186, WO 2006101761, WO 2006110390, WO 2006044825, WO 2006078574, WO 2005060654, WO 2004092147, WO 2004037171, WO 2004058700, WO 2003050064, WO 2003105855, WO 2022037665, WO 2018114804, WO 2017162663, WO 2016207089, WO 2012073375, JP 2014162787, JP 2019189590, JP2013166713, and KR 20220145566, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

v) DYRK1 inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more Dual-specificity tyrosine phosphorylation-regulated kinase 1 (DYRK1) inhibitors. A DYRK1 inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. DYRK1 is a member of the DYRK (dual-specificity tyrosine phosphorylation-regulated kinase) family of protein kinases. It plays essential roles in various cellular processes, including cell cycle regulation, neuronal development, and transcriptional control. In some embodiments, a DYRK1 inhibitor is one or more of harmine, INDY, D4476, and AZ191. In some embodiments, reference to the term DYRK1 inhibitor includes any such DYRK1 inhibitor disclosed in any one of the following patent applications: WO 2023277331, WO 2023140846, WO 2017181087, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

h) Anti-Apoptotic Protein Inhibitors

Compositions and methods described herein may include a compound of the present invention in combination with one or more anti-apoptotic protein inhibitors. In some embodiments, an anti-apoptotic protein inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. Anti-apoptotic inhibitors target proteins that play a role in preventing apoptosis, a form of programmed cell death. Apoptosis is a critical mechanism for eliminating damaged or unwanted cells. Anti-apoptotic proteins are a family of proteins that inhibit the apoptotic pathway, thereby preventing cell death. There are several known classes of anti-apoptotic inhibitors, including Bcl-2 inhibitors, XIAP inhibitors, survivin inhibitors, Mcl-1 inhibitors, and FLIP inhibitors. These inhibitors work by binding to specific anti-apoptotic proteins and preventing their activity, thereby promoting cell death in cancer cells. In some embodiments, compositions described herein may include one or more anti-apoptotic protein inhibitors. An anti-apoptotic protein inhibitor may be administered or formulated in combination with a RAS(ON) inhibitor and/or any additional therapeutic

agent described herein. In some embodiments, the anti-apoptotic protein inhibitor includes a MCL-1 inhibitor. Non-limiting examples of MCL-1 inhibitors include, AMG-176, MIK665, and S63845. The myeloid cell leukemia-1 (MCL-1) protein is one of the key anti-apoptotic members of the B-cell lymphoma-2 (BCL-2) protein family. Over-expression of MCL-1 has been closely related to tumor progression as well as to resistance, not only to traditional chemotherapies but also to targeted therapeutics including BCL-2 inhibitors such as ABT-263. In some embodiments, the anti-apoptotic protein inhibitor includes a BCL protein inhibitor. Examples of BCL protein inhibitors include but are not limited to Venetoclax (Venclexta™), Navitoclax (ABT-263), A-1331852, S63845, and AT-101.

i) Autophagy Inhibitors

Compositions and methods described herein may include a compound of the present invention in combination with one or more autophagy inhibitors. In some embodiments, an autophagy inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. Autophagy inhibitors include, but are not limited to chloroquine, 3-methyladenine, hydroxychloroquine (Plaquenil™), spautin-1, SAR405, bafilomycin A1, 5-amino-4-imidazole carboxamide riboside (AICAR), okadaic acid, autophagy-suppressive algal toxins which inhibit protein phosphatases of type 2A or type 1, analogues of cAMP, and drugs which elevate cAMP levels such as adenosine, LY204002, N6-mercaptopurine riboside, and vinblastine. In addition, antisense or siRNA that inhibits expression of proteins including but not limited to ATG5 (which are implicated in autophagy), may also be used. In some embodiments, the one or more additional therapies include an autophagy inhibitor.

a) ULK inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more Unc-51-like kinase (ULK) inhibitors. An ULK inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. In some embodiments, a ULK inhibitor is a ULK1/2 inhibitor. In some embodiments, an ULK inhibitor is one or more of ULK-101, MRT68921, SBI-0206965, MRT67307, MRT68920, MRT68922, MRT199665, LY3009120, and Dorsomorphin.

b) VPS inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more Vacuolar protein sorting protein (VPS) inhibitors. A VPS inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. VPS (proteins are a family of proteins that play a critical role in the process of autophagy by regulating the formation and function of autophagosomes, structures that engulf and transport cellular components to lysosomes for degradation. Dysregulation of VPS proteins has been implicated in various diseases, including cancer, neurodegenerative disorders, and infectious diseases. In some embodiments, a VPS inhibitor is a VPS34 inhibitor. In some embodiments, a VPS inhibitor is one or more of PIK-III, VPS34-IN1, SAR405, Spautin-1, and NSC185058.

c) Macropinocytosis inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more macropinocytosis inhibitors. A macropinocytosis inhibitor may be administered or formulated in combination with a RAS(ON) inhibitor and/or any additional therapeutic agent described herein. Macropinocytosis inhibitors are compounds that can block or reduce the process of macropinocytosis. In some embodiments, a macropinocytosis inhibitor is one or more of EIPA (ethylisopropylamiloride), Wortmannin, Amiloride, Apilimod, Dyngo-4a, and Latrunculin B.

j) WNT/b-catenin Pathway Inhibitors

Compositions and methods described herein may include a compound of the present invention in combination with one or more WNT/beta-catenin pathway inhibitors. In some embodiments, a WNT/beta-catenin pathway inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. The WNT/beta-catenin pathway is an important signaling pathway that plays a crucial role in development, tissue homeostasis, and disease. Dysregulation of this pathway has been implicated in various cancers, making it an attractive target for cancer therapy. WNT/beta-catenin pathway inhibitors target various components of the pathway, including WNT ligands, receptors, and downstream effectors.

i) Beta-catenin inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention and one or more beta-catenin inhibitors. A beta-catenin inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. Beta-catenin is a protein that plays an important role in the WNT signaling pathway, which regulates various cellular processes including cell proliferation, differentiation, and migration. In normal cells, beta-catenin levels are tightly regulated by a destruction complex, which marks beta-catenin for degradation. However, in many cancer cells, the destruction complex is impaired, leading to the accumulation of beta-catenin in the nucleus and the activation of target genes involved in tumor growth and metastasis. In some embodiments, a WNT/beta-catenin inhibitor is one or more of FOG-001, OMP-131R10, Foxy-5, LGK974, RXC004, ETC-159, OMP-54F28, Niclosamide, OMP-18R5, OTSA-101, BNC101, DKN-01, Sulindac, Pyrvinium, E7449, BC2059, PRI-724, SM08502, IWP1, IWP2, IWP3, IWP4, IWP12, IWP L6, C59, GNF-6231, GNF-1331, DK-520, DK-419, IgG-2919, Fz7-21, RHPD-P1, SRI37892, 1094-0205, 2124-0331, 3235-0367, NSC36784, NSC654259, IgG-2919, Salinomycin, BMD4702, 3289-8625, J01-017a, FJ9, KY-02061, KY-02327, NSC668036, Peptide Pen-N3, SSTC3, CCT031374, TCS 183, XAV939, AZ1366, G007-LK, MSC2504877, G244-LM, IWR-1, JW74, JW55, K-756, NVP-TNKS656, MN-64, RK-287107, WIKI4, KY1220, KYA1797K, MSAB, PKF115-584, CGP049090, AV-65, PNU-74654, Windorphen, IQ-1 tegavivant, foscenvivant, PNPB-29, ZW4864, SAH-BCL9, Carnosic acid, xStAx-VHL, NRX-252114, Septuximab vedotin, PF-06647020, LGR5-mc-vc-PAB-MMAE, LGR5-NMS818, CWP232291, PRI-724 (also known as ICG-001), C-82, and BC2059. In some embodiments, reference to the term beta-catenin inhibitor includes any such beta-catenin inhibitor disclosed in any one of the following patent applications: CN 104388427 and CN 103830211, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

ii) PORCN inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more Porcupine (PORCN) inhibitors. A PORCN inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. PORCN is a membrane-bound O-acyltransferase enzyme that plays a critical role in the WNT signaling pathway by mediating the palmitoylation of WNT ligands. This palmitoylation is essential for the secretion and signaling activity of WMT proteins. Inhibition of PORCN leads to reduced WNT signaling activity. In some embodiments, a PORCN inhibitor is one or more of LGK974 (WNT974), ETC-1922159, CGX1321, and CWP232291.

iii) GSK3 inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more Glycogen synthase kinase (GSK3) inhibitors. A GSK3 inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. The GSK3 family consists of two closely related serine/threonine kinases: GSK3α and GSK3β. These kinases are involved in numerous cellular processes, including glycogen metabolism, cell cycle regulation, and Wnt signaling. GSK inhibitors have been investigated as potential therapeutics for various diseases, including cancer, diabetes, Alzheimer's disease, and bipolar disorder. In some embodiments, a GSK3 inhibitor is one or more of Tideglusib, laduviglusib, LiCl (Lithium chloride), CHIR99021, SB216763, AZD1080, and LY2090314. In some embodiments, reference to the term GSK3 inhibitor includes any such GSK3 inhibitor disclosed in any one of the following patent applications: WO 2017153834, WO 2014059383, WO 2010012398, WO 2009017455, WO 2003037891, CN 107151235, and CN 102258783, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

iv) CLK inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more Cdc2-like kinase (CLK) inhibitors. A CLK inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. LKs (Cdc2-like kinases) are a family of serine/threonine kinases that play a crucial role in pre-mRNA splicing, specifically in the regulation of alternative splicing. There are four members of the CLK family: CLK1, CLK2, CLK3, and CLK4. The CLK family of kinases have been shown to be involved in several diseases, including cancer, neurodegenerative disorders, and viral infections. In some embodiments, a CLK inhibitor is a CLK 2 inhibitor. In some embodiments, a CLK2 inhibitor is one or more of lorecivivint, SM08502, SM04690, TG003, KH-CB19, Cmpd-1, T3.5, and CX-4945. In some embodiments, reference to the term CLK inhibitor includes any such CLK inhibitor disclosed in WO 2020006115, which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

k) JAK/STAT Pathway Inhibitors

Compositions and methods described herein may include a compound of the present invention in combination with one or more JAK/STAT pathway inhibitors. In some embodiments, a JAK/STAT

pathway inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. The Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway is a signaling pathway involved in many cellular processes, including immune response, cell growth, and differentiation. Dysregulation of this pathway has been linked to various diseases, including inflammatory disorders, cancer, and autoimmune diseases. Inhibitors of the JAK/STAT pathway can be used for the treatment of these diseases. In some embodiments, a JAK/STAT pathway inhibitor is an inhibitor of JAK1, JAK2 and/or JAK3. In some embodiments, a JAK inhibitor is one or more of Ruxolitinib (Jakafi®), Pacritinib, Fedratinib, Tofacitinib (Xeljanz®), Abrocitinib, Filgotinib, Oclacitinib, Peficitinib, Upadacitinib, Deucravacitinib, Delgocitinib, and Baricitinib (Olumiant®). In some embodiments, reference to the term JAK inhibitor includes any such JAK inhibitor disclosed in any one of the following patent applications: WO 2023011301, WO 2023201044, WO 2022143629, WO 2022251434, WO 2022067106, WO 2022033551, WO 2021244323, WO 2021238817, WO 2021238818, WO 2021178991, WO 2021136345, WO 2021190647, WO 2020219639, WO 2020182159, WO 2020155931, WO 2020038457, WO 2020219524, WO 2020173400, WO 2018204233, WO 2018204238, WO 2018169875,WO 2018117152, WO 2017215630, WO 2016070697, WO 2016027195, CN 117815195, CN 117815367, and CN 115969796, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

In some embodiments, the JAK/STAT pathway inhibitor is a STAT inhibitor. In some embodiments, the STAT inhibitor is an inhibitor of STAT3 and/or STAT5. In some embodiments, the STAT inhibitor is a STAT3 degrader. In some embodiments, the STAT inhibitor is one or more of TTI-101, C-188-9, WP1066, VVD-130850, LLL12B, STA-21, SD-36, Stattic, S3I-201, OPB-31121, and Napabucasin (BBI608). In some embodiments, reference to the term STAT inhibitor includes any such STAT inhibitor disclosed in any one of the following patent applications: WO 2024030628, WO 2023164680, WO 2023192960, WO 2023133336, WO 2020206424, WO 2023107706, WO 2021150543, WO 2008151037, and CN 109288845, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

l) Epigenetic Modulators

Compositions and methods described herein may include a compound of the present invention in combination with one or more epigenetic modulators. Epigenetic modulators are a class of therapeutics that target enzymes responsible for modifying the structure and function of chromatin, the complex of DNA and proteins that make up chromosomes. These enzymes, including histone deacetylases (HDACs), histone methyltransferases (HMTs), and DNA methyltransferases (DNMTs), play critical roles in gene expression and regulation by modifying the packaging of DNA and affecting how it is read and transcribed. Epigenetic modulators work by altering the activity of these enzymes, either by inhibiting or enhancing their function, to regulate gene expression in specific ways. By targeting specific epigenetic modifications, such as acetylation, methylation, and DNA methylation, these therapies have the potential to treat a wide range of diseases, including cancer, inflammatory disorders, and neurological disorders.

i) HDAC inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more histone deacetylase (HDAC) inhibitors. A HDAC inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. There are several classes of HDACs, including class I, class IIa, class IIb, class III, and class IV. Class I HDACs are further divided into HDAC1, HDAC2, HDAC3, and HDAC8, while class IIa HDACs include HDAC4, HDAC5, HDAC7, and HDAC9. Class IIb HDACs consist of HDAC6 and HDAC10, and class III HDACs are known as sirtuins. HDAC inhibitors can target different classes of HDACs, and their specific effects on gene expression can vary depending on which HDACs they target. In some embodiments, a HDAC inhibitor is one or more of Vorinostat (Zolinza™), Romidepsin (Istodax™), Belinostat (Beleodaq™), Panobinostat (Farydak™), Entinostat (MS-275), Valproic acid (Depakene™), Trichostatin A (TSA), Sodium butyrate, and Mocetinostat (MGCD0103). Non-limiting examples of HDAC inhibitors include trichostatin, sodium butyrate, apicidan, suberoyl anilide hydroamic acid, vorinostat, LBH 589, romidepsin, ACY-1215, and Panobinostat. In some embodiments, reference to the term HDAC inhibitor includes any such HDAC inhibitor disclosed in any one of the following patent applications: WO 2022110958, WO 2021252628, WO 2019204550, WO 2018178060, WO 2016126724, WO 2014143666, WO 2013041480, and WO 2006120456, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

ii) BET inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more bromodomain and extra-terminal protein (BET) inhibitors. A BET inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. BET (bromodomain and extra-terminal) proteins are a family of epigenetic reader proteins that recognize and bind to acetylated lysine residues on histones, leading to chromatin remodeling and gene expression regulation. There are four BET proteins in humans: BRD2, BRD3, BRD4, and BRDT. BET inhibitors specifically target the bromodomains of BET proteins, inhibiting their binding to acetylated lysine residues on histones and leading to alterations in gene expression. BET inhibitors are useful in the treatment of cancer and other diseases characterized by dysregulated gene expression. In some embodiments, a BET inhibitor is one or more of JQ1, I-BET762, OTX015, RVX-208, and CPI-0610. In some embodiments, reference to the term BET inhibitor includes any such BET inhibitor disclosed in any one of the following patent applications: WO 2022046682, WO 2022182857, WO 2021107657, WO 2021107656, WO 2020221006, WO 2020053660, WO 2018097977, WO 2017222977, WO 2017142881, WO 2015075665, WO 2015011084, and CN 113264930, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

iii) EZH2 inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more Enhancer of Zeste Homolog 2 (EZH2) inhibitors. An EZH2 inhibitor may be administered or formulated in combination with a compound of the present

invention and/or any additional therapeutic agent described herein. EZH2 is a histone-lysine N-methyltransferase that is a member of the Polycomb repressive complex 2 (PRC2) family. EZH2 plays a crucial role in gene expression regulation, specifically by catalyzing the trimethylation of histone H3 at lysine 27 (H3K27me3), leading to transcriptional repression of target genes. EZH2 has been found to be overexpressed in several types of cancers and is associated with tumor progression and poor prognosis. In some embodiments, an EZH2 inhibitor is one or more of Tazemetostat, GSK2816126, and CPI-1205 (lirametostat). In some embodiments, reference to the term EZH2 inhibitor includes any such EZH2 inhibitor disclosed in any one of the following patent applications: WO 2023030299, WO 2022179584, WO 2020224607, WO 2021243060, WO 2021086069, WO 2019206155, WO 2018133795, WO 2018137639, WO 2017184999, WO 2017218953, WO 2016201328, WO 2015195848, WO 2013155317, WO 2013138361, and CN 114621191, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

iv) Co-REST inhibitors

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more Co-REST inhibitors. A Co-REST inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. Co-REST is a transcriptional co-repressor protein that interacts with a variety of transcription factors to regulate gene expression. Co-REST acts by recruiting histone deacetylases (HDACs) to chromatin, leading to the repression of gene expression. Inhibition of Co-REST has been proposed as a potential therapeutic strategy for the treatment of various diseases, including neurodegenerative disorders and cancer. In some embodiments, a co-REST inhibitor is one or more of Nocodazole, NSC 1892, and Anacardic acid.

v) EP300

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more E1A-binding protein p300 (EP300) inhibitors. An EP300 inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. EP300 is a transcriptional co-activator involved in the regulation of numerous cellular processes, including chromatin remodeling, DNA damage response, and cell cycle progression. EP300 acts as a histone acetyltransferase, catalyzing the transfer of acetyl groups to lysine residues on histone proteins, which leads to changes in chromatin structure and gene expression. EP300 activity has been implicated in diseases, such as cancer, cardiovascular and neurological disorders. In some embodiments, an EP300 inhibitor is one or more of C646, A-485, NU9056, and L002. In some embodiments, reference to the term EP300 inhibitor includes any such EP300 inhibitor disclosed in any one of the following patent applications: WO 2021213521 and WO 2016044694, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

vi) LSD1

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more Lysine-specific demethylase 1 (LSD1) inhibitors. A

LSD1 inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. LSD1 is an enzyme that plays a crucial role in regulating gene expression through histone modification. It specifically removes the methyl group from lysine 4 on histone 3, leading to gene repression. Dysregulation of LSD1 has been associated with various diseases including cancer and neurodegenerative disorders. In some embodiments, a LSD1 inhibitor is one or more of GSK2879552, IMG-7289, ORY-1001, IMG-8419, SP-2577, CC-90011, HCI-2509, and INCB059872. In some embodiments, reference to the term LSD1 inhibitor includes any such LSD1 inhibitor disclosed in any one of the following patent applications: WO 2021095840, WO 2021175079, WO 2021058024, WO 2020047198, WO 2020052649, WO 2020015745, WO 2020052647, WO 2018137644, WO 2017184934, WO 2017027678, WO 2017116558, WO 2017149463, WO 2016161282, WO 2015123465, WO 2015123424, WO 2013057322, WO 2013057320, WO 2012135113, CN 114805261, CN 111072610 CN 107174584, CN 110478352, CN 106432248, and CN 106045881, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

vii) PRMT5

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more Protein arginine methyltransferase 5 (PRMT5) inhibitors. A PRMT5 inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. PRMT5 is a member of the PRMT family, which catalyzes the transfer of a methyl group from S-adenosylmethionine (SAM) to the nitrogen atoms of arginine residues in target proteins. PRMT5 is involved in various biological processes, including gene expression regulation, signal transduction, and DNA repair. In some embodiments, a PRMT5 inhibitor is one or more of TNG908, TNG462, AMG193, GSK591, EPZ015666, TC-E 5003, and MS023. In some embodiments, reference to the term PRMT5 inhibitor includes any such PRMT5 inhibitor disclosed in any one of the following patent applications: WO 2023001133, WO 2022206964, WO 2022153161, WO 2021068953, WO 2021088992, WO 2020259478, WO 2020205660, WO 2020250123, WO 2020033288, WO 2019102494, WO 2019112719, WO 2019180631, WO 2018065365, WO 2017153186, WO 2017212385, WO 2017032840, WO 2016022605, WO 2014100695, WO 2014145214, WO 2014100719, CN 111825656, CN 114558014, CN 11304554, and CN 112778275, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

viii) MAT2A

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more methionine adenosyltransferase 2A (MAT2A) inhibitors. A MAT2A inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. MAT2A is an enzyme that catalyzes the production of S-adenosylmethionine (SAM), which is an important cofactor in many biological processes, including DNA methylation, protein methylation, and polyamine synthesis. Elevated MAT2A expression has been associated with various cancers. In some embodiments, a MAT2A inhibitor is one or more of cycloleucine and 2-hydroxy-4-methylthiobutanoic acid. In some embodiments, reference

to the term MAT2A inhibitor includes any such MAT2A inhibitor disclosed in any one of the following patent applications: WO 2022256808, WO 2022256806, WO 2019191470, and CN 115716831, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

ix) DOT1L

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more Disruptor of Telomeric silencing 1-like (DOT1L) inhibitors. A DOT1L inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. DOT1L is a histone methyltransferase enzyme that catalyzes the methylation of lysine 79 on histone H3. This modification is associated with transcriptional elongation and is important for the maintenance of gene expression programs. The DOT1L family includes enzymes that are involved in epigenetic regulation and transcriptional control, and their dysregulation has been linked to various diseases, including cancer. In some embodiments, a DOT1L inhibitor is one or more of EPZ-5676 (pinometostat) and EPZ-004777. In some embodiments, reference to the term DOT1L inhibitor includes any such DOT1L inhibitor disclosed in any one of the following patent applications: WO 2016090271, WO 2014100662, and CN 108997480, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

iix) UBA1

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more ubiquitin-activating enzyme inhibitors (e.g., a UBA1 inhibitor). A UBA1 inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. UBA1, also known as ubiquitin-activating enzyme 1, is a key enzyme involved in the ubiquitination process, a fundamental cellular mechanism for protein degradation and regulation. Ubiquitination involves the covalent attachment of ubiquitin molecules to target proteins, marking them for degradation by the proteasome or modulating their activity, localization, or interactions within the cell. Several inhibitors have been developed to modulate UBA1 activity, with the aim of disrupting ubiquitination-mediated processes in diseased cells. These inhibitors include but are not limited to adenosine-based inhibitors which typically compete with ATP for binding to the active site of UBA1, thereby preventing the activation of ubiquitin (e.g., PYR-41 and MLN7243); covalent inhibitors which form irreversible bonds with specific amino acid residues in the active site of UBA1, leading to inhibition of its activity (e.g., TAK-243 (formerly known as MLN4924)); allosteric inhibitors which bind to sites on UBA1 distinct from the active site, inducing conformational changes that inhibit its catalytic activity (e.g., compound 2i); and fragment-based inhibitors which are designed based on smaller molecular fragments that bind to UBA1. In some embodiments, a UBA1 inhibitor is one or more of PYR-41, MLN7243, and TAK-243. In some embodiments, reference to the term UBA1 inhibitor includes any such UBA1 inhibitor disclosed in any one of the following patent applications: WO 2016069393, WO 2016069392, and JP 2013237627, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

m) Additional Therapeutic Agents Useful for Combination Therapy

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more Farnesyl transferase inhibitors. A farnesyl transferase inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. Farnesyl transferase inhibitors (FTIs) are a class of drugs that target the farnesyl transferase enzyme, which plays a role in a process called protein prenylation. Protein prenylation is an important step in the process of activating certain proteins involved in signal transduction, cell growth, and differentiation. In some embodiments, a farnesyl transferase inhibitor is one or more of tipifarnib, lonafarnib, and rilapladib. In some embodiments, reference to the term farnesyl transferase inhibitor includes any such farnesyl transferase inhibitor disclosed in any one of the following patent applications: WO 2010057028, WO 2007042465, WO 200136395, WO 200064891, WO 200042849, WO 199938862, WO 199928315, WO 199829390, WO 199426723, CN 107312000, CN 107365310, KR 100375421, KR 100388790, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more casein kinase inhibitors. In some embodiments, a casein inhibitor is, SR-3029, a potent and ATP competitive CK1δ and CK1ε inhibitor.

In some embodiments, compositions and methods described herein may include one or more FLT3 inhibitors in combination with a compound of the present invention disclosed herein. FLT3 (Fms-like tyrosine kinase 3), also known as CD135, is a receptor tyrosine kinase (RTK) that plays a crucial role in regulating hematopoiesis, the process by which blood cells are formed. It is primarily expressed on hematopoietic stem cells (HSCs) and progenitor cells in the bone marrow, where it controls cell proliferation, survival, and differentiation. In some embodiments, a FLT3 inhibitor includes, but are not limited to, midostaurin, gilteritinib, sorafenib, quizartinib, crenolanib, ponatinib and quizartinib.

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more one or more TGFb pathway inhibitors. In some embodiments, compositions and methods described herein may include one or more TGFb inhibitors. A TGFb inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. TGFb (transforming growth factor beta) is a multifunctional cytokine involved in various cellular processes, including cell growth, differentiation, apoptosis, and immune response. Dysregulation of the TGFb signaling pathway has been implicated in various diseases, including cancer, fibrosis, and autoimmune disorders. In some embodiments, a TGFb inhibitor is one or more of galunisertib (LY2157299), and vactosertib (TEW-7197). In some embodiments, a TGFb inhibitor is one or more of galunisertib, LY2157299, fresolimumab, lerdelimumab, trabedersen, curcumin, resveratrol and small interfering RNA (siRNA) to silence TGFb receptor expression. In some embodiments, reference to the term TGFb inhibitor includes any such TGFb inhibitor disclosed in any one of the following patent applications: WO 2023043473, WO 2020104648, WO 2020128850, WO 2016140884, WO 2007018818, WO 2004024159, WO 200226935, WO 2002062753, WO 2002062776, and JP 2012087076, each of which is incorporated herein by reference in

its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more HSP90 inhibitors. A HSP90 inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. HSP90, also known as heat shock protein 90, is a molecular chaperone that plays a critical role in regulating the folding, stability, and activity of a large number of client proteins involved in various cellular processes, including cell cycle progression, signal transduction, and apoptosis. In some embodiments, a HSP90 inhibitor is one or more of Geldanamycin and its derivatives (e.g., 17-AAG, 17-DMAG), KOS 953, Radicicol and its derivatives (e.g., PU-H71), SNX-2112, Ganetespib, AT13387, Onalespib, Luminespib, and KW-2478. In some embodiments, reference to the term HSP90 inhibitor includes any such HSP90 inhibitor disclosed in any one of the following patent applications: WO 2021137665, WO 2018200534, WO 2017151425, WO 2015200514, WO 2013053833, WO 2013009657, WO 2013119985, WO 2012138894, WO 2011044394, WO 2009097578, WO 2008115719, CN 105237533, and CN 104030904, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more Glutathione peroxidase 4 (GPX4) inhibitors. A GPX4 inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. GPX4 is an antioxidant enzyme that plays a critical role in protecting cells against oxidative stress-induced cell death. GPX4 catalyzes the reduction of lipid hydroperoxides to their corresponding alcohols and acts as a regulator of ferroptosis, a form of regulated cell death driven by lipid peroxidation. In some embodiments, a GPX4 inhibitor is one or more of RSL3, ML162, DPI7, FINO2, MCB-613, CBS9106, ML210, ODSH, and TLN232. In some embodiments, reference to the term GPX4 inhibitor includes any such GPX4 inhibitor disclosed in any one of the following patent applications: WO 2021132592, US 2021244715, and KR 20220115536, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more NRF2 inhibitors. A NRF2 inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. NRF2 is a transcription factor that regulates the expression of genes involved in the cellular antioxidant response, detoxification, and other cytoprotective pathways. It plays a critical role in cellular defense mechanisms against oxidative stress and other forms of cellular damage. In some embodiments, a NRF2 inhibitor is one or more of ML385, Brusatol, CDDO-Im, RTA-408, and trigonelline. In some embodiments, reference to the term NRF2 inhibitor includes any such NRF2 inhibitor disclosed in any one of the following patent applications: WO 2023051088, WO 2021202720, KR 2022013610, and CN 107519168, each of which is incorporated herein by reference in its entirety,

including the compound structures disclosed therein which are specifically incorporated herein by reference.

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more TEA domain (TEAD) inhibitors. A TEAD inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. TEAD is a family of transcription factors that play a key role in regulating gene expression during embryonic development and tissue homeostasis. The four members of the TEAD family (TEAD1-4) are transcriptional co-activators that bind to DNA through their conserved TEA domain and interact with other transcription factors to activate the expression of target genes. In some embodiments, a TEAD inhibitor is one or more of VT-107, a pan-TEAD, VT-104, Verteporfin, CA3, IAG933, K-975, IK-595, and Statins (see, e.g., Chapeau, Emilie and Schmelzle, Tobias (2023) IAG933, an oral selective YAP1-TAZ/pan-TEAD protein-protein interaction inhibitor (PPIi) with pre-clinical activity in monotherapy and combinations with MAPK inhibitors. Nature cancer). In some embodiments, reference to the term TEAD inhibitor includes any such TEAD inhibitor disclosed in any one of the following patent applications: WO 2023280254, WO 2023031781, WO 2022258040, WO 2020070181 WO 2018185266, and WO 2017064277, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more NOTCH/Gamma secretase inhibitors. A NOTCH/Gamma secretase inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. In some embodiments, a NOTCH/Gamma secretase inhibitor is nirogacestat. In some embodiments, reference to the term NOTCH/Gamma secretase inhibitor includes any such NOTCH/Gamma secretase inhibitor disclosed in any one of the following patent applications: WO 2020208572, WO 2017200969, WO 2014047390, WO 2014047372, WO 2011041336, WO 2010090954, WO 2009008980, WO 2009087130, WO 2007110335, CN 103664904, CN 105560244, and KR 20200077480, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more Hedgehog inhibitors. A hedgehog inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. The hedgehog (Hh) family of proteins are secreted signaling molecules that play a crucial role in embryonic development and tissue homeostasis in adults. The Hh signaling pathway is involved in regulating cell growth, differentiation, and survival. In some embodiments, a hedgehog inhibitor is one or more of Vismodegib (Erivedge), Sonidegib (Odomzo), and Glasdegib (Daurismo). In some embodiments, reference to the term hedgehog inhibitor includes any such hedgehog inhibitor disclosed in any one of the following patent applications: WO 2011063309, and CN 107163028, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

Compositions and methods described herein may include a compound of the present invention in combination with one or more NFkB pathway inhibitors. An NFkB inhibitor may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. NF-kappa B (NFκB) is a family of transcription factors involved in regulating various cellular processes, including inflammation, immunity, cell survival, and proliferation. Non-limiting examples of NFkB inhibitors include Bortezomib (Velcade), Curcumin, Parthenolide, IKK inhibitors (e.g., IKK-16, BAY 11-7082), Resveratrol, Andrographolide and Proteasome inhibitors (e.g., MG132, lactacystin).

In some embodiments, the additional therapy is the administration of side-effect limiting agents (e.g., agents intended to lessen the occurrence or severity of side effects of treatment. For example, in some embodiments, a compound of the present invention can also be used in combination with a therapeutic agent that treats nausea. Examples of agents that can be used to treat nausea include: dronabinol, granisetron, metoclopramide, ondansetron, and prochlorperazine, or pharmaceutically acceptable salts thereof.

In some embodiments, the one or more additional therapies includes a non-drug treatment (e.g., surgery or radiation therapy). In some embodiments, the one or more additional therapies includes a therapeutic agent (e.g., a compound or biologic that is an anti-angiogenic agent, signal transduction inhibitor, antiproliferative agent, glycolysis inhibitor, or autophagy inhibitor). In some embodiments, the one or more additional therapies includes a non-drug treatment (e.g., surgery or radiation therapy) and a therapeutic agent (e.g., a compound or biologic that is an anti-angiogenic agent, signal transduction inhibitor, antiproliferative agent, glycolysis inhibitor, or autophagy inhibitor).

Examples of non-drug treatments include, but are not limited to, radiation therapy, cryotherapy, hyperthermia, surgery (e.g., surgical excision of tumor tissue), and T cell adoptive transfer (ACT) therapy.

In some embodiments, a compound of the present invention may be used as an adjuvant therapy after surgery. In some embodiments, a compound of the present invention may be used as a neo-adjuvant therapy prior to surgery.

Radiation therapy may be used for inhibiting abnormal cell growth or treating a hyperproliferative disorder, such as cancer, in a subject (e.g., mammal (e.g., human)). Techniques for administering radiation therapy are known in the art. Radiation therapy can be administered through one of several methods, or a combination of methods, including, without limitation, external-beam therapy, internal radiation therapy, implant radiation, stereotactic radiosurgery, systemic radiation therapy, radiotherapy, and permanent or temporary interstitial brachy therapy. The term "brachy therapy," as used herein, refers to radiation therapy delivered by a spatially confined radioactive material inserted into the body at or near a tumor or other proliferative tissue disease site. The term is intended, without limitation, to include exposure to radioactive isotopes (e.g., At-211, I-131, I-125, Y-90, Re-186, Re-188, Sm-153, Bi-212, P-32, and radioactive isotopes of Lu). Suitable radiation sources for use as a cell conditioner of the present disclosure include both solids and liquids. By way of non-limiting example, the radiation source can be a radionuclide, such as I-125, I-131, Yb-169, Ir-192 as a solid source, I-125 as a solid source, or other radionuclides that emit photons, beta particles, gamma radiation, or other therapeutic rays. The radioactive material can also be a fluid made from any solution of radionuclide(s), e.g., a solution of I-125

or I-131, or a radioactive fluid can be produced using a slurry of a suitable fluid containing small particles of solid radionuclides, such as Au-198, or Y-90. Moreover, the radionuclide(s) can be embodied in a gel or radioactive micro spheres.

In some embodiments, a compound of the present invention can render abnormal cells more sensitive to treatment with radiation for purposes of killing or inhibiting the growth of such cells. Accordingly, this disclosure further relates to a method for sensitizing abnormal cells in a mammal to treatment with radiation which comprises administering to the mammal an amount of a compound of the present disclosure, which amount is effective to sensitize abnormal cells to treatment with radiation. The amount of the compound in this method can be determined according to the means for ascertaining effective amounts of such compounds described herein. In some embodiments, a compound of the present invention may be used as an adjuvant therapy after radiation therapy or as a neo-adjuvant therapy prior to radiation therapy.

In some embodiments, the non-drug treatment is a T cell adoptive transfer (ACT) therapy. In some embodiments, the T cell is an activated T cell. The T cell may be modified to express a chimeric antigen receptor (CAR). CAR modified T (CAR-T) cells can be generated by any method known in the art. For example, the CAR-T cells can be generated by introducing a suitable expression vector encoding the CAR to a T cell. Prior to expansion and genetic modification of the T cells, a source of T cells is obtained from a subject. T cells can be obtained from a number of sources, including peripheral blood mononuclear cells, bone marrow, lymph node tissue, cord blood, thymus tissue, tissue from a site of infection, ascites, pleural effusion, spleen tissue, and tumors. In certain embodiments of the present disclosure, any number of T cell lines available in the art may be used. In some embodiments, the T cell is an autologous T cell. Whether prior to or after genetic modification of the T cells to express a desirable protein (e.g., a CAR), the T cells can be activated and expanded generally using methods as described, for example, in U.S. Patents 6,352,694; 6,534,055; 6,905,680; 6,692,964; 5,858,358; 6,887,466; 6,905,681; 7,144,575; 7,067,318; 7,172,869; 7,232,566; 7,175,843; 7,572,631; 5,883,223; 6,905,874; 6,797,514; and 6,867,041.

In some embodiments, compositions and methods described herein may include a compound of the present invention in combination with one or more Claudin-18 targeting agents. A Claudin-18 targeting agents may be administered or formulated in combination with a compound of the present invention and/or any additional therapeutic agent described herein. Claudin-18 (e.g., claudin 18.2; CLDN18.2) has become a promising target for the treatment of patients with digestive malignancies, such as gastric cancer (GC), gastroesophageal junction (GEJ) cancer, esophageal cancer, and pancreatic cancer, because of its limited expression in healthy tissues and abnormal overexpression in a range of malignancies. Multiple clinical trials of CLDN18.2-targeted therapies, including monoclonal antibodies, bispecific antibodies, antibody-drug conjugates (ADCs), and chimeric antigen receptor (CAR) T-cell therapies, are ongoing, with some showing promising early results. Malignant transformation of gastric epithelial tissue leads to disruption of cell polarity and then to exposure of CLDN18.2 epitopes on the cell surface. Although targeted monoclonal antibodies are largely unable to access CLDN18.2 located in tight-junction supramolecular complexes in normal tissue, the perturbations in cell polarity that expose CLDN18.2 epitopes may theoretically enable CLDN18.2 targeted agents to bind to CLDN18.2 in

malignant tissues with minimal off-target effects, making CLDN18.2 an attractive target for therapy. In some embodiments, a Claudin-18 targeting agent is one or more of Zolbetuximab, ASKB589, Osemitamab (TST001), PT886 (a bispecific antibody that targets CLDN18.2 and CD47), TJ-CD4B, CMG901 (an ADC that is composed of an antiCLDN18.2 monoclonal antibody joined to a cytotoxic payload, monomethyl auristatin E), and CT041 (autologous T cells genetically engineered to express a CLDN18.2-targeted CAR). In some embodiments, reference to the term Claudin-18 targeting agent includes any such Claudin-18 targeting agent disclosed in any one of the following patent applications: WO 2024081544, WO 2024131683, WO 2024137619, WO 2024140670, WO 2024136594, WO 2023034922, WO 2023046202, WO 2022203090, WO 2022133169, WO 2022100613, WO 2022256449, WO 2022136642, WO 2021155380, WO 2021129765, WO 2021011885, WO 2021058000, WO 2021218874, WO 2021027850, WO 2020156554, WO 2020025792, WO 2020114480, WO 2020211792, WO 2020239005, WO 2019219089, WO 2018157147, WO 2018108106, WO 2016166122, WO 2014146778, CN 118290582, CN 118203658, and CN 118286201, each of which is incorporated herein by reference in its entirety, including the compound structures disclosed therein which are specifically incorporated herein by reference.

In some embodiments, a therapeutic agent for combination therapy may be a steroid. Accordingly, in some embodiments, the one or more additional therapies includes a steroid. Suitable steroids may include, but are not limited to, 21-acetoxypregnenolone, alclometasone, algestone, amcinonide, beclomethasone, betamethasone, budesonide, chloroprednisone, clobetasol, clocortolone, cloprednol, corticosterone, cortisone, cortivazol, deflazacort, desonide, desoximetasone, dexamethasone, diflorasone, diflucortolone, difuprednate, enoxolone, fluazacort, fiucloronide, flumethasone, flunisolide, fluocinolone acetonide, fluocinonide, fluocortin butyl, fluocortolone, fluorometholone, fluperolone acetate, fluprednidene acetate, fluprednisolone, flurandrenolide, fluticasone propionate, formocortal, halcinonide, halobetasol propionate, halometasone, hydrocortisone, loteprednol etabonate, mazipredone, medrysone, meprednisone, methylprednisolone, mometasone furoate, paramethasone, prednicarbate, prednisolone, prednisolone 25-diethylaminoacetate, prednisolone sodium phosphate, prednisone, prednival, prednylidene, rimexolone, tixocortol, triamcinolone, triamcinolone acetonide, triamcinolone benetonide, triamcinolone hexacetonide, and salts or derivatives thereof.

Further examples of therapeutic agents that may be used in combination therapy with a compound of the present invention include compounds described in the following patents: U.S. Patent Nos. 6,258,812, 6,630,500, 6,515,004, 6,713,485, 5,521,184, 5,770,599, 5,747,498, 5,990,141, 6,235,764, and 8,623,885, and International Patent Applications WO 200137820, WO 200132651, WO 200268406, WO 200266470, WO 200255501, WO 200405279, WO 200407481, WO 200407458, WO 200409784, WO 200259110, WO 199945009, WO 200059509, WO 199961422, WO 200012089, and WO 200002871.

An additional therapeutic agent may be a biologic (e.g., cytokine (e.g., interferon or an interleukin such as IL-2)) used in treatment of cancer or symptoms associated therewith. In some embodiments, the biologic is an immunoglobulin-based biologic, e.g., a monoclonal antibody (e.g., a humanized antibody, a fully human antibody, an Fc fusion protein, or a functional fragment thereof) that agonizes a target to

stimulate an anti-cancer response or antagonizes an antigen important for cancer. Also included are antibody-drug conjugates.

An additional therapeutic agent may be an immune modulatory agent. For example, an additional therapeutic agent may be a T-cell checkpoint inhibitor. In one embodiment, the checkpoint inhibitor is an inhibitory antibody (e.g., a monospecific antibody such as a monoclonal antibody). The antibody may be, e.g., humanized or fully human. In some embodiments, the checkpoint inhibitor is a fusion protein, e.g., an Fc-receptor fusion protein. In some embodiments, the checkpoint inhibitor is an agent, such as an antibody, which interacts with a checkpoint protein. In some embodiments, the checkpoint inhibitor is an agent, such as an antibody, which interacts with the ligand of a checkpoint protein. In some embodiments, the checkpoint inhibitor is an inhibitor (e.g., an inhibitory antibody or small molecule inhibitor) of CTLA-4 (e.g., an anti-CTLA-4 antibody or fusion a protein). In some embodiments, the checkpoint inhibitor is an inhibitor or antagonist (e.g., an inhibitory antibody or small molecule inhibitor) of PD-1. In some embodiments, the checkpoint inhibitor is an inhibitor or antagonist (e.g., an inhibitory antibody or small molecule inhibitor) of PD-L1. In some embodiments, the checkpoint inhibitor is an inhibitor or antagonist (e.g., an inhibitory antibody or Fc fusion or small molecule inhibitor) of PD-L2 (e.g., a PD-L2/Ig fusion protein). In some embodiments, the checkpoint inhibitor is an inhibitor or antagonist (e.g., an inhibitory antibody or small molecule inhibitor) of B7-H3, B7-H4, BTLA, HVEM, TIM3, GAL9, LAG3, VISTA, KIR, 2B4, CD160, CGEN-15049, CHK 1, CHK2, A2aR, B-7 family ligands, or a combination thereof. In some embodiments, the checkpoint inhibitor is pembrolizumab, nivolumab, PDR001 (NVS), REGN2810 (Sanofi/Regeneron), a PD-L1 antibody such as, *e.g.,* avelumab, durvalumab, atezolizumab, pidilizumab, JNJ-63723283 (JNJ), BGB-A317 (BeiGene & Celgene) or a checkpoint inhibitor disclosed in Preusser, M. et al. (2015) Nat. Rev. Neurol., including, without limitation, ipilimumab, tremelimumab, nivolumab, pembrolizumab, AMP224, AMP514/ MEDI0680, BMS936559, MEDI4736, MPDL3280A, MSB0010718C, BMS986016, IMP321, lirilumab, IPH2101, 1-7F9, and KW-6002. Non-limiting examples of immune modulatory agent includes targets identified in Table 3.

Table 3: Exemplary Immune Modulatory Targets

Target	Biological Function
CTLA-4	Inhibitory Receptor
PD-1	Inhibitory Receptor
PD-L1	Ligand for PD-1
LAG-3	Inhibitory Receptor
B7.1	Costimulatory Molecule
B7-H3	Inhibitory Ligand
B7-H4	Inhibitory Ligand
TIM3	Inhibitory Receptor
VISTA	Inhibitory Receptor
CD137	Costimulatory Molecule
OX-40	Costimulatory Receptor
CD40 agonist	Costimulatory Molecule

Target	Biological Function
CD40 agonist + FLT3 ligand	Costimulatory Molecule
CD27	Costimulatory Receptor
CCR4	Costimulatory Receptor
GITR	Costimulatory Receptor
NKG2D	Activating Receptor
KIR	Costimulatory Receptor
NKG2A	Inhibitory Receptor
ENPP1	Inhibitory Receptor
TIGIT	Inhibitory Receptor
A2aR	Inhibitory Receptor
CD73	Inhibitory Receptor
CD39	Inhibitory Receptor
PVRIG	Inhibitory Receptor
IDO	Inhibitory enzyme
CSF1R	Inhibitory Receptor
LIF	Inhibitory Cytokine
CD47	Inhibitory Receptor
SIRPa	Inhibitory Receptor
IL-2	Effector Cytokines
IL-15	Effector Cytokines
IL-12	Effector Cytokines
TREM2	Receptor
TGFb	Multifunctional Cytokine
CD73/TGFb trap	Multifunctional Cytokine
TCR-T cells directed to $KRAS^{MUT}$, mesothelin, or PRAME	Cell therapy
mRNA cancer vaccines	vaccines
BiTEs	Bi-specific T-cell engager
Dual EP2/EP4 inhibitor	E-prostanoid receptor
Gamma delta T Cells	Cell therapy
NK cells	Cell therapy

Note: CTLA4, cytotoxic T-lymphocyte-associated antigen 4; LAG3, lymphocyte activation gene 3; PD-1,programmed cell death protein 1; PD-L1, PD-1 ligand; TIM3, T cell membrane protein 3; VISTA, V-domain immunoglobulin (Ig)-containing suppressor of T-cell activation; KIR, killer IgG-like receptor, APC (Antigen Presenting Cells); TREM2 (Triggering receptor expressed on myeloid cells 2); TGF-b (Transforming growth factor beta).

An additional therapeutic agent may be an anti-TIGIT antibody, such as MBSA43, BMS-986207, MK-7684, COM902, AB154, MTIG7192A or OMP-313M32 (etigilimab).

In some embodiments, the combination therapy includes a compound of the present invention and a cancer vaccine composition. In some embodiments, the cancer vaccine composition is HB-700, mRNA-4157, mRNA-5671, BNT111, GVAX Pancreas, IMA901, DCVax, SOT101, Sipuleucel-T, PROSTVAC-VF or TG01.

An additional therapeutic agent may be an agent that treats cancer or symptoms associated therewith (e.g., a cytotoxic agent, non-peptide small molecules, or other compound useful in the treatment of cancer or symptoms associated therewith, collectively, an “anti-cancer agent”). Anti-cancer agents can be, e.g., chemotherapeutics or targeted therapy agents.

Anti-cancer agents include mitotic inhibitors, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, alkylating agents, antimetabolites, folic acid analogs, pyrimidine analogs, purine analogs and related inhibitors, vinca alkaloids, epipodopyyllotoxins, antibiotics, L-Asparaginase, topoisomerase inhibitors, interferons, platinum coordination complexes, anthracenedione substituted urea, methyl hydrazine derivatives, adrenocortical suppressant, adrenocorticosteroides, progestins, estrogens, antiestrogen, androgens, antiandrogen, and gonadotropin-releasing hormone analog. Further anti-cancer agents include leucovorin (LV), irinotecan, oxaliplatin, capecitabine, paclitaxel, and doxetaxel. In some embodiments, the one or more additional therapies includes two or more anti-cancer agents. The two or more anti-cancer agents can be used in a cocktail to be administered in combination or administered separately. Suitable dosing regimens of combination anti-cancer agents are known in the art and described in, for example, Saltz et al., *Proc. Am. Soc. Clin. Oncol.* 18:233a (1999), and Douillard et al., *Lancet* 355(9209):1041-1047 (2000).

Other non-limiting examples of anti-cancer agents include Gleevec® (Imatinib Mesylate); Kyprolis® (carfilzomib); Velcade® (bortezomib); Casodex (bicalutamide); Iressa® (gefitinib); alkylating agents such as thiotepa and cyclosphosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramide, triethiylenethiophosphoramide and trimethylolomelamine; acetogenins (especially bullatacin and bullatacinone); a camptothecin (including the synthetic analogue topotecan); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogues); cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogues, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; sarcodictyin A; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimustine; antibiotics such as the enediyne antibiotics (e.g., calicheamicin, such as calicheamicin gammall and calicheamicin omegall (see, e.g., *Agnew, Chem. Intl. Ed Engl.* 33:183-186 (1994)); dynemicin such as dynemicin A; bisphosphonates such as clodronate; an esperamicin; neocarzinostatin chromophore and related chromoprotein enediyne antiobiotic chromophores, aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, calicheamicin,

carabicin, caminomycin, carminomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo- 5-oxo-L-norleucine, adriamycin (doxorubicin), morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin, deoxydoxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenishers such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfomithine; elliptinium acetate; an epothilone such as epothilone B; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidamine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK® polysaccharide complex (JHS Natural Products, Eugene, OR); razoxane; rhizoxin; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2''-trichlorotriethylamine; trichothecenes such as T- 2 toxin, verracurin A, roridin A and anguidine; urethane; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxoids, e.g., Taxol® (paclitaxel), Abraxane® (cremophor-free, albumin-engineered nanoparticle formulation of paclitaxel), and Taxotere® (doxetaxel); chloranbucil; tamoxifen (Nolvadex™); raloxifene; aromatase inhibiting 4(5)-imidazoles; 4-hydroxytamoxifen; trioxifene; keoxifene; LY 117018; onapristone; toremifene (Fareston®); flutamide, nilutamide, bicalutamide, leuprolide, goserelin; chlorambucil; Gemzar® gemcitabine; 6-thioguanine; mercaptopurine; platinum coordination complexes such as cisplatin, oxaliplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine; Navelbine® (vinorelbine); novantrone; teniposide; edatrexate; daunomycin; aminopterin; ibandronate; irinotecan (e.g., CPT-11); topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoids such as retinoic acid; esperamicins; capecitabine (e.g., Xeloda®); and pharmaceutically acceptable salts of any of the above.

Additional non-limiting examples of anti-cancer agents include trastuzumab (Herceptin®), bevacizumab (Avastin®), cetuximab (Erbitux®), rituximab (Rituxan®), Taxol®, Arimidex®, ABVD, avicine, abagovomab, acridine carboxamide, adecatumumab, 17-N-allylamino-17-demethoxygeldanamycin, alpharadin, alvocidib, 3-aminopyridine-2-carboxaldehyde thiosemicarbazone, amonafide, anthracenedione, anti-CD22 immunotoxins, antineoplastics (e.g., cell-cycle nonspecific antineoplastic agents, and other antineoplastics described herein), antitumorigenic herbs, apaziquone, atiprimod, azathioprine, belotecan, bendamustine, BIBW 2992, biricodar, brostallicin, bryostatin, buthionine sulfoximine, CBV (chemotherapy), calyculin, dichloroacetic acid, discodermolide, elsamitrucin, enocitabine, eribulin, exatecan, exisulind, ferruginol, forodesine, fosfestrol, ICE chemotherapy regimen, IT-101, imexon, imiquimod, indolocarbazole, irofulven, laniquidar, larotaxel, lenalidomide, lucanthone,

lurtotecan, mafosfamide, mitozolomide, nafoxidine, nedaplatin, olaparib, ortataxel, PAC-1, pawpaw, pixantrone, proteasome inhibitors, rebeccamycin, resiquimod, rubitecan, SN-38, salinosporamide A, sapacitabine, Stanford V, swainsonine, talaporfin, tariquidar, tegafur-uracil, temodar, tesetaxel, triplatin tetranitrate, tris(2-chloroethyl)amine, troxacitabine, uramustine, vadimezan, vinflunine, ZD6126, and zosuquidar.

Further non-limiting examples of anti-cancer agents include natural products such as vinca alkaloids (e.g., vinblastine, vincristine, and vinorelbine), epidipodophyllotoxins (e.g., etoposide and teniposide), antibiotics (e.g., dactinomycin (actinomycin D), daunorubicin, and idarubicin), anthracyclines, mitoxantrone, bleomycins, plicamycin (mithramycin), mitomycin, enzymes (e.g., L-asparaginase which systemically metabolizes L-asparagine and deprives cells which do not have the capacity to synthesize their own asparagine), antiplatelet agents, antiproliferative/antimitotic alkylating agents such as nitrogen mustards (e.g., mechlorethamine, cyclophosphamide and analogs, melphalan, and chlorambucil), ethylenimines and methylmelamines (e.g., hexamethylmelaamine and thiotepa), alkyl sulfonates (e.g., busulfan), nitrosoureas (e.g., carmustine (BCNU) and analogs, and streptozocin), trazenes-dacarbazinine (DTIC), antiproliferative/antimitotic antimetabolites such as folic acid analogs, pyrimidine analogs (e.g., fluorouracil, floxuridine, and cytarabine), purine analogs and related inhibitors (e.g., mercaptopurine, thioguanine, pentostatin, and 2-chlorodeoxyadenosine), aromatase inhibitors (e.g., anastrozole, exemestane, and letrozole), and platinum coordination complexes (e.g., cisplatin and carboplatin), procarbazine, hydroxyurea, mitotane, aminoglutethimide, DNA binding agents (e.g., Zalypsis®), PI3K inhibitors such as PI3K delta inhibitor (e.g., GS-1101 and TGR-1202), PI3K delta and gamma inhibitor (e.g., CAL-130), copanlisib, alpelisib and idelalisib; multi-kinase inhibitor (e.g., TG02 and sorafenib), hormones (e.g., estrogen) and hormone agonists such as luteinizing hormone releasing hormone (LHRH) agonists (e.g., goserelin, leuprolide and triptorelin), BAFF-neutralizing antibody (e.g., LY2127399), IKK inhibitors, p38MAPK inhibitors, anti-IL-6 (e.g., CNT0328), telomerase inhibitors (e.g., GRN 163L), cell surface monoclonal antibodies (e.g., anti-CD38 (HUMAX-CD38), anti-CSI (e.g., elotuzumab, P13K / Akt inhibitors (e.g., perifosine), PKC inhibitors (e.g., enzastaurin), FTIs (e.g., Zarnestra™), anti-CD138 (e.g., BT062), Torcl/2 specific kinase inhibitors (e.g., INK128), ER/UPR targeting agents (e.g., MKC-3946), and cFMS inhibitors (e.g., ARRY-382).

In some embodiments, an anti-cancer agent is selected from mechlorethamine, camptothecin, ifosfamide, tamoxifen, raloxifene, gemcitabine, Navelbine®, sorafenib, or any analog or derivative variant of the foregoing. In some embodiments, the anti-cancer agent is JAB-3312.

In some embodiments, an anti-cancer agent is a PD-1 or PD-L1 antagonist.

In some embodiments, additional therapeutic agents include ALK inhibitors, HER2 inhibitors, EGFR inhibitors, IGF-1R inhibitors, MEK inhibitors, PI3K inhibitors, AKT inhibitors, TOR inhibitors, MCL-1 inhibitors, BCL-2 inhibitors, SHP2 inhibitors, proteasome inhibitors, and immune modulatory therapies, such as an immune checkpoint inhibitor. In some embodiments, a therapeutic agent may be a pan-RTK inhibitor, such as afatinib.

In some embodiments, the additional therapeutic agent is selected from the group consisting of a MEK inhibitor, a HER2 inhibitor, a SHP2 inhibitor, a CDK4/6 inhibitor, an mTOR inhibitor, a SOS1 inhibitor, and a PD-L1 inhibitor. In some embodiments, the additional therapeutic agent is selected from

the group consisting of a MEK inhibitor, a SHP2 inhibitor, and a PD-L1 inhibitor. See, e.g., Hallin et al., Cancer Discovery, DOI: 10.1158/2159-8290 (October 28, 2019) and Canon et al., Nature, 575:217 (2019). In some embodiments, a RAS(ON) inhibitor of the present disclosure is used in combination with a MEK inhibitor and a SOS1 inhibitor. In some embodiments, a RAS(ON) inhibitor of the present disclosure is used in combination with a PD-L1 inhibitor and a SOS1 inhibitor. In some embodiments, a RAS(ON) inhibitor of the present disclosure is used in combination with a PD-L1 inhibitor and a SHP2 inhibitor. In some embodiments, a RAS(ON) inhibitor of the present disclosure is used in combination with a MEK inhibitor and a SHP2 inhibitor. In some embodiments, the cancer is colorectal cancer, and the treatment comprises administration of a Ras inhibitor of the present disclosure in combination with a second or third therapeutic agent.

Proteasome inhibitors include, but are not limited to, carfilzomib (Kyprolis®), bortezomib (Velcade®), and oprozomib.

Immune therapies include, but are not limited to, monoclonal antibodies, immunomodulatory imides (IMiDs), GITR agonists, genetically engineered T-cells (e.g., CAR-T cells), bispecific antibodies (e.g., BiTEs), and anti-PD-1, anti-PD-L1, anti-CTLA4, anti-LAGI, and anti-OX40 agents).

Immunomodulatory agents (IMiDs) are a class of immunomodulatory drugs (drugs that adjust immune responses) containing an imide group. The IMiD class includes thalidomide and its analogues (lenalidomide, pomalidomide, and apremilast).

Exemplary anti-PD-1 antibodies and methods for their use are described by Goldberg et al., Blood 2007, 110(1):186-192; Thompson et al., Clin. Cancer Res. 2007, 13(6):1757-1761; and WO 2006121168), as well as described elsewhere herein.

GITR agonists include, but are not limited to, GITR fusion proteins and anti-GITR antibodies (e.g., bivalent anti-GITR antibodies), such as, a GITR fusion protein described in U.S. Pat. No. 6,111,090, U.S. Pat. No. 8,586,023, WO 2010003118 and WO 2011090754; or an anti-GITR antibody described, e.g., in U.S. Pat. No. 7,025,962, EP 1947183, U.S. Pat. No. 7,812,135, U.S. Pat. No. 8,388,967, U.S. Pat. No. 8,591,886, U.S. Pat. No. 7,618,632, EP 1866339, and WO 2011028683, WO 2013039954, WO 2005007190, WO 2007133822, WO 2005055808, WO 199940196, WO 200103720, WO 199920758, WO 2006083289, WO 2005115451, and WO 2011051726.

Another example of a therapeutic agent that may be used in combination with a compound of the present invention is an anti-angiogenic agent. Anti-angiogenic agents are inclusive of, but not limited to, in vitro synthetically prepared chemical compositions, antibodies, antigen binding regions, radionuclides, and combinations and conjugates thereof. An anti-angiogenic agent can be an agonist, antagonist, allosteric modulator, toxin or, more generally, may act to inhibit or stimulate its target (e.g., receptor or enzyme activation or inhibition), and thereby promote cell death or arrest cell growth. In some embodiments, the one or more additional therapies include an anti-angiogenic agent.

Anti-angiogenic agents can be MMP-2 (matrix-metalloproteinase 2) inhibitors, MMP-9 (matrix-metalloproteinase 9) inhibitors, and COX-II (cyclooxygenase 11) inhibitors. Non-limiting examples of anti-angiogenic agents include rapamycin, temsirolimus (CCI-779), everolimus (RAD001), sorafenib, sunitinib, and bevacizumab. Examples of useful COX-II inhibitors include alecoxib, valdecoxib, and rofecoxib. Examples of useful matrix metalloproteinase inhibitors are described in WO 199633172, WO 199627583,

WO 199807697, WO 199803516, WO 199834918, WO 199834915, WO 199833768, WO 199830566, WO 199005719, WO 199952910, WO 199952889, WO 199929667, WO 1999007675, EP 0606046, EP 0780386, EP 1786785, EP 1181017, EP 0818442, EP 1004578, and US 20090012085, and U.S. Patent Nos. 5,863,949 and 5,861,510. Preferred MMP-2 and MMP-9 inhibitors are those that have little or no activity inhibiting MMP-1. More preferred, are those that selectively inhibit MMP-2 or AMP-9 relative to the other matrix- metalloproteinases (i.e., MAP-1, MMP-3, MMP-4, MMP-5, MMP-6, MMP- 7, MMP- 8, MMP-10, MMP-11, MMP-12, and MMP-13). Some specific examples of MMP inhibitors are AG-3340, RO 32-3555, and RS 13-0830.

Further exemplary anti-angiogenic agents include KDR (kinase domain receptor) inhibitory agents (e.g., antibodies and antigen binding regions that specifically bind to the kinase domain receptor), EGFR inhibitory agents (e.g., antibodies or antigen binding regions that specifically bind thereto) such as Vectibix® (panitumumab), erlotinib (Tarceva®), anti-Angl and anti-Ang2 agents (e.g., antibodies or antigen binding regions specifically binding thereto or to their receptors, e.g., Tie2/Tek), and anti-Tie2 kinase inhibitory agents (e.g., antibodies or antigen binding regions that specifically bind thereto). Other anti-angiogenic agents include Campath, IL-8, B-FGF, Tek antagonists (US 20030162712; US 6,413,932), anti-TWEAK agents (e.g., specifically binding antibodies or antigen binding regions, or soluble TWEAK receptor antagonists; see US 6,727,225), ADAM distintegrin domain to antagonize the binding of integrin to its ligands (US 20020042368), specifically binding anti-eph receptor or anti-ephrin antibodies or antigen binding regions (U.S. Patent Nos. 5,981,245; 5,728,813; 5,969,110; 6,596,852; 6,232,447; 6,057,124 and patent family members thereof), and anti-PDGF-BB antagonists (e.g., specifically binding antibodies or antigen binding regions) as well as antibodies or antigen binding regions specifically binding to PDGF-BB ligands, and PDGFR kinase inhibitory agents (e.g., antibodies or antigen binding regions that specifically bind thereto). Additional anti-angiogenic agents include: SD-7784 (Pfizer, USA); cilengitide (Merck KGaA, Germany, EPO 0770622); pegaptanib octasodium, (Gilead Sciences, USA); Alphastatin, (BioActa, UK); M-PGA, (Celgene, USA, US 5712291); ilomastat, (Arriva, USA, US5892112); emaxanib, (Pfizer, USA, US 5792783); vatalanib, (Novartis, Switzerland); 2-methoxyestradiol (EntreMed, USA); TLC ELL-12 (Elan, Ireland); anecortave acetate (Alcon, USA); alpha-D148 Mab (Amgen, USA); CEP-7055 (Cephalon, USA); anti-Vn Mab (Crucell, Netherlands), DACantiangiogenic (ConjuChem, Canada); Angiocidin (InKine Pharmaceutical, USA); KM-2550 (Kyowa Hakko, Japan); SU-0879 (Pfizer, USA); CGP-79787 (Novartis, Switzerland, EP 0970070); ARGENT technology (Ariad, USA); YIGSR-Stealth (Johnson & Johnson, USA); fibrinogen-E fragment (BioActa, UK); angiogenic inhibitor (Trigen, UK); TBC-1635 (Encysive Pharmaceuticals, USA); SC-236 (Pfizer, USA); ABT-567 (Abbott, USA); Metastatin (EntreMed, USA); maspin (Sosei, Japan); 2-methoxyestradiol (Oncology Sciences Corporation, USA); ER-68203-00 (IV AX, USA); BeneFin (Lane Labs, USA); Tz-93 (Tsumura, Japan); TAN-1120 (Takeda, Japan); FR-111142 (Fujisawa, Japan, JP 02233610); platelet factor 4 (RepliGen, USA, EP 407122); vascular endothelial growth factor antagonist (Borean, Denmark); bevacizumab (pINN) (Genentech, USA); angiogenic inhibitors (SUGEN, USA); XL 784 (Exelixis, USA); XL 647 (Exelixis, USA); MAb, alpha5beta3 integrin, second generation (Applied Molecular Evolution, USA and MedImmune, USA); enzastaurin hydrochloride (Lilly, USA); CEP 7055 (Cephalon, USA and Sanofi-Synthelabo, France); BC 1 (Genoa Institute of Cancer Research, Italy); rBPI 21 and BPI-derived

antiangiogenic (XOMA, USA); PI 88 (Progen, Australia); cilengitide (Merck KGaA, German; Munich Technical University, Germany, Scripps Clinic and Research Foundation, USA); AVE 8062 (Ajinomoto, Japan); AS 1404 (Cancer Research Laboratory, New Zealand); SG 292, (Telios, USA); Endostatin (Boston Childrens Hospital, USA); ATN 161 (Attenuon, USA); 2-methoxyestradiol (Boston Childrens Hospital, USA); ZD 6474, (AstraZeneca, UK); ZD 6126, (Angiogene Pharmaceuticals, UK); PPI 2458, (Praecis, USA); AZD 9935, (AstraZeneca, UK); AZD 2171, (AstraZeneca, UK); vatalanib (pINN), (Novartis, Switzerland and Schering AG, Germany); tissue factor pathway inhibitors, (EntreMed, USA); pegaptanib (Pinn), (Gilead Sciences, USA); xanthorrhizol, (Yonsei University, South Korea); vaccine, gene-based, VEGF-2, (Scripps Clinic and Research Foundation, USA); SPV5.2, (Supratek, Canada); SDX 103, (University of California at San Diego, USA); PX 478, (ProlX, USA); METASTATIN, (EntreMed, USA); troponin I, (Harvard University, USA); SU 6668, (SUGEN, USA); OXI 4503, (OXiGENE, USA); o-guanidines, (Dimensional Pharmaceuticals, USA); motuporamine C, (British Columbia University, Canada); CDP 791, (Celltech Group, UK); atiprimod (pINN), (GlaxoSmithKline, UK); E 7820, (Eisai, Japan); CYC 381, (Harvard University, USA); AE 941, (Aeterna, Canada); vaccine, angiogenic, (EntreMed, USA); urokinase plasminogen activator inhibitor, (Dendreon, USA); oglufanide (pINN), (Melmotte, USA); HIF-lalfa inhibitors, (Xenova, UK); CEP 5214, (Cephalon, USA); BAY RES 2622, (Bayer, Germany); Angiocidin, (InKine, USA); A6, (Angstrom, USA); KR 31372, (Korea Research Institute of Chemical Technology, South Korea); GW 2286, (GlaxoSmithKline, UK); EHT 0101, (ExonHit, France); CP 868596, (Pfizer, USA); CP 564959, (OSI, USA); CP 547632, (Pfizer, USA); 786034, (GlaxoSmithKline, UK); KRN 633, (Kirin Brewery, Japan); drug delivery system, intraocular, 2-methoxyestradiol; anginex (Maastricht University, Netherlands, and Minnesota University, USA); ABT 510 (Abbott, USA); AAL 993 (Novartis, Switzerland); VEGI (ProteomTech, USA); tumor necrosis factor-alpha inhibitors; SU 11248 (Pfizer, USA and SUGEN USA); ABT 518, (Abbott, USA); YH16 (Yantai Rongchang, China); S-3APG (Boston Childrens Hospital, USA and EntreMed, USA); MAb, KDR (ImClone Systems, USA); MAb, alpha5 beta (Protein Design, USA); KDR kinase inhibitor (Celltech Group, UK, and Johnson & Johnson, USA); GFB 116 (South Florida University, USA and Yale University, USA); CS 706 (Sankyo, Japan); combretastatin A4 prodrug (Arizona State University, USA); chondroitinase AC (IBEX, Canada); BAY RES 2690 (Bayer, Germany); AGM 1470 (Harvard University, USA, Takeda, Japan, and TAP, USA); AG 13925 (Agouron, USA); Tetrathiomolybdate (University of Michigan, USA); GCS 100 (Wayne State University, USA) CV 247 (Ivy Medical, UK); CKD 732 (Chong Kun Dang, South Korea); irsogladine, (Nippon Shinyaku, Japan); RG 13577 (Aventis, France); WX 360 (Wilex, Germany); squalamine, (Genaera, USA); RPI 4610 (Sirna, USA); heparanase inhibitors (InSight, Israel); KL 3106 (Kolon, South Korea); Honokiol (Emory University, USA); ZK CDK (Schering AG, Germany); ZK Angio (Schering AG, Germany); ZK 229561 (Novartis, Switzerland, and Schering AG, Germany); XMP 300 (XOMA, USA); VGA 1102 (Taisho, Japan); VE-cadherin-2 antagonists(ImClone Systems, USA); Vasostatin (National Institutes of Health, USA); Flk-1 (ImClone Systems, USA); TZ 93 (Tsumura, Japan); TumStatin (Beth Israel Hospital, USA); truncated soluble FLT 1 (vascular endothelial growth factor receptor 1) (Merck & Co, USA); Tie-2 ligands (Regeneron, USA); and thrombospondin 1 inhibitor (Allegheny Health, Education and Research Foundation, USA).

Further examples of therapeutic agents that may be used in combination with a compound of the present invention include agents (e.g., antibodies, antigen binding regions, or soluble receptors) that specifically bind and inhibit the activity of growth factors, such as antagonists of hepatocyte growth factor (HGF, also known as Scatter Factor), and antibodies or antigen binding regions that specifically bind its receptor, c-Met.

Another example of a therapeutic agent that may be used in combination with a compound of the present invention is an anti-neoplastic agent. In some embodiments, the one or more additional therapies include an anti-neoplastic agent. Non-limiting examples of anti-neoplastic agents include acemannan, aclarubicin, aldesleukin, alemtuzumab, alitretinoin, altretamine, amifostine, aminolevulinic acid, amrubicin, amsacrine, anagrelide, anastrozole, ancer, ancestim, arglabin, arsenic trioxide, BAM-002 (Novelos), bexarotene, bicalutamide, broxuridine, capecitabine, celmoleukin, cetrorelix, cladribine, clotrimazole, cytarabine ocfosfate, DA 3030 (Dong-A), daclizumab, denileukin diftitox, deslorelin, dexrazoxane, dilazep, docetaxel, docosanol, doxercalciferol, doxifluridine, doxorubicin, bromocriptine, carmustine, cytarabine, fluorouracil, HIT diclofenac, interferon alfa, daunorubicin, doxorubicin, tretinoin, edelfosine, edrecolomab, eflornithine, emitefur, epirubicin, epoetin beta, etoposide phosphate, exemestane, exisulind, fadrozole, filgrastim, finasteride, fludarabine phosphate, formestane, fotemustine, gallium nitrate, gemcitabine, gemtuzumab zogamicin, gimeracil/oteracil/tegafur combination, glycopine, goserelin, heptaplatin, human chorionic gonadotropin, human fetal alpha fetoprotein, ibandronic acid, idarubicin, (imiquimod, interferon alfa, interferon alfa, natural, interferon alfa-2, interferon alfa-2a, interferon alfa-2b, interferon alfa-Nl, interferon alfa-n3, interferon alfacon-1, interferon alpha, natural, interferon beta, interferon beta-la, interferon beta-lb, interferon gamma, natural interferon gamma- la, interferon gamma-lb, interleukin-1 beta, iobenguane, irinotecan, irsogladine, lanreotide, LC 9018 (Yakult), leflunomide, lenograstim, lentinan sulfate, letrozole, leukocyte alpha interferon, leuprorelin, levamisole + fluorouracil, liarozole, lobaplatin, lonidamine, lovastatin, masoprocol, melarsoprol, metoclopramide, mifepristone, miltefosine, mirimostim, mismatched double stranded RNA, mitoguazone, mitolactol, mitoxantrone, molgramostim, nafarelin, naloxone + pentazocine, nartograstim, nedaplatin, nilutamide, noscapine, novel erythropoiesis stimulating protein, NSC 631570 octreotide, oprelvekin, osaterone, oxaliplatin, paclitaxel, pamidronic acid, pegaspargase, peginterferon alfa-2b, pentosan polysulfate sodium, pentostatin, picibanil, pirarubicin, rabbit antithymocyte polyclonal antibody, polyethylene glycol interferon alfa-2a, porfimer sodium, raloxifene, raltitrexed, rasburiembodiment, rhenium Re 186 etidronate, RII retinamide, rituximab, romurtide, samarium (153 Sm) lexidronam, sargramostim, sizofiran, sobuzoxane, sonermin, strontium-89 chloride, suramin, tasonermin, tazarotene, tegafur, temoporfin, temozolomide, teniposide, tetrachlorodecaoxide, thalidomide, thymalfasin, thyrotropin alfa, topotecan, toremifene, tositumomab-iodine 131, trastuzumab, treosulfan, tretinoin, trilostane, trimetrexate, triptorelin, tumor necrosis factor alpha, natural, ubenimex, bladder cancer vaccine, Maruyama vaccine, melanoma lysate vaccine, valrubicin, verteporfin, vinorelbine, virulizin, zinostatin stimalamer, or zoledronic acid; abarelix; AE 941 (Aeterna), ambamustine, antisense oligonucleotide, bcl-2 (Genta), APC 8015 (Dendreon), decitabine, dexaminoglutethimide, diaziquone, EL 532 (Elan), EM 800 (Endorecherche), eniluracil, etanidazole, fenretinide, filgrastim SD01 (Amgen), fulvestrant, galocitabine, gastrin 17 immunogen, HLA-B7 gene therapy (Vical), granulocyte macrophage colony stimulating factor, histamine dihydrochloride,

ibritumomab tiuxetan, ilomastat, IM 862 (Cytran), interleukin-2, iproxifene, LDI 200 (Milkhaus), leridistim, lintuzumab, CA 125 MAb (Biomira), cancer MAb (Japan Pharmaceutical Development), HER-2 and Fc MAb (Medarex), idiotypic 105AD7 MAb (CRC Technology), idiotypic CEA MAb (Trilex), LYM-1-iodine 131 MAb (Techni clone), polymorphic epithelial mucin-yttrium 90 MAb (Antisoma), marimastat, menogaril, mitumomab, motexafin gadolinium, MX 6 (Galderma), nelarabine, nolatrexed, P 30 protein, pegvisomant, pemetrexed, porfiromycin, prinomastat, RL 0903 (Shire), rubitecan, satraplatin, sodium phenylacetate, sparfosic acid, SRL 172 (SR Pharma), SU 5416 (SUGEN), TA 077 (Tanabe), tetrathiomolybdate, thaliblastine, thrombopoietin, tin ethyl etiopurpurin, tirapazamine, cancer vaccine (Biomira), melanoma vaccine (New York University), melanoma vaccine (Sloan Kettering Institute), melanoma oncolysate vaccine (New York Medical College), viral melanoma cell lysates vaccine (Royal Newcastle Hospital), or valspodar.

Additional examples of therapeutic agents that may be used in combination with a compound of the present invention include ipilimumab (Yervoy®); tremelimumab; galiximab; nivolumab, also known as BMS-936558 (Opdivo®); pembrolizumab (Keytruda®); avelumab (Bavencio®); AMP224; BMS-936559; MPDL3280A, also known as RG7446; MEDI-570; AMG557; MGA271; IMP321; BMS-663513; PF-05082566; CDX-1127; anti-OX40 (Providence Health Services); huMAbOX40L; atacicept; CP-870893; lucatumumab; dacetuzumab; muromonab-CD3; ipilumumab; MEDI4736 (Imfinzi®); MSB0010718C; AMP 224; adalimumab (Humira®); ado-trastuzumab emtansine (Kadcyla®); aflibercept (Eylea®); alemtuzumab (Campath®); basiliximab (Simulect®); belimumab (Benlysta®); basiliximab (Simulect®); belimumab (Benlysta®); brentuximab vedotin (Adcetris®); canakinumab (Ilaris®); certolizumab pegol (Cimzia®); daclizumab (Zenapax®); daratumumab (Darzalex®); denosumab (Prolia®); eculizumab (Soliris®); efalizumab (Raptiva®); gemtuzumab ozogamicin (Mylotarg®); golimumab (Simponi®); ibritumomab tiuxetan (Zevalin®); infliximab (Remicade®); motavizumab (Numax®); natalizumab (Tysabri®); obinutuzumab (Gazyva®); ofatumumab (Arzerra®); omalizumab (Xolair®); palivizumab (Synagis®); pertuzumab (Perjeta®); pertuzumab (Perjeta®); ranibizumab (Lucentis®); raxibacumab (Abthrax®); tocilizumab (Actemra®); tositumomab; tositumomab-i-131; tositumomab and tositumomab-i-131 (Bexxar®); ustekinumab (Stelara®); AMG 102; AMG 386; AMG 479; AMG 655; AMG 706; AMG 745; and AMG 951.

The compounds described herein can be used in combination with the agents disclosed herein or other suitable agents, depending on the condition being treated. Hence, in some embodiments the one or more compounds of the disclosure will be co-administered with other therapies as described herein. When used in combination therapy, the compounds described herein may be administered with the second agent simultaneously or separately. This administration in combination can include simultaneous administration of the two agents in the same dosage form, simultaneous administration in separate dosage forms, and separate administration. That is, a compound described herein and any of the agents described herein can be formulated together in the same dosage form and administered simultaneously. Alternatively, a compound of the invention and any of the therapies described herein can be simultaneously administered, wherein both the agents are present in separate formulations. In another alternative, a compound of the present disclosure can be administered and followed by any of the therapies described herein, or vice versa. In some embodiments of the separate administration protocol,

a compound of the invention and any of the therapies described herein are administered a few minutes apart, or a few hours apart, or a few days apart.

In some embodiments of any of the methods described herein, the first therapy (e.g., a compound of the invention) and one or more additional therapies are administered simultaneously or sequentially, in either order. The first therapeutic agent may be administered immediately, up to 1 hour, up to 2 hours, up to 3 hours, up to 4 hours, up to 5 hours, up to 6 hours, up to 7 hours, up to, 8 hours, up to 9 hours, up to 10 hours, up to 11 hours, up to 12 hours, up to 13 hours, 14 hours, up to hours 16, up to 17 hours, up 18 hours, up to 19 hours up to 20 hours, up to 21 hours, up to 22 hours, up to 23 hours, up to 24 hours, or up to 1-7, 1-14, 1-21 or 1-30 days before or after the one or more additional therapies.

The invention also features kits including (a) a pharmaceutical composition including an agent (e.g., a compound of the invention) described herein, and (b) a package insert with instructions to perform any of the methods described herein. In some embodiments, the kit includes (a) a pharmaceutical composition including an agent (e.g., a compound of the invention) described herein, (b) one or more additional therapies (e.g., non-drug treatment or therapeutic agent), and (c) a package insert with instructions to perform any of the methods described herein.

As one aspect of the present invention contemplates the treatment of the disease or symptoms associated therewith with a combination of pharmaceutically active compounds that may be administered separately, the invention further relates to combining separate pharmaceutical compositions in kit form. The kit may comprise two separate pharmaceutical compositions: a compound of the present invention, and one or more additional therapies. The kit may comprise a container for containing the separate compositions such as a divided bottle or a divided foil packet. Additional examples of containers include syringes, boxes, and bags. In some embodiments, the kit may comprise directions for the use of the separate components. The kit form is particularly advantageous when the separate components are preferably administered in different dosage forms (e.g., oral and parenteral), are administered at different dosage intervals, or when titration of the individual components of the combination is desired by the prescribing health care professional.

Examples

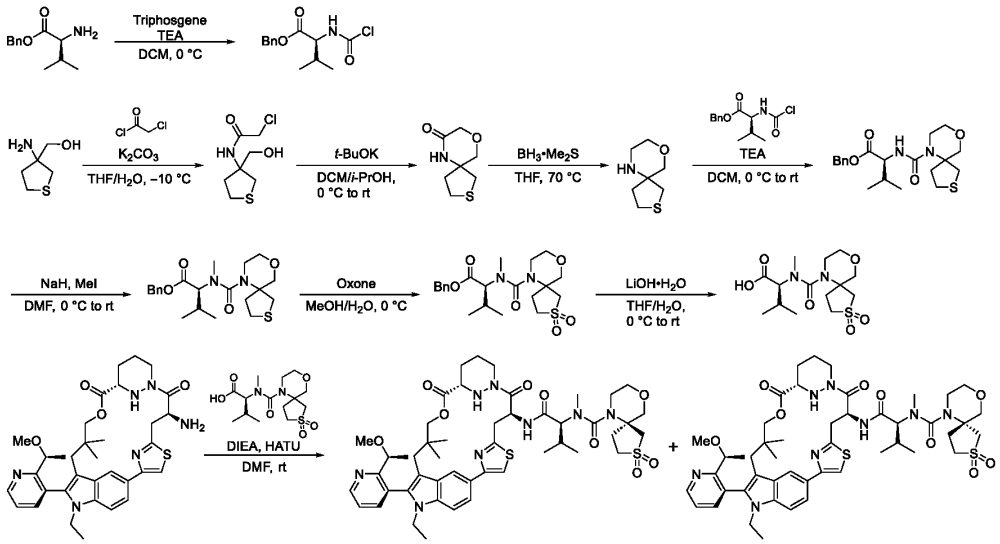
The disclosure is further illustrated by the following examples and synthesis examples, which are not to be construed as limiting this disclosure in scope or spirit to the specific procedures herein described. It is to be understood that the examples are provided to illustrate certain embodiments and that no limitation to the scope of the disclosure is intended thereby. It is to be further understood that resort may be had to various other embodiments, modifications, and equivalents thereof which may suggest themselves to those skilled in the art without departing from the spirit of the present disclosure or scope of the appended claims.

Instrumentation

Mass spectrometry data collection took place with a Shimadzu LCMS-2020, an Agilent 1260LC-6120/6125MSD, a Shimadzu LCMS-2010EV, or a Waters Acquity UPLC, with either a QDa detector or SQ Detector 2. Samples were injected in their liquid phase onto a C-18 reverse phase. The compounds

were eluted from the column using an acetonitrile gradient and fed into the mass analyzer. Initial data analysis took place with either Agilent ChemStation, Shimadzu LabSolutions, or Waters MassLynx. NMR data was collected with either a Bruker AVANCE III HD 400MHz, a Bruker Ascend 500MHz instrument, or a Varian 400MHz, and the raw data was analyzed with either TopSpin or Mestrelab Mnova E.

Examples A803 and A804: Synthesis of (5*S*)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^1-ethyl-1^2-(2-((*S*)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-9-oxa-2-thia-6-azaspiro[4.5]decane-6-carboxamide 2,2-dioxide and (5*R*)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^1-ethyl-1^2-(2-((*S*)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-9-oxa-2-thia-6-azaspiro[4.5]decane-6-carboxamide 2,2-dioxide



Step 1. To a stirred solution of triphosgene (4.29 g, 14.5 mmol) in DCM (180 mL), a solution of benzyl (2*S*)-2-amino-3-methylbutanoate (6.00 g, 28.9 mmol) and triethylamine (16.1 mL, 116 mmol) in DCM (180 mL) was added dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 2 h. The reaction mixture was then quenched with cold H_2O at 0 °C and the DCM extract was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to afford benzyl (2*S*)-2-((chlorocarbonyl)amino)-3-methylbutanoate (7.71 g, 99% yield) as a clear oil. The material was shown to be pure by ^{1}H NMR analysis and was used in the next reaction without further purification. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 7.45 – 7.32 (m, 5H), 5.28 (d, *J* = 12.2 Hz, 1H), 5.20 (d, *J* = 12.2 Hz, 1H), 4.37 (s, 2H), 2.30 – 2.05 (m, 1H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.75 (d, *J* = 6.7 Hz, 3H).

Step 2. To a solution of (3-aminothiolan-3-yl)methanol (980 mg, 7.36 mmol) in THF (15 mL) stirred at –10 °C was added a solution of potassium carbonate (3.05 g, 22.1 mmol) in H_2O (15 mL). The resulting mixture was stirred for 5 minutes at –10 °C, after which time chloroacetyl chloride (957 µL, 11.8 mmol) was added dropwise. The reaction mixture was stirred for 2 h at –10 °C, and was then quenched with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced

pressure to afford 2-chloro-*N*-(3-(hydroxymethyl)thiolan-3-yl)acetamide (1.46 g, crude). This material was used in the next step without further purification.

Step 3. To a stirred solution of 2-chloro-*N*-(3-(hydroxymethyl)thiolan-3-yl)acetamide (1.46 g, crude) in anhydrous DCM (22 mL) was added dropwise a solution of *t*-BuOK (3.13 g, 27.9 mmol) in anhydrous *i*-PrOH (22 mL) at 0 °C under an atmosphere of argon. The resulting mixture was stirred for 2 h at room temperature. The reaction mixture was then neutralized to pH 7 by the addition of 1.0 M aq. HCl and concentrated under reduced pressure. The resulting crude material was diluted in EtOAc and washed with H_2O. The aqueous solution was further extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford 9-oxa-2-thia-6-azaspiro[4.5]decan-7-one (1.08 g, crude). This material was used in the next step without further purification.

Step 4. To a stirred solution of 9-oxa-2-thia-6-azaspiro[4.5]decan-7-one (1.06 g, crude) in anhydrous THF (31.8 mL) was added a solution of BH_3•Me_2S (2.0 M in THF, 929 µL, 12.2 mmol) dropwise under an atmosphere of argon. The resulting mixture was stirred overnight under reflux and was then cooled to 0 °C, treated with an aqueous solution of HCl (3.0 M, 101 mL, 306 mmol), and stirred under reflux for 2 h. The reaction mixture was concentrated under reduced pressure, diluted in a mixture of DCM:MeOH (v/v, 95/5) and filtered. The filtrate was dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford 9-oxa-2-thia-6-azaspiro[4.5]decane (624 mg, 53% yield over 3 steps). LCMS (ESI) *m/z*: [M + H] calcd for $C_7H_{13}NOS$: 160.1; found 160.6.

Step 5. To a stirred solution of 9-oxa-2-thia-6-azaspiro[4.5]decane (574 mg, 3.60 mmol) and triethylamine (1.46 mL, 14.4 mmol) in DCM (17 mL) was added a solution of benzyl (2*S*)-2-((chlorocarbonyl)amino)-3-methylbutanoate (1.34 g, 3.96 mmol) in DCM (5.0 mL) at 0 °C. The resulting mixture was stirred for 16 hours at room temperature. The reaction mixture was then quenched with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford benzyl (2*S*)-3-methyl-2-((9-oxa-2-thia-6-azaspiro[4.5]decane-6-carbonyl)amino)butanoate (1.64 g, 57% yield). ^{1}H NMR (300 MHz, CD_3OD) δ 7.46 – 7.25 (m, 5H), 5.29 – 5.03 (m, 2H), 4.28 – 4.04 (m, 1H), 3.89 – 3.60 (m, 2H), 3.59 – 3.33 (m, 2H), 3.29 – 2.77 (m, 3H), 2.77 – 2.35 (m, 2H), 2.33 – 1.93 (m, 2H), 1.92 – 1.57 (m, 1H), 1.44 – 1.02 (m, 1H), 0.99 – 0.81 (m, 6H).

Step 6. To a stirred solution of benzyl (2*S*)-3-methyl-2-((9-oxa-2-thia-6-azaspiro[4.5]decane-6-carbonyl)amino)butanoate (1.60 g, 4.08 mmol) in DMF (23 mL) was added iodomethane (434 µL, 6.97 mmol) was added at room temperature. The mixture was cooled to 0 °C and sodium hydride (60% dispersion in mineral oil, 159 mg, 3.98 mmol) was added. The resulting mixture was stirred at 0 °C for 10 minutes and was then stirred at room temperature for 1 hour. The reaction mixture was quenched by the addition of H_2O, extracted with Et_2O, washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford benzyl (2*S*)-3-methyl-2-(methyl((9-oxa-2-thia-6-azaspiro[4.5]decane-6-carbonyl))amino)butanoate (1.26 g, 76% yield). ^{1}H NMR (300 MHz, CD_3OD) δ 7.42 – 7.25 (m, 5H), 5.30 – 5.00 (m, 2H), 4.25 – 4.01 (m, 1H), 3.82 – 3.41 (m, 3H), 3.24 – 2.75 (m, 7H), 2.72 – 2.53 (m, 1H), 2.37 – 2.06 (m, 2H), 2.05 – 1.66 (m, 2H), 1.37 – 1.18 (m, 1H), 1.04 – 0.80 (m, 6H).

Step 7. To a stirred solution of benzyl (2*S*)-3-methyl-2-(methyl((9-oxa-2-thia-6-azaspiro[4.5]decane-6-carbonyl))amino)butanoate (250 mg, 0.61 mmol) in MeOH (7.5 mL) and H_2O (1.3 mL) was added Oxone (1.21 g, 7.99 mmol) at 0 °C under an atmosphere of argon. The resulting mixture was stirred at 0 °C for 3 h. The reaction mixture was then quenched with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford benzyl (2*S*)-2-((2,2-dioxo-9-oxa-2λ⁶-thia-6-azaspiro[4.5]decane-6-carbonyl)(methyl)amino)-3-methylbutanoate (330 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{21}H_{30}N_2O_6S$: 439.2; found 439.3.

Step 8. To a stirred solution of benzyl (2*S*)-2-((2,2-dioxo-9-oxa-2λ⁶-thia-6-azaspiro[4.5]decane-6-carbonyl)(methyl)amino)-3-methylbutanoate (330 mg, 0.75 mmol) in THF (10 mL) and H_2O (10 mL) was added LiOH•H_2O (88.0 mg, 2.10 mmol) at 0 °C. The resulting mixture was stirred for 16 h at room temperature and was then concentrated under reduced pressure. The crude residue was lyophilized to afford (2*S*)-2-((2,2-dioxo-9-oxa-2λ⁶-thia-6-azaspiro[4.5]decane-6-carbonyl)(methyl)amino)-3-methylbutanoate (lithium salt, 274 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{14}H_{24}N_2O_6S$: 349.1; found 349.3.

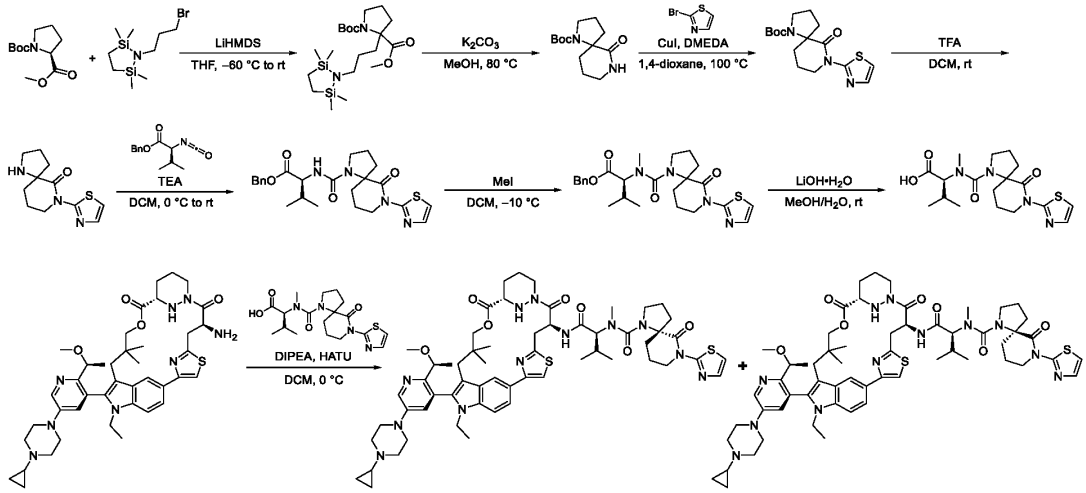
Step 9. To a stirred solution of (6^3*S*,4*S*)-4-amino-1^1-ethyl-1^2-(2-((*S*)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-5,7-dione (677 mg, 0.69 mmol), (2*S*)-2-((2,2-dioxo-9-oxa-2λ⁶-thia-6-azaspiro[4.5]decane-6-carbonyl)(methyl)amino)-3-methylbutanoate (lithium salt, 274 mg, crude) and DIEA (1.37 mL, 7.73 mmol) in DMF (8.2 mL) was added HATU (441 mg, 1.16 mmol). The resulting mixture was stirred at room temperature for 90 minutes. The reaction mixture was then quenched with H_2O, extracted with EtOAc (x3), dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by reversed-phase prep-HPLC to obtain two diastereomers of *N*-((2*S*)-1-(((6^3*S*,4*S*)-1^1-ethyl-1^2-(2-((*S*)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-9-oxa-2-thia-6-azaspiro[4.5]decane-6-carboxamide 2,2-dioxide.

A804: (68 mg, 9% yield); LCMS (ESI) *m/z*: [M + H] calcd for $C_{48}H_{64}N_8O_9S_2$: 961.4; found 961.9; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.75 (dd, *J* = 4.8, 1.8 Hz, 1H), 8.65 (d, *J* = 8.2 Hz, 1H), 8.51 – 8.45 (m, 1H), 7.87 (s, 1H), 7.79 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.74 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.58 (d, *J* = 8.7 Hz, 1H), 7.52 (dd, *J* = 7.7, 4.7 Hz, 1H), 5.44 (t, *J* = 8.3 Hz, 1H), 5.08 (d, *J* = 12.2 Hz, 1H), 4.39 – 4.07 (m, 6H), 3.85 – 3.78 (m, 1H), 3.74 (d, *J* = 13.3 Hz, 1H), 3.69 – 3.60 (m, 2H), 3.60 – 3.49 (m, 3H), 3.45 – 3.38 (m, 2H), 3.31 – 3.21 (m, 5H), 3.26 – 3.11 (m, 2H), 3.05 – 2.91 (m, 2H), 2.86 (s, 3H), 2.82 – 2.73 (m, 1H), 2.39 (d, *J* = 14.4 Hz, 1H), 2.22 – 2.13 (m, 1H), 2.13 – 2.02 (m, 2H), 1.92 – 1.74 (m, 3H), 1.59 – 1.44 (m, 1H), 1.36 (d, *J* = 6.1 Hz, 3H), 0.94 – 0.80 (m, 12H), 0.32 (s, 3H).

A803: (128 mg, 17% yield); LCMS (ESI) *m/z*: [M + H] calcd for $C_{48}H_{64}N_8O_9S_2$: 961.4; found 961.5; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.75 (dd, *J* = 4.8, 1.8 Hz, 1H), 8.51 – 8.42 (m, 2H), 7.86 (s, 1H), 7.79 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.74 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.58 (d, *J* = 8.7 Hz, 1H), 7.52 (dd, *J* = 7.7, 4.7 Hz, 1H), 5.50 (t, *J* = 8.7 Hz, 1H), 5.09 (d, *J* = 12.2 Hz, 1H), 4.44 – 4.00 (m, 6H), 3.80 (d, *J* = 10.5 Hz, 1H), 3.76 – 3.60 (m, 4H), 3.60 – 3.49 (m, 2H), 3.41 – 3.33 (m, 4H), 3.27 (s, 3H), 3.25

– 3.17 (m, 2H), 3.06 – 2.90 (m, 5H), 2.83 – 2.69 (m, 1H), 2.39 (d, *J* = 14.4 Hz, 1H), 2.13 – 1.98 (m, 3H), 1.88 – 1.64 (m, 3H), 1.58 – 1.45 (m, 1H), 1.36 (d, *J* = 6.1 Hz, 3H), 1.02 – 0.73 (m, 12H), 0.32 (s, 3H).

Examples A52 and A53: Synthesis of (5*S*)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-12-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-6-oxo-7-(thiazol-2-yl)-1,7-diazaspiro[4.5]decane-1-carboxamide and (5*R*)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-12-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-6-oxo-7-(thiazol-2-yl)-1,7-diazaspiro[4.5]decane-1-carboxamide.



Step 1. To a stirred solution of *N*-Boc-*L*-proline methyl ester (3.00 g, 13.1 mmol) in THF (60 mL), lithium bis(trimethylsilyl) amide (1.0 M in THF, 19.6 mL, 19.6 mmol) was added dropwise at –60 °C. The mixture was stirred at –60 °C for 20 minutes, after which time a solution of 1-(3-bromopropyl)-2,2,5,5-tetramethyl-1,2,5-azadisilolidine (5.76 g, 14.4 mmol) in THF (10 mL) was added dropwise. The resulting mixture was stirred at –60 °C for 2 h and was then stirred at room temperature for 16 h. The reaction mixture was quenched with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford 1-*tert*-butyl-2-methyl-2-(3-(2,2,5,5-tetramethyl-1,2,5-azadisilolidin-1-yl)propyl)pyrrolidine-1,2-dicarboxylate (6.30 g, crude). This material was used in the next reaction without further purification.

Step 2. To a stirred solution of 1-*tert*-butyl-2-methyl-2-(3-(2,2,5,5-tetramethyl-1,2,5-azadisilolidin-1-yl)propyl)pyrrolidine-1,2-dicarboxylate (6.30 g, crude) in MeOH (126 mL), potassium carbonate (3.04 g, 22.04 mmol) was added. The resulting mixture was stirred at 80 °C for 3 h. The reaction mixture was then concentrated under reduced pressure, suspended in H_2O (20 mL), extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and triturated with Et_2O (10 mL) to

afford *tert*-butyl 6-oxo-1,7-diazaspiro[4.5]decane-1-carboxylate (2.30 g, 69% yield over 2 steps). LCMS (ESI) *m/z*: [M + H] calcd for $C_{13}H_{22}N_2O_3$: 255.2; found 255.9.

Step 3. To a stirred solution of *tert*-butyl 6-oxo-1,7-diazaspiro[4.5]decane-1-carboxylate (200 mg, 0.786 mmol) in 1,4-dioxane (7.0 mL), copper(I) iodide (26.0 mg, 0.137 mmol), *N*,*N*'-dimethylethane-1,2-diamine (16.0 mg, 0.182 mmol) and 2-bromothiazole (140 mg, 0.854 mmol) were added. The mixture was sparged with argon gas, the reaction vial was sealed, and the resulting mixture was stirred at 100 °C for 16 h. The reaction mixture was then quenched with H_2O, extracted with DCM, washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford *tert*-butyl 6-oxo-7-(1,3-thiazol-2-yl)-1,7-diazaspiro[4.5]decane-1-carboxylate (70 mg, 26% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{16}H_{23}N_3O_3S$: 338.2; found 338.9.

Step 4. To a stirred solution of *tert*-butyl 6-oxo-7-(1,3-thiazol-2-yl)-1,7-diazaspiro[4.5]decane-1-carboxylate (170 mg, 0.504 mmol) in DCM (8.5 mL), trifluoroacetic acid (570 µL, 5.0 mmol) was slowly added at room temperature. The resulting mixture was stirred for 1 h at room temperature. The reaction mixture was then slowly basified to pH 7 with sat. aq. $NaHCO_3$, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford 7-(1,3-thiazol-2-yl)-1,7-diazaspiro[4.5]decan-6-one (110 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{11}H_{15}N_3OS$: 238.1; found 238.3.

Step 5. To a stirred solution of 7-(1,3-thiazol-2-yl)-1,7-diazaspiro[4.5]decan-6-one (110 mg, crude) and triethylamine (200 µL, 1.39 mmol) in anhydrous DCM (5.5 mL), a solution of benzyl (2*S*)-2-isocyanato-3-methylbutanoate (130 mg, 0.55 mmol) in DCM (1.0 mL) was added at 0 °C. The resulting mixture was warmed to room temperature and stirred was for 30 minutes. The reaction mixture was then quenched with a 10% aqueous solution of citric acid, extracted with DCM, washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford benzyl (2*S*)-3-methyl-2-((6-oxo-7-(1,3-thiazol-2-yl)-1,7-diazaspiro[4.5]decane-1-carbonyl)amino)butanoate (180 mg, 76% yield over 2 steps) as a mixture of two epimers. LCMS (ESI) *m/z*: [M – H] calcd for $C_{24}H_{30}N_4O_4S$: 469.2; found 469.7.

Step 6. To a stirred solution of benzyl (2*S*)-3-methyl-2-((6-oxo-7-(1,3-thiazol-2-yl)-1,7-diazaspiro[4.5]decane-1-carbonyl)amino)butanoate (180 mg, 0.382 mmol) in DMF (3.5 mL), methyl iodide (30 µL, 0.46 mmol) was added. The mixture was cooled to –10 °C, sodium hydride (60% dispersion in mineral oil, 11 mg, 0.46 mmol) was added, and the resulting mixture was stirred at –10 °C for 30 minutes. The reaction mixture was then poured into ice-cold H_2O, extracted with DCM, washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford benzyl (2*S*)-3-methyl-2-(methyl(6-oxo-7-(1,3-thiazol-2-yl)-1,7-diazaspiro[4.5]decane-1-carbonyl)amino)butanoate (130 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{25}H_{32}N_4O_4S$: 485.2; found 486.1.

Step 7. To a stirred solution of benzyl (2*S*)-3-methyl-2-(methyl(6-oxo-7-(1,3-thiazol-2-yl)-1,7-diazaspiro[4.5]decane-1-carbonyl)amino)butanoate (130 mg, crude) in THF (2.5 mL), MeOH (2.5 mL), and H_2O (1.4 mL), lithium hydroxide monohydrate (56.0 mg, 1.34 mmol) was added. The resulting mixture was stirred for 1 h at room temperature. The reaction mixture was then diluted with H_2O, acidified to pH 2 with an aqueous solution of HCl (1.0 M), extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and

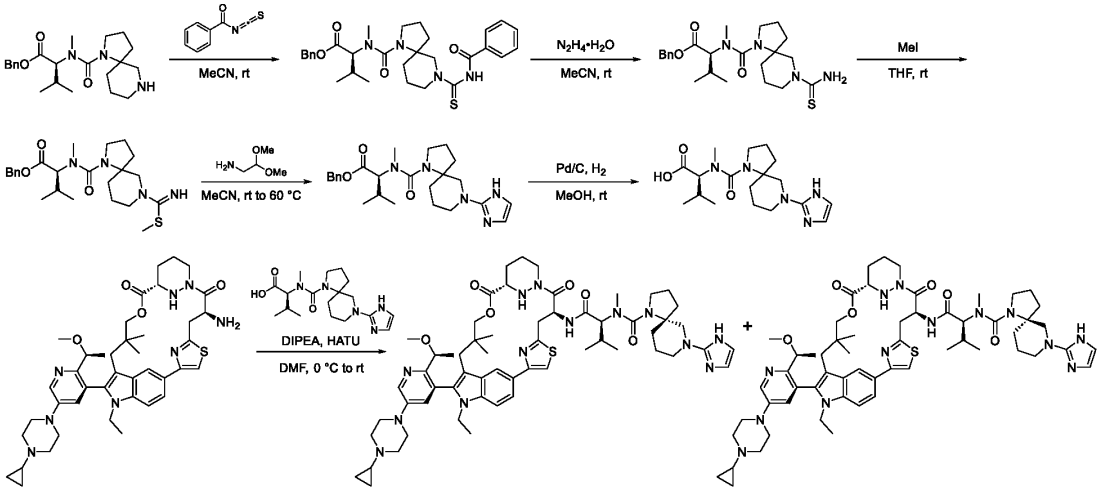
concentrated under reduced pressure to afford (2*S*)-3-methyl-2-(methyl(6-oxo-7-(1,3-thiazol-2-yl)-1,7-diazaspiro[4.5]decane-1-carbonyl)amino)butanoic acid (90 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{18}H_{26}N_4O_4S$: 395.2; found 396.0.

Step 8. To a stirred solution of (6^3S,4*S*)-4-amino-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-5,7-dione (100 mg, 0.132 mmol) in DMF (5.0 mL), DIPEA (110 µL, 0.631 mmol) and (2*S*)-3-methyl-2-(methyl(6-oxo-7-(1,3-thiazol-2-yl)-1,7-diazaspiro[4.5]decane-1-carbonyl)amino)butanoic acid (64 mg, crude) were added at 0 °C. The mixture was stirred for 5 minutes, after which time HATU (71 mg, 0.19 mmol) was added and the resulting mixture was stirred at 0 °C for 1 h. The reaction mixture was then quenched with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase prep-HPLC to afford two diastereomers of *N*-((2*S*)-1-((((6^3S,4*S*)-12-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-6-oxo-7-(thiazol-2-yl)-1,7-diazaspiro[4.5]decane-1-carboxamide.

A53: (13 mg, 9% yield); LCMS (ESI) *m/z*: [M + H] calcd for $C_{59}H_{78}N_{12}O_7S_2$: 1131.6; found 1131.6; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 – 8.31 (m, 3H), 7.81 (d, *J* = 12 Hz, 1H), 7.71 (d, *J* = 4 Hz, 1H), 7.54 (d, *J* = 8.7 Hz, 1H), 7.23 – 7.16 (m, 1H), 7.09 (d, *J* = 3.6 Hz, 1H), 6.70 – 6.68 (m, 1H), 5.51 – 5.39 (m, 1H), 5.08 (d, *J* = 12.1 Hz, 1H), 4.37 – 4.03 (m, 7H), 3.74 – 3.61 (m, 1H), 3.61 – 3.49 (m, 2H), 3.49 – 3.37 (m, 2H), 3.37 – 3.29 (m, 1H), 3.27 – 3.15 (m, 8H), 2.98 – 2.92 (m, 4H), 2.81 – 2.71 (m, 2H), 2.70 – 2.61 (m, 4H), 2.42 (d, *J* = 14.4 Hz, 1H), 2.15 – 1.95 (m, 3H), 1.95 – 1.73 (m, 5H), 1.72 – 1.57 (m, 3H), 1.55 – 1.40 (m, 2H), 1.32 (d, *J* = 6.1 Hz, 3H), 1.02 – 0.99 (m, 3H), 0.91 (s, 3H), 0.93 – 0.79 (m, 6H), 0.48 – 0.40 (m, 2H), 0.37 – 0.28 (m, 5H).

A52: (13 mg, 9% yield); LCMS (ESI) *m/z*: [M + H] calcd for $C_{59}H_{78}N_{12}O_7S_2$: 1131.6; found 1131.5; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 – 8.45 (m, 1H), 8.44 (d, *J* = 2.9 Hz, 1H), 8.17 (d, *J* = 8.9 Hz, 1H), 7.82 – 7.77 (m, 1H), 7.73 – 7.68 (m, 1H), 7.55 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.20 (d, *J* = 2.8 Hz, 1H), 7.10 (dd, *J* = 8.0, 4.0 Hz, 1H), 6.70 (dd, *J* = 8.0, 4.0 Hz, 1H), 5.58 – 5.46 (m, 1H), 5.16 – 5.03 (m, 1H), 4.34 – 4.02 (m, 7H), 3.74 – 3.60 (m, 1H), 3.61 – 3.48 (m, 2H), 3.48 – 3.37 (m, 2H), 3.36 – 3.28 (m, 1H), 3.27 – 3.12 (m, 8H), 2.97 – 2.93 (s, 4H), 2.82 – 2.68 (m, 2H), 2.73 – 2.62 (m, 4H), 2.43 (d, *J* = 14.6 Hz, 1H), 2.12 – 1.93 (m, 3H), 1.92 – 1.72 (m, 5H), 1.71 – 1.55 (m, 3H), 1.55 – 1.37 (m, 2H), 1.32 (d, *J* = 6.1 Hz, 3H), 0.96 (t, *J* = 6.7 Hz, 3H), 0.94 – 0.85 (m, 6H), 0.83 (dd, *J* = 15.0, 8.0 Hz, 3H), 0.47 – 0.40 (m, 2H), 0.38 – 0.28 (m, 5H).

Examples A45 and A46: Synthesis of (5*R*)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-7-(1*H*-imidazol-2-yl)-*N*-methyl-1,7-diazaspiro[4.5]decane-1-carboxamide and (5*S*)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-7-(1*H*-imidazol-2-yl)-*N*-methyl-1,7-diazaspiro[4.5]decane-1-carboxamide



Step 1. To a stirred solution of benzyl (2*S*)-2-((1,7-diazaspiro[4.5]decane-1-carbonyl)(methyl)amino)-3-methylbutanoate (1.23 g, 2.54 mmol) in anhydrous MeCN (19 mL), benzoyl isothiocyanate (497 mg, 3.05 mmol) was added at room temperature. The reaction mixture was stirred for 1 h at room temperature. The reaction mixture was then quenched with H_2O, extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford benzyl (2*S*)-3-methyl-2-(methyl((7-((phenylformamido)methanethioyl)-1,7-diazaspiro[4.5]decane-1-carbonyl))amino)butanoate (1.70 g, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{30}H_{38}N_4O_4S$: 551.3; found 551.3.

Step 2. To a stirred solution of benzyl (2*S*)-3-methyl-2-(methyl((7-((phenylformamido)methanethioyl)-1,7-diazaspiro[4.5]decane-1-carbonyl))amino)butanoate (1.70 g, crude) in anhydrous MeCN (34 mL), hydrazine hydrate (1.19 mL, 24.4 mmol) was added at room temperature. The resulting mixture was stirred for 16 h at room temperature. The reaction mixture was then concentrated under reduced pressure and purified by normal phase flash column chromatography to afford benzyl (2*S*)-2-((7-carbamothioyl-1,7-diazaspiro[4.5]decane-1-carbonyl)(methyl)amino)-3-methylbutanoate (73% purity, 796 mg, 47% yield over 2 steps). LCMS (ESI) *m/z*: [M + H] calcd for $C_{23}H_{34}N_4O_3S$: 447.2; found 448.1.

Step 3. To a stirred solution of benzyl (2*S*)-2-((7-carbamothioyl-1,7-diazaspiro[4.5]decane-1-carbonyl)(methyl)amino)-3-methylbutanoate (796 mg, 1.30 mmol) in anhydrous THF (16 mL), methyl iodide (243 µL, 3.90 mmol) was added at room temperature. The resulting mixture was stirred for 16 h at

room temperature. The reaction mixture was then concentrated under reduced pressure and purified by normal phase flash column chromatography to afford benzyl (2*S*)-3-methyl-2-(methyl((7-methylsulfanylcarboximidoyl-1,7-diazaspiro[4.5]decane-1-carbonyl))amino)butanoate (491 mg, 82% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{24}H_{36}N_4O_3S$: 461.3; found 461.5.

Step 4. To a stirred solution of benzyl (2*S*)-3-methyl-2-(methyl((7-methylsulfanylcarboximidoyl-1,7-diazaspiro[4.5]decane-1-carbonyl))amino)butanoate (410 mg, 0.89 mmol) in anhydrous MeCN (12 mL), aminoacetaldehyde dimethyl acetal (776 µL, 7.12 mmol) was added at room temperature. The resulting mixture was stirred at 60 °C for 16 h, after which time HCl (3.0 M in H_2O, 2.97 mL, 8.91 mmol) was added and the resulting mixture was stirred at 60 °C for 1.5 h. The reaction mixture was then quenched with sat. aq. $NaHCO_3$, extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford benzyl (2*S*)-2-((7-(1*H*-imidazol-2-yl)-1,7-diazaspiro[4.5]decane-1-carbonyl)(methyl)amino)-3-methylbutanoate (245 mg, 58% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{25}H_{35}N_5O_3$: 454.3; found 454.5.

Step 5. A solution of benzyl (2*S*)-2-((7-(1*H*-imidazol-2-yl)-1,7-diazaspiro[4.5]decane-1-carbonyl)(methyl)amino)-3-methylbutanoate (127 mg, 0.280 mmol) in MeOH (5.1 mL) was sparged with argon gas for 5 minutes. Pd/C (10% wt., 57 mg) was then added and the reaction flask was evacuated and backfilled three times with hydrogen gas. The resulting mixture was stirred at room temperature for 16 h under an atmosphere of hydrogen gas. The reaction mixture was then filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure to afford (2*S*)-2-((7-(1*H*-imidazol-2-yl)-1,7-diazaspiro[4.5]decane-1-carbonyl)(methyl)amino)-3-methyl-butanoic acid (83 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{18}H_{29}N_5O_3$: 364.2; found 364.4.

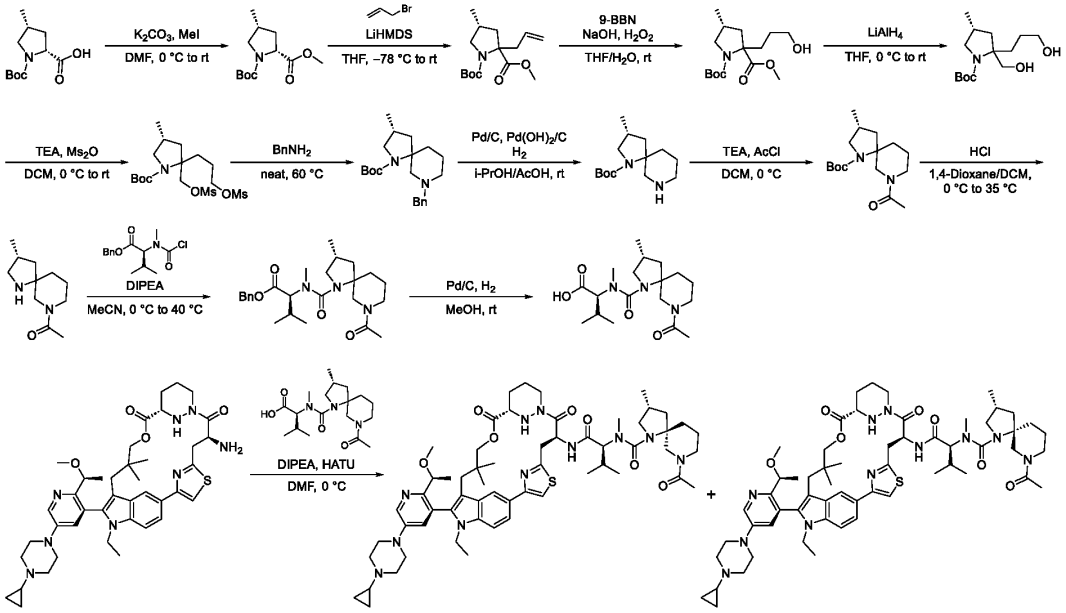
Step 6. To a stirred solution of (6^3S,4*S*)-4-amino-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-5,7-dione (100 mg, 0.132 mmol) and (2*S*)-2-((7-(1*H*-imidazol-2-yl)-1,7-diazaspiro[4.5]decane-1-carbonyl)(methyl)amino)-3-methyl-butanoic acid (61.0 mg, 0.168 mmol) in anhydrous DMF (3.0 mL), DIPEA (115 µL, 0.660 mmol) was added and the resulting solution was stirred at 0 °C for 5 minutes. Subsequently, HATU (65.0 mg, 0.171 mmol) was added and the resulting mixture was stirred at room temperature for 15 minutes. The reaction mixture was then quenched with H_2O, extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase prep-HPLC to afford two separated diastereomers of ((2*S*)-1-((((6^3S,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-7-(1*H*-imidazol-2-yl)-*N*-methyl-1,7-diazaspiro[4.5]decane-1-carboxamide.

A46: (11.5 mg, 8% yield); LCMS (ESI) *m/z*: [M + H] calcd for $C_{59}H_{81}N_{13}O_6S$: 1100.6; found 1100.6; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.77 (s, 1H), 8.54 (d, *J* = 8.7 Hz, 1H), 8.47 – 8.41 (m, 2H), 7.68 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.58 (s, 1H), 7.56 (d, *J* = 8.7 Hz, 1H), 7.21 (d, *J* = 2.9 Hz, 1H), 6.67 (t, *J* = 1.6 Hz, 1H), 6.48 (t, *J* = 1.5 Hz, 1H), 5.51 (t, *J* = 8.9 Hz, 1H), 5.10 (d, *J* = 12.2 Hz, 1H),

4.34 – 4.18 (m, 3H), 4.18 – 4.09 (m, 2H), 3.84 – 3.73 (m, 2H), 3.68 (d, *J* = 11.7 Hz, 1H), 3.60 – 3.49 (m, 4H), 3.46 – 3.37 (m, 1H), 3.37 – 3.33 (m, 1H), 3.24 – 3.19 (m, 7H), 3.17 – 3.06 (m, 1H), 2.93 (d, *J* = 14.3 Hz, 1H), 2.84 – 2.72 (m, 5H), 2.71 – 2.66 (m, 4H), 2.63 – 2.53 (m, 1H), 2.46 – 2.38 (m, 1H), 2.19 – 2.05 (m, 2H), 1.93 – 1.83 (m, 3H), 1.83 – 1.74 (m, 3H), 1.71 – 1.60 (m, 3H), 1.56 – 1.45 (m, 2H), 1.32 (d, *J* = 6.0 Hz, 3H), 0.92 – 0.86 (m, 12H), 0.48 – 0.40 (m, 2H), 0.38 – 0.28 (m, 5H).

A45: (16.8 mg, 11% yield); LCMS (ESI) *m/z*: [M + H] calcd for $C_{59}H_{81}N_{13}O_6S$: 1100.6; found 1100.6; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.73 (s, 1H), 8.48 – 8.46 (m, 1H), 8.45 – 8.40 (m, 2H), 7.81 (s, 1H), 7.74 (dd, *J* = 8.6, 1.4 Hz, 1H), 7.55 (d, *J* = 8.7 Hz, 1H), 7.20 (d, *J* = 2.9 Hz, 1H), 6.65 (t, *J* = 1.6 Hz, 1H), 6.45 (t, *J* = 1.5 Hz, 1H), 5.66 – 5.57 (m, 1H), 5.16 (d, *J* = 12.0 Hz, 1H), 4.34 – 4.18 (m, 3H), 4.19 – 4.10 (m, 2H), 3.89 – 3.77 (m, 3H), 3.77 – 3.65 (m, 1H), 3.62 – 3.54 (m, 2H), 3.54 – 3.48 (m, 1H), 3.43 – 3.36 (m, 2H), 3.25 – 3.19 (m, 7H), 3.07 – 2.97 (m, 1H), 2.97 – 2.89 (m, 1H), 2.83 – 2.74 (m, 4H), 2.69 – 2.65 (m, 4H), 2.61 – 2.52 (m, 2H), 2.45 – 2.39 (m, 1H), 2.27 – 2.19 (m, 1H), 2.14 – 2.03 (m, 2H), 1.99 – 1.88 (m, 1H), 1.87 – 1.74 (m, 3H), 1.73 – 1.59 (m, 3H), 1.57 – 1.42 (m, 3H), 1.33 (d, *J* = 6.1 Hz, 3H), 0.92 – 0.85 (m, 12H), 0.47 – 0.40 (m, 2H), 0.38 – 0.28 (m, 5H).

Examples A249 and A325: Synthesis of (3*R*,5*R*)-7-acetyl-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*,3-dimethyl-1,7-diazaspiro[4.5]decane-1-carboxamide and (3*R*,5*S*)-7-acetyl-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*,3-dimethyl-1,7-diazaspiro[4.5]decane-1-carboxamide



Step 1. To a stirred mixture of (2*R*,4*R*)-1-(*tert*-butoxycarbonyl)-4-methylpyrrolidine-2-carboxylic acid (3.00 g, 13.1 mmol) and K_2CO_3 (3.61 g, 26.2 mmol) in DMF (30 mL), methyl iodide (2.04 g, 14.4 mmol) was added dropwise at 0 °C. The resulting mixture was stirred for 16 h at room temperature under an atmosphere of nitrogen gas. The reaction mixture was then diluted with H_2O (300 mL), extracted with EtOAc (3 x 300 mL), washed with brine (3 x 250 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford 1-*tert*-butyl 2-methyl (2*R*,4*R*)-4-methylpyrrolidine-1,2-dicarboxylate (1.80 g, 57% yield) as a green oil. LCMS (ESI) *m/z*: [M – C_4H_8 – CO_2 + H] calcd for $C_{12}H_{21}NO_4$: 144.1; found 144.2.

Step 2. To a stirred solution of 1-*tert*-butyl 2-methyl (2*R*,4*R*)-4-methylpyrrolidine-1,2-dicarboxylate (1.80 g, 7.40 mmol) in THF (27 mL), LiHMDS (1.0 M in THF, 22.2 mL, 22.2 mmol) was added dropwise at –78 °C under an atmosphere of argon gas. The resulting mixture was stirred for 1 h at –78 °C. Subsequently, allyl bromide (1.79 g, 14.8 mmol) was added dropwise at –78 °C and the resulting mixture was stirred for additional 16 h at room temperature. The reaction mixture was then quenched with sat. aq. NH_4Cl at 0 °C, extracted with EtOAc (3 x 400 mL), washed with brine (3 x 300 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase flash column chromatography to afford 1-*tert*-butyl 2-methyl (4*R*)-4-methyl-2-(prop-2-en-1-yl)pyrrolidine-1,2-

dicarboxylate (1.30 g, 62% yield) as an off-white oil. LCMS (ESI) *m/z*: [M + H] calcd for $C_{15}H_{25}NO_4$: 284.2; found 284.0.

Step 3. To a stirred solution of 1-*tert*-butyl 2-methyl (4*R*)-4-methyl-2-(prop-2-en-1-yl)pyrrolidine-1,2-dicarboxylate (1.22 g, 4.31 mmol) in THF (43 mL), 9-borabicyclo[3.3.1]nonane (12.9 mL, 6.46 mmol) was added dropwise at room temperature. The resulting mixture was stirred at room temperature for 1 h, after which time additional 9-borabicyclo[3.3.1]nonane (12.9 mL, 6.46 mmol) was added dropwise at room temperature. This mixture was stirred at room temperature at 1 h, after which time an additional batch of 9-borabicyclo[3.3.1]nonane (12.9 mL, 6.46 mmol) was added dropwise at room temperature and the resulting mixture was stirred for 16 h at room temperature. Subsequently, NaOH (3.0 M in H_2O, 12.9 mL, 12.9 mmol) and H_2O_2 (12.9 mL) were added at room temperature and the resulting mixture was stirred for 45 minutes at room temperature. The reaction mixture was then extracted with EtOAc (3 x 200 mL), washed with brine (3 x 100 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase flash column chromatography to afford 1-*tert*-butyl 2-methyl (4*R*)-2-(3-hydroxypropyl)-4-methylpyrrolidine-1,2-dicarboxylate (1.00 g, 77% yield) as an off-white oil. LCMS (ESI) *m/z*: [M + H] calcd for $C_{15}H_{27}NO_5$: 302.2; found 302.3.

Step 4. To a stirred solution 1-*tert*-butyl 2-methyl (4*R*)-2-(3-hydroxypropyl)-4-methylpyrrolidine-1,2-dicarboxylate (1.00 g, 3.32 mmol) in THF (20 mL), $LiAlH_4$ (3.98 mL, 9.95 mmol) was added dropwise at 0 °C. The resulting mixture was stirred for 3 h at room temperature. The reaction mixture was then quenched with $10H_2O•Na_2SO_4$ at 0 °C, filtered, extracted with EtOAc (3 x 100 mL), concentrated under reduced pressure, and purified by reversed-phase flash column chromatography to afford *tert*-butyl (4*R*)-2-(hydroxymethyl)-2-(3-hydroxypropyl)-4-methylpyrrolidine-1-carboxylate (620 mg, 68% yield) as an off-white oil. LCMS (ESI) *m/z*: [M + H] calcd for $C_{14}H_{27}NO_4$: 274.2; found 274.2.

Step 5. To a stirred solution of *tert*-butyl (4*R*)-2-(hydroxymethyl)-2-(3-hydroxypropyl)-4-methylpyrrolidine-1-carboxylate (520 mg, 1.90 mmol) in DCM (5 mL), TEA (962 mg, 9.51 mmol) was added dropwise at 0 °C and the resulting mixture was stirred for 30 minutes at 0°C. Subsequently, methanesulfonic anhydride (994 mg, 5.71 mmol) was added dropwise at 0 °C and the resulting mixture was stirred for 30 minutes at 0 °C and was then stirred for 1 h at room temperature. The reaction mixture was then diluted with H_2O (100 mL), extracted with EtOAc (3 x 200 mL), washed with brine (3 x 100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford *tert*-butyl (4*R*)-2-((methanesulfonyloxy)methyl)-2-(3-(methanesulfonyloxy)propyl)-4-methylpyrrolidine-1-carboxylate (730 mg, crude) as an off-white oil. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{16}H_{31}NO_8S_2$: 430.2; found 430.0.

Step 6. A neat mixture of *tert*-butyl (4*R*)-2-((methanesulfonyloxy)methyl)-2-(3-(methanesulfonyloxy)propyl)-4-methylpyrrolidine-1-carboxylate (730 mg, crude) in benzylamine (22 mL) was stirred for 16 h at 60 °C. The reaction mixture was then neutralized to pH 7 with aqueous HCl (1.0 M), extracted with EtOAc (3 x 100 mL), washed with brine (3 x 50 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase flash column chromatography to afford *tert*-butyl (3*R*)-7-benzyl-3-methyl-1,7-diazaspiro[4.5]decane-1-carboxylate (150 mg, 23% yield over 2 steps) as an off-white oil. LCMS (ESI) *m/z*: [M + H] calcd for $C_{21}H_{32}N_2O_2$: 345.3; found 345.3.

Step 7. To a stirred solution of *tert*-butyl (3*R*)-7-benzyl-3-methyl-1,7-diazaspiro[4.5]decane-1-carboxylate (100 mg, 0.290 mmol) in *i*-PrOH (3 mL) and AcOH (0.3 mL), Pd/C (10% wt., 75.1 mg) and $Pd(OH)_2/C$ (10% wt., 75.2 mg) were added under an atmosphere of nitrogen gas. The resulting mixture was stirred for 16 h at room temperature under an atmosphere of hydrogen gas. The reaction mixture was then filtered, the filter cake was washed with MeOH (3 x 50 mL), and the filtrate was concentrated under reduced pressure to afford *tert*-butyl (3*R*)-3-methyl-1,7-diazaspiro[4.5]decane-1-carboxylate (200 mg, crude) as a red oil. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{14}H_{26}N_2O_2$: 255.2; found 255.3.

Step 8. To a stirred solution of *tert*-butyl (3*R*)-3-methyl-1,7-diazaspiro[4.5]decane-1-carboxylate (200 mg, crude) and TEA (159 mg, 1.57 mmol) in DCM (3.0 mL), acetyl chloride (92.6 mg, 1.18 mmol) was added dropwise at 0 °C under an atmosphere of argon gas. The resulting mixture was stirred for 2 h at 0°C under an atmosphere of argon gas. The reaction mixture was then diluted with H_2O (60 mL), extracted with EtOAc (3 x 60 mL), washed with brine (3 x 40 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford *tert*-butyl (3*R*)-7-acetyl-3-methyl-1,7-diazaspiro[4.5]decane-1-carboxylate (120 mg, crude) as a colorless oil. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{16}H_{28}N_2O_3$: 297.2; found 297.1.

Step 9. To a stirred solution of *tert*-butyl (3*R*)-7-acetyl-3-methyl-1,7-diazaspiro[4.5]decane-1-carboxylate (115 mg, crude) in DCM (1.2 mL), HCl (4.0 M in 1,4-dioxane, 0.9 mL, 3.6 mmol) was added at 0 °C. The resulting mixture was stirred at 35 °C for 2 h, after which time it was concentrated under reduced pressure to afford 1-((3*R*)-3-methyl-1,7-diazaspiro[4.5]decan-7-yl)ethanone (76.0 mg, crude) as a red oil. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{11}H_{20}N_2O$: 197.2; found 197.3.

Step 10. To a stirred mixture of 1-((3*R*)-3-methyl-1,7-diazaspiro[4.5]decan-7-yl)ethanone (76.0 mg, crude) and benzyl (2*S*)-2-((chlorocarbonyl)(methyl)amino)-3-methylbutanoate (36.9 mg, 0.131 mmol) in MeCN (1.0 mL), DIPEA (150 mg, 1.16 mmol) was added dropwise at 0 °C under an atmosphere of argon gas. The resulting mixture was stirred for 16 h at 40 °C. The reaction mixture was then concentrated under reduced pressure and purified by reversed-phase flash column chromatography to afford benzyl (2*S*)-2-((3*R*)-7-acetyl-3-methyl-1,7-diazaspiro[4.5]decane-1-carbonyl(methyl)amino)-3-methylbutanoate (86.0 mg, 70% yield over 4 steps) as a red oil. LCMS (ESI) *m/z*: [M + H] calcd for $C_{25}H_{37}N_3O_4$: 444.3; found 444.2.

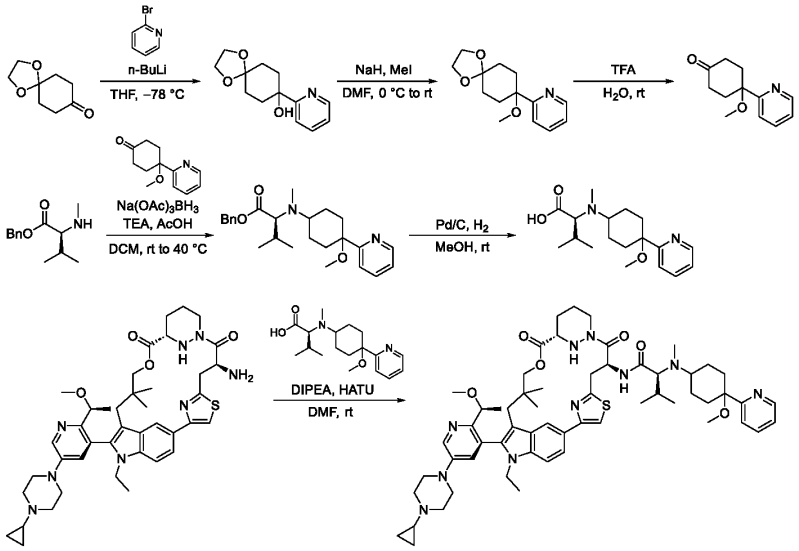
Step 11. To a stirred solution of benzyl (2*S*)-2-((3*R*)-7-acetyl-3-methyl-1,7-diazaspiro[4.5]decane-1-carbonyl(methyl)amino)-3-methylbutanoate (76.0 mg, 0.171 mmol) in MeOH (1.0 mL), Pd/C (10% wt., 152 mg) was added at room temperature under an atmosphere of nitrogen gas. The resulting mixture was stirred for 2 h at room temperature under an atmosphere of hydrogen gas. The reaction mixture was then filtered, the filter cake was washed with MeOH (3 x 50 mL), and the filtrate was concentrated under reduced pressure to afford (2*S*)-2-((3*R*)-7-acetyl-3-methyl-1,7-diazaspiro[4.5]decane-1-carbonyl(methyl)amino)-3-methylbutanoic acid (63 mg, crude) as an off-white solid. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{18}H_{31}N_3O_4$: 354.2; found 354.3.

Step 12. To a stirred solution of (6^3S,4*S*)-4-amino-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-5,7-dione (142 mg, 0.178 mmol) in DMF (1.4 mL), DIPEA (115 mg, 0.890 mmol) and (2*S*)-2-((3*R*)-7-acetyl-3-methyl-1,7-diazaspiro[4.5]decane-1-carbonyl(methyl)amino)-3-methylbutanoic acid (63 mg, crude) were added in portions at 0 °C under an atmosphere of argon gas. Subsequently, a solution of HATU (88.1 mg, 0.231 mmol) in DMF (0.2 mL) was added dropwise at 0 °C and the resulting mixture was stirred for 2 h at 0 °C under an atmosphere of argon gas. The reaction mixture was then diluted with H_2O (50 mL), extracted with EtOAc (3 x 30 mL), washed with brine (3 x 20 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase prep-HPLC to afford (3*R*)-7-acetyl-*N*-((2*S*)-1-((((6^3S,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*,3-dimethyl-1,7-diazaspiro[4.5]decane-1-carboxamide (50.0 mg, 26% yield) as a mixture of two diastereomers. This material was further purified by chiral prep-HPLC to afford two separated diastereomers of the product. **A325** (25.9 mg, 13% yield) as a white solid and **A249** (3.1 mg, 1.5% yield) as a white solid.

A325: (25.9 mg, 13% yield); LCMS (ESI) *m/z*: [M + H] calcd for $C_{59}H_{83}N_{11}O_7S$: 1090.6; found 1090.6; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 – 8.42 (m, 2H), 8.37 (d, *J* = 9.4 Hz, 1H), 7.79 (s, 1H), 7.73 (d, *J* = 8.6 Hz, 1H), 7.55 (d, *J* = 8.6 Hz, 1H), 7.20 (d, *J* = 2.8 Hz, 1H), 5.64 (t, *J* = 9.3 Hz, 1H), 5.17 (d, *J* = 12.1 Hz, 1H), 4.37 – 4.11 (m, 6H), 3.84 – 3.72 (m, 2H), 3.56 (s, 2H), 3.50 – 3.38 (m, 1H), 3.21 (s, 7H), 3.04 – 2.89 (m, 3H), 2.79 (d, *J* = 4.6 Hz, 4H), 2.67 (s, 5H), 2.34 (s, 1H), 2.14 – 2.05 (m, 2H), 2.02 (s, 2H), 1.98 (s, 3H), 1.84 – 1.77 (m, 2H), 1.68 – 1.61 (m, 2H), 1.54 – 1.45 (m, 3H), 1.44 – 1.37 (m, 1H), 1.33 (d, *J* = 6.1 Hz, 3H), 1.24 (s, 1H), 1.19 (s, 1H), 1.11 (s, 1H), 1.05 (dd, *J* = 18.1, 6.2 Hz, 3H), 0.95 – 0.82 (m, 12H), 0.44 (d, *J* = 6.0 Hz, 2H), 0.34 (d, *J* = 5.8 Hz, 5H).

A249: (3.1 mg, 1.5% yield); LCMS (ESI) *m/z*: [M + H] calcd for $C_{59}H_{83}N_{11}O_7S$: 1090.6; found 1090.6; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 – 8.42 (m, 2H), 8.40 – 8.31 (m, 1H), 7.82 – 7.70 (m, 2H), 7.55 (d, *J* = 8.6 Hz, 1H), 7.21 (s, 1H), 5.64 (t, *J* = 9.5 Hz, 1H), 5.16 (d, *J* = 12.1 Hz, 1H), 4.46 – 4.05 (m, 6H), 3.90 – 3.70 (m, 2H), 3.54 (s, 3H), 3.48 – 3.34 (m, 3H), 3.21 (s, 7H), 3.10 – 3.01 (m, 2H), 2.98 – 2.89 (m, 2H), 2.80 – 2.73 (m, 4H), 2.68 (d, *J* = 6.2 Hz, 5H), 2.49 – 2.30 (m, 2H), 2.29 – 2.17 (m, 1H), 2.13 – 2.05 (m, 3H), 1.98 (s, 3H), 1.88 – 1.73 (m, 2H), 1.66 – 1.58 (m, 4H), 1.55 – 1.40 (m, 2H), 1.33 (d, *J* = 6.1 Hz, 5H), 1.24 (s, 2H), 1.19 (s, 1H), 1.09 – 1.01 (m, 4H), 0.96 – 0.78 (m, 14H), 0.44 (d, *J* = 6.4 Hz, 2H), 0.34 (d, *J* = 5.8 Hz, 5H).

Example A111: Synthesis of (2*S*)-*N*-((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)-2-((4-methoxy-4-(pyridin-2-yl)cyclohexyl)(methyl)amino)-3-methylbutanamide



Step 1. To a stirred solution of 1,4-cyclohexanedione monoethylene ketal (10.0 g, 64.0 mmol) in anhydrous THF (400 mL) was added 2-bromopyridine (9.40 mL, 96.0 mmol) was added under an atmosphere of argon. The resulting mixture was stirred at –78 °C for 10 minutes, after which time *n*-BuLi (2.5 M in hexanes, 76.8 mL, 192 mmol) was added and the resulting mixture was stirred for 1.5 h at –78 °C. The reaction mixture was then quenched with sat. aq. NH_4Cl, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, purified by normal phase flash column chromatography to afford 8-(pyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (9.94 g, 66% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{13}H_{17}NO_3$: 236.1; found 236.1.

Step 2. To a stirred solution of 8-(pyridin-2-yl)-1,4-dioxaspiro[4.5]decan-8-ol (1.00 g, 4.25 mmol) in anhydrous DMF (10.0 mL) at 0 °C under an atmosphere of argon was added methyl iodide (926 µL, 14.9 mmol). The resulting reaction mixture was stirred for 5 minutes, after which time sodium hydride (60% dispersion in mineral oil, 408 mg, 17.0 mmol) was added slowly in portions. The resulting mixture was gradually warmed to room temperature and was stirred for 16 h. The reaction mixture was quenched with H_2O, extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford 2-(8-methoxy-1,4-dioxaspiro[4.5]decan-8-yl)pyridine (1.09 g, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{14}H_{19}NO_3$: 250.1; found 250.0.

Step 3. To a stirred suspension of 2-(8-methoxy-1,4-dioxaspiro[4.5]decan-8-yl)pyridine (1.09 g, crude) in H_2O (10.9 mL) was added trifluoroacetic acid (47.0 mL, 610 mmol) at room temperature. The resulting mixture was stirred for 16 hours at room temperature. The reaction mixture was then quenched by the addition of sat. aq $NaHCO_3$, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure pressure to afford 4-methoxy-4-(pyridin-2-yl)cyclohexan-1-one (895

mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{12}H_{15}NO_2$: 206.1; found 206.0.

Step 4. To a stirred solution of benzyl (2*S*)-3-methyl-2-(methylamino)butanoate hydrochloride (1.20 g, 4.67 mmol) in anhydrous DCM (27 mL), triethylamine (816 µL, 4.25 mmol) was added dropwise at room temperature. The resulting mixture was stirred for 10 minutes, after which time 4-methoxy-4-(pyridin-2-yl)cyclohexan-1-one (890 mg, crude) and glacial acetic acid (464 µL, 8.50 mmol) were added and the reaction mixture was stirred for 16 h at room temperature. Subsequently, sodium triacetoxyborohydride (1.80 g, 8.50 mmol) was added and the resulting mixture was stirred for 16 h at 40 °C. The reaction mixture was then cooled to room temperature, quenched with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by normal phase flash column chromatography. The resulting material was further purified by reversed-phase flash column chromatography to afford two separated isomers of benzyl (2*S*)-2-((4-methoxy-4-(pyridin-2-yl)cyclohexyl)(methyl)amino)-3-methylbutanoate.

Isomer 1: (186 mg, 10% yield); LCMS (ESI) *m/z*: [M + H] calcd for $C_{25}H_{34}N_2O_3$: 411.3; found 411.4.

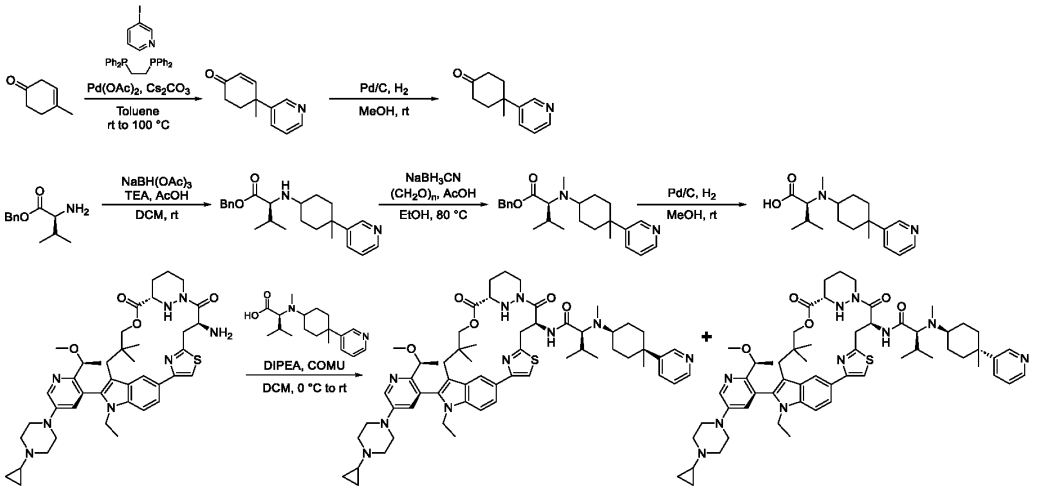
Isomer 2: (266 mg, 14% yield); LCMS (ESI) *m/z*: [M + H] calcd for $C_{25}H_{34}N_2O_3$: 411.3; found 411.4.

Step 5. To a stirred solution of benzyl (2*S*)-2-((4-methoxy-4-(pyridin-2-yl)cyclohexyl)(methyl)amino)-3-methylbutanoate (*Isomer 1* from previous reaction, 185 mg, 0.44 mmol) in MeOH (9.3 mL), 25% wt. Pd/C (47 mg) was added under an atmosphere of argon. The resulting mixture was evacuated and backfilled with hydrogen gas three times, after which time it was stirred for 2 h at room temperature under an atmosphere of hydrogen. The reaction mixture was then filtered through a pad of Celite® and concentrated under reduced pressure to afford (2*S*)-2-((4-methoxy-4-(pyridin-2-yl)cyclohexyl)(methyl)amino)-3-methylbutanoic acid (143 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{18}H_{28}N_2O_3$: 321.2; found 321.1.

Step 6. To a stirred solution of (2*S*)-2-((4-methoxy-4-(pyridin-2-yl)cyclohexyl)(methyl)amino)-3-methylbutanoic acid (60 mg, crude) in anhydrous DMF (2.3 mL) were added DIPEA (221 µL, 0.94 mmol) and (6^3*S*,4*S*)-4-amino-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-5,7-dione (75 mg, 0.099 mmol). The resulting mixture was stirred for 10 minutes at room temperature, after which time HATU (72 mg, 0.19 mmol) was added and the mixture was stirred at room temperature overnight. The reaction mixture was then quenched with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase prep-HPLC. HPLC fractions containing the desired product were combined, washed with sat. aq. $NaHCO_3$, extracted with DCM, washed with H_2O, and evaporated to give (2*S*)-*N*-((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)-2-((4-methoxy-4-(pyridin-2-yl)cyclohexyl)(methyl)amino)-3-methylbutanamide (31.1 mg, 30% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{59}H_{80}N_{10}O_6S$: 1057.6; found 1057.2; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.58 – 8.54 (m, 1H), 8.47 (s, 1H), 8.44 (d, *J* = 2.9 Hz, 1H), 8.34 – 8.26 (m, 1H), 7.90 (s, 1H), 7.85 – 7.78

(m, 1H), 7.78 – 7.72 (m, 1H), 7.60 – 7.50 (m, 2H), 7.28 (dd, *J* = 7.4, 4.9 Hz, 1H), 7.21 (d, *J* = 2.9 Hz, 1H), 5.50 – 5.39 (m, 1H), 5.05 (d, *J* = 12.0 Hz, 1H), 4.35 – 4.12 (m, 5H), 3.62 – 3.50 (m, 2H), 3.30 – 3.28 (m, 3H), 3.25 – 3.19 (m, 8H), 2.99 – 2.93 (m, 1H), 2.91 (s, 3H), 2.89 – 2.85 (m, 1H), 2.71 – 2.64 (m, 5H), 2.42 – 2.30 (m, 2H), 2.16 (s, 3H), 2.03 – 1.73 (m, 6H), 1.70 – 1.45 (m, 6H), 1.33 (d, *J* = 6.1 Hz, 3H), 0.95 – 0.84 (m, 12H), 0.49 – 0.39 (m, 2H), 0.37 – 0.29 (m, 5H).

Examples A27 and A28: Synthesis of (2*S*)-*N*-((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,^{65},6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)-3-methyl-2-(methyl((1*s*,4*R*)-4-methyl-4-(pyridin-3-yl)cyclohexyl)amino)butanamide and (2*S*)-*N*-((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,^{65},6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)-3-methyl-2-(methyl((1*r*,4*S*)-4-methyl-4-(pyridin-3-yl)cyclohexyl)amino)butanamide



Step 1. A stirred solution of 4-methylcyclohex-3-en-1-one (800 mg, 7.26 mmol), 3-iodopyridine (2.97 g, 14.5 mmol), Cs_2CO_3 (2.97 g, 14.5 mmol), and 1,2-bis(diphenylphosphino)ethane (1.16 g, 2.90 mmol) in anhydrous toluene (18 mL) was purged with argon gas for 15 minutes, after which time $Pd(OAc)_2$ (326 mg, 1.45 mmol) was added and the resulting mixture was purged with argon gas for an additional 15 minutes. The reaction mixture was stirred for 16 hours at 100 °C under an atmosphere of argon, after which time it was cooled to room temperature, filtered through a pad of Celite®, washed with EtOAc, and concentrated under reduced pressure. The resulting material was purified by normal phase flash column chromatography to afford 4-methyl-4-(pyridin-3-yl)cyclohex-2-en-1-one (412 mg, 27% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{12}H_{13}NO$: 188.1; found 188.0.

Step 2. A solution of 4-methyl-4-(pyridin-3-yl)cyclohex-2-en-1-one (400 mg, 1.92 mmol) in MeOH (28 mL) was purged with argon gas for 5 minutes. Pd/C (10% wt., 409 mg) was then added, and the resulting mixture was evacuated and backfilled with hydrogen gas three times. The reaction mixture was stirred at room temperature under an atmosphere of hydrogen gas for 1 hour, after which time it was

filtered through a pad of Celite® and concentrated under reduced pressure to afford 4-methyl-4-(pyridin-3-yl)cyclohexan-1-one (288 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{12}H_{15}NO$: 190.1; found 190.1.

Step 3. To a stirred solution of benzyl (2*S*)-2-amino-3-methylbutanoate hydrochloride (317 mg, 1.30 mmol) in anhydrous DCM (14 mL), triethylamine (225 µL, 1.18 mmol) was added dropwise at room temperature. The resulting mixture was stirred for 10 minutes at room temperature, after which time 4-methyl-4-(pyridin-3-yl)cyclohexan-1-one (288 mg, crude) and glacial acetic acid (135 µL, 2.37 mmol) were added and the reaction mixture was stirred for 16 h at room temperature. Subsequently, sodium triacetoxyborohydride (502 mg, 2.37 mmol) was added and the resulting mixture was stirred for 2 h at room temperature. The reaction mixture was then quenched with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by normal phase prep-TLC to afford benzyl (2*S*)-3-methyl-2-((4-methyl-4-(pyridin-3-yl)cyclohexyl)amino)butanoate (309 mg, 62% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{24}H_{32}N_2O_2$: 381.3; found 381.3.

Step 4. To a stirred solution of benzyl (2*S*)-3-methyl-2-((4-methyl-4-(pyridin-3-yl)cyclohexyl)amino)butanoate (300 mg, 0.70 mmol) in EtOH (12.0 mL), paraformaldehyde (83.0 mg, 2.78 mmol), glacial acetic acid (79 µL, 1.39 mmol), and sodium cyanoborohydride (188 mg, 3.15 mmol) were added at room temperature. The resulting mixture was stirred for 16 h at 80 °C. The reaction mixture was then cooled down to room temperature and concentrated under reduced pressure. The resulting residue was diluted with DCM, washed with H_2O, extracted with DCM, washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase prep-TLC to afford benzyl (2*S*)-3-methyl-2-(methyl(4-methyl-4-(pyridin-3-yl)cyclohexyl)amino)butanoate (189 mg, 86% yield) as a mixture of two diastereomers. LCMS (ESI) *m/z*: [M + H] calcd for $C_{25}H_{34}N_2O_2$: 395.3; found 395.3.

Step 5. A solution of benzyl (2*S*)-3-methyl-2-(methyl(4-methyl-4-(pyridin-3-yl)cyclohexyl)amino)butanoate (185 mg, 0.44 mmol) in MeOH (9.3 mL) was purged with argon gas for 5 minutes. Subsequently, Pd/C (32% wt., 60 mg) was added, and the headspace of the reaction flask was evacuated and backfilled with hydrogen gas three times. The reaction mixture was stirred at room temperature under an atmosphere of hydrogen gas for 2 hours, after which time it was filtered through a pad of Celite®, the pad was washed with MeOH, and the filtrate was concentrated under reduced pressure to afford (2*S*)-3-methyl-2-(methyl(4-methyl-4-(pyridin-3-yl)cyclohexyl)amino)butanoic acid (126 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{18}H_{28}N_2O_2$: 305.2; found 304.7.

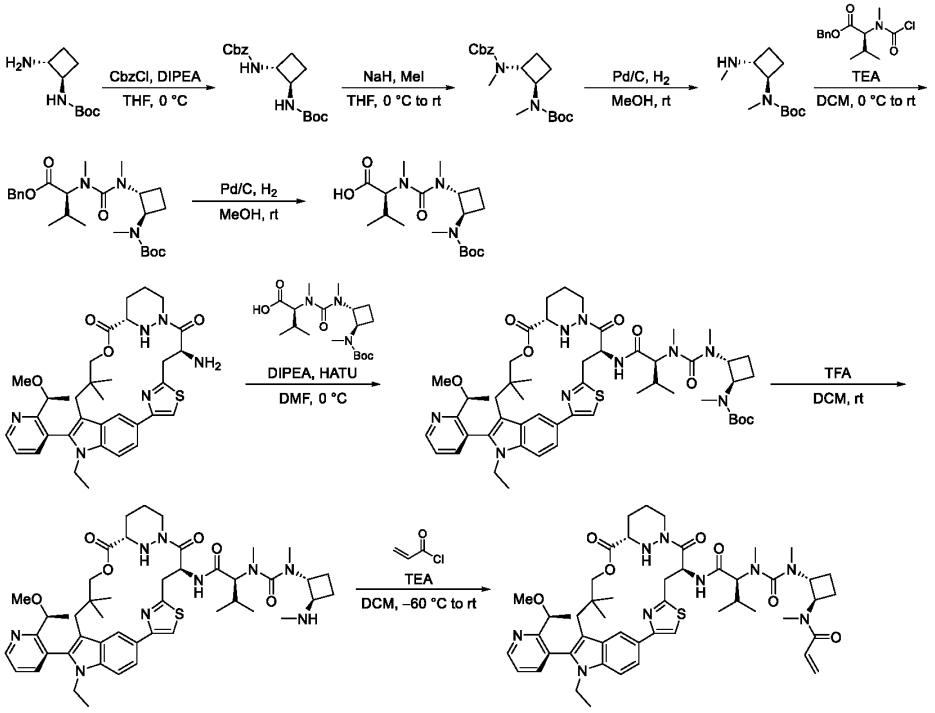
Step 6. To a stirred solution of (6^3*S*,4*S*)-4-amino-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-5,7-dione (150 mg, 0.199 mmol) in anhydrous DCM (4.5 mL) were added DIPEA (173 µL, 0.99 mmol) and (2*S*)-3-methyl-2-(methyl(4-methyl-4-(pyridin-3-yl)cyclohexyl)amino)butanoic acid (87 mg, 0.26 mmol) were added at 0 °C. After 15 minutes of stirring, COMU (128 mg, 0.299 mmol) was added at 0 °C and the resulting mixture was stirred for 16 hours at room temperature. The reaction mixture was then quenched with H_2O, extracted with DCM, washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by normal phase prep-TLC. The resulting material was further purified by reversed-phase prep-HPLC to afford two separated

diastereomers of (2*S*)-*N*-((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,^{65}6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)-3-methyl-2-(methyl-4-methyl-4-(pyridin-3-yl)cyclohexyl)amino)butanamide.

A28: (23.5 mg, 11% yield); LCMS (ESI) *m/z*: [M + H] calcd for $C_{59}H_{80}N_{10}O_5S$: 1041.6; found 1041.3; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.62 (d, *J* = 2.4 Hz, 1H), 8.51 – 8.46 (m, 1H), 8.44 (d, *J* = 2.8 Hz, 1H), 8.43 – 8.37 (m, 1H), 8.25 (d, *J* = 8.2 Hz, 1H), 7.89 (s, 1H), 7.82 – 7.69 (m, 2H), 7.57 (d, *J* = 8.6 Hz, 1H), 7.34 (dd, *J* = 8.0, 4.6 Hz, 1H), 7.20 (d, *J* = 2.9 Hz, 1H), 5.54 – 5.40 (m, 1H), 5.07 (d, *J* = 12.1 Hz, 1H), 4.36 – 4.08 (m, 5H), 3.60 – 3.53 (m, 2H), 3.26 – 3.16 (m, 8H), 2.93 (d, *J* = 14.3 Hz, 1H), 2.82 – 2.74 (m, 2H), 2.72 – 2.62 (m, 5H), 2.45 – 2.41 (m, 1H), 2.39 – 2.30 (m, 2H), 2.16 – 2.09 (m, 1H), 2.07 (s, 3H), 1.94 – 1.85 (m, 1H), 1.83 – 1.73 (m, 3H), 1.70 – 1.60 (m, 2H), 1.58 – 1.40 (m, 3H), 1.33 (d, *J* = 6.1 Hz, 3H), 1.30 – 1.24 (m, 1H), 1.14 (s, 3H), 1.21 – 1.06 (m, 2H), 0.94 – 0.87 (m, 6H), 0.86 – 0.82 (m, 6H), 0.50 – 0.40 (m, 2H), 0.39 – 0.28 (m, 5H).

A27: (28.3 mg, 13% yield); LCMS (ESI) *m/z*: [M + H] calcd for $C_{59}H_{80}N_{10}O_5S$: 1041.6; found 1041.2; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.68 – 8.61 (m, 1H), 8.46 – 8.43 (m, 2H), 8.41 (dd, *J* = 4.7, 1.6 Hz, 1H), 8.29 (d, *J* = 8.3 Hz, 1H), 7.82 – 7.77 (m, 2H), 7.71 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.54 (d, *J* = 8.7 Hz, 1H), 7.38 – 7.31 (m, 1H), 7.20 (d, *J* = 2.9 Hz, 1H), 5.55 – 5.42 (m, 1H), 5.07 (d, *J* = 12.1 Hz, 1H), 4.34 – 4.06 (m, 5H), 3.60 – 3.50 (m, 2H), 3.26 – 3.17 (m, 8H), 2.92 (d, *J* = 14.3 Hz, 1H), 2.86 (d, *J* = 9.7 Hz, 1H), 2.82 – 2.75 (m, 1H), 2.71 – 2.64 (m, 4H), 2.63 – 2.56 (m, 1H), 2.47 – 2.40 (m, 2H), 2.33 (s, 3H), 2.15 – 2.08 (m, 1H), 2.00 – 1.90 (m, 1H), 1.89 – 1.84 (m, 2H), 1.72 – 1.62 (m, 8H), 1.57 – 1.49 (m, 1H), 1.32 (d, *J* = 6.0 Hz, 3H), 1.28 – 1.24 (m, 4H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.92 – 0.85 (m, 9H), 0.48 – 0.39 (m, 2H), 0.38 – 0.26 (m, 5H).

Example A1001: Synthesis of (2*S*)-2-(1,3-dimethyl-3-((1*R*,2*R*)-2-(*N*-methylacrylamido)cyclobutyl)ureido)-*N*-((6^3*S*,4*S*)-1^1-ethyl-1^2-(2-((*S*)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)-3-methylbutanamide



Step 1. To a stirred solution of *tert*-butyl *N*-((1*R*,2*R*)-2-aminocyclobutyl)carbamate (700 mg, 3.76 mmol) in anhydrous THF (21 mL), DIPEA (1.00 mL, 5.64 mmol) and a solution of benzyl chloroformate (602 µL, 4.13 mmol) in anhydrous THF (6.0 mL) were added at 0 °C. The resulting mixture was stirred at 0 °C for 1 h. The reaction mixture was then quenched with H_2O, extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude material was triturated with a 1:1 vol. mixture of isopropanol/hexane, the resulting mixture was filtered, and the solid material was dried under reduced pressure to afford benzyl *N*-((1*R*,2*R*)-2-(((*tert*-butoxy)carbonyl)amino)cyclobutyl)carbamate (740 mg, 61% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{17}H_{24}N_2O_4$: 321.2; found 321.4.

Step 2. To a stirred solution of benzyl *N*-((1*R*,2*R*)-2-(((*tert*-butoxy)carbonyl)amino)cyclobutyl)carbamate (735 mg, 2.30 mmol) in anhydrous THF (22 mL), iodomethane (1.43 mL, 23.0 mmol) was added at 0 °C. Subsequently, sodium hydride (60% wt. in mineral oil, 921 mg, 23.0 mmol) was added in portions at 0 °C and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was then quenched with H_2O, extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford benzyl *N*-((1*R*,2*R*)-2-(((*tert*-butoxy)carbonyl)(methyl)amino)cyclobutyl)-*N*-methylcarbamate (603 mg, 75% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{19}H_{28}N_2O_4$: 349.2; found 348.7.

Step 3. A solution of benzyl *N*-((1*R*,2*R*)-2-(((*tert*-butoxy)carbonyl)(methyl)amino)cyclobutyl)-*N*-methylcarbamate (600 mg, 1.72 mmol) in MeOH (18 mL) was sparged with argon gas. Subsequently, Pd/C (10% wt., 550 mg) was added and the reaction flask was evacuated and backfilled with hydrogen gas. The resulting mixture was stirred under an atmosphere of hydrogen gas for 2 h at room temperature. The reaction mixture was then filtered through a pad of Celite®, the pad was washed with MeOH, and the filtrate was concentrated under reduced pressure to afford *tert*-butyl *N*-methyl-*N*-((1*R*,2*R*)-2-(methylamino)cyclobutyl)carbamate (303 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{11}H_{22}N_2O_2$: 215.2; found 215.2.

Step 4. To a stirred solution of *tert*-butyl *N*-methyl-*N*-((1*R*,2*R*)-2-(methylamino)cyclobutyl)carbamate (200 mg, crude) and triethylamine (520 µL, 3.73 mmol) in DCM (12 mL), benzyl (2*S*)-2-((chlorocarbonyl)(methyl)amino)-3-methylbutanoate (265 mg, 0.93 mmol) was added dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 30 minutes and was then stirred at room temperature for 16 h. The reaction mixture was quenched with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford benzyl (2*S*)-2-((((1*R*,2*R*)-2-(((*tert*-butoxy)carbonyl)(methyl)amino)cyclobutyl)(methyl)-carbamoyl)(methyl)amino)-3-methylbutanoate (89% purity, 335 mg, 69% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{25}H_{39}N_3O_5$: 462.3; found 462.0.

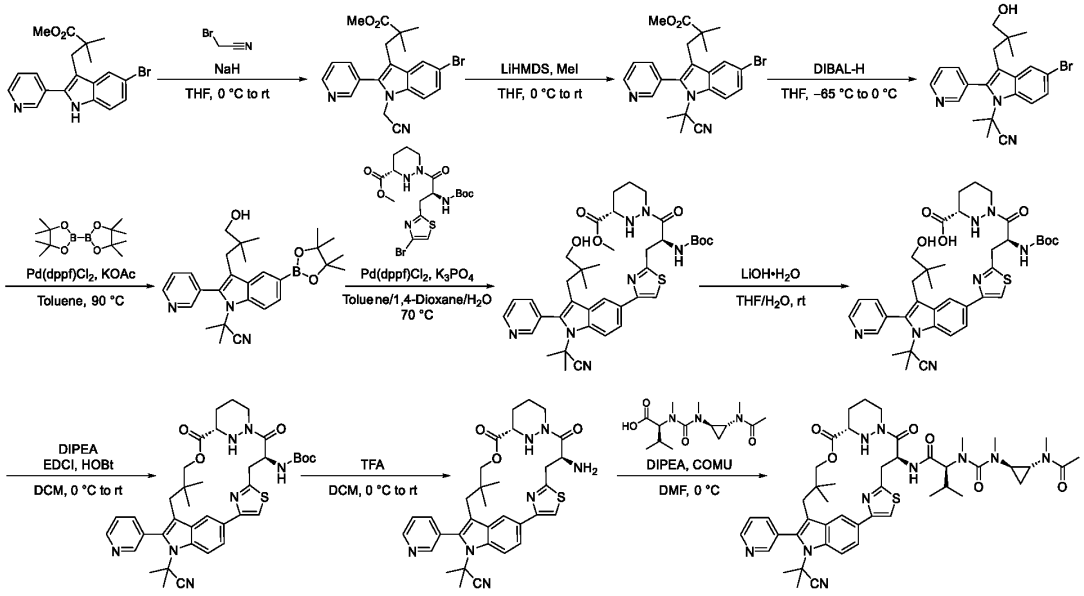
Step 5. To a stirred solution of benzyl (2*S*)-2-((((1*R*,2*R*)-2-(((*tert*-butoxy)carbonyl)(methyl)amino)cyclobutyl)(methyl)-carbamoyl)(methyl)amino)-3-methylbutanoate (89% purity, 330 mg, 0.636 mmol) in MeOH (9.9 mL), Pd/C (10% wt., 228 mg) was added under an atmosphere of argon gas. The resulting mixture was placed under an atmosphere of hydrogen gas and was stirred for 2 h at room temperature. The reaction mixture was then filtered through a pad of Celite®, the pad was washed with MeOH, and the filtrate was concentrated under reduced pressure to afford (2*S*)-2-((((1*R*,2*R*)-2-(((*tert*-butoxy)carbonyl)(methyl)amino)-cyclobutyl)(methyl)carbamoyl)(methyl)amino)-3-methylbutanoic acid (243 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{18}H_{33}N_3O_5$: 372.2; found 371.7.

Step 6. To a stirred solution of (6^3S,4*S*)-4-amino-1^1-ethyl-1^2-(2-((*S*)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1H-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-5,7-dione (100 mg, 0.159 mmol) and (2*S*)-2-((((1*R*,2*R*)-2-(((*tert*-butoxy)carbonyl)(methyl)amino)-cyclobutyl)(methyl)carbamoyl)(methyl)amino)-3-methylbutanoic acid (77 mg, crude) in anhydrous DMF (3.0 mL), DIPEA (282 µL, 1.60 mmol) was added at 0 °C. The resulting mixture was stirred for 5 minutes, after which time HATU (90 mg, 0.24 mmol) was added and the mixture was stirred for 2 h at 0 °C. The reaction mixture was then quenched with H_2O, extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford *tert*-butyl ((1*R*,2*R*)-2-(3-((2*S*)-1-(((6^3*S*,4*S*)-1^1-ethyl-1^2-(2-((*S*)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1H-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-1,3-dimethylureido)cyclobutyl)(methyl)carbamate (126 mg, 81% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{52}H_{73}N_9O_8S$: 984.5; found 985.1.

Step 7. To a stirred solution of *tert*-butyl ((1*R*,2*R*)-2-(3-((2*S*)-1-(((6^3*S*,4*S*)-1^1-ethyl-1^2-(2-((*S*)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-1,3-dimethylureido)cyclobutyl)(methyl)carbamate (113 mg, 0.115 mmol) in DCM (4.5 mL), trifluoroacetic acid (439 µL, 5.74 mmol) was added dropwise at 0 °C. The resulting mixture was stirred for 2 h at room temperature. The reaction mixture was then quenched with sat. aq. $NaHCO_3$, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford (2*S*)-2-(1,3-dimethyl-3-((1*R*,2*R*)-2-(methylamino)cyclobutyl)ureido)-*N*-((6^3*S*,4*S*)-1^1-ethyl-1^2-(2-((*S*)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)-3-methylbutanamide (100 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{47}H_{65}N_9O_6S$: 884.5; found 884.9.

Step 8. To a stirred solution of (2*S*)-2-(1,3-dimethyl-3-((1*R*,2*R*)-2-(methylamino)cyclobutyl)ureido)-*N*-((6^3*S*,4*S*)-1^1-ethyl-1^2-(2-((*S*)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)-3-methylbutanamide (99 mg, crude) in DCM (3.0 mL), triethylamine (78 µl, 0.56 mmol) and acryloyl chloride (8 µl, 0.10 mmol) were added at –60 °C. The resulting mixture was stirred at –60 °C for 20 minutes. The reaction mixture was then warmed to room temperature, quenched with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by reversed-phase prep-HPLC to afford (2*S*)-2-(1,3-dimethyl-3-((1*R*,2*R*)-2-(*N*-methylacrylamido)cyclobutyl)ureido)-*N*-((6^3*S*,4*S*)-1^1-ethyl-1^2-(2-((*S*)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)-3-methylbutanamide (50 mg, 47% yield over 2 steps). LCMS (ESI) *m/z*: [M + H] calcd for $C_{50}H_{67}N_9O_7S$: 938.5; found 939.0; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.75 (dd, *J* = 4.7, 1.7 Hz, 1H), 8.49 – 8.46 (m, 1H), 8.28 (d, *J* = 8.9 Hz, 1H), 7.82 – 7.70 (m, 3H), 7.58 (d, *J* = 8.6 Hz, 1H), 7.55 – 7.48 (m, 1H), 6.86 – 6.64 (m, 1H), 6.20 – 6.04 (m, 1H), 5.69 (dd, *J* = 10.4, 2.4 Hz, 1H), 5.56 (t, *J* = 8.9 Hz, 1H), 5.14 (d, *J* = 12.1 Hz, 1H), 4.70 – 4.60 (m, 1H), 4.38 – 4.04 (m, 7H), 3.85 (d, *J* = 10.9 Hz, 1H), 3.57 (s, 2H), 3.37 (s, 1H), 3.26 (s, 3H), 3.13 – 3.00 (m, 1H), 3.00 – 2.90 (m, 3H), 2.87 – 2.80 (m, 4H), 2.75 (s, 3H), 2.40 (d, *J* = 14.2 Hz, 1H), 2.16 – 2.04 (m, 2H), 1.95 – 1.76 (m, 6H), 1.57 – 1.45 (m, 1H), 1.37 (d, *J* = 6.0 Hz, 3H), 0.92 – 0.78 (m, 12H), 0.32 (s, 3H).

Example A1056: Synthesis of (2*S*)-*N*-((6^3*S*,4*S*)-1^1-(2-cyanopropan-2-yl)-10,10-dimethyl-5,7-dioxo-1^2-(pyridin-3-yl)-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)-2-(1,3-dimethyl-3-((1*R*,2*R*)-2-(*N*-methylacetamido)cyclopropyl)ureido)-3-methylbutanamide



Step 1. To a stirred solution of 3-(5-bromo-2-(pyridin-3-yl)-1*H*-indol-3-yl)-2,2-dimethylpropanoate (5.00 g, 12.9 mmol) in anhydrous THF (100 mL), bromoacetonitrile (2.30 mL, 32.3 mmol) and NaH (60% wt. in mineral oil, 1.19 g, 29.7 mmol) were added in portions at 0 °C under an atmosphere of argon gas. The resulting mixture was stirred for 16 h at room temperature. The reaction mixture was then concentrated under reduced pressure, diluted with an aqueous solution of NH_4Cl (10%), extracted with DCM, washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford methyl 3-(5-bromo-1-(cyanomethyl)-2-(pyridin-3-yl)-1*H*-indol-3-yl)-2,2-dimethylpropanoate (1.30 g, 24% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{21}H_{20}BrFN_3O_2$: 428.1; found 427.4; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.74 (dd, *J* = 4.9, 1.6 Hz, 1H), 8.68 – 8.65 (m, 1H), 7.94 (dt, *J* = 7.9, 1.9 Hz, 1H), 7.78 (d, *J* = 1.9 Hz, 1H), 7.69 (d, *J* = 8.7 Hz, 1H), 7.63 (dd, *J* = 7.9, 4.8 Hz, 1H), 7.44 (dd, *J* = 8.7, 1.9 Hz, 1H), 5.30 (s, 2H), 3.33 (s, 3H), 3.00 (s, 2H), 0.88 (s, 6H).

Step 2. To a stirred solution of methyl 3-(5-bromo-1-(cyanomethyl)-2-(pyridin-3-yl)-1*H*-indol-3-yl)-2,2-dimethylpropanoate (1.30 g, 3.05 mmol) in anhydrous THF (39.0 mL) methyl iodide (759 µl, 12.2 mmol) and LiHMDS (1.0 M in THF, 9.15 mL, 9.15 mmol) were added at 0 °C. The resulting mixture was stirred for 16 h at room temperature. The reaction mixture was then quenched with sat. aq. NH_4Cl, extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford methyl 3-(5-bromo-1-(1-cyano-1-methylethyl)-2-(pyridin-3-yl)-1*H*-indol-3-yl)-2,2-dimethylpropanoate (1.04 g, 75% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{23}H_{24}BrN_3O_2$: 456.1; found 455.9.

Step 3. To a stirred solution of methyl 3-(5-bromo-1-(1-cyano-1-methylethyl)-2-(pyridin-3-yl)-1*H*-indol-3-yl)-2,2-dimethylpropanoate (1.00 g, 2.20 mmol) in anhydrous THF (20 mL), DIBAL (25% wt. in toluene, 5.16 mL, 7.70 mmol) was added at –65 °C under an atmosphere of argon gas. The resulting mixture was stirred at –65 °C for 30 minutes. The reaction mixture was then warmed to 0 °C, diluted with EtOAc, and treated by the dropwise addition of sat. aq. potassium sodium tartrate until the separation of two phases. The resulting mixture was stirred for 30 minutes at room temperature, extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford 2-(5-bromo-3-(3-hydroxy-2,2-dimethylpropyl)-2-(pyridin-3-yl)-1*H*-indol-1-yl)-2-methylpropanenitrile (550 mg, 58% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{22}H_{24}BrN_3O$: 428.1; found 427.4; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.69 – 8.61 (m, 2H), 8.01 (d, *J* = 2.0 Hz, 1H), 7.94 (dt, *J* = 7.8, 1.9 Hz, 1H), 7.78 (d, *J* = 9.0 Hz, 1H), 7.54 – 7.47 (m, 1H), 7.41 (dd, *J* = 9.0, 2.0 Hz, 1H), 4.61 (t, *J* = 5.2 Hz, 1H), 2.97 (d, *J* = 5.3 Hz, 2H), 2.42 (s, 2H), 1.80 (s, 6H), 0.54 (s, 6H).

Step 4. To a stirred solution of 2-(5-bromo-3-(3-hydroxy-2,2-dimethylpropyl)-2-(pyridin-3-yl)-1*H*-indol-1-yl)-2-methylpropanenitrile (530 mg, 1.24 mmol) in anhydrous toluene (5.3 mL), bis(pinacolato)diboron (474 mg, 1.86 mmol), Pd(dppf)Cl_2 (91.0 mg, 0.124 mmol) and KOAc (244 mg, 2.49 mmol) were added at room temperature under an atmosphere of argon gas. The reaction mixture was then stirred at 90 °C for 16 h. The reaction mixture was then filtered through a pad of Celite®, the pad was washed with EtOAc, and the filtrate was concentrated under reduced pressure to afford 2-(3-(3-hydroxy-2,2-dimethylpropyl)-2-(pyridin-3-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-1-yl)-2-methylpropanenitrile (820 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{28}H_{36}BN_3O_3$: 474.3; found 474.3.

Step 5. To a stirred solution of 2-(3-(3-hydroxy-2,2-dimethylpropyl)-2-(pyridin-3-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-1-yl)-2-methylpropanenitrile (800 mg, crude) in toluene (16 mL), 1,4-dioxane (5.6 mL), and H_2O (5.6 mL), methyl (3*S*)-1-((2*S*)-3-(4-bromo-1,3-thiazol-2-yl)-2-(((*tert*-butoxy)carbonyl)amino)propanoyl)-1,2-diazinane-3-carboxylate (1.23 g, 2.53 mmol), K_3PO_4 (897 mg, 4.22 mmol) and Pd(dppf)Cl_2 (247 mg, 0.338 mmol) were added at room temperature under an atmosphere of argon gas. The resulting mixture was stirred at 70 °C for 16 h. The reaction mixture was then cooled to room temperature, quenched with H_2O, extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford methyl (3*R*)-1-((3*R*)-3-(((*tert*-butoxy)carbonyl)amino)-3-(4-(1-(1-cyano-1-methylethyl)-3-(3-hydroxy-2,2-dimethylpropyl)-2-(pyridin-3-yl)-1*H*-indol-5-yl)-1,3-thiazol-2-yl)propanoyl)-1,2-diazinane-3-carboxylate (89% purity, 505 mg, 50% yield over 2 steps). LCMS (ESI) *m/z*: [M + H] calcd for $C_{39}H_{49}N_7O_6S$: 744.4 found 744.7.

Step 6. To a stirred solution of methyl (3*R*)-1-((3*R*)-3-(((*tert*-butoxy)carbonyl)amino)-3-(4-(1-(1-cyano-1-methylethyl)-3-(3-hydroxy-2,2-dimethylpropyl)-2-(pyridin-3-yl)-1*H*-indol-5-yl)-1,3-thiazol-2-yl)propanoyl)-1,2-diazinane-3-carboxylate (89% purity, 505 mg, 0.604 mmol) in anhydrous THF (20 mL) and H_2O (13 mL), LiOH•H_2O (86.0 mg, 2.05 mmol) was added at room temperature. The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was then acidified to pH 6 with aqueous HCl (1.0 M), extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced

pressure to afford (3*R*)-1-((3*R*)-3-(((*tert*-butoxy)carbonyl]amino)-3-(4-(1-(1-cyano-1-methylethyl)-3-(3-hydroxy-2,2-dimethylpropyl)-2-(pyridin-3-yl)-1*H*-indol-5-yl)-1,3-thiazol-2-yl)propanoyl)-1,2-diazinane-3-carboxylic acid (503 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{38}H_{47}N_7O_6S$: 730.3; found 730.8.

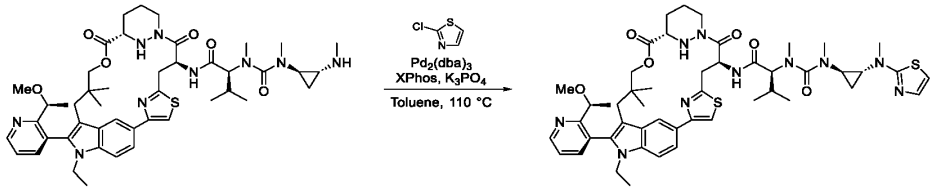
Step 7. To a stirred solution of (3*R*)-1-((3*R*)-3-(((*tert*-butoxy)carbonyl]amino)-3-(4-(1-(1-cyano-1-methylethyl)-3-(3-hydroxy-2,2-dimethylpropyl)-2-(pyridin-3-yl)-1*H*-indol-5-yl)-1,3-thiazol-2-yl)propanoyl)-1,2-diazinane-3-carboxylic acid (500 mg, crude) in DCM (50 mL), HOBt hydrate (525 mg, 3.43 mmol), DIPEA (3.66 mL, 20.6 mmol) and EDCI HCl (3.68 g, 19.2 mmol) were added at 0 °C. The resulting mixture was stirred at room temperature for 16 h. The reaction mixture was then quenched with H_2O, washed with aqueous HCl (1.0 M), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford *tert*-butyl ((6^3*S*,4*S*)-1^1-(2-cyanopropan-2-yl)-10,10-dimethyl-5,7-dioxo-1^2-(pyridin-3-yl)-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)carbamate (277 mg, 65% yield over 2 steps). LCMS (ESI) *m/z*: [M + H] calcd for $C_{38}H_{45}N_7O_5S$: 712.3; found 712.7.

Step 8. To a stirred solution of *tert*-butyl ((6^3*S*,4*S*)-1^1-(2-cyanopropan-2-yl)-10,10-dimethyl-5,7-dioxo-1^2-(pyridin-3-yl)-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)carbamate (225 mg, 0.316 mmol) in anhydrous DCM (5.0 mL), trifluoroacetic acid (1.37 mL, 17.9 mmol) was added dropwise at 0 °C. The resulting mixture was stirred at room temperature for 2 h. The reaction mixture was then quenched with sat. aq. $NaHCO_3$, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford 2-((6^3*S*,4*S*)-4-amino-10,10-dimethyl-5,7-dioxo-1^2-(pyridin-3-yl)-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-1^1-yl)-2-methylpropanenitrile (225 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{33}H_{37}N_7O_3S$: 612.3; found 612.5.

Step 9. To a stirred solution of 2-((6^3*S*,4*S*)-4-amino-10,10-dimethyl-5,7-dioxo-1^2-(pyridin-3-yl)-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-1^1-yl)-2-methylpropanenitrile (220 mg, crude) in DMF (6.6 mL), DIPEA (63 µL, 3.60 mmol) and *N*-methyl-*N*-(methyl((1*R*,2*R*)-2-(*N*-methylacetamido)cyclopropyl)carbamoyl)-*L*-valine (215 mg, 0.718 mmol) were added at 0 °C and the resulting mixture was stirred for 5 minutes. After this time, COMU (308 mg, 0.719 mmol) was added and the resulting mixture was stirred at 0 °C for 2 h. The reaction mixture was then quenched with H_2O, extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase prep-HPLC to afford of (2*S*)-*N*-((6^3*S*,4*S*)-1^1-(2-cyanopropan-2-yl)-10,10-dimethyl-5,7-dioxo-1^2-(pyridin-3-yl)-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)-2-(1,3-dimethyl-3-((1*R*,2*R*)-2-(*N*-methylacetamido)cyclopropyl)ureido)-3-methylbutanamide (148 mg, 54% yield over 2 steps). LCMS (ESI) *m/z*: [M + H] calcd for $C_{47}H_{60}N_{10}O_6S$: 893.4; found 893.8; ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 8.79 – 8.62 (m, 2H), 8.51 – 8.43 (m, 2H), 7.94 – 7.81 (m, 3H), 7.53 (q, *J* = 6.0 Hz, 1H), 5.50 (t, *J* = 8.8 Hz, 1H), 5.12 (d, *J* = 12.2 Hz, 1H), 4.29 – 4.16 (m, 2H), 4.01 (d, *J* = 10.8 Hz, 1H), 3.60 (d, *J* = 12.0 Hz, 1H), 3.51 (d, *J* = 12.0 Hz, 1H), 3.39 – 3.34 (m, 1H), 3.21 – 3.08 (m, 1H), 3.03 – 2.89 (m, 5H), 2.88 – 2.78 (m, 6H), 2.76 – 2.67

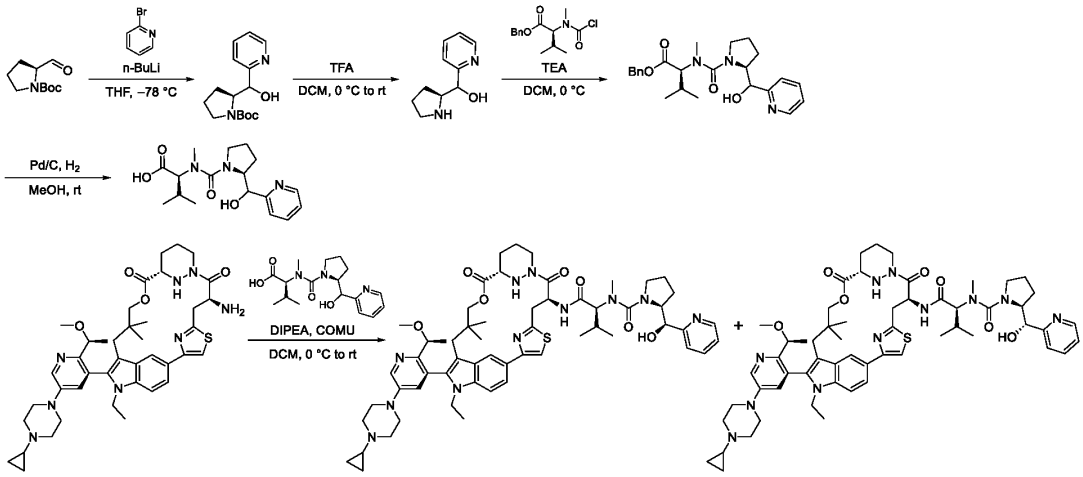
(m, 2H), 2.31 – 2.22 (m, 1H), 2.18 – 2.01 (m, 5H), 1.98 (d, *J* = 12.7 Hz, 3H), 1.87 – 1.76 (m, 2H), 1.76 – 1.69 (m, 3H), 1.59 – 1.43 (m, 1H), 1.26 – 1.17 (m, 2H), 0.95 – 0.78 (m, 9H), 0.32 (br s, 3H).

Example A964: Synthesis of (2*S*)-2-(1,3-dimethyl-3-((1*R*,2*R*)-2-(methyl(thiazol-2-yl)amino)cyclopropyl)ureido)-*N*-((6^3*S*,4*S*)-1^1-ethyl-1^2-(2-((*S*)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)-3-methylbutanamide



Step 1. A mixture of (2*S*)-2-(1,3-dimethyl-3-((1*R*,2*R*)-2-(methylamino)cyclopropyl)ureido)-*N*-((6^3*S*,4*S*)-1^1-ethyl-1^2-(2-((*S*)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)-3-methylbutanamide (200 mg, 0.23 mmol, 1.0 eq), 2-chlorothiazole (20 µL, 0.23 mmol), XPhos (27 mg, 0.06 mmol) and K_3PO_4 (122 mg, 0.575 mmol) in toluene (6.0 mL) was sparged with argon gas. Subsequently $Pd_2(dba)_3$ (11 mg, 0.012 mmol) was added and the resulting mixture was stirred at 110 °C for 16 h. The reaction mixture was then filtered through a pad of Celite® and the filtrate was diluted with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase prep-HPLC to afford (2*S*)-2-(1,3-dimethyl-3-((1*R*,2*R*)-2-(methyl(thiazol-2-yl)amino)cyclopropyl)ureido)-*N*-((6^3*S*,4*S*)-1^1-ethyl-1^2-(2-((*S*)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)-3-methylbutanamide (14.0 mg, 6% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{49}H_{64}N_{10}O_6S_2$: 953.5; found 953.5; ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 8.75 (dd, *J* = 4.6, 1.8 Hz, 1H), 8.46 (s, 1H), 8.41 (d, *J* = 8.7 Hz, 1H), 7.79 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.71 – 7.66 (m, 1H), 7.65 (s, 1H), 7.57 (d, *J* = 8.6 Hz, 1H), 7.52 (dd, *J* = 7.7, 4.7 Hz, 1H), 7.24 (br s, 1H), 6.84 (br s, 1H), 5.55 (t, *J* = 8.9 Hz, 1H), 5.13 (d, *J* = 12.0 Hz, 1H), 4.37 – 4.07 (m, 6H), 3.99 (d, *J* = 10.9 Hz, 1H), 3.57 – 3.54 (m, 2H), 3.25 (d, *J* = 2.9 Hz, 6H), 3.16 – 3.06 (m, 1H), 3.06 – 2.93 (m, 2H), 2.90 (s, 3H), 2.83 (s, 3H), 2.61 – 2.59 (m, 1H), 2.39 (d, *J* = 14.6 Hz, 1H), 2.15 – 2.04 (m, 2H), 1.83 – 1.73 (m, 2H), 1.57 – 1.44 (m, 1H), 1.36 (d, *J* = 6.0 Hz, 3H), 1.26 – 1.20 (m, 2H), 1.17 – 1.10 (m, 1H), 0.95 – 0.80 (m, 12H), 0.31 (s, 3H).

Examples A82 and A213: Synthesis of (2*S*)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-2-((*S*)-hydroxy(pyridin-2-yl)methyl)-*N*-methylpyrrolidine-1-carboxamide and (2*S*)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-2-((*R*)-hydroxy(pyridin-2-yl)methyl)-*N*-methylpyrrolidine-1-carboxamide



Step 1. To a stirred solution of *tert*-butyl (2*S*)-2-formylpyrrolidine-1-carboxylate (5.00 g, 25.1 mmol) and 2-bromopyridine (5.95 g, 37.6 mmol) in anhydrous THF (150 mL), *n*-BuLi (2.5 M in hexanes, 30.1 mL, 75.3 mmol) was added dropwise at –78 °C. The resulting mixture was stirred for 1 h at –78 °C. The reaction mixture was then quenched with H_2O, extracted with DCM, washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford *tert*-butyl (2*S*)-2-(hydroxy(pyridin-2-yl)methyl)pyrrolidine-1-carboxylate (740 mg, 11% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{15}H_{22}N_2O_3$: 279.2; found 279.4.

Step 2. To a stirred solution of *tert*-butyl (2*S*)-2-(hydroxy(pyridin-2-yl)methyl)pyrrolidine-1-carboxylate (740 mg, 2.66 mmol) in anhydrous DCM (7.4 mL), trifluoroacetic acid (9.40 mL, 122 mmol) was added dropwise at 0 °C. The resulting mixture was stirred at room temperature for 2 h. The reaction mixture was then concentrated under reduced pressure to afford (pyridin-2-yl)((2*S*)-pyrrolidin-2-yl)methanol TFA salt (800 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{10}H_{14}N_2O$: 179.1; found 179.3.

Step 3. To a stirred solution of (pyridin-2-yl)((2*S*)-pyrrolidin-2-yl)methanol TFA salt (800 mg, crude) and triethylamine (2.60 mL, 18.9 mmol) in anhydrous DCM (10 mL), benzyl (2*S*)-2-((chlorocarbonyl)(methyl)amino)-3-methylbutanoate (802 mg, 2.83 mmol) was added at 0 °C. The resulting mixture was warmed to room temperature and stirred for 16 h. The reaction mixture was then quenched with H_2O, extracted with DCM (x3), washed with an aqueous HCl solution (0.1 M), treated with brine, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by

normal phase flash column chromatography to afford benzyl (2*S*)-2-(((2*S*)-2-(hydroxy(pyridin-2-yl)methyl)pyrrolidine-1-carbonyl)(methyl)amino)-3-methylbutanoate (597 mg, 53% yield over 2 steps). LCMS (ESI) *m/z*: [M + H] calcd for $C_{24}H_{31}N_3O_4$: 426.2; found 426.5.

Step 4. To a stirred solution of benzyl (2*S*)-2-(((2*S*)-2-(hydroxy(pyridin-2-yl)methyl)pyrrolidine-1-carbonyl)(methyl)amino)-3-methylbutanoate (100 mg, 0.235 mmol) in MeOH (2.0 mL), Pd/C (10% wt., 2.0 mg) was added under an atmosphere or argon gas. The reaction flask was evacuated and backfilled twice with hydrogen gas, and the resulting mixture was stirred for 16 h at room temperature under an atmosphere of hydrogen gas. The reaction mixture was then filtered through a pad of Celite®, the pad washed with MeOH, and the filtrate was concentrated under reduced pressure to afford (2*S*)-2-(((2*S*)-2-(hydroxy(pyridin-2-yl)methyl)pyrrolidine-1-carbonyl)(methyl)amino)-3-methylbutanoic acid (75 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{17}H_{25}N_3O_4$: 336.2; found 336.4.

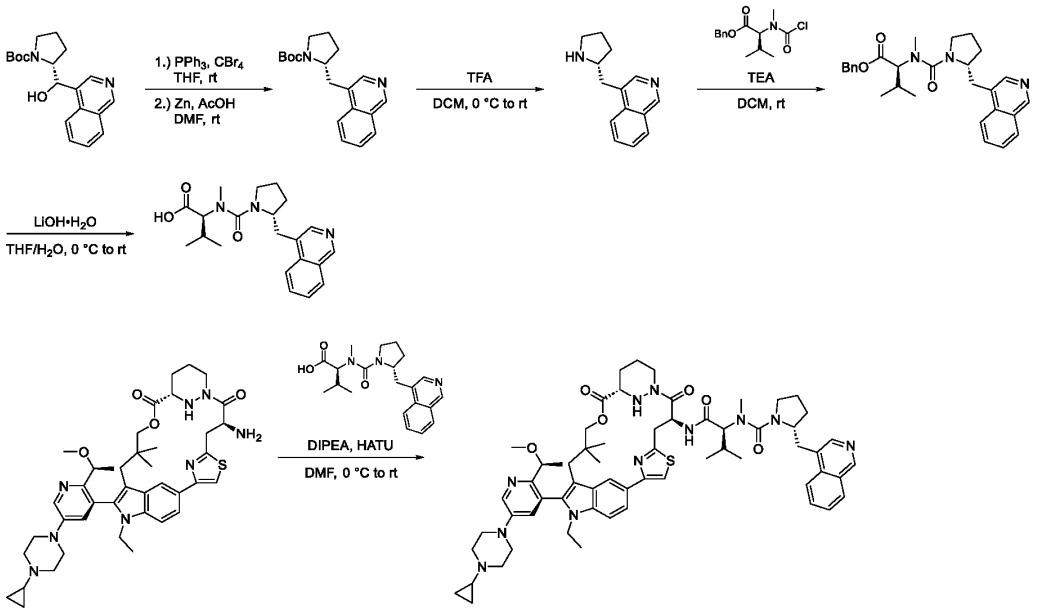
Step 5. To a stirred solution of (6^3*S*,4*S*)-4-amino-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-5,7-dione (100 mg, 0.132 mmol) in anhydrous DMF (2.0 mL), DIPEA (219 µL, 1.26 mmol) and (2*S*)-2-(((2*S*)-2-(hydroxy(pyridin-2-yl)methyl)pyrrolidine-1-carbonyl)(methyl)amino)-3-methylbutanoic acid (51 mg, crude) were added at 0 °C. The mixture was stirred for 15 minutes, after which time COMU (81 mg, 0.19 mmol) was added. The resulting mixture was stirred for 1 h at 0 °C and was then stirred at room temperature for 16 h. The reaction mixture was then quenched with H_2O, extracted with EtOAc, washed with sat. aq. $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase prep-HPLC to afford two separated diastereomers of (2*S*)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-2-(hydroxy(pyridin-2-yl)methyl)-*N*-methylpyrrolidine-1-carboxamide.

A213: (12.2 mg, 9% yield); LCMS (ESI) *m/z*: [M + H] calcd for $C_{58}H_{77}N_{11}O_7S$: 1072.6; found 1072.2; ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 9.38 (br s, 1H), 8.75 – 8.65 (m, 1H), 8.49 – 8.40 (m, 2H), 7.87 (s, 1H), 7.86 – 7.78 (m, 1H), 7.79 – 7.71 (m, 1H), 7.60 – 7.48 (m, 2H), 7.38 – 7.32 (m, 1H), 7.28 – 7.11 (m, 1H), 5.67 – 5.58 (m, 1H), 5.52 – 5.41 (m, 1H), 5.10 (d, *J* = 12.0 Hz, 1H), 4.92 – 4.83 (m, 1H), 4.72 – 4.60 (m, 1H), 4.43 – 4.01 (m, 6H), 3.94 (d, *J* = 10.8 Hz, 1H), 3.65 – 3.42 (m, 3H), 3.31 – 3.13 (m, 10H), 3.14 – 3.00 (m, 1H), 2.99 – 2.88 (m, 1H), 2.80 – 2.61 (m, 4H), 2.61 (s, 3H), 2.42 – 2.36 (m, 1H), 2.25 – 2.16 (m, 1H), 2.15 – 2.02 (m, 1H), 1.96 – 1.72 (m, 3H), 1.72 – 1.41 (m, 4H), 1.32 (d, *J* = 6.0 Hz, 3H), 0.92 (s, 3H), 0.91 – 0.78 (m, 9H), 0.53 – 0.37 (m, 2H), 0.37 – 0.25 (m, 5H).

A82: (37.4 mg, 26% yield); LCMS (ESI) *m/z*: [M + H] calcd for $C_{58}H_{77}N_{11}O_7S$: 1072.6; found 1072.2; ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 8.62 (d, *J* = 8.6 Hz, 1H), 8.49 (d, *J* = 4.7 Hz, 1H), 8.47 – 8.41 (m, 2H), 7.81 (s, 1H), 7.79 – 7.69 (m, 2H), 7.54 (d, *J* = 8.6 Hz, 1H), 7.49 (d, *J* = 7.9 Hz, 1H), 7.27 – 7.17 (m, 2H), 5.51 – 5.41 (m, 1H), 5.37 (d, *J* = 4.7 Hz, 1H), 5.09 (d, *J* = 12.1 Hz, 1H), 4.88 – 4.78 (m, 1H), 4.63 – 4.52 (m, 1H), 4.35 – 4.08 (m, 6H), 3.61 – 3.47 (m, 2H), 3.39 – 3.37 (m, 2H), 3.31 – 3.24 (m, 7H), 3.22 (s, 3H), 2.94 (d, *J* = 14.2 Hz, 1H), 2.83 – 2.73 (m, 5H), 2.70 (s, 3H), 2.46 – 2.35 (m, 1H), 2.26 – 2.14 (m, 1H),

2.14 – 2.04 (m, 1H), 1.88 – 1.74 (m, 4H), 1.70 – 1.59 (m, 1H), 1.55 – 1.41 (m, 2H), 1.32 (d, *J* = 6.0 Hz, 3H), 0.95 – 0.82 (m, 9H), 0.79 (d, *J* = 6.7 Hz, 3H), 0.53 – 0.45 (m, 2H), 0.44 – 0.36 (m, 2H), 0.32 (s, 3H).

Example A54: Synthesis of (2*R*)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-2-(isoquinolin-4-ylmethyl)-*N*-methylpyrrolidine-1-carboxamide



Step 1. To a stirred solution of *tert*-butyl (2*R*)-2-(hydroxy(isoquinolin-4-yl)methyl)pyrrolidine-1-carboxylate (336 mg, 1.02 mmol) in anhydrous THF (20 mL), triphenylphosphine (564 mg, 2.15 mmol) and carbon tetrabromide (679 mg, 2.05 mmol) were added at room temperature and the resulting mixture was stirred at room temperature for 3 days. The reaction mixture was then diluted with DCM, filtered through a pad of Celite®, concentrated under reduced pressure, and dissolved in DMF (8.4 mL). Subsequently, zinc powder (334 mg, 5.12 mmol) and acetic acid (2.52 mL) were added and the resulting mixture was stirred for 3 h at room temperature. The reaction mixture was then diluted with H_2O, neutralized to pH 7 with sat. aq. $NaHCO_3$, extracted with Et_2O, dried over anhydrous $MgSO_4$, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford *tert*-butyl (2*R*)-2-((isoquinolin-4-yl)methyl)pyrrolidine-1-carboxylate (88% purity, 171 mg, 47% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{19}H_{24}N_2O_2$: 313.2 found 313.9.

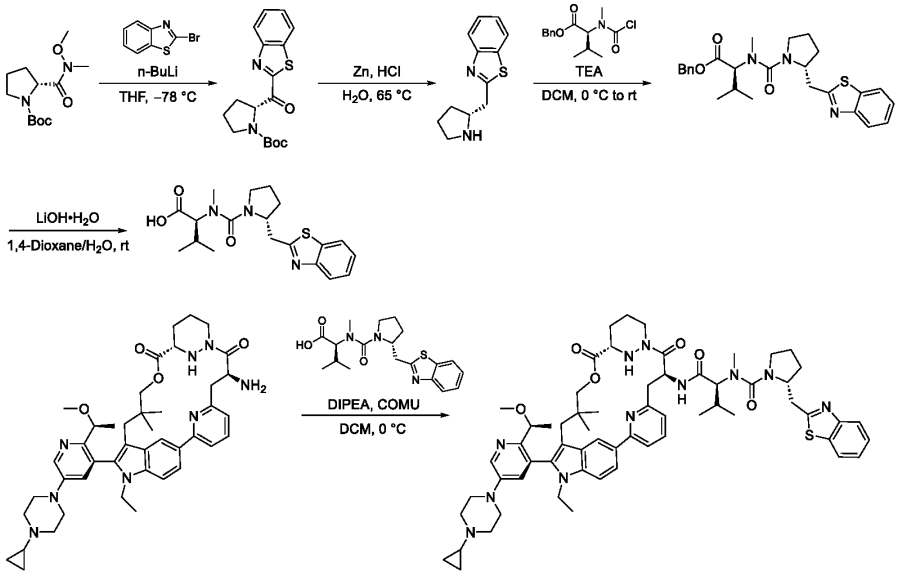
Step 2. To a stirred solution of *tert*-butyl (2*R*)-2-((isoquinolin-4-yl)methyl)pyrrolidine-1-carboxylate (88% purity, 169 mg, 0.476 mmol) in anhydrous DCM (5.1 mL), trifluoroacetic acid (1.46 mL, 19.0 mmol) was added dropwise at 0 °C. The resulting mixture was stirred for 16 h at room temperature. The reaction mixture was then basified to pH 8 with sat. aq. $NaHCO_3$, extracted with a mixture 3:1 vol. mixture of CH_3Cl:MeOH, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to afford 4-(((2*R*)-pyrrolidin-2-yl)methyl)isoquinoline (98.0 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{14}H_{16}N_2$: 213.1 found 213.2.

Step 3. To a stirred solution of 4-(((2*R*)-pyrrolidin-2-yl)methyl)isoquinoline (96.0 mg, crude) in anhydrous DCM (1.9 mL), triethylamine (196 µL, 1.36 mmol) and benzyl (2*S*)-2-((chlorocarbonyl)(methyl)amino)-3-methylbutanoate (176 mg, 0.620 mmol) were added at room temperature. The resulting mixture was stirred for 1 h at room temperature. The reaction mixture was then washed with H_2O and the organic extract was dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford benzyl (2*S*)-2-(((2*R*)-2-((isoquinolin-4-yl)methyl)pyrrolidine-1-carbonyl)(methyl)amino)-3-methylbutanoate (158 mg, 72% yield over 2 steps). LCMS (ESI) *m/z*: [M + H] calcd for $C_{28}H_{33}N_3O_3$: 460.3; found 461.1.

Step 4. To a stirred solution of benzyl (2*S*)-2-(((2*R*)-2-((isoquinolin-4-yl)methyl)pyrrolidine-1-carbonyl)(methyl)amino)-3-methylbutanoate (158 mg, 0.344 mmol) in THF (1.6 mL), a solution of lithium hydroxide monohydrate (41.0 mg, 0.977 mmol) in H_2O (1.6 mL) was added at 0 °C. The resulting mixture was stirred for 1 h at 0 °C and was then stirred for 3 days at room temperature. Subsequently, additional lithium hydroxide monohydrate (7.0 mg, 0.17 mmol) was added and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was then washed with Et_2O, and the aqueous extract was acidified to pH 5 with an aqueous HCl solution (1.0 M) and was extracted with a 3:1 vol mixture of DCM:MeOH. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford (2*S*)-2-(((2*R*)-2-((isoquinolin-4-yl)methyl)pyrrolidine-1-carbonyl)(methyl)amino)-3-methylbutanoic acid (73.0 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{21}H_{27}N_3O_3$: 370.2; found 370.8.

Step 5. To a stirred solution of (6^3*S*,4*S*)-4-amino-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-5,7-dione (80.0 mg, 0.106 mmol) and (2*S*)-2-(((2*R*)-2-((isoquinolin-4-yl)methyl)pyrrolidine-1-carbonyl)(methyl)amino)-3-methylbutanoic acid (59.0 mg, crude) in anhydrous DMF (2.4 mL), DIPEA (55 µL, 0.32 mmol) was added followed by HATU (64 mg, 0.17 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 15 minutes, after which time it was stirred at room temperature for 30 minutes. The reaction mixture was then quenched with H_2O, extracted with DCM, washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase prep-HPLC to afford (2*R*)-*N*-((2*S*)-1-((((6^3*S*,4*S*,*Z*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-2-(isoquinolin-4-ylmethyl)-*N*-methylpyrrolidine-1-carboxamide (79.8 mg, 68% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{62}H_{79}N_{11}O_6S$: 1106.6; found 1106.6; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.20 (s, 1H), 8.62 (d, *J* = 8.5 Hz, 1H), 8.44 – 8.41 (m, 3H), 8.38 (d, *J* = 8.9 Hz, 1H), 8.12 (d, *J* = 8.0 Hz, 1H), 7.89 – 7.82 (m, 1H), 7.73 – 7.69 (m, 1H), 7.68 (s, 1H), 7.65 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.51 (d, *J* = 8.6 Hz, 1H), 7.19 (d, *J* = 2.9 Hz, 1H), 5.63 (t, *J* = 9.0 Hz, 1H), 5.16 (d, *J* = 12.2 Hz, 1H), 4.33 – 4.09 (m, 6H), 4.05 (d, *J* = 10.9 Hz, 1H), 3.86 – 3.76 (m, 1H), 3.70 – 3.59 (m, 1H), 3.55 (s, 2H), 3.41 – 3.36 (m, 1H), 3.32 – 3.30 (m, 1H), 3.25 – 3.17 (m, 7H), 3.13 – 3.05 (m, 1H), 2.92 (s, 3H), 2.91 – 2.87 (m, 1H), 2.82 – 2.74 (m, 1H), 2.74 – 2.69 (m, 1H), 2.68 – 2.63 (m, 4H), 2.41 (d, *J* = 14.2 Hz, 1H), 2.18 – 2.04 (m, 2H), 1.93 – 1.85 (m, 1H), 1.84 – 1.73 (m, 2H), 1.70 – 1.59 (m, 4H), 1.57 – 1.45 (m, 1H), 1.32 (d, *J* = 6.2 Hz, 3H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.92 – 0.81 (m, 9H), 0.47 – 0.39 (m, 2H), 0.38 – 0.26 (m, 5H).

Example A623: Synthesis of (2*R*)-2-(benzo[d]thiazol-2-ylmethyl)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-6(1,3)-pyridazina-2(2,6)-pyridinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methylpyrrolidine-1-carboxamide



Step 1. To a stirred solution of 7-bromo-1,3-benzothiazole (1.99 g, 9.29 mmol) in anhydrous THF (20 mL), n-BuLi (2.5 M in hexanes, 3.72 mL, 9.30 mmol) was added dropwise at –78 °C and the mixture was stirred at –78 °C for 1 h. This mixture was then transferred by cannula to a stirred solution of *tert*-butyl (2*R*)-2-(methoxy(methyl)carbamoyl)pyrrolidine-1-carboxylate (2.00 g, 7.74 mmol) in anhydrous THF (40 mL) at –78 °C. The resulting mixture was stirred at –78 °C for 1.5 h. The reaction mixture was then warmed to 0 °C, quenched with H_2O, extracted with DCM, washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase flash column chromatography to afford *tert*-butyl (2*R*)-2-(1,3-benzothiazole-2-carbonyl)pyrrolidine-1-carboxylate (960 mg, 37% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{17}H_{20}N_2O_3S$: 333.1 found 332.6.

Step 2. To a stirred solution of *tert*-butyl (2*R*)-2-(1,3-benzothiazole-2-carbonyl)pyrrolidine-1-carboxylate (950 mg, 2.86 mmol) in concentrated HCl (44 mL), zinc powder (1.68 g, 25.7 mmol) was added in portions. The resulting mixture was stirred at 65 °C for 18 h. The reaction mixture was then cooled to 0 °C, basified to pH 8 by the slow addition of Na_2CO_3, extracted with DCM, washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford 2-(((2*R*)-pyrrolidin-2-yl)methyl)-1,3-benzothiazole (840 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{12}H_{14}N_2S$: 219.1; found 218.7.

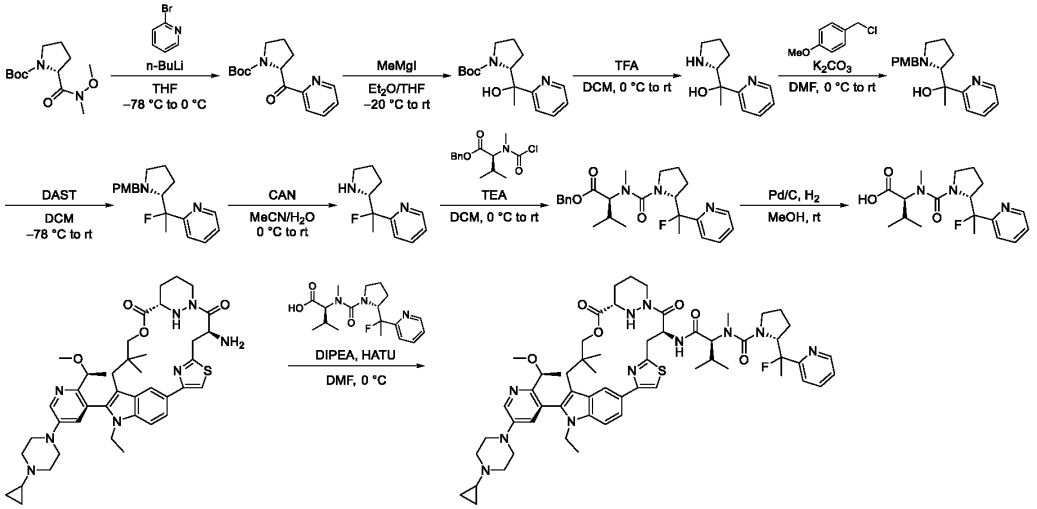
Step 3. To a stirred solution of benzyl (2*S*)-2-((chlorocarbonyl)(methyl)amino)-3-methylbutanoate (570 mg, 2.01 mmol) in anhydrous DCM (29 mL), triethylamine (840 µL, 6.03 mmol) and 2-(((2*R*)-pyrrolidin-2-yl)methyl)-1,3-benzothiazole (830 mg, crude) were added at 0 °C. The resulting mixture was stirred for 30 minutes at 0 °C and was then stirred for 16 h at room temperature. The reaction mixture was

then diluted with H_2O, extracted with DCM, washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford benzyl (2*S*)-2-(((2*R*)-2-((1,3-benzothiazol-2-yl)methyl)pyrrolidine-1-carbonyl)(methyl)amino)-3-methylbutanoate (168 mg, 17% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{26}H_{31}N_3O_3S$: 466.2; found 466.0.

Step 4. To a stirred solution of benzyl (2*S*)-2-(((2*R*)-2-((1,3-benzothiazol-2-yl)methyl)pyrrolidine-1-carbonyl)(methyl)amino)-3-methylbutanoate (145 mg, 0.311 mmol) in 1,4-dioxane (7.2 mL) and H_2O (2.2 mL), $LiOH•H_2O$ (38.0 mg, 0.906 mmol) was added. The reaction mixture was stirred at room temperature for 2 days, after which time it was concentrated under reduced to afford lithium (2*S*)-2-(((2*R*)-2-((1,3-benzothiazol-2-yl)methyl)pyrrolidine-1-carbonyl)(methyl)amino)-3-methylbutanoate (190 mg, crude). This material was used in the next step without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{19}H_{25}N_3O_3S$: 376.2; found 375.6.

Step 5. To a stirred solution of (6^3*S*,4*S*)-4-amino-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-6(1,3)-pyridazina-2(2,6)-pyridinacycloundecaphane-5,7-dione (98.0 mg, 0.131 mmol) and lithium (2*S*)-2-(((2*R*)-2-((1,3-benzothiazol-2-yl)methyl)pyrrolidine-1-carbonyl)(methyl)amino)-3-methylbutanoate (84 mg, crude) in anhydrous DCM (5.0 mL), DIPEA (219 µL, 1.26 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 10 minutes, after which time COMU (161 mg, 0.376 mmol) was added. The resulting mixture was stirred at 0 °C for 2 h. The reaction mixture was then quenched with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, purified by reversed-phase prep-HPLC and further purified by normal phase prep-TLC to afford (2*R*)-2-(benzo[d]thiazol-2-ylmethyl)-*N*-((2*S*)-1-((((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-6(1,3)-pyridazina-2(2,6)-pyridinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-N-methylpyrrolidine-1-carboxamide (4.5 mg, 3% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{62}H_{79}N_{11}O_6S$: 1106.6; found 1106.6; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.80 (s, 1H), 8.47 (d, *J* = 2.9 Hz, 1H), 8.04 (d, *J* = 7.9 Hz, 1H), 7.99 (d, *J* = 8.1 Hz, 1H), 7.97 – 7.93 (m, 1H), 7.78 – 7.75 (m, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.58 (t, *J* = 7.7 Hz, 1H), 7.53 – 7.49 (m, 2H), 7.44 – 7.40 (m, 1H), 7.27 (d, *J* = 2.9 Hz, 1H), 7.02 – 6.96 (m, 1H), 5.93 – 5.85 (m, 1H), 5.49 – 5.42 (m, 1H), 4.42 – 4.36 (m, 1H), 4.35 – 4.31 (m, 1H), 4.16 – 4.06 (m, 2H), 4.03 – 3.92 (m, 1H), 3.84 (d, *J* = 11.0 Hz, 1H), 3.82 – 3.76 (m, 1H), 3.76 – 3.72 (m, 1H), 3.63 (d, *J* = 10.6 Hz, 1H), 3.52 (dd, *J* = 14.5, 3.8 Hz, 1H), 3.45 – 3.39 (m, 1H), 3.30 (s, 2H), 3.27 – 3.18 (m, 6H), 3.13 – 3.07 (m, 1H), 3.02 (d, *J* = 13.1 Hz, 1H), 2.96 (s, 3H), 2.88 – 2.76 (m, 2H), 2.68 (t, *J* = 5.1 Hz, 4H), 2.62 (s, 3H), 2.03 – 1.93 (m, 3H), 1.85 – 1.74 (m, 2H), 1.69 – 1.53 (m, 4H), 1.39 (d, *J* = 6.2 Hz, 3H), 1.13 – 1.06 (m, 3H), 0.86 (d, *J* = 6.5 Hz, 3H), 0.80 (d, *J* = 6.6 Hz, 3H), 0.73 – 0.67 (m, 3H), 0.62 (s, 3H), 0.46 – 0.42 (m, 2H), 0.36 – 0.32 (m, 2H).

Example A273: Synthesis of (2*R*)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-2-(1-fluoro-1-(pyridin-2-yl)ethyl)-*N*-methylpyrrolidine-1-carboxamide



Step 1. To a stirred solution of 2-bromopyridine (4.50 g, 28.5 mmol) in anhydrous THF (130 mL), n-BuLi (2.5 M in hexanes, 22.8 mL, 57.0 mmol) was added dropwise at –78 °C under an atmosphere of argon gas. The resulting mixture was stirred at –78 °C for 1 h, after which time it was transferred via cannula to a solution of *tert*-butyl (2*R*)-2-(methoxy(methyl)carbamoyl)pyrrolidine-1-carboxylate (5.00 g, 19.4 mmol) in anhydrous THF (20 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 90 minutes. Subsequently, the mixture was warmed 0 °C, quenched by the slow addition of H_2O, extracted with DCM, washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford *tert*-butyl (2*R*)-2-(pyridine-2-carbonyl)pyrrolidine-1-carboxylate (2.90 g, 54% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{15}H_{20}N_2O_3$: 277.2; found 276.9.

Step 2. To a stirred solution of CH_3MgI (3.0 M in Et_2O, 1.76 mL, 5.28 mol) in anhydrous THF (60 mL), a solution of *tert*-butyl (2*R*)-2-(pyridine-2-carbonyl)pyrrolidine-1-carboxylate (500 mg, 1.81 mmol) in anhydrous THF (15 mL) was slowly added at –20 °C under an atmosphere of argon gas. The resulting mixture was gradually warmed to room temperature and was stirred for 16 hours. The reaction mixture was then quenched with sat. aq. NH_4Cl, extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford *tert*-butyl (2*R*)-2-(1-hydroxy-1-(pyridin-2-yl)ethyl)pyrrolidine-1-carboxylate (438 mg, 83% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{16}H_{24}N_2O_3$: 293.2; found 293.0.

Step 3. To a stirred solution of *tert*-butyl (2*R*)-2-(1-hydroxy-1-(pyridin-2-yl)ethyl)pyrrolidine-1-carboxylate (435 mg, 1.49 mmol) in anhydrous DCM (4.4 mL), trifluoroacetic acid (5.64 mL, 73.7 mmol) was added dropwise at 0 °C. The resulting mixture was warmed to room temperature and was stirred for 2.5 h. The reaction mixture was then concentrated under reduced pressure, the resulting residue was suspended in toluene, and the suspension was concentrated under reduced pressure to afford 1-(pyridin-

2-yl)-1-((2*R*)-pyrrolidin-2-yl)ethan-1-ol TFA salt (825 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{20}H_{29}FN_2O_5S$: 193.1; found 193.0.

Step 4. To a stirred solution of 1-(pyridin-2-yl)-1-((2*R*)-pyrrolidin-2-yl)ethan-1-ol TFA salt (1.90 g, crude) and potassium carbonate (5.14 g, 37.2 mmol) in anhydrous DMF (57 mL), 4-methoxybenzyl chloride (2.51 mL, 18.6 mmol) was added dropwise at 0 °C. The resulting mixture was warmed to room temperature and stirred for 16 h. The reaction mixture was then cooled to 0 °C, neutralized to pH 7 by the addition of an aqueous HCl solution (0.5 M), extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford 1-((2*R*)-1-((4-methoxyphenyl)methyl)pyrrolidin-2-yl)-1-(pyridin-2-yl)ethan-1-ol (1.13 g, 99% yield over 2 steps). LCMS (ESI) *m/z*: [M + H] calcd for $C_{19}H_{24}N_2O_2$: 313.2; found 313.2.

Step 5. To a stirred solution of 1-((2*R*)-1-((4-methoxyphenyl)methyl)pyrrolidin-2-yl)-1-(pyridin-2-yl)ethan-1-ol (1.13 g, 3.62 mmol) in dry DCM (70 mL), DAST (1.12 mL, 8.48 mmol) was added at –78 °C. The resulting mixture was stirred at –78 °C for 2 h and was then warmed to room temperature and stirred overnight. The reaction mixture was then quenched with sat. aq. $NaHCO_3$, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford 2-(1-fluoro-1-((2*R*)-1-((4-methoxyphenyl)methyl)pyrrolidin-2-yl)ethyl)pyridine (480 mg, 42% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{19}H_{23}FNO_2$: 315.2; found 315.0.

Step 6. To a stirred solution of 2-(1-fluoro-1-((2*R*)-1-((4-methoxyphenyl)methyl)pyrrolidin-2-yl)ethyl)pyridine (480 mg, 1.53 mmol) in anhydrous MeCN (24 mL), a solution of CAN (3.82 g, 6.97 mmol) in H_2O (12 mL) was added dropwise at 0 °C. The resulting mixture was warmed to room temperature and stirred for 16 h. The reaction mixture was then concentrated under reduced pressure to afford 2-(1-fluoro-1-((2*R*)-pyrrolidin-2-yl)ethyl)pyridine (370 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{11}H_{15}FN_2$: 195.1; found 195.1.

Step 7. To a stirred solution of benzyl (2*S*)-2-((chlorocarbonyl)(methyl)amino)-3-methylbutanoate (810 mg, 2.85 mmol) in DCM (11 mL), a solution of triethylamine (2.65 mL, 19.1 mmol) and 2-(1-fluoro-1-((2*R*)-pyrrolidin-2-yl)ethyl)pyridine (370 mg, crude) in DCM (5.0 mL) were added dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 30 minutes, after which time it was warmed to room temperature and stirred for 16 hours. The reaction mixture was then quenched with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressured, and purified by normal phase flash column chromatography to afford two separated epimers of benzyl (2*S*)-2-(((2*R*)-2-(1-fluoro-1-(pyridin-2-yl)ethyl)pyrrolidine-1-carbonyl)(methyl)amino)-3-methylbutanoate. *Isomer 1* was taken forward to the next reaction.

Isomer A: (370 mg, 55% yield over 2 steps); LCMS (ESI) *m/z*: [M + H] calcd for $C_{25}H_{32}FN_3O_3$: 442.2; found 442.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 – 8.55 (m, 1H), 7.87 – 7.81 (m, 1H), 7.49 – 7.44 (m, 1H), 7.40 – 7.28 (m, 6H), 5.20 – 5.08 (m, 2H), 5.00 – 4.87 (m, 1H), 4.01 (d, *J* = 10.4 Hz, 1H), 3.24 – 3.16 (m, 2H), 2.95 (s, 3H), 2.21 – 2.10 (m, 1H), 1.57 – 1.48 (m, 3H), 1.46 – 1.38 (m, 3H), 0.93 (dd, *J* = 6.5, 1.5 Hz, 6H), 0.89 – 0.78 (m, 1H).

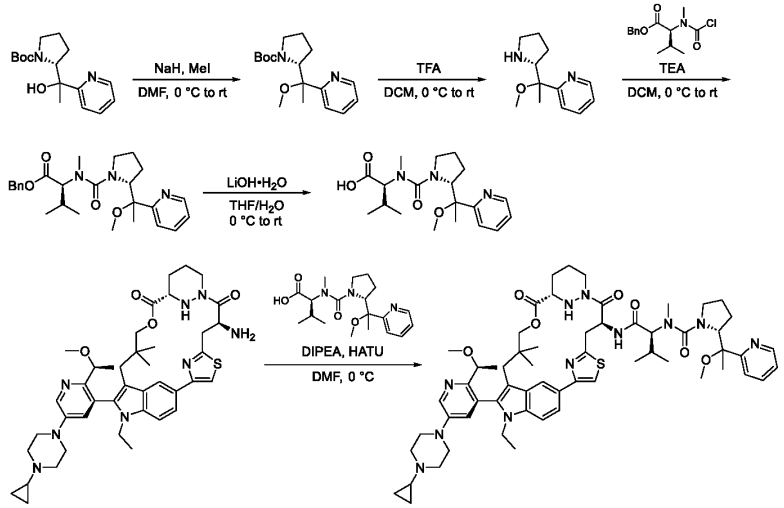
Isomer B: (65 mg, 10% yield over 2 steps); LCMS (ESI) *m/z*: [M + H] calcd for $C_{25}H_{32}FN_3O_3$: 442.2; found 442.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 – 8.44 (m, 1H), 7.77 – 7.71 (m, 1H), 7.45 – 7.41 (m, 1H), 7.40 – 7.31 (m, 5H), 7.27 – 7.22 (m, 1H), 5.13 – 5.05 (m, 2H), 4.73 – 4.62

(m, 1H), 3.86 – 3.81 (m, 1H), 3.11 – 3.05 (m, 2H), 2.83 (s, 3H), 2.10 – 1.99 (m, 1H), 1.89 – 1.80 (m, 2H), 1.67 – 1.59 (m, 3H), 1.58 – 1.47 (m, 2H), 0.82 (dd, *J* = 12.8, 6.6 Hz, 6H).

Step 8. A solution of benzyl (2*S*)-2-(((2*R*)-2-(1-fluoro-1-(pyridin-2-yl)ethyl)pyrrolidine-1-carbonyl)(methyl)amino)-3-methylbutanoate (*Isomer A* from previous reaction, 350 mg, 0.793 mmol) in MeOH (18 mL) was purged with argon gas for 5 minutes. Subsequently, Pd/C (10% wt., 49 mg) was added, the headspace of the reaction flask was evacuated and backfilled with hydrogen gas three times, and the reaction mixture was stirred at room temperature under atmosphere of hydrogen gas for 2.5 h. The mixture was then filtered through a pad of Celite®, the pad was washed with MeOH, and the filtrate was concentrated under reduced pressure to afford (2*S*)-2-(((2*R*)-2-(1-fluoro-1-(pyridin-2-yl)ethyl)pyrrolidine-1-carbonyl)(methyl)amino)-3-methylbutanoic acid (299 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{18}H_{26}FN_3O_3$: 352.2; found 352.1.

Step 9. To a stirred solution of (2*S*)-2-(((2*R*)-2-(1-fluoro-1-(pyridin-2-yl)ethyl]pyrrolidine-1-carbonyl)(methyl)amino)-3-methylbutanoic acid (153 mg, crude) in anhydrous DMF (6.0 mL), DIPEA (210 µL, 1.19 mmol) and (6^3*S*,4*S*)-4-amino-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-5,7-dione (100 mg, 0.132 mmol) were added at 0 °C. The mixture was stirred for 5 minutes at 0 °C, after which time HATU (68 mg, 0.18 mmol) was added. The resulting mixture was stirred for 1 h at 0 °C. The reaction mixture was then quenched with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase prep-HPLC to afford (2*R*)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-2-(1-fluoro-1-(pyridin-2-yl)ethyl)-*N*-methylpyrrolidine-1-carboxamide (68.0 mg, 47% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{59}H_{78}FN_{11}O_6S$: 1088.6; found 1088.5; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 – 8.58 (m, 1H), 8.47 – 8.41 (m, 2H), 8.36 (d, *J* = 9.3 Hz, 1H), 7.87 (td, *J* = 7.8, 1.8 Hz, 1H), 7.79 (s, 1H), 7.71 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.55 – 7.51 (m, 2H), 7.38 – 7.32 (m, 1H), 7.20 (d, *J* = 2.9 Hz, 1H), 5.66 (t, *J* = 9.0 Hz, 1H), 5.17 (d, *J* = 12.1 Hz, 1H), 5.14 – 5.03 (m, 1H), 4.31 – 4.11 (m, 5H), 4.02 (d, *J* = 10.9 Hz, 1H), 3.61 – 3.51 (m, 2H), 3.50 – 3.42 (m, 1H), 3.41 – 3.32 (m, 2H), 3.25 – 3.18 (m, 8H), 3.04 – 2.98 (m, 1H), 2.96 (s, 3H), 2.91 (d, *J* = 14.2 Hz, 1H), 2.83 – 2.71 (m, 1H), 2.71 – 2.64 (m, 4H), 2.49 – 2.40 (m, 1H), 2.17 – 2.06 (m, 2H), 1.85 – 1.77 (m, 3H), 1.68 – 1.64 (m, 1H), 1.64 – 1.56 (m, 5H), 1.55 – 1.47 (m, 1H), 1.33 (d, *J* = 6.0 Hz, 3H), 0.95 – 0.86 (m, 12H), 0.46 – 0.41 (m, 2H), 0.37 – 0.31 (m, 5H).

Example A252: Synthesis of (2*R*)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-2-(1-methoxy-1-(pyridin-2-yl)ethyl)-*N*-methylpyrrolidine-1-carboxamide



Step 1. To a stirred solution of *tert*-butyl (2*R*)-2-(1-hydroxy-1-(pyridin-2-yl)ethyl)pyrrolidine-1-carboxylate (600 mg, 2.05 mmol) in anhydrous DMF (6.0 mL), methyl iodide (420 µL, 6.75 mmol) was added at 0 °C under inert atmosphere. The mixture was stirred for 5 minutes, after which time NaH (60% dispersion in mineral oil, 308 mg, 12.8 mmol) was slowly added in portions. The resulting mixture was gradually warmed to room temperature and was stirred for 16 h. The reaction mixture was quenched with the addition of brine, extracted with a 3:1 vol. mixture of Et_2O:EtOAc, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase prep-TLC to afford two separated epimers of *tert*-butyl (2*R*)-2-(1-methoxy-1-(pyridin-2-yl)ethyl)pyrrolidine-1-carboxylate.

Isomer A: (460 mg, 73% yield); LCMS (ESI) *m/z*: [M + H] calcd for $C_{17}H_{26}N_2O_3$: 307.2; found 307.2; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.57 – 8.49 (m, 1H), 7.76 – 7.67 (m, 1H), 7.37 – 7.30 (m, 1H), 7.29 – 7.19 (m, 1H), 4.05 – 3.95 (m, 1H), 3.49 – 3.32 (m, 1H), 3.04 (s, 3H), 2.99 – 2.88 (m, 1H), 2.09 – 1.96 (m, 1H), 1.83 – 1.66 (m, 1H), 1.62 – 1.49 (m, 4H), 1.36 – 1.27 (m, 1H), 1.25 – 1.04 (m, 9H).

Isomer B: (95 mg, 15% yield); LCMS (ESI) *m/z*: [M + H] calcd for $C_{17}H_{26}N_2O_3$: 307.2; found 307.2; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.58 – 8.51 (m, 1H), 7.83 – 7.74 (m, 1H), 7.49 – 7.42 (m, 1H), 7.31 – 7.19 (m, 1H), 4.25 – 4.16 (m, 1H), 3.55 – 3.40 (m, 1H), 3.17 (s, 3H), 3.13 – 3.03 (m, 1H), 1.83 – 1.67 (m, 2H), 1.65 – 1.57 (m, 1H), 1.53 (s, 3H), 1.41 – 1.33 (m, 9H), 1.20 – 1.12 (m, 1H).

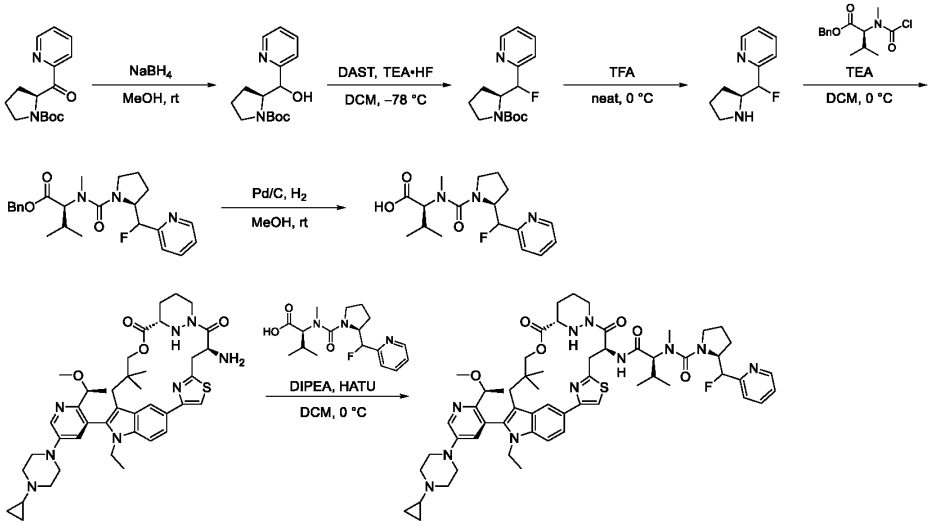
Step 2. To a stirred solution of *tert*-butyl (2*R*)-2-(1-methoxy-1-(pyridin-2-yl)ethyl)pyrrolidine-1-carboxylate (*Isomer A* from previous reaction, 110 mg, 0.359 mmol) in anhydrous DCM (1.0 mL), trifluoroacetic acid (1.37 mL, 18.0 mmol) was added dropwise at 0 °C. The resulting mixture was warmed to room temperature and was stirred for 2.5 h. The reaction mixture was then concentrated under reduced pressure and the resulting residue was dried by suspension and evaporation in toluene five times to afford 2-(1-methoxy-1-((2*R*)-pyrrolidin-2-yl)ethyl)pyridine TFA salt (120 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{12}H_{18}N_2O$: 207.1; found 207.4.

Step 3. To a stirred solution of benzyl (2*S*)-2-((chlorocarbonyl)(methyl)amino)-3-methylbutanoate (230 mg, 0.81 mmol) in DCM (3.6 mL), a solution of triethylamine (510 µL, 3.68 mmol) and 2-(1-methoxy-1-((2*R*)-pyrrolidin-2-yl)ethyl)pyridine TFA salt (174 mg, crude) in DCM (3.6 mL) was added dropwise at 0 °C. The resulting mixture was stirred for 30 minutes, after which time it was warmed to room temperature and stirred for 16 h. The reaction mixture was then quenched with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase prep-TLC to afford benzyl (2*S*)-2-(((2*R*)-2-(1-methoxy-1-(pyridin-2-yl)ethyl)pyrrolidine-1-carbonyl)(methyl)amino)-3-methylbutanoate (200 mg, 85% yield over 2 steps). LCMS (ESI) *m/z*: [M + H] calcd for $C_{26}H_{35}N_3O_4$: 454.3; found 454.5.

Step 4. To a stirred solution of benzyl (2*S*)-2-(((2*R*)-2-(1-methoxy-1-(pyridin-2-yl)ethyl)pyrrolidine-1-carbonyl)(methyl)amino)-3-methylbutanoate (160 mg, 0.353 mmol) in THF (3.2 mL) and H_2O (1.6 mL), $LiOH•H_2O$ (167 mg, 3.96 mmol) was added at 0 °C. The resulting mixture was warmed to room temperature and was stirred for 16 h. The reaction was then concentrated under reduced pressure to afford lithium (2*S*)-2-(((2*R*)-2-(1-methoxy-1-(pyridin-2-yl)ethyl)pyrrolidine-1-carbonyl)(methyl)amino)-3-methylbutanoate (128 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{19}H_{29}N_3O_4$: 364.2; found 364.2.

Step 5. To a stirred solution of lithium (2*S*)-2-(((2*R*)-2-(1-methoxy-1-(pyridin-2-yl)ethyl)pyrrolidine-1-carbonyl)(methyl)amino)-3-methylbutanoate (52 mg, crude) in anhydrous DMF (9.0 mL), DIPEA (210 µL, 1.19 mmol) and (6^3*S*,4*S*)-4-amino-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-5,7-dione (100 mg, 0.132 mmol) were added at 0 °C. The resulting mixture was stirred for 5 minutes, after which time HATU (68 mg, 0.18 mmol) was added and the mixture was stirred for 1 h at 0 °C. The reaction mixture was then quenched with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase prep-HPLC to afford (2*R*)-*N*-((2*S*)-1-((((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-2-(1-methoxy-1-(pyridin-2-yl)ethyl)-*N*-methylpyrrolidine-1-carboxamide (76.0 mg, 52% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{60}H_{81}N_{11}O_7S$: 1100.6; found 1100.3; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 – 8.53 (m, 1H), 8.46 – 8.45 (m, 1H), 8.44 (d, *J* = 2.9 Hz, 1H), 8.39 – 8.30 (m, 1H), 7.84 (s, 1H), 7.79 (td, *J* = 7.7, 1.9 Hz, 1H), 7.73 (dd, *J* = 8.7, 1.7 Hz, 1H), 7.55 (d, *J* = 8.6 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.29 – 7.24 (m, 1H), 7.20 (d, *J* = 2.9 Hz, 1H), 5.67 (t, *J* = 9.2 Hz, 1H), 5.17 (d, *J* = 12.2 Hz, 1H), 4.83 – 4.70 (m, 1H), 4.30 – 4.09 (m, 5H), 3.96 (d, *J* = 10.9 Hz, 1H), 3.60 – 3.53 (m, 2H), 3.39 – 3.35 (m, 1H), 3.24 – 3.18 (m, 7H), 3.15 – 3.09 (m, 1H), 3.09 – 3.02 (m, 1H), 3.00 (s, 3H), 2.94 – 2.87 (m, 5H), 2.79 – 2.75 (m, 1H), 2.69 – 2.65 (m, 4H), 2.48 – 2.42 (m, 1H), 2.12 – 2.04 (m, 2H), 1.83 – 1.74 (m, 2H), 1.68 – 1.61 (m, 3H), 1.59 (s, 3H), 1.56 – 1.47 (m, 2H), 1.51 – 1.40 (m, 1H), 1.33 (d, *J* = 6.1 Hz, 3H), 0.92 – 0.87 (m, 9H), 0.83 (d, *J* = 6.6 Hz, 3H), 0.46 – 0.40 (m, 2H), 0.37 – 0.30 (m, 5H).

Example A113: Synthesis of (2*S*)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-2-(fluoro(pyridin-2-yl)methyl)-*N*-methylpyrrolidine-1-carboxamide



Step 1. To a stirred solution of *tert*-butyl (2*S*)-2-(pyridine-2-carbonyl)pyrrolidine-1-carboxylate (6.00 g, 21.5 mmol) in anhydrous MeOH (240 mL), sodium borohydride (3.26 g, 86.0 mmol) was added at 0 °C. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was then quenched with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford *tert*-butyl (2*S*)-2-(hydroxy(pyridin-2-yl)methyl)pyrrolidine-1-carboxylate (5.75 g, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{15}H_{22}N_2O_3$: 279.2; found 278.4.

Step 2. To a stirred solution of *tert*-butyl (2*S*)-2-(hydroxy(pyridin-2-yl)methyl)pyrrolidine-1-carboxylate (4.14 g, crude) in anhydrous DCM (130 mL), DAST (4.40 mL, 27.6 mmol) and TEA•HF (7.60 mL, 43.5 mmol) were added dropwise at –78 °C. The resulting mixture was stirred at –78 °C for 2 h. The reaction mixture was then allowed to warm to room temperature and was quenched with sat. aq. $NaHCO_3$, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase prep-TLC to afford two separated diastereomers of *tert*-butyl (2*S*)-2-(fluoro(pyridin-2-yl)methyl)pyrrolidine-1-carboxylate.

Isomer 1: (90.0 mg, 2.1% yield over 2 steps); LCMS (ESI) *m/z*: [M + H] calcd for $C_{15}H_{21}FN_2O_2$: 281.2 found 280.8; ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 8.63 – 8.49 (m, 1H), 7.94 – 7.81 (m, 1H), 7.48 – 7.41 (m, 1H), 7.40 – 7.29 (m, 1H), 6.07 – 5.69 (m, 1H), 4.39 – 4.15 (m, 1H), 1.91 – 1.58 (m, 4H), 1.41 (s, 9H), 1.21 – 1.05 (m, 1H), 0.98 – 0.76 (m, 1H).

Isomer 2: (50.0 mg, 1.2% yield over 2 steps), LCMS (ESI) *m/z*: [M + H] calcd for $C_{15}H_{21}FN_2O_2$: 281.2 found 280.8; ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 8.48 (d, *J* = 4.9 Hz, 1H), 7.76 (q, *J* = 6.5 Hz, 1H), 7.48 (d, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.24 (dt, *J* = 12.2, 5.5 Hz, 1H), 5.49 (d, *J* = 5.2 Hz, 1H), 4.03 – 4.10 (m, 1H), 1.92 – 1.82 (m, 1H), 1.80 – 1.55 (m, 3H), 1.44 – 1.35 (m, 9H), 0.92 – 0.83 (m, 1H).

Step 3. A neat mixture of *tert*-butyl (2*S*)-2-(fluoro(pyridin-2-yl)methyl)pyrrolidine-1-carboxylate (*Isomer 1* from previous reaction, 90.0 mg, 0.321 mmol) in trifluoroacetic acid (1.2 mL) was stirred for 20 minutes at 0 °C. The reaction mixture was then quenched with sat. aq. $NaHCO_3$, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford 2-(fluoro((2*S*)-pyrrolidin-2-yl)methyl)pyridine (63.0 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{10}H_{13}FN_2$: 181.1; found 181.1.

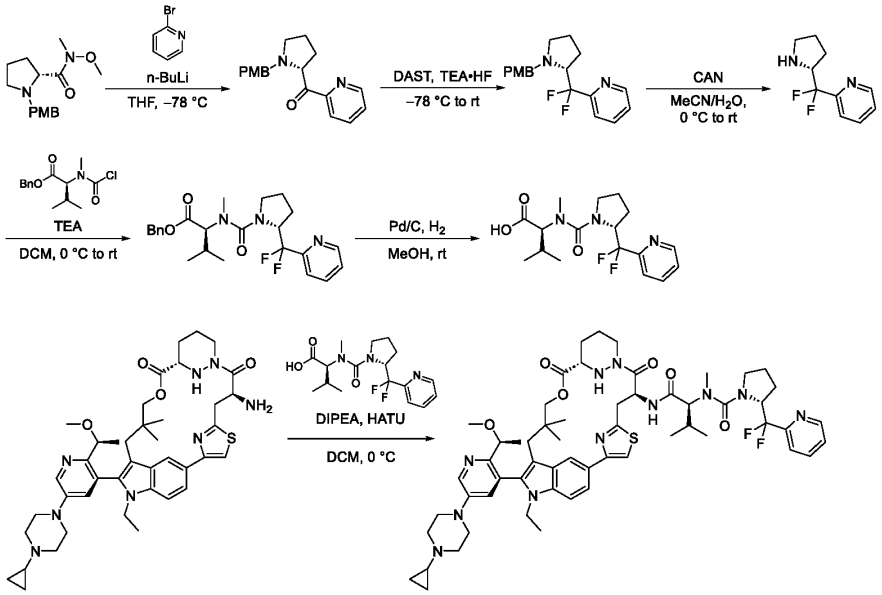
Step 4. To a stirred solution of 2-(fluoro((2*S*)-pyrrolidin-2-yl)methyl)pyridine (54.0 mg, crude) in DCM (1.6 mL), triethylamine (404 µL, 2.90 mmol) and benzyl (2*S*)-2-((chlorocarbonyl)(methyl)amino)-3-methylbutanoate (123 mg, 0.433 mmol) were added at 0 °C. The resulting mixture was stirred for 16 h at 0 °C. The reaction mixture was then quenched with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal-phase prep-TLC to afford benzyl (2*S*)-2-(((2*S*)-2-(fluoro(pyridin-2-yl)methyl)pyrrolidine-1-carbonyl)(methyl)amino)-3-methylbutanoate (47.0 mg, 40% yield over 2 steps). LCMS (ESI) *m/z*: [M + H] calcd for $C_{24}H_{30}FN_3O_3$: 428.2 found 428.3.

Step 5. To a stirred solution of benzyl (2*S*)-2-(((2*S*)-2-(fluoro(pyridin-2-yl)methyl)pyrrolidine-1-carbonyl)(methyl)amino)-3-methylbutanoate (47.0 mg, 0.110 mmol) in MeOH (4.5 mL), Pd/C (10% wt., 14 mg) was added under an atmosphere of argon gas. The reaction flask was evacuated and backfilled twice with hydrogen gas and the resulting mixture was stirred for 2 h at room temperature under an atmosphere of hydrogen gas. The reaction mixture was then filtered through a pad of Celite®, the pad was washed with MeOH, the filtrate was concentrated under reduced pressure, and the resulting material was purified by normal-phase prep-TLC to afford (2*S*)-2-(((2*S*)-2-(fluoro(pyridin-2-yl)methyl)pyrrolidine-1-carbonyl)(methyl)amino)-3-methylbutanoic acid (23.0 mg, 61% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{17}H_{24}FN_3O_3$: 338.2 found 338.1.

Step 6. To a stirred solution of (6^3S,4*S*)-4-amino-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-5,7-dione (25.0 mg, 0.0331 mmol) in anhydrous DCM (1.0 mL), DIPEA (54 µL, 0.31 mmol) and (2*S*)-2-(((2*S*)-2-(fluoro(pyridin-2-yl)methyl)pyrrolidine-1-carbonyl)(methyl)amino)-3-methylbutanoic acid (23 mg, 0.068 mmol) were added at 0 °C. The resulting mixture was stirred at 0 °C for 15 minutes, after which time HATU (35 mg, 0.092 mmol) was added and the mixture was stirred for 2 h at 0 °C. The reaction mixture was then quenched with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure, and purified by reversed-phase prep-HPLC to afford (2*S*)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-2-(fluoro(pyridin-2-yl)methyl)-*N*-methylpyrrolidine-1-carboxamide (14.7 mg, 41% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{58}H_{76}FN_{11}O_6S$: 1074.6 found 1074.2; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.69 – 8.63 (m, 1H), 8.61 – 8.55 (m, 1H), 8.48 – 8.39 (m, 2H), 7.92 – 7.82 (m, 1H), 7.79 (s, 1H), 7.75 – 7.68 (m, 1H), 7.54 (d, *J* = 8.7 Hz, 1H), 7.49 – 7.44 (m, 1H), 7.41 – 7.29 (m, 1H), 7.25 – 7.14 (m, 1H), 5.61 (dd, *J* = 49.1, 3.6 Hz, 1H), 5.49 – 5.40 (m, 1H), 5.08 (d, *J* = 12.1 Hz, 1H), 4.82 – 4.64 (m, 1H), 4.33 – 4.08 (m, 6H), 3.61 – 3.48 (m, 2H), 3.44 – 3.36 (m, 1H), 3.29 – 3.27 (m, 3H), 3.24 – 3.17 (m, 7H), 2.99 – 2.89 (m, 1H), 2.76 –

2.71 (m, 4H), 2.70 – 2.64 (m, 4H), 2.41 – 2.37 (m, 1H), 2.24 – 2.16 (m, 1H), 2.14 – 2.04 (m, 1H), 1.94 – 1.61 (m, 7H), 1.58 – 1.44 (m, 1H), 1.32 (d, *J* = 6.1 Hz, 3H), 0.93 – 0.85 (m, 9H), 0.74 (d, *J* = 6.7 Hz, 3H), 0.49 – 0.40 (m, 2H), 0.37 – 0.28 (m, 5H).

Example A212: Synthesis of (2*R*)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-2-(difluoro(pyridin-2-yl)methyl)-*N*-methylpyrrolidine-1-carboxamide



Step 1. To a stirred solution of (2*R*)-*N*-methoxy-1-((4-methoxyphenyl)methyl)-*N*-methylpyrrolidine-2-carboxamide (200 mg, 0.719 mmol) in anhydrous THF (6.0 mL), 2-bromopyridine (170 mg, 1.08 mmol) was added at –78 °C under an atmosphere of argon. *n*-BuLi (2.5 M in hexane, 862 µL, 2.16 mmol) was then added and the resulting mixture was stirred for 15 minutes at –78 °C. The reaction mixture was quenched with sat. aq. $NaHCO_3$, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford 2-((2*R*)-1-((4-methoxyphenyl)methyl)pyrrolidine-2-carbonyl)pyridine (67% purity, 245 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{18}H_{20}N_2O_2$: 297.2; found 297.5.

Step 2. To a stirred solution of 2-((2*R*)-1-((4-methoxyphenyl)methyl)pyrrolidine-2-carbonyl)pyridine (100 mg, crude) in DAST (3.0 mL, 22 mmol) was added TEA•HF (181 µL, 1.11 mmol) dropwise at –78 °C. The resulting mixture was warmed to room temperature and stirred for 16 h. The reaction mixture was then quenched with sat. aq. $NaHCO_3$, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, purified by normal phase flash column chromatography, and purified further by normal phase prep-TLC to afford 2-(difluoro((2*R*)-1-((4-methoxyphenyl)methyl)pyrrolidin-2-yl)methyl)pyridine (122 mg, 13% yield over 2 steps). LCMS (ESI) *m/z*: [M + H] calcd for $C_{18}H_{20}F_2N_2O$: 319.2; found 318.6.

Step 3. To a stirred solution of 2-(difluoro((2*R*)-1-((4-methoxyphenyl)methyl)pyrrolidin-2-yl)methyl)pyridine (122 mg, 0.383 mmol) in MeCN (6.1 mL) and H_2O (3.0 mL), CAN (987 mg, 1.80 mmol) was added at 0 °C. The resulting mixture was stirred for 15 minutes at 0 °C and was then stirred for 16 h at room temperature. The reaction mixture was concentrated under reduced pressure to afford 2-(difluoro((2*R*)-pyrrolidin-2-yl)methyl)pyridine (1.06 g, crude). The crude material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{10}H_{12}F_2N_2$: 199.1; found 199.1.

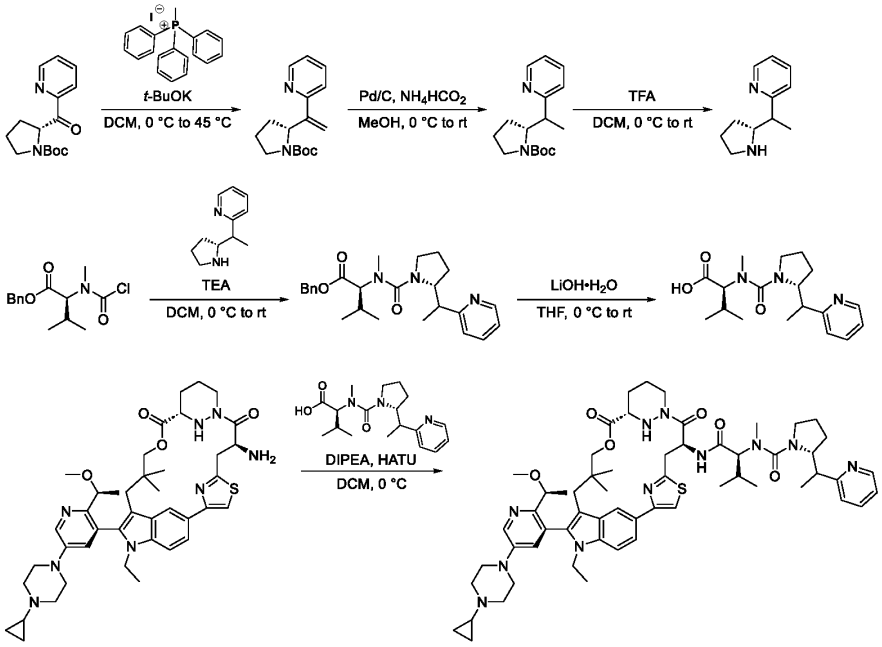
Step 4. To a stirred solution of 2-(difluoro((2*R*)-pyrrolidin-2-yl)methyl)pyridine (76 mg, crude) and triethylamine (267 µL, 1.91 mmol) in DCM (1.0 mL), benzyl (2*S*)-2-((chlorocarbonyl)(methyl)amino)-3-methylbutanoate (195 mg, 0.687 mmol) was added at 0 °C. The resulting mixture was stirred for 2 h at room temperature. The reaction mixture was then quenched with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase prep-TLC to afford benzyl (2*S*)-2-(((2*R*)-2-(difluoro(pyridin-2-yl)methyl)pyrrolidine-1-carbonyl)(methyl)amino)-3-methylbutanoate (64 mg, 21% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{24}H_{29}F_2N_3O_3$: 446.2; found 446.6.

Step 5. To a stirred solution of benzyl (2*S*)-2-(((2*R*)-2-(difluoro(pyridin-2-yl)methyl)pyrrolidine-1-carbonyl)(methyl)amino)-3-methylbutanoate (59 mg, 0.13 mmol) in MeOH (3.0 mL), Pd/C (5% wt., 3.0 mg) was added under an atmosphere of argon. The reaction flask was evacuated and backfilled twice with H_2 gas and the resulting mixture was stirred for 2 h at room temperature under an atmosphere of H_2. The reaction mixture was then filtered through a pad of Celite®, the filter pad was washed with MeOH, and the filtrate was concentrated under reduced pressure to afford (2*S*)-2-(((2*R*)-2-(difluoro(pyridin-2-yl)methyl)pyrrolidine-1-carbonyl)(methyl)amino)-3-methylbutanoic acid (43 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{17}H_{23}F_2N_3O_3$: 356.2; found 355.9.

Step 6. To a stirred solution of (6^3*S*,4*S*)-4-amino-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-5,7-dione (70 mg, 0.093 mmol) in anhydrous DCM (2.1 mL), DIPEA (145 µL, 0.832 mmol) and (2*S*)-2-(((2*R*)-2-(difluoro(pyridin-2-yl)methyl)pyrrolidine-1-carbonyl)(methyl)amino)-3-methylbutanoic acid (38 mg, crude) were added at 0 °C. The resulting mixture was stirred for 15 minutes, after which time HATU (126 mg, 0.331 mmol) was added and the mixture was stirred for 2 h at 0 °C. The reaction mixture was then quenched with sat. aq. $NaHCO_3$, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase prep-HPLC to afford (2*R*)-*N*-((2*S*)-1-((((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-2-(difluoro(pyridin-2-yl)methyl)-*N*-methylpyrrolidine-1-carboxamide (24.0 mg, 24% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{58}H_{75}F_2N_{11}O_6S$: 1092.6; found 1092.9; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.68 (d, *J* = 4.8 Hz, 1H), 8.46 – 8.43 (m, 2H), 8.36 – 8.30 (m, 1H), 7.99 – 7.92 (m, 1H), 7.80 (s, 1H), 7.75 – 7.70 (m, 1H), 7.67 (d, *J* = 7.9 Hz, 1H), 7.57 – 7.49 (m, 2H), 7.20 (d, *J* = 2.9 Hz, 1H), 5.60 (t, *J* = 8.9 Hz, 1H), 5.38 – 5.23 (m, 1H), 5.15 (d, *J* = 12.2 Hz, 1H), 4.35 – 4.08 (m, 5H), 3.95 (d, *J* = 10.8 Hz, 1H), 3.62 – 3.52 (m, 3H), 3.39 – 3.31 (m, 1H), 3.26 – 3.17 (m, 8H), 3.09 – 2.99 (m, 1H), 2.95 – 2.85 (m, 4H), 2.82 – 2.76 (m, 1H),

2.70 – 2.64 (m, 4H), 2.48 – 2.39 (m, 1H), 2.14 – 2.03 (m, 2H), 1.94 – 1.71 (m, 6H), 1.70 – 1.61 (m, 1H), 1.57 – 1.43 (m, 1H), 1.35 – 1.30 (m, 3H), 0.96 – 0.83 (m, 9H), 0.79 – 0.74 (m, 3H), 0.46 – 0.40 (m, 2H), 0.36 – 0.31 (m, 5H).

Example A347: Synthesis of (2*R*)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-2-(1-(pyridin-2-yl)ethyl)pyrrolidine-1-carboxamide



Step 1. To a stirred suspension of methyl triphenylphosphonium iodide (25.5 g, 63.2 mmol) in dry DCM (80 mL), potassium *tert*-butoxide (7.09 g, 63.2 mmol) was added at 0 °C. The resulting mixture was stirred at 0 °C for 30 minutes, after which time a solution of *tert*-butyl (2*R*)-2-(pyridine-2-carbonyl)pyrrolidine-1-carboxylate (1.50 g, 5.43 mmol) in DCM (10 mL) was added. The mixture was warmed to 45 °C and stirred for 16 h. The reaction mixture was then quenched with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford *tert*-butyl (2*R*)-2-(1-(pyridin-2-yl)ethenyl)pyrrolidine-1-carboxylate (464 mg, 31% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{16}H_{22}N_2O_2$: 275.2; found 274.7.

Step 2. To a stirred mixture of *tert*-butyl (2*R*)-2-(1-(pyridin-2-yl)ethenyl)pyrrolidine-1-carboxylate (464 mg, 1.69 mmol) and Pd/C (10% wt., 10 mg.) in MeOH (14.5 mL), ammonium formate (1.06 g, 16.9 mmol) was added in portions at 0 °C. The resulting mixture was stirred at room temperature for 16 h. The reaction mixture was then filtered through a pad of Celite®, the pad was washed with MeOH, the filtrate was concentrated under reduced pressure, and the resulting crude material was purified by normal phase flash column chromatography to afford *tert*-butyl (2*R*)-2-(1-(pyridin-2-yl)ethyl)pyrrolidine-1-carboxylate (437 mg, 93% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{16}H_{24}N_2O_2$: 277.2; found 276.7.

Step 3. To a stirred solution of *tert*-butyl (2*R*)-2-(1-(pyridin-2-yl)ethyl)pyrrolidine-1-carboxylate (437 mg, 1.58 mmol) in DCM (2.5 mL), trifluoroacetic acid (9.00 mL, 79.1 mmol) was added dropwise at 0 °C under an atmosphere of argon gas. The resulting mixture was stirred at room temperature for 16 h. The reaction mixture was then concentrated under reduced pressure to afford 2-(1-((2*R*)-pyrrolidin-2-yl)ethyl)pyridine TFA salt (1.09 g, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{11}H_{16}N_2$: 177.1; found 176.7.

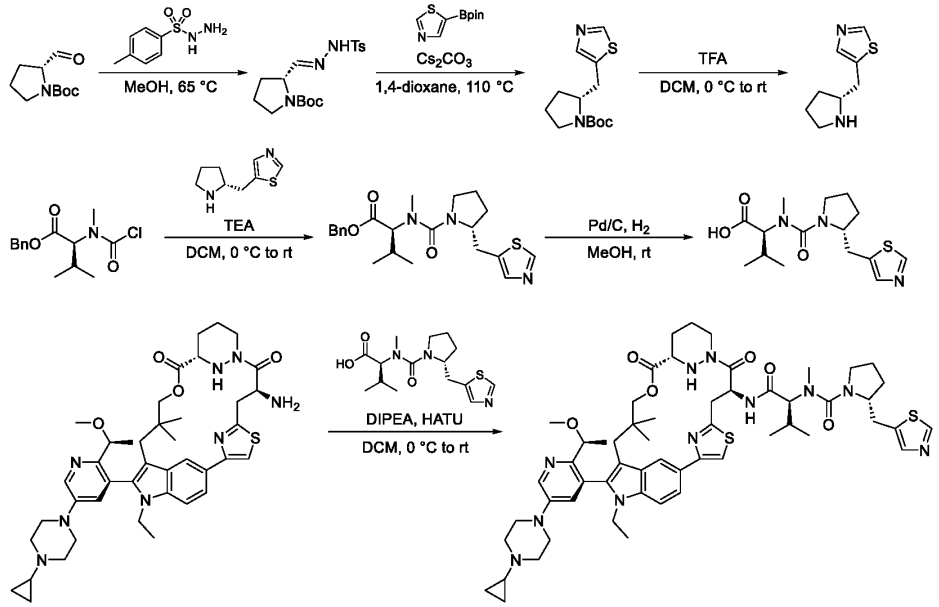
Step 4. To a stirred solution of benzyl (2*S*)-2-((chlorocarbonyl)(methyl)amino)-3-methylbutanoate (885 mg, 3.12 mmol) in DCM (20 mL), a solution of triethylamine (3.95 mL, 28.4 mmol) and 2-(1-((2*R*)-pyrrolidin-2-yl)ethyl)pyridine TFA salt (500 mg, crude) in DCM (10.0 mL) was added dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 10 minutes, after which time it was warmed to room temperature and stirred for 90 minutes. The reaction mixture was then quenched with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography afford benzyl (2*S*)-3-methyl-2-(methyl((2*R*)-2-(1-(pyridin-2-yl)ethyl)pyrrolidine-1-carbonyl)amino)butanoate (140 mg, 11% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{25}H_{33}N_3O_3$: 424.3; found 424.1.

Step 5. To a stirred solution of benzyl (2*S*)-3-methyl-2-(methyl((2*R*)-2-(1-(pyridin-2-yl)ethyl)pyrrolidine-1-carbonyl)amino)butanoate (140 mg, 0.331 mmol) in THF (2.8 mL), a solution of lithium hydroxide monohydrate (67.0 mg, 1.60 mmol) in H_2O (700 µL) was added at 0 °C. The resulting mixture was stirred at room temperature for 16 h. The reaction mixture was acidified to pH 5 with aqueous HCl (1.0 M), extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford (2*S*)-3-methyl-2-(methyl((2*R*)-2-(1-(pyridin-2-yl)ethyl)pyrrolidine-1-carbonyl)amino)butanoic acid (80 mg, crude). This material used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{18}H_{27}N_3O_3$: 334.4; found 333.9.

Step 6. To a stirred solution of (6^3S,4*S*)-4-amino-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-5,7-dione (115 mg, 0.152 mmol) in DCM (3.5 mL), DIPEA (26 µL, 1.49 mmol) and (2*S*)-3-methyl-2-(methyl((2*R*)-2-(1-(pyridin-2-yl)ethyl)pyrrolidine-1-carbonyl)amino)butanoic acid (60 mg, crude) were added at 0 °C. The resulting mixture was stirred at 0 °C for 5 minutes, after which time HATU (85 mg, 0.22 mmol) was added and the mixture was stirred for 1 h at 0 °C. The reaction mixture was then quenched with H_2O, extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase prep-HPLC to afford (2*R*)-*N*-((2*S*)-1-((((6^3S,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-2-(1-(pyridin-2-yl)ethyl)pyrrolidine-1-carboxamide (11.0 mg, 7% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{59}H_{79}N_{11}O_6S$: 1070.6; found 1071.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 – 8.51 (m, 1H), 8.47 – 8.42 (m, 2H), 8.37 (d, *J* = 9.2 Hz, 1H), 7.76 (s, 1H), 7.71 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.66 (td, *J* = 7.6, 1.9 Hz, 1H), 7.53 (d, *J* = 8.7 Hz, 1H), 7.23 – 7.18 (m, 2H), 7.17 – 7.14 (m, 1H), 5.67 (t, *J* = 9.0 Hz, 1H), 5.17 (d, *J* = 12.1 Hz, 1H), 4.54 – 4.47 (m, 1H), 4.32 – 4.10 (m, 5H), 3.97 (d, *J* = 11.0 Hz, 1H), 3.61 – 3.51 (m, 2H), 3.42 – 3.36 (m, 1H), 3.24 – 3.14 (m, 10H), 3.10 – 3.01 (m, 1H), 2.93 – 2.87 (m, 1H), 2.83 (s, 3H), 2.78 – 2.72 (m, 1H), 2.69 –

2.65 (m, 4H), 2.49 – 2.41 (m, 1H), 2.14 – 2.03 (m, 2H), 1.83 – 1.68 (m, 4H), 1.68 – 1.59 (m, 2H), 1.58 – 1.43 (m, 2H), 1.33 (d, *J* = 6.1 Hz, 3H), 1.27 (d, *J* = 7.0 Hz, 3H), 0.94 – 0.83 (m, 12H), 0.48 – 0.39 (m, 2H), 0.38 – 0.31 (m, 5H).

Example A312: Synthesis of (2*R*)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-2-(thiazol-5-ylmethyl)pyrrolidine-1-carboxamide



Step 1. To a stirred solution of *p*-toluenesulfonyl hydrazide (2.80 g, 15.1 mmol) in MeOH (200 mL), *N*-boc-*D*-prolinal (3.00 g, 15.1 mmol) was added. The resulting mixture was refluxed for 16 h, after which time it was concentrated under reduced pressure to afford *tert*-butyl (2*R*)-2-((*E*)-((4-methylbenzenesulfonamido)imino)methyl)pyrrolidine-1-carboxylate (5.50 g, crude). This material was used in the next reaction without further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.11 – 10.93 (m, 1H), 7.71 – 7.61 (m, 2H), 7.43 – 7.34 (m, 2H), 7.22 – 7.08 (m, 1H), 4.24 – 4.05 (m, 1H), 3.29 – 3.11 (m, 2H), 2.37 (s, 3H), 1.99 – 1.81 (m, 1H), 1.80 – 1.63 (m, 2H), 1.63 – 1.49 (m, 1H), 1.36 (s, 3H), 1.19 (s, 6H).

Step 2. To a stirred solution of *tert*-butyl (2*R*)-2-((*E*)-((4-methylbenzenesulfonamido)imino)methyl)pyrrolidine-1-carboxylate (2.16 g, crude) in 1,4-dioxane (26 mL), thiazol-5-yl-boronic acid pinacol ester (1.86 g, 8.82 mmol) and cesium carbonate (2.87 g, 8.82 mmol) were added under an atmosphere of argon. The resulting mixture was stirred at 110 °C for 16 h. The reaction mixture was then cooled to room temperature, quenched by the slow addition of H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford *tert*-butyl (2*R*)-2-((1,3-thiazol-5-yl)methyl)pyrrolidine-1-carboxylate (145 mg, 9% yield over 2 steps). LCMS (ESI) *m/z*: [M + H] calcd for $C_{13}H_{20}N_2O_2S$: 269.1; found 269.5.

Step 3. To a stirred solution of *tert*-butyl (2*R*)-2-((1,3-thiazol-5-yl)methyl)pyrrolidine-1-carboxylate (145 mg, 0.540 mmol) in anhydrous DCM (1.5 mL), trifluoroacetic acid (2.06 mL, 26.7 mmol) was added dropwise at 0 °C. The resulting mixture was stirred at room temperature for 2.5 h, after which time it was concentrated under reduced pressure to afford 5-(((2*R*)-pyrrolidin-2-yl)methyl)-1,3-thiazole TFA salt (90 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_8H_{12}N_2S$: 169.1; found 168.4.

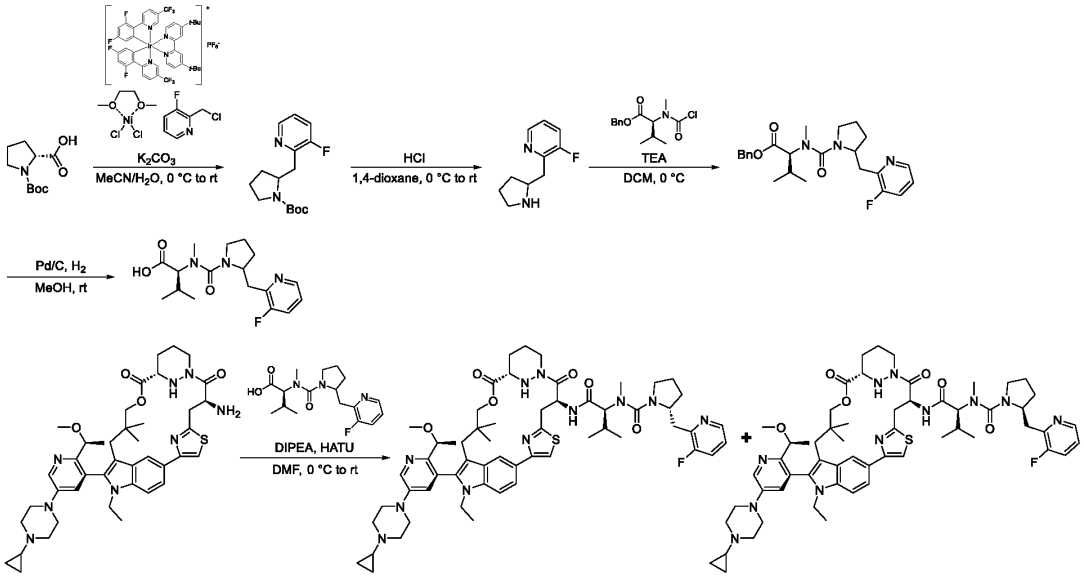
Step 4. To a stirred solution of 5-(((2*R*)-pyrrolidin-2-yl)methyl)-1,3-thiazole TFA salt (90 mg, crude) in anhydrous DCM (5.5 mL), triethylamine (1.12 mL, 8.02 mmol) was added at 0 °C. The mixture was stirred for 15 minutes, after which time a solution of benzyl (2*S*)-2-((chlorocarbonyl)(methyl)amino)-3-methylbutanoate (228 mg, 0.804 mmol) in DCM (2.0 mL) was added dropwise. The resulting mixture was stirred at 0 °C for 15 minutes, after which time it was warmed to room temperature and stirred for 16 h. The reaction mixture was then quenched with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase prep-TLC to afford benzyl (2*S*)-3-methyl-2-(methyl((2*R*)-2-((1,3-thiazol-5-yl)methyl)pyrrolidine-1-carbonyl)amino)butanoate (100 mg, 0.241 mmol, 45% yield over 2 steps). LCMS (ESI) *m/z*: [M + H] calcd for $C_{22}H_{29}N_3O_3S$: 416.2; found 416.5.

Step 5. To a solution of benzyl (2*S*)-3-methyl-2-(methyl((2*R*)-2-((1,3-thiazol-5-yl)methyl)pyrrolidine-1-carbonyl)amino)butanoate (100 mg, 0.241 mmol) in MeOH (2.0 mL), palladium on carbon (10% wt., 16 mg) was added under an atmosphere of argon gas. The reaction flask was evacuated and backfilled twice with hydrogen gas and the resulting mixture was stirred for 16 h at room temperature under an atmosphere of hydrogen gas. The reaction mixture was subsequently filtered through a pad of Celite®, the pad was washed with MeOH, and the filtrate was concentrated under reduced pressure to afford (2*S*)-3-methyl-2-(methyl((2*R*)-2-((1,3-thiazol-5-yl)methyl]pyrrolidine-1-carbonyl)amino)butanoic acid (38 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{15}H_{23}N_3O_3S$: 326.2; found 326.5.

Step 6. To a stirred solution of (6^3*S*,4*S*)-4-amino-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-5,7-dione (80 mg, 0.106 mmol) in anhydrous DCM (2.4 mL), DIPEA (166 µL, 0.95 mmol) and (2*S*)-3-methyl-2-(methyl((2*R*)-2-((1,3-thiazol-5-yl)methyl]pyrrolidine-1-carbonyl)amino)butanoic acid (37 mg, crude) were added at 0 °C. The mixture was stirred for 15 minutes at 0 °C, after which time HATU (54 mg, 0.14 mmol) was added. The resulting mixture was stirred for 1 h at 0 °C and was then stirred for 16 h at room temperature. The reaction mixture was then quenched with H_2O, extracted with DCM, washed with sat. aq. $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase prep-HPLC to afford (2*R*)-*N*-((2*S*)-1-((((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-2-(thiazol-5-ylmethyl)pyrrolidine-1-carboxamide (30.1 mg, 27% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{56}H_{75}N_{11}O_6S_2$: 1062.5; found 1062.2; ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 8.96 (s, 1H), 8.47 – 8.40 (m, 2H), 8.23 (d, *J* = 9.0 Hz, 1H), 7.71 – 7.65 (m, 2H), 7.63 (s, 1H), 7.53 (d, *J* = 8.7 Hz, 1H), 7.24 – 7.17 (m, 1H),

5.61 (t, *J* = 8.9 Hz, 1H), 5.15 (d, *J* = 12.1 Hz, 1H), 4.29 – 4.08 (m, 6H), 3.96 (d, *J* = 10.9 Hz, 1H), 3.60 – 3.51 (m, 2H), 3.49 – 3.39 (m, 3H), 3.31 – 3.18 (m, 10H), 3.14 – 3.01 (m, 2H), 2.96 – 2.87 (m, 4H), 2.72 – 2.64 (m, 4H), 2.48 – 2.37 (m, 1H), 2.13 – 2.03 (m, 2H), 1.95 – 1.86 (m, 1H), 1.85 – 1.74 (m, 2H), 1.68 – 1.62 (m, 2H), 1.53 – 1.40 (m, 2H), 1.32 (d, *J* = 6.1 Hz, 3H), 0.99 – 0.82 (m, 12H), 0.47 – 0.39 (m, 2H), 0.37 – 0.31 (m, 5H).

Examples A412 and A413: Synthesis of (2*R*)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-2-((3-fluoropyridin-2-yl)methyl)-*N*-methylpyrrolidine-1-carboxamide and (2*S*)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-2-((3-fluoropyridin-2-yl)methyl)-*N*-methylpyrrolidine-1-carboxamide



Step 1. A solution of Boc-*D*-proline (1.09 g, 5.08 mmol), 4,4-di-*tert*-butyl-2,2-dipyridyl (92 mg, 0.34 mmol), nickel(II) chloride ethylene glycol dimethyl ether complex (75 mg, 0.34 mmol), potassium carbonate (1.42 g, 10.3 mmol) and [Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)]PF$_6$ (71 mg, 0.063 mmol) in MeCN (10 mL) was sparged with argon gas at 0 °C. H_2O (1.24 mL, 68.7 mmol) was then added, followed by 2-(chloromethyl)-3-fluoropyridine (500 mg, 3.44 mmol). The resulting mixture was stirred for 20 h at room temperature under blue LEDs (450 nm). The reaction mixture was then filtered, the filter was washed with EtOAc, the filtrate was concentrated under reduced pressure, and the resulting material was purified by normal phase flash column chromatography to afford *tert*-butyl 2-((3-fluoropyridin-2-yl)methyl)pyrrolidine-1-carboxylate *(*89% purity, 120 mg, 11% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{15}H_{21}FN_2O_2$: 281.2; found 281.1.

Step 2. To a stirred solution of *tert*-butyl 2-((3-fluoropyridin-2-yl)methyl)pyrrolidine-1-carboxylate (89% purity, 110 mg, 0.349 mmol) in DCM (3.3 mL), HCl (4.0 M 1,4-dioxane, 870 µL, 3.48 mmol) was added dropwise at 0 °C. The reaction mixture was stirred for 16 h at room temperature, after which time it was concentrated under reduced pressure to afford 3-fluoro-2-((pyrrolidin-2-yl)methyl)pyridine HCl salt (110 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{10}H_{13}FN_2$: 181.1; found 180.9.

Step 3. To a stirred solution of 3-fluoro-2-((pyrrolidin-2-yl)methyl)pyridine HCl salt (100 mg, crude) in DCM (6.0 mL), triethylamine (0.26 mL, 1.89 mmol) and a solution of benzyl (2*S*)-2-((chlorocarbonyl)(methyl)amino)-3-methylbutanoate (105 mg, 0.370 mmol) in DCM (6.0 mL) were added at 0 °C. The resulting mixture was stirred at 0 °C for 1 h. The reaction mixture was then quenched with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford benzyl (2*S*)-2-((2-((3-fluoropyridin-2-yl)methyl)pyrrolidine-1-carbonyl)(methyl)amino)-3-methylbutanoate (87 mg, 55% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{24}H_{30}FN_3O_3$: 428.2; found 428.3.

Step 4. To a solution of benzyl (2*S*)-2-((2-((3-fluoropyridin-2-yl)methyl)pyrrolidine-1-carbonyl)(methyl)amino)-3-methylbutanoate (77 mg, 0.17 mmol) in MeOH (3.8 mL), palladium on carbon (10% wt., 18 mg) was added under an atmosphere of argon gas. The reaction flask was evacuated and backfilled twice with hydrogen gas. The resulting mixture was then stirred for 16 h at room temperature under an atmosphere of hydrogen gas. The reaction mixture was then filtered through a pad of Celite®, the pad was washed with MeOH, and the filtrate was concentrated under reduced pressure to afford (2*S*)-2-((2-((3-fluoropyridin-2-yl)methyl)pyrrolidine-1-carbonyl)(methyl)amino)-3-methylbutanoic acid (51 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{17}H_{24}FN_3O_3$: 338.2; found 338.6.

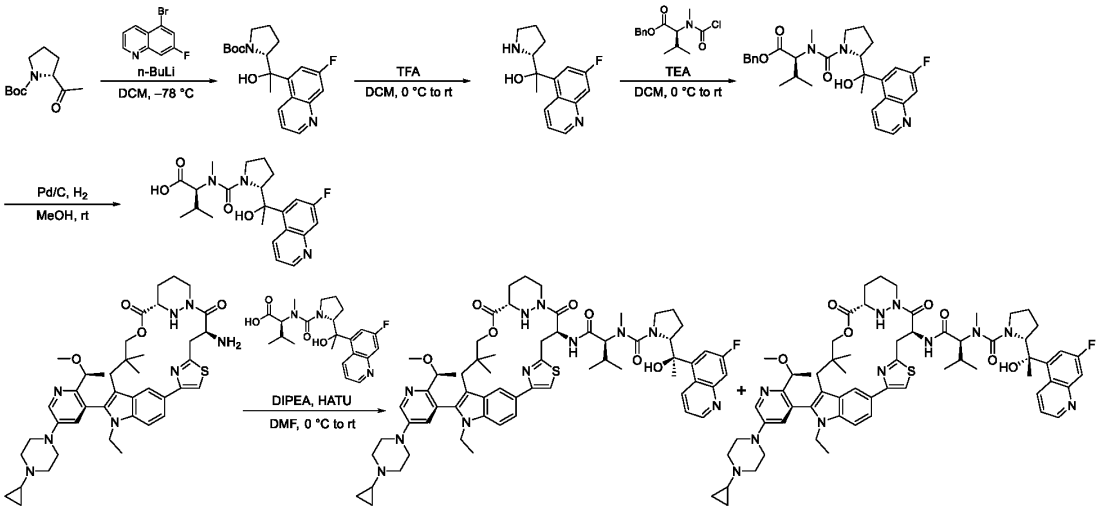
Step 5. To a stirred solution of (6^3S,4*S*)-4-amino-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-5,7-dione (92 mg, 0.12 mmol) and (2*S*)-2-((2-((3-fluoropyridin-2-yl)methyl)pyrrolidine-1-carbonyl)(methyl)amino)-3-methylbutanoic acid (45 mg, crude) in DMF (2.7 mL), DIPEA (63 µL, 0.36 mmol) and HATU (60 mg, 0.15 mmol) were added at 0 °C. The resulting mixture was stirred for 10 minutes at 0 °C and was then warmed to room temperature. The reaction mixture was then quenched with H_2O, extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase prep-HPLC to afford two separated diastereomers of *N*-((2*S*)-1-((((6^3S,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-2-((3-fluoropyridin-2-yl)methyl)-*N*-methylpyrrolidine-1-carboxamide.

A413: (17 mg, 13% yield); LCMS (ESI) *m/z*: [M + H] calcd for $C_{58}H_{76}FN_{11}O_6S$: 1074.6; found 1074.5; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.67 (d, *J* = 8.4 Hz, 1H), 8.46 – 8.42 (m, 2H), 8.38 (d, *J* = 4.7 Hz, 1H), 7.78 (s, 1H), 7.72 (d, *J* = 8.5 Hz, 1H), 7.62 (t, *J* = 8.6 Hz, 1H), 7.54 (d, *J* = 8.7 Hz, 1H), 7.35 – 7.29 (m, 1H), 7.19 (d, *J* = 2.8 Hz, 1H), 5.49 – 5.37 (m, 1H), 5.07 (d, *J* = 12.2 Hz, 1H), 4.52 – 4.43 (m, 1H), 4.34 – 4.10 (m, 6H), 3.59 – 3.48 (m, 2H), 3.28 – 3.17 (m, 12H), 3.13 – 3.04 (m, 1H), 3.01 – 2.89 (m, 2H), 2.70

– 2.63 (m, 8H), 2.41 – 2.36 (m, 2H), 2.24 – 2.15 (m, 1H), 2.12 – 2.03 (m, 1H), 2.00 – 1.89 (m, 1H), 1.84 – 1.75 (m, 2H), 1.68 – 1.61 (m, 2H), 1.59 – 1.46 (m, 1H), 1.32 (d, *J* = 6.0 Hz, 3H), 0.91 – 0.85 (m, 9H), 0.78 (d, *J* = 6.7 Hz, 3H), 0.47 – 0.40 (m, 2H), 0.36 – 0.30 (m, 5H).

A412: (9 mg, 7% yield), LCMS (ESI) *m/z*: [M + H] calcd for $C_{58}H_{76}FN_{11}O_6S$: 1074.6; found 1074.5; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.46 – 8.45 (m, 1H), 8.44 (d, *J* = 2.8 Hz, 1H), 8.41 – 8.32 (m, 1H), 8.28 (d, *J* = 9.4 Hz, 1H), 7.77 (s, 1H), 7.71 (d, *J* = 8.6 Hz, 1H), 7.66 – 7.58 (m, 1H), 7.54 (d, *J* = 8.7 Hz, 1H), 7.36 – 7.28 (m, 1H), 7.20 (d, *J* = 3.0 Hz, 1H), 5.63 (t, *J* = 9.0 Hz, 1H), 5.16 (d, *J* = 12.1 Hz, 1H), 4.46 – 4.37 (m, 1H), 4.32 – 4.09 (m, 6H), 3.94 (d, *J* = 10.8 Hz, 1H), 3.57 – 3.48 (m, 3H), 3.42 – 3.37 (m, 1H), 3.30 – 3.25 (m, 2H), 3.27 – 3.23 (m, 8H), 3.08 – 3.01 (m, 1H), 3.02 – 2.91 (m, 1H), 2.89 (d, *J* = 6.2 Hz, 1H), 2.84 (s, 3H), 2.81 – 2.74 (m, 1H), 2.70 – 2.64 (m, 4H), 2.45 – 2.38 (m, 2H), 2.13 – 2.04 (m, 2H), 1.93 – 1.75 (m, 3H), 1.68 – 1.61 (m, 1H), 1.59 – 1.44 (m, 1H), 1.32 (d, *J* = 6.1 Hz, 3H), 0.92 – 0.83 (m, 12H), 0.46 – 0.40 (m, 2H), 0.36 – 0.31 (m, 5H).

Examples A49 and A60: Synthesis of (2*R*)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-2-((*R*)-1-(7-fluoroquinolin-5-yl)-1-hydroxyethyl)-*N*-methylpyrrolidine-1-carboxamide and (2*R*)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-2-((*S*)-1-(7-fluoroquinolin-5-yl)-1-hydroxyethyl)-*N*-methylpyrrolidine-1-carboxamide.



Step 1. To a stirred solution of 5-bromo-7-fluoroquinoline (603 mg, 2.67 mmol) in anhydrous DCM (173 mL), *n*-butyllithium (2.5 M in hexanes, 2.3 mL, 5.71 mmol) was slowly added at –78 °C under an inert atmosphere. Subsequently, a solution of *tert*-butyl (2*R*)-2-acetylpyrrolidine-1-carboxylate (811 mg, 3.80 mmol) in anhydrous DCM (35 mL) was added and the resulting mixture was stirred at –78 °C for 35 minutes. The reaction mixture was quenched at –78 °C with a mixture of *i*-PrOH and sat. aq. NH_4Cl, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and

purified by normal phase flash column chromatography to afford *tert*-butyl (2*R*)-2-(1-(7-fluoroquinolin-5-yl)-1-hydroxyethyl)pyrrolidine-1-carboxylate (75% purity, 384 mg, 30% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{20}H_{25}FN_2O_3$: 361.2; found 361.1.

Step 2. To a stirred solution of *tert*-butyl (2*R*)-2-(1-(7-fluoroquinolin-5-yl)-1-hydroxyethyl)pyrrolidine-1-carboxylate (75% purity, 360 mg, 0.749 mmol) in DCM (3.6 mL), trifluoroacetic acid (3.50 mL, 45.9 mmol) was added at 0 °C. The resulting mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was then quenched by the addition of H_2O, extracted with DCM, and washed with sat. aq $NaHCO_3$. The aqueous phase was further extracted with DCM, and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford 1-(7-fluoroquinolin-5-yl)-1-((2*R*)-pyrrolidin-2-yl)ethan-1-ol (125 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{15}H_{17}FN_2O$: 261.1; found 261.1.

Step 3. To a stirred solution of 1-(7-fluoroquinolin-5-yl)-1-((2*R*)-pyrrolidin-2-yl)ethan-1-ol (122 mg, crude) and benzyl (2*S*)-2-((chlorocarbonyl)(methyl)amino)-3-methylbutanoate (246 mg, 0.867 mmol) in DCM (6.1 mL), triethylamine (200 µL, 1.41 mmol) was added at 0 °C. The resulting mixture was slowly warmed to room temperature and was stirred for 16 h. The reaction mixture was then quenched with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford benzyl (2*S*)-2-(((2*R*)-2-(1-(7-fluoroquinolin-5-yl)-1-hydroxyethyl)pyrrolidine-1-carbonyl)(methyl)amino)-3-methylbutanoate (163 mg, 44% yield over 2 steps). LCMS (ESI) *m/z*: [M + H] calcd for $C_{29}H_{34}FN_3O_4$: 508.3; found 508.5.

Step 4. A solution of benzyl (2*S*)-2-(((2*R*)-2-(1-(7-fluoroquinolin-5-yl)-1-hydroxyethyl)pyrrolidine-1-carbonyl)(methyl)amino)-3-methylbutanoate (161 mg, 0.317 mmol) in MeOH (32 mL) was sparged with argon gas for 5 minutes. Pd/C (5% wt., 43 mg) was added and the reaction flask was evacuated and backfilled three times with hydrogen gas. The resulting mixture was then stirred under an atmosphere of hydrogen gas for 1.5 h. The reaction mixture was filtered through a pad of Celite®, the pad was washed with MeOH, and the filtrate was concentrated under reduced pressure to afford (2*S*)-2-(((2*R*)-2-(1-(7-fluoroquinolin-5-yl)-1-hydroxyethyl)pyrrolidine-1-carbonyl)(methyl)amino)-3-methylbutanoic acid (127 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{22}H_{28}FN_3O_4$: 418.2; found 418.2.

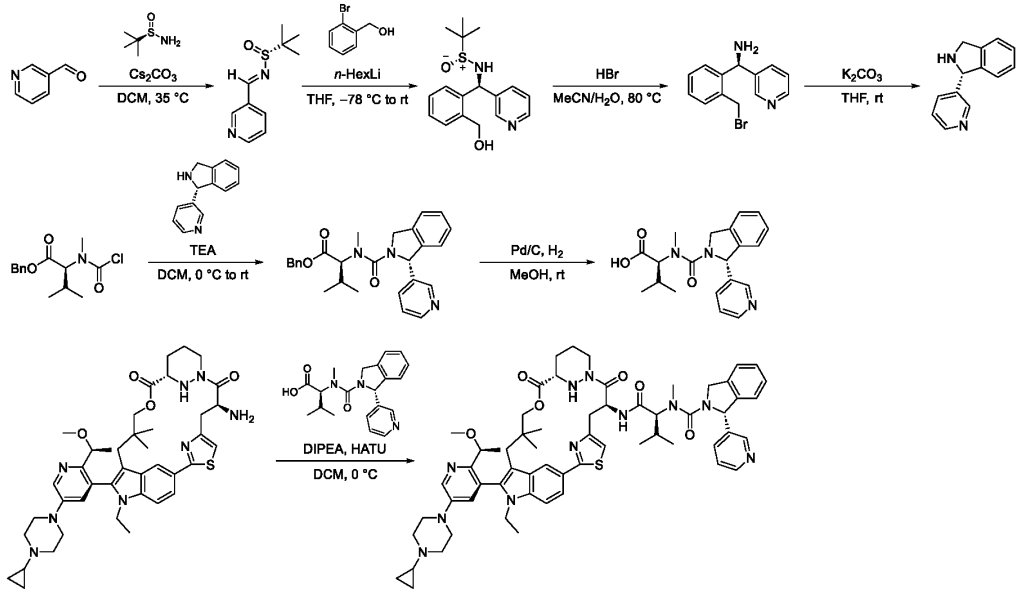
Step 5. To a stirred solution of (6^3*S*,4*S*)-4-amino-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-5,7-dione (161 mg, 0.213 mmol), DIPEA (360 µL, 2.13 mmol) and (2*S*)-2-(((2*R*)-2-(1-(7-fluoroquinolin-5-yl)-1-hydroxyethyl)pyrrolidine-1-carbonyl)(methyl)amino)-3-methylbutanoic acid (126 mg, crude) in anhydrous DMF (9.7 mL), HATU (189 mg, 0.497 mmol) was added at 0 °C. The resulting mixture was warmed to room temperature and stirred for 1 h under an atmosphere of argon gas. The reaction mixture was then quenched with H_2O, extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase prep-HPLC to afford two separated diastereomers of (2*R*)-*N*-((2*S*)-1-((((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-

pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-2-(1-(7-fluoroquinolin-5-yl)-1-hydroxyethyl)-*N*-methylpyrrolidine-1-carboxamide.

A60: (73.4 mg, 30% yield); LCMS (ESI) *m/z*: [M + H] calcd for $C_{63}H_{80}FN_{11}O_7S$: 1154.6; found 1154.1; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.17 (d, *J* = 8.9 Hz, 1H), 8.92 (dd, *J* = 4.1, 1.3 Hz, 1H), 8.47 – 8.41 (m, 2H), 8.38 (d, *J* = 9.1 Hz, 1H), 7.81 (dd, *J* = 11.1, 2.9 Hz, 1H), 7.74 – 7.62 (m, 3H), 7.57 (dd, 1H), 7.50 (d, *J* = 8.7 Hz, 1H), 7.19 (d, *J* = 2.9 Hz, 1H), 5.65 (t, *J* = 8.9 Hz, 1H), 5.39 (s, 1H), 5.29 – 5.21 (m, 1H), 5.14 (d, *J* = 12.1 Hz, 1H), 4.31 – 4.06 (m, 6H), 3.68 – 3.48 (m, 3H), 3.41 – 3.30 (m, 2H), 3.24 – 3.16 (m, 7H), 3.13 – 2.99 (m, 4H), 2.96 – 2.85 (m, 1H), 2.85 – 2.74 (m, 1H), 2.71 – 2.60 (m, 4H), 2.61 – 2.51 (m, 1H), 2.49 – 2.38 (m, 1H), 2.21 – 2.02 (m, 2H), 1.94 – 1.83 (m, 1H), 1.83 – 1.70 (m, 6H), 1.69 – 1.60 (m, 1H), 1.60 – 1.41 (m, 2H), 1.32 (d, *J* = 6.1 Hz, 3H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.92 – 0.83 (m, 9H), 0.48 – 0.40 (m, 2H), 0.39 – 0.29 (m, 5H).

A49: (44.3 mg 18% yield); LCMS (ESI) *m/z*: [M + H] calcd for $C_{63}H_{80}FN_{11}O_7S$: 1154.6; found 1154.1; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.60 (d, *J* = 8.5 Hz, 1H), 8.89 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.51 – 8.37 (m, 3H), 7.73 (s, 1H), 7.71 – 7.63 (m, 2H), 7.60 – 7.45 (m, 3H), 7.19 (d, *J* = 2.9 Hz, 1H), 5.77 (s, 1H), 5.63 (t, *J* = 8.8 Hz, 1H), 5.23 – 5.04 (m, 2H), 4.40 – 4.07 (m, 5H), 4.00 (d, *J* = 10.7 Hz, 1H), 3.70 – 3.45 (m, 3H), 3.43 – 3.32 (m, 2H), 3.25 – 3.05 (m, 8H), 3.02 – 2.84 (m, 4H), 2.83 – 2.75 (m, 1H), 2.70 – 2.61 (m, 4H), 2.60 – 2.49 (m, 1H), 2.49 – 2.35 (m, 1H), 2.15 – 1.99 (m, 2H), 1.86 – 1.60 (m, 7H), 1.58 – 1.41 (m, 3H), 1.32 (d, *J* = 6.1 Hz, 3H), 0.99 – 0.84 (m, 9H), 0.81 (d, *J* = 6.5 Hz, 3H), 0.49 – 0.40 (m, 2H), 0.39 – 0.28 (m, 5H).

Example A337: Synthesis of (1*R*)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(2,4)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-1-(pyridin-3-yl)isoindoline-2-carboxamide



Step 1. To a stirred solution of (*R*)-(+)-2-methyl-2-propanesulfinamide (5.70 g, 47.0 mmol) in DCM (6.0 mL), pyridine-3-carbaldehyde (5.00 g, 46.7 mmol) and cesium carbonate (15.20 g, 46.7 mmol) were added. The resulting suspension was stirred vigorously at 35 °C for 16 h. The reaction mixture was then filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure to afford (*R*)-2-methyl-*N*-((*E*)-(pyridin-3-yl)methylidene)propane-2-sulfinamide (9.59 g, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{10}H_{14}N_2OS$: 211.1; found 210.7.

Step 2. To a stirred solution of 2-bromobenzyl alcohol (1.10 g, 5.59 mmol) in anhydrous THF (5.0 mL), *n*-HexLi (2.5 M in hexane, 3.0 mL, 7.5 mmol) was added dropwise at –78 °C and the mixture was stirred for 30 minutes. The mixture was then added dropwise to a stirred solution of (*R*)-2-methyl-*N*-((*E*)-(pyridin-3-yl)methylidene)propane-2-sulfinamide (1.00 g, crude) in THF (10 mL) at –78 °C. The resulting mixture was stirred at –78 °C for 1 h. The reaction mixture was then warmed to room temperature, quenched with H_2O, extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford (*R*)-*N*-((*R*)-(2-(hydroxymethyl)phenyl)(pyridin-3-yl)methyl)-2-methylpropane-2-sulfinamide (488 mg, 31% yield over 2 steps). LCMS (ESI) *m/z*: [M + H] calcd for $C_{17}H_{22}N_2O_2S$: 319.1; found 318.6.

Step 3. To a stirred solution of (*R*)-*N*-((*R*)-(2-(hydroxymethyl)phenyl)(pyridin-3-yl)methyl)-2-methylpropane-2-sulfinamide (200 mg, 0.628 mmol) in MeCN (5.0 mL), an aqueous solution of hydrobromic acid (6.0 M, 2.0 mL, 12 mmol) was added at room temperature. The reaction mixture was stirred at 80 °C for 16 h, after which time it was concentrated under reduced pressure to afford (1*R*)-1-(2-(bromomethyl)phenyl)-1-(pyridin-3-yl)methanamine (180 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{13}H_{13}BrN_2$: 277.0; found 277.0.

Step 4. To a stirred solution of (1*R*)-1-(2-(bromomethyl)phenyl)-1-(pyridin-3-yl)methanamine (180 mg, crude) in THF (10 mL), potassium carbonate (167 mg, 1.21 mmol) was added. The resulting mixture was stirred at room temperature for 15 minutes. The reaction mixture was then filtered, and the filtrate was concentrated under reduced pressure. The resulting crude material was diluted with H_2O, extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford (1*R*)-1-(pyridin-3-yl)-2,3-dihydro-1*H*-isoindole (553 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{13}H_{12}N_2$: 197.1; found 196.6.

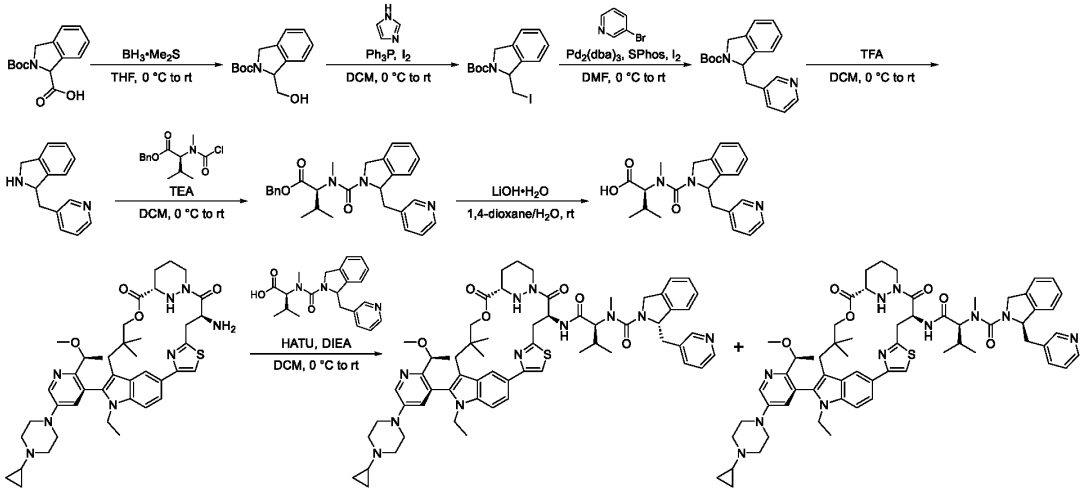
Step 5. To a stirred solution of (1*R*)-1-(pyridin-3-yl)-2,3-dihydro-1*H*-isoindole (20 mg, crude) in anhydrous DCM (3.0 mL), benzyl (2*S*)-2-((chlorocarbonyl)(methyl)amino)-3-methylbutanoate (35 mg, 0.12 mmol) was added. The mixture was cooled to 0 °C and triethylamine (57 µL, 0.41 mmol) was added dropwise. The resulting mixture was stirred for 16 h at room temperature. The reaction mixture was then concentrated under reduced pressure, diluted with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, purified by normal phase flash column chromatography to afford benzyl (2*S*)-3-methyl-2-(methyl((1*R*)-1-(pyridin-3-yl)-2,3-dihydro-1*H*-isoindole-2-carbonyl)amino)butanoate (43 mg, 81% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{27}H_{29}N_3O_3$: 444.2; found 444.3.

Step 6. To a stirred solution of benzyl (2*S*)-3-methyl-2-(methyl((1*R*)-1-(pyridin-3-yl)-2,3-dihydro-1*H*-isoindole-2-carbonyl)amino)butanoate (40 mg, 0.090 mmol) in MeOH (3.0 mL), Pd/C (10% wt., 13 mg)

was added under an atmosphere of argon gas. The reaction flask was twice evacuated and backfilled with hydrogen gas, and the resulting mixture was stirred for 16 h at room temperature under an atmosphere of hydrogen gas. The reaction mixture was then filtered through a pad of Celite®, the pad was washed with MeOH, and the filtrate was concentrated under reduced pressure to afford (2*S*)-3-methyl-2-(methyl((1*R*)-1-(pyridin-3-yl)-2,3-dihydro-1*H*-isoindole-2-carbonyl)amino)butanoic acid (46 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{20}H_{23}N_3O_3$: 354.2; found 354.0.

Step 7. To a stirred solution of (2*S*)-3-methyl-2-(methyl((1*R*)-1-(pyridin-3-yl)-2,3-dihydro-1*H*-isoindole-2-carbonyl)amino)butanoic acid (46 mg, crude) in anhydrous DCM (6.0 mL), DIPEA (171 µL, 0.982 mmol) and (6^3*S*,4*S*)-4-amino-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(2,4)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-5,7-dione (74 mg, 0.098 mmol) were added at 0 °C. The resulting mixture was stirred for 15 minutes, after which time HATU (56 mg, 0.15 mmol) was added and the mixture was stirred at 0 °C for 1 h. The reaction mixture was then quenched with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase prep-HPLC to afford (1*R*)-*N*-((2*S*)-1-((((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(2,4)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-1-(pyridin-3-yl)isoindoline-2-carboxamide (12.6 mg, 12% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{61}H_{75}N_{11}O_6S$: 1090.6; found 1091.1; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.72 – 8.70 (m, 1H), 8.51 – 8.44 (m, 3H), 8.05 (d, *J* = 8.7 Hz, 1H), 7.83 – 7.77 (m, 1H), 7.61 (d, *J* = 8.7 Hz, 1H), 7.54 – 7.48 (m, 1H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.39 – 7.31 (m, 2H), 7.27 (t, *J* = 7.5 Hz, 1H), 7.22 (d, *J* = 2.8 Hz, 1H), 7.13 (d, *J* = 7.5 Hz, 1H), 6.62 (s, 1H), 6.51 (s, 1H), 5.59 (t, *J* = 9.2 Hz, 1H), 5.37 – 5.28 (m, 1H), 5.06 (d, *J* = 12.1 Hz, 1H), 4.62 (d, *J* = 14.2 Hz, 1H), 4.34 – 4.09 (m, 5H), 3.88 (d, *J* = 11.1 Hz, 1H), 3.61 (d, *J* = 11.0 Hz, 1H), 3.51 (d, *J* = 11.0 Hz, 1H), 3.25 – 3.20 (m, 4H), 3.19 (s, 3H), 3.00 – 2.93 (m, 4H), 2.95 – 2.84 (m, 1H), 2.84 – 2.72 (m, 1H), 2.72 – 2.63 (m, 4H), 2.65 – 2.53 (m, 2H), 2.13 – 1.93 (m, 2H), 1.85 – 1.59 (m, 3H), 1.60 – 1.46 (m, 1H), 1.33 (d, *J* = 6.0 Hz, 3H), 0.96 – 0.83 (m, 9H), 0.74 (d, *J* = 6.5 Hz, 3H), 0.47 – 0.41 (m, 2H), 0.40 – 0.30 (m, 5H).

Examples A170 and A171: Synthesis of (1*S*)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-12-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-1-(pyridin-3-ylmethyl)isoindoline-2-carboxamide and (1*R*)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-12-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-1-(pyridin-3-ylmethyl)isoindoline-2-carboxamide



Step 1. To a stirred solution of 2-((*tert*-butoxy)carbonyl)-2,3-dihydro-1*H*-isoindole-1-carboxylic acid (5.00 g, 17.0 mmol) in anhydrous THF (400 mL) was added borane dimethyl sulfide complex (95.0 mL, 189.9 mmol) in portions at 0 °C. The resulting mixture stirred for 16 h at room temperature. The reaction mixture was then quenched with cold H_2O, concentrated under reduced pressure and the remaining aqueous mixture was extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford *tert*-butyl 1-(hydroxymethyl)-2,3-dihydro-1*H*-isoindole-2-carboxylate (3.80 g, crude). This material was taken to the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{14}H_{19}NO_3$: 250.1; found 250.0.

Step 2. To a stirred solution of *tert*-butyl 1-(hydroxymethyl)-2,3-dihydro-1*H*-isoindole-2-carboxylate (3.80 g, crude) in anhydrous DCM (152 mL) were added imidazole (1.93 g, 28.4 mmol), triphenylphosphine (5.58 g, 21.3 mmol) and iodine (5.40 g, 21.3 mmol) under an atmosphere of argon at 0 °C. The resulting mixture was stirred for 16 hours at room temperature. The reaction mixture was then quenched with sat. aq. $Na_2S_2O_3$, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford *tert*-butyl 1-(iodomethyl)-2,3-dihydro-1*H*-isoindole-2-carboxylate (3.80 g, 63% yield over 2 steps). ^{1}H NMR (300 MHz, DMSO-d_6) 7.46 – 7.23 (m, 4H), 4.94 (s, 1H), 4.67 – 4.48 (m, 2H), 4.12 (dd, *J* = 10.2, 3.9 Hz, 0.5H), 3.97 (dd, *J* = 10.4, 4.0 Hz, 0.5H), 3.85 – 3.69 (m, 1H), 1.47 (s, 9H).

Step 3. To a stirred solution of zinc (535 mg, 8.18 mmol) in anhydrous DMF (1.5 mL) was added iodine (32.0 mg, 0.120 mmol) followed by $Pd_2(dba)_3$ (19.0 mg, 0.0207 mmol), SPhos (17.0 mg, 0.0414 mmol) and 3-bromopyridine (158 mL, 1.64 mmol) at room temperature. The resulting mixture was cooled

to 0 °C and a solution of *tert*-butyl 1-(iodomethyl)-2,3-dihydro-1*H*-isoindole-2-carboxylate (300 mg, 0.835 mmol) in anhydrous DMF (1.5 mL) was added dropwise over 5 h with regular agitation of the mixture. The resulting mixture was stirred vigorously for 16 hours at room temperature. The reaction mixture was then filtered through a pad of Celite®, quenched with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford *tert*-butyl 1-[(pyridin-3-yl)methyl]-2,3-dihydro-1*H*-isoindole-2-carboxylate (43 mg, 17% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{19}H_{22}N_2O_2$: 311.2; found 311.4.

Step 4. To a stirred solution of *tert*-butyl 1-((pyridin-3-yl)methyl)-2,3-dihydro-1*H*-isoindole-2-carboxylate (176 mg, 0.567 mmol) in anhydrous DCM (8.8 mL) was added trifluoroacetic acid (2.20 mL, 28.3 mmol) at 0 °C under an atmosphere of argon. The resulting mixture was stirred for 2.5 h at room temperature. The reaction mixture was then quenched with sat. aq. $NaHCO_3$, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford 1-((pyridin-3-yl)methyl)-2,3-dihydro-1*H*-isoindole (114 mg, crude). This material was taken to the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{14}H_{14}N_2$: 211.1; found 211.0.

Step 5. To a stirred solution of 1-((pyridin-3-yl)methyl)-2,3-dihydro-1*H*-isoindole (147 mg, crude) in anhydrous DCM (3.0 mL) were added triethylamine (581 µL, 4.19 mmol) and a solution of benzyl (2*S*)-2-((chlorocarbonyl)(methyl)amino)-3-methylbutanoate (238 mg, 0.839 mmol) in anhydrous DCM (3.0 mL) at 0 °C. The resulting mixture was stirred for 16 hours at room temperature. The reaction mixture was then quenched with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford benzyl (2*S*)-3-methyl-2-(methyl((1-((pyridin-3-yl)methyl)-2,3-dihydro-1*H*-isoindole-2-carbonyl))amino)butanoate (176 mg, 53% yield over 2 steps). LCMS (ESI) *m/z*: [M + H] calcd for $C_{28}H_{31}N_3O_3$: 458.2; found 458.4.

Step 6. To a stirred solution of benzyl (2*S*)-3-methyl-2-(methyl((1-((pyridin-3-yl)methyl)-2,3-dihydro-1*H*-isoindole-2-carbonyl))amino)butanoate (166 mg, 0.363 mmol) in 1,4-dioxane (5.3 mL) and H_2O (1.3 mL) was added LiOH•H_2O (45.0 mg, 1.07 mmol). The resulting mixture was stirred for 16 hours at room temperature. The reaction mixture was then acidified to pH 4 by the addition of 1.0 M aq. HCl, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford (2*S*)-3-methyl-2-(methyl((1-((pyridin-3-yl)methyl)-2,3-dihydro-1*H*-isoindole-2-carbonyl))amino)butanoic acid (130 mg, crude). This material was taken to the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{21}H_{25}N_3O_3$: 368.2; found 368.1.

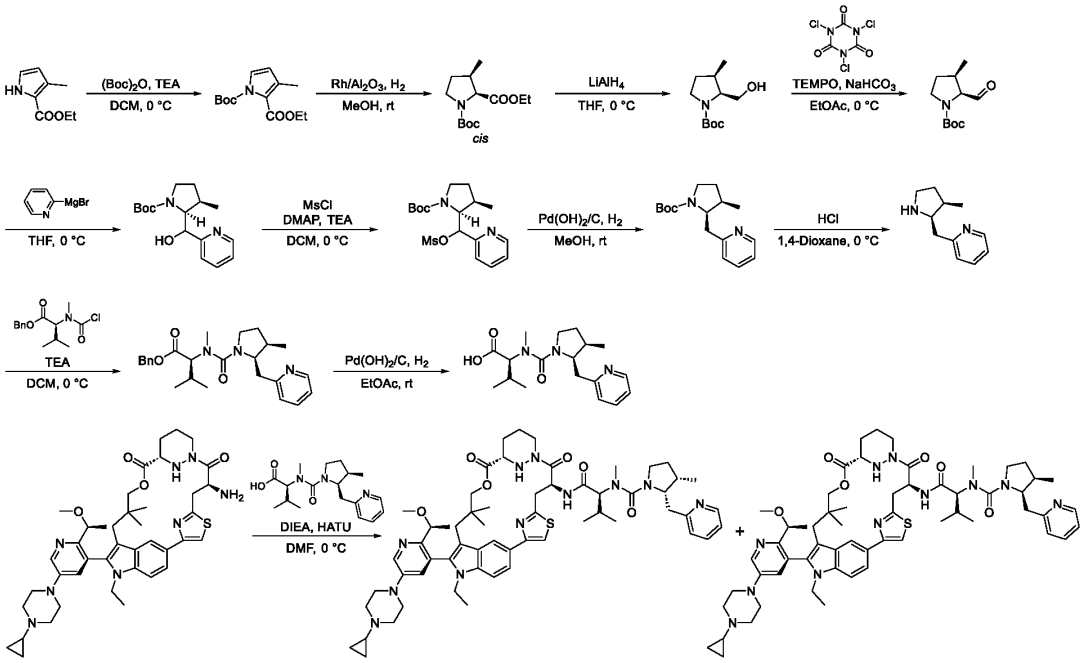
Step 7. To a stirred solution of ((2*S*)-3-methyl-2-(methyl((1-[(pyridin-3-yl)methyl)-2,3-dihydro-1*H*-isoindole-2-carbonyl))amino)butanoic acid (68.0 mg, crude) in anhydrous DCM (2.0 mL) were added DIPEA (166 mL, 0.950 mmol) and (6^3*S*,4*S*)-4-amino-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-5,7-dione (80.0 mg, 0.106 mmol) under and atmosphere of argon at 0 °C. After 15 minutes, HATU (54.0 mg, 0.140 mmol) was added and the resulting mixture was stirred for 2 h at 0 °C and then was stirred for 16 h at room temperature. The reaction mixture was then quenched with H_2O, extracted with DCM, washed with sat. aq. $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase prep-HPLC to afford two diastereomers of *N*-((2*S*)-1-((((6^3*S*,4*S*)-12-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-

1-methoxyethyl)pyridin-3-yl)-1^{1}-ethyl-10,10-dimethyl-5,7-dioxo-6^{1},6^{2},6^{3},6^{4},6^{5},6^{6}-hexahydro-1^{1}*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-1-(pyridin-3-ylmethyl)isoindoline-2-carboxamide.

A171: (20.1 mg, 19% yield); LCMS (ESI) *m/z*: [M + H] calcd for $C_{62}H_{77}N_{11}O_6S$: 1104.6; found 1104.2; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.61 (d, *J* = 8.3 Hz, 1H), 8.48 – 8.38 (m, 2H), 8.38 – 8.28 (m, 1H), 8.28 – 8.15 (m, 1H), 7.72 – 7.62 (m, 1H), 7.56 (d, *J* = 8.6 Hz, 1H), 7.47 (s, 1H), 7.45 – 7.38 (m, 2H), 7.38 – 7.28 (m, 2H), 7.28 – 7.22 (m, 1H), 7.22 – 7.14 (m, 2H), 5.92 – 5.81 (m, 1H), 5.47 – 5.35 (m, 1H), 5.07 (d, *J* = 12.1 Hz, 1H), 4.51 (d, *J* = 14.0 Hz, 1H), 4.42 – 4.35 (m, 1H), 4.34 – 4.06 (m, 6H), 3.60 – 3.47 (m, 2H), 3.29 – 3.16 (m, 10H), 3.16 – 3.07 (m, 1H), 2.99 – 2.91 (m, 2H), 2.79 (s, 3H), 2.75 – 2.62 (m, 4H), 2.41 (d, *J* = 14.2 Hz, 1H), 2.26 – 2.16 (m, 1H), 2.13 – 2.02 (m, 1H), 1.83 – 1.72 (m, 2H), 1.70 – 1.61 (m, 1H), 1.57 – 1.44 (m, 1H), 1.33 (d, *J* = 6.0 Hz, 3H), 0.98 – 0.79 (m, 9H), 0.73 (d, *J* = 6.7 Hz, 3H), 0.48 – 0.39 (m, 2H), 0.39 – 0.26 (m, 5H).

A170: (15.0 mg, 14% yield); LCMS (ESI) *m/z*: [M + H] calcd for $C_{62}H_{77}N_{11}O_6S$: 1104.6; found 1104.0; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.48 – 8.46 (m, 1H), 8.44 (d, *J* = 2.9 Hz, 1H), 8.36 – 8.29 (m, 2H), 8.21 – 8.12 (m, 1H), 7.78 (s, 1H), 7.72 (d, *J* = 8.5 Hz, 1H), 7.54 (d, *J* = 8.7 Hz, 1H), 7.38 – 7.29 (m, 3H), 7.29 – 7.24 (m, 1H), 7.24 – 7.15 (m, 3H), 5.89 – 5.81 (m, 1H), 5.66 (t, *J* = 8.9 Hz, 1H), 5.17 (d, *J* = 12.1 Hz, 1H), 4.47 – 4.35 (m, 2H), 4.33 – 4.10 (m, 5H), 4.01 (d, *J* = 10.8 Hz, 1H), 3.63 – 3.51 (m, 2H), 3.46 – 3.36 (m, 1H), 3.26 – 3.11 (m, 10H), 3.01 – 2.88 (m, 4H), 2.83 – 2.75 (m, 1H), 2.71 – 2.62 (m, 4H), 2.47 – 2.37 (m, 1H), 2.18 – 2.04 (m, 2H), 1.87 – 1.74 (m, 2H), 1.72 – 1.60 (m, 1H), 1.60 – 1.43 (m, 1H), 1.33 (d, *J* = 6.0 Hz, 3H), 0.97 – 0.81 (m, 12H), 0.48 – 0.40 (m, 2H), 0.39 – 0.28 (m, 5H).

Examples A120 and A121: Synthesis of (2*S*,3*S*)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*,3-dimethyl-2-(pyridin-2-ylmethyl)pyrrolidine-1-carboxamide and **(2*R*,3*R*)-N-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*,3-dimethyl-2-(pyridin-2-ylmethyl)pyrrolidine-1-carboxamide**



Step 1. To a stirred solution of ethyl 3-methyl-1*H*-pyrrole-2-carboxylate (10.0 g, 65.3 mmol) in DCM (100 mL), triethylamine (33.3 g, 326 mmol) and di-*tert*-butyl dicarbonate (42.7 g, 196 mmol) were added in portions at 0 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred at 0 °C for 16 h. The reaction mixture was diluted with H_2O (300 mL), extracted with DCM (2 x 100 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford 1-*tert*-butyl 2-ethyl 3-methylpyrrole-1,2-dicarboxylate (20.0 g, crude) as a yellow oil. Several impurities were observed in the product and the material was used the next reaction without further purification. LCMS (ESI) *m/z*: [M + H – C_4H_8] calcd for $C_{13}H_{19}NO_4$: 198.1; found 198.0.

Step 2. A stirred solution of 1-*tert*-butyl 2-ethyl 3-methylpyrrole-1,2-dicarboxylate (20.0 g, crude) in MeOH (200 mL) was treated with Rh/Al_2O_3 (5% wt., 1.0 g). The resulting mixture was stirred for 24 h at room temperature under an atmosphere of hydrogen gas (10 atm). The reaction mixture was then filtered, the filter cake was washed with MeOH (3 x 200 mL), and the filtrate was concentrated under reduced pressure to afford 1-*tert*-butyl 2-ethyl 3-methylpyrrolidine-1,2-dicarboxylate (17 g, crude, mixture of *cis*-isomers) as a yellow oil. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H – C_4H_8] calcd for $C_{13}H_{23}NO_4$: 202.1; found 202.1.

Step 3. To a stirred solution of 1-*tert*-butyl 2-ethyl 3-methylpyrrolidine-1,2-dicarboxylate (3.00 g, crude) in THF (30 mL), $LiAlH_4$ (14.6 mL, 29.1 mmol) was added at 0 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred at 0 °C for 5 h. The reaction mixture was then quenched by the slow addition of a mixture of H_2O (1.1 mL) and 10% aq. NaOH (1.1 mL) at 0 °C. The resulting mixture was extracted with THF (2 x 50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to afford *tert*-butyl 2-(hydroxymethyl)-3-methylpyrrolidine-1-carboxylate (2.5 g, crude) as a yellow oil. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H – C_4H_8] calcd for $C_{11}H_{21}NO_3$: 160.1; found 160.2.

Step 4. To a stirred mixture of *tert*-butyl 2-(hydroxymethyl)-3-methylpyrrolidine-1-carboxylate (2.5 g, crude), $NaHCO_3$ (2.93 g, 34.8 mmol) and TEMPO (540 mg, 3.48 mmol) in EtOAc (25 mL), a solution of trichloroisocyanuric acid (5.13 g, 22.1 mmol) in EtOAc (10 mL) was added dropwise under an atmosphere of nitrogen gas. The resulting mixture was stirred at 0 °C for 2 h. The reaction mixture was then diluted with H_2O (100 mL), extracted with EtOAc (2 x 40 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford *tert*-butyl 2-formyl-3-methylpyrrolidine-1-carboxylate (3.0 g, crude) as a yellow oil. This material was used in the next reaction without further purification.

Step 5. To a stirred mixture of *tert*-butyl 2-formyl-3-methylpyrrolidine-1-carboxylate (3.0 g, crude) in THF (60 mL), 2-pyridylmagnesium bromide (0.25 M in THF, 70.3 mL, 17.6 mmol) was added dropwise at 0 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred at 0 °C for 16 h. The reaction mixture was then quenched with sat. aq. NH_4Cl (100 mL), extracted with EtOAc (2 x 30 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase flash column chromatography to afford *tert*-butyl 2-(hydroxy(pyridin-2-yl)methyl)-3-methylpyrrolidine-1-carboxylate (600 mg, 18% yield over 5 steps) as a colorless oil. LCMS (ESI) *m/z*: [M + H] calcd for $C_{16}H_{24}N_2O_3$: 293.2; found 293.3.

Step 6. To a stirred solution of *tert*-butyl 2-(hydroxy(pyridin-2-yl)methyl)-3-methylpyrrolidine-1-carboxylate (590 mg, 2.02 mmol) and TEA (613 mg, 6.05 mmol) in DCM (6.0 mL), MsCl (347 mg, 3.03 mmol) and DMAP (49.3 mg, 0.404 mmol) were added dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 4 h. The reaction mixture was then diluted with H_2O (300 mL), extracted with DCM (2 x 40 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase flash column chromatography to afford *tert*-butyl 2-((methanesulfonyloxy)(pyridin-2-yl)methyl)-3-methylpyrrolidine-1-carboxylate (220 mg, crude) as a colorless oil. Several impurities were observed in the product and the material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{17}H_{26}N_2O_5S$: 371.2; found 371.1.

Step 7. To a stirred solution of *tert*-butyl 2-((methanesulfonyloxy)(pyridin-2-yl)methyl)-3-methylpyrrolidine-1-carboxylate (210 mg, crude) in MeOH (5.0 mL), $Pd(OH)_2/C$ (20% wt., 420 mg) was added in portions under an atmosphere of nitrogen gas. The headspace of the reaction flask was then evacuated and backfilled three times with hydrogen gas. The resulting mixture was stirred for 4 h at room temperature under an atmosphere of hydrogen gas. The reaction mixture was then filtered, the filter cake was washed with a 10:1 vol. mixture of DCM:MeOH (2 x 20 mL), and the filtrate was concentrated under reduced pressure to afford *tert*-butyl 3-methyl-2-(pyridin-2-ylmethyl)pyrrolidine-1-carboxylate (200 mg,

crude) as a colorless oil. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{16}H_{24}N_2O_2$: 277.2; found 277.1.

Step 8. To a stirred solution of *tert*-butyl 3-methyl-2-(pyridin-2-ylmethyl)pyrrolidine-1-carboxylate (190 mg, crude) in 1,4-dioxane (2.0 mL), HCl (4.0 M in 1,4-dioxane, 2.0 mL, 8.0 mmol) was added dropwise at 0 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred at 0 °C for 1 h, after which time it was concentrated under reduced pressure to afford 2-((3-methylpyrrolidin-2-yl)methyl)pyridine (220 mg, crude) as a yellow solid. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{11}H_{16}N_2$: 177.1; found 177.1.

Step 9. To a stirred solution of 2-((3-methylpyrrolidin-2-yl)methyl)pyridine (220 mg, crude) and triethylamine (253 mg, 2.50 mmol) in DCM (5.0 mL), benzyl (2S)-2-((chlorocarbonyl)(methyl)amino)-3-methylbutanoate (708 mg, 2.50 mmol) was added in portions at 0 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred for 4 h at 0 °C. The reaction mixture was then diluted with H_2O (60 mL), extracted with DCM (2 x 20 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase flash column chromatography to afford benzyl (2*S*)-3-methyl-2-(methyl(3-methyl-2-(pyridin-2-ylmethyl)pyrrolidine-1-carbonyl)amino)butanoate (105 mg, 14% yield over 4 steps) as a yellow oil. LCMS (ESI) *m/z*: [M + H] calcd for $C_{25}H_{33}N_3O_3$: 424.3; found 424.2.

Step 10. To a stirred solution of benzyl (2*S*)-2-((benzylcarbamoyl)(methyl)amino)-3-methylbutanoate (100 mg, 0.236 mmol) in EtOAc (4.0 mL), $Pd(OH)_2/C$ (20% wt., 200 mg) was added in portions. The resulting mixture was stirred for 2 h at room temperature under an atmosphere of hydrogen gas. The reaction mixture was then filtered, the filter cake was washed with a 10:1 vol. mixture of DCM:MeOH (2 x 20 mL), and the filtrate was concentrated under reduced pressure. To afford (2*S*)-3-methyl-2-(methyl(3-methyl-2-(pyridin-2-ylmethyl)pyrrolidine-1-carbonyl)amino)butanoic acid (80 mg, crude) as a yellow oil. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{18}H_{27}N_3O_3$: 334.2; found 334.3.

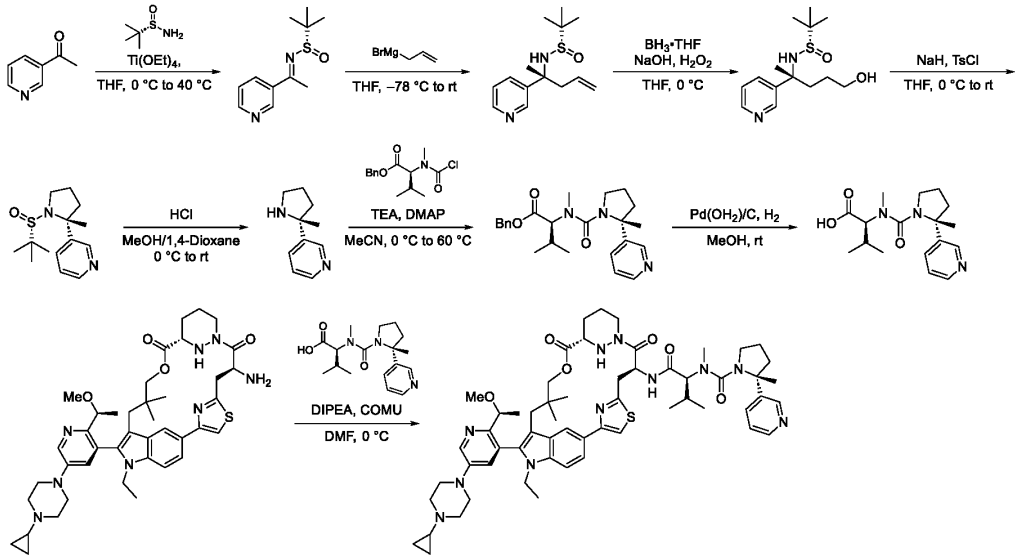
Step 10. To a stirred solution of (6^3S,4*S*)-4-amino-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1H-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-5,7-dione (90.0 mg, 0.119 mmol) in DMF (4.0 mL), DIPEA (154 mg, 1.19 mmol), (2*S*)-3-methyl-2-(methyl(3-methyl-2-(pyridin-2-ylmethyl)pyrrolidine-1-carbonyl)amino)butanoic acid (79.5 mg, crude) and HATU (58.9 mg, 0.155 mmol) were added in portions at 0 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred at 0 °C for 2 h. The reaction mixture was then diluted in brine (100 mL), extracted with EtOAc (2 x 20 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase prep-TLC to afford two separated stereoisomers of *N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1H-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*,3-dimethyl-2-(pyridin-2-ylmethyl)pyrrolidine-1-carboxamide, each as a white solid.

A121: (6.0 mg, 5% yield); LCMS (ESI) *m/z*: [M + H] calcd for $C_{59}H_{79}N_{11}O_6S$: 1070.6; found 1070.5; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.85 (d, *J* = 8.5 Hz, 1H), 8.54 (d, *J* = 4.6 Hz, 1H), 8.44 (d, *J* = 1.6 Hz, 2H), 7.76 (s, 1H), 7.76 – 7.68 (m, 2H), 7.54 (d, *J* = 8.7 Hz, 1H), 7.26 – 7.16 (m, 3H), 5.46 (t, *J* = 8.8 Hz, 1H), 5.06 (d, *J* = 12.1 Hz, 1H), 4.33 – 4.04 (m, 6H), 3.90 (q, *J* = 5.1 Hz,

1H), 3.60 – 3.48 (m, 2H), 3.34 – 3.15 (m, 10H), 3.08 – 2.98 (m, 2H), 2.98 – 2.90 (m, 1H), 2.82 – 2.71 (m, 1H), 2.71 – 2.62 (m, 7H), 2.42 (d, *J* = 14.8 Hz, 1H), 2.32 – 2.22 (m, 1H), 2.13 – 2.05 (m, 1H), 2.03 – 1.95 (m, 1H), 1.90 – 1.72 (m, 4H), 1.66 (tt, *J* = 6.6, 3.6 Hz, 1H), 1.57 – 1.46 (m, 1H), 1.40 – 1.28 (m, 3H), 0.96 – 0.83 (m, 16H), 0.44 (dt, *J* = 6.7, 3.6 Hz, 2H), 0.35 – 0.28 (m, 5H).

A120: (9.0 mg, 7% yield) LCMS (ESI) *m/z*: [M + H] calcd for $C_{59}H_{79}N_{11}O_6S$: 1070.6; found 1070.5; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.52 – 8.42 (m, 3H), 8.29 (d, *J* = 9.1 Hz, 1H), 7.75 – 7.62 (m, 3H), 7.56 – 7.51 (m, 1H), 7.26 – 7.12 (m, 3H), 5.64 (t, *J* = 9.1 Hz, 1H), 5.15 (d, *J* = 12.1 Hz, 1H), 4.32 – 4.21 (m, 2H), 4.20 – 4.10 (m, 3H), 3.98 – 3.85 (m, 2H), 3.57 (s, 2H), 3.29 – 3.16 (m, 9H), 3.15 – 3.02 (m, 1H), 3.01 – 2.88 (m, 3H), 2.82 (s, *J* = 2.4 Hz, 3H), 2.80 – 2.74 (m, 1H), 2.68 (t, *J* = 5.2 Hz, 4H), 2.45 (d, *J* = 14.3 Hz, 1H), 2.15 – 2.04 (m, 2H), 2.02 – 1.94 (m, 1H), 1.93 – 1.85 (m, 1H), 1.83 – 1.75 (m, 2H), 1.69 – 1.62 (m, 1H), 1.56 – 1.48 (m, 1H), 1.40 – 1.33 (m, 1H), 1.33 (d, *J* = 6.0 Hz, 3H), 1.01 (d, *J* = 6.9 Hz, 1H), 0.94 – 0.83 (m, 12H), 0.78 (d, *J* = 6.4 Hz, 3H), 0.43 (dt, *J* = 6.4, 4.2 Hz, 2H), 0.38 – 0.30 (m, 5H).

Example A603: Synthesis of (2*R*)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*,2-dimethyl-2-(pyridin-3-yl)pyrrolidine-1-carboxamide



Step 1. To a stirred solution of 3-acetylpyridine (5.00 g, 41.3 mmol) and (*S*)-2-methylpropane-2-sulfinamide (5.50 g, 45.4 mmol) in THF (50 mL), Ti(OEt)$_4$ (14.1 g, 61.9 mmol) was added at 0 °C. The resulting mixture was stirred for 16 h at 40 °C. The reaction mixture was then quenched with sat. aq. $NaHCO_3$ at 0 °C, filtered, washed with H_2O (2 x 10 mL), extracted with EtOAc (3 x 10 mL), concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford (*S*)-2-methyl-*N*-((1*E*)-1-(pyridin-3-yl)ethylidene)propane-2-sulfinamide (4.37 g, 47% yield) as a yellow oil. LCMS (ESI) *m/z*: [M + H] calcd for $C_{11}H_{16}N_2OS$: 225.1; found 225.2.

Step 2. To a stirred solution of (*S*)-2-methyl-*N*-((1*E*)-1-(pyridin-3-yl)ethylidene)propane-2-sulfinamide (1.80 g, 8.02 mmol) in THF (100 mL), allylmagnesium bromide (1.0 M in Et_2O, 24 mL, 24 mmol) was added dropwise at –78 °C under an atmosphere of argon gas. The resulting mixture was stirred for 16 h at room temperature. The reaction mixture was then quenched with H_2O at 0 °C and purified by reversed-phase flash column chromatography to afford (*S*)-2-methyl-*N*-((2*R*)-2-(pyridin-3-yl)pent-4-en-2-yl)propane-2-sulfinamide (1.18 g, 55% yield) as a yellow oil. LCMS (ESI) *m/z*: [M + H] calcd for $C_{14}H_{22}N_2OS$: 267.2; found 267.2.

Step 3. To a stirred solution of (*S*)-2-methyl-*N*-((2*R*)-2-(pyridin-3-yl)pent-4-en-2-yl)propane-2-sulfinamide (1.18 g, 4.43 mmol) in THF (12 mL), BH_3•THF (1.0 M in THF, 17.7 mL, 17.7 mmol) was added dropwise at 0 °C. The resulting mixture was stirred for 1 h at 0 °C. Subsequently, NaOH (1.0 M in H_2O, 8.86 mL, 8.86 mmol) was added and the resulting mixture was stirred for 10 minutes at 0 °C. To this stirred mixture was added H_2O_2 (30% wt., 1.00 g, 8.820 mmol) dropwise at 0 °C and the mixture was stirred for 30 minutes at 0 °C. The reaction mixture was then quenched with MeOH (10 mL) followed by H_2O (10 mL) at 0 °C, extracted with EtOAc (3 x 10 mL), concentrated under reduced pressure, and purified by reversed-phase flash column chromatography. The fractions containing desired product were basified to pH 8 with sat. aq. $NaHCO_3$ and concentrated under reduced pressure to afford (*S*)-*N*-((2*R*)-5-hydroxy-2-(pyridin-3-yl)pentan-2-yl)-2-methylpropane-2-sulfinamide (454 mg, 36% yield) as a white solid. LCMS (ESI) *m/z*: [M + H] calcd for $C_{14}H_{24}N_2O_2S$: 285.2; found 285.1.

Step 4. To a stirred solution of (*S*)-*N*-((2*R*)-5-hydroxy-2-(pyridin-3-yl)pentan-2-yl)-2-methylpropane-2-sulfinamide (100 mg, 0.352 mmol) in THF (10 mL), NaH (60% wt. in mineral oil, 42.2 mg, 1.06 mmol) was added at 0 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred at 0 °C for 10 minutes, after which time TsCl (201 mg, 1.06 mmol) was added. The resulting mixture was stirred for 16 h at room temperature. The reaction mixture was then diluted with H_2O (10 mL), extracted with EtOAc (2 x 10 mL), concentrated under reduced pressure, and purified by reversed-phase flash column chromatography to afford 3-[(2*R*)-2-methyl-1-((*S*)-2-methylpropane-2-sulfinyl)pyrrolidin-2-yl]pyridine (45 mg, 48% yield) as a yellow oil. LCMS (ESI) *m/z*: [M + H] calcd for $C_{14}H_{22}N_2OS$: 267.2; found 267.1.

Step 5. To a stirred mixture of 3-((2*R*)-2-methyl-1-((*S*)-2-methylpropane-2-sulfinyl)pyrrolidin-2-yl)pyridine (45.0 mg, 0.169 mmol) in MeOH (1 mL), a solution of HCl (4.0 M in 1,4-dioxane, 0.1 mL, 0.4 mmol) was added dropwise at 0 °C. The resulting mixture was stirred at room temperature of 16 h, after which time it was concentrated under reduced pressure to afford 3-((2*R*)-2-methylpyrrolidin-2-yl)pyridine (37 mg, crude) as a yellow oil. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{10}H_{14}N_2$: 163.1; found 163.1.

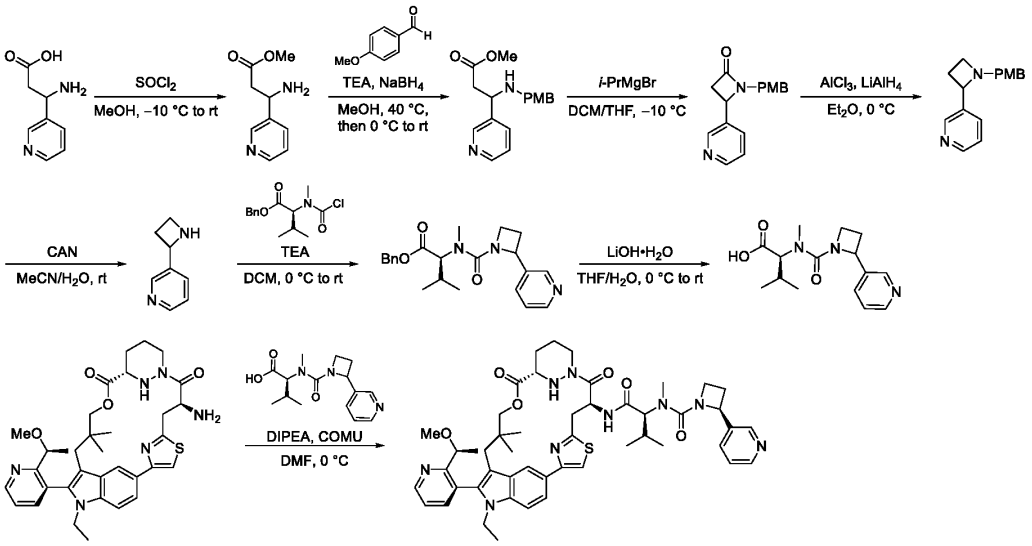
Step 6. To a stirred mixture of 3-((2*R*)-2-methylpyrrolidin-2-yl)pyridine (90.0 mg, crude), TEA (561 mg, 5.55 mmol), and DMAP (67.8 mg, 0.555 mmol) in MeCN (20 mL), benzyl (2*S*)-2-((chlorocarbonyl)(methyl)amino)-3-methylbutanoate (630 mg, 2.22 mmol) was added at 0 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred for 16 h at 60 °C. The reaction mixture was then quenched with H_2O (10 mL) at 0 °C, extracted with DCM (2 x 10 mL), concentrated under reduced pressure, and purified by reversed-phase flash column chromatography to afford benzyl (2*S*)-3-methyl-2-

(methyl((2*R*)-2-methyl-2-(pyridin-3-yl)pyrrolidine-1-carbonyl)amino)butanoate (50.0 mg, 30% yield over 2 steps) as a yellow oil. LCMS (ESI) *m/z*: [M + H] calcd for $C_{24}H_{31}N_3O_3$: 410.2; found 410.2.

Step 7. To a stirred solution of benzyl (2*S*)-3-methyl-2-(methyl((2*R*)-2-methyl-2-(pyridin-3-yl)pyrrolidine-1-carbonyl)amino)butanoate (50.0 mg, 0.122 mmol) in MeOH (2.0 mL), $Pd(OH)_2$/C (50.0 mg, 0.356 mmol) was added under an atmosphere of nitrogen gas. The resulting mixture was stirred for 30 minutes at room temperature under an atmosphere of hydrogen gas. The reaction mixture was then filtered, the filter cake was washed with MeOH (2 x 10 mL), and the filtrate was concentrated under reduced pressure to afford (2*S*)-3-methyl-2-(methyl((2*R*)-2-methyl-2-(pyridin-3-yl)pyrrolidine-1-carbonyl)amino)butanoic acid (44 mg, crude) as a yellow oil. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{17}H_{25}N_3O_3$: 320.2; found 320.2.

Step 8. To a stirred solution of (6^3S,4*S*)-4-amino-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-5,7-dione (50 mg, 0.066 mmol) in DMF (1.0 mL), DIPEA (85.6 mg, 0.660 mmol), (2*S*)-3-methyl-2-(methyl((2*R*)-2-methyl-2-(pyridin-3-yl)pyrrolidine-1-carbonyl)amino)butanoic acid (31.7 mg, crude), and COMU (34.0 mg, 0.079 mmol) were added at 0 °C. The resulting mixture was stirred at 0 °C for 30 minutes. The reaction mixture was then quenched with H_2O (10 mL) at 0 °C, extracted with EtOAc (3 x 20 mL), washed with brine (3 x 20 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase prep-HPLC to afford (2*R*)-*N*-((2*S*)-1-((((6^3S,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*,2-dimethyl-2-(pyridin-3-yl)pyrrolidine-1-carboxamide (5.8 mg, 8% yield) as a white solid. LCMS (ESI) *m/z*: [M + H] calcd for $C_{58}H_{77}N_{11}O_6S$: 1056.6; found 1056.4; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (s, 1H), 8.56 – 8.15 (m, 4H), 7.87 – 7.74 (d, *J* = 11.9 Hz, 3H), 7.57 (s, 1H), 7.22 (br s, 2H), 5.68 - 5.52 (m, 1H), 5.12 (d, *J* = 11.9 Hz, 1H), 4.39 – 4.08 (m, 5H), 3.96 – 3.79 (m, 2H), 3.56 (s, 3H), 3.23 (s, 6H), 2.96 – 2.80 (m, 4H), 2.79 – 2.60 (m, 7H), 2.07 (br s, 4H), 1.98 – 1.57 (m, 9H), 1.55 – 1.07 (m, 6H), 1.05 – 0.60 (m, 13H), 0.51 – 0.25 (m, 8H).

Example A857: Synthesis of (2*S*)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^1-ethyl-1^2-(2-((*S*)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-2-(pyridin-3-yl)azetidine-1-carboxamide



Step 1. To a stirred solution of 3-amino-3-(3-pyridyl)propanoic acid (600 mg, 3.61 mmol) in MeOH (30 mL), thionyl chloride (1.32 mL, 18.1 mmol) was added dropwise at –10 °C. The resulting mixture was stirred at room temperature for 18 h, after which time it was concentrated under reduced pressure to afford methyl 3-amino-3-(pyridin-2-yl)propanoate dihydrochloride salt (920 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_9H_{12}N_2O_2$: 181.1; found 180.7.

Step 2. Methyl 3-amino-3-(pyridin-2-yl)propanoate dichydrochloride salt (913 mg, crude) was added to a stirred solution of triethylamine (2.08 mL, 14.6 mmol) and *p*-anisaldehyde (530 µL, 4.38 mmol) in MeOH (18.3 mL). The resulting mixture was stirred for 18 h at 40 °C. Subsequently, sodium borohydride (276 mg, 7.30 mmol) was added in portions at 0 °C and the resulting mixture was stirred for 2 h at room temperature. The reaction mixture was quenched with H_2O and was concentrated under reduced pressure. The resulting aqueous mixture was extracted with EtOAc, washed with brine, dried over anhydrous $MgSO_4$, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford methyl 3-(((4-methoxyphenyl)methyl)amino)-3-(pyridin-3-yl)propanoate (90% purity, 510 mg, 43% yield over 2 steps). LCMS (ESI) *m/z*: [M + H] calcd for $C_{17}H_{20}N_2O_3$: 301.2; found 300.8.

Step 3. To a stirred solution of methyl 3-(((4-methoxyphenyl)methyl)amino)-3-(pyridin-3-yl)propanoate (90% purity, 500 mg, 1.50 mmol) in anhydrous DCM (50 mL), isopropylmagnesium chloride (2.0 M in THF, 1.66 mL, 3.32 mmol) was added dropwise at –10 °C. The resulting mixture was stirred for 2 h at –10 °C. The reaction mixture was then quenched with H_2O, extracted with EtOAc, dried over anhydrous $MgSO_4$, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford 1-((4-methoxyphenyl)methyl)-4-(pyridin-3-yl)azetidin-2-one (90% purity, 170 mg, 38% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{16}H_{16}N_2O_2$: 269.1; found 268.6.

Step 4. A mixture of $AlCl_3$ (894 mg, 6.70 mmol) and $LiAlH_4$ (254 mg, 6.70 mmol) was refluxed in Et_2O (9.0 mL) for 30 minutes. Subsequently, 1-((4-methoxyphenyl)methyl)-4-(pyridin-3-yl)azetidin-2-one (90% purity, 300 mg, 1.01 mmol) was added at 0 °C and the resulting mixture was stirred at 0 °C for 90 minutes. The reaction mixture was then quenched with sat. aq. $NaHCO_3$ at 0 °C, extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford 3-(1-((4-methoxyphenyl)methyl)azetidin-2-yl)pyridine (300 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{16}H_{18}N_2O$: 255.1; found 254.9.

Step 5. To a stirred solution of 3-(1-((4-methoxyphenyl)methyl]azetidin-2-yl)pyridine (300 mg, crude) in MeCN (60 mL) and H_2O (0.6 mL), ceric ammonium nitrate (1.94 g, 3.54 mmol) was added and the resulting mixture was stirred at room temperature for 48 h. The reaction mixture was then quenched with H_2O and concentrated under reduced pressure to afford a mixture of inorganic salts and 3-(azetidin-2-yl)pyridine (2.3 g, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_8H_{10}N_2$: 135.1; found 134.7.

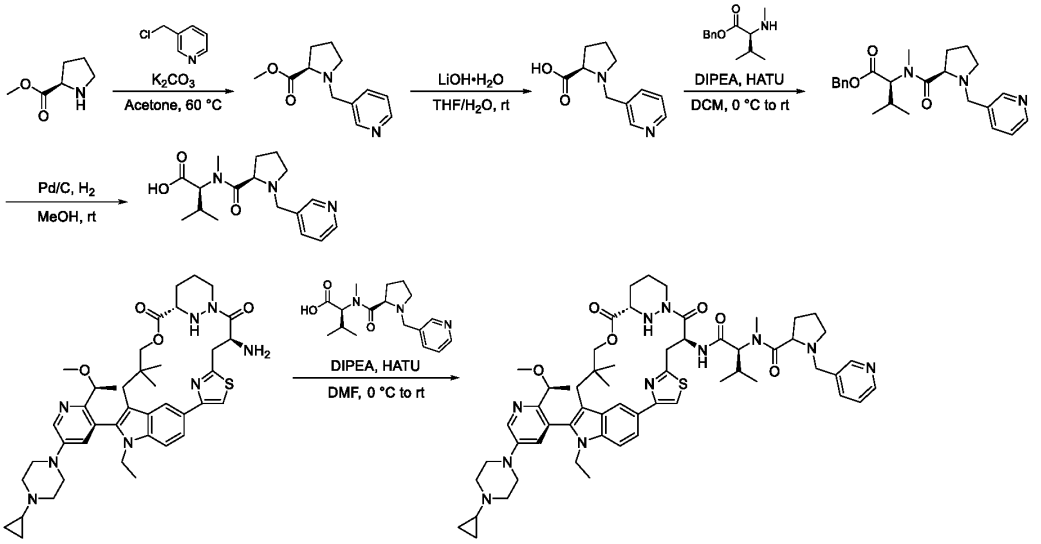
Step 6. To a stirred mixture of benzyl (2*S*)-2-((chlorocarbonyl)(methyl)amino)-3-methylbutanoate (350 mg, 1.23 mmol) in anhydrous DCM (15 mL), triethylamine (669 µL, 3.33 mmol) was added at room temperature. The resulting mixture was cooled to 0 °C and a mixture of crude 3-(azetidin-2-yl)pyridine from the previous reaction (2.3 g, crude) and commercially-sourced 3-(azetidin-2-yl)pyridine HCl salt (100 mg, 0.239 mmol) was added. The mixture was stirred at room temperature for 16 h. The reaction mixture was then quenched with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford benzyl (2*S*)-3-methyl-2-(methyl(2-(pyridin-3-yl)azetidine-1-carbonyl)amino)butanoate (230 mg, 49% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{22}H_{27}N_3O_3$: 382.2; found 382.2.

Step 7. To a stirred solution of benzyl (2*S*)-3-methyl-2-(methyl(2-(pyridin-3-yl)azetidine-1-carbonyl]amino)butanoate (210 mg, 0.550 mmol) in THF (21.6 mL) and water (2.1 mL), lithium hydroxide monohydrate (71.0 mg, 1.69 mmol) was added at 0 °C. The resulting mixture was stirred for 16 h at room temperature. The reaction mixture was then acidified to pH 5 with aqueous HCl (1.0 M), extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford (2*S*)-3-methyl-2-(methyl(2-(pyridin-3-yl)azetidine-1-carbonyl)amino)butanoic acid (250 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{15}H_{21}N_3O_3$: 292.2; found 291.8.

Step 8. To a stirred solution of (6^3*S*,4*S*)-4-amino-1^1-ethyl-1^2-(2-((*S*)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-5,7-dione (300 mg, 0.476 mmol) in anhydrous DMF (9.0 mL), DIPEA (828 µL, 4.76 mmol) and (2*S*)-3-methyl-2-(methyl(2-(pyridin-3-yl)azetidine-1-carbonyl)amino)butanoic acid (152 mg, crude) were added at 0 °C. The mixture was stirred for 5 minutes, after which time COMU (387 mg, 0.904 mmol) was added at 0 °C. The resulting mixture was stirred for 1 h at 0 °C. The reaction mixture was then quenched with H_2O, extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase prep-HPLC. The HPLC fractions containing the desired product were combined, treated with sat. aq. $NaHCO_3$, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and dried by

lyophilization to afford (2*S*)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^1-ethyl-1^2-(2-((*S*)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-2-(pyridin-3-yl)azetidine-1-carboxamide (8.0 mg, 2% yield). (Note: the absolute configuration of the 3-pyridyl azetidine substituent was determined though synthesis of the epimeric compound from commercially-sourced enantiopure 3-((2*R*)-azetidin-2-yl)pyridine). LCMS (ESI) *m/z*: [M + H] calcd for $C_{49}H_{61}N_9O_6S$: 904.5; found 904.5; ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 8.76 (dd, *J* = 4.7, 1.7 Hz, 1H), 8.62 (d, *J* = 2.3 Hz, 1H), 8.50 – 8.46 (m, 2H), 8.10 (d, *J* = 8.8 Hz, 1H), 7.84 – 7.74 (m, 3H), 7.73 – 7.71 (m, 1H), 7.59 (d, *J* = 8.7 Hz, 1H), 7.52 (dd, *J* = 7.7, 4.7 Hz, 1H), 7.40 (dd, *J* = 7.8, 4.7 Hz, 1H), 5.51 (t, *J* = 8.8 Hz, 1H), 5.39 (t, *J* = 8.1 Hz, 1H), 5.10 (d, *J* = 12.1 Hz, 1H), 4.37 – 4.07 (m, 7H), 3.99 – 3.85 (m, 1H), 3.60 – 3.48 (m, 2H), 3.27 (s, 3H), 3.12 – 3.01 (m, 2H), 3.01 – 2.91 (m, 1H), 2.85 (s, 3H), 2.78 – 2.61 (m, 2H), 2.40 (d, *J* = 14.3 Hz, 1H), 2.25 – 2.15 (m, 1H), 2.13 – 1.96 (m, 2H), 1.86 – 1.73 (m, 2H), 1.58 – 1.44 (m, 1H), 1.37 (d, *J* = 6.0 Hz, 3H), 0.93 – 0.83 (m, 9H), 0.79 (d, *J* = 6.5 Hz, 3H), 0.32 (s, 3H).

Example A479: Synthesis of *N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-1-(pyridin-3-ylmethyl)pyrrolidine-2-carboxamide.



Step 1. To a stirred mixture of 3-picolyl chloride HCl salt (272 mg, 1.66 mmol) and *D*-proline methyl ester HCl salt (250 mg, 1.51 mmol) in acetone (5.0 mL), K_2CO_3 (834 mg, 6.04 mmol) was added at room temperature. The resulting mixture was warmed to 60 °C and was stirred for 16 h. The reaction mixture was then cooled to room temperature, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford methyl (2*R*)-1-((pyridin-3-yl)methyl)pyrrolidine-2-carboxylate (300 mg, 90% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{12}H_{16}N_2O_2$: 221.1; found 221.7.

Step 2. To a stirred solution of methyl (2*R*)-1-((pyridin-3-yl)methyl)pyrrolidine-2-carboxylate (300 mg, 1.36 mmol) in THF (3.0 mL) and H_2O (3.0 mL), LiOH•H_2O (114 mg, 2.72 mmol) was added at room temperature. The resulting mixture was stirred at room temperature for 16 h. The reaction mixture was

then concentrated under reduced pressure and further dried by lyophilization to afford lithium (2*R*)-1-((pyridin-3-yl)methyl)pyrrolidine-2-carboxylate (220 mg, crude). This material was used in the next reaction without purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{11}H_{14}N_2O_2$: 207.1; found 207.6.

Step 3. To a stirred solution of benzyl (2*S*)-3-methyl-2-(methylamino)butanoate (535 mg, 1.04 mmol) and lithium (2*R*)-1-((pyridin-3-yl)methyl)pyrrolidine-2-carboxylate (220 mg, crude) in DMF (8.0 mL) DIPEA (718 µL, 4.15 mmol) and HATU (473 mg, 1.24 mmol) were added at 0 °C. The resulting mixture was stirred at 0 °C for 30 minutes and was then stirred at room temperature for 3 h. The reaction mixture was poured into brine and filtered. The precipitate was isolated, dissolved in DCM, dried over anhydrous $MgSO_4$, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford benzyl (2*S*)-3-methyl-2-(*N*-methyl-1-((2*R*)-1-((pyridin-3-yl)methyl)pyrrolidin-2-yl)formamido)butanoate (260 mg, 47% yield over 2 steps). LCMS (ESI) *m/z*: [M + H] calcd for $C_{24}H_{31}N_3O_3$: 410.2; found 410.9.

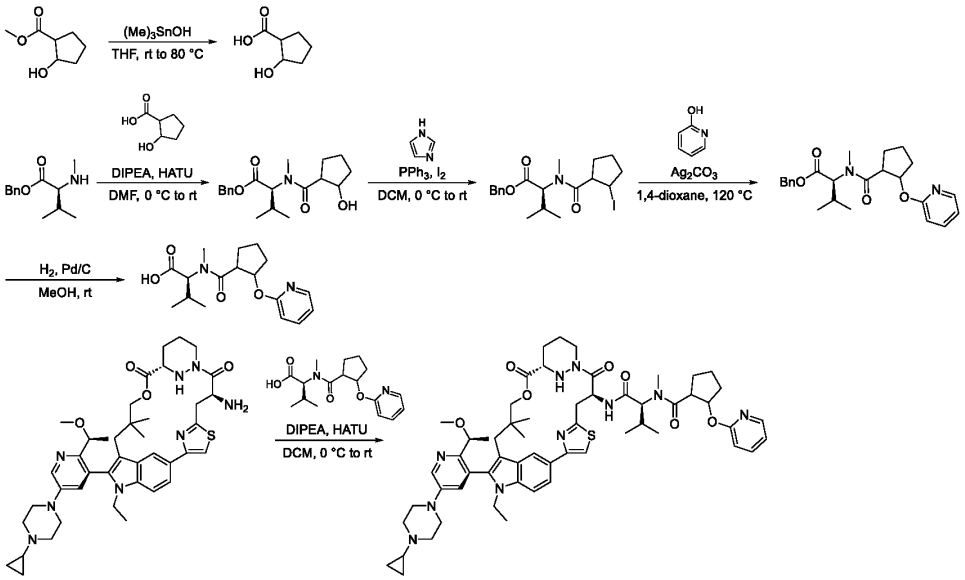
Step 4. To a stirred solution of benzyl (2*S*)-3-methyl-2-(*N*-methyl-1-((2*R*)-1-((pyridin-3-yl)methyl)pyrrolidin-2-yl)formamido)butanoate (648 mg, 1.06 mmol) in MeOH (6.5 mL), Pd/C (10% wt., 68 mg) was added. The resulting mixture was stirred at room temperature for 1 h under an atmosphere of hydrogen gas. The reaction mixture was then filtered through a pad of Celite®, concentrated under reduced pressure, and purified by reversed-phase flash column chromatography to afford (2*S*)-3-methyl-2-(*N*-methyl-1-(1-((pyridin-3-yl)methyl)pyrrolidin-2-yl)formamido)butanoic acid (123 mg, 39% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{17}H_{25}N_3O_3$: 320.2; found 320.2.

Step 5. To a stirred solution of (2*S*)-3-methyl-2-(*N*-methyl-1-((2*S*)-1-((pyridin-3-yl)methyl)pyrrolidin-2-yl)formamido)butanoic acid (110 mg, 0.344 mmol) and (6^3S,4*S*)-4-amino-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-5,7-dione (262 mg, 0.347 mmol) in DMF (10.5 mL), DIPEA (178 µL, 1.03 mmol) and HATU (157 mg, 0.413 mmol) were added at 0 °C. The resulting mixture was stirred for 30 minutes at 0 °C and was then stirred for 30 minutes at room temperature. (Note: epimerization of the desired product was observed while monitoring the reaction). The reaction mixture was quenched with H_2O and the resulting suspension was filtered. The isolated precipitate was dissolved in DCM, dried over anhydrous $MgSO_4$, filtered, concentrated under reduced pressure, and purified by reversed-phase prep-HPLC to afford two separated isomers of *N*-((2*S*)-1-(((6^3S,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-1-(pyridin-3-ylmethyl)pyrrolidine-2-carboxamide.

Isomer 1 (A479): (4.2 mg, 1% yield); LCMS (ESI) *m/z*: [M + H] calcd for $C_{58}H_{77}N_{11}O_6S$: 1056.6; found 1056.6; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 – 8.39 (m, 4H), 7.94 – 7.86 (m, 1H), 7.80 – 7.70 (m, 1H), 7.72 – 7.60 (m, 1H), 7.58 – 7.48 (m, 1H), 7.41 – 7.30 (m, 1H), 7.20 (d, *J* = 2.9 Hz, 1H), 5.65 – 5.55 (m, 1H), 5.47 – 5.38 (m, 1H), 5.18 – 5.06 (m, 1H), 4.79 (d, *J* = 10.9 Hz, 1H), 4.36 – 4.07 (m, 4H), 4.05 – 3.97 (m, 2H), 3.96 – 3.79 (m, 1H), 3.62 – 3.48 (m, 3H), 3.32 – 3.26 (m, 3H), 3.26 – 3.16 (m, 7H), 3.01 – 2.89 (m, 1H), 2.97 – 2.78 (m, 3H), 2.85 – 2.78 (m, 1H), 2.71 – 2.64 (m, 5H), 2.46 – 2.37 (m, 2H), 2.15 – 2.04 (m, 2H), 1.92 – 1.74 (m, 5H), 1.70 – 1.60 (m,

1H), 1.57 – 1.42 (m, 1H), 1.32 (d, *J* = 6.0 Hz, 3H), 0.95 – 0.83 (m, 8H), 0.82 (d, *J* = 6.5 Hz, 1H), 0.74 (t, *J* = 7.4 Hz, 3H), 0.47 – 0.40 (m, 2H), 0.37 – 0.29 (m, 5H).

Example A112: Synthesis of *N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-2-(pyridin-2-yloxy)cyclopentane-1-carboxamide



Step 1. To a stirred solution of methyl 2-hydroxycyclopentylcarboxylate (2.00 g, 13.9 mmol) in anhydrous THF (20 mL) was added trimethyltin hydroxide (5.02 g, 27.8 mmol) at room temperature. The resulting mixture was stirred for 16 hours at 80 °C. The reaction mixture was then diluted with acetone (20 mL), filtered, and concentrated under reduced pressure to afford 2-hydroxycyclopentane-1-carboxylic acid (1.81 g, crude). This material was taken to the next reaction without further purification.

Step 2. To a stirred solution of benzyl (2*S*)-3-methyl-2-(methylamino)butanoate hydrochloride (2.38 g, 9.23 mmol) and DIPEA (16.1 mL, 92.3 mmol) in DMF (95 mL) was added 2-hydroxycyclopentane-1-carboxylic acid (1.80 g, crude). The resulting mixture was stirred for 15 minutes at 0 °C, after which time HATU (17.5 g, 46.1 mmol) was added and the mixture was stirred for 16 h at room temperature. The reaction mixture was then quenched with H_2O, extracted with DCM, washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford benzyl (2*S*)-2-(1-(2-hydroxycyclopentyl)-*N*-methylformamido)-3-methylbutanoate (1.15 g, 32% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{19}H_{27}NO_4$: 334.2; found 334.3.

Step 3. To a stirred solution of benzyl (2*S*)-2-(1-(2-hydroxycyclopentyl)-*N*-methylformamido)-3-methylbutanoate (1.15 g, 2.92 mmol) in anhydrous DCM (46 mL) were added imidazole (398 mg, 5.84 mmol), triphenylphosphine (1.15 g, 4.38 mmol) and iodine (1.11 g, 4.38 mmol) at 0 °C. The resulting mixture was stirred for 16 hours at room temperature. The reaction mixture was then quenched with sat. aq. $Na_2S_2O_3$, extracted with DCM, washed with brine, dried over anhydrous Na_2SO_4, filtered,

concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford benzyl (2*S*)-2-(1-(2-iodocyclopentyl)-*N*-methylformamido)-3-methylbutanoate (759 mg, 59% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{19}H_{26}INO_3$: 444.1; found 444.2.

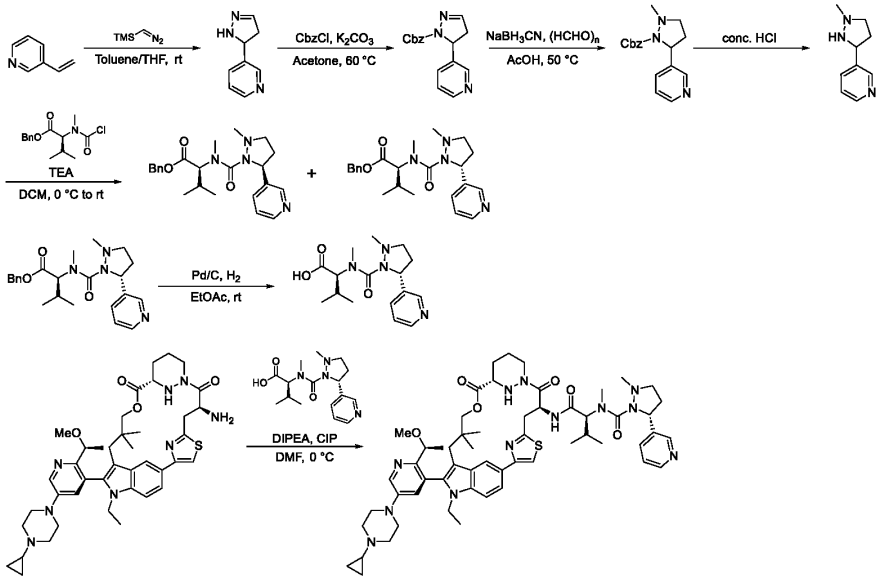
Step 4. To a stirred solution of benzyl (2*S*)-2-(1-(2-iodocyclopentyl)-*N*-methylformamido)-3-methylbutanoate (759 mg, 1.71 mmol) and 2-hydroxypyridine (326 mg, 3.43 mmol) in 1,4-dioxane (30 mL) was added silver carbonate (1.04 g, 3.77 mmol). The resulting mixture was stirred for 16 h at 120 °C in a sealed tube. The reaction mixture was then filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure to afford benzyl (2*S*)-3-methyl-2-(*N*-methyl-1-(2-(pyridin-2-yloxy)cyclopentyl)formamido)butanoate (661 mg, crude). This material was taken to the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{24}H_{30}N_2O_4$: 411.2; found 411.4.

Step 5. To a stirred solution of benzyl (2*S*)-3-methyl-2-(*N*-methyl-1-(2-(pyridin-2-yloxy)cyclopentyl)formamido)butanoate (630 mg, crude) in MeOH (12.6 mL) was added palladium on carbon (10% wt., 20 mg) under at atmosphere of argon. The reaction flask was evacuated and backfilled with H_2 gas and the resulting mixture was stirred for 2 h at room temperature under an atmosphere of H_2. The reaction mixture was then filtered through a pad of Celite®, washed with MeOH, and concentrated under reduced pressure to give of (2*S*)-3-methyl-2-(*N*-methyl-1-(2-(pyridin-2-yloxy)cyclopentyl)formamido)butanoic acid (432 mg, crude). This material was taken to the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{17}H_{24}N_2O_4$: 321.2; found 321.3.

Step 6. To a stirred solution of (6^3*S*,4*S*)-4-amino-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-5,7-dione (300 mg, 0.40 mmol) in anhydrous DCM (9.0 mL) were added DIPEA (686 µL, 3.94 mmol) and (2*S*)-3-methyl-2-(*N*-methyl-1-(2-(pyridin-2-yloxy)cyclopentyl)formamido)butanoic acid (152 mg, crude) at 0 °C. This mixture was stirred for 15 minutes at 0 °C, after which time HATU (224 mg, 0.60 mmol) was added and the resulting mixture was stirred at room temperature for 16 h. The reaction mixture was then quenched with H_2O, extracted with DCM, washed with sat. aq. $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase prep-HPLC to obtain one fraction containing a mixture of three diastereomers of *N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-2-(pyridin-2-yloxy)cyclopentane-1-carboxamide and one fraction containing a single isolated diastereomer of *N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-2-(pyridin-2-yloxy)cyclopentane-1-carboxamide (**A112**) (14.2 mg, 3.4% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{58}H_{76}N_{10}O_7S$: 1057.6; found 1057.3; ^{1}H NMR (600 MHz, DMSO-*d*$_6$) δ 8.80 – 8.40 (m, 1H), 8.48 – 8.44 (m, 2H), 8.16 – 8.10 (m, 1H), 7.86 – 7.46 (m, 1H), 7.75 – 7.65 (m, 2H), 7.58 – 7.53 (m, 1H), 7.21 (t, *J* = 3.5 Hz, 1H), 6.98 – 6.90 (m, 1H), 6.81 – 6.74 (m, 1H), 5.71 – 5.44 (m, 2H), 5.14 – 4.80 (m, 2H), 4.25 – 4.12 (m, 5H), 3.70 – 3.52 (m, 3H), 3.41 – 3.36 (m, 1H), 3.27 – 3.20 (m, 8H), 3.20 – 3.14 (m, 1H), 3.00 – 3.85 (m, 4H), 2.82 – 2.73 (m, 1H), 2.72 – 2.65 (m, 4H), 2.47 – 2.42 (m, 1H), 2.37 – 2.28 (m, 1H), 2.24 –

2.05 (m, 3H), 1.88 – 1.77 (m, 4H), 1.76 – 1.59 (m, 3H), 1.57 – 1.47 (m, 1H), 1.33 (d, *J* = 6.0 Hz, 3H), 0.95 – 0.87 (m, 9H), 0.77 – 0.70 (m, 3H), 0.47 – 0.42 (m, 2H), 0.38 – 0.31 (m, 5H).

Example A649: Synthesis of (5*R*)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-2-dimethyl-5-(pyridin-3-yl)pyrazolidine-1-carboxamide



Step 1. To a stirred solution of 3-vinylpyridine (1.00 g, 9.51 mmol) in THF (10 mL) and toluene (10 mL), (diazomethyl)trimethylsilane (1.30 g, 11.4 mmol) was added at room temperature. The resulting mixture was stirred for 20 h at room temperature under an atmosphere of nitrogen gas. The reaction mixture was then was quenched with H_2O (10 mL) at 0 °C, extracted with EtOAc (3 x 10 mL), washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford 3-(4,5-dihydro-1*H*-pyrazol-5-yl) pyridine (1.10 g, crude) as a yellow oil. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_8H_9N_3$: 148.1; found 148.1.

Step 2. A mixture of 3-(4,5-dihydro-1*H*-pyrazol-5-yl) pyridine (1.10 g, crude), CbzCl (2.55 g, 15.0 mmol), and K_2CO_3 (2.07 g, 15.0 mmol) in acetone (30 mL) was stirred for 2 h at 60 °C under an atmosphere of nitrogen gas. The reaction mixture was then quenched with H_2O (50 mL) at 0 °C, extracted with EtOAc (3 x 50 mL), washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford benzyl 5-(pyridin-3-yl)-4,5-dihydro-1*H*-pyrazole-1-carboxylate (1.50 g, 56% yield over 2 steps) as a yellow oil. LCMS (ESI) *m/z*: [M + H] calcd for $C_{16}H_{15}N_3O_2$: 282.1; found 282.1.

Step 3. To a stirred solution of benzyl 5-(pyridin-3-yl)-4,5-dihydropyrazole-1-carboxylate (1.00 g, 3.56 mmol) in AcOH (10 mL), $NaBH_3CN$ (670 mg, 10.7 mmol) was added in portions at 50 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred for 2 h at 50 °C. Subsequently, paraformaldehyde (961 mg, 10.7 mmol) was added and the resulting mixture was stirred for another 2 h

at 50 °C under an atmosphere of nitrogen gas. The reaction mixture was then quenched with H_2O (50 mL) at 0 °C, extracted with EtOAc (3 x 50 mL), washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford benzyl 2-methyl-5-(pyridin-3-yl)pyrazolidine-1-carboxylate (1.0 g, 95% yield) as a yellow oil. LCMS (ESI) *m/z*: [M + H] calcd for $C_{17}H_{19}N_3O_2$: 298.2; found 298.1.

Step 4. A solution of benzyl 2-methyl-5-(pyridin-3-yl) pyrazolidine-1-carboxylate (300 mg, 1.01 mmol) in concentrated hydrogen chloride (12 M, 45 mL) was stirred for 16 h at room temperature under an atmosphere of nitrogen gas. The reaction mixture was then slowly diluted with H_2O (30 mL), basified to pH 8 with sat. aq. $NaHCO_3$, extracted with DCM (3 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford 3-(1-methylpyrazolidin-3-yl) pyridine (300 mg, crude) as a yellow oil. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_9H_{13}N_3$: 164.1; found 164.2.

Step 5. To a stirred solution of 3-(1-methylpyrazolidin-3-yl) pyridine (300 mg, crude) and TEA (562 mg, 5.52 mmol) in DCM (5 mL), benzyl *N*-(chlorocarbonyl)-*N*-methyl-*L*-valinate (1.04 g, 3.68 mmol) was added at 0 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred for 16 h at room temperature. The reaction mixture was then quenched with H_2O (10 mL) at 0 °C, extracted with DCM (3 x 10 mL), washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford benzyl *N*-methyl-*N*-(3-(pyridin-3-yl) isoxazolidine-2-carbonyl)-*L*-valinate (220 mg, 53% over 2 steps) as a yellow oil. LCMS (ESI) *m/z*: [M + H] calcd for $C_{23}H_{30}N_4O_3$: 411.2; found 411.2. This material was further purified by chiral prep-HPLC (polysaccharide column) to afford two separated diastereomers of the product.

Isomer 1: (65.0 mg, 16% yield over 2 steps)

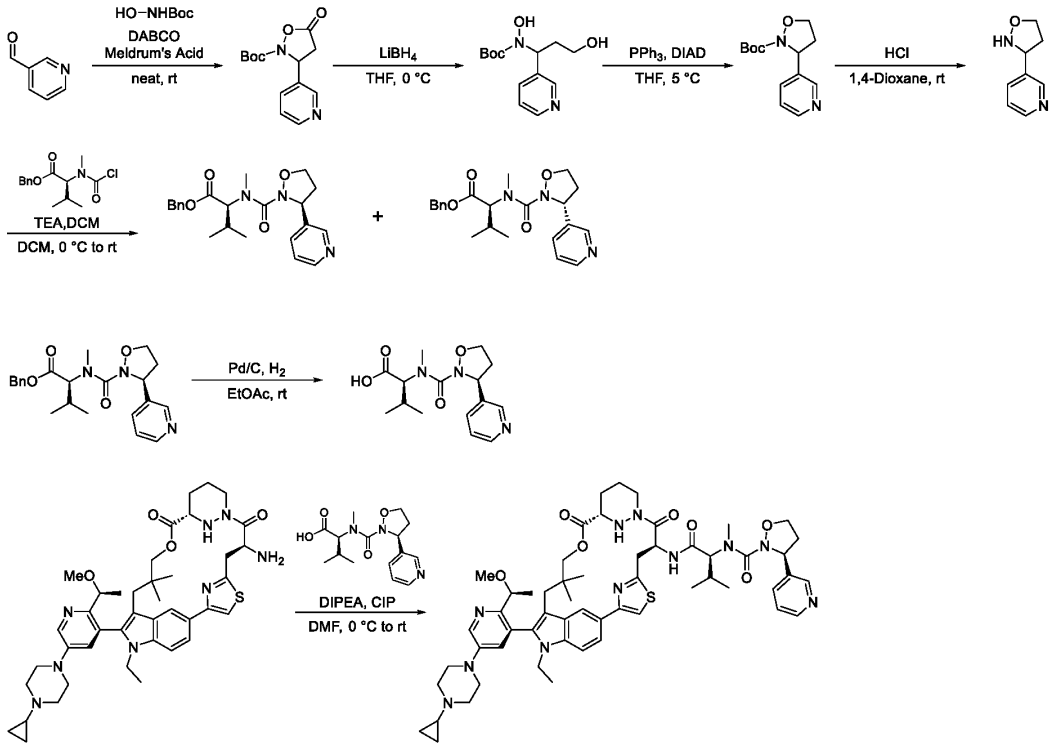
Isomer 2: (67.0 mg, 16% yield over 2 steps)

Step 6. To a stirred solution of benzyl (2*S*)-3-methyl-2-(methyl((5*R*)-2-methyl-5-(pyridin-3-yl)pyrazolidine-1-carbonyl)amino)butanoate (*Isomer 2* from previous reaction, 65.0 mg, 0.158 mmol, assumed absolute configuration) in EtOAc (3.0 mL), Pd/C (10% wt., 65.0 mg) was added in portions at room temperature. The resulting mixture was stirred for 5 h at room temperature under an atmosphere of hydrogen gas. The reaction mixture was then filtered, the filter cake was washed with a 10:1 vol. mixture of DCM:MeOH (2 x 20 mL), and the filtrate was concentrated under reduced pressure to afford (2*S*)-3-methyl-2-(methyl((5*R*)-2-methyl-5-(pyridin-3-yl) pyrazolidine-1-carbonyl)amino)butanoic acid (54.0 mg, crude) as a white solid. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{16}H_{24}N_4O_3$: 321.2; found 321.2.

Step 7. To a stirred solution of (6^3S,4*S*)-4-amino-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-5,7-dione (90.0 mg, 0.119 mmol) and DIPEA (46.2 mg, 0.357 mmol) in DMF (3.0 mL), (2*S*)-3-methyl-2-(methyl((5*R*)-2-methyl-5-(pyridin-3-yl) pyrazolidine-1-carbonyl)amino)butanoic acid (49.7 mg, crude) and CIP (48.5 mg, 0.174 mmol) were added in portions at 0 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred for 1 h at 0 °C. The resulting mixture was diluted with brine (100 mL), extracted with EtOAc (2 x 30 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase prep-HPLC to afford (5*R*)-

N-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-2-dimethyl-5-(pyridin-3-yl)pyrazolidine-1-carboxamide (11.0 mg, 9% yield) as a white solid. LCMS (ESI) *m/z*: [M + H] calcd for $C_{57}H_{76}N_{12}O_6S$: 1057.6; found 1057.8; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (d, *J* = 2.3 Hz, 1H), 8.49 – 8.38 (m, 4H), 7.82 (s, 1H), 7.78 – 7.72 (m, 2H), 7.55 (d, *J* = 8.7 Hz, 1H), 7.33 (dd, *J* = 8.0, 4.8 Hz, 1H), 7.20 (d, *J* = 2.9 Hz, 1H), 5.58 – 5.43 (m, 2H), 5.08 (d, *J* = 12.1 Hz, 1H), 4.45 (d, *J* = 10.7 Hz, 1H), 4.34 – 4.11 (m, 5H), 3.62 – 3.53 (m, 2H), 3.30 – 3.21 (m, 2H), 3.22 (s, 6H), 3.02 – 2.95 (m, 2H), 2.99 (s, 4H), 2.84 – 2.75 (m, 1H), 2.69 (d, *J* = 6.1 Hz, 4H), 2.43 (d, *J* = 14.1 Hz, 1H), 2.24 – 2.06 (m, 4H), 1.80 (br s, 3H), 1.67 – 1.63 (m, 1H), 1.55 – 1.47 (m, 1H), 1.33 (d, *J* = 6.1 Hz, 3H), 1.24 (s, 1H), 0.94 – 0.83 (m, 10H), 0.77 (d, *J* = 6.7 Hz, 3H), 0.43 (d, *J* = 2.4 Hz, 2H), 0.34 (d, *J* = 2.8 Hz, 6H).

Example A828: Synthesis of (3*S*)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-3-(pyridin-3-yl)isoxazolidine-2-carboxamide



Step 1. To a stirred neat mixture of 3-pyridinecarboxaldehyde (1.00 g, 9.34 mmol), *tert*-butyl *N*-hydroxycarbamate (2.49 g, 18.7 mmol), and 2,2-dimethyl-1,3-dioxane-4,6-dione (673 mg, 4.67 mmol), DABCO (1.05 g, 9.34 mmol) was added in portions at room temperature under an atmosphere of nitrogen gas. The resulting mixture was stirred for 16 h at room temperature. The reaction mixture was then filtered, the filter cake was washed with EtOAc (3 x 10 mL), and the filtrate was concentrated under reduced pressure to afford *tert*-butyl 5-oxo-3-(pyridin-3-yl)isoxazolidine-2-carboxylate (2.20 g, crude) as a

yellow oil. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{13}H_{16}N_2O_4$: 265.1; found 265.1.

Step 2. To a stirred solution of *tert*-butyl 5-oxo-3-(pyridin-3-yl) isoxazolidine-2-carboxylate (2.10 g, crude) in THF (30 mL), $LiBH_4$ (493 mg, 22.6 mmol) was added at 0 °C. The resulting mixture was stirred for 2 h at 0 °C under an atmosphere of nitrogen gas. The reaction mixture was then quenched with H_2O (50 mL) at 0 °C, extracted with EtOAc (3 x 50 mL), washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford *tert*-butyl hydroxy(3-hydroxy-1-(pyridin-3-yl) propyl) carbamate (2.10 g, crude) as a yellow oil. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{13}H_{20}N_2O_4$: 269.1; found 269.2.

Step 3. To a stirred solution of *tert*-butyl hydroxy(3-hydroxy-1-(pyridin-3-yl) propyl) carbamate (2.10 g, crude) and PPh_3 (2.93 g, 11.2 mmol) in THF (30mL), DIAD (2.26 g, 11.2 mmol) was added dropwise at 5 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred for 10 minutes at 5 °C and was then concentrated under reduced pressure to afford *tert*-butyl 3-(pyridin-3-yl)isoxazolidine-2-carboxylate (7.50 g, crude) as a brown oil. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{13}H_{18}N_2O_3$: 251.1; found 251.1.

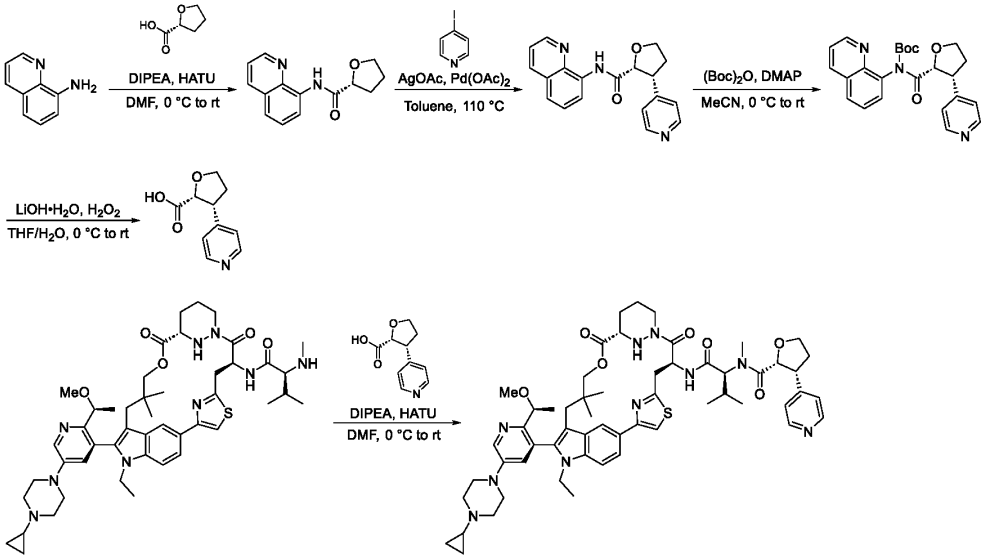
Step 4. A solution of *tert*-butyl 3-(pyridin-3-yl)-1,2-oxazolidine-2-carboxylate (7.00 g, crude) and hydrogen chloride (4.0 M in 1,4-dioxane, 45 mL) was stirred for 16 h at room temperature under an atmosphere of nitrogen gas. The reaction mixture was then diluted with H_2O (30 mL), basified to pH 8 with sat. aq. $NaHCO_3$, extracted with DCM (3 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford 3-(pyridin-3-yl)isoxazolidine (800 mg, crude) as a yellow oil. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_8H_{10}N_2O$: 151.1; found 151.2.

Step 5. To a stirred solution of 3-(1,2-oxazolidin-3-yl) pyridine (800 mg, crude) and TEA (1.62 g, 16.0 mmol) in DCM (8.0 mL), benzyl *N*-(chlorocarbonyl)-*N*-methyl-*L*-valinate (3.02 g, 10.7 mmol) was added dropwise at 0 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred for 16 h at room temperature. The reaction mixture was then quenched with H_2O (10 mL) at 0 °C, extracted with DCM (3 x 10 mL), washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford benzyl *N*-methyl-*N*-(3-(pyridin-3-yl)isoxazolidine-2-carbonyl)-*L*-valinate (870 mg, 26% yield over 5 steps) as a mixture of two diastereomers. LCMS (ESI) *m/z*: [M + H] calcd for $C_{22}H_{27}N_3O_4$: 398.2; found 398.1. This material was further purified by reversed-phase chiral prep-HPLC to afford two separated diastereomers (400 mg isomer 1 and 300 mg isomer 2).

Step 6. A mixture of benzyl *N*-methyl-*N*-((*S*)-3-(pyridin-3-yl) isoxazolidine-2-carbonyl)-*L*-valinate (400 mg, 1.01 mmol) and Pd/C (10% wt., 300 mg) in EtOAc (5.0 mL) was stirred for 2 h at room temperature under an atmosphere of hydrogen gas. The reaction mixture was then filtered, the filter cake was washed with EtOAc (3 x 10 mL), and the filtrate was concentrated under reduced pressure to afford *N*-methyl-*N*-((*S*)-3-(pyridin-3-yl)isoxazolidine-2-carbonyl)-*L*-valine (300 mg, crude) as a clear oil. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{15}H_{21}N_3O_4$: 308.2; found 308.2.

Step 7. To a stirred solution of (6^3S,4*S*)-4-amino-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-11-ethyl-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-5,7-dione (200 mg, 0.265 mmol) and *N*-methyl-*N*-((S)-3-(pyridin-3-yl)isoxazolidine-2-carbonyl)-*L*-valine (122 mg, crude) in DMF (2.0 mL), DIPEA (103 mg, 0.795 mmol) and CIP (148 mg, 0.530 mmol) were added at 0 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred for 2 h at room temperature. The reaction mixture was then quenched with H_2O (10 mL) at 0 °C, extracted with EtOAc (3 x 100 mL), washed with brine (3 x 10 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase prep-HPLC to afford (3*S*)-*N*-((2*S*)-1-((((6^3S,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-3-(pyridin-3-yl)isoxazolidine-2-carboxamide (15 mg, 5% yield) as a white solid. LCMS (ESI) *m/z*: [M + H] calcd for $C_{56}H_{73}N_{11}O_7S$: 1044.5; found 1044.4; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (s, 1H), 8.59 – 8.55 (m, 1H), 8.49 – 8.42 (m, 3H), 7.89 – 7.84 (m, 1H), 7.82 (s, 1H), 7.74 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.55 (d, *J* = 8.8 Hz, 1H), 7.40 – 7.35 (m, 1H), 7.20 (d, *J* = 2.8 Hz, 1H), 5.54 – 5.43 (m, 2H), 5.10 (d, *J* = 12.1 Hz, 1H), 4.45 (d, *J* = 10.6 Hz, 1H), 4.32 – 4.11 (m, 6H), 3.96 (q, *J* = 8.1 Hz, 1H), 3.54 (dd, *J* = 18.2, 7.2 Hz, 2H), 3.32 – 3.27 (m, 1H), 3.22 (s, 4H), 2.95 – 2.91 (m, 1H), 2.94 (s, 3H), 2.89 – 2.82 (m, 2H), 2.68 (br s, 4H), 2.41 (d, *J* = 14.4 Hz, 1H), 2.33 – 2.08 (m, 3H), 1.85 – 1.78 (m, 2H), 1.69 – 1.63 (m, 1H), 1.58 – 1.47 (m, 1H), 1.34 (d, *J* = 6.1 Hz, 3H), 1.24 (s, 1H), 0.97 – 0.81 (m, 13H), 0.47 – 0.42 (m, 2H), 0.34 (s, 5H).

Example A870: Synthesis of (2*R*,3*R*)-*N*-((2*S*)-1-((((6^3S,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-3-(pyridin-4-yl)tetrahydrofuran-2-carboxamide



Step 1. To a stirred solution of 8-aminoquinoline (20.0 g, 139 mmol) and DIPEA (143 g, 1110 mmol) in DMF (200 mL), (2*R*)-oxolane-2-carboxylic acid (19.3 g, 166 mmol) and HATU (105 g, 277 mmol) were added in portions at 0 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred for 1 h at room temperature. The reaction mixture was then quenched with sat. aq. NH_4Cl (100 mL) at 0 °C, extracted with EtOAc (3 x 100 mL), washed with brine (3 x 400 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford (*R*)-*N*-(quinolin-8-yl)tetrahydrofuran-2-carboxamide (24.0 g, 71% yield) as a yellow oil. LCMS (ESI) *m/z*: [M + H] calcd for $C_{14}H_{14}N_2O_2$: 243.1; found 243.0.

Step 2. A mixture of (*R*)-*N*-(quinolin-8-yl) tetrahydrofuran-2-carboxamide (8.00 g, 33.0 mmol), 4-iodopyridine (27.1 g, 132 mmol), AgOAc (12.1 g, 72.6 mmol) and $Pd(OAc)_2$ (740 mg, 3.302 mmol) in toluene (80 mL) was stirred for 56 h at 110 °C under an atmosphere of argon gas. The reaction mixture was then filtered and the filter cake was washed with MeOH (3 x 50 mL). The filtrate was concentrated under reduced pressure and purified by reversed-phase flash column chromatography to afford (2*R*,3*R*)-3-(pyridin-4-yl)-*N*-(quinolin-8-yl)-tetrahydrofuran-2-carboxamide (1.60 g, 15% yield) as a light yellow solid. LCMS (ESI) *m/z*: [M + H] calcd for $C_{19}H_{17}N_3O_2$: 320.1; found 320.1.

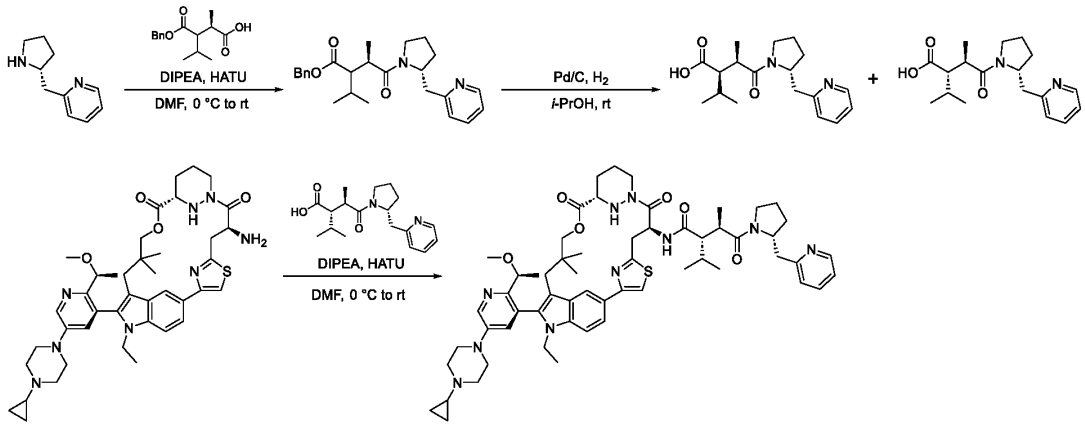
Step 3. To a stirred solution of (2*R*,3*R*)-3-(pyridin-4-yl)-*N*-(quinolin-8-yl)-tetrahydrofuran-2-carboxamide (800 mg, 2.51 mmol) and DMAP (367 mg, 3.01 mmol) in MeCN (10 mL), $(Boc)_2O$ (1.64 g, 7.52 mmol) was added in portions at 0 °C under an atmosphere of argon. The resulting mixture was stirred for 3 h at room temperature. The reaction mixture was then concentrated under reduced pressure and purified by normal phase prep-TLC to afford *tert*-butyl ((2*R*,3*R*)-3-(pyridin-4-yl)-tetrahydrofuran-2-carbonyl)(quinolin-8-yl) carbamate (780 mg, 74% yield) as light yellow oil. LCMS (ESI) *m/z*: [M + H] calcd for $C_{24}H_{25}N_3O_4$: 420.2; found 420.4.

Step 4. To a stirred solution of *tert*-butyl ((2*R*,3*R*)-3-(pyridin-4-yl)-tetrahydrofuran-2-carbonyl)(quinolin-8-yl) carbamate (700 mg, 1.67 mmol) in THF (7.5 mL) and H_2O (7.5 mL), $LiOH{\bullet}H_2O$ (140 mg, 3.34 mmol) and H_2O_2 (30% wt., 568 mg, 5.01 mmol) were added dropwise at 0 °C under an atmosphere of argon gas. The resulting mixture was stirred for 3 h at room temperature. The reaction mixture was then extracted with EtOAc (20 mL). The resulting aqueous extract was acidified to pH 3 with 1M aq. HCl and was then dried by lyophilization to afford (2*R*,3*R*)-3-(pyridin-4-yl) tetrahydrofuran-2-carboxylic acid (3.30 g, crude) as a light yellow solid. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{10}H_{11}NO_3$: 194.1; found 194.2.

Step 5. To a stirred solution of (2*S*)-*N*-((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)-3-methyl-2-(methylamino)butanamide (90.0 mg, 0.104 mmol) and (2*R*,3*R*)-3-(pyridin-4-yl)oxolane-2-carboxylic acid (60.1 mg, crude) in DMF (1.0 mL), HATU (118 mg, 0.312 mmol) and DIPEA (53.6 mg, 0.416 mmol) were added in portions at 0 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred for 16 h at room temperature. The reaction was then quenched with H_2O (5 mL) at 0 °C, extracted with EtOAc (3 x 10 mL), concentrated under reduced pressure, and purified by reversed-phase flash column chromatography to afford (2*R*,3*R*)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-

2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-3-(pyridin-4-yl)tetrahydrofuran-2-carboxamide (8.8 mg, 8% yield) as a white solid. LCMS (ESI) *m/z*: [M + H] calcd for $C_{57}H_{74}N_{10}O_7S$: 1043.6; found 1043.4; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 – 8.37 (m, 6H), 8.26 (d, *J* = 6.8 Hz, 1H), 7.81 (s, 1H), 7.79 – 7.71 (m, 1H), 7.55 (d, *J* = 8.7 Hz, 1H), 7.33 – 7.27 (m, 2H), 7.24 – 7.18 (m, 2H), 5.41 (t, *J* = 8.4 Hz, 1H), 5.12 (d, *J* = 7.3 Hz, 1H), 5.03 (d, *J* = 12.1 Hz, 1H), 4.38 (d, *J* = 10.6 Hz, 1H), 4.30 – 4.23 (m, 2H), 4.23 – 4.11 (m, 3H), 3.29 – 3.18 (m, 5H), 2.85 (s, 2H), 2.68 (s, 6H), 2.61 (s, 1H), 2.55 – 2.40 (m, 4H), 2.34 – 2.23 (m, 2H), 2.10 – 2.03 (m, 1H), 1.86 – 1.74 (m, 2H), 1.60 – 1.45 (m, 1H), 1.32 (d, *J* = 6.2 Hz, 4H), 1.24 (s, 1H), 0.98 – 0.85 (m, 8H), 0.72 (d, *J* = 6.5 Hz, 3H), 0.47 – 0.37 (m, 3H), 0.34 (s, 5H), 0.06 (d, *J* = 3.8 Hz, 2H).

Example A190: Synthesis of (2*S*,3*R*)-*N*-((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)-2-isopropyl-3-methyl-4-oxo-4-((*R*)-2-(pyridin-2-ylmethyl)pyrrolidin-1-yl)butanamide



Step 1. To a stirred solution of 2-((2*R*)-pyrrolidin-2-ylmethyl)pyridine (600 mg, 3.70 mmol) and (2*R*)-3-((benzyloxy)carbonyl)-2,4-dimethylpentanoic acid (978 mg, 3.70 mmol) in DMF (20 mL), DIPEA (6.44 mL, 37.0 mmol) and HATU (2.83 g, 7.43 mmol) were added dropwise at 0 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred at room temperature for 2 h. The reaction mixture was then diluted with H_2O (20 mL), extracted with EtOAc (3 x 20 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase prep-TLC to afford benzyl (3*R*)-2-isopropyl-3-methyl-4-oxo-4-((*R*)-2-(pyridin-2-ylmethyl)pyrrolidin-1-yl)butanoate (600 mg, 40% yield) as an off-white solid. LCMS (ESI) *m/z*: [M + H] calcd for $C_{25}H_{32}N_2O_3$: 409.2; found 409.2.

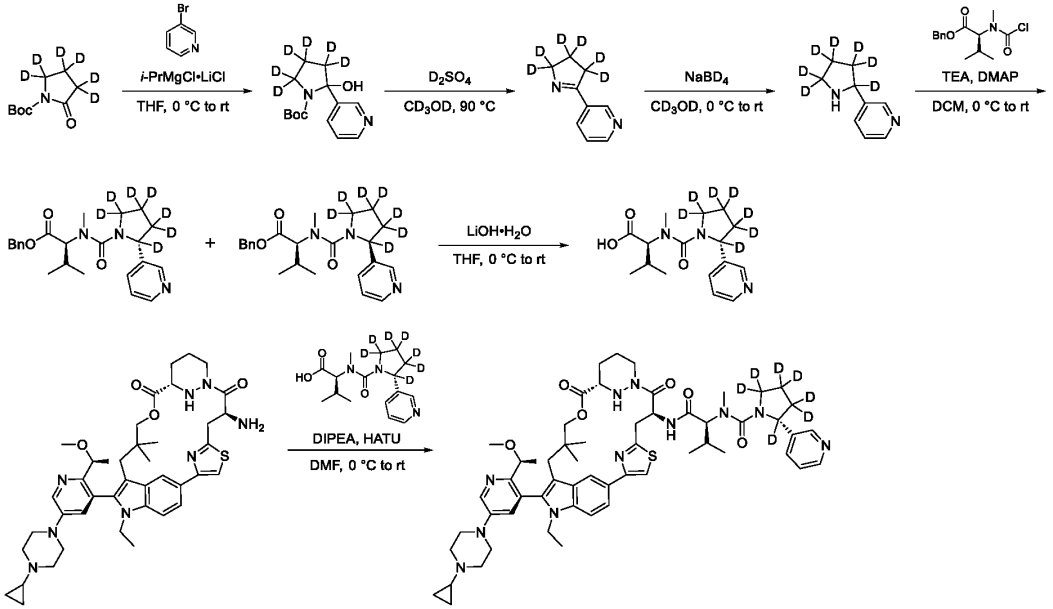
Step 2. To a stirred solution of benzyl (3*R*)-2-isopropyl-3-methyl-4-oxo-4-((*R*)-2-(pyridin-2-ylmethyl)pyrrolidin-1-yl)butanoate (300 mg, 0.734 mmol) in *i*-PrOH (5 mL), Pd/C (10% wt., 300 mg) was added at room temperature. The resulting mixture was stirred at room temperature for 12 h under an atmosphere of hydrogen gas. The reaction mixture was then filtered, the filter cake was washed with *i*-PrOH (20 mL), and the filtrate was concentrated under reduced pressure to afford (3*R*)-2-isopropyl-3-methyl-4-oxo-4-((*R*)-2-(pyridin-2-ylmethyl)pyrrolidin-1-yl)butanoic acid (230 mg, crude) as an off-white solid. This material was further purified by prep-SFC to afford two separated diastereomers of the product.

Isomer 1: (150 mg, 64% yield); LCMS (ESI) *m/z*: [M + H] calcd for $C_{18}H_{26}N_2O_3$: 319.2; found 319.2.

Isomer 2: (35.0 mg, 15% yield); LCMS (ESI) *m/z*: [M + H] calcd for $C_{18}H_{26}N_2O_3$: 319.2; found 319.2.

Step 3. To a stirred solution of (6^3S,4*S*)-4-amino-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-5,7-dione (70.0 mg, 0.0927 mmol) and (2*S*,3*R*)-2-isopropyl-3-methyl-4-oxo-4-((*R*)-2-(pyridin-2-ylmethyl)pyrrolidin-1-yl)butanoic acid (*Isomer 2* from previous reaction, 35.4 mg, 0.112 mmol) in DMF (5 mL), DIPEA (120 mg, 0.930 mmol) and HATU (70.5 mg, 0.186 mmol) were added at 0 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred at room temperature for 2 h. The reaction mixture was then quenched by the addition of cold H_2O (30 mL), extracted with EtOAc (3 x 30 mL), washed with brine (3 x 50 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford (2*S*,3*R*)-*N*-((6^3S,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)-2-isopropyl-3-methyl-4-oxo-4-((*R*)-2-(pyridin-2-ylmethyl)pyrrolidin-1-yl)butanamide (10.9 mg, 11% yield) as a white solid. LCMS (ESI) *m/z*: [M + H] calcd for $C_{59}H_{78}N_{10}O_6S$: 1055.6; found 1055.5; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.52 – 8.46 (m, 1H), 8.46 – 8.36 (m, 3H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.74 – 7.68 (m, 2H), 7.54 (d, *J* = 8.7 Hz, 1H), 7.24 – 7.17 (m, 3H), 5.46 – 5.38 (m, 1H), 5.02 (d, *J* = 12.0 Hz, 1H), 4.43 – 4.25 (m, 3H), 4.23 – 4.08 (m, 4H), 3.59 – 3.49 (m, 3H), 3.31 – 3.10 (m, 10H), 2.97 – 2.89 (m, 2H), 2.80 – 2.60 (m, 6H), 2.48 – 2.39 (m, 2H), 2.13 – 2.04 (m, 1H), 2.02 – 1.93 (m, 1H), 1.85 – 1.59 (m, 6H), 1.58 – 1.43 (m, 1H), 1.32 (d, *J* = 6.0 Hz, 3H), 1.24 (s, 1H), 1.05 (d, *J* = 6.4 Hz, 3H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.98 – 0.82 (m, 9H), 0.43 (dd, *J* = 6.5, 4.3 Hz, 2H), 0.34 (d, *J* = 3.8 Hz, 5H).

Example A562: Synthesis of (2*R*)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-2-(pyridin-3-yl)pyrrolidine-1-carboxamide-2,3,3,4,4,5,5-*d*$_7$



Step 1. To a stirred solution of 3-bromopyridine (1.12 mL, 11.7 mmol) in anhydrous THF (9.3 mL), *i*-PrMgCl•LiCl (1.3 M in THF, 8.98 mL, 11.7 mmol) was added dropwise at 0 °C. The resulting mixture was stirred at room temperature for 1 h. The mixture was then added slowly to a stirred solution of *tert*-butyl 2-oxo($^2H_6$)pyrrolidine-1-carboxylate (930 mg, 4.86 mmol) in anhydrous THF (28 mL) at 0 °C and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was then quenched with H_2O, extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford *tert*-butyl 2-hydroxy-2-(pyridin-3-yl)($^2H_6$)pyrrolidine-1-carboxylate (2.40 g, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{14}H_{14}D_6N_2O_3$: 271.2; found 271.8.

Step 2. To a stirred solution of *tert*-butyl 2-hydroxy-2-(pyridin-3-yl)($^2H_6$)pyrrolidine-1-carboxylate (2.30 g, crude) in CD_3OD (69 mL), sulfuric acid-*d*$_2$ (3.66 ml, 68.1 mmol) was added dropwise. The resulting mixture was stirred for 2 h at 90 °C. The reaction mixture was then neutralized to pH 7 with sat. aq. $NaHCO_3$, extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by trituration with Et_2O. The resulting filtrate was concentrated under reduced pressure to afford 3-(3,4-dihydro(2,2,3,3,4,4-$^2H_6$)-2*H*-pyrrol-5-yl)pyridine (1.12 g, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_9H_4D_6N_2$: 153.1; found 153.6.

Step 3. To a stirred solution of 3-(3,4-dihydro(2,2,3,3,4,4-$^2H_6$)-2*H*-pyrrol-5-yl)pyridine (920 mg, crude) in MeOH-*d*$_4$ (18.4 mL), sodium borodeuteride (759 mg, 18.1 mmol) was added in portions at 0 °C. The resulting mixture was stirred at room temperature for 16 h. The reaction mixture was then quenched by the addition of solid NH_4Cl, stirred for an additional 16 h, and filtered through a pad of Celite®. The pad

was washed with MeOH and the filtrate was concentrated under reduced pressure to afford 3-((2,3,3,4,4,5,5-$^{2}H_{7}$)pyrrolidin-2-yl)pyridine (2.83 g, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_9H_5D_7N_2$: 156.1; found 156.7.

Step 4. To a stirred solution of 3-((2,3,3,4,4,5,5-$^{2}H_{7}$)pyrrolidin-2-yl)pyridine (1.20 g, 1.55 mmol) in DCM (36 mL), triethylamine (862 µL, 6.18 mmol) and a solution of benzyl (2*S*)-2-((chlorocarbonyl)(methyl)amino)-3-methylbutanoate (1.10 g, 3.09 mmol) in DCM (24 mL) were added dropwise at 0 °C. Subsequently, DMAP (38 mg, 0.31 mmol) was added and the resulting mixture was stirred at room temperature for 16 h. The reaction mixture was then quenched with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford two separated diastereomers of benzyl (2*S*)-3-methyl-2-(methyl((2*S*)-2-(pyridin-3-yl)(2,3,3,4,4,5,5-$^{2}H_{7}$)pyrrolidine-1-carbonyl)amino)butanoate.

Isomer 1: (80% purity, 104 mg, 7% yield); LCMS (ESI) *m/z*: [M + H] calcd for $C_{23}H_{22}D_7N_3O_3$: 403.3; found 403.9; ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.54 (d, *J* = 1.9 Hz, 1H), 8.42 (dd, *J* = 4.9, 1.6 Hz, 1H), 7.62 (dt, *J* = 7.9, 1.9 Hz, 1H), 7.32 – 7.29 (m, 5H), 7.21 (dd, *J* = 7.8, 4.9 Hz, 1H), 5.12 (d, *J* = 12.2 Hz, 1H), 5.06 (d, *J* = 12.3 Hz, 1H), 4.27 (d, *J* = 10.4 Hz, 1H), 2.81 (s, 3H), 2.37 – 2.15 (m, 1H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H).

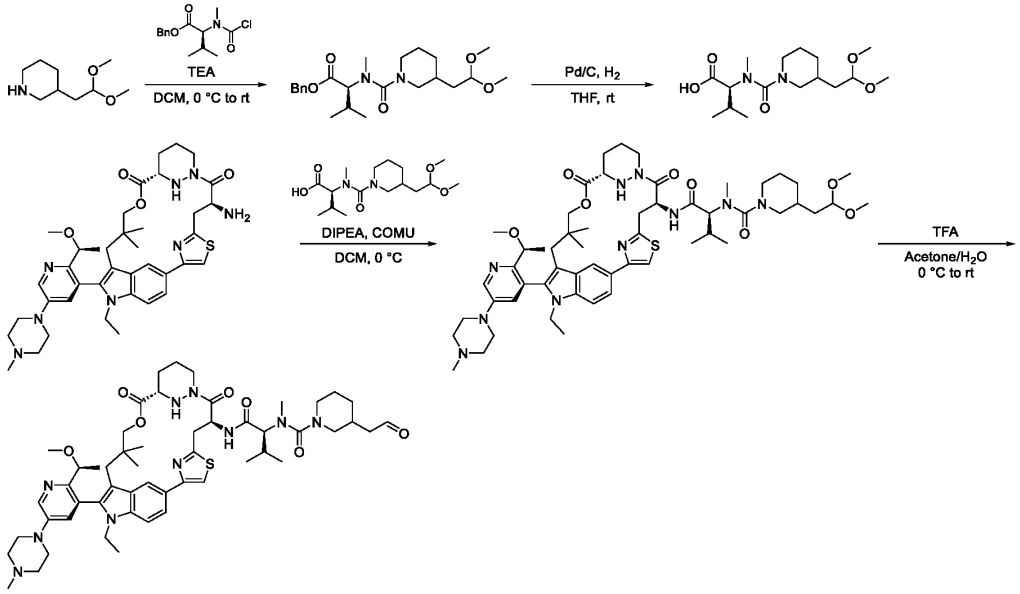
Isomer 2: (43% purity, 105 mg, 4% yield); LCMS (ESI) *m/z*: [M + H] calcd for $C_{23}H_{22}D_7N_3O_3$: 403.3; found 403.9; ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.60 (s, 1H), 8.49 (d, *J* = 5.1 Hz, 1H), 7.87 (d, *J* = 8.1 Hz, 1H), 7.44 (dd, *J* = 7.4, 5.0 Hz, 1H), 7.36 – 7.29 (m, 5H), 5.16 (s, 1H), 5.15 (s, 1H), 4.04 (d, *J* = 10.5 Hz, 1H), 2.95 (s, 3H), 2.23 – 2.17 (m, 1H), 0.89 (d, *J* = 6.6 Hz, 3H), 0.82 (d, *J* = 6.6 Hz, 3H).

Step 5. To a stirred solution of benzyl (2*S*)-3-methyl-2-(methyl((2*R*)-2-(pyridin-3-yl)(2,3,3,4,4,5,5-$^{2}H_{7}$)pyrrolidine-1-carbonyl)amino)butanoate (*Isomer 2* from previous reaction, 43% purity, 105 mg, 0.112 mmol) in THF (3.2 mL) and D_2O (2.1 mL), lithium hydroxide monohydrate (26 mg, 0.63 mmol) was added at 0 °C. The resulting mixture was stirred for 16 h at room temperature. The reaction mixture was then concentrated under reduced pressure and lyophilized to afford lithium (2*S*)-3-methyl-2-(methyl((2*R*)-2-(pyridin-3-yl)(2,3,3,4,4,5,5-$^{2}H_{7}$)pyrrolidine-1-carbonyl)amino)butanoate (113 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{16}H_{16}D_7N_3O_3$: 313.2; found 313.0.

Step 6. To a stirred solution of (6^{3}*S*,4*S*)-4-amino-1^{2}-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^{1}-ethyl-10,10-dimethyl-6^{1},6^{2},6^{3},6^{4},6^{5},6^{6}-hexahydro-1^{1}*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-5,7-dione (80.0 mg, 0.106 mmol) and lithium (2*S*)-3-methyl-2-(methyl((2*R*)-2-(pyridin-3-yl)(2,3,3,4,4,5,5-$^{2}H_{7}$)pyrrolidine-1-carbonyl)amino)butanoate (83.0 mg, crude) in anhydrous DMF (2.4 mL), DIPEA (55 µL, 0.32 mmol) was added. Subsequently, HATU (97 mg, 0.25 mmol) was added at 0 °C. The resulting mixture was stirred for 10 minutes at 0 °C and was then stirred for 1 h at room temperature. The reaction mixture was then quenched with H_2O, extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase prep-HPLC to afford (2*R*)-*N*-((2*S*)-1-(((6^{3}*S*,4*S*)-1^{2}-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^{1}-ethyl-10,10-dimethyl-5,7-dioxo-6^{1},6^{2},6^{3},6^{4},6^{5},6^{6}-hexahydro-1^{1}*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-

N-methyl-2-(pyridin-3-yl)pyrrolidine-1-carboxamide-2,3,3,4,4,5,5-d_7 (30.0 mg, 27% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{57}H_{68}D_7N_{11}O_6S$: 1049.6; found 1049.8; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.57 (d, *J* = 2.1 Hz, 1H), 8.46 – 8.39 (m, 2H), 8.36 (dd, *J* = 4.7, 1.6 Hz, 1H), 8.13 (d, *J* = 9.3 Hz, 1H), 7.79 – 7.68 (m, 3H), 7.57 (d, *J* = 8.7 Hz, 1H), 7.24 (dd, *J* = 7.5, 4.2 Hz, 1H), 7.21 (d, *J* = 3.4 Hz, 1H), 5.52 (t, *J* = 9.1 Hz, 1H), 5.12 (d, *J* = 12.1 Hz, 1H), 4.38 – 4.09 (m, 5H), 3.92 (d, *J* = 10.9 Hz, 1H), 3.54 (s, 2H), 3.30 – 3.28 (m, 1H), 3.30 – 3.18 (m, 8H), 2.93 (d, *J* = 14.7 Hz, 1H), 2.87 (s, 3H), 2.73 – 2.60 (m, 5H), 2.39 (d, *J* = 10.8 Hz, 2H), 2.11 – 2.00 (m, 2H), 1.78 – 1.75 (m, 1H), 1.69 – 1.63 (m, 1H), 1.50 – 1.45 (m, 1H), 1.32 (d, *J* = 6.0 Hz, 3H), 1.03 – 0.83 (m, 9H), 0.74 (d, *J* = 6.5 Hz, 3H), 0.49 – 0.42 (m, 2H), 0.36 – 0.30 (m, 5H).

Example B102: Synthesis of *N*-((2*S*)-1-(((6^3*S*,4*S*)-1^1-ethyl-1^2-(2-((*S*)-1-methoxyethyl)-5-(4-methylpiperazin-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-3-(2-oxoethyl)piperidine-1-carboxamide



Step 1. To a stirred solution of 3-(2,2-dimethoxyethyl)piperidine (183 mg, 1.10 mmol) and triethylamine (46 µL, 3.30 mmol) in DCM (16 mL), a solution of benzyl (2*S*)-2-((chlorocarbonyl)(methyl)amino)-3-methylbutanoate (300 mg, 1.10 mmol) in DCM (5.0 mL) was added at 0 °C. The resulting mixture was stirred at room temperature for 2 h. The reaction mixture was then quenched with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford benzyl (2*S*)-2-((3-(2,2-dimethoxyethyl)piperidine-1-carbonyl)(methyl)amino)-3-methylbutanoate (323 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{23}H_{36}N_2O_5$: 421.3; found 421.2.

Step 2. To a stirred solution of benzyl (2*S*)-2-((3-(2,2-dimethoxyethyl)piperidine-1-carbonyl)(methyl)amino)-3-methylbutanoate (325 mg, crude) in THF (7.0 mL), Pd/C (10% wt., 41 mg) was added under an atmosphere of argon gas. The resulting mixture was stirred at room temperature for 1 h under an atmosphere of hydrogen gas. The reaction mixture was then filtered through a pad of Celite®

and the filtrate was concentrated under reduced pressure to afford (2*S*)-2-((3-(2,2-dimethoxyethyl)piperidine-1-carbonyl)(methyl)amino)-3-methylbutanoic acid (278 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{16}H_{30}N_2O_5$: 331.2; found 331.6.

Step 3. To a stirred solution of (6^3S,4*S*)-4-amino-1^1-ethyl-1^2-(2-((*S*)-1-methoxyethyl)-5-(4-methylpiperazin-1-yl)pyridin-3-yl)-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1H-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-5,7-dione (394 mg, 0.540 mmol) in DCM (12 mL), DIPEA (940 µL, 5.40 mmol) and (2*S*)-2-((3-(2,2-dimethoxyethyl)piperidine-1-carbonyl)(methyl)amino)-3-methylbutanoic acid (268 mg, crude) were added at 0 °C. After 5 minutes of stirring, COMU (440 mg, 1.00 mmol) was added and the resulting mixture was stirred for 1 h at 0 °C. The reaction mixture was then quenched with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford 3-(2,2-dimethoxyethyl)-*N*-((2*S*)-1-((((6^3S,4*S*)-1^1-ethyl-1^2-(2-((*S*)-1-methoxyethyl)-5-(4-methylpiperazin-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1H-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methylpiperidine-1-carboxamide (377 mg). This material was further purified by chiral prep-HPLC to afford two separated diastereomers of the product.

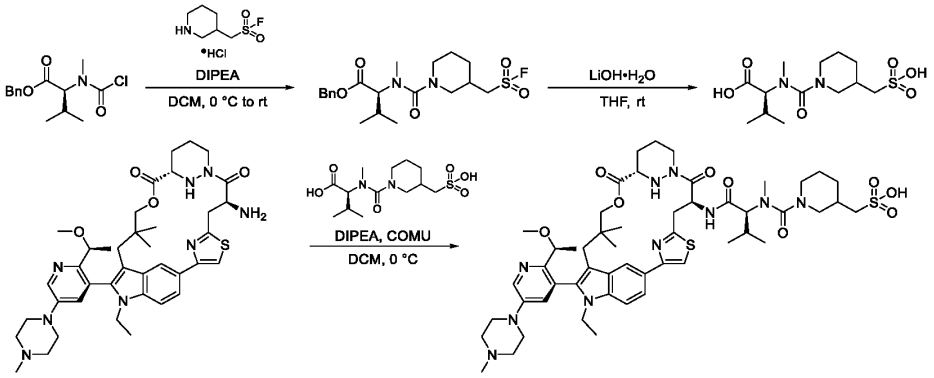
Isomer 1: (85% purity, 106 mg, 16% yield); LCMS (ESI) *m/z*: [M + H] calcd for $C_{55}H_{80}N_{10}O_8S$: 1041.6; found 1041.2; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.49 – 8.46 (m, 1H), 8.44 (d, *J* = 2.9 Hz, 1H), 8.30 (d, *J* = 8.7 Hz, 1H), 7.84 (s, 1H), 7.77 – 7.69 (m, 1H), 7.55 (d, *J* = 8.7 Hz, 1H), 7.21 (d, *J* = 2.9 Hz, 1H), 5.54 (t, *J* = 8.9 Hz, 1H), 5.13 (d, *J* = 12.1 Hz, 1H), 4.46 (t, *J* = 5.7 Hz, 1H), 4.35 – 4.09 (m, 5H), 3.87 (d, *J* = 11.0 Hz, 1H), 3.64 – 3.47 (m, 4H), 3.29 – 3.17 (m, 14H), 3.12 – 3.01 (m, 1H), 2.99 – 2.83 (m, 1H), 2.82 – 2.65 (m, 5H), 2.47 – 2.40 (m, 6H), 2.21 (s, 3H), 2.17 – 2.04 (m, 2H), 1.86 – 1.61 (m, 5H), 1.56 – 1.36 (m, 4H), 1.33 (d, *J* = 6.1 Hz, 3H), 1.21 – 1.09 (m, 1H), 0.93 – 0.82 (m, 12H), 0.34 (s, 3H).

Isomer 2: (81% purity, 117 mg, 17% yield); LCMS (ESI) *m/z*: [M + H] calcd for $C_{55}H_{80}N_{10}O_8S$: 1041.6; found 1041.2; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.48 – 8.46 (m, 1H), 8.44 (d, *J* = 2.8 Hz, 1H), 8.31 (d, *J* = 8.7 Hz, 1H), 7.80 (s, 1H), 7.75 – 7.70 (m, 1H), 7.55 (d, *J* = 8.6 Hz, 1H), 7.21 (d, *J* = 2.9 Hz, 1H), 5.53 (t, *J* = 8.9 Hz, 1H), 5.13 (d, *J* = 12.1 Hz, 1H), 4.43 (t, *J* = 5.6 Hz, 1H), 4.34 – 4.09 (m, 5H), 3.92 (d, *J* = 10.9 Hz, 1H), 3.65 – 3.52 (m, 4H), 3.29 – 3.23 (m, 5H), 3.21 (s, 3H), 3.18 (s, 6H), 3.16 – 3.02 (m, 1H), 2.99 – 2.85 (m, 1H), 2.78 (s, 3H), 2.75 – 2.63 (m, 2H), 2.47 – 2.40 (m, 6H), 2.21 (s, 3H), 2.17 – 2.05 (m, 2H), 1.86 – 1.74 (m, 3H), 1.66 – 1.39 (m, 6H), 1.32 (d, *J* = 6.1 Hz, 3H), 1.18 – 1.03 (m, 1H), 0.97 – 0.76 (m, 12H), 0.34 (s, 3H).

Step 4. To a stirred solution of 3-(2,2-dimethoxyethyl)-*N*-((2*S*)-1-((((6^3S,4*S*)-1^1-ethyl-1^2-(2-((*S*)-1-methoxyethyl)-5-(4-methylpiperazin-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1H-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methylpiperidine-1-carboxamide (85% purity, *Isomer 1* from previous reaction, 86.0 mg, 0.0702 mmol) in acetone (2.5 mL) and H_2O (2.5 mL), trifluoroacetic acid (15 µL, 0.20 mmol) was added dropwise at 0 °C. The resulting mixture was stirred at room temperature for 16 h. The reaction mixture was then quenched with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered,

concentrated under reduced pressure, and purified by reversed-phase prep-HPLC to afford *N*-((2*S*)-1-(((6^3*S*,4*S*)-1^1-ethyl-1^2-(2-((*S*)-1-methoxyethyl)-5-(4-methylpiperazin-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-3-(2-oxoethyl)piperidine-1-carboxamide (17.2 mg, 25% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{53}H_{74}N_{10}O_7S$: 995.6; found 995.5; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.69 (s, 1H), 8.47 (d, *J* = 1.6 Hz, 1H), 8.44 (d, *J* = 2.9 Hz, 1H), 8.29 (d, *J* = 8.8 Hz, 1H), 7.83 (s, 1H), 7.72 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.55 (d, *J* = 8.7 Hz, 1H), 7.21 (d, *J* = 2.9 Hz, 1H), 5.54 (t, *J* = 8.9 Hz, 1H), 5.13 (d, *J* = 12.1 Hz, 1H), 4.34 – 4.11 (m, 5H), 3.90 (d, *J* = 11.0 Hz, 1H), 3.61 – 3.46 (m, 4H), 3.40 – 3.32 (m, 2H), 3.28 – 3.24 (m, 4H), 3.21 (s, 3H), 3.11 – 3.03 (m, 1H), 2.96 – 2.91 (m, 1H), 2.89 – 2.84 (m, 1H), 2.81 (s, 3H), 2.79 – 2.72 (m, 1H), 2.62 – 2.52 (m, 2H), 2.47 – 2.43 (m, 5H), 2.42 – 2.38 (m, 2H), 2.21 (s, 3H), 2.20 – 2.05 (m, 2H), 1.85 – 1.75 (m, 3H), 1.72 – 1.64 (m, 1H), 1.58 – 1.42 (m, 1H), 1.33 (d, *J* = 6.1 Hz, 3H), 1.21 – 1.13 (m, 1H), 0.92 – 0.86 (m, 9H), 0.83 (d, *J* = 6.6 Hz, 3H), 0.34 (s, 3H).

Example A396: Synthesis of (1-(((2*S*)-1-(((6^3*S*,4*S*)-1^1-ethyl-1^2-(2-((*S*)-1-methoxyethyl)-5-(4-methylpiperazin-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)(methyl)carbamoyl)piperidin-3-yl)methanesulfonic acid



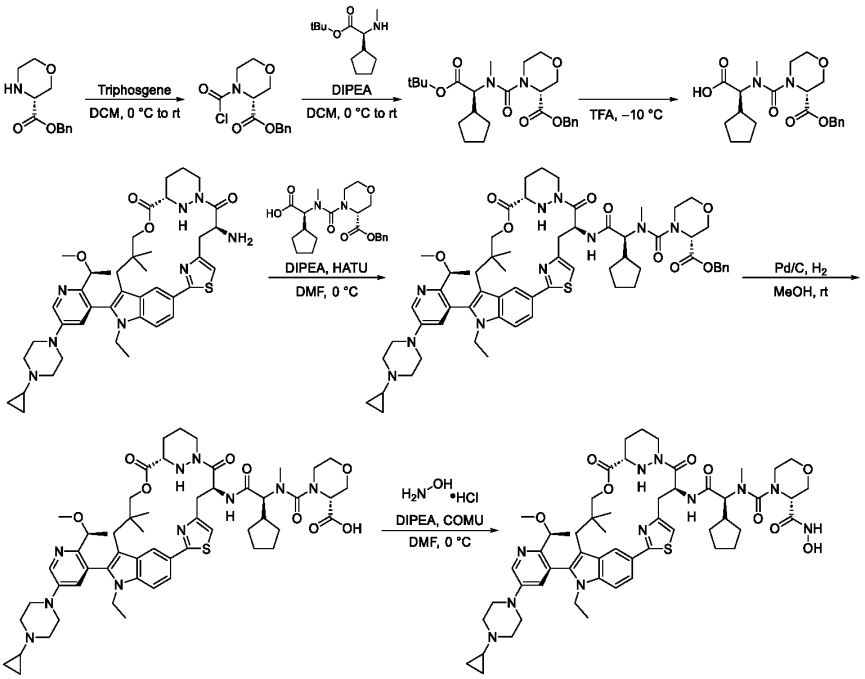
Step 1. To a stirred solution of (piperidin-3-yl)methanesulfonyl fluoride HCl salt (250 mg, 1.15 mmol) and triethylamine (916 µL, 6.89 mmol) in DCM (20 mL), a solution of benzyl (2*S*)-2((chlorocarbonyl)(methyl)amino)-3-methylbutanoate (300 mg, 1.15 mmol) in DCM (5.0 mL) was added at 0 °C. The resulting mixture was warmed to room temperature and stirred for 16 h. The reaction mixture was then quenched with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford benzyl *N*-(3-((fluorosulfonyl)methyl)piperidine-1-carbonyl)-*N*-methyl-*L*-valinate (302 mg, 61% yield) as a mixture of epimers. LCMS (ESI) *m/z*: [M + H] calcd for $C_{20}H_{29}FN_2O_5S$: 429.2; found 428.8.

Step 2. To a stirred solution benzyl *N*-(3-((fluorosulfonyl)methyl)piperidine-1-carbonyl)-*N*-methyl-*L*-valinate (300 mg, 0.70 mmol) in THF (3.0 mL) and H_2O (300 µL), LiOH•H_2O (99.0 mg, 2.36 mmol) was added. The resulting mixture was stirred at room temperature for 16 h. The reaction mixture was then concentrated under reduced pressure and the residue was further dried by lyophilization to afford lithium *N*-methyl-*N*-(3-(sulfomethyl)piperidine-1-carbonyl)-*L*-valinate (290 mg, crude) as a mixture of epimers.

This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{13}H_{24}N_2O_6S$: 337.1; found 336.6.

Step 3. To a stirred solution of (6^3S,4*S*)-4-amino-1^1-ethyl-1^2-(2-((*S*)-1-methoxyethyl)-5-(4-methylpiperazin-1-yl)pyridin-3-yl)-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-5,7-dione (150 mg, 0.206 mmol) in DCM (3.8 mL), DIPEA (358 µL, 2.06 mmol) and lithium *N*-methyl-*N*-(3-(sulfomethyl)piperidine-1-carbonyl)-*L*-valinate (70 mg, crude) were added at 0 °C. The resulting mixture was stirred at 0 °C for 5 minutes, after which time COMU (185 mg, 0.432 mmol) was added and the mixture was stirred for 1 h at 0 °C. The reaction mixture was then quenched with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase prep-HPLC to afford (1-(((2*S*)-1-((((6^3S,4*S*)-1^1-ethyl-1^2-(2-((*S*)-1-methoxyethyl)-5-(4-methylpiperazin-1-yl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)(methyl)carbamoyl)piperidin-3-yl)methanesulfonic acid (18.1 mg, 8% yield) as a mixture of diastereomers. LCMS (ESI) *m/z*: [M + H] calcd for $C_{52}H_{74}N_{10}O_9S_2$: 1047.5; found 1047.4; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 – 8.45 (m, 2H), 8.35 – 8.26 (m, 1H), 7.92 – 7.87 (m, 1H), 7.76 – 7.67 (m, 1H), 7.55 (d, *J* = 8.8 Hz, 1H), 7.38 – 7.25 (m, 1H), 5.59 – 5.50 (m, 1H), 5.18 – 5.07 (m, 1H), 4.37 – 4.07 (m, 5H), 4.03 – 3.95 (m, 1H), 3.93 – 3.84 (m, 2H), 3.61 – 3.45 (m, 6H), 3.30 – 3.19 (m, 4H), 3.19 – 3.03 (m, 1H), 2.96 (d, *J* = 14.7 Hz, 1H), 2.79 (d, *J* = 11.5 Hz, 5H), 2.75 – 2.67 (m, 5H), 2.55 – 2.50 (m, 3H), 2.46 – 2.34 (m, 5H), 2.14 – 2.03 (m, 2H), 1.89 – 1.73 (m, 2H), 1.73 – 1.63 (m, 1H), 1.57 – 1.39 (m, 1H), 1.33 (d, *J* = 6.0 Hz, 3H), 0.93 – 0.82 (m, 14H), 0.34 (s, 3H).

Example A70: Synthesis of (3*R*)-*N*^{4}-((1*S*)-1-cyclopentyl-2-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(2,4)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-2-oxoethyl)-*N*^{3}-hydroxy-*N*^{4}-methylmorpholine-3,4-dicarboxamide



Step 1. To a stirred solution of triphosgene (960 mg, 3.24 mmol) in DCM (11.7 mL), methyl benzyl (3*R*)-morpholine-3-carboxylate (685 mg, 2.94 mmol) and a solution of triethylamine (1.64 mL, 11.8 mmol) in DCM (9.6 mL) were added dropwise at 0 °C. The resulting mixture was stirred for 16 hours at room temperature. The reaction mixture was then quenched with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford benzyl (3*R*)-4-(carbonochloridoyl)morpholine-3-carboxylate (1.35 g, crude). This material was used in the next reaction without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.45 – 7.33 (m, 5H), 5.31 – 5.24 (m, 1H), 4.34 – 4.21 (m, 1H), 4.01 – 3.82 (m, 1H), 3.78 – 3.67 (m, 1H), 3.56 – 3.44 (m, 1H), 3.38 – 3.31 (m, 1H), 3.30 – 3.03 (m, 1H).

Step 2. To a stirred solution of *tert*-butyl (2*S*)-2-cyclopentyl-2-(methylamino)acetate (700 mg, 3.28 mmol) and DIPEA (2.29 mL, 13.1 mmol) in DCM (35 mL), benzyl (3*R*)-4-(carbonochloridoyl)morpholine-3-carboxylate (1.33 g, crude) was added at 0 °C. The resulting mixture was stirred at room temperature for 5 days. The reaction mixture was then quenched with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford benzyl (3*R*)-4-(((1S)-2-(*tert*-butoxy)-1-cyclopentyl-2-oxoethyl)(methyl)carbamoyl)morpholine-3-carboxylate (773 mg, 51% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{25}H_{36}N_2O_6$: 461.3; found 461.2.

Step 3. A solution of benzyl (3*R*)-4-(((1S)-2-(*tert*-butoxy)-1-cyclopentyl-2-oxoethyl)(methyl)carbamoyl)morpholine-3-carboxylate (500 mg, 1.09 mmol) in trifluoroacetic acid (7.48 mL, 97.7 mmol) was stirred at –10 °C for 5 h. The reaction mixture was then quenched with H_2O, neutralized to pH 6 with sat. aq. $NaHCO_3$, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford (2*S*)-2-(((3*R*)-3-((benzyloxy)carbonyl)morpholine-4-carbonyl)(methyl)amino)-2-cyclopentylacetic acid (404 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{21}H_{28}N_2O_6$: 405.2; found 405.1.

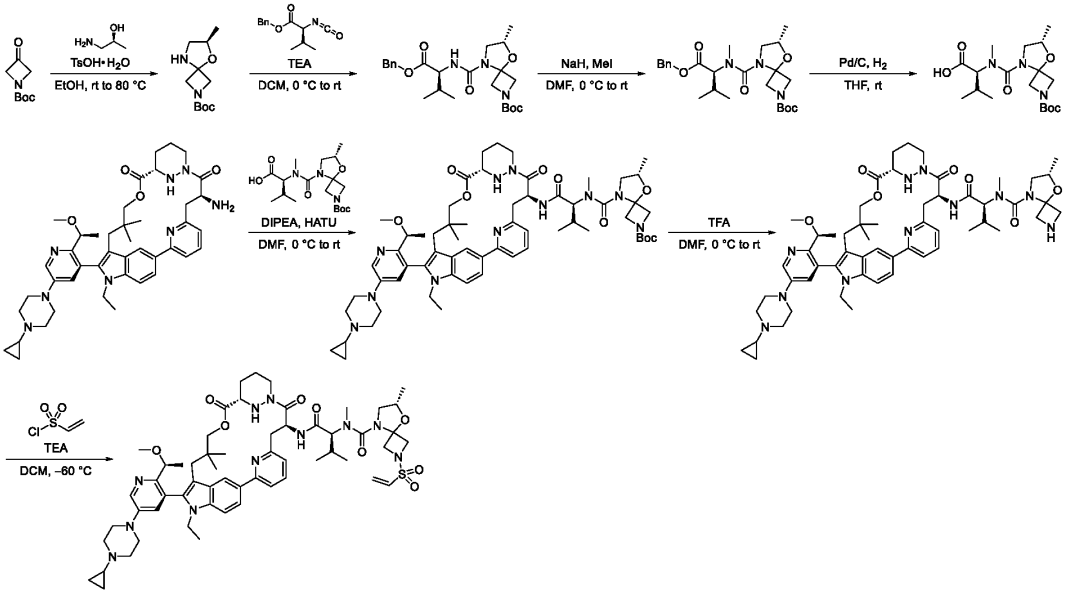
Step 4. To a stirred solution of (6^3*S*,4*S*)-4-amino-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(2,4)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-5,7-dione (100 mg, 0.132 mmol) in DMF (3.0 mL), DIPEA (226 µL, 1.30 mmol) and (2*S*)-2-(((3*R*)-3-((benzyloxy)carbonyl)morpholine-4-carbonyl)(methyl)amino)-2-cyclopentylacetic acid (60 mg, crude) were added at 0 °C. The resulting mixture was stirred for 5 minutes, after which time HATU (74 mg, 0.19 mmol) was added and the mixture was stirred for 1 h at 0 °C. The reaction mixture was then quenched with H_2O, extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase prep-TLC to afford benzyl (3*R*)-4-(((1*S*)-1-cyclopentyl-2-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(2,4)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-2-oxoethyl)(methyl)carbamoyl)morpholine-3-carboxylate (148 mg, 98% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{62}H_{80}N_{10}O_9S$ 1141.6; found 1140.9.

Step 5. A solution of benzyl (3*R*)-4-(((1*S*)-1-cyclopentyl-2-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(2,4)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-2-oxoethyl)(methyl)carbamoyl)morpholine-3-carboxylate (154 mg, 0.135 mmol) in MeOH (7.5 mL) was sparged with argon gas for 5 minutes. Pd/C (10% wt., 56 mg) was then added and the reaction flask was evacuated and backfilled three times with H_2 gas. The resulting mixture was stirred at room temperature under an atmosphere of H_2 for 1 h. The reaction mixture was then filtered through a pad of Celite®, the pad was washed with MeOH, and the filtrate was concentrated under reduced pressure to afford (3*R*)-4-(((1*S*)-1-cyclopentyl-2-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(2,4)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-2-oxoethyl)(methyl)carbamoyl)morpholine-3-carboxylic acid (120 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{55}H_{74}N_{10}O_9S$ 1051.5; found 1051.5.

Step 6. To a stirred solution of (3*R*)-4-(((1*S*)-1-cyclopentyl-2-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(2,4)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-2-oxoethyl)(methyl)carbamoyl)morpholine-3-carboxylic acid (60 mg, crude) in DMF (1.5 mL), COMU (46 mg, 0.11 mmol) was added at 0 °C. Separately, DIPEA (94 µL, 0.54 mmol) was added to a stirred solution of hydroxylamine HCl (6 mg, 0.08 mmol) in DMF (1.5 mL) at 0 °C. Each solution was

stirred separately for 15 minutes at 0 °C, after which time the two solutions were mixed together. The resulting mixture was stirred for 1 h at 0 °C. The reaction mixture was then quenched with H_2O, extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase prep-HPLC. HPLC fractions containing the desired product were combined, washed with sat. aq. $NaHCO_3$, extracted with DCM, washed with water, and concentrated under reduced pressure to afford (3*R*)-*N*^{4}-((1*S*)-1-cyclopentyl-2-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(2,4)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-2-oxoethyl)-*N*^{3}-hydroxy-*N*^{4}-methylmorpholine-3,4-dicarboxamide (17 mg, 24% yield over 2 steps). LCMS (ESI) *m/z*: [M + H] calcd for $C_{55}H_{75}N_{11}O_9S$ 1066.6; found 1066.3; ^{1}H NMR (600 MHz, DMSO-*d*$_6$) δ 10.61 – 10.52 (m, 1H), 8.86 (s, 1H), 8.53 (s, 1H), 8.45 (d, *J* = 2.9 Hz, 1H), 8.02 – 7.96 (m, 1H), 7.60 (d, *J* = 8.6 Hz, 1H), 7.57 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.22 (d, *J* = 3.0 Hz, 1H), 7.17 (s, 1H), 5.67 (t, *J* = 9.0 Hz, 1H), 5.11 (d, *J* = 12.0 Hz, 1H), 4.33 – 4.21 (m, 2H), 4.21 – 4.08 (m, 4H), 3.97 – 3.92 (m, 2H), 3.77 – 3.67 (m, 2H), 3.63 (d, *J* = 10.8 Hz, 1H), 3.55 – 3.48 (m, 3H), 3.24 – 3.20 (m, 4H), 3.17 (s, 3H), 3.10 – 3.06 (m, 1H), 3.01 (d, *J* = 14.0 Hz, 1H), 2.89 – 2.85 (m, 1H), 2.81 (s, 3H), 2.80 – 2.75 (m, 2H), 2.70 – 2.65 (m, 4H), 2.45 – 2.40 (m, 1H), 2.32 – 2.24 (m, 1H), 2.11 – 2.06 (m, 1H), 1.84 – 1.78 (m, 1H), 1.77 – 1.68 (m, 1H), 1.68 – 1.60 (m, 2H), 1.58 – 1.43 (m, 5H), 1.34 (d, *J* = 6.1 Hz, 3H), 1.20 – 1.10 (m, 3H), 0.92 (t, *J* = 7.1 Hz, 3H), 0.88 (s, 3H), 0.46 – 0.42 (m, 2H), 0.39 (s, 3H), 0.36 – 0.32 (m, 2H).

Example B97: Synthesis of (6*S*)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-6(1,3)-pyridazina-2(2,6)-pyridinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*,6-dimethyl-2-(vinylsulfonyl)-5-oxa-2,8-diazaspiro[3.4]octane-8-carboxamide



Step 1. A solution of *tert*-butyl 3-oxoazetidine-1-carboxylate (600 mg, 3.50 mmol), *p*-toluenesulfonic acid monohydrate (68 mg, 0.35 mmol), and (2*S*)-1-aminopropan-2-ol (1.10 mL, 14.02

mmol) in EtOH (48 mL) was stirred for 30 minutes at room temperature and was then refluxed for 16 h. The reaction mixture was then concentrated under reduced pressure, diluted with H_2O, extracted with EtOAc, washed with H_2O, treated with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford *tert*-butyl (6*S*)-6-methyl-5-oxa-2,8-diazaspiro[3.4]octane-2-carboxylate (790 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{11}H_{20}N_2O_3$: 229.2; found 229.2.

Step 2. To a stirred solution of *tert*-butyl (6*S*)-6-methyl-5-oxa-2,8-diazaspiro[3.4]octane-2-carboxylate (400 mg, crude) and triethylamine (733 µL, 4.57 mmol) in DCM (20 mL), a solution of benzyl (2*S*)-2-isocyanato-3-methylbutanoate (54% purity, 1.51 g, 3.50 mmol) in DCM (10 mL) was added at 0 °C. The resulting mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was then washed with sat. aq. citric acid, treated with brine, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford *tert*-butyl (6*S*)-8-(((2*S*)-1-(benzyloxy)-3-methyl-1-oxobutan-2-yl)carbamoyl)-6-methyl-5-oxa-2,8-diazaspiro[3.4]octane-2-carboxylate (729 mg, 89% yield over 2 steps). LCMS (ESI) *m/z*: [M + H] calcd for $C_{24}H_{35}N_3O_6$: 462.3; found 462.3.

Step 3. To a stirred solution of *tert*-butyl (6*S*)-8-(((2*S*)-1-(benzyloxy)-3-methyl-1-oxobutan-2-yl)carbamoyl)-6-methyl-5-oxa-2,8-diazaspiro[3.4]octane-2-carboxylate (679 mg, 1.47 mmol) in DMF (20 mL), methyl iodide (295 µL, 4.74 mmol) was added in one portion. The mixture was cooled to 0 °C and sodium hydride (60% dispersion in mineral oil, 108 mg, 2.71 mmol) was added in portions. The resulting mixture was stirred for 5 minutes at 0 °C and was then stirred for 1 h at room temperature. The reaction mixture was poured into cold H_2O, extracted with Et_2O, washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford *tert*-butyl (6*S*)-8-(((2*S*)-1-(benzyloxy)-3-methyl-1-oxobutan-2-yl)(methyl)carbamoyl)-6-methyl-5-oxa-2,8-diazaspiro[3.4]octane-2-carboxylate (260 mg, 37% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{25}H_{37}N_3O_6$: 476.3; found 476.3.

Step 4. A solution of *tert*-butyl (6*S*)-8-(((2*S*)-1-(benzyloxy)-3-methyl-1-oxobutan-2-yl)(methyl)carbamoyl)-6-methyl-5-oxa-2,8-diazaspiro[3.4]octane-2-carboxylate (260 mg, 0.547 mmol) in THF (13 mL) was sparged with argon gas for 5 minutes, after which time palladium on carbon (10% wt., 78 mg) was added to the solution. The reaction flask headspace was evacuated and backfilled with hydrogen gas twice and the resulting mixture was stirred for 1 h under an atmosphere of hydrogen gas. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to afford (2*S*)-2-(((6*S*)-2-((*tert*-butoxy)carbonyl)-6-methyl-5-oxa-2,8-diazaspiro[3.4]octane-8-carbonyl)(methyl)amino)-3-methylbutanoic acid (236 mg, crude). This material was used in next reaction without purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{18}H_{31}N_3O_6$: 386.2; found 386.2.

Step 5. To a stirred solution of (6^3S,4*S*)-4-amino-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-6(1,3)-pyridazina-2(2,6)-pyridinacycloundecaphane-5,7-dione (200 mg, 0.267 mmol), (2*S*)-2-(((6*S*)-2-((*tert*-butoxy)carbonyl)-6-methyl-5-oxa-2,8-diazaspiro[3.4]octane-8-carbonyl)(methyl)amino)-3-methylbutanoic acid (133 mg, crude), and DIPEA (133 µL, 0.764 mmol) in anhydrous DMF (6.0 mL), HATU (125 mg, 0.329 mmol) was added at 0 °C. The resulting mixture was warmed to room temperature

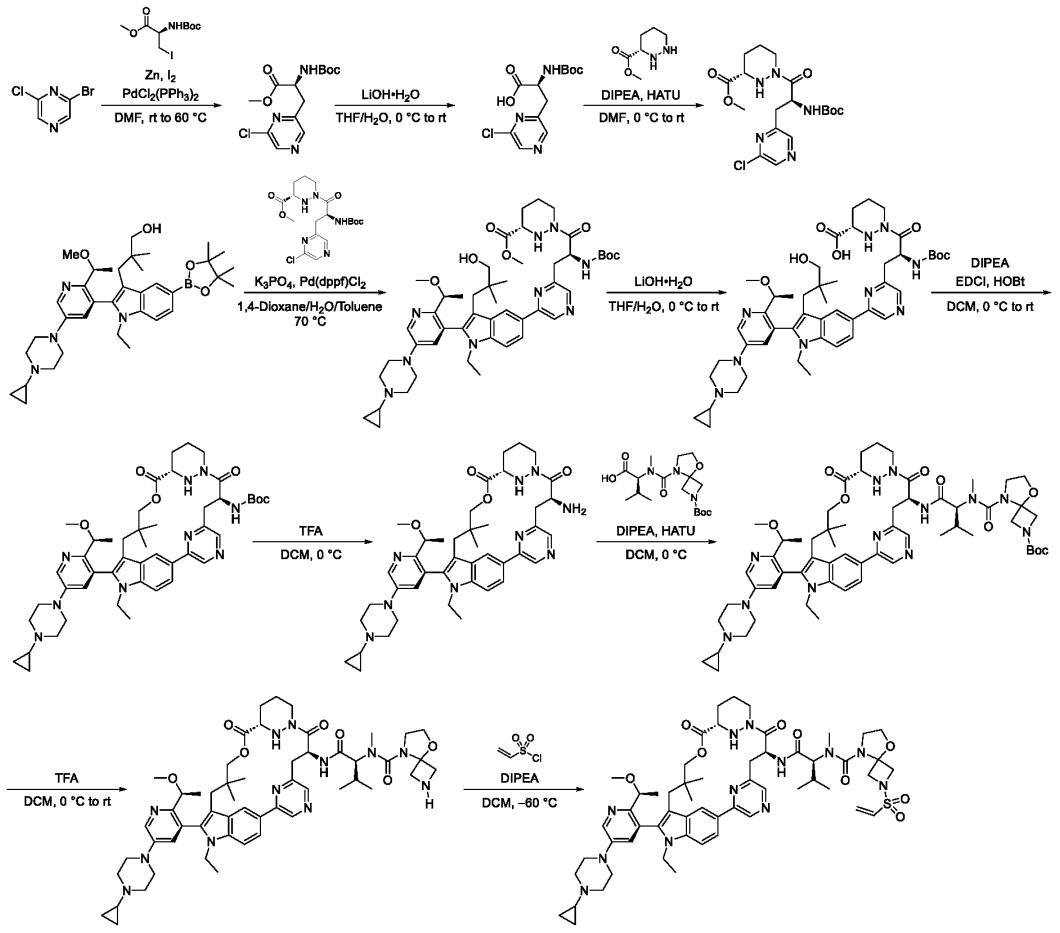
and stirred for 1 h. The reaction mixture was then poured into H_2O and filtered. The residue on the filter was collected, dissolved in DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford *tert*-butyl (6*S*)-8-(((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-6(1,3)-pyridazina-2(2,6)-pyridinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)(methyl)carbamoyl)-6-methyl-5-oxa-2,8-diazaspiro[3.4]octane-2-carboxylate (259 mg, 87% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{61}H_{85}N_{11}O_9$: 1116.7; found 1117.6.

Step 6. To a stirred solution of *tert*-butyl (6*S*)-8-(((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-6(1,3)-pyridazina-2(2,6)-pyridinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)(methyl)carbamoyl)-6-methyl-5-oxa-2,8-diazaspiro[3.4]octane-2-carboxylate (259 mg, 0.232 mmol) in anhydrous DCM (10.4 mL), trifluoroacetic acid (1.16 mL, 15.2 mmol) was added at 0 °C. The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was then quenched with sat. aq. $NaHCO_3$, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford (6*S*)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-6(1,3)-pyridazina-2(2,6)-pyridinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*,6-dimethyl-5-oxa-2,8-diazaspiro[3.4]octane-8-carboxamide (241 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{56}H_{77}N_{11}O_7$: 1016.6; found 1016.5.

Step 7. To a solution of (6*S*)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-6(1,3)-pyridazina-2(2,6)-pyridinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*,6-dimethyl-5-oxa-2,8-diazaspiro[3.4]octane-8-carboxamide (241 mg, crude) and triethylamine (99 µL, 0.71 mmol) in anhydrous DCM (7.2 mL), 4Å molecular sieves were added. The mixture was cooled to –60 °C and ethenesulfonyl chloride (43 µL, 0.47 mmol) was added in one portion. The resulting mixture was stirred for 15 minutes at –60 °C. The reaction mixture was then diluted with H_2O, extracted with DCM, washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase prep-HPLC to afford (6*S*)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-6(1,3)-pyridazina-2(2,6)-pyridinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*,6-dimethyl-2-(vinylsulfonyl)-5-oxa-2,8-diazaspiro[3.4]octane-8-carboxamide (56 mg, 22% yield over 2 steps). LCMS (ESI) *m/z*: [M + H] calcd for $C_{58}H_{79}N_{11}O_9S$: 1106.6; found 1106.5; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.81 (s, 1H), 8.47 (d, *J* = 2.8 Hz, 1H), 7.99 (d, *J* = 9.0 Hz, 1H), 7.86 (dd, *J* = 9.0, 1.7 Hz, 1H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.67 (t, *J* = 7.7 Hz, 1H), 7.57 (d, *J* = 8.7 Hz, 1H), 7.27 (d, *J* = 2.9 Hz, 1H), 7.03 (dd, *J* = 16.5, 10.0 Hz, 1H), 6.98 (d, *J* = 7.1 Hz, 1H), 6.30 (d, *J* = 10.1 Hz, 1H), 6.19 (d, *J* = 16.5 Hz, 1H), 5.90 (t, *J* = 9.7 Hz, 1H), 5.46 (d, *J* = 12.2 Hz, 1H), 4.79 (d, *J* = 8.5 Hz, 1H), 4.38 – 4.28 (m, 2H), 4.20 – 4.06 (m, 3H), 4.05 – 3.96 (m, 1H), 3.92 (d, *J* = 9.2 Hz, 1H), 3.89 – 3.77 (m, 2H), 3.78 – 3.70 (m, 2H), 3.65 (d, *J* = 10.7 Hz, 1H), 3.37 – 3.33 (m, 1H), 3.26 – 3.19 (m, 4H), 3.19 – 3.15 (m, 1H), 3.05 (d, *J* =

13.2 Hz, 1H), 3.01 – 2.97 (m, 1H), 2.96 (s, 3H), 2.89 – 2.77 (m, 2H), 2.72 – 2.64 (m, 4H), 2.54 (s, 3H), 2.46 – 2.36 (m, 1H), 2.04 – 1.98 (m, 1H), 1.97 – 1.89 (m, 1H), 1.88 – 1.78 (m, 1H), 1.73 – 1.61 (m, 2H), 1.61 – 1.50 (m, 1H), 1.38 (d, *J* = 6.1 Hz, 3H), 1.29 (d, *J* = 5.9 Hz, 3H), 1.15 – 1.05 (m, 3H), 0.84 (d, *J* = 6.4 Hz, 3H), 0.78 (d, *J* = 6.5 Hz, 3H), 0.68 (s, 3H), 0.63 (s, 3H), 0.49 – 0.40 (m, 2H), 0.38 – 0.30 (m, 2H).

Example B94: Synthesis of *N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-2(2,6),6(1,3)-dipyrazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-2-(vinylsulfonyl)-5-oxa-2,8-diazaspiro[3.4]octane-8-carboxamide



Step 1. To a stirred mixture of zinc (595 mg, 9.11 mmol) and iodine (34 mg, 0.14 mmol) in DMF (7.5 mL), a solution of methyl (2*R*)-2-((*tert*-butoxycarbonyl)amino)-3-iodopropanoate (1.50 g, 4.58 mmol) in DMF (7.5 mL) was added dropwise at room temperature under an atmosphere of argon gas. The resulting mixture was stirred at room temperature for 30 minutes, after which time it was filtered and the filtrate was added dropwise to a mixture of 2-bromo-6-chloropyrazine (1.32 g, 6.84 mmol) in DMF (100 mL) at room temperature. Subsequently, $PdCl_2(PPh_3)_2$ (159 mg, 0.227 mmol) was added and the resulting mixture was stirred at 60 °C for 30 minutes under an atmosphere of argon gas. The reaction mixture was then quenched with sat. aq. NH_4Cl, extracted with EtOAc, washed with brine, dried over

anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford methyl (2*S*)-2-(((*tert*-butoxy)carbonyl)amino)-3-(6-chloropyrazin-2-yl)propanoate (332 mg, 22% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{13}H_{18}ClN_3O_4$: 316.1; found 315.6.

Step 2. To a stirred solution of methyl (2*S*)-2-(((*tert*-butoxy)carbonyl)amino)-3-(6-chloropyrazin-2-yl)propanoate (330 mg, 1.05 mmol) in THF (1.7 mL) and H_2O (0.7 mL), $LiOH•H_2O$ (129 mg, 3.07 mmol) was added at 0 °C. The resulting mixture was stirred for 1.5 h at room temperature. The reaction mixture was then concentrated under reduced pressure, acidified to pH 5 with sat. aq. $KHSO_4$, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford (2*S*)-2-(((*tert*-butoxy)carbonyl)amino)-3-(6-chloropyrazin-2-yl)propanoic acid (320 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{12}H_{16}ClN_3O_4$: 302.1; found 301.6.

Step 3. To a stirred mixture of (2*S*)-2-(((*tert*-butoxy)carbonyl)amino)-3-(6-chloropyrazin-2-yl)propanoic acid (312 mg, crude) in anhydrous DMF (11 mL), methyl-(3*S*)-1,2-diazinane-3-carboxylate (bis-TFA salt, 350 mg, 1.05 mmol) and DIPEA (821 µL, 4.70 mmol) were added at 0 °C. The mixture was stirred at 0 °C for 10 minutes, after which time HATU (429 mg, 1.12 mmol) was added. The resulting mixture was stirred for 1.5 h at room temperature. The reaction mixture was then quenched with H_2O, extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford methyl (3*S*)-1-((2*S*)-2-(((*tert*-butoxy)carbonyl)amino)-3-(6-chloropyrazin-2-yl)propanoyl)-1,2-diazinane-3-carboxylate (449 mg, quantitative). LCMS (ESI) *m/z*: [M + H] calcd for $C_{18}H_{26}ClN_5O_5$: 228.2; found 227.6.

Step 4. To a stirred solution of 3-((2*M*)-2-(5-(4-cyclopropylpiperazin-1-yl)-2-((1*S*)-1-methoxyethyl)pyridin-3-yl)-1-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-3-yl)-2,2-dimethylpropan-1-ol (650 mg, 1.05 mmol, 1.0 eq) in toluene (13 mL), 1,4-dioxane (4.5 mL) and H_2O (4.5 mL), methyl (3*S*)-1-((2*S*)-2-(((*tert*-butoxy)carbonyl)amino)-3-(6-chloropyrazin-2-yl)propanoyl)-1,2-diazinane-3-carboxylate (449 mg, 1.05 mmol), K_3PO_4 (335 mg, 1.58 mmol) and $Pd(dppf)Cl_2$ (95.0 mg, 0.130 mmol) were added at room temperature under an atmosphere of argon gas. The resulting mixture was stirred for 24 h at 70 °C. The reaction mixture was then quenched with H_2O at room temperature, extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford methyl (*S*)-1-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(6-(2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)-1*H*-indol-5-yl)pyrazin-2-yl)propanoyl)hexahydropyridazine-3-carboxylate (88% purity, 370 mg, 35% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{48}H_{67}N_9O_7$: 882.5; found 881.7.

Step 5. To a stirred solution of methyl (*S*)-1-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(6-(2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)-1*H*-indol-5-yl)pyrazin-2-yl)propanoyl)hexahydropyridazine-3-carboxylate (88% purity, 350 mg, 0.349 mmol) in a mixture of THF (7.0 mL) and H_2O (1.8 mL), $LiOH•H_2O$ (58.0 mg, 1.38 mmol) was added at 0 °C. The resulting mixture was stirred for 1.5 h at room temperature. The reaction mixture was then acidified to pH 6 with sat. aq. $KHSO_4$, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford (*S*)-1-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(6-(2-(5-(4-

cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)-1*H*-indol-5-yl)pyrazin-2-yl)propanoyl)hexahydropyridazine-3-carboxylic acid (355 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{47}H_{65}N_9O_7$: 868.5; found 867.7.

Step 6. To a stirred solution of (*S*)-1-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(6-(2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)-1*H*-indol-5-yl)pyrazin-2-yl)propanoyl)hexahydropyridazine-3-carboxylic acid (350 mg, crude), HOBt hydrate (275 mg, 1.79 mmol) and DIPEA (1.88 mL, 10.8 mmol) in DCM (35 mL), EDCI (HCl salt, 1.93 g, 10.1 mmol) was added at 0 °C. The resulting mixture was stirred for 16 h at room temperature. The reaction mixture was then quenched with H_2O, washed with aqueous HCl (1.0 M), concentrated under reduced pressure, and purified by normal phase prep-TLC to afford *tert*-butyl ((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-2(2,6),6(1,3)-dipyrazinacycloundecaphane-4-yl)carbamate (100 mg, 34% yield over 2 steps). LCMS (ESI) *m/z*: [M + H] calcd for $C_{47}H_{63}N_9O_6$: 850.5; found 850.7.

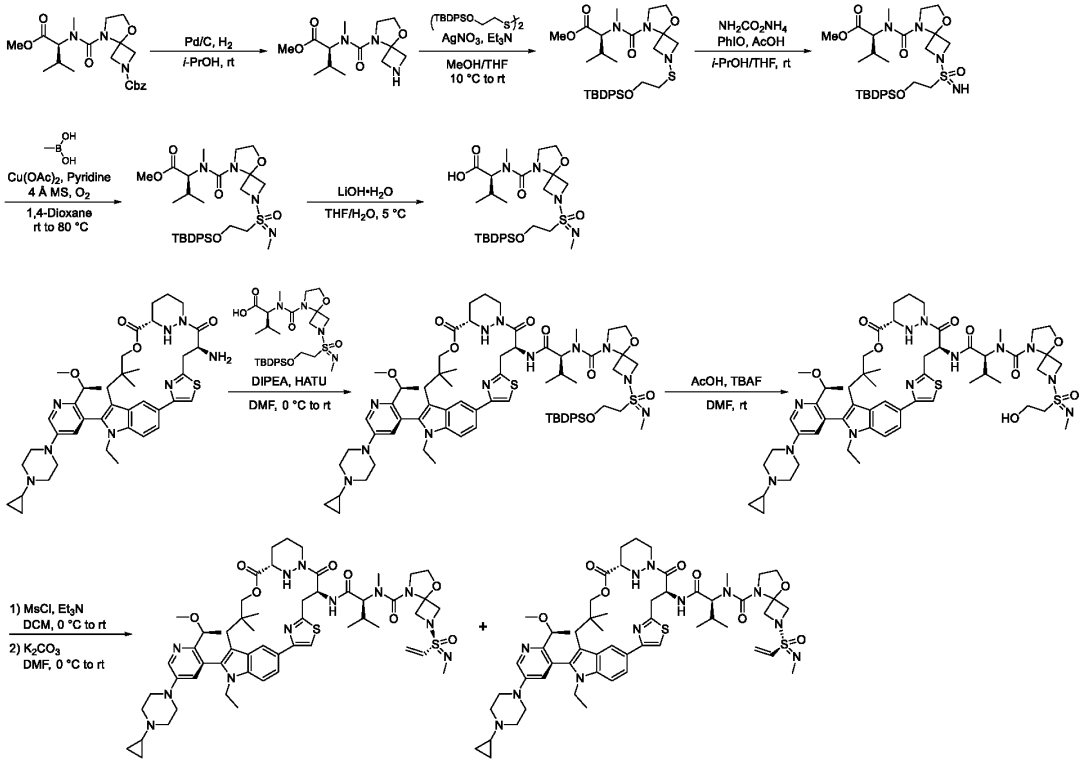
Step 7. To a stirred solution of *tert*-butyl ((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-2(2,6),6(1,3)-dipyrazinacycloundecaphane-4-yl)carbamate (80.0 mg, 0.094 mmol) in anhydrous DCM (3.2 mL), trifluoroacetic acid (353 µL, 4.61 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was then quenched with sat. aq. $NaHCO_3$, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford (6^3*S*,4*S*)-4-amino-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-2(2,6),6(1,3)-dipyrazinacycloundecaphane-5,7-dione (62.0 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{42}H_{55}N_9O_4$: 750.4; found 749.7.

Step 8. To a stirred solution of (6^3*S*,4*S*)-4-amino-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-2(2,6),6(1,3)-dipyrazinacycloundecaphane-5,7-dione (235 mg, crude) in DCM (7.0 mL), DIPEA (354 µL, 2.04 mmol) and (2*S*)-2-((2-((*tert*-butoxy)carbonyl)-5-oxa-2,8-diazaspiro[3.4]octane-8-carbonyl)(methyl)amino)-3-methylbutanoic acid (119 mg, 0.320 mmol) were added at 0 °C. The mixture was stirred for 5 minutes at 0 °C, after which time HATU (116 mg, 0.305 mmol) was added and the resulting mixture was stirred at 0 °C for 1 h. The reaction mixture was then quenched with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford *tert*-butyl 8-(((2*S*)-1-(((6^3*S*,4*S*)-12-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-2(2,6),6(1,3)-dipyrazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)(methyl)carbamoyl)-5-oxa-2,8-diazaspiro[3.4]octane-2-carboxylate (80% purity, 222 mg, 45% yield over 2 steps). LCMS (ESI) *m/z*: [M + H] calcd for $C_{59}H_{82}N_{12}O_9$: 1103.6; found 1102.8.

Step 9. To a stirred solution of *tert*-butyl 8-(((2*S*)-1-(((6^3*S*,4*S*)-12-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-2(2,6),6(1,3)-dipyrazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)(methyl)carbamoyl)-5-oxa-2,8-diazaspiro[3.4]octane-2-carboxylate (80% purity, 200 mg, 0.145 mmol) in anhydrous DCM (1.0 mL), trifluoroacetic acid (555 µL, 7.25 mmol) was added dropwise at 0 °C. The resulting mixture was stirred at room temperature for 2 h. The reaction mixture was then quenched with sat. aq. $NaHCO_3$, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford *N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-2(2,6),6(1,3)-dipyrazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-5-oxa-2,8-diazaspiro[3.4]octane-8-carboxamide (155 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{54}H_{74}N_{12}O_7$: 1003.6; found 1002.7.

Step 10. To a stirred solution of *N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-2(2,6),6(1,3)-dipyrazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-5-oxa-2,8-diazaspiro[3.4]octane-8-carboxamide (120 mg, crude) and 4 Å molecular sieves in anhydrous DCM (3.6 mL), DIPEA (63 µL, 0.36 mmol, 3.0 eq) was added at room temperature. The mixture was cooled to –60 °C and 2-chloroethanesulfonyl chloride (19 µL, 0.18 mmol) was added. The resulting mixture was stirred at –60 °C for 30 minutes. The reaction mixture was then filtered through a pad of Celite® and the pad was washed with DCM. The resulting filtrate was diluted with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase prep-HPLC to afford *N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-2(2,6),6(1,3)-dipyrazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-2-(vinylsulfonyl)-5-oxa-2,8-diazaspiro[3.4]octane-8-carboxamide (17.7 mg, 14% yield over 2 steps). LCMS (ESI) *m/z*: [M + H] calcd for $C_{56}H_{76}N_{12}O_9S$: 1093.6; found 1093.5; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.12 (s, 1H), 8.79 (s, 1H), 8.47 (d, *J* = 2.9 Hz, 1H), 8.23 (s, 1H), 8.15 (d, *J* = 9.0 Hz, 1H), 8.04 (dd, *J* = 8.9, 1.7 Hz, 1H), 7.62 (d, *J* = 8.7 Hz, 1H), 7.28 (d, *J* = 2.9 Hz, 1H), 7.03 (dd, *J* = 16.5, 10.0 Hz, 1H), 6.28 (d, *J* = 10.0 Hz, 1H), 6.18 (d, *J* = 16.5 Hz, 1H), 5.83 (t, *J* = 9.7 Hz, 1H), 5.48 (d, *J* = 12.3 Hz, 1H), 4.62 (d, *J* = 8.9 Hz, 1H), 4.46 (d, *J* = 9.1 Hz, 1H), 4.37 – 4.28 (m, 1H), 4.23 – 4.12 (m, 1H), 4.11 – 4.06 (m, 1H), 4.06 – 3.96 (m, 2H), 3.94 – 3.80 (m, 5H), 3.79 – 3.71 (m, 2H), 3.63 (d, *J* = 10.7 Hz, 1H), 3.54 – 3.43 (m, 1H), 3.27 – 3.17 (m, 6H), 3.05 (d, *J* = 13.3 Hz, 1H), 3.00 – 2.92 (m, 4H), 2.91 – 2.79 (m, 1H), 2.72 – 2.65 (m, 4H), 2.58 – 2.55 (m, 3H), 2.04 – 1.91 (m, 2H), 1.87 – 1.79 (m, 1H), 1.75 – 1.63 (m, 2H), 1.63 – 1.49 (m, 1H), 1.37 (d, *J* = 6.2 Hz, 3H), 1.10 (t, *J* = 7.0 Hz, 3H), 0.83 (d, *J* = 6.5 Hz, 3H), 0.78 (d, *J* = 6.6 Hz, 3H), 0.69 (s, 3H), 0.64 (s, 3H), 0.47 – 0.40 (m, 2H), 0.37 – 0.31 (m, 2H).

Examples B19 and B20: Synthesis of *N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-2-((*S*)-*N*-methylvinylsulfonimidoyl)-5-oxa-2,8-diazaspiro[3.4]octane-8-carboxamide and *N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-2-((*R*)-*N*-methylvinylsulfonimidoyl)-5-oxa-2,8-diazaspiro[3.4]octane-8-carboxamide



Step 1. To a stirred solution of benzyl 8-(((2*S*)-1-methoxy-3-methyl-1-oxobutan-2-yl)(methyl)carbamoyl)-5-oxa-2,8-diazaspiro[3.4]octane-2-carboxylate (16.0 g, 38.1 mmol) in *i*-PrOH (100 mL), Pd/C (10% wt., 8.00 g) was added in portions at room temperature under an atmosphere of nitrogen gas. The reaction vessel was twice evacuated under vacuum and backfilled with hydrogen gas. The resulting mixture was stirred for 16 h at room temperature under an atmosphere of hydrogen gas. The reaction mixture was then filtered, the filter cake was washed with EtOAc (3 x 200 mL), and the filtrate was concentrated under reduced pressure to afford methyl (2*S*)-3-methyl-2-(methyl(5-oxa-2,8-diazaspiro[3.4]octane-8-carbonyl)amino)butanoate (10.0 g, crude) as a dark solid. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{13}H_{23}N_3O_4$: 286.2; found 286.3.

Step 2. To a stirred solution of methyl (2*S*)-3-methyl-2-(methyl(5-oxa-2,8-diazaspiro[3.4]octane-8-carbonyl)amino)butanoate (8.00 g, crude) and TEA (13.6 mL, 98.1 mmol) in MeOH (100 mL) and THF (100 mL), 2,2,13,13-tetramethyl-3,3,12,12-tetraphenyl-4,11-dioxa-7,8-dithia-3,12-disilatetradecane (19.5

g, 30.8 mmol) and $AgNO_3$ (9.53 g, 56.1 mmol) were added in portions at 10 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred for 16 h at room temperature. The reaction mixture was then quenched with H_2O (200 mL), extracted with EtOAc (2 x 200 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford methyl (2*S*)-2-(2-((2-((*tert*-butyldiphenylsilyl)oxy)ethyl)sulfanyl)-5-oxa-2,8-diazaspiro[3.4]octane-8-carbonyl(methyl)amino)-3-methylbutanoate (18.0 g, crude) as dark oil. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{31}H_{45}N_3O_5SSi$: 600.3; found 600.3.

Step 3. To a stirred solution of methyl (2*S*)-2-(2-((2-((*tert*-butyldiphenylsilyl)oxy)ethyl)sulfanyl)-5-oxa-2,8-diazaspiro[3.4]octane-8-carbonyl(methyl)amino)-3-methylbutanoate (18.0 g, crude) and AcOH (1.72 mL, 30.0 mmol) in THF (150 mL) and *i*-PrOH (150 mL), ammonium carbamate (4.69 g, 60.0 mmol) and PhIO (16.5 g, 75.0 mmol) were added in portions at room temperature under an atmosphere of nitrogen gas. The resulting mixture was stirred for 2 h at room temperature. The reaction mixture was then filtered and the filter cake was washed with EtOAc (3 x 100 mL). The filtrate was washed with brine (3 x 100 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford methyl (2*S*)-2-(2-((2-((*tert*-butyldiphenylsilyl)oxy)ethyl))imino)oxo-λ^6-sulfanyl)-5-oxa-2,8-diazaspiro[3.4]octane-8-carbonyl(methyl)amino)-3-methylbutanoate (4.50 g, 23% yield over 3 steps, mixture of two diastereomers) as a yellow oil. LCMS (ESI) *m/z*: [M + H] calcd for $C_{31}H_{46}N_4O_6SSi$: 631.3; found 631.3.

Step 4. To a stirred solution of methyl (2*S*)-2-(2-((2-((*tert*-butyldiphenylsilyl)oxy)ethyl))imino)oxo-λ^6-sulfanyl)-5-oxa-2,8-diazaspiro[3.4]octane-8-carbonyl(methyl)amino)-3-methylbutanoate (4.70 g, 7.45 mmol) and pyridine (2.95 g, 37.3 mmol) in 1,4-dioxane (100 mL), 4 Å molecular sieves (9.0 g), $Cu(OAc)_2$ (2.03 g, 11.2 mmol), and methylboronic acid (2.13 g, 35.7 mmol) were added in portions at room temperature under an atmosphere of nitrogen gas. The resulting mixture was stirred for 2 h at 80 °C under an atmosphere of O_2. The resulting mixture was filtered and the filter cake was washed with EtOAc (3 x 100 mL). The filtrate was washed with brine (2 x 100 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford methyl (2*S*)-2-(2-(8,8-dimethyl-3-oxo-7,7-diphenyl-6-oxa-3-λ^6-thia-2-aza-7-silanon-2-en-3-yl)-5-oxa-2,8-diazaspiro[3.4]octane-8-carbonyl(methyl)amino)-3-methylbutanoate (3.30 g, 69% yield) as a yellow oil. LCMS (ESI) *m/z*: [M + H] calcd for $C_{32}H_{48}N_4O_6SSi$: 645.3; found 645.3.

Step 5. To a stirred solution of methyl (2*S*)-2-(2-(8,8-dimethyl-3-oxo-7,7-diphenyl-6-oxa-3-λ^6-thia-2-aza-7-silanon-2-en-3-yl)-5-oxa-2,8-diazaspiro[3.4]octane-8-carbonyl(methyl)amino)-3-methylbutanoate (1.00 g, 1.55 mmol) in THF (20 mL) and H_2O (40 mL), $LiOH•H_2O$ (1.30 g, 31.0 mmol) was added in portions at 5 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred at 5 °C for 16 h. The reaction mixture was then acidified to pH 6 with concentrated HCl, extracted with EtOAc (3 x 100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford (2*S*)-2-(2-(8,8-dimethyl-3-oxo-7,7-diphenyl-6-oxa-3-λ^6-thia-2-aza-7-silanon-2-en-3-yl)-5-oxa-2,8-diazaspiro[3.4]octane-8-carbonyl(methyl)amino)-3-methylbutanoic acid (650 mg, crude) as a yellow oil. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{31}H_{46}N_4O_6SSi$: 631.1; found 631.3.

Step 6. To a stirred solution of (6^3S,4*S*)-4-amino-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1H-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-5,7-dione (800 mg, 1.06 mmol) and DIPEA (1.85 mL, 10.6 mmol) in DMF (10 mL), (2*S*)-2-(2-(8,8-dimethyl-3-oxo-7,7-diphenyl-6-oxa-3-λ^6-thia-2-aza-7-silanon-2-en-3-yl)-5-oxa-2,8-diazaspiro[3.4]octane-8-carbonyl(methyl)amino)-3-methylbutanoic acid (602 mg, crude) and HATU (483 mg, 1.27 mmol) were added in portions at 0 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred for 1 h at room temperature. The reaction mixture was then quenched with H_2O (10 mL), extracted with EtOAc (3 x 10 mL), washed with brine (3 x 20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford 2-(2-((*tert*-butyldiphenylsilyl)oxy)-*N*-methylethylsulfonimidoyl)-*N*-((2*S*)-1-((((6^3S,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1H-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-5-oxa-2,8-diazaspiro[3.4]octane-8-carboxamide (1.00 g, crude) as a yellow solid. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{72}H_{98}N_{12}O_9S_2Si$: 1367.6; found 1367.7.

Step 7. To a stirred solution of 2-(2-((*tert*-butyldiphenylsilyl)oxy)-*N*-methylethylsulfonimidoyl)-*N*-((2*S*)-1-((((6^3S,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1H-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-5-oxa-2,8-diazaspiro[3.4]octane-8-carboxamide (1.00 g, crude) in DMF (15 mL), AcOH (0.63 mL, 11.0 mmol) and TBAF (1.91 g, 7.31 mmol) were added in portions at room temperature. The resulting mixture was stirred for 1 h at room temperature. The reaction mixture was then quenched with H_2O (20 mL), extracted with EtOAc (3 x 20 mL), washed with brine (3 x 40 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase flash column chromatography to afford *N*-((2*S*)-1-((((6^3S,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1H-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-2-(2-hydroxy-*N*-methylethylsulfonimidoyl)-*N*-methyl-5-oxa-2,8-diazaspiro[3.4]octane-8-carboxamide (300 mg, 25% yield over 2 steps) as a yellow solid. LCMS (ESI) *m/z*: [M + H] calcd for $C_{56}H_{80}N_{12}O_9S_2$: 1129.6; found 1129.6.

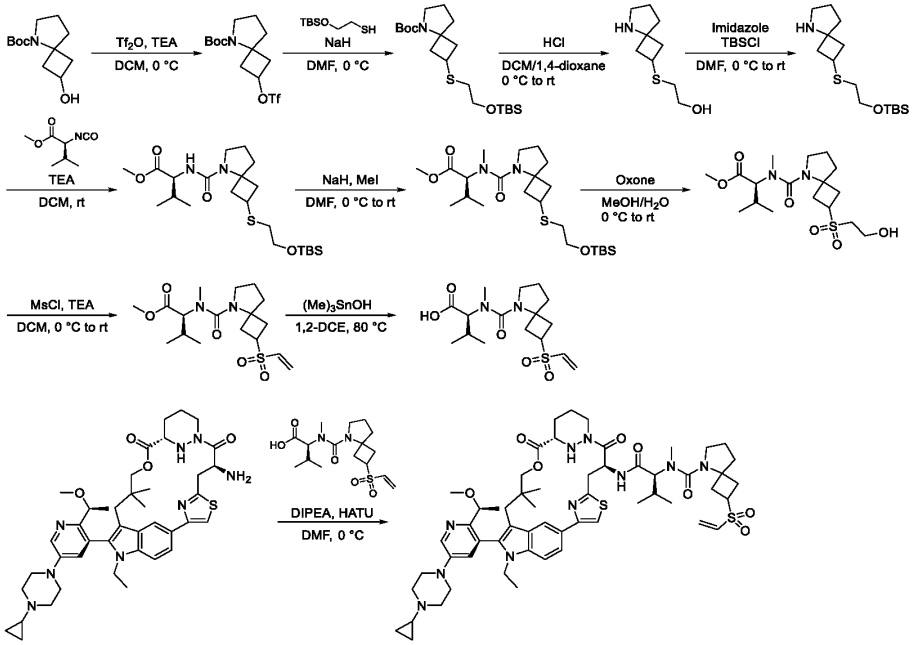
Step 8. To a stirred solution of *N*-((2*S*)-1-((((6^3S,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1H-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-2-(2-hydroxy-*N*-methylethylsulfonimidoyl)-*N*-methyl-5-oxa-2,8-diazaspiro[3.4]octane-8-carboxamide (290 mg, 0.257 mmol) and Et_3N (0.36 mL, 2.61 mmol) in DCM (5 mL), MsCl (58.8 mg, 0.514 mmol) was added dropwise at 0 °C. The resulting mixture was stirred for 1 h at room temperature. The reaction mixture was then quenched with sat. aq. $NaHCO_3$ at 0 °C, extracted with EtOAc (3 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting material was suspended in DMF (5.0 mL), and K_2CO_3 (887 mg, 6.43 mmol) was added in portions at 0 °C. The resulting mixture was stirred for 1 h at room temperature. The reaction mixture was then diluted with EtOAc (5 mL), treated with sat. aq. NH_4Cl (10 mL) at 0 °C, extracted with EtOAc (3 x 10 mL), washed with brine (3 x 20 mL), dried

over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase prep-HPLC to afford *N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-2-(*N*-methylvinylsulfonimidoyl)-5-oxa-2,8-diazaspiro[3.4]octane-8-carboxamide (120 mg, 42% yield, mixture of two diastereomers) as a white solid. This material was further purified by chiral prep-HPLC (polysaccharide column) to afford two separated diastereomers.

B20: (44.0 mg, 15% yield); LCMS (ESI) *m/z*: [M + H] calcd for $C_{56}H_{78}N_{12}O_8S_2$: 1111.6; found 1111.6; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.47 (s, 1H), 8.44 (d, *J* = 2.8 Hz, 1H), 8.38 (d, *J* = 8.9 Hz, 1H), 7.80 (s, 1H), 7.71 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.56 (d, *J* = 8.6 Hz, 1H), 7.21 (d, *J* = 2.9 Hz, 1H), 6.79 (dd, *J* = 16.5, 9.9 Hz, 1H), 6.15 (d, *J* = 16.8 Hz, 1H), 6.15 (d, *J* = 10.0 Hz, 1H), 5.57 (t, *J* = 9.0 Hz, 1H), 5.15 (d, *J* = 12.1 Hz, 1H), 4.54 (d, *J* = 8.8 Hz, 1H), 4.34 (d, *J* = 9.1 Hz, 1H), 4.31 – 4.21 (m, 2H), 4.20 – 4.10 (m, 2H), 4.09 – 4.01 (m, 2H), 3.90 (q, *J* = 7.6 Hz, 1H), 3.64 (q, *J* = 7.7 Hz, 1H), 3.56 (q, *J* = 7.7 Hz, 1H), 3.56 (s, 2H), 3.45 – 3.35 (m, 2H), 3.23 (br s, 6H), 3.24 – 3.10 (m, 2H), 2.94 (d, *J* = 14.4 Hz, 1H), 2.85 (s, 3H), 2.80 – 2.74 (m, 1H), 2.68 (d, *J* = 5.3 Hz, 4H), 2.62 (s, 3H), 2.43 (d, *J* = 14.2 Hz, 1H), 2.19 – 2.05 (m, 2H), 1.81 (br s, 2H), 1.69 – 1.61 (m, 1H), 1.56 – 1.47 (m, 1H), 1.33 (d, *J* = 6.0 Hz, 3H), 1.24 – 1.16 (m, 2H), 0.94 – 0.84 (m, 12H), 0.43 (d, *J* = 4.4 Hz, 2H), 0.34 (s, 5H).

B19: (32.0 mg, 11% yield); LCMS (ESI) *m/z*: [M + H] calcd for $C_{56}H_{78}N_{12}O_8S_2$: 1111.6; found 1111.6; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.47 (s, 1H), 8.44 (d, *J* = 2.8 Hz, 1H), 8.33 (d, *J* = 9.1 Hz, 1H), 7.80 (d, *J* = 1.8 Hz, 1H), 7.72 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.56 (d, *J* = 8.6 Hz, 1H), 7.21 (d, *J* = 2.9 Hz, 1H), 6.80 (dd, *J* = 16.6, 9.9 Hz, 1H), 6.17 (d, *J* = 10.0 Hz, 1H), 6.13 (d, *J* = 16.4 Hz, 1H), 5.59 (t, *J* = 9.1 Hz, 1H), 5.16 (d, *J* = 12.1 Hz, 1H), 4.58 (d, *J* = 8.7 Hz, 1H), 4.35 – 4.21 (m, 7H), 4.20 – 4.10 (m, 2H), 4.06 (d, *J* = 10.7 Hz, 2H), 3.89 (q, *J* = 7.7 Hz, 1H), 3.79 (d, *J* = 8.9 Hz, 1H), 3.66 (d, *J* = 8.7 Hz, 2H), 3.56 (s, 2H), 3.22 (br s, 6H), 3.08 (dd, *J* = 14.7, 9.1 Hz, 2H), 2.94 (d, *J* = 14.3 Hz, 1H), 2.85 (s, 3H), 2.81 – 2.73 (m, 1H), 2.68 (s, 4H), 2.62 (s, 3H), 2.43 (d, *J* = 13.9 Hz, 1H), 2.18 – 2.06 (m, 2H), 1.81 (br s, 2H), 1.69 – 1.62 (m, 1H), 1.58 – 1.45 (m, 1H), 1.33 (d, *J* = 6.1 Hz, 3H), 1.24 – 1.26 (m, 2H), 0.94 – 0.84 (m, 12H), 0.47 (d, *J* = 4.4 Hz, 2H), 0.34 (s, 5H).

Example B32: Synthesis of *N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-2-(vinylsulfonyl)-5-azaspiro[3.4]octane-5-carboxamide



Step 1. To a stirred solution of *tert*-butyl 2-hydroxy-5-azaspiro[3.4]octane-5-carboxylate (250 mg, 1.10 mmol) in DCM (20 mL), triethylamine (229 µL, 1.65 mmol) was added at room temperature. The resulting mixture was cooled to 0 °C and triflic anhydride (193 µL, 1.10 mmol) was subsequently added. The reaction mixture was stirred at 0 °C for 30 minutes, after which time it was extracted with DCM, washed with ice-cold water, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford *tert*-butyl 2-(trifluoromethanesulfonyloxy)-5-azaspiro[3.4]octane-5-carboxylate (395 mg, crude). Due to potential product instability, this material was quickly used in the next reaction without further purification or characterization.

Step 2. To a stirred solution of 2-((*tert*-butyldimethylsilyl)oxy)ethane-1-thiol (211 mg, 1.10 mmol) in DMF (7.9 mL), sodium hydride (60% dispersion in mineral oil, 65 mg, 1.63 mmol) was added at 0 °C. The resulting mixture was stirred at 0 °C for 30 minutes, after which time a solution of *tert*-butyl 2-(trifluoromethanesulfonyloxy)-5-azaspiro[3.4]octane-5-carboxylate (395 mg, crude) in DMF (3.9 mL) was added. The reaction mixture was stirred for 30 minutes at 0 °C, after which time it was poured into cold H_2O, extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford *tert*-butyl 2-((2-((*tert*-butyldimethylsilyl)oxy)ethyl)sulfanyl)-5-azaspiro[3.4]octane-5-carboxylate (321 mg, 73% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 3.80 – 3.69 (m, 2H), 3.63 – 3.50 (m, 1H), 3.35 (t, *J* = 6.7 Hz, 3H), 2.61 (t, *J* = 7.4 Hz, 2H), 2.18 (t, *J* = 6.7 Hz, 2H), 1.96 – 1.83 (m, 2H), 1.75 – 1.63 (m, 3H), 1.52 (s, 9H), 0.92 (d, J = 1.9 Hz, 9H), 0.10 – 0.08 (m, 6H).

Step 3. To a stirred solution of *tert*-butyl 2-((2-((*tert*-butyldimethylsilyl)oxy)ethyl)sulfanyl)-5-azaspiro[3.4]octane-5-carboxylate (1.20 g, 3.00 mmol) in anhydrous DCM (36 mL) was added HCl (4.0 M in 1,4-dioxane, 15.0 mL, 60.0 mmol) at 0 °C. The resulting mixture was stirred for 16 hours at room temperature. The reaction mixture was then quenched with sat. aq. $NaHCO_3$, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford 2-(5-azaspiro[3.4]octan-2-ylsulfanyl)ethan-1-ol (778 mg, crude). This material was used in the next reaction without further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.26 (s, 1H), 4.83 (s, 1H), 3.68 – 3.59 (m, 1H), 3.55 – 3.42 (m, 2H), 3.20 – 3.05 (m, 2H), 2.90 – 2.75 (m, 2H), 2.55 (t, *J* = 6.9 Hz, 2H), 2.15 – 2.02 (m, 2H), 2.03 – 1.93 (m, 2H), 1.93 – 1.72 (m, 2H).

Step 4. To a stirred solution of 2-(5-azaspiro[3.4]octan-2-ylsulfanyl)ethan-1-ol (778 mg, crude) in DMF (14 mL), imidazole (1.20 g, 17.9 mmol) and *tert*-butyldimethylsilyl chloride (1.10 g, 7.18 mmol) were added at 0 °C. The resulting mixture was stirred for 16 hours at room temperature. The reaction mixture was then quenched with H_2O, extracted with DCM, washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford 2-((2-((*tert*-butyldimethylsilyl)oxy)ethyl)sulfanyl)-5-azaspiro[3.4]octane (372 mg, 41% yield over 2 steps). LCMS (ESI) *m/z*: [M + H] calcd for $C_{15}H_{31}NOSSi$: 302.2; found 302.8.

Step 5. To a stirred solution of methyl (2*S*)-2-isocyanato-3-methylbutanoate (471 mg, 3.00 mmol) in DCM (10.9 mL), triethylamine (669 µL, 4.80 mmol) and 2-((2-((*tert*-butyldimethylsilyl)oxy)ethyl)sulfanyl)-5-azaspiro[3.4]octane (362 mg, 1.20 mmol) were added at room temperature. The resulting mixture was stirred for 3 hours at room temperature. The reaction mixture was washed with H_2O, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford methyl (2*S*)-2-((2-((2-((*tert*-butyldimethylsilyl)oxy)ethyl)sulfanyl)-5-azaspiro[3.4]octane-5-carbonyl)amino)-3-methylbutanoate (417 mg, 76% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{22}H_{42}N_2O_4SSi$: 459.3; found 460.00.

Step 6. To a stirred solution of methyl (2*S*)-2-((2-((2-((*tert*-butyldimethylsilyl)oxy)ethyl)sulfanyl)-5-azaspiro[3.4]octane-5-carbonyl)amino)-3-methylbutanoate (417 mg, 0.909 mmol) in DMF (12.5 mL) was added methyl iodide (198 µL, 3.18 mmol). The solution was cooled to 0 °C, after which time sodium hydride (60% dispersion in mineral oil, 72.0 mg, 1.80 mmol) was added in portions. The resulting mixture was stirred for 5 minutes at 0 °C and was then stirred for 16 hours at room temperature. The reaction mixture was poured into H_2O, extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford methyl (2*S*)-2-((2-((2-((*tert*-butyldimethylsilyl)oxy]ethyl)sulfanyl)-5-azaspiro[3.4]octane-5-carbonyl)(methyl)amino)-3-methylbutanoate (350 mg, 80% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 3.94 (d, *J* = 10.6 Hz, 1H), 3.73 (s, 3H), 3.69 (d, *J* = 7.8 Hz, 2H), 3.67 – 3.58 (m, 1H), 3.54 – 3.26 (m, 3H), 3.26 – 3.17 (m, 1H), 2.88 (s, 3H), 2.63 – 2.51 (m, 2H), 2.26 – 2.09 (m, 2H), 1.96 – 1.64 (m, 5H), 0.96 (d, *J* = 6.6 Hz, 6H), 0.89 (s, 9H), 0.05 (s, 6H).

Step 7. To a stirred solution of methyl (2*S*)-2-((2-((2-((*tert*-butyldimethylsilyl)oxy]ethyl)sulfanyl)-5-azaspiro[3.4]octane-5-carbonyl)(methyl)amino)-3-methylbutanoate (235 mg, 0.497 mmol) in MeOH (4.7 mL) and H_2O (2.4 mL), Oxone® (1.50 g, 4.87 mmol) was added at 0 °C. The resulting mixture was stirred for 2 h at room temperature. The reaction mixture was then quenched with H_2O, extracted with DCM,

dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford methyl (2*S*)-2-((2-(2-hydroxyethanesulfonyl)-5-azaspiro[3.4]octane-5-carbonyl)(methyl)amino)-3-methylbutanoate (195 mg, 95% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{17}H_{30}N_2O_6S$: 391.2; found 391.9.

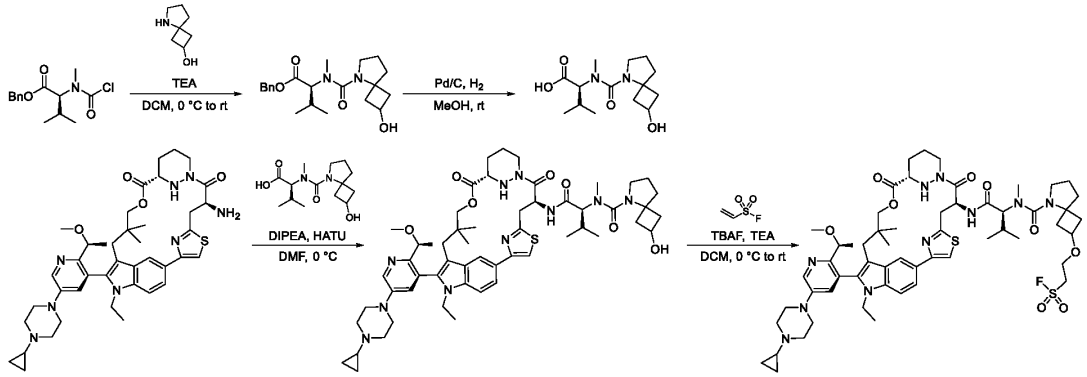
Step 8. To a solution of methyl (2*S*)-2-((2-(2-hydroxyethanesulfonyl)-5-azaspiro[3.4]octane-5-carbonyl)(methyl)amino)-3-methylbutanoate (195 mg, 0.46 mmol) in anhydrous DCM (19.5 mL), triethylamine (258 µL, 1.86 mmol) was added. Subsequently, methanesulfonyl chloride (37 µL, 0.49 mmol) was added at 0 °C and the mixture was stirred for 16 h at room temperature. The reaction mixture was then washed with H_2O, extracted with DCM, washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford methyl (2*S*)-2-((2-(ethenesulfonyl)-5-azaspiro[3.4]octane-5-carbonyl)(methyl)amino)-3-methylbutanoate (93% purity, 186 mg, quantitative). LCMS (ESI) *m/z*: [M + H] calcd for $C_{21}H_{30}N_2O_4$: 373.2; found 374.0.

Step 9. To a stirred solution of methyl (2*S*)-2-((2-(ethenesulfonyl)-5-azaspiro[3.4]octane-5-carbonyl)(methyl)amino)-3-methylbutanoate (65 mg, 0.16 mmol) in 1,2-DCE (6.0 mL), trimethyltin hydroxide (1.18 g, 6.49 mmol) was added. The resulting mixture was stirred for 16 hours at 80 °C. The reaction mixture was then acidified to pH 5 by the addition of a 1.0 M aq HCl solution, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford (2*S*)-2-((2-(ethenesulfonyl)-5-azaspiro[3.4]octane-5-carbonyl)(methyl)amino)-3-methylbutanoic acid (109 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{16}H_{26}N_2O_5S$: 359.2; found 359.3.

Step 10. To a stirred solution of (6^3S,4*S*)-4-amino-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-5,7-dione (70 mg, 0.093 mmol) and (2*S*)-2-((2-(ethenesulfonyl)-5-azaspiro[3.4]octane-5-carbonyl)(methyl)amino)-3-methylbutanoic acid (90 mg, crude) in anhydrous DMF (4.2 mL), DIPEA (61 µL, 0.35 mmol) and HATU (43 mg, 0.11 mmol) were added at 0 °C under an atmosphere of argon. The resulting mixture was stirred for 90 minutes at 0 °C. The reaction mixture was then quenched with H_2O, extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase prep-HPLC to afford *N*-((2*S*)-1-((((6^3S,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-2-(vinylsulfonyl)-5-azaspiro[3.4]octane-5-carboxamide (55 mg, 57% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{57}H_{78}N_{10}O_8S_2$: 1095.5; found 1095.7; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (d, *J* = 1.7 Hz, 1H), 8.44 (d, *J* = 2.9 Hz, 1H), 8.42 (d, *J* = 8.7 Hz, 1H), 7.78 (s, 1H), 7.72 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.55 (d, *J* = 8.7 Hz, 1H), 7.20 (d, *J* = 2.9 Hz, 1H), 7.02 (dd, *J* = 16.6, 10.0 Hz, 1H), 6.28 (d, *J* = 16.6 Hz, 1H), 6.25 (d, *J* = 10.0 Hz, 1H), 5.55 (t, *J* = 9.0 Hz, 1H), 5.13 (d, *J* = 12.2 Hz, 1H), 4.34 – 4.11 (m, 5H), 4.06 – 3.96 (m, 1H), 3.92 (d, *J* = 10.9 Hz, 1H), 3.60 – 3.48 (m, 3H), 3.37 (d, *J* = 14.6 Hz, 1H), 3.32 – 3.27 (m, 1H), 3.26 – 3.18 (m, 7H), 3.17 – 3.05 (m, 2H), 3.02 – 2.89 (m, 2H), 2.79 (s, 3H), 2.78 – 2.72 (m, 1H), 2.70 – 2.64 (m, 4H), 2.46 – 2.36 (m, 2H), 2.30 – 2.22 (m, 1H), 2.18 – 2.03 (m, 3H), 1.93 – 1.84 (m, 1H), 1.85 – 1.70 (m, 4H), 1.70 –

1.61 (m, 1H), 1.59 – 1.45 (m, 1H), 1.32 (d, *J* = 6.0 Hz, 3H), 0.96 – 0.82 (m, 12H), 0.48 – 0.39 (m, 2H), 0.38 – 0.29 (m, 5H).

Example B35: Synthesis of 2-((5-(((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)(methyl)carbamoyl)-5-azaspiro[3.4]octan-2-yl)oxy)ethane-1-sulfonyl fluoride



Step 1. To a stirred solution of 5-azaspiro[3.4]octan-2-ol TFA salt (312 mg, 1.39 mmol) in DCM (6.2 mL) were added triethylamine (1.30 mL, 0.91 mmol) and a solution of benzyl (2*S*)-2-((chlorocarbonyl)(methyl)amino)-3-methylbutanoate (257 mg, 0.906 mmol) in DCM (6.2 mL) at 0 °C. The resulting mixture was stirred for 30 min at 0 °C and was then stirred for 16 hours at room temperature. The reaction mixture was then quenched with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase flash column chromatography to afford benzyl (2*S*)-2-((2-hydroxy-5-azaspiro[3.4]octane-5-carbonyl)(methyl)amino)-3-methylbutanoate (104 mg, 31% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{21}H_{30}N_2O_4$: 375.2; found 375.1.

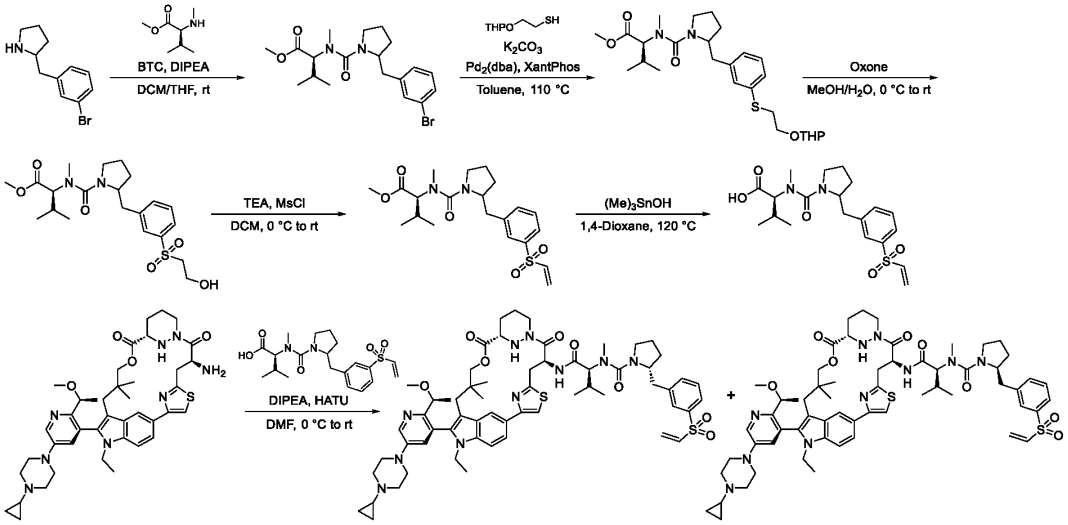
Step 2. To a stirred solution of benzyl (2*S*)-2-((2-hydroxy-5-azaspiro[3.4]octane-5-carbonyl)(methyl)amino)-3-methylbutanoate (104 mg, 0.278 mmol) in MeOH (7.3 mL), Pd/C (35% wt., 35.0 mg) was added at room temperature. The resulting mixture stirred for 16 hours at room temperature under an atmosphere of hydrogen gas. The reaction mixture was then filtered through a pad of Celite®, the pad was washed with MeOH, and the filtrate was concentrated under reduced pressure to afford (2*S*)-2-((2-hydroxy-5-azaspiro[3.4]octane-5-carbonyl)(methyl)amino)-3-methylbutanoic acid (80.0 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{14}H_{24}N_2O_4$: 285.2; found 285.0.

Step 3. To a stirred solution of (2*S*)-2-((2-hydroxy-5-azaspiro[3.4]octane-5-carbonyl)(methyl)amino)-3-methylbutanoic acid (33 mg, crude) in anhydrous DMF (2.6 mL), DIPEA (186 µL, 1.07 mmol) and (6^3*S*,4*S*)-4-amino-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-5,7-dione (81 mg, 0.11 mmol) were added at 0 °C. This mixture was stirred for 10 minutes, after which time HATU (61 mg, 0.16 mmol) was added and the resulting mixture was stirred at 0 °C for 1 h. The reaction mixture was then quenched with H_2O, extracted with EtOAc (x3), washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure, and

purified by normal phase prep-TLC to afford *N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-2-hydroxy-*N*-methyl-5-azaspiro[3.4]octane-5-carboxamide (24 mg, 21% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{55}H_{76}N_{10}O_7S$: 1021.6; found 1022.1.

Step 4. To a stirred solution of *N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-2-hydroxy-*N*-methyl-5-azaspiro[3.4]octane-5-carboxamide (20 mg, 0.020 mmol) in DCM (1.0 mL), ethenesulfonyl fluoride (20 µL, 0.26 mmol), TBAF (1.0 M in THF, 18 µL, 0.018 mmol) and triethylamine (37 µL, 0.26 mmol) were added slowly in portions at 0 °C over a period of several days. The reaction mixture was then quenched with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase prep-HPLC to afford 2-((5-(((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)(methyl)carbamoyl)-5-azaspiro[3.4]octan-2-yl)oxy)ethane-1-sulfonyl fluoride (2.6 mg, 13% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{57}H_{79}FN_{10}O_9S_2$: 1031.6; found 1031.8; ^{1}H NMR (600 MHz, DMSO-*d*$_6$) δ 8.49 – 8.45 (m, 1H), 8.44 (s, 1H), 8.41 (d, *J* = 9.0 Hz, 1H), 7.79 (s, 1H), 7.72 (dd, *J* = 8.7, 1.7 Hz, 1H), 7.55 (d, *J* = 8.7 Hz, 1H), 7.23 – 7.18 (m, 1H), 5.56 (t, *J* = 9.1 Hz, 1H), 5.13 (d, *J* = 12.2 Hz, 1H), 4.32 – 4.12 (m, 8H), 3.90 (d, *J* = 10.8 Hz, 1H), 3.89 – 3.84 (m, 1H), 3.81 – 3.74 (m, 2H), 3.59 – 3.54 (m, 2H), 3.52 – 3.47 (m, 1H), 3.39 – 3.34 (m, 1H), 3.27 – 3.21 (m, 8H), 3.10 – 3.03 (m, 2H), 2.97 – 2.92 (m, 1H), 2.81 – 2.76 (m, 1H), 2.75 (s, 3H), 2.71 – 2.64 (m, 4H), 2.45 – 2.41 (m, 1H), 2.13 – 2.08 (m, 3H), 2.07 – 2.02 (m, 1H), 1.92 – 1.87 (m, 1H), 1.85 – 1.77 (m, 4H), 1.76 – 1.70 (m, 1H), 1.69 – 1.63 (m, 1H), 1.56 – 1.46 (m, 1H), 1.33 (d, *J* = 6.1 Hz, 3H), 0.93 – 0.87 (m, 9H), 0.85 (d, *J* = 6.6 Hz, 3H), 0.47 – 0.41 (m, 2H), 0.36 – 0.30 (m, 5H).

Examples B52 and B54: Synthesis of (2*S*)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-2-(3-(vinylsulfonyl)benzyl)pyrrolidine-1-carboxamide and (2*R*)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-2-(3-(vinylsulfonyl)benzyl)pyrrolidine-1-carboxamide



Step 1. To a stirred solution of triphosgene (343 mg, 1.16 mmol) in anhydrous DCM (8.0 mL), a mixture of methyl (2*S*)-3-methyl-2-(methylamino)butanoate HCl (525 mg, 2.89 mmol) and DIPEA (1.11 mL, 6.36 mmol) in anhydrous DCM (20 mL) and anhydrous THF (20 mL) was added dropwise over 30 minutes at room temperature. The resulting mixture was stirred at room temperature for 30 minutes. Subsequently, a mixture of 2-((3-bromophenyl)methyl)pyrrolidine HCl (400 mg, 1.45 mmol) and DIPEA (560 µL, 3.18 mmol) in anhydrous DCM (12 mL) was added and the resulting mixture was stirred at room temperature for 16 h. The reaction mixture was then concentrated under reduced pressure, diluted with aqueous citric acid (0.1 M), extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford methyl (2*S*)-2-((2-((3-bromophenyl)methyl)pyrrolidine-1-carbonyl)(methyl)amino)-3-methylbutanoate (500 mg, 84% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{19}H_{27}BrN_2O_3$: 411.1; found 411.7.

Step 2. To a stirred solution of 2-((tetrahydro-2*H*-pyran-2-yl)oxy)ethanethiol (247 mg, 1.52 mmol) in anhydrous toluene (5.0 mL), K_2CO_3 (106 mg, 0.767 mmol) was added at 0 °C. The resulting mixture was stirred at room temperature for 1 h. In a separate round-bottom flask, a mixture of methyl (2*S*)-2-((2-((3-bromophenyl)methyl)pyrrolidine-1-carbonyl)(methyl)amino)-3-methylbutanoate (500 mg, 1.22 mmol), Xantphos (77 mg, 0.13 mmol) and $Pd_2(dba)_3$ (111 mg, 0.121 mmol) in toluene (5.5 mL) was stirred at room temperature for 20 minutes and was then transferred to the first mixture. The resulting mixture was stirred at 110 °C for 16 h. The reaction mixture was then quenched with H_2O, extracted with EtOAc, dried

over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford methyl (2*S*)-3-methyl-2-(methyl((2-((3-((2-(oxan-2-yloxy)ethyl)sulfanyl)phenyl)methyl)pyrrolidine-1-carbonyl))amino)butanoate (1.11 g, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{25}H_{40}N_2O_5S$: 493.3; found 493.3.

Step 3. To a stirred solution of methyl (2*S*)-3-methyl-2-(methyl((2-((3-((2-(oxan-2-yloxy)ethyl)sulfanyl)phenyl)methyl)pyrrolidine-1-carbonyl))amino)butanoate (1.11 g, crude) in MeOH (22 mL), a solution of OXONE® (6.14 g, 20.0 mmol) in H_2O (11 mL) was added at 0 °C. The resulting mixture was stirred at room temperature for 16 h. The reaction mixture was then diluted with H_2O, extracted with DCM, washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford methyl (2*S*)-2-((2-((3-(2-hydroxyethanesulfonyl)phenyl)methyl)pyrrolidine-1-carbonyl)(methyl)amino)-3-methylbutanoate (86% purity, 353 mg, 56% yield over 2 steps). LCMS (ESI) *m/z*: [M + H] calcd for $C_{21}H_{32}N_2O_6S$: 441.2; found 441.1.

Step 4. To a stirred solution of methyl (2*S*)-2-((2-((3-(2-hydroxyethanesulfonyl)phenyl)methyl)pyrrolidine-1-carbonyl)(methyl)amino)-3-methylbutanoate (86% purity, 293 mg, 0.572 mmol) in anhydrous DCM (29 mL), triethylamine (319 µL, 2.29 mmol) and methanesulfonyl chloride (46 µL, 0.60 mmol) were added at 0 °C. The resulting mixture was stirred at room temperature for 16 h. The reaction mixture was then concentrated under reduced pressure and purified by normal phase flash column chromatography to afford methyl (2*S*)-2-((2-((3-(ethenesulfonyl)phenyl)methyl)pyrrolidine-1-carbonyl)(methyl)amino)-3-methylbutanoate (205 mg, 85% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{21}H_{30}N_2O_5S$: 423.2; found 423.7.

Step 5. To a stirred solution of methyl (2*S*)-2-((2-((3-(ethenesulfonyl)phenyl)methyl)pyrrolidine-1-carbonyl)(methyl)amino)-3-methylbutanoate (185 mg, 0.438 mmol) in anhydrous 1,4-dioxane (7.4 mL), trimethyltin hydroxide (1.47 g, 8.14 mmol) was added at room temperature. The resulting mixture was stirred at 120 °C for 16 h. The reaction mixture was then acidified to pH 5 with aqueous HCl (1.0 M), extracted with a 3:1 vol. mixture of DCM:MeOH, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford (2*S*)-2-((2-((3-(ethenesulfonyl)phenyl)methyl)pyrrolidine-1-carbonyl)(methyl)amino)-3-methylbutanoic acid (97 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{20}H_{28}N_2O_5S$: 409.2; found 409.8.

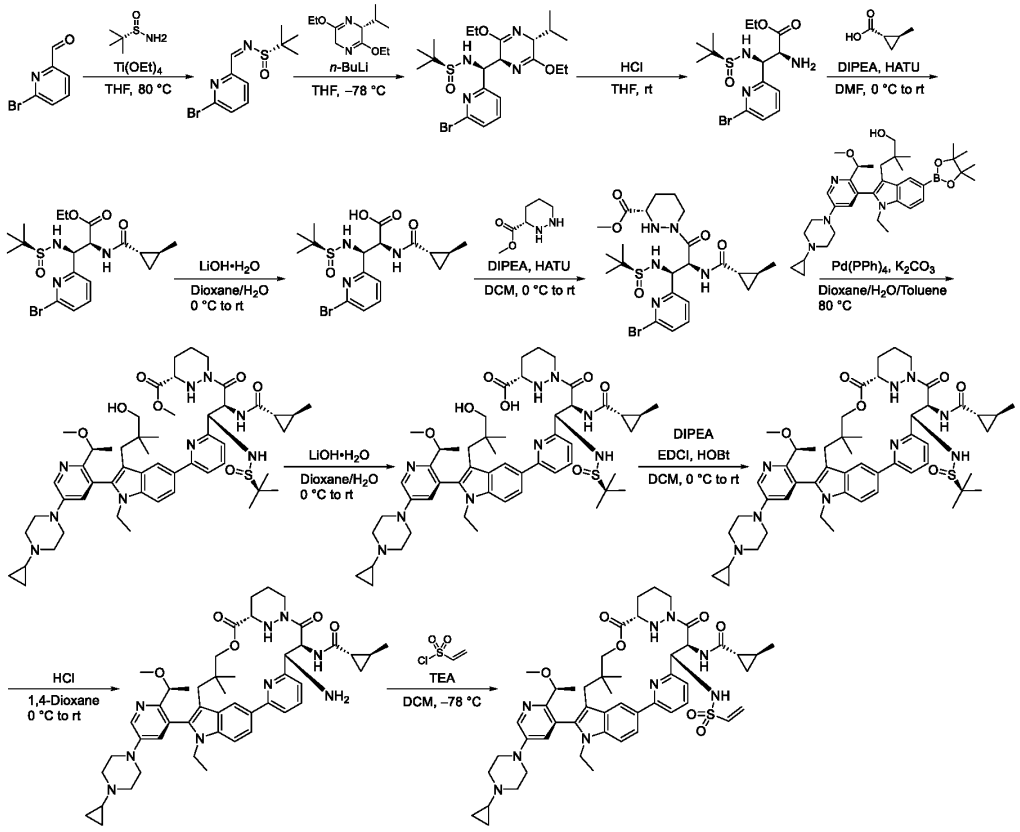
Step 6. To a stirred solution of (6^3S,4*S*)-4-amino-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-5,7-dione (150 mg, 0.199 mmol) and (2*S*)-2-((2-((3-(ethenesulfonyl)phenyl)methyl)pyrrolidine-1-carbonyl)(methyl)amino)-3-methylbutanoic acid (97 mg, crude) in anhydrous DMF (4.5 mL), DIPEA (101 µL, 0.58 mmol) was added at 0 °C. Subsequently, HATU (99 mg, 0.26 mmol) was added and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was then quenched with H_2O, extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and separated by reversed-phase prep-HPLC to afford two separated diastereomers of *N*-((2*S*)-1-((((6^3S,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-

N-methyl-2-(3-(vinylsulfonyl)benzyl)pyrrolidine-1-carboxamide. LCMS (ESI): exact mass for C61H80N10O8S2: 1144.56.

B52: (4.3 mg, 1.9% yield); LCMS (ESI) *m/z*: [M + H] calcd for $C_{61}H_{80}N_{10}O_8S_2$: 1145.6; found 1145.7; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.66 (d, *J* = 8.6 Hz, 1H), 8.48 – 8.38 (m, 2H), 7.78 (s, 1H), 7.76 – 7.64 (m, 3H), 7.63 – 7.50 (m, 3H), 7.20 (d, *J* = 2.2 Hz, 1H), 7.10 (dd, *J* = 16.3, 9.8 Hz, 1H), 6.32 (d, *J* = 16.5 Hz, 1H), 6.20 (d, *J* = 9.9 Hz, 1H), 5.50 – 5.39 (m, 1H), 5.07 (d, *J* = 12.1 Hz, 1H), 4.30 – 4.10 (m, 7H), 3.66 – 3.53 (m, 2H), 3.50 – 3.39 (m, 1H), 3.29 – 3.25 (m, 2H), 3.25 – 3.18 (m, 8H), 3.02 – 2.93 (m, 1H), 2.91 – 2.81 (m, 2H), 2.72 (s, 3H), 2.72 – 2.63 (m, 4H), 2.43 – 2.34 (m, 1H), 2.26 – 2.19 (m, 1H), 2.15 – 2.02 (m, 1H), 1.91 – 1.74 (m, 4H), 1.72 – 1.59 (m, 2H), 1.57 – 1.41 (m, 2H), 1.32 (d, *J* = 6.0 Hz, 3H), 1.04 (d, *J* = 6.1 Hz, 1H), 0.95 – 0.82 (m, 9H), 0.80 (d, *J* = 6.6 Hz, 3H), 0.48 – 0.39 (m, 2H), 0.36 – 0.29 (m, 5H).

B54: (10 mg, 4.4% yield); LCMS (ESI) *m/z*: [M + H] calcd for $C_{61}H_{80}N_{10}O_8S_2$: 1145.6; found 1145.8; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.58 – 8.38 (m, 2H), 8.28 (d, *J* = 9.1 Hz, 1H), 7.76 – 7.65 (m, 4H), 7.62 – 7.57 (m, 2H), 7.53 (d, *J* = 8.7 Hz, 1H), 7.20 (d, *J* = 2.9 Hz, 1H), 7.11 (dd, *J* = 16.4, 9.9 Hz, 1H), 6.32 (d, *J* = 16.4 Hz, 1H), 6.18 (d, *J* = 9.8 Hz, 1H), 5.61 (t, *J* = 9.0 Hz, 1H), 5.15 (d, *J* = 12.1 Hz, 1H), 4.35 – 4.09 (m, 6H), 3.96 (d, *J* = 10.7 Hz, 1H), 3.60 – 3.55 (m, 2H), 3.52 – 3.46 (m, 1H), 3.41 – 3.36 (m, 1H), 3.28 – 3.26 (m, 1H), 3.24 – 3.16 (m, 9H), 3.15 – 3.01 (m, 1H), 2.92 (d, *J* = 14.9 Hz, 1H), 2.86 (s, 3H), 2.79 – 2.72 (m, 2H), 2.69 – 2.65 (m, 4H), 2.44 – 2.33 (m, 1H), 2.16 – 2.06 (m, 2H), 1.85 – 1.77 (m, 4H), 1.69 – 1.61 (m, 1H), 1.55 – 1.45 (m, 2H), 1.32 (d, *J* = 6.0 Hz, 3H), 0.94 – 0.81 (m, 12H), 0.47 – 0.40 (m, 2H), 0.38 – 0.27 (m, 5H).

Example B30: Synthesis of (1*S*,2*S*)-*N*-((6^3*S*,3S,4S)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-3-(vinylsulfonamido)-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-6(1,3)-pyridazina-2(2,6)-pyridinacycloundecaphane-4-yl)-2-methylcyclopropane-1-carboxamide



Step 1. To a stirred solution of 6-bromopyridine-2-carbaldehyde (5.00 g, 26.9 mmol) in THF (150 mL), (*S*)-(-)-2-methyl-2-propanesulfinamide (4.89 g, 40.3 mmol) and titanium ethoxide (15.3 g, 67.2 mmol) were added at room temperature. The resulting mixture was stirred at 80 °C for 1 h. The reaction mixture was then quenched with H_2O, filtered extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford (*S*)-*N*-[(*Z*)-(6-bromopyridin-2-yl)methylidene]-2-methylpropane-2-sulfinamide (4.25 g, 55% yield). The crude product was used in the next step without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{10}H_{13}BrN_2OS$: 289.0; found 288.9.

Step 2. To a stirred solution of (2*R*)-3,6-diethoxy-2-(propan-2-yl)-2,5-dihydropyrazine (4.20 g, 19.8 mmol) in THF (212 mL) at –78 °C, *n*-BuLi (2.5 M in hexanes, 8.50 mL, 21.3 mmol) was added dropwise and the resulting mixture was stirred for 30 min at –78 °C. Subsequently, a solution of (*S*)-*N*-((*Z*)-(6-bromopyridin-2-yl)methylidene)-2-methylpropane-2-sulfinamide (4.24 g, crude) in THF (40 mL) was pre-cooled to –78 °C and added dropwise. The resulting mixture was stirred at –78 °C for 2 h. The reaction mixture was then quenched at 0 °C with sat. aq. NH_4Cl solution, extracted with DCM, washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by normal phase flash column chromatography to afford (*S*)-*N*-((*S*)-(6-bromopyridin-2-yl)((2*S*,5*R*)-3,6-diethoxy-5-(propan-2-yl)-

2,5-dihydropyrazin-2-yl)methyl)-2-methylpropane-2-sulfinamide (6.51 g, 32% yield over 2 steps). LCMS (ESI) *m/z*: [M + H] calcd for $C_{21}H_{33}BrN_4O_3S$: 501.2; found 501.2.

Step 3. To a stirred solution of (*S*)-*N*-((*S*)-(6-bromopyridin-2-yl)((2*S*,5*R*)-3,6-diethoxy-5-(propan-2-yl)-2,5-dihydropyrazin-2-yl)methyl)-2-methylpropane-2-sulfinamide (6.51 g, 13.0 mmol) in THF (260 mL), HCl (0.4 M in H_2O, 135 mL, 54.0 mmol) was added at room temperature. The resulting mixture was stirred for 16 h at room temperature. The reaction mixture was then quenched with H_2O, neutralized with sat. aq $NaHCO_3$, extracted with DCM, washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford ethyl (2*S*,3*S*)-2-amino-3-(6-bromopyridin-2-yl)-3-(((*S*)-2-methylpropane-2-sulfinyl)amino)propanoate (4.77 g, 84% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{14}H_{22}BrN_3O_3S$: 392.1; found 392.2.

Step 4. To a stirred solution of ethyl (2*S*,3*S*)-2-amino-3-(6-bromopyridin-2-yl)-3-(((*S*)-2-methylpropane-2-sulfinyl)amino)propanoate (1.80 g, 4.13 mmol) in anhydrous DMF (90 mL), DIPEA (7.20 mL, 41.3 mmol) and (1*S*,2*S*)-2-methylcyclopropane-1-carboxylic acid (455 mg, 4.54 mmol) were added. The resulting mixture was stirred for 15 minutes, after which time HATU (2.36 g, 6.19 mmol) was added at 0 °C and the resulting mixture was stirred for 16 hours at room temperature. The reaction mixture was then quenched with H_2O, extracted with DCM, washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford ethyl (2*S*,3*S*)-3-(6-bromopyridin-2-yl)-2-{[(1*S*,2*S*)-2-methylcyclopropyl]formamido}-3-{[(*S*)-2-methylpropane-2-sulfinyl]amino}propanoate (50% purity, 3.90 g, 99% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{19}H_{28}BrN_3O_4S$: 474.1; found 474.2.

Step 5. To a stirred solution of ethyl (2*S*,3*S*)-3-(6-bromopyridin-2-yl)-2-(((1*S*,2*S*)-2-methylcyclopropyl)formamido)-3-(((*S*)-2-methylpropane-2-sulfinyl)amino)propanoate (3.50 g, 3.68 mmol) in 1,4-dioxane (112 mL) and H_2O (28 mL), $LiOH{\bullet}H_2O$ (464 mg, 11.1 mmol) was added at 0 °C. The resulting mixture was stirred for 16 hours at room temperature. The reaction mixture was then quenched with H_2O, neutralized to pH 7 with a aqueous solution of HCl (1.0 M), extracted with DCM, washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford (2*S*,3*S*)-3-(6-bromopyridin-2-yl)-2-(((1*S*,2*S*)-2-methylcyclopropyl)formamido)-3-(((*S*)-2-methylpropane-2-sulfinyl)amino)propanoic acid (1.36 g, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{17}H_{24}BrN_3O_4S$: 446.1; found 446.1.

Step 6. To a stirred solution of (2*S*,3*S*)-3-(6-bromopyridin-2-yl)-2-(((1*S*,2*S*)-2-methylcyclopropyl)formamido)-3-(((*S*)-2-methylpropane-2-sulfinyl)amino)propanoic acid (1.36 g, crude) in anhydrous DCM (136 mL), DIPEA (5.00 mL, 28.9 mmol) and methyl (3*S*)-1,2-diazinane-3-carboxylate (1.54 g, 2.89 mmol, bis-TFA salt) were added at 0 °C. The resulting mixture was stirred for 15 minutes, after which time HATU (1.65 g, 4.34 mmol) was added at 0 °C and the mixture was stirred for 16 h at room temperature. The reaction mixture was then quenched with H_2O, extracted with DCM, washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford (3*S*)-1-((2*S*,3*S*)-3-(6-bromopyridin-2-yl)-2-(((1*S*,2*S*)-2-methylcyclopropyl)formamido)-3-(((*S*)-2-methylpropane-2-sulfinyl)amino)propanoyl)-1,2-diazinane-3-

carboxylate (233 mg, 11% yield over 2 steps). LCMS (ESI) *m/z*: [M + H] calcd for $C_{23}H_{34}BrN_5O_5S$: 572.2; found 572.2.

Step 7. To a stirred solution of 3-((2*M*)-2-(5-(4-cyclopropylpiperazin-1-yl)-2-((1*S*)-1-methoxyethyl)pyridin-3-yl)-1-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-3-yl)-2,2-dimethylpropan-1-ol (330 mg, 0.42 mmol) in toluene (8.8 mL), 1,4-dioxane (3.1 mL) and H_2O (3.1 mL), (3*S*)-1-((2*S*,3*S*)-3-(6-bromopyridin-2-yl)-2-(((1*S*,2*S*)-2-methylcyclopropyl)formamido)-3-(((*S*)-2-methylpropane-2-sulfinyl)amino)propanoyl)-1,2-diazinane-3-carboxylate (220 mg, 0.38 mmol) and potassium carbonate (132 mg, 0.96 mmol) were added at room temperature. The resulting mixture was purged with argon gas for 15 minutes, after which time $Pd(PPh_3)_4$ (89 mg, 0.077 mmol) was added at room temperature and the mixture was stirred for 16 h at 80 °C. The reaction mixture was then cooled to room temperature, quenched with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford methyl (3*S*)-1-((2*S*,3*S*)-3-(6-((2*M*)-2-(5-(4-cyclopropylpiperazin-1-yl)-2-((1*S*)-1-methoxyethyl)pyridin-3-yl)-1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)-1*H*-indol-5-yl)pyridin-2-yl)-2-(((1*S*,2*S*)-2-methylcyclopropyl)formamido)-3-((2-methylpropane-2-sulfinyl)amino)propanoyl)-1,2-diazinane-3-carboxylate (142 mg, 36% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{53}H_{75}N_9O_7S$: 982.6; found 983.0.

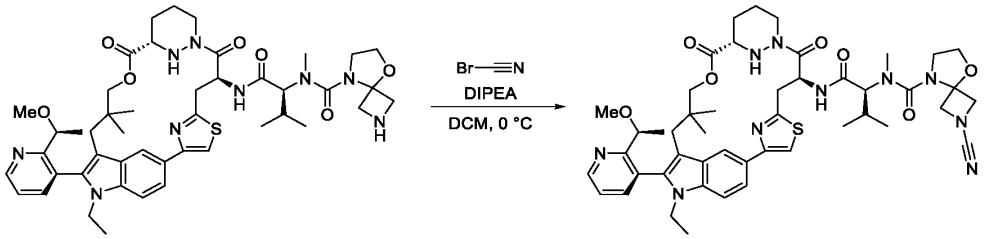
Step 8. To a stirred solution of methyl (3*S*)-1-((2*S*,3*S*)-3-(6-((2*M*)-2-(5-(4-cyclopropylpiperazin-1-yl)-2-((1*S*)-1-methoxyethyl)pyridin-3-yl)-1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)-1*H*-indol-5-yl)pyridin-2-yl)-2-(((1*S*,2*S*)-2-methylcyclopropyl)formamido)-3-((2-methylpropane-2-sulfinyl)amino)propanoyl)-1,2-diazinane-3-carboxylate (140 mg, 0.143 mmol) in a mixture of 1,4-dioxane (1.1 mL) and H_2O (400 µL), $LiOH•H_2O$ (17 mg, 0.41 mmol) was added at 0 °C. The resulting mixture was stirred for 16 hours at room temperature. The reaction mixture was then acidified to pH 4 with 1.0 M aq. HCl, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford (3*S*)-1-((2*S*,3*S*)-3-(6-((2*M*)-2-(5-(4-cyclopropylpiperazin-1-yl)-2-((1*S*)-1-methoxyethyl]pyridin-3-yl)-1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)-1*H*-indol-5-yl)pyridin-2-yl)-2-(((1*S*,2*S*)-2-methylcyclopropyl)formamido)-3-((2-methylpropane-2-sulfinyl)amino)propanoyl)-1,2-diazinane-3-carboxylic acid (120 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{52}H_{73}N_9O_7S$: 968.5; found 969.0.

Step 9. To a solution of (3*S*)-1-((2*S*,3*S*)-3-(6-((2*M*)-2-(5-(4-cyclopropylpiperazin-1-yl)-2-((1*S*)-1-methoxyethyl]pyridin-3-yl)-1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)-1*H*-indol-5-yl)pyridin-2-yl)-2-(((1*S*,2*S*)-2-methylcyclopropyl)formamido)-3-((2-methylpropane-2-sulfinyl)amino)propanoyl)-1,2-diazinane-3-carboxylic acid (115 mg, crude) in DCM (11.5 mL), $HOBt•H_2O$ (86 mg, 0.56 mmol), DIPEA (590 µL, 3.39 mmol) and EDCI•HCl (606 mg, 3.16 mmol) were added at 0 °C. The resulting mixture was stirred for 16 h at room temperature. The reaction mixture was then quenched with H_2O, extracted with DCM, washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase prep-TLC to afford (1*S*,2*S*)-*N*-((6^3*S*,3S,4*S*)-3-(((*S*)-*tert*-butylsulfinyl)amino)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-6(1,3)-pyridazina-2(2,6)-pyridinacycloundecaphane-4-yl)-2-methylcyclopropane-1-carboxamide (45 mg, 35% yield over 2 steps). LCMS (ESI) *m/z*: [M + H] calcd for $C_{52}H_{71}N_9O_6S$: 950.5; found 951.0.

Step 10. To a stirred solution of (1*S*,2*S*)-*N*-((6^3*S*,3S,4*S*)-3-(((*S*)-*tert*-butylsulfinyl)amino)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-6(1,3)-pyridazina-2(2,6)-pyridinacycloundecaphane-4-yl)-2-methylcyclopropane-1-carboxamide (45 mg, 0.047 mmol) in anhydrous 1,4-dioxane (500 µL), HCl (4.0 M in 1,4-dioxane, 114 µL, 0.456 mmol) was added at room temperature. The resulting mixture was stirred for 3 h at room temperature. The reaction mixture was then quenched with sat. aq. $NaHCO_3$, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford (1*S*,2*S*)-*N*-((6^3*S*,3*S*,4*S*)-3-amino-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-6(1,3)-pyridazina-2(2,6)-pyridinacycloundecaphane-4-yl)-2-methylcyclopropane-1-carboxamide (35 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{48}H_{63}N_9O_5$: 846.4; found 846.8.

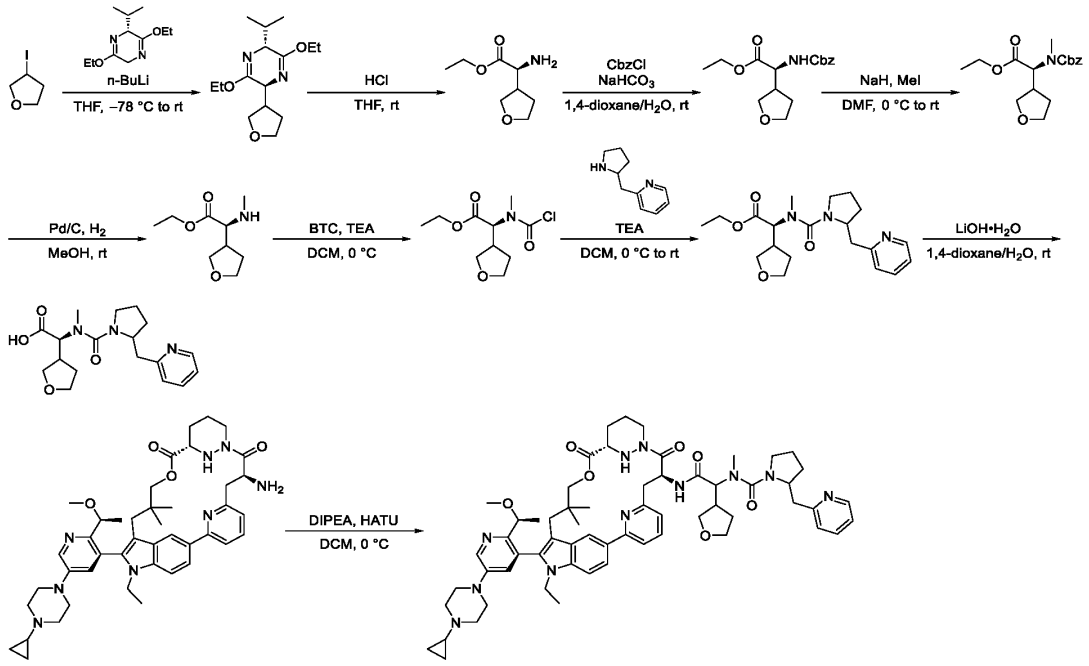
Step 11. To a stirred solution of (1*S*,2*S*)-*N*-((6^3*S*,3*S*,4*S*)-3-amino-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-6(1,3)-pyridazina-2(2,6)-pyridinacycloundecaphane-4-yl)-2-methylcyclopropane-1-carboxamide (35 mg, crude) and triethylamine (15 µL, 0.11 mmol) in DCM (1.4 mL), 4Å molecular sieves were added at –78 °C. The resulting mixture was stirred for 10 minutes, after which time ethenesulfonyl chloride (6 µL, 0.07 mmol) was added and the mixture was stirred at –78 °C for 1 h. The reaction mixture was then diluted with DCM, quenched with H_2O, extracted with DCM, washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase prep-HPLC to afford (1*S*,2*S*)-*N*-((6^3*S*,3S,4S)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-3-(vinylsulfonamido)-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-6(1,3)-pyridazina-2(2,6)-pyridinacycloundecaphane-4-yl)-2-methylcyclopropane-1-carboxamide (7.3 mg, 17% yield over 2 steps). LCMS (ESI) *m/z*: [M + H] calcd for $C_{50}H_{65}N_9O_7S$: 936.5; found 936.6; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.94 – 8.85 (m, 1H), 8.47 (d, *J* = 2.8 Hz, 1H), 8.12 (d, *J* = 10.5 Hz, 1H), 7.95 – 7.85 (m, 2H), 7.84 – 7.74 (m, 1H), 7.64 (d, *J* = 10.0 Hz, 1H), 7.56 (d, *J* = 8.7 Hz, 1H), 7.31 (d, *J* = 2.9 Hz, 1H), 7.21 (d, *J* = 7.5 Hz, 1H), 6.65 (dd, *J* = 16.4, 9.9 Hz, 1H), 6.11 – 6.04 (m, 1H), 6.01 (d, *J* = 16.4 Hz, 1H), 5.85 (d, *J* = 9.9 Hz, 1H), 5.75 (d, *J* = 12.3 Hz, 1H), 4.99 (d, *J* = 10.3 Hz, 1H), 4.39 – 4.27 (m, 1H), 4.10 – 4.00 (m, 2H), 3.99 – 3.75 (m, 3H), 3.59 (d, *J* = 10.8 Hz, 1H), 3.29 – 3.26 (m, 1H), 3.26 – 3.16 (m, 4H), 2.94 – 2.83 (m, 1H), 2.79 (s, 3H), 2.72 – 2.64 (m, 4H), 2.46 – 2.40 (m, 1H), 2.11 – 1.96 (m, 2H), 1.91 – 1.80 (m, 1H), 1.72 – 1.53 (m, 3H), 1.39 (d, *J* = 6.3 Hz, 3H), 1.22 – 1.17 (m, 2H), 1.18 – 1.12 (m, 1H), 1.04 – 0.96 (m, 3H), 0.95 – 0.88 (m, 1H), 0.88 – 0.84 (m, 3H), 0.61 – 0.54 (m, 1H), 0.51 (s, 3H), 0.47 – 0.40 (m, 2H), 0.38 – 0.29 (m, 3H).

Example B131: Synthesis of 2-cyano-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^1-ethyl-1^2-(2-((*S*)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-5-oxa-2,8-diazaspiro[3.4]octane-8-carboxamide



Step 1. To a stirred solution of *N*-((2*S*)-1-(((6^3*S*,4*S*)-1^1-ethyl-1^2-(2-((*S*)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-5-oxa-2,8-diazaspiro[3.4]octane-8-carboxamide (154 mg, 0.174 mmol) and DIPEA (152 µL, 0.87 mmol) in DCM (4.0 mL), cyanogen bromide (24 mg, 0.23 mmol) was added at 0 °C. The resulting mixture was stirred for 10 minutes at 0 °C. The reaction mixture was then with EtOAc, washed with sat. aq $NaHCO_3$, washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase prep-HPLC to afford 2-cyano-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^1-ethyl-1^2-(2-((*S*)-1-methoxyethyl)pyridin-3-yl)-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-5-oxa-2,8-diazaspiro[3.4]octane-8-carboxamide (36.0 mg, 23% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{47}H_{60}N_{10}O_7S$: 909.4; found 909.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 (dd, *J* = 4.7, 1.8 Hz, 1H), 8.48 (s, 1H), 8.44 (d, *J* = 8.6 Hz, 1H), 7.83 – 7.77 (m, 2H), 7.73 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.57 (d, *J* = 8.7 Hz, 1H), 7.52 (dd, *J* = 7.7, 4.7 Hz, 1H), 5.53 (t, *J* = 8.9 Hz, 1H), 5.11 (d, *J* = 12.2 Hz, 1H), 4.92 (d, *J* = 8.4 Hz, 1H), 4.79 (d, *J* = 8.6 Hz, 1H), 4.41 – 4.16 (m, 5H), 4.16 – 4.02 (m, 4H), 3.94 (q, *J* = 7.4 Hz, 1H), 3.64 (q, *J* = 7.4 Hz, 1H), 3.60 – 3.52 (m, 2H), 3.50 – 3.43 (m, 1H), 3.40 – 3.31 (m, 1H), 3.26 (s, 3H), 3.21 (dd, *J* = 14.9, 9.2 Hz, 1H), 2.96 (d, *J* = 14.4 Hz, 1H), 2.87 (s, 3H), 2.82 – 2.72 (m, 1H), 2.39 (d, *J* = 14.5 Hz, 1H), 2.22 – 2.02 (m, 2H), 1.88 – 1.70 (m, 2H), 1.64 – 1.44 (m, 1H), 1.36 (d, *J* = 6.1 Hz, 3H), 0.94 (d, *J* = 6.0 Hz, 3H), 0.90 – 0.73 (m, 9H), 0.32 (s, 3H).

Examples A40, A41, A42, and A50: Synthesis of *N*-(2-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-6(1,3)-pyridazina-2(2,6)-pyridinacycloundecaphane-4-yl)amino)-2-oxo-1-(tetrahydrofuran-3-yl)ethyl)-*N*-methyl-2-(pyridin-2-ylmethyl)pyrrolidine-1-carboxamide



Step 1. To a stirred solution of (3*R*)-2,5-diethoxy-3-isopropyl-3,6-dihydropyrazine (1.03 g, 4.85 mmol) in anhydrous THF (40 mL), *n*-BuLi (2.5 M in hexanes, 1.60 mL, 4.0 mmol) was added dropwise at –78 °C and the mixture was stirred for 30 minutes under an atmosphere of argon. This mixture was then added dropwise by cannula to a stirred solution of 3-iodotetrahydrofuran (800 mg, 4.05 mmol) in anhydrous THF (40 mL) at –78 °C. The resulting mixture was stirred at –78 °C for 3 h and then at room temperature for 16 h. The reaction mixture was then quenched with ice-cold H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford (2*S*,5*R*)-3,6-diethoxy-2-(oxolan-3-yl)-5-(propan-2-yl)-2,5-dihydropyrazine (468 mg, 41% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{15}H_{26}N_2O_3$: 283.2; found 283.1.

Step 2. To a stirred solution of (2*S*,5*R*)-3,6-diethoxy-2-(oxolan-3-yl)-5-(propan-2-yl)-2,5-dihydropyrazine (440 mg, 1.56 mmol) in THF (44 mL), an aqueous solution of hydrochloric acid (0.4 M, 9.6 mL, 3.8 mmol) was added. The resulting mixture was stirred at room temperature for 16 h. The reaction mixture was then neutralized to pH 7 with sat. aq. $NaHCO_3$, and extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford of ethyl (2*S*)-2-amino-2-(oxolan-3-yl)acetate (347 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_8H_{15}NO_3$: 174.1; found 174.0.

Step 3. To a stirred solution of ethyl (2*S*)-2-amino-2-(oxolan-3-yl)acetate (347 mg, crude) in a mixture of H_2O (17.4 mL) and 1,4-dioxane (17.4 mL), $NaHCO_3$ (421 mg, 5.01 mmol) and benzyl chloroformate (513 µL, 3.01 mmol) were added at room temperature. The resulting mixture was stirred at

room temperature for 16 h. The reaction mixture was then extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford ethyl (2*S*)-2-(((benzyloxy)carbonyl)amino)-2-(oxolan-3-yl)acetate (268 mg, 56% yield over 2 steps). LCMS (ESI) *m/z*: [M + H] calcd for $C_{16}H_{21}NO_5$: 308.1; found 308.1.

Step 4. To a stirred solution of ethyl (2*S*)-2-(((benzyloxy)carbonyl)amino)-2-(oxolan-3-yl)acetate (248 mg, 0.807 mmol) in anhydrous DMF (17.4 mL), methyl iodide (201 µL, 3.23 mmol) and sodium hydride (60% dispersion in mineral oil, 63.0 mg, 1.61 mmol) were added at 0 °C. The resulting mixture was stirred at 0 °C for 10 minutes and then at room temperature for 1 h. The reaction mixture was then quenched with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford ethyl (2*S*)-2-(((benzyloxy)carbonyl)(methyl)amino)-2-(oxolan-3-yl)acetate (199 mg, 77% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{17}H_{23}NO_5$: 322.2; found 322.0.

Step 5. To a stirred solution of ethyl (2*S*)-2-(((benzyloxy)carbonyl)(methyl)amino)-2-(oxolan-3-yl)acetate (199 mg, 0.619 mmol) in MeOH (14 mL), Pd/C (40% wt., 80 mg) was added at room temperature. The resulting mixture was placed under an atmosphere of hydrogen gas and stirred at room temperature for 16 h. The reaction mixture was then filtered through a pad of Celite®, the pad was washed with MeOH, and the filtrate was concentrated under reduced pressure to afford ethyl (2*S*)-2-(methylamino)-2-(oxolan-3-yl)acetate (103 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_9H_{17}NO_3$: 188.1; found 188.0.

Step 6. To a stirred solution of triphosgene (63 mg, 0.21 mmol) in anhydrous DCM (2.4 mL), a solution of ethyl (2*S*)-2-(methylamino)-2-(oxolan-3-yl)acetate (80 mg, crude) and triethylamine (300 µL, 2.13 mmol) in DCM (2.4 mL) was added dropwise at 0 ºC. The resulting mixture was stirred for 2 h at 0 ºC. The reaction mixture was then quenched with ice-cold H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford ethyl (2*S*)-2-((chlorocarbonyl)(methyl)amino)-2-(oxolan-3-yl)acetate (150 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{10}H_{16}ClNO_4$: 250.1; found 250.0.

Step 7. To a stirred solution of 2-((pyrrolidin-2-yl)methyl)pyridine dihydrochloride salt (97 mg, 0.41 mmol) and triethylamine (290 µL, 2.08 mmol) in anhydrous DCM (4.5 mL), a solution of ethyl (2*S*)-2-((chlorocarbonyl)(methyl)amino)-2-(oxolan-3-yl)acetate (150 mg, crude) in DCM (4.5 mL) was added at 0 °C. The resulting mixture was stirred at 0 °C for 30 minutes and was then stirred at room temperature for 16 h. The reaction mixture was quenched with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase flash column chromatography to afford ethyl (2*S*)-2-(methyl((2-((pyridin-2-yl)methyl)pyrrolidine-1-carbonyl))amino)-2-(oxolan-3-yl)acetate (103 mg, 67% yield). LCMS (ESI) *m/z*: [M + H] calcd for $C_{20}H_{29}N_3O_4$: 376.2; found 376.1.

Step 8. To a stirred solution of ethyl (2*S*)-2-(methyl((2-((pyridin-2-yl)methyl)pyrrolidine-1-carbonyl))amino)-2-(oxolan-3-yl)acetate (98 mg, 0.26 mmol) in 1,4-dioxane (8.0 mL) and H_2O (2.0 mL), lithium hydroxide monohydrate (33 mg, 0.78 mmol) was added. The resulting mixture was stirred at room temperature for 16 h, and was then concentrated under reduced pressure to afford lithium (2S)-2-

(methyl((2-((pyridin-2-yl)methyl)pyrrolidine-1-carbonyl))amino)-2-(oxolan-3-yl)acetate (87 mg, crude). This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{18}H_{25}N_3O_4$: 348.2; found 348.1.

Step 9. To a stirred solution of (6^3S,4*S*)-4-amino-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-6(1,3)-pyridazina-2(2,6)-pyridinacycloundecaphane-5,7-dione (136 mg, 0.182 mmol) in DMF (4.1 mL), DIPEA (297 µL, 1.71 mmol) and lithium (2S)-2-(methyl((2-((pyridin-2-yl)methyl)pyrrolidine-1-carbonyl))amino)-2-(oxolan-3-yl)acetate (100 mg, crude) were added at 0 °C. The mixture was stirred for 5 minutes, after which time HATU (97 mg, 0.26 mmol) was added and the resulting mixture was stirred at 0 °C for 2 h. The reaction mixture was then quenched with H_2O, extracted with DCM, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford 330 mg crude material. (Note: isomerization was observed during the course of the reaction and a total of 8 isomers were detected in the crude material). The crude material was purified by normal phase prep-TLC (eluting with DCM and acetone) and was then further purified by prep-SFC to afford 3 separate fractions containing 33.7 mg, 36.8 mg and 80.1 mg of material, respectively. The material from each fraction was dissolved in DCM, washed with sat. aq. $NaHCO_3$, concentrated under reduced pressure, and purified by normal phase prep-TLC (eluting with $CHCl_3$ and *i*-PrOH) to afford 5 isolated diastereomers of *N*-(2-((((6^3S,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-6(1,3)-pyridazina-2(2,6)-pyridinacycloundecaphane-4-yl)amino)-2-oxo-1-(tetrahydrofuran-3-yl)ethyl)-*N*-methyl-2-(pyridin-2-ylmethyl)pyrrolidine-1-carboxamide.

Isomer 1: (95% purity, 15.4 mg, 7% yield); LCMS (ESI) *m/z*: [M + H] calcd for $C_{61}H_{79}N_{11}O_7$: 1078.6; found 1078.2; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.89 – 8.77 (m, 1H), 8.50 – 8.44 (m, 2H), 8.38 – 8.23 (m, 1H), 7.91 – 7.86 (m, 1H), 7.85 – 7.80 (m, 1H), 7.72 – 7.63 (m, 2H), 7.59 – 7.54 (m, 1H), 7.27 (d, *J* = 2.9 Hz, 1H), 7.22 – 7.14 (m, 2H), 7.12 – 7.07 (m, 1H), 5.93 – 5.77 (m, 1H), 5.48 – 5.40 (m, 1H), 4.37 – 4.20 (m, 3H), 4.20 – 4.06 (m, 2H), 4.05 – 3.92 (m, 1H), 3.85 – 3.72 (m, 2H), 3.72 – 3.59 (m, 2H), 3.57 – 3.44 (m, 2H), 3.38 – 3.35 (m, 1H), 3.27 – 3.13 (m, 5H), 3.11 – 2.96 (m, 3H), 2.96 – 2.91 (m, 3H), 2.82 – 2.75 (m, 1H), 2.73 – 2.64 (m, 4H), 2.60 (s, 2H), 2.58 (s, 1H), 2.46 – 2.28 (m, 3H), 2.04 – 1.93 (m, 1H), 1.90 – 1.40 (m, 11H), 1.38 (d, *J* = 6.1 Hz, 3H), 1.20 – 1.07 (m, 4H), 0.72 (s, 3H), 0.61 (s, 3H), 0.48 – 0.40 (m, 2H), 0.38 – 0.31 (m, 2H).

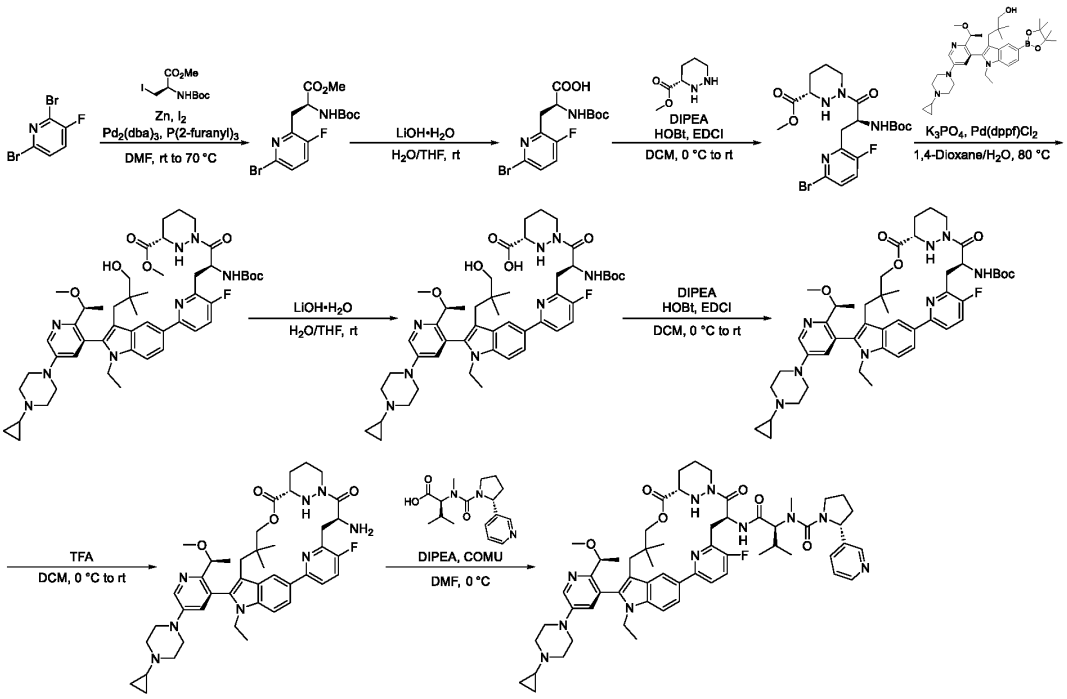
Isomer 2 (A50): (97% purity, 14.8 mg, 7% yield); LCMS (ESI) *m/z*: [M + H] calcd for $C_{61}H_{79}N_{11}O_7$: 1078.6; found 1078.1; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.87 (s, 1H), 8.54 – 8.49 (m, 1H), 8.47 (d, *J* = 2.8 Hz, 1H), 8.19 – 8.09 (m, 1H), 7.92 – 7.83 (m, 2H), 7.73 – 7.65 (m, 2H), 7.59 – 7.55 (m, 1H), 7.31 – 7.26 (m, 2H), 7.24 – 7.18 (m, 1H), 7.11 (t, *J* = 7.1 Hz, 1H), 5.98 – 5.84 (m, 1H), 5.56 – 5.44 (m, 1H), 4.38 – 4.25 (m, 2H), 4.18 – 3.91 (m, 4H), 3.86 – 3.71 (m, 2H), 3.69 – 3.55 (m, 2H), 3.57 – 3.44 (m, 1H), 3.27 – 3.19 (m, 4H), 3.16 – 3.00 (m, 5H), 2.94 – 2.89 (m, 3H), 2.91 – 2.76 (m, 2H), 2.73 – 2.64 (m, 4H), 2.60 – 2.58 (m, 3H), 2.45 – 2.30 (m, 4H), 2.04 – 1.91 (m, 1H), 1.90 – 1.50 (m, 10H), 1.39 (d, *J* = 6.2 Hz, 3H), 1.25 – 1.08 (m, 4H), 0.74 (s, 3H), 0.59 (s, 3H), 0.48 – 0.40 (m, 2H), 0.37 – 0.31 (m, 2H).

Isomer 3 (A42): (96% purity, 8.3 mg, 4% yield); LCMS (ESI) *m/z*: [M + H] calcd for $C_{61}H_{79}N_{11}O_7$: 1078.6; found 1078.3; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.90 – 8.83 (m, 1H), 8.53 – 8.50 (m, 1H), 8.47 (d, *J* = 2.8 Hz, 1H), 8.14 – 8.07 (m, 1H), 7.93 – 7.83 (m, 1H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.73 – 7.63 (m, 2H), 7.59 – 7.53 (m, 1H), 7.31 – 7.19 (m, 3H), 6.95 (d, *J* = 7.4 Hz, 1H), 6.03 – 5.84 (m, 1H), 5.49 (d, *J* = 12.2 Hz, 1H), 4.41 – 4.25 (m, 2H), 4.20 – 3.89 (m, 4H), 3.85 – 3.71 (m, 2H), 3.71 – 3.57 (m, 3H), 3.56 – 3.43 (m, 2H), 3.31 – 3.19 (m, 6H), 3.21 – 3.11 (m, 1H), 3.10 – 3.01 (m, 2H), 2.93 (s, 3H), 2.91 – 2.78 (m, 1H), 2.79 – 2.74 (m, 1H), 2.73 – 2.61 (m, 5H), 2.61 – 2.53 (m, 1H), 2.44 – 2.39 (m, 2H), 2.37 – 2.30 (m, 1H), 2.04 – 1.93 (m, 1H), 1.90 – 1.49 (m, 10H), 1.48 – 1.32 (m, 4H), 1.17 – 1.09 (m, 3H), 0.73 (s, 3H), 0.60 (s, 3H), 0.49 – 0.40 (m, 2H), 0.37 – 0.30 (m, 2H).

Isomer 4 (A40): (97% purity, 4.3 mg, 2% yield); LCMS (ESI) *m/z*: [M + H] calcd for $C_{61}H_{79}N_{11}O_7$: 1078.6; found 1078.3; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.84 (s, 1H), 8.54 – 8.49 (m, 1H), 8.47 (d, *J* = 2.9 Hz, 1H), 8.10 (d, *J* = 9.3 Hz, 1H), 7.85 (dd, *J* = 8.9, 1.7 Hz, 1H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.68 (td, *J* = 7.6, 1.9 Hz, 1H), 7.68 (td, *J* = 7.6, 1.9 Hz, 1H), 7.55 (d, *J* = 8.7 Hz, 1H), 7.27 (d, *J* = 2.9 Hz, 1H), 7.25 – 7.19 (m, 2H), 6.98 (d, *J* = 7.4 Hz, 1H), 6.02 – 5.94 (m, 1H), 5.51 – 5.44 (m, 1H), 4.36 – 4.27 (m, 2H), 4.17 – 4.06 (m, 4H), 4.03 – 3.95 (m, 1H), 3.84 – 3.74 (m, 2H), 3.72 – 3.62 (m, 3H), 3.61 – 3.54 (m, 1H), 3.29 – 3.24 (m, 3H), 3.24 – 3.20 (m, 4H), 3.12 – 3.04 (m, 2H), 2.94 (s, 3H), 2.88 – 2.81 (m, 1H), 2.77 – 2.71 (m, 1H), 2.70 – 2.66 (m, 4H), 2.58 – 2.53 (m, 1H), 2.43 (s, 3H), 2.02 – 1.96 (m, 1H), 1.93 – 1.87 (m, 1H), 1.85 – 1.74 (m, 3H), 1.73 – 1.64 (m, 4H), 1.63 – 1.51 (m, 3H), 1.49 – 1.41 (m, 1H), 1.39 (d, *J* = 6.2 Hz, 3H), 1.11 (t, *J* = 7.1 Hz, 3H), 0.71 (s, 3H), 0.61 (s, 3H), 0.46 – 0.41 (m, 2H), 0.37 – 0.32 (m, 2H).

Isomer 5: (A41): (98% purity, 7.8 mg, 4% yield); LCMS (ESI) *m/z*: [M + H] calcd for $C_{61}H_{79}N_{11}O_7$: 1078.6; found 1078.3; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.88 (d, *J* = 9.0 Hz, 1H), 8.51 – 8.44 (m, 2H), 8.42 – 8.30 (m, 1H), 7.90 – 7.77 (m, 2H), 7.71 – 7.58 (m, 2H), 7.55 (d, *J* = 8.7 Hz, 1H), 7.28 (s, 1H), 7.22 – 7.12 (m, 2H), 7.07 – 7.00 (m, 1H), 5.96 – 5.86 (m, 1H), 5.58 – 5.46 (m, 1H), 4.36 – 4.21 (m, 3H), 4.15 – 4.03 (m, 2H), 4.01 – 3.89 (m, 1H), 3.87 – 3.56 (m, 5H), 3.55 – 3.43 (m, 2H), 3.27 – 3.17 (m, 6H), 3.19 – 3.07 (m, 1H), 3.06 – 2.94 (m, 3H), 2.92 – 2.85 (m, 4H), 2.81 – 2.65 (m, 5H), 2.47 – 2.41 (m, 1H), 2.26 – 2.19 (m, 3H), 2.03 – 1.94 (m, 1H), 1.92 – 1.49 (m, 10H), 1.42 – 1.34 (m, 3H), 1.19 – 1.10 (m, 4H), 0.79 – 0.75 (m, 3H), 0.58 – 0.55 (m, 3H), 0.49 – 0.41 (m, 2H), 0.37 – 0.30 (m, 2H).

Example A771: Synthesis of (2*R*)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-2^5-fluoro-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-6(1,3)-pyridazina-2(2,6)-pyridinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-2-(pyridin-3-yl)pyrrolidine-1-carboxamide



Step 1. To a stirred mixture of zinc (3.00 g, 45.9 mmol) in DMF (30 mL), I_2 (89.6 mg, 0.353 mmol) was added in portions at room temperature under an atmosphere of argon gas. Subsequently, a solution of methyl (2*R*)-2-((*tert*-butoxycarbonyl)amino)-3-iodopropanoate (7.55 g, 23.0 mmol) in DMF (7.5 mL) was added dropwise at room temperature and the resulting mixture was stirred at room temperature for 10 minutes. After this time, a solution of 2,6-dibromo-3-fluoropyridine (4.50 g, 17.7 mmol), tris(furan-2-yl)phosphane (246 mg, 1.06 mmol) and $Pd_2(dba)_3$ (323 mg, 0.353 mmol) in DMF (40 mL) was added. The resulting mixture was stirred for 2 h at 70 °C under an atmosphere of argon gas. The reaction mixture was then cooled to room temperature, quenched with sat. aq. NH_4Cl at 0 °C, extracted with EtOAc (3 x 30 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase prep-TLC to afford methyl (2*S*)-3-(4-bromopyrimidin-2-yl)-2-((*tert*-butoxycarbonyl)amino)propanoate (524 mg, 56% yield) as a yellow oil. LCMS (ESI) *m/z*: [M + H] calcd for $C_{14}H_{18}BrFN_2O_4$: 379.1; found 379.2.

Step 2. To a stirred solution of methyl (2*S*)-3-(6-bromo-3-fluoropyridin-2-yl)-2-((*tert*-butoxycarbonyl)amino)propanoate (3.20 g, 8.48 mmol) in THF (30 mL) and H_2O (6 mL), $LiOH•H_2O$ (534 mg, 12.7 mmol) was added. The resulting mixture was stirred for 2 h at room temperature under an atmosphere of nitrogen gas. The reaction mixture was then acidified to pH 5 with an aqueous solution of HCl, extracted with DCM (3 x 20 mL), and concentrated under reduced pressure to afford (2*S*)-3-(6-bromo-3-fluoropyridin-2-yl)-2-((*tert*-butoxycarbonyl)amino)propanoic acid (2.90 g, crude) as a yellow solid.

This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{13}H_{16}BrFN_2O_4$: 365.0; found 365.1.

Step 3. To a stirred mixture of (2*S*)-3-(6-bromo-3-fluoropyridin-2-yl)-2-((*tert*-butoxycarbonyl)amino)propanoic acid (2.90 g, crude), methyl (*S*)-hexahydropyridazine-3-carboxylate (3.45 g, 24.0 mmol), HOBt (5.39 g, 39.9 mmol), and EDCI (23.0 g, 120 mmol) in DCM (30 mL), DIPEA (31.0 g, 240 mmol) was added dropwise at 0 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred for 2 h at room temperature. The reaction mixture was then extracted with DCM (3 x 50 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase prep-TLC to afford methyl (3*S*)-1-((2*S*)-3-(6-bromo-3-fluoropyridin-2-yl)-2-((*tert*-butoxycarbonyl)amino)propanoyl)-1,2-diazinane-3-carboxylate (3.23 g, 78% yield over 2 steps) as a yellow solid. LCMS (ESI) *m/z*: [M + H] calcd for $C_{19}H_{26}BrFN_4O_5$: 489.1; found 489.1.

Step 4. To a stirred mixture of 3-((2*M*)-2-(5-(4-cyclopropylpiperazin-1-yl)-2-((1*S*)-1-methoxyethyl)pyridin-3-yl)-1-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indol-3-yl)-2,2-dimethylpropan-1-ol (2.90 g, 4.70 mmol) and methyl (3*S*)-1-((2*S*)-3-(6-bromo-3-fluoropyridin-2-yl)-2-((*tert*-butoxycarbonyl)amino)propanoyl)-1,2-diazinane-3-carboxylate (2.53 g, 5.17 mmol) in 1,4-dioxane (30 mL) and H_2O (5 mL), K_2CO_3 (1.62 g, 11.8 mmol) and Pd(dppf)Cl_2 (688 mg, 0.941 mmol) were added at room temperature under an atmosphere of nitrogen gas. The resulting mixture was stirred for 2 h at 80 °C. The reaction mixture was then cooled to room temperature, quenched with H_2O (50 mL), extracted with EtOAc (3 x 50 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase prep-TLC to afford methyl (*S*)-1-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(6-(2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)-1*H*-indol-5-yl)-3-fluoropyridin-2-yl)propanoyl)hexahydropyridazine-3-carboxylate (3.23 g, 76% yield) as a yellow oil. LCMS (ESI) *m/z*: [M + H] calcd for $C_{49}H_{67}FN_8O_7$: 899.5; found 899.6.

Step 5. To a stirred mixture of methyl (*S*)-1-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(6-(2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)-1*H*-indol-5-yl)-3-fluoropyridin-2-yl)propanoyl)hexahydropyridazine-3-carboxylate (1.50 g, 1.69 mmol) in THF (15 mL) and H_2O (3.0 mL), LiOH•H_2O (105 mg, 2.50 mmol) was added at room temperature. The resulting mixture was stirred for 2 h at room temperature under an atmosphere of nitrogen gas. The reaction mixture was then neutralized to pH 7 with an aqueous solution of HCl, extracted with EtOAc (3 x 20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford (*S*)-1-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(6-(2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)-1*H*-indol-5-yl)-3-fluoropyridin-2-yl)propanoyl)hexahydropyridazine-3-carboxylic acid (1.30 g, crude) as a yellow solid. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{48}H_{65}FN_8O_7$: 885.5; found 885.5.

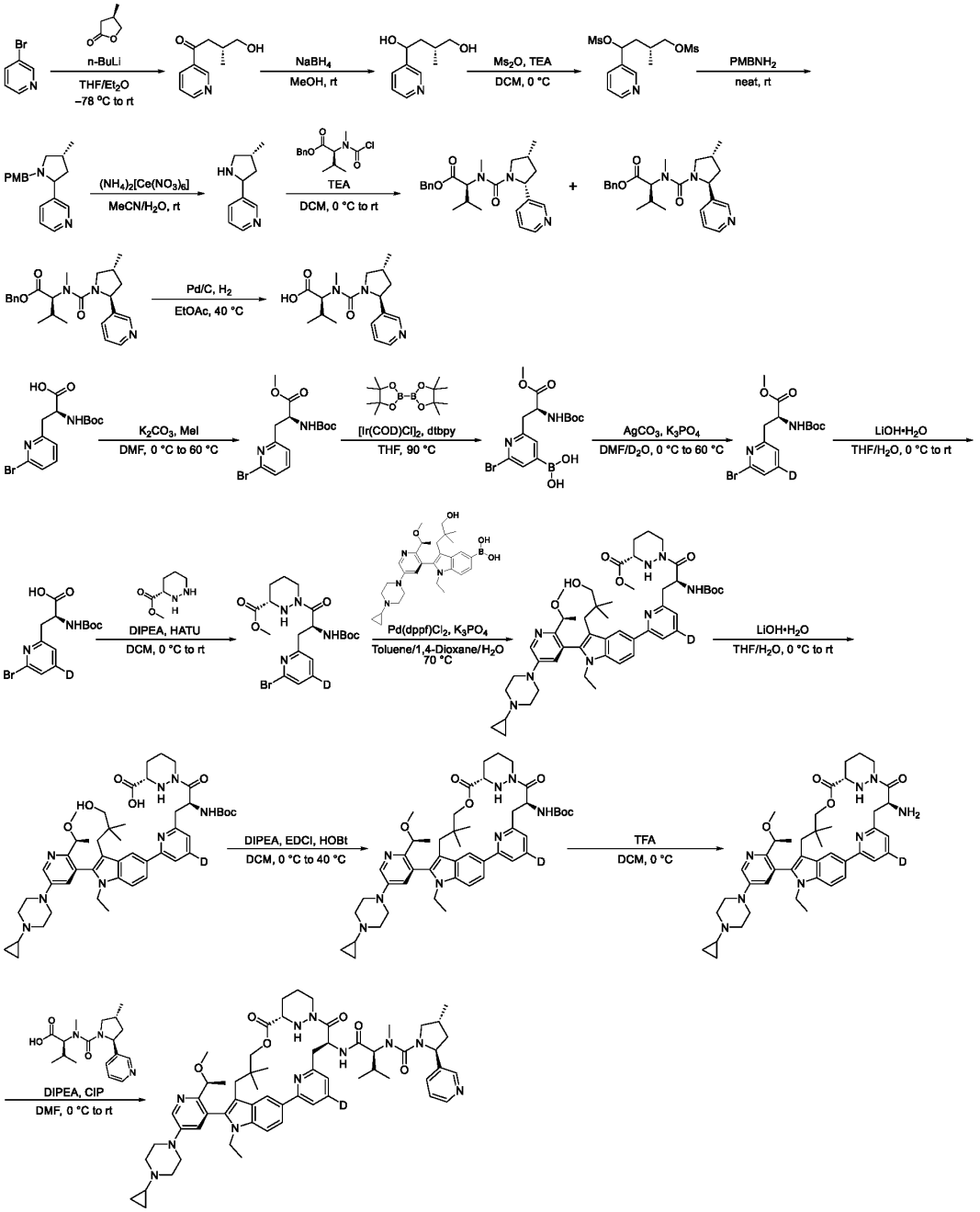
Step 6. To a stirred mixture of (*S*)-1-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(6-(2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)-1*H*-indol-5-yl)-3-fluoropyridin-2-yl)propanoyl)hexahydropyridazine-3-carboxylic acid (1.30 g, crude) and DIPEA (6.64 g, 51.4 mmol) in DCM (130 mL), HOBt (990 mg, 7.35 mmol) and EDCI (7.88 g, 41.1 mmol) were added at 0 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred for 2 h at

room temperature. The resulting mixture was quenched with H_2O (100 mL), extracted with DCM (3 x 100 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase prep-TLC to afford *tert*-butyl ((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-2^5-fluoro-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-6(1,3)-pyridazina-2(2,6)-pyridinacycloundecaphane-4-yl)carbamate (830 mg, 57% yield over 2 steps) as a yellow solid. LCMS (ESI) *m/z*: [M + H] calcd for $C_{48}H_{63}FN_8O_6$: 867.5; found 867.5.

Step 7. To a stirred mixture of *tert*-butyl ((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-2^5-fluoro-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-6(1,3)-pyridazina-2(2,6)-pyridinacycloundecaphane-4-yl)carbamate (300 mg, 0.346 mmol) in DCM (3.0 mL), TFA (1.0 mL, 13.1 mmol) was added dropwise at 0 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred for 2 h at room temperature. The reaction mixture was then concentrated under reduced pressure, diluted with DCM (5 mL), neutralized to pH 7 with sat. aq. $NaHCO_3$, extracted with DCM (3 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford (6^3*S*,4*S*)-4-amino-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-2^5-fluoro-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-6(1,3)-pyridazina-2(2,6)-pyridinacycloundecaphane-5,7-dione (221 mg, crude) as a yellow solid. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{43}H_{55}FN_8O_4$: 767.4; found 767.5.

Step 8. To a stirred mixture of (6^3*S*,4*S*)-4-amino-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-2^5-fluoro-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-6(1,3)-pyridazina-2(2,6)-pyridinacycloundecaphane-5,7-dione (200 mg, crude), DIPEA (674 mg, 5.22 mmol) and (2*S*)-3-methyl-2-(methyl((2*R*)-2-(pyridin-3-yl)pyrrolidine-1-carbonyl)amino)butanoic acid (119 mg, crude) in DMF (3.0 mL), COMU (90.2 mg, 0.339 mmol) was added dropwise at 0 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred at 0 °C for 1 h. The reaction mixture was then diluted with H_2O (20 mL), extracted with EtOAc (3 x 20 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase prep-TLC to afford (2*R*)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-2^5-fluoro-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-6(1,3)-pyridazina-2(2,6)-pyridinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-2-(pyridin-3-yl)pyrrolidine-1-carboxamide (59.2 mg, 18% yield over 2 steps) as a white solid. LCMS (ESI) *m/z*: [M + H] calcd for $C_{59}H_{76}FN_{11}O_6$: 1054.6; found 1054.8; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.80 (s, 1H), 8.52 – 8.48 (m, 2H), 8.41 (d, *J* = 4.4 Hz, 1H), 7.91 – 7.78 (m, 2H), 7.66 (d, *J* = 10.4 Hz, 1H), 7.61 – 7.51 (m, 2H), 7.33 – 7.26 (m, 2H), 6.16 – 6.11 (m, 1H), 5.63 (d, *J* = 16.4 Hz, 1H), 4.97 – 4.92 (m, 1H), 4.33 (d, *J* = 12.0 Hz, 1H), 4.05 (q, *J* = 6.2 Hz, 1H), 4.98 – 3.57 (m, 6H), 3.28 – 3.13 (m, 5H), 3.11 – 2.90 (m, 2H), 2.84 (s, 4H), 2.76 – 2.65 (m, 4H), 2.48 (s, 2H), 2.37 – 2.26 (m, 1H), 2.17 – 2.08 (m, 1H), 1.99 – 1.79 (m, 4H), 1.71 – 1.52 (m, 5H), 1.41 (d, *J* = 8.0 Hz, 3H), 1.31 – 1.15 (m, 6H), 0.85 (br s, 3H), 0.81 (d, *J* = 8.0 Hz, 3H), 0.69 – 0.50 (m, 6H), 0.46 (dt, *J* = 6.0, 2.8 Hz, 2H), 0.34 (p, *J* = 4.0 Hz, 2H), –0.06 (s, 2H); ^{19}F NMR (282 MHz, DMSO-*d*$_6$) δ –131.7

Example A426: Synthesis of (2*S*,4*R*)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-6(1,3)-pyridazina-2(2,6)-pyridinacycloundecaphane-4-yl-2^4-^{2}H)amino)-3-methyl-1-oxobutan-2-yl)-*N*,4-dimethyl-2-(pyridin-3-yl)pyrrolidine-1-carboxamide



Step 1. To a stirred solution of 3-bromopyridine (1.70 g, 10.8 mmol) in Et_2O (30 mL), *n*-BuLi (2.5 M in THF, 5.2 mL, 13 mmol) was added dropwise at –78 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred at –78 °C for 1 h, after which time (4*R*)-4-methyloxolan-2-one (1.08 g, 10.8

mmol) was added and the mixture was stirred at room temperature for 16 h. The reaction mixture was then quenched with brine (20 mL), concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford (3*R*)-4-hydroxy-3-methyl-1-(pyridin-3-yl)butan-1-one (1.00 g, 52% yield) as an off-white oil. LCMS (ESI) *m/z*: [M + H] calcd for $C_{10}H_{13}NO_2$: 180.1; found 180.0.

Step 2. To a stirred solution of (3*R*)-4-hydroxy-3-methyl-1-(pyridin-3-yl)butan-1-one (1.50 g, 8.37 mmol) in MeOH (20 mL), $NaBH_4$ (633 mg, 16.7 mmol) was added at room temperature under an atmosphere of nitrogen gas. The resulting mixture was stirred at room temperature for 16 h. The reaction mixture was then concentrated under reduced pressure, suspended in DCM (5 mL), filtered, and concentrated under reduced pressure to afford (3*R*)-3-methyl-1-(pyridin-3-yl)butane-1,4-diol (1.10 g, crude) as a yellow oil. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{10}H_{15}NO_2$: 182.1; found 182.1.

Step 3. To a stirred mixture of (3*R*)-3-methyl-1-(pyridin-3-yl)butane-1,4-diol (16.0 g, crude) and triethylamine (36.8 mL, 265 mmol) in DCM (160 mL), methanesulfonic anhydride (30.8 g, 177 mmol) was added at 0 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred for 2 h at 0 °C. The reaction mixture was then quenched with H_2O (100 mL) and the organic extract was concentrated under reduced pressure to afford (2*R*)-4-(methanesulfonyloxy)-2-methyl-4-(pyridin-3-yl)butyl methanesulfonate (24.0 g, crude) as a brown oil. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{12}H_{19}NO_6S_2$: 338.1; found 338.1.

Step 4. A neat mixture of (2*R*)-4-(methanesulfonyloxy)-2-methyl-4-(pyridin-3-yl)butyl methanesulfonate (1.00 g, crude) in 4-methoxybenzylamine (10 mL) was stirred for 16 h at room temperature under an atmosphere of nitrogen gas. The reaction mixture was then directly purified by reversed-phase flash column chromatography to afford 3-((4*R*)-1-(4-methoxybenzyl)-4-methylpyrrolidin-2-yl)pyridine (250 mg, 17% yield over 3 steps) as a yellow oil. LCMS (ESI) *m/z*: [M + H] calcd for $C_{18}H_{22}N_2O$: 283.2; found 282.1.

Step 5. A mixture of 3-((4R)-1-((4-methoxyphenyl)methyl)-4-methylpyrrolidin-2-yl)pyridine (250 mg, 0.885 mmol) and CAN (974 mg, 1.78 mmol) in MeCN (1.0 mL) and H_2O (1.0 mL) was stirred for 16 h at room temperature under an atmosphere of nitrogen gas. The reaction mixture was then concentrated under reduced pressure and purified by reversed-phase flash column chromatography to afford 3-((4*R*)-4-methylpyrrolidin-2-yl)pyridine (100 mg, 70% yield) as a brown oil. LCMS (ESI) *m/z*: [M + H] calcd for $C_{10}H_{14}N_2$: 163.1; found 163.1.

Step 6. To a stirred solution of 3-((4*R*)-4-methylpyrrolidin-2-yl)pyridine (1.00 g, 6.16 mmol) and triethylamine (1.87 g, 18.5 mmol) in DCM (10 mL), benzyl (2*S*)-2-((chlorocarbonyl)(methyl)amino)-3-methylbutanoate (1.75 g, 12.3 mmol) was added dropwise at 0 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred for 16 h at room temperature. The reaction mixture was then quenched with H_2O (10 mL), extracted with DCM (3 x 10 mL), concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford benzyl *N*-methyl-*N*-((4*R*)-4-methyl-2-(pyridin-3-yl)pyrrolidine-1-carbonyl)-*L*-valinate (1.0 g, crude) as a yellow oil. This material was further purified by chiral SFC to afford two separated isomers of the desired product.

Isomer 1: (420 mg, 17% yield); LCMS (ESI) *m/z*: [M + H] calcd for $C_{24}H_{31}N_3O_3$: 410.2; found 410.3.

Isomer 2: (450 mg, 18% yield); LCMS (ESI) *m/z*: [M + H] calcd for $C_{24}H_{31}N_3O_3$: 410.2; found 410.3.

Step 7. A mixture of benzyl (2*S*)-3-methyl-2-(methyl((2*S*,4*R*)-4-methyl-2-(pyridin-3-yl)pyrrolidine-1-carbonyl)amino)butanoate (*Isomer 2* from previous reaction, 120 mg, 0.293 mmol) and Pd/C (10% wt., 120 mg) in EtOAc (2.0 mL) was stirred at 40 °C for 2 h under an atmosphere of hydrogen gas. The resulting mixture was then filtered through Celite®, the filter cake was washed with EtOAc (3 x 10 mL), and the filtrate was concentrated under reduced pressure to afford (2*S*)-3-methyl-2-(methyl((2*S*,4*R*)-4-methyl-2-(pyridin-3-yl)pyrrolidine-1-carbonyl)amino)butanoic acid (84.6 mg, crude) as a white solid. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{17}H_{25}N_3O_3$: 320.2; found 320.2.

Step 8. To a stirred mixture of (2*S*)-3-(6-bromopyridin-2-yl)-2-((*tert*-butoxycarbonyl)amino)propanoic acid (3.00 g, 8.69 mmol) and K_2CO_3 (2.40 g, 17.4 mmol) in DMF (30 mL), methyl iodide (1.85 g, 13.0 mmol) was added dropwise at 0 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred at 60 °C for 1 h. The reaction mixture was then quenched with H_2O at 0 °C, extracted with EtOAc (3 x 100 mL), washed with brine (3 x 50 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford methyl (2*S*)-3-(6-bromopyridin-2-yl)-2-((*tert*-butoxycarbonyl)amino)propanoate (2.70 g, 86% yield) as a yellow oil. LCMS (ESI) *m/z*: [M + H] calcd for $C_{14}H_{19}BrN_2O_4$: 359.1; found 358.9.

Step 9. To a stirred solution of methyl (2*S*)-3-(6-bromopyridin-2-yl)-2-((*tert*-butoxycarbonyl)amino)propanoate (1.00 g, 2.78 mmol) and 4,4,5,5-tetramethyl-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (2.12 g, 8.35 mmol) in THF (4.0 mL), 4,4′-bis(*tert*-butyl)-2,2′-bipyridine (112 mg, 0.418 mmol) and $[Ir(COD)Cl]_2$ (56.1 mg, 0.084 mmol) were added at room temperature. The resulting mixture was stirred at 90 °C for 1 h under an atmosphere of nitrogen gas. The reaction mixture was then concentrated under reduced pressure and was purified by normal phase flash column chromatography to afford methyl (2*S*)-3-(6-bromo-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)-2-((*tert*-butoxycarbonyl)amino)propanoate (660 mg, 59% yield) as a brown solid. LCMS (ESI) *m/z*: [M + H] calcd for $C_{14}H_{20}BBrN_2O_6$: 403.1; found 403.1.

Step 10. To a stirred solution of methyl (2*S*)-3-(6-bromo-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)-2-((*tert*-butoxycarbonyl)amino)propanoate (640 mg, 1.59 mmol) and K_3PO_4 (674 mg, 3.18 mmol) in DMF (2.0 mL), Ag_2CO_3 (175 mg, 0.635 mmol) and D_2O (2 mL) were added in portions at 0 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred at 60 °C for 2 h. The reaction mixture was then quenched with H_2O at 0 °C, extracted with EtOAc (3 x 50 mL), washed with brine (3 x 30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford methyl (2*S*)-3-(6-bromo(4-^{2}*H*)pyridin-2-yl)-2-((*tert*-butoxycarbonyl)amino)propanoate (500 mg, crude) as a yellow solid. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{14}H_{18}DBrN_2O_4$: 360.1; found 360.0.

Step 11. To a stirred mixture of methyl (2*S*)-3-(6-bromo(4-^{2}*H*)pyridin-2-yl)-2-((*tert*-butoxycarbonyl)amino)propanoate (500 mg, crude) in THF (3.0 mL), a solution of $LiOH•H_2O$ (116 mg, 2.78 mmol) in H_2O (1.0 mL) was added dropwise at 0 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was then neutralized to pH

6 with aqueous HCl (1.0 M), extracted with EtOAc (3 x 30 mL), and concentrated under reduced pressure to afford (2*S*)-3-(6-bromo(4-^{2}H)pyridin-2-yl)-2-((*tert*-butoxycarbonyl)amino)propanoic acid (500 mg, crude) as a yellow solid. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{13}H_{16}DBrN_2O_4$: 346.0; found 345.9.

Step 12. To a stirred solution of (2*S*)-3-(6-bromo(4-^{2}H)pyridin-2-yl)-2-((*tert*-butoxycarbonyl)amino)propanoic acid (500 mg, 1.44 mmol) and methyl (3*S*)-1,2-diazinane-3-carboxylate (bis-TFA salt, 1.87 g, 5.53 mmol) in DCM (5.0 mL), DIPEA (1.51 mL, 8.66 mmol) and HATU (1.10 g, 2.888 mmol) were added dropwise at 0 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was then quenched with H_2O at 0 °C, extracted with EtOAc (3 x 30 mL), washed with brine (3 x 30 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford methyl (3*S*)-1-((2*S*)-3-(6-bromo(4-^{2}H)pyridin-2-yl)-2-((*tert*-butoxycarbonyl)amino)propanoyl)-1,2-diazinane-3-carboxylate (400 mg, 53% yield over 2 steps) as a yellow solid. LCMS (ESI) *m/z*: [M + H] calcd for $C_{19}H_{26}DBrN_4O_5$: 472.1; found 472.1.

Step 13. To a stirred solution of (2*M*)-2-(5-(4-cyclopropylpiperazin-1-yl)-2-((1*S*)-1-methoxyethyl)pyridin-3-yl)-1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)indol-5-ylboronic acid (680 mg, 1.27 mmol) and methyl (3*S*)-1-((2*S*)-3-(6-bromo(4-^{2}H)pyridin-2-yl)-2-((*tert*-butoxycarbonyl)amino)propanoyl)-1,2-diazinane-3-carboxylate (721 mg, 1.53 mmol) in toluene (3.0 mL), 1,4-dioxane (1.0 mL), and H_2O (1.0 mL), K_3PO_4 (540 mg, 2.54 mmol) and Pd(dppf)Cl_2 (93.1 mg, 0.127 mmol) were added. The resulting mixture was stirred for 2 h at 70 °C under an atmosphere of nitrogen gas. The reaction mixture was then concentrated under reduced pressure, suspended in EtOAc (20 mL), washed with brine (3 x 20 mL), and concentrated under reduced pressure to afford methyl (*S*)-1-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(6-(2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)-1*H*-indol-5-yl)pyridin-2-yl-4-^{2}H)propanoyl)hexahydropyridazine-3-carboxylate (800 mg, crude) as a brown solid. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{49}H_{67}DN_8O_7$: 882.5; found 882.2.

Step 14. To a stirred solution of methyl (*S*)-1-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(6-(2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)-1*H*-indol-5-yl)pyridin-2-yl-4-^{2}H)propanoyl)hexahydropyridazine-3-carboxylate (800 mg, crude) in THF (6.0 mL), a solution of LiOH•H_2O (57.1 mg, 1.36 mmol) in H_2O (3.0 mL) was added dropwise at 0 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was then neutralized to pH 6 with aqueous HCl, extracted with EtOAc (3 x 50 mL), and concentrated under reduced pressure to afford (*S*)-1-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(6-(2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)-1*H*-indol-5-yl)pyridin-2-yl-4-^{2}H)propanoyl)hexahydropyridazine-3-carboxylic acid (700 mg, crude) as a yellow solid. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{48}H_{65}DN_8O_7$: 868.5; found 868.4.

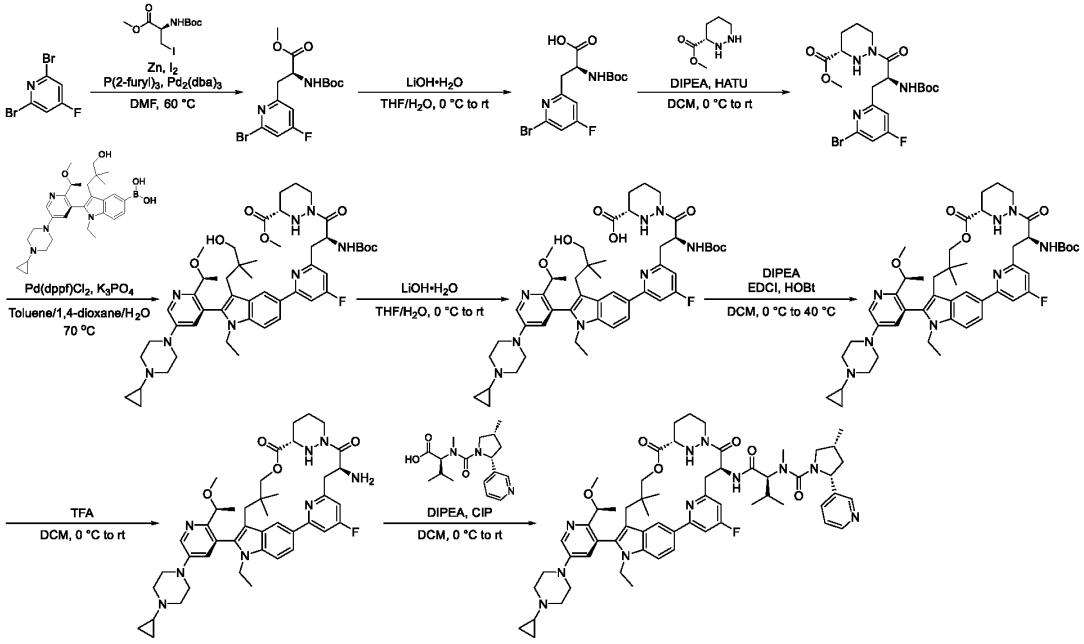
Step 15. To a stirred solution of (*S*)-1-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(6-(2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)-1*H*-indol-5-yl)pyridin-2-yl-4-^{2}H)propanoyl)hexahydropyridazine-3-carboxylic acid (700 mg, crude) and

DIPEA (2.80 g, 21.7 mmol) in DCM (70 mL), HOBt (488 mg, 3.62 mmol) and EDCI (3.95 g, 20.6 mmol) were added dropwise at 0 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred at 40 °C for 2 h. The reaction mixture was then quenched with H_2O at 0 °C, extracted with DCM (3 x 50 mL), concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford *tert*-butyl ((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-6(1,3)-pyridazina-2(2,6)-pyridinacycloundecaphane-4-yl-2$^{4-2}$*H*)carbamate (380 mg, 29% yield over 3 steps) as a yellow solid. LCMS (ESI) *m/z*: [M + H] calcd for $C_{48}H_{63}DN_8O_6$: 850.5; found 850.5.

Step 16. A stirred solution of *tert*-butyl ((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-6(1,3)-pyridazina-2(2,6)-pyridinacycloundecaphane-4-yl-2$^{4-2}$*H*)carbamate (150 mg, 0.176 mmol) in DCM (1.0 mL) was treated with TFA (0.5 mL, 6.5 mmol) at 0 °C. The resulting mixture was stirred for 1 h at 0 °C under an atmosphere of nitrogen gas. The reaction mixture was then basified to pH 8 with sat. aq. $NaHCO_3$, extracted with DCM (3 x 30 mL) and concentrated under reduced pressure to afford (6^3*S*,4*S*)-4-amino-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-6(1,3)-pyridazina-2(2,6)-pyridinacycloundecaphane-5,7-dione-2$^{4-2}$*H* (150 mg, crude) as a yellow solid. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{43}H_{55}DN_8O_4$: 750.5; found 750.4.

Step 17. To a stirred solution of (6^3*S*,4*S*)-4-amino-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-6(1,3)-pyridazina-2(2,6)-pyridinacycloundecaphane-5,7-dione-2$^{4-2}$*H* (80 mg, crude) and (2*S*)-3-methyl-2-(methyl((2*S*,4*R*)-4-methyl-2-(pyridin-3-yl)pyrrolidine-1-carbonyl)amino)butanoic acid (40.9 mg, crude) in DMF (2.0 mL), DIPEA (27.6 mg, 0.214 mmol) and CIP (59.4 mg, 0.214 mmol) were added dropwise at 0 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was then quenched with H_2O (5 mL) at 0 °C, extracted with EtOAc (3 x 10 mL), washed with brine (3 x 30 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford (2*S*,4*R*)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-6(1,3)-pyridazina-2(2,6)-pyridinacycloundecaphane-4-yl-2$^{4-2}$*H*)amino)-3-methyl-1-oxobutan-2-yl)-*N*,4-dimethyl-2-(pyridin-3-yl)pyrrolidine-1-carboxamide (31.8 mg, 32% yield over 2 steps) as a white solid. LCMS (ESI) *m/z*: [M + H] calcd for $C_{60}H_{78}ClN_3O_4$: 1051.6; found 1051.5; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.84 (s, 1H), 8.47 (br s, 2H), 8.37 (dd, *J* = 4.7, 1.6 Hz, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.83 (s, 1H), 7.64 (dt, *J* = 8.0, 2.0 Hz, 1H), 7.56 (d, *J* = 8.7 Hz, 1H), 7.32 – 7.22 (m, 2H), 6.98 (s, 1H), 5.85 (br s, 1H), 5.47 (d, *J* = 12.1 Hz, 1H), 5.09 (t, *J* = 7.3 Hz, 1H), 4.35 – 4.27 (m, 1H), 4.10 (q, *J* = 6.3 Hz, 2H), 4.02 – 3.95 (m, 2H), 3.77 (d, *J* = 10.9 Hz, 2H), 3.69 – 3.61 (m, 2H), 3.23 (br s, 4H), 3.06 – 3.80 (m, 8H), 2.69 (t, *J* = 4.9 Hz, 4H), 2.43 (s, 3H), 2.34 – 2.26 (m, 2H), 2.13 – 1.93 (m, 3H), 1.88 – 1.71 (m, 2H), 1.71 – 1.49 (m, 3H), 1.39 (d, *J* = 6.2 Hz, 3H), 1.23 (s, 1H), 1.12 (t, *J* = 7.3 Hz, 3H), 0.99 (d, *J* = 6.7 Hz, 3H), 0.77 (d, *J* = 6.3 Hz, 3H), 0.71 (br s, 2H), 0.62 (d, *J* = 7.2 Hz, 6H), 0.44 (dt, *J* = 4.2, 3.7 Hz, 2H), 0.36 (dt, *J* = 4.4, 3.9 Hz, 2H).

Example A425: Synthesis of (2*S*,4*R*)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-2^4-fluoro-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-6(1,3)-pyridazina-2(2,6)-pyridinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-4-dimethyl-2-(pyridin-3-yl)pyrrolidine-1-carboxamide



Step 1. To a stirred mixture of Zn (667 mg, 10.2 mmol) and I_2 (99.6 mg, 0.392 mmol) in DMF (20 mL), a solution of methyl (2*R*)-2-((*tert*-butoxycarbonyl)amino)-3-iodopropanoate (775 mg, 2.35 mmol) in DMF (20 mL) was added dropwise at room temperature under an atmosphere of argon gas. The resulting mixture was stirred at room temperature for 30 minutes. This solution was then added to a solid mixture of 2,6-dibromo-4-fluoropyridine (1.00 g, 3.92 mmol), $Pd_2(dba)_3$ (180 mg, 0.196 mmol), and tri-(2-furyl)-phosphine (27.2 mg, 0.196 mmol) at room temperature. The resulting mixture was stirred at 60 °C for 1 h. The reaction mixture was then quenched with sat. aq. NH_4Cl (50 mL) at 0 °C, extracted with EtOAc (50 mL), washed with brine (3 x 30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford methyl (2*S*)-3-(6-bromo-4-fluoropyridin-2-yl)-2-((*tert*-butoxycarbonyl)amino)propanoate (2.20 g, crude) as a yellow solid. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{14}H_{18}BrFN_2O_4$: 377.0; found 377.0.

Step 2. To a stirred solution of methyl (2*S*)-3-(6-bromo-4-fluoropyridin-2-yl)-2-((*tert*-butoxycarbonyl)amino)propanoate (2.2 g, crude) in THF (12 mL), a solution of LiOH•H_2O (279 mg, 11.7 mmol) in H_2O (4.0 mL) was added dropwise at 0 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was then neutralized to pH 6 with aqueous HCl, extracted with EtOAc (3 x 30 mL), washed with brine (3 x 20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford (2*S*)-3-(6-bromo-4-fluoropyridin-2-yl)-2-((*tert*-butoxycarbonyl)amino)propanoic acid (700 mg, crude) as a yellow solid. This material was

used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{13}H_{16}BrFN_2O_4$: 363.0; found 363.0.

Step 3. To a stirred solution of (2*S*)-3-(6-bromo-4-fluoropyridin-2-yl)-2-((*tert*-butoxycarbonyl)amino)propanoic acid (700 mg, crude) and methyl (3*S*)-1,2-diazinane-3-carboxylate (bis-TFA salt, 2.50 g, 7.39 mmol) in DCM (7.0 mL), DIPEA (1.49 g, 11.6 mmol) and HATU (1.47 g, 3.85 mmol) were added dropwise at 0 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was then quenched with H_2O (10 mL) at 0 °C, extracted with DCM (3 x 30 mL), concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford methyl (3*S*)-1-((2*S*)-3-(6-bromo-4-fluoropyridin-2-yl)-2-((*tert*-butoxycarbonyl)amino)propanoyl)-1,2-diazinane-3-carboxylate (480 mg, 42% yield over 3 steps) as a yellow solid. LCMS (ESI) *m/z*: [M + H] calcd for $C_{19}H_{26}BrFN_4O_5$: 489.1; found 489.1.

Step 4. To a stirred solution of (2*M*)-2-(5-(4-cyclopropylpiperazin-1-yl)-2-((1*S*)-1-methoxyethyl)pyridin-3-yl)-1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)indol-5-ylboronic acid (450 mg, 0.842 mmol) and methyl (3*S*)-1-((2*S*)-3-(6-bromo-4-fluoropyridin-2-yl)-2-((*tert*-butoxycarbonyl)amino)propanoyl)-1,2-diazinane-3-carboxylate (477 mg, 0.975 mmol) in toluene (3.0 mL), 1,4-dioxane (1.0 mL), and H_2O (1.0 mL), K_3PO_4 (357 mg, 1.68 mmol) and Pd(dppf)Cl_2 (61.6 mg, 0.084 mmol) were added at room temperature. The resulting mixture was stirred for 1 h at 70 °C under an atmosphere of nitrogen gas. The reaction mixture was then concentrated under reduced pressure to afford methyl (*S*)-1-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(6-(2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)-1*H*-indol-5-yl)-4-fluoropyridin-2-yl)propanoyl)hexahydropyridazine-3-carboxylate (900 mg, crude) as a brown solid. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{49}H_{67}FN_8O_7$: 899.5; found 899.5.

Step 5. To a stirred solution of methyl (*S*)-1-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(6-(2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)-1*H*-indol-5-yl)-4-fluoropyridin-2-yl)propanoyl)hexahydropyridazine-3-carboxylate (900 mg, crude) in THF (6.0 mL), a solution of LiOH•H_2O (63.0 mg, 1.50 mmol) in H_2O (2.0 mL) was added at 0 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was then neutralized to pH 6 with aqueous HCl, extracted with EtOAc (30 mL), washed with brine (3 x 20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford (*S*)-1-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(6-(2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)-1*H*-indol-5-yl)-4-fluoropyridin-2-yl)propanoyl)hexahydropyridazine-3-carboxylic acid (700 mg, crude) as a brown solid. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{48}H_{65}FN_8O_7$: 885.5; found 885.5.

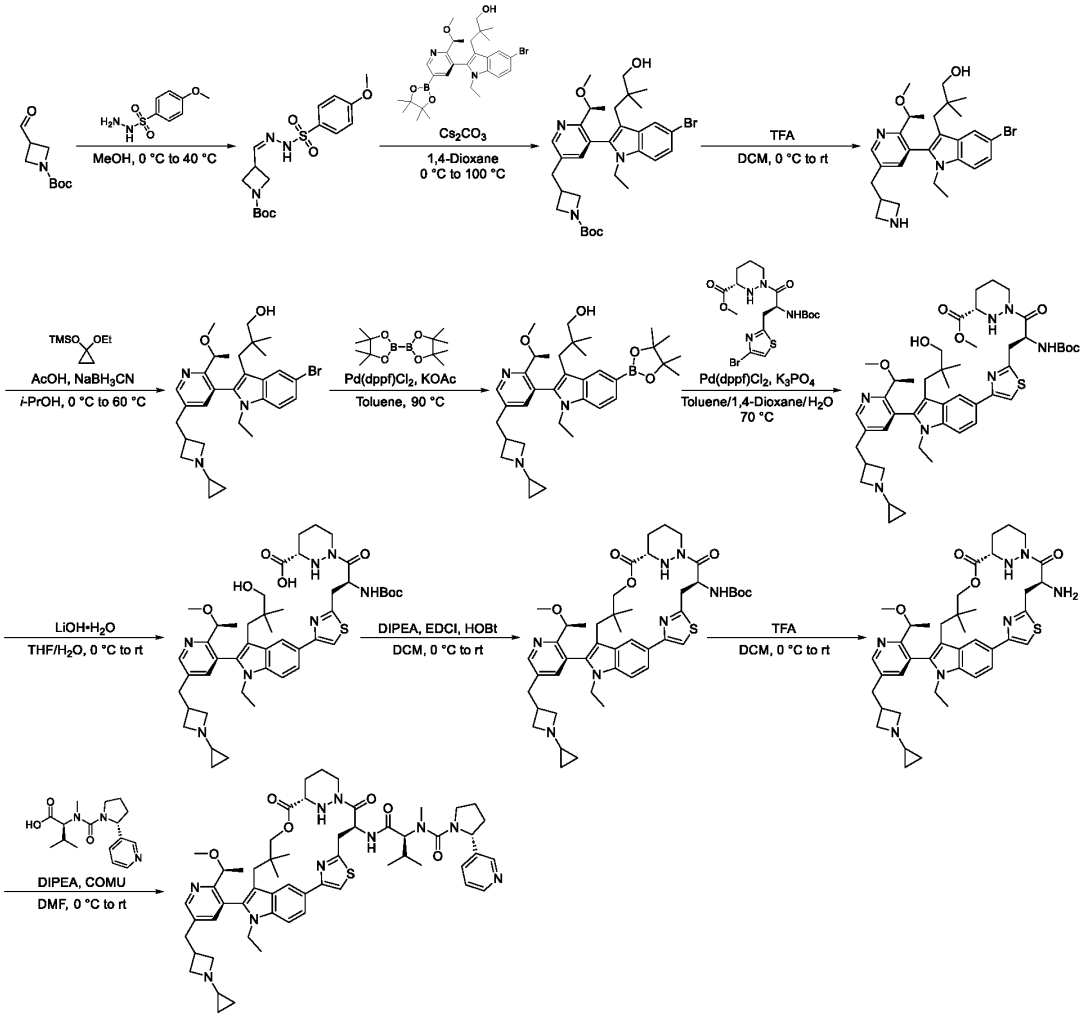
Step 6. To a stirred solution of (*S*)-1-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(6-(2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)-1*H*-indol-5-yl)-4-fluoropyridin-2-yl)propanoyl)hexahydropyridazine-3-carboxylic acid (700 mg, crude) and DIPEA (2.80 g, 21.7 mmol) in DCM (70 mL), EDCI (3.95 g, 20.6 mmol) and HOBt (488 mg, 3.62 mmol) were added in portions at 0 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred at 40 °C for 1 h. The reaction mixture was then quenched with H_2O (20 mL) at 0 °C, extracted with DCM (3 x

30 mL), concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford *tert*-butyl ((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-2^4-fluoro-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-6(1,3)-pyridazina-2(2,6)-pyridinacycloundecaphane-4-yl)carbamate (400 mg, 47% yield over 3 steps) as a yellow solid. LCMS (ESI) *m/z*: [M + H] calcd for $C_{48}H_{63}FN_8O_6$: 867.5; found 867.3.

Step 7. To a stirred solution of *tert*-butyl ((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-2^4-fluoro-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-6(1,3)-pyridazina-2(2,6)-pyridinacycloundecaphane-4-yl)carbamate (150 mg, 0.173 mmol) in DCM (1.0 mL), TFA (1.0 mL, 13 mmol) was added dropwise at 0 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was then quenched with sat. aq. $NaHCO_3$ (50 mL) at 0 °C, extracted with DCM (3 x 30 mL), and concentrated under reduced pressure to afford (6^3*S*,4*S*)-4-amino-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-2^4-fluoro-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-6(1,3)-pyridazina-2(2,6)-pyridinacycloundecaphane-5,7-dione (150 mg, crude) as a yellow solid. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{43}H_{55}FN_8O_4$: 767.4; found 767.4.

Step 8. To a stirred solution of (6^3*S*,4*S*)-4-amino-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-2^4-fluoro-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-6(1,3)-pyridazina-2(2,6)-pyridinacycloundecaphane-5,7-dione (80 mg, crude) and (2*S*)-3-methyl-2-(methyl((2*S*,4*R*)-4-methyl-2-(pyridin-3-yl)pyrrolidine-1-carbonyl)amino)butanoic acid (34.1 mg, crude) in DMF (1.0 mL), DIPEA (23.0 mg, 0.178 mmol) and CIP (76.2 mg, 0.178 mmol) were added dropwise at 0 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was then quenched with H_2O (30 mL) at 0 °C, extracted with EtOAc (30 mL), washed with brine (3 x 30 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford (2*S*,4*R*)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-(4-cyclopropylpiperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-2^4-fluoro-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-1(5,3)-indola-6(1,3)-pyridazina-2(2,6)-pyridinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-4-dimethyl-2-(pyridin-3-yl)pyrrolidine-1-carboxamide (31.6 mg, 32% yield over 2 steps) as a white solid. LCMS (ESI) *m/z*: [M + H] calcd for $C_{60}H_{78}FN_{11}O_6$: 1068.6; found 1068.5; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.86 (s, 1H), 8.48 (d, *J* = 2.8 Hz, 1H), 8.45 (d, *J* = 1.6 Hz, 1H), 8.37 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 7.92 (dd, *J* = 8.9, 1.7 Hz, 1H), 7.78 (dd, *J* = 11.6, 2.1 Hz, 1H), 7.66 – 7.53 (m, 2H), 7.30 – 7.24 (m, 2H), 6.89 (dd, *J* = 9.3, 2.1 Hz, 1H), 5.82 (br s, 1H), 5.51 (d, *J* = 12.1 Hz, 1H), 5.09 (t, *J* = 7.2 Hz, 1H), 4.30 (d, *J* = 12.1 Hz, 1H), 4.20 – 4.05 (m, 2H), 4.04 – 3.95 (m, 2H), 3.87 – 3.77 (m, 2H), 3.68 – 3.60 (m, 2H), 3.23 (q, *J* = 4.1 Hz, 4H), 3.03 (d, *J* = 13.0 Hz, 3H), 2.98 – 2.80 (m, 6H), 2.68 (t, *J* = 5.0 Hz, 4H), 2.46 (s, 2H), 2.37 – 2.23 (m, 2H), 2.10 – 1.97 (m, 3H), 1.87 – 1.70 (m, 2H), 1.70 – 1.49 (m, 3H), 1.39 (d, *J* = 6.1 Hz, 3H), 1.23 (s, 1H), 1.12 (t, *J* = 7.2 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.77 (d, *J* = 6.0 Hz, 3H), 0.72 (s, 2H), 0.63 – 0.55 (m, 6H), 0.44 (dt, *J* = 6.2, 2.8 Hz, 2H), 0.35 (p, *J* = 3.0 Hz, 2H).

Example A455: Synthesis of (2*R*)-*N*-((2*S*)-1-(((6^3*S*,4*S*)-1^2-(5-((1-cyclopropylazetidin-3-yl)methyl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-2-(pyridin-3-yl)pyrrolidine-1-carboxamide



Step 1. To a stirred solution of *tert*-butyl 3-formylazetidine-1-carboxylate (1.00 g, 5.40 mmol) in MeOH (10 mL), 4-methoxybenzenesulfonohydrazide (1.09 g, 5.40 mmol) was added in portions at 0 °C. The resulting mixture was stirred for 16 h at 40 °C. The reaction mixture was then filtered, the filter was washed with MeOH (3 x 20 mL), and the filtrate was concentrated under reduced pressure to afford *tert*-butyl (*Z*)-3-((2-((4-methoxyphenyl)sulfonyl)hydrazineylidene)methyl)azetidine-1-carboxylate (2.0 g, crude) as a white solid. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{16}H_{23}N_3O_5S$: 370.1; found 370.1.

Step 2. To a stirred solution of *tert*-butyl (*Z*)-3-((2-((4-methoxyphenyl)sulfonyl)hydrazineylidene)methyl)azetidine-1-carboxylate (2.0 g, crude) and Cs_2CO_3 (2.65 g, 8.12 mmol) in 1,4-dioxane (20 mL), (*S*)-3-(5-bromo-1-ethyl-2-(2-(1-methoxyethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)-1*H*-indol-3-yl)-2,2-dimethylpropan-1-ol (4.64 g, 8.12

mmol) was added in portions at 0 °C. The resulting mixture was stirred for 16 h at 100 °C under an atmosphere of nitrogen gas. The reaction mixture was then quenched with H_2O (30 mL) at 0 °C, extracted with EtOAc (3 x 50 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford *tert*-butyl (*S*)-3-((5-(5-bromo-1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)-1*H*-indol-2-yl)-6-(1-methoxyethyl)pyridin-3-yl)methyl)azetidine-1-carboxylate (1.24 g, 37% yield over 2 steps) as a yellow oil. LCMS (ESI) *m/z*: [M + H] calcd for $C_{32}H_{44}BrN_3O_4$: 614.3; found 614.2.

Step 3. To a stirred solution of *tert*-butyl (*S*)-3-((5-(5-bromo-1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)-1*H*-indol-2-yl)-6-(1-methoxyethyl)pyridin-3-yl)methyl)azetidine-1-carboxylate (1.70 g, 2.77 mmol) in DCM (15 mL), TFA (5.0 mL, 65.3 mmol) was added dropwise at 0 °C. The resulting mixture was stirred for 1 h at room temperature. The reaction mixture was then basified to pH 7 with sat. aq. $NaHCO_3$, extracted with DCM (3 x 20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford (*S*)-3-(2-(5-(azetidin-3-ylmethyl)-2-(1-methoxyethyl)pyridin-3-yl)-5-bromo-1-ethyl-1*H*-indol-3-yl)-2,2-dimethylpropan-1-ol (1.70 g, crude) as a yellow oil. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{27}H_{36}BrN_3O_2$: 514.2; found 514.3.

Step 4. To a stirred solution of (*S*)-3-(2-(5-(azetidin-3-ylmethyl)-2-(1-methoxyethyl)pyridin-3-yl)-5-bromo-1-ethyl-1*H*-indol-3-yl)-2,2-dimethylpropan-1-ol (2.21 g, crude) and AcOH (770 mg, 12.9 mmol) in *i*-PrOH (22 mL), (1-ethoxycyclopropoxy)trimethylsilane (2.25 g, 12.9 mmol), and $NaBH_3CN$ (810 mg, 12.9 mmol) were added in portions at 0 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred for 3 h at 60 °C. The reaction mixture was then basified to pH 7 with sat. aq. $NaHCO_3$, extracted with EtOAc (3 x 30 mL), washed with brine (3 x 30 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford (*S*)-3-(5-bromo-2-(5-((1-cyclopropylazetidin-3-yl)methyl)-2-(1-methoxyethyl)pyridin-3-yl)-1-ethyl-1*H*-indol-3-yl)-2,2-dimethylpropan-1-ol (1.24 g, 62% yield over 2 steps) as a yellow oil. LCMS (ESI) *m/z*: [M + H] calcd for $C_{30}H_{40}BrN_3O_2$: 554.2; found 554.4.

Step 5. To a stirred solution of (*S*)-3-(5-bromo-2-(5-((1-cyclopropylazetidin-3-yl)methyl)-2-(1-methoxyethyl)pyridin-3-yl)-1-ethyl-1*H*-indol-3-yl)-2,2-dimethylpropan-1-ol (1.00 g, 1.80 mmol) in toluene (10 mL), KOAc (389 mg, 3.97 mmol), $Pd(dppf)Cl_2$ (264 mg, 0.361 mmol) and bis(pinacolato)diboron (2.29 g, 9.02 mmol) were added at room temperature under an atmosphere of argon gas. The resulting mixture was stirred for 3 h at 90 °C. The reaction mixture was then filtered, the filter cake was washed with EtOAc (3 x 20 mL), the filtrate was concentrated under reduced pressure, and the resulting residue was purified by reversed-phase flash column chromatography to afford (*S*)-3-(2-(5-((1-cyclopropylazetidin-3-yl)methyl)-2-(1-methoxyethyl)pyridin-3-yl)-1-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-3-yl)-2,2-dimethylpropan-1-ol (240 mg, 21% yield) as a yellow solid. LCMS (ESI) *m/z*: [M + H] calcd for $C_{36}H_{52}BN_3O_4$: 602.4; found 602.7.

Step 6. To a stirred mixture of (*S*)-3-(2-(5-((1-cyclopropylazetidin-3-yl)methyl)-2-(1-methoxyethyl)pyridin-3-yl)-1-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-3-yl)-2,2-dimethylpropan-1-ol (240 mg, 0.399 mmol) in 1,4-dioxane (0.8 mL), H_2O (0.8 mL), and toluene (2.4 mL), methyl (*S*)-1-((*S*)-3-(4-bromothiazol-2-yl)-2-((*tert*-butoxycarbonyl)amino)propanoyl)hexahydropyridazine-3-carboxylate (229 mg, 0.479 mmol), K_3PO_4 (169 mg, 0.798 mmol), and $Pd(dtbpf)Cl_2$ (26.0 mg, 0.040

mmol) were added at room temperature under an atmosphere of argon gas. The resulting mixture was stirred for 2 h at 70 °C. The reaction mixture was then quenched with H_2O (10 mL) at room temperature, extracted with EtOAc (3 x 30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford methyl (*S*)-1-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-(2-(5-((1-cyclopropylazetidin-3-yl)methyl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)-1*H*-indol-5-yl)thiazol-2-yl)propanoyl)hexahydropyridazine-3-carboxylate (437 mg, crude) as yellow oil. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{47}H_{65}N_7O_7S$: 872.5; found 872.4.

Step 7. To a stirred solution of methyl (*S*)-1-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-(2-(5-((1-cyclopropylazetidin-3-yl)methyl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)-1*H*-indol-5-yl)thiazol-2-yl)propanoyl)hexahydropyridazine-3-carboxylate (430 mg, crude) in THF (3.0 mL), a solution of LiOH•H_2O (41.4 mg, 0.986 mmol) in H_2O (3.0 mL) was added dropwise at 0 °C. The resulting mixture was stirred for 2 h at room temperature. The reaction mixture was then acidified to pH 6 with aqueous HCl (1 M), extracted with DCM (3 x 20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford (*S*)-1-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-(2-(5-((1-cyclopropylazetidin-3-yl)methyl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)-1*H*-indol-5-yl)thiazol-2-yl)propanoyl)hexahydropyridazine-3-carboxylic acid (329 mg, crude) as a yellow solid. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{46}H_{63}N_7O_7S$: 858.5; found 858.4.

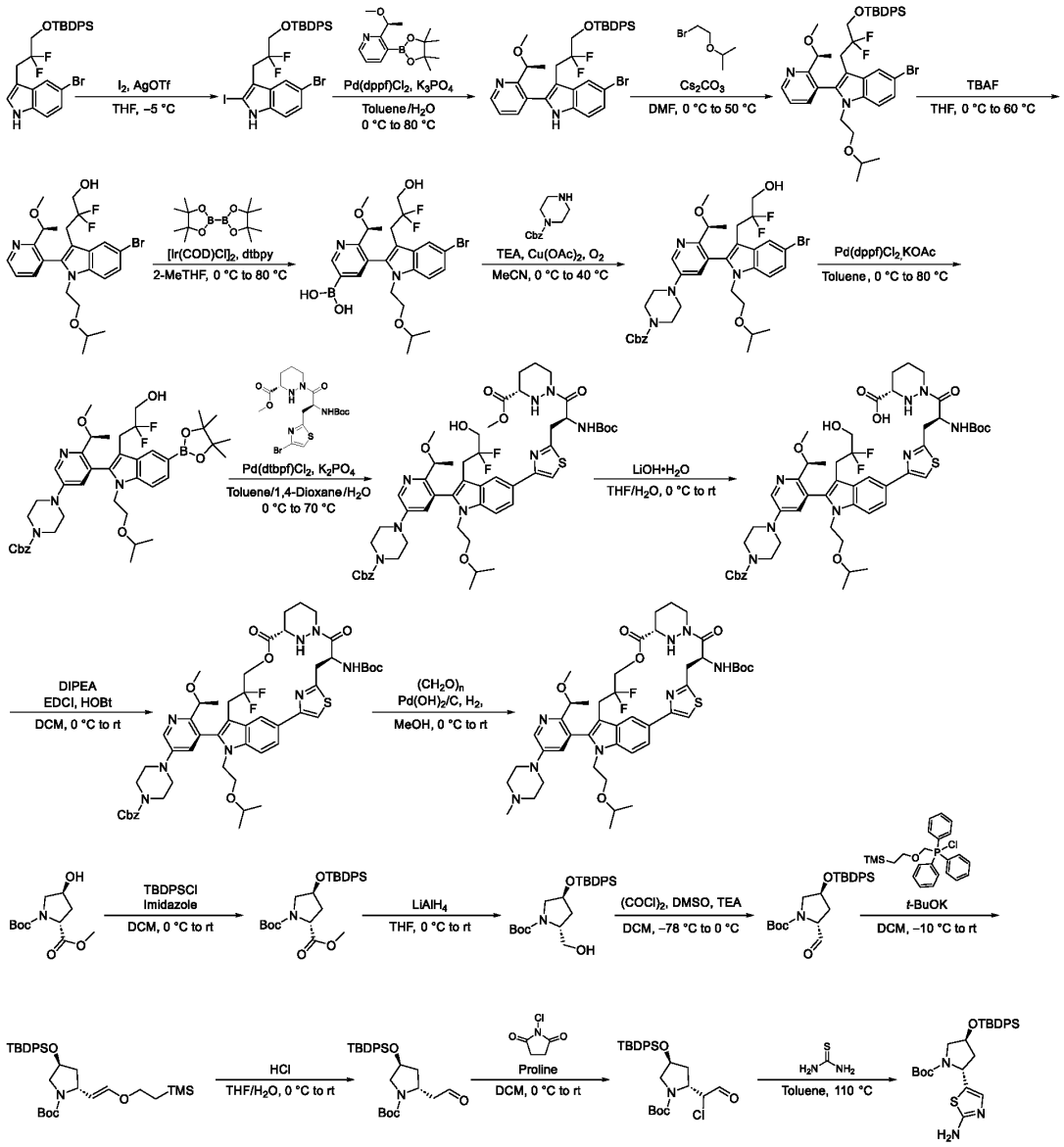
Step 8. To a stirred solution of (*S*)-1-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-(2-(5-((1-cyclopropylazetidin-3-yl)methyl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1-ethyl-3-(3-hydroxy-2,2-dimethylpropyl)-1*H*-indol-5-yl)thiazol-2-yl)propanoyl)hexahydropyridazine-3-carboxylic acid (320 mg, crude) and DIPEA (1.45 g, 11.2 mmol) in DCM (32 mL), EDCI (1.43 g, 7.46 mmol) and HOBt (504 mg, 3.73 mmol) were added in portions at 0 °C. The resulting mixture was stirred for 16 h at room temperature. The reaction mixture was then acidified to pH 6 with aqueous HCl (1 M), extracted with DCM (3 x 30 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase flash column chromatography to afford *tert*-butyl ((6^3*S*,4*S*)-1^2-(5-((1-cyclopropylazetidin-3-yl)methyl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)carbamate (122 mg, 38% yield over 3 steps) as a yellow solid. LCMS (ESI) *m/z*: [M + H] calcd for $C_{46}H_{61}N_7O_6S$: 840.4; found 840.5.

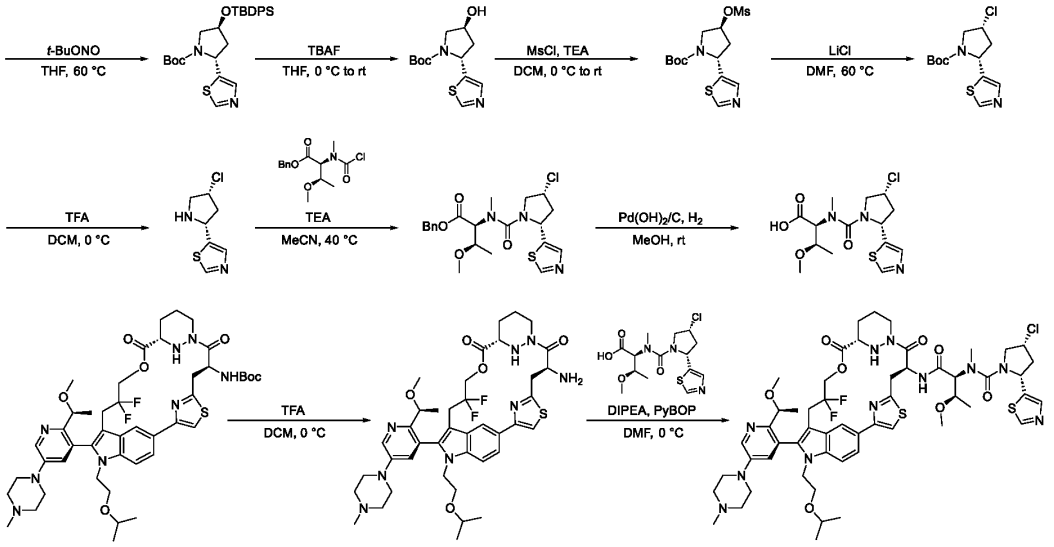
Step 9. To a stirred solution of *tert*-butyl ((6^3*S*,4*S*)-1^2-(5-((1-cyclopropylazetidin-3-yl)methyl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)carbamate (120 mg, 0.143 mmol) in DCM (1.5 mL), TFA (0.3 mL, 3.92 mmol) was added in portions at 0 °C. The resulting mixture was stirred for 1 h at room temperature. The reaction mixture was then basified to pH 8 with sat. aq. $NaHCO_3$, extracted with DCM (3 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford (6^3*S*,4*S*)-4-amino-1^2-(5-((1-cyclopropylazetidin-3-yl)methyl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-5,7-dione (94.0 mg, crude) as a yellow solid. This

material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{41}H_{53}N_7O_4S$: 740.4; found 740.4.

Step 10. To a stirred mixture of (6^3S,4*S*)-4-amino-1^2-(5-((1-cyclopropylazetidin-3-yl)methyl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1H-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-5,7-dione (90.0 mg, crude), DIPEA (157 mg, 1.22 mmol) and *N*-methyl-*N*-((*R*)-2-(pyridin-3-yl)pyrrolidine-1-carbonyl)-*L*-valine (111 mg, 0.366 mmol) in DMF (2.0 mL), COMU (104 mg, 0.244 mmol) was added in portions at 0 °C. The resulting mixture was stirred for 1 h at room temperature. The reaction mixture was then was quenched with H_2O (10 mL), extracted with EtOAc (3 x 10 mL), washed with brine (3 x 10 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase prep-HPLC to afford (2*R*)-*N*-((2*S*)-1-((((6^3S,4*S*)-1^2-(5-((1-cyclopropylazetidin-3-yl)methyl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-1^1-ethyl-10,10-dimethyl-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1H-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methyl-1-oxobutan-2-yl)-*N*-methyl-2-(pyridin-3-yl)pyrrolidine-1-carboxamide (26.4 mg, 19% yield over 2 steps) as a white solid. LCMS (ESI) *m/z*: [M + H] calcd for $C_{57}H_{74}N_{10}O_6S$: 1027.6; found 1027.4; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 (s, 2H), 8.30 (s, 1H), 8.21 (d, *J* = 4.8 Hz, 1H), 7.97 (d, *J* = 9.4 Hz, 1H), 7.62 – 7.54 (m, 3H), 7.45 – 7.39 (m, 2H), 7.08 (br s, 1H), 5.45 – 5.35 (m, 1H), 4.96 (d, *J* = 12.1 Hz, 1H), 4.89 – 4.81 (m, 1H), 4.22 – 3.93 (m, 5H), 3.80 – 3.67 (m, 2H), 3.46 – 3.33 (m, 5H), 3.22 – 3.06 (m, 5H), 2.92 – 2.66 (m, 7H), 2.63 – 2.43 (m, 3H), 2.35 (s, 2H), 2.30 – 2.15 (m, 2H), 2.05 – 1.80 (m, 3H), 1.78 – 1.49 (m, 5H), 1.41 – 1.26 (m, 1H), 1.19 (d, *J* = 6.0 Hz, 3H), 0.79 – 0.65 (m, 9H), 0.59 (d, *J* = 6.4 Hz, 3H), 0.13 (br s, 5H)

Example A231: Synthesis of (2*R*,4*R*)-4-chloro-*N*-((2*S*,3*R*)-1-(((6^3*S*,4*S*)-10,10-difluoro-1^1-(2-isopropoxyethyl)-1^2-(2-((*S*)-1-methoxyethyl)-5-(4-methylpiperazin-1-yl)pyridin-3-yl)-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methoxy-1-oxobutan-2-yl)-*N*-methyl-2-(thiazol-5-yl)pyrrolidine-1-carboxamide





Step 1. To a stirred solution of 5-bromo-3-(3-((*tert*-butyldiphenylsilyl)oxy)-2,2-difluoropropyl)-1*H*-indole (10.0 g, 18.9 mmol) in THF (100 mL), a mixture of silver triflate (5.83 g, 22.7 mmol) and I_2 (4.80 g, 18.9 mmol) in THF (50 mL) was added dropwise at –5 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred at –5 °C for 3 h. The reaction mixture was then quenched with H_2O at 0 °C, extracted with EtOAc (3 x 150 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford 5-bromo-3-(3-((*tert*-butyldiphenylsilyl)oxy)-2,2-difluoropropyl)-2-iodo-1*H*-indole (13.2 g, 90% yield) as a brown solid. LCMS (ESI) *m/z*: [M + H] calcd for $C_{27}H_{27}BrF_2INOSi$: 654.0; found 653.9.

Step 2. To a stirred mixture of K_3PO_4 (2.59 g, 12.2 mmol), Pd(dppf)Cl_2 (450 mg, 0.611 mmol), and (*S*)-2-(1-methoxyethyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (1.93 g, 7.33 mmol) in toluene (35 mL), a solution of 5-bromo-3-(3-((*tert*-butyldiphenylsilyl)oxy)-2,2-difluoropropyl)-2-iodo-1*H*-indole (4.00 g, 6.11 mmol) in toluene (35 mL) and H_2O (7.0 mL) was added dropwise at 0 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred at 80 °C for 2 h. The reaction mixture was then quenched with H_2O at 0 °C, extracted with EtOAc (3 x 120 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford (*S*)-5-bromo-3-(3-((*tert*-butyldiphenylsilyl)oxy)-2,2-difluoropropyl)-2-(2-(1-methoxyethyl)pyridin-3-yl)-1*H*-indole (3.40 g, 75% yield) as a brown solid. LCMS (ESI) *m/z*: [M + H] calcd for $C_{35}H_{37}BrF_2N_2O_2Si$: 663.2; found 663.1.

Step 3. To a stirred solution of (*S*)-5-bromo-3-(3-((*tert*-butyldiphenylsilyl)oxy)-2,2-difluoropropyl)-2-(2-(1-methoxyethyl)pyridin-3-yl)-1*H*-indole (3.40 g, 5.12 mmol) and 2-(2-bromoethoxy)propane (4.28 g, 25.6 mmol) in DMF (34 mL), Cs_2CO_3 (3.34 g, 10.3 mmol) was added in portions at 0 °C . The resulting mixture was stirred at 50 °C for 16 h. The reaction mixture was then quenched with H_2O at 0 °C, extracted with EtOAc (3 x 60 mL), washed with brine (3 x 60 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford (*S*)-5-bromo-3-(3-((*tert*-butyldiphenylsilyl)oxy)-2,2-difluoropropyl)-1-(2-isopropoxyethyl)-2-(2-(1-methoxyethyl)pyridin-3-yl)-1*H*-indole (3.99 g, crude) as a yellow oil. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{40}H_{47}BrF_2N_2O_3Si$: 749.3; found 749.1.

Step 4. To a stirred solution of (*S*)-5-bromo-3-(3-((*tert*-butyldiphenylsilyl)oxy)-2,2-difluoropropyl)-1-(2-isopropoxyethyl)-2-(2-(1-methoxyethyl)pyridin-3-yl)-1*H*-indole (3.99 g, crude) in THF (40 mL), TBAF (1.0 M in THF, 16.0 mL, 16.0 mmol) was added dropwise at 0 °C. The resulting mixture was stirred at 60 °C for 16 h. The reaction mixture was then quenched with H_2O at 0 °C, extracted with EtOAc (3 x 20 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford (*S*)-3-(5-bromo-1-(2-isopropoxyethyl)-2-(2-(1-methoxyethyl)pyridin-3-yl)-1*H*-indol-3-yl)-2,2-difluoropropan-1-ol (2.39 g, 91% yield over 2 steps) as a yellow oil. LCMS (ESI) *m/z*: [M + H] calcd for $C_{24}H_{29}BrF_2N_2O_3$: 511.1; found 511.1.

Step 5. To a stirred solution of 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (701 mg, 2.49 mmol), $[Ir(COD)Cl]_2$ (112 mg, 0.166 mmol), and 4,4′-di-*tert*-butyl-2,2′-dipyridyl (89.2 mg, 0.332 mmol) in 2-MeTHF (7.0 mL), a solution of (*S*)-3-(5-bromo-1-(2-isopropoxyethyl)-2-(2-(1-methoxyethyl)pyridin-3-yl)-1*H*-indol-3-yl)-2,2-difluoropropan-1-ol (850 mg, 1.66 mmol) in 2-MeTHF (3.5 mL) was added dropwise at 0 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred at 80 °C for 16 h. The reaction mixture was then quenched with H_2O at 0 °C, extracted with EtOAc (3 x 30 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase flash column chromatography to afford (*S*)-(5-(5-bromo-3-(2,2-difluoro-3-hydroxypropyl)-1-(2-isopropoxyethyl)-1*H*-indol-2-yl)-6-(1-methoxyethyl)pyridin-3-yl)boronic acid (300 mg, 25% yield) as brown-yellow oil. LCMS (ESI) *m/z*: [M + H] calcd for $C_{24}H_{30}BBrF_2N_2O_5$: 555.1; found 555.1.

Step 6. To a stirred solution of (*S*)-(5-(5-bromo-3-(2,2-difluoro-3-hydroxypropyl)-1-(2-isopropoxyethyl)-1*H*-indol-2-yl)-6-(1-methoxyethyl)pyridin-3-yl)boronic acid (280 mg, 0.504 mmol), benzyl piperazine-1-carboxylate (278 mg, 1.26 mmol), and 4 Å molecular sieves in MeCN (3.0 mL), triethylamine (153 mg, 1.51 mmol) and $Cu(OAc)_2$ (45.8 mg, 0.252 mmol) were added in portions at 0 °C under an atmosphere of oxygen gas. The resulting mixture was stirred at 40 °C for 16 h under an atmosphere of oxygen gas. The reaction mixture was then quenched with H_2O at 0 °C, the resulting slurry was filtered, and the filter cake was washed with MeCN (2 x 100 mL). The combined filtrate was then concentrated under reduced pressure, extracted with EtOAc (3 x 100 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford benzyl (*S*)-4-(5-(5-bromo-3-(2,2-difluoro-3-hydroxypropyl)-1-(2-isopropoxyethyl)-1*H*-indol-2-yl)-6-(1-methoxyethyl)pyridin-3-yl)piperazine-1-carboxylate (240 mg, 52% yield) as a brown oil. LCMS (ESI) *m/z*: [M + H] calcd for $C_{36}H_{43}BrF_2N_4O_5$: 729.2; found 729.2.

Step 7. To a stirred solution of 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (260 mg, 0.924 mmol), $Pd(dppf)Cl_2$ (45.1 mg, 0.062 mmol), and KOAc (90.8 mg, 0.924 mmol) in toluene (7.0 mL), a solution of (*S*)-4-(5-(5-bromo-3-(2,2-difluoro-3-hydroxypropyl)-1-(2-isopropoxyethyl)-1*H*-indol-2-yl)-6-(1-methoxyethyl)pyridin-3-yl)piperazine-1-carboxylate (225 mg, 0.308 mmol) in toluene (3.0 mL) was added dropwise at 0 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred at 80 °C for 4 h. The resulting mixture was then concentrated under reduced pressure and purified by normal phase flash column chromatography to afford benzyl (*S*)-4-(5-(3-(2,2-difluoro-3-hydroxypropyl)-1-(2-isopropoxyethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-2-yl)-6-(1-methoxyethyl)pyridin-3-yl)piperazine-1-carboxylate (168 mg, 60% yield) as a yellow oil. LCMS (ESI) *m/z*: [M + H] calcd for $C_{42}H_{55}BF_2N_4O_7$: 777.4; found 777.3.

Step 8. To a stirred mixture of K_3PO_4 (121 mg, 0.573 mmol), Pd(dtbpf)Cl_2 (12.4 mg, 0.019 mmol) and methyl (*S*)-1-((*S*)-3-(4-bromothiazol-2-yl)-2-((*tert*-butoxycarbonyl)amino)propanoyl)hexahydropyridazine-3-carboxylate (127 mg, 0.267 mmol) in toluene (1.2 mL), 1,4-dioxane (0.4 mL) and H_2O (0.4 mL), benzyl (*S*)-4-(5-(3-(2,2-difluoro-3-hydroxypropyl)-1-(2-isopropoxyethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-2-yl)-6-(1-methoxyethyl)pyridin-3-yl)piperazine-1-carboxylate (148 mg, 0.191 mmol) was added in portions at 0 °C under an atmosphere of nitrogen gas. The resulting mixture was stirred at 70 °C for 2 h. The reaction mixture was then quenched with H_2O at room temperature, extracted with EtOAc (3 x 30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford methyl (*S*)-1-((*S*)-3-(4-(2-(5-(4-((benzyloxy)carbonyl)piperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-3-(2,2-difluoro-3-hydroxypropyl)-1-(2-isopropoxyethyl)-1*H*-indol-5-yl)thiazol-2-yl)-2-((*tert*-butoxycarbonyl)amino)propanoyl)hexahydropyridazine-3-carboxylate (288 mg, crude) as a yellow oil. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{53}H_{68}F_2N_8O_{10}S$: 1047.5; found 1047.3.

Step 9. To a stirred solution of methyl (*S*)-1-((*S*)-3-(4-(2-(5-(4-((benzyloxy)carbonyl)piperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-3-(2,2-difluoro-3-hydroxypropyl)-1-(2-isopropoxyethyl)-1*H*-indol-5-yl)thiazol-2-yl)-2-((*tert*-butoxycarbonyl)amino)propanoyl)hexahydropyridazine-3-carboxylate (278 mg, crude) in THF (2.0 mL), a solution of LiOH•H_2O (22.3 mg, 0.531 mmol) in H_2O (2 mL) was added dropwise at 0 °C. The resulting mixture was stirred for 2 h at room temperature. The reaction mixture was then acidified to pH 6 with aqueous HCl, extracted with DCM (3 x 20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford (*S*)-1-((*S*)-3-(4-(2-(5-(4-((benzyloxy)carbonyl)piperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-3-(2,2-difluoro-3-hydroxypropyl)-1-(2-isopropoxyethyl)-1*H*-indol-5-yl)thiazol-2-yl)-2-((*tert*-butoxycarbonyl)amino)propanoyl)hexahydropyridazine-3-carboxylic acid (330 mg, crude) as a light yellow solid. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{52}H_{66}F_2N_8O_{10}S$: 1033.5; found 1033.4.

Step 10. To a stirred solution of (*S*)-1-((*S*)-3-(4-(2-(5-(4-((benzyloxy)carbonyl)piperazin-1-yl)-2-((*S*)-1-methoxyethyl)pyridin-3-yl)-3-(2,2-difluoro-3-hydroxypropyl)-1-(2-isopropoxyethyl)-1*H*-indol-5-yl)thiazol-2-yl)-2-((*tert*-butoxycarbonyl)amino)propanoyl)hexahydropyridazine-3-carboxylic acid (320 mg, crude) and DIPEA (1.60 g, 12.4 mmol) in DCM (32 mL), HOBt (419 mg, 3.10 mmol) and EDCI (1.78 g, 9.30 mmol) were added dropwise at 0 °C. The resulting mixture was stirred at room temperature for 16 h. The reaction mixture was then quenched with H_2O at 0 °C, extracted with DCM (3 x 20 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase prep-TLC to afford benzyl 4-(5-((6^3*S*,4*S*)-4-((*tert*-butoxycarbonyl)amino)-10,10-difluoro-1^1-(2-isopropoxyethyl)-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-1^2-yl)-6-((*S*)-1-methoxyethyl)pyridin-3-yl)piperazine-1-carboxylate (120 mg, 47% yield over 3 steps) as a yellow oil. LCMS (ESI) *m/z*: [M + H] calcd for $C_{52}H_{64}BrF_2N_8O_9S$: 1015.5; found 1015.4.

Step 11. To a stirred solution of benzyl 4-(5-((6^3*S*,4*S*)-4-((*tert*-butoxycarbonyl)amino)-10,10-difluoro-1^1-(2-isopropoxyethyl)-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-

indola-6(1,3)-pyridazinacycloundecaphane-1^2-yl)-6-((*S*)-1-methoxyethyl)pyridin-3-yl)piperazine-1-carboxylate (120 mg, 0.118 mmol) in MeOH (2.0 mL), $Pd(OH)_2$/C (120 mg) and paraformaldehyde (21.3 mg, 0.236 mmol) were added in portions at 0 °C under an atmosphere of nitrogen gas. The headspace of the reaction vessel was evacuated and backfilled with hydrogen gas and the resulting mixture was stirred for 16 h at rt under an atmosphere of hydrogen gas. The reaction mixture was then filtered, the filter cake was washed with MeOH (3 x 150 mL), the filtrate was concentrated under reduced pressure, and the resulting residue was purified by normal phase prep-TLC to afford *tert*-butyl ((6^3*S*,4*S*)-10,10-difluoro-1^1-(2-isopropoxyethyl)-1^2-(2-((*S*)-1-methoxyethyl)-5-(4-methylpiperazin-1-yl)pyridin-3-yl)-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)carbamate (20.0 mg, 19% yield) as an off-white oil. LCMS (ESI) *m/z*: [M + H] calcd for $C_{45}H_{60}F_2N_8O_7S$: 895.4; found 895.5.

Step 12. To a stirred solution of 1-*tert*-butyl-2-methyl-(2*R*,4*S*)-4-hydroxypyrrolidine-1,2-dicarboxylate (11.0 g, 44.8 mmol) in DCM (100 mL), imidazole (7.63 g, 112 mmol) and TBDPSCl (16.0 g, 58.3 mmol) were added at 0 °C. The resulting mixture was stirred at room temperature for 2 h. The reaction mixture was then quenched with H_2O (100 mL) at 0 °C, extracted with DCM (3 x 100 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford 1-*tert*-butyl-2-methyl-(2*R*,4*S*)-4-((*tert*-butyldiphenylsilyl)oxy)pyrrolidine-1,2-dicarboxylate (19.6 g, 90% yield) as a white solid. LCMS (ESI) *m/z*: [M + H] calcd for $C_{27}H_{37}NO_5Si$: 484.2; found 484.3.

Step 13. A stirred solution of 1-*tert*-butyl-2-methyl-(2*R*,4*S*)-4-((*tert*-butyldiphenylsilyl)oxy)pyrrolidine-1,2-dicarboxylate (13.5 g, 27.9 mmol) in THF (130 mL) was treated with $LiAlH_4$ (2.0 M in THF, 27.9 mL, 55.8 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 2 h. The reaction mixture was then quenched by the addition of EtOAc (100 mL) at 0 °C followed by the addition of Na_2SO_4•$10H_2O$ in portions at room temperature. The mixture was stirred at room temperature for 1 h, the resulting slurry was filtered, the filter cake was washed with EtOAc (3 x 100 mL), the filtrate was concentrated under reduced pressure, and the residue was purified by normal phase flash column chromatography to afford *tert*-butyl (2*R*,4*S*)-4-((*tert*-butyldiphenylsilyl)oxy)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (11.5 g, 90% yield) as a white solid. LCMS (ESI) *m/z*: [2M + Na] calcd for $C_{26}H_{37}NO_4Si$: 933.5; found 933.3.

Step 14. A solution of oxalyl chloride (4.68 g, 36.9 mmol) and DMSO (5.76 g, 73.7 mmol) in DCM (800 mL) was stirred at –78 °C for 30 minutes under an atmosphere of nitrogen gas. Subsequently, a solution of *tert*-butyl (2*R*,4*S*)-4-((*tert*-butyldiphenylsilyl)oxy)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (11.2 g, 24.6 mmol) in DCM (20 mL) was added dropwise at –78 °C over a period of 1 h. The resulting mixture was treated with triethylamine (19.9 g, 196 mmol) at –78 °C and the resulting solution was stirred at 0 °C for 30 minutes. The reaction mixture was then quenched by the addition of H_2O (50 mL) at 0 °C, extracted with DCM (3 x 100 mL), washed with brine (3 x 50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford *tert*-butyl (2*R*,4*S*)-4-((*tert*-butyldiphenylsilyl)oxy)-2-formylpyrrolidine-1-carboxylate (9.5 g, crude) as a yellow oil. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + Na] calcd for $C_{26}H_{35}NO_4Si$: 476.2; found 476.2.

Step 15. A solution of triphenyl((2-(trimethylsilyl)ethoxy)methyl)phosphonium chloride (22.5 g, 52.4 mmol) and *t*-BuOK (1.0 M in THF, 52.4 mL, 52.4 mmol) in THF (60 mL) was stirred at –10 °C for 30 minutes under an atmosphere of nitrogen gas. Subsequently, a solution of *tert*-butyl (2*R*,4*S*)-4-((*tert*-butyldiphenylsilyl)oxy)-2-formylpyrrolidine-1-carboxylate (9.5 g, crude) in THF (40 mL) was added dropwise at –10 °C and the resulting solution was stirred at room temperature for 2 h. The reaction mixture was then quenched with sat. aq. NH_4Cl (80 mL) at 0 °C, extracted with EtOAc (3 x 80 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford *tert*-butyl (2*R*,4*S*)-4-((*tert*-butyldiphenylsilyl)oxy)-2-(2-(2-(trimethylsilyl)ethoxy)ethenyl)pyrrolidine-1-carboxylate (7.70 g, 55% yield over 2 steps) as a yellow oil. LCMS (ESI) *m/z*: [M + H] calcd for $C_{32}H_{49}NO_4Si_2$: 568.3 found 568.2.

Step 16. A stirred solution of *tert*-butyl (2*R*,4*S*)-4-((*tert*-butyldiphenylsilyl)oxy)-2-(2-(2-(trimethylsilyl)ethoxy)ethenyl)pyrrolidine-1-carboxylate (7.70 g, 13.6 mmol) in THF (100 mL) was treated with HCl (1.0 M in H_2O, 10 mL, 10 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 16 h. The reaction mixture was then basified to pH 7 with sat. aq. $NaHCO_3$, extracted with EtOAc (3 x 60 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford *tert*-butyl (2*R*,4*S*)-4-((*tert*-butyldiphenylsilyl)oxy)-2-(2-oxoethyl)pyrrolidine-1-carboxylate (7.57 g, crude) as a yellow oil. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{27}H_{37}NO_4Si$: 468.3; found 468.2.

Step 17. A stirred solution of *N*-chlorosuccinimide (2.16 g, 16.2 mmol) in DCM (60 mL) was treated with proline (190 mg, 1.62 mmol) at 0 °C under an atmosphere of nitrogen gas. Subsequently, a solution of *tert*-butyl (2*R*,4*S*)-4-((*tert*-butyldiphenylsilyl)oxy)-2-(2-oxoethyl)pyrrolidine-1-carboxylate (7.57 g, crude) in DCM (20 mL) was added dropwise at 0 °C and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was then quenched by the addition of cold H_2O (30 mL) at 0 °C, extracted with DCM (3 x 60 mL), washed with brine (3 x 30 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford *tert*-butyl (2*R*,4*S*)-4-((*tert*-butyldiphenylsilyl)oxy)-2-(1-chloro-2-oxoethyl)pyrrolidine-1-carboxylate (81% purity, 5.00 g, 59% yield over 2 steps) as an opaque oil. LCMS (ESI) *m/z*: [M + Na] calcd for $C_{27}H_{36}ClNO_4Si$: 524.2; found 524.1.

Step 18. A solution of *tert*-butyl (2*R*,4*S*)-4-((*tert*-butyldiphenylsilyl)oxy)-2-(1-chloro-2-oxoethyl)pyrrolidine-1-carboxylate (81% purity, 5.00 g, 8.07 mmol) and thiourea (2.27 g, 29.9 mmol) in toluene (50 mL) was stirred at 110 °C for 16 h under an atmosphere of nitrogen gas. The reaction mixture was then quenched by the addition of cold H_2O (100 mL) at 0 °C, extracted with EtOAc (3 x 60 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase flash column chromatography to afford *tert*-butyl (2*R*,4*S*)-2-(2-amino-1,3-thiazol-5-yl)-4-((*tert*-butyldiphenylsilyl)oxy)pyrrolidine-1-carboxylate (750 mg, 18% yield) as a yellow solid. LCMS (ESI) *m/z*: [M + H] calcd for $C_{28}H_{37}N_3O_3SSi$: 524.2; found 524.2.

Step 19. To a stirred solution of *tert*-butyl (2*R*,4*S*)-2-(2-amino-1,3-thiazol-5-yl)-4-((*tert*-butyldiphenylsilyl)oxy)pyrrolidine-1-carboxylate (700 mg, 1.336 mmol) in THF (10 mL), *tert*-butylnitrite (207 mg, 2.00 mmol) was added. The resulting mixture was stirred at 60 °C for 2 h under an atmosphere of nitrogen gas. The reaction mixture was then quenched with H_2O (10 mL) at 0 °C, extracted with EtOAc

(3 x 50 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase flash column chromatography to afford *tert*-butyl (2*R*,4*S*)-4-((*tert*-butyldiphenylsilyl)oxy)-2-(1,3-thiazol-5-yl)pyrrolidine-1-carboxylate (200 mg, 29% yield) as a yellow oil. LCMS (ESI) *m/z*: [M + H] calcd for $C_{28}H_{36}N_2O_3SSi$: 509.2; found 509.3.

Step 20. To a stirred solution of *tert*-butyl (2*R*,4*S*)-4-((*tert*-butyldiphenylsilyl)oxy)-2-(1,3-thiazol-5-yl)pyrrolidine-1-carboxylate (200 mg, 0.393 mmol) in THF (2.0 mL), TBAF (206 mg, 0.786 mmol) was added at 0 °C. The resulting mixture was stirred at room temperature for 2 h. The reaction mixture was then quenched by the addition of H_2O (20 mL) at 0 °C, extracted with EtOAc (3 x 40 mL), washed with H_2O (3 x 40 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase prep-TLC to afford *tert*-butyl (2*R*,4*S*)-4-hydroxy-2-(1,3-thiazol-5-yl)pyrrolidine-1-carboxylate (100 mg, 94% yield) as a yellow oil. LCMS (ESI) *m/z*: [M + H] calcd for $C_{12}H_{18}N_2O_3S$: 271.1; found 271.0.

Step 21. A stirred solution of *tert*-butyl (2*R*,4*S*)-4-hydroxy-2-(1,3-thiazol-5-yl)pyrrolidine-1-carboxylate (100 mg, 0.370 mmol) in DCM (2.0 mL) was treated with triethylamine (112 mg, 1.11 mmol) and methanesulfonyl chloride (63.6 mg, 0.555 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 2 h. The reaction mixture was then quenched with H_2O (20 mL) at 0 °C, extracted with DCM (3 x 60 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford *tert*-butyl (2*R*,4*S*)-4-(methanesulfonyloxy)-2-(1,3-thiazol-5-yl)pyrrolidine-1-carboxylate (140 mg, crude) as a yellow oil. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{13}H_{20}N_2O_5S_2$: 349.1; found 349.1.

Step 22. A mixture of *tert*-butyl (2*R*,4*S*)-4-(methanesulfonyloxy)-2-(1,3-thiazol-5-yl)pyrrolidine-1-carboxylate (140 mg, crude) and LiCl (170 mg, 4.02 mmol) in DMF (2.0 mL) was stirred at 60 °C for 16 h under an atmosphere of nitrogen gas. The reaction mixture was then quenched with H_2O (20 mL) at 0 °C, extracted with EtOAc (3 x 20 mL), washed with brine (3 x 20 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by normal phase prep-TLC to afford *tert*-butyl (2*R*,4*R*)-4-chloro-2-(1,3-thiazol-5-yl)pyrrolidine-1-carboxylate (90% purity, 90.0 mg, 76% yield over 2 steps) as a white oil. LCMS (ESI) *m/z*: [M + H] calcd for $C_{12}H_{17}ClN_2O_2S$: 289.1; found 289.1.

Step 23. To a stirred solution of *tert*-butyl (2*R*,4*R*)-4-chloro-2-(1,3-thiazol-5-yl)pyrrolidine-1-carboxylate (90.0 mg, 0.280 mmol) in DCM (1.0 mL), TFA (0.2 mL, 2.6 mmol) was added dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 1 h. The reaction mixture was then basified to pH 7 with sat. aq. $NaHCO_3$, extracted with DCM (3 x 50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford 5-((2*R*,4*R*)-4-chloropyrrolidin-2-yl)-1,3-thiazole (70 mg, crude) as yellow oil. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_7H_9ClN_2S$: 189.0; found 189.1.

Step 24. A stirred solution of 5-((2*R*,4*R*)-4-chloropyrrolidin-2-yl)-1,3-thiazole (70 mg, crude) in MeCN (2.0 mL) was treated with triethylamine (188 mg, 1.86 mmol) and benzyl (2*S*,3*R*)-2-((chlorocarbonyl)(methyl)amino)-3-methoxybutanoate (167 mg, 0.556 mmol). The resulting mixture was stirred at 40 °C for 16 h under an atmosphere of nitrogen gas. The reaction mixture was then quenched with H_2O (20 mL) at 0 °C, extracted with EtOAc (3 x 20 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase flash column chromatography to

afford benzyl (2*S*,3*R*)-2-((2*R*,4*R*)-4-chloro-2-(1,3-thiazol-5-yl)pyrrolidine-1-carbonyl(methyl)amino)-3-methoxybutanoate (50.0 mg, 40% yield over 2 steps) as a yellow solid. LCMS (ESI) *m/z*: [M + H] calcd for $C_{21}H_{26}ClN_3O_4S$: 452.1; found 452.1.

Step 25. A mixture of benzyl (2*S*,3*R*)-2-((2*R*,4*R*)-4-chloro-2-(1,3-thiazol-5-yl)pyrrolidine-1-carbonyl(methyl)amino)-3-methoxybutanoate (50.0 mg, 0.111 mmol) and $Pd(OH)_2$/C (25 mg) in MeOH (2 mL) was stirred at room temperature for 1 h under an atmosphere of hydrogen gas. The reaction mixture was then filtered, the filter cake was washed with MeOH (3 x 20 mL), and the filtrate was concentrated under reduced pressure to afford (2*S*,3*R*)-2-((2*R*,4*R*)-4-chloro-2-(1,3-thiazol-5-yl)pyrrolidine-1-carbonyl(methyl)amino)-3-methoxybutanoic acid (35 mg, crude) as a yellow solid. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{14}H_{20}ClN_3O_4S$: 362.1; found 362.0.

Step 26. A stirred solution of *tert*-butyl ((6^3*S*,4*S*)-10,10-difluoro-1^1-(2-isopropoxyethyl)-1^2-(2-((*S*)-1-methoxyethyl)-5-(4-methylpiperazin-1-yl)pyridin-3-yl)-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)carbamate (100 mg, 0.112 mmol) in DCM (0.6 mL) was treated with TFA (0.2 mL, 2.6 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 1 h. The reaction mixture was then basified to pH 7 with sat. aq. $NaHCO_3$, extracted with DCM (3 x 20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford (6^3*S*,4*S*)-4-amino-10,10-difluoro-1^1-(2-isopropoxyethyl)-1^2-(2-((*S*)-1-methoxyethyl)-5-(4-methylpiperazin-1-yl)pyridin-3-yl)-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-5,7-dione (85 mg, crude) as a yellow solid. This material was used in the next reaction without further purification. LCMS (ESI) *m/z*: [M + H] calcd for $C_{40}H_{52}F_2N_8O_5S$: 795.4; found 795.4.

Step 27. A stirred solution of (6^3*S*,4*S*)-4-amino-10,10-difluoro-1^1-(2-isopropoxyethyl)-1^2-(2-((*S*)-1-methoxyethyl)-5-(4-methylpiperazin-1-yl)pyridin-3-yl)-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-5,7-dione (40 mg, crude) in DMF (2.0 mL) was treated with DIPEA (260 mg, 2.00 mmol), (2*S*,3*R*)-2-((2*R*,4*R*)-4-chloro-2-(1,3-thiazol-5-yl)pyrrolidine-1-carbonyl(methyl)amino)-3-methoxybutanoic acid (36.4 mg, crude), and PyBOP (39.3 mg, 0.075 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 30 minutes. The reaction mixture was then quenched with H_2O (10 mL) at 0 °C, extracted with EtOAc (3 x 20 mL), washed with brine (3 x 20 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by reversed-phase prep-HPLC to afford (2*R*,4*R*)-4-chloro-*N*-((2*S*,3*R*)-1-(((6^3*S*,4*S*)-10,10-difluoro-1^1-(2-isopropoxyethyl)-1^2-(2-((*S*)-1-methoxyethyl)-5-(4-methylpiperazin-1-yl)pyridin-3-yl)-5,7-dioxo-6^1,6^2,6^3,6^4,6^5,6^6-hexahydro-1^1*H*-8-oxa-2(4,2)-thiazola-1(5,3)-indola-6(1,3)-pyridazinacycloundecaphane-4-yl)amino)-3-methoxy-1-oxobutan-2-yl)-*N*-methyl-2-(thiazol-5-yl)pyrrolidine-1-carboxamide (7.5 mg, 12% yield over 2 steps) as a white solid. LCMS (ESI) *m/z*: [M + H] calcd for $C_{54}H_{70}ClF_2N_{11}O_8S_2$: 1138.5; found 1138.6; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.97 (s, 1H), 8.44 (s, 2H), 8.34 (d, *J* = 9.0 Hz, 1H), 8.00 – 7.70 (m, 3H), 7.64 (d, *J* = 8.7 Hz, 1H), 7.25 (s, 1H), 5.52 (br s, 1H), 5.42 (br s, 1H), 5.22 (d, *J* = 12.2 Hz, 1H), 4.66 – 4.54 (m, 1H), 4.41 – 4.18 (m, 4H), 4.14 – 4.00 (m, 2H), 3.99 – 3.84 (m, 3H), 3.83 – 3.72 (m, 3H), 3.60 – 3.48 (m, 5H), 3.47 – 3.36 (m, 4H), 3.22 (s, 4H), 3.18 – 3.06 (m, 5H), 2.96 – 2.84 (m, 2H), 2.83 – 2.68 (m, 3H), 2.31 – 2.02 (m, 5H),

1.90 – 1.65 (m, 3H), 1.62 – 1.48 (m, 1H), 1.42 – 1.19 (m, 4H), 1.07 (d, *J* = 5.9 Hz, 3H), 0.89 (s, 3H), 0.87 (s, 3H).

Table 3. Exemplary Compound Prepared by Methods of the Present Invention

Ex#	MS Found	Ex#	MS Found	Ex#	MS Found	Ex#	MS Found
A1	1079.3	A312	531.8	A623	1106.6	A934	950.4
A2	1078.2	A313	1062.4	A624	1050.6	A935	950.4
A3	1078.2	A314	552.0	A625	1055.6	A936	950.4
A4	1092.3	A315	1090.4	A626	1054.8	A937	534.1
A5	1154.8	A316	1052.1	A627	1055.7	A938	925.56
A6	1219.0	A317	1092.69	A628	1009.5	A939	918.8
A7	1219.0	A318	1057.2	A629	1057.9	A940	919.8
A8	1092.3	A319	1057.1	A630	950.9	A941	880.7
A9	1154.3	A320	1107.2	A631	951.0	A942	900.8
A10	1170.8	A321	1062.5	A632	1070.76	A943	900.8
A11	1170.8	A322	551.9	A633	1085.47	A944	980.3
A12	1072.3	A323	552.0	A634	1085.66	A945	1042.9
A13	1072.2	A324	1090.5	A635	1066.48	A946	1060.4
A14	1065.4	A325	1090.5	A636	1064.3	A947	1017.0
A15	1065.7	A326	1116.9	A637	1092.8	A948	936.9
A16	1120.67	A327	1116.9	A638	1099.35	A949	916.1
A17	1120.93	A328	1112.4	A639	1065.4	A950	939.1
A18	1040.2	A329	1112.4	A640	1096	A951	965.46
A19	1040.3	A330	1090.9	A641	1096.0	A952	903.48
A20	1057.79	A331	1090.9	A642	1096.0	A953	932.8
A21	1067.44	A332	1052.1	A643	1095.9	A954	937.52
A22	1067.63	A333	1074.3	A644	1081.33	A955	954.55
A23	1059.63	A334	1019.32	A645	1098.8	A956	958.4
A24	1059.6	A335	1019.61	A646	1065.4	A957	966.56
A25	1041.65	A336	1018.5	A647	1108.65	A958	987.51
A26	1119.3	A337	1090.3	A648	1058.4	A959	1024.9
A27	1041.2	A338	1154.83	A649	1057.8	A960	1011.0
A28	1041.3	A339	1136.67	A650	1057.8	A961	964.9
A29	1066.6	A340	1087.0	A651	1046.51	A962	964.9
A30	1066.76	A341	1112.4	A652	1095.43	A963	975.3
A31	1066.7	A342	1112.4	A653	1022.1	A964	953.51
A32	1041.79	A343	1086.7	A654	1022.1	A965	952.56
A33	1055.3	A344	1086.7	A655	1019.6	A966	971.48
A34	1071.62	A345	1135.68	A656	1106.6	A967	939.5
A35	1154.4	A346	1136.0	A657	1106.6	A968	882.9
A36	1185.71	A347	1071.2	A658	969.1	A969	938.53
A37	1185.87	A348	1086.43	A659	1003.67	A970	952.51
A38	1118.8	A349	1086.84	A660	970.54	A971	936.53

Ex#	MS Found	Ex#	MS Found	Ex#	MS Found	Ex#	MS Found
A39	1118.9	A350	1118.2	A661	970.49	A972	956.4
A40	1078.3	A351	1118.25	A662	1092.0	A973	926.3
A41	1078.3	A352	1118.0	A663	1092.0	A974	942.3
A42	1078.3	A353	1118.25	A664	1040.8	A975	962.4
A43	1102.95	A354	1057.3	A665	1056.7	A976	983.3
A44	1103.25	A355	1057.6	A666	1042.8	A977	977.3
A45	1100.6	A356	1075.65	A667	1056.7	A978	941.4
A46	1100.61	A357	1147.5	A668	1056.7	A979	934.9
A47	1101.5	A358	1152.5	A669	1056.7	A980	981.44
A48	1116.55	A359	1090.9	A670	1056.8	A981	981.45
A49	1154.1	A360	1057.15	A671	1091.1	A982	964.52
A50	1078.1	A361	1057.15	A672	1091.2	A983	966.56
A51	1086.2	A362	1068.9	A673	1071.0	A984	960.8
A52	1131.51	A363	1075.65	A674	1071.0	A985	960.7
A53	1131.64	A364	1157.15	A675	1077.1	A986	924.8
A54	1106.62	A365	548.9	A676	1077.1	A987	979.8
A55	1164.3	A366	1086.5	A677	1065.0	A988	966.9
A56	1164.3	A367	1086.5	A678	1065.0	A989	918.8
A57	1037.7	A368	1076.5	A679	1106.7	A990	883.0
A58	1037.8	A369	1111.56	A680	968.3	A991	983.0
A59	1080.7	A370	1111.6	A681	1080.59	A992	924.8
A60	1154.2	A371	1111.38	A682	970.56	A993	924.8
A61	1154.2	A372	1111.52	A683	970.57	A994	923.8
A62	1154.2	A373	1068.46	A684	1009.61	A995	924.61
A63	1091.45	A374	1049.49	A685	980.8	A996	924.63
A64	1116.4	A375	1049.54	A686	1057.0	A997	923.9
A65	1032.9	A376	1128.6	A687	932.5	A998	962.8
A66	1092.35	A377	480.9	A688	1104.7	A999	942.1
A67	1033.2	A378	1078.6	A689	1070.8	A1000	926.9
A68	1110.2	A379	1078.6	A690	1070.8	A1001	938.9
A69	1110.2	A380	1152.5	A691	926.9	A1002	938.56
A70	1066.3	A381	989.3	A692	1051.0	A1003	960.58
A71	1106.57	A382	989.3	A693	927.0	A1004	940.53
A72	1186.7	A383	553.9	A694	1026.1	A1005	954.43
A73	1101.6	A384	553.8	A695	964.41	A1006	938.74
A74	1117.4	A385	1152.7	A696	1059.74	A1007	924.56
A75	1117.4	A386	894.3	A697	1027.7	A1008	940.57
A76	1070.55	A387	1103.2	A698	1093.0	A1009	940.6
A77	1070.55	A388	1057.6	A699	1082.1	A1010	934.9
A78	1045.2	A389	1110.55	A700	881.5	A1011	914.7
A79	1045.2	A390	1085.68	A701	966.9	A1012	912.8
A80	1086.2	A391	1085.68	A702	948.3	A1013	918.8
A81	1074.2	A392	1118.6	A703	1065.9	A1014	960.52

Ex#	MS Found	Ex#	MS Found	Ex#	MS Found	Ex#	MS Found
A82	1072.2	A393	1070.4	A704	1066.0	A1015	960.39
A83	1066.2	A394	1072.5	A705	1088.3	A1016	940.9
A84	1066.2	A395	1072.5	A706	1075.9	A1017	920.9
A85	1217.45	A396	1047.4	A707	1050.5	A1018	926.58
A86	1217.45	A397	1076.5	A708	1043.6	A1019	942.51
A87	1111.45	A398	1057.46	A709	1084.0	A1020	951.51
A88	1009.8	A399	1057.49	A710	1084.0	A1021	938.59
A89	1057.3	A400	1057.39	A711	1066.45	A1022	938.51
A90	1093.2	A401	1063.5	A712	1007.24	A1023	895.8
A91	1093.8	A402	1063.5	A713	930.9	A1024	922.9
A92	1093.68	A403	1080.5	A714	1046.93	A1025	932.9
A93	1093.72	A404	1080.5	A715	1073.5	A1026	933.9
A94	1057.2	A405	1057.55	A716	1059.0	A1027	894.9
A95	1075.2	A406	1130.58	A717	1095.4	A1028	921.9
A96	1092.3	A407	1130.49	A718	1095.7	A1029	895.8
A97	1080.3	A408	1147.44	A719	1040.8	A1030	921.7
A98	1118.63	A409	973.6	A720	1051.0	A1031	855.7
A99	1118.6	A410	1130.65	A721	1060.94	A1032	922.9
A100	1154.7	A411	1051.6	A722	1054.8	A1033	918.6
A101	1091.45	A412	1074.47	A723	1047.78	A1034	874.9
A102	1074.4	A413	1074.46	A724	1089.69	A1035	902.9
A103	1074.45	A414	1129.53	A725	1089.55	A1036	885.8
A104	1076.45	A415	483.4	A726	1006.6	A1037	947.9
A105	1104.6	A416	1067.57	A727	1061.84	A1038	918.6
A106	1084.5	A417	1069.44	A728	1060.94	A1039	950.6
A107	1084.5	A418	1088.0	A729	951.4	A1040	932.9
A108	1057.6	A419	1090.52	A730	1034.4	A1041	932.9
A109	1092.8	A420	1088.63	A731	1072.8	A1042	962.8
A110	1090.2	A421	1088.38	A732	1050.9	A1043	918.9
A111	1057.2	A422	1056.65	A733	1051.0	A1044	935.1
A112	1057.3	A423	1051.5	A734	1051.0	A1045	950.57
A113	1074.9	A424	1068.5	A735	1120.2	A1046	950.59
A114	1016.62	A425	1068.5	A736	1077.1	A1047	931.0
A115	1099.45	A426	1051.5	A737	1078.1	A1048	919.0
A116	1099.77	A427	1076.5	A738	1052.0	A1049	904.9
A117	1091.45	A428	1076.4	A739	1051.9	A1050	942.06
A118	1091.5	A429	456.9	A740	1079.7	A1051	931.1
A119	1085.4	A430	974.5	A741	1079.7	A1052	951.58
A120	1070.45	A431	999.3	A742	955.2	A1053	953.91
A121	1070.45	A432	1115.0	A743	954.6	A1054	954.06
A122	1057.6	A433	1115.0	A744	955.1	A1055	865.8
A123	1092.9	A434	1115.2	A745	1048.62	A1056	893.8
A124	1082.3	A435	1115.1	A746	1012.51	A1057	946.2

Ex#	MS Found	Ex#	MS Found	Ex#	MS Found	Ex#	MS Found
A125	1133.3	A436	1068.5	A747	1058.15	A1058	926.37
A126	1016.56	A437	1068.57	A748	970.66	A1059	940.03
A127	962.59	A438	1074.37	A749	970.54	A1060	935.95
A128	962.56	A439	1074.34	A750	938.03	A1061	923.98
A129	1083.9	A440	1102.52	A751	1009.09	A1062	909.96
A130	1084.0	A441	1132.49	A752	970.55	A1063	940.7
A131	1055.5	A442	1077.4	A753	1085.77	A1064	940.8
A132	1057.6	A443	1130.45	A754	1085.71	A1065	953.96
A133	1092.9	A444	1098.55	A755	998.75	A1066	966.9
A134	1092.8	A445	1082.7	A756	1006.56	A1067	966.9
A135	1009.8	A446	1062.4	A757	929.55	A1068	956.9
A136	1086.2	A447	1062.4	A758	1097.97	A1069	956.9
A137	1105.2	A448	1098.6	A759	1097.95	A1070	918.8
A138	1093.2	A449	1085.0	A760	1127.6	A1071	951.8
A139	1093.2	A450	1051.5	A761	1037.7	A1072	970.8
A140	1112.63	A451	1051.5	A762	1048.4	A1073	970.1
A141	1112.77	A452	1104.88	A763	1048.3	A1074	982.0
A142	1101.85	A453	1104.6	A764	1063.5	A1075	981.8
A143	1112.69	A454	1147.47	A765	1063.2	A1076	955.54
A144	1112.69	A455	1027.4	A766	1076.8	A1077	968.8
A145	1092.9	A456	1128.0	A767	1050.3	A1078	969.8
A146	1055.45	A457	1128.1	A768	1050.0	A1079	948.12
A147	1111.45	A458	1133.45	A769	1046.1	A1080	927.83
A148	1070.6	A459	1133.75	A770	1046.1	A1081	962.9
A149	1057.45	A460	1133.45	A771	1054.8	A1082	962.8
A150	1057.45	A461	493.5	A772	1043.4	A1083	926.9
A151	1057.4	A462	1084.9	A773	1100.3	A1084	926.9
A152	1124.5	A463	1125.1	A774	1057.2	A1085	919.3
A153	1124.5	A464	1042.75	A775	1051.9	A1086	936.4
A154	1108.0	A465	1082.55	A776	1050.2	A1087	942.41
A155	1070.6	A466	1082.55	A777	1078.1	A1088	955.43
A156	1070.2	A467	1082.52	A778	932.8	A1089	938.46
A157	1154.51	A468	1069.2	A779	932.9	A1090	967.51
A158	1074.65	A469	1069.2	A780	1021.7	A1091	913.16
A159	1106.73	A470	1054.0	A781	938.5	A1092	954.44
A160	537.9	A471	1054.0	A782	951.58	A1093	913.1
A161	537.9	A472	1067.9	A783	1031.51	B1	1124.2
A162	1104.6	A473	1049.1	A784	1049.75	B2	1124.2
A163	1087.55	A474	1049.0	A785	1046.76	B3	1124.2
A164	1085.45	A475	1118.64	A786	1050.62	B4	1124.2
A165	1057.5	A476	1124.62	A787	928.69	B5	1165.2
A166	1091.45	A477	1087.48	A788	1090.7	B6	1166.2
A167	1091.5	A478	1148.63	A789	1054.2	B7	1166.4

Ex#	MS Found	Ex#	MS Found	Ex#	MS Found	Ex#	MS Found
A168	1091.5	A479	1056.58	A790	982.9	B8	1159.8
A169	1125.1	A480	1082.57	A791	982.9	B9	1159.2
A170	1104.2	A481	1082.48	A792	1021.9	B10	1090.3
A171	1104.2	A482	1110.9	A793	988.9	B11	1096.8
A172	1027.1	A483	1047.2	A794	936.5	B12	1166.7
A173	1113.0	A484	1109.5	A795	924.88	B13	1166.8
A174	1105.6	A485	990.5	A796	1044.1	B14	1090.3
A175	1089.0	A486	990.5	A797	1044.2	B15	1126.8
A176	1090.2	A487	972.49	A798	1062.4	B16	1096.6
A177	1094.3	A488	973.49	A799	968.66	B17	1212.9
A178	1112.61	A489	979.59	A800	1067.62	B18	1111.7
A179	1112.7	A490	979.49	A801	1041.49	B19	1111.8
A180	1099.62	A491	979.49	A802	1035.27	B20	1111.8
A181	1099.65	A492	988.4	A803	960.88	B21	1213.0
A182	1106.59	A493	968.49	A804	960.49	B22	1125.0
A183	1104.8	A494	1079.9	A805	890.8	B23	1124.9
A184	1104.8	A495	1011.9	A806	1043.1	B24	1110.7
A185	1098.1	A496	1146.47	A807	1094.5	B25	1124.3
A186	1087.5	A497	1146.68	A808	1078.8	B26	1124.4
A187	1085.5	A498	1119.63	A809	954.3	B27	1126.7
A188	1085.45	A499	1049.52	A810	1090.3	B28	1126.8
A189	1085.45	A500	1049.63	A811	952.5	B29	1125.1
A190	1055.5	A501	1049.59	A812	956.5	B30	936.6
A191	1112.6	A502	1049.48	A813	953.1	B31	1089.6
A192	1112.65	A503	1098.52	A814	952.8	B32	1095.7
A193	1124.55	A504	1098.4	A815	1048.0	B33	1120.2
A194	1124.55	A505	1098.42	A816	1048.03	B34	1120.2
A195	1124.55	A506	1063.2	A817	1056.9	B35	1131.8
A196	1124.5	A507	1063.2	A818	1057.0	B36	1122.8
A197	1100.1	A508	1063.1	A819	924.8	B37	1122.9
A198	1112.67	A509	1063.1	A820	924.8	B38	1132.8
A199	1112.86	A510	881.4	A821	968.7	B39	936.3
A200	1089.2	A511	959.5	A822	1092.35	B40	1120.7
A201	1104.2	A512	1012.0	A823	991.35	B41	1120.8
A202	1104.2	A513	1089.55	A824	991.4	B42	1152.7
A203	1090.3	A514	1088.59	A825	954.32	B43	942.5
A204	1089.5	A515	995.5	A826	1114.9	B44	1074.5
A205	1087.75	A516	1147.58	A827	1044.5	B45	1090.3
A206	1087.7	A517	1092.58	A828	1044.4	B46	1090.2
A207	1085.5	A518	1092.46	A829	1049.4	B47	1110.7
A208	1085.5	A519	1106.65	A830	1030.8	B48	1110.7
A209	1104.2	A520	1090.67	A831	1007.6	B49	942.4
A210	1119.8	A521	1090.54	A832	958.5	B50	1112.7

Ex#	MS Found	Ex#	MS Found	Ex#	MS Found	Ex#	MS Found
A211	1103.3	A522	1089.1	A833	996.5	B51	1138.7
A212	1092.9	A523	1089.1	A834	952.49	B52	1145.7
A213	1072.3	A524	1071.1	A835	972.44	B53	1102.0
A214	1103.86	A525	1071.1	A836	956.45	B54	1145.8
A215	1103.68	A526	1090.7	A837	1057.0	B55	1127.0
A216	1099.57	A527	1049.0	A838	943.9	B56	1126.7
A217	1111.85	A528	1053.2	A839	1043.8	B57	1110.7
A218	1101.56	A529	1113.0	A840	1071.1	B58	1111.2
A219	1099.6	A530	1113.0	A841	1042.8	B59	1112.7
A220	1099.66	A531	1095.0	A842	1016.3	B60	1126.6
A221	1104.8	A532	1095.0	A843	1043.3	B61	931.2
A222	1104.8	A533	1092.9	A844	1062.9	B62	1106.8
A223	1085.55	A534	1092.9	A845	1059.3	B63	1106.3
A224	1154.55	A535	1107.1	A846	1121.2	B64	1126.8
A225	1095.45	A536	1107.0	A847	1119.3	B65	1112.7
A226	1095.5	A537	983.1	A848	1062.8	B66	1112.7
A227	1070.55	A538	996.5	A849	993.4	B67	1112.8
A228	1074.5	A539	996.5	A850	993.6	B68	1138.6
A229	1074.5	A540	996.4	A851	950.6	B69	1101.8
A230	1091.45	A541	984.49	A852	950.6	B70	1101.9
A231	1138.55	A542	984.49	A853	970.5	B71	982.6
A232	1086.2	A543	1079.5	A854	970.5	B72	980.5
A233	1086.1	A544	1008.9	A855	954.9	B73	980.5
A234	1056.2	A545	1008.5	A856	954.6	B74	1139.6
A235	1056.1	A546	964.51	A857	904.5	B75	1112.6
A236	1066.1	A547	961.47	A858	1035.58	B76	1106.8
A237	1027.2	A548	961.45	A859	1053.7	B77	1022.5
A238	1100.3	A549	1070.65	A860	1036.69	B78	997.7
A239	1100.2	A550	1070.72	A861	913.4	B79	996.8
A240	1119.7	A551	1064.2	A862	913.51	B80	996.9
A241	1103.4	A552	1073.0	A863	1057.2	B81	996.9
A242	1103.4	A553	1063.0	A864	1057.2	B82	1090.2
A243	1074.37	A554	1062.5	A865	964.7	B83	1090.3
A244	1074.49	A555	1074.5	A866	964.8	B84	1099.7
A245	1105.5	A556	1074.6	A867	1036.9	B85	1098.6
A246	1070.55	A557	932.45	A868	1037.2	B86	1084.7
A247	1070.45	A558	932.49	A869	1084.8	B87	1112.6
A248	1057.55	A559	932.52	A870	1043.4	B88	1061.0
A249	1090.6	A560	932.48	A871	882.5	B89	1106.6
A250	1072.2	A561	1049.6	A872	882.5	B90	980.4
A251	1072.3	A562	1049.78	A873	953.37	B91	980.4
A252	1100.3	A563	919.8	A874	1073.9	B92	1064.4
A253	1086.3	A564	919.7	A875	1074.0	B93	1048.3

Ex#	MS Found	Ex#	MS Found	Ex#	MS Found	Ex#	MS Found
A254	1088.9	A565	1076.42	A876	1074.0	B94	1093.5
A255	1089.0	A566	1076.2	A877	1074.0	B95	966.4
A256	1083.0	A567	1074.6	A878	1055.9	B96	1106.4
A257	1083.1	A568	1113.3	A879	964.9	B97	1106.5
A258	1167.63	A569	1088.25	A880	918.8	B98	995.9
A259	1099.53	A570	976.13	A881	975.7	B99	1113.0
A260	1099.57	A571	976.13	A882	1090.0	B100	1106.5
A261	1081.3	A572	986.17	A883	836.84	B101	1106.4
A262	1081.3	A573	986.2	A884	835.94	B102	995.5
A263	1074.3	A574	994.5	A885	984.68	B103	994.4
A264	1074.3	A575	1006.16	A886	1056.9	B104	982.3
A265	1091.4	A576	1037.29	A887	926.9	B105	1107.5
A266	1091.45	A577	962.47	A888	1016.9	B106	1097.1
A267	1038.55	A578	1070.41	A889	1066.8	B107	1097.0
A268	1103.8	A579	1068.8	A890	1016.4	B108	952.4
A269	1185.2	A580	1063.0	A891	1016.4	B109	958.2
A270	1086.3	A581	938.6	A892	993.45	B110	1118.5
A271	1105.9	A582	1063.0	A893	950.51	B111	937.3
A272	1089.0	A583	1065.0	A894	970.51	B112	938.5
A273	1088.4	A584	1093.0	A895	954.48	B113	1112.5
A274	1080.4	A585	1092.1	A896	926.7	B114	1090.5
A275	1080.3	A586	973.4	A897	936.8	B115	1092.5
A276	1084.3	A587	989.5	A898	937.7	B116	1105.8
A277	1084.3	A588	1091.9	A899	937.8	B117	968.4
A278	1060.55	A589	1092.2	A900	938.7	B118	944.4
A279	1060.55	A590	1069.2	A901	912.8	B119	1110.6
A280	1159.47	A591	1069.2	A902	955.0	B120	1097.1
A281	1141.55	A592	1055.2	A903	954.9	B121	972.5
A282	1141.58	A593	1055.3	A904	934.9	B122	972.5
A283	1142.65	A594	1036.2	A905	938.59	B123	1106.5
A284	1099.67	A595	1036.2	A906	938.53	B124	845.4
A285	537.9	A596	1063.0	A907	938.58	B125	974.4
A286	1106.4	A597	1063.1	A908	928.51	B126	1112.4
A287	1106.3	A598	1043.2	A909	921.44	B127	1000.2
A288	1086.3	A599	1077.7	A910	937.8	B128	1000.2
A289	1112.9	A600	1091.3	A911	962.4	B129	1098.6
A290	1100.7	A601	1108.4	A912	961.7	B130	1117.1
A291	1075.71	A602	1057.8	A913	950.6	B131	909.2
A292	1075.4	A603	1056.4	A914	991.8	B132	988.2
A293	535.8	A604	1049.8	A915	940.9	B133	1112.7
A294	535.8	A605	1070.7	A916	1036.5	B134	834.4
A295	1122.4	A606	1056.09	A917	1058.5	B135	958.5
A296	1131.2	A607	1009.45	A918	1064.5	B136	1085.0

Ex#	MS Found	Ex#	MS Found	Ex#	MS Found	Ex#	MS Found
A297	1084.3	A608	1112.45	A919	934.9	B137	1091.7
A298	1113.69	A609	1112.73	A920	1079.25	B138	1097.4
A299	1032.55	A610	945.8	A921	982.43	B139	1085.1
A300	1032.55	A611	945.8	A922	982.44	B140	1066.6
A301	1074.4	A612	1065.1	A923	938.52	B141	1072.7
A302	1074.5	A613	1065.1	A924	1040.41	B142	1046.8
A303	1122.4	A614	1048.9	A925	1049.0	B143	1053.6
A304	1099.7	A615	1087.1	A926	1044.9	B144	1070.7
A305	1084.3	A616	1087.1	A927	994.9	B145	1027.8
A306	1076.11	A617	1081.2	A928	946.9	B146	929.6
A307	1117.72	A618	1081.3	A929	981.51	B147	974.1
A308	1117.68	A619	1071.0	A930	980.68	B148	1070.0
A309	1062.4	A620	1070.9	A931	938.51	B149	1070.0
A310	1086.4	A621	1078.8	A932	925.45	B150	960.4
A311	1086.4	A622	946.9	A933	991.8		

Disruption of B-Raf Ras-binding Domain ($BRAF^{RBD}$) Interaction with K-Ras by Compounds of the Invention (also called a Ras-Raf binding or disruption assay, a FRET assay or an MOA assay)

The purpose of this biochemical assay is to measure the ability of test compounds to facilitate ternary complex formation between a nucleotide-loaded K-Ras isoform and cyclophilin A; the resulting ternary complex disrupts binding to a $BRAF^{RBD}$ construct, inhibiting K-Ras signaling through a RAF effector. Data is reported as IC50 values. Other Ras variants may be used.

In assay buffer containing 25 mM HEPES pH 7.3, 0.002% Tween20, 0.1% BSA, 100 mM NaCl and 5 mM $MgCl_2$, tagless cyclophilin A, His6-K-Ras-GMPPNP, and GST-$BRAF^{RBD}$ are combined in a 384-well assay plate at final concentrations of 25 µM, 12.5 nM and 50 nM, respectively. Compound is present in plate wells as a 10-point 3-fold dilution series starting at a final concentration of 30 µM. After incubation at 25°C for 3 hours, a mixture of Anti-His Eu-W1024 and anti-GST allophycocyanin is then added to assay sample wells at final concentrations of 10 nM and 50 nM, respectively, and the reaction incubated for an additional 1.5 hours. TR-FRET signal is read on a microplate reader (Ex 320 nm, Em 665/615 nm). Compounds that facilitate disruption of a Ras:RAF complex are identified as those eliciting a decrease in the TR-FRET ratio relative to DMSO control wells.

Each of Examples A1-A1093 and B1-B150 exhibited an IC50 of less than 1 µM in with respect to K-Ras Q61K, N-Ras Q61H, N-Ras Q61K, N-Ras Q61R, or N-Ras Q61L in this assay.

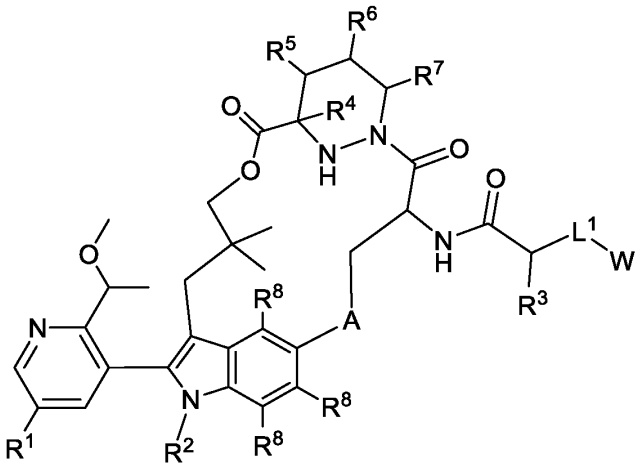
While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and

including such departures from the present disclosure come within known or customary practice within the art to which the invention pertains and may be applied to the essential features set forth herein.

All publications, patents and patent applications are herein incorporated by reference in their entirety to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety.

Claims

1. A compound having the structure of Formula I:



Formula I

or pharmaceutically acceptable salt thereof, wherein

A is optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 6-membered heteroarylene;

L^1 is absent or a linker;

W is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl. optionally substituted 3 to 10-membered heterocycloalkyl, optionally substituted 3 to 10-membered cycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 to 10-membered heteroaryl, $C(O)OR^t$, $C(O)R^t$, optionally substituted acetamido, optionally substituted sulfonyl, or an optionally substituted cross-linking group comprising a vinyl ketone, a vinyl sulfone, an ynone, an alkynyl sulfone, or a sulfonyl halide;

R^t is hydrogen, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 heteroalkyl;

R^1 is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 15-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl;

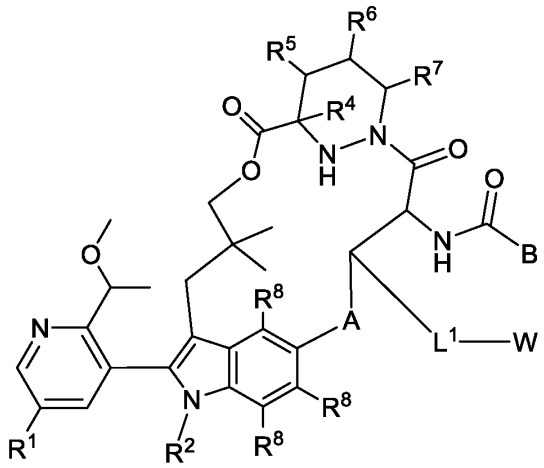
R^2 is optionally substituted C_1-C_6 alkyl or optionally substituted C_1-C_6 heteroalkyl;

R^3 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_3 heteroalkyl, optionally substituted C_3-C_6 cycloalkyl, or optionally substituted 3 to 6-membered heterocycloalkyl;

each of R^4, R^5, R^6, and R^7 is hydrogen; or R^4 and R^6 are hydrogen and R^5 and R^7 combine, together with the atoms to which they are attached, to form an optionally substituted four-membered cycloalkyl; or R^5 and R^7 are hydrogen and R^4 and R^6 combine, together with the atoms to which they are attached, to form an optionally substituted four-membered cycloalkyl; and

each R^8 is, independently, hydrogen or halo.

2. A compound having the structure of Formula II:



Formula II

or pharmaceutically acceptable salt thereof, wherein

A is optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 6-membered heteroarylene;

B is optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6-membered aryl, or optionally substituted 5 to 6-membered heteroaryl;

L^1 is absent or a linker;

W is optionally substituted 3 to 10-membered heterocycloalkyl, optionally substituted 3 to 10-membered cycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 to 6-membered heteroaryl, optionally substituted acetamido, or an optionally substituted cross-linking group comprising a vinyl ketone, a vinyl sulfone, an ynone, an alkynyl sulfone, or a sulfonyl halide;

R^1 is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 15-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl;

R^2 is optionally substituted C_1-C_6 alkyl or optionally substituted C_1-C_6 heteroalkyl;

R^3 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_3 heteroalkyl, or optionally substituted 3 to 6-membered heterocycloalkyl;

each of R^4, R^5, R^6, and R^7 is hydrogen; or R^4 and R^6 are hydrogen and R^5 and R^7 combine, together with the atoms to which they are attached, to form an optionally substituted four-membered cycloalkyl; or R^5 and R^7 are hydrogen and R^4 and R^6 combine, together with the atoms to which they are attached, to form an optionally substituted four-membered cycloalkyl; and

each R^8 is, independently, hydrogen or halo.

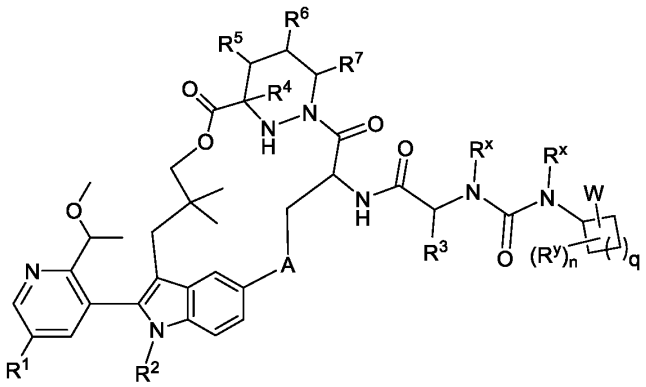
3. The compound of claim 1 or 2, or pharmaceutically acceptable salt thereof, wherein the linker L^1 is the structure of Formula III:

$$A^1\text{-}(B^1)_f\text{-}(C^1)_g\text{-}(B^2)_h\text{-}(D^1)\text{-}(B^3)_i\text{-}(C^2)_j\text{-}(B^4)_k\text{–}A^2$$

Formula III,

wherein A^1 is a bond to the linker; A^2 is a bond to W; B^1, B^2, B^3, and B^4 each, independently, is selected from optionally substituted C_1-C_2 alkylene, optionally substituted C_1-C_3 heteroalkylene, O, S, and NR^N; each R^N is, independently, hydrogen, optionally substituted C_1–C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, optionally substituted 3 to 14-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted C_1-C_7 heteroalkyl; C^1 and C^2 are each, independently, selected from carbonyl, thiocarbonyl, sulphonyl, or phosphoryl; f, g, h, i, j, and k are each, independently, 0 or 1; and D^1 is optionally substituted C_1-C_{10} alkylene, optionally substituted C_2-C_{10} alkenylene, optionally substituted C_2-C_{10} alkynylene, optionally substituted 3 to 14-membered heterocycloalkylene, optionally substituted 5 to 10-membered heteroarylene, optionally substituted 3 to 8-membered cycloalkylene, optionally substituted 6 to 10-membered arylene, optionally substituted C_2-C_{10} polyethylene glycolene, or optionally substituted C_1-C_{10} heteroalkylene, or a chemical bond linking A^1-$(B^1)_f$-$(C^1)_g$-$(B^2)_h$- to -$(B^3)_i$-$(C^2)_j$-$(B^4)_k$–A^2.

4. The compound of claim 1 having the structure of Formula Ia:



Formula Ia

or a pharmaceutically acceptable salt thereof, wherein

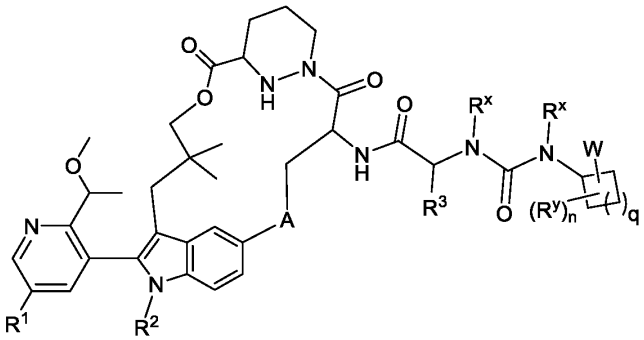
R^x is optionally substituted C_1–C_4 alkyl;

each R^y, if present, is independently optionally substituted C_1–C_4 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, optionally substituted 3 to 14-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl, or halogen;

q is 0, 1, or 2; and

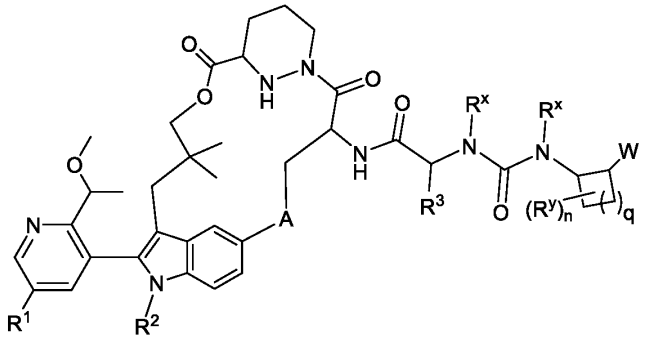
n is 0, 1, or 2.

5. The compound of claim 4 having the structure of Formula Ia-1



or a pharmaceutically acceptable salt thereof.

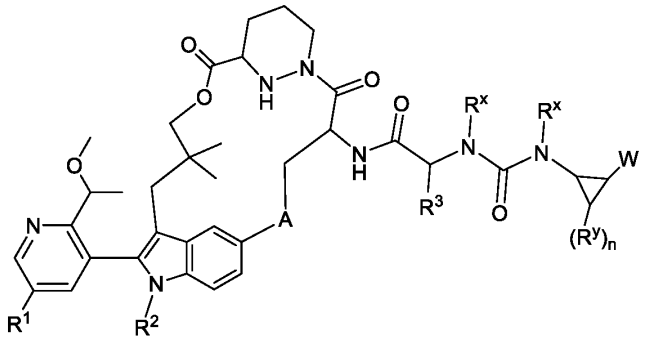
6. The compound of claim 5 having the structure of Formula Ia-2:



Formula Ia-2

or a pharmaceutically acceptable salt thereof.

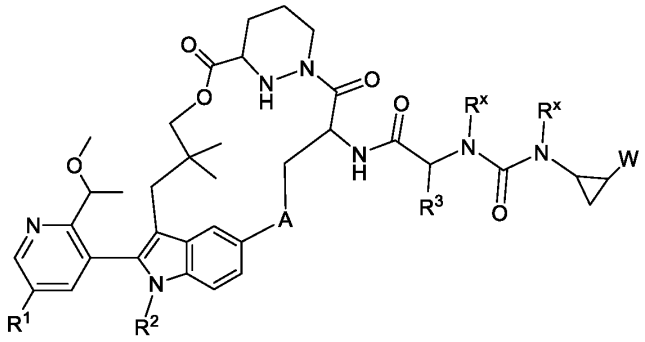
7. The compound of claim 6 having the structure of Formula Ia-3:



Formula Ia-3

or a pharmaceutically acceptable salt thereof.

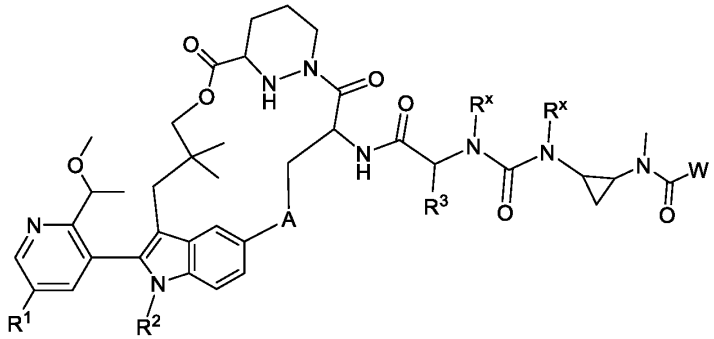
8. The compound of claim 7 having the structure of Formula Ia-4:



Formula Ia-4

or a pharmaceutically acceptable salt thereof.

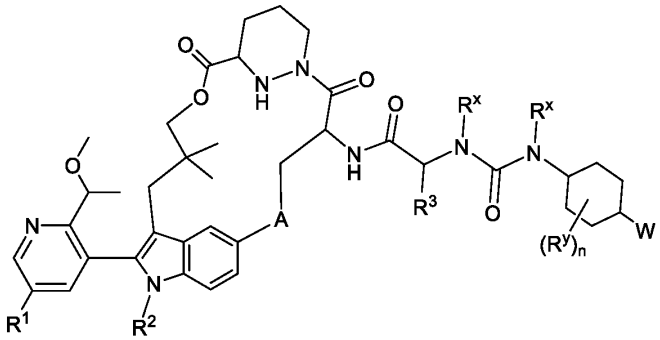
9. The compound of claim 8 having the structure of Formula Ia-5:



Formula Ia-5

or a pharmaceutically acceptable salt thereof.

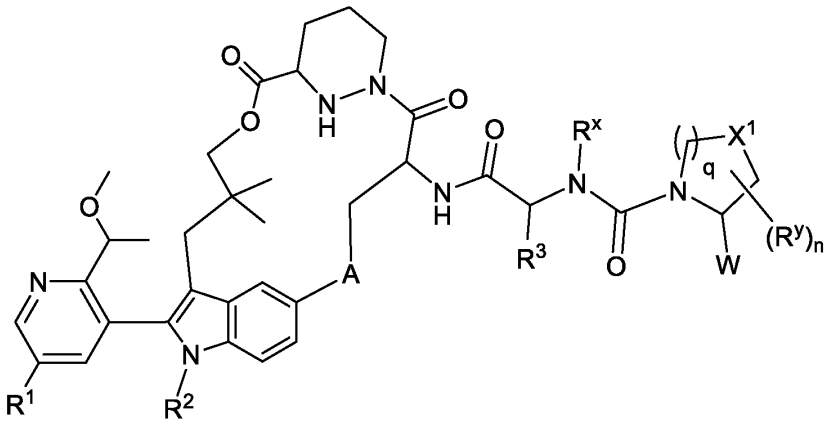
10. The compound of claim 4 having the structure of Formula Ia-6:



Formula Ia-6

or a pharmaceutically acceptable salt thereof.

11. The compound of claim 1 having the structure of Formula Ib:



Formula Ib

or a pharmaceutically acceptable salt thereof wherein

R^x is optionally substituted C_1–C_4 alkyl;

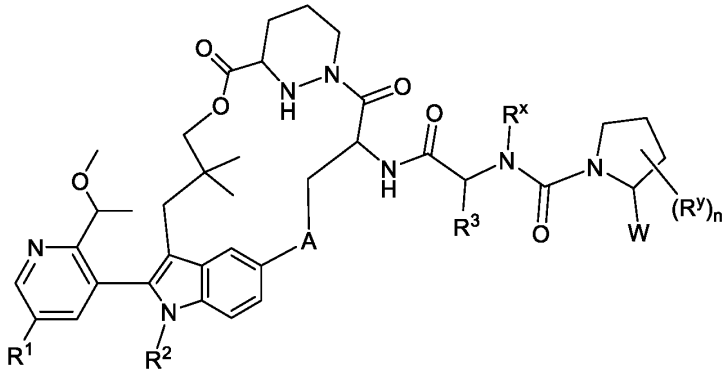
each R^y, if present, is independently optionally substituted C_1–C_4 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, optionally substituted 3 to 14-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl, or halogen;

X^1 is CH_2, O, or NH;

n is 0, 1, or 2; and

q is 0, 1, or 2.

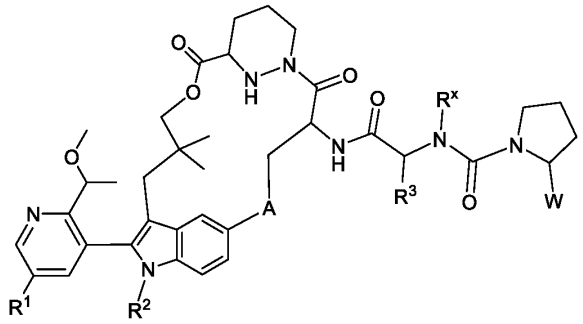
12. The compound of claim 11 having the structure of Formula Ib-1:



Formula Ib-1

or a pharmaceutically acceptable salt thereof.

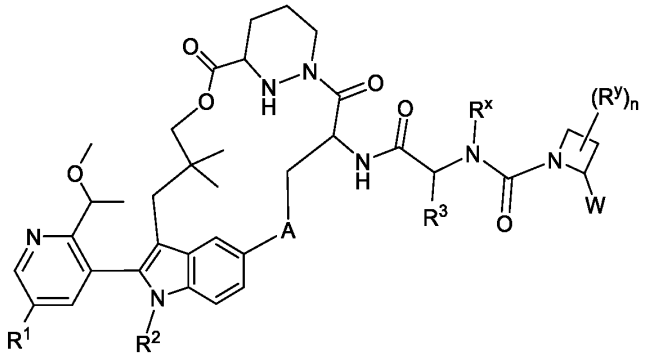
13. The compound of claim 12 having the structure of Formula Ib-2:



Formula Ib-2

or a pharmaceutically acceptable salt thereof.

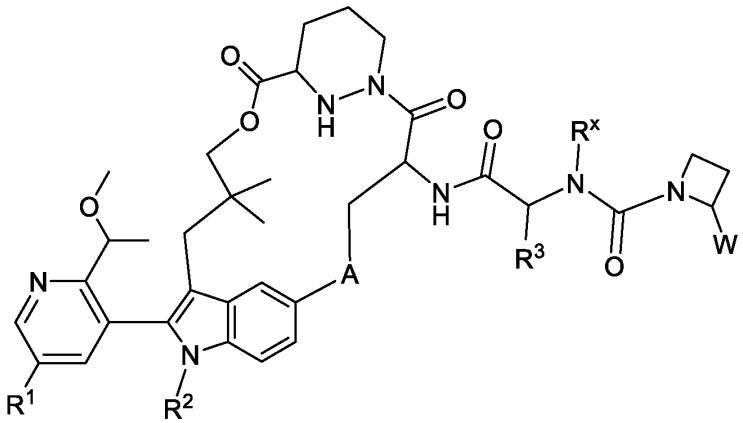
14. The compound of claim 11 having the structure of Formula Ib-3:



Formula Ib-3

or a pharmaceutically acceptable salt thereof.

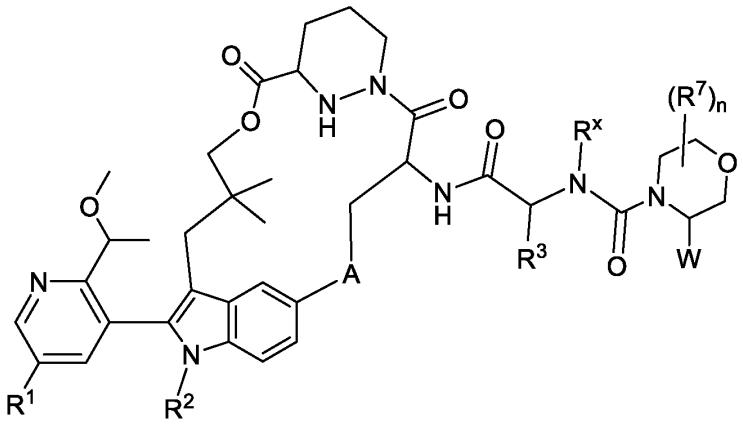
15. The compound of claim 14 having the structure of Formula Ib-4:



Formula Ib-4

or a pharmaceutically acceptable salt thereof.

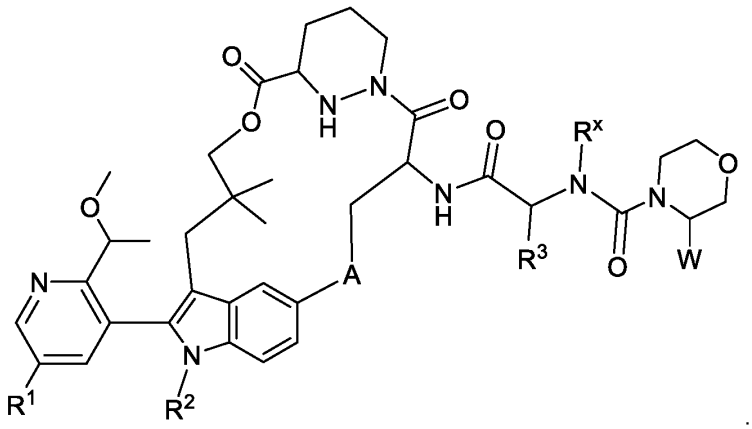
16. The compound of claim 11 having the structure of Formula Ib-5:



Formula Ib-5

or a pharmaceutically acceptable salt thereof.

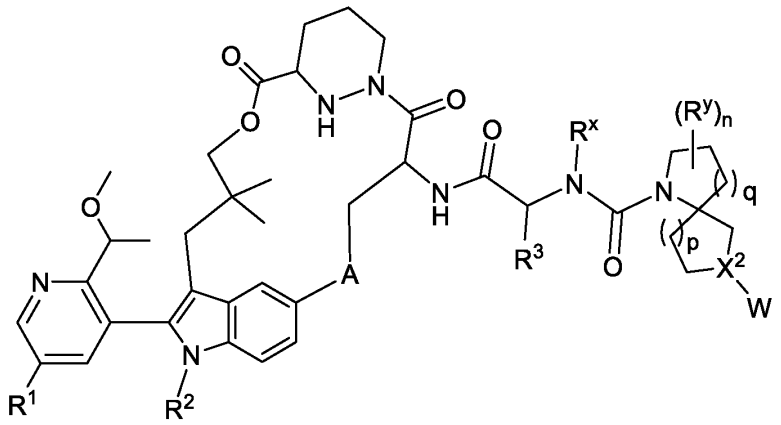
17. The compound of claim 16 having the structure of Formula Ib-6:



Formula Ib-6

or a pharmaceutically acceptable salt thereof.

18. The compound of claim 1 having the structure of Formula Ic:



Formula Ic

or a pharmaceutically acceptable salt thereof, wherein

R^x is optionally substituted C_1–C_4 alkyl;

each R^y, if present, is independently optionally substituted C_1–C_4 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, optionally substituted 3 to 14-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl, or halogen;

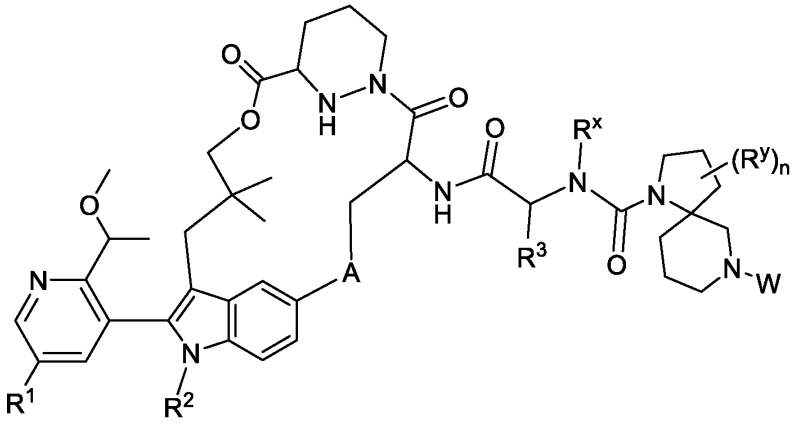
X^2 is CH or N;

n is 0, 1, or 2;

q is 0, 1, or 2; and

p is 0, 1, or 2.

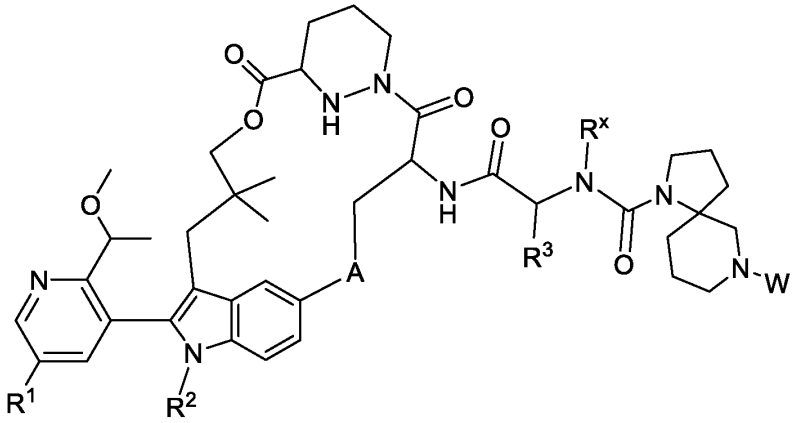
19. The compound of claim 18 having the structure of Formula Ic-1:



Formula Ic-1

or a pharmaceutically acceptable salt thereof.

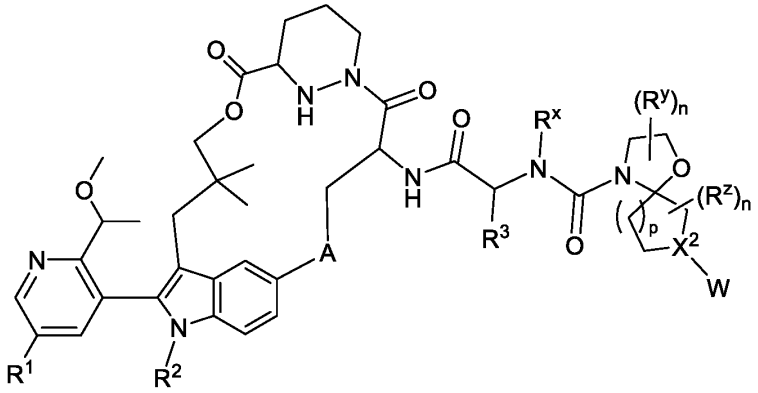
20. The compound of claim 19 having the structure of Formula Ic-2:



Formula Ic-2

or a pharmaceutically acceptable salt thereof.

21. The compound of claim 1 having the structure of Formula Id:



Formula Id

or a pharmaceutically acceptable salt thereof, wherein

R^x is optionally substituted C_1–C_4 alkyl;

each R^y, if present, is independently optionally substituted C_1–C_4 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, optionally substituted 3 to 14-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl, or halogen;

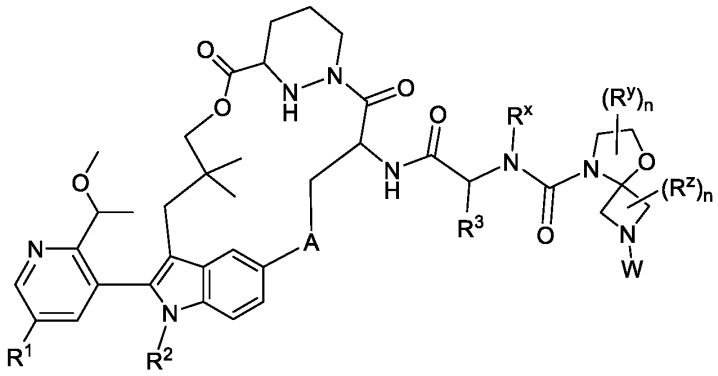
each R^z, if present, is independently optionally substituted C_1–C_4 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, optionally substituted 3 to 14-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl, or halogen;

X^2 is CH or N;

each n is, independently, 0, 1, or 2; and

p is 0, 1, or 2.

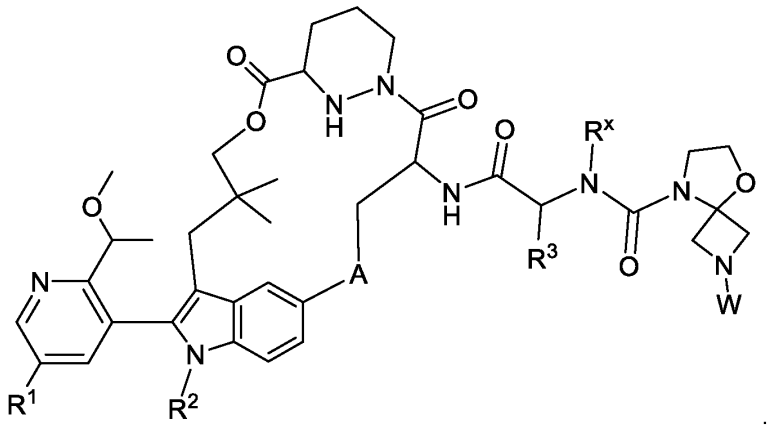
22. The compound of claim 21 having the structure of Formula Id-1:



Formula Id-1

or a pharmaceutically acceptable salt thereof.

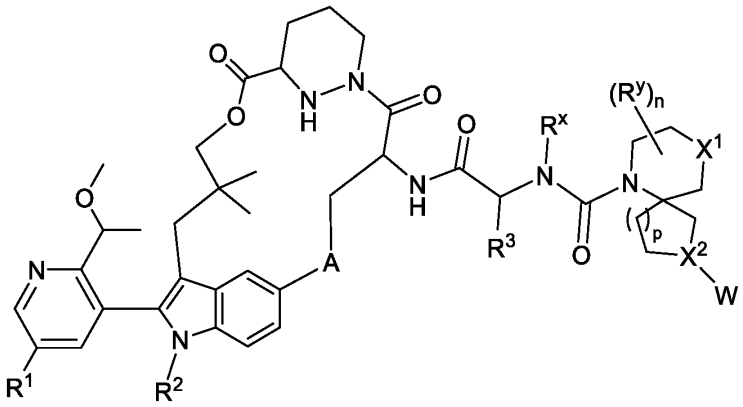
23. The compound of claim 22 having the structure of Formula Id-2:



Formula Id-2

or a pharmaceutically acceptable salt thereof.

24. The compound of claim 1 having the structure of Formula Ie:



Formula Ie

or a pharmaceutically acceptable salt thereof, wherein

R^x is optionally substituted C_1–C_4 alkyl;

each R^y, if present, is independently optionally substituted C_1–C_4 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, optionally substituted 3 to 14-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl, or halogen;

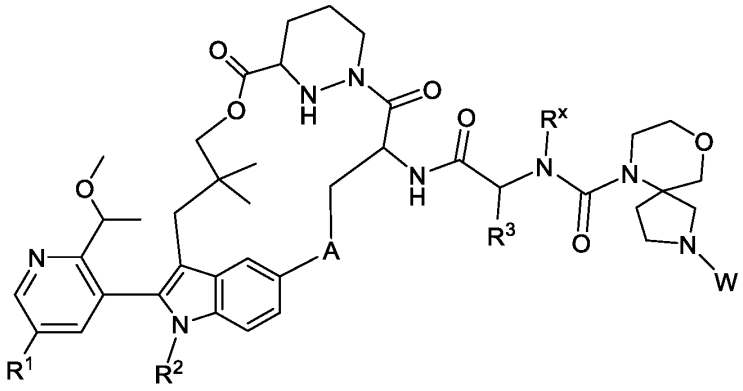
X^1 is CH_2, O, or NH;

X^2 is CH or N;

n is 0, 1, or 2; and

p is 0, 1, or 2.

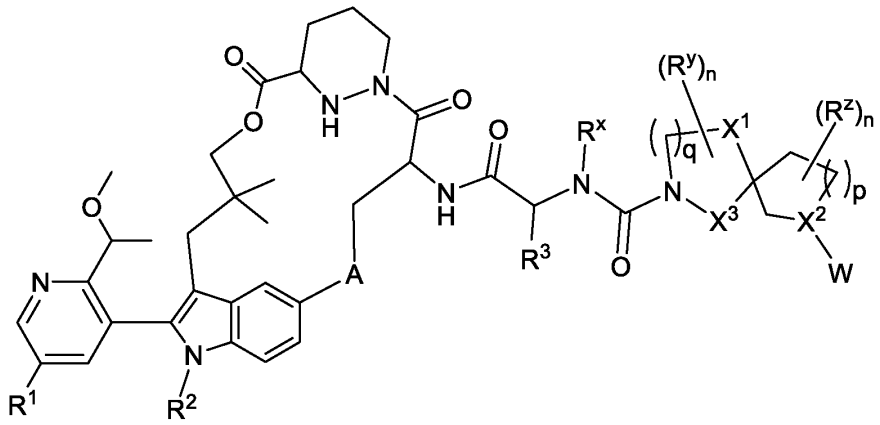
25. The compound of claim 24 having the structure of Formula Ie-1:



Formula Ie-1

or a pharmaceutically acceptable salt thereof.

26. The compound of claim 1 having the structure of Formula If:



Formula If

or a pharmaceutically acceptable salt thereof, wherein

R^x is optionally substituted C_1–C_4 alkyl;

each R^y, if present, is independently optionally substituted C_1–C_4 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, optionally substituted 3 to 14-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl, or halogen;

each R^z, if present, is independently optionally substituted C_1–C_4 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, optionally substituted 3 to 14-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl, or halogen;

X^1 is CH_2, O, or NH;

X^2 is CH or N;

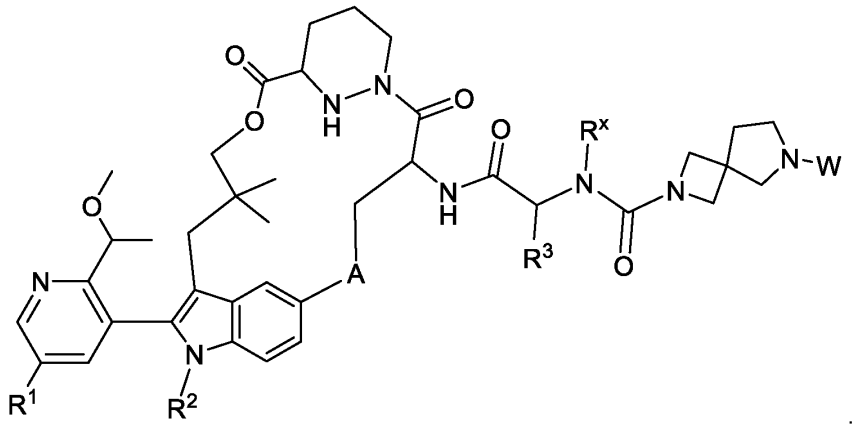
X^3 is CH_2, carbonyl, or NH;

each n is, independently, 0, 1, or 2;

q is 0, 1, or 2; and

p is 0, 1, or 2.

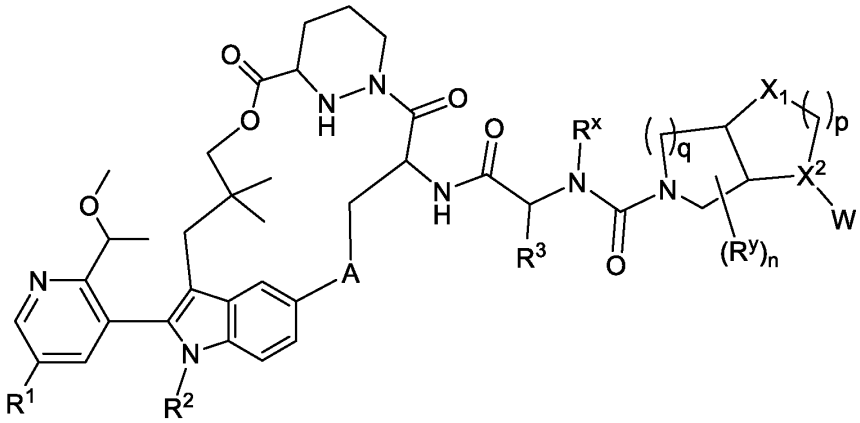
27. The compound of claim 26 having the structure of Formula If-1:



Formula If-1

or a pharmaceutically acceptable salt thereof.

28. The compound of claim 1 having the structure of Formula Ig:



Formula Ig

or a pharmaceutically acceptable salt thereof, wherein

R^x is optionally substituted C_1-C_4 alkyl;

each R^y, if present, is independently optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, optionally substituted 3 to 14-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl, or halogen;

X^1 is CH_2, O, S, or NH;

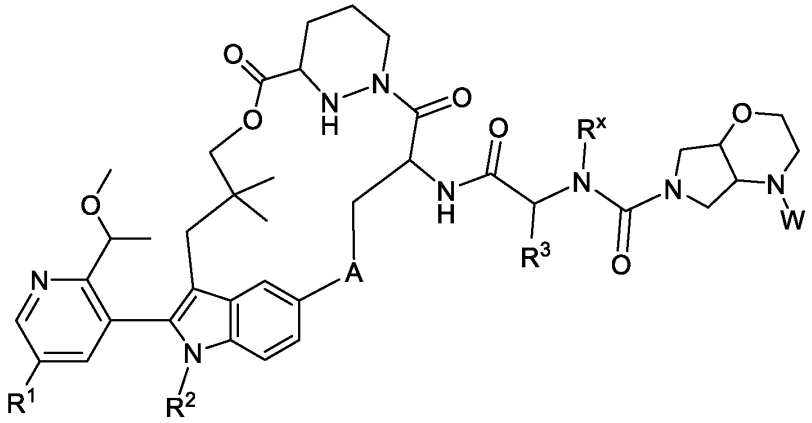
X^2 is CH or N;

n is 0, 1, or 2;

q is 0, 1, or 2; and

p is 0, 1, or 2.

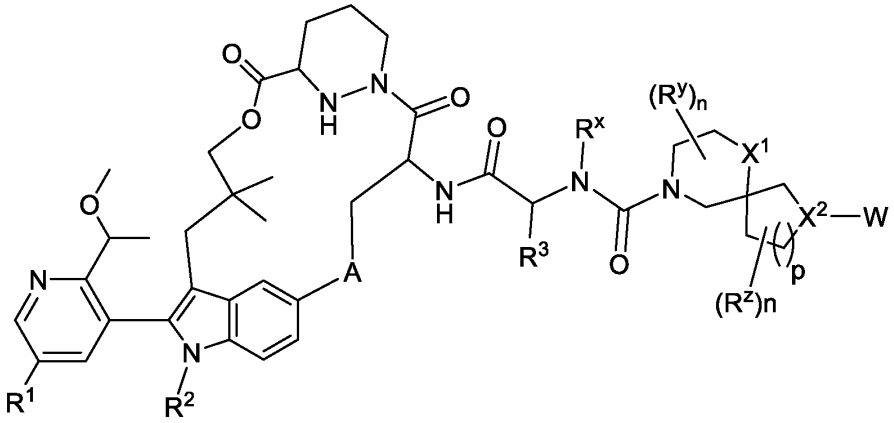
29. The compound of claim 26 having the structure of Formula Ig-1:



Formula Ig-1

or a pharmaceutically acceptable salt thereof.

30. The compound of claim 1 having the structure of Formula Ih:



Formula Ih

or a pharmaceutically acceptable salt thereof, wherein

R^x is optionally substituted C_1–C_4 alkyl;

each R^y, if present, is independently optionally substituted C_1–C_4 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, optionally substituted 3 to 14-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl, or halogen;

each R^z, if present, is independently optionally substituted C_1–C_4 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, optionally substituted 3 to 14-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl, or halogen;

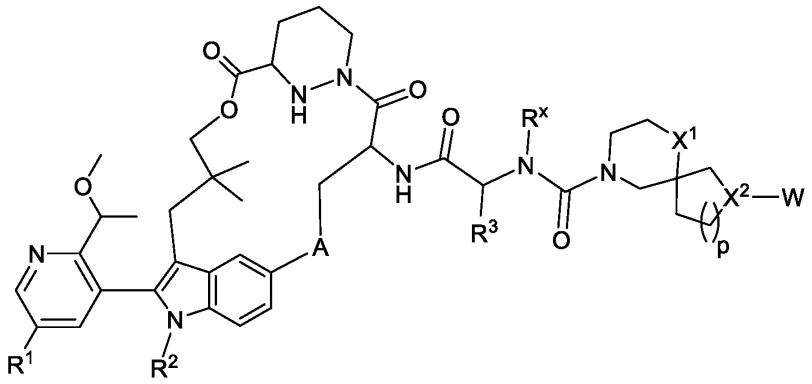
X^1 is CH_2, O, or NH;

X^2 is CH or N;

each n is, independently, 0, 1, or 2; and

p is 0, 1, or 2.

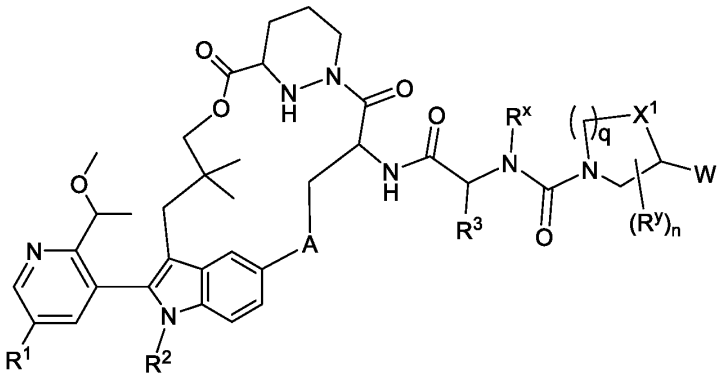
31. The compound of claim 30 having the structure of Formula Ih-1



Formula Ih-1

or a pharmaceutically acceptable salt thereof.

32. The compound of claim 1 having the structure of Formula Ii:



Formula Ii

or a pharmaceutically acceptable salt thereof, wherein

R^x is optionally substituted C_1–C_4 alkyl;

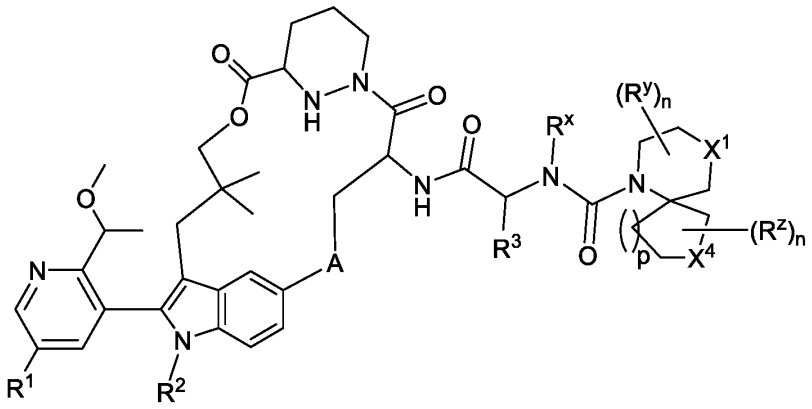
each R^y, if present, is independently optionally substituted C_1–C_4 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, optionally substituted 3 to 14-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl, or halogen;

X^1 is CH_2, O, or NH;

n is 0, 1, or 2; and

q is 0, 1, or 2.

33. The compound of claim 1 having the structure of Formula Ij:



Formula Ij

or a pharmaceutically acceptable salt thereof, wherein

R^x is optionally substituted C_1–C_4 alkyl;

each R^y, if present, is independently optionally substituted C_1–C_4 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, optionally substituted 3 to 14-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl, or halogen;

each R^z, if present, is independently optionally substituted C_1–C_4 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, optionally substituted 3 to 14-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl, or halogen;

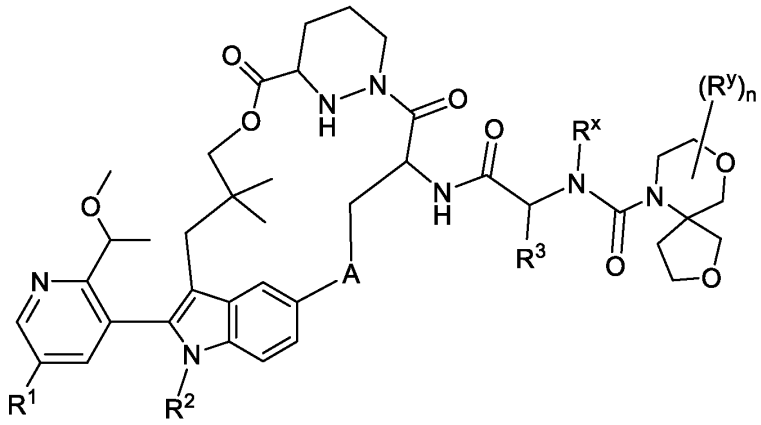
X^1 is CH_2, O, or NH;

X^4 is CH_2, NH, O, S, or sulfonyl;

each n is, independently, 0, 1, or 2; and

q is 0, 1, or 2.

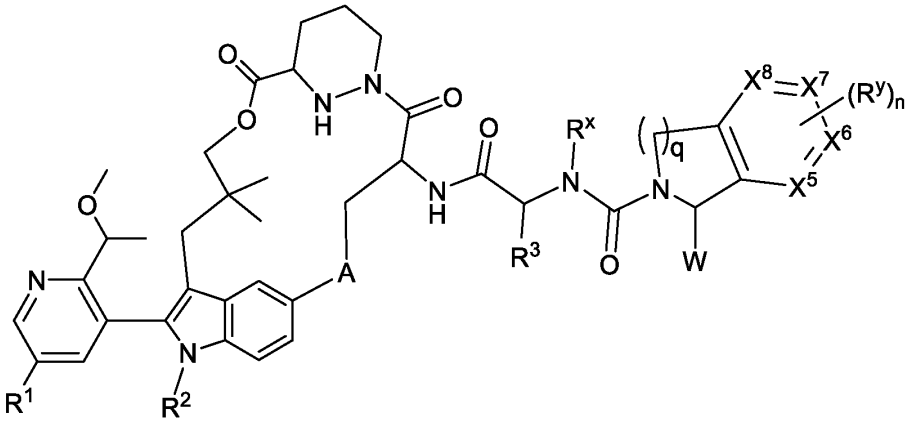
34. The compound of claim 33 having the structure of Formula Ij-1:



Formula Ij-1

or a pharmaceutically acceptable salt thereof.

35. The compound of claim 1 having the structure of Formula Ik:



Formula Ik

or a pharmaceutically acceptable salt thereof, wherein

R^x is optionally substituted C_1–C_4 alkyl;

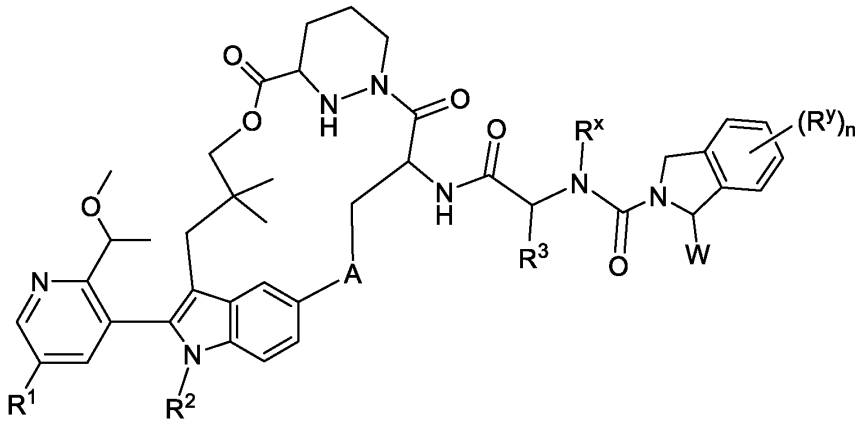
each R^y, if present, is independently optionally substituted C_1–C_4 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, optionally substituted 3 to 14-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl, or halogen;

X^5, X^6 , X^7, and X^8 are, independently, CH, N, or S;

n is 0, 1, or 2; and

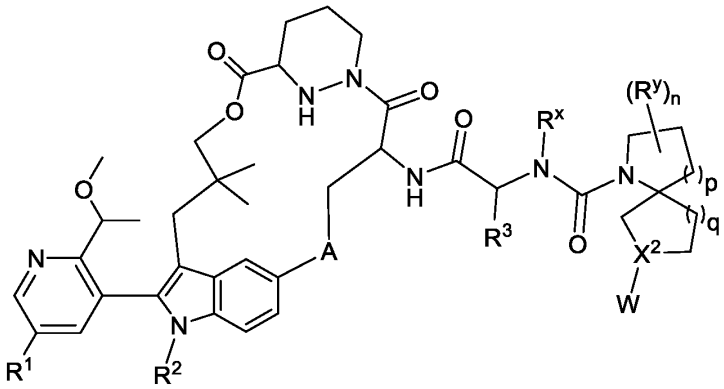
q is 0, 1, or 2.

36. The compound of claim 35 having the structure of Formula Ik-1:



or a pharmaceutically acceptable salt thereof.

37. The compound of claim 1 having the structure of Formula Im:



Formula Im

or a pharmaceutically acceptable salt thereof, wherein

R^x is optionally substituted C_1–C_4 alkyl;

each R^y, if present, is independently optionally substituted C_1–C_4 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, optionally substituted 3 to 14-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl, or halogen;

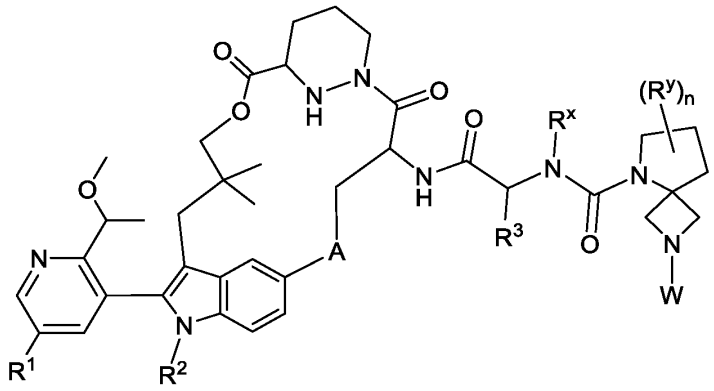
X^2 is CH or N;

n is 0, 1, or 2;

q is 0, 1, or 2; and

p is 0, 1, or 2.

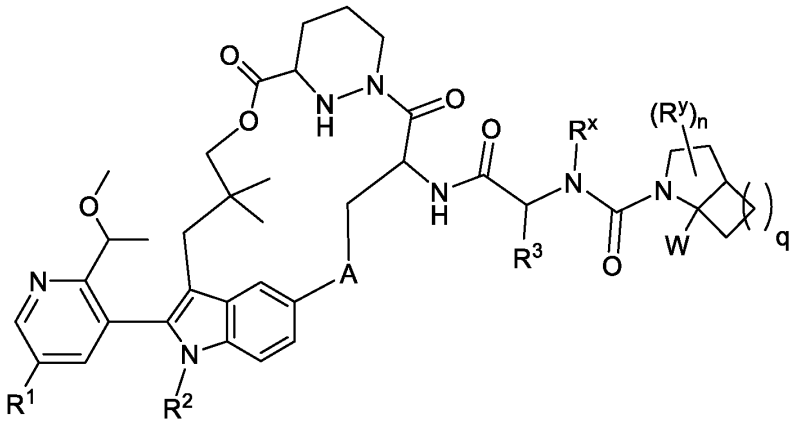
38. The compound of claim 37 having the structure of Formula Im-1:



Formula Im-1

or a pharmaceutically acceptable salt thereof.

39. The compound of claim 1 having the structure of Formula In:



Formula In

or a pharmaceutically acceptable salt thereof, wherein

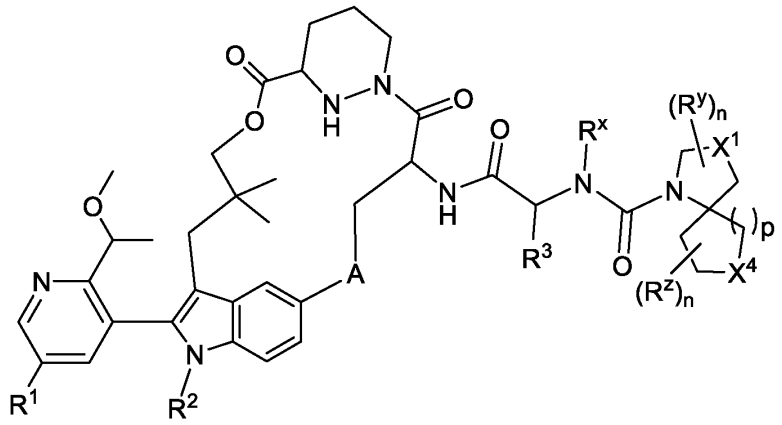
R^x is optionally substituted C_1–C_4 alkyl;

each R^y, if present, is independently optionally substituted C_1–C_4 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, optionally substituted 3 to 14-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl, or halogen;

n is 0, 1, or 2; and

q is 0, 1, or 2.

40. The compound of claim 1 having the structure of Formula Io:



Formula Io

or a pharmaceutically acceptable salt thereof, wherein

R^x is optionally substituted C_1–C_4 alkyl;

each R^y, if present, is independently optionally substituted C_1–C_4 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, optionally substituted 3 to 14-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl, or halogen;

each R^z, if present, is independently optionally substituted C_1–C_4 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, optionally substituted 3 to 14-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, optionally substituted 5 to 10-membered heteroaryl, or halogen;

X^1 is CH_2, O, or NH;

X^4 is CH_2, NH, O, S, or sulfonyl;

each n is, independently, 0, 1, or 2; and

p is 0, 1, or 2.

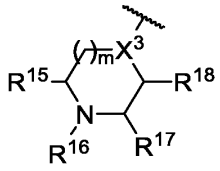
41. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein each of R^4, R^5, R^6, and R^7 are hydrogen.

42. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^4 and R^6 are hydrogen and R^5 and R^7 combine, together with the atoms to which they are attached, to form an optionally substituted four-membered cycloalkyl.

43. The compound of any one of claims 1 to 42, or a pharmaceutically acceptable salt thereof, wherein R^1 is hydrogen.

44. The compound of any one of claims 1 to 42, or a pharmaceutically acceptable salt thereof, wherein R^1 is optionally substituted 3- to 6-membered heterocycloalkyl.

45. The compound of any one of claims 1 to 42, or a pharmaceutically acceptable salt thereof, wherein R^1 is



wherein X^3 is N or CH;

m is 1 or 2;

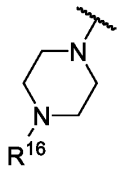
R^{15}, R^{16}, R^{17}, and R^{18} are each independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl; or

R^{16} and R^{17} combine with the atoms to which they are attached to form an optionally substituted 3 to 8-membered heterocycloalkyl; or

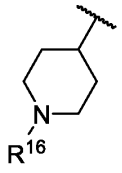
R^{17} and R^{18} combine with the atoms to which they are attached to form an optionally substituted 3 to 8-membered heterocycloalkyl; or

R^{17} and R^{15} combine with the atoms to which they are attached to form an optionally substituted 4 to 8-membered heterocycloalkyl.

46. The compound of claim 45, or a pharmaceutically acceptable salt thereof, wherein R^1 is



47. The compound of claim 45, or a pharmaceutically acceptable salt thereof, wherein R^1 is



48. The compound of any one of claims 45 to 47, or a pharmaceutically acceptable salt thereof, wherein R^{16} is methyl.

49. The compound of any one of claims 45 to 47, or a pharmaceutically acceptable salt thereof, wherein R^{16} is cyclopropyl.

50. The compound of any one of claims 1 to 49, or a pharmaceutically acceptable salt thereof, wherein W is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl. optionally substituted 3 to 10-membered heterocycloalkyl, optionally substituted 3 to 10-membered cycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5- to 10-membered heteroaryl, $C(O)OR^t$, $C(O)R^t$, optionally substituted acetamido, or optionally substituted sulfonyl..

51. The compound of claim 50, or a pharmaceutically acceptable salt thereof, wherein W is optionally substituted 3 to 10-membered heterocycloalkyl.

52. The compound of claim 51, or a pharmaceutically acceptable salt thereof, wherein W is 3- to 10-membered heterocycloalkyl.

53. The compound of claim 52, or a pharmaceutically acceptable salt thereof, wherein W is 5- to 7-membered heterocycloalkyl.

54. The compound of claim 50, or a pharmaceutically acceptable salt thereof, wherein W is optionally substituted 3- to 10-membered cycloalkyl.

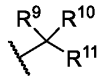
55. The compound of claim 54, or a pharmaceutically acceptable salt thereof, wherein W is 3- to 10-membered cycloalkyl.

56. The compound of claim 55, or a pharmaceutically acceptable salt thereof, wherein W is 5- to 7-membered cycloalkyl.

57. The compound of claim 50, or a pharmaceutically acceptable salt thereof, wherein W is optionally substituted C_1-C_6 alkyl.

58. The compound of claim 57, or a pharmaceutically acceptable salt thereof, wherein W is C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of 5- or 6-membered heteroaryl, 5- or 6- membered cycloalkyl, C_1-C_3 alkyl, 5- or 6- membered heterocycloalkyl.

59. The compound of claim 58, or a pharmaceutically acceptable salt thereof, wherein W is



wherein R^9 and R^{10} are each, independently, hydrogen, hydroxyl, or C_1-C_3 alkyl, and

R^{11} is cyano, 5- or 6-membered heteroaryl, 6-membered aryl, or 5- or 6-membered heterocycloalkyl.

60. The compound of claim 50, or a pharmaceutically acceptable salt thereof, wherein W is optionally substituted 6-membered aryl.

61. The compound of claim 60, or a pharmaceutically acceptable salt thereof, wherein W is phenyl.

62. The compound of claim 50, or a pharmaceutically acceptable salt thereof, wherein W is optionally substituted 5- to 10-membered heteroaryl.

63. The compound of claim 62, or a pharmaceutically acceptable salt thereof, wherein W is optionally substituted 5- or 6-membered heteroaryl.

64. The compound of claim 63, or a pharmaceutically acceptable salt thereof, wherein W is 5-membered heteroaryl.

65. The compound of claim 64, or a pharmaceutically acceptable salt thereof, wherein W is 6-membered heteroaryl.

66. The compound of claim 65, or a pharmaceutically acceptable salt thereof, wherein W is pyridyl.

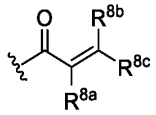
67. The compound of claim 50, or a pharmaceutically acceptable salt thereof, wherein W is $C(O)OR^t$ or $C(O)R^t$.

68. The compound of claim 67, or a pharmaceutically acceptable salt thereof, wherein R^t is hydrogen.

69. The compound of claim 67, or a pharmaceutically acceptable salt thereof, wherein R^t is optionally substituted C_1-C_6 alkyl.

70. The compound of any one of claims 1 to 49, or a pharmaceutically acceptable salt thereof, wherein W is an optionally substituted cross-linking group comprising a vinyl ketone, a vinyl sulfone, an ynone, an alkynyl sulfone, or a sulfonyl halide.

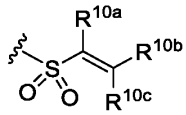
71. The compound of claim 70, or a pharmaceutically acceptable salt thereof, wherein W is a vinyl ketone having the structure of Formula IVa:



Formula IVa,

wherein R^{8a}, R^{8b}, and R^{8c} are, independently, hydrogen, -CN, halogen, or -C_1-C_3 alkyl optionally substituted with one or more substituents independently selected from -OH, -O-C_1-C_3 alkyl, -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, or a 4 to 7-membered saturated heterocycloalkyl.

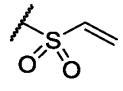
72. The compound of claim 70, or a pharmaceutically acceptable salt thereof, wherein W is a vinyl sulfone having the structure of Formula IVc:



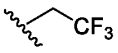
Formula IVc,

wherein R^{10a}, R^{10b}, and R^{10c} are each, independently, hydrogen, -CN, or -C_1-C_3 alkyl optionally substituted with one or more substituents independently selected from -OH, -O-C_1-C_3 alkyl, -NH_2, -NH(C_1-C_3 alkyl), -N(C_1-C_3 alkyl)$_2$, or a 4 to 7-membered saturated heterocycloalkyl.

73. The compound of claim 72, or a pharmaceutically acceptable salt thereof, wherein R^{10a}, R^{10b}, and R^{10c} are each, independently, hydrogen or -C_1-C_3 alkyl.

74. The compound of claim 72, or a pharmaceutically acceptable salt thereof, wherein W has the structure of .

75. The compound of any one of claims 1 to 74, or a pharmaceutically acceptable salt thereof, wherein R^2 is optionally substituted C_1-C_6 alkyl.

76. The compound of claim 75, or a pharmaceutically acceptable salt thereof, wherein R^2 is:  or .

77. The compound of any one of claims 1 to 74, or a pharmaceutically acceptable salt thereof, wherein R^3 is optionally substituted C_1-C_6 alkyl.

78. The compound of claim 77, or a pharmaceutically acceptable salt thereof, wherein R^3 is: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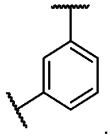
79. The compound of any one of claims 1 to 78, or a pharmaceutically acceptable salt thereof, wherein R^X is methyl.

80. The compound of any one of claims 1 to 79, or a pharmaceutically acceptable salt thereof, wherein A is optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 6-membered heteroarylene.

81. The compound of claim 80, or a pharmaceutically acceptable salt thereof, wherein A is optionally substituted 6-membered arylene, or optionally substituted 5- to 6-membered heteroarylene.

82. The compound of claim 81, or a pharmaceutically acceptable salt thereof, wherein A is optionally substituted 6-membered arylene.

83. The compound of claim 82, or a pharmaceutically acceptable salt thereof, wherein A is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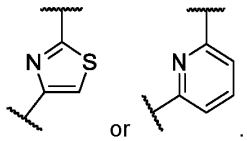
84. The compound of claim 81, or a pharmaceutically acceptable salt thereof, wherein A is optionally substituted 5- or 6-membered heteroarylene.

85. The compound of claim 84, or a pharmaceutically acceptable salt thereof, wherein A is:



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86. A compound of Table 1, or a pharmaceutically acceptable salt thereof.

87. A compound of Table 2, or a pharmaceutically acceptable salt thereof.

88. A pharmaceutical composition comprising a compound, or a pharmaceutically acceptable salt thereof, of any one of claims 1 to 87 and a pharmaceutically acceptable excipient

89. A method of treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, of any one of claims 1 to 87 or a pharmaceutical composition of claim 88.

90. The method of claim 89, wherein the cancer is pancreatic cancer, colorectal cancer, non-small cell lung cancer, gastric cancer, esophageal cancer, ovarian cancer, or uterine cancer.

91. The method of claim 89, wherein the cancer is melanoma.

92. The method of any one of claims 89-91, wherein the cancer comprises a Ras mutation.

93. The method of claim 92, wherein the Ras mutation is K-Ras Q61K, N-Ras Q61H, N-Ras Q61K, N-Ras Q61R, or N-Ras Q61L.

94. A method of treating a Ras protein-related disorder in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, of any one of claims 1 to 87 or a pharmaceutical composition of claim 88.

95. The method of any one of claims 89 to 94, wherein the method further comprises administering an additional anticancer therapy.

96. The method of claim 95, wherein the additional anticancer therapy is an EGFR inhibitor, a second Ras inhibitor, a SHP2 inhibitor, a SOS1 inhibitor, a Raf inhibitor, a MEK inhibitor, an ERK inhibitor, a PI3K inhibitor, a PTEN inhibitor, an AKT inhibitor, an mTORC1 inhibitor, a BRAF inhibitor, a PD-L1 inhibitor, a PD-1 inhibitor, a CDK4/6 inhibitor, a HER2 inhibitor, or a combination thereof.