NOVEL KETOAMIDES WITH CYCLIC P4'S AS INHIBITORS OF NS3 SERINE PROTEASE OF HEPATITIS C VIRUS

Field of the Invention

The present invention relates to novel hepatitis C virus ("HCV") protease inhibitors, pharmaceutical compositions containing one or more such inhibitors, methods of preparing such inhibitors and methods of using such inhibitors to treat hepatitis C and related disorders. This invention additionally discloses novel macrocyclic compounds as inhibitors of the HCV NS3/NS4a serine protease. This application claims priority from U.S. provisional patent application Serial Number 60/548,506 filed February 27, 2004.

Background of the Invention

Hepatitis C virus (HCV) is a (+)-sense single-stranded RNA virus that has been implicated as the major causative agent in non-A, non-B hepatitis (NANBH), particularly in blood-associated NANBH (BB-NANBH) (*see*, International Patent Application Publication No. WO 89/04669 and European Patent Application Publication No. EP 381 216). NANBH is to be distinguished from other types of viral-induced liver disease, such as hepatitis A virus (HAV), hepatitis B virus (HBV), delta hepatitis virus (HDV), cytomegalovirus (CMV) and Epstein-Barr virus (EBV), as well as from other forms of liver disease such as alcoholism and primary biliar cirrhosis.

Recently, an HCV protease necessary for polypeptide processing and viral replication has been identified, cloned and expressed. (*See*, e.g., U.S. Patent No. 5,712,145). This approximately 3000 amino acid polyprotein contains, from the amino terminus to the carboxy terminus, a nucleocapsid protein (C), envelope proteins (E1 and E2) and several non-structural proteins (NS1, 2, 3, 4a, 5a and 5b). NS3 is an approximately 68 kda protein, encoded by approximately 1893 nucleotides of the HCV genome, and has two distinct domains: (a) a serine protease domain consisting of approximately 200 of the N-terminal amino acids; and (b) an RNA-dependent ATPase domain at the C-terminus of the protein. The NS3 protease is considered a member of the

chymotrypsin family because of similarities in protein sequence, overall three-dimensional structure and mechanism of catalysis. Other chymotrypsin-like enzymes are elastase, factor Xa, thrombin, trypsin, plasmin, urokinase, tPA and PSA. The HCV NS3 serine protease is responsible for proteolysis of the polypeptide (polyprotein) at the NS3/NS4a, NS4a/NS4b, NS4b/NS5a and NS5a/NS5b junctions and is thus responsible for generating four viral proteins during viral replication. This has made the HCV NS3 serine protease an attractive target for antiviral chemotherapy. The inventive compounds can inhibit such protease. They also can modulate the processing of hepatitis C virus (HCV) polypeptide.

It has been determined that the NS4a protein, an approximately 6 kda polypeptide, is a co-factor for the serine protease activity of NS3. Autocleavage of the NS3/NS4a junction by the NS3/NS4a serine protease occurs intramolecularly (i.e., *cis*) while the other cleavage sites are processed intermolecularly (i.e., *trans*).

Analysis of the natural cleavage sites for HCV protease revealed the presence of cysteine at P1 and serine at P1' and that these residues are strictly conserved in the NS4a/NS4b, NS4b/NS5a and NS5a/NS5b junctions. The NS3/NS4a junction contains a threonine at P1 and a serine at P1'. The Cys→Thr substitution at NS3/NS4a is postulated to account for the requirement of *cis* rather than *trans* processing at this junction. *See*, e.g., Pizzi et al. (1994) Proc. Natl. Acad. Sci. (USA) 91:888-892, Failla et al. (1996) Folding & Design 1:35-42. The NS3/NS4a cleavage site is also more tolerant of mutagenesis than the other sites. *See*, e.g., Kollykhalov et al. (1994) J. Virol. 68:7525-7533. It has also been found that acidic residues in the region upstream of the cleavage site are required for efficient cleavage. *See*, e.g., Komoda et al. (1994) J. Virol. 68:7351-7357.

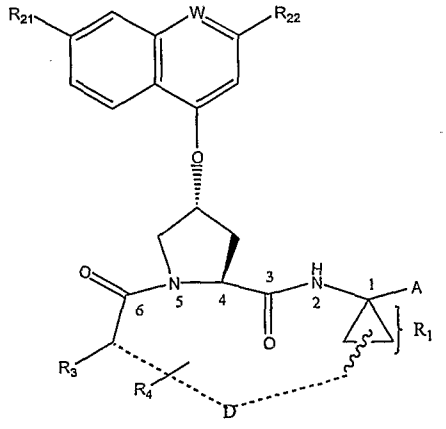
Inhibitors of HCV protease that have been reported include antioxidants (*see*, International Patent Application Publication No. WO 98/14181), certain peptides and peptide analogs (*see*, International Patent Application Publication No. WO 98/17679, Landro et al. (1997) Biochem. 36:9340-9348, Ingallinella et al. (1998) Biochem. 37:8906-8914, Llinàs-Brunet et al. (1998) Bioorg. Med. Chem. Lett. 8:1713-1718), inhibitors based

on the 70-amino acid polypeptide eglin c (Martin et al. (1998) Biochem. 37:11459-11468, inhibitors affinity selected from human pancreatic secretory trypsin inhibitor (hPSTI-C3) and minibody repertoires (MBip) (Dimasi et al. (1997) J. Virol. 71:7461-7469), cV_HE2 (a "camelized" variable domain antibody fragment) (Martin et al.(1997) Protein Eng. 10:607-614), and α1-antichymotrypsin (ACT) (Elzouki et al.) (1997) J. Hepat. 27:42-28). A ribozyme designed to selectively destroy hepatitis C virus RNA has recently been disclosed (*see, BioWorld Today* 9(217): 4 (November 10, 1998)).

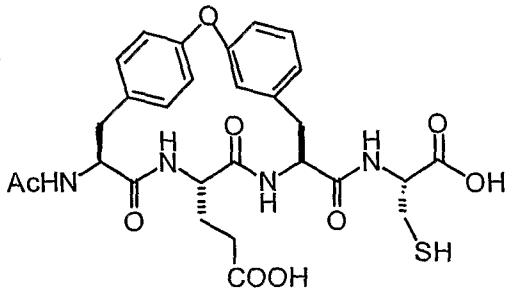
Reference is also made to the PCT Publications, No. WO 98/17679, published April 30, 1998 (Vertex Pharmaceuticals Incorporated); WO 98/22496, published May 28, 1998 (F. Hoffmann-La Roche AG); and WO 99/07734, published February 18, 1999 (Boehringer Ingelheim Canada Ltd.).

HCV has been implicated in cirrhosis of the liver and in induction of hepatocellular carcinoma. The prognosis for patients suffering from HCV infection is currently poor. HCV infection is more difficult to treat than other forms of hepatitis due to the lack of immunity or remission associated with HCV infection. Current data indicates a less than 50% survival rate at four years post cirrhosis diagnosis. Patients diagnosed with localized resectable hepatocellular carcinoma have a five-year survival rate of 10-30%, whereas those with localized unresectable hepatocellular carcinoma have a five-year survival rate of less than 1%.

Reference is made to WO 00/59929 (US 6,608,027, Assignee: Boehringer Ingelheim (Canada) Ltd.; Published October 12, 2000) which discloses peptide derivatives of the formula:

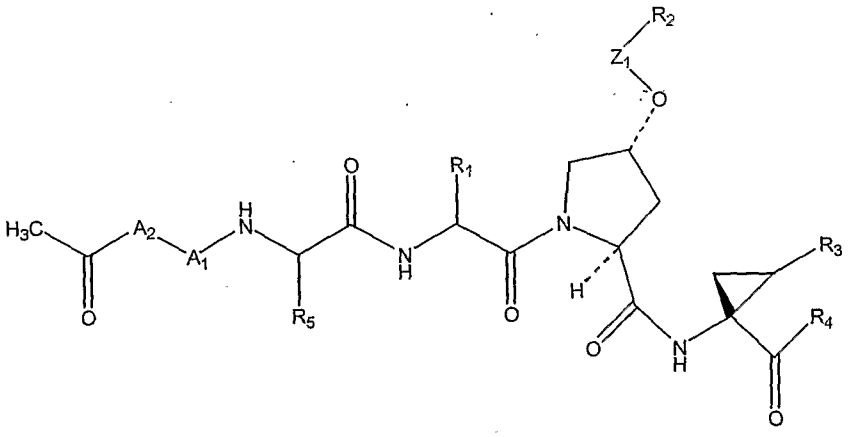


Reference is made to A. Marchetti *et al*, *Synlett*, S1, 1000-1002 (1999) describing the synthesis of bicylic analogs of an inhibitor of HCV NS3 protease. A compound disclosed therein has the formula:

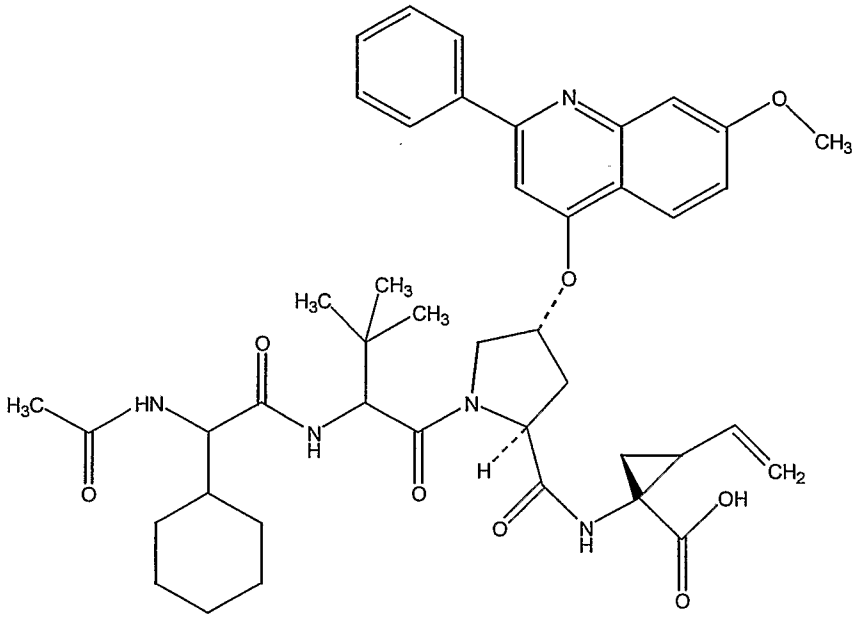


Reference is also made to W. Han *et al*, *Bioorganic & Medicinal Chem. Lett,* (2000) 10, 711-713, which describes the preparation of certain α-ketoamides, α-ketoesters and α-diketones containing allyl and ethyl functionalities.

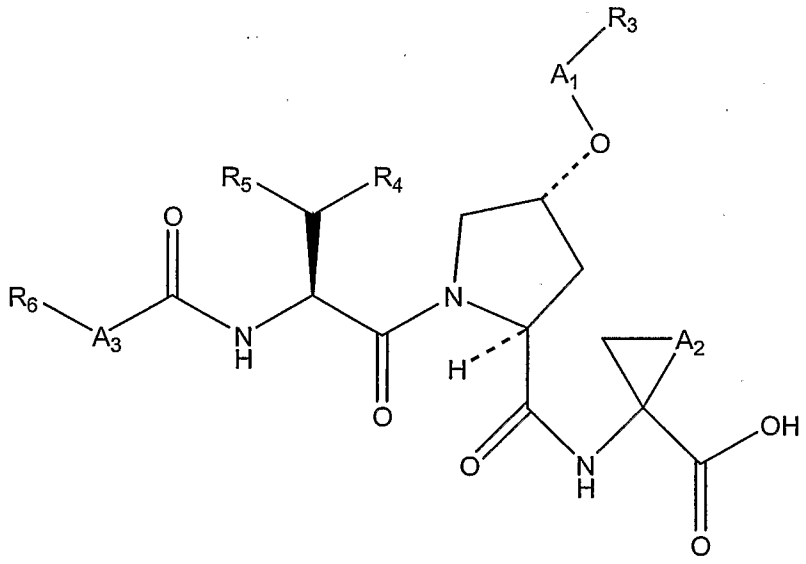
Reference is also made to WO 00/09558 (Assignee: Boehringer Ingelheim Limited; Published February 24, 2000) which discloses peptide derivatives of the formula:



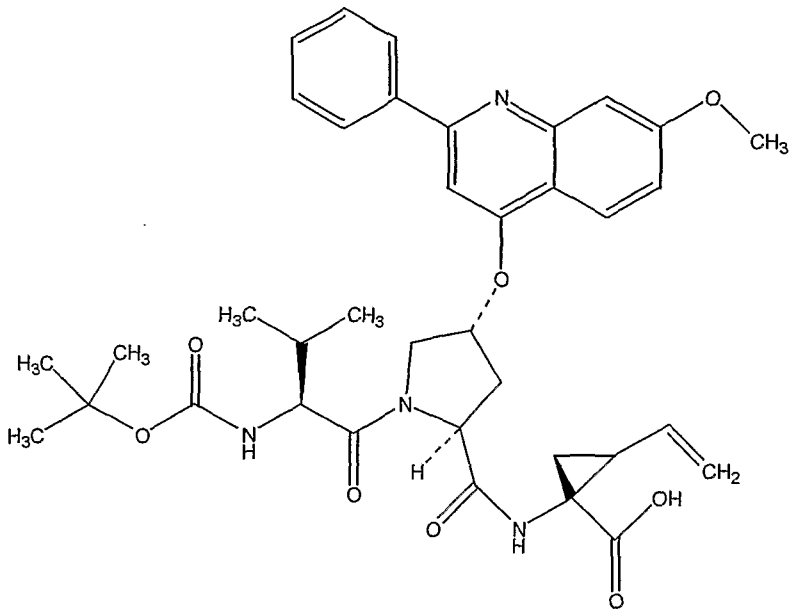
where the various elements are defined therein. An illustrative compound of that series is:



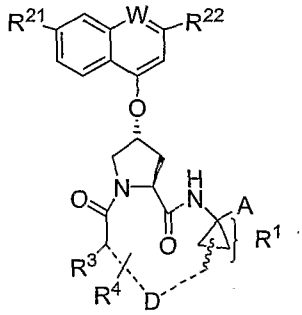
Reference is also made to WO 00/09543 (Assignee: Boehringer Ingelheim Limited; Published February 24, 2000) which discloses peptide derivatives of the formula:



where the various elements are defined therein. An illustrative compound of that series is:



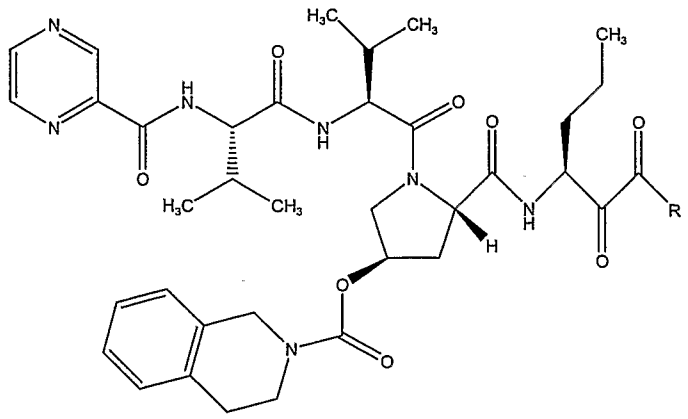
Reference is also made to U.S. 6,608,027 (Boehringer Ingelheim, Canada) which discloses NS3 protease inhibitors of the type:



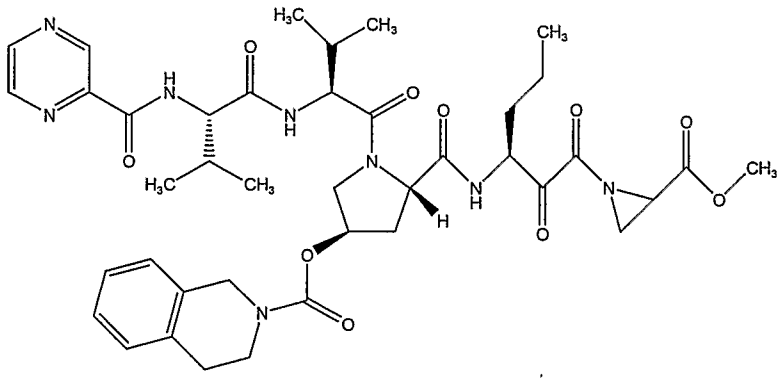
wherein the various moieties are defined therein.

Current therapies for hepatitis C include interferon-α (INF_{α}) and combination therapy with ribavirin and interferon. *See*, e.g., Beremguer et al. (1998) Proc. Assoc. Am. Physicians 110(2):98-112. These therapies suffer from a low sustained response rate and frequent side effects. *See*, e.g., Hoofnagle et al. (1997) N. Engl. J. Med. 336:347. Currently, no vaccine is available for HCV infection.

Reference is further made to WO 01/74768 (Assignee: Vertex Pharmaceuticals Inc) published October 11, 2001, which discloses certain compounds of the following general formula (R is defined therein) as NS3-serine protease inhibitors of Hepatitis C virus:



A specific compound disclosed in the afore-mentioned WO 01/74768 has the following formula:



PCT Publications WO 01/77113; WO 01/081325; WO 02/08198; WO 02/08256; WO 02/08187; WO 02/08244; WO 02/48172; WO 02/08251; and pending U.S. patent application, Serial No. 10/052,386, filed January 18, 2002, disclose various types of peptides and/or other compounds as NS-3 serine protease inhibitors of hepatitis C virus. The disclosures of those applications are incorporated herein by reference thereto.

There is a need for new treatments and therapies for HCV infection. There is a need for compounds useful in the treatment or prevention or amelioration of one or more symptoms of hepatitis C.

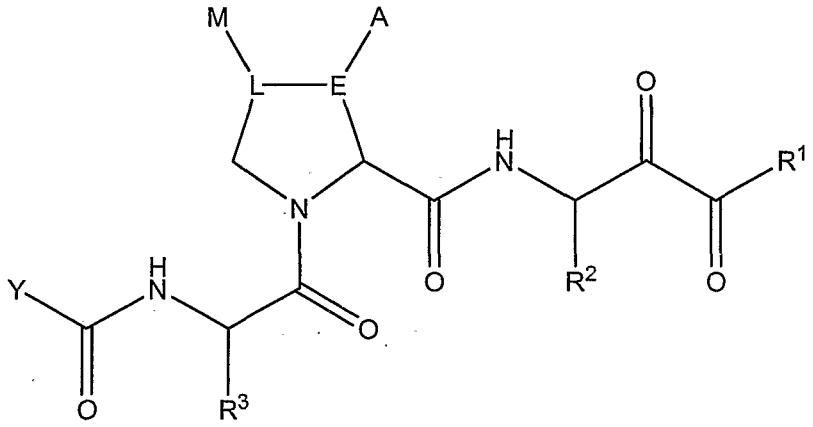
There is a need for methods of treatment or prevention or amelioration of one or more symptoms of hepatitis C.

There is a need for methods for modulating the activity of serine proteases, particularly the HCV NS3/NS4a serine protease, using the compounds provided herein.

There is a need for methods of modulating the processing of the HCV polypeptide using the compounds provided herein.

Summary of the Invention

In its many embodiments, the present invention provides a novel class of inhibitors of the HCV protease, pharmaceutical compositions containing one or more of the compounds, methods of preparing pharmaceutical formulations comprising one or more such compounds, and methods of treatment or prevention of HCV or amelioration of one or more of the symptoms of hepatitis C using one or more such compounds or one or more such formulations. Also provided are methods of modulating the interaction of an HCV polypeptide with HCV protease. Among the compounds provided herein, compounds that inhibit HCV NS3/NS4a serine protease activity are preferred. The present invention discloses compounds having the general structure shown in structural Formula 1:

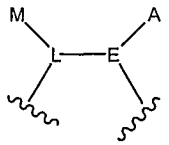


Formula I

wherein:

R^1 is H, OR^8, NR^9R^{10}, or CHR^9R^{10}, wherein R^8, R^9 and R^{10} can be the same or different, each being independently selected from the group consisting of H, alkyl-, alkenyl-, alkynyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, heterocyclyl-, arylalkyl-, and heteroarylalkyl;

A and M can be the same or different, each being independently selected from R, OR, NHR, NRR', SR, SO_2R, and halo; or A and M are connected to each other (in other words, A-E-L-M taken together) such that the moiety:



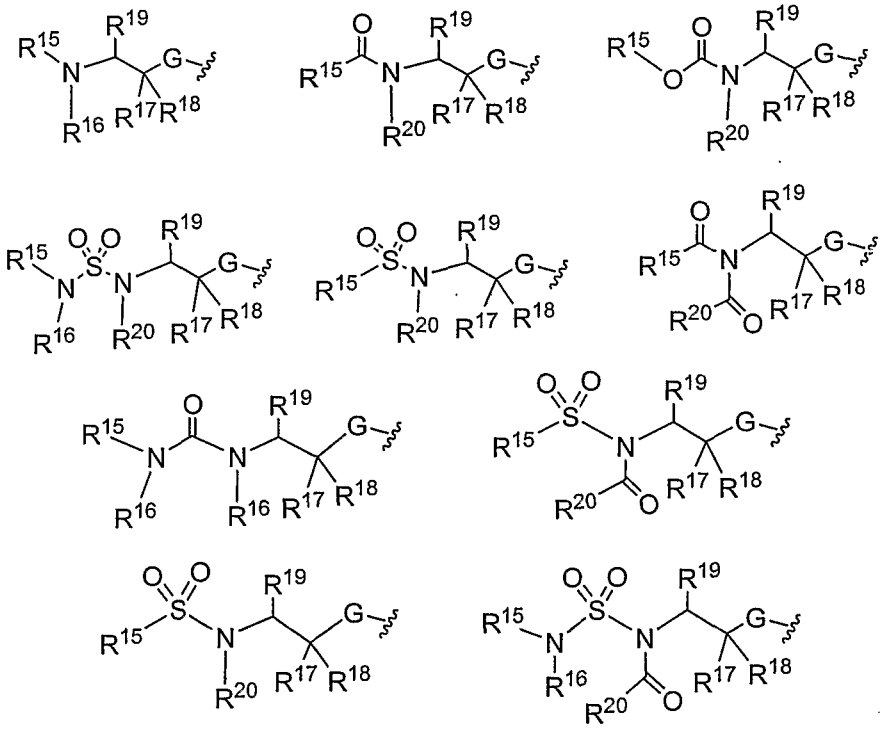
shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl;

E is C(H) or C(R);

L is C(H), C(R), $CH_2C(R)$, or $C(R)CH_2$;

R, R', R^2, and R^3 can be the same or different, each being independently selected from the group consisting of H, alkyl-, alkenyl-, alkynyl-, cycloalkyl-, heteroalkyl-, heterocyclyl-, aryl-, heteroaryl-, (cycloalkyl)alkyl-, (heterocyclyl)alkyl-, aryl-alkyl-, and heteroaryl-alkyl-; or alternately R and R' in NRR' are connected to each other such that NRR' forms a four to eight-membered heterocyclyl;

and Y is selected from the following moieties:

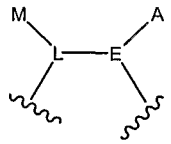


wherein G is NH or O, and R^{15}, R^{16}, R^{17} , R^{18}, R^{19} and R^{20} can be the same or different, each being independently selected from the group consisting of H, C_1-C_{10} alkyl, C_1-C_{10} heteroalkyl, C_2-C_{10} alkenyl, C_2-C_{10} heteroalkenyl, C_2-C_{10} alkynyl, C_2-C_{10} heteroalkynyl, C_3-C_8 cycloalkyl, C_3-C_8 heterocyclyl, aryl, heteroaryl, or alternately: (i) either R^{15} and R^{16} can be connected to each other to form a four to eight-membered cycloalkyl or heterocyclyl, or R^{15} and R^{19} are connected to each other to form a five to eight-membered cycloalkyl or heterocyclyl, or R^{15} and R^{20} are connected to

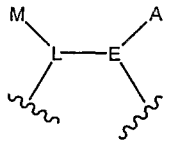
each other to form a five to eight-membered cycloalkyl or heterocyclyl, and (ii) likewise, independently, R^{17} and R^{18} are connected to each other to form a three to eight-membered cycloalkyl or heterocyclyl,

wherein each of said alkyl, aryl, heteroaryl, cycloalkyl or heterocyclyl can be unsubstituted or optionally independently substituted with one or more moieties selected from the group consisting of: hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, amido, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, sulfonamido, alkylsulfonamido, arylsulfonamido, keto, carboxy, carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyloxy, alkylureido, arylureido, halo, cyano, and nitro.

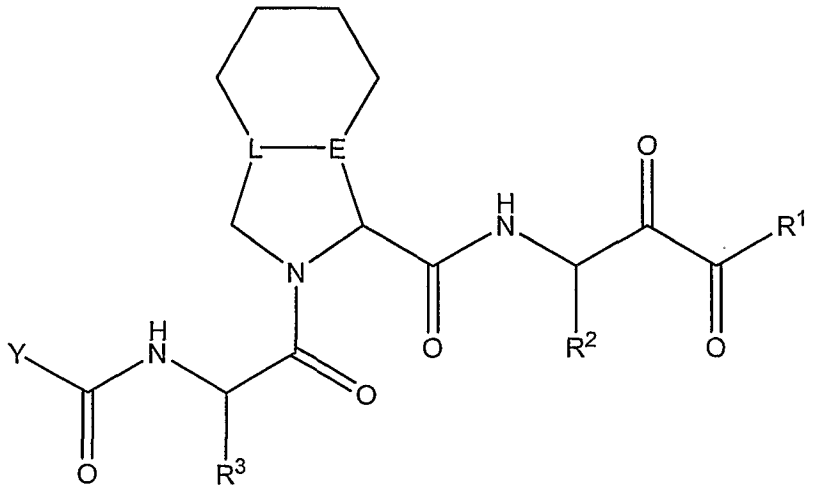
The above-noted statement "A and M are connected to each other such that the moiety:



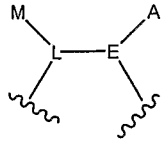
shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl" can be illustrated in a non-limiting matter as follows. Thus, for example, in the case where A and M are connected such that the moiety:



shown above in Formula I forms a six -membered cycloalkyl (cyclohexyl), Formula I can be depicted as:



One with ordinary skill in the art will appreciate that similar depictions for Formula I can be arrived at when A and M shown above in the moiety:



(i.e., M-L-E-A taken together) are connected to form a three, four, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl.

In the above-noted definitions of R, R', R^2, and R^3 preferred alkyl is made of one to ten carbon atoms, preferred alkenyl or alkynyl is made of two to ten carbon atoms, preferred cycloalkyl is made of three to eight carbon atoms, and preferred heteroalkyl, heteroaryl or heterocycloalkyl has one to six oxygen, nitrogen, sulfur, or phosphorus atoms.

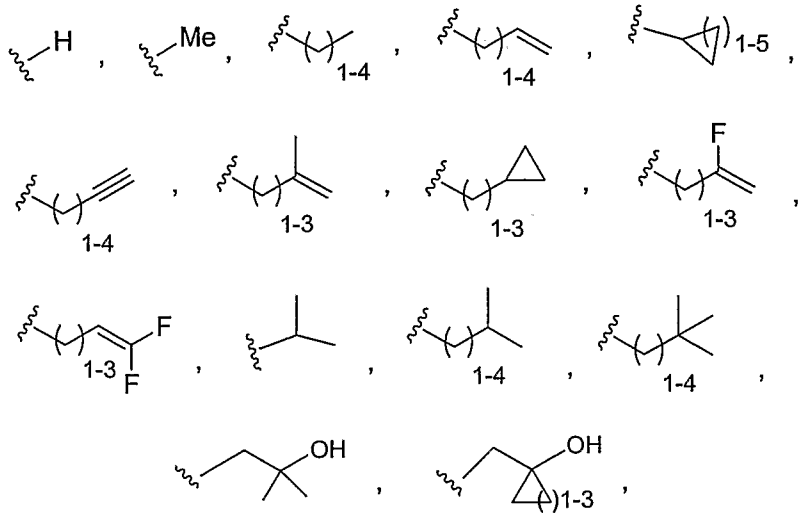
The compounds represented by Formula I, by themselves or in combination with one or more other suitable agents disclosed herein, can be useful for treating diseases such as, for example, HCV, HIV, AIDS (Acquired Immune Deficiency Syndrome), and related disorders, as well as for modulating the activity of hepatitis C virus (HCV) protease, preventing HCV, or ameliorating one or more symptoms of hepatitis C. Such modulation, treatment, prevention or amelioration can be done with the inventive compounds as well as with pharmaceutical compositions or formulations comprising such compounds. Without being limited to theory, it is believed that the HCV protease may be the NS3 or NS4a protease. The inventive compounds can inhibit such protease. They can also modulate the processing of hepatitis C virus (HCV) polypeptide.

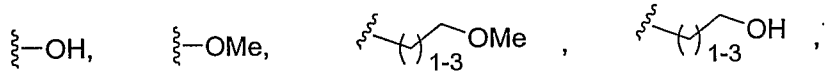
Detailed Description

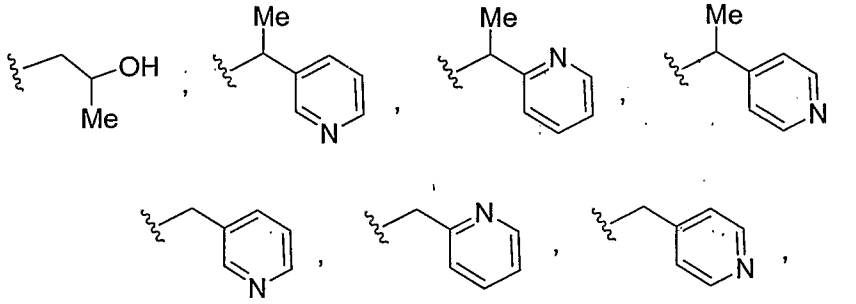
In an embodiment, the present invention discloses compounds which are represented by structural Formula 1 or a pharmaceutically acceptable salt, solvate or ester thereof, wherein the various moieties are as defined above.

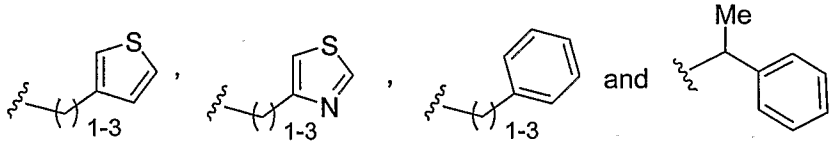
In another embodiment, R^1 is NR^9R^{10}, and R^9 is H, R^{10} is H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, alkyl-aryl, alkyl-heteroaryl, aryl-alkyl, alkenyl, alkynyl or heteroaryl-alkyl.

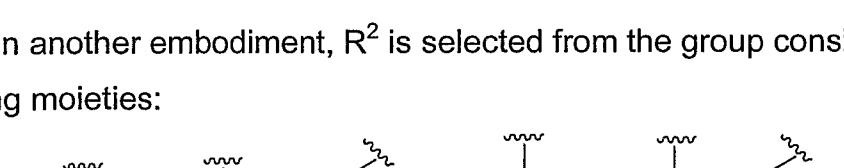
In another embodiment, R^{10} is selected from the group consisting of:



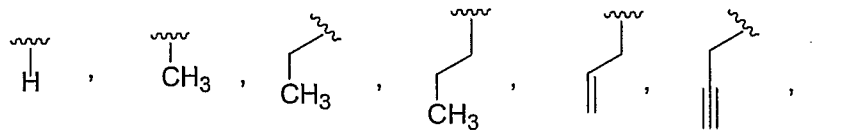


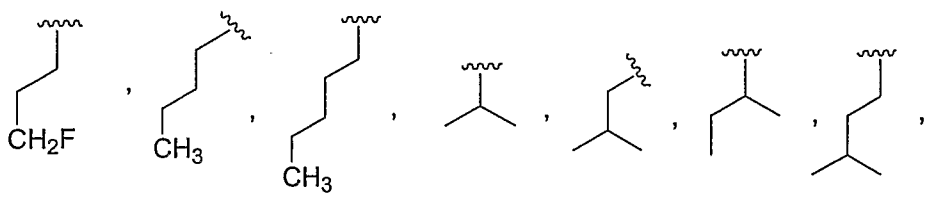


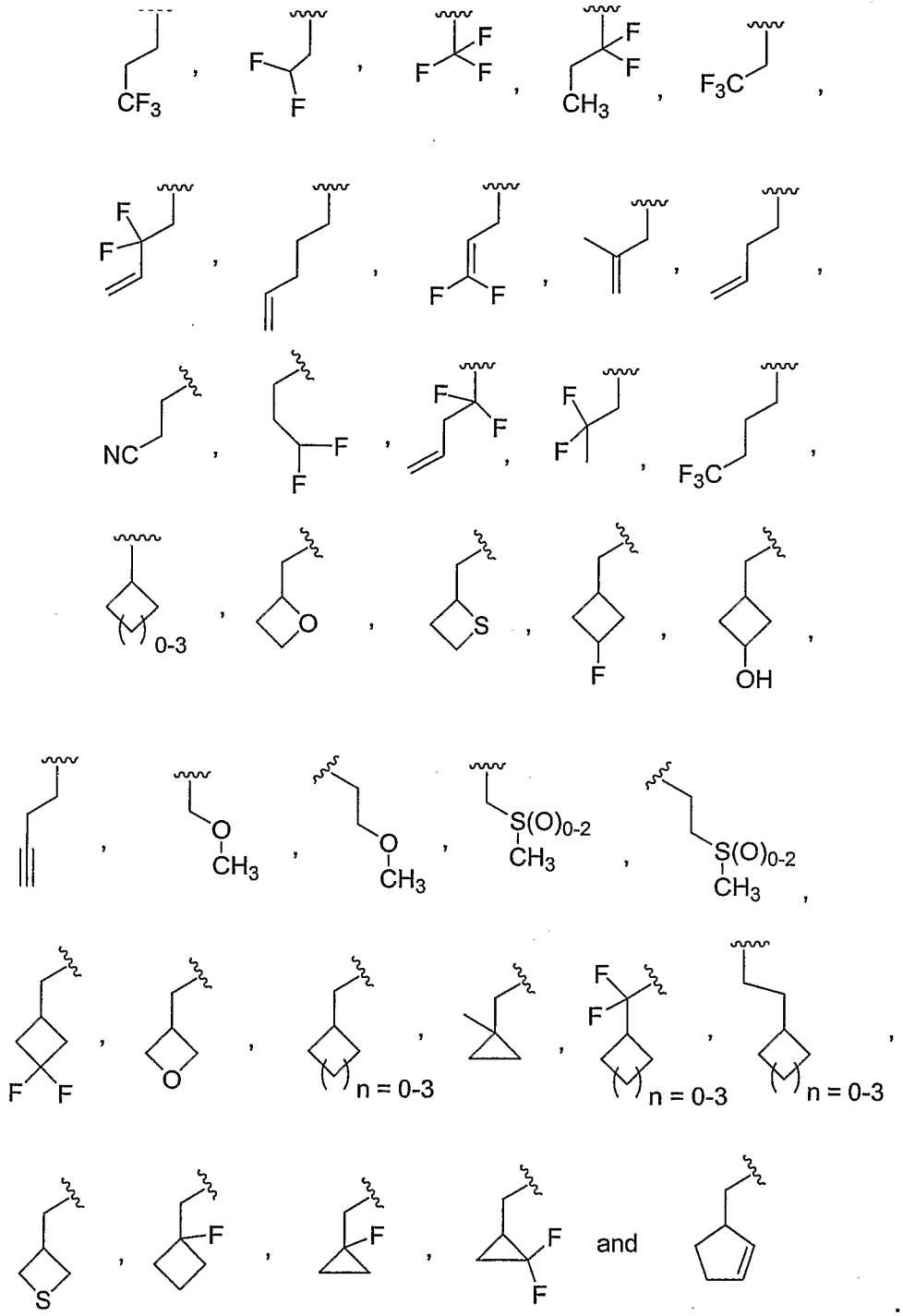




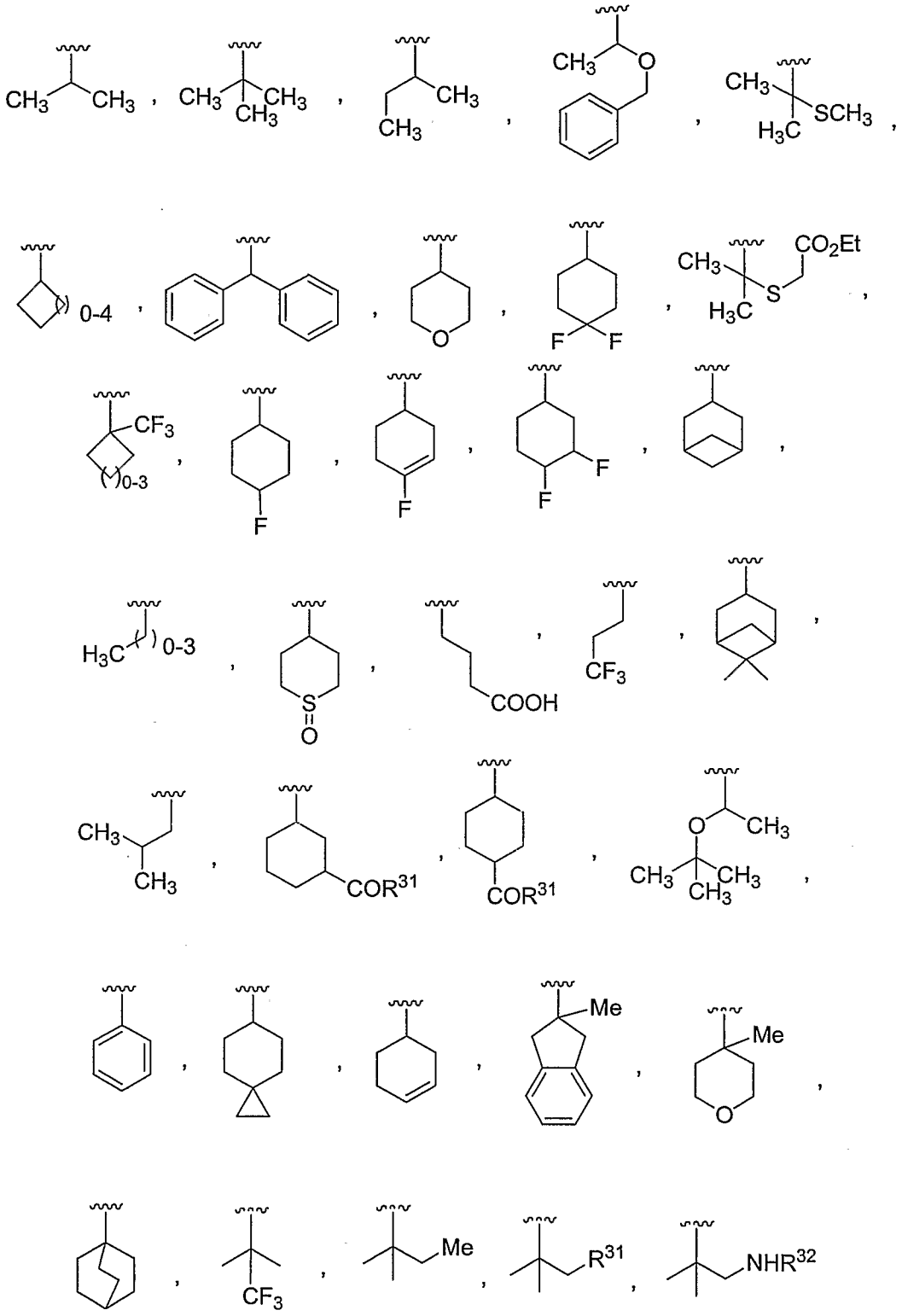
In another embodiment, R^2 is selected from the group consisting of the following moieties:

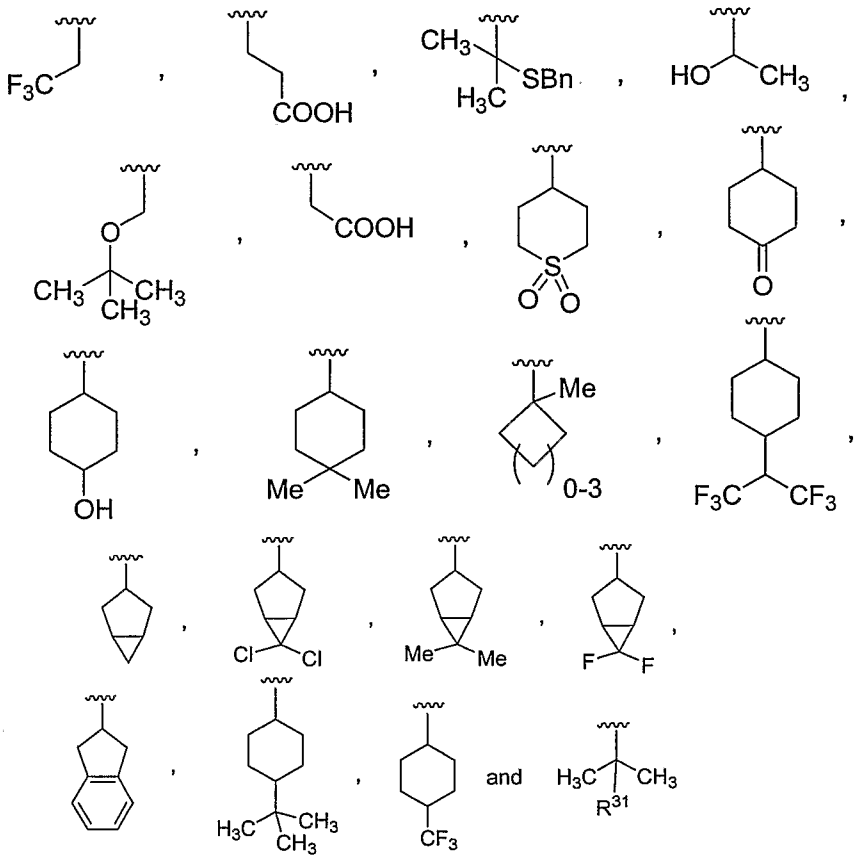






In another embodiment, R^3 is selected from the group consisting of:

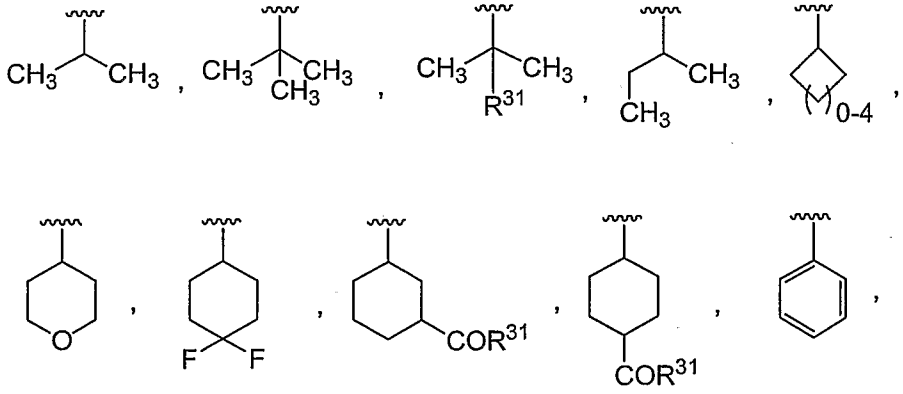

CH3
CH3
CH3
CH3
CH3
CH3
CH3
CH3
O
CH3
H3C
SCH3
0-4
O
F
F
CH3
H3C
S
CO2Et
CF3
0-3
F
F
F
H3C
0-3
S
O
COOH
CF3
CH3
CH3
COR31
COR31
O
CH3
CH3
CH3
Me
Me
O
Me
CF3
R31
NHR32

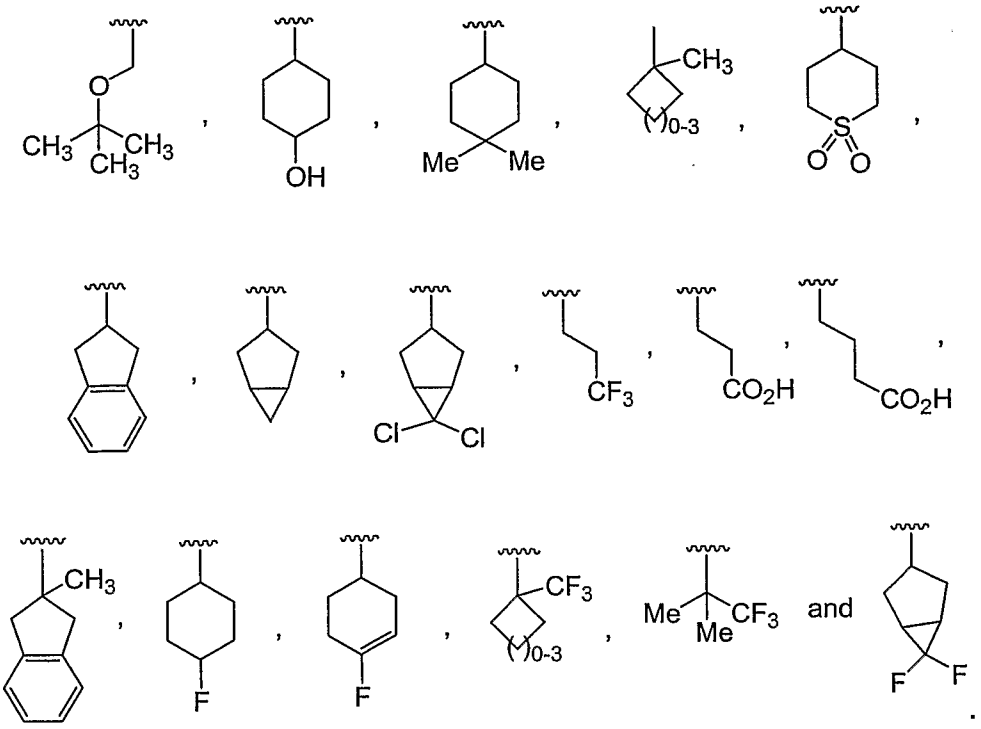


wherein R^{31} is OH or O-alkyl; and

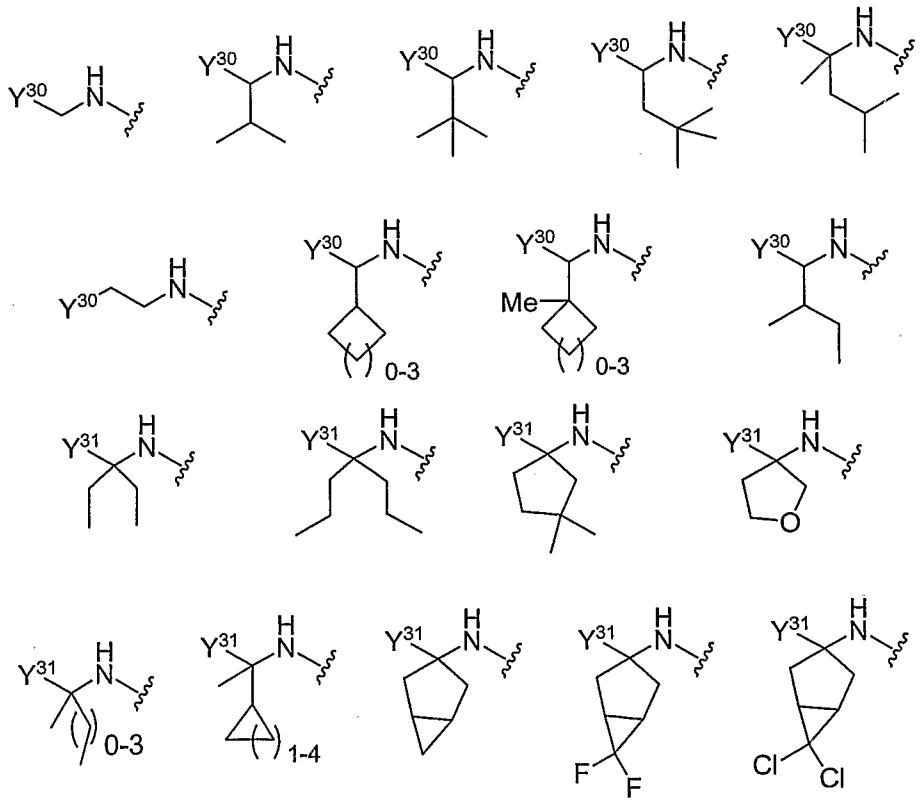
R^{32} is H, $C(O)CH_3$, C(O)OtBu or C(O)N(H)tBu.

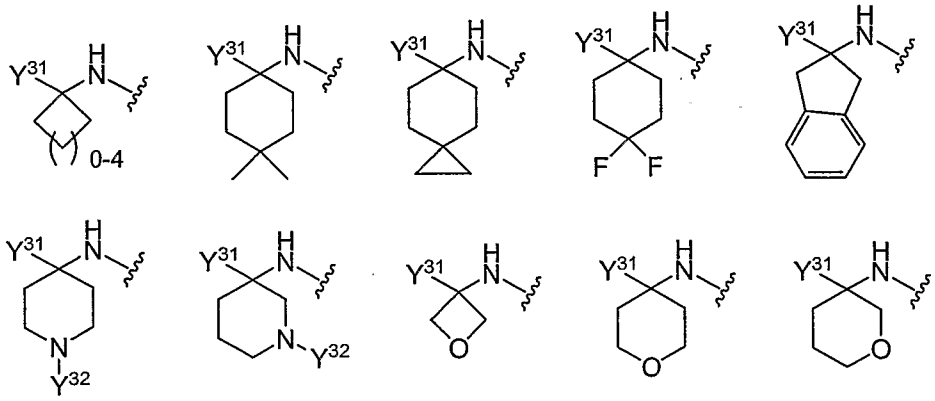
In an additional embodiment, R^3 is selected from the group consisting of the following moieties:



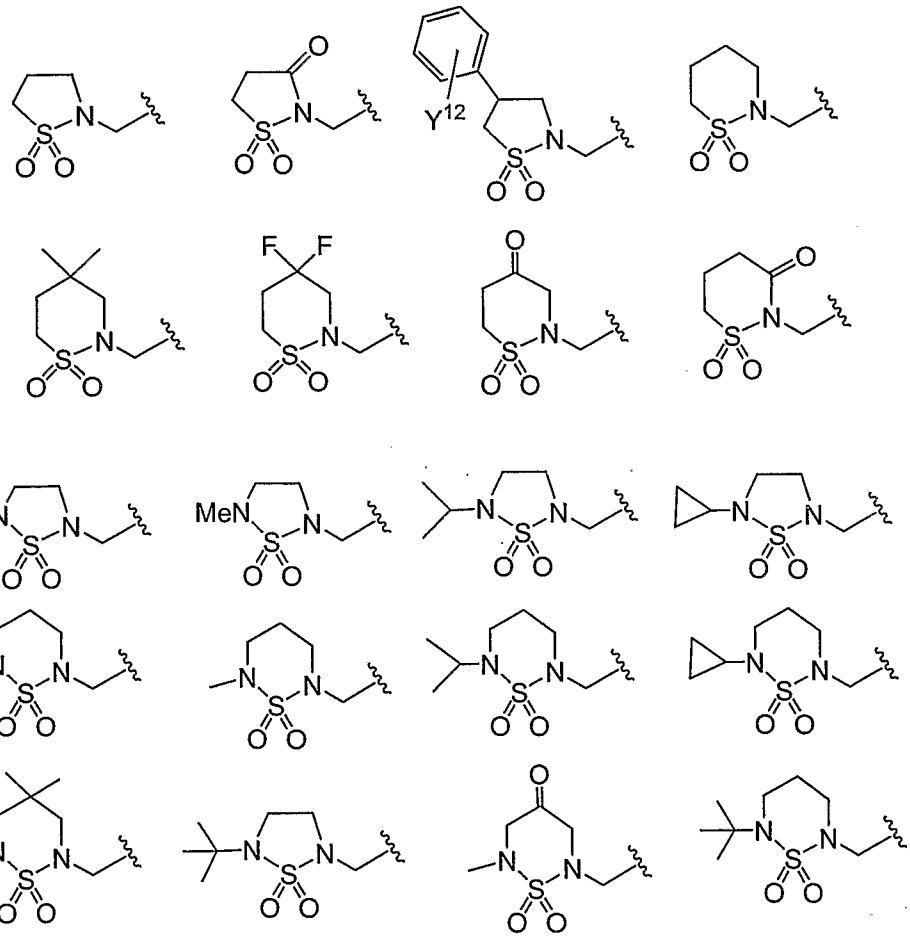


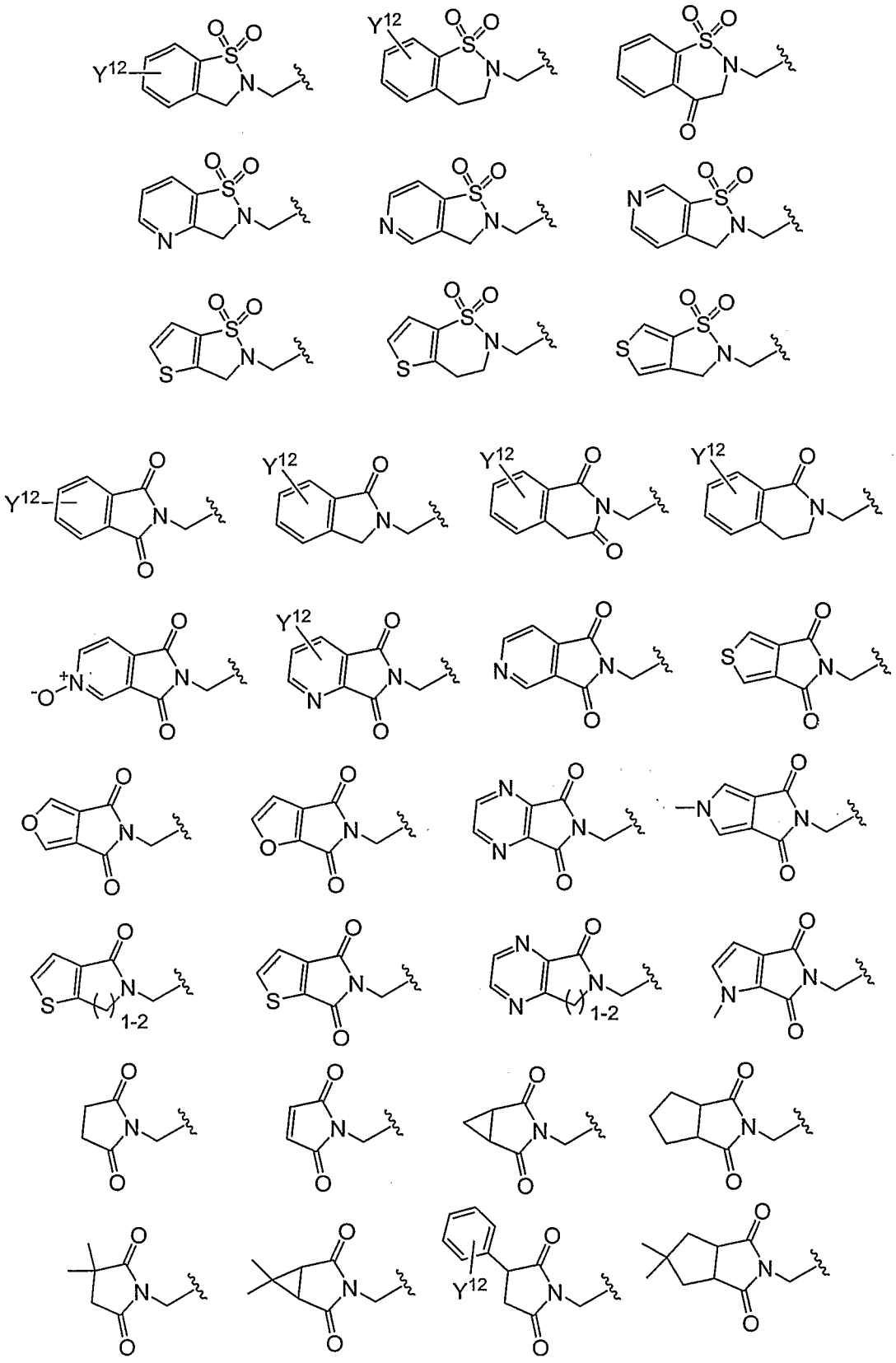
In another embodiment, Y is selected from the group consisting of:

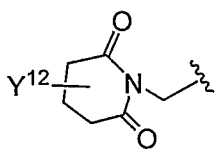
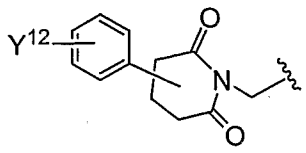
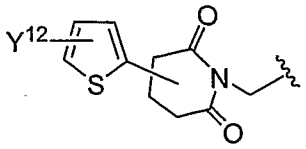
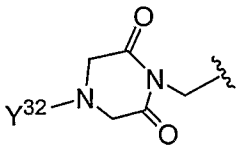
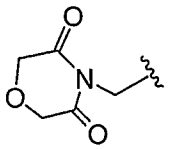
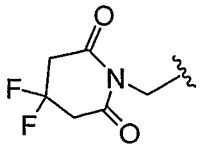
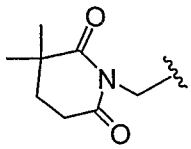
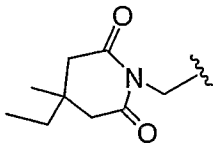
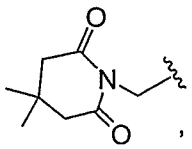
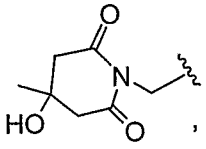
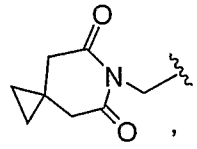
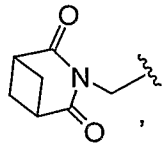
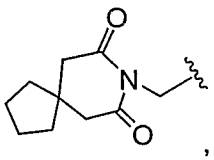
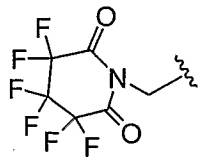
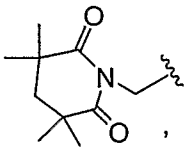
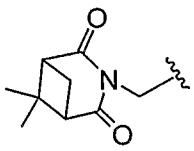




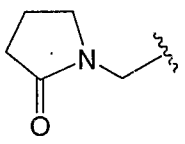
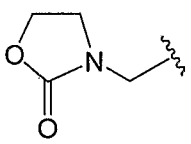
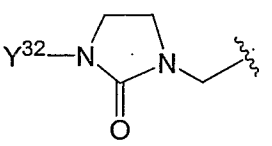
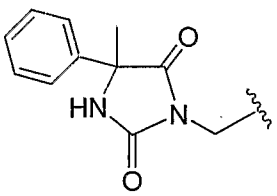
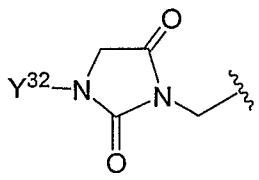
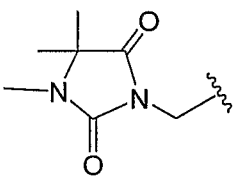
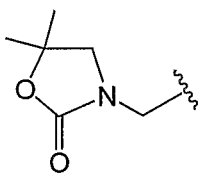
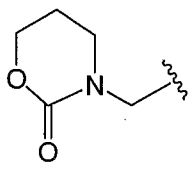
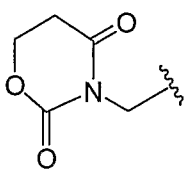
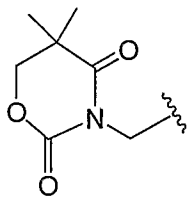
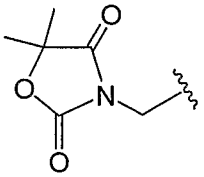
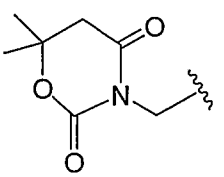
wherein Y^{30} and Y^{31} are selected from the group consisting of:



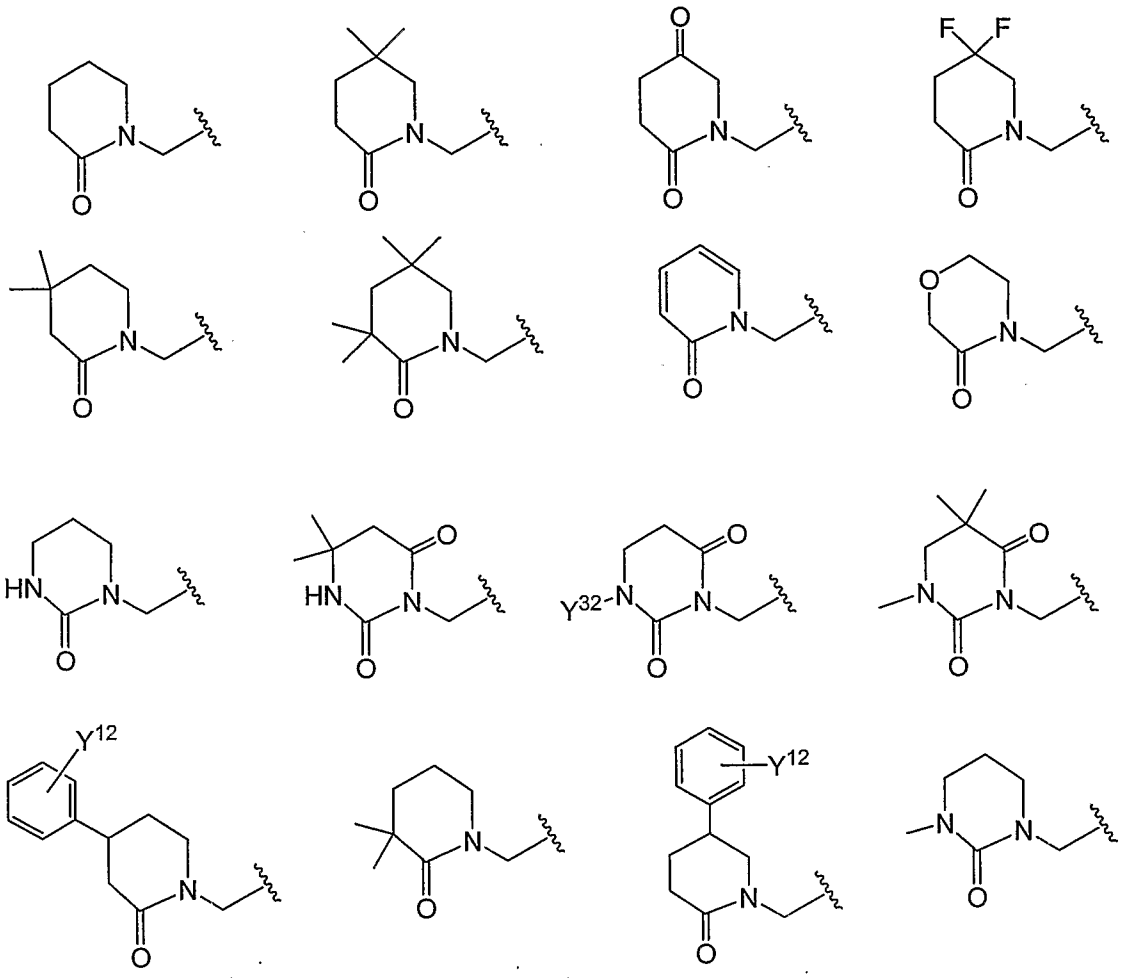

Y12
1-2

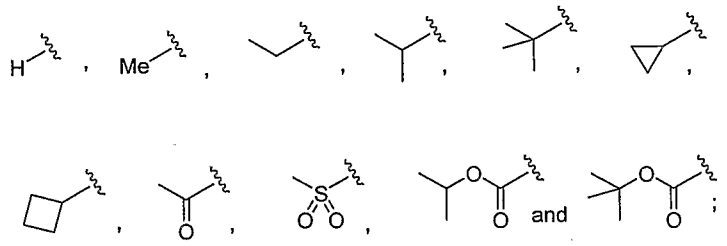
5

,

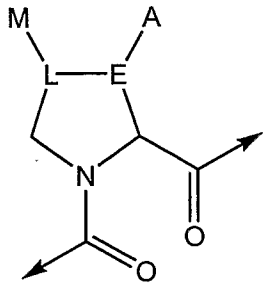


Y^{32} is selected from the group consisting of:

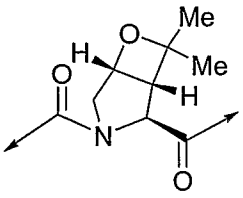
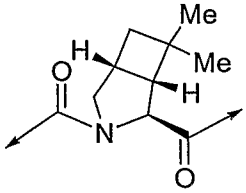
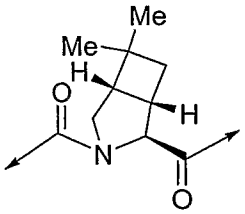
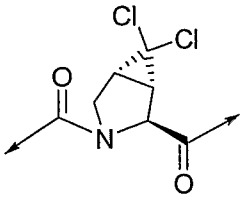
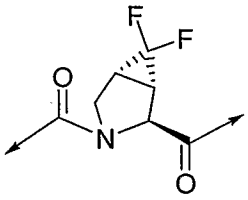
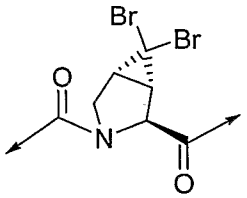
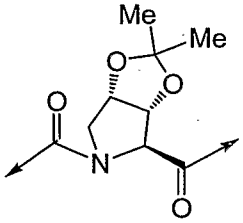
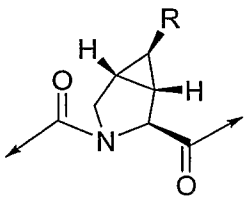
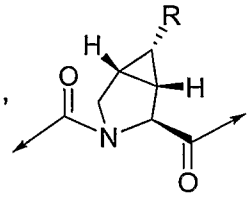
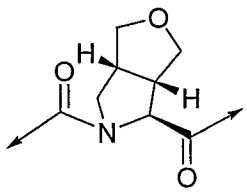
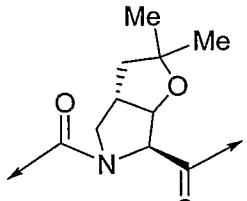
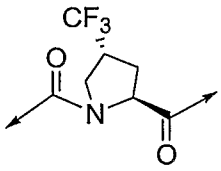
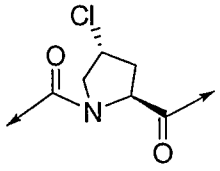
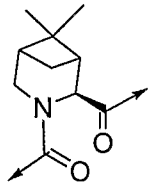
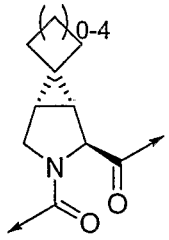


and Y^{12} is selected from H, COOH, COOMe, $CONH_2$, OMe, OH, OCF_3, $OCH(CH_3)_2$, $OC(CH_3)_3$, F, Cl, Br, NH_2, $NHSO_2CH_3$, $NHC(O)CH_3$, $NHCO_2CH_3$, NO_2, SO_2NH_2, CF_3, Me, Et, isopropyl, cyclopropyl, *t*-butyl, phenyl.

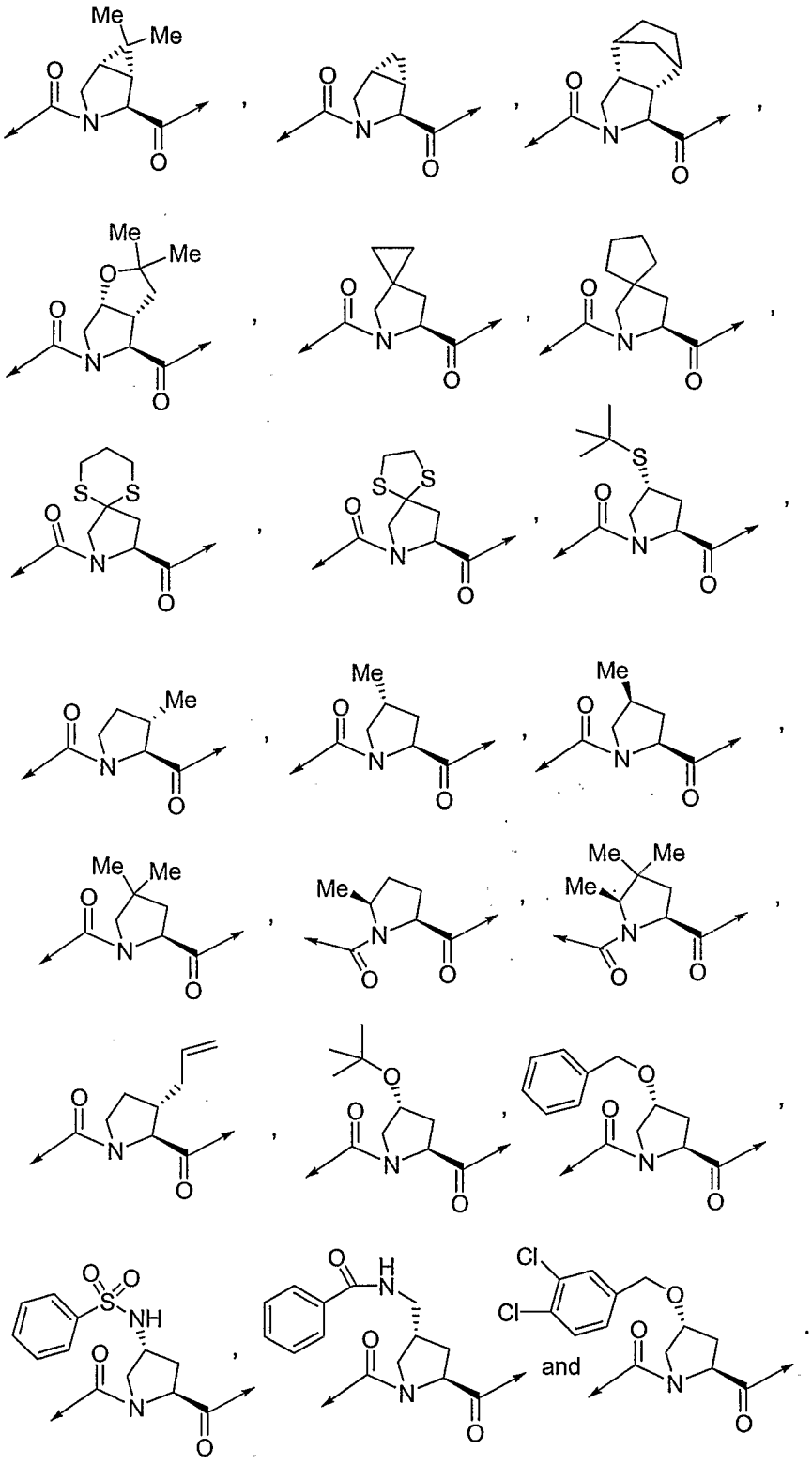
In another embodiment, the moiety:



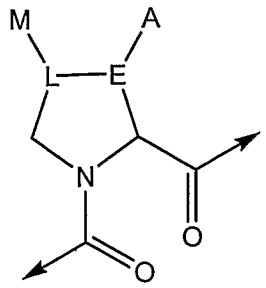
is selected from the following structures:

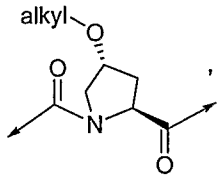
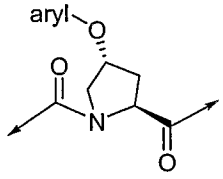
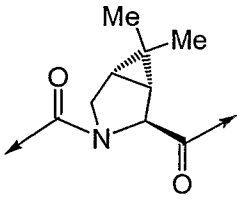
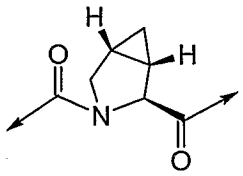
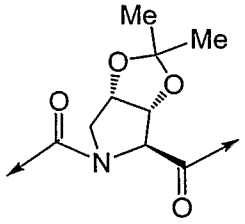
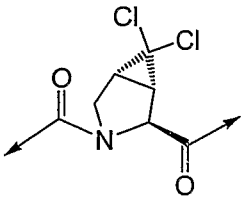
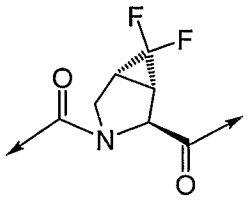
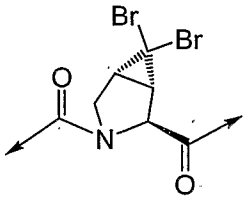
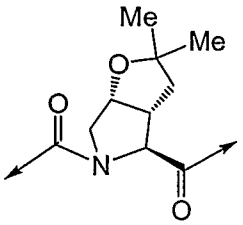
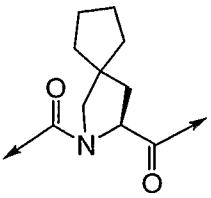
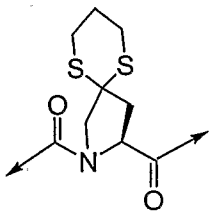
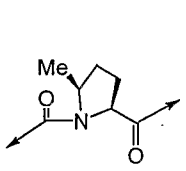
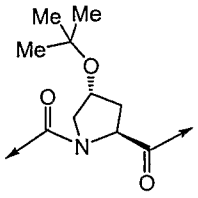
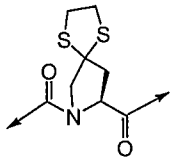
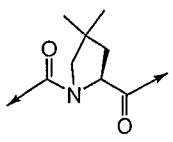
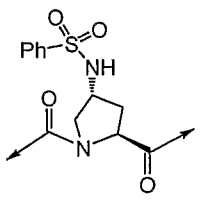
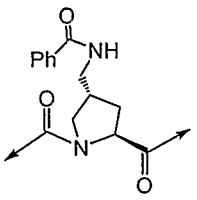
5

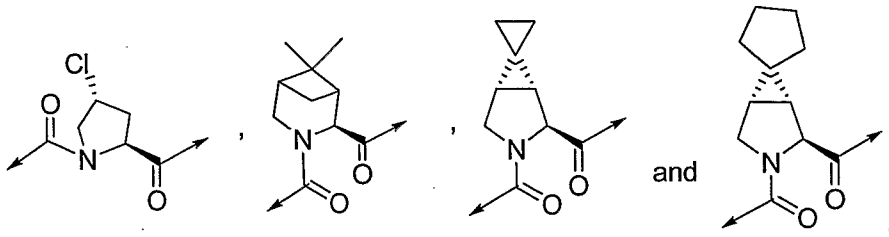


In an additional embodiment, the moiety:

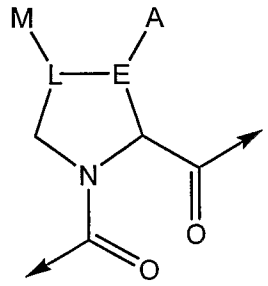


is selected from the following structures:

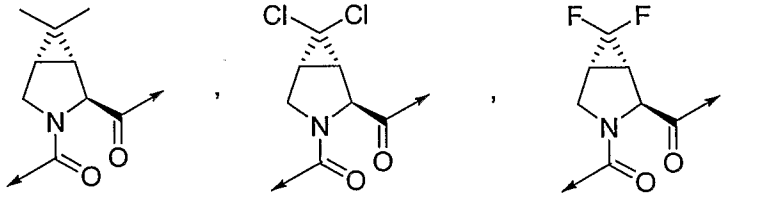


















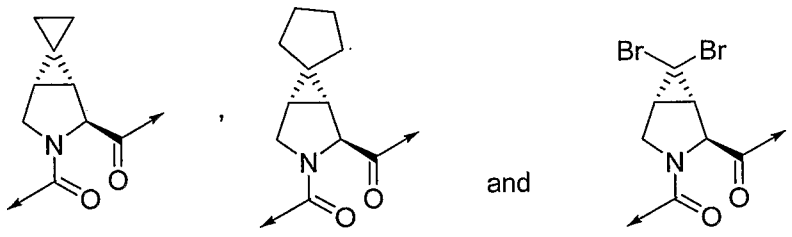


In a still additional embodiment, the moiety:

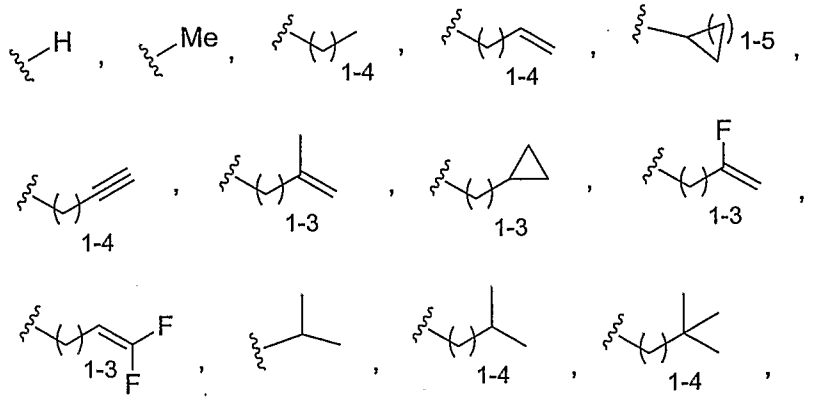


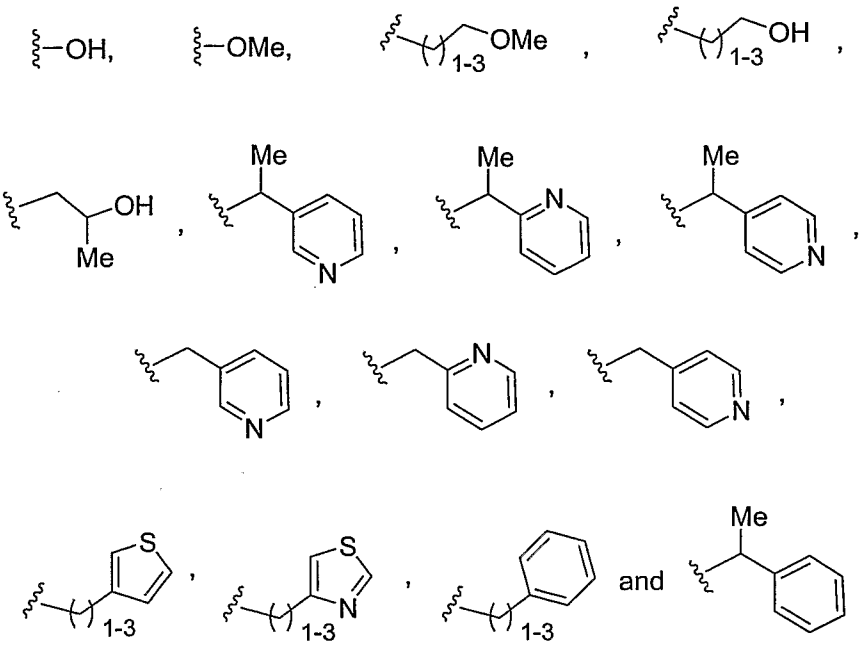
is selected from the following structures:





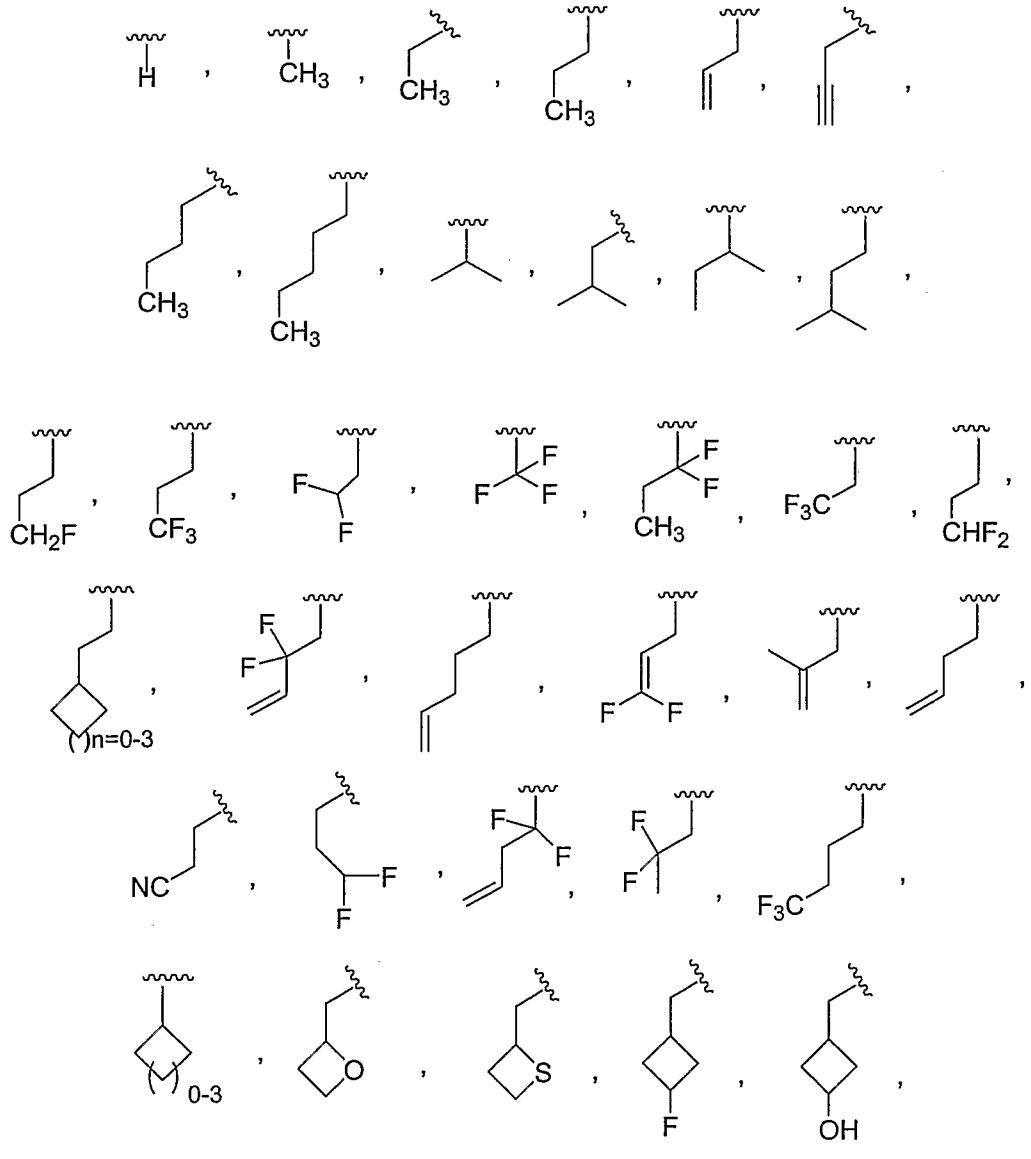
In a further additional embodiment, R^1 is NHR^{10}, where R^{10} is selected from the group consisting of:

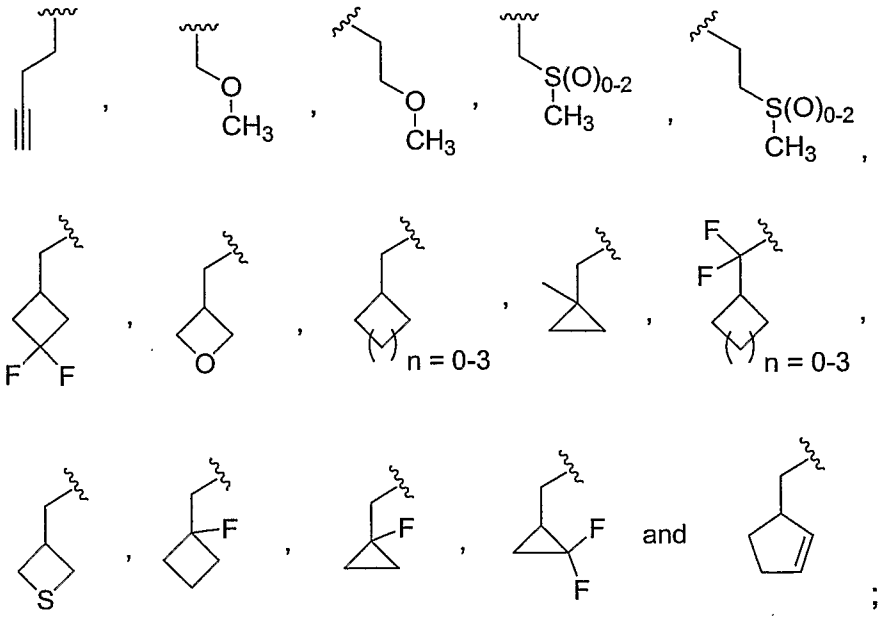




;

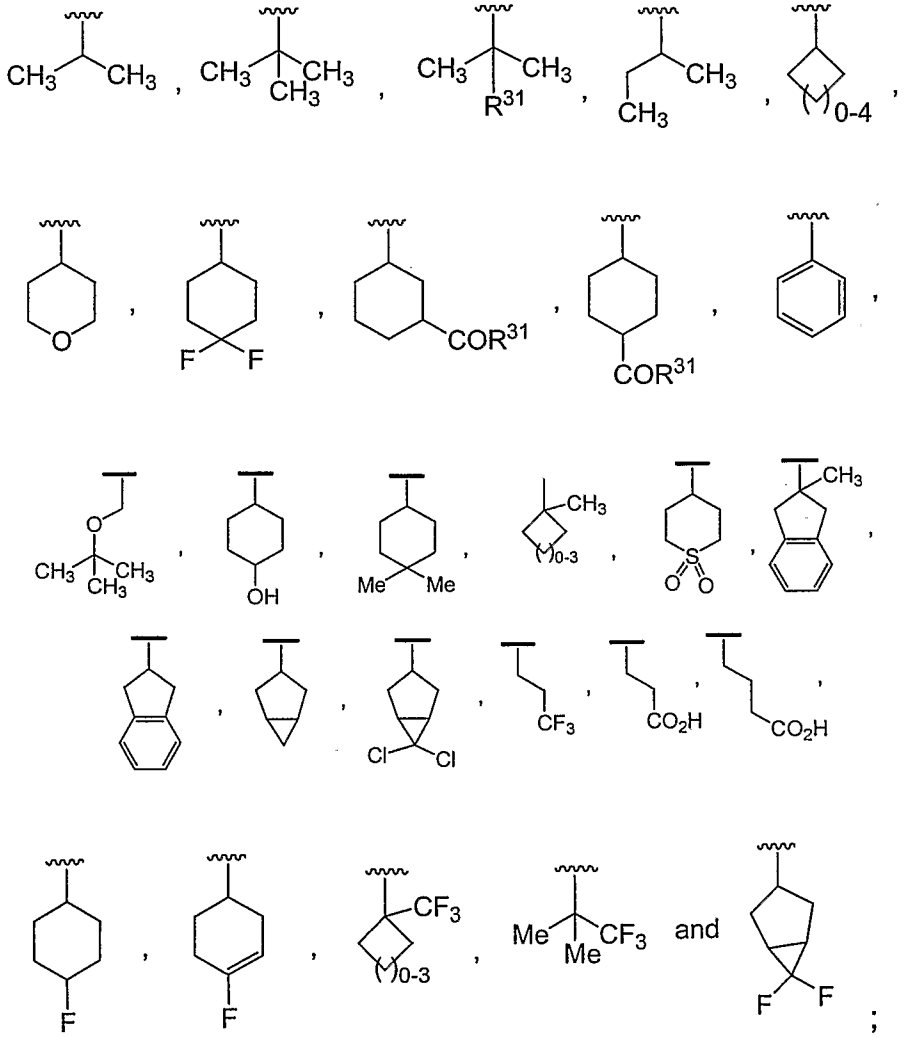
R^2 is selected from the group consisting of the following moieties:





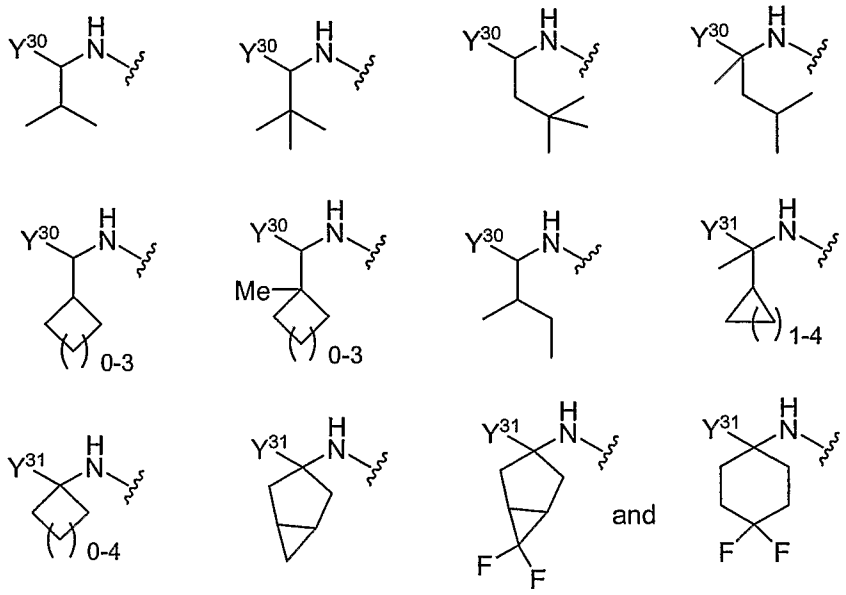
;

R^3 is selected from the group consisting of the following moieties:

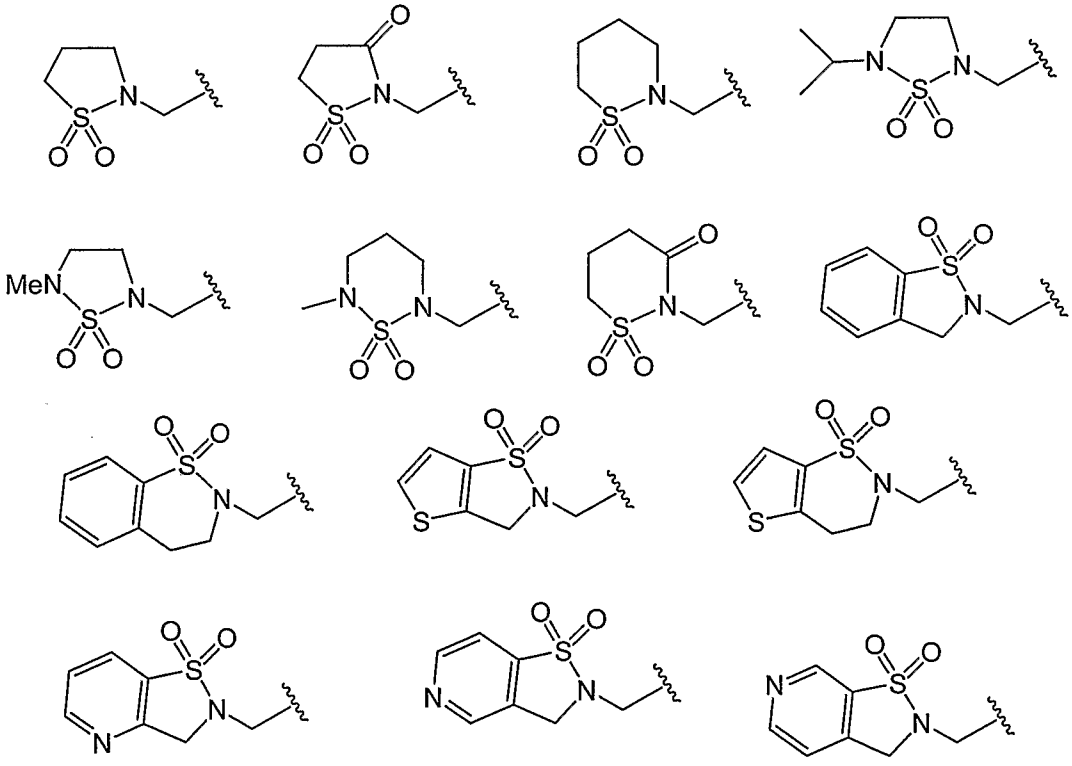


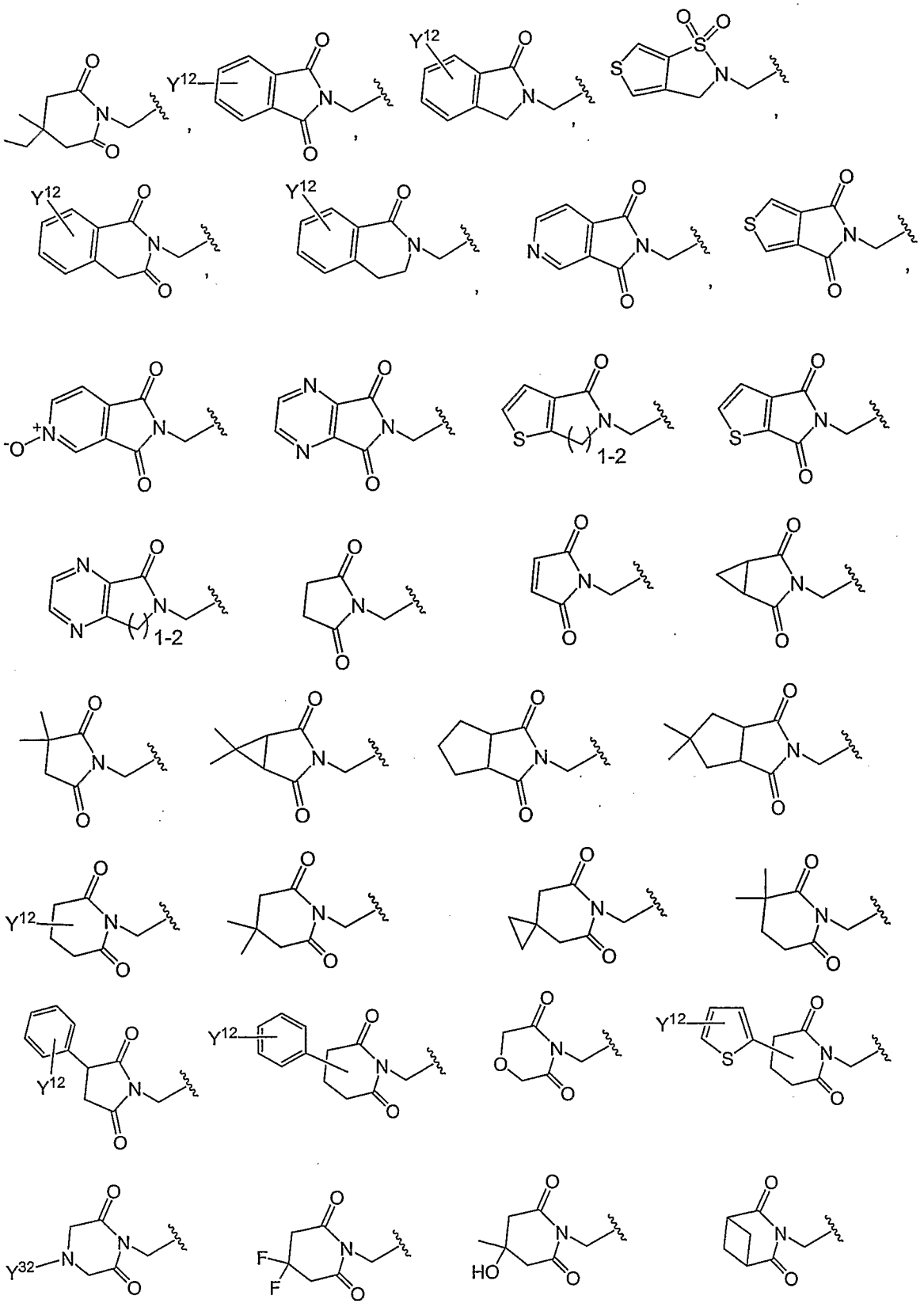
;

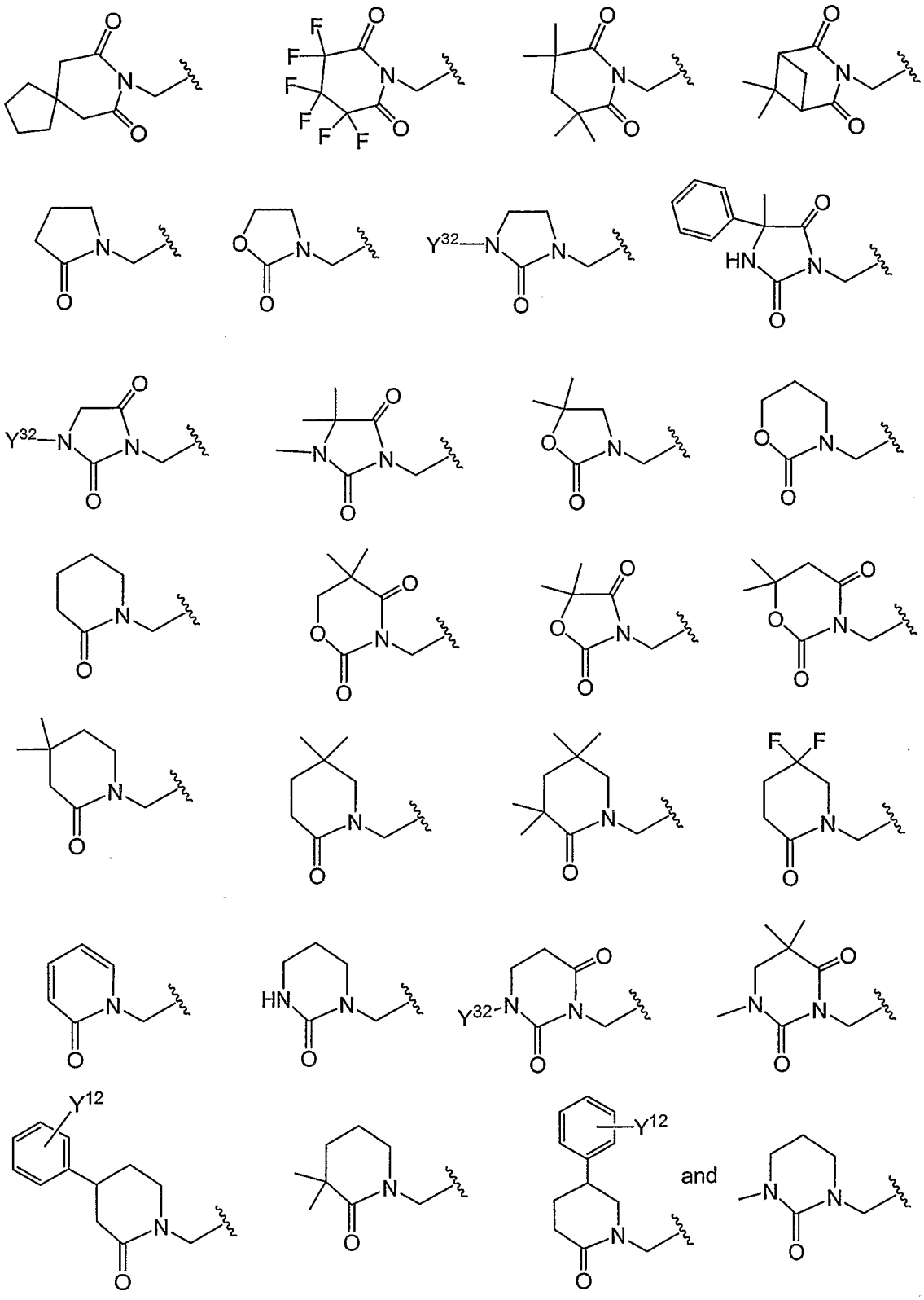
Y is selected from the group consisting of:



wherein Y^{30} and Y^{31} can be the same or different, each being independently selected from the group consisting of:

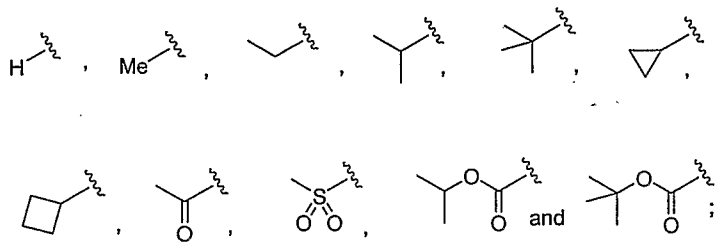



Y12
1-2
Y32
HO



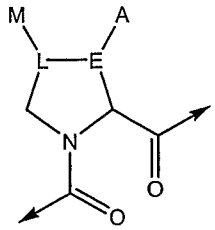
and

wherein Y^{32} is selected from the group consisting of:

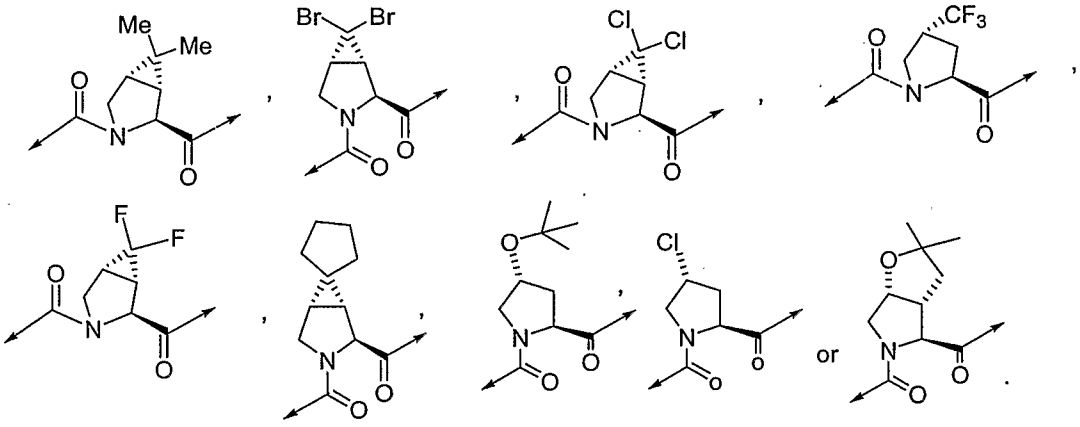


and Y^{12} is selected from H, COOH, COOMe, $CONH_2$, OMe, OH, OCF_3, $OCH(CH_3)_2$, $OC(CH_3)_3$, F, Cl, Br, NH_2, $NHSO_2CH_3$, $NHC(O)CH_3$, $NHCO_2CH_3$, NO_2, SO_2NH_2, CF_3, Me, Et, isopropyl, cyclopropyl, *t*-butyl, or phenyl;

and the moiety:



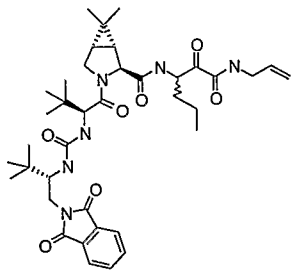
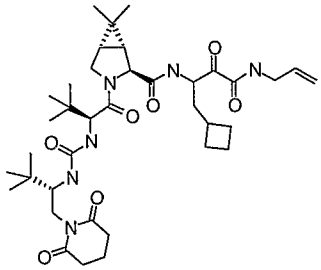
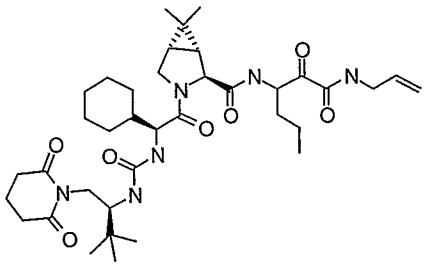
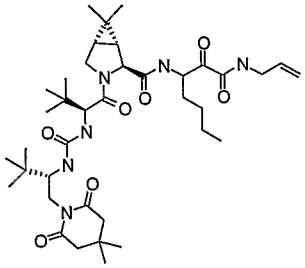
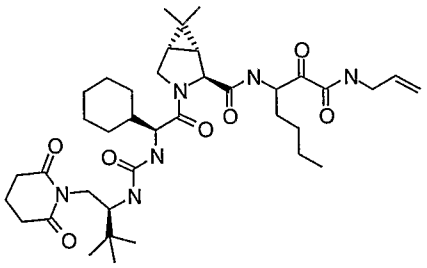
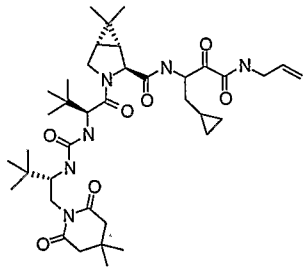
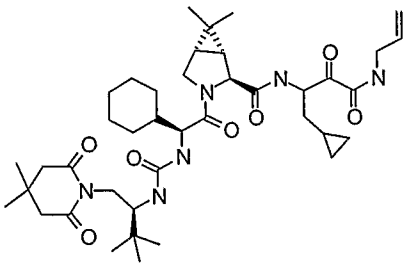
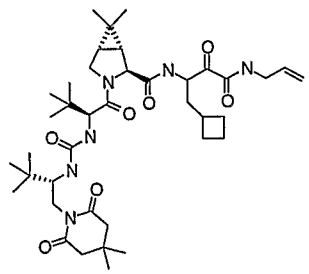
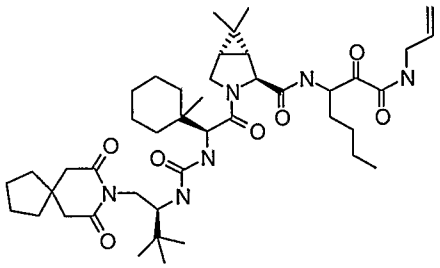
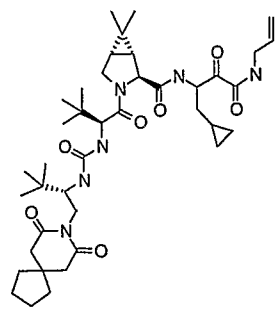
is:

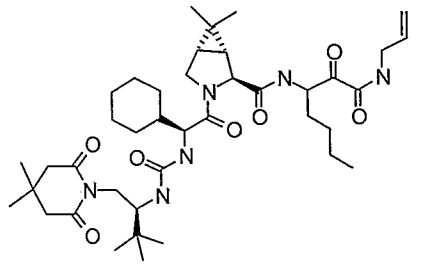
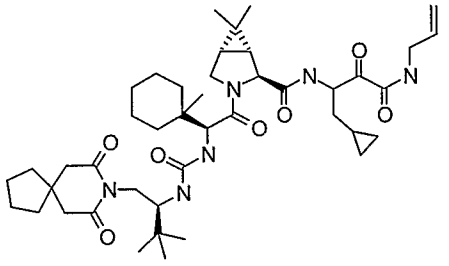
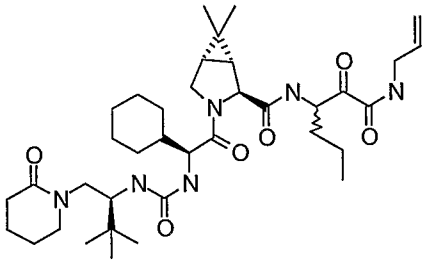
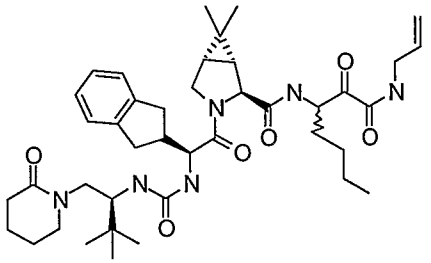
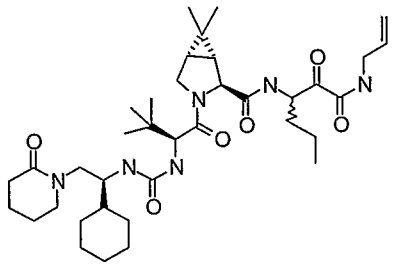
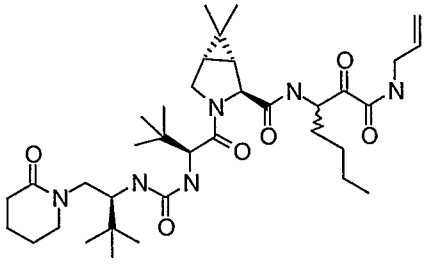
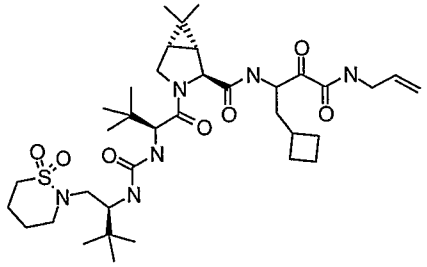
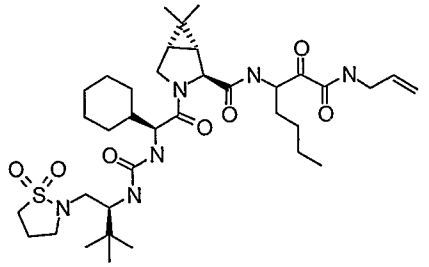


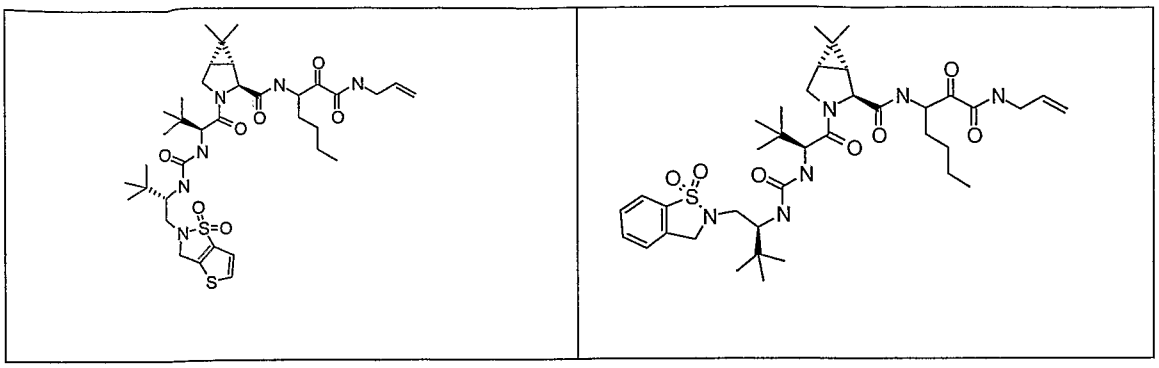
Representative compounds of the invention which exhibit excellent HCV protease inhibitory activity are listed later in this Description in **Tables 1**and **2** along with their biological activity in HCV continuous assay (ranges of Ki* values in nanomolar, nM).

In an additional embodiment, this invention discloses the following compounds in **Table 3**:

Table 3



As used above, and throughout this disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

"Patient" includes both human and animals.

"Mammal" means humans and other mammalian animals.

"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched and comprising about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups contain about 1 to about 12 carbon atoms in the chain. More preferred alkyl groups contain about 1 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkyl chain. "Lower alkyl" means a group having about 1 to about 6 carbon atoms in the chain which may be straight or branched. The term "substituted alkyl" means that the alkyl group may be substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, aryl, cycloalkyl, cyano, hydroxy, alkoxy, alkylthio, amino, -NH(alkyl), -NH(cycloalkyl), -N(alkyl)$_2$, -N(alkyl)$_2$, carboxy and –C(O)O-alkyl. Non-limiting examples of suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl and t-butyl.

"Alkenyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon double bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkenyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkenyl chain. "Lower alkenyl" means about 2 to about 6 carbon

atoms in the chain which may be straight or branched. The term "substituted alkenyl" means that the alkenyl group may be substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkyl. aryl, cycloalkyl, cyano, alkoxy and –S(alkyl). Non-limiting examples of suitable alkenyl groups include ethenyl, propenyl, n-butenyl, 3-methylbut-2-enyl, n-pentenyl, octenyl and decenyl.

"Alkynyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkynyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkynyl chain. "Lower alkynyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkynyl groups include ethynyl, propynyl, 2-butynyl and 3-methylbutynyl. The term "substituted alkynyl" means that the alkynyl group may be substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of alkyl, aryl and cycloalkyl.

"Aryl" means an aromatic monocyclic or multicyclic ring system comprising about 6 to about 14 carbon atoms, preferably about 6 to about 10 carbon atoms. The aryl group can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein. Non-limiting examples of suitable aryl groups include phenyl and naphthyl.

"Heteroaryl" means an aromatic monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the ring atoms is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. Preferred heteroaryls contain about 5 to about 6 ring atoms. The "heteroaryl" can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The prefix aza, oxa or thia before the heteroaryl root name means that at least a nitrogen, oxygen

or sulfur atom respectively, is present as a ring atom. A nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide. Non-limiting examples of suitable heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridone (including N-substituted pyridones), isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalinyl, phthalazinyl, oxindolyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like. The term "heteroaryl" also refers to partially saturated heteroaryl moieties such as, for example, tetrahydroisoquinolyl, tetrahydroquinolyl and the like.

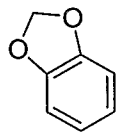
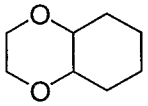
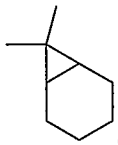
"Aralkyl" or "arylalkyl" means an aryl-alkyl- group in which the aryl and alkyl are as previously described. Preferred aralkyls comprise a lower alkyl group. Non-limiting examples of suitable aralkyl groups include benzyl, 2-phenethyl and naphthalenylmethyl. The bond to the parent moiety is through the alkyl.

"Alkylaryl" means an alkyl-aryl- group in which the alkyl and aryl are as previously described. Preferred alkylaryls comprise a lower alkyl group. Non-limiting example of a suitable alkylaryl group is tolyl. The bond to the parent moiety is through the aryl.

"Cycloalkyl" means a non-aromatic mono- or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms. Preferred cycloalkyl rings contain about 5 to about 7 ring atoms. The cycloalkyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkyls include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Non-limiting examples of suitable multicyclic cycloalkyls include 1-decalinyl, norbornyl, adamantyl and the like, as well as partially saturated species such as, for example, indanyl, tetrahydronaphthyl and the like.

"Halogen" or "halo" means fluorine, chlorine, bromine, or iodine. Preferred are fluorine, chlorine and bromine.

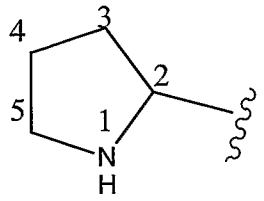
"Ring system substituent" means a substituent attached to an aromatic or non-aromatic ring system which, for example, replaces an available hydrogen on the ring system. Ring system substituents may be the same or different, each being independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, alkylaryl, heteroaralkyl, heteroarylalkenyl, heteroarylalkynyl, alkylheteroaryl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkyl, heterocyclyl, -C(=N-CN)-NH_2, -C(=NH)-NH_2, -C(=NH)-NH(alkyl), Y_1Y_2N-, Y_1Y_2N-alkyl-, $Y_1Y_2NC(O)$-, $Y_1Y_2NSO_2$- and -$SO_2NY_1Y_2$, wherein Y_1 and Y_2 can be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, cycloalkyl, and aralkyl. "Ring system substituent" may also mean a single moiety which simultaneously replaces two available hydrogens on two adjacent carbon atoms (one H on each carbon) on a ring system. Examples of such moiety are methylene dioxy, ethylenedioxy, -$C(CH_3)_2$- and the like which form moieties such as, for example:



and

.

"Heterocyclyl" means a non-aromatic saturated monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclyls contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. Any –NH in a heterocyclyl ring may exist protected such as, for example, as an -N(Boc), -N(CBz), -N(Tos) group and the like; such protections are also considered part of this invention. The heterocyclyl can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The nitrogen or

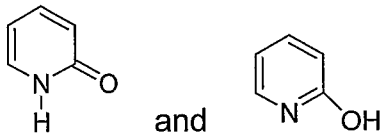
sulfur atom of the heterocyclyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic heterocyclyl rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, lactam, lactone, and the like.

It should be noted that in hetero-atom containing ring systems of this invention, there are no hydroxyl groups on carbon atoms adjacent to a N, O or S, as well as there are no N or S groups on carbon adjacent to another heteroatom. Thus, for example, in the ring:



there is no -OH attached directly to carbons marked 2 and 5.

It should also be noted that tautomeric forms such as, for example, the moieties:



are considered equivalent in certain embodiments of this invention.

"Alkynylalkyl" means an alkynyl-alkyl- group in which the alkynyl and alkyl are as previously described. Preferred alkynylalkyls contain a lower alkynyl and a lower alkyl group. The bond to the parent moiety is through the alkyl. Non-limiting examples of suitable alkynylalkyl groups include propargylmethyl.

"Heteroaralkyl" means a heteroaryl-alkyl- group in which the heteroaryl and alkyl are as previously described. Preferred heteroaralkyls contain a lower alkyl group. Non-limiting examples of suitable aralkyl groups include pyridylmethyl, and quinolin-3-ylmethyl. The bond to the parent moiety is through the alkyl.

"Hydroxyalkyl" means a HO-alkyl- group in which alkyl is as previously defined. Preferred hydroxyalkyls contain lower alkyl. Non-limiting examples of suitable hydroxyalkyl groups include hydroxymethyl and 2-hydroxyethyl.

"Acyl" means an H-C(O)-, alkyl-C(O)- or cycloalkyl-C(O)-, group in which the various groups are as previously described. The bond to the parent moiety is through the carbonyl. Preferred acyls contain a lower alkyl. Non-limiting examples of suitable acyl groups include formyl, acetyl and propanoyl.

"Aroyl" means an aryl-C(O)- group in which the aryl group is as previously described. The bond to the parent moiety is through the carbonyl. Non-limiting examples of suitable groups include benzoyl and 1- naphthoyl.

"Alkoxy" means an alkyl-O- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy and n-butoxy. The bond to the parent moiety is through the ether oxygen.

"Aryloxy" means an aryl-O- group in which the aryl group is as previously described. Non-limiting examples of suitable aryloxy groups include phenoxy and naphthoxy. The bond to the parent moiety is through the ether oxygen.

"Aralkyloxy" means an aralkyl-O- group in which the aralkyl group is as previously described. Non-limiting examples of suitable aralkyloxy groups include benzyloxy and 1- or 2-naphthalenemethoxy. The bond to the parent moiety is through the ether oxygen.

"Alkylthio" means an alkyl-S- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkylthio groups include methylthio and ethylthio. The bond to the parent moiety is through the sulfur.

"Arylthio" means an aryl-S- group in which the aryl group is as previously described. Non-limiting examples of suitable arylthio groups include phenylthio and naphthylthio. The bond to the parent moiety is through the sulfur.

"Aralkylthio" means an aralkyl-S- group in which the aralkyl group is as previously described. Non-limiting example of a suitable aralkylthio group is benzylthio. The bond to the parent moiety is through the sulfur.

"Alkoxycarbonyl" means an alkyl-O-CO- group. Non-limiting examples of suitable alkoxycarbonyl groups include methoxycarbonyl and ethoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aryloxycarbonyl" means an aryl-O-C(O)- group. Non-limiting examples of suitable aryloxycarbonyl groups include phenoxycarbonyl and naphthoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aralkoxycarbonyl" means an aralkyl-O-C(O)- group. Non-limiting example of a suitable aralkoxycarbonyl group is benzyloxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Alkylsulfonyl" means an alkyl-S(O_2)- group. Preferred groups are those in which the alkyl group is lower alkyl. The bond to the parent moiety is through the sulfonyl.

"Arylsulfonyl" means an aryl-S(O_2)- group. The bond to the parent moiety is through the sulfonyl.

The term “substituted” means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom’s normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By “stable compound’ or “stable structure” is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term “one or more” or “at least one”, when indicating the number of substituents, compounds, combination agents and the like, refers to at least one, and up to the maximum number of chemically and physically permissible, substituents, compounds, combination agents and the like, that are present or added, depending on the context. Such techniques and knowledge are well known within the skills of the concerned artisan.

The term “optionally substituted” means optional substitution with the specified groups, radicals or moieties.

The term "isolated" or "in isolated form" for a compound refers to the physical state of said compound after being isolated from a synthetic process or natural source or combination thereof. The term "purified" or "in purified form" for a compound refers to the physical state of said compound after being obtained from a purification process or processes described herein or well known to the skilled artisan, in sufficient purity to be characterizable by

standard analytical techniques described herein or well known to the skilled artisan.

It should also be noted that any carbon or heteroatom with unsatisfied valences in the text, schemes, examples and Tables herein is assumed to have the hydrogen atom(s) to satisfy the valences.

When a functional group in a compound is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by reference to standard textbooks such as, for example, T. W. Greene *et al*, *Protective Groups in organic Synthesis* (1991), Wiley, New York.

When any variable (e.g., aryl, heterocycle, R^2, etc.) occurs more than one time in any constituent or in Formula 1, its definition on each occurrence is independent of its definition at every other occurrence.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

Prodrugs and solvates of the compounds of the invention are also contemplated herein. The term "prodrug", as employed herein, denotes a compound that is a drug precursor which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of Formula 1 or a salt and/or solvate thereof. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design,* (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press, both of which are incorporated herein by reference thereto.

"Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the

crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H_2O.

"Effective amount" or "therapeutically effective amount" is meant to describe an amount of compound or a composition of the present invention effective in inhibiting the CDK(s) and thus producing the desired therapeutic, ameliorative, inhibitory or preventative effect.

The compounds of Formula 1 can form salts which are also within the scope of this invention. Reference to a compound of Formula 1 herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of Formula 1 contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful. Salts of the compounds of the Formula 1 may be formed, for example, by reacting a compound of Formula 1 with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) and the like. Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl *et al*, Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and Use.* (2002) Zurich: Wiley-VCH; S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977)

66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamines, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (e.g. methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, and dibutyl sulfates), long chain halides (e.g. decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Pharmaceutically acceptable esters of the present compounds include the following groups: (1) carboxylic acid esters obtained by esterification of the hydroxy groups, in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (for example, acetyl, n-propyl, t-butyl, or n-butyl), alkoxyalkyl (for example, methoxymethyl), aralkyl (for example, benzyl), aryloxyalkyl (for example, phenoxymethyl), aryl (for example, phenyl optionally substituted with, for example, halogen, C_{1-4}alkyl, or C_{1-4}alkoxy or amino); (2) sulfonate esters, such as alkyl- or aralkylsulfonyl (for example, methanesulfonyl); (3) amino acid esters (for example, L-valyl or L-isoleucyl); (4) phosphonate esters and (5) mono-, di- or triphosphate esters. The phosphate esters may be further esterified by, for example, a C_{1-20} alcohol or reactive derivative thereof, or by a 2,3-di (C_{6-24})acyl glycerol.

Compounds of Formula 1, and salts, solvates, esters and prodrugs thereof, may exist in their tautomeric form (for example, as an amide or imino

ether). All such tautomeric forms are contemplated herein as part of the present invention.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates, esters and prodrugs of the compounds as well as the salts and solvates of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention, as are positional isomers (such as, for example, 4-pyridyl and 3-pyridyl). Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the *IUPAC* 1974 Recommendations. The use of the terms "salt", "solvate" "prodrug" and the like, is intended to equally apply to the salt, solvate and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates or prodrugs of the inventive compounds.

Polymorphic forms of the compounds of Formula I, and of the salts, solvates, esters and prodrugs of the compounds of Formula I, are intended to be included in the present invention.

It is to be understood that the utility of the compounds of Formula 1 for the therapeutic applications discussed herein is applicable to each compound by itself or to the combination or combinations of one or more compounds of Formula 1 as illustrated, for example, in the next immediate paragraph. The same understanding also applies to pharmaceutical composition(s) comprising such compound or compounds and method(s) of treatment involving such compound or compounds.

The compounds according to the invention can have pharmacological properties; in particular, the compounds of Formula 1 can be inhibitors of HCV protease, each compound by itself or one or more compounds of Formula 1 can be combined with one or more compounds selected from within Formula 1. The compound(s) can be useful for treating diseases such as, for example, HCV, HIV, (AIDS, Acquired Immune Deficiency Syndrome), and related

disorders, as well as for modulating the activity of hepatitis C virus (HCV) protease, preventing HCV, or ameliorating one or more symptoms of hepatitis C.

The compounds of Formula 1 may be used for the manufacture of a medicament to treat disorders associated with the HCV protease, for example, the method comprising bringing into intimate contact a compound of Formula 1 and a pharmaceutically acceptable carrier.

In another embodiment, this invention provides pharmaceutical compositions comprising the inventive compound or compounds as an active ingredient. The pharmaceutical compositions generally additionally comprise at least one pharmaceutically acceptable carrier diluent, excipient or carrier (collectively referred to herein as carrier materials). Because of their HCV inhibitory activity, such pharmaceutical compositions possess utility in treating hepatitis C and related disorders.

In yet another embodiment, the present invention discloses methods for preparing pharmaceutical compositions comprising the inventive compounds as an active ingredient. In the pharmaceutical compositions and methods of the present invention, the active ingredients will typically be administered in admixture with suitable carrier materials suitably selected with respect to the intended form of administration, i.e. oral tablets, capsules (either solid-filled, semi-solid filled or liquid filled), powders for constitution, oral gels, elixirs, dispersible granules, syrups, suspensions, and the like, and consistent with conventional pharmaceutical practices. For example, for oral administration in the form of tablets or capsules, the active drug component may be combined with any oral non-toxic pharmaceutically acceptable inert carrier, such as lactose, starch, sucrose, cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, talc, mannitol, ethyl alcohol (liquid forms) and the like. Moreover, when desired or needed, suitable binders, lubricants, disintegrating agents and coloring agents may also be incorporated in the mixture. Powders and tablets may be comprised of from about 5 to about 95 percent inventive composition.

Suitable binders include starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, carboxymethylcellulose, polyethylene glycol and waxes. Among the lubricants

there may be mentioned for use in these dosage forms, boric acid, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrants include starch, methylcellulose, guar gum and the like.

Sweetening and flavoring agents and preservatives may also be included where appropriate. Some of the terms noted above, namely disintegrants, diluents, lubricants, binders and the like, are discussed in more detail below.

Additionally, the compositions of the present invention may be formulated in sustained release form to provide the rate controlled release of any one or more of the components or active ingredients to optimize the therapeutic effects, i.e. HCV inhibitory activity and the like. Suitable dosage forms for sustained release include layered tablets containing layers of varying disintegration rates or controlled release polymeric matrices impregnated with the active components and shaped in tablet form or capsules containing such impregnated or encapsulated porous polymeric matrices.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injections or addition of sweeteners and pacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier such as inert compressed gas, e.g. nitrogen.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides such as cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein by stirring or similar mixing. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions may take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

The compounds of the invention may also be administered orally, intravenously, intranasally or subcutaneously.

The compounds of the invention may also comprise preparations which are in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active components, e.g., an effective amount to achieve the desired purpose.

The quantity of the inventive active composition in a unit dose of preparation may be generally varied or adjusted from about 1.0 milligram to about 1,000 milligrams, preferably from about 1.0 to about 950 milligrams, more preferably from about 1.0 to about 500 milligrams, and typically from about 1 to about 250 milligrams, according to the particular application. The actual dosage employed may be varied depending upon the patient's age, sex, weight and severity of the condition being treated. Such techniques are well known to those skilled in the art.

Generally, the human oral dosage form containing the active ingredients can be administered 1 or 2 times per day. The amount and frequency of the administration will be regulated according to the judgment of the attending clinician. A generally recommended daily dosage regimen for oral administration may range from about 1.0 milligram to about 1,000 milligrams per day, in single or divided doses.

Some useful terms are described below:

Capsule - refers to a special container or enclosure made of methyl cellulose, polyvinyl alcohols, or denatured gelatins or starch for holding or containing compositions comprising the active ingredients. Hard shell capsules are typically made of blends of relatively high gel strength bone and pork skin gelatins. The capsule itself may contain small amounts of dyes, opaquing agents, plasticizers and preservatives.

Tablet- refers to a compressed or molded solid dosage form containing the active ingredients with suitable diluents. The tablet can be prepared by

compression of mixtures or granulations obtained by wet granulation, dry granulation or by compaction.

Oral gel- refers to the active ingredients dispersed or solubilized in a hydrophillic semi-solid matrix.

Powder for constitution refers to powder blends containing the active ingredients and suitable diluents which can be suspended in water or juices.

Diluent - refers to substances that usually make up the major portion of the composition or dosage form. Suitable diluents include sugars such as lactose, sucrose, mannitol and sorbitol; starches derived from wheat, corn, rice and potato; and celluloses such as microcrystalline cellulose. The amount of diluent in the composition can range from about 10 to about 90% by weight of the total composition, preferably from about 25 to about 75%, more preferably from about 30 to about 60% by weight, even more preferably from about 12 to about 60%.

Disintegrant - refers to materials added to the composition to help it break apart (disintegrate) and release the medicaments. Suitable disintegrants include starches; "cold water soluble" modified starches such as sodium carboxymethyl starch; natural and synthetic gums such as locust bean, karaya, guar, tragacanth and agar; cellulose derivatives such as methylcellulose and sodium carboxymethylcellulose; microcrystalline celluloses and cross-linked microcrystalline celluloses such as sodium croscarmellose; alginates such as alginic acid and sodium alginate; clays such as bentonites; and effervescent mixtures. The amount of disintegrant in the composition can range from about 2 to about 15% by weight of the composition, more preferably from about 4 to about 10% by weight.

Binder - refers to substances that bind or "glue" powders together and make them cohesive by forming granules, thus serving as the "adhesive" in the formulation. Binders add cohesive strength already available in the diluent or bulking agent. Suitable binders include sugars such as sucrose; starches derived from wheat, corn rice and potato; natural gums such as acacia, gelatin and tragacanth; derivatives of seaweed such as alginic acid, sodium alginate and ammonium calcium alginate; cellulosic materials such as methylcellulose and sodium carboxymethylcellulose and hydroxypropylmethylcellulose; polyvinylpyrrolidone; and inorganics such as

magnesium aluminum silicate. The amount of binder in the composition can range from about 2 to about 20% by weight of the composition, more preferably from about 3 to about 10% by weight, even more preferably from about 3 to about 6% by weight.

Lubricant - refers to a substance added to the dosage form to enable the tablet, granules, etc. after it has been compressed, to release from the mold or die by reducing friction or wear. Suitable lubricants include metallic stearates such as magnesium stearate, calcium stearate or potassium stearate; stearic acid; high melting point waxes; and water soluble lubricants such as sodium chloride, sodium benzoate, sodium acetate, sodium oleate, polyethylene glycols and d'l-leucine. Lubricants are usually added at the very last step before compression, since they must be present on the surfaces of the granules and in between them and the parts of the tablet press. The amount of lubricant in the composition can range from about 0.2 to about 5% by weight of the composition, preferably from about 0.5 to about 2%, more preferably from about 0.3 to about 1.5% by weight.

Glident - material that prevents caking and improve the flow characteristics of granulations, so that flow is smooth and uniform. Suitable glidents include silicon dioxide and talc. The amount of glident in the composition can range from about 0.1% to about 5% by weight of the total composition, preferably from about 0.5 to about 2% by weight.

Coloring agents - excipients that provide coloration to the composition or the dosage form. Such excipients can include food grade dyes and food grade dyes adsorbed onto a suitable adsorbent such as clay or aluminum oxide. The amount of the coloring agent can vary from about 0.1 to about 5% by weight of the composition, preferably from about 0.1 to about 1%.

Bioavailability - refers to the rate and extent to which the active drug ingredient or therapeutic moiety is absorbed into the systemic circulation from an administered dosage form as compared to a standard or control.

Conventional methods for preparing tablets are known. Such methods include dry methods such as direct compression and compression of granulation produced by compaction, or wet methods or other special procedures. Conventional methods for making other forms for administration

such as, for example, capsules, suppositories and the like are also well known.

Another embodiment of the invention discloses the use of the inventive compounds or pharmaceutical compositions disclosed above for treatment of diseases such as, for example, hepatitis C and the like. The method comprises administering a therapeutically effective amount of the inventive compound or pharmaceutical composition to a patient having such a disease or diseases and in need of such a treatment.

In yet another embodiment, the compounds of the invention may be used for the treatment of HCV in humans in monotherapy mode or in a combination therapy (e.g., dual combination, triple combination etc.) mode such as, for example, in combination with antiviral and/or immunomodulatory agents. Examples of such antiviral and/or immunomodulatory agents include Ribavirin (from Schering-Plough Corporation, Madison, New Jersey) and Levovirin™ (from ICN Pharmaceuticals, Costa Mesa, California), VP 50406™ (from Viropharma, Incorporated, Exton, Pennsylvania), ISIS 14803™ (from ISIS Pharmaceuticals, Carlsbad, California), Heptazyme™ (from Ribozyme Pharmaceuticals, Boulder, Colorado), VX 497™ (from Vertex Pharmaceuticals, Cambridge, Massachusetts), Thymosin™ (from SciClone Pharmaceuticals, San Mateo, California), Maxamine™ (Maxim Pharmaceuticals, San Diego, California), mycophenolate mofetil (from Hoffman-LaRoche, Nutley, New Jersey), interferon (such as, for example, interferon-alpha, PEG-interferon alpha conjugates) and the like. "PEG-interferon alpha conjugates" are interferon alpha molecules covalently attached to a PEG molecule. Illustrative PEG-interferon alpha conjugates include interferon alpha-2a (Roferon™, from Hoffman La-Roche, Nutley, New Jersey) in the form of pegylated interferon alpha-2a (e.g., as sold under the trade name Pegasys™), interferon alpha-2b (Intron™, from Schering-Plough Corporation) in the form of pegylated interferon alpha-2b (e.g., as sold under the trade name PEG-Intron™), interferon alpha-2c (Berofor Alpha™, from Boehringer Ingelheim, Ingelheim, Germany) or consensus interferon as defined by determination of a consensus sequence of naturally occurring interferon alphas (Infergen™, from Amgen, Thousand Oaks, California).

As stated earlier, the invention includes tautomers, rotamers, enantiomers and other stereoisomers of the inventive compounds also. Thus, as one skilled in the art appreciates, some of the inventive compounds may exist in suitable isomeric forms. Such variations are contemplated to be within the scope of the invention.

Another embodiment of the invention discloses a method of making the compounds disclosed herein. The compounds may be prepared by several techniques known in the art. Illustrative procedures are outlined in the following reaction schemes. The illustrations should not be construed to limit the scope of the invention which is defined in the appended claims. Alternative mechanistic pathways and analogous structures will be apparent to those skilled in the art.

It is to be understood that while the following illustrative schemes describe the preparation of a few representative inventive compounds, suitable substitution of any of both the natural and unnatural amino acids will result in the formation of the desired compounds based on such substitution. Such variations are contemplated to be within the scope of the invention.

For the procedures described below, the following abbreviations are used:

Abbreviations

Abbreviations which are used in the descriptions of the schemes, preparations and the examples that follow are:

THF: Tetrahydrofuran

DMF: N,N-Dimethylformamide

EtOAc: Ethyl acetate

AcOH: Acetic acid

HOOBt: 3-Hydroxy-1,2,3-benzotriazin-4(3H)-one

EDCI: 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

NMM: N-Methylmorpholine

ADDP: 1,1'-(Azodicarbobyl)dipiperidine

DEAD: Diethylazodicarboxylate

DIAD: Diisopropylazodicarboxylate

MeOH: Methanol

EtOH: Ethanol

Et_2O: Diethyl ether

DMSO: Dimethylsulfoxide

HOBt: N-Hydroxybenzotriazole

PyBrOP: Bromo-tris-pyrrolidinophosphonium hexafluorophosphate

DCM: Dichloromethane

DCC: 1,3-Dicyclohexylcarbodiimide

TEMPO: 2,2,6,6-Tetramethyl-1-piperidinyloxy

Phg: Phenylglycine

Chg: Cyclohexylglycine

Bn: Benzyl

Bz: Benzyl

Et: Ethyl

Ph: Phenyl

iBoc: isobutoxycarbonyl

iPr: isopropyl

^tBu or Bu^t: tert-Butyl

Boc: tert-Butyloxycarbonyl

Cbz: Benzyloxycarbonyl

Cp: Cylcopentyldienyl

Ts: p-toluenesulfonyl

Me: Methyl

Ms or Mesyl: Methane sulfonyl

HATU: O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate

DMAP: 4-N,N-Dimethylaminopyridine

Bop: Benzotriazol-1-yl-oxy-tris(dimethylamino)hexafluorophosphate

PCC: Pyridiniumchlorochromate

DIBAL-H: diisopropyl aluminum hydride

rt or RT: Room temperature

quant.: Quantitative yield

h or hr: hour

min: minute

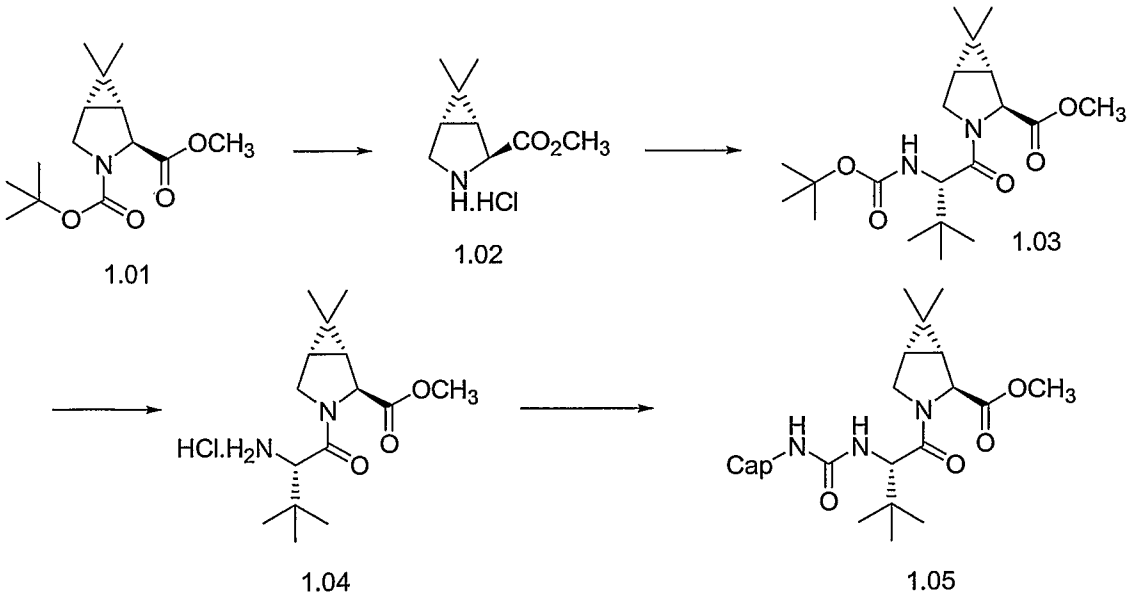
TFA: Trifluoroacetic acid

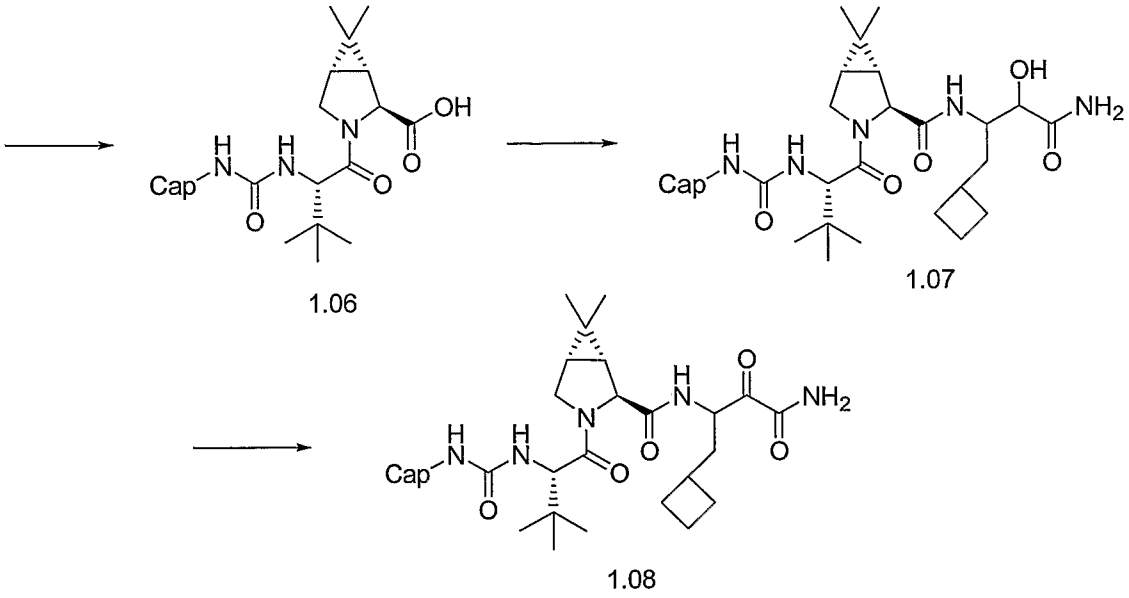
General Schemes for Preparation of Target Compounds

Compounds of the present invention were synthesized using the general schemes (Methods A-E) described below.

Method A:

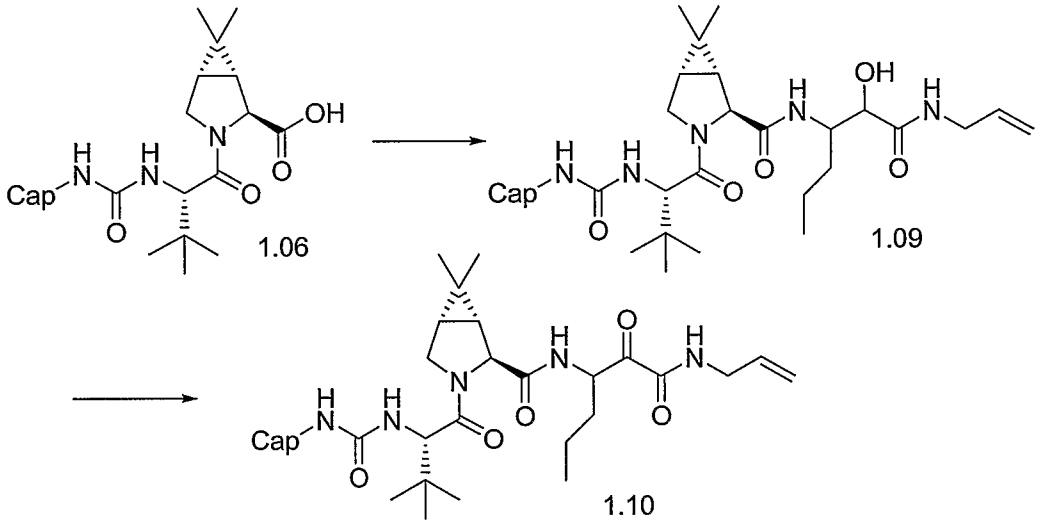
Deprotection of the N-Boc functionality of 1.01 under acidic conditions provided the hydrochloride salt 1.02 which was subsequently coupled with N-Boc-tert-leucine under peptide coupling methodology to afford 1.03. N-Boc deprotection followed by treatment with appropriate isocyanate gave the urea 1.05. Hydrolysis of the methyl ester provided the acid 1.06. Peptide coupling of the acid 1.06 with the appropriate P_1-P' primary amide moiety afforded the hydroxyl amide 1.07. Oxidation (Moffatt or related process - T.T.Tidwell, *Synthesis*, **1990**, 857; or Dess-Martin's periodinane (*J. Org. Chem.*, **1983**, *48*, 4155) resulted in the target compound 1.08.





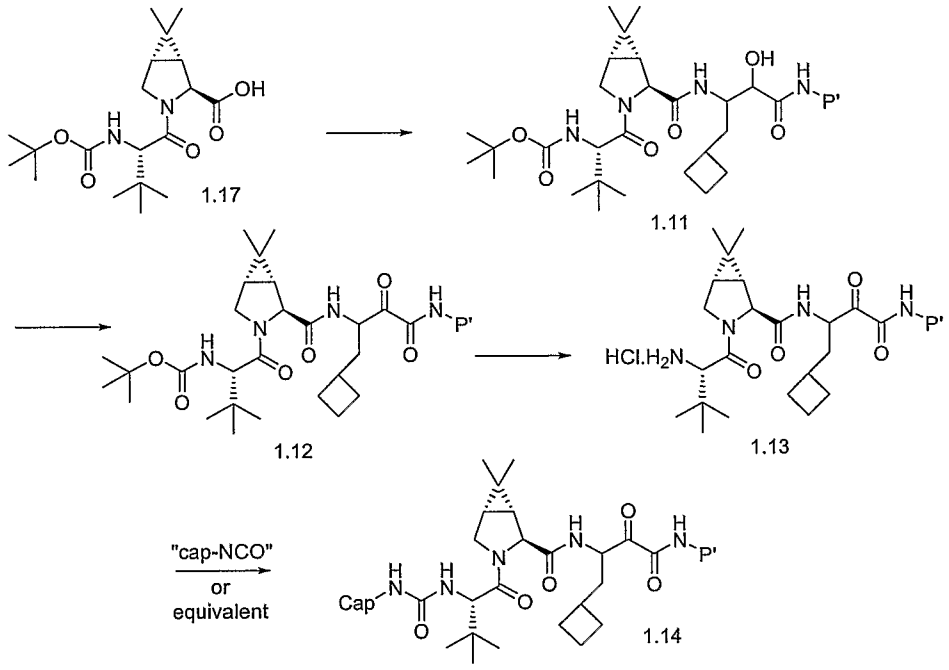
Method B

Peptide coupling of the acid 1.06 with the appropriate P_1-P' secondary amide moiety afforded the hydroxyl amide 1.09. Oxidation (Moffatt or Dess-Martin's) resulted in the target compound 1.10.



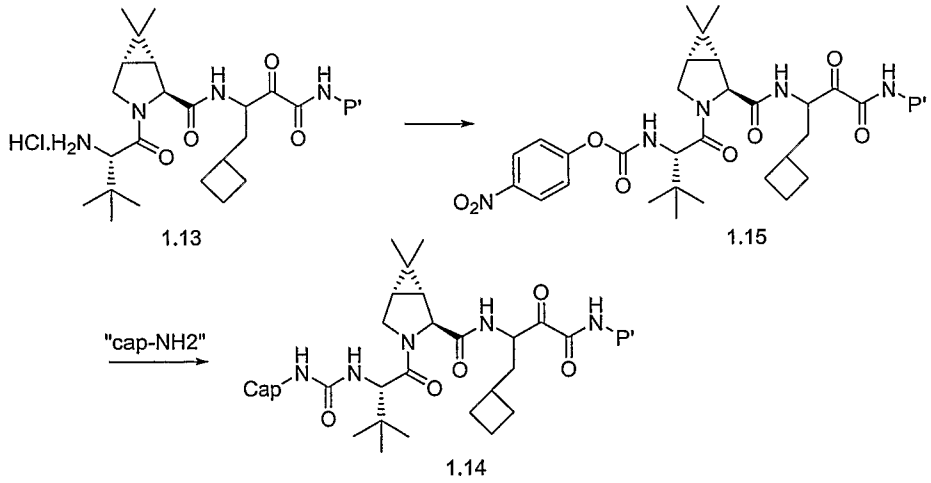
Method C

In another variation, peptide coupling of the N-Boc-P_2-P_3-acid 1.17 with the appropriate P_1-P' amide moiety afforded the hydroxyl amide 1.11. Oxidation (Moffatt or Dess-Martin's) resulted in the keto amide 1.12. Deprotection of the N-Boc functionality gave the hydrochloride salt 1.13. Treatment with a suitable isocyanate (or isocyanate equivalent) resulted in the target compound 1.14.



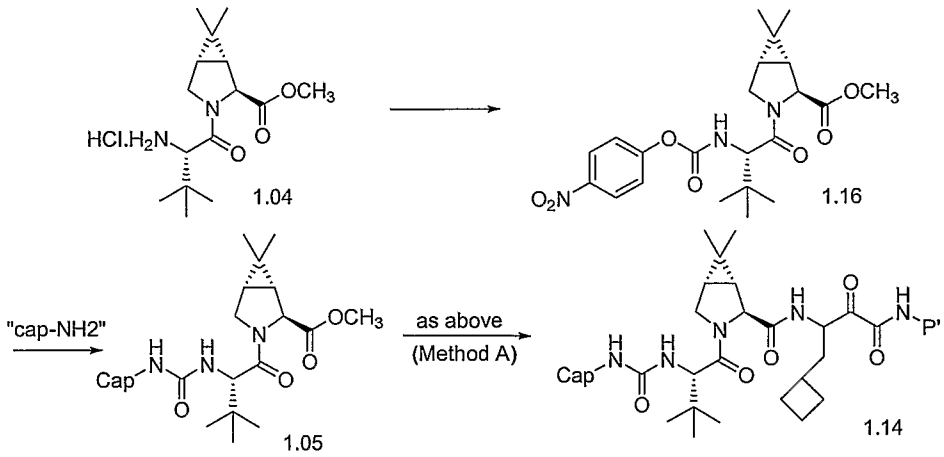
Method D

In yet another variation, the hydrochloride salt 1.13 was converted to the 4-nitrophenyl carbamate 1.15 by reaction with 4-nitrophenyl chloroformate. Subsequent treatment with an amine (or amine hydrochloride salt) of choice provided the target compound 1.14.



Method E

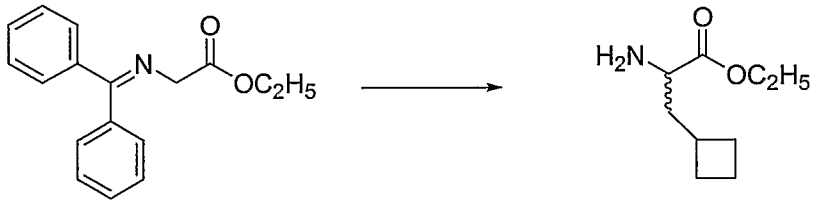
In yet another variation, the dipeptide hydrochloride salt 1.03 was converted to the 4-nitrophenyl carbamate as described above. Treatment with an amine (or amine hydrochloride salt) of choice provided the urea derivative 1.05. Hydrolysis and further elaboration as described in Methods A/B provided the target compounds 1.14.



Preparation of Intermediates

Preparation of Intermediates **10.11** and **10.12:**

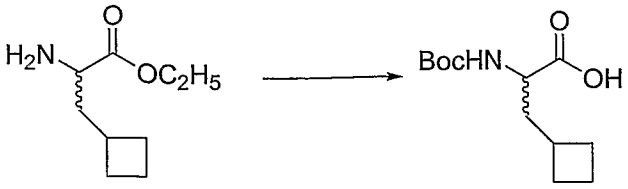
Step 1:



10.01 **10.02**

A stirred solution of ketimine **10.01** (50 g, 187.1 mmol) under N_2 in dry THF (400 mL) was cooled to –78 ^{0}C and treated with 1 M solution of K-^{t}BuO (220 mL, 1.15 equiv.) in THF. The reaction mixture was warmed to 0 ^{0}C and stirred for 1 h and treated with bromomethyl cyclobutane (28 mL, 249 mmol). The reaction mixture was stirred at room temperature for 48 h and concentrated *in vacuo*. The residue was dissolved in Et_2O (300 mL) and treated with aq. HCl (2 M, 300 mL) The resulting solution was stirred at room temperature for 5 h and extracted with Et_2O (1 L). The aqueous layer was made basic to pH ~12-14 with NaOH (50 % aq.) and extracted with CH_2Cl_2 (3x300 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give the pure amine (**10.02**, 18 g) as a colorless oil.

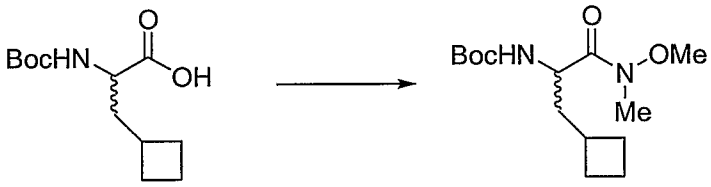
Step 2



10.02 10.03

A solution of the amine **10.02** (18g, 105.2 mmol) at 0 ^{0}C in CH_2Cl_2 (350 mL) was treated with di-*tert*-butyldicarbonate (23 g, 105.4 mmol) and stirred at rt. for 12 h. After the completion of the reaction (TLC), the reaction mixture was concentrated in *vacuo* and the residue was dissolved in THF/H_2O (200 ml, 1:1) and treated with LiOH•H_2O (6.5 g, 158.5 mmol) and stirred at room temperature for 3 h. The reaction mixture was concentrated and the basic aqueous layer was extracted with Et_2O. The aqueous layer was acidified with conc. HCl to pH~1-2 and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield **10.03** as a colorless viscous oil which was used for the next step without any further purification.

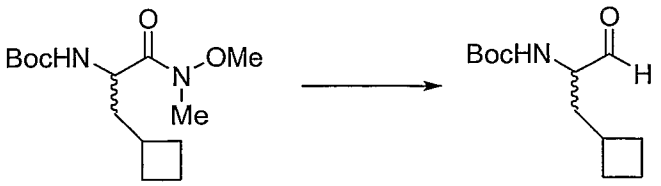
Step 3



10.03 10.04

A solution of the acid **10.03** (15.0 g, 62 mmol) in CH_2Cl_2 (250 mL) was treated with BOP reagent (41.1 g, 93 mmol), N-methyl morpholine (27 mL), N,O-dimethyl hydroxylamine hydrochloride (9.07 g, 93 mmol) and stirred overnight at rt. The reaction mixture was diluted with 1 N aq. HCl (250 mL), and the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x300 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* and purified by chromatography (SiO_2, EtOAc/Hex 2:3) to yield the amide **10.04** (15.0 g) as a colorless solid.

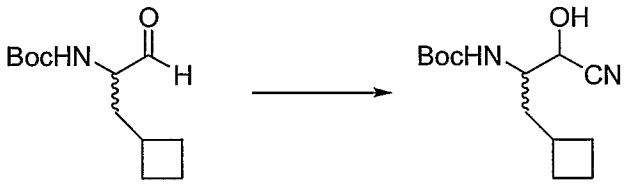
Step 4



10.04 10.05

A solution of the amide **10.04** (15 g, 52.1 mmol) in dry THF (200 mL) was treated dropwise with a solution of $LiAlH_4$ (1M, 93 mL, 93 mmol) at 0 ^{0}C. The reaction mixture was stirred at room temperature for 1 h and carefully quenched at 0 °C with a solution of $KHSO_4$ (10% aq.) and stirred for 0.5 h. The reaction mixture was diluted with aq. HCl (1 M, 150 mL) and extracted with CH_2Cl_2 (3x200 mL), The combined organic layers were washed with aq. HCl (1 M), saturated $NaHCO_3$, brine, and dried ($MgSO_4$). The mixture was filtered and concentrated *in vacuo* to yield **10.05** as a viscous colorless oil (14 g).

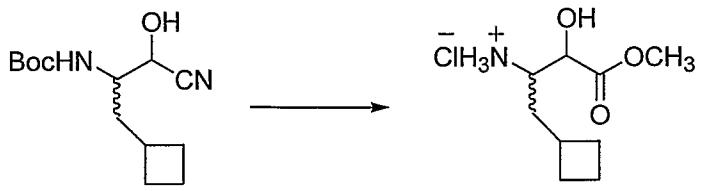
Step 5



10.05 10.06

A solution of the aldehyde **10.05** (14 g, 61.6 mmol) in CH_2Cl_2 (50 mL), was treated with Et_3N (10.73 mL, 74.4 mmol), and acetone cyanohydrin (10.86 g, 127.57 mmol) and stirred at room temperature for 24 hrs. The reaction mixture was concentrated *in vacuo* and diluted with aq. HCl (1 M, 200 mL) and extracted into CH_2Cl_2 (3x200 mL). The combined organic layer were washed with H_2O, brine, dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by chromatography (SiO_2, EtOAc/Hex 1:4) to yield **10.06** (10.3 g) as a colorless liquid

Step 6

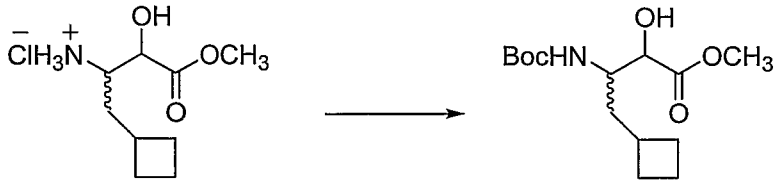


10.06 10.07

Methanol saturated with HCl*, prepared by bubbling HCl gas through CH_3OH (700 ml) at 0 °C, was treated with the cyanohydrin **10.06** and heated to reflux for 24 h. The reaction was concentrated *in vacuo* to yield **10.07**, which was used in the next step without purification.

* Alternatively 6M HCl prepared by addition of AcCl to dry methanol can also be used.

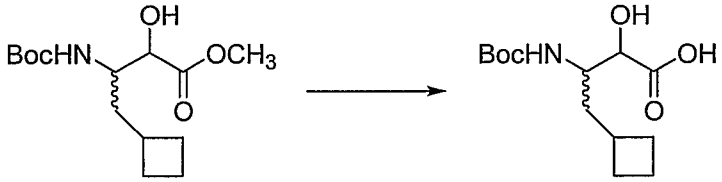
Step 7



10.07 **10.08**

A solution of the amine hydrochloride **10.07** in CH_2Cl_2 (200 mL) was treated with Et_3N (45.0 mL, 315 mmol) and Boc_2O (45.7g, 209 mmol) at –78 °C. The reaction mixture was then stirred at room temperature overnight and diluted with HCl (2 M, 200 mL) and extracted into CH_2Cl_2. The combined organic layer were dried ($MgSO_4$) filtered, concentrated *in vacuo* and purified by chromatography (EtOAc/Hex 1:4) to yield hydroxy ester **10.08**.

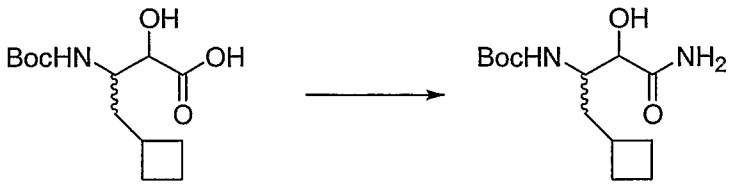
Step 8.



10.08 **10.09**

A solution of methyl ester **10.08** (3g, 10.5 mmol) in THF/H_2O (1:1) was treated with LiOH•H_2O (645 mg, 15.75 mmol) and stirred at rt. for 2 h. The reaction mixture was acidified with aq HCl (1 M, 15 mL) and concentrated *in vacuo*. The residue was dried in vacuum to afford **10.09** in quantitative yield.

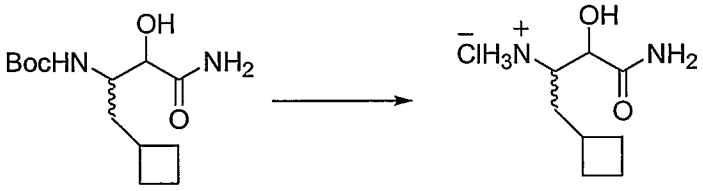
Step 9



10.09 **10.10**

A solution of the acid **10.09** (from above) in CH_2Cl_2 (50 mL) and DMF (25 mL) was treated with NH_4Cl (2.94 g, 55.5 mmol), EDCI (3.15 g, 16.5 mmol), HOOBt (2.69 g, 16.5 mmol), and NMM (4.4 g, 44 mmol). The reaction mixture was stirred at room temperature for 3 d. The solvents were removed under *vacuo* and the residue was diluted with aq. HCl (250 mL) and extracted with CH_2Cl_2. The combined organic layers were washed with aq. Sat'd. $NaHCO_3$, dried ($MgSO_4$) filtered concentrated in vacuo to obtain **10.10**, which was used as it was in the following steps. (Alternatively **10.10** can also be obtained directly by the reaction of **10.06** (4.5 g, 17.7 mmol) with aq. H_2O_2 (10 mL), $LiOH•H_2O$ (820 mg, 20.8 mmol) at 0 °C in 50 mL of CH_3OH for 0.5 h.)

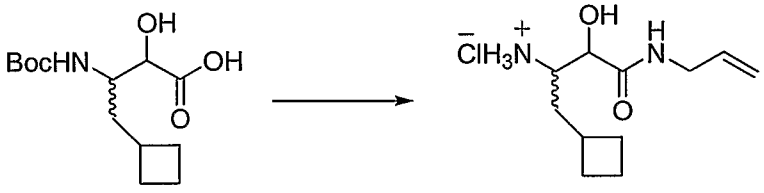
Step 10



10.10 **10.11**

A solution of **10.10** obtained in the previous step was dissolved in 4 N HCl in dioxane and stirred at rt. for 2 h. The reaction mixture was concentrated in *vacuo* to give the intermediate **10.11** as a solid, which was used without further purification.

Step 11

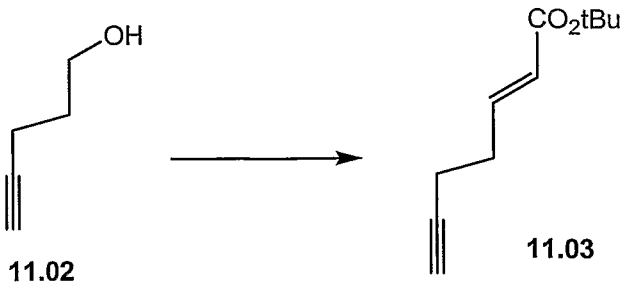


10.09 **10.12**

The required intermediate **10.12** was obtained from compound **10.09** using essentially the procedures described above in Steps 9, 10 with appropriate reagents.

Preparation of Intermediate **11.01**

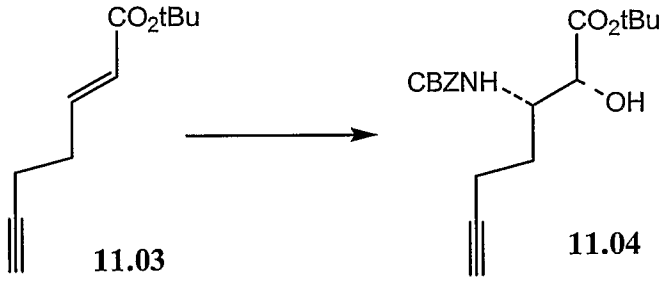
Step 1



11.02 11.03

To a solution of 4-pentyn-1-ol, **11.02** (4.15g; Aldrich) was added Dess-Martin Periodinane (30.25g; Aldrich) and the resulting mixture was stirred for 45min. before the addition of (tert-Butoxycarbonylmethylene)triphenylphosphorane (26.75g; Aldrich). The resulting dark reaction was stirred overnight, diluted with EtOAc), washed with aq. sodium sulfite. sat. aq. NaHCO3, water, brine and dried. The volatiles were removed under reduced pressure and the residue was purified by silica gel column chromatography using 1% EtOAc in hexanes as eluent to give the desired compound, **11.03** (3.92g). Some impure fractions were also obtained but set aside at this time.

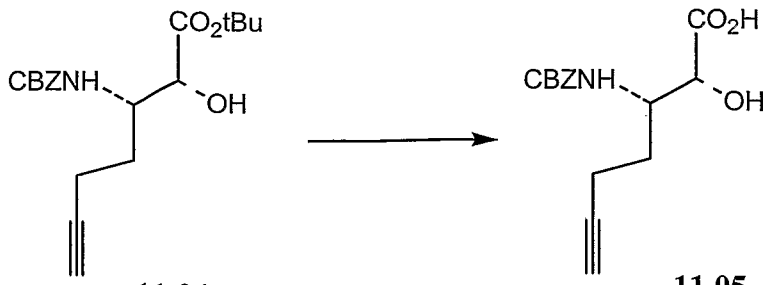
Step 2



11.03 11.04

Using the alkene **11.03** (1.9g) in n-propanol (20ml; Aldrich)), benzyl carbamate (4.95g; Aldrich) in n-propanol (40ml), NaOH (1.29g) in water (79ml), tert-butyl hypochlorite (3.7ml), (DHQ)2PHAL (0.423g; Aldrich)) in n-propanol (37.5ml), and potassium osmate:dehydrate (0.1544g; Aldrich) and the procedure set forth in *Angew. Chem. Int. Ed. Engl* (1998), 35, (23/24), pp. 2813-7.gave a crude product which was purified by silica gel column chromatography using EtOAc:Hexanes (1:5) to give the desired amino alcohol **11.04** (1.37g, 37%) as a white solid.

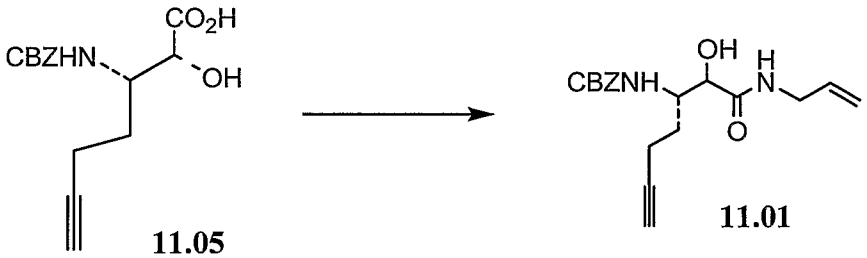
Step 3



11.04 **11.05**

To the ester **11.04** (0.700g) was added 4M HCl in dioxane (20ml; Aldrich) and the resulting mixture was allowed to stand at room temperature overnight. The volatiles were removed under reduced pressure to give the acid **11.05** (0.621g) as a white solid.

Step 4

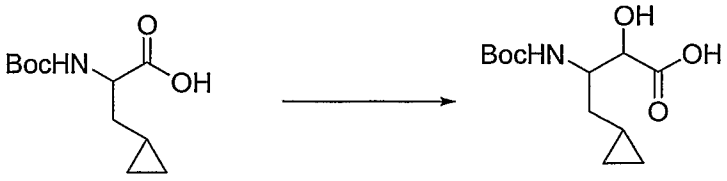


11.05 **11.01**

BOP reagent (3.65g; Sigma) followed by triethylamine (3.45ml) were added to a dichloromethane (20ml) solution of the carboxylic acid **11.05** (2.00g) and allyl amine (0.616ml) at room temperature and the resulting mixture was stirred overnight. The reaction mixture was partitioned between EtOAc and 10% aq. HCl. The organic phase was separated, washed with sat. aq. sodium bicarbonate, water, dried (magnesium sulfate). The crude reaction product was purified by silica gel column chromatography using (EtOAc:Hexanes; 70:30) as eluent to provide the desired amide **11.01** (1.73g) as a viscous yellow oil.

Preparation of Intermediates **12.03** and **12.04**

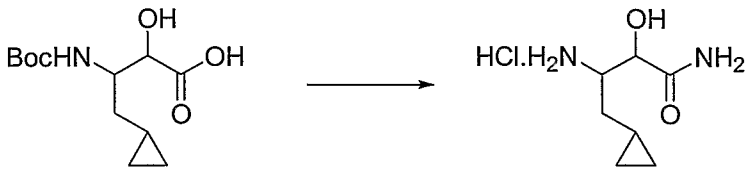
Step 1



12.01 **12.02**

Compound **12.01** was converted to the required material **12.02** using essentially the procedures described for Intermediate **10.11**, Steps 3-8.

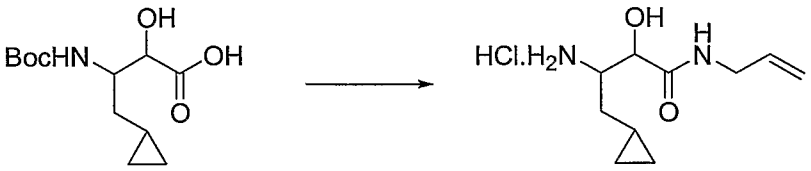
Step 2



12.02 12.03

Compound **12.02** was converted to the required intermediate **12.03** using essentially the procedures described for Intermediate **10.11**, Steps 9, 10..

Step 3

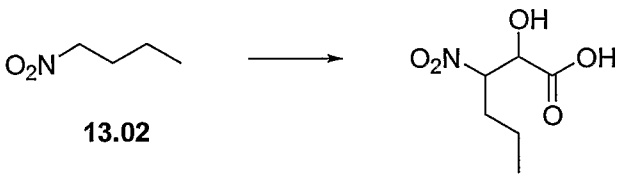


12.02 12.04

Compound **12.02** was converted to the required intermediate **12.03** using essentially the procedures described for Intermediate **10.12**, Step 11.

Preparation of Intermediate **13.01**

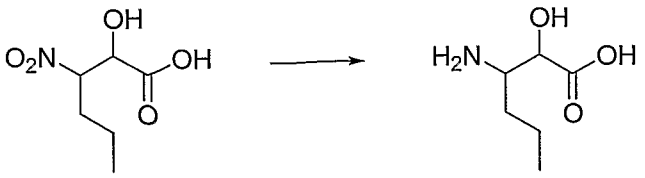
Step 1



13.02 13.03

To a stirred solution of 1-nitrobutane, **13.02** (16.5 g, 0.16 mol) and glyoxylic acid in H_2O (28.1 g, 0.305 mol) and MeOH (122 mL) at 0°C-5°C, was added dropwise triethylamine (93 mL, 0.667 mol) over 2 hrs. The solution was warmed to room temperature, stirred overnight and concentrated to dryness to give an oil. The oil was then dissolved in H_2O and acidified to pH =1 with 10% HCl, followed by extraction with EtOAc. The combined organic solution was washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness to give the product **13.03** (28.1 g, 99% yield).

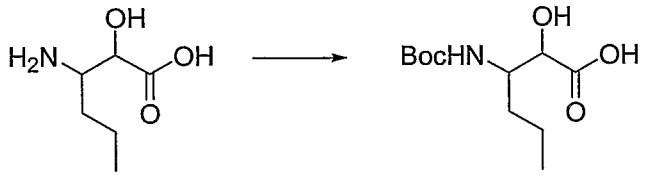
Step 2



13.03 13.04

To a stirred solution of compound **13.03** (240 g, 1.35 mol) in acetic acid (1.25 L) was added 10% Pd/C (37 g). The resulting solution was hydrogenated at 59 psi for 3 hrs and then at 60 psi overnight. The acetic acid was then evaporated and azeotroped 3 times with toluene, then triturated with MeOH and ether. The solution was then filtered and azeotroped twice with toluene to afford **13.04** as an off white solid (131 g, 0.891 mol, 66%).

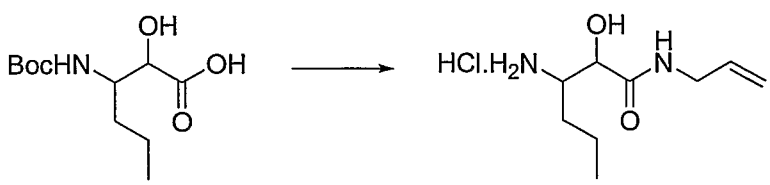
Step 3



13.04 13.05

To a stirred solution of the amino acid **13.04** (2.0 g, 13.6 mmol) in dioxane (10 mL) and H_2O (5mL) at 0°C, was added 1N NaOH solution (4.3 mL, 14.0 mmol). The resulting solution was stirred for 10 minutes, followed by addition of di-*t*-butyldicarbonate (0.110 g, 14.0 mmol) and stirred at 0^0C for 15 minutes. The solution was then warmed to room temperature, stirred for 45 minutes and kept at refrigerator overnight and concentrated to dryness to give a crude material. To the solution of this crude material in EtOAc (100 mL) and ice, was added $KHSO_4$ (3.36 g) and H_2O (32 mL) and stirred for 4-6 minutes. The organic layer was then separated and the aqueous layer was extracted twice with EtOAc and the combined organic layer was washed with water, brine, dried over Na_2SO_4, filtered and concentrated to dryness to give the product **13.05** as a clear gum (3.0 g, 89% yield).

Step 4

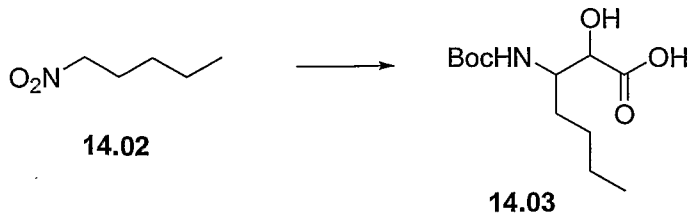


13.05 13.01

Compound **13.05** was converted to the required intermediate **13.01** using essentially the procedures described for Intermediate **10.12**, Step 11.

Preparation of Intermediate **14.01**

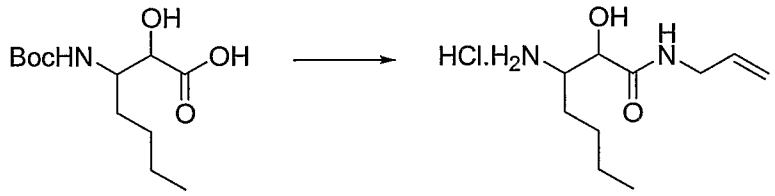
Step 1



14.02 **14.03**

Compound **14.02** was converted to the required material **14.03** using essentially the procedures described for Intermediate **13.01**, Steps 1-3.

Step 2

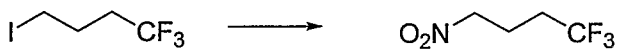


14.03 **14.01**

Compound **14.03** was converted to the required intermediate **14.01** using essentially the procedures described for Intermediate **10.12**, Step 11.

Preparation of Intermediate **15.01**

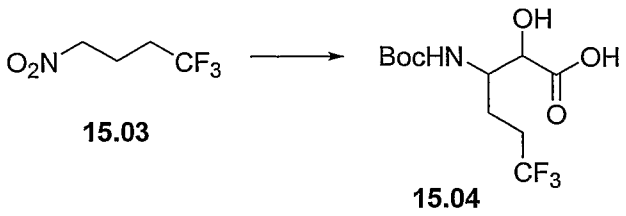
Step 1



15.02 **15.03**

To a suspension of silver nitrite (9 g, 58.5 mmol) in diethyl ether (25 mL) at 0°C was added a solution of 4-iodo-1,1,1-trifluorobutane, **15.02** (10 g, 42.0 mmol) in diethyl ether (25 mL) slowly through an addition funnel (approx. 15 min). The resulting mixture was vigorously stirred at 0°C and warmed to rt. After 50 h, the solid material was filtered off through a celite pad. The resulting diethyl ether solution was concentrated *in vacuo* to give **15.03** as colorless oil, which was used without further purification.

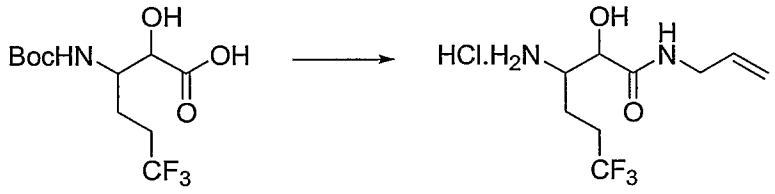
Step 2



15.03 15.04

Compound **15.03** was converted to the required material **15.04** using essentially the procedures described for Intermediate **13.01**, Steps 1-3.

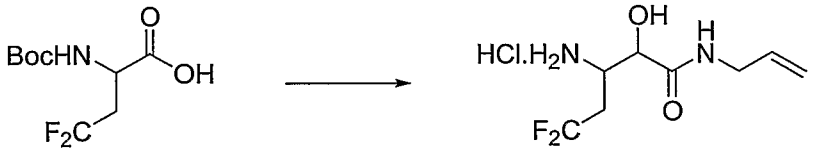
Step 3



15.04 15.01

Compound **15.04** was converted to the required intermediate **15.01** using essentially the procedures described for Intermediate **10.12**, Step 11.

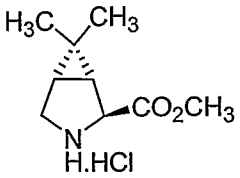
Preparation of Intermediate **16.01**



16.02 16.01

The acid **16.02** (Winkler, D.; Burger, K., *Synthesis*, **1996**, 1419) is processed as described above (preparation of Intermediate **10.12**) to give the expected intermediate **16.01.**

Preparation of Intermediate **20.01**



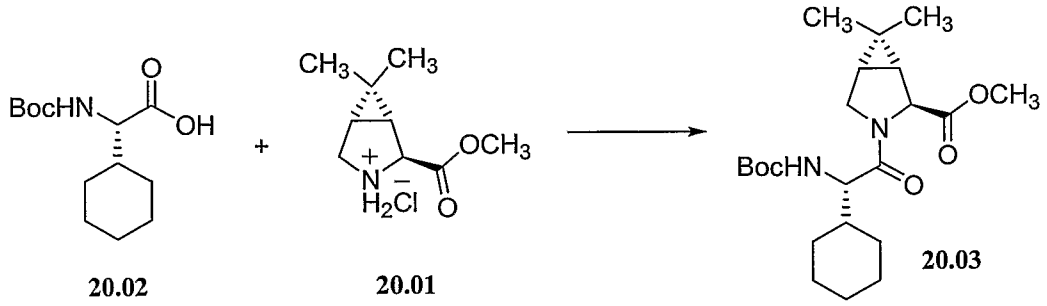
20.01

The amino ester **20.01** was prepared following the method of R. Zhang and J. S. Madalengoitia (*J. Org. Chem.* **1999**, *64*, 330), with the exception that the Boc group was cleaved by the reaction of the Boc-protected amino acid with methanolic HCl (4M HCl in dioxane was also employed for the

deprotection). In a variation of the reported synthesis, the sulfonium ylide was replaced with the corresponding phosphonium ylide.

Preparation of Intermediate **20.04**

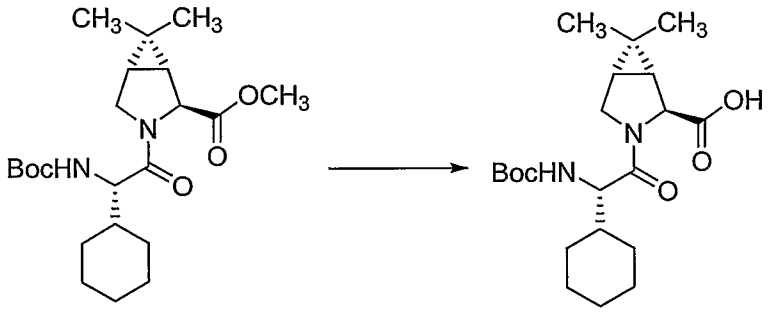
Step 1



20.02 **20.01** **20.03**

A solution of commercial amino acid Boc-Chg-OH, **20.02** (Senn chemicals, 6.64 g, 24.1 mmol) and amine hydrochloride **20.01** (4.5 g, 22 mmol) in CH_2Cl_2 (100 mL) at 0 °C was treated with BOP reagent and stirred at rt. for 15 h. The reaction mixture was concentrated *in vacuo*, then it was diluted with aq. 1 M HCl and extracted into EtOAc (3x200 mL). The combined organic layers were washed with sat'd. $NaHCO_3$ (200 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*, and chromatographed (SiO_2, EtOAc/Hex 3:7) to obtain **20.03** (6.0 g) as a colorless solid.

Step 2

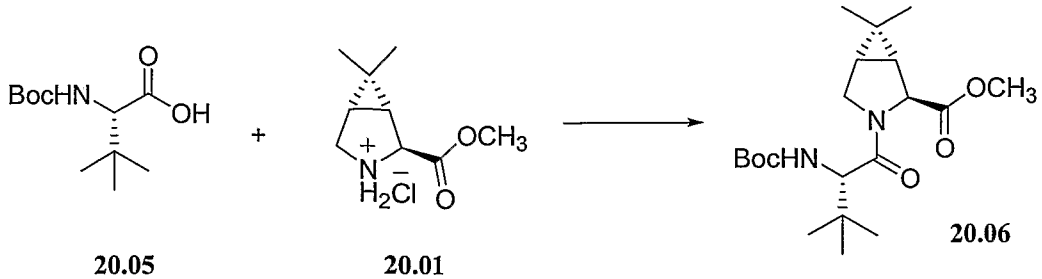


20.03 **20.04**

A solution of methyl ester **20.03** (4.0 g, 9.79 mmol) in THF/H_2O (1:1) was treated with LiOH•H_2O (401 mg, 9.79 mmol) and stirred at rt. for 3 h. The reaction mixture was acidified with aq. HCl and concentrated in *vacuo* to obtain the required intermediate, free acid **20.04**.

Preparation of Intermediate **20.08**

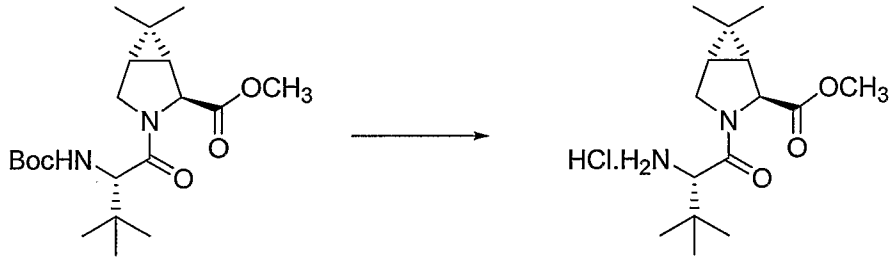
Step 1



20.05 20.01 20.06

A solution of Boc-tert-Leu **20.05** (Fluka, 5.0 g 21.6 mmol) in dry CH_2Cl_2/DMF (50 mL, 1:1) was cooled to 0 °C and treated with the amine salt **20.01** (5.3 g, 25.7 mmol), NMM (6.5 g, 64.8 mmol) and BOP reagent (11.6 g, 25.7 mmol). The reaction was stirred at rt. for 24h, diluted with aq. HCl (1 M) and extracted with CH_2Cl_2. The combined organic layers were washed with HCl (aq, 1 M), sat'd. $NaHCO_3$, brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* and purified by chromatography (SiO2, Acetone/Hexane 1:5) to yield **20.06** as a colorless solid.

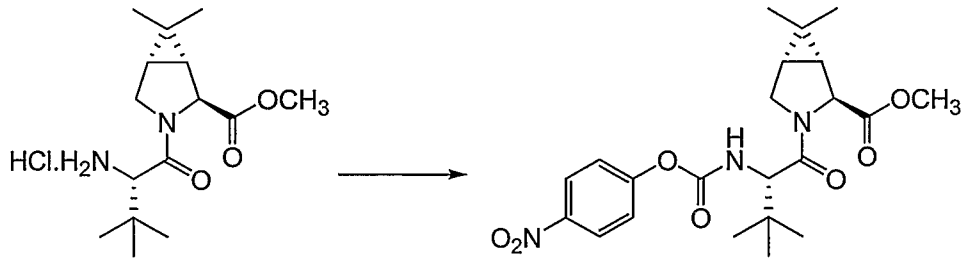
Step 2



20.06 20.07

A solution of methyl ester **20.06** (4.0 g, 10.46 mmol) was dissolved in 4M HCl in dioxane and stirred at rt. for 3 h. The reaction mixture was concentrated in *vacuo* to obtain the amine hydrochloride salt, **20.07** which was used without purification.

Step 3



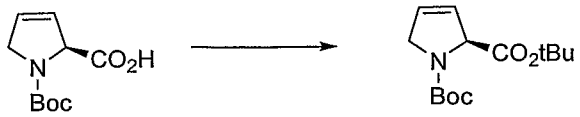
20.07 20.08

A solution of the amine salt **20.07** (840 mg, 2.64 mmol) in THF (14 mL)/acetonitrile (2 mL) was cooled to 0°C. 4-Nitrophenylchloroformate (800

mg, 3.96 mmol) was added followed by pyridine (0.64 mL, 7.92 mmol). The reaction was slowly warmed to room temperature over 3 hrs when TLC indicated reaction completion. Diethyl ether (50 mL) was added and the resulting precipitate was filtered off. The filtrate was washed with saturated ammonium chloride solution (1 x), brine (1 x), dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography using 20/80 EtOAc/hexanes which afforded 1.15 g of the required intermediate **20.08**.

Preparation of Intermediate **21.01**

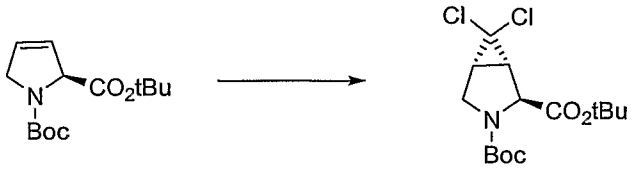
Step 1



21.02 **21.03**

To a stirred solution of *N*-Boc-3,4-dehydroproline **21.02** (5.0 g, 23.5 mmol), di-*tert*-butyl dicarbonate (7.5 g, 34.4 mmol), and 4-*N,N*-dimethylaminopyridine (0.40 g, 3.33 mmol) in acetonitrile (100 mL) at room temperature was added triethylamine (5.0 mL, 35.6 mmol). The resulting solution was stirred at this temperature for 18 h before it was concentrated *in vacuo*. The dark brown residue was purified by flash column chromatography eluting with 10-25% EtOAc/hexane to give the product **21.03** as a pale yellow oil (5.29 g, 84%).

Step 2

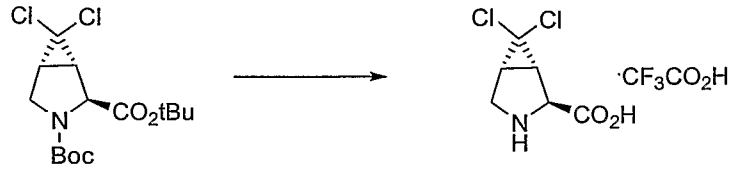


21.03 **21.04**

To a stirred solution of the dehydroproline derivative **21.03** (10.1 g, 37.4 mmol), benzyltriethylammonium chloride (1.60 g, 7.02 mmol) in chloroform (120 mL) at room temperature was added 50% aqueous sodium hydroxide (120 g). After vigorously stirred at this temperature for 24 h, the dark mixture was diluted with CH_2Cl_2 (200 mL) and diethyl ether (600 mL). After the layers were separated, the aqueous solution was extracted with CH_2Cl_2/Et_2O (1:2, 3x600 mL). The organic solution was dried ($MgSO_4$) and

concentrated. The residue was purified by flash column chromatography using 5-20% EtOAc/hexane to afford 9.34 g (71%) of **21.04** as an off-white solid.

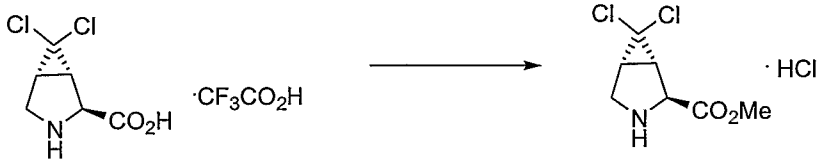
Step 3



21.04 **21.05**

The solution of **21.04** (9.34 g, 26.5 mmol) in CH_2Cl_2 (25 mL) and CF_3CO_2H (50 mL) was stirred at room temperature for 4.5 h before it was concentrated *in vacuo* to give a brown residue, **21.05** which was used in Step 4 without further purification.

Step 4

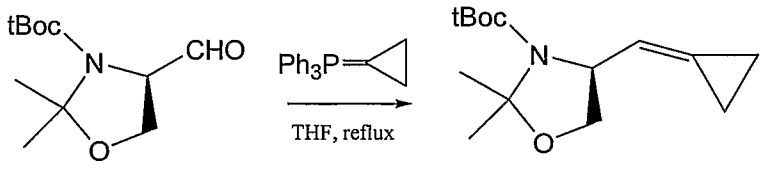


21.05 **21.01**

Concentrated hydrochloric acid (4.5 mL) was added to a solution of the residue **21.05** from Step 3 in methanol (70 mL) and the resulting mixture was warmed to 65°C in an oil bath. After 18 h, the mixture was concentrated *in vacuo* to give a brown oil **21.01**, which was used further without purification.

Preparation of Intermediate **22.01**

Step 1

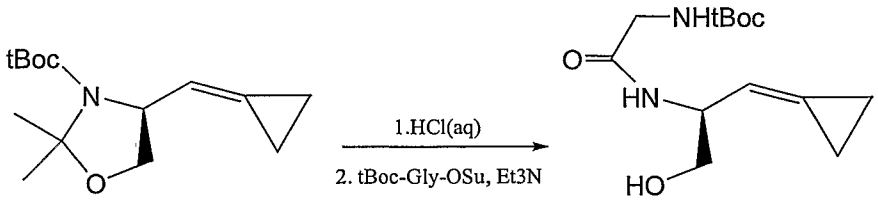


22.02 **22.03**

Potassium bis(trimethylsilyl)amide (158ml of a 0.5M solution in toluene; 79mmol) was added to a stirred suspension of cyclopropyltriphenyl-phosphonium bromide (33.12g; 86.4mmol) in anhydrous tetrahydrofuran (130ml) and the resulting orange mixture was stirred under an atmosphere of

nitrogen at room temperature for a period of 1h., before the addition of the aldehyde **22.02** (9.68g; 42.2mmol) in THF (8ml). The reaction was then refluxed under an atmosphere of nitrogen for a period of 2h. After cooling, methanol, diethyl ether and Rochelles salt were added. The organic phase was separated, washed with brine, dried and concentrated under reduced pressure. The crude reaction product was purified by silica gel column chromatography using EtOAc-hexane (1:99) to EtOAc-hexane (5:95) to provide the alkene **22.03** (8.47g) as a yellow oil.

Step 2

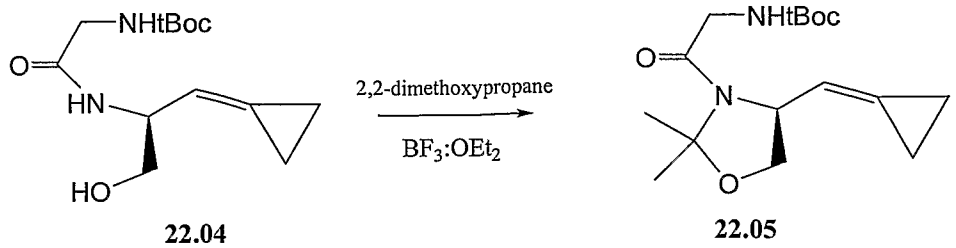


22.03 **22.04**

A solution of 1M HCl in MeOH/MeOAc was prepared by adding 14.2ml of acetyl chloride dropwise into cold methanol and diluting the resulting solution to 200ml at room temperature. The carbamate **22.03** (9.49g; 37.5mmol) was dissolved in methanol (12ml) and added to 1M HCl in MeOH/MeOAc (150ml) while cooled in an ice bath. The resulting mixture was maintained at this temperature for 1h., then the ice bath was removed and stirring continued overnight at room temperature. The volatiles were removed under reduced pressure to yield a yellow oil which was used in the next step without purification.

The yellow oil was dissolved in a mixture of THF (30ml) and MeOH (20ml) and treated with triethylamine (15ml; 108mmol) until the solution was pH=9-10. After placing in an ice bath, the mixture was treated with N-Boc-Gly-OSu (11.22g; 41mmol). The ice bath was withdrawn and the reaction stirred at room temp. for 1h. The volatiles were removed under reduced pressure and the residue was purified by silica gel column chromatography using methanol (1-3%) in dichloromethane providing the desired amide **22.04** (9.09g).

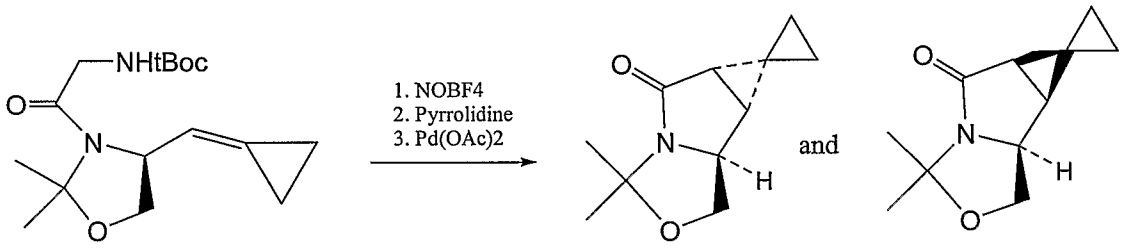
Step 3



22.04 22.05

The alcohol **22.04** (9.09g; 33.6mmol) was dissolved in acetone (118.5ml) and treated with 2,2-dimethoxypropane (37.4ml;304mmol) and BF_3:Et_2O (0.32ml; 2.6mmol) and the resulting mixture was stirred at room temperature for a period of 5.5h The reaction solution was treated with a few drops of triethylamine and the volatiles were removed under reduced pressure. The residue was purified by silica gel column chromatography using 5-25% EtOAc in hexanes to provide the N,O-acetal **22.05** (8.85g).

Step 4



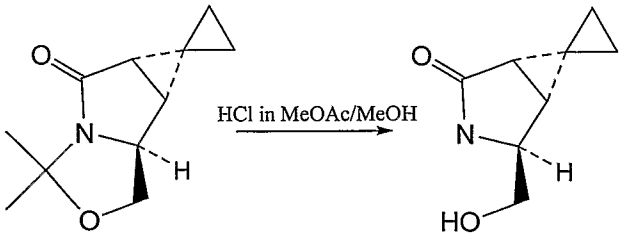
22.05 22.06 22.07

The carbamate **22.05** (8.81g; 28.4mmol) was dissolved in acetonitrile (45ml) and the solution was cooled to –40°C under an atmosphere of nitrogen. Pyridine (6.9ml; 85.3mmol) followed by nitrosium tetrafluoroborate (6.63g; 56.8mmol) were added and the resulting reaction mixture maintained below 0°C until TLC indicated that no starting material remained (approx. 2.25h.). Pyrrolidine (20ml; 240mmol) was added and the cooling bath was withdrawn and stirring was continued at room temperature for 1h. and then the volatiles were removed under reduced pressure. The residue was quickly passed through a pad of silica gel to provide a yellow oil.

The yellow oil was dissolved in anhydrous benzene (220ml) and palladium acetate (0.317g; 1.41mmol) was added before heating the resulting mixture to reflux, under an atmosphere of nitrogen for a period of 1.5h. After cooling, the volatiles were removed under reduced pressure and the dark residue was purified by silica gel column chromatography using EtOAc-hexane (1:4) to

provide the I) the trans- pyrrolidinone **22.06** (1.94g) followed by ii) the cis-pyrrolidinone **22.07** (1.97g).

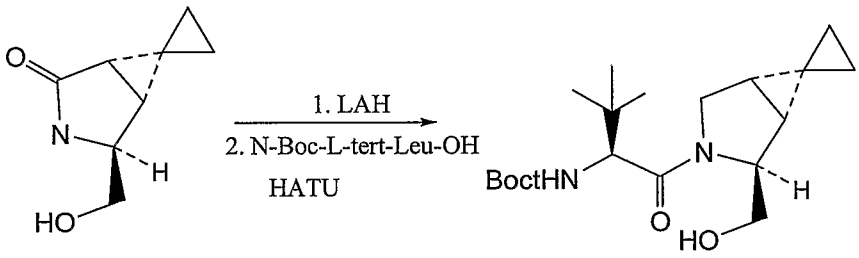
Step 5



22.06 **22.08**

Freshly prepared 1M HCl in MeOAc/MeOH (10ml; as described above) was added to the N,O-acetal **22.06** and stirred at room temperature for 1h. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography using 0-4%MeOH in dichloromethane as eluent to provide the desired alcohol **22.08** (1.42g), a yellow oil.

Step 6



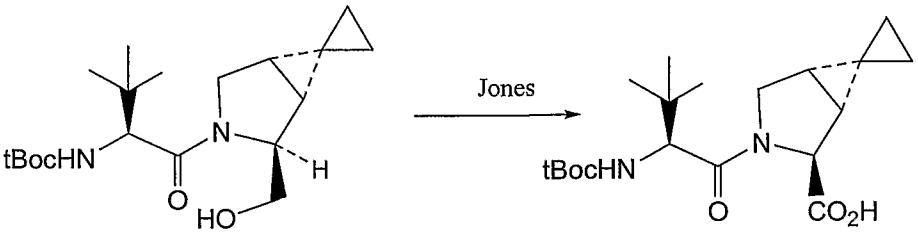
22.08 **22.09**

To a solution of the lactam **22.08** (1.29g; 8.44mmol) in anhydrous tetrahydrofuran (55ml) was added lithium aluminum hydride (2.40g; 63.2mmol) and the resulting mixture was refluxed for 8h. After cooling, water, followed by 15% aq. NaOH were added and the resulting mixture was filtered through celite and the solid was washed thoroughly with THF and MeOH. The solvent was removed under reduced pressure and the residue redissolved in dichloromethane, dried and concentrated under reduced pressure to provide the pyrrolidine, used without purification.

Hunigs base (4.5ml; 25.8mmol) was added to a mixture of N-Boc-L-tert-Leu-OH (1.76g; 7.6mmol), The crude pyrrolidine and HATU (2.89g; 7.6mmol) in anhydrous dichloromethane (50ml) at –60°C, under an atmosphere of nitrogen. The resulting reaction was allowed to come to room

temperature slowly, overnight. EtOAc was added and the yellow solution was washed with dil. aq. HCl, sat. aq. sodium bicarbonate, water, brine. The organic layer was dried and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc:hexanes (1:3) to give the desired amide **22.09** (2.00g).

Step 7

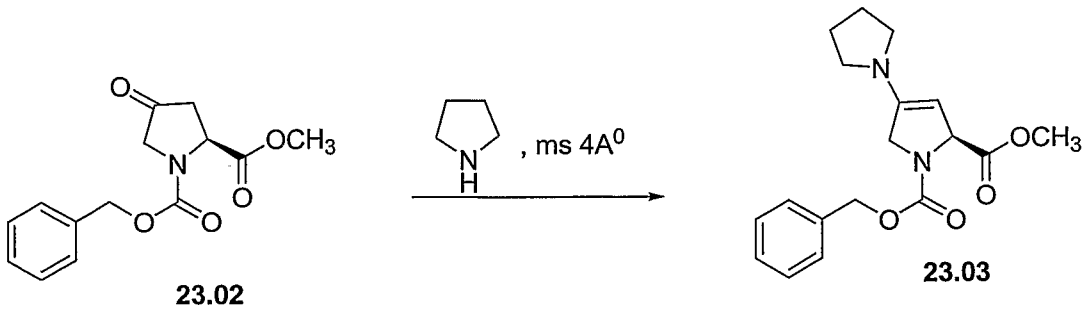


22.09 **22.01**

The alcohol **22.09** (2.00g; 5.67mmol) was dissolved in acetone (116ml) and cooled in an ice bath for 10min. This solution was then added to a cooled Jones reagent (14.2ml; approx 2mmol/ml) and the resulting mixture was stirred at 5C for 0.5h and the cooling bath was removed. The reaction was stirred for a further 2h. at room temp., before adding to sodium sulfate (28.54g), celite (15g) in EtOAc (100ml). Isopropanol (15ml) was added after 1min and then stirred for a further 10min. and filtered. The filtrate was concentrated under reduced pressure, providing a brown oil which was dissolved in EtOAc. This solution was washed with water, 3% aq. citric acid, brine, dried and concentrated to provide the desired carboxylic acid **22.01** (1.64g) as a white solid.

Preparation of Intermediate **23.01**

Step 1

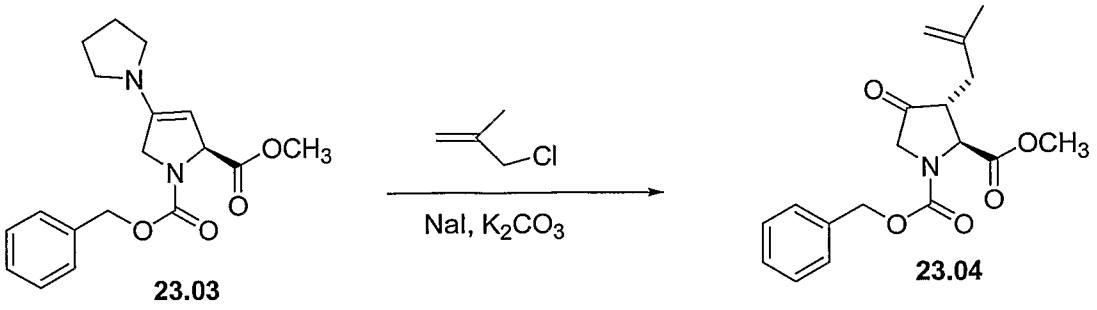


23.02 **23.03**

To the mixture of ester **23.02** (6.0g) and molecular sieve (5.2g) in anhydrous methylene chloride (35 mL) was added pyrrolidine (5.7 mL, 66.36 mmoL). The resulting brown slurry was stirred at room temperature under N_2

for 24 h, filtered and washed with anhydrous CH_3CN. The combined filtrate was concentrated to yield the desired product, **23.03**.

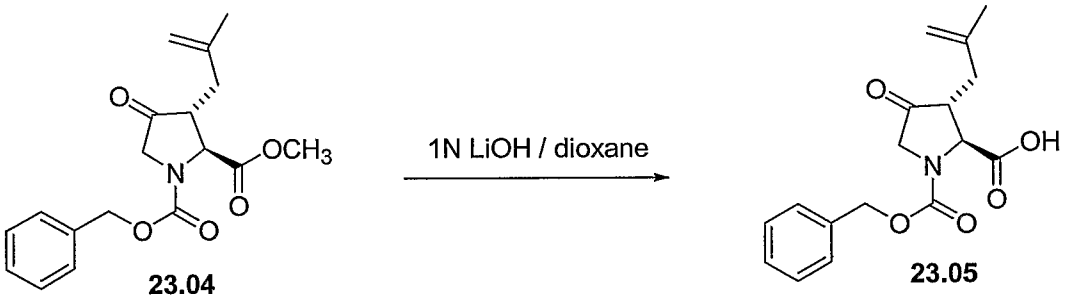
Step 2



23.03 **23.04**

To a solution of the product **23.03** from proceeding step in CH_3CN (35 mL) was added anhydrous K_2CO_3, methallyl chloride (2.77g, 30.5 mmoL), NaI (1.07g, 6.7 mmoL). The resulting slurry was stirred at ambient temperature under N_2 for 24 h. 50 mL of ice-cold water was added followed by 2N $KHSO_4$ solution until pH was 1. EtOAc (100 mL) was added and the mixture was stirred for 0.75h. Combined organic layer was collected and washed with brine, dried over $MgSO_4$, and evaporated to yield the desired product, **23.04**.

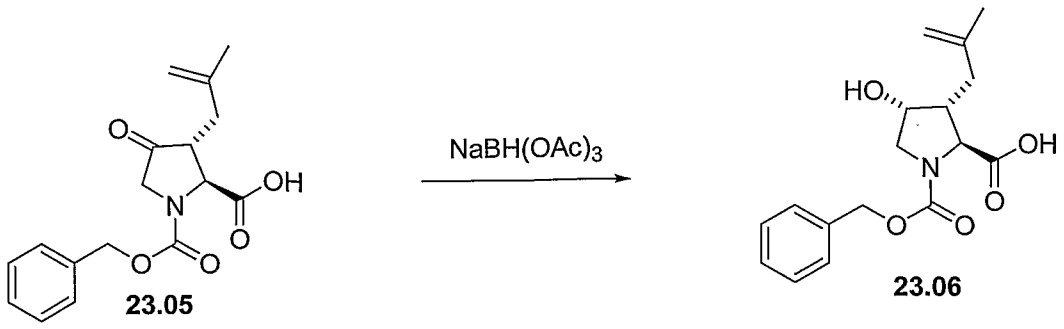
Step 3



23.04 **23.05**

The product **23.04** from the preceding step (2.7 g, 8.16 mmoL) was dissolved in dioxane (20 mL) and treated with freshly prepared 1N LiOH (9 mL). The reaction mixture was stirred at ambient temperature under N_2 for 20 h. The reaction mixture was taken in EtOAc and washed with H_2O. The combined aqueous phase was cooled to 0^0C and acidified to pH 1.65 using 1N HCl. The turbid mixture was extracted with EtOAc (2 x 100 mL). Combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated to give the desired acid, **23.05** (3.40 g).

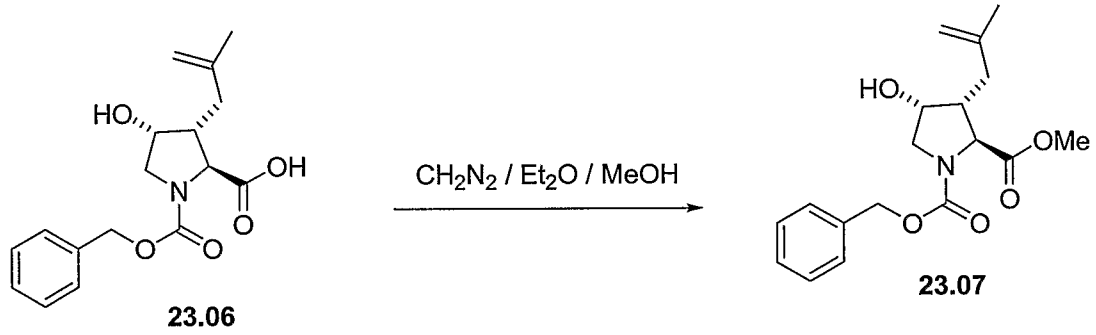
Step 4



23.05 **23.06**

To a suspension of $NaBH(OAc)_3$ (3.93g, 18.5 mmoL) in CH_2Cl_2 (55 mL) was added a solution of product **23.05** from preceding step in anhydrous CH_2Cl_2 (20 mL) and acetic acid (2 mL). The slurry was stirred at ambient temperature for 20 h . Ice cold water (100 mL) was added to the slurry and stirred for 1/2 hr. Organic layer was separated, filtered, dried and evaporated to yield the desired product, **23.06**.

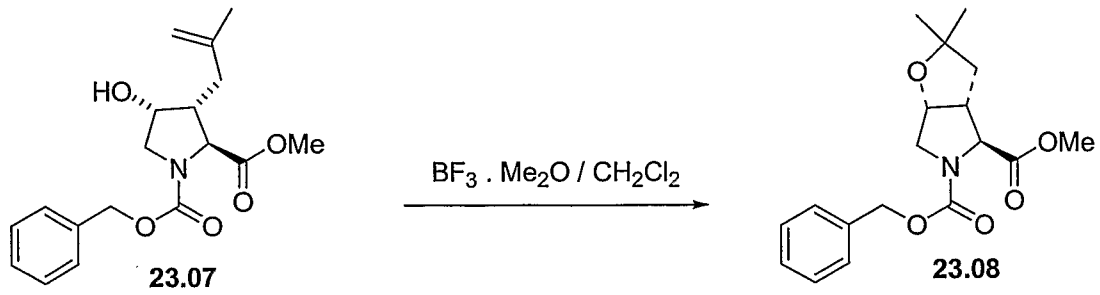
Step 5



23.06 **23.07**

To a solution of the product **23.06** from preceding step (1.9g) in MeOH (40 mL) was treated with excess of CH_2N_2 / Et_2O solution and stirred for overnight. The reaction mixture was concentrated to dryness to yield a crude residue. The residue was chromatographed on silica gel, eluting with a gradient of EtOAc / hexane to afford 1.07 g of the pure desired product, **23.07**.

Step 6

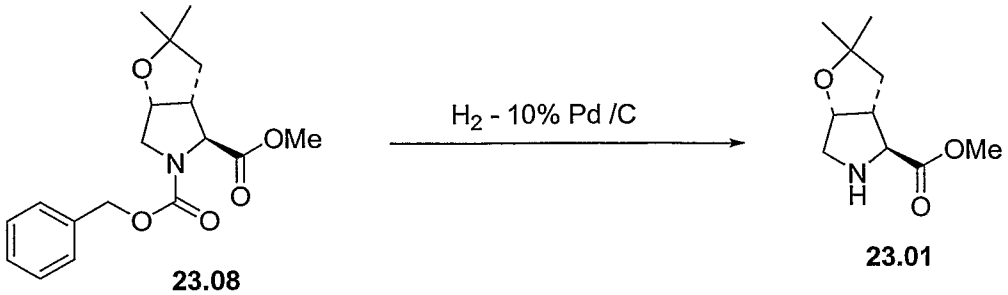


23.07 **23.08**

To a solution of product **23.07** from preceding step (1.36 g) in anhydrous CH_2Cl_2 (40 mL) was treated with BF_3. Me_2O (0.7 mL). The reaction mixture was stirred at ambient temperature for 20 h and quenched

with sat. $NaHCO_3$ (30 mL) ad stirred for 1/2 hr. Organic layer was separated and combined organic layer was washed with brine, dried over $MgSO_4$, concentrated to give crude residue. The residue was chromatographed on silica gel eluting with a gradient of EtOAc / hexane to afford 0.88 g of the desired compound, **23.08**.

Step 7

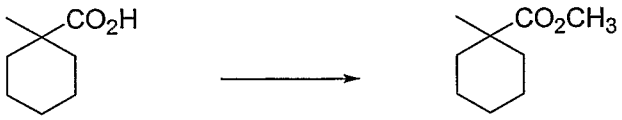


23.08 **23.01**

To a solution of the product **23.08** (0.92 g) from preceding step in MeOH (30 mL) was added 10 % Pd/C (0.16 g) at room temperature and hydrogenated at ambient temperature under 1 atm. Pressure. The reaction mixture was stirred for 4 h and concentrated to dryness to yield the desired compound, **23.01**.

Preparation of Intermediate **50.01**

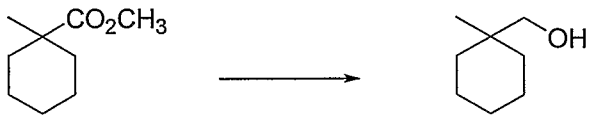
Step 1



50.02 **50.03**

To a solution of **50.02** (15 g) in MeOH (150 mL) was added conc HCl (3-4 mL) and the mixture was refluxed for 16 h. The reaction mixture was cooled to room temperature and concentrated. The residue was taken in diethyl ether (250 mL) and washed with cold saturated sodium bicarbonate solution, and brine. The organic layer was dried (Na_2SO_4) and concentrated to afford the methyl ester **50.03** (12.98 g) which was carried forward without further purification.

Step 2



50.03 **50.04**

The methyl ester **50.03** from above was dissolved in methylene chloride (100 mL) and cooled to -78°C, under nitrogen atmosphere. DIBAL (1.0 M solution in methylene chloride, 200 mL) was added dropwise over 2 h period. The reaction mixture was warmed to room temperature over 16 h. The reaction mixture was cooled to 0°C and MeOH (5-8 mL) was added dropwise. A solution of aqueous 10% sodium potassium tartarate (200 mL) was slowly added with stirring. Diluted with methylene chloride (100 mL) and separated the organic layer (along with some white precipitate). The organic layer was washed with 1 N HCl (250 mL), brine (200 mL), dried (Na_2SO_4) and concentrated to provide the alcohol **50.04** (11.00 g) as a clear oil.

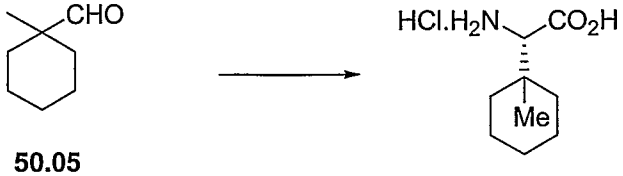
Step 3



50.04 **50.05**

The alcohol **50.04**from above was dissolved in methylene chloride (400 mL) and cooled to 0°C under nitrogen atmosphere. PCC (22.2 g) was added in portions and the reaction mixture was slowly warmed to room temperature over 16 h. The reaction mixture was diluted with diethyl ether (500 mL) and filtered through a pad of celite. The filtrate was concentrated and the residue was taken in diethyl ether (500 mL). This was passed through a pad of silica gel and the filtrate was concentrated to provide the aldehyde **50.05** which was carried forward without further purification.

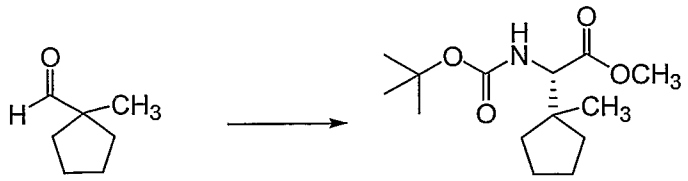
Step 4



50.05 **50.01**

The aldehyde **50.05** from above was converted to the desired material **50.01** using essentially the method of Chakraborty *et. al* (Tetrahedron, **1995**, 51(33), 9179-90).

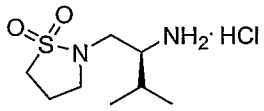
Preparation of Intermediate **51.01**



51.02 **51.01**

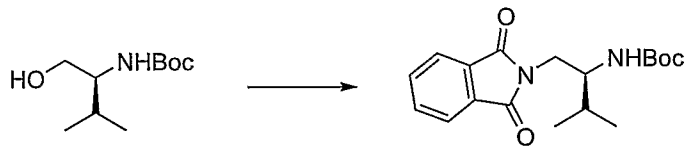
The required intermediate **51.01** was obtained from the aldehyde **51.02** using the literature described procedure (T. K. Chakraborty et al., *Tetrahedron*, **1995**, 51 (33), 9179-90).

Preparation of compound **5000**:



5000

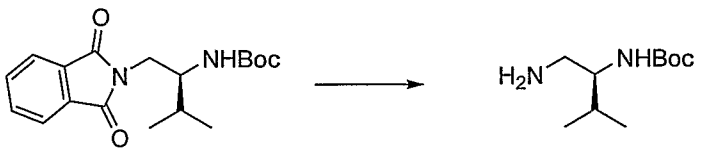
Step 1



5000a **5000b**

To a stirred solution of *N*-Boc-(*S*)-valinol **5000a** (10.0 g,49.2 mmol), phthalimide (7.40 g, 50.3 mmol) and triphenylphosphine (13.0 g, 49.6 mmol) in anhydrous THF (100 mL) at 0°C was added diisopropylazodicarboxylate (DIAD, 9.8 mL, 49.4 mmol). The resulting solution was then stirred at rt for 18 h before it was concentrated to dryness. The residue was dissolved in CH_2Cl_2 and purified by silica gel flash chromatography (10-40% EtOAc in hexanes) to give product **5000b**.

Step 2



5000b **5000c**

To a stirred solution of **5000b** (8.8 g, 26.5 mmol) in methanol (100 mL) at rt was added hydrazine monohydrate (1.4 mL, 28.8 mmol) and the resulting

solution was stirred at rt for 18 h. Additional hydrazine monohydrate (0.5 mL, 10.3 mmol) was added and the mixture was brought to reflux and stirred for 4 h before it was cooled to rt. The precipitate was filtered off and the solution was concentrated to dryness. The residue was dissolved in CH_2Cl_2 and the precipitate was again filtered off. After concentration, a yellow oil was obtained (8.0 g, quant.).

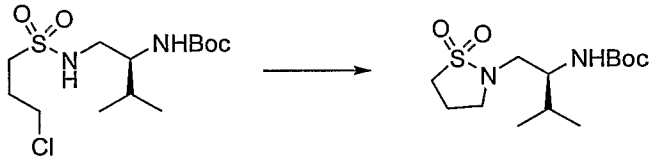
Step 3



5000c **5000d**

To a solution of **5000c** (1.0 g, 4.94 mmol) in CH_2Cl_2 I (100 mL) at -30°C in an acetone bath was added 3-chloropropyl sulfonyl chloride (0.60 mL, 4.93 mmol) and triethylamine (1.10 mL, 7.89 mmol). The resulting solution was warmed to rt along with the bath and stirred for 18 h. Additional CH_2Cl_2 and 1 N Na_2CO_3 solution were added and the layers were separated. The aqueous solution was extracted with CH_2Cl_2 (2 x 100 mL). The organic solutions were combined, filtered, dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography using 10-40% acetone/hexanes to afford 1.0 g (59%) of **5000d**.

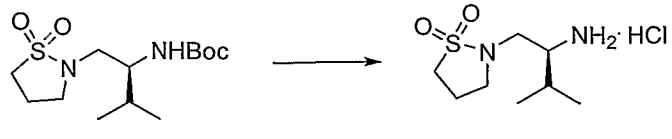
Step 4



5000d **5000e**

The suspension of **5000d** (1.0 g, 2.92 mmol) and sodium hydride (0.32 g, 60%, 8.0 mmol) in anhydrous DMF (100 mL) was stirred at rt for 8 h. After cooled to 0°C, 5% aqueous phosphoric acid solution (110 mL) was cautiously added followed by EtOAc (150 mL). The layers were separated and the organic solution was washed with 5% aqueous phosphoric acid solution (100 mL) and saturated sodium bicarbonate solution (2 x 100 mL) before it was dried, filtered and concentrated. The residue was purified by silica gel flash chromatography (0-40% acetone in hexanes) to give 0.63 g product **5000e** (70%).

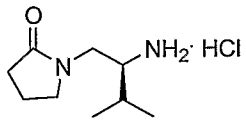
Step 5



5000e 5000

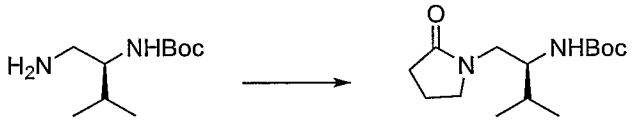
The solution of **5000e** (0.62 g, 2.02 mmol) in 4 N HCl in dioxane was stirred at rt for 4 h. It was then concentrated to dryness *in vacuo* to give 0.60 g product **5000** (quant.).

Preparation of compound of formula 5001



5001

Step 1



5000c 5001a

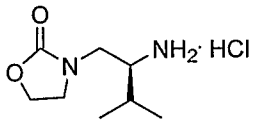
Compound **5001a** was prepared from **5000c** and 4-bromobutyryl chloride according to the procedures described for the preparation of compound **5000d**.

Step 2



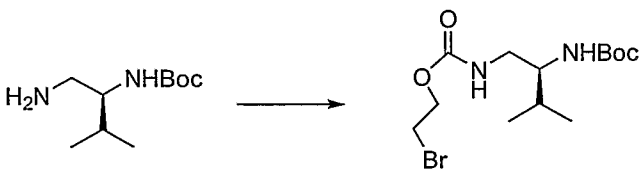
5001a 5001

Preparation of compound of formula 5002



5002

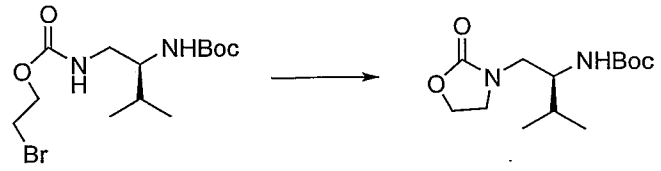
Step 1



5000c 5002a

Compound **5002a** was prepared from **5000c** and 2-bromoethyl chloroformate according to the procedures described for the preparation of compound **5000d**.

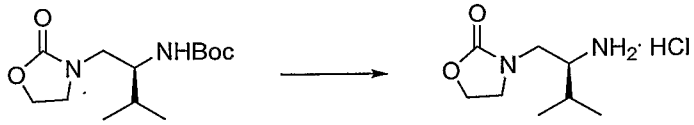
Step 2



5002a **5002b**

Compound **5002b** was prepared from **5002a** according to the procedures described for the preparation of compound **5000e**.

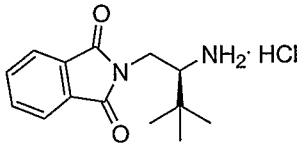
Step 3



5002b **5002**

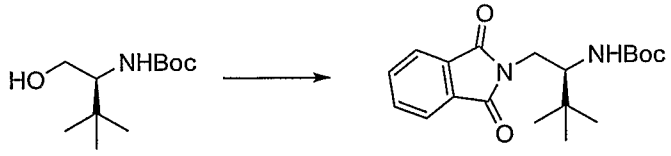
Compound **5002** was prepared from **5002b** according to the procedures described for the preparation of compound **5000** (Step 5).

Preparation of compound of formula 5003



5003

Step 1



5003a **5003b**

Compound **5003b** was prepared from *N*-Boc-(*S*)-*tert*-leucinol **5003a** according to the procedures described for the preparation of compound **5000b** (Step 1).

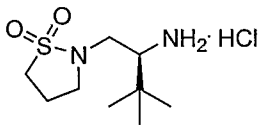
Step 2



5003b 5003

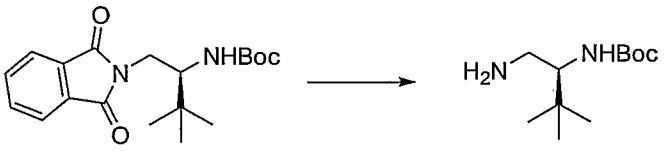
Compound **5003** was prepared from **5003b** according to the procedures described for the preparation of compound **5000** (Step 5).

Preparation of compound of formula 5004



5004

Step 1



5003b 5004a

Compound **5004a** was prepared from **5003b** according to the procedures described for the preparation of compound **5000c** (Step 2).

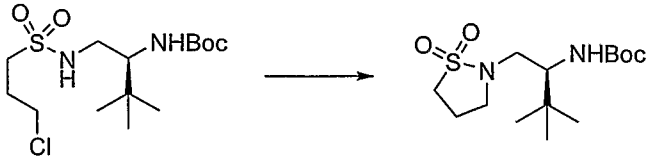
Step 2



5004a 5004b

Compound **5004b** was prepared from **5004a** according to the procedures described for the preparation of compound **5000d** (Step 3).

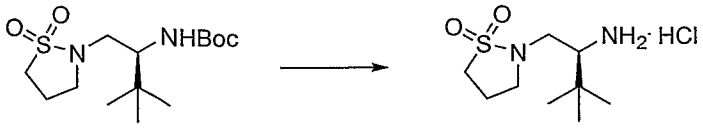
Step 3



5004b 5004c

Compound **5004c** was prepared from **5004b** according to the procedures described for the preparation of compound **5000e** (Step 4).

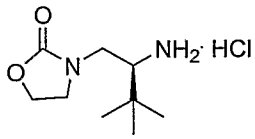
Step 4



5004c 5004

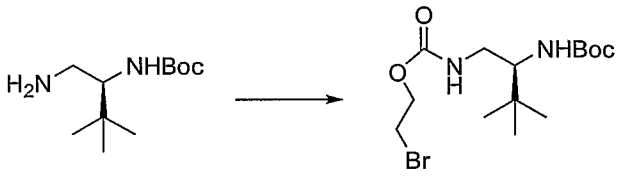
Compound **5004** was prepared from **5004c** according to the procedures described for the preparation of compound **5000** (Step 5).

Preparation of compound of formula 5005



5005

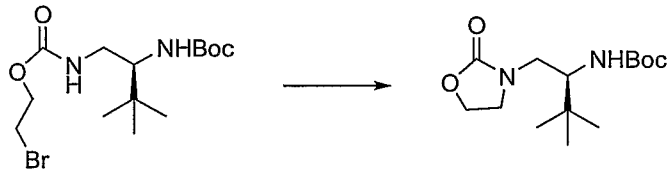
Step 1



5004a 5005a

Compound **5005a** was prepared from **5004a** according to the procedures described for the preparation of compound **5002a** (Step 1).

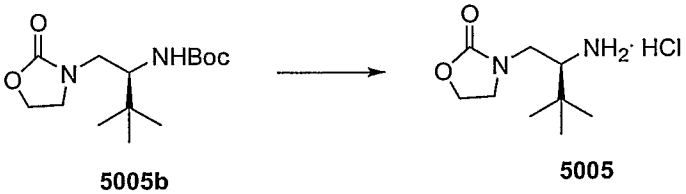
Step 2



5005a 5005b

Compound **5005b** was prepared from **5005a** according to the procedures described for the preparation of compound **5002b** (Step 2).

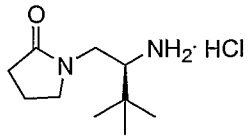
Step 3



5005b 5005

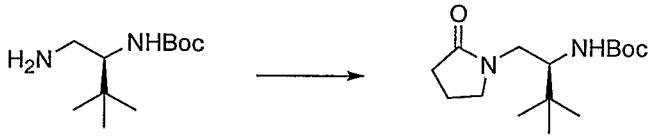
Compound **5005** was prepared from **5005b** according to the procedures described for the preparation of compound **5000** (Step 5).

Preparation of compound of formula 5006



5006

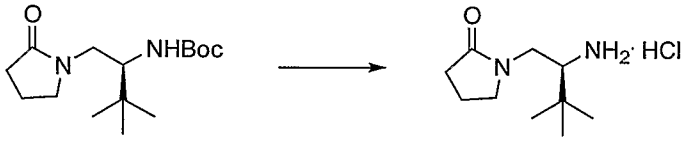
Step 1



5004a **5006a**

Compound **5006a** was prepared from **5004a** and 4-bromobutyryl chloride according to the procedures described for the preparation of compound **5000d**.

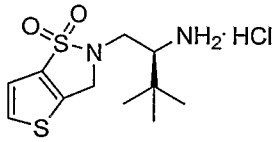
Step 2



5006a **5006**

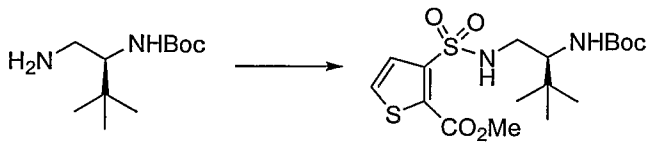
Compound **5006** was prepared from **5006a** according to the procedures described for the preparation of compound **5000** (Step 5).

Preparation of compound of formula 5007



5007

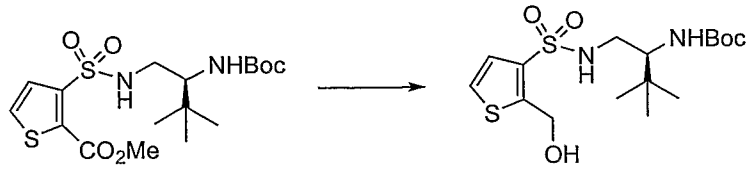
Step 1



5004a **5007a**

Compound **5007a** was prepared from **5004a** and 2-carbomethoxy-3-thiophenesulfonyl chloride according to the procedures described for the preparation of compound **5000d**.

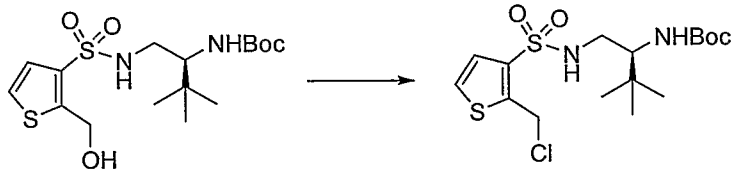
Step 2



5007a 5007b

To the solution of ester **5007a** (4.65 g, 11.1 mmol) in anhydrous toluene (40 mL) at -78°C was added a solution of DIBAL-H in toluene (23.0 mL, 34.5 mmol). The mixture was stirred at -78°C for 20 min and at rt for 2 h. Methanol (20 mL) was added followed by 10% aqueous citric acid solution (100 mL). After stirred for 5 min, EtOAc (200 mL) was added and layers were separated. The aqueous solution was extracted with EtOAc (2 x 100 mL). The organic solutions were combined, dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash column chromatography using 10-50% acetone/hexanes to give 4.6 g (quant.) of **5007b**.

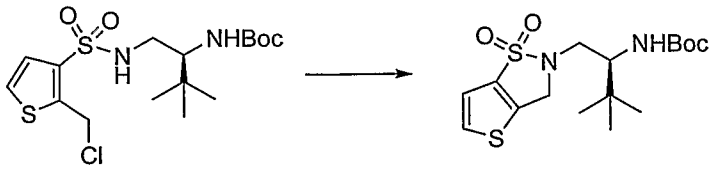
Step 3



5007b 5007c

To a solution of **5007b** (1.04 g, 2.65 mmol) in CH_2Cl_2 I (50 mL) at -0°C was added methanesulfonyl chloride (0.23 mL, 2.97 mmol) and triethylamine (0.80 mL, 5.74 mmol). The mixture was warmed to rt along with ice bath and stirred for 18 h. EtOAc (200 mL) and 5% H_3PO_4 solution (100 mL) was added and the layers were separated. The organic solutions were washed with 1 N sodium carbonate solution (100 mL) before it was dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash column chromatography using 10-50% acetone/hexanes to give 0.80 g (73%) of **5007c**.

Step 4

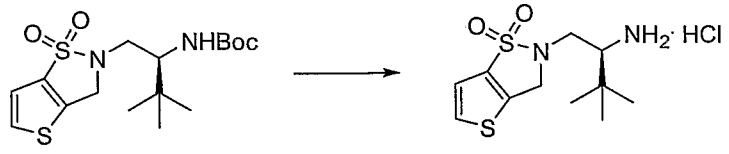


5007c 5007d

The suspension of **5007d** (1.17 g, 2.85 mmol) and cesium carbonate (1.40 g, 4.30 mmol) in anhydrous DMF (100 mL) was stirred at rt for 18 h.

Water (50 mL), brine (50 mL) and EtOAc (300 mL) were added and the layers were separated. The organic solution was washed water (3 x 150 mL) before it was dried, filtered and concentrated to give 0.99 g of the desired product **5007d** (93%).

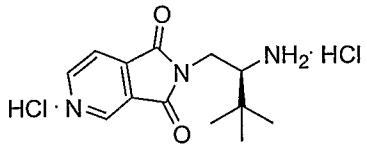
Step 5



5007d **5007**

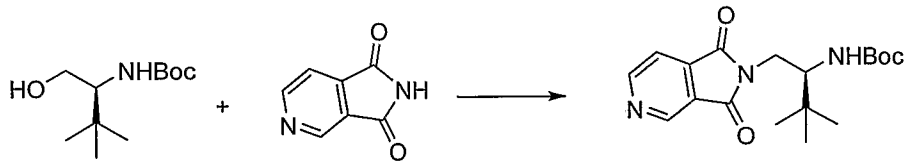
Compound **5007** was prepared from **5007d** according to the procedures described for the preparation of compound **5000**.

Preparation of compound of formula 5008



5008

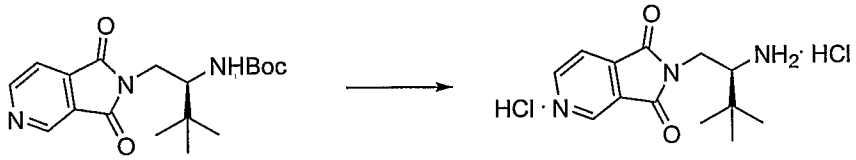
Step 1



5003a **5008a** **5008b**

Compound **5008b** was prepared from **5003a** and **5008a** according to the procedures described for the preparation of compound **5000b**.

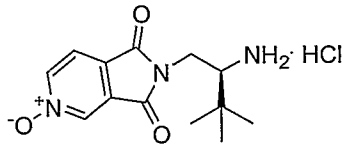
Step 2



5008b **5008**

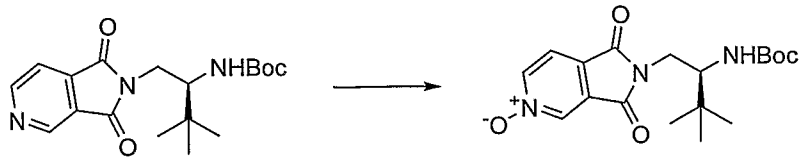
Compound **5008** was prepared from **5008b** according to the procedures described for the preparation of compound **5000**.

Preparation of compound of formula 5009



5009

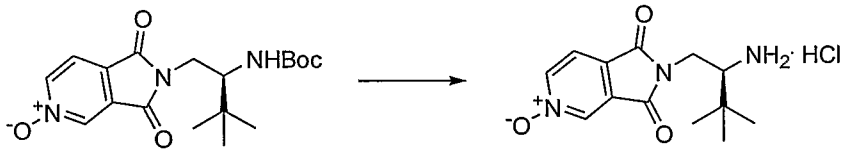
Step 1



5008b **5009a**

To a solution of **5008b** (1.02 g, 2.93 mmol) in CH_2Cl_2 (50 mL) at -18°C was added *m*-chloroperoxybenzoic acid (3.03 g, 17.6 mmol) and the resulting solution was stirred at -18°C for 1 h before it was placed in a refrigerator overnight (16 h). After stirred at rt for another 6 h, additional CH_2Cl_2 was added and the solution was washed with 10% $NaHSO_4$ and 1 N Na_2CO_3. The organic solutions was dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash column chromatography using 5-60% acetone/hexanes to afford 0.49 g (46%) of product **5009a**.

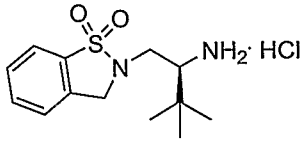
Step 2



5009a **5009**

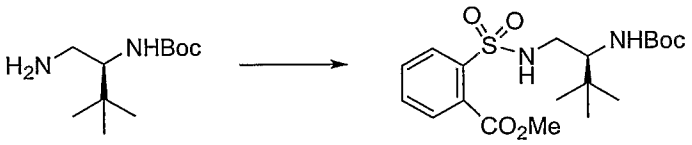
Compound **5009** was prepared from **5009a** according to the procedures described for the preparation of compound **5000**.

Preparation of compound of formula 5010



5010

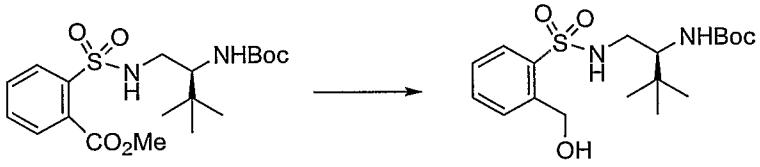
Step 1



5004a 5010a

Compound **5010a** was prepared from **5004a** and methyl 2-(chlorosulfonyl) benzoate according to the procedures described for the preparation of compound **5000d**.

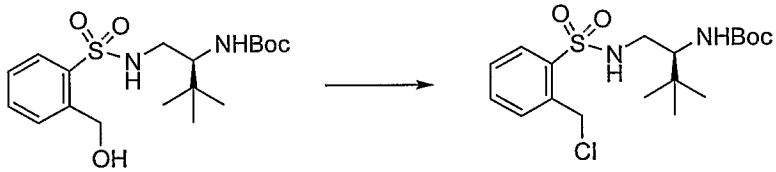
Step 2



5010a 5010b

Compound **5010b** was prepared from **5010a** according to the procedures described for the preparation of compound **5007b**.

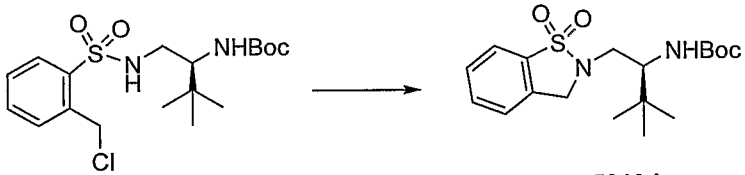
Step 3



5010b 5010c

Compound **5010c** was prepared from **5010b** according to the procedures described for the preparation of compound **5007c**.

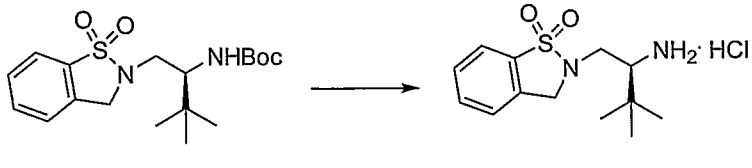
Step 4



5010c 5010d

Compound **5010d** was prepared from **5010c** according to the procedures described for the preparation of compound **5007d**.

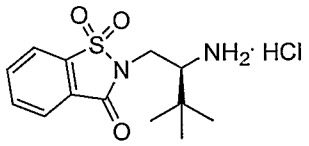
Step 5



5010d 5010

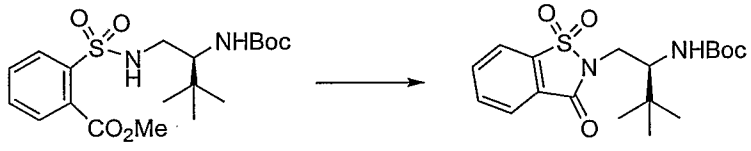
Compound **5010** was prepared from **5010d** according to the procedures described for the preparation of compound **5000**.

Preparation of compound of formula 5011



5011

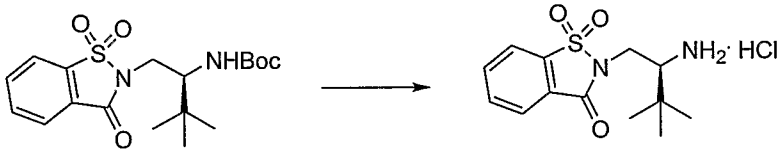
Step 1



5010a **5011a**

The suspension of **5010a** (0.60 g, 1.45 mmol) and cesium carbonate (0.707 g, 2.17 mmol) in anhydrous DMF was stirred at 40°C for 18 h. Water (50 mL), brine (50 mL) and EtOAc (150 mL) were added and the layers were separated. The organic solution was washed water (3 x 80 mL) before it was dried, filtered and concentrated to give 0.17 g of the desired product **5011a** (31%).

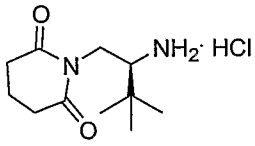
Step 2



5011a **5011**

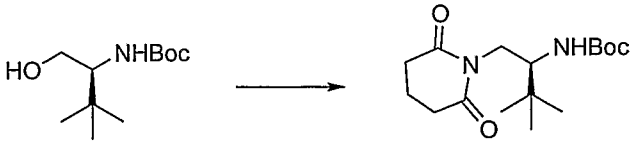
Compound **5011** was prepared from **5011a** according to the procedures described in Step 5 of the preparation of compound **5000.**

Preparation of compound of formula 5012



5012

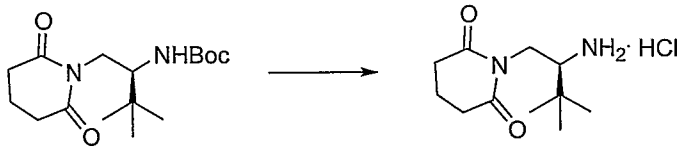
Step 1



5003a **5012a**

Compound **5012a** was prepared from **5003a** and glutarimide according to the procedures described for the preparation of compound **5000b**.

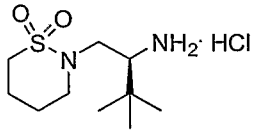
Step 2



5012a **5012**

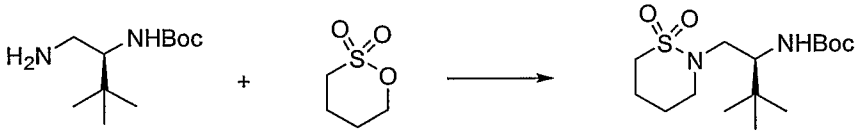
Compound **5012** was prepared from **5012a** according to the procedures described for the preparation of compound **5000**.

Preparation of compound of formula 5013



5013

Step 1



5004a **5013a**

The solution of amine **5004a** (3.0 g, 13.9 mmol) and 1,4-butane sultone (1.8 mL, 17.7 mmol) in anhydrous THF (25 mL) was refluxed for 16 h. More sultone (0.6 mL, 5.89 mmol) was added and the mixture was refluxed for another 4 h. Phosphorus oxychloride (2.6 mL, 27.9 mmol) was added and the solution was stirred at rt for 4 h. After cooled to 0°C, 50% w/w NaOH solution was added slowly along with water (30 mL) until PH is greater than 12. Ether (200 mL) was then added and layers were separated. The aqueous solution was extracted with THF/diethyl ether (1:1, 150 mL) twice. Organic solutions were combined, dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash column chromatography using 10-50% acetone/hexanes to give 1.49 g of **5013a** (32%).

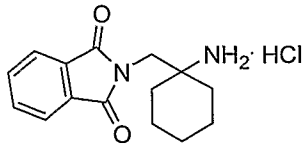
Step 2



5013a **5013**

Compound **5013** was prepared from **5013a** according to the procedures described for the preparation of compound **5000**.

Preparation of compound of formula 5014



5014

Step 1



5014a **5014b**

To the suspension of **5014a** (10.0 g, 41.1 mmol), HOOBt (8.7 g, 53.3 mmol), EDCI (10.0 g, 52.2 mmol) and ammonium chloride (8.90 g, 166 mmol) in anhydrous DMF (400 mL) at rt was added 4-methylmorpholine (22.5 mL, 204.5 mmol). The mixture was stirred at rt for 70 h. Brine (150 mL) and 5% aqueous phosphoric acid solution (150 mL) were added followed by EtOAc (800 mL). The layers were separated and the organic solution was washed with 5% aqueous phosphoric acid solution (400 mL) and saturated sodium bicarbonate solution (2 x 400 mL) before it was dried, filtered and concentrated to give 8.35 g product **5014b** (84%).

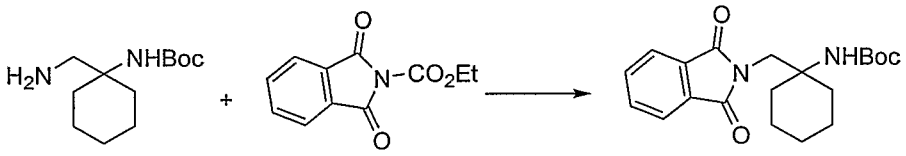
Step 2



5014b **5014c**

The solution of amide **5014b** (8.35 g, 34.5 mmol) in anhydrous THF (100 mL) at rt was added a solution of borane methyl sulfide complex in toluene (43.0 mL, 86.0 mmol) and the mixture was refluxed for 4 h. More THF (100 mL) was added and 3 N HCl solution was added slowly until no gas evolution was observed. To the mixture was added 50% w/w NaOH solution slowly until PH is greater than 12. Ether (200 mL) was then added and layers were separated. The aqueous solution was extracted with THF/diethyl ether (1:1, 150 mL) twice. Organic solutions were combined, dried ($MgSO_4$), filtered and concentrated to give 6.50 g of the product **5014c** (83%).

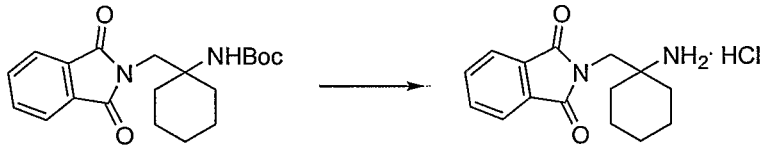
Step 3



5014c 5014d 5014e

To the solution of the amine **5014c** (0.80 g, 3.50 mmol) and N-carbethoxy phthalimide **5014d** (0.90 g, 4.11 mmol) in anhydrous THF (50 mL) at rt was added triethylamine (1.0 mL, 7.17 mmol). The mixture was stirred at rt for 18 h. EtOAc (100 mL) and 5% aqueous phosphoric acid solution (100 mL) were added and the layers were separated. The organic solution was washed with 5% aqueous phosphoric acid solution (80 mL) and dried, filtered and concentrated. The residue was purified by silica gel flash chromatography (5-50% EtOAc in hexanes) to give 0.82 g product **5014e** (65%).

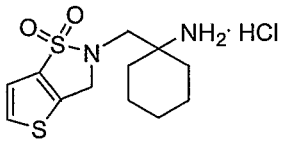
Step 4



5014e 5014

Compound **5014** was prepared from **5014e** according to the procedures described for the preparation of compound **5000**.

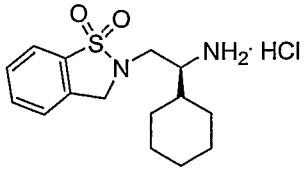
Preparation of compound of formula 5015



5015

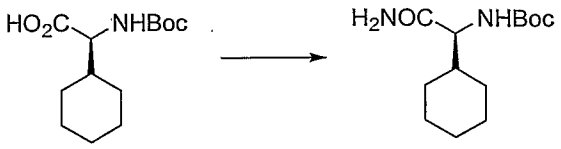
Compound **5015** was prepared from **5014c** according to the procedures steps 1-5 described for the preparation of compound **5007**.

Preparation of compound of formula 5016



5016

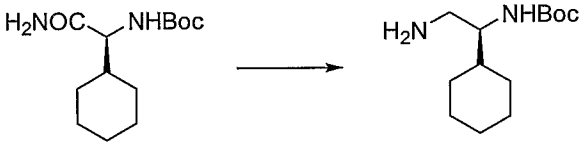
Step 1



5016a 5016b

Compound **5016b** was prepared from **5016a** according to the procedure step 1 described for the preparation of compound **5014b**.

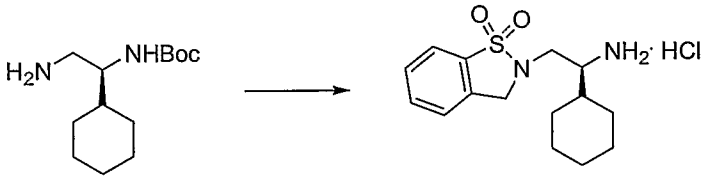
Step 2



5016b 5016c

Compound **5016c** was prepared from **5016b** according to the procedure step 2 described for the preparation of compound **5014c**.

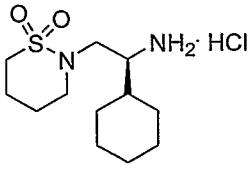
Steps 3-7



5016c 5016

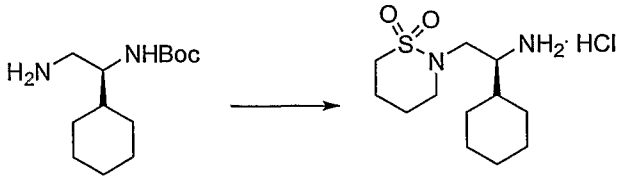
Compound **5016** was prepared from **5016c** according to the procedure steps 3-7 described for the preparation of compound **5010**.

Preparation of compound of formula 5017



5017

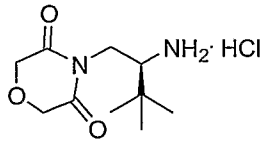
Steps 1-2



5016c 5017

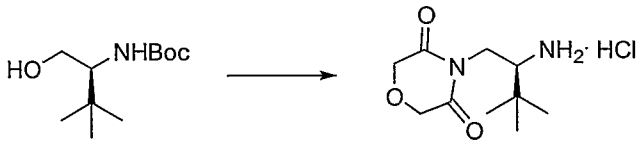
Compound **5017** was prepared from **5016c** and 1,4-butane sultone according to the procedures in steps 1-2 described for the preparation of compound **5013**.

Preparation of compound of formula 5018



5018

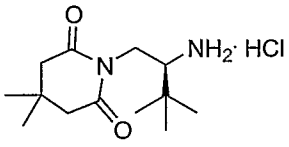
Steps 1-2



5003a **5018**

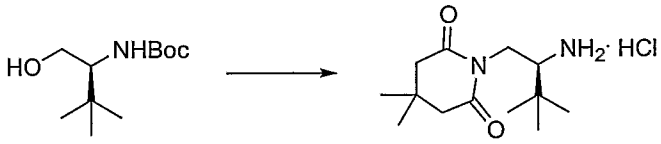
Compound **5018** was prepared from **5003a** and morpholine 3,5-dione according to the procedures in steps 1-2 described for the preparation of compound **5012**.

Preparation of compound of formula 5019



5019

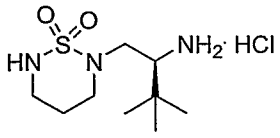
Steps 1-2



5003a **5019**

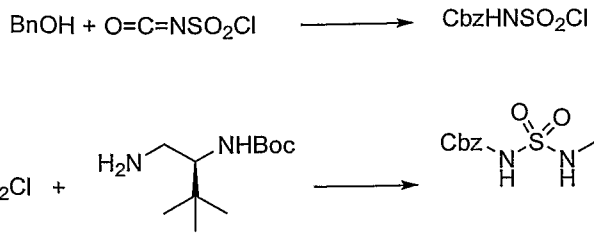
Compound **5019** was prepared from **5003a** and 3,3-dimethyl glutarimide according to the procedures in steps 1-2 described for the preparation of compound **5012**.

Preparation of compound of formula 5020



5020

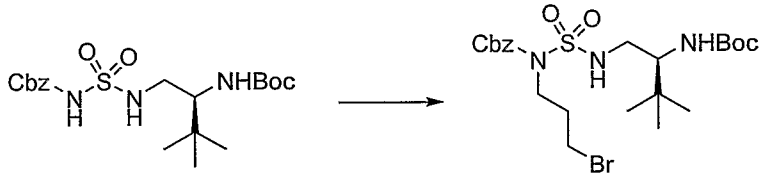
Step 1



5020a **5020b**

To the solution of chlorosulfonyl isocyanate (0.80 mL, 9.25 mmol) in anhydrous CH_2Cl_2 (20 mL) at 0°C was added slowly benzyl alcohol (0.96 mL, 9.25 mmol). The resulting solution was stirred at 0°C for 30 min before it was added slowly to a solution of amine **5020a** (2.0 g, 9.25 mmol) in anhydrous CH_2Cl_2 at 0°C. The mixture was stirred at 0°C for 1 h and at rt for another hour before it was concentrated to dryness. The residue was dissolved in EtOAc and washed with 1 N HCl solution twice and brine once. It was then dried, filtered and concentrated. The products were purified by silica gel flash chromatography (20-70% acetone in hexanes) to give product **5020b** (3.11g, 78%).

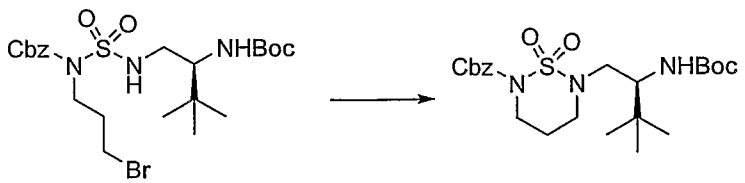
Step 2



5020b **5020c**

To the solution of **5020b** (1.60 g, 3.73 mmol), triphenylphosphine (1.46 g, 5.57 mmol) and 3-bromo-1-propanol (0.36 mL, 4.12 mmol) in anhydrous CH_2Cl_2 (40 mL) at 0°C was added diisopropylazodicarboxylate (DIAD, 1.10 mL, 5.55 mmol). The resulting solution was then stirred at rt for 2 h before it was concentrated *in vacuo* to dryness. The residue was purified by silica gel flash chromatography (10-40% acetone in hexanes) to give the product **5020c** (1.62 g, 79%).

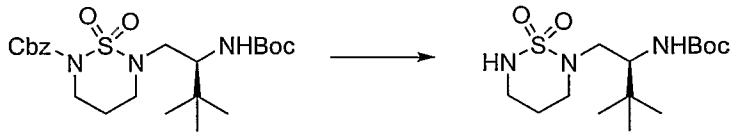
Step 3



5020c **5020d**

The suspension of **5020d** (1.61 g, 2.93 mmol) and cesium carbonate (1.43 g, 4.39 mmol) in anhydrous DMF (100 mL) was stirred at rt for 18 h. Water (50 mL), brine (50 mL) and EtOAc (300 mL) were added and the layers were separated. The organic solution was washed water (3 x 150 mL) before it was dried, filtered and concentrated to give the desired product **5020d** (1.40 g, quant.).

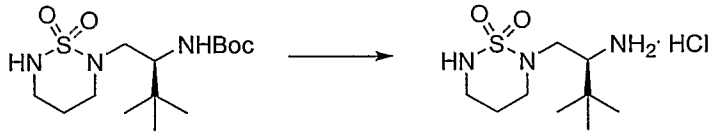
Step 4



5020d **5020e**

The mixture of **5020d** (1.40 g, 2.98 mmol) and 10% Pd-C (wet basis) in absolute ethanol (50 mL) and methanol (50 mL) was vigorously stirred at rt for 2.5 h. The catalyst was filtered off through a celite pad to give product **5020e** (1.10 g, quant.).

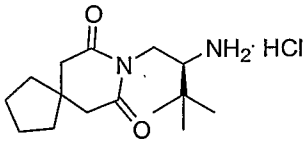
Step 5



5020e **5020**

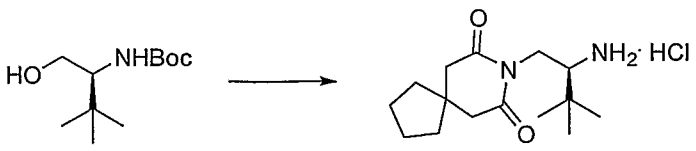
The solution of **5020e** in 4 N HCl in dioxane was stirred at rt for 4 h. It was then concentrated to dryness *in vacuo* to give product **5020**.

Preparation of compound of formula 5021



5021

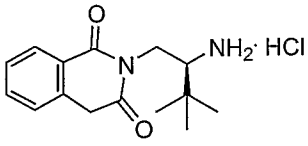
Steps 1-2



5003a **5021**

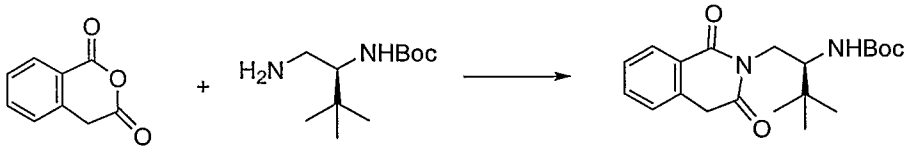
Compound **5021** was prepared from **5003a** and tetramethylene glutarimide according to the procedures in steps 1-2 described for the preparation of compound **5012**.

Preparation of compound of formula 5022



5022

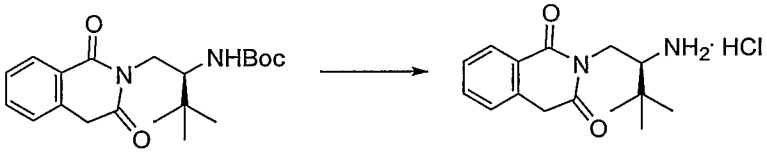
Step 1



5022a **5004a** **5022b**

The mixture of anhydride **5022a** and amine **5004a** in anhydrous toluene was brought to reflux and stirred for 46 h before it was cooled and concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (5-40% EtOAc in hexanes) to give the product **5022b** (2.90 g, 79%).

Step 2

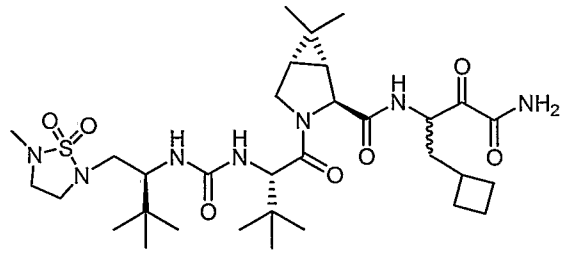


5022b **5022**

The compound **5022b** was treated with 4 N HCl for 30 min at rt and concentrated *in vacuo* to give product **5022**.

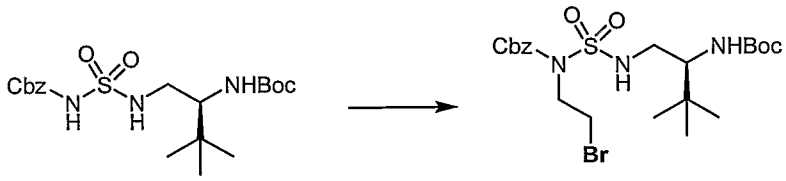
PREPARATION OF EXAMPLES

Preparation of compound of 5146



5146

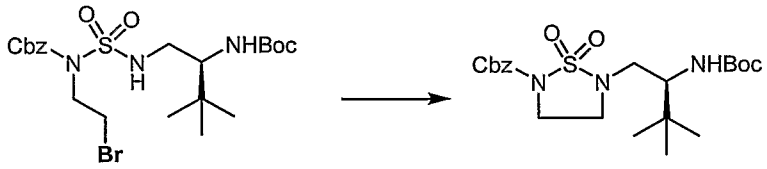
Step 1



5020b **5051a**

To the solution of **5020b** (2.0 g, 4.66 mmol), triphenylphosphine (1.83g, 6.99 mmol) and 2-bromo-ethanol (0.31 mL, 5.12mmol) in anhydrous CH_2Cl_2 (30 mL) at 0°C was added diisopropylazodicarboxylate (DIAD, 0.996 mL, 6.99 mmol). The resulting solution was then stirred at rt for 2 h before it was concentrated *in vacuo* to dryness. The residue was purified by silica gel flash chromatography (10-40% acetone in hexanes) to give the product **5051a** (1.50 g, 63%).

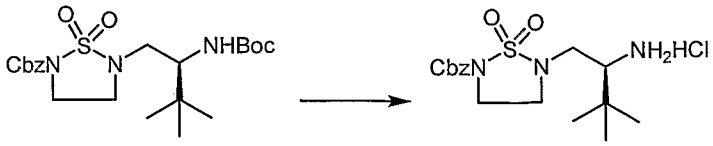
Step 2



5051 a **5051b**

The suspension of **5051a** (1.5 g, 2.79 mmol) and cesium carbonate (1.36 g, 4.19 mmol) in anhydrous DMF (100 mL) was stirred at rt for 18 h. Water (50 mL), brine (50 mL) and EtOAc (300 mL) were added and the layers were separated. The organic solution was washed water (3 x 150 mL) before it was dried, filtered and concentrated to afford 1.37 g of crude product. Purified via flash column(10-30 % Acetone-hexane) to afford 0.98 g of **5051 b** (82 %).

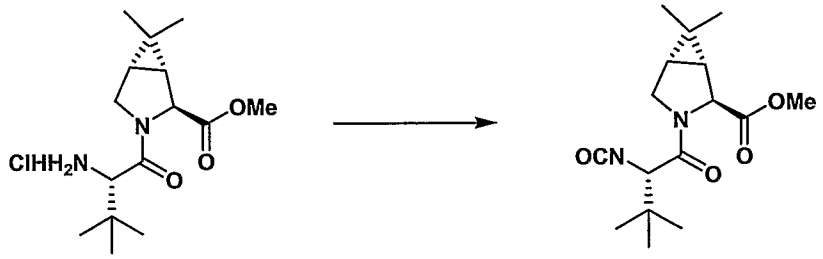
Step 3



5051b **5051c**

To compound **5051b** (0.98 g, 2.15 mmol, 1 equiv.) was added 4 M HCl in dioxane (25 mL) at room temp. Stirred for 1 hr. TLC showed no starting material. Evaporated off the solvent and azeotroped with hexane and then with ether. Washed out the non-polar material with ether and kept under high vac. over the weekend to give the product as a pale yellow solid (842 mg, quant.). Product was used without purification.

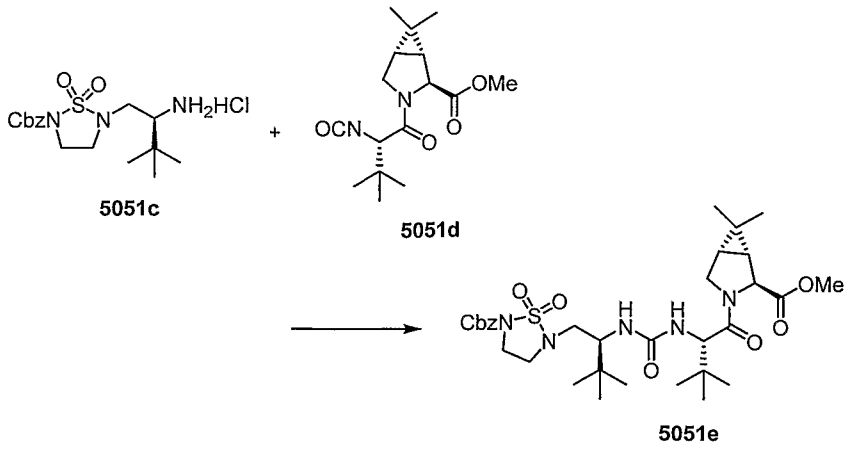
Step 4



1.04 **5051d**

To the amine hydrochloride **1.04** (3g, 9.4 mmol) in Dichloromethane (50 ml) was added 50 ml of saturated $NaHCO_3$. Stirred vigorously at ice temperature for 5 min. Stopped stirring and phosgene (2 equiv. 20 % in toluene, 10 mL) was syringed out to the lower layer and restored the vigorous stirring immediately. Checked the TLC at times and after 2 hrs it showed complete consumption of starting material and then separated the layers. Washed the water layer one more time with dichloromethane(3 ml) and dried over anhydrous sodium sulfate. Filtered and evaporated off the solvent using rotary evaporator under reduced pressure without hot bath to half the volume and then flushed N_2 for 15 minutes. Diluted to 33.5 mL with dichloromethane and used as 0.28 M solution for further couplings.

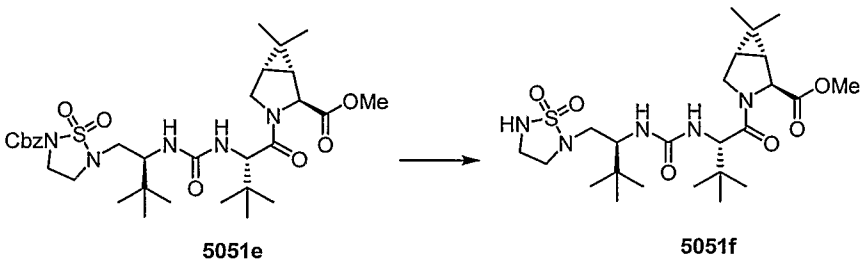
Step 5



5051c 5051d 5051e

To the amine **5051c**, prepared as described before (741 mg, 2.09 mmol, 1 equiv.) in DCM (10 ml) was added DIPEA (8 equiv., 2.19 mL, 12.54 mmol) at ice temperature. Added isocyanate **5051d** (1 equiv, 7.46 of 0.028M solun) under N_2 atm and stirred for 30 min at ice temperature and 90 min at room temperature. Quenched with 10 % citric acid and extracted with EtOAc and washed with brine. Dried over anhydrous sodium sulfate and filtered and evaporated off the solvent. The crude product was purified via flash column (10-40 % % Acetone-hexane) to afford 800 mg of **5051e** as a white solid (58 %). ^{1}H NMR ($CDCl_3$, 300 MHz), δ, 7.4(m, 5 H), 5.3(bs, 2 H), 4.4(d, 2 H,), 4-3.6 (m, 6 H), 3.6 (s, 3H), 3.25 (m,2H), 3(m, 2 H), 1.02- 0.98 (m, 25 H).

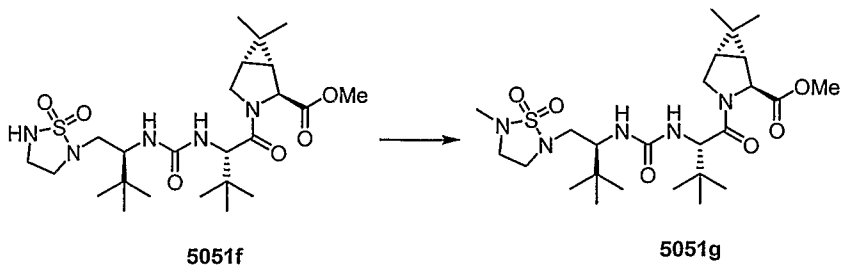
Step 6



5051e 5051f

The mixture of **5051e** (0.600g, 0.904 mmol) and 10% Pd-C (10 % wt., 60 mg) in methanol (10 mL) was vigorously stirred at rt for 1.5 h. The reaction mixture was filtered through a celite pad to give product **5051f** (0.45 g, 94 %.).

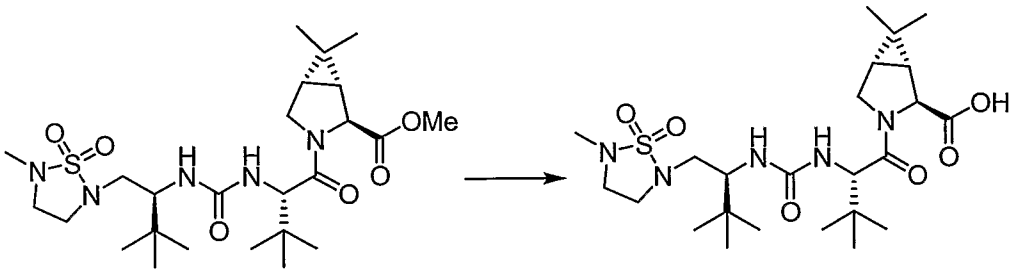
Step 7



5051f 5051g

To the sulfamide **5051f** (400 mg,0.756 mmol, 1 equiv.) in DMF(10 mL) at ice temperature , added Cs_2CO_3 (368 mg, 1.5 equiv, 1.134 mmol) and MeI (3.78mmol, 5 equiv., 0.355 mL) under nitrogen atmosphere. Stirred at room temperature for overnight. As the TLC and LCMS showed no starting material , quenched with water and extracted with EtOAC. Washed 4 times with water and with brine and dried over anhydrous sodium sulfate. Filtered and evaporated off the solvent and purified via flash column(20-40 % acetone-hexane) to afford 390 mg of **5051g** (95%). ^{1}H NMR ($CDCl_3$, 300 MHz) 4.4(d, 1 H,), 3.99-4.01 (d, 1 H), 3.8 (d, 2H), 3.7(s, 3H), 3.6 (m, 2H), 3.25(m, 2H), 3.01 (m,3H), 2.8(s, 3H), 1.4(m, 1H). 1.2(m, 1H), 1.00- 0.98 (m, 24 H).

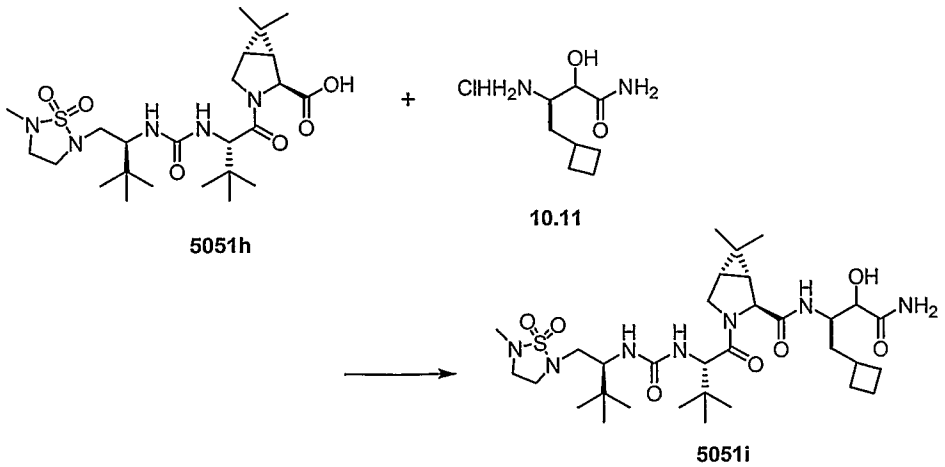
Step 8



5051g **5051h**

To the methyl ester, **5051g** (300 mg, 0.607mmol, 1 equiv.) in dioxane (10 ml) was added LiOH (1.8 mL, 1N in water, 3 equiv) and stirred overnight. Quenched with 1 N HCl and extracted with EtOAC. Washed with brine and dried over anhydrous sodium sulfate. Filtered and evaporated off the solvent to give the crude product (290 mg, 90 %).

Step 9



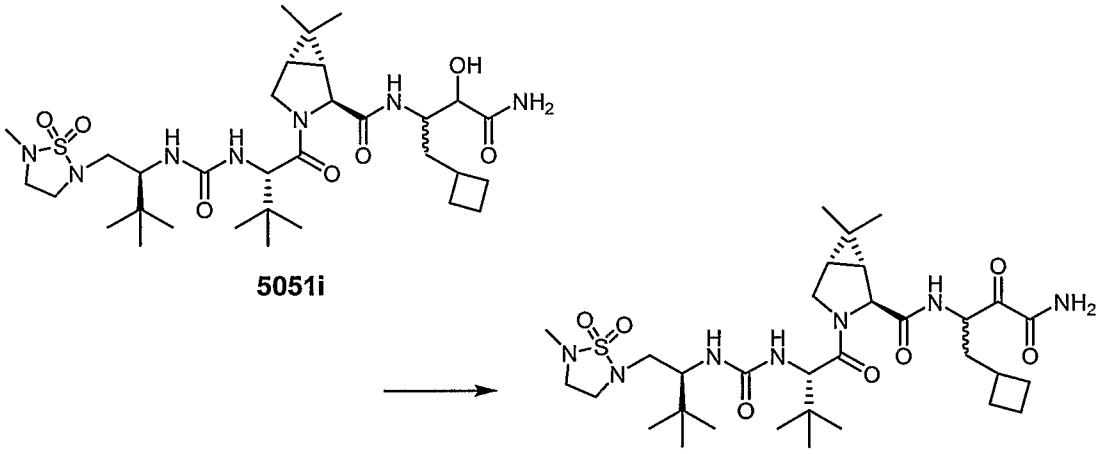
5051h **10.11**

5051i

To solution of the amine **10.11**, prepared as described before (16.51 mg, 0.079mmol, 1.2 equiv.), and **5051h** (35 mg, 0.066 mmol, 1 equiv.) in

DMF (10 ml) at 0 ^{u}C was added HATU (1.2 equiv., 0.079 mmol, 30.18 mg) followed by DIPEA (8 equiv., 92.44 μL, 0.529 mmol). Stirred for 1 h at ice temperature and then 2 h at room temperature. Quenched with 1 N HCl and extracted with EtOAC. Washed with sat'd sodium bicarbonate and then with brine. Dried over anhydrous sodium sulfate, filtered and evaporated off the solvent to give the product (52mg, 100 %).

Step 10

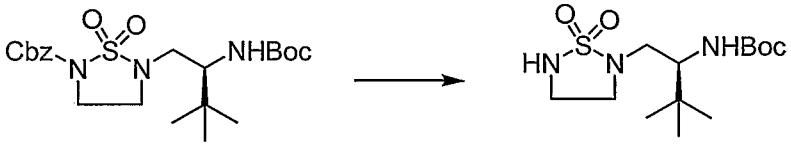


5051i **5146**

To the hydroxy amide **5051i** (60 mg, 0.087mmol, 1 equiv.) in 1:1 mixture of DMF/toluene(6 mL) at ice temperature was added EDCI.HCl(167 mg, 10 equiv., 0.878 mmol) and dichloroacetic acid(36.29 μL, 5 equiv., 0.439 mmol) and stirred for 5 min. Then stirred at room temperature for further 3 hrs. Quenched with brine and washed with 1 N HCl followed by sat'd $NaHCO_3$ and again with brine. Dried over anhydrous sodium sulfate, filtered and evaporated off the solvent. The crude product was purified by preparative TLC (40 % acetone-hexane) to afford 25.2 mg of **5146** (43 %). LRMS , m/z, 682[(M+1)], 375.

Preparation of compound of formula 5237

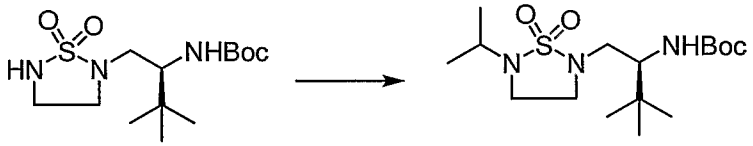
Step 1



5051b **5052a**

To compound **5051b** (1.16 g, 2.5 mmol) in methanol was added Pd/C (5% by wt, 116 mg) under N_2 atmosphere after evacuation. Evacuated again and stirred under H_2 for 90 min. TLC showed complete consumption of starting material. Filtered and evaporated off the solvent to afford **5052a** (819 mg, 100%).

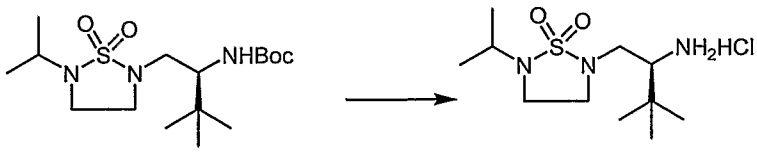
Step 2



5052a **5052b**

To the amino compound (285 mg, 1equiv.) in DMF(10ml) added 2-iodo propane(5 equiv.) and Cesium carbonate (1.5 equiv.) at ice temperature and stirred for overnight. Temperature of the reaction mixture was slowly raised to room temperature. Quenched with water and extracted with EtOAc and washed the combined organic extracts with brine. Dried over anhydrous sodium sulfate , filtered and evaporated off the solvent. The crude product, 5052b was used as it is for next step (310 mg, 96 %). **^{1}H NMR** ($CDCl_3$, 300 MHz) 4.5(d, 1 H,), 3.8-3.6 (m, 2 H), 3.4-3.2 (m, 2H), 3.01-2.8(m, 2H), 1.9 (m, 1H), 1.4 (s,9H), 1.2(dd, 6H), 0.98(s, 9H).

Step 3

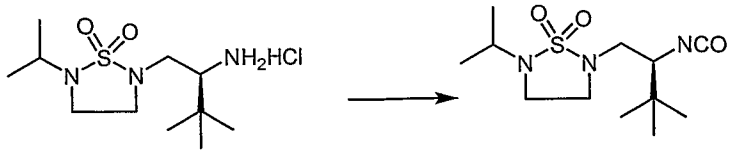


5052b **5052c**

Compound **5052b** was dissolved in 4 N HCl in dioxane at rt and the solution was stirred for 1 hr. TLC showed no starting material. Evaporated off

the solvent and azeotroped with hexane and then with ether. Kept under high vac. for overnight to afford 221 mg of **5052c** (96 %).

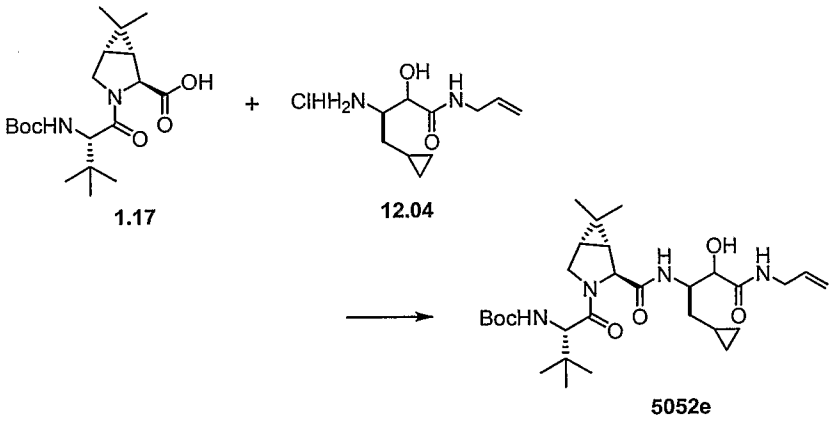
Step 4



5052c **5052d**

Dissolved the amine salt (180mg, 0.60mmol, 1 equiv.) in DCM (5 ml) and added 5 mL of $NaHCO_3$ (sat'd) at ice temperature. Stirred vigorously for 2 min. Stopped stirring and syringed out phosgene (2 equiv.) to the reaction mixture and restored the vigorous stirring. After 90 min. separated the layers and dried over anhydrous sodium sulfate. Filtered and evaporated off the solvent without hot bath under vac. Diluted with DCM and kept as stock solution of 0.02 M.

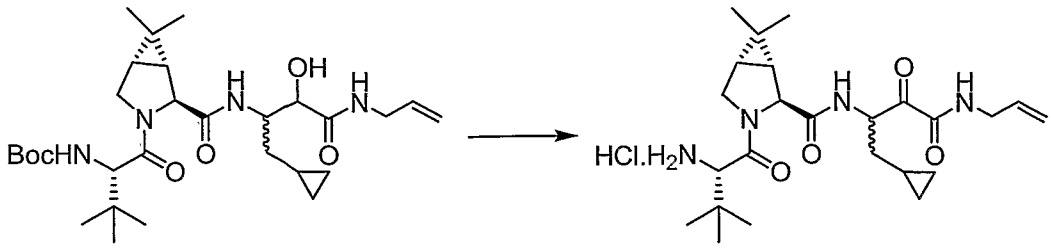
Step 5



1.17 **12.04** **5052e**

To a mixture of acid **1.17** (500mg, 1.37 mmol, 1 equiv.) and amine hydrochloride(317.8 mg, 1.37 mmol, 1 equiv.) in DMF at ice temperature was added HATU (1.2 equiv. 619 mg) and DIPEA (6 equiv., 8.15mmol, 1.42 mL) under N_2 and stirred for overnight . The temperature was slowly allowed to raise to room temperature. Quenched with 1 N HCl and extracted with EtOAc. Washed with $NaHCO_3$ (sat) and then with brine. Washed with ice-cold water(5 x 20 ml) and again with brine. Dried over anhydrous Na_2SO_4.Filtered and evaporated off the solvent to afford 580 mg of **5052e** (77 %).

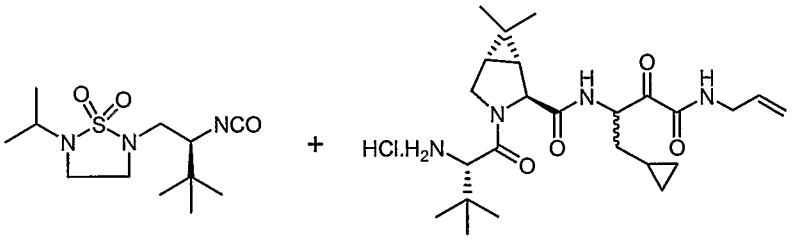
Step 6



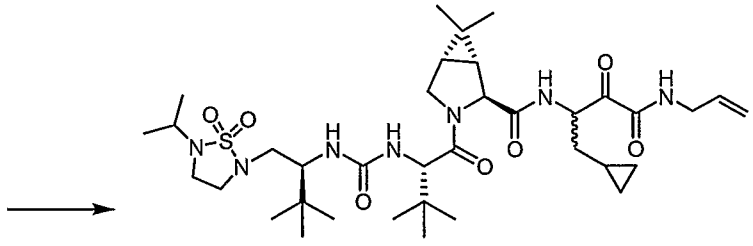
5052e 5052f

To the crude hydroxy amide **5052e** (1.05mmol, 580mg, 1 equiv.) in DCM (15 mL) at room temperature, was added Dess-Martin Periodinane(897mg, 2.11 mmol, 2 equiv.). Stirred for 5 h at rt. Quenched with saturated $NaHCO_3$ and sodium bisulfite and extracted with EtOAc. Washed with brine and dried over anhydrous sodium sulfate . Filtered and evaporated off the solvent. Crude product was purified by flash column(10-40 % acetone-hexane) to afford 450 mg of the ketoamide product. The product was dissolved in 4 N HCl solution in dioxane and stirred at rt for 3 h before it was concentrated to dryness *in vacuo* to give **5052f** (0.40 g, 77 %).

Step 7



5052d 5052f

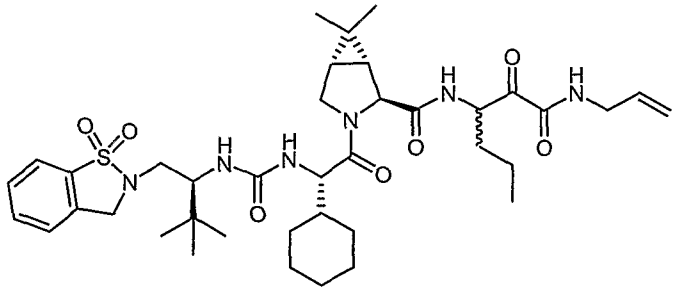


5237

To the amine salt, **5052f**, (20mg, 0.041mmol, 1 equiv.) in DCM (5 ml) was added DIPEA (6 equiv.) at ice temperature. Added isocyanate, **5052d** (1.1 equiv, 0.045 mmol, 2.27mL of 0.02M solun) under N2 atm and stirred for 30 min at ice temperature and 90 min at room temperature. Quenched with citric acid and extracted with EtOAc and washed with brine. Dried over anhydrous sodium sulfate and filtered and evaporated off the solvent. The

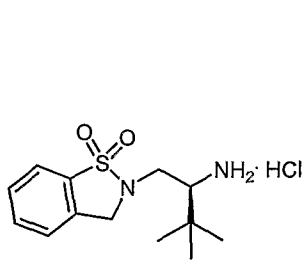
crude product was purified via flash column (10-40 % acetone-hexane) to afford 12 mg of **5237** (40 %).

Preparation of Compound 5250



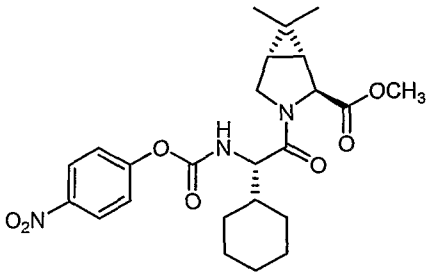
5250

Step 1

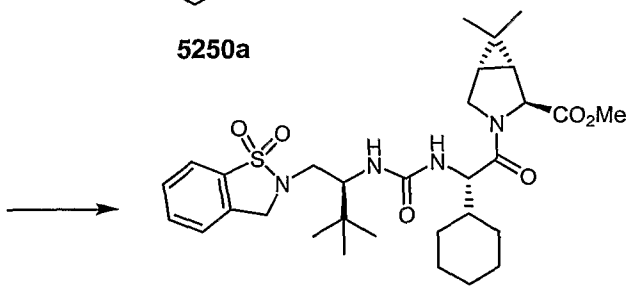


5010

+



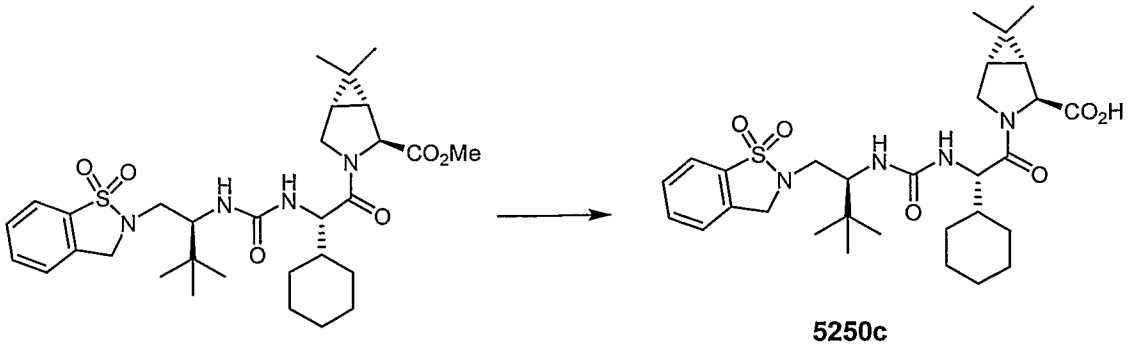
5250a



5250b

Compound **5250a** was prepared from compound **20.03** according to the procedures described for the preparation of **20.08**. To the solution of amine **5010** (0.817 g, 2.68 mmol) and carbamate **5250a** (0.976 g, 2.06 mmol) in anhydrous DCM (60 mL) at 0°C was added DIPEA (0.90 mL, 5.15 mmol). The solution was allowed to warm to rt along with ice bath and stirred for 18 h before it was concentrated. The residue was dissolved in EtOAc and washed with 5% H_3PO_4 solution and saturated sodium bicarbonate solution. It The products were purified by silica gel flash chromatography to give product **5250b** (1.07 g, 86%).

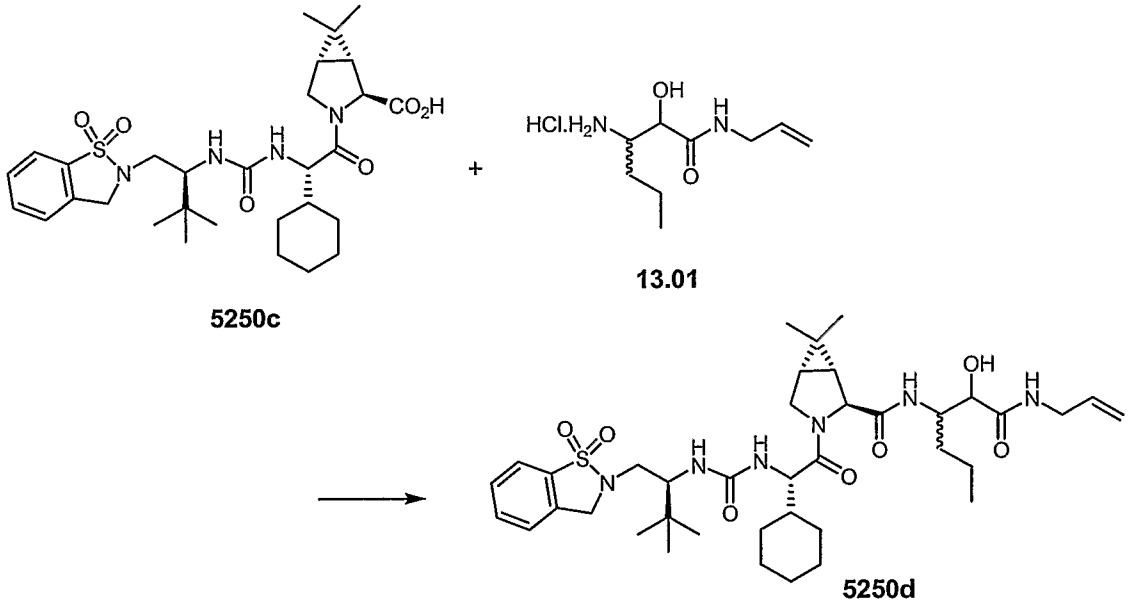
Step 2



5250b 5250c

The solution of methyl ester **5250b** (1.06 g, 1.76 mmol) and LiOH (0.105 g, 4.40 mmol) in THF/MeOH/H_2O (1:1:1, 30 mL) was stirred at room temperature for 4 h. Methanol and THF were removed under reduced pressure. The aqueous solution was acidified to PH~2 using 1 N aqueous HCl solution (50 mL) and saturated with solid sodium chloride before it was extracted with EtOAc (3x150 mL). The organic solutions were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a white solid **5250c** (quantitative).

Step 3

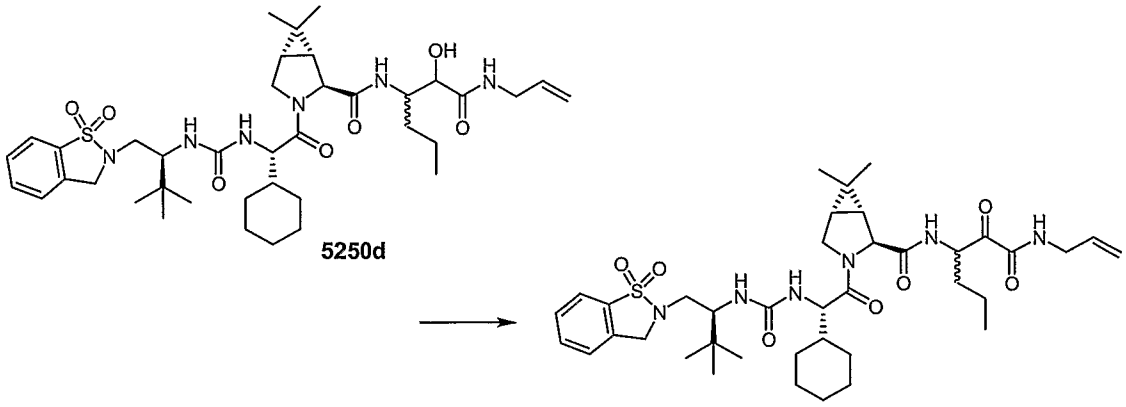


5250c 13.01 5250d

To the suspension of **5250c** (0.052 g, 0.088 mmol), HOOBt (0.022 g, 0.132 mmol), EDCI (0.027 g, 0.141 mmol) and amine hydrochloride **13.01** (0.030 g, 0.132 mmol) in anhydrous DMF (6 mL) and DCM (6 mL) at -20°C was added 4-methylmorpholine (0.030 mL, 0.273 mmol). The mixture was stirred at -20°C for 20 min and then in a refrigerator for 18 h. Brine (30 mL) and 5% aqueous phosphoric acid solution (30 mL) were added followed by

EtOAc (100 mL). The layers were separated and the organic solution was washed with 5% aqueous phosphoric acid solution (50 mL) and saturated sodium bicarbonate solution (2 x 50 mL) before it was dried, filtered and concentrated to give product **5250d** (quantitative).

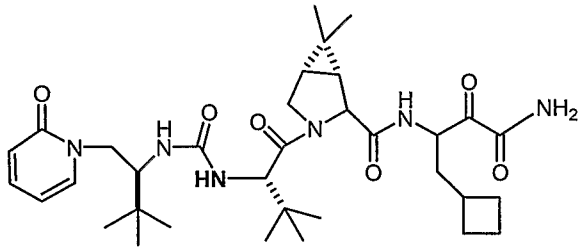
Step 4



5250d **5250**

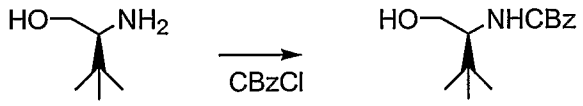
The mixture of hydroxyamide **5250d** and Dess-Martin periodinane (g) in CH_2Cl_2 was stirred for 2 h, quenched with saturated $Na_2S_2O_3$ solution and saturated $NaHCO_3$ solution. After layers were separated, the organic solution was extracted with DCM twice and the combined organic solution was dried, filtered and concentrated to give g product **5250** (0.048 g, 72 %, two steps).

Preparation of compound 5648



5648

Step 1

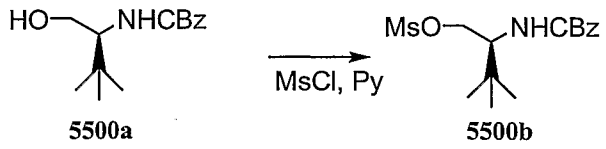


(S) -*tert*-leucinol **5500a**

To a cooled solution (0 °C) of (S) –*tert*-leucinol (5.0 g, 42.7 mmol) in CH_2Cl_2 (100.0 mL) was added benzyl chloroformate (6.7 mL, 47.0 mmol), followed by Hunig's base (9.3 mL, 53.3 mmol). The reaction mixture was allowed to warm to room temperature overnight, diluted with ethyl acetate

(500 mL), washed with 10 %KH_2PO_4, followed by saturated $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$ and concentrated to yield **5500a** (10.7 g, 100%).

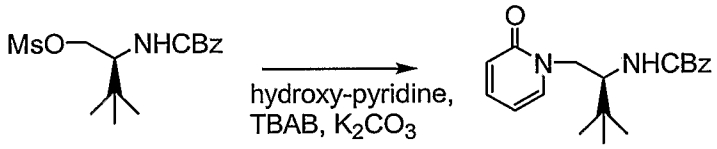
Step 2



5500a **5500b**

To a cooled solution (0 °C) of **5500a** (10.7 g, 42.7 mmol) in CH_2Cl_2 (100.0 mL) was added pyridine (20.0 mL), followed by methanesulfonyl chloride(3.63 mL, 47.0 mmol). The reaction mixture was allowed to warm to room temperature overnight, concentrated, redissolved in ethyl acetate (500 mL), washed with saturated $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, concentrated and purified by flash chromatography over SiO_2 using ethyl acetate/hexane (1:4) to yield **5500b** (14.0 g, 100 %).

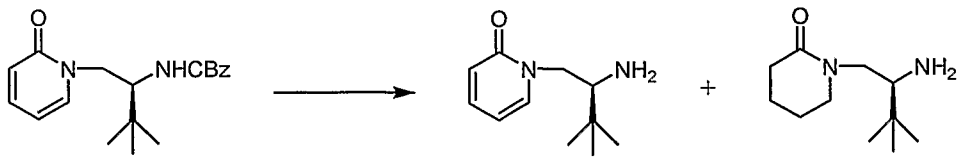
Step 3



5500b **5500c**

To a solution of **5500b** (3.1g, 9.9 mmol) in PhMe(72 mL) containing water (400 μL) was added TBAB (582 mg, 1.8 mmol), K_2CO_3(2.72 g, 1.97 mmol), 1-hydroxypyridine (937 mg, 9.85 mmol). The reaction mixture was refluxed overnight with stirring, filtered, evaporated and concentrated. The crude was purified by flash chromatography over SiO_2 using ethyl acetate/CH_2Cl_2 (1:9 to 1:1) to yield **5500c**(1.15 g, 35 %).

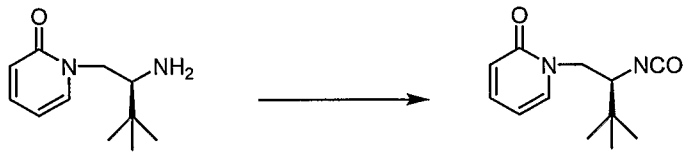
Step 4



5500c **5500d** **5500e**

To a solution of **5500c** (1.15 g) in MeOH (50 mL) was added Pd/C(10% w/w, 450 mg) and placed in a Parr shaker under a hydrogen atmosphere (40 PSI).**5500d** was formed quantitatively when the reaction was stopped after 1.2 h and **5500e** was formed quantitatively after 4 h. In either case the reaction mixture was filtered over a short pad of celite to yield the corresponding amine.

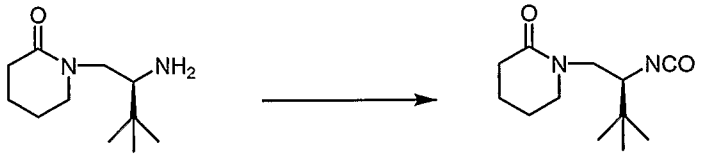
Step 5



5500d **5500f**

Saturated $NaHCO_3$ (7.0 mL) was added to an ice-cold solution of **5500d** (194.0 mg, 1 mmol) in CH_2Cl_2 (7 mL). The reaction mixture was stirred vigorously for 10 min. and $COCl_2$ (1.85 M solution in toluene, 1.35 mL) was added to it and stirring was continued at room temperature for 1h. The organic layer was dried over $MgSO_4$, filtered and concentrated to half the volume to yield **5500f** as a solution in CH_2Cl_2. **5500f** was stored as a 0.05 M solution in CH_2Cl_2.

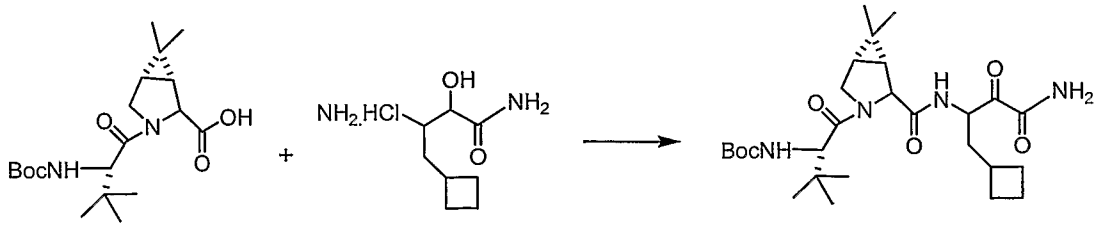
Step 6



5500e **5500g**

Compound **5500g** was synthesized using the procedure of step 5 in the preparation of **5500**.

Step 7

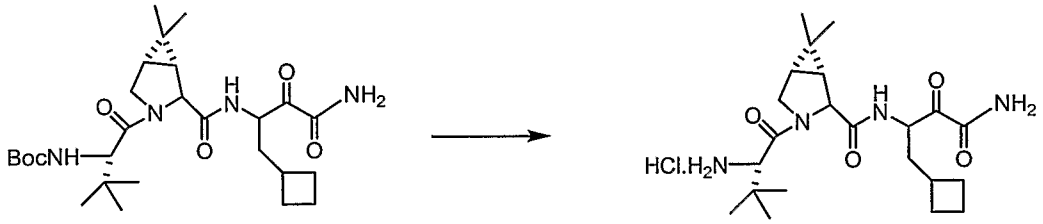


1.17 10.11 5500h

To a cooled solution (O oC) of the acid (**1.17**, 368.5 mg) and (**10.11**, 565.3mg) in DMF (10.0 mL) was added HATU (1.03 g), followed by DIPEA (1.382 mL). The reaction mixture was stirred at 0 oC for 1h and at room temperature for 2h, diluted with ethyl acetate (20.0 mL), washed with 1N HCl, brine, dried over $NaHCO_3$, filtered, concentrated.

To the crude in PhMe/DMSO (10.0 mL, 1:1) at 0 °C was added EDCI (5.2 g), followed by dichloroacetic acid (447 μL). The ice bath was removed and the reaction was stirred at room temperature for 2 h. To it was added EtOAc (75 mL) the reaction mixture was washed with H_2O (25.0 mL), with saturated $NaHCO_3$ and brine, then purified over SiO_2 using acetone/ hexane (1:9 to 9:1) to yield **5500h**.

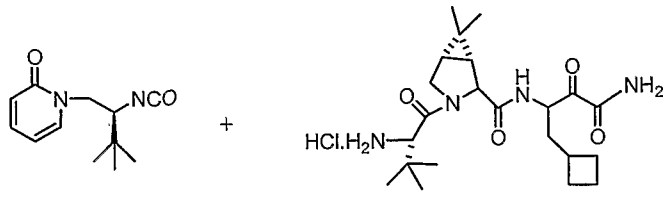
Step 9



5500h 5500i

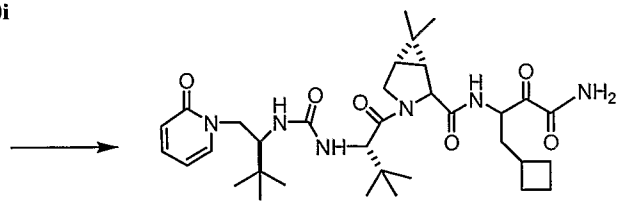
Compound **5500h** was dissolved in 4N HCl in dioxane (25 mL). The reaction was stirred at room temperature for 30 min. and concentrated to yield a white solid, **5500i** (350.0 mg).

Step 10



5500f

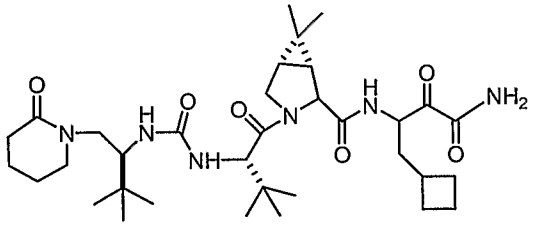
5500i



5648

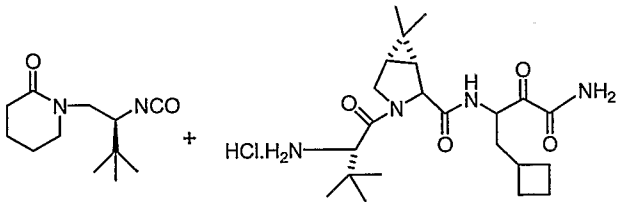
To a cooled solution (O ^{0}C) of the amine hydrochloride **5500i** (25 .0 mg, 0.051 mmol) in CH_2Cl_2 (2.0 mL) was added **5500f** (2.5 mL, 0.135 mmol), followed by DIPEA (68 uL, 0.4 mmol). The reaction mixture was stirred at room temperature for 1.2 h, diluted with ethyl acetate (20.0 mL), washed with 3% citric acid, brine, dried over $NaHCO_3$, filtered , concentrated and purified over SiO_2 using acetone-hexane (1:9) to yield **5648** (10.0 mg).LCMS 641.2 (M+H).

Preparation of compound 5644



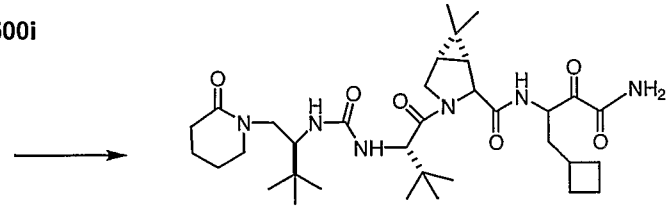
5644

Step 11 .



5500g

5500i

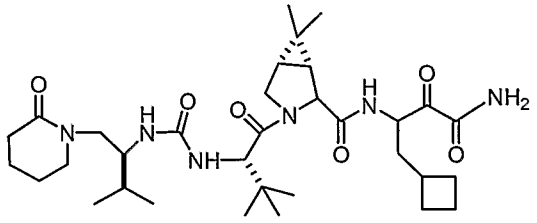


5644

Compound **5644** was synthesized using the procedures described for the preparation of **5648**. LCMS 645.0 (M+H).

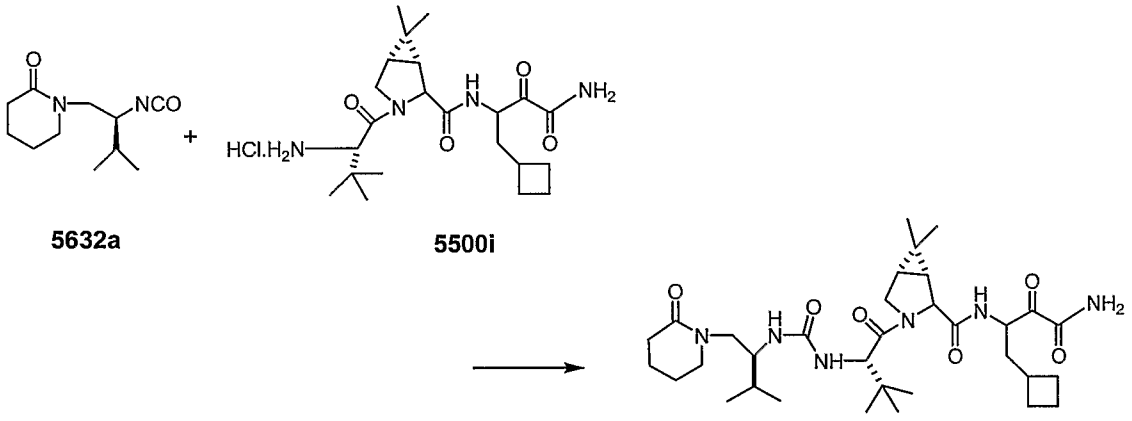
A number of analogs of **5644**, described in **Table 2** were prepared from **5500g** using the procedures described in the preparation of **5644**.

Preparation of compound 5632



5632

Step 1

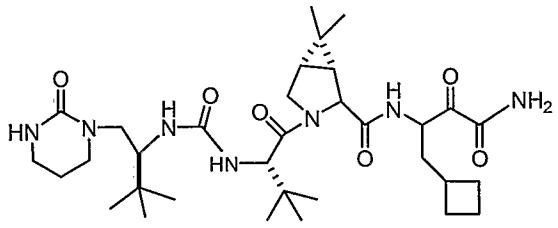


5632a **5500i** **5632**

Compound **5632a** was prepared from (*S*)-N-boc valinol according to the procedures in the preparation of **5500g** (steps 1-6). Compound **5632** was synthesized according to procedures described for the preparation of **5648**. LCMS: 631.1 (M+H)

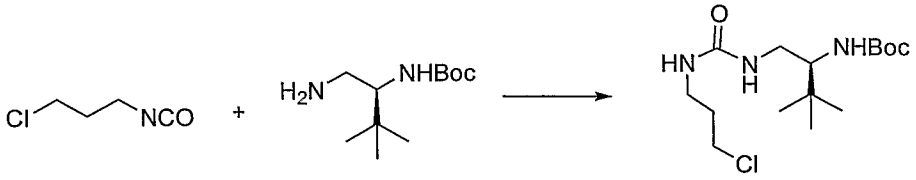
A number of analogs of compound **5632** in **Table 2** were prepared from **5632a** using the same procedures as in the preparation of **5632**.

Preparation of compound 5665



5665

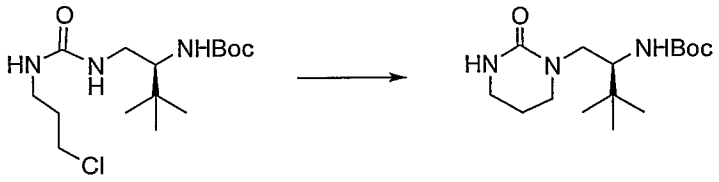
Step 1



5022a **5004a** **5520a**

To a cooled (0 ^{0}C) of amine **5004a** (560.0 mg, 2.58 mmol) in CH_2Cl_2 (15.0 mL) was added chloropropyl isocyanate (Aldrich, 531 mL, 5.16 mmol) and the reaction mixture was stirred at room temperature for 12 h, washed with saturated $NaHCO_3$, brine, dried over $MgSO_4$, filtered, concentrated and purified over SiO_2 using ethyl-acetate-hexane (1:1) to yield **5520a** (660 mg, 1.91 mmol, 76%).

Step 2



5520a **5520b**

To a cooled solution of **5520a** (660.0 mg, 1.96 mmol) in THF (30 mL) was added NaH. (60% dispersion in mineral oil, 313.0 mg, 7.84 mmol). The reaction mixture was allowed to warm up to room temperature over 4 hour, carefully quenched with ice cold water, extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$ filtered and concentrated. The crude was purified over SiO_2 using ethyl acetate-hexane (1:1) to yield **5520b** (220.0 mg, 1.0 mmol).

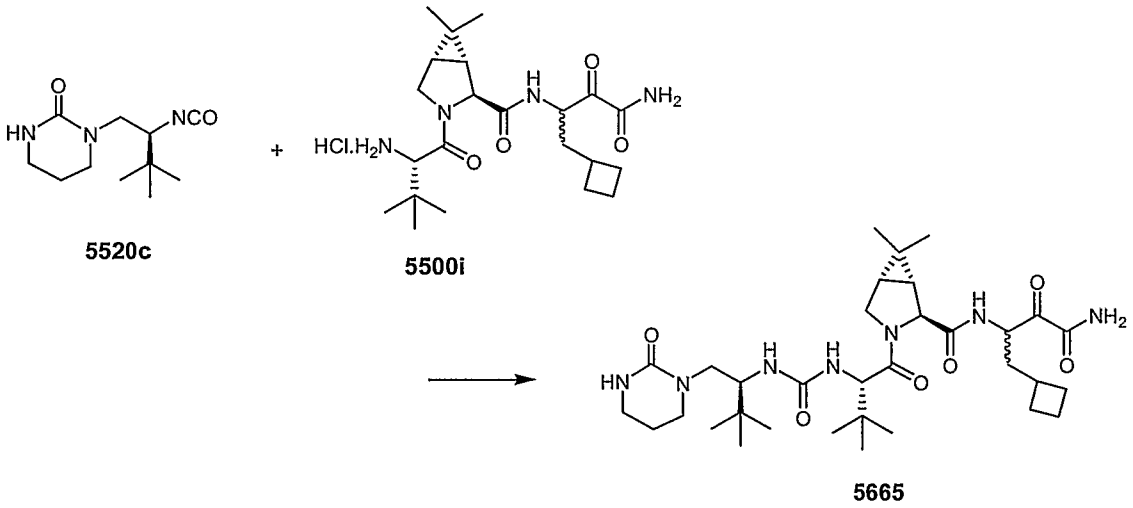
Step 3



5520b 5520c

To **5520b** (660.0 mg, 1.96 mmol) was added 4N HCl in dioxane (25 mL). The reaction was stirred at room temperature for 30 min and concentrated to yield a white solid which was dissolved in CH_2Cl_2 (7.0 mL) and sat'd $NaHCO_3$ (7.0 mL) was added to it. After stirring vigorously for 10 min, the layers were allowed to separate and phosgene (2.5 equiv.) was added to the organic layer in one shot. Vigorous stirring was resumed immediately, the ice bath was removed and stirring was continued for 1 h, the layers were separated. The organic layer was dried over $MgSO_4$, filtered and concentrated to half to its volume and **5520c** was stored as a 0.05 M solution in CH_2Cl_2.

Step 4

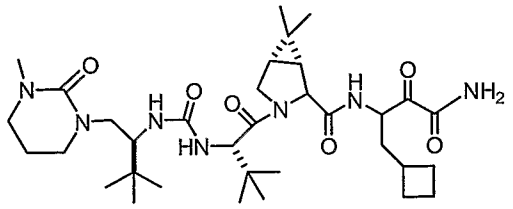


5520c 5500i 5665

To a cooled solution (O ^{0}C) of the amine hydrochloride **5500i** (25 .0 mg, 0.051 mmol) in CH_2Cl_2 (2.0 mL) was added **5520c** (2.5 mL, 0.135 mmol), followed by DIPEA (68 uL, 0.4 mmol). The reaction mixture was stirred at room temperature for 1.2 h, diluted with ethyl acetate (20.0 mL), washed with 3% citric acid, brine, dried over $NaHCO_3$, filtered , concentrated and purified over SiO_2 using acetone-hexane (1:9) to yield **5665** (10.0 mg). LCMS 646.2 (M+H).

A number of analogs of **5665** described in **Table 2** were prepared using **5520c** according to the procedures described for the preparation of **5648**.

Preparation of compound **5688**



5688

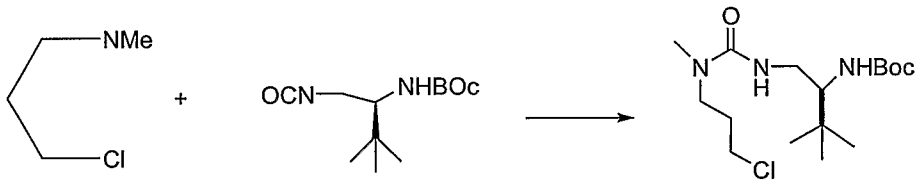
Step 1



5004a **5030a**

Amine **5004a** (998.0 mg, 4.6 mmol) was converted into the corresponding isocyanate **5030a** using the procedure of step 5 in the preparation of **5648**.

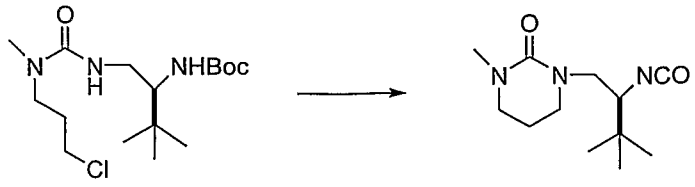
Step 2



5030b **5030a** **5530c**

To the isocyanate in CH_2Cl_2 (10.0 mL) was added *N*-methyl chloropropyl amine **5030b** (Aldrich, 490.0 mg, 4.6 mmol) and the reaction mixture was stirred at room temperature for 12 h, washed with sat'd $NaHCO_3$, brine, dried over $MgSO_4$, filtered, concentrated and purified over SiO_2 using ethyl acetate/hexane to give **5530c** (1.6 g, 4.6 mmol) in 100% yield.

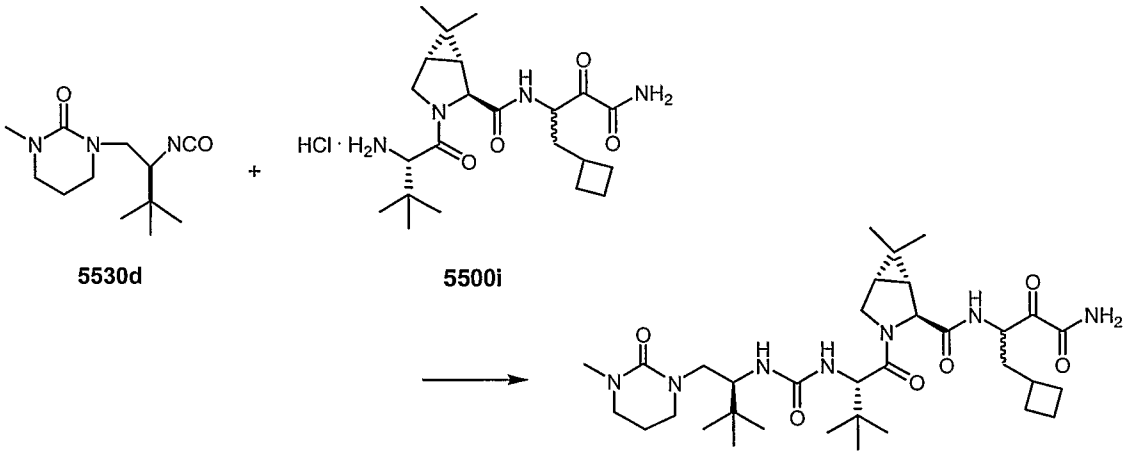
Step 3



5530c **5530d**

Compound **5530c** was converted to **5530d** using the experimental procedures Step 2 and Step 3 in the preparation of compound **5665.**

Step 4

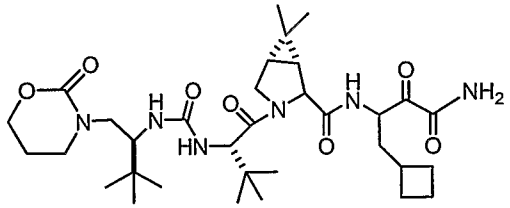


5530d **5500i** **5688**

To a cooled solution (O ^{0}C) of the amine hydrochloride **5500i** (25 .0 mg, 0.051 mmol) in CH_2Cl_2 (2.0 mL) was added **5530d** (2.5 mL, 0.135 mmol), followed by DIPEA (68 uL, 0.4 mmol). The reaction mixture was stirred at room temperature for 1.2 h, diluted with ethyl acetate (20.0 mL), washed with 3% citric acid, brine, dried over $NaHCO_3$, filtered , concentrated and purified over SiO_2 using acetone-hexane (1:9) to yield **5688** (17.0 mg). LCMS 660.2 (M+H).

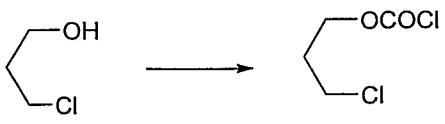
A number of analogs of compound **5688** in **Table 2** were prepared from **5530d** using the procedures described above.

Preparation of compound 5700



5700

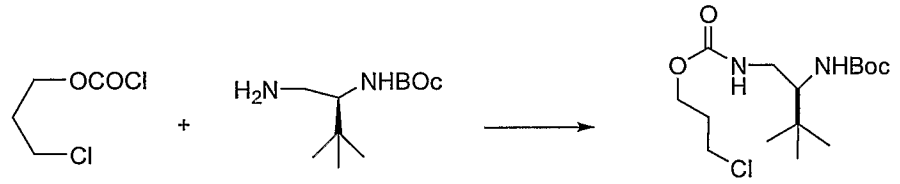
Step 1



5540a **5540b**

Compound 3-chloro-propanol (181uL, 2.51 mmol) was converted into the corresponding chloroformate **5540b** using the procedure step 5 in the preparation of **5648**.

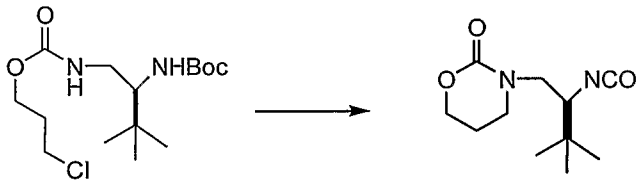
Step 2



5540b **5004a** **5540c**

To the ice-cooled chloroformate in THF (10.0 mL) was added amine **5004a** (543.0 mg, 2.51 mmol) and the reaction mixture was stirred at room temperature for 12 h, diluted with EtOAc (250.0 mL) washed with sat'd $NaHCO_3$, brine, dried over $MgSO_4$, filtered, concentrated to yield **5540c** (664 mg, 1.97 mmol). The crude was used directly in the next step.

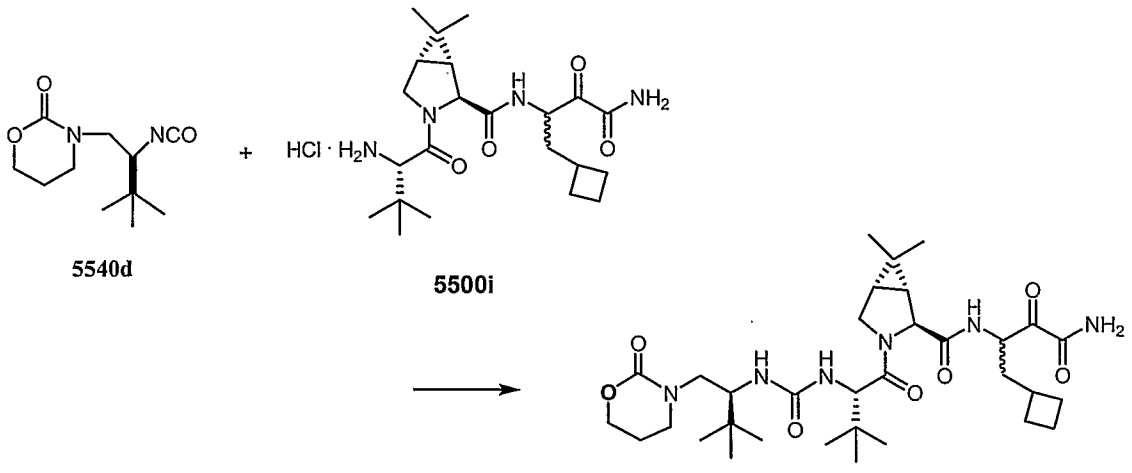
Step 3



5540c **5540d**

Compound **5540c** was converted to **5540d** using the experimental procedures from Step 2 and Step 3 in the preparation of compound **5665**.

Step 4



5540d **5500i**

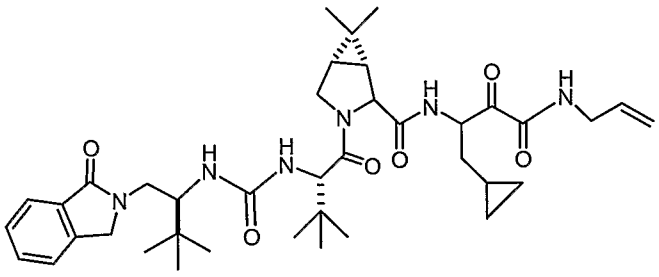
5700

To a cooled solution (0 ^{0}C) of the amine hydrochloride **5500i** (30 .0 mg, 0.0.6 mmol) in CH_2Cl_2 (2.0 mL) was added **5540d** (2.6 mL, 0.131 mmol),

followed by DIPEA (91 uL, 0.52 mmol). The reaction mixture was stirred at room temperature for 1.2 h, diluted with ethyl acetate (20.0 mL), washed with 3% citric acid, brine, dried over $NaHCO_3$, filtered , concentrated and purified over SiO_2 using acetone-hexane (1:9) to yield **5700** (28.0 mg). LCMS 647.2 (M+H).

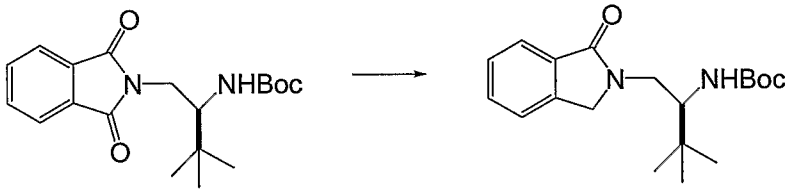
A number of analogs of **5700** in **Table 2** were prepared from **5540d** using procedures described above.

Preparation of target compound 5743



5743

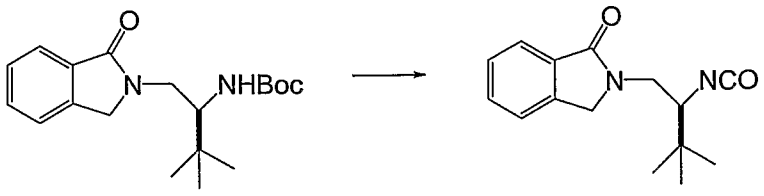
Step 1



5003b **5550a**

To a solution of **5003b** (1.0 g, 2.9 mmol) in MeOH at -4 °C was added $NaBH_4$ (11.52 mmol, 430.0 mg). After stirring for 20 min, the reaction was quenched with CH_2Cl_2/ sat'd $NaHCO_3$ (1:1, 60 mL). The aqueous layer was extracted with DCM (3x 20 mL). The organic layer was dried over $MgSO_4$ and concentrated to yield a white solid which was used directly in the next step. The crude from the previous step was re-dissolved in EtOH (50.0 mL) and Pd/C (10% by weight , 200 mg) was added. The reaction mixture was stirred under a H_2 atmosphere for 12 h, filtered over a pad of celite and concentrated to yield **5550a** (0.99g).

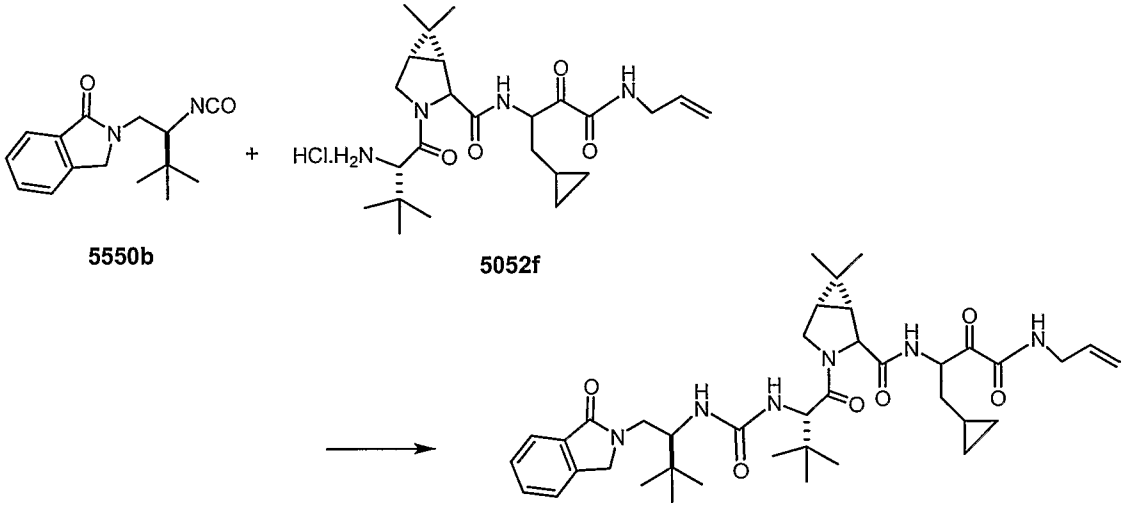
Step2



5550a **5550b**

Compound **5550a** was converted to **5550b** using the experimental procedures from Step 3 in the preparation of compound **5665**.

Step 3

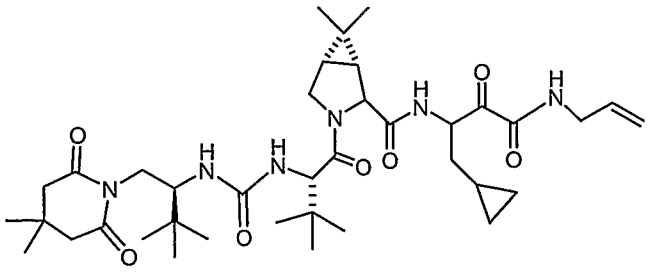


5550b **5052f** **5743**

To a cooled solution (0 ^{0}C) of the amine hydrochloride **5550d** (45 .0 mg, 0.094 mmol) in CH_2Cl_2 (2.0 mL) was added **5550b** (2.8 mL, 2.0 mmol), followed by DIPEA (100 uL, 0.52 mmol). The reaction mixture was stirred at room temperature for 1.2 h, diluted with ethyl acetate (0.0 mL), washed with 3% citric acid, brine, dried over $NaHCO_3$, filtered , concentrated and purified over SiO_2 using EtOAc-CH_2Cl_2 (1:9 to 9:1) to yield product **5743** (32.0 mg). LCMS 705.2 (M+H).

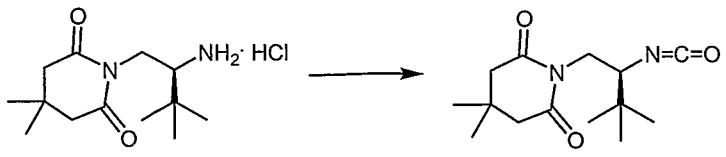
A number of analogs of **5743** in **Table 2** were prepared from **5550b** using procedures described above.

Preparation of compound 5754



5754

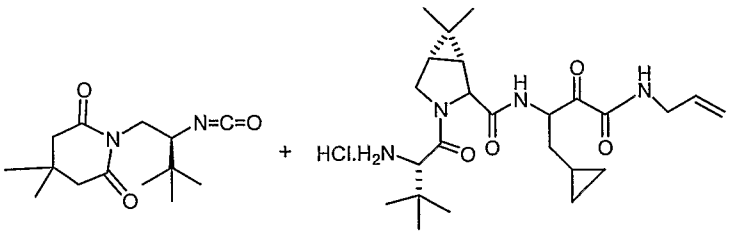
Step 1



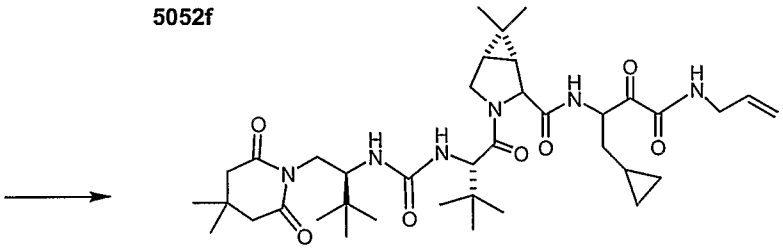
5019 5754a

The isocyanate **5754a** was prepared from amine **5019** according to the procedures described for the preparation of **5052d** from **5052c**.

Step 2



5754a 5052f

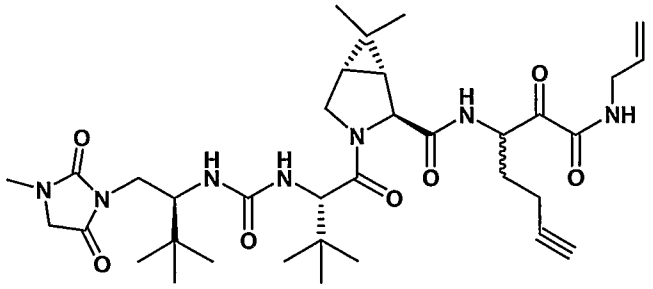


5754

The product **5754** was prepared from **5754a** and **5052f** according to the procedures described for the preparation of compound **5237**.

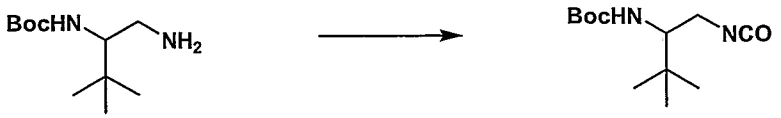
A number of analogs of **5754** in **Table 2** were prepared from **5754a** using procedures described above.

Preparation of compound 5812



5812

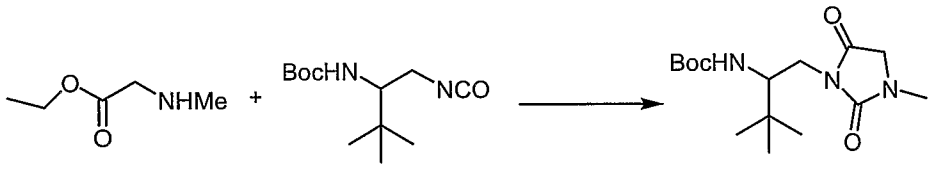
Step 1



5004a **5812a**

To the amine, (1.2 g, 5.5 mmol, 1 equiv.) in DCM (50 mL) was added 50 ml of sat. $NaHCO_3$. Stirred vigorously at ice temperature for 5 min. Stopped stirring and phosgene (2 equiv., 11.09 mmol, 20 % in toluene, 5.96 mL) was syringed out to the lower layer and restored the vigorous stirring immediately. Separated the layers after 1 h. Washed the water layer one more time with DCM (3 ml) and dried over sodium sulfate. Filtered and evaporated at high vac. with out hot bath to half the volume and then purged N_2 for 15 minutes. Diluted to 100 mL in DCM. Used as it is for further reaction.

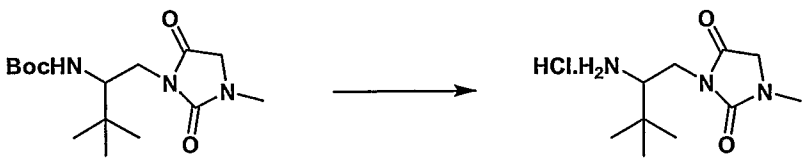
Step 2



5812b **5812a** **5812c**

To the amine **5812b** (Aldrich, 0.5 g, 4.2 mmol, 1 equiv.) in methanol (20 mL) was added the isocyanate (5.5 mmol, 1.3 equiv.) and triethyl amine (3.4 ml, 6 equiv, 25.2 mmol) and refluxed the reaction mixture at 90°C for 48 h. Stirring was continued at 100°C for another 5 h. The mixture was concentrated and purified through a flash column chromatography to give product **5812c** in 96.7 % yield.

Step 3

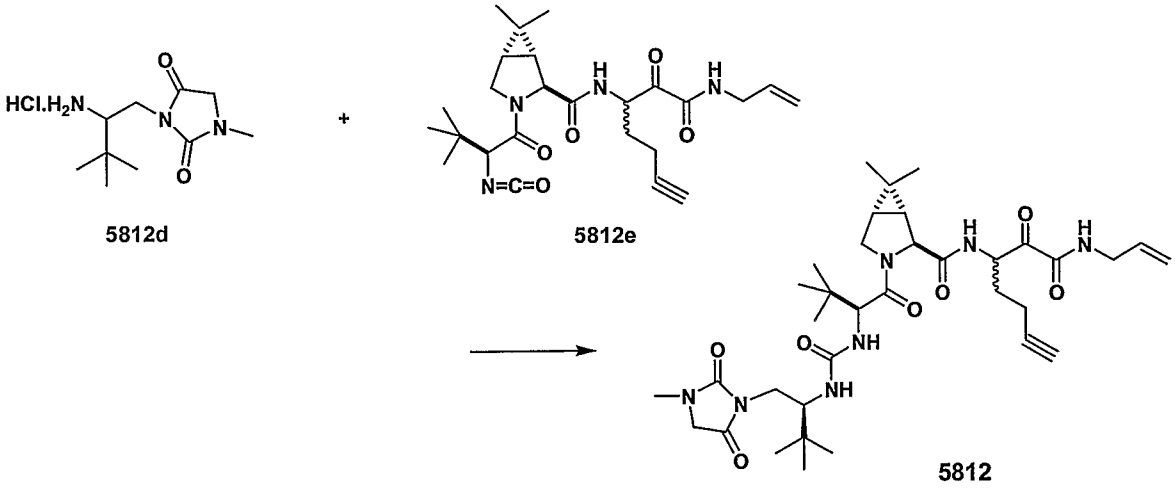


5812c **5812d**

To compound **5812c** (650 mg) was added 4 M HCl/ Dioxane (25 mL) and stirred at room temperature for 0.5 h. Evaporated off the solvent and

azeotroped with hexane and then with ether. Kept under high vac for 4 h to give the product in quantitative yield.

Step 4

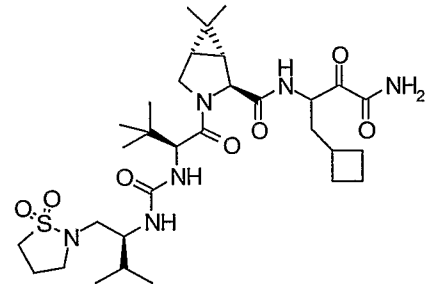
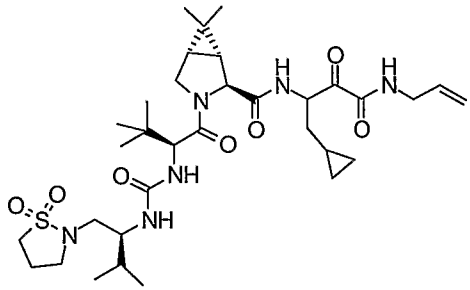
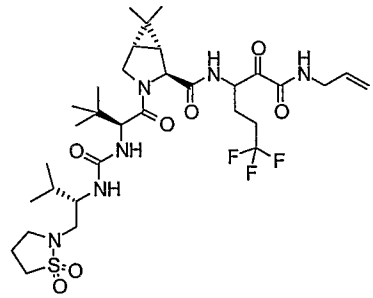


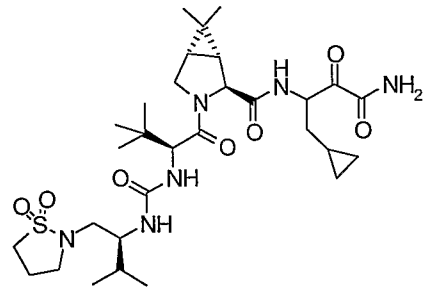
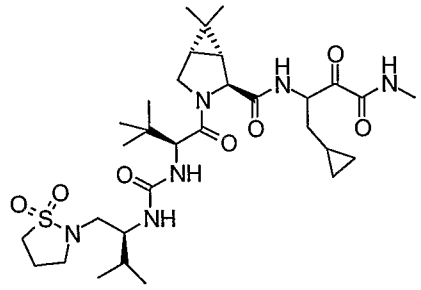
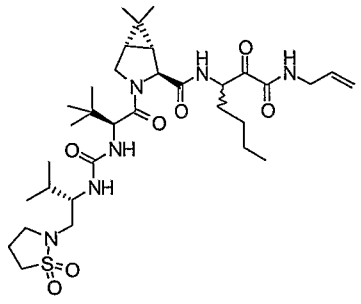
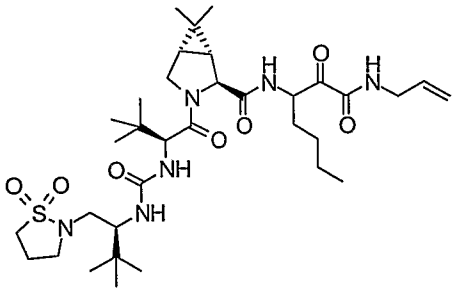
5812d 5812e 5812

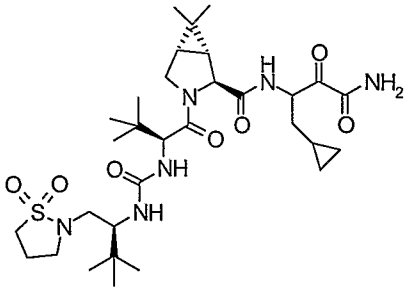
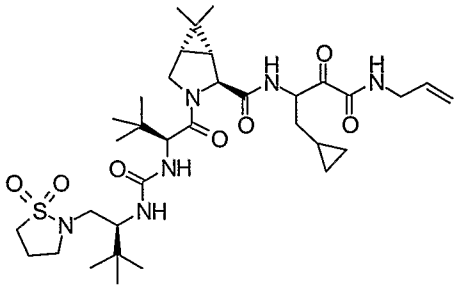
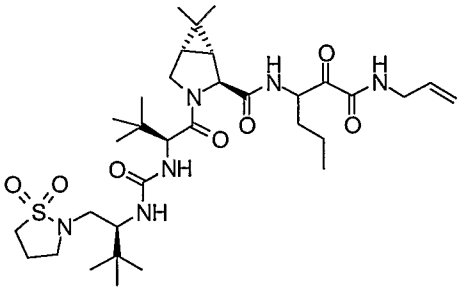
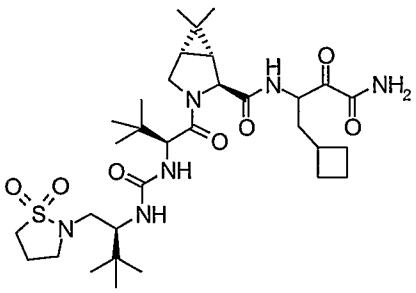
To the amine hydrochloride (20 mg, 0.08 mmol, 1.3 equiv.) in DCM (5 ml) was added DIPEA (6 equiv.) at 0°C. Added isocyanate(3 mL, 0.02M in DCM) under N_2 atmosphere. After stirred for 30 min at 0°C and 90 min at room temperature. Quenched with citric acid and extracted with EtOAc and washed with brine. Dried over anhydrous sodium sulfate and filtered and evaporated off the solvent. The crude product was purified via flash column chromatography (10-40 % acetone-hexane) to give compound **5812** in 41 % yield.

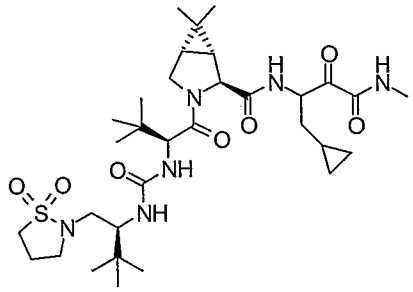
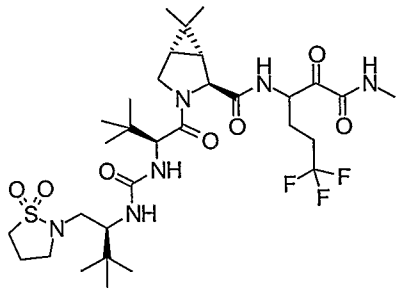
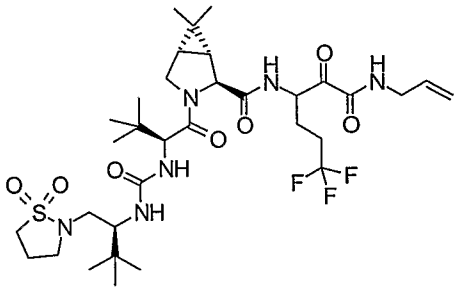
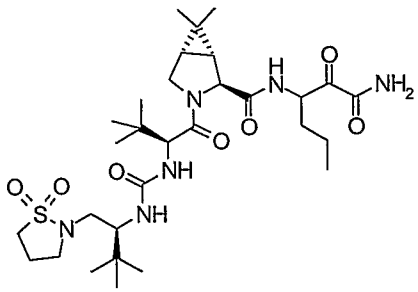
Representative compounds of the invention which exhibit excellent HCV protease inhibitory activity are listed below in **Tables 1**and **2** along with their biological activity in HCV continuous assay (ranges of Ki* values in nanomolar, nM): category A ≤50 nM; category B > 50 nM.

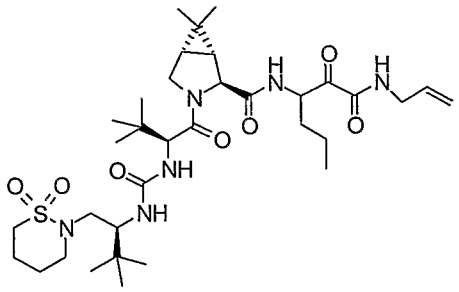
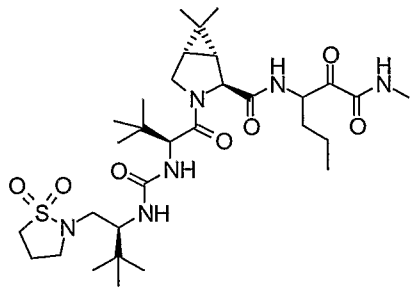
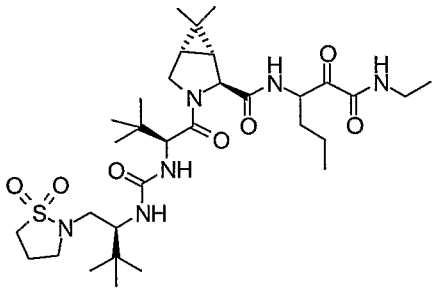
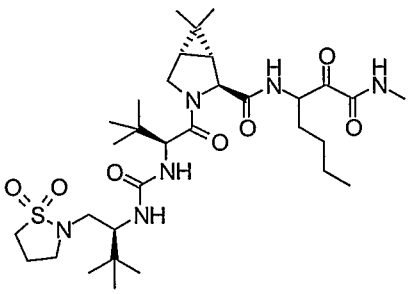
Table 1

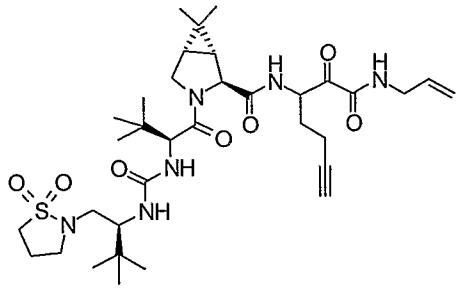
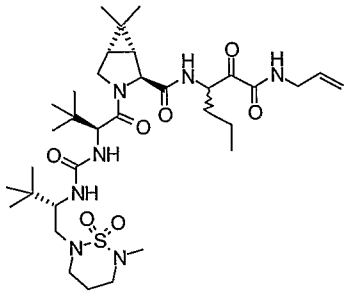
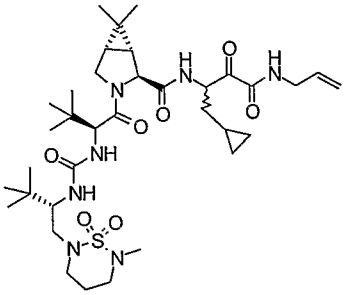
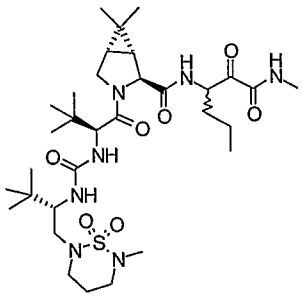
Compound number	structure	Ki*	mol weight
5106		A	652.86009
5107		A	678.89833
5108		B	720.85847

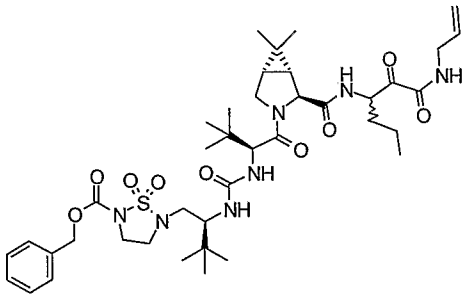
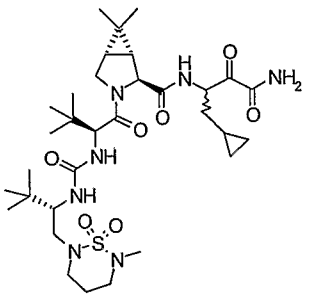
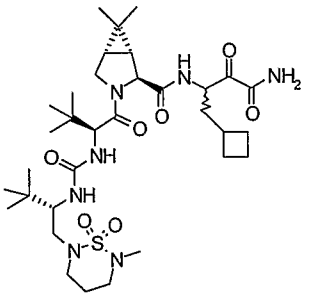
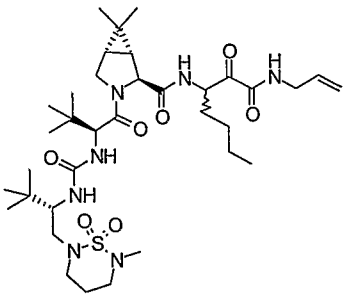
5109		A	638.833
5110		A	652.86009
5111		A	680.91427
5112		A	694.94136

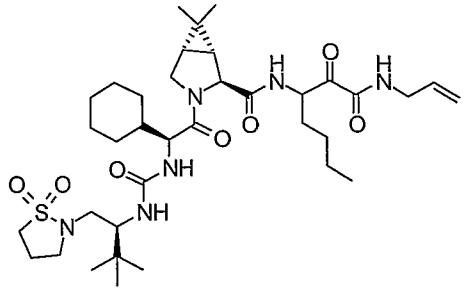
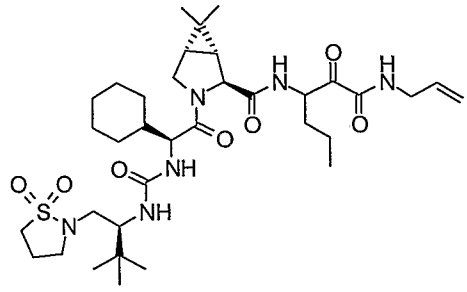
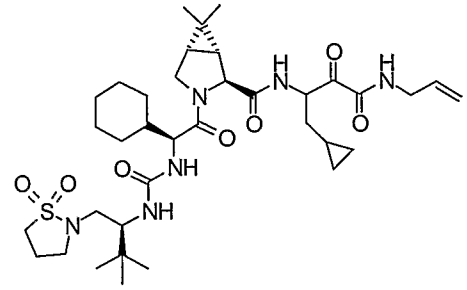
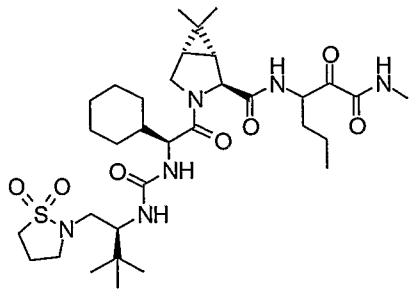
5113		A	652.86009
5114		A	692.92542
5115		A	680.91427
5116		A	666.88718

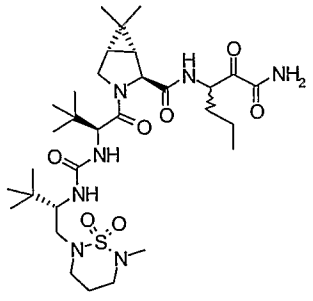
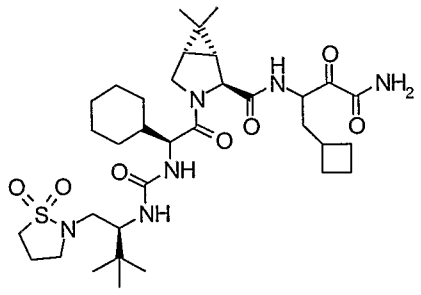
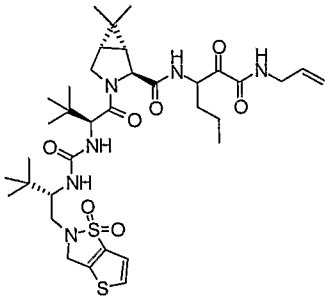
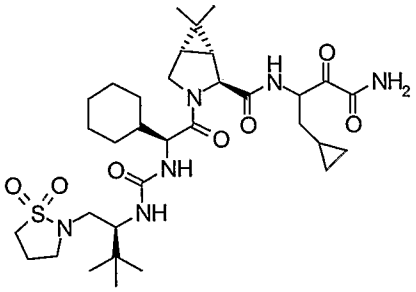
5117		A	666.88718
5118		A	708.84732
5119		A	734.88556
5120		A	640.84894

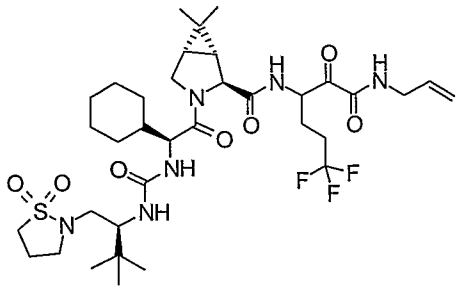
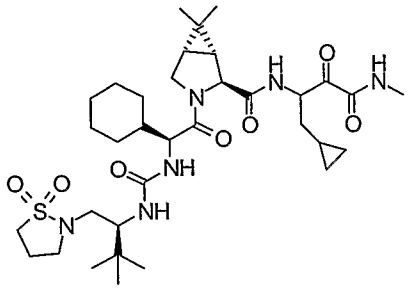
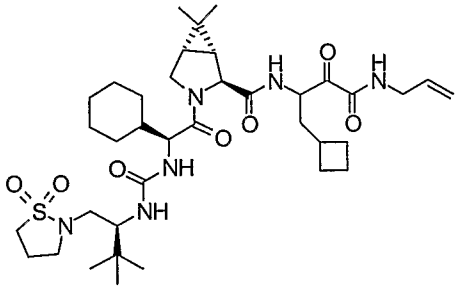
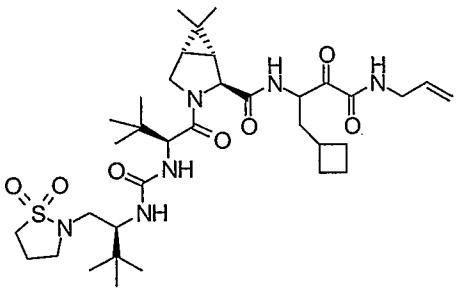
5121		A	694.94136
5122		A	654.87603
5123		A	668.90312
5124		A	668.90312

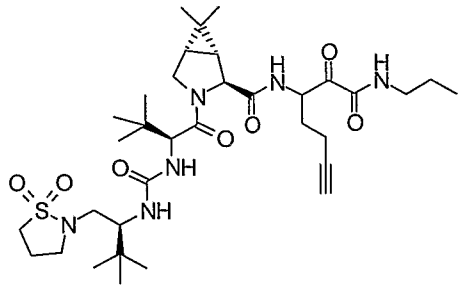
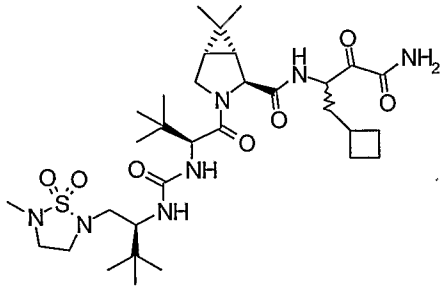
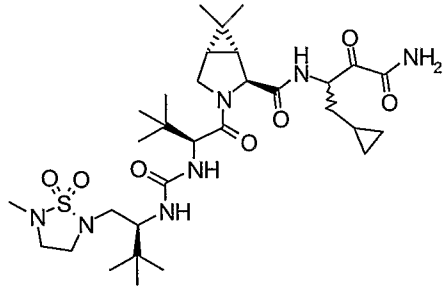
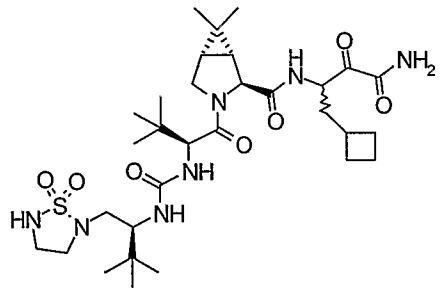
5125		A	690.90948
5126		A	709.95603
5127		A	721.96718
5128		A	683.91779

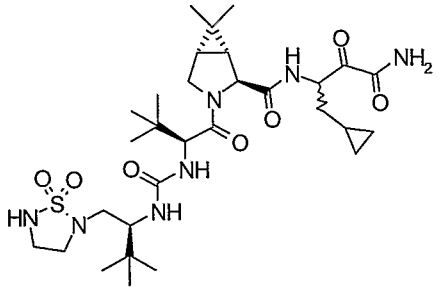
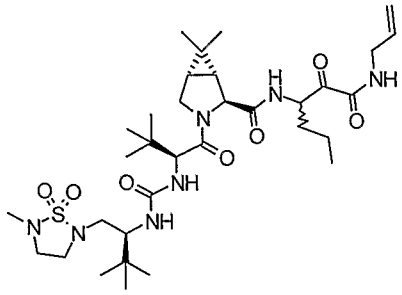
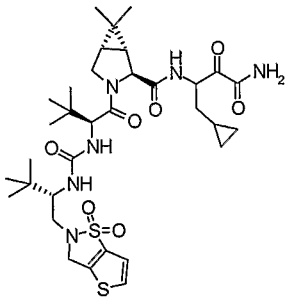
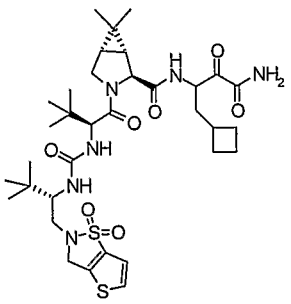
5129		A	816.03767
5130		A	681.90185
5131		A	695.92894
5132		A	723.98312

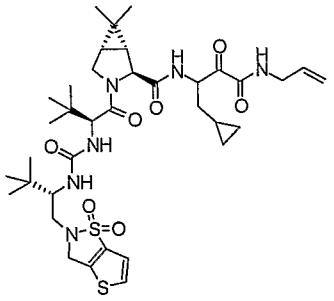
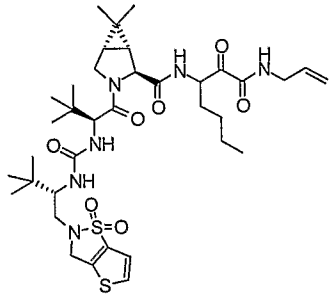
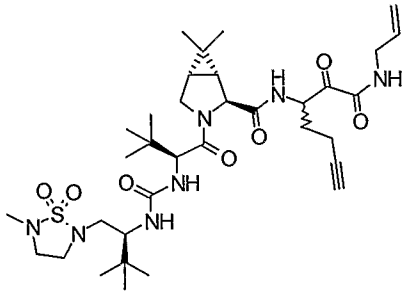
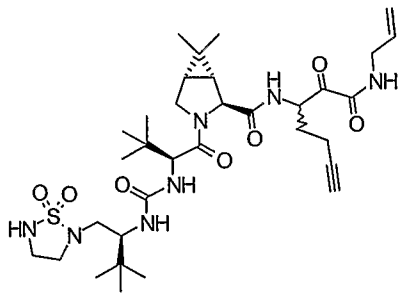
5133		A	720.9796
5134		A	706.95251
5135		A	718.96366
5136		A	680.91427

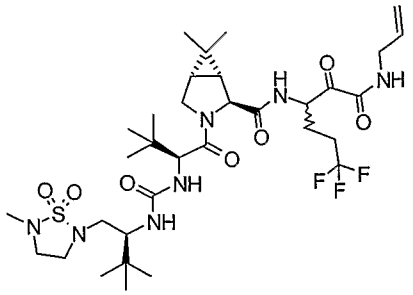
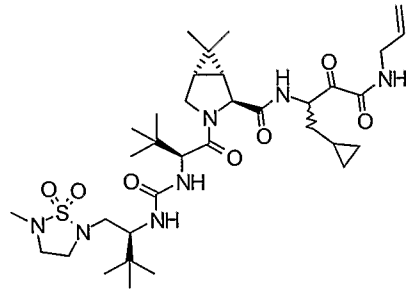
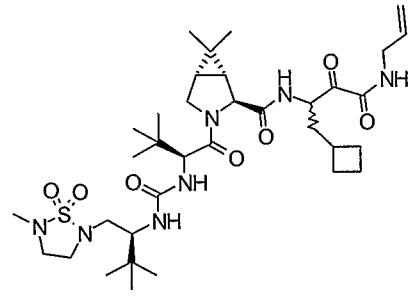
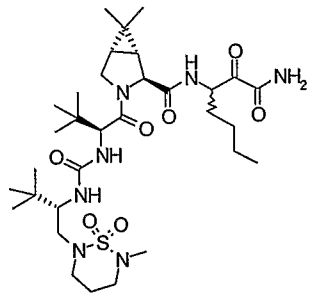
5137		A	669.8907
5138		A	692.92542
5139		A	734.98463
5140		A	678.89833

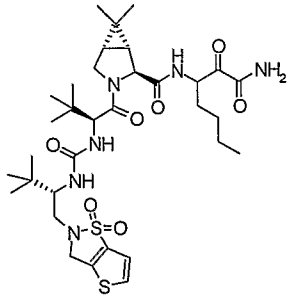
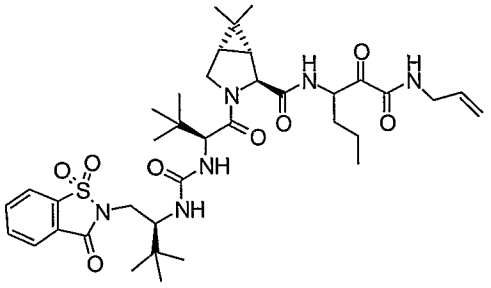
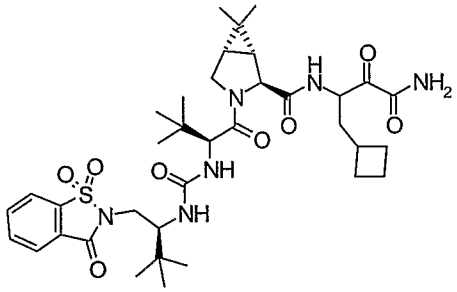
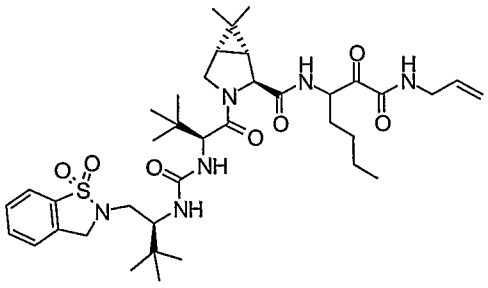
5141		A	760.9238
5142		A	692.92542
5143		A	732.99075
5144		A	706.95251

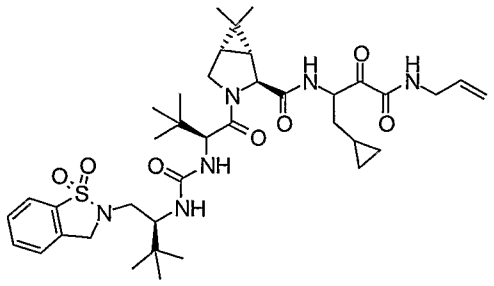
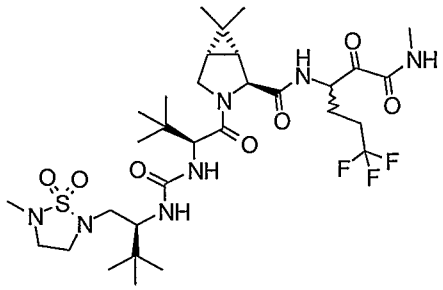
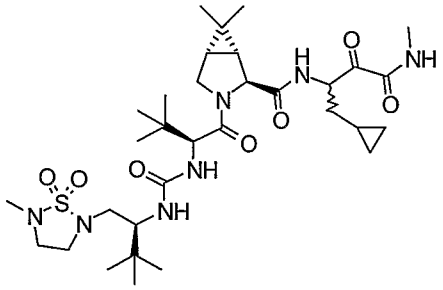
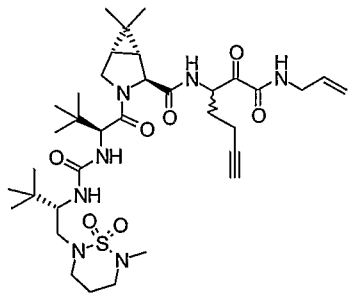
5145		A	692.92542
5146		A	681.90185
5147		A	667.87476
5148		A	667.87476

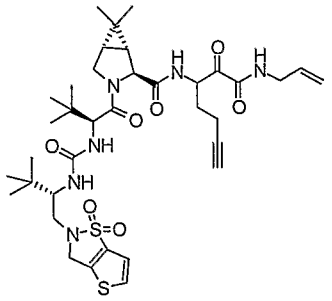
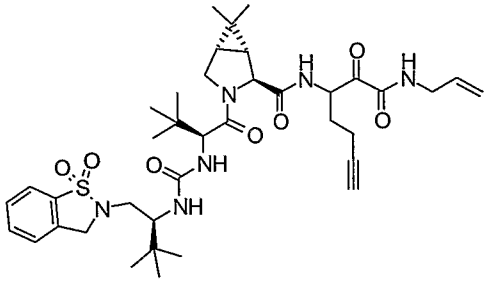
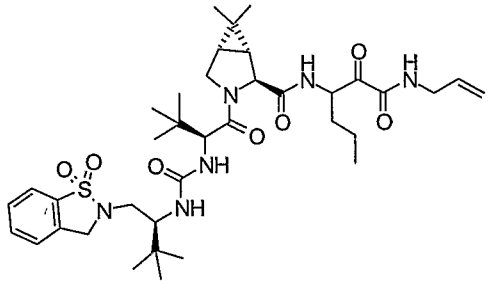
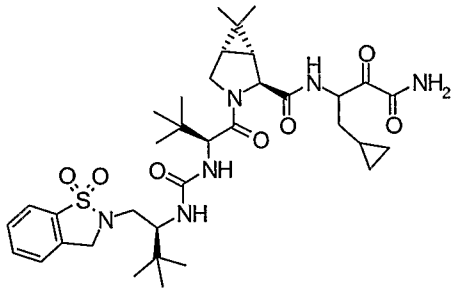
5149		A	653.84767
5150		A	695.92894
5151		A	706.93045
5152		A	720.95754

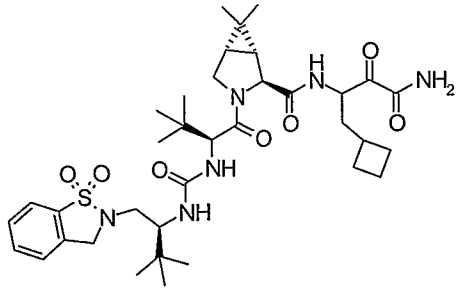
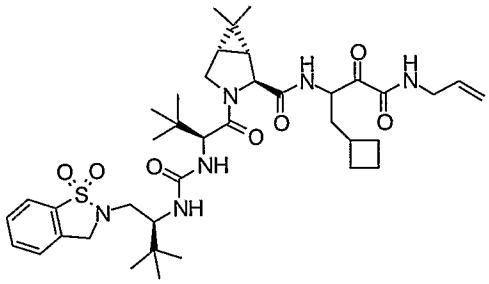
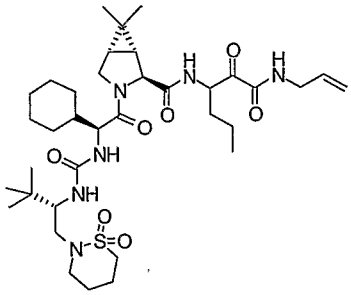
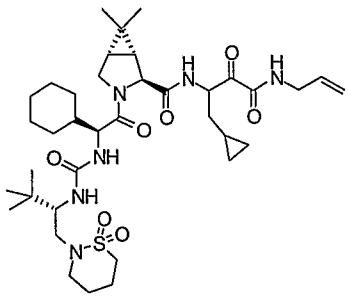
5153		A	746.99578
5154		A	749.01172
5155		A	705.92415
5156		A	691.89706

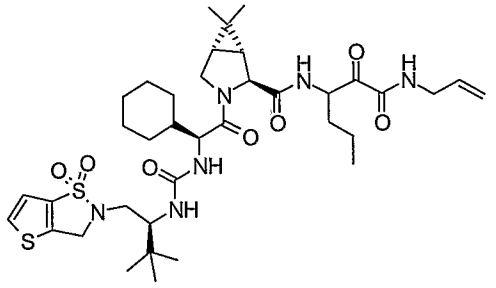
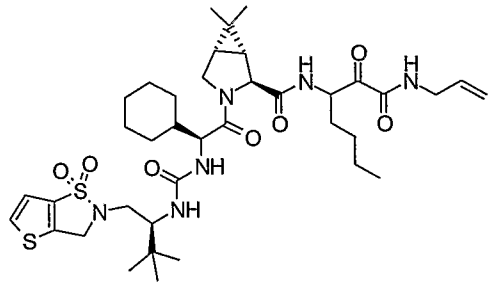
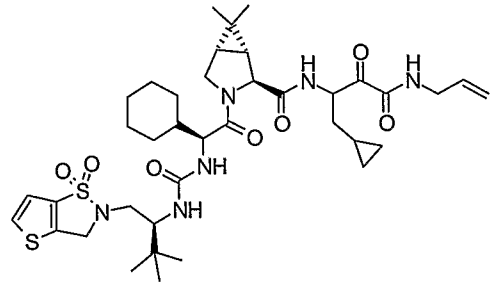
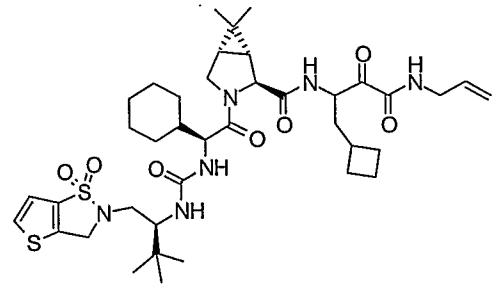
5157		A	749.90023
5158		A	707.94009
5159		A	721.96718
5160		A	683.91779

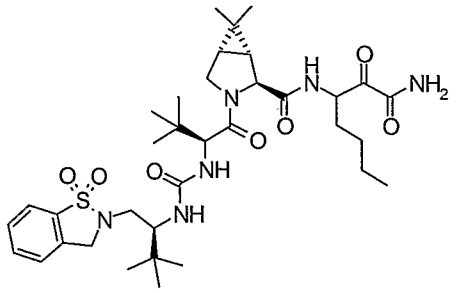
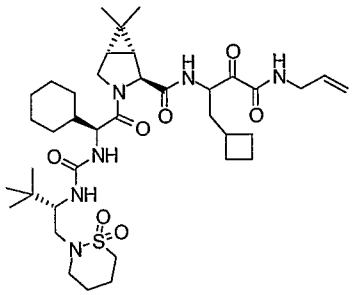
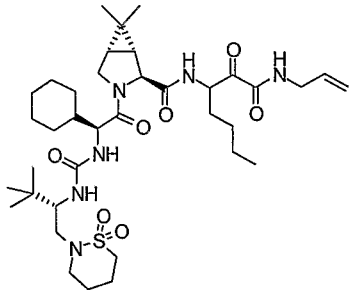
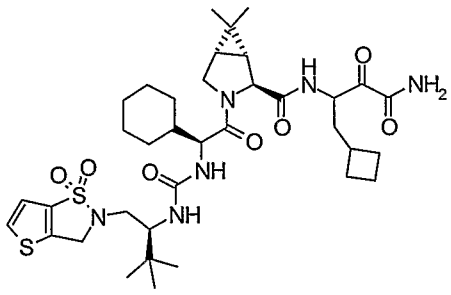
5161		A	708.94639
5162		A	742.94233
5163		A	728.91524
5164		A	742.98596

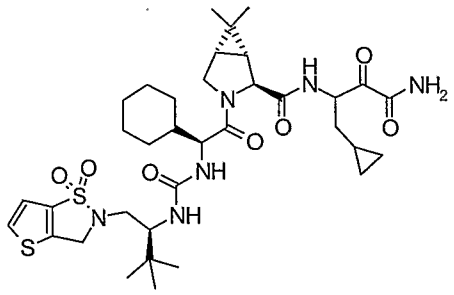
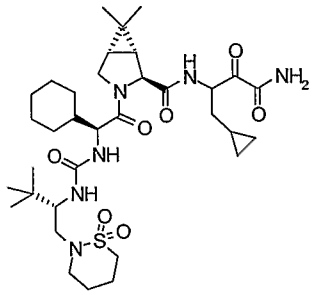
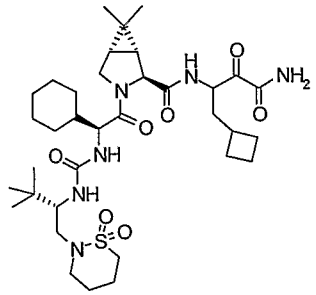
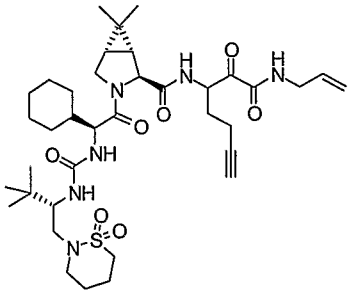
5165		A	740.97002
5166		A	723.86199
5167		A	681.90185
5168		A	719.95124

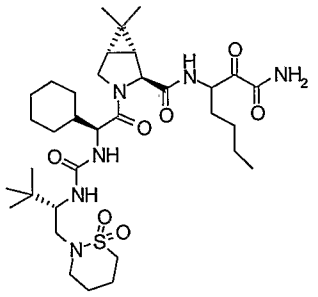
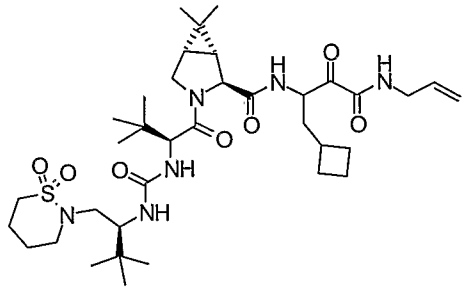
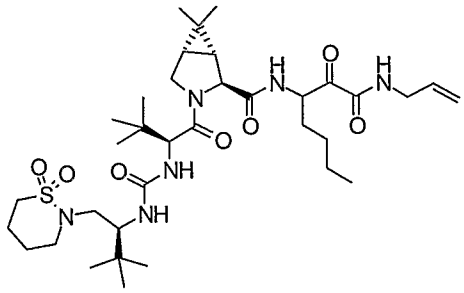
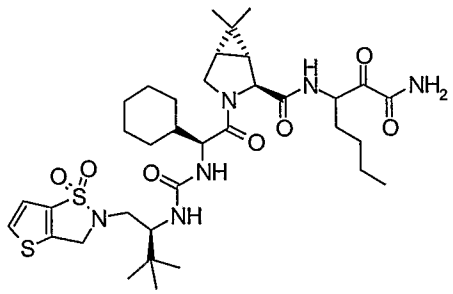
5169		A	744.97984
5170		A	738.95408
5171		A	728.95887
5172		A	700.90469

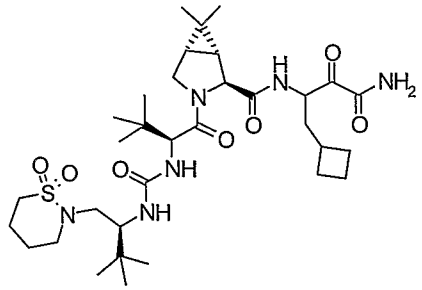
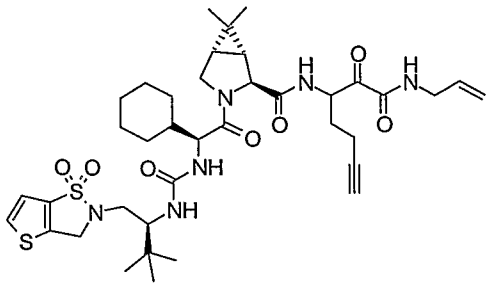
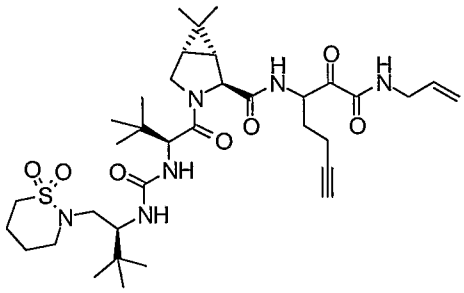
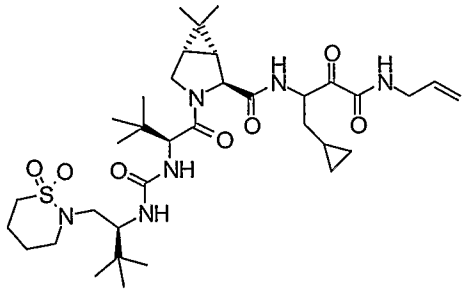
5173		A	714.93178
5174		A	754.99711
5175		A	720.9796
5176		A	732.99075

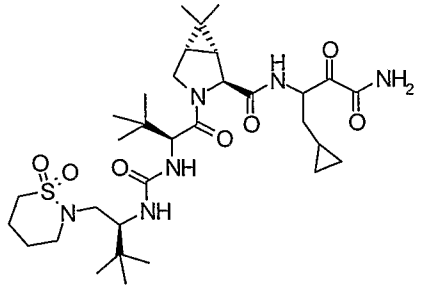
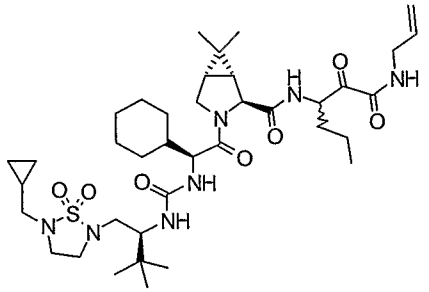
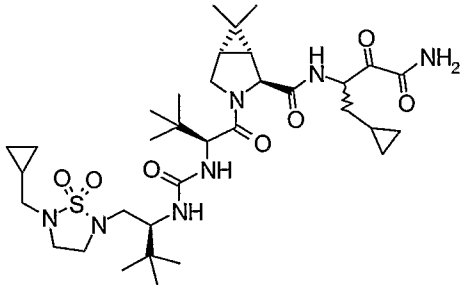
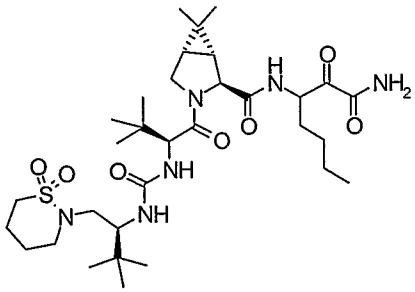
5177		A	761.02287
5178		A	775.04996
5179		A	773.03402
5180		A	787.06111

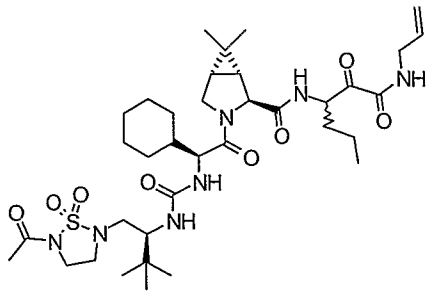
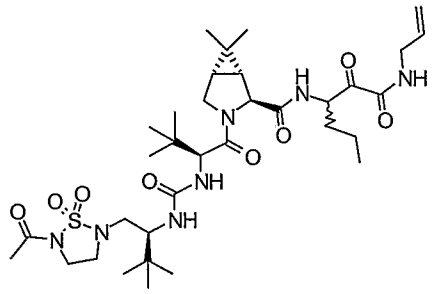
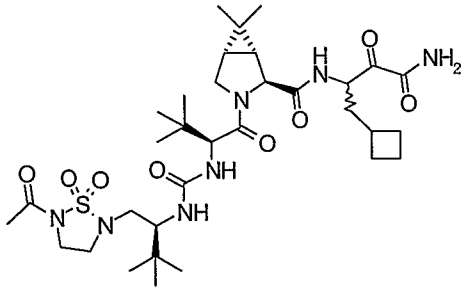
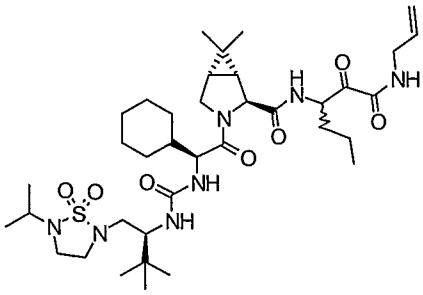
5181		A	702.92063
5182		A	747.01784
5183		A	735.00669
5184		A	746.99578

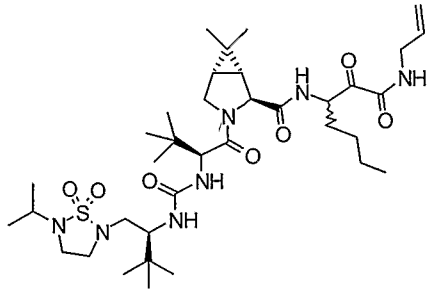
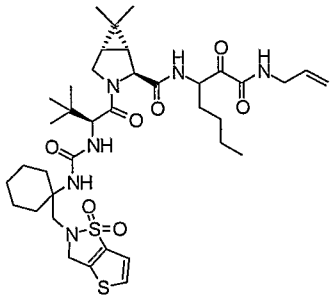
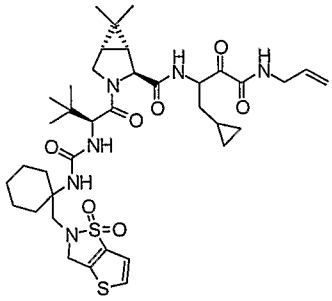
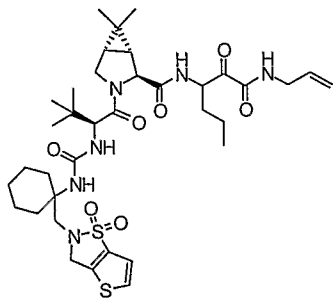
5185		A	732.96869
5186		A	692.92542
5187		A	706.95251
5188		A	730.97481

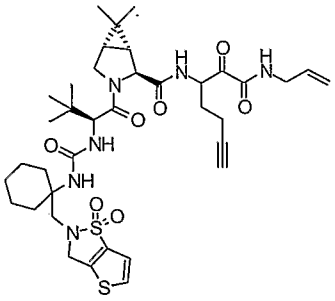
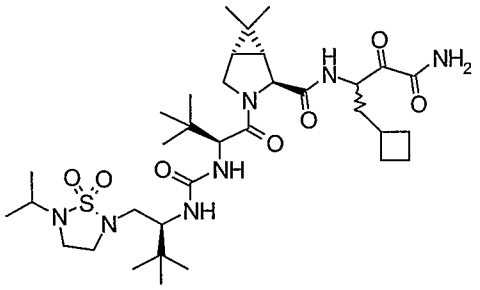
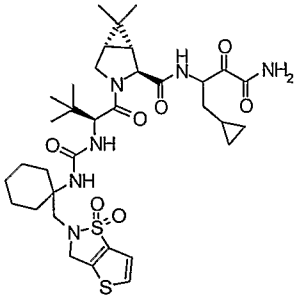
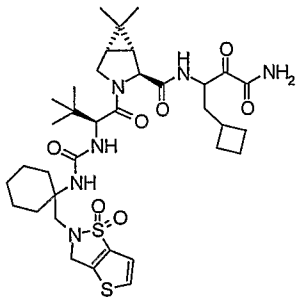
5189		A	694.94136
5190		A	720.9796
5191		A	708.96845
5192		A	734.98463

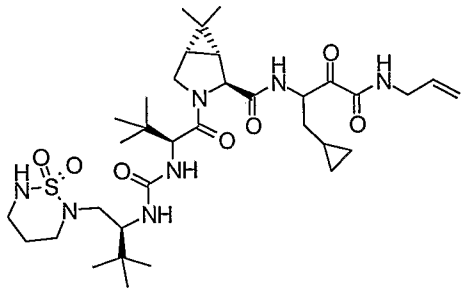
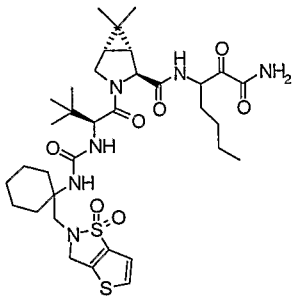
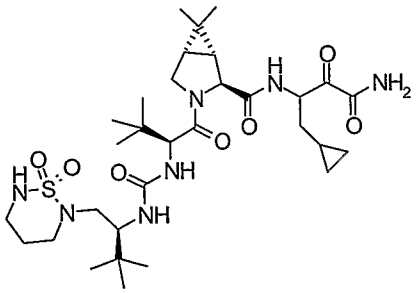
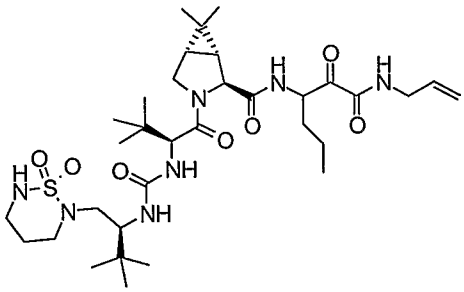
5193		A	680.91427
5194		A	771.01808
5195		A	704.93657
5196		A	706.95251

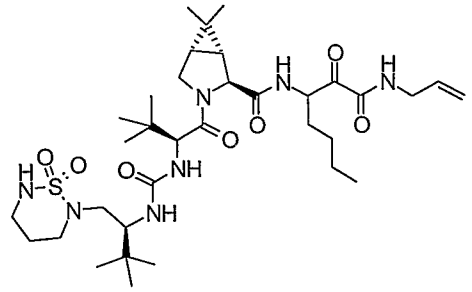
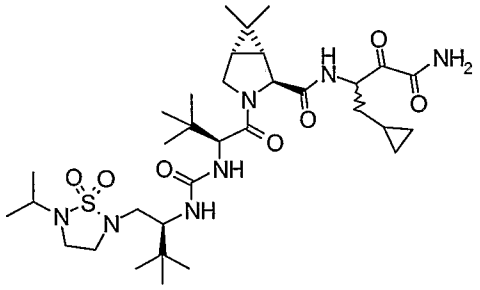
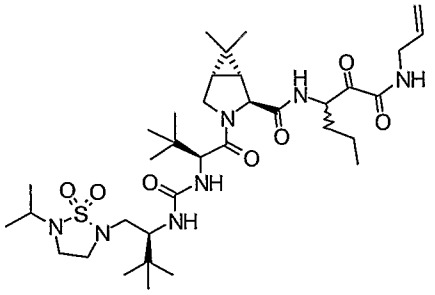
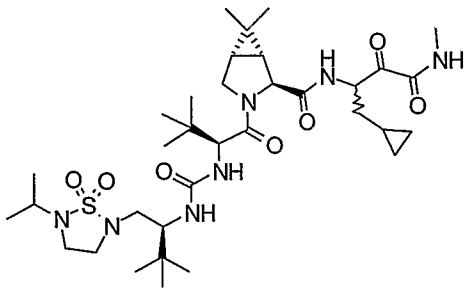
5197		A	666.88718
5198		A	762.03251
5199		A	707.94009
5200		A	668.90312

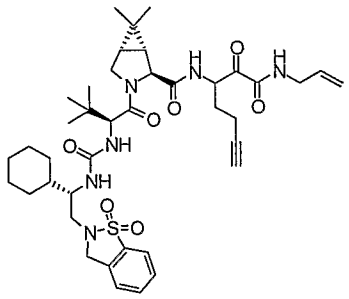
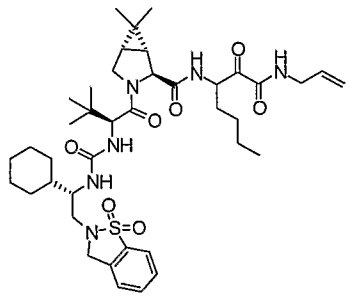
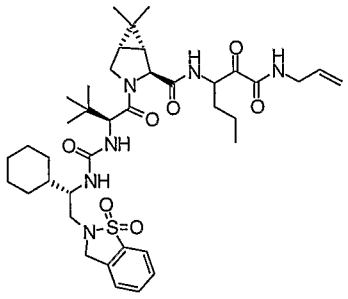
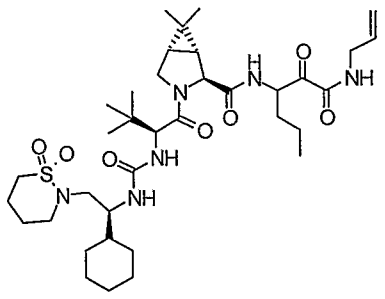
5201		A	749.97773
5202		A	723.93949
5203		A	709.9124
5204		A	750.02136

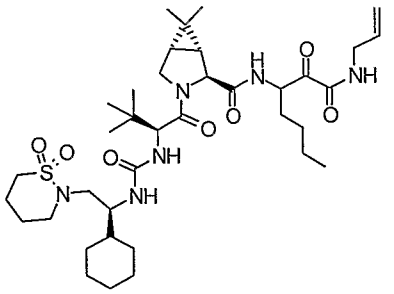
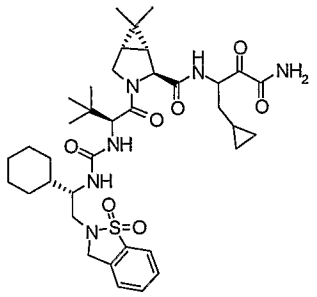
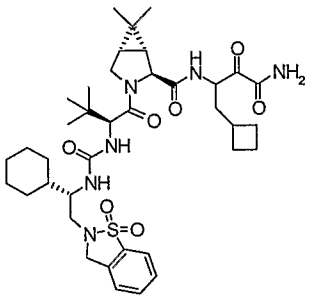
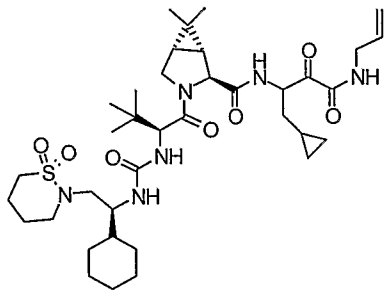
5205		A	738.01021
5206		A	761.02287
5207		B	759.00693
5208		A	746.99578

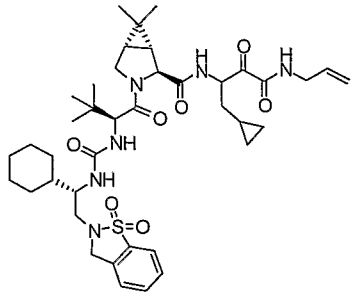
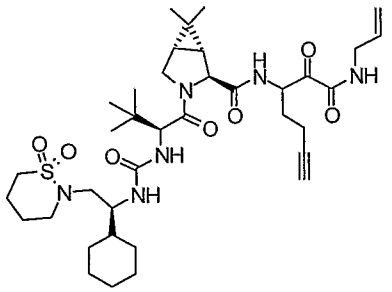
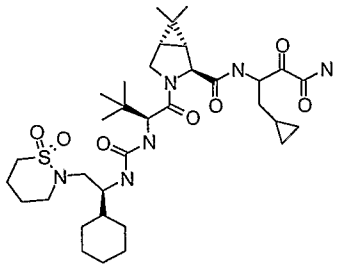
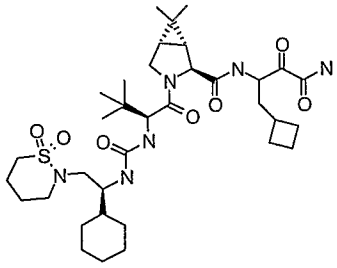
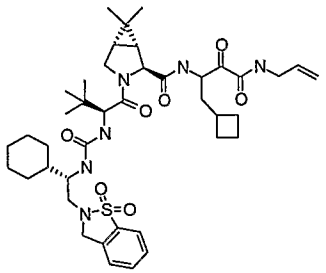
5209		A	756.99099
5210		A	709.95603
5211		A	718.9416
5212		A	732.96869

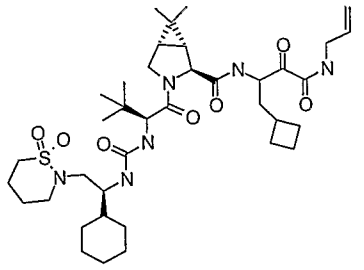
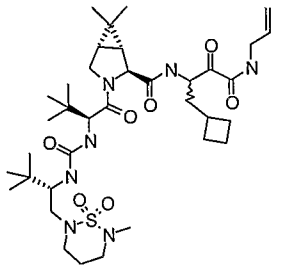
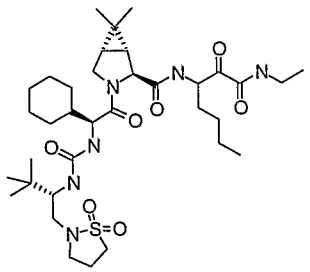
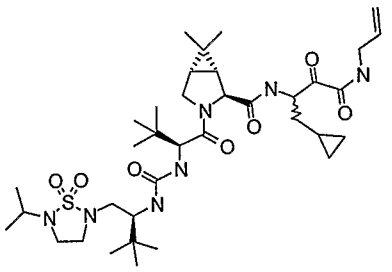
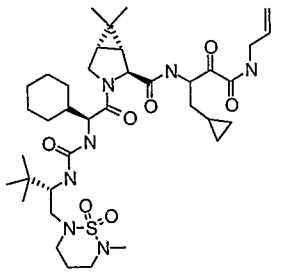
5213		B	707.94009
5214		A	720.95754
5215		A	667.87476
5216		B	695.92894

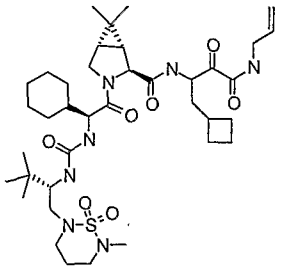
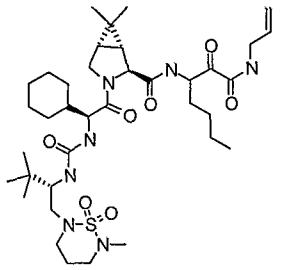
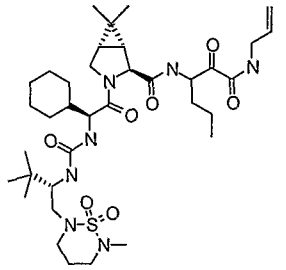
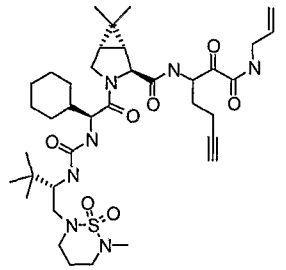
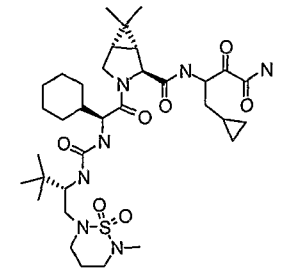
5217		B	709.95603
5218		A	695.92894
5219		A	723.98312
5220		A	709.95603

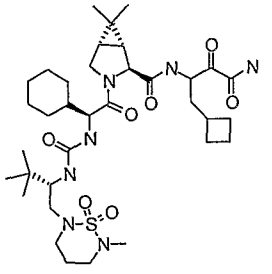
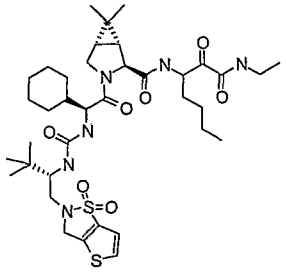
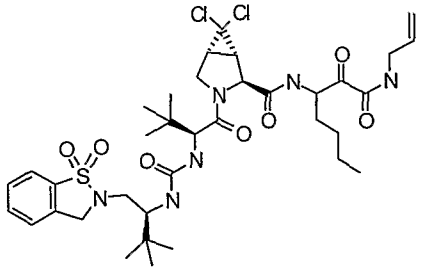
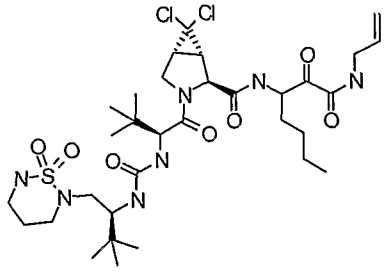
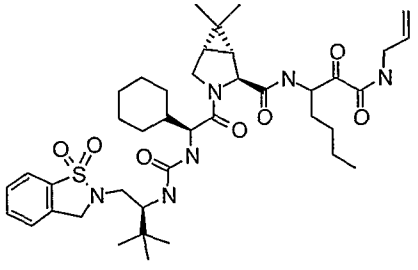
5221		A	764.99232
5222		A	769.0242
5223		A	754.99711
5224		A	720.9796

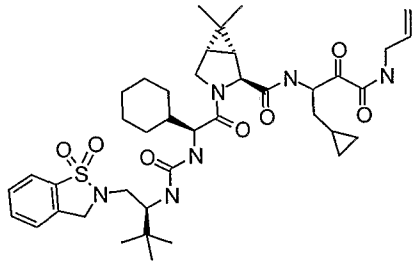
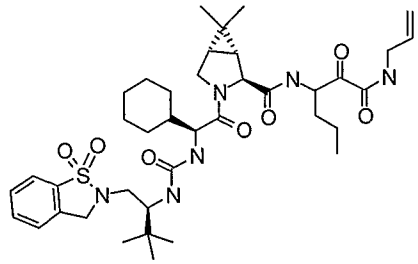
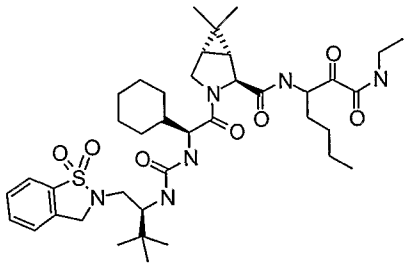
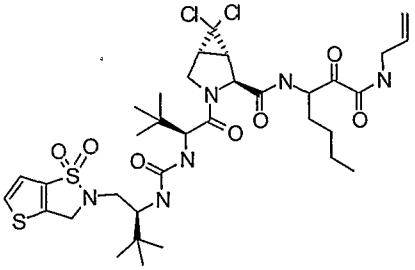
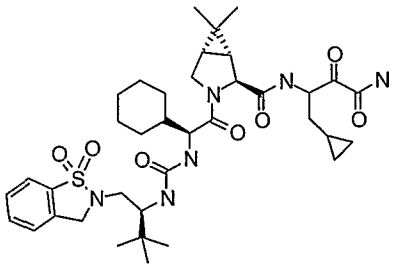
5225		A	735.00669
5226		A	726.94293
5227		A	740.97002
5228		A	732.99075

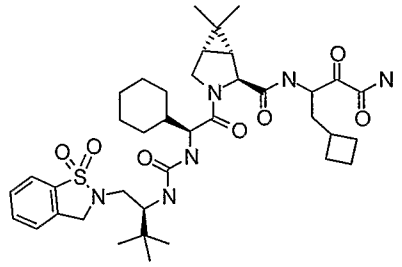
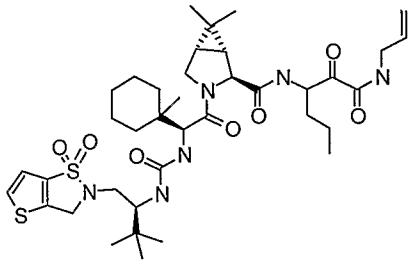
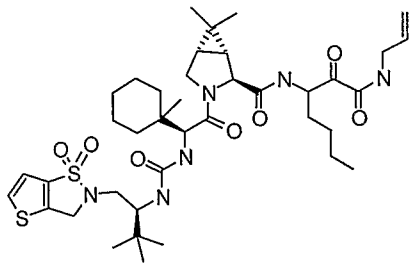
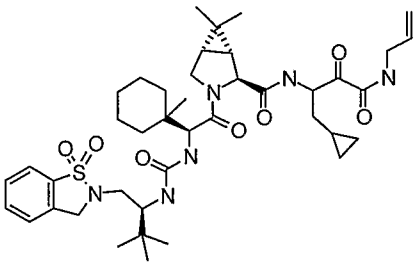
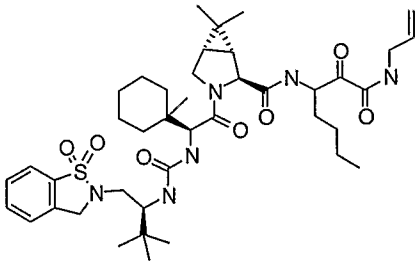
5229		A	767.00826
5230		A	730.97481
5231		A	692.93
5232		A	706.95
5233		B	781.04

5234		B	747.02
5235		A	735.99
5236		A	708.97
5237		A	735.99
5238		A	748.01

5239		A	762.03
5240		A	750.02
5241		A	735.99
5242		A	745.99
5243		A	707.94009

5244		A	721.96718
5245		A	763.03881
5246		A	783.82184
5247		A	750.79191
5248		A	769.0242

5249		A	767.00826
5250		A	754.99711
5251		A	757.01305
5252		A	789.8476
5253		A	726.94293

5254		A	740.97002
5255		A	775.04996
5256		A	789.07705
5257		A	781.03535
5258		A	783.05129

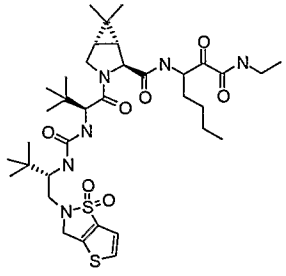
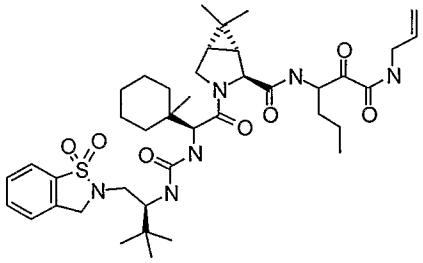
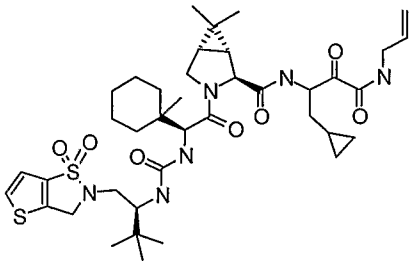
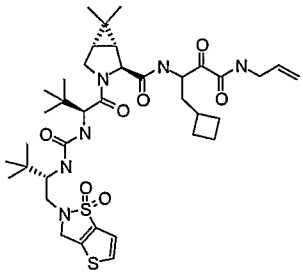
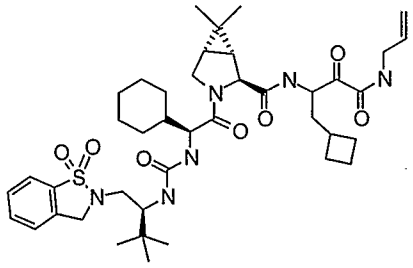
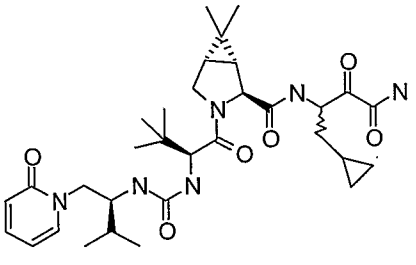
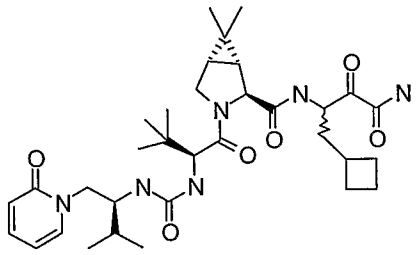
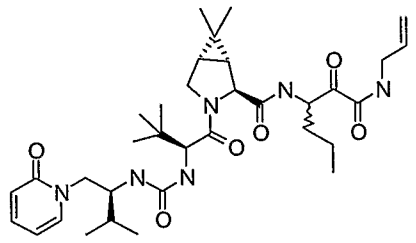
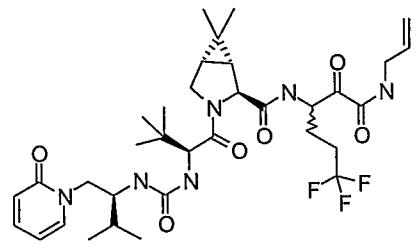
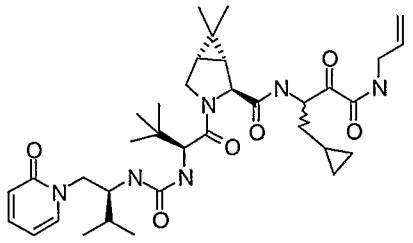
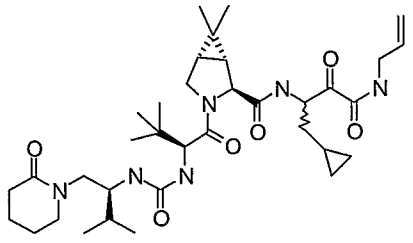
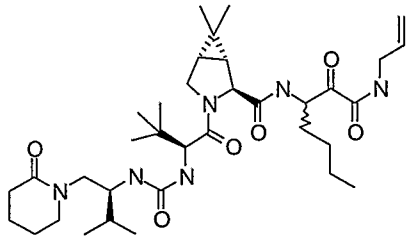
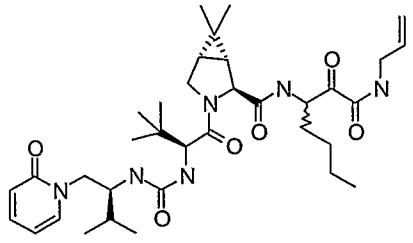
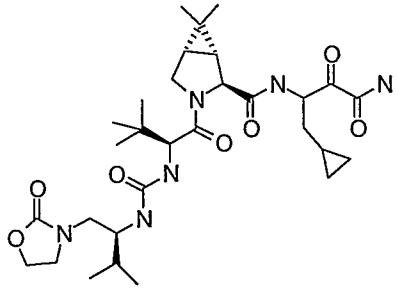
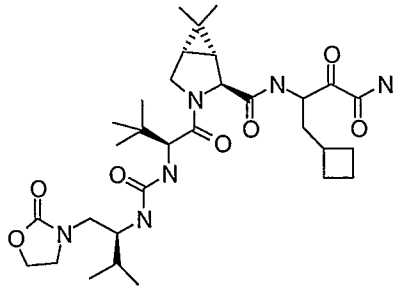
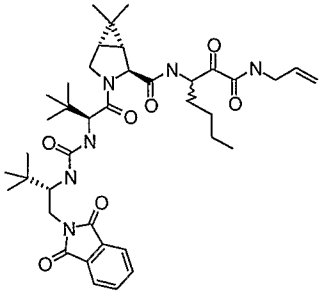
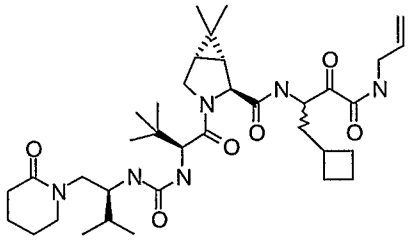
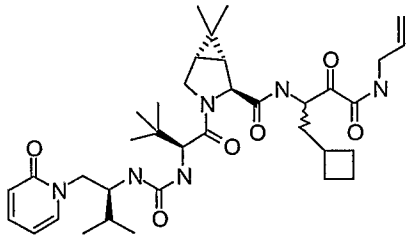
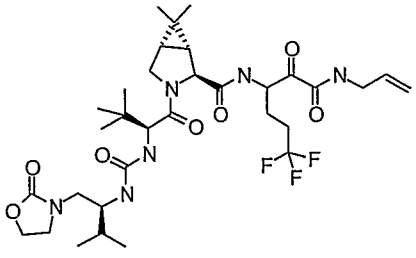
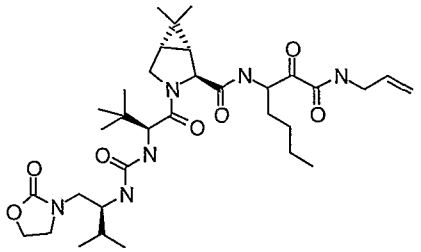
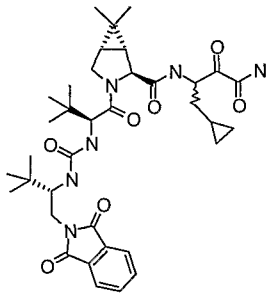
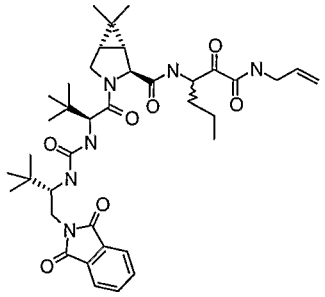
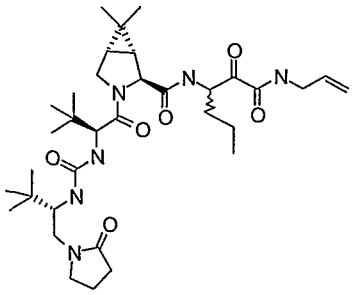
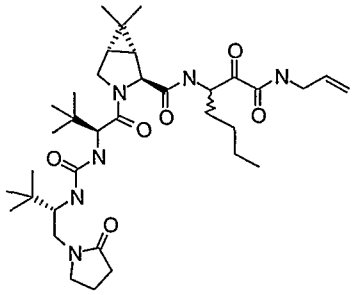
5259		A	737.00057
5260		A	769.0242
5261		A	787.06111
5262		A	761.02287
5263		A	781.03535

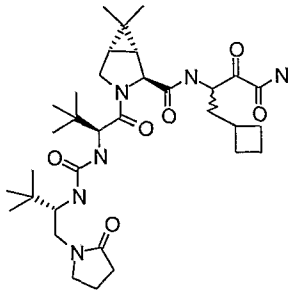
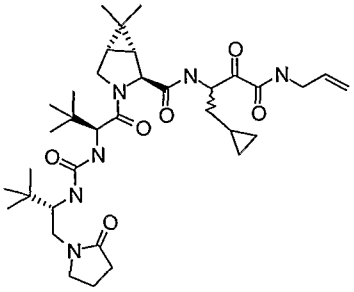
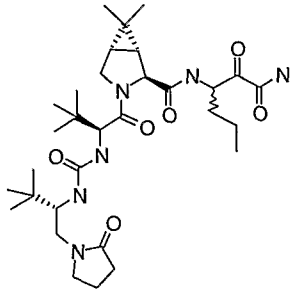
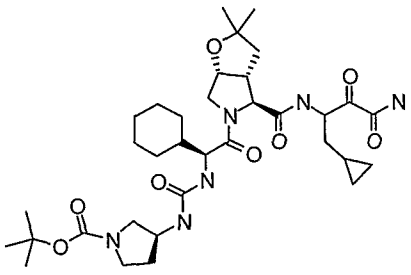
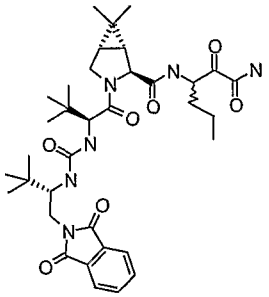
Table 2

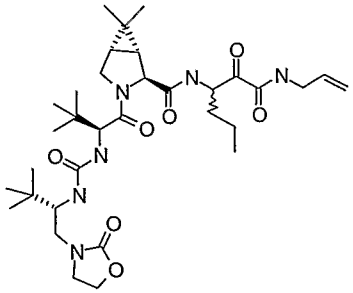
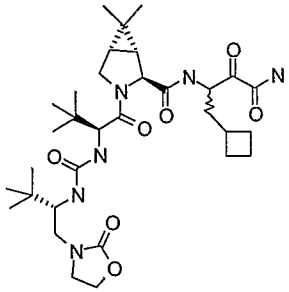
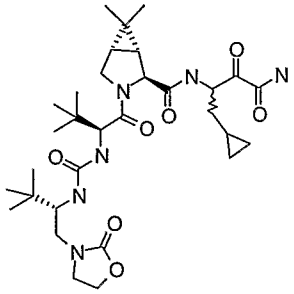
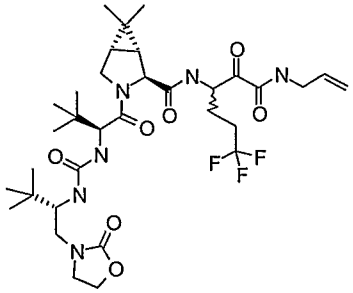
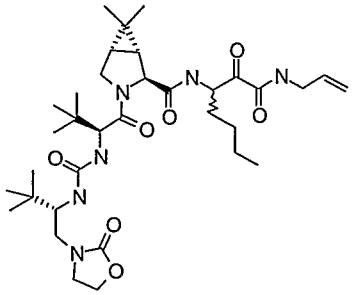
Compound number	structure	Ki*	mol weight
5603		A	612.77596
5604		A	626.80305
5605		A	640.83014
5606		A	694.80143

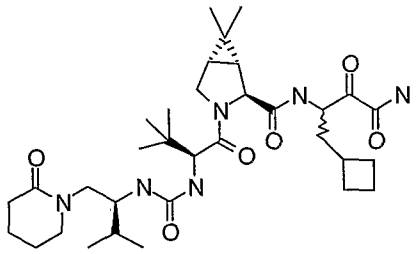
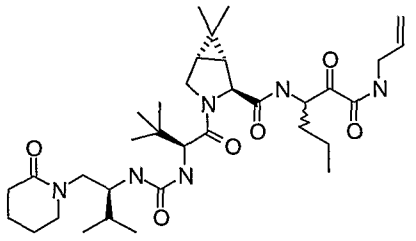
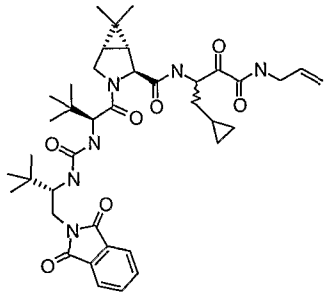
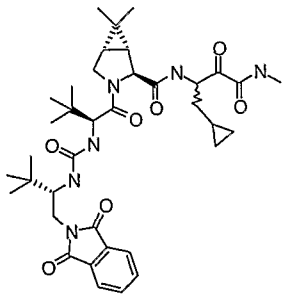
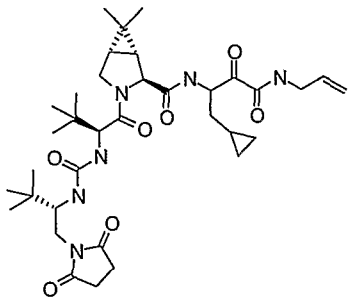
5607		B	652.84129
5608		B	656.87317
5609		B	658.88911
5610		A	654.85723
5611		A	604.75306

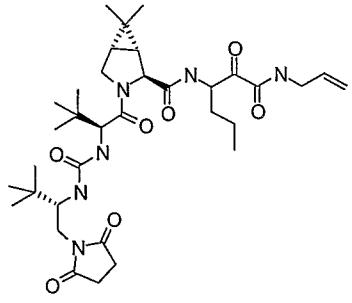
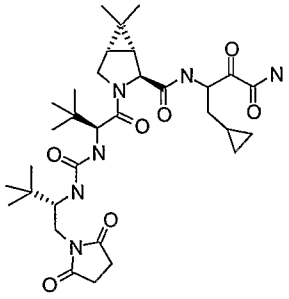
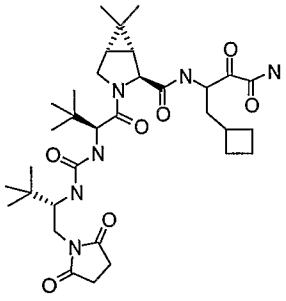
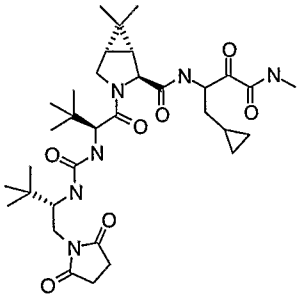
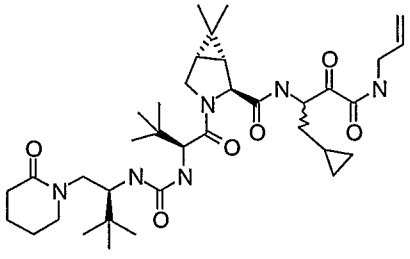
5612		A	618.78015
5613		A	720.91717
5614		A	670.90026
5615		B	666.86838
5616		A	686.77853

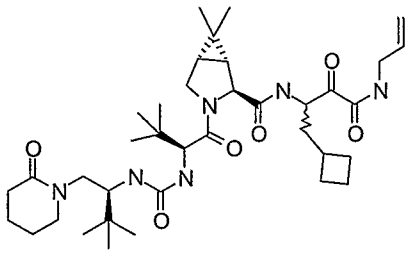
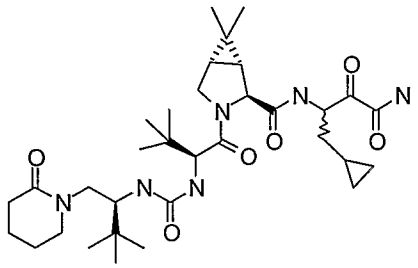
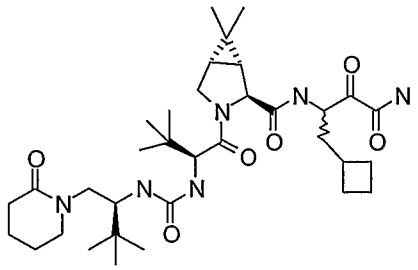
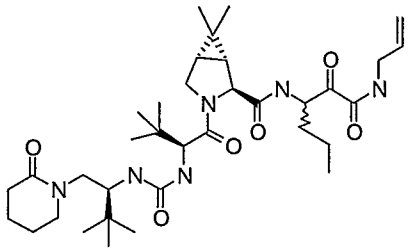
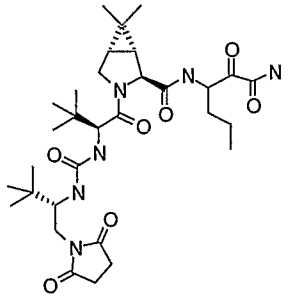
5617		A	646.83433
5618		A	678.8359
5619		A	706.89008
5620		A	644.86202
5621		B	658.88911

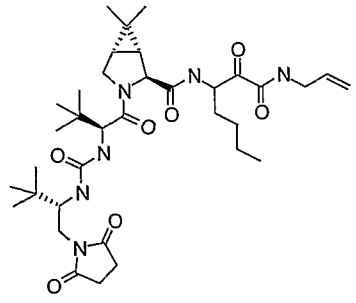
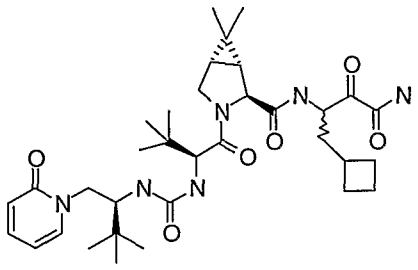
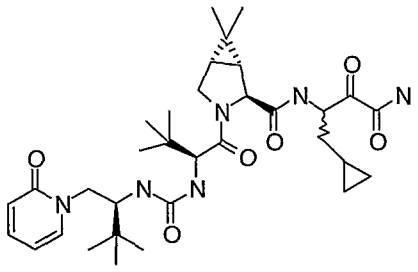
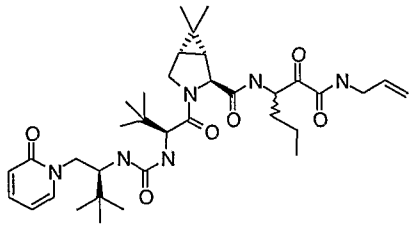
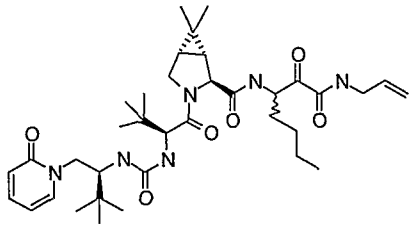
5622		A	630.83493
5623		A	656.87317
5624		A	604.79669
5625		B	674.84488
5626		A	666.82475

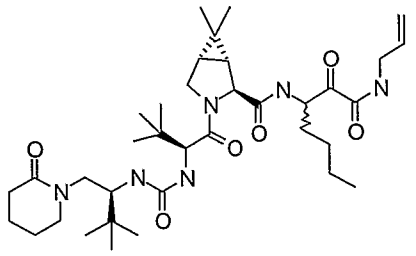
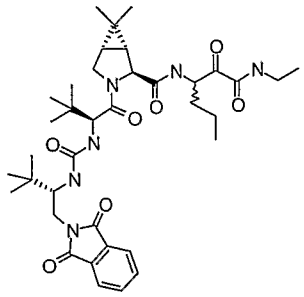
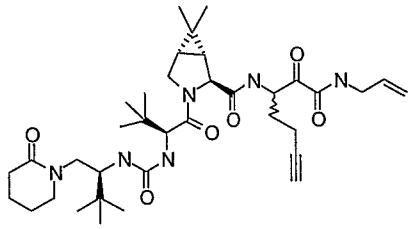
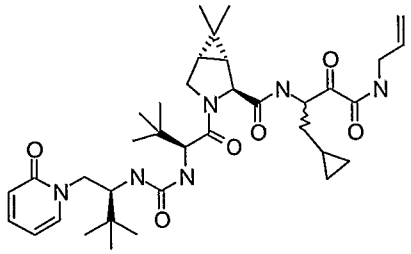
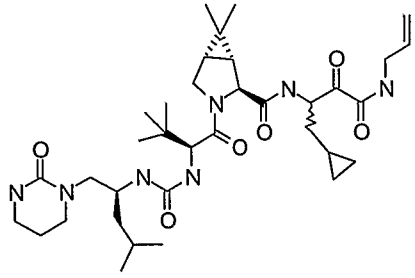
5627		A	646.83433
5628		A	632.80724
5629		A	618.78015
5630		A	700.80562
5631		A	660.86142

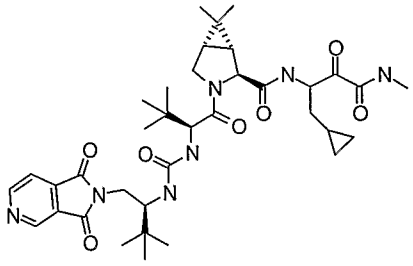
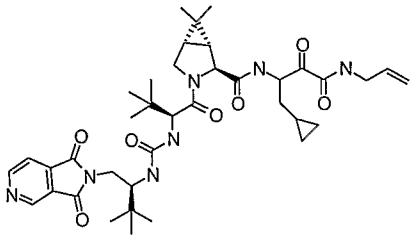
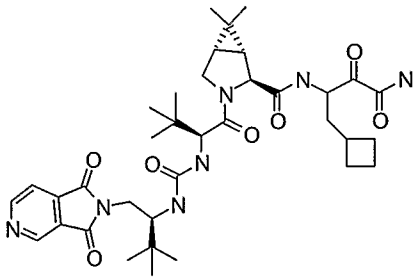
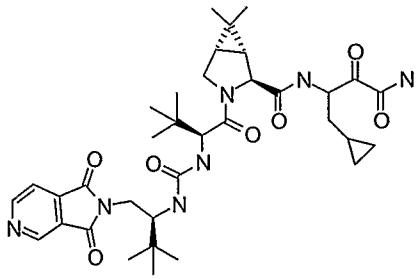
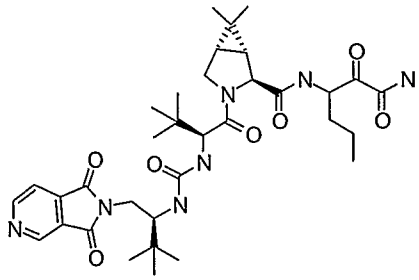
5632		A	630.83493
5633		A	644.86202
5634		A	718.90123
5635		A	692.86299
5636		A	670.85663

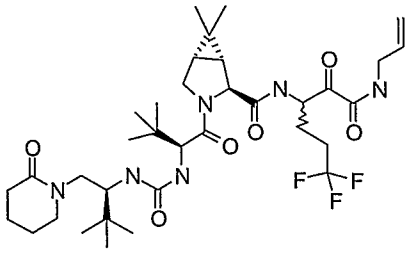
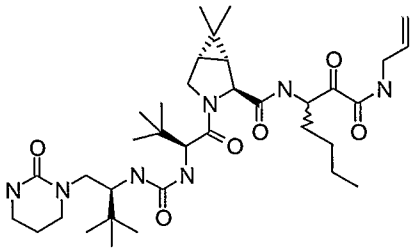
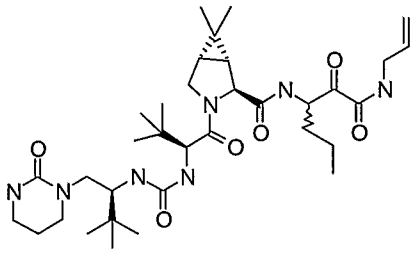
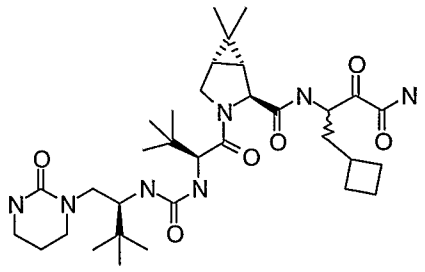
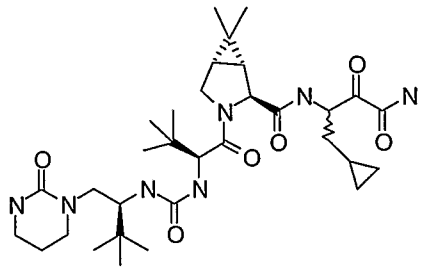
5637		A	658.84548
5638		A	630.7913
5639		A	644.81839
5640		A	644.81839
5641		A	670.90026

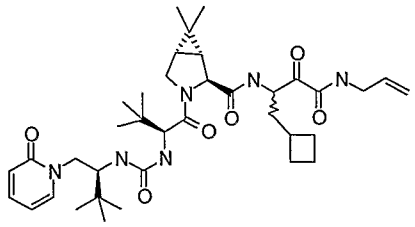
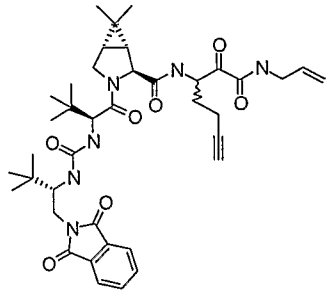
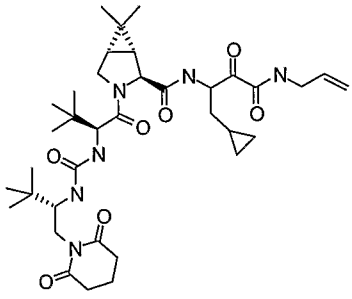
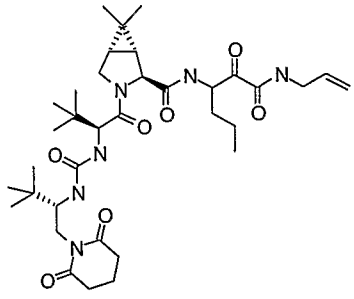
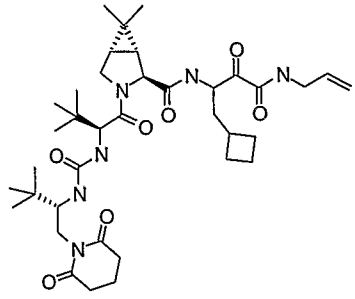
5642		A	684.92735
5643		A	630.83493
5644		A	644.86202
5645		A	658.88911
5646		A	618.78015

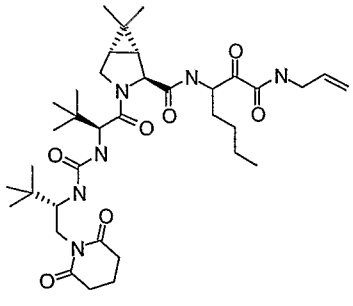
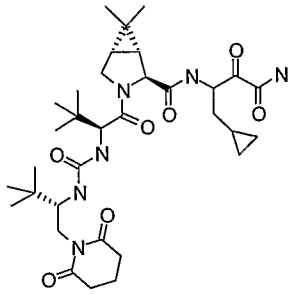
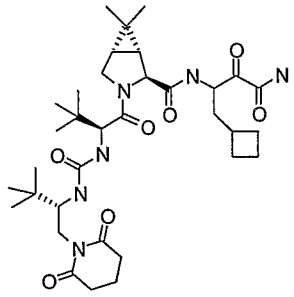
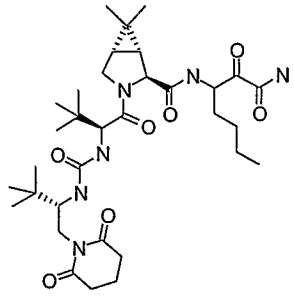
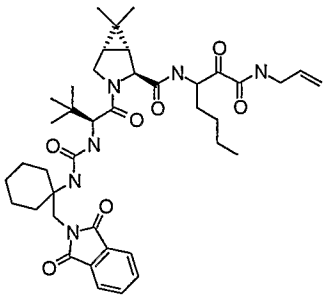
5647		A	672.87257
5648		A	640.83014
5649		A	626.80305
5650		A	654.85723
5651		A	668.88432

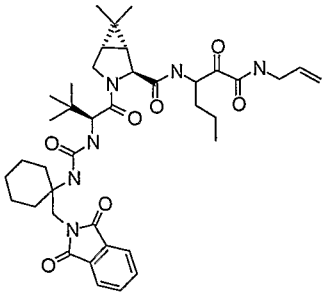
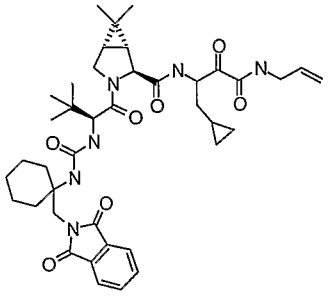
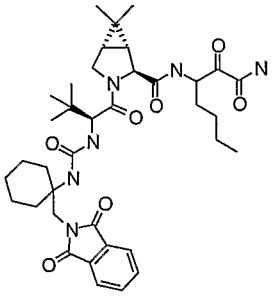
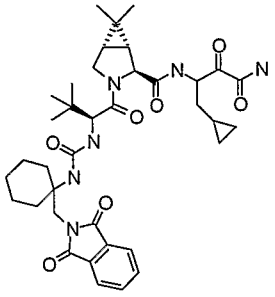
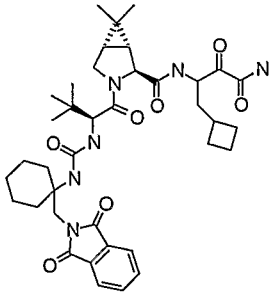
5652		A	672.9162
5653		A	694.87893
5654		A	668.88432
5655		A	666.86838
5656		B	671.88784

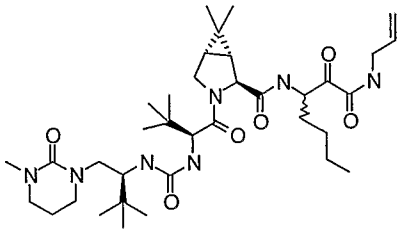
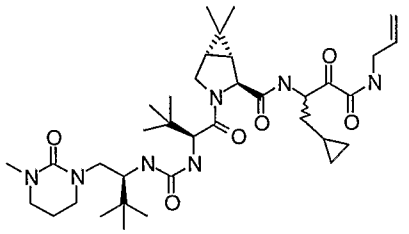
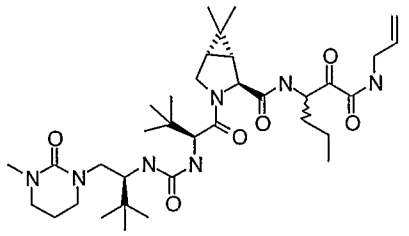
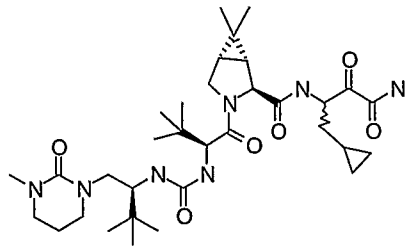
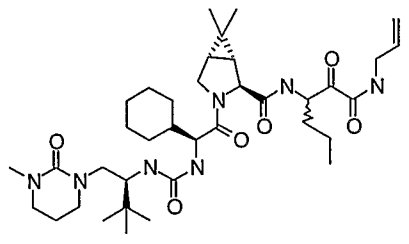
5657		A	693.85057
5658		A	719.88881
5659		A	693.85057
5660		A	679.82348
5661		A	667.81233

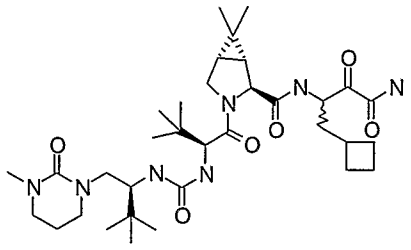
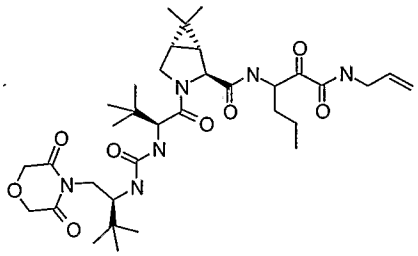
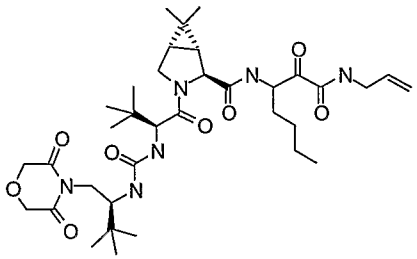
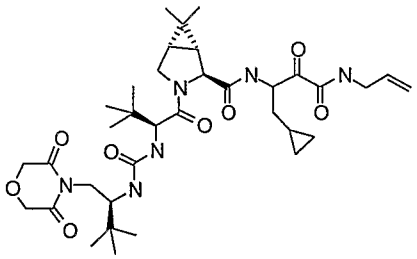
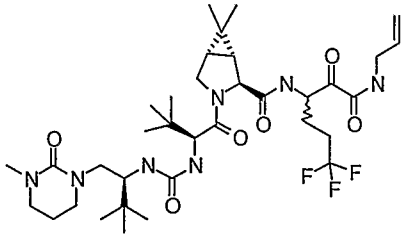
5662		A	712.8604
5663		A	673.90378
5664		A	659.87669
5665		A	645.8496
5667		A	631.82251

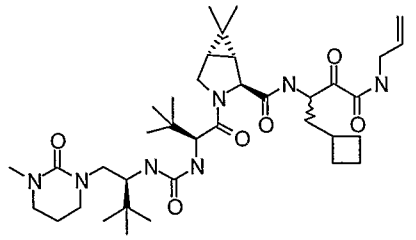
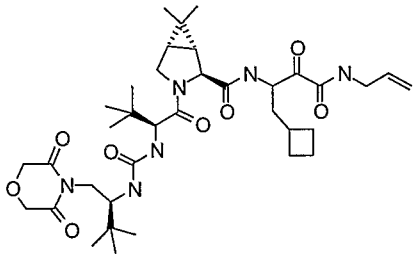
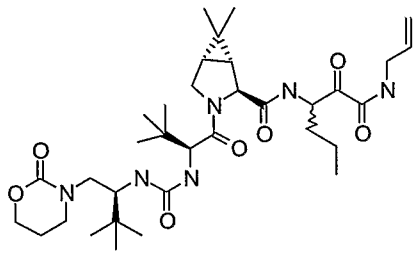
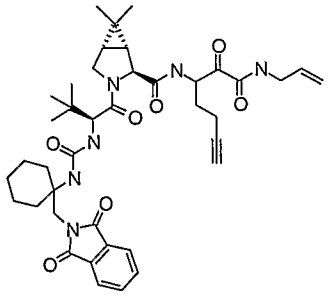
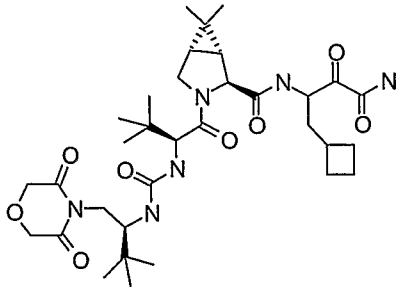
5668		A	680.89547
5669		A	716.88529
5670		A	684.88372
5671		A	672.87257
5672		A	698.91081

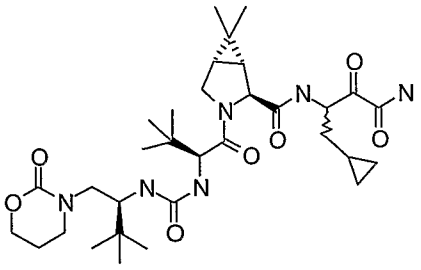
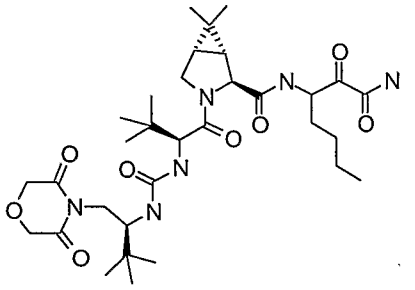
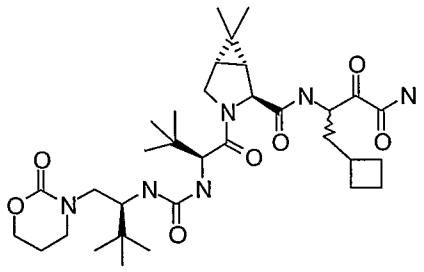
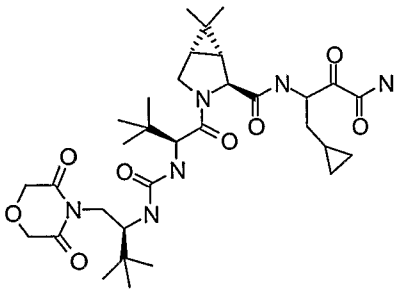
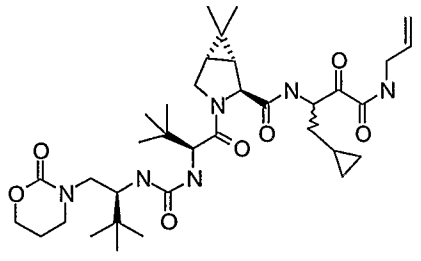
5673		A	686.89966
5674		A	644.81839
5675		A	658.84548
5676		A	646.83433
5677		B	732.92832

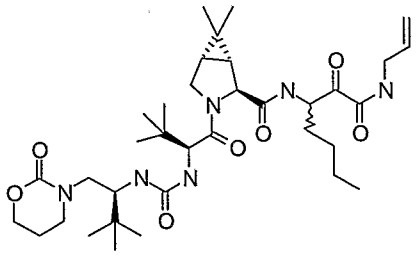
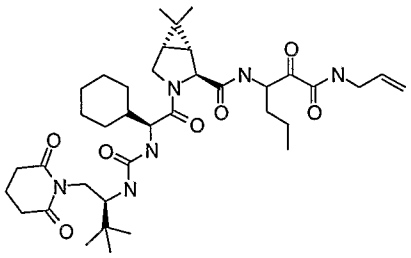
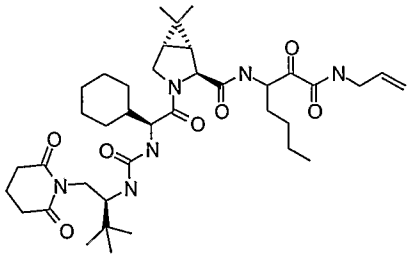
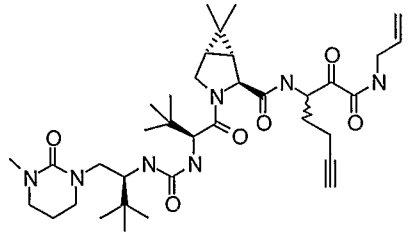
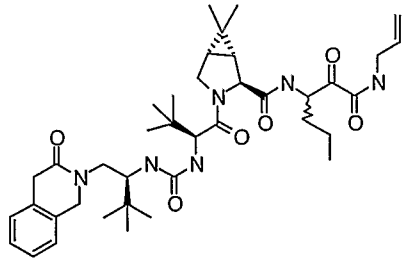
5678		A	718.90123
5679		B	730.91238
5680		A	692.86299
5681		A	690.84705
5682		A	704.87414

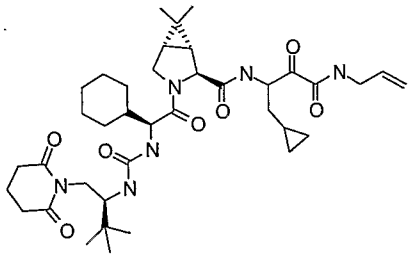
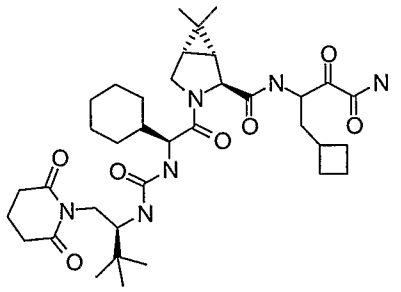
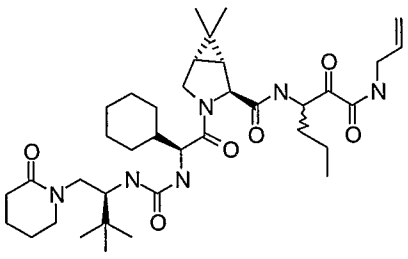
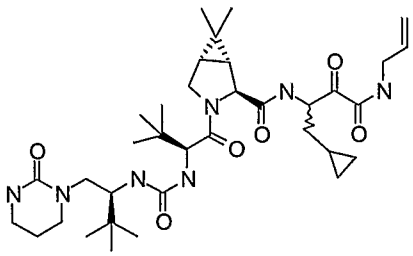
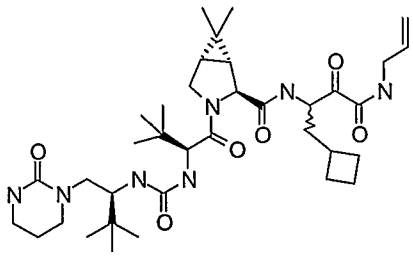
5683		B	687.93087
5684		B	685.91493
5685		B	673.90378
5686		A	645.8496
5687		B	699.94202

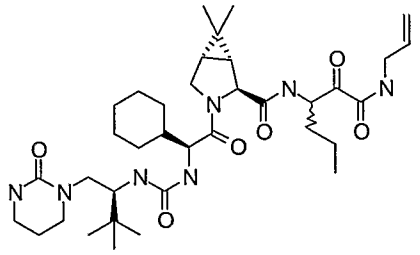
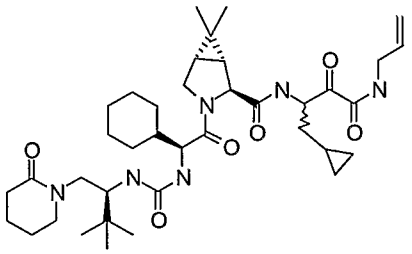
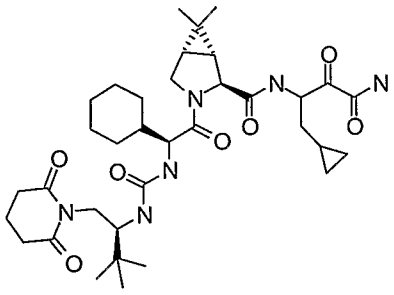
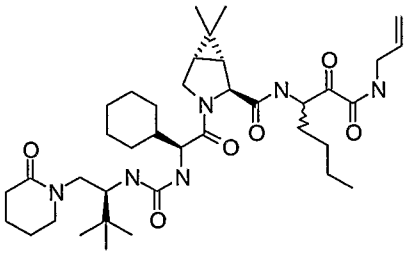
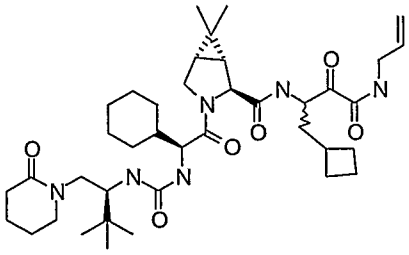
5688		A	659.87669
5689		A	674.84488
5690		A	688.87197
5691		A	686.85603
5692		B	727.87507

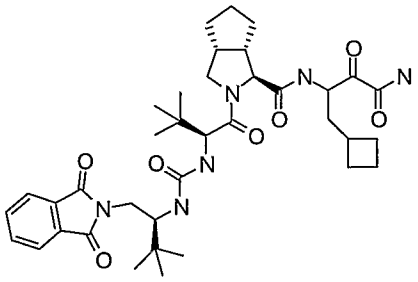
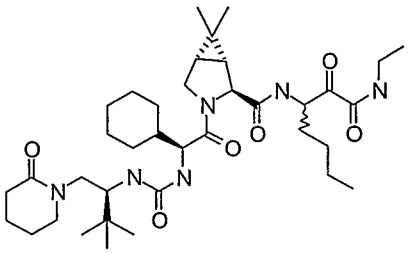
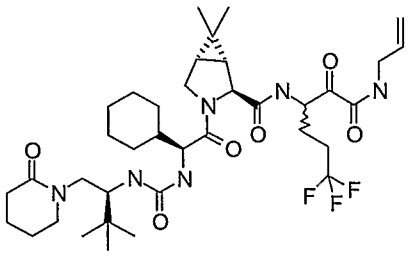
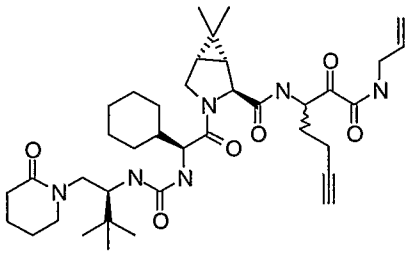
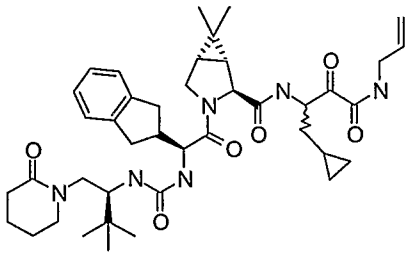
5693		B	699.94202
5694		A	700.88312
5695		A	660.86142
5696		A	728.89644
5697		A	660.81779

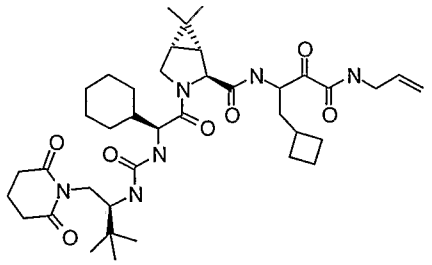
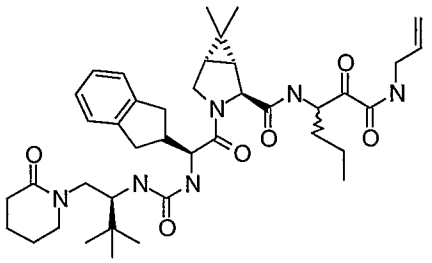
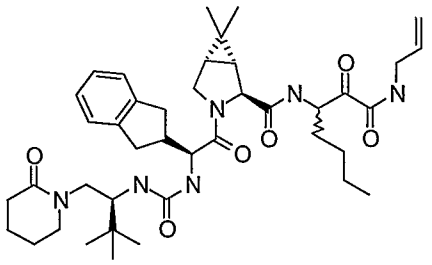
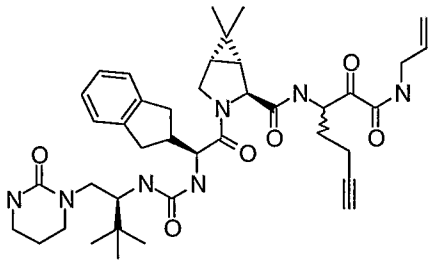
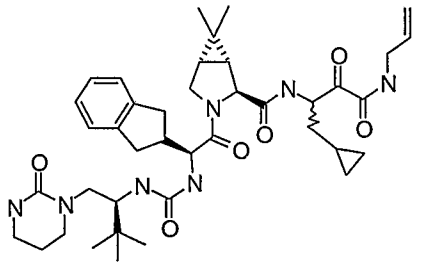
5698		A	632.80724
5699		A	648.80664
5700		A	646.83433
5701		A	646.7907
5702		A	672.87257

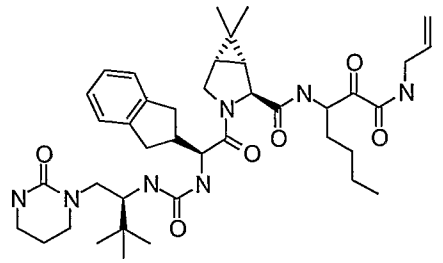
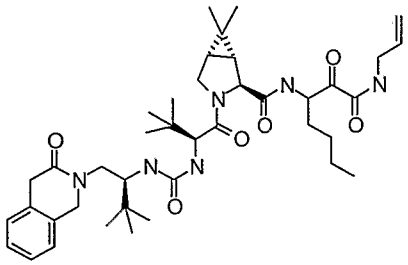
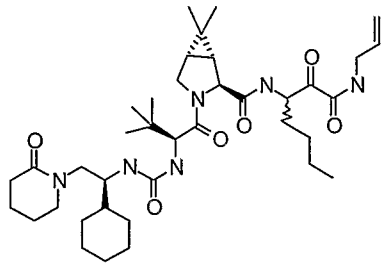
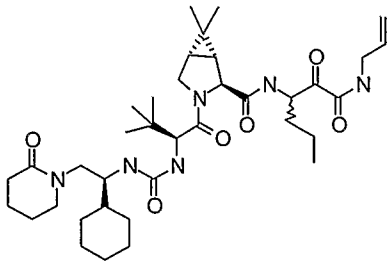
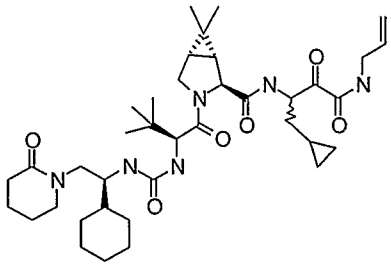
5703		A	674.88851
5704		A	698.91081
5705		A	712.9379
5706		B	683.89899
5707		A	706.93371

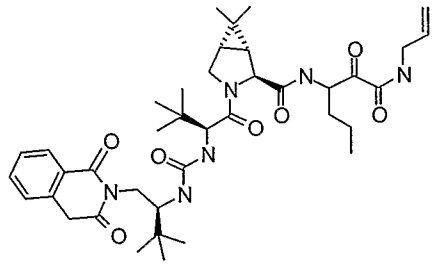
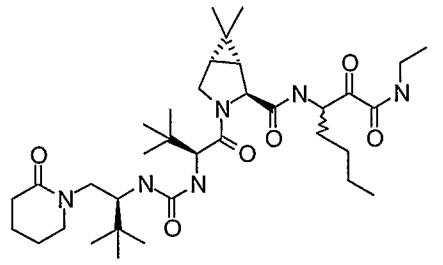
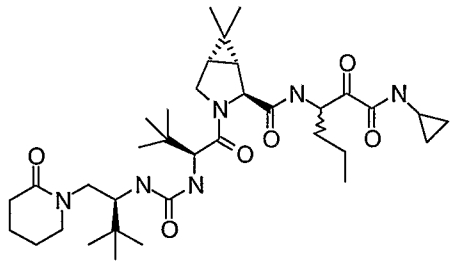
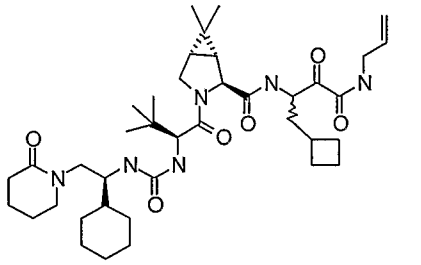
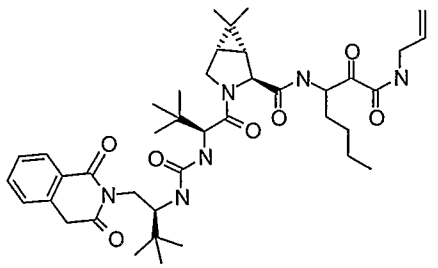
5708		A	710.92196
5709		A	684.88372
5710		A	684.92735
5711		A	671.88784
5712		A	685.91493

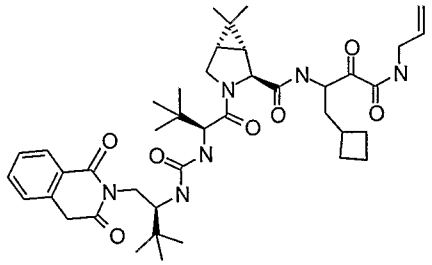
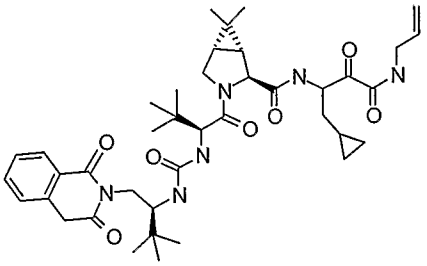
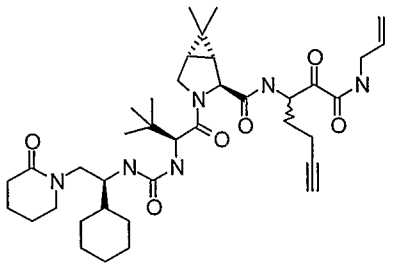
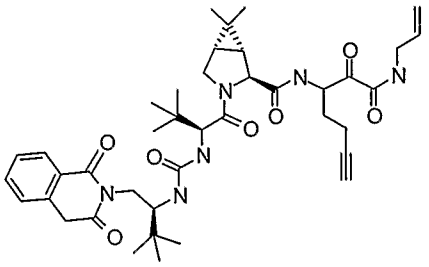
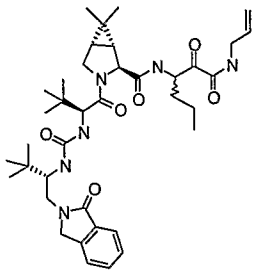
5713		A	685.91493
5714		A	696.9385
5715		A	670.85663
5716		A	698.95444
5717		A	710.96559

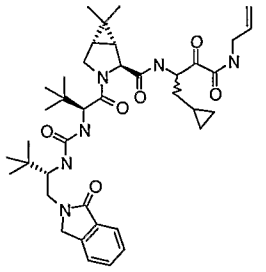
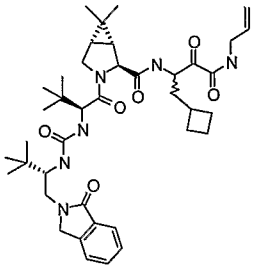
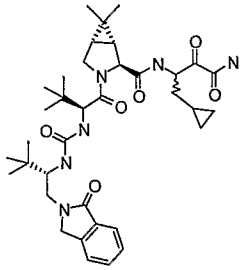
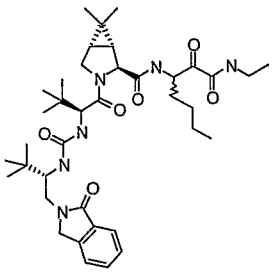
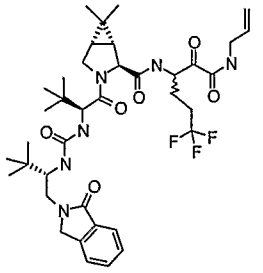
5718		A	692.86299
5719		A	686.94329
5720		A	738.89864
5721		A	694.92256
5722		A	730.95601

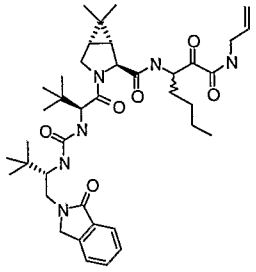
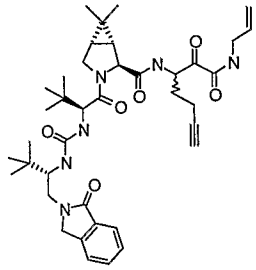
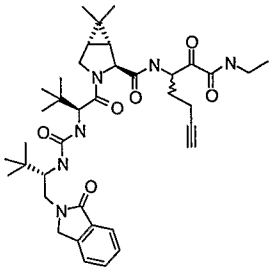
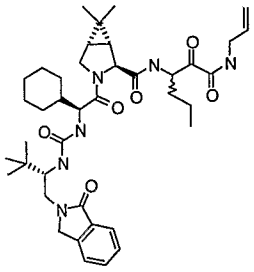
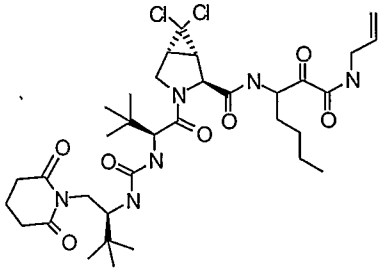
5723		A	724.95
5724		A	718.94
5725		A	732.97
5726		A	729.93
5727		A	731.94

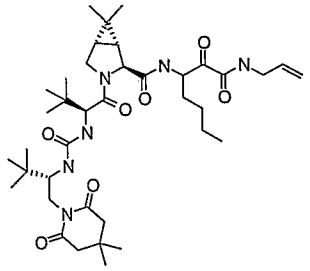
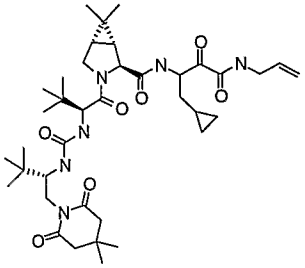
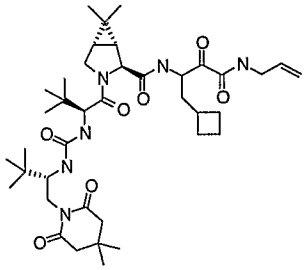
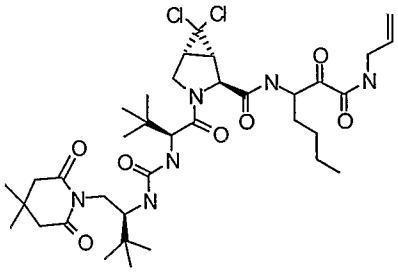
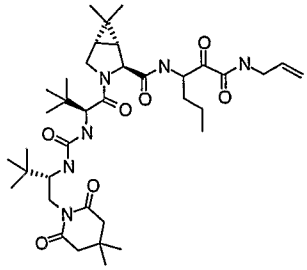
5728		A	733.96
5729		A	720.96
5730		A	698.95
5731		A	684.93
5732		A	696.94

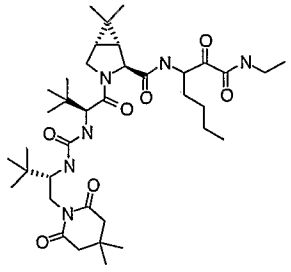
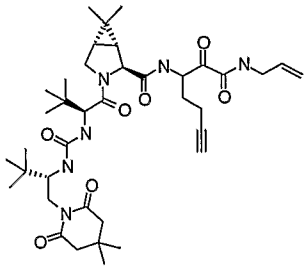
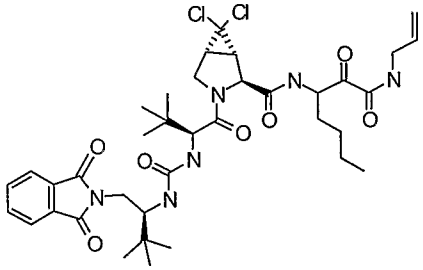
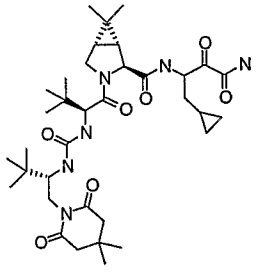
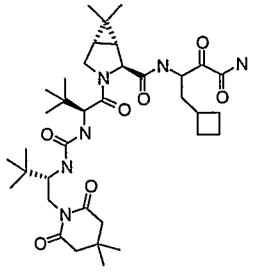
5733		A	720.92
5734		A	660.91
5735		A	658.89
5736		A	710.97
5737		A	734.94

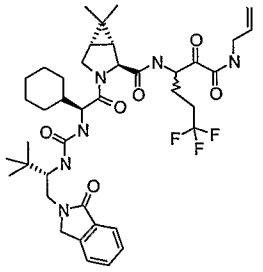
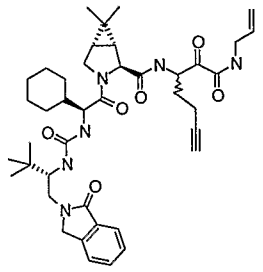
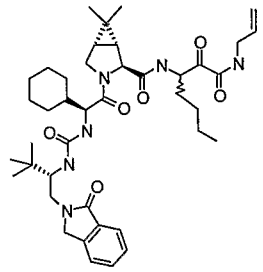
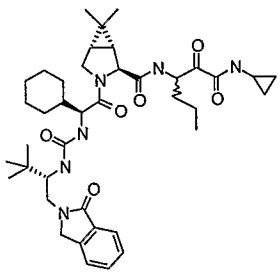
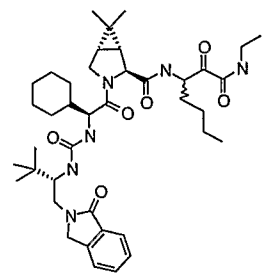
5738		B	746.96
5739		A	732.93
5740		A	694.92
5741		A	730.91
5742		B	692.91

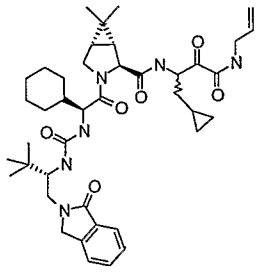
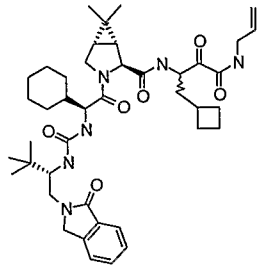
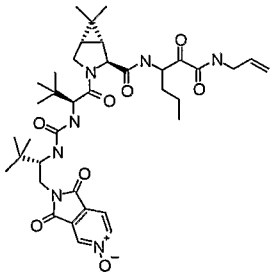
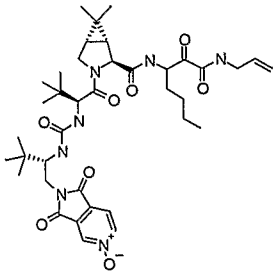
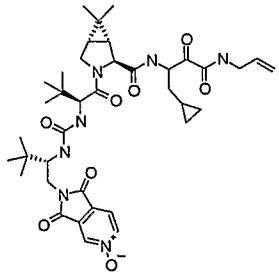
5743		A	704.92
5744		B	718.94
5745		A	664.85
5746		B	694.92256
5747		A	746.87791

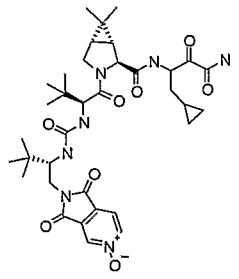
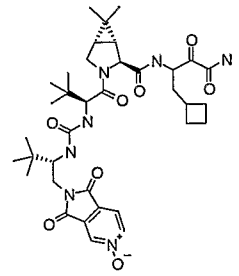
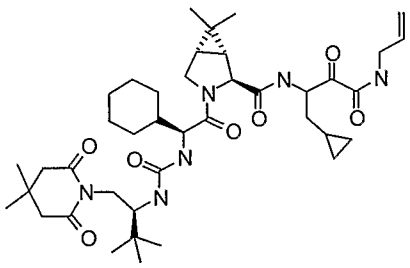
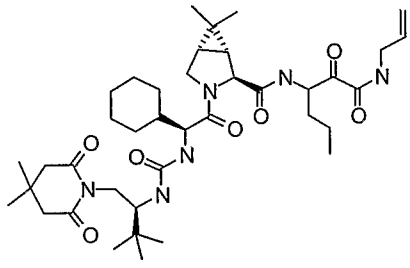
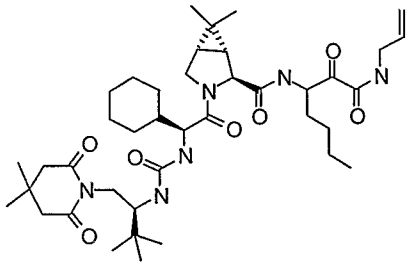
5748		A	706.93371
5749		A	702.90183
5750		A	690.89068
5751		A	718.94486
5752		A	727.73554

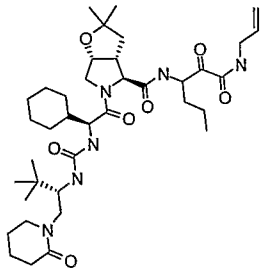
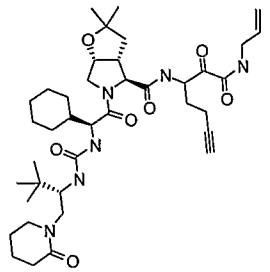
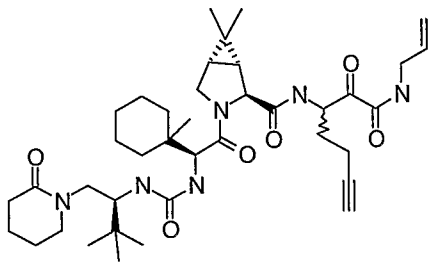
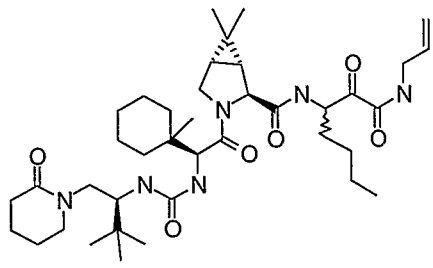
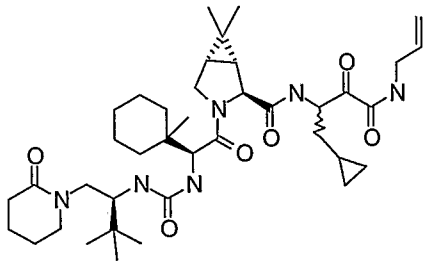
5753		A	714.95384
5754		A	712.9379
5755		A	726.96499
5756		A	755.78972
5757		A	700.92675

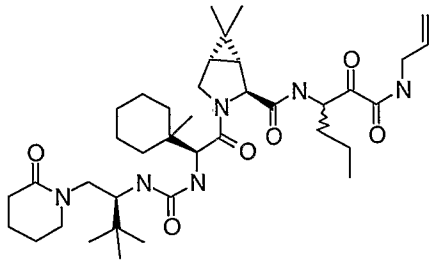
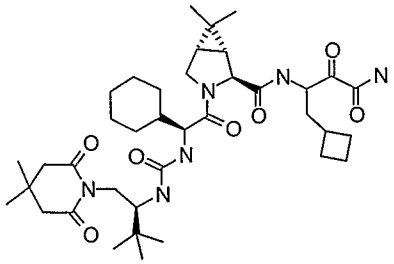
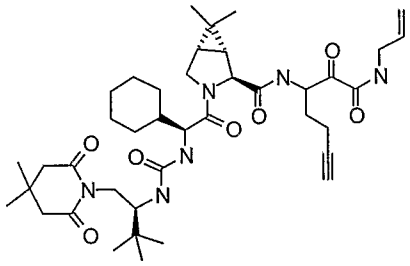
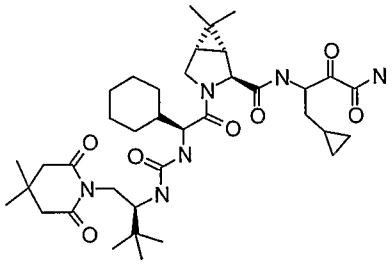
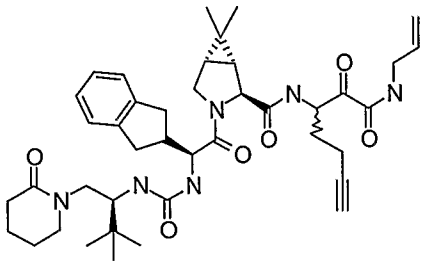
5758		A	702.94269
5759		A	710.92196
5760		A	761.75305
5761		A	672.87257
5762		A	686.89966

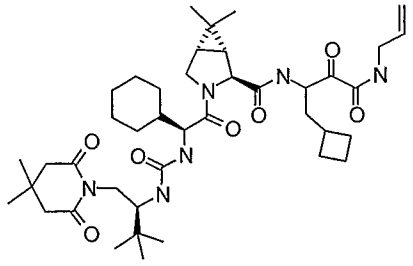
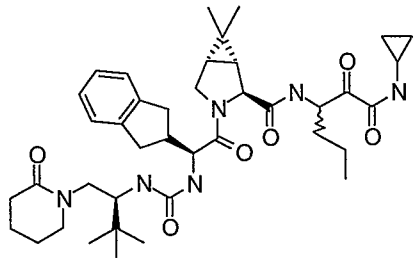
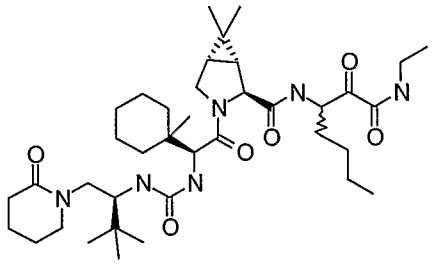
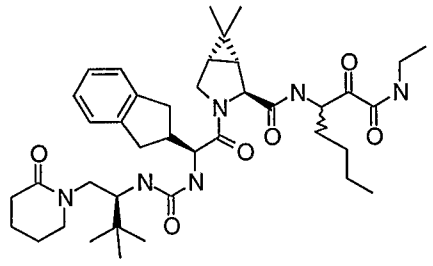
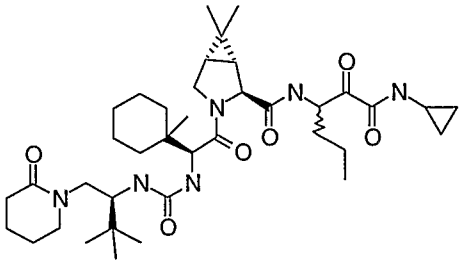
5763		A	772.91615
5764		A	728.94007
5765		A	732.97195
5766		A	718.94486
5767		A	720.9608

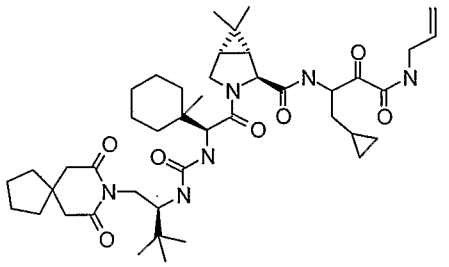
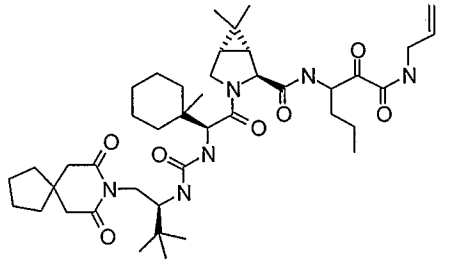
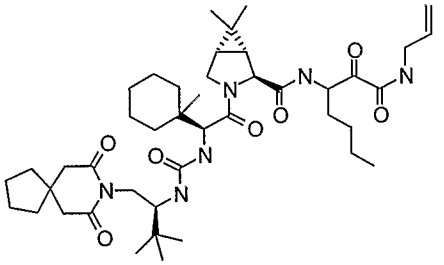
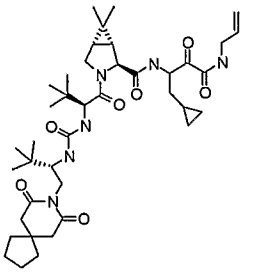
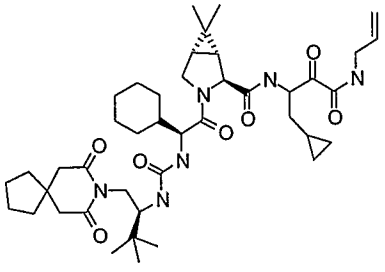
5768		A	730.95601
5769		A	744.9831
5770		A	723.87706
5771		A	737.90415
5772		A	735.88821

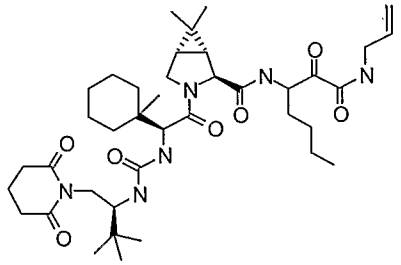
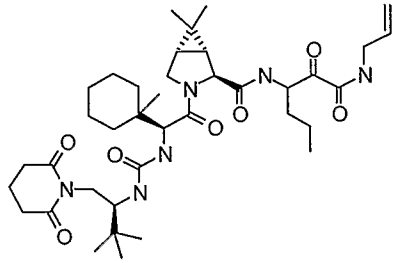
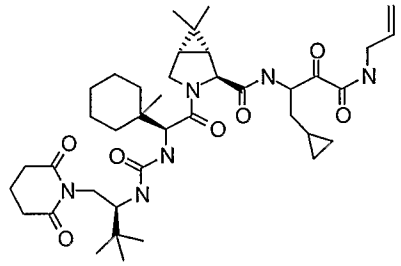
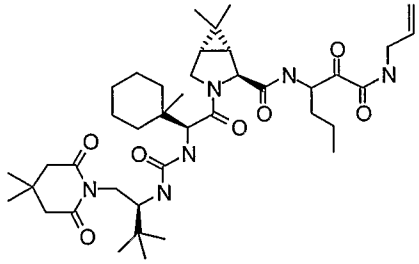
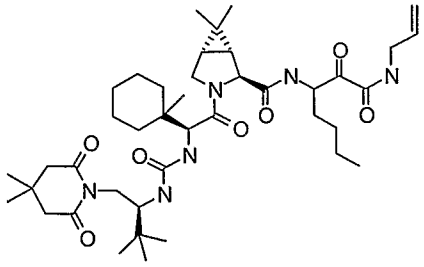
5773		A	695.82288
5774		A	709.84997
5775		A	738.97614
5776		A	726.96499
5777		A	740.99208

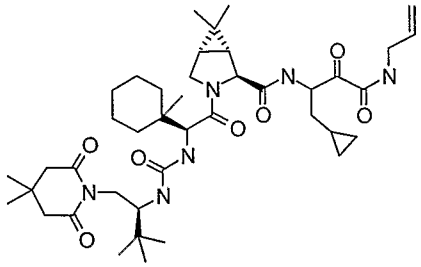
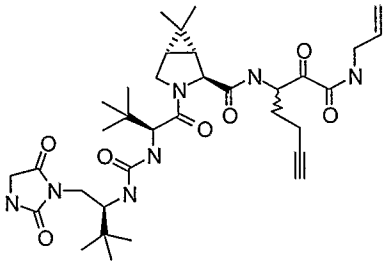
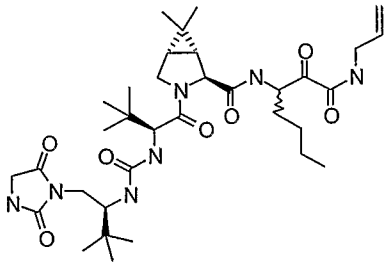
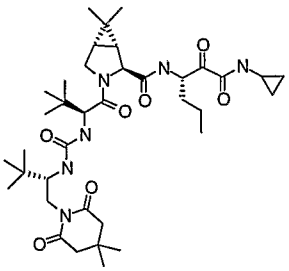
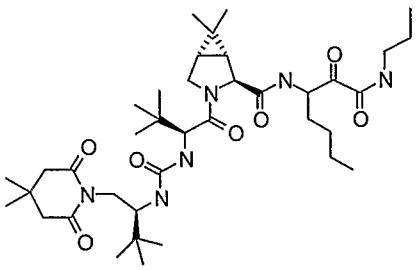
5778		A	714.95384
5779		A	724.94905
5780		A	708.94965
5781		A	712.98153
5782		A	710.96559

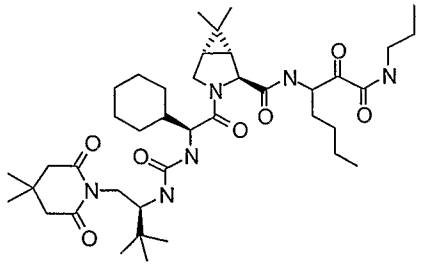
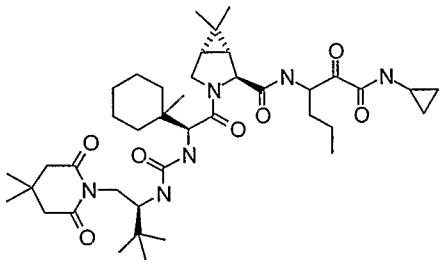
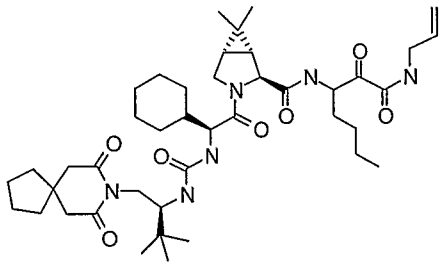
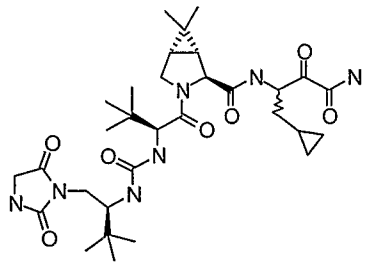
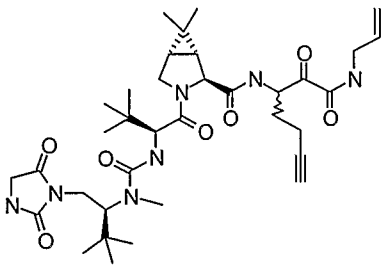
5783		A	698.95444
5784		A	712.9379
5785		A	736.9602
5786		A	698.91081
5787		A	728.94007

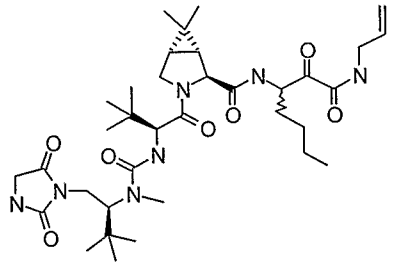
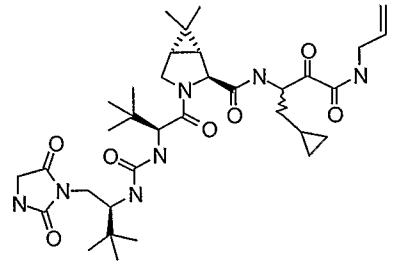
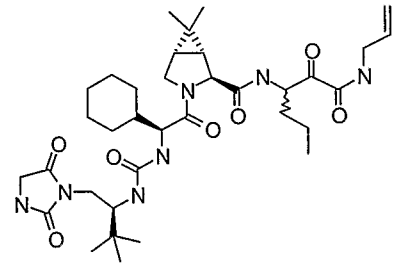
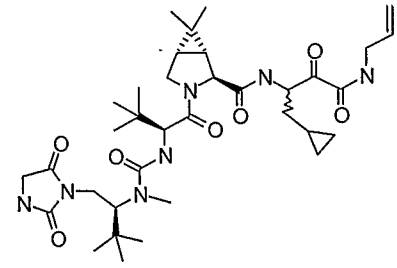
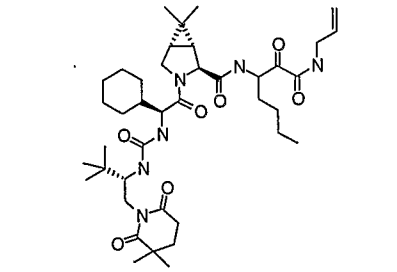
5788		A	753.00323
5789		A	718.94486
5790		A	700.97038
5791		A	720.9608
5792		A	698.95444

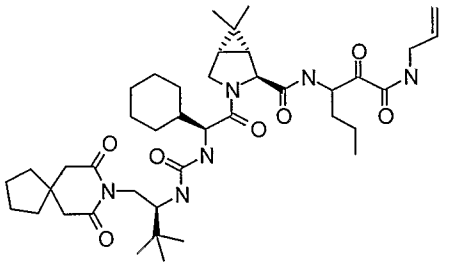
5793		A	779.04147
5794		A	767.03032
5795		A	781.05741
5796		A	738.97614
5797		A	765.01438

5798		A	726.96499
5799		A	712.9379
5800		A	724.94905
5801		A	740.99208
5802		A	755.01917

5803		A	753.00323
5804		A	669.82827
5805		A	673.86015
5806		A	700.92675
5807		A	716.96978

5808		A	743.00802
5809		A	740.99208
5810		A	767.03032
5811		A	631.77888
5812		A	683.85536

5813		A	687.88724
5814		A	671.84421
5815		A	685.8713
5816		A	685.8713
5817		A	740.99208

5818		A	753.00323

The present invention relates to novel HCV protease inhibitors. This utility can be manifested in their ability to inhibit the HCV NS3/NS4a serine protease. A general procedure for such demonstration is illustrated by the following *in vitro* assay.

Assay for HCV Protease Inhibitory Activity:

Spectrophotometric Assay: Spectrophotometric assay for the HCV serine protease can be performed on the inventive compounds by following the procedure described by R. Zhang *et al*, *Analytical Biochemistry*, 270 (1999) 268-275, the disclosure of which is incorporated herein by reference. The assay based on the proteolysis of chromogenic ester substrates is suitable for the continuous monitoring of HCV NS3 protease activity. The substrates are derived from the P side of the NS5A-NS5B junction sequence (Ac-DTEDVVX(Nva), where X = A or P) whose C-terminal carboxyl groups are esterified with one of four different chromophoric alcohols (3- or 4-nitrophenol, 7-hydroxy-4-methyl-coumarin, or 4-phenylazophenol). Illustrated below are the synthesis, characterization and application of these novel spectrophotometric ester substrates to high throughput screening and detailed kinetic evaluation of HCV NS3 protease inhibitors.

Materials and Methods:

Materials: Chemical reagents for assay related buffers are obtained from Sigma Chemical Company (St. Louis, Missouri). Reagents for peptide synthesis were from Aldrich Chemicals, Novabiochem (San Diego, California), Applied Biosystems (Foster City, California) and Perseptive Biosystems (Framingham, Massachusetts). Peptides are synthesized manually or on an automated ABI model 431A synthesizer (from Applied Biosystems). UV/VIS Spectrometer model LAMBDA 12 was from Perkin Elmer (Norwalk, Connecticut) and 96-well UV plates were obtained from Corning (Corning, New York). The prewarming block can be from USA Scientific (Ocala, Florida) and the 96-well plate vortexer is from Labline Instruments (Melrose Park, Illinois). A Spectramax Plus microtiter plate reader with monochrometer is obtained from Molecular Devices (Sunnyvale, California).

Enzyme Preparation: Recombinant heterodimeric HCV NS3/NS4A protease (strain 1a) is prepared by using the procedures published previously (D. L.

Sali *et al*, *Biochemistry*, 37 (1998) 3392-3401). Protein concentrations are determined by the Biorad dye method using recombinant HCV protease standards previously quantified by amino acid analysis. Prior to assay initiation, the enzyme storage buffer (50 mM sodium phosphate pH 8.0, 300 mM NaCl, 10% glycerol, 0.05% lauryl maltoside and 10 mM DTT) is exchanged for the assay buffer (25 mM MOPS pH 6.5, 300 mM NaCl, 10% glycerol, 0.05% lauryl maltoside, 5 μM EDTA and 5 μM DTT) utilizing a Biorad Bio-Spin P-6 prepacked column.

Substrate Synthesis and Purification: The synthesis of the substrates is done as reported by R. Zhang *et al*, (*ibid.*) and is initiated by anchoring Fmoc-Nva-OH to 2-chlorotrityl chloride resin using a standard protocol (K. Barlos *et al, Int. J. Pept. Protein Res.*, 37 (1991), 513-520). The peptides are subsequently assembled, using Fmoc chemistry, either manually or on an automatic ABI model 431 peptide synthesizer. The N-acetylated and fully protected peptide fragments are cleaved from the resin either by 10% acetic acid (HOAc) and 10% trifluoroethanol (TFE) in dichloromethane (DCM) for 30 min, or by 2% trifluoroacetic acid (TFA) in DCM for 10 min. The combined filtrate and DCM wash is evaporated azeotropically (or repeatedly extracted by aqueous Na_2CO_3 solution) to remove the acid used in cleavage. The DCM phase is dried over Na_2SO_4 and evaporated.

The ester substrates are assembled using standard acid-alcohol coupling procedures (K. Holmber *et al, Acta Chem. Scand.*, B33 (1979) 410-412). Peptide fragments are dissolved in anhydrous pyridine (30-60 mg/ml) to which 10 molar equivalents of chromophore and a catalytic amount (0.1 eq.) of para-toluenesulfonic acid (pTSA) were added. Dicyclohexylcarbodiimide (DCC, 3 eq.) is added to initiate the coupling reactions. Product formation is monitored by HPLC and can be found to be complete following 12-72 hour reaction at room temperature. Pyridine solvent is evaporated under vacuum and further removed by azeotropic evaporation with toluene. The peptide ester is deprotected with 95% TFA in DCM for two hours and extracted three times with anhydrous ethyl ether to remove excess chromophore. The deprotected substrate is purified by reversed phase HPLC on a C3 or C8 column with a 30% to 60% acetonitrile gradient (using six column volumes).

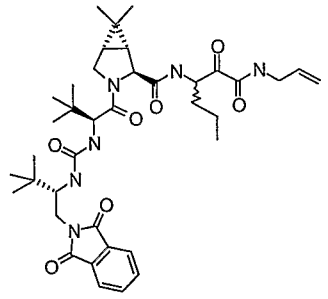
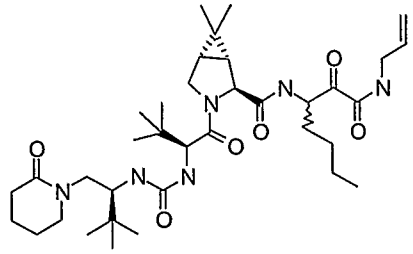
The overall yield following HPLC purification can be approximately 20-30%. The molecular mass can be confirmed by electrospray ionization mass spectroscopy. The substrates are stored in dry powder form under desiccation.

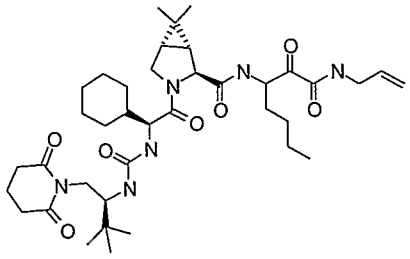
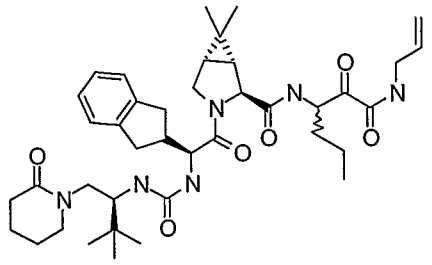
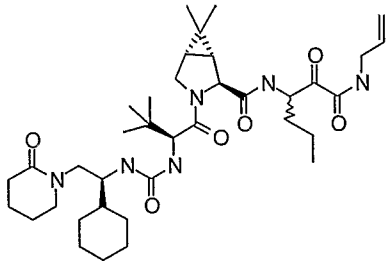
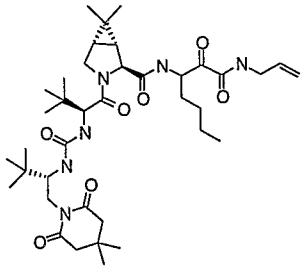
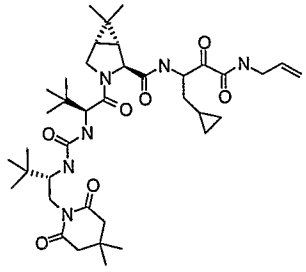
Spectra of Substrates and Products: Spectra of substrates and the corresponding chromophore products are obtained in the pH 6.5 assay buffer. Extinction coefficients are determined at the optimal off-peak wavelength in 1-cm cuvettes (340 nm for 3-Np and HMC, 370 nm for PAP and 400 nm for 4-Np) using multiple dilutions. The optimal off-peak wavelength is defined as that wavelength yielding the maximum fractional difference in absorbance between substrate and product (product OD - substrate OD)/substrate OD).

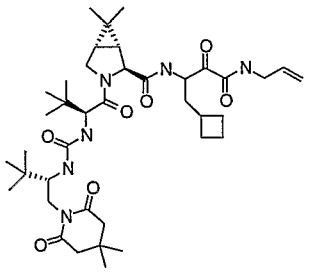
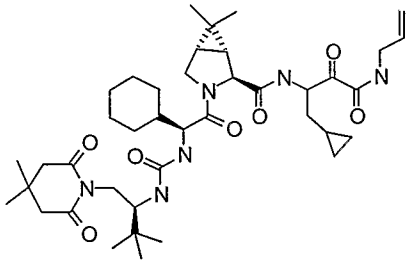
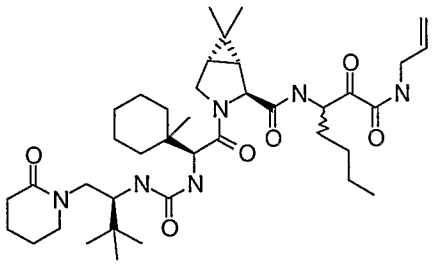
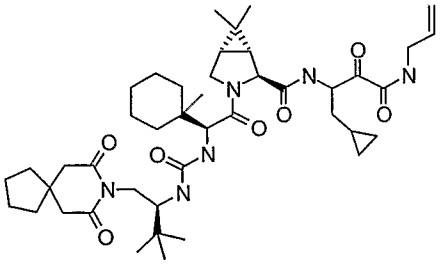
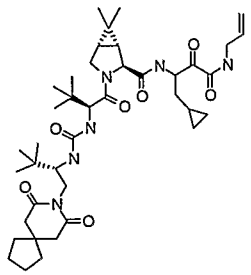
Protease Assay: HCV protease assays are performed at 30°C using a 200 µl reaction mix in a 96-well microtiter plate. Assay buffer conditions (25 mM MOPS pH 6.5, 300 mM NaCl, 10% glycerol, 0.05% lauryl maltoside, 5 µM EDTA and 5 µM DTT) are optimized for the NS3/NS4A heterodimer (D. L. Sali *et al*, *ibid.*)). Typically, 150 µl mixtures of buffer, substrate and inhibitor are placed in wells (final concentration of DMSO ≤4 % v/v) and allowed to preincubate at 30 °C for approximately 3 minutes. Fifty µls of prewarmed protease (12 nM, 30°C) in assay buffer, is then used to initiate the reaction (final volume 200 µl).The plates are monitored over the length of the assay (60 minutes) for change in absorbance at the appropriate wavelength (340 nm for 3-Np and HMC, 370 nm for PAP, and 400 nm for 4-Np) using a Spectromax Plus microtiter plate reader equipped with a monochrometer (acceptable results can be obtained with plate readers that utilize cutoff filters). Proteolytic cleavage of the ester linkage between the Nva and the chromophore is monitored at the appropriate wavelength against a no enzyme blank as a control for non-enzymatic hydrolysis. The evaluation of substrate kinetic parameters is performed over a 30-fold substrate concentration range (~6-200 µM). Initial velocities are determined using linear regression and kinetic constants are obtained by fitting the data to the Michaelis-Menten equation using non-linear regression analysis (Mac Curve Fit 1.1, K. Raner). Turnover numbers (k_{cat}) are calculated assuming the enzyme is fully active.

Evaluation of Inhibitors and Inactivators: The inhibition constants (K_i) for the competitive inhibitors Ac-D-(D-Gla)-L-I-(Cha)-C-OH (27), Ac-DTEDVVA(Nva)-OH and Ac-DTEDVVP(Nva)-OH are determined experimentally at fixed concentrations of enzyme and substrate by plotting v_o/v_i vs. inhibitor concentration ($[I]_o$) according to the rearranged Michaelis-Menten equation for competitive inhibition kinetics: $v_o/v_i = 1 + [I]_o/(K_i (1 + [S]_o/K_m))$, where v_o is the uninhibited initial velocity, v_i is the initial velocity in the presence of inhibitor at any given inhibitor concentration ($[I]_o$) and $[S]_o$ is the substrate concentration used. The resulting data are fitted using linear regression and the resulting slope, $1/(K_i(1+[S]_o/K_m)$, is used to calculate the K_i value. The Ki* values (in nanoMolar) for some of the inventive compounds are in the following **Table 4**:

Table 4

Compound number	structure	Ki*
5619		11
5652		19

5705		3
5724		19
5731		15
5753		4
5754		4

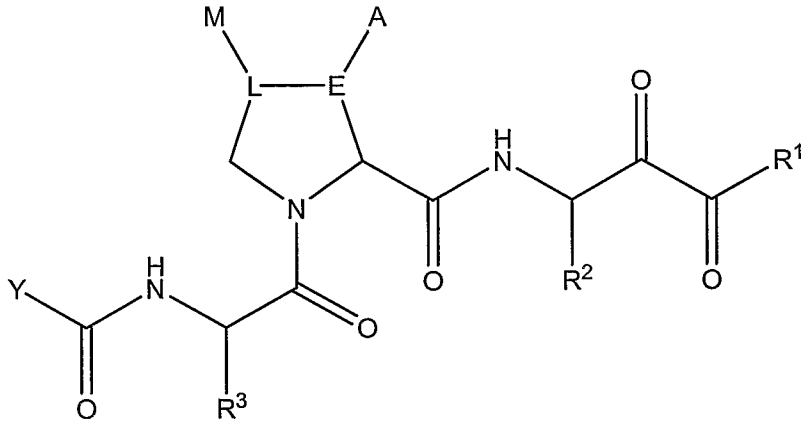
5755		7
5775		5
5781		9
5793		11
5796		3.2

While the present invention has been described with in conjunction with the specific embodiments set forth above, many alternatives, modifications and other variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

Claims

What is claimed is:

1. A compound, or enantiomers, stereoisomers, rotamers, tautomers, and racemates of said compound, or a pharmaceutically acceptable salt, solvate or ester of said compound, said compound having the general structure shown in Formula I:

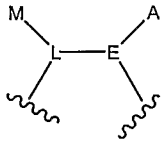


Formula I

wherein:

R^1 is H, OR^8, NR^9R^{10}, or CHR^9R^{10}, wherein R^8, R^9 and R^{10} can be the same or different, each being independently selected from the group consisting of H, alkyl-, alkenyl-, alkynyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, heterocyclyl-, arylalkyl-, and heteroarylalkyl;

A and M can be the same or different, each being independently selected from R, OR, NHR, NRR', SR, SO_2R, and halo; or A and M are connected to each other (in other words, A-E-L-M taken together) such that the moiety:



shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl;

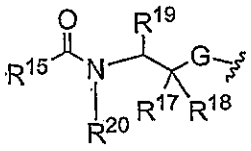
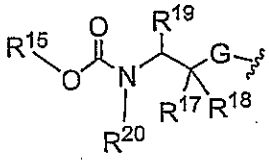
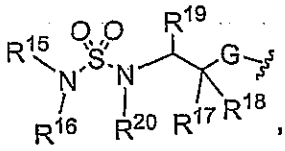
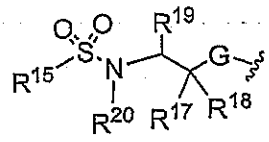
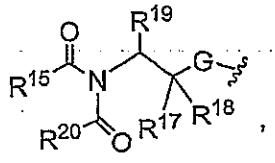
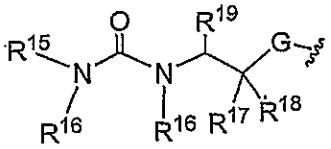
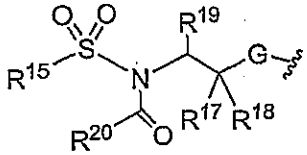
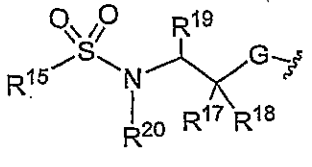
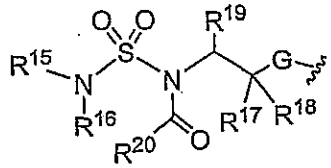
E is C(H) or C(R);

L is C(H), C(R), $CH_2C(R)$, or $C(R)CH_2$;

R, R', R^2, and R^3 can be the same or different, each being independently selected from the group consisting of H, alkyl-, alkenyl-,

alkynyl-, cycloalkyl-, heteroalkyl-, heterocyclyl-, aryl-, heteroaryl-, (cycloalkyl)alkyl-, (heterocyclyl)alkyl-, aryl-alkyl-, and heteroaryl-alkyl-; or alternately R and R' in NRR' are connected to each other such that NRR' forms a four to eight-membered heterocyclyl;

and Y is selected from the following moieties:


,

,

,

,

,

,

,

or


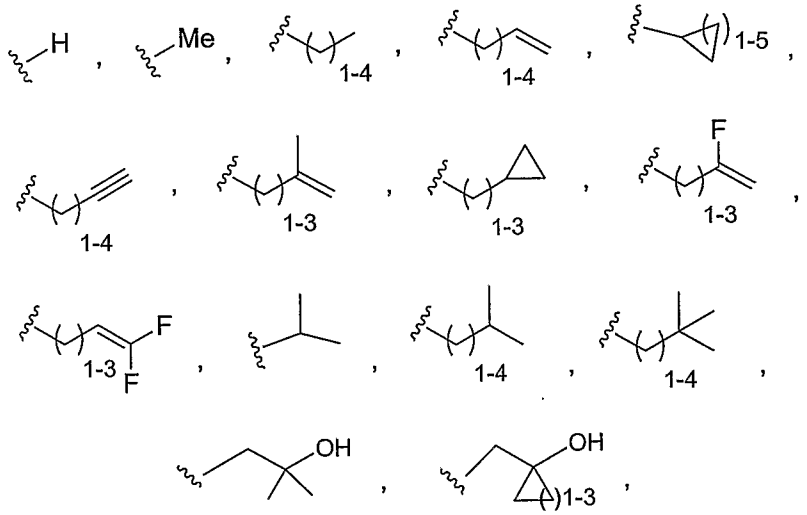
wherein G is NH or O, and R^{15}, R^{16}, R^{17} , R^{18}, R^{19} and R^{20} can be the same or different, each being independently selected from the group consisting of H, C_1-C_{10} alkyl, C_1-C_{10} heteroalkyl, C_2-C_{10} alkenyl, C_2-C_{10} heteroalkenyl, C_2-C_{10} alkynyl, C_2-C_{10} heteroalkynyl, C_3-C_8 cycloalkyl, C_3-C_8 heterocyclyl, aryl, heteroaryl, or alternately: (i) either R^{15} and R^{16} can be connected to each other to form a four to eight-membered cycloalkyl or heterocyclyl, or R^{15} and R^{19} are connected to each other to form a five to eight-membered cycloalkyl or heterocyclyl, or R^{15} and R^{20} are connected to each other to form a five to eight-membered cycloalkyl or heterocyclyl, and (ii) likewise, independently, R^{17} and R^{18} are connected to each other to form a three to eight-membered cycloalkyl or heterocyclyl,

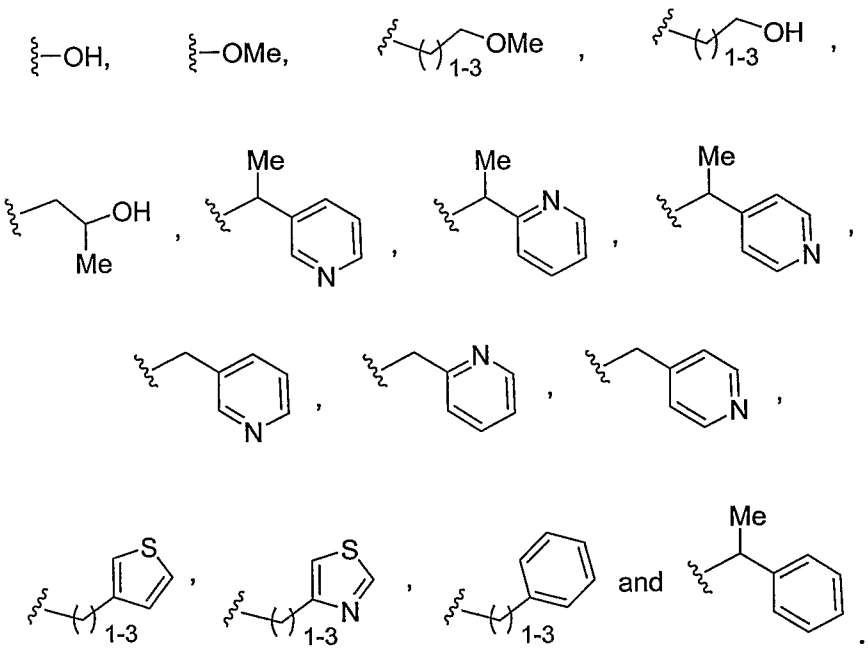
wherein each of said alkyl, aryl, heteroaryl, cycloalkyl or heterocyclyl can be unsubstituted or optionally independently substituted with one or more moieties selected from the group consisting of: hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, amido, alkylamino, arylamino, alkylsulfonyl,

arylsulfonyl, sulfonamido, alkylsulfonamido, arylsulfonamido, keto, carboxy, carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyloxy, alkylureido, arylureido, halo, cyano, and nitro.

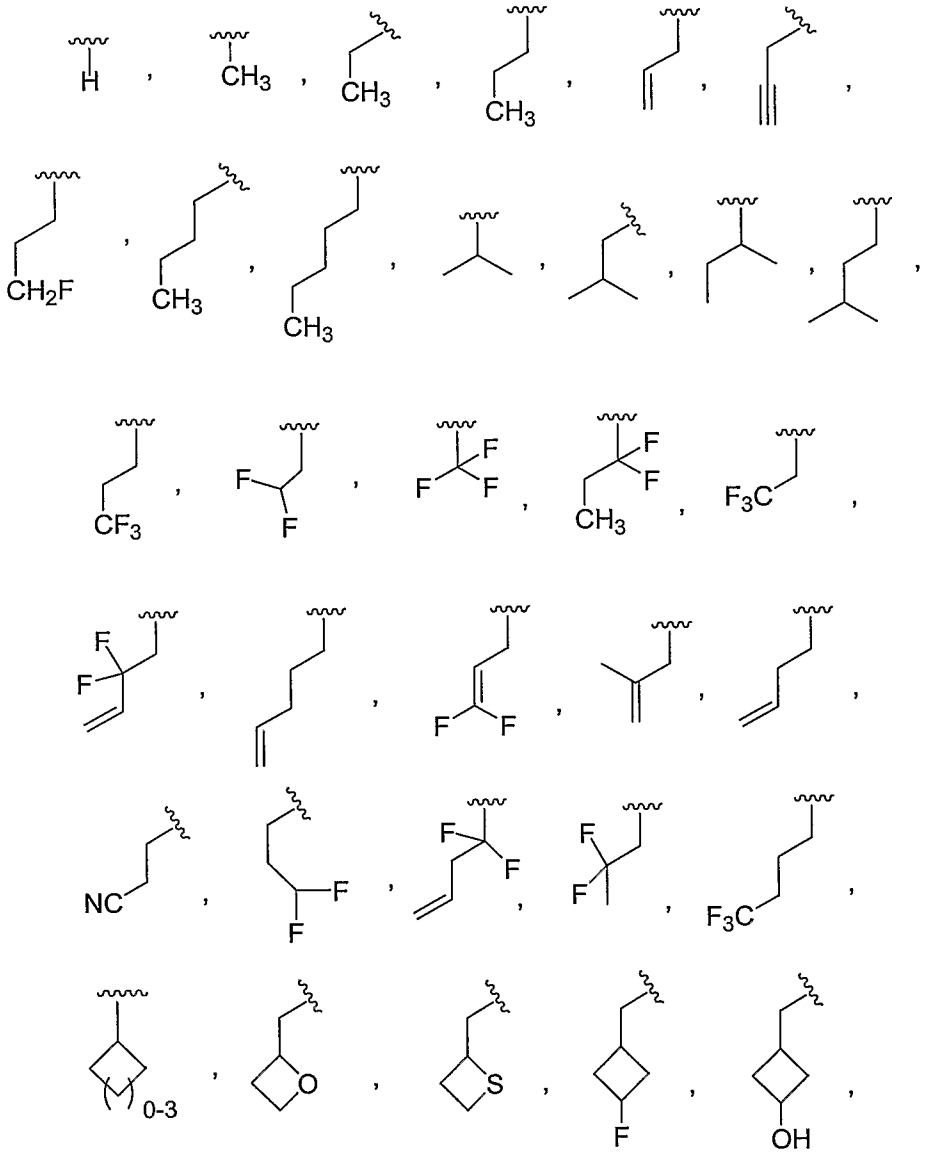
2. The compound of claim 1, wherein R^1 is NR^9R^{10}, and R^9 is H, R^{10} is H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, alkyl-aryl, alkyl-heteroaryl, aryl-alkyl, alkenyl, alkynyl or heteroaryl-alkyl.

3. The compound of claim 2, wherein R^{10} is selected from the group consisting of:

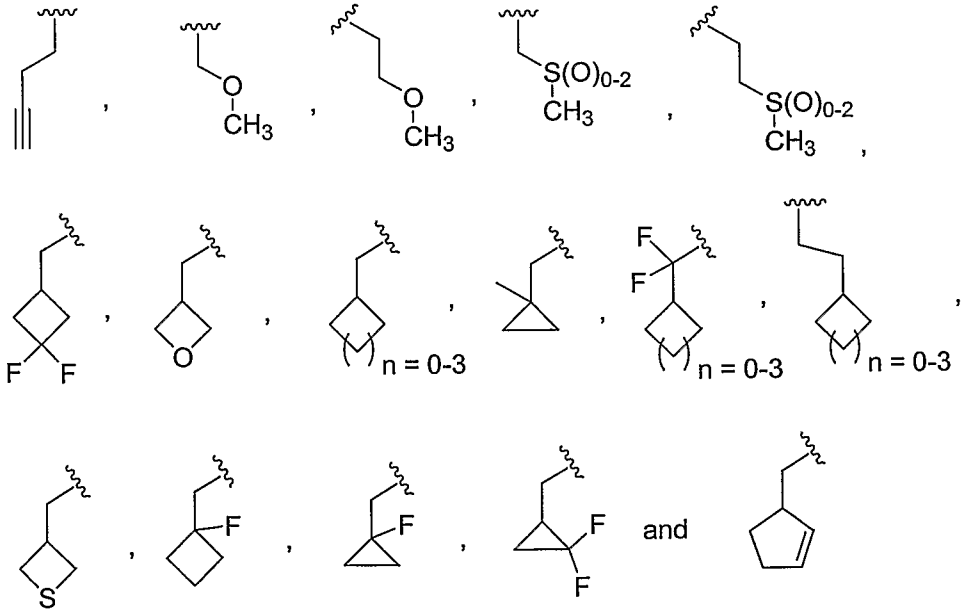




4. The compound of claim 1, wherein R^2 is selected from the group consisting of the following moieties:

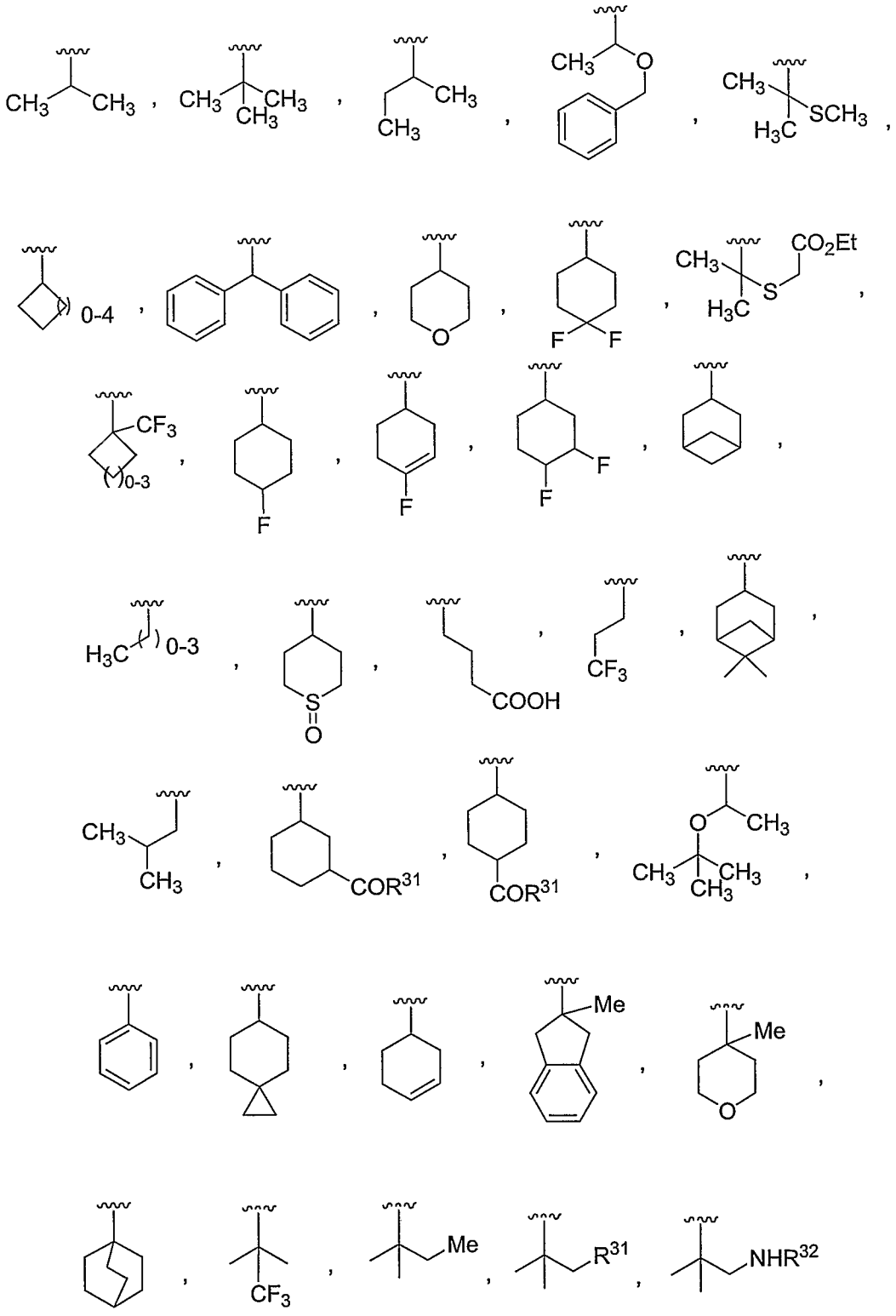

H
CH3
CH3
CH3
CH2F
CH3
CH3
CF3
F
F
F
F
F
CH3
F3C
F
F
F
F
NC
F
F
F
F
F
F3C
0-3
O
S
F
OH

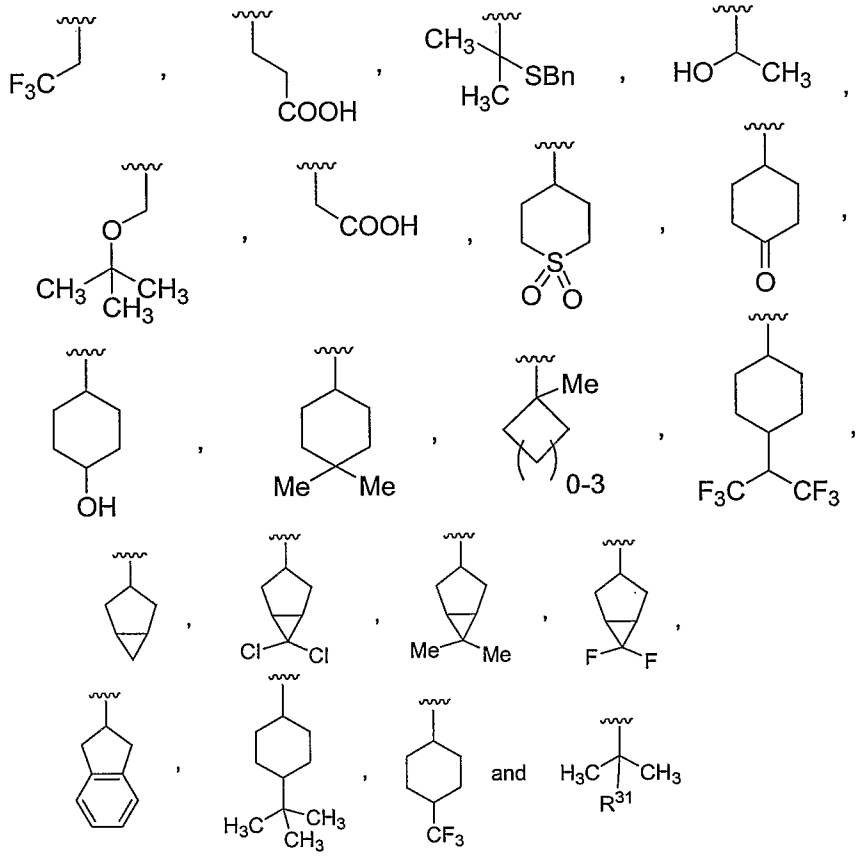
5


O
CH3
O
CH3
S(O)0-2
CH3
S(O)0-2
CH3
F
F
O
n = 0-3
F
F
n = 0-3
n = 0-3
S
F
F
F
F
and

.

5. The compound of claim 1, wherein R^3 is selected from the group consisting of:

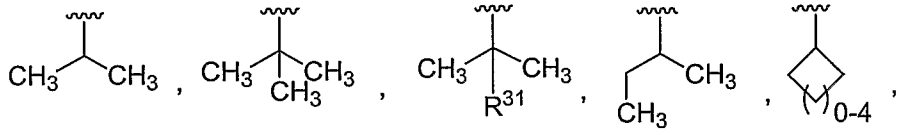


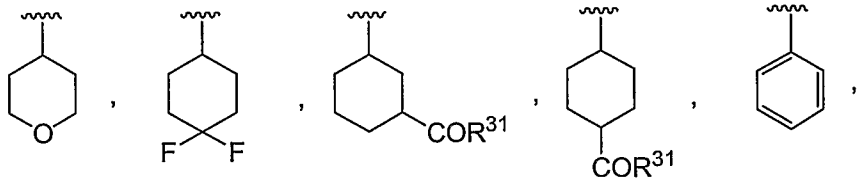


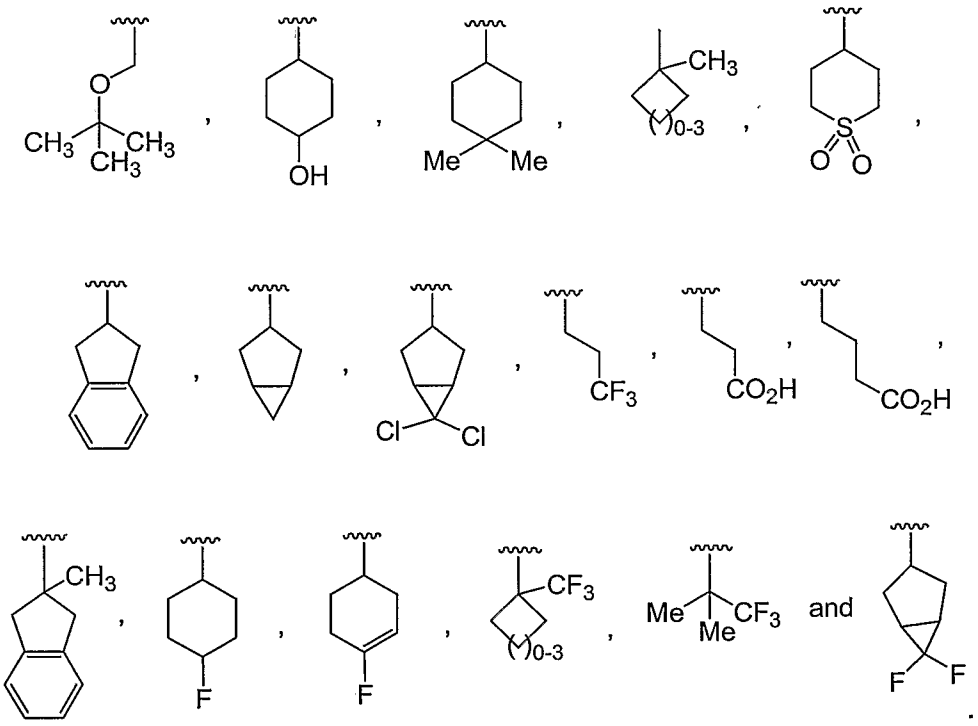
wherein R^{31} is OH or O-alkyl; and

R^{32} is H, $C(O)CH_3$, C(O)OtBu or C(O)N(H)tBu.

6. The compound of claim 5, wherein R^3 is selected from the group consisting of the following moieties:

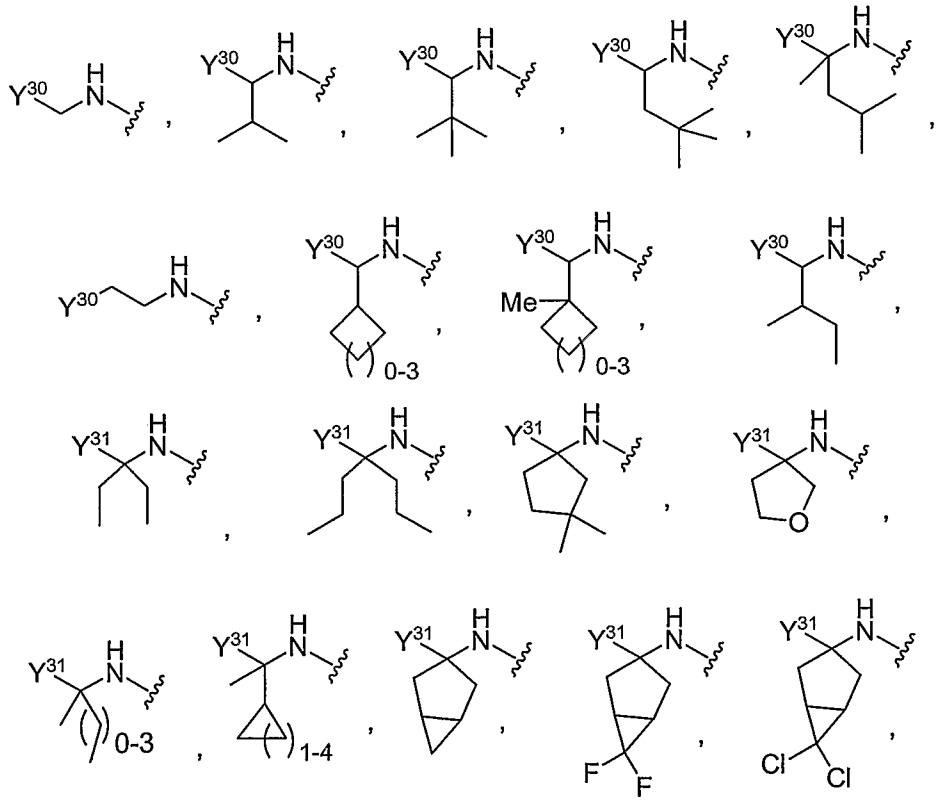


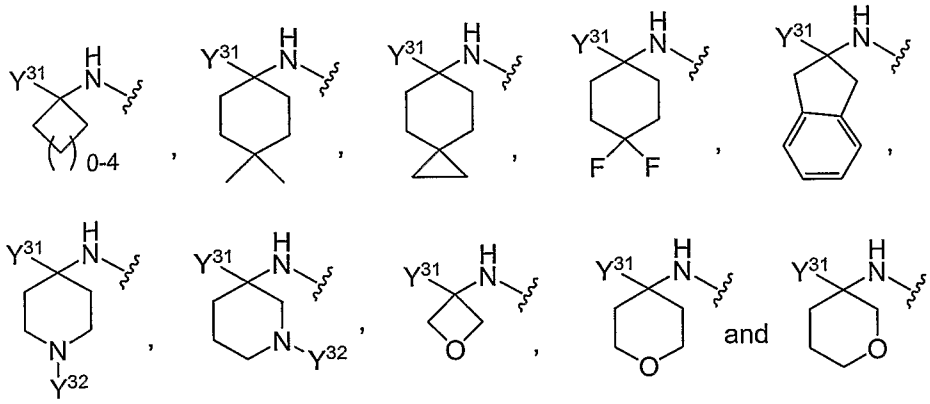




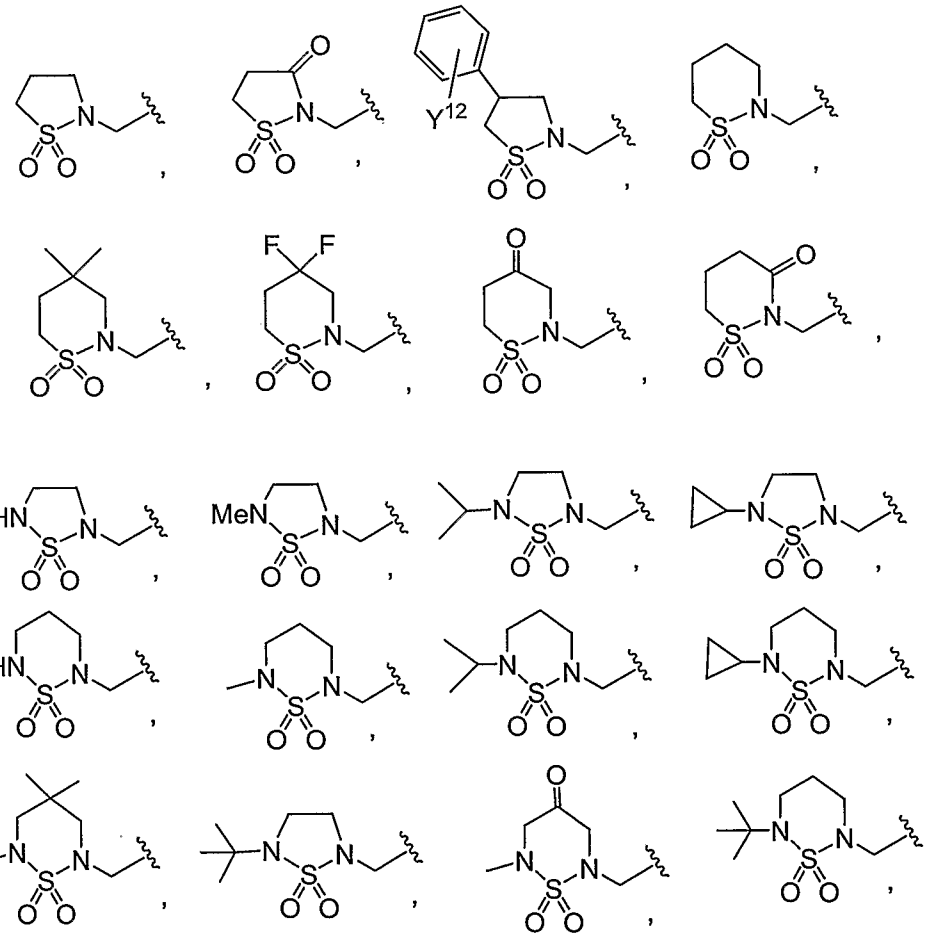
7. The compound of claim 1, wherein G is NH.

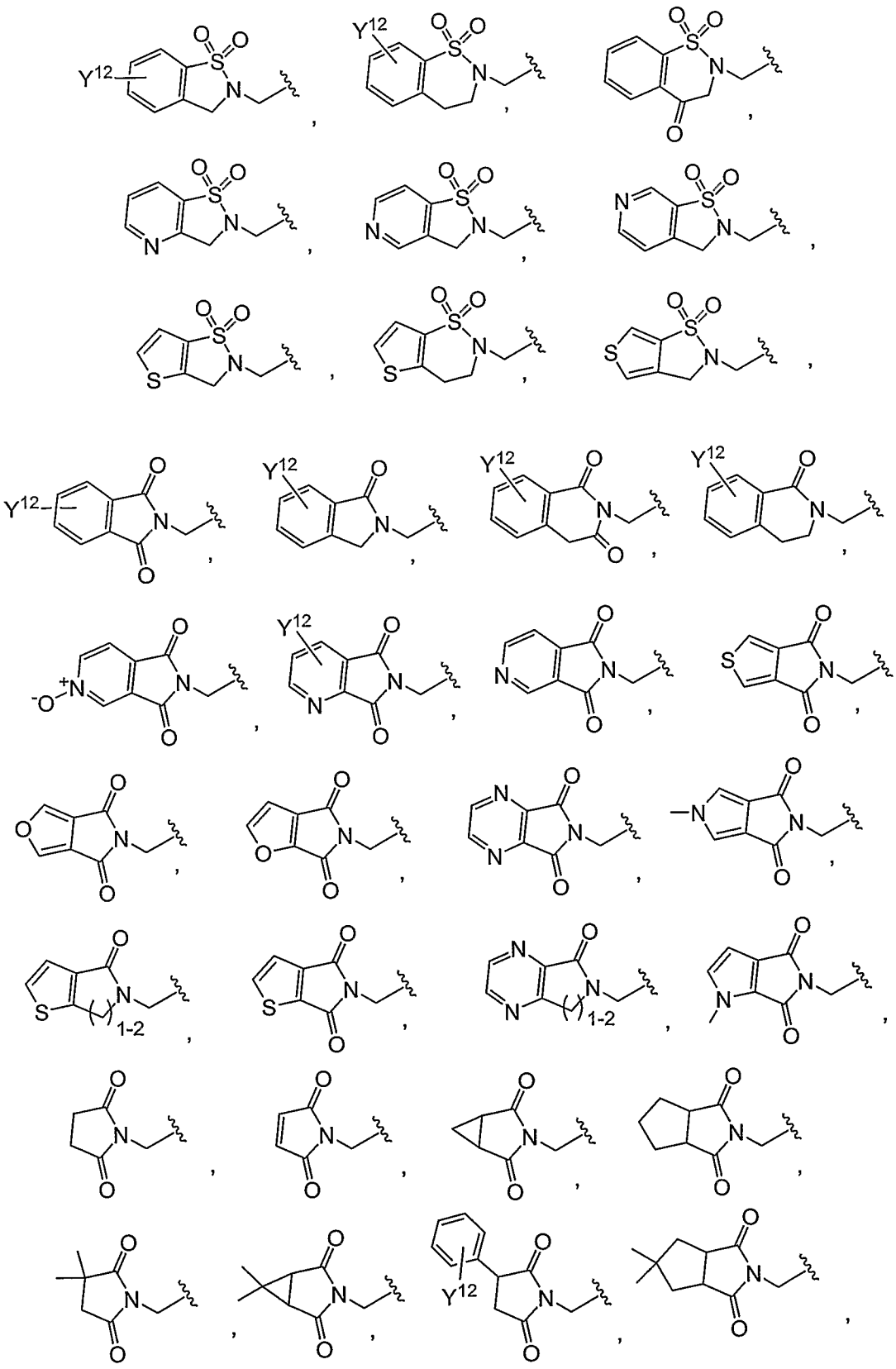
8. The compound of claim 1, wherein Y is selected from the group consisting of:

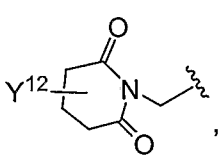
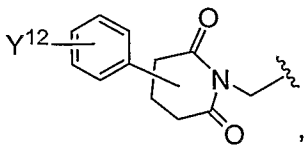
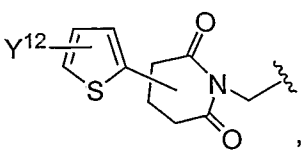
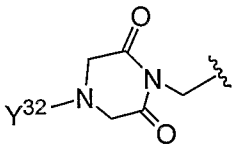
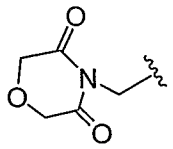
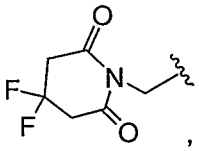
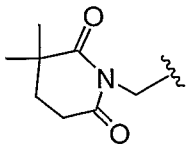
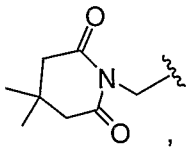
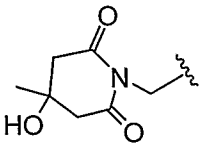
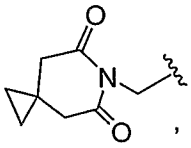
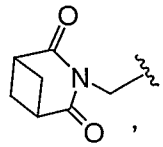
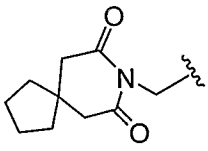
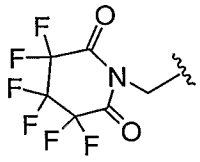
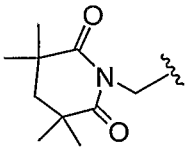
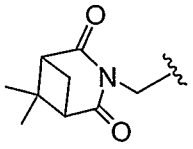
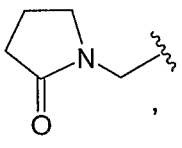
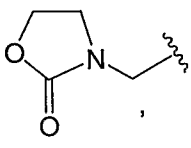
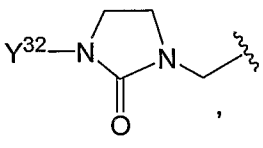
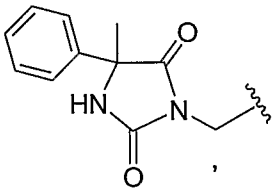
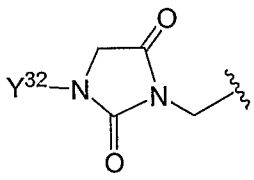
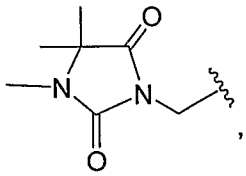
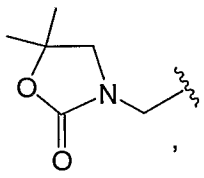
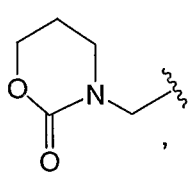
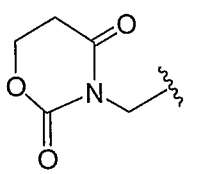
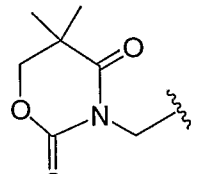
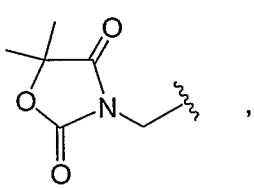
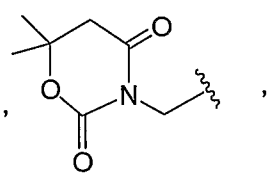
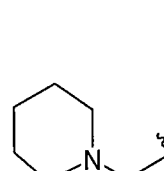
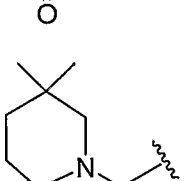
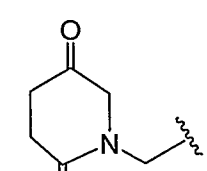
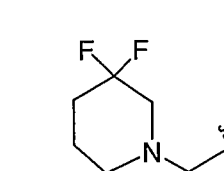
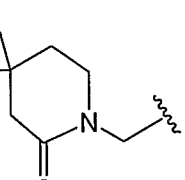
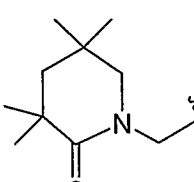
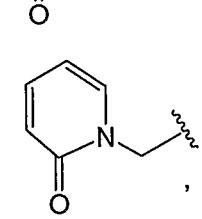
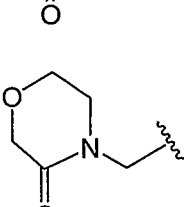




wherein Y^{30} and Y^{31} are selected from the group consisting of:






,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

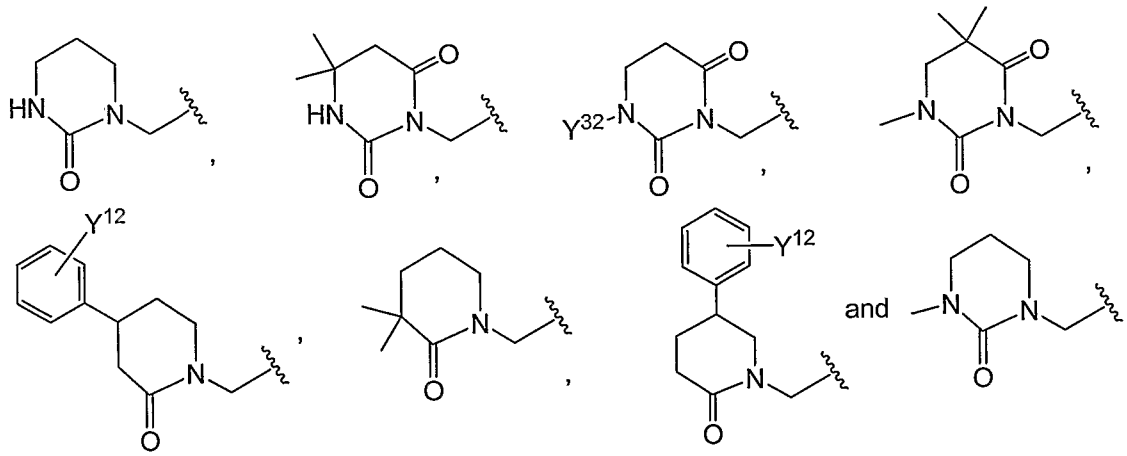
,

,

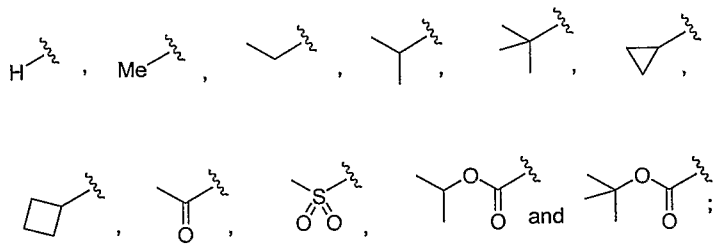
,

,

5

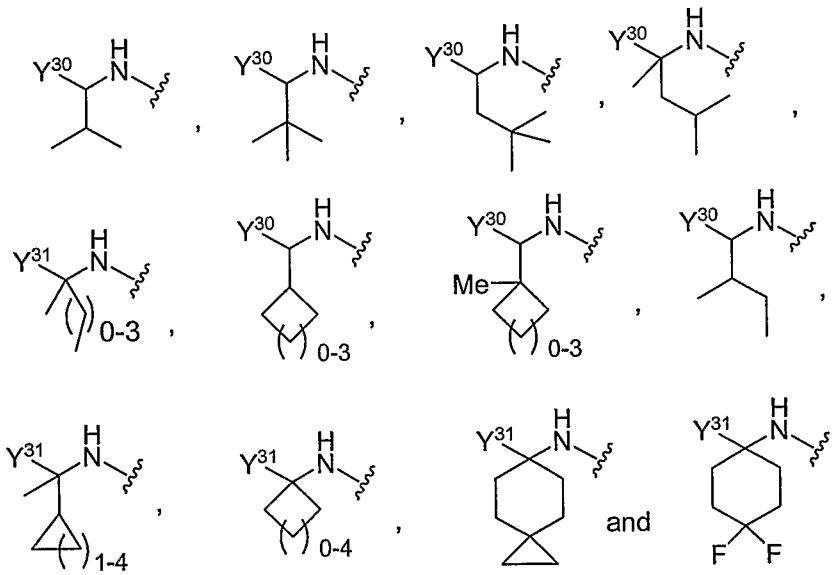


Y^{32} is selected from the group consisting of:

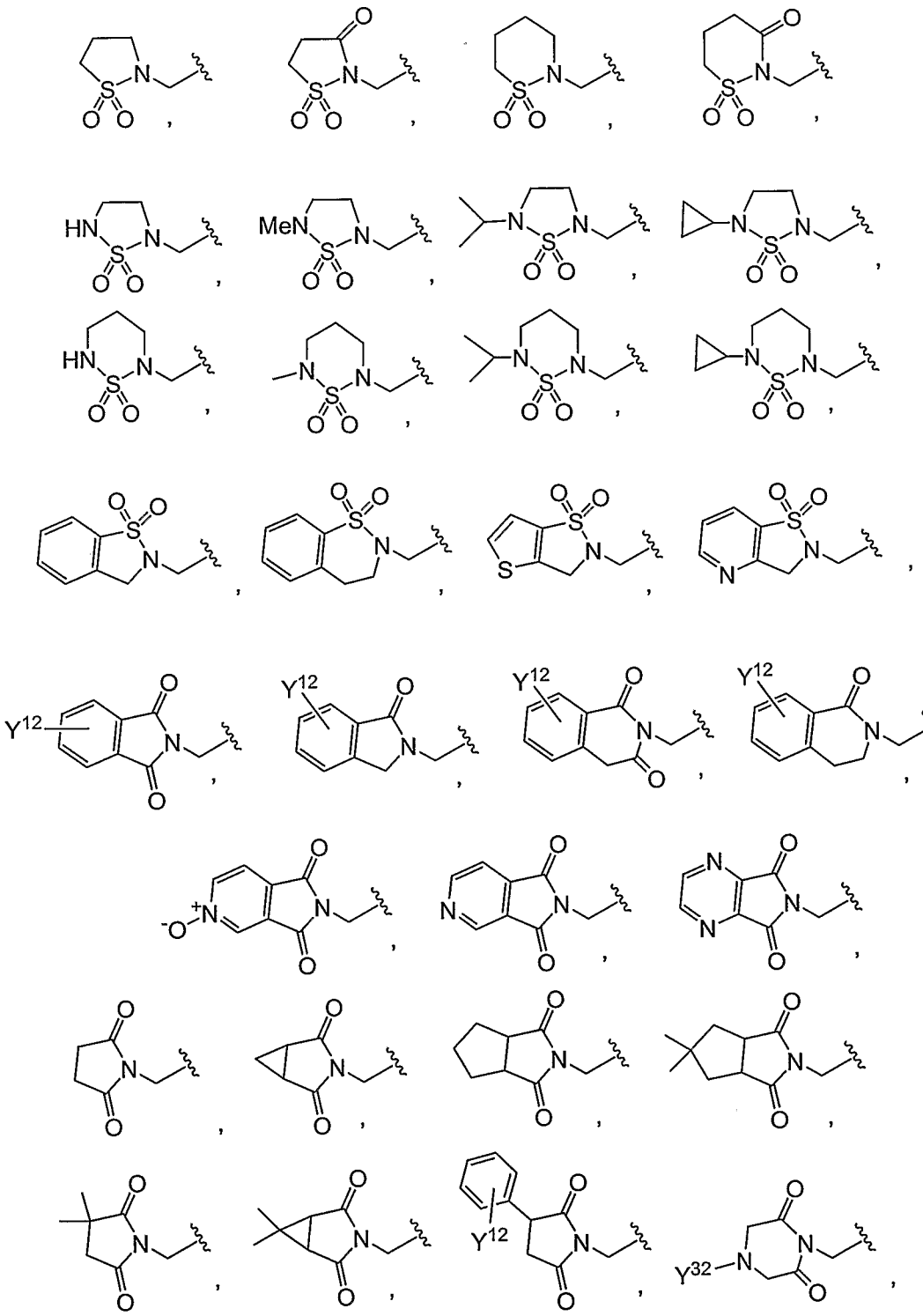


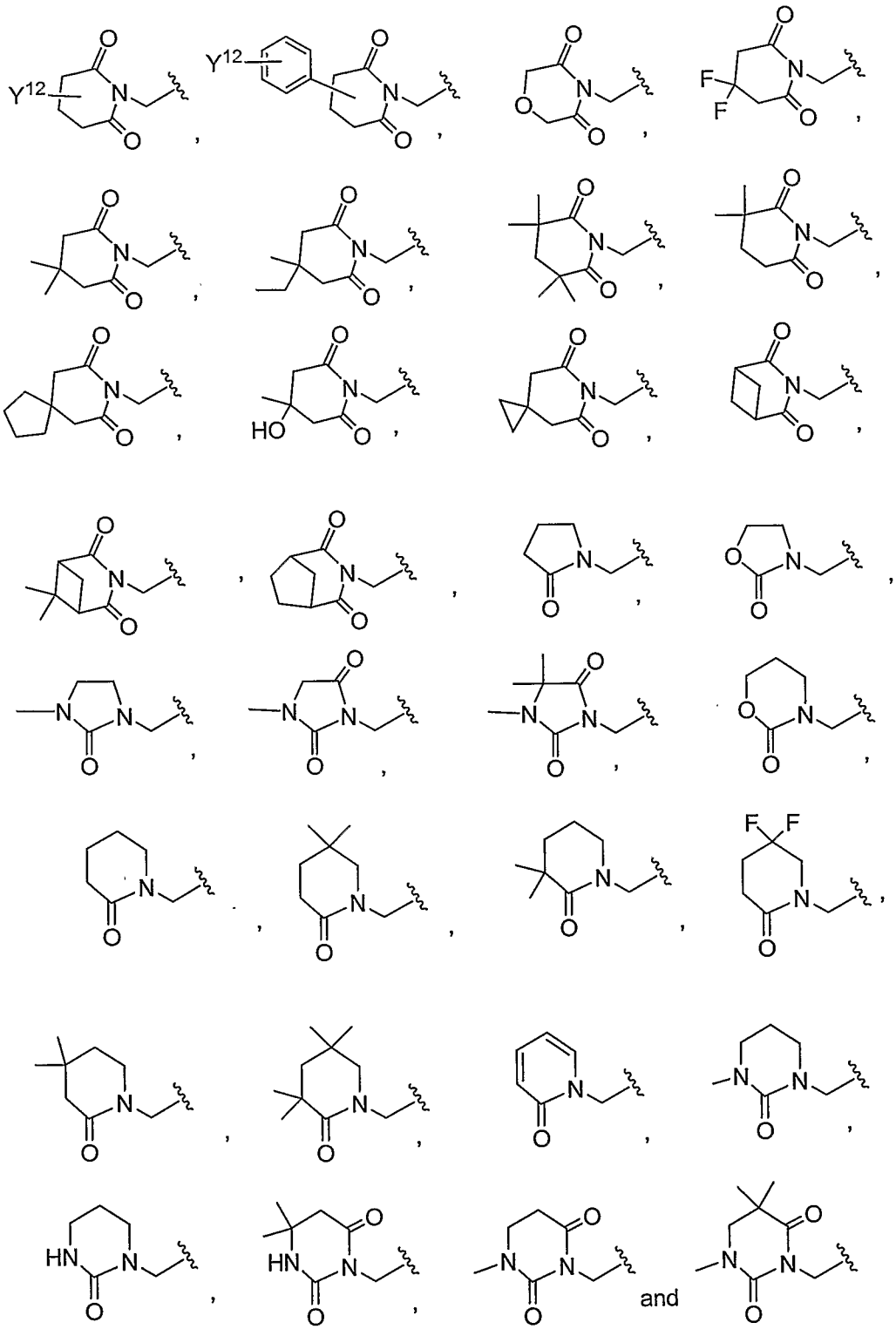
and Y^{12} is selected from H, COOH, COOMe, $CONH_2$, OMe, OH, OCF_3, $OCH(CH_3)_2$, $OC(CH_3)_3$, F, Cl, Br, NH_2, $NHSO_2CH_3$, $NHC(O)CH_3$, $NHCO_2CH_3$, NO_2, SO_2NH_2, CF_3, Me, Et, isopropyl, cyclopropyl, *t*-butyl and phenyl.

9. The compound of claim 8, wherein Y is selected from the group consisting of:



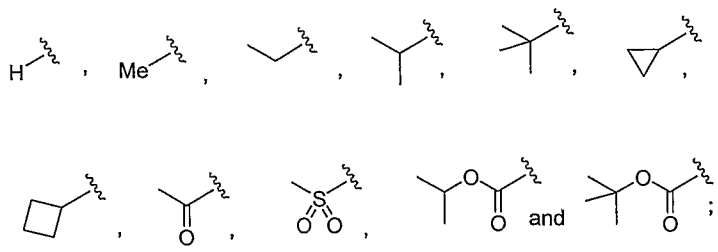
wherein Y^{30} and Y^{31} are selected from the group consisting of:





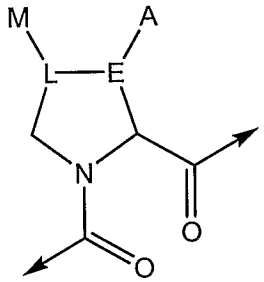
and

Y^{32} is selected from the group consisting of:

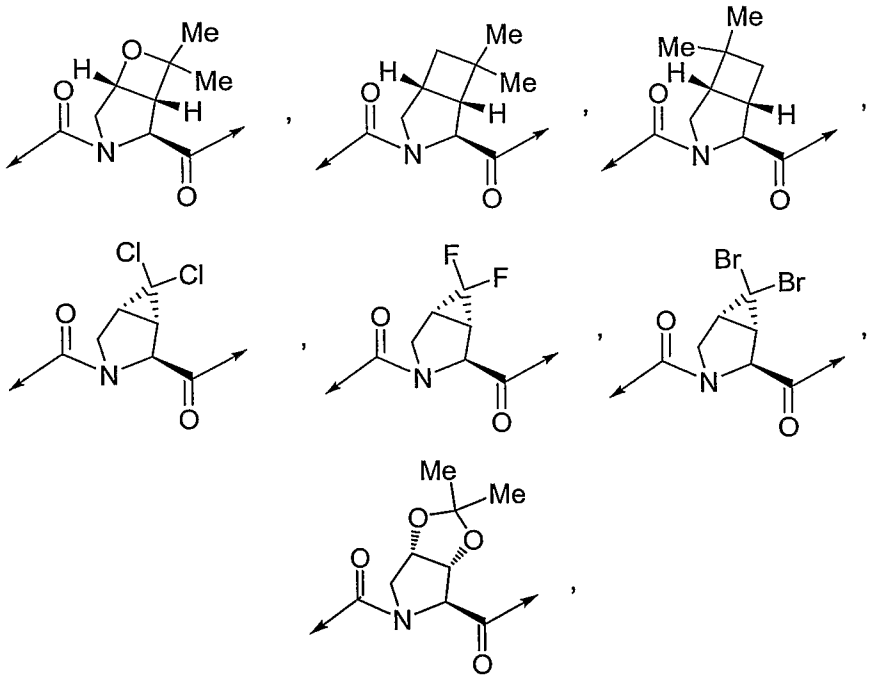


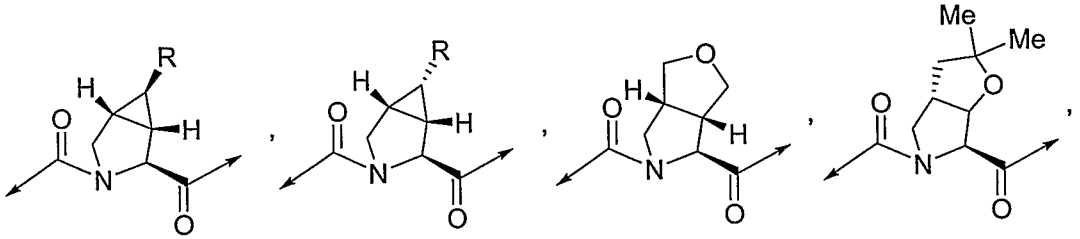
and Y^{12} is selected from H, COOH, COOMe, $CONH_2$, OMe, OH, OCF_3, $OCH(CH_3)_2$, $OC(CH_3)_3$, F, Cl, Br, NH_2, $NHSO_2CH_3$, $NHC(O)CH_3$, $NHCO_2CH_3$, NO_2, SO_2NH_2, CF_3, Me, Et, isopropyl, cyclopropyl, *t*-butyl and phenyl.

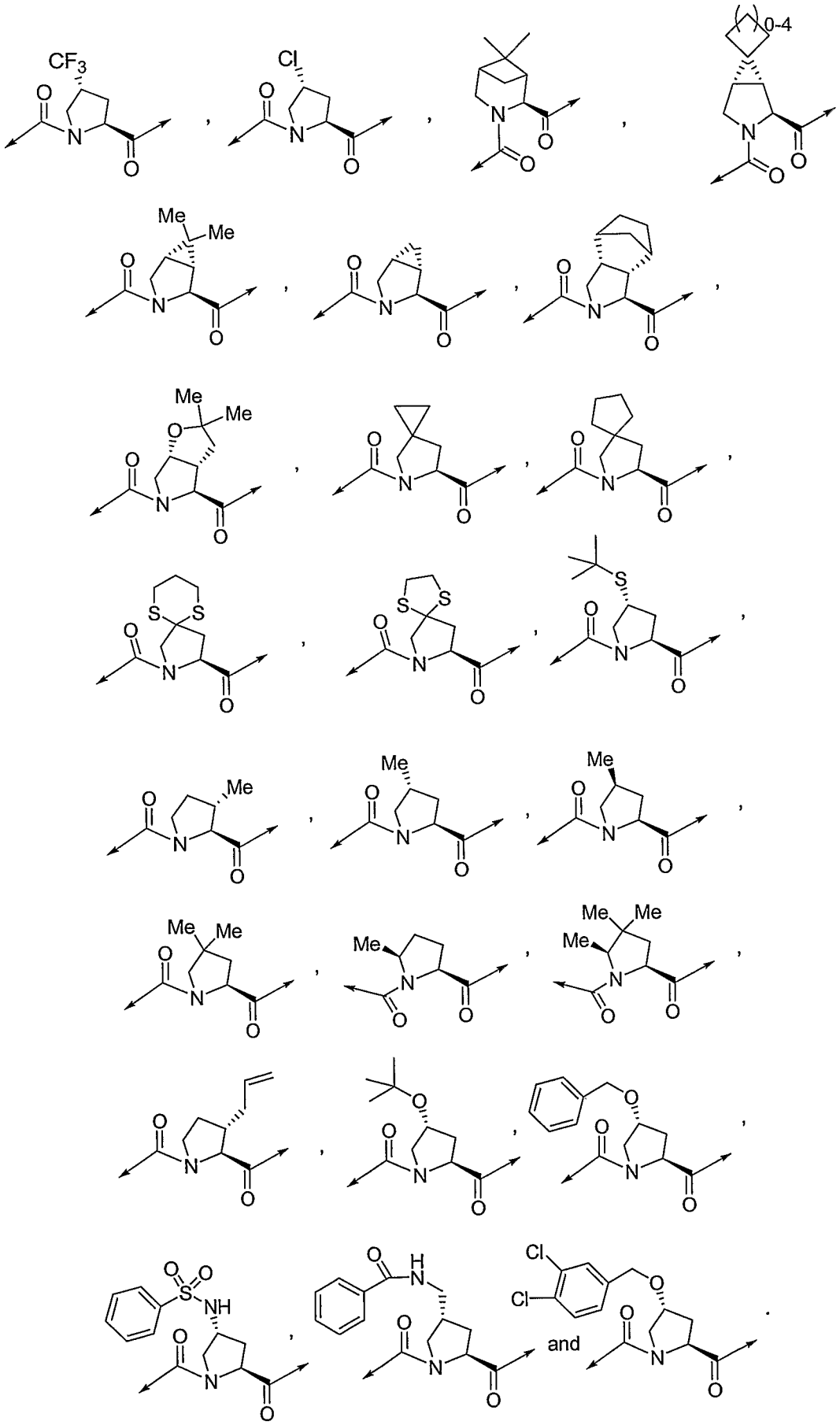
10. The compound of claim 1, wherein the moiety:



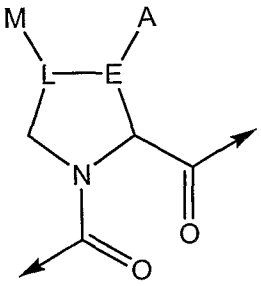
is selected from the following structures:



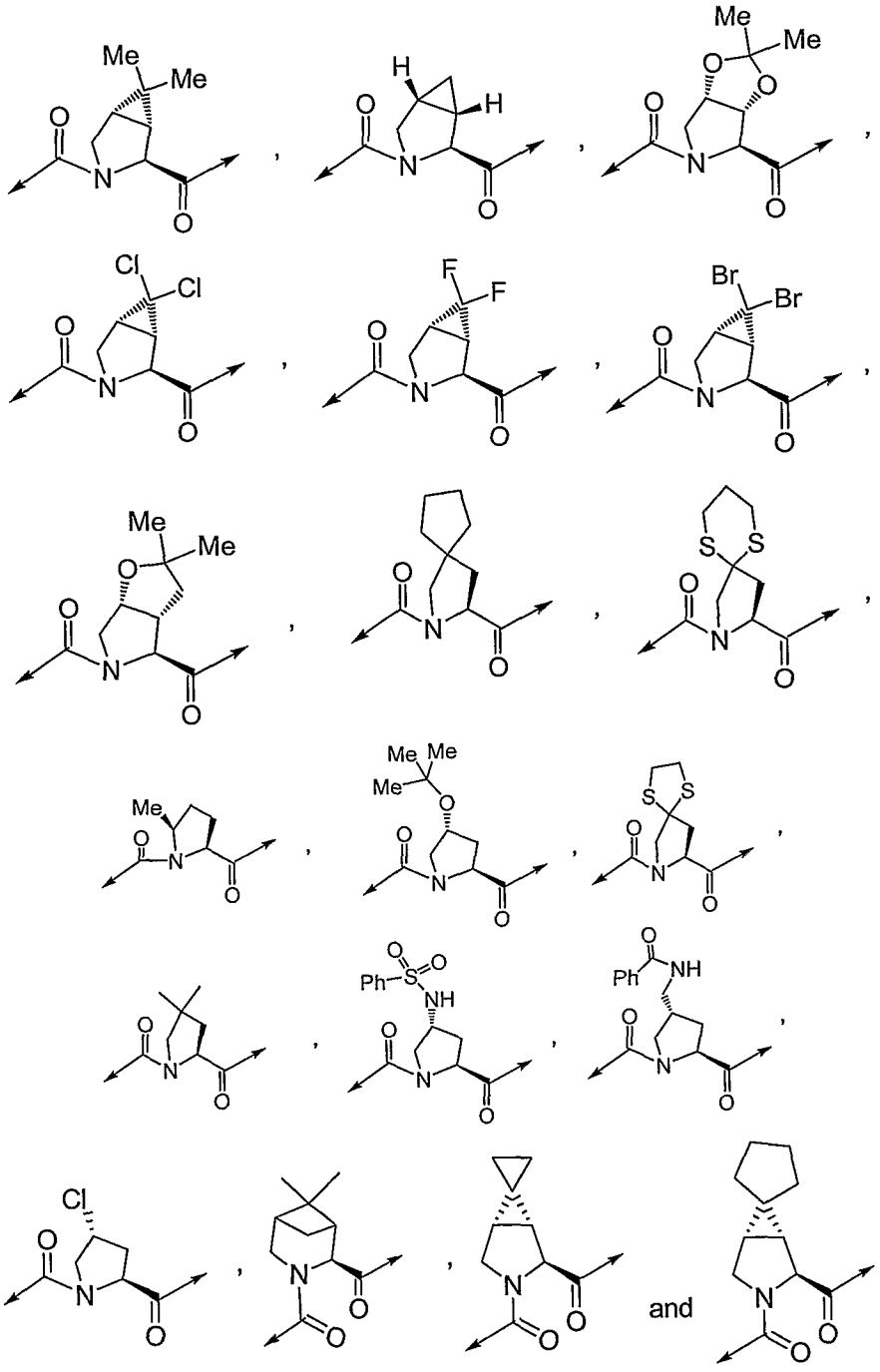




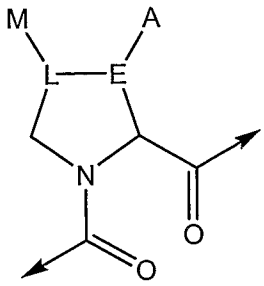
11. The compound of claim 10, wherein the moiety:



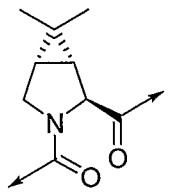
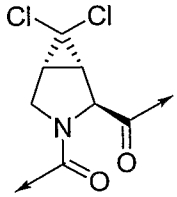
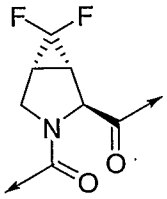
is selected from the following structures:

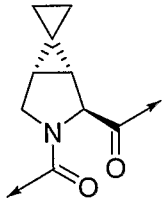
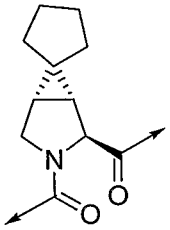
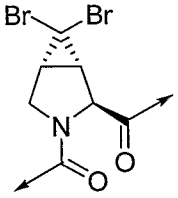


12. The compound of claim 11, wherein the moiety:

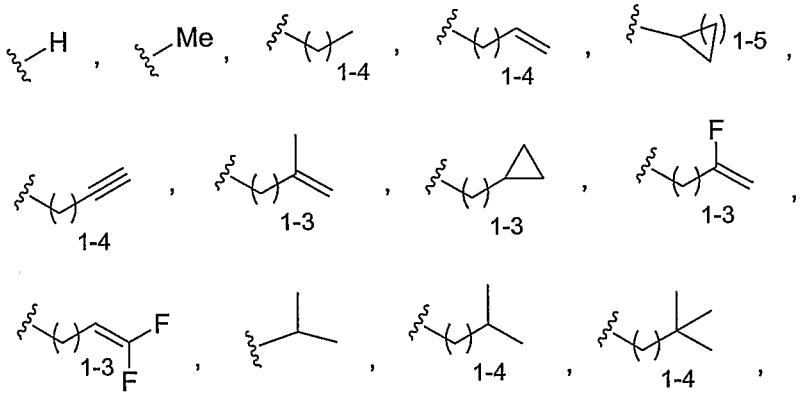


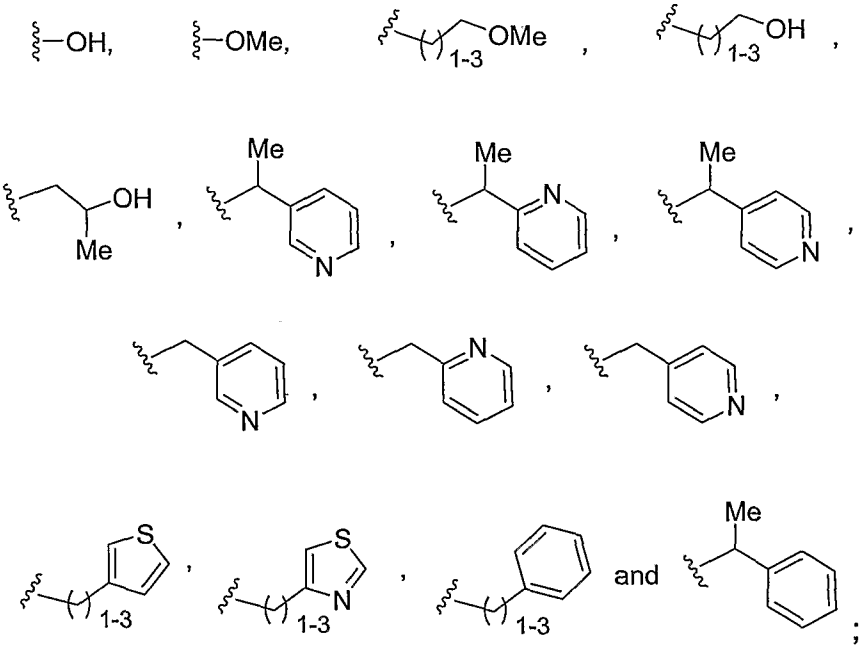
is selected from the following structures:


,

,



,

and

.

13. The compound of claim 1, wherein R^1 is NHR^{10}, where R^{10} is selected from the group consisting of:

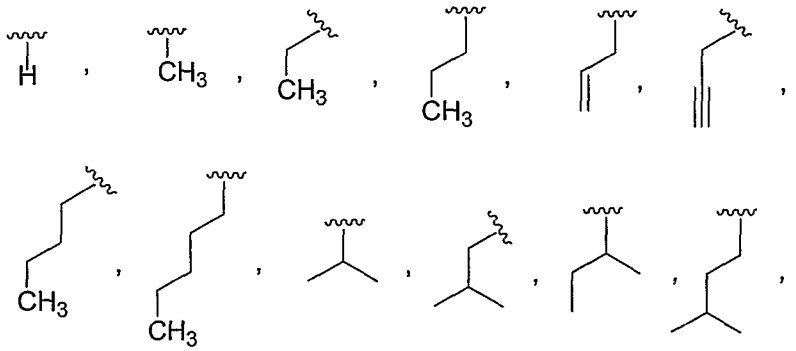


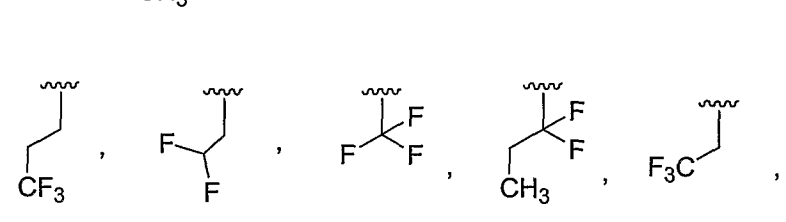


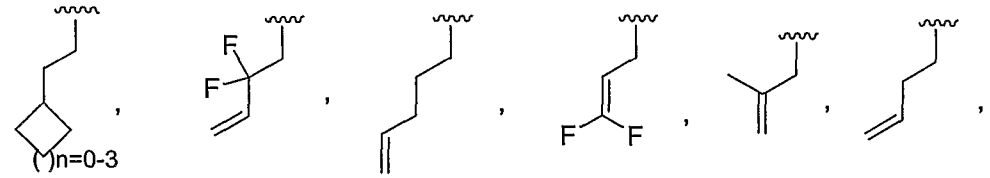
and

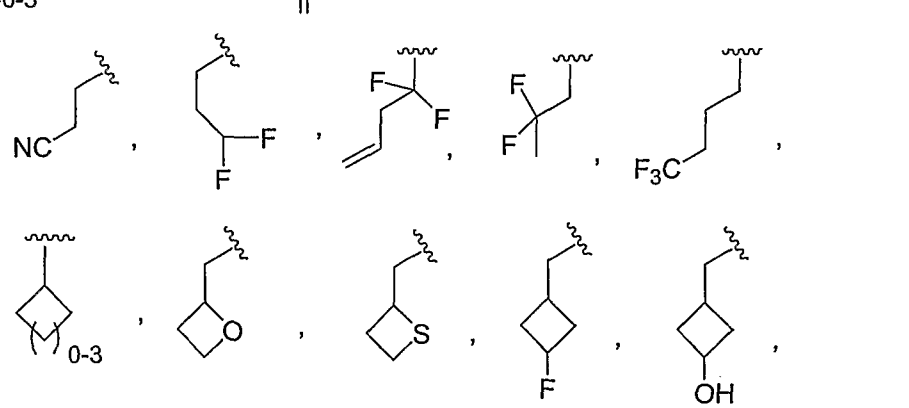
;

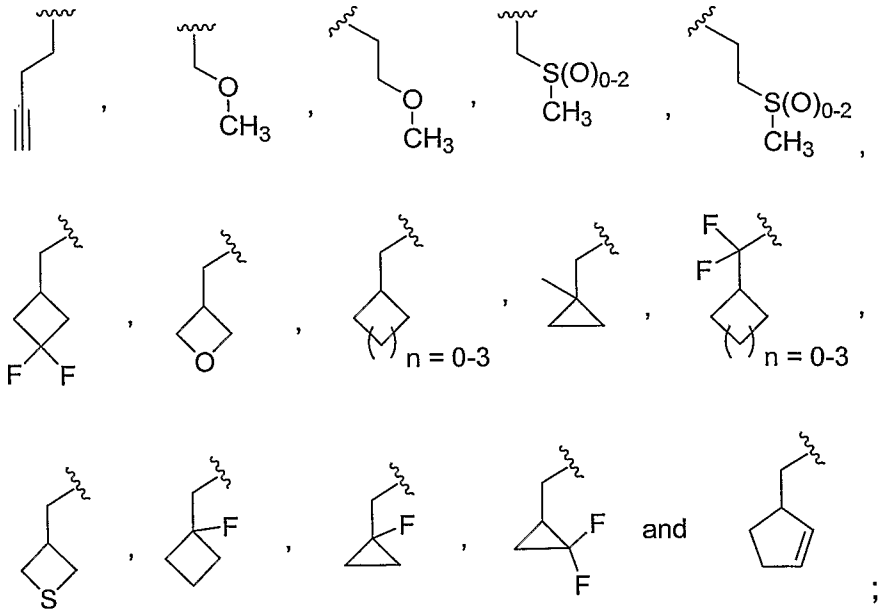
R^2 is selected from the group consisting of the following moieties:





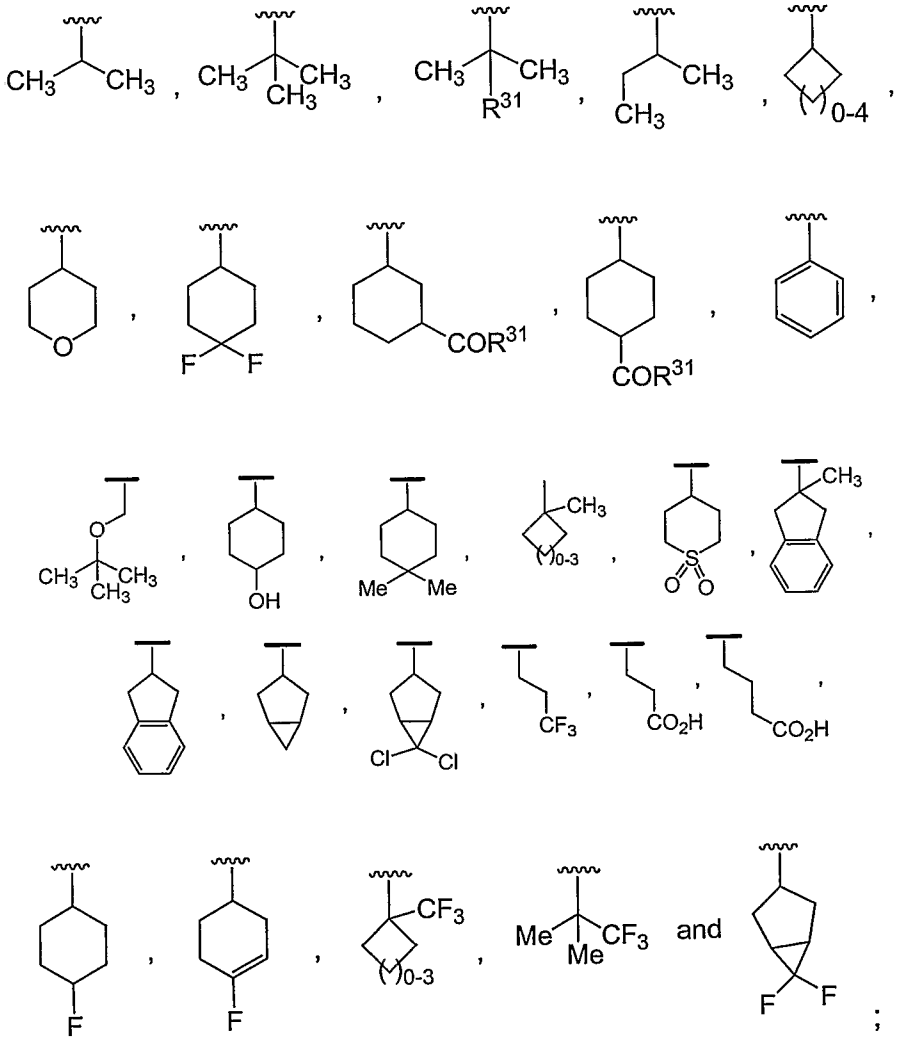






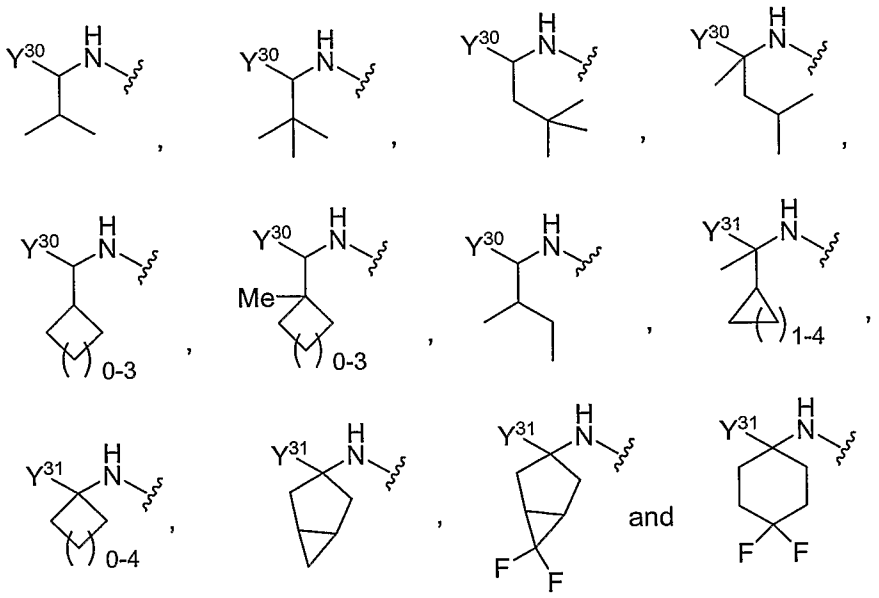
;

R^3 is selected from the group consisting of the following moieties:

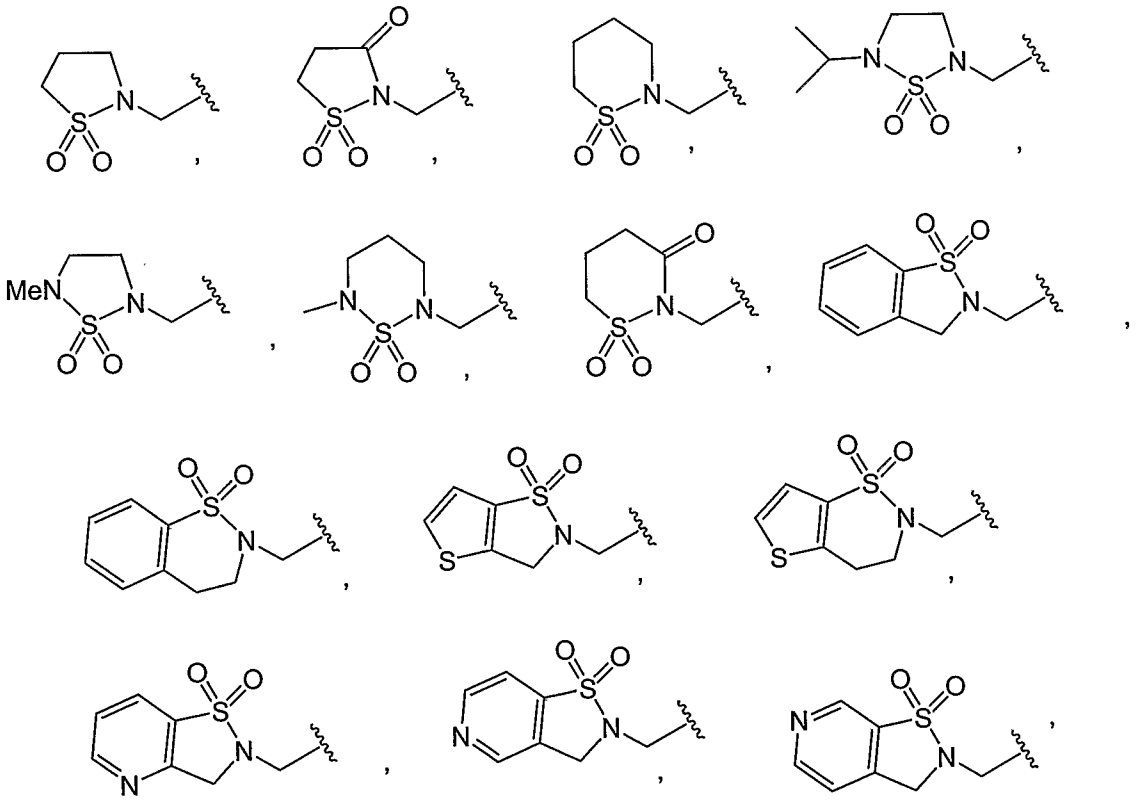


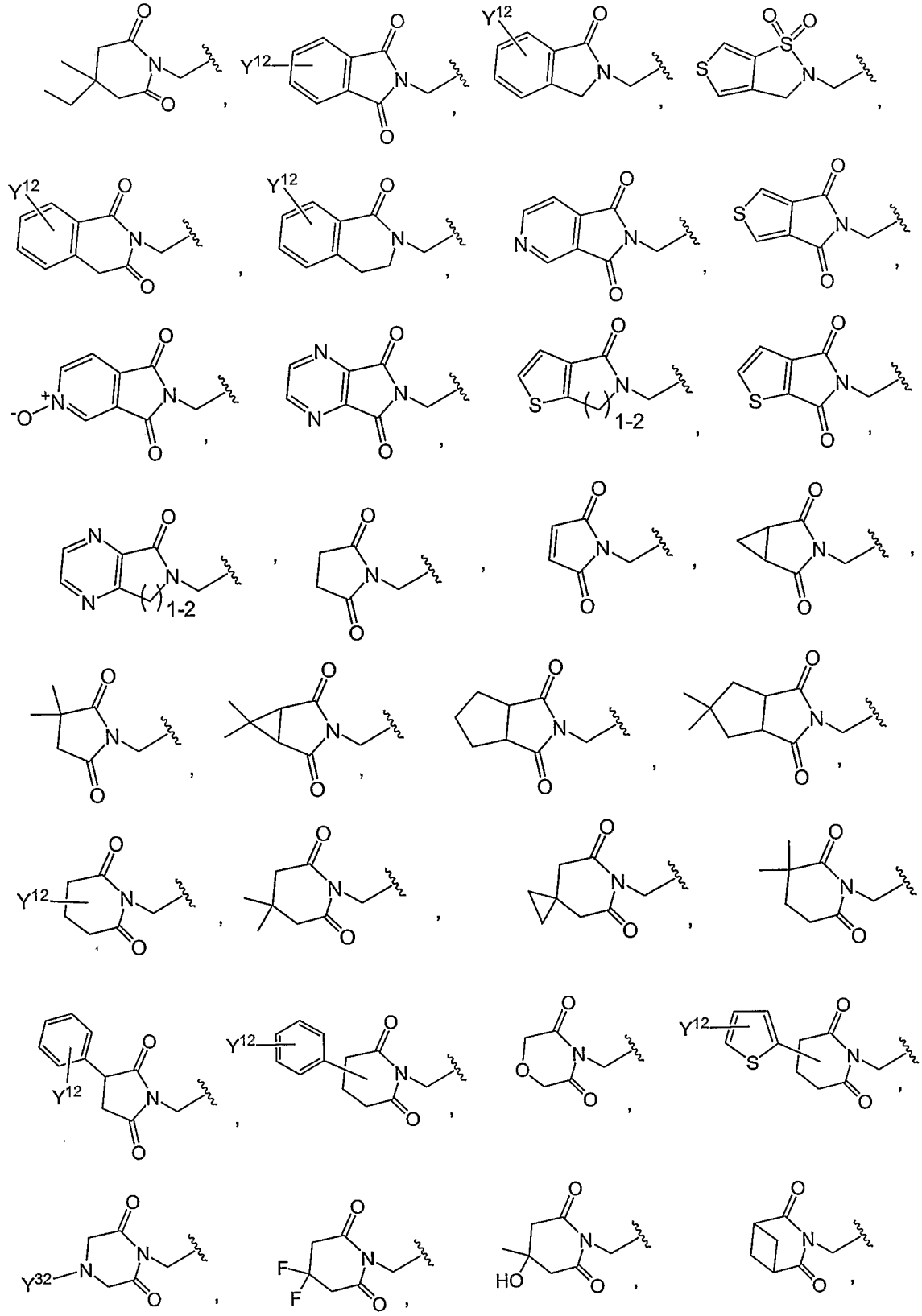
;

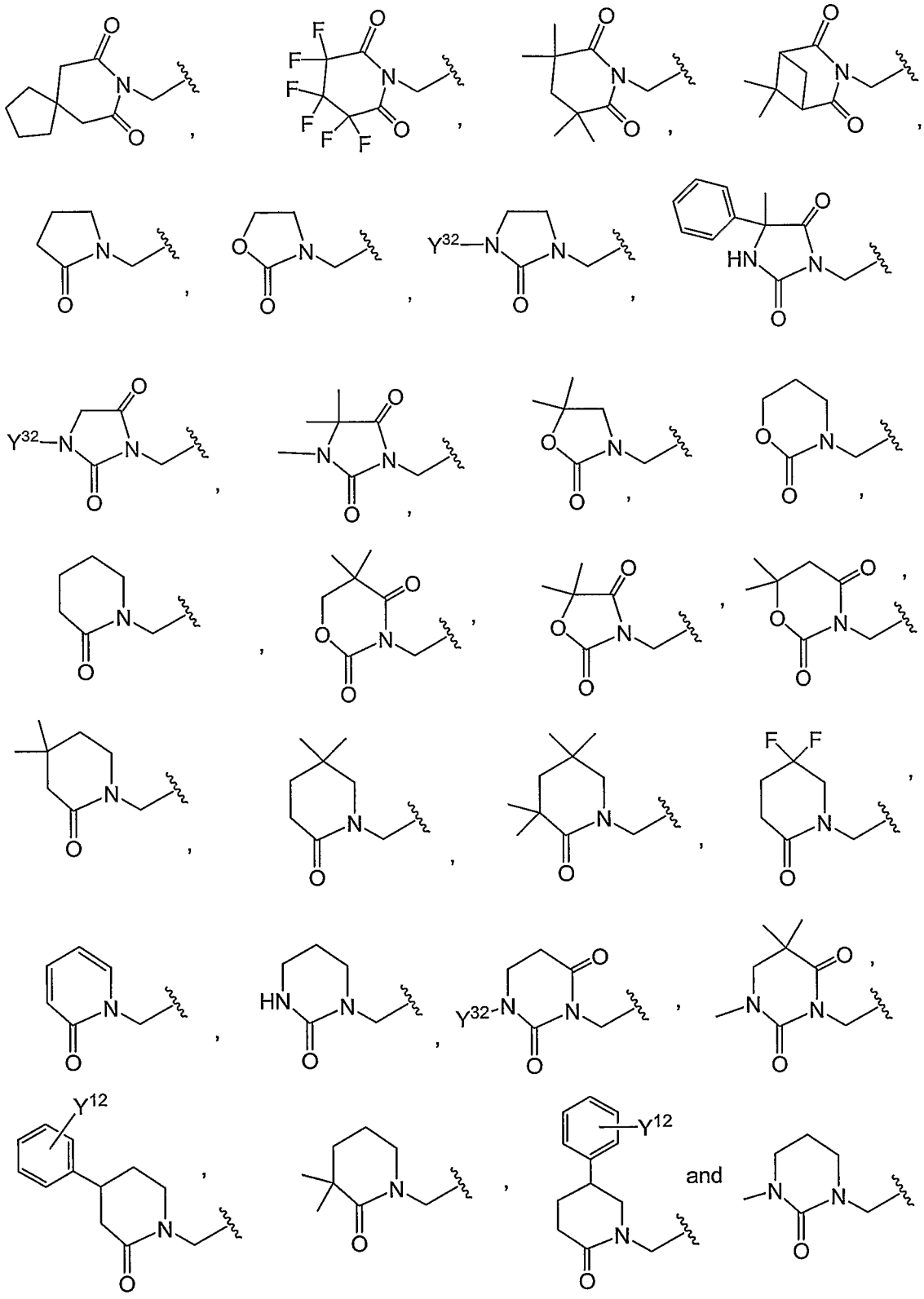
Y is selected from the group consisting of:



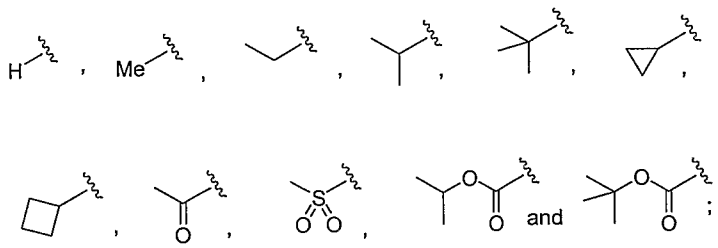
wherein Y^{30} and Y^{31} can be the same or different, each being independently selected from the group consisting of:





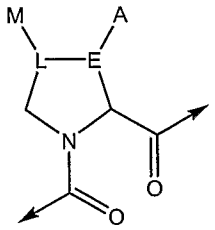


wherein Y^{32} is selected from the group consisting of:

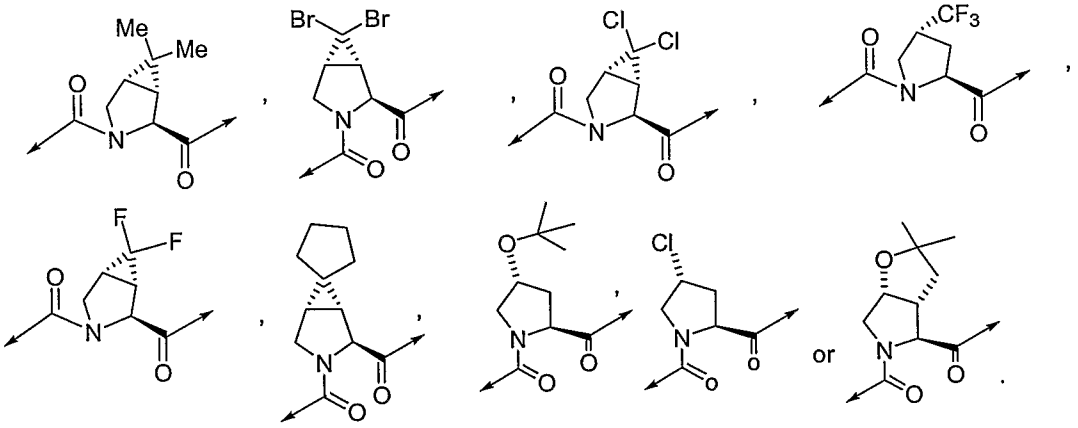


and Y^{12} is selected from H, COOH, COOMe, $CONH_2$, OMe, OH, OCF_3, $OCH(CH_3)_2$, $OC(CH_3)_3$, F, Cl, Br, NH_2, $NHSO_2CH_3$, $NHC(O)CH_3$, $NHCO_2CH_3$, NO_2, SO_2NH_2, CF_3, Me, Et, isopropyl, cyclopropyl, *t*-butyl, or phenyl;

and the moiety:



is:



14. A pharmaceutical composition comprising as an active ingredient at least one compound of claim 1.

15. The pharmaceutical composition of claim 14 for use in treating disorders associated with HCV.

16. The pharmaceutical composition of claim 15 additionally comprising at least one pharmaceutically acceptable carrier.

17. The pharmaceutical composition of claim 16, additionally containing at least one antiviral agent.

18. The pharmaceutical composition of claim 17, still additionally containing at least one interferon.

19. The pharmaceutical composition of claim 18, wherein said at least one antiviral agent is ribavirin and said at least one interferon is a-interferon or pegylated interferon.

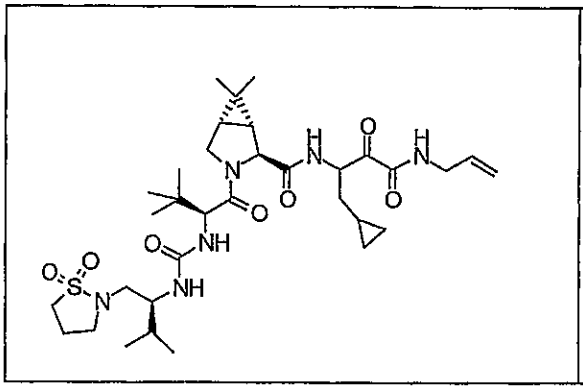
20. The use of a pharmaceutical composition comprising a therapeutically effective amount of at least one compound of claim 1 for the manufacture of a medicament to treat disorders associated with the HCV.

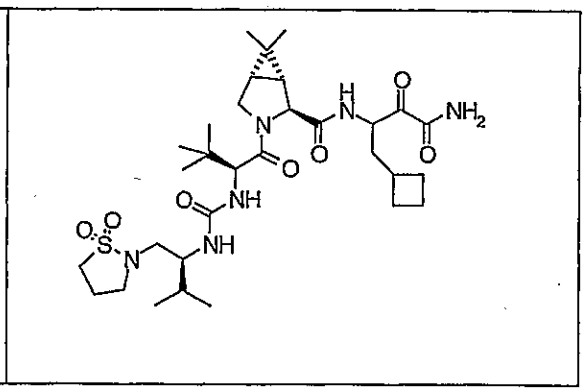
21. The use of claim 20, wherein said medicament is formulated for oral or subcutaneous administration.

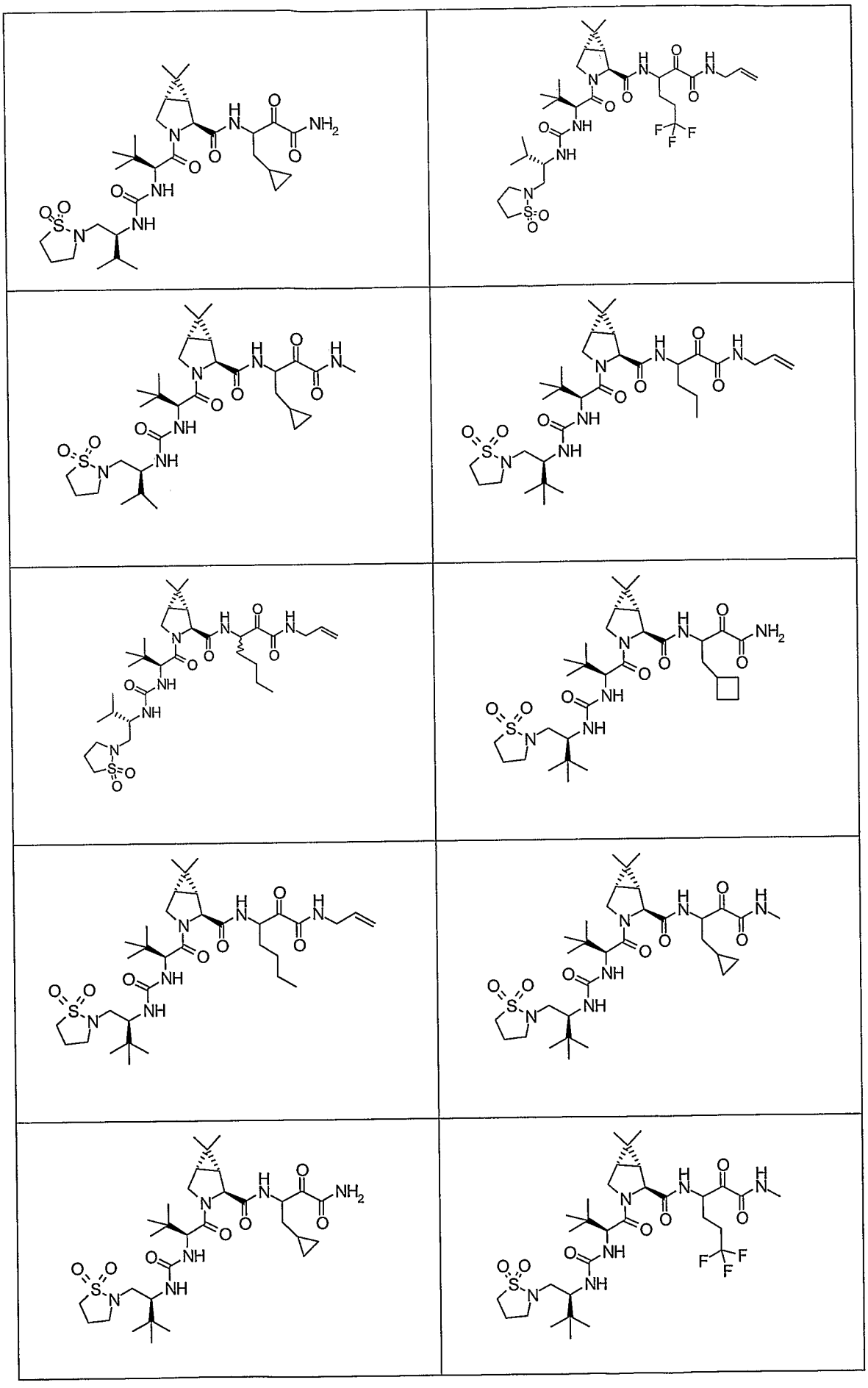
22. The use of a compound of claim 1 for the manufacture of a medicament to treat disorders associated with the HCV.

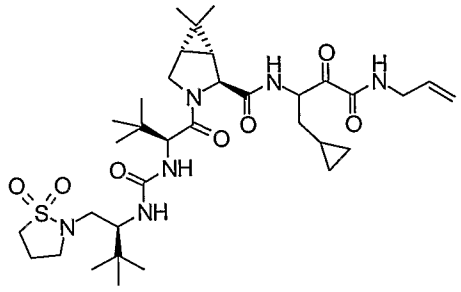
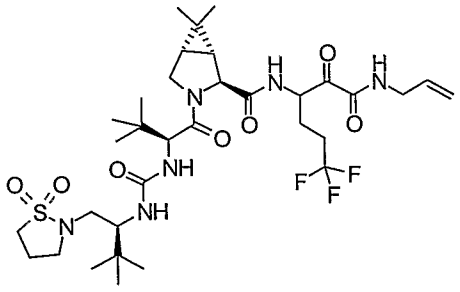
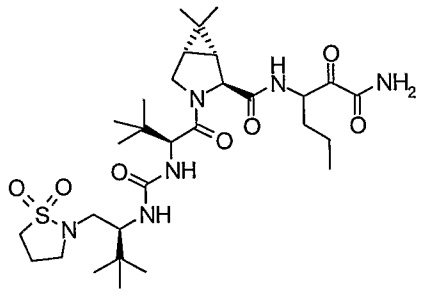
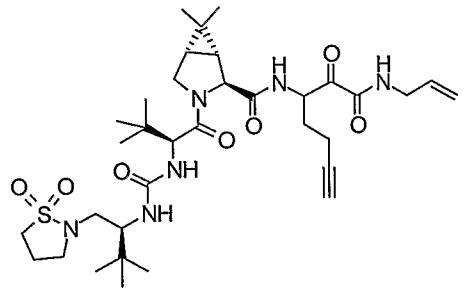
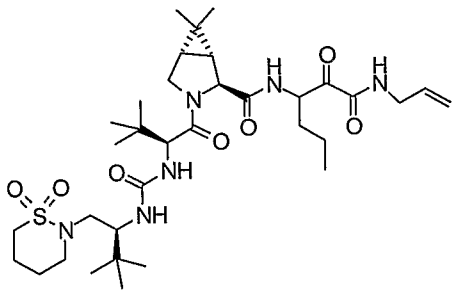
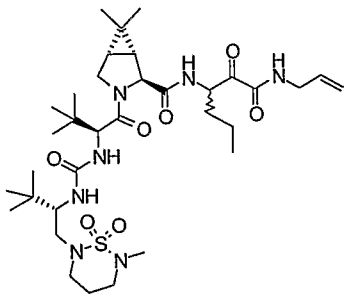
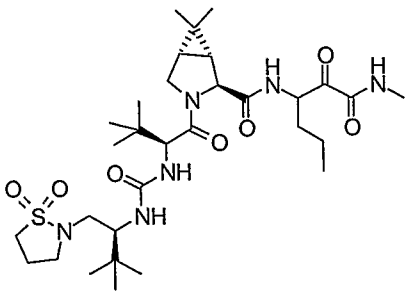
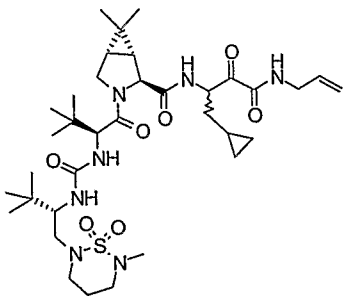
23. A method of preparing a pharmaceutical composition for treating the disorders associated with the HCV, said method comprising bringing into intimate physical contact at least one compound of claim 1 and at least one pharmaceutically acceptable carrier.

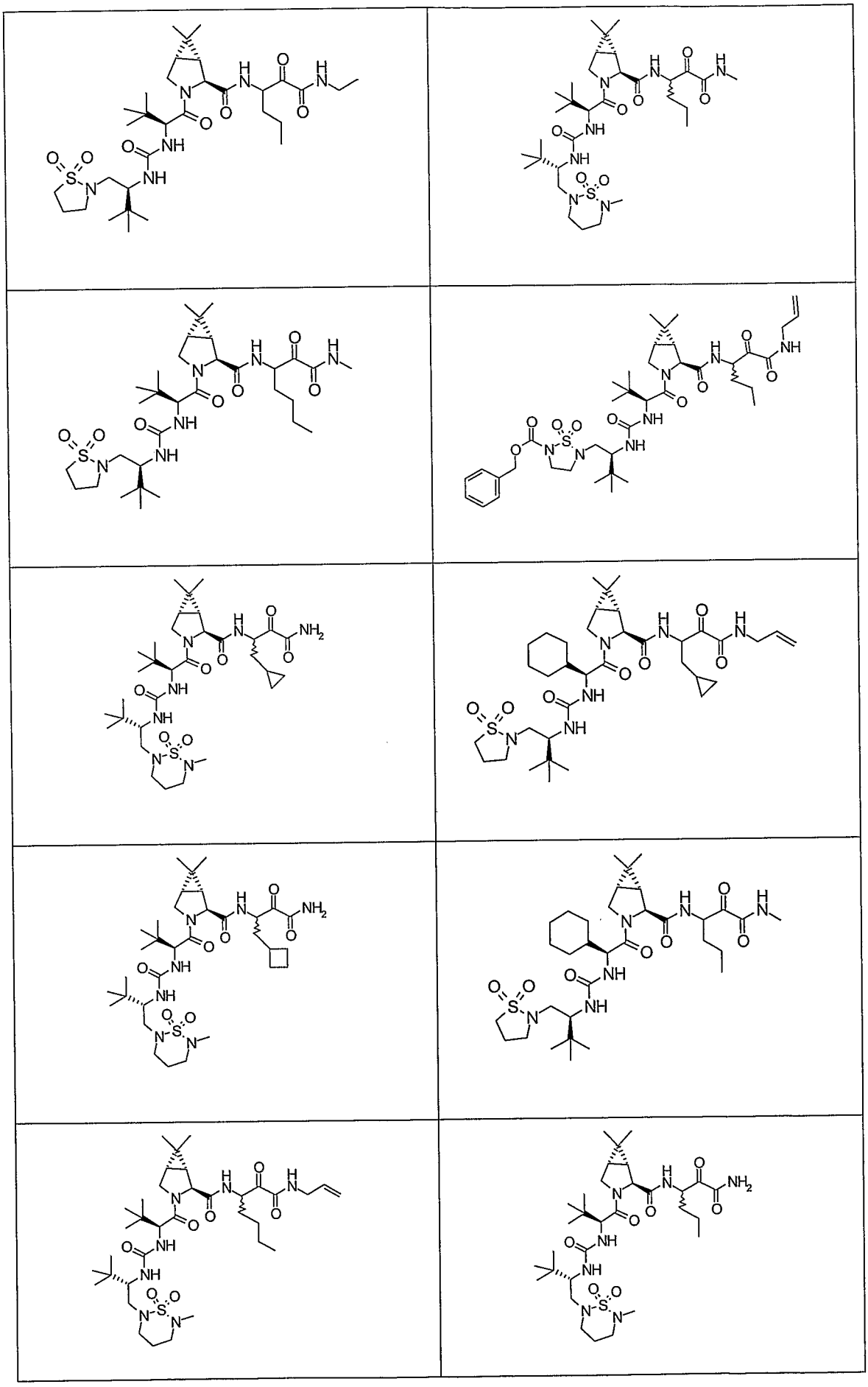
24. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, and racemates of said compound, or a pharmaceutical acceptable salt, solvate or ester of said compound, said compound being selected from the compounds of structures listed below :

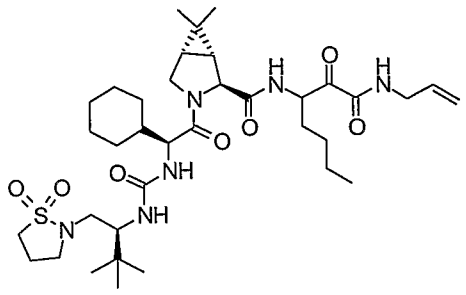
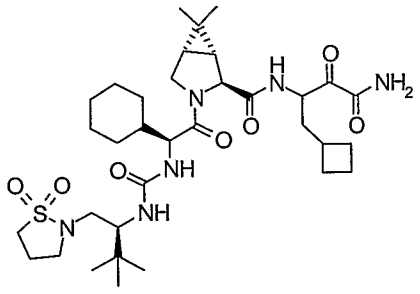
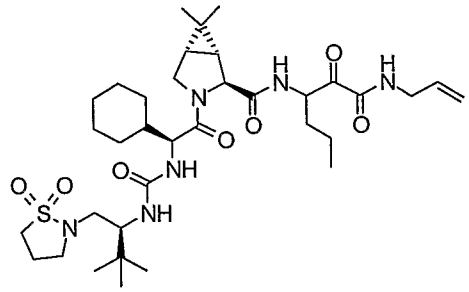
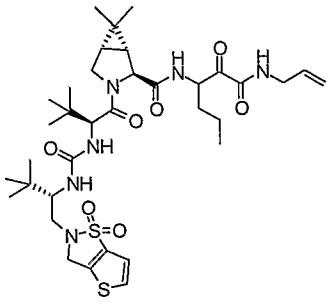
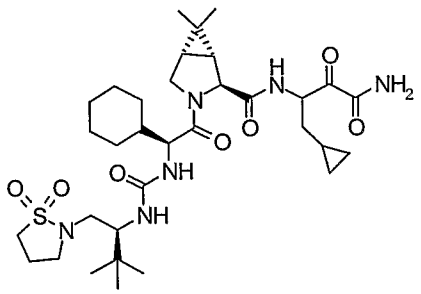
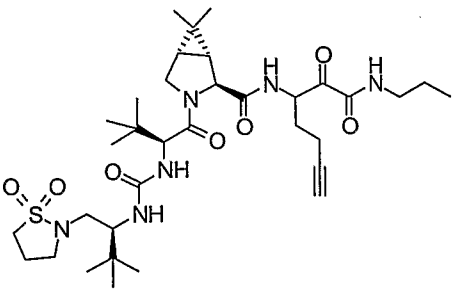
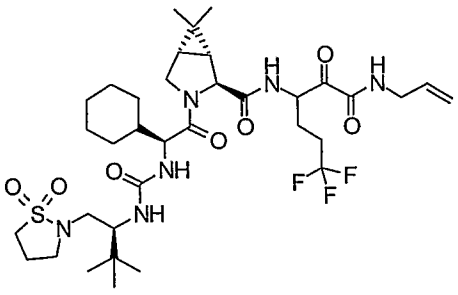
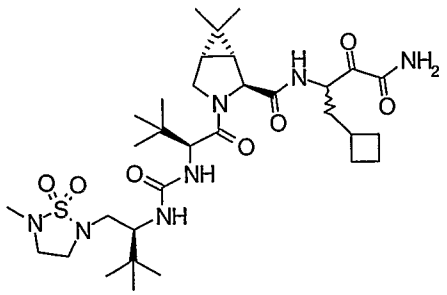


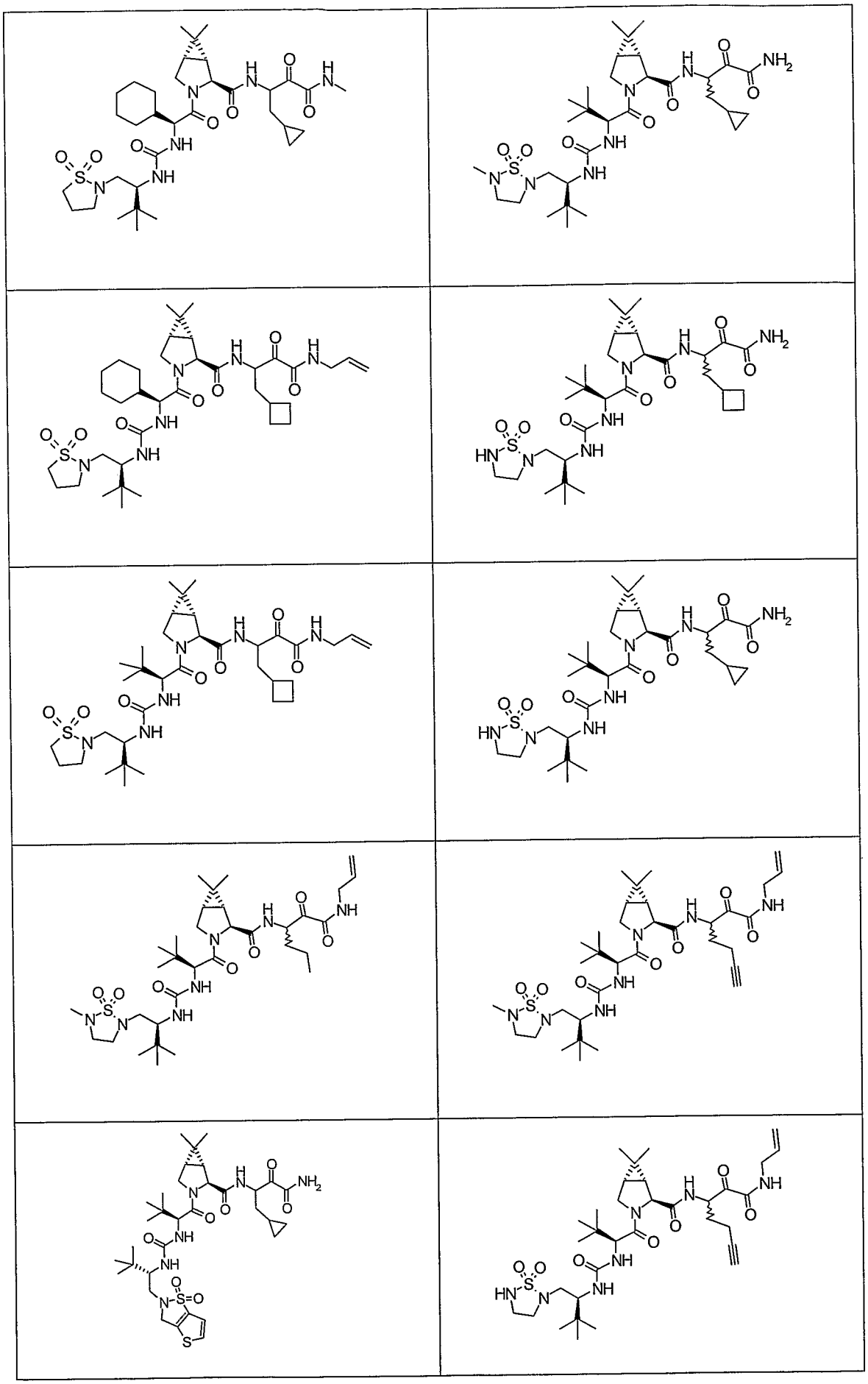


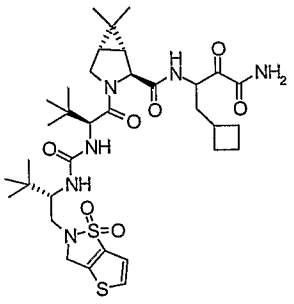
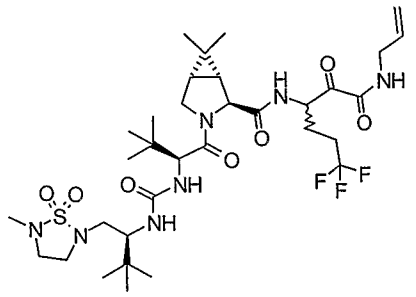
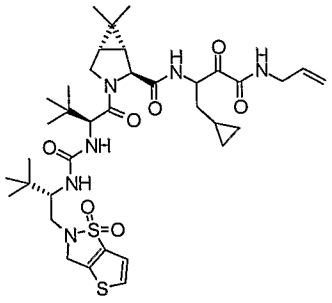
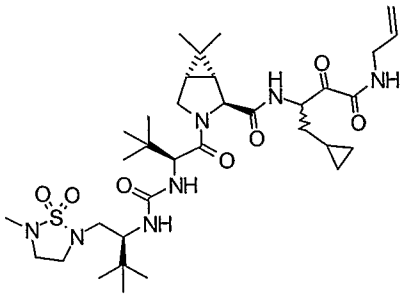
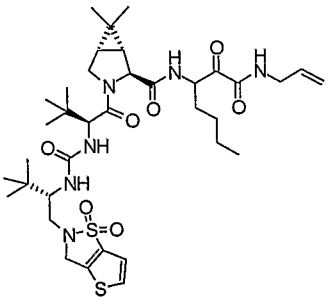
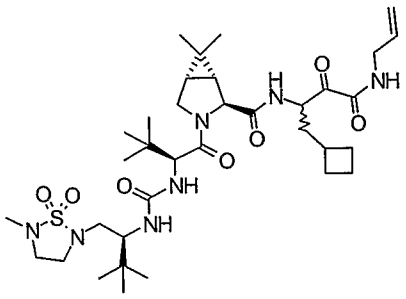
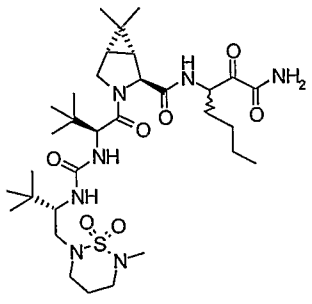
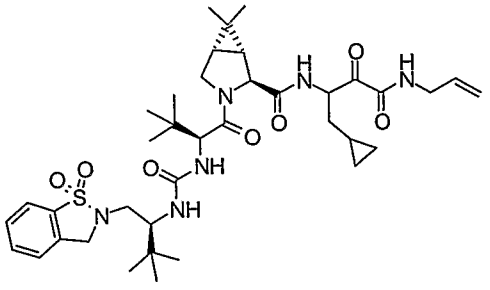


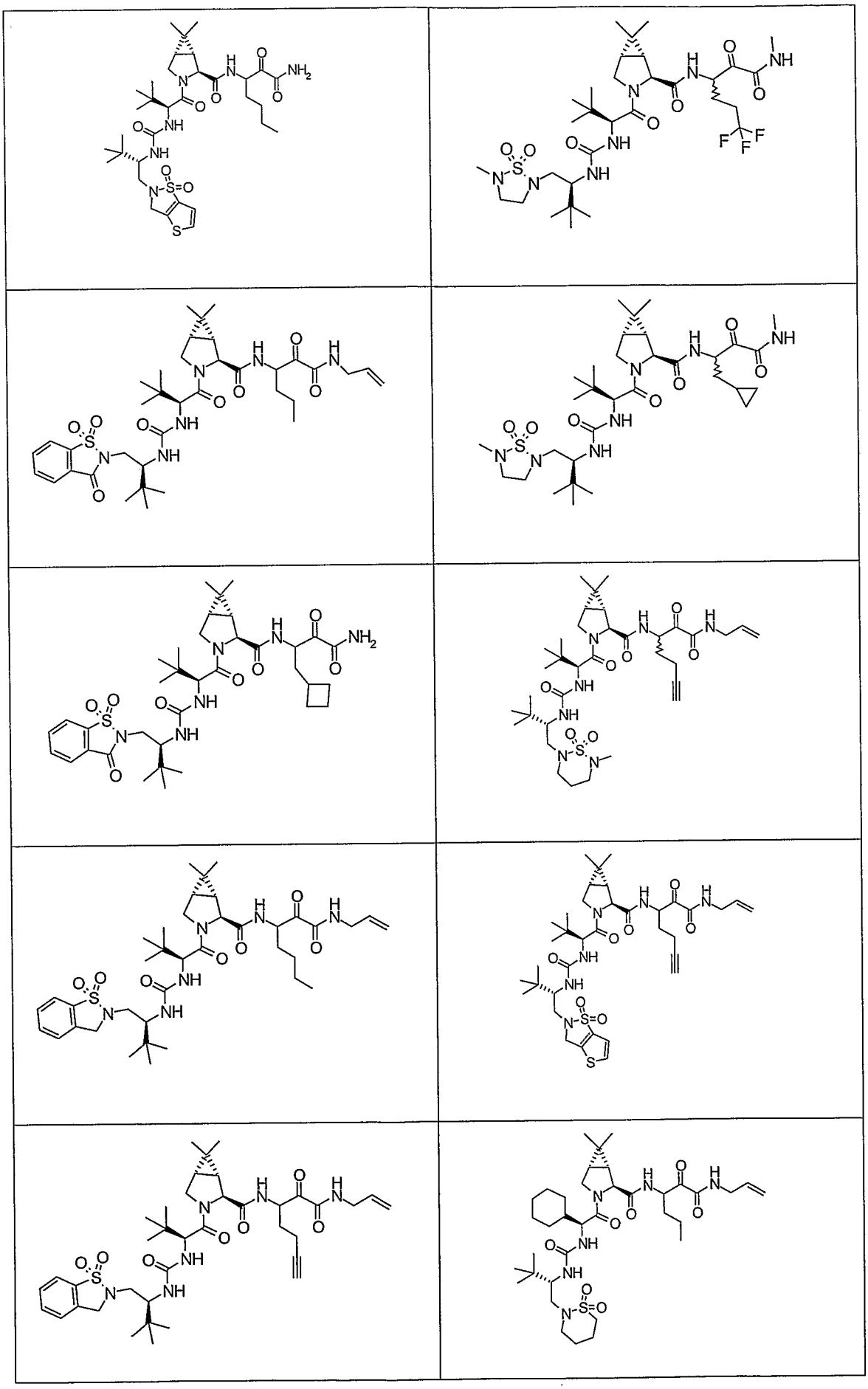
	
	
	
	

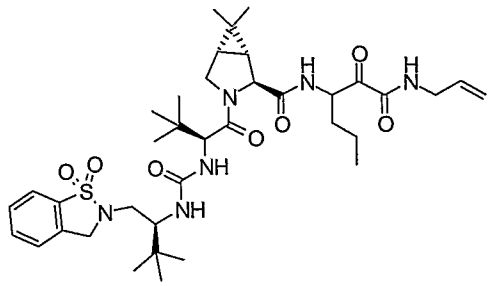
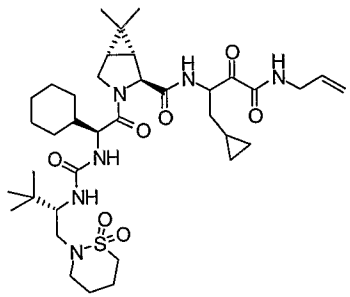
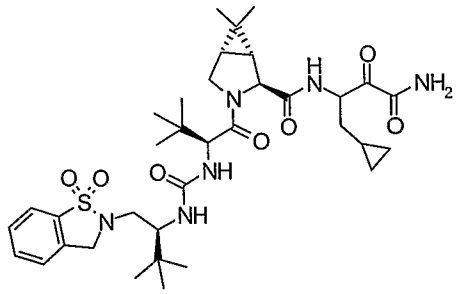
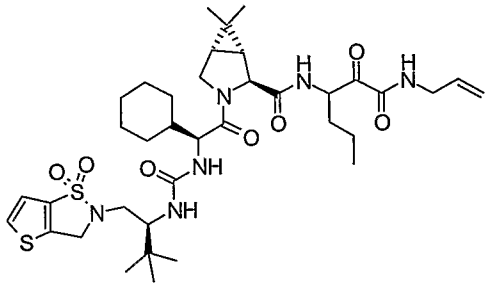
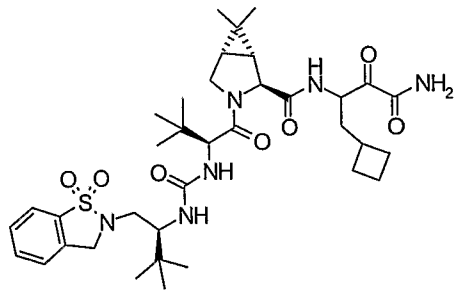
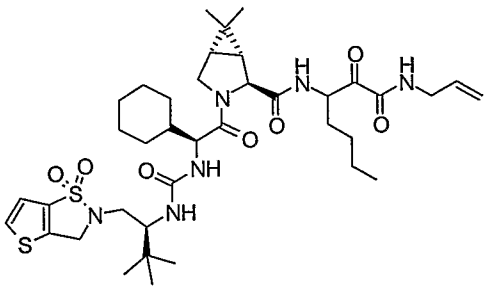
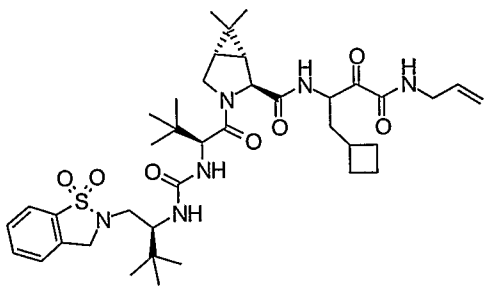
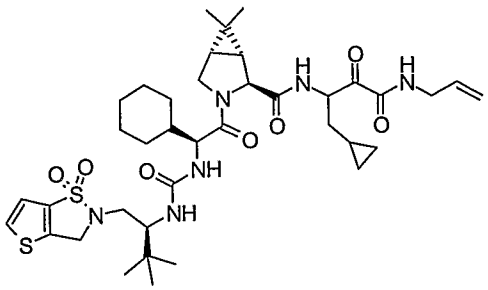


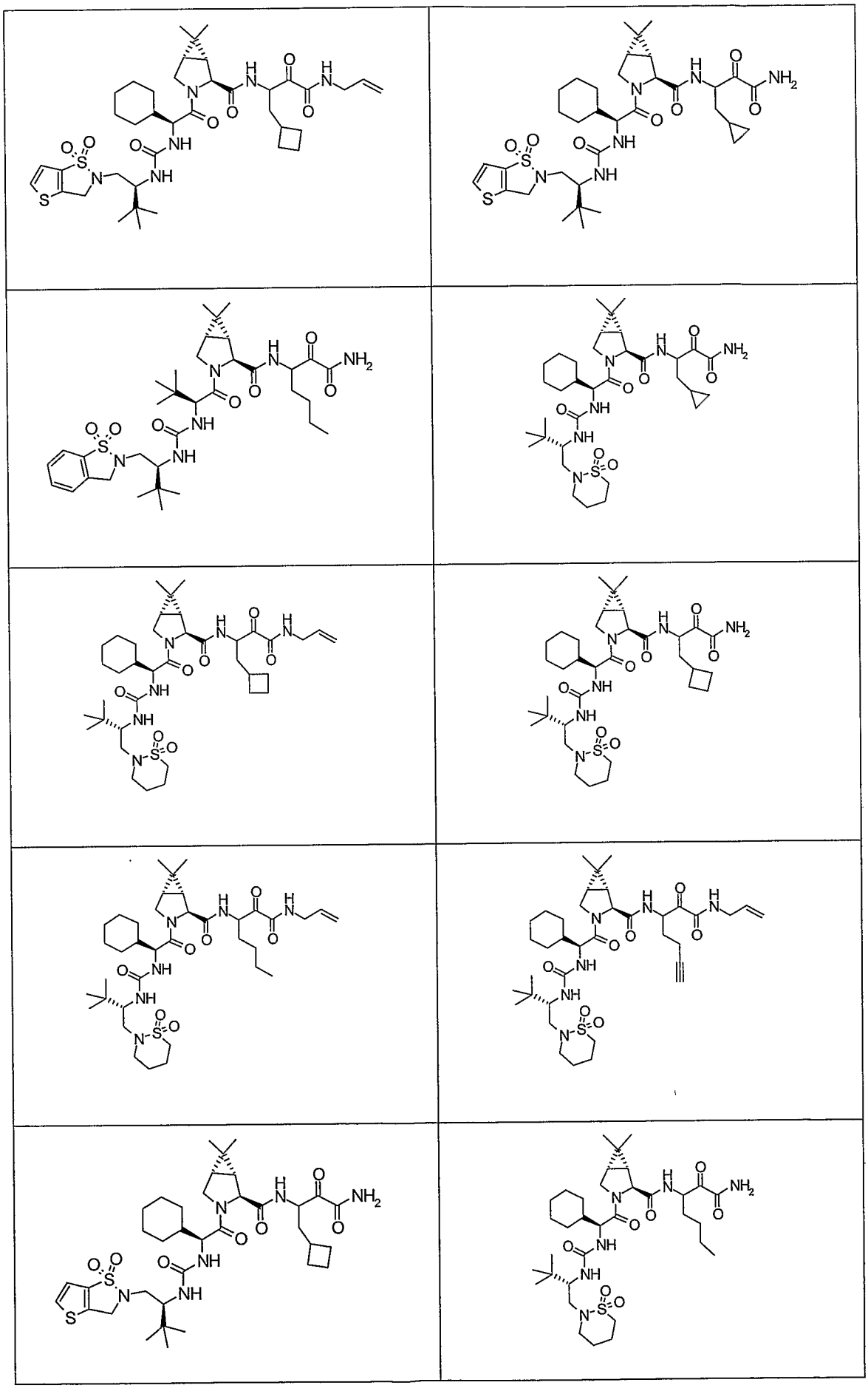
	
	
	
	

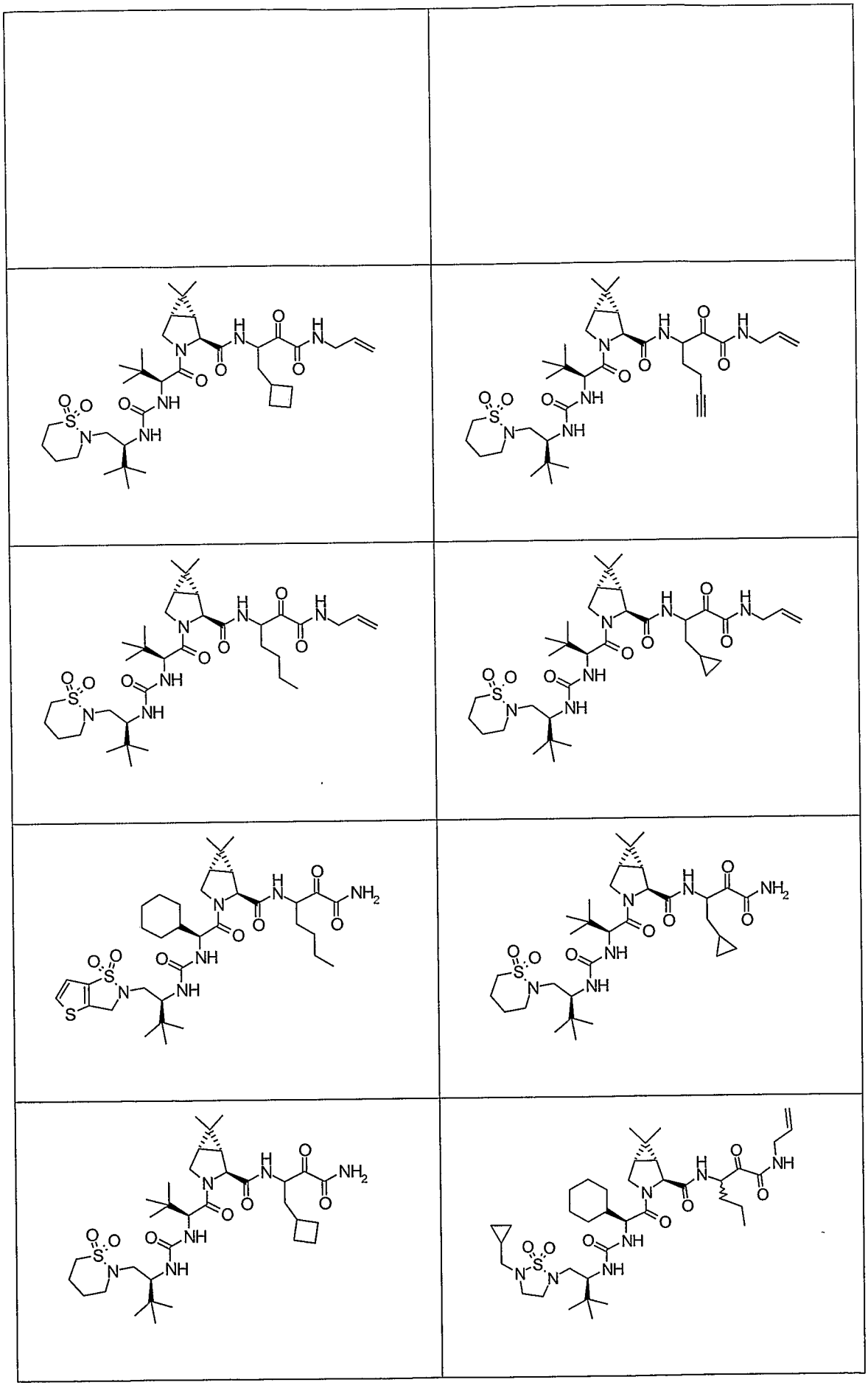


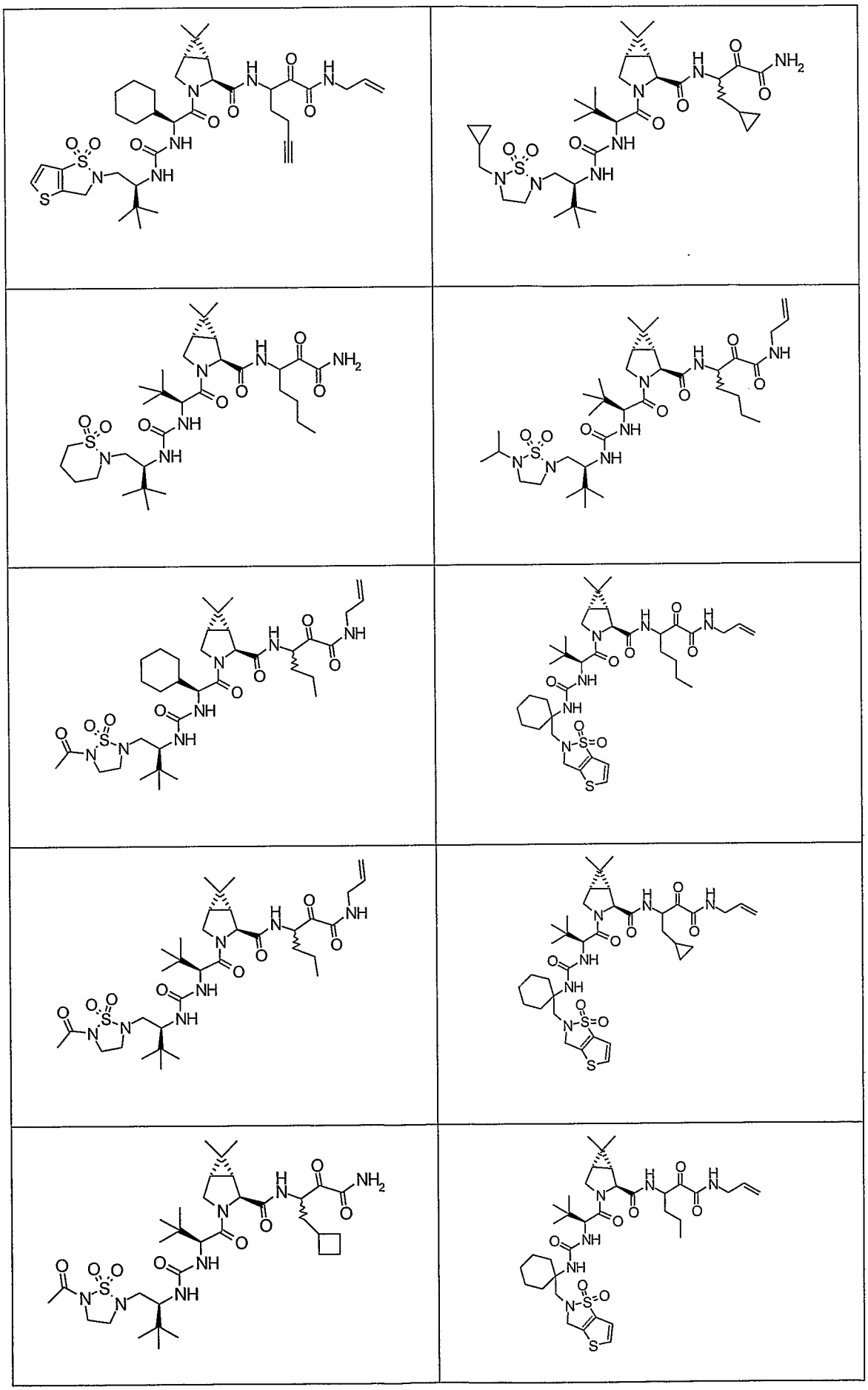
	
	
	
	

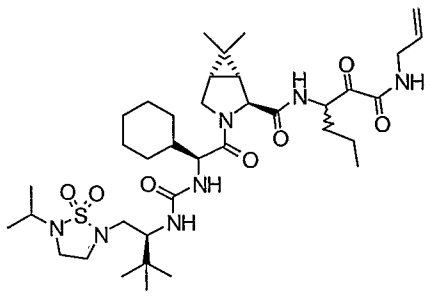
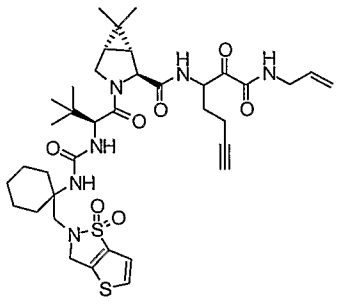
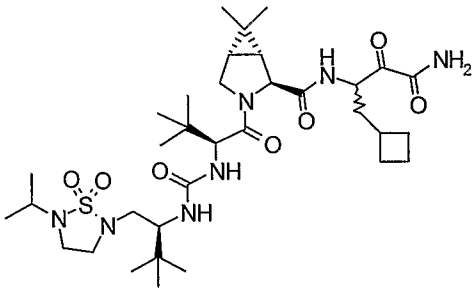
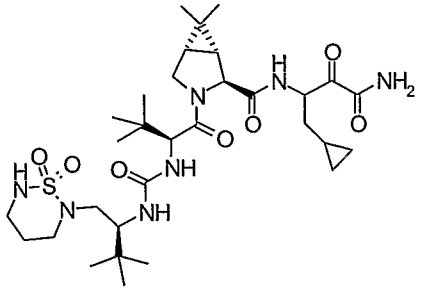
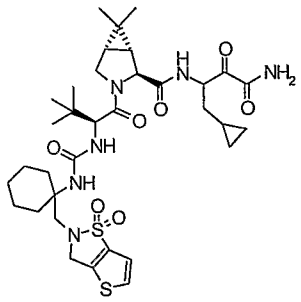
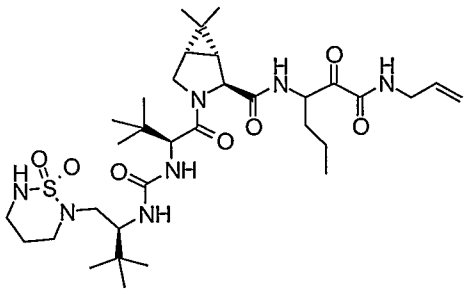
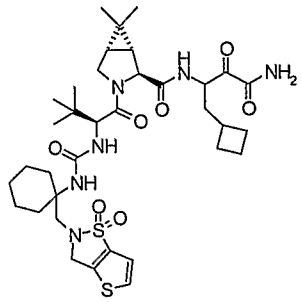
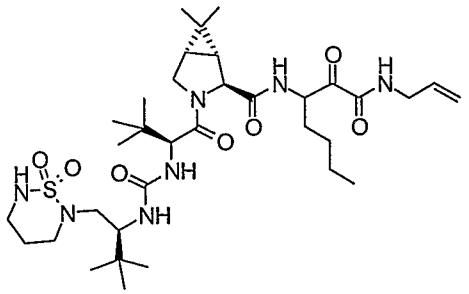


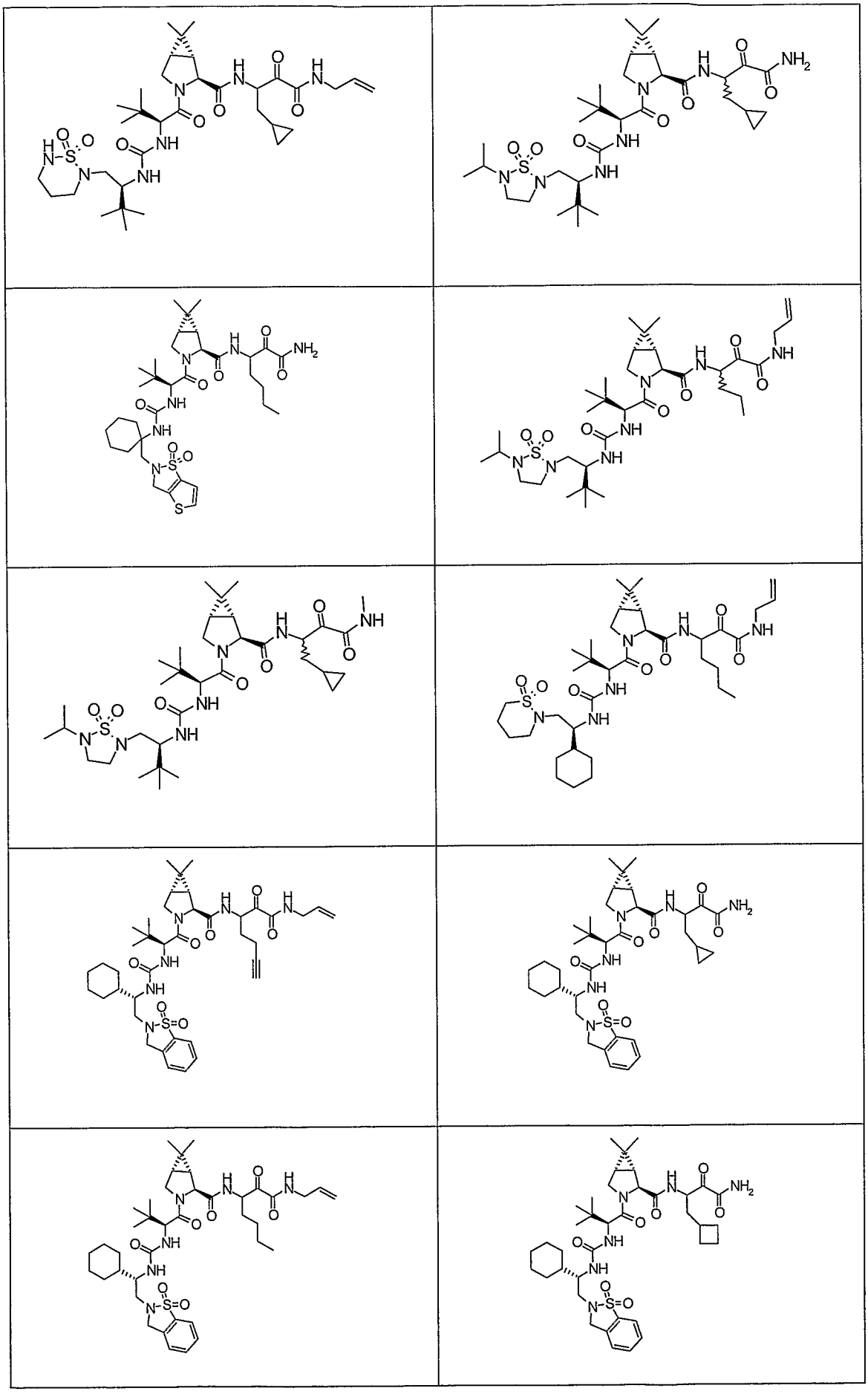
	
	
	
	

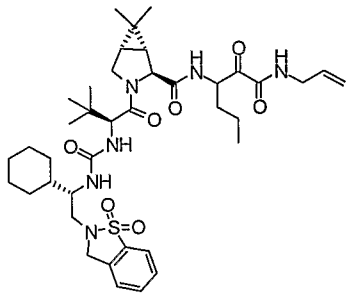
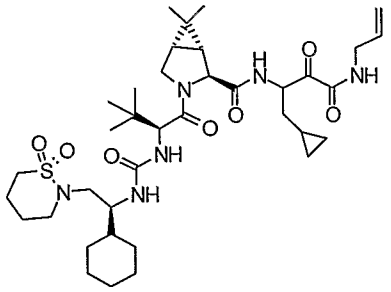
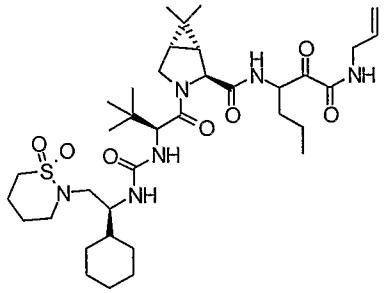
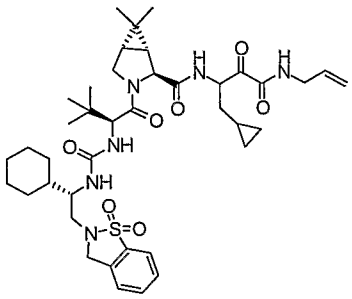
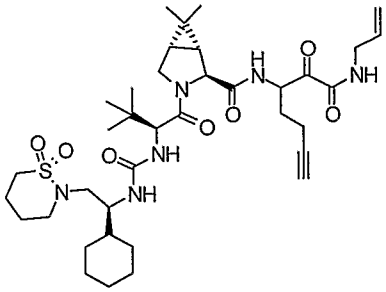
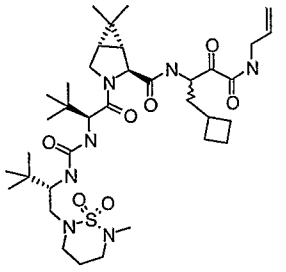
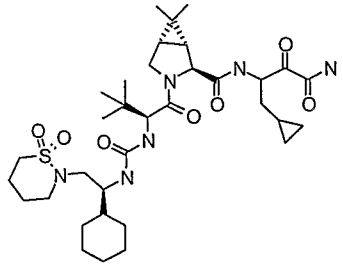
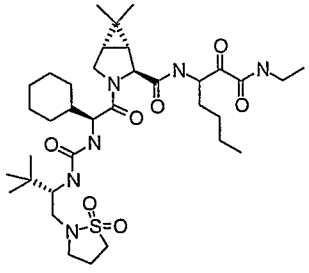


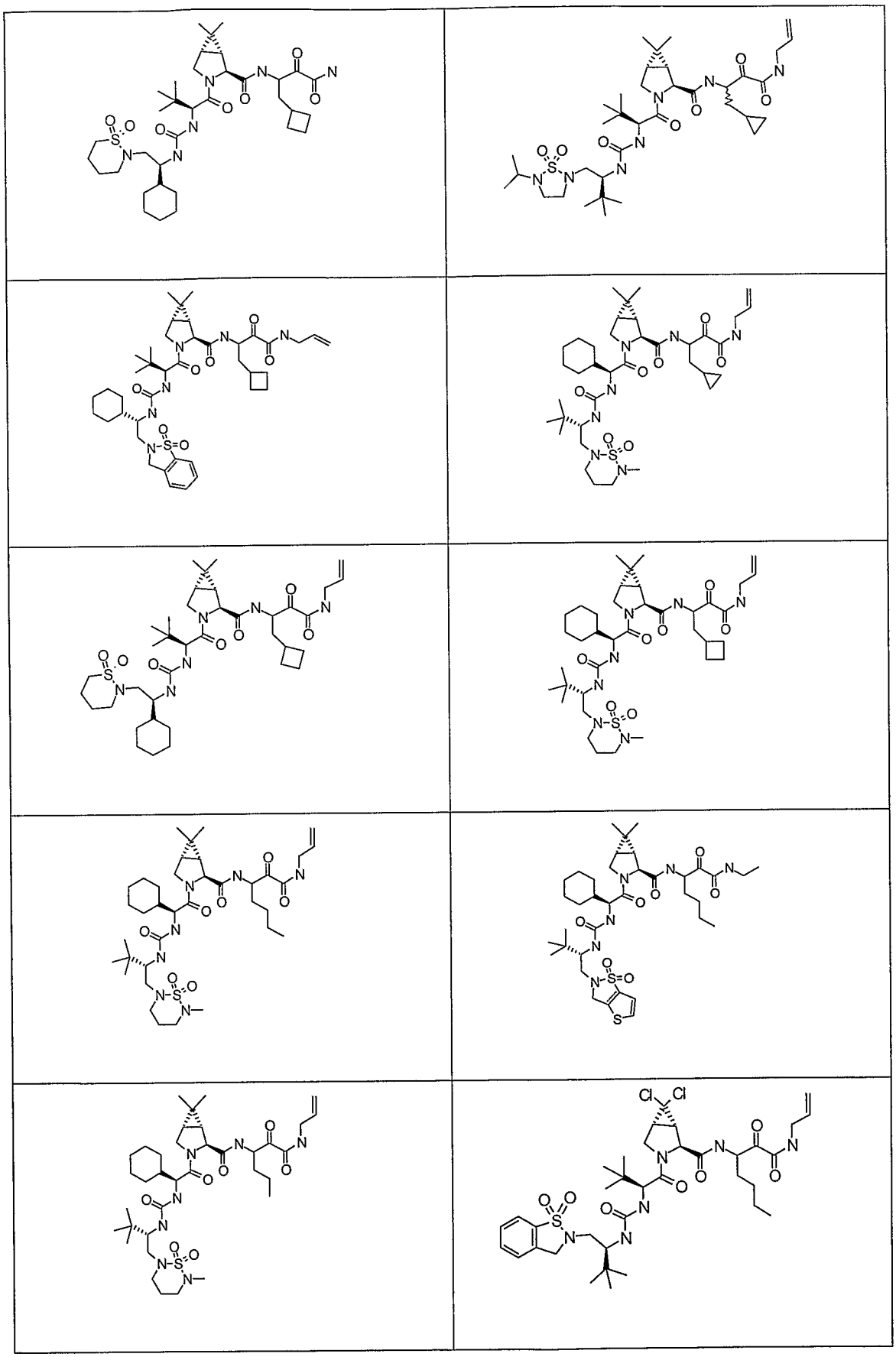


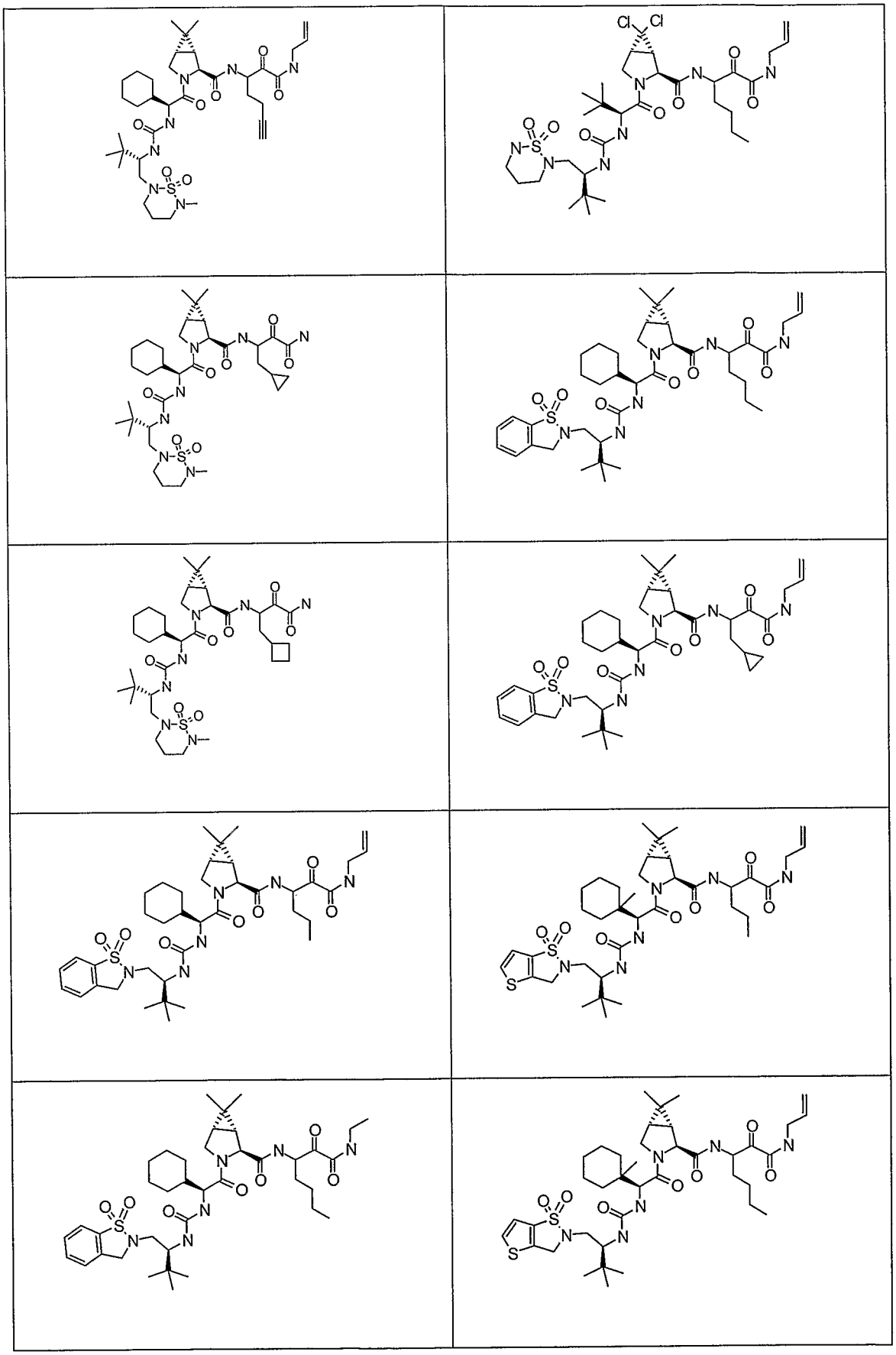


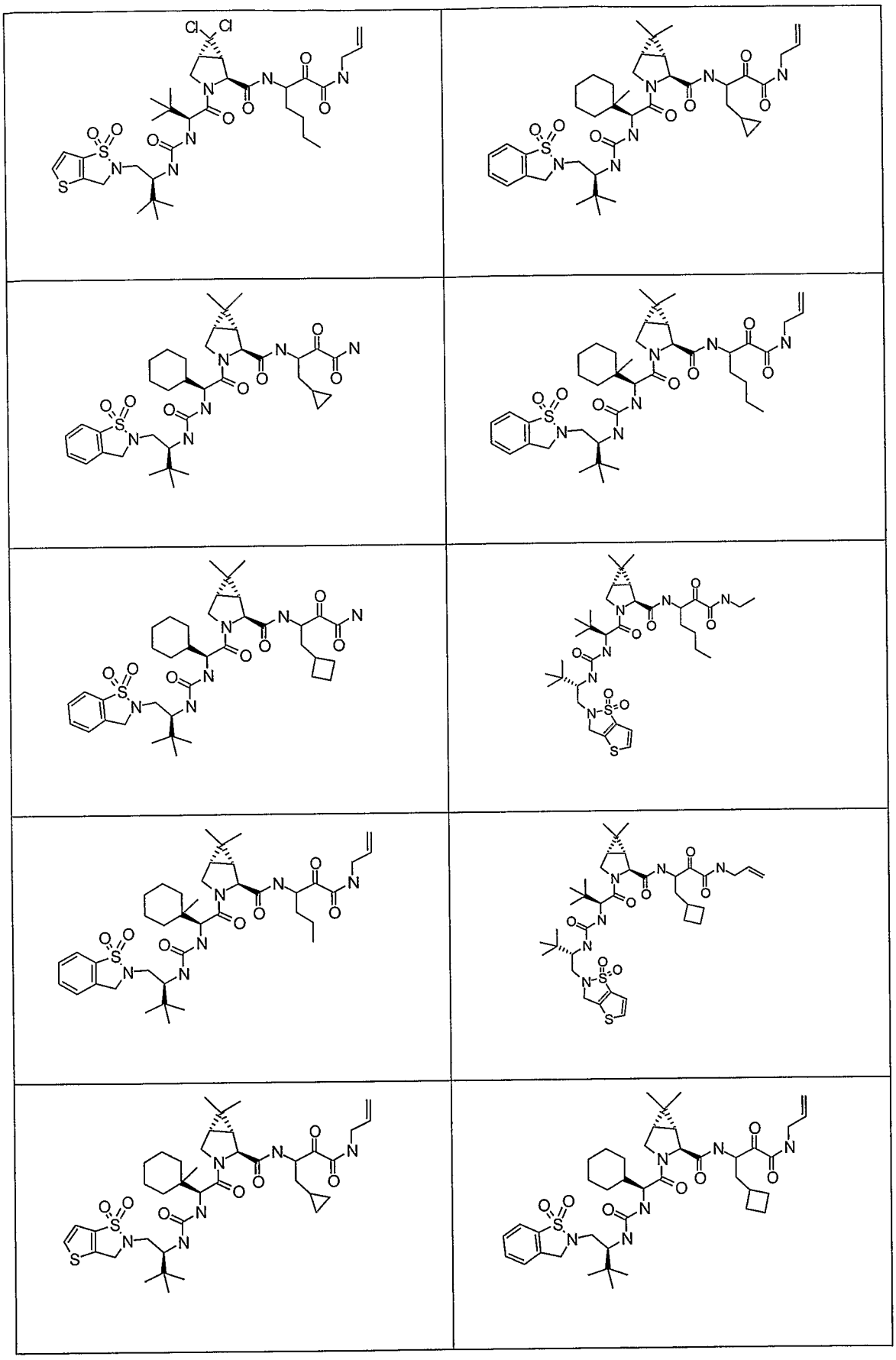
	
	
	
	

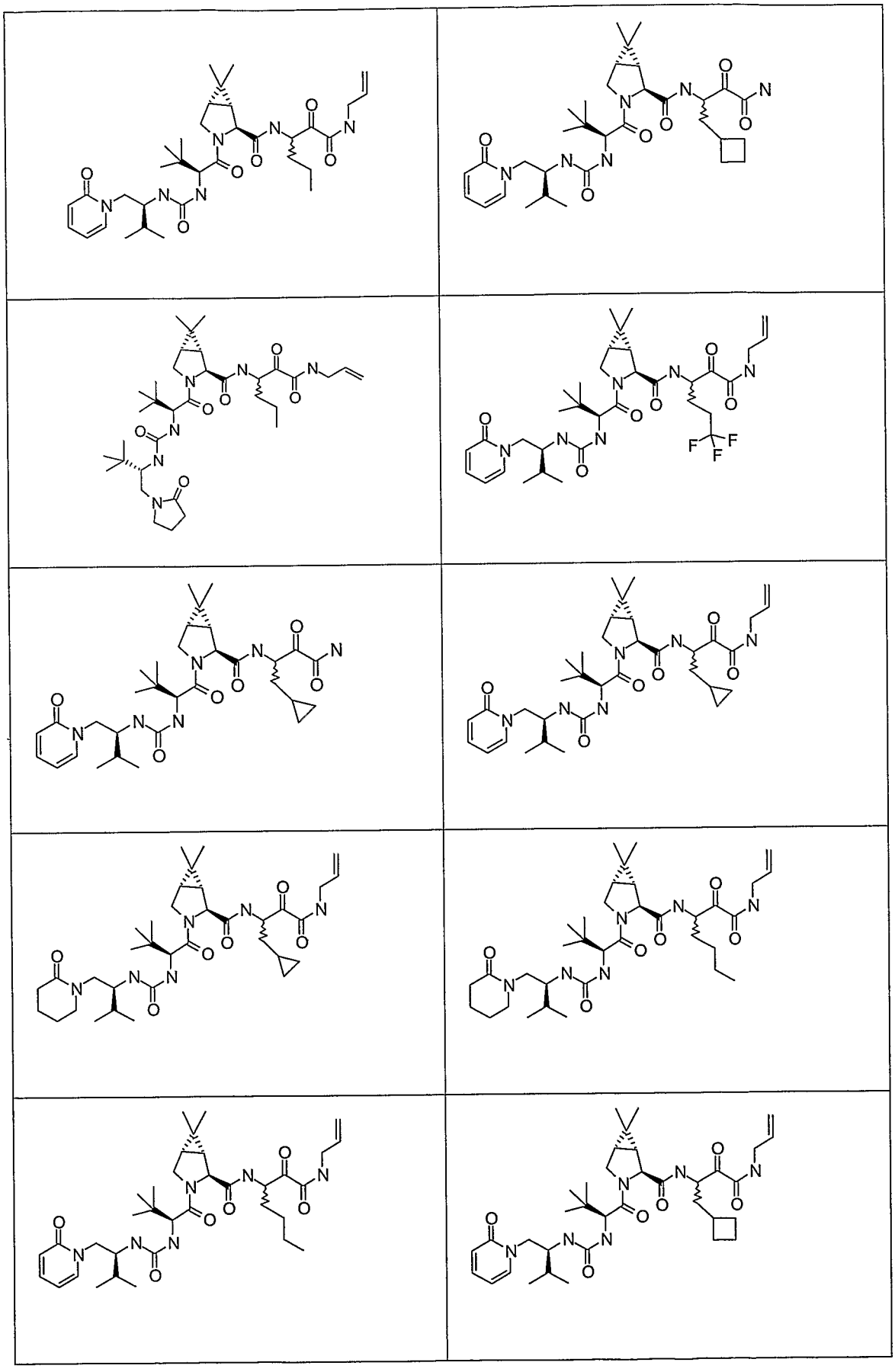


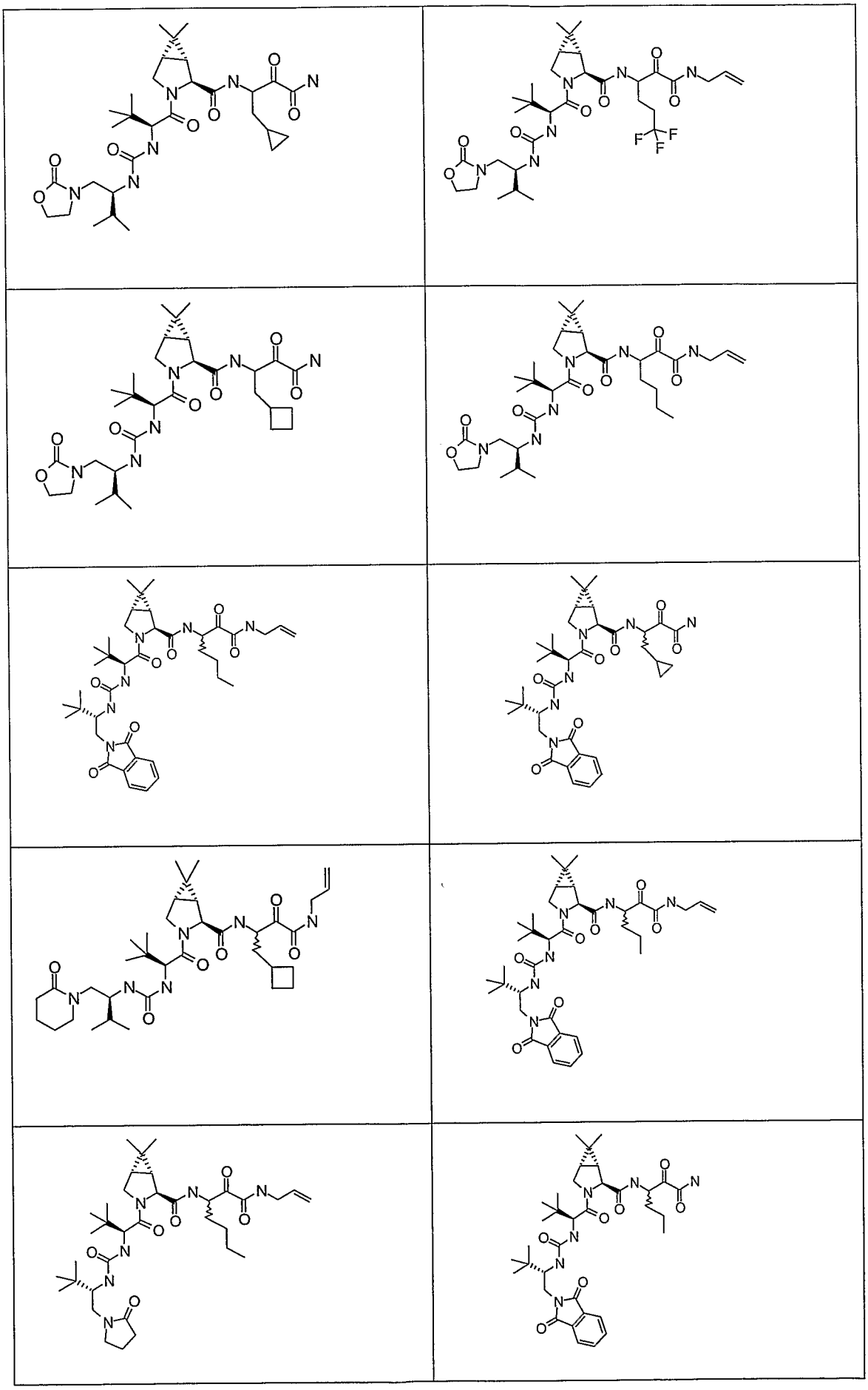
	
	
	
	

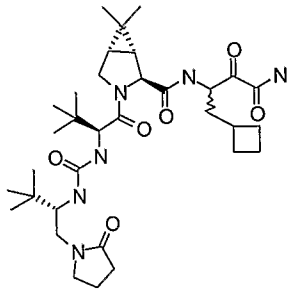
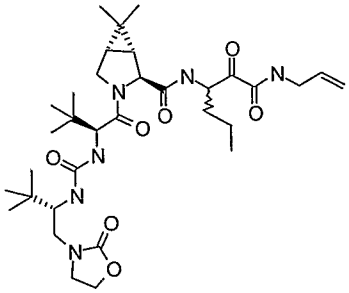
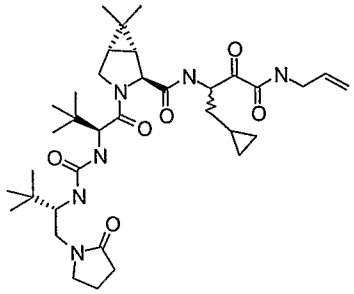
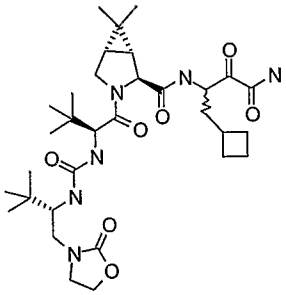
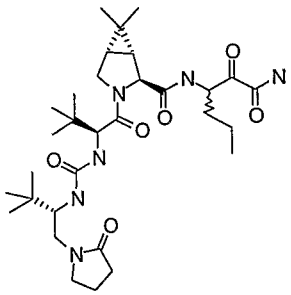
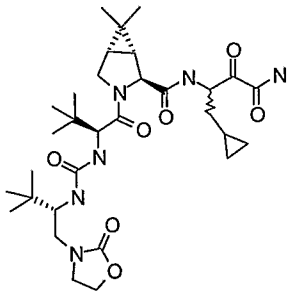
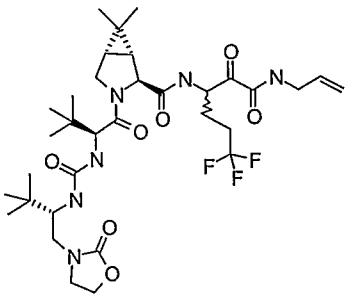
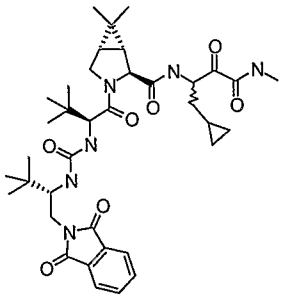


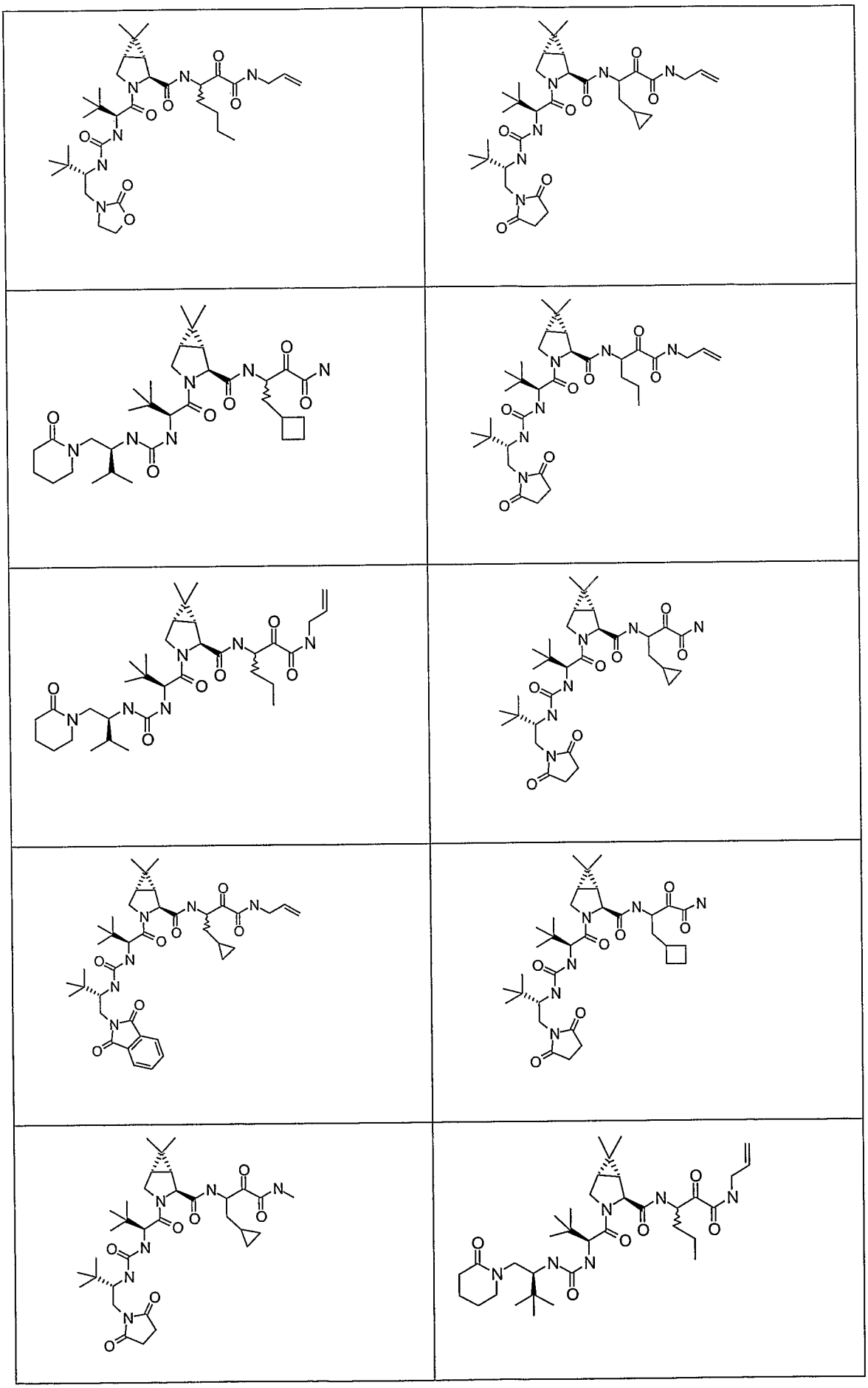


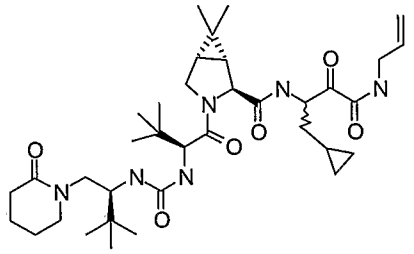
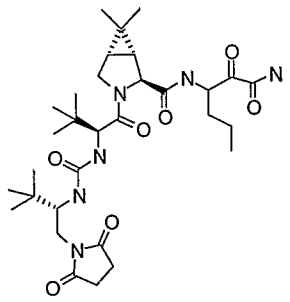
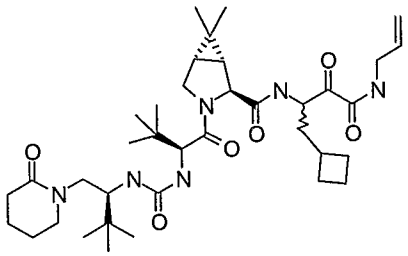
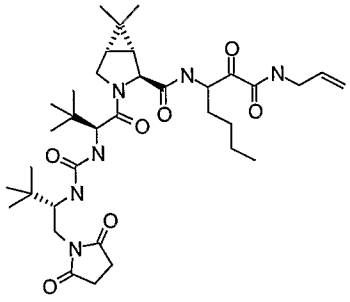
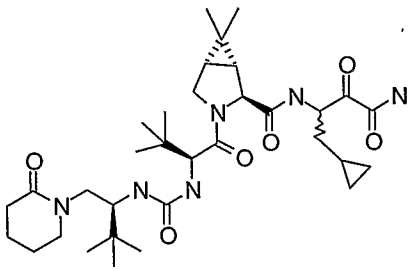
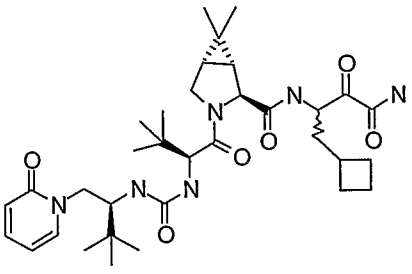
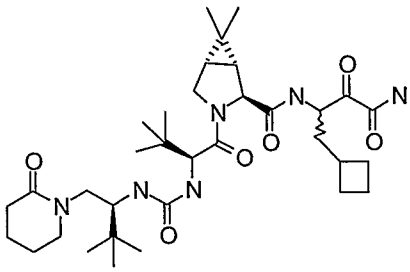
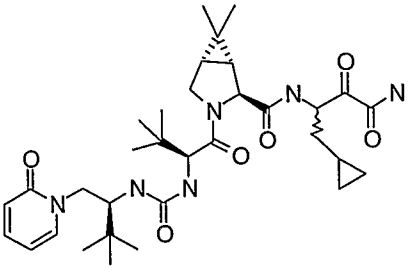


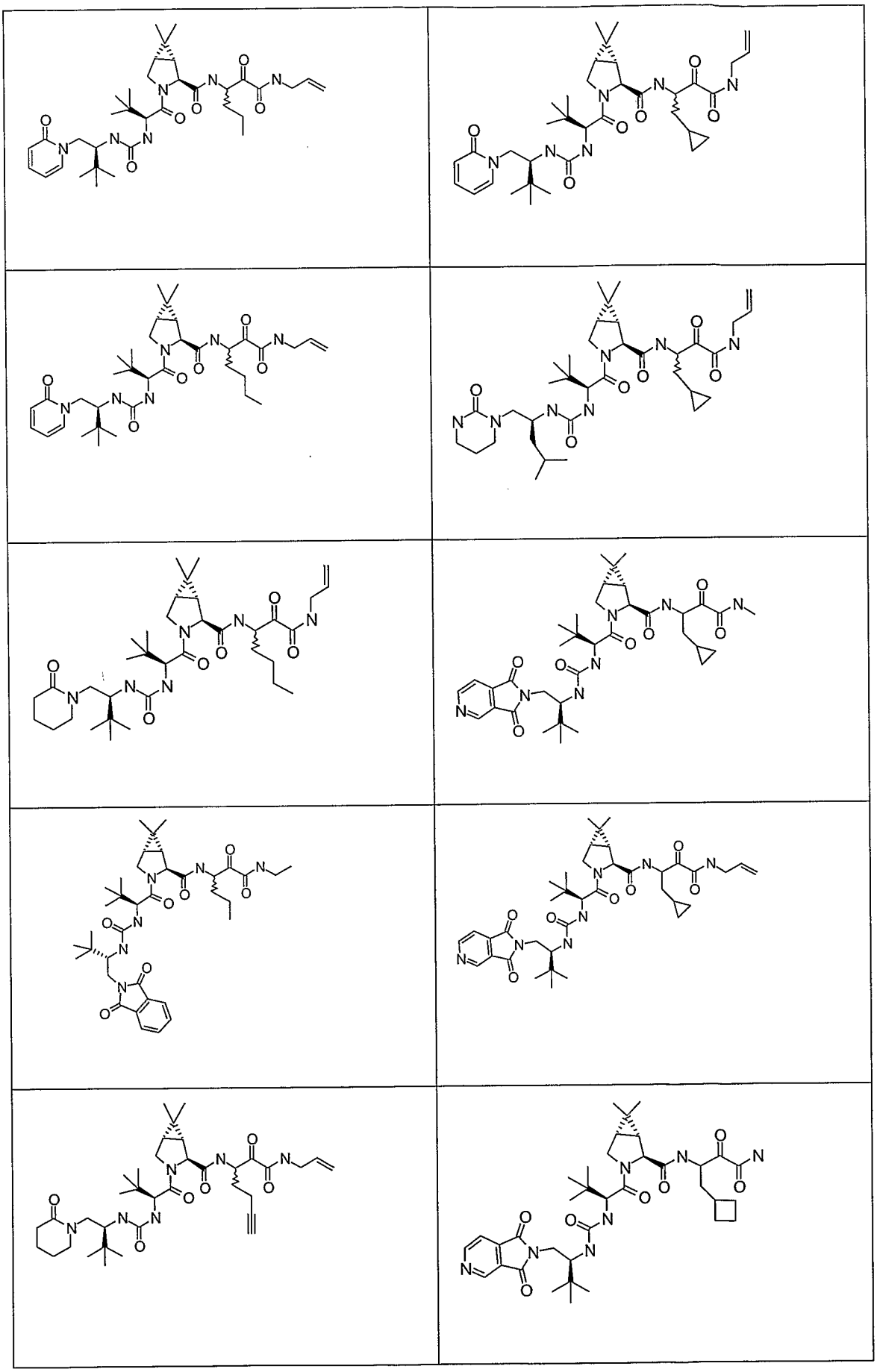


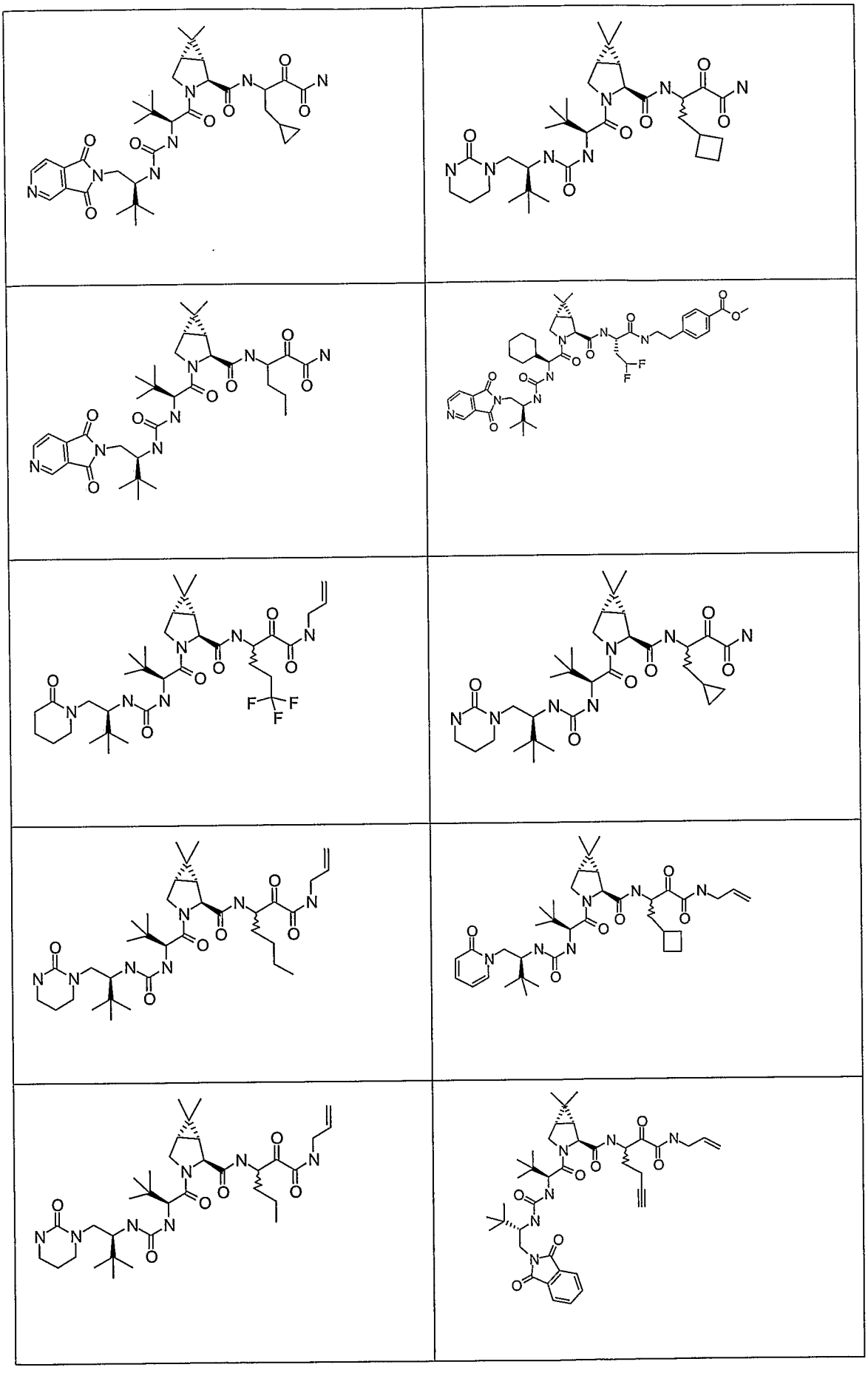


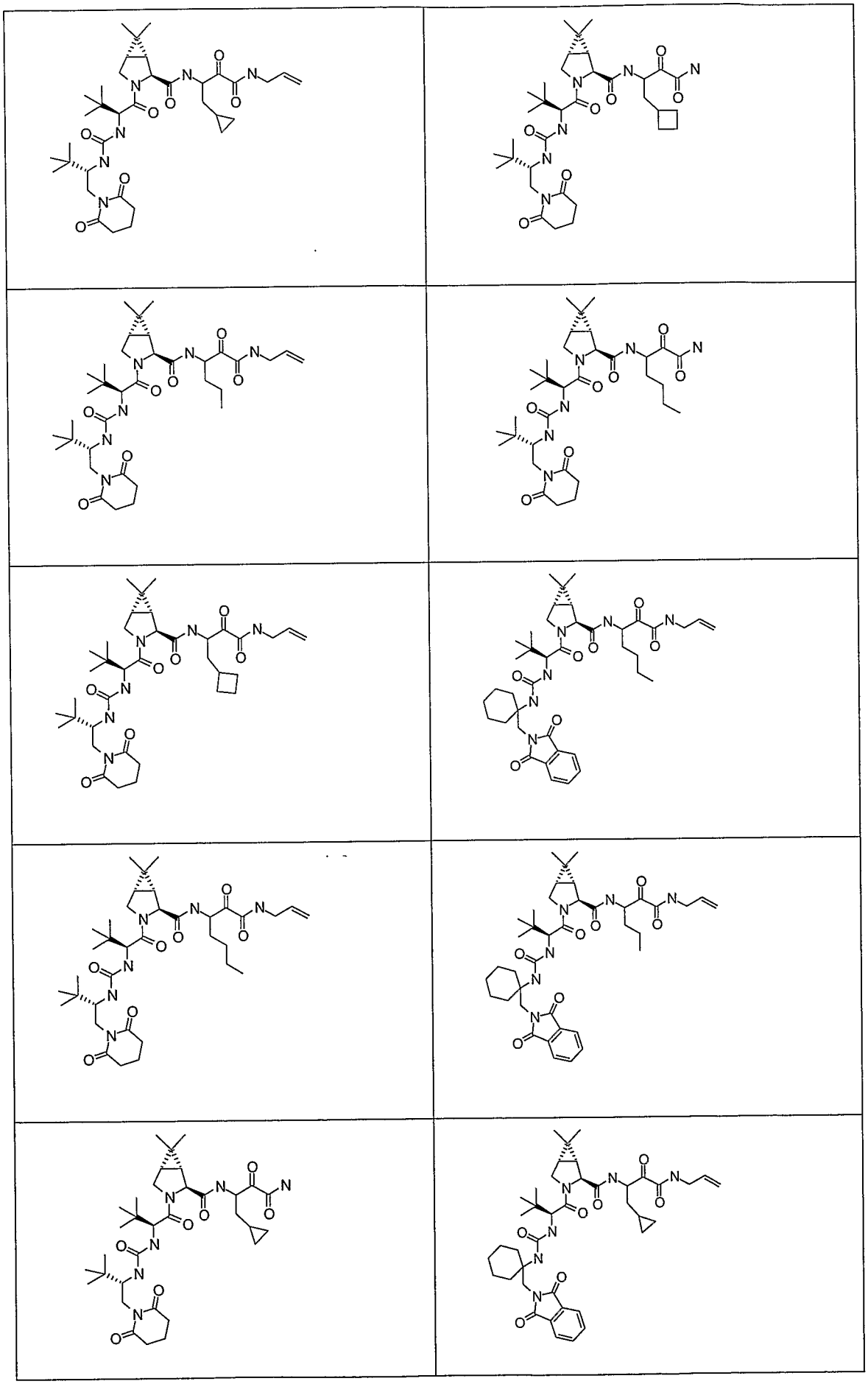
	
	
	
	

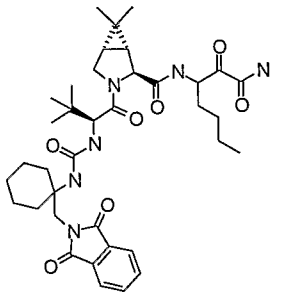
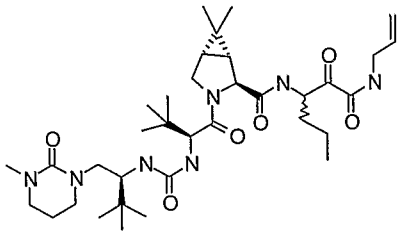
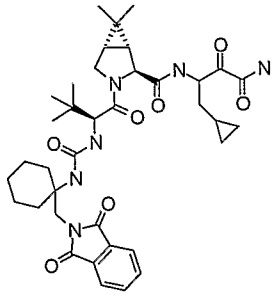
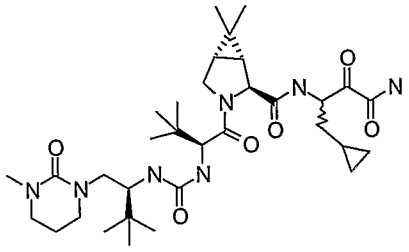
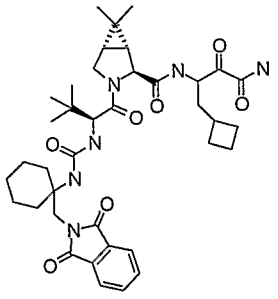
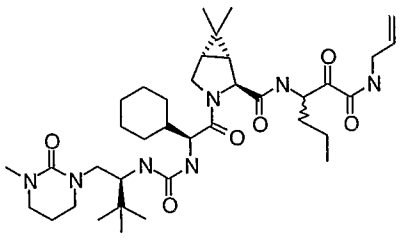
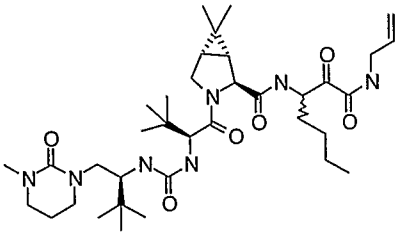
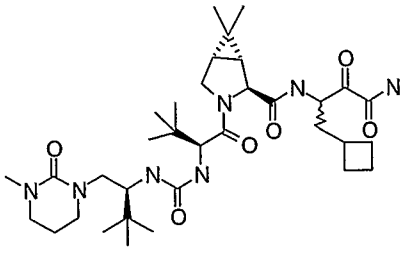


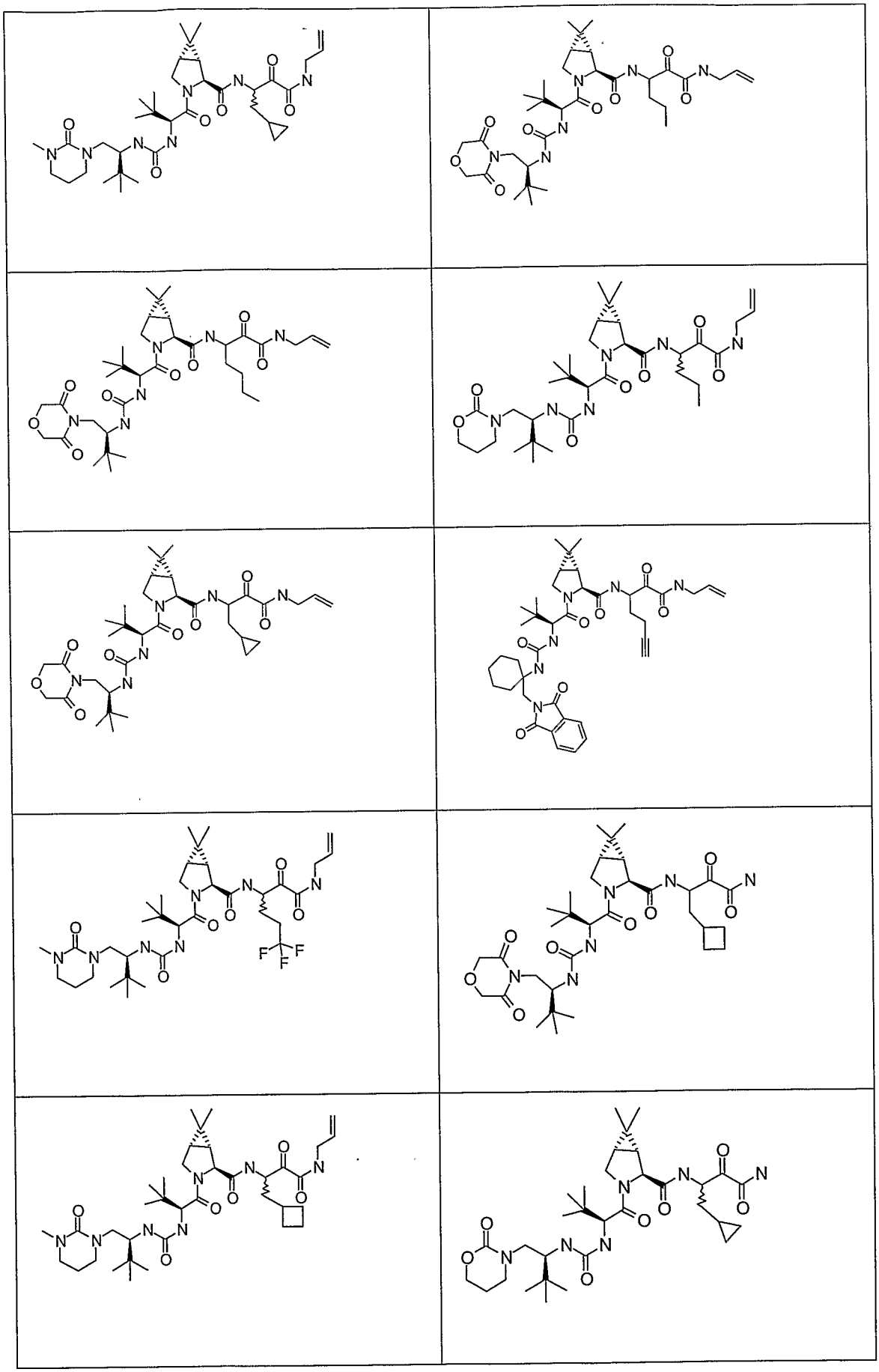
	
	
	
	

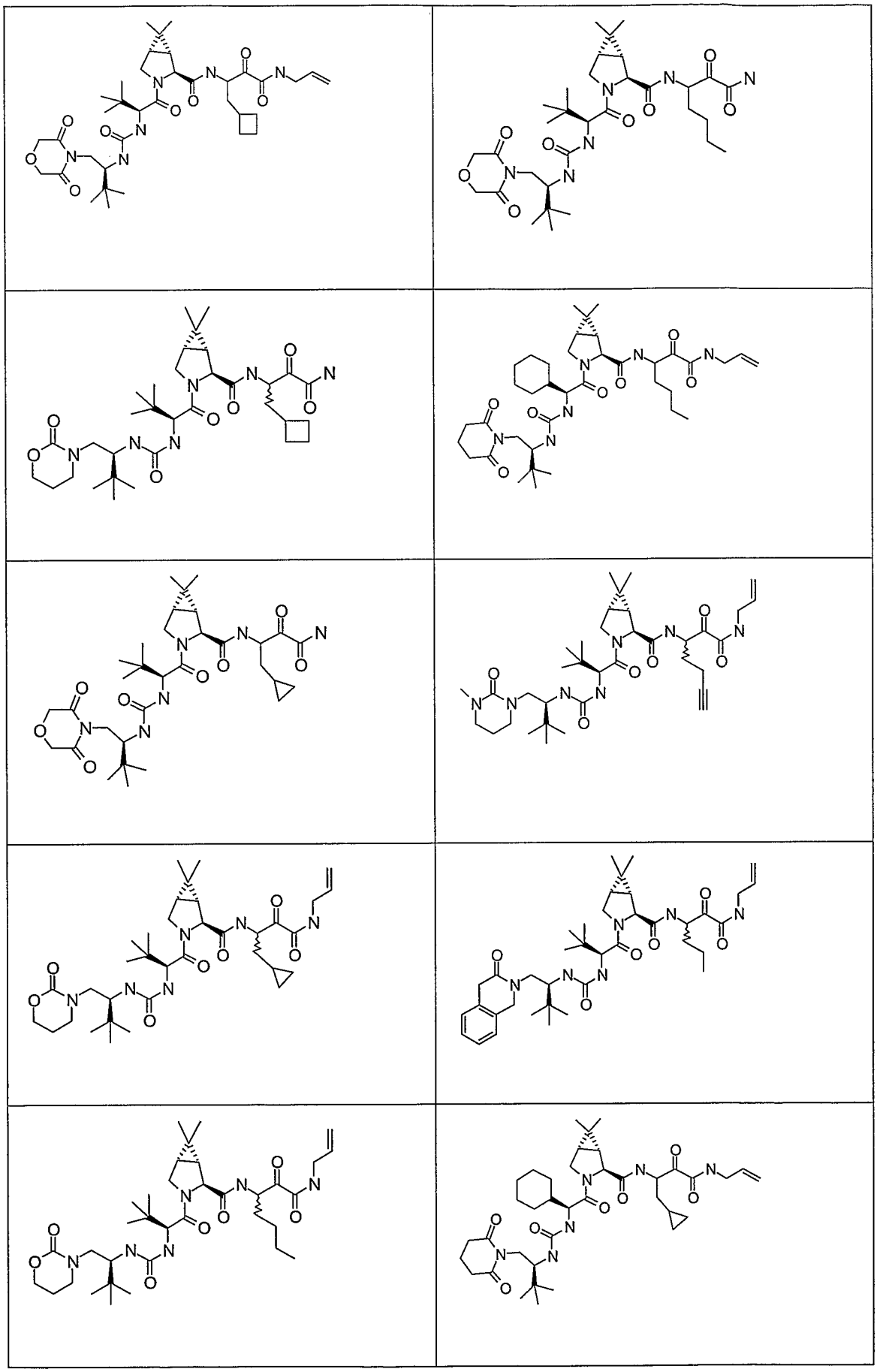


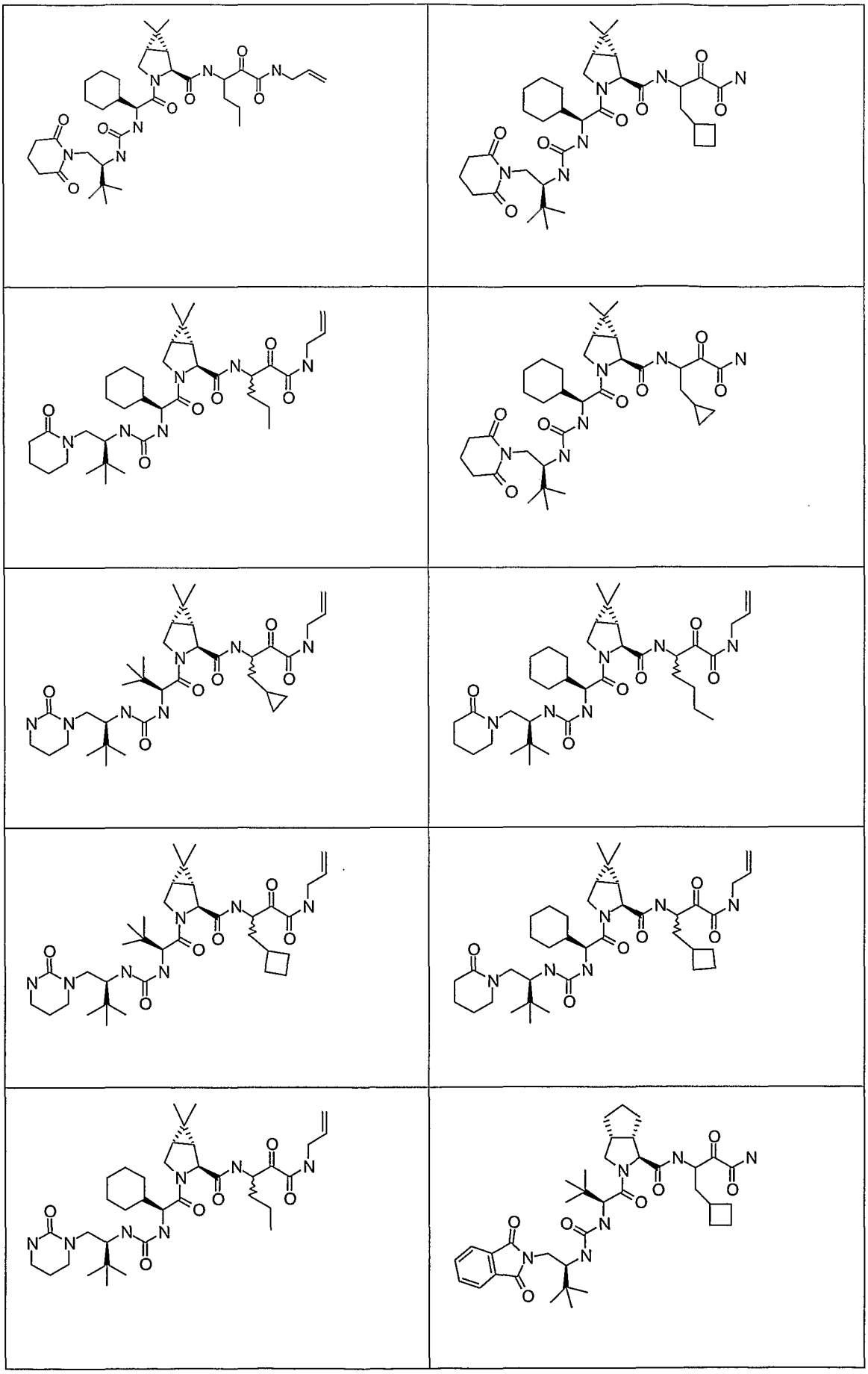


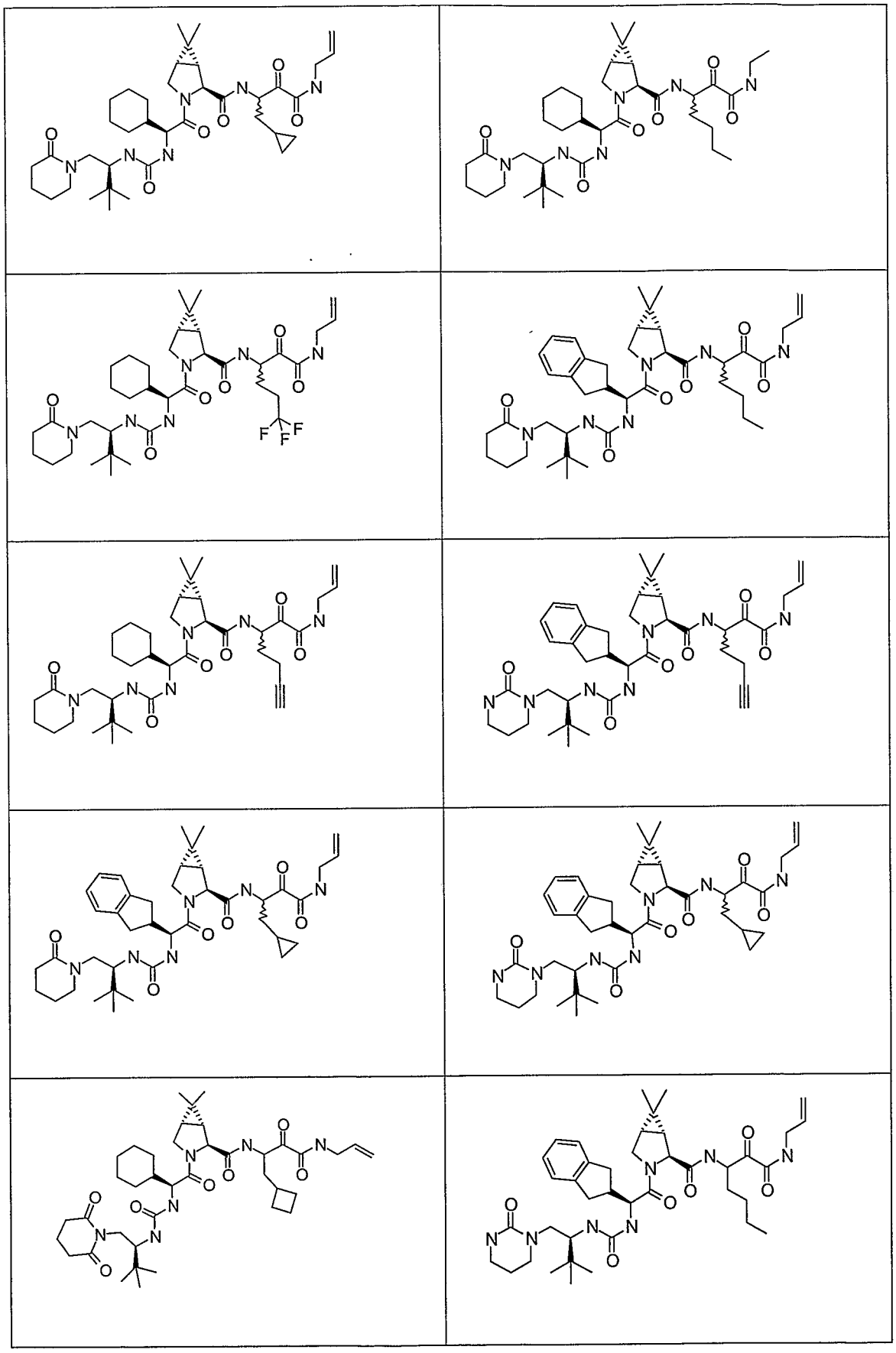


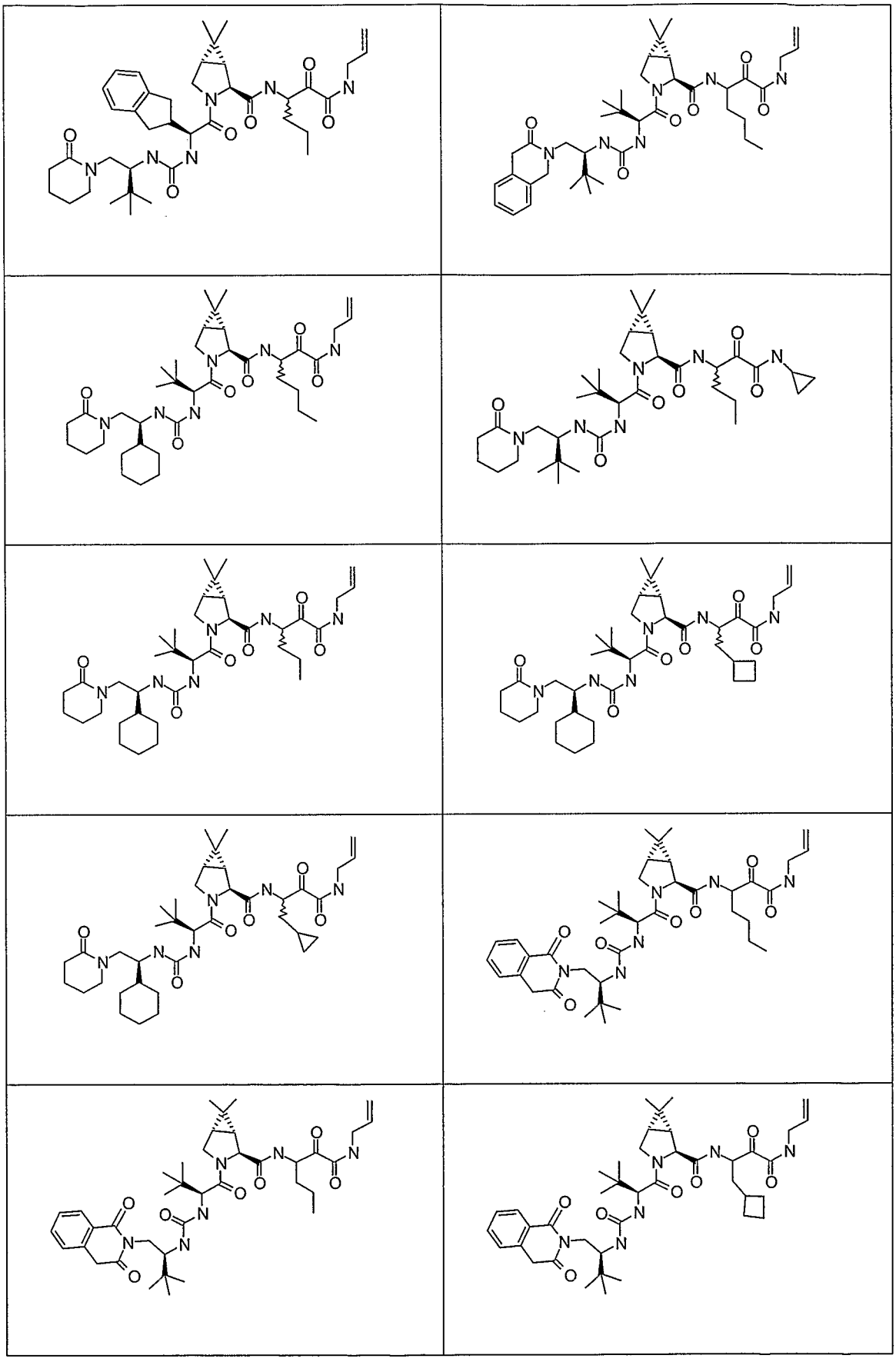
	
	
	
	

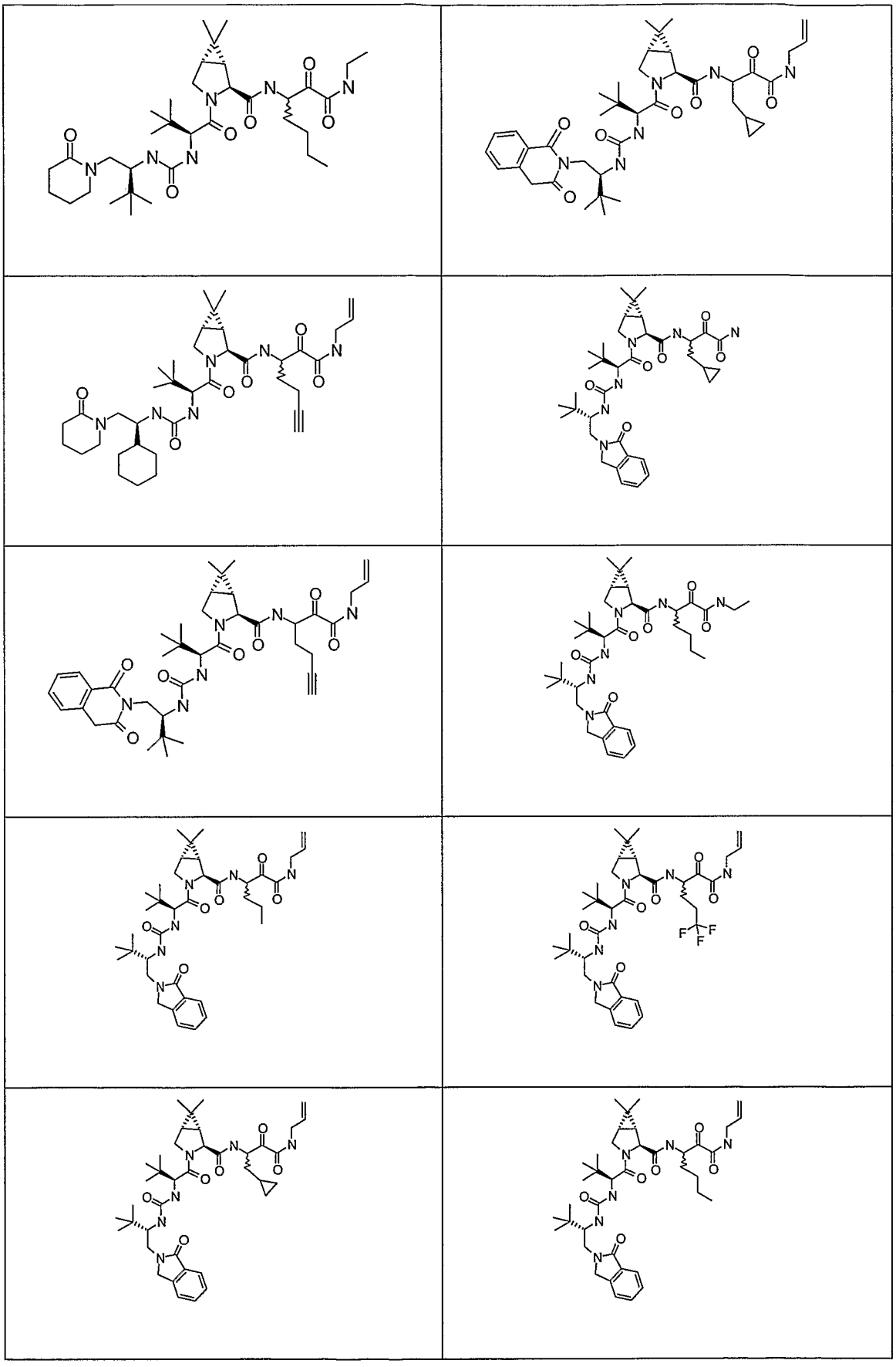


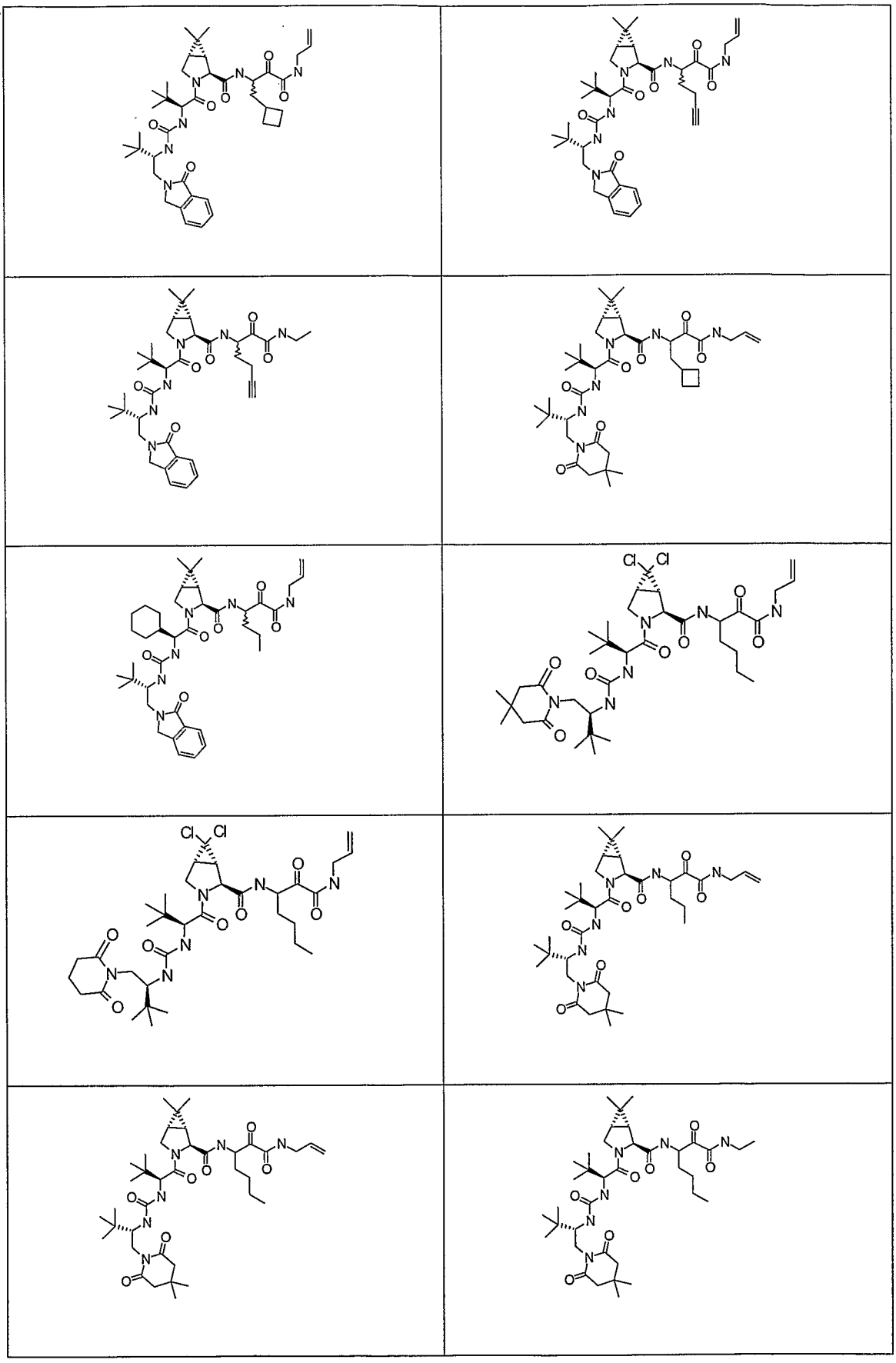


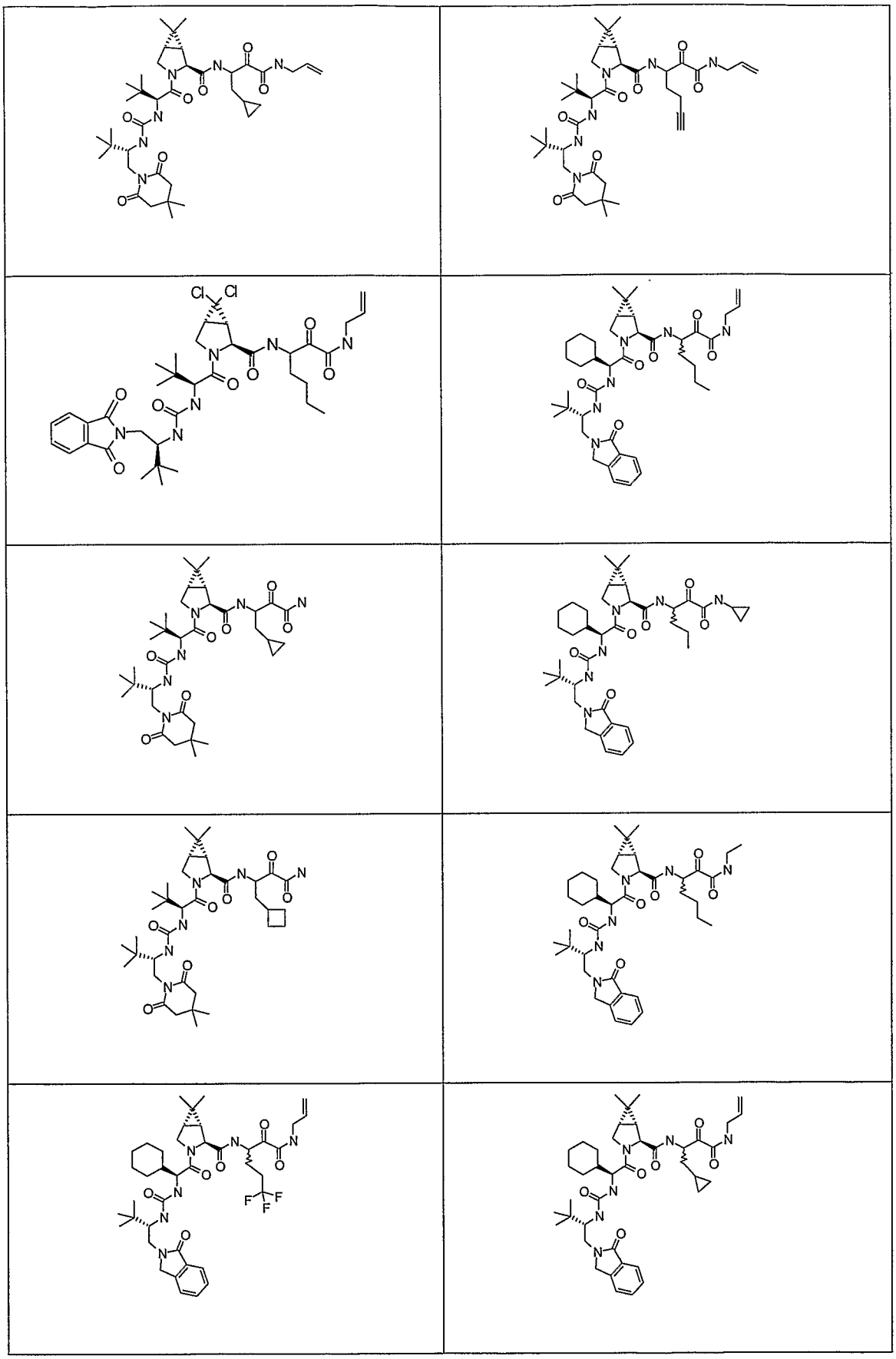


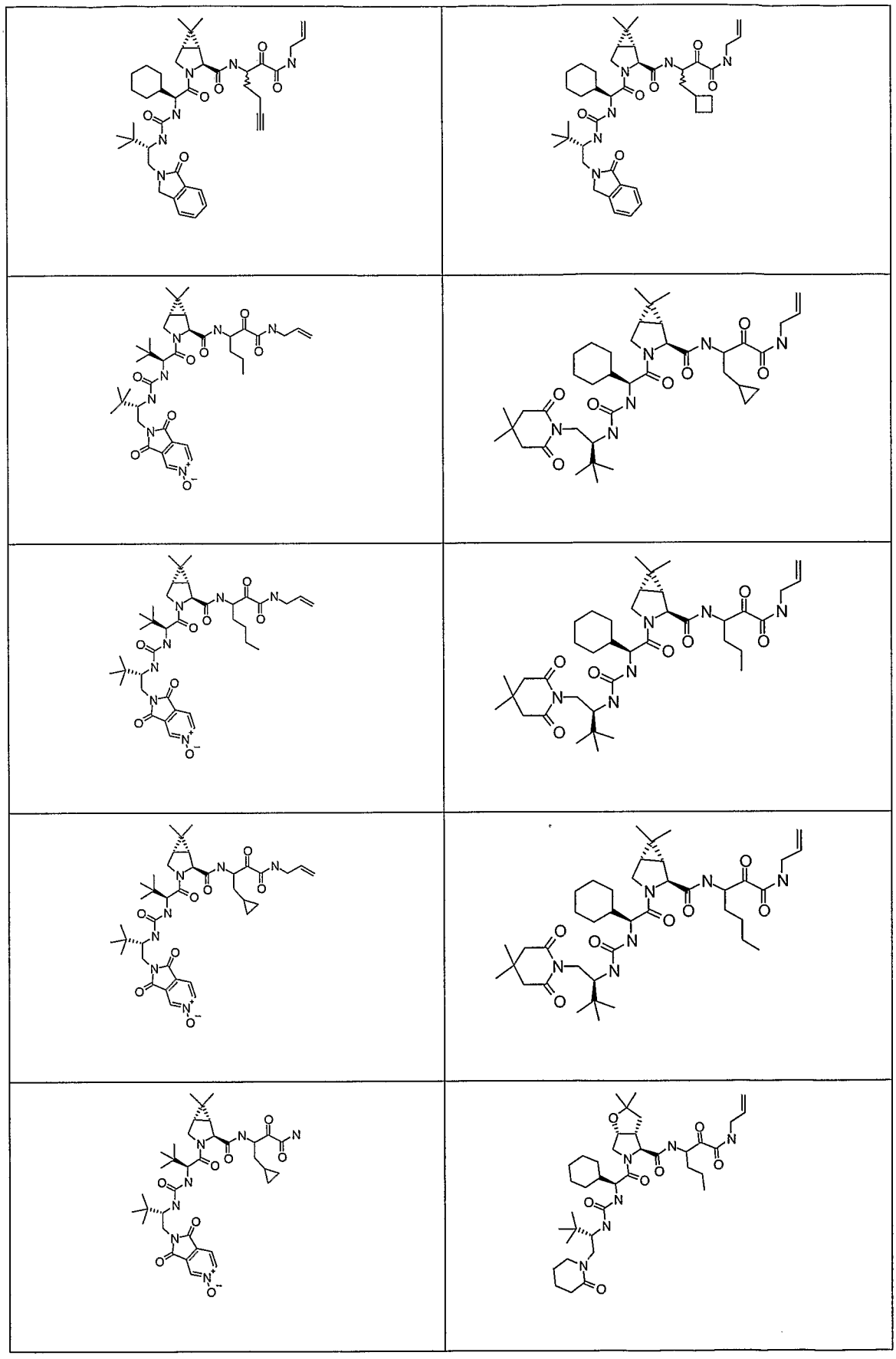


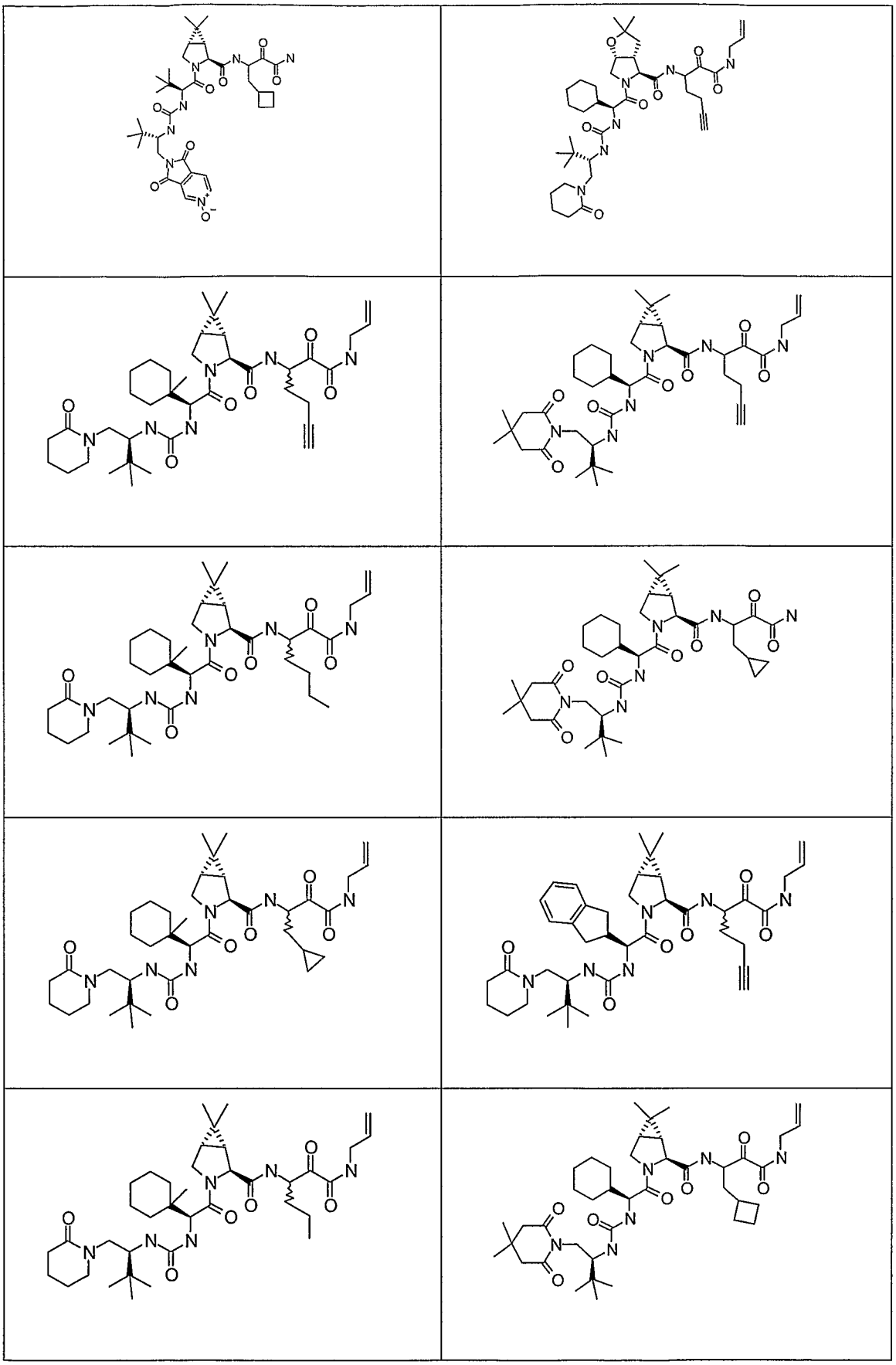


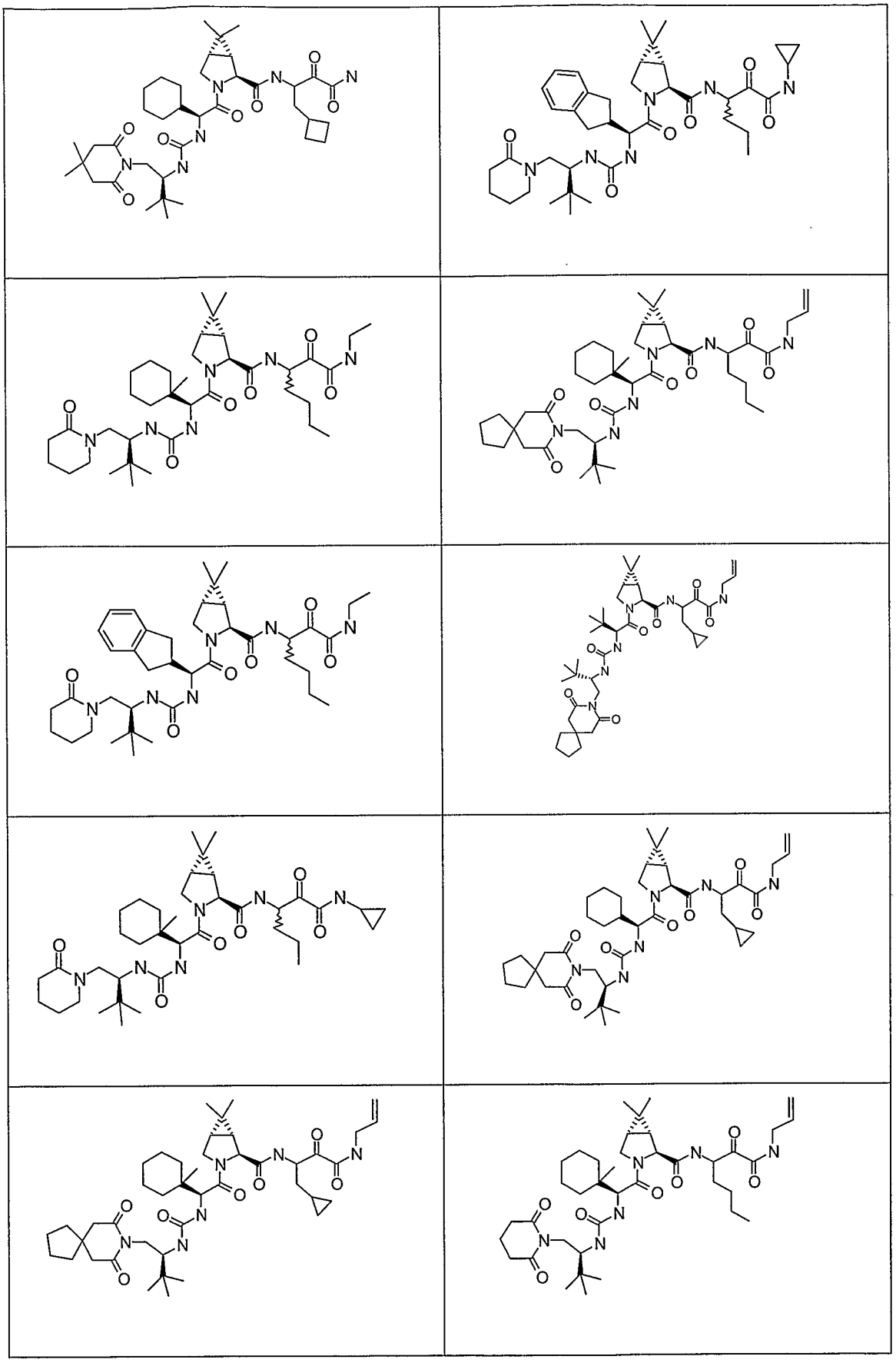


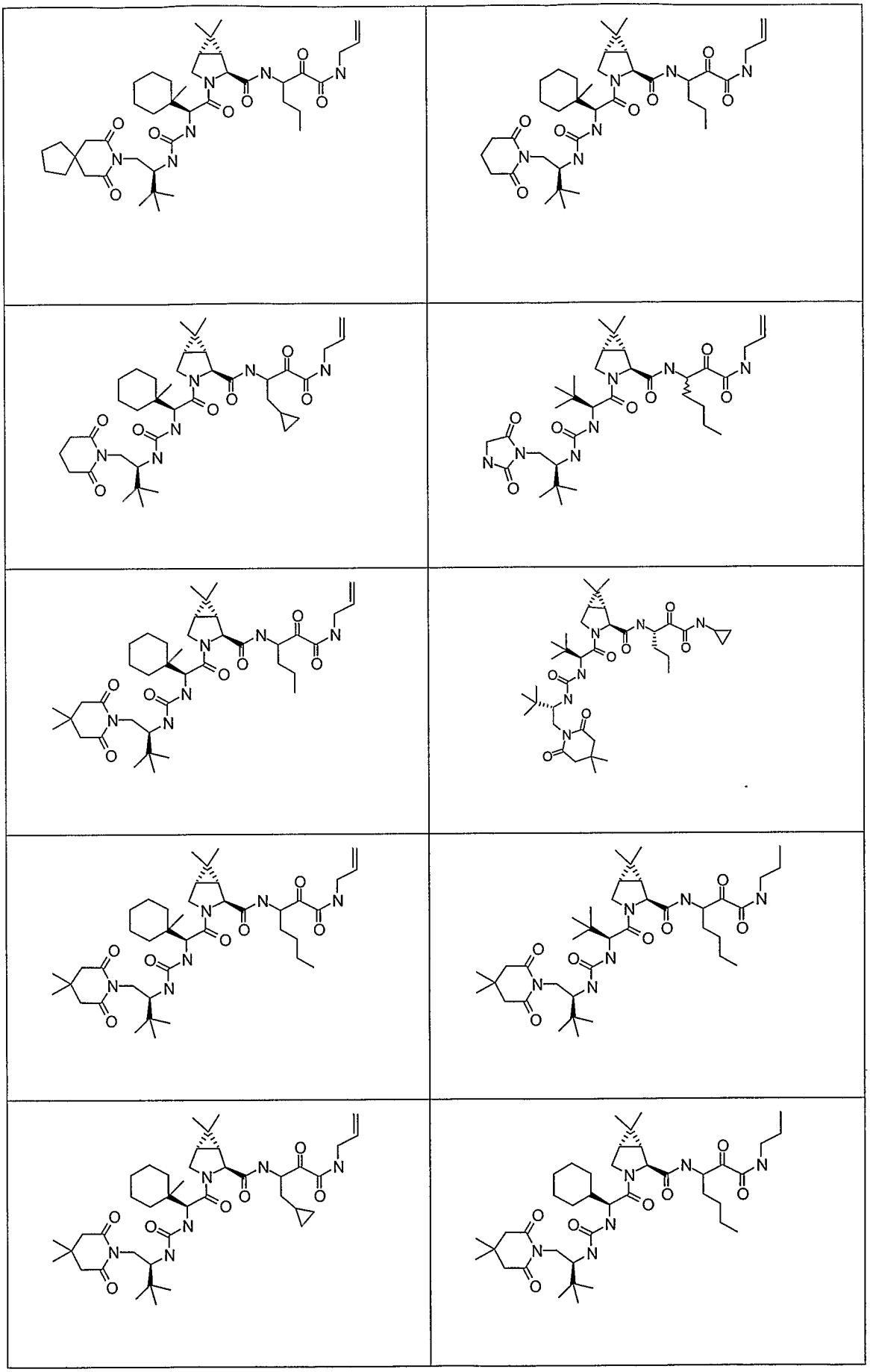


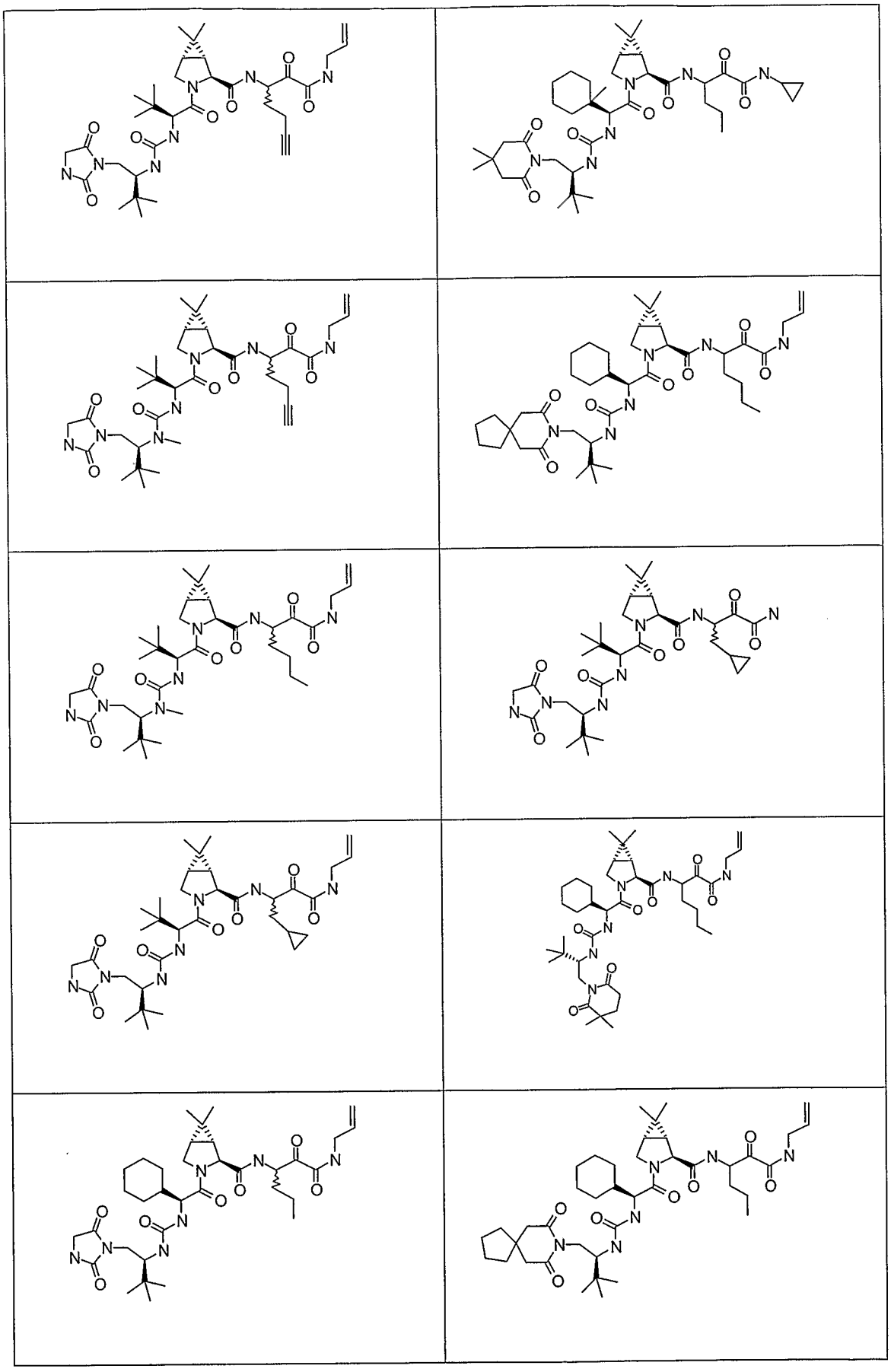


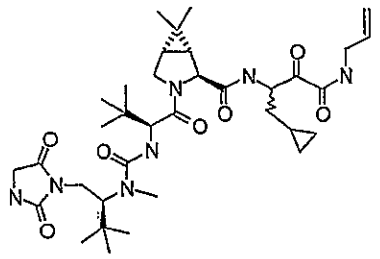










25. A pharmaceutical composition for treating disorders associated with the hepatitis C virus ("HCV"), said composition comprising therapeutically effective amount of one or more compounds in claim 24 and a pharmaceutically acceptable carrier.

26. The pharmaceutical composition of claim 25, additionally containing at least one antiviral agent.

27. The pharmaceutical composition of claim 26, additionally containing at least one interferon or PEG-interferon alpha conjugate ("pegylated interferon").

28. The pharmaceutical composition of claim 27, wherein said at least one antiviral agent is ribavirin and said at least one interferon is α-interferon or pegylated interferon.

29. The use of one or more compounds of claim 24 in the manufacture of a medicament for the therapeutic and/or prophylactic treatment of a hepatitis C virus associated disorder.

30. The use of one or more compounds of claim 24 in the manufacture of a medicament for the therapeutic and/or prophylactic treatment of symptoms of hepatitis C viral infection.

31. The use of one or more compounds of claim 24 in the manufacture of a medicament to modulate the activity of hepatitis C virus (HCV) protease for the therapeutic and/or prophylactic treatment of a hepatitis C virus associated disorder.

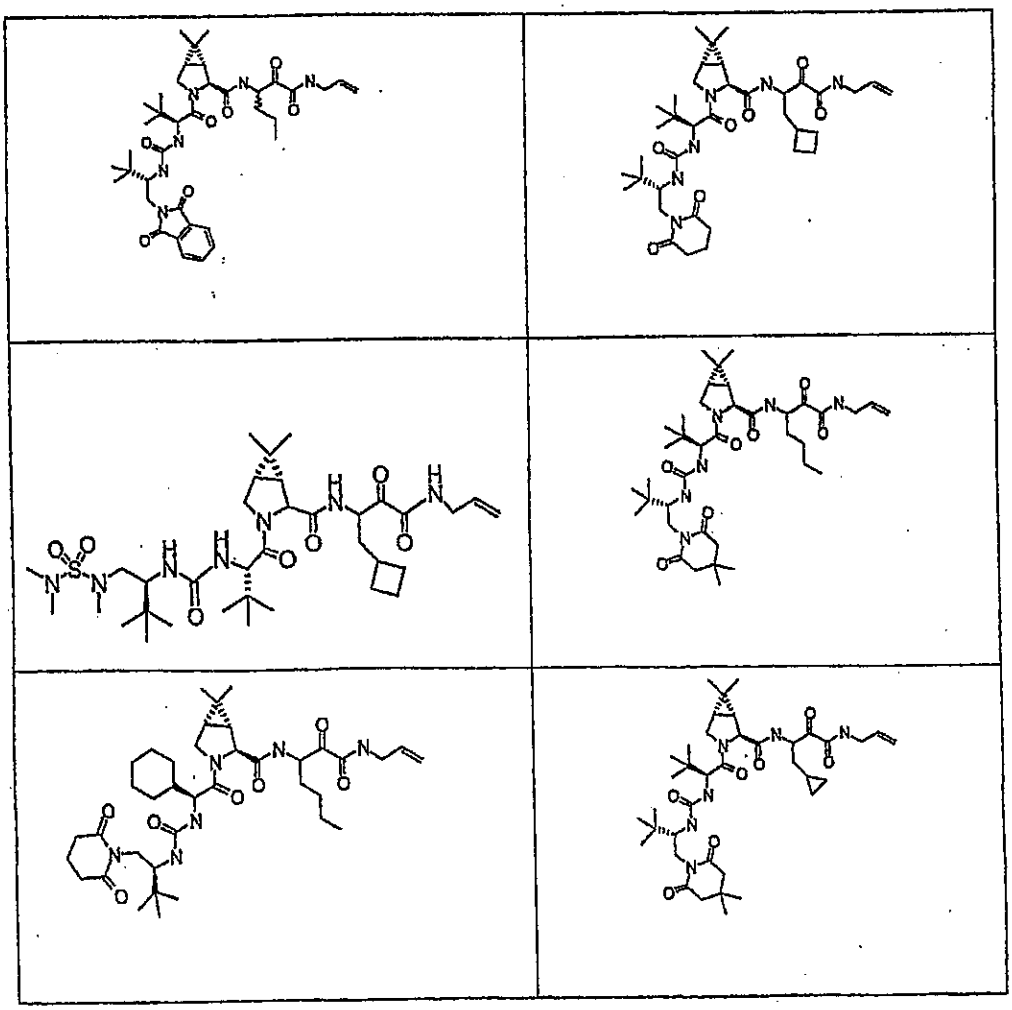
32. The use of claim 31, wherein the HCV protease is the NS3/NS4a protease.

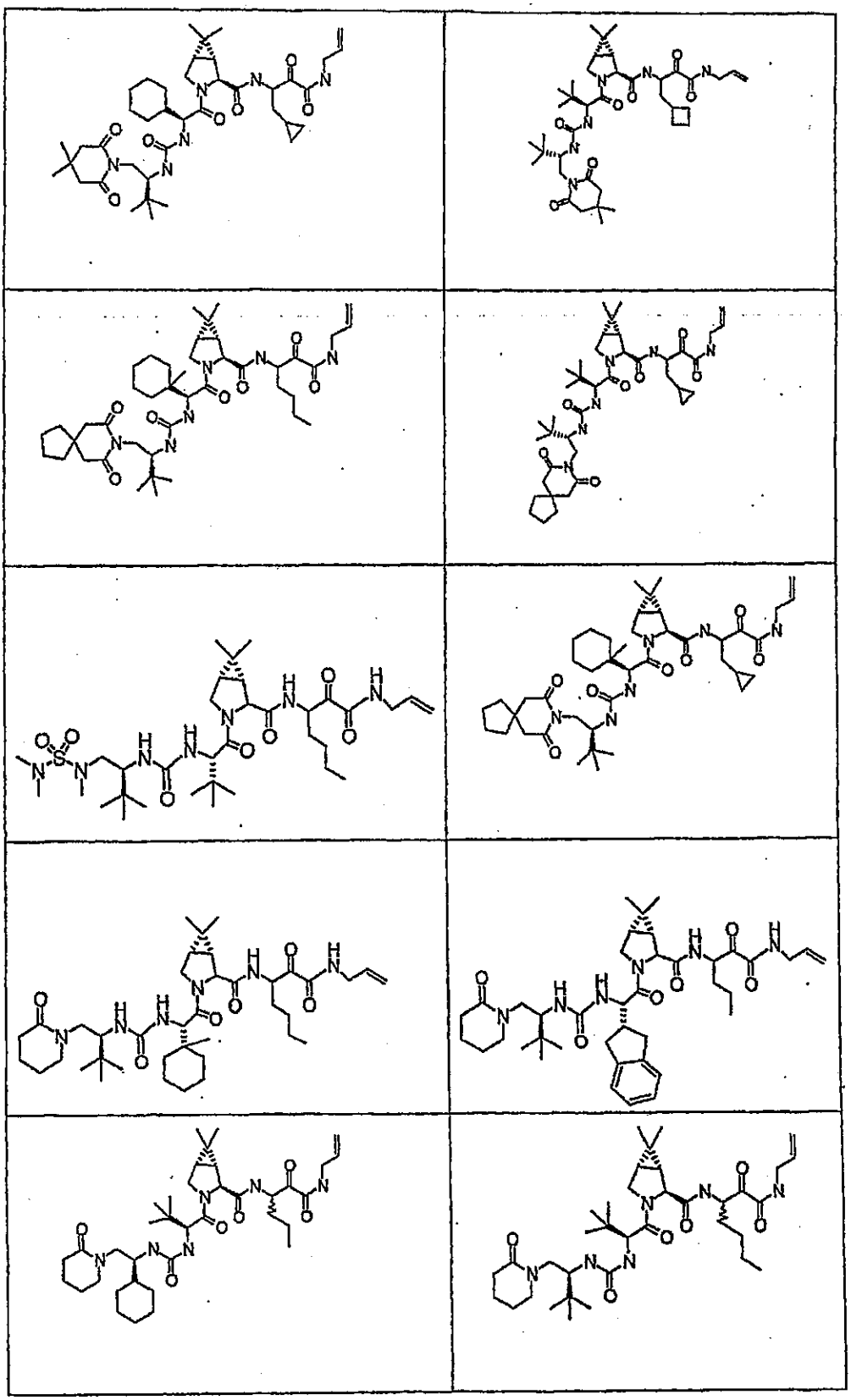
33. The use of claim 32, wherein the compound or compounds inhibit HCV NS3/NS4a protease.

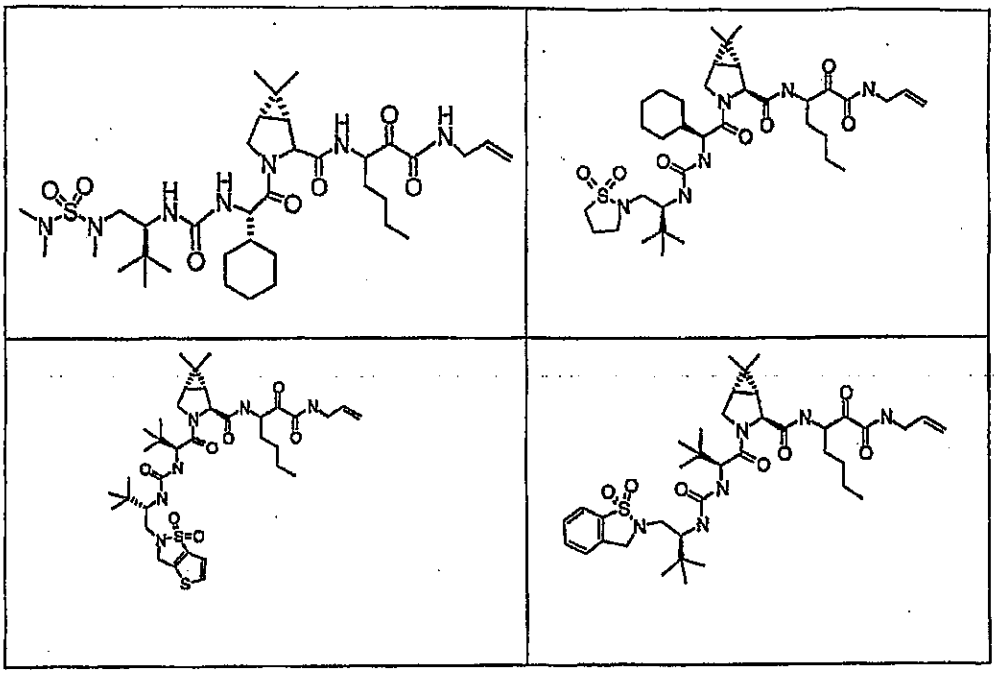
34. The use of one or more compounds of claim 24 in the manufacture of a medicament to modulate the processing of hepatitis C virus (HCV) polypeptide for the therapeutic and/or prophylactic treatment of a hepatitis C virus associated disorder.

35. The use of claim 34 comprising contacting the HCV polypeptide under conditions in which said polypeptide is processed with the medicament.

36. The use of an at least one compound, or enantiomers, stereoisomers, rotamers, tautomers, and racemates of the at least one compound, or a pharmaceutically acceptable salt, solvate or ester of the at least one compound in the manufacture of a medicament for the therapeutic and/or prophylactic treatment of disorders associated with the Hepatitis C Virus ("HCV"), the at least one compound being selected from the following:







37. A compound of claim 1 in purified form.