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(54) Title: ORGANIC COMPOUNDS AND THEIR USES

(57) Abstract: The present application describes organic compounds that are useful for the treatment, prevention and/or amelioration of human diseases.

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ORGANIC COMPOUNDS AND THEIR USES

Background

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). 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. Pat. 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. 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.

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).

HCV has been implicated in cirrhosis of the liver and in induction of hepatocellular carcinoma. The prognosis for patients suffering from HCV infection is

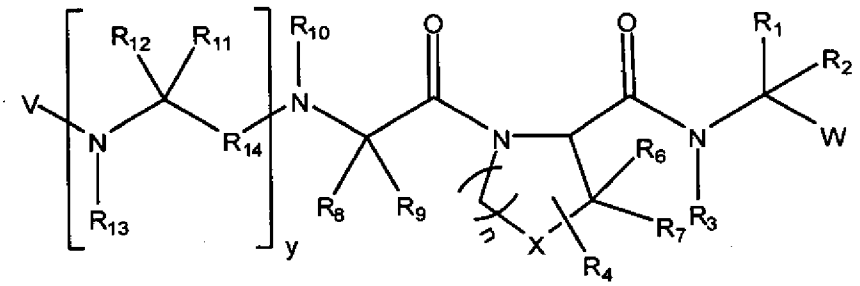
currently poor. HCV infection is more difficult to treat than other forms of hepatitis due to the lack of immunity or remission associated with HCV infection. Current data indicates a less than 50% survival rate at four years post cirrhosis diagnosis. Patients diagnosed with localized resectable hepatocellular 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%.

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.

Summary of the Invention

There remains a need for new treatments and therapies for HCV infection, as well as HCV-associated disorders. There is also a need for compounds useful in the treatment or prevention or amelioration of one or more symptoms of HCV, as well as a need for methods of treatment or prevention or amelioration of one or more symptoms of HCV. Furthermore, there is a need for methods for modulating the activity of HCV-serine proteases, particularly the HCV NS3/NS4a serine protease, using the compounds provided herein.

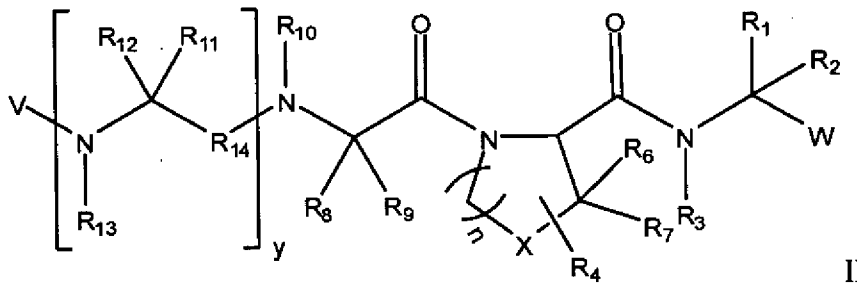
In one aspect, the invention provides compounds of Formula I:



I

and pharmaceutically acceptable salts and stereoisomers thereof.

In another aspect, the invention provides compounds of Formula III:



III

and pharmaceutically acceptable salts and stereoisomers thereof wherein X or R_6 and R_7, taken in combination, comprise a spirocyclic ring system which is spiro to the ring comprising the X variable.

In one embodiment, the invention provides a method of treating an HCV-associated disorder comprising administering to a subject in need thereof a pharmaceutically acceptable amount of a compound of the invention, such that the HCV-associated disorder is treated.

In another embodiment, the invention provides a method of treating an HIV infection comprising administering to a subject in need thereof a pharmaceutically acceptable amount of a compound of the invention.

In still another embodiment, the invention provides a method of treating, inhibiting or preventing the activity of HCV in a subject in need thereof, comprising administering to the subject a pharmaceutically acceptable amount of a compound of the invention. In one embodiment, the compounds of the invention inhibit the activity of the NS2 protease, the NS3 protease, the NS3 helicase, the NS5a protein, and/or the NS5b polymerase. In another embodiment, the interaction between the NS3 protease and NS4A cofactor is disrupted. In yet another embodiment, the compounds of the invention prevent or alter the severing of one or more of the NS4A-NS4B, NS4B-NS5A and NS5A-NS5B junctions of the HCV. In another embodiment, the invention provides a method of inhibiting the activity of a sèrine protease, comprising the step of contacting said serine protease with a compound of the invention. In another embodiment, the invention provides a method of treating, inhibiting or preventing the activity of HCV in a subject in need thereof, comprising administering to the subject a pharmaceutically acceptable amount of a compound of the invention, wherein the compound interacts with any target in the HCV life cycle. In one embodiment, the target of the HCV life cycle is

selected from the group consisting of NS2 protease, NS3 protease, NS3 helicase, NS5a protein andNS5b polymerase.

In another embodiment, the invention provides a method of decreasing the HCV RNA load in a subject in need thereof comprising administering to the subject a pharmaceutically acceptable amount of a compound of the invention.

In another embodiment, the compounds of the invention exhibit HCV protease activity. In one embodiment, the compounds are an HCV NS3-4A protease inhibitor.

In another embodiment, the invention provides a method of treating an HCV-associated disorder in a subject, comprising administering to a subject in need thereof a pharmaceutically acceptable amount of a compound of the invention, and a pharmaceutically acceptable carrier, such that the HCV-associated disorder is treated.

In still another embodiment, the invention provides a method of treating an HCV-associated disorder comprising administering to a subject in need thereof a pharmaceutically effective amount of a compound of the invention, in combination with a pharmaceutically effective amount of an additional HCV-modulating compound, such as interferon or derivatized interferon, or a cytochrome P450 monooxygenase inhibitor, such that the HCV-associated disorder is treated. In one embodiment, the additional HCV-modulating compound is selected from the group consisting of Sch 503034 and VX-950.

In another embodiment, the invention provides a method of inhibiting hepatitis C virus replication in a cell, comprising contacting said cell with a compound of the invention.

In yet another embodiment, the invention provides a packaged HCV-associated disorder treatment, comprising an HCV-modulating compound of the invention, packaged with instructions for using an effective amount of the HCV-modulating compound to treat an HCV-associated disorder.

In certain embodiments, the HCV-associated disorder is selected from the group consisting of HCV infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma, cryoglobulinaemia, non-Hodgkin's lymphoma, and a suppressed innate intracellular immune response.

In another embodiment, the invention provides a method of treating HCV infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma,

cryoglobulinaemia, non-Hodgkin's lymphoma, and/or a suppressed innate intracellular immune response in subject in

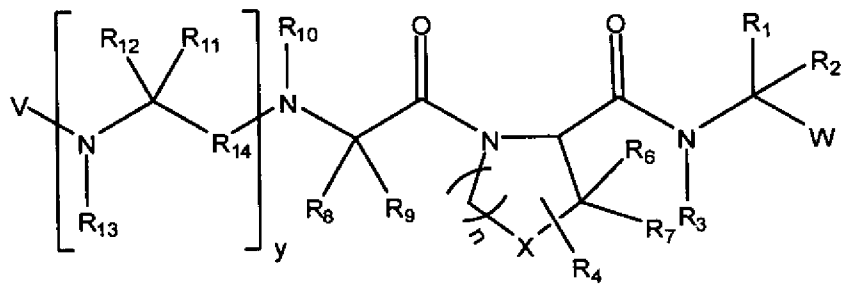
need thereof comprising administering to the subject a pharmaceutically acceptable amount of a compound of the invention.

In one embodiment, the HCV to be treated is selected of any HCV genotype. In another embodiment, the HCV is selected from HCV genotype 1, 2 and/or 3.

Detailed Description of the Invention

This invention is directed to compounds, *e.g.*, peptide compounds, and intermediates thereto, as well as pharmaceutical compositions containing the compounds for use in treatment of HCV infection. This invention is also directed to the compounds of the invention or compositions thereof as protease inhibitors, particularly as serine protease inhibitors, and more particularly as HCV NS3 protease inhibitors. The compounds are particularly useful in interfering with the life cycle of the hepatitis C virus and in treating or preventing an HCV infection or physiological conditions associated therewith. The present invention is also directed to methods of combination therapy for inhibiting HCV replication in cells, or for treating or preventing an HCV infection in patients using the compounds of the invention or pharmaceutical compositions, or kits thereof.

In one aspect, the compounds of the invention are of Formula I:



I

and pharmaceutically acceptable salts and stereoisomers thereof;

wherein

y is 0 or 1;

n is 0, 1 or 2;

R^{14} is C(O) or SO_2;

R^1, R^2, W, R^{13} and V are each, independently, selected from hydrogen or from the group consisting of alkyl, alkyl-aryl, heteroalkyl, heterocyclyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyloxy, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocyclyloxy, cycloalkyloxy, amino, alkylamino, arylamino, alkyl-arylamino, arylamino, heteroarylamino, cycloalkylamino, carboxyalkylamino, mono- and di-alkylcarboxamide, arylalkyloxy and heterocyclylamino; each of which may be further independently substituted one or more times with X^1 and X^2 (or more preferably, each of which may be further substituted with 1, 2, 3, 4, or 5 residues independently selected from X^1 and X^2); wherein X^1 is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, aralkyl, aryloxy, arylthio, arylheteroaryl, heteroaryl, heterocyclylamino, alkylheteroaryl, or heteroaralkyl; wherein X^1 can be independently substituted with one or more X^2 moieties (or more preferably with 1, 2, 3, 4, or 5 X^2 moieties) which can be the same or different and are independently selected; wherein X^2 is hydroxy, oxo, alkyl, cycloalkyl, spirocycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, aryloxy, thio, alkylthio, amino, mono- and di-alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyl, alkoxycarbonyloxy, alkylureido, arylureido, halogen, cyano, or nitro; wherein each X^2 residue selected to be alkyl, alkoxy, and aryl can be unsubstituted or optionally independently substituted with one or more moieties (or more preferably with 1, 2, 3, 4, or 5 moieties) which can be the same or different and are independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, aralkyl, arylheteroaryl, heteroaryl, heterocyclylamino, alkylheteroaryl and heteroaralkyl;

W is also selected from the group consisting of C(O)-C(O)H, C(=N-O-R_{24})-C(O)-amine, C(O)-C(O)-amine, C(O)$NR_{24}S(O)_pR_{24}$, C(O)$NR_{24}S(O)_pN(R_{24})_2$ and C(O)-$[C(O)]_a$-heterocycle, wherein the heterocycle may be independently substituted one or more times (or preferably between one and five times) with aryl, C_{1-4}-alkyl, C_{1-4}-alkyl substituted by one or more halogen atoms, and C_{3-6}-cycloalkyl, wherein a is 0 or 1, wherein each R_{24} is independently selected from hydrogen or from the group consisting of C_{1-4}-alkyl, C_{3-6}-cycloalkylC_{0-4}alkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocycle, each of which may be independently substituted one or more

times (or preferably between one and five times) with a halogen atom or C_{1-4}-alkyl;

V is also selected from the group consisting of $-Q^1-Q^2$, wherein Q^1 is absent, C(O), N(H), N(C_{1-4}-alkyl), C=N(CN), C=N(SO_2CH_3), C=N-COH-C_{1-4}-alkyl, or C=N-COH, and Q^2 is hydrogen or is selected from the group consisting of C_{1-4}-alkyl, O-C_{1-4}-alkyl, NH_2, N(H)-C_{1-4}-alkyl, N(C_{1-4}-alkyl)$_2$, SO_2-aryl, SO_2-C_{1-4}-alkyl, C_{3-6}-cycloalkyl-C_{0-4}-alkyl, aryl, heteroaryl and heterocycle, each of which may be independently substituted one or more times with a halogen atom, C_{1-4}-alkyl, C_{1-4}-alkyl substituted by one or more halogen atoms, or C_{3-6}-cycloalkyl;

or R^1 and R^2 may together form a 3, 4, 5, 6 or 7-membered ring that is aromatic or non-aromatic and may contain one or more heteroatoms, wherein the ring may be further substituted one or more times (or preferably between one and five times);

R^3 is selected from the group consisting of hydrogen, C_{1-4}-alkyl and C_{3-6}-cycloalkylC_{0-4}alkyl;

X is O, S, N, NR^5, CR^5 or CR^5R^{5a};

R^4 is selected from hydrogen or from the group consisting of C_{1-4}-alkyl, C_{3-6}-cycloalkyl, aryl, heterocycle and heteroaryl, each of which may be independently substituted one or more times (or preferably between one and five times) with a halogen atom or C_{1-4}-alkyl;

R^5 is selected from hydrogen or oxo or from the group consisting of hydroxyl, C_{1-8}-alkyl, C_{2-8}-alkenyl, C_{2-8}-alkynyl, C_{3-8}-cycloalkyl-C_{0-4}-alkyl, aryl-C_{0-4}-alkyl, heterocycle-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl , C_{3-8}-cycloalkyloxy, aryloxy, and heteroaryloxy each of which may be independently substituted one or more times (or preferably between one and five times) with a halogen atom, aryl, trihalomethyl, or C_{1-4}-alkyl;

R^{5a} is selected from the group consisting of hydrogen, hydroxyl, C_{1-8}-alkyl, C_{2-8}-alkenyl, C_{2-8}-alkynyl, C_{3-8}-cycloalkyl-C_{0-4}-alkyl, aryl-C_{0-4}-alkyl and heteroaryl-C_{0-4}-alkyl,

or R^4 and R^5 may together form a fused dimethyl cyclopropyl ring, a fused cyclopentane ring, a fused phenyl ring or a fused pyridyl ring, each of which may be substituted with a halogen atom, aryl, trihalomethyl, or C_{1-4}-alkyl;

or R^5 and R^6 may together form a fused dimethyl cyclopropyl ring, a fused cyclopentane ring, a fused phenyl ring or a fused pyridyl ring, each of which may be substituted with a halogen atom, aryl, trihalomethyl, or C_{1-4}-alkyl;

or R^5 and R^{5a} may together form a spirocyclic ring having between 3 and 7 ring atoms and having 0, 1, or 2 ring heteroatoms, which is optionally substituted by 0-4 substituents selected from cyano, halogen, hydroxyl, amino, thiol, C_{1-8}-alkyl, C_{2-8}-alkenyl, C_{2-8}-alkynyl, C_{1-8}-alkoxy-C_{0-4}alkyl, C_{1-8}-haloalkyl, C_{2-8}-haloalkenyl, C_{2-8}-haloalkynyl, C_{1-8}-haloalkoxy, C_{1-8}-alkylthio, C_{1-8}-alkylsulfonyl, C_{1-8}-alkylsulfoxy, C_{1-8}-alkanoyl, C_{1-8}-alkoxycarbonyl, C_{3-7}-cycloalkyl-C_{0-4}-alkyl, aryl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, COOH, $C(O)NH_2$, mono- and di-C_{1-4}-alkyl-carboxamide, mono- and di-C_{1-4}-alkyl-amino-C_{0-4}alkyl, SO_3H, SO_2NH_2, and mono-and di-C_{1-4}-alkylsulfonamide, or two of said 0-4 substituents taken together form a fused or spirocyclic 3 to 7 membered ring having 0, 1 or 2 ring heteroatoms selected from N, O and S, which fused or spirocyclic ring has 0 to 2 independently selected substituents selected from cyano, halogen, hydroxyl, amino, thiol, C_{1-8}-alkyl, C_{2-8}-alkenyl, C_{2-8}-alkynyl, C_{1-8}-alkoxy-C_{0-4}alkyl, C_{1-8}-haloalkyl, C_{2-8}-haloalkenyl, C_{2-8}-haloalkynyl, C_{1-8}-haloalkoxy, C_{1-8}-alkylthio, C_{1-8}-alkylsulfonyl, C_{1-8}-alkylsulfoxy, C_{1-8}-alkanoyl, C_{1-8}-alkoxycarbonyl, C_{3-7}-cycloalkyl-C_{0-4}-alkyl, aryl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, COOH, $C(O)NH_2$, mono- and di-C_{1-4}-alkyl-carboxamide, mono- and di-C_{1-4}-alkyl-amino-C_{0-4}alkyl, SO_3H, SO_2NH_2, and mono-and di-C_{1-4}-alkylsulfonamide;

R^6, R^7, R^8, R^9, R^{10}, R^{11} and R^{12} are each, independently, selected from the group consisting of hydrogen, C_{1-4}-alkyl and C_{3-6}-cycloalkylC_{0-4}alkyl;

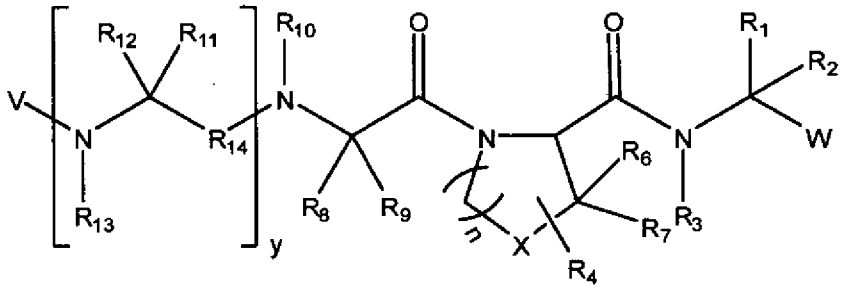
or R^6 and R^7 may together form a spirocyclic ring having between 3 and 7 ring atoms and having 0, 1, or 2 ring heteroatoms, which is optionally substituted by 0-4 substituents selected from cyano, halogen, hydroxyl, amino, thiol, C_{1-8}-alkyl, C_{2-8}-alkenyl, C_{2-8}-alkynyl, C_{1-8}-alkoxy-C_{0-4}alkyl, C_{1-8}-haloalkyl, C_{2-8}-haloalkenyl, C_{2-8}-haloalkynyl, C_{1-8}-haloalkoxy, C_{1-8}-alkylthio, C_{1-8}-alkylsulfonyl, C_{1-8}-alkylsulfoxy, C_{1-8}-alkanoyl, C_{1-8}-alkoxycarbonyl, C_{3-7}-cycloalkyl-C_{0-4}-alkyl, aryl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, COOH, $C(O)NH_2$, mono- and di-C_{1-4}-alkyl-carboxamide, mono- and di-C_{1-4}-alkyl-amino-C_{0-4}alkyl, SO_3H, SO_2NH_2, and mono-and di-C_{1-4}-alkylsulfonamide, or two substituents taken together form a fused or spirocyclic 3 to 7 membered ring having 0, 1 or 2 ring heteroatoms selected from N, O and S, which fused or spirocyclic ring has 0 to 2 independently selected substituents selected from halogen, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, mono- and di-C_{1-4}-alkylamino, mono- and di-C_{1-4}-alkyl-carboxamide, C_{1-4}-

alkoxycarbonyl, and phenyl;

or R^3 and W may together form a 3, 4, 5, 6 or 7-membered ring that is aromatic or non-aromatic and may contain one or more heteroatoms, wherein the ring may be further substituted one or more times (or preferably between one and five times); and

or when y is 0, R^{10} and V may together form a 3, 4, 5, 6 or 7-membered ring that is aromatic or non-aromatic and may contain one or more heteroatoms, wherein the ring may be further substituted one or more times (or preferably between one and five times).

In another aspect, the compounds of the invention are of Formula III:



III

and pharmaceutically acceptable salts and stereoisomers thereof;

wherein

y is 0 or 1;

n is 0, 1 or 2;

R^{14} is C(O) or SO_2;

R^1, R^2, W, R^{13} and V are each, independently, selected from hydrogen or from the group consisting of alkyl, alkyl-aryl, heteroalkyl, heterocyclyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyloxy, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocyclyloxy, cycloalkyloxy, amino, alkylamino, arylamino, alkyl-arylamino, arylamino, heteroarylamino, cycloalkylamino, carboxyalkylamino, mono- and di-alkylcarboxamide, aralkyloxy and heterocyclylamino; each of which may be further independently substituted one or more times with X^1 and X^2 (or more preferably, each of which may be further substituted with 1, 2, 3, 4, or 5 residues independently selected from X^1 and X^2); wherein X^1 is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, aralkyl, aryloxy, arylthio, arylheteroaryl, heteroaryl, heterocyclylamino, alkylheteroaryl, or heteroaralkyl; wherein X^1 can be independently substituted with one or more X^2 moieties (or more preferably with 1, 2, 3,

4, or 5 X^2 moieties) which can be the same or different and are independently selected; wherein X^2 is hydroxy, oxo, alkyl, cycloalkyl, spirocycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, aryloxy, thio, alkylthio, amino, mono- and di-alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyl, alkoxycarbonyloxy, alkylureido, arylureido, halogen, cyano, or nitro; wherein each X^2 residue selected to be alkyl, alkoxy, and aryl can be unsubstituted or optionally independently substituted with one or more moieties (or more preferably with 1, 2, 3, 4, or 5 moieties) which can be the same or different and are independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, aralkyl, arylheteroaryl, heteroaryl, heterocyclylamino, alkylheteroaryl and heteroaralkyl;

W is also selected from the group consisting of C(O)OH, $C(O)OR_{24}$, C(O)-amine, $P(O)(OR_{24})_2$, C(O)-C(O)OH, $C(=N\text{-}O\text{-}R_{24})$-C(O)-amine, $C(O)NHS(O)_2R_{24}$, $C(O)NHS(O)_2N(R_{24})_2$, C(O)-C(O)-amine, $CONHSO_2$-amine and C(O)-$[C(O)]_a$-heterocycle, wherein the heterocycle may be substituted or unsubstituted, wherein a is 0 or 1, wherein each R_{24} is independently selected from the group consisting of hydrogen, halogen, hydroxyl, formyl, carboxylate, amide, amino, substituted or unsubstituted-$C_{1\text{-}4}$-alkyl, substituted or unsubstituted-$C_{1\text{-}4}$-alkoxy, substituted or unsubstituted-$C_{1\text{-}4}$-alkanoyl, substituted or unsubstituted-$C_{1\text{-}4}$-alkoxycarbonyl, substituted or unsubstituted-$C_{1\text{-}4}$-alkanoyloxy, substituted or unsubstituted mono- and di-$C_{1\text{-}4}$-alkylamino, substituted or unsubstituted-$C_{3\text{-}6}$cycloalkyl-$C_{0\text{-}4}$alkyl, substituted or unsubstituted aryl-$C_{0\text{-}4}$alkyl, and substituted or unsubstituted heterocycle-$C_{0\text{-}4}$alkyl;

V is also selected from the group consisting of $-Q^1\text{-}Q^2$, wherein Q^1 is absent, C(O), N(H), N($C_{1\text{-}4}$-alkyl), C=N(CN), $C=N(SO_2CH_3)$, C=N-COH-$C_{1\text{-}4}$-alkyl, or C=N-COH, and Q^2 is hydrogen or is selected from the group consisting of $C_{1\text{-}4}$-alkyl, O-$C_{1\text{-}4}$-alkyl, NH_2, N(H)-$C_{1\text{-}4}$-alkyl, N($C_{1\text{-}4}$-alkyl)$_2$, SO_2-aryl, SO_2-$C_{1\text{-}4}$-alkyl, $C_{3\text{-}6}$-cycloalkyl-$C_{0\text{-}4}$-alkyl, aryl, heteroaryl and heterocycle, each of which may be independently substituted one or more times with a halogen atom, $C_{1\text{-}4}$-alkyl, $C_{1\text{-}4}$-alkyl substituted by one or more halogen atoms, or $C_{3\text{-}6}$-cycloalkyl;

or R^1 and R^2 may together form a 3, 4, 5, 6 or 7-membered ring that is aromatic or non-aromatic and may contain one or more heteroatoms, wherein the ring may be further

substituted one or more times (or preferably between one and five times);

R^3 is selected from the group consisting of hydrogen, C_{1-4}-alkyl and C_{3-6}-cycloalkylC_{0-4}alkyl;

X is CR^5R^{5a};

R^4 represents 0-4 substituents, each of which is independently selected from hydrogen or from the group consisting of C_{1-4}-alkyl, C_{3-6}-cycloalkyl, aryl, heterocycle and heteroaryl, each of which may be independently substituted one or more times (or preferably between one and five times) with a halogen atom or C_{1-4}-alkyl;

R^5 is selected from hydrogen or oxo or the group consisting of hydroxyl, C_{1-8}-alkyl, C_{2-8}-alkenyl, C_{2-8}-alkynyl, C_{3-8}-cycloalkyl-C_{0-4}-alkyl, aryl-C_{0-4}-alkyl, heterocycle-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl , C_{3-8}-cycloalkyloxy, aryloxy, and heteroaryloxy each of which may be independently substituted one or more times (or preferably between one and five times) with a halogen atom, aryl, trihalomethyl, or C_{1-4}-alkyl;

R^{5a} is selected from the group consisting of hydrogen, hydroxyl, C_{1-8}-alkyl, C_{2-8}-alkenyl, C_{2-8}-alkynyl, C_{3-8}-cycloalkyl-C_{0-4}-alkyl, aryl-C_{0-4}-alkyl and heteroaryl-C_{0-4}-alkyl,

or R^4 and R^5 may together form a fused dimethyl cyclopropyl ring, a fused cyclopentane ring, a fused phenyl ring or a fused pyridyl ring, each of which may be substituted with a halogen atom, aryl, trihalomethyl, or C_{1-4}-alkyl;

or R^5 and R^{5a} may together form a spirocyclic ring having between 3 and 7 ring atoms and having 0, 1, or 2 ring heteroatoms, which is optionally substituted by 0-4 substituents selected from cyano, halogen, hydroxyl, amino, thiol, C_{1-8}-alkyl, C_{2-8}-alkenyl, C_{2-8}-alkynyl, C_{1-8}-alkoxy-C_{0-4}alkyl, C_{1-8}-haloalkyl, C_{2-8}-haloalkenyl, C_{2-8}-haloalkynyl, C_{1-8}-haloalkoxy, C_{1-8}-alkylthio, C_{1-8}-alkylsulfonyl, C_{1-8}-alkylsulfoxy, C_{1-8}-alkanoyl, C_{1-8}-alkoxycarbonyl, C_{3-7}-cycloalkyl-C_{0-4}-alkyl, aryl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, COOH, $C(O)NH_2$, mono- and di-C_{1-4}-alkyl-carboxamide, mono- and di-C_{1-4}-alkyl-amino-C_{0-4}alkyl, SO_3H, SO_2NH_2, and mono-and di-C_{1-4}-alkylsulfonamide, or two of said 0-4 substitutents taken together form a fused or spirocyclic 3 to 7 membered ring having 0, 1 or 2 ring heteroatoms selected from N, O and S, which fused or spirocyclic ring has 0 to 2 independently selected substituents selected from cyano, halogen, hydroxyl, amino, thiol, C_{1-8}-alkyl, C_{2-8}-alkenyl, C_{2-8}-alkynyl, C_{1-8}-alkoxy-C_{0-4}alkyl, C_{1-8}-haloalkyl, C_{2-8}-haloalkenyl, C_{2-8}-haloalkynyl, C_{1-8}-haloalkoxy, C_{1-8}-alkylthio, C_{1-8}-alkylsulfonyl, C_{1-8}-

alkylsulfoxy, C_{1-8}-alkanoyl, C_{1-8}-alkoxycarbonyl, C_{3-7}-cycloalkyl-C_{0-4}-alkyl, aryl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, COOH, $C(O)NH_2$, mono- and di-C_{1-4}-alkyl-carboxamide, mono- and di-C_{1-4}-alkyl-amino-C_{0-4}alkyl, SO_3H, SO_2NH_2, and mono-and di-C_{1-4}-alkylsulfonamide;

R^6 and R^7 are each, independently, selected from the group consisting of hydroxy, amino, C_{1-4}alkyl, C_{1-4}alkoxy, and mono- and di-C_{1-4}alkylamino, and C_{3-6}cycloalkylC_{0-4}alkyl;

R^8, R^9, R^{10}, R^{11} and R^{12} are each, independently, selected from the group consisting of hydrogen, C_{1-4}-alkyl and C_{3-6}-cycloalkylC_{0-4}alkyl;

or R^6 and R^7 may together form a spirocyclic ring having between 3 and 7 ring atoms and having 0, 1, or 2 ring heteroatoms, which is optionally substituted by 0-4 substituents selected from cyano, halogen, hydroxyl, amino, thiol, C_{1-8}-alkyl, C_{2-8}-alkenyl, C_{2-8}-alkynyl, C_{1-8}-alkoxy-C_{0-4}alkyl, C_{1-8}-haloalkyl, C_{2-8}-haloalkenyl, C_{2-8}-haloalkynyl, C_{1-8}-haloalkoxy, C_{1-8}-alkylthio, C_{1-8}-alkylsulfonyl, C_{1-8}-alkylsulfoxy, C_{1-8}-alkanoyl, C_{1-8}-alkoxycarbonyl, C_{3-7}-cycloalkyl-C_{0-4}-alkyl, aryl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, COOH, $C(O)NH_2$, mono- and di-C_{1-4}-alkyl-carboxamide, mono- and di-C_{1-4}-alkyl-amino-C_{0-4}alkyl, SO_3H, SO_2NH_2, and mono-and di-C_{1-4}-alkylsulfonamide, or two substituents taken together form a fused or spirocyclic 3 to 7 membered ring having 0, 1 or 2 ring heteroatoms selected from N, O and S, which fused or spirocyclic ring has 0 to 2 independently selected substituents selected from halogen, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, mono- and di-C_{1-4}-alkylamino, mono- and di-C_{1-4}-alkyl-carboxamide, C_{1-4}-alkoxycarbonyl, and phenyl;

wherein at least one of R^5 and R^{5a} or R^6 and R^7, taken in combination, form a spirocyclic ring having at least one spirocyclic ring substituent;

or R^3 and W may together form a 3, 4, 5, 6 or 7-membered ring that is aromatic or non-aromatic and may contain one or more heteroatoms, wherein the ring may be further substituted one or more times (or preferably between one and five times); and

or when y is 0, R^{10} and V may together form a 3, 4, 5, 6 or 7-membered ring that is aromatic or non-aromatic and may contain one or more heteroatoms, wherein the ring may be further substituted one or more times (or preferably between one and five times).

In one embodiment of fomula I, y is 0 or 1;

n is 0 or 1;

R^{14} is C(O) or SO_2

R^1 is selected from the group consisting of H and C_{1-4}-alkyl;

R^2 is selected from the group consisting of C_{1-4}-alkyl, $C(O)C_{1-4}$-alkyl, $C(O)OC_{1-4}$-alkyl, and C_{3-6}-cycloalkylC_{0-4}alkyl;

or R^1 and R^2 together form a cyclopropane ring;

W is also selected from the group consisting of C(O)-C(O)H, $C(=N\text{-}O\text{-}R_{24})$-C(O)-amine, C(O)-C(O)-amine and C(O)-$[C(O)]_a$-heterocycle, wherein the heterocycle may be independently substituted one or more times (or preferably between one and five times) with aryl, C_{1-4}-alkyl, C_{1-4}-alkyl substituted by one or more halogen atoms, and C_{3-6}-cycloalkyl, wherein a is 0 or 1, wherein each R_{24} is independently selected from hydrogen or from the group consisting of C_{1-4}-alkyl, C_{3-6}-cycloalkylC_{0-4}alkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocycle, each of which may be independently substituted one or more times (or preferably between one and five times) with a halogen atom or C_{1-4}-alkyl;

R^3 is selected from the group consisting of H and C_{1-4}-alkyl;

X is O, NR^5 or CR^5R^{5a};

R^4 is selected from hydrogen or from the group consisting of C_{1-4}-alkyl, C_{3-6}-cycloalkyl, aryl, heterocycle and heteroaryl, each of which may be independently substituted one or more times (or preferably between one and five times) with a halogen atom or C_{1-4}-alkyl;

R^5 is selected from hydrogen or oxo or the group consisting of hydroxyl, C_{1-8}-alkyl, C_{2-8}-alkenyl, C_{2-8}-alkynyl, C_{3-8}-cycloalkyl-C_{0-4}-alkyl, aryl-C_{0-4}-alkyl, heterocycle-C_{0-4}-alkyl and heteroaryl-C_{0-4}-alkyl, each of which may be independently substituted one or more times (or preferably between one and five times) with a halogen atom, aryl, trihalomethyl, or C_{1-4}-alkyl;

R^{5a} is selected from the group consisting of hydrogen, hydroxyl, C_{1-8}-alkyl, C_{2-8}-alkenyl, C_{2-8}-alkynyl, C_{3-8}-cycloalkyl-C_{0-4}-alkyl, aryl-C_{0-4}-alkyl and heteroaryl-C_{0-4}-alkyl,

or R^4 and R^5 may together form a fused dimethyl cyclopropyl ring, a fused cyclopentane ring, a fused phenyl ring or a fused pyridyl ring, each of which may be

substituted with a halogen atom, aryl, trihalomethyl, or C_{1-4}-alkyl;

or R^5 and R^{5a} may together form a spirocarbocyclic saturated ring having between 3 and 6 carbon ring atoms which is optionally substituted by 0-2 substituents selected from halogen, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{1-6}-alkoxy, C_{3-7}-cycloalkyl-C_{0-4}-alkyl, phenyl-C_{0-4}-alkyl, naphthyl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, or two substituents taken together form a fused or spirocyclic 3 to 7 membered carbocyclic ring, each of which is substituted with 0-3 independently selected halogen atoms or C_{1-4}-alkyl groups;

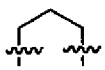
R^8, R^{10} and R^{11} are each, independently, selected from the group consisting of H and C_{1-4}-alkyl;

R^6, R^7 and R^{13} is H;

R^9 and R^{12} are each, independently, selected from the group consisting of hydrogen, C_{1-4}-alkyl and C_{3-6}-cycloalkyl; and

V is also selected from the group consisting of $-Q^1$-Q^2, wherein Q^1 is absent, C(O), N(H), N(C_{1-4}-alkyl), C=N(CN), C=N(SO_2CH_3), C=N-COH-C_{1-4}-alkyl, or C=N-COH, and Q^2 is hydrogen or is selected from the group consisting of C_{1-4}-alkyl, O-C_{1-4}-alkyl, NH_2, N(H)-C_{1-4}-alkyl, N(C_{1-4}-alkyl)$_2$, SO_2-aryl, SO_2-C_{1-4}-alkyl, C_{3-6}-cycloalkyl-C_{0-4}-alkyl, aryl, heteroaryl and heterocycle, each of which may be independently substituted one or more times with a halogen atom, C_{1-4}-alkyl, C_{1-4}-alkyl substituted by one or more halogen atoms, or C_{3-6}-cycloalkyl;

or R^3 and W can together form a 6-membered ring of the formula II:



II

wherein formula II may be further substituted;

or when y is 0, R^{10} and V can form a cyclopropyl ring that may be further substituted by an amide group.

In another embodiment of Formula I or Formula III, R^{14} is C(O).

In yet another embodiment of Formula I or Formula III, y is 0, and R^{10} and V form a cyclopropyl ring that is substituted with C(O)N(H)-pyrazine.

In still another embodiment of Formula I, wherein R^4, R^6 and R^7 are hydrogen, and R^5 is aryl-C_{0-3}-alkyl, -O-heteroaryl, or heteroaryl-C_{0-3}-alkyl, wherein aryl and heteroaryl may be independently substituted one or more times (or preferably between

one and five times) with a halogen atom, aryl, trihalomethyl, C_{3-6}-cycloalkyl or C_{1-4}-alkyl.

In one embodiment of Formula I, n is 1, and R^4 and R^5 together form the following fused ring systems:

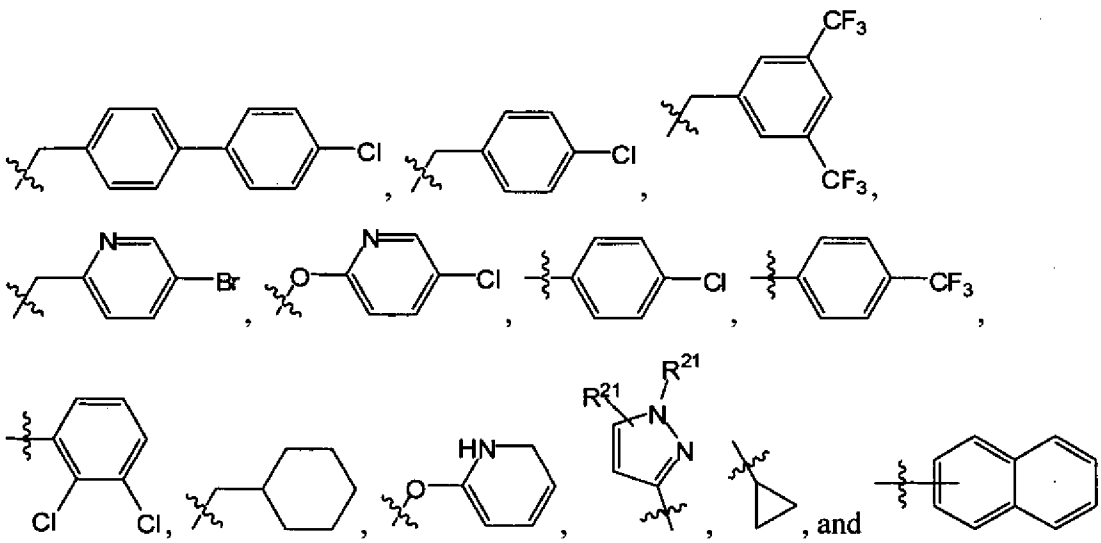


wherein R^{18} is selected from the group consisting of hydrogen, a halogen atom, aryl, trihalomethyl, and C_{1-4}-alkyl.

In another embodiment of Formula I, R^5 is selected from the group consisting of piperidine, phenyl, -O-pyridinyl and CH_2-pyridinyl, wherein the phenyl and pyridinyl groups may be independently substituted one or more times (or preferably between one and five times) with a halogen atom or C_{1-4}-alkyl.

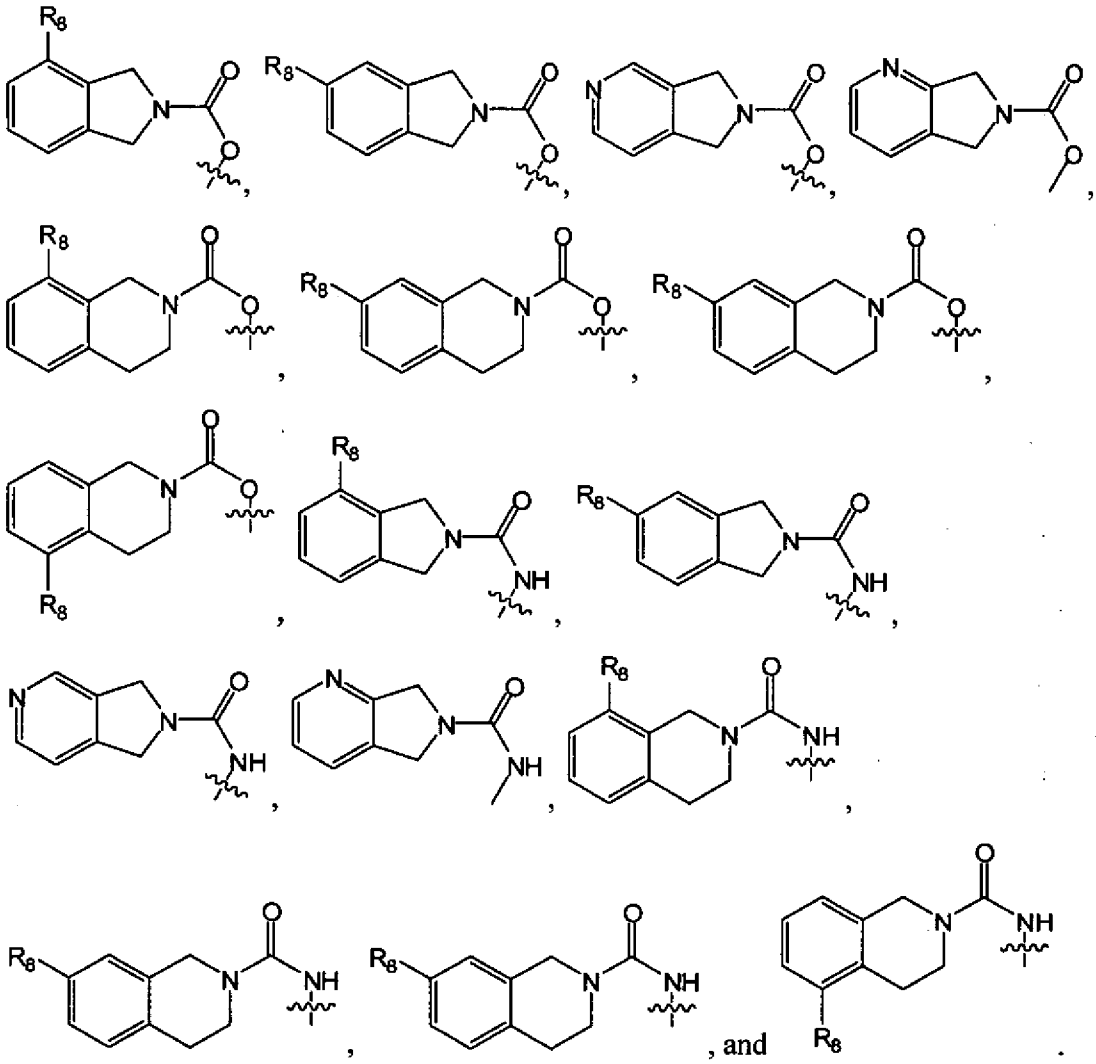
In yet another embodiment of Formula I, R^5 is 5-chloro-pyridin-2-yl.

In still another embodiment of Formula I, R^5 is selected from the group consisting of

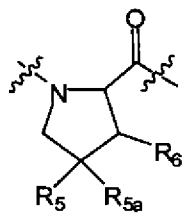


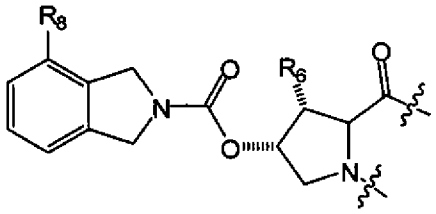
wherein R^{21} is independently selected from the group consisting of C_{1-4}-alkyl and aryl.

Yet other compounds of Formula I or Formula III include those compounds in which X is CR_{5a}, R_{5a} is hydrogen or methyl, and R_5 is a residue selected from the group consisting of:



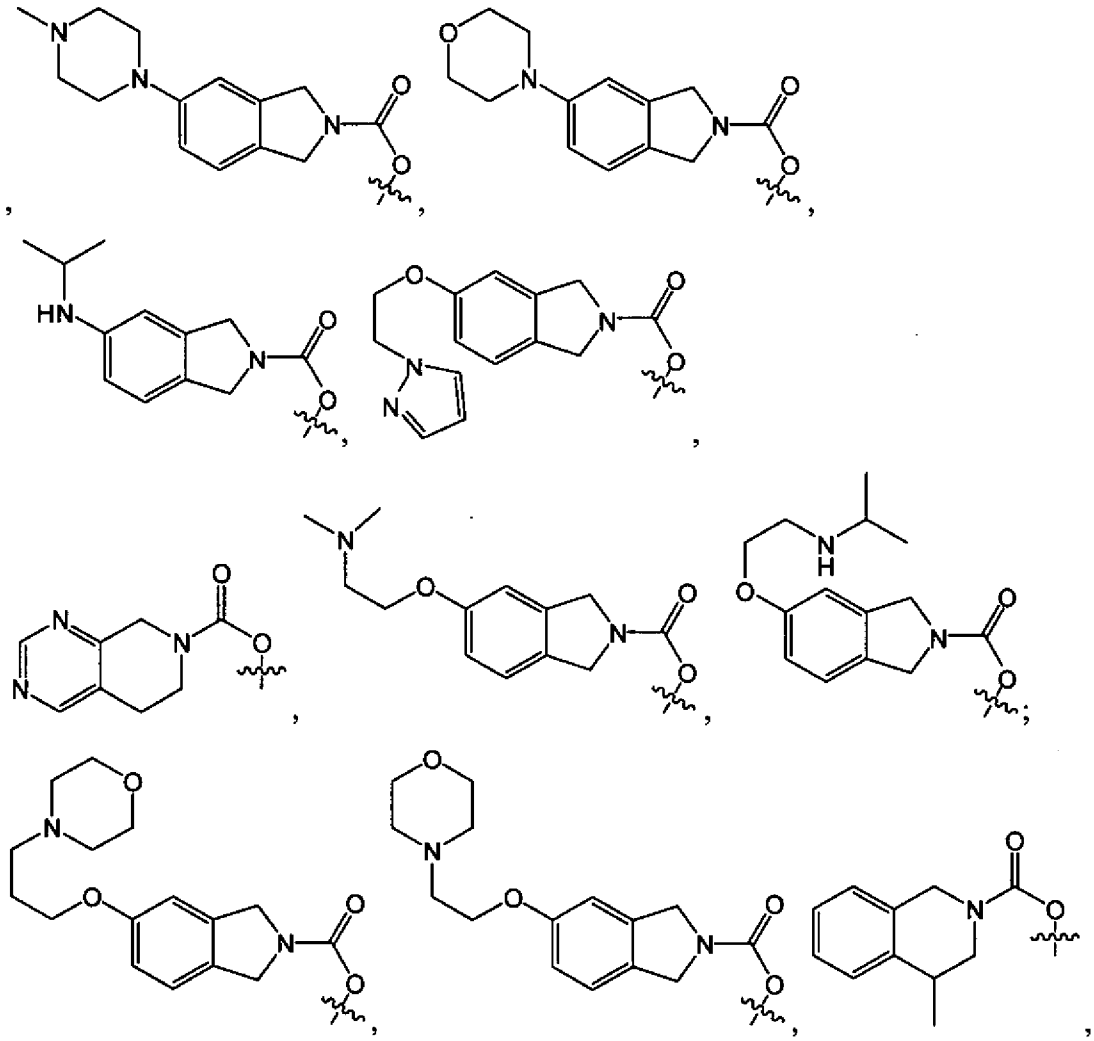
wherein R_8 is selected from hydrogen, methyl, ethyl, mono-, di-, or tri-fluoromethyl, mono-, di-, or tri-fluoromethoxy, fluoro, and chloro.

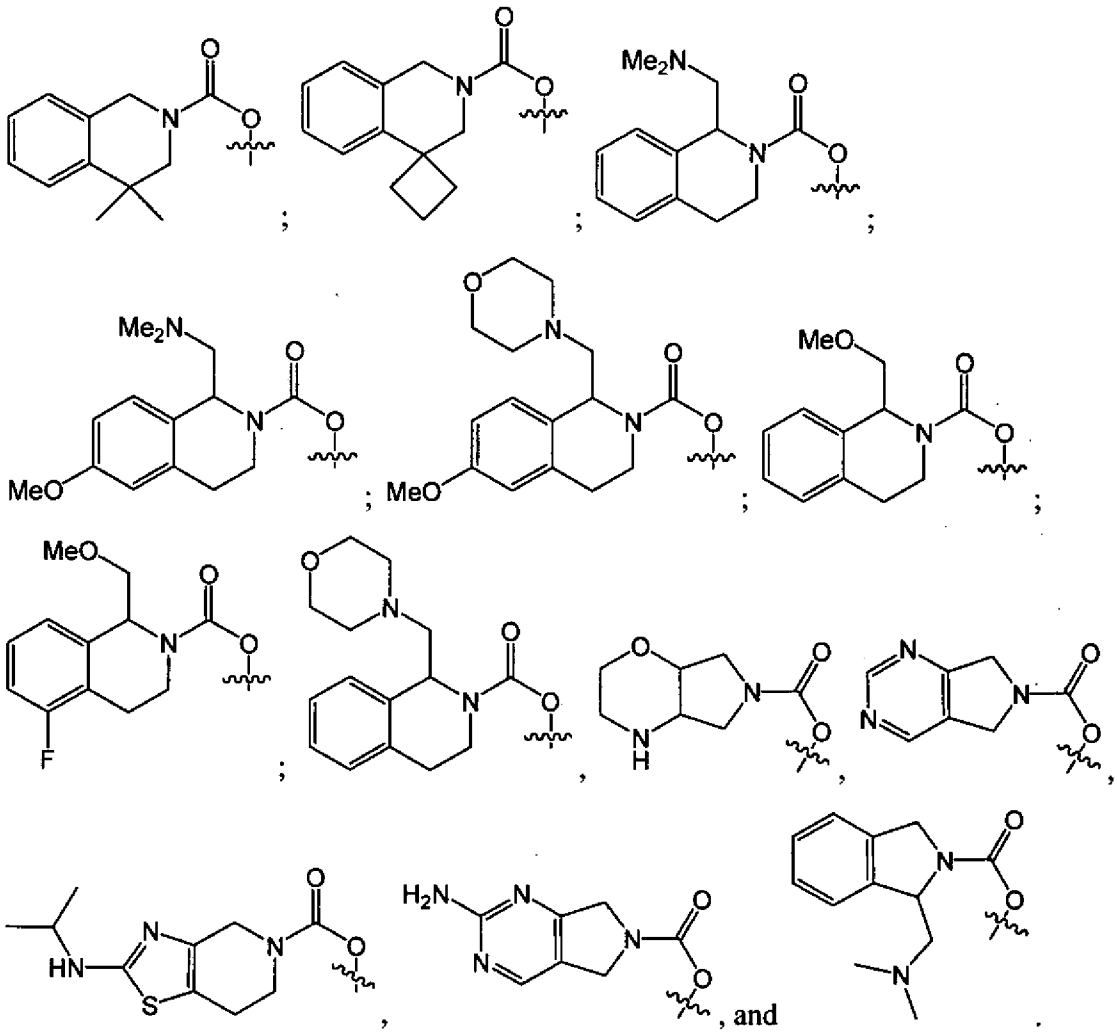
In still other compounds of Formula I or Formula III include those compounds in which the residue  is a residue of the formula:



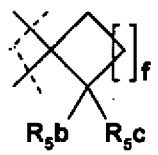
wherein wherein R_6 is hydrogen, methyl, ethyl, and mono-, di-, and tri-fluoromethyl; R_8 is selected from R_8 is selected from hydrogen, methyl, ethyl, mono-, di-, or tri-fluoromethyl, mono-, di-, or tri-fluoromethoxy, fluoro, and chloro.

Still other compounds of Formula I or Formula III include those compounds in which X is CR_{5a}, R_{5a} is hydrogen or methyl, and R_5 is a residue selected from the group consisting of:





In still other embodiments, compounds of Formula I include those compounds in which CR^5R^{5a}, when taken in combination, form a spirocyclic 3 to 6 member carbocyclic ring. Certain spirocyclic rings include groups of the formula:



wherein

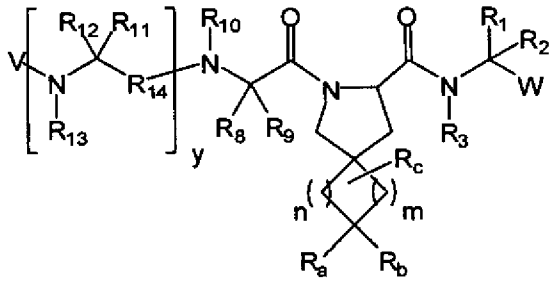
f is 0, 1, 2, 3, 4 or 5;

R_{5b} and R_{5c} are independently selected from hydrogen halogen, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{1-6}-alkoxy, C_{3-7}-cycloalkyl-C_{0-4}-alkyl, phenyl-C_{0-4}-alkyl, naphthyl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, or two substituents taken together form a fused or spirocyclic

3 to 7 membered carbocyclic ring, each of which is substituted with 0-3 independently selected halogen atoms or C_{1-4}-alkyl groups.

In still other embodiments, compounds of Formula I include those compounds in which X is CR^5R^{5a}, R^4 is hydrogen, and R^5 and R^{5a} taken in combination form a 3 to 6 member spirocyclic carbocycle substituted with 0-2 substituents selected from halogen, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{1-6}-alkoxy, C_{3-7}-cycloalkyl-C_{0-4}-alkyl, phenyl-C_{0-4}-alkyl, naphthyl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, or two substituents taken together form a fused or spirocyclic 3 to 7 membered carbocyclic ring, each of which is substituted with 0-3 independently selected halogen atoms or C_{1-4}-alkyl groups.

Certain compounds of Formula I include those compounds of the formula:



wherein

m and n are 0 or 1 such that a sum of m and n equals 1 or 2;

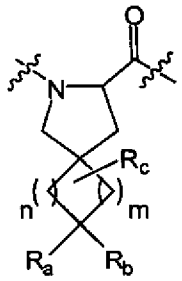
R_a is hydrogen, C_{1-4}alkyl, or phenyl;

R_b is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy-C_{0-4}alkyl, mono- and di-C_{1-4}alkylaminoC_{0-4}alkyl, mono- and di-C_{1-4}alkyl carboxamide, C_{1-4}alkanoyl, C_{1-4}alkoxycarbonyl, or phenyl

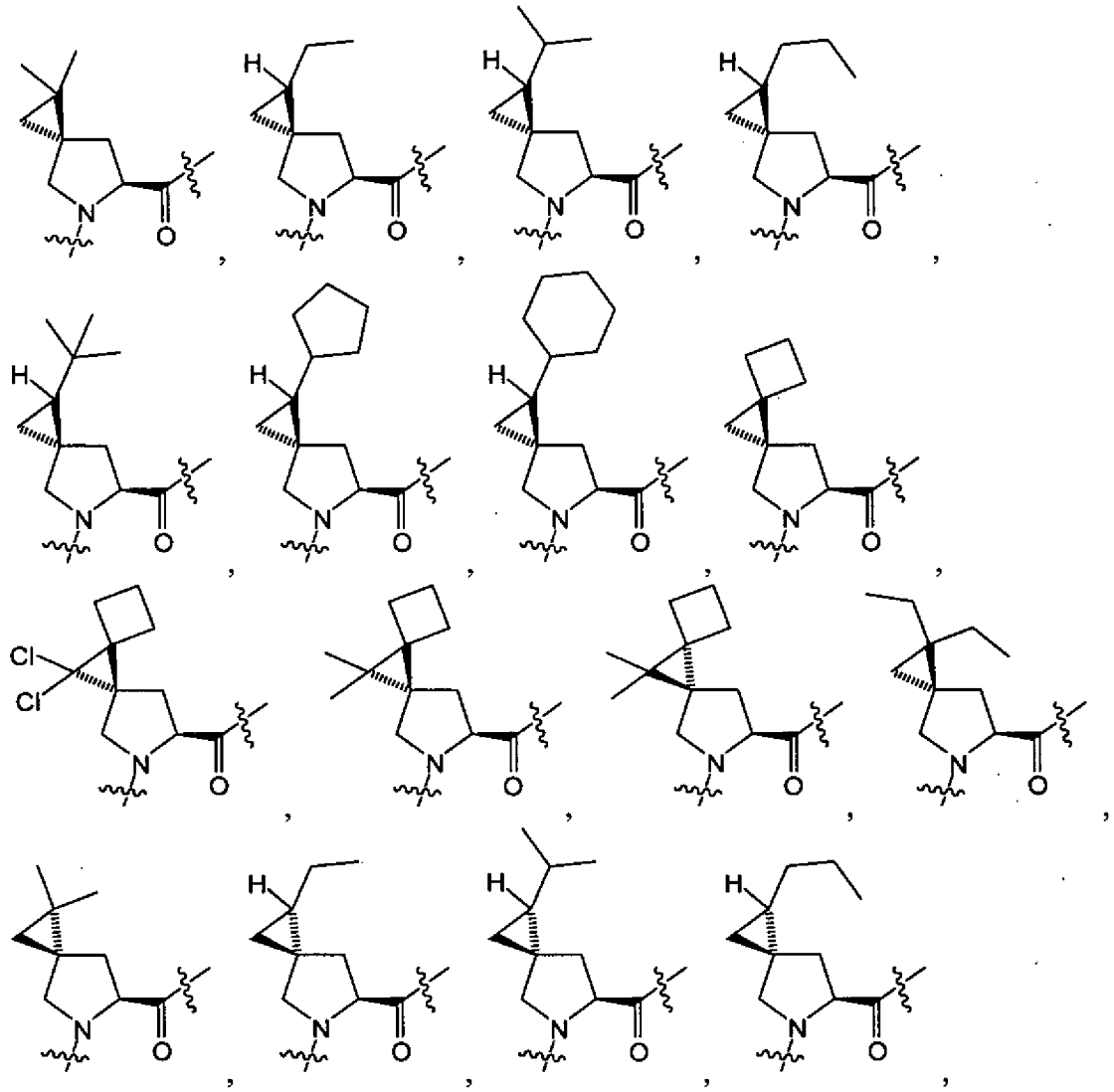
or R_a and R_b taken together form a fused or spirocyclic 3 to 6 membered ring having 0, 1 or 2 ring heteroatoms selected from N, O and S, which fused or spirocyclic ring has 0 to 2 independently selected substituents selected from halogen, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, and phenyl; and

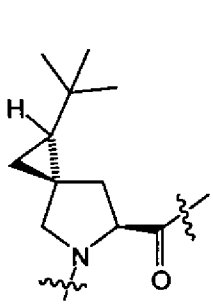
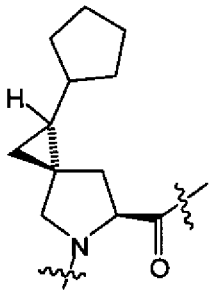
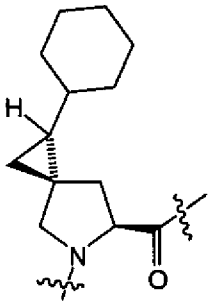
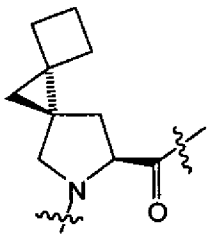
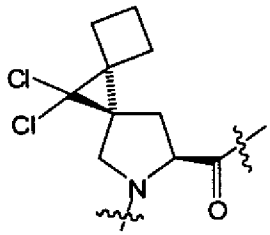
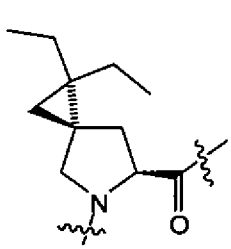
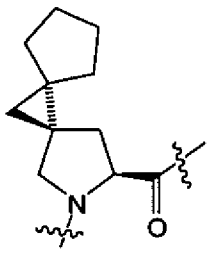
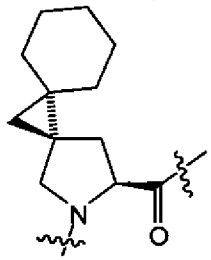
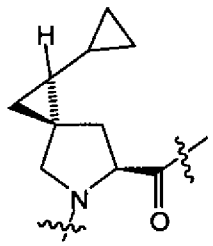
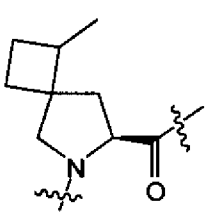
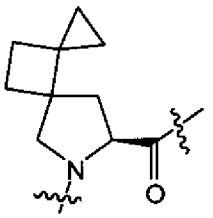
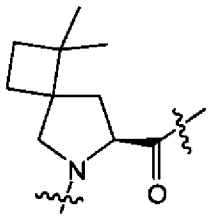
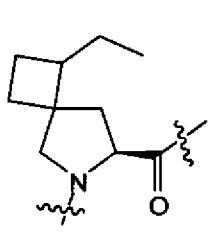
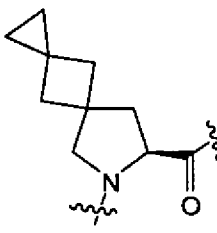
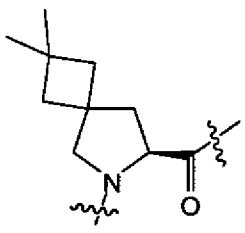
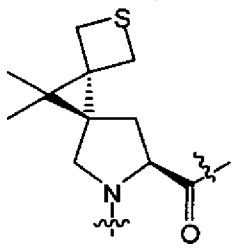
R_c represents 0 to 4 substituents which are independently selected at each occurrence of R_c from the group consisting of halogen, C_{1-4}alkyl, and phenyl, or two *geminal* R_c substituents, taken in combination form a 3 to 6 member spirocyclic ring.

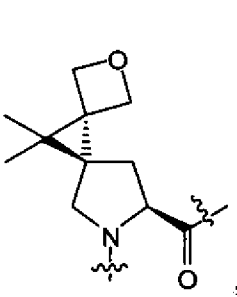
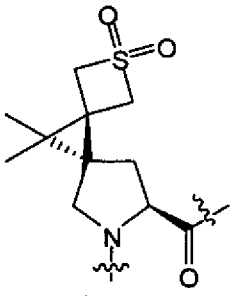
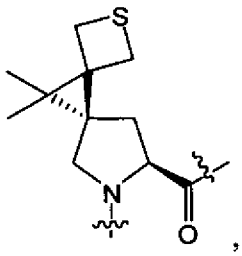
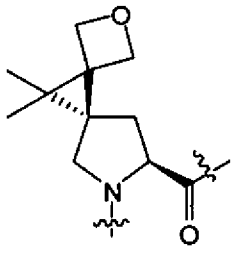
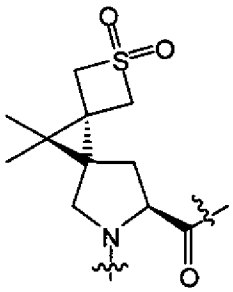
In certain other embodiments, compounds of Formula I include those compounds in which the divalent residue:



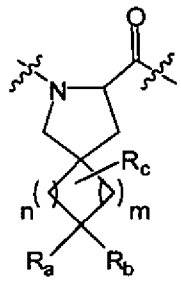
is selected from the group consisting of:



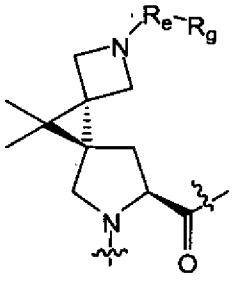
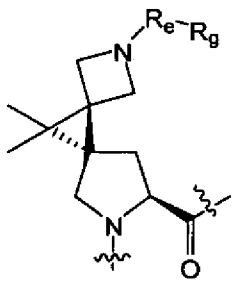


















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,

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and

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In certain other embodiments, compounds of Formula I include those compounds in which the divalent residue:



is selected from the group consisting of:

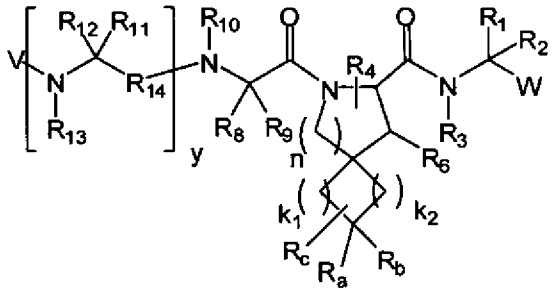

and


wherein R_e is absent, C(O), or $S(O)_2$; and R_g is selected hydrogen or selected from the group consisting of $C_{1\text{-}6}$alkyl, aryl$C_{0\text{-}4}$alkyl, heteroaryl$C_{0\text{-}4}$alkyl, heterocyclyl$C_{0\text{-}4}$alkyl, and $C_{3\text{-}7}$cycloalkyl$C_{0\text{-}4}$alkyl, each of which is substituted with 0 to 4 independently selected substituents selected from the group consisting of cyano, halogen, hydroxyl, amino, thiol, $C_{1\text{-}8}$-alkyl, $C_{2\text{-}8}$-alkenyl, $C_{2\text{-}8}$-alkynyl, $C_{1\text{-}8}$-alkoxy-$C_{0\text{-}4}$alkyl, $C_{1\text{-}8}$-haloalkyl, $C_{2\text{-}8}$-haloalkenyl, $C_{2\text{-}8}$-haloalkynyl, $C_{1\text{-}8}$-haloalkoxy, $C_{1\text{-}8}$-alkylthio, $C_{1\text{-}8}$-alkylsulfonyl,

C_{1-8}-alkylsulfoxy, C_{1-8}-alkanoyl, C_{1-8}-alkoxycarbonyl, C_{3-7}-cycloalkyl-C_{0-4}-alkyl, aryl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, COOH, $C(O)NH_2$, mono- and di-C_{1-4}-alkyl-carboxamide, mono- and di-C_{1-4}-alkyl-amino-C_{0-4}alkyl, SO_3H, SO_2NH_2, and mono-and di-C_{1-4}-alkylsulfonamide.

In certain embodiments, compounds of Formula III include those compounds in which R^5 and R^{5a}, taken in combination, form a spirocyclic ring having between 3 and 7 ring atoms and having 0, 1, or 2 ring heteroatoms, which spirocyclic ring is substituted with a spirocyclic 3 to 7 membered ring having 0, 1 or 2 ring heteroatoms selected from N, O and S, and wherein each of the spirocyclic rings has 0 to 2 independently selected substituents selected from cyano, halogen, hydroxyl, amino, thiol, C_{1-8}-alkyl, C_{2-8}-alkenyl, C_{2-8}-alkynyl, C_{1-8}-alkoxy-C_{0-4}alkyl, C_{1-8}-haloalkyl, C_{2-8}-haloalkenyl, C_{2-8}-haloalkynyl, C_{1-8}-haloalkoxy, C_{1-8}-alkylthio, C_{1-8}-alkylsulfonyl, C_{1-8}-alkylsulfoxy, C_{1-8}-alkanoyl, C_{1-8}-alkoxycarbonyl, C_{3-7}-cycloalkyl-C_{0-4}-alkyl, aryl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, COOH, $C(O)NH_2$, mono- and di-C_{1-4}-alkyl-carboxamide, mono- and di-C_{1-4}-alkyl-amino-C_{0-4}alkyl, SO_3H, SO_2NH_2, and mono-and di-C_{1-4}-alkylsulfonamide.

In another embodiment, compounds of Formula III include compounds of the formula:



wherein

k_1 and k_2 are 0 or 1 such that a sum of k_1 and k_2 equals 1 or 2;

R_a and R_b taken together form a spirocyclic 3 to 6 membered ring having 0, 1 or 2 ring heteroatoms selected from N, O and S, which fused or spirocyclic ring has 0 to 2 independently selected substituents selected from halogen, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, and phenyl;

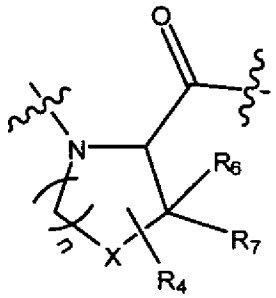
R_c represents 0 to 2 substituents which are independently selected at each occurrence of

R_c from the group consisting of halogen, C_{1-4}alkyl, and phenyl, or two *geminal* R_c substituents, taken in combination form a 3 to 6 member spirocyclic ring;

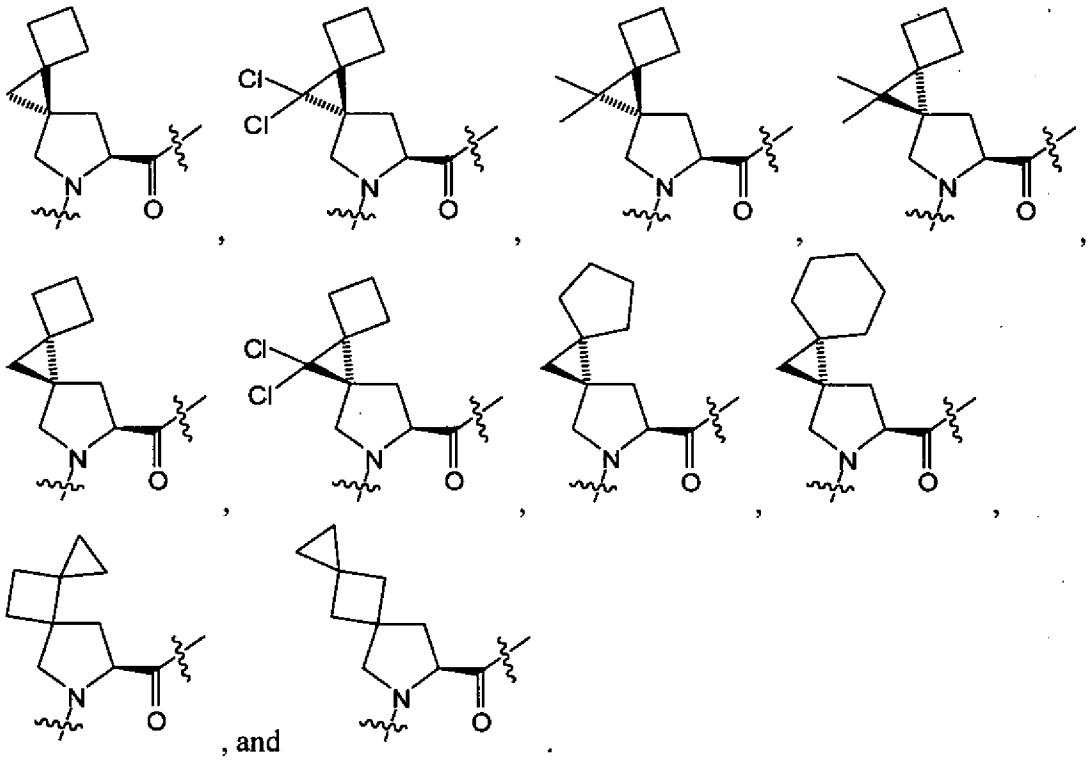
R_4 represents 0, 1, or 2 substituents each of which is independently selected from H and C_{1-4}-alkyl; and

R_6 is hydrogen or C_{1-4}alkyl.

In still another aspect, compounds of Formula III include those compounds in which the divalent residue:



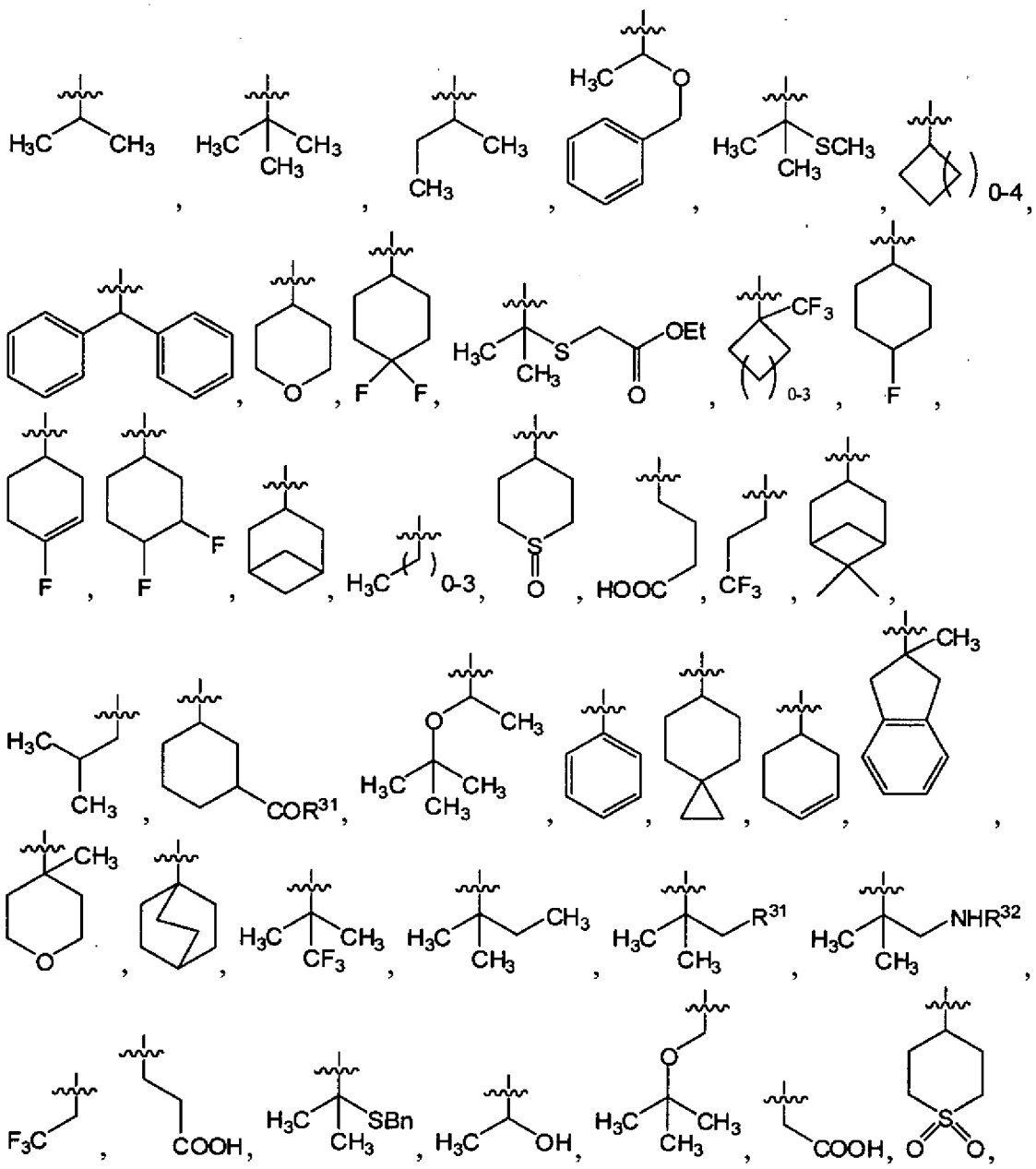
is selected from the group consisting of:

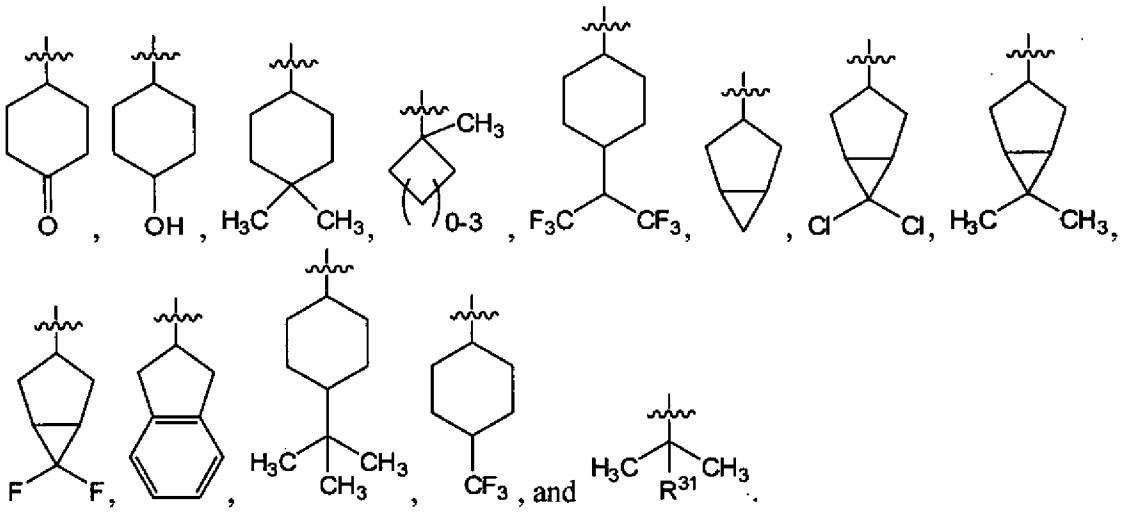


, and

In yet other embodiments, compounds having the structure of Formula I or

Formula III have substituents at R^6, R^9, R^{11}, and R^{12} which are each, independently, selected from the group consisting of:

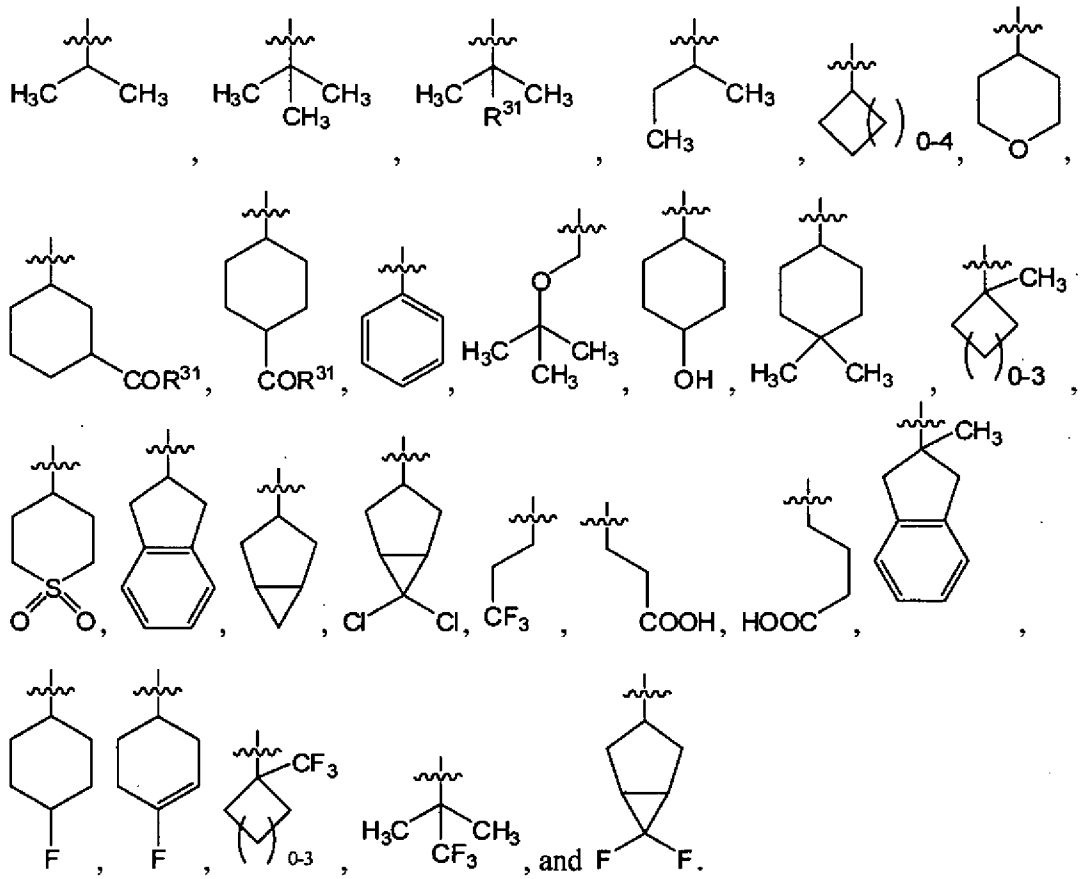




wherein R^{31} is hydroxy or C_{1-6}alkoxy; and

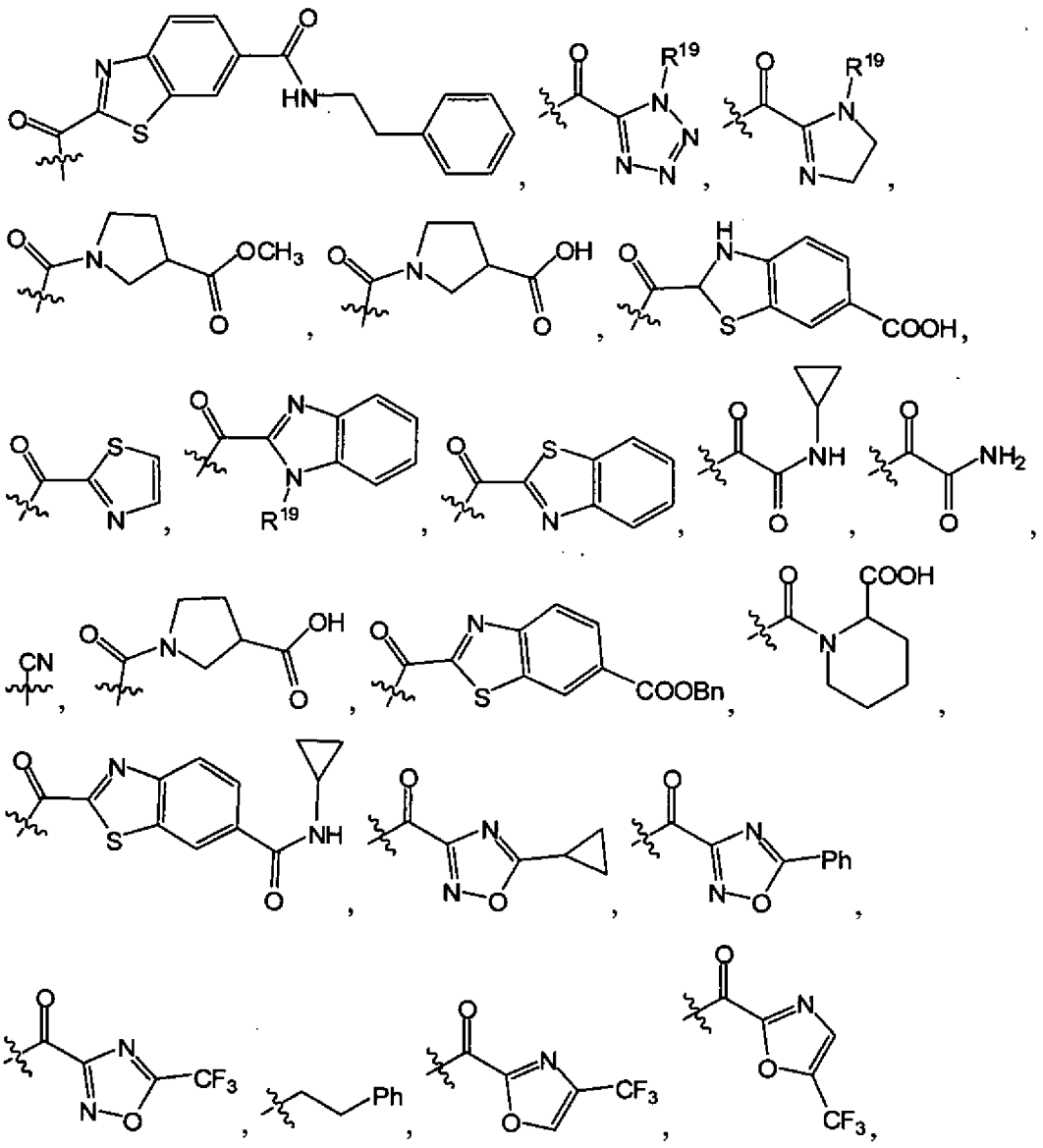
R^{32} is hydrogen, acetyl, C(O)O^{t}Bu, or C(O)N(H)^{t}Bu.

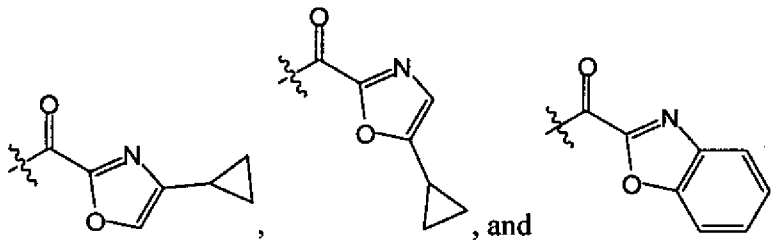
In certain other embodiments, compounds having the structure of Formula I or Formula III, are substituted at R^3 with a substituent selected from the group consisting of:



In one embodiment of Formula I or Formula III, W is selected from the group consisting of C(O)-C(O)NH_2, C(O)-C(O)N(H)-cyclopropyl, C(O)-benzothiazole, C(O)-benzoimidazole, C(O)-oxazole, C(O)-imidazole, and C(O)-oxadiazole, wherein the benzothiazole, benzoimidazole, oxazole and oxadiazole groups may be independently substituted one or more times (or preferably between one and five times) with a halogen atom, aryl, trihalomethyl, C_{3-6}-cycloalkyl or C_{1-4}-alkyl.

In another embodiment of Formula I or Formula III, W is selected from the group consisting of





wherein R^{19} is selected from the group consisting of hydrogen, aryl, trihalomethyl, and C_{1-4}-alkyl.

In yet another embodiment of Formula I or Formula III, R^2 is selected from the group consisting of propyl and $(CH_2)_2$-cyclobutyl.

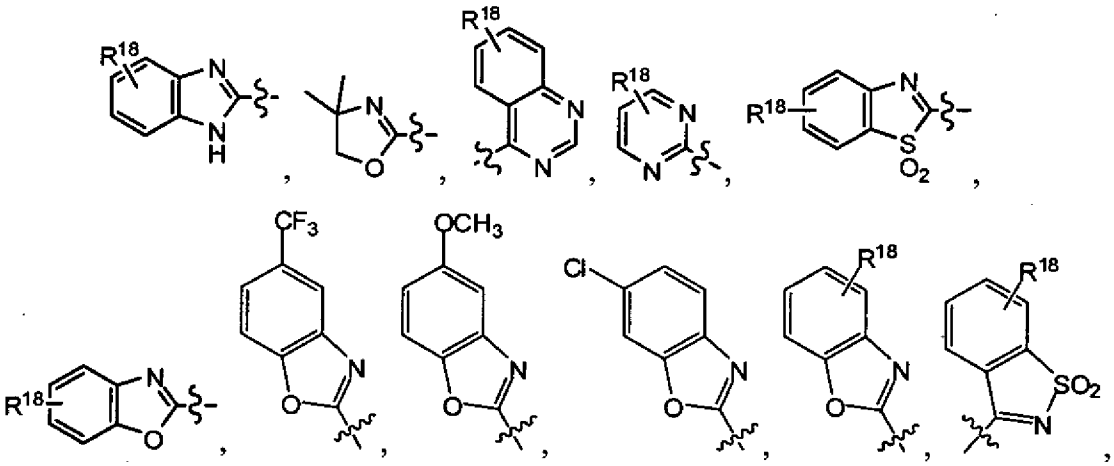
In still another embodiment of Formula I or Formula III, R^{11} is H and R^{12} is C_{3-6}-cycloalkyl.

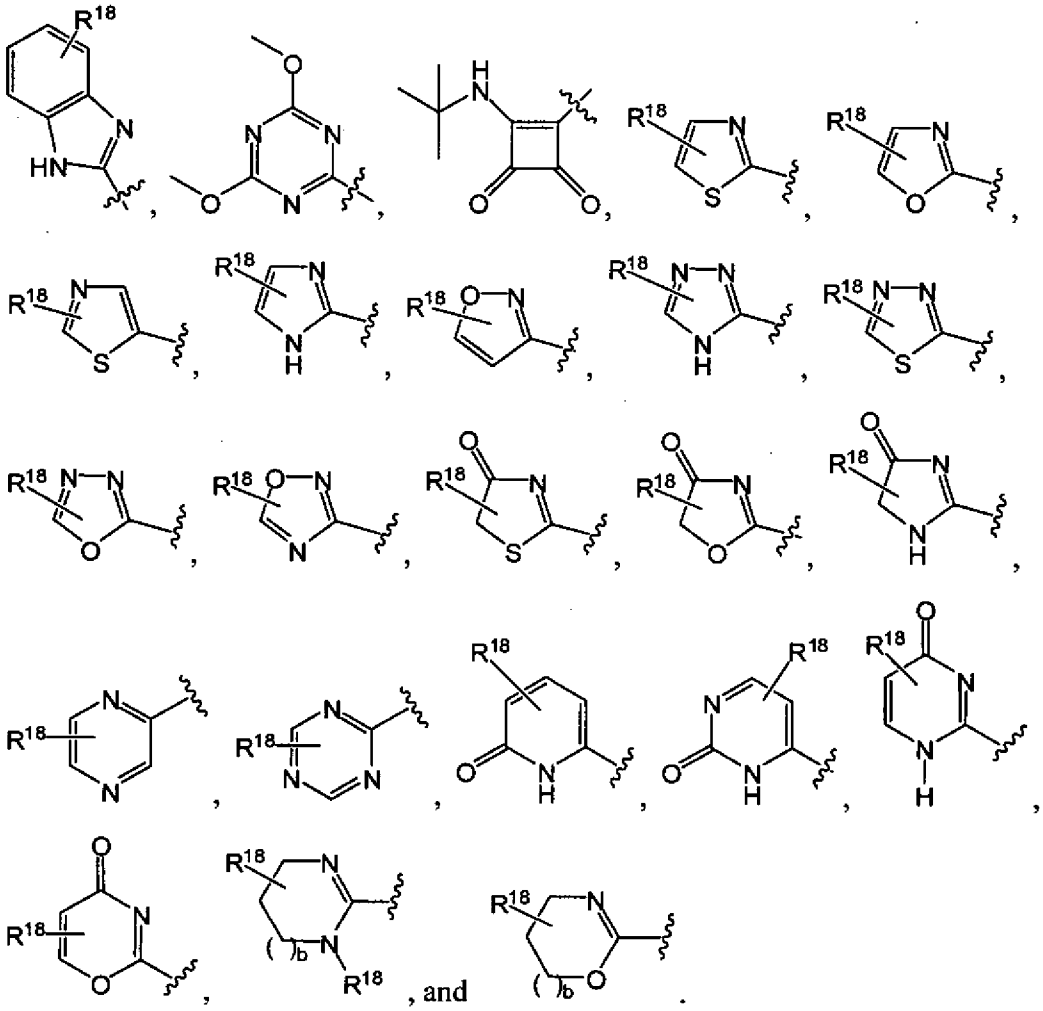
In one embodiment of Formula I or Formula III, R^{12} is cyclohexyl.

In another embodiment of Formula I or Formula III, V is selected from the group consisting of C(O)-N(H)-*t*-butyl.

In yet another embodiment of Formula I or Formula III, V is $C(O)-R^{20}$, wherein R^{20} is selected from the group consisting of C_{3-6}-cycloalkyl, phenyl, pyrazine, benzoxazole, 4,4-dimethyl-4,5-dihydro-oxazole, benzoimidazole, pyrimidine, benzothiazole 1,1-dioxide and quinazoline, each of which may be further independently substituted with a halogen atom, CF_3, C_{1-4}-alkyl or C_{3-6}-cycloalkyl.

In still another embodiment of Formula I or Formula III, V is R^{20} or $C(O)-R^{20}$, wherein R^{20} is selected from the group consisting of

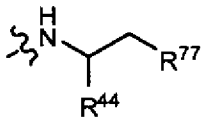




wherein b is 0, 1, or 2; and R_{18} is selected from the group consisting of hydrogen, a halogen atom, aryl, trihalomethyl, and C_{1-4}-alkyl.

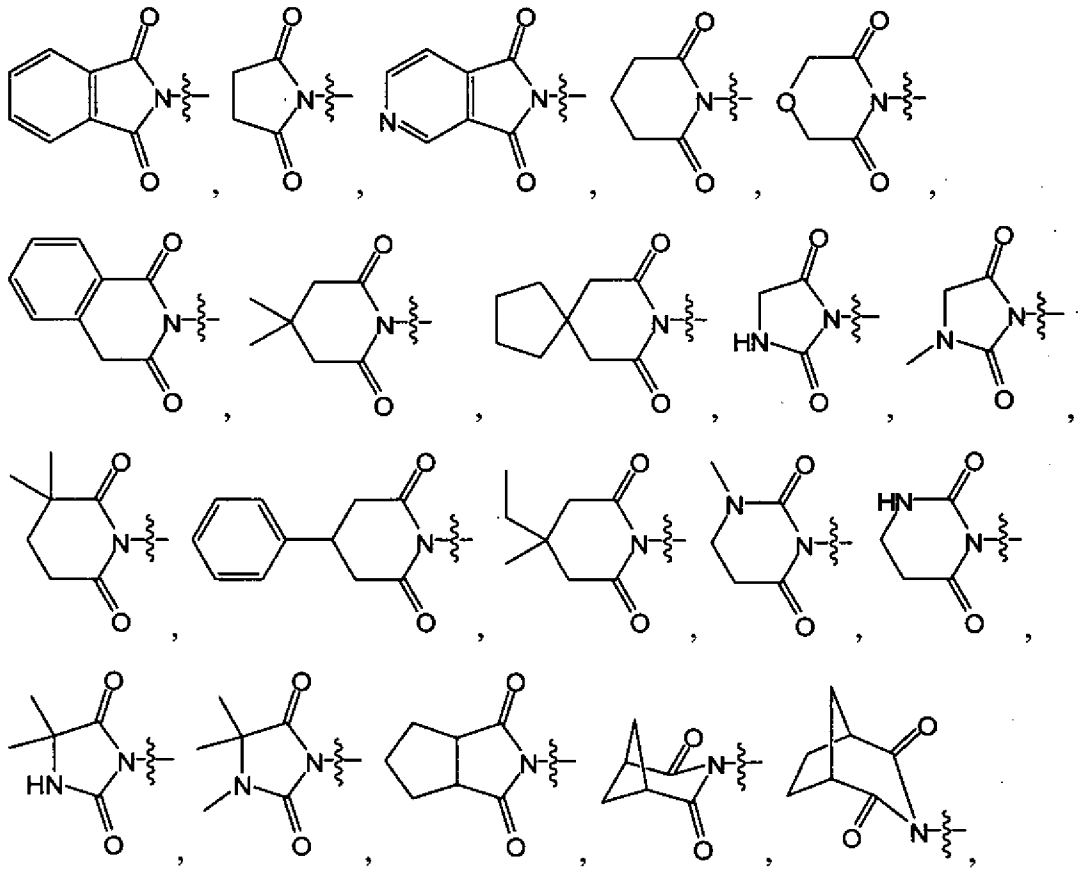
In another embodiment of Formula I or Formula III, V is selected from the group consisting of C_{3-6}-cycloalkyl, phenyl, pyrazine, benzooxazole, 4,4-dimethyl-4,5-dihydro-oxazole, benzoimidazole, pyrimidine, benzothiazole 1,1-dioxide and quinazoline, each of which may be further independently substituted with a halogen atom, CF_3, C_{1-4}-alkyl or C_{3-6}-cycloalkyl.

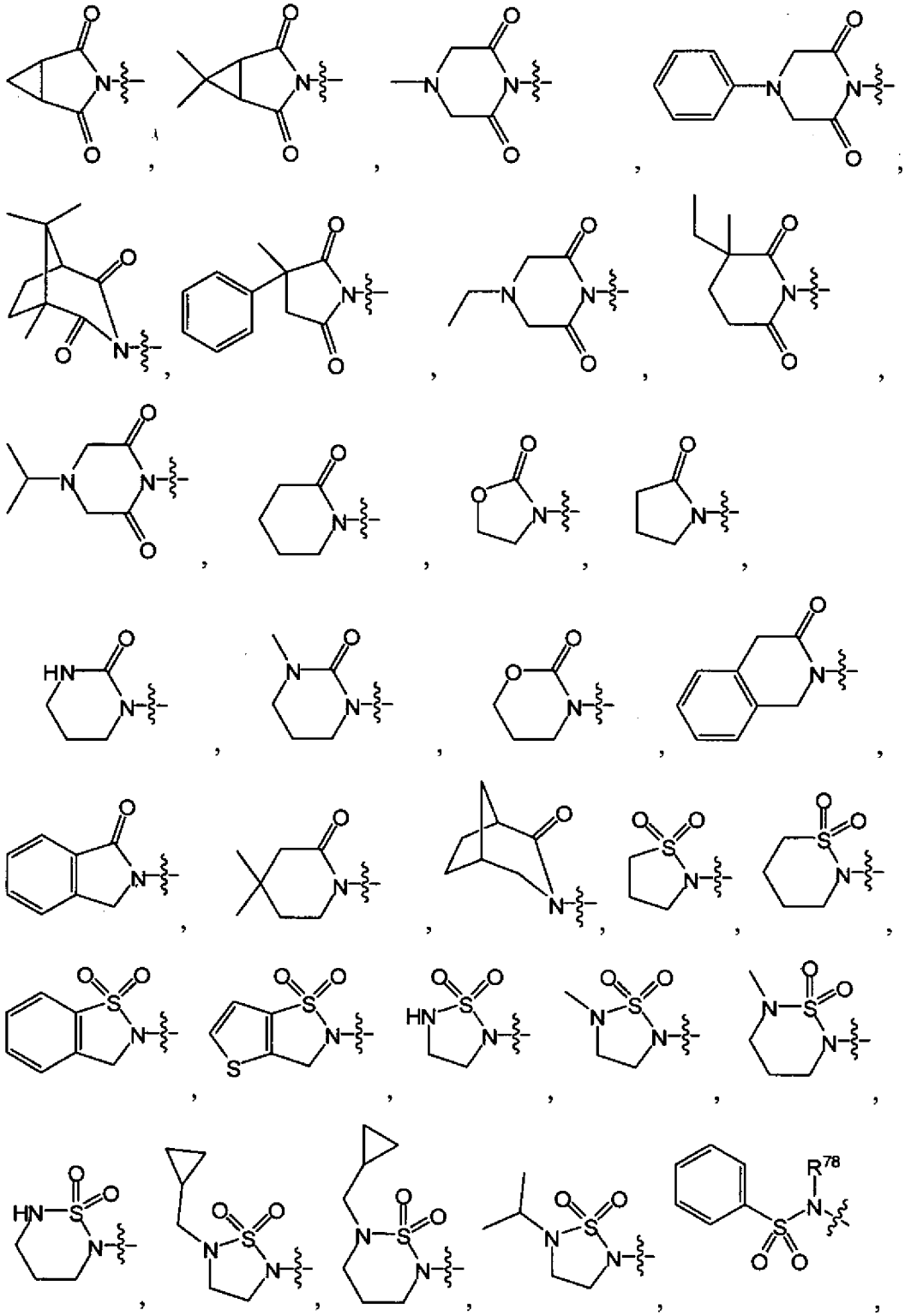
In certain embodiments, compounds of Formula I or Formula III comprise a V group selected from residues having the formula $-C(O)-R^{20}$, wherein R^{20} is a residue of the formula (i):

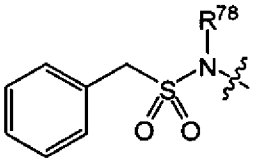
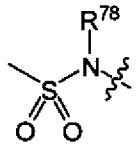
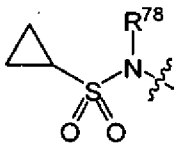
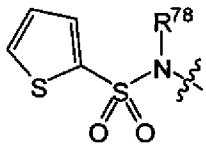
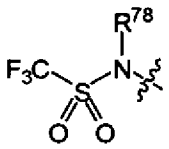
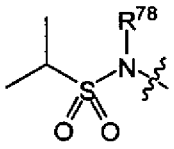
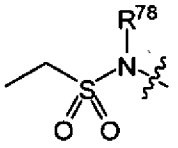
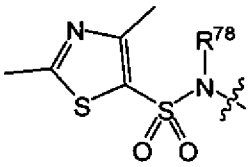
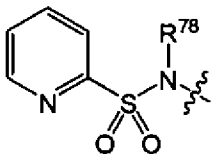
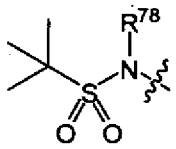
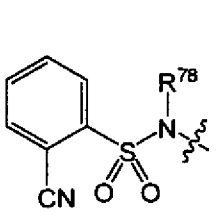
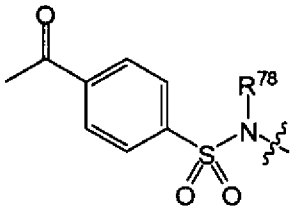
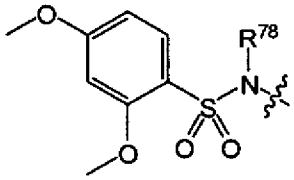
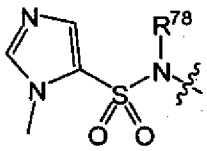
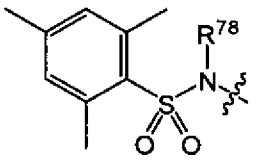
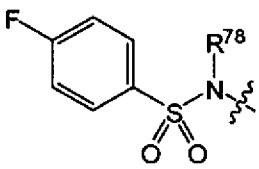
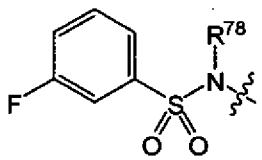
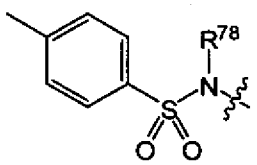
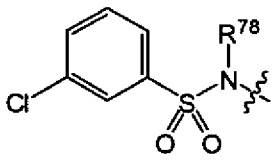
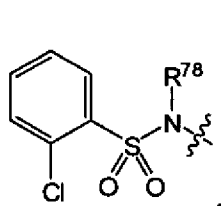
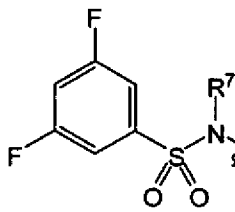


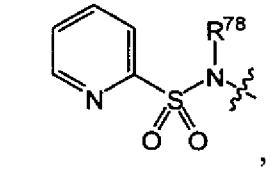
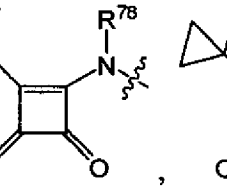
wherein R^{44} is selected from the group consisting of: *tert*-butyl, isopropyl, cyclohexyl, spirocyclohexyl (e.g., ) and 1-methylcyclohexyl;

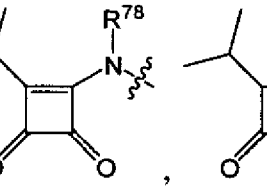
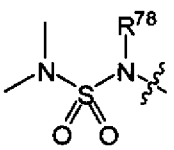
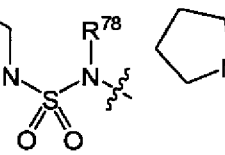
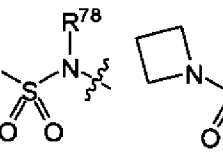
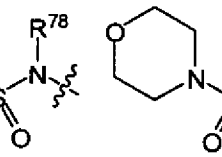
and R^{77} is selected from the group consisting of:

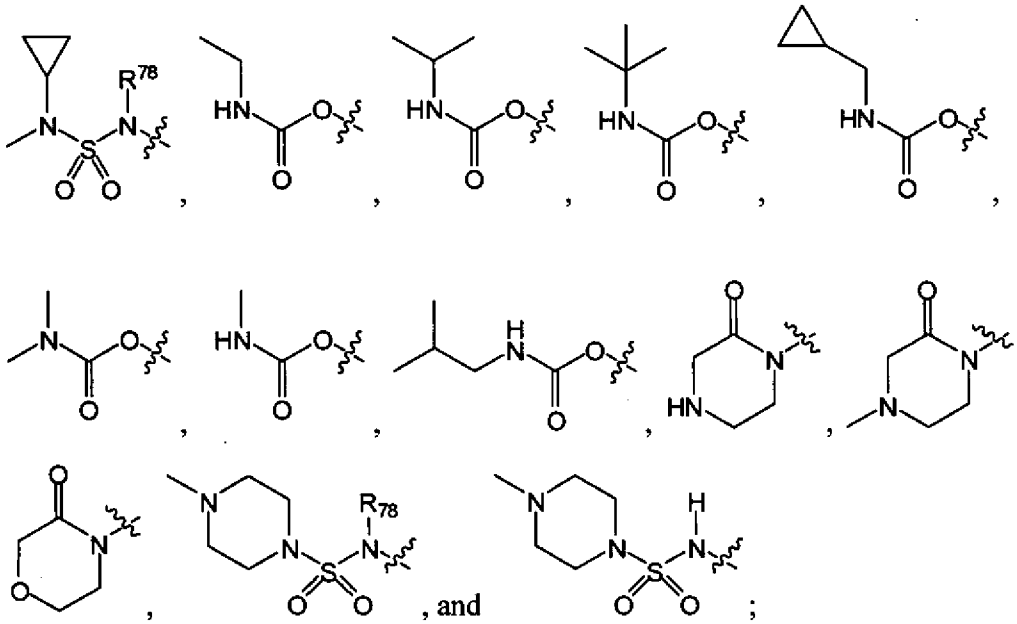




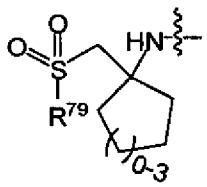





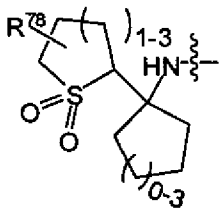
Where R^{78} is selected from methyl, ethyl, isopropyl, tert-butyl and phenyl.

In yet other embodiments, compounds of Formula I or Formula III comprise a V group selected from residues having the formula –C(O)-V′, wherein V′ is a residue of the formula (ii):



wherein R^{79} is selected form the group consisting of methyl, ethyl, isopropyl, tert-butyl, sec-butyl, 4-methyl-butyl, 1,1-dimethylpropyl, 1,1-dimethylbutyl, phenyl, benzyl, cyclopentyl, cyclohexyl, furylmethyl, and pyridyl (e.g., 2-pyridyl, 3-pyridyl, or 4-pyridyl).

In certain other embodiments, compounds of Formula I or Formula III comprise a V group selected from residues having the formula –C(O)-V′, wherein V′ is a residue of the formula (iii):

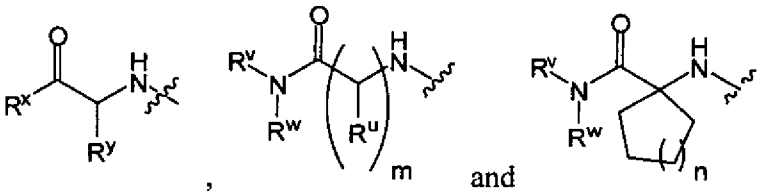


(iii)

wherein R^{78} represents 0-3 groups independently selected from C_{1-6}alkyl and C_{3-6}cycloalkyl.

In certain embodiments, compounds of Formula I or Formula III comprise a V group selected from residues having the formula –C(O)-V′, wherein V′ is a residue of the formula (iv):

(iv)



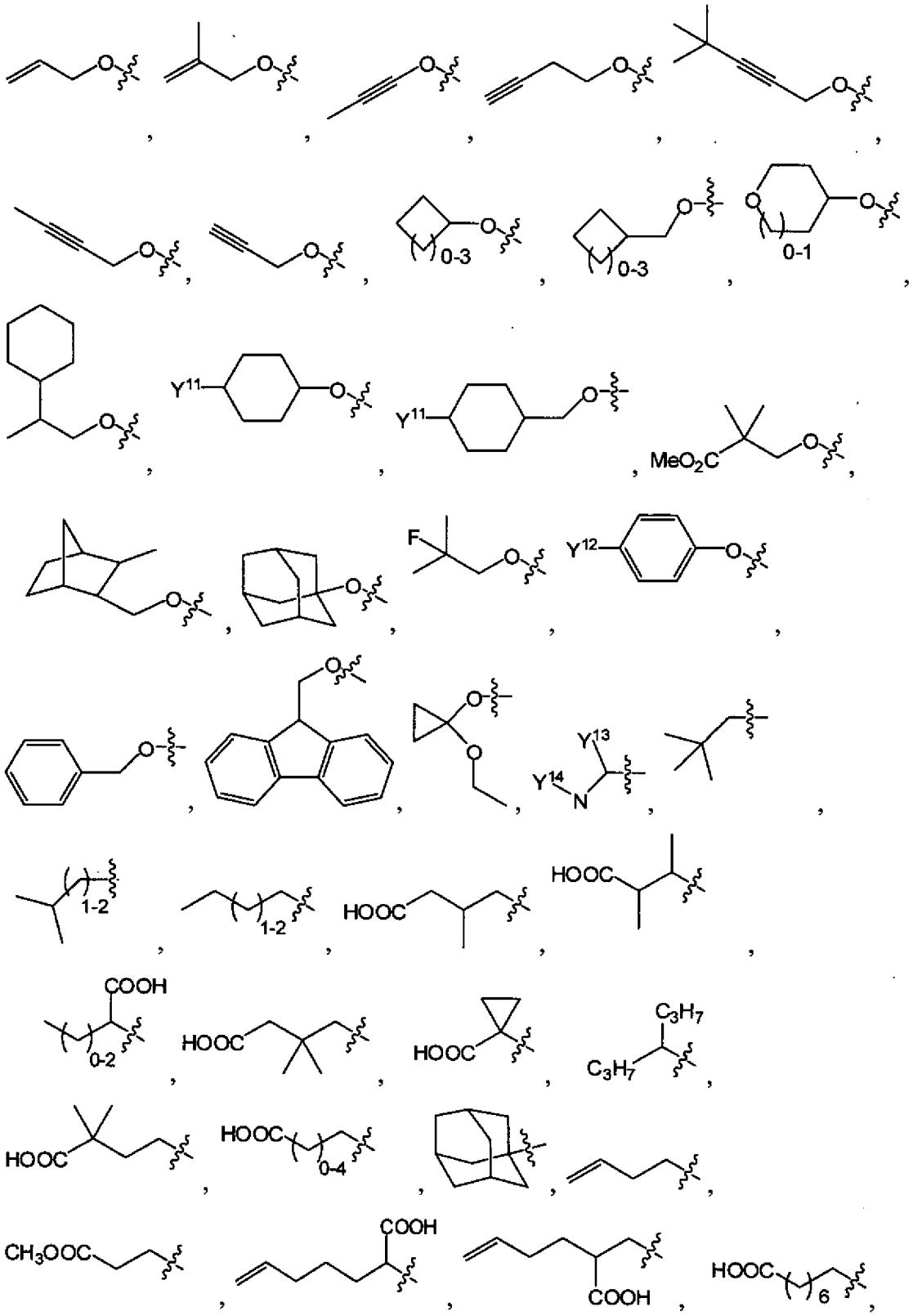
wherein m is 1 or 2; n is 0, 1, 2, or 3;

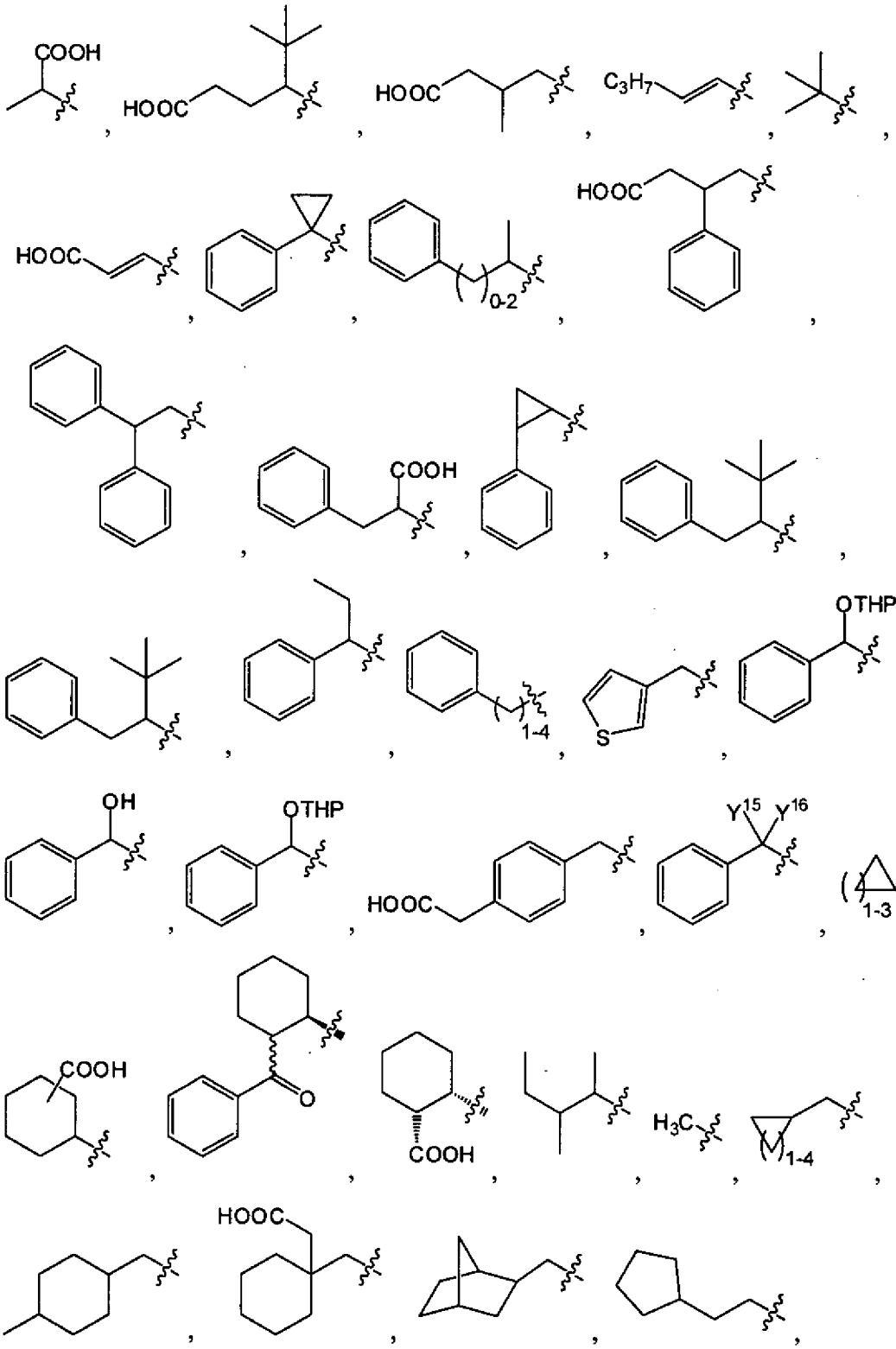
R^u, R^v, and R^w, are independently selected at each occurrence from the group consisting of hydrogen, C_{1-6}alkyl, arylC_{0-4}alkyl, heteroarylC_{0-4}alkyl, heterocyclylC_{0-4}alkyl, and cycloalkylC_{0-4}alkyl; or

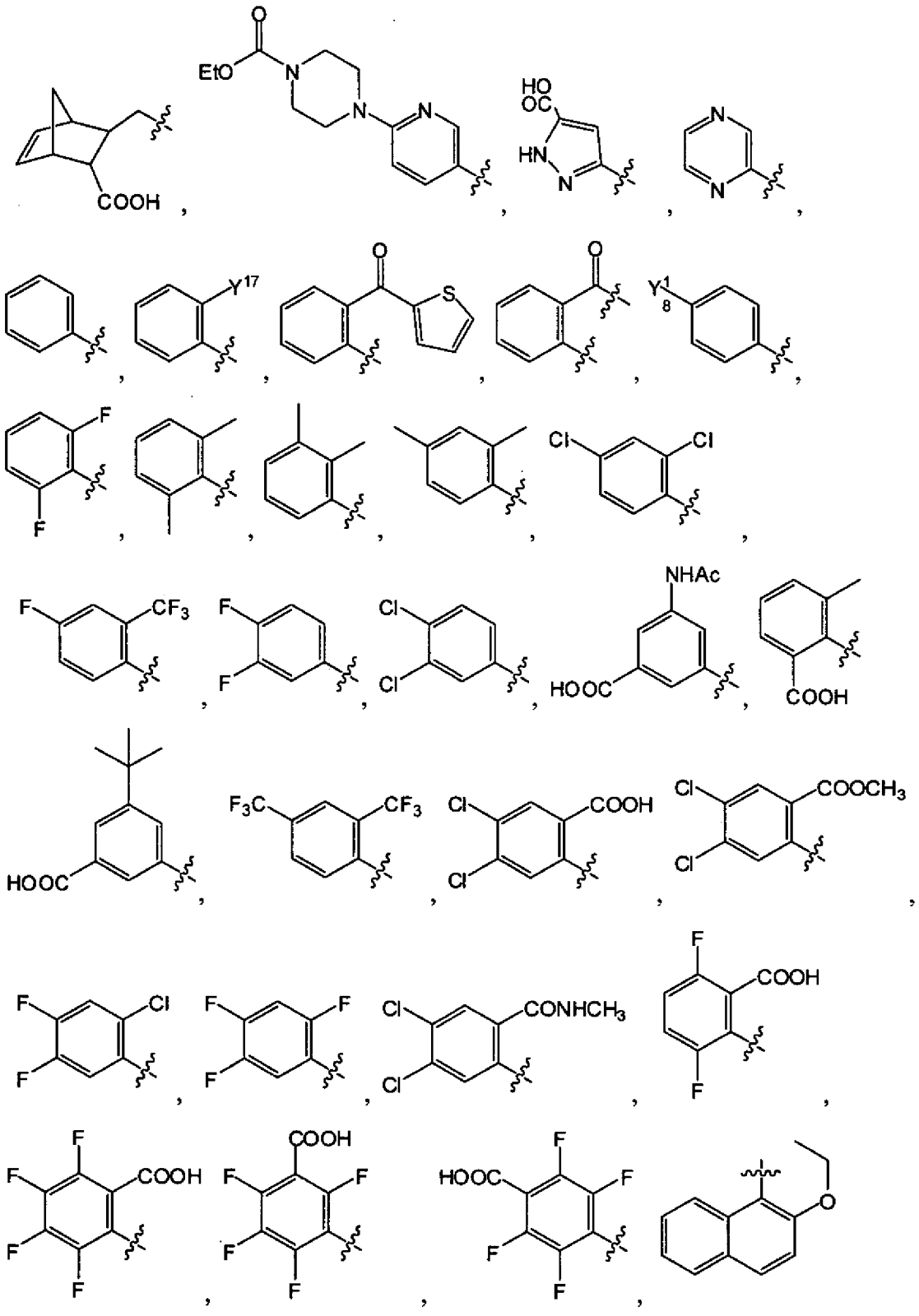
R^v and R^w, taken in combination, form a ring having between 3 and 7 ring atoms and having 0, 1, 2 ring heteroatoms which is substituted with 0-2 alkyl groups and 0-1 spirocyclic groups.

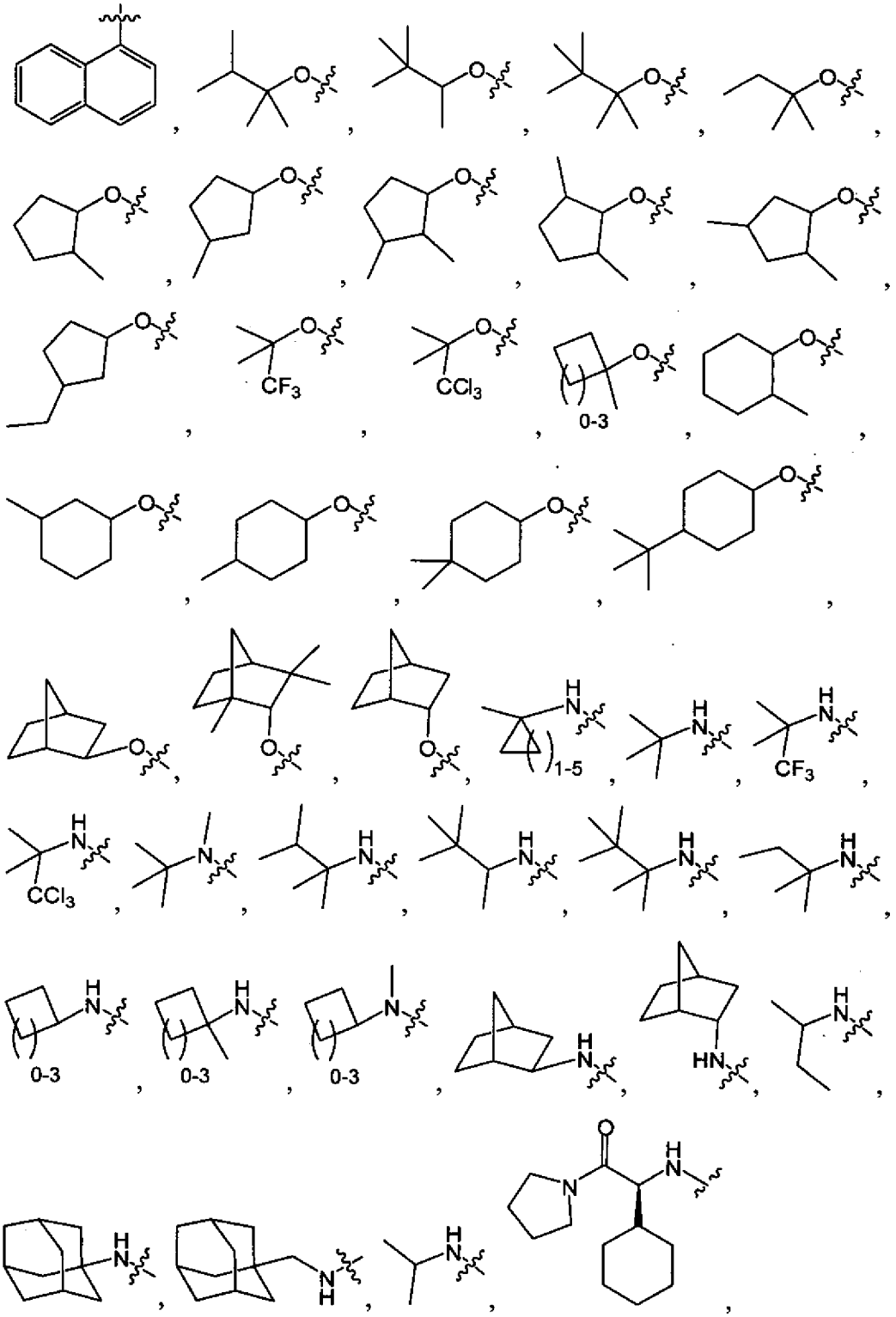
R^x and R^y are each independently selected from the group consisting of phenyl, C_{1-6}alkyl, and C_{3-6}cycloalkyl, or R^x and R^y are each independently selected from the group consisting of phenyl, cyclopropyl, isopropyl, tert-butyl, and cyclohexyl.

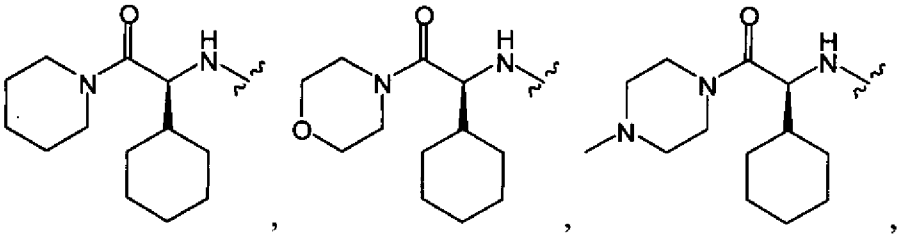
In certain embodiments, compounds of Formula I or Formula III comprise a V group selected from residues having the formula –C(O)-V′, wherein V′ is a residue selected from the group consisting of tert-butoxy, 2,2-dimethylpropoxy, sec-butoxy, 1,2-dimethylpropoxy, 3-pentoxy, isopropoxy, C_{1-9}alkoxy, 2,2,2-trichloroethoxy,


0-3
0-3
0-1
Y11
Y11
MeO2C
F
Y12
Y13
Y14
N
1-2
1-2
HOOC
HOOC
COOH
0-2
HOOC
HOOC
C3H7
C3H7
HOOC
HOOC
0-4
CH3OOC
COOH
COOH
HOOC
6

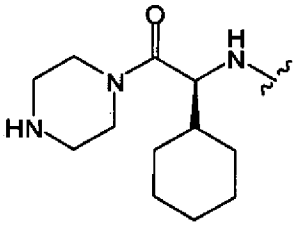
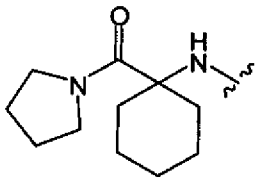
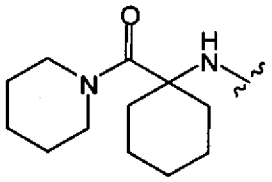
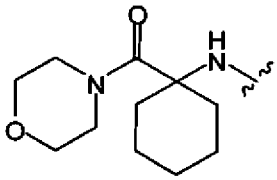
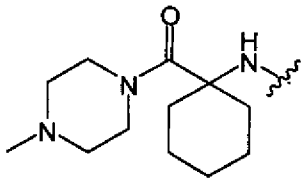
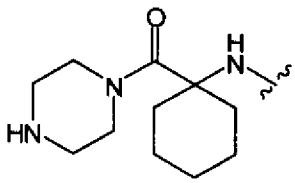

COOH
HOOC
HOOC
C_3H_7
HOOC
0-2
HOOC
COOH
1-4
S
OTHP
OH
OTHP
HOOC
Y^{15} Y^{16}
1-3
COOH
O
COOH
H_3C
1-4
HOOC




CF3
CCl3
0-3
1-5
CF3
CCl3
0-3
0-3
0-3
HN


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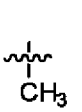
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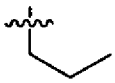
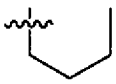
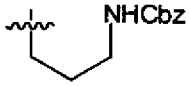
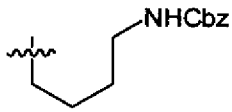
wherein

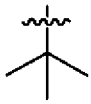
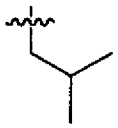
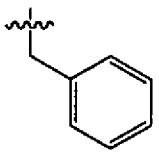
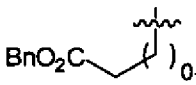
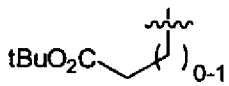
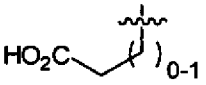
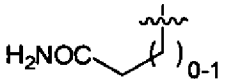
Y^{11} is selected from the group consisting of hydrogen, -C(O)OH, -C(O)OEt, -OMe, -Ph, -OPh, -NHMe, -NHAc, -NHPh, $-CH(Me)_2$, 1-triazolyl, 1-imidazolyl, and $-NHCH_2COOH$;

Y^{12} is selected from the group consisting of hydrogen, -C(O)OH, -C(O)OMe, -OMe, F, Cl, and Br;

Y^{13} is selected from the group consisting of the following moieties:


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Y^{14} is $S(O)_2Me$, -C(O)Me, -Boc, -iBoc, Cbz, or –Alloc;

Y^{15} and Y^{16} can be the same or different and are independently selected from the group consisting of alkyl, aryl, heteroalkyl, and heteroaryl;

Y^{17} is $–CF_3$, $-NO_2$, $-C(O)NH_2$, -OH, $-C(O)OCH_3$, $-OCH_3$, $-OC_6H_5$, $-C_6H_5$, $-C(O)C_6H_5$, $-NH_2$, or –C(O)OH; and

Y^{18} is $–C(O)OCH_3$, $-NO_2$, $-N(CH_3)_2$, F, $-OCH_3$, $-C(H)_2C(O)OH$, -C(O)OH, $-S(O)_2NH_2$, or $–N(H)C(O)CH_3$

In one embodiment, any of the C_{3-6}-cycloalkyl groups may be independently substituted one or more times (or preferably between one and five times) with a halogen atom, aryl, trihalomethyl, or C_{1-4}-alkyl.

In another embodiment of formula I, R^4 is H and R^5 is aryl-C_{0-3}-alkyl, -O-heterocycle, or heterocycle-C_{0-3}-alkyl, wherein aryl and heterocycle may be independently substituted one or more times (or preferably between one and five times) with a halogen atom, aryl, trihalomethyl, C_{3-6}-cycloalkyl or C_{1-4}-alkyl.

In yet another embodiment of Formula I or Formula III, W is selected from the group consisting of $C(O)-C(O)N(R^{23})_2$, wherein R^{23} is independently selected from hydrogen or from the group consisting of C_{1-4}-alkyl, C_{3-6}-cycloalkylC_{0-4}alkyl, aryl and heterocycle, each of which may be independently substituted one or more times (or preferably between one and five times) with a halogen atom or C_{1-4}-alkyl.

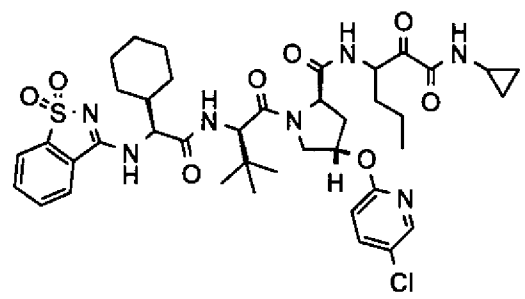
In still another embodiment of Formula I or Formula III, W is C(O)-C(O)-cyclopropyl

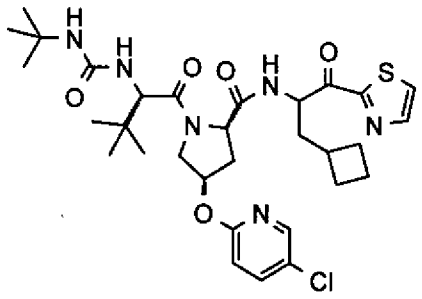
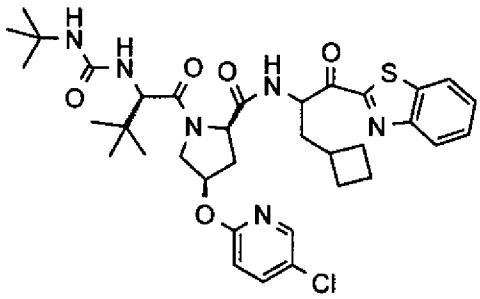
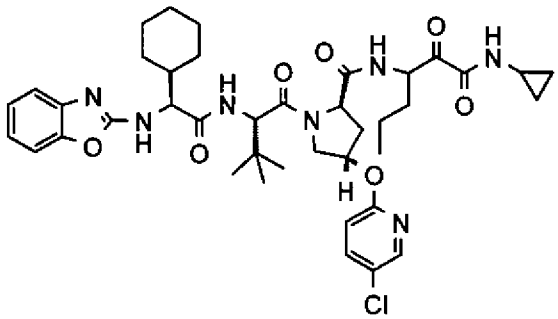
In one embodiment of Formula I or Formula III, any of the heterocycle groups are independently selected from the group consisting of acridinyl, carbazolyl, cinnolinyl, quinoxalinyl, pyrazolyl, indolyl, benzotriazolyl, furanyl, thienyl, benzothienyl, benzofuranyl, quinolinyl, isoquinolinyl, oxazolyl, isoxazolyl, indolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, tetrahydroquinoline, benzoimidazolyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxazoline, isoxazoline, oxetanyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl,

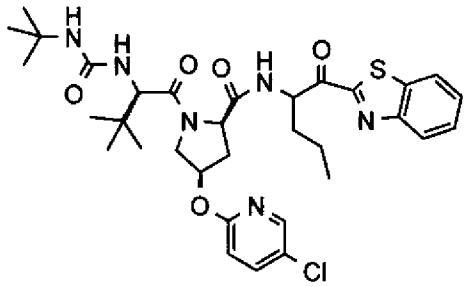
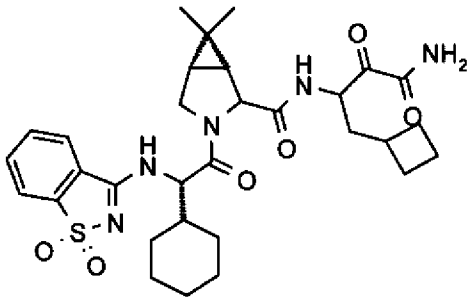
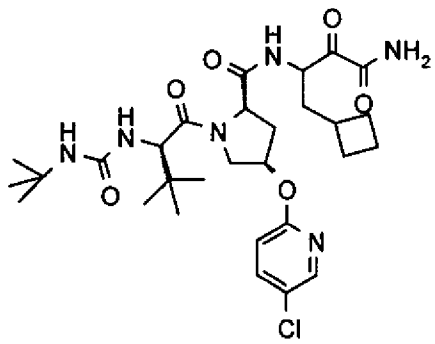
pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, tetrahydropyranyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyridin-2-onyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzoimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl, and N-oxides thereof, each of which may be independently further substituted one or more times (or preferably between one and five times) with a halogen atom, C_{1-4}-alkyl, C_{1-4}-alkyl substituted by one or more halogen atoms, or C_{3-6}-cycloalkyl.

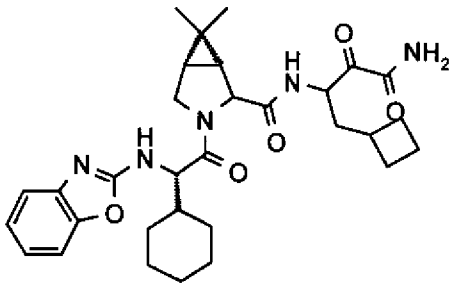
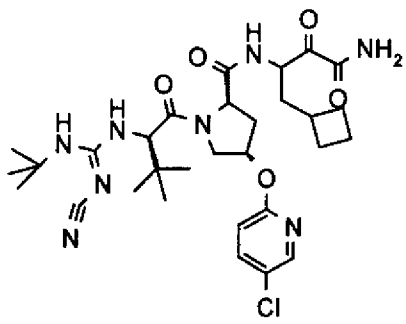
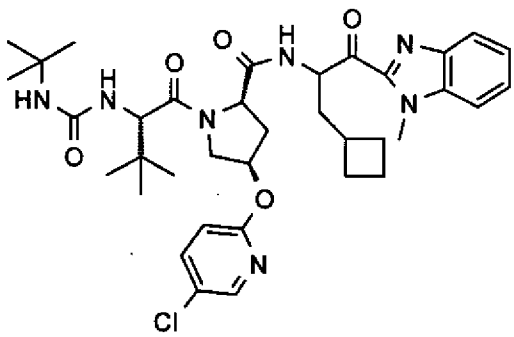
Preferred embodiments of the compounds of the invention (including pharmaceutically acceptable salts thereof, as well as enantiomers, stereoisomers, rotamers, tautomers, diastereomers, or racemates thereof) are shown below in Table A and Table B, and are also considered to be "compounds of the invention."

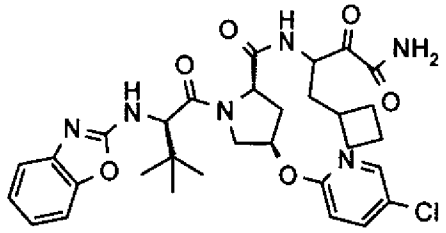
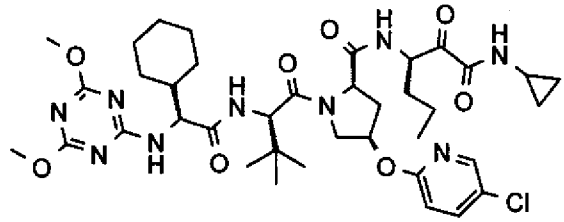
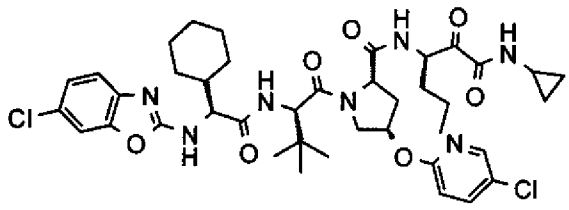
TABLE A

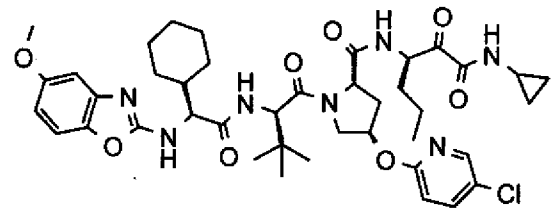
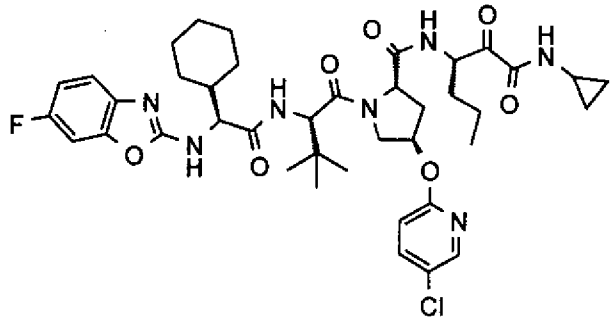
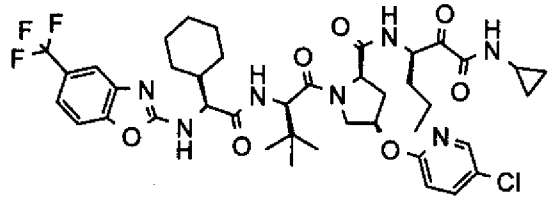
Structure	Compound No.
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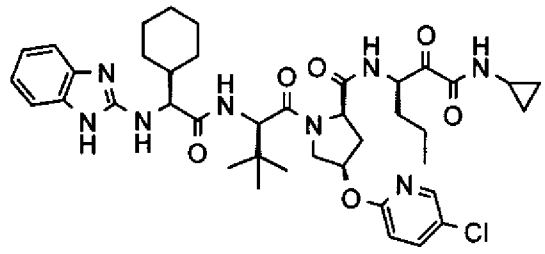
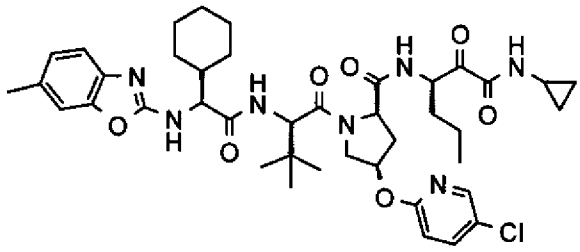
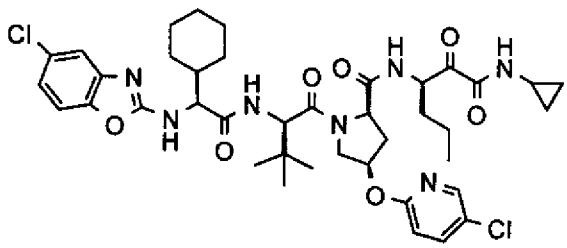
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	A-4

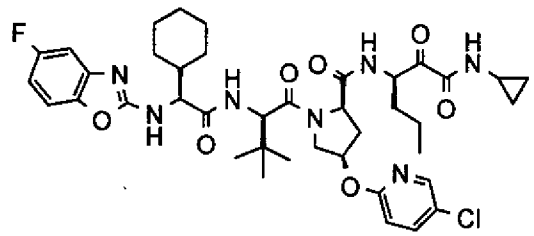
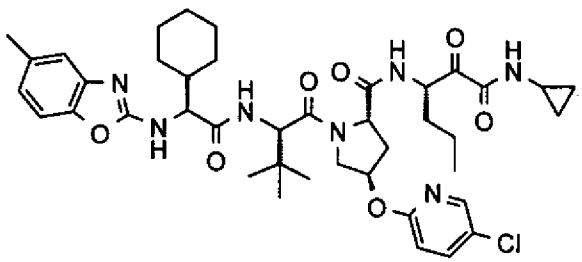
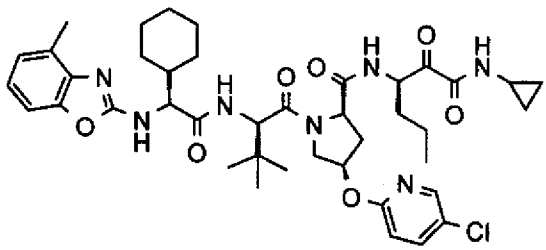
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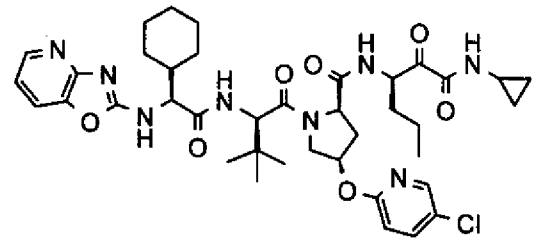
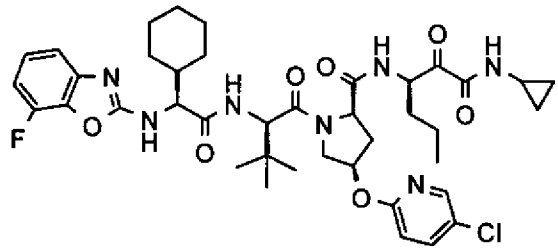
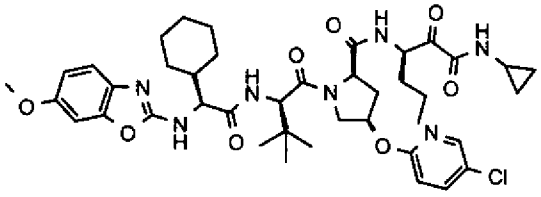
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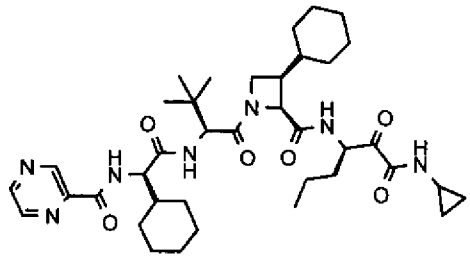
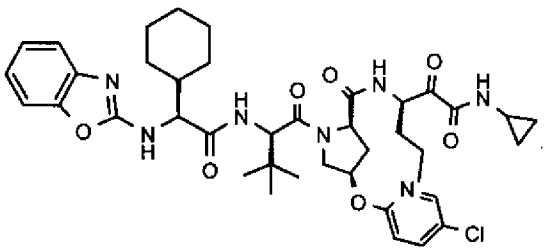
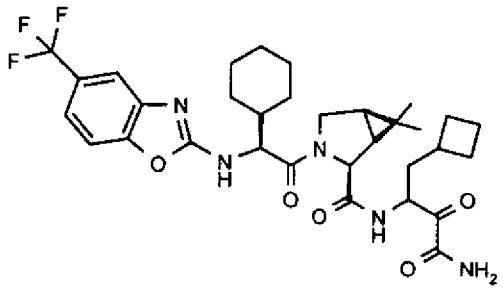
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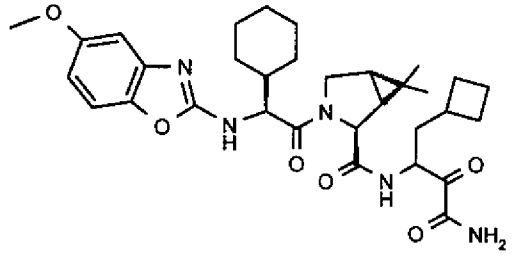
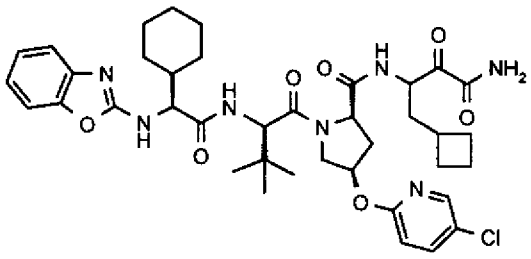
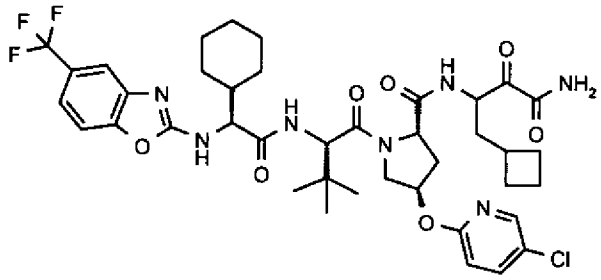
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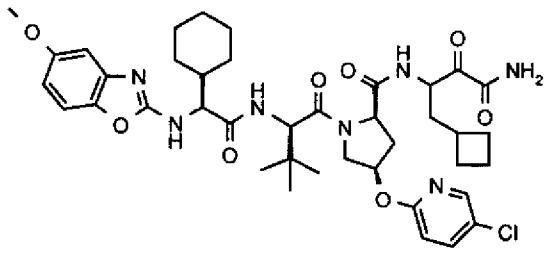
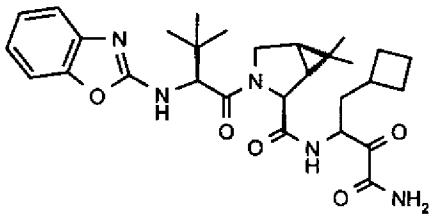
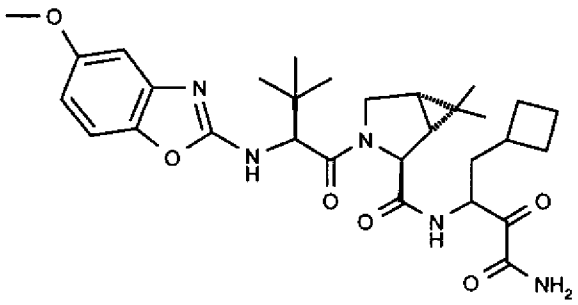
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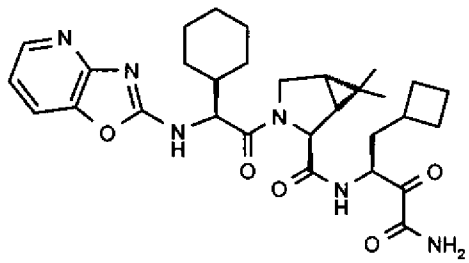
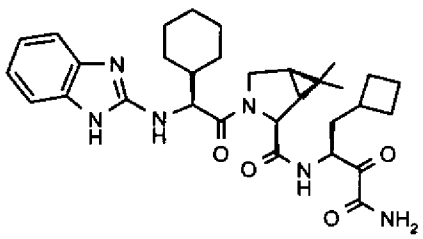
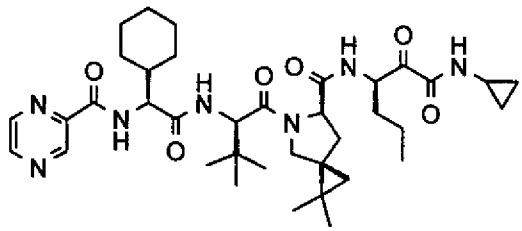
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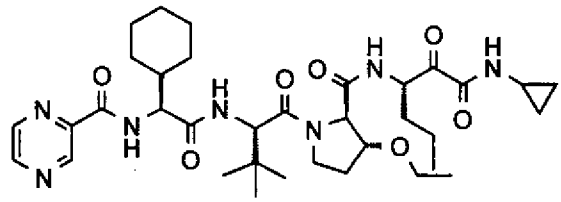
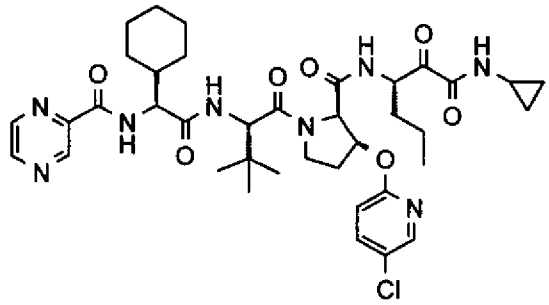
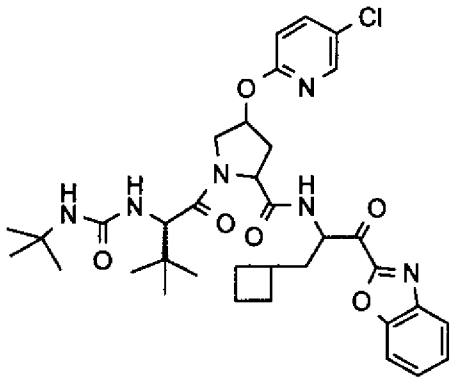
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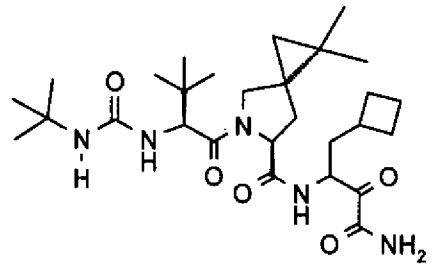
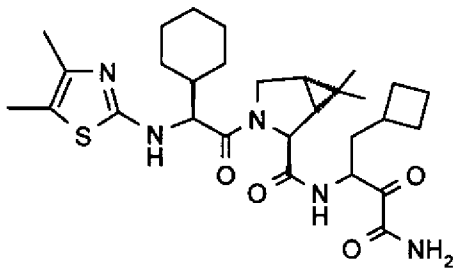
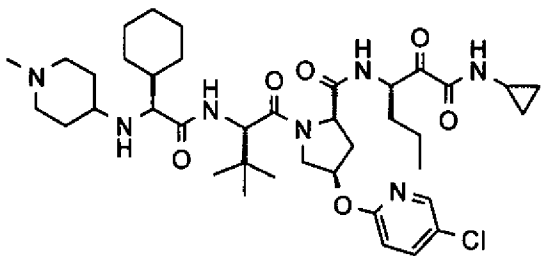
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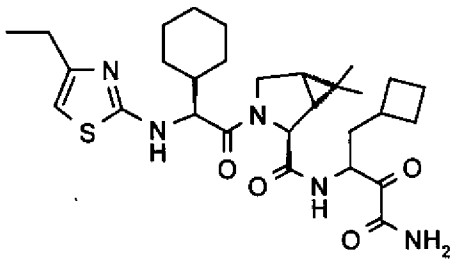
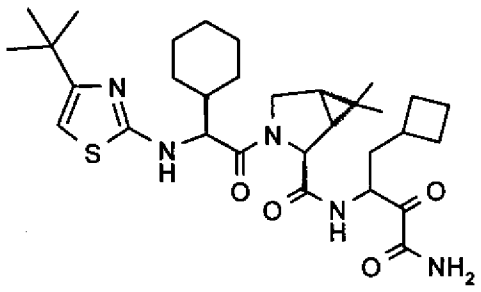
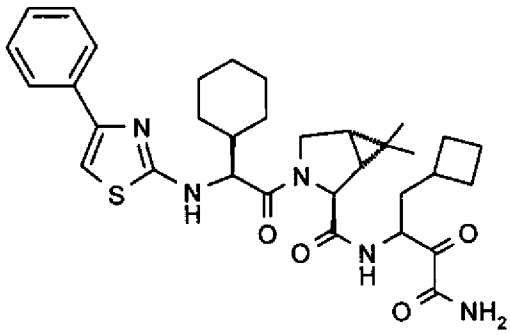
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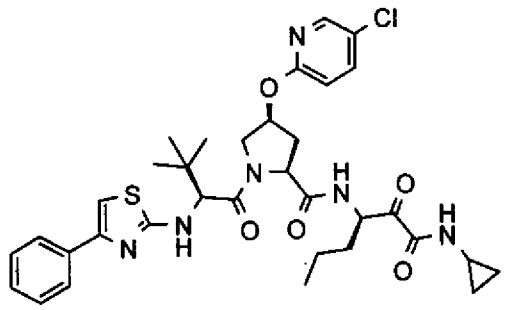
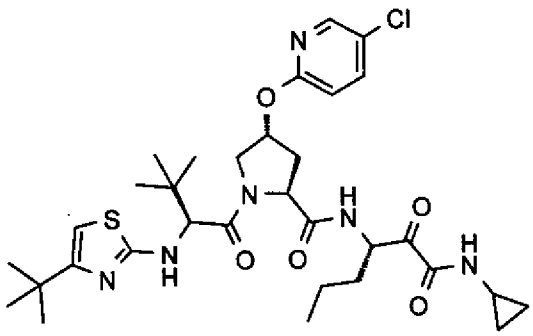
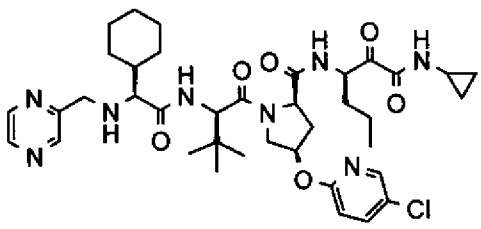
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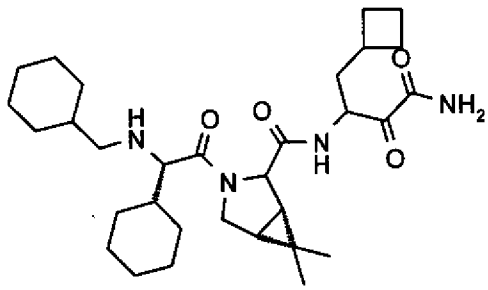
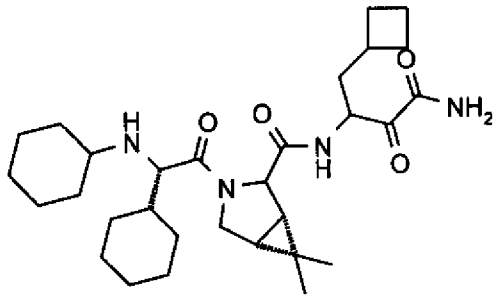
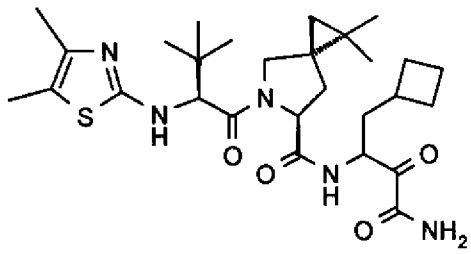
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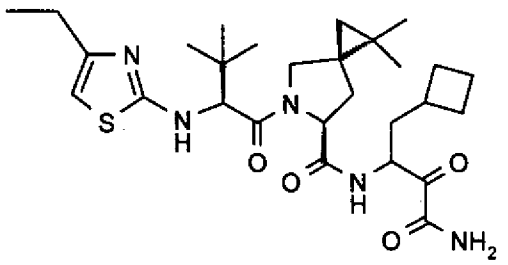
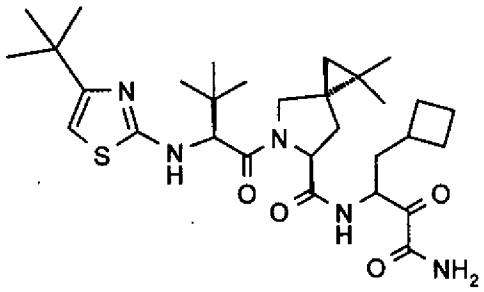
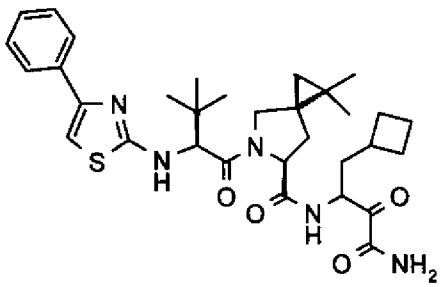
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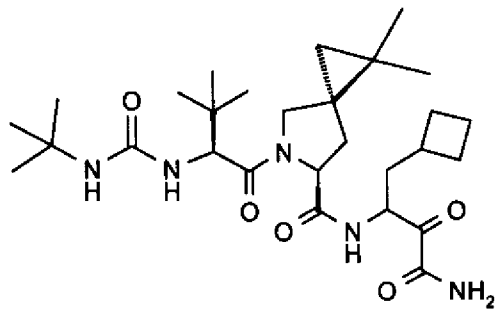
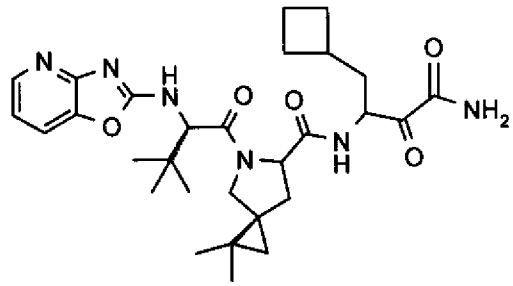
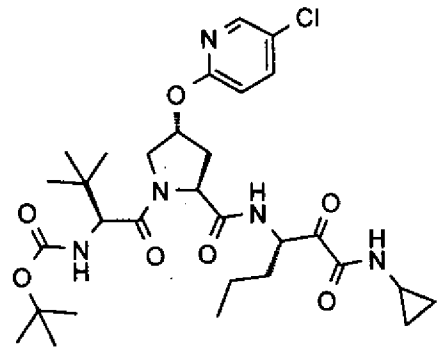
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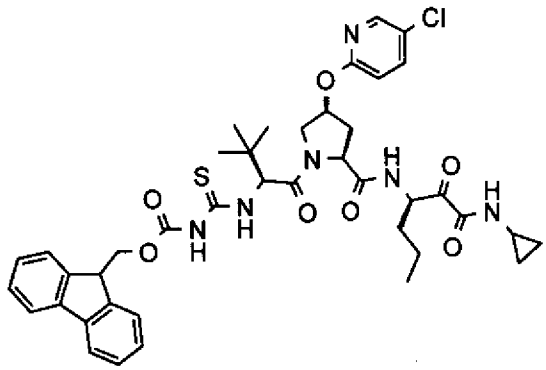
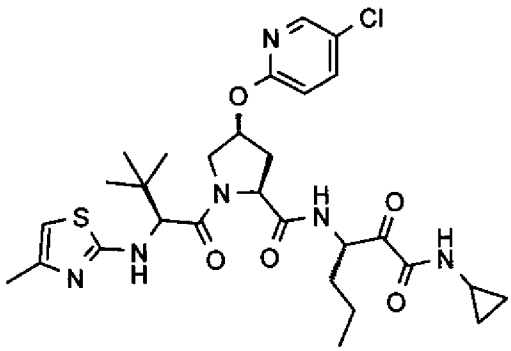
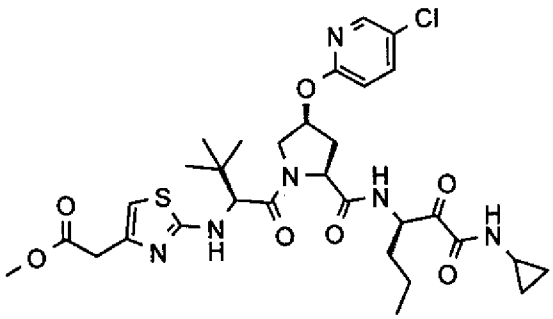
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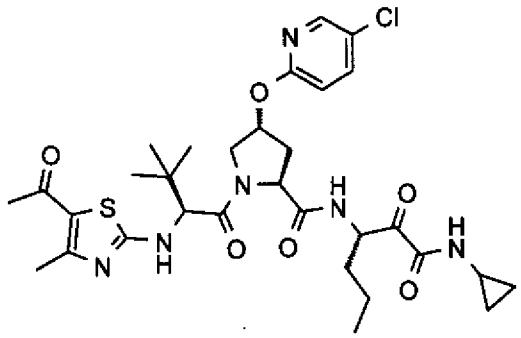
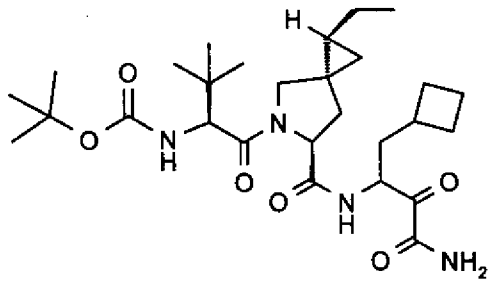
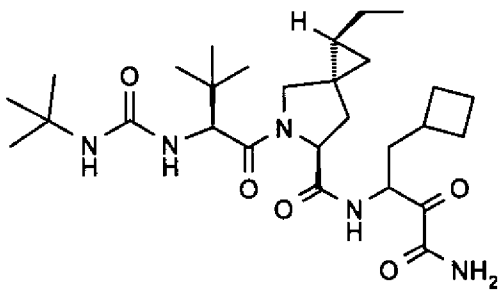
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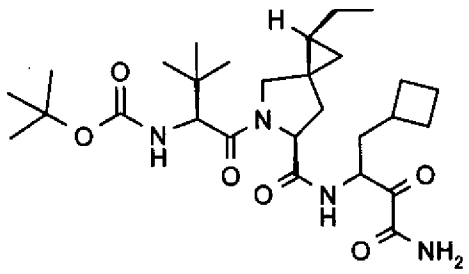
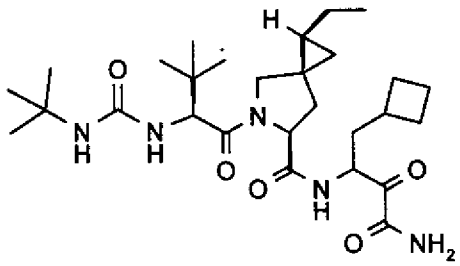
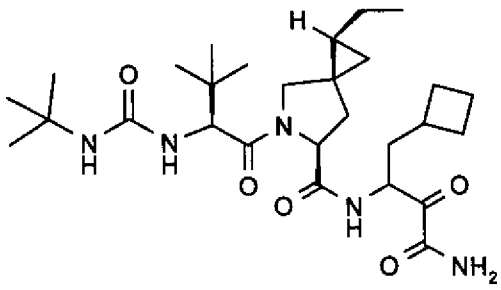
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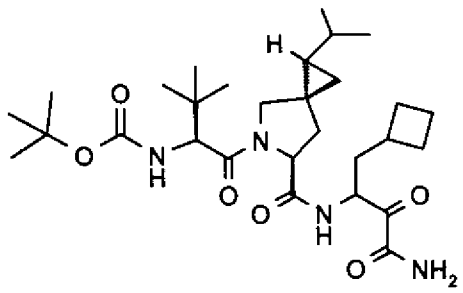
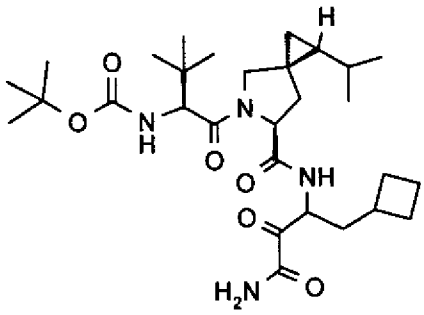
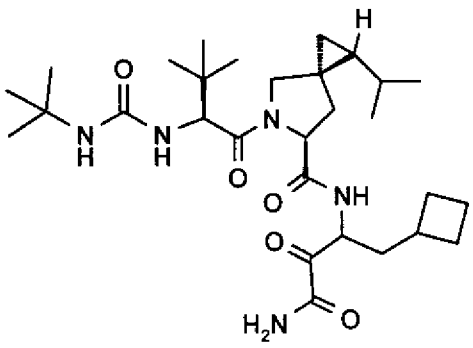
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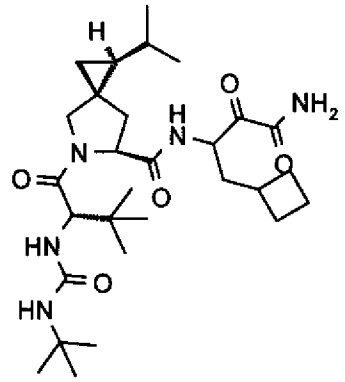
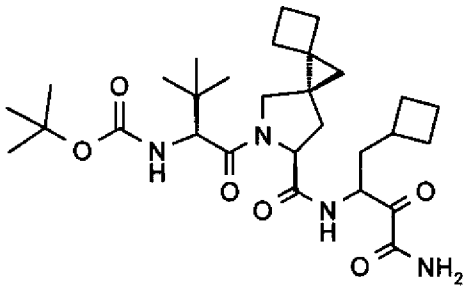
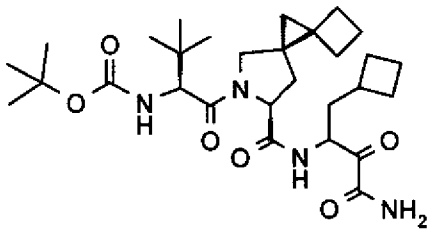
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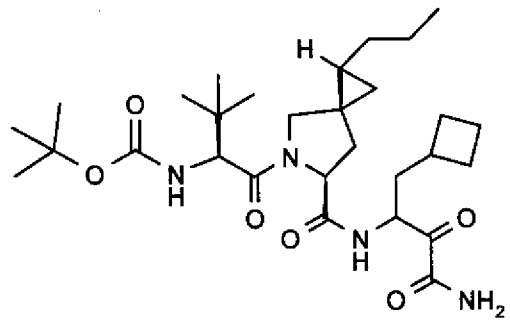
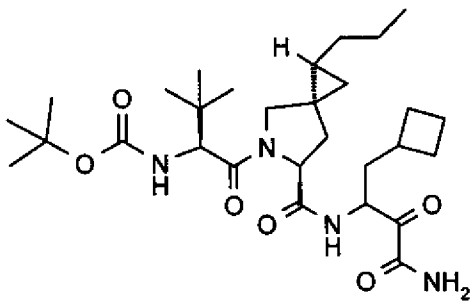
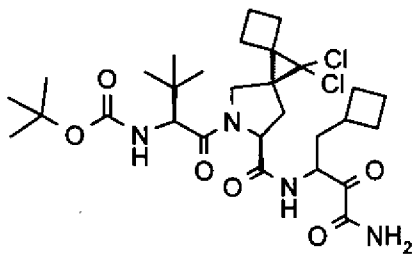
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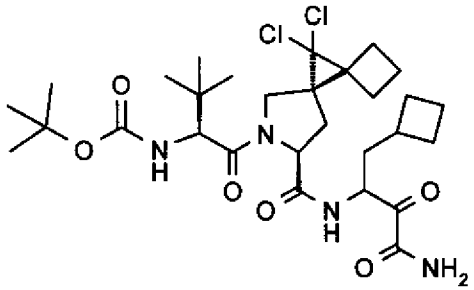
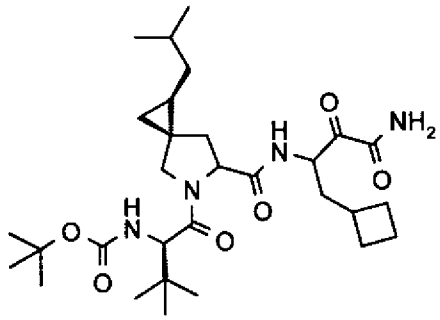
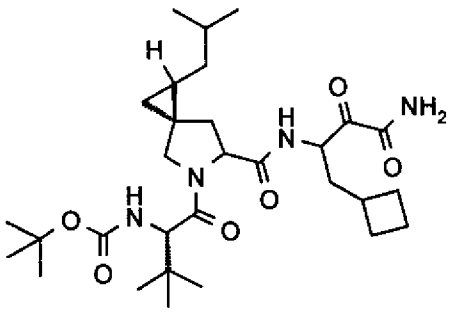
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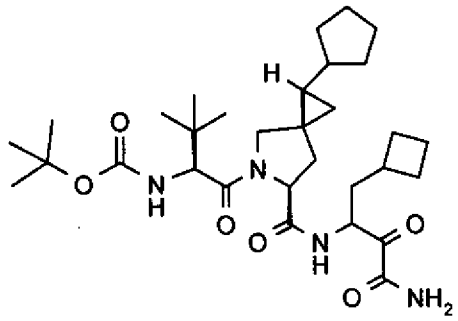
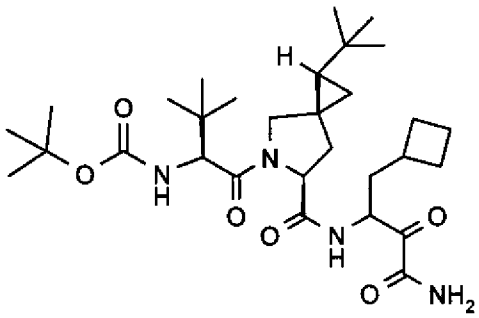
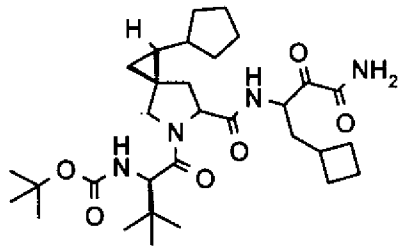
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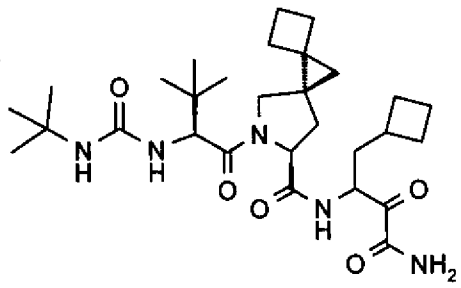
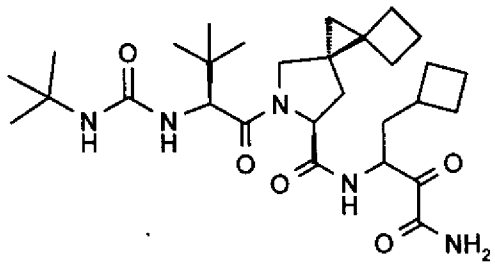
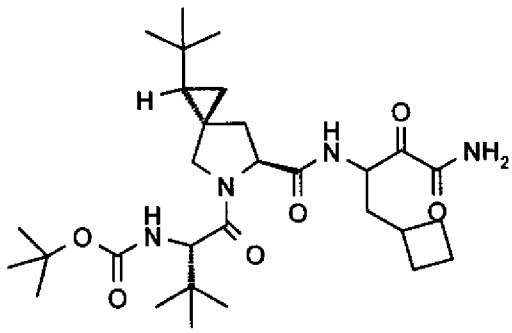
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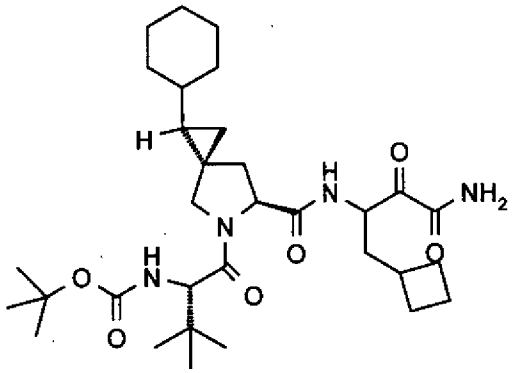
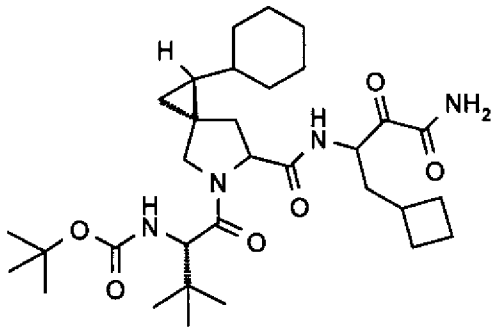
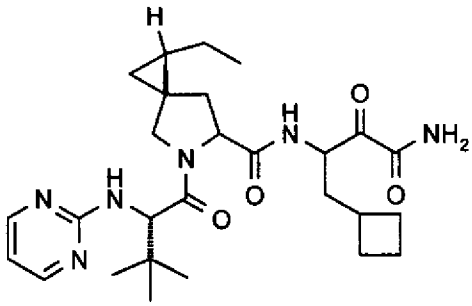
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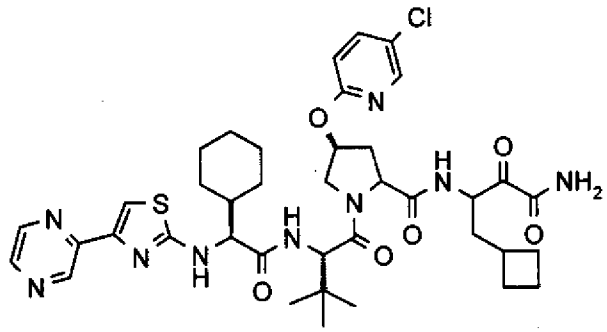
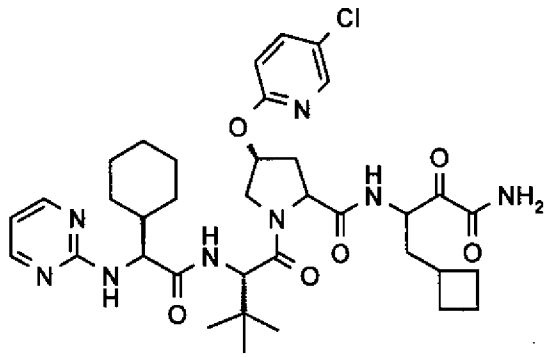
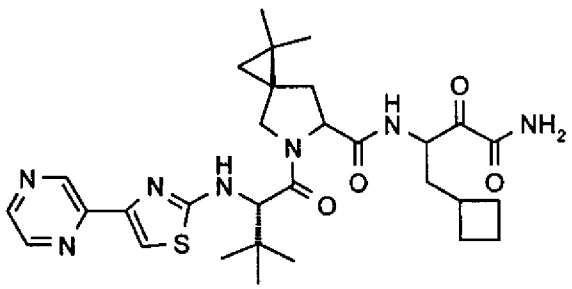
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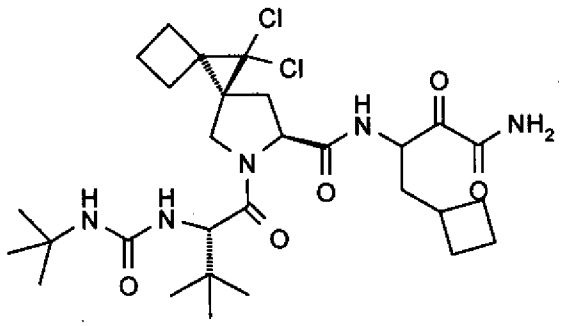
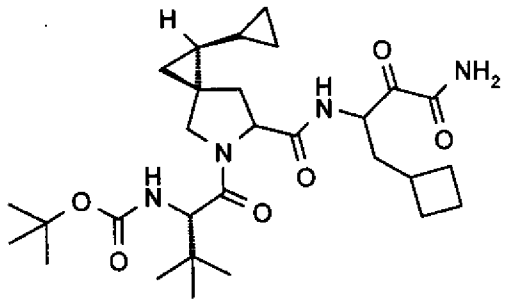
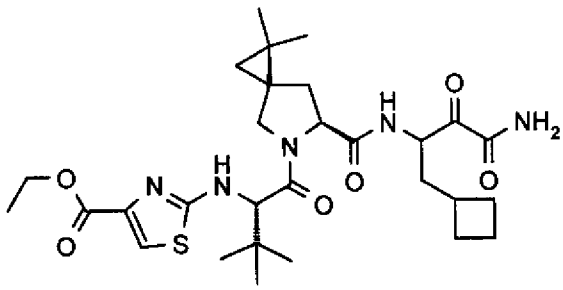
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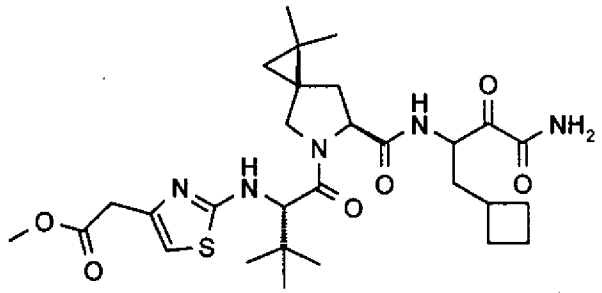
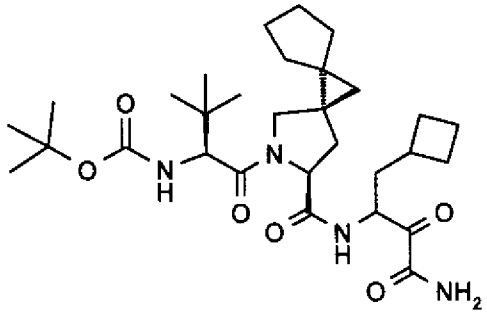
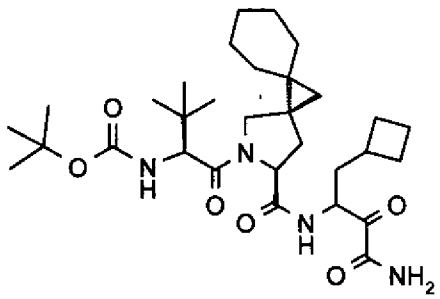
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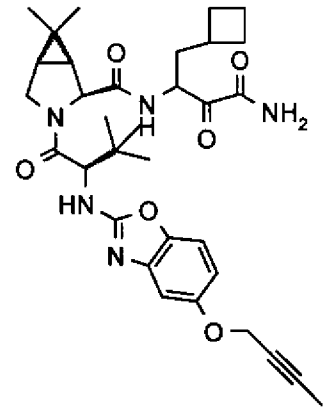
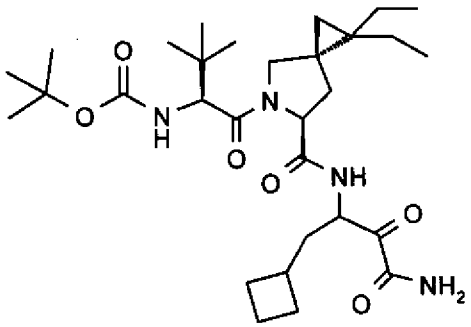
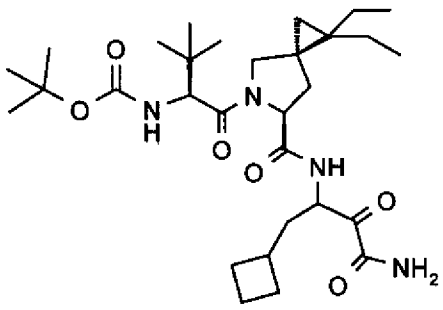
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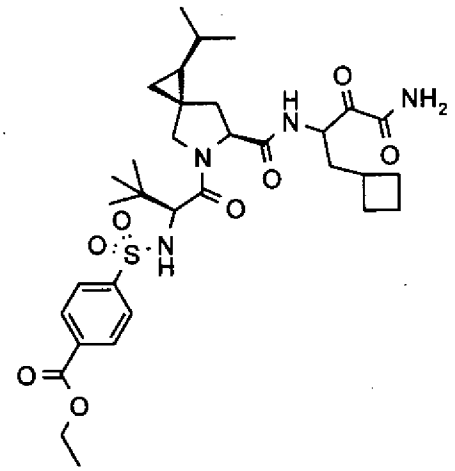
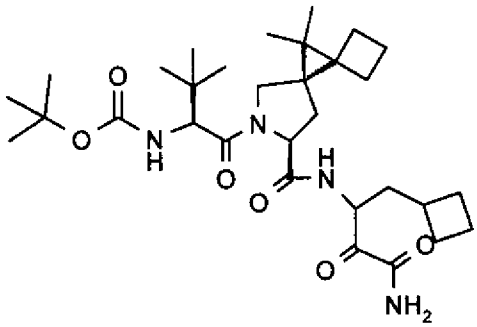
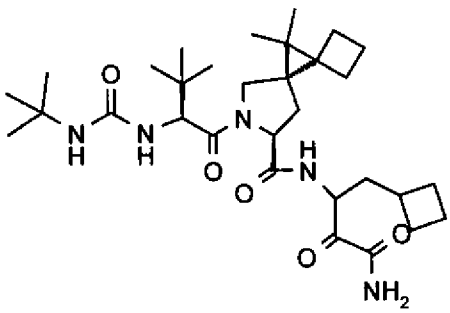
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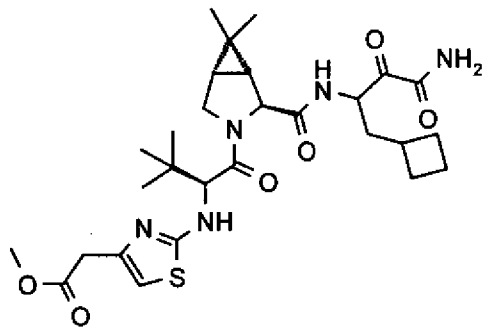
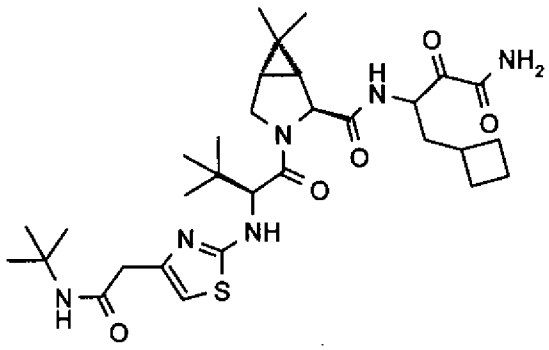
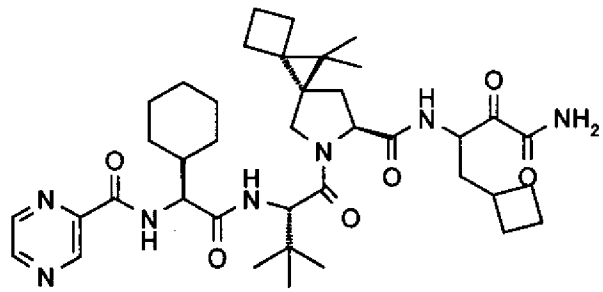
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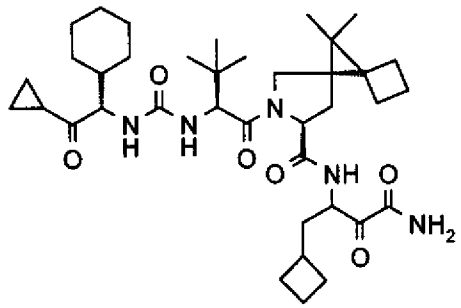
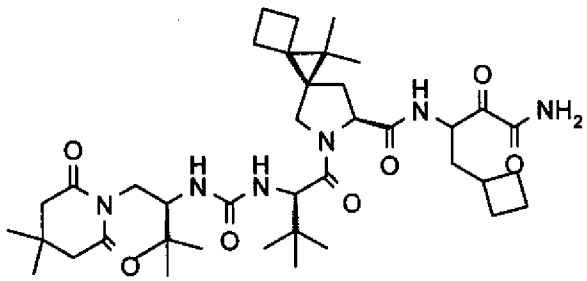
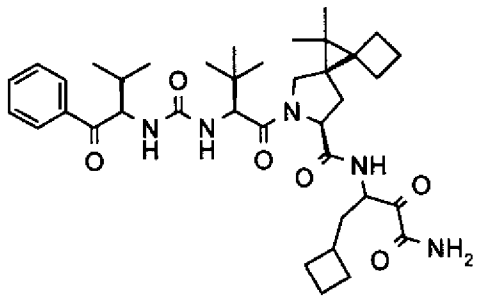
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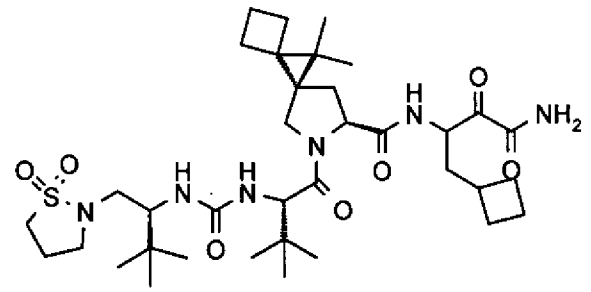
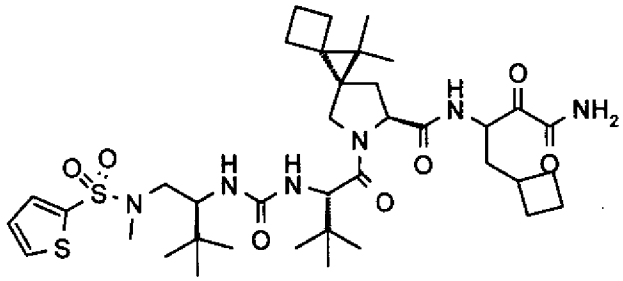
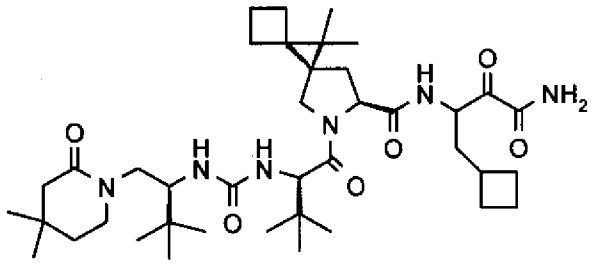
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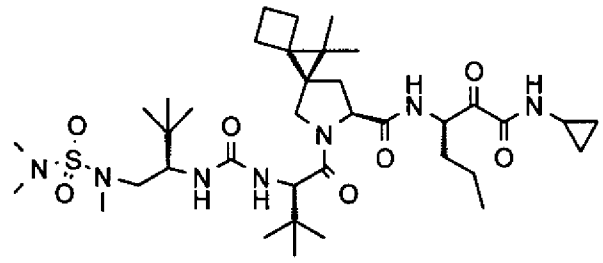
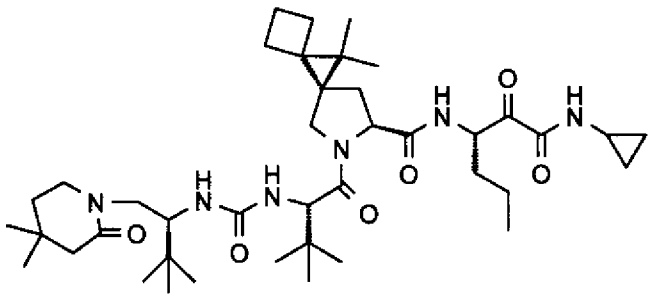
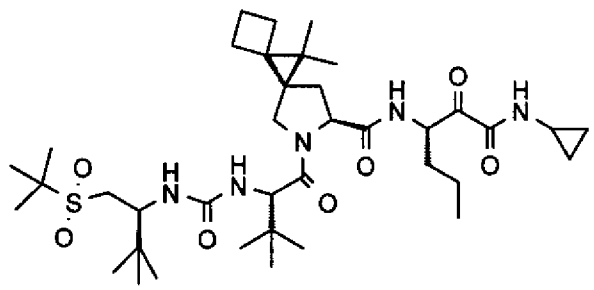
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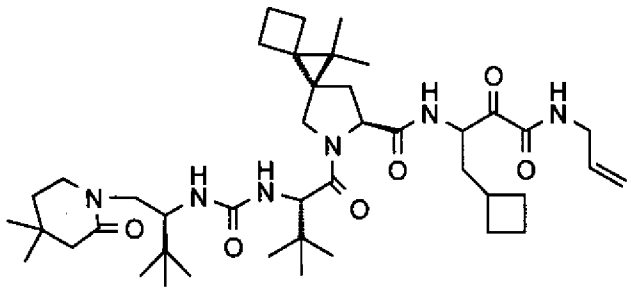
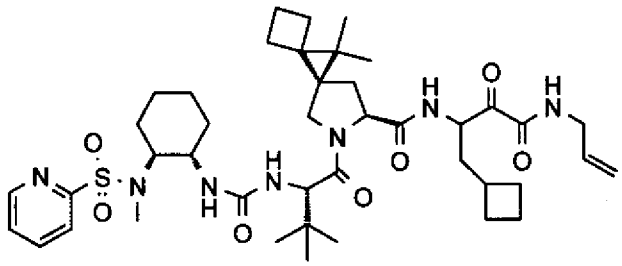
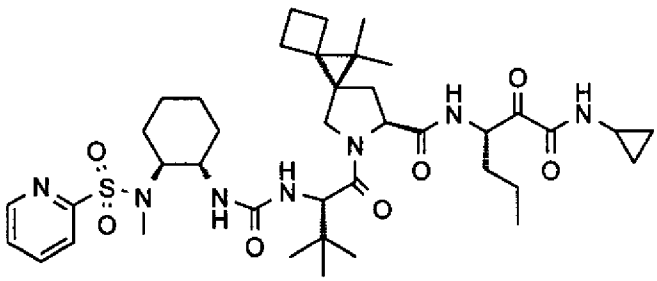
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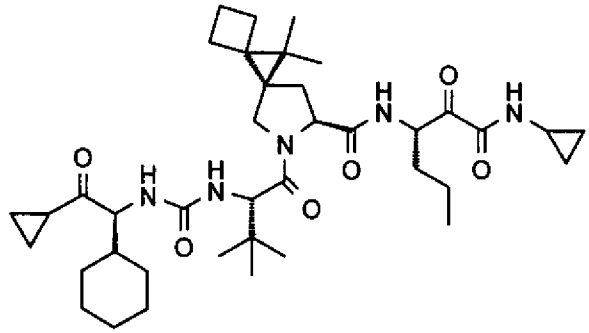
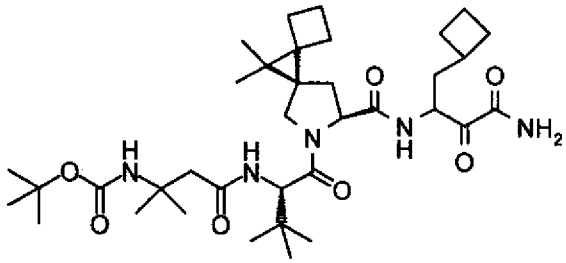
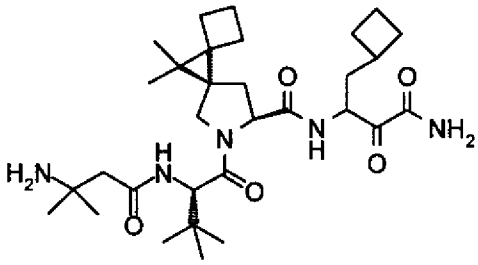
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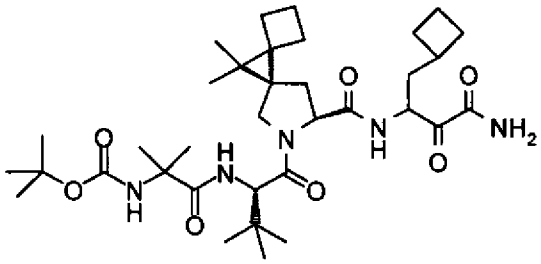
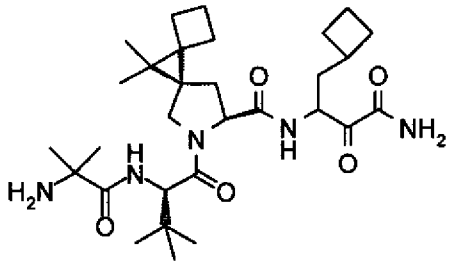
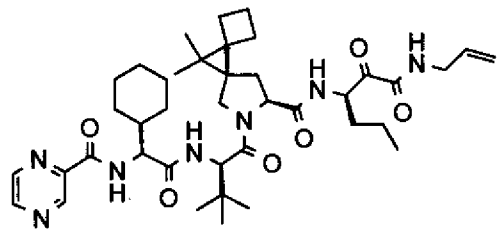
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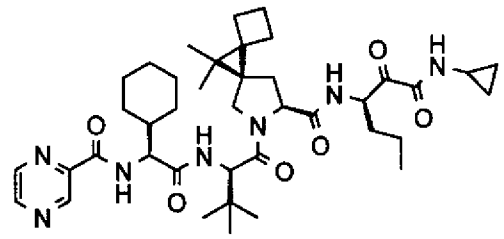
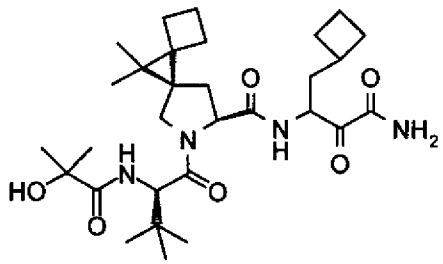
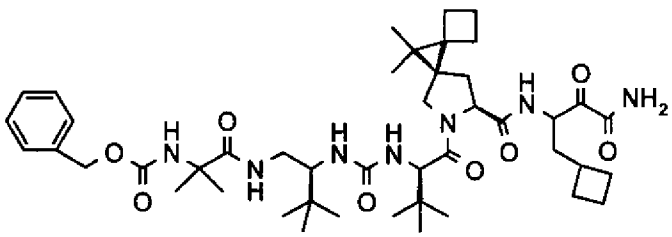
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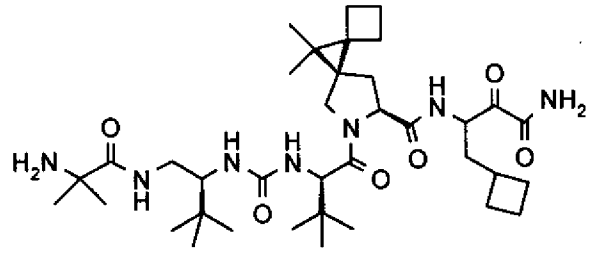
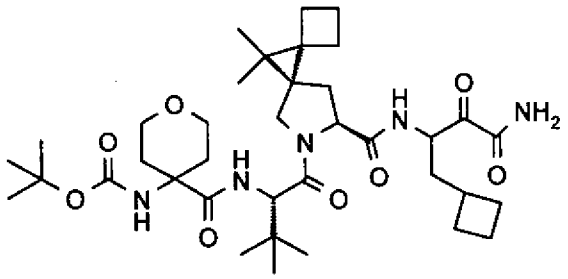
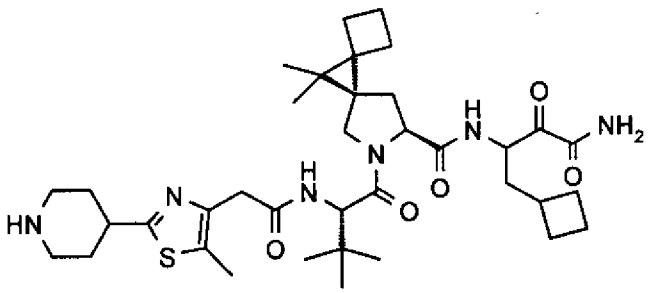
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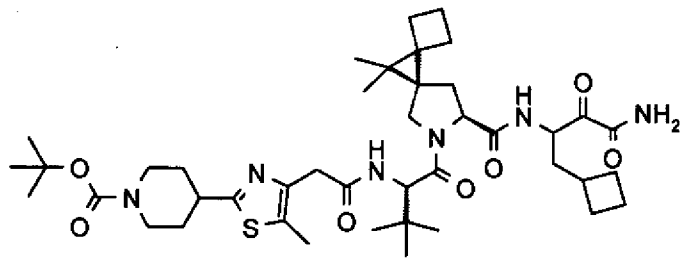
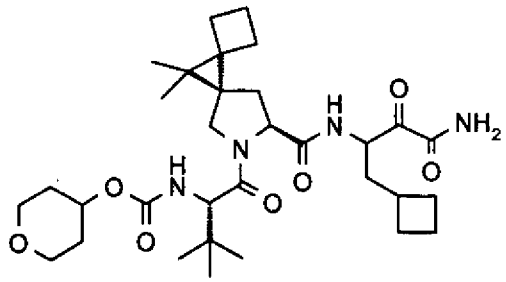
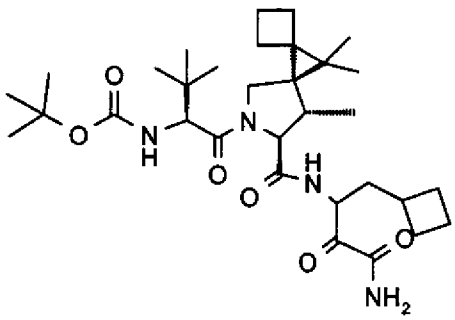
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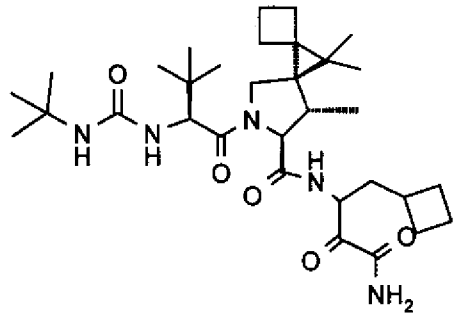
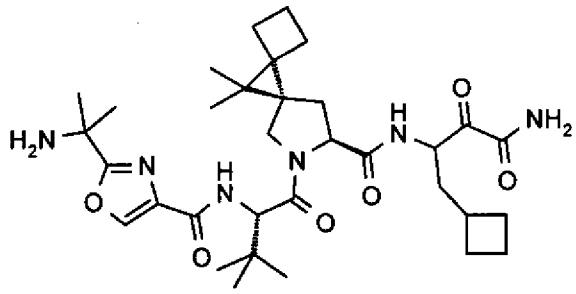
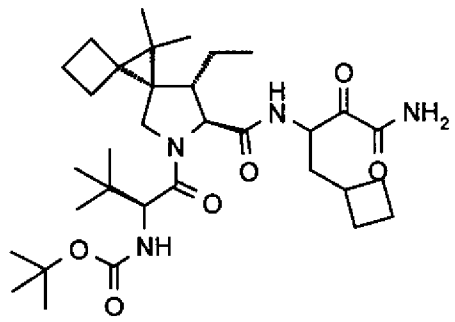
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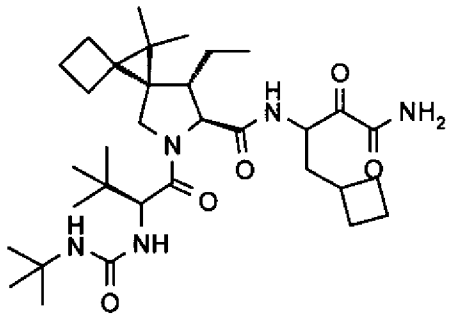
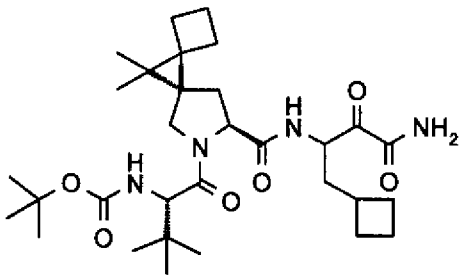
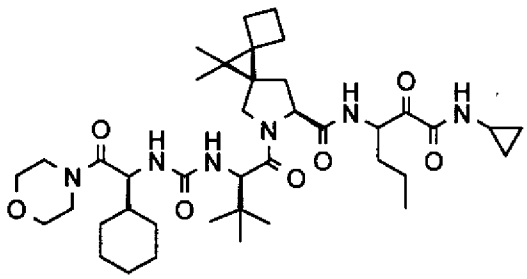
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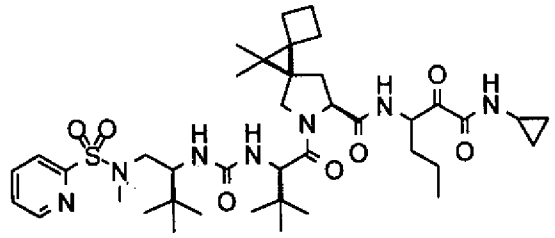
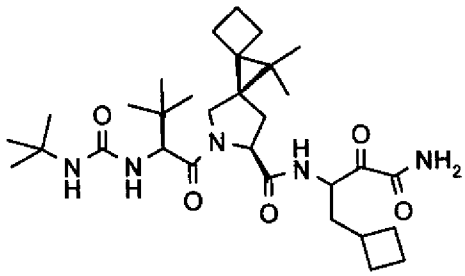
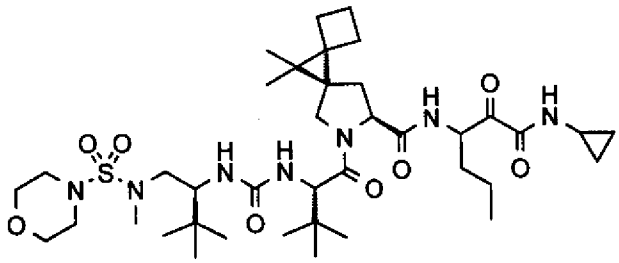
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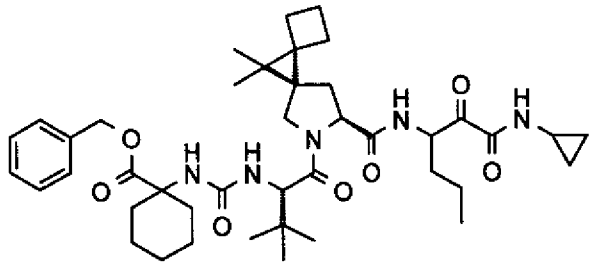
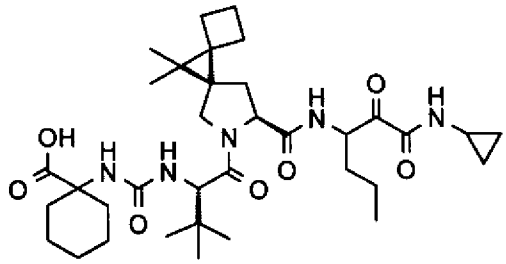
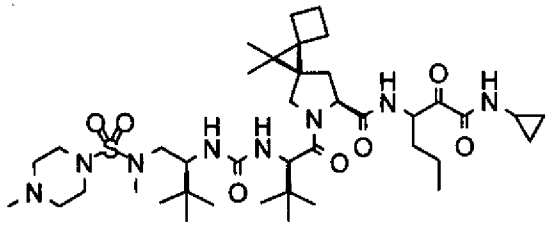
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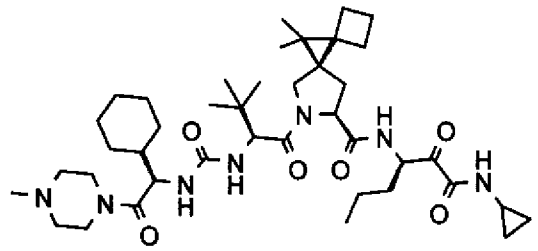
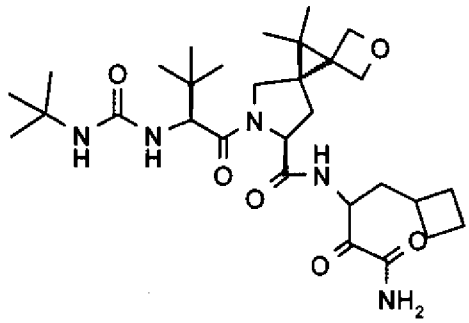
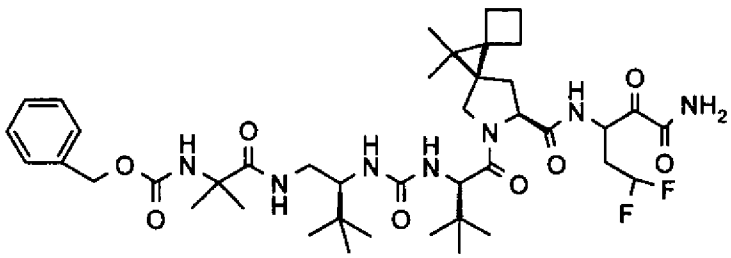
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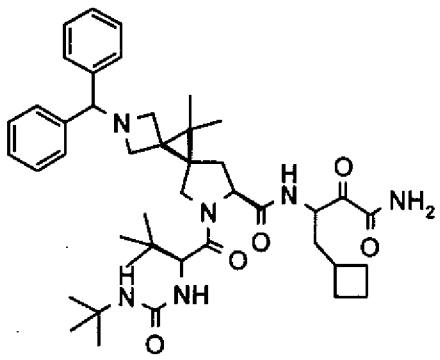
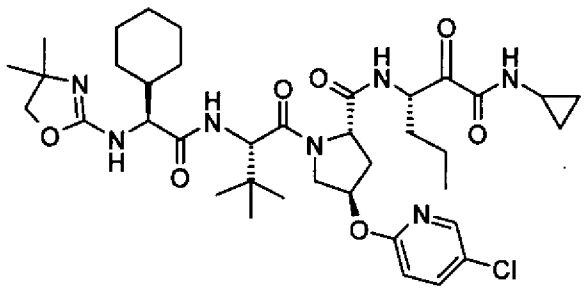
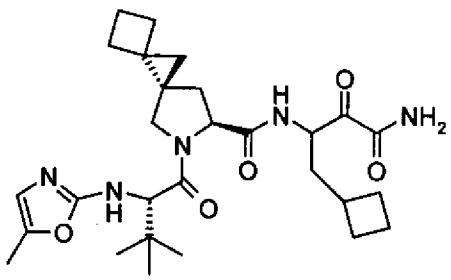
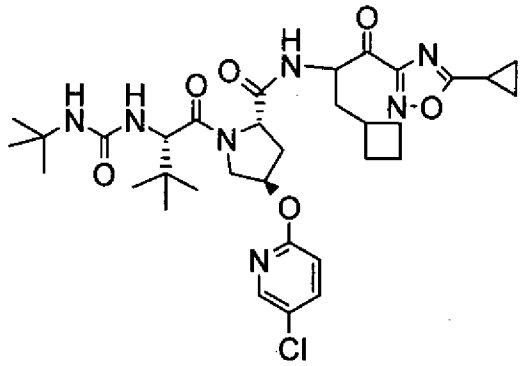
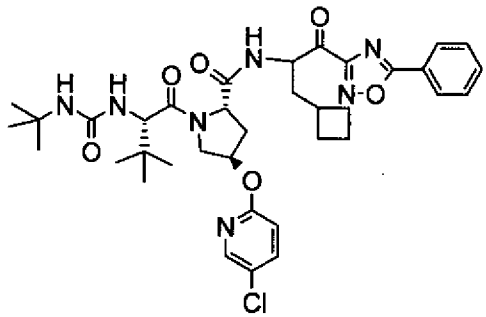
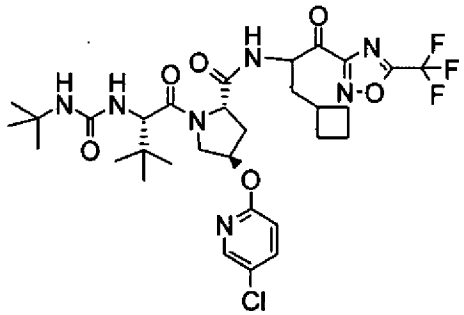
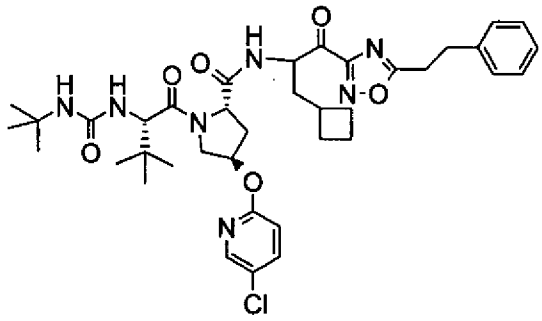
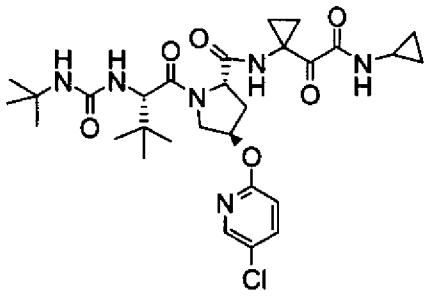
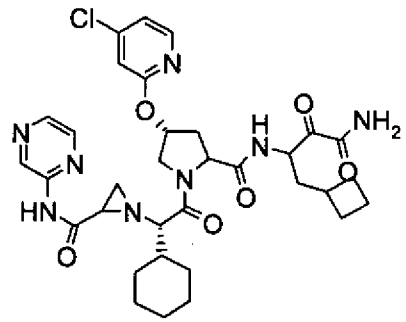
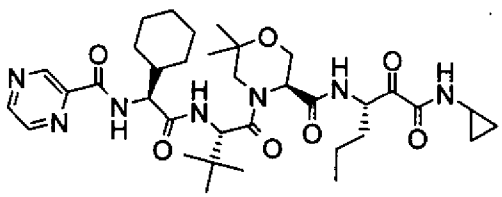
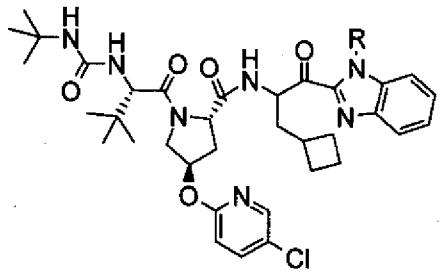
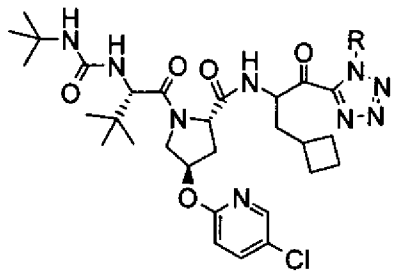
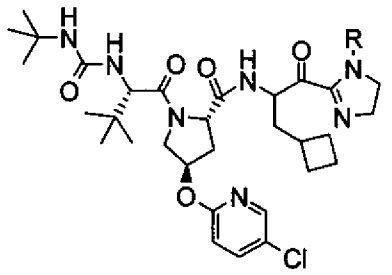
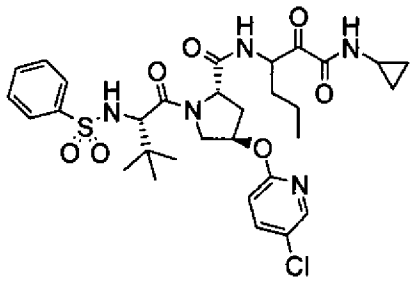
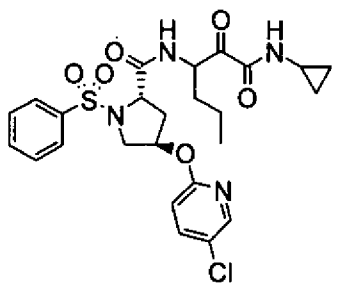
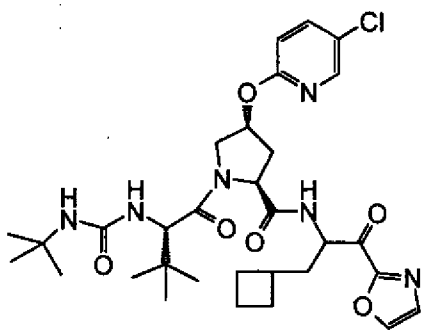
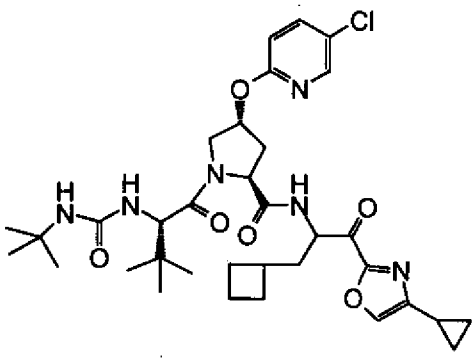
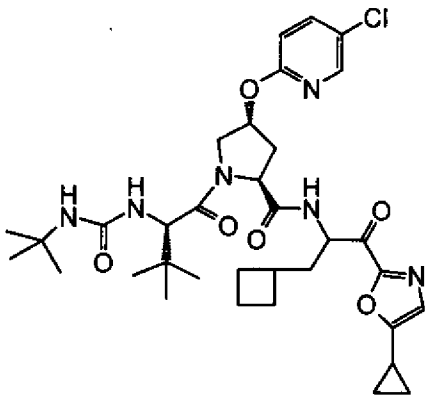
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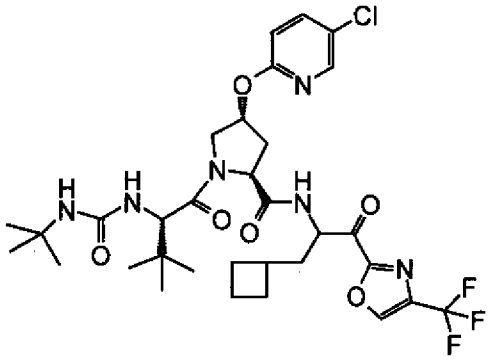
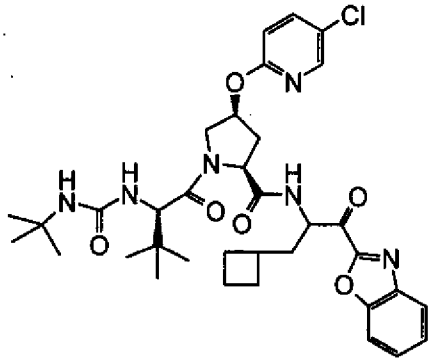
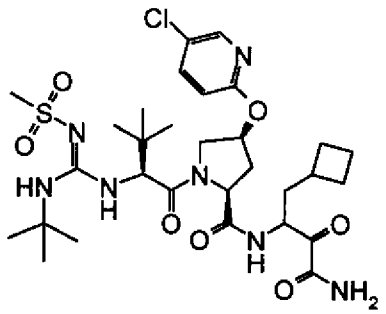
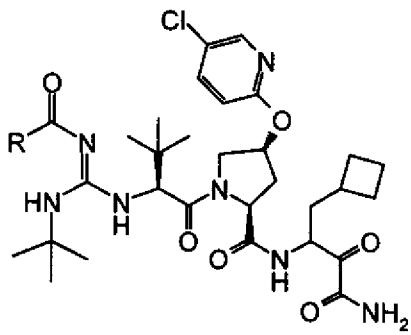
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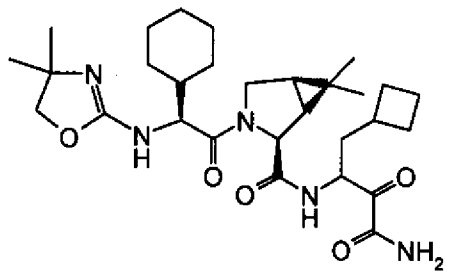
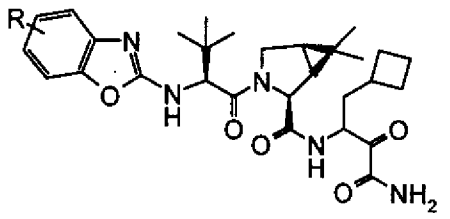
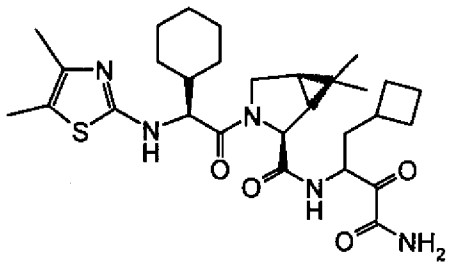
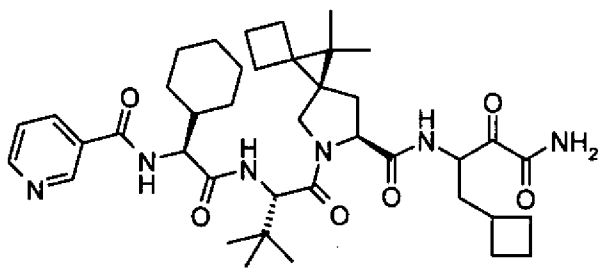
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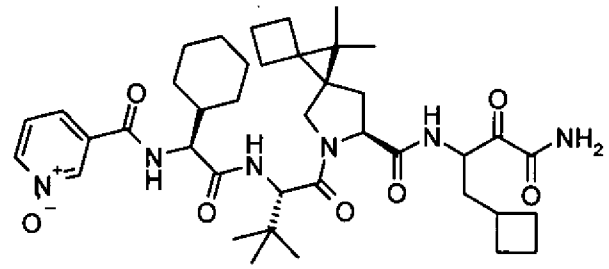
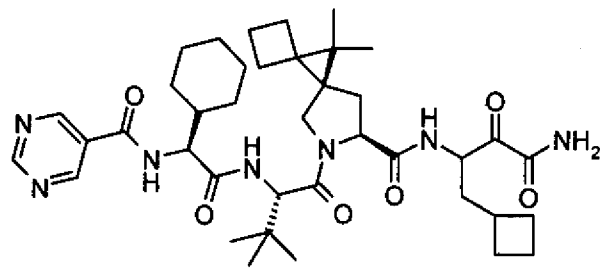
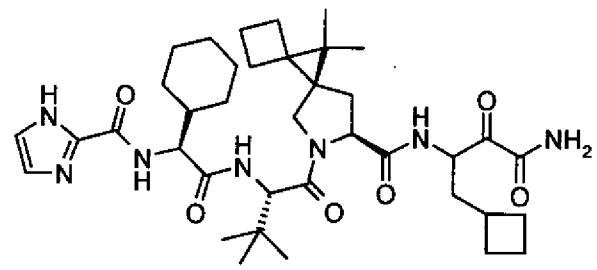
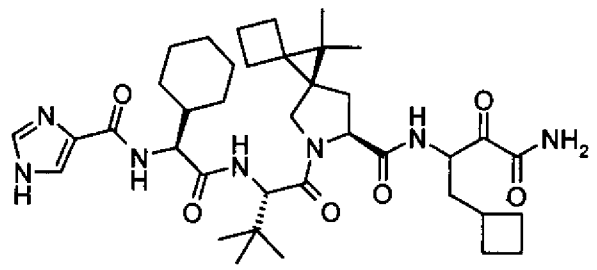
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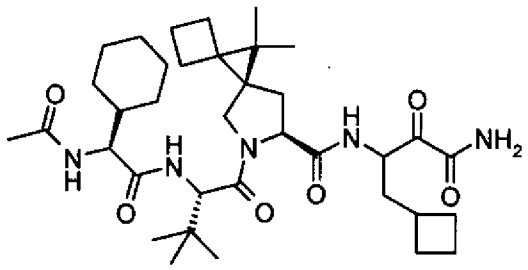
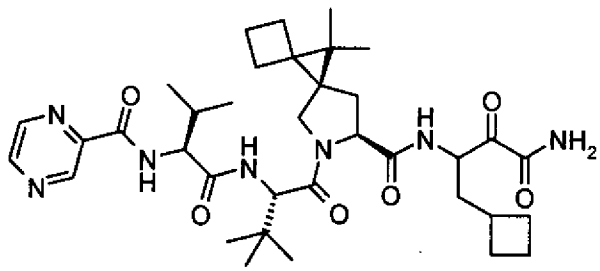
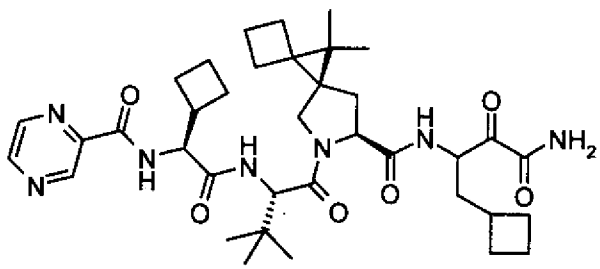
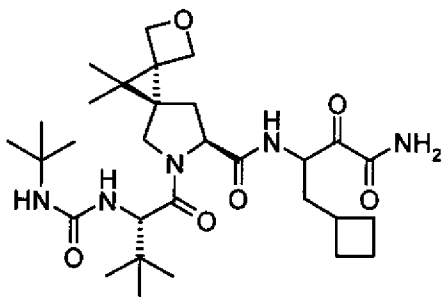
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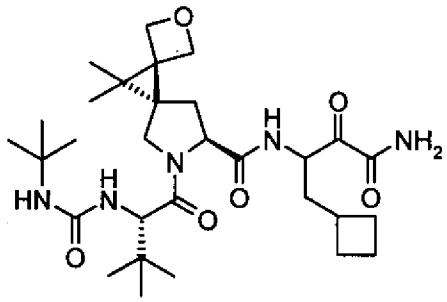
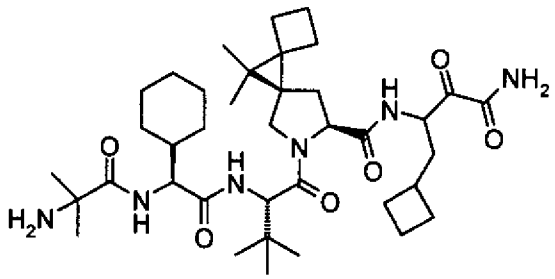
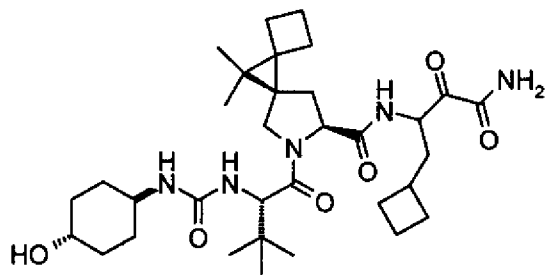
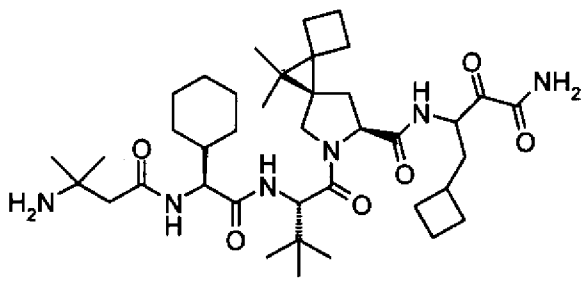
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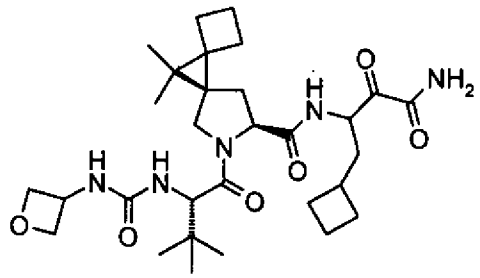
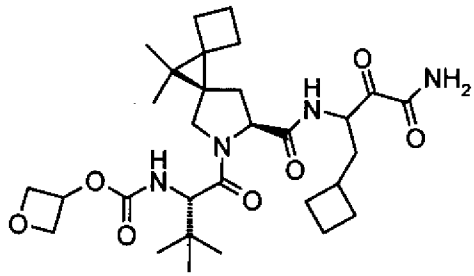
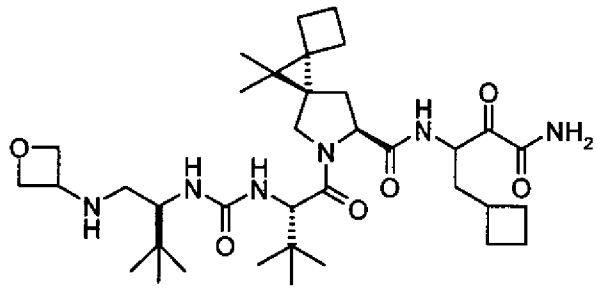
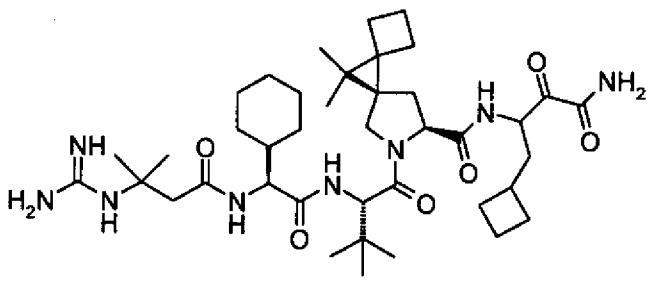
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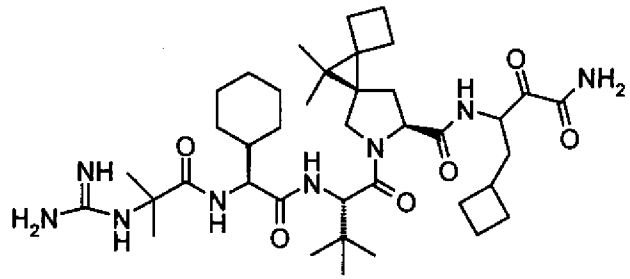
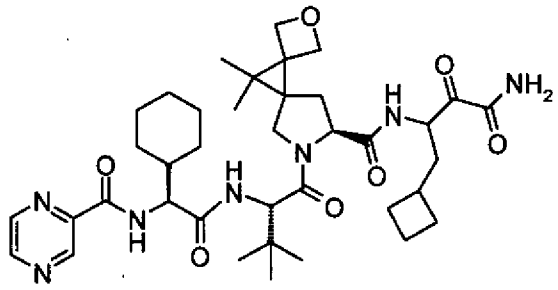
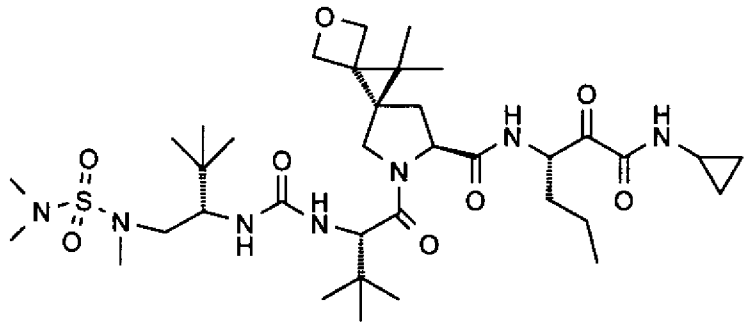
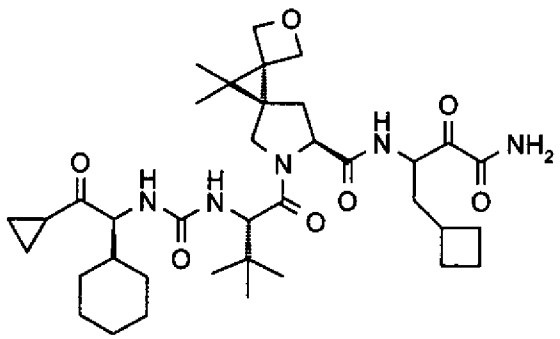
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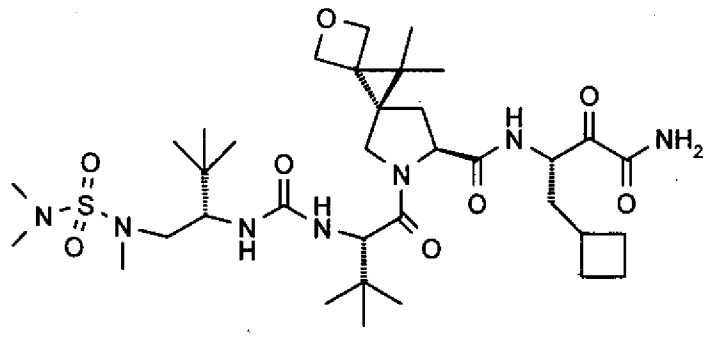
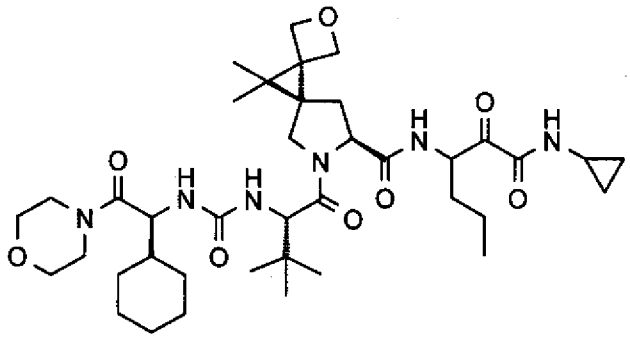
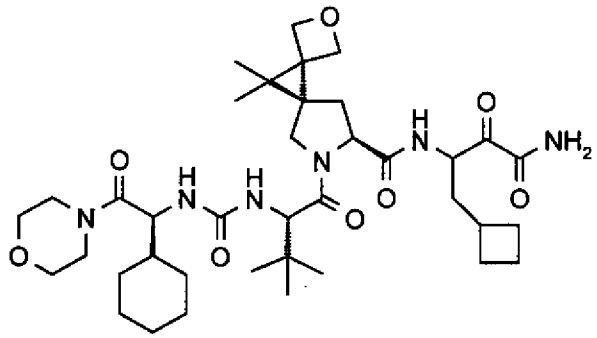
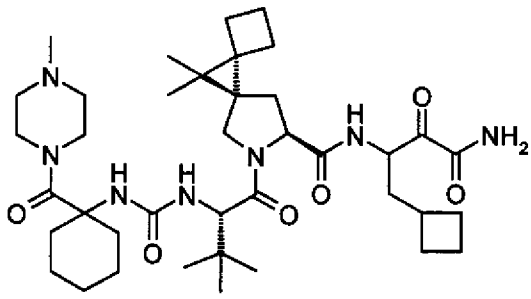
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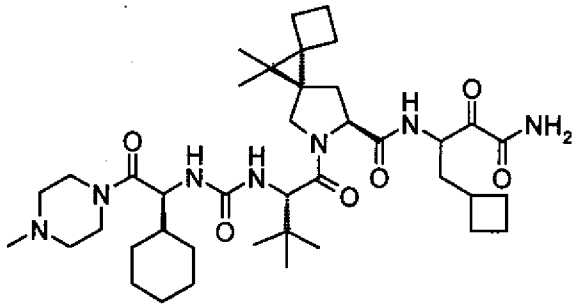
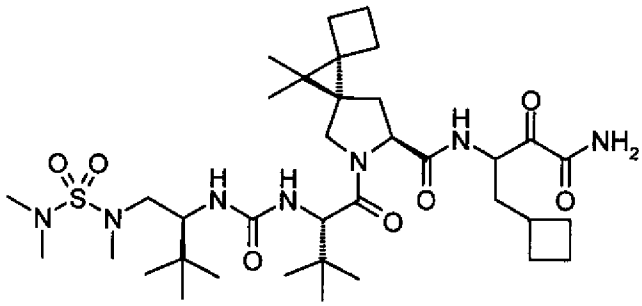
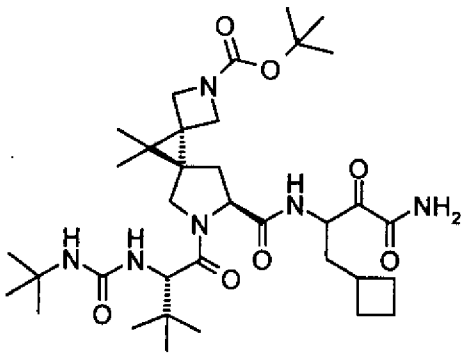
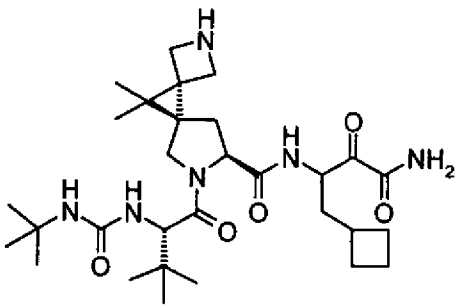
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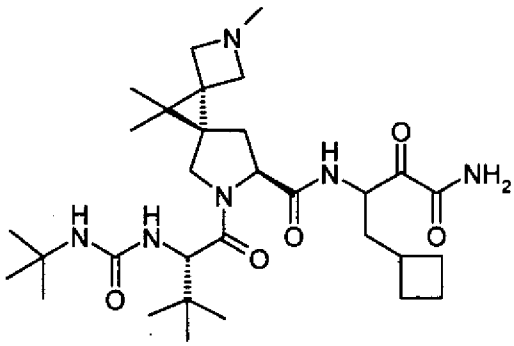
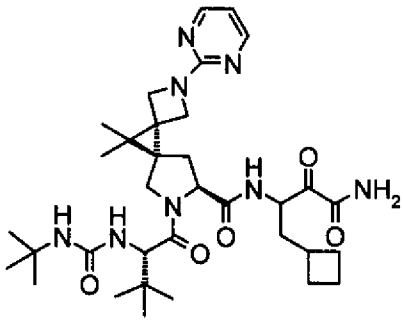
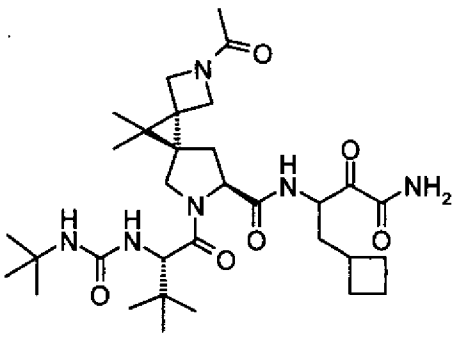
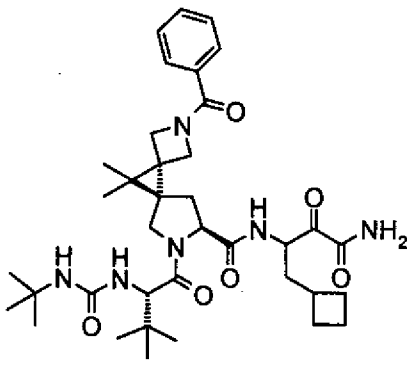
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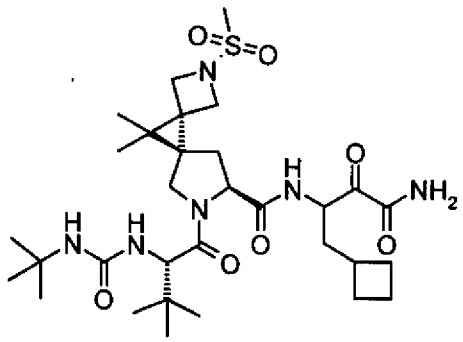
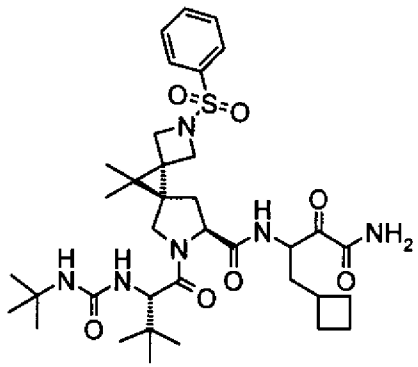
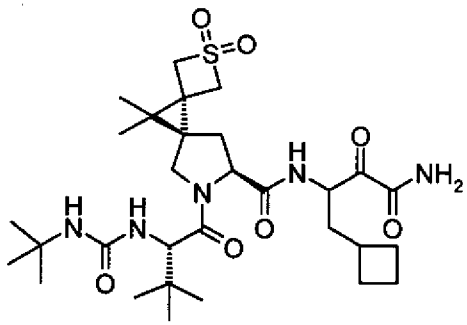
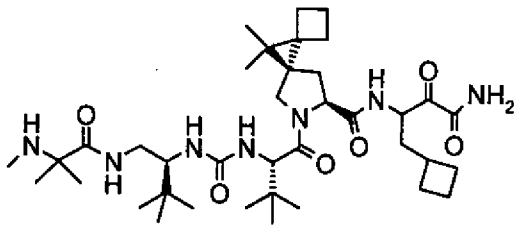
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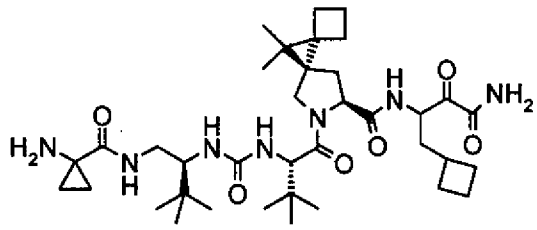
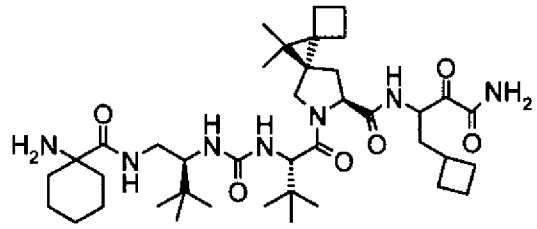
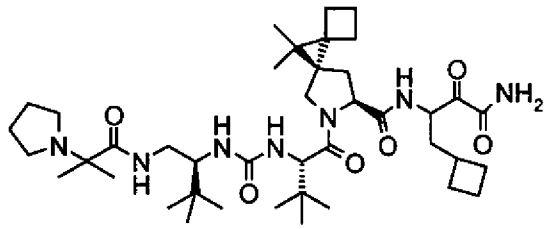
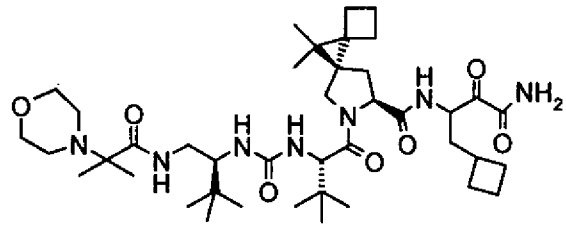
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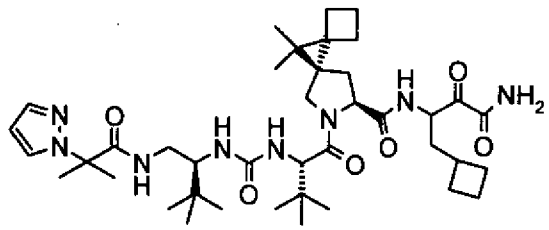
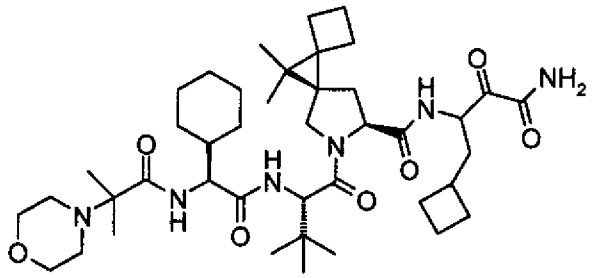
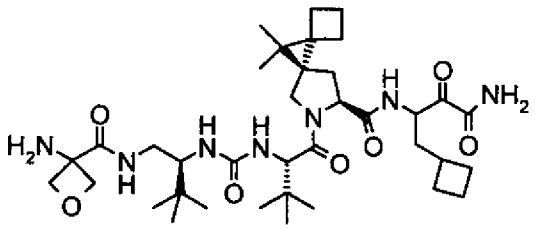
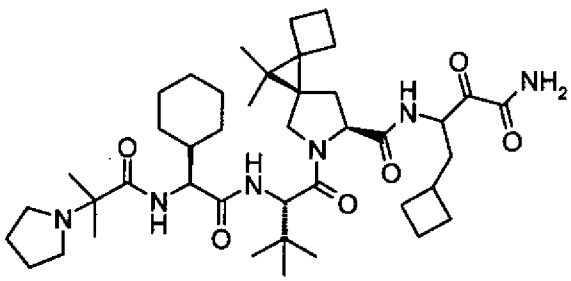
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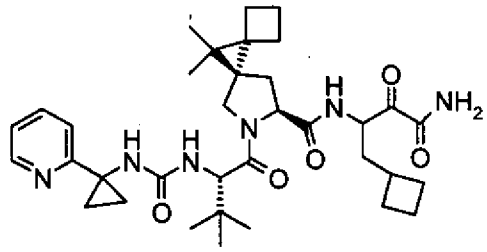
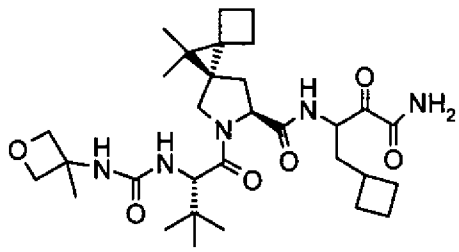
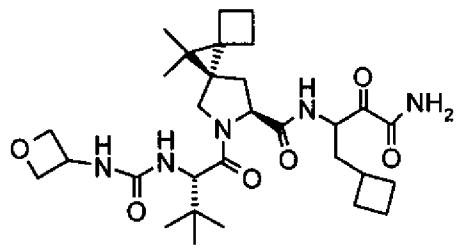
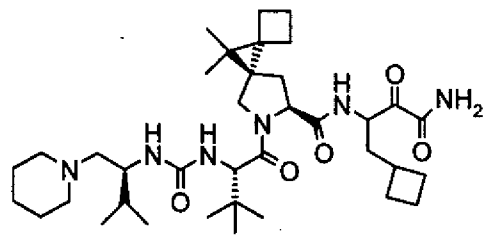
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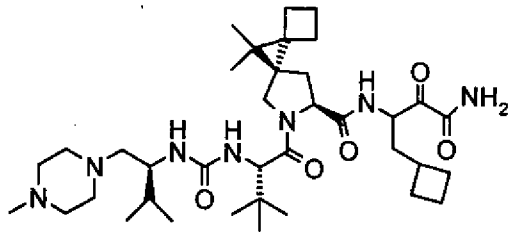
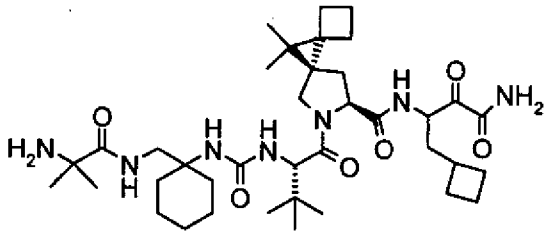
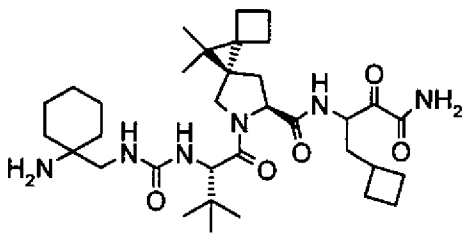
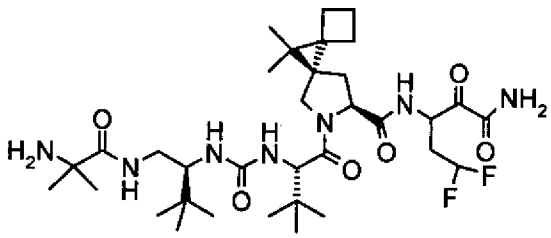
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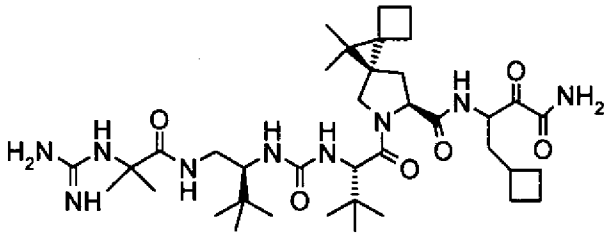
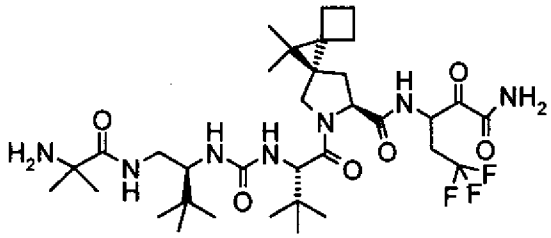
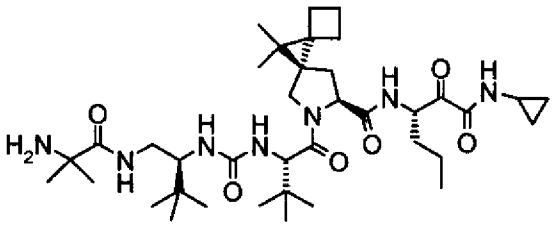
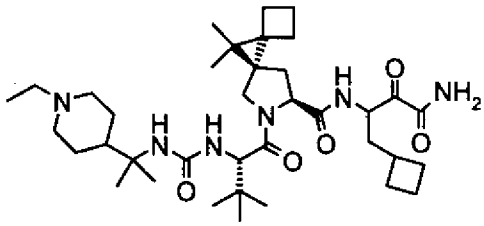
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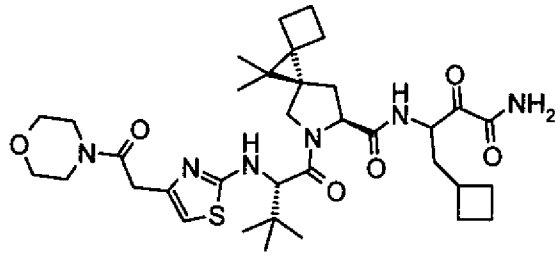
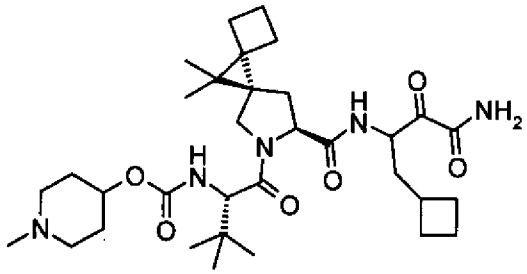
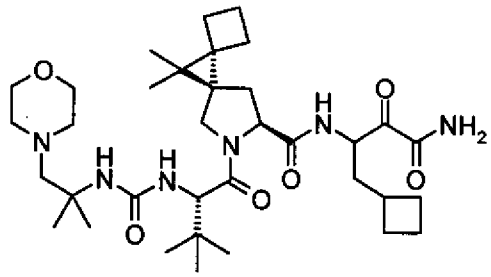
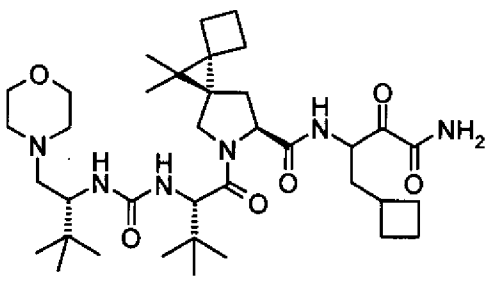
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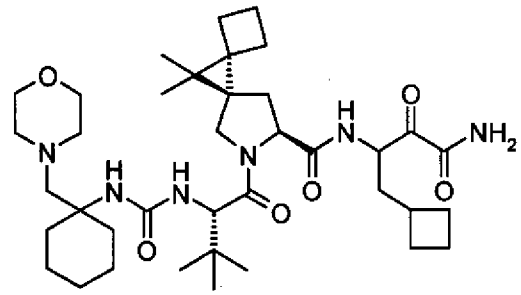
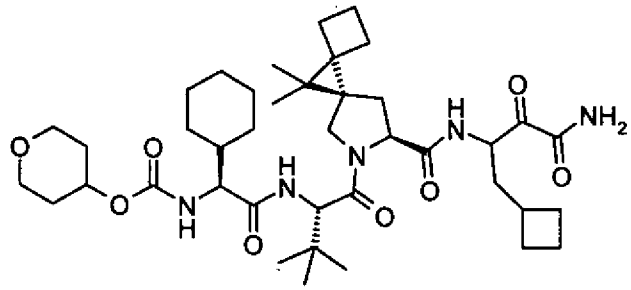
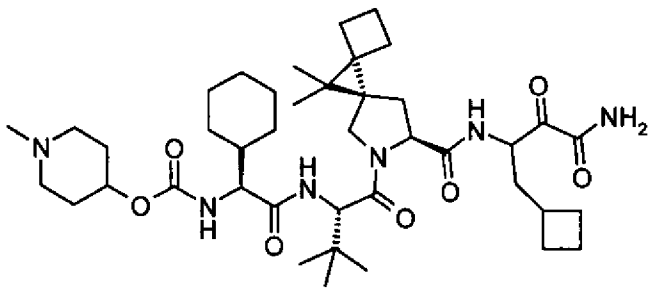
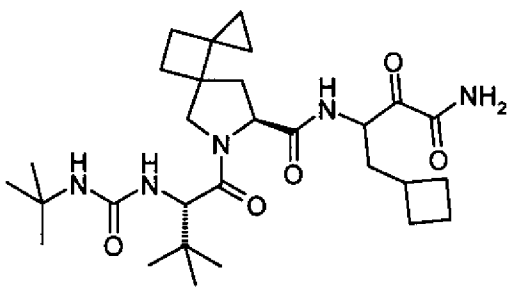
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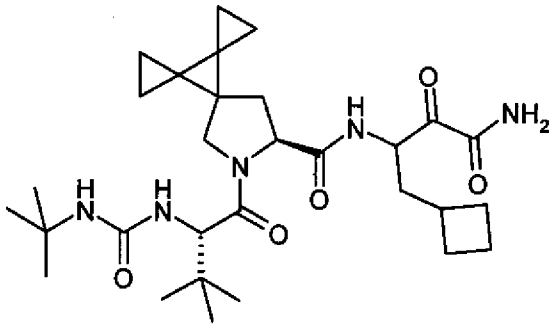
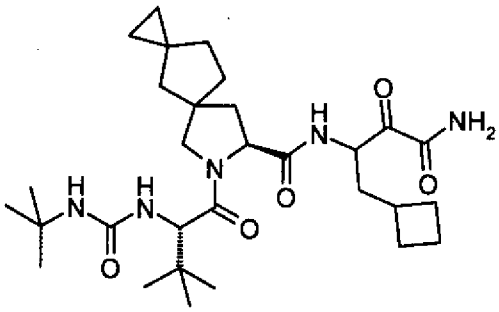
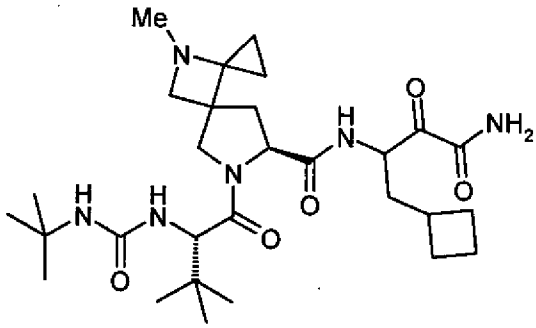
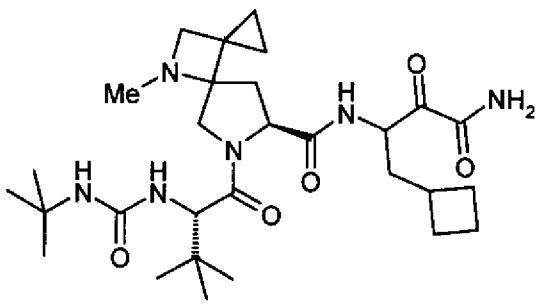
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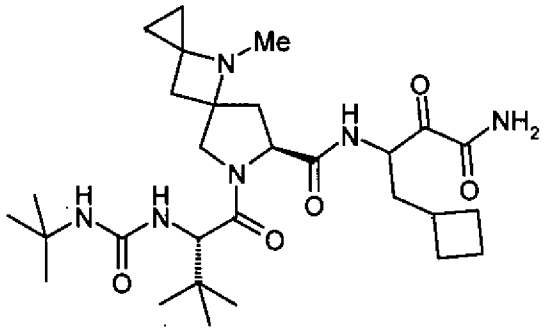
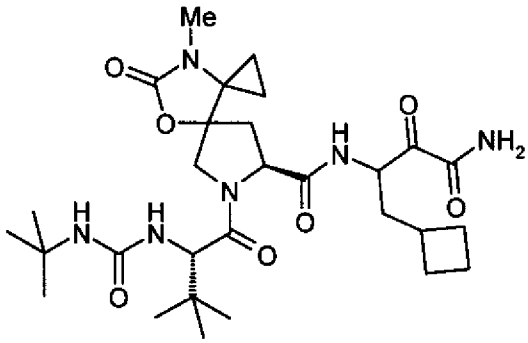
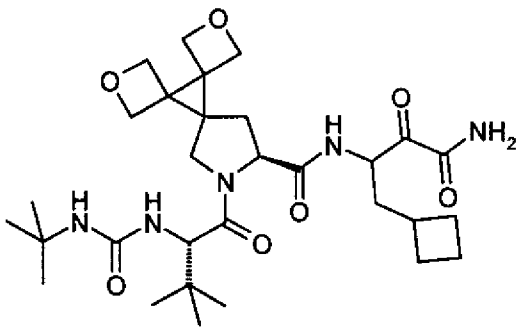
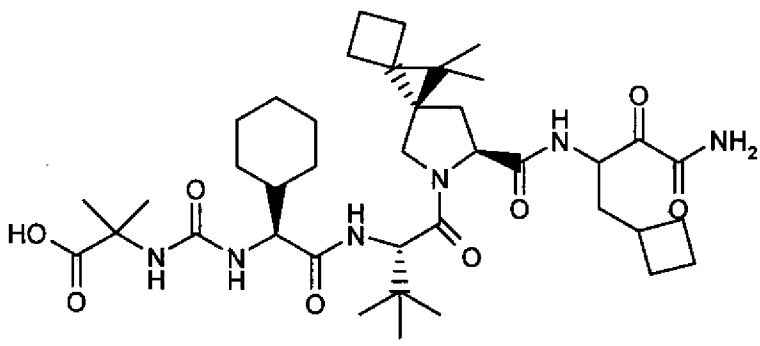
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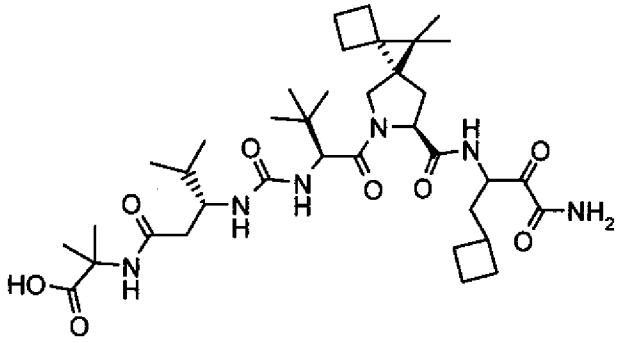
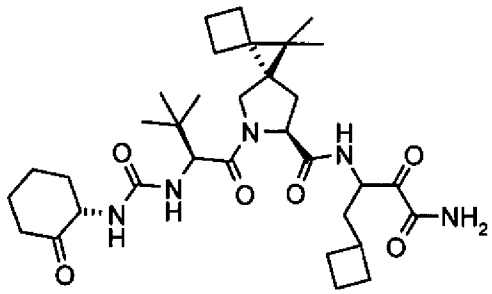
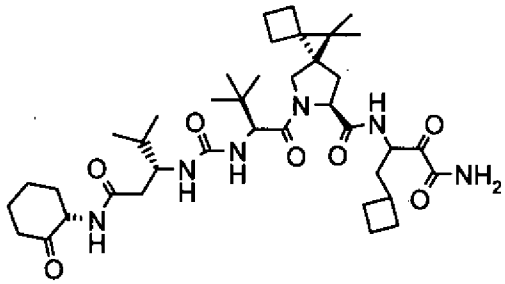
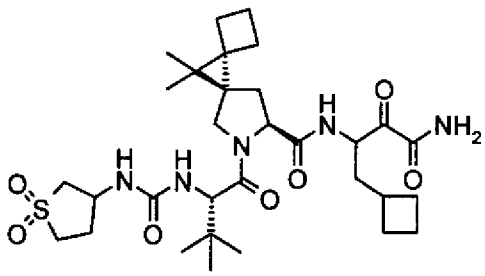
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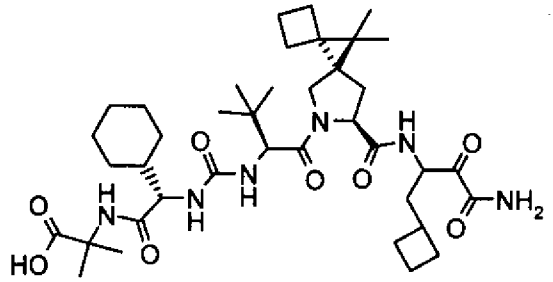
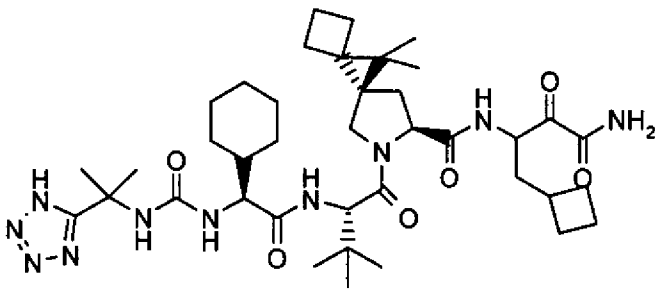
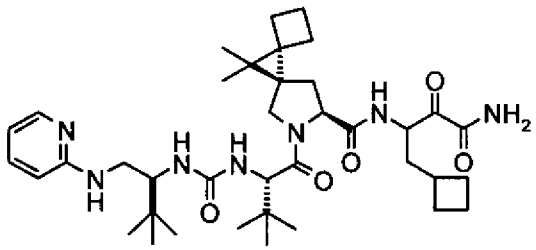
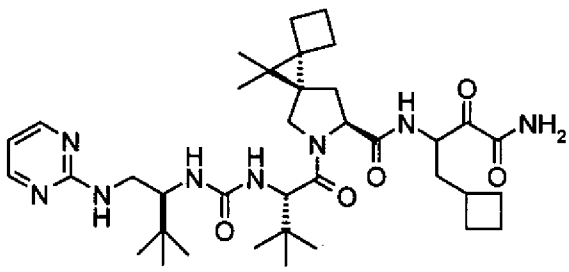
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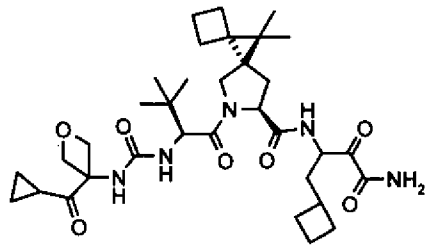
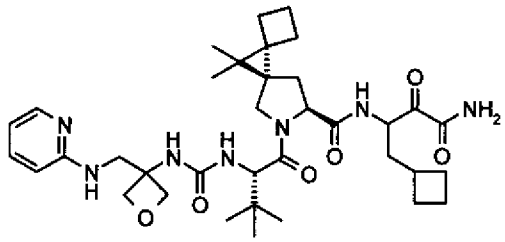
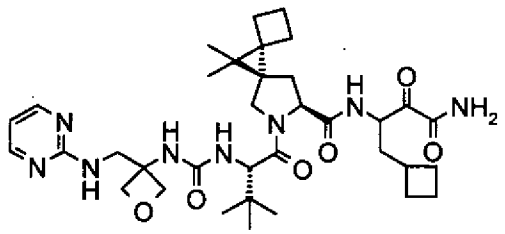
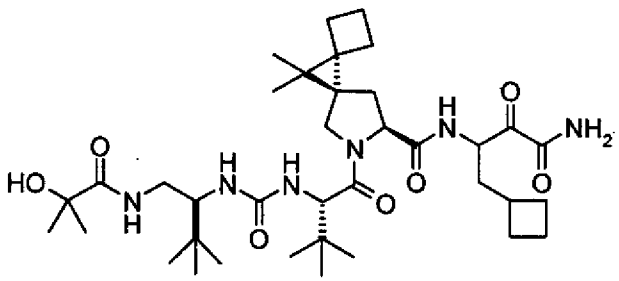
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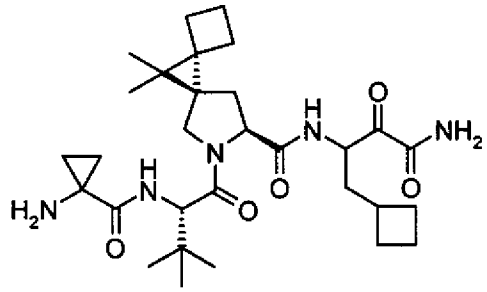
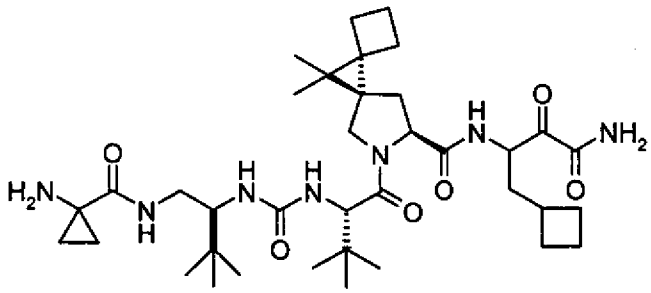
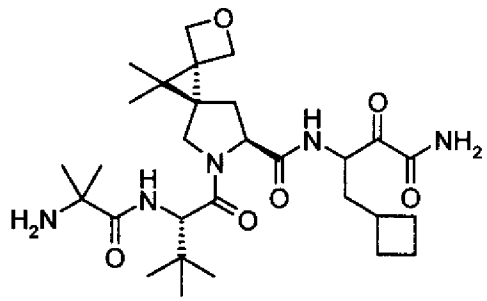
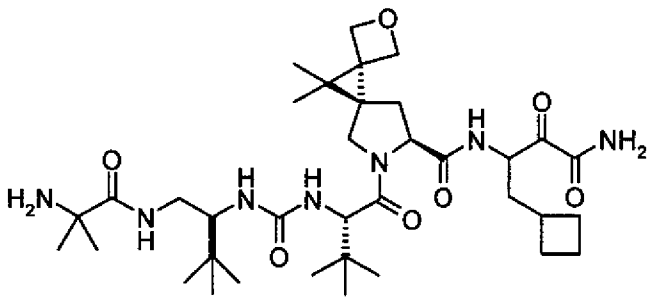
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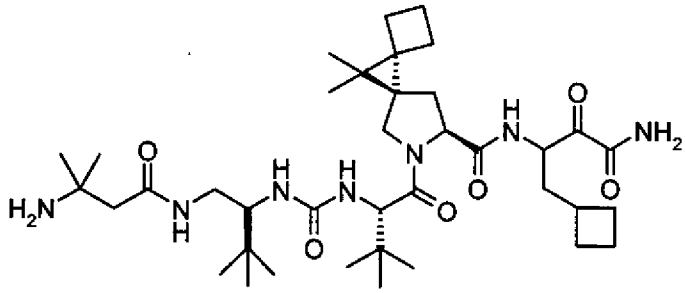
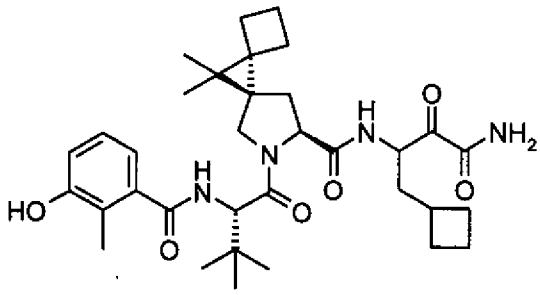
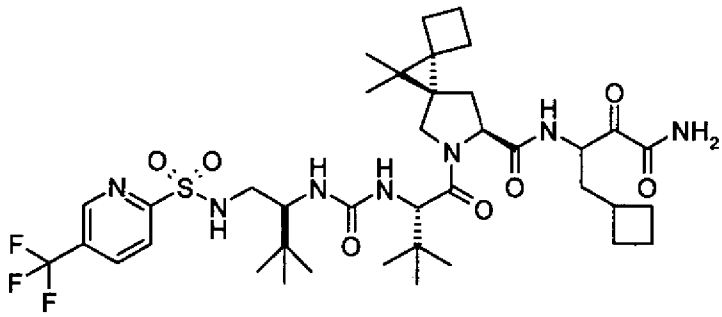
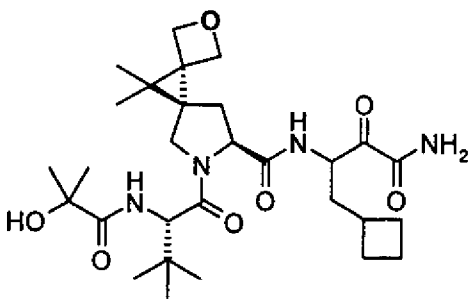
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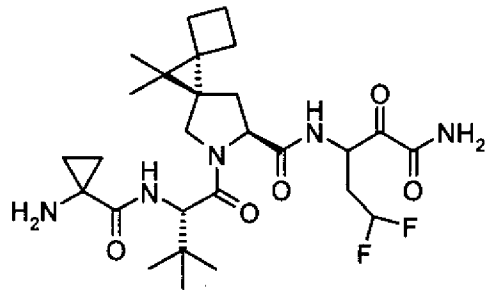
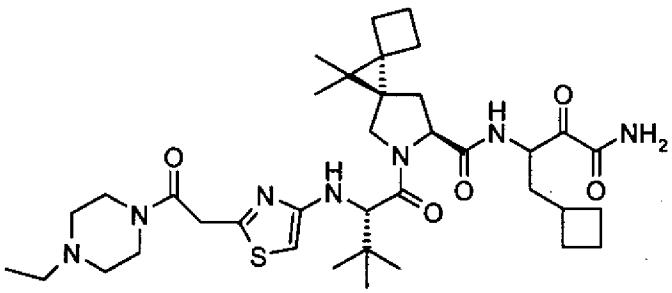
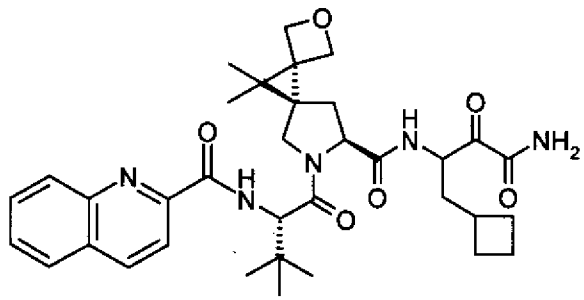
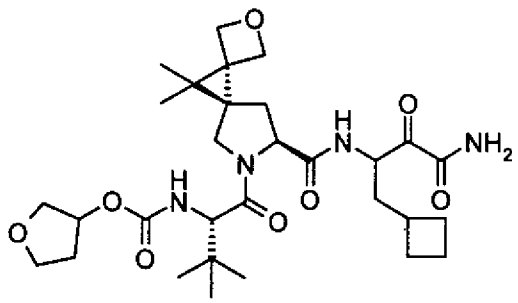
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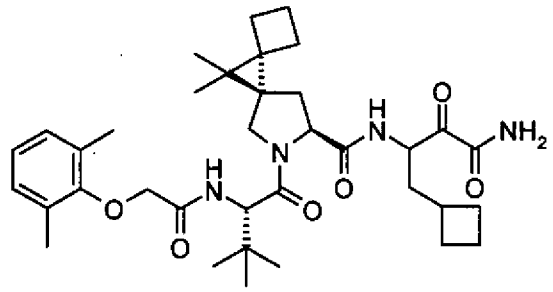
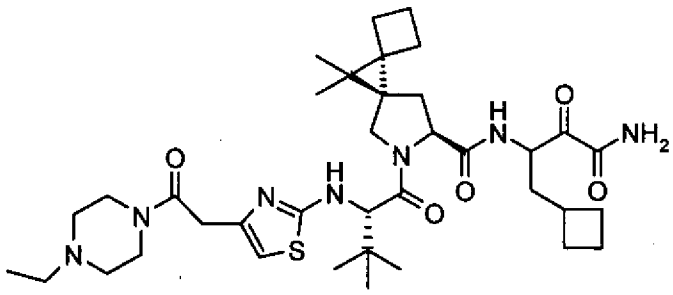
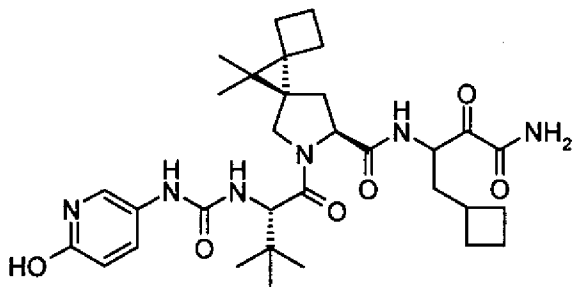
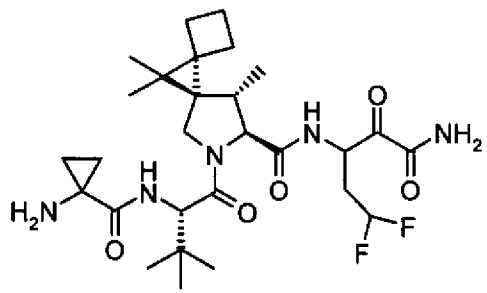
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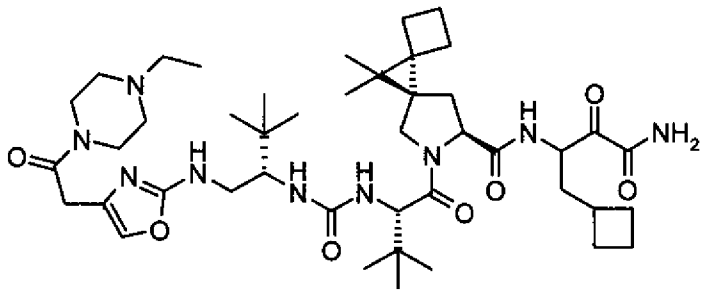
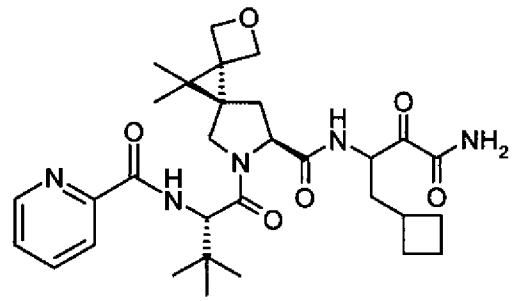
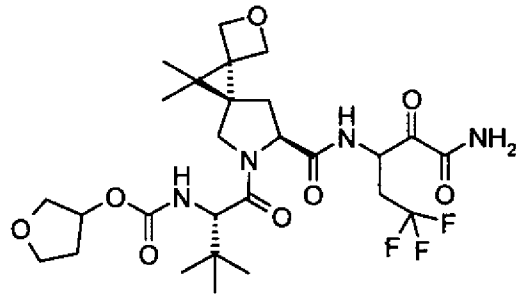
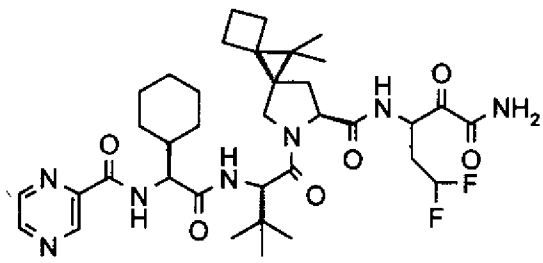
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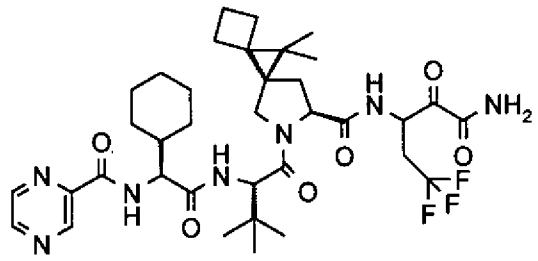
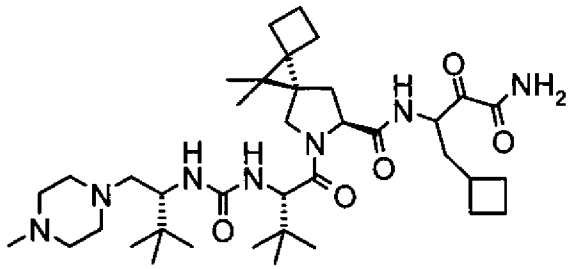
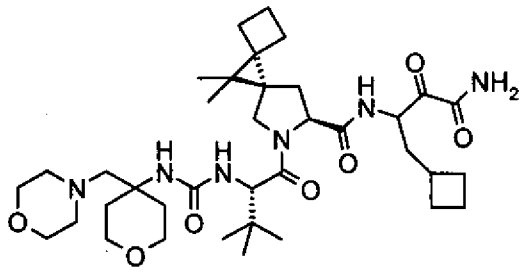
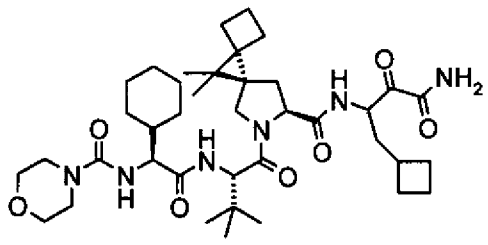
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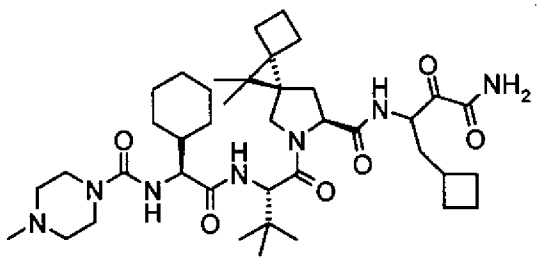
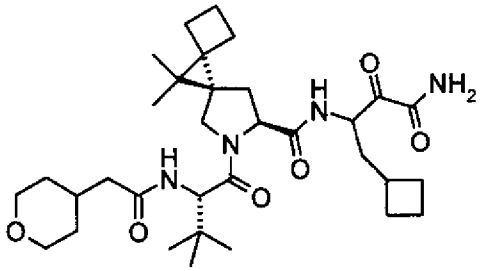
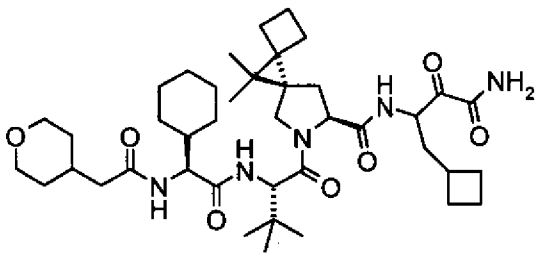
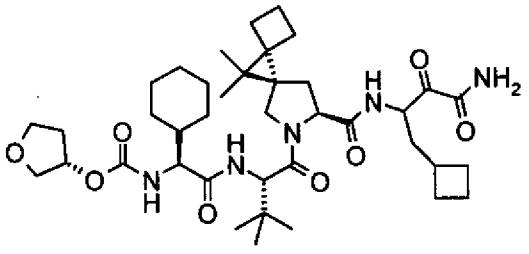
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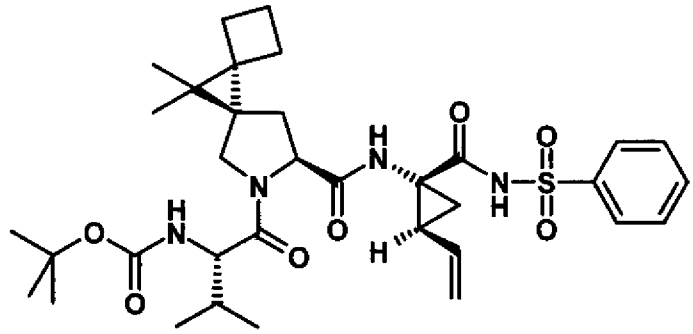
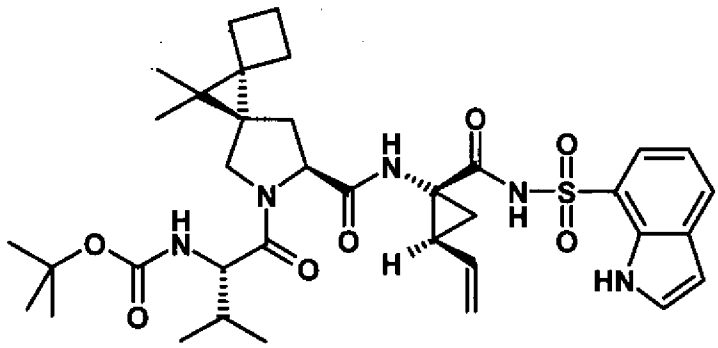
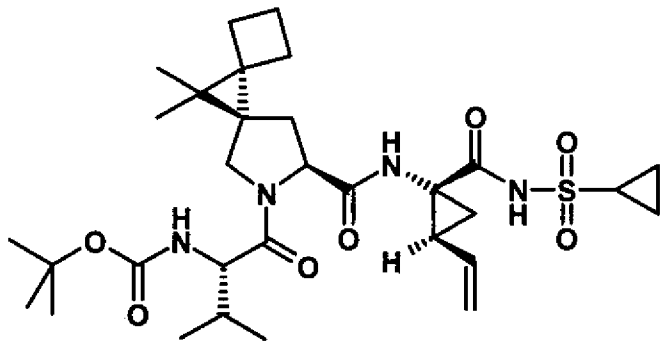
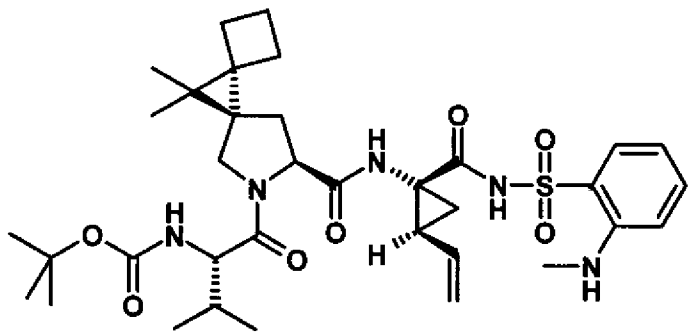
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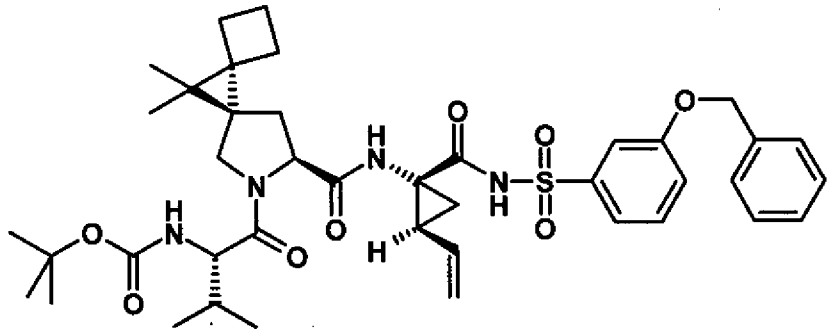
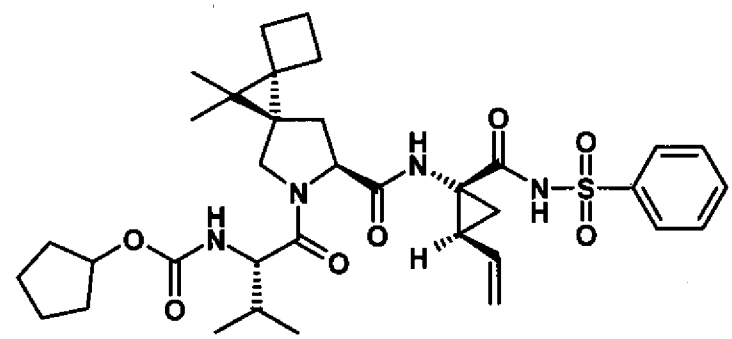
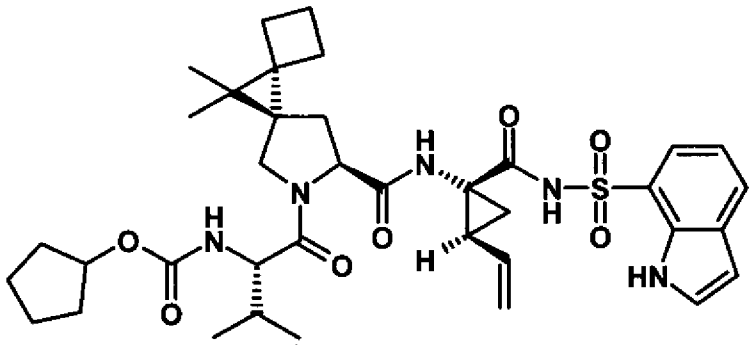
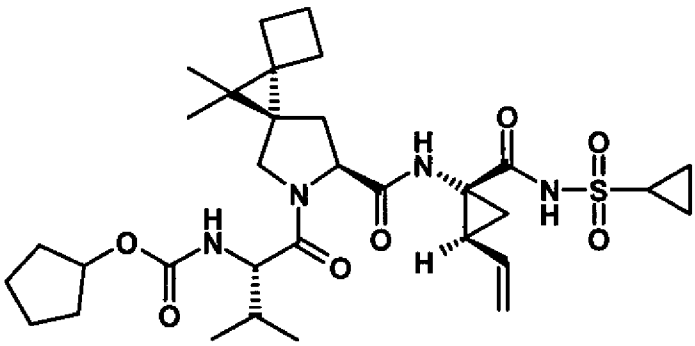
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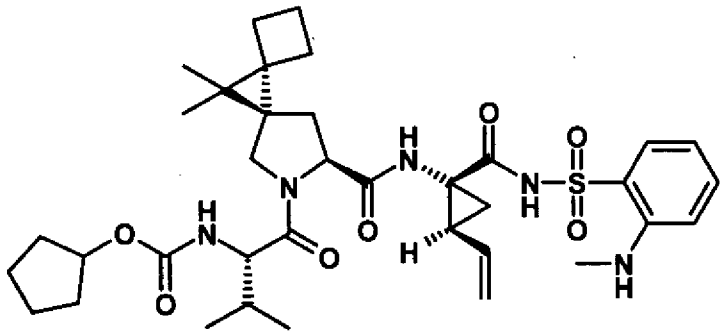
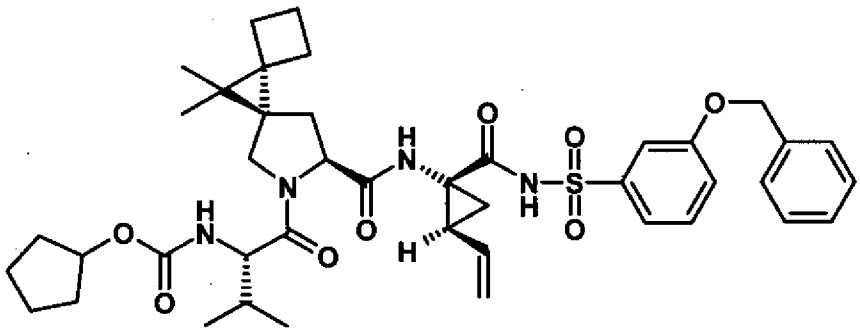
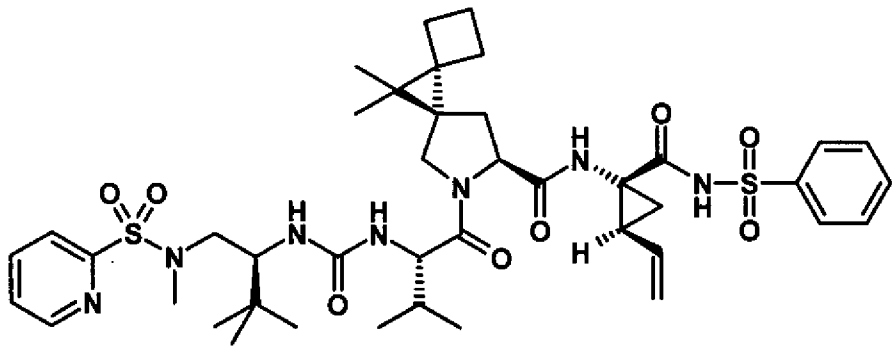
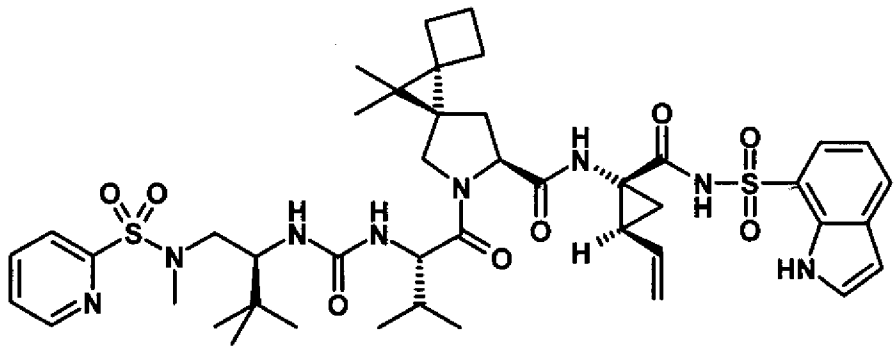
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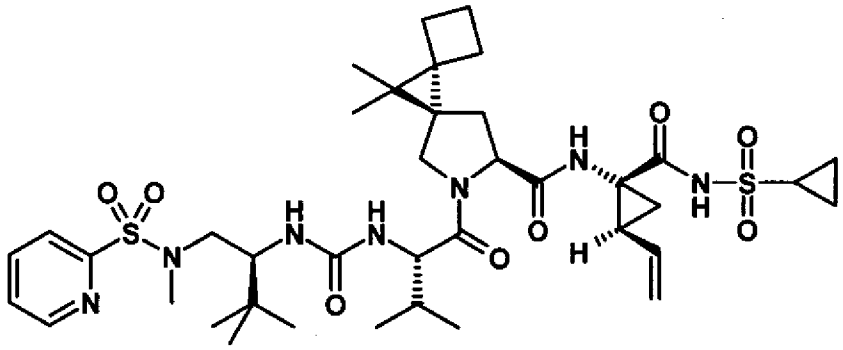
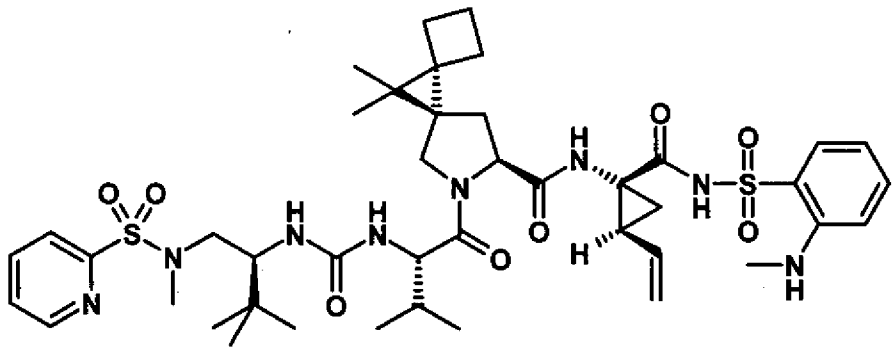
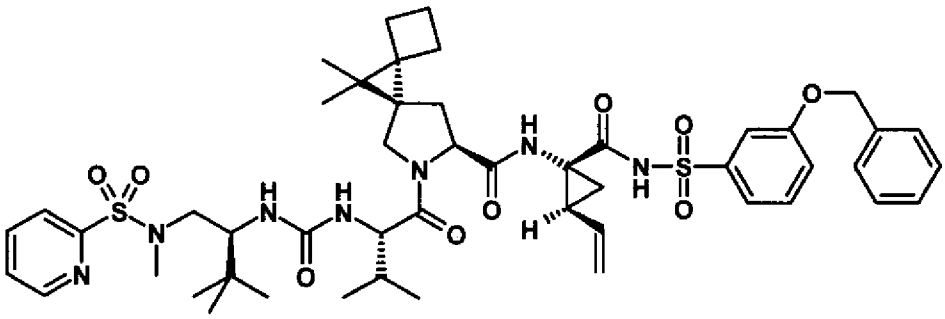
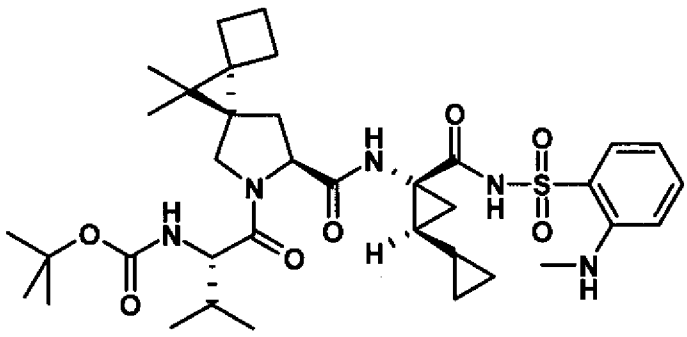
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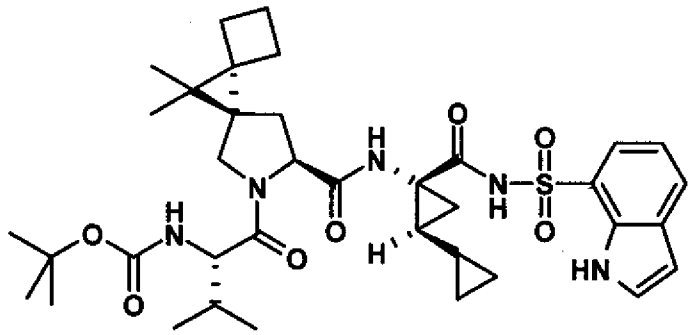
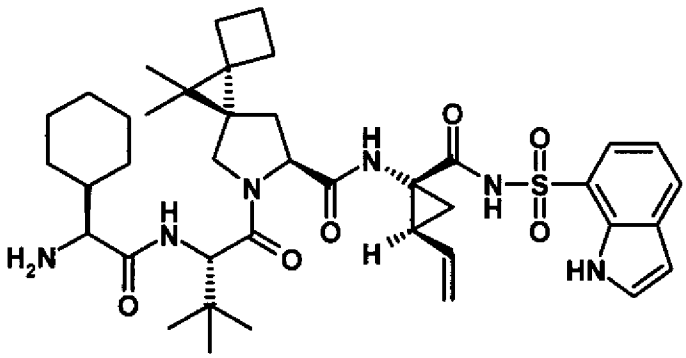
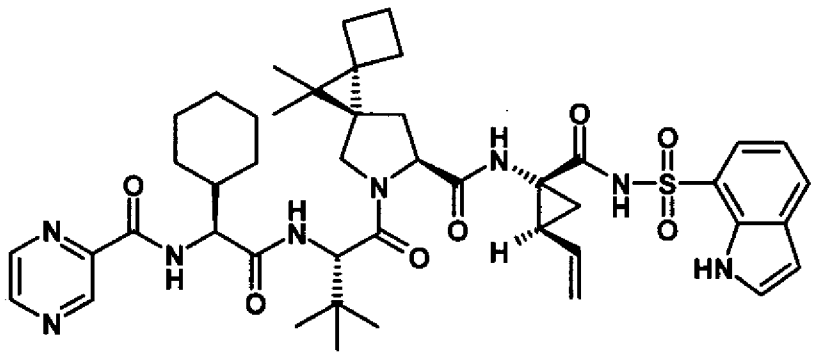
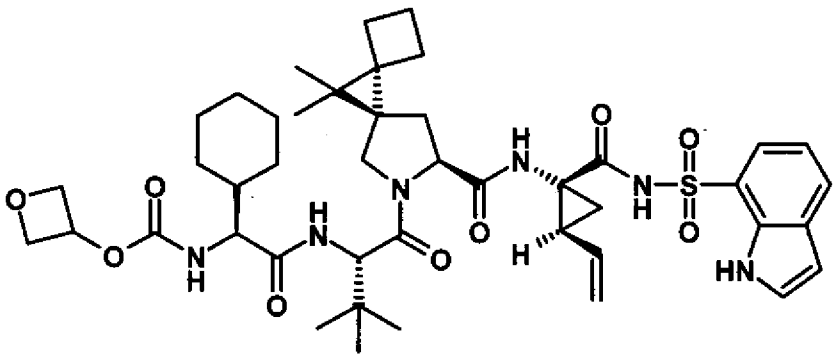
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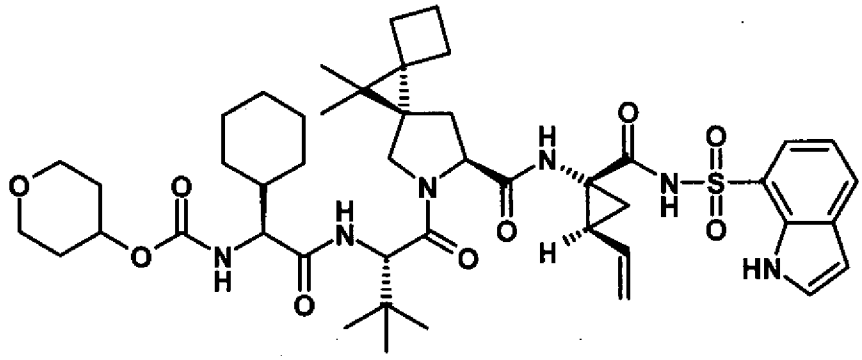
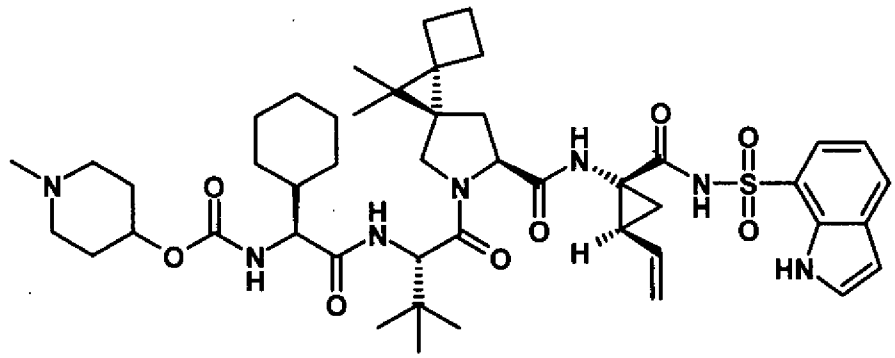
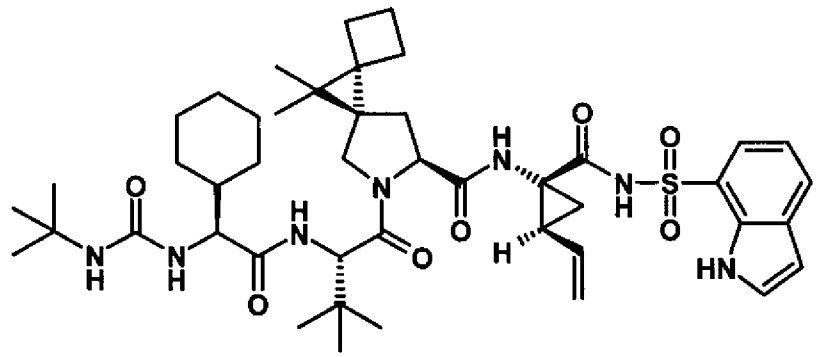
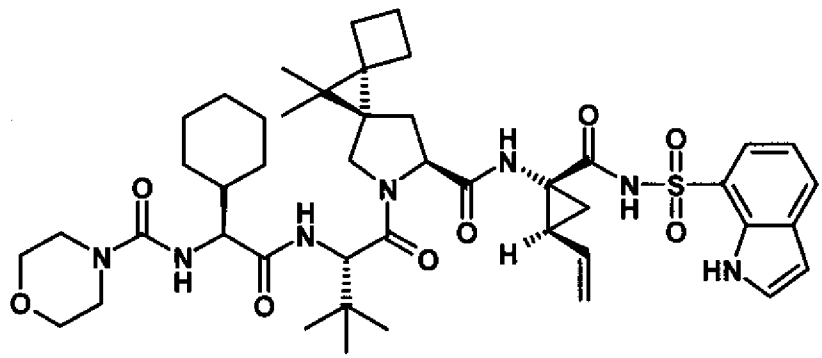
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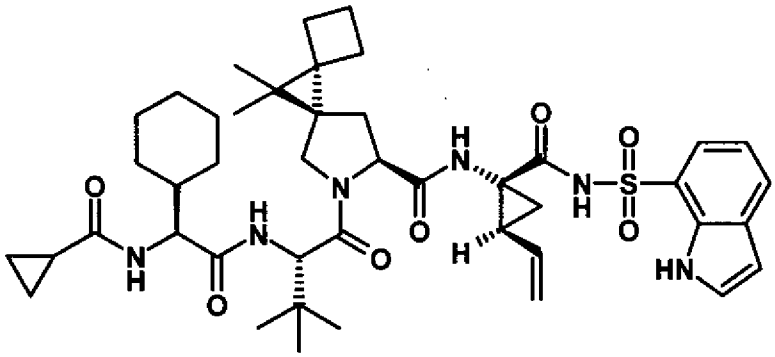
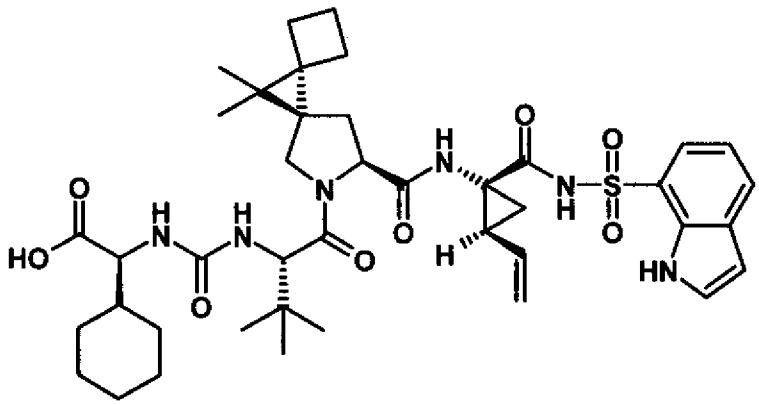
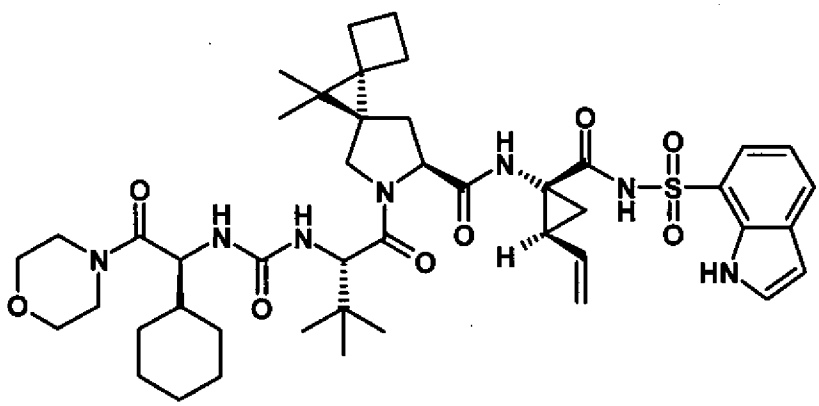
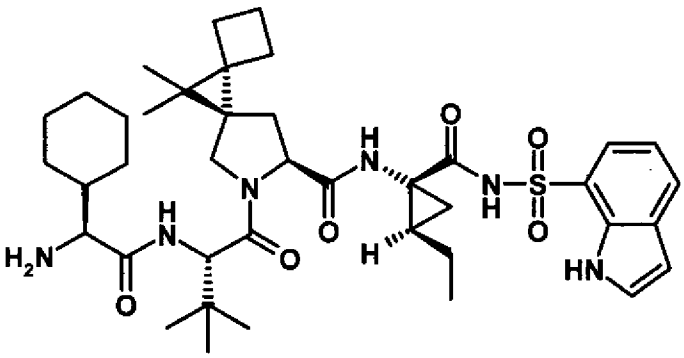
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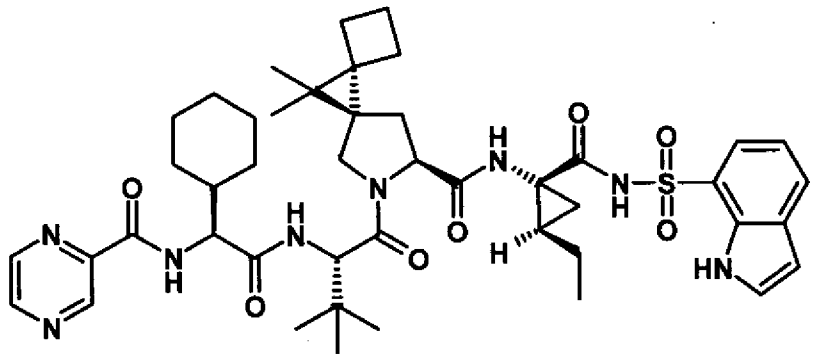
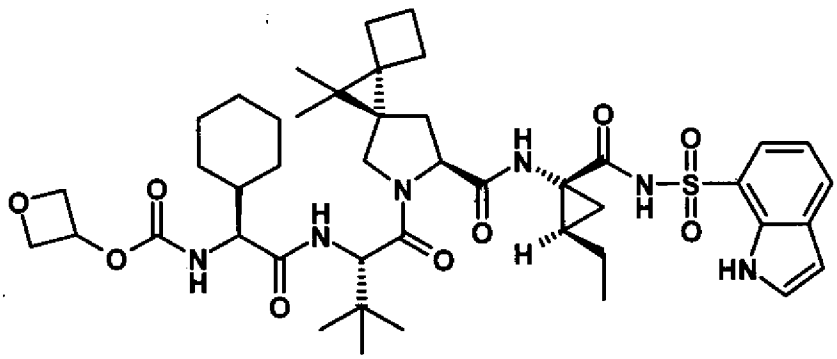
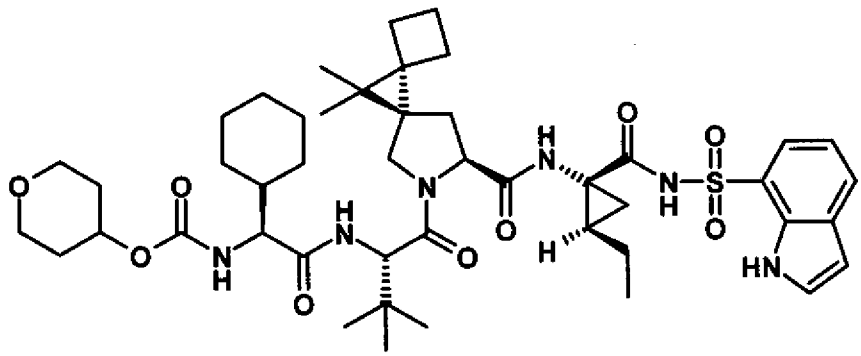
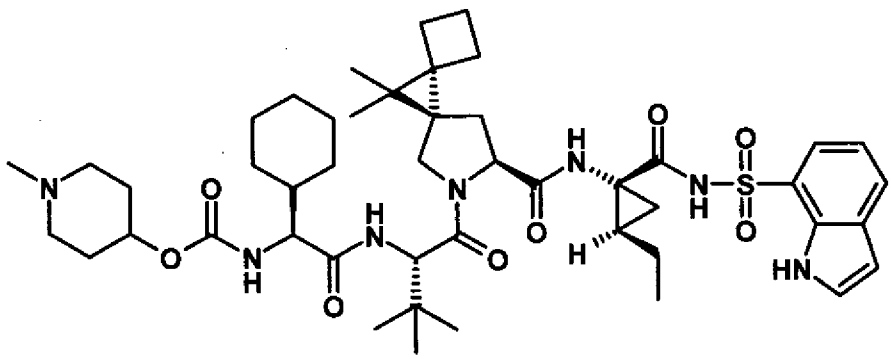
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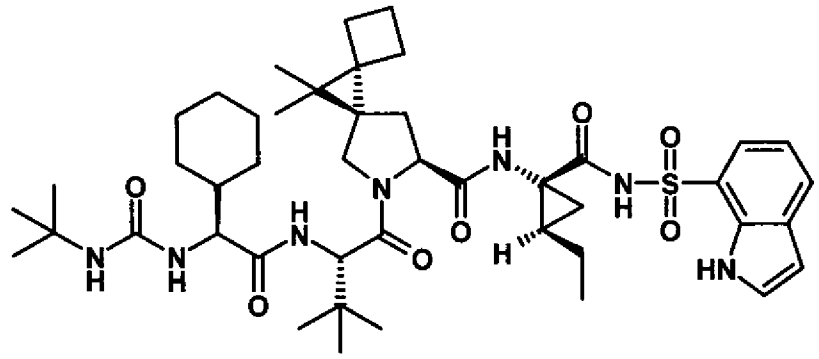
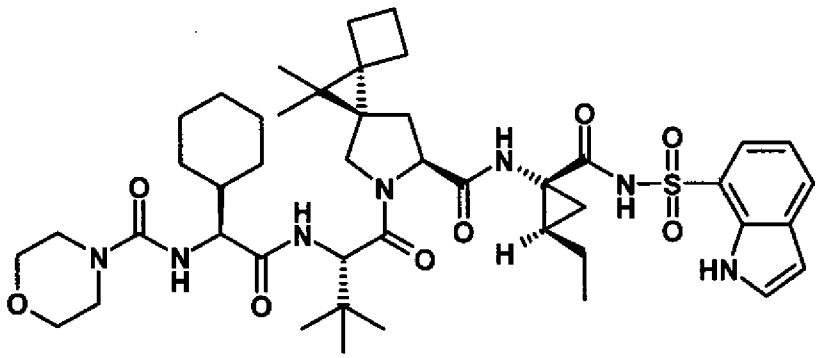
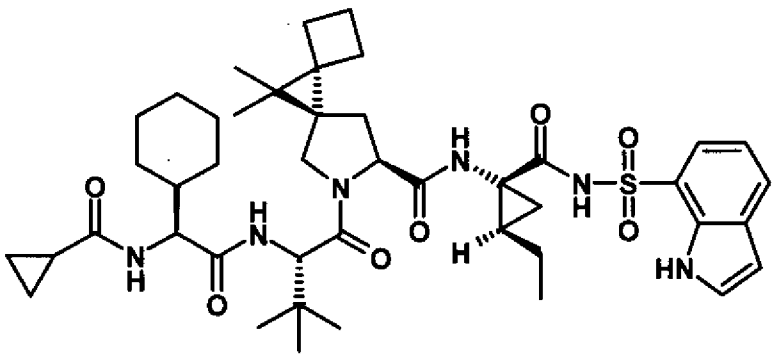
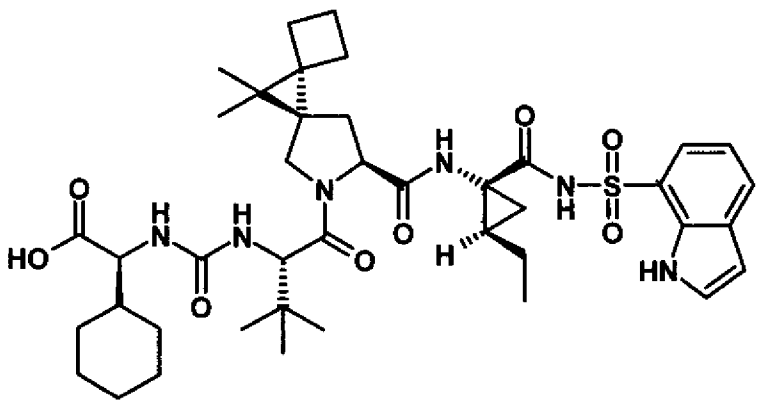
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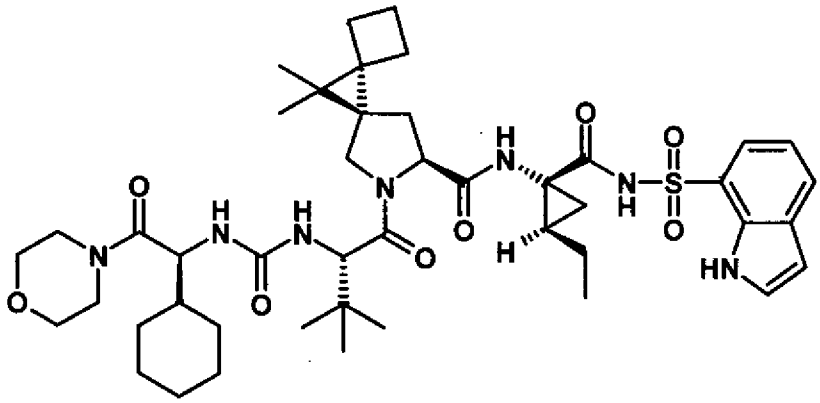
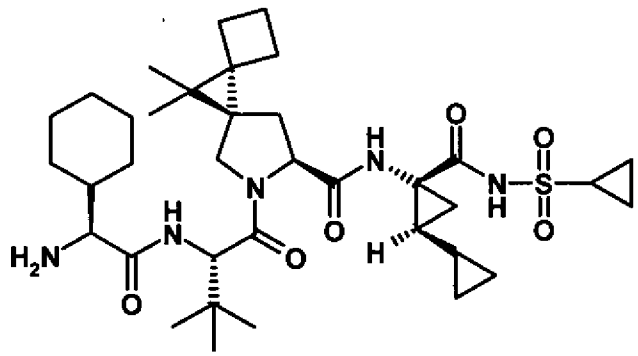
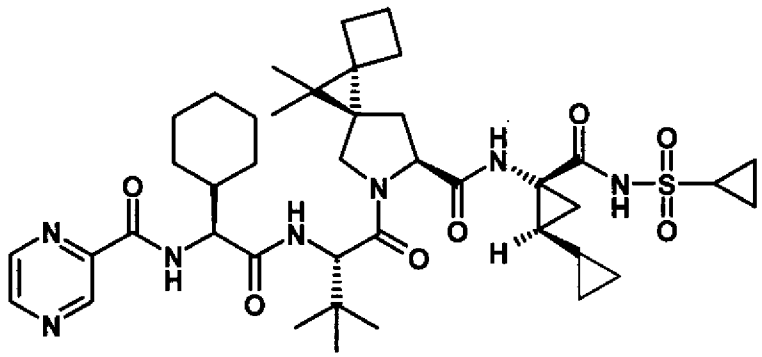
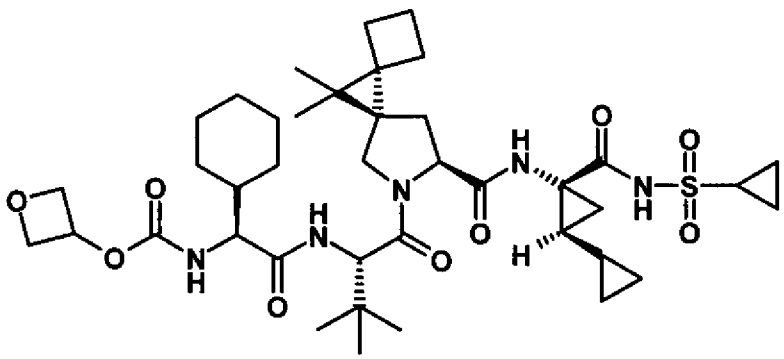
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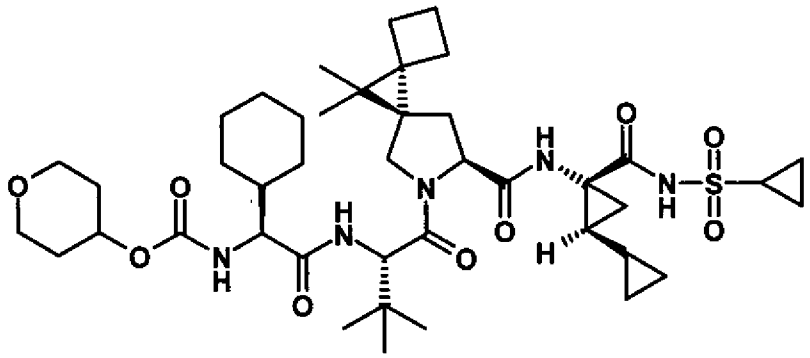
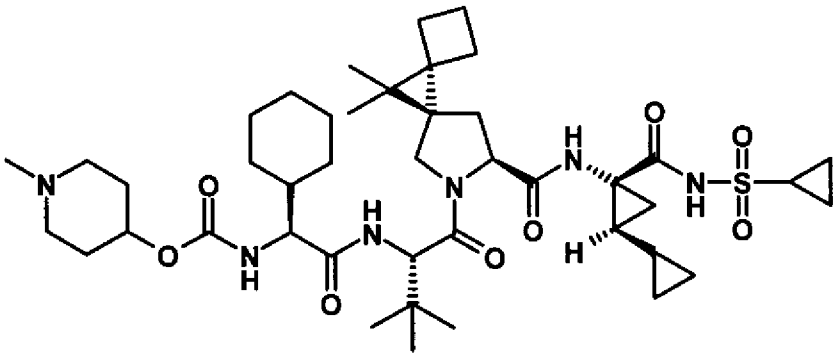
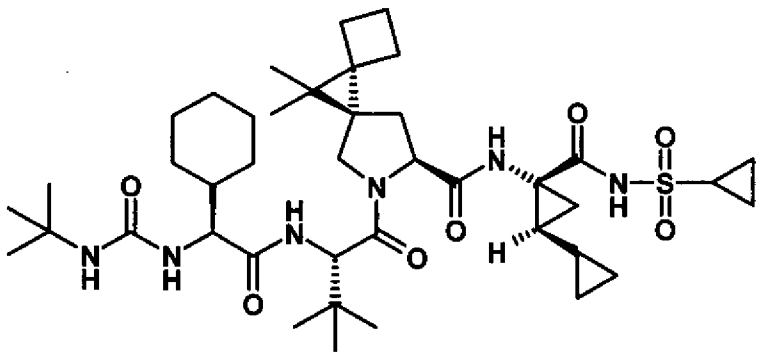
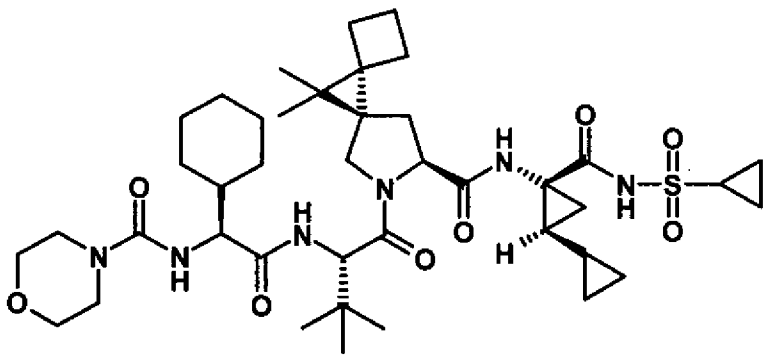
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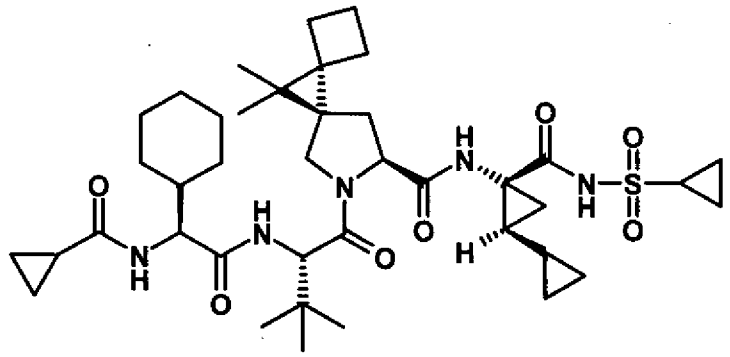
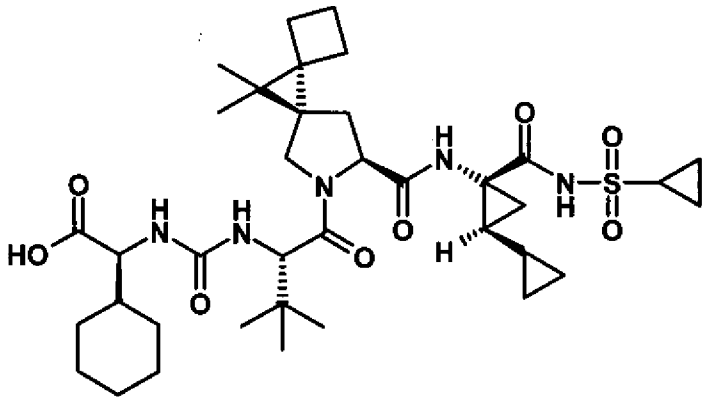
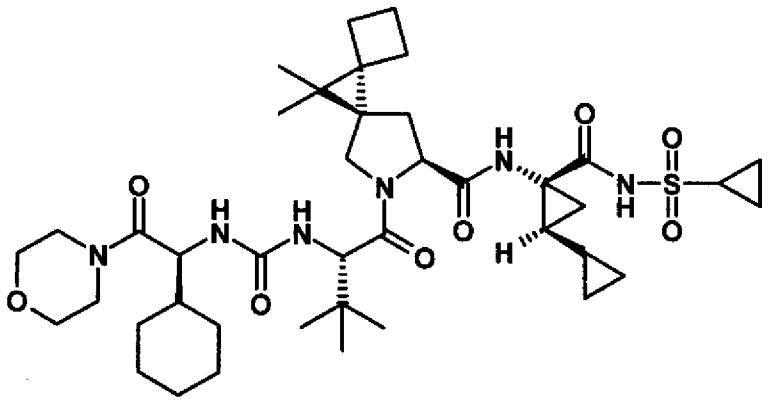
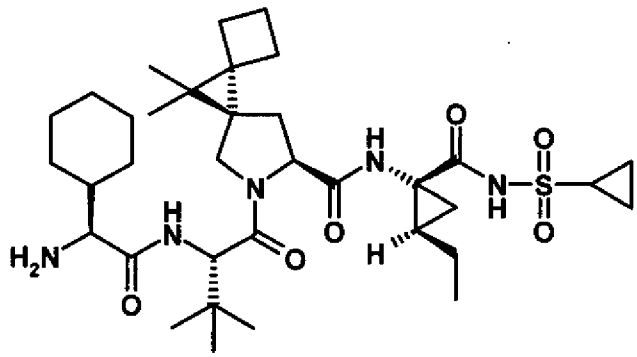
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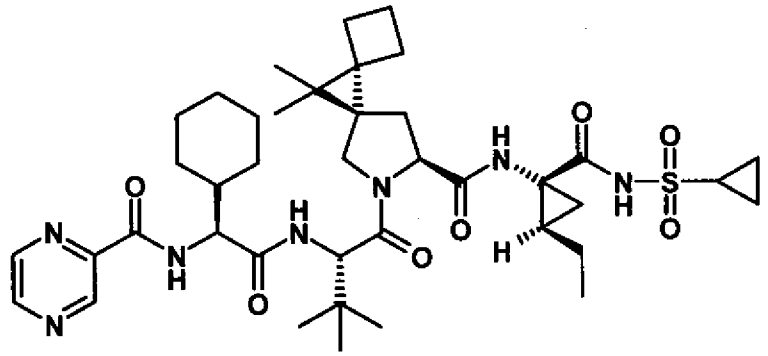
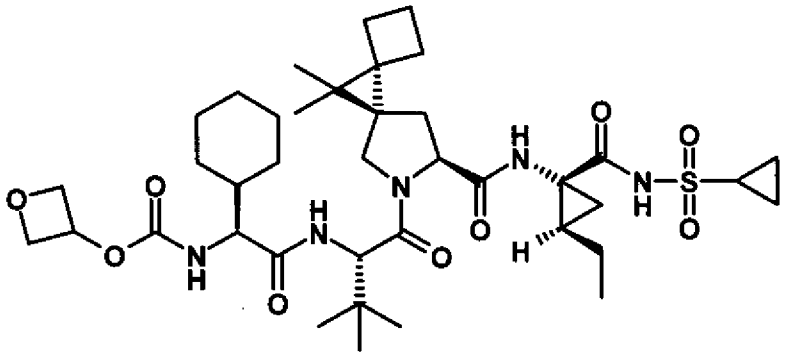
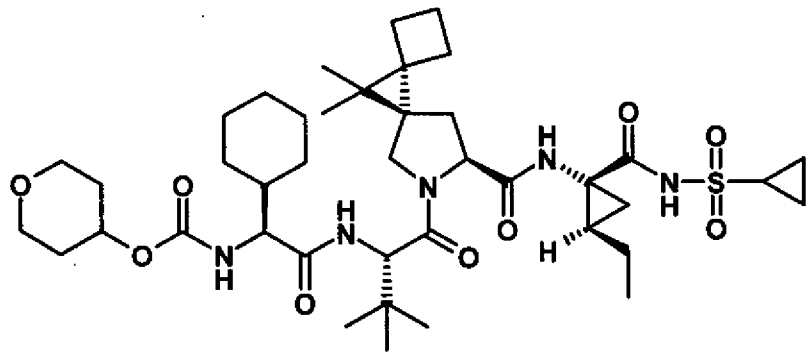
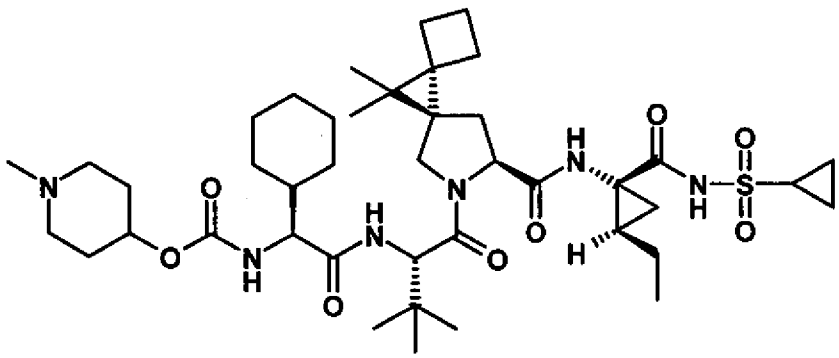
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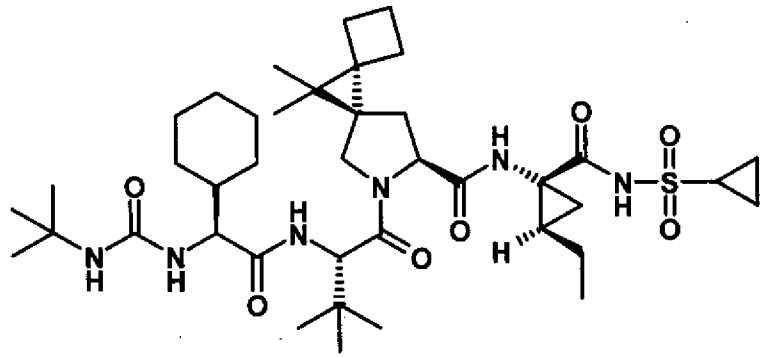
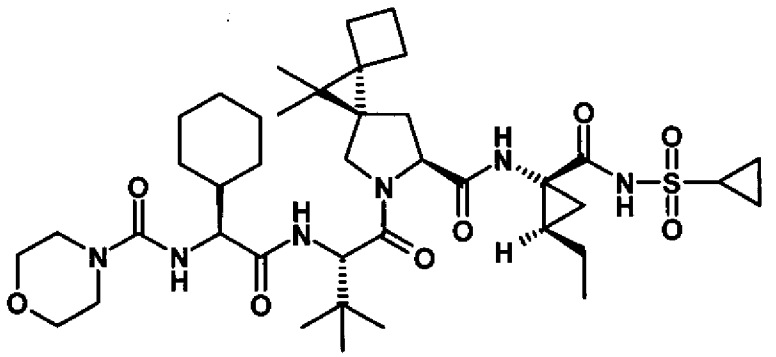
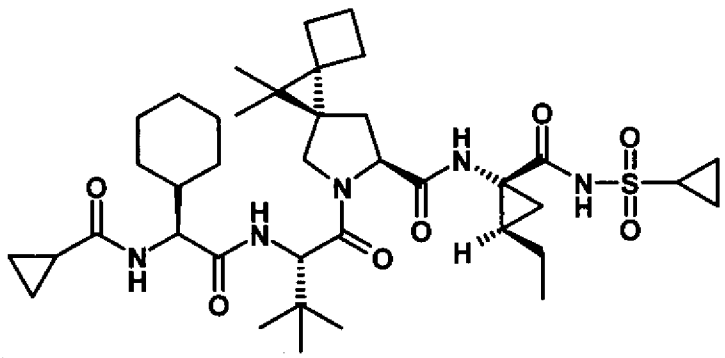
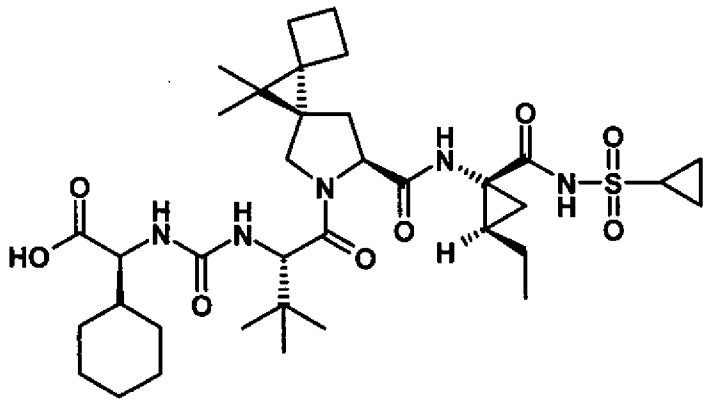
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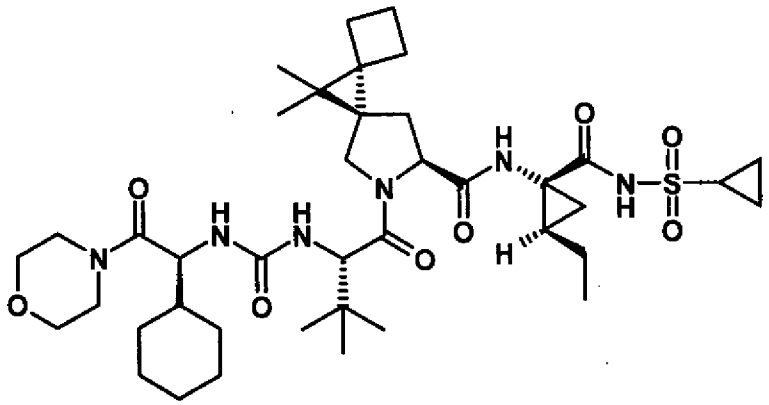
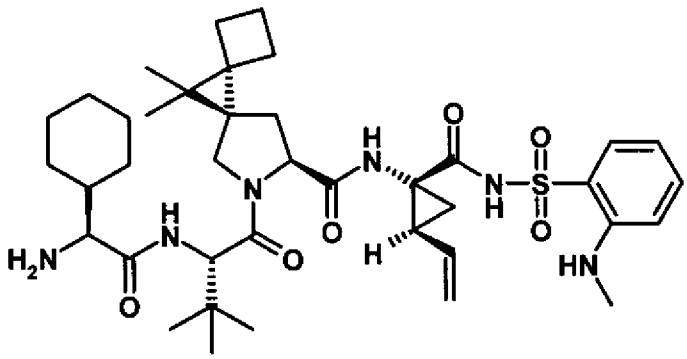
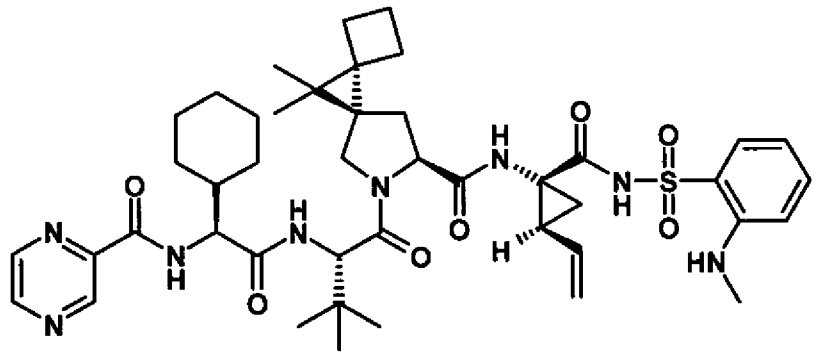
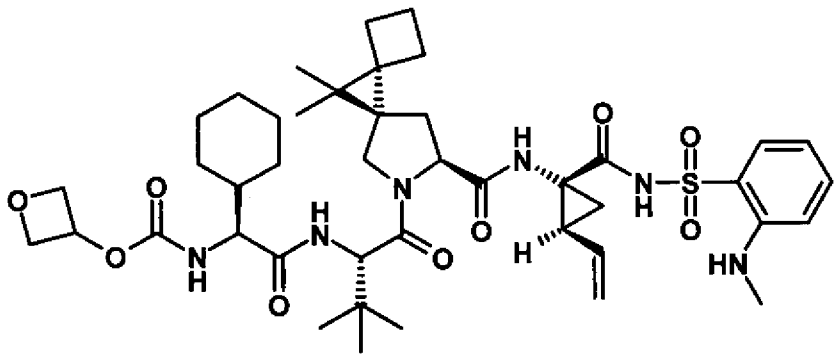
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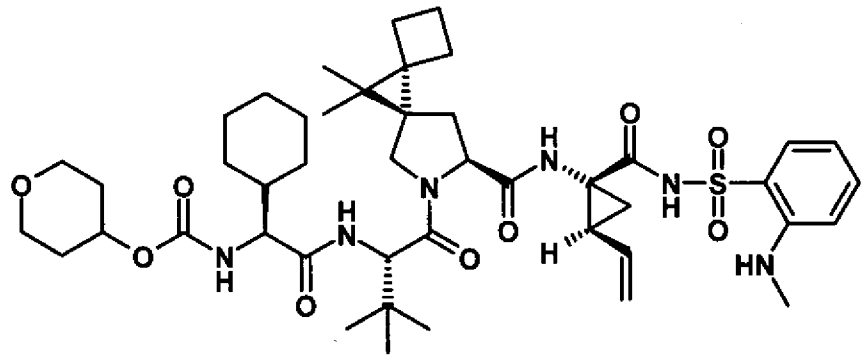
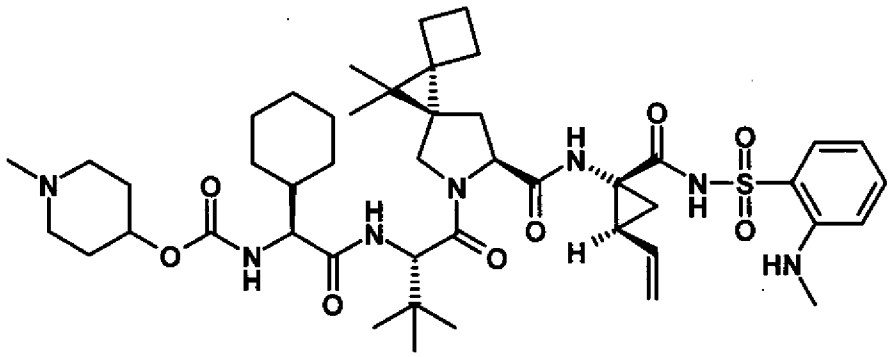
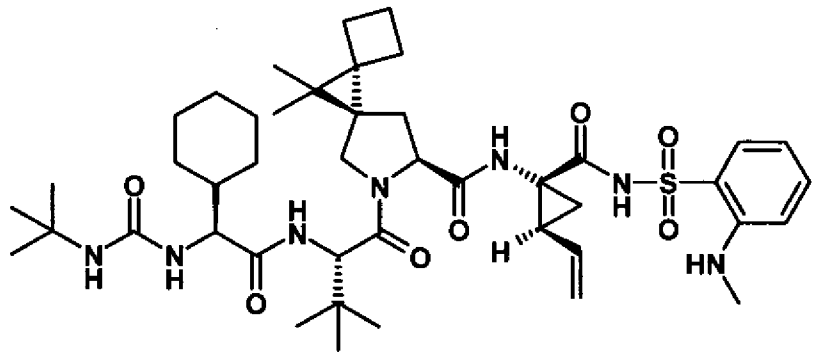
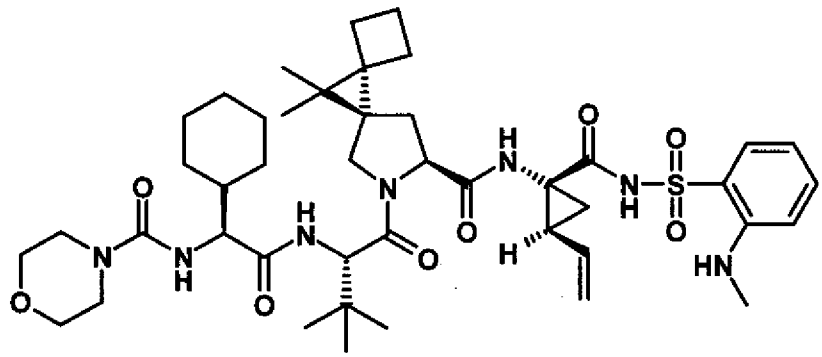
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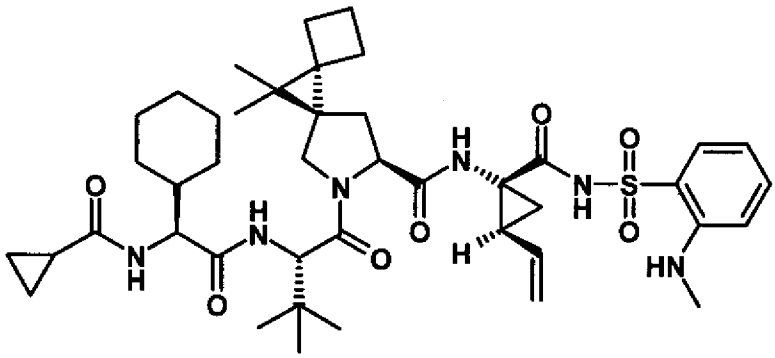
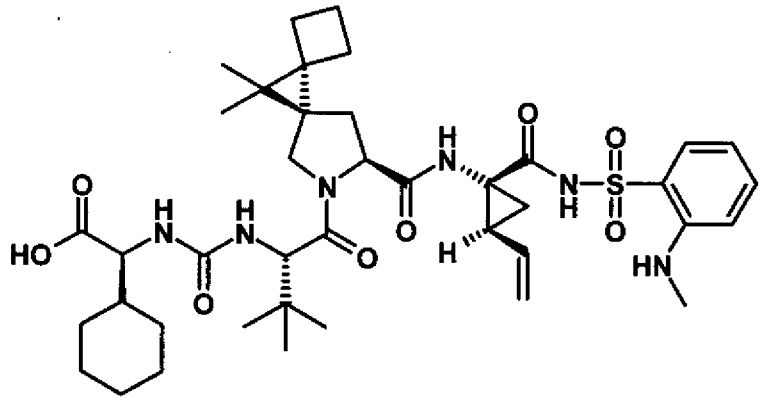
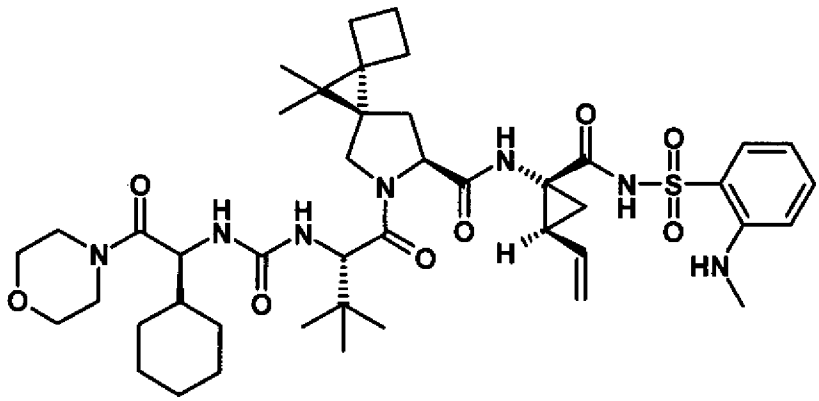
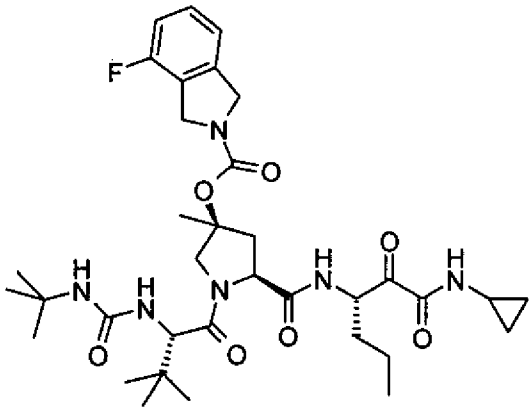
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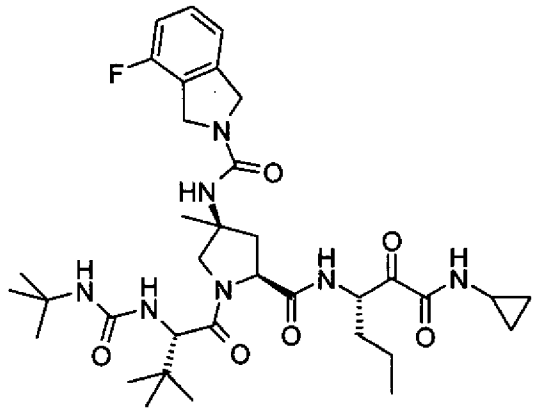
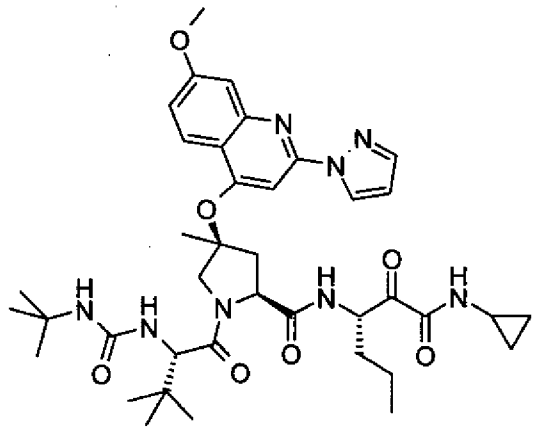
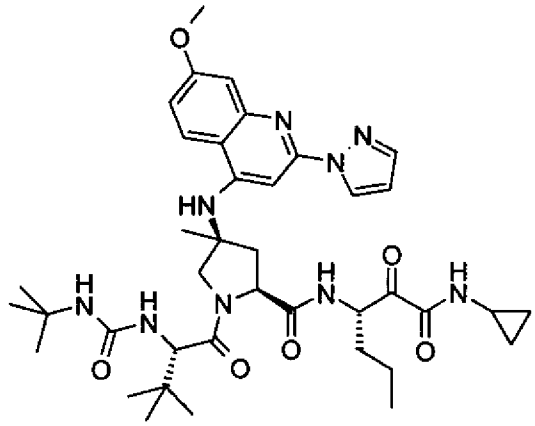
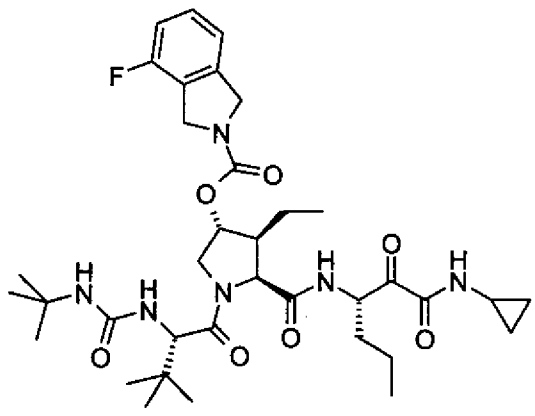
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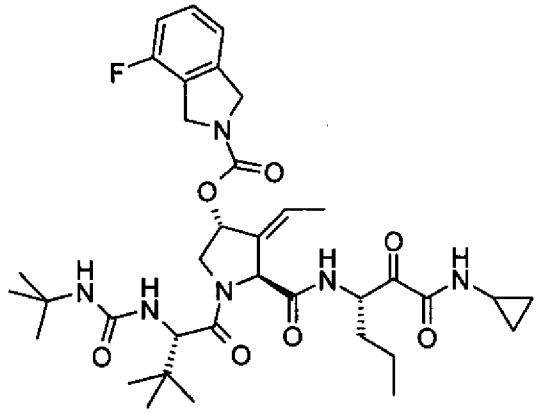
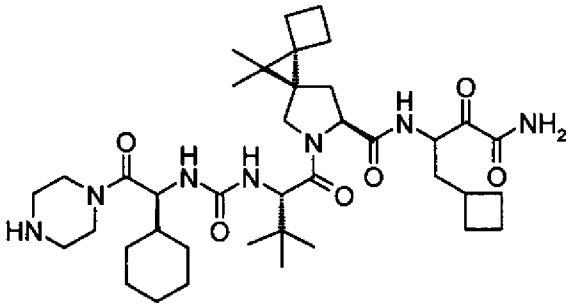
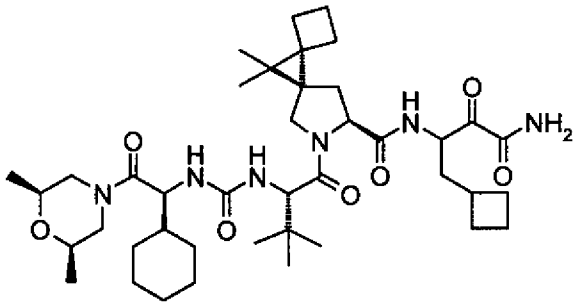
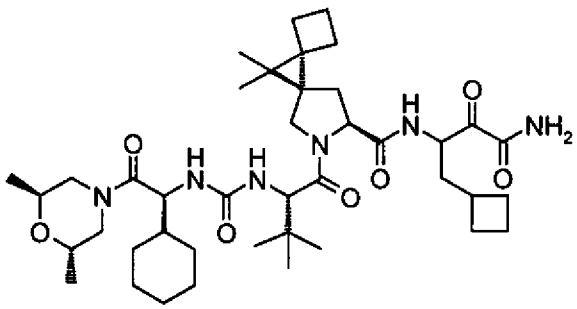
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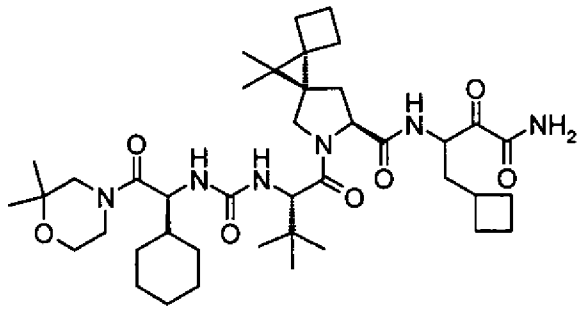
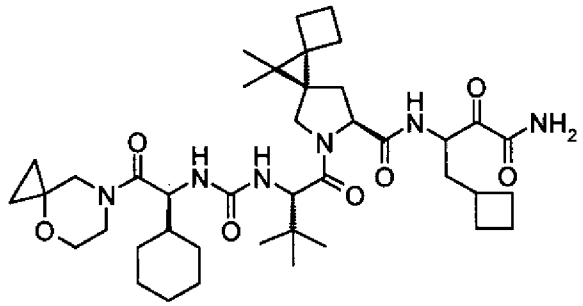
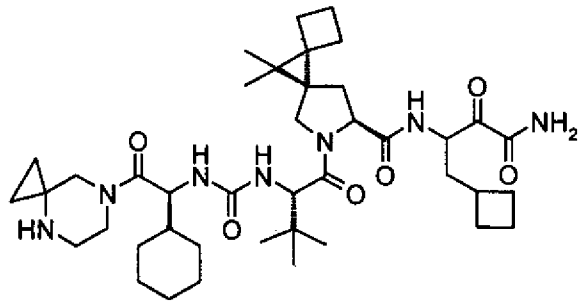
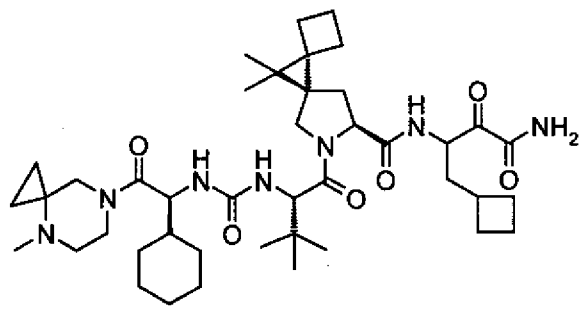
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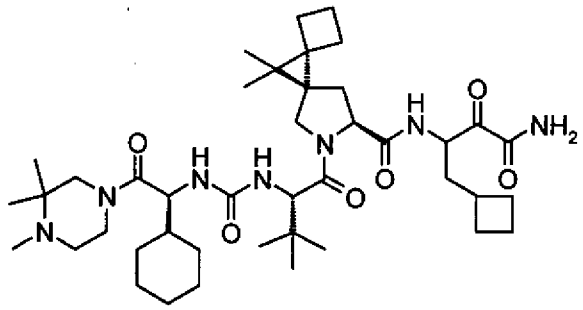
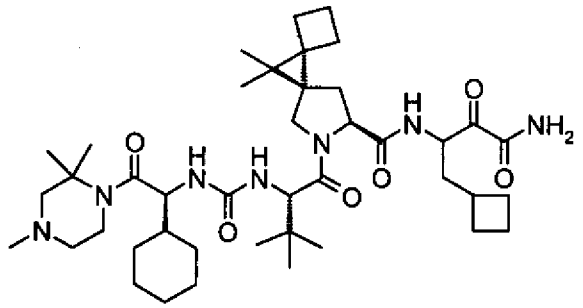
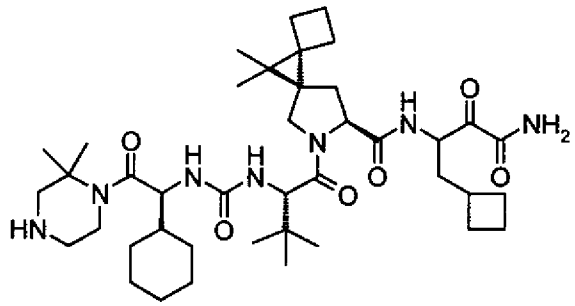
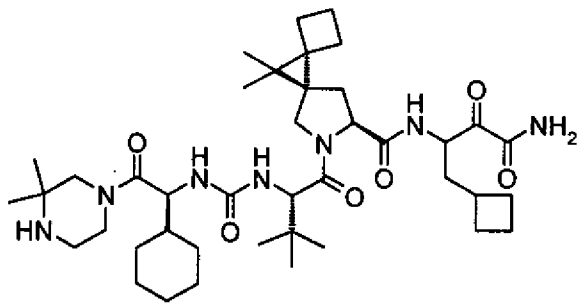
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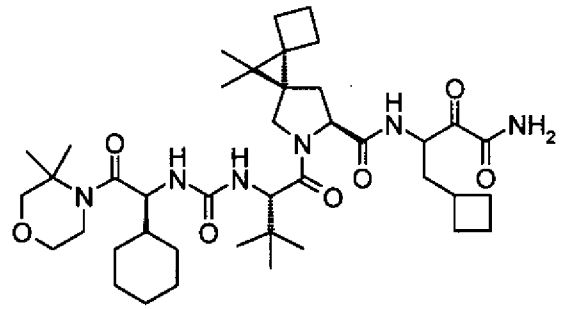
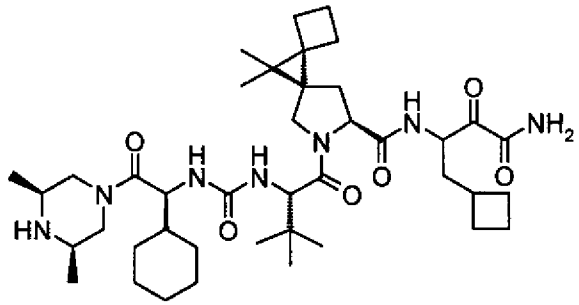
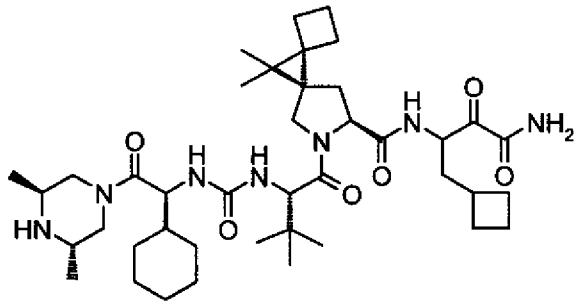
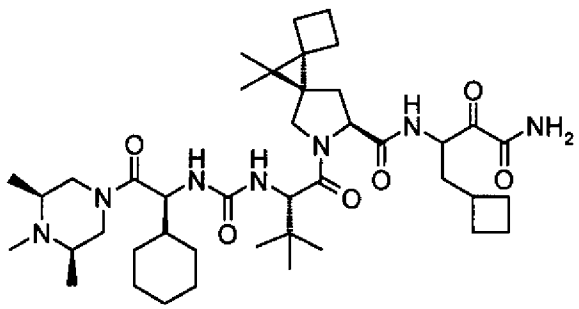
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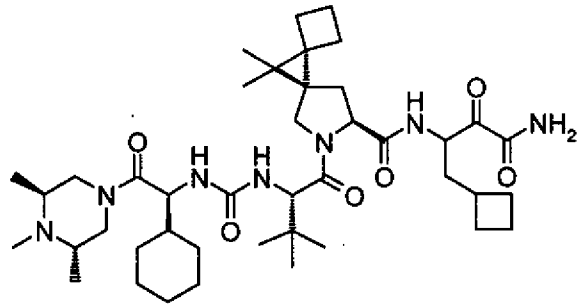
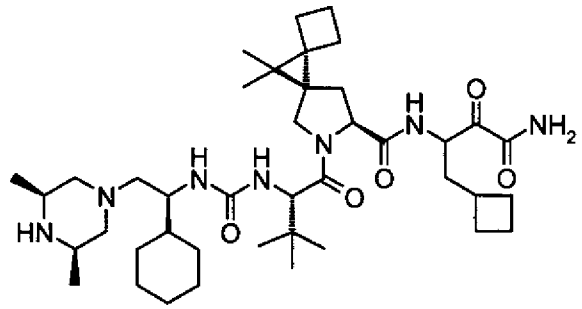
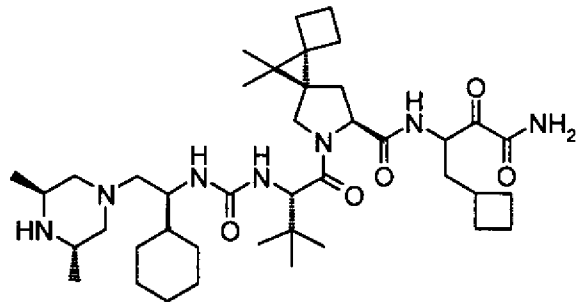
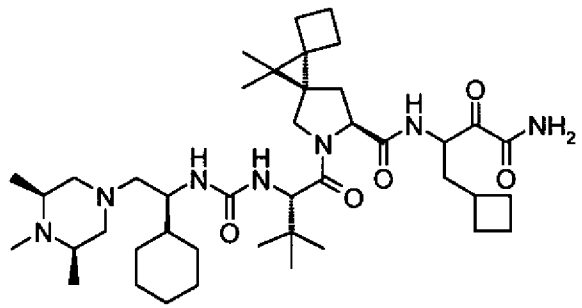
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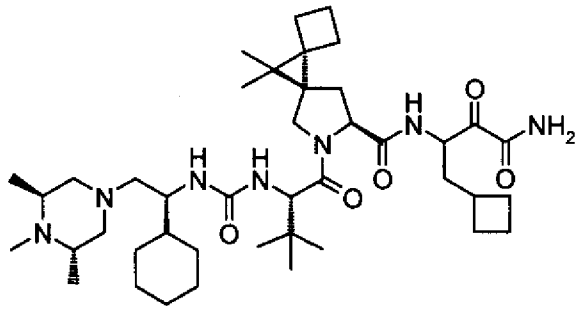
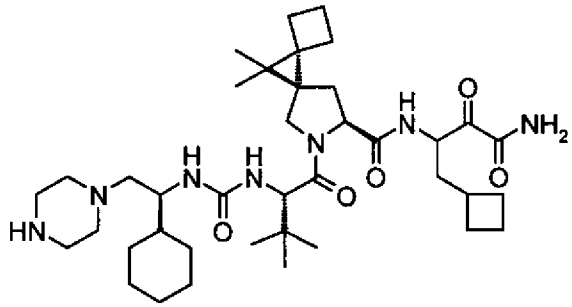
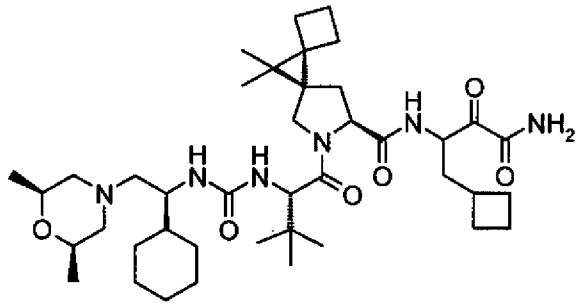
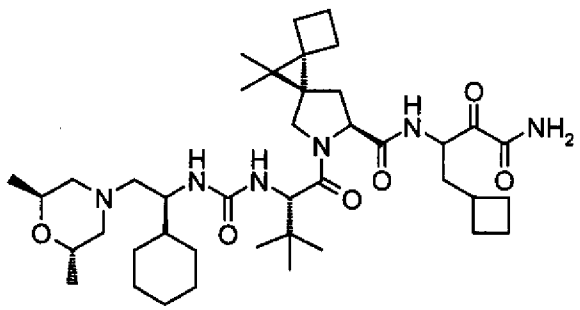
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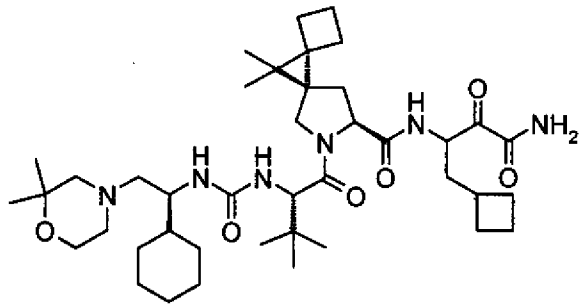
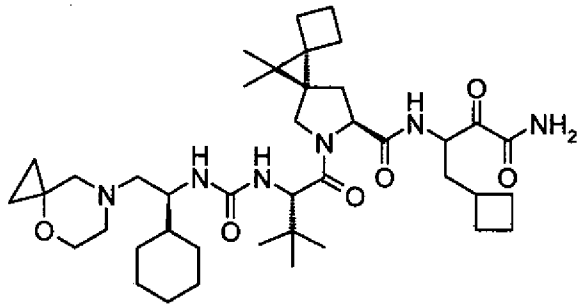
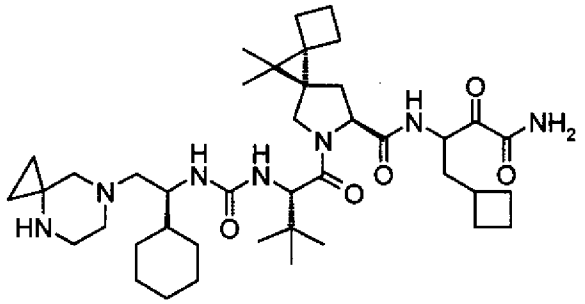
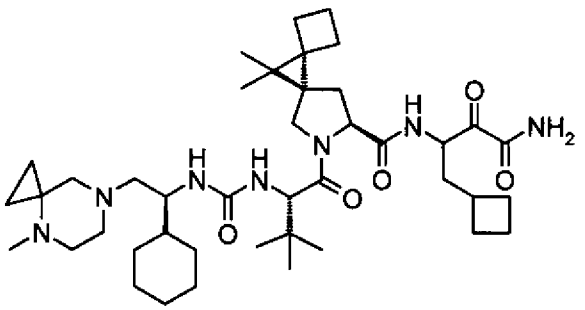
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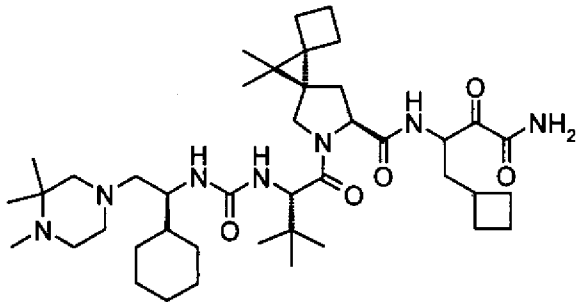
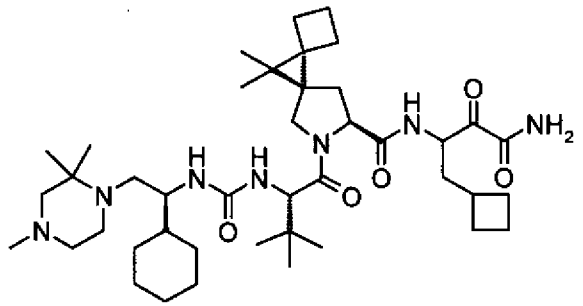
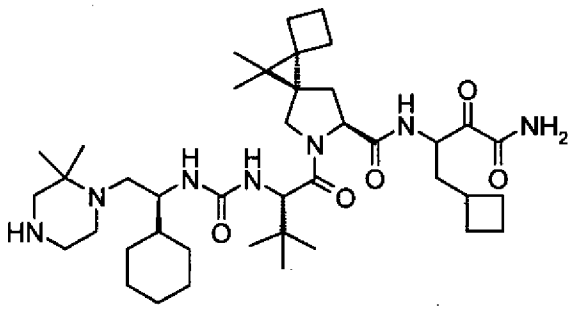
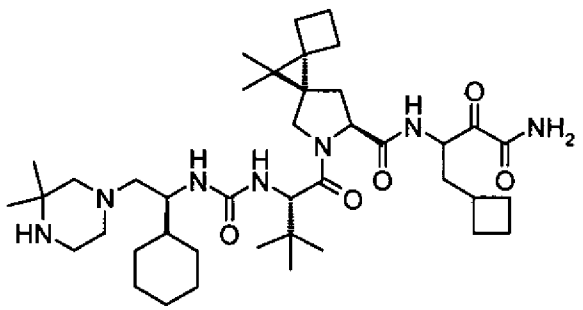
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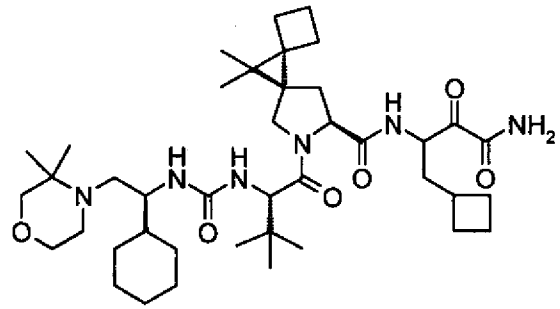
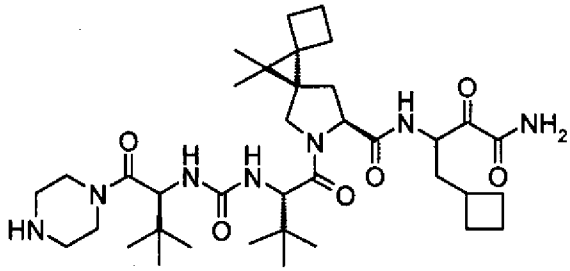
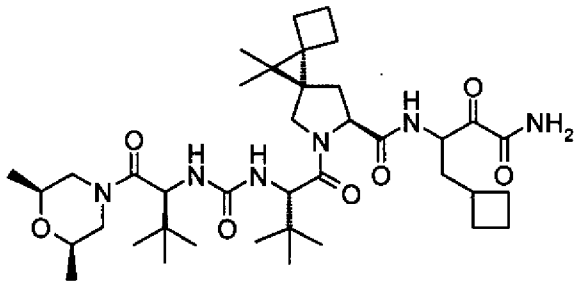
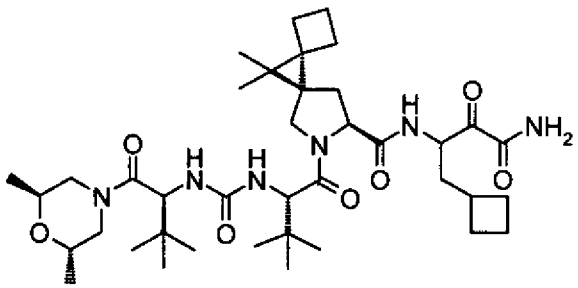
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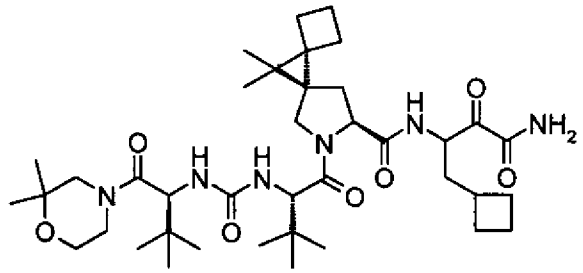
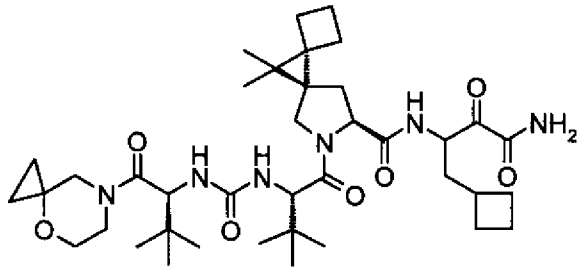
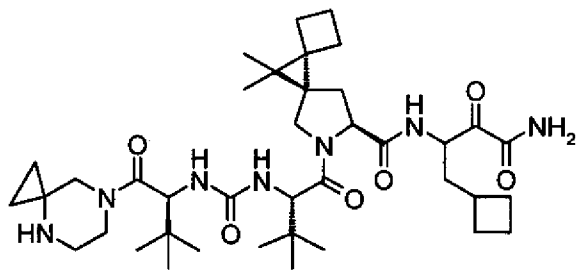
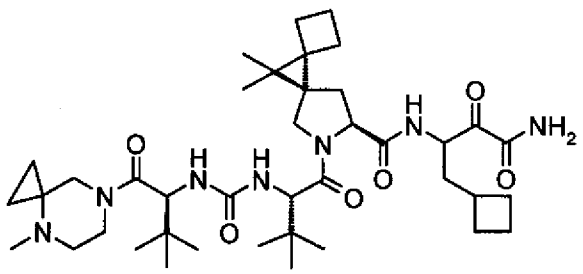
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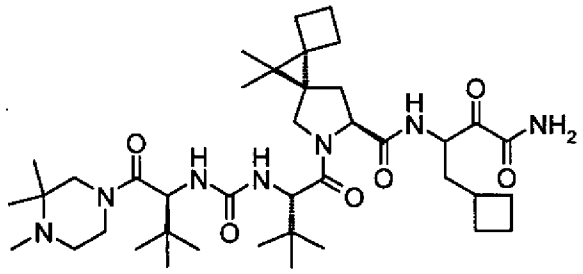
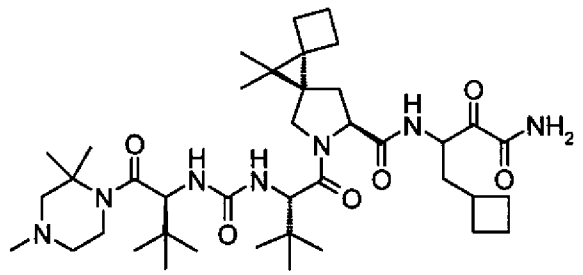
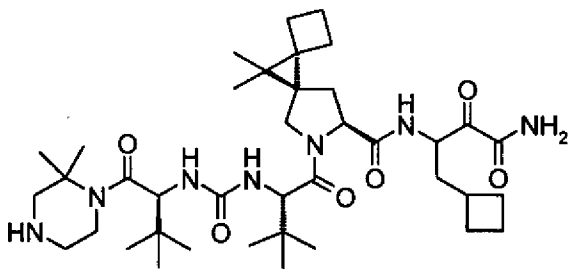
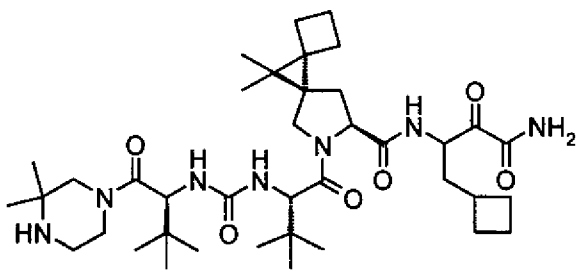
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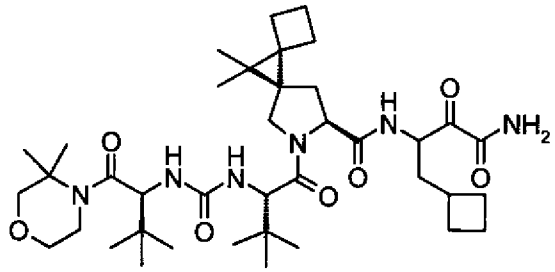
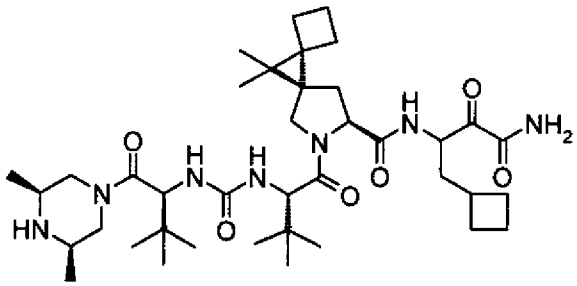
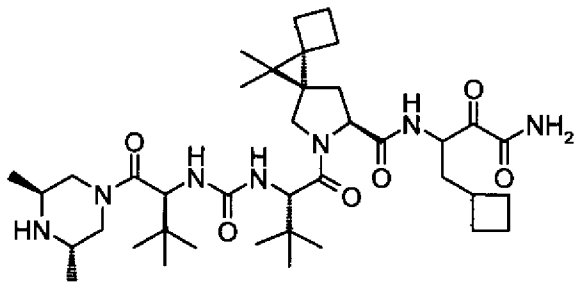
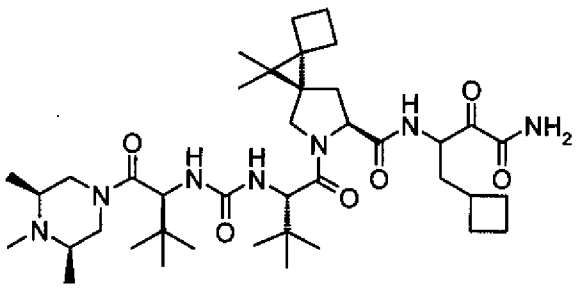
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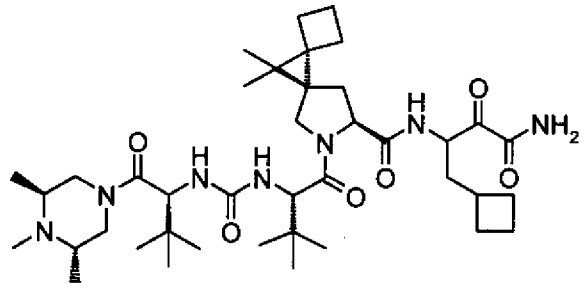
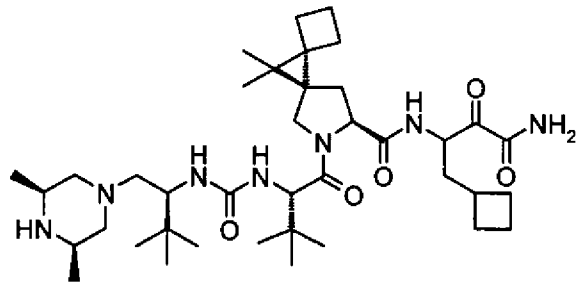
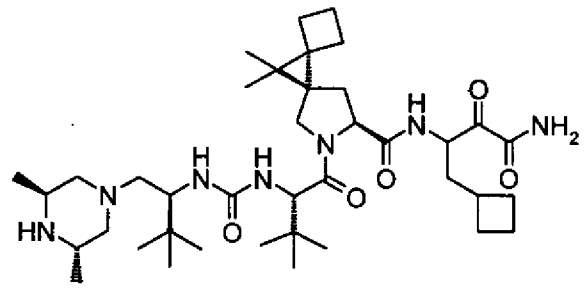
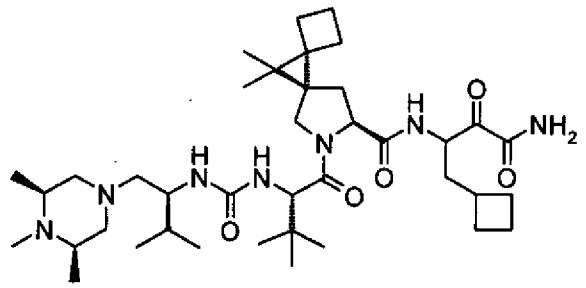
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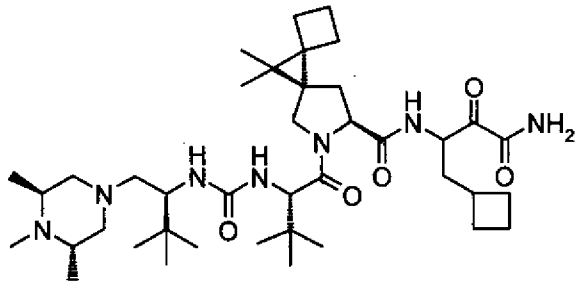
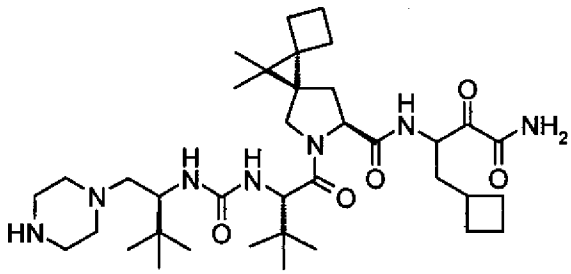
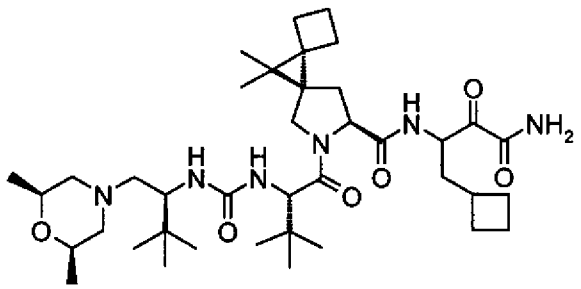
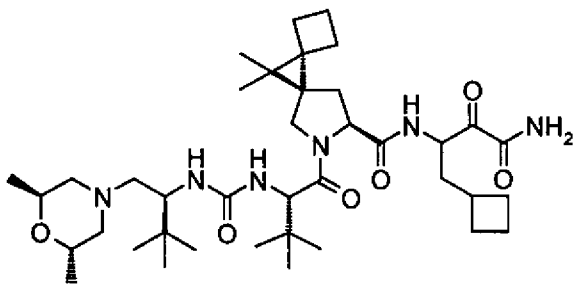
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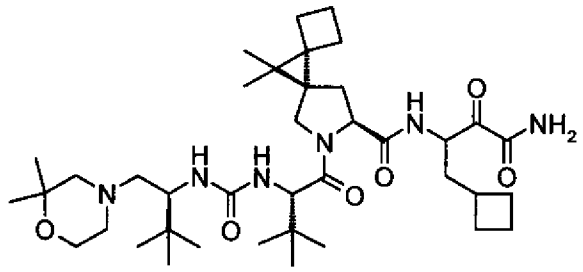
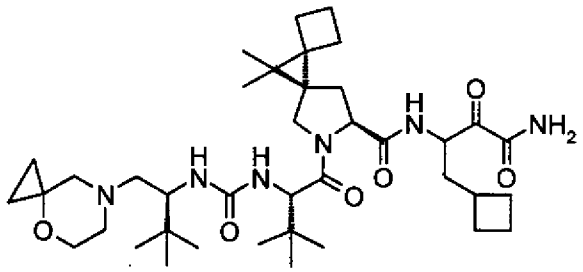
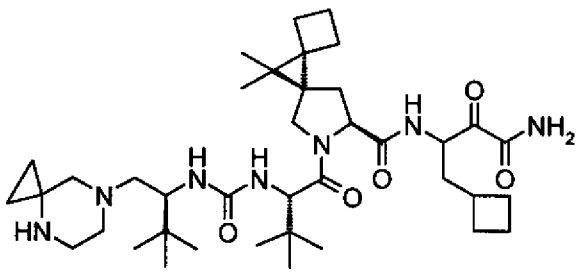
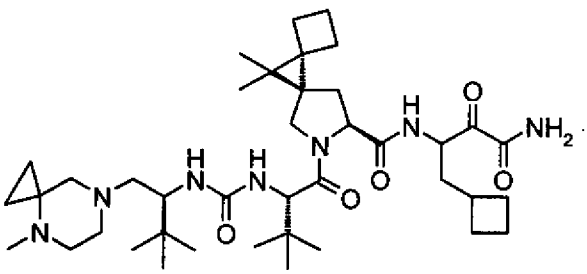
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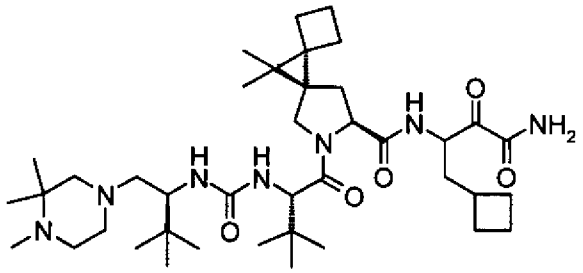
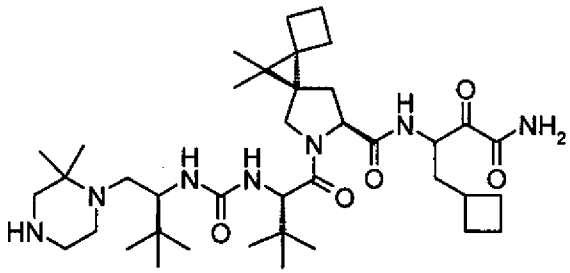
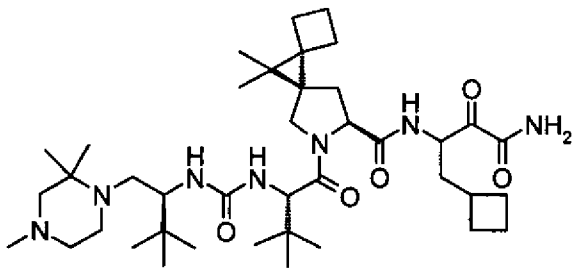
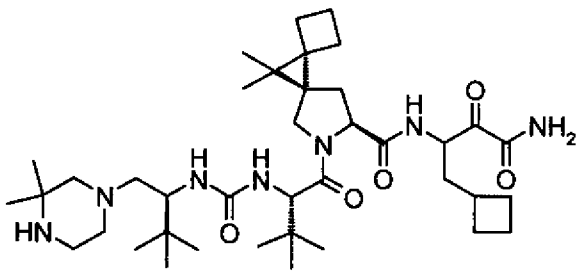
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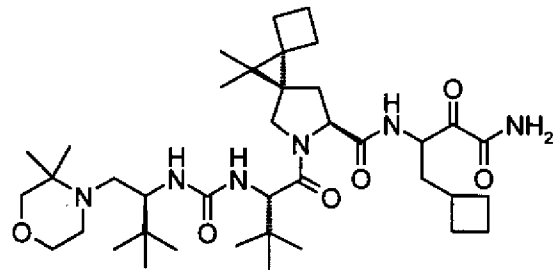
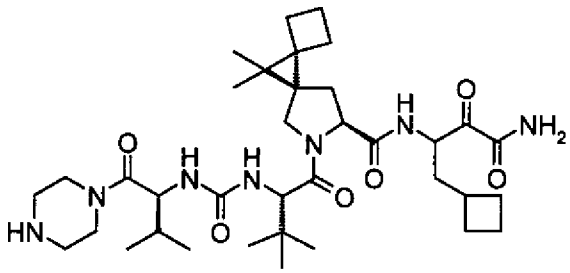
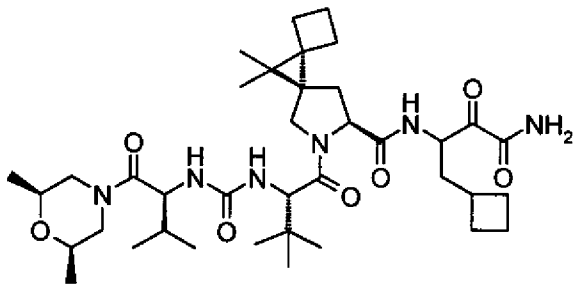
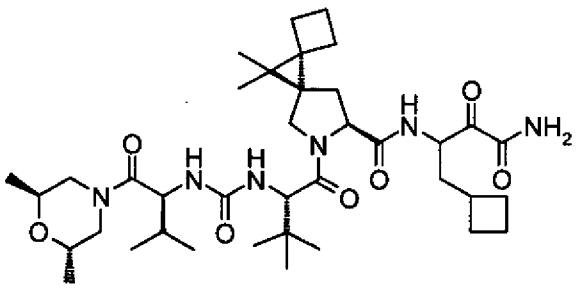
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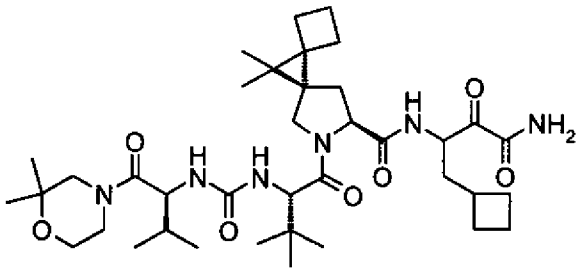
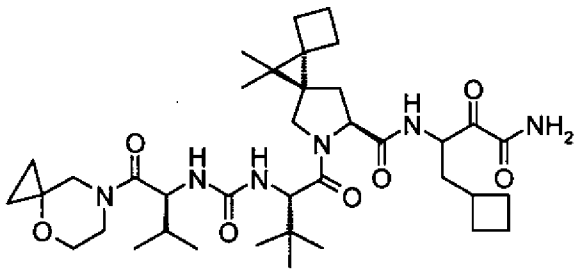
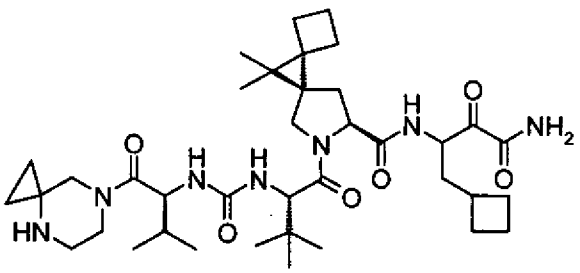
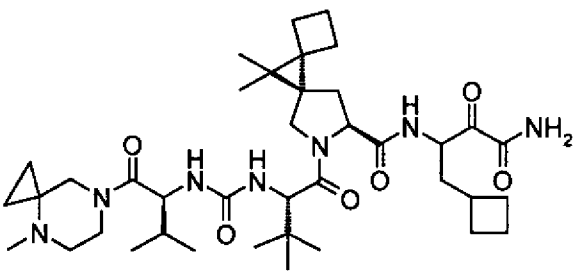
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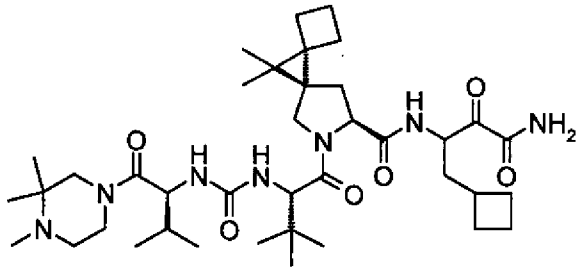
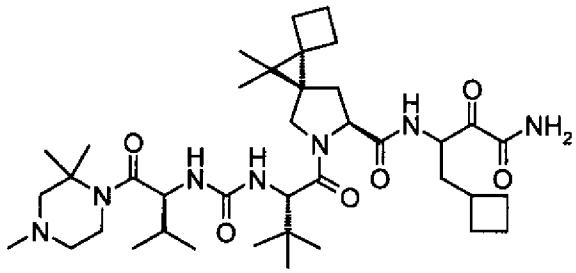
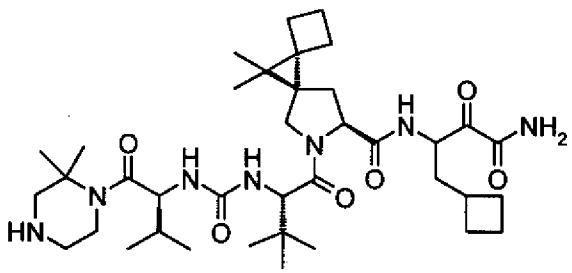
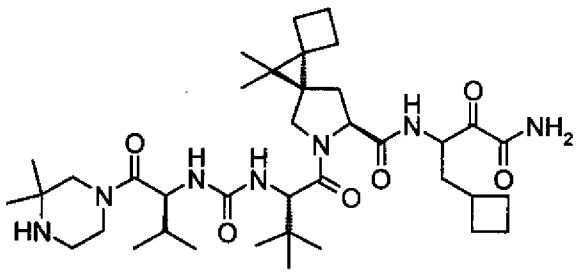
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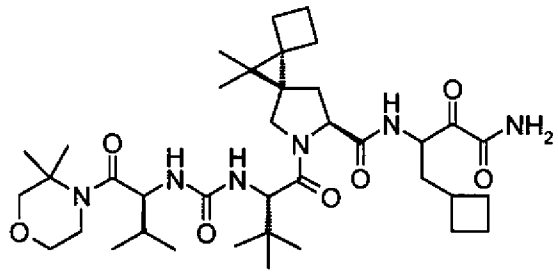
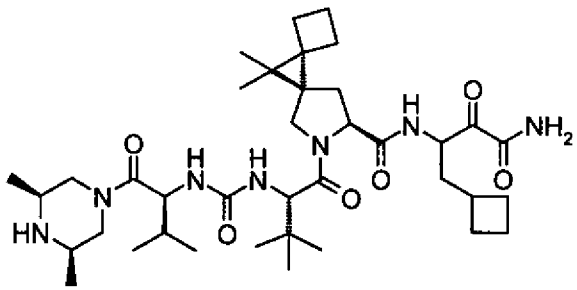
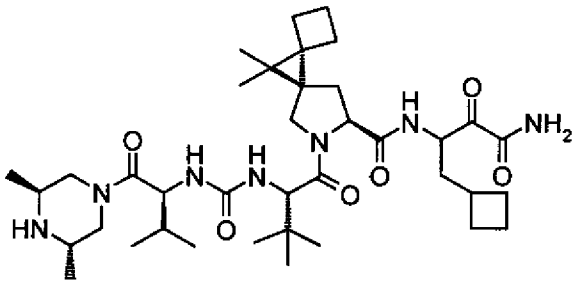
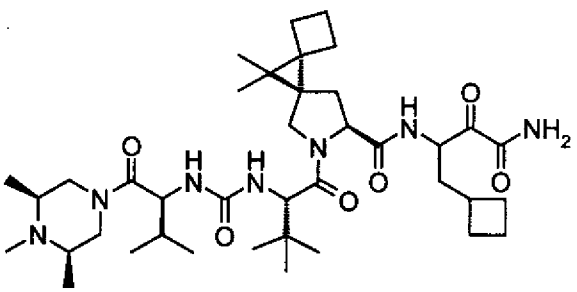
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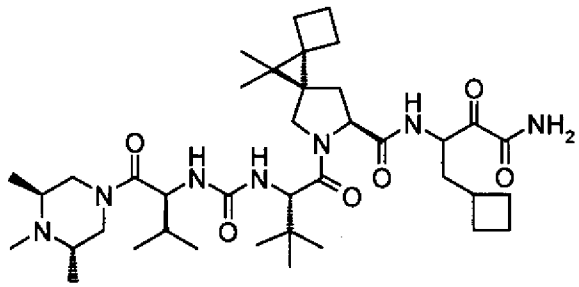
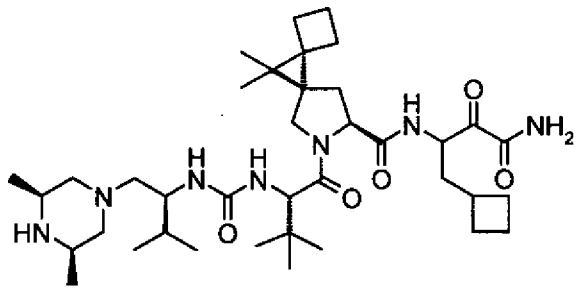
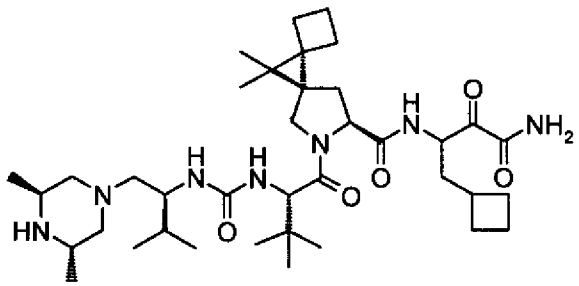
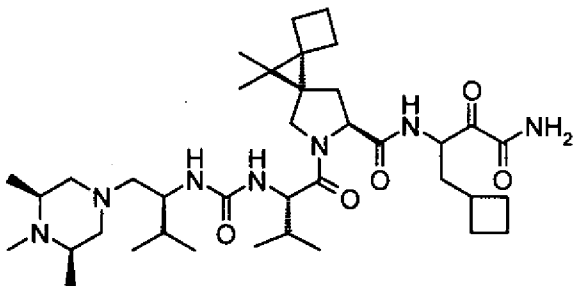
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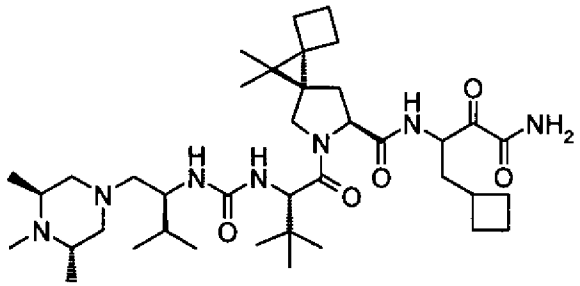
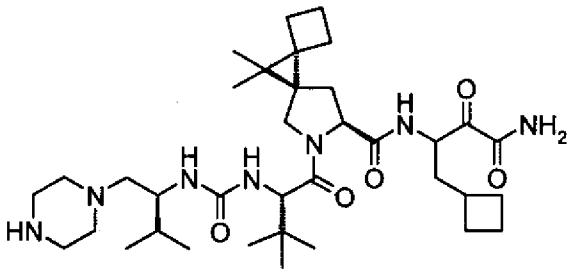
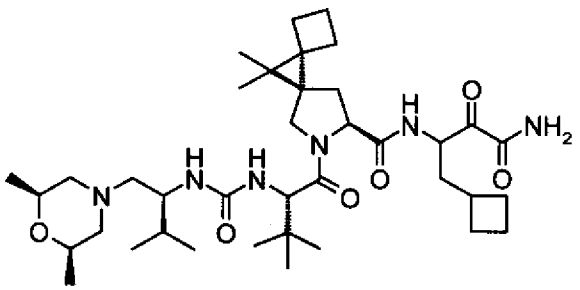
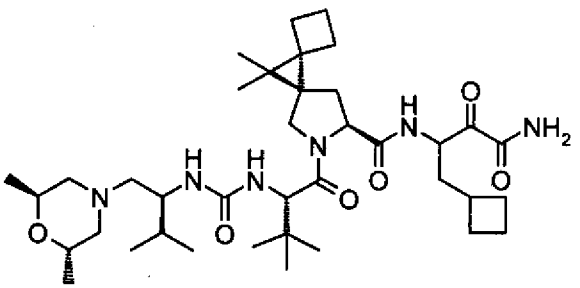
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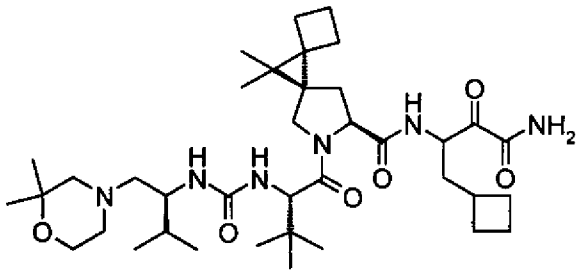
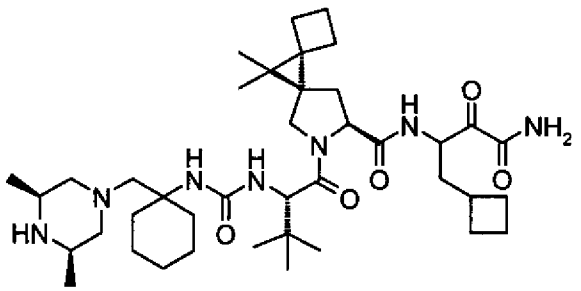
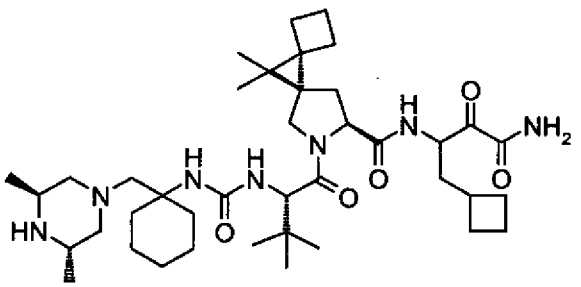
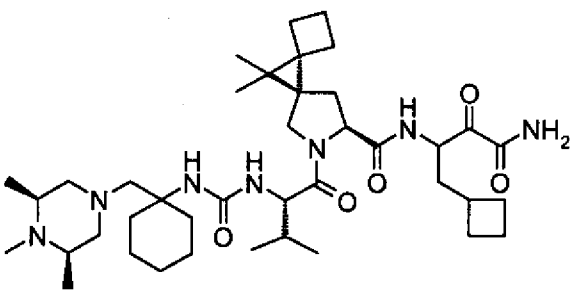
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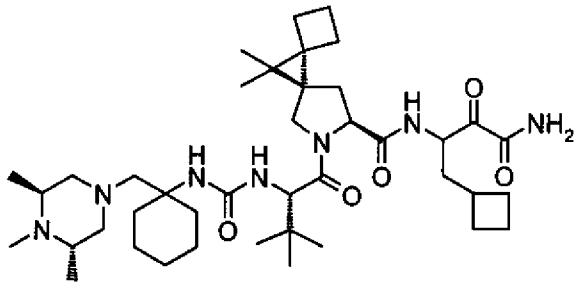
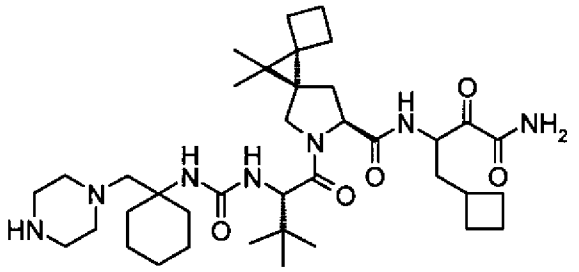
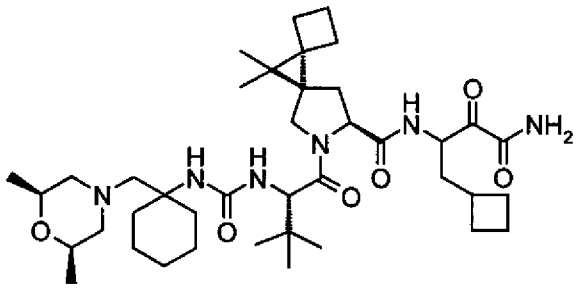
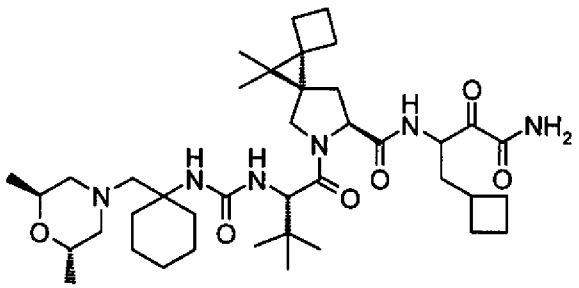
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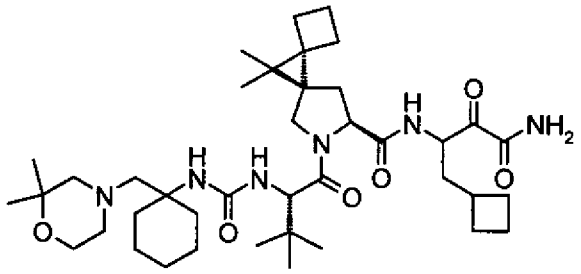
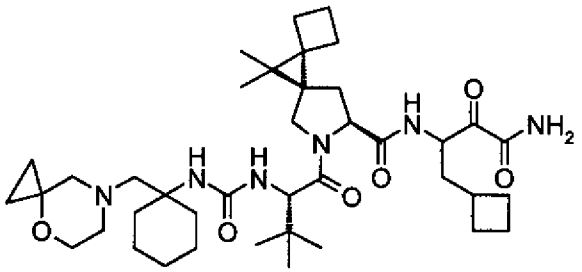
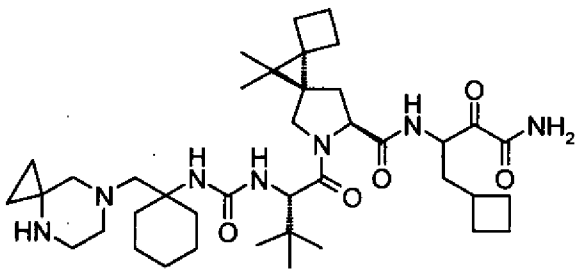
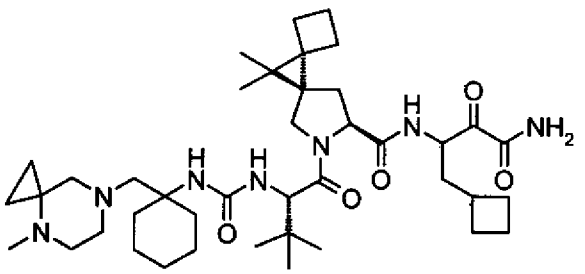
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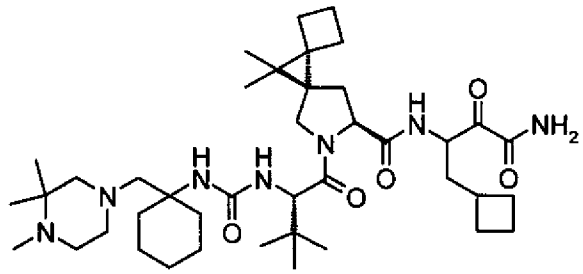
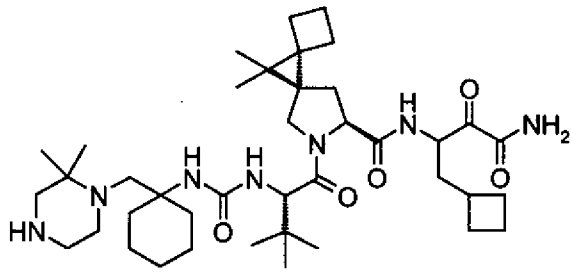
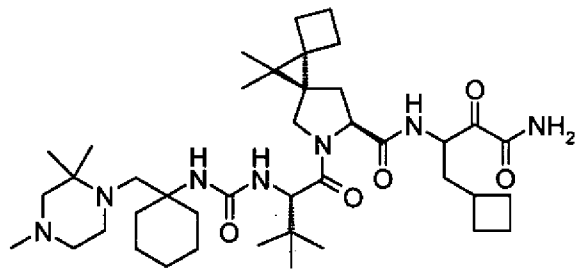
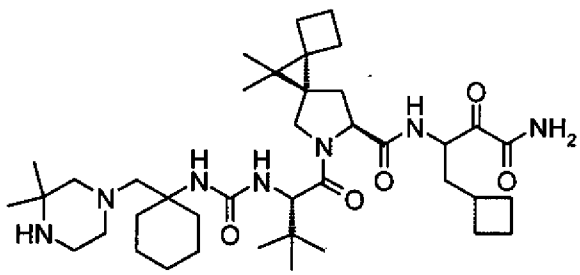
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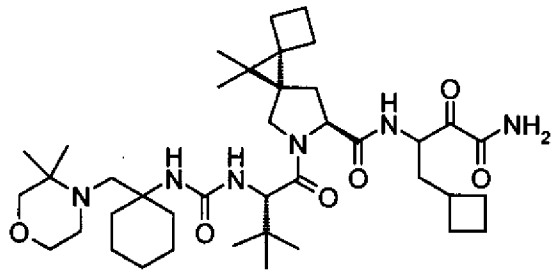
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Using the HCV NS3-4A protease and Luciferase-HCV replicon assays described in the exemplification section below, the compounds of the invention (including compounds of Table A depicted above) are found to show IC_{50} values for HCV inhibition in the range from 10 to more than 100 μM, or 0.5 to 30 μM, including, for example, the range from 0.5 to10 μM or less.

In certain embodiments, a compound of the present invention is further characterized as a modulator of HCV, including a mammalian HCV, and especially including a human HCV. In a preferred embodiment, the compound of the invention is an HCV inhibitor.

In certain embodiments, the compound of the invention is not VX-950 or Sch 503034 (see, *e.g.*, Curr. Med. Chem., 2005, 12, 2317-2342; and Antimicrob Agents Chemother. 2006 Mar;50(3):1013-20, both of which are incorporated herein by reference in their entirety).

In other embodiments, the compounds of the invention are not the species described in International Patent Application Nos. WO 2005/058821, WO/2005/021584, WO/01/18369, WO/03/062265, WO/02/18369, WO/2003/087092 and U.S. Pat. App. No. 2002/0032175.

The terms "HCV-associated state" or "HCV-associated disorder" include disorders and states (*e.g.*, a disease state) that are associated with the activity of HCV, *e.g.*, infection of HCV in a subject. HCV-associated states include HCV-infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma, cryoglobulinaemia, non-Hodgkin's lymphoma, and a suppressed innate intracellular immune response.

HCV-associated states are often associated with the NS3 serine protease of HCV, which is responsible for several steps in the processing of the HCV polyprotein into smaller functional proteins. NS3 protease forms a heterodimeric complex with the NS4A protein, an essential cofactor that enhances enzymatic activity, and is believed to help anchor HCV to the endoplasmic reticulum. NS3 first autocatalyzes hydrolysis of the NS3-NS4A juncture, and then cleaves the HCV polyprotein intermolecularly at the NS4A-NS4B, NS4B-NS5A and

NS5A-NS5B intersections. This process is associated with replication of HCV in a subject. Inhibiting or modulating the activity of one or more of the NS3, NS4A, NS4B, NS5A and NS5B proteins will inhibit or modulate replication of HCV in a subject, thereby preventing or treating the HCV-associated state. In a particular embodiment, the HCV-associated state is associated with the activity of the NS3 protease. In another particular embodiment, the HCV-associated state is associated with the activity of NS3-NS4A heterodimeric complex.

In one embodiment, the compounds of the invention are NS3/NS4A protease inhibitors. In another embodiment, the compounds of the invention are NS2/NS3 protease inhibitors.

Without being bound by theory, it is believed that the disruption of the above protein-protein interactions by the compounds of the invention will interfere with viral polyprotein processing by the NS3 protease and thus viral replication.

HCV-associated disorders also include HCV-dependent diseases. HCV-dependent diseases include, *e.g.*, any disease or disorder that depend on or related to activity or misregulation of at least one strain of HCV.

The present invention includes treatment of HCV-associated disorders as described above, but the invention is not intended to be limited to the manner by which the compound performs its intended function of treatment of a disease. The present invention includes treatment of diseases described herein in any manner that allows treatment to occur, *e.g.*, HCV infection.

In a related embodiment, the compounds of the invention can be useful for treating diseases related to HIV, as well as HIV infection and AIDS (Acquired Immune Deficiency Syndrome).

In certain embodiments, the invention provides a pharmaceutical composition of any of the compounds of the present invention. In a related embodiment, the invention provides a pharmaceutical composition of any of the compounds of the present invention and a pharmaceutically acceptable carrier or excipient of any of these compounds. In certain embodiments, the invention includes the compounds as novel chemical entities.

In one embodiment, the invention includes a packaged HCV-associated disorder treatment. The packaged treatment includes a compound of the invention packaged with instructions for using an effective amount of the compound of the invention for an intended use.

The compounds of the present invention are suitable as active agents in pharmaceutical compositions that are efficacious particularly for treating HCV-associated

disorders. The pharmaceutical composition in various embodiments has a pharmaceutically effective amount of the present active agent along with other pharmaceutically acceptable excipients, carriers, fillers, diluents and the like. The phrase, "pharmaceutically effective amount" as used herein indicates an amount necessary to administer to a host, or to a cell, issue, or organ of a host, to achieve a therapeutic result, especially an anti-HCV effect, *e.g.*, inhibition of proliferation of the HCV virus, or of any other HCV-associated disease.

In one embodiment, the diseases to be treated by compounds of the invention include, for example, HCV infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma, cryoglobulinaemia, non-Hodgkin's lymphoma, and a suppressed innate intracellular immune response.

In other embodiments, the present invention provides a method for inhibiting the activity of HCV. The method includes contacting a cell with any of the compounds of the present invention. In a related embodiment, the method further provides that the compound is present in an amount effective to selectively inhibit the activity of one or more of the NS3, NS4A, NS4B, NS5A and NS5B proteins. In another related embodiment, the method provides that the compound is present in an amount effective to diminish the HCV RNA load in a subject.

In other embodiments, the present invention provides a use of any of the compounds of the invention for manufacture of a medicament to treat HCV infection in a subject.

In other embodiments, the invention provides a method of manufacture of a medicament, including formulating any of the compounds of the present invention for treatment of a subject.

Definitions

The term "treat," "treated," "treating" or "treatment" includes the diminishment or alleviation of at least one symptom associated or caused by the state, disorder or disease being treated. In certain embodiments, the treatment comprises the induction of an HCV-inhibited state, followed by the activation of the HCV-modulating compound, which would in turn diminish or alleviate at least one symptom associated or caused by the HCV-associated state, disorder or disease being treated. For example, treatment can be diminishment of one or several symptoms of a disorder or complete eradication of a disorder.

The term "subject" is intended to include organisms, *e.g.*, prokaryotes and eukaryotes, which are capable of suffering from or afflicted with an HCV-associated disorder. Examples of subjects include mammals, *e.g.*, humans, dogs, cows, horses, pigs, sheep, goats, cats, mice,

rabbits, rats, and transgenic non-human animals. In certain embodiments, the subject is a human, *e.g.*, a human suffering from, at risk of suffering from, or potentially capable of suffering from an HCV-associated disorder, and for diseases or conditions described herein, *e.g.*, HCV infection. In another embodiment, the subject is a cell.

The language "HCV-modulating compound," "modulator of HCV" or "HCV inhibitor" refers to compounds that modulate, *e.g.*, inhibit, or otherwise alter, the activity of HCV. Similarly, an "NS3/NS4A protease inhibitor," or an "NS2/NS3 protease inhibitor" refers to a compound that modulates, *e.g.*, inhibits, or otherwise alters, the interaction of these proteases with one another. Examples of HCV-modulating compounds include compounds of Formula I or Formula III, as well as Table A and Table B (including pharmaceutically acceptable salts thereof, as well as enantiomers, stereoisomers, rotamers, tautomers, diastereomers, or racemates thereof).

Additionally, the method includes administering to a subject an effective amount of an HCV-modulating compound of the invention, *e.g.*, HCV-modulating compounds of Formula I or Formula III, as well as Table A and Table B (including pharmaceutically acceptable salts thereof, as well as enantiomers, stereoisomers, rotamers, tautomers, diastereomers, or racemates thereof).

The term "alkyl" includes saturated aliphatic groups, including straight-chain alkyl groups (*e.g.*, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, *etc.*), branched-chain alkyl groups (isopropyl, tert-butyl, isobutyl, *etc.*), cycloalkyl (alicyclic) groups (cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl), alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. Furthermore, the expression "C_x-C_y-alkyl", wherein x is 1-5 and y is 2-10 indicates a particular alkyl group (straight- or branched-chain) of a particular range of carbons. For example, the expression C_1-C_4-alkyl includes, but is not limited to, methyl, ethyl, propyl, butyl, isopropyl, tert-butyl, isobutyl and sec-butyl. Moreover, the term C_{3-6}-cycloalkyl includes, but is not limited to, cyclopropyl, cyclopentyl, and cyclohexyl. As discussed below, these alkyl groups, as well as cycloalkyl groups, may be further substituted. "C_0-$C_n$alkyl" refers to a single covalent bond (C_0) or an alkyl group having from 1 to n carbon atoms; for example "C_0-C_4alkyl" refers to a single covalent bond or a C_1-C_4alkyl group; "C_0-C_8alkyl" refers to a single covalent bond or a C_1-C_8alkyl group. In some instances, a substituent of an alkyl group is specifically indicated. For example, "C_1-C_4hydroxyalkyl" refers to a C_1-C_4alkyl group that has at least one hydroxy substituent.

"Alkylene" refers to a divalent alkyl group, as defined above. C_0-C_4alkylene is a single covalent bond or an alkylene group having from 1 to 4 carbon atoms; and C_0-C_6alkylene is a single covalent bond or an alkylene group having from 1 to 6 carbon atoms.

A "cycloalkyl" is a group that comprises one or more saturated and/or partially saturated rings in which all ring members are carbon, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, adamantyl, decahydro-naphthalenyl, octahydro-indenyl, and partially saturated variants of the foregoing, such as cyclohexenyl. Cycloalkyl groups do not comprise an aromatic ring or a heterocyclic ring. Certain cycloalkyl groups are C_3-C_8cycloalkyl, in which the group contains a single ring with from 3 to 8 ring members. A "(C_3-C_8cycloalkyl)C_0-C_4alkyl" is a C_3-C_8cycloalkyl group linked via a single covalent bond or a C_1-C_4alkylene group.

Moreover, alkyl (*e.g.*, methyl, ethyl, propyl, butyl, pentyl, hexyl, *etc.*) include both "unsubstituted alkyl" and "substituted alkyl", the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone, which allow the molecule to perform its intended function.

The term "substituted" is intended to describe moieties having substituents replacing a hydrogen on one or more atoms, *e.g.* C, O or N, of a molecule. Such substituents can include, for example, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, morpholino, phenol, benzyl, phenyl, piperazine, cyclopentane, cyclohexane, pyridine, 5H-tetrazole, triazole, piperidine, or an aromatic or heteroaromatic moiety.

Further examples of substituents of the invention, which are not intended to be limiting, include moieties selected from straight or branched alkyl (preferably C_1-C_5), cycloalkyl (preferably C_3-C_8), alkoxy (preferably C_1-C_6), thioalkyl (preferably C_1-C_6), alkenyl (preferably C_2-C_6), alkynyl (preferably C_2-C_6), heterocyclic, carbocyclic, aryl (*e.g.*, phenyl), aryloxy (*e.g.*, phenoxy), aralkyl (*e.g.*, benzyl), aryloxyalkyl (*e.g.*, phenyloxyalkyl), arylacetamidoyl, alkylaryl, heteroaralkyl, alkylcarbonyl and arylcarbonyl or other such acyl group, heteroarylcarbonyl, or heteroaryl group,

$(CR'R")_{0-3}NR'R"$ (*e.g.*, $-NH_2$), $(CR'R")_{0-3}CN$ (*e.g.*, -CN), $-NO_2$, halogen (*e.g.*, -F, -Cl, -Br, or -I), $(CR'R")_{0-3}C(halogen)_3$ (*e.g.*, $-CF_3$), $(CR'R")_{0-3}CH(halogen)_2$, $(CR'R")_{0-3}CH_2(halogen)$, $(CR'R")_{0-3}CONR'R"$, $(CR'R")_{0-3}(CNH)NR'R"$, $(CR'R")_{0-3}S(O)_{1-2}NR'R"$, $(CR'R")_{0-3}CHO$, $(CR'R")_{0-3}O(CR'R")_{0-3}H$, $(CR'R")_{0-3}S(O)_{0-3}R'$ (*e.g.*, $-SO_3H$, $-OSO_3H$), $(CR'R")_{0-3}O(CR'R")_{0-3}H$ (*e.g.*, $-CH_2OCH_3$ and $-OCH_3$), $(CR'R")_{0-3}S(CR'R")_{0-3}H$ (*e.g.*, -SH and $-SCH_3$), $(CR'R")_{0-3}OH$ (*e.g.*, -OH), $(CR'R")_{0-3}COR'$, $(CR'R")_{0-3}$(substituted or unsubstituted phenyl), $(CR'R")_{0-3}(C_3-C_8$ cycloalkyl), $(CR'R")_{0-3}CO_2R'$ (*e.g.*, $-CO_2H$), or $(CR'R")_{0-3}OR'$ group, or the side chain of any naturally occurring amino acid; wherein R' and R" are each independently hydrogen, a C_1-C_5 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, or aryl group. Such substituents can include, for example, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, oxime, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, or an aromatic or heteroaromatic moiety. In certain embodiments, a carbonyl moiety (C=O) may be further derivatized with an oxime moiety, *e.g.*, an aldehyde moiety may be derivatized as its oxime (-C=N-OH) analog. It will be understood by those skilled in the art that the moieties substituted on the hydrocarbon chain can themselves be substituted, if appropriate. Cycloalkyls can be further substituted, *e.g.*, with the substituents described above. An "aralkyl" moiety is an alkyl substituted with an aryl (*e.g.*, phenylmethyl (*i.e.*, benzyl)).

The term "alkenyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but which contain at least one double bond.

For example, the term "alkenyl" includes straight-chain alkenyl groups (*e.g.*, ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl, etc.), branched-chain alkenyl groups, cycloalkenyl (alicyclic) groups (cyclopropenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl), alkyl or alkenyl substituted cycloalkenyl groups, and cycloalkyl or cycloalkenyl substituted alkenyl groups. The term alkenyl further includes alkenyl groups that include oxygen, nitrogen, sulfur or phosphorous atoms replacing one or more carbons of the hydrocarbon backbone. In certain embodiments, a straight chain or branched chain alkenyl group has 6 or fewer carbon atoms in its backbone (*e.g.*, C_2-C_6 for

straight chain, C_3-C_6 for branched chain). Likewise, cycloalkenyl groups may have from 3-8 carbon atoms in their ring structure, and more preferably have 5 or 6 carbons in the ring structure. The term C_2-C_6 includes alkenyl groups containing 2 to 6 carbon atoms.

Moreover, the term alkenyl includes both "unsubstituted alkenyls" and "substituted alkenyls", the latter of which refers to alkenyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkyl groups, alkynyl groups, halogens, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

The term "alkynyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but which contain at least one triple bond.

For example, the term "alkynyl" includes straight-chain alkynyl groups (*e.g.*, ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl, *etc.*), branched-chain alkynyl groups, and cycloalkyl or cycloalkenyl substituted alkynyl groups. The term alkynyl further includes alkynyl groups that include oxygen, nitrogen, sulfur or phosphorous atoms replacing one or more carbons of the hydrocarbon backbone. In certain embodiments, a straight chain or branched chain alkynyl group has 6 or fewer carbon atoms in its backbone (*e.g.*, C_2-C_6 for straight chain, C_3-C_6 for branched chain). The term C_2-C_6 includes alkynyl groups containing 2 to 6 carbon atoms.

Moreover, the term alkynyl includes both "unsubstituted alkynyls" and "substituted alkynyls", the latter of which refers to alkynyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkyl groups, alkynyl groups, halogens, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino,

sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

The term "amine" or "amino" should be understood as being broadly applied to both a molecule, or a moiety or functional group, as generally understood in the art, and may be primary, secondary, or tertiary. The term "amine" or "amino" includes compounds where a nitrogen atom is covalently bonded to at least one carbon, hydrogen or heteroatom. The terms include, for example, but are not limited to, "alkylamino," "arylamino," "diarylamino," "alkylarylamino," "alkylaminoaryl," "arylaminoalkyl," "alkaminoalkyl," "amide," "amido," and "aminocarbonyl." The term "alkyl amino" comprises groups and compounds wherein the nitrogen is bound to at least one additional alkyl group. The term "dialkyl amino" includes groups wherein the nitrogen atom is bound to at least two additional alkyl groups. The term "arylamino" and "diarylamino" include groups wherein the nitrogen is bound to at least one or two aryl groups, respectively. The term "alkylarylamino," "alkylaminoaryl" or "arylaminoalkyl" refers to an amino group which is bound to at least one alkyl group and at least one aryl group. The term "alkaminoalkyl" refers to an alkyl, alkenyl, or alkynyl group bound to a nitrogen atom which is also bound to an alkyl group.

The term "amide," "amido" or "aminocarbonyl" includes compounds or moieties which contain a nitrogen atom which is bound to the carbon of a carbonyl or a thiocarbonyl group. The term includes "alkaminocarbonyl" or "alkylaminocarbonyl" groups which include alkyl, alkenyl, aryl or alkynyl groups bound to an amino group bound to a carbonyl group. It includes arylaminocarbonyl and arylcarbonylamino groups which include aryl or heteroaryl moieties bound to an amino group which is bound to the carbon of a carbonyl or thiocarbonyl group. The terms "alkylaminocarbonyl," "alkenylaminocarbonyl," "alkynylaminocarbonyl," "arylaminocarbonyl," "alkylcarbonylamino," "alkenylcarbonylamino," "alkynylcarbonylamino," and "arylcarbonylamino" are included in term "amide." Amides also include urea groups (aminocarbonylamino) and carbamates (oxycarbonylamino).

The term "aryl" includes groups, including 5- and 6-membered single-ring aromatic groups that may include from zero to four heteroatoms, for example, phenyl, pyrrole, furan, thiophene, thiazole, isothiaozole, imidazole, triazole, tetrazole, pyrazole, oxazole, isoxazole, pyridine, pyrazine, pyridazine, and pyrimidine, and the like. Furthermore, the term "aryl" includes multicyclic aryl groups, *e.g.*, tricyclic, bicyclic, *e.g.*, naphthalene, benzoxazole, benzodioxazole, benzothiazole, benzoimidazole, benzothiophene, methylenedioxyphenyl,

quinoline, isoquinoline, anthryl, phenanthryl, napthridine, indole, benzofuran, purine, benzofuran, deazapurine, or indolizine. Those aryl groups having heteroatoms in the ring structure may also be referred to as "aryl heterocycles", "heterocycles," "heteroaryls" or "heteroaromatics." The aromatic ring can be substituted at one or more ring positions with such substituents as described above, as for example, alkyl, halogen, hydroxyl, alkoxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkylaminoacarbonyl, aralkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, alkenylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety. Aryl groups can also be fused or bridged with alicyclic or heterocyclic rings which are not aromatic so as to form a polycycle (*e.g.*, tetralin).

Certain aryl groups recited herein are C_6-C_{10}arylC_0-C_8alkyl groups (*i.e.*, groups in which a 6- to 10-membered carbocyclic group comprising at least one aromatic ring is linked via a single covalent bond or a C_1-C_8alkylene group). Such groups include, for example, phenyl and indanyl, as well as groups in which either of the foregoing is linked via C_1-C_8alkylene, preferably via C_1-C_4alkylene. Phenyl groups linked via a single covalent bond or C_1-C_6alkylene group are designated phenylC_0-C_6alkyl (*e.g.*, benzyl, 1-phenyl-ethyl, 1-phenyl-propyl and 2-phenyl-ethyl).

The term heteroaryl, as used herein, represents a stable monocyclic or bicyclic ring of up to 7 atoms in each ring, wherein at least one ring is aromatic and contains from 1 to 4 heteroatoms selected from the group consisting of O, N and S. Heteroaryl groups within the scope of this definition include but are not limited to: acridinyl, carbazolyl, cinnolinyl, quinoxalinyl, pyrrazolyl, indolyl, benzotriazolyl, furanyl, thienyl, benzothienyl, benzofuranyl, quinolinyl, isoquinolinyl, oxazolyl, isoxazolyl, indolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, tetrahydroquinoline. As with the definition of heterocycle below, "heteroaryl" is also understood to include the N-oxide derivative of any nitrogen-containing heteroaryl. In cases where the heteroaryl substituent is bicyclic and one ring is non-aromatic or contains no heteroatoms, it is understood that attachment is via the aromatic ring or via the heteroatom containing ring, respectively.

The term "heterocycle" or "heterocyclyl" as used herein is intended to mean a 5- to 10-membered aromatic or nonaromatic heterocycle containing from 1 to 4 heteroatoms selected from the group consisting of O, N and S, and includes bicyclic groups. "Heterocyclyl" therefore includes the above mentioned heteroaryls, as well as dihydro and tetrathydro analogs thereof. Further examples of "heterocyclyl" include, but are not limited to the following: benzoimidazolyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxazoline, isoxazoline, oxetanyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, tetrahydropyranyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyridin-2-onyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzoimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl, and N-oxides thereof. Attachment of a heterocyclyl substituent can occur via a carbon atom or via a heteroatom.

A "heterocycleC_0-C_8alkyl" is a heterocyclic group linked via a single covalent bond or C_1-C_8alkylene group. A (4- to 7-membered heterocycle)C_0-C_8alkyl is a heterocyclic group (*e.g.*, monocyclic or bicyclic) having from 4 to 7 ring members linked via a single covalent bond or an alkylene group having from 1 to 8 carbon atoms. A "(6-membered heteroaryl)C_0-C_6alkyl" refers to a heteroaryl group linked via a direct bond or C_1-C_6alkyl group.

The term "acyl" includes compounds and moieties which contain the acyl radical (CH_3CO-) or a carbonyl group. The term "substituted acyl" includes acyl groups where one or more of the hydrogen atoms are replaced by for example, alkyl groups, alkynyl groups, halogens, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino,

arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

The term "acylamino" includes moieties wherein an acyl moiety is bonded to an amino group. For example, the term includes alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido groups.

The term "alkoxy" includes substituted and unsubstituted alkyl, alkenyl, and alkynyl groups covalently linked to an oxygen atom. Examples of alkoxy groups include methoxy, ethoxy, isopropyloxy, propoxy, butoxy, and pentoxy groups and may include cyclic groups such as cyclopentoxy. Examples of substituted alkoxy groups include halogenated alkoxy groups. The alkoxy groups can be substituted with groups such as alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moieties. Examples of halogen substituted alkoxy groups include, but are not limited to, fluoromethoxy, difluoromethoxy, trifluoromethoxy, chloromethoxy, dichloromethoxy, trichloromethoxy, *etc.*

The term "carbonyl" or "carboxy" includes compounds and moieties which contain a carbon connected with a double bond to an oxygen atom, and tautomeric forms thereof. Examples of moieties that contain a carbonyl include aldehydes, ketones, carboxylic acids, amides, esters, anhydrides, *etc.* The term "carboxy moiety" or "carbonyl moiety" refers to groups such as "alkylcarbonyl" groups wherein an alkyl group is covalently bound to a carbonyl group, "alkenylcarbonyl" groups wherein an alkenyl group is covalently bound to a carbonyl group, "alkynylcarbonyl" groups wherein an alkynyl group is covalently bound to a carbonyl group, "arylcarbonyl" groups wherein an aryl group is covalently attached to the carbonyl group. Furthermore, the term also refers to groups wherein one or more heteroatoms are covalently bonded to the carbonyl moiety. For example, the term includes moieties such as, for example, aminocarbonyl moieties, (wherein a nitrogen atom is bound to

the carbon of the carbonyl group, *e.g.*, an amide), aminocarbonyloxy moieties, wherein an oxygen and a nitrogen atom are both bond to the carbon of the carbonyl group (*e.g.*, also referred to as a "carbamate"). Furthermore, aminocarbonylamino groups (*e.g.*, ureas) are also include as well as other combinations of carbonyl groups bound to heteroatoms (*e.g.*, nitrogen, oxygen, sulfur, *etc.* as well as carbon atoms). Furthermore, the heteroatom can be further substituted with one or more alkyl, alkenyl, alkynyl, aryl, aralkyl, acyl, *etc.* moieties.

The term "thiocarbonyl" or "thiocarboxy" includes compounds and moieties which contain a carbon connected with a double bond to a sulfur atom. The term "thiocarbonyl moiety" includes moieties that are analogous to carbonyl moieties. For example, "thiocarbonyl" moieties include aminothiocarbonyl, wherein an amino group is bound to the carbon atom of the thiocarbonyl group, furthermore other thiocarbonyl moieties include, oxythiocarbonyls (oxygen bound to the carbon atom), aminothiocarbonylamino groups, *etc.*

The term "ether" includes compounds or moieties that contain an oxygen bonded to two different carbon atoms or heteroatoms. For example, the term includes "alkoxyalkyl" which refers to an alkyl, alkenyl, or alkynyl group covalently bonded to an oxygen atom that is covalently bonded to another alkyl group.

The term "ester" includes compounds and moieties that contain a carbon or a heteroatom bound to an oxygen atom that is bonded to the carbon of a carbonyl group. The term "ester" includes alkoxycarboxy groups such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, pentoxycarbonyl, *etc.* The alkyl, alkenyl, or alkynyl groups are as defined above.

The term "thioether" includes compounds and moieties which contain a sulfur atom bonded to two different carbon or hetero atoms. Examples of thioethers include, but are not limited to alkthioalkyls, alkthioalkenyls, and alkthioalkynyls. The term "alkthioalkyls" include compounds with an alkyl, alkenyl, or alkynyl group bonded to a sulfur atom that is bonded to an alkyl group. Similarly, the term "alkthioalkenyls" and alkthioalkynyls" refer to compounds or moieties wherein an alkyl, alkenyl, or alkynyl group is bonded to a sulfur atom which is covalently bonded to an alkynyl group.

The term "hydroxy" or "hydroxyl" includes groups with an –OH or –O$^-$.

The term "halogen" includes fluorine, bromine, chlorine, iodine, *etc.* The term "perhalogenated" generally refers to a moiety wherein all hydrogens are replaced by halogen atoms.

The terms "polycyclyl" or "polycyclic radical" include moieties with two or more rings (*e.g.*, cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls) in which

two or more carbons are common to two adjoining rings, *e.g.*, the rings are "fused rings". Rings that are joined through non-adjacent atoms are termed "bridged" rings. Each of the rings of the polycycle can be substituted with such substituents as described above, as for example, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkoxycarbonyl, alkylaminoacarbonyl, aralkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, alkenylcarbonyl, aminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkyl, alkylaryl, or an aromatic or heteroaromatic moiety.

The term "heteroatom" includes atoms of any element other than carbon or hydrogen. Preferred heteroatoms are nitrogen, oxygen, sulfur and phosphorus.

Additionally, the phrase "any combination thereof" implies that any number of the listed functional groups and molecules may be combined to create a larger molecular architecture. For example, the terms "phenyl," "carbonyl" (or "=O"), "-O-," "–OH," and $C_{1\text{-}6}$ (*i.e.*, $-CH_3$ and $-CH_2CH_2CH_2-$) can be combined to form a 3-methoxy-4-propoxybenzoic acid substituent. It is to be understood that when combining functional groups and molecules to create a larger molecular architecture, hydrogens can be removed or added, as required to satisfy the valence of each atom.

It is to be understood that all of the compounds of the invention described above will further include bonds between adjacent atoms and/or hydrogens as required to satisfy the valence of each atom. That is, bonds and/or hydrogen atoms are added to provide the following number of total bonds to each of the following types of atoms: carbon: four bonds; nitrogen: three bonds; oxygen: two bonds; and sulfur: two bonds.

Groups that are "optionally substituted" are unsubstituted or are substituted by other than hydrogen at one or more available positions, typically 1, 2, 3, 4 or 5 positions, by one or more suitable groups (which may be the same or different). Optional substitution is also indicated by the phrase "substituted with from 0 to X substituents," where X is the maximum number of possible substituents. Certain optionally substituted groups are substituted with from 0 to 2, 3 or 4 independently selected substituents (*i.e.*, are unsubstituted or substituted with up to the recited maximum number of substitutents).

It will be noted that the structures of some of the compounds of this invention include

asymmetric carbon atoms. It is to be understood accordingly that the isomers arising from such asymmetry (*e.g.*, all enantiomers, stereoisomers, rotamers, tautomers, diastereomers, or racemates) are included within the scope of this invention. Such isomers can be obtained in substantially pure form by classical separation techniques and by stereochemically controlled synthesis. Furthermore, the structures and other compounds and moieties discussed in this application also include all tautomers thereof. Compounds described herein may be obtained through art recognized synthesis strategies.

It will also be noted that the substituents of some of the compounds of this invention include isomeric cyclic structures. It is to be understood accordingly that constitutional isomers of particular substituents are included within the scope of this invention, unless indicated otherwise. For example, the term "tetrazole" includes tetrazole, 2*H*-tetrazole, 3*H*-tetrazole, 4*H*-tetrazole and 5*H*-tetrazole.

Use in HCV-associated disorders

The compounds of the present invention have valuable pharmacological properties and are useful in the treatment of diseases. In certain embodiments, compounds of the invention are useful in the treatment of HCV-associated disorders, *e.g.*, as drugs to treat HCV infection.

The term "use" includes any one or more of the following embodiments of the invention, respectively: the use in the treatment of HCV-associated disorders; the use for the manufacture of pharmaceutical compositions for use in the treatment of these diseases, *e.g.*, in the manufacture of a medicament; methods of use of compounds of the invention in the treatment of these diseases; pharmaceutical preparations having compounds of the invention for the treatment of these diseases; and compounds of the invention for use in the treatment of these diseases; as appropriate and expedient, if not stated otherwise. In particular, diseases to be treated and are thus preferred for use of a compound of the present invention are selected from HCV-associated disorders, including those corresponding to HCV-infection, as well as those diseases that depend on the activity of one or more of the NS3, NS4A, NS4B, NS5A and NS5B proteins, or a NS3-NS4A, NS4A-NS4B, NS4B-NS5A or NS5A-NS5B complex. The term "use" further includes embodiments of compositions herein which bind to an HCV protein sufficiently to serve as tracers or labels, so that when coupled to a fluor or tag, or made radioactive, can be used as a research reagent or as a diagnostic or an imaging agent.

In certain embodiments, a compound of the present invention is used for treating HCV-associated diseases, and use of the compound of the present invention as an inhibitor of

any one or more HCVs. It is envisioned that a use can be a treatment of inhibiting one or more strains of HCV.

Assays

The inhibition of HCV activity may be measured as using a number of assays available in the art. An example of such an assay can be found in Anal Biochem. 1996 240(1): 60-7; which is incorporated by reference in its entirety. Assays for measurement of HCV activity are also described in the experimental section below.

Pharmaceutical Compositions

The language "effective amount" of the compound is that amount necessary or sufficient to treat or prevent an HCV-associated disorder, *e.g.* prevent the various morphological and somatic symptoms of an HCV-associated disorder, and/or a disease or condition described herein. In an example, an effective amount of the HCV -modulating compound is the amount sufficient to treat HCV infection in a subject. In another example, an effective amount of the HCV-modulating compound is the amount sufficient to treat HCV infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma, cryoglobulinaemia, non-Hodgkin's lymphoma, and a suppressed innate intracellular immune response in a subject. The effective amount can vary depending on such factors as the size and weight of the subject, the type of illness, or the particular compound of the invention. For example, the choice of the compound of the invention can affect what constitutes an "effective amount." One of ordinary skill in the art would be able to study the factors contained herein and make the determination regarding the effective amount of the compounds of the invention without undue experimentation.

The regimen of administration can affect what constitutes an effective amount. The compound of the invention can be administered to the subject either prior to or after the onset of an HCV-associated state. Further, several divided dosages, as well as staggered dosages, can be administered daily or sequentially, or the dose can be continuously infused, or can be a bolus injection. Further, the dosages of the compound(s) of the invention can be proportionally increased or decreased as indicated by the exigencies of the therapeutic or prophylactic situation.

Compounds of the invention may be used in the treatment of states, disorders or diseases as described herein, or for the manufacture of pharmaceutical compositions for use in the treatment of these diseases. Methods of use of compounds of the present invention in the treatment of these diseases, or pharmaceutical preparations having compounds of the

present invention for the treatment of these diseases.

The language "pharmaceutical composition" includes preparations suitable for administration to mammals, *e.g.*, humans. When the compounds of the present invention are administered as pharmaceuticals to mammals, *e.g.*, humans, they can be given per se or as a pharmaceutical composition containing, for example, 0.1 to 99.5% (more preferably, 0.5 to 90%) of active ingredient in combination with a pharmaceutically acceptable carrier.

The phrase "pharmaceutically acceptable carrier" is art recognized and includes a pharmaceutically acceptable material, composition or vehicle, suitable for administering compounds of the present invention to mammals. The carriers include liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting the subject agent from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically acceptable carriers include: sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients, such as cocoa butter and suppository waxes; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol; phosphate buffer solutions; and other non-toxic compatible substances employed in pharmaceutical formulations.

Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

Examples of pharmaceutically acceptable antioxidants include: water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, α-tocopherol, and the like; and metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

Formulations of the present invention include those suitable for oral, nasal, topical, transdermal, buccal, sublingual, rectal, vaginal and/or parenteral administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient that can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound that produces a therapeutic effect. Generally, out of one hundred per cent, this amount will range from about 1 per cent to about ninety-nine percent of active ingredient, preferably from about 5 per cent to about 70 per cent, most preferably from about 10 per cent to about 30 per cent.

Methods of preparing these formulations or compositions include the step of bringing into association a compound of the present invention with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound of the present invention with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

Formulations of the invention suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound of the present invention as an active ingredient. A compound of the present invention may also be administered as a bolus, electuary or paste.

In solid dosage forms of the invention for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the active ingredient is mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; humectants, such as glycerol; disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; solution retarding agents, such as paraffin; absorption accelerators, such as quaternary ammonium compounds; wetting agents, such as, for example, cetyl alcohol and glycerol monostearate; absorbents, such as kaolin and bentonite clay; lubricants, such a talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and coloring agents. In the

case of capsules, tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

The tablets, and other solid dosage forms of the pharmaceutical compositions of the present invention, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions that can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

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

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

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

Formulations of the pharmaceutical compositions of the invention for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing one or more compounds of the invention with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active compound.

Formulations of the present invention which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate.

Dosage forms for the topical or transdermal administration of a compound of this invention include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants that may be required.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to a compound of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

Transdermal patches have the added advantage of providing controlled delivery of a compound of the present invention to the body. Such dosage forms can be made by dissolving or dispersing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be

controlled by either providing a rate controlling membrane or dispersing the active compound in a polymer matrix or gel.

Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of this invention.

Pharmaceutical compositions of this invention suitable for parenteral administration comprise one or more compounds of the invention in combination with one or more pharmaceutically acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

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

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents that delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally-administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsule matrices of the subject compounds in biodegradable polymers such as polylactide-polyglycolide. Depending on the

ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions that are compatible with body tissue.

The preparations of the present invention may be given orally, parenterally, topically, or rectally. They are of course given by forms suitable for each administration route. For example, they are administered in tablets or capsule form, by injection, inhalation, eye lotion, ointment, suppository, *etc.*, administration by injection, infusion or inhalation; topical by lotion or ointment; and rectal by suppositories. Oral administration is preferred.

The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion.

The phrases "systemic administration," "administered systemically," "peripheral administration" and "administered peripherally" as used herein mean the administration of a compound, drug or other material other than directly into the central nervous system, such that it enters the patient's system and, thus, is subject to metabolism and other like processes, for example, subcutaneous administration.

These compounds may be administered to humans and other animals for therapy by any suitable route of administration, including orally, nasally, as by, for example, a spray, rectally, intravaginally, parenterally, intracisternally and topically, as by powders, ointments or drops, including buccally and sublingually.

Regardless of the route of administration selected, the compounds of the present invention, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the present invention, are formulated into pharmaceutically acceptable dosage forms by conventional methods known to those of skill in the art.

Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

The selected dosage level will depend upon a variety of factors including the activity of the particular compound of the present invention employed, or the ester, salt or amide

thereof, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the compounds of the invention employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

In general, a suitable daily dose of a compound of the invention will be that amount of the compound that is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above. Generally, intravenous and subcutaneous doses of the compounds of this invention for a patient, when used for the indicated analgesic effects, will range from about 0.0001 to about 100 mg per kilogram of body weight per day, more preferably from about 0.01 to about 50 mg per kg per day, and still more preferably from about 1.0 to about 100 mg per kg per day. An effective amount is that amount treats an HCV-associated disorder.

If desired, the effective daily dose of the active compound may be administered as two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms.

While it is possible for a compound of the present invention to be administered alone, it is preferable to administer the compound as a pharmaceutical composition.

Synthetic Procedure

Compounds of the present invention are prepared from commonly available compounds using procedures known to those skilled in the art, including any one or more of the following conditions without limitation:

Within the scope of this text, only a readily removable group that is not a constituent of the particular desired end product of the compounds of the present invention is designated a "protecting group," unless the context indicates otherwise. The protection of functional groups by such protecting groups, the protecting groups themselves, and their cleavage reactions are described for example in standard reference works, such as *e.g.*, Science of Synthesis: Houben-Weyl Methods of Molecular Transformation. Georg Thieme Verlag,

Stuttgart, Germany. 2005. 41627 pp. (URL: http://www.science-of-synthesis.com (Electronic Version, 48 Volumes)); J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London and New York 1973, in T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", Third edition, Wiley, New York 1999, in "The Peptides"; Volume 3 (editors: E. Gross and J. Meienhofer), Academic Press, London and New York 1981, in "Methoden der organischen Chemie" (*Methods of Organic Chemistry*), Houben Weyl, 4th edition, Volume 15/I, Georg Thieme Verlag, Stuttgart 1974, in H.-D. Jakubke and H. Jeschkeit, "Aminosäuren, Peptide, Proteine" (*Amino acids, Peptides, Proteins*), Verlag Chemie, Weinheim, Deerfield Beach, and Basel 1982, and in Jochen Lehmann, "Chemie der Kohlenhydrate: Monosaccharide und Derivate" (*Chemistry of Carbohydrates: Monosaccharides and Derivatives*), Georg Thieme Verlag, Stuttgart 1974. A characteristic of protecting groups is that they can be removed readily (*i.e.*, without the occurrence of undesired secondary reactions) for example by solvolysis, reduction, photolysis or alternatively under physiological conditions (*e.g.*, by enzymatic cleavage).

Salts of compounds of the present invention having at least one salt-forming group may be prepared in a manner known per se. For example, salts of compounds of the present invention having acid groups may be formed, for example, by treating the compounds with metal compounds, such as alkali metal salts of suitable organic carboxylic acids, *e.g.*, the sodium salt of 2-ethylhexanoic acid, with organic alkali metal or alkaline earth metal compounds, such as the corresponding hydroxides, carbonates or hydrogen carbonates, such as sodium or potassium hydroxide, carbonate or hydrogen carbonate, with corresponding calcium compounds or with ammonia or a suitable organic amine, stoichiometric amounts or only a small excess of the salt-forming agent preferably being used. Acid addition salts of compounds of the present invention are obtained in customary manner, *e.g.*, by treating the compounds with an acid or a suitable anion exchange reagent. Internal salts of compounds of the present invention containing acid and basic salt-forming groups, *e.g.*, a free carboxy group and a free amino group, may be formed, *e.g.*, by the neutralisation of salts, such as acid addition salts, to the isoelectric point, *e.g.*, with weak bases, or by treatment with ion exchangers.

Salts can be converted in customary manner into the free compounds; metal and ammonium salts can be converted, for example, by treatment with suitable acids, and acid addition salts, for example, by treatment with a suitable basic agent.

Mixtures of isomers obtainable according to the invention can be separated in a manner known per se into the individual isomers; diastereoisomers can be separated, for

example, by partitioning between polyphasic solvent mixtures, recrystallisation and/or chromatographic separation, for example over silica gel or by, *e.g.*, medium pressure liquid chromatography over a reversed phase column, and racemates can be separated, for example, by the formation of salts with optically pure salt-forming reagents and separation of the mixture of diastereoisomers so obtainable, for example by means of fractional crystallisation, or by chromatography over optically active column materials.

Intermediates and final products can be worked up and/or purified according to standard methods, *e.g.*, using chromatographic methods, distribution methods, (re-) crystallization, and the like.

General process conditions

The following applies in general to all processes mentioned throughout this disclosure.

The process steps to synthesize the compounds of the invention can be carried out under reaction conditions that are known per se, including those mentioned specifically, in the absence or, customarily, in the presence of solvents or diluents, including, for example, solvents or diluents that are inert towards the reagents used and dissolve them, in the absence or presence of catalysts, condensation or neutralizing agents, for example ion exchangers, such as cation exchangers, *e.g.*, in the H^+ form, depending on the nature of the reaction and/or of the reactants at reduced, normal or elevated temperature, for example in a temperature range of from about -100 °C to about 190°C, including, for example, from approximately -80°C to approximately 150°C, for example at from -80 to -60°C, at room temperature, at from -20 to 40°C or at reflux temperature, under atmospheric pressure or in a closed vessel, where appropriate under pressure, and/or in an inert atmosphere, for example under an argon or nitrogen atmosphere.

At all stages of the reactions, mixtures of isomers that are formed can be separated into the individual isomers, for example diastereoisomers or enantiomers, or into any desired mixtures of isomers, for example racemates or mixtures of diastereoisomers, for example analogously to the methods described in Science of Synthesis: Houben-Weyl Methods of Molecular Transformation. Georg Thieme Verlag, Stuttgart, Germany. 2005.

The solvents from which those solvents that are suitable for any particular reaction may be selected include those mentioned specifically or, for example, water, esters, such as lower alkyl-lower alkanoates, for example ethyl acetate, ethers, such as aliphatic ethers, for example diethyl ether, or cyclic ethers, for example tetrahydrofurane or dioxane, liquid

aromatic hydrocarbons, such as benzene or toluene, alcohols, such as methanol, ethanol or 1- or 2-propanol, nitriles, such as acetonitrile, halogenated hydrocarbons, such as methylene chloride or chloroform, acid amides, such as dimethylformamide or dimethyl acetamide, bases, such as heterocyclic nitrogen bases, for example pyridine or N-methylpyrrolidin-2-one, carboxylic acid anhydrides, such as lower alkanoic acid anhydrides, for example acetic anhydride, cyclic, linear or branched hydrocarbons, such as cyclohexane, hexane or isopentane, or mixtures of those solvents, for example aqueous solutions, unless otherwise indicated in the description of the processes. Such solvent mixtures may also be used in working up, for example by chromatography or partitioning.

The compounds, including their salts, may also be obtained in the form of hydrates, or their crystals may, for example, include the solvent used for crystallization. Different crystalline forms may be present.

The invention relates also to those forms of the process in which a compound obtainable as an intermediate at any stage of the process is used as starting material and the remaining process steps are carried out, or in which a starting material is formed under the reaction conditions or is used in the form of a derivative, for example in a protected form or in the form of a salt, or a compound obtainable by the process according to the invention is produced under the process conditions and processed further in situ.

Pro-drugs

The present invention also relates to pro-drugs of a compound of the present invention that are converted in vivo to the compounds of the present invention as described herein. Any reference to a compound of the present invention is therefore to be understood as referring also to the corresponding pro-drugs of the compound of the present invention, as appropriate and expedient.

Combinations

A compound of the present invention may also be used in combination with other agents, *e.g.*, an additional HCV-modulating compound that is or is not of the formula I, for treatment of and HCV-associated disorder in a subject.

By the term "combination", is meant either a fixed combination in one dosage unit form, or a kit of parts for the combined administration where a compound of the present invention and a combination partner may be administered independently at the same time or separately within time intervals that especially allow that the combination partners show a

cooperative, *e.g.*, synergistic, effect, or any combination thereof.

For example, WO 2005/042020, incorporated herein by reference in its entirety, describes the combination of various HCV inhibitors with a cytochrome P450 ("CYP") inhibitor. Any CYP inhibitor that improves the pharmacokinetics of the relevant NS3/4A protease may be used in combination with the compounds of this invention. These CYP inhibitors include, but are not limited to, ritonavir (WO 94/14436, incorporated herein by reference in its entirety), ketoconazole, troleandomycin, 4-methyl pyrazole, cyclosporin, clomethiazole, cimetidine, itraconazole, fluconazole, miconazole, fluvoxamine, fluoxetine, nefazodone, sertraline, indinavir, nelfinavir, amprenavir, fosamprenavir, saquinavir, lopinavir, delavirdine, erythromycin, VX-944, and VX-497. Preferred CYP inhibitors include ritonavir, ketoconazole, troleandomycin, 4-methyl pyrazole, cyclosporin, and clomethiazole.

Methods for measuring the ability of a compound to inhibit CYP activity are known (see, *e.g.*, US 6,037,157 and Yun, et al. Drug Metabolism & Disposition, vol. 21, pp. 403-407 (1993); incorporated herein by reference). For example, a compound to be evaluated may be incubated with 0.1, 0.5, and 1.0 mg protein/ml, or other appropriate concentration of human hepatic microsomes (e. g., commercially available, pooled characterized hepatic microsomes) for 0, 5, 10, 20, and 30 minutes, or other appropriate times, in the presence of an NADPH-generating system. Control incubations may be performed in the absence of hepatic microsomes for 0 and 30 minutes (triplicate). The samples may be analyzed for the presence of the compound. Incubation conditions that produce a linear rate of compound metabolism will be used a guide for further studies. Experiments known in the art can be used to determine the kinetics of the compound metabolism (K_m and V_{max}). The rate of disappearance of compound may be determined and the data analyzed according to Michaelis-Menten kinetics by using Lineweaver-Burk, Eadie-Hofstee, or nonlinear regression analysis.

Inhibition of metabolism experiments may then be performed. For example, a compound (one concentration, $< K_m$) may be incubated with pooled human hepatic microsomes in the absence or presence of a CYP inhibitor (such as ritonavir) under the conditions determined above. As would be recognized, control incubations should contain the same concentration of organic solvent as the incubations with the CYP inhibitor. The concentrations of the compound in the samples may be quantitated, and the rate of disappearance of parent compound may be determined, with rates being expressed as a percentage of control activity.

Methods for evaluating the influence of co-administration of a compound of the invention and a CYP inhibitor in a subject are also known (see, *e.g.*, US2004/0028755; incorporated herein by reference). Any such methods could be used in connection with this invention to determine the pharmacokinetic impact of a combination. Subjects that would benefit from treatment according to this invention could then be selected.

Accordingly, one embodiment of this invention provides a method for administering an inhibitor of CYP3A4 and a compound of the invention. Another embodiment of this invention provides a method for administering an inhibitor of isozyme 3A4 ("CYP3A4"), isozyme 2C19 ("CYP2C19"), isozyme 2D6 ("CYP2D6"), isozyme 1A2 ("CYP1A2"), isozyme 2C9 ("CYP2C9"), or isozyme 2E1 ("CYP2E1"). In embodiments where the protease inhibitor is VX-950 (or a sterereoisomer thereof), the CYP inhibitor preferably inhibits CYP3A4.

As would be appreciated, CYP3A4 activity is broadly observed in humans. Accordingly, embodiments of this invention involving inhibition of isozyme 3A4 would be expected to be applicable to a broad range of patients.

Accordingly, this invention provides methods wherein the CYP inhibitor is administered together with the compound of the invention in the same dosage form or in separate dosage forms.

The compounds of the invention (e.g., compound of Formula I or subformulae thereof) may be administered as the sole ingredient or in combination or alteration with other antiviral agents, especially agents active against HCV. In combination therapy, effective dosages of two or more agents are administered together, whereas in alternation or sequential-step therapy, an effective dosage of each agent is administered serially or sequentially. In general, combination therapy is typically preferred over alternation therapy because it induces multiple simultaneous stresses on the virus. The dosages given will depend on absorption, inactivation and excretion rate of the drug as well as other factors. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens and schedules should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions. The efficacy of a drug against the viral infection can be prolonged, augmented, or restored by administering the compound in combination or alternation with a second, and perhaps third antiviral compound that induces a different gene mutation than that caused by the principle

drug in a drug resistant virus. Alternatively, the pharmacokinetic, biodistribution or other parameters of the drug can be altered by such combination or alternation therapy.

Daily dosages required in practicing the method of the present invention will vary depending upon, for example, the compound of the invention employed , the host, the mode of administration, the severity of the condition to be treated. A preferred daily dosage range is about from 1 to 50 mg/kg per day as a single dose or in divided doses. Suitable daily dosages for patients are on the order of from e.g. 1 to 20 mg/kg p.o or i.v. Suitable unit dosage forms for oral administration comprise from ca. 0.25 to 10 mg/kg active ingredient, e.g. compound of Formula I or any subformulae thereof, together with one or more pharmaceutically acceptable diluents or carriers therefor. The amount of co-agent in the dosage form can vary greatly, e.g., 0.00001 to 1000mg/kg active ingredient.

Daily dosages with respect to the co-agent used will vary depending upon, for example, the compound employed, the host, the mode of administration and the severity of the condition to be treated. For example, lamivudine may be administered at a daily dosage of 100mg. The pegylated interferon may be administered parenterally one to three times per week, preferably once a week, at a total weekly dose ranging from 2 to 10 million IU, more preferable 5 to 10 million IU, most preferable 8 to 10 million IU. Because of the diverse types of co-agent that may be used, the amounts can vary greatly, e.g., .0001 to 5,000 mg/kg per day.

The current standard of care for treating hepatitis C is the combination of pegylated interferon alpha with ribavirin, of which the recommended doses are1.5 μg/kg/wk peginterferon alfa-2b or 180 μg/wk peginterferon alfa-2a, plus 1,000 to 1,200 mg daily of ribavirin for 48 weeks for genotype I patients, or 800 mg daily of ribavirin for 24 weeks for genotype 2/3 patients.

The compound of the invention (e.g., compound of Formula I or subformulae thereof) and co-agents of the invention may be administered by any conventional route, in particular enterally, e.g. orally, for example in the form of solutions for drinking, tablets or capsules or parenterally, for example in the form of injectable solutions or suspensions. Certain preferred pharmaceutical compositions may be e.g. those based on microemulsions as described in UK 2,222,770 A.

The compound of the invention (e.g., compound of Formula I or subformulae thereof) are administered together with other drugs (co-agents) e.g. a drug which has anti-viral activity, especially anti-Flaviviridae activity, most especially anti-HCV activity, e.g. an interferon, e.g. interferon-α-2a or interferon-α-2b, e.g. Intron^{R} A, Roferon^{R}, Avonex^{R}, Rebif^{R}

or Betaferon^R, or an interferon conjugated to a water soluble polymer or to human albumin, e.g. albuferon, an anti-viral agent, e.g. ribavirin, lamivudine, the compounds disclosed in US patent no. 6,812,219 and WO 2004/002422 A2 (the disclosures of which are incorporated herein by reference in their entireties), an inhibitor of the HCV or other Flaviviridae virus encoded factors like the NS3/4A protease, helicase or RNA polymerase or a prodrug of such an inhibitor, an anti-fibrotic agent, e.g. a N-phenyl-2-pyrimidine-amine derivative, e.g. imatinib, an immune modulating agent, e.g. mycophenolic acid, a salt or a prodrug thereof, e.g. sodium mycophenolate or mycophenolate mofetil, or a S1P receptor agonist, e.g. FTY720 or an analogue thereof optionally phosphorylated, e.g. as disclosed in EP627406A1, EP778263A1, EP1002792A1, WO02/18395, WO02/76995, WO 02/06268, JP2002316985, WO03/29184, WO03/29205, WO03/62252 and WO03/62248, the disclosures of which are incorporated herein by reference in their entireties.

Conjugates of interferon to a water-soluble polymer are meant to include especially conjugates to polyalkylene oxide homopolymers such as polyethylene glycol (PEG) or polypropylene glycols, polyoxyethylenated polyols, copolymers thereof and block copolymers thereof. As an alternative to polyalkylene oxide-based polymers, effectively non-antigenic materials such as dextran, polyvinyl pyrrolidones, polyacrylamides, polyvinyl alcohols, carbohydrate-based polymers and the like can be used. Such interferon-polymer conjugates are described in U.S. Pat. Nos. 4,766,106, 4,917,888, European Patent Application No. 0 236 987, European Patent Application No. 0 510 356 and International Application Publication No. WO 95/13090, the disclosures of which are incorporated herein by reference in their entireties. Since the polymeric modification sufficiently reduces antigenic responses, the foreign interferon need not be completely autologous. Interferon used to prepare polymer conjugates may be prepared from a mammalian extract, such as human, ruminant or bovine interferon, or recombinantly produced. Preferred are conjugates of interferon to polyethylene glycol, also known as pegylated interferons.

Especially preferred conjugates of interferon are pegylated alfa-interferons, for example pegylated interferon-α-2a, pegylated interferon-α-2b; pegylated consensus interferon or pegylated purified interferon- α product. Pegylated interferon- α -2a is described e.g. in European Patent 593,868 (incorporated herein by reference in its entirety) and commercially available e. g. under the tradename PEGASYS® (Hoffmann-La Roche). Pegylated interferon-α -2b is described, e.g. in European Patent 975,369 (incorporated herein by reference in its entirety) and commercially available e.g. under the tradename PEG-INTRON A® (Schering Plough). Pegylated consensus interferon is described in WO 96/11953 (incorporated herein

by reference in its entirety). The preferred pegylated α-interferons are pegylated interferon-α-2a and pegylated interferon-α-2b. Also preferred is pegylated consensus interferon.

Other preferred co-agents are fusion proteins of an interferon, for example fusion proteins of interferon- α -2a, interferon- α -2b; consensus interferon or purified interferon-α product, each of which is fused with another protein. Certain preferred fusion proteins comprise an interferon (e.g., interferon- α -2b) and an albumin as described in U.S. Patent 6,973,322 and international publications WO02/60071, WO05/003296 and WO05/077042 (Human Genome Sciences). A preferred interferon conjugated to a human albumin is Albuferon (Human Genome Sciences).

Cyclosporins which bind strongly to cyclophilin but are not immunosuppressive include those cyclosporins recited in U.S. Patents 5,767,069 and 5,981,479 and are incorporated herein by reference. MeIle^4-Cyclosporin is a preferred non-immunosuppressive cyclosporin. Certain other cyclosporin derivatives are described in WO2006039668 (Scynexis) and WO2006038088 (Debiopharm SA) and are incorporated herein by reference. A cyclosporin is considered to be non-immunosuppressive when it has an activity in the Mixed Lymphocyte Reaction (MLR) of no more than 5%, preferably no more than 2%, that of cyclosporin A. The Mixed Lymphocyte Reaction is described by T. Meo in "Immunological Methods", L. Lefkovits and B. Peris, Eds., Academic Press, N.Y. pp. 227 – 239 (1979). Spleen cells (0.5×10^6) from Balb/c mice (female, 8 – 10 weeks) are co-incubated for 5 days with 0.5×10^6 irradiated (2000 rads) or mitomycin C treated spleen cells from CBA mice (female, 8 – 10 weeks). The irradiated allogeneic cells induce a proliferative response in the Balb c spleen cells which can be measured by labeled precursor incorporation into the DNA. Since the stimulator cells are irradiated (or mitomycin C treated) they do not respond to the Balb/c cells with proliferation but do retain their antigenicity. The IC_{50} found for the test compound in the MLR is compared with that found for cyclosporin A in a parallel experiment. In addition, non-immunosuppressive cyclosporins lack the capacity of inhibiting CN and the downstream NF-AT pathway. [MeIle]^4-ciclosporin is a preferred non-immunosuppressive cyclophilin-binding cyclosporin for use according to the invention.

Ribavirin (1-β-D-ribofuranosyl-1-1,2,4-triazole-3-caroxamide) is a synthetic, non-interferon-inducing, broad spectrum antiviral nucleoside analog sold under the trade name, Virazole (The Merck Index, 11th edition, Editor: Budavar, S, Merck & Co., Inc., Rahway, NJ, p1304,1989). United States Patent No. 3,798,209 and RE29,835 (incorporated herein by reference in their entireties) disclose and claim ribavirin. Ribavirin is structurally similar to

guanosine, and has *in vitro* activity against several DNA and RNA viruses including *Flaviviridae* (Gary L. Davis, Gastroenterology 118:S104-S114, 2000).

Ribavirin reduces serum amino transferase levels to normal in 40% of patients, but it does not lower serum levels of HCV-RNA (Gary L. Davis, Gastroenterology 118:S104-S114, 2000). Thus, ribavirin alone is not effective in reducing viral RNA levels. Additionally, ribavirin has significant toxicity and is known to induce anemia. Ribavirin is not approved for monotherapy against HCV; it is approved in combination with interferon alpha-2a or interferon alpha-2b for the treatment of HCV.

A further preferred combination is a combination of a compound of the invention (e.g., a compound of Formula I or any subformulae thereof) with a non-immunosuppressive cyclophilin-binding cyclosporine, with mycophenolic acid, a salt or a prodrug thereof, and/or with a S1P receptor agonist, e.g. FTY720.

Additional examples of compounds that can be used in combination or alternation treatments include:

(1) Interferons, including interferon alpha 2a or 2b and pegylated (PEG) interferon alpha 2a or 2b, for example:

(a) Intron-A®, interferon alfa-2b (Schering Corporation, Kenilworth, NJ);

(b) PEG-Intron®, peginteferon alfa-2b (Schering Corporation, Kenilworth, NJ);

(c) Roferon®, recombinant interferon alfa-2a (Hoffmann-La Roche, Nutley, NJ);

(d) Pegasys®, peginterferon alfa-2a (Hoffmann-La Roche, Nutley, NJ);

(e) Berefor®, interferon alfa 2 available (Boehringer Ingelheim Pharmaceutical, Inc., Ridgefield, CT);

(f) Sumiferon®, a purified blend of natural alpha interferons (Sumitomo, Japan)

(g) Wellferon®, lymphoblastoid interferon alpha n1 (GlaxoSmithKline);

(h) Infergen®, consensus alpha interferon (InterMune Pharmaceuticals, Inc., Brisbane, CA);

(i) Alferon®, a mixture of natural alpha interferons (Interferon Sciences, and Purdue Frederick Co., CT);

(j) Viraferon®;

(k) Consensus alpha interferon from Amgen, Inc., Newbury Park, CA,

Other forms of interferon include: interferon beta, gamma, tau and omega, such as Rebif (Interferon beta 1a) by Serono, Omniferon (natural interferon) by Viragen, REBIF (interferon beta-1a) by Ares-Serono, Omega Interferon by BioMedicines; oral Interferon

Alpha by Amarillo Biosciences; an interferon conjugated to a water soluble polymer or to a human albumin, e.g., Albuferon (Human Genome Sciences), an antiviral agent, a consensus interferon, ovine or bovine interferon-tau

Conjugates of interferon to a water-soluble polymer are meant to include especially conjugates to polyalkylene oxide homopolymers such as polyethylene glocol (PEG) or polypropylene glycols, polyoxyethylenated polyols, copolymers thereof and block copolymers thereof. As an alternative to polyalkylene oxid-based polymers, effectively non-antigenic materials such as dextran, polyvinyl pyrrolidones, polyacrylamides, polyvinyl alcohols, carbohydrate-based polymers and the like can be used. Since the polymeric modification sufficiently reduces antigenic response, the foreign interferon need not be completely autologous. Interferon used to prepare polymer conjugates may be prepared from a mammalian extract, such as human, ruminant or bovine interferon, or recombinantly produced. Preferred are conjugates of interferon to polyethylene glycol, also known as pegylated interferons.

(2) Ribavirin, such as ribavirin (1-beta-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide) from Valeant Pharmaceuticals, Inc., Costa Mesa, CA); Rebetol® from Schering Corporation, Kenilworth, NJ, and Copegus® from Hoffmann-La Roche, Nutley, NJ; and new ribavirin analogues in development such as Levovirin and Viramidine by Valeant,

(3) Thiazolidine derivatives which show relevant inhibition in a reverse-phase HPLC assay with an NS3/4A fusion protein and NS5A/5B substrate (Sudo K. et al., *Antiviral Research*, 1996, 32, 9-18), especially compound RD-1-6250, possessing a fused cinnamoyl moiety substituted with a long alkyl chain, RD4 6205 and RD4 6193;

(4) Thiazolidines and benzanilides identified in Kakiuchi N. et al. *J. FEBS Letters* 421, 217-220; Takeshita N. et al. *Analytical Biochemistry, 1997, 247, 242-246;*

(5) A phenan-threnequinone possessing activity against protease in a SDS-PAGE and autoradiography assay isolated from the fermentation culture broth of Streptomyces sp., Sch 68631 (Chu M. et al., *Tetrahedron Letters*, 1996, 37, 7229-7232), and Sch 351633, isolated from the fungus *Penicillium griseofulvum,* which demonstrates activity in a scintillation proximity assay (Chu M. et al, *Bioorganic and Medicinal Chemistry Letters* 9, 1949-1952);

(6) Protease inhibitors.

Examples include substrate-based NS3 protease inhibitors (Attwood et al., *Antiviral peptide derivatives*, PCT WO 98/22496, 1998; Attwood et al., *Antiviral Chemistry and Chemotherapy* 1999, 10, 259-273; Attwood et al, *Preparation and use of amino acid derivatives as anti-viral agents*, German Patent Pub. DE 19914474; Tung et al. *Inhibitors of*

serine proteases, particularly hepatitis C virus NS3 protease; PCT WO 98/17679), including alphaketoamides and hydrazinoureas, and inhibitors that terminate in an electrophile such as a boronic acid or phosphonate (Llinas-Brunet et al. *Hepatitis C inhibitor peptide analogues*, PCT WO 99/07734) are being investigated.

Non-substrate-based NS3 protease inhibitors such as 2,4,6-trihydroxy-3-nitro-benzamide derivatives (Sudo K. et al., *Biochemical and Biophysical Research Communications*, 1997, 238 643-647; Sudo K. et al. *Antiviral Chemistry and Chemotherapy*, 1998, 9, 186), including RD3-4082 and RD3-4078, the former substituted on the amide with a 14 carbon chain and the latter processing a *para*-phenoxyphenyl group are also being investigated.

Sch 68631, a phenanthrenequinone, is an HCV protease inhibitor (Chu M et al., *Tetrahedron Letters* 37:7229-7232, 1996). In another example by the same authors, Sch 351633, isolated from the fungus *Penicillium grieofulvum*, was identified as a protease inhibitor (Chu M. et al., *Bioorganic and Medicinal Chemistry Letters* 9:1949-1952). Nanomolar potency against the HCV NS3 protease enzyme has been achieved by the design of selective inhibitors based on the macromolecule eglin c. Eglin c, isolated from leech, is a potent inhibitor of several serine proteases such as S. griseus proteases A and B, ∀-chymotrypsin, chymase and subtilisin. Qasim M.A. et al., *Biochemistry* 36:1598-1607, 1997.

U.S. patents disclosing protease inhibitors for the treatment of HCV include, for example, U.S. Patent No. 6,004,933 to Spruce et al (incorporated herein by reference in its entirety) which discloses a class of cysteine protease inhibitors for inhibiting HCV endopeptidase 2; U.S. Patent No. 5,990,276 to Zhang et al.(incorporated herein by reference in its entirety) which discloses synthetic inhibitors of hepatitis C virus NS3 protease; U.S. Patent No. 5,538,865 to Reyes et al.(incorporated herein by reference in its entirety). Peptides as NS3 serine protease inhibitors of HCV are disclosed in WO 02/008251 to Corvas International, Inc., and WO 02/08187 and WO 02/008256 to Schering Corporation (incorporated herein by reference in their entireties). HCV inhibitor tripeptides are disclosed in U.S. Patent Nos. 6,534,523, 6,410,531 and 6,420,380 to Boehringer Ingelheim and WO 02/060926 to Bristol Myers Squibb (incorporated herein by reference in their entireties). Diaryl peptides as NS3 serine protease inhibitors of HCV are disclosed in WO 02/48172 to Schering Corporation (incorporated herein by reference). Imidazoleidinones as NS3 serine protease inhibitors of HCV are disclosed in WO 02/18198 to Schering Corporation and WO 02/48157 to Bristol Myers Squibb (incorporated herein by reference in their entireties). WO

98/17679 to Vertex Pharmaceuticals and WO 02/48116 to Bristol Myers Squibb also disclose HCV protease inhibitors (incorporated herein by reference in their entireties).

HCV NS3-4A serine protease inhibitors including BILN 2061 by Boehringer Ingelheim, VX-950 by Vertex, SCH 6/7 by Schering-Plough, and other compounds currently in preclinical development;

Substrate-based NS3 protease inhibitors, including alphaketoamides and hydrazinoureas, and inhibitors that terminate in an elecrophile such as a boronic acid or phosphonate; Non-substrate-based NS3 protease inhibitors such as 2,4,6-trihydroxy-3-nitro-benzamide derivatives including RD3-4082 and RD3-4078, the former substituted on the amide with a 14 carbon chain and the latter processing a para-phenoxyphenyl group; and Sch68631, a phenanthrenequinone, an HCV protease inhibitor.

Sch 351633, isolated from the fungus *Penicillium griseofulvum* was identified as a protease inhibitor. Eglin c, isolated from leech is a potent inhibitor of several serine proteases such as S. griseus proteases A and B, a-chymotrypsin, chymase and subtilisin.

US patent no. 6004933 (incorporated herein by reference in its entirety) discloses a class of cysteine protease inhibitors from inhibiting HCV endopeptidase 2; synthetic inhibitors of HCV NS3 protease (pat), HCV inhibitor tripeptides (pat), diaryl peptides such as NS3 serine protease inhibitors of HCV (pat), Imidazolidindiones as NS3 serine protease inhibitors of HCV (pat).

Thiazolidines and benzanilides (ref). Thiazolidine derivatives which show relevant inhibition in a reverse-phase HPLC assay with an NS3/4A fusion protein and NS5A/5B substrate especially compound RD-16250 possessing a fused cinnamoyl moiety substituted with a long alkyl chain, RD4 6205 and RD4 6193

Phenan-threnequinone possessing activity against protease in a SDS-PAGE and autoradiography assay isolated from the fermentation culture broth of *Streptomyces* sp, Sch68631 and Sch351633, isolated from the fungus *Penicillium griseofulvum*, which demonstrates activity in a scintillation proximity assay.

(7) Nucleoside or non-nucleoside inhibitors of HCV NS5B RNA-dependent RNA polymerase, such as 2'-C-methyl-3'-O-L-valine ester ribofuranosyl cytidine (Idenix) as disclosed in WO 2004/002422 A2 (incorporated herein by reference in its entirety), R803 (Rigel), JTK-003 (Japan Tabacco), HCV-086 (ViroPharma/Wyeth) and other compounds currently in preclinical development;

gliotoxin (ref) and the natural product cerulenin;

2'-fluoronucleosides;

other nucleoside analogues as disclosed in WO 02/057287 A2, WO 02/057425 A2, WO 01/90121, WO 01/92282, and US patent no. 6,812,219, the disclosures of which are incorporated herein by reference in their entirety.

Idenix Pharmaceuticals discloses the use of branched nucleosides in the treatment of flaviviruses (including HCV) and pestiviruses in International Publication Nos. WO 01/90121 and WO 01/92282 (incorporated herein by reference in their entireties). Specifically, a method for the treatment of hepatitis C infection (and flaviviruses and pestiviruses) in humans and other host animals is disclosed in the Idenix publications that includes administering an effective amount of a biologically active 1', 2', 3' or 4'-branced B-D or B-L nucleosides or a pharmaceutically acceptable salt or prodrug thereof, administered either alone or in combination with another antiviral agent, optionally in a pharmaceutically acceptable carrier. Certain preferred biologically active 1', 2', 3', or 4' branched B-D or B-L nucleosides, including Telbivudine, are described in U.S. Patents 6,395,716 and 6,875,751, each of which are incorporated herein by reference.

Other patent applications disclosing the use of certain nucleoside analogs to treat hepatitis C virus include: PCTCA00/01316 (WO 01/32153; filed November 3, 2000) and PCT/CA01/00197 (WO 01/60315; filed February 19, 2001) filed by BioChem Pharma, Inc., (now Shire Biochem, Inc.); PCT/US02/01531 (WO 02/057425; filed January 18, 2002) and PCT/US02/03086 (WO 02/057287; filed January 18, 2002) filed by Merck & Co., Inc., PCT/EP01/09633 (WO 02/18404; published August 21, 2001) filed by Roche, and PCT Publication Nos. WO 01/79246 (filed April 13, 2001), WO 02/32920 (filed October 18, 2001) and WO 02/48165 by Pharmasset, Ltd. (the disclosures of which are incorporated herein by reference in their entireties)

PCT Publication No. WO 99/43691 to Emory University (incorporated herein by reference in its entirety), entitled "2'-Fluoronucleosides" discloses the use of certain 2'-fluoronucleosides to treat HCV.

Eldrup et al. (Oral Session V, Hepatitis C Virus, Flaviviridae; 16th International Conference on Antiviral Research (April 27, 2003, Savannah, GA)) described the structure activity relationship of 2'-modified nucleosides for inhibition of HCV.

Bhat et al. (Oral Session V, Hepatitis C Virus, Flaviviridae, 2003 (Oral Session V, Hepatitis C Virus, Flaviviridae; 16th International conference on Antiviral Research (April 27, 2003, Savannah, GA); p A75) describes the synthesis and pharmacokinetic properties of nucleoside analogues as possible inhibitors of HCV RNA replication. The authors report that 2'-modified nucleosides demonstrate potent inhibitory activity in cell-based replicon assays.

Olsen et al. (Oral Session V, Hepatitis C Virus, Flaviviridae; 16th International Conference on Antiviral Research (April 27, 2003, Savannah, Ga)p A76) also described the effects of the 2'-modified nucleosides on HCV RNA replication.

(8) Nucleotide polymerase inhibitors and gliotoxin (Ferrari R. et al. *Journal of Virology*, 1999, 73, 1649-1654), and the natural product cerulenin (Lohmann V. et al. *Virology*, 1998, 249, 108-118);

(9) HCV NS3 helicase inhibitors, such as VP_50406 by ViroPhama and compounds from Vertex. Other helicase inhibitors (Diana G.D. et al., *Compounds, compositions and methods for treatment of hepatitis C*, U.S. Patent No. 5,633,358 (incorporated herein by reference in its entirety); Diana G.D. et al., *Piperidine derivatives, pharmaceutical compositions thereof and their use in the treatment of hepatitis C,* PCT WO 97/36554);

(10) Antisense phosphorothioate oligodeoxynucleotides (S-ODN) complementary to sequence stretches in the 5' non-coding region (NCR) of the virus (Alt M. et al., *Hepatology*, 1995, 22, 707-717), or nucleotides 326-348 comprising the 3' end of the NCR and nucleotides 371-388 located in the core coding region of the HCV RNA (Alt M. et al., *Archives of Virology*, 1997, 142, 589-599; Galderisi U. et al., *Journal of Cellular Physiology*, 199, 181, 251-257); such as ISIS 14803 by Isis Pharm/Elan, antisense by Hybridon, antisense by AVI bioPharma,

(11) Inhibitors of IRES-dependent translation (Ikeda N et al., *Agent for the prevention and treatment of hepatitis C*, Japanese Patent Pub. JP-08268890; Kai Y et al. *Prevention and treatment of viral diseases,* Japanese Patent Pub. JP-10101591); such as ISIS 14803 by Isis Pharm/Elan, IRES inhibitor by Anadys, IRES inhibitors by Immusol, targeted RNA chemistry by PTC Therapeutics

(12) Ribozymes, such as nuclease-resistant ribozymes (Maccjak, D.J. et al., *Hepatology* 1999, 30, abstract 995) and those directed in U.S. Patent No. 6,043,077 to Barber et al., and U.S. Patent Nos. 5,869,253 and 5,610,054 to Draper et al.(incorporated herein by reference in their entireties) for example, HEPTAZYME by RPI

(13) siRNA directed against HCV genome

(14) HCV replication inhibitor of any other mechanisms such as by VP50406ViroPharama/Wyeth, inhibitors from Achillion, Arrow

(15) An inhibitor of other targets in the HCV life cycle including viral entry, assembly and maturation

(16) An immune modulating agent such as an IMPDH inhibitor, mycophenolic acid, a salt or a prodrug thereof sodium mycophenolate or mycophenolate mofetil, or Merimebodib

(VX-497); thymosin alpha-1 (Zadaxin, by SciClone); or a S1P receptor agonist, e.g. FTY720 or analogue thereof optionally phosphorylated.

(17) An anti-fibrotic agent, such as a N-phenyl-2-pyrimidine-amine derivative, imatinib (Gleevac), IP-501 by Indevus, and Interferon gamma 1b from InterMune

(18) Therapeutic vaccine by Intercell, Epimmune/Genecor, Merix, Tripep (Chron-VacC), immunotherapy (Therapore) by Avant, T cell therapy by CellExSys, monoclonal antibody XTL-002 by STL, ANA 246 and ANA 246 BY Anadys,

(19) Other miscellaneous compounds including 1-amino-alkylcyclohexanes (U.S. Patent No. 6,034,134 to Gold et al.), alkyl lipids (U.S. Pat. No. 5,922,757 to Chojkier et al.), vitamin E and other anti-oxidants (U.S. Patent. No. 5,922,757 to Chojkier et al.), amantadine, bile acids (U.S. Pat. No. 5,846,99964 to Ozeki et al.), N-(phosphonoacetl)-L-aspartic acid,)U.S. Pat. No. 5,830,905 to Diana et al.), benzenedicarboxamides (U.S. Pat. No. 5,633,388 to Diane et al.), polyadenylic acid derivatives (U.s. Pat. No. 5,496,546 to Wang et al.), 2'3'-dideoxyinosine (U.S. Pat. No. 5,026,687 to Yarchoan et al.), benzimidazoles (U.S. Pat. No. 5,891,874 to Colacino et al.), plant extracts (U.S. Pat. No. 5,837,257 to Tsai et al., U.S. Pat. No. 5,725,859 to Omer et al., and U.S. Pat. No. 6,056,961) and piperidines (U.S. Pat. No. 5,830,905 to Diana et al.); the disclosures of which are incorporated herein by reference in their entireties. Also,squalene, telbivudine, N-(phosphonoacetyl)-L-aspartic acid, benzenedicarboxamides, polyadenylic acid derivatives, glycosylation inhibitors, and nonspecific cytoprotective agents that block cell injury caused by the virus infection.

(20) Any other compound currently in preclinical or clinical development for the treatment of HCV, including Interleukin-10 (Schering-Plough), AMANTADINE (Symmetrel) by Endo Labs Solvay, caspase inhibitor IDN-6556 by Idun Pharma, HCV/MF59 by Chiron, CIVACIR (Hepatitis C Immune Globulin) by NABI, CEPLENE (histamine dichloride) by Maxim, IDN-6556 by Idun PHARM, T67, a beta-tubulin inhibitor, by Tularik, a therapeutic vaccine directed to E2 by Innogenetics, FK788 by Fujisawa Helathcare, IdB1016 (Siliphos, oral silybin-phosphatidyl choline phytosome), fusion inhibitor by Trimeris, Dication by Immtech, hemopurifier by Aethlon Medical, UT 231B by United Therapeutics.

(21) Purine nucleoside analog antagonists of TlR7 (toll-like receptors) developed by Anadys, e.g., Isotorabine (ANA245) and its prodrug (ANA975), which are described in European applications EP348446 and EP636372, International Publications WO03/045968, WO05/121162 and WO05/25583, and U.S. Patent 6/973322, each of which is incorporated by reference.

(21) Non-nucleoside inhibitors developed by Genelabs and described in International Publications WO2004/108687, WO2005/12288, and WO2006/076529, each of which is incorporated by reference.

(22) Other co-agents (*e.g.*, non-immunomodulatory or immunomodulatory compounds) that may be used in combination with a compound of this invention include, but are not limited to, those specified in WO 02/18369, which is incorporated herein by reference.

Methods of this invention may also involve administration of another component comprising an additional agent selected from an immunomodulatory agent; an antiviral agent; an inhibitor of HCV protease; an inhibitor of another target in the HCV life cycle; a CYP inhibitor; or combinations thereof.

Accordingly, in another embodiment, this invention provides a method comprising administering a compound of the invention and another anti-viral agent, preferably an anti-HCV agent. Such anti-viral agents include, but are not limited to, immunomodulatory agents, such as α, β, and δ interferons, pegylated derivatized interferon-a compounds, and thymosin; other anti-viral agents, such as ribavirin, amantadine, and telbivudine; other inhibitors of hepatitis C proteases (NS2-NS3 inhibitors and NS3-NS4A inhibitors); inhibitors of other targets in the HCV life cycle, including helicase, polymerase, and metalloprotease inhibitors; inhibitors of internal ribosome entry; broad-spectrum viral inhibitors, such as IMPDH inhibitors (*e.g.*, compounds of United States Patent 5,807, 876,6, 498,178, 6,344, 465,6, 054,472, WO 97/40028, WO 98/40381, WO 00/56331, and mycophenolic acid and derivatives thereof, and including, but not limited to VX-497, VX-148, and/or VX-944); or combinations of any of the above.

In accordance with the foregoing the present invention provides in a yet further aspect:

- A pharmaceutical combination comprising a) a first agent which is a compound of the invention, e.g. a compound of formula I or any subformulae thereof, and b) a co-agent, e.g. a second drug agent as defined above.
- A method as defined above comprising co-administration, e.g. concomitantly or in sequence, of a therapeutically effective amount of a compound of the invention, e.g. a compound of formula I or any subformulae thereof, and a co-agent, e.g. a second drug agent as defined above.

The terms "co-administration" or "combined administration" or the like as utilized herein are meant to encompass administration of the selected therapeutic agents to a single

patient, and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time. Fixed combinations are also within the scope of the present invention. The administration of a pharmaceutical combination of the invention results in a beneficial effect, e.g. a synergistic therapeutic effect, compared to a monotherapy applying only one of its pharmaceutically active ingredients.

Each component of a combination according to this invention may be administered separately, together, or in any combination thereof. As recognized by skilled practitioners, dosages of interferon are typically measured in IU (*e.g.*, about 4 million IU to about 12 million IU).

If an additional agent is selected from another CYP inhibitor, the method would, therefore, employ two or more CYP inhibitors. Each component may be administered in one or more dosage forms. Each dosage form may be administered to the patient in any order.

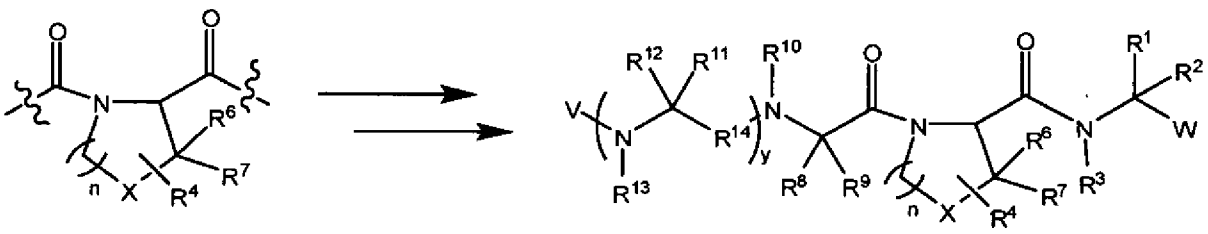
The compound of the invention and any additional agent may be formulated in separate dosage forms. Alternatively, to decrease the number of dosage forms administered to a patient, the compound of the invention and any additional agent may be formulated together in any combination. For example, the compound of the invention inhibitor may be formulated in one dosage form and the additional agent may be formulated together in another dosage form. Any separate dosage forms may be administered at the same time or different times.

Alternatively, a composition of this invention comprises an additional agent as described herein. Each component may be present in individual compositions, combination compositions, or in a single composition.

Exemplification of the Invention

The invention is further illustrated by the following examples, which should not be construed as further limiting. The assays used throughout the Examples are accepted. Demonstration of efficacy in these assays is predictive of efficacy in subjects.

GENERAL SYNTHESIS METHODS



All starting materials, building blocks, reagents, acids, bases, dehydrating agents, solvents, and catalysts utilized to synthesis the compounds of the present invention are either commercially available or can be produced by organic synthesis methods known to one of ordinary skill in the art (Houben-Weyl 4th Ed. 1952, Methods of Organic Synthesis, Thieme, Volume 21). Further, the compounds of the present invention can be produced by organic synthesis methods known to one of ordinary skill in the art as shown in the following examples.

LIST OF ABBREVIATIONS

Ac	acetyl
ACN	Acetonitrile
AcOEt / EtOAc	Ethyl acetate
AcOH	acetic acid
aq	aqueous
Ar	aryl
Bn	benzyl
Bu	butyl (nBu = n-butyl, tBu = tert-butyl)
CDI	Carbonyldiimidazole
CH_3CN	Acetonitrile
DBU	1,8-Diazabicyclo[5.4.0]-undec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DIPEA	N-Ethyldiisopropylamine
DMAP	Dimethylaminopyridine
DMF	N,N'-Dimethylformamide
DMSO	Dimethylsulfoxide
EI	Electrospray ionisation
Et_2O	Diethylether
Et_3N	Triethylamine
Ether	Diethylether
EtOH	Ethanol
FC	Flash Chromatography
h	hour(s)

HATU	O-(7-Azabenzotriazole-1-yl)-N,N,N'N'-tetramethyluronium hexafluorophosphate
HBTU	O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HCl	Hydrochloric acid
HOBt	1-Hydroxybenzotriazole
HPLC	High Performance Liquid Chromatography
H_2O	Water
L	liter(s)
LC-MS	Liquid Chromatography Mass Spectrometry
Me	methyl
MeI	Iodomethane
MeOH	Methanol
mg	milligram
min	minute(s)
mL	milliliter
MS	Mass Spectrometry
Pd/C	palladium on charcoal
PG	protecting group
Ph	phenyl
Prep	Preparative
Rf	ratio of fronts
RP	reverse phase
Rt	Retention time
rt	Room temperature
SiO_2	Silica gel
TBAF	Tetrabutylammonium fluoride
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofurane
TLC	Thin Layer Chromatography

HPLC methods:

Method A:

HPLC

Instrument: Agilent system

column: waters symmetry C18, 3.5 μm , 2.1 x 50mm , flow 0.6 ml/min

solvent: CH_3CN (0.1% CF_3CO_2H); H_2O (0.1% CF_3CO_2H)

gradient: 0-3.5 min : 20-95% CH_3CN, 3.5-5 min : 95% CH_3CN, 5.5-5.55 min 95 % to 20% CH_3CN

Method B:

Agilent 1100 LC chromatographic system with Micromass ZMD MS detection. A binary gradient composed of A (water containing 5 % acetonitrile and 0.05% trifluoroacetic acid) and B (acetonitrile containing 0.045% trifluoroacetic acid) is used as a mobile phase on a Waters X Terra™ C-18 column (30 x 3 mm, 2.5 μm particle size) as a stationary phase. The following elution profile is applied: a linear gradient of 3.5 minutes at a flow rate of 0.6 ml/min from 5% of B to 95% of B, followed by an isocratic elution of 0.5 minutes at a flow rate of 0.7 ml/min of 95% of B, followed by an isocratic elution of 0.5 minutes at a flow rate of 0.8 ml/min of 95% of B, followed by a linear gradient of 0.2 minutes at a flow rate of 0.8 ml/min from 95% of B to 5% of B, followed by a isocratic elution of 0.2 minutes at a flow rate of 0.7 ml/min of 5% of B.

Method C:

HPLC

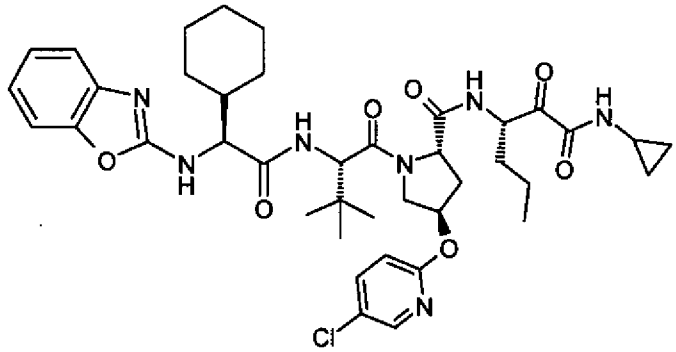
Instrument: Kontron, Kroma-System

Column: Macherey-Nagel, Lichrosphere 100-5 RP 18

Solvent: CH_3CN (0.1% CF_3CO_2H); H_2O (0.1% CF_3CO_2H)

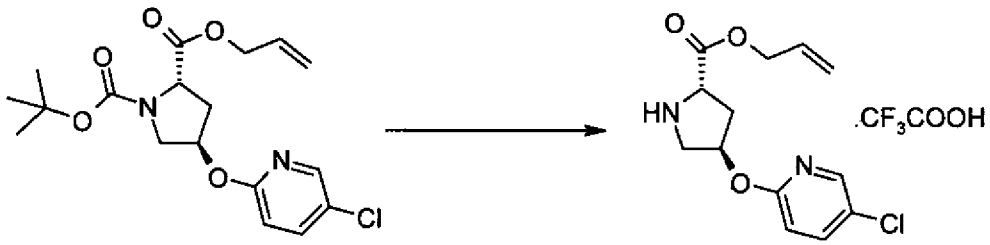
Gradient: 0-5 min: 10-100% CH_3CN; 5-7.5 min: 100% CH_3CN (Flow 1.5mL/min)

Example 1:



1

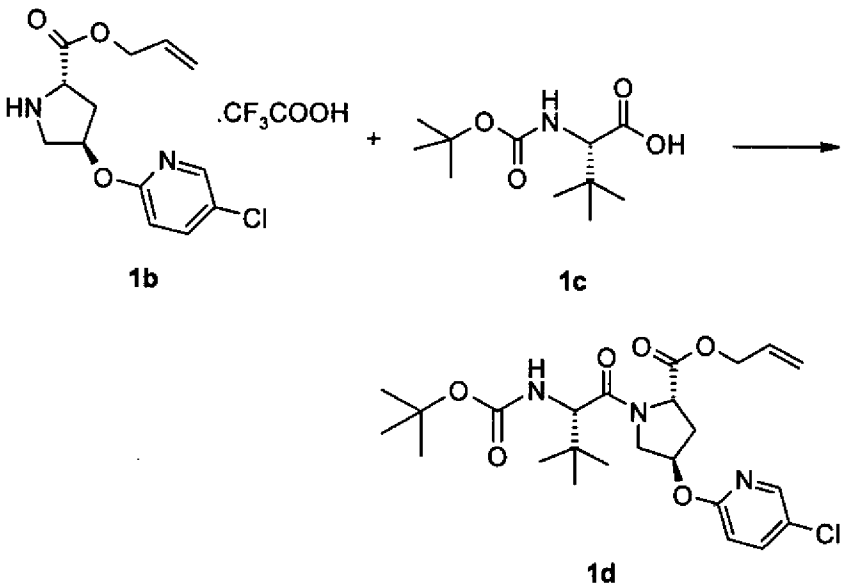
Step 1-A:



1a 1b

To a solution of **1a** (3.0 g, 7.84 mmol) in dichloromethane (20 mL) at room temperature is added TFA (20 mL). The mixture is stirred for 3 hours after which the solvent is evaporated in vacuo to give the desired product (4.5 g). Found m/z ES+ = 283 and ES- = 281.

Step 1-B:

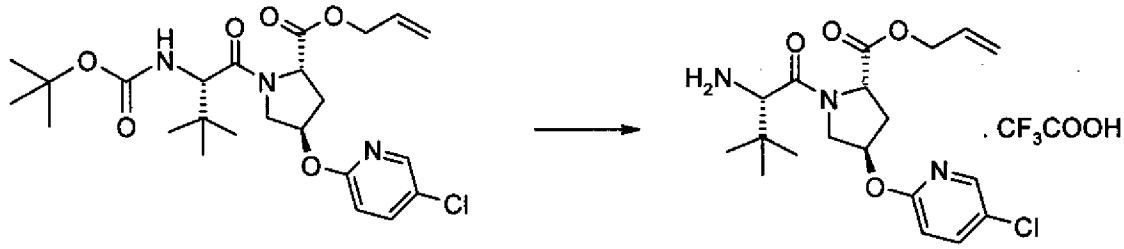


1b 1c 1d

A solution of **1c** (2.18 g, 9.45 mmol) in anhydrous dichloromethane (57 mL) and

anhydrous DMF (57 mL) is stirred at 0 °C is added HATU (1.4 eq, 5.0 g, 13.23 mmol). **1b** (1.2 eq, 4.50 g, 11.34 mmol) is added in small portions. Then, N-methylmorpholine (4.0 eq, 3.82 g, 37.8 mmol) is added dropwise. The reaction mixture is gradually warmed to room temperature and stirred for overnight. All the volatiles are removed under vacuum and the residue is dissolved in ethyl acetate. The organic layer is washed with water, 1.0 N HCl aq. solution, aq. sat. $NaHCO_3$ solution, and brine. The organic layer is dried over Na_2SO_4, filtered and concentrated in vacuo. The residue is chromatographed on silica gel (gradient: acetone/hexane; 2:8 to 1:1) to afford **1d** (3.11 g). Found m/z ES+ = 496.

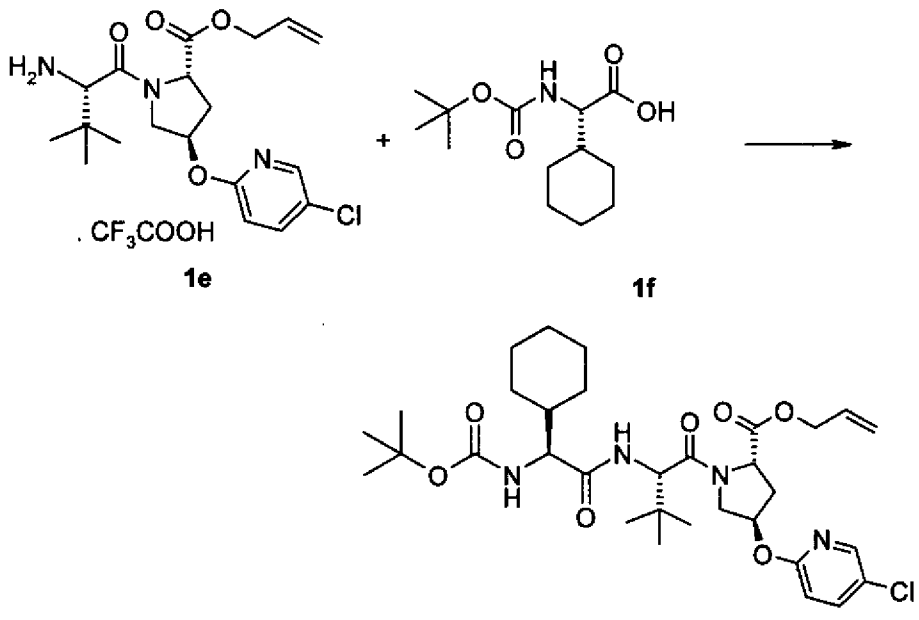
Step 1-C:



1d **1e**

To a solution of **1d** (3.1 g, 6.25 mmol) in dichloromethane (15 mL) at room temperature is added TFA (15 mL). The mixture is stirred for 3 hours after which the solvent is evaporated in vacuo to give 4.7 g of **1e**. Found m/z ES+ = 396.

Step 1-D:

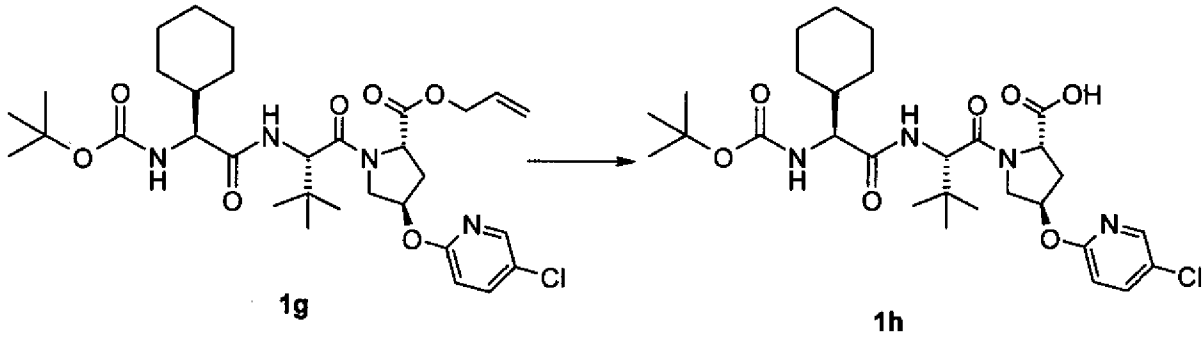


1e **1f** **1g**

A solution of Boc-L-2-cyclohexylglycine **1f** (2.0 g, 7.79 mmol) in anhydrous

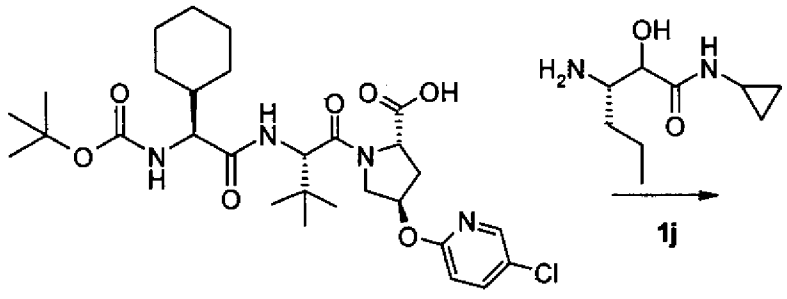
dichloromethane (40 mL) and anhydrous DMF (40 mL) is stirred at 0 °C and treated with HATU (1.4 eq, 4.14 g, 10.90 mmol). **1e** (1.2 eq, 4.77 g, 9.35 mmol) is added in small portions. Then, N-methylmorpholine (4.0 eq, 3.15 g, 31.16 mmol) is added dropwise. The reaction mixture is gradually warmed to room temperature and stirred for overnight. All the volatiles are removed under vacuum and the residue is dissolved in ethylacetate. The organic layer is washed with water, aq. 1.0 N HCl solution, sat. aq. $NaHCO_3$ solution, and brine. The organic layer is dried over Na_2SO_4, filtered and concentrated in vacuo. The residue is chromatographed on silica gel (gradient: acetone/hexane; 2:8 to 1:1) to afford 3.0 g of **1g**. Found m/z ES+ = 635.

Step 1-E:



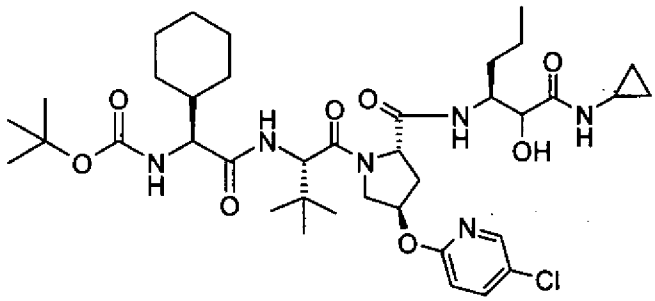
A solution of **1g** (3.0 g, 4.72 mmol) in 45 mL of a 1:1:1 mixture of THF/MeOH/water is added lithium hydroxide monohydrate (2 eq, 394 mg). The mixture is stirred for overnight. All the volatiles are evaporated in a vacuo and to the residue is added dichloromethane (100 mL). The pH of the aqueous layer is adjusted to pH 5 with dropwise addition of aq. 1.0 N HCl solution. The layers are separated and the aqueous layer is extracted with dichloromethane. The combined organic layers are dried (Na_2SO_4), filtered, and concentrated to afford 1.87 g of **1h** (1.87 g). Found m/z ES+ = 595 and ES- = 593

Step 1-F:



1i

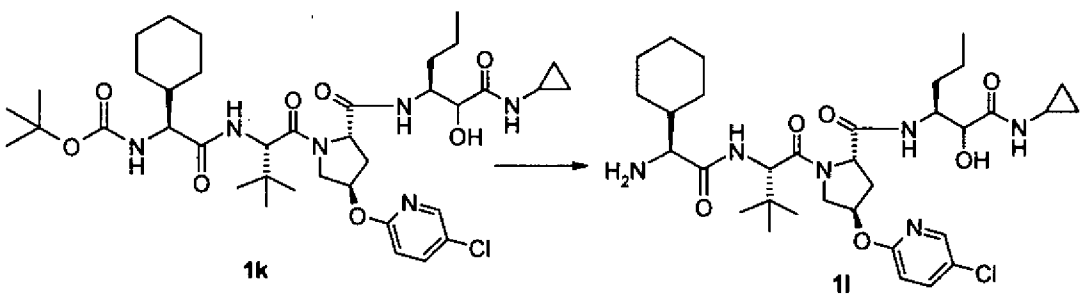
1j



1k

A solution of **1i** (2.80 g, 4.7 mmol) in anhydrous dichloromethane (24 mL) and anhydrous DMF (24 mL) is stirred at 0 °C and treated with HATU (1.4 eq, 2.5 g, 6.58 mmol). The hydroxy ketoamide amine **1j** (1.2 eq, 1.05 g, 5.66 mmol) is added in small portions. Then, N-methylmorpholine (4.0 eq, 1.90 g, 18.80 mmol) is added dropwise. The reaction mixture is gradually warmed to room temperature and stirred for overnight. All the volatiles are removed under vacuum and the residue is dissolved in ethylacetate. The organic layer is washed with water, aq. 1.0 N HCl solution, sat. aq. $NaHCO_3$ solution, and brine. The organic layer is dried over Na_2SO_4, filtered and concentrated in vacuo. The residue is chromatographed on silica gel (gradient: acetone/hexane; 2:8 to 1:1) to afford 3.0 g of **1k**. Found m/z ES+ = 763 and ES- = 761.

Step 1-G:

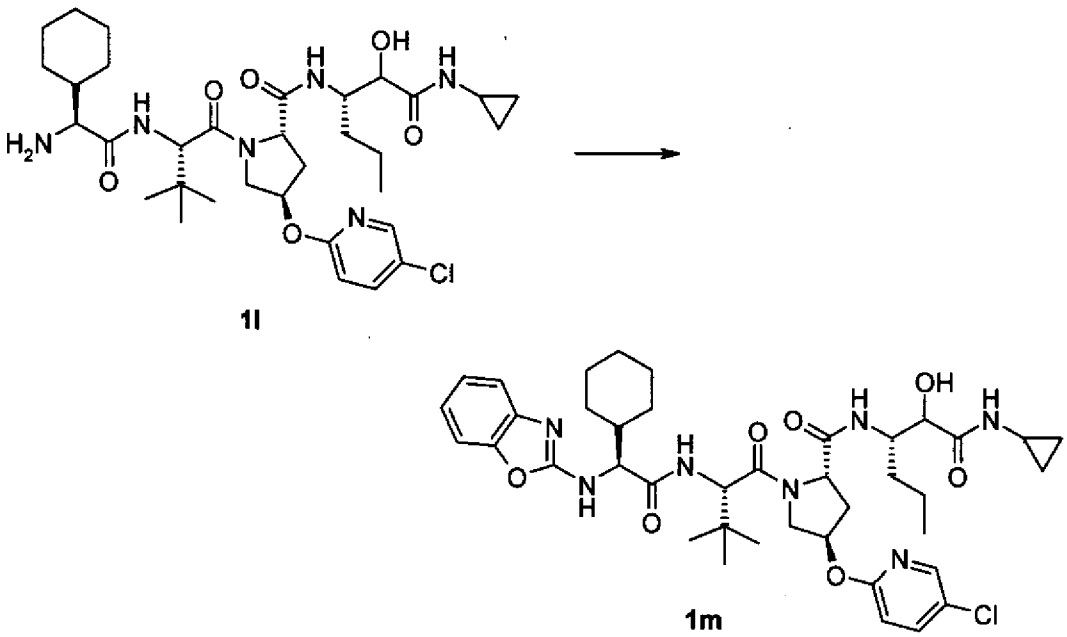


1k 1l

To a solution of **1k** (4.0 g, 5.24 mmol) in dichloromethane (26 mL) at room temperature is added TFA (26 mL). The mixture is stirred for 3 hours after which the

solvent is evaporated in vacuo and to the residue is added dichloromethane (100 mL). The pH is adjusted to 8 by dropwise addition of sat. aq. $NaHCO_3$ solution. The layers are separated. The organic layer is washed with brine, dried over Na_2SO_4, filtered and concentrated to give 4.0 g of **1l** (4.0 g). Found m/z ES+ = 663 and ES- = 661.

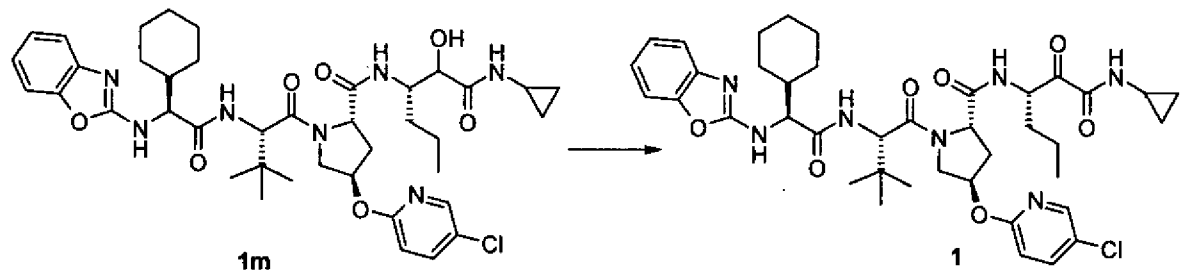
Step 1-H:



1l **1m**

To a solution of **1l** (350 mg, 0.53 mmol) in dioxane (1.0 mL) at room temperature added 2-chlorobenzaxazole (122 mg, 0.79 mmol) and $NaHCO_3$ (89 mg, 1.1 mmol). The mixtures are stirred at 65 °C for 6 hours. The mixture then is loaded directly to silica gel column and eluted with hexane/EtOH (from 95/5 to 85/15) to give 360 mg of **1m**. Found m/z ES+ = 780 and ES- = 778.

Step 1-I:

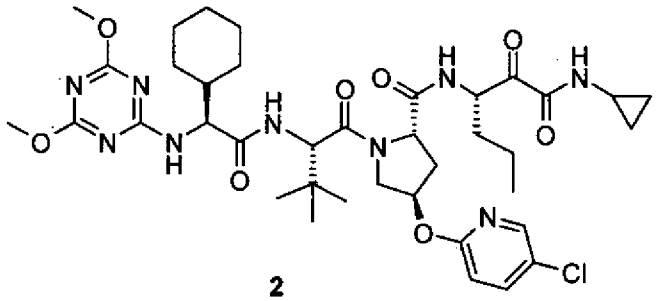


1m **1**

To a solution of **1m** (253 mg, 0.32 mmol) in CH_2Cl_2 (1.6 mL) at 0 °C is added DIPEA (1.3 mmol, 168 mg) followed by a solution of pyridine sulfoxide (0.65 mmol, 103 mg) in DMSO (1.6 mL). The solution is stirred at 0 °C for 10 min. To the solution is added

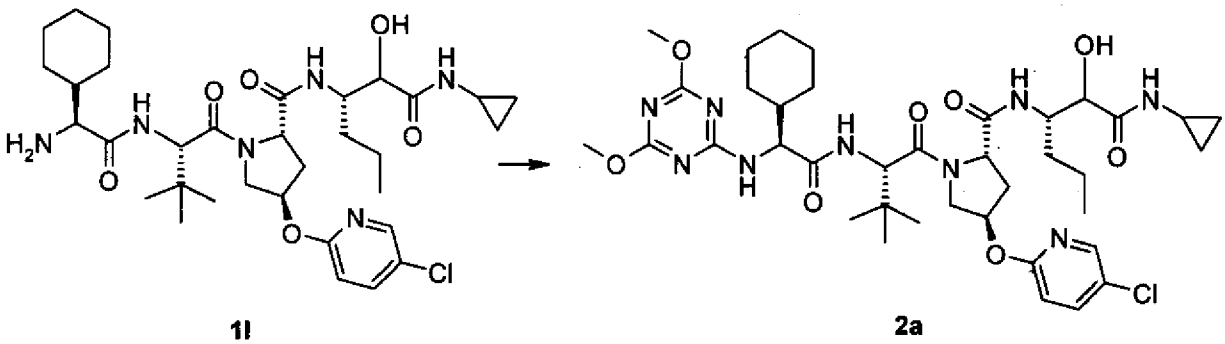
EtOAc and sat. aq. NH_4Cl solution. The two phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, washed with brine, dried over Na_2SO_4 and concentrated. The residue is purified by silica gel column chromatography (hexane/Acetone, 1/1) to give 245 mg of **1**. Found m/z in ES+ 778, m/z in ES- = 776.

Example 2:



2

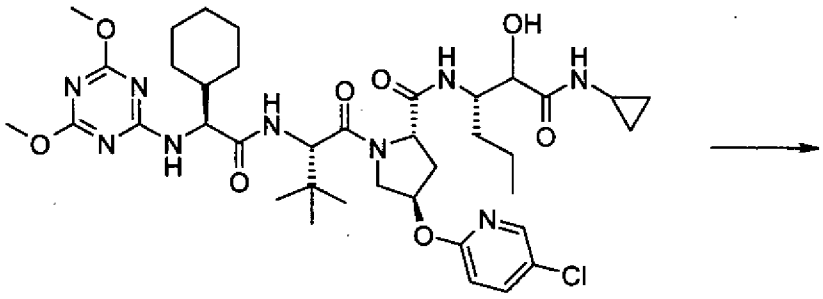
Step 2-A:



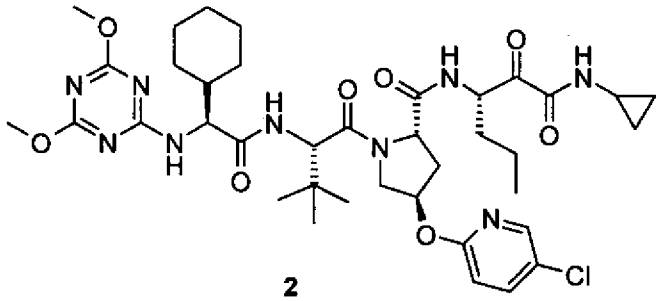
1l **2a**

To a solution of the amine **1l** (50 mg, 0.07 mmol) in dioxane (350 mL) at room temperature is added 2-chloro-4,6-dimethoxytriazine (20 mg, 0.11 mmol) and $NaHCO_3$ (13 mg, 0.16 mmol). The mixtures are stirred at 80 °C for 2 hours. The reaction mixture is concentrated in a vacuo and to the residue is added ethyl acetate (30 mL). The organic layer is washed with aq. 1.0 N HCl solution, sat. aq. $NaHCO_3$ solution and brine. The organic solution is then dried over sodium sulfate and concentrated. Purification using preparative TLC (eluent: Acetone/hexane, 1:1) afford 48 mg of **2a**. Found m/z ES+ = 802 and ES- = 800.

Step 2-B:



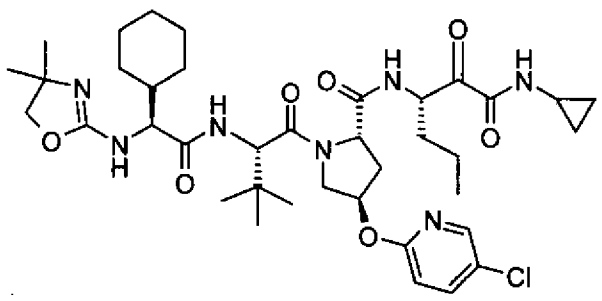
2a



2

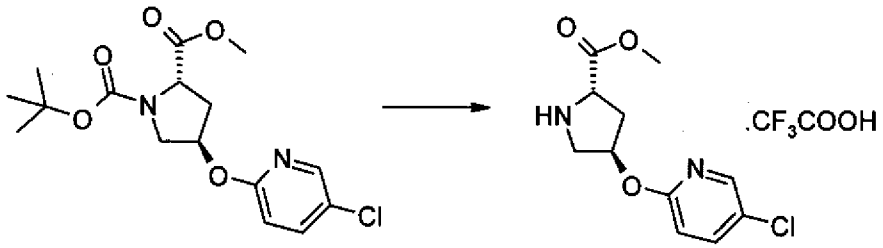
A solution o **2a** (48 mg, 0.06 mmol) in anhydrous dichloromethane (0.6 mL) is treated with DMP (2.0 eq, 51 mg). The reaction mixture is stirred at room temperature for 30 minutes. The mixture is added aq. 1.0 M sodium thiosulfate solution (2 mL) and the resulted mixtures are stirred for 5 minutes. Aq. sat. sodium bicarbonate solution (2 mL) is added and the stirring is continued for another 10 minutes. The phases are separated and the aqueous layer is extracted with dichloromethane. The combined organic layer are dried over sodium sulfate, filtered and concentrated. The residue is chromatographed using silica gel preparative TLC (Eluent: acetone/hexanes, 4:6) to afford 36 mg of **2**. Found m/z ES+ = 800.

Example 3:



3

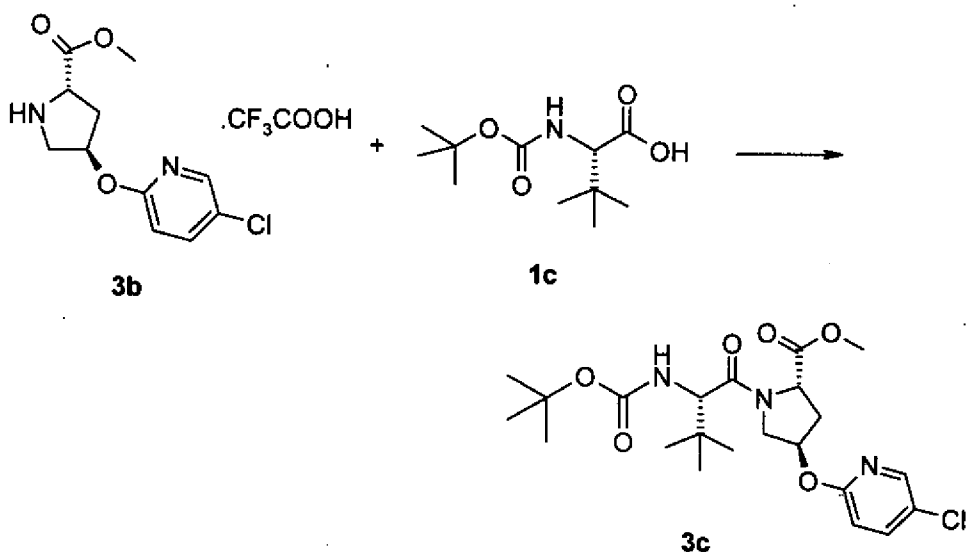
Step 3-A:



3a 3b

To a solution of **3a** (2.5 g, 7.0 mmol) in dichloromethane (6.0 mL) at room temperature is added TFA (6 mL). The mixture is stirred for 3 hours after which the solvent is evaporated in vacuo to give 4.0 g of **3b**. Found m/z ES+ = 257.

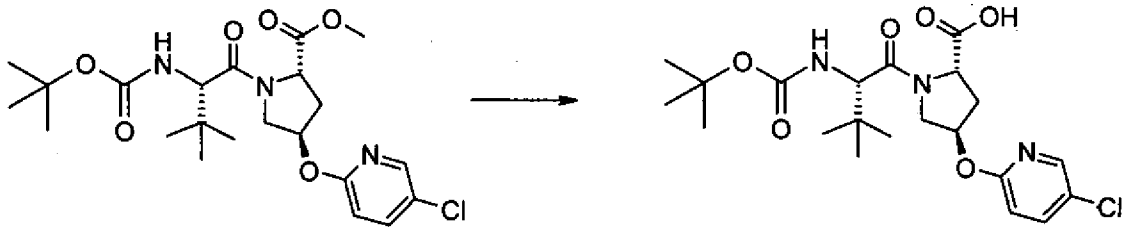
Step 3-B:



3b 1c 3c

A solution of **1c** (219 mg, 2.68 mmol) in anhydrous dichloromethane (13 mL) and anhydrous DMF (13 mL) is stirred at 0 °C and treated with HATU (1.4 eq, 1.42 g, 3.75 mmol). **3b** (1.0 eq, 0.99 g, 2.67 mmol) is added in small portions. Then, N-methylmorpholine (4.0 eq, 1.08 g, 10.7 mmol) is added dropwise. The reaction mixture is gradually warmed to room temperature and stirred for overnight. All the volatiles are removed under vacuum and the residue is dissolved in ethylacetate. The organic layer is washed with water, aq. 1.0 N HCl solution, sat. aq. sodium bicarbonate solution, and brine. The organic layer is dried over Na_2SO_4, filtered and concentrated in vacuo. The residue is chromatographed on silica gel (gradient: EtOAc/Hexane, 1:1)) to afford 1.3 g of **3c**. Found m/z ES+ = 470.

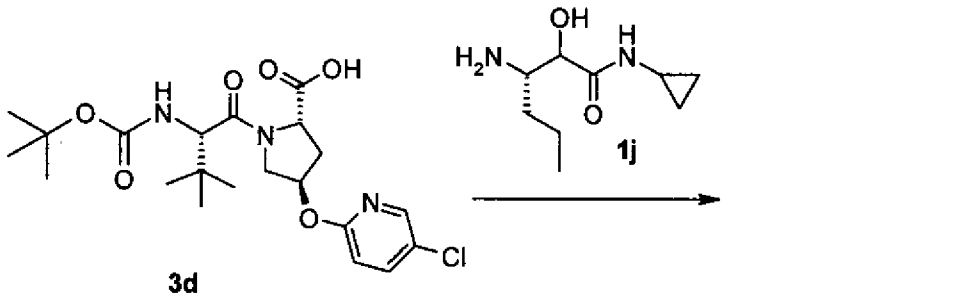
Step 3-C:



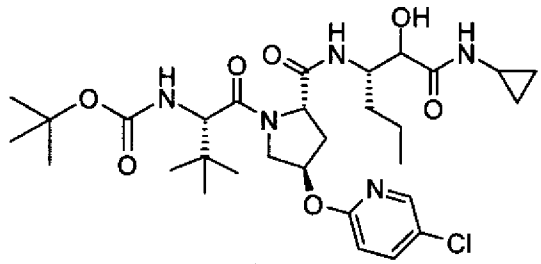
3c **3d**

A solution of **3c** (1.2 g, 2.55 mmol) in 12 mL of a 1:1:1 mixture of THF/MeOH/water is added lithium hydroxide monohydrate (2.0 eq, 214 mg). The mixture is stirred overnight. All the volatiles are evaporated in a vacuo and to the residue is added dichloromethane. The pH of the aqueous layer is adjusted to 5 with dropwise addition of aq. 1.0 N HCl solution and layers are separated. The aqueous layer is extracted with dichloromethane. The combined organic layers are dried over sodium sulfate, filtered, and concentrated to afford 822 mg of **3d**. Found m/z ES+ = 456 and ES- = 454.

Step 3-D:



3d **1j**

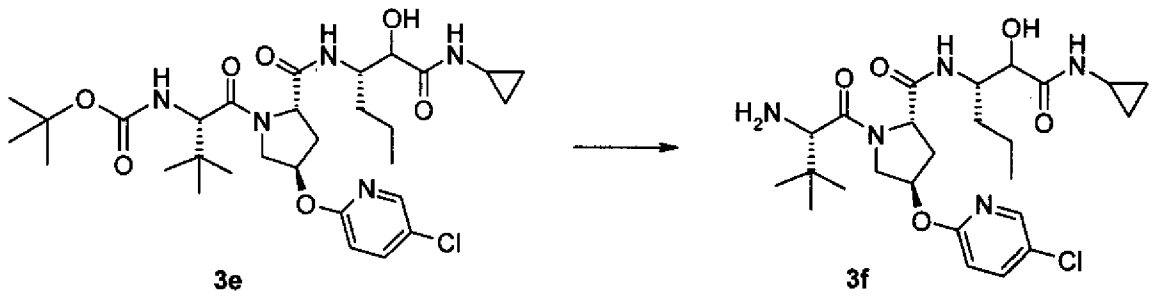


3e

A solution of **3d** (822 mg, 1.8 mmol) in anhydrous dichloromethane (4.5 mL) and anhydrous DMF (4.5 mL) is stirred at 0 °C and treated with HATU (1.4 eq, 962 mg, 2.53 mmol). **1j** (1.0 eq, 335 mg, 1.8 mmol) is added in small portions. Then, N-methylmorpholine (4.0 eq, 731 mg, 7.23 mmol) is added dropwise. The reaction mixture is gradually warmed to room temperature and stirred overnight. All the volatiles are removed under vacuum and the residue is dissolved in ethylacetate. The organic layer is washed with water, aq. 1.0 N HCl solution, sat. aq. sodium bicarbonate solution, and brine. The organic layer is dried over

Na_2SO_4, filtered and concentrated in vacuo. The residue is chromatographed on silica gel (gradient: acetone/Hexanes, 3:7) to afford 800 mg of **3e**. Found m/z ES+ = 624.

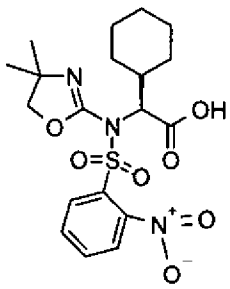
Step 3-E:



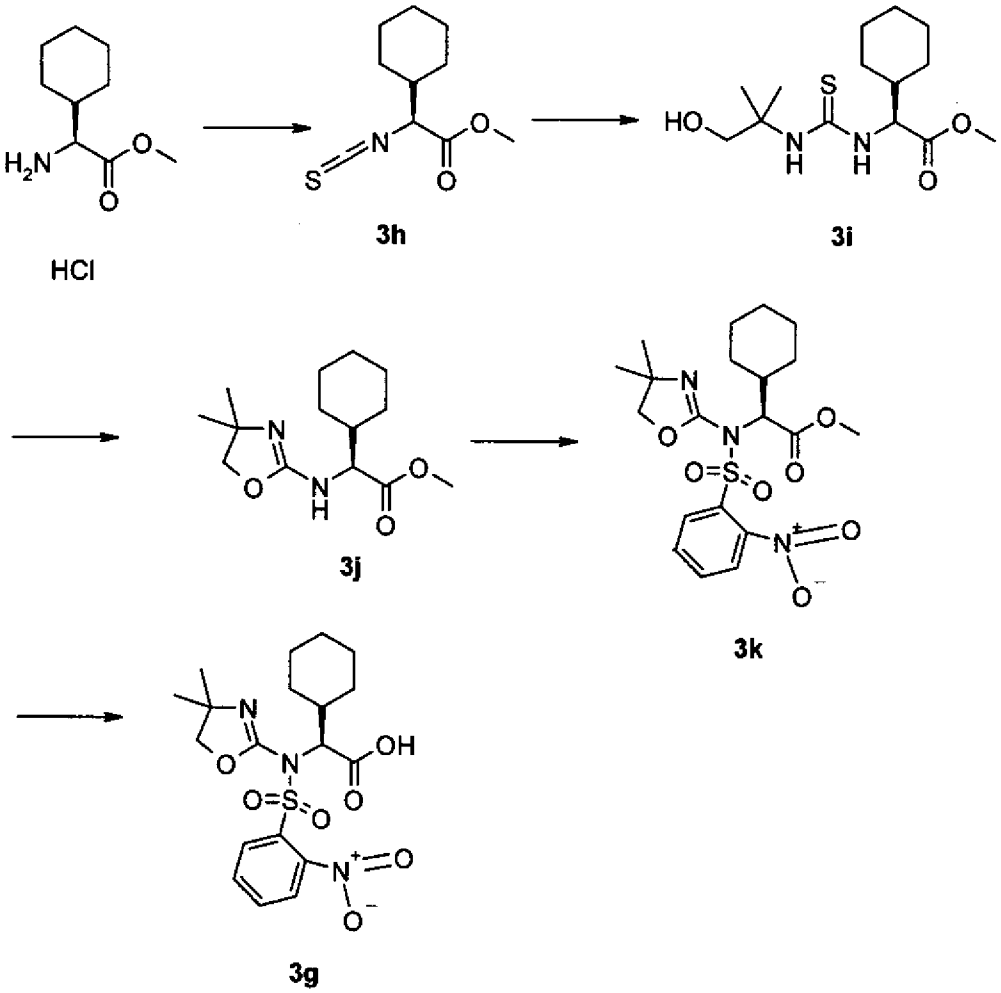
3e **3f**

To a solution of **3e** (800 mg, 1.28 mmol) in dichloromethane (3.5 mL) at room temperature is added triflouroacetic acid (3.5 mL). The mixture is stirred for 3 hours after which the solvent is evaporated in vacuo and to the residue is added dichloromethane. The pH is adjusted to 8 by dropwise addition of sat. aq. sodium bicarbonate solution. The layers are separated. The organic layer is washed with brine, dried over Na_2SO_4, and concentrated to give **3f**. Found m/z ES+ = 524.

Step 3-F:



3g



To mixtures of H-cyclohexyl-gly-OMe•HCl (2.07 g, 10 mmol) in CH_2Cl_2 (100 mL) and saturated aqueous $NaHCO_3$ solution (100 mL) at room temperature added $CSCl_2$ (0.804 mL, 10 mmol). The mixture is stirred at room temperature for 30 minutes. The two phases are separated and the aqueous layer is extracted with CH_2Cl_2. The organic layers are combined, dried over Na_2SO_4 and concentrated to give 2.1 g of **3h**, which is continued to the next step with no further purification.

To a solution of 2-amino-2-methyl-1-propanol (178 mg, 2.0 mmol) in THF (2.0 mL) added **3h** (426 mg, 2.0 mmol). The solution is stirred at room temperature for 12 hours after which the solvent is evaporated. The residue is purified by silica gel column chromatography (hexane/EtOAc, 2/1) to give 438 mg of **3i**. Found m/z in ES+ = 303, m/z in ES- = 301.

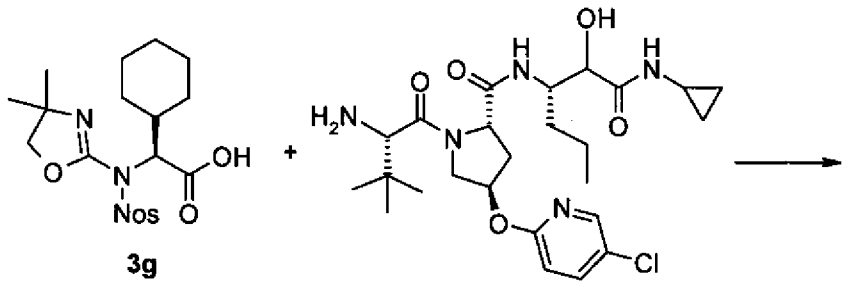
To a solution of **3i** (60 mg, 0.2 mmol) in CH_3CN (2.0 mL) at 0 °C is added a solution of 2-chloro-3-ethylbenzoxazolium tetrafluroborate (81 mg, 0.3 mmol, 1.5 equiv) in CH_3CN (1.0 mL). The solution is stirred at room temperature for 30 minutes after which TEA (0.139 mL, 1.0 mmol, 5.0 equiv) is added and the solution is stirred at room temperature for another

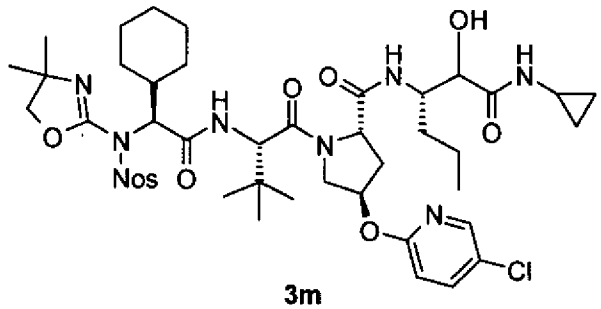
30 minutes. The solvent is then evaporated and the residue is purified by silica gel column chromatography (hexane/EtOAc, 4/1 to 0/1) to give 40 mg of **3j**. Found m/z in ES+ = 269.

To a solution of **3j** (57 mg, 0.2 mmol) in CH_2Cl_2 (0.2 mL) added TEA (0.056 mL, 0.4 mmol, 2.0 equiv), 2-nitrobenzenesulfonyl chloride (66mg, 0.3 mmol, 1.5 equiv) and DMAP (10 mg). The solution is stirred at room temperature for 4 hours. The mixtures are then directly loaded to silica gel column and flushed with hexane/EtOAc (9/1 to 1/1) to give 67 mg of **3k**. Found m/z in ES+ = 454.

To a solution of **3k** (40 mg) in THF (0.3 mL), MeOH (0.3 mL) at 0 °C is added a solution of $LiOH•H_2O$ (12 mg) in water (0.3 mL). The solution is stirred at room temperature for 8 hours, after which aq. 1.0 N HCl solution is added. The mixtures are extracted with CH_2Cl_2. The combined organic layer is dried over Na_2SO_4 and concentrated to give **3g**. Found m/z in ES+ = 440, m/z in ES- = 438.

Step 3-G:

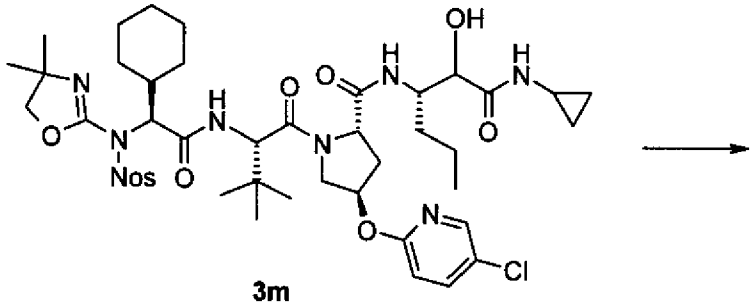




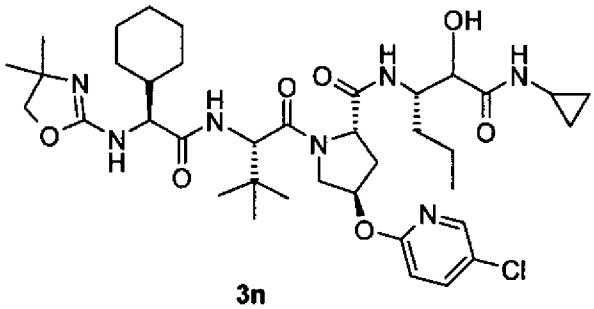
A solution of the acid **3g** (47 mg, 0.11 mmol) in anhydrous dichloromethane (0.5 mL) and anhydrous DMF (0.5 mL) is stirred at 0 °C and treated with HATU (1.4 eq, 57 mg, 0.15 mmol). To the solution **3f** (1.2 eq, 62 mg, 0.12 mmol) is added in small portions. Then, N-methylmorpholine (4.0 eq, 0.047 mL, 0.43 mmol) is added dropwise. The reaction mixture is gradually warmed to room temperature and stirred for overnight. All the volatiles are removed under vacuum and the residue is dissolved in ethylacetate. The organic layer is

washed with water, aq. 1.0 N HCl solution, aq. sat. sodium bicarbonate solution, and brine. The organic layer is dried over Na_2SO_4, filtered and concentrated in vacuo. The residue is chromatographed on silica gel (eluent: acetone/hexane; 1:1) to afford the desired product **3m**. Found m/z ES+ = 945.

Step 3-H:



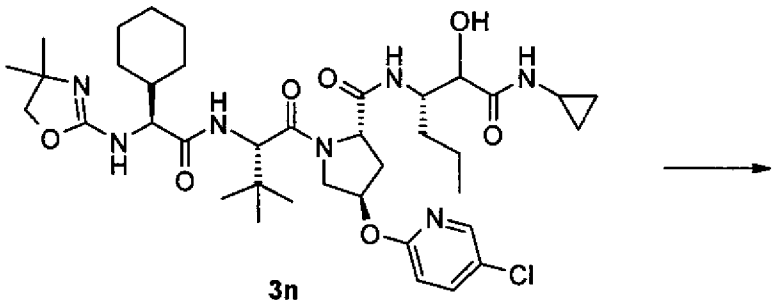
3m



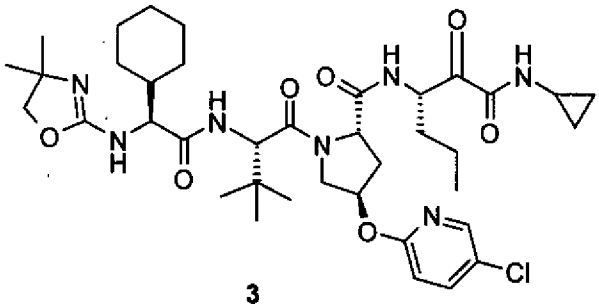
3n

To a solution of **3m** (50 mg, 0.05 mmol) in DMF (0.5 mL) is added mercaptoacetic acid (19 mg, 0.21 mmol) and monohydrate lithium hydroxide (18 mg, 0.42 mmol) at room temperature. The reaction mixture is stirred for 3 hours after which sat. aq. sodium bicarbonate solution is added. The phases are separated and the aqueous layer is extracted with ethyl acetate. The combined organic layers are washed with brine, dried over sodium sulfate, and concentrated to give the desired product **3n**. Found m/z ES+ = 760.

Step 3-I:



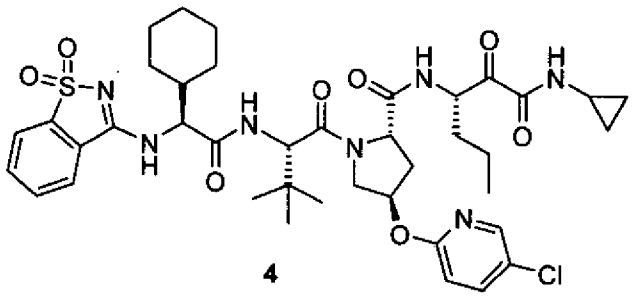
3n



3

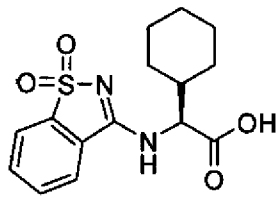
To a solution of **3n** (35 mg, 0.05 mmol) in anhydrous dichloromethane (0.5 mL) is added Dess-Martin periodinane (2.0 eq, 39 mg) and the mixtures are stirred at room temperature for 30 minutes. To the reaction mixtures is added aq. 1.0 M sodium thiosulfate solution (1 mL) and stirred for 5 minutes. Aq. sat. sodium bicarbonate solution (2 mL) is added and the stirring is continued for another 10 minutes. The mixtures are extracted with dichloromethane. The combined organic layers are dried over sodium sulfate, and concentrated. The residue is purified using silica gel preparative TLC plate (Eluent: acetone/hexanes, 1:1) to afford the desired product **3**. Found m/z ES+ = 758

Example 4:

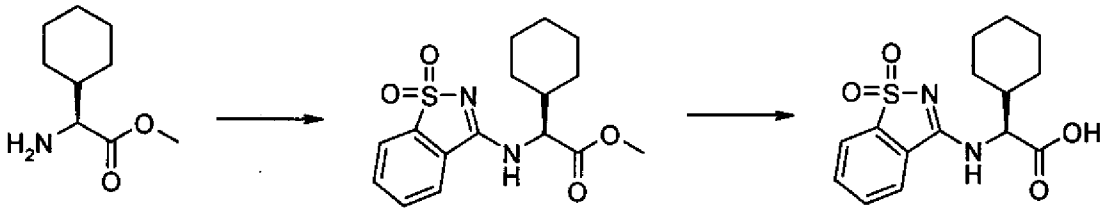


4

Step 4-A:



4a

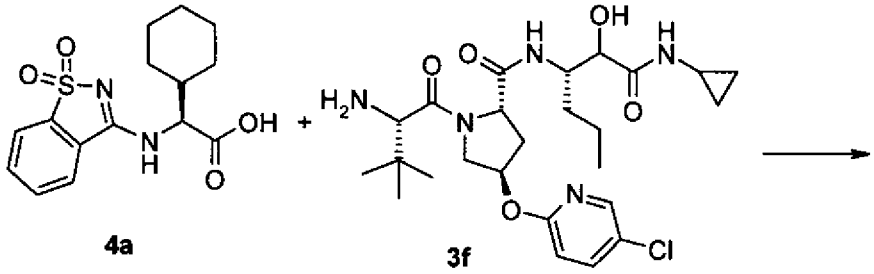


HCl 4b 4a

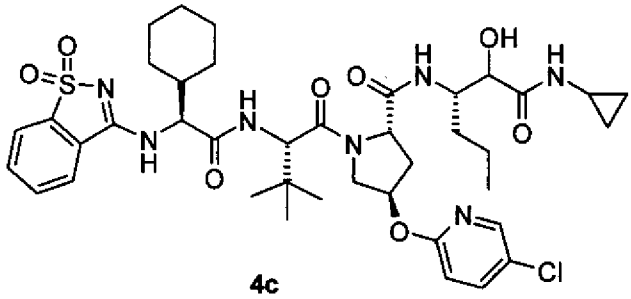
To a solution of H-cyclohexyl-gly-OMe•HCl in water (1.0 mL) and dioxane (1.0 mL) added NaOH (60 mg, 1.5 mmol, 3.0 equiv) and 3-chloro-benzoisothiazole 1,1-dioxide (220 mg, 1.0 mmol, 1.0 equiv). The solution is stirred at room temperature for 1 hour, after which the pH of the solution is adjusted to 5 by addition of 1.0 N HCl aqueous solution.. The two phases are separated and the aqueous phase is extracted with CH_2Cl_2. The organic layers are combined, washed with brine, dried over Na_2SO_4, concentrated. The residue is purified by silica gel column chromatography (hexane/EtOAc, 1/1) to give 150 mg of **4b**. Found m/z in ES+ = 337, m/z in ES- = 335.

To a solution of methyl ester **4b** (100 mg) in THF (0.3 mL) and MeOH (0.3 mL) at 0 °C is added a solution of $LiOH•H_2O$ (25 mg) in water (0.3 mL). The solution is stirred at room temperature for 3 hours. The pH of the solution is then adjusted to 6 by addition of 1.0 N HCl aqueous solution. CH_2Cl_2 is then added and the two phases are separated. The aqueous layer is extracted with CH_2Cl_2. The organic layers are combined, washed with brine, dried over Na_2SO_4 and concentrated to give 75 mg of **4a**. Found m/z in ES+ = 323, m/z in ES- = 321.

Step 4-B:



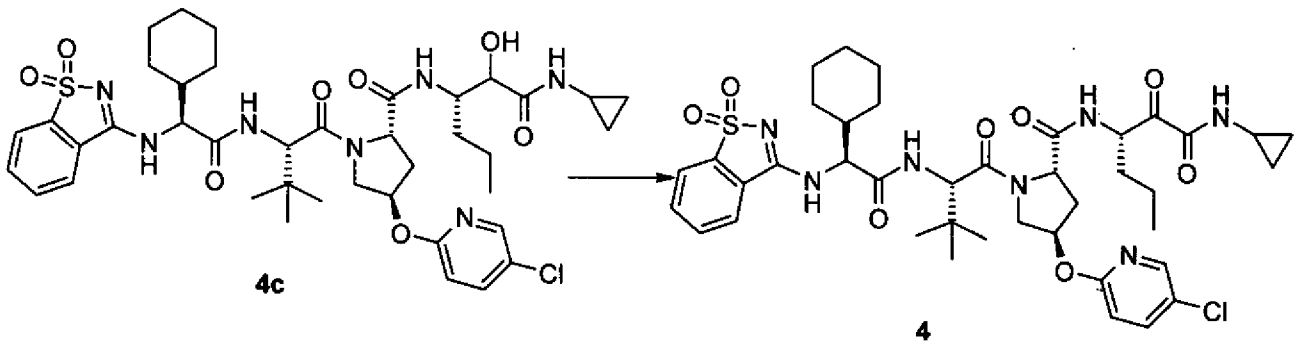
4a 3f



4c

A solution of **4a** (74 mg, 0.23 mmol) in anhydrous dichloromethane (1.0 mL) and anhydrous DMF (1.0 mL) is stirred at 0 °C and treated with HATU (1.4 eq, 105 mg, 0.27 mmol). To this solution is added **3f** (1 eq, 120 mg, 0.23 mmol) is added in small portions. Then, N-methylmorpholine (4.0 eq, 0.101 mL, 0.92 mmol) is added dropwise. The reaction mixture is gradually warmed to room temperature and stirred for overnight. All the volatiles are removed under vacuum and the residue is dissolved in ethylacetate. The organic layer is washed with water, aq. 1.0 N HCl solution, aqueous saturated sodium bicarbonate solution, and brine. The organic layer is dried over Na_2SO_4 and concentrated in vacuo. The residue is chromatographed on silica gel (eluent: acetone/hexane; 1:1) to afford the desired product **4c**. Found m/z ES+ = 828.

Step 4-C:

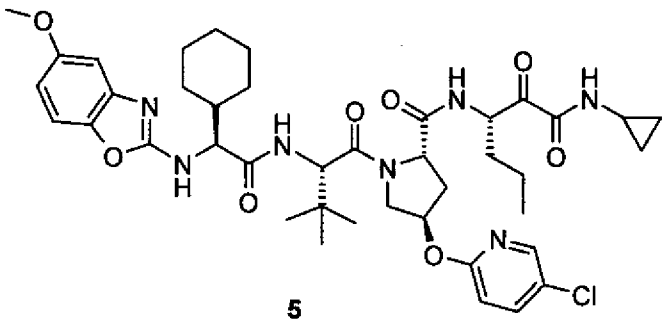


4c 4

A solution of **4c** (41 mg, 0.05 mmol) in anhydrous dichloromethane (3 mL) is treated with Dess-Martin periodinane (3.0 eq, 63 mg) and the reaction mixtures are stirred at room

temperature for 30 minutes. To the mixture is added aqueous 1.0 M sodium thiosulfate solution (2 mL) and stirred for 5 minutes. Aqueous saturated sodium bicarbonate solution (2 mL) is added and stirring is continued for another 10 minutes. The mixture is extracted with dichloromethane. The combined organic layers are dried over sodium sulfate, filtered and concentrated. The residue is purified by silica gel column chromatography (acetone/hexanes, 1:1) to afford the desired product **4**. Found m/z ES+ = 826 and m/z ES- = 824.

Example 5:



5

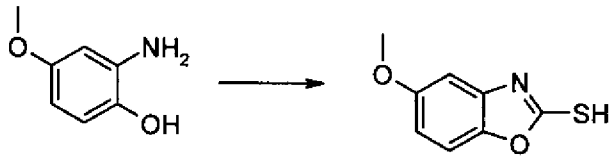
Step 5-A:



5a **5b**

To a solution of **5a** (5.0 g, 29.56 mmol) in ethanol (60 mL) is added Pd/C (20 %, 1.0 g). The reaction mixture is then stirred under 1.0 atm. of H_2 balloon for 12h. The reaction mixture is then filtered through celite 545 and the filtrate is concentrated to give 3.6 g of **5b**.

Step 5-B:



5b **5c**

Mixtures of **5b** (1.2 g, 8.62 mmol), potassium hydroxide (581 mg, 10.34 mmol) and carbon disulfide (10 mL, 173 mmol) in ethanol (17 mL) are heated to refluxed overnight. The solvent is then evaporated. To the residue aqueous 1.0 N HCl solution (10 mL) and ethylacetate (100 mL) are added. The phases are separated. The organic layer is washed with water, brine, dried over sodium sulfate and concentrated to give 1.2 g of **5c**.

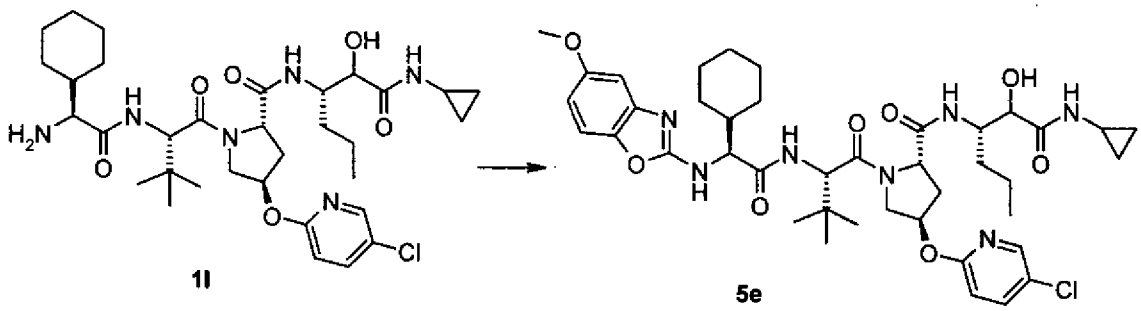
Step 5-C:



5c **5d**

To **5c** (1.0 g, 5.5 mmol) and thionyl chloride (6 mL, 66 mmol)is added two drops of DMF and the resulted mixtures are heated at 70 °C for 30 minutes. The solution is then cooled to room temperature and diluted with dichloromethane. The solvent is then evaporated. To the residue is added another 10 mL of dichloromethane and the solution is concentrated. The residue is dissolved in hot hexanes and then filtered. The filtrate is concentrated to give 1.0 g of **5d**.

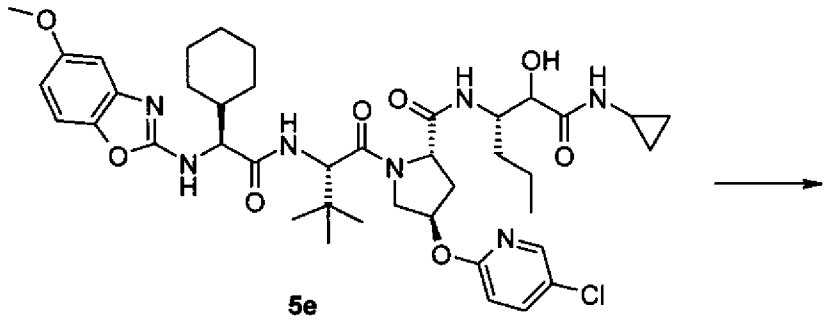
Step 5-D:



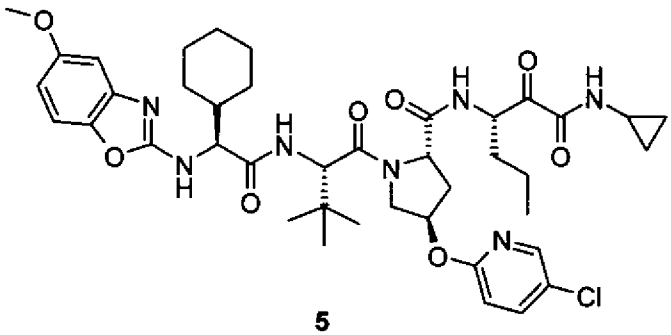
1l **5e**

To a solution of **1l** (75 mg, 0.11 mmol) in dioxane (0.4 mL) at room temperature is added **5d** (31 mg, 0.17 mmol) and sodium bicarbonate (19 mg, 0.23 mmol). The mixtures are stirred at 65 °C for 12 hours. The mixtures are loaded directly to silica gel column and eluted with hexane/EtOH (from 95/5 to 85/15) to give **5e**. Found m/z ES+ = 810 and ES- = 808.

Step 5-E:



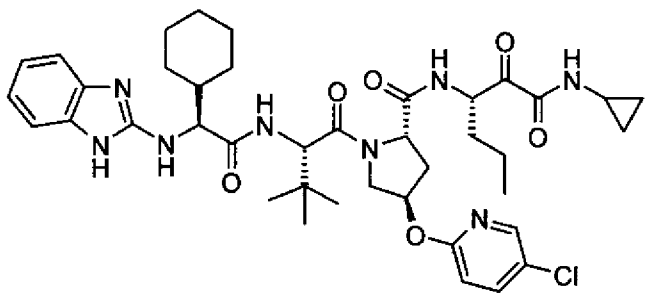
5e



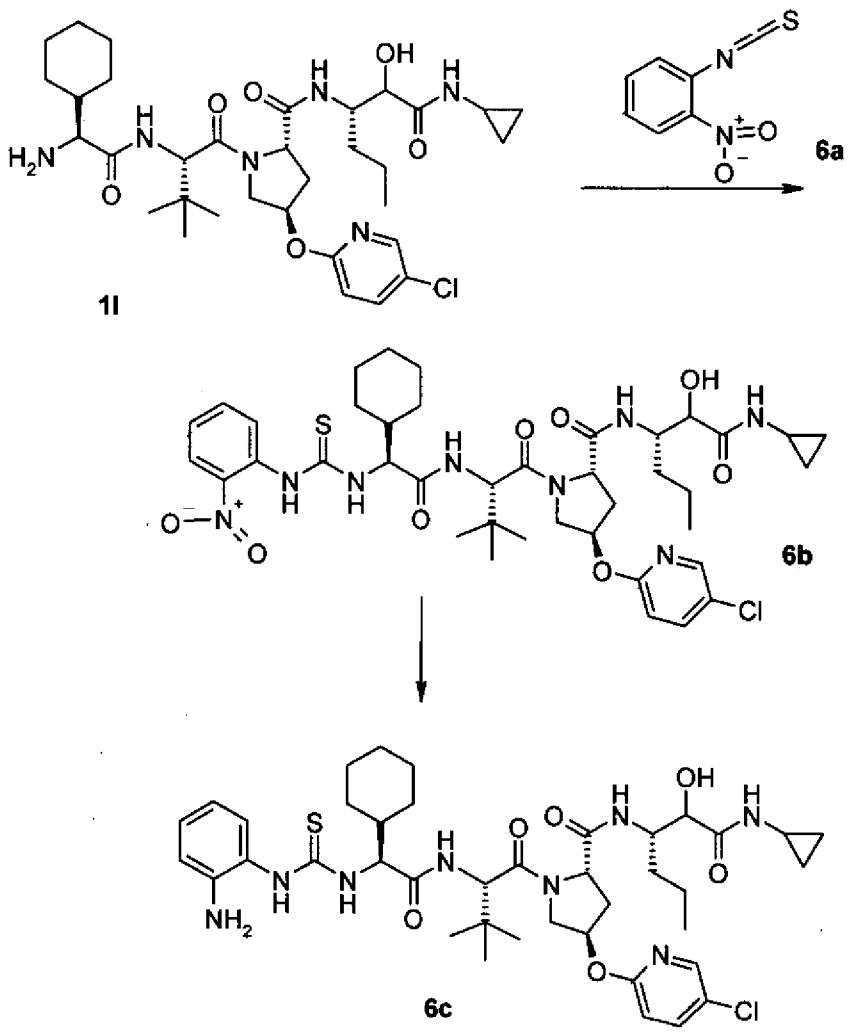
5

A solution of **5e** (62 mg, 0.08 mmol) in anhydrous dichloromethane (0.80 mL) is added Dess-Martin periodinane (2.0 eq, 65 mg). The reaction mixture is stirred at room temperature for 30 minutes. To the mixture is added aqueous 1.0 M sodium thiosulfate solution (2 mL) and stirred for 5 minutes. Aqueous saturated sodium bicarbonate solution (2 mL) is added and stirring is continued for another 10 minutes. The mixture is extracted with dichloromethane. The combined organic layers are dried over sodium sulfate, filtered and concentrated. The residue is purified using silica gel preparative TLC (gradient: acetone/hexanes, 3:7 to 1:1) to afford the desired product **5**. Found m/z ES+ = 808 and ES- = 806.

Example 6:

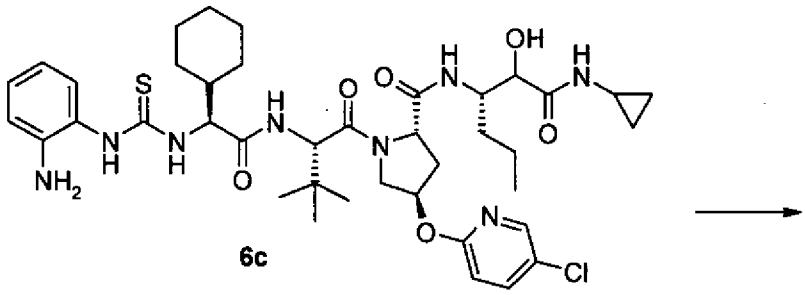


6

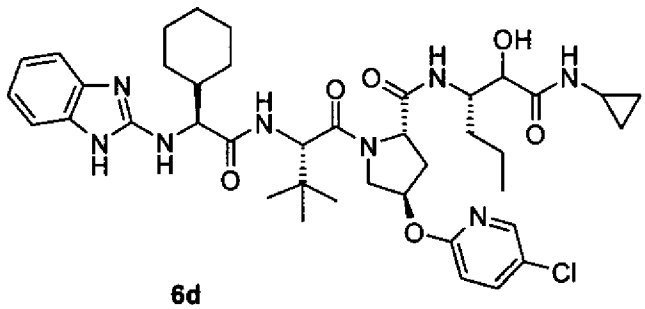


A solution of **1l** (100 mg, 0.15 mmol, 1.0 equiv) and **6a** (27 mg, 0.15 mmol, 1.0 equiv) in EtOH (0.5 mL) is stirred at room temperature for 1 hour. Found m/z for **6b** ES+ = 843, m/z in ES- = 841.

To the above solution added $SnCl_2$ (142 mg, 0.75 mmol) and the mixtures are heated at 70 °C for 30 minutes. The solution is then cooled at 0 °C. Ice is added followed by saturated aqueous $NaHCO_3$ and EtOAc. The phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, washed with brine, dried over Na_2SO_4, concentrated to give crude product **6c**, which is continued to the next step without further purification. Found m/z in ES+ = 813, m/z in ES- = 811.

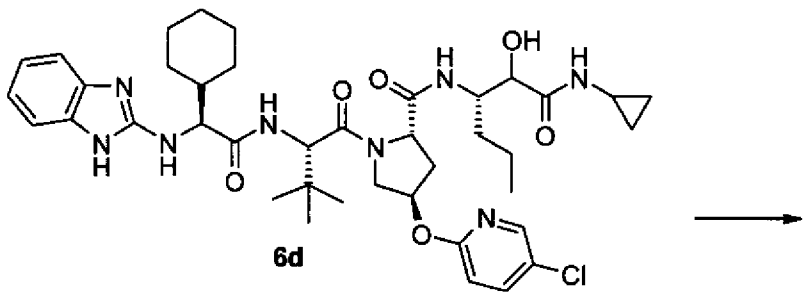


6c

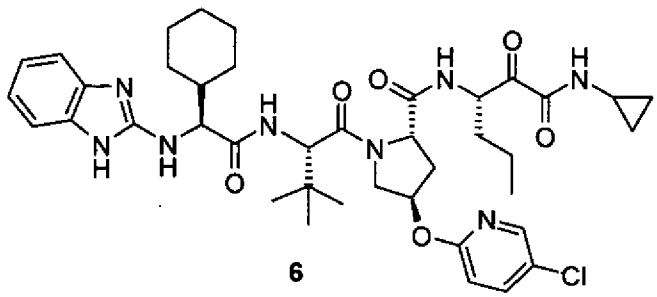


6d

To a solution of **6c** (120 mg, 0.15 mmol) in toluene (0.6 mL) added HgO (64.8 mg, 0.3 mmol, 2.0 equiv) and sulfur (4.8 mg, 0.15 mmol, 1.0 equiv) and the mixtures are stirred at 90 °C for 1 hour. The mixtures are filtered, washed with CH_2Cl_2 and the solution is concentrated. The residue is purified by silica gel column chromatography (hexane/EtOH = 4/1) to give desired product **6d** (54 mg). Found m/z in ES+ = 779.



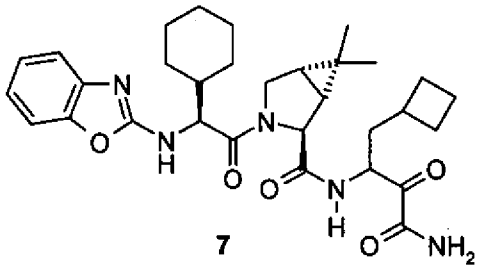
6d



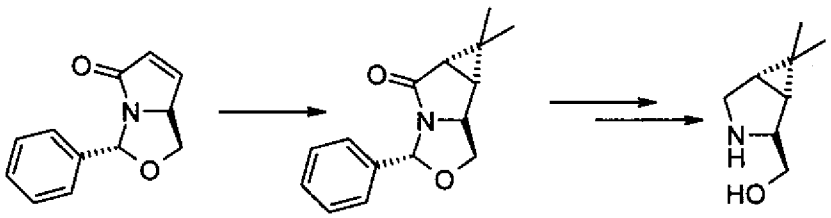
6

To a solution of alcohol **6d** (54 mg, 0.069 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C is added DMP (58.7 mg, 0.138 mmol, 2.0 equiv). The solution is stirred at room temperature for 4 hours. The solution is then added saturated aqueous $NaHCO_3$ and 1.0 M $Na_2S_2O_3$ aqueous solution. The phases are separated and the aqueous layer is extracted with CH_2Cl_2. The organic layers combined, washed with brine, dried over Na_2SO_4 and concentrated. The residue is purified by silica gel column chromatography (hexane/acetone 1/1) to give product **6**. Found m/z in ES+ = 777.

Example 7:

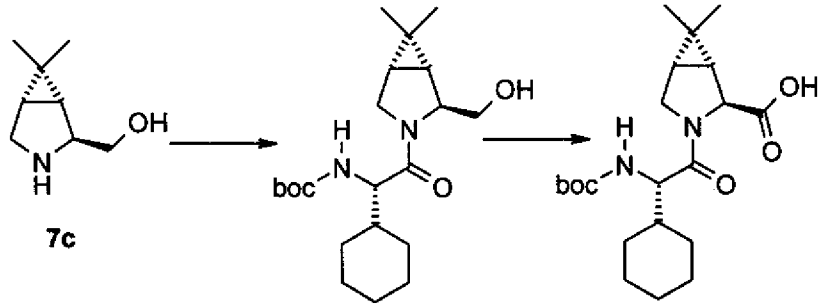


7



7a **7b** **7c**

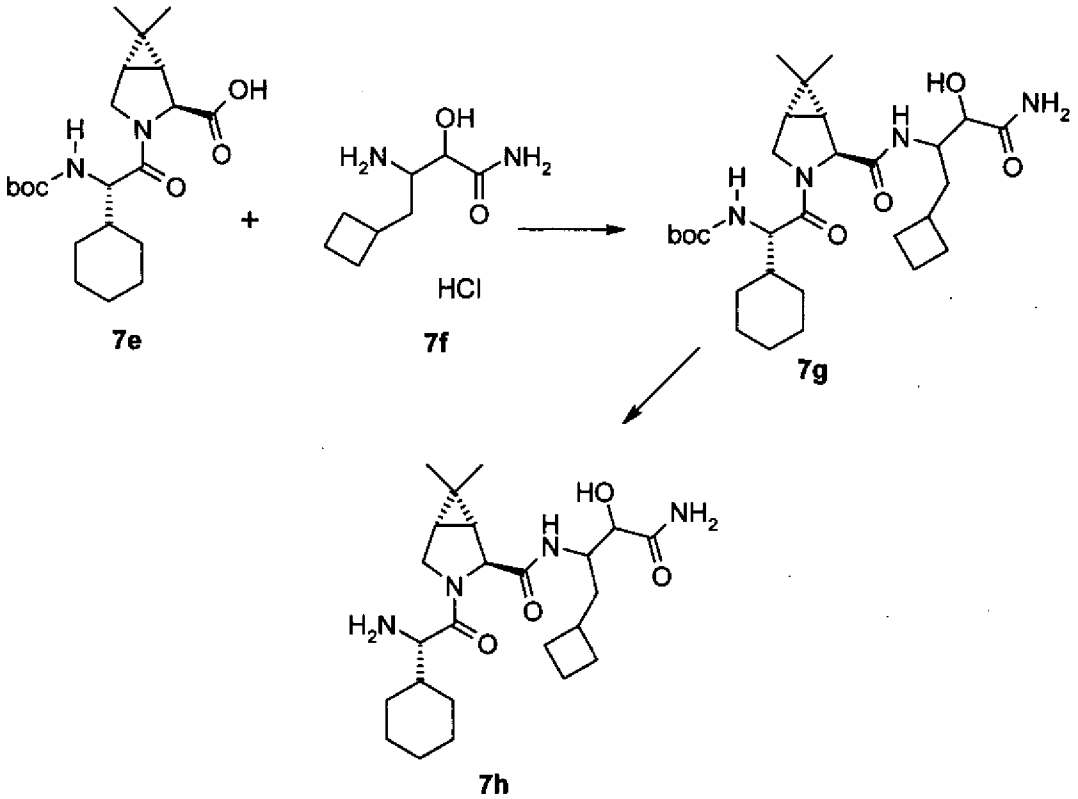
To a solution of isopropyldiphenylsulfonium tetrafluroborate (ref. Matsuyama, H. *et al. J. Org. Chem.* **2000**, *65*, 4796.) (13.4 g, 42.5 mmol, 1.7 equiv) in THF at -78 °C is added *t*-BuLi (22.0 mL, 37.5 mmol, 1.70 M in pentane, 1.5 equiv) and the solution is stirred at this temperature for 30 minutes. To the solution is then added a solution of **7a** (5.0 g, 25 mmol, 1.0 equiv) in THF (20 mL). The solution is stirred at -78 °C for 1 hour. The reaction is quenched by addition of saturated aqueous $NaHCO_3$. The solution is warmed to room temperature and diluted with EtOAc. The two phases are separated and the organic layer is washed with brine, dried over Na_2SO_4 and concentrated. The residue is purified by silica gel column chromatography (hexane/EtOAc, 9/1 to 3/1) to give 5.1 g of **7b**. **7b** is converted to the amino alcohol **7c** according to the reference: *J. Org. Chem.* **1999**, *64*, 330.



7c **7d** **7e**

To a solution of Boc-L-cyclohexyl-gly-OH (2.57 g, 10 mmol, 1.0 equiv) in CH_3CN (60.0 mL) at 0 °C is added HATU (3.878 g, 10.2 mmol, 1.02 equiv), HOAT (1.38g, 10.2 mmol, 1.02 equiv) followed by **7c** (1.39 g, 10 mmol, 1.0 equiv) and DIPEA (6.95 mL, 40 mmol, 4.0 equiv). The solution is stirred at room temperature for 12 hours, after which the solvent is evaporated. The residue is partitioned between EtOAc and water. The phases are separated and the organic layer is washed with saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated. The residue is purified by silica gel column chromatography (hexane/EtOAc, 1/1) to give product **7d** (3.43 g).

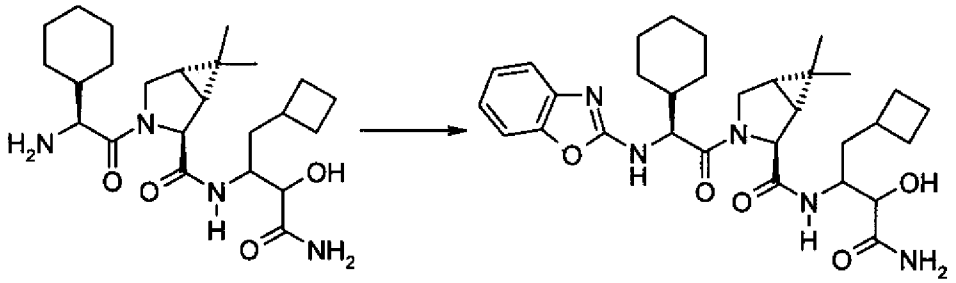
To a solution of **7d** (2.4 g, 6.5 mmol) in acetone (40.0 mL) at -5 °C is added a solution of Jones's reagent (3.0 M, 10.7 mL). The mixture is warmed to 0 °C and stirred at this temperature for 2 hours. The reaction is then quenched by slow addition of *i*-PrOH (10 mL) and the mixture is then filtered. The phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, washed with brine, dried (Na_2SO_4) and concentrated to give desired product **7e** 2.35 g. The material is continued to the next step with no further purification. Found m/z in ES+ = 395, m/z in ES- = 393.



7e 7f 7g 7h

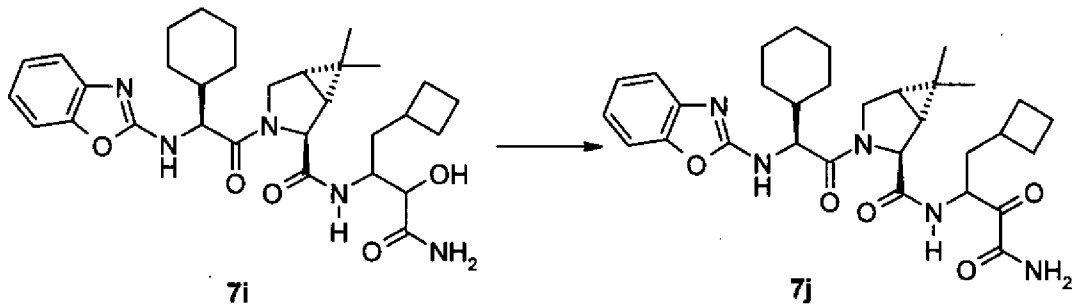
To a solution of **7e** (1.0 g, 2.5 mmol) in DMF (5.0 mL) and CH_2Cl_2 (5.0 mL) at 0 °C is added HATU (1.05 g, 2.75 mmol, 1.1 equiv), **7f** (0.53 g, 2.5 mmol, 1.0 equiv) and N-methyl-morpholine (0.825 mL, 7.5 mmol, 3.0 equiv). The solution is stirred at 0 °C for 30 minutes then at room temperature for 6 hours. To the reaction mixture is added saturated aqueous $NaHCO_3$ solution and EtOAc. The two phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, washed with brine, dried over Na_2SO_4 and concentrated. The crude material is purified by silica gel column chromatography (hexane/EtOH, 9/1) to give product **7g** (950 mg). Found m/z in ES+ = 549.

To a solution of **7g** (110 mg) in CH_2Cl_2 (2.0 mL) added TFA (2.0 mL) and the solution is stirred at room temperature for 1 hour. The solvent is then evaporated. The residue is added saturated aqueous $NaHCO_3$ solution and EtOAc. The two phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, dried over Na_2SO_4 and concentrated to give desired product **7h** (67 mg). Found m/z in ES+ = 449.



7h 7i

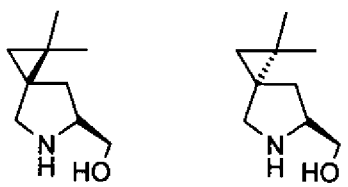
To a solution of **7h** (150 mg, 0.33 mmol)in dioxane (1.0 mL) at room temperature added 2-chlorobenzaxazole (76 mg, 0.50 mmol, 1.5 equiv) and $NaHCO_3$ (84 mg, 1.0 mmol, 3.0 equiv). The mixture is stirred at 60 °C for 6 hours. The mixture are then loaded directly to silica gel column and eluted with hexane/acetone (2/1) to give desired product **7i** (145 mg). Found m/z in ES+ = 566, m/z in ES- = 564.



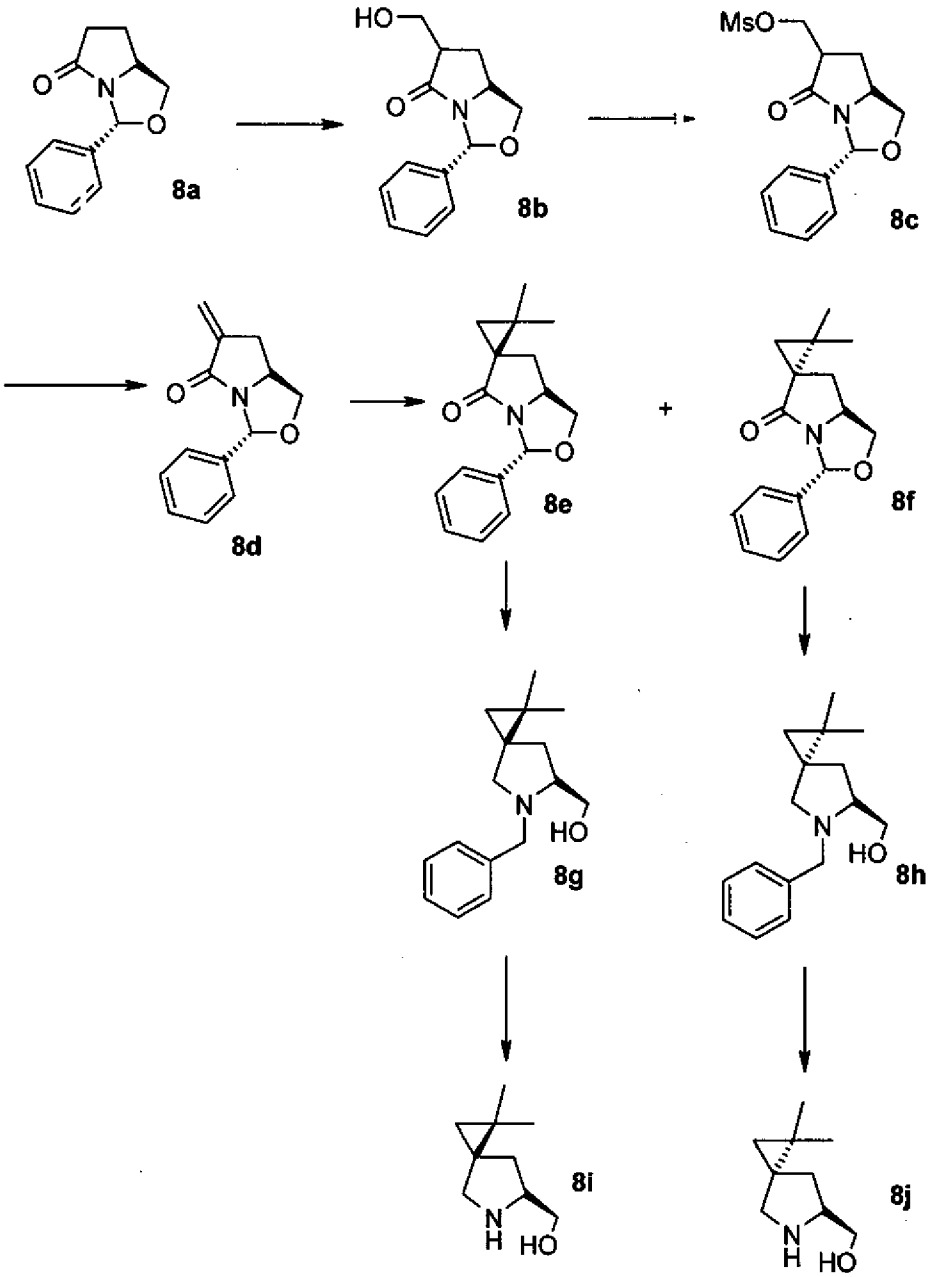
7i 7j

To a solution of **7i** (120 mg, 0.21 mmol) in CH_2Cl_2 (2.0 mL) at 0 °C is added DIPEA (0.148 mL, 0.848 mmol, 4.0 equiv) followed by a solution of $Py{\bullet}SO_3$ (67.6 mg, 0.424 mmol, 2.0 equiv) in DMSO (2.0 mL). The solution is then stirred at 0 °C for 10 minutes. To the solution is added EtOAc and saturated aqueous $NaHCO_3$ solution. The two phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, washed with brine, dried over Na_2SO_4 and concentrated. The residue is purified by silica gel column chromatography (hexane/Acetone, 1/1) to give product **7j** (108 mg). Found m/z in ES+ = 564, m/z in ES- = 562.

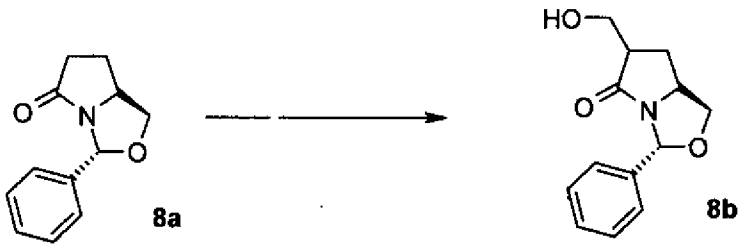
Example 8:



8i 8j



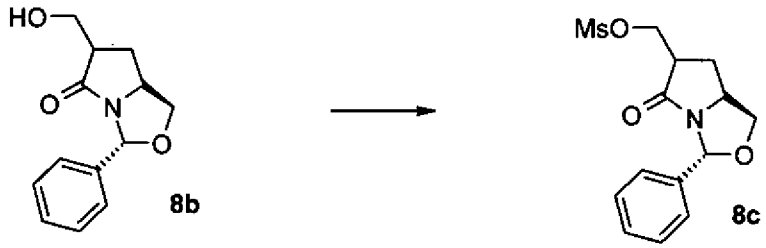
Step 8-A:



To a solution of DIPA (12.4 mL, 88.6 mmol, 1.2 equiv) in THF (400 mL) at -30 °C is added *n*-BuLi (50 mL, 1.60 M in hexane, 81.0 mmol, 1.10 equiv). The solution is stirred at this temperature for 30 minutes. A solution of **8a** (**8a** is prepared according to *J. Org. Chem.*

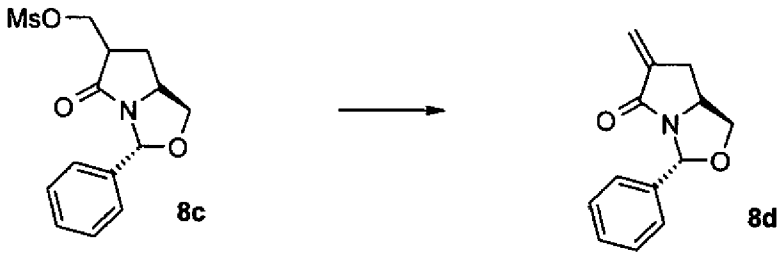
1986, *51*, 3140.) (15.0 g, 73.8 mmol, 1.0 equiv) is subsequently added to the solution, which is then stirred at -30 °C for 30 minutes. A stream of HCHO (22.0g, 738 mmol, 10 equiv) and N_2 gas is bubbled through this solution over 10 minutes. The reaction mixture is warmed up to 0 °C over 30 minutes and quenched by addition of 2.0 N HCl aqueous solution until pH=3. EtOAc is added and the phases are separated. The aqueous layer is extracted with EtOAc three times. The combined organic layer is washed with brine, dried over Na_2SO_4 and concentrated to give **8b**, which is used in the next step without purification.

Step 8-B:



To a solution of **8b** in CH_2Cl_2 (200 mL) at 0 °C is added TEA (30.9 mL, 222 mmol, 3.0 equiv), DMAP (902 mg, 7.4 mmol, 0.1 equiv) and MsCl (11.5 mL, 148 mmol, 2.0 equiv). The reaction temperature is maintained <5 °C. The solution is stirred at room temperature for 2 hours. Then saturated aqueous NH_4Cl solution is added followed by 1/1 mixture of EtOAc/TBME. The phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, washed with brine, dried with Na_2SO_4 and concentrated to afford **8c**, which is continued to the next step with no purification.

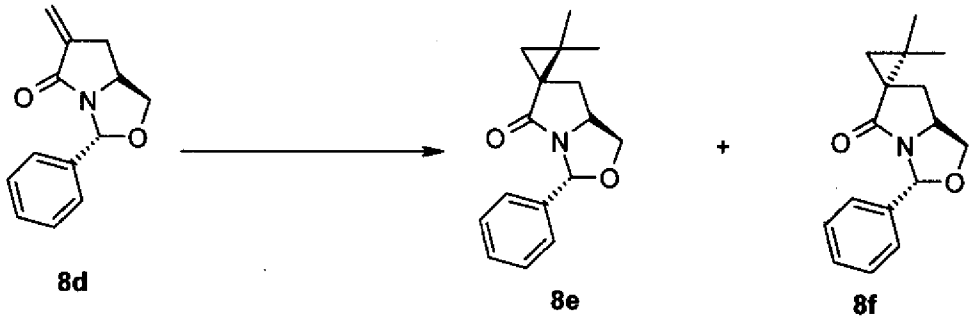
Step 8-C:



The residue **8c** from previous step is dissolved in CH_2Cl_2/toluene (20 mL/20 mL). At 0 °C, 15 mL of DBU is added. The internal temperature is kept below 20 °C. The solution is stirred at room temperature for 2 hours. The mixture is loaded directly to silica gel column and flushed with hexane/EtOAc (2/1 to 1/1) to give product **5** (7.4 g). The product **8d** is carried onto the next step immediately.

Found m/z in ES+ = 216; LC-MS (method A) t_R = 0.86 min

Step 8-D:



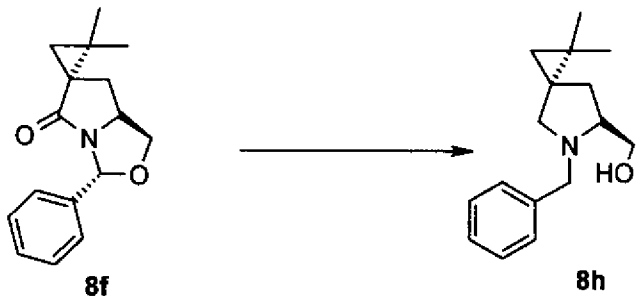
dr **8e/8f** = 1/2

To a solution of isopropyl triphenyl phosphine iodide (10.4 g, 24.1 mmol, 1.4 equiv) in THF (70 mL) at -30 °C is added *n*-BuLi (1.60 M, 13.9 mL, 22.4 mmol). The solution is stirred at 0 °C for 30 minutes, then cooled at -30 °C. A solution of **8d** (3.7 g, 17.2 mmol, 1.0 equiv) is added to above solution. The resulted reaction mixture are warmed up to room temperature over 1 hour and stirred at room temperature for 3 hour. The reaction is quenched by addition of saturated aqueous $NaHCO_3$ solution. After diluted with EtOAc, the mixture is filtered. The two phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, washed with brine, dried over Na_2SO_4 and concentrated. The residue is purified by silica gel column chromatography (hexane/EtOAc 3/1 to 2/1) to give product **8e** (1.1 g), and **8f** (2.3 g).

TLC, Rf (EtOAc/heptane 1:2) = 0.53 (**8e**) and 0.46 (**8f**)

Step 8-E:

Procedure for the synthesis of **8j**.

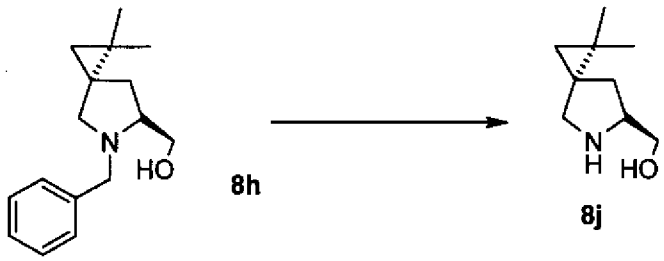


To a solution of **8f** (5.0 g, 19.5 mmol) in THF (75 mL) at 0 °C is added $LiAlH_4$ (2.2 g, 58.4 mmol, 3. equiv). The solution is heated to reflux for 5 hours. After cooled to 0 °C, the

reaction solution is slowly added 5.0 mL of saturated aqueous Na_2SO_4 solution. The mixtures are diluted with EtOAc and stirred at room temperature for 30 minutes. The mixture is filtered and the solution is concentrated to give product **8h** (~5.0 g).

HPLC (method B) t_R = 2.64 min
TLC, Rf (CH_2Cl_2/MeOH 9:1) = 0.48
MS (method C): 246 [M+H]

Step 8-F:

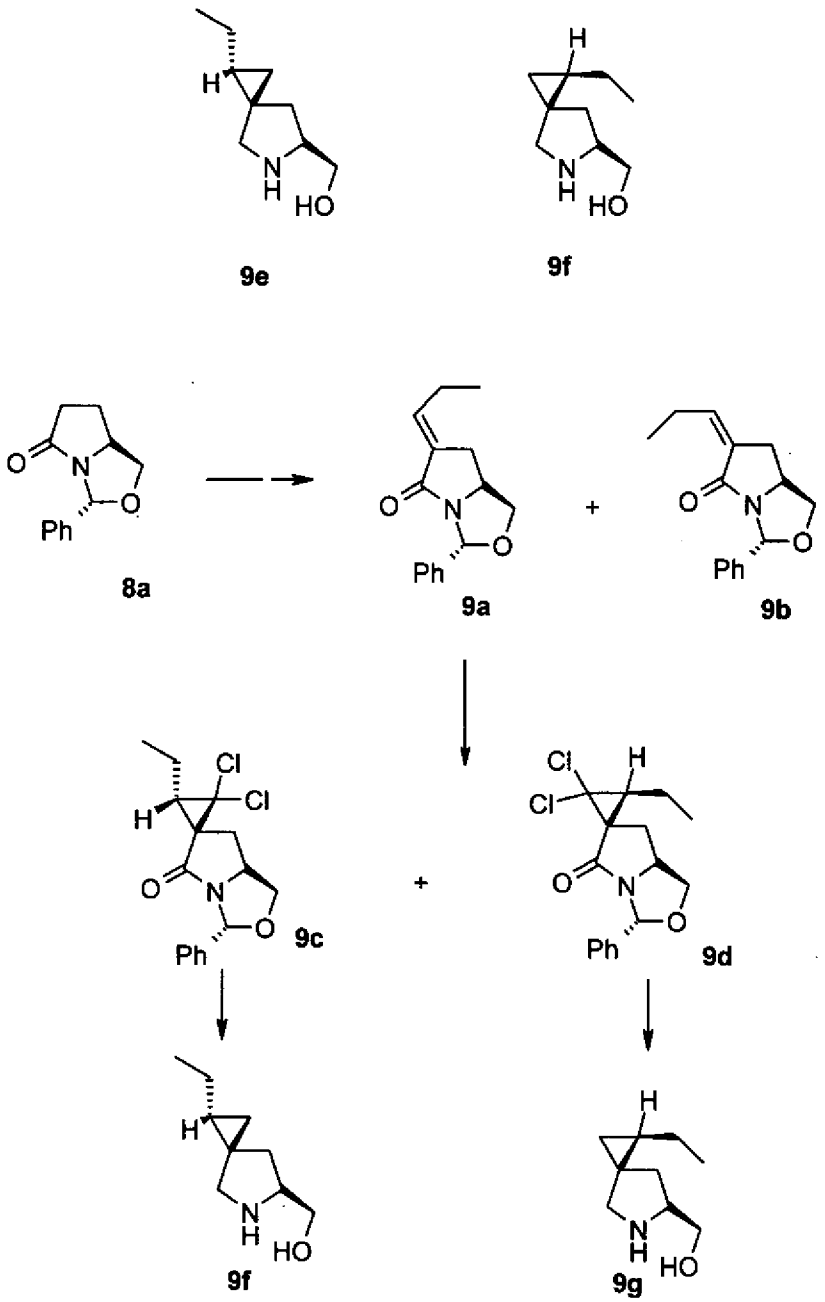


To a solution of **8h** (3.0 g) in EtOAc/HOAc (40 mL/40 mL) at room temperature added Pd (10% on carbon) 2.0 g. The mixture is placed under 40 psi H_2 parr shaker for 3 hours. The mixture is diluted with CH_2Cl_2 and filtered. The solution is concentrated. Most of the HOAc is removed under vacuum at 30 Torr, 40 °C. The solution is basified to pH = 13 with 6.0 M aqueous NaOH solution. After diluted with CH_2Cl_2, the solution is filtered. The two phases are separated and the aqueous layer is extracted with CH_2Cl_2. The organic layers are combined, washed with brine, dried over Na_2SO_4, K_2CO_3, concentrated to give product **8j** (1.8 g).

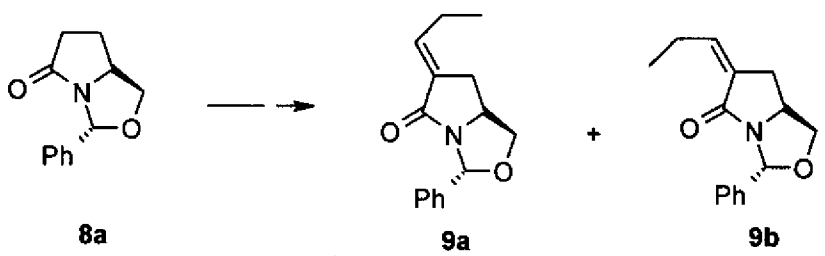
TLC, R_f (CH_2Cl_2/MeOH 4:1) = 0.29
MS (method C): 156 [M+H]

Compound **8i** is prepared from **8g** by analogous procedure used to convert **8h** to **8j**.

Example 9:



Step 9-A:



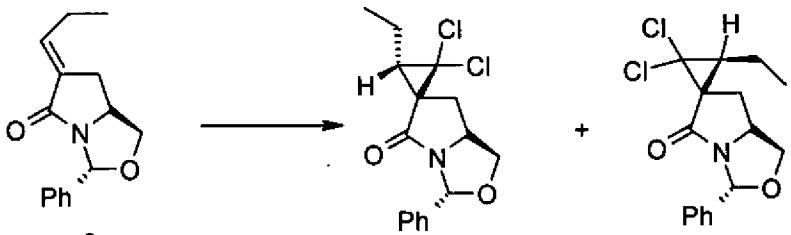
To a solution of DIPA (6.6 mL, 47.3 mmol, 1.2 equiv) in THF (200 mL) at -30 °C is added *n*-BuLi (27 mL, 1.60 M in hexane, 43.3 mmol, 1.10 equiv). The solution is stirred at this temperature for 30 minutes. Then a solution of **8a** (15.0 g, 73.8 mmol, 1.0 equiv), which

is prepared according to *J. Org. Chem.* **1986**, *51*, 3140, is added to the reaction and the solution is stirred at -78 °C for 30 minutes. To this solution is added propanal (3.4 mL, 47.3 mmol, 1.2 equiv). After 1.5 hours, the reaction is quenched by addition of 4.0 N HCl aqueous solution until pH=3. EtOAc is added and the phases are separated. The aqueous layer is extracted with EtOAc three times. The combined organic layer is washed with brine, dried over Na_2SO_4 and concentrated. The residue is continued to the next step with no further purification.

The product obtained from the previous step are dissolved in CH_2Cl_2 (40 mL). To this solution at 0 °C is added TEA (10.9 mL, 78.8 mmol, 2.0 equiv), DMAP (950 mg, 7.8 mmol, 0.2 equiv), followed by SLOW addition of MsCl (4.6 mL, 59.1 mmol, 1.5 equiv). The reaction temperature is maintained <5 °C. The solution is stirred at room temperature for 2 hours. Then saturated aqueous NH_4Cl solution is added followed by 1/1 mixture of EtOAc/diethyl ether. The phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, washed with brine, dried with Na_2SO_4 and concentrated.

The residue from the previous step is dissolved in CH_2Cl_2 (30.0 mL). At 0 °C, 10 mL of DBU is added. The internal temperature is kept below 20 °C. The solution is stirred at room temperature for 2 hours. The mixture is loaded directly to silica gel column and flushed with hexane/EtOAc (2/1 to 1/1) to give products **9a** (3.7 g) and **9b** (4.2 g).

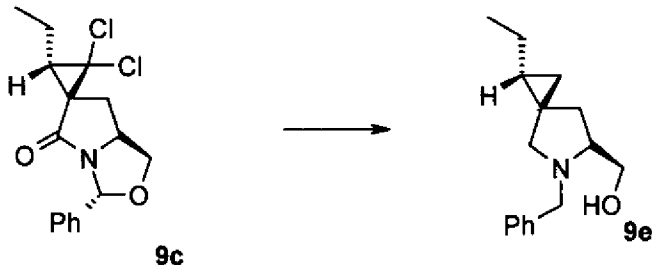
Step 9-B:



9a **9c** **9d**

To a solution of **9a** (1.7 g) in $CHCl_3$ (10 mL) at room temperature is added aq. NaOH solution (12 g, 1/1 mixtures) and benzyltriethylammonium chloride (227 mg). The solution is stirred at room temperature for 12 hours. Then the mixtures are partitioned between EtOAc and water. The aqueous layer is separated and extracted with EtOAc. The organic layers are combined, washed with brine, dried over Na_2SO_4 and concentrated. The residue is purified by flash chromatography (9/1 heptane/EtOAc to 2/2 heptane/EtOAc) to give product **9c** and **9d**.

Step 9-C:

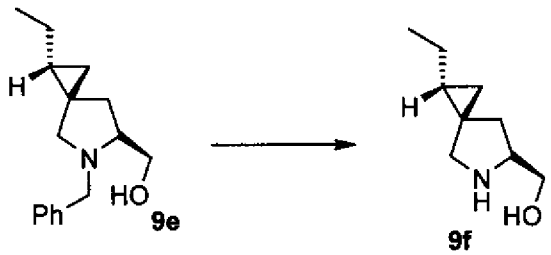


9c **9e**

To a solution of **9c** (1.8 g, 5.5 mmol) in THF (30 mL) at 0 °C is slowly added $LiAlH_4$ (1.05 g, 27.6 mmol, 5.0 equiv). The solution is heated to reflux for 5 hours. After cooled to 0 °C, the reaction solution is slowly added 2.5 mL of saturated aqueous Na_2SO_4 solution. The mixture is diluted with EtOAc and stirred at room temperature for 30 minutes. The mixture is filtered and the solution is concentrated. The residue is used in the subsequent step without further purification.

The isolated material (1.0 g) from previous step is dissolved in 18 mL of THF and 5.0 g of *t*-BuOH. To the solution is added small sodium pieces (1.6 g, 71 mmol, 20 equiv). The mixture is heated to reflux for about 6 hours. The sodium is taken out and quenched with EtOH. The solution is added 5 mL of EtOH and stirred at room temperature until there is no sodium left. The mixture is added ice and diluted with EtOAc. The two phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined and washed with brine, dried over Na_2SO_4 and concentrated. The residue is purified by silica gel chromatography (heptane/EtOAc, 1/1) to give product **9e**.

Step 9-D:



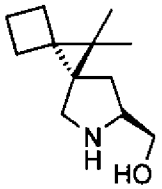
9e **9f**

Palladium on carbon (10%; 300 mg) is added to a solution of **9e** (500 mg) in EtOAc/HOAc (4.0 mL/3.0 mL) at room temperature. The mixture is placed under 40 PSI H_2 ($2.7x10^5$ Pa) in a Parr shaker for 3 hours. The mixture is diluted with CH_2Cl_2 and filtered. The solution is concentrated. Most of the HOAc is removed under vacuum at 30 Torr, 40 °C. The solution is basified to pH = 13 with 6.0 M aqueous NaOH solution. After diluted with

CH_2Cl_2, the solution is filtered. The two phases are separated and the aqueous layer is extracted with CH_2Cl_2. The organic layers are combined, washed with brine, dried over Na_2SO_4, K_2CO_3 and concentrated to give product **9f**.

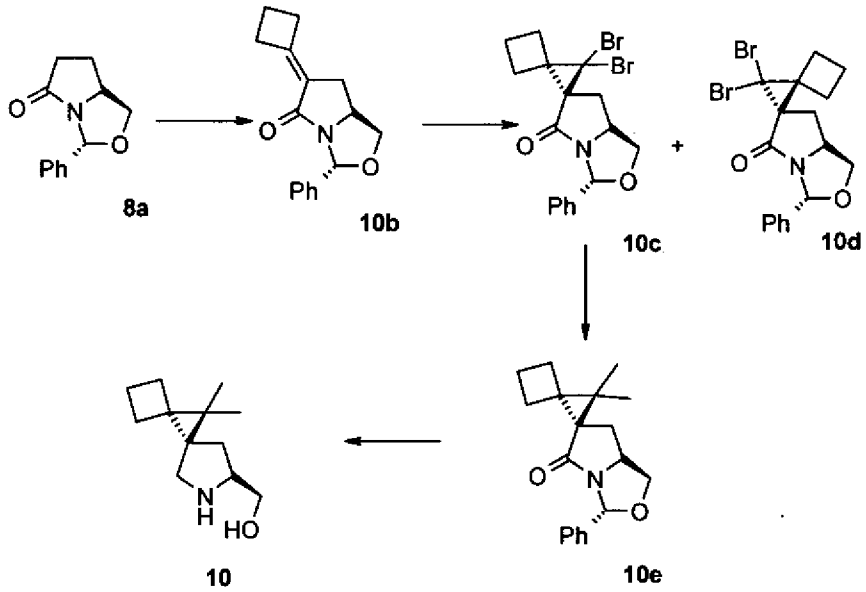
Compound **9g** is prepared from **9b** by analogous procedure used to convert **9a** to **9f**.

Example 10:

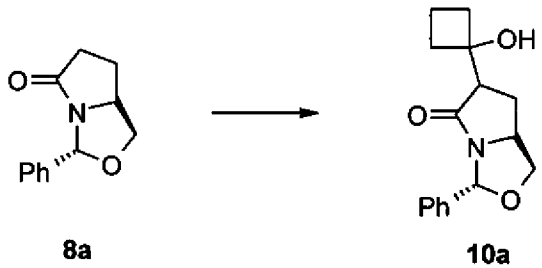


10

Scheme:



Step 10-A:

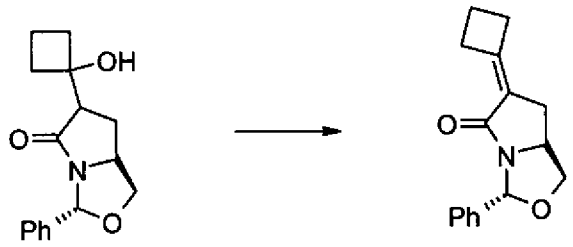


8a **10a**

To a solution of DIPA (7.66 mL, 54.2 mmol, 1.1 equiv) in THF (100 mL) at 0 °C is added *n*-BuLi (33.9 mL, 1.60 M in hexane 54.2 mmol, 1.10 equiv). The solution is stirred at this temperature for 30 minutes. A solution of **8a** (10.0 g, 49.3 mmol, 1.0 equiv) in THF (10.0 mL) is added to the mixture and the solution is stirred at -78 °C for 60 minutes.

Cyclobutanone (3.76 g, 49.3 mmol, 1.0 equiv) and $Et_2O•BF_3$ (6.19 mL, 49.3 mmol) is added to this solution. The reaction mixture is stirred for another 2.5 hours and quenched by addition of saturated NH_4Cl (100 mL). EtOAc is added and the phases are separated. The aqueous layer is extracted with EtOAc. The combined organic layers are washed with brine, dried over Na_2SO_4 and concentrated to afford **10a**, which is used in the subsequent reaction without further purification. Found m/z in ES+ = 274.

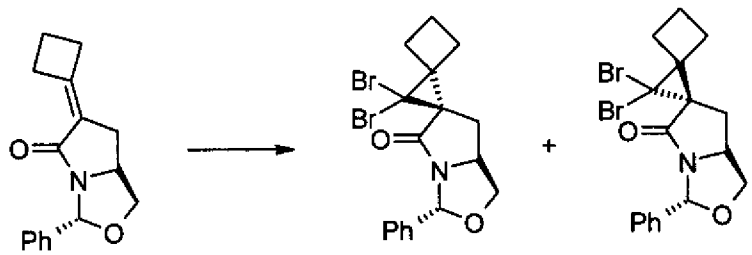
Step 10-B:



10a **10b**

The residue containing compound **10a** from the previous step is dissolved in CH_2Cl_2 (150 mL). Triethyl amine (TEA) (52.1 mL, 374 mmol) and MsCl (2.89 mL, 37.4 mmol) are added to the solution, which is stirred at reflux for 8 hours. The reaction mixture is then added water and the phases are separated. The aqueous layer is extracted with CH_2Cl_2. The organic layers are combined, washed with brine, dried with Na_2SO_4 and concentrated to afford compound **10b**. Found m/z in ES+ = 256.

Step 10-C:

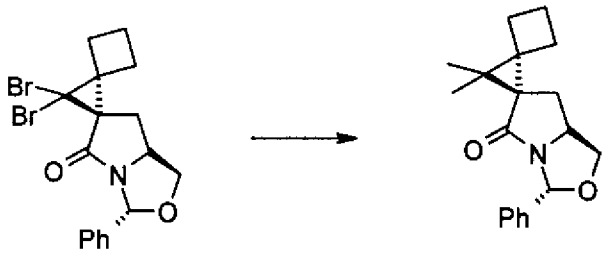


10b **10c** **10d**

To a solution of **10b** (2.54 g, 10 mmol) in $CHBr_3$ (25 mL) is added sequentially benzyl triethyl ammonium chloride (0.46 g, 2 mmol) and 50% NaOH/water (20 mL) at 0°C. The mixture is stirred at room temperature for 2 hours and then at 50°C for 1 hour. The reaction mixture is diluted with water and the aqueous phase is extracted at least twice with CH_2Cl_2. The combined organic phases are washed by brine, dried over Na_2SO_4 and concentrated. The isomers **10c** and **10d** are separated by flash chromatography

(Heptane/EtOAc, 4:1). The upper spot by thin layer chromatography is **10c** (1.43 g). Found m/z in ES+ = 428.

Step 10-D:



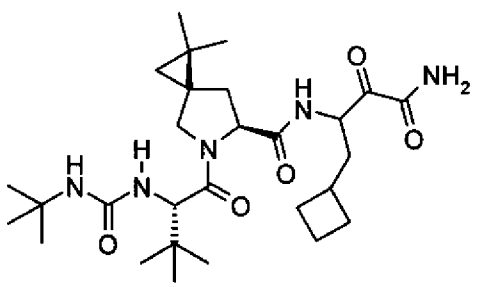
10c **10e**

MeLi (16.5 mL 1.6 M solution, 26.4 mmol) is added dropwise to a suspension of CuI in THF at 0°C to form a clear solution which is maintained at 0°C for 10 minutes. A solution of **10c** (800 mg) in THF (8.0 mL) is added dropwise to the mixture at a temperature of -50°C or less. After complete addition, the reaction mixture is warmed to 0°C over 20 minutes. The solution is then cooled at -78 °C. To this solution is added methyl iodide (10 mL). The reaction mixture is warmed to room temperature over 1 hour. Saturated aqueous NH_4Cl solution (50 mL) is the added to the solution and the solution is stirred for 10 minutes. The precipitate removed by filtration. The filtrate is partitioned between EtOAc and water. The two phases are separated and the aqueous phase is extracted with EtOAc. The combined organic phases are dried over Na_2SO_4, concentrated. The residue is purified by silica gel column chromatography (heptane/EtOAc, 4/1) to give **10e** (380 mg). Found m/z ES+ = 298.

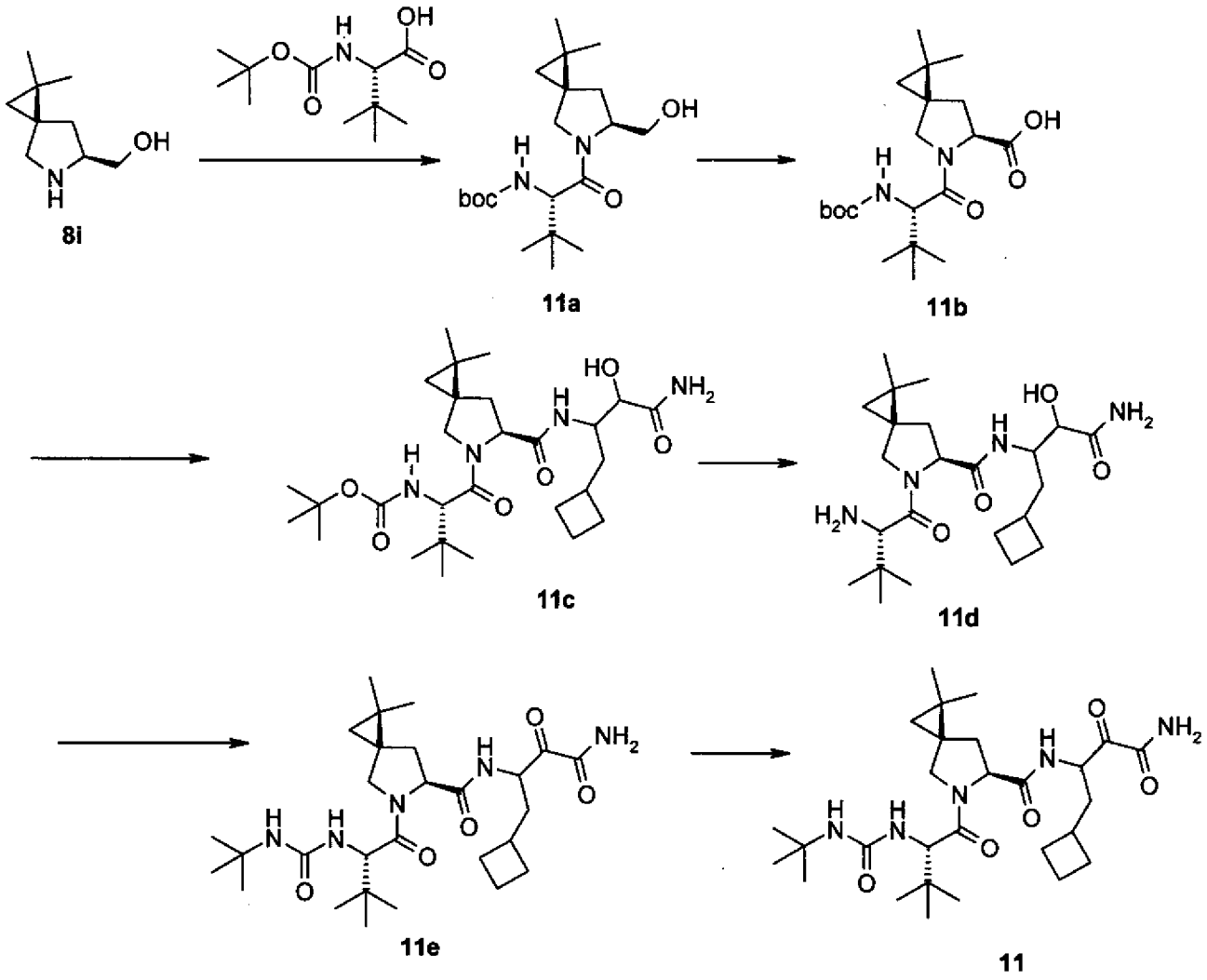
Step 10-E:

Compound **10e** is converted to amino alcohol **10** according to the procedure described for transforming compound **8f** to **8j**.

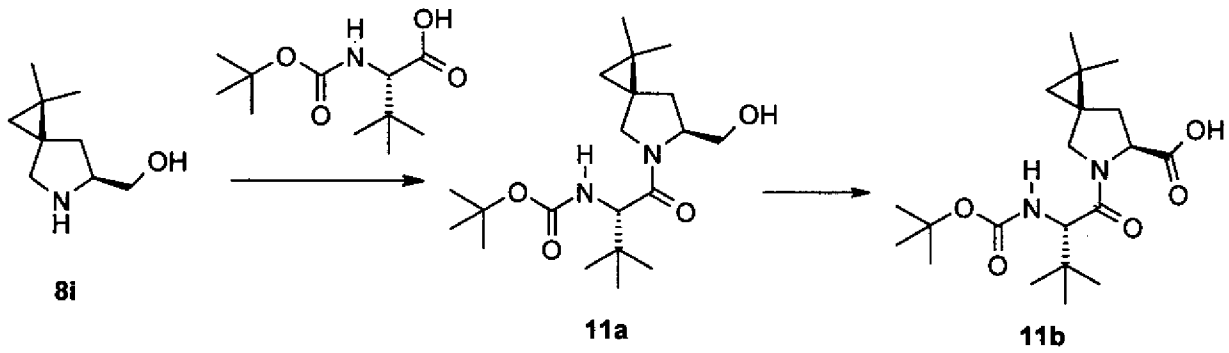
Example 11:



11



Step 11-A:

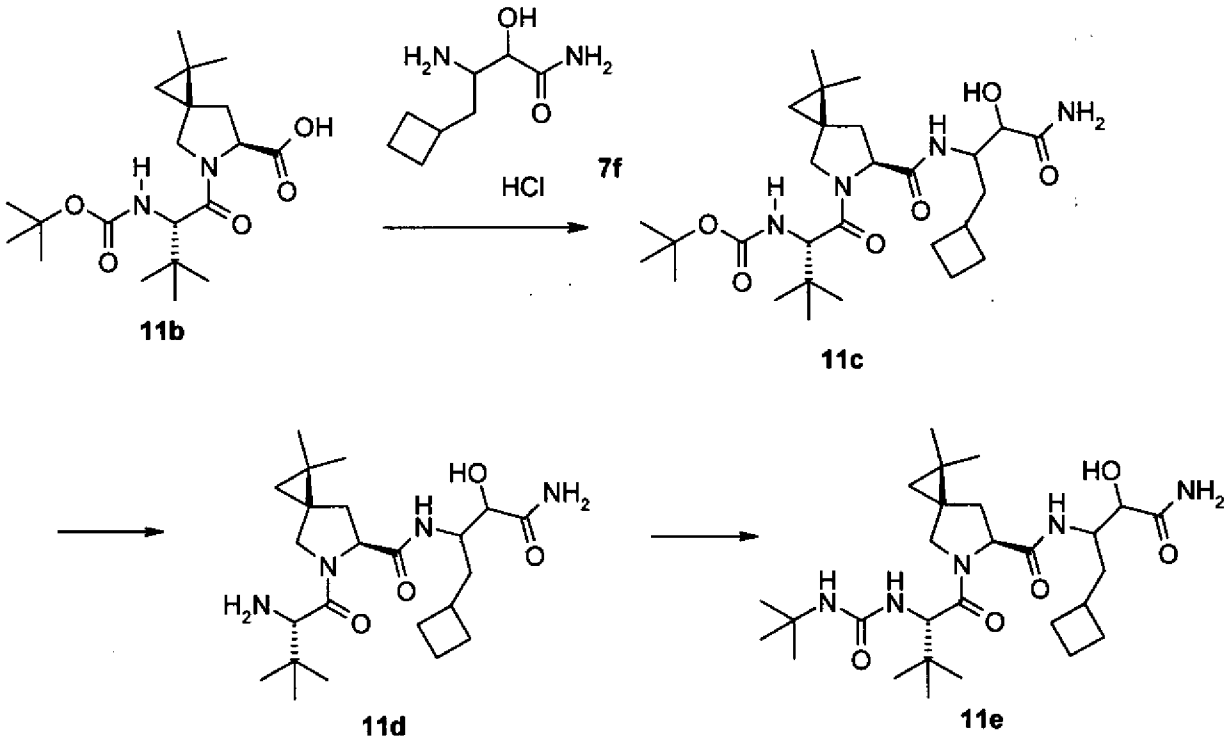


To a solution of Boc-L-t-butyl-gly-OH (907 mg, 3.92 mmol, 1.0 equiv) and amino alcohol **8i** (600 mg, 3.92 mmol, 1.0 equiv) in CH_2Cl_2 (20.0 mL) at 0 °C is added HATU (1.638 g, 4.31 mmol, 1.1 equiv) followed by and DIPEA (2.0 mL, 11.76 mmol, 3.0 equiv). The solution is stirred at -20 °C for 24 hours, 0 °C for 3 hour and room temperature for 1 hour. The reaction mixture is diluted with EtOAc and washed with 10 % citric acid. The

phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined and washed with saturated aqueous $HaHCO_3$, brine, dried over Na_2SO_4 and concentrated. The residue is purified by silica gel column chromatography (hexane/EtOAc, 1/1) to give product **11a** (1.2 g).

To a solution of alcohol **11a** (1.2 g) in acetone (20.0 mL) at -5 °C is added a solution of Jones' reagent (3.0 M, 5.0 mL). The mixture is warmed to 0 °C and stirred at this temperature for 2 hours. The reaction is then quenched by slow addition of *i*-PrOH (5.0 mL) and the mixture is then diluted with EtOAc. The phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, washed with brine, dried (Na_2SO_4) and concentrated to give **11b** (1.16 g).

Step 11-B:



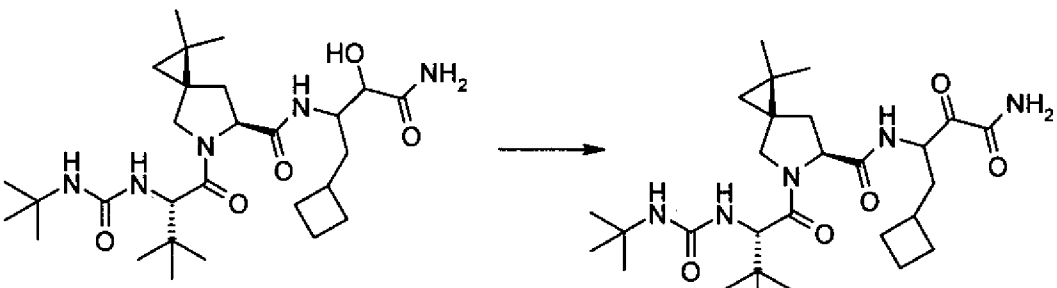
To a solution of **11b** (768 mg, 2.0 mmol) in DMF (2.0 mL) and CH_2Cl_2 (2.0 mL) at 0 °C is added HATU (836 mg, 2.2 mmol, 1.1 equiv), **7f** (417 mg, 2.0 mmol, 1.0 equiv) and N-methyl-morpholine (0.658 mL, 6.0 mmol, 3.0 equiv). The solution is stirred at room temperature for 3 hours. The reaction mixture is added saturated aqueous $NaHCO_3$ solution and EtOAc/diethyl ether 1/1. The two phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, washed with 1.0 N HCl, brine, dried over

Na_2SO_4 and concentrated. The crude material is purified by silica gel column chromatography (hexane/EtOH, 9/1) to give product **11c**.

Trifluoroacetic acid (3.0 mL) is added to a solution of **11c** in CH_2Cl_2 (3.0 mL) and the solution is stirred at room temperature for 1 hour. The solvent is then evaporated. Saturated aqueous $NaHCO_3$ solution and CH_2Cl_2 are added to the residue. The two phases are separated and the aqueous layer is extracted with CH_2Cl_2. The organic layers are combined, dried over Na_2SO_4 and concentrated to give **11d**.

To a solution of N-methyl-morpholine (0.028 mL) and *t*-butylisocyanate (25 mg) in CH_2Cl_2 is added **11d** (100 mg). The solution is stirred at room temperature for 4 hours. The solution is loaded to silica gel and flushed with heptane/acetone (1/1) to give product **11e** (91 mg).

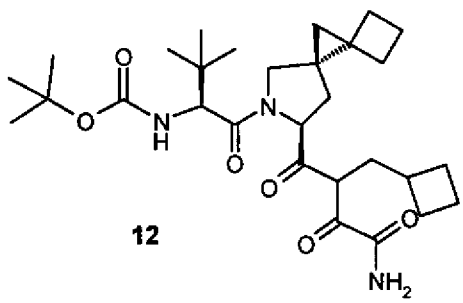
Step 11-C:



11e **11**

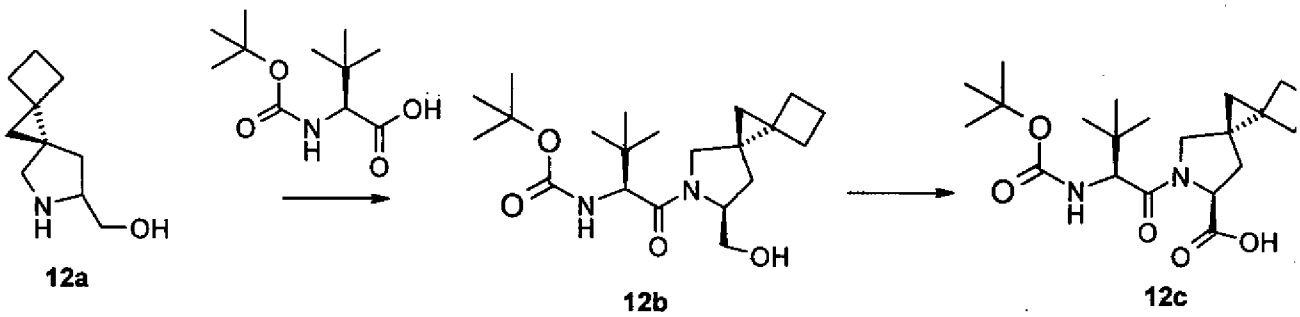
To a solution of alcohol **11e** (91 mg) in CH_2Cl_2 (0.6 mL) at 0 °C is added DIPEA (0.160 mL) followed by a solution of $Py{\bullet}SO_3$ (89 mg) in DMSO (0.6 mL). The solution is stirred at 0 °C for 10 minutes. The mixture is loaded directed to silica gel column and flushed with heptane/acetone (1/1) to give product **11** (65 mg). Found m/z ES+ = 534.

Example 12:



12

Step 12-A:



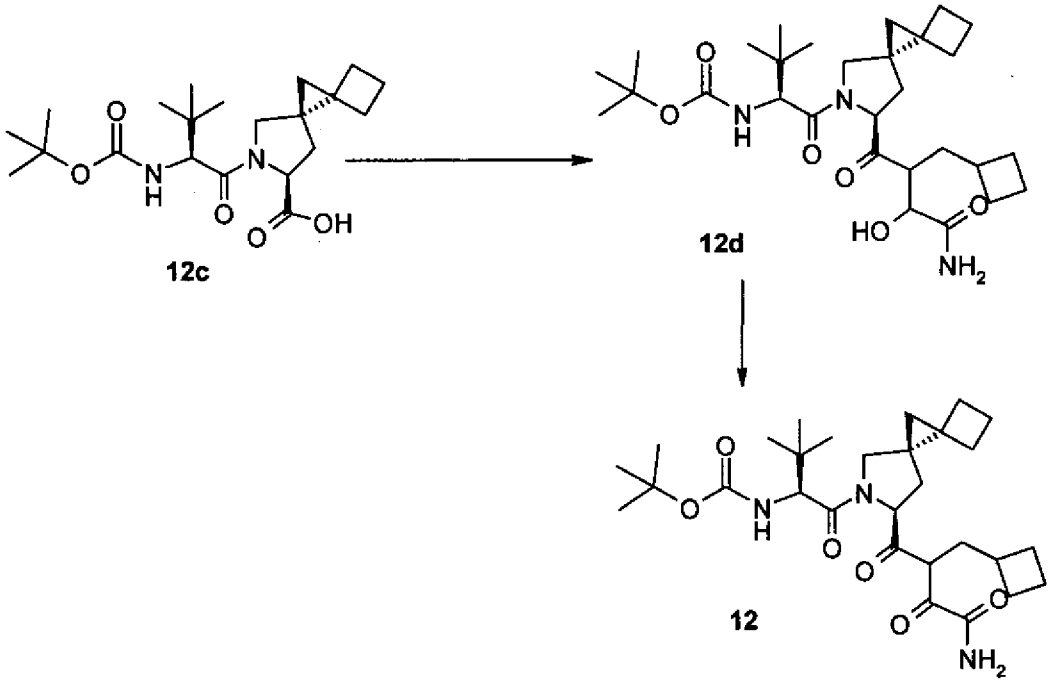
12a 12b 12c

Amino alcohol **12 a** is prepared from **8a** and cyclobutanone according to the procedure described for the synthesis of **9f** from **8a**.

To a solution of Boc-L-t-butyl-gly-OH (277 mg, 1.20 mmol, 1.0 equiv) and **12a** (200 mg, 1.20 mmol, 1.0 equiv) in CH_2Cl_2 (10.0 mL) at -20 °C is added HATU (0.55 g, 1.44 mmol, 1.2 equiv) followed by and DIPEA (0.63 mL, 3.60 mmol, 3.0 equiv). The solution is stirred at -20 °C for 24 hours and 0 °C for 1 h. The reaction mixture is diluted with EtOAc and washed with 10 % citric acid. The phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined and washed with saturated aqueous $NaHCO_3$, brine, dried (Na_2SO_4) and concentrated. The residue is purified by silica gel column chromatography (hexane/EtOAc, 1/1) to give product **12b**.

To a solution of **12b** (0.40 g, 1.05 mmol) in acetone (10.0 mL) at 0 °C is added a solution of Jones' reagent (3.0 M, 2.1 mL, 5.3 mmol). The mixture is kept at 0 °C for 1 hour. The reaction is then quenched by slow addition of *i*-PrOH (3.0 mL) and the mixture is then diluted with EtOAc. The phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, washed with brine, dried (Na_2SO_4) and concentrated to yield **12c**.

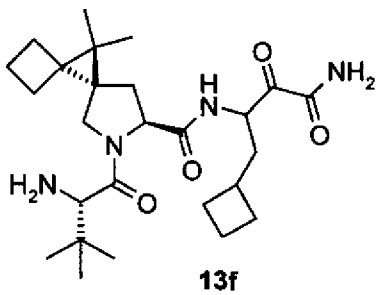
Step 12-B:



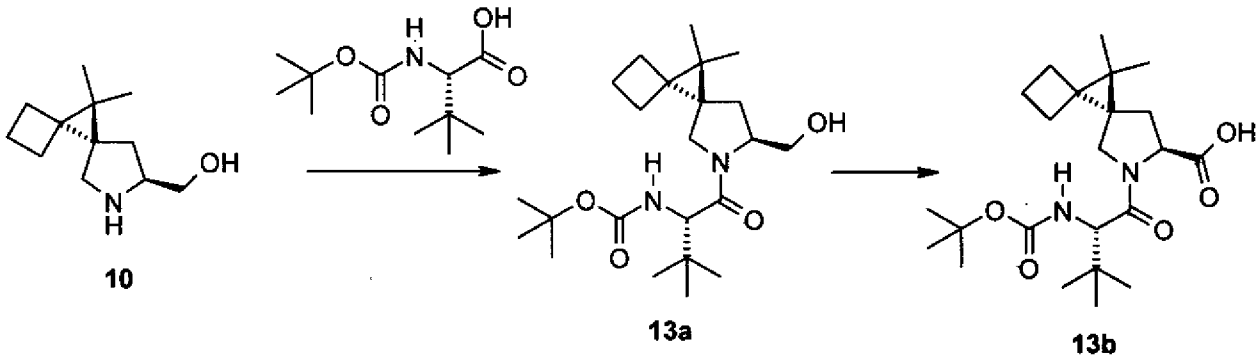
To a solution of acid **12c** (0.39 mg, 0.99 mmol) and **7f** (206 mg, 0.99 mmol, 1.0 equiv) in DMF (8.0 mL) and CH_2Cl_2 (8.0 mL) at 0 °C is added HATU (452 mg, 1.19 mmol, 1.2 equiv) and N-methyl-morpholine (0.33 mL, 2.97 mmol, 3.0 equiv). The solution is stirred at room temperature for 4 hours. To the reaction mixture is added saturated aqueous $NaHCO_3$ solution and EtOAc/diethyl ether (1/1). The two phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, washed with 1.0 N HCl aq. solution, brine, dried (Na_2SO_4) and concentrated. The residue is purified by silica gel column chromatography (hexane/EtOH, 9/1) to give product **12d**.

To a solution of **12d** (100 mg, 0.18 mmol) in CH_2Cl_2 (1.0 mL) and DMSO (1.0 mL) at 0 °C is added DIPEA (0.19 mL, 1.10 mmol, 6 eq) followed by Py•SO_3 (87 mg, 0.55 mmol, 3 eq). The solution is stirred at 0 °C for 10 minutes. The mixture is loaded directly to silica gel column and flushed with heptane/Acetone (1:1) to give 55 mg of product **12**. Found m/z ES+ = 532.

Example 13:



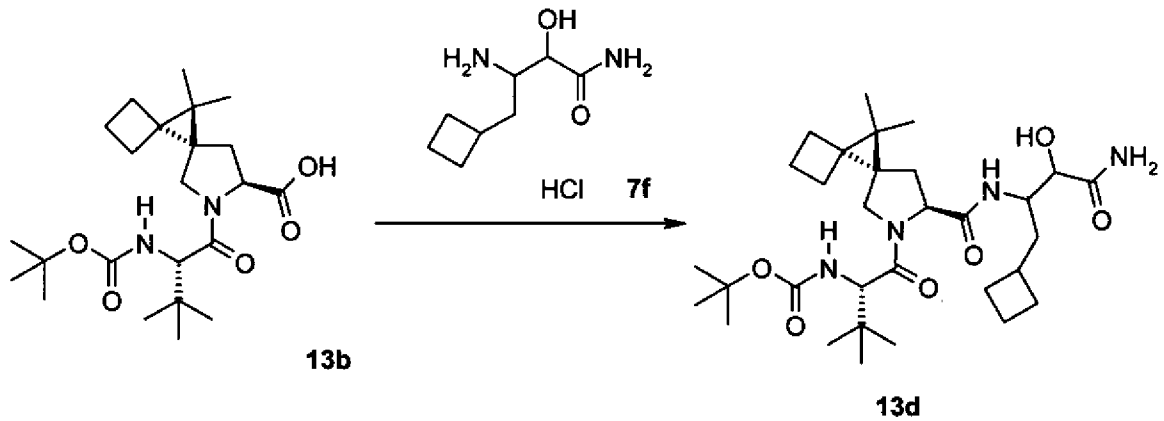
Step 13-A:



To a solution of Boc-L-t-butyl-gly-OH (711 mg, 3..08 mmol, 1.0 equiv) and amino alcohol **10** (600 mg, 3.08 mmol, 1.0 equiv) in CH_2Cl_2 (15.0 mL) at -20 °C is added HATU (1.4 g, 3.69 mmol, 1.2 equiv), followed by DIPEA (1.6 mL, 9.2 mmol, 3.0 equiv). The solution is stirred at -20 °C for 24 hours, 0 °C for 3 hours and room temperature for 1 hour. The reaction mixture is diluted with EtOAc and washed with 1.0 N HCl aq. solution. The phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined and washed with saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated. The residue is purified by silica gel column chromatography (hexane/EtOAc, 1/1) to give product **13a**. Found m/z ES+ = 409.

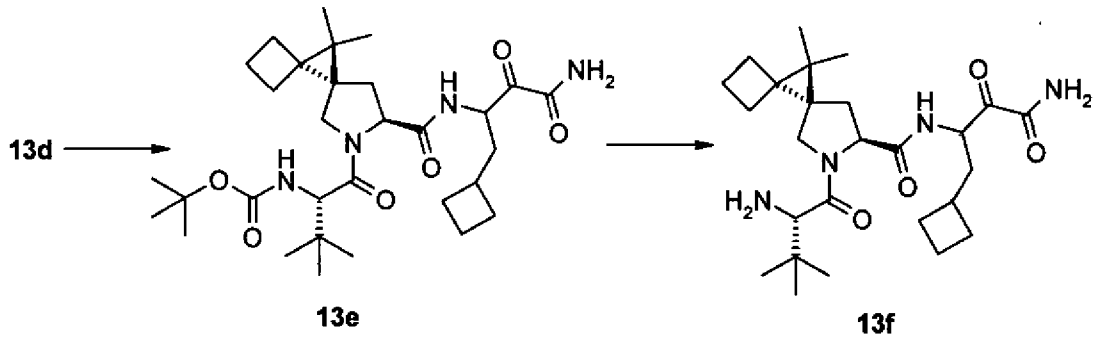
To a solution of alcohol **13a** (890 mg) in acetone (10.0 mL) at -5 °C is added a solution of Jones' reagent (3.0 M, 5.0 mL). The mixture is warmed to 0 °C and stirred at this temperature for 2 hours. The reaction is then quenched by slow addition of *i*-PrOH (5.0 mL) and the mixture is then diluted with EtOAc. The phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, washed with brine, dried (Na_2SO_4) and concentrated to give product **13b**. Found m/z ES+ = 423.

Step 13-B:



To a solution of acid (906 mg, 2.1 mmol) in DMF (8.0 mL) and CH_2Cl_2 (8.0 mL) at 0 °C is added HATU (958 mg, 2.5 mmol, 1.2 equiv), amino alcohol (492 mg, 2.4 mmol, 1.1 equiv) and N-methyl-morpholine (0.692 mL, 6.3 mmol, 3.0 equiv). The solution is stirred at room temperature for 3 hours. The reaction mixture is added saturated aqueous $NaHCO_3$ solution and EtOAc/diethyl ether 1/1. The two phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, washed with 1N HCl, brine, dried over Na_2SO_4 and concentrated. The crude material is purified by silica gel column chromatography (hexane/EtOH, 9/1) to give product **13d**. Found m/z ES+ = 577.

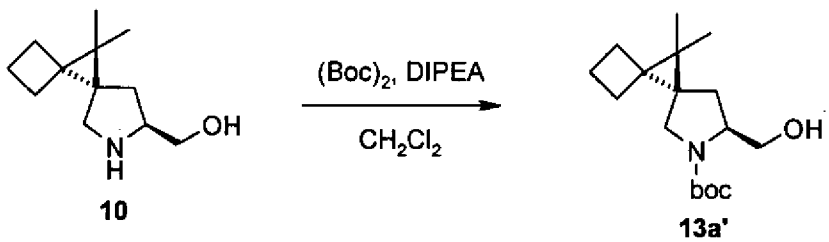
Step 13-C:



To a solution of alcohol **13d** (450 mg) in CH_2Cl_2 (0.6 mL) at 0 °C is added DIPEA (0.504 mL) followed by a solution of Py•SO_3 complex (372 mg) in DMSO (0.6 mL). The solution is stirred at 0 °C for 10 minutes. The mixture is loaded directed to silica gel column and flushed with heptane/Acetone to give product **13e**. Found m/z ES+ = 575.

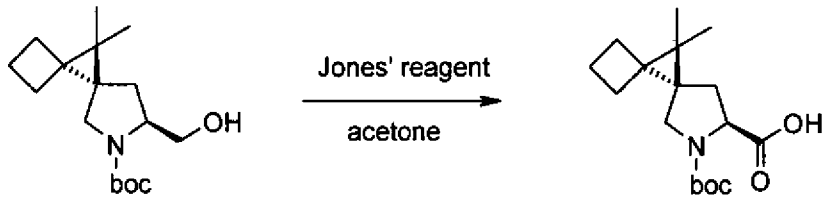
The product is dissolved in 15 mL of 4.0 M HCl in dioxane. The solution was stirred at room temperature for 2 hours. The solution is diluted with 50 mL heptane and concentrated to give crude product **13f**, which is carried on to the next step with no purification. Found m/z ES+ = 475.

Alternative synthetic route from 10 to 13d.



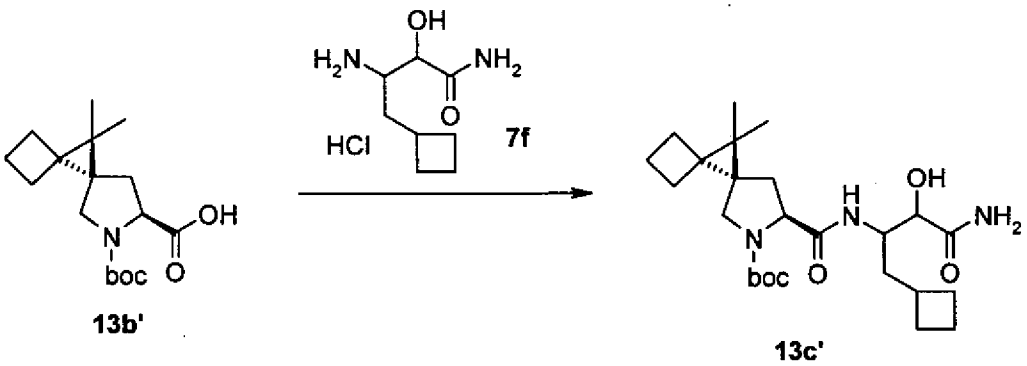
To a solution of **10** (1.95 g, 10 mmol) in CH_2Cl_2 (20.0 mL) at room temperature added Boc anhydride and DIPEA (0.434 mL, 10.5 mmol, 1.05 equiv). The solution is stirred

at room temperature for 2 hours. The solvent is evaporated and the residue is purified by silica gel chromatography (heptane/EtOAc, 2/1) to give product **13a'** 2.1 g.



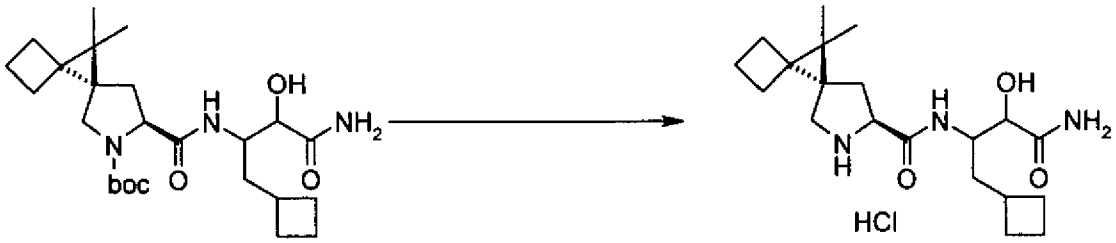
13a' **13b'**

To a solution of alcohol **13a'** (3.0 g, 10.2 mmol) in acetone (30.0 mL) at 0 °C added Jones' reagent (12.2 mL, 30.5 mmol, 3.0 equiv). The solution is stirred at 0 °C for 1.0 hour. The reaction is quenched by addition of i-PrOH (5.0 mL). The solution is then diluted with EtOAc and filtered. The phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, washed with brine, dried over Na_2SO_4 and concentrated. The crude material is continued to the next step without further purification.



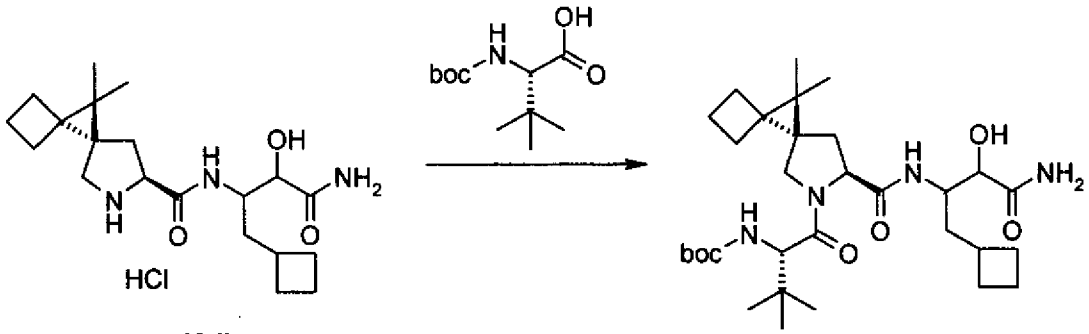
13b' **13c'**

To a solution of carboxylic acid **13b'** (1.0 g, 3.2 mmol) in CH_2Cl_2 (8.0 mL) and DMF (8.0 mL) at 0 °C added **11c** (673 mg, 3.2 mmol, 1.0 equiv) followed by HATU (1.45 g, 3.8 mmol, 1.2 equiv) and N-methyl morpholine (1.05 mL, 9.6 mmol, 3.0 equiv). The solution is stirred at room temperature for 4 hours. To the solution is added EtOAc and sat. aq. $NaHCO_3$. The phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, washed with 1.0 N HCl aq. solution, brine, dried over Na_2SO_4 and concentrated. The residue is purified by silica gel chromatography (heptane/acetone, 1/1) to give product **13c'** 975 mg. Found MS ES+ = 464.



13c' 13d'

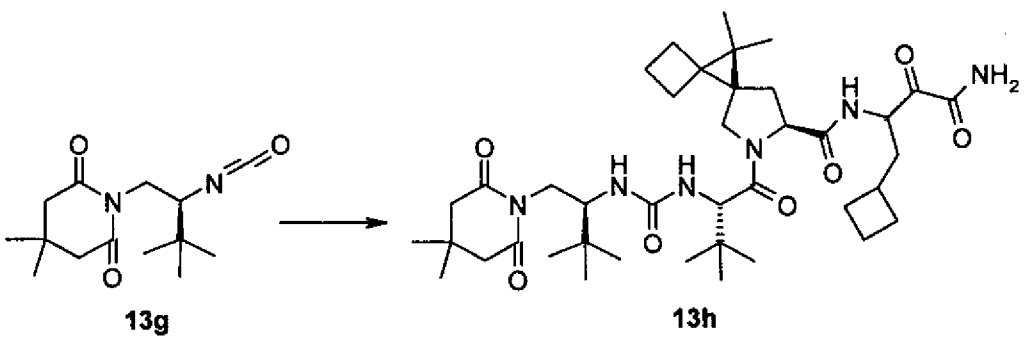
To a flask containing **13c'** added 10 mL of 4.0 N HCl in dioxane. The solution is stirred at room temperature for 1.0 hour. The solvent is then evaporated give crude product **13d'**, which is continued to the next step without purification. Found MS ES+ = 364, ES- = 362.



13d' 13d

To mixtures of Boc-L-t-butyl-gly-OH (297 mg, 1.29 mmol, 1.0 equiv), **13d'** (515 mg, 1.29 mmol, 1.0 equiv) in CH_2Cl_2 (7.0 mL) at -20 °C added HATU (585 mg, 1.54 mmol, 1.2 equiv) and DIPEA (0.696 mL, 4.0 mmol, 3.0 equiv). The solution is stirred at -20 °C for 12 hours then 0 °C for 1.0 hour. To the solution is added EtOAc and sat. aq. $NaHCO_3$ solution. The phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, washed with 1.0 N HCl aq. solution, brine, dried over Na_2SO_4 and concentrated. The residue is purified by silica gel chromatography (heptane/acetone, 1/1) to give product 610 mg. Found MS ES+ = 577, ES- = 575.

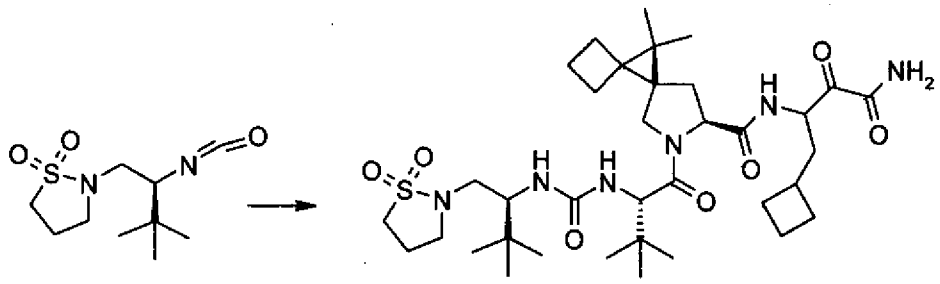
Example 13h:



13g 13h

To a solution of amine hydrochloride salt **13f** (37.5 mg) in CH_2Cl_2 (1.0 mL) is added DIPEA (0.012 mL) and a solution of **13g** (23 mg) in toluene (1.5 mL). The solution is stirred at room temperature for 2 hours. The solution is concentrated and the crude material is purified by silica gel column chromatography to give 20 mg of product **13h**. Found m/z ES+ = 741.

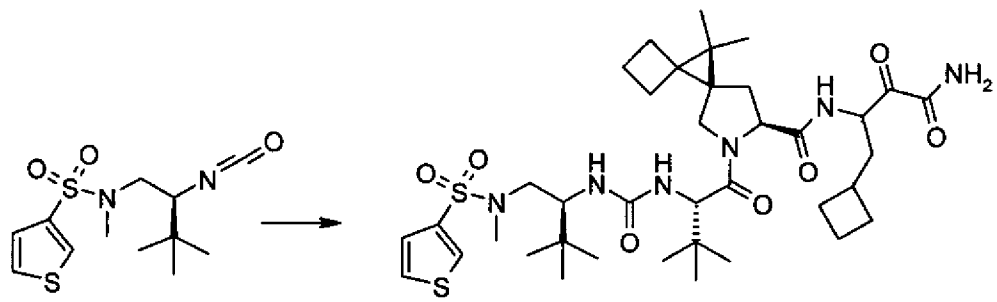
Example 13j:



13i **13j**

To a solution of amine hydrochloride salt **13f** (37 mg) in CH_2Cl_2 is added DIPEA (0.012 mL) and a solution of **13i** (21 mg) in toluene (1.5 mL). The solution is stirred at room temperature for 2 hours. The solution is concentrated and the crude material is purified by silica gel column chromatography to give 6 mg of product **13j**. Found m/z ES+ = 721.

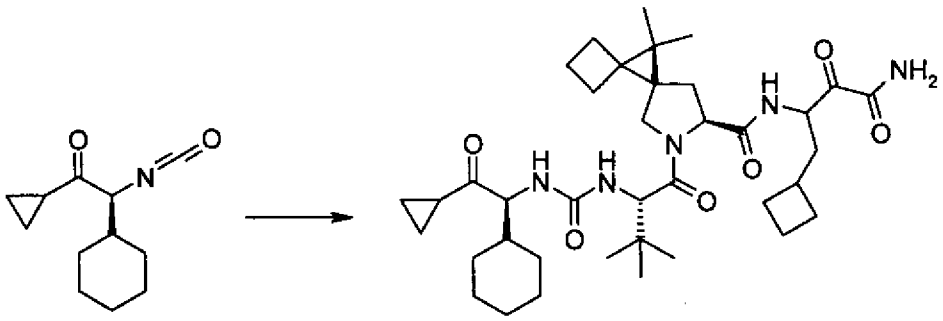
Example 13l:



13k **13l**

To a solution of amine hydrochloride salt **13f** (37 mg) in CH_2Cl_2 is added DIPEA (0.012 mL) and a solution of **13k** (26 mg) in toluene (1.5 mL). The solution is stirred at room temperature for 2 hours. The solution is concentrated and the crude material is purified by silica gel column chromatography to give 15 mg of product **13l**. Found m/z ES+ = 777.

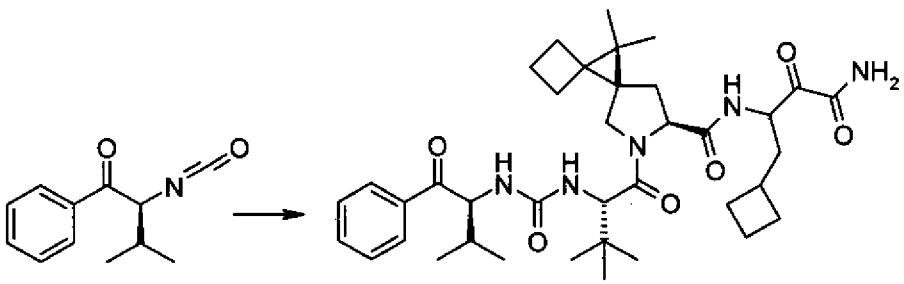
Example 13n:



13m 13n

To a solution of amine hydrochloride salt **13f** (37 mg) in CH_2Cl_2 is added DIPEA (0.012 mL) and a solution of **13m** (18 mg) in toluene (1.5 mL). The solution is stirred at room temperature for 2 hours. The solution is concentrated and the crude material is purified by silica gel column chromatography to give 29 mg of product **13n**. Found m/z ES+ = 682.

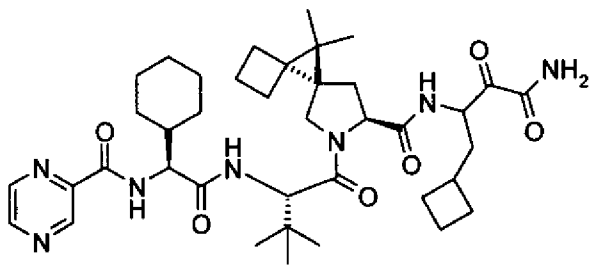
Example 13p:



13o 13p

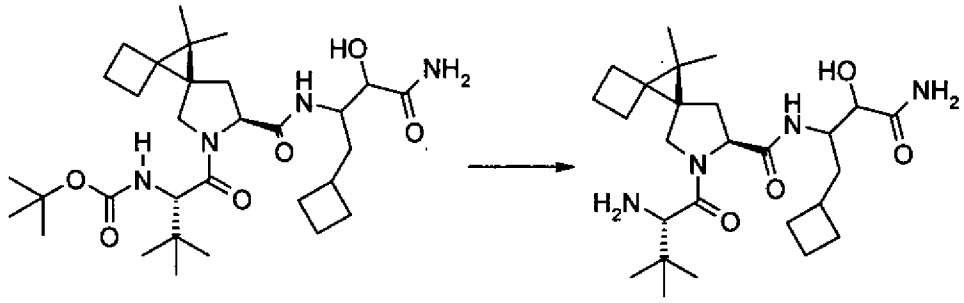
To a solution of amine hydrochloride salt **13f** (37 mg) in CH_2Cl_2 is added DIPEA (0.012 mL) and a solution of **13o** (18 mg) in toluene (1.5 mL). The solution is stirred at room temperature for 2 hours. The solution is concentrated and the crude material is purified by silica gel column chromatography to give 37.6 mg of product **13p**. Found m/z ES+ = 678.

Example 14:



14

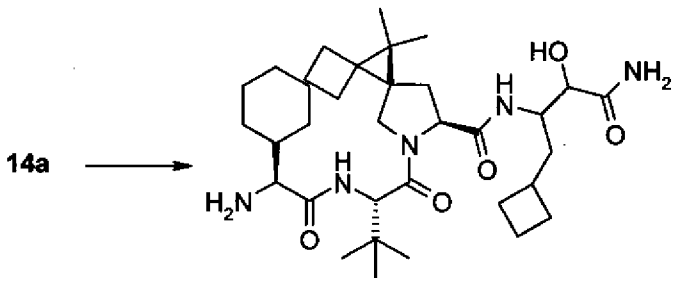
Step 14-A:



13d 14a

To a solution of N-Boc amine **13d** (690 mg) in dichloromethane (5.0 mL) at room temperature is added TFA (5.0 mL). The mixture is stirred for 3 hours after which the solvent is evaporated in vacuo and dichloromethane (100 mL) is added to the residue. The pH is adjusted to pH 8 by dropwise addition of saturated sodium bicarbonate. The layers are separated and the organic layer with washed with brine, dried over Na_2SO_4, filtered and concentrated to give the product amine **14a**. Found m/z ES+ =477.

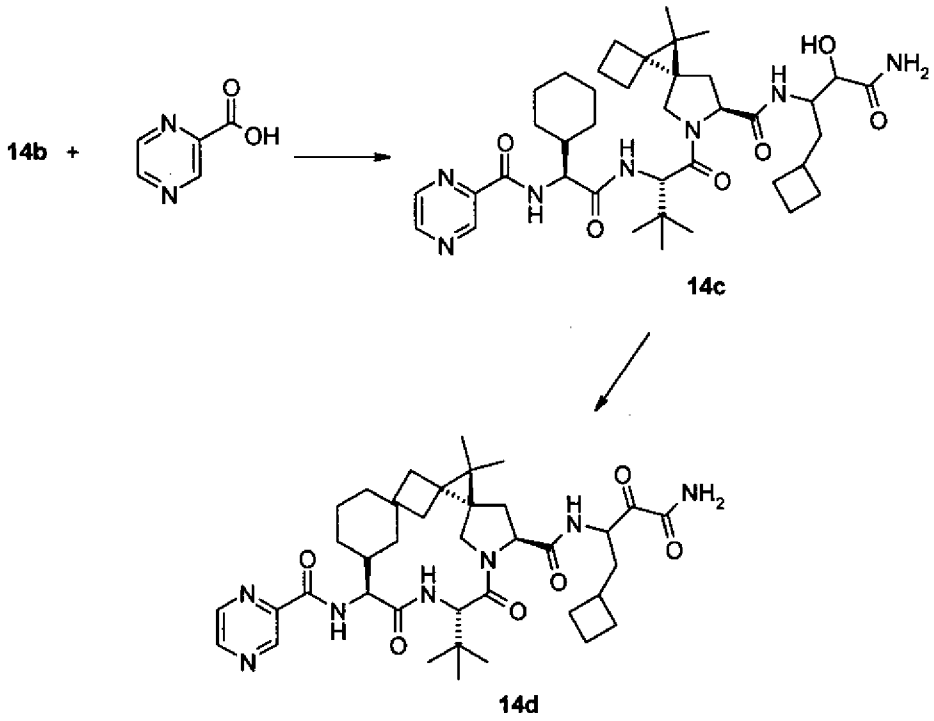
Step 14-B:



14b

To a solution of (S)-2-(tert-butoxycarbonylamino)-2-cyclohexylacetic acid (51.4 mg, 0.2 mmol) in DMF (1.0 mL) and CH_2Cl_2 (1.0 mL) at 0 °C is added HATU (91 mg, 0.24 mmol, 1.2 equiv), amine **14a** (95 mg, 0.2 mmol, 1.0 equiv) and N-methyl-morpholine (0.066 mL, 0.6 mmol, 3.0 equiv). The solution is stirred at room temperature for 3 hours. To the reaction mixture is added saturated aqueous $NaHCO_3$ solution and EtOAc/diethyl ether 1/1. The two phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, washed with 1N HCl, brine, dried over Na_2SO_4 and concentrated. The crude material is purified by silica gel column chromatography (hexane/EtOH, 9/1) to give Boc-protected amine (Found m/z ES+ =716). The product is dissolved in dichloromethane (5 mL) at room temperature and TFA (5 mL) is added. The mixture is stirred for 3 hours after which the solvent is evaporated in vacuo. The residue is dissolved in dichloromethane (100 mL). The pH is adjusted to pH 8 by dropwise addition of saturated sodium bicarbonate. The layers are separated and the organic layer with washed with brine, dried over Na_2SO_4, filtered and concentrated to give the product **14b**. Found m/z ES+ =616.

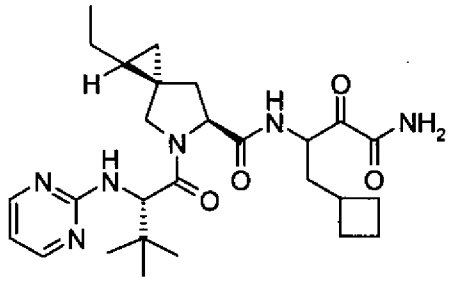
Step 14-C:



To a solution of pyrazine-2-carboxylic acid (20 mg, 0.16 mmol) in DMF (1.0 mL) and CH_2Cl_2 (1.0 mL) at 0 °C is added HATU (73 mg, 0.19 mmol, 1.2 equiv), amine **14b** (100 mg, 0.16 mmol, 1.0 equiv) and N-methyl-morpholine (0.053 mL, 0.48 mmol, 3.0 equiv). The solution is stirred at room temperature for 3 hours. To the reaction mixture is added saturated aqueous $NaHCO_3$ solution and EtOAc/diethyl ether 1/1. The two phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, washed with 1N HCl, brine, dried over Na_2SO_4 and concentrated. The crude material is purified by silica gel column chromatography (hexane/EtOH, 9/1) to give product **14c**. Found m/z ES+ =722.

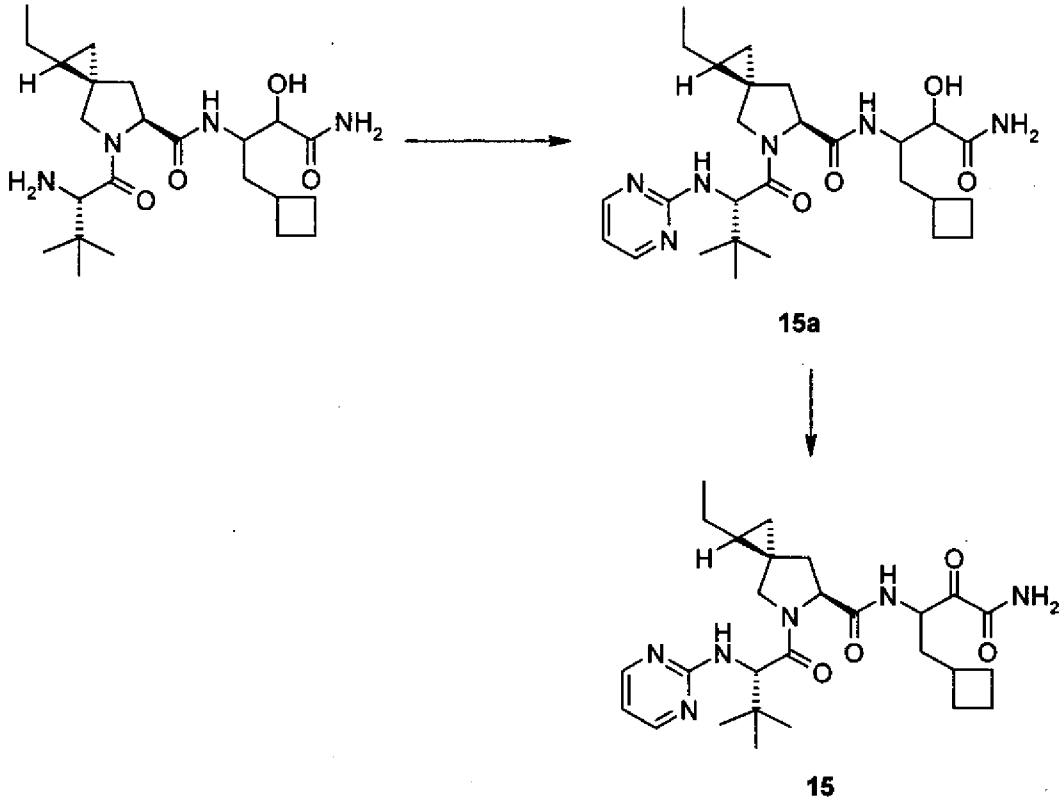
To a solution of alcohol **14c** (110 mg) in CH_2Cl_2 (0.6 mL) at 0 °C is added DIPEA (0.160 mL) followed by a solution of sulfur trioxide pyridine complex (89 mg) in DMSO (0.6 mL). The solution is stirred at 0 °C for 10 mines. The mixture is loaded directly onto a silica gel column and flushed with heptane/Acetone to give product **14d** (71 mg). Found m/z ES+ = 720.

Example 15:



15

Scheme:



15a

15

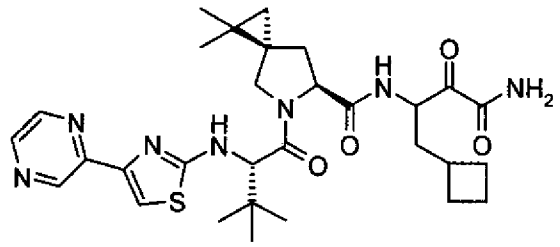
Step 15-A:

To a solution of amine (87 mg, 0.2 mmol, 1.0 equiv) in IPA (0.4 mL) at room temperature is added 2-bromo-pyrimidine (32 mg, 0.2 mmol, 1.0 equiv) and DIPEA (0.034 mL, 0.2 mmol, 1.0 equiv). The solution is heated at 80 °C for 24 hours. The crude material is purified by silica gel chromatography (heptane/acetone, 1/1) to give desired product. Found m/z ES+ = 515.

Step 15-B:

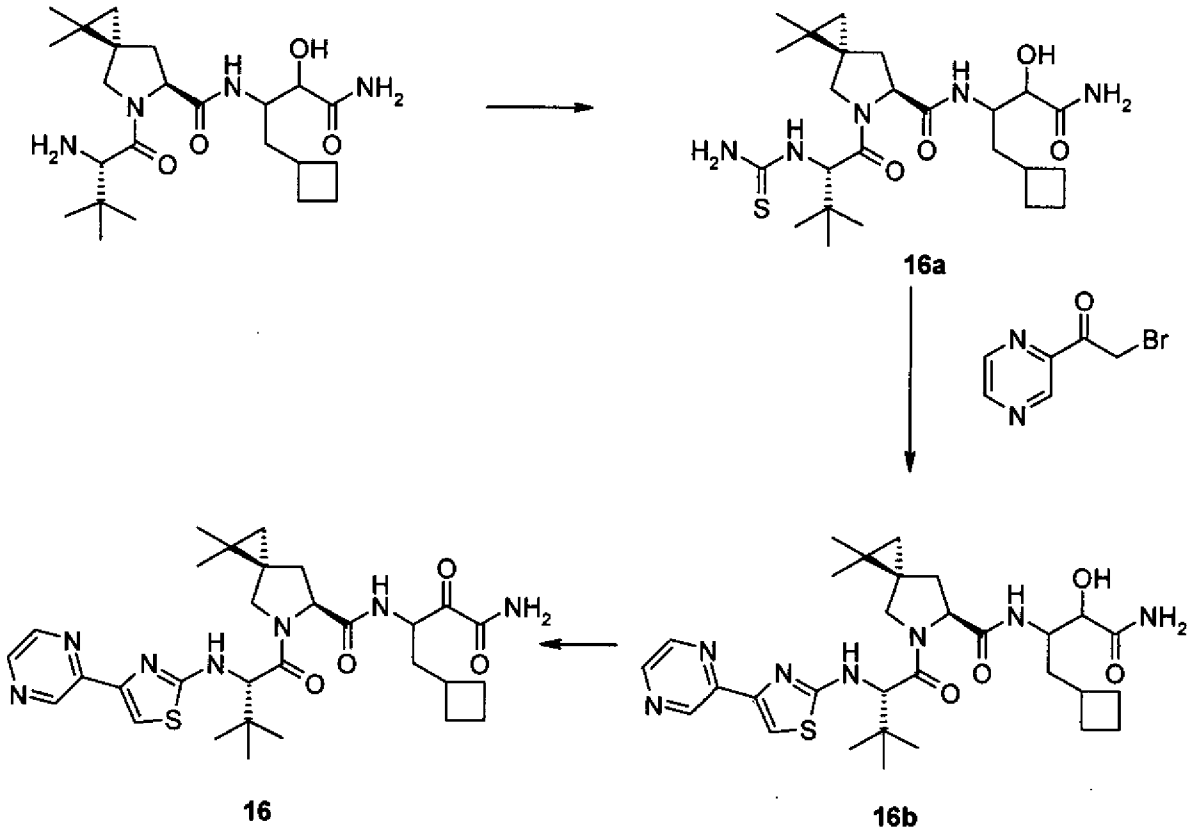
To a solution of **15a** (90 mg) in CH_2Cl_2 (0.6 mL) add DIPEA (0.12 mL) and a solution of $Py•SO_3$ (80 mg) in DMSO (0.6 mL). The solution is stirred at rt for 10 mins. The solution is loaded to silica gel and flushed with heptane/acetone (1/1) to give 28 mg of product **15**. Found m/z ES+ = 513.

Example 16:



16

Synthesis of thiazole:



16a

16

16b

Step 16-A:

Benzoyl isothiocyanate (162 mg) is added to a solution of amine (400 mg) in acetone (4.0 mL) . The solution is heated at 70 °C for 2 hours. Potassium carbonate (40 mg), water (0.4 mL) and MeOH (4.0 mL) are then added to the solution. The solution is then heated at 80 °C for 4 hours. The mixture is concentrated and the crude residue is purified by silica gel chromatography (CH_2Cl_2/MeOH, 4/1) to give thiourea intermediate **16a**. Found m/z ES+ = 497.

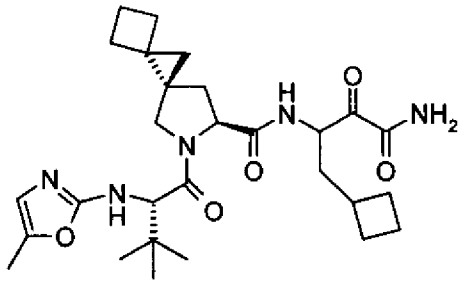
Step 16-B:

The thiourea (70 mg) and 2-bromo-1-pyrazin-2yl-ethanone (30 mg) are dissolved in ethanol (0.5 mL) and the solution is heated to reflux for 1 hour. The crude material is purified by silica gel chromatography (CH_2Cl_2/EtOH, 9/1) to give product **16b**. Found m/z ES+ = 598.

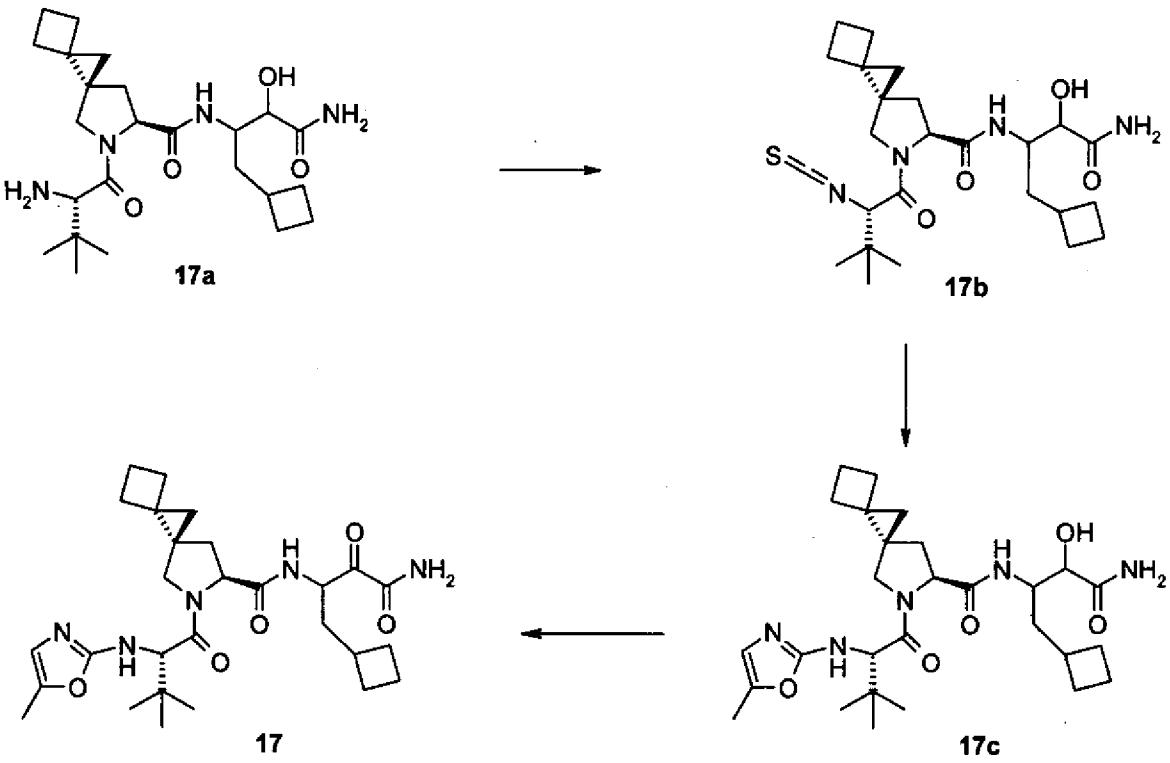
Step 16-C:

To a solution of **16b** (70 mg) in CH_2Cl_2 (1.0 mL) add DIPEA (0.12 mL) and a solution of Py•SO_3 (80 mg) in DMSO (0.6 mL). The solution is stirred at rt for 10 mins. The solution is loaded to silica gel and flushed with heptane/acetone (1/1) to give 25 mg of product **16**. Found m/z ES+ = 513.

Example 17:



17



Step 17-A:

To a solution of **17a** (5.31 g, 11.86 mmol) in CH_2Cl_2 (40 mL) at 0 °C add sat. aq. $NaHCO_3$ (40 mL) and $CSCl_2$ (1.1 mL, 14.23 mmol) is added. The mixture is stirred at room temperature for 30 minutes. The phases are separated and the organic layer is washed with brine, dried over Na_2SO_4, and concentrated. The crude material is purified by silica gel chromatography (heptane/EtOAc, 1/1) to give product **17b** (1.20 g, 21% yield) as light yellow solid. Found m/z ES+ = 491.

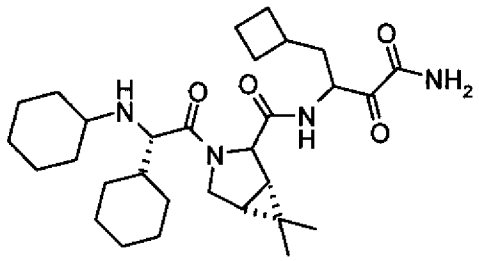
Step 17-B:

To a solution of **17b** (60 mg, 0.122 mmol) in dioxane is added PPh_3 (38.6 mg, 0.147 mmol) and followed by 1-azidopropan-2-one (14.5 mg, 0.147 mmol). The solution is heated at 90 °C for 1 hour. Then 2-methyl-propane-1,2 diamine (0.20 mL) is added and the solution is heated at 50 °C for 30 minutes. The crude mixture is separated by silica gel column chromatography (CH_2Cl_2/EtOH, 4/1) to afford **17c** (22 mg). Found m/z ES+ = 530.

Step 17-C:

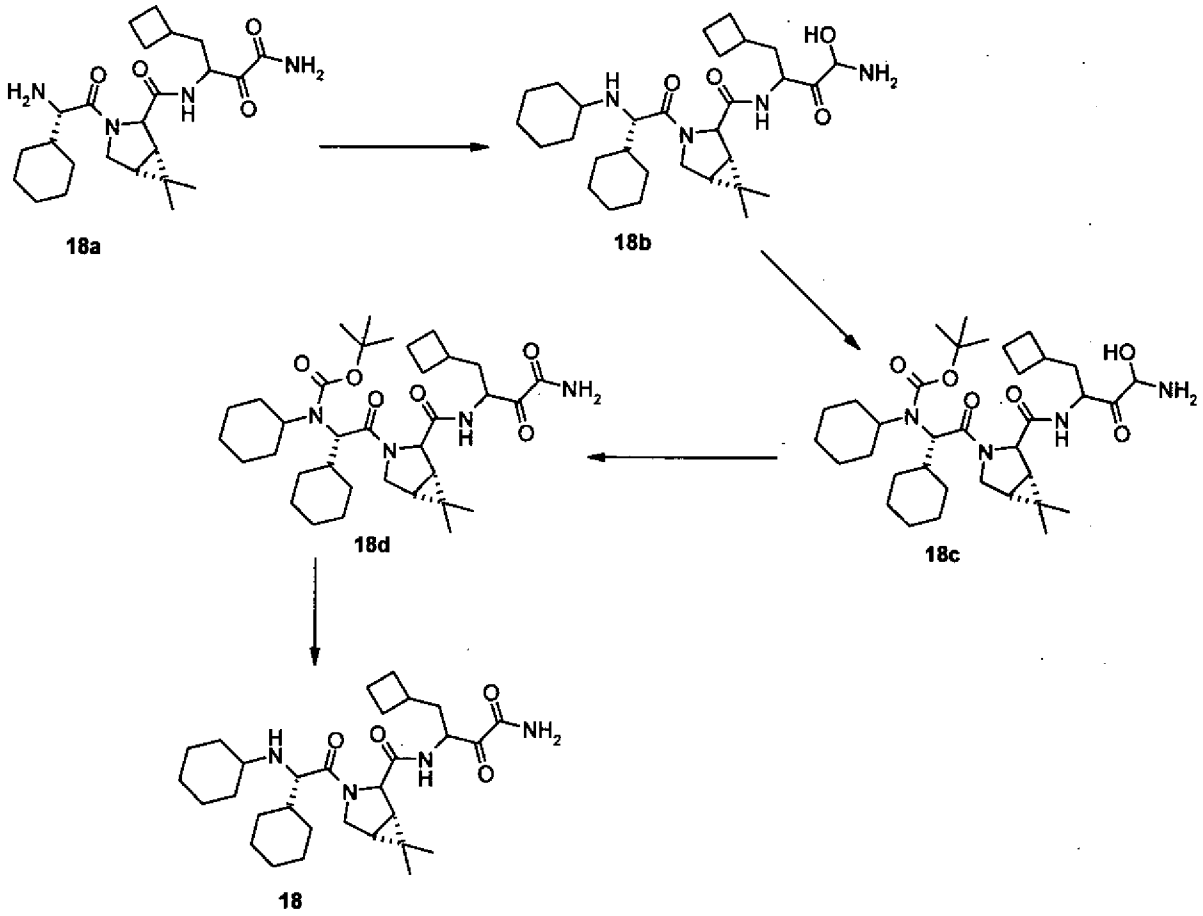
To a solution of **17c** (22 mg, 0.042 mmol) in CH_2Cl_2 add DIPEA (0.044 mL, 0.252 mmol) and DMSO (0.5 mL). Then the solution is cooled to 0 °C and Py•SO_3 (20 mg, 0.125 mmol) is added. The solution is stirred at 0 °C for 10 minutes. The mixtures are separated by chromatography (Heptane/Acetone, 1/1) to afford **17** (5 mg). Found m/z ES+ =528.

Example18:



18

Scheme:



Step 18-A:

A solution of **18a** (89 mg, 0.2 mmol) in CH_2Cl_2 (1.0 mL) is added cyclohexanone (0.22 mmol, 0.023 mL). The solution is stirred for 20 minutes at room temperature after which sodium triacetoxy borohydride (0.4 mmol, 84 mg) is added and stirred for another 20 minutes. To the reaction mixtures add sat. aq. $NaHCO_3$ solution. The organic layer is separated from aqueous layer and the aqueous layer is extracted with dichloromethane (3 X

10 mL). The organic layers are combined, dried (Na_2SO_4) and concentrated to give 97 mg of **18b**.

Step 18-B:

A solution of **18b** (97 mg, 0.183 mmol) in DCM is added Et_3N (0.366 mmol, 51 μL) and $(Boc)_2O$ (0.274 mmol, 60 mg). The solution is stirred at room temperature for an hour after which it is washed with 1.0 N HCl aq. solution (1 mL), sat. aq. $NaHCO_3$ solution (1 mL) and brine. The organic layer is dried over Na_2SO_4, and concentrated. The residue is purified by silica gel column chromatography (eluent: acetone/heptane, 1:1) to give 95 mg of **18c**.

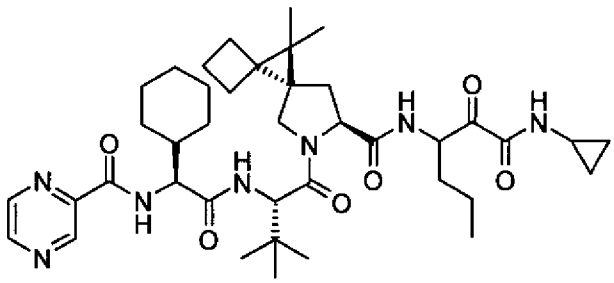
Step 18-C:

To a solution of **18c** (73 mg, 0.12mmol) in CH_2Cl_2 (0.5 mL), DIPEA (81 μL, 0.46 mmol) and DMSO (0.5 mL) are added. Then the solution is cooled to 0 °C and Py•SO_3 (37 mg, 0.23 mmol) is added. The solution is stirred at 0 °C for 10 minutes. The mixtures are separated by silica gel chromatography (Heptanes/Acetone, 1/1) to afford 67 mg of **18d**.

Step 18-D:

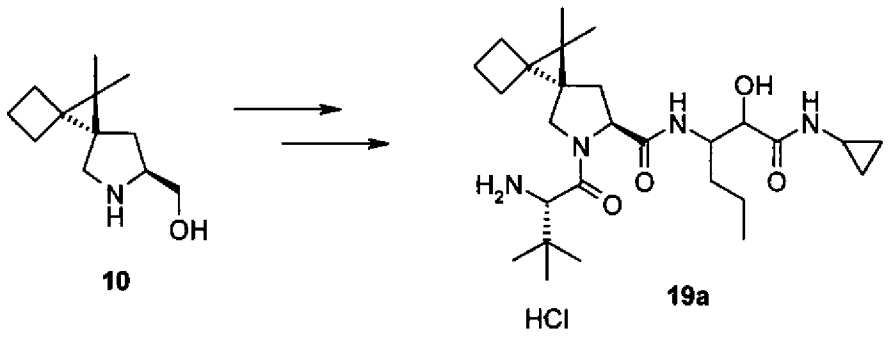
The product **18d** (66 mg, 0.104 mmol) is dissolved in dioxane (0.2 mL) and the solution is added 4.0 N HCl in dioxane (0.105 mL) at 0 °C. The reaction mixture is stirred at rt for 24 hours after which the reaction mixture is concentrated. The residue is dissolved in DCM and the solution is washed with sat. $NaHCO_3$ aq. solution, brine. The organic layer is dried over Na_2SO_4, chromatographed (Eluent: Acetone/heptane, 1:1) to give 33.5 mg of **18**.

Example 19:



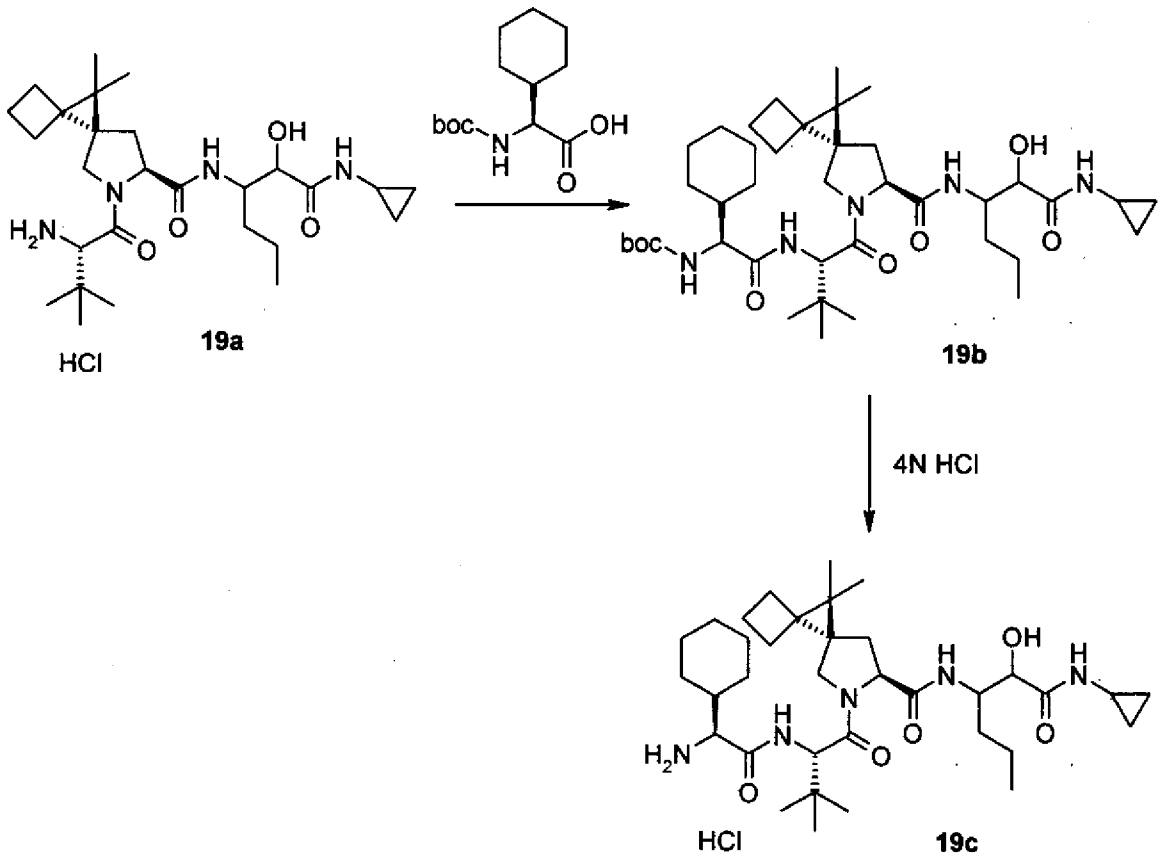
19

Step 19-A:



Intermediate **19a** is prepared according to the procedure described for the synthesis of **13d**. Found MS ES+ = 491.

Step 19-B:

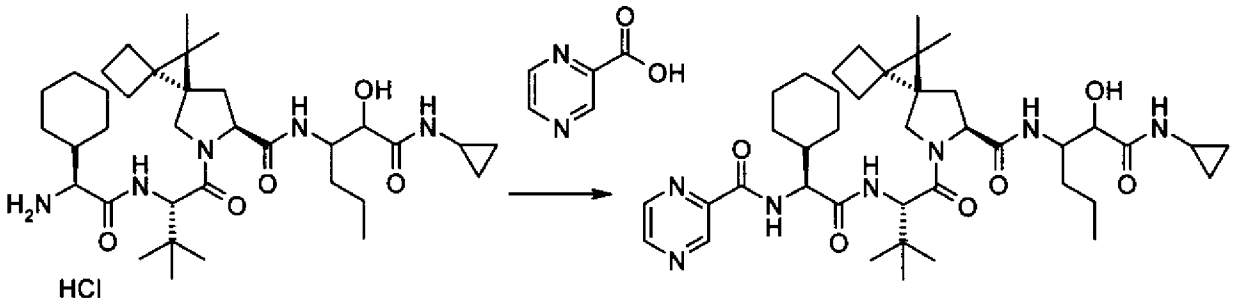


To a solution of Boc-L-cyclohexyl-gly-OH (0.391 g, 1.53 mmol) and **19a** (800 mg, 1.53 mmol, 1.0 equiv) in CH_2Cl_2 (7.0 mL) and DMF (7.0 mL) at 0 °C added HATU (697 mg, 1.8 mmol, 1.2 equiv) and N-methyl morpholine (0.505 mL, 4.6 mmol, 3.0 equiv). The solution is stirred at room temperature for 4 hours. To the solution is added EtOAc and sat. aq. $NaHCO_3$. The phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, washed with 1.0 N HCl aq. solution, brine, dried over Na_2SO_4

and concentrated. The residue is purified by silica gel chromatography (heptane/acetone, 1/1) to give product **19b**. Found MS ES+ = 730, ES- = 728.

To a flask containing **19b** (1.02 g) added 4.0 N HCl in dioxane (10.0 mL). The solvent is evaporated to give crude material **19c**, which is continued to the next step without purification. Found MZ ES+ = 630, ES- = 628.

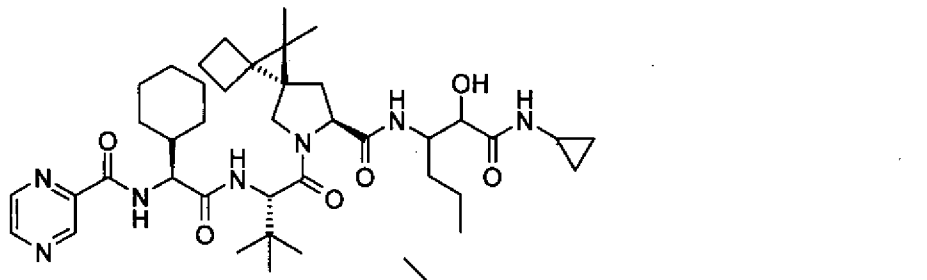
Step 19-C:



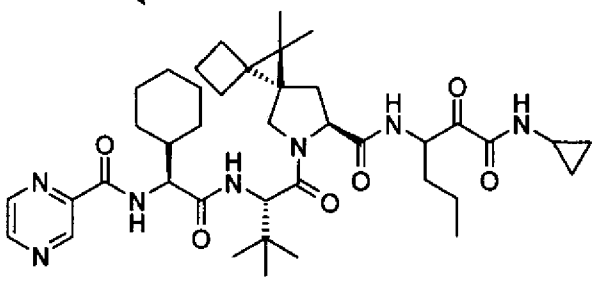
19c **19d**

To a solution of pyrazine-2-carboxylic acid (0.175 g, 1.40 mmol) and **19c** (938 mg, 1.40 mmol, 1.0 equiv) in CH_2Cl_2 (7.0 mL) and DMF (3.0 mL) at 0 °C added HATU (639 mg, 1.7 mmol, 1.2 equiv) and N-methyl morpholine (0.461 mL, 4.2 mmol, 3.0 equiv). The solution is stirred at room temperature for 4 hours. To the solution is added EtOAc and sat. aq. $NaHCO_3$. The phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, washed with 1.0 N HCl aq. solution, brine, dried over Na_2SO_4 and concentrated. The residue is purified by silica gel chromatography (heptane/acetone, 1/1) to give product **19d**. Found MZ ES+ = 736, ES- = 734.

Step 19-D:



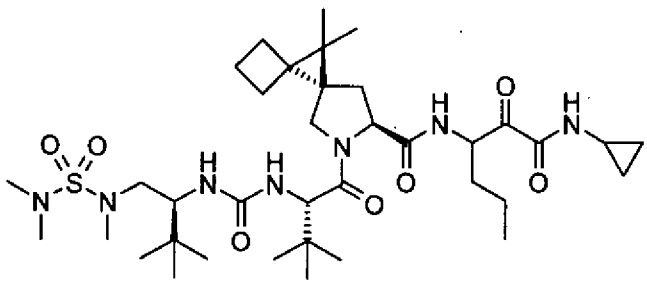
19d



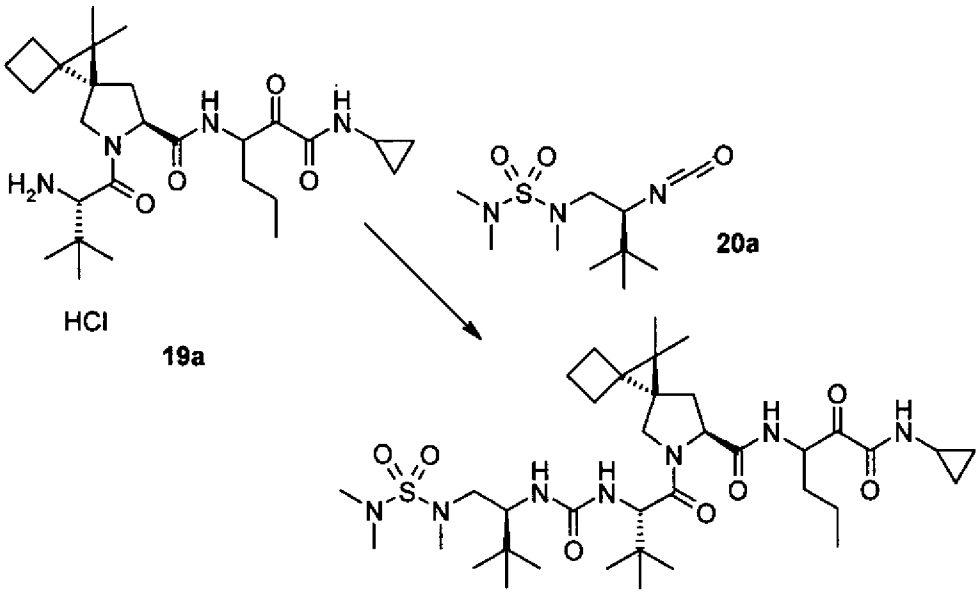
19

To a solution of **19d** (670 mg, 0.91 mmol) in CH_2Cl_2 (2.0 mL) at 0 °C added DIPEA (0.95 mL, 5.46 mmol, 6.0 equiv) followed by a solution of Py•SO_3 (440 mg, 2.73 mmol, 2.0 equiv) in DMSO (2.0 mL). The solution is stirred at 0 °C for 10 minutes, after which it is added sat. aq. NH_4Cl solution and EtOAc. The phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, dried over Na_2SO_4 and concentrated. The residue is purified by silica gel chromatography (heptane/acetone, 1/1) to give 71 mg of **19**. Found MZ ES+ = 734, ES- = 732.

Example 20:

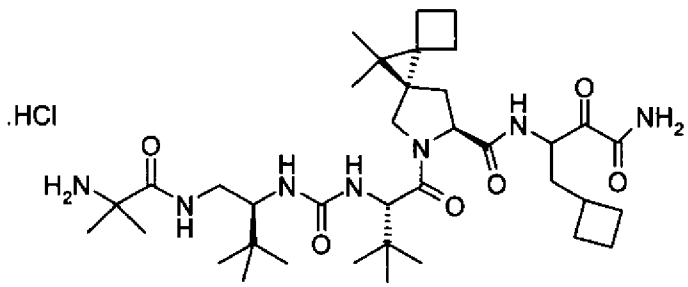


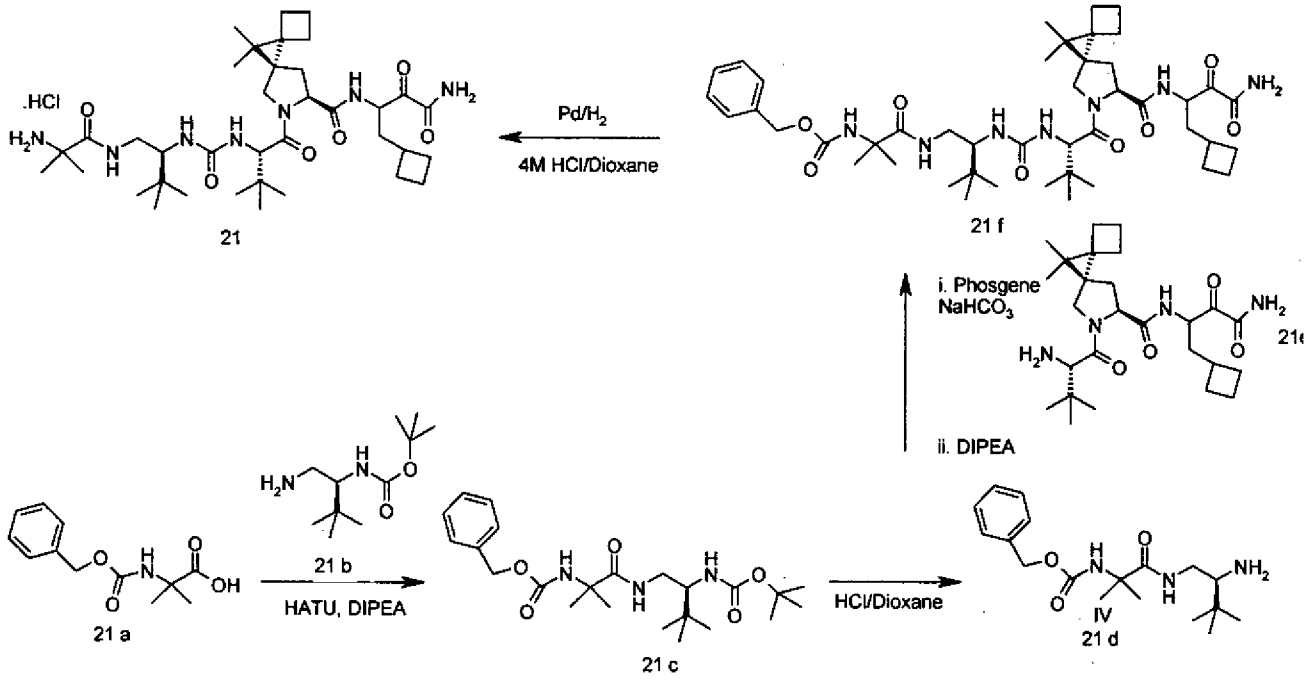
20



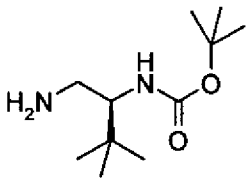
To mixtures of **19a** (75 mg, 0.14 mmol) in CH_2Cl_2 (1 mL) added DIPEA (0.05 mL, 0.29 mmol) at 0 °C, **20a** (0.18 mmol, in toluene solution). The solution is stirred at 0°C for 30 min after which it is quenched by addition of citric acid (10% aq. solution, 5 mL) and EtOAc. The phases are separated and the aqueous layer is extracted with EtOAc. The combined organic layers are washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue is purified by silica gel chromatography (heptane/acetone, 1/1) to give 59 mg of **20**. Found MZ, ES+ = 752, ES- = 750.

Example 21:





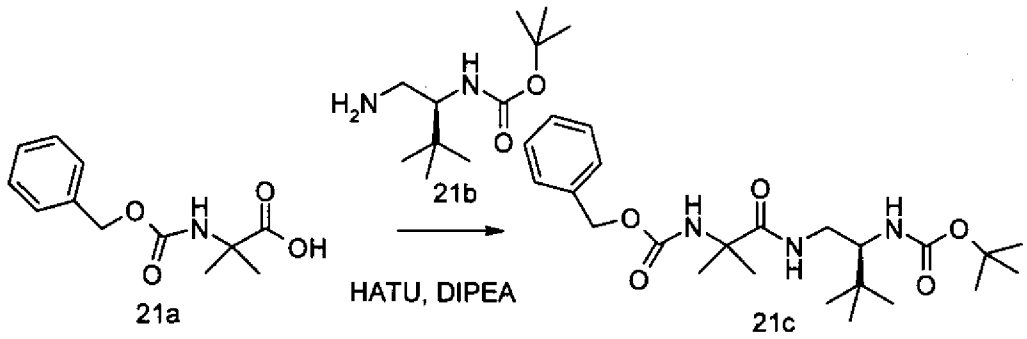
Step 21-A:



21b

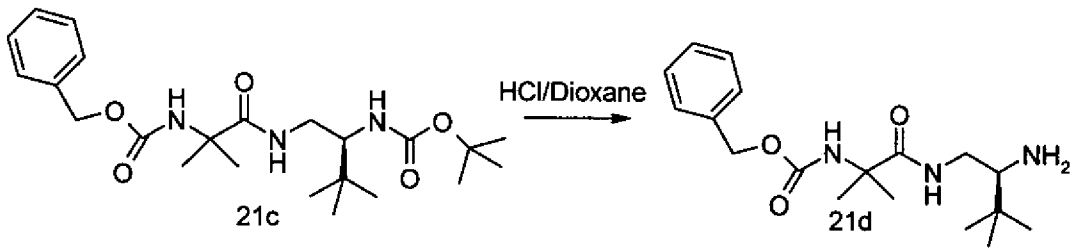
Synthesis of compound **21b** is carried out in a three step sequence following a literature procedure by Busacca, C. A. ; Grossbach, D. Spinelli, E. *Tetrahedron: Asymmetry*, **2000,** 11(9), 1907-1910.

Step 21-B:



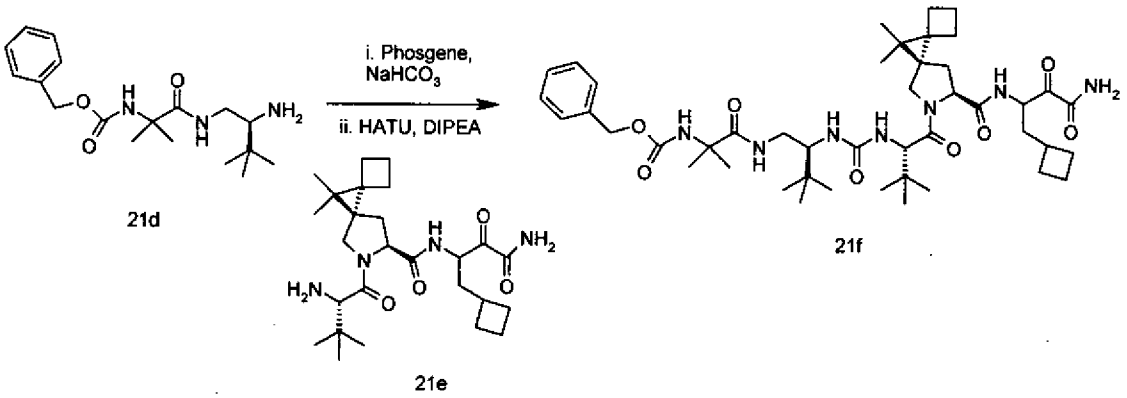
To a solution of N-Carbobenzyloxy-2-methylalanine **21a** (817 mg, 3.44 mmol, 1.2 equiv) and amine **21b** (620 mg, 2.87 mmol, 1.0 equiv) in CH_2Cl_2 (15.0 mL) at 0 °C is added HATU (1.31 g, 3.44 mmol, 1.2 equiv), followed by DIPEA (1.25 mL, 7.16 mmol, 2.5 equiv). The solution is stirred overnight at RT. The reaction mixture is diluted with EtOAc (75 mL) and washed with 1.0 N HCl (2 X 10 mL). The phases were separated and the aqueous layer extracted with EtOAc (2 x 50 mL). The organic layers are combined and washed with saturated aqueous $NaHCO_3$ (50 mL), brine (50 mL), dried over Na_2SO_4 and concentrated. The residue is purified by silica gel column chromatography (hexane/EtOAc, 1/1) to give1g of the product **21c**. ESMS; $[M + H]^+ = 436$.

Step 21-C:



The N-Boc protected amine **21c** (388 mg, 0.89 mmol) is dissolved in HCl (2.5 mL, 4.0 M HCl in dioxane) and the solution stirred at room temperature for 2 hours. The solution is diluted with 50 mL heptane and concentrated to give crude product **21d**, This compound did not require purification and is used directly in the next step. ESMS; $[M + H]^+ = 335$.

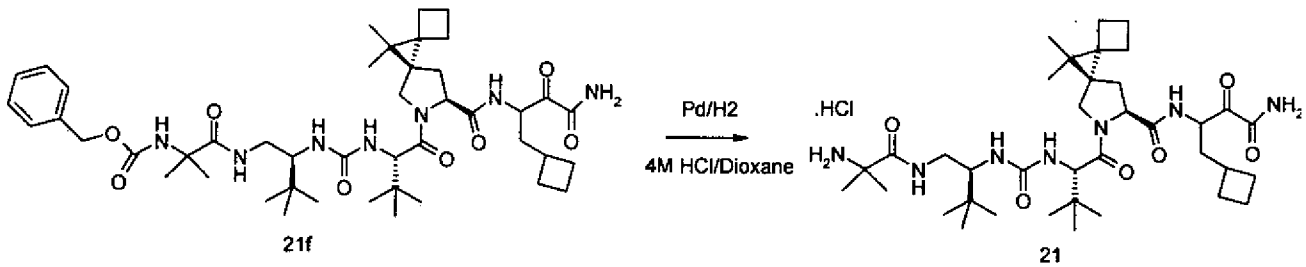
Step 21-D:



Amine **21d** (169 mg, 0.46 mmol) is dissolved in Dichloromethane (2.3 mL) and the solution cooled to 0 °C. Saturated $NaHCO_3$ (2.3 mL) is added and the solution stirred vigorously for 5 min. Stirring is stopped and Phosgene (0.46 mL, 0.92 mmol of 2M solution in Toluene) is added to the lower Dichloromethane layer and vigorous stirring is continued for 1 h at room temperature. The solution is diluted with Dichloromethane (10 mL), the layers separated and the organic layer collected and dried over Na_2SO_4. The solution is then evaporated to dryness and is used directly in the next step.

A solution of the isocyanate of **21d** in CH_2Cl_2 (7 mL) generated above is added to a cooled solution (0 °C) of amine hydrochloride salt **21e** (82 mg, 0.17 mmol) in CH_2Cl_2 (7 mL). DIPEA (0.24 mL) is then added and the solution stirred at room temperature for 2 hours. The solution is then concentrated and the crude material purified by silica gel column chromatography (Acetone: Heptane 40 %-75 % acetone) to give 50 mg of product **21f**. ESMS; $[M + H]^+ = 836$.

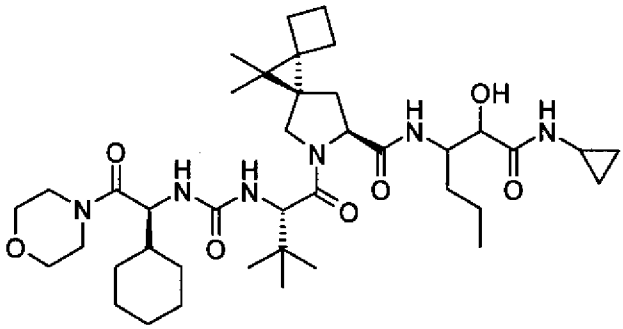
Step 21-E:



Benzyloxycarbamate **21f** (11 mg, 0.013 mmol) is dissolved in EtOAc (3 mL). Air was evacuated and flask purged with N_2. Palladium (10 % on C, 2 mg) is added and the mixture

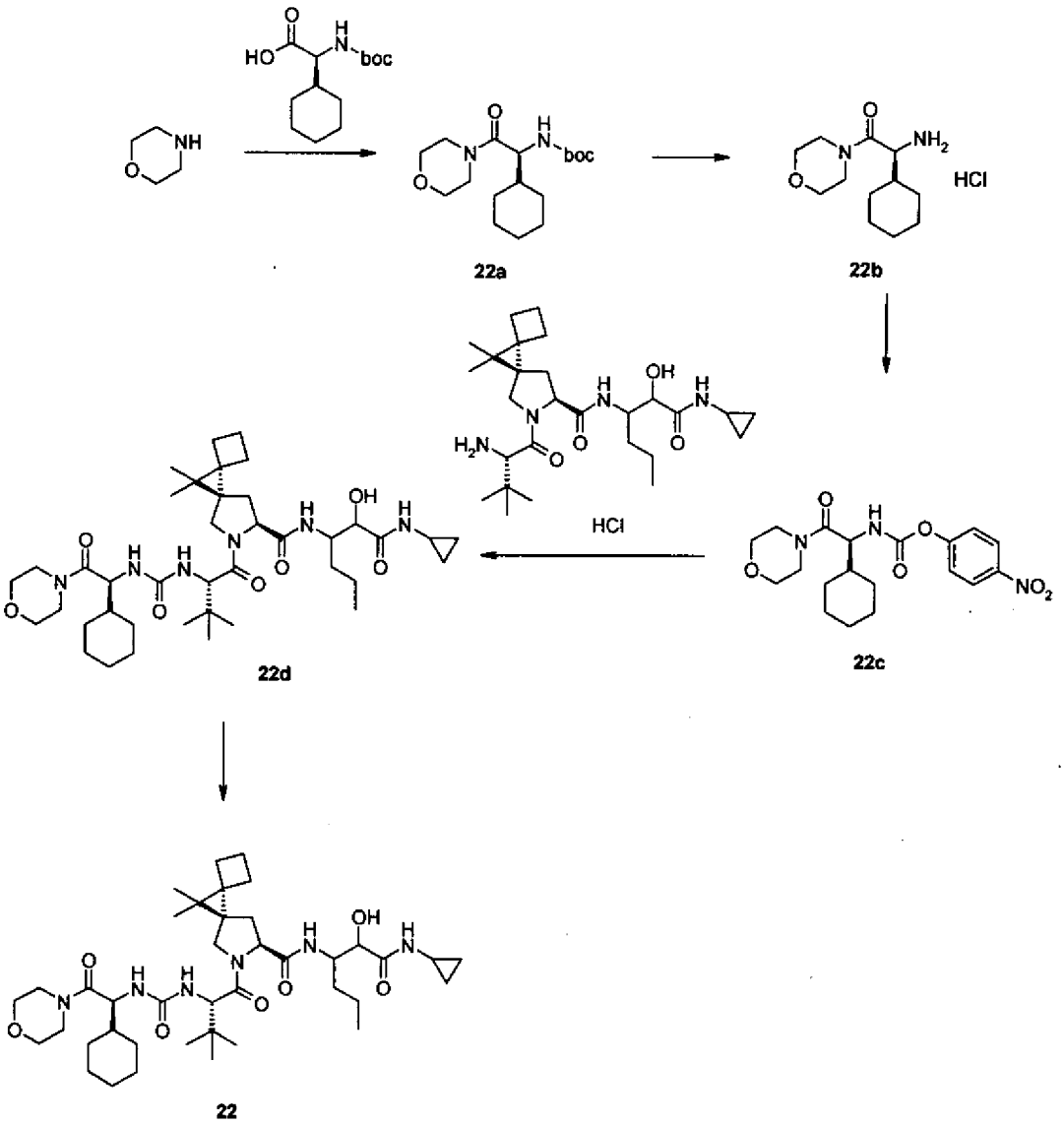
fitted with H_2 balloon. The reaction is allowed to proceed for 5 h and then stopped by filtering the mixture through a celite bed. The filtrate is then concentrated. HCl (4M HCl in Dioxane, 2 mL) is added and the solution stirred for 2 min and then evaporated to dryness. The solid sample is washed with heptane (5 mL) and EtOAc (2 mL) then dissolved in H_2O (3 mL) and lyophilized overnight to afford 7 mg of a white solid **21.** ESMS; $[M + H]^+ = 702$.

Example 22:



22

Scheme:



Step 22-A:

To a solution of Boc-L-cyclohexyl-gly-OH (2.0 g, 7.8 mmol) in CH_2Cl_2 (15.0 mL) at room temperature add HATU (3.5 g, 9.3 mmol, 1.2 equiv), morpholine (0.679 mL, 7.8 mmol, 1.0 equiv) and N-methyl-morpholine (2.6 mL, 23.4 mmol, 3.0 equiv). The solution is stirred at room temperature for 3 hours. The solution is then added EtOAc and sat. aq. $NaHCO_3$. The phases are separated and the organic phase is washed with 1.0 N aq. HCl, and brine. The solution is dried over Na_2SO_4 and concentrated. The residue is purified by silica gel column chromatography, heptane/EtOAc, 1/1 to give product **22a** 1.2 g.

Step 22-B:

The product **22a** is dissolved in 4.0 N HCl in dioxane and the solution is stirred at room temperature for 1 hour. The solution is then concentrated to dryness to give product **22b**.

To a solution of 4-nitrophenyl chloroformate (201 mg, 1.1 mol, 1.0 equiv) in CH_2Cl_2 at room temperature added **22b** (263 mg, 1.0 mmol, 1.0 equiv) and pyridine (0.242 mL, 3.0 mmol, 3.0 equiv). After stirred at room temperature for 1h, the solution is directly loaded to silica gel column and the column is flushed with heptane/EtOAc (1/1 to 100% EtOAc) to give product **22c** 315 mg. Found ES+ = 392.

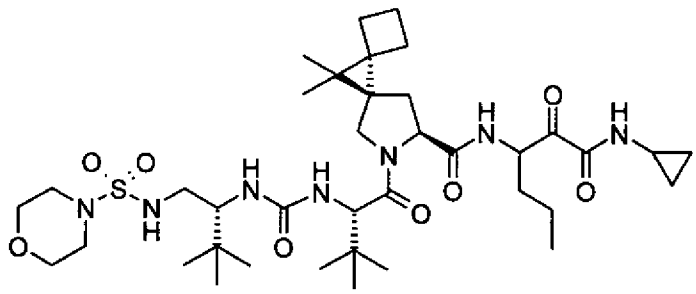
Step 22-C:

To a solution of **22c** (49 mg 0.127 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) added **19c** (67 mg, 0.127 mmol, 1.0 equiv) and TEA (0.042 mL, 0.3 mmol, 3.0 equiv). The solution is stirred at room temperature for 2 hours. The solution is then loaded to silica gel column and the column is flushed with heptane/acetone (1/1) to give product **22d** 80 mg. Found m/z, ES+ = 743

Step 22-D:

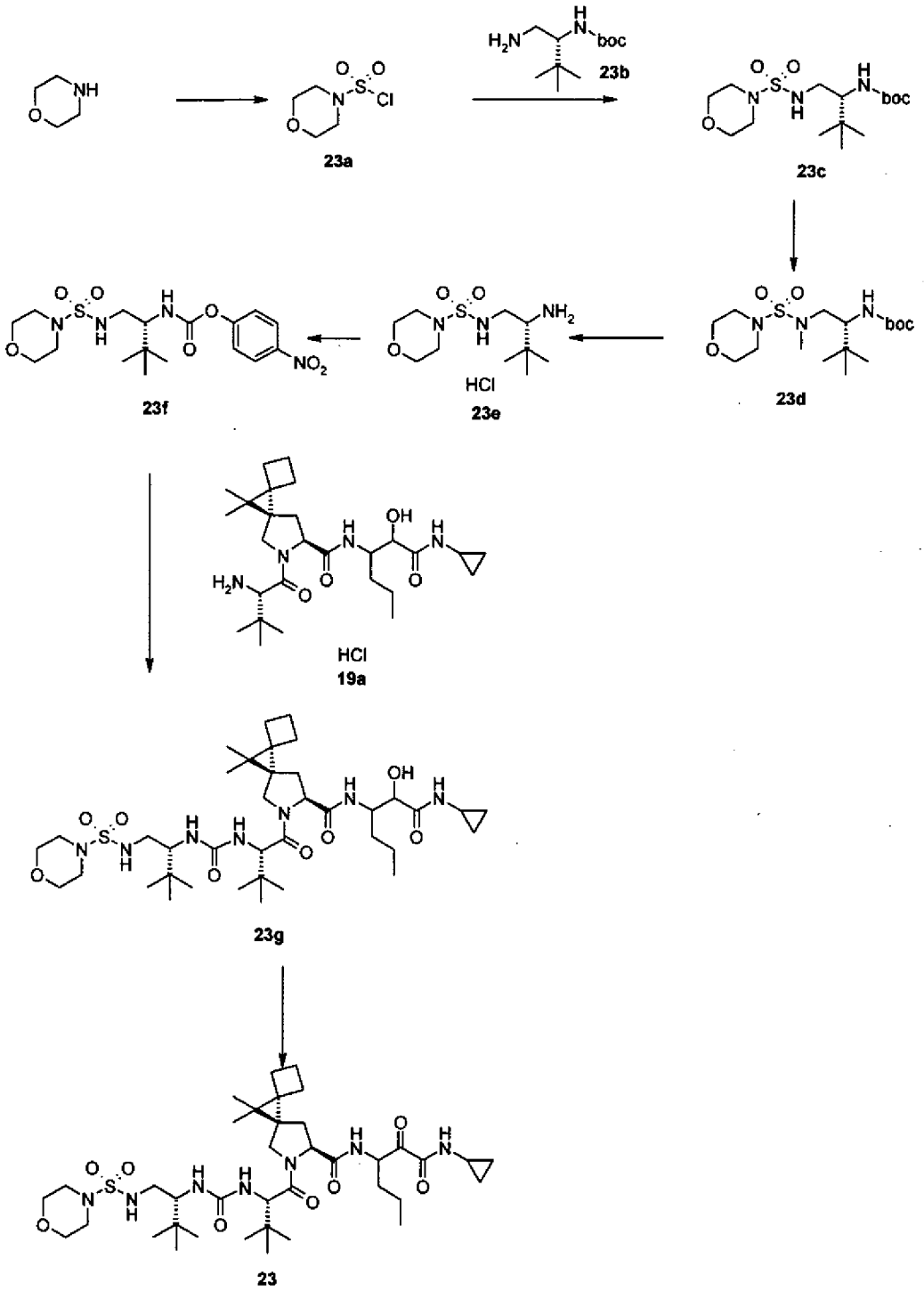
To a solution of **22d** (80 mg, 0.107 mmol) in CH_2Cl_2 (1.0 mL) add DIPEA (0.093 mL, 0.535 mmol, 5.0 equiv) and a solution of $Py{\bullet}SO_3$ (51 mg, 0.323 mmol, 3.0 equiv) in DMSO (0.5 mL). The solution is stirred at room temperature for 10 minutes. The solution is loaded to silica gel column and the column is flushed with heptane/acetone (1/1) to give product **22** 75 mg. Found m/z, ES+ = 741.

Example 23:



23

Scheme:



Step 23-A:

To a solution of sulfuryl chloride (1.62 mL, 20.0 mmol, 1.0 equiv) in $CHCl_3$ (20.0 mL) at 0 °C slowly added a solution of morpholine (1.7 mL, 20.0 mmol, 1.0 equiv) and TEA (2.78 mL) in $CHCl_3$ (5.0 mL) over 1 hour. The solution is stirred at 0 °C for 1 hour then room temperature for 1 hour. The solution is concentrated and then partitioned between ether

and 1.0 N aq. HCl solution. The phases are separated and the organic layer is washed with brine. The organic layer is dried over Na_2SO_4 and concentrated to give product **23a** (2.5 g).

Step 23-B:

To a solution of **23a** (559 mg, 3.0 mmol, 1.0 equiv) in CH_2Cl_2 (10.0 mL) at -20 °C added **23b** (648 mg, 3.0 mmol, 1.0 equiv) and TEA (0.836 mL, 6.0 mmol, 2.0 equiv). The solution is stirred at room temperature for 24 hours and at 40 °C for 4 hours. The solution is loaded to silica gel column and the column is flushed with heptane/EtOAc (1/1) to give product **23c** (760 mg).

Step 23-C:

To a solution of **23c** (760 mg, 2.07 mmol, 1.0 equiv) in DMF (6.0 mL) at 0 °C add Cs_2CO_3 (2.0 g, 6.2 mmol, 3.0 equiv) and MeI (0.154 mL, 2.48 mmol, 1.2 equiv). The solution is stirred at room temperature for 1.0 hours. The solution is filtered and the solvent is evaporated. The residue is purified by silica gel column chromatography, heptane/EtOAc (1/2) to give product **23d** (510 mg).

Step 23-D:

The product **23d** is dissolved in 4.0 N HCl in dioxane and stirred at room temperature for 1 hour. The solution is then concentrated to dryness to give product **23e**.

To a solution of 4-nitrophenyl chloroformate (179 mg, 0.89 mol, 1.0 equiv) in CH_2Cl_2 (4.0 mL) at room temperature added **23e** (270 mg, 0.89 mmol, 1.0 equiv) and pyridine (0.144 mL, 2.0 mmol, 2.0 equiv). The solution is stirred at room temperature for 1 hour. The solution is loaded to silica gel column and the column is flushed with heptane/EtOAc (1/1 to 100% EtOAc) to give product **23f** (210 mg).

Step 23-E:

To a solution of **23f** (63 mg, 0.14 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL) added **19c** (75 mg, 0.14 mmol, 1.0 equiv) and TEA (0.031 mL, 0.42 mmol, 3.0 equiv). The solution is stirred at room temperature for 2 hours. The solution is then loaded to silica gel column and the column is flushed with heptane/acetone (1/1 to 100% acetone) to give product **23g** 101 mg. Found m/z, ES+ = 796.

Step 23-F:

To a solution of **23g** (101 mg) in CH_2Cl_2 (1.0 mL) add DIPEA (0.120 mL) and a solution of $Py{\bullet}SO_3$ (70 mg) in DMSO (0.5 mL). The solution is stirred at room temperature for 10 minutes. The solution is loaded to silica gel column and the column is flushed with heptane/acetone (1/1) to give product **22** 71 mg. Found m/z, ES+ = 794.

BIOLOGICAL ACTIVITY

Example 24: HCV NS3-4A protease assay

The inhibitory activity of certain compounds of Table A against HCV NS3-4A serine protease is determined in a homogenous assay using the full-length NS3-4A protein (genotype 1a, strain HCV-1) and a commercially available internally-quenched fluorogenic peptide substrate as described by Taliani, M., et al. 1996 Anal. Biochem. 240:60-67, which is incorporated by reference in its entirety.

Example 25: Luciferase-based HCV replicon assay

The antiviral activity and cytotoxicity of certain compounds of Table A is determined using a subgenomic genotype 1b HCV replicon cell line (Huh-Luc/neo-ET) containing a luciferase reporter gene, the expression of which is under the control of HCV RNA replication and translation. Briefly, 5,000 replicon cells are seeded in each well of 96-well tissue culture plates and are allowed to attach in complete culture media without G418 overnight. On the next day, the culture media are replaced with media containing a serially diluted compound of Table A in the presence of 10% FBS and 0.5% DMSO. After a 48-h treatment with the compound of Table A, the remaining luciferase activities in the cells are determined using BriteLite reagent (Perkin Elmer, Wellesley, Massachusetts) with a LMaxII plate reader (Molecular Probe, Invitrogen). Each data point represents the average of four replicates in cell culture. IC_{50} is the concentration of the at which the luciferase activity in the replicon cells is reduced by 50%. The cytotoxicity of the compound of Table A is evaluated using an MTS-based cell viability assay.

Compounds in Table A *supra* have been tested in at least one of the protease assay of Example 24 or the replicon assay of Example 25 and exhibit an IC_{50} of less than about 10 μM or less in at least one of the assays recited in Example 24 and 25.

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments and methods described herein. Such equivalents are intended to be encompassed by the scope of the following claims.

Incorporation by Reference

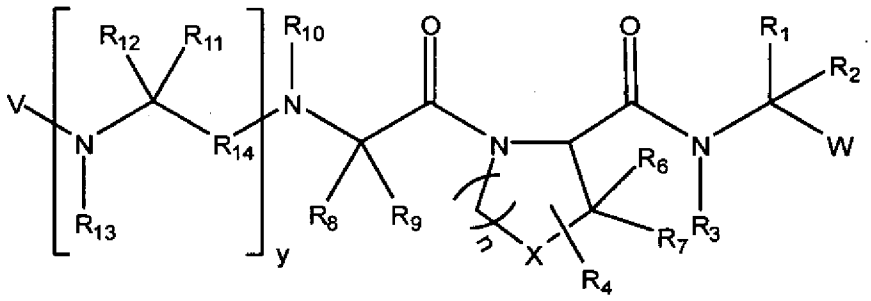
The entire contents of all patents, published patent applications and other references cited herein are hereby expressly incorporated herein in their entireties by reference. The

entire contents of copending provisional patent applications U.S.S.N. 60/791,611, U.S.S.N. 60/791,578, and U.S.S.N. 60/791,320, each of which was filed on April 11, 2006, and non-provisional patent applications claiming the benefit therefrom are expressly incorporated herein, in their entirety, as applied to the compounds of the present invention.

CLAIMS

What is claimed is:

1. A compound of the Formula I:



I

and pharmaceutically acceptable salts and stereoisomers thereof;

wherein

y is 0 or 1;

n and p are each independently selected from 0, 1 or 2;

R^{14} is C(O) or SO_2;

R^1, R^2, W, R^{13} and V are each, independently, selected from hydrogen or from the group consisting of alkyl, alkyl-aryl, heteroalkyl, heterocyclyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyloxy, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocyclyloxy, cycloalkyloxy, amino, alkylamino, arylamino, alkyl-arylamino, arylamino, heteroarylamino, cycloalkylamino, carboxyalkylamino, mono- and di-alkylcarboxamide, aralkyloxy and heterocyclylamino; each of which may be further independently substituted one or more times with X^1 and X^2; wherein X^1 is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, aralkyl, aryloxy, arylthio, arylheteroaryl, heteroaryl, heterocyclylamino, alkylheteroaryl, or heteroaralkyl; wherein X^1 can be independently substituted with one or more X^2 moieties which can be the same or different and are independently selected; wherein X^2 is hydroxy, oxo, alkyl, cycloalkyl, spirocycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, aryloxy, thio, alkylthio, amino, mono- and di-alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyl, alkoxycarbonyloxy, alkylureido, arylureido, halogen, cyano, or nitro; wherein each X_2 residue selected to be alkyl, alkoxy, and aryl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different and are

independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, aralkyl, arylheteroaryl, heteroaryl, heterocyclylamino, alkylheteroaryl and heteroaralkyl;

W is also selected from the group consisting of C(O)-C(O)H, C(=N-O-R_{24})-C(O)-amine, C(O)-C(O)-amine, C(O)$NR_{24}S(O)_pR_{24}$, C(O)$NR_{24}S(O)_pN(R_{24})_2$ and C(O)-$[C(O)]_a$-heterocycle, wherein the heterocycle may be independently substituted one or more times with aryl, C_{1-4}-alkyl, C_{1-4}-alkyl substituted by one or more halogen atoms, and C_{3-6}-cycloalkyl, wherein a is 0 or 1, wherein each R_{24} is independently selected from hydrogen or the group consisting of C_{1-4}-alkyl, C_{3-6}-cycloalkylC_{0-4}alkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocycle, each of which may be independently substituted one or more times with a halogen atom or C_{1-4}-alkyl;

V is also selected from the group consisting of $-Q^1-Q^2$, wherein Q^1 is absent, C(O), N(H), N(C_{1-4}-alkyl), C=N(CN), C=N(SO_2CH_3), C=N-COH-C_{1-4}-alkyl, or C=N-COH, and Q^2 is hydrogen or is selected from the group consisting of C_{1-4}-alkyl, O-C_{1-4}-alkyl, NH_2, N(H)-C_{1-4}-alkyl, N(C_{1-4}-alkyl)$_2$, SO_2-aryl, SO_2-C_{1-4}-alkyl, C_{3-6}-cycloalkyl-C_{0-4}-alkyl, aryl, heteroaryl and heterocycle, each of which may be independently substituted one or more times with a halogen atom, C_{1-4}-alkyl, C_{1-4}-alkyl substituted by one or more halogen atoms, or C_{3-6}-cycloalkyl;

or R^1 and R^2 may together form a 3, 4, 5, 6 or 7-membered ring that is aromatic or non-aromatic and may contain one or more heteroatoms, wherein the ring may be further substituted one or more times;

R^3 is selected from the group consisting of hydrogen, C_{1-4}-alkyl and C_{3-6}cycloalkylC_{0-4}alkyl;

X is O, S, N, NR^5, CR^5 or CR^5R^{5a};

R^4 represents 0-4 substituents, each of which is independently selected from hydrogen or from the group consisting of C_{1-4}-alkyl, C_{3-6}-cycloalkyl, aryl, heterocycle and heteroaryl, each of which may be independently substituted one or more times with a halogen atom or C_{1-4}-alkyl;

R^5 is selected from hydrogen or oxo or from the group consisting of hydroxyl, C_{1-8}-alkyl, C_{2-8}-alkenyl, C_{2-8}-alkynyl, C_{3-8}-cycloalkyl-C_{0-4}-alkyl, aryl-C_{0-4}-alkyl, heterocycle-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl , C_{3-8}-cycloalkyloxy, aryloxy, and heteroaryloxy each of which may be independently substituted one or more times with a halogen atom, aryl, trihalomethyl, or C_{1-4}-alkyl;

R^{5a} is hydrogen or is selected from the group consisting of hydroxyl, C_{1-8}-alkyl, C_{2-8}-

alkenyl, C_{2-8}-alkynyl, C_{3-8}-cycloalkyl-C_{0-4}-alkyl, aryl-C_{0-4}-alkyl and heteroaryl-C_{0-4}-alkyl,

or R^4 and R^5 may together form a fused dimethyl cyclopropyl ring, a fused cyclopentane ring, a fused phenyl ring or a fused pyridyl ring, each of which may be substituted with a halogen atom, aryl, trihalomethyl, or C_{1-4}-alkyl;

or R^5 and R^6 may together form a fused dimethyl cyclopropyl ring, a fused cyclopentane ring, a fused phenyl ring or a fused pyridyl ring, each of which may be substituted with a halogen atom, aryl, trihalomethyl, or C_{1-4}-alkyl;

or R^5 and R^{5a} may together form a spirocyclic ring having between 3 and 7 ring atoms and having 0, 1, or 2 ring heteroatoms, which is optionally substituted by 0-4 substituents selected from cyano, halogen, hydroxyl, amino, thiol, C_{1-8}-alkyl, C_{2-8}-alkenyl, C_{2-8}-alkynyl, C_{1-8}-alkoxy-C_{0-4}alkyl, C_{1-8}-haloalkyl, C_{2-8}-haloalkenyl, C_{2-8}-haloalkynyl, C_{1-8}-haloalkoxy, C_{1-8}-alkylthio, C_{1-8}-alkylsulfonyl, C_{1-8}-alkylsulfoxy, C_{1-8}-alkanoyl, C_{1-8}-alkoxycarbonyl, C_{3-7}-cycloalkyl-C_{0-4}-alkyl, aryl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, COOH, $C(O)NH_2$, mono- and di-C_{1-4}-alkyl-carboxamide, mono- and di-C_{1-4}-alkyl-amino-C_{0-4}alkyl, SO_3H, SO_2NH_2, and mono-and di-C_{1-4}-alkylsulfonamide, or two of said 0-4 substitutents taken together form a fused or spirocyclic 3 to 7 membered ring having 0, 1 or 2 ring heteroatoms selected from N, O and S, which fused or spirocyclic ring has 0 to 2 independently selected substituents selected from cyano, halogen, hydroxyl, amino, thiol, C_{1-8}-alkyl, C_{2-8}-alkenyl, C_{2-8}-alkynyl, C_{1-8}-alkoxy-C_{0-4}alkyl, C_{1-8}-haloalkyl, C_{2-8}-haloalkenyl, C_{2-8}-haloalkynyl, C_{1-8}-haloalkoxy, C_{1-8}-alkylthio, C_{1-8}-alkylsulfonyl, C_{1-8}-alkylsulfoxy, C_{1-8}-alkanoyl, C_{1-8}-alkoxycarbonyl, C_{3-7}-cycloalkyl-C_{0-4}-alkyl, aryl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, COOH, $C(O)NH_2$, mono- and di-C_{1-4}-alkyl-carboxamide, mono- and di-C_{1-4}-alkyl-amino-C_{0-4}alkyl, SO_3H, SO_2NH_2, and mono-and di-C_{1-4}-alkylsulfonamide;

R^6 and R^7 are each, independently, selected from the group consisting of hydrogen, hydroxy, amino, C_{1-4}alkyl, C_{1-4}alkoxy, and mono- and di-C_{1-4}alkylamino, and C_{3-6}cycloalkylC_{0-4}alkyl;

R^8, R^9, R^{10}, R^{11} and R^{12} are each, independently, selected from the group consisting of hydrogen, C_{1-4}-alkyl and C_{3-6}cycloalkylC_{0-4}alkyl;

or R^6 and R^7 may together form a spirocyclic ring having between 3 and 7 ring atoms and having 0, 1, or 2 ring heteroatoms, which is optionally substituted by 0-4 substituents selected from cyano, halogen, hydroxyl, amino, thiol, C_{1-8}-alkyl, C_{2-8}-alkenyl, C_{2-8}-alkynyl, C_{1-8}-alkoxy-C_{0-4}alkyl, C_{1-8}-haloalkyl, C_{2-8}-haloalkenyl, C_{2-8}-haloalkynyl, C_{1-8}-haloalkoxy, C_{1-8}-alkylthio, C_{1-8}-alkylsulfonyl, C_{1-8}-alkylsulfoxy, C_{1-8}-alkanoyl, C_{1-8}-alkoxycarbonyl, C_{3-7}-cycloalkyl-C_{0-4}-alkyl, aryl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, COOH, $C(O)NH_2$, mono- and di-

C_{1-4}-alkyl-carboxamide, mono- and di-C_{1-4}-alkyl-amino-C_{0-4}alkyl, SO_3H, SO_2NH_2, and mono-and di-C_{1-4}-alkylsulfonamide, or two substituents taken together form a fused or spirocyclic 3 to 7 membered ring having 0, 1 or 2 ring heteroatoms selected from N, O and S, which fused or spirocyclic ring has 0 to 2 independently selected substituents selected from halogen, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, mono- and di-C_{1-4}-alkylamino, mono- and di-C_{1-4}-alkyl-carboxamide, C_{1-4}-alkoxycarbonyl, and phenyl;

or R^3 and W may together form a 3, 4, 5, 6 or 7-membered ring that is aromatic or non-aromatic and may contain one or more heteroatoms, wherein the ring may be further substituted one or more times; and

or when y is 0, R^{10} and V may together form a 3, 4, 5, 6 or 7-membered ring that is aromatic or non-aromatic and may contain one or more heteroatoms, wherein the ring may be further substituted one or more times.

2. The compound of claim 1,

wherein

y is 0 or 1;

n is 0 or 1;

R^{14} is C(O) or SO_2

R^1 is selected from the group consisting of H and C_{1-4}-alkyl;

R^2 is selected from the group consisting of C_{1-4}-alkyl, $C(O)C_{1-4}$-alkyl, $C(O)OC_{1-4}$-alkyl, and C_{3-6}cycloalkylC_{0-4}alkyl;

or R^1 and R^2 together form a cyclopropane ring;

W is also selected from the group consisting of C(O)-C(O)H, C(=N-O-R_{24})-C(O)-amine, C(O)-C(O)-amine, $C(O)NR_{24}S(O)_pR_{24}$, $C(O)NR_{24}S(O)_pN(R_{24})_2$ and C(O)-$[C(O)]_a$-heterocycle, wherein the heterocycle may be independently substituted one or more times with aryl, C_{1-4}-alkyl, C_{1-4}-alkyl substituted by one or more halogen atoms, and C_{3-6}-cycloalkyl, wherein a is 0 or 1, wherein each R_{24} is independently selected from hydrogen or from the group consisting of C_{1-4}-alkyl, C_{3-6}cycloalkylC_{0-4}alkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocycle, each of which may be independently substituted one or more times with a halogen atom or C_{1-4}-alkyl;

p is 0, 1 or 2;

R^3 is selected from the group consisting of H and C_{1-4}-alkyl;

X is O, NR^5 or CR^5R^{5a};

R^4 is selected from hydrogen or from the group consisting of C_{1-4}-alkyl, C_{3-6}-

cycloalkyl, aryl, heterocycle and heteroaryl, each of which may be independently substituted one or more times with a halogen atom or C_{1-4}-alkyl;

R^5 is selected from hydrogen or oxo or from the group consisting of hydroxyl, C_{1-8}-alkyl, C_{2-8}-alkenyl, C_{2-8}-alkynyl, C_{3-8}-cycloalkyl-C_{0-4}-alkyl, aryl-C_{0-4}-alkyl, heterocycle-C_{0-4}-alkyl and heteroaryl-C_{0-4}-alkyl, each of which may be independently substituted one or more times with a halogen atom, aryl, trihalomethyl, or C_{1-4}-alkyl;

R^{5a} is selected from hydrogen or from the group consisting of hydroxyl, C_{1-8}-alkyl, C_{2-8}-alkenyl, C_{2-8}-alkynyl, C_{3-8}-cycloalkyl-C_{0-4}-alkyl, aryl-C_{0-4}-alkyl and heteroaryl-C_{0-4}-alkyl,

or R^4 and R^5 may together form a fused dimethyl cyclopropyl ring, a fused cyclopentane ring, a fused phenyl ring or a fused pyridyl ring, each of which may be substituted with a halogen atom, aryl, trihalomethyl, or C_{1-4}-alkyl;

or R^5 and R^{5a} may together form a spirocyclic ring having between 3 and 7 ring atoms and having 0, 1, or 2 ring heteroatoms, which is optionally substituted by 0-4 substituents selected from cyano, halogen, hydroxyl, amino, thiol, C_{1-8}-alkyl, C_{2-8}-alkenyl, C_{2-8}-alkynyl, C_{1-8}-alkoxy-C_{0-4}alkyl, C_{1-8}-haloalkyl, C_{2-8}-haloalkenyl, C_{2-8}-haloalkynyl, C_{1-8}-haloalkoxy, C_{1-8}-alkylthio, C_{1-8}-alkylsulfonyl, C_{1-8}-alkylsulfoxy, C_{1-8}-alkanoyl, C_{1-8}-alkoxycarbonyl, C_{3-7}-cycloalkyl-C_{0-4}-alkyl, aryl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, COOH, $C(O)NH_2$, mono- and di-C_{1-4}-alkyl-carboxamide, mono- and di-C_{1-4}-alkyl-amino-C_{0-4}alkyl, SO_3H, SO_2NH_2, and mono-and di-C_{1-4}-alkylsulfonamide, or two substituents taken together form a fused or spirocyclic 3 to 7 membered ring having 0, 1 or 2 ring heteroatoms selected from N, O and S, which fused or spirocyclic ring has 0 to 2 independently selected substituents selected from halogen, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, mono- and di-C_{1-4}-alkylamino, mono- and di-C_{1-4}-alkyl-carboxamide, C_{1-4}-alkoxycarbonyl, and phenyl;

R^8, R^{10} and R^{11} are each, independently, selected from the group consisting of H and C_{1-4}-alkyl;

R^6 and R^7 are each, independently, selected from the group consisting of hydrogen, hydroxy, amino, C_{1-4}alkyl, C_{1-4}alkoxy, and mono- and di-C_{1-4}alkylamino;

R^{13} is H;

R^9 and R^{12} are each, independently, selected from the group consisting of hydrogen, C_{1-4}-alkyl and C_{3-6}-cycloalkyl; and

V is also selected from the group consisting of $-Q^1$-Q^2, wherein Q^1 is absent, C(O), N(H), N(C_{1-4}-alkyl), C=N(CN), C=N(SO_2CH_3), C=N-COH-C_{1-4}-alkyl, or C=N-COH, and Q^2 is hydrogen or is selected from the group consisting of C_{1-4}-alkyl, O-C_{1-4}-alkyl, NH_2, N(H)-C_{1-4}-alkyl, N(C_{1-4}-alkyl)$_2$, SO_2-aryl, SO_2-C_{1-4}-alkyl, C_{3-6}-cycloalkyl-C_{0-4}-alkyl, aryl,

heteroaryl and heterocycle, each of which may be independently substituted one or more times with a halogen atom, C_{1-4}-alkyl, C_{1-4}-alkyl substituted by one or more halogen atoms, or C_{3-6}-cycloalkyl;

or R^3 and W can together form a 6-membered ring of the formula II:



II

wherein formula II may be further substituted;

or when y is 0, R^{10} and V can form a cyclopropyl ring that may be further substituted by an amide group.

3. The compound of claim 1, wherein R^{14} is C(O).

4. The compound of claim 1, wherein y is 0, and R^{10} and V form a cyclopropyl ring that is substituted with C(O)N(H)-pyrazine.

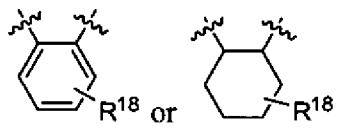
5. The compound of claim 1, wherein R^4, R^6 and R^7 are hydrogen, and R^5 is arylC_{0-3}alkyl, heteroaryloxy, or heteroarylC_{0-3}alkyl, wherein aryl and heteroaryl may be independently substituted one or more times with a halogen atom, aryl, trihalomethyl, C_{3-6}-cycloalkyl or C_{1-4}-alkyl.

6. The compound of claim 1, wherein R^1 and R^2, are independently selected from hydrogen or from the group consisting of C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{3-6}cycloalkylC_{0-4}alkyl, C_{3-6}cycloalkenylC_{0-4}alkyl, C_{1-4}alkoxyC_{0-4}alkyl, and heterocycloalkylC_{0-4}alkyl, each of which is unsubstituted or substituted with one or more groups selected from fluoro, chloro, hydroxy, C_{1-2}alkylS, C_{1-2}alkylS(O), and C_{1-2}alkylS$(O)_2$, and wherein the heterocycloalkyl is a 3 to 6 membered ring having one or two N, O or S ring atoms.

7. The compound of claim 1, wherein R_1 is hydrogen and R_2 is selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, allyl, propargyl, 3-fluoro-n-propyl, n-butyl, n-pentyl, iso-propyl, sec-butyl, iso-butyl, 3-methyl-n-butyl, 3,3,3-trifluoro-n-propyl, 2,2-difluoroethyl, trifluoromethyl, 1,1-difluoro-n-propyl, 2,2,2-trifluoroethyl, 2,2-difluoro-n-but-3-enyl, 4-pentenyl, 3,3-difluoro-allyl, 2-methyl-allyl, 3-butenyl, 2-cyanoethyl, 3,3-difluoropropyl, 2,2-difluoro-3-butenyl, 2,2-difluoro-n-propyl, 4,4,4-trifluorobutyl, C_{3-6}cycloalkyl, oxetan-2-ylmethyl, thietan-2-ylmethyl, 3-fluorocyclobutylmethyl, 3-

hydroxycyclobutylmethyl, 3-butynyl, methoxymethyl, 2-methoxyethyl, methyl-$S(O)_{0-2}C_{1-2}$alkyl, 3,3-difluorocyclobutylmethyl, oxetan-3-ylmethyl, C_{3-6}cycloalkylmethyl, 1-methylcyclopropylmethyl, C_{3-6}cycloalkyl-difluoromethyl, C_{3-6}cycloalkylethyl, thietan-3-ylmethyl, 1-fluorocyclobutylmethyl, 1-fluorocyclopropylmethyl, 2,2-difluorocyclopropylmethyl, and cyclopenten-2-ylmethyl.

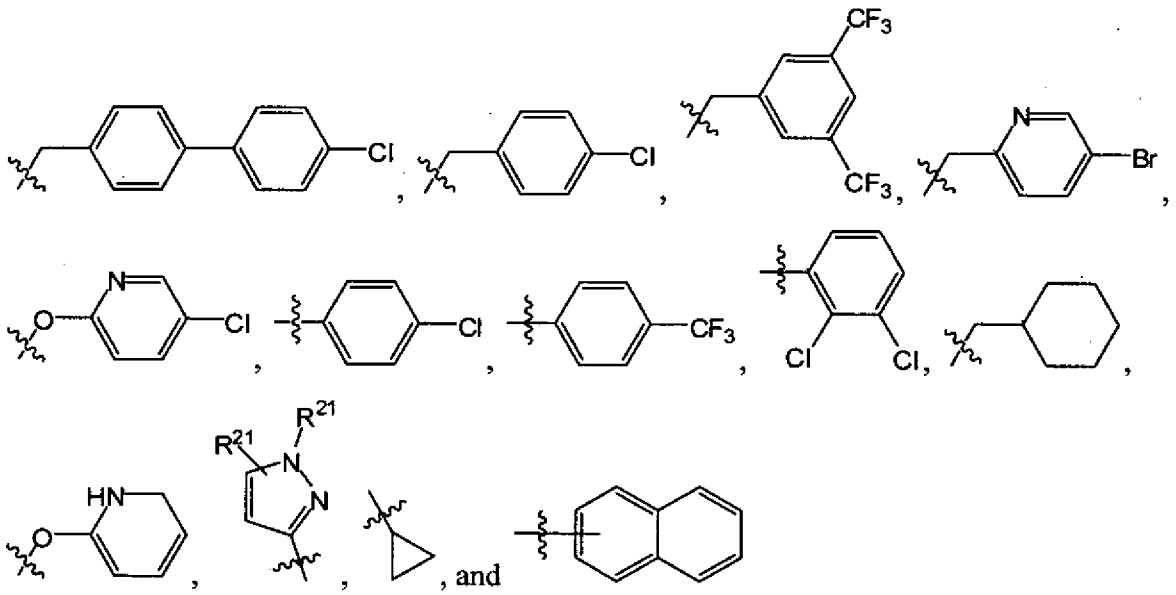
8. The compound of claim 1, wherein n is 1, and R^4 and R^5 together form a fused ring system selected from:



wherein R^{18} is selected from the group consisting of hydrogen, a halogen atom, aryl, trihalomethyl, and C_{1-4}-alkyl.

9. The compound of claim 1, wherein X is CR^5R^{5a}, R^{5a} is hydrogen, and R^5 is selected from the group consisting of piperidine, phenyl, pyridinyl, pyridinyloxy and pyridinylmethyl, wherein the phenyl and pyridinyl groups may be independently substituted one or more times with a halogen atom or C_{1-4}-alkyl.

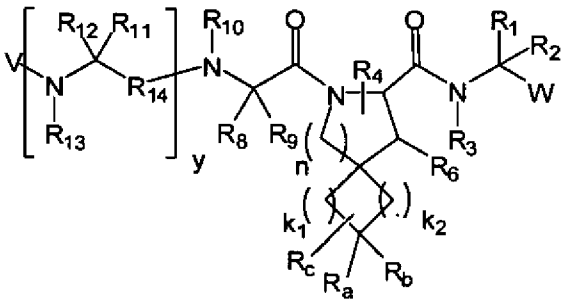
10. The compound of claim 9, wherein X is CR^5R^{5a}, R^{5a} is hydrogen, and R^5 is selected from the group consisting of



wherein R^{21} is independently selected from the group consisting of C_{1-4}-alkyl and aryl.

11. The compound of claim 1, wherein X is CR^5R^{5a}, R^4 is hydrogen, and R^5 and R^{5a} taken in combination form a 3 to 6 member spirocyclic carbocycle substituted with 0-2 substituents selected from halogen, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{1-6}-alkoxy, C_{3-7}-cycloalkyl-C_{0-4}-alkyl, phenyl-C_{0-4}-alkyl, naphthyl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, or two substituents taken together form a fused or spirocyclic 3 to 7 membered carbocyclic ring, each of which is substituted with 0-3 independently selected halogen atoms or C_{1-4}-alkyl groups.

12. A compound of claim 1 according to the formula:



wherein

k_1 and k_2 are 0 or 1 such that a sum of k_1 and k_2 equals 1 or 2;

R_a is hydrogen, C_{1-4}alkyl, or phenyl;

R_b is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy-C_{0-4}alkyl, mono- and di-C_{1-4}alkylaminoC_{0-4}alkyl, mono- and di-C_{1-4}alkyl carboxamide, C_{1-4}alkanoyl, C_{1-4}alkoxycarbonyl, or phenyl;

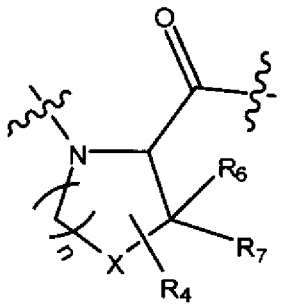
or R_a and R_b, taken together, form a spirocyclic 3 to 6 membered ring having 0, 1 or 2 ring heteroatoms selected from N, O and S, which fused or spirocyclic ring has 0 to 2 independently selected substituents selected from halogen, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, and phenyl;

R_c represents 0 to 4 substituents which are independently selected at each occurrence of R_c from the group consisting of halogen, C_{1-4}alkyl, and phenyl, or two *geminal* R_c substituents, taken in combination form a 3 to 6 member spirocyclic ring;

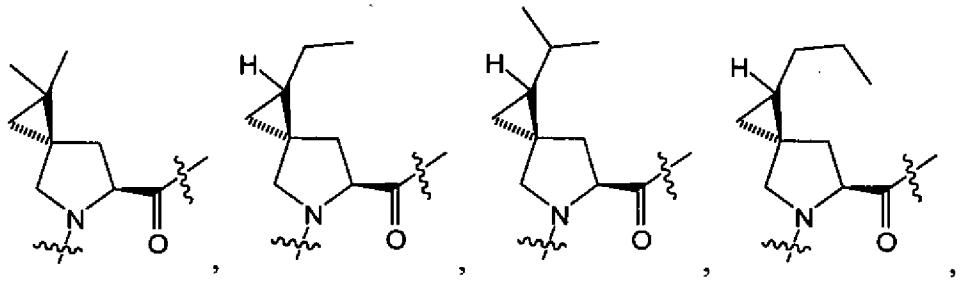
R_4 represents 0, 1, or 2 substituents each of which is independently selected from H and C_{1-4}-alkyl; and

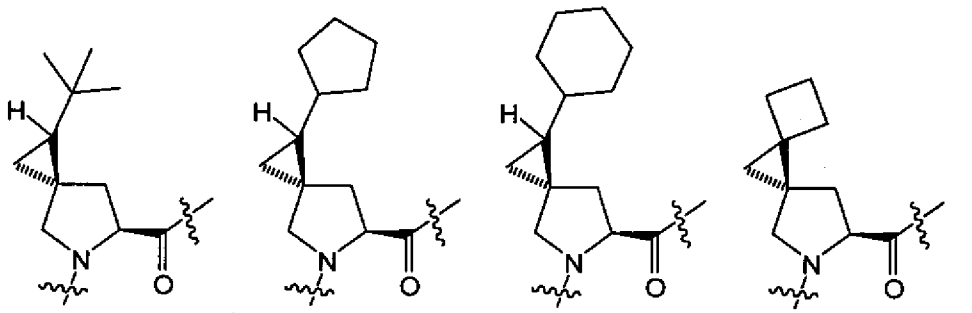
R_6 is hydrogen or C_{1-4}alkyl.

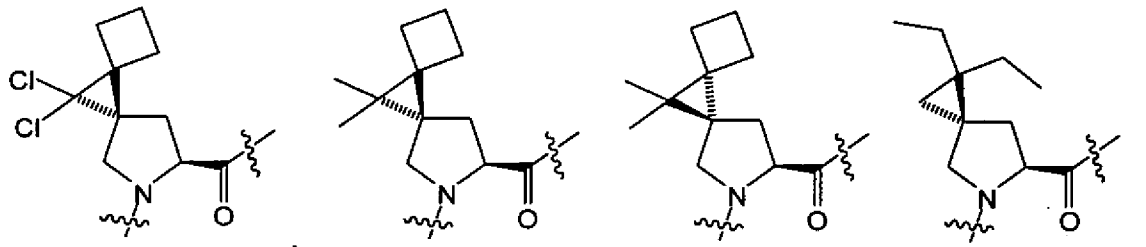
13. The compound of claim 1, wherein the divalent residue:

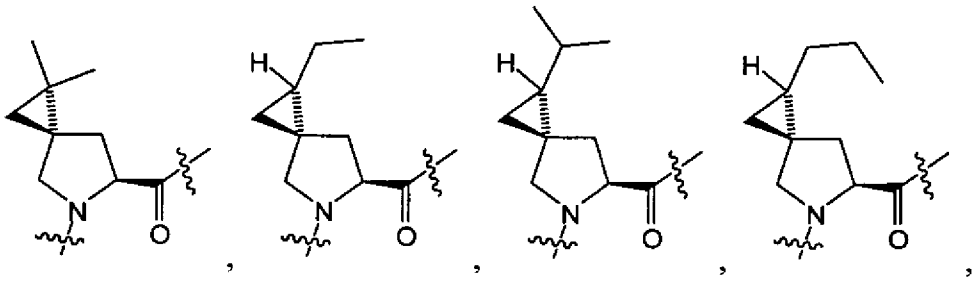


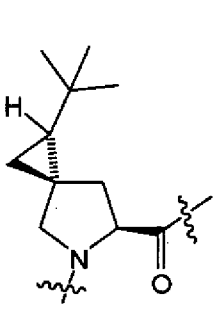
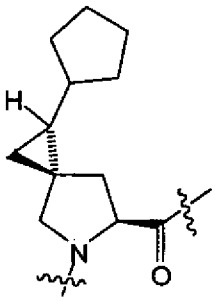
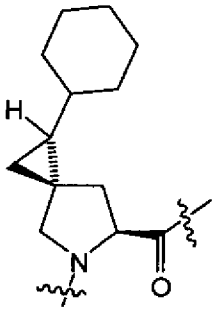
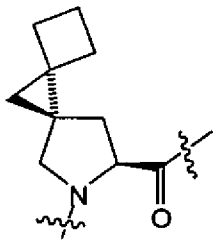
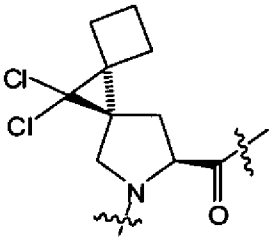
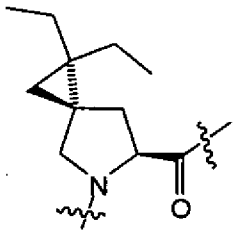
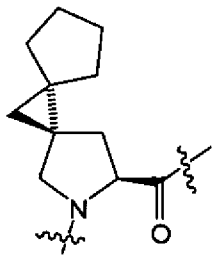
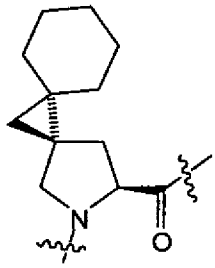
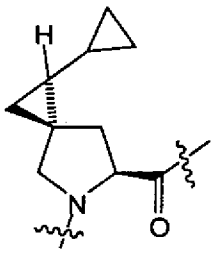
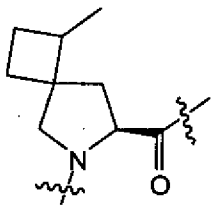
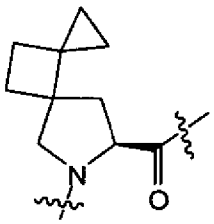
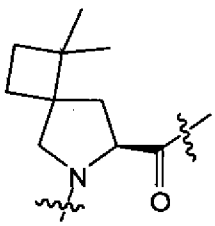
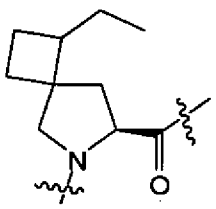
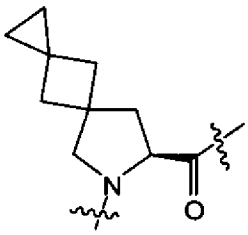
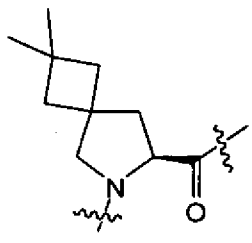
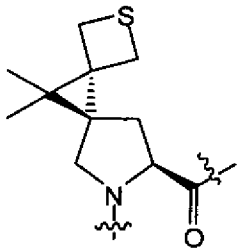
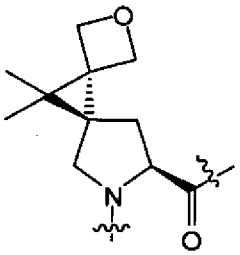
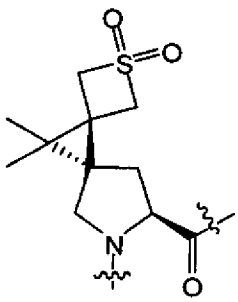
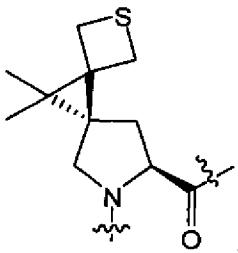
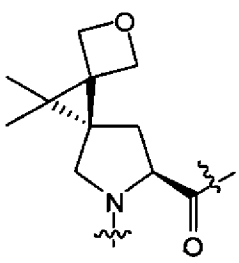
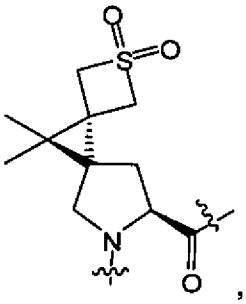
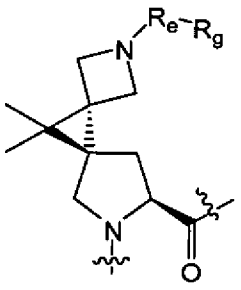
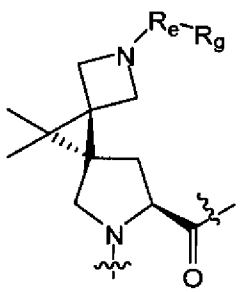
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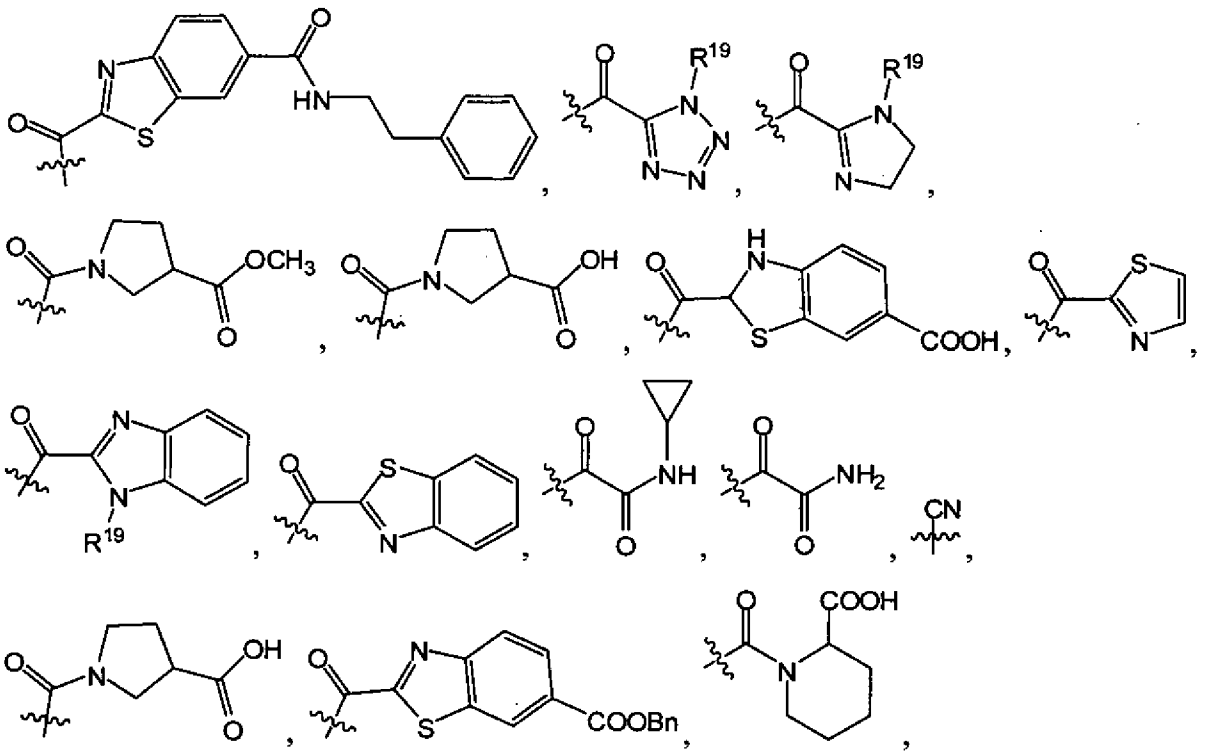


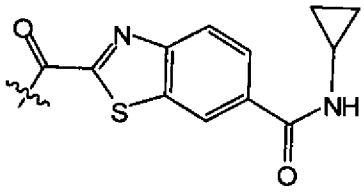
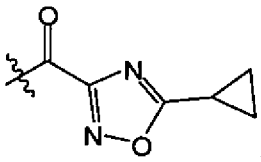
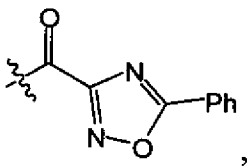
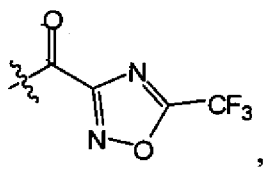
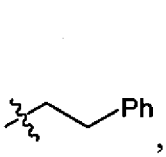
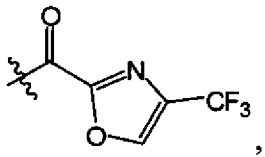
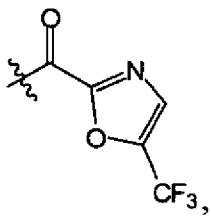
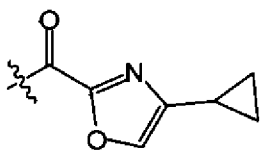
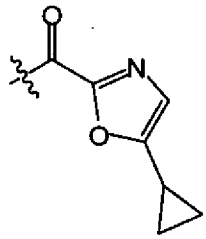
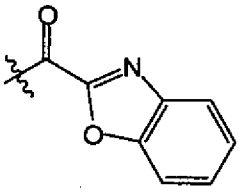

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wherein R_e is absent, C(O), or $S(O)_2$; and R_g is selected hydrogen or selected from the group consisting of C_{1-6}alkyl, arylC_{0-4}alkyl, heteroarylC_{0-4}alkyl, heterocyclylC_{0-4}alkyl, and C_{3-7}cycloalkylC_{0-4}alkyl, each of which is substituted with 0 to 4 independently selected substituents selected from the group consisting of cyano, halogen, hydroxyl, amino, thiol, C_{1-8}-alkyl, C_{2-8}-alkenyl, C_{2-8}-alkynyl, C_{1-8}-alkoxy-C_{0-4}alkyl, C_{1-8}-haloalkyl, C_{2-8}-haloalkenyl, C_{2-8}-haloalkynyl, C_{1-8}-haloalkoxy, C_{1-8}-alkylthio, C_{1-8}-alkylsulfonyl, C_{1-8}-alkylsulfoxy, C_{1-8}-alkanoyl, C_{1-8}-alkoxycarbonyl, C_{3-7}-cycloalkyl-C_{0-4}-alkyl, aryl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, COOH, $C(O)NH_2$, mono- and di-C_{1-4}-alkyl-carboxamide, mono- and di-C_{1-4}-alkyl-amino-C_{0-4}alkyl, SO_3H, SO_2NH_2, and mono-and di-C_{1-4}-alkylsulfonamide.

14. The compound of claim 1, wherein W is selected from the group consisting of $C(O)$-$C(O)NH_2$, C(O)-C(O)N(H)-cyclopropyl, C(O)-benzothiazole, C(O)-benzoimidazole, C(O)-oxazole, C(O)-imidazole, and C(O)-oxadiazole, wherein the benzothiazole, benzoimidazole, oxazole and oxadiazole groups may be independently substituted one or more times with a halogen atom, aryl, trihalomethyl, C_{3-6}-cycloalkyl or C_{1-4}-alkyl.

15. The compound of claim 14, wherein W is selected from the group consisting of

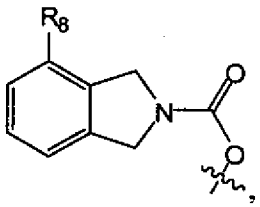
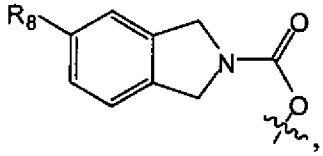
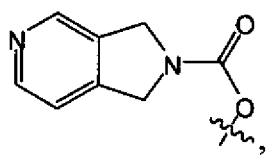
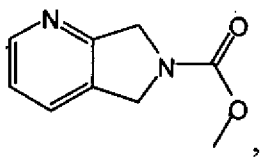
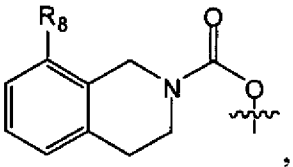
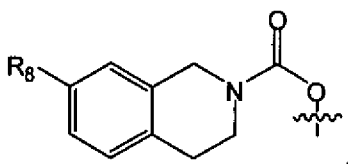
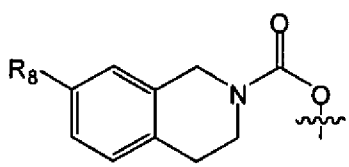
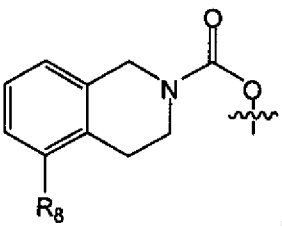
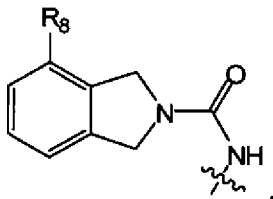
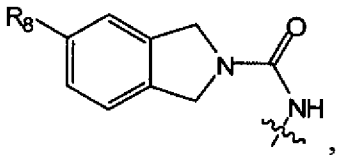


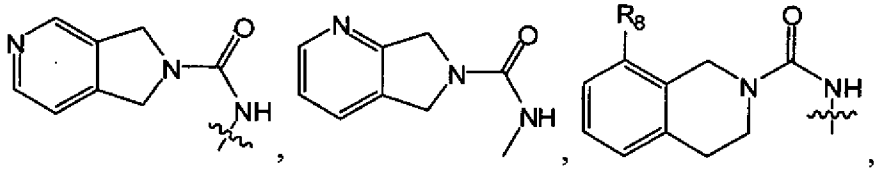









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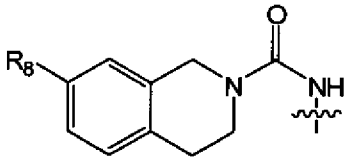
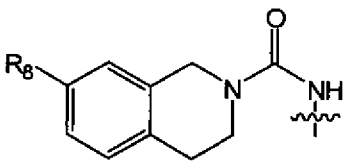
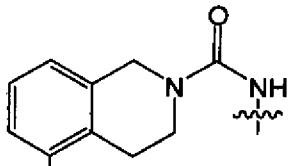
wherein R^{19} is selected from the group consisting of hydrogen, aryl, trihalomethyl, and C_{1-4}-alkyl.

16. The compound of claim 1, wherein R^2 is selected from the group consisting of propyl and $(CH_2)_2$-cyclobutyl.

17. The compound of claim 1, wherein X is CR_5R_{5a}, R_{5a} is hydrogen or methyl, and R_5 is a residue selected from the group consisting of:






, and

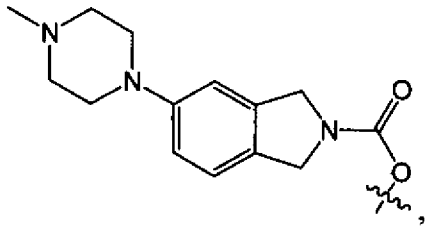
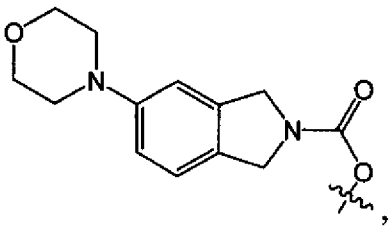
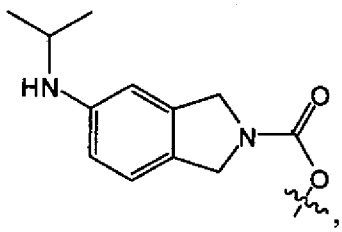
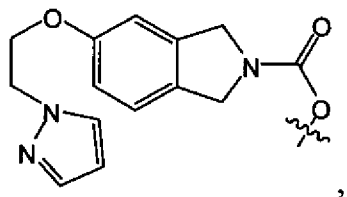
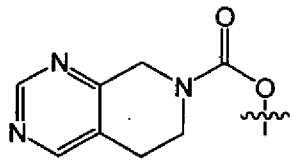
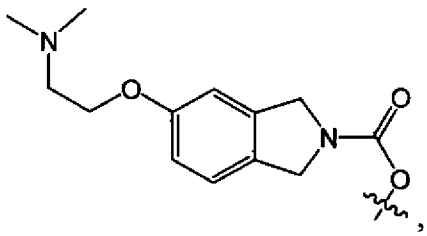
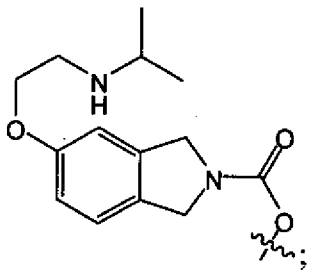
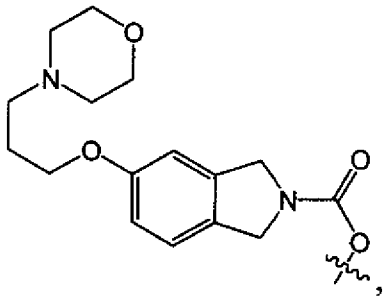
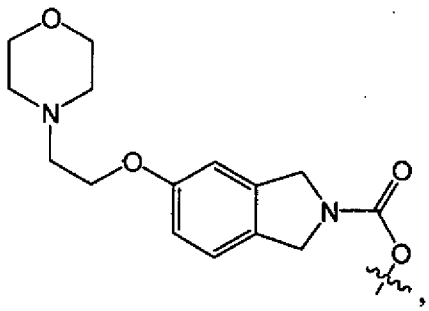
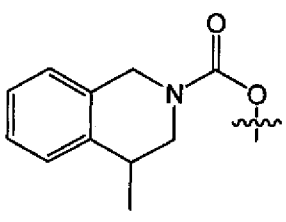
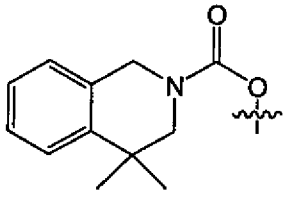
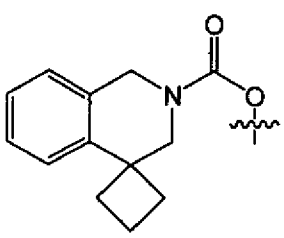
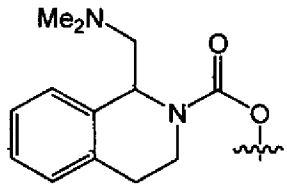
wherein R_8 is selected from hydrogen, methyl, ethyl, mono-, di-, or tri-fluoromethyl, mono-, di-, or tri-fluoromethoxy, fluoro, and chloro.

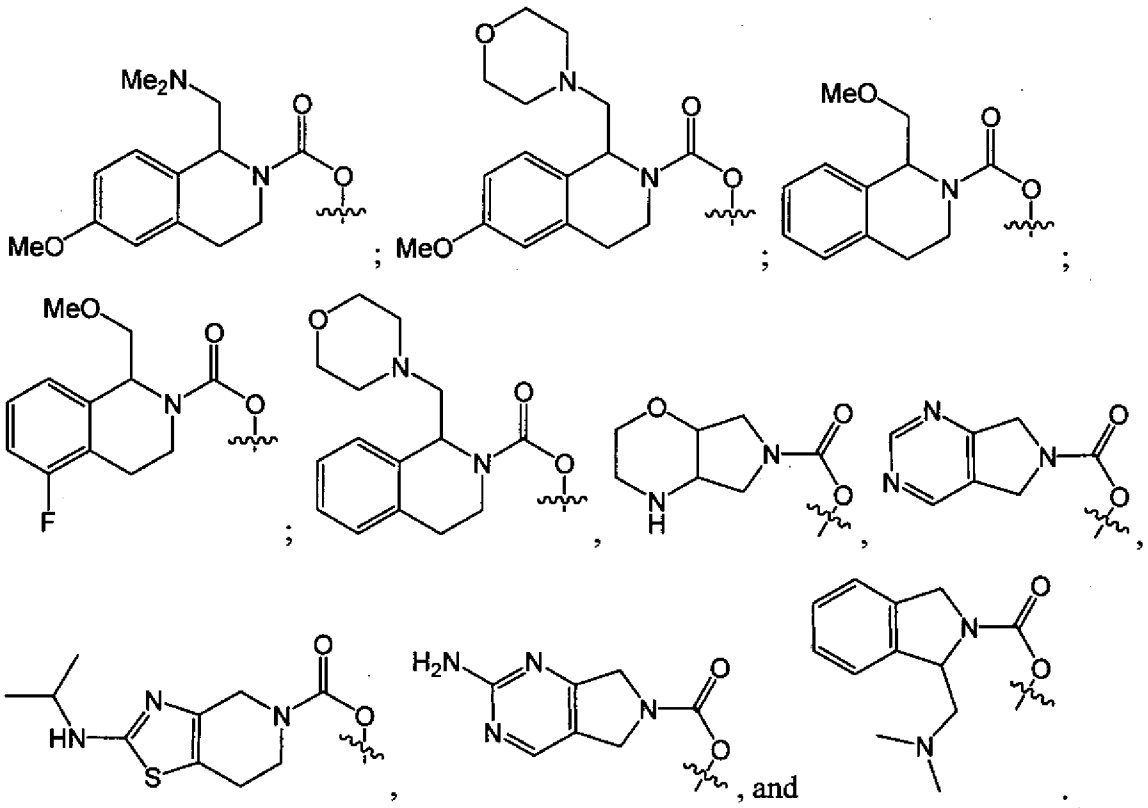
18. The compound of claim 1, wherein X is CR_5R_{5a};

R_{5a} is hydrogen or methyl;

R_6 is hydrogen, methyl, ethyl, and mono-, di-, and tri-fluoromethyl;

R_5 is a residue selected from the group consisting of:

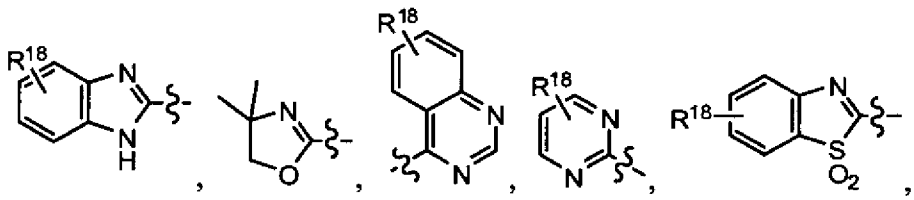














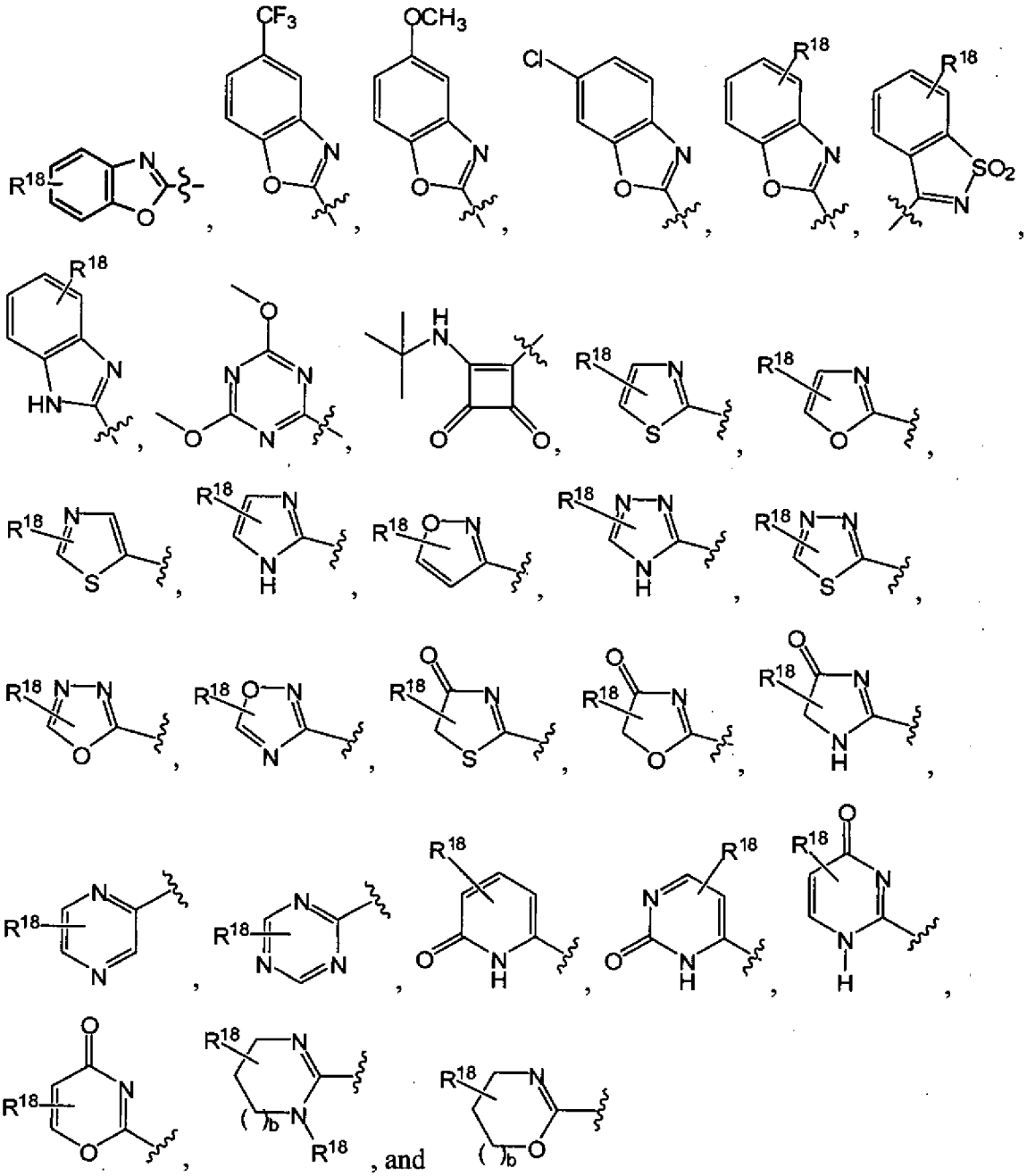


19. The compound of claim 1, wherein R^{11} is H and R^{12} is C_{3-6}-cycloalkyl.

20. The compound of claim 1, wherein V is R^{20} or C(O)-R^{20}, wherein R^{20} is selected from the group consisting of C_{3-6}-cycloalkyl, mono- and di-C_{1-4}alkylamino, phenyl, pyrazine, benzooxazole, 4,4-dimethyl-4,5-dihydro-oxazole, benzoimidazole, pyrimidine, benzothiazole 1,1-dioxide and quinazoline, each of which may be further independently substituted with a halogen atom, CF_3, C_{1-4}-alkyl or C_{3-6}-cycloalkyl.

21. The compound of claim 1, wherein V is selected from R^{20} or C(O)R^{20}, wherein R^{20} is selected from the group consisting of





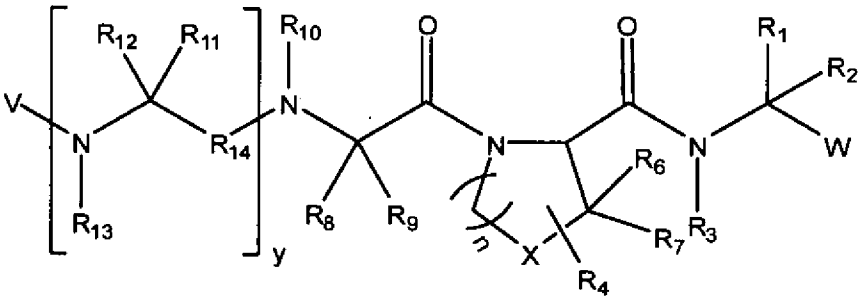
wherein b is 0, 1, or 2; and R_{18} is selected from the group consisting of hydrogen, a halogen atom, aryl, trihalomethyl, and C_{1-4}-alkyl.

22. The compound of claim 1, wherein X is CR^5R^{5a}, R^4 and R^{5a} are hydrogen, and R^5 is aryl-C_{0-3}-alkyl, -O-heterocycle, or heterocycle-C_{0-3}-alkyl, wherein aryl and heterocycle may be independently substituted one or more times with a halogen atom, aryl, trihalomethyl, C_{3-6}-cycloalkyl or C_{1-4}-alkyl.

23. The compound of claim 1, wherein W is selected from the group consisting of $C(O)$-$C(O)N(R^{23})_2$, wherein R^{23} is independently selected from hydrogen or from the group

consisting of C_{1-4}-alkyl, C_{3-6}-cycloalkylC_{0-4}alkyl, aryl and heterocycle, each of which may be independently substituted one or more times with a halogen atom or C_{1-4}-alkyl.

24. A compound of the formula III:



III

and pharmaceutically acceptable salts and stereoisomers thereof;

wherein

y is 0 or 1;

n is 0, 1 or 2;

R^{14} is C(O) or SO_2;

R^1, R^2, W, R^{13} and V are each, independently, selected from hydrogen or from the group consisting of alkyl, alkyl-aryl, heteroalkyl, heterocyclyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyloxy, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocyclyloxy, cycloalkyloxy, amino, alkylamino, arylamino, alkyl-arylamino, arylamino, heteroarylamino, cycloalkylamino, mono and dialkylcarboxamide, carboxyalkylamino, arlylalkyloxy and heterocyclylamino; each of which may be further independently substituted one or more times with X^1 and X^2; wherein X^1 is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, aralkyl, aryloxy, arylthio, arylheteroaryl, heteroaryl, heterocyclylamino, alkylheteroaryl, or heteroaralkyl; wherein X^1 can be independently substituted with one or more X^2 moieties which can be the same or different and are independently selected; wherein X^2 is hydroxy, oxo, alkyl, cycloalkyl, spirocycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, aryloxy, thio, alkylthio, amino, mono- and di-alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyl, alkoxycarbonyloxy, alkylureido, arylureido, halogen, cyano, or nitro; wherein each X_2 residue selected to be alkyl, alkoxy, and aryl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different and are independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, aralkyl, arylheteroaryl, heteroaryl,

heterocyclylamino, alkylheteroaryl and heteroaralkyl;

W is also selected from the group consisting of C(O)OH, $C(O)OR_{24}$, C(O)-amine, $P(O)(OR_{24})_2$, C(O)-C(O)OH, $C(=N\text{-}O\text{-}R_{24})$-C(O)-amine, $C(O)NHS(O)_2R_{24}$, $C(O)NHS(O)_pN(R_{24})_2$, $C(O)NR_{24}S(O)_pN(R_{24})_2C(O)$-C(O)-amine, $CON(H)SO_2$-amine and $C(O)\text{-}[C(O)]_a$-heterocycle, wherein the heterocycle may be substituted or unsubstituted, wherein a is 0 or 1, wherein each R_{24} is independently selected from the group consisting of hydrogen, halogen, hydroxyl, formyl, carboxylate, amide, amino, substituted or unsubstituted-C_{1-4}-alkyl, substituted or unsubstituted-C_{1-4}-alkoxy, substituted or unsubstituted-C_{1-4}-alkanoyl, substituted or unsubstituted-C_{1-4}-alkoxycarbonyl, substituted or unsubstituted-C_{1-4}-alkanoyloxy, substituted or unsubstituted mono- and di-C_{1-4}-alkylamino, substituted or unsubstituted-C_{3-6}cycloalkyl-C_{0-4}alkyl, substituted or unsubstituted aryl-C_{0-4}alkyl, and substituted or unsubstituted heterocycle-C_{0-4}alkyl;

V is also selected from the group consisting of $-Q^1\text{-}Q^2$, wherein Q^1 is absent, C(O), N(H), $N(C_{1-4}$-alkyl), C=N(CN), $C=N(SO_2CH_3)$, or C=N-COH, and Q^2 is hydrogen or is selected from the group consisting of C_{1-4}-alkyl, O-C_{1-4}-alkyl, NH_2, N(H)-C_{1-4}-alkyl, $N(C_{1-4}$-alkyl$)_2$, SO_2-aryl, SO_2-C_{1-4}-alkyl, C_{3-6}-cycloalkyl-C_{0-4}-alkyl, aryl, heteroaryl and heterocycle, each of which may be independently substituted one or more times with a halogen atom, C_{1-4}-alkyl, C_{1-4}-alkyl substituted by one or more halogen atoms, or C_{3-6}-cycloalkyl;

or R^1 and R^2 may together form a 3, 4, 5, 6 or 7-membered ring that is aromatic or non-aromatic and may contain one or more heteroatoms, wherein the ring may be further substituted one or more times;

R^3 is selected from the group consisting of hydrogen, C_{1-4}-alkyl and C_{3-6}-cycloalkylC_{0-4}alkyl;

X is CR^5R^{5a};

R^4 represents 0-4 substituents, each of which is independently selected from hydrogen or from the group consisting of C_{1-4}-alkyl, C_{3-6}-cycloalkyl, aryl, heterocycle and heteroaryl, each of which may be independently substituted one or more times with a halogen atom or C_{1-4}-alkyl;

R^5 is selected from hydrogen or oxo or from the group consisting of hydroxyl, C_{1-8}-alkyl, C_{2-8}-alkenyl, C_{2-8}-alkynyl, C_{3-8}-cycloalkyl-C_{0-4}-alkyl, aryl-C_{0-4}-alkyl, heterocycle-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl , C_{3-8}-cycloalkyloxy, aryloxy, and heteroaryloxy each of which may be independently substituted one or more times with a halogen atom, aryl, trihalomethyl, or C_{1-4}-alkyl;

R^{5a} is selected from the group consisting of hydrogen, hydroxyl, C_{1-8}-alkyl, C_{2-8}-

alkenyl, C_{2-8}-alkynyl, C_{3-8}-cycloalkyl-C_{0-4}-alkyl, aryl-C_{0-4}-alkyl and heteroaryl-C_{0-4}-alkyl, or R^4 and R^5 may together form a fused dimethyl cyclopropyl ring, a fused cyclopentane ring, a fused phenyl ring or a fused pyridyl ring, each of which may be substituted with a halogen atom, aryl, trihalomethyl, or C_{1-4}-alkyl;

or R^5 and R^{5a} may together form a spirocyclic ring having between 3 and 7 ring atoms or R^5 and R^{5a} may together form a spirocyclic ring having between 3 and 7 ring atoms and having 0, 1, or 2 ring heteroatoms, which is optionally substituted by 0-4 substituents selected from cyano, halogen, hydroxyl, amino, thiol, C_{1-8}-alkyl, C_{2-8}-alkenyl, C_{2-8}-alkynyl, C_{1-8}-alkoxy-C_{0-4}alkyl, C_{1-8}-haloalkyl, C_{2-8}-haloalkenyl, C_{2-8}-haloalkynyl, C_{1-8}-haloalkoxy, C_{1-8}-alkylthio, C_{1-8}-alkylsulfonyl, C_{1-8}-alkylsulfoxy, C_{1-8}-alkanoyl, C_{1-8}-alkoxycarbonyl, C_{3-7}-cycloalkyl-C_{0-4}-alkyl, aryl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, COOH, $C(O)NH_2$, mono- and di-C_{1-4}-alkyl-carboxamide, mono- and di-C_{1-4}-alkyl-amino-C_{0-4}alkyl, SO_3H, SO_2NH_2, and mono-and di-C_{1-4}-alkylsulfonamide, or two of said 0-4 substitutents taken together form a fused or spirocyclic 3 to 7 membered ring having 0, 1 or 2 ring heteroatoms selected from N, O and S, which fused or spirocyclic ring has 0 to 2 independently selected substituents selected from cyano, halogen, hydroxyl, amino, thiol, C_{1-8}-alkyl, C_{2-8}-alkenyl, C_{2-8}-alkynyl, C_{1-8}-alkoxy-C_{0-4}alkyl, C_{1-8}-haloalkyl, C_{2-8}-haloalkenyl, C_{2-8}-haloalkynyl, C_{1-8}-haloalkoxy, C_{1-8}-alkylthio, C_{1-8}-alkylsulfonyl, C_{1-8}-alkylsulfoxy, C_{1-8}-alkanoyl, C_{1-8}-alkoxycarbonyl, C_{3-7}-cycloalkyl-C_{0-4}-alkyl, aryl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, COOH, $C(O)NH_2$, mono- and di-C_{1-4}-alkyl-carboxamide, mono- and di-C_{1-4}-alkyl-amino-C_{0-4}alkyl, SO_3H, SO_2NH_2, and mono-and di-C_{1-4}-alkylsulfonamide;

R^6 and R^7 are each, independently, selected from the group consisting of hydroxy, amino, C_{1-4}alkyl, C_{1-4}alkoxy, and mono- and di-C_{1-4}alkylamino, and C_{3-6}cycloalkylC_{0-4}alkyl;

R^8, R^9, R^{10}, R^{11} and R^{12} are each, independently, selected from the group consisting of hydrogen, C_{1-4}-alkyl and C_{3-6}-cycloalkylC_{0-4}alkyl;

or R^6 and R^7 may together form a spirocyclic ring having between 3 and 7 ring atoms and having 0, 1, or 2 ring heteroatoms, which is optionally substituted by 0-4 substituents selected from cyano, halogen, hydroxyl, amino, thiol, C_{1-8}-alkyl, C_{2-8}-alkenyl, C_{2-8}-alkynyl, C_{1-8}-alkoxy-C_{0-4}alkyl, C_{1-8}-haloalkyl, C_{2-8}-haloalkenyl, C_{2-8}-haloalkynyl, C_{1-8}-haloalkoxy, C_{1-8}-alkylthio, C_{1-8}-alkylsulfonyl, C_{1-8}-alkylsulfoxy, C_{1-8}-alkanoyl, C_{1-8}-alkoxycarbonyl, C_{3-7}-cycloalkyl-C_{0-4}-alkyl, aryl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, COOH, $C(O)NH_2$, mono- and di-C_{1-4}-alkyl-carboxamide, mono- and di-C_{1-4}-alkyl-amino-C_{0-4}alkyl, SO_3H, SO_2NH_2, and mono-and di-C_{1-4}-alkylsulfonamide, or two substituents taken together form a fused or spirocyclic 3 to 7 membered ring having 0, 1 or 2 ring heteroatoms selected from N, O and S,

which fused or spirocyclic ring has 0 to 2 independently selected substituents selected from halogen, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, mono- and di-C_{1-4}-alkylamino, mono- and di-C_{1-4}-alkyl-carboxamide, C_{1-4}-alkoxycarbonyl, and phenyl;

wherein at least one of R^5 and R^{5a} or R^6 and R^7, taken in combination, form a spirocyclic ring having at least one spirocyclic ring substituent;

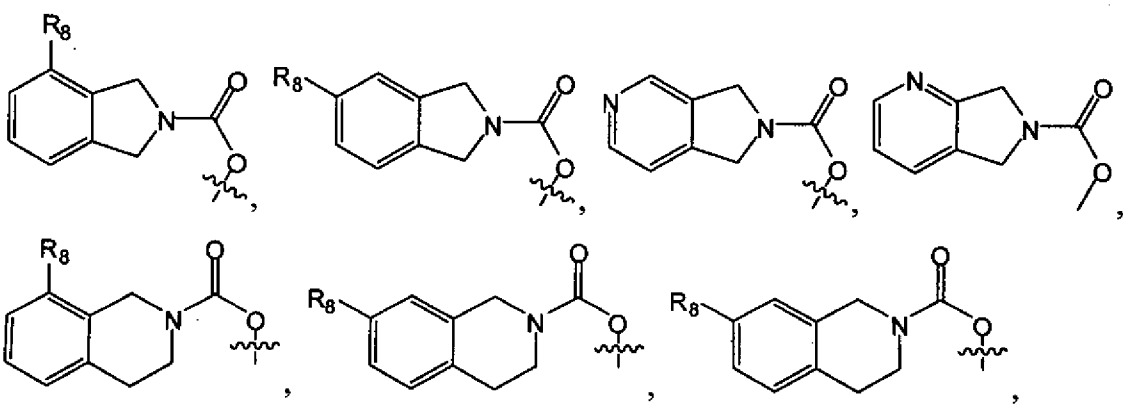
or R^3 and W may together form a 3, 4, 5, 6 or 7-membered ring that is aromatic or non-aromatic and may contain one or more heteroatoms, wherein the ring may be further substituted one or more times; and

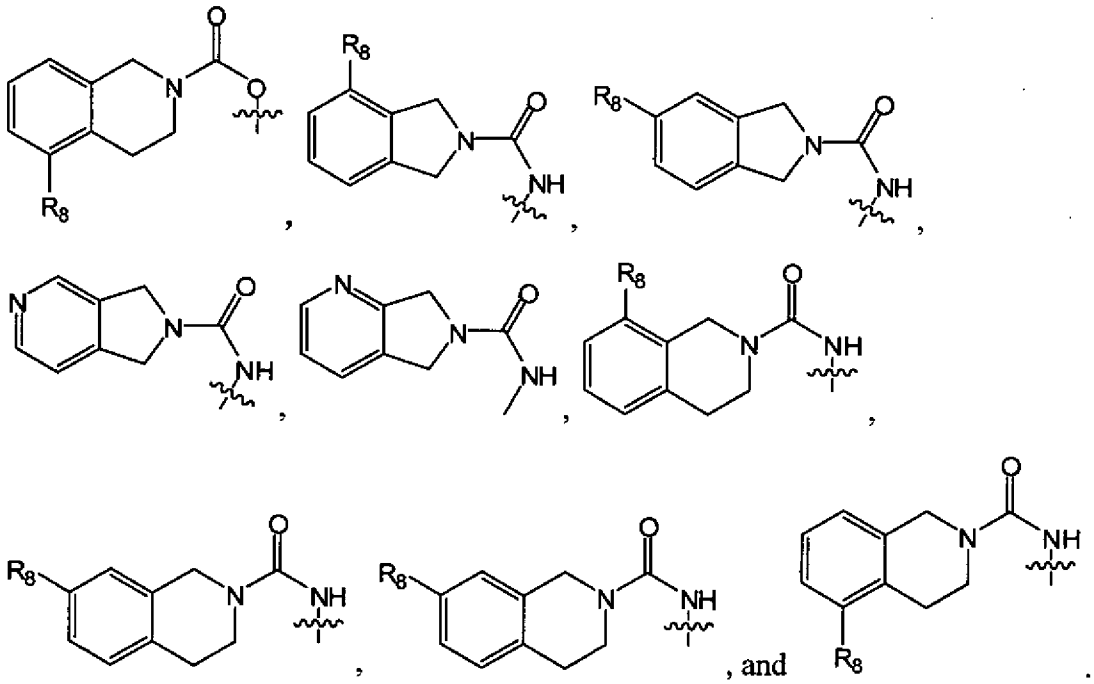
or when y is 0, R^{10} and V may together form a 3, 4, 5, 6 or 7-membered ring that is aromatic or non-aromatic and may contain one or more heteroatoms, wherein the ring may be further substituted one or more times.

25. The compound of claim 24, wherein R^5 and R^{5a}, taken in combination, form a spirocyclic ring having between 3 and 7 ring atoms and having 0, 1, or 2 ring heteroatoms, which spirocyclic ring is substituted with a spirocyclic 3 to 7 membered ring having 0, 1 or 2 ring heteroatoms selected from N, O and S, and wherein each of the spirocyclic rings has 0 to 2 independently selected substituents selected from cyano, halogen, hydroxyl, amino, thiol, C_{1-8}-alkyl, C_{2-8}-alkenyl, C_{2-8}-alkynyl, C_{1-8}-alkoxy-C_{0-4}alkyl, C_{1-8}-haloalkyl, C_{2-8}-haloalkenyl, C_{2-8}-haloalkynyl, C_{1-8}-haloalkoxy, C_{1-8}-alkylthio, C_{1-8}-alkylsulfonyl, C_{1-8}-alkylsulfoxy, C_{1-8}-alkanoyl, C_{1-8}-alkoxycarbonyl, C_{3-7}-cycloalkyl-C_{0-4}-alkyl, aryl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, COOH, $C(O)NH_2$, mono- and di-C_{1-4}-alkyl-carboxamide, mono- and di-C_{1-4}-alkyl-amino-C_{0-4}alkyl, SO_3H, SO_2NH_2, and mono-and di-C_{1-4}-alkylsulfonamide.

26. The compound of claim 24, wherein R^{14} is C(O).

27. The compound of claim 24, wherein X is CR_5R_{5a}, R_{5a} is hydrogen or methyl, and R_5 is a residue selected from the group consisting of:





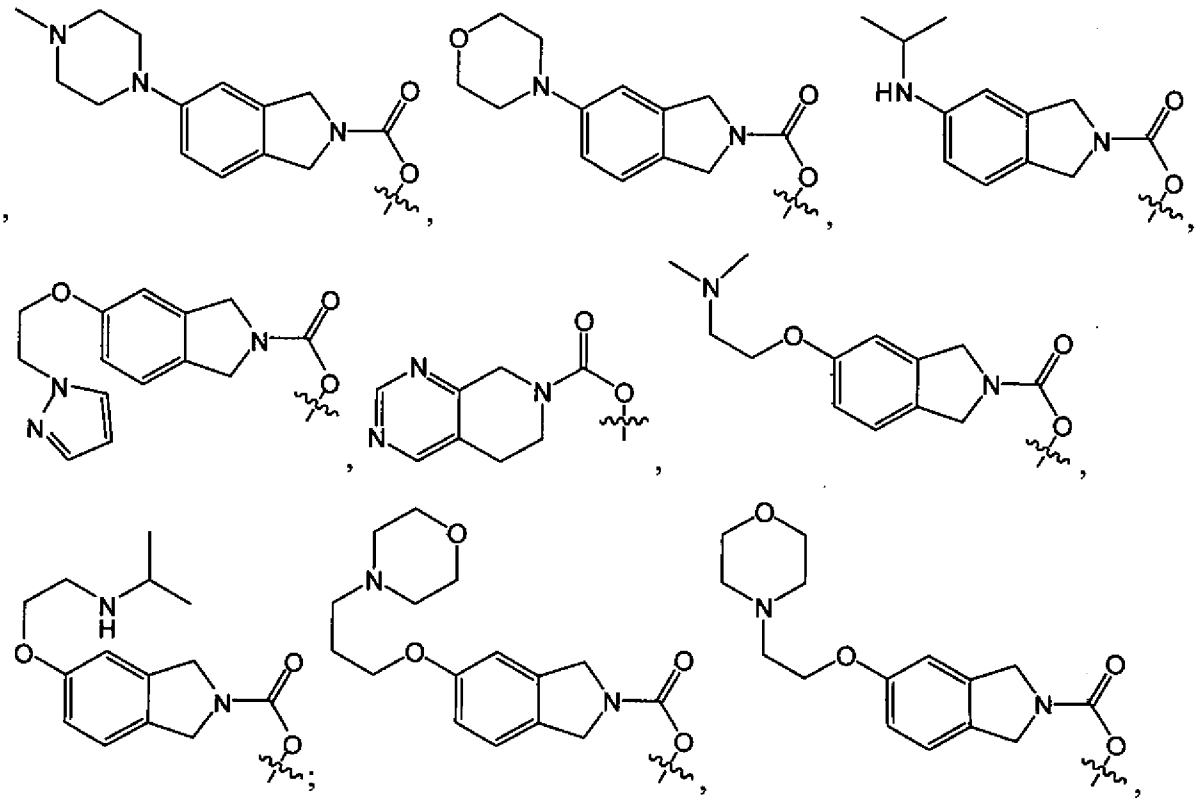
wherein R_8 is selected from hydrogen, methyl, ethyl, mono-, di-, or tri-fluoromethyl, mono-, di-, or tri-fluoromethoxy, fluoro, and chloro.

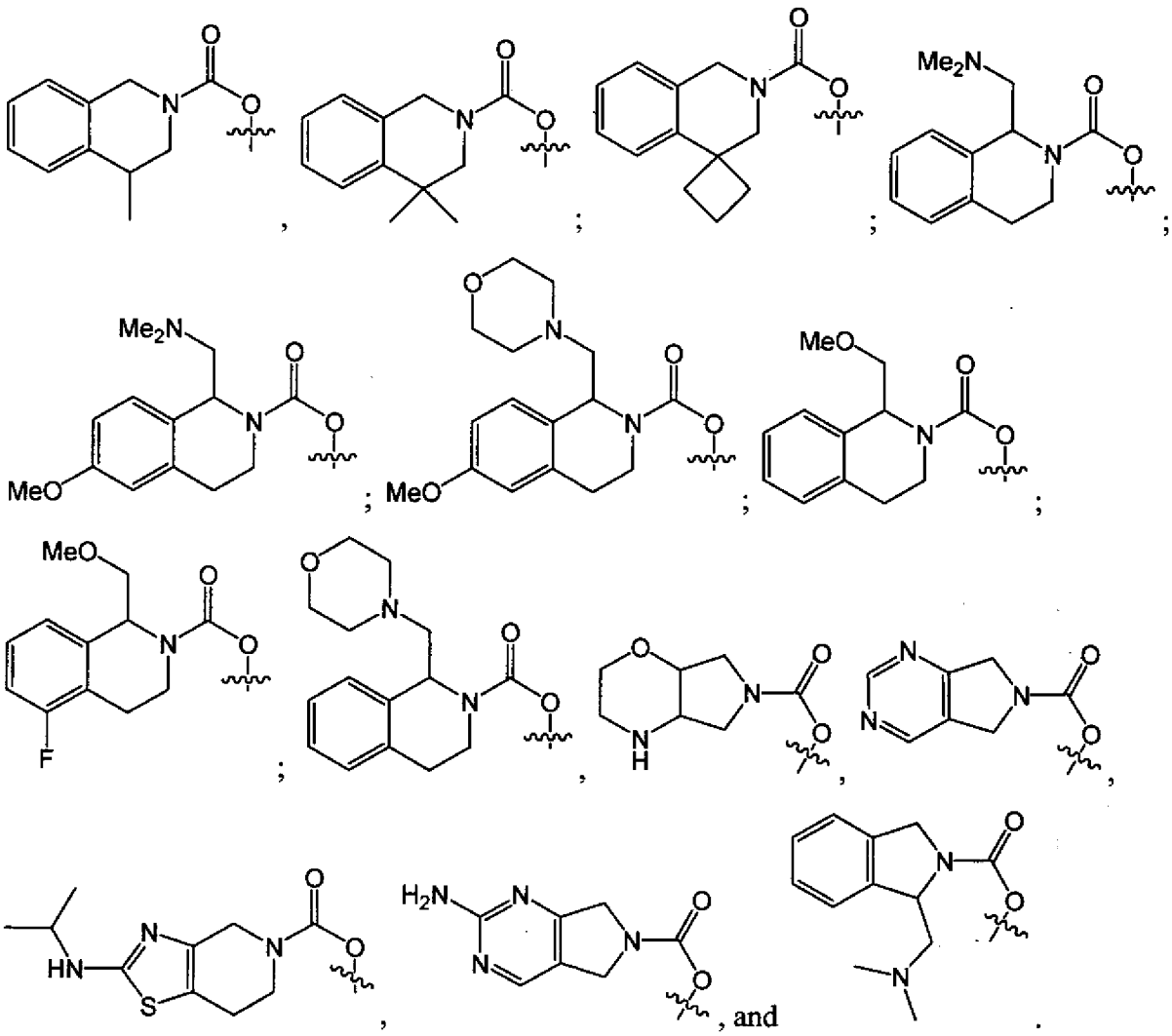
28. The compound of claim 24, wherein X is CR_5R_{5a};

R_{5a} is hydrogen or methyl;

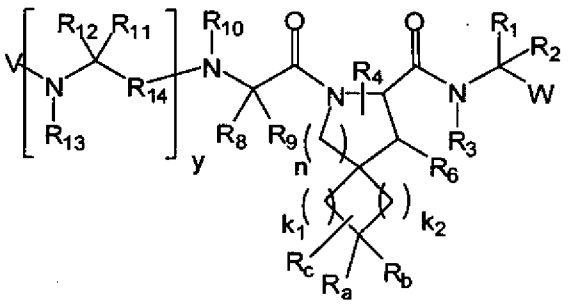
R_6 is hydrogen, methyl, ethyl, and mono-, di-, and tri-fluoromethyl;

R_5 is a residue selected from the group consisting of:





29. A compound of claim 24, according to the formula:



wherein

k_1 and k_2 are 0 or 1 such that a sum of k_1 and k_2 equals 1 or 2;

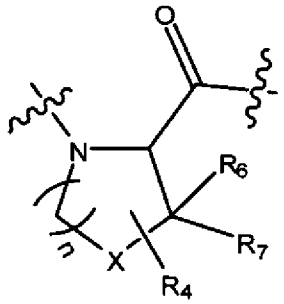
R_a and R_b taken together form a spirocyclic 3 to 6 membered ring having 0, 1 or 2 ring heteroatoms selected from N, O and S, which fused or spirocyclic ring has 0 to 2 independently selected substituents selected from halogen, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, and phenyl;

R_c represents 0 to 2 substituents which are independently selected at each occurrence of R_c from the group consisting of halogen, C_{1-4}alkyl, and phenyl, or two *geminal* R_c substituents, taken in combination form a 3 to 6 member spirocyclic ring;

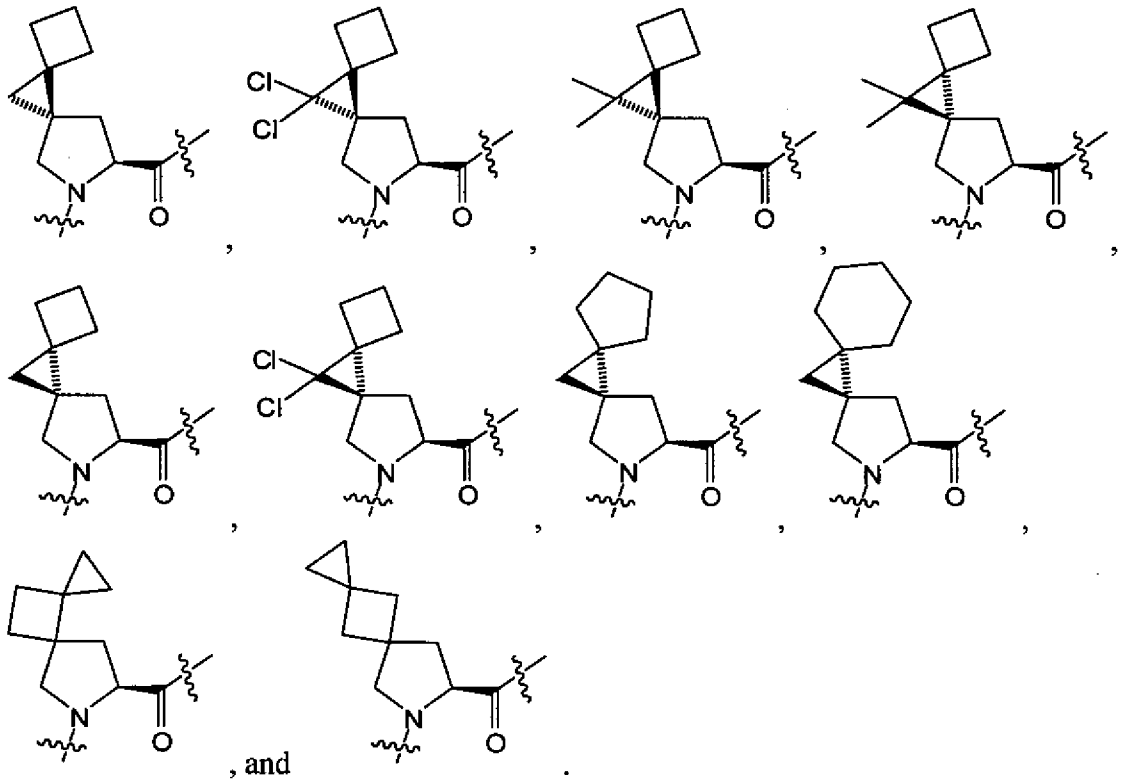
R_4 represents 0, 1, or 2 substituents each of which is independently selected from H and C_{1-4}-alkyl; and

R_6 is hydrogen or C_{1-4}alkyl.

30. The compound of claim 24, wherein the divalent residue:



is selected from the group consisting of:

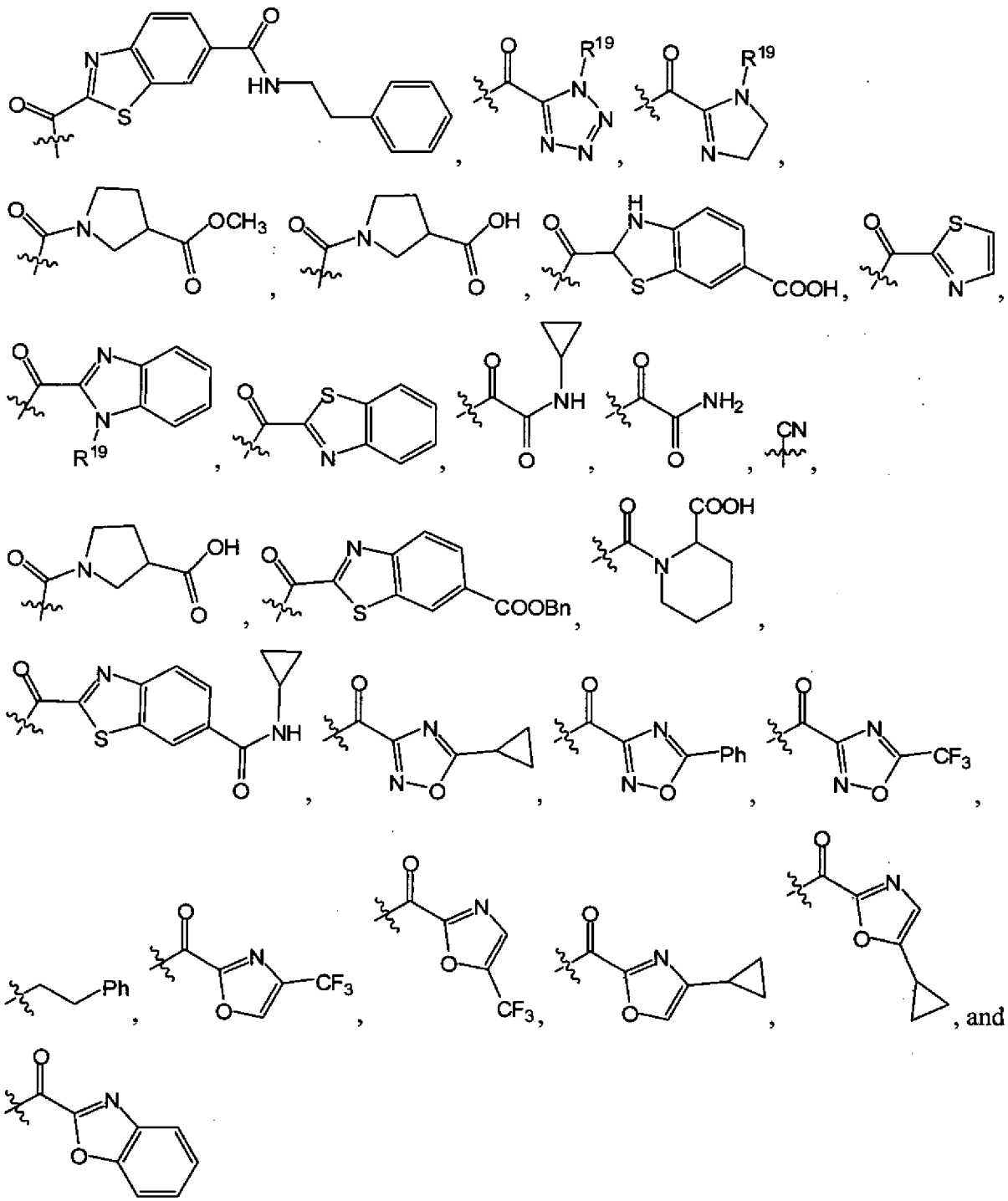


, and .

31. The compound of claim 24, wherein W is selected from the group consisting of C(O)-C(O)NH_2, C(O)-C(O)N(H)-cyclopropyl, C(O)-benzothiazole, C(O)-benzoimidazole, C(O)-oxazole, C(O)-imidazole, and C(O)-oxadiazole, wherein the benzothiazole, benzoimidazole, oxazole and oxadiazole groups may be independently substituted one or

more times with a halogen atom, aryl, trihalomethyl, C_{3-6}-cycloalkyl or C_{1-4}-alkyl.

32. The compound of claim 24, wherein W is selected from the group consisting of



wherein R^{19} is selected from the group consisting of hydrogen, aryl, trihalomethyl, and C_{1-4}-alkyl.

33. The compound of claim 24, wherein R^2 is selected from the group consisting

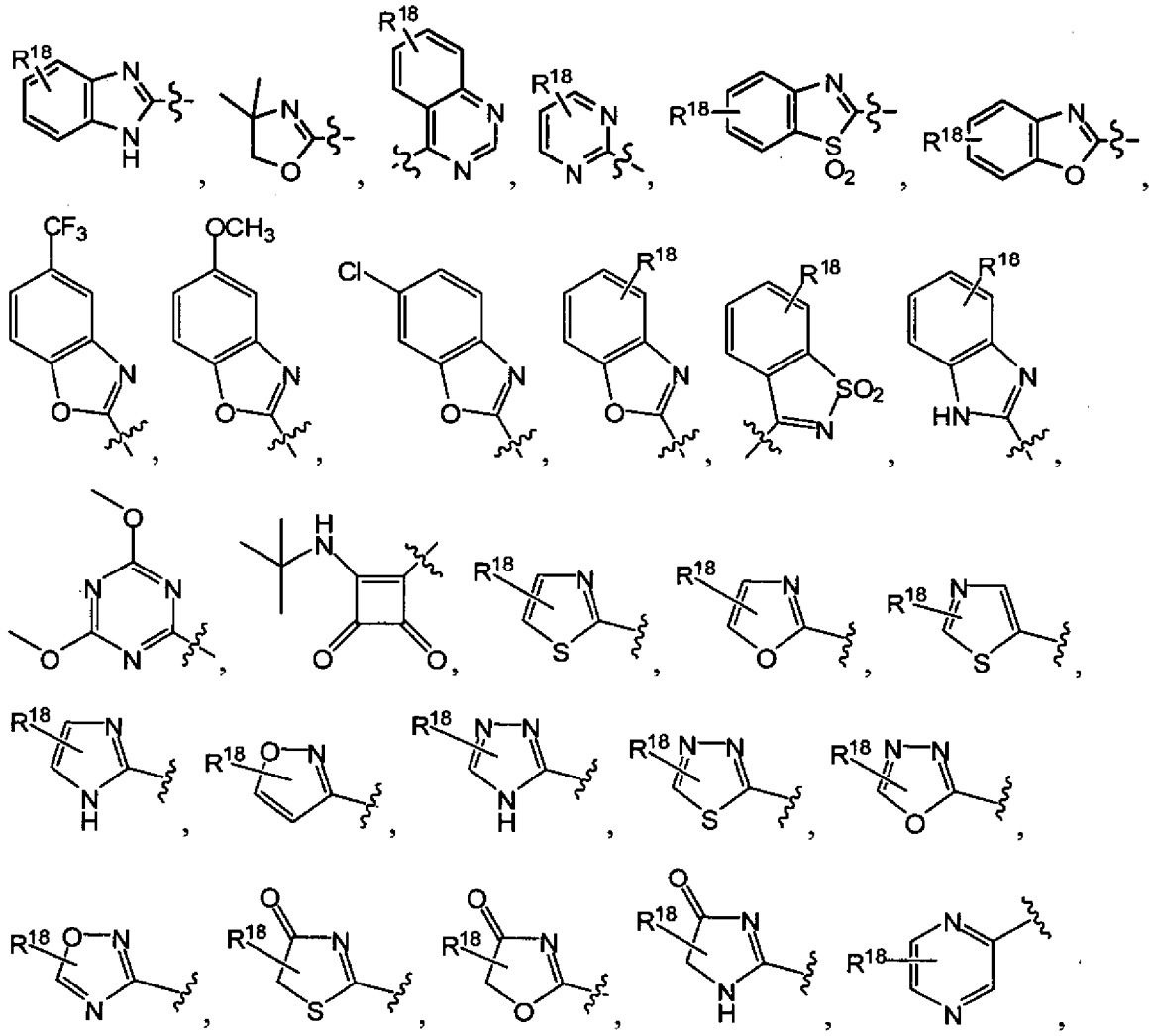
of propyl and $(CH_2)_2$-cyclobutyl.

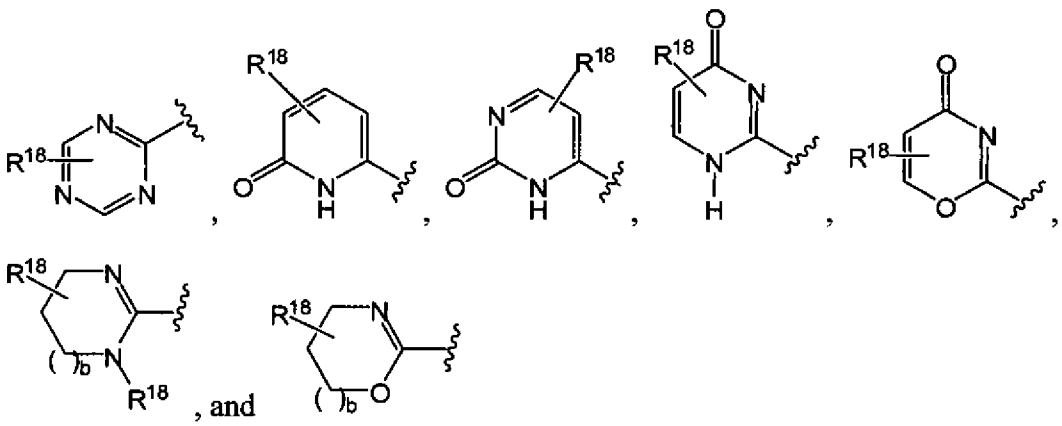
34. The compound of claim 24, wherein R^{11} is H and R^{12} is C_{3-6}-cycloalkyl.

35. The compound of claim 24, wherein R^{12} is cyclohexyl.

36. The compound of claim 24, wherein V is R^{20} or C(O)-R^{20}, wherein R^{20} is selected from the group consisting of C_{3-6}-cycloalkyl, mono- and di-C_{1-4}alkylamino, phenyl, pyrazine, benzooxazole, 4,4-dimethyl-4,5-dihydro-oxazole, benzoimidazole, pyrimidine, benzothiazole 1,1-dioxide and quinazoline, each of which may be further independently substituted with a halogen atom, CF_3, C_{1-4}-alkyl or C_{3-6}-cycloalkyl.

37. The compound of claim 24, wherein V is R^{20} or C(O)-R^{20}, wherein R^{20} is selected from the group consisting of





wherein b is 0, 1, or 2; and R_{18} is selected from the group consisting of hydrogen, a halogen atom, aryl, trihalomethyl, and C_{1-4}-alkyl.

38. The compound of claim 24, wherein X is CR^5R^{5a}, R^4 and R^{5a} are hydrogen, and R^5 is aryl-C_{0-3}-alkyl, -O-heterocycle, or heterocycle-C_{0-3}-alkyl, wherein aryl and heterocycle may be independently substituted one or more times with a halogen atom, aryl, trihalomethyl, C_{3-6}-cycloalkyl or C_{1-4}-alkyl.

39. The compound of claim 24, wherein W is selected from the group consisting of C(O)-C(O)N$(R^{23})_2$, wherein R^{23} is independently selected from hydrogen or the group consisting of C_{1-4}-alkyl, C_{3-6}-cycloalkylC_{0-4}alkyl, aryl and heterocycle, each of which may be independently substituted one or more times with a halogen atom or C_{1-4}-alkyl.

40. A method of treating an HCV-associated disorder comprising administering to a subject in need thereof a pharmaceutically acceptable amount of a compound of claim 1 or claim 24, such that the HCV-associated disorder is treated.

41. The method of claim 40, wherein the HCV-associated disorder is selected from the group consisting of HCV infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma, cryoglobulinaemia, non-Hodgkin's lymphoma, and a suppressed innate intracellular immune response.

42. A method of treating an HIV infection comprising administering to a subject in need thereof a pharmaceutically acceptable amount of a compound of claim 1 or claim 24.

43. A method of treating, inhibiting or preventing the activity of HCV in a subject

in need thereof, comprising administering to the subject a pharmaceutically acceptable amount of a compound of claim 1 or claim 24.

44. A method of inhibiting the activity of a serine protease, comprising the step of contacting said serine protease with a compound according to claim 1 or claim 24.

45. The method of claim 44, wherein the activity of the NS2 protease is inhibited.

46. The method of claim 44, wherein the activity of the NS3 protease is inhibited.

47. The method of claim 44, wherein the activity of the NS3 helicase is inhibited.

48. The method of claim 44, wherein the activity of the NS5a protein is inhibited.

49. The method of claim 44, wherein the activity of the NS5b polymerase is inhibited.

50. The method of claim 44, wherein the interaction between the NS3 protease and NS4A cofactor is disrupted.

51. The method of claim 44 wherein the severing of one or more of the NS4A-NS4B, NS4B-NS5A and NS5A-NS5B junctions of the HCV is prevented or altered.

52. The method of any one of claims 44-51, wherein an HCV-associated disorder is treated in a subject in need thereof.

53. The method of claim 52, wherein the HCV-associated disorder is selected from the group consisting of HCV infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma, cryoglobulinaemia, non-Hodgkin's lymphoma, and a suppressed innate intracellular immune response.

54. A method of treating, inhibiting or preventing the activity of HCV in a subject in need thereof, comprising administering to the subject a pharmaceutically acceptable amount of a compound of claim 1 or claim 24,wherein the compound interacts with any

target in the HCV life cycle.

55. The method of claim 54, wherein the target is selected from the group consisting of NS2 protease, NS3 protease, NS3 helicase, NS5a protein andNS5b polymerase.

56. A method of decreasing the HCV RNA load in a subject in need thereof comprising administering to the subject a pharmaceutically acceptable amount of a compound of claim 1 or claim 24, such that the HCV RNA load in the subject is decreased.

57. A compound exhibiting HCV protease activity, wherein the compound is a compound of claim 1 or claim 24.

58. The compound of claim 57, wherein the compound is a HCV NS3-4A protease inhibitor.

59. A method of treating an HCV-associated disorder in a subject, comprising administering to a subject in need thereof a pharmaceutically acceptable amount of a compound of claim 1 or claim 24 and a pharmaceutically acceptable carrier, such that the HCV-associated disorder is treated.

60. A method of treating an HCV-associated disorder comprising administering to a subject in need thereof a pharmaceutically effective amount of a compound of claim 1 or claim 24, in combination with a pharmaceutically effective amount of an additional HCV-modulating compound, such that the HCV-associated disorder is treated.

61. The method of claim 60, wherein the additional HCV-modulating compound is selected from the group consisting of Sch 503034 and VX-950.

62. The method of claim 60 wherein the additional HCV-modulating compound is interferon or derivatized interferon.

63. The method of claim 62, wherein the interferon is selected from the group consisting of interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, lymphoblastoid interferon, and interferon tau; and said compound having anti-

hepatitis C virus activity is selected from the group consisting of interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, double stranded RNA, double stranded RNA complexed with tobramycin, Imiquimod, ribavirin, an inosine 5'-monophosphate dehydrogenase inhibitor, amantadine, and rimantadine.

64. The method of claim 60, wherein the additional HCV-modulating compound is a cytochrome P450 monooxygenase inhibitor.

65. The method of claim 64, wherein the cytochrome P450 inhibitor is selected from the group consisting of ritonavir, ketoconazole, troleandomycin, 4-methyl pyrazole, cyclosporin, and clomethiazole.

66. The method of claim 59 or claim 60, wherein the HCV-associated disorder is selected from the group consisting of HCV infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma, cryoglobulinaemia, non-Hodgkin's lymphoma, and a suppressed innate intracellular immune response.

67. A method of inhibiting hepatitis C virus replication in a cell, comprising contacting said cell with a compound of claim 1 or claim 24.

68. A packaged HCV-associated disorder treatment, comprising an HCV-modulating compound of claim 1 or claim 24, packaged with instructions for using an effective amount of the HCV-modulating compound to treat an HCV-associated disorder.

69. The treatment of claim 68, wherein the HCV-associated disorder is selected from the group consisting of HCV infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma, cryoglobulinaemia, non-Hodgkin's lymphoma, and a suppressed innate intracellular immune response.

70. A method of treating HCV infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma, cryoglobulinaemia, non-Hodgkin's lymphoma, and/or a suppressed innate intracellular immune response in subject in need thereof comprising administering to the subject a pharmaceutically acceptable amount of a compound of claim 1 or claim 24.

71. The method of claim 40, wherein the HCV is selected from any HCV genotype.

72. The method of claim 71, wherein the HCV is selected from HCV genotype 1, 2 and/or 3.