SULFUR COMPOUNDS AS INHIBITORS OF HEPATITIS C VIRUS NS3 SERINE PROTEASE

Field of the Invention

The present invention relates to novel hepatitis C virus ("HCV") protease inhibitors, pharmaceutical compositions containing one or more such inhibitors, methods of preparing such inhibitors and methods of using such inhibitors to treat hepatitis C and related disorders. This invention additionally discloses novel compounds as inhibitors of the HCV NS3/NS4a serine protease. This application claims priority from U.S. provisional application Serial No. 60/548,670 filed February 27, 2004.

Background of the Invention

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

Recently, an HCV protease necessary for polypeptide processing and viral replication has been identified, cloned and expressed. (*See*, e.g., U.S. Patent No. 5,712,145). This approximately 3000 amino acid polyprotein contains, from the amino terminus to the carboxy terminus, a nucleocapsid protein (C), envelope proteins (E1 and E2) and several non-structural proteins

(NS1, 2, 3, 4a, 5a and 5b). NS3 is an approximately 68 kda protein, encoded by approximately 1893 nucleotides of the HCV genome, and has two distinct domains: (a) a serine protease domain consisting of approximately 200 of the N-terminal amino acids; and (b) an RNA-dependent ATPase domain at the C-terminus of the protein. The NS3 protease is considered a member of the chymotrypsin family because of similarities in protein sequence, overall three-dimensional structure and mechanism of catalysis. Other chymotrypsin-like enzymes are elastase, factor Xa, thrombin, trypsin, plasmin, urokinase, tPA and PSA. The HCV NS3 serine protease is responsible for proteolysis of the polypeptide (polyprotein) at the NS3/NS4a, NS4a/NS4b, NS4b/NS5a and NS5a/NS5b junctions and is thus responsible for generating four viral proteins during viral replication. This has made the HCV NS3 serine protease an attractive target for antiviral chemotherapy. The inventive compounds can inhibit such protease. They also can modulate the processing of hepatitis C virus (HCV) polypeptide.

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

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

tolerant of mutagenesis than the other sites. *See*, e.g., Kollykhalov et al. (1994) J. Virol. 68:7525-7533. It has also been found that acidic residues in the region upstream of the cleavage site are required for efficient cleavage. *See*, e.g., Komoda et al. (1994) J. Virol. 68:7351-7357.

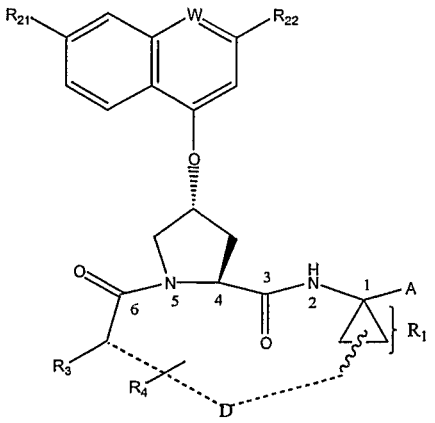
Inhibitors of HCV protease that have been reported include antioxidants (*see*, International Patent Application Publication No. WO 98/14181), certain peptides and peptide analogs (*see*, International Patent Application Publication No. WO 98/17679, Landro et al. (1997) Biochem. 36:9340-9348, Ingallinella et al. (1998) Biochem. 37:8906-8914, Llinàs-Brunet et al. (1998) Bioorg. Med. Chem. Lett. 8:1713-1718), inhibitors based on the 70-amino acid polypeptide eglin c (Martin et al. (1998) Biochem. 37:11459-11468, inhibitors affinity selected from human pancreatic secretory trypsin inhibitor (hPSTI-C3) and minibody repertoires (MBip) (Dimasi et al. (1997) J. Virol. 71:7461-7469), cV_HE2 (a "camelized" variable domain antibody fragment) (Martin et al.(1997) Protein Eng. 10:607-614), and α1-antichymotrypsin (ACT) (Elzouki et al.) (1997) J. Hepat. 27:42-28). A ribozyme designed to selectively destroy hepatitis C virus RNA has recently been disclosed (*see*, *BioWorld Today* 9(217): 4 (November 10, 1998)).

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

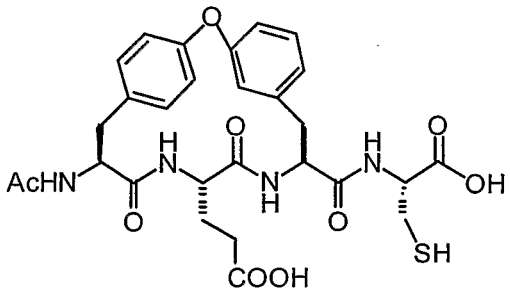
HCV has been implicated in cirrhosis of the liver and in induction of hepatocellular carcinoma. The prognosis for patients suffering from HCV infection is currently poor. HCV infection is more difficult to treat than other forms of hepatitis due to the lack of immunity or remission associated with HCV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

hepatocellular carcinoma have a five-year survival rate of 10-30%, whereas those with localized unresectable hepatocellular carcinoma have a five-year survival rate of less than 1%.

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

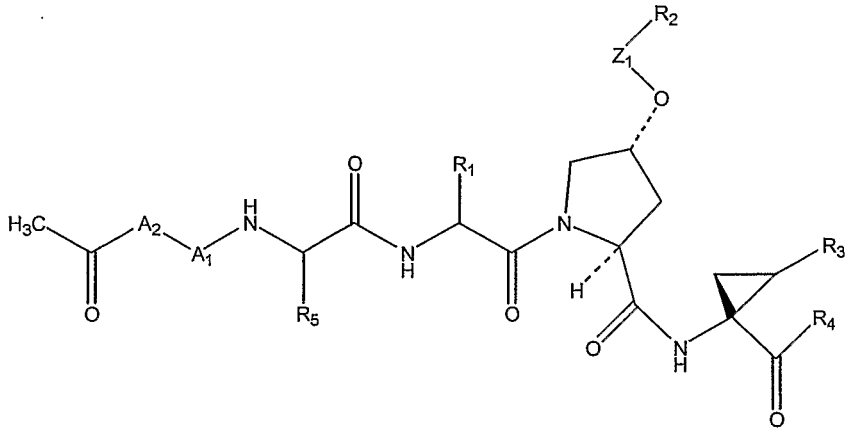


Reference is made to A. Marchetti *et al*, *Synlett*, S1, 1000-1002 (1999) describing the synthesis of bicylic analogs of an inhibitor of HCV NS3 protease. A compound disclosed therein has the formula:

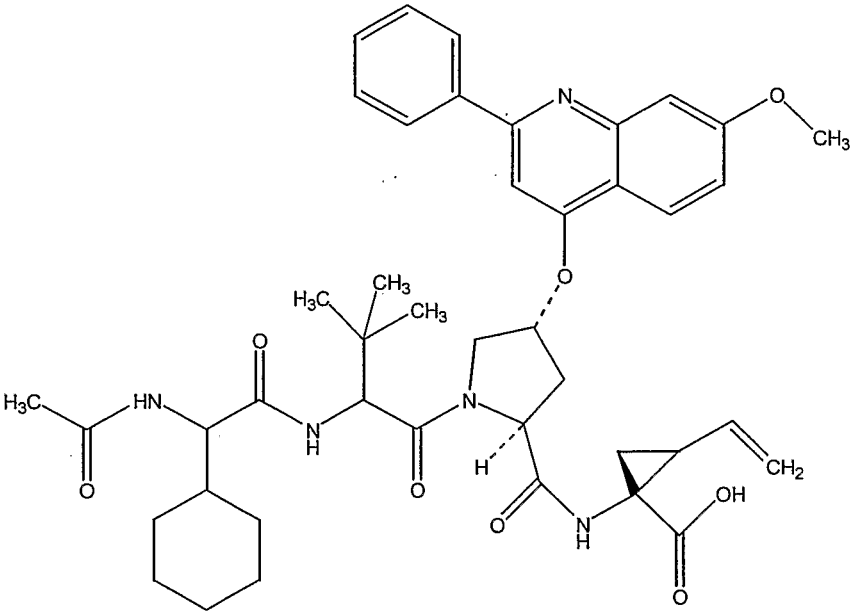


Reference is also made to W. Han *et al*, *Bioorganic & Medicinal Chem. Lett,* (2000) 10, 711-713, which describes the preparation of certain α-ketoamides, α-ketoesters and α-diketones containing allyl and ethyl functionalities.

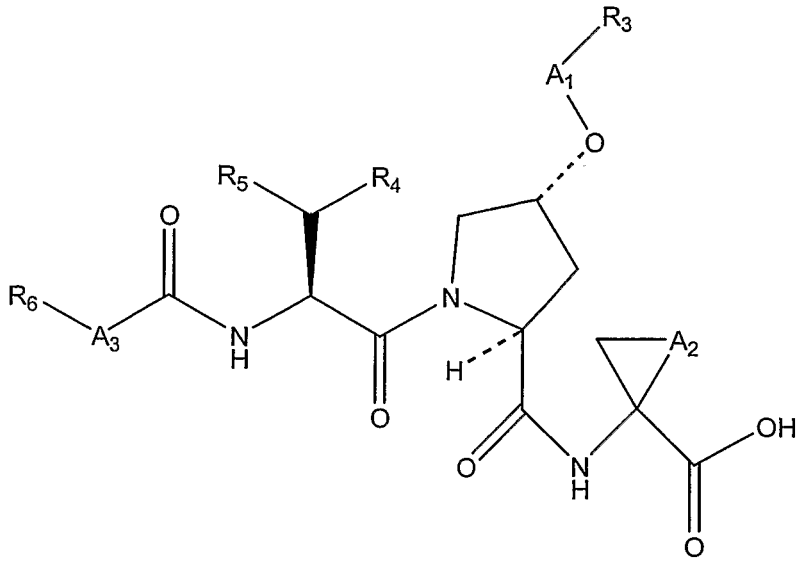
Reference is also made to WO 00/09558 (Assignee: Boehringer Ingelheim Limited; Published February 24, 2000) which discloses peptide derivatives of the formula:



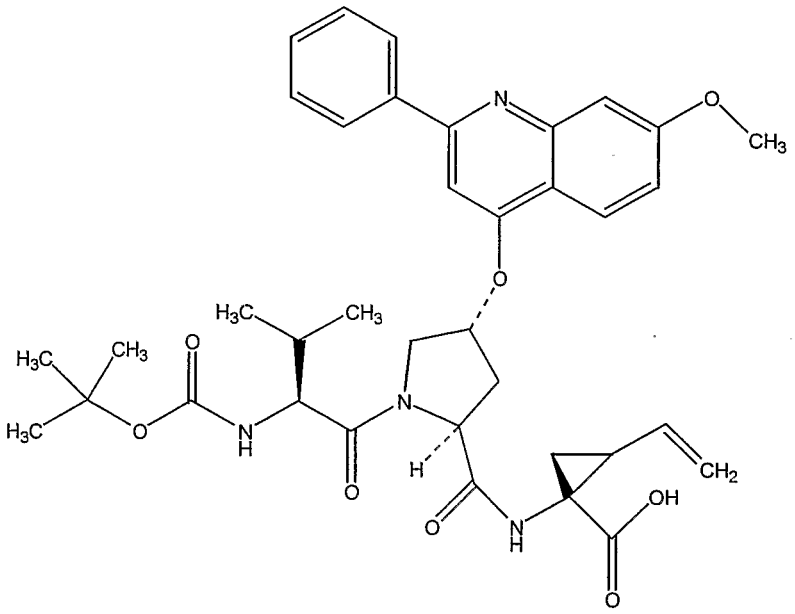
where the various elements are defined therein. An illustrative compound of that series is:



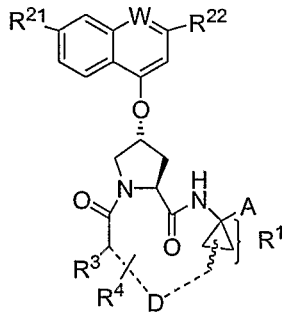
Reference is also made to WO 00/09543 (Assignee: Boehringer Ingelheim Limited; Published February 24, 2000) which discloses peptide derivatives of the formula:



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



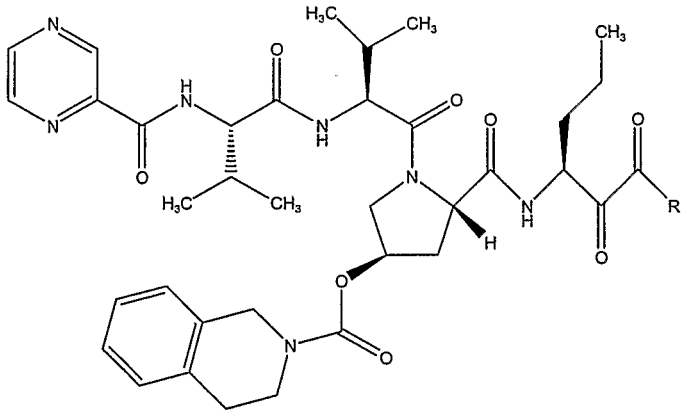
Reference is also made to U.S. 6,608,027 (Boehringer Ingelheim, Canada) which discloses NS3 protease inhibitors of the type:



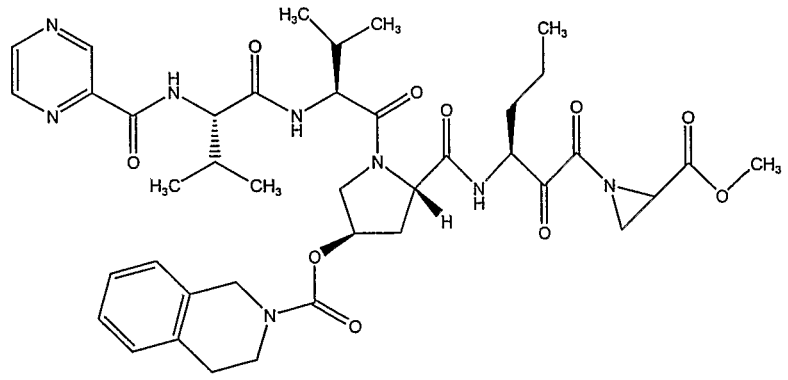
wherein the various moieties are defined therein.

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

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



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



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

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

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

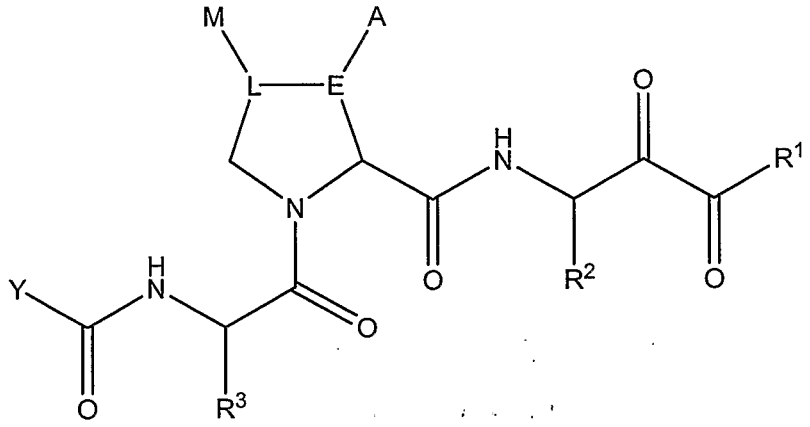
There is a need for methods for modulating the activity of serine proteases, particularly the HCV NS3/NS4a serine protease, using the compounds provided herein.

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

Summary of the Invention

In its many embodiments, the present invention provides a novel class of inhibitors of the HCV protease, pharmaceutical compositions containing one or more of the compounds, methods of preparing pharmaceutical

formulations comprising one or more such compounds, and methods of treatment or prevention of HCV or amelioration of one or more of the symptoms of hepatitis C using one or more such compounds or one or more such formulations. Also provided are methods of modulating the interaction of an HCV polypeptide with HCV protease. Among the compounds provided herein, compounds that inhibit HCV NS3/NS4a serine protease activity are preferred. The present invention discloses compounds, as well as pharmaceutically acceptable salts, solvates or esters of said compounds, said compounds having the general structure shown in structural Formula I:

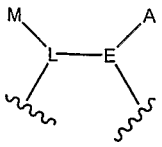


Formula I

wherein:

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

A and M can be the same or different, each being independently selected from R, OR, NHR, NRR', SR, SO_2R, and halo; or A and M are connected to each other such that the moiety:



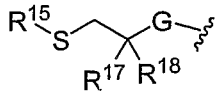
shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl;

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

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

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

and Y is selected from the following moieties: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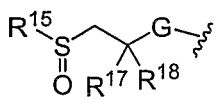
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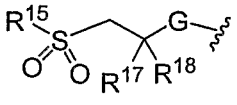
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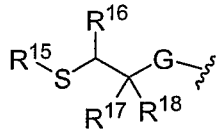
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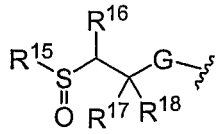
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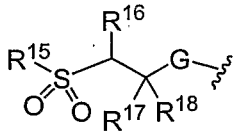
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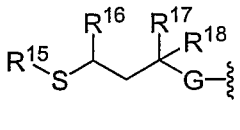
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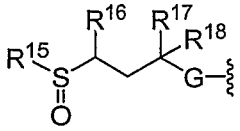
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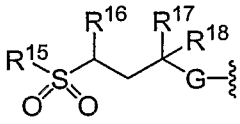
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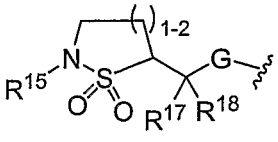
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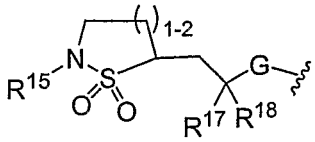
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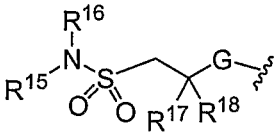
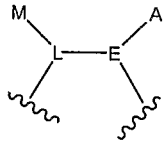
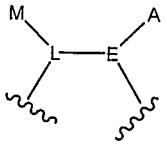


wherein G is NH or O; and R^{15}, R^{16}, R^{17} and R^{18} can be the same or different, each being independently selected from the group consisting of H, alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, or alternately, (i) R^{15} and R^{16} are connected to each other to form a four to eight-membered cyclic structure, and (ii) likewise, independently R^{17} and R^{18} are connected to each other to form a three to eight-membered cycloalkyl or heterocyclyl; wherein each of said alkyl, aryl, heteroaryl, cycloalkyl or heterocyclyl can be unsubstituted or optionally independently substituted with one or more moieties selected from the group consisting of: hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, amido, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, sulfonamido, alkylsulfonamido, arylsulfonamido, alkyl, aryl, heteroaryl, keto, carboxy, carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyloxy, alkylureido, arylureido, halo, cyano, and nitro.

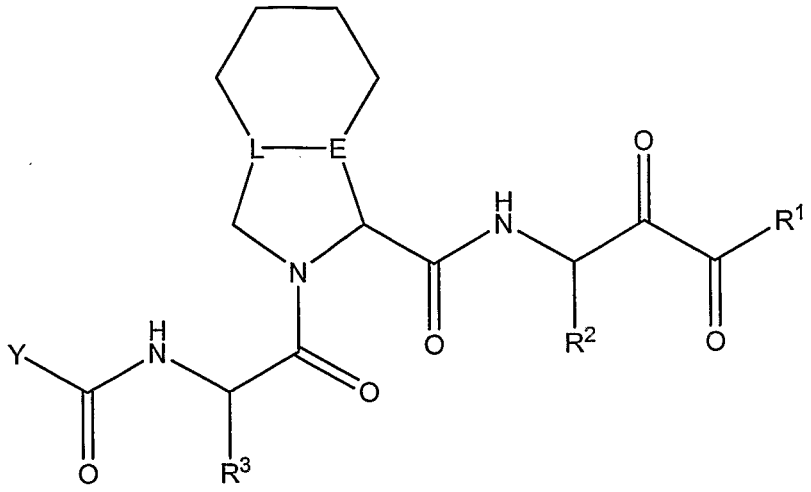
The above-noted statement "A and M are connected to each other such that the moiety:



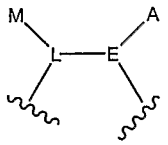
shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl" can be illustrated in a non-limiting manner as follows. Thus, for example, in the case where A and M are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



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



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



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

The statement "alternately, (i) R^{15} and R^{16} are connected to each other to form a four to eight-membered cyclic structure, and (ii) likewise, independently R^{17} and R^{18} are connected to form a three to eight-membered cycloalkyl or heterocyclyl" means the following possibilities: (i) R^{15} and R^{16} are connected to form a cyclic structure while R^{17} and R^{18} are not; (ii) R^{17} and R^{18} are connected to form a cyclic structure while R^{15} and R^{16} are not; and (iii) R^{15} and R^{16} are connected to form a cyclic structure, *and* R^{17} and R^{18} are also

connected to form a cyclic structure. These possibilities can occur independent of one another.

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

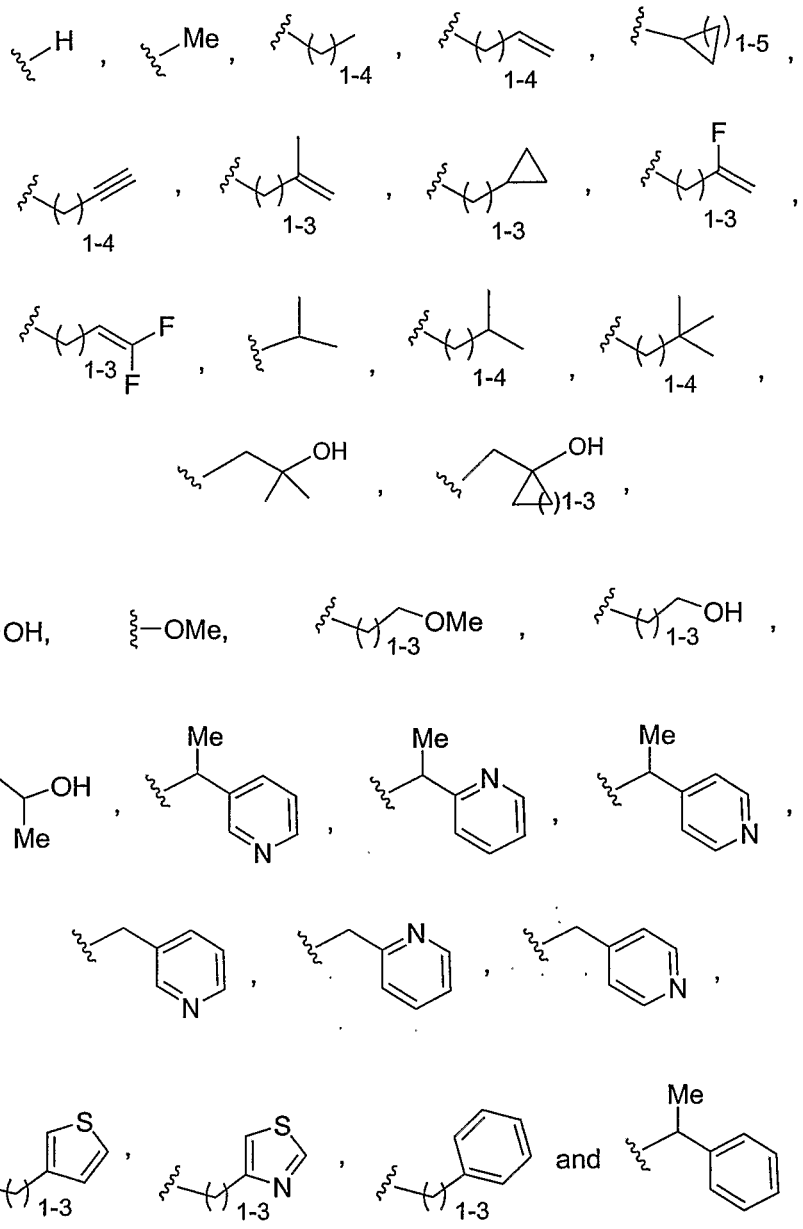
The compounds represented by Formula I, by themselves or in combination with one or more other suitable agents disclosed herein, can be useful for treating diseases such as, for example, HCV, HIV, (AIDS, Acquired Immune Deficiency Syndrome), and related disorders, as well as for modulating the activity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

Detailed Description

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

In another embodiment, R^1 is NR^9R^{10}, and R^9 is H, R^{10} is H, or R^{14} wherein R^{14} is H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, alkyl-aryl, alkyl-heteroaryl, aryl-alkyl, alkenyl, alkynyl or heteroaryl-alkyl.

In another embodiment, R^{14} is selected from the group consisting of:


H
Me
1-4
1-4
1-5
1-4
1-3
1-3
F
1-3
F
1-3
F
1-4
1-4
OH
OH
1-3
—OH,
—OMe,
OMe
1-3
OH
1-3
OH
Me
Me
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Me
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1-3
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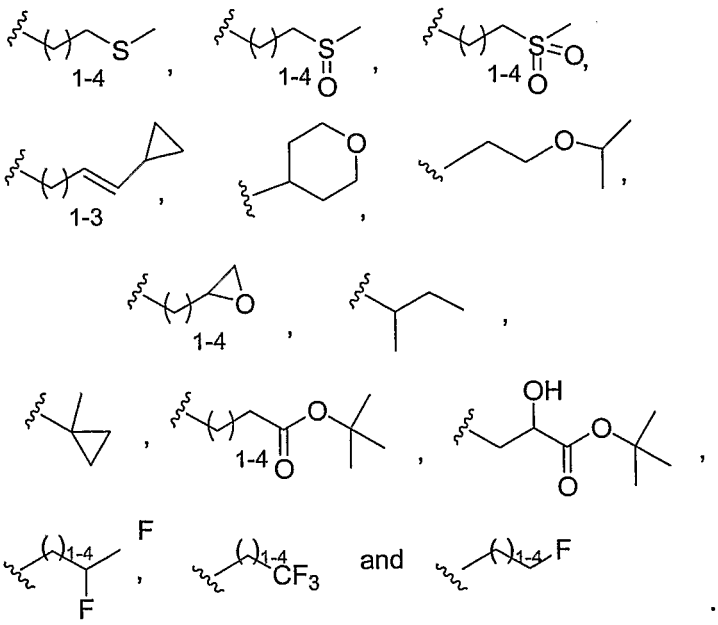
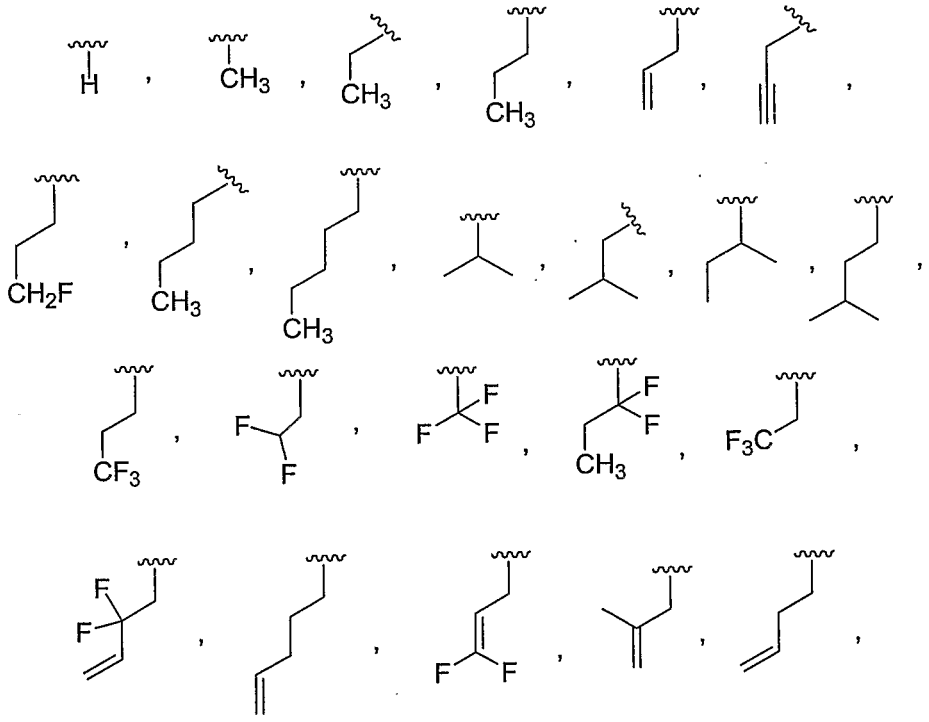
and
Me



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



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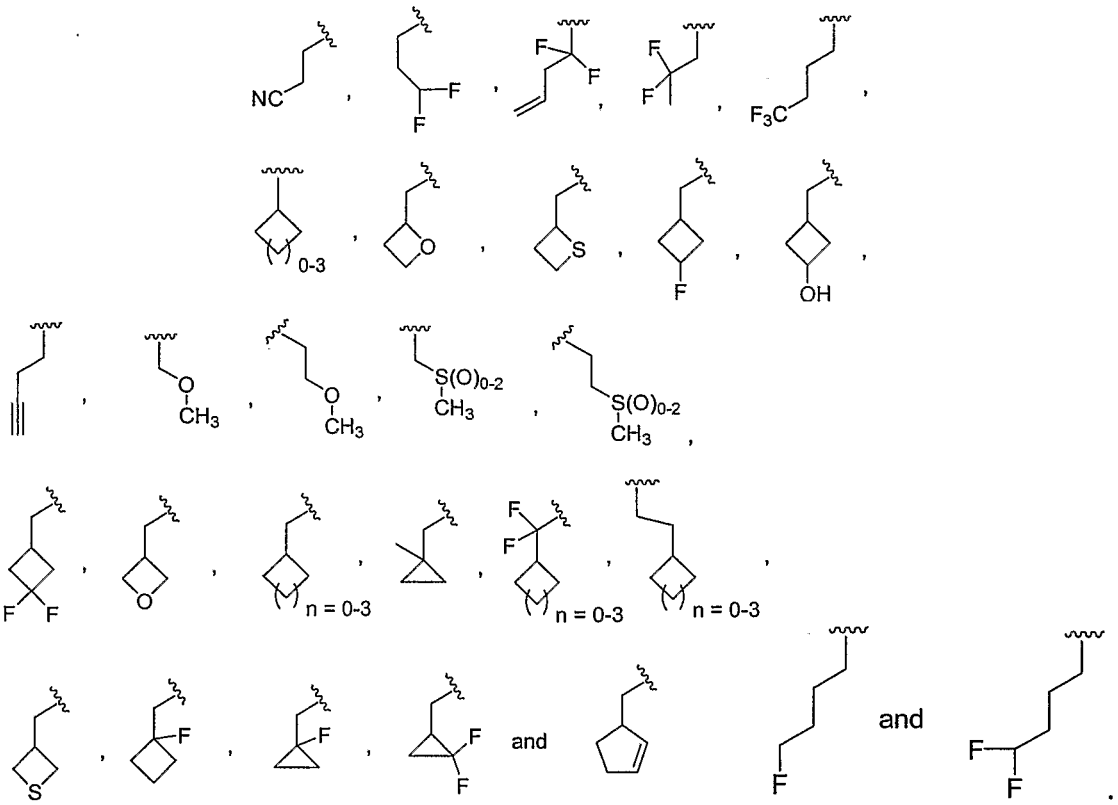
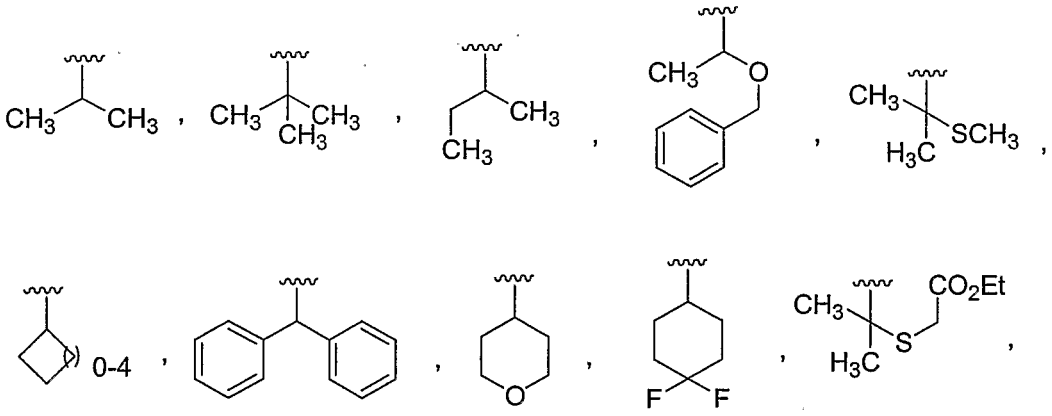
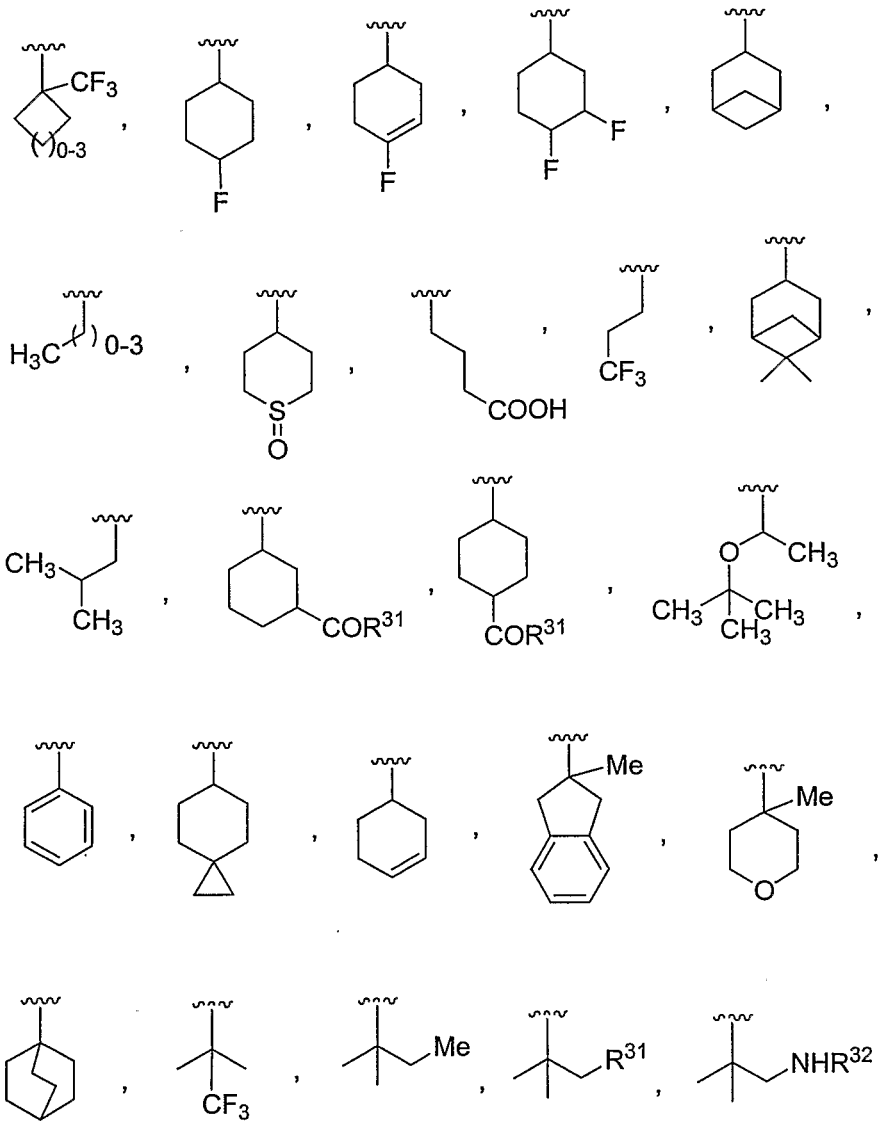


In another embodiment, R^3 is selected from the group consisting of:




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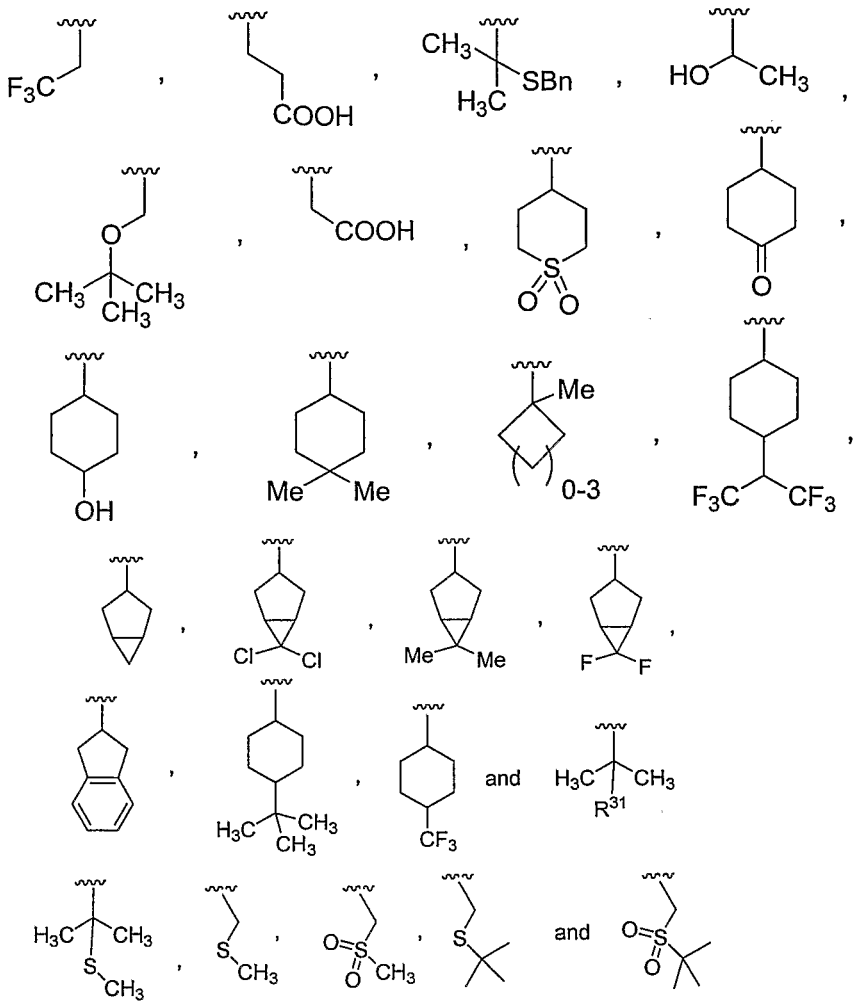
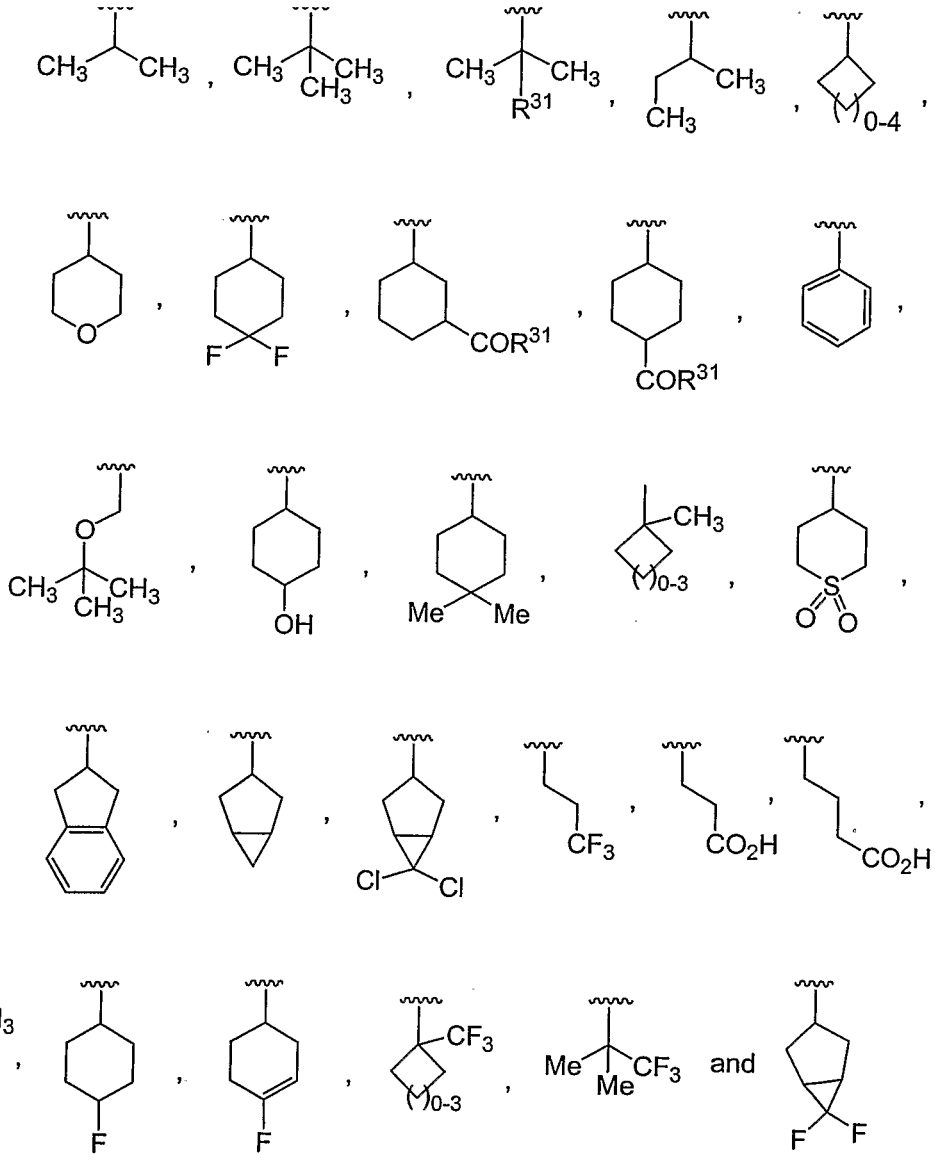
Me
O
CF3
Me
R31
NHR32



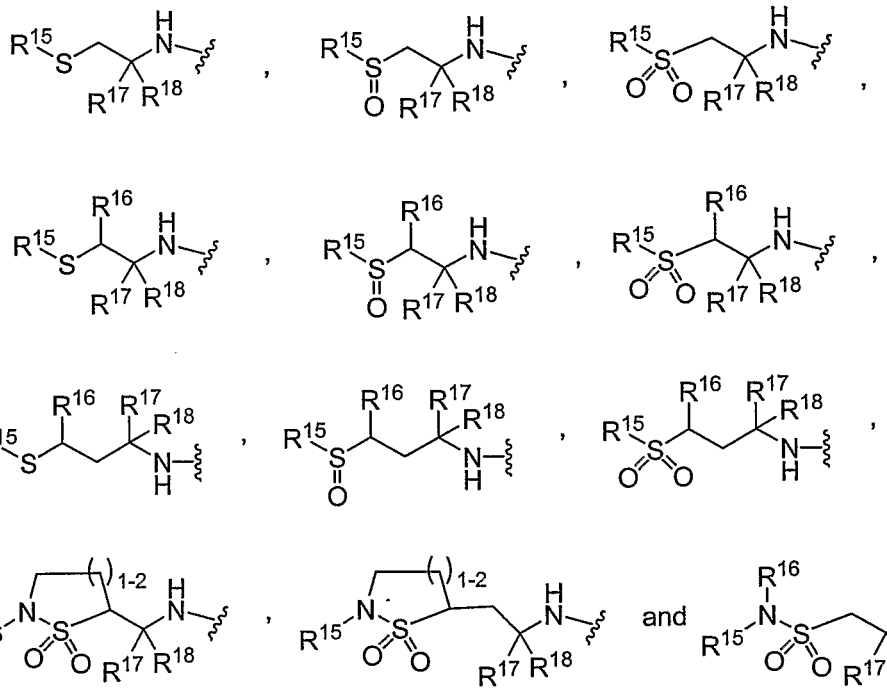
wherein R^{31} is OH or O-alkyl; and

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

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

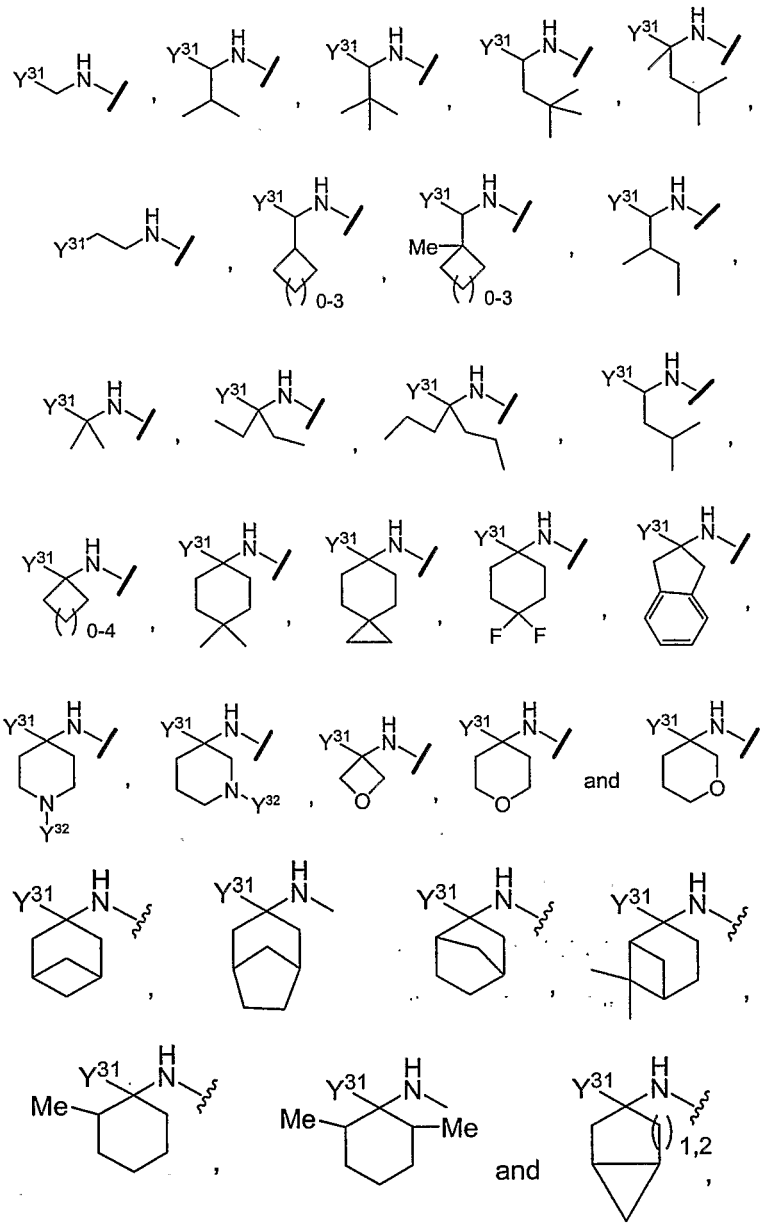


In another embodiment, Y is selected from the following moieties:

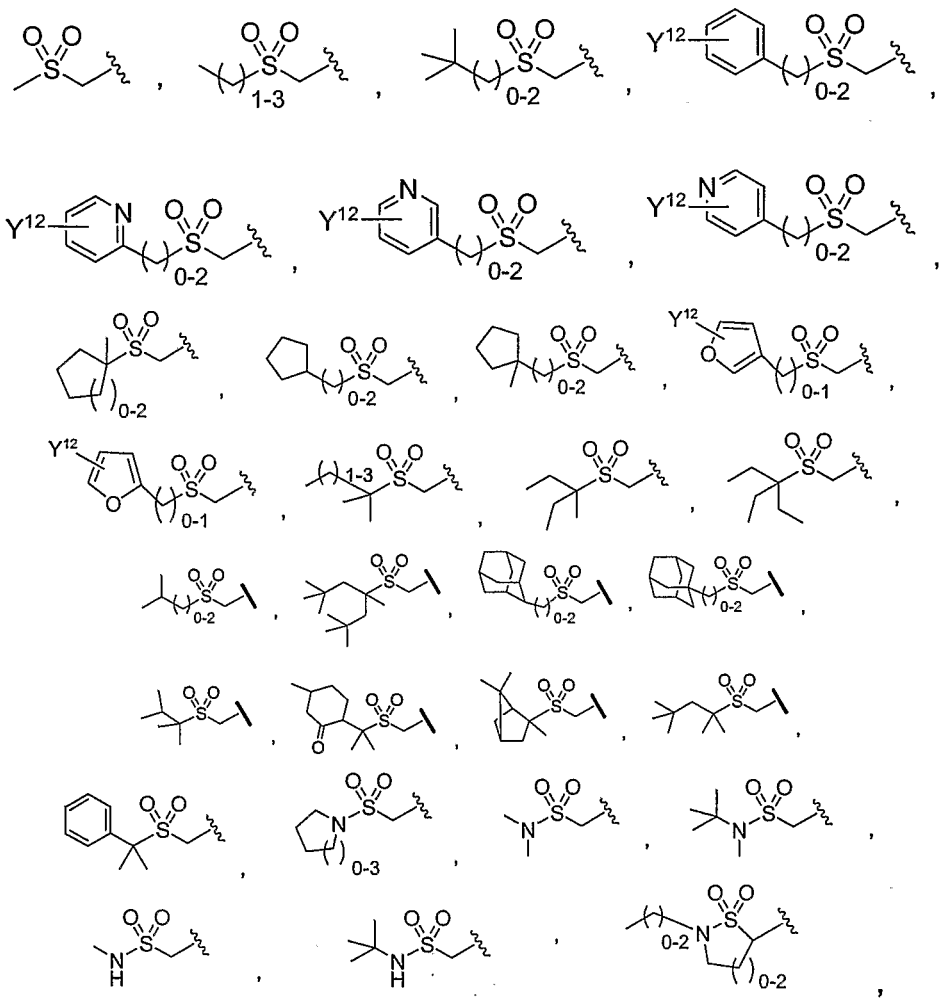


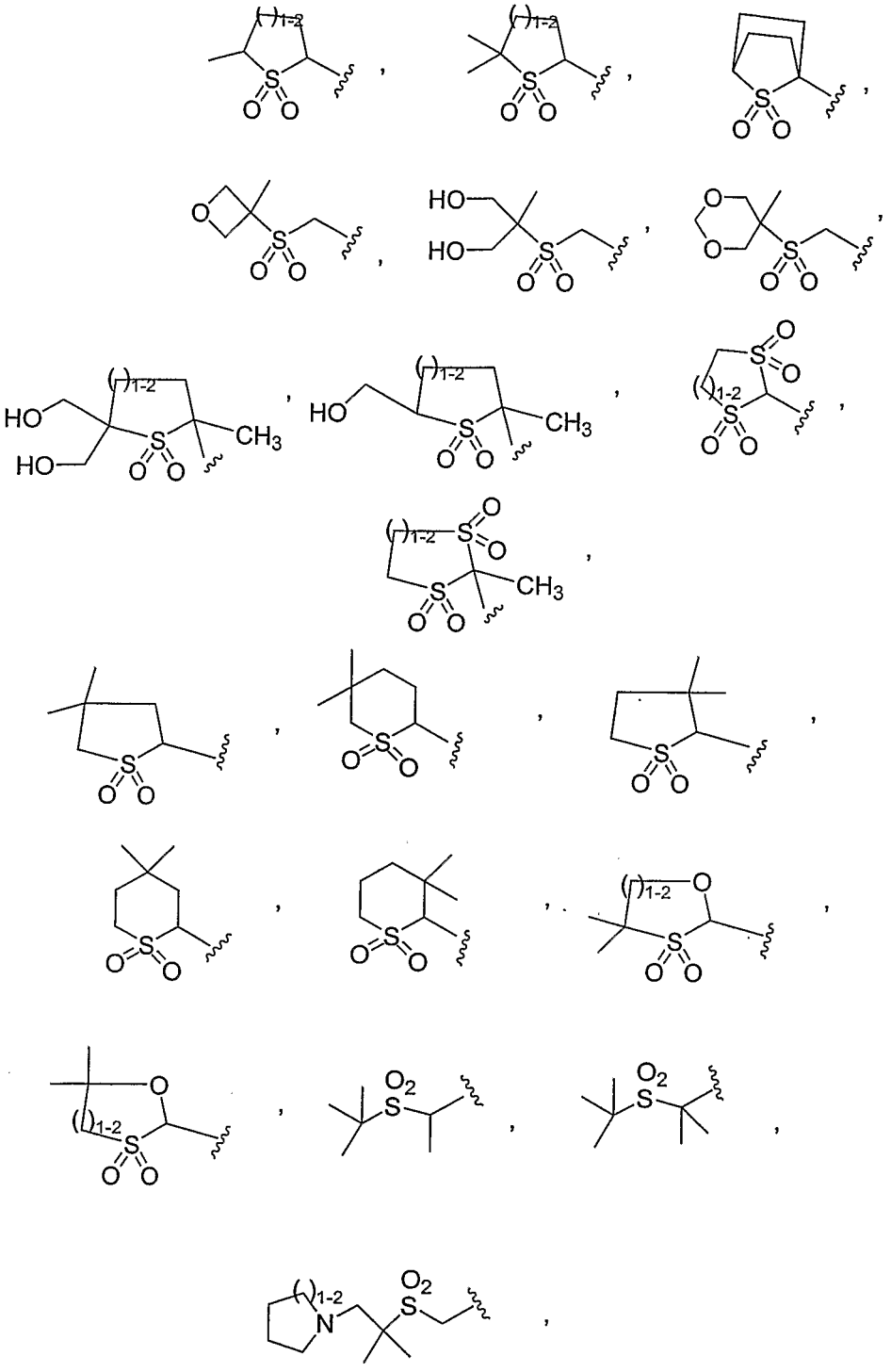
wherein R^{15}, R^{16}, R^{17} and R^{18} can be the same or different, each being independently selected from the group consisting of H, alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, or alternately, R^{15} and R^{16} are connected to each other to form a four to eight-membered cycloalkyl or heterocyclic structure, and/or R^{17} and R^{18} are connected to each other to form a three to eight-membered cycloalkyl or heterocyclyl, wherein each of said aryl, heteroaryl, cycloalkyl or heterocyclyl can be unsubstituted or optionally independently substituted with one or more moieties selected from the group consisting of: hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, amido, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, sulfonamido, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyloxy, alkylureido, arylureido, halo, cyano, and nitro.

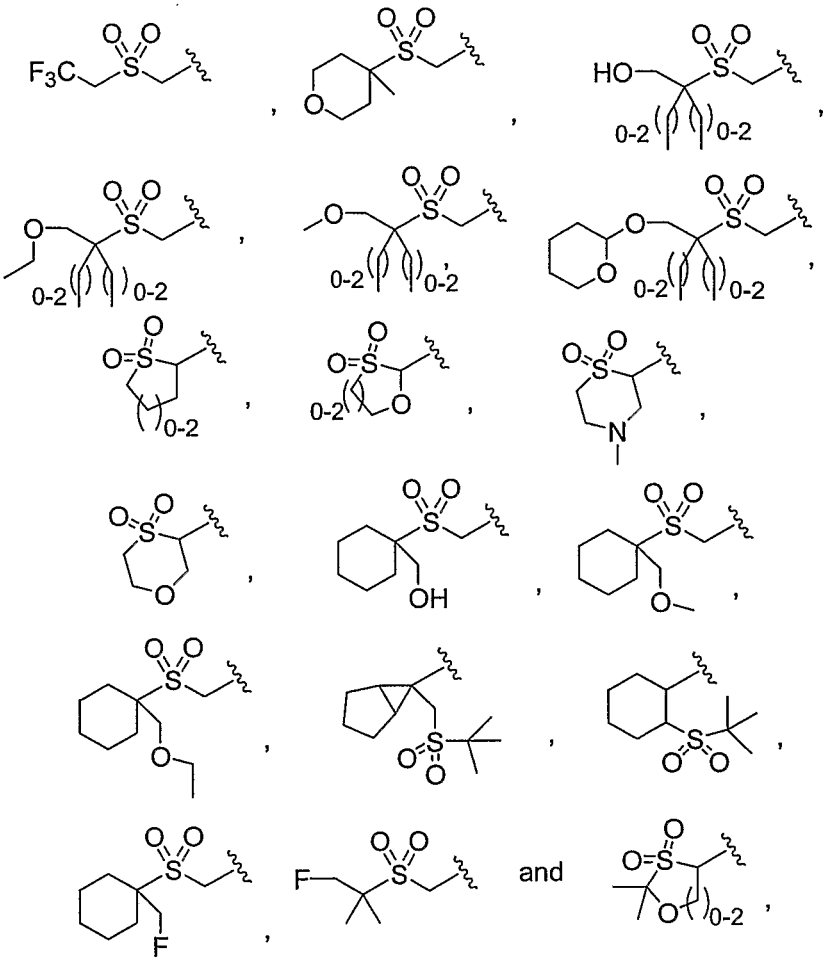
In an additional embodiment, Y is selected from the group consisting of:



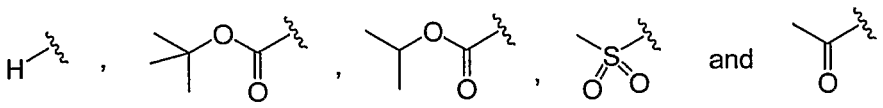
wherein Y^{31} is selected from the group consisting of:





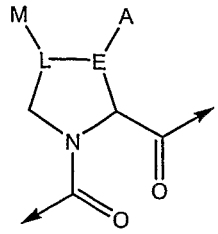


Y^{32} is selected from the group consisting of:

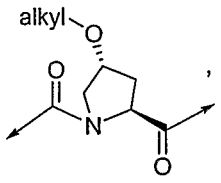
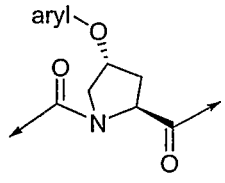
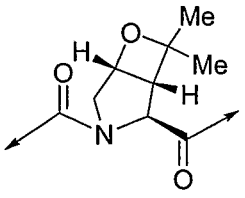
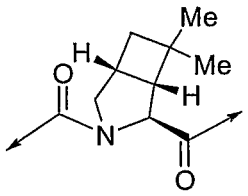
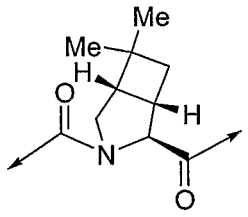
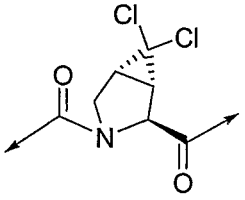
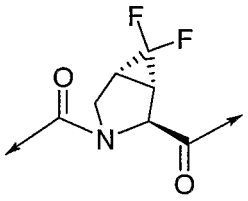
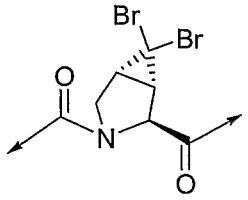
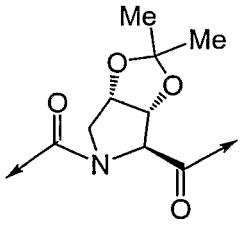


and Y^{12} is selected from the group consisting of H, CO_2H, CO_2Me, OMe, F, Cl, Br, NH_2, $N(H)S(O_2)CH_3$, $N(H)C(O)CH_3$, NO_2, $S(O_2)NH_2$, CF_3, Me, OH, OCF_3, and $C(O)NH_2$.

In another embodiment, the moiety:



is selected from the following structures:

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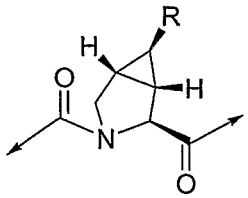
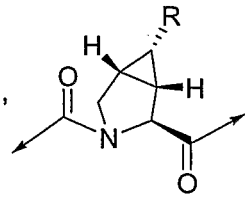
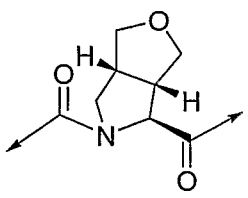
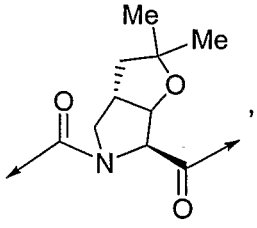
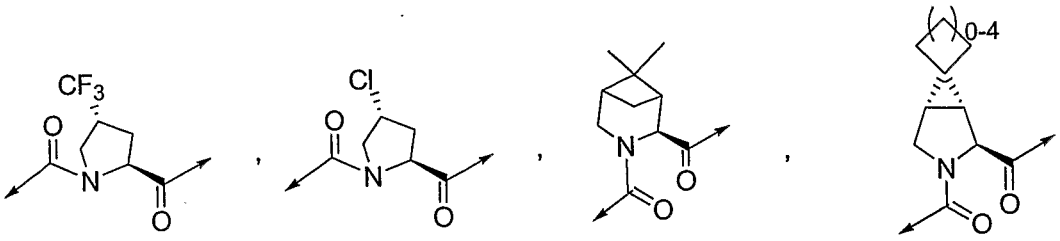
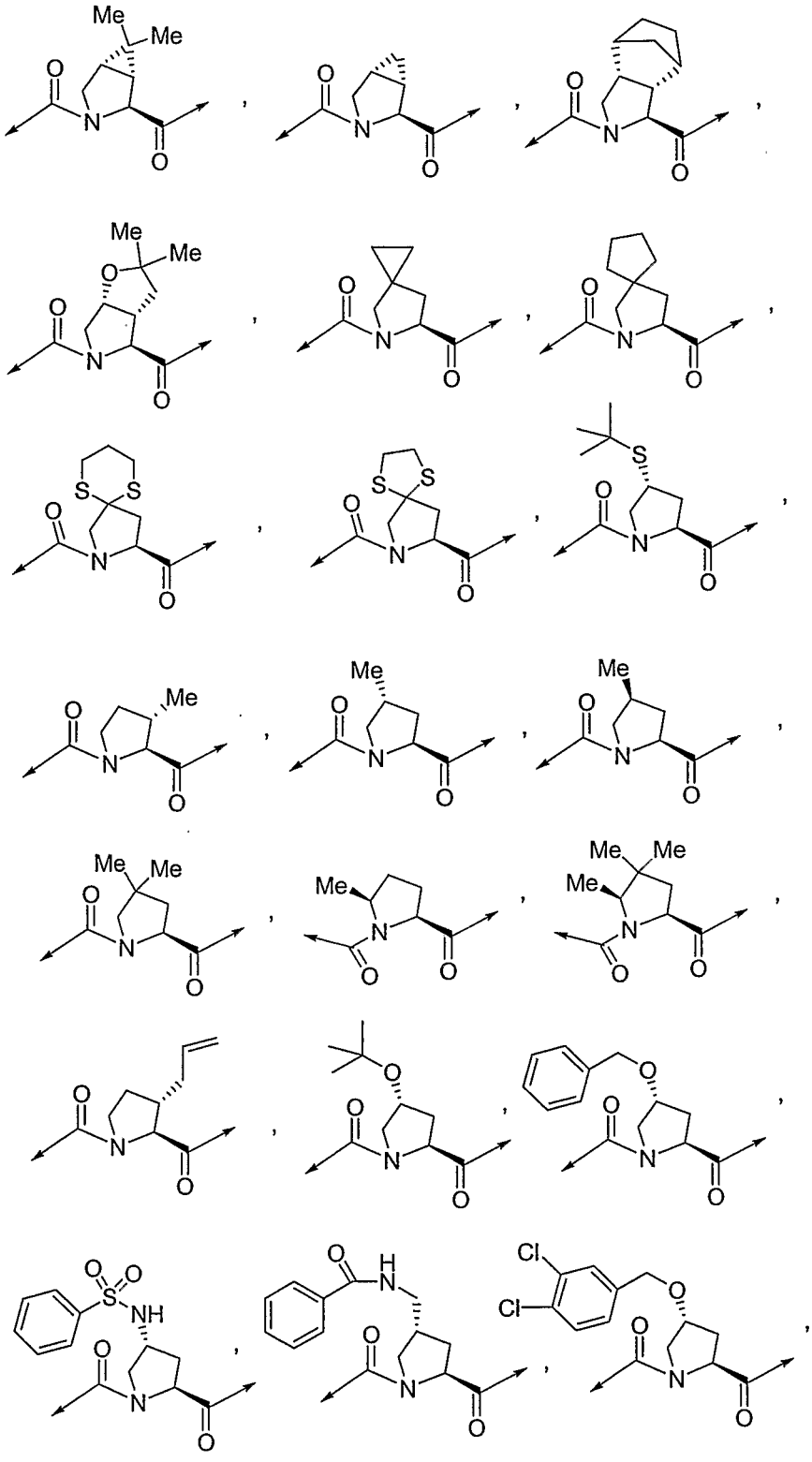
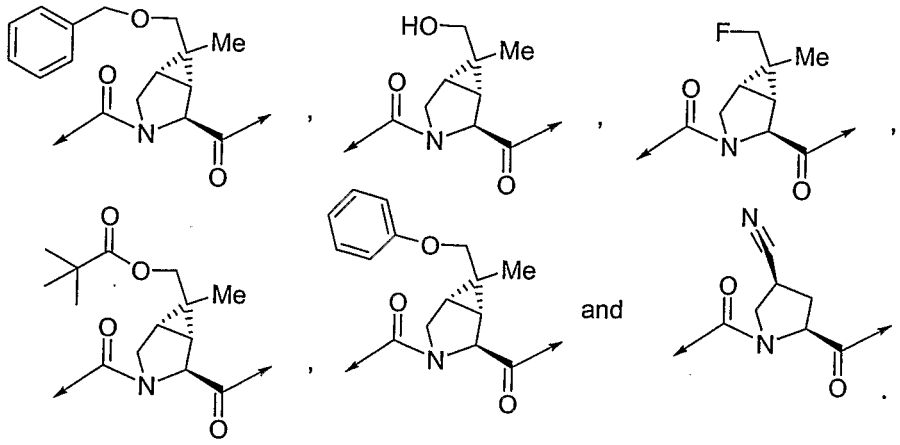
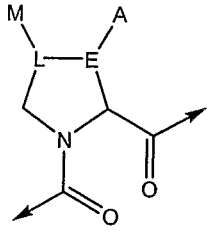






CF3
O
N
O
,
Cl
O
N
O
,
N
O
O
,
0-4
N
O
O

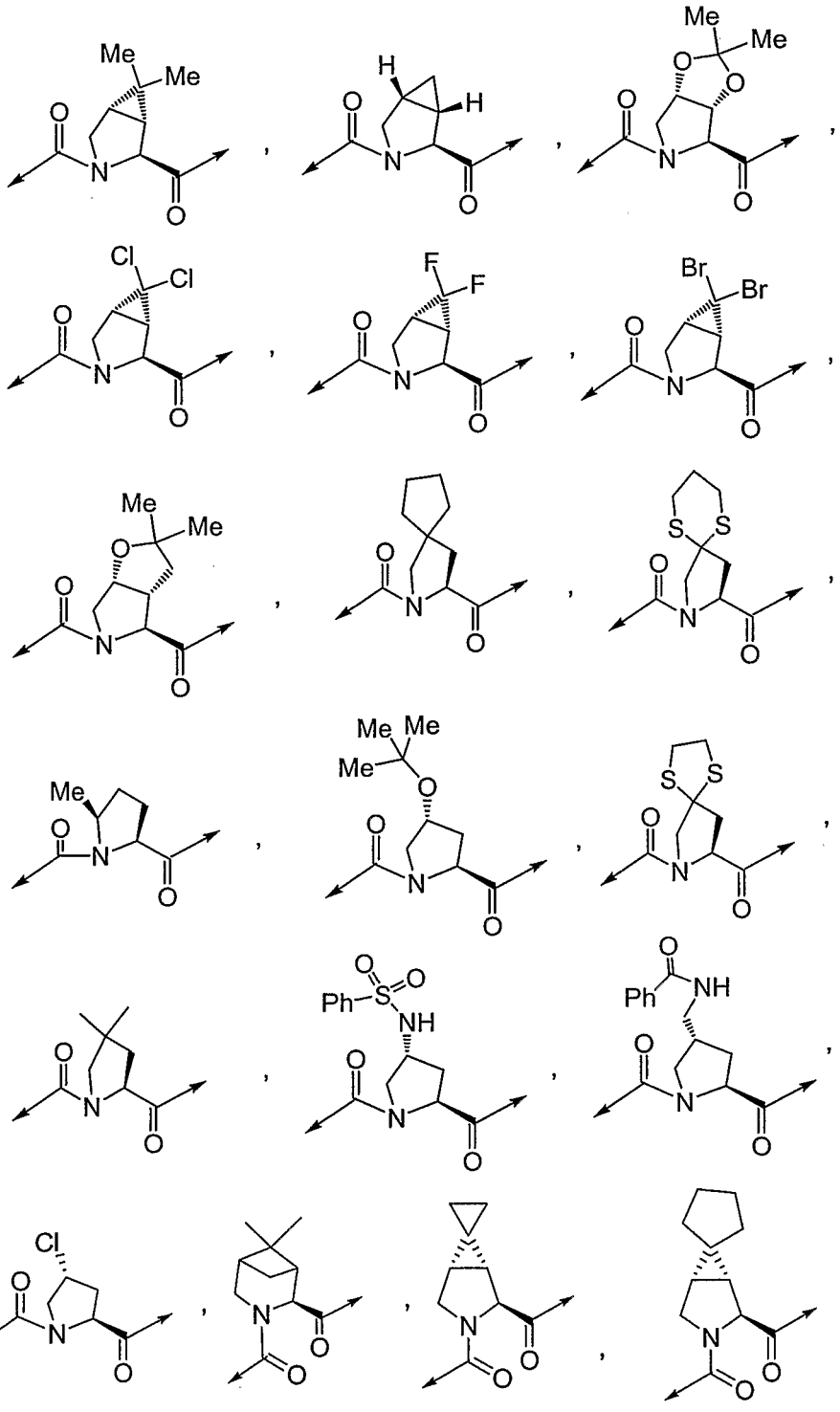


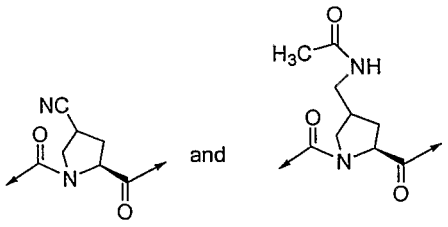


In an additional embodiment, the moiety:

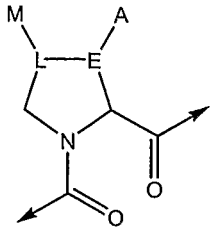


is selected from the following structures:

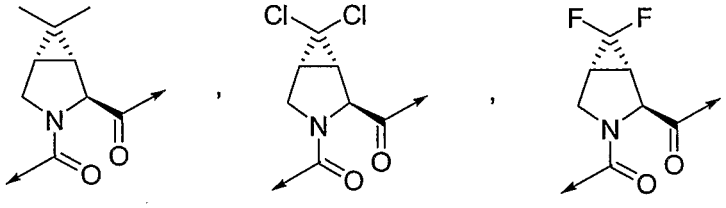


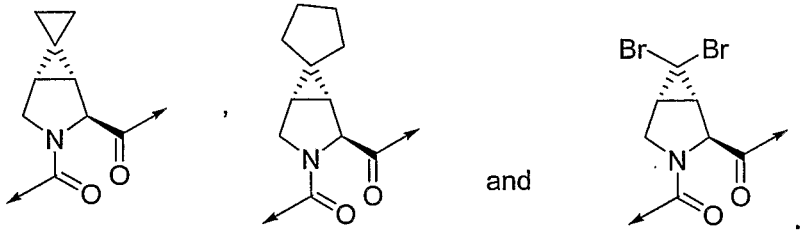


In an additional embodiment, the moiety:



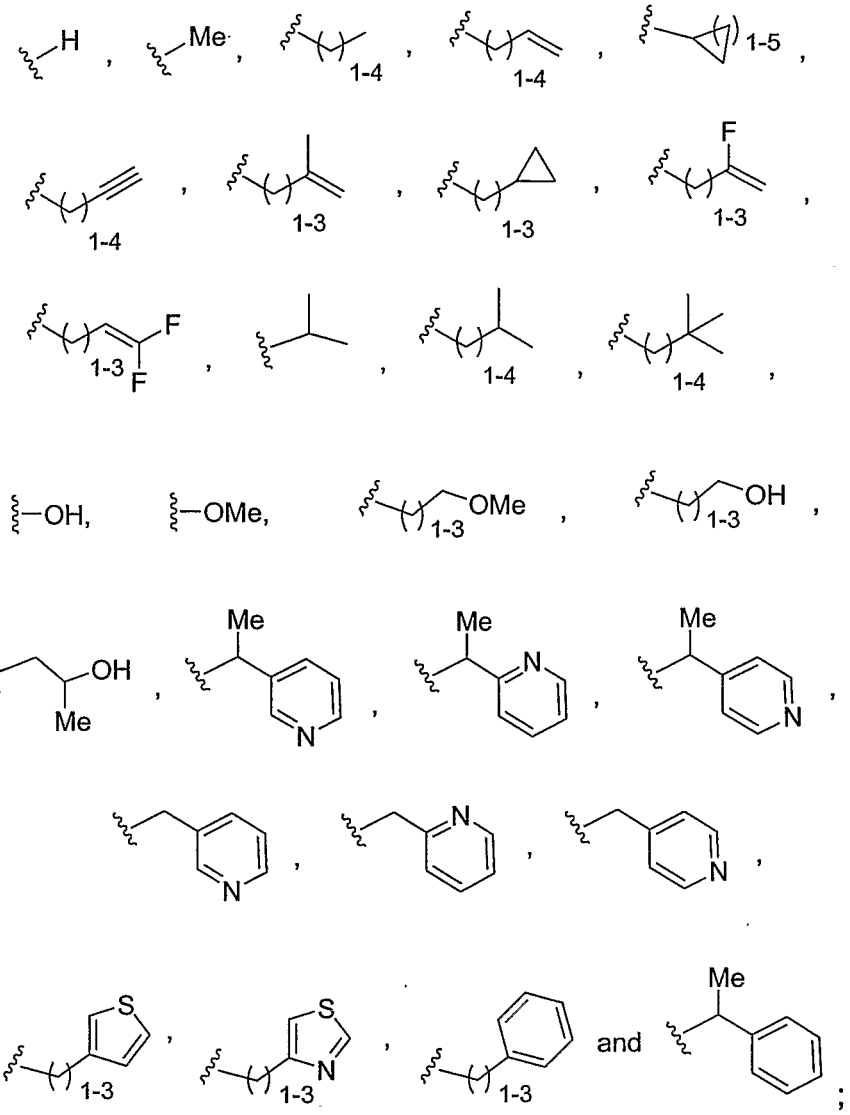
is selected from the following structures:





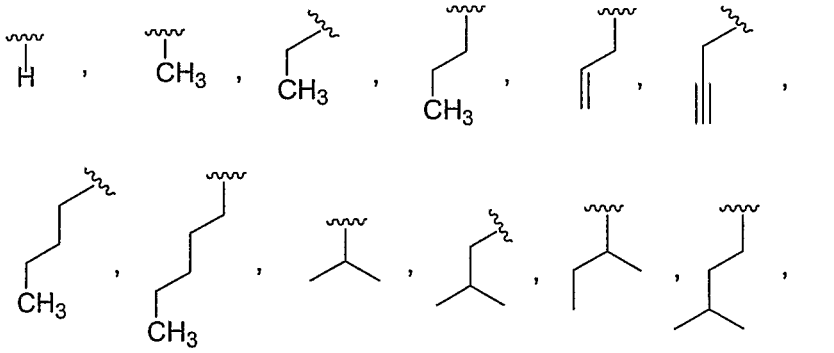
and

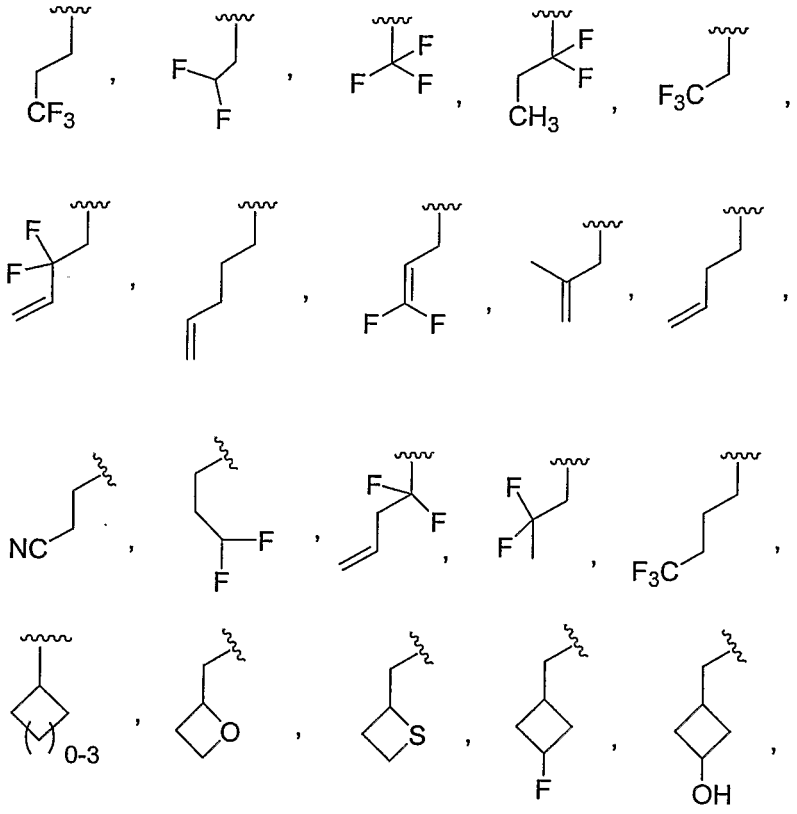
In a still additional embodiment, R^1 is NHR^{14}, where R^{14} is selected from the group consisting of:



;

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




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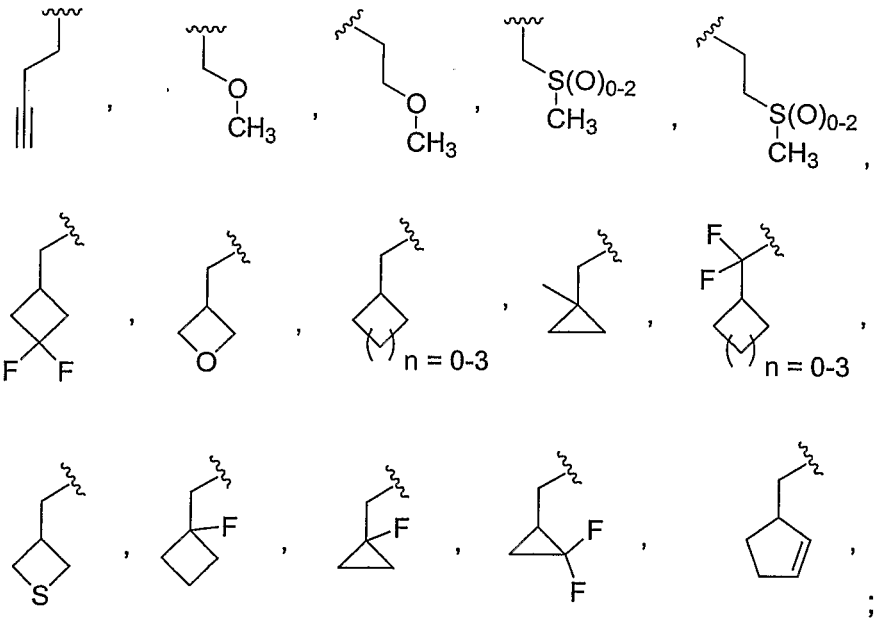
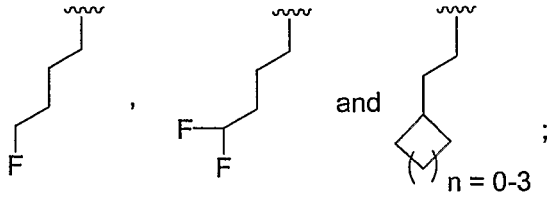
0-3
O
S
F
OH

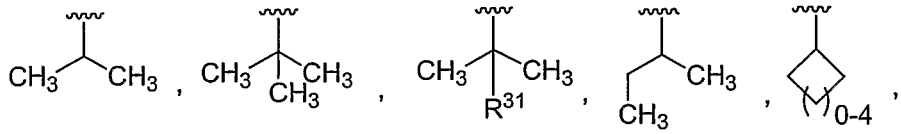
5

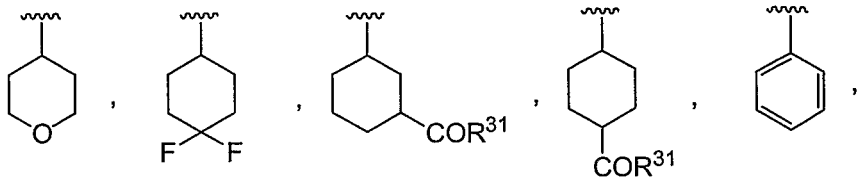

O
CH3
O
CH3
S(O)0-2
CH3
S(O)0-2
CH3
F
F
O
n = 0-3
F
F
n = 0-3
S
F
F
F
F

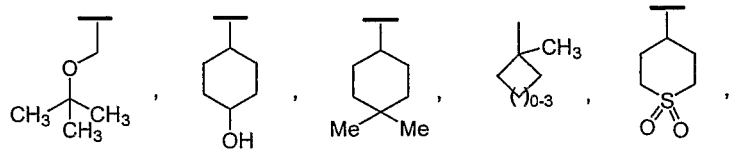
;

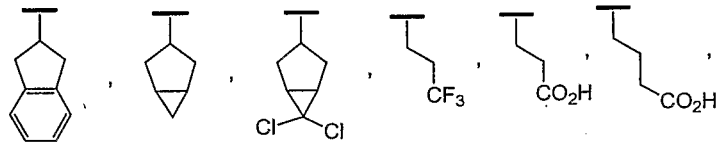


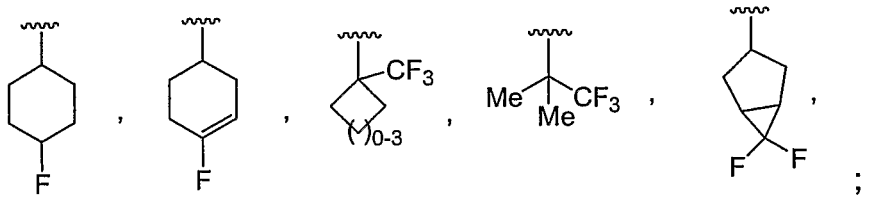
R^3 is selected from the group consisting of the following moieties:



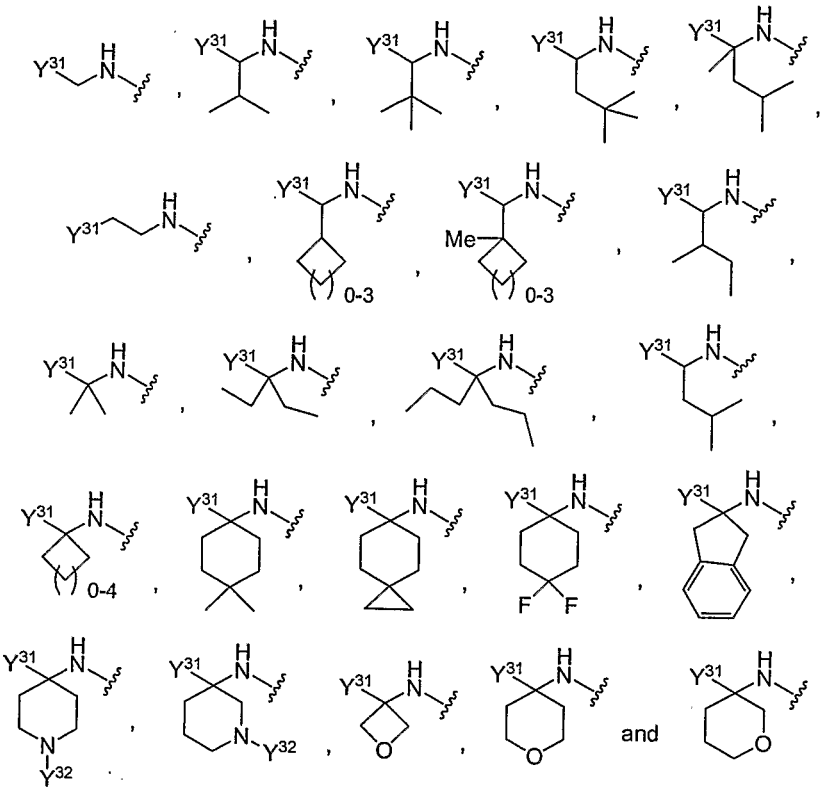




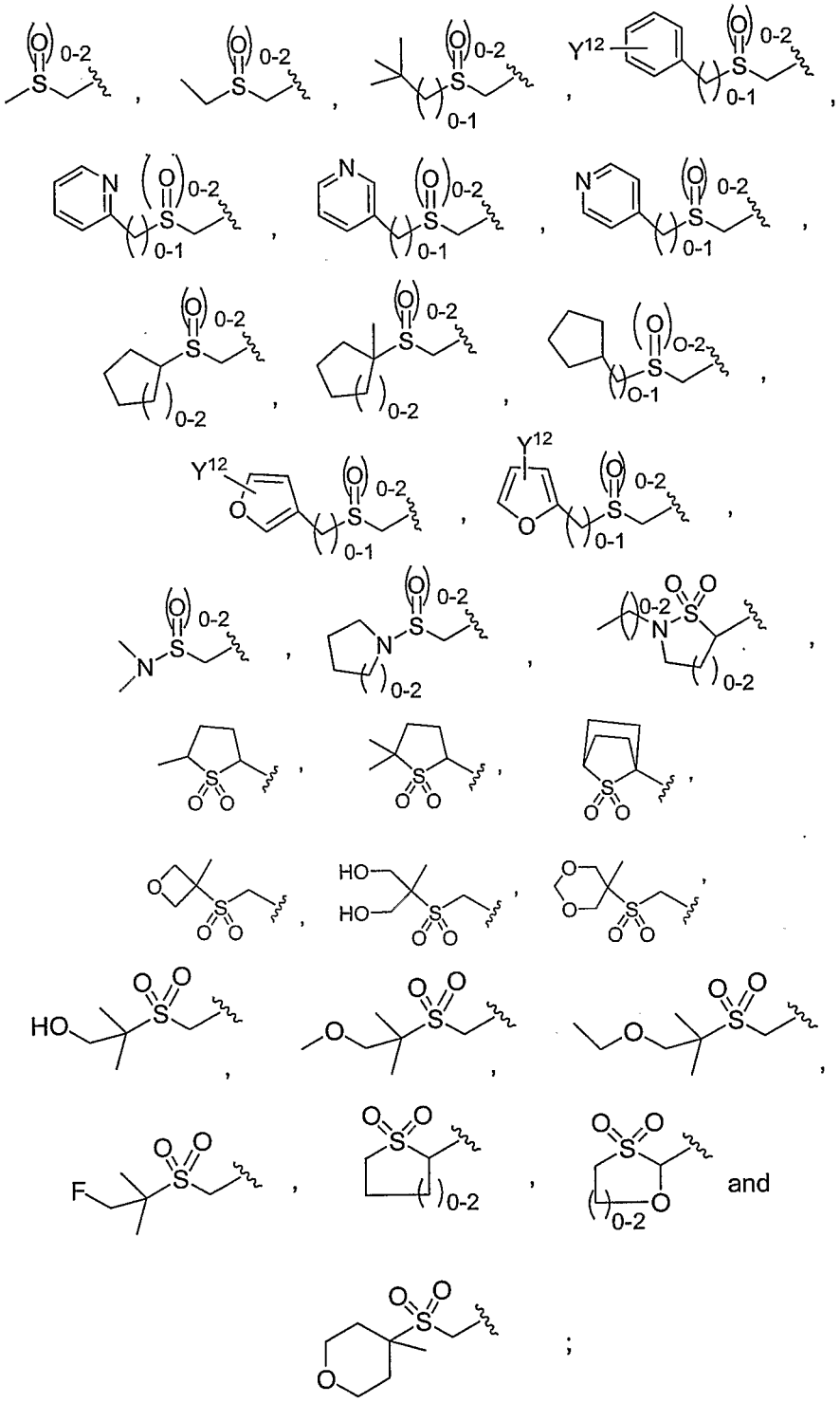




Y is selected from the group consisting of:



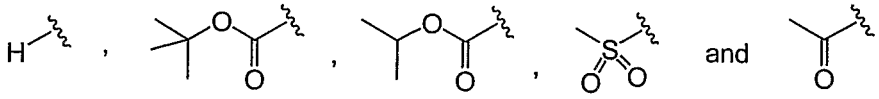
wherein Y^{31} is selected from the group consisting of:



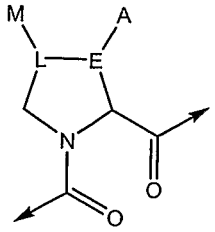
and

;

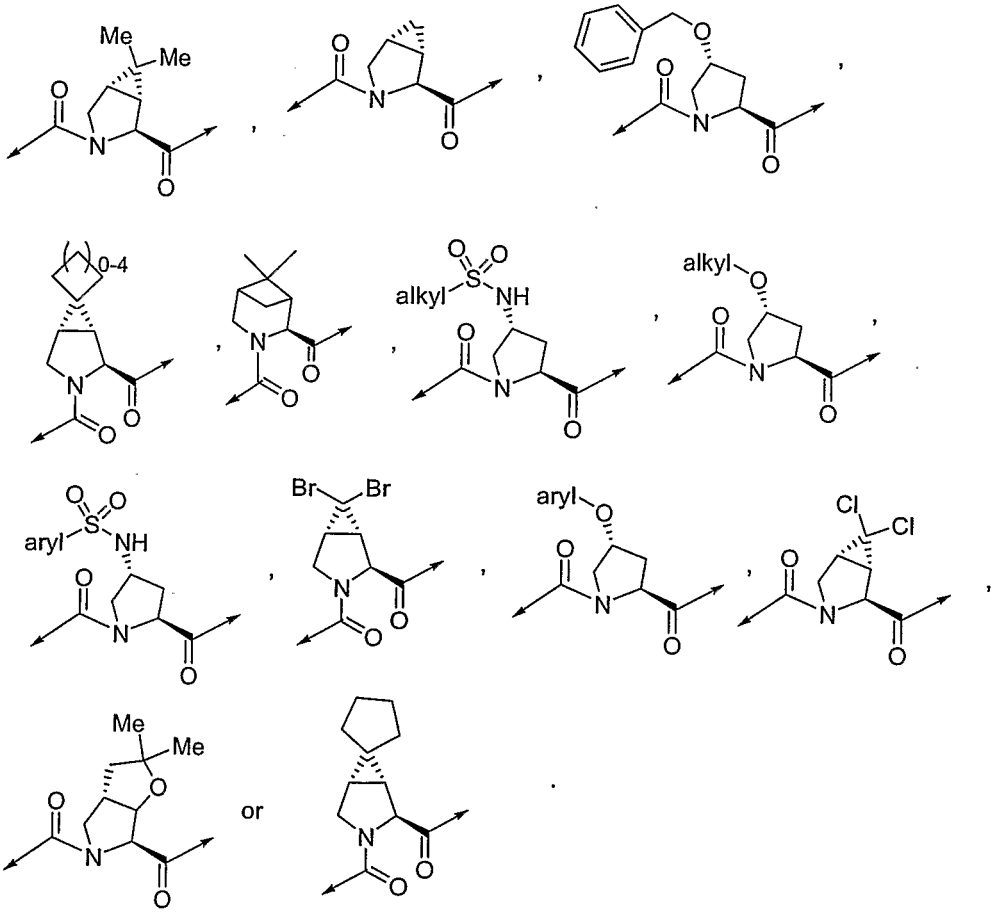
Y^{32} is selected from the group consisting of:



and Y^{12} is selected from the group consisting of H, CO_2H, CO_2Me, OMe, F, Cl, Br, NH_2, $N(H)S(O_2)CH_3$, $N(H)C(O)CH_3$, NO_2, $S(O_2)NH_2$, CF_3, Me, OH, OCF_3, and $C(O)NH_2$; and the moiety:

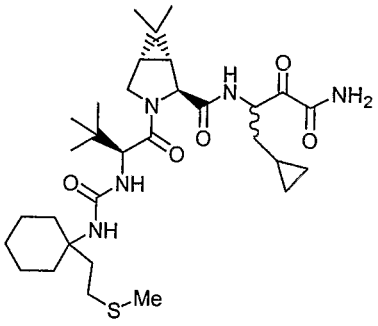


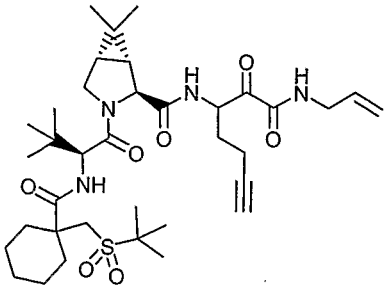
is:

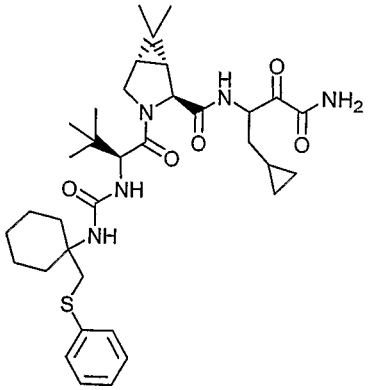


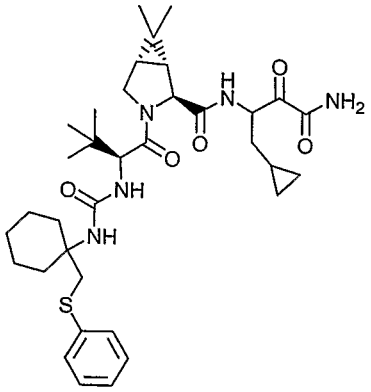
Yet another embodiment of the invention discloses compounds in **Table 1** below, as well as shown later in **Table 1**, **Table 3**, **Table 3A**, **Table 4**, **Table 4A** and **Table 5**:

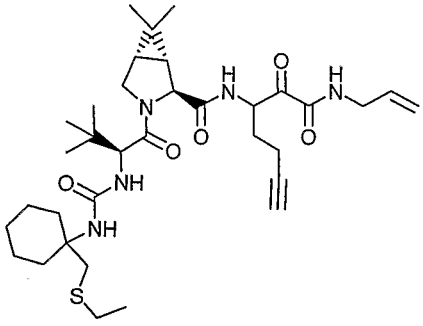
Table 1

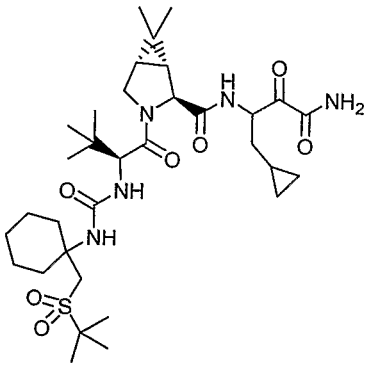


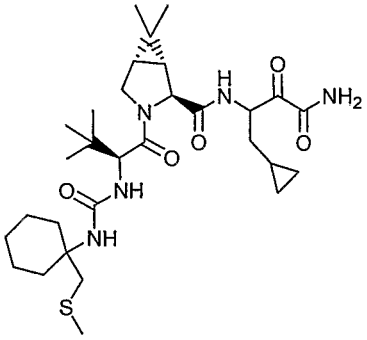


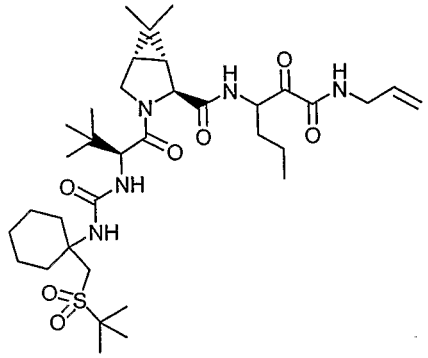


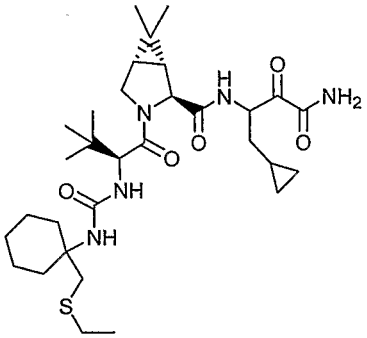


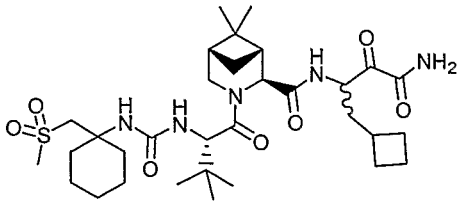


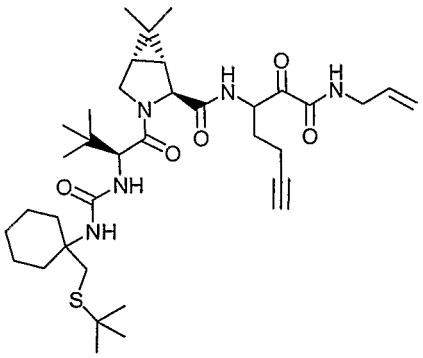


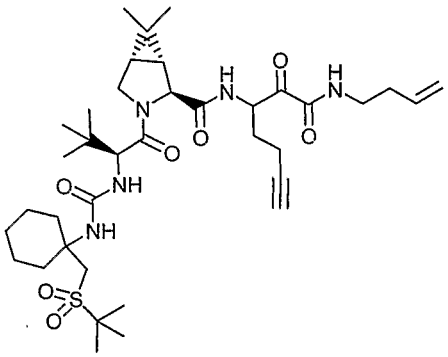


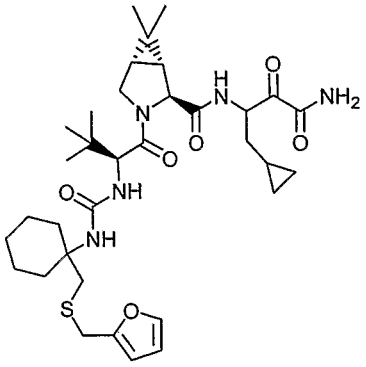


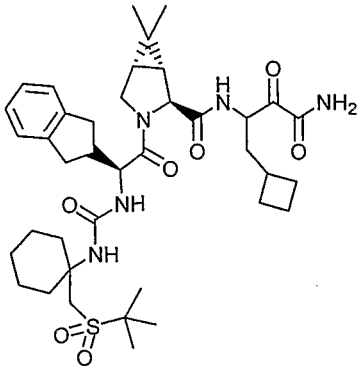


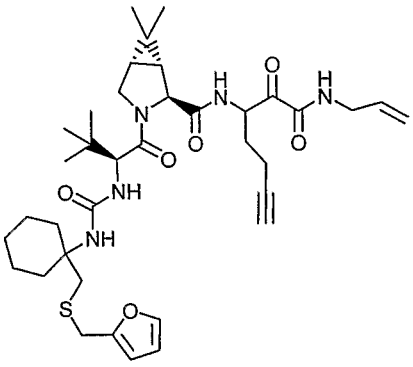


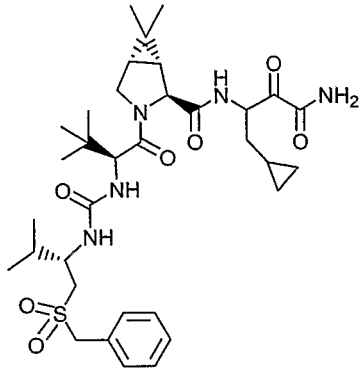


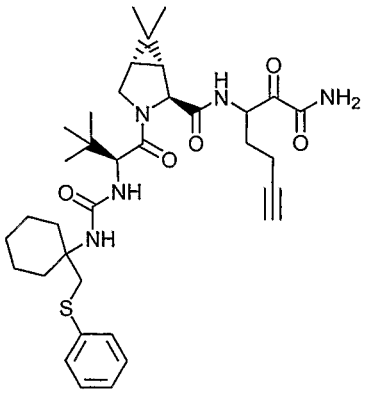


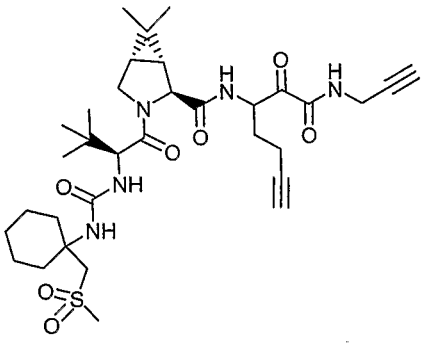


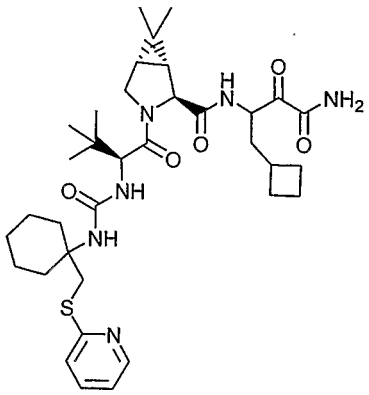


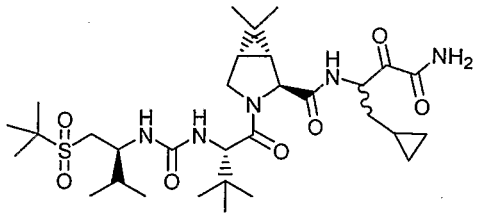


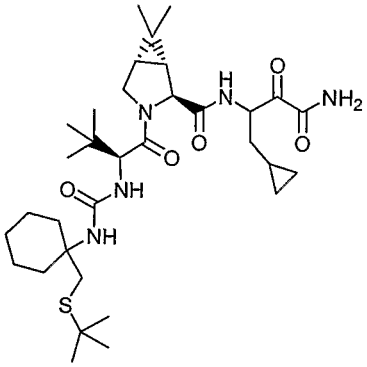


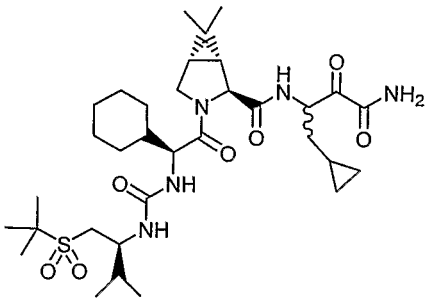


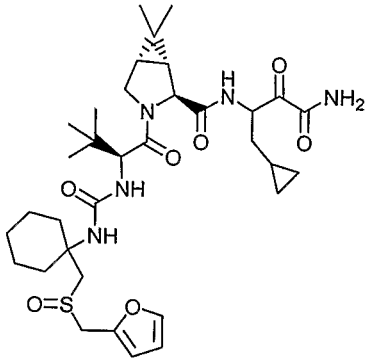


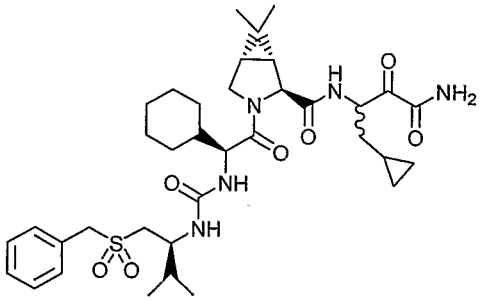


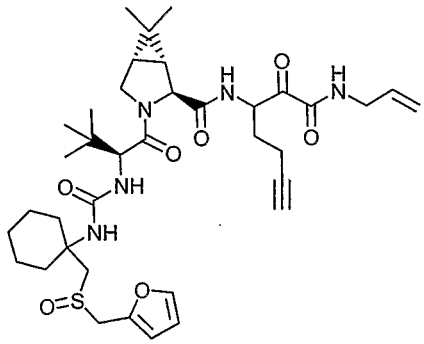


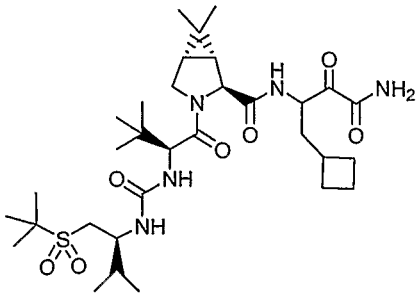


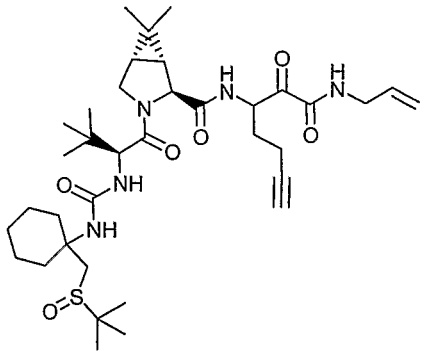


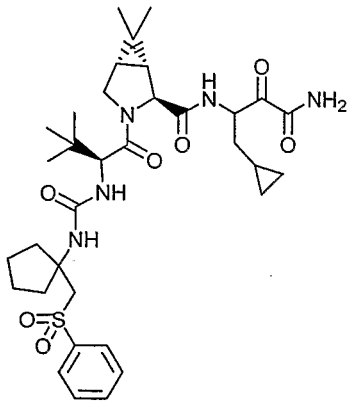


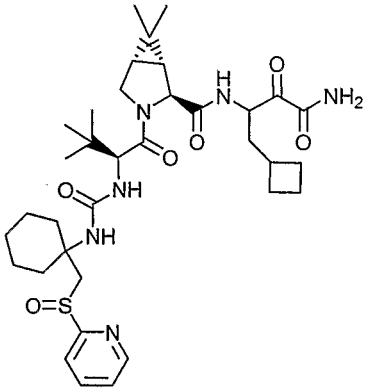


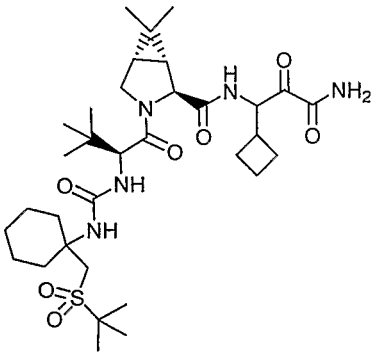


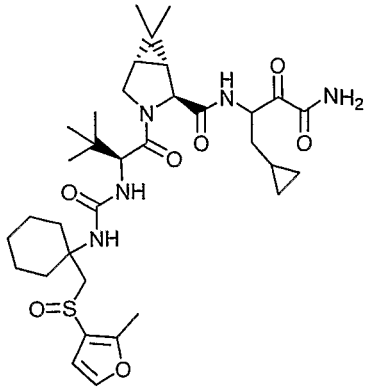


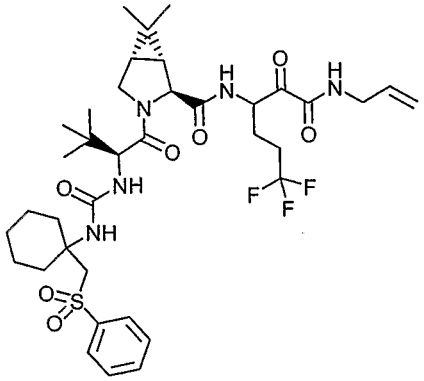


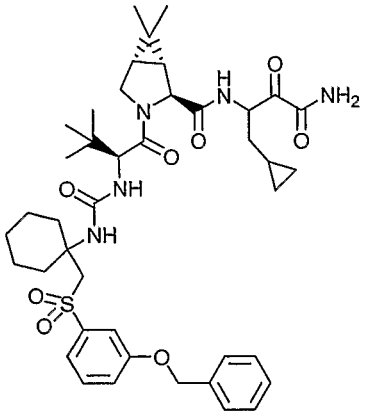


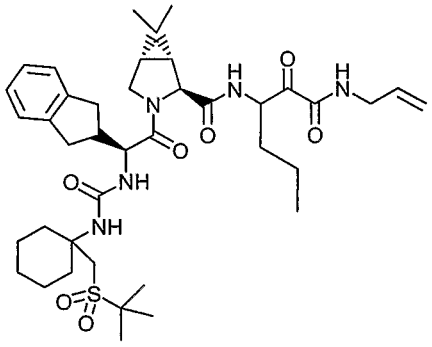


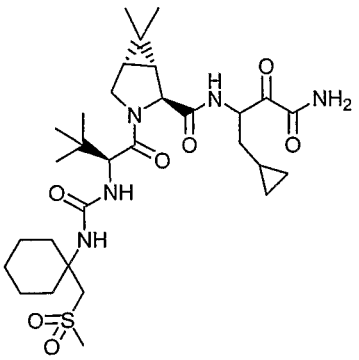


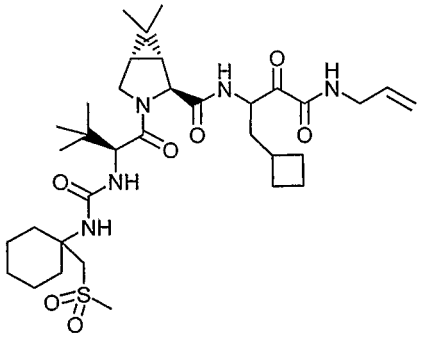


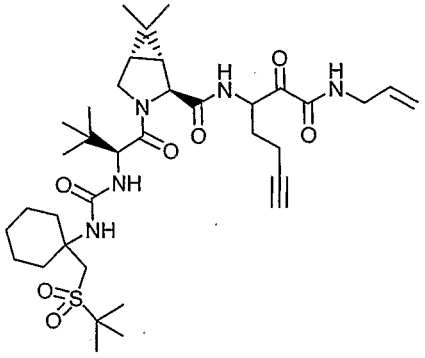


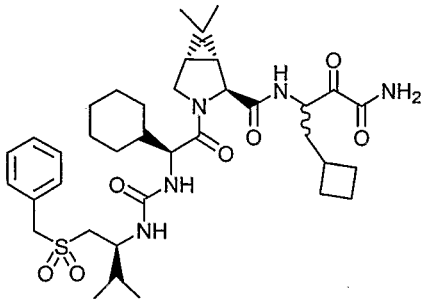


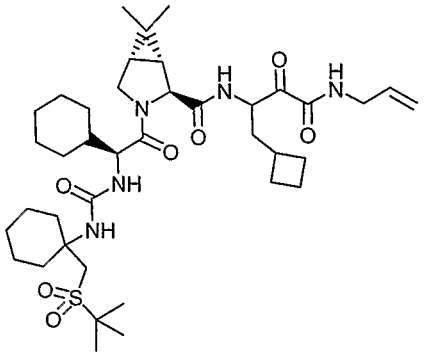


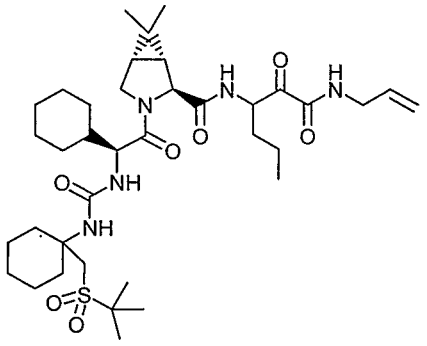


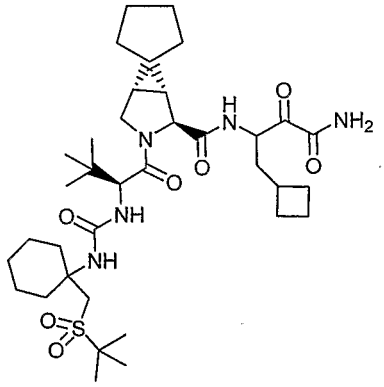


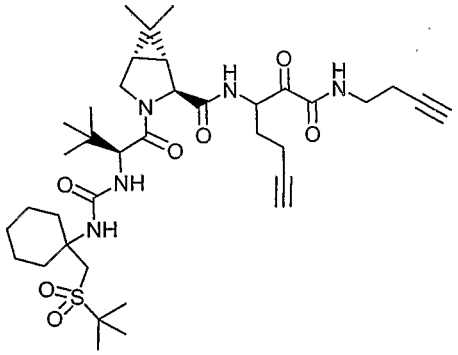


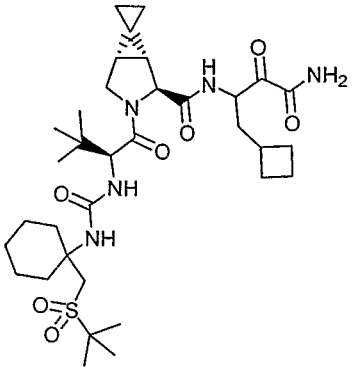


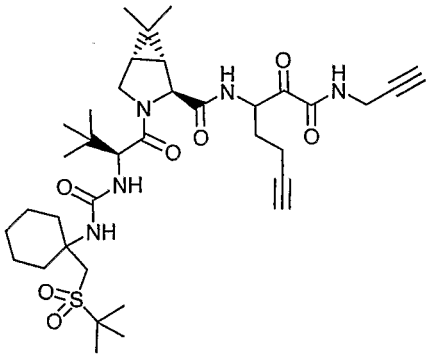


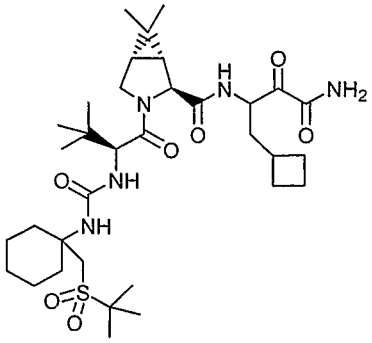


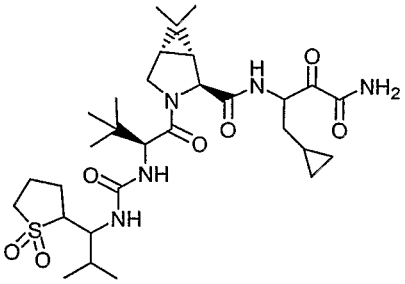


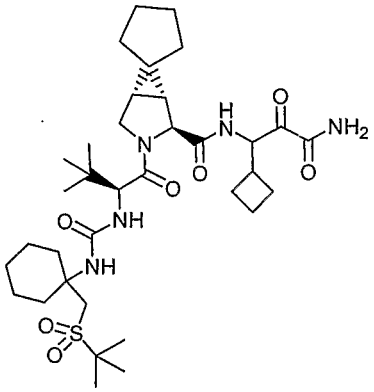


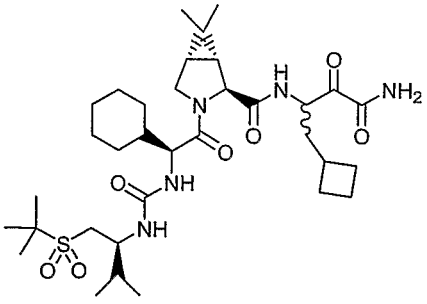


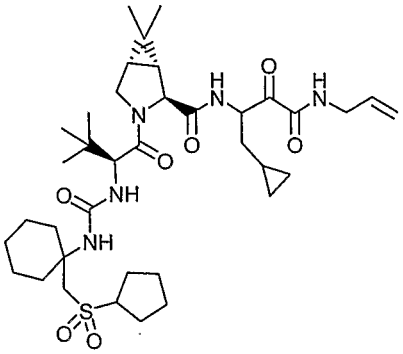


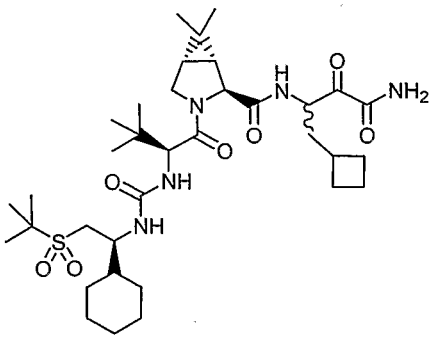


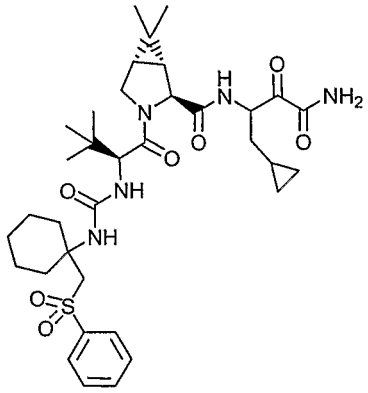


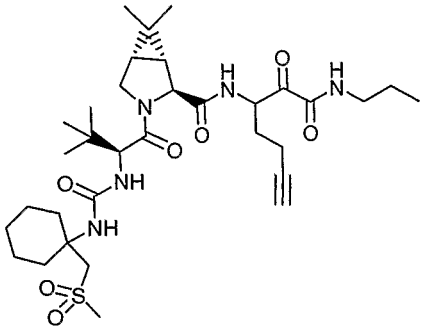


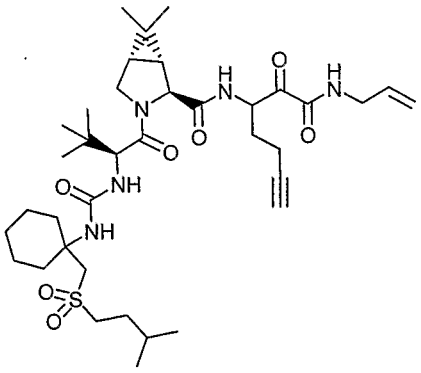


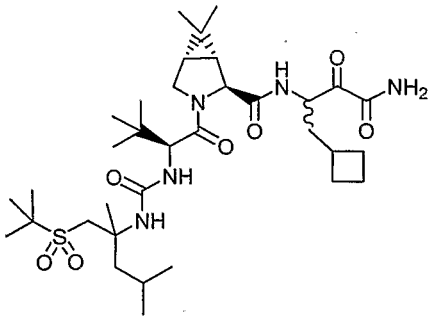


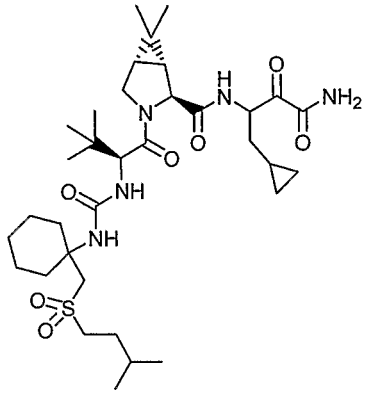


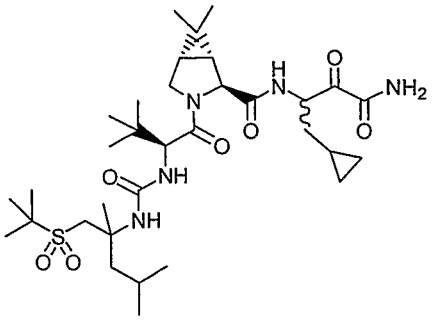


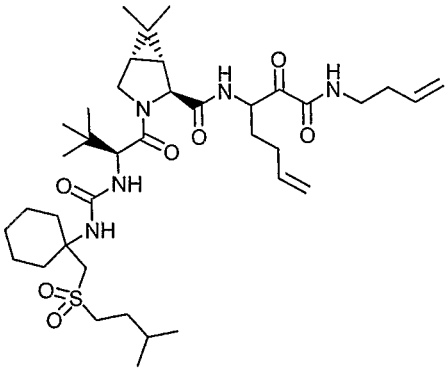


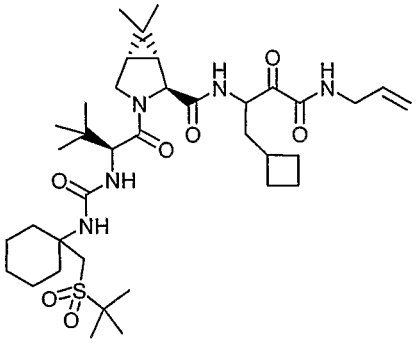


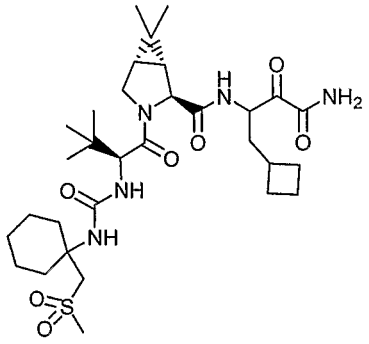


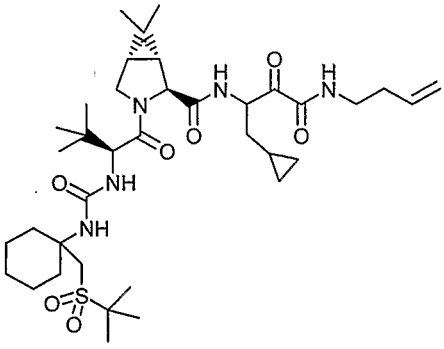


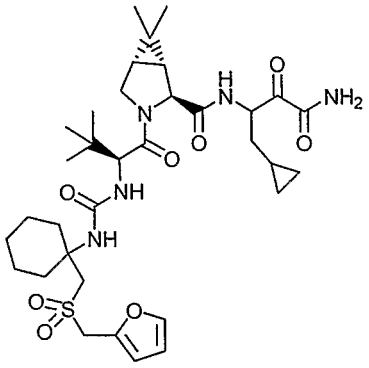


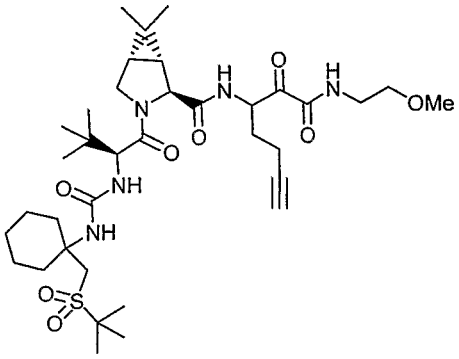


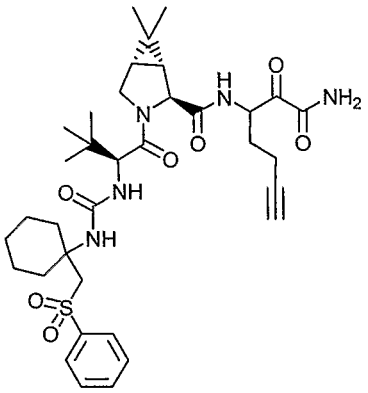


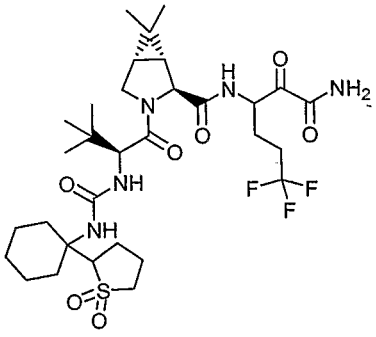


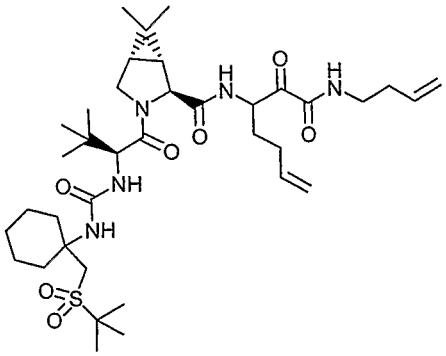


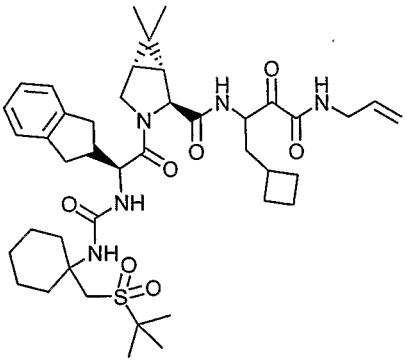


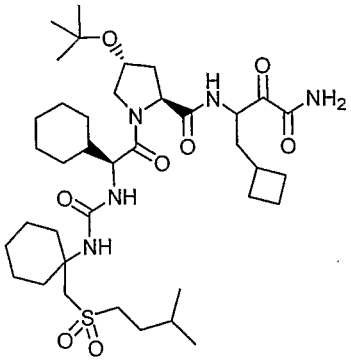


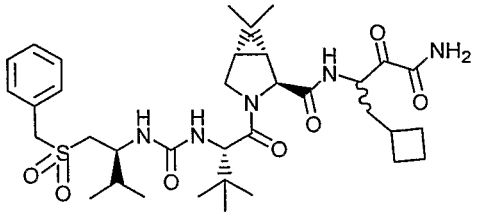


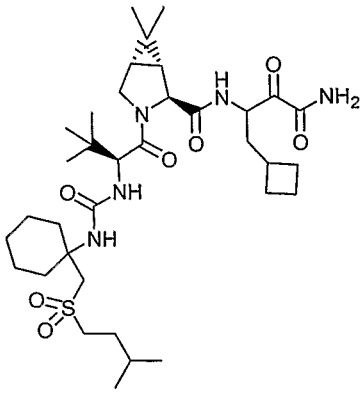


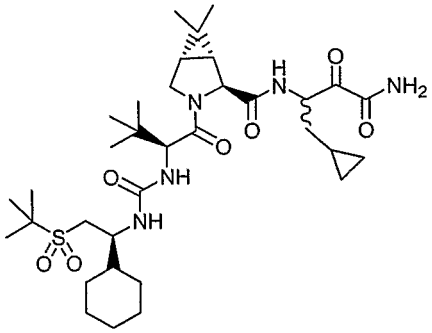


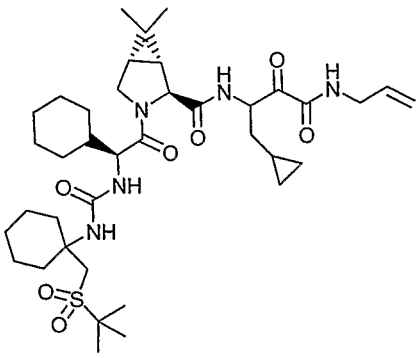


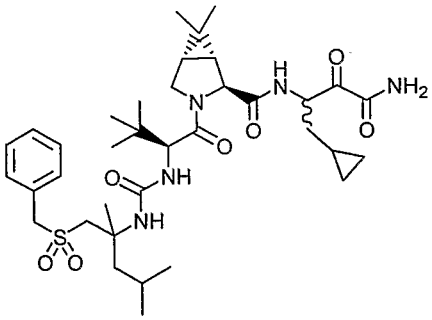


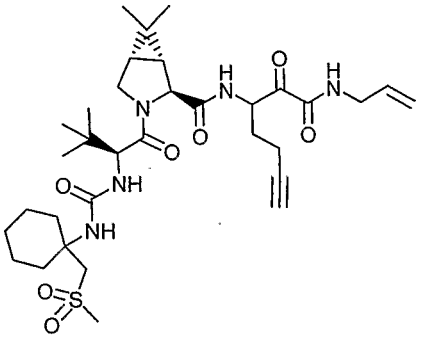


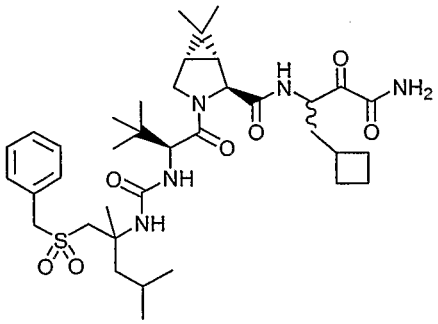


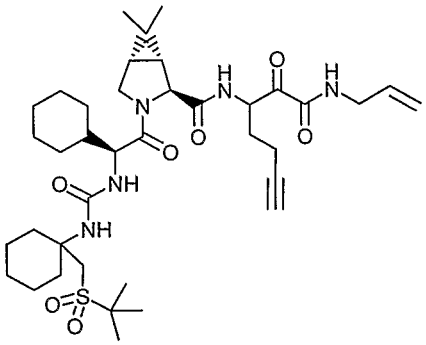


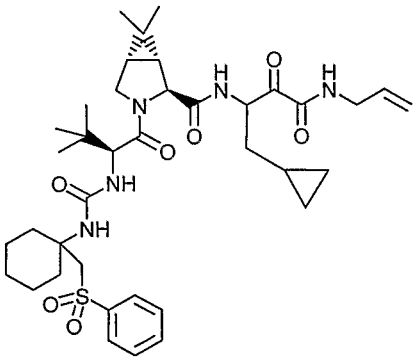


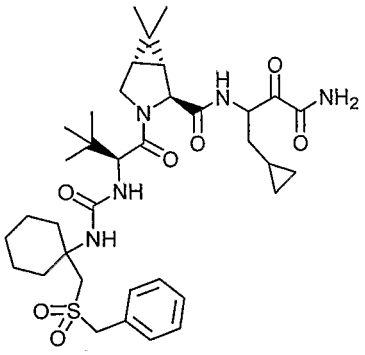


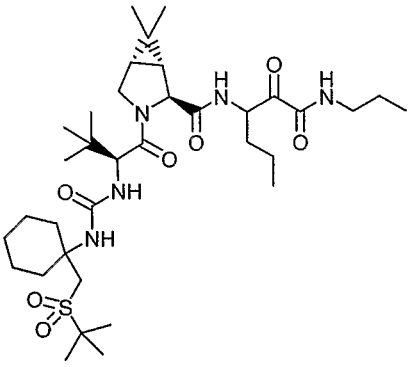


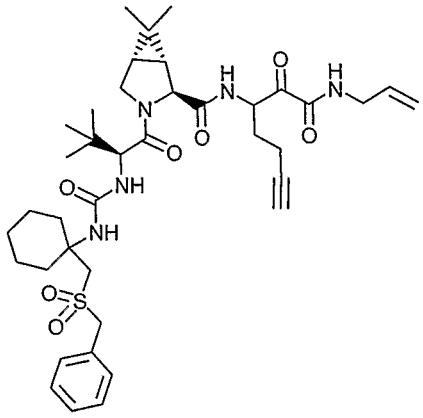


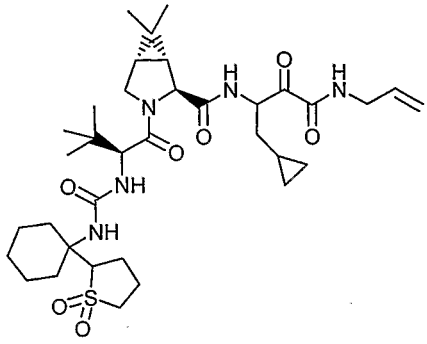


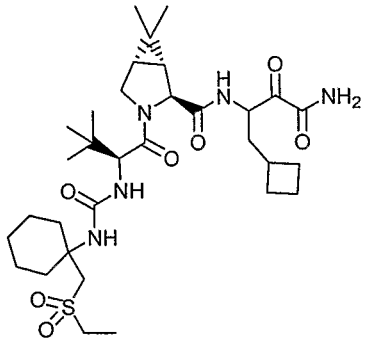


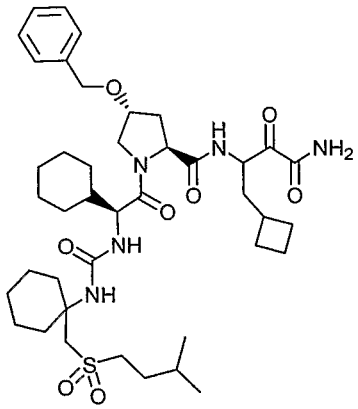


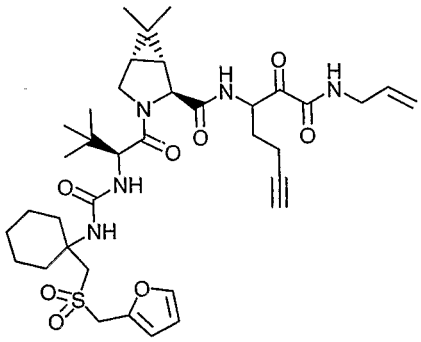


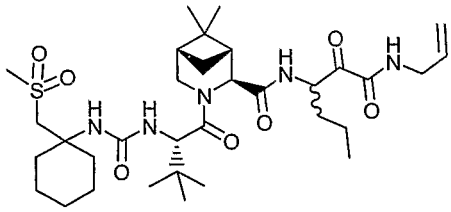


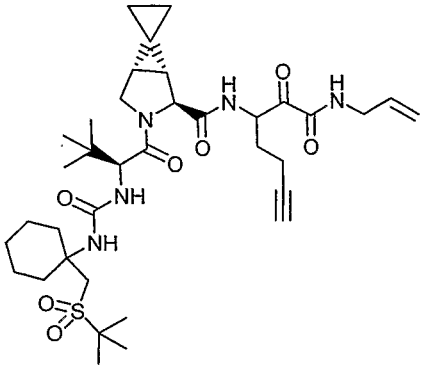


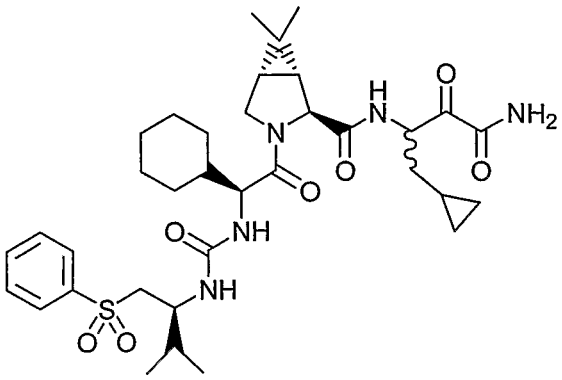


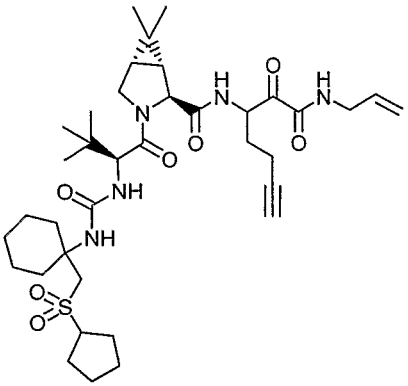


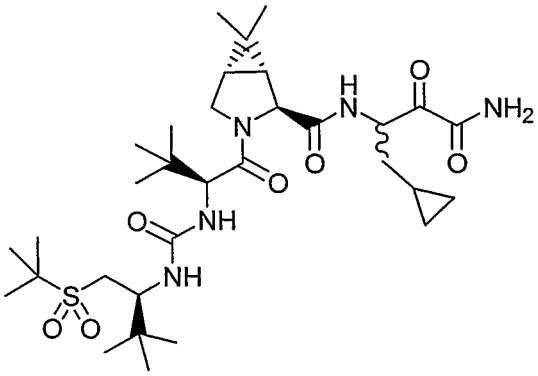


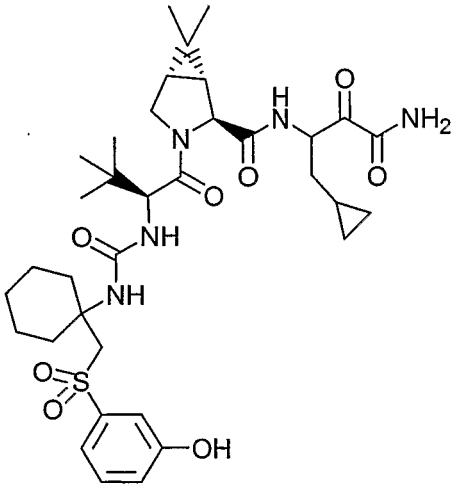


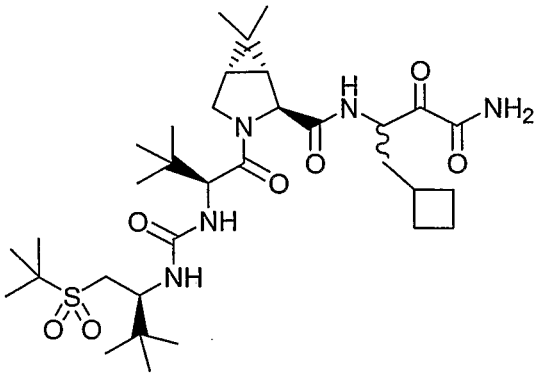


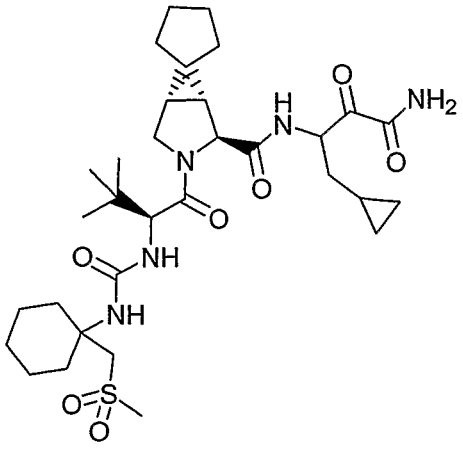


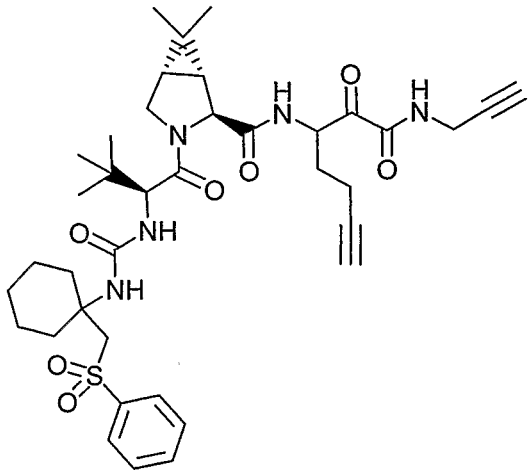


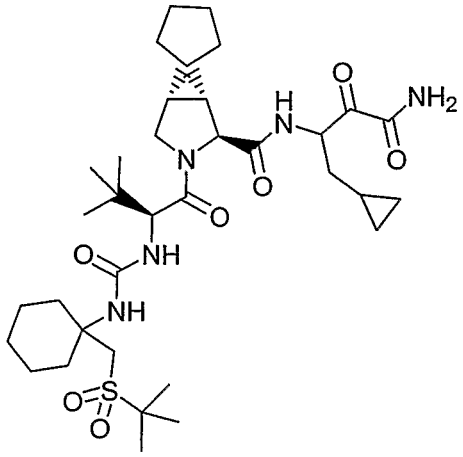


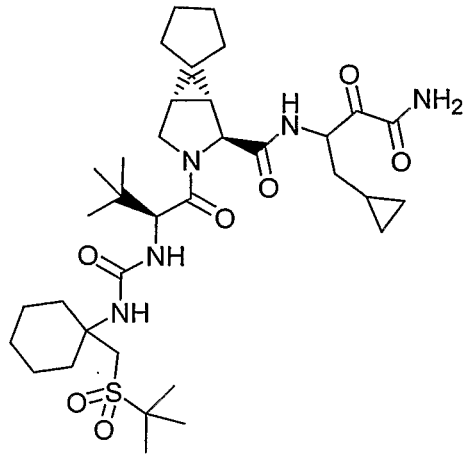


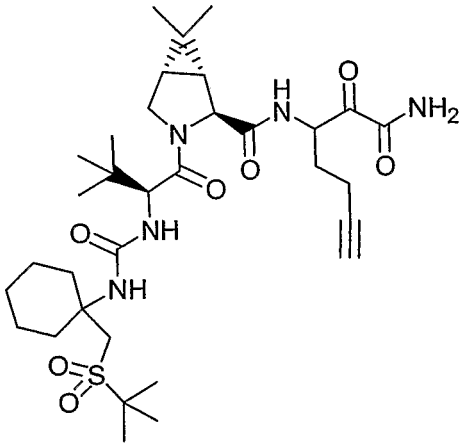


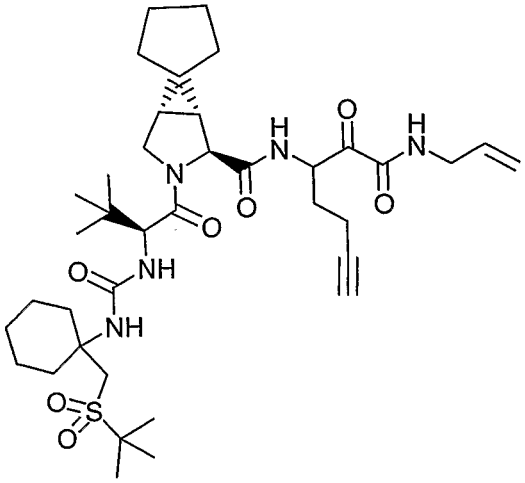


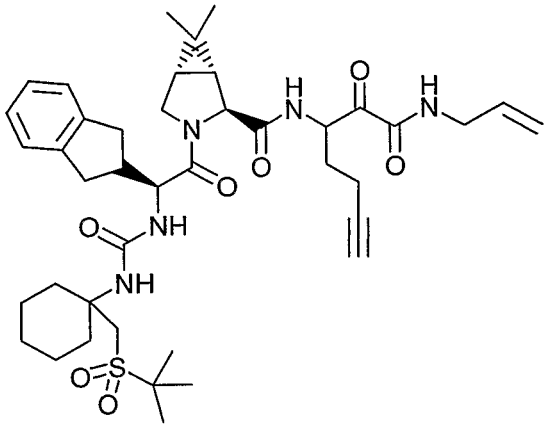


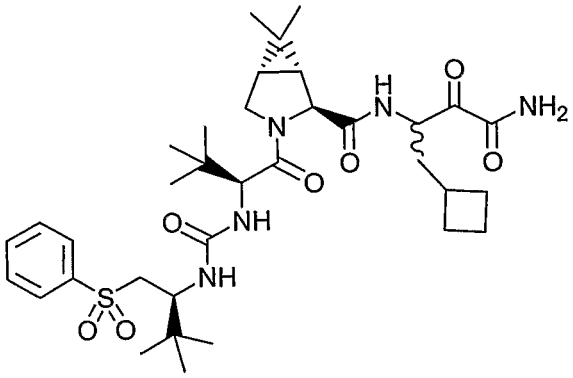


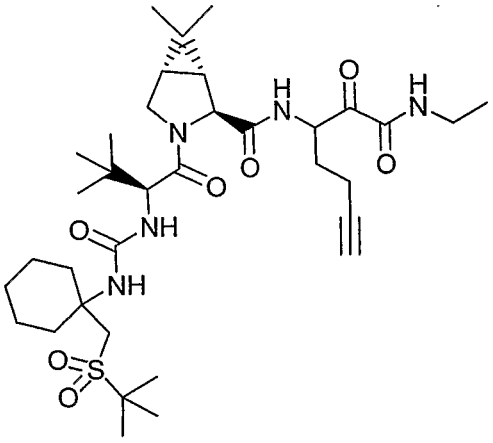


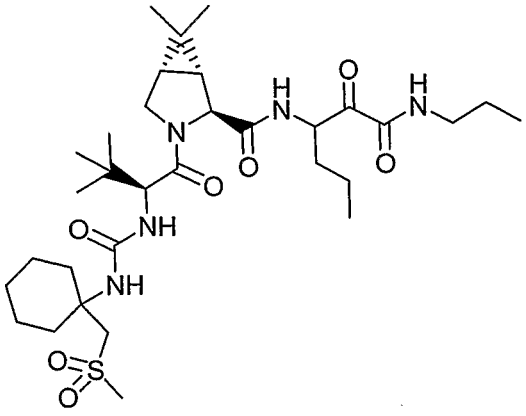


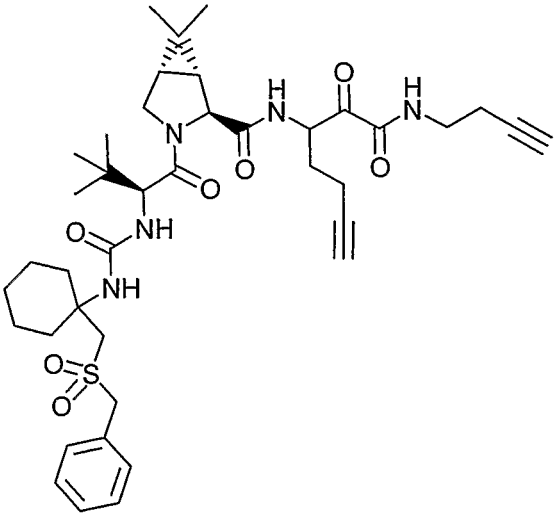


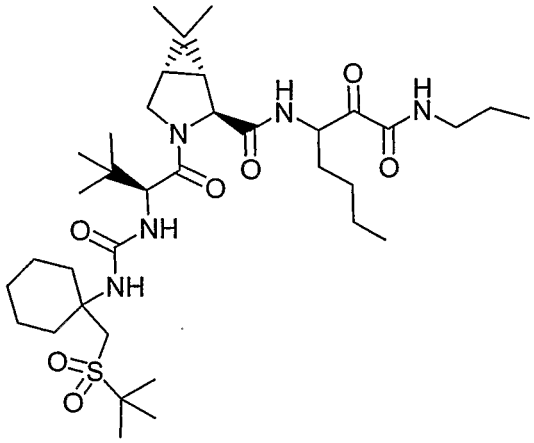


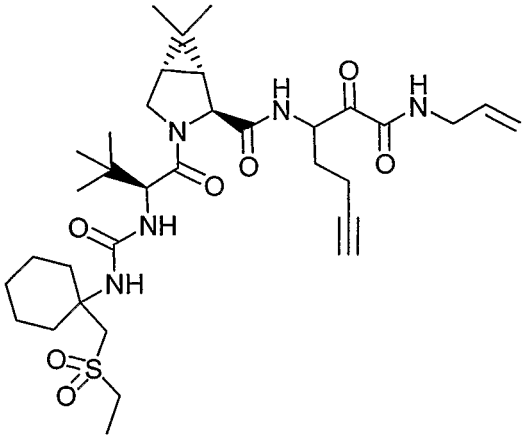


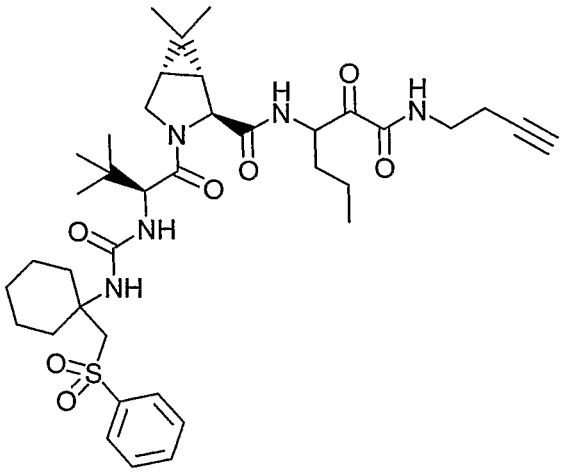


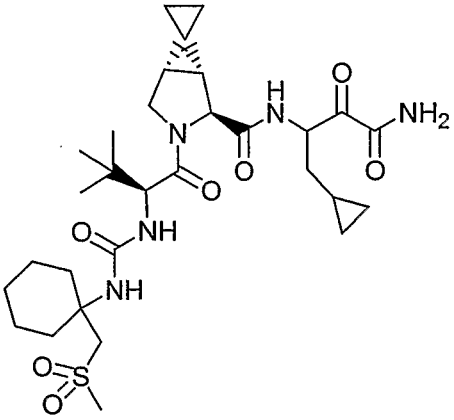


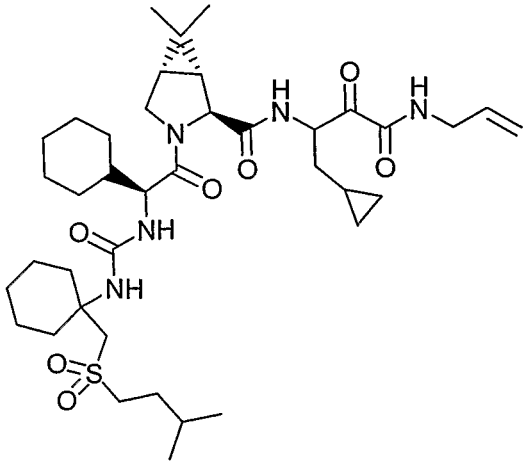


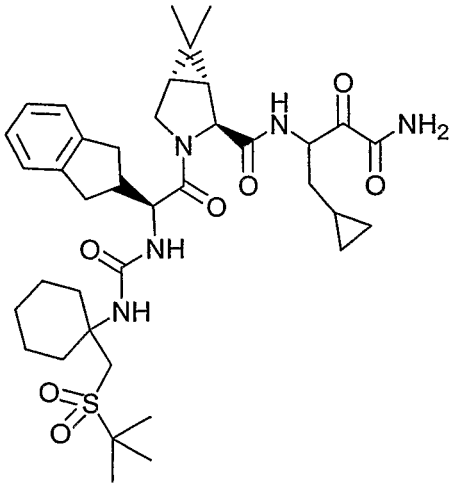


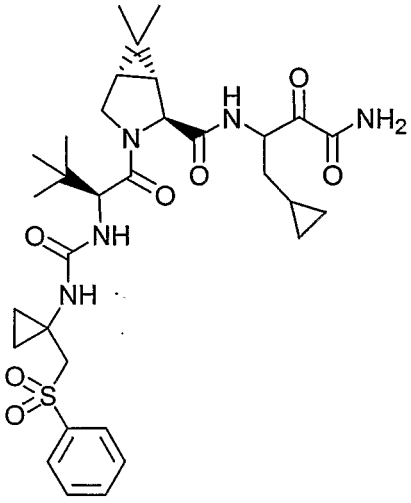


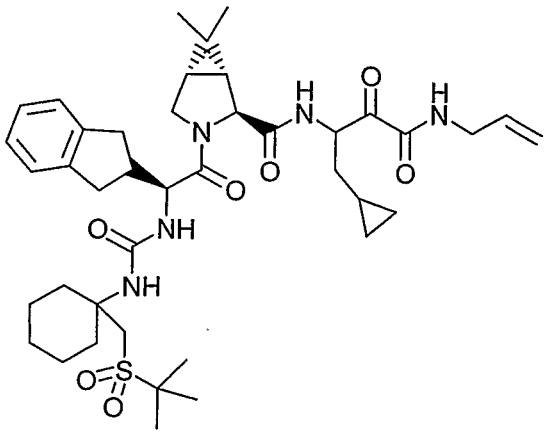


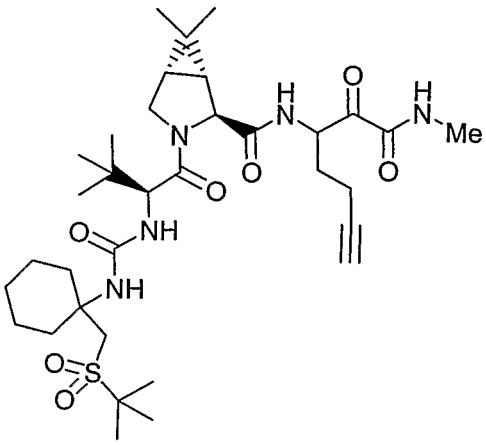


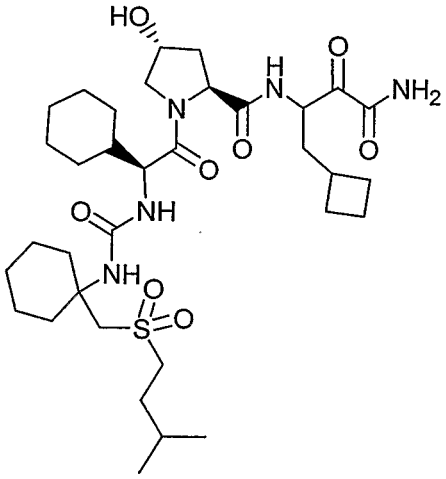


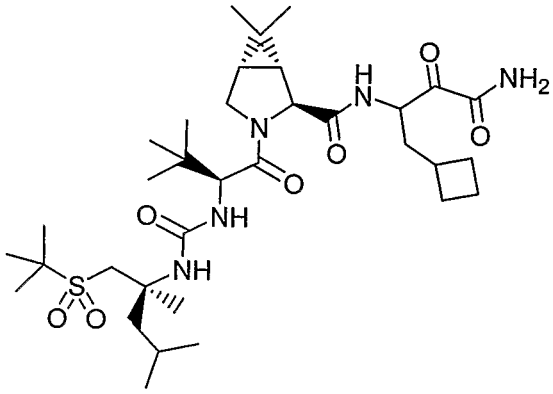


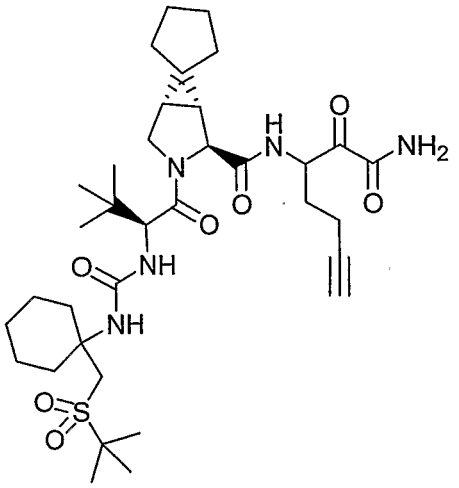


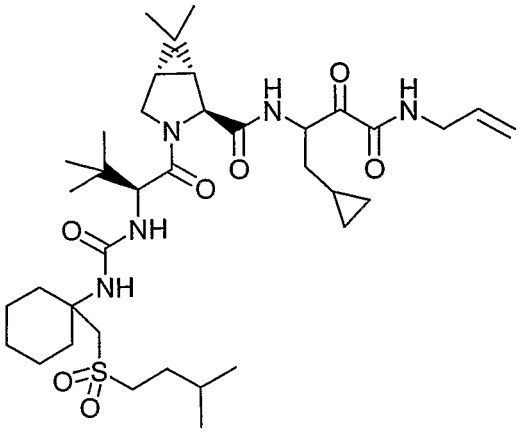


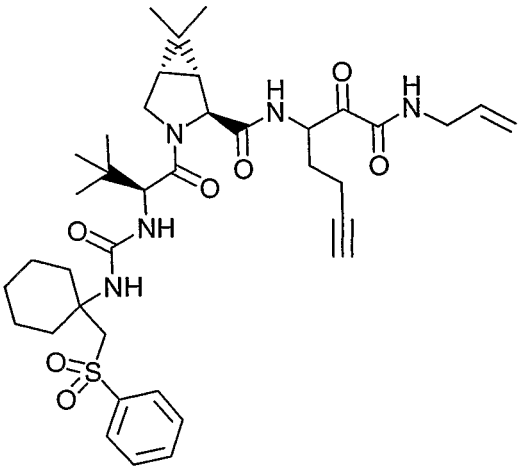


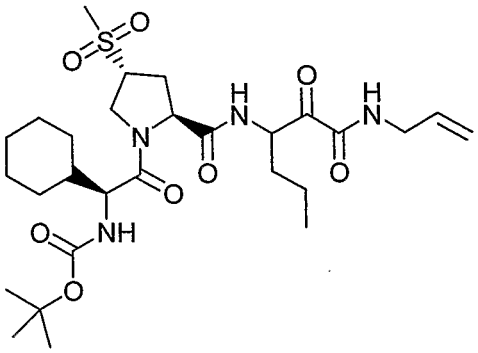


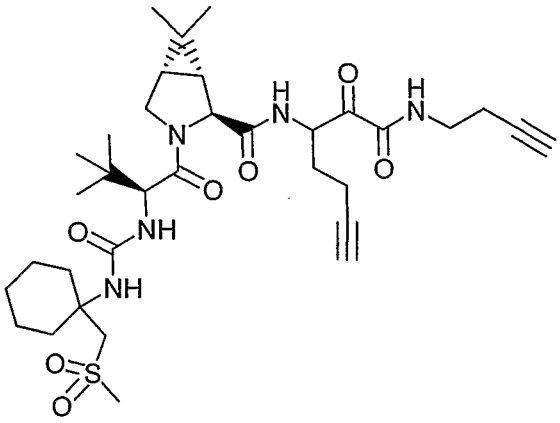


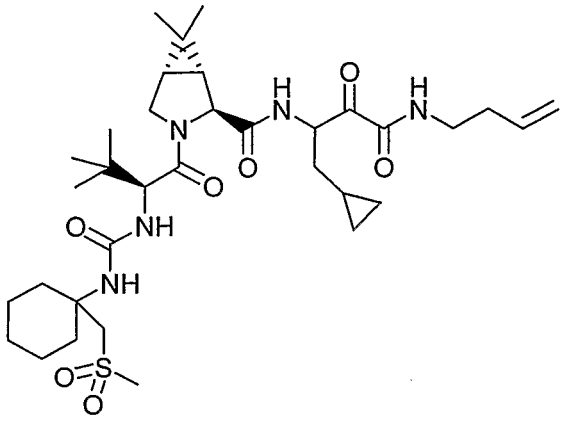


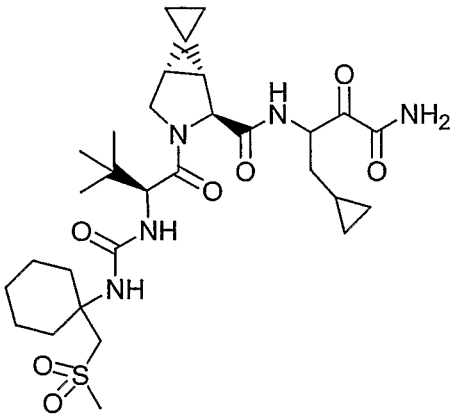


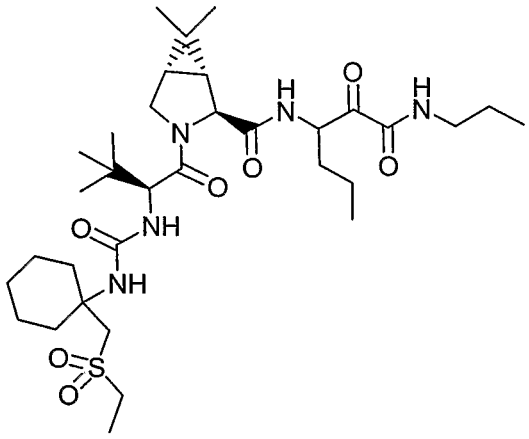


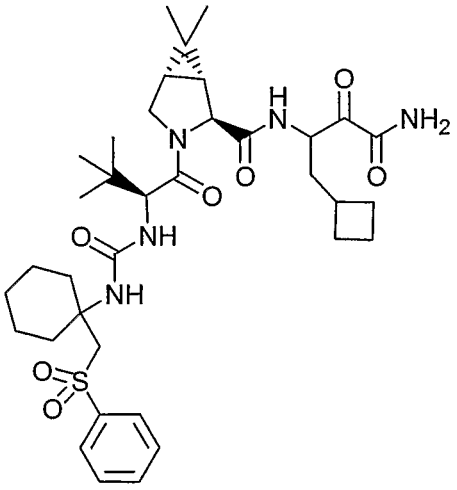


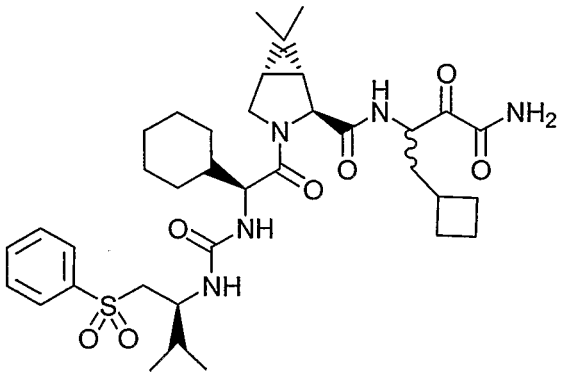


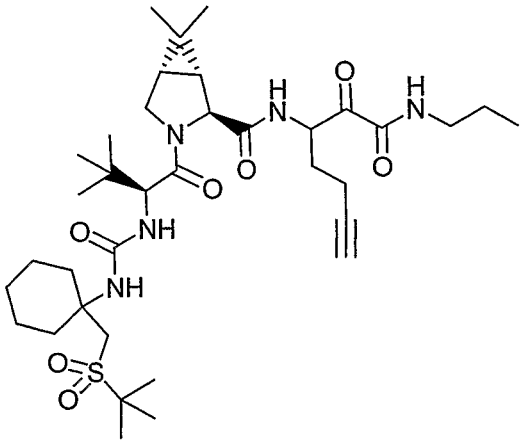


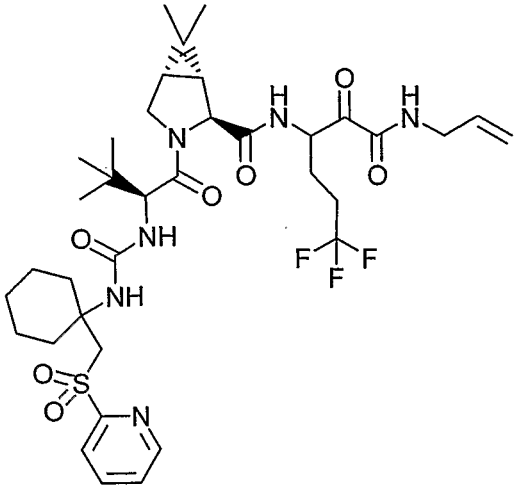


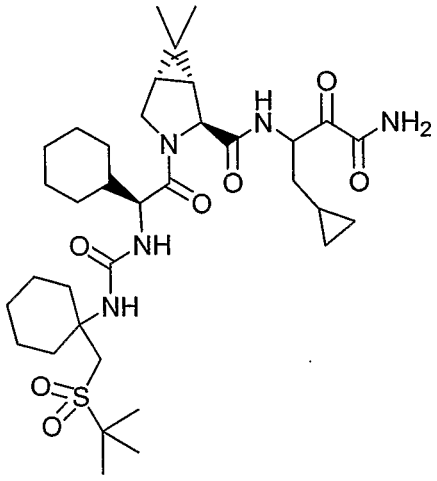


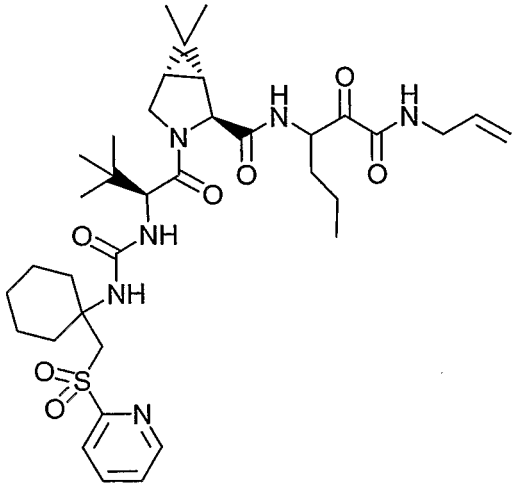


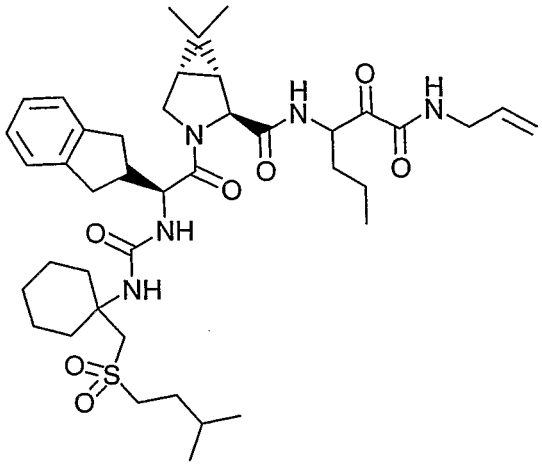


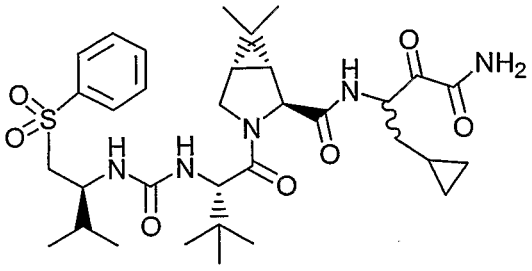


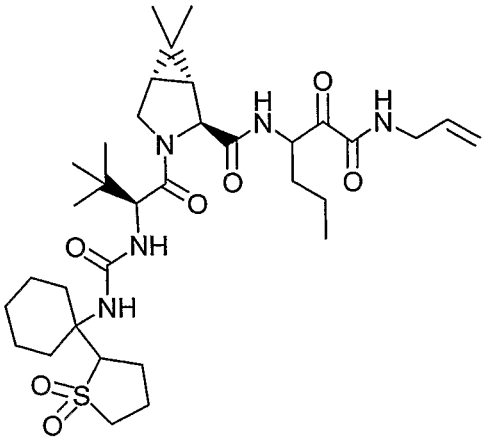


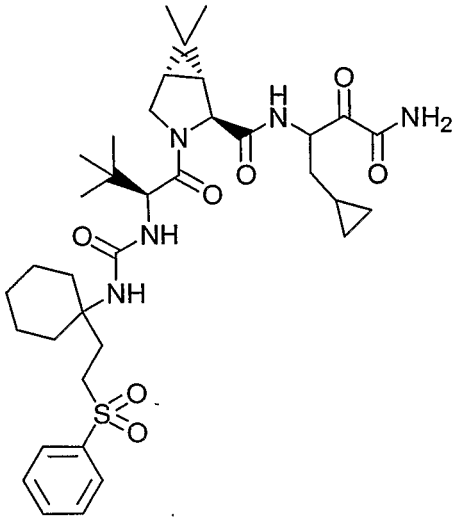


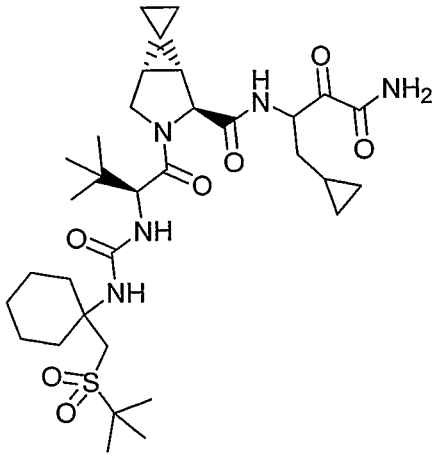


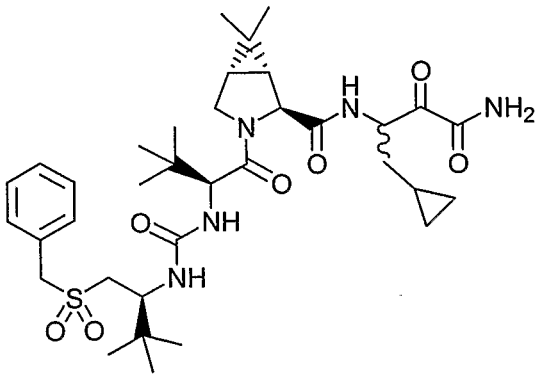


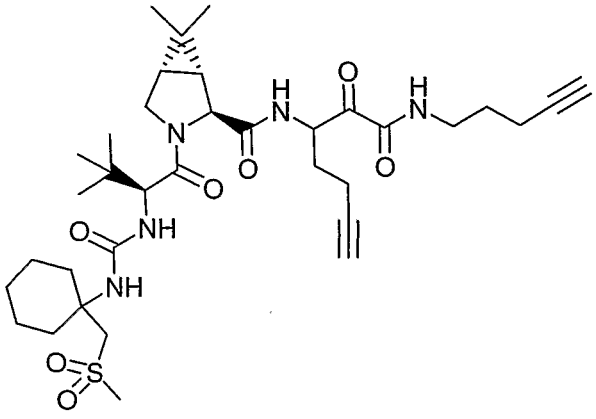


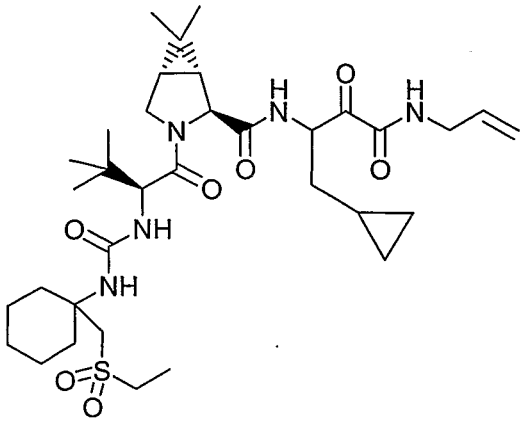


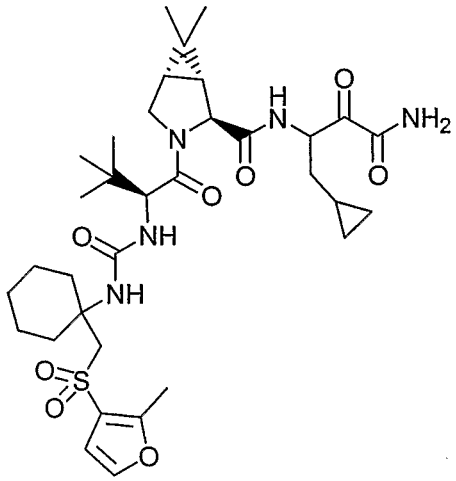


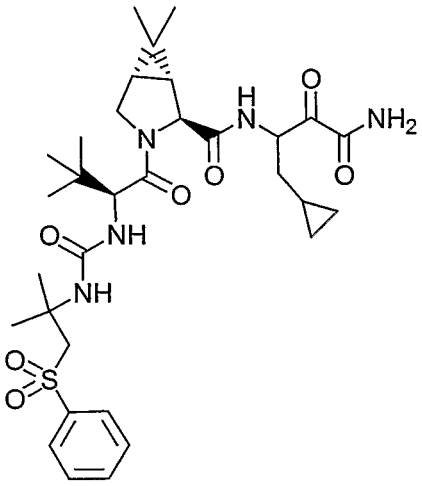


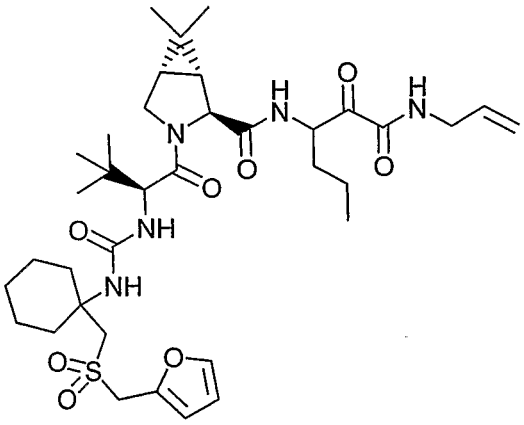


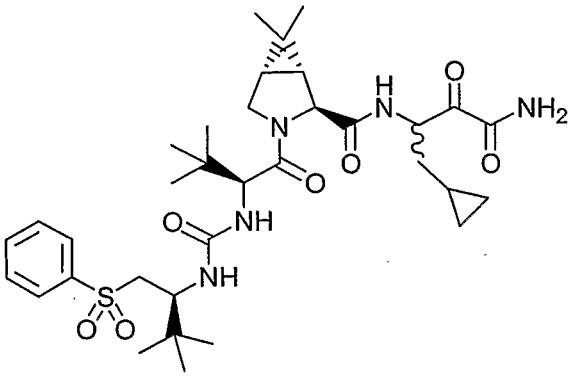


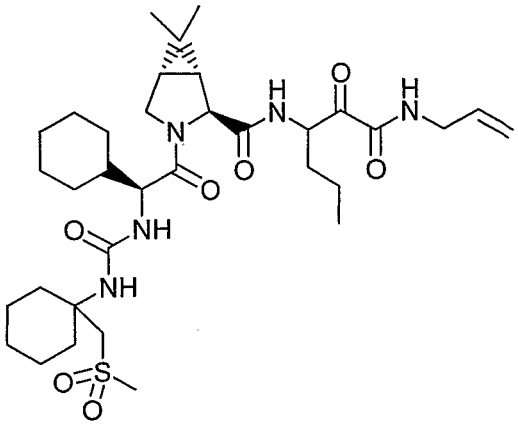


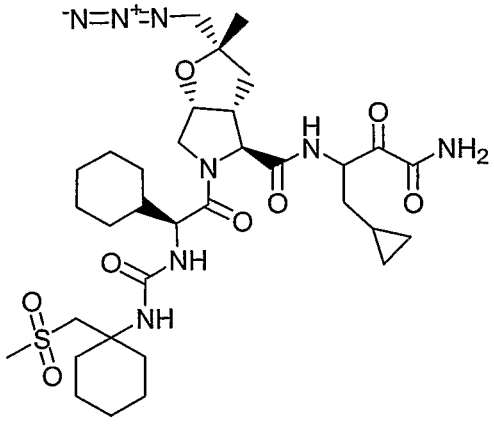


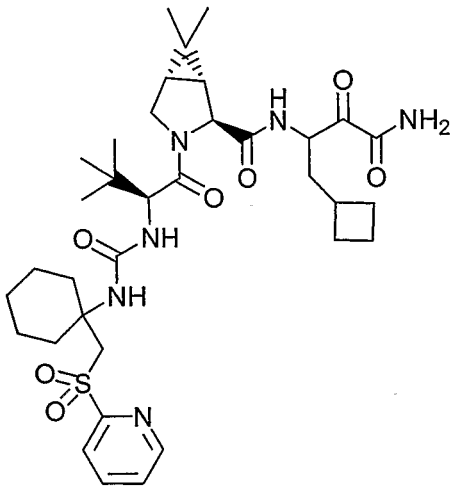


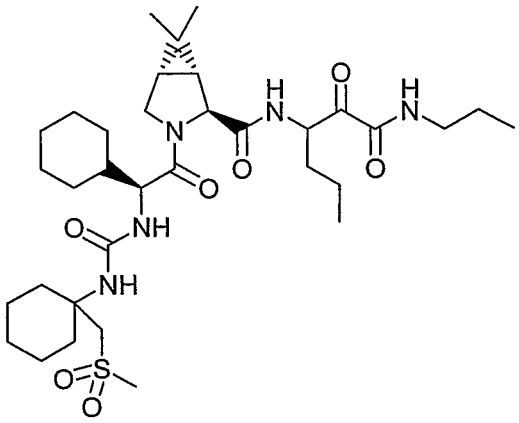


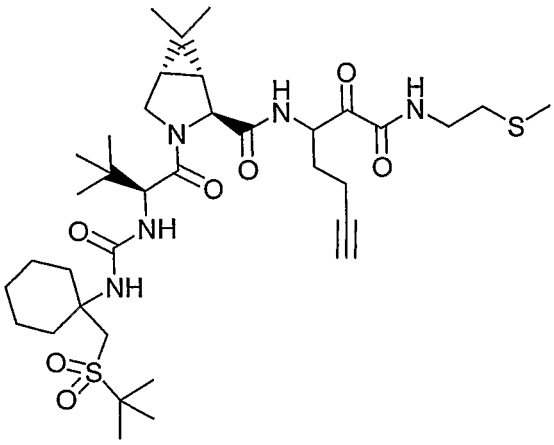


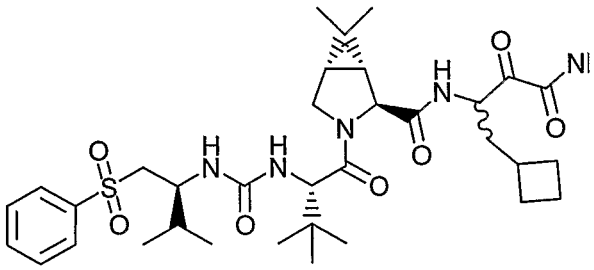


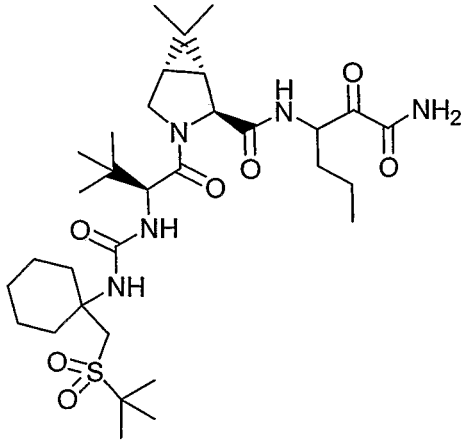


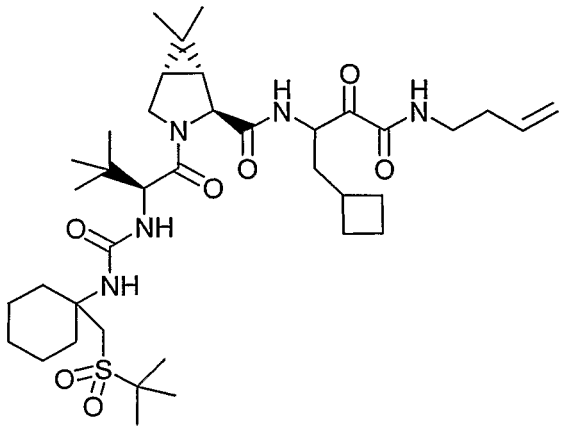


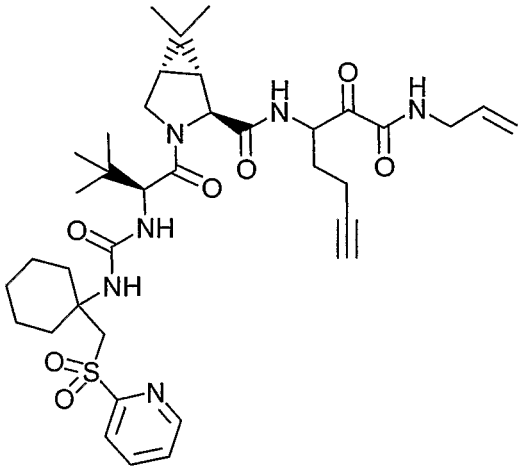


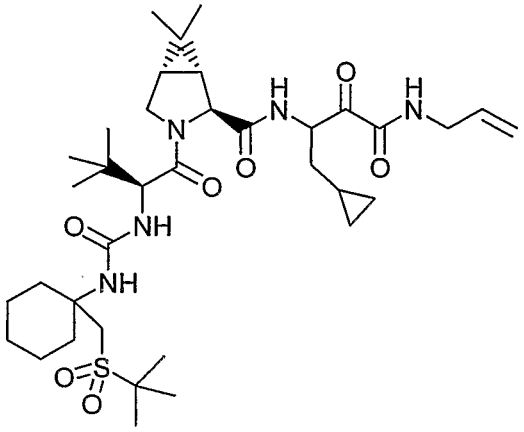


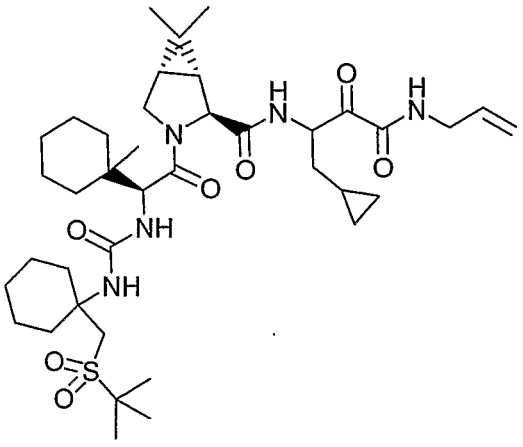


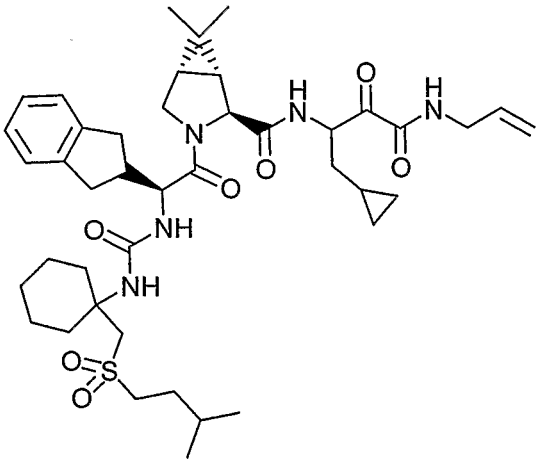


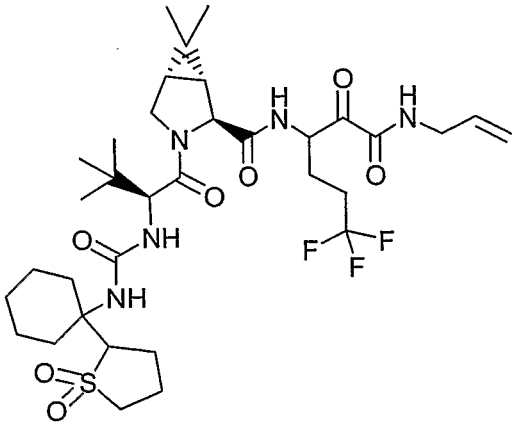


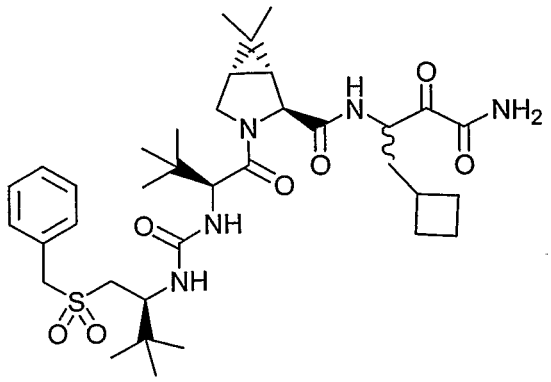


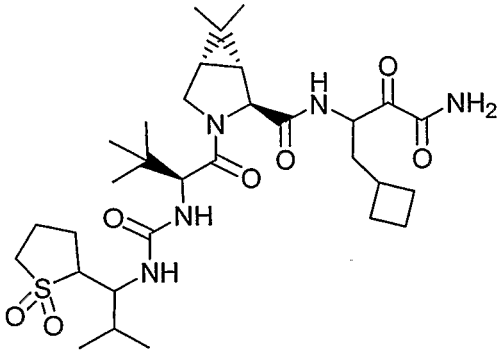


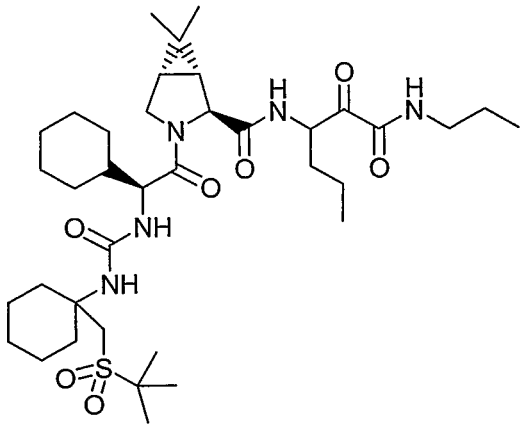


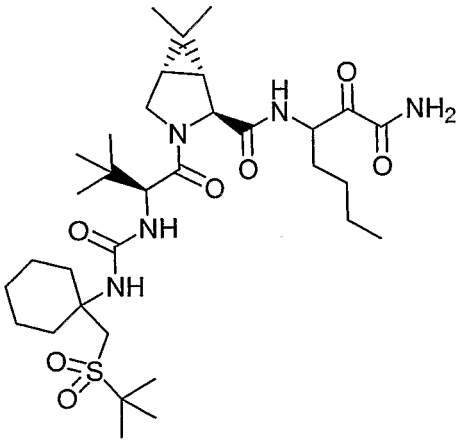


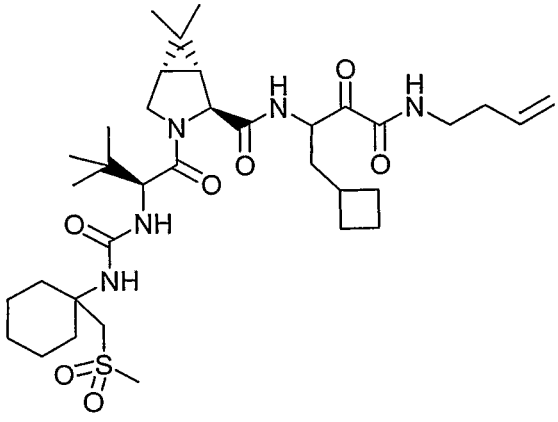


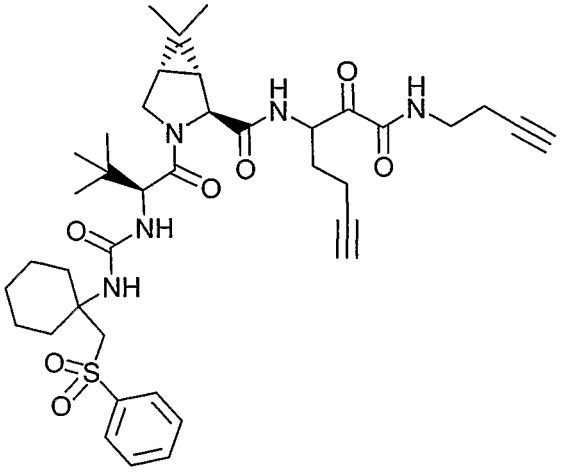


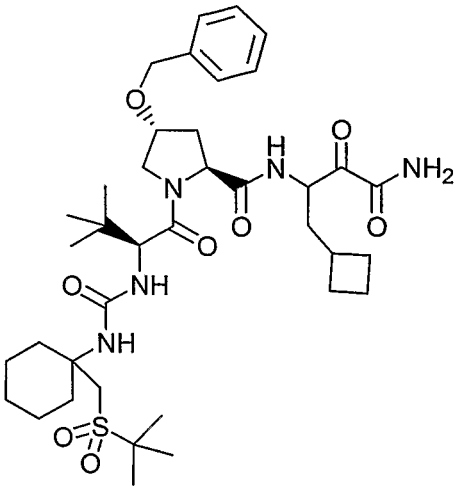


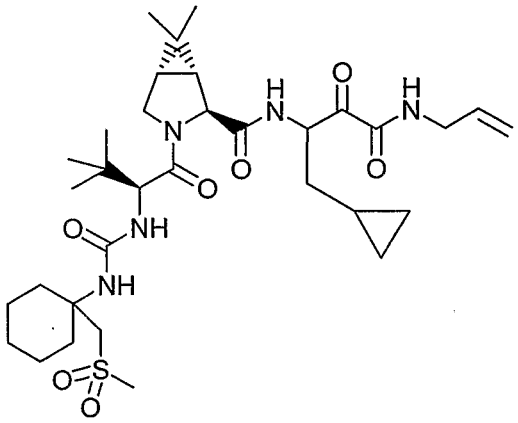


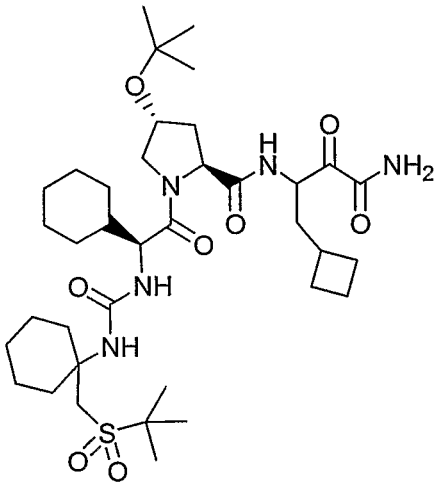


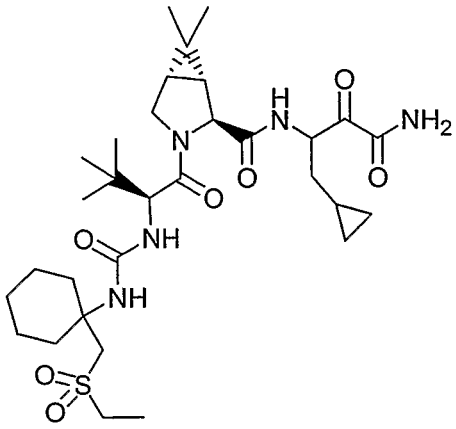


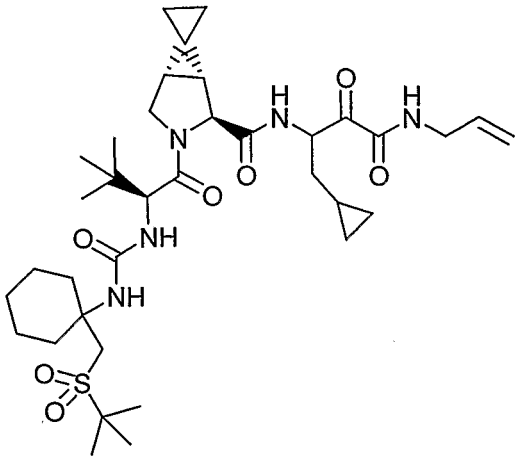


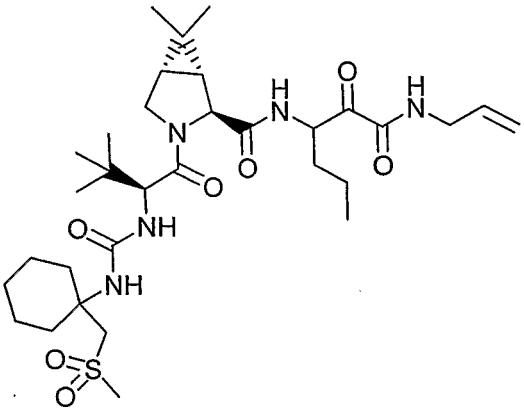


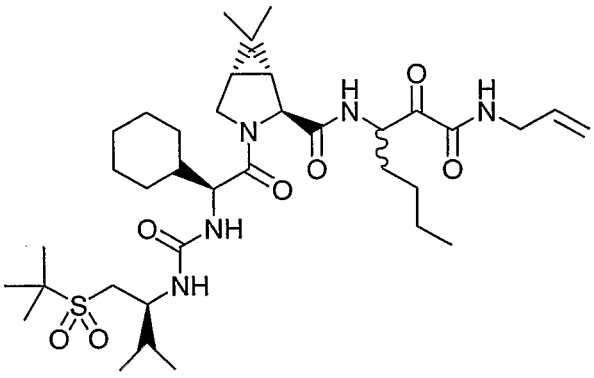


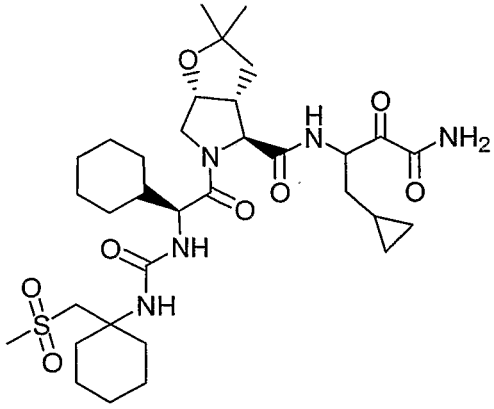


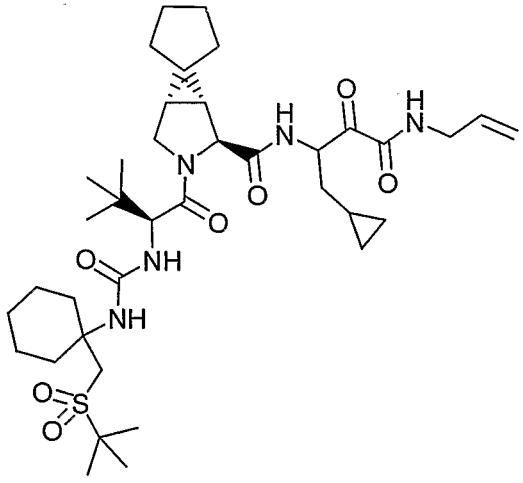


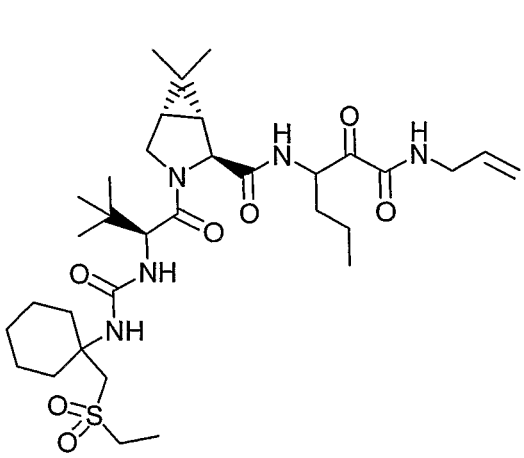


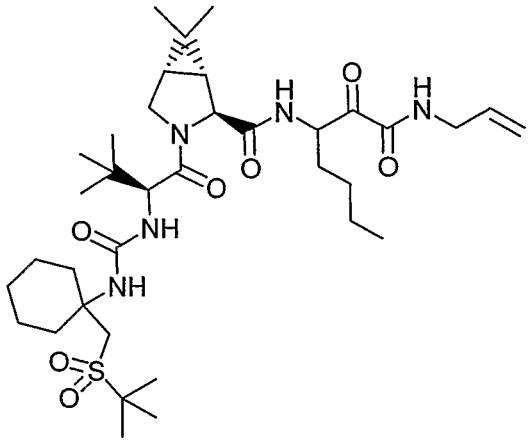






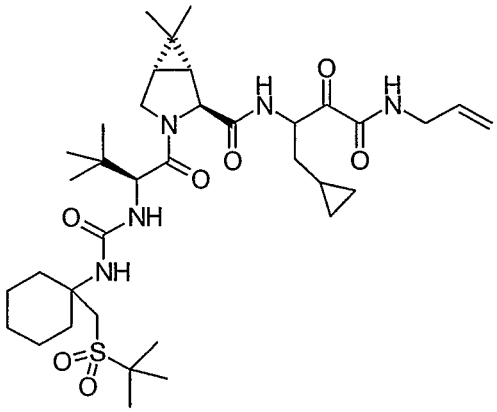


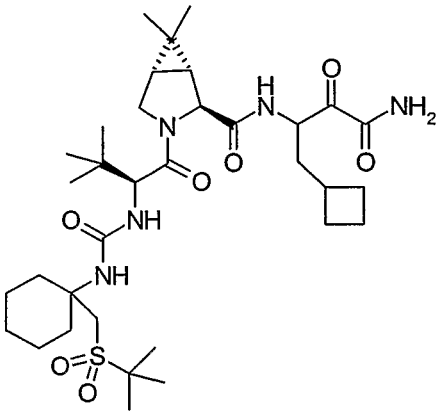


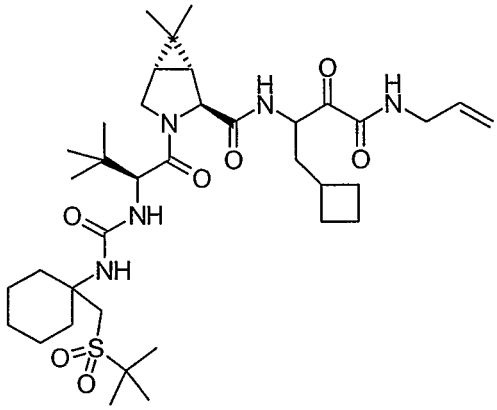


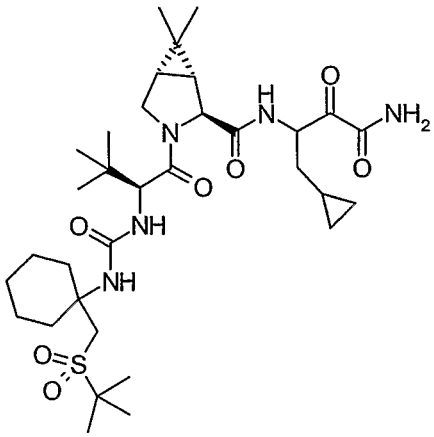
In an additional embodiment, this invention discloses the following compounds in **Table 2**:

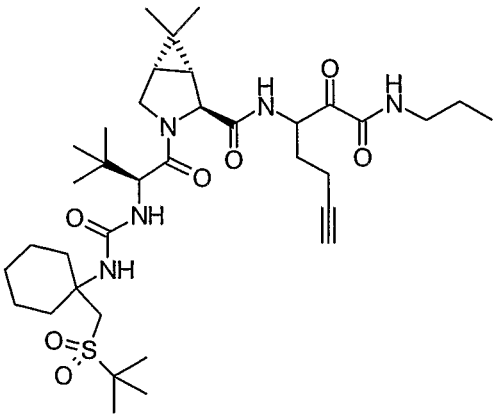
Table 2

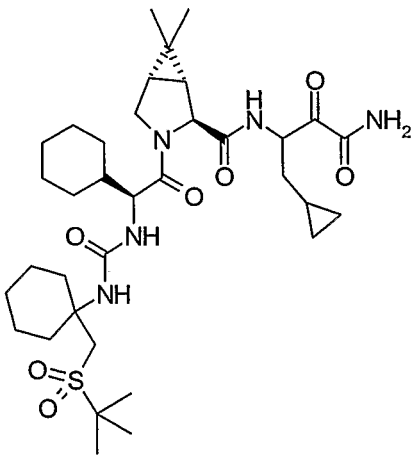


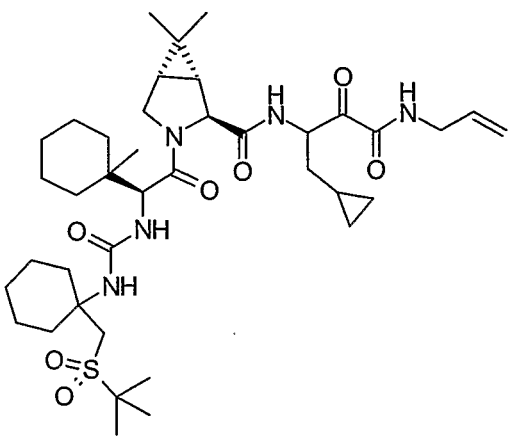


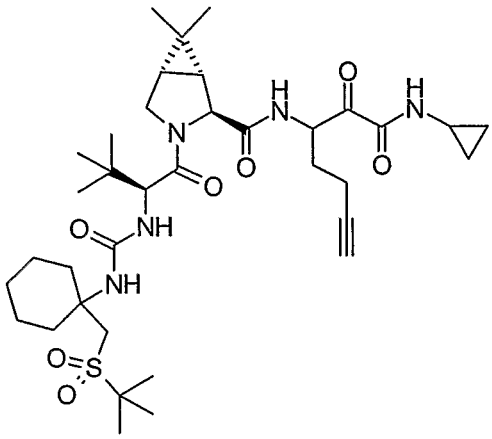


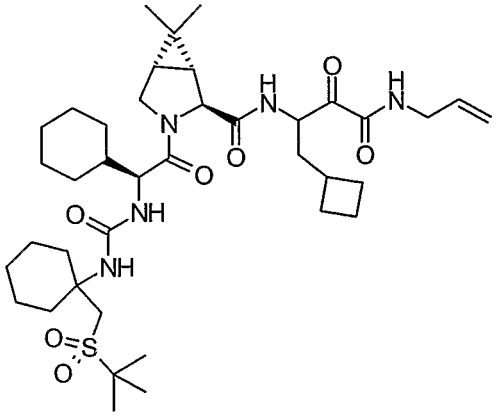


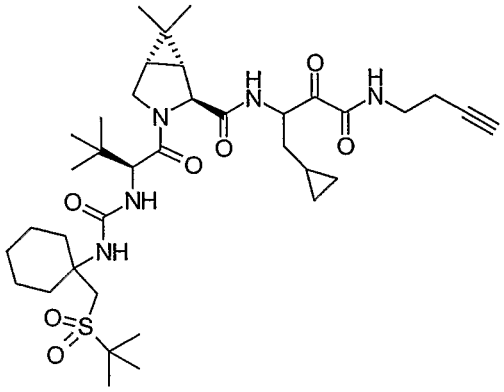


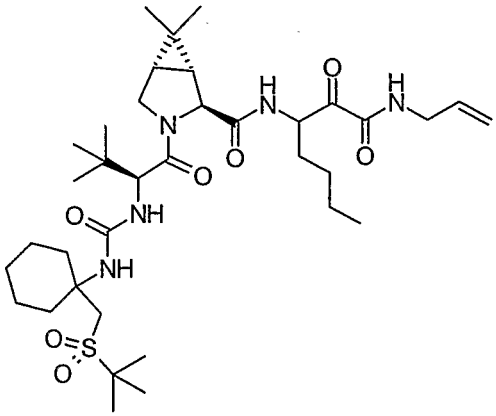


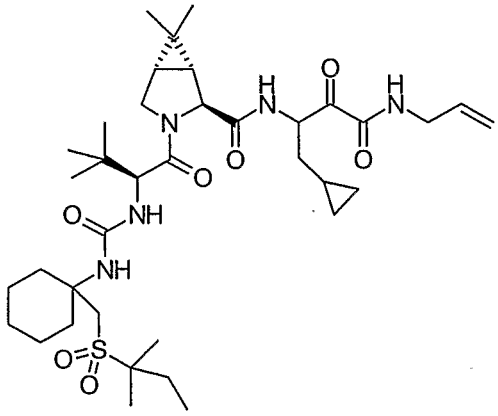


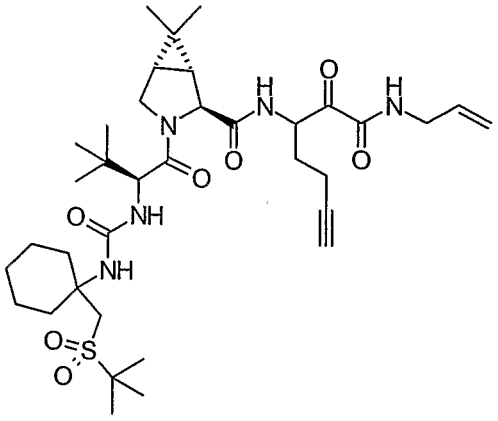


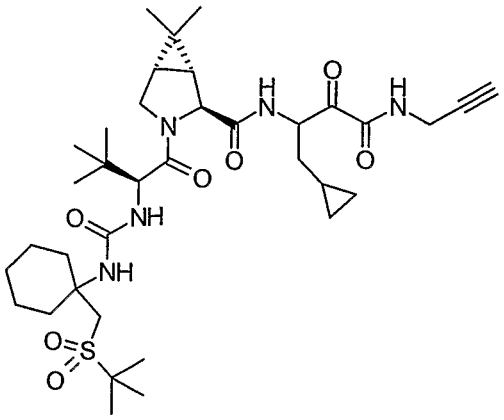


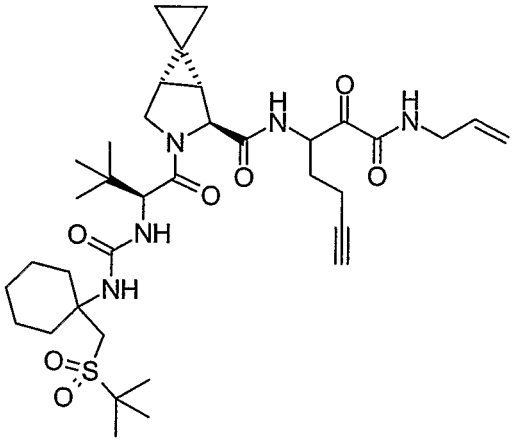












As used above, and throughout this disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

"Patient" includes both human and animals.

"Mammal" means humans and other mammalian animals.

"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched and comprising about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups contain about 1 to about 12 carbon atoms in the chain. More preferred alkyl groups contain about 1 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl,

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

"Alkenyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon double bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkenyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkenyl chain. "Lower alkenyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. The term "substituted alkenyl" means that the alkenyl group may be substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkyl. aryl, cycloalkyl, cyano, alkoxy and –S(alkyl). Non-limiting examples of suitable alkenyl groups include ethenyl, propenyl, n-butenyl, 3-methylbut-2-enyl, n-pentenyl, octenyl and decenyl.

"Alkynyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkynyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that

one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkynyl chain. "Lower alkynyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkynyl groups include ethynyl, propynyl, 2-butynyl and 3-methylbutynyl. The term "substituted alkynyl" means that the alkynyl group may be substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of alkyl, aryl and cycloalkyl.

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

"Heteroaryl" means an aromatic monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the ring atoms is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. Preferred heteroaryls contain about 5 to about 6 ring atoms. The "heteroaryl" can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The prefix aza, oxa or thia before the heteroaryl root name means that at least a nitrogen, oxygen or sulfur atom respectively, is present as a ring atom. A nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide. Non-limiting examples of suitable heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridone (including N-substituted pyridones), isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalinyl, phthalazinyl,

oxindolyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like. The term "heteroaryl" also refers to partially saturated heteroaryl moieties such as, for example, tetrahydroisoquinolyl, tetrahydroquinolyl and the like.

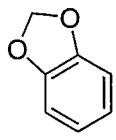
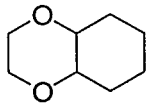
"Aralkyl" or "arylalkyl" means an aryl-alkyl- group in which the aryl and alkyl are as previously described. Preferred aralkyls comprise a lower alkyl group. Non-limiting examples of suitable aralkyl groups include benzyl, 2-phenethyl and naphthalenylmethyl. The bond to the parent moiety is through the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

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

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

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

"Ring system substituent" means a substituent attached to an aromatic or non-aromatic ring system which, for example, replaces an available hydrogen on the ring system. Ring system substituents may be the same or different, each being independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, alkylaryl, heteroaralkyl, heteroarylalkenyl, heteroarylalkynyl, alkylheteroaryl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkyl, heterocyclyl, $-C(=N-CN)-NH_2$, $-C(=NH)-NH_2$, $-C(=NH)-NH(alkyl)$, Y_1Y_2N-, $Y_1Y_2N-alkyl-$, $Y_1Y_2NC(O)-$, $Y_1Y_2NSO_2-$ and $-SO_2NY_1Y_2$, wherein Y_1 and Y_2 can be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, cycloalkyl, and aralkyl. "Ring system substituent" may also mean a single moiety which simultaneously replaces two available hydrogens on two adjacent carbon atoms (one H on each carbon) on a ring system. Examples of such moiety are methylene dioxy, ethylenedioxy, $-C(CH_3)_2-$ and the like which form moieties such as, for example: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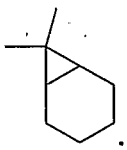
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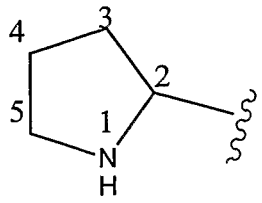
"Heterocyclyl" means a non-aromatic saturated monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclyls contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclyl root

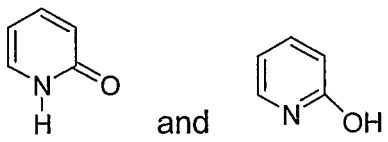
name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. Any –NH in a heterocyclyl ring may exist protected such as, for example, as an -N(Boc), -N(CBz), -N(Tos) group and the like; such protections are also considered part of this invention. The heterocyclyl can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The nitrogen or sulfur atom of the heterocyclyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic heterocyclyl rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, lactam, lactone, and the like.

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



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

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



are considered equivalent in certain embodiments of this invention.

"Alkynylalkyl" means an alkynyl-alkyl- group in which the alkynyl and alkyl are as previously described. Preferred alkynylalkyls contain a lower

alkynyl and a lower alkyl group. The bond to the parent moiety is through the alkyl. Non-limiting examples of suitable alkynylalkyl groups include propargylmethyl.

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

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

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

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

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

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

"Aralkyloxy" means an aralkyl-O- group in which the aralkyl group is as previously described. Non-limiting examples of suitable aralkyloxy groups

include benzyloxy and 1- or 2-naphthalenemethoxy. The bond to the parent moiety is through the ether oxygen.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H_2O.

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

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

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates,

oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) and the like. Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl *et al*, Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and Use.* (2002) Zurich: Wiley-VCH; S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

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

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

Pharmaceutically acceptable esters of the present compounds include the following groups: (1) carboxylic acid esters obtained by esterification of

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

Compounds of Formula I, and salts, solvates, esters and prodrugs thereof, may exist in their tautomeric form (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present invention.

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

"prodrug" and the like, is intended to equally apply to the salt, solvate and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates or prodrugs of the inventive compounds.

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

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

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

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

In another embodiment, this invention provides pharmaceutical compositions comprising the inventive compound or compounds as an active

ingredient. The pharmaceutical compositions generally additionally comprise at least one pharmaceutically acceptable carrier diluent, excipient or carrier (collectively referred to herein as carrier materials). Because of their HCV inhibitory activity, such pharmaceutical compositions possess utility in treating hepatitis C and related disorders.

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

Suitable binders include starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, carboxymethylcellulose, polyethylene glycol and waxes. Among the lubricants there may be mentioned for use in these dosage forms, boric acid, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrants include starch, methylcellulose, guar gum and the like.

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

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

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

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

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

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or

parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

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

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

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

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

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

Some useful terms are described below:

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

Tablet- refers to a compressed or molded solid dosage form containing the active ingredients with suitable diluents. The tablet can be prepared by compression of mixtures or granulations obtained by wet granulation, dry granulation or by compaction.

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

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

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

Disintegrant - refers to materials added to the composition to help it break apart (disintegrate) and release the medicaments. Suitable disintegrants include starches; "cold water soluble" modified starches such as sodium carboxymethyl starch; natural and synthetic gums such as locust bean, karaya, guar, tragacanth and agar; cellulose derivatives such as methylcellulose and sodium carboxymethylcellulose; microcrystalline

celluloses and cross-linked microcrystalline celluloses such as sodium croscarmellose; alginates such as alginic acid and sodium alginate; clays such as bentonites; and effervescent mixtures. The amount of disintegrant in the composition can range from about 2 to about 15% by weight of the composition, more preferably from about 4 to about 10% by weight.

Binder - refers to substances that bind or "glue" powders together and make them cohesive by forming granules, thus serving as the "adhesive" in the formulation. Binders add cohesive strength already available in the diluent or bulking agent. Suitable binders include sugars such as sucrose; starches derived from wheat, corn rice and potato; natural gums such as acacia, gelatin and tragacanth; derivatives of seaweed such as alginic acid, sodium alginate and ammonium calcium alginate; cellulosic materials such as methylcellulose and sodium carboxymethylcellulose and hydroxypropylmethylcellulose; polyvinylpyrrolidone; and inorganics such as magnesium aluminum silicate. The amount of binder in the composition can range from about 2 to about 20% by weight of the composition, more preferably from about 3 to about 10% by weight, even more preferably from about 3 to about 6% by weight.

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

by weight of the composition, preferably from about 0.5 to about 2%, more preferably from about 0.3 to about 1.5% by weight.

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

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

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

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

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

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

As stated earlier, the invention includes tautomers, rotamers, enantiomers and other stereoisomers of the inventive compounds also. Thus, as one skilled in the art appreciates, some of the inventive compounds may

exist in suitable isomeric forms. Such variations are contemplated to be within the scope of the invention.

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

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

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

THF: Tetrahydrofuran

DMF: N,N-Dimethylformamide

EtOAc: Ethyl acetate

AcOH: Acetic acid

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

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

NMM: N-Methylmorpholine

ADDP: 1,1'-(Azodicarbobyl)dipiperidine

DEAD: Diethylazodicarboxylate

MeOH: Methanol

EtOH: Ethanol

Et2O: Diethyl ether

DMSO: Dimethylsulfoxide

HOBt: N-Hydroxybenzotriazole

PyBrOP: Bromo-tris-pyrrolidinophosphonium hexafluorophosphate

DCM: Dichloromethane

DCC: 1,3-Dicyclohexylcarbodiimide

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

Phg: Phenylglycine

Chg: Cyclohexylglycine

Bn: Benzyl

Bzl: Benzyl

Et: Ethyl

Ph: Phenyl

DMF-DMA: N,N-Dimethylformamide-dimethylacetal

iBoc: isobutoxycarbonyl

iPr: isopropyl

^{t}Bu or Bu^{t}: tert-Butyl

Boc: tert-Butyloxycarbonyl

Cbz: Benzyloxycarbonyl

Cp: Cylcopentyldienyl

Ts: p-toluenesulfonyl

Me: Methyl

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

DMAP: 4-N,N-Dimethylaminopyridine

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

PCC: Pyridiniumchlorochromate

KHMDS: Potassium Hexamethyldisilazide or Potassium bis(trimethylsilylamide)

NaHMDS: Sodium Hexamethyldisilazide or Sodium bis(trimethylsilylamide)

LiHMDS: Lithium Hexamethyldisilazide or Lithium bis(trimethylsilylamide)

10% Pd/C: 10% Palladium on carbon (by weight).

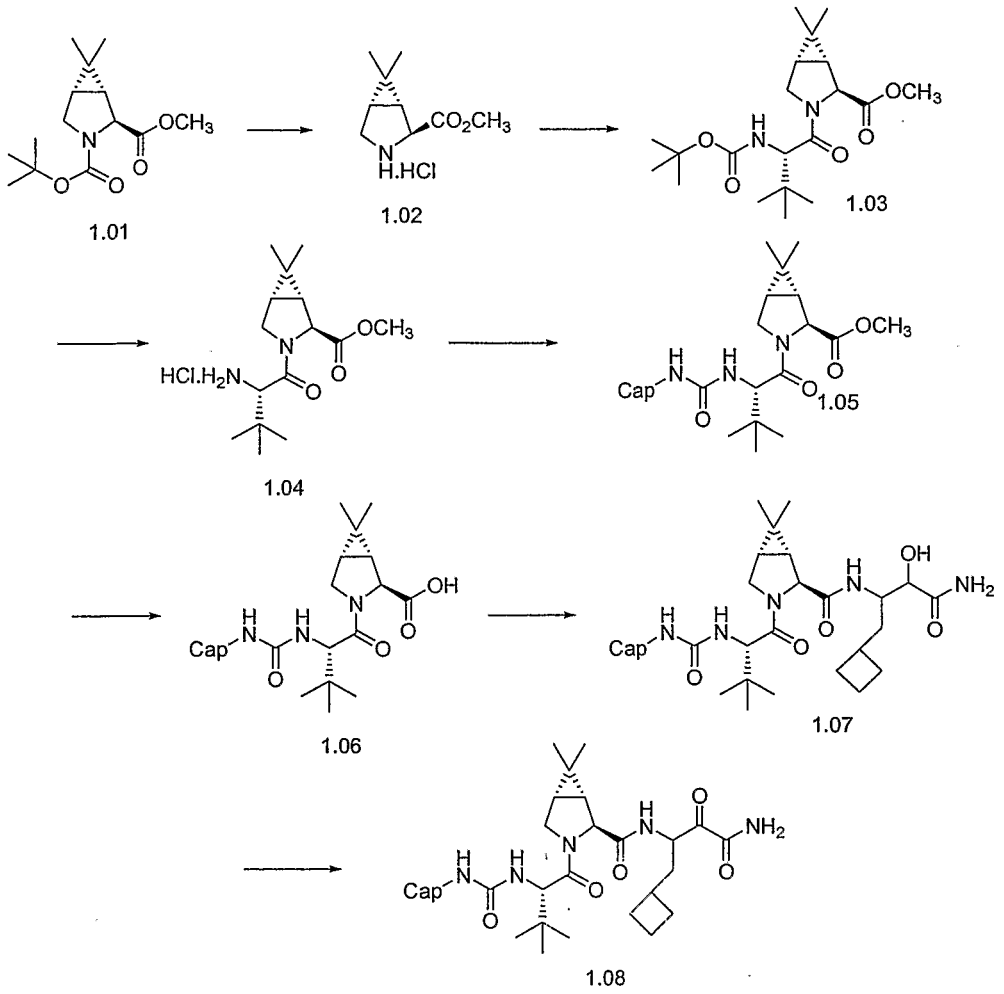
TG: Thioglycerol

General Schemes for Preparation of Target Compounds

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

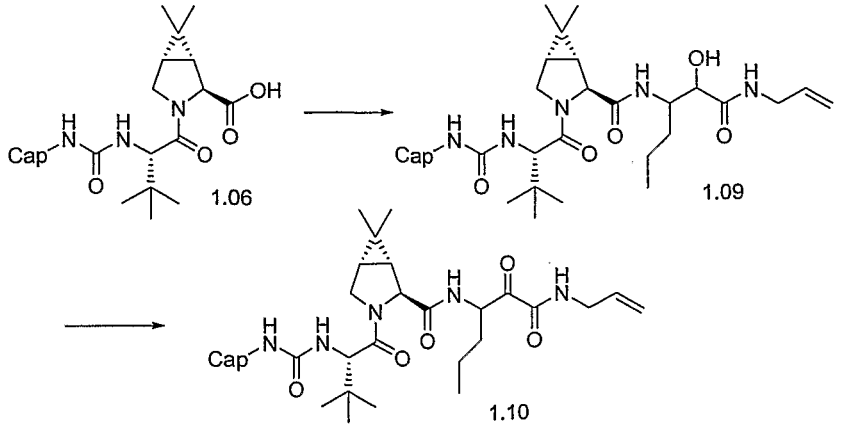
Method A

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



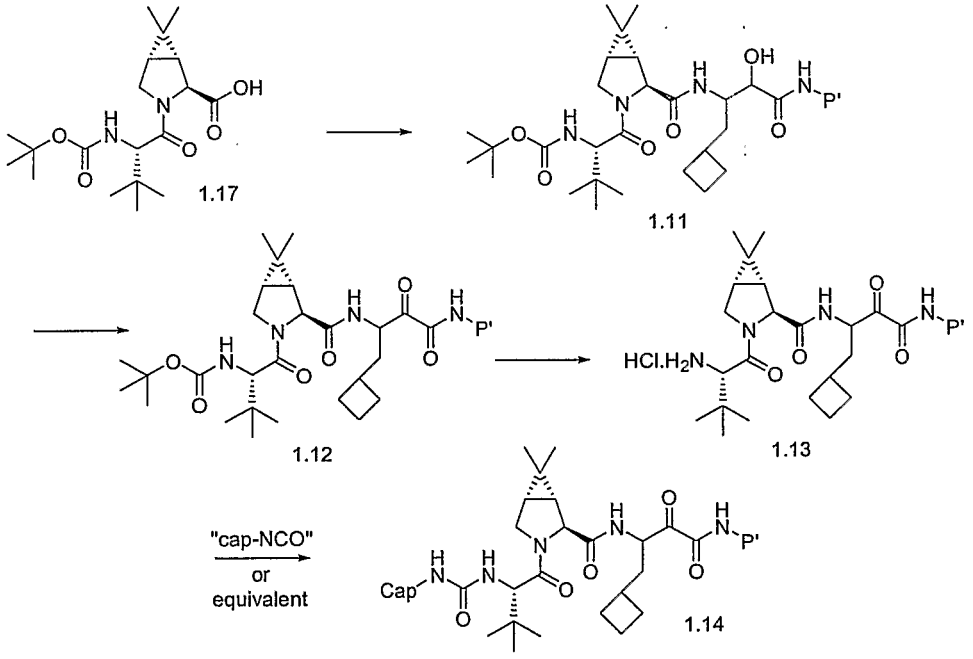
Method B

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



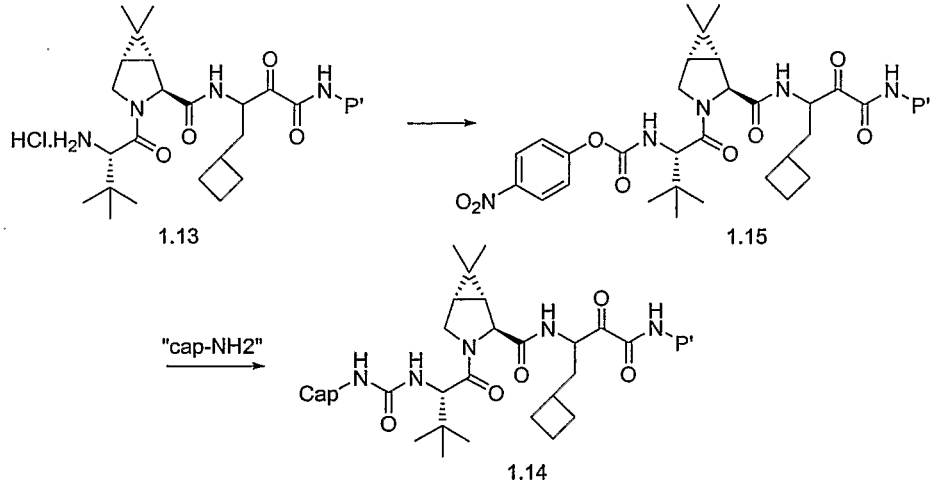
Method C

In another variation, peptide coupling of the N-Boc-P2-P_3-acid 1.17 with the appropriate P_1-P' amide moiety afforded the hydroxyl amide 1.11. Oxidation (Moffatt or Dess-Martin Periodinane) resulted in the keto amide 1.12. Deprotection of the N-Boc functionality gave the hydrochloride salt 1.13. Treatment with a suitable isocyanate (or isocyanate equivalent) resulted in the target compound 1.14.



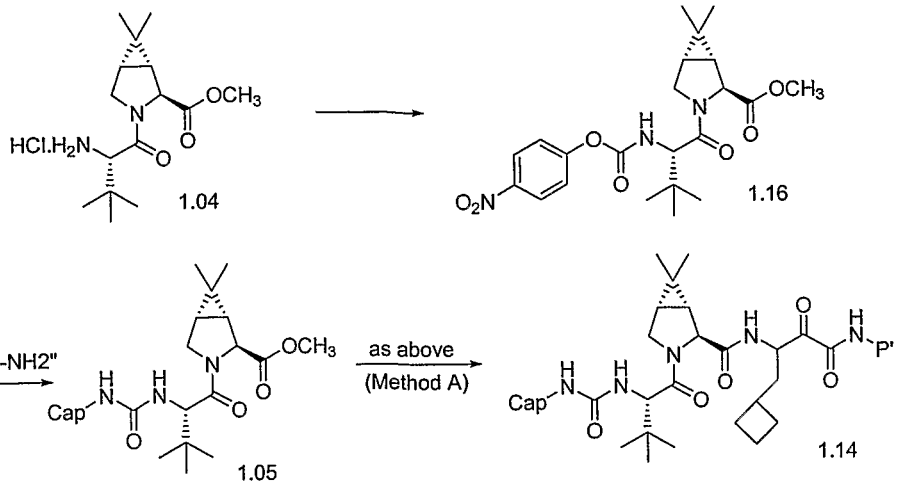
Method D

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



Method E

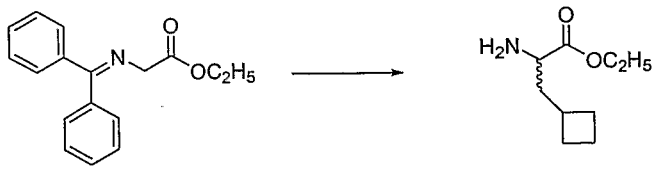
In yet another variation, the dipeptide hydrochloride salt 1.03 was converted to the 4-nitrophenyl carbamate as described above. Treatment with an amine (or amine hydrochloride salt) of choice provided the urea derivative 1.05. Hydrolysis and further elaboration as described in Methods A/B provided the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



Preparation of P1-P' moieties

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

Step 1.



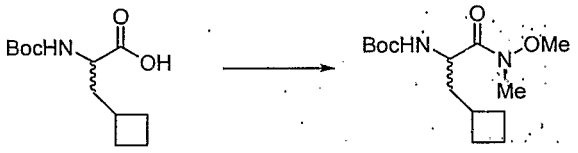
A stirred solution of ketimine **10.01** (50 g, 187.1 mmol) under N_2 in dry THF (400 mL) was cooled to –78 ^{0}C and treated with 1 M solution of K-^{t}BuO (220 mL, 1.15 equiv.) in THF. The reaction mixture was warmed to 0 ^{0}C and stirred for 1 h and treated with bromomethyl cyclobutane (28 mL, 249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

Step 2.

10.02 10.03

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

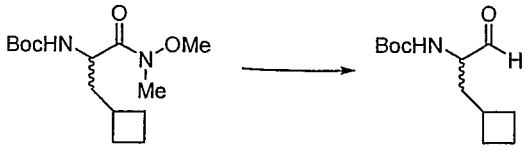
Step 3.



10.03 10.04

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

Step 4.



10.04 10.05

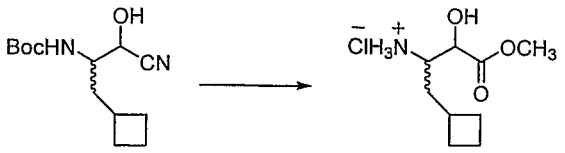
A solution of the amide **10.04** (15 g, 52.1 mmol) in dry THF (200 mL) was treated dropwise with a solution of $LiAlH_4$ (1M, 93 mL, 93 mmol) at 0 ^{0}C. The reaction mixture was stirred at room temperature for 1 h and carefully quenched at 0 °C with a solution of $KHSO_4$ (10% aq.) and stirred for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

Step 5:

10.05 10.06

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

Step 6.

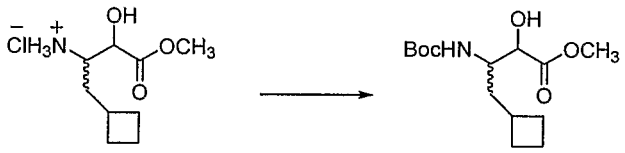


10.06 10.07

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

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

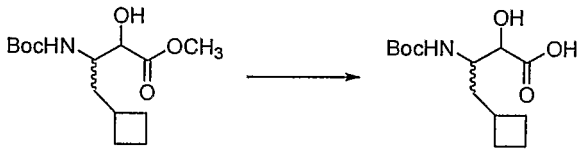
Step 7.



10.07 10.08

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

Step 8.

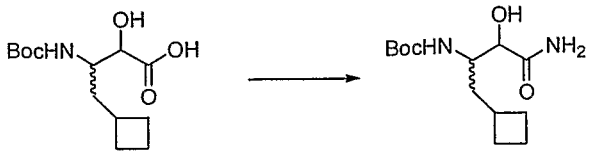


10.08 10.09

A solution of methyl ester **10.08** (3g, 10.5 mmol) in THF/H_2O (1:1) was treated with LiOH•H_2O (645 mg, 15.75 mmol) and stirred at rt. for 2 h. The

reaction mixture was acidified with aq HCl (1 M, 15 mL) and concentrated *in vacuo*. The residue was dried in vacuum to afford **10.09** in quantitative yield.

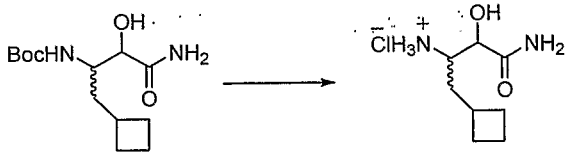
Step 9



10.09 **10.10**

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

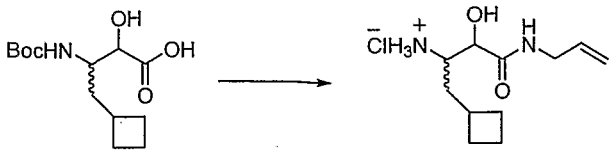
Step 10.



10.10 **10.11**

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

Step 11.

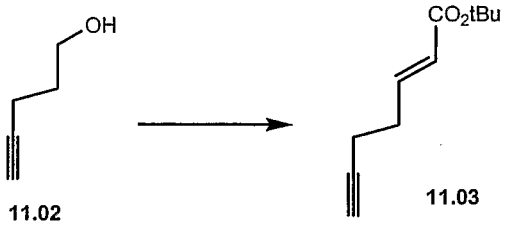


10.09 10.12

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

Preparation of Intermediate **11.01**

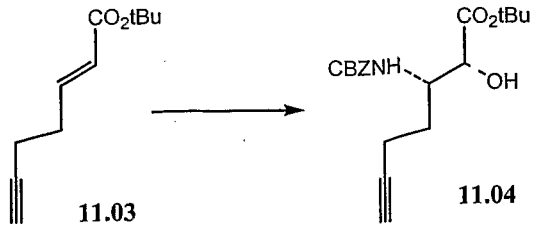
Step 1



11.02 11.03

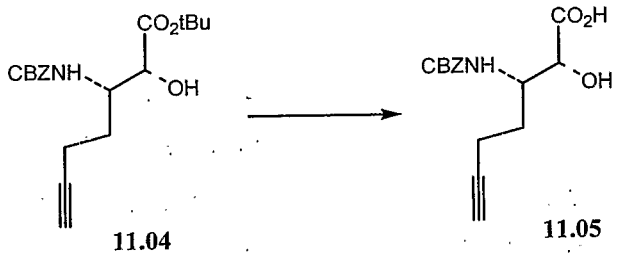
To a solution of 4-pentyn-1-ol, **11.02** (4.15g; Aldrich) was added Dess-Martin Periodinane (30.25g; Aldrich) and the resulting mixture was stirred for 45min. before the addition of (tert-Butoxycarbonylmethylene)triphenylphosphorane (26.75g; Aldrich). The resulting dark reaction was stirred overnight,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

Step 2



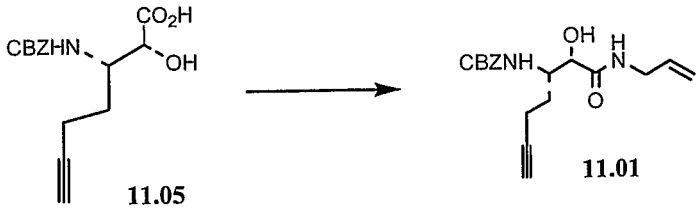
Using the alkene **11.03** (1.9g) in n-propanol (20ml; Aldrich)), benzyl carbamate (4.95g; Aldrich) in n-propanol (40ml), NaOH (1.29g) in water (79ml), tert-butyl hypochlorite (3.7ml), (DHQ)2PHAL (0.423g; Aldrich)) in n-propanol (37.5ml), and potassium osmate:dehydrate (0.1544g; Aldrich) and the procedure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

Step 3



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

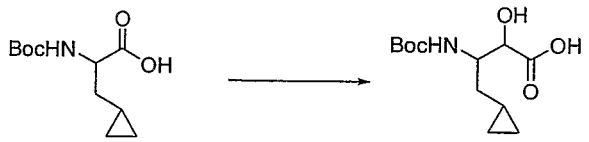
Step 4



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

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

Step 1



12.01 **12.02**

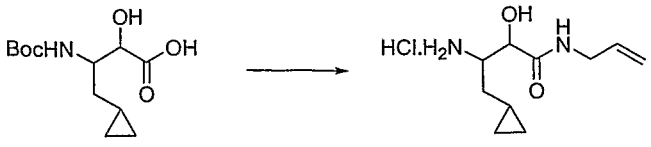
Compound **12.01** was converted to the required material **12.02** using essentially the procedures described for Intermediate **10.11**, Steps 3-8.

Step 2

12.02 **12.03**

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

Step 3



12.02 12.04

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

Preparation of Intermediate **13.01**

Step 1

13.02 13.03

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

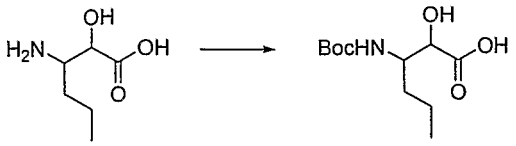
Step 2

13.03 13.04

To a stirred solution of compound **13.03** (240 g, 1.35 mol) in acetic acid (1.25 L) was added 10% Pd/C (37 g). The resulting solution was hydrogenated at 59 psi for 3 hrs and then at 60 psi overnight. The acetic acid was then evaporated and azeotroped 3 times with toluene, then triturated with

MeOH and ether. The solution was then filtered and azeotroped twice with toluene to afford **13.04** as an off white solid (131 g, 0.891 mol, 66%).

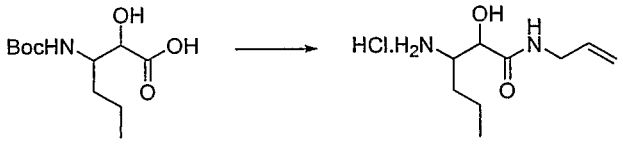
Step 3



13.04 **13.05**

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

Step 4

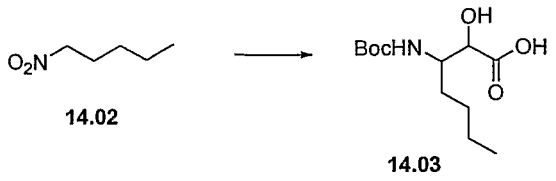


13.05 **13.01**

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

Preparation of Intermediate **14.01**

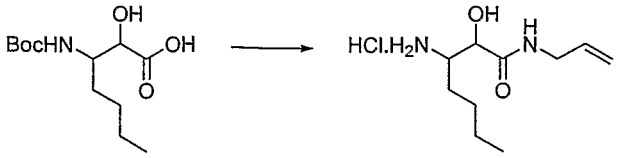
Step 1



14.02 14.03

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

Step 2

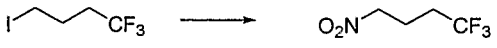


14.03 14.01

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

Preparation of Intermediate **15.01**

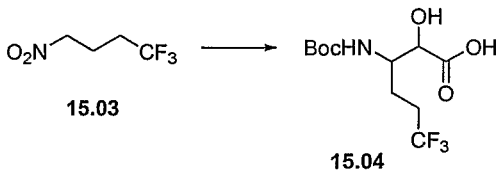
Step 1



15.02 15.03

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

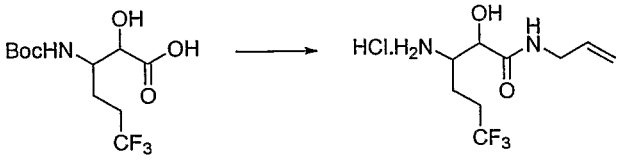
Step 2



15.03 15.04

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

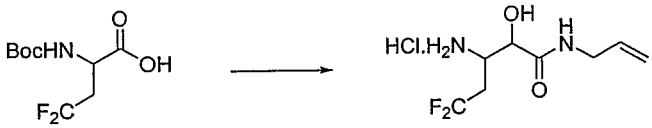
Step 3



15.04 **15.01**

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

Preparation of Intermediate **16.01**

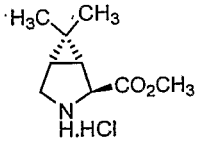


16.02 **16.01**

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

PREPARATION OF P2 / P3-P2 MOIETIES

Preparation of Intermediate **20.01**



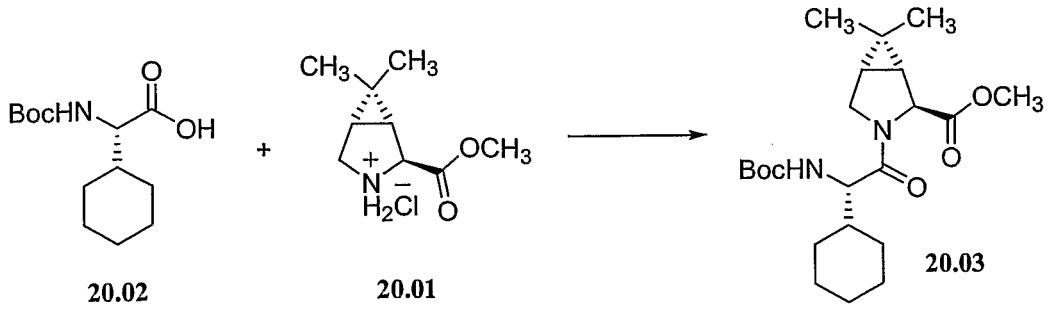
20.01

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

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

Preparation of Intermediate **20.04**

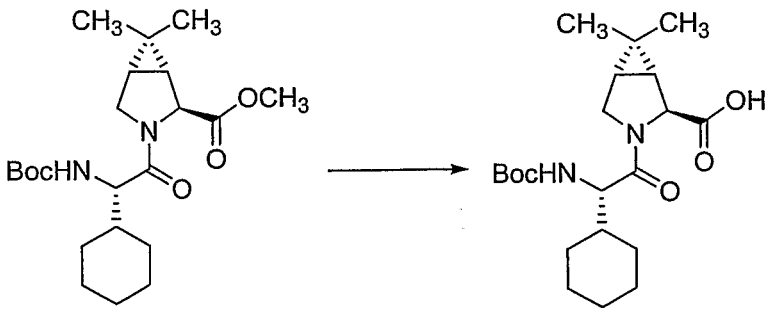
Step 1



20.02 **20.01** **20.03**

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

Step 2

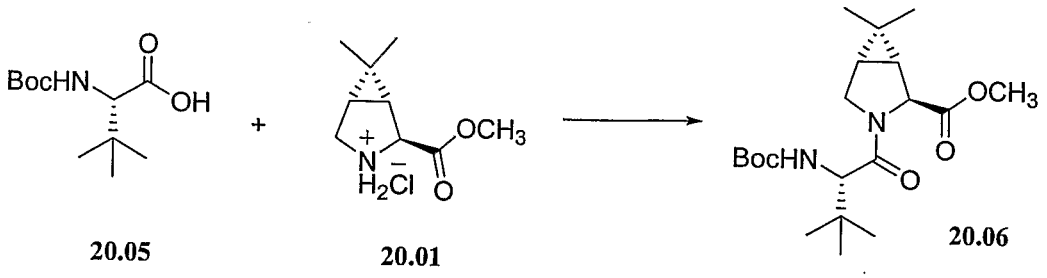


20.03 **20.04**

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

Preparation of Intermediate **20.07**

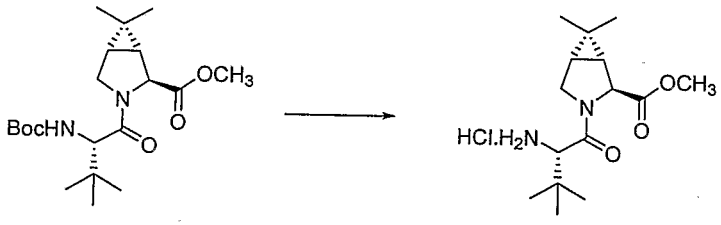
Step 1



20.05 **20.01** **20.06**

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

Step 2

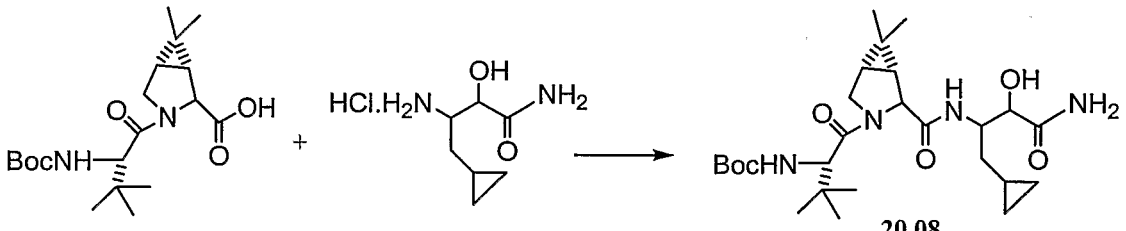


20.06 **20.07**

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

Preparation of Intermediate **20.10**

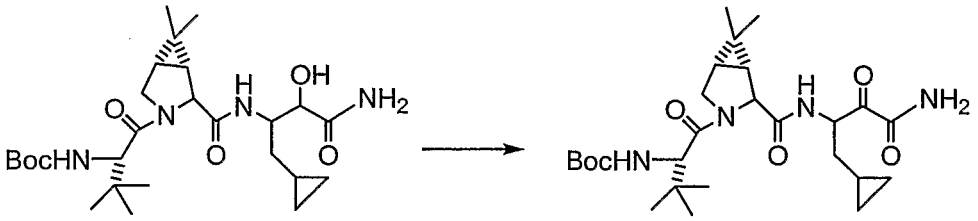
Step 1



1.17 **12.03** **20.08**

To a -20°C solution **1.17** (10.4 g, 28 mmol) in DCM (300 mL) was added HATU (1.05 equiv, 29.4mmol, 11.2g), amine salt, Intermediate **12.03** (1.0 equiv, 28 mmol, 5.48 g). After 10 min at -20°C, DIPEA (3.6 equiv, 100 mmol, 17.4 mL) was added. Reaction was stirred at this temp for 16 hr. After 16 hr, the reaction was diluted with EtOAc and washed successively with $NaHCO_3$, citric acid (10% w/w) and brine. Organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield 14 g of the required intermediate **20.08**.

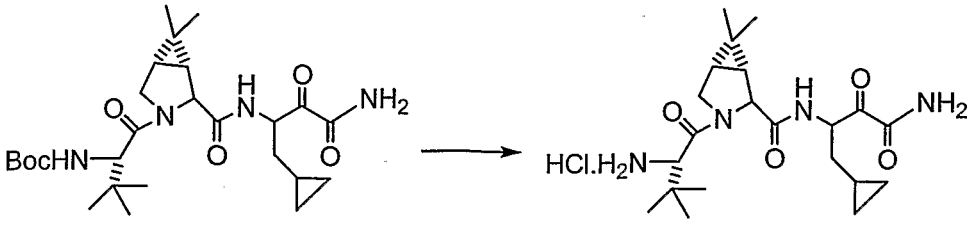
Step 2



20.08 **20.09**

The hydroxyamide **20.08** was oxidized to the required ketoamide **20.09** in a manner described for Example **198 (Step 8)**. LC-MS = 507 $(M+H)^+$.

Step 3

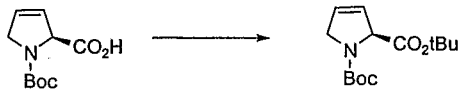


20.09 20.10

Deprotection of the t-Boc functionality of **20.09** to give the required material **20.10** was carried out as described for the transformation of **20.06** to **20.07**.

Preparation of Intermediate **21.01:**

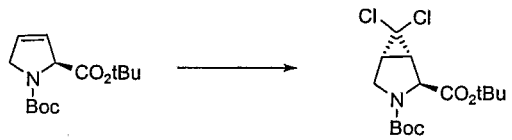
Step 1:



21.02 21.03

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

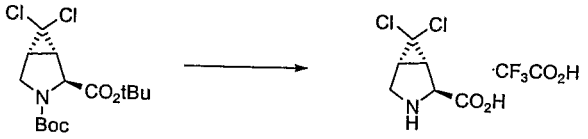
Step 2:



21.03 21.04

To a stirred solution of the dehydroproline derivative **21.03** (10.1 g, 37.4 mmol), benzyltriethylammonium chloride (1.60 g, 7.02 mmol) in chloroform (120 mL) at room temperature was added 50% aqueous sodium hydroxide (120 g). After vigorously stirred at this temperature for 24 h, the dark mixture was diluted with CH_2Cl_2 (200 mL) and diethyl ether (600 mL). After the layers were separated, the aqueous solution was extracted with CH_2Cl_2/Et_2O (1:2, 3x600 mL). The organic solution was dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography using 5-20% EtOAc/hexane to afford 9.34 g (71%) of **21.04** as an off-white solid.

Step 3:



21.04 **21.05**

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

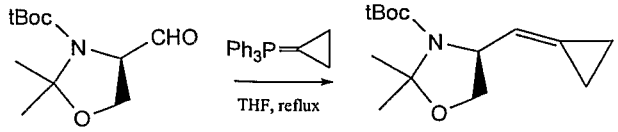
Step 4

21.05 **21.01**

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

Preparation of Intermediate **22.01**

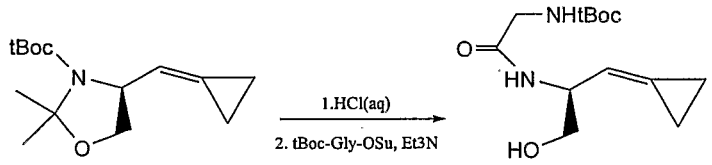
Step 1



22.02 **22.03**

Potassium bis(trimethylsilyl)amide (158ml of a 0.5M solution in toluene; 79mmol) was added to a stirred suspension of cyclopropyltriphenylphosphonium bromide (33.12g; 86.4mmol) in anhydrous tetrahydrofuran (130ml) and the resulting orange mixture was stirred under an atmosphere of nitrogen at room temperature for a period of 1h., before the addition of the aldehyde **22.02** (9.68g; 42.2mmol) in THF (8ml). The reaction was then refluxed under an atmosphere of nitrogen for a period of 2h. After cooling, methanol, diethyl ether and Rochelles salt were added. The organic phase was separated, washed with brine, dried and concentrated under reduced pressure. The crude reaction product was purified by silica gel column chromatography using EtOAc-hexane (1:99) to EtOAc-hexane (5:95) to provide the alkene **22.03** (8.47g) as a yellow oil.

Step 2



22.03 **22.04**

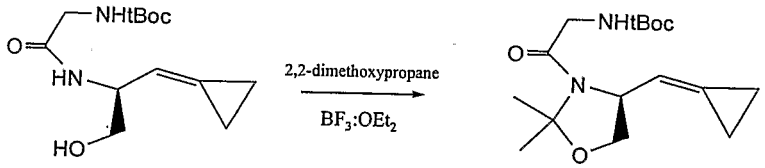
A solution of 1M HCl in MeOH/MeOAc was prepared by adding 14.2ml of acetyl chloride dropwise into cold methanol and diluting the resulting solution to 200ml at room temperature.

The carbamate **22.03** (9.49g; 37.5mmol) was dissolved in methanol (12ml) and added to 1M HCl in MeOH/MeOAc (150ml) while cooled in an ice bath. The resulting mixture was maintained at this temperature for 1h., then

the ice bath was removed and stirring continued overnight at room temperature. The volatiles were removed under reduced pressure to yield a yellow oil which was used in the next step without purification.

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

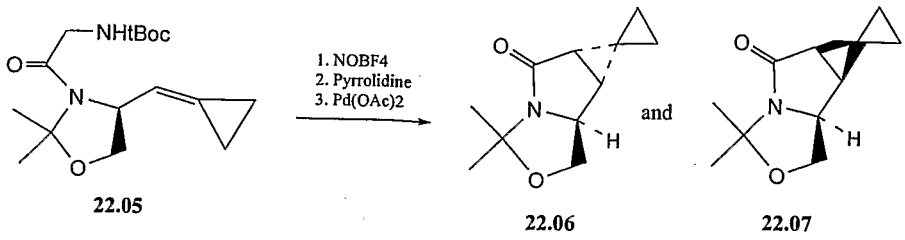
Step 3



22.04 **22.05**

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

Step 4

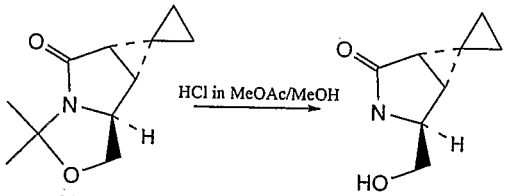


22.05 22.06 22.07

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

The yellow oil was dissolved in anhydrous benzene (220ml) and palladium acetate (0.317g; 1.41mmol) was added before heating the resulting mixture to reflux, under an atmosphere of nitrogen for a period of 1.5h. After cooling, the volatiles were removed under reduced pressure and the dark residue was purified by silica gel column chromatography using EtOAc-hexane (1:4) to provide the I) the trans- pyrrolidinone **22.06** (1.94g) followed by ii) the cis-pyrrolidinone **22.07** (1.97g).

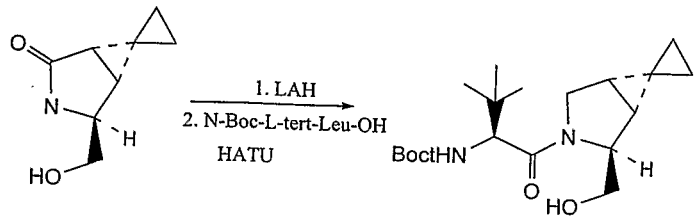
Step 5



22.06 22.08

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

Step 6



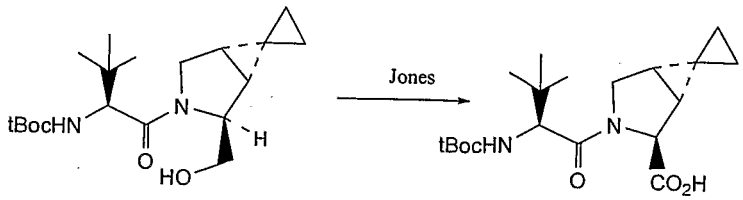
22.08 **22.09**

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

Hunigs base (4.5ml; 25.8mmol) was added to a mixture of N-Boc-L-tert-Leu-OH (1.76g; 7.6mmol), The crude pyrrolidine and HATU (2.89g; 7.6mmol) in anhydrous dichloromethane (50ml) at –60°C, under an atmosphere of nitrogen. The resulting reaction was allowed to come to room temperature slowly, overnight. EtOAc was added and the yellow solution was washed with dil. aq. HCl, sat. aq. sodium bicarbonate, water, brine. The organic layer was dried and concentrated under reduced pressure. The

residue was purified by silica gel column chromatography using EtOAc:hexanes (1:3) to give the desired amide **22.09** (2.00g).

Step 7

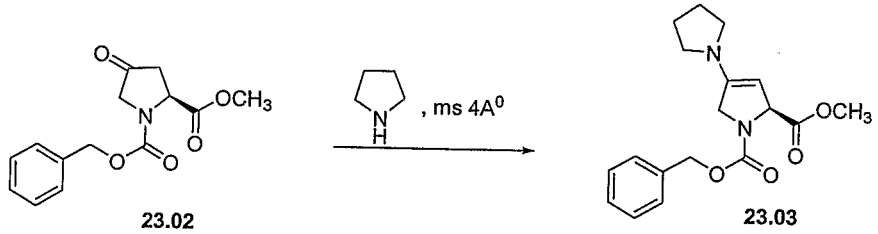


22.09 **22.01**

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

Preparation of Intermediate **23.01**

Step 1:

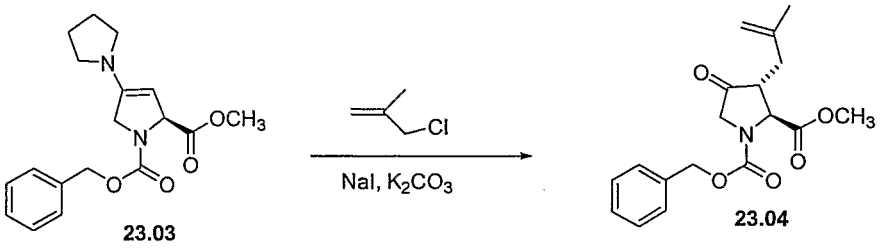


23.02 **23.03**

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

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

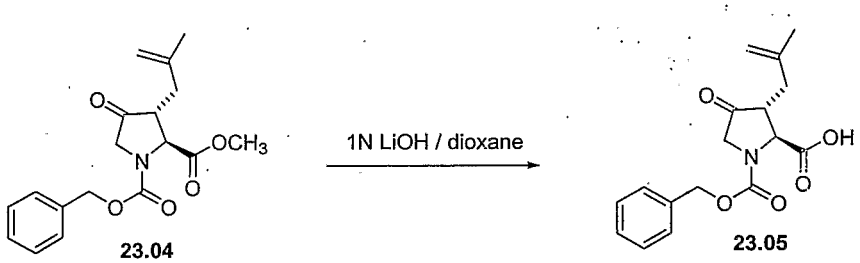
Step 2:



23.03 23.04

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

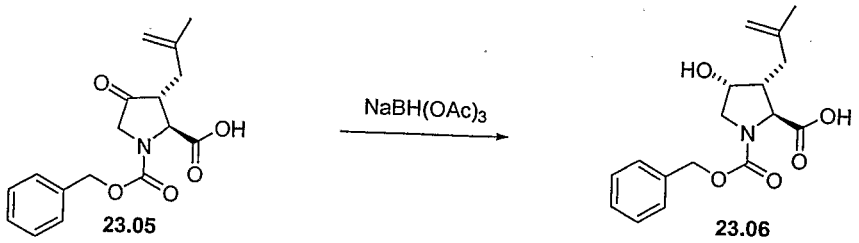
Step 3:



23.04 23.05

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

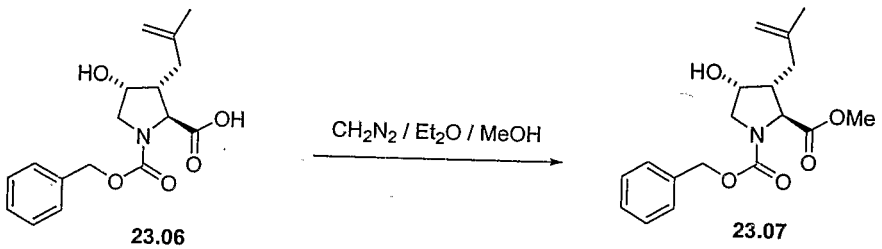
Step 4:



23.05 23.06

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

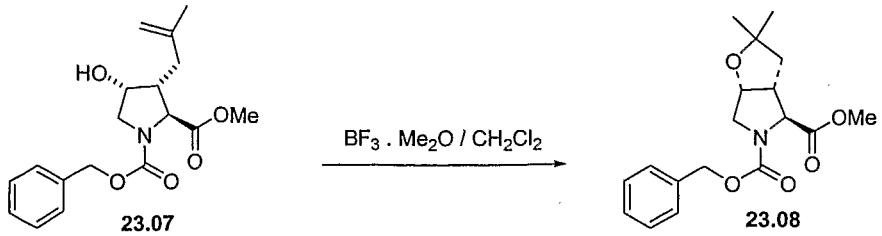
Step 5:



23.06 23.07

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

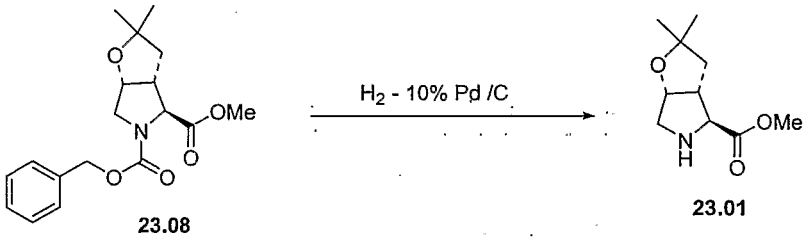
Step 6:



23.07 23.08

To a solution of product **23.07** from preceding step (1.36 g) in anhydrous CH_2Cl_2 (40 mL) was treated with BF_3. Me_2O (0.7 mL). The reaction mixture was stirred at ambient temperature for 20 h and quenched with sat. $NaHCO_3$ (30 mL) ad stirred for 1/2 hr. Organic layer was separated and combined organic layer was washed with brine, dried over $MgSO_4$, concentrated to give crude residue. The residue was chromatographed on silica gel eluting with a gradient of EtOAc / hexane to afford 0.88 g of the desired compound, **23.08.**

Step 7:



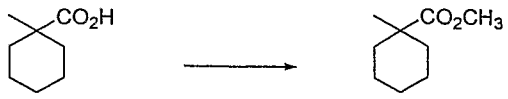
23.08 23.01

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

PREPARATION OF P3 MOIETIES

Preparation of Intermediate **50.01**

Step 1



50.02 50.03

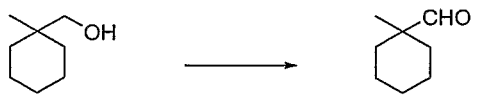
To a solution of **50.02** (15 g) in MeOH (150 mL) was added conc HCl (3-4 mL) and the mixture was refluxed for 16 h. The reaction mixture was cooled to room temperature and concentrated. The residue was taken in diethyl ether (250 mL) and washed with cold saturated sodium bicarbonate solution, and brine.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

Step 2

50.03 50.04

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

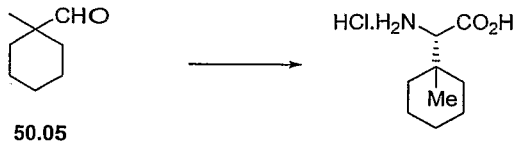
Step 3



50.04 50.05

The alcohol **50.**04 from above was dissolved in methylene chloride (400 mL) and cooled to 0°C under nitrogen atmosphere. PCC (22.2 g) was added in portions and the reaction mixture was slowly warmed to room temperature over 16 h. The reaction mixture was diluted with diethyl ether (500 mL) and filtered through a pad of celite. The filtrate was concentrated and the residue was taken in diethyl ether (500 mL). This was passed through a pad of silica gel and the filtrate was concentrated to provide the aldehyde **50.05** which was carried forward without further purification.

Step 4

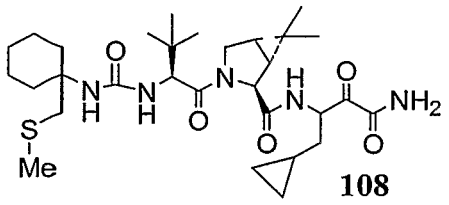


50.05 **50.01**

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

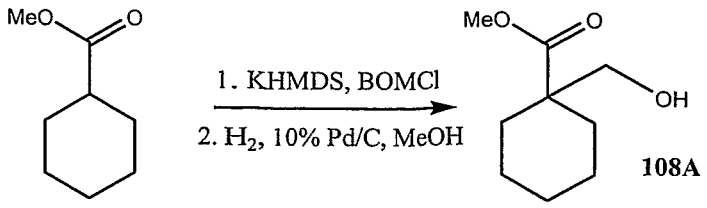
PREPARATION OF SPECIFIC EXAMPLES

Example 108:



108

Steps 1 and 2:



108A

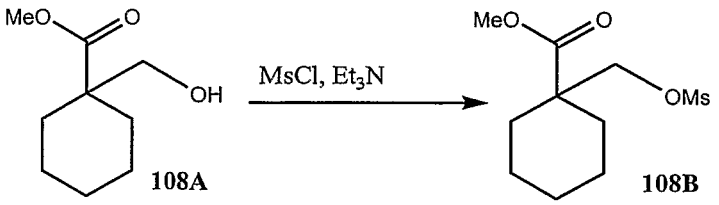
Step1:

KHMDS (200ml of a 0.5M solution in toluene) was added, dropwise to a stirred solution of Methyl cyclohexanecarboxylate (11.1g; 78mmol) in anhydrous THF (200ml), at -78C under an atmosphere of nitrogen. When the addition was complete the reaction was maintained at this temperature for a further 0.5h. before the addition of Benzyl Chloromethyl Ether (18.6ml; 134mmol). The reaction was allowed to warm to room temperature overnight and water (100ml) was added. Aqueous work-up provided a residue which was purified by silica gel column chromatography using EtOAc; hexanes (1:10) as eluent to give the desired, impure, intermediate ether (14.98g) as a colorless oil.

Step2:

A black suspension of 10% Pd/C (0.5g) and the aforementioned crude ether (4.1g) in MeOH (80ml) was exposed to an atmosphere of nitrogen (balloon) at room temp., overnight. The reaction was filtered through a pad of celite and the solid was washed thoroughly with methanol. The combined filtrate was concentrated under reduced pressure and the crude product was purified by silica gel column chromatography using EtOAc; hexanes (1:5) to give the primary alcohol (**108A**; 0.62g), a colorless oil.

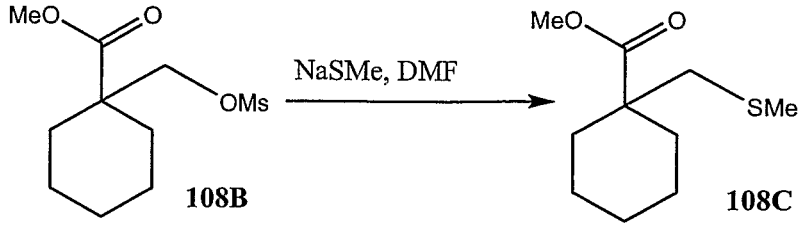
Step 3:



108A 108B

Methanesulfonyl Chloride (0.31ml) followed by triethylamine (0.75ml) were added to a stirred solution of the primary alcohol (**108A**; 0.62g) at 0C, under an atmosphere of nitrogen. The resulting mixture was stirred at this temperature for 0.5h. The reaction mixture was extracted into EtOAc and washed with aqueous 1M HCl, sat. aq. NaHCO3, water, dried (MgSO4) and concentrated. The residue (mesylate **108B**; 0.74g), was obtained as a yellow oil, which was used in subsequent steps without purification.

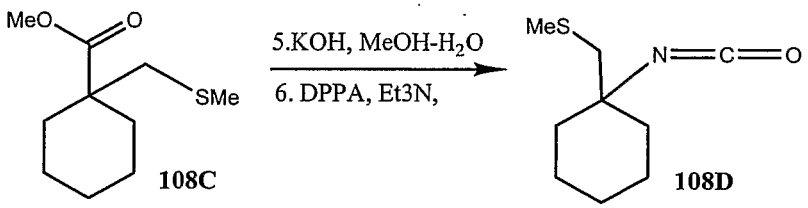
Step 4:



108B **108C**

Sodium Methanethiolate (0.236g; 2eq.) was added to a DMF (2ml) solution of the mesylate (**108B**; 0.42g) and the mixture was heated to 100C for 1h. Aqueous work-up and purification of the crude reaction product by silica gel column chromatography using EtOAc; hexanes (1:20) gave the sulfide (**108C**; 0.089g).

Steps 5 and 6:



108C **108D**

Step 5:

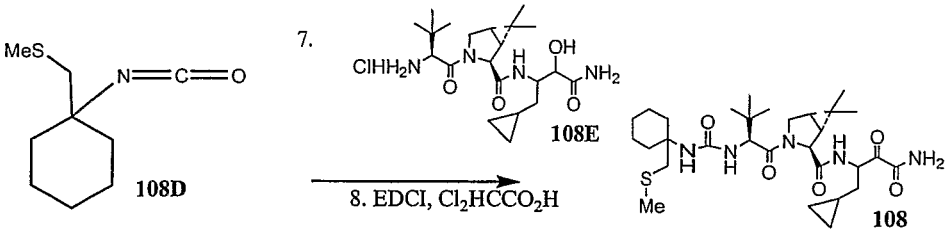
Potassium hydroxide (0.25g) was dissolved in a mixture of water (1ml) and ethanol (5ml) and added to the methyl ester (**108C**;0.089g) and the resulting mixture was heated to reflux, under an atmosphere of nitrogen over a week-end (approx. 72h.). After cooling, the reaction was partitioned between EtOAc and dilute aq. HCl. The organic phase was separated,

washed with brine, dried and concentrated to yield the crude intermediate carboxylic acid, used without purification.

Step 6:

Triethylamine (61ul) followed by DPPA (95ul) were added to a toluene solution of the carboxylic acid from the previous step and the reaction was heated to 100C overnight. After cooling, the reaction mixture was partitioned between EtOAc and sat. aq. sodium bicarbonate. The organic phase was separated, dried and concentrated to yield the isocyanate (**108D**; 50mgs), used without purification.

Steps 7 and 8:



Step 7:

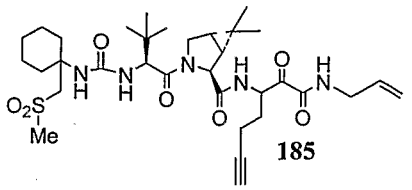
The isocyanate (**108D**; 50mg) in dichloromethane (1ml) was added to a mixture of the hydrochloride salt (**108E**; prepared from 20.08 in a manner described for the transformation of 20.06 to 20.07; 100mg) and triethylamine (111ul) in dichloromethane (2ml) and the resulting mixture was stirred at room temperature for 4 hours. The reaction mixture was partitioned between EtOAc and 10% aq. HCl. The organic phase was separated, washed with sat. aq. sodium bicarbonate, water, dried (magnesium sulfate) and concentrated to yield a residue which was used in step 8 without purification.

Step 8:

The residue in the aforementioned step was dissolved in a mixture of toluene (3ml) and dimethylsulfoxide (3ml) and EDCI (647 mg) followed by dichloroacetic acid (140ul) were added and the resulting reaction mixture was

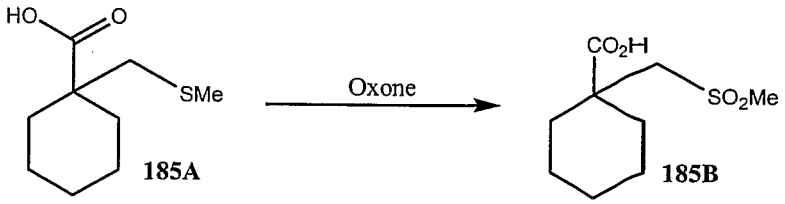
stirred at room temperature for a period of 4h. The reaction mixture was partitioned between EtOAc and 5% aq. sodium sulfite. The organic phase was separated, washed with 10% aq. HCl, sat. aq. sodium bicarbonate, water, dried (magnesium sulfate) and concentrated to yield a residue which was purified by silica gel column chromatography using acetone: hexanes (40:60) as eluent to provide the desired keto-amide (**108**; 11.5mgs). MS: MH+, 592.1.

Example 185:



185

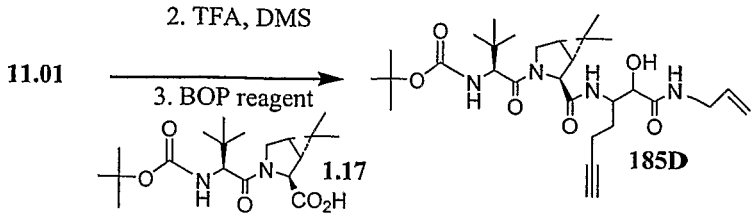
Step 1:



185A **185B**

Oxone (5.68g) was dissolved in water (5ml) and added to the carboxylic acid **185A** (1.25g) in methanol (5ml) while cooled in an ice bath. The reaction mixture was allowed to warm to room temp., overnight. The volatiles were removed under reduced pressure and the residue was partitioned between methylene chloride and water. The aqueous phase was separated and extracted with methylene chloride (X2). The combined organic phases were dried and concentrated to yield the sulfone (**185B**; 1.10g) as a white solid, used in subsequent procedures without purification.

Steps 2 and 3:



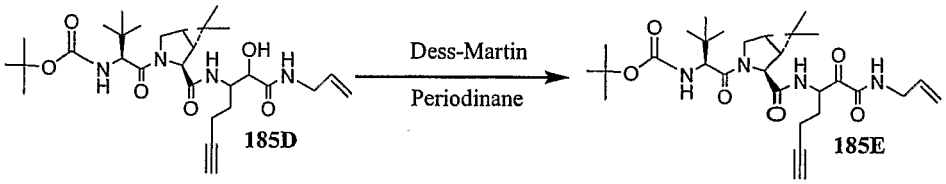
Step 2:

The benzyl carbamate (**11.01**;0.16g) was dissolved in TFA (7ml) and dimethyl sulfide (1.78ml) was added and the resulting mixture was allowed to stand at room temperature for a period of 3h., before removing the volatiles under reduced pressure. This gave a residue which was used in step 3 below.

Step3:

Triethylamine (111ul) was added to a mixture of the residue from step 2, the carboxylic acid (**1.17**; 0.180g) and BOP reagent (0.236g) in dichloromethane (5ml) and the reaction mixture was stirred at room temperature overnight. The reaction was partitioned between ethyl acetate and aq. 10% HCl. The organic phase was separated, washed with sat. aq. sodium bicarbonate, water, dried (magnesium sulfate) and the volatiles removed under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc: Hexanes (70:30) as eluent to give the desired hydroxy-amide (**185D**; 0.165g) as a white solid.

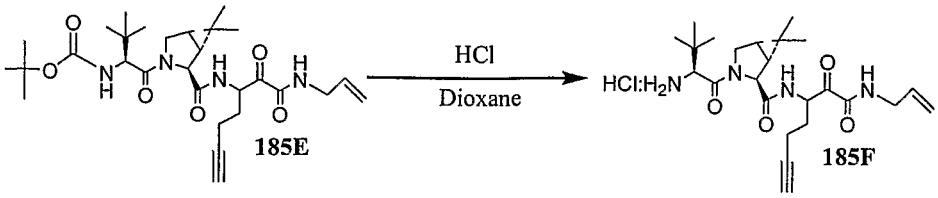
Step 4:



The periodinane (0.236g) was added to a stirred solution of the alcohol (**185D**; 0.152g) in dichloromethane (5ml) and the resulting white suspension was stirred for a period of 2h. before being added to a mixture of EtOAc and 5% aq. sodium sulfite. The organic phase was separated washed with sat. aq.

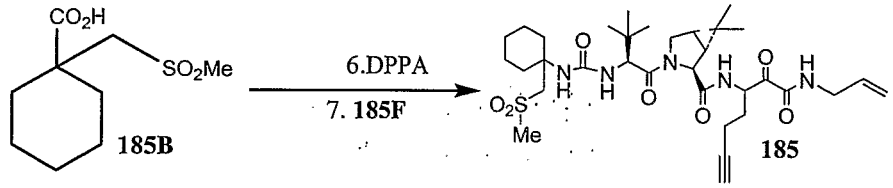
sodium bicarbonate, water, dried and the volatiles removed under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc: Hexanes (40:60) as eluent to give the desired keto-amide (**185E**; 0.147g) as a white solid. MS: MH+, 545.5.

Step 5;



A solution of HCl in dioxane (4M; 5ml; Aldrich) was added to the carbamate (**185E**; 0.14g) and allowed to stand at room temperature for a period of 3h. The volatiles were removed under reduced pressure to provide the hydrochloride salt (**185F**; 0.126g: contains a small quantity of dioxane).

Steps 6 and 7:



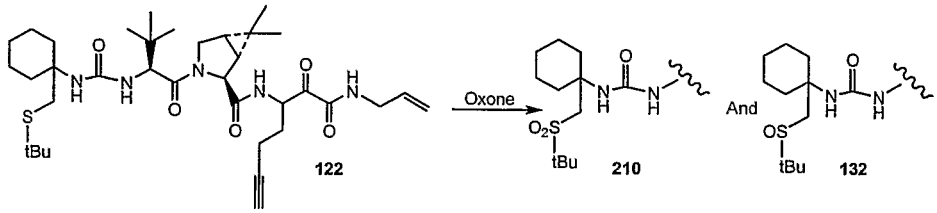
Step 6:

DPPA (19ul) was added to a mixture of the carboxylic acid (**185B**; 20mgs) and triethylamine (13ul) in toluene (1ml) and the resulting reaction mixture was heated to reflux for a period of 1h. After cooling, the reaction was partitioned between EtOAc and sat. aq. sodium bicarbonate. The organic phase was separated, dried and the volatiles removed under reduced pressure. Gave the crude intermediate isocyanate which was used in step 7, below without purification.

Step 7:

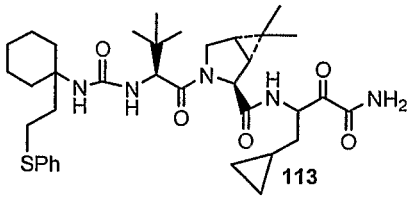
The product from step 6 was dissolved in dichloromethane (1mL) and added to a mixture of the hydrochloride salt (**185F**; 20mgs) and triethylamine (60ul) in dichloromethane (1ml) and the resulting mixture was stirred at room temperature for a period of 1h. The reaction was partitioned between EtOAc and 10% aq. HCl. The organic phase was separated, washed with sat. aq. sodium bicarbonate, water, dried and the volatiles were removed under reduced pressure. The resulting residue was purified by silica gel plate chromatography using EtOAc: Hexanes (1:1) as eluent to provide the keto-amide (**185**; 16.3mgs) as a white solid. MS: MH+, 662.5.

Preparation of Compounds of Formulas **132** and **210** Directly From a Compound of Formula I**22**

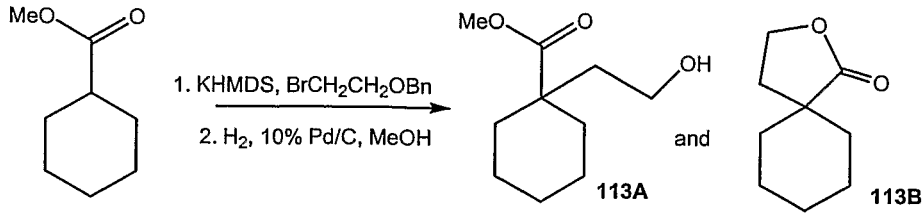


Using the sulfide **122** (prepared in a similar manner as 108 using methyl ester 210A rather than 108C; 20mg), oxone (27mg; 1.5eq.), water (1ml), methanol (1ml) and the procedure set forth previously (**185A** to **185B**) gave a crude reaction product which was purified by silica gel plate chromatography using EtOAc as eluent. Gave the sulfone (**210**; MH+= 704.4; 5.6mg) as a white solid followed by a mixture of sulfoxides (**132**; MH+ = 688.5; 6.3mg), also a white solid.

Preparation of Compound **113**



Steps 1 and 2:



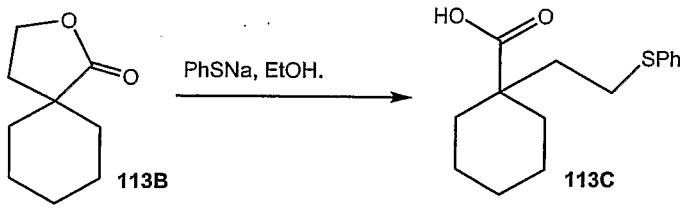
Step 1:

Using Methyl cyclohexanecarboxylate (5.55g), KHMDS (100ml of a 0.5M solution in toluene), anhydrous THF (100ml) and benzyl 2-bromoethyl ether (10.09g) and the procedure set forth previously(Example **108**, Step1), the desired intermediate benzyl ether (6.83g) was obtained after silica gel column chromatography (EtOAc:Hexanes:15:85).

Step 2:

Using the aforementioned benzyl ether (5.00g), 10% Pd/C (1.00g), methanol (20ml) and the procedure set forth previously (Example **108**; Step2) the lactone (**113B**; 0.87g), followed by the alcohol (113A; 2.01g) were obtained following column chromatography on silica gel (EtOAc; Hexanes; 1:10).

Step 3:



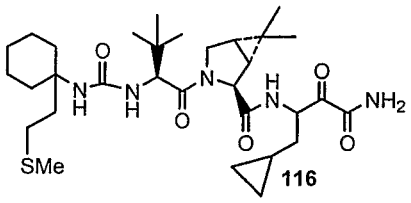
Step 3:

Sodium thiophenoxide (0.68g) was added to a solution of the lactone (**113B**; 0.84g) in ethanol (15ml) and the resulting mixture was heated to reflux, under an atmosphere of nitrogen overnight. After cooling, aqueous work-up and purification of the crude reaction product by silica gel column

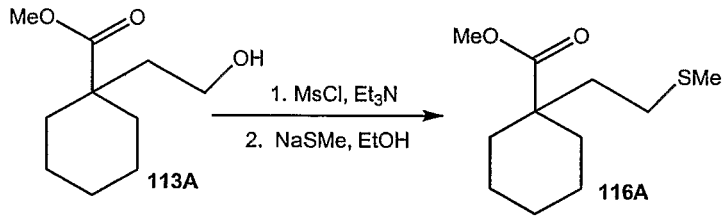
chromatography (EtOAc-Hexanes; 30:70) gave the carboxylic acid (**113C**; 0.32g), as a yellow solid.

Using previously described chemistry for the conversion of **108C** to **108, 113C** was converted to **113** in a similar manner. MS, MH+, 668.3.

Preparation of Compound **116:**



Steps 1 and 2



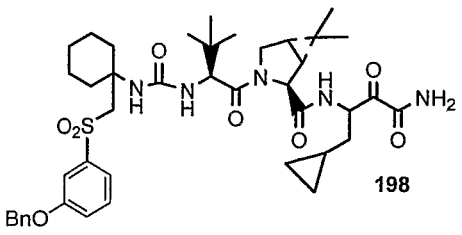
Step 1:

Using the alcohol (**113A**; 1.00g), methane sulfonylchloride (1.12g), triethylamine (0.82g), methylene chloride (10ml) and the procedure set forth previously (**108A** to **108B**), the desired, intermediate mesylate was obtained and was used in the next step, without purification.

Step 2:

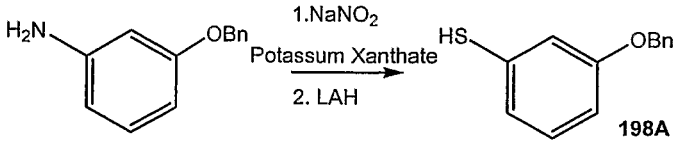
Using the aforementioned mesylate, sodium methanethiolate (0.75g), ethanol (10ml) and the procedure set forth previously (**108B** to **108C**) at room temperature, the desired sulfide (**116A**; 0.78g) was obtained after silica gel column chromatography (EtOAc-Hexanes; 1:10). Using the procedures set forth previously (**108C** to **108D**) and (**108D** to **108**), intermediate **116A** was transformed into **116**. MS; MH+, 606.1.

Preparation of Compound **198**



198

Steps 1 and 2"



198A

Steps 1 and 2:

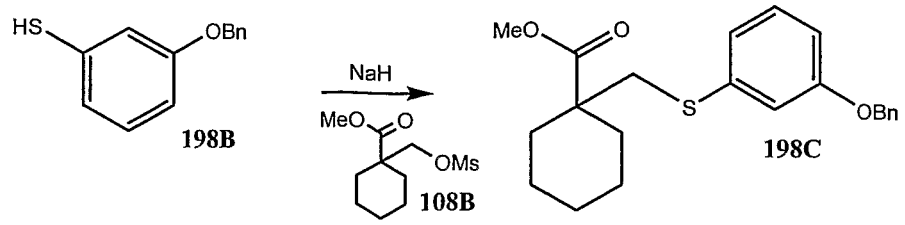
Step 1:

3-Benzyloxyaniline (5.00g; Aldrich) was dissolved in a mixture of conc. HCl (10ml) and ice (10.00g) was added. Sodium nitrite (1.85g) in water (10ml) was added while cooled in an ice bath. When the addition was complete, Potassium O-Ethylxanthate was added and stirred at this temperature until the evolution of nitrogen gas ceased, then heated at 40-45C for a period of 1.5h. After cooling, aqueous work-up and purification by silica gel column chromatography (2-5% EtOAc in hexanes) to give the intermediate xanthate (3.60g).

Step 2:

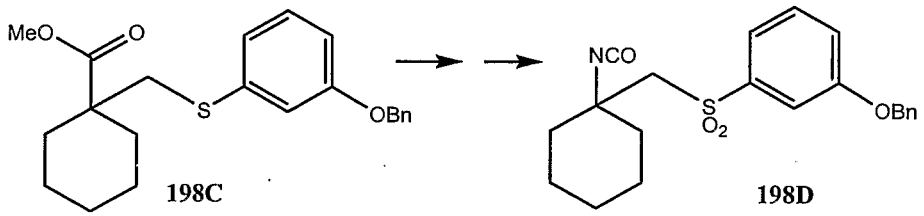
Lithium Aluminum Hydride (6.4ml of a 1M solution in THF) was added dropwise to a stirred solution of the aforementioned xanthate (1.49g) in THF (10ml) and stirred at R.T. for a period of 0.5h. The reaction was quenched with excess acetone and partitioned between EtOAc and aq. 1M HCl. The organic phase was separated, dried and concentrated. The crude reaction product was purified by silica gel column chromatography (1-2% EtOAc in hexanes) to give the thiophenol (**198A**; 0.84g), a white solid.

Step 3:



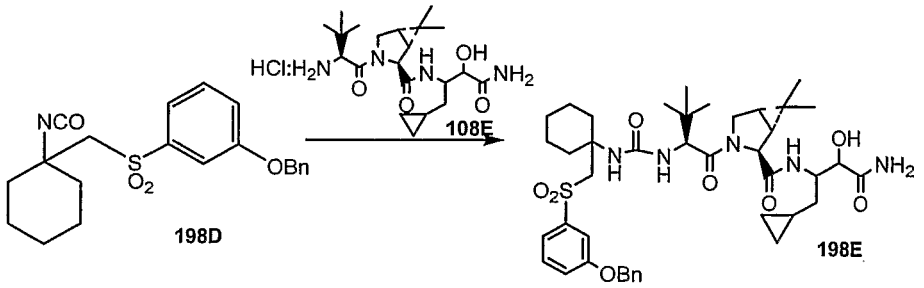
The mercaptan (**198B**; 0.72g) was added to a suspension of NaH (0.08g of a 60% dispersion in mineral oil) in anhydrous DMF, while cooled in an ice bath under an atmosphere of nitrogen. The resulting mixture was stirred for 1h. and the mesylate (**108B**; 0.417g) was added and the reaction was allowed to warm to R.T., overnight. Aqueous work-up and purification of the crude reaction product by silica gel column chromatography (3% EtOAc in hexanes) gave the sulfide (**198C**; 0.313g).

Steps 4-6:



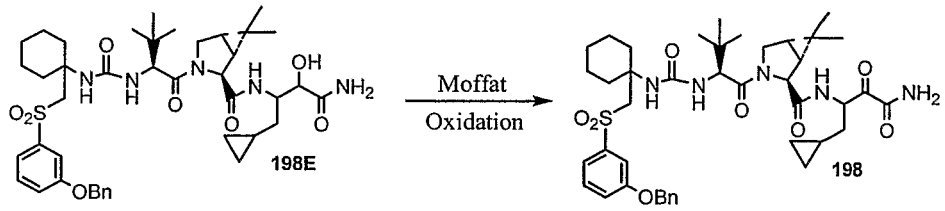
Using the sulfide (**198C**) generated in the previous step, the isocyanate (**198D**) is produced using procedures set forth in (**108C** to **108D**) and **185A** to **185D**). The isocyanate (**198D**) is used in subsequent procedures without purification.

Step 7:



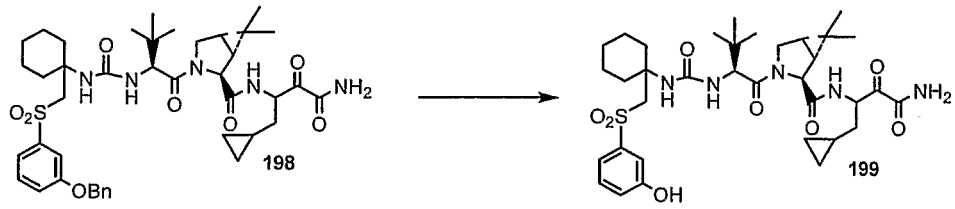
The isocyanate (**198D**; 0.139g) in a minimal amount of dichloromethane (approx. 1ml) was added to a mixture of the hydrochloride salt (**108E**; 0.080g) and triethylamine (0.126ml) and the resulting mixture was stirred at room temperature for a period of 4 hours. The reaction mixture was partitioned between EtOAc and 10% aq. HCl. The organic phase was separated, washed with sat. aq. sodium bicarbonate, water, dried and concentrated. The crude reaction product (**198E**) was used crude in the next step.

Step 8:



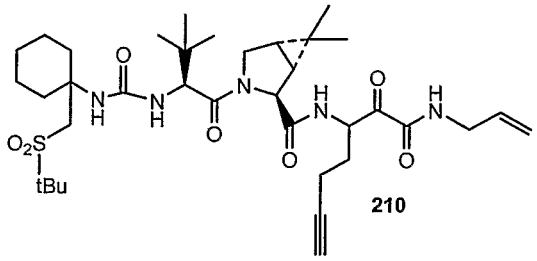
The crude product from the previous step (**198E**) was dissolved in DMSO (3ml) and toluene (3ml) and EDCI (0.346g) followed by dichloroacetic acid (0.074ml) was added and the resulting mixture was stirred at room temperature for a period of 4 hours. The reaction was partitioned between EtOAc and 5% aq. sodium sulfite. The organic phase was separated, washed with sat. aq. sodium bicarbonate, water, dried and concentrated. The crude reaction product was purified by silica gel column chromatography using acetone:hexane (30:70) as eluent to give the keto-amide (**198**; MH+ = 792.2; 55mgs).

Preparation of the Phenol **199** from Benzyl Ether **198:**



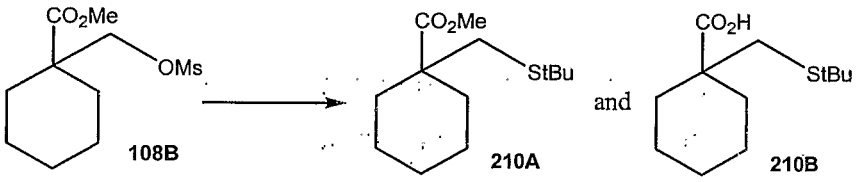
10% Pd-C (25mg) followed by formic acid (0.125ml) were added to a solution of the benzyl ether (**198**; 50mg) in ethanol (4ml) and the resulting black suspension was refluxed for a period of 1hour. After cooling, the reaction was filtered through a pad of celite and the solid was washed with methanol. The combined filtrate was concentrated under reduced pressure to give the desired phenol (**199**; MH+= 702.2; 23mg).

Alternative Preparation of Compound of Formula **210:**



210

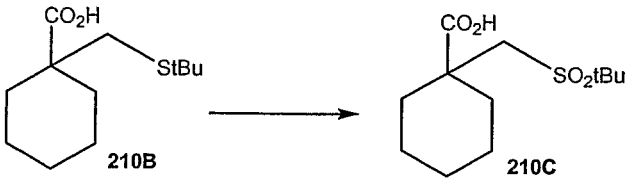
Step1:



Dimethylformamide (20ml; anhydrous; Aldrich) was added to sodium hydride (0.56g; Aldrich) and tert-butyl mercaptan was added to the suspension while cooled in an ice bath under an atmosphere of nitrogen. Once the addition was complete the mesylate (**108B**; prepared as above from 2.00g of alcohol; **108A**) was added and the resulting mixture was stirred overnight at room temperature. The reaction was partitioned between EtOAc and water and the organic phase was separated, dried (MgSO4). column chromatography on silica gel using EtOAc-Hexanes (2:98) to provide the methyl ester-sulfide (**210A**; 1.75g).

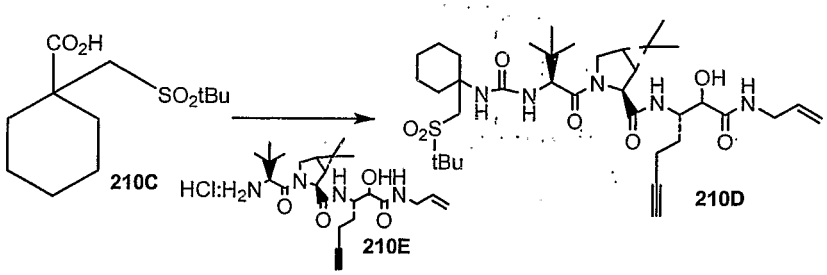
EtOAc was added to the aqueous phase and 10% aq. HCl was added until the water layer pH=1. The organic layer was separated, washed with water, dried and concentrated under reduced pressure to give the sulfide-carboxylic acid (**210B**; 0.747g) as a white solid.

Step 2:



To the sulfide (**210B**; 2.287g) in methanol (75ml) was added a solution of oxone (18.00g; Aldrich) and the resulting white suspension was stirred overnight at room temperature. The volatiles were removed under reduced pressure and the white solid partitioned between EtOAc and water. The organic phase was separated, dried and concentrated to provide the sulfone (**210C**; 2.52g; contains some solvent).

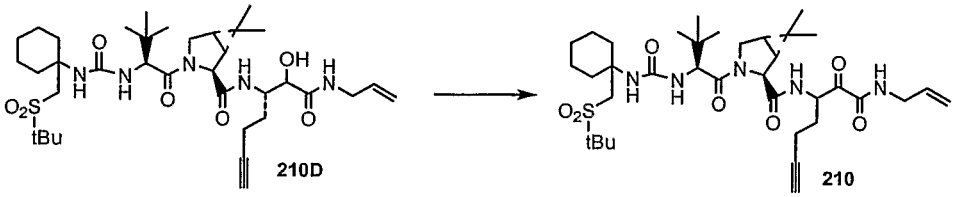
Step 3:



Triethylamine (0.173ml), followed by DPPA (0.268ml) were added to a solution of the carboxylic acid (**210E**; 0.325g) in toluene (3ml) and the resulting mixture was heated to 110C (oil bath) for a period of 1 hour. After cooling the reaction mixture was partitioned between EtOAc and sat. aq. sodium bicarbonate. The organic phase was separated, dried and concentrated. The residue was dissolved in dichloromethane (1ml) and added to a mixture of the hydrochloride salt (**185F**; 0.300g) and triethylamine

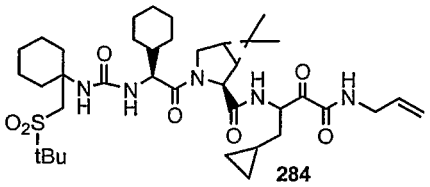
(0.044ml) in dichloromethane (3ml) and the resulting reaction mixture was stirred at room temperature overnight. The reaction was partitioned between EtOAc and 10% aq. HCl, The organic phase was separated, washed with saturated aq. sodium bicarbonate, water, dried and concentrated to yield a crude product which was used in the next step without purification.

Step 4:

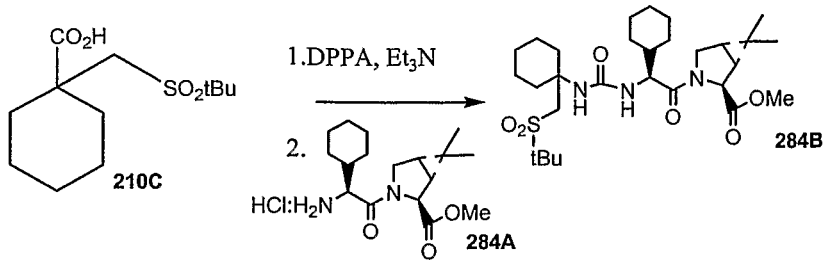


The residue from the previous step (**210D**) was dissolved in dichloromethane (5ml) and Dess-Martin periodinane (0.527g) was added and the reaction mixture was stirred at room temperature for 3 hours. The reaction was partitioned between EtOAc and 5% aq. sodium sulfite. The organic phase was separated, washed with sat. aq. sodium bicarbonate, water, dried and the volatiles removed under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc-Hexanes (70:30) as eluent to give the desired keto-amide (**210**; 0.310g).

Preparation of Compound of Formula **284:**



Steps 1 and 2:



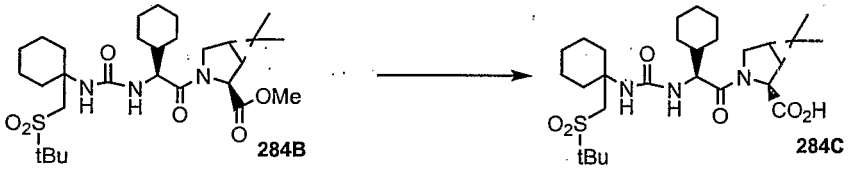
Step1:

Using the carboxylic acid (**210C**; 2.52g), DPPA (2.07ml), triethylamine (1.34ml) in toluene (10ml) and the procedure set above the crude isocyanate was formed.

Step 2:

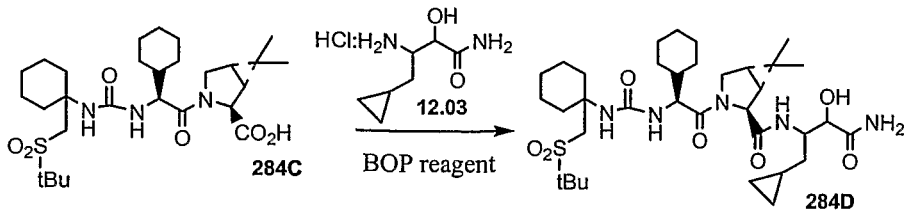
The intermediate isocyanate was dissolved in dichloromethane (2ml) and added to a mixture of the hydrochloride salt **284A** (prepared from 20.04 using the transformation described for 20.06 to 20.07; 1.66g) and triethylamine (3.4ml) and the mixture stirred at room temperature overnight. Aqueous work-up and purification of the residue on silica gel using EtOAc-Hexanes (3:97) gave the desired urea (**284B**) .

Step 3:



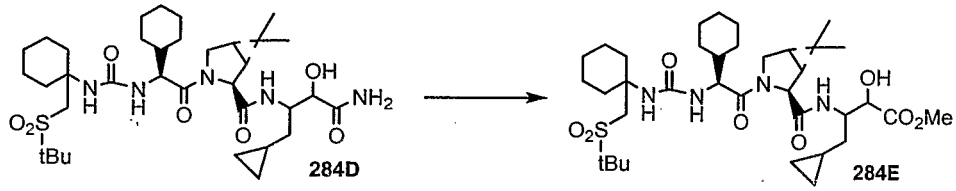
The methyl Ester (**284B**) was dissolved in a mixture of dioxane (90ml) and water (30ml) and lithium hydroxide: monohydrate (0.402g; 2eq) was added and the reaction was allowed to stir at room temperature for 3 hours. The reaction mixture was partitioned between EtOAc and 10% aq. HCl. The organic phase was separated, dried and concentrated to yield the carboxylic acid (**284C**; 2.65g).

Step 4:



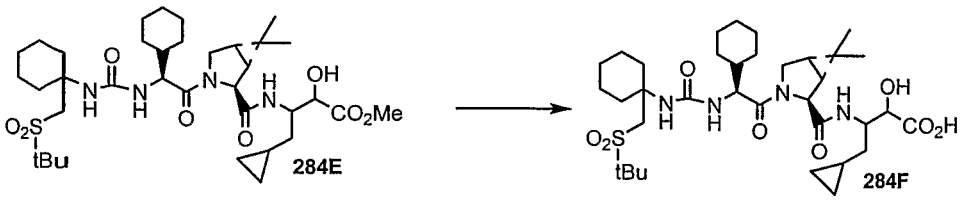
BOP reagent (2.54g) followed by triethylamine (2.4ml) were added to a solution of the carboxylic acid (**284C**; 2.65g) and the hydrochloride salt (**12.03**; 0.933g) in dichloromethane (20ml) and stirred at room temperature overnight. The reaction was partitioned between EtOAc and 10% aq. HCl. The organic phase was separated, washed with sat. aq. sodium bicarbonate, water, dried and concentrated. The residue was purified by silica gel column chromatography using 2-10% MeOH in dichloromethane as eluent to give the desired amide (**284D**; 2.92g).

Step 5:



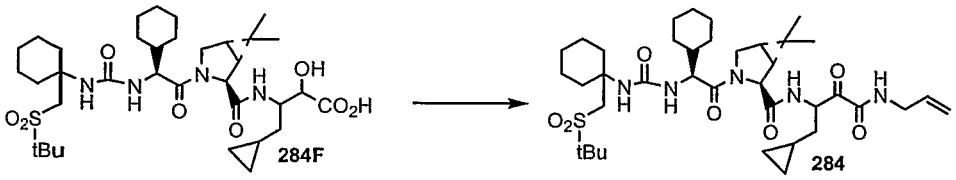
To a solution of the carboxamide (**284D**; 2.92g) in methanol (30ml) was added DMF-DMA (1.12ml) and the resulting mixture was stirred at room temperature for 3 hours and then refluxed for 1.5 hours until T.L.C. indicated that no starting material was left. After cooling, the reaction was partitioned between diethyl ether and 1N aq. HCl. The organic phase was separated, dried and concentrated. Silica gel column chromatography of the residue gave the methyl ester (**284E**), which was treated as shown in Step 6, below.

Step 6:



The methyl ester (**284E**) was dissolved in a mixture of dioxane (30ml) and water (10ml) and lithium hydroxide: monohydrate (0.354g) was added and the resulting mixture was stirred for 3 hours. The reaction was partitioned between EtOAc and 10% aq. HCl. The organic phase was separated, dried and concentrated to provide the carboxylic acid (**284F**; 2.80g).

Steps 7 and 8:



Step 7:

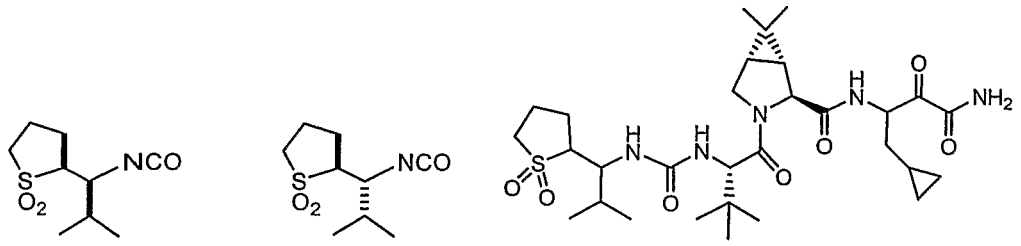
Allyl amine (0.045ml), BOP reagent (0.266g) and triethylamine (0.25ml) were added to a mixture of a solution of the hydroxy-acid (**284F**; 0.348g) in dichloromethane (5ml) and the resulting mixture was stirred at room temperature overnight. The reaction was partitioned between EtOAc and 10% aq. HCl. The organic phase was separated, washed with sat. aq. sodium bicarbonate, water, dried and concentrated to provide a residue, used without purification in Step 8, below..

Step 8:

The residue was dissolved in dichloromethane (5ml) and Dess-Martin periodinane (0.424g) was added and the reaction mixture was stirred at room temperature for 3 hours. The reaction was partitioned between EtOAc and 5% aq. sodium sulfite. The organic phase was separated, washed with sat. aq, sodium bicarbonate, water, dried and concentrated. The crude reaction

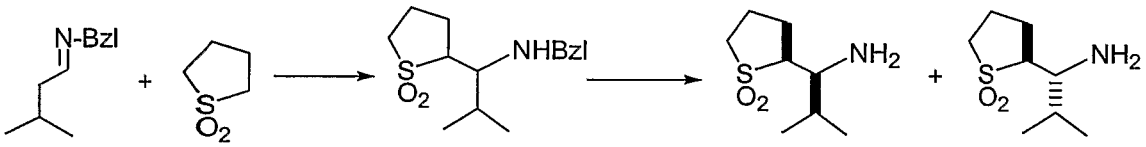
product was purified by silica gel column chromatography to yield the desired keto-amide (**284**; 0.296g). MH+, 732.2.

Preparative Example **331**. Preparation of Intermediates of Formulas **331D** and **331E** for the Compound of Formula **331**:



rac-**331D** rac-**331E** **331**

Step 1. Preparation of Compounds of Formulas **331B** and **331C**:

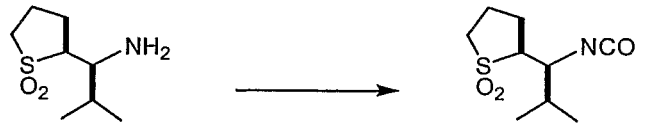


331A **331B** **331C**

N-benzyl-4-methylbutanimine (prepared as described: *Synthesis*, **1985**, 679) and tetrahydrothiophene 1,1-dioxide were reacted in the manner described in Example 336, except at -78° C, to afford compound **331A**, which was hydrogenolyzed in the manner described in Example 336, except at a pressure of 1 atm. The crude product was chromatographed on silica gel, eluting with a gradient of EtOAc to 1:1 acetone-EtOAc to obtain first one racemic diastereomer: H^1-NMR ($CDCl_3$) δ 3.2 (m, 1H), 3.1-2.9 (m, 3H), 2.3-2.1 (m, 2H), 2.1-1.9 (m, 1H), 1.9-1.7 (m, 2H), 1.02 (d, 3H), 0.85 (d, 3H).

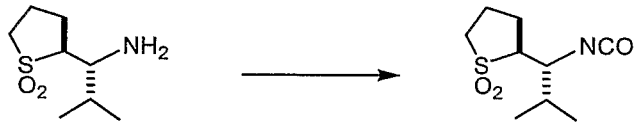
Further elution afforded the other racemic diastereomer: H^1-NMR ($CDCl_3$) δ 3.2 (m, 1H), 3.2-2.9 (m, 4H), 2.3-2.1 (m, 3H), 2.1-2.0 (m, 1H), 1.78 (sex., 1H), 0.96 (m, 6H).

Step 2. Preparation of Compounds of Formulas **331D** and **331E**.



and

331B **331D**



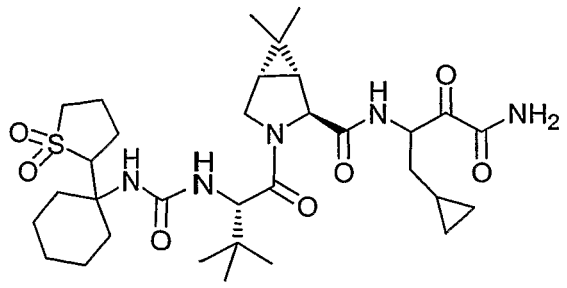
331C **331E**

Compounds **331B** and **331C** were separately reacted with phosgene in the manner described in Example 336 to afford two diastereomeric isocyanates:

the one, from the higher R_f amine: H^1 -NMR ($CDCl_3$)) δ 3.79 (dd, J_1 = 9.9 Hz, J_2 = 3.0 Hz, 1H), 3.25 (m, 1H), 3.1-3.0 (m, 2H), 2.25 (m, 2H), 2.2-2.0 (m, 1H), 2.0-1.7 (m, 2H), 1.09 (d, J = 6.9 Hz, 3H), 0.93 (d, J = 6.9 Hz, 3H).

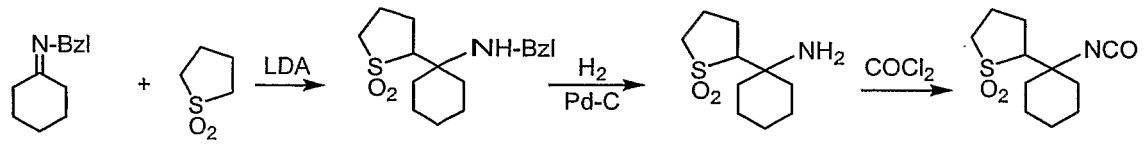
the other, from the lower R_f amine: H^1 –NMR ($CDCl_3$)) δ 3.92 (dd, J_1 = 6.6 Hz, J_2 = 4.8 Hz, 1H), 3.3-2.9 (m, 3H), 2.4 (m, 1H), 2.3 (m, 1H), 2.2-2.0 (m, 3H), 1.03 (t, Δv= 6.3, 6H).

Preparative Example 336. Preparation of Compound of Formula 336.



336

SCHEME 336-1



336A **336B** **336C**

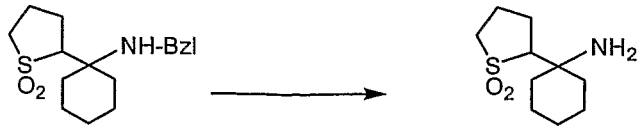
Step 1. Preparation of Compound of Formula **336A**.

336A

A solution of 20 mL of 2N LDA in hexane-THF was added to 60 mL THF and the solution was cooled to -30° C. Then 4.80 g of tetrahydrothiophene 1,1-dioxide (Aldrich Chemical Co.) was added slowly between -30° C and -10° C, and the stirred at -10° C for an additional 10 min. At -10° C, 7.5 g of N-benzylcyclohexylimine (prepared as described: *Synthesis*, **1998**, 1609.) was added at once. After 0.5 h at ambient temperature the mixture was quenched with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The extracts are dried over anhydrous Mg_2SO_4, filtered, and the filtrate evaporated. The residue was chromatographed on silica gel, eluting with EtOAc-hexane (3:7) to afford 1.3 g of compound **336A**:

H^1-NMR ($CDCl_3$): δ 7.5-7.2 (m, 5H), 3.76 (ABq, Δv = 230 Hz, J = 12, 2H), 3.41 (m, 1H), 3.13 (m, 1H), 2.94 (m, 1H), 2.4-1.3 (m, 14H).

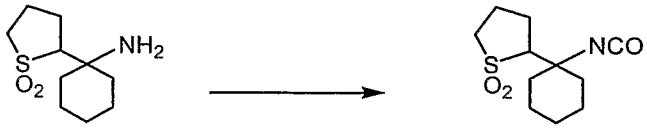
Step 2. Preparation of Compound of Formula **336B**.



336A **336B**

A solution of 1.3 g of compound **336A**, 30 mL EtOH, 1.2 mL of 4n HCl/dioxane solution, and 0.35 g of 10% Pd-C was hydrogenated at 3 atm for 1.5 h. The mixture was filtered, and the filtrate evaporated. The residue was treated with 2 n NaOH and extracted with CH_2Cl_2, the extract was dried and evaporated to leave 0.51 g of compound **336B**, which solidified on standing: H^1-NMR ($CDCl_3\delta$ 3.2-2.9 (m, 3H), 2.4-1.8 (m, 6H), 1.7-1.2 (m, 8H).

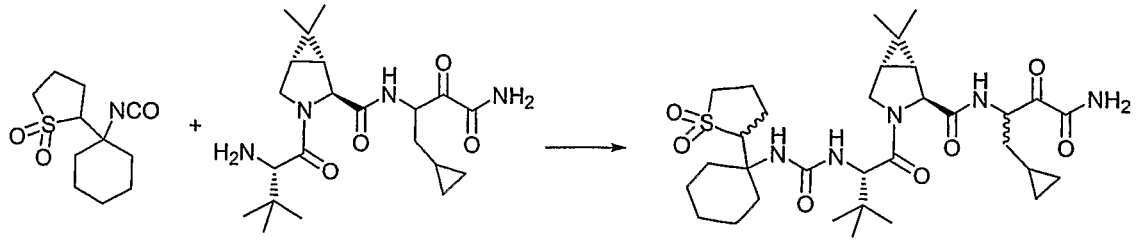
Step 3. Preparation of Compound of Formula **336C**



336B **336C**

To a solution of 0.75 g phosgene in 30 mL toluene at 0° C was slowly a solution of 0.5 g of compound **336B** and 0.80 mL diisopropylethylamine in 10 mL CH_2Cl_2. The mixture was stirred at room temperature for 5 h, concentrated to 15 mL, filtered, then diluted with fresh toluene to 18 mL to produce a 0.12 M solution of compound **336C**, which was used for subsequent reactions. .

Step 4. Preparation of Compound of Formula **336**

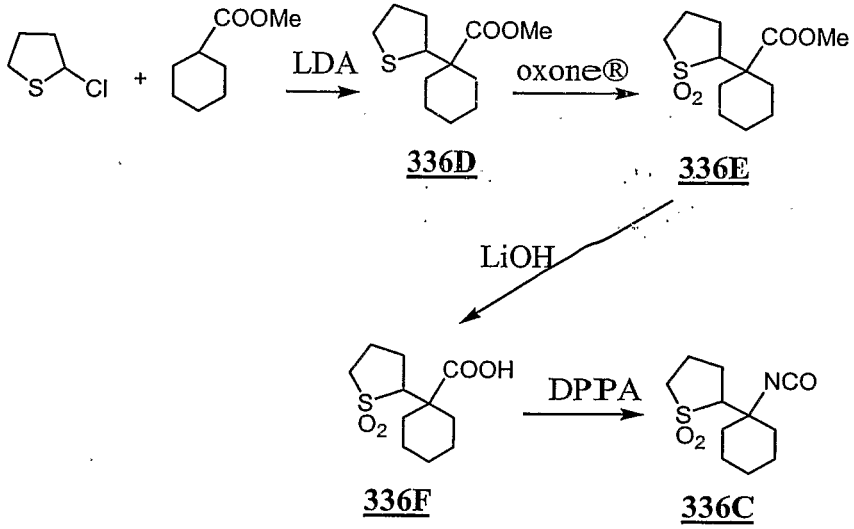


336C **20.10** **336**

Compound **336C** was reacted with compound **20.10** in the manner described in preparative example 108 to produce compound **336** as a mixture of diastereomers H^1-NMR (DMSO-d_6) δ 8.40(m), 8.33 (m), 8.00 (d), 7.75 (s), 6.25 (m), 6.10 (s), 6.01 (s), 4.18 (m), 3.92(m), 3.83 (m), 3.78 (m), 3.13 (m), 2.90 (m) 2.47 (m), 2.1-0.8 (m; Me_A: 1.01; Me_B: 0.82; Bu^t: 0.91), 0.40 (m), 0.19 (m).

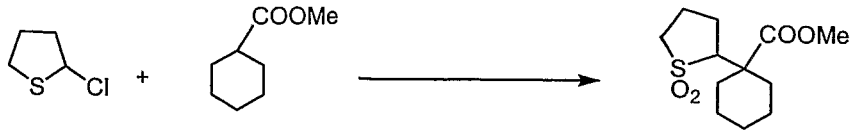
Example **336C**. Alternate synthesis of compound **336C**.

SCHEME 336-2



336D **336E** **336F** **336C**

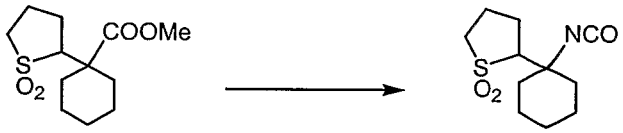
Step 1. Preparation of Compound of Formula **336E**.



336E

2-Chlorotetrahydrothiophene (prepared as described: *Chem. Pharm. Bull.*, ***1986***, *34*(9), 3644) was reacted with α-lithiocyclohexanecarboxylic acid in the manner described in preceding examples to afford sulfide ester compound **336D** in 39% yield. Compound **336D** was oxidized with oxone® in the manner described in preceding examples to afford sulfone ester compound **336E**: H^1 NMR($CDCl_3$) δ 3.73 (s, 3H) 3.3-3.0 (m, 2H), 3.0-2.9 (m, 1H), 2.6-2.4 (m, 1H), 2.4-1.3 (m, 13H).

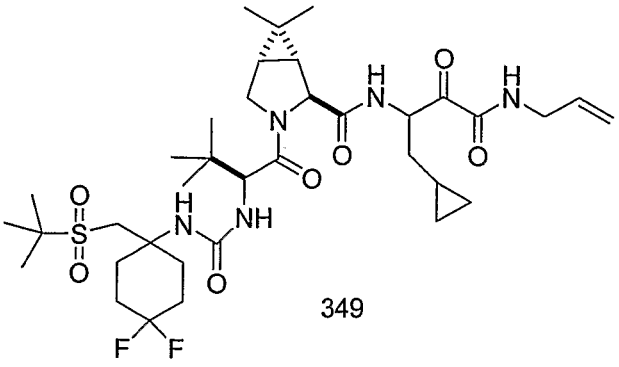
Step 2. Preparation of Compound of Formula **336C**.



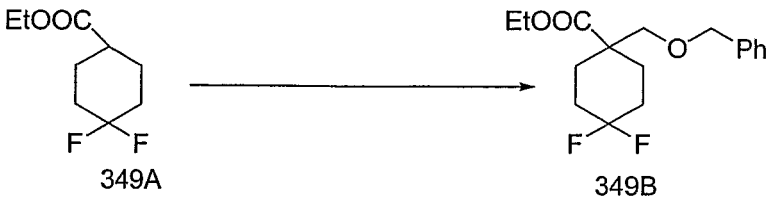
336E **336C**

Compound **336E** was hydrolyzed with LiOH in water-dioxane at 100° C in the manner described in preceding examples to afford sulfone carboxylic acid compound **336F**: H^1 NMR($CDCl_3$) δ 3.4-3.2(m, 1H), 3.2-3.1 (m, 1H), 3.1-2.9 (m, 1H), 2.3-2.1 (m, 3H), 2.1-1.8 (m, 3H), 1.8-1.3 (m, 7H). Compound **336F** was reacted with diphenylphosphorylazide in the manner described in preceding examples to afford compound **336C** as a colorless solid: H^1 NMR($CDCl_3$) δ 3.2 (m, 1H), 3.1-2.9 (m, 2H), 2.45 (d, 1H), 2.4-1.9 (m, 4H), 1.85-1.5 (m, 7H), 1.5-1.2 (m, 2H).

Synthesis of Compound 349:

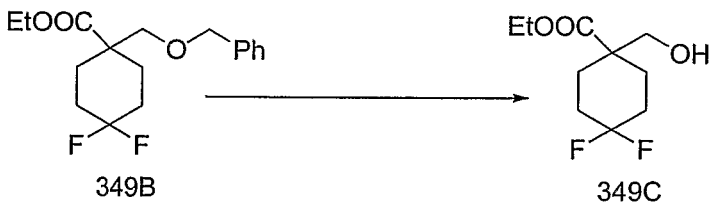


349



349A 349B

To a solution of the ethyl ester (**349A**; 10 g; 0.052 mol.) in diethyl ether (50 ml) at -78^0 C (bath temp.) was added KHMDS (0.5 M in toluene; 156.087 ml; 1.5 equiv.). The resulting solution was stirred for 30 minutes, then benzyl chloromethyl ether (11.89 ml; density 1.13; 1.65 equiv.) was added. The reaction mixture was stirred at -78^0 C to R.T. for 24 h. Reaction was stopped by addition of saturated aq. NH_4Cl. It was then diluted with ethyl acetate and the combined organic phase was washed with brine, dried over Na_2SO_4 and evaporated to dryness *in vacuo* to provide a light brown oil (24.2 g). It was chromatographed over silica gel (300 g). The column was eluted with 1% - 4% ethyl acetate in n-hexane providing in some of the fractions pure **349B** (6.54 g).



349B 349C

A solution of the benzyl ether (**239B**; 2.8316 g; 0.0091 mol.) in $CHCl_3$ (49.5 ml) was treated with methane sulfonic acid (22.65 ml) and the reaction mixture stirred at room temperature for ~70 minutes. Ice was added to the reaction mixture and it was diluted with ethyl acetate. The organic phase was washed with saturated $NaHCO_3$, dried over Na_2SO_4 and evaporated to dryness *in vacuo* to provide yellowish oil (2.86 g). It was chromatographed over SiO_2 (65 g). The column was eluted with 15% - 25% ethyl acetate in n-hexane providing in some of the fractions pure **349C** (1.5913 g).

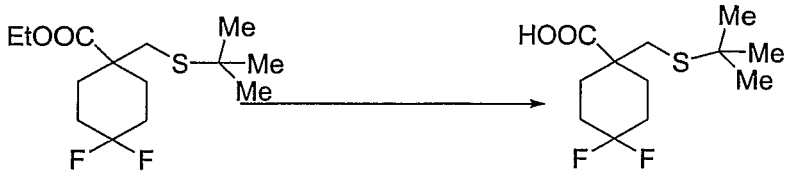
349C 349D

A stirred solution of the alcohol (**349C**; 1.14 g; 0.0051 mol.) in methylene chloride (6.4 ml) was cooled in ice bath and treated with Et_3N (0.7857 ml; density 0.726; 1.1 equiv.) and methanesulfonyl chloride (0.4168 ml; density 1.48; 1.05 equiv.). After ~2 hrs the reaction mixture was diluted with methylene chloride and it was washed with 6N HCl followed by saturated $NaHCO_3$. The organic phase was dried over Na_2SO_4 and evaporated to dryness *in vacuo* to provide the mesylate **349D** (1.5447 g) as a light yellow oil.

349D 349E

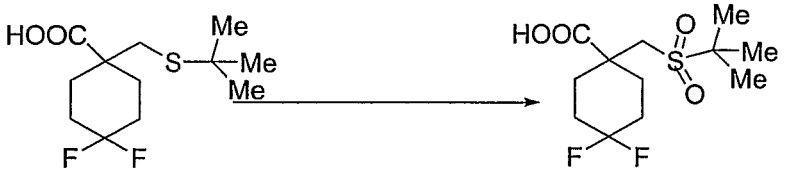
A stirred suspension of NaH (0.4114 g; 60% dispersion in mineral oil; 2 equiv.) in dry DMF was treated with tert.-butyl thiol (1.16 ml; density 0.8; 2 equiv.) with ice bath cooling. The reaction mixture was stirred for 30 minutes after which the mesylate (**349D**; 1.5447 g; 1 equiv.) was added in dry DMF (8+2 ml). Ice bath was removed and the reaction mixture was stirred at room

temperature overnight. The reaction mixture was acidified with 6N HCl and extracted with ethyl acetate. The ethyl acetate extract was dried over Na_2SO_4 and evaporated to dryness *in vacuo* to provide crude 349D (2.87 g) which was chromatographed over SiO_2 (60 g). The column was eluted with 3% ethyl acetate providing in some of the fractions pure **349E** (1.38 g) as a colorless oil.



349E 349F

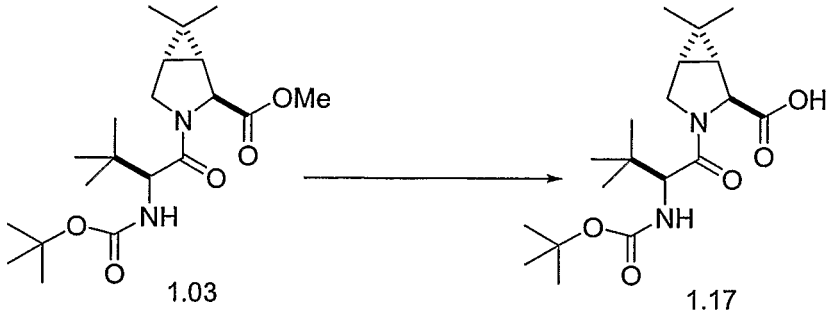
A solution of the ethyl ester (**349E**; 1.38 g; 0.00468 mol.) in ethanol (16 ml) and water (4.13 ml) was treated with KOH pellets (2.63 g; 10 equiv.). The resulting solution was refluxed for 7 h and then allowed to cool to room temperature overnight. Ethanol was evaporated *in vacuo* and the residue partitioned between CH_2Cl_2/water, acidified with 6N HCl to pH 1. The organic phase was separated and the aqueous phase extracted three times with CH_2Cl_2. The combined organic phase was dried over Na_2SO_4 and evaporated to dryness *in vacuo* to provide **349F** (1.19 g) as a off white solid, m.p. 93-95^0 C.



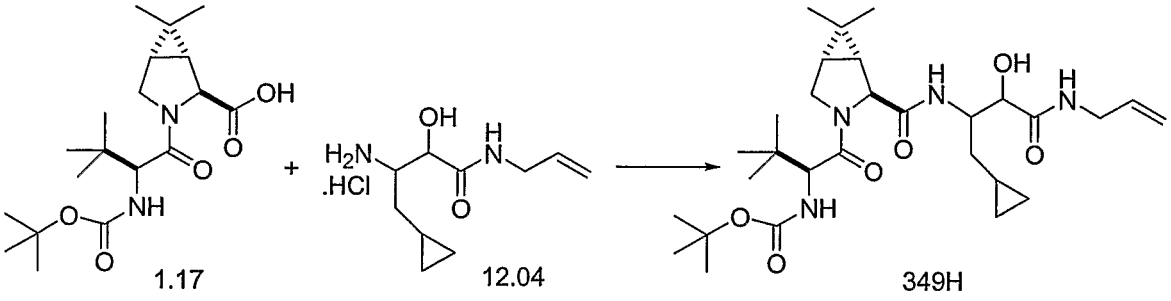
349F 349G

The oxone (8.24 g; 3 equiv.) dissolved in water (31 ml) was added to a stirred solution of the sulfide (**349F**; 1.19 g; 1 equiv.) in methanol (31 ml) at 0^0 C (bath temp). The reaction was stirred at 0^0 C to R.T. over the weekend. Solvents were evaporated in-vacuo and the residue partitioned between

CH_2Cl_2/water. The organic layer was separated and the aqueous layer extracted twice with CH_2Cl_2. The combined organic phase was dried over Na_2SO_4 and evaporated to dryness *in vacuo* to provide **349G** (1.29 g) as a crystalline solid, m.p. 212^0 C.

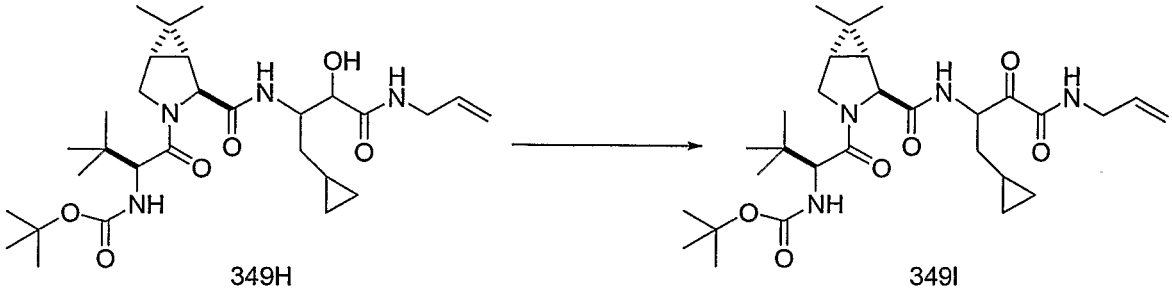


To a cooled (ice bath) solution of the ester (**1.03**; 4.56 g; 0.0119 mol.) in dioxane (18.23 ml) was added with stirring 1.0 N LiOH (18.23 ml). The reaction mixture was stirred for 2 hrs. TLC indicated some starting material still remaining, so added 2+1 ml 1.0 N LiOH and stirred overnight. Reaction complete by TLC. 6N HCl was added to acidify the reaction mixture to pH 1 and ethyl acetate (150 ml) added. After shaking, the ethyl acetate phase was separated and the aqueous phase extracted with ethyl acetate. The combined ethyl acetate phase was washed once with brine, dried (Na_2SO_4) and evaporated to dryness *in vacuo* to provide **1.17** as a amorphous solid (4.7805 g; occluded solvent).



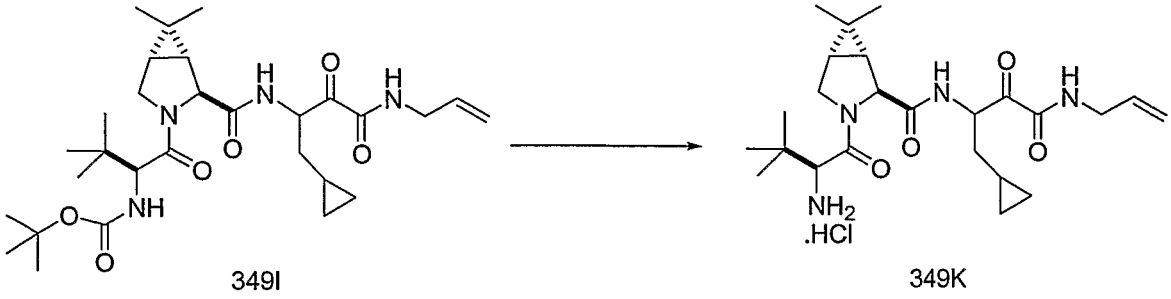
To a -20^0 C solution of the acid **1.17** (0.7079 g; 0.00192 mol.) and the amine salt (**12.04**; 0.5231 g; 1.16 equiv.) in CH_2Cl_2 (10 ml) was added HATU

(0.77 g; 1.05 equiv.) followed by diisopropylethylamine (0.8913 g; 1.2 ml; 3.59 equiv.). The reaction mixture was stirred at -20^0 C for ~16 hrs. It was then diluted with EtOAc (~150 ml) and washed successively with satd. $NaHCO_3$, 10% citric acid and dried over Na_2SO_4. Evaporation of the solvent *in vacuo* provided a amorphous solid which was chromatographed over SiO_2 (42 g). Elution of the column with 50%-60% EtOAc in n-hexane provided in some of the fractions pure **349H** (0.7835 g).



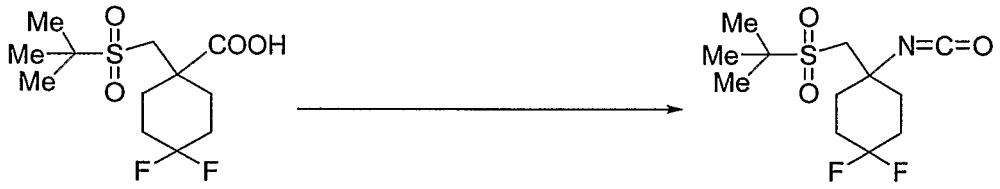
349H 349I

A solution of the hydroxyamide **349H** (0.7835 g; 0.00142 mol.) in dry methylene chloride (32 ml) was treated with stirring and cooling (ice bath) with Dess-Martin reagent (1.5134 g; 2.5 equiv.). Ice bath was removed and the reaction mixture was allowed to stir at room temperature for 2.5 hrs. Saturated $Na_2S_2O_3$ (32 ml) was added to destroy excess oxidant and stirring continued until the cloudy solution turned clear two-phase system. The reaction mixture was then diluted with CH_2Cl_2 (~100 ml), the organic phase separated and washed once with satd. $NaHCO_3$, water then dried. Evaporation to dryness *in vacuo* provided **349I** (0.7466 g) as an amorphous solid.



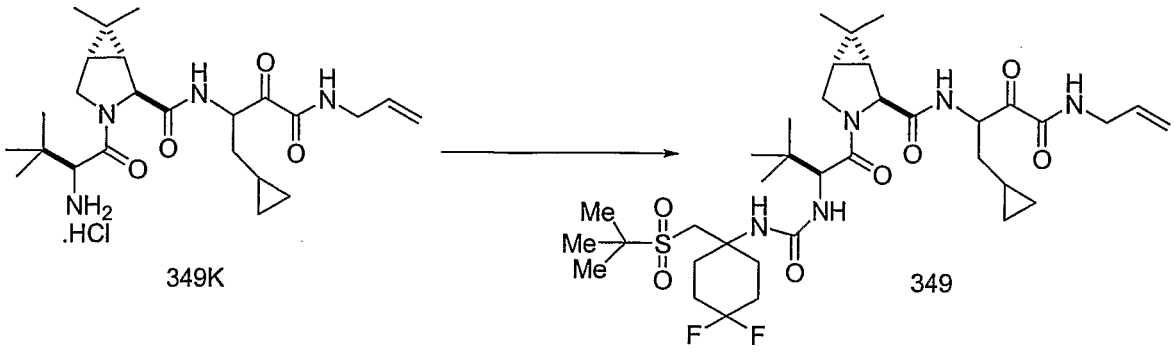
349I 349K

The tert.-butylcarbamate **349I** (0.7466 g) was treated with 4M HCl/dioxane (20 ml) and left in a stoppered flask for 45 minutes. Most of the dioxane was evaporated in-vacuo and the residue evaporated with n-hexane twice; the remaining residue was triturated with ether leaving **349K** (0.6341 g) as a free flowing solid.



349G 349J

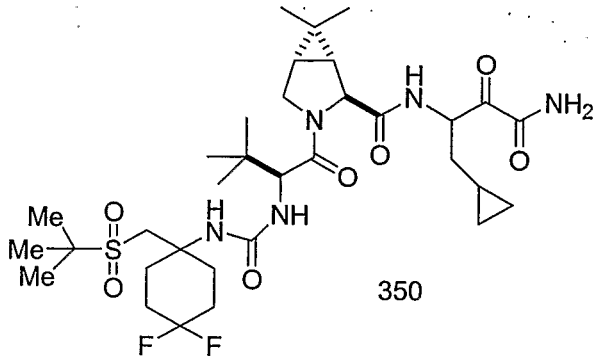
To a toluene solution (7.5 ml) of the acid **349G** (0.1 g; 0.0003351 mol.) were added Et_3N (0.0467 ml; 46.7 µl; 1 equiv.) followed by diphenylphosphoryl azide (0.072; 72 µl; 1equiv.). The reaction mixture was refluxed for 1 h. After cooling down, it was treated with ethyl acetate (~50 ml), the organic phase washed with saturated $NaHCO_3$ and concentrated *in vacuo* to provide **349J** (0.1 g).



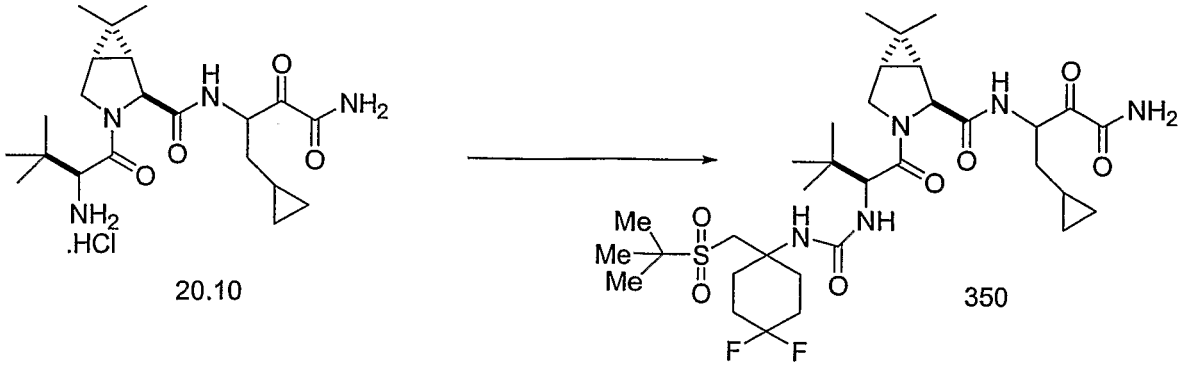
349K 349

To a stirred suspension of the amine hydrochloride **349K** (0.1 g; 0.000207 mol.) in methylene chloride (5 ml) was added diisopropylethylamine (0.135 g; 5 equiv.). After 1 minute was added the isocyanate **349J** (0.1 g; 0.0003385 mol.). The reaction mixture was stirred at room temperature for 2 hrs. It was then diluted with EtOAc and washed with 1N HCl, satd. $NaHCO_3$, dried over Na_2SO_4 and finally evaporated to dryness in-vacuo to provide an amorphous solid. It was subjected to preparatory TLC on silica gel plates using 40% acetone in n-hexane as eluent. The uv positive band was extracted with 60% acetone in methylene chloride to provide **349** (0.122 g) as an amorphous solid.

Synthesis of Compound 350:



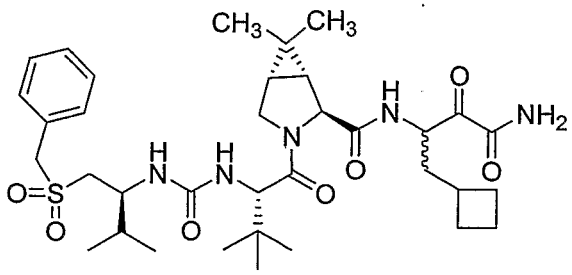
350



20.10 350

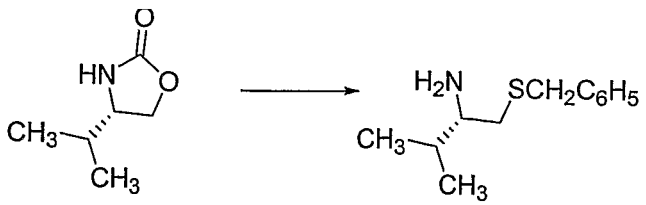
To a stirred suspension of the amine hydrochloride **20.10** (0.0966 g; 0.000223 mol.) in methylene chloride (5 ml) was added diisopropylethylamine (0.144 g; 5 equiv.). After 1 minute was added the isocyanate **349H** (0.1 g; 0.0003385 mol.). The reaction mixture was stirred at room temperature for 2 hrs. It was then diluted with EtOAc (~100 ml), then washed with 1N HCl, satd. $NaHCO_3$, dried over Na_2SO_4 and finally evaporated to dryness *in vacuo* to provide an amorphous white solid (0.1731 g). It was subjected to preparatory TLC on silica gel using 40% acetone in n-hexane as eluent. The uv positive band was extracted with 60% acetone in methylene chloride to provide **350** (0.0671 g) as an amorphous solid.

Example 145 Preparation of compound of formula I45:



145

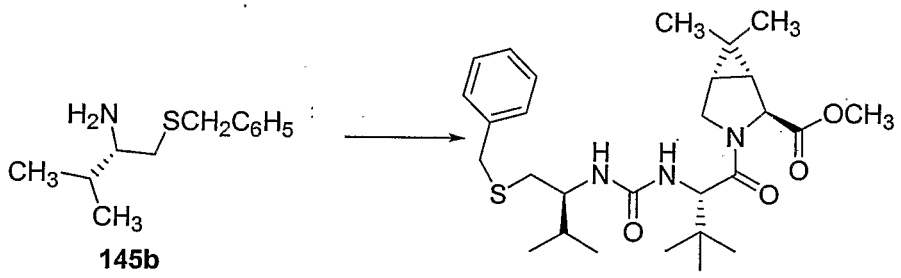
Step 1



145a 145b

1-Propanol was treated with metallic sodium (361 mg, 15.7 mmol) and stirred at RT for 1 h. After complete dissolution of sodium, benzylthiol (2.74 mL, 23.2 mmol) was added and the reaction mixture was stirred at RT for 0.5 h. (S)-4-isopropyl-oxazolidinone (Aldrich, 1g, 7.74 mmol) was added and the reaction mixture was heated at reflux for 16 h. The reaction mixture was concentrated in *vacuo* and the crude mixture was diluted with cold water and extracted with ether (3x150 mL). The combined organic layers were dried, filtered concentrated in *vacuo* to yield amine **145b.** It was converted to the hydrochloride salt with 4 M HCl and dried in high vacuum to yield **145b.HCl** (1.9 g).

Step 2

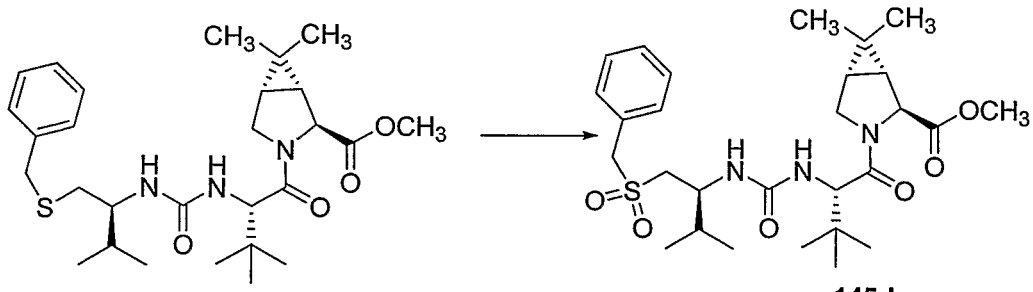


145b 145c

A solution of **145b.HCl** (1 g, 4.07 mmol) in CH_2Cl_2 (50 mL) and satd. $NaHCO_3$ (70 mL) at 0° C was treated with phosgene (15% in toluene 10 mL) and stirred at 0° C for 3 h. The reaction mixture was poured into a separatory funnel and the organic layer was separated. The organic layer was washed with cold $NaHCO_3$, brine and dried ($MgSO_4$). It was concentrated and used as it is in next step.

Amine hydrochloride salt (**1.04**; 865 mg, 2.7 mmol) was dissolved in CH_2Cl_2/DMF 1:1 and cooled to 0° C. The mixture was treated with $(C_2H_5)_3N$ (682 mg, 6.75 mmol) and isocyanate prepared as above (950 mg, 4.07 mmol) and stirred at RT overnight. The solvent was evaporated and the residue was dissolved in EtOAc. The organic layer was washed with aq. HCl, aq NaHCO3, brine. The reaction mixture was dried, filtered and concentrated in *vacuo*. The residue was purified by chromatography (SiO_2, EtOAc/Hexanes 1:3) to yield **145c** (880 mg).

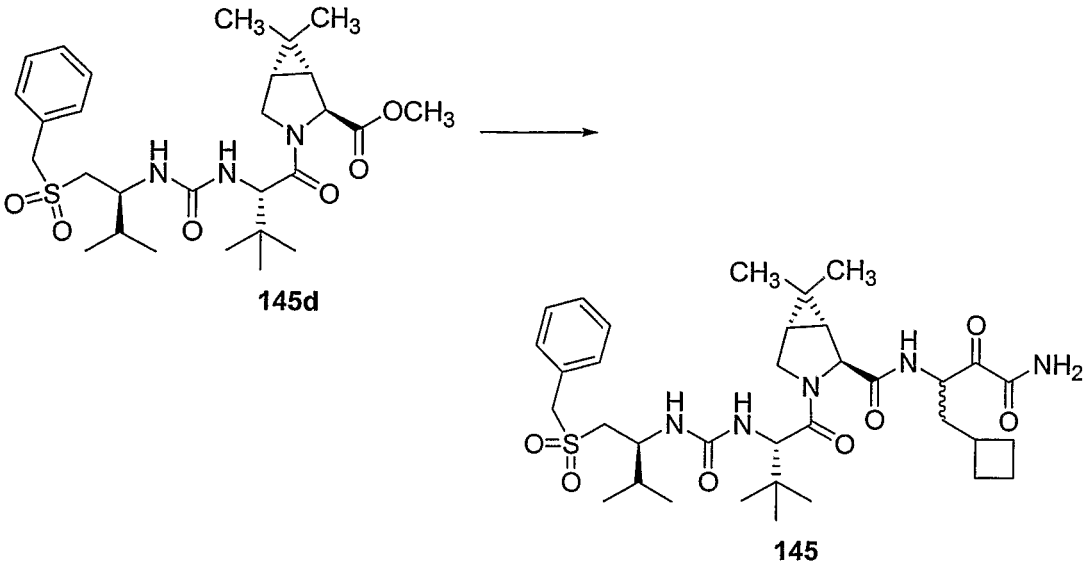
Step 3



145c **145d**

A solution of **145c** (500 mg, 0.9 mmol) in 1,2 dichloroethane (10 mL) was treated with MCPBA (70%, 500 mg,) and 0° C and diluted with ether and aq. solution of $Na_2S_2O_3$. The organic layer was separated and washed extensively with aq. saturated NaHCO3 and brine. The reaction mixture was dried (MgSO4) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, EtOAc/Hexane 2:3) to yield **145d** (530 mg). MS (ESI) 550 [$(M+1)^+$, 100], 381 (95), 353 (20).

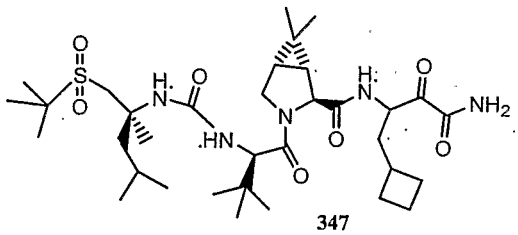
Step 4



145d **145**

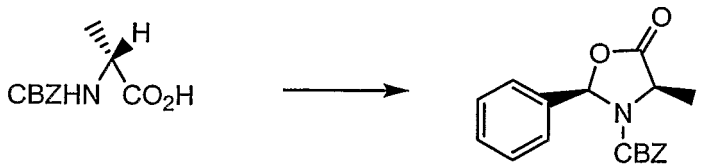
The conversion of **145d** to **145** was identical to the procedure described in the conversion of **284B** to **284D** and **108D** to **108** MS (ESI) 690 [(M+1)$^+$, 100), 381 (30).

Preparation of Intermediate of Formula 347:



347

Step1:

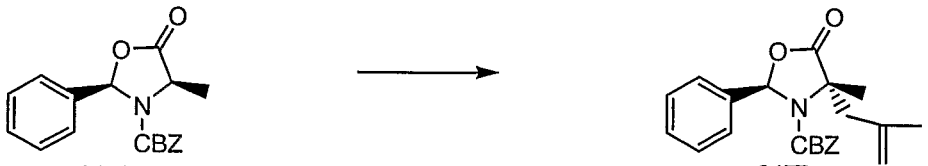


347A

Dimethyl benzaldehyde acetal (10.0 mL, 67.2 mmol) was added to a cooled solution of CBZ-*D*-alanine (15.0 g, 67.2 mmol) in Et_2O (180 mL), followed by $BF_3.Et_2O$ (50.6 mL, 403.2 mmol) over 15 min. The reaction

mixture was stirred at -20 °C for 4 days and quenched by addition of ice cold saturated $NaHCO_3$ (350.0 mL). The organic layer was diluted with Et_2O (500 mL), separated, washed with $NaHCO_3$ (5% aqueous solution), brine, dried over $MgSO_4$, filtered and concentrated. The crude was recrystallized using Et_2O/hexane to yield **347A** (13.6 g, 65%).

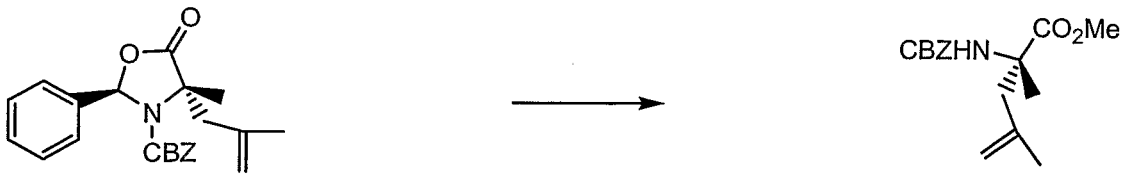
Step 2



347A **347B**

THF(48.0 mL) was added to a flame dried flask and cooled to -35 °C. KHDMS(0.5 M solution in PhMe, 42.0 mL, 21 mmol) was added to it, followed by dropwise addition of a mixture of **347A** (6.22g, 20.0 mol) and 3-bromo-2-propene (2.02 mL, 20 mmol) maintaining the internal temperature between -30 and -35 °C. The reaction mixture was stirred at -35 °C for 2 h, then allowed to warm up over 2.5 h, quenched by addition of ice cold saturated $NaHCO_3$ (400.0 mL). The organic layer was diluted with Et_2O (600 mL), separated, washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude was purified over SiO_2 using CH_2Cl_2 to yield **347B** (14.2 g, 90%).

Step 3

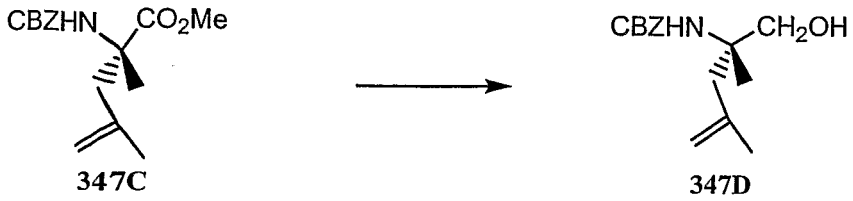


347B **347C**

To a solution of **347B** (10.7 g, 29.4 mmol) in MeOH (200 mL) was added LiOH (4N, 15 mL) and stirred at RT for 30 min, diluted with H_2O (500 mL), extracted with EtOAc (4 x 400 mL), washed with brine, dried over

$MgSO_4$, filtered and concentrated. The crude was purified over SiO_2 using CH_2Cl_2 to yield **347C** (8.65 g, 88%).

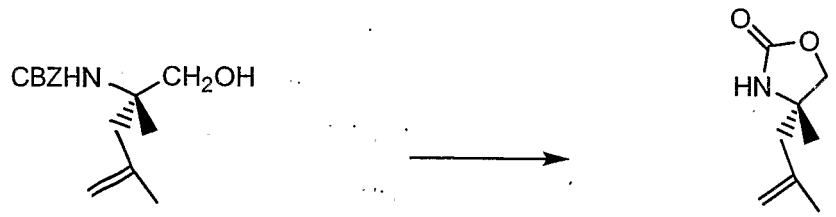
Step 4



347C **347D**

To a ice-cold solution of **347C** (8.56 g, 29.4 mmol) in EtOH (100 mL) was added $LiBH_4$ (960 mg, 44.1 mmol) and stirred at RT for 12h, another portion of $LiBH_4$ (960 mg) was added to it at 5 °C and stirred at RT for 4h, diluted with H_2O (100 mL) and MeOH(100 mL), evaporated to dryness, dissolved in H_2O (100 ml), extracted with EtOAc (500 mL), washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude was purified over SiO_2 using EtOAc (1-8%) in CH_2Cl_2 to yield **347D** (4.7 g, 60%).

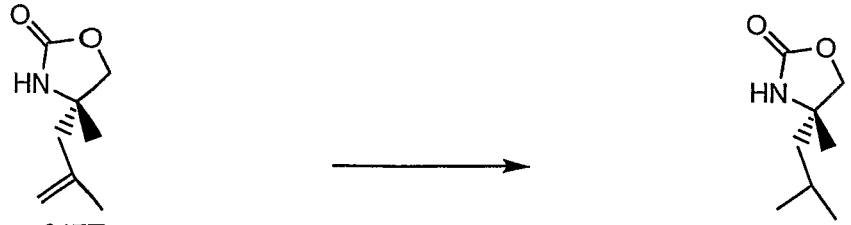
Step 5



347D **347E**

t-BuOK (1M in THF, 3.85 mL) was added to a cooled (-5 °C) solution of **347D** (4.06 g, 15.4 mmol) in THF (20 mL) and stirred at that temperature for 2h. The reaction mixture was concentrated, redissolved in EtOAc (250 mL) and NaOH (2N, 50 mL). The organic layer was diluted with EtOAc (600 mL), separated, washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude was purified over SiO_2 using 10% CH_2Cl_2 in EtOAc to yield **347E** (1.4 g).

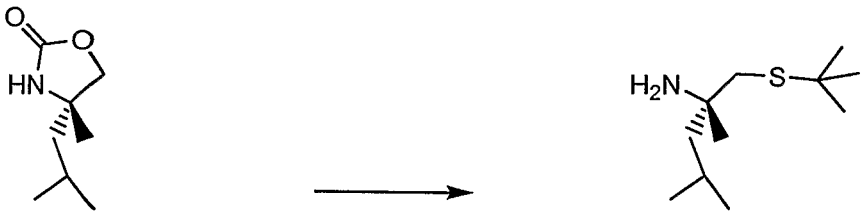
Step 6



347E 347F

347E (1.37 g, 8.82mmol) was dissolved in EtOH (25 mL) and Pd-C (10% by weight, 275.0 mg) was added to it. The reaction mixture was stirred under a hydrogen atmosphere for 12h, filtered, concentrated and purified over SiO_2 using 10% CH_2Cl_2 in EtOAc to yield **347F** (1.04g, 75%).

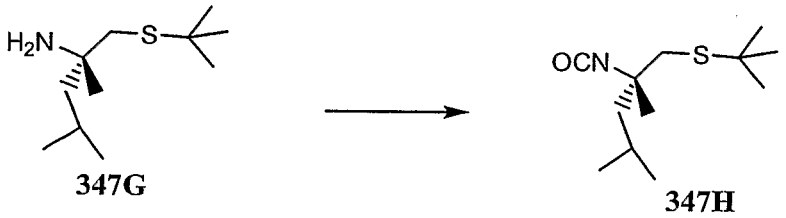
Step 7



347F 347G

347F (2.58 g, 16.4mmol) was dissolved in PrOH (40 mL) and NaSBu-*t*(10.2 g, 82 mmol) was added to it. The reaction mixture was refluxed for 136 h, cooled, evaporated and redissolved in EtOAc, washed with H_2O and the organic layer dried over $MgSO_4$, filtered and concentrated. The crude was purified over SiO_2 using 30% acetone in CH_2Cl_2 to yield **347G** (0.6 g, 19%) and **347F** (1.1g).

Step 8

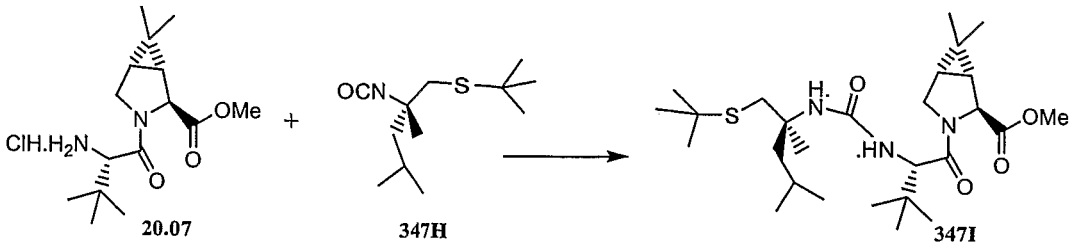


347G 347H

Saturated $NaHCO_3$ was added to an ice-cold solution of **347G** (0.6 g, 3.0 mmol) in CH_2Cl_2 (30 mL). The reaction mixture was stirred vigorously for

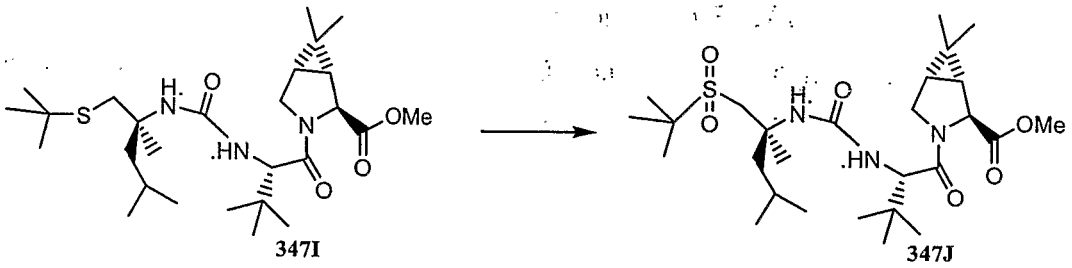
10 min. and $COCl_2$ (1.85 M solution in PhMe, 4.51 mL) was added to it and stirring was continued at room temperature for 1h. The organic layer was dried over MgSO4, filtered and concentrated to half the volume to yield **347H** as a solution in CH_2Cl_2.

Step 9



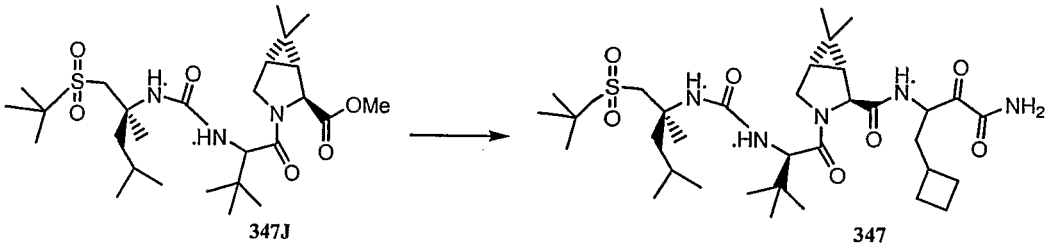
To a cooled solution (O ^{0}C) of **347H** (685 mg, 3.0 mmol) in DMF (10.0 mL) was added **20.07** (1.05 g, 3.34 mmol), followed by DIPEA (1.45 mL, 8.35 mmol). The reaction mixture was stirred at room temperature for 1.2 h, diluted with ethyl acetate, washed with 3% citric acid, brine, dried over $MgSO_4$, filtered, concentrated and purified over SiO_2 using acetone/CH_2Cl_2 (1:9) to yield **347I** (1.57g).

Step 10



To a cooled solution (O ^{0}C) of the **347I** (1.5 g, 3.34 mmol) in CH_2Cl_2 (100.0 mL) was added ***m*-CPBA** (2.51g, 10.02 mmol). The reaction mixture was warmed to room temperature over 12 h, diluted with CH_2Cl_2 (300.0 mL), washed with brine, dried over $MgSO_4$, filtered, concentrated and purified over SiO_2 using acetone/CH_2Cl_2 (1:9) to yield **347J** (1.57g).

Step 11



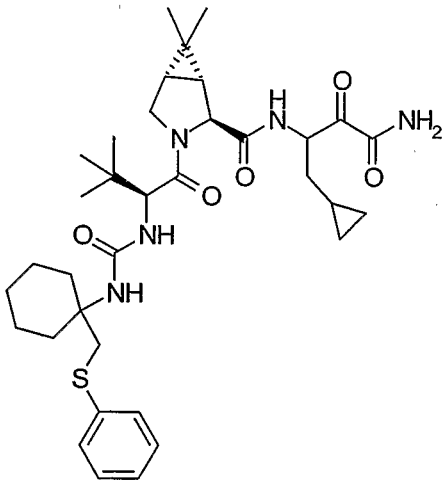
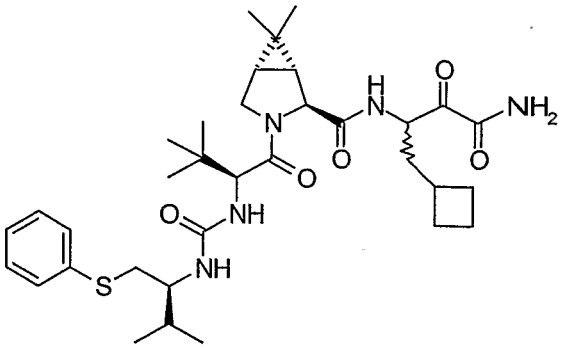
347J 347

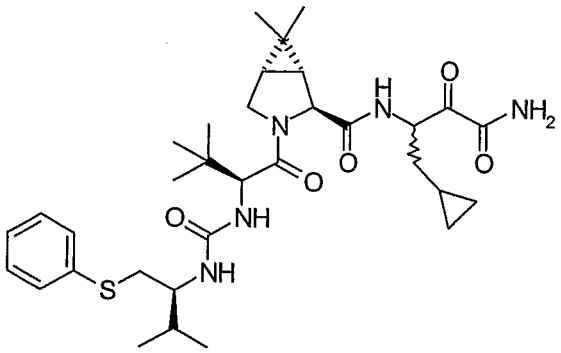
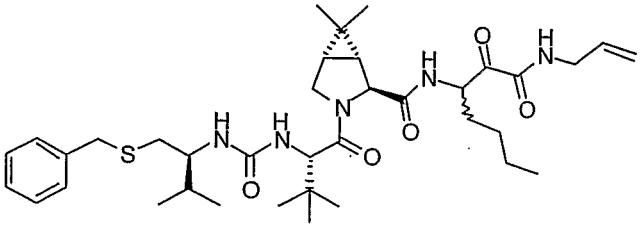
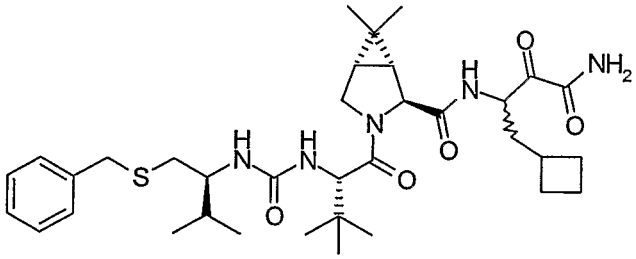
The conversion of **347J** to **347** was similar in procedure to those described in the conversion of **284B** to **284D** and **108D** to **108** MS(LCMS) calcd. 681.94, found (MH^+) 683.2.

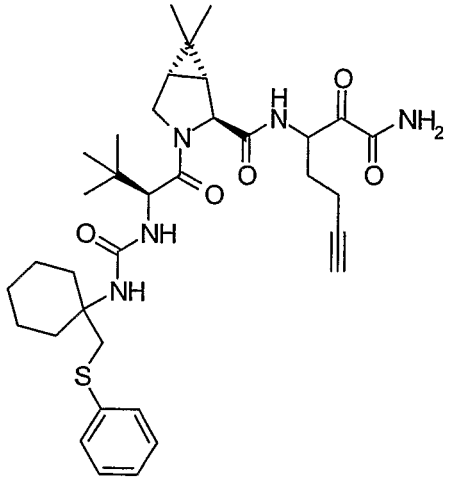
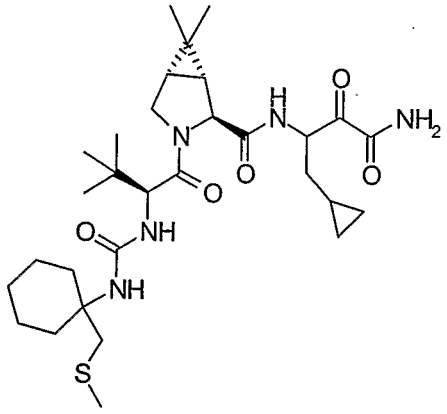
Table 3 lists some of the inventive compounds and their HCV serine protease inhibitory activity ranges, as determined by the assay described later. The activity is shown as Ki* ranges (nanoMolar), which are: A = <75 nM; B = 75 - 250 nM; and C = >250 nM.

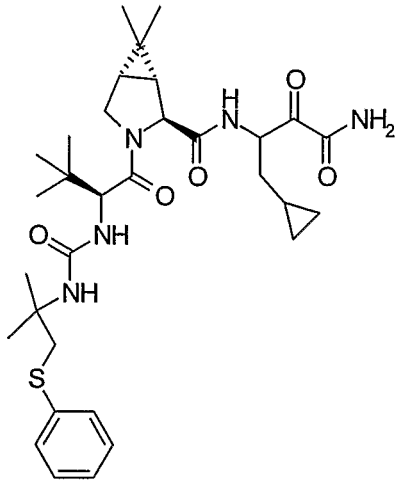
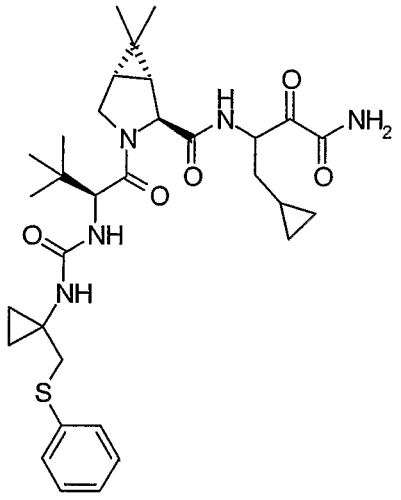
Table 3

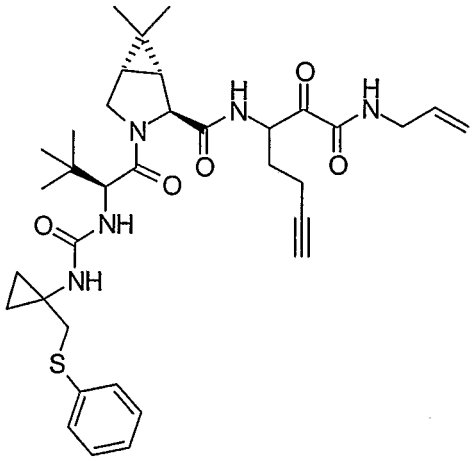
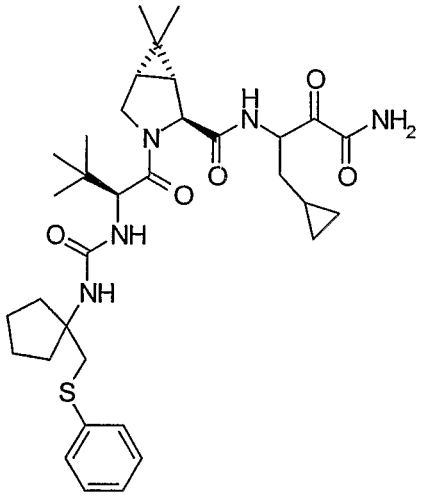
Sulfide Compounds

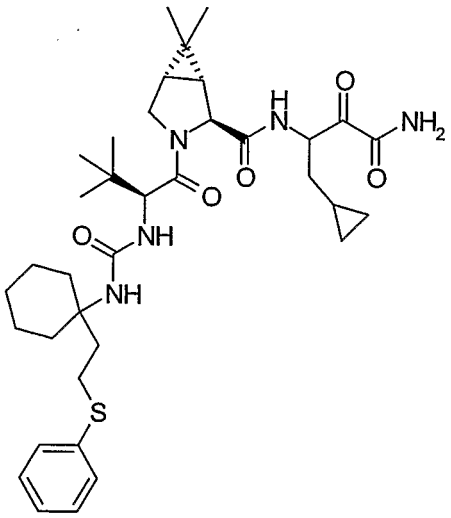
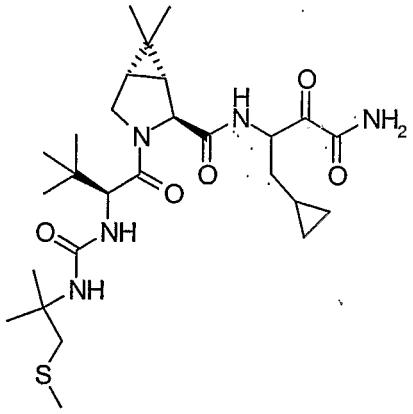
Prep. Ex.	COMPOUND	Select Mass Spectra Data	Ki* range
	[Ki* ranges are: A = <75 nM; B = 75 - 250 nM; C = >250 nM]		
102		LCMS; MH^+, 654.1	A
103			B

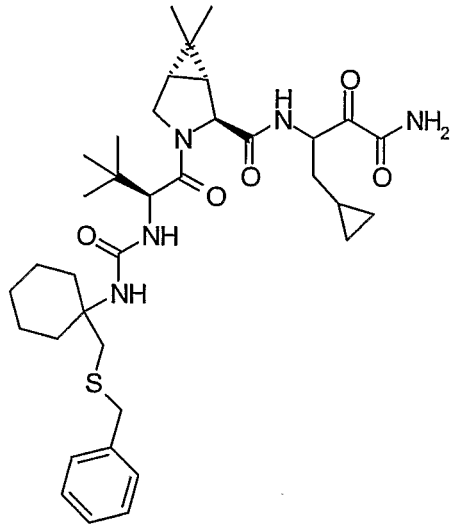
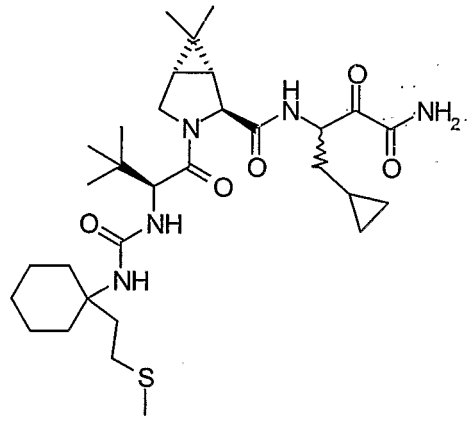
Prep. Ex.	COMPOUND	Select Mass Spectra Data	Ki* range
104			A
105			C
106			B

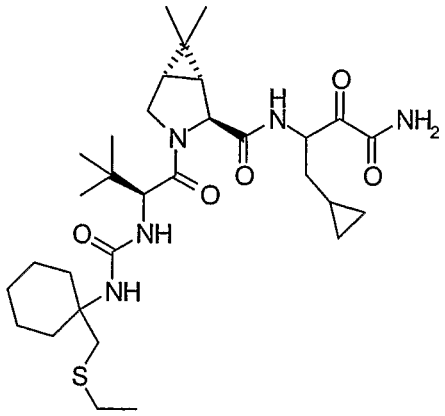
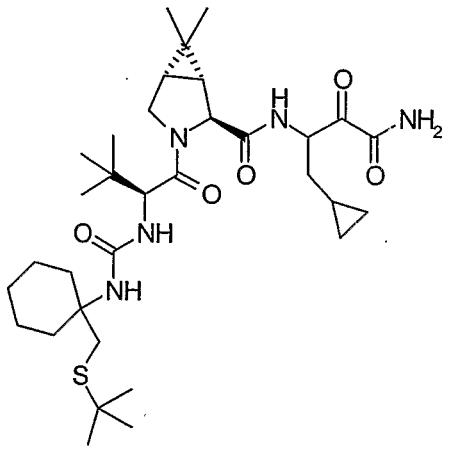
Prep. Ex.	COMPOUND	Select Mass Spectra Data	Ki* range
107		FABMS, $(M+TG)^+$, 760.5. TG= thioglycerol	A
108			A

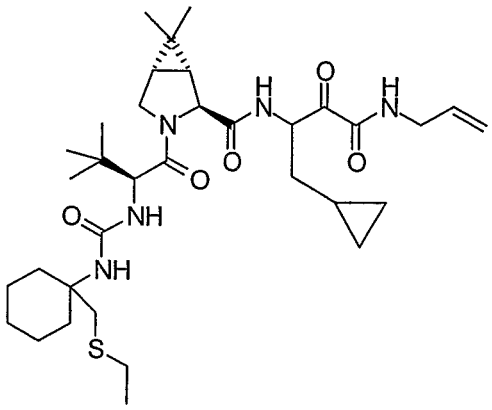
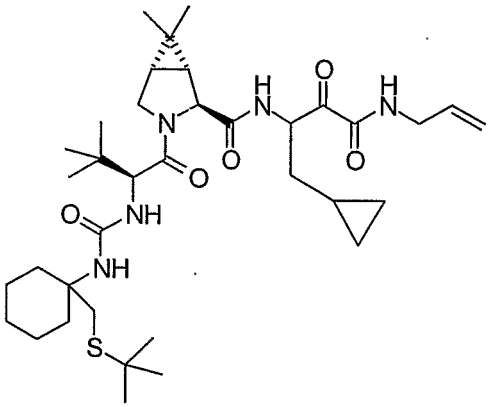
Prep. Ex.	COMPOUND	Select Mass Spectra Data	Ki* range
109			A
110			A

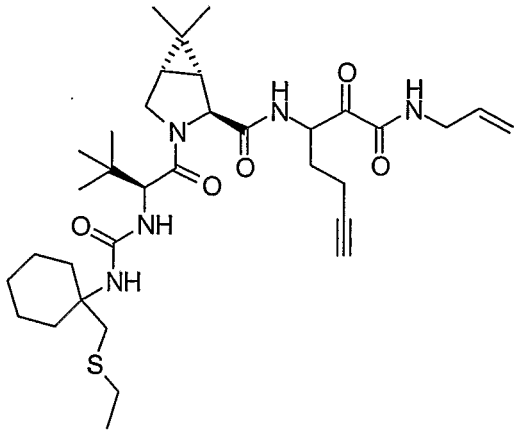
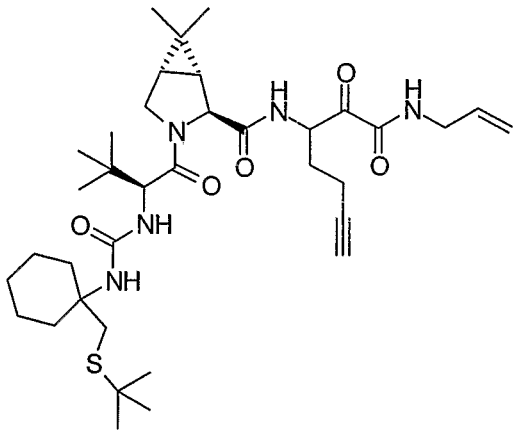
Prep. Ex.	COMPOUND	Select Mass Spectra Data	Ki* range
111		FABMS: (MH)+, 650.3.	B
112			A

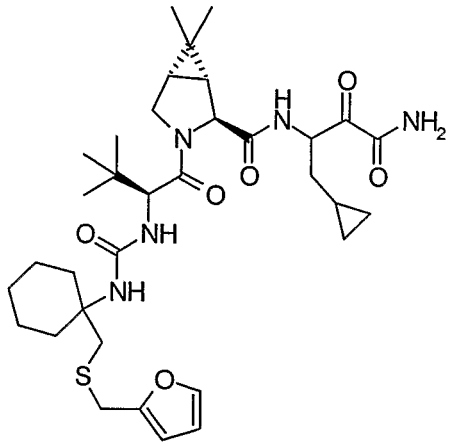
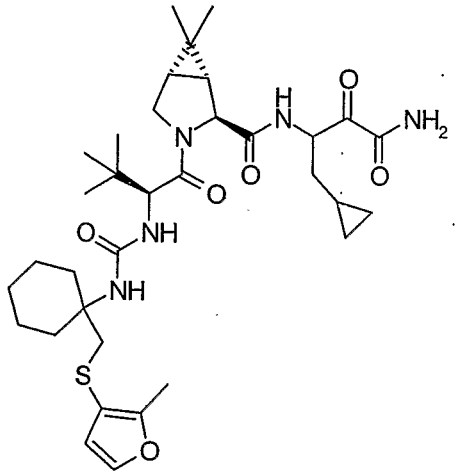
Prep. Ex.	COMPOUND	Select Mass Spectra Data	Ki* range
113		FABMS: $(MH)^+$,668.3	A
114			A

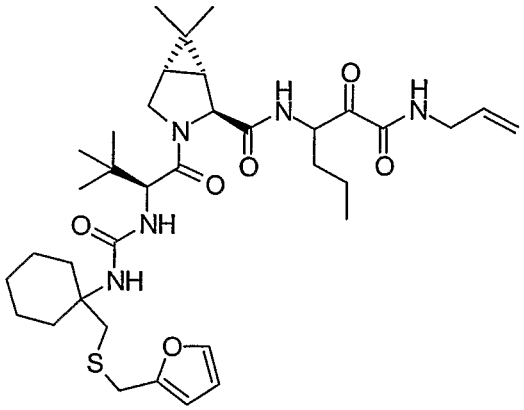
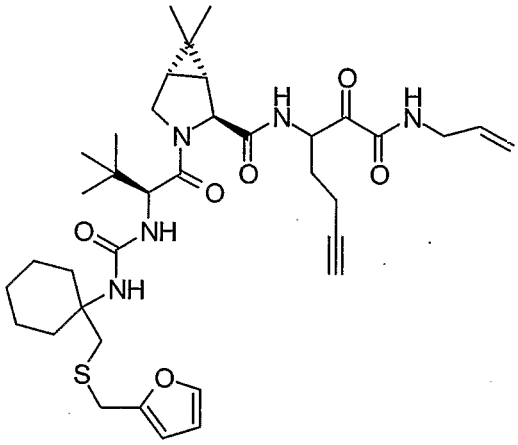
Prep. Ex.	COMPOUND	Select Mass Spectra Data	Ki* range
115			A
116		LCMS; MH+, 606.1.	A

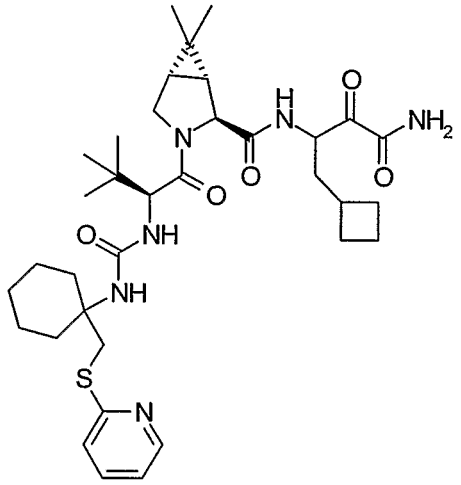
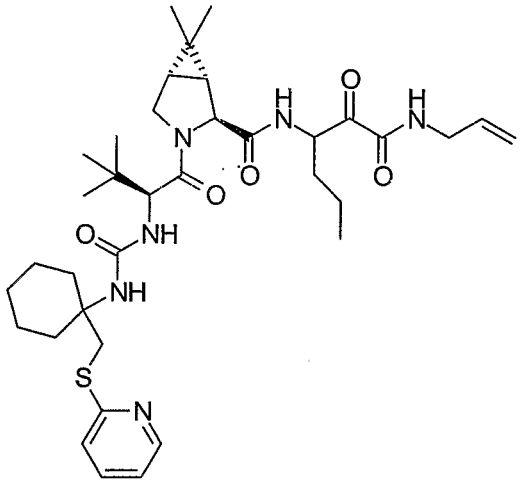
Prep. Ex.	COMPOUND	Select Mass Spectra Data	Ki* range
117			A
118			A

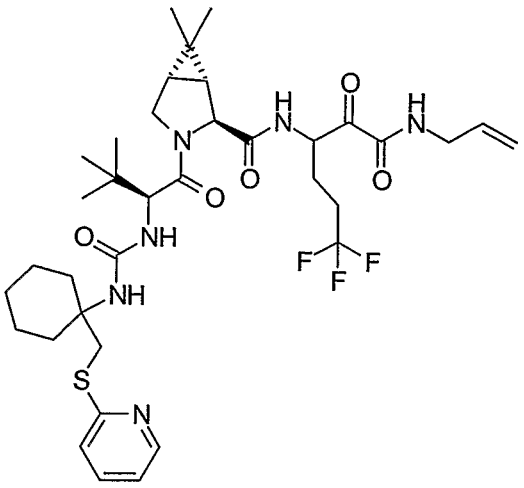
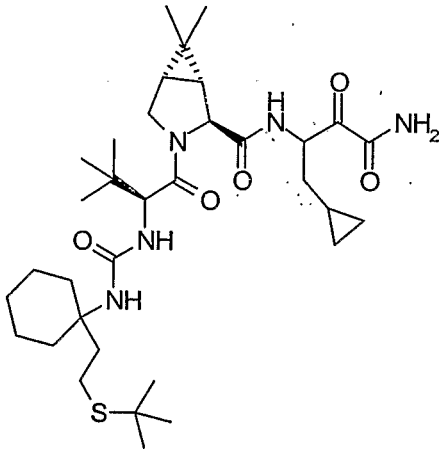
Prep. Ex.	COMPOUND	Select Mass Spectra Data	Ki* range
119			B
120			C

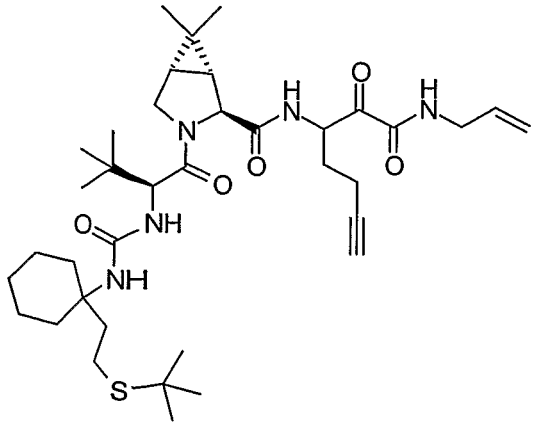
Prep. Ex.	COMPOUND	Select Mass Spectra Data	Ki* range
121		FABMS; MH^+, 644.2	A
122		FABMS; MH^+, 672.5.	A

Prep. Ex.	COMPOUND	Select Mass Spectra Data	Ki* range
123			A
124			B

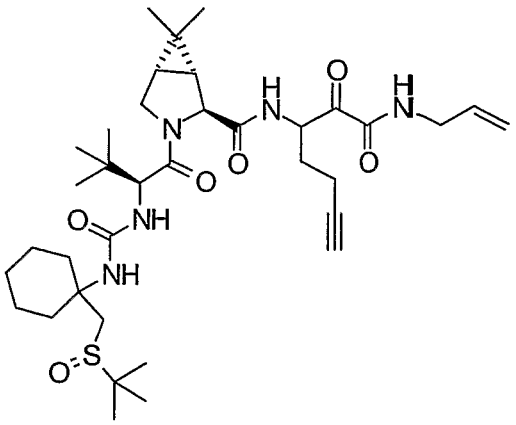
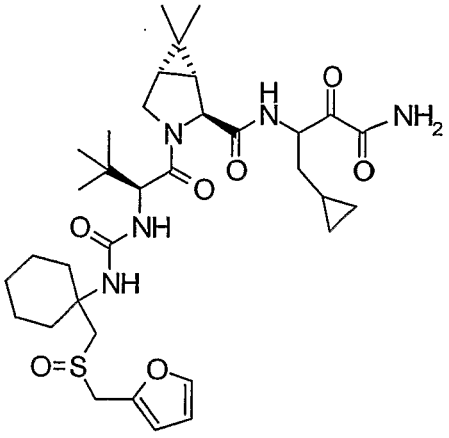
Prep. Ex.	COMPOUND	Select Mass Spectra Data	Ki* range
125			B
126			A

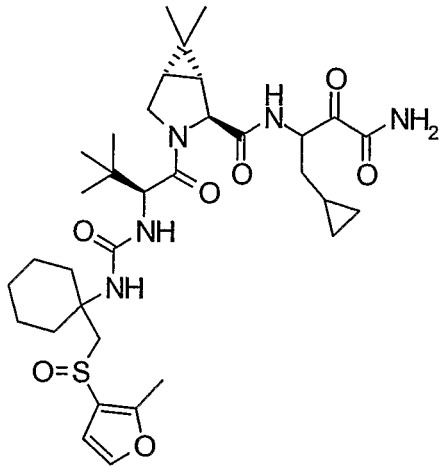
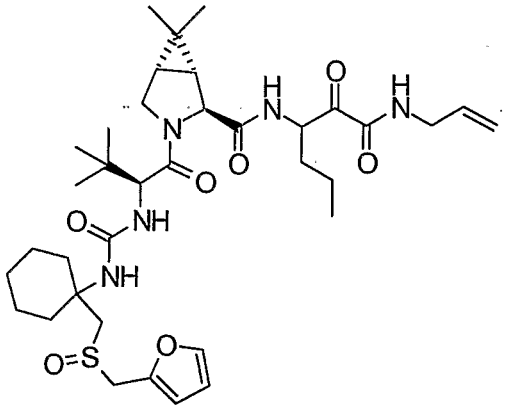
Prep. Ex.	COMPOUND	Select Mass Spectra Data	Ki* range
127			A
128			B

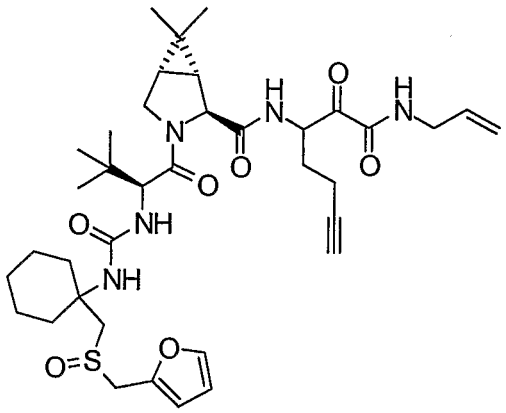
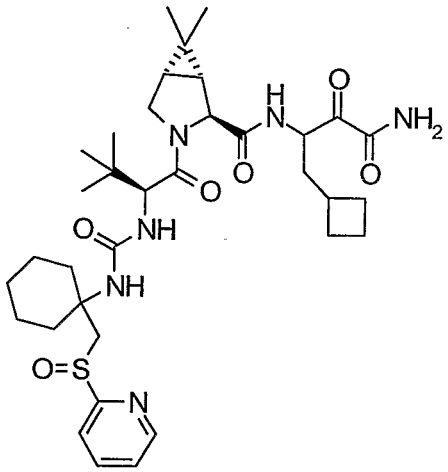
Prep. Ex.	COMPOUND	Select Mass Spectra Data	Ki* range
129			C
130			B

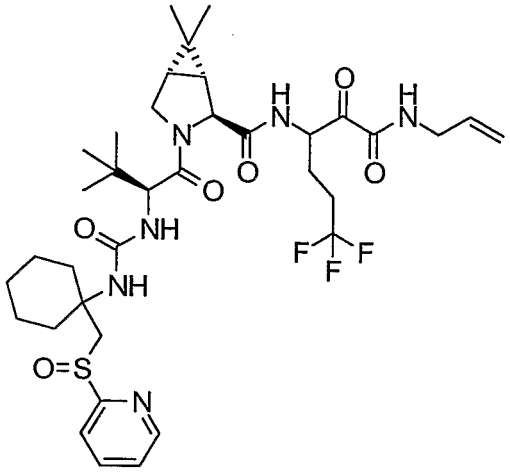
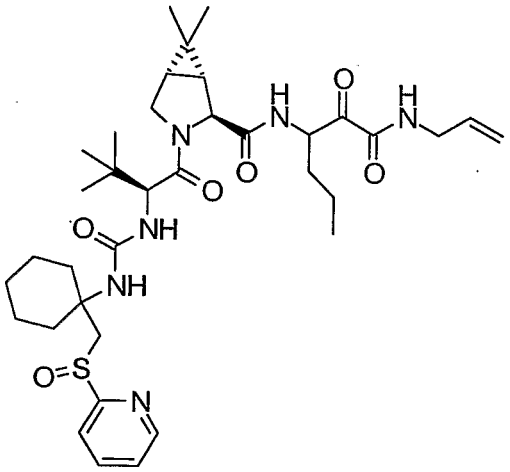
Prep. Ex.	COMPOUND	Select Mass Spectra Data	Ki* range
131			B

Sulfoxide Compounds

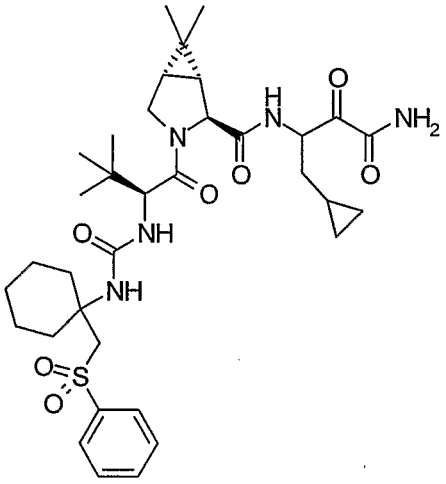
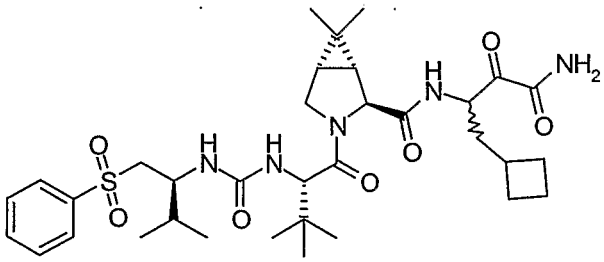
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
	[Ki* ranges are: A = <75 nM; B = 75 - 250 nM; C = >250 nM]		
132		FABMS; MH^+, 688.5.	A
133			A

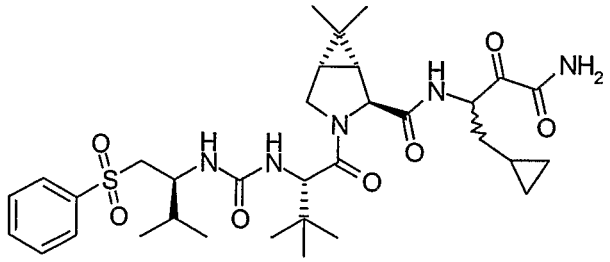
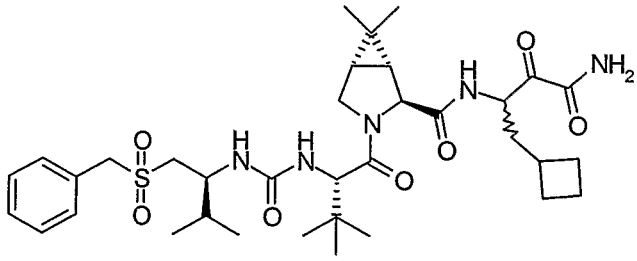
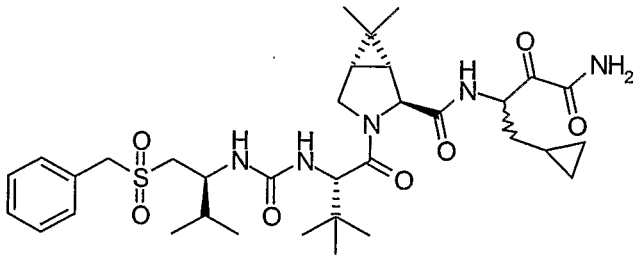
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
134			A
135			A

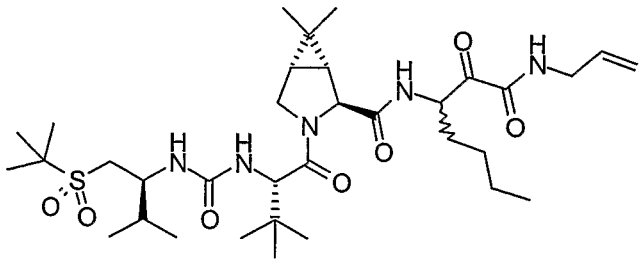
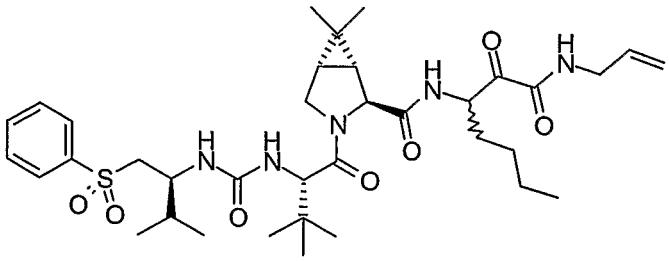
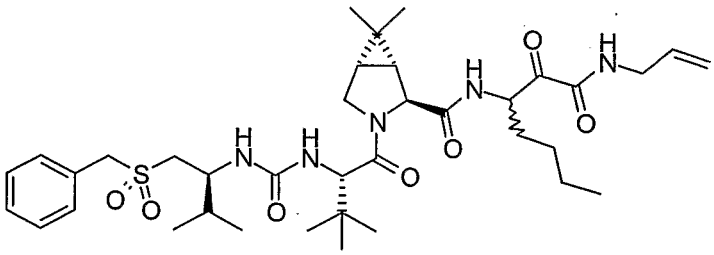
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
136			A
137			A

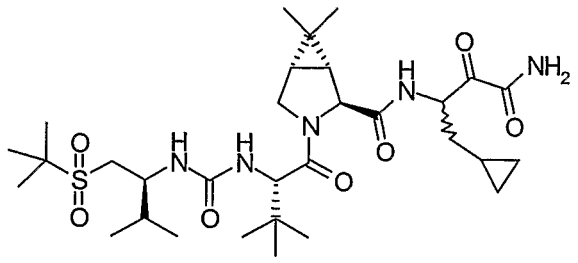
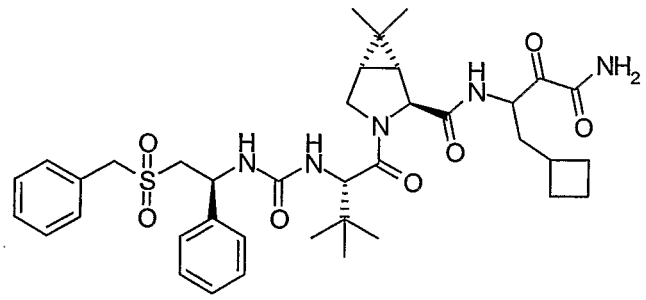
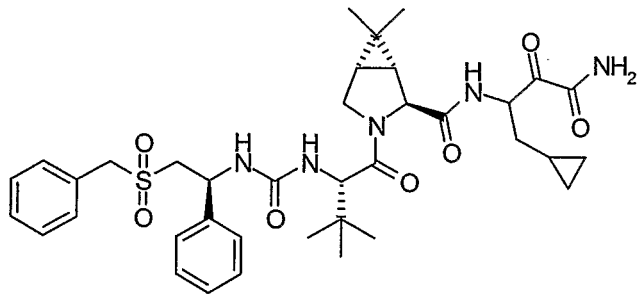
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
138			B
139			A

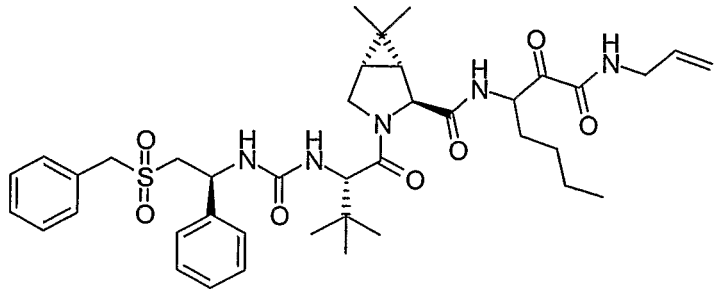
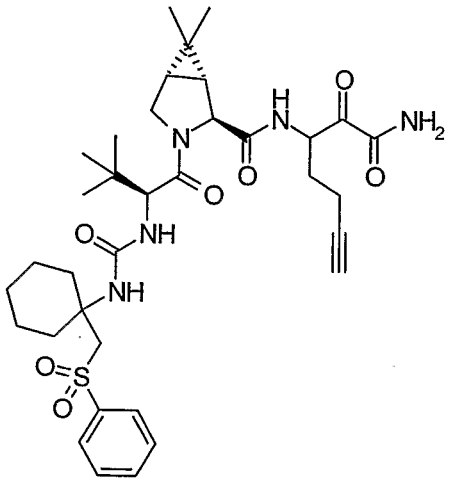
Sulfone Compounds

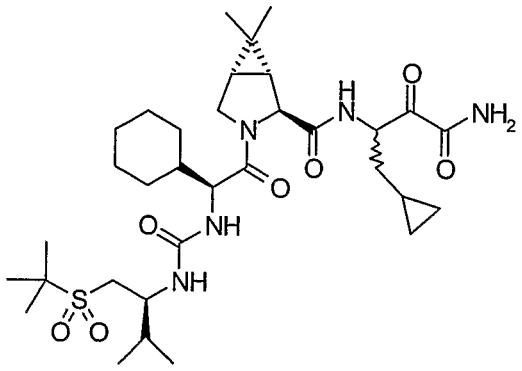
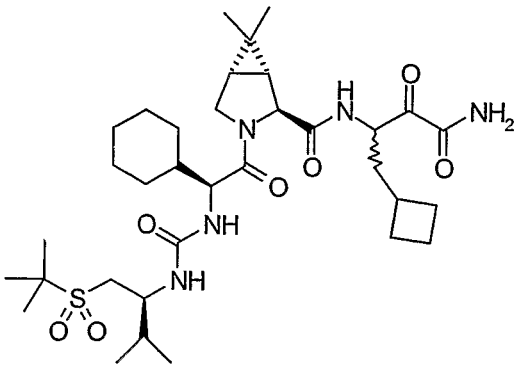
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
	[Ki* ranges are: A = <75 nM; B = 75 - 250 nM; C = >250 nM]		
142		LCMS: MH^+, 686.1.	A
143			A

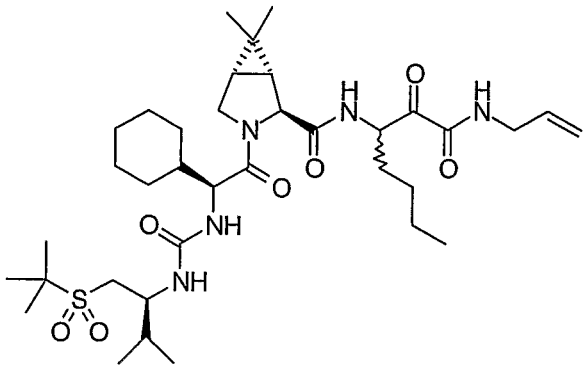
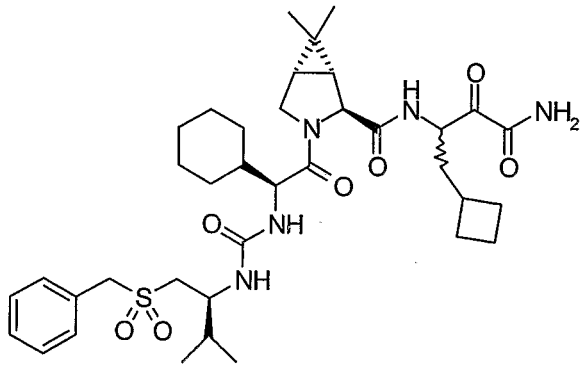
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
144			A
145			A
146			A

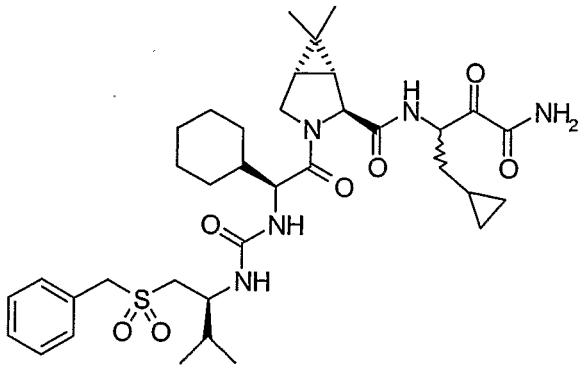
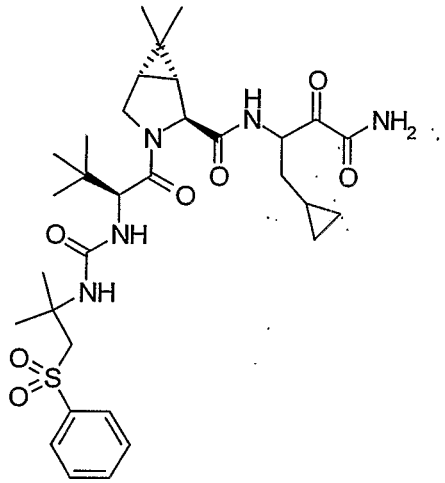
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
147			B
148			B
149			B

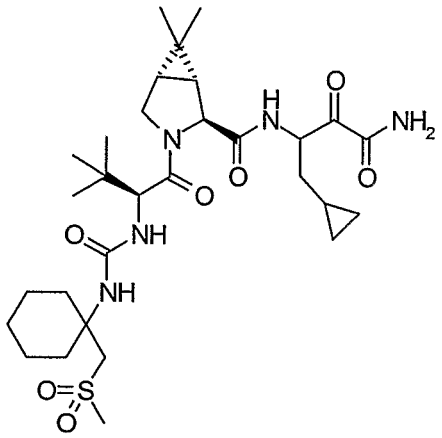
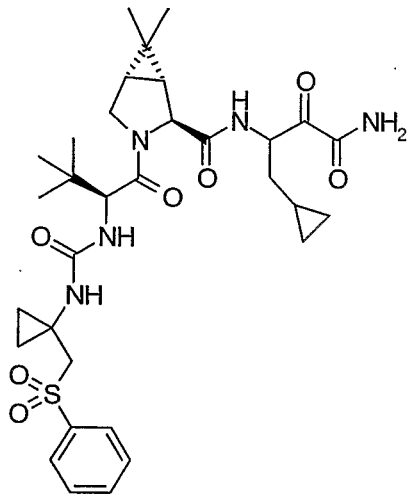
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
150			A
151			B
152			B

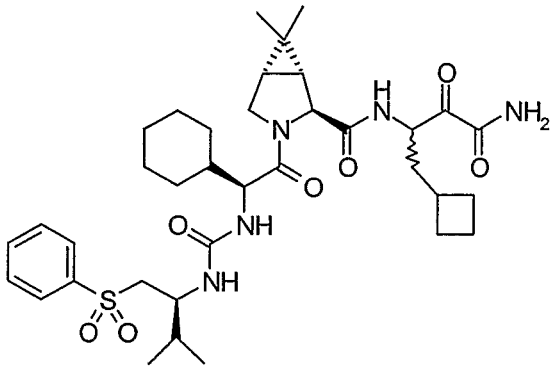
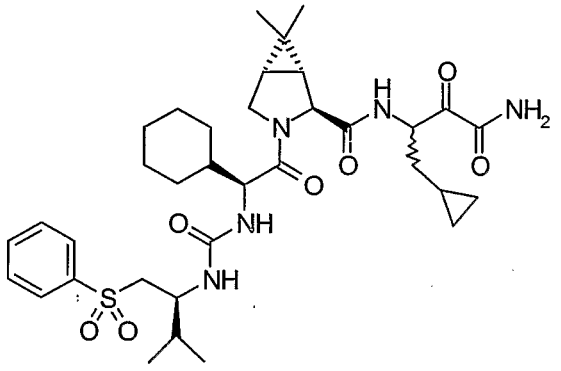
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
153			C
154		FABMS; MH^+, 684.2.	A

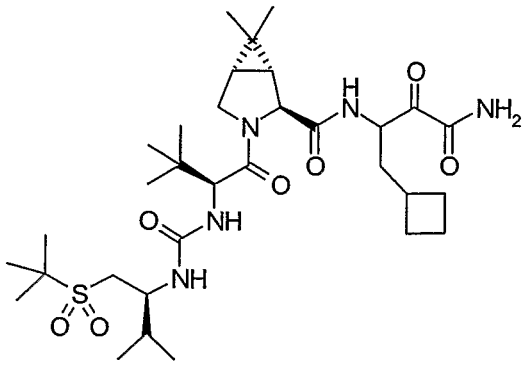
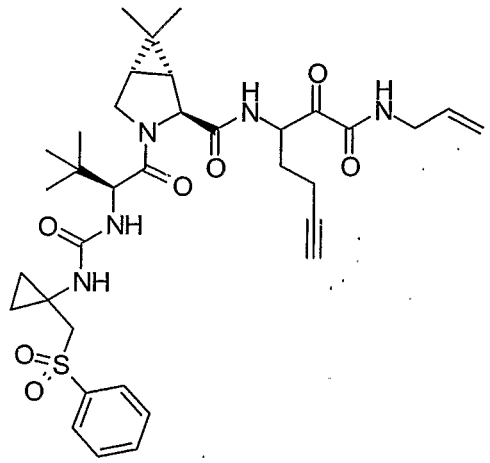
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
155			A
156			A

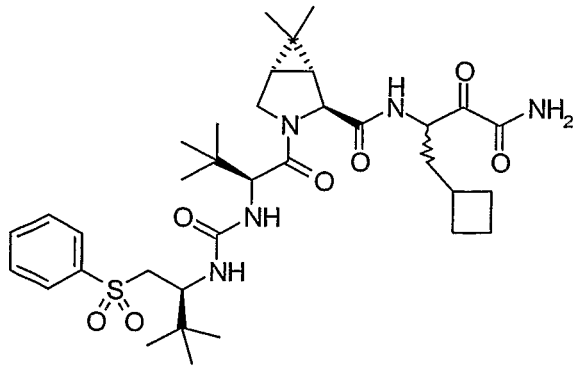
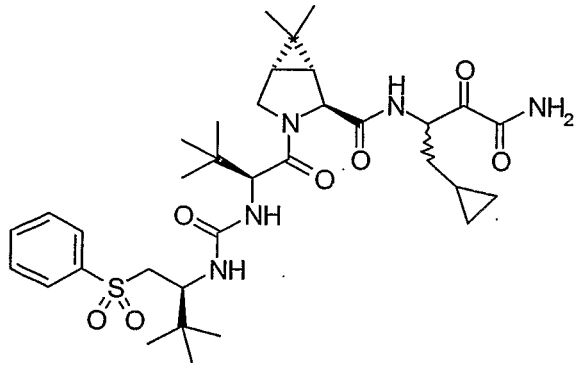
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
157			A
158			A

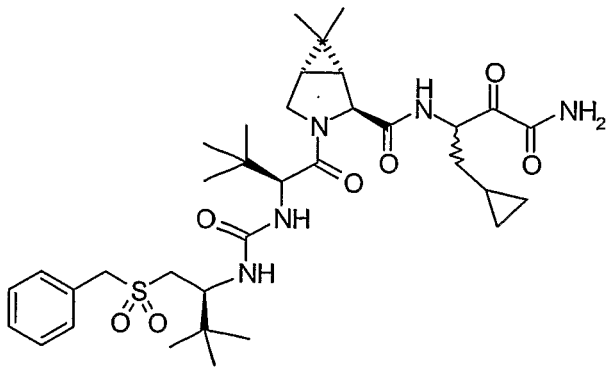
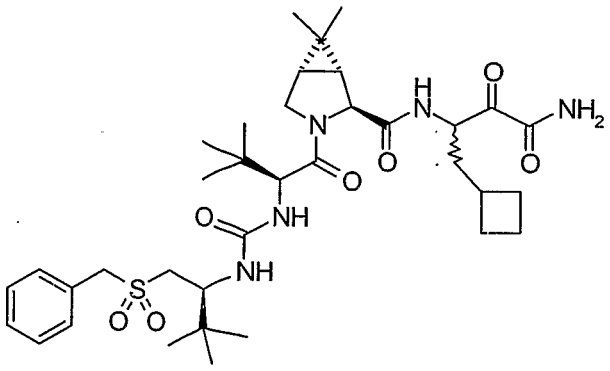
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
159			A
160			A

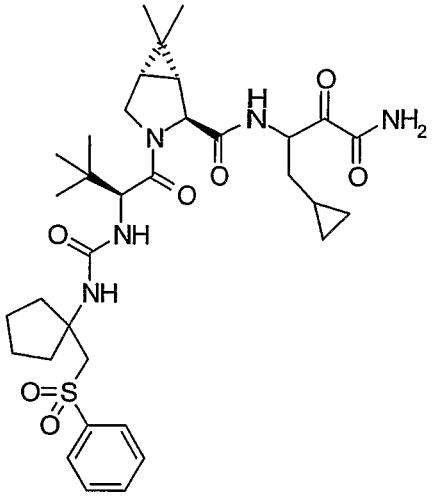
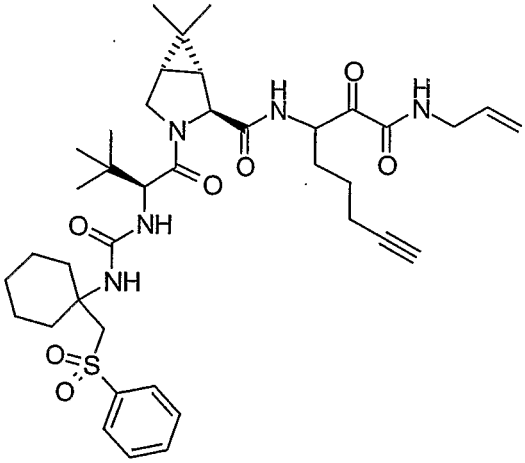
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
161			A
162			A

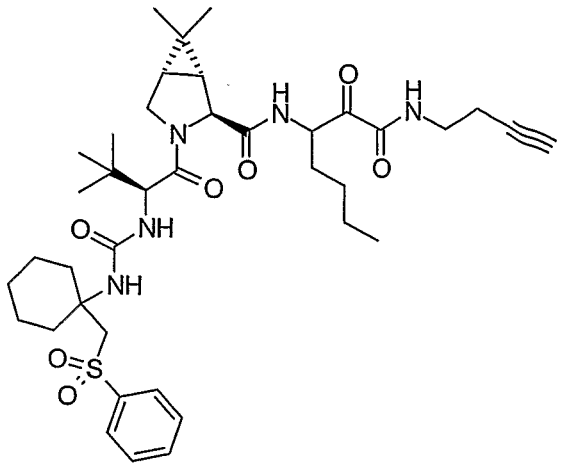
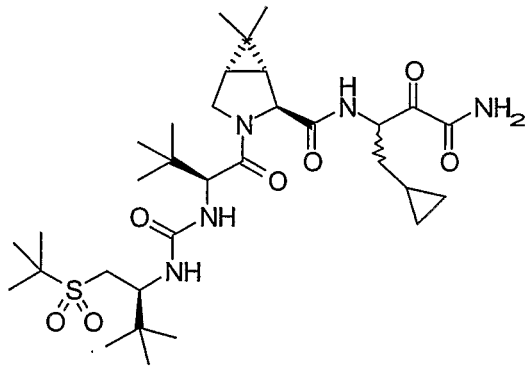
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
163			A
164			A

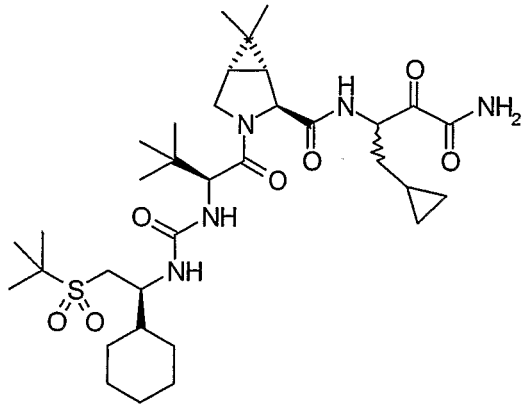
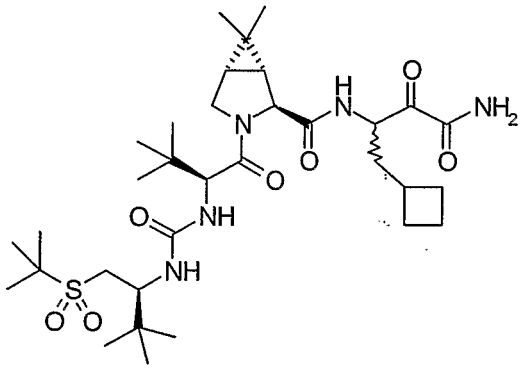
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
165			A
166		FABMS; MH^+, 682.3.	B

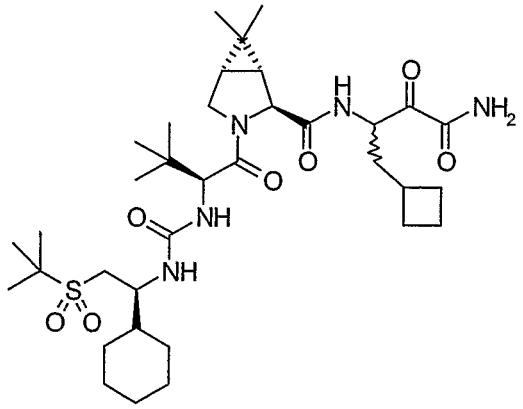
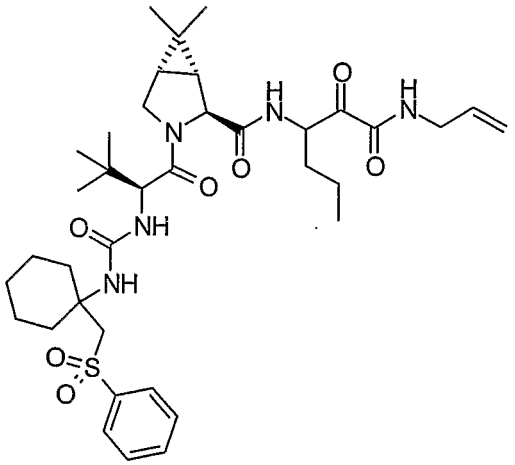
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
167			A
168			A

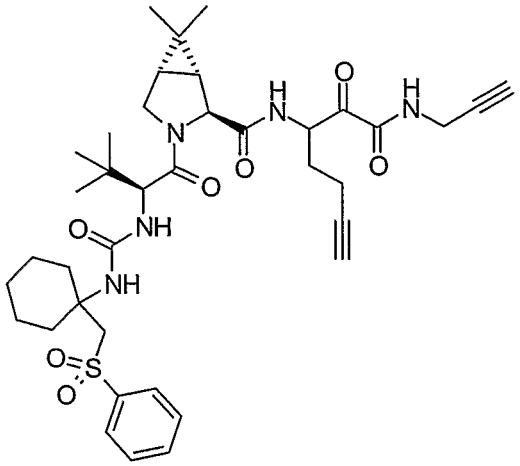
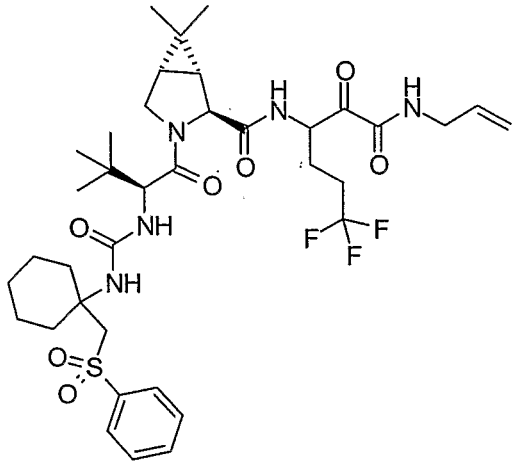
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
169			A
170			A

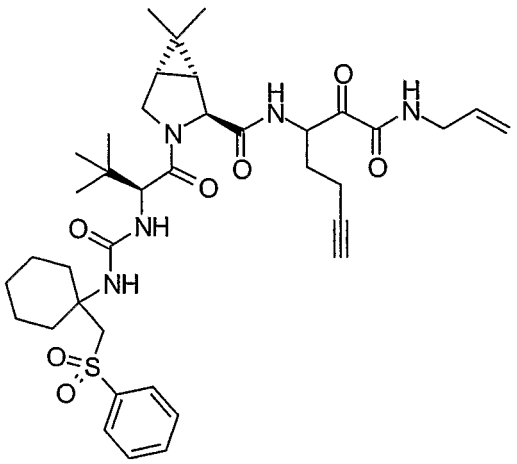
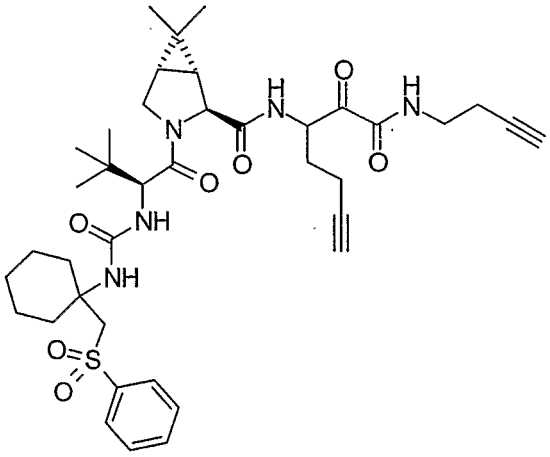
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
171			A
172		LCMS; MH^+, 738.2.	B

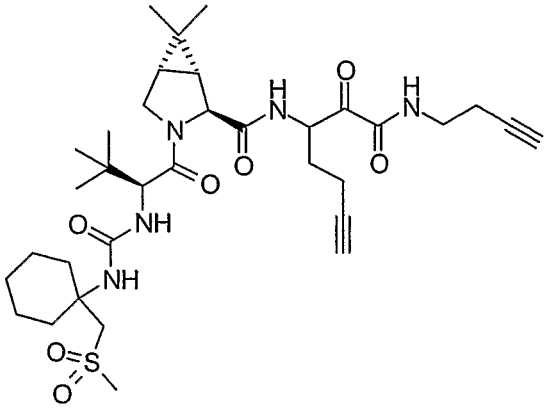
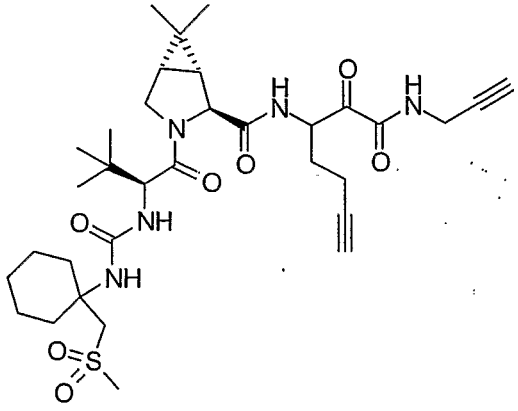
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
173			A
174			A

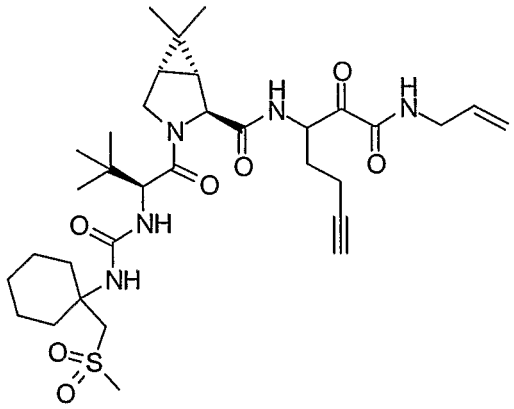
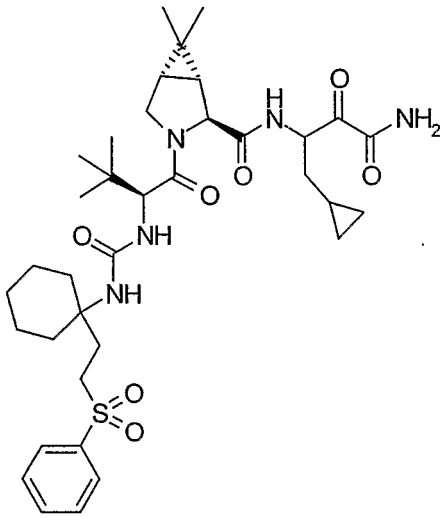
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
175			A
176			A

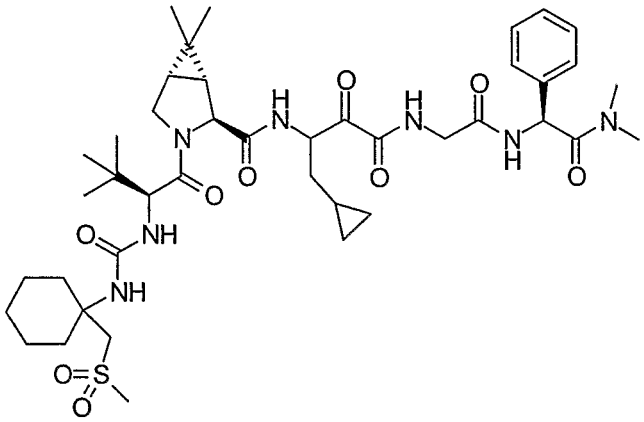
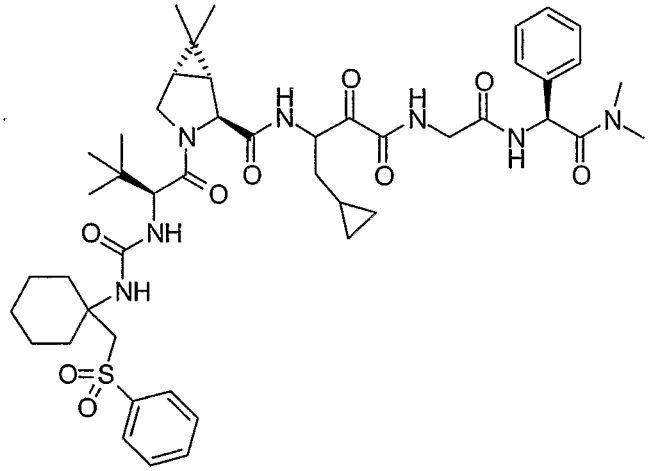
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
177			A
178		LCMS; MH^+, 714.1.	A

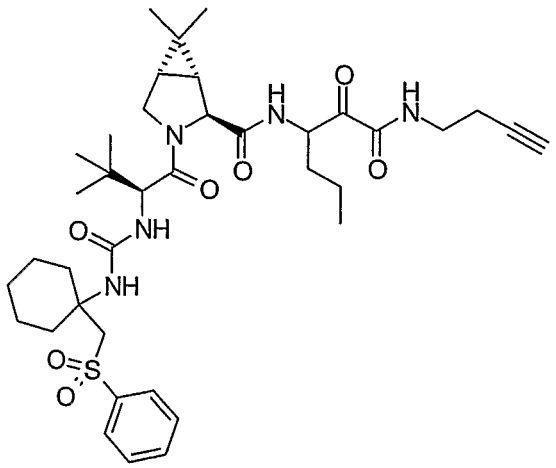
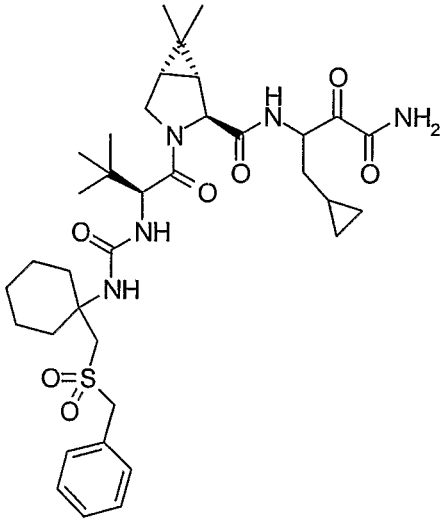
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
179			A
180			A

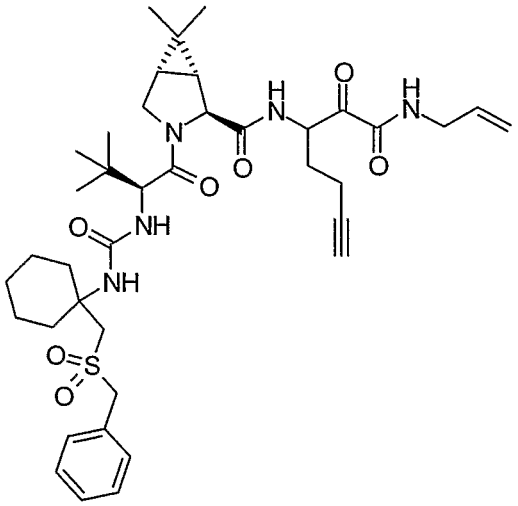
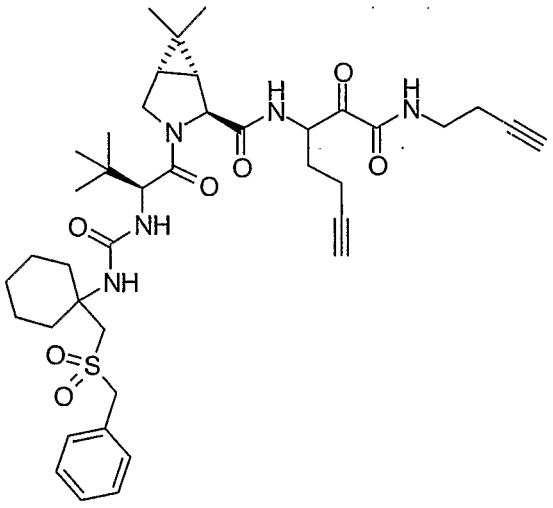
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
181		FABMS; MH^+, 724.6.	A
182		FABMS; MH^+, 736.5.	A

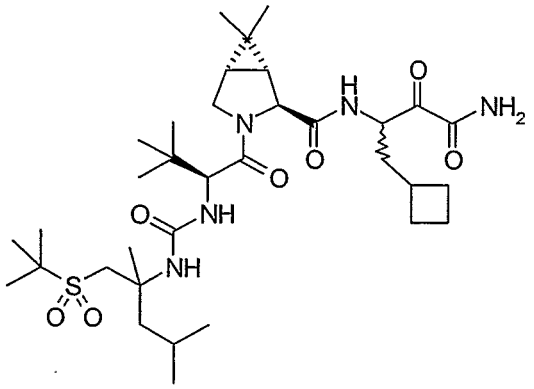
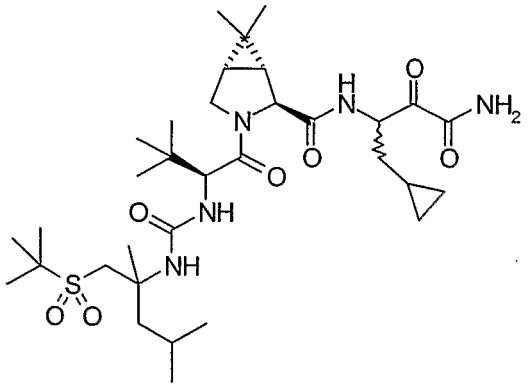
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
183			A
184			A

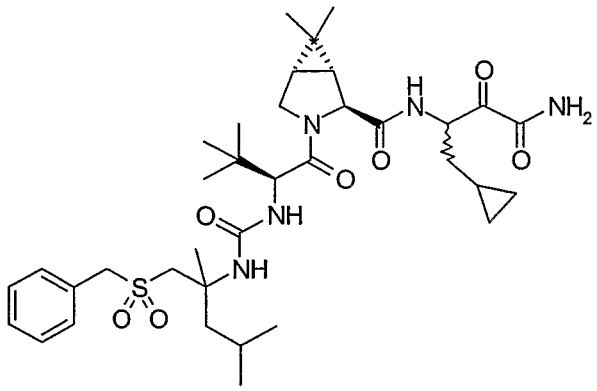
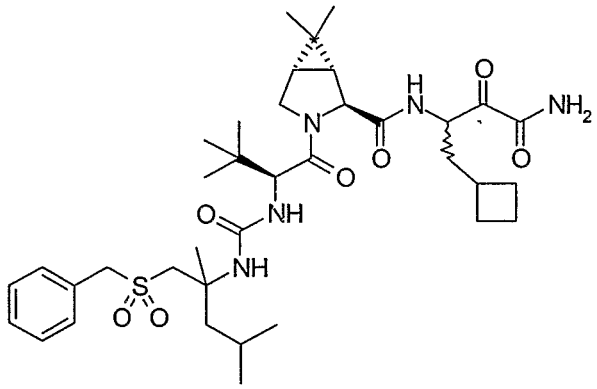
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
185		FABMS; MH^+, 662.5.	A
186		FABMS; MH^+, 700.3.	A

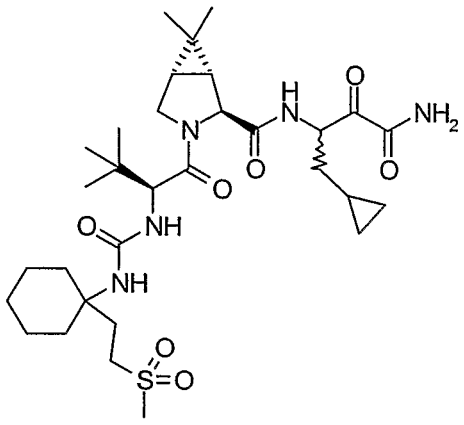
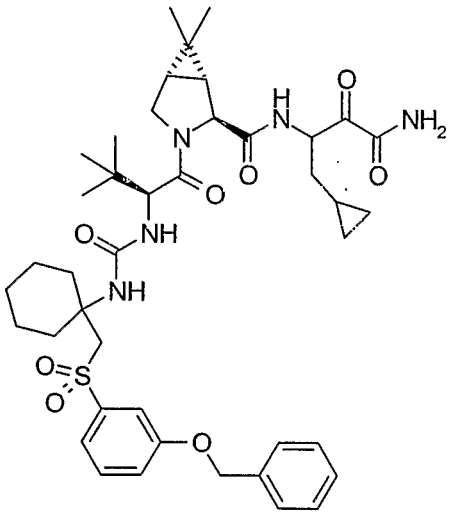
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
187			A
188			A

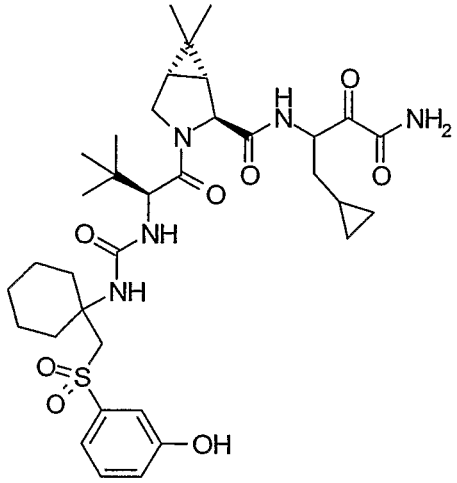
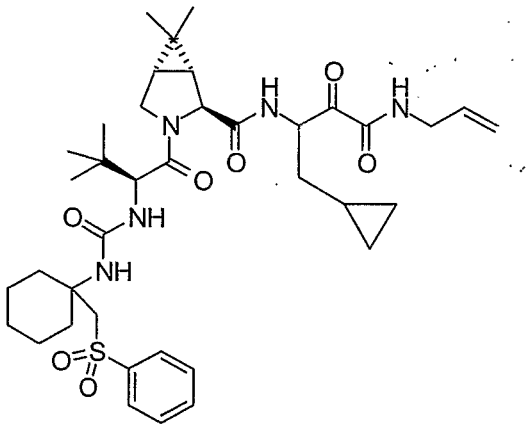
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
189			A
190			A

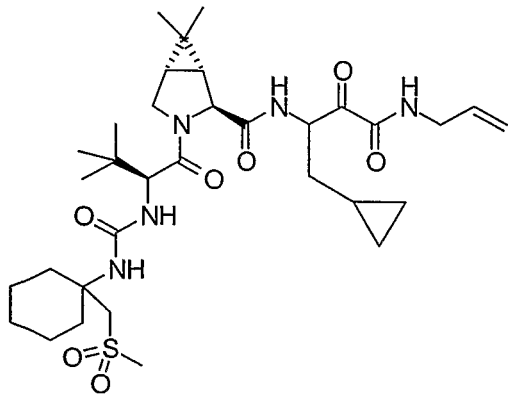
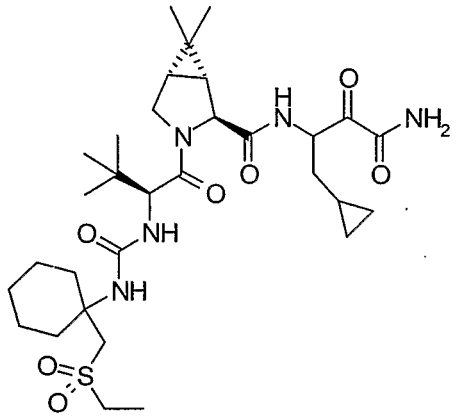
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
191		FABMS; MH^+, 738.4.	A
192			A

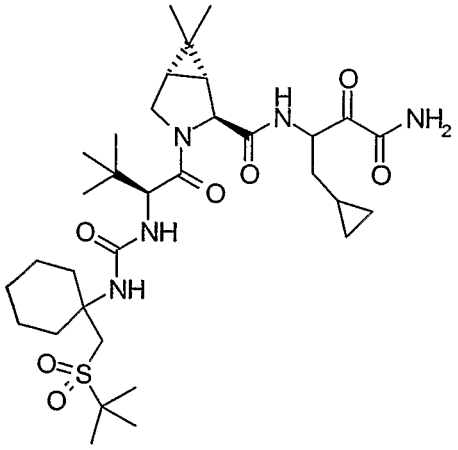
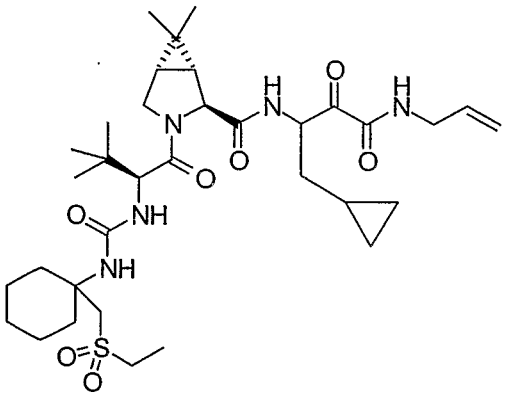
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
193			A
194			A

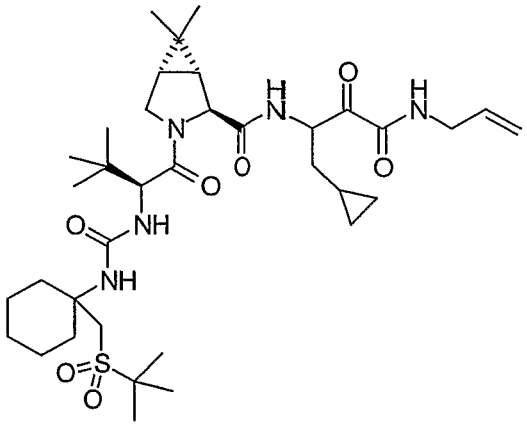
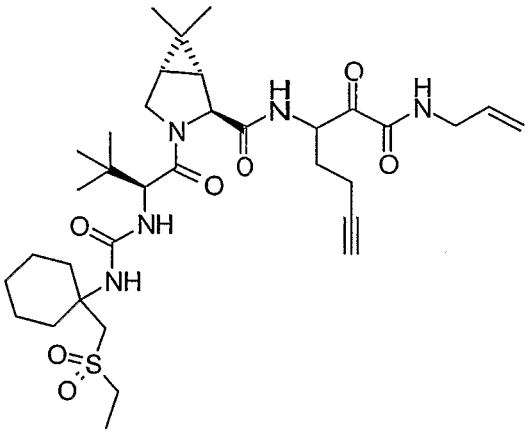
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
195			A
196			A

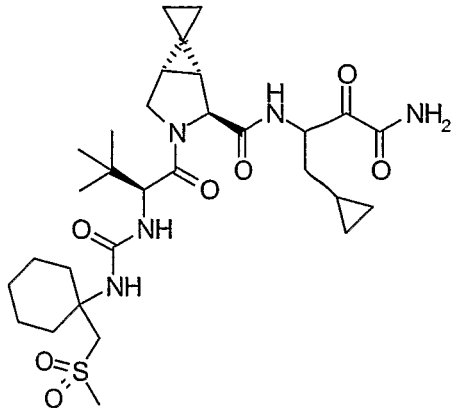
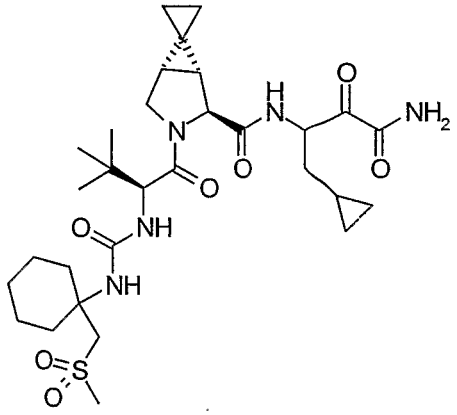
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
197		FABMS; MH^+, 638.3.	A
198		LCMS; MH^+, 792.2.	A

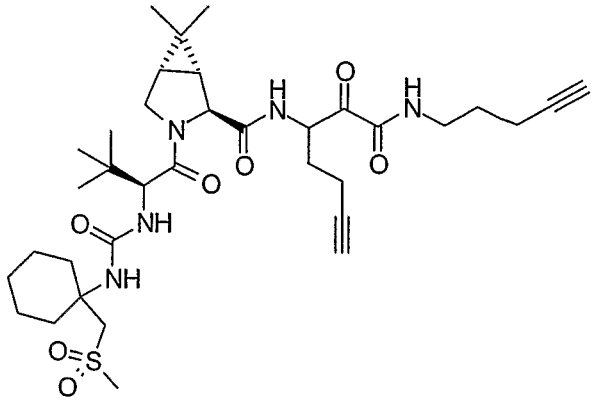
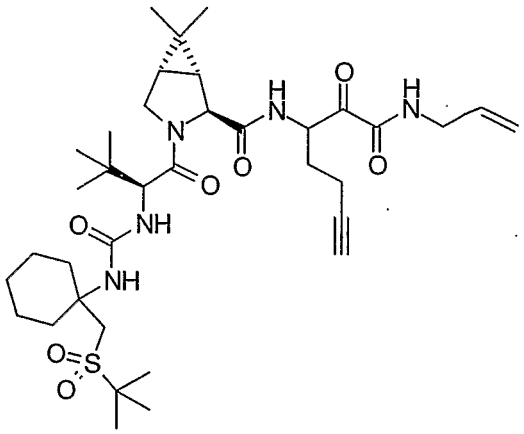
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
199		LCMS: MH^+, 702.2.	A
200		FABMS; MH^+, 726.5.	A

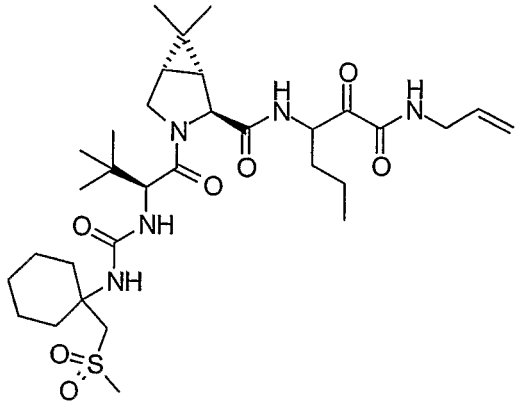
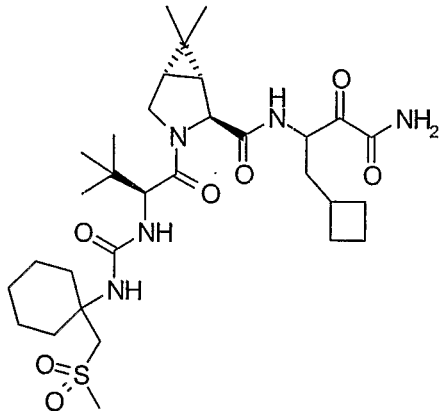
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
201			A
202			A

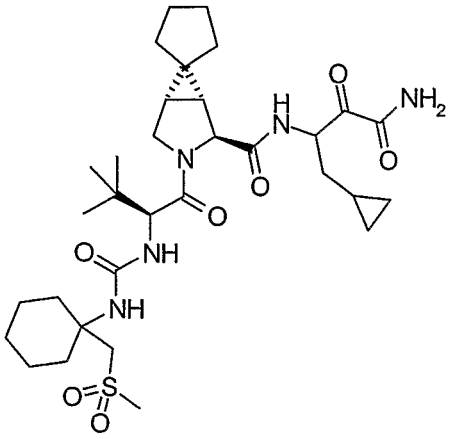
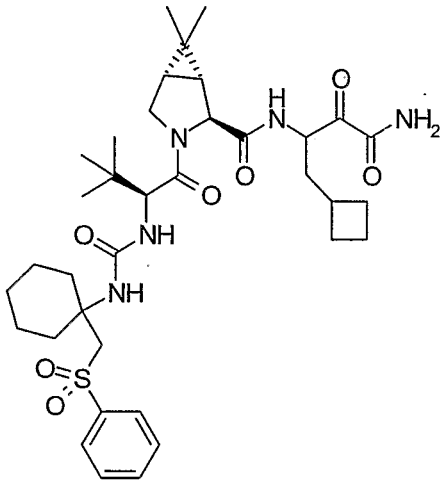
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
203			A
204			A

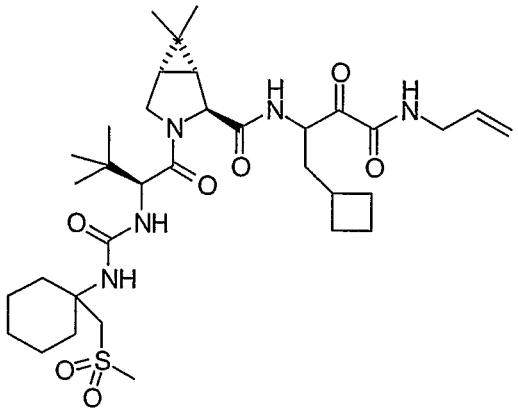
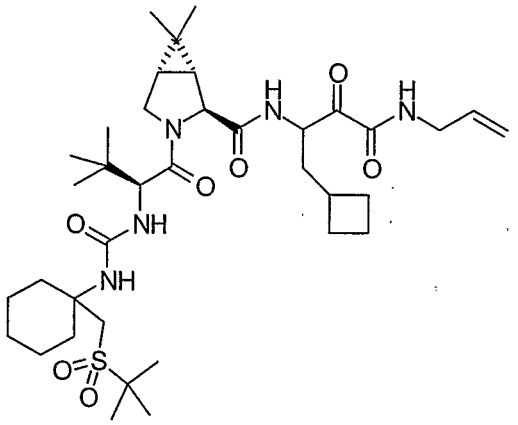
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
205			A
206		FABMS; MH^+, 676.7.	A

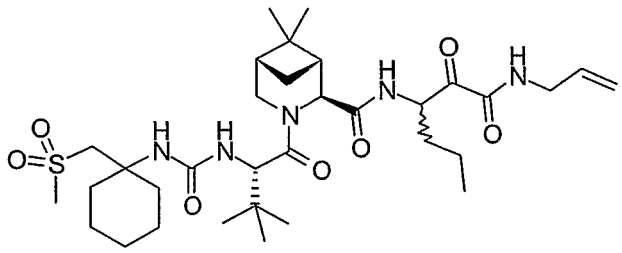
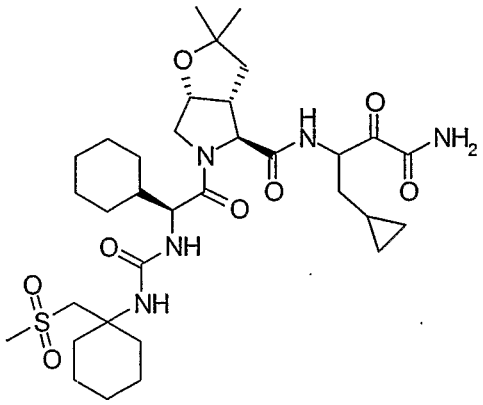
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
207			A
208			A

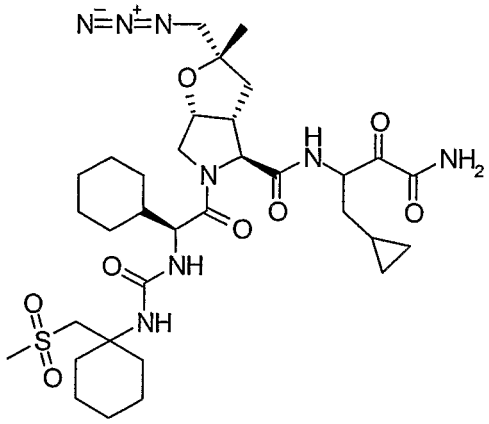
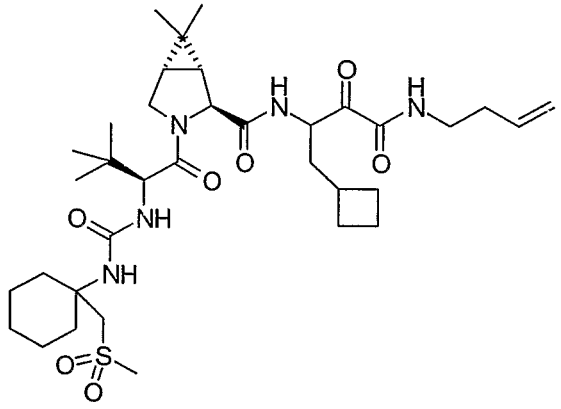
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
209		FABMS; MH^+, 688.3.	A
210		FABMS; MH^+, 704.4.	A

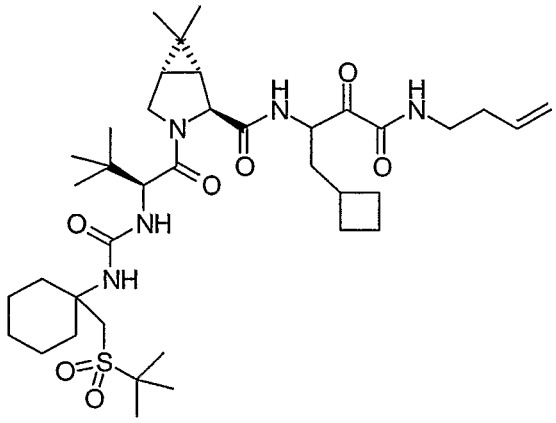
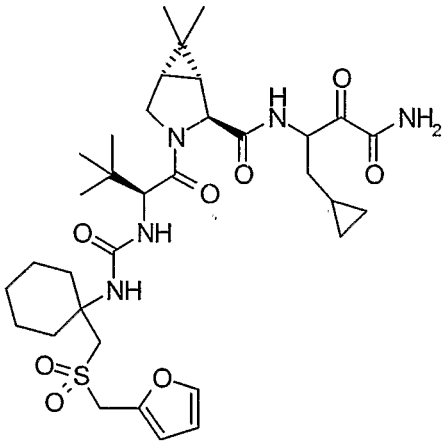
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
211			A
212			A

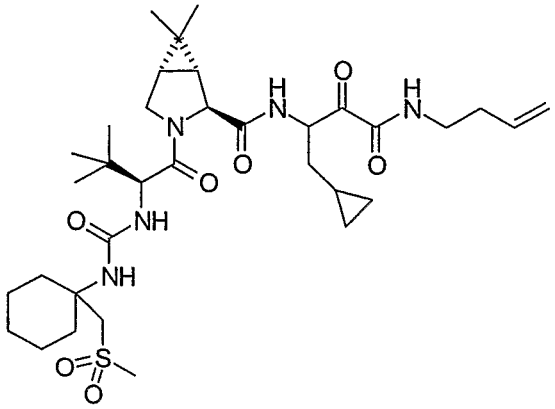
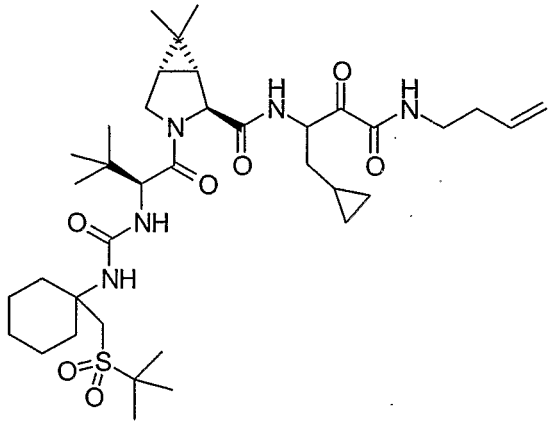
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
213			A
214			A

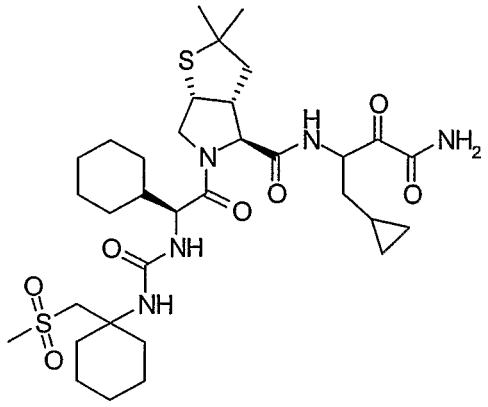
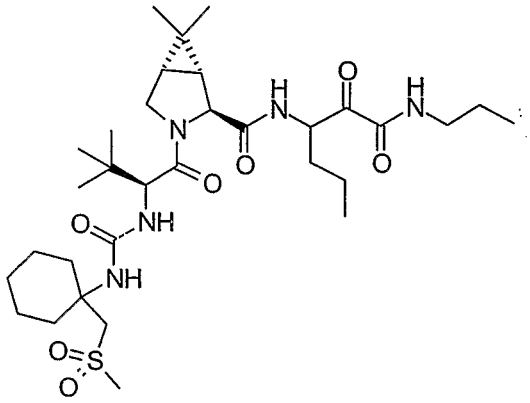
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
215		FABMS; MH^+, 678.6.	A
216		FABMS; MH^+, 720.6.	A

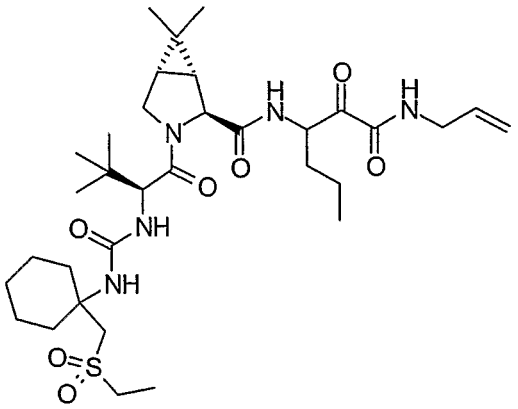
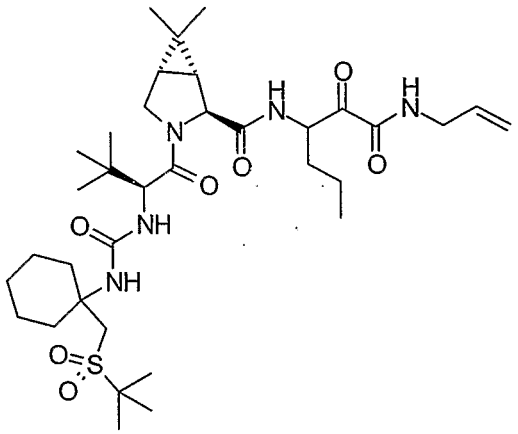
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
217			A
218			A

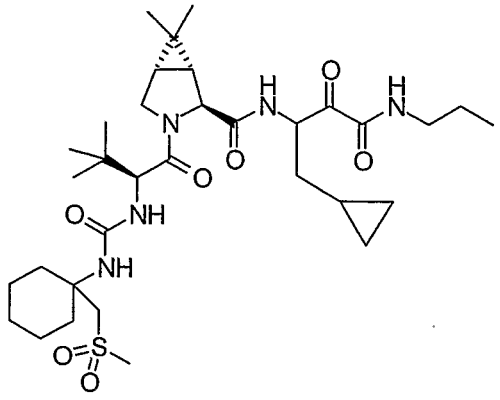
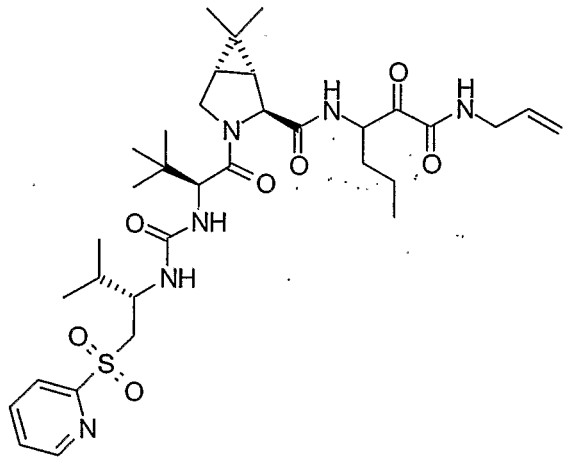
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
219			A
220		FABMS; MH^+, 692.5.	A

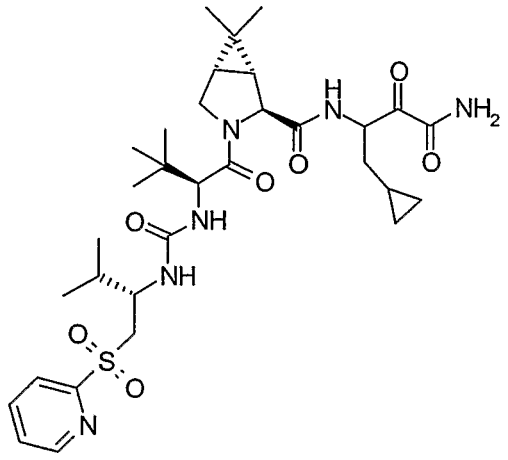
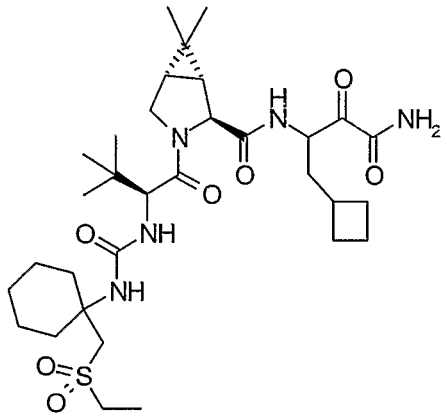
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
221		FABMS; MH^+, 734.5.	A
222			A

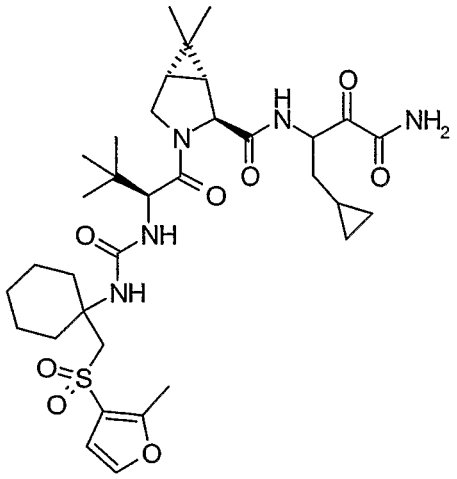
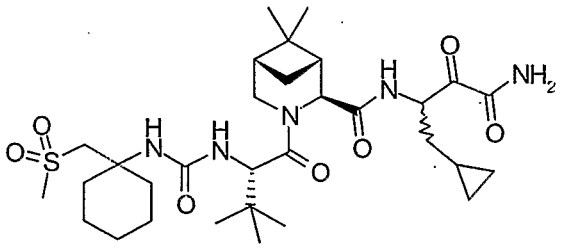
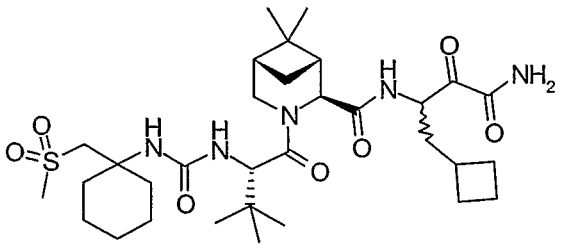
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
223		FABMS; MH^+, 678.4.	A
224		FABMS; MH^+, 720.8.	A

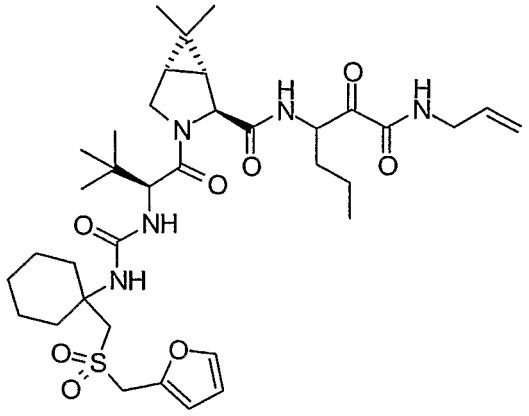
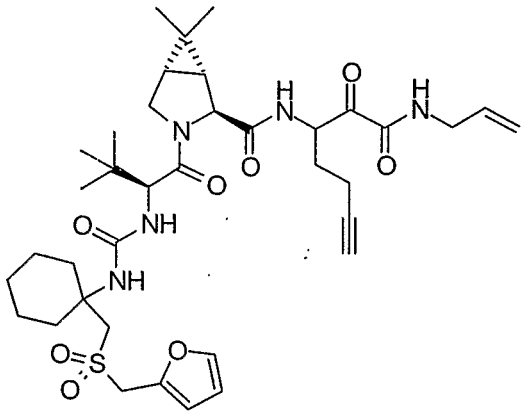
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
225			B
226		LCMS; MH^+, 654.1.	A

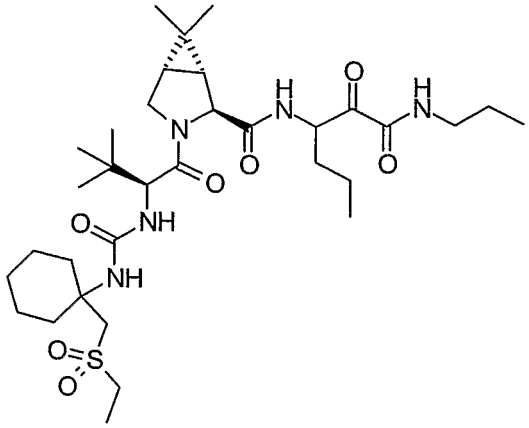
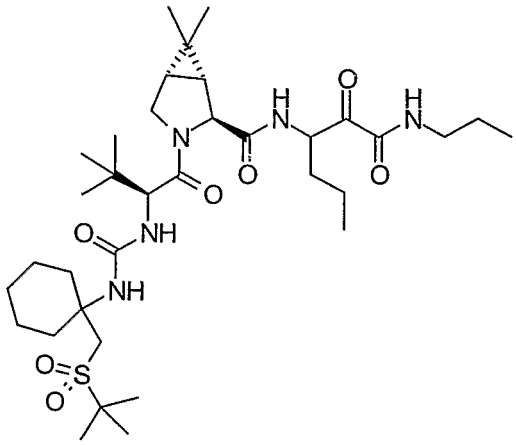
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
227			A
228			A

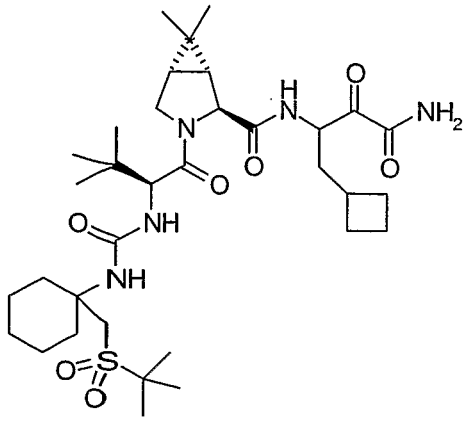
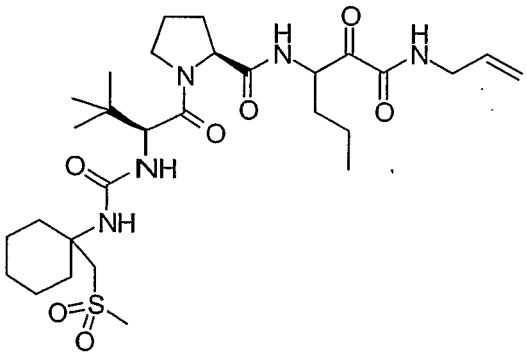
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
229		FABMS; MH+, 666.5.	A
230			C

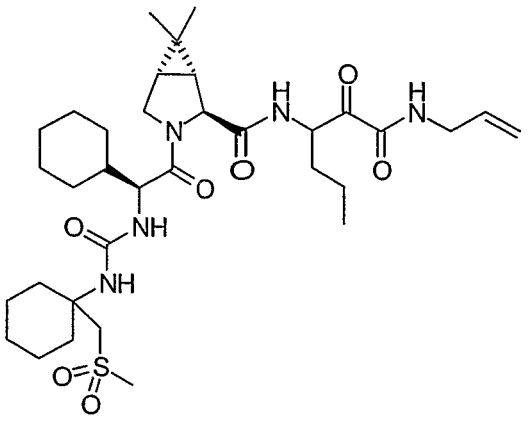
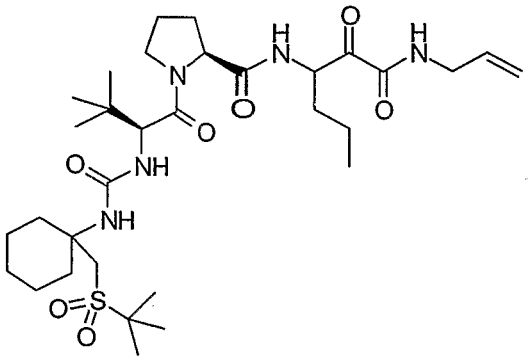
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
231			A
232			A

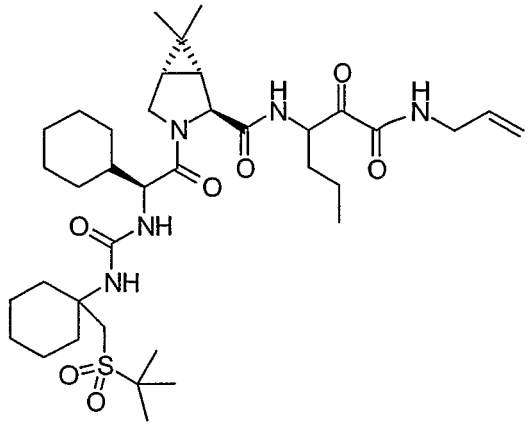
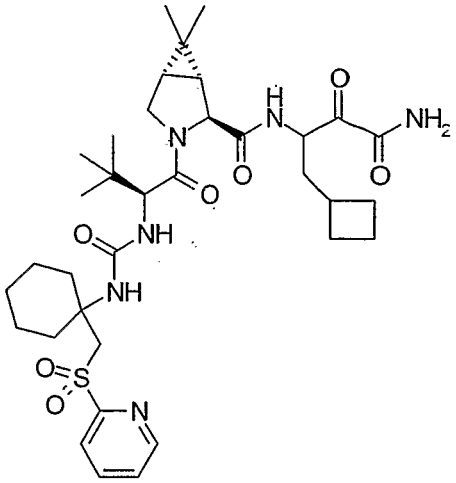
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
233			A
234			C
235			A

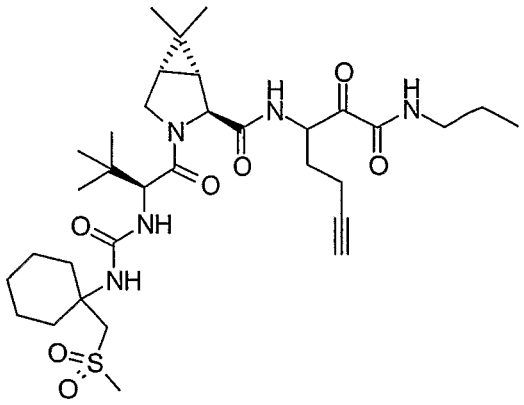
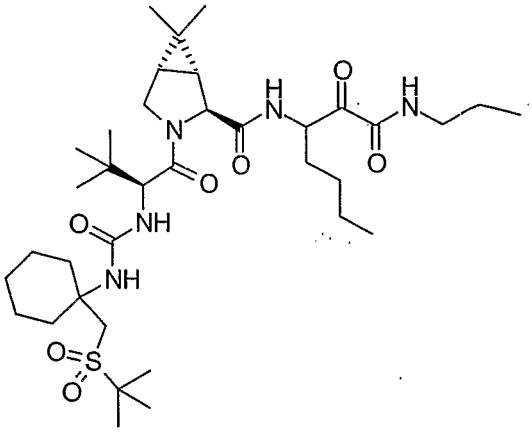
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
236			A
237			A

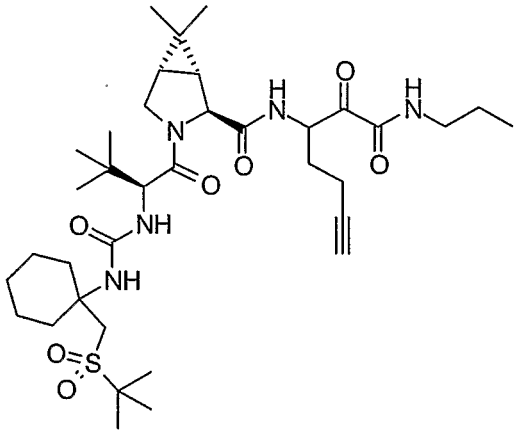
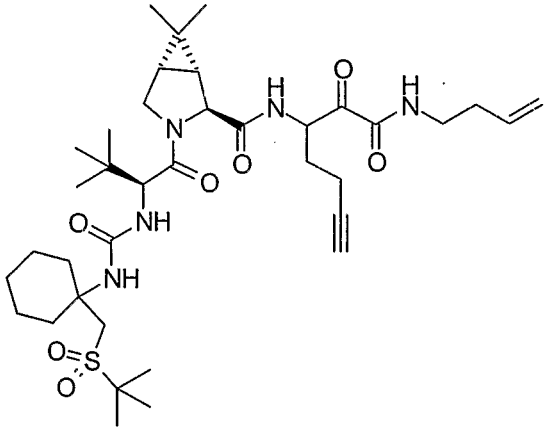
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
238			A
239			A

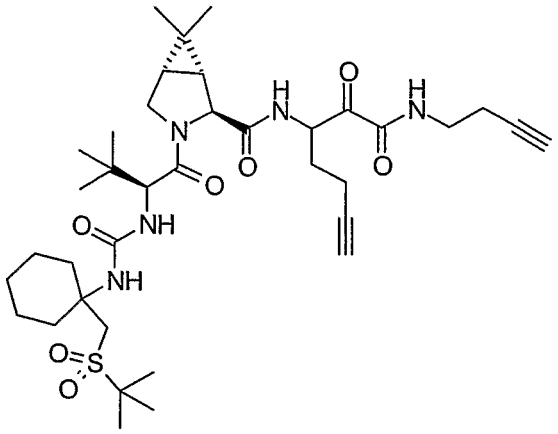
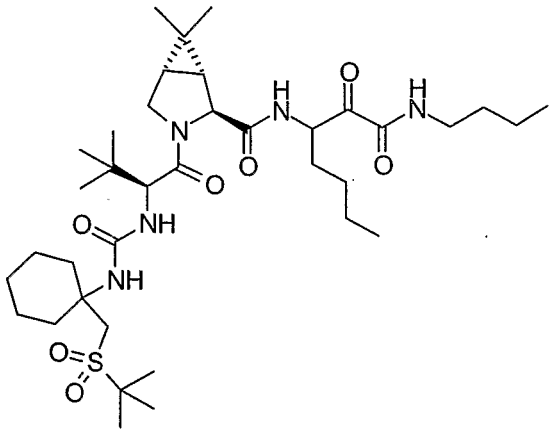
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
240			A
241			C

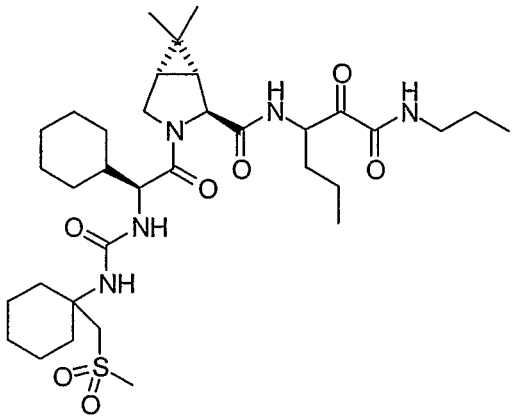
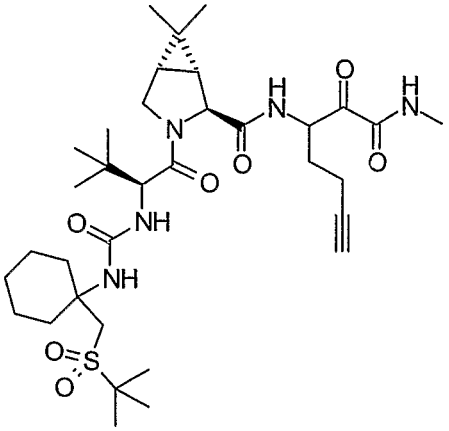
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
242			A
243			C

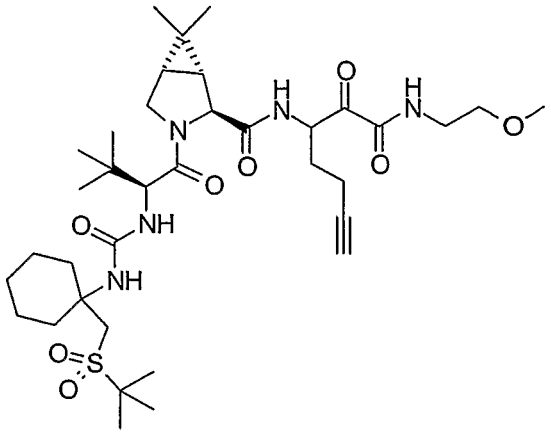
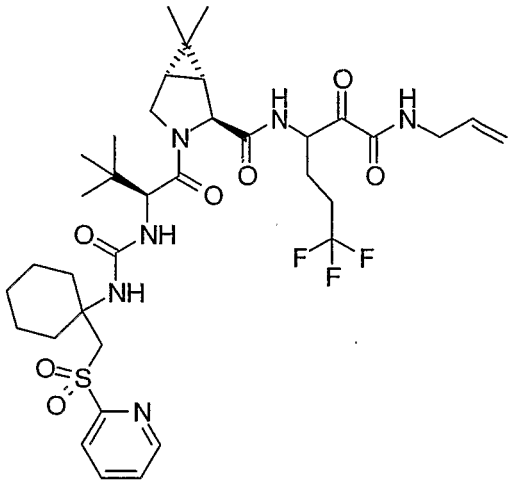
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
244			A
245			A

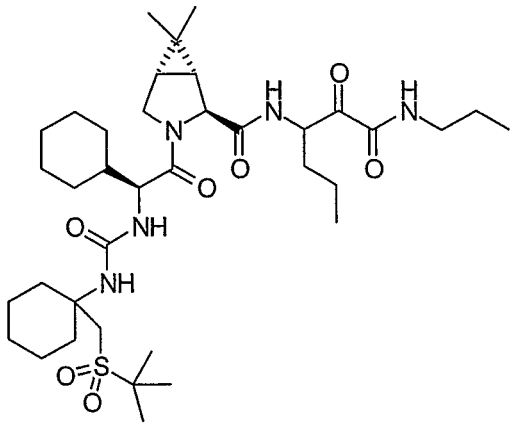
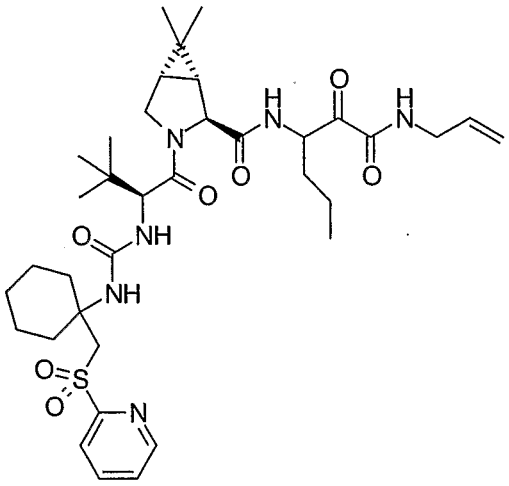
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
246		FABMS; MH^+, 664.2.	A
247		FABMS; MH^+, 710.3.	A

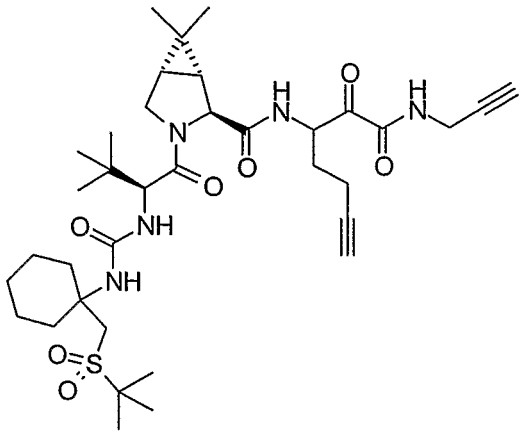
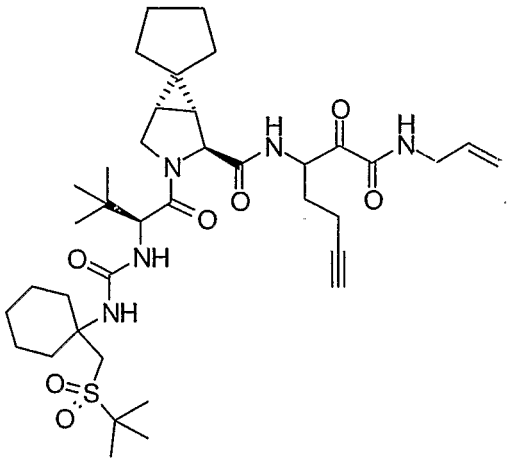
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
248		FABMS; MH^+, 706.5.	A
249		FABMS; MH^+, 718.2.	A

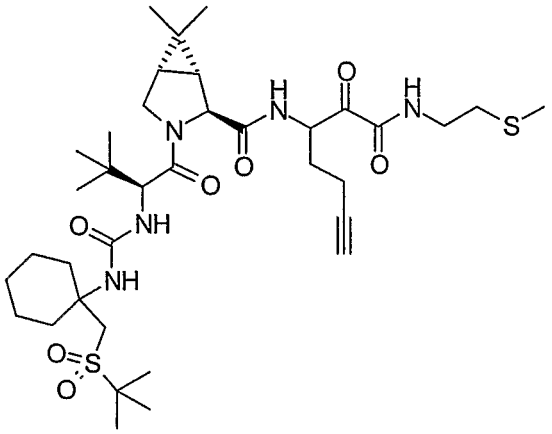
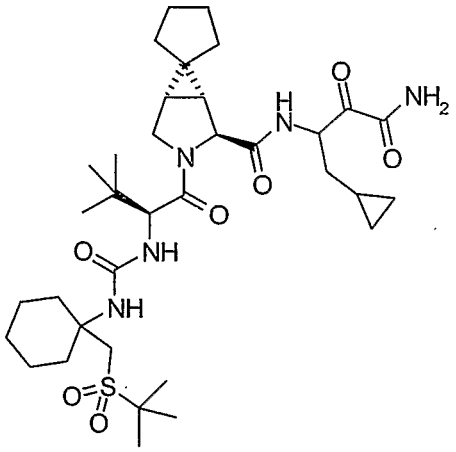
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
250			A
251		FABMS; MH^+, 724.5.	A

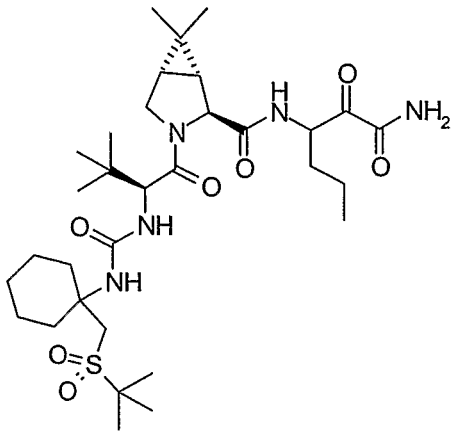
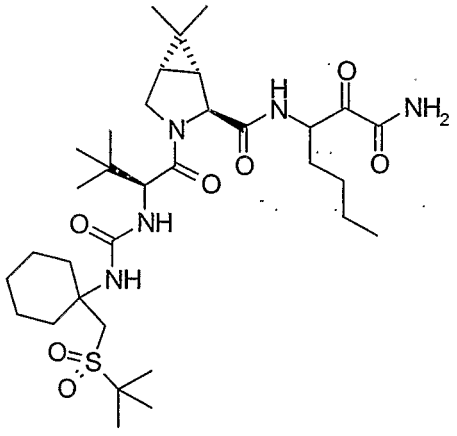
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
252		FABMS; MH^+, 680.4.	A
253			A

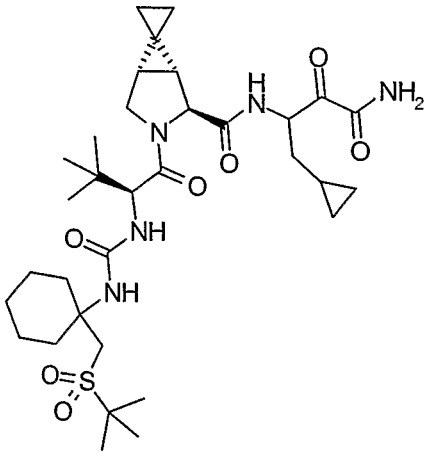
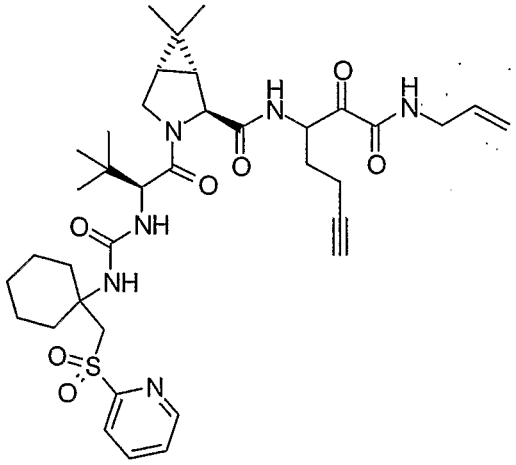
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
254		FABMS; MH^+, 722.1.	A
255			A

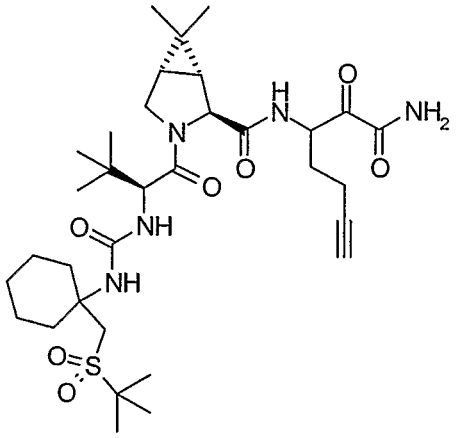
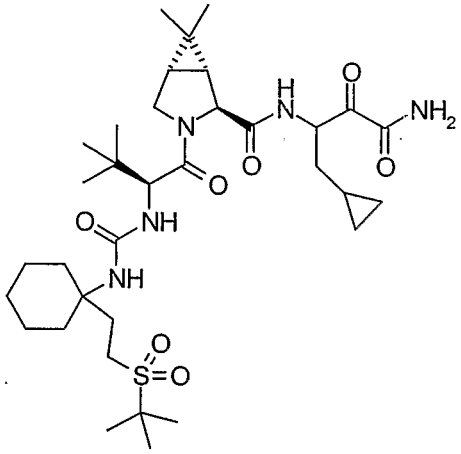
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
256			A
257			A

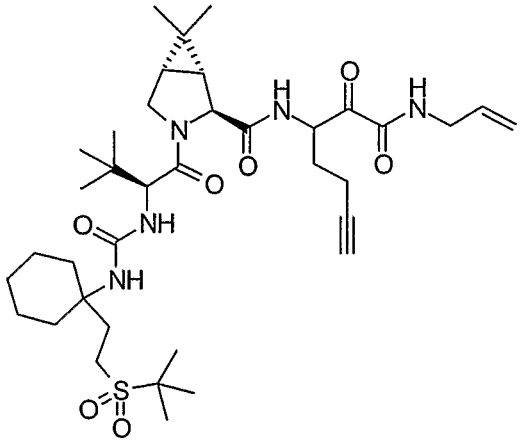
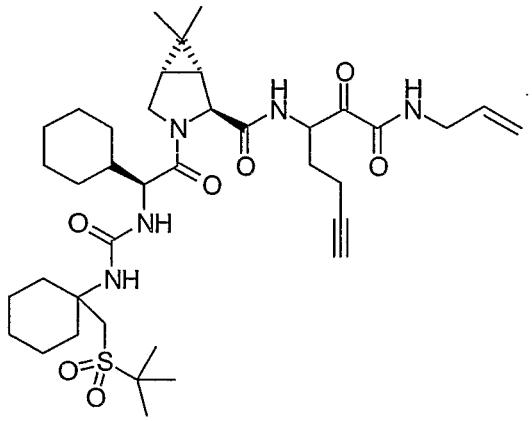
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
258		FABMS; MH+, 702.3.	A
259		FABMS; MH^+, 730.5.	A

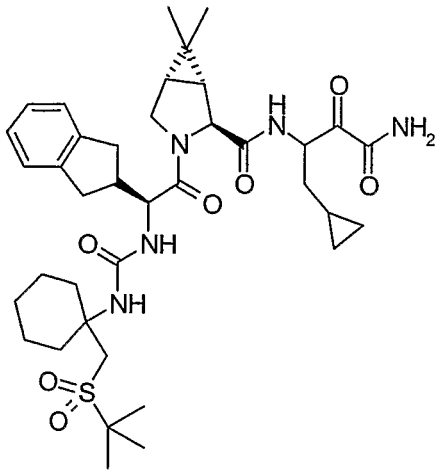
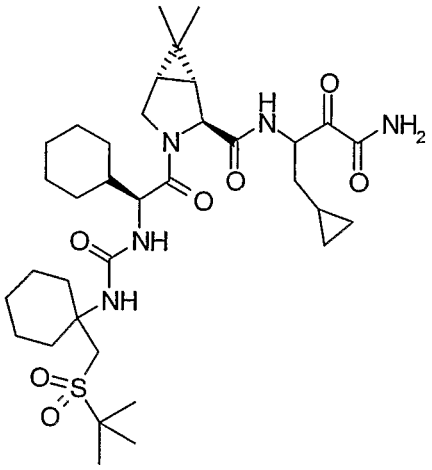
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
260		FABMS; MH^+, 738.4.	A
261		FABMS; MH^+, 692.5.	A

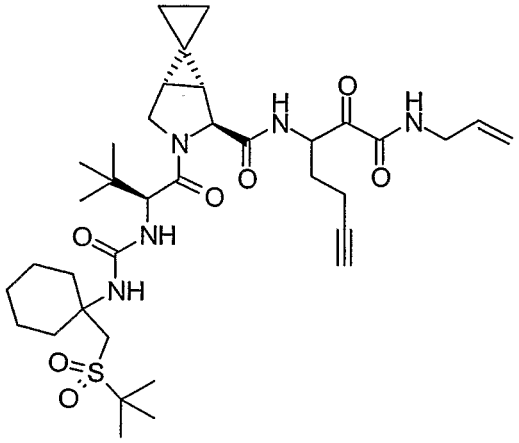
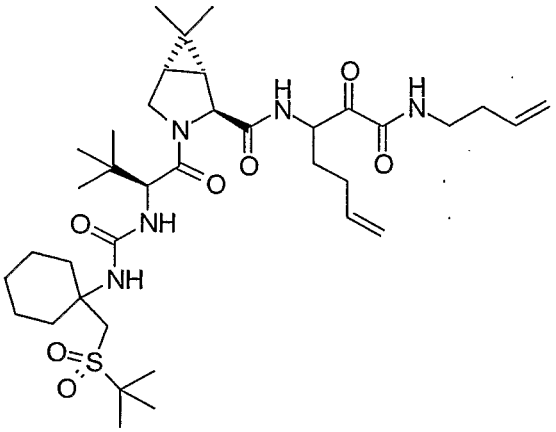
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
262			A
263			A

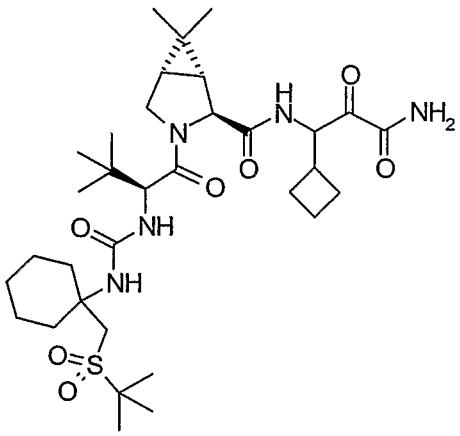
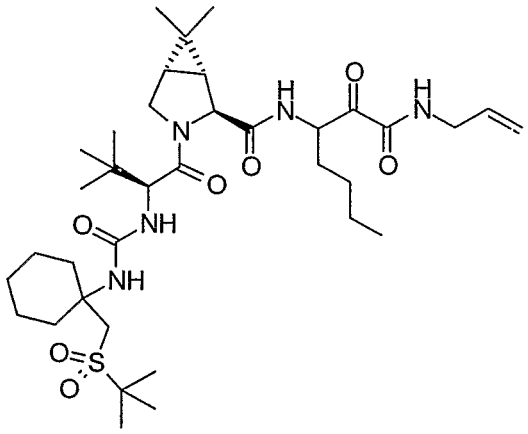
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
264		FABMS; MH^+, 664.4.	A
265			A

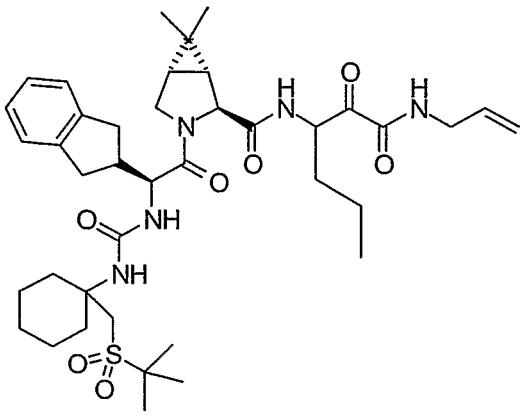
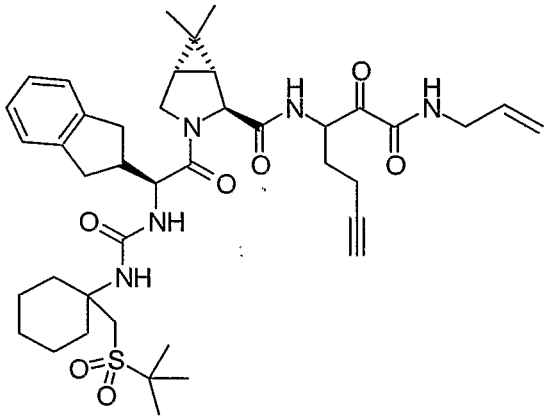
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
266		FABMS; MH^+, 664.2.	A
267			B

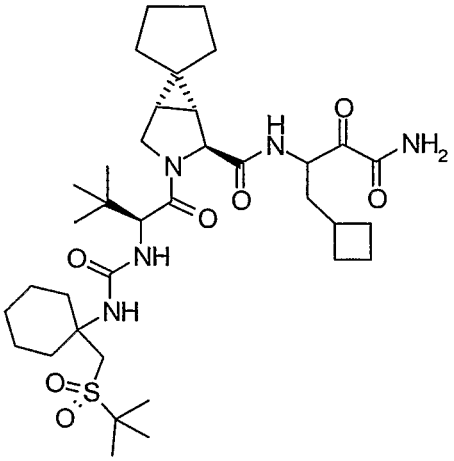
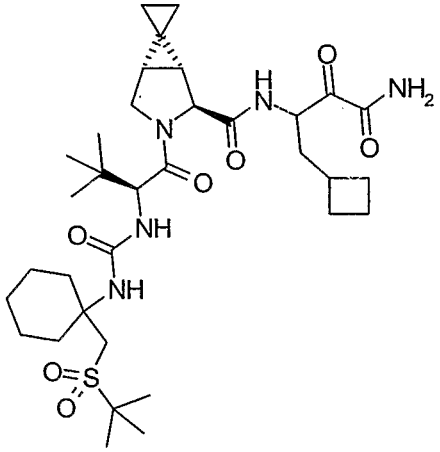
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
268			B
269			A

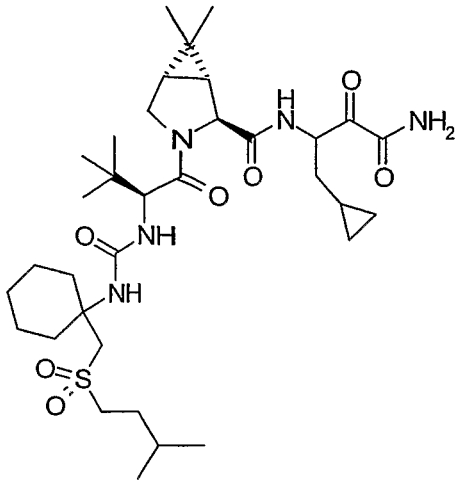
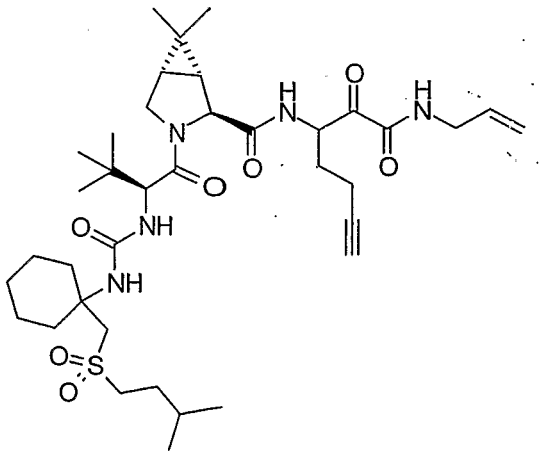
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
270			A
271			A

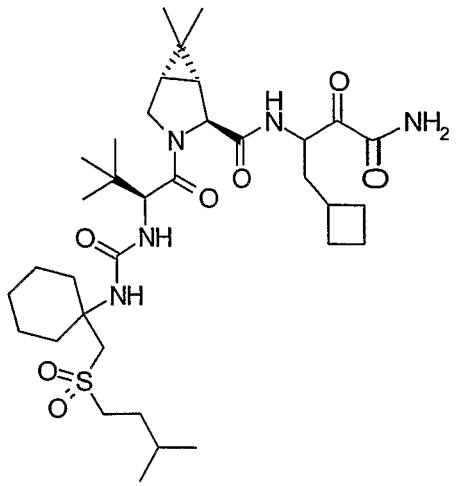
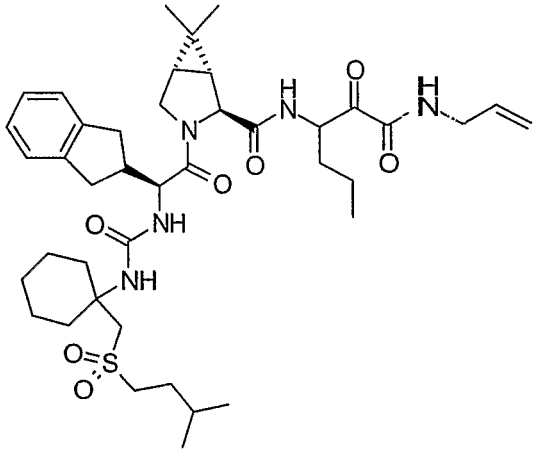
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
272		FABMS; MH^+, 702.3.	A
273		FABMS; MH^+, 720.5.	A

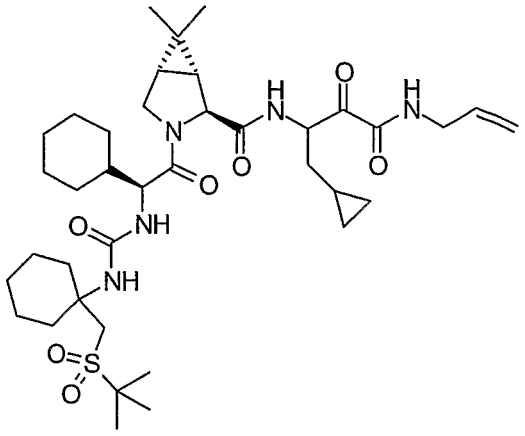
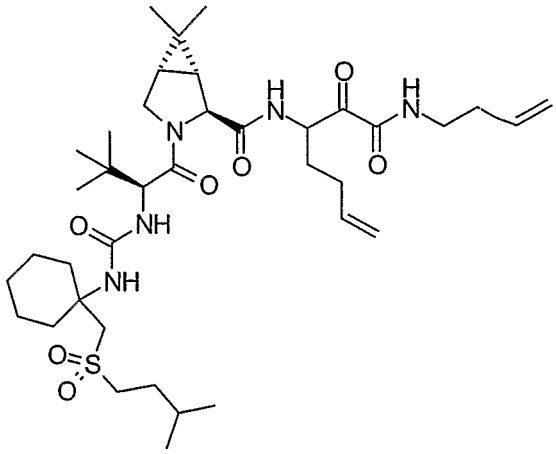
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
274			A
275			A

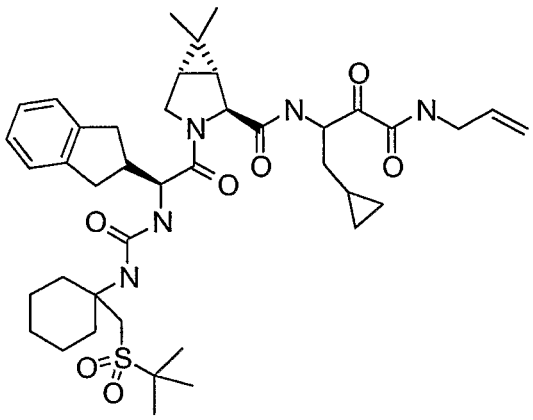
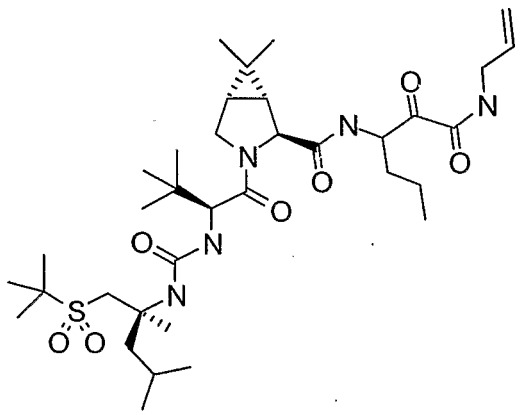
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
276			A
277		FABMS; MH^+, 764.8.	A

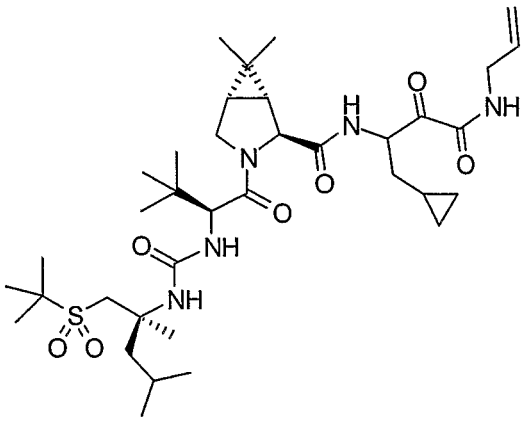
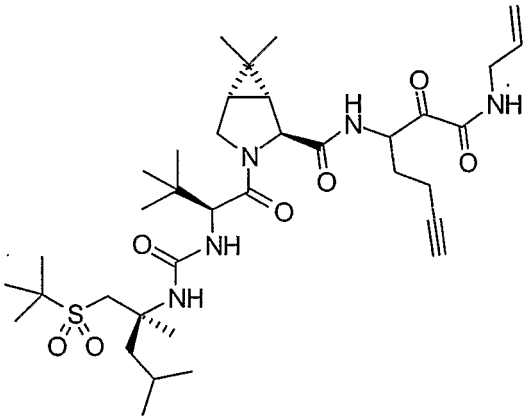
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
278		LCMS; MH^+, 706.2.	A
279		FABMS; MH^+, 678.2.	A

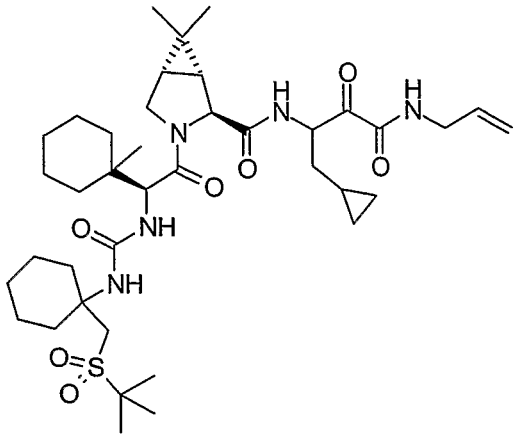
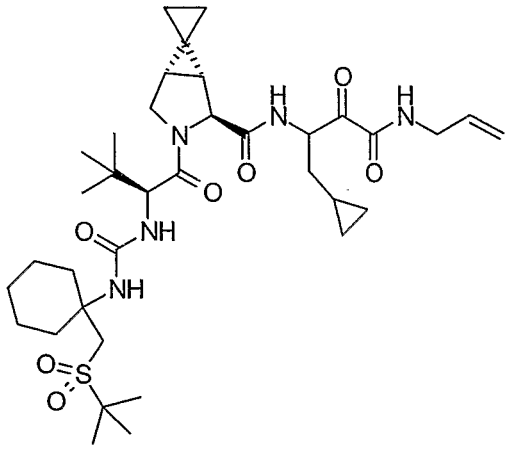
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
280			A
281			A

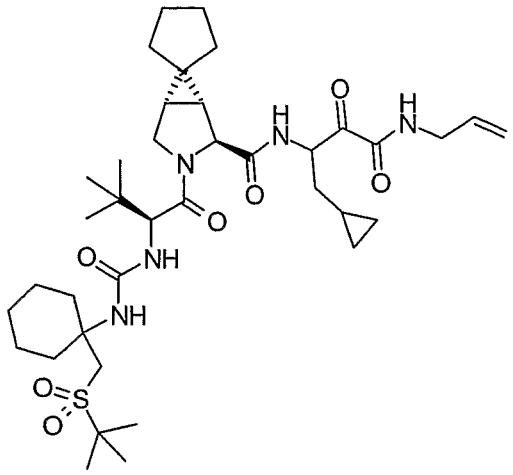
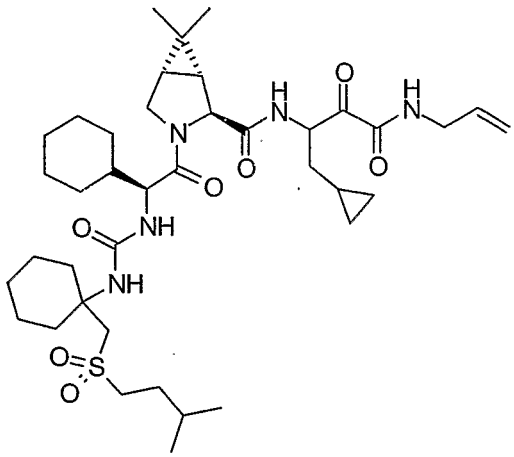
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
282			A
283			A

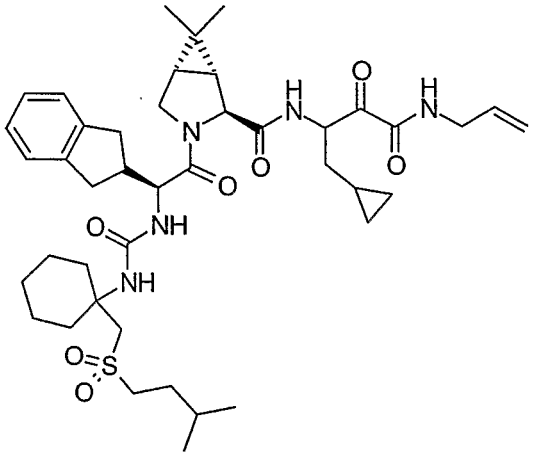
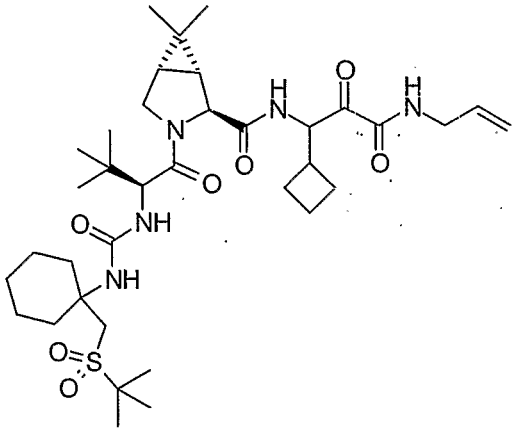
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
284			A
285			A

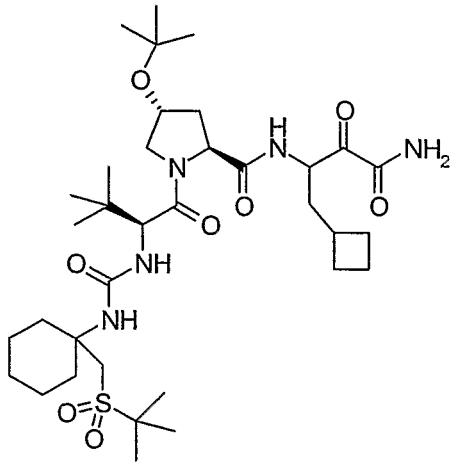
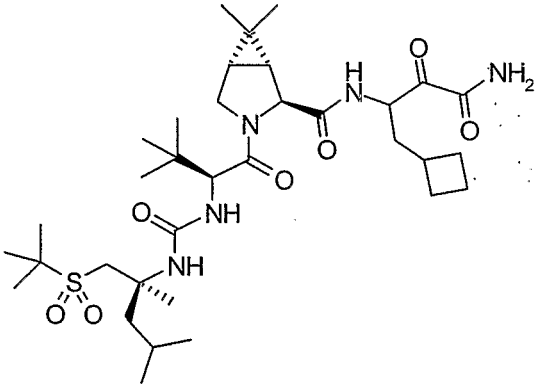
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
286		LCMS; MH^+, 766.2.	A
287			C

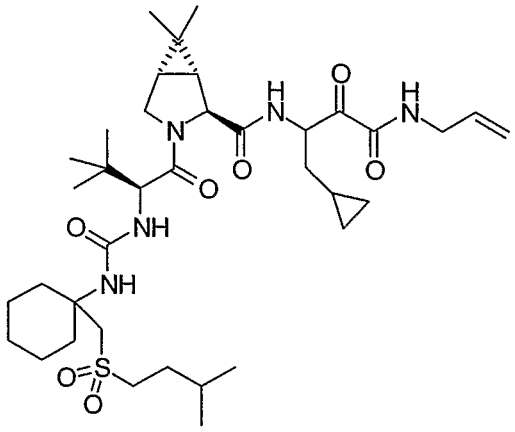
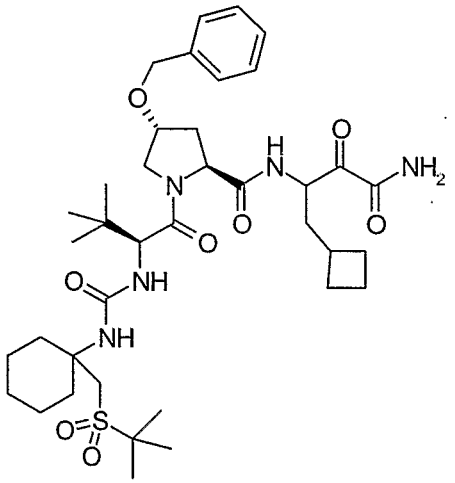
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
288			C
289			B

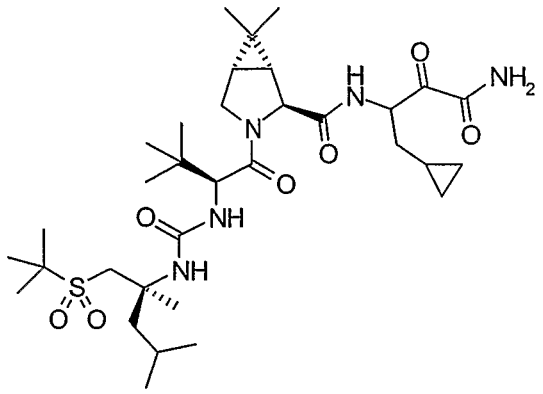
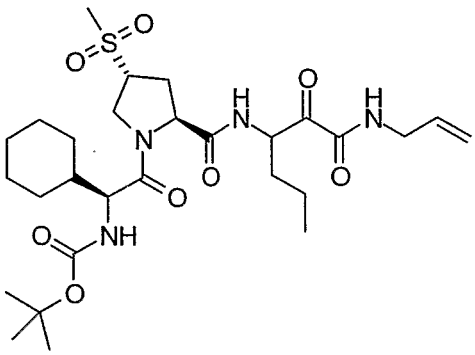
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
290			A
291			A

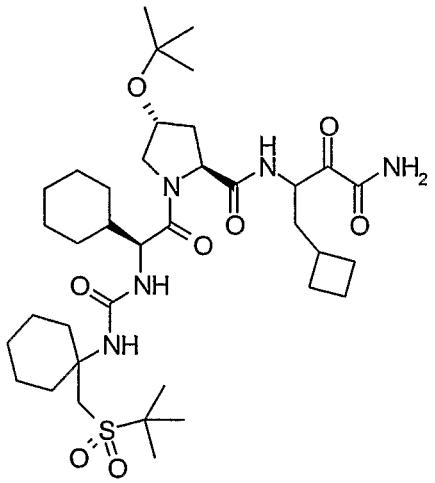
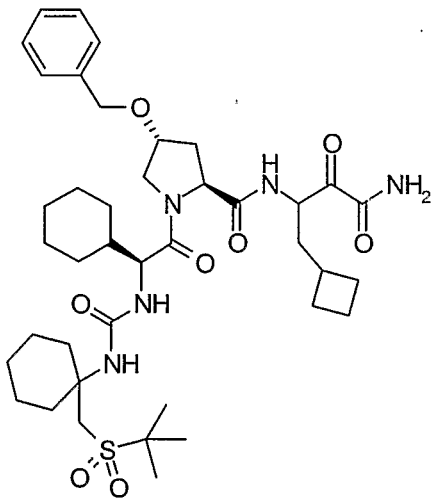
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
292			A
293			A

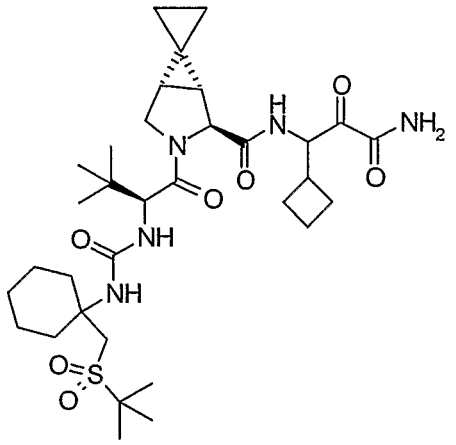
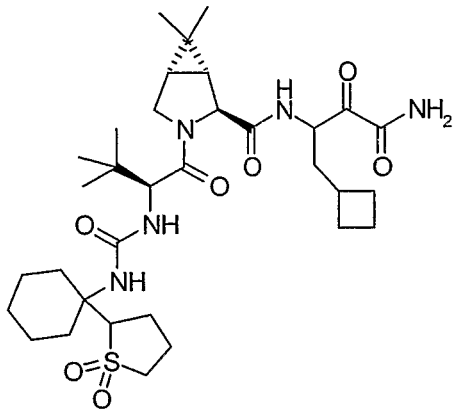
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
294			A
295			B

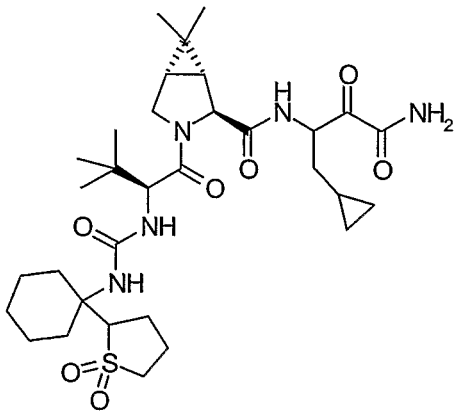
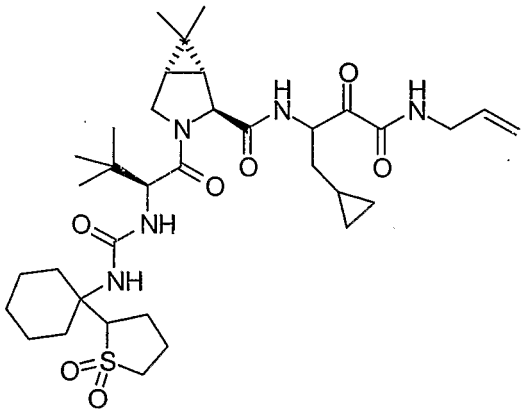
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
296		LCMS; MH^+, 712.3.	A
297			A

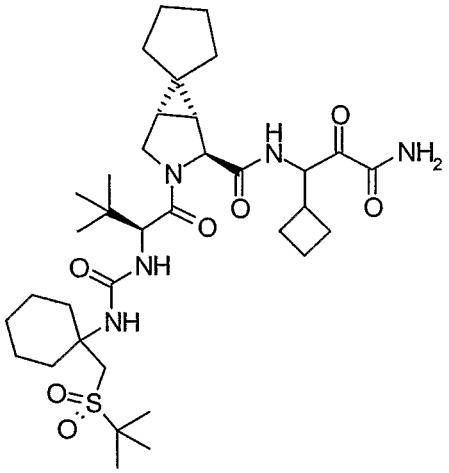
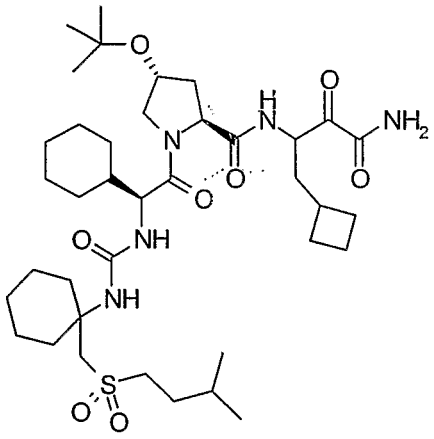
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
298			A
299		LCMS; MH^+, 746.2.	A

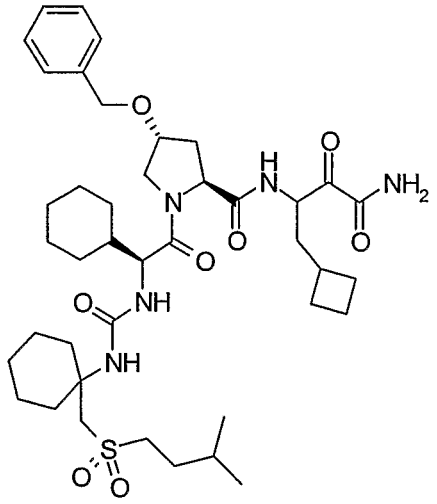
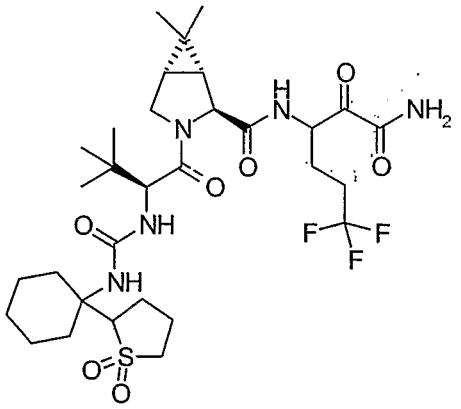
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
300			B
301			A

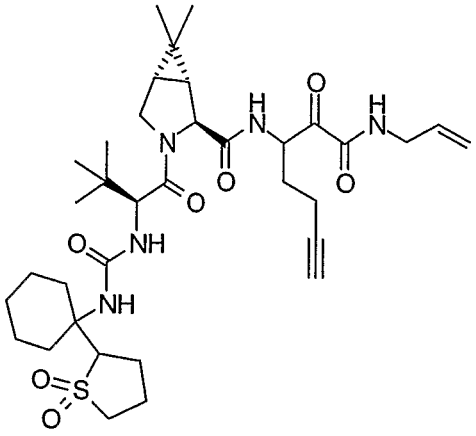
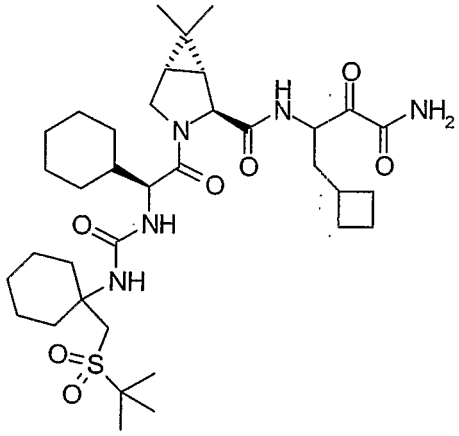
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
302			A
303			B

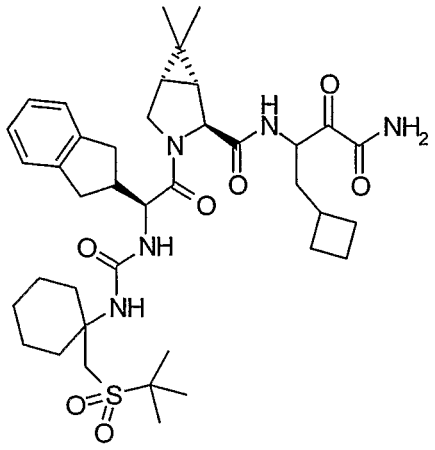
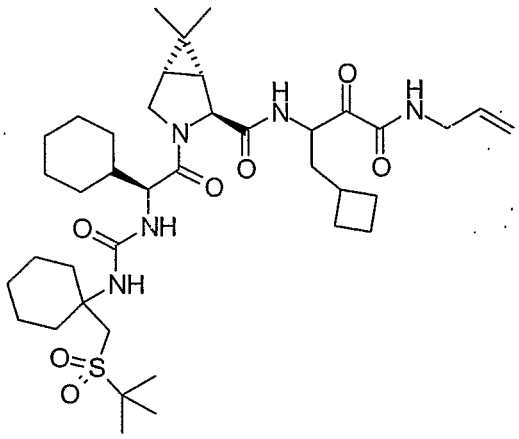
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
304		LCMS; MH^+, 664.1.	C
305			B

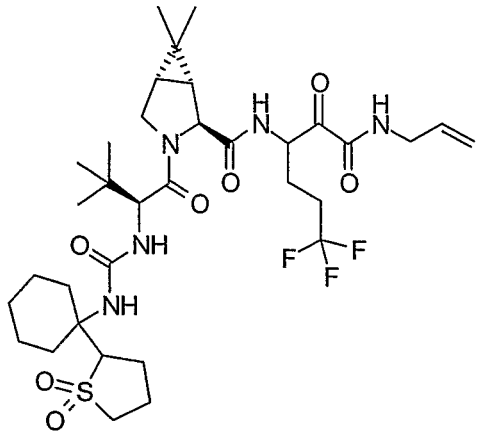
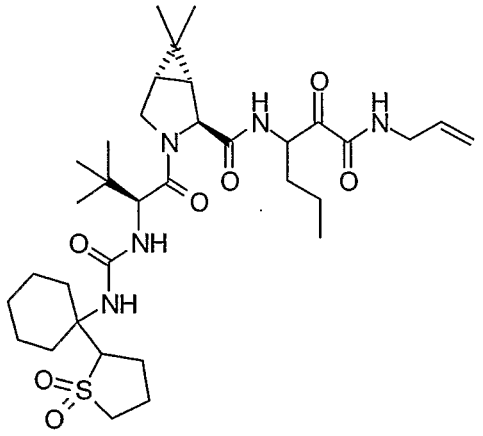
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
306			A
307			A

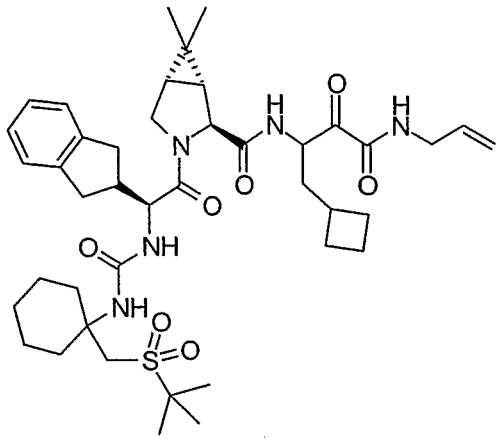
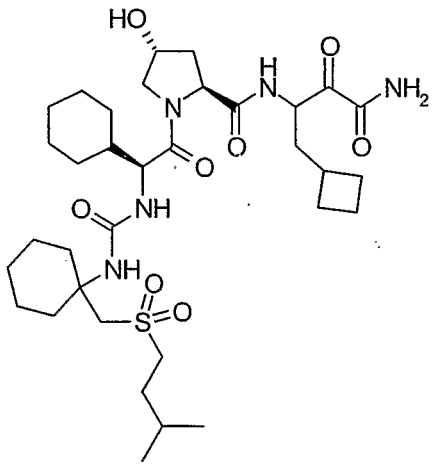
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
308		LCMS; MH^+, 692.1.	A
309			A

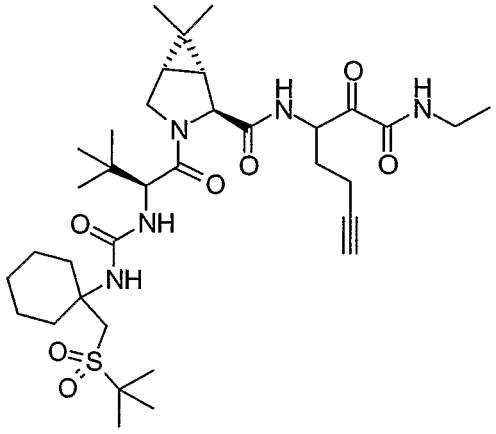
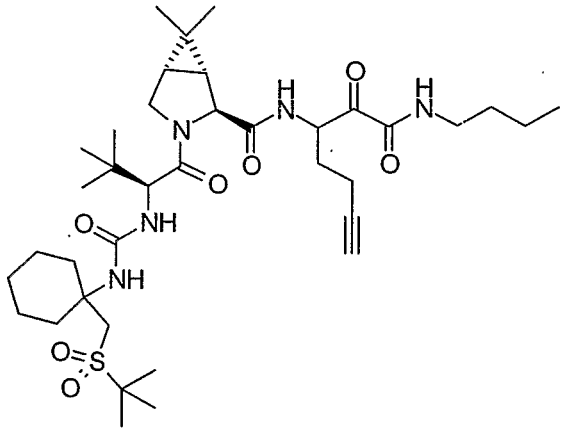
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
310			A
311			A

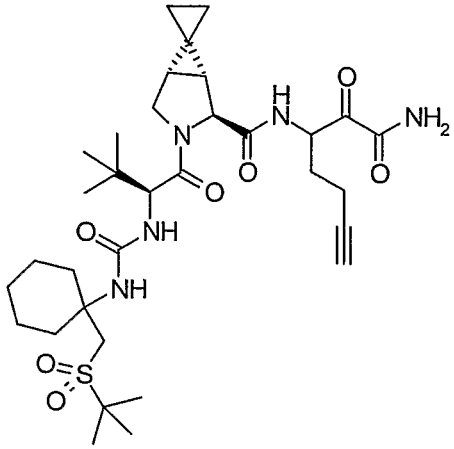
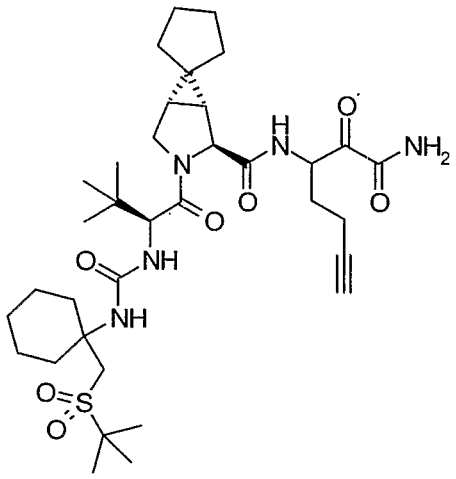
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
312			A
313			A

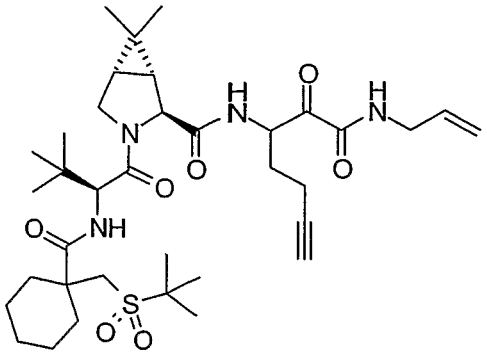
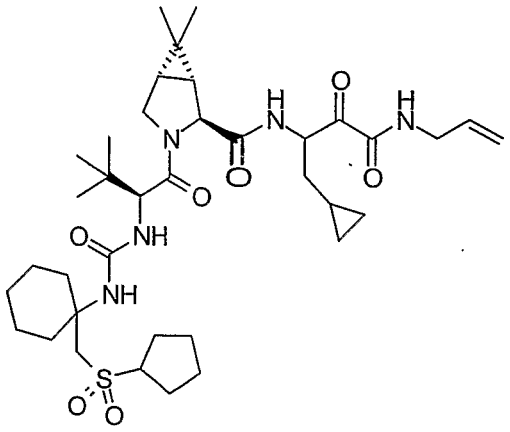
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
314			A
315			A

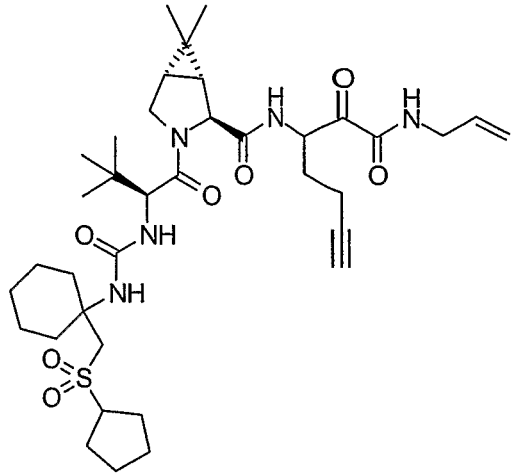
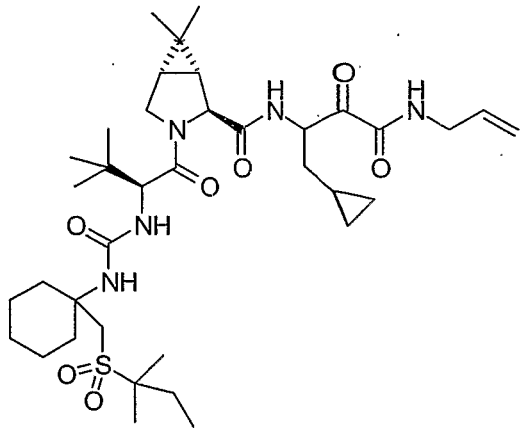
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
316			A
317			A

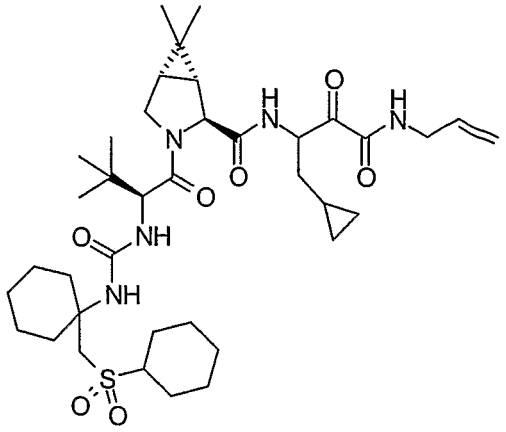
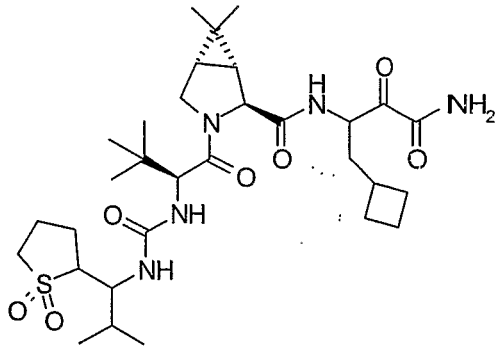
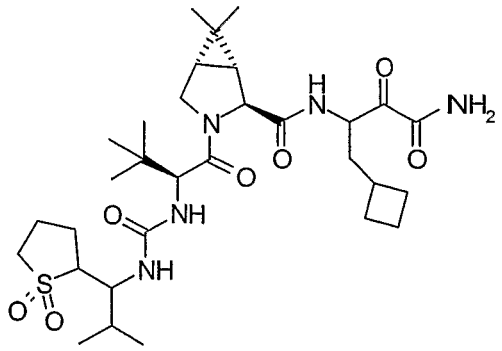
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
318			A
319			A

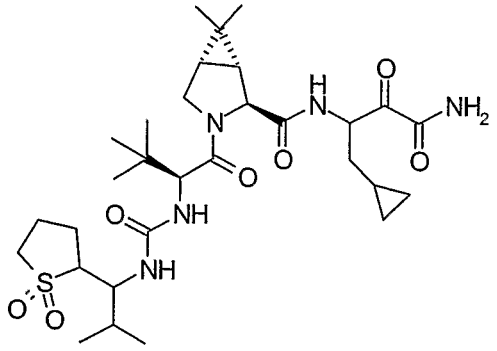
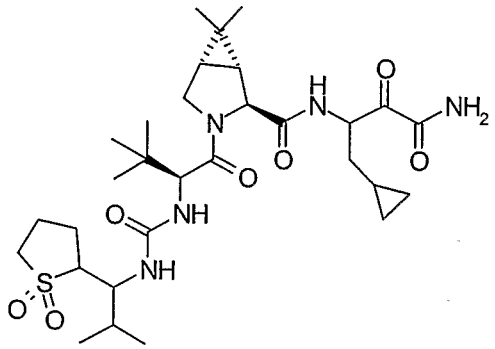
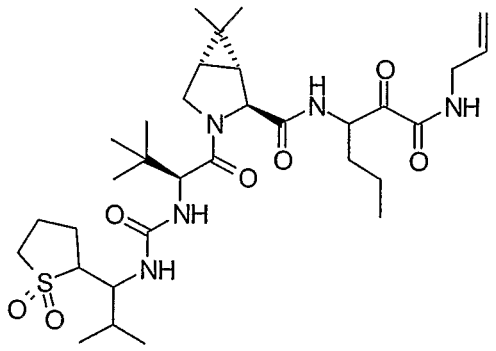
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
320		692.3LC MS; MH^+, 692.2.	A
321		LCMS; MH^+, 720.2.	B

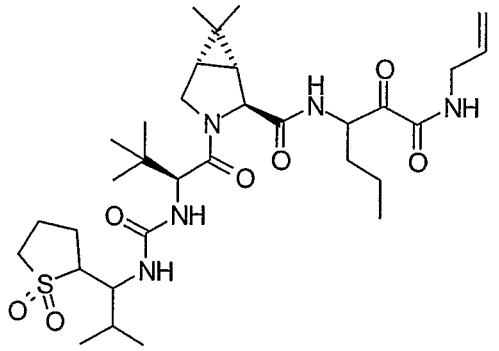
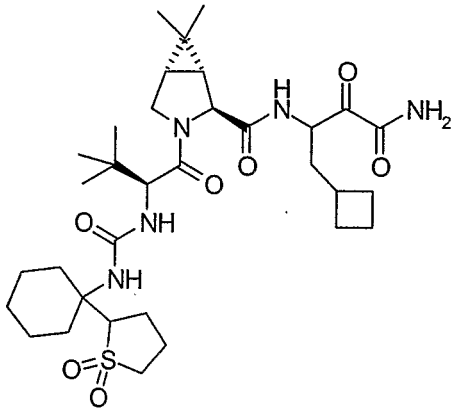
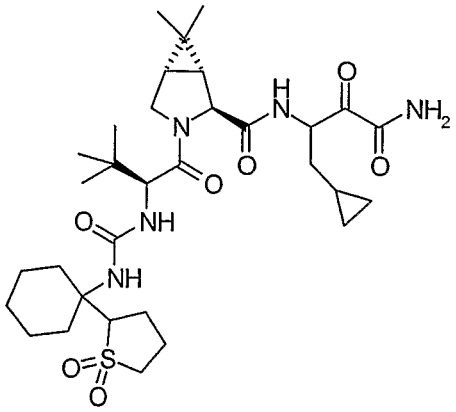
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
322			B
323			A

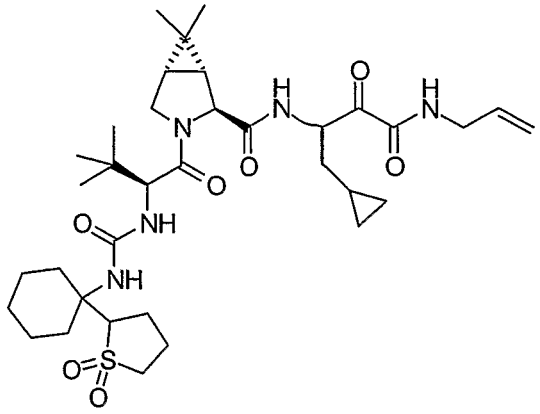
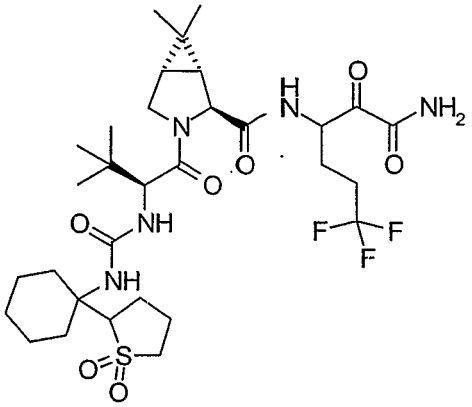
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
324			A
325			A

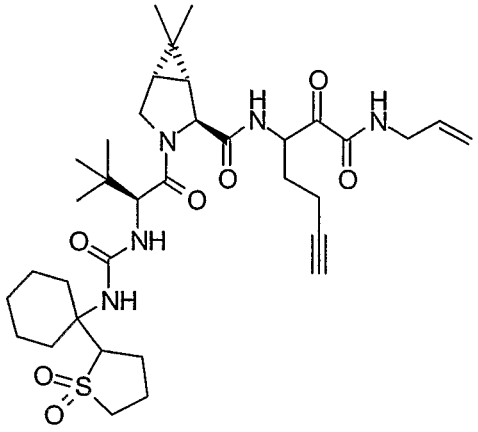
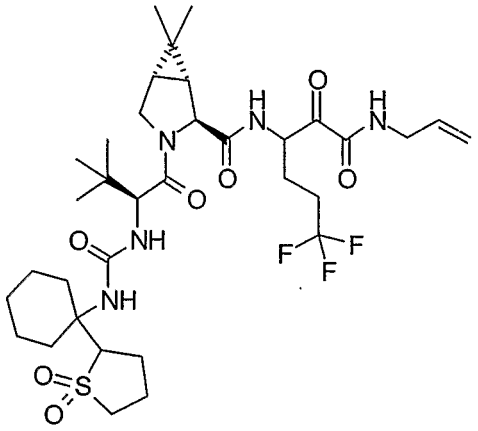
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
326			A
327		LCMS; MH^+, 720.2.	C

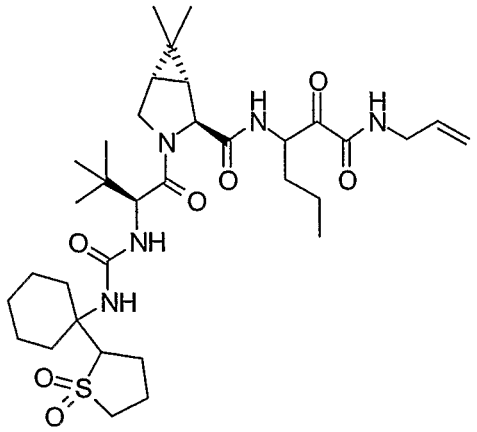
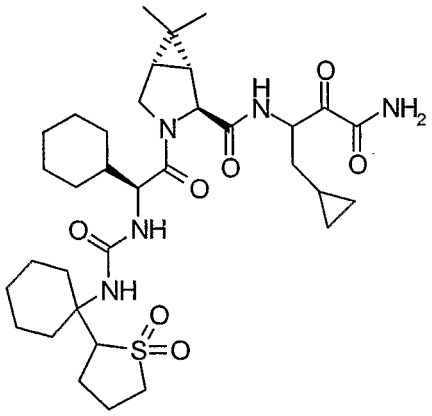
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
328			NA
329			A
330			C

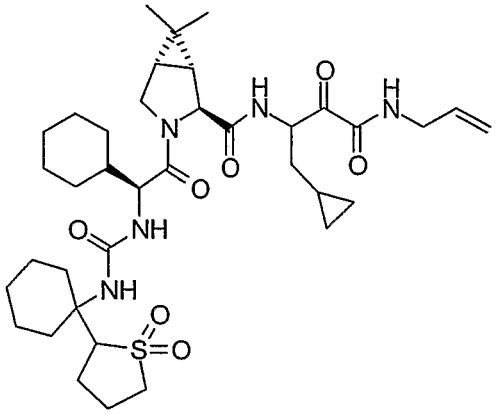
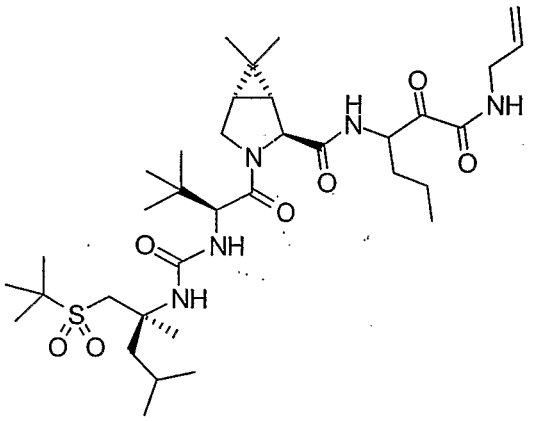
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
331			A
332			C
333			C

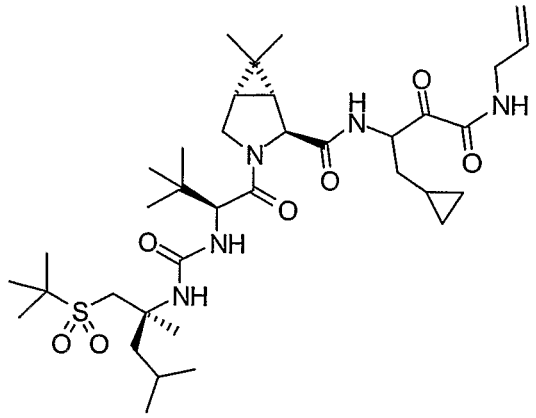
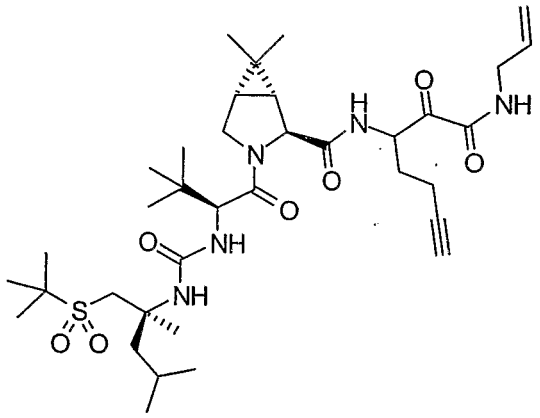
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
334			A
335			A
336			A

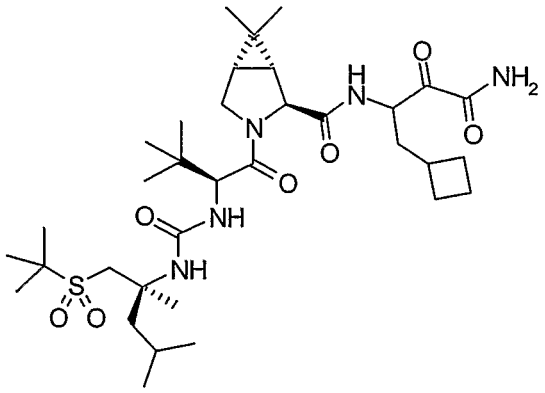
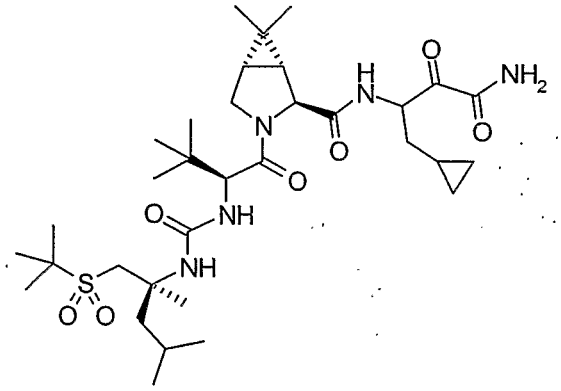
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
337			A
338			A

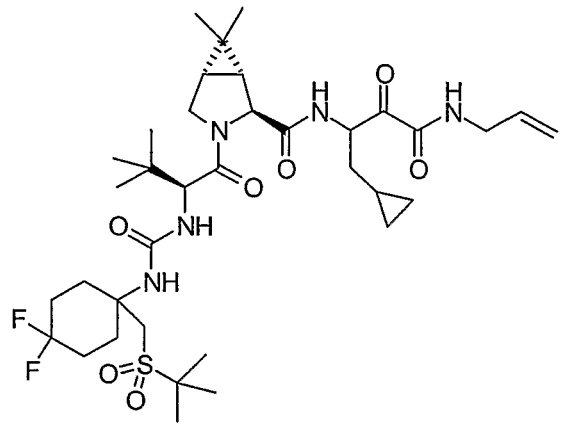
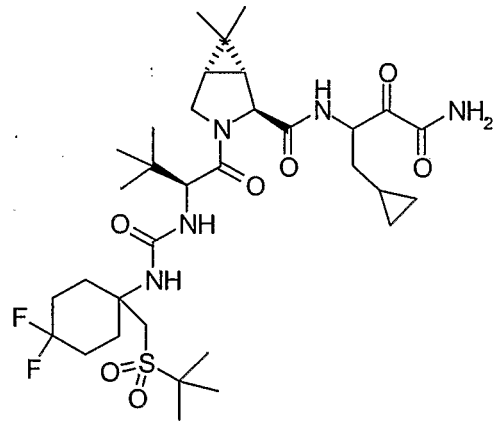
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
339			A
340			A

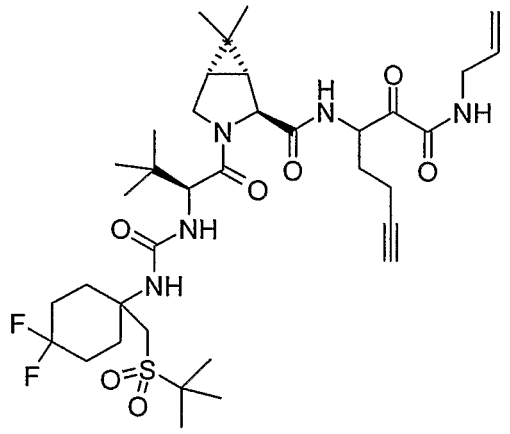
Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
341			A
342			A

Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
343			A
344			C

Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
345			C
346			B

Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
347			B
348			B

Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
349			A
350			A

Prep. Ex.	COMPOUND	Select Mass Spectral Data	Ki* range
351			A

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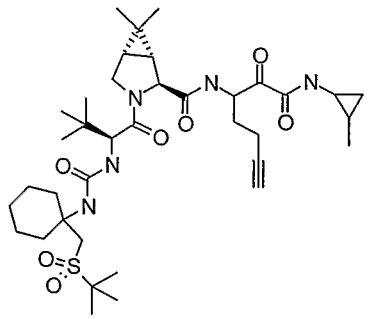
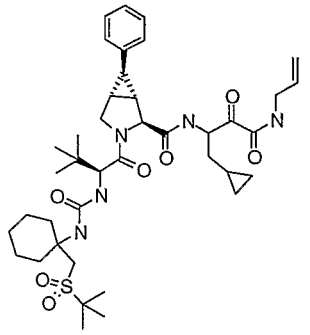
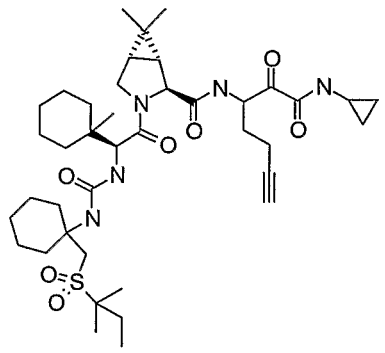
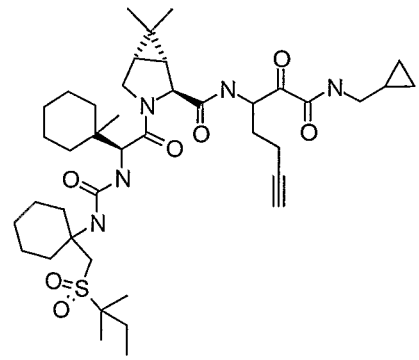
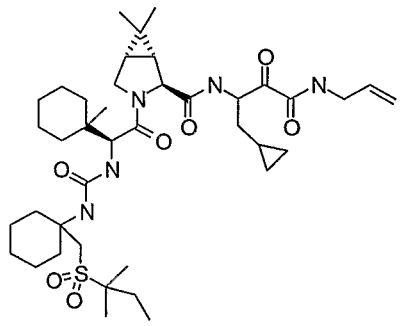
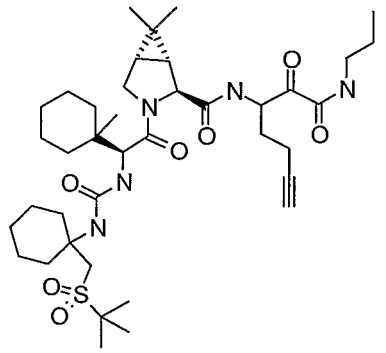
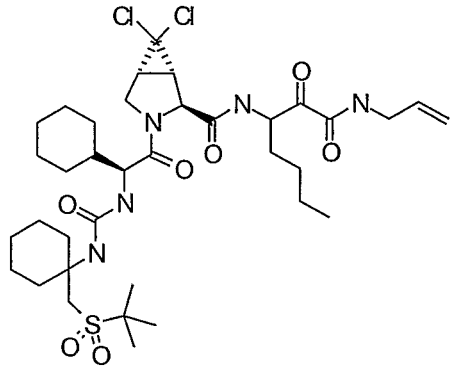
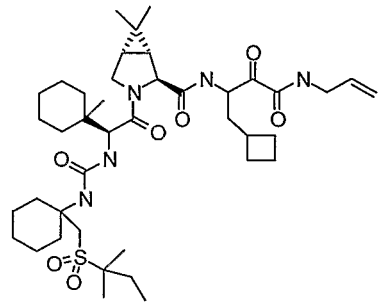
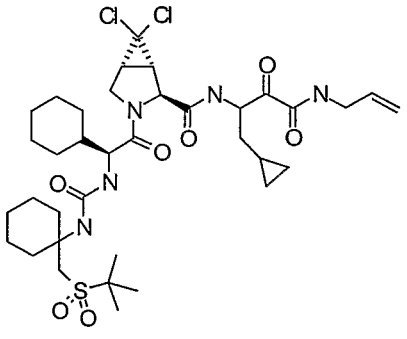
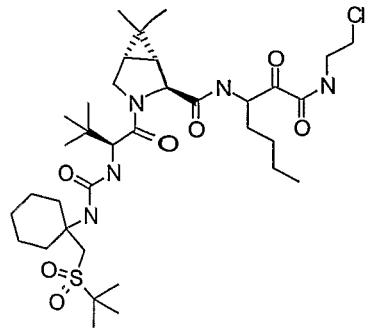
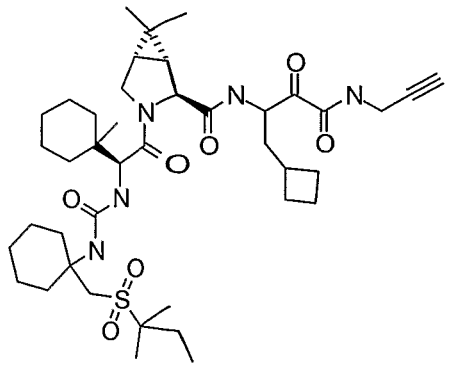
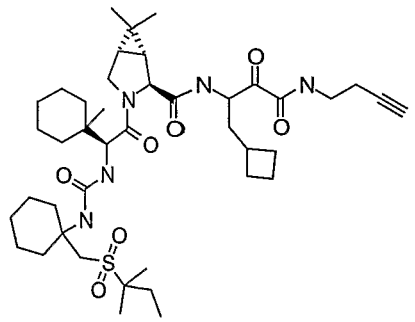
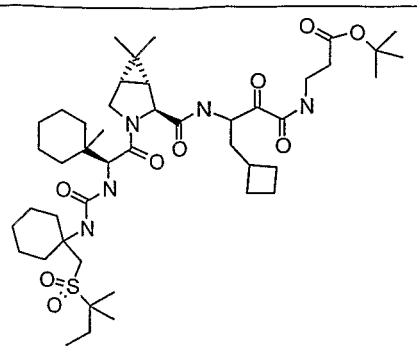
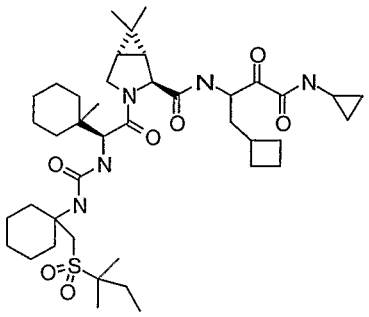
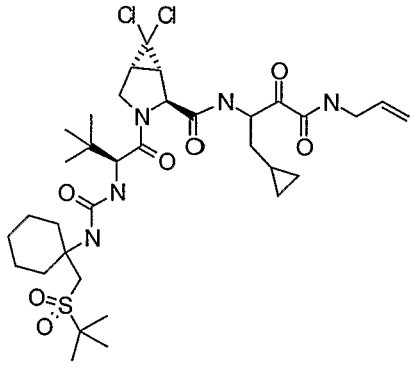
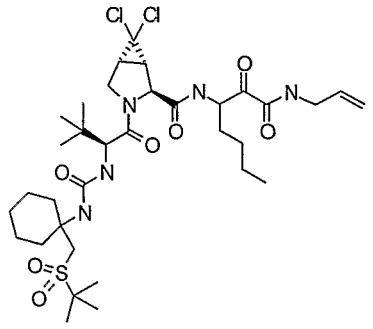
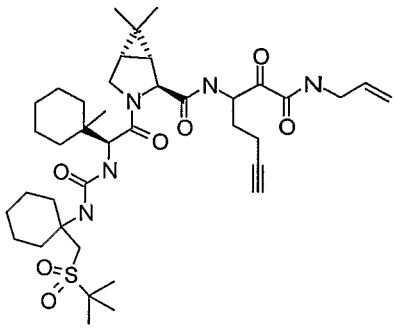
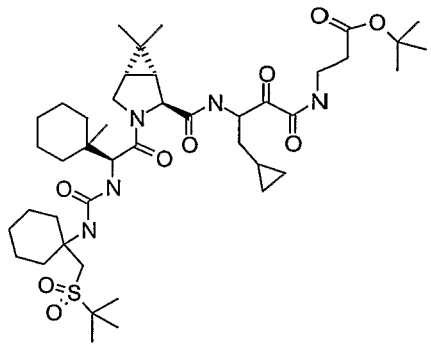
	18	717.9761
	C	754.0095
	7	758.0414

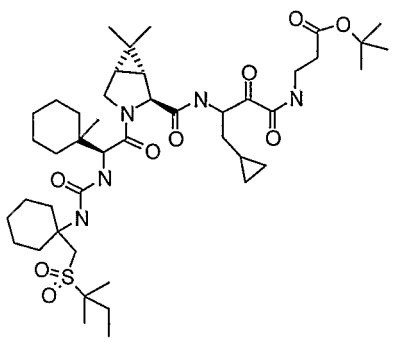
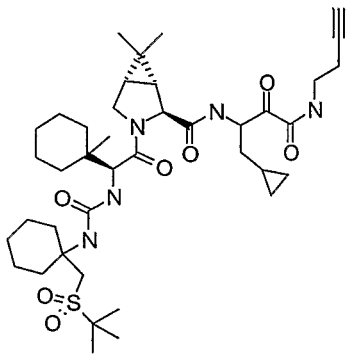
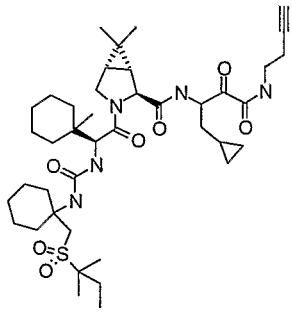
	10	772.0685
	14	760.0574
	4	746.0303

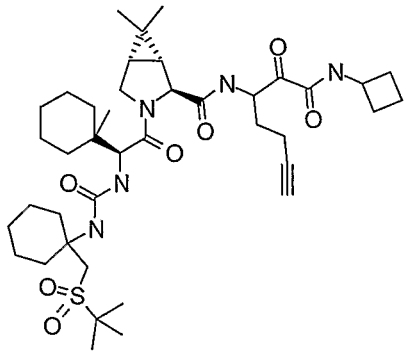
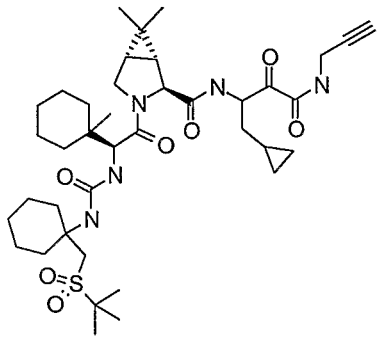
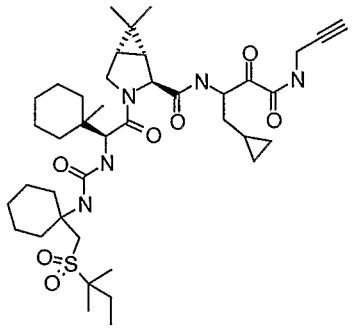
	5	774.855
	37	774.0844
	18	772.8391

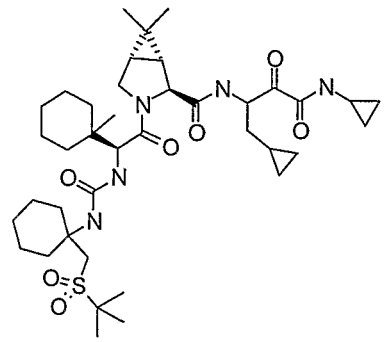
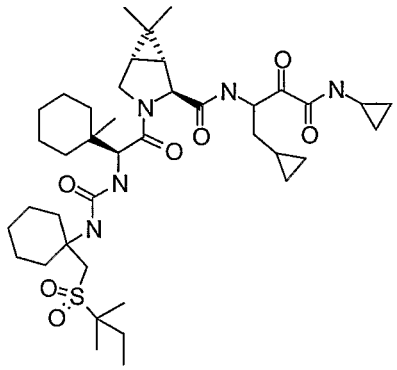
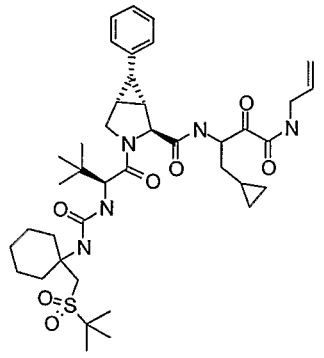
	27	730.4148
	34	772.0685
	48	786.0956

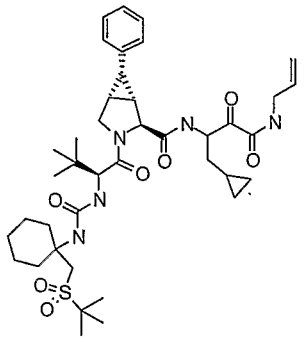
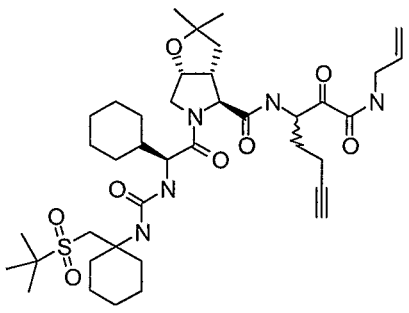
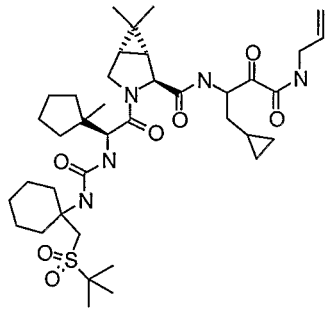
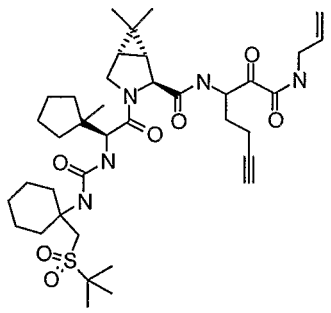
	52	862.1916
	54	774.0844
	9	746.8008

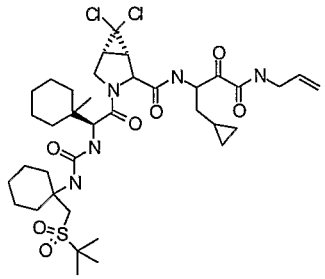
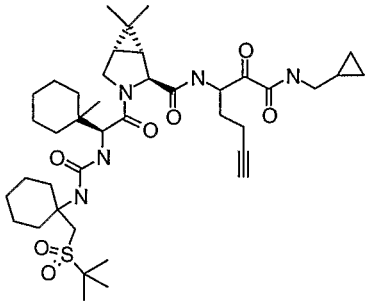
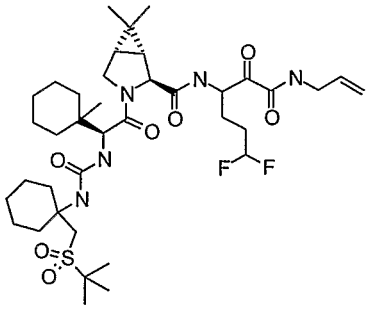
	8	748.8168
	5	744.0143
	17	834.1374

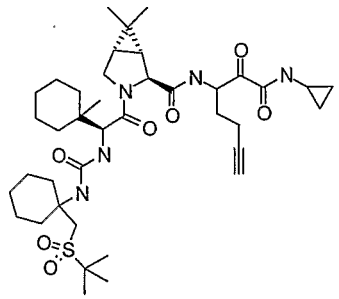
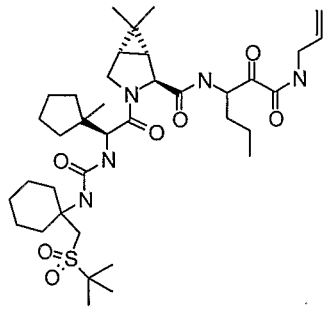
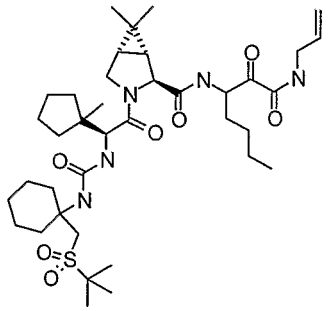
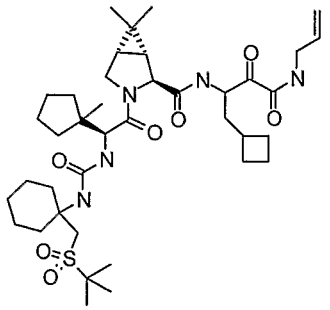
	19	848.1645
	17	758.0414
	20	772.0685

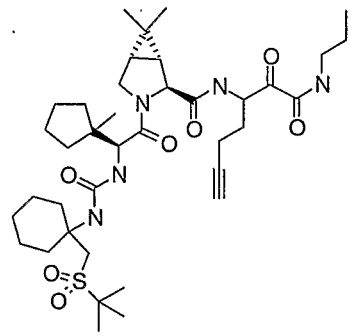
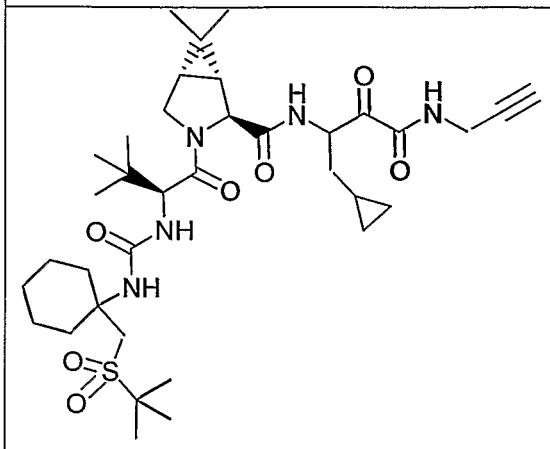
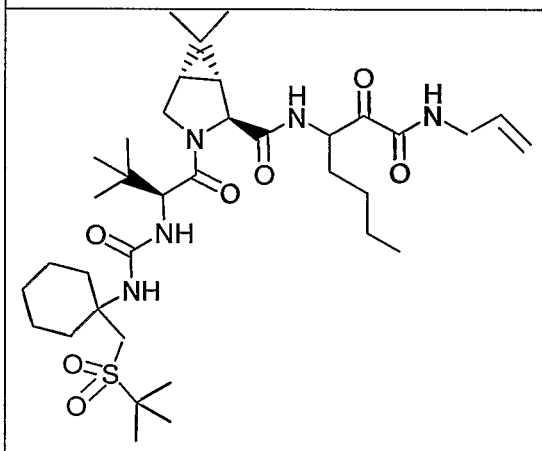
	10	758.0414
	8	744.0143
	17	758.0414

	12	746.0303
	13	760.0574
	C	754.0095

	C	754.0095
	23	760.0137
	12	732.0032
	2.4	729.9872

	B	786.8661
	4	758.0414
	6	770

	6	744.0143
	22	719.992
	22	734.0191
	34	746.0303

	13	732.0032
		
		

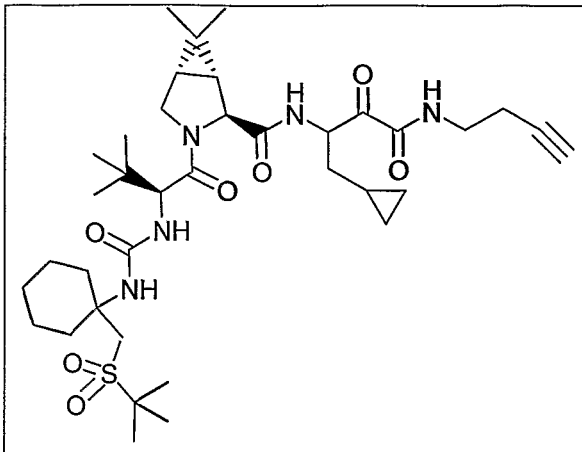
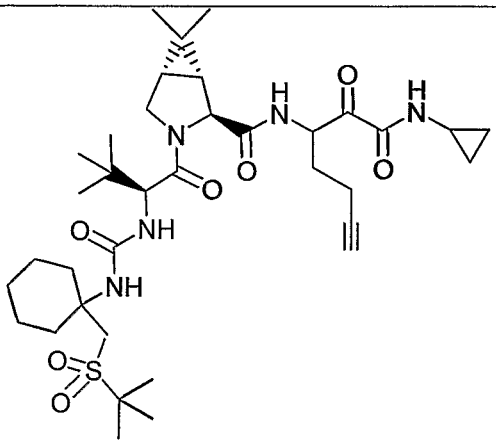
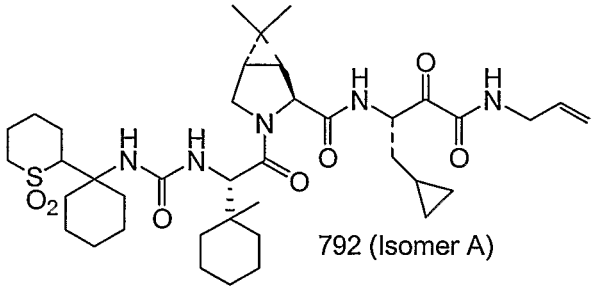
		
		

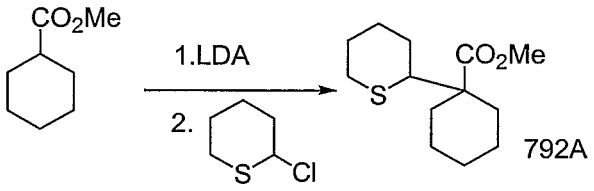
Table 3A lists additional compounds made in accordance with this invention. The following experimental procedures describe the preparation of the compounds shown in **Table 3A** which follows the experimentals.

Example 792



792 (Isomer A)

Step1



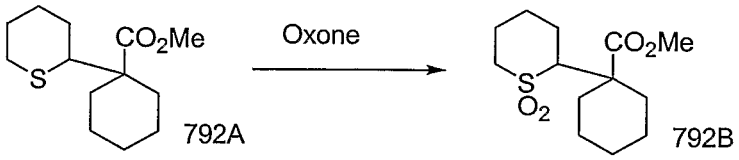
792A

To a solution of pentamethylene sulfide (10.09g) in dry benzene (120ml)was added, portionwise (over a period of 40 min.) , N-chlorosuccinimide (13.02g) while maintaining the internal temperature below 9^0C. The resulting reaction mixture was stirred below 15^0C for 45 min. The precipitate was filtered and the supernatant was concentrated under reduced pressure. The residue was diluted with cold hexane, filtered and the supernatant concentrated under reduced pressure to provide the chloride as a yellow oil (11.88g).

To diisopropylamine (12.5ml) in anhydrous THF (15ml) was added n-BuLi (53ml of a 1.6M solution in hexanes) at -78^0C, under an atmosphere of nitrogen, and the resulting mixture was maintained at this temperature for a period of 15 min., before the addition of methyl cyclohexanecarboxylic acid (12.47ml) and the reaction was maintained at -78^0C for a further 40 min. The chloride in anhydrous THF (50ml) was added to the reaction mixture and the flask was removed from the cooling bath and allowed to warm slowly to room temperature. The reaction was quenched with 5% aq. KH_2PO_4 (100ml) containing conc. aq. HCl (2.7ml). The organics were extracted into

Et_2O/EtOAc, dried ($MgSO_4$) and concentrated under reduced pressure to yield a residue which was purified by silica gel column chromatography using 0-2% EtOAc in hexanes as eluent. Gave the bicycle (792A; 8.12g) as a yellow oil.

Step 2

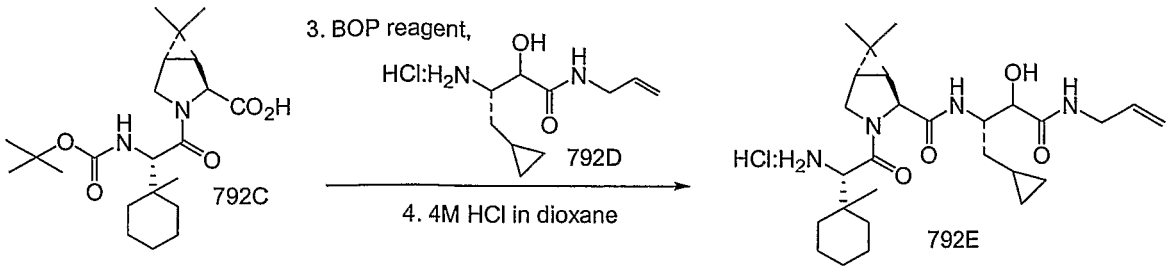


792A 792B

A solution of the sulfide (792A; 0.780g) in 50% aq. MeOH (8ml) was cooled to 0^0C and added to a cooled (0^0C) suspension of oxone (5.97g) in 50% aq. MeOH (8ml) and the reaction was allowed to warm to room temperature overnight before partitioning between methylene chloride and water. The aqueous layer was further extracted with methylene chloride and the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using (25-35%) EtOAc in hexanes to give the sulfone (792B; 0.1598g) . The reaction was repeated using the sulfide (792A; 8.12g), oxone (62.06g), methanol (30ml), water (30ml) to give the sulfone (792B; 4.73g).

The racemic mixture (792B; 0.4925g) was further purified by chiral HPLC using a preparatory Chiralpak AS column using 40% i-PrOH in hexanes (45ml/min; monitored at 218nm. Gave (792B-enantiomer A; 0.247g; retention time 37 min.) followed by (792B-enantiomer B; 0.249g; retention time 63min).

Steps 3 and 4:



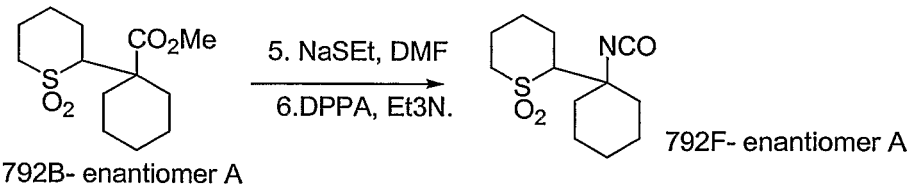
Step 3

To a solution of the carboxylic acid (792C; 0.172g) and the hydrochloride salt (792D) in dichloromethane (5ml) was added BOP reagent (0.246g) followed by triethylamine (0.232ml) and the resulting reaction mixture was stirred overnight at room temperature. The reaction mixture was partitioned between EtOAc and 10% aq. HCl. The organic phase was separated, washed with sat. aq. $NaHCO_3$, water, dried ($MgSO_4$) and the volatiles were removed under reduced pressure to yield a residue which was used in step 4 without purification.

Step 4

To the residue from step 3 was added 4M HCl in dioxane (10ml) and the solution was allowed to stand at room temperature for a period of 2h. The volatiles were removed under reduced pressure to yield the hydrochloride salt (792E), used without purification.

Steps 5 and 6



792B- enantiomer A

792F- enantiomer A

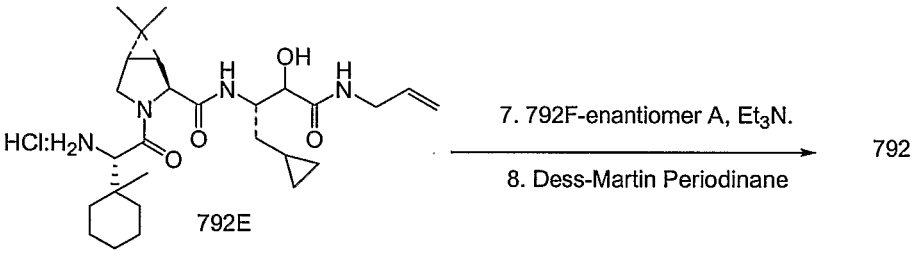
Step 5

To a solution of the methyl ester (792B-enantiomer A; 0.100g) was dissolved in anhydrous DMF (1ml) and sodium ethanethiolate (0.122g) was added and the reaction mixture was allowed to stir at room temperature for approx 72h. The reaction was partitioned between EtOAc and 10% aq. HCl. The organic phase was separated, washed with water (X4), dried ($MgSO_4$) and the volatiles were removed under reduced pressure.

Step 6

To the residue from step 5 was dissolved in anhydrous toluene (2ml) and DPPA (0.083ml) and Et_3N (0.054ml) were added and the reaction was heated to 120^{0}C, under an atmosphere of nitrogen for 1h. After cooling, the reaction was partitioned between EtOAc and sat. aq. $NaHCO_3$. The organic phase was separated, dried ($MgSO_4$) and the volatiles were removed under reduced pressure to provide the isocyanate (792F-enantiomer A), used without purification.

Steps 7 and 8



Step 7

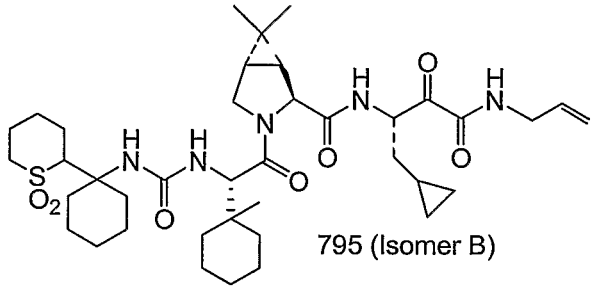
To the hydrochloride salt (792E; 0.050g) in dichloromethane (3ml) was added triethylamine (0.100ml) followed by the isocyanate (792F; approx. 0.040g) in toluene (1ml) and the reaction mixture was stirred at room temperature overnight. The reaction mixture was partitioned between EtOAc and 10% aq. HCl. The organic phase was separated, washed with sat. aq. sodium bicarbonate, water, dried ($MgSO_4$). The volatiles were removed under

reduced pressure to yield a residue which was usedwithout purification in step 8.

Step 8

The residue from step 7 was dissolved in dichloromethane (3ml) and Dess-Martin peridinane (0.100g) was added and the reaction was stirred at room temperature for 1h. The reaction was partitioned between EtOAc and 10% aq. sodium thiosulfate. The organic phase was separated, washed with sat. aq. sodium bicarbonate, dried ($MgSO_4$) and the volatiles removed under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc-hexanes (1:1) as eluent to give the keto-amide (792; 0.0436g) as a white solid.

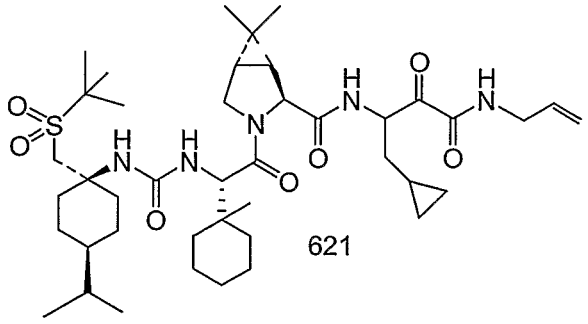
Example 795



795 (Isomer B)

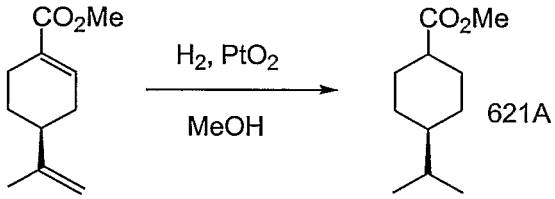
Using the procedures described for the preparation of 792, 792B-enantiomer B was transformed into the corresponding isocyanate as described in steps 5 and 6. Further by utilizing 792E and steps 7 and 8 and the isocyanate derived from 792B-enantiomer B, 795 was produced.

Example 621:



621

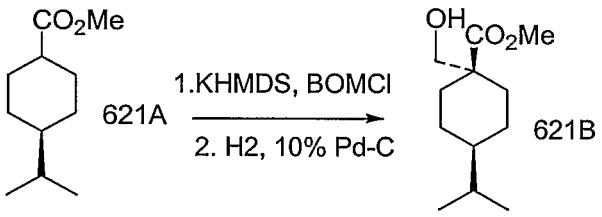
Steps 1



621A

To Methyl Perillate (3g) in methanol (20ml) was added PtO_2 (0.3g) and the resulting suspension was placed under anatmosphere of hydrogen (balloon) overnight. The suspension was filtered through a pad of celite and the solid was washed thoroughly with methanol. The filtrate was concentrated under reduced pressure to yield the cyclohexane (621A; 2.93g), a mixture of diastereomers, as a colorless oil.

Steps 2 and 3



621B

Step 2

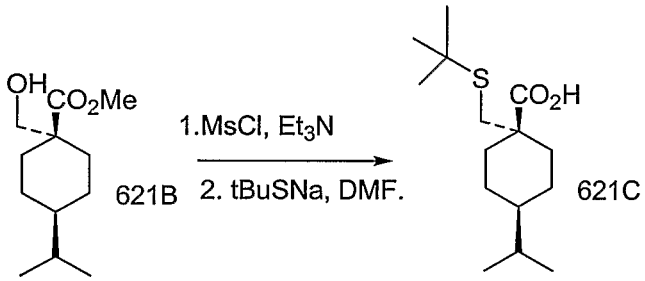
The carboxylic esters (621A;3.75g) were dissolved in anhydrous diethyl ether (50ml) and cooled to -78^{0}C, under an atmosphere of nitrogen. KHMDS (69ml of a 0.5M solution in toluene) was added dropwise and the resulting mixture was stirred for a further 15 min., before the addition of BOMCl (1.7eq.) and the reaction flask was removed from the cooling vessel and allowed to

warm slowly to room temperature. Water (approx. 10ml) was added and the mixture was partitioned between EtOAc and 10% aq. HCl. The organic phase was separated, washed with sat. aq. sodium bicarbonate, water, dried ($MgSO_4$), and the volatiles removed under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc:Hexanes (1:20) as eluent, providing the intermediate benzyl ether (3.01g), a colorless oil.

Step 3

To the benzyl ether from step 2 (2g) was added methanol (10ml) followed by 10% Pd-C (1g) and the black suspension was placed under an atmosphere of hydrogen (balloon) overnight. The reaction was filtered through a pad of celite and the solid was washed thoroughly with methanol. The filtrate was concentrated to provide the desired alcohol (621B;1.362g) as a colorless oil.

Steps 4 and 5



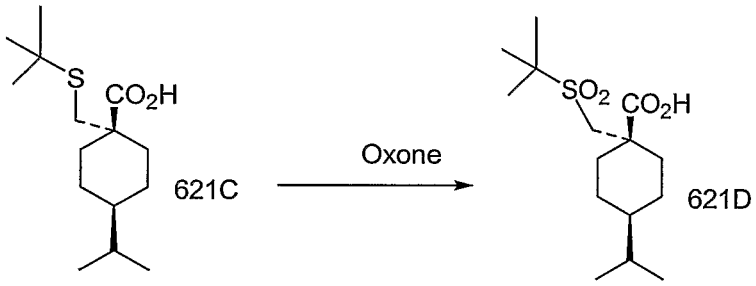
Step 4

The alcohol (621B; 0.32g) was dissolved in dichloromethane (5ml) and methane sulfonyl chloride (0.166ml) followed by triethylamine (0.37ml) were added and the resulting reaction was stirred for 0.5h before partitioning between EtOAc and 10% aq. HCl. The organic phase was separated washed with sat. aq. sodium bicarbonate, water, dried (MgSO4) and the volatiles removed under reduced pressure to yield a residue which was used in step 5 without purification.

Step 5

The residue from step 4 was dissolved in DMF (10ml) and sodium tert-butyl thiolate was added and the resulting reaction mixture was stirred at room temperature under an atmosphere of nitrogen overnight. The reaction mixture was partitioned between EtOAc and aq. 10% HCl. The organic phase was separated, washed with water (X4), dried ($MgSO_4$) and the volatiles removed under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc-Hexanes (3:7) as eluent to give the carboxylic acid (621C;0.214g).

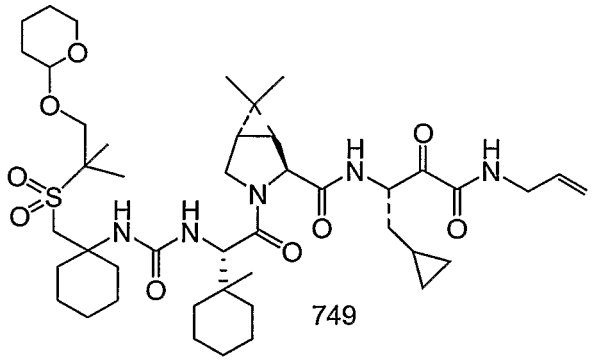
Step 6



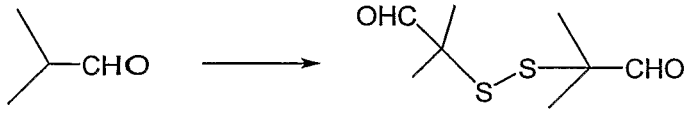
Using the sulfide (621C; 0.090g), oxone (0.61g), methanol (2ml), water (2ml) and the procedure set forth in example 792 (Step 2), the sulfone (621D; 0.091g) was obtained as a white solid.

As described above (Example 792; Steps 6 through 8), the sulfone-carboxylic acid was converted to compound 621.

Example 749:



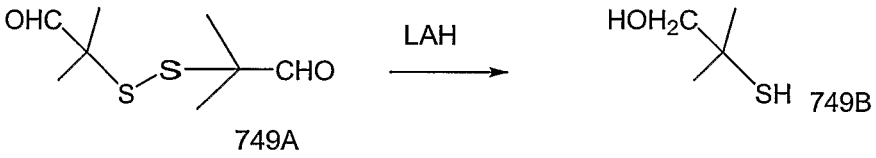
Step 1



749A

Procedure: To Isobutyraldehyde (59g, 0.69mol) in CCl4 was added sulfur monochloride (27.6mL, 0.345mol, 0.5eq.) dropwise at 50°C. After a short lag (10min), evolution of HCl gas began. After HCl evolution ceased, the mixture was stirred at 55°C for 2.5hrs, which TLC indicated the reaction almost completed. Then cooled to room temperature. Crude was concentrated it to dryness. The oily residue, the disulfide (749A), was used without purification.

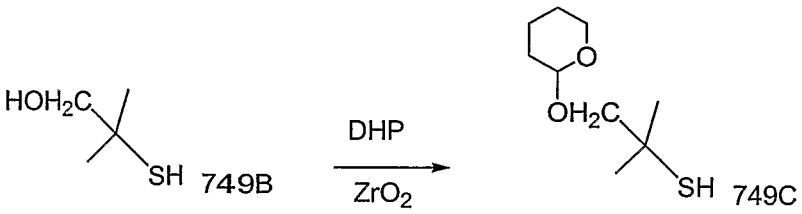
Step 2



749A 749B

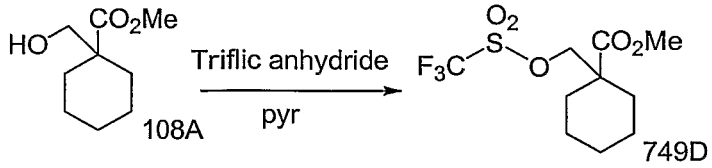
To the disulfide (749A; 7.5g, 36mmol) in THF was added $LiAlH_4$ (2.76g, 72.7mmol, 2eq.) at 0°C very slowly. The mixture was stirred at RT for 3hrs then Sat. Na2SO4 was added dropwise until white grey solid appeared. Stirred at RT for 10min. Diltued it with CH_2Cl_2. Dried over $MgSO_4$. Filtered and concentrated to dryness. Purified it by HPFC with 2~20% EtOAc in hexane to give the alcohol (749B; 6.81g). Yield 89%.

Step 3



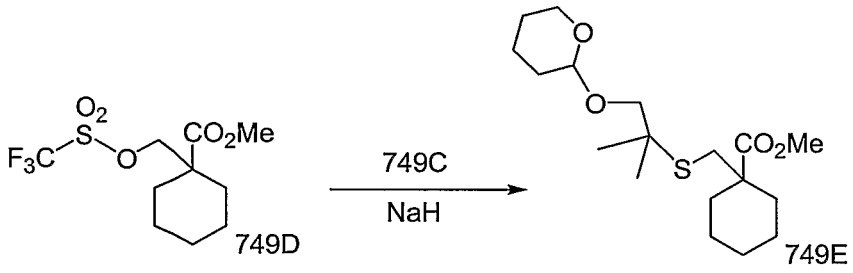
To the alcohol (749B; 10g, 94.2mmol) was added 3,4-dihydro-2H-pyran (8.8mL, 94.2mmol, 1equiv) and ZrO_2. (2.0g, 20% w/w). The mixture was stirred at 80°C for 2hrs. reaction was diluted it with CH_2Cl_2 and filtered. The filtrate was concentrated to dryness and purified by HPFC with 2~10% EtOAc in hexane to give 14.3g of product (749C). Yield 80%.

Step 4



To the alcohol (108A; 3.0g, 17.4mmol, 1equiv) in CH_2Cl_2 was added pyridine (2.4mL, 29.6mmol, 1.7equiv) and triflic anhydride (3.8mL, 22.6mmol, 1.3equiv) at -20°C. The reaction was stirred at -20~10°C for 2hr which MS and TLC indicated the reaction completed. Diluted it with EtOAc, Washed with sat. NH4Cl and brine. Dried over MgSO4. Concentrated it to dryness to give the sulfonate (749D; 5.21g). Yield 98%.

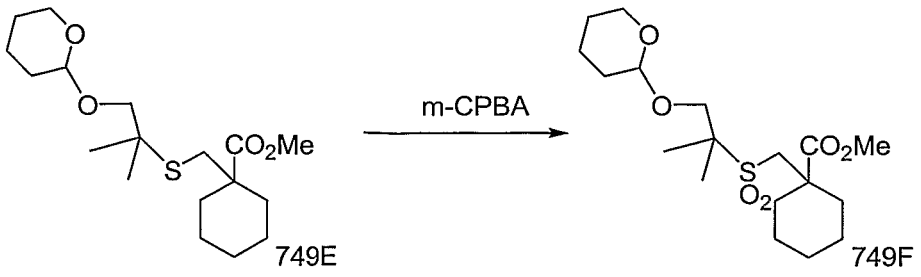
Step 5



To THF at 0°C was added NaH(1.02g, 25.6mmol, 1.5eq.), then (749C; 4.88g, 25.6mmol, 1.5eq.) . The mixture was stirred at 0°C for 10min, then (749D; 5.21g, 17.1mmol) was added at 0°C. The reaction was stirred at RT for 1hr, which TLC indicated no starting materials. Diluted it with EtOAc and water. Extracted aqueous layer with EtOAc. Combined organic layer was

washed with H_2O and brine. Organic layer was dried over $MgSO_4$. Concentrated it to dryness. Purified it by HPFC with 2~8% EtOAc in hexane to give (749E;5.89g) of product. Yield 100%.

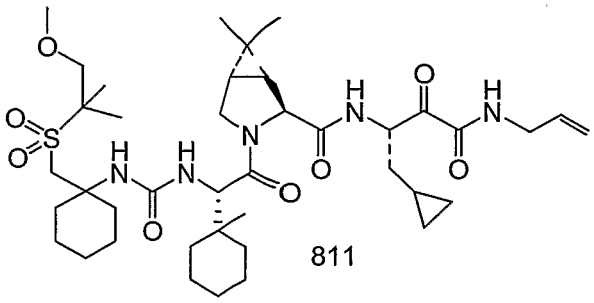
Step 6



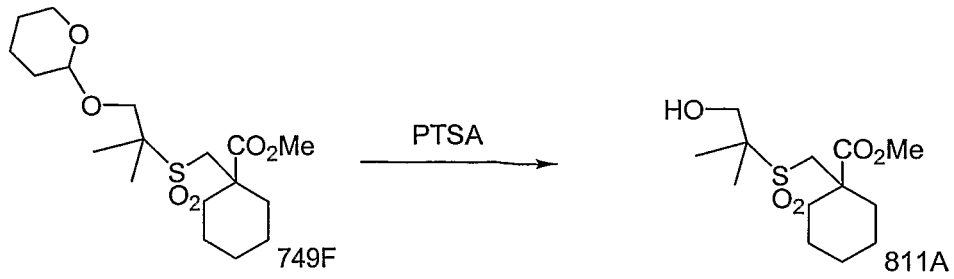
To the sulfide (749E; 0.17g, 0.49mmol) in CH_2Cl_2 was added $NaHCO_3$ (0.205g, 2.45mmol, 5equiv) , mCPBA(0.304g, 1.23mmol, 2.5eq.) at 0°C . The reaction was stirred at RT for 2hrs, which TLC and MS showed the reaction completed. Diluted with CH2Cl2. Washed with sat. NaHCO3 and brine. Dried over MgSO4. Purified it by HPFC with 5~20% EtOAc in hexane to give 0.14g of the sulfone (749F). Yield 76%.

The methyl ester (749F) can be converted to the corresponding carboxylic acid and subsequently the isocyanate (Example 108; Steps 5 and 6) and converted to 749 (Example 792; Steps 7 and 8).

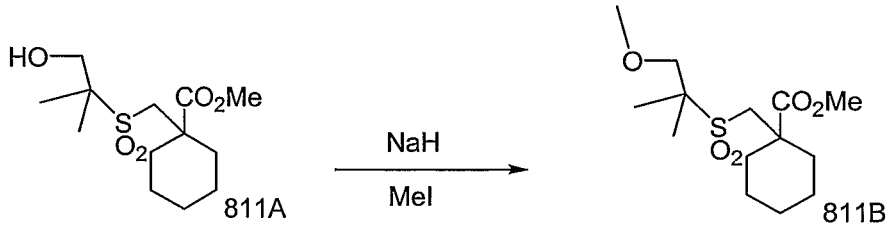
Example 811:



Step 1



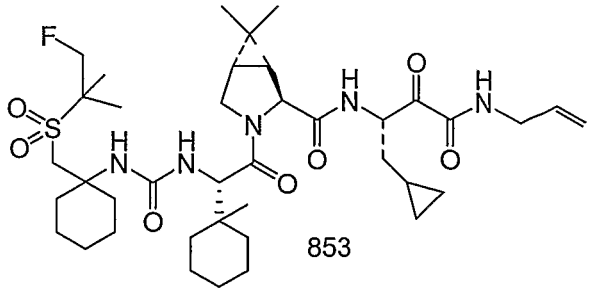
To 749F (70mg,0.18mmol) in MeOH was added pTsOH. The reaction was stirred at RT for overnight. MS showed the reaction almost completed. Concentrated it to dryness. Diluted with EtOAc. Washed with sat $NaHCO_3$, brine. Purified by HPFC with 10 ~40% EtOAc in hexane to give 52mg of the alcohol (811A) Yield 99%.



To NaH (88mg, 2.21mmol, 1.3equiv) in DMF at 0°C was added the alcohol(811A; 0.5g, 1.7mmol) and MeI (0.16mL, 2.56mmol, 1.5equiv) . The reaction was stirred at RT for 2hrs which TLC indicated the reaction didn't completed. 1 equiv MeI was added again. The reaction was stirred at RT for overnight. Diluted it with EtOAc. Washed with water, brine. Dried over MgSO4. Purified it by HPFC with 2~10~40% EtOAc in hexane to give the ether (811B; 0.283g) Yield 54%.

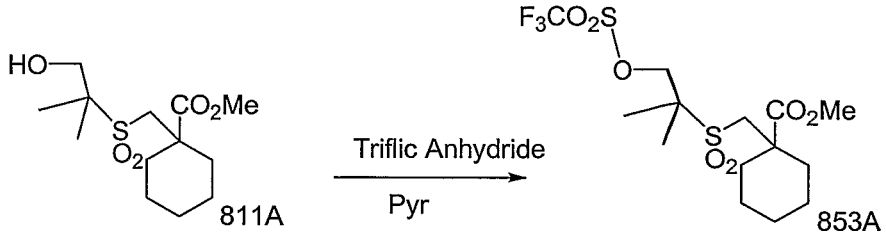
The methyl ester (811B) can be converted to the corresponding carboxylic acid and subsequently the isocyanate (Example 108; Steps 5 and 6) and converted to 749 (Example 792; Steps 7 and 8).

Example 853:



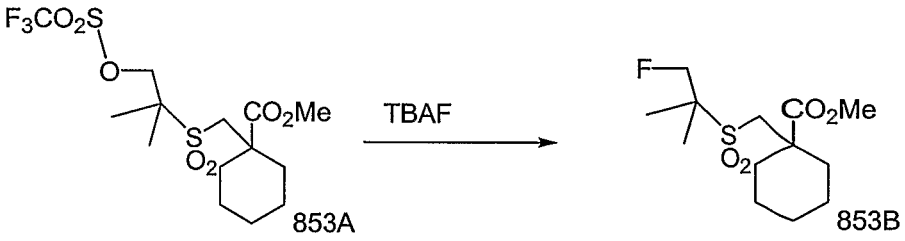
853

Step 1



To the alcohol (811A; 56mg, 0.19mmol, 1equiv) in CH_2Cl_2 was added pyridine (0.026mL, 0.32mmol, 1.7equiv) and triflic anhydride (0.042mL, 0.25mmol, 1.3equiv) at -20°C. The reaction was stirred at -20~10°C for 2hr which MS and TLC indicated the reaction completed. Diluted it with EtOAc, Washed with sat. NH4Cl and brine. Dried over MgSO4. Concentrated it to dryness to give 75.9 mg of crude product (853A)

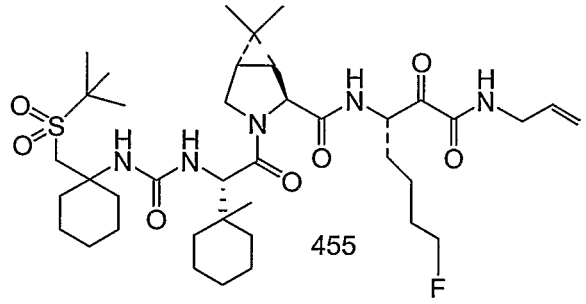
Step2



To 853A (75.9mg, 0.18mmol, 1equiv) in ether was added tetra-n-butyl ammonium fluoride (0.23mL, 0.23mmol, 1.3equiv) dropwise at -15°C. The reaction was stirred at RT for over night. Diluted it with ether, washed with sat. NH4Cl and brine. Dried over $MgSO_4$. Purified it with 2~10% EtOAc in hexane to give 32mg of the fluoride (853B). Yield 60%.

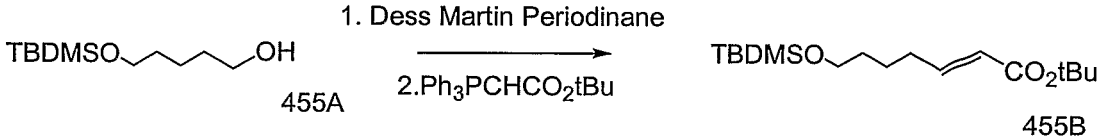
The methyl ester (853B) can be converted to the corresponding carboxylic acid and subsequently the isocyanate (Example 108; Steps 5 and 6) and converted to 749 (Example 792; Steps 7 and 8).

Example 455:



455

Steps 1 and 2



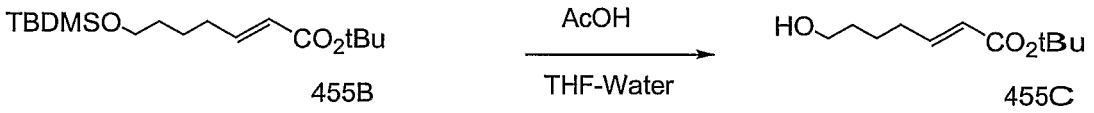
455A 455B

Steps 1 and 2 ('one-pot')

Dess-Martin Periodinane (21.35g) was added to a solution of the alcohol (455A; 10.00g) in dichloromethane (100ml) and stirred for 45 min., before the addition of the phosphorane (17.42g) and stirred overnight. The reaction mixture was partitioned between 5% aq. sodium thiosulfate and EtOAc and the organic phase was separated, washed with sat. aq. sodium bicarbonate,

water, dried ($MgSO_4$) and concentrated under reduced pressure. Hexanes was added to the residue and the resulting suspension was stirred vigorously for 2h and filtered. The filtrate was concentrated under reduced pressure and purified by silica gel ciolumn chromatography using EtOAc-hexanes (1:99) as eluent to give the desired alkene (455B; 7.33g) as a yellow oil.

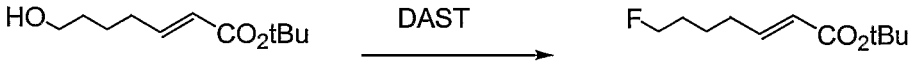
Step 3



455B 455C

Acetic acid (26ml) was added to a solution of the silyl ether in THF (6ml) and water (14ml) and the resulting mixture was stirred at room temperature overnight. The reaction was partitioned between EtOAc and sat. aq. sodium bicarbonate. The organic phase was separated, washed with water, dried ($MgSO_4$) and the volatiles removed under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc-hexanes (1:5) as eluent to give the alcohol (455C; 4.46g) as a colorless oil.

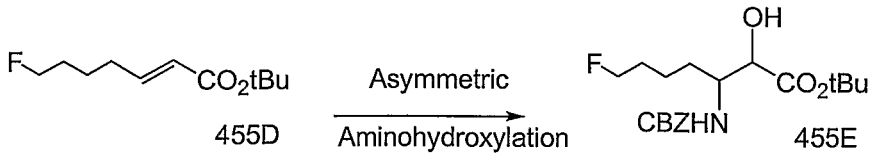
Step 4



455C 455D

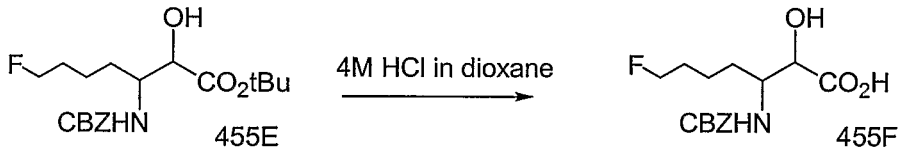
DAST (1.32ml) was added to a stirred solution of the alcohol (455C; 2.00g) in dichloromethane (50ml) at -78C, under an atmosphere of nitrogen. When the addition was complete the cooling bath was removed and the reaction allowed to stir at room temperature for 2h., before partitioning between EtOAc and water. The organic phase was separated, dried ($MgSO_4$) and the volatiles removed under reduced pressure before purification by column chromatography. Gave the fluoride (455D; 0.758g).

Step 5



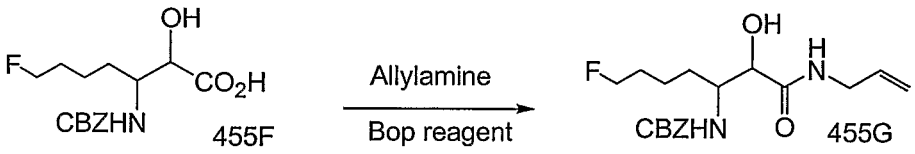
Using benzylcarbamate (2.06g) in n-PrOH (18ml), the alkene (455D; 0.881g), NaOH (0.537g), freshly prepared tBuOCl (1.54ml), $(DHQ)_2PHAL$ (0.176g) in nPrOH (16ml), potassium osmate (0.065g) and the procedure set for in Angewandte Int. Ed. (Engl), 1996, 35, 2813 a crude product was formed which was purified by silica gel column chromatography using EtOAc-Hexanes (1:5) as eluent to give the desired hydroxyamide (455E; 0.892g).

Step 6



4M HCl in dioxane (25ml) (ex. Aldrich) was added to the t-Bu ester (455E; 0.69g) and the resulting solution was allowed to stand at room temperature for 2h. The volatiles were removed under reduced pressure to yield the carboxylic acid (455F; 0.613g), used in subsequent reactions without purification.

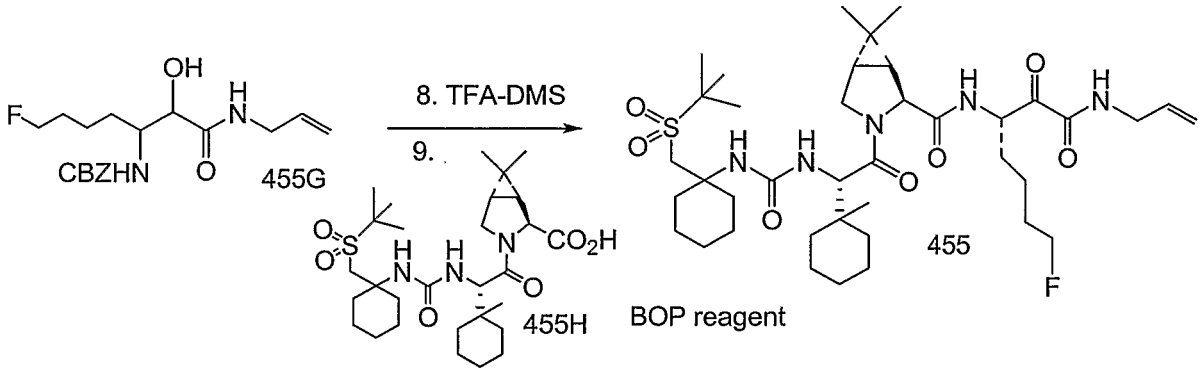
Step 7



Bop reagent (0.254g) followed by triethylamine (0.240ml) were added to a mixture of the carboxylic acid (455F; 0.15g) and allylamine (0.043ml) in

dichloromethane (5ml) and the resulting reaction mixture was stirred at room temperature overnight. The reaction was partitioned between EtOAc and 10% aq. HCl. The organic phase was separated, washed with sat. aq. sodium bicarbonate, waster , dried ($MgSO_4$) and the volatiles removed under reduced pressure. The residue was purified by silica gel column chromatography on silica gel using EtOAc:Hexanes (7:3) as eluent to give the amide (455G; 0.151g) as a white solid.

Steps 8, 9 and 10



Step 8

To the benzylcarbamate (455G; 0.037g) was added TFA (2ml) followed by methylsulfide (0.5ml) and the resulting solution was allowed to stand at room temperature for 3h., before removal of the volatiles. The crude reaction product was used in step 9, below, without purification.

Step 9

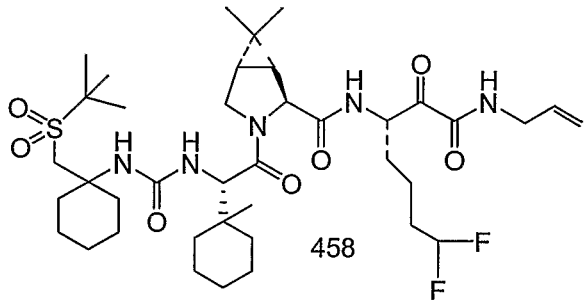
To the residue from step 8 was added dichloromethane (3ml), the carboxylic acid (455H; 0.050g), Bop reagent (0.047g) and finally triethylamine (0.044ml) and the resulting mixture was stirred at room temperature overnight. The reaction was partitioned between EtOAc and 10% aq. HCl. The organic phase was separated, washed with sat. aq. sodium bicarbonate, dried

($MgSO_4$) and the volatiles removed under reduced pressure to yield a residue which was used, in step 10, below, without purification.

Step 10

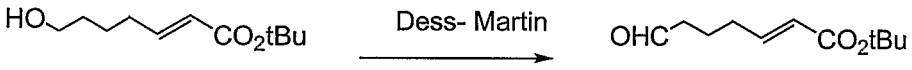
To the residue from step 9, was added dichloromethane (3ml) followed by Dess-Martin periodinane (0.075g) and the suspension was stirred at room temperature for 2h., before partitioning between EtOAc and 5% aq. sodium thiosulfate. The organic phase was separated, washed with sat. aq. sodium bicarbonate, water, dried ($MgSO_4$) and the volatiles removed under reduced pressure. The crude reaction product was purified by silica gel column chromatography to give the desired keto-amide (455; 0.0467g) as a white solid.

Example 458:



458

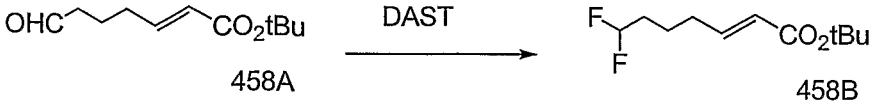
Step 1



455C 458A

To a solution of the alcohol (455C; 1.66g) in dichloromethane (20ml) was added Dess-Martin periodinane (4.22g) and the resulting mixture stirred at room temperature for a period of 1h., before partitioning between EtOAc and 5% aq. sodium thiosulfate. The organic phase was separated, washed with sat. aq. sodium bicarbonate, water, dried ($MgSO_4$) and the volatiles removed under reduced to yield the aldehyde (458A; 0.775g) used with purification.

Step 2

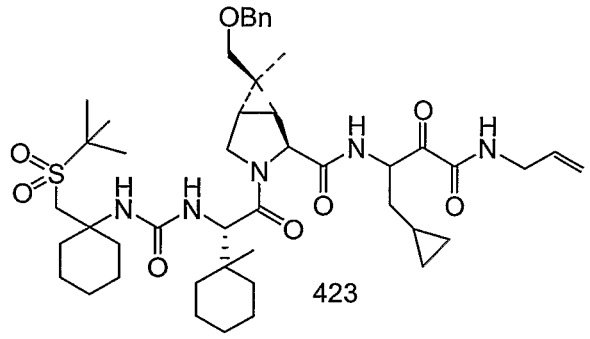


458A 458B

DAST (1.11ml) was added dropwise to a stirred solution of the aldehyde (458A; 0.755g) in dichloromethane (50 ml) while cooled in an ice bath, under an atmosphere of nitrogen. After completion of the addition the resulting mixture was stirred at room temperature for a period of 2h., before partitioning between EtOAc and water. The organic phase was separated, dried ($MgSO_4$) and the volatiles removed under reduced pressure. The residue was purified by silica gel column chromatography to give the desired difluoride (458B; 0.758g).

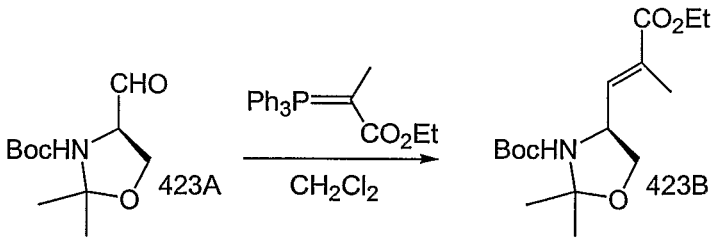
Using 458B and the procedures outlined in example 455 (Steps 5 through 10) target 458 was produced.

Example 423:



423

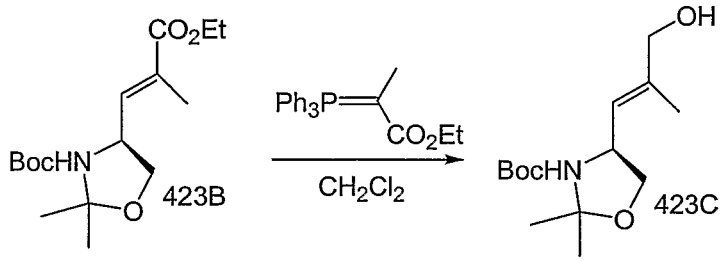
Step 1



423A 423B

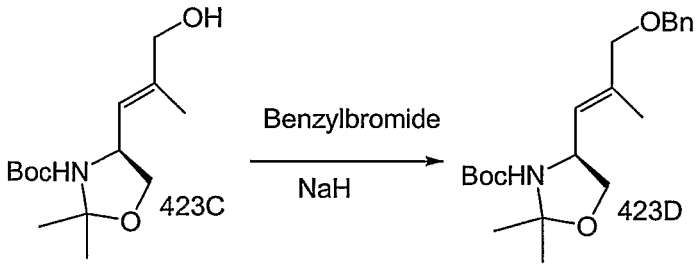
To a solution of Garner aldehyde (423A; 10.7g) in dichloromethane (110ml) was added (carbethoxyethylidene)triphenylphosphorane (28.75g) the resulting solution was stirred at room temperature overnight. The volatiles were removed under reduced pressure and the residue purified by silica gel column chromatography using 4-10% EtOAc in hexanes to give the desired alkene (423B; 12.7g), as a colorless oil.

Step 2



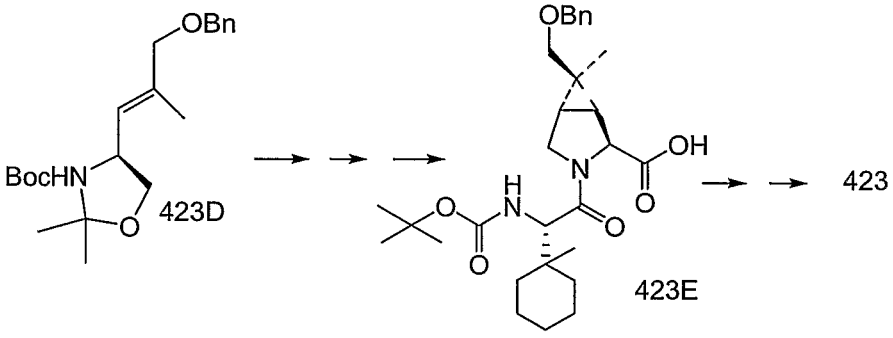
To a solution of the ethyl ester (423B;12.72g) in dichloromethane (20ml) was added DIBAL-H (90ml of a 1M solution in dichloromethane) at -78C, under an atmosphere of nitrogen. When the addition was complete the reaction was maintained at this temperature for a further 30 min the at room temperature for 1h., before the addition of MeOH (3ml) and sat aq. potassium sodium tartrate (3ml) and EtOAc. The organic phase was separated, washed with 1M aq HCl, brine, dried ($MgSO_4$). The volatiles were removed under reduced pressure and the residue purified by silica gel column chromatography using 6-35% EtOAc in hexanes to give the alcohol (9.06g), as a colorless oil.

Step 3

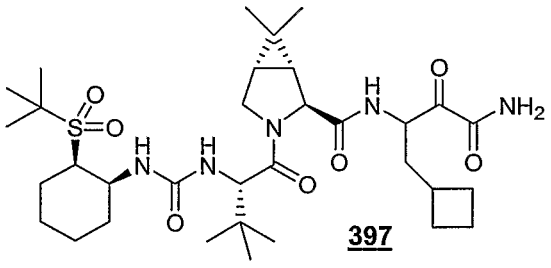


To a solution of the alcohol (423C; 8.66g) in anhydrous DMF (30ml), while cooled in an ice bath, was added NaH (1.38g) and the resulting mixture was maintained at that temperatuefor 45 min., before the addition of benzyl bromide (5ml). The reaction was allowed to warm to room temperature overnight befor the addition of ether followed bt 10% aq. HCl. The organic phase was separated, washed with sat aq. sodium bicarbonate, brine, dried (Na_2SO_4). The volatiles were removed under reduced pressure to yield a residue which was purified by silica gel column chromatography using 8% EtOAc in hexanes to yield the benzyl ether (8.10g) as a yellow oil.

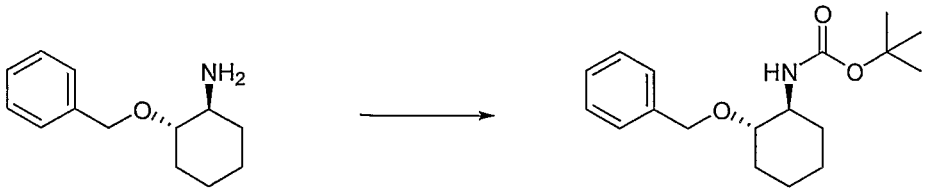
Using analogous procedures described above for the conversion of 22.03 to 22.01, 423D was transformed into 423E



Example 397:



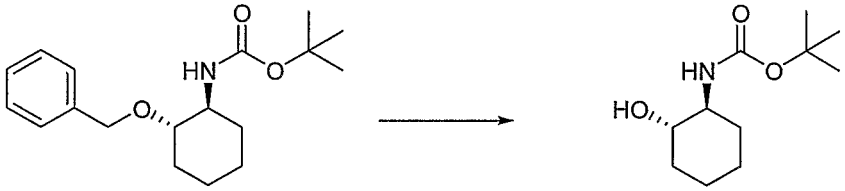
Step A



397a 397b

A solution of benzyloxycyclohexyl amine **397a** (10.6 g, Lancaster) and N-methylmorpholine (8.5 mL, d 0.920) in 200 mL of dry dichloromethane was cooled to -78 °C. Boc-anhydride in 100 mL of dry dichloromethane was added over 15 min using an addition funnel. After addition was completed, the cooling bath was removed and the mixture was stirred of further 30 min. The reaction mixture was partitioned between 300 mL of ether and 100 mL of aqueous 1N HCl. The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford the product **397b** (15.7 g; 99 %) as a white solid which was used without further purification.

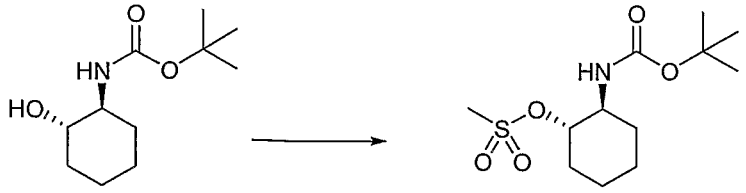
Step B



397b 397c

20% palladium dihydroxide on carbon (30 mol%; 10.8 g) was added to a solution of benzyl ether **397b** (15.7 g) in 300 mL of methanol. The heterogeneous mixture was subjected to hydrogenation at 40 psi until no more starting material was detected by TLC (ethyl acetate/hexanes; 2:8). The mixture was filtered thru celite and the filtrate was concentrated under reduced pressure. No further purification was carried out for the product **397c** (11.1 g; 99%).

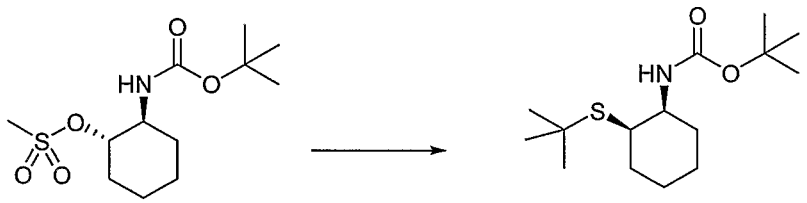
Step C



397c 397d

Pyridine (25.0 mL) was added to a solution of cyclohexanol **397c** in 300 mL of dry dichloromethane at 0 °C. Methanesulfonyl chloride (8.0 mL) in 100 mL of dry dichloromethane was added over 15 min. The reaction mixture turned to a homogeneous yellow solution. The reaction mixture was stirred at 0 °C for 15 min and then the cooling bath was removed. Reaction was stirred at room temp for about 3 h. The mixture was partitioned between ether (500 mL) and aqueous 1N HCl (100 mL). The organic layer was washed with aqueous saturated sodium bicarbonate (100 mL), brine (100 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: ethyl acetate/(hexanes-dichloromethane, 1:1); 0:10 to 2:8) to afford the product **397d** (9.7 g; 64 %) as a white solid.

Step D

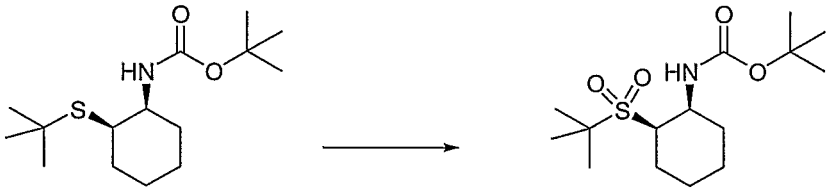


397d 397e

A 250 mL-flask was charged with mesylate **397d** (3.0 g) and t-butylthiol sodium salt (3.44 g). The flask was flushed with nitrogen and 100 mL of dry DMF were added. The resulting solution was degassed (vacuum/nitrogen-flush) and heated to 70 °C. The flow of the reaction was monitored by TLC (ethyl acetate/hexanes; 2:8). All the starting material was consumed in about

3 h. The reaction mixture was dissolved in 300 mL of ethyl acetate and washed with water (3 x 50 mL) and brine (1 x 50 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated. No further purification was done for the product **397e** (2.78 g; 95 %).

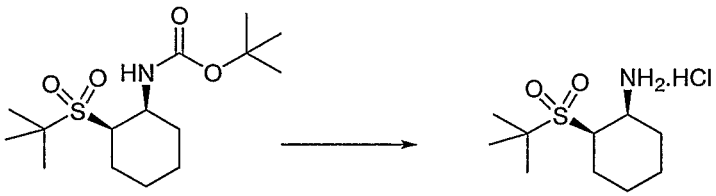
Step E



397e **397f**

A solution of sulfide **397e** (10.22 mmol) in dry dichloromethane (60 mL) was treated with m-CPBA (5.28 g; 60%). The homogeneous mixture was heated at 45 °C for about 3 h. TLC analysis (ethyl acetate/hexanes; 1:9) showed that all the starting material had been consumed. The mixture was concentrated under reduced pressure and the residue was dissolved in 20 mL of ether and treated with aqueous sodium thiosulfate solution at 0 °C. The mixture was diluted with ether (350 mL) and washed with aqueous saturated sodium bicarbonate (5 x 30 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel (gradient: acetone/hexane; 3:97 to 2:8) to afford the product **397f** (2.45 g; 75 %) as a white solid.

Step F

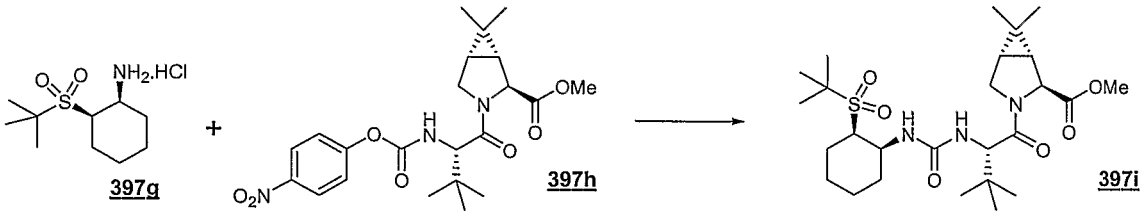


397f **397g**

The N-Boc protected amine **397f** (2.43 g) was dissolved in 20 mL of 4M HCl in dioxanes. The mixture was stirred at room temperature until all the starting

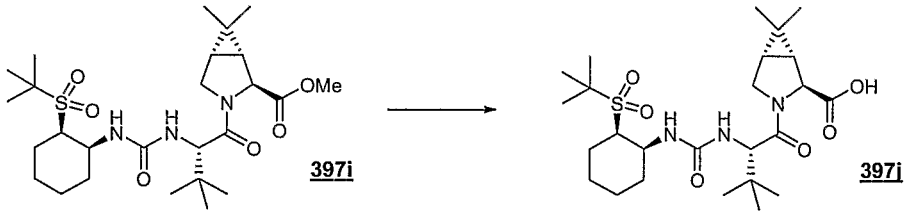
material had been consumed as determined by TLC analysis (ethyl acetate/hexanes; 2:8). After 3 h, all the volatiles were removed under reduced pressure to afford the product **397g** (1.90 g; 98 %) as a white solid.

Step G



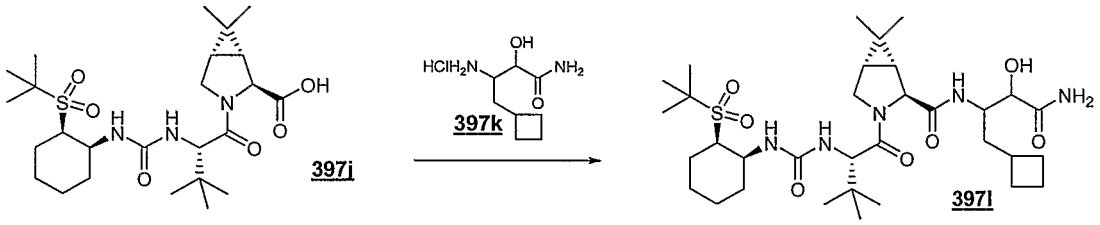
A solution of the p-nitrophenylcarbamate **397h** (640 mg) in 10 mL of acetonitrile was treated with amine hydrochloride **397g** (350 mg). N-methylmorpholine (0.37 mL, d 0.920) was added to the heterogeneous mixture and the reaction mixture was stirred at room temperature. The reaction was completed after 7 h as determined by TLC analysis (acetone/hexanes; 2:8). The reaction mixture was concentrated under reduced pressure. The residue was dissolved in 150 mL of dichloromethane and washed with aqueous 1N HCl (1 x 30 mL), and aqueous saturated sodium bicarbonate (2 x 30 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The product was purified on silica gel (gradient: acetone/hexanes; 1:9 to 4:6) to afford the product **397i** (625 mg; 87 %) as a white solid.

Step H



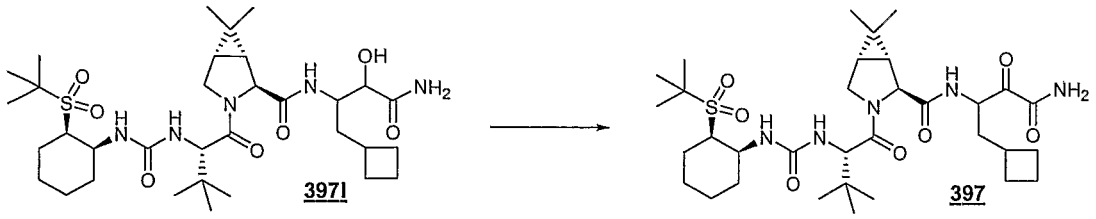
A solution of methyl ester **397i** (610 mg) in 15 mL of a mixture of THF/MeOH/water (1:1:1) was treated with lithium hydroxyde monohydrate (121 mg). Reaction was stirred at room temperature and monitored by TLC (acetone/hexanes; 3:7). After 3 h, all the volatiles were removed under reduced pressure. The residue was partitioned between 30 mL of aqueous 1N HCl and 100 mL of dichloromethane. The aqueous layer was back extracted with dichloromethane (2 x 30 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford the product **397j** (570 mg; 96 %) as a white solid.

Step I



A solution of acid **397j** (120 mg) in 2 mL of dry dichloromethane and 2 mL of dry DMF was stirred at 0 °C and treated with HATU (124 mg). The amine hydrochloride **397k** (63 mg) was added followed by addition of N-methyl morpholine (0.10 mL, d 0.920). The reaction mixture was gradually warmed to room temperature and stirred overnight. All the volatiles were removed under vacuum and the residue was taken into 100 mL of ethyl acetate. The organic layer was washed with aqueous 1N HCl (15 mL), aqueous saturated sodium bicarbonate (15 mL), and brine (15 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford the desired product **397l** (150 mg; 96 %) which was used without further purification.

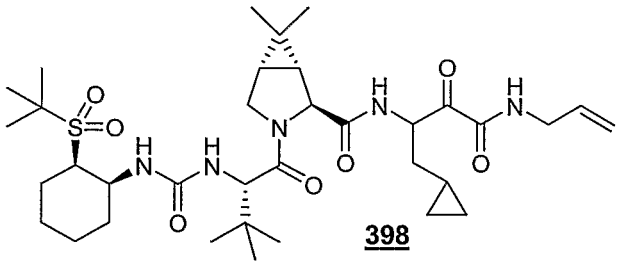
Step J



3971 397

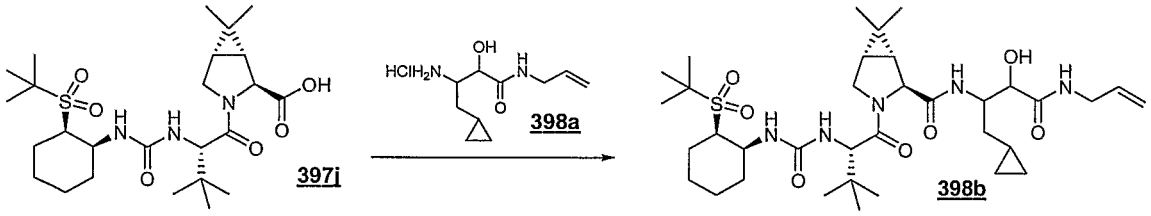
A solution of **3971** (150 mg) in 6 mL of a 1:1 mixture of toluene/DMSO was treated with EDCI (430 mg) and dichloroacetic acid (0.09 mL, d 1.563). Reaction mixture was stirred at room temperature for about 2 h. The reaction mixture was diluted with dichloromethane (100 mL) and washed with aqueous saturated sodium bicarboante (15 mL), aqueous 1N HCl (15 mL), and brine (15 mL). The organic layer was dried over magnesium sulfate, filtrated, and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 2:8 to 5:5) to afford the product **397** (94 mg; 64 %) as a white solid. HRMS calcd for $C_{33}H_{56}N_5O_7S$ $[M+H]^+$: 666.3900, found 666.3883.

Example 398:



398

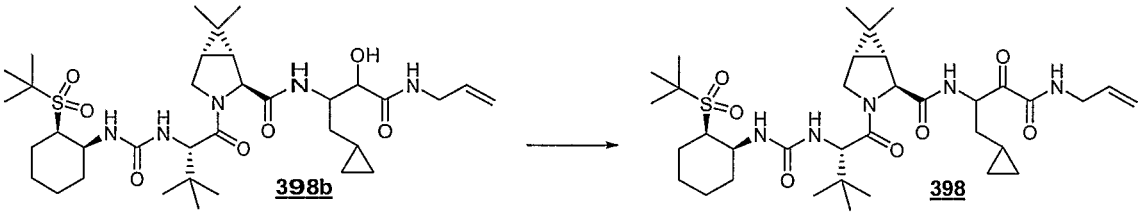
Step A



397i 398a 398b

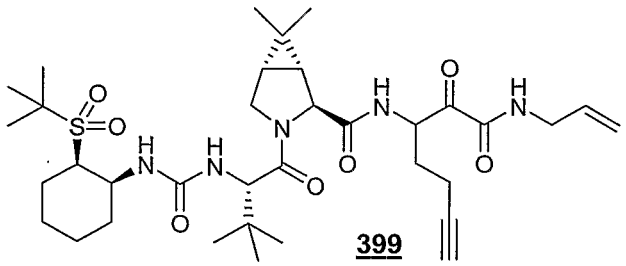
A solution of acid **397j** (100 mg) in 2 mL of dry dichloromethane and 2 mL of dry DMF was stirred at 0 °C and treated with HATU (103 mg). The amine hydrochloride **398a** (60 mg) was added followed by addition of N-methyl morpholine (0.09 mL, d 0.920). The reaction mixture was gradually warmed to room temperature and stirred overnight. All the volatiles were removed under vacuum and the residue was taken into 100 mL of ethyl acetate. The organic layer was washed with aqueous 1N HCl (15 mL), aqueous saturated sodium bicarbonate (15 mL), and brine (15 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford the desired product **398b** (115 mg; 86 %).

Step B



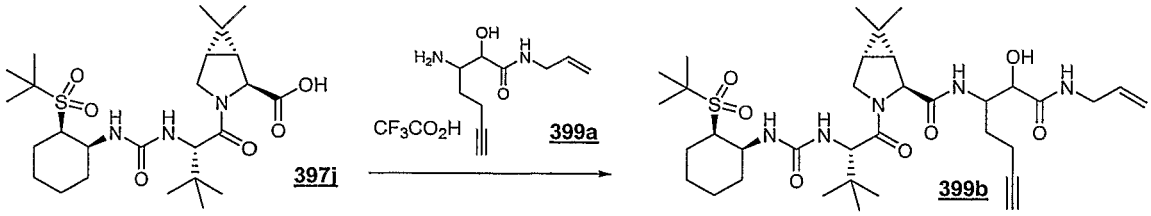
A solution of hydroxyamide **398b** (115 mg) in 10 mL of dry dichloromethane was treated with Dess-Martin periodinane (210 mg). Reaction mixture was stirred at room temperature for 1 h. The mixture was treated with aqueous 1M sodium sulfite solution (10 mL) and aqueous saturated sodium bicarbonate (10 mL) and stirred for 15 min. The mixture was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 2:8 to 5:5) to afford the product **398** (60 mg; 53 %) as a white solid. HRMS calcd for $C_{35}H_{58}N_5O_7S$ $[M+H]^+$: 692.4057, found 692.4081.

Example 399:



399

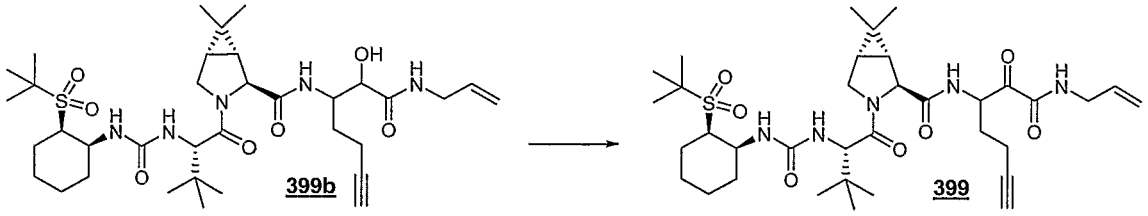
Step A



397j 399a 399b

A solution of acid **397j** (100 mg) in 2 mL of dry dichloromethane and 2 mL of dry DMF was stirred at 0 °C and treated with HATU (106 mg). A solution of the amine salt **399a** (0.252 mmol) and N-methyl morpholine (0.09 mL, d 0.920) in 1 mL of dichloromethane was added dropwise. The reaction mixture was gradually warmed to room temperature and stirred overnight. All the volatiles were removed under vacuum and the residue was taken into 100 mL of ethyl acetate. The organic layer was washed with aqueous 1N HCl (15 mL), aqueous saturated sodium bicarbonate (15 mL), and brine (15 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford the desired product **399b** (85 mg; 63 %).

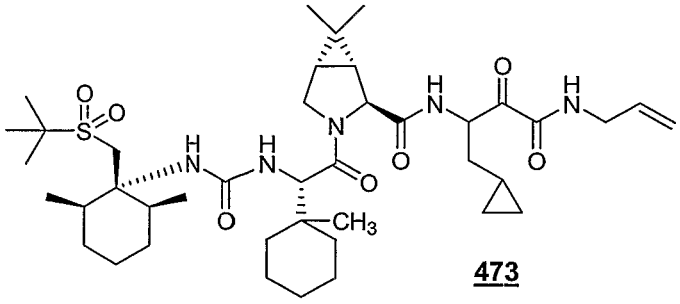
Step B



399b 399

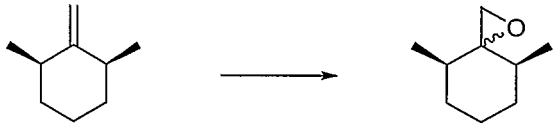
A solution of hydroxyamide **399b** (85 mg) in 10 mL of dry dichloromethane was treated with Dess-Martin periodinane (157 mg). Reaction mixture was stirred at room temperature for 1 h. The mixture was treated with aqueous 1M sodium thiosulfate solution (10 mL) and aqueous saturated sodium bicarbonate (10 mL) and stirred for 15 min. The mixture was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 2:8 to 4:6) to afford the product **399** (50 mg; 60 %) as a white solid. HRMS calcd for $C_{33}H_{55}N_6O_7S$ $[M+H]^+$: 679.3853, found 679.3834.

Example 473:



473

Step A

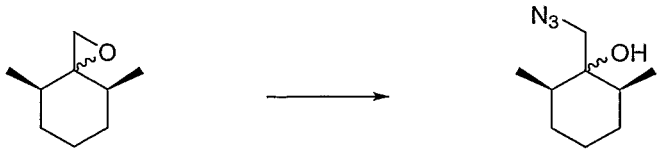


473a **473b**

Cis-2,6-dimethyl-1-methylene cyclohexane (3.0 g, ChemSamp Co.) was added to a stirred suspension of solid sodium bicarbonate (6 eq, 12.19 g) in 150 mL of dichloromethane. The mixture was cooled to 0 °C and a slurry of 70% m-CPBA (3 eq, 17.4 g) in 150 mL of dichloromethane was added in small portions. After addition was completed, the cooling bath was removed and the mixture was stirred for about 2h. The excess m-CPBA was quenched at 0 °C by careful addition of aqueous saturated sodium thiosulfate solution.

The mixture was washed with aqueous saturated sodium bicarbonate solution (100 mL). The organic layer was concentrated in the rotavap (ice-water bath was used). The residue was dissolved in ether (80 mL) and hexanes (120 mL) and washed several times with aqueous saturated sodium bicarbonate solution. The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure (ice-water bath). The residue was chromatographed on silica gel (gradient: ether/hexanes; 0:10 to 8:92) to afford the product **473b** (3.0 g; 90 %) as a colorless oil.

Step B



473b **473b**

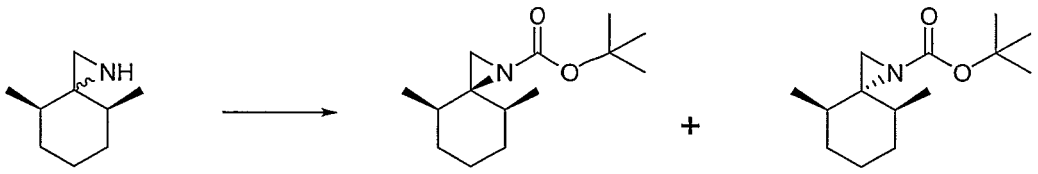
A heterogeneous mixture of epoxide **473b** (3 g) and ammonium chloride (5 eq, 5.72 g) in 80 mL of methanol was treated with sodium azide (5 eq, 7.17 g) and heated at 65 °C for 3 h. TLC analysis showed some starting material left and more ammonium chloride (1.5 eq, 1.71 g) and sodium azide (1.5 eq, 2.15 g) were added. The mixture was heated (65 °C) overnight. The reaction mixture was diluted with 30 mL of water and extracted with ether (3 x 100 mL). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: ether/hexanes; 0:10 to 2:8) to afford the corresponding diastereomeric product **473b** (2.73 g; 71 %) as a colorless oil.

Step C

473b 473c

A solution of azidoalcohol **473b** (1.73 g) in 50 mL of acetonitrile was treated with triphenylphosphine (1.1 eq, 2.69 g) and refluxed for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was chromatographed on silica gel (gradient: ether/hexanes; 5:5 to 9:1) to afford the desired aziridine product **473c** (2.0 g; 98 %).

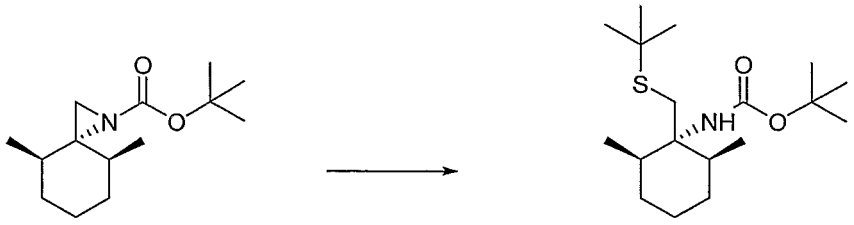
Step D



473c 473d 473e

A solution of aziridine **473c** (aprox 1.5 g) in dry dichloromethane (50 mL) was cooled to 0 °C and treated with di-tert-butyldicarbonate (1.3 eq, 3.0 g) in 50 mL of dry dichloromethane. N-methylmorpholine (2.5 eq, 2.9 mL, d 0.920) was added dropwise and the mixture was stirred overnight (temp: 0 to 25 °C). The mixture was diluted with ether (300 mL) and washed with aqueous 1M HCl (100 mL), aqueous saturated sodium bicarbonate (80 mL) and brine (80 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: ether/hexanes; 0:10 to 1:9) to afford the products **473d** and **473e** as clear oils (970 mg).

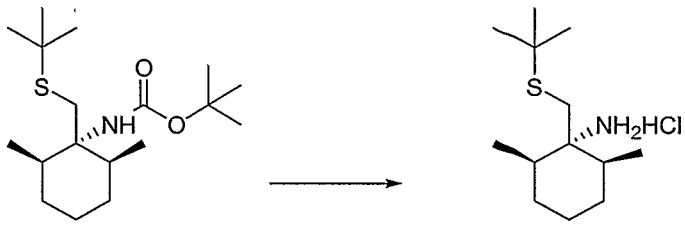
Step E



473e 473f

A 20 mL vial was charged with a solution of N-Boc-aziridine **473e** (469 mg) in 20 mL of dry DMF and sodium tert-butylthiolate (2 eq, 438 mg). The reaction was carried out in a microwave oven at 130 °C for 30 min. The reaction mixture was diluted with 100 mL of ether and washed with water (3 x 30 mL) and brine (20 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: hexanes to ether/hexanes, 4:96) to afford the product **473e** (140 mg) as a white solid and unreacted starting material (120 mg).

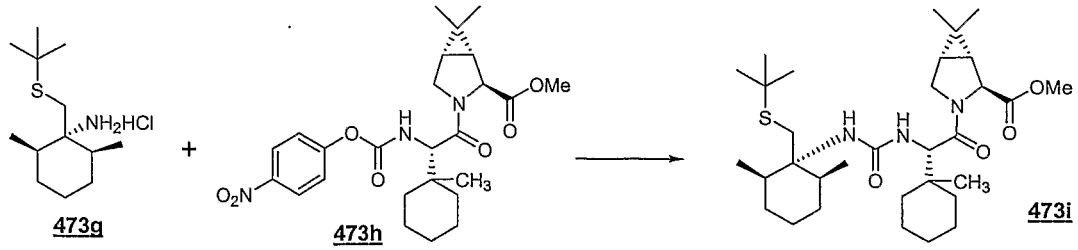
Step F



473f 473g

The N-Boc protected amine **473f** (140 mg) was dissolved in 10 mL of 4M HCl solution in dioxanes. The resulting solution was stirred at room temperature for 30 min until all the starting material had been consumed as determined by TLC analysis (ether/hexanes; 5:95). All the volatiles were removed under reduced pressure and the residue was placed under high vacuum for 3 h to afford the product **473g** (112 mg; 98 %) as a white solid.

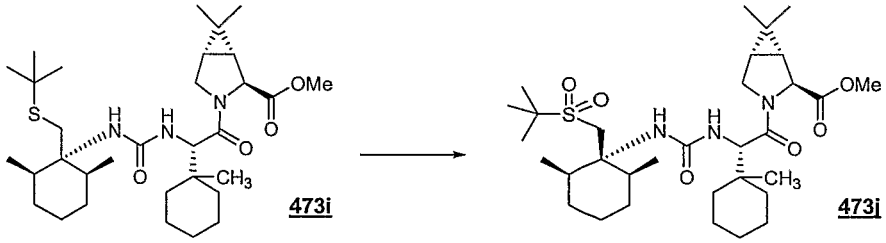
Step G



473g 473h 473i

A solution of the p-nitrophenylcarbamate **473h** (1.05 eq, 212 mg) in 3 mL of acetonitrile was treated with amine hydrochloride **473g** (110 mg) in 2 mL of acetonitrile. N-methylmorpholine (2.5 eq, 0.11 mL, d 0.920) was added and the resulting yellow solution was stirred at room temperature for 8 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in 100 mL of dichloromethane and washed with aqueous 1N HCl (1 x 20 mL), and aqueous saturated sodium bicarbonate solution (2 x 20 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The product was purified on silica gel (gradient: hexanes to acetone/hexanes, 2:8) to afford the product **473i** (150 mg; 63 %).

Step H

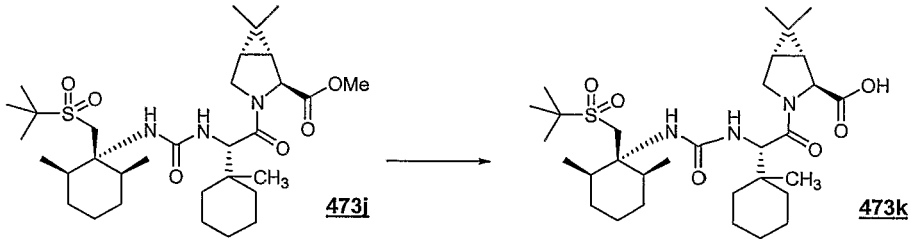


473i 473j

A solution of sulfide **473i** (150 mg) in dry dichloromethane (15 mL) was treated with 60% m-CPBA (3 eq, 134 mg). The homogeneous mixture was heated at 45 °C for about 1.5 h. Excess m-CPBA was quenched by addition of aqueous sodium thiosulfate solution (20 mL) and stirring was continued for 10 min. Aqueous saturated sodium bicarbonate solution (20 mL) was added and the product was taken into ethyl acetate (100 mL). The organic layer was

concentrated and the residue was dissolved in ethyl acetate (80 mL). The organic layer was washed with aqueous saturated sodium bicarbonate solution (3 x 10 mL) and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated. The residue was chromatographed on silica gel (gradient: ethyl acetate/hexanes; 1:3 to 5:5) to afford the product **473j** (120 mg; 76%) as a colorless oil.

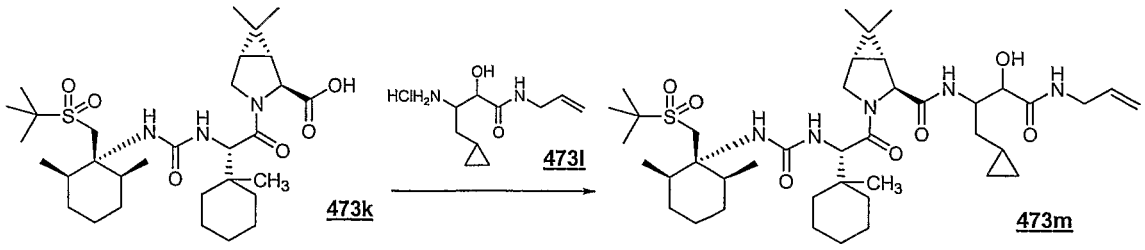
Step I



473j 473k

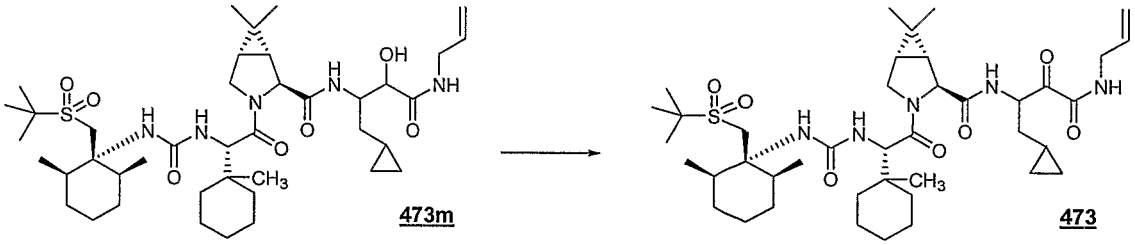
A solution of methyl ester **473j** (110 mg) in 10 mL of a 1:1:1 mixture of THF/water/MeOH was cooled to 0 °C and treated with lithium hydroxide monohydrate (2.5 eq, 19 mg). The cooling bath was removed after 30 min and the mixture was stirred at room temp for further 2 h until all the starting material had been consumed as determined by TLC analysis (ethyl acetate/hexanes; 3:7). The reaction mixture was treated with 20 mL of aqueous 1M HCl (pH of mixture = 1) and the organic solvents were removed under reduced pressure. The aqueous residue was extracted with dichloromethane (3 x 50 mL). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated under reduced pressure to afford the product **473k** (105 mg; 98 %) as a clear oil.

Step J



A solution of acid **473k** (50 mg) in 2 mL of dry dichloromethane and 1 mL of dry DMF was stirred at 0 °C and treated with HATU (1.4 eq, 44 mg). The amine salt (1.3 eq, 25 mg) was added followed by N-methylmorpholine (4 eq, 0.036 mL, d 0.920). The reaction mixture was stirred overnight (temp 0 to 25 °C). All the volatiles were removed under vacuum and the residue was dissolved in 50 mL of ethyl acetate. The organic layer was washed with water (20 mL), aqueous 1M HCl (10 mL), aqueous saturated sodium bicarbonate solution (10 mL), and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The product **473m** (64 mg) was used without further purification.

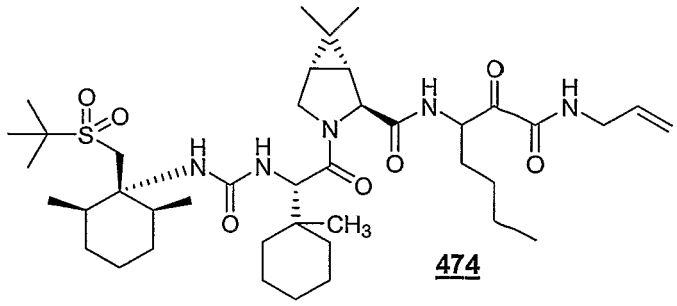
Step K



A solution of hydroxyamide **473m** (0.083 mmol) in 10 mL of dry dichloromethane was treated with Dess-Martin periodinane (2.0 eq, 70 mg). The reaction mixture was stirred at room temperature for 30 min. The mixture was treated with aqueous 1M sodium thiosulfate solution (10 mL) and stirred for 5 min. Aqueous saturated sodium bicarbonate solution (20 mL) was also added and stirring was continued for further 10 min. The mixture was extracted with dichloromethane (3 x 30 mL). The combined organic layers

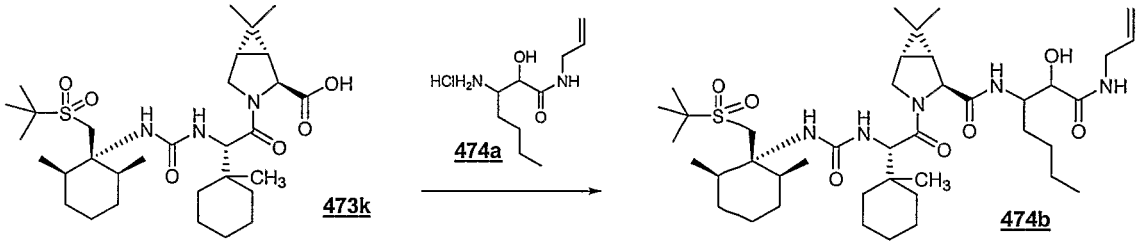
were dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 1:9 to 4:6) to afford the product **473** (40 mg; 62% for two steps) as white solid. HRMS calcd for $C_{41}H_{68}N_5O_7S$ $[M+H]^+$: 774.4839, found 774.4834.

Example 474:



474

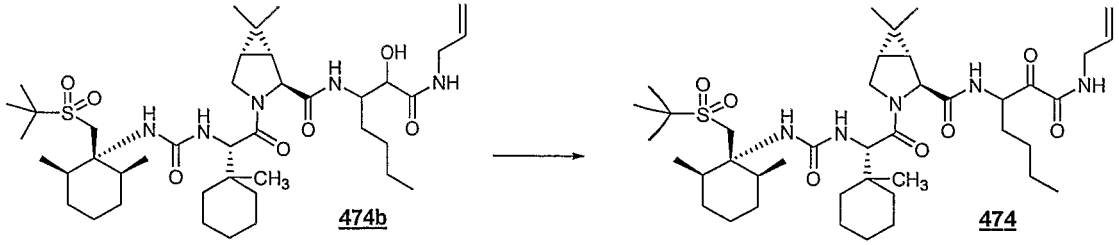
Step A



473k **474a** **474b**

A solution of acid **473k** (50 mg) in 2 mL of dry dichloromethane and 1 mL of dry DMF was stirred at 0 °C and treated with HATU (1.4 eq, 44 mg). The amine salt **474a** (1.3 eq, 25 mg) was added followed by N-methylmorpholine (4 eq, 0.036 mL, d 0.920). The reaction mixture was stirred overnight (temp 0 to 25 °C). All the volatiles were removed under vacuum and the residue was dissolved in 50 mL of ethyl acetate. The organic layer was washed with water (20 mL), aqueous 1M HCl (10 mL), aqueous saturated sodium bicarbonate solution (10 mL), and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The product **474b** (65 mg) was used without further purification.

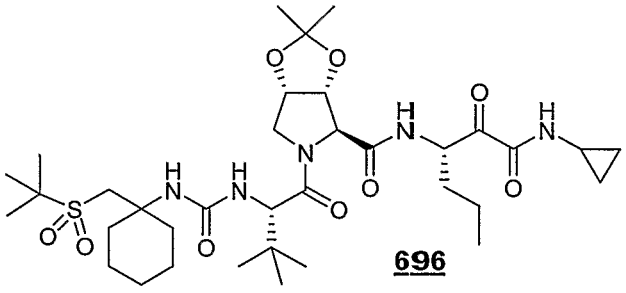
Step B



474b 474

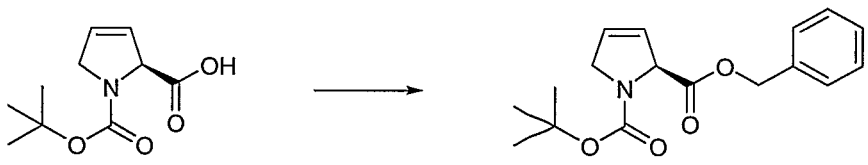
A solution of hydroxyamide **474b** (0.083 mmol) in 10 mL of dry dichloromethane was treated with Dess-Martin periodinane (2.0 eq, 70 mg). The reaction mixture was stirred at room temperature for 30 min. The mixture was treated with aqueous 1M sodium thiosulfate solution (10 mL) and stirred for 5 min. Aqueous saturated sodium bicarbonate solution (20 mL) was also added and stirring was continued for further 10 min. The mixture was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 1:9 to 4:6) to afford the product **474** (40 mg; 62% for two steps) as white solid. HRMS calcd for $C_{41}H_{70}N_5O_7S$ $[M+H]^+$: 776.4995, found 776.5005.

Example 696:



696

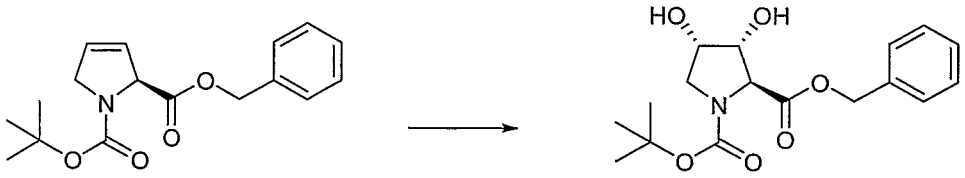
Step A



696a 696b

A solution of acid **696a** (3.0 g) in 140 mL of dry DMF was cooled to 0 °C and treated with cesium carbonate (1.1 eq, 5.04 g) followed by addition of benzyl bromide (1.2 eq, 2.00 mL, d 1.438). The reaction mixture was stirred for 24 h (temp: 0 to 25 °C). The mixture was diluted with ethyl acetate (350 mL) and washed with water (3 x 50 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: hexanes to ethyl acetate/hexanes 25:75) to afford the product **696b** (3.82 g; 90 %) as a clear oil.

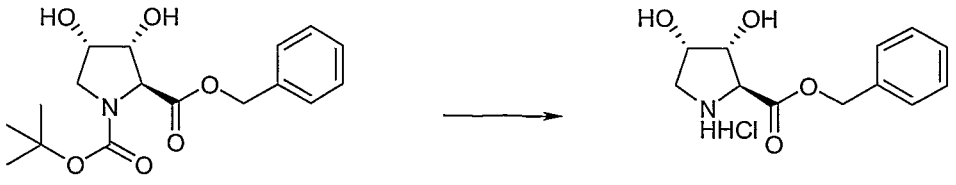
Step B



696b **696c**

A solution of N-methylmorpholine-N-oxide (1.3 eq, 1.9 g) in tert-butanol (20 mL), THF (7 mL) and water (3.5 mL) under argon atmosphere was treated with osmium tetroxide (0.1 eq, 318 mg). The resulting pale yellow solution was stirred for 5 min followed by dropwise addition of benzylester **696b** (3.8 g) in 30 mL of THF. The reaction mixture was stirred at room temperature for 20 h. The mixture was filtered thru a short path of silica gel and the solids were washed with ethyl acetate (500 mL). The organic layer was washed with brine (80 mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 2:8 to 55:45) to afford the product **696c** (3.5 g; 83 %) as a paste.

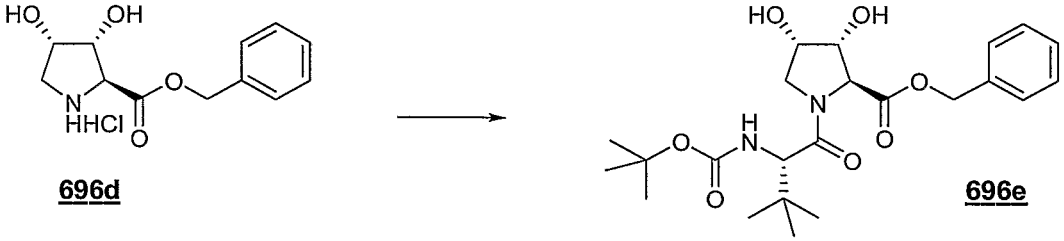
Step C



696c 696d

The N-Boc amine **696c** (3.5 g) was dissolved in 60 mL of 4M HCl in dioxane. The resulting solution was stirred at room temperature for about 2 h. All the volatiles were removed under reduced pressure to afford the product **696d** (2.8 g; 98 %) which was used without further purification.

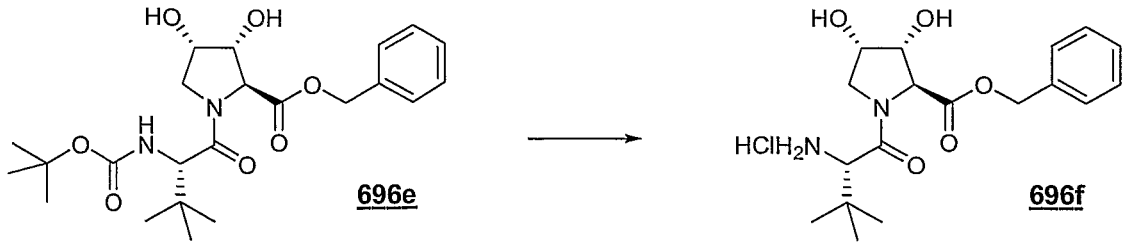
Step D



696d 696e

A solution of N-Boc-tert-butyl glycine (2.15 g) in 100 mL of dry dichloromethane and 20 mL of dry DMF was stirred at 0 °C and treated with HATU (1.4 eq, 4.96 g). The amine salt **696d** (1.1 eq, 2.8 g) was added in 30 mL of DMF followed by addition of N-methylmorpholine (4 eq, 4.08 mL, d 0.920). The reaction mixture was stirred at 0 °C overnight. All the volatiles were removed under vacuum and the residue was dissolved in 300 mL of ethyl acetate. The organic layer was washed with water (1 x 100 mL), aqueous 1M HCl (100 mL), aqueous saturated sodium bicarbonate solution (100 mL), and brine (100 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (ethyl acetate/hexanes; 6:4) to afford the product **696e** (3.29 g; 79 %) as a colorless oil.

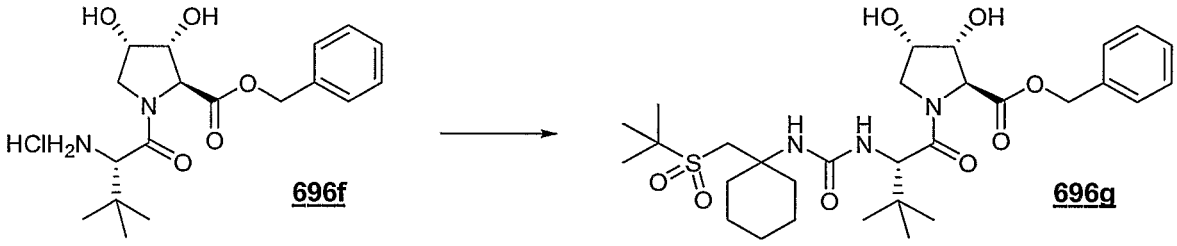
Step E



696e 696f

The N-Boc amine **696e** (1.24 g) was dissolved in 30 mL of 4M HCl in dioxane. The resulting solution was stirred at room temperature for about 2h. All the volatiles were removed under reduced pressure to afford the product **696f** (1.06 g; 98 %) as a white solid.

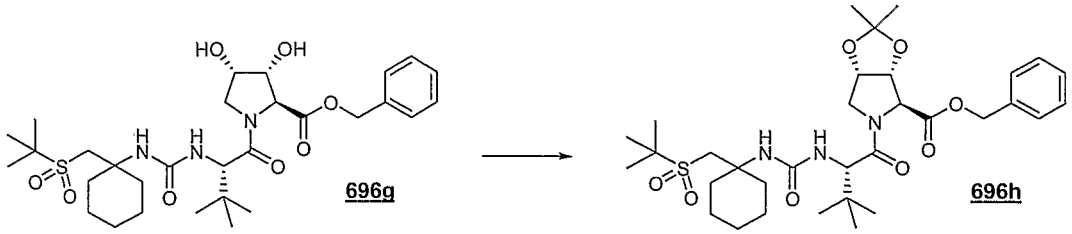
Step F



696f 696g

N-methyl morpholine (1.3 eq, 0.39 mL, d 0.920) was added to a heterogeneous mixture of amine-diol **696f** (1.06 g) in 50 mL of dichloromethane. After 5 min, a solution of isocyanate (1.05 eq, 9.63 mL of a 0.3M soln in toluene) was added. DMF (5 mL) was also added and the slurry was stirred at room temperature. The mixture gradually converted (over 4 h) to a clear homogeneous solution. The mixture was diluted with ethyl acetate (300 mL) and washed with aqueous 1M HCl. The aqueous layer was back extracted with 100 mL of ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 3:7 to 6:4) to give the product **696g** (1.6 g; 98 %) as a colorless oil.

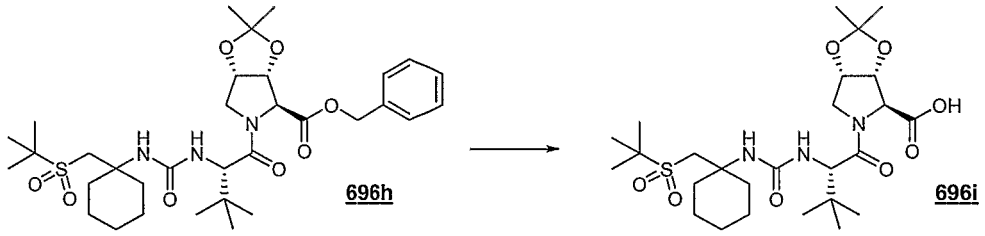
Step G



696g 696h

A solution of diol **696g** (1.5 g) was treated with 2,2-dimethoxypropane (2 eq, 0.6 mL, d 0.847) and a catalytic amount of pyridinium p-toluenesulfonic acid (0.1 eq, 62 mg). The mixture was stirred overnight at 50 °C. The mixture was diluted with 200 mL of ethyl acetate and washed with 50 mL of aqueous saturated sodium bicarbonate soln. The aqueous layer was extracted with ethyl acetate (100 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 5:95 to 35:65) to afford the product **696h** (1.33 g; 83 %) as a white solid.

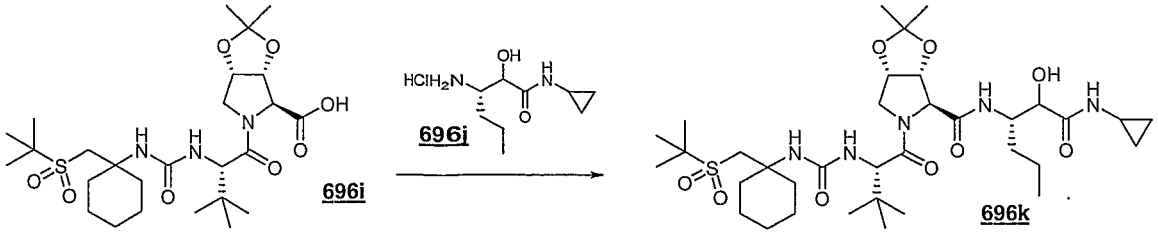
Step H



696h 696i

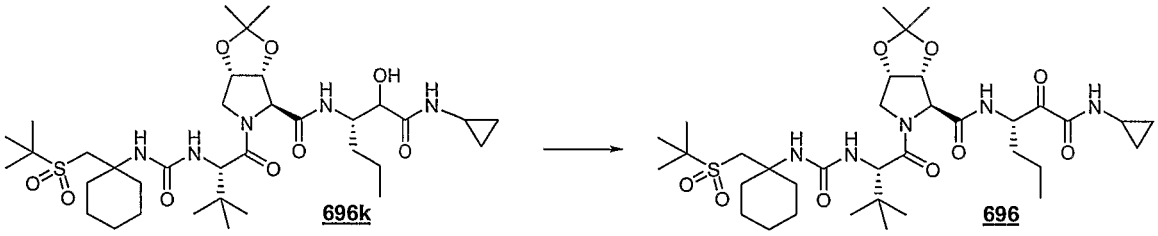
The benzyl ester **696h** (1.33 g) was dissolved in 70 mL of ethyl acetate and treated with 20% palladium dihydroxide on carbon (0.1 mol%; 144 mg). The heterogeneous mixture was hydrogenated at 50 psi for 3 h. The mixture was diluted with 200 mL of dichloromethane and filtered thru a short path of celite. The filtrate was concentrated under reduced pressure to afford the product **696i** (1.14 g; 98 %) as a white solid.

Step I



A solution of acid **696i** (100 mg) in 3 mL of dry dichloromethane and 3 mL of dry DMF was stirred at 0 °C and treated with HATU (1.4 eq, 93 mg). The amine salt **696j** (1.2 eq, 47 mg) was added followed by N-methylmorpholine (4 eq, 0.08 mL, d 0.920). The reaction mixture was stirred overnight (temp 0 to 25 °C). All the volatiles were removed under vacuum and the residue was dissolved in 50 mL of ethyl acetate. The organic layer was washed with water (10 mL), aqueous 1M HCl (10 mL), aqueous saturated sodium bicarbonate solution (10 mL), and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The product **696k** was used without further purification.

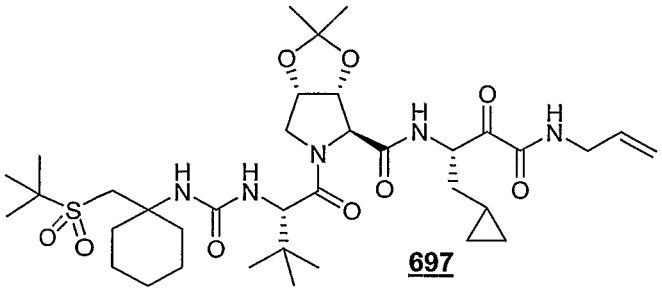
Step J



A solution of hydroxyamide **696k** (0.178 mmol) in 10 mL of dry dichloromethane was treated with Dess-Martin periodinane (2.0 eq, 150 mg). The reaction mixture was stirred at room temperature for 30 min. The mixture was treated with aqueous 1M sodium thiosulfate solution (10 mL) and stirred for 5 min. Aqueous saturated sodium bicarbonate solution (10 mL) was also added and stirring was continued for further 10 min. The mixture was extracted with dichloromethane (3 x 30 mL). The combined organic layers

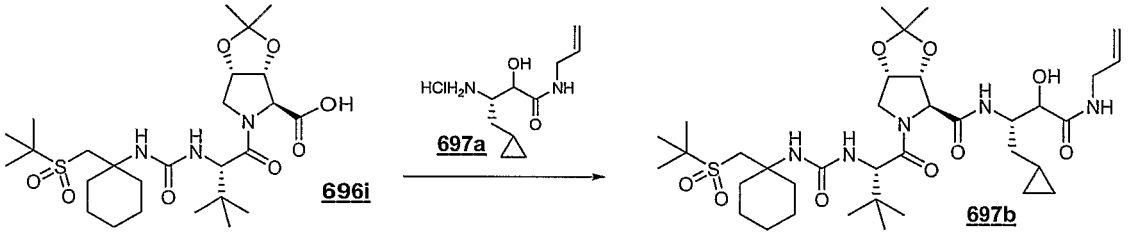
were dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 15:85 to 1:1) to afford the product **696** (120 mg; 93 %) as white solid. HRMS calcd for $C_{35}H_{60}N_5O_9S$ $[M+H]^+$: 726.4112, found 726.4128.

Example 697:



697

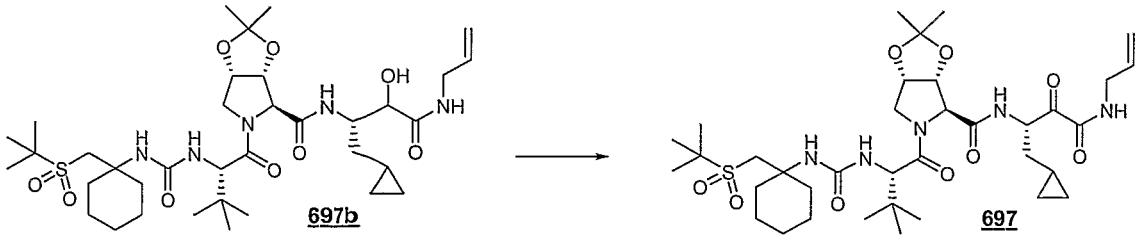
Step A



696i **697a** **697b**

A solution of acid **696i** (100 mg) in 3 mL of dry dichloromethane and 3 mL of dry DMF was stirred at 0 °C and treated with HATU (1.4 eq, 93 mg). The amine salt **697a** (1.2 eq, 50 mg) was added followed by N-methylmorpholine (4 eq, 0.08 mL, d 0.920). The reaction mixture was stirred overnight (temp 0 to 25 °C). All the volatiles were removed under vacuum and the residue was dissolved in 50 mL of ethyl acetate. The organic layer was washed with water (10 mL), aqueous 1M HCl (10 mL), aqueous saturated sodium bicarbonate solution (10 mL), and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The product **697b** was used without further purification.

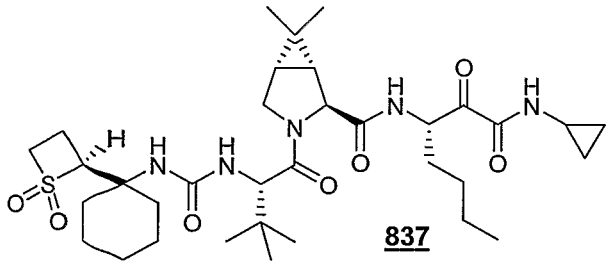
Step B



697b 697

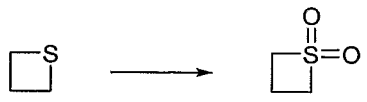
A solution of hydroxyamide **697b** (0.178 mmol) in 10 mL of dry dichloromethane was treated with Dess-Martin periodinane (2.0 eq, 150 mg). The reaction mixture was stirred at room temperature for 30 min. The mixture was treated with aqueous 1M sodium thiosulfate solution (10 mL) and stirred for 5 min. Aqueous saturated sodium bicarbonate solution (10 mL) was also added and stirring was continued for further 10 min. The mixture was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 15:85 to 1:1) to afford the product **697** (120 mg; 91 %) as white solid. HRMS calcd for $C_{36}H_{60}N_5O_9S$ $[M+H]^+$: 738.4112, found 738.4092.

Example 837:



837

Step A

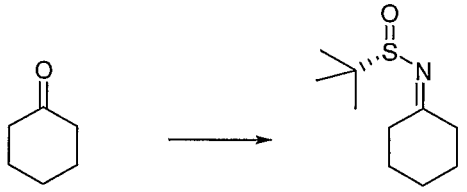


837a 837b

A solution of thietane (10 g, 9.727 mL, d 1.028, Aldrich) in 200 mL of dichloromethane was treated with a slurry of m-chloroperoxybenzoic acid (2.3

eq, 76 g of 70% m-CPBA) in dichloromethane (400 mL) at 0 °C. The cooling bath was removed and the mixture was stirred for 3 h. The solids were removed by filtration and the filtrate was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (400 mL) and the solution was extensively washed with aqueous saturated sodium bicarbonate solution. The organic layer was dried over magnesium sulfate, filtered and concentrated. The residue was purified by column chromatography to afford the product **837b** as a white solid.

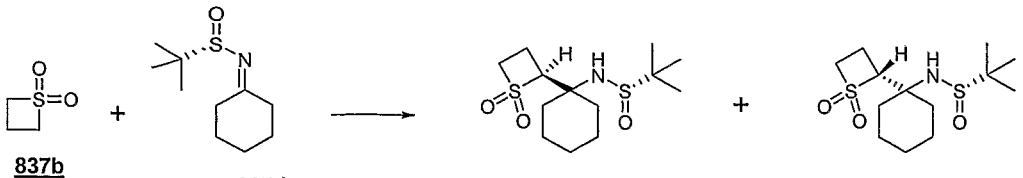
Step B



837c **837d**

Titanium tetraethoxide (2 eq, 24.2 mL, d 1.088) was added to a solution of cyclohexanone (1.2 eq, 7.18 mL, d 0.947) in 150 mL of dry THF under nitrogen atmosphere. After 5 min, t-butanesulfinamide (7.0 g, Aldrich) in 50 mL of THF was added dropwise. The mixture was heated to 60 °C overnight. The reaction mixture was poured into an equal volume of aqueous saturated sodium bicarbonate solution with rapid stirring and immediately filtered through filter paper whatman #1. The filter cake was washed with ethyl acetate (100 mL). The layers in the filtrate were separated and the aqueous layer was extracted with ethyl acetate (100 mL). The combined organic layers were washed with aqueous saturated sodium bicarbonate solution (100 mL), dried over magnesium sulfate, filtered and concentrated. The residue was chromatographed on silica gel (ethyl acetate/hexanes; 3:7) to afford the product **837d** (7.5 g; 55 %) as a colorless oil. The product is kept under inert atmosphere at -20 °C.

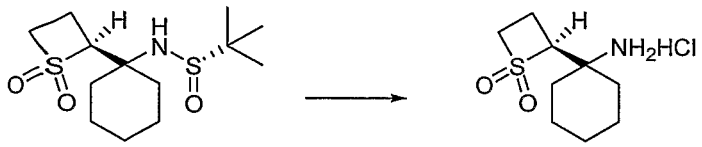
Step C



837b 837d 837e 837f

n-Butyl lithium (1.1 eq, 7.6 mL of a 1.6M soln in cyclohexane) was added dropwise to a cooled (-78 °C) solution of sulfone **837b** (1.15 eq, 1.35 g) in 100 mL of dry THF under anhydrous atmosphere. The mixture was stirred for 1 h at that temperature and then transferred via cannula to a pre-cooled (-78 °C) solution of sulfinylimine **837d** (2.23 g) in 100 mL of dry THF. The resulting mixture was stirred at -78 °C and monitored by TLC (acetone/hexanes; 3:7). All the sulfinylimine **837d** starting material was consumed in 2 h. The reaction was quenched by addition of aqueous saturated ammonium chloride solution (5 mL). The mixture was allowed to reach room temperature and partitioned between ethyl acetate (200 mL) and aqueous saturated sodium bicarbonate (80 mL). The aqueous layer was back extracted with ethyl acetate (2 x 60 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: dichloromethane to acetone/dichloromethane; 3:7) to afford the corresponding diastereomeric products **837e** and **837f** as a 1.4:1 mixture (1.64 g; 50 % comb.yield).

Step D



837e 837g

The sulfinamide **837e** (910 mg) was dissolved in 50 mL of methanol and treated with 20 mL of 4M HCl solution in dioxane. The mixture was stirred for

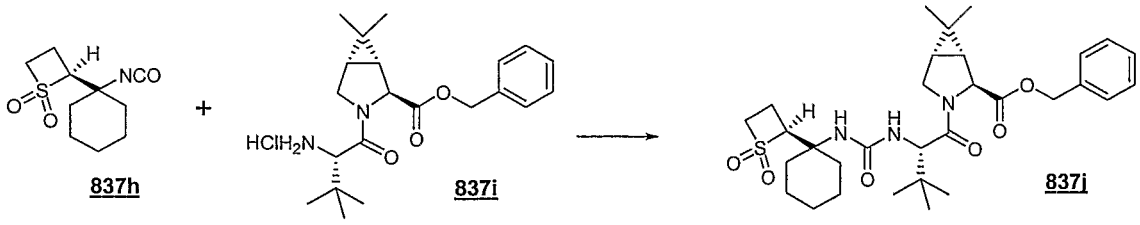
about 1 h until all the starting material had been consumed as determined by TLC (acetone/hexanes; 1:9). The mixture was concentrated to dryness. Dichloromethane (10 mL) was added to make a homogeneous solution then ether was added (80 mL) and a white precipitate was formed. The amine hydrochloride product **837g** (700 mg; 98 %) was recovered by filtration as a white solid.

Step E

837g **837h**

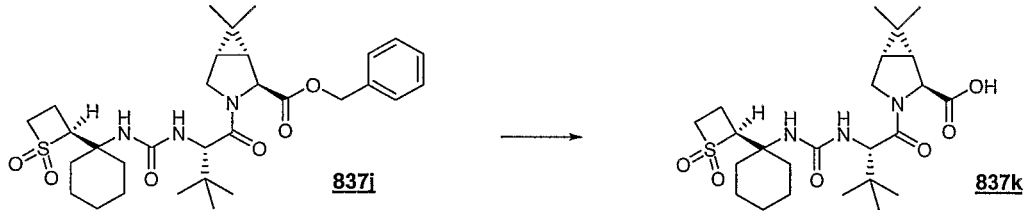
A solution of amine hydrochloride **837g** (2.960 mmol) in 40 mL of dichloromethane was treated with 20 mL of aqueous saturated sodium bicarbonate solution and stirred vigorously for 10 min at 0 °C. Stirring was stopped and layers were allowed to separate. Phosgene (10 mL of 20% soln in toluene) was added through a needle to the organic layer (lower layer) in one portion. The mixture was vigorously stirred immediately after addition for 10 min at 0 °C and further stirred at room temp for 3 h. The mixture was diluted with 100 mL of dichloromethane and layers were separated. The organic layer was washed with 50 mL of cold aqueous saturated sodium bicarbonate solution and dried over magnesium sulfate. The organic layer was filtered and diluted with 50 mL of toluene. The resulting solution was concentrated and kept as a 0.118M solution in toluene.

Step F



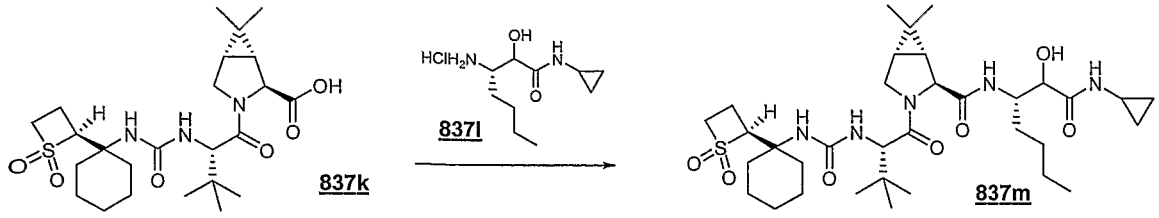
A solution of amine hydrochloride **837i** (1.5 mmol) in 30 mL of dichloromethane was treated with 5 mL of aqueous saturated sodium bicarbonate. The mixture was stirred for 10 min followed by addition of the isocyanate **837h** (1.03 eq, 13.1 mL of a 0.118M solution in toluene. The reaction mixture was stirred overnight. The reaction mixture was diluted with dichloromethane (200 mL) and washed with aqueous saturated sodium bicarbonate solution (40 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 1:9 to 1:1) to afford the product **837j** (740 mg; 84 %) as a white solid.

Step G



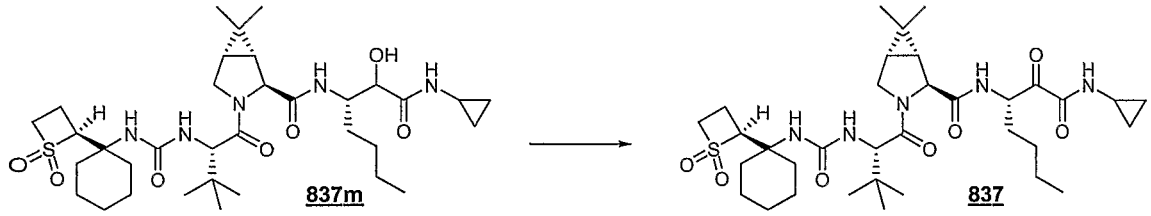
The benzyl ester **837j** (740 mg) was dissolved in 20 mL of methanol and treated with 20% palladium dihydroxide on carbon (0.1 mol%; 90 mg). The heterogeneous mixture was hydrogenated at 50 psi for 2 h. TLC (acetone/hexanes; 35:65) showed that all the starting material had been consumed. The mixture was diluted with 100 mL of dichloromethane and filtered thru a short path of celite. The filtrate was concentrated under reduced pressure to afford the product **837k** (620 mg; 98 %) as a white solid.

Step H



A solution of acid **837k** (69 mg) in 2 mL of dry dichloromethane and 2 mL of dry DMF was stirred at 0 °C and treated with HATU (1.4 eq, 74 mg). The amine salt **837l** (1.2 eq, 39 mg) was added followed by N-methylmorpholine (4 eq, 0.06 mL, d 0.920). The reaction mixture was stirred overnight (temp 0 to 25 °C). All the volatiles were removed under vacuum and the residue was dissolved in 50 mL of ethyl acetate. The organic layer was washed with water (10 mL), aqueous 1M HCl (10 mL), aqueous saturated sodium bicarbonate solution (10 mL), and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The product **837m** was used without further purification.

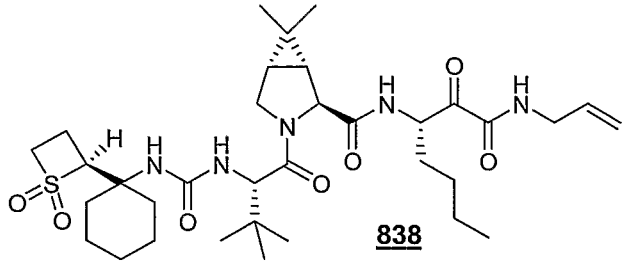
Step I



A solution of hydroxyamide **837m** (0.138 mmol) in 10 mL of dry dichloromethane was treated with Dess-Martin periodinane (2.0 eq, 117 mg). The reaction mixture was stirred at room temperature for 30 min. The mixture was treated with aqueous 1M sodium thiosulfate solution (10 mL) and stirred for 5 min. Aqueous saturated sodium bicarbonate solution (10 mL) was also added and stirring was continued for further 10 min. The mixture was extracted with dichloromethane (3 x 30 mL). The combined organic layers

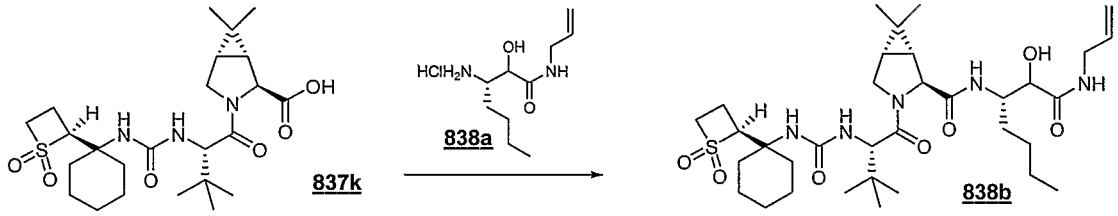
were dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 2:8 to 1:1) to afford the product **837** (66 mg; 70 %) as white solid. HRMS calcd for $C_{34}H_{56}N_5O_7S$ $[M+H]^+$: 678.3900, found 678.3883.

Example 838:



838

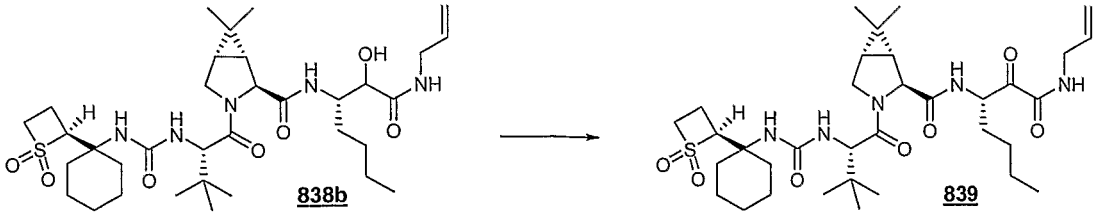
Step A



837k **838a** **838b**

A solution of acid **837k** (69 mg) in 2 mL of dry dichloromethane and 2 mL of dry DMF was stirred at 0 °C and treated with HATU (1.4 eq, 74 mg). The amine salt **838a** (1.2 eq, 39 mg) was added followed by N-methylmorpholine (4 eq, 0.06 mL, d 0.920). The reaction mixture was stirred overnight (temp 0 to 25 °C). All the volatiles were removed under vacuum and the residue was dissolved in 50 mL of ethyl acetate. The organic layer was washed with water (10 mL), aqueous 1M HCl (10 mL), aqueous saturated sodium bicarbonate solution (10 mL), and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The product **838b** was used without further purification.

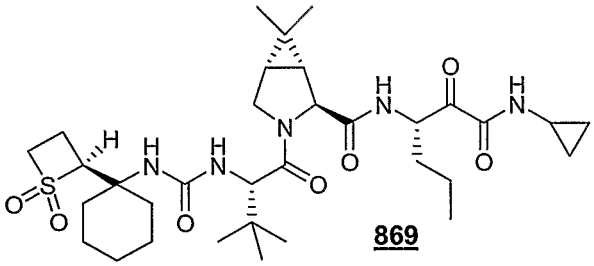
Step B



838b 839

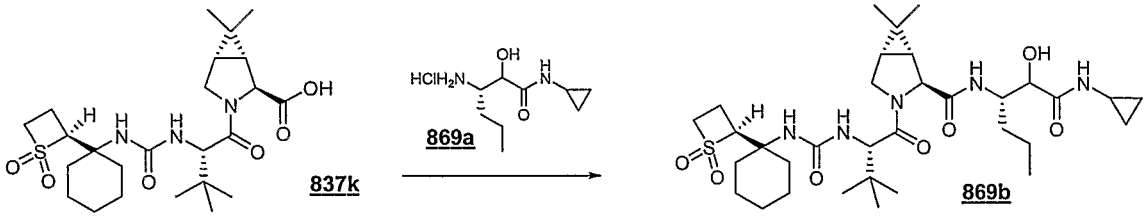
A solution of hydroxyamide **838b** (0.138 mmol) in 10 mL of dry dichloromethane was treated with Dess-Martin periodinane (2.0 eq, 117 mg). The reaction mixture was stirred at room temperature for 30 min. The mixture was treated with aqueous 1M sodium thiosulfate solution (10 mL) and stirred for 5 min. Aqueous saturated sodium bicarbonate solution (10 mL) was also added and stirring was continued for further 10 min. The mixture was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 1:9 to 4:6) to afford the product **838** (71 mg; 76 %) as white solid. HRMS calcd for $C_{34}H_{56}N_5O_7S$ $[M+H]^+$: 678.3900, found 678.3883.

Example 869:



869

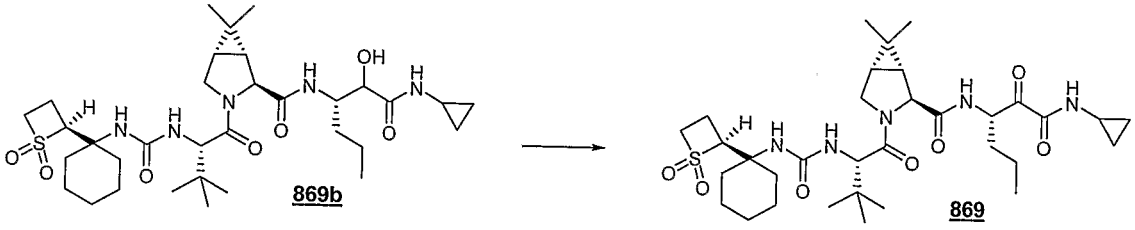
Step A



837k 869a 869b

A solution of acid **837k** (69 mg) in 2 mL of dry dichloromethane and 2 mL of dry DMF was stirred at 0 °C and treated with HATU (1.4 eq, 74 mg). The amine salt **869a** (1.2 eq, 37 mg) was added followed by N-methylmorpholine (4 eq, 0.06 mL, d 0.920). The reaction mixture was stirred overnight (temp 0 to 25 °C). All the volatiles were removed under vacuum and the residue was dissolved in 50 mL of ethyl acetate. The organic layer was washed with water (10 mL), aqueous 1M HCl (10 mL), aqueous saturated sodium bicarbonate solution (10 mL), and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The product **869b** was used without further purification.

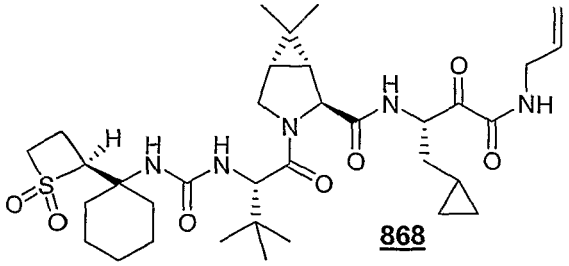
Step B



869b **869**

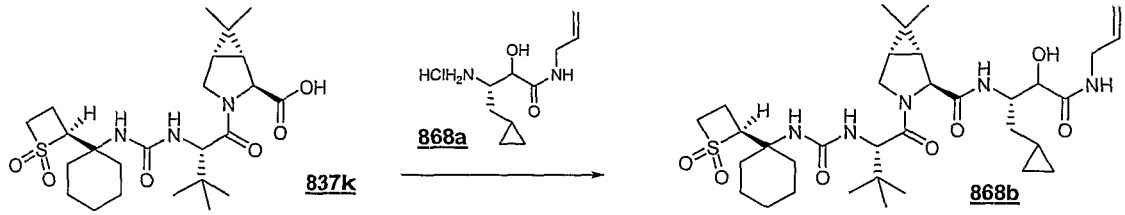
A solution of hydroxyamide **869b** (0.138 mmol) in 10 mL of dry dichloromethane was treated with Dess-Martin periodinane (2.0 eq, 117 mg). The reaction mixture was stirred at room temperature for 30 min. The mixture was treated with aqueous 1M sodium thiosulfate solution (10 mL) and stirred for 5 min. Aqueous saturated sodium bicarbonate solution (10 mL) was also added and stirring was continued for further 10 min. The mixture was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 18:85 to 45:55) to afford the product **869** (69 mg; 75 %) as white solid.

Preparative Example 868:



868

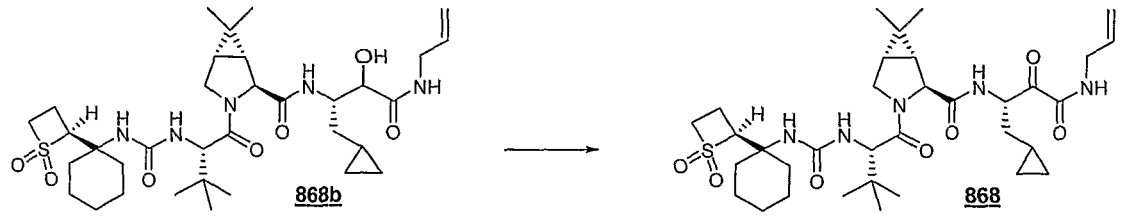
Step A



837k 868a 868b

A solution of acid **837k** (69 mg) in 2 mL of dry dichloromethane and 2 mL of dry DMF was stirred at 0 °C and treated with HATU (1.4 eq, 74 mg). The amine salt **868a** (1.2 eq, 39 mg) was added followed by N-methylmorpholine (4 eq, 0.06 mL, d 0.920). The reaction mixture was stirred overnight (temp 0 to 25 °C). All the volatiles were removed under vacuum and the residue was dissolved in 50 mL of ethyl acetate. The organic layer was washed with water (10 mL), aqueous 1M HCl (10 mL), aqueous saturated sodium bicarbonate solution (10 mL), and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The product **868b** was used without further purification.

Step B

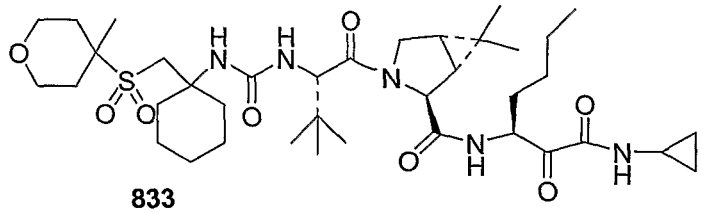


868b 868

A solution of hydroxyamide **868b** (0.138 mmol) in 10 mL of dry dichloromethane was treated with Dess-Martin periodinane (2.0 eq, 117 mg).

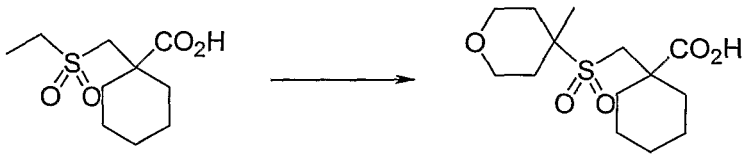
The reaction mixture was stirred at room temperature for 30 min. The mixture was treated with aqueous 1M sodium thiosulfate solution (10 mL) and stirred for 5 min. Aqueous saturated sodium bicarbonate solution (10 mL) was also added and stirring was continued for further 10 min. The mixture was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 1:9 to 4:6) to afford the product **868** (73 mg; 78 %) as white solid.

Example **833**:



833

Step 1

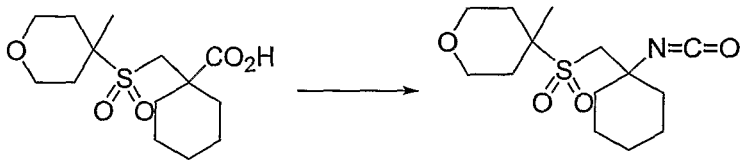


833a **833b**

To a solution of ethylsulfone acid **833a** (2.06 g, 8.79 mmol) in anhydrous THF at -78°C under N_2 was added LiHMDS solution (19.3 mL, 1.0 Min THF). The mixture was stirred at -78°C for 30 min before it was allowed to warmed to 0°C along with a cold acetone bath. It was then re-cooled to -78°C and to it was added 2-bromoethyl ether (1.8 mL, 13.2 mmol). After stirred at -78°C for 30 min, the mixture was warmed to rt and stirred for 2 h. It was again re-cooled to -78°C and to it was added LiHMDS solution (10.6 mL, 10.6 mmol). After stirred at -78°C for 30 min, the mixture was warmed to rt and stirred for 3 h before it was quenched with 1 N aqueous HCl solution until the pH is about 1-2. The solution was extracted with CH_2Cl_2 (2x450 mL).

Combined organic solution was dried ($MgSO_4$), filtered and concentrated. The crude product was dissolved in 1 N NaOH solution (300 mL) and extracted with EtOAc (100 mL). After layers were separated, the organic solution was washed with 1 N NaOH (2x150 mL). The combined aqueous solution was acidified to pH~1 using 6 N HCl solution. It was extracted with EtOAc (3 x 300 mL). The organic solutions were combined, dried ($MgSO_4$), filtered and concentrated to give 2.3 g product (**833b**; 7.56 mmol, 89%).

Step 2

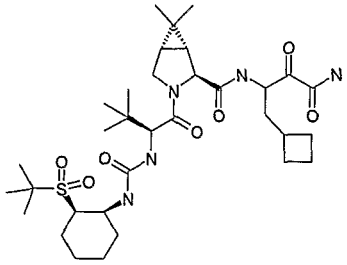
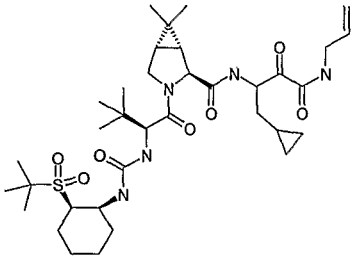
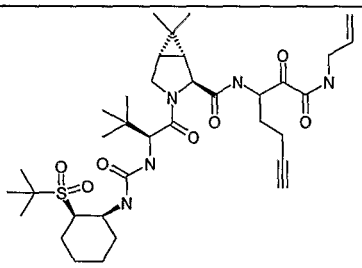


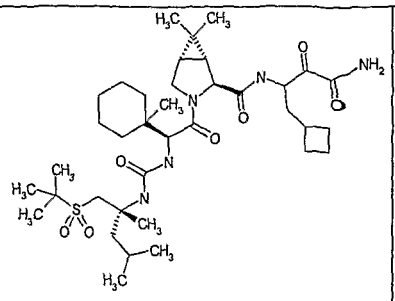
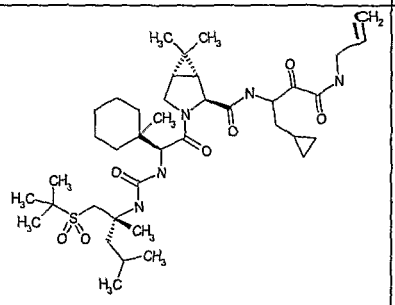
833b **833c**

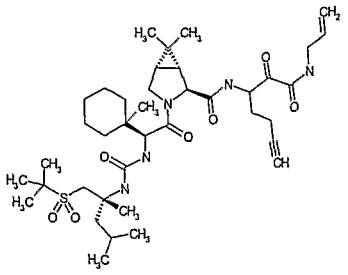
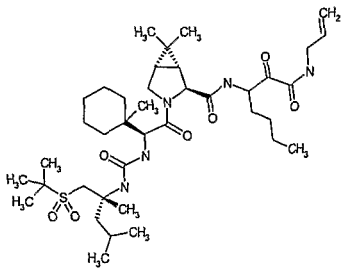
To the acid **833b** (2.30 g, 7.56 mmol) in toluene at rt under N_2 was added triethylamine (1.15 mL, 8.32 mmol) and diphenylphosphoryl azide (1.79 mL, 8.32 mmol). The resulting mixture was stirred at rt for 30 min and heated to reflux for 5.5 h. After it was cooled to rt, more toluene was added to make up a 0.19 M solution of the isocyanate **833c**, which was used without further purification.

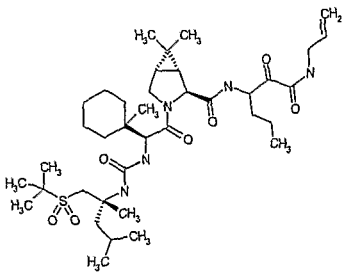
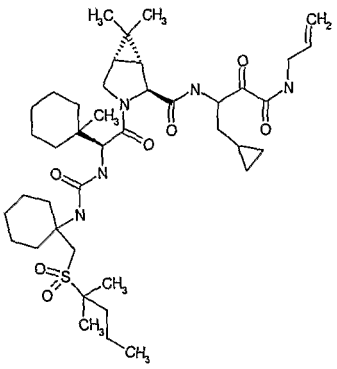
Using the aforementioned procedures **833c** was transformed into **833**.

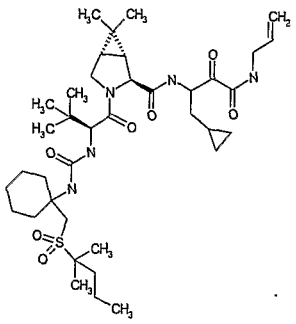
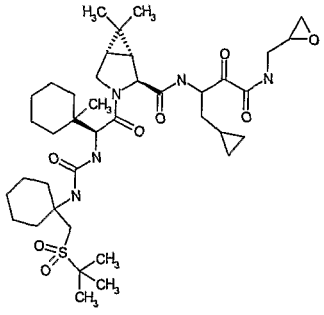
Table 3A

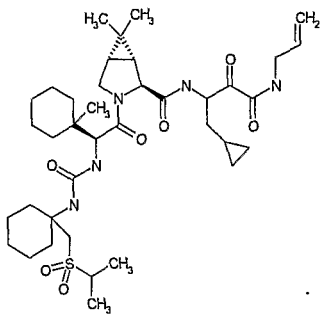
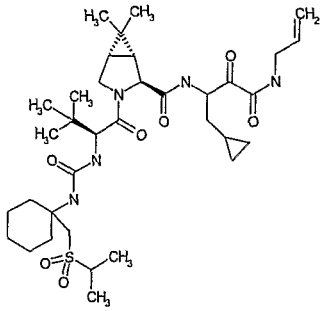
Compo -und #	structure	mol weight structure	Select LC-MS Data (M+H)	Ki* Range
397		665.887	666.3	B
398		691.925	692.4	C
399		689.909	690.3	B

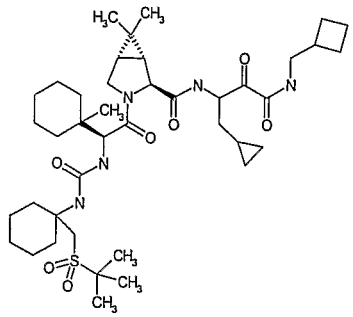
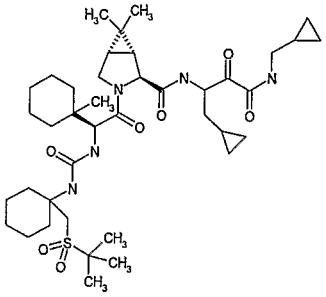
400		722.008	722.4	A
401		748.0462	748.4	A

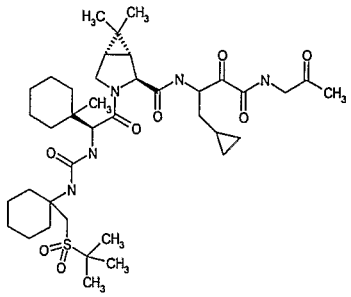
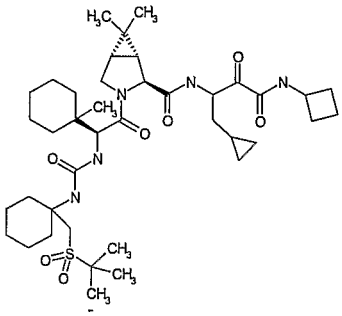
402		746.0303	746.2	A
403		750.0621	750.4	A

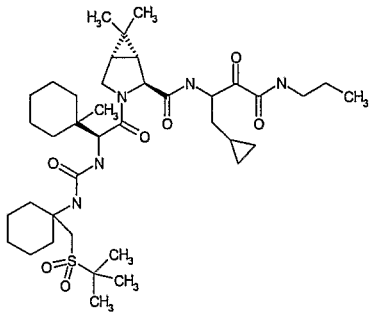
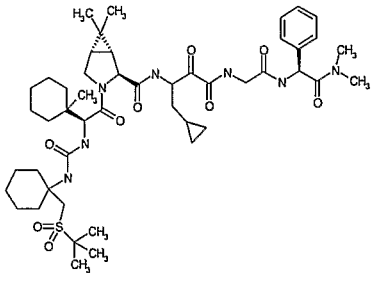
404		736.0351	736.4	A
405		774.0844		A

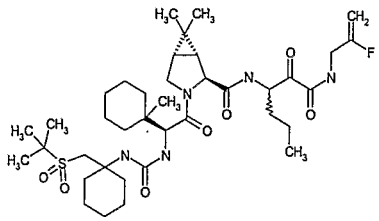
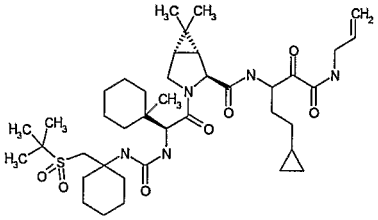
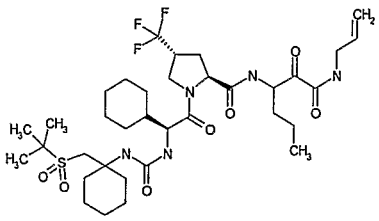
406		734.0191		A
407		762.0297		A

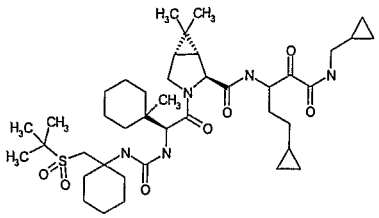
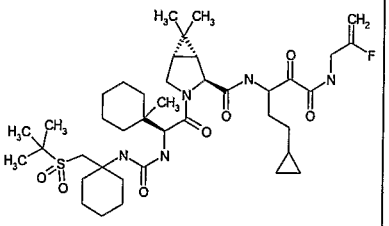
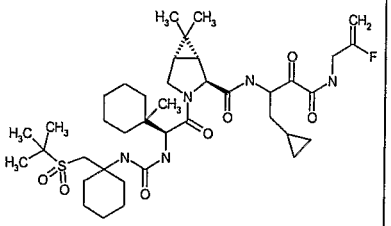
408		732.0032		A
409		691.9378		A

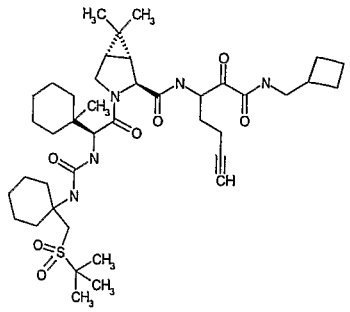
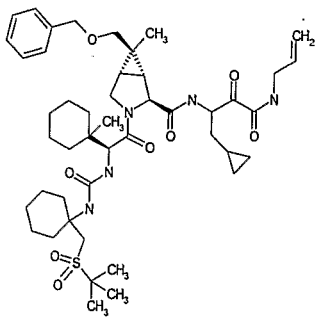
410		774.0844		A
411		760.0574		A

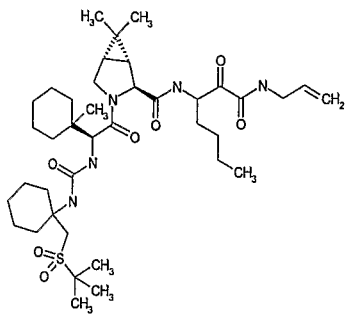
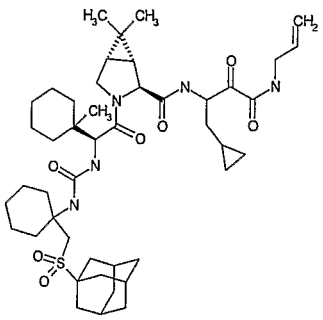
412		762.0297		A
413		760.0574		A

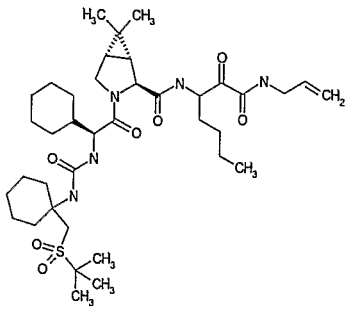
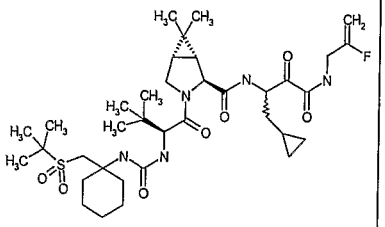
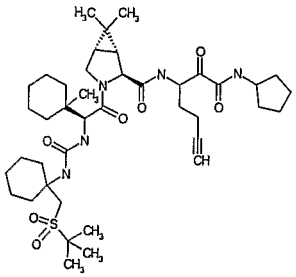
414		748.0462		A
415		924.2225		B

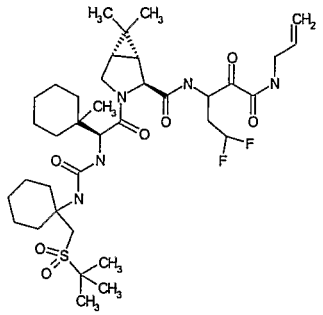
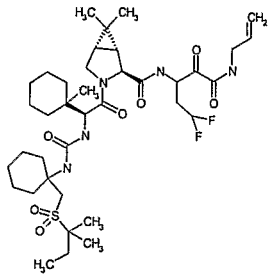
416		752.0095		A
417		760.0574		A
418		747.9251		A

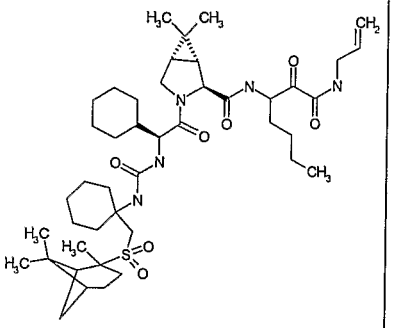
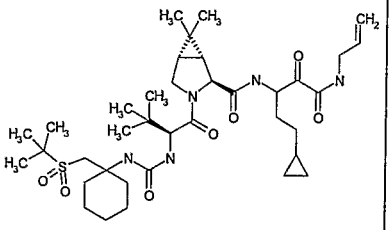
419		774.0844		A
420		778.0478		A
421		764.0207		A

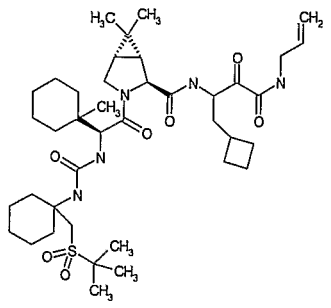
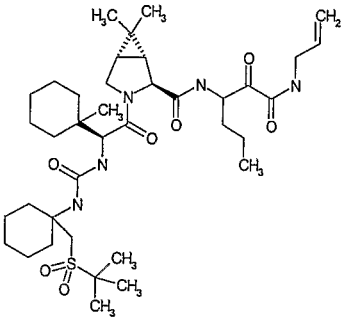
422		772.0685		A
423		852.1555	852.5	A

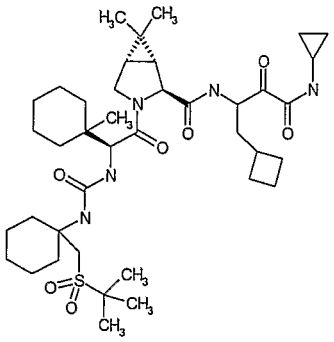
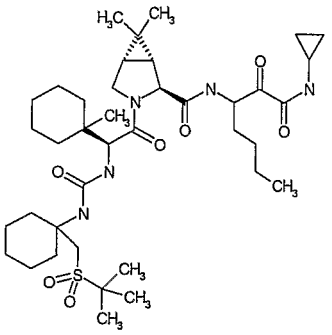
424		748.0462		A
425		824.145		A

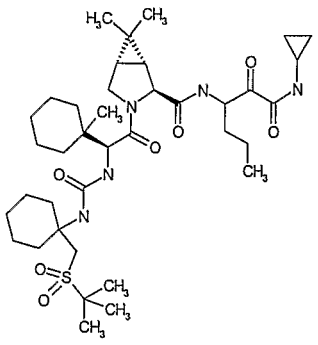
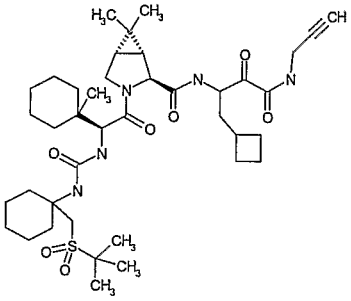
426		734.0191		A
427		723.9554		A
428		772.0685		A

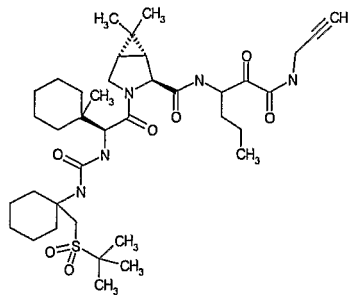
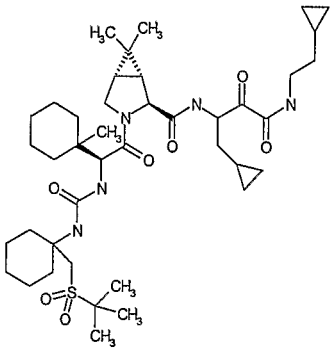
429		755.9729		A
430		770		A

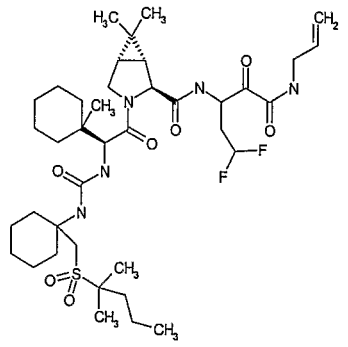
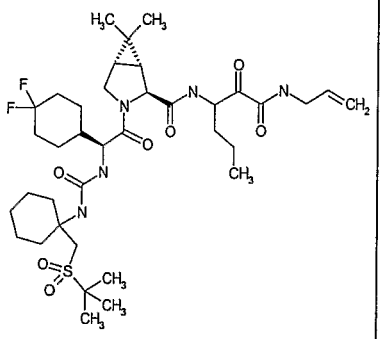
431		814.1498		A
432		719.992		A

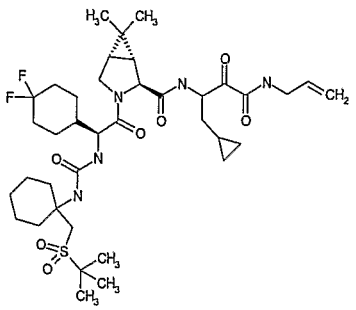
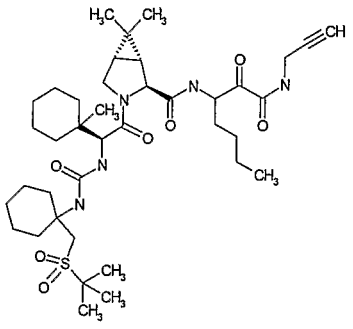
433		760.0574		A
434		734.0191		A

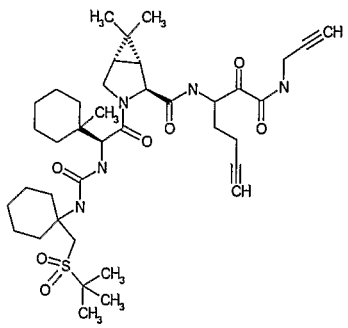
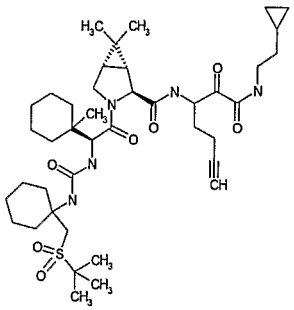
435		760.0574		A
436		748.0462		A

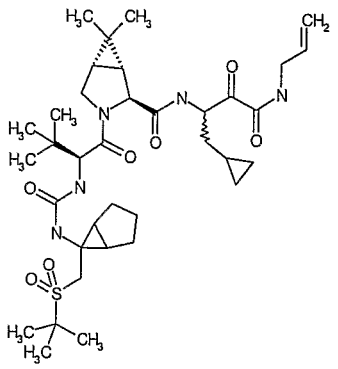
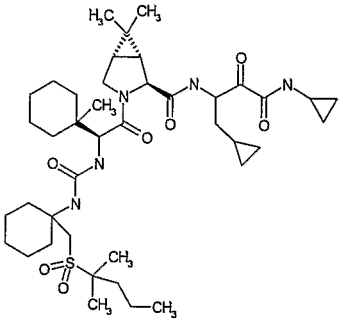
437		734.0191		A
438		758.0414		A

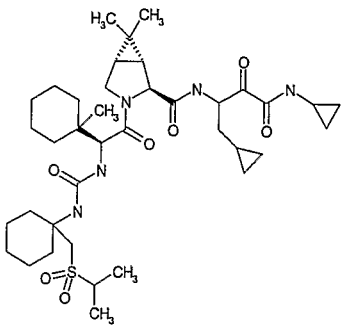
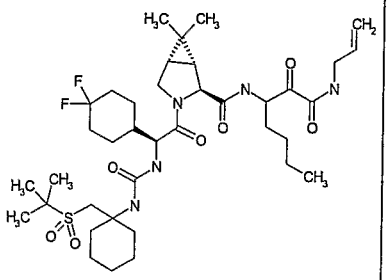
439		732.0032		A
440		774.0844	774.2	A

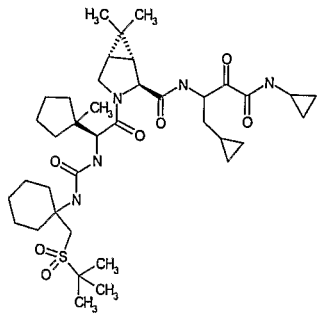
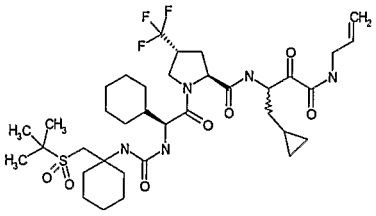
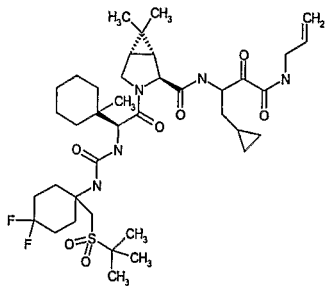
441		784.0271	784.2	A
442		755.9729	756.2	A

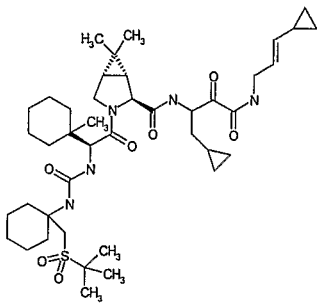
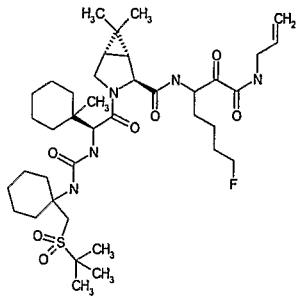
443		767.984	768.4	A
444		746.0303		A

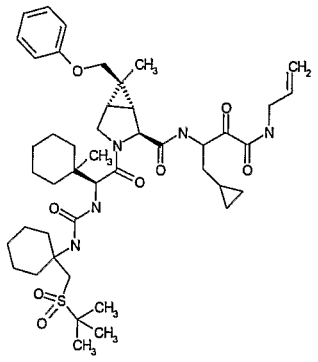
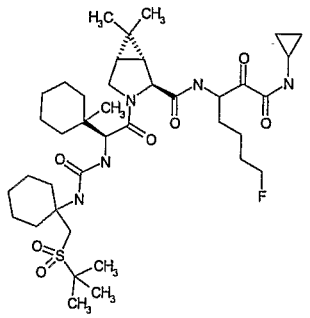
445		741.9984		A
446		772.0685		A

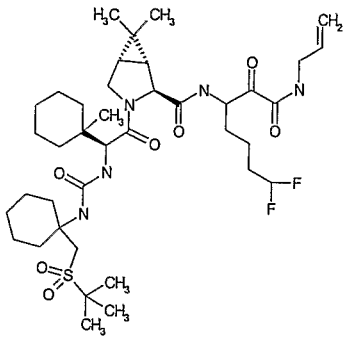
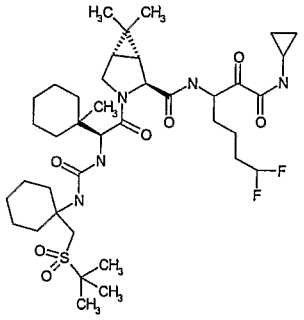
447		703.949	704.4	A
448		774.0844		A

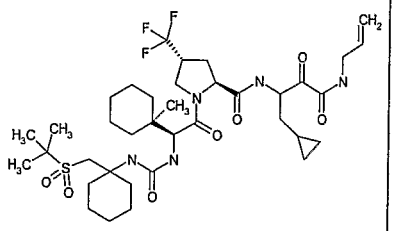
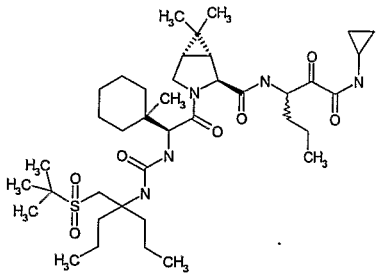
449		732.0032		A
450		770	770.2	A

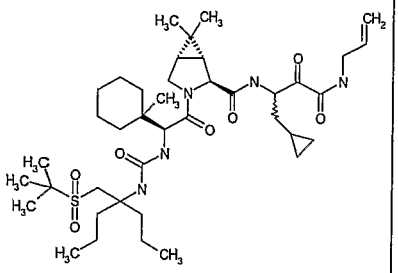
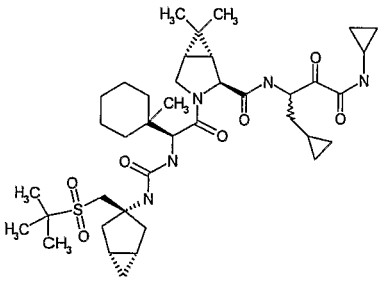
451		732.0032	732.2	A
452		759.9362		A
453		782.0111		A

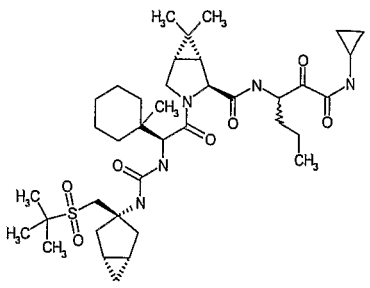
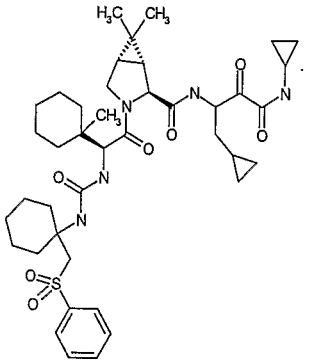
454		786.0956		A
455		766.0366		A

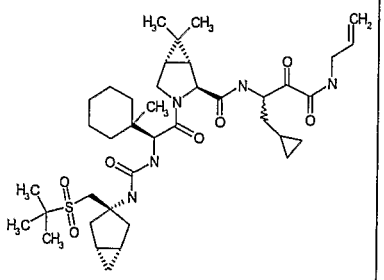
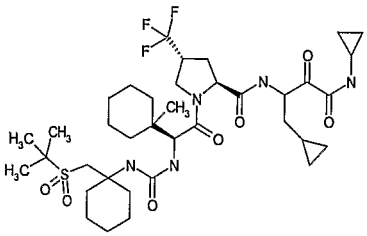
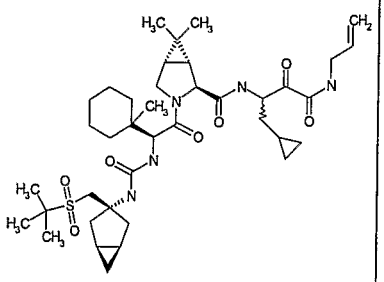
456		838.1284		B
457		766.0366	766.4	A

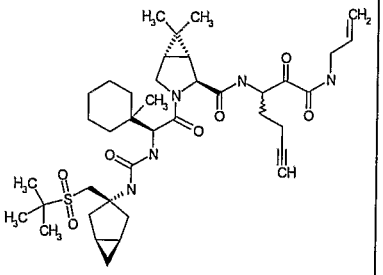
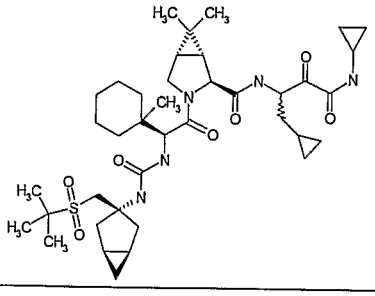
458		784.0271	784.4	A
459		784.0271	784.2	A

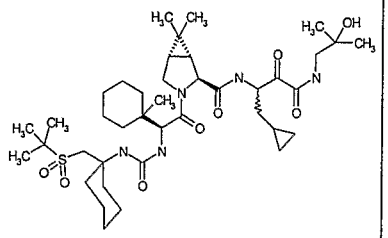
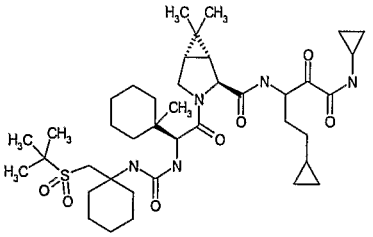
460		773.9633		A
461		750.0621	750.9	B

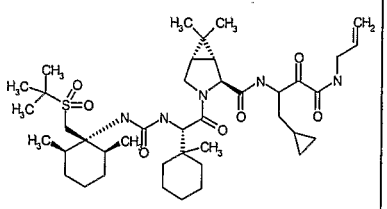
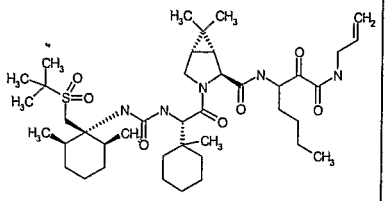
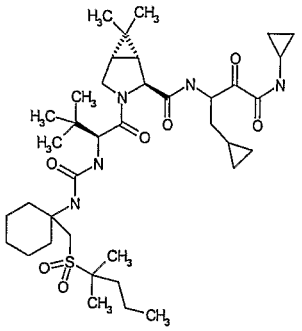
462		762.0733	762.41	C
463		744.0143	744.2	B

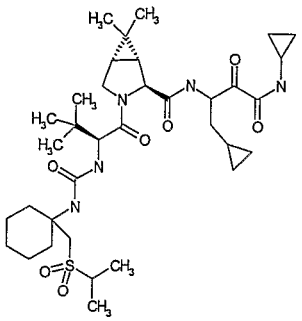
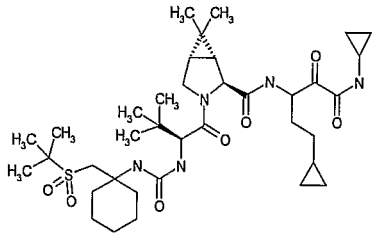
464		732.0032	732.4	A
465		766.0207		B

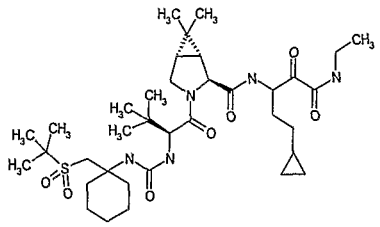
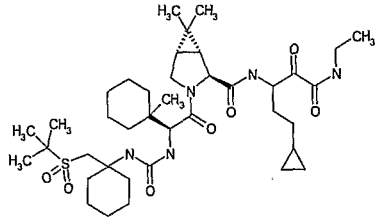
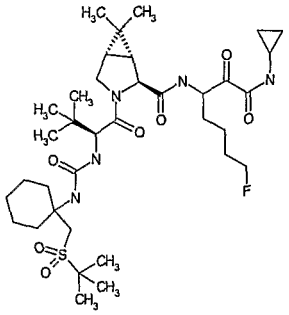
466		744.0143	744.4	A
467		773.9633		B
468		744.0143	744.70	B

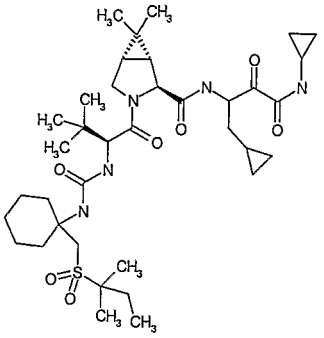
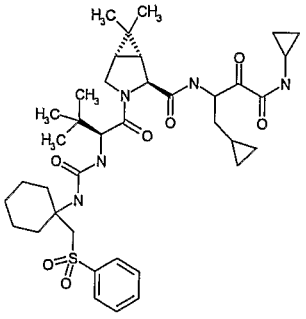
469		741.9984	742.40	A
470		744.0143	744.38	B

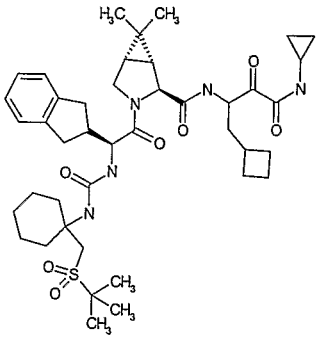
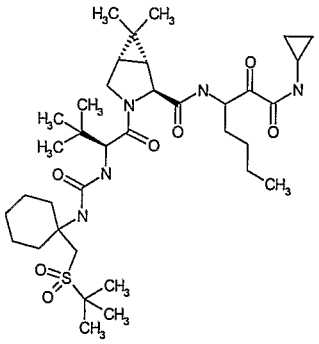
471		778.0727	778.7	B
472		760.0574		A

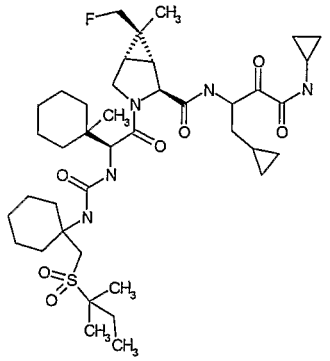
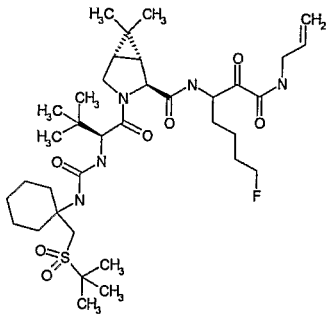
473		774.0844	774.4	A
474		776.1004	776.5	A
475		734.0191		A

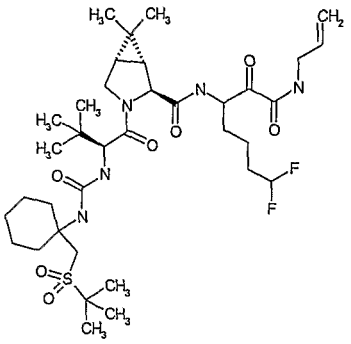
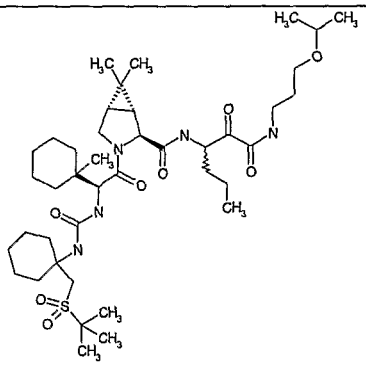
476		691.9378		B
477		719.992		A

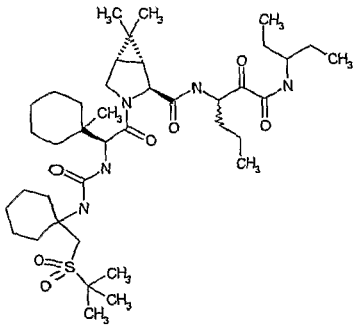
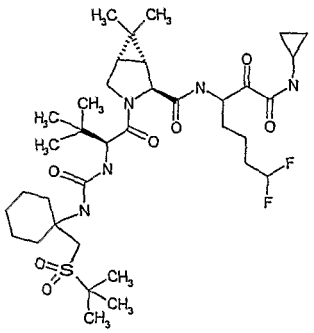
478		707.9809		A
479		748.0462		A
480		725.9713	726.4	A

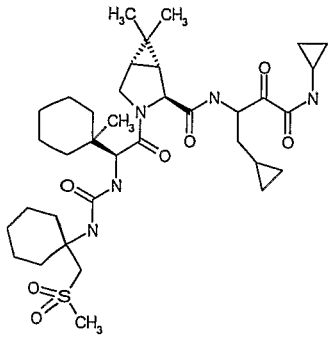
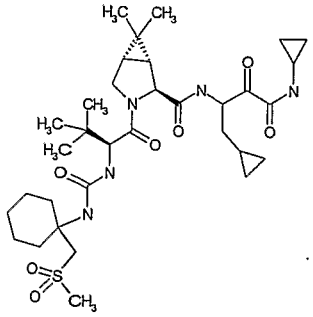
481		719.992		A
482		725.9554		B

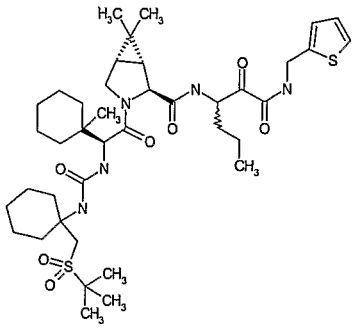
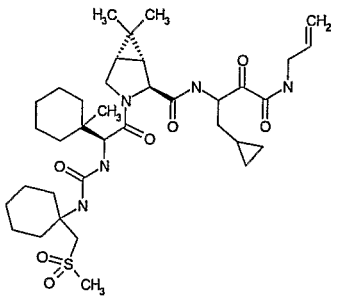
483		780.0478		B
484		707.9809		A

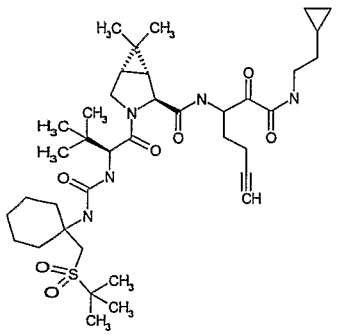
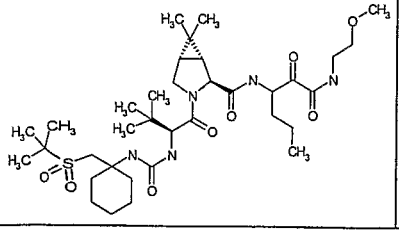
485		778.0478		B
486		725.9713		A

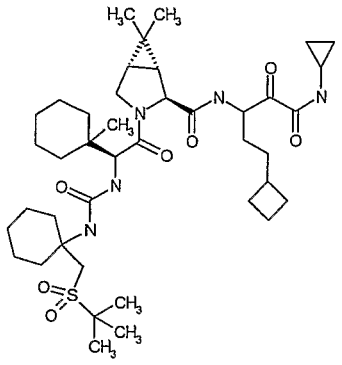
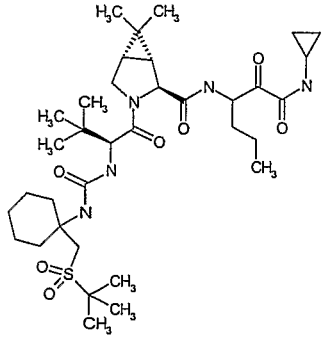
487		743.9617		A
488		794.1157	794.2	B

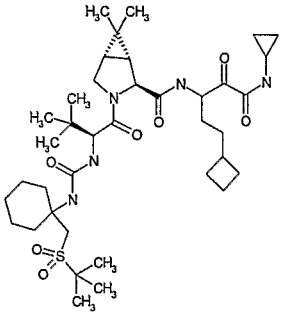
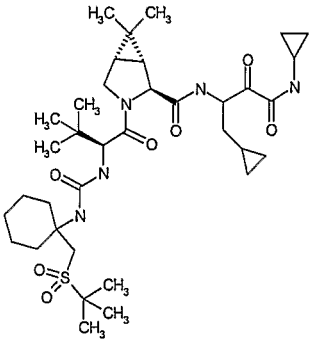
489		764.0892	764.1	B
490		743.9617	744.4	A

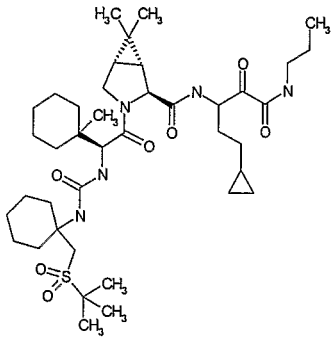
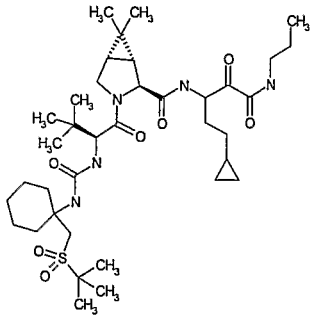
491		703.949		A
492		663.8837		A

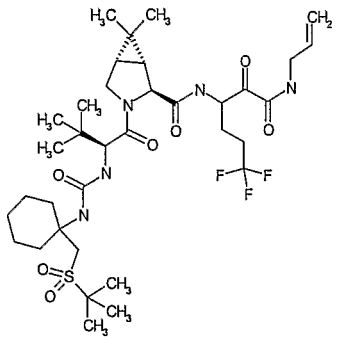
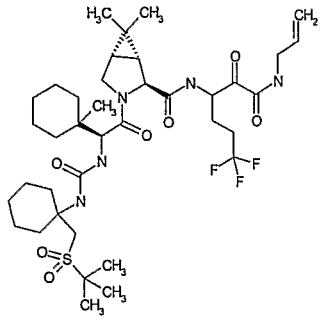
493		790.1054	791.4	A
494		703.949		A

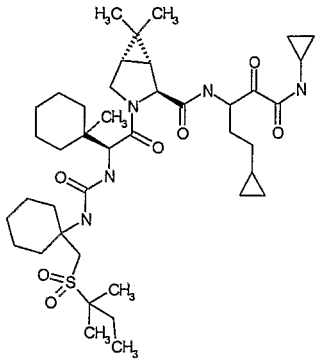
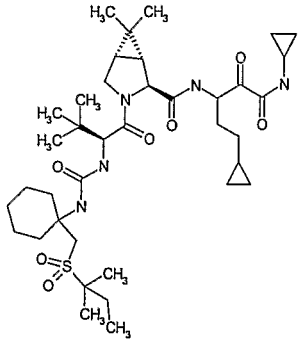
495		732.0032		A
496		712		A

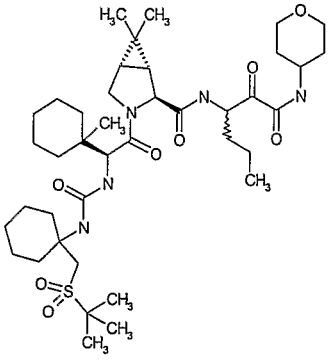
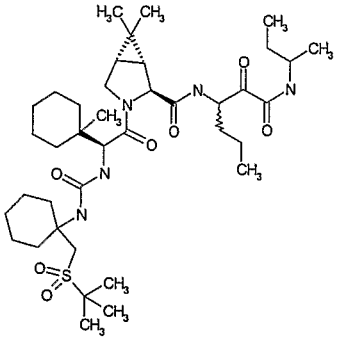
497		774	774.2	A
498		693.9538		A

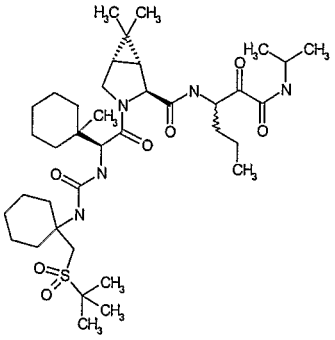
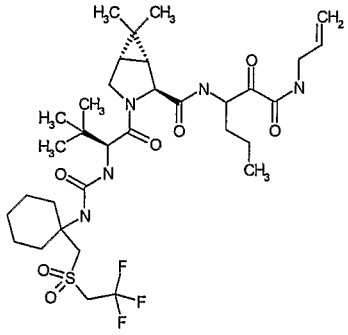
499		734	735.2	A
500		706		A

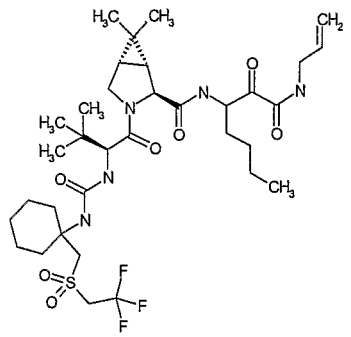
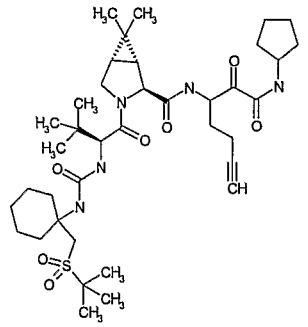
501		762		A
502		722		A

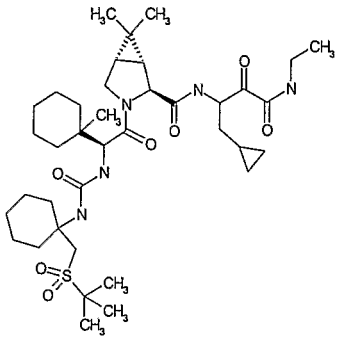
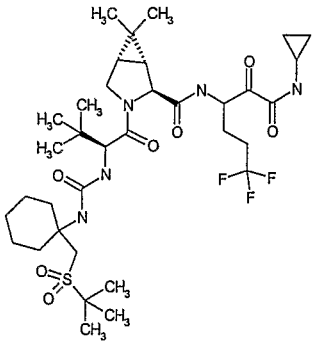
503		748		A
504		788		A

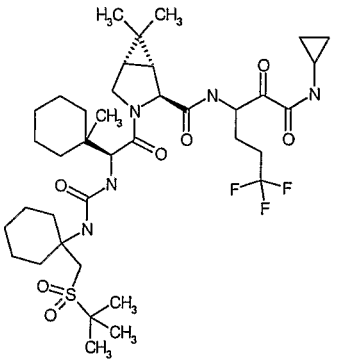
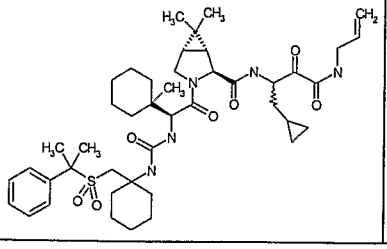
505		774		A
506		734		A

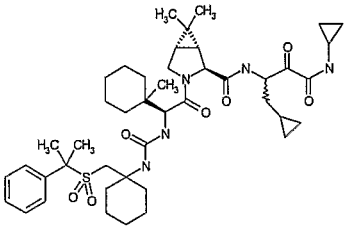
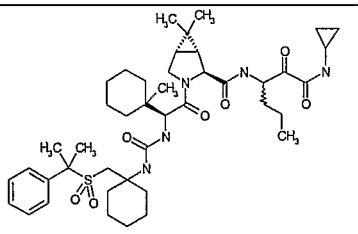
507		778	778.2	C
508		750	750.5	B

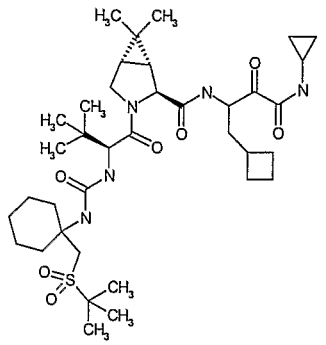
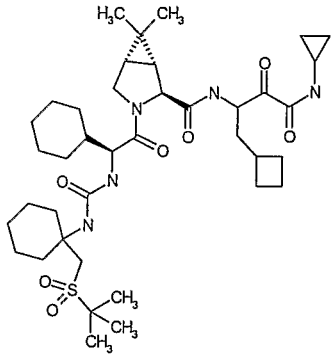
509		736	736.2	A
510		720		A

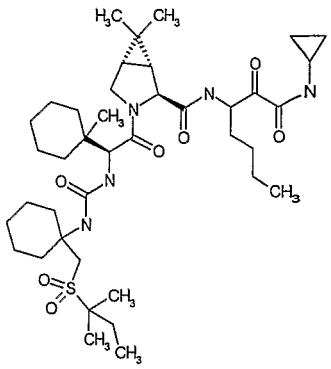
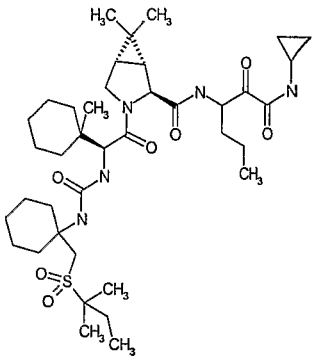
511		734		A
512		732	733.4	A

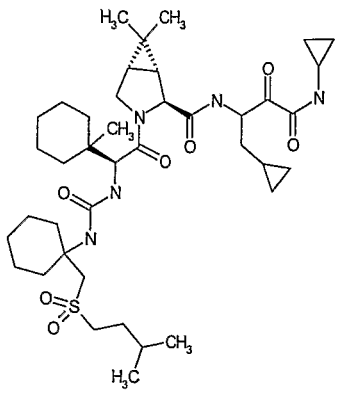
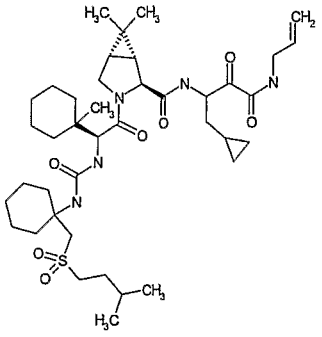
513		734	734.4	A
514		748		A

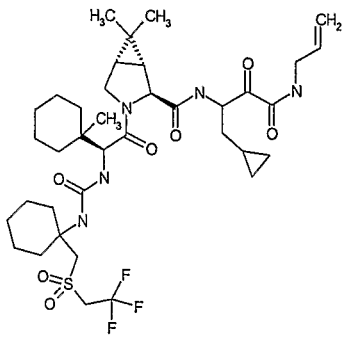
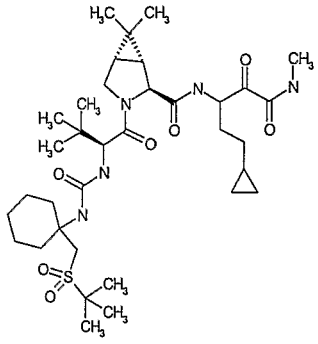
515		788		A
516		808.102	809.1	A

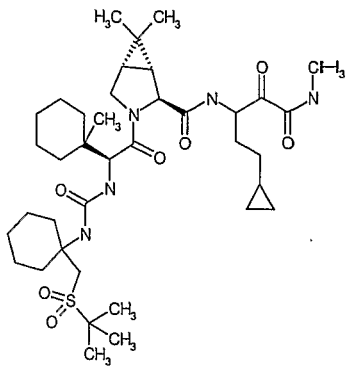
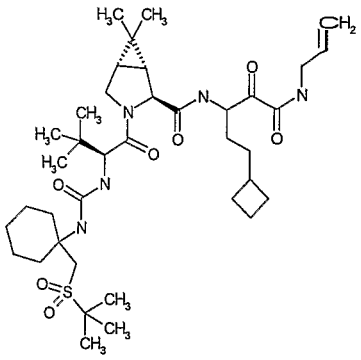
517		808.102	809.1	B
518		796.0908	797.1	A

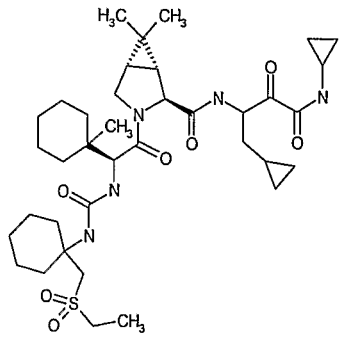
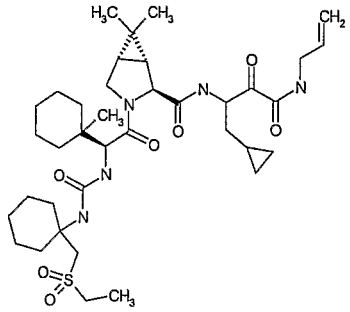
519		719.992		A
520		746.0303		B

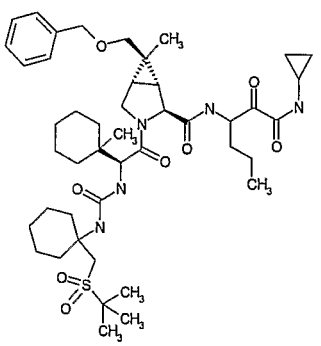
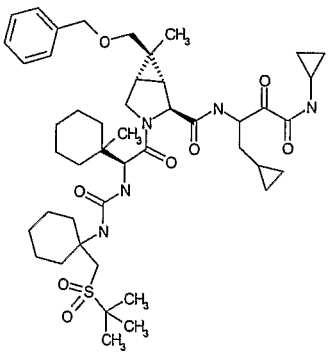
521		762.0733		A
522		748.0462		A

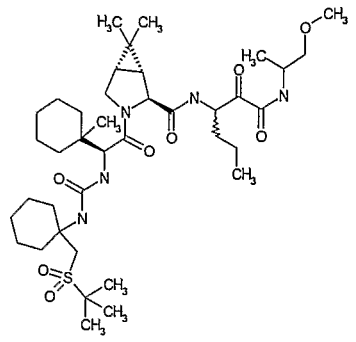
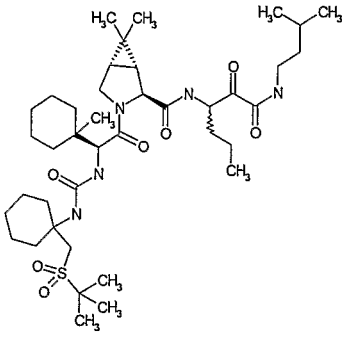
523		760.0574		A
524		760.0574		A

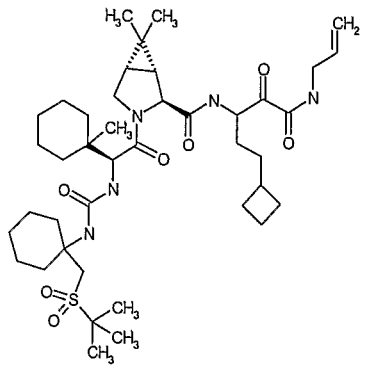
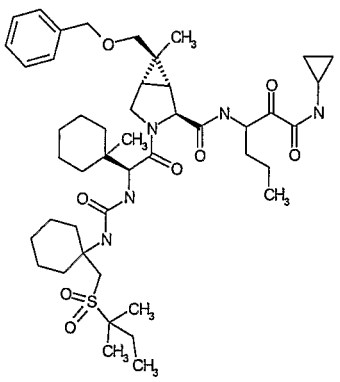
525		771.9474		A
526		693.9538		A

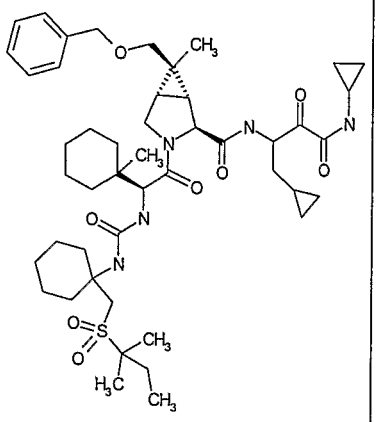
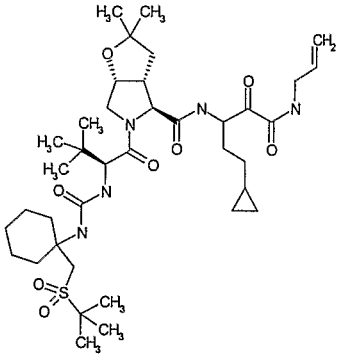
527		734.0191		A
528		734.0191		A

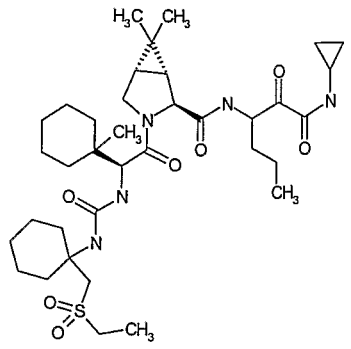
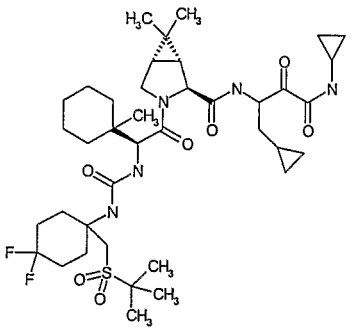
529		717.9761		A
530		717.9761		A

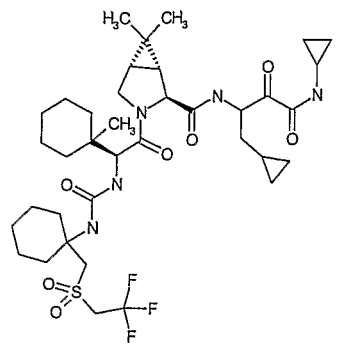
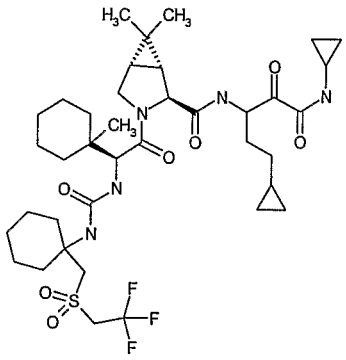
531		840.1444		A
532		852.1555		A

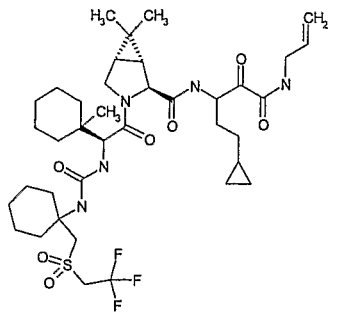
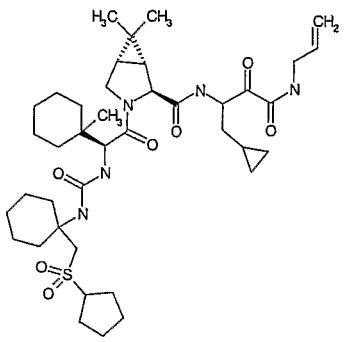
533		766.0615	766.4	B
534		764.0892	764.4	C

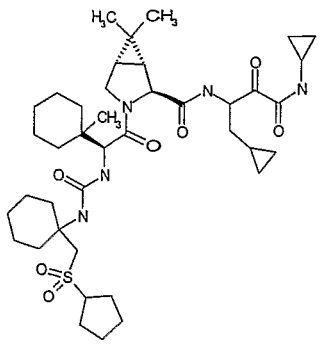
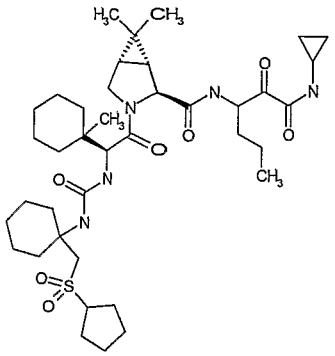
535		774.0844		A
536		854.1715		A

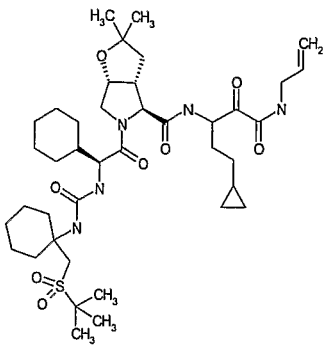
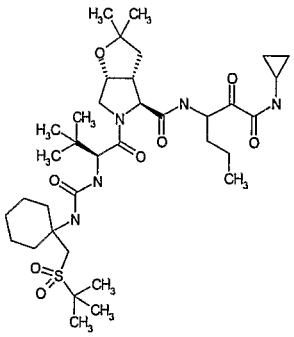
537		866.1826		A
538		750.0185	750.4	A

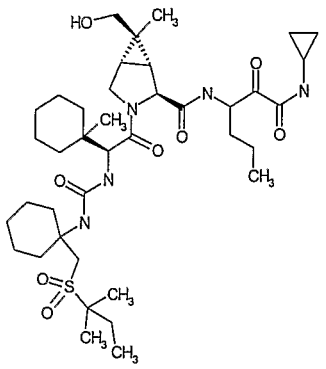
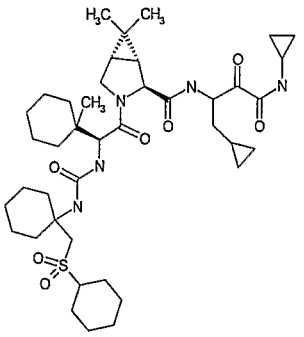
539		705.9649		A
540		782.0111		A

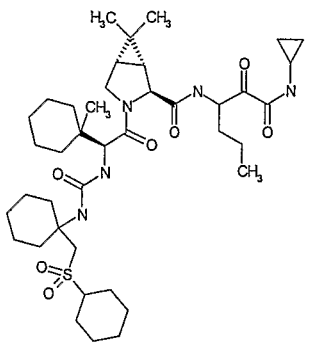
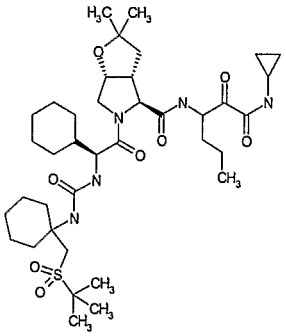
541		771.9474		A
542		785.9745		A

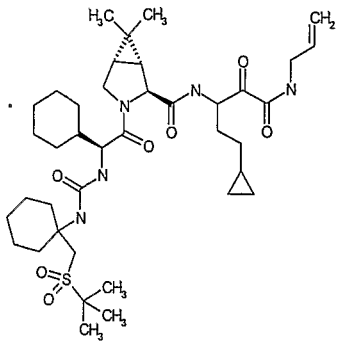
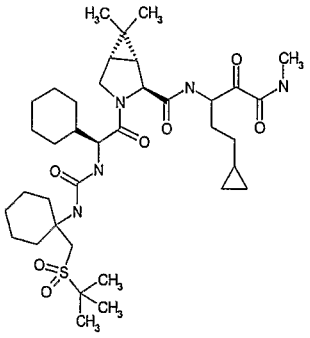
543		785.9745		A
544		758.0414		A

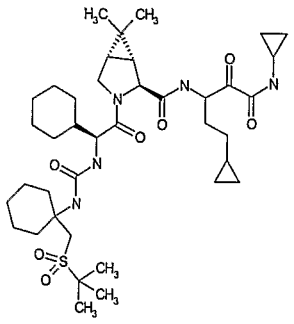
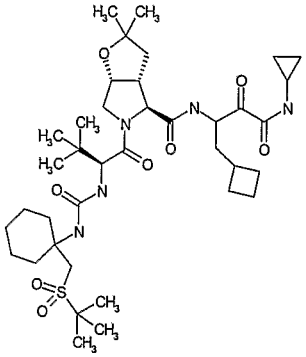
545		758.0414		A
546		746.0303		A

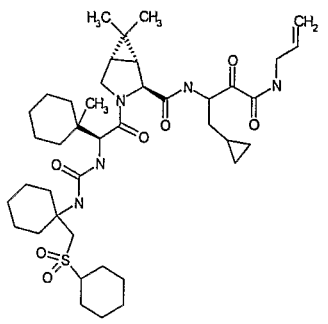
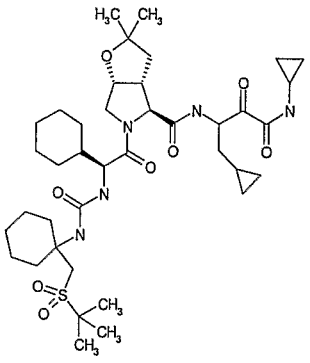
547		776.0568	776.4	A
548		723.9803	724.4	B

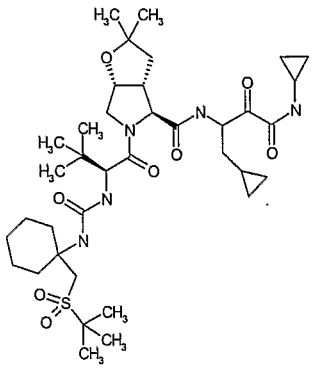
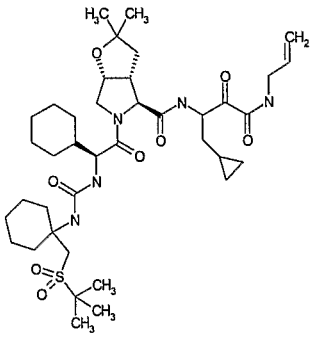
549		764.0456		A
550		772.0685		A

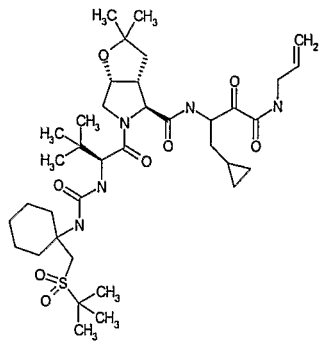
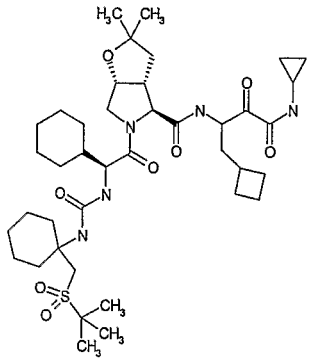
551		760.0574		A
552		750.0185	750.1	B

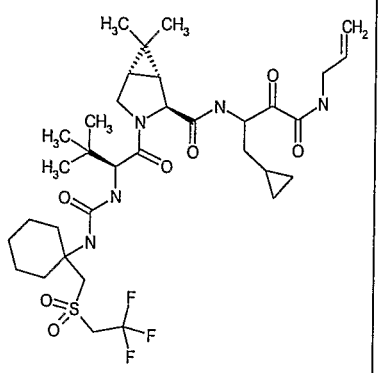
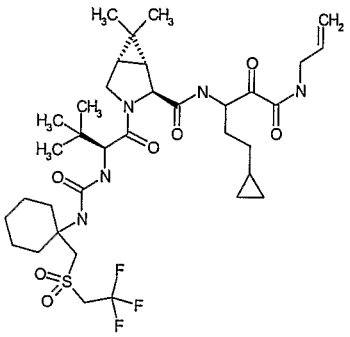
553		746.0303		A
554		719.992		A

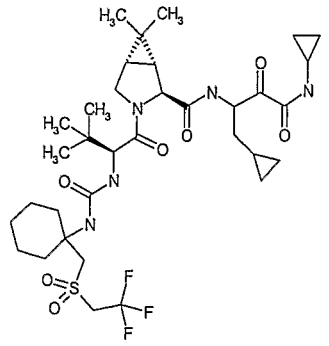
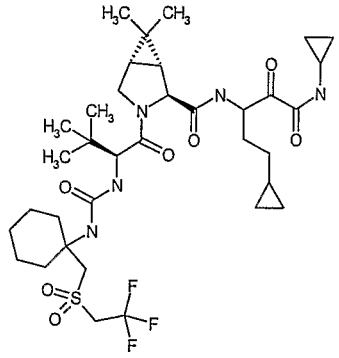
555		746.0303		A
556		750.0185	750.1	B

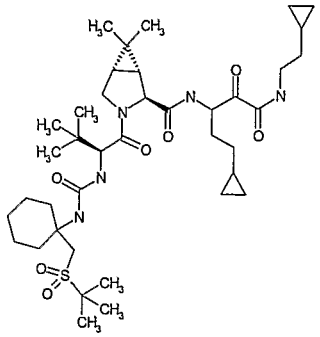
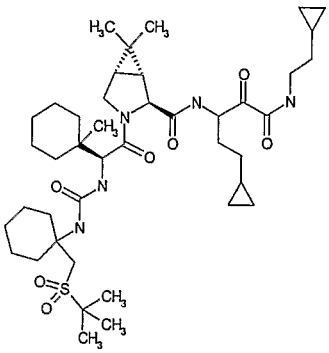
557		772.0685		A
558		762.0297		B

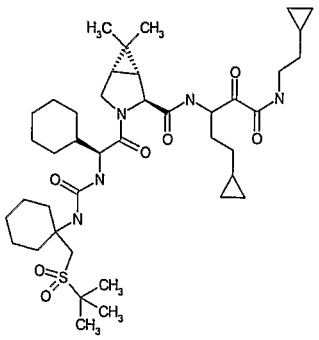
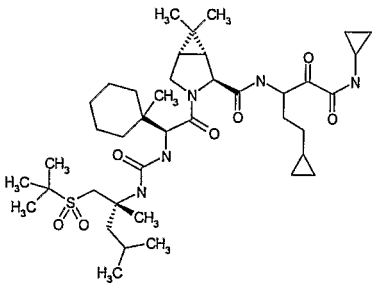
559		735.9914		B
560		762.0297		A

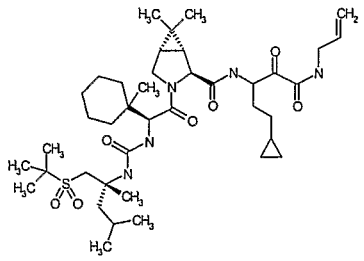
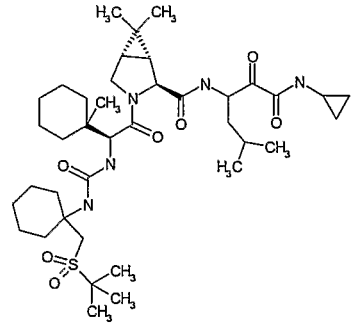
561		735.9914		A
562		776.0568		B

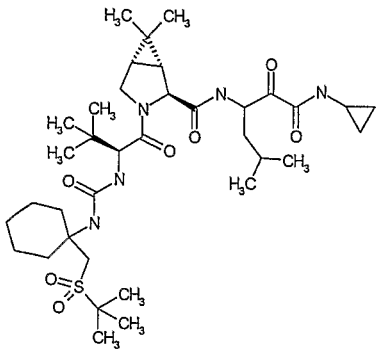
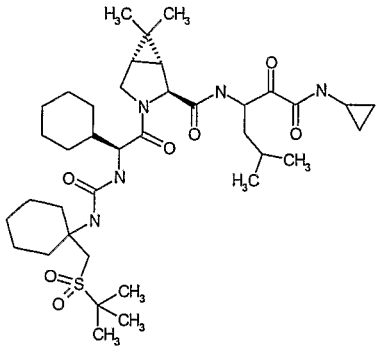
563		731.882		A
564		745.9091		A

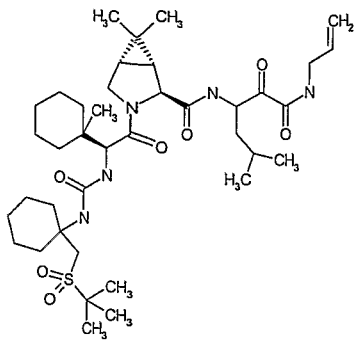
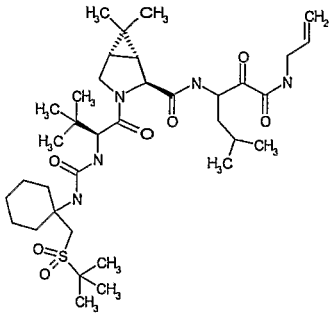
565		731.882		A
566		745.9091		1A

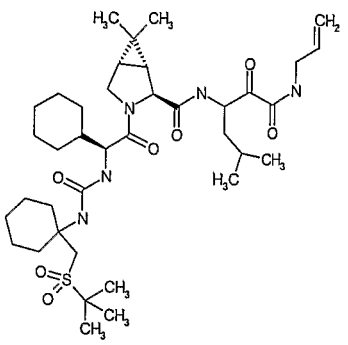
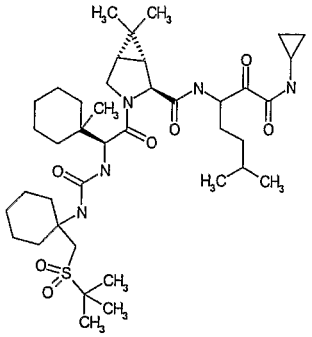
567		748.0462		A
568		788.1115		A

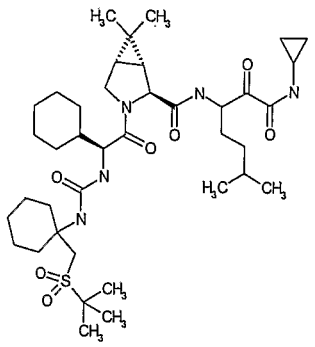
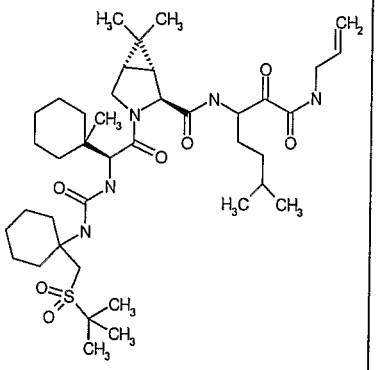
569		774.0844		A
570		762.0733	763.1	A

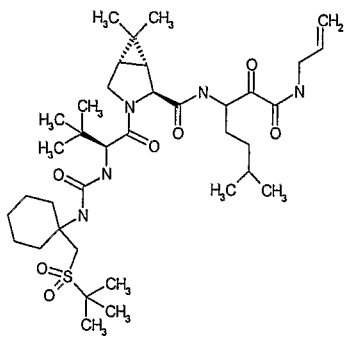
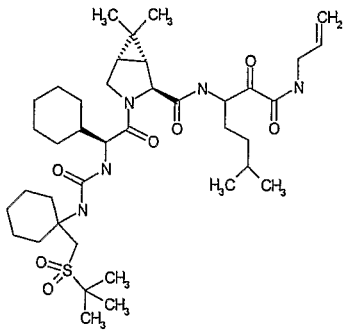
571		762.0733	763.1	A
572		748.0462		B

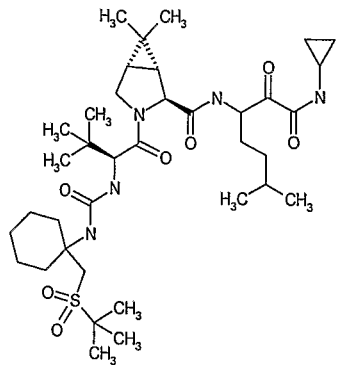
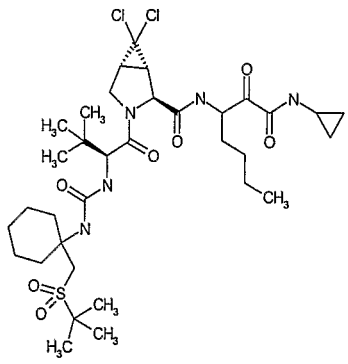
573		707.9809		B
574		734.0191		B

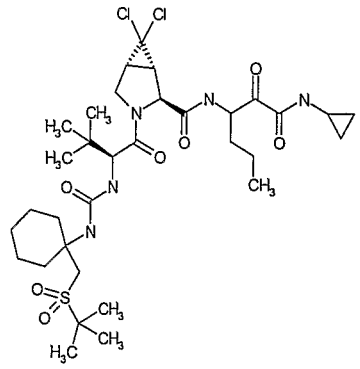
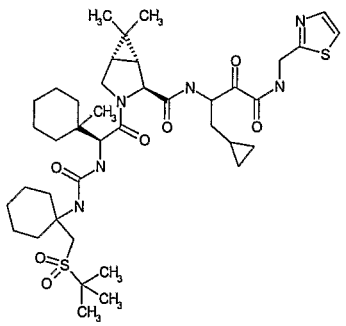
575		748.0462		B
576		707.9809		B

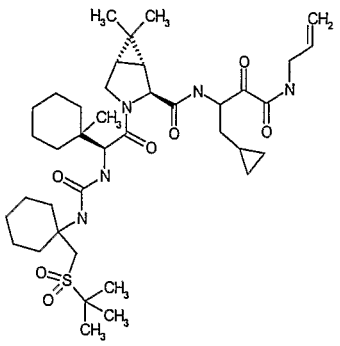
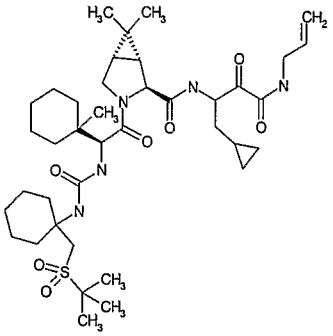
577		734.0191		C
578		762.0733	762.4	B

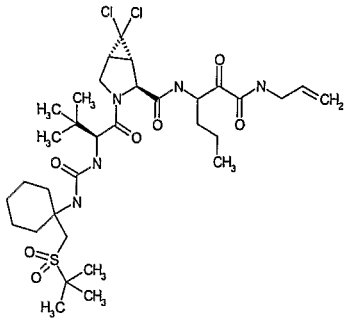
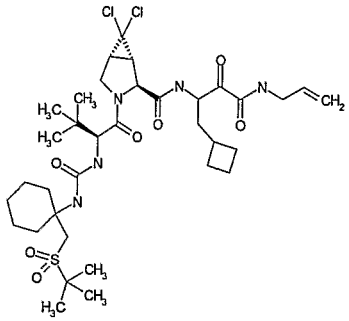
579		748.0462	748.4	A
580		762.0733		A

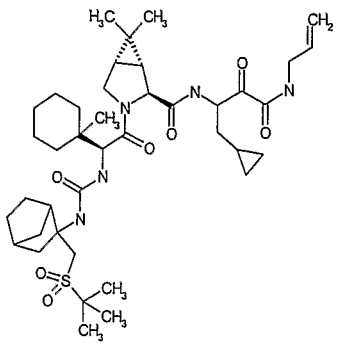
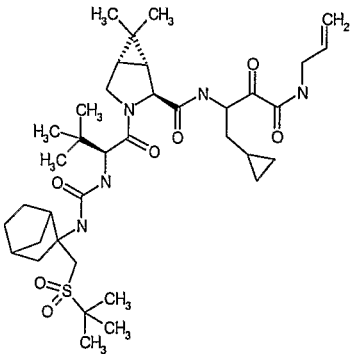
581		722.008		A
582		748.0462		A

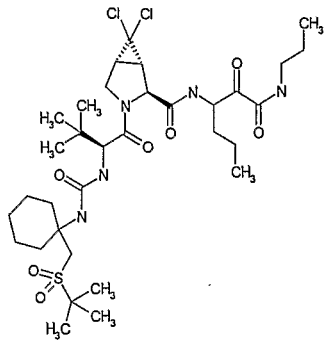
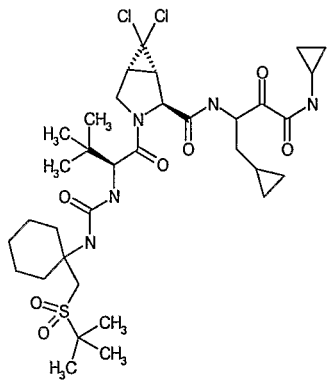
583		722.008	722.4	A
584		748.8168	748.4	A

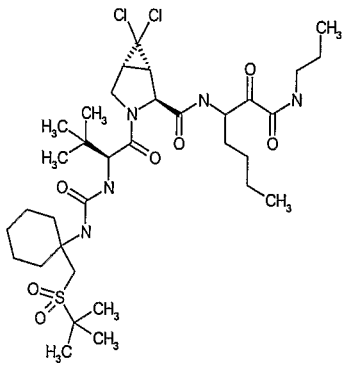
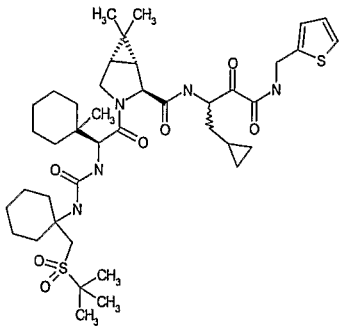
585		734.7897	734.4	A
586		803.1041	803.4	A

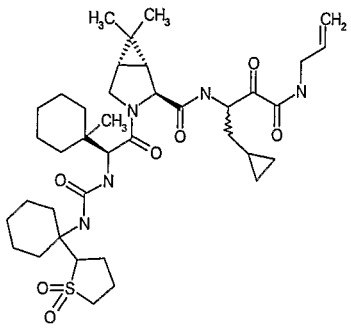
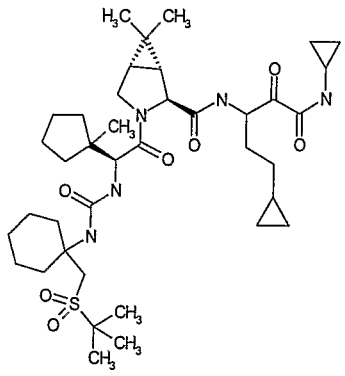
587		746.0303		C
588		746.0303		6

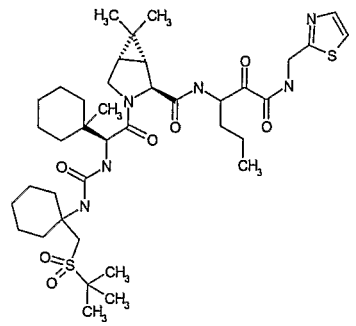
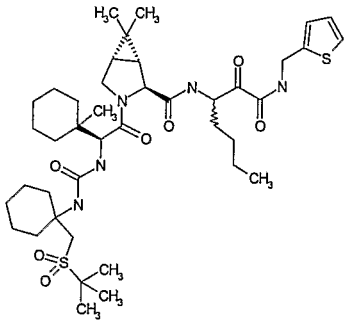
589		734.7897	734.1	A
590		760.8279	760.1	A

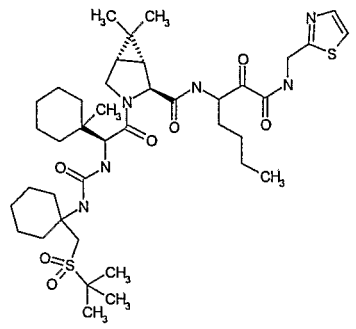
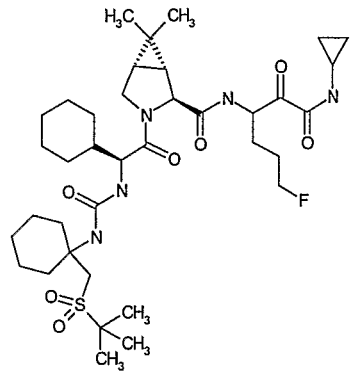
591		758.0414		A
592		717.9761		A

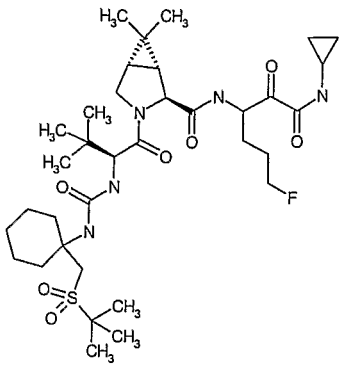
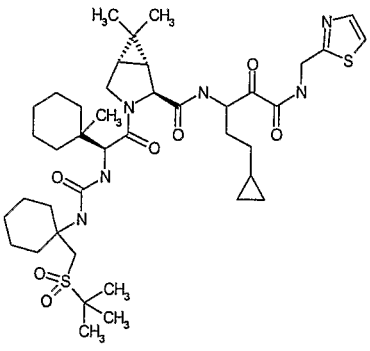
593		736.8056	736.1	A
594		746.8008	746.1	A

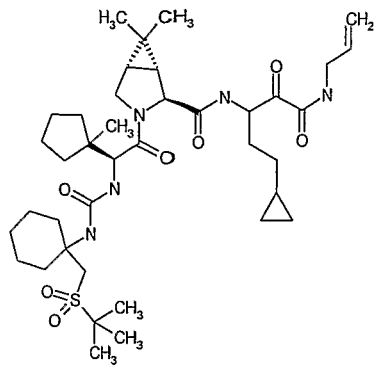
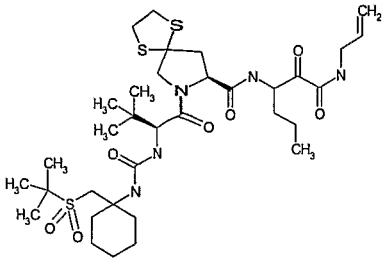
595		750.8327	750.4	A
596		802.1166	802.5	A

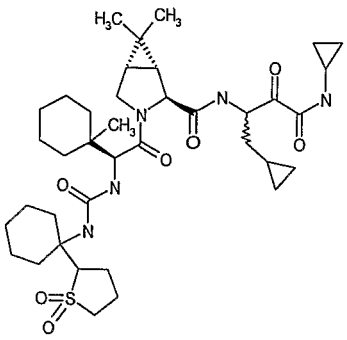
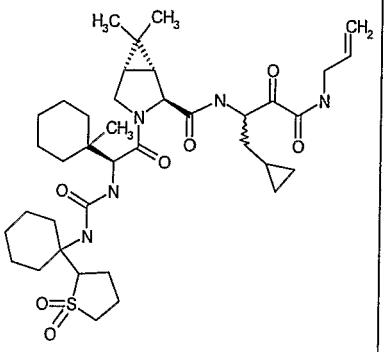
597		729.9872	731.4	A
598		746.0303	746.4	A

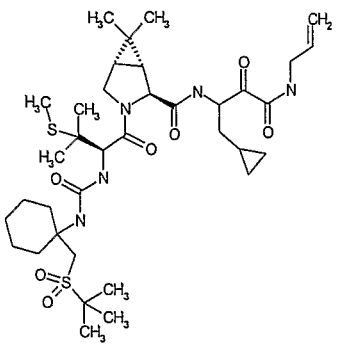
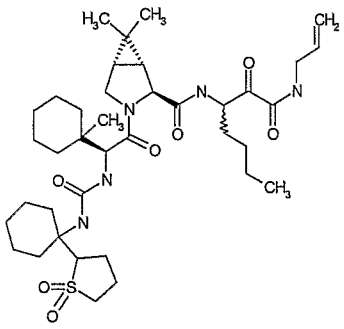
599		791.093	791.4	A
600		804.1325	804.5	A

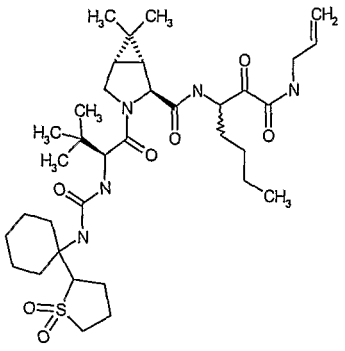
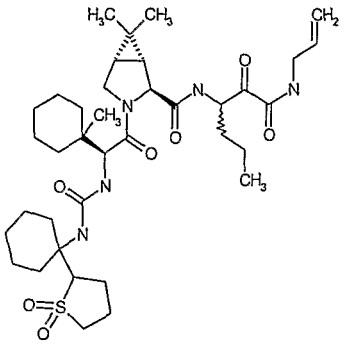
601		805.1201	805.4	A
602		737.9825		A

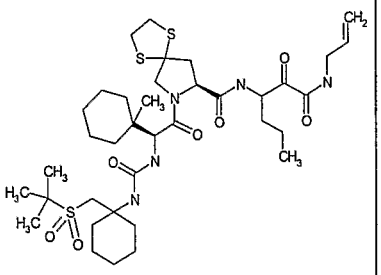
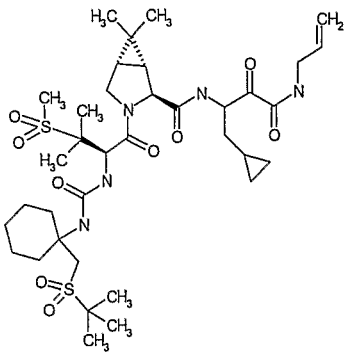
603		711.9442		A
604		817.1312	817.4	A

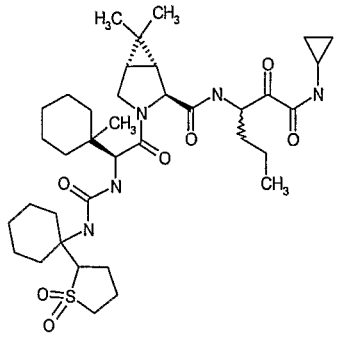
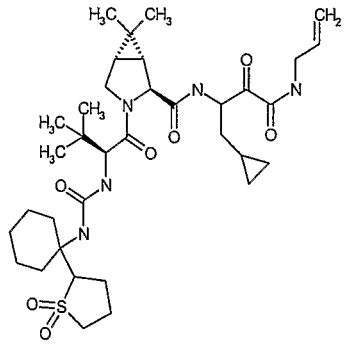
605		746.0303	746.4	A
606		744.0547	745.1	A

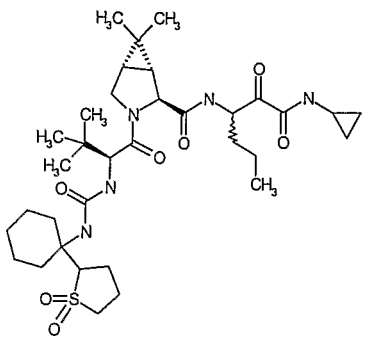
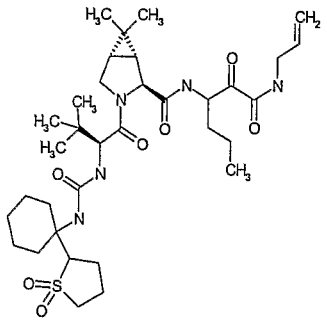
607		729.9872		A
608		729.9872	730.4	A

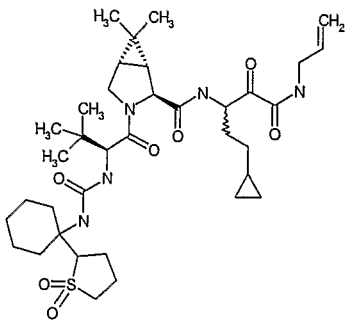
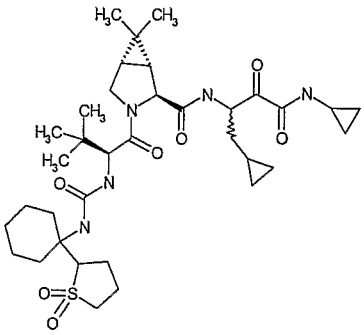
609		738.0289	738.1	A
610		732.0032	732.1	A

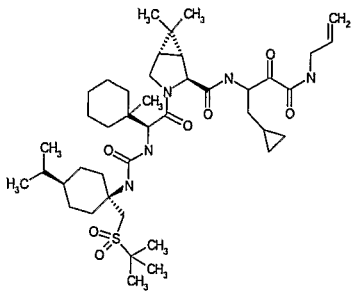
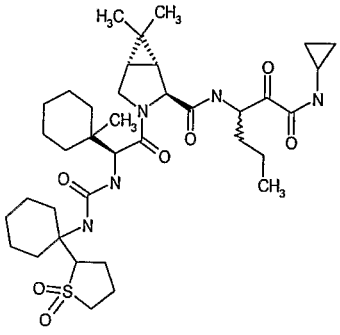
611		691.9378	692.1	3.8
612		717.9761	718.1	A

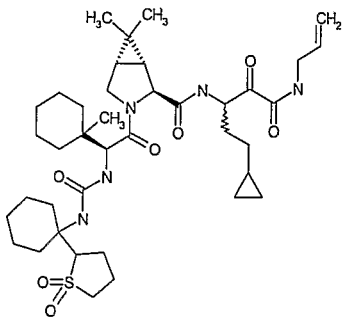
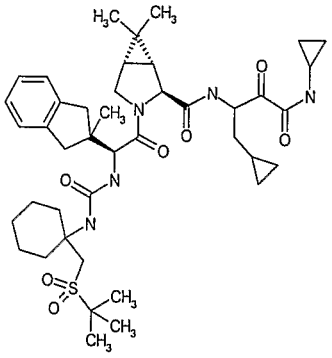
613		784.12	784.2	A
614		770.0277	770.2	B

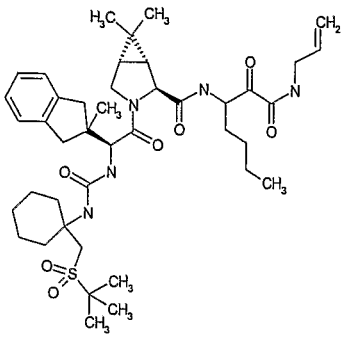
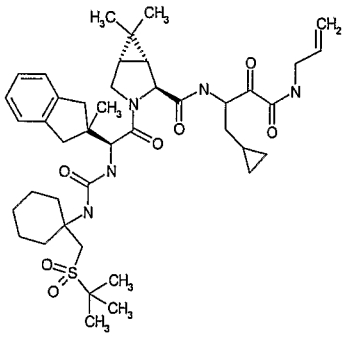
615		717.9761		A
616		689.9219		A

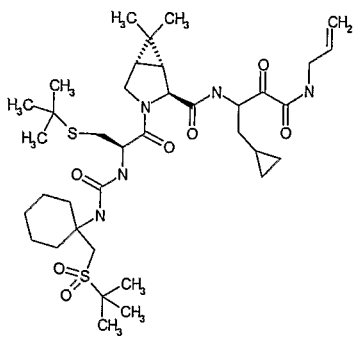
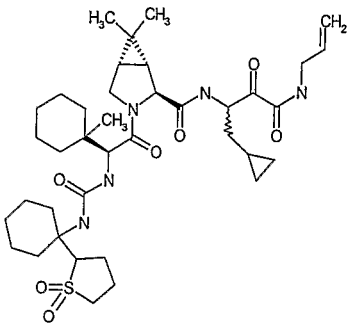
617		677.9108	678.4	A
618		677.9108	678.4	A

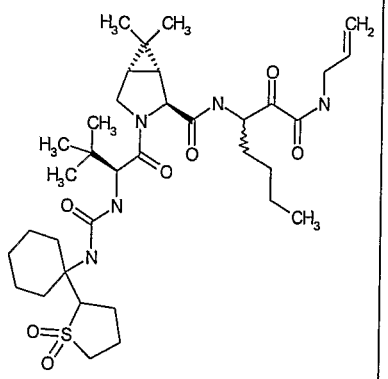
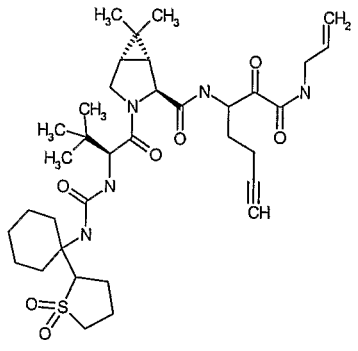
619		703.949	704.4	A
620		689.9219	690.4	A

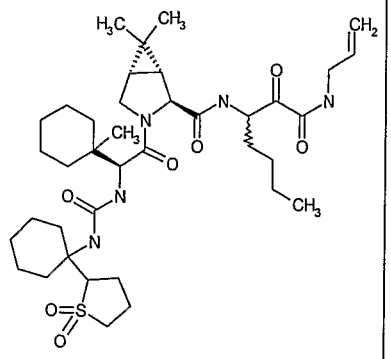
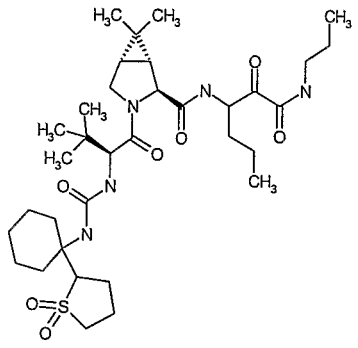
621		788.1115	789.4	C
622		717.9761	718.1	A

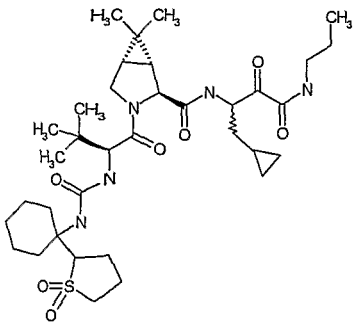
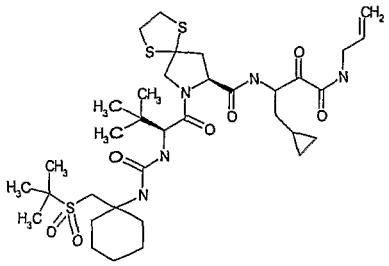
623		744.0143	744.1	A
624		780.0478	780.5	B

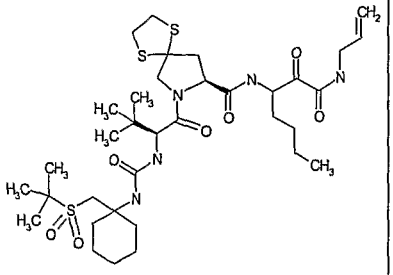
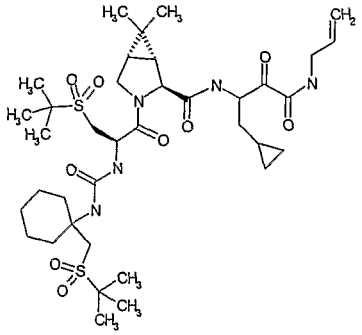
625		782.0637	782.5	A
626		780.0478	780.5	A

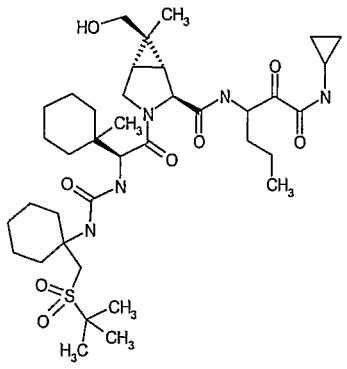
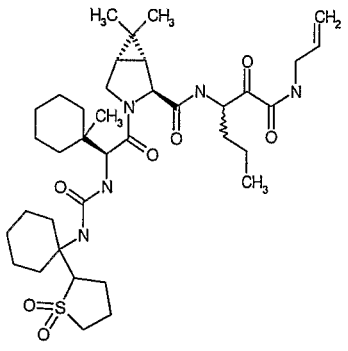
627		752.056	752.1	C
628		729.9872	730.4	A

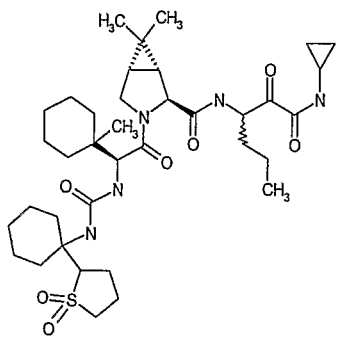
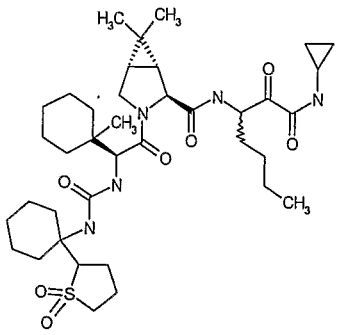
629		691.9378	692.4	A
630		687.906	688.4	A

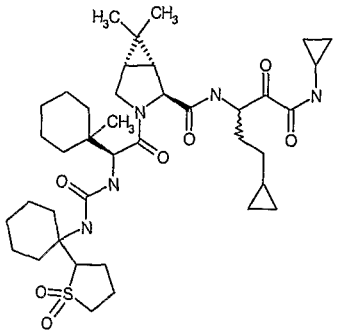
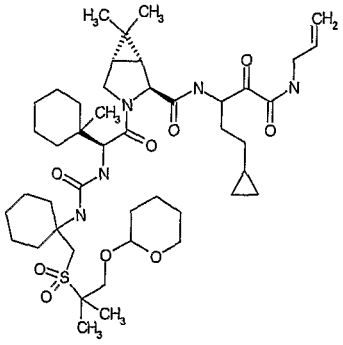
631		732.0032	732.4	A
632		679.9267	680.4	A

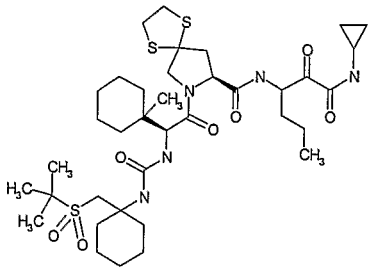
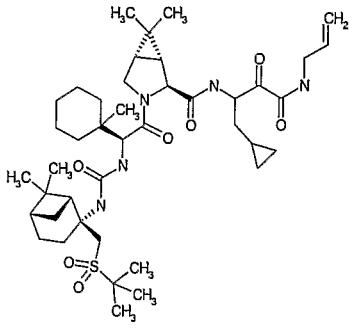
633		691.9378	692.4	A
634		756.0658	756.1	A

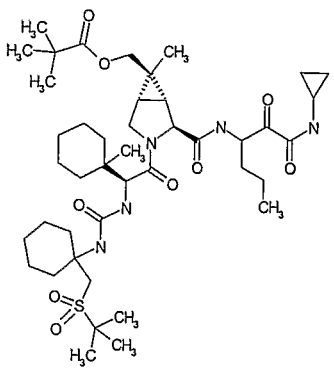
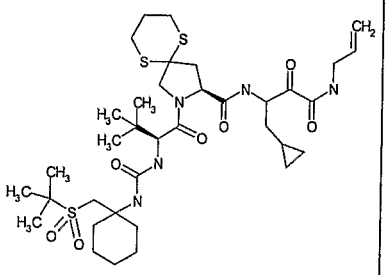
635		758.0818	758.1	A
636		784.0548	784.2	C

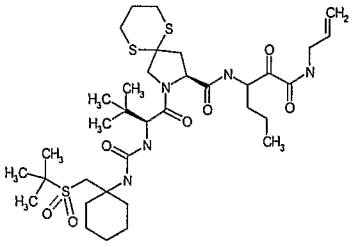
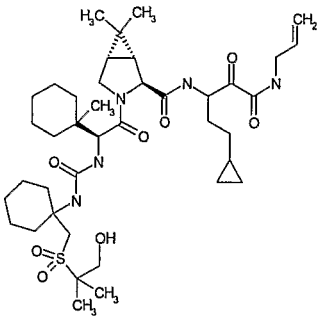
637		750.0185		B
638		717.9761	718.4	A

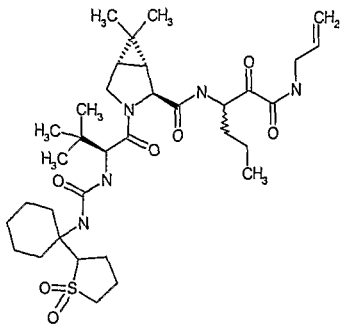
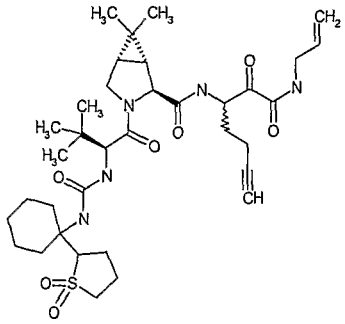
639		717.9761	718.4	A
640		732.0032	732.4	A

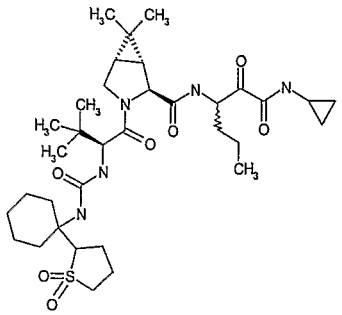
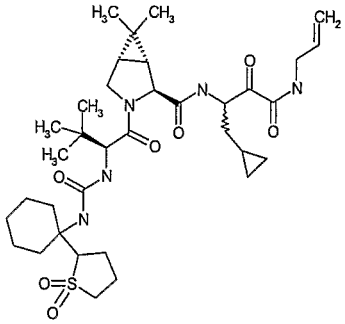
641		744.0143	744.4	A
642		860.1757		A

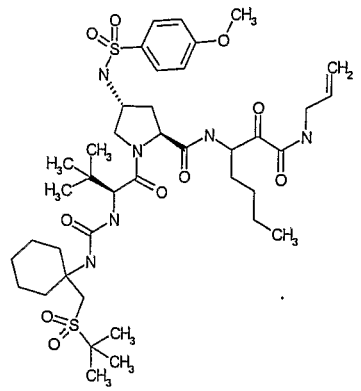
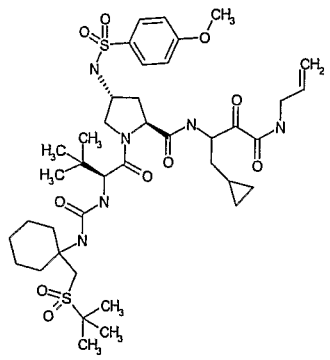
643		784.12		B
644		786.0956		B

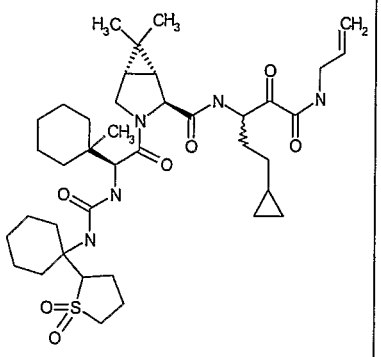
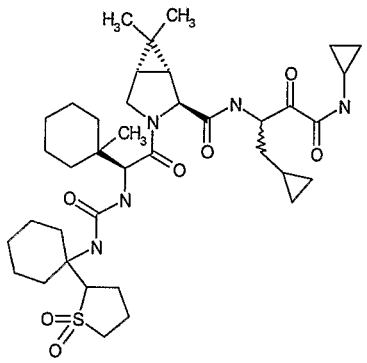
645		834.1374		B
646		770.0929	770.2	A

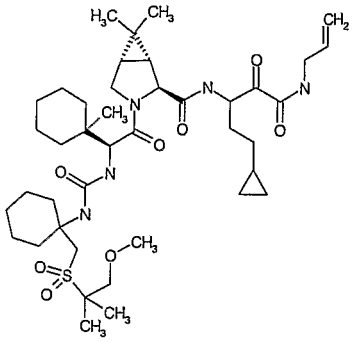
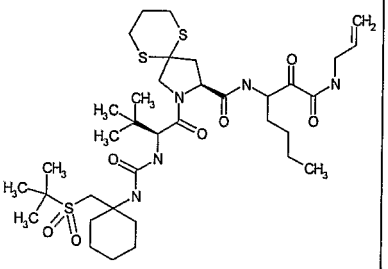
647		758.0818	758.2	A
648		776.0568		A

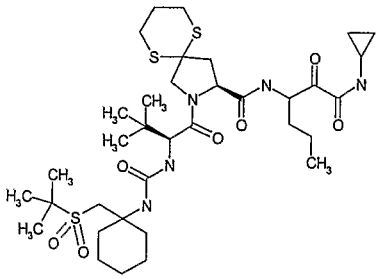
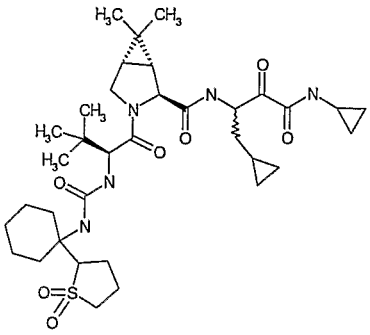
649		677.9108	678.2	A
650		687.906	688.2	A

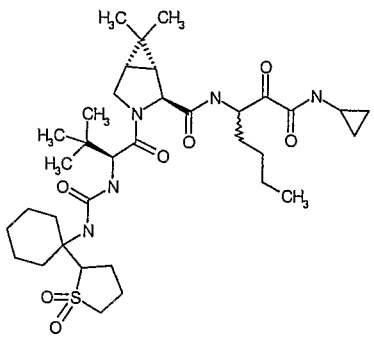
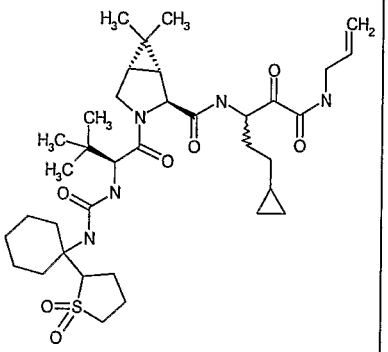
651		677.9108	678.2	A
652		689.9219	690.2	A

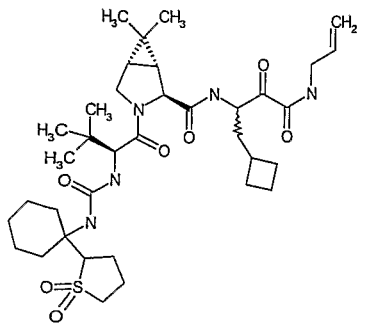
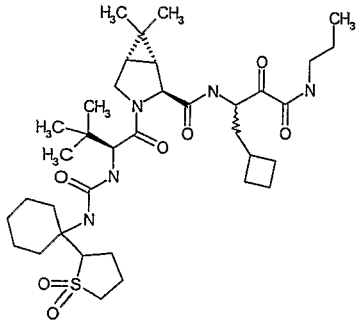
653		853.1183	853.4	C
654		851.1023	851.4	C

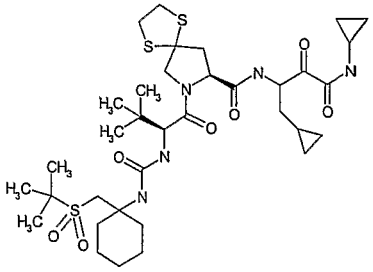
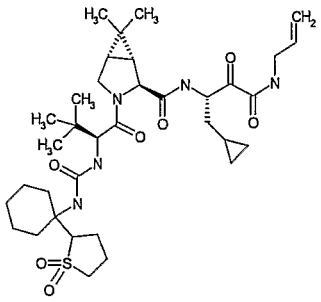
655		744.0143	744.1	A
656		729.9872	730.1	A

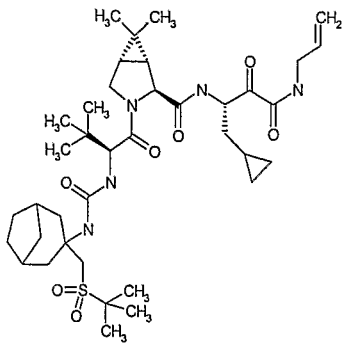
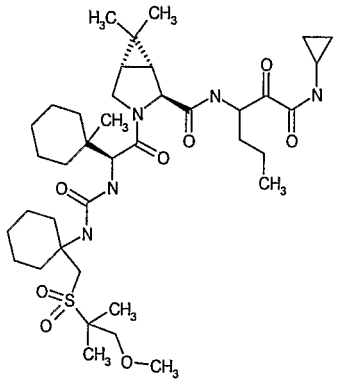
657		790.0838		A
658		772.1089	772.2	A

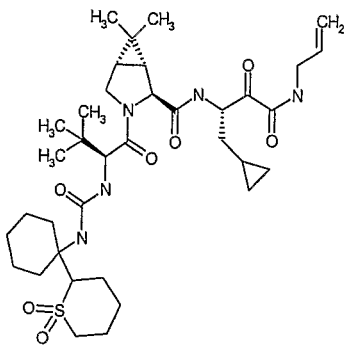
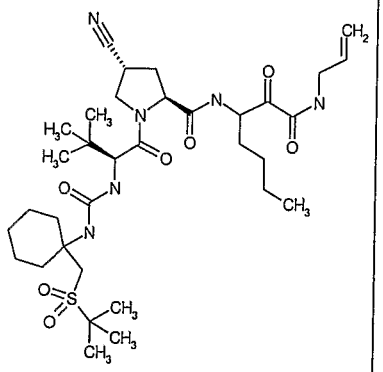
659		758.0818	758.2	A
660		689.9219	690.1	A

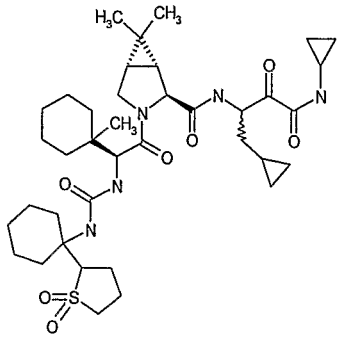
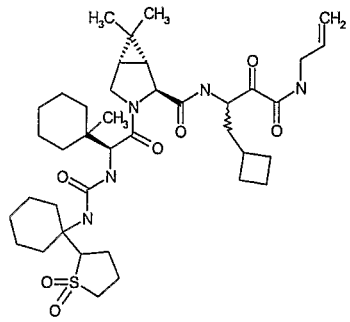
661		691.9378	692.1	A
662		703.949	704.1	A

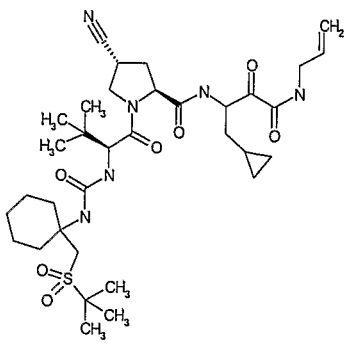
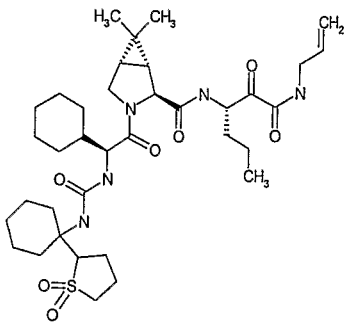
663		703.949	704.1	A
664		705.9649	706.2	A

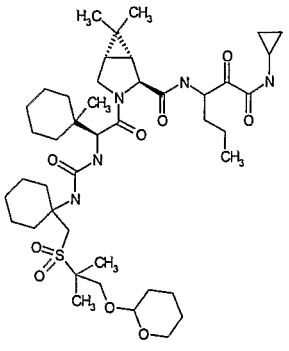
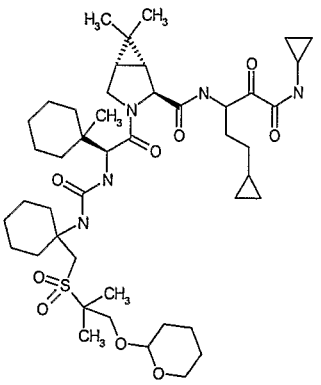
665		756.0658		B
666		689.9219		A

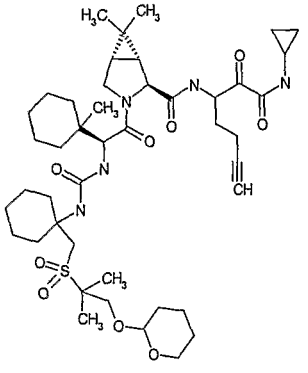
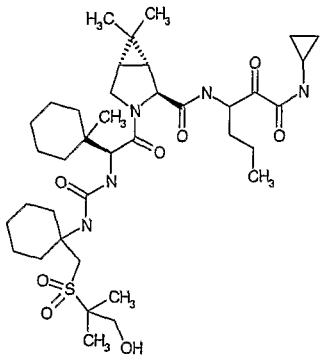
667		732.0032		A
668		764.0456		A

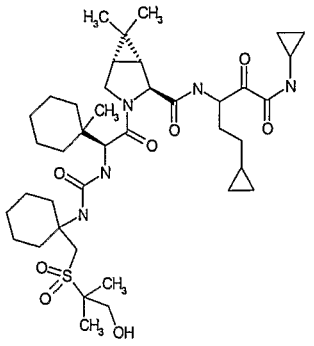
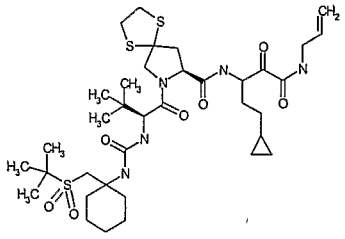
669		703.949		A
670		692.9254	693.3	C

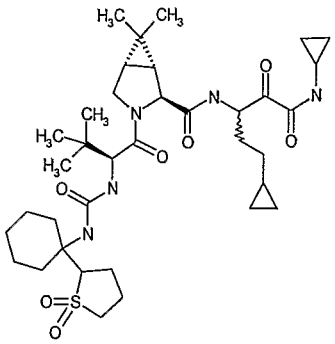
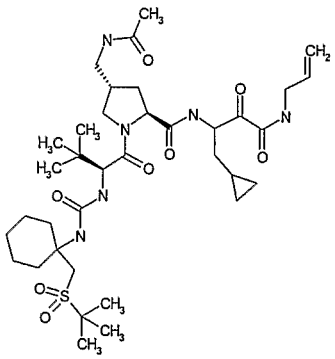
671		729.9872	730.1	A
672		744.0143	744.1	A

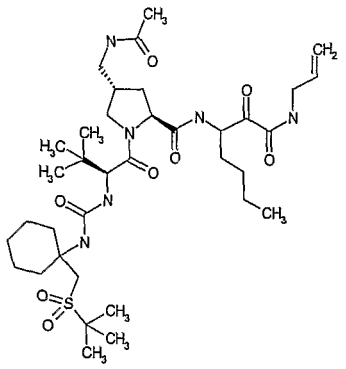
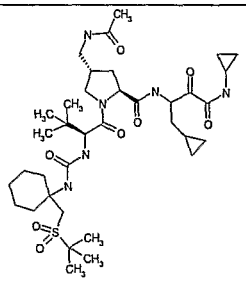
673		690.9095	691.35	C
674		703.949		A

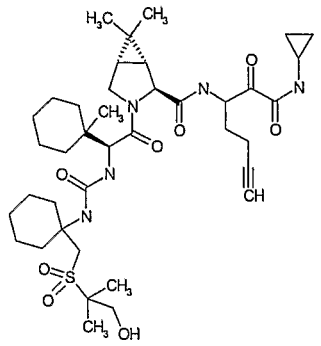
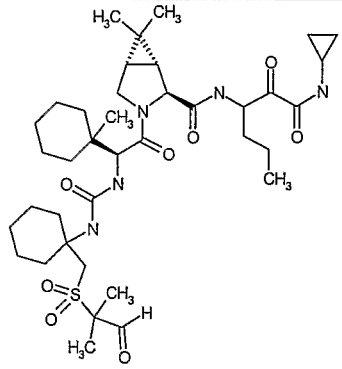
675		834.1374		A
676		860.1757		A

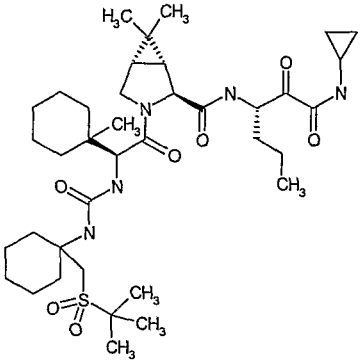
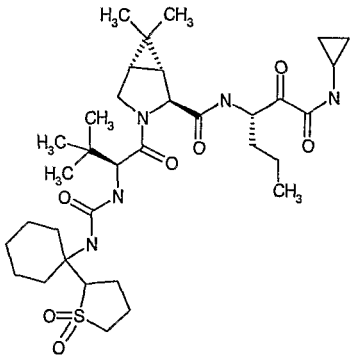
677		844.1326		A
678		750.0185		A

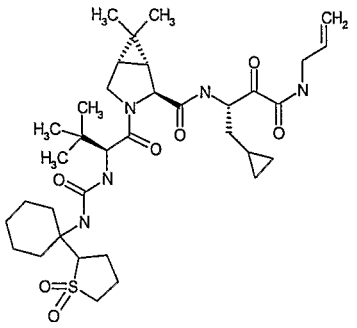
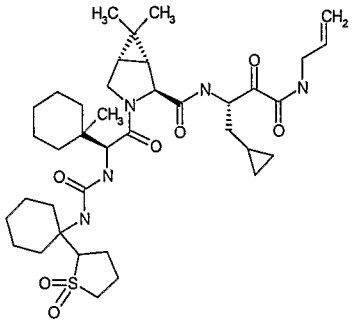
679		776.0568		A
680		770.0929	770.4	A

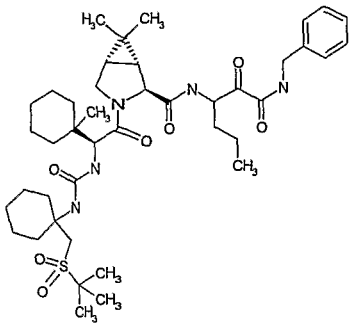
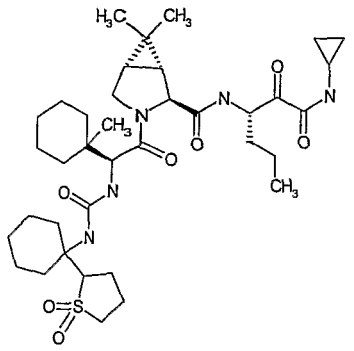
681		703.949	704.2	A
682		736.979	737.5	C

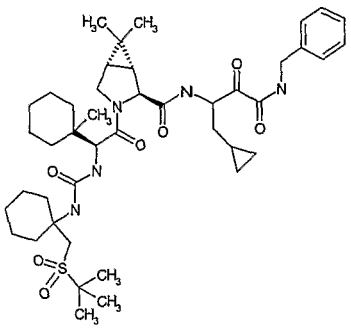
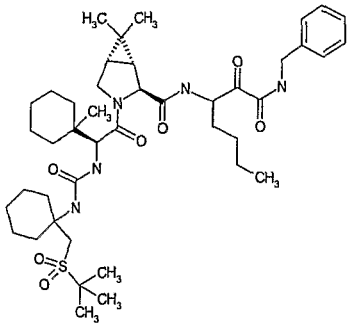
683		738.9949	739.4	C
684		736.979	737.4	C

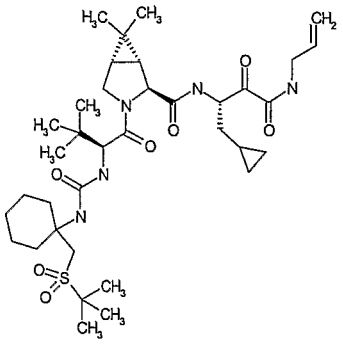
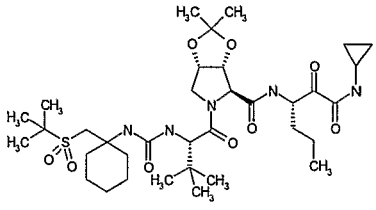
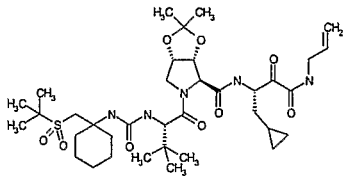
685		760.0137		A
686		748.0026		A

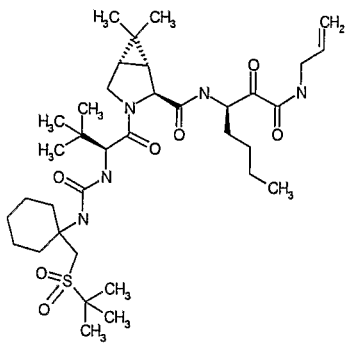
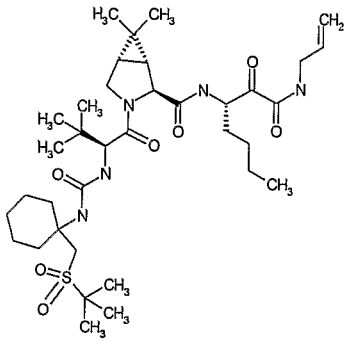
687		734.0191		A
688		677.9108	678.2	A

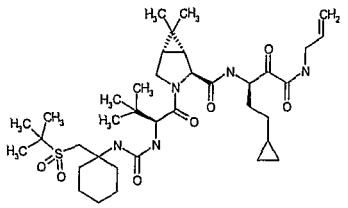
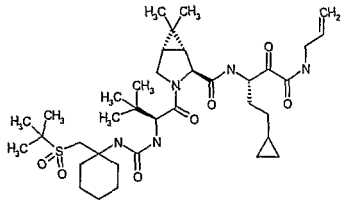
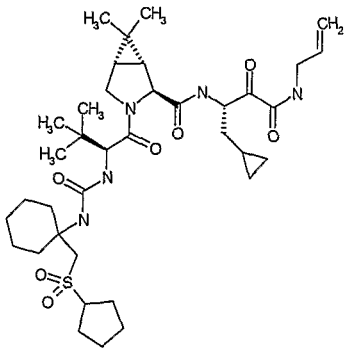
689		689.9219	690.2	A
690		729.9872	730.2	A

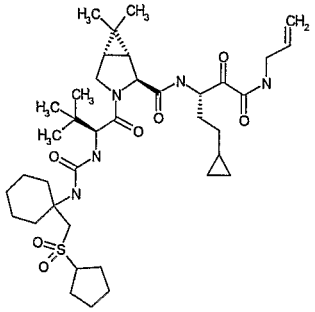
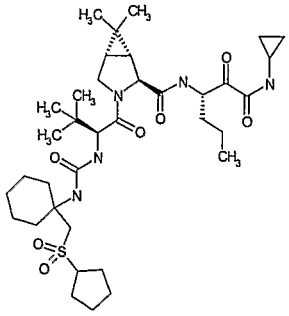
691		784.0797	784.2	A
692		717.9761		A

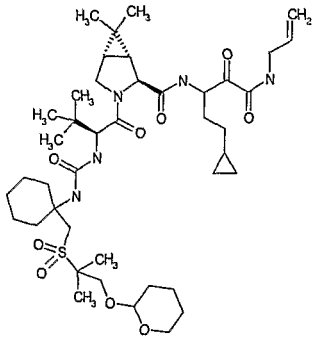
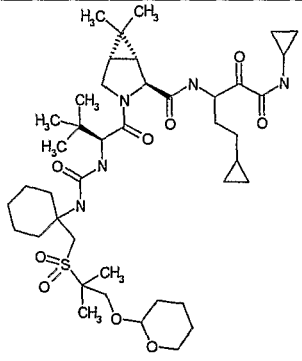
693		796.0908	796.2	A
694		798.1067	798.2	A

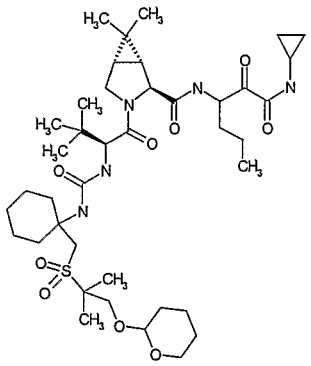
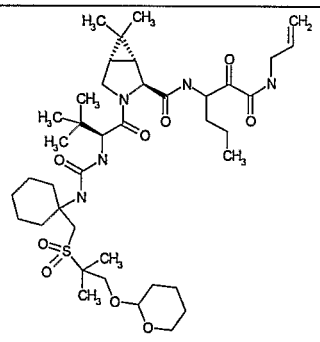
695		705.9649		5
696		725.9526	726.4	A
697		737.9637	738.4	A

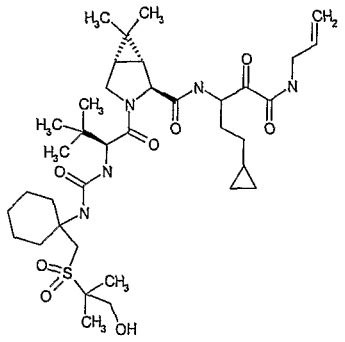
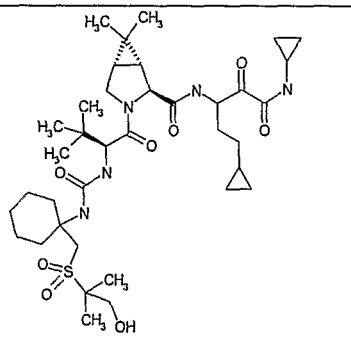
698		707.9809	708.4	B
699		707.9809	708.4	A

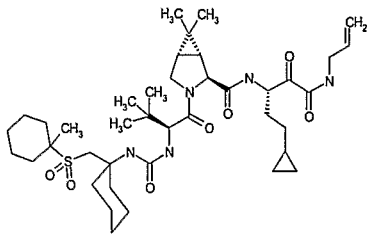
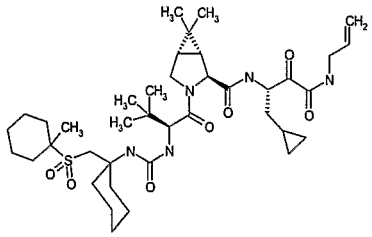
700		719.992		A
701		719.992		6
702		717.9761	718.60	A

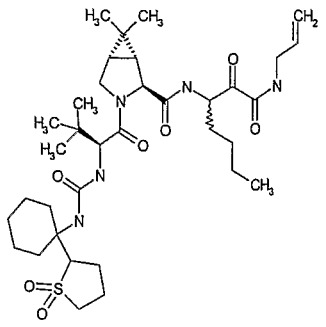
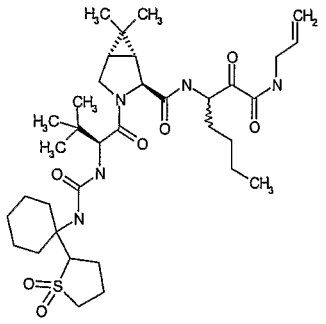
703		732.0032	732.6	A
704		705.9649	706.6	A

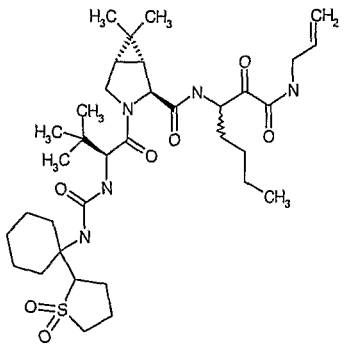
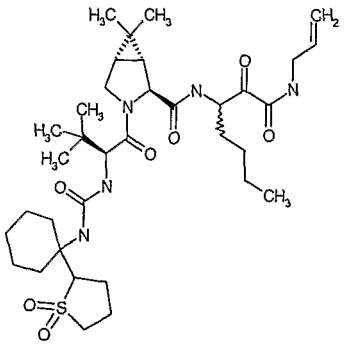
705		820.1103		A
706		820.1103		A

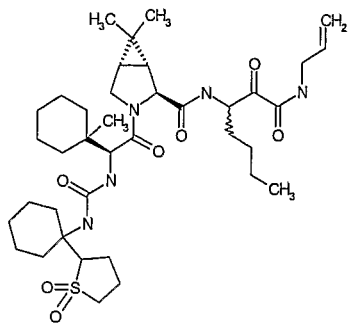
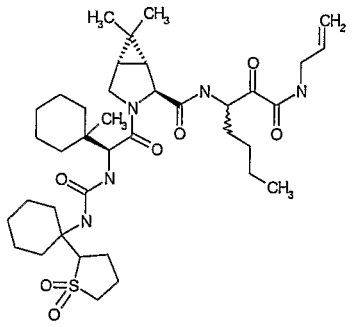
707		794.0721		A
708		794.0721		A

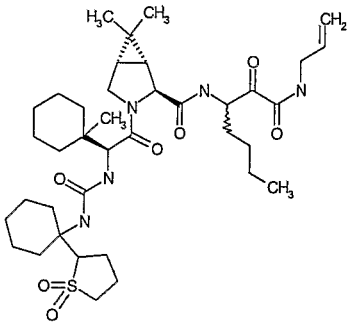
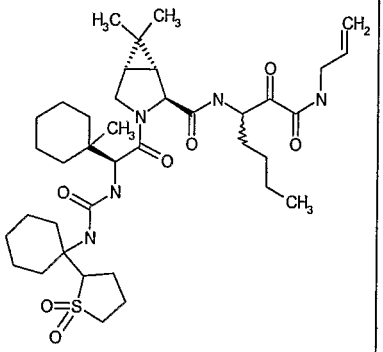
709		735.9914		A
710		735.9914		A

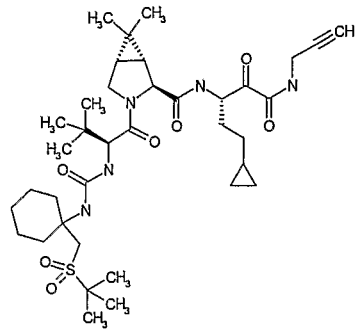
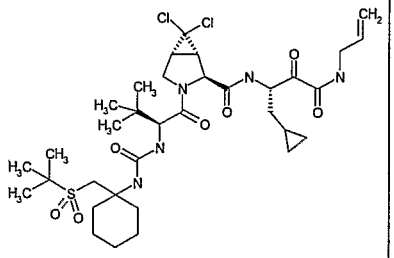
711		760.0574		A
712		746.0303		A

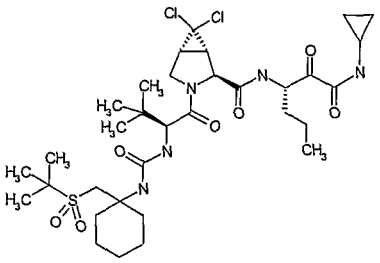
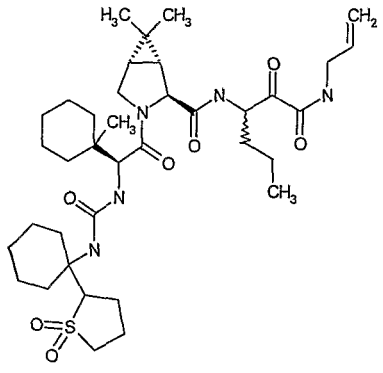
713		691.9378	692.2	B
714		691.9378	692.2	A

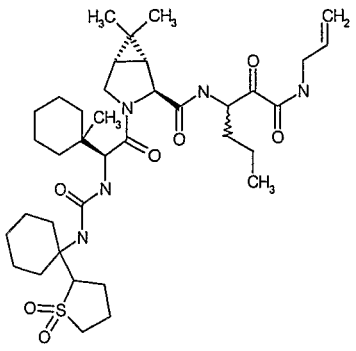
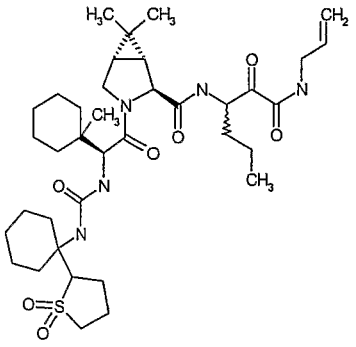
715		691.9378	692.2	A
716		691.9378	692.2	A

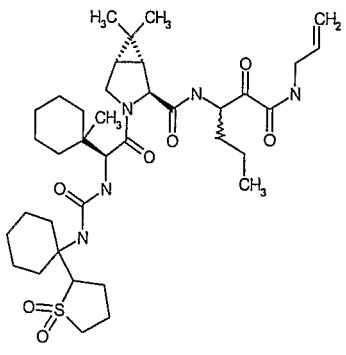
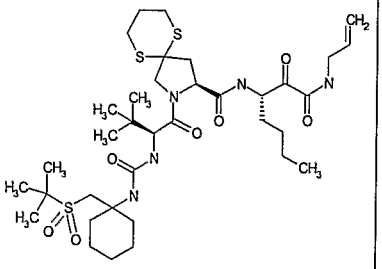
717		732.0032	732.2	B
718		732.0032	732.2	B

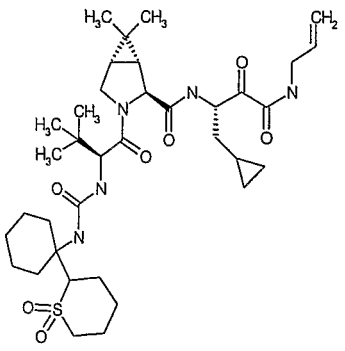
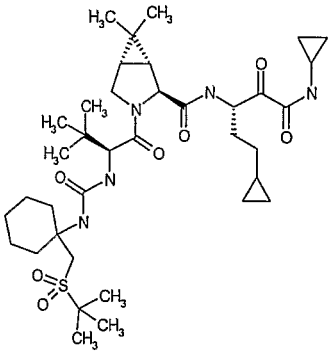
719		732.0032	732.2	A
720		732.0032	732.2	A

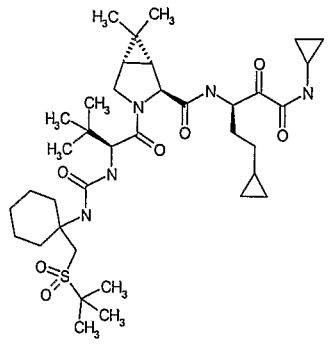
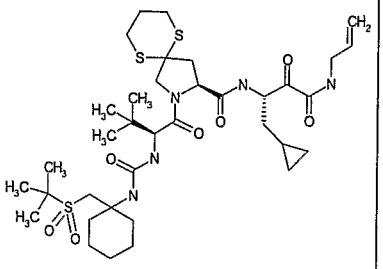
721		717.9761	718.1	A
722		746.8008		A

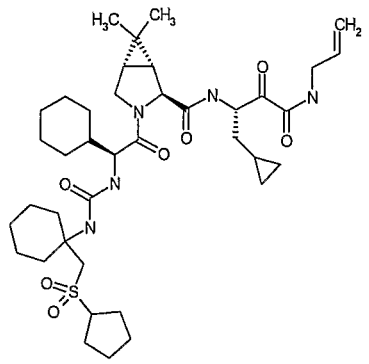
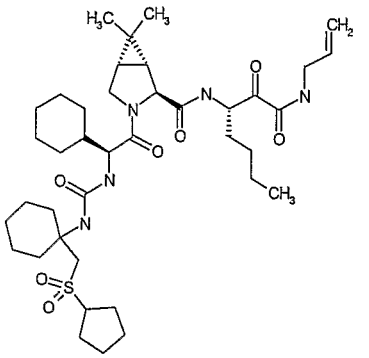
723		734.7897		A
724		717.9761	718.2	B

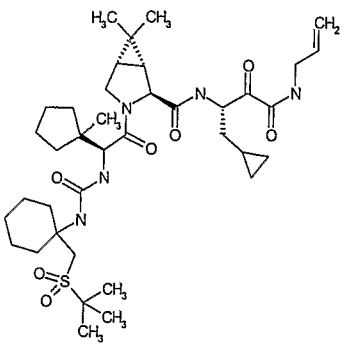
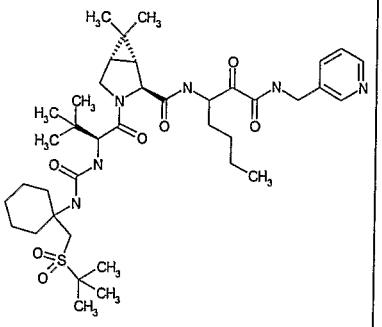
725		717.9761	718.2	A
726		717.9761	718.2	A

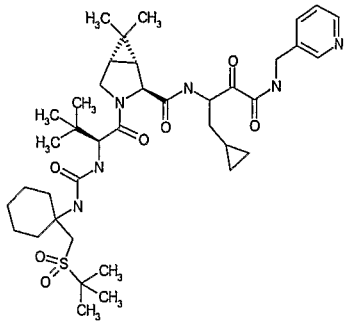
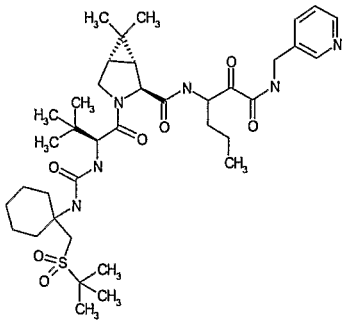
727		717.9761	718.2	A
728		772.1089		A

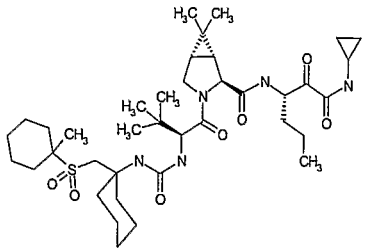
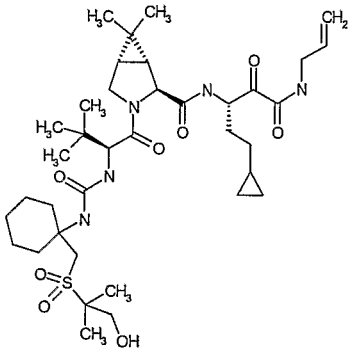
729		703.949	704.2	A
730		719.992		5.6

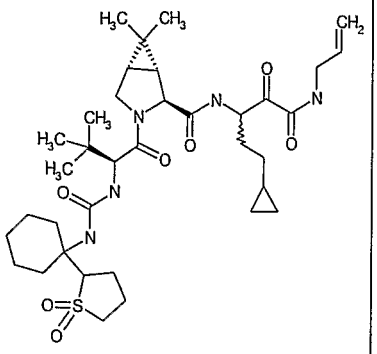
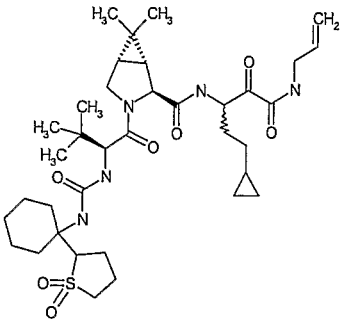
731		719.992		64
732		770.0929	770.2	A

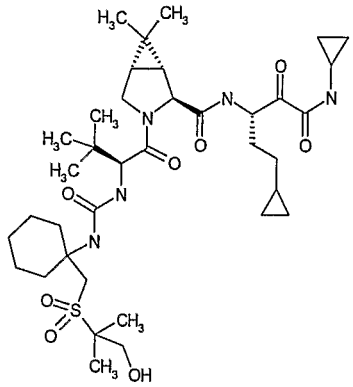
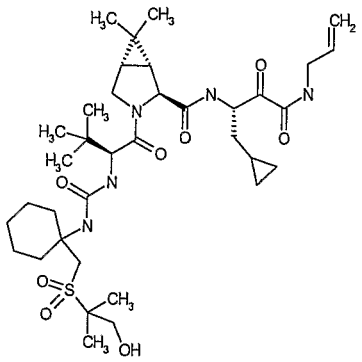
733		744.0143	744.3	A
734		746.0303	746.2	A

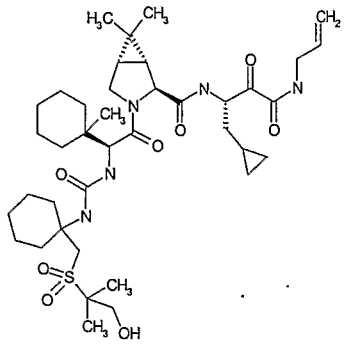
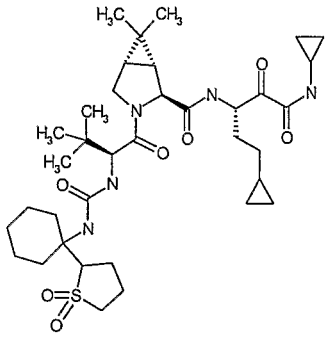
735		732.0032	732.4	A
736		759.029	759.4	A

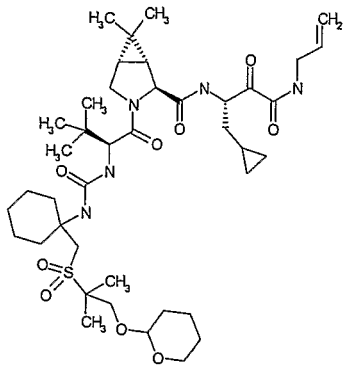
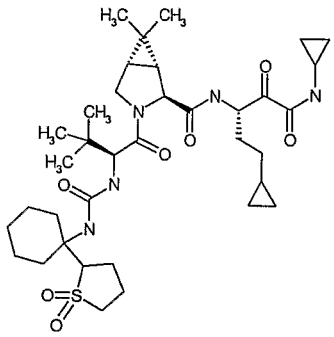
737		757.0131	757.4	A
738		745.0019	745.4	A

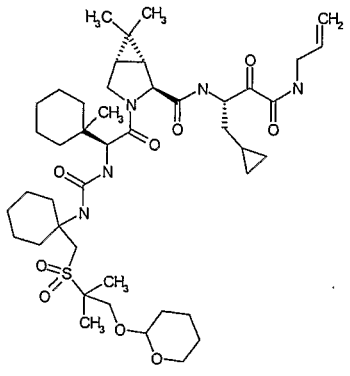
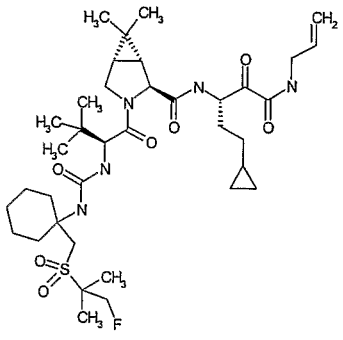
739		734.0191	734.3	18
740		735.9914		A

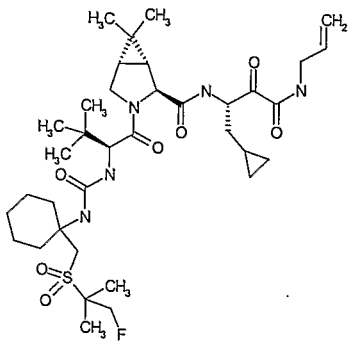
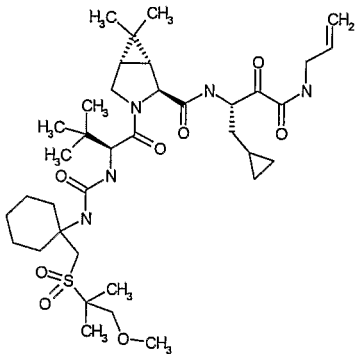
741		703.949	704.2	A
742		703.949	704.2	A

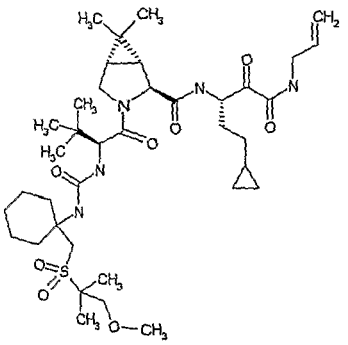
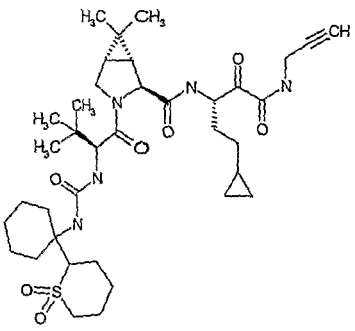
743		735.9914		A
744		721.9643		A

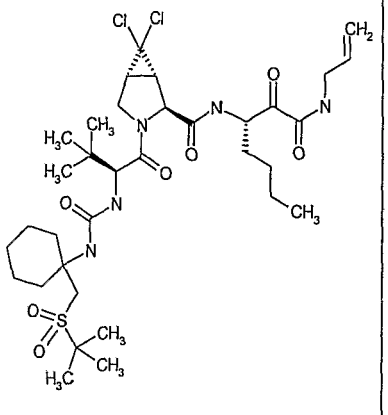
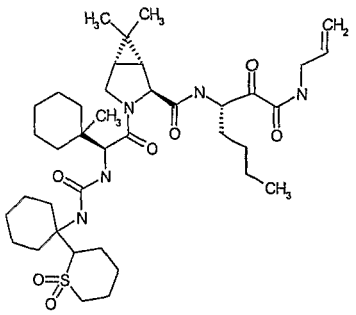
745		762.0297		A
746		703.949	704.2	A

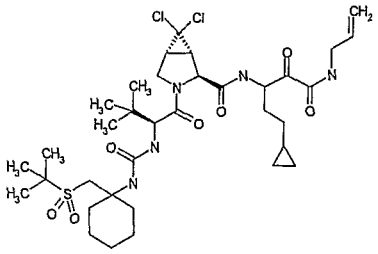
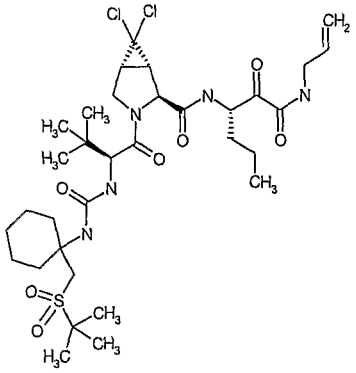
747		806.0832		A
748		703.949	704.2	A

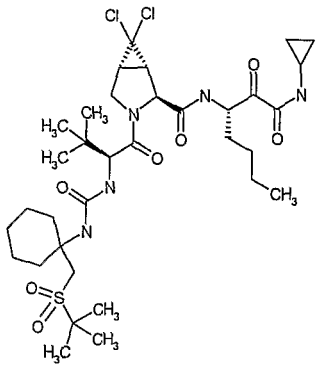
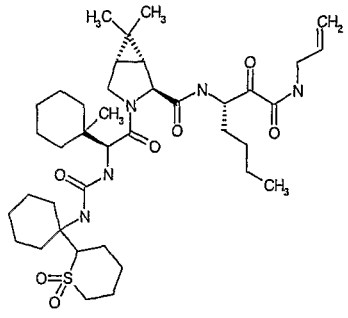
749		846.1486		A
750		737.9825		A

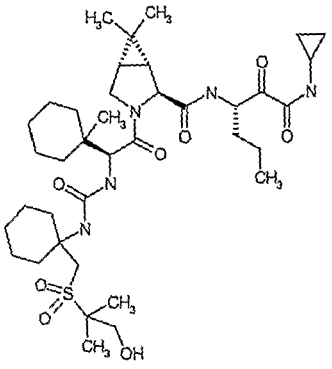
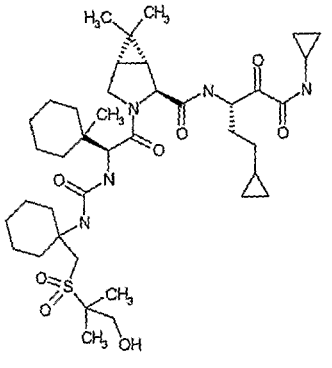
751		723.9554		A
752		735.9914		A

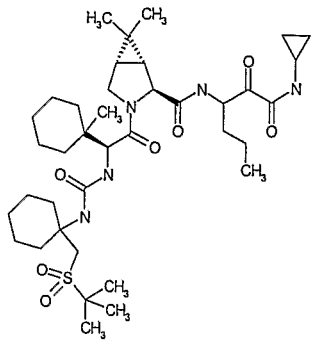
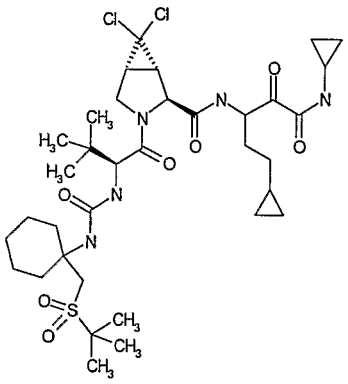
753		750.0185		A
754		715.9601	716.1	A

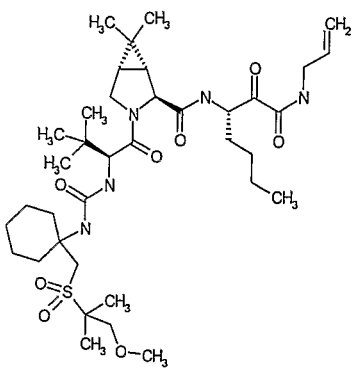
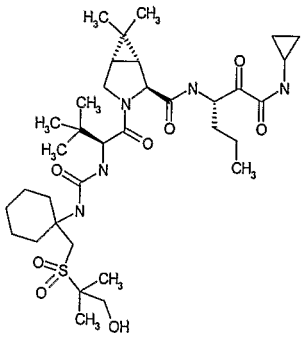
755		748.8168	748.1	A
756		746.0303	746.1	A

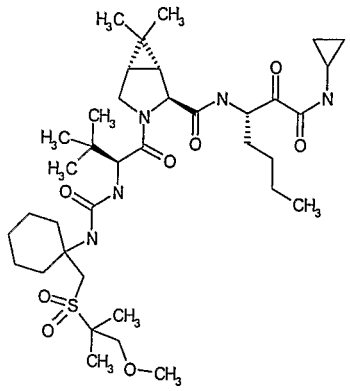
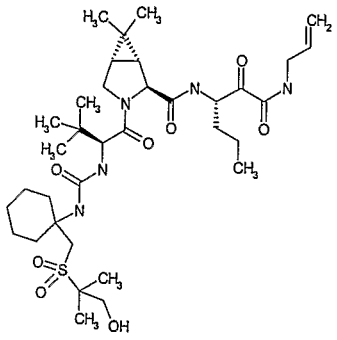
757		760.8279	760.1	A
758		734.7897	734.1	A

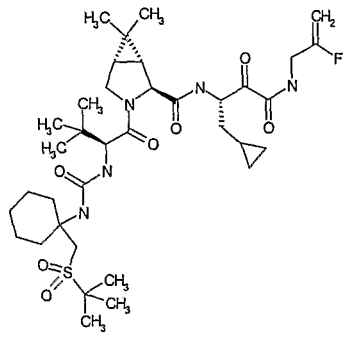
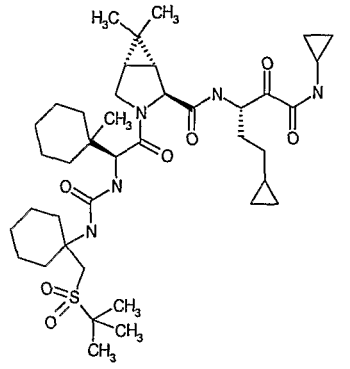
759		748.8168	748.1	A
760		746.0303		A

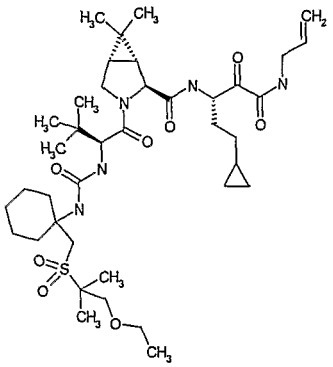
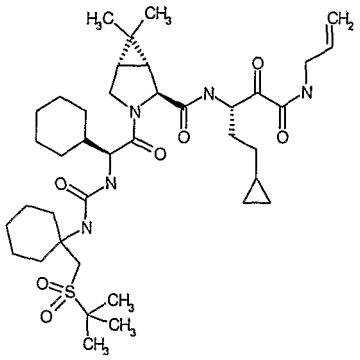
761		750.0185		A
762		776.0568		A

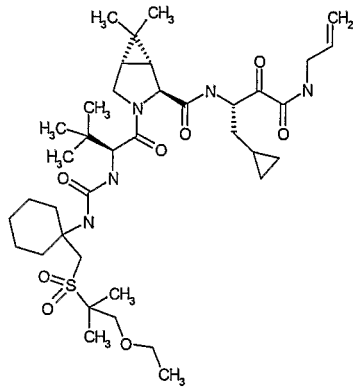
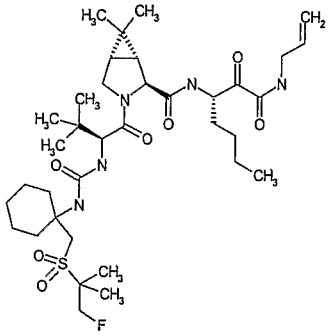
763		734.0191		B
764		760.8279	760.1	A

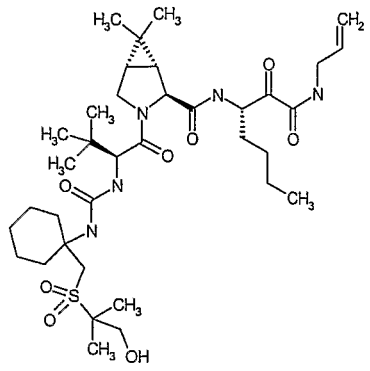
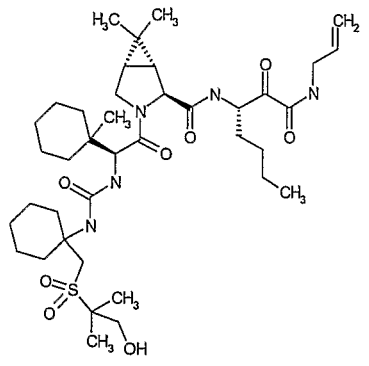
765		738.0074		A
766		709.9532		A

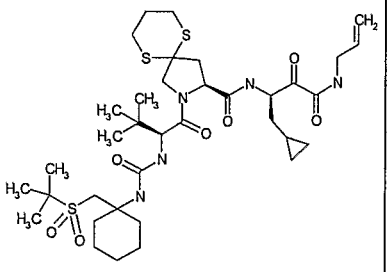
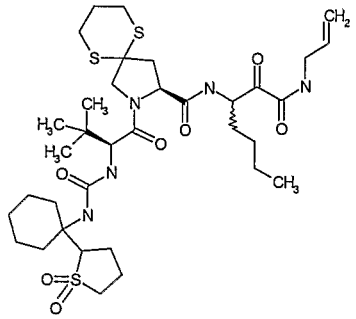
767		738.0074		A
768		709.9532		A

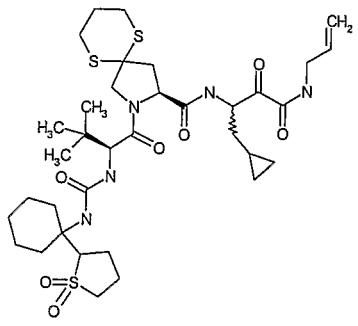
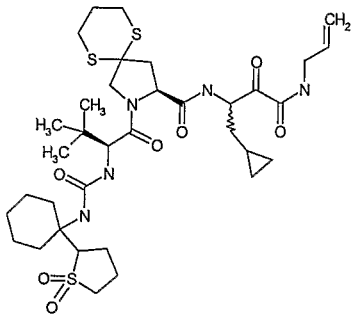
769		723.9554		A
770		760.0574		A

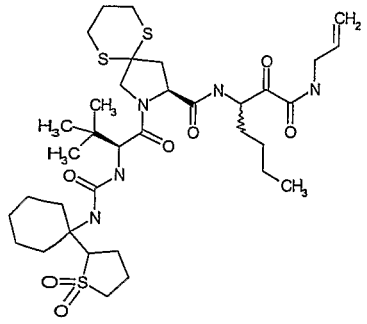
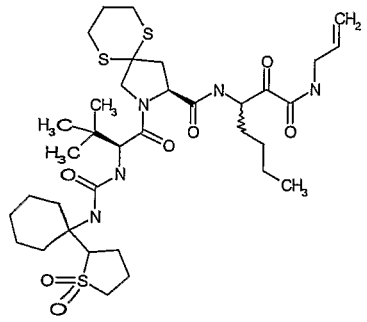
771		764.0456		A
772		746.0303		A

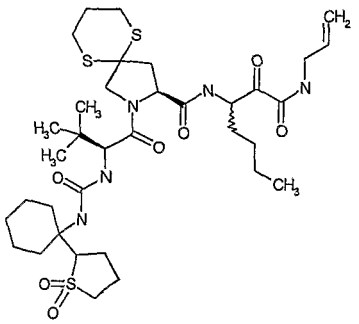
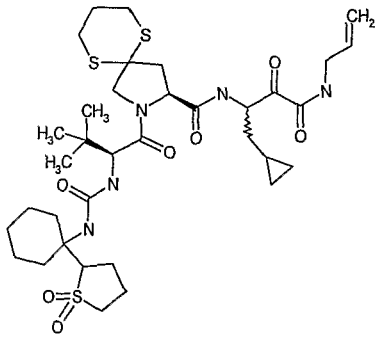
773		750.0185		A
774		725.9713		A

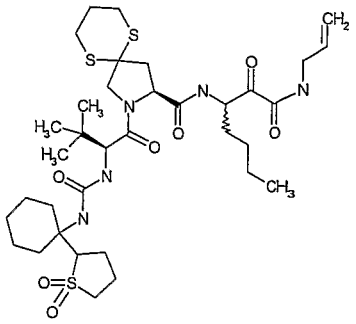
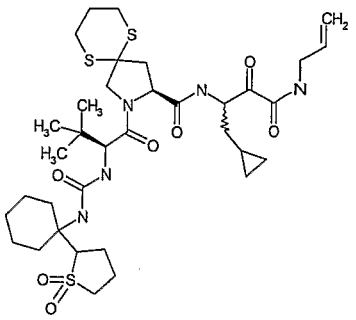
775		723.9803		A
776		764.0456		A

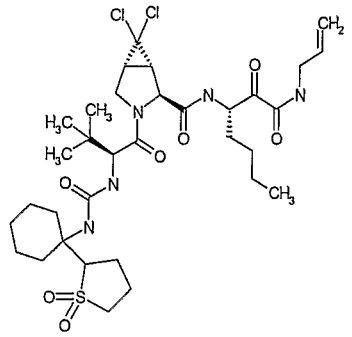
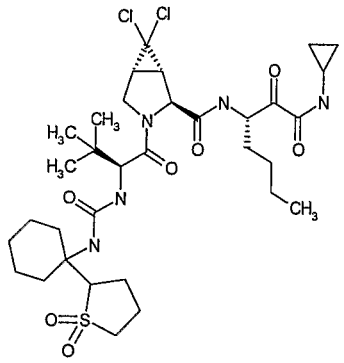
777		770.0929	770.2	B
778		756.0658	756.1	A

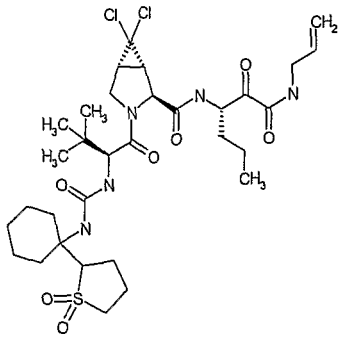
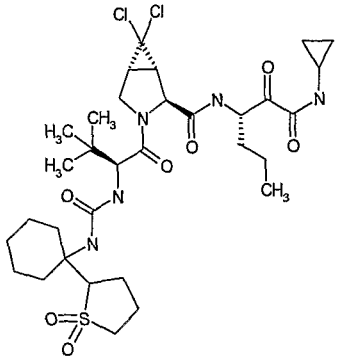
779		754.0499	754.1	A
780		754.0499	754.1	A

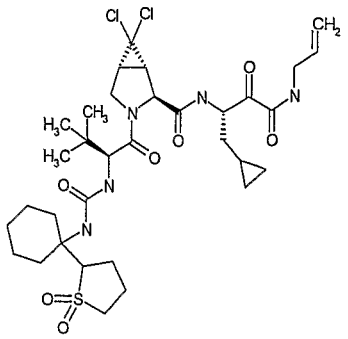
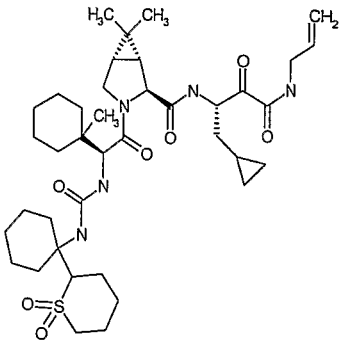
781		756.0658	756.1	A
782		756.0658	756.1	A

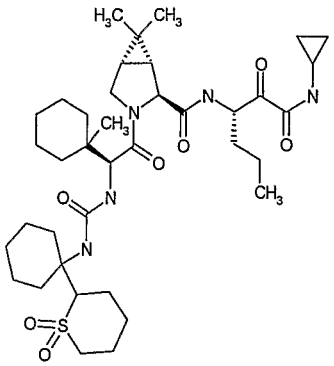
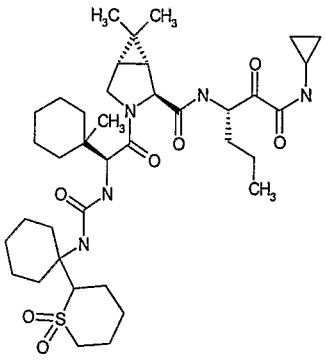
783		756.0658	756.1	A
784		754.0499	754.1	A

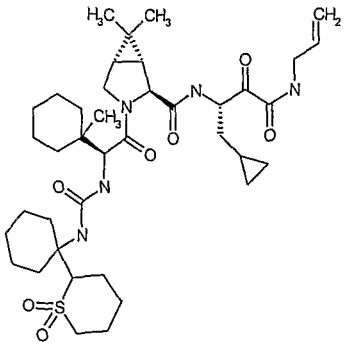
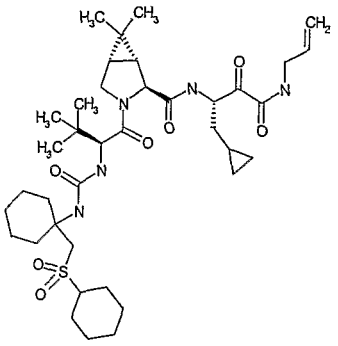
785		756.0658	756.1	A
786		754.0499	754.1	A

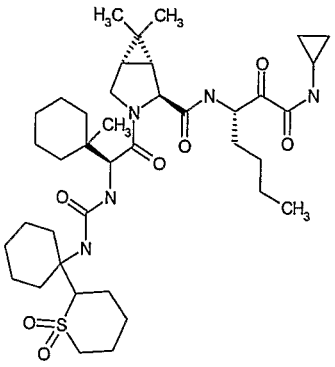
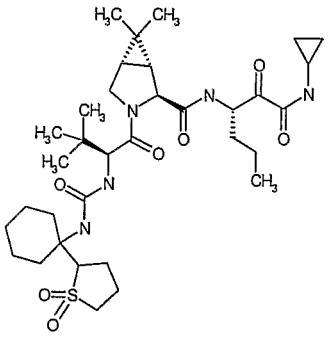
787		732.7737	732.1	A
788		732.7737	732.1	A

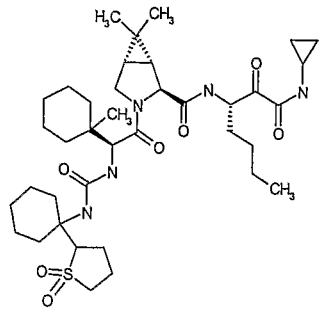
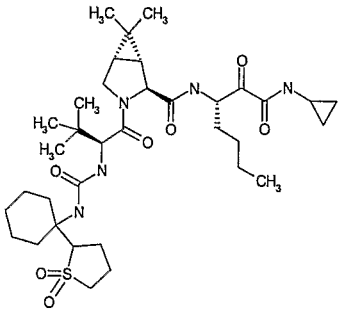
789		718.7466	718.2	A
790		718.7466	718.2	A

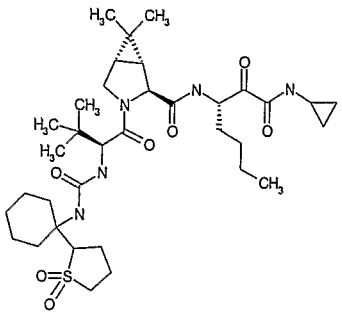
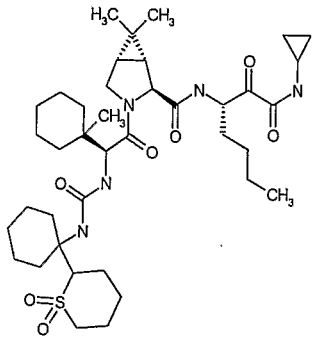
791		730.7578	730.2	A
792		744.0143		A

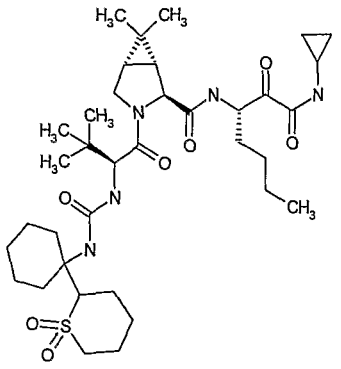
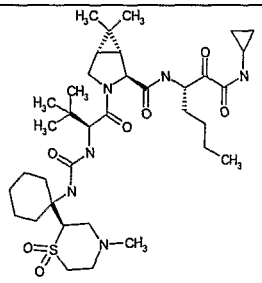
793		732.0032	732.1	A
794		732.0032		A

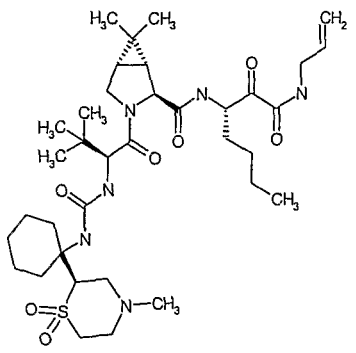
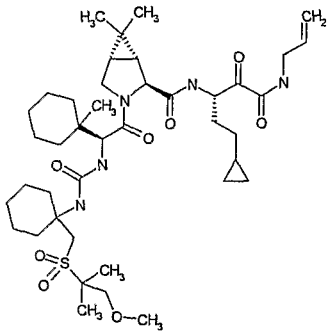
795		744.0143		A
796		732.0032	732.1	A

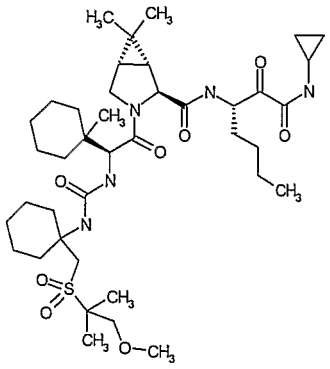
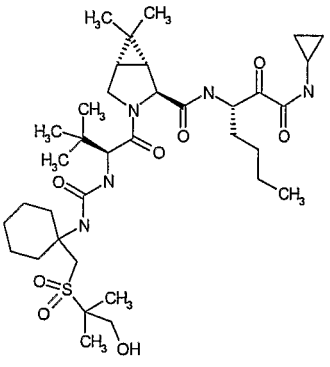
797		746.0303		A
798		677.9108	678.1	A

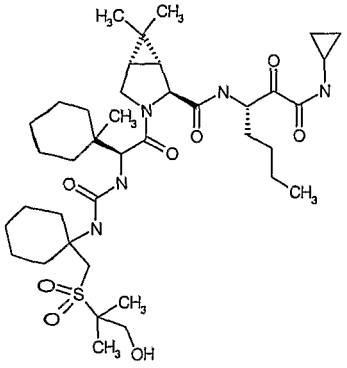
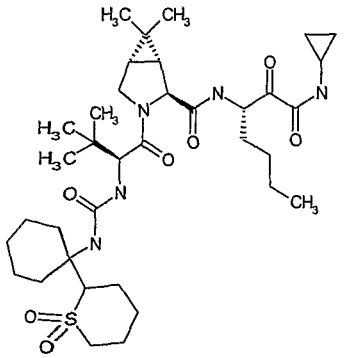
799		732.0032	732.2	A
800		691.9378	692.2	A

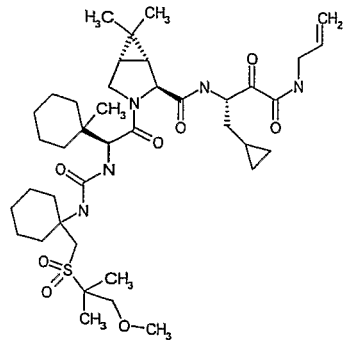
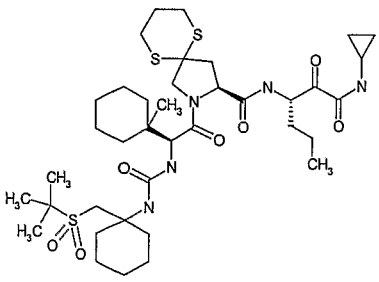
801		692	692.2	A
802		746.0303		A

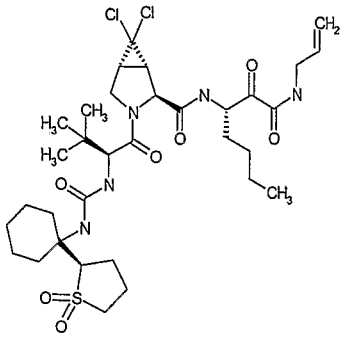
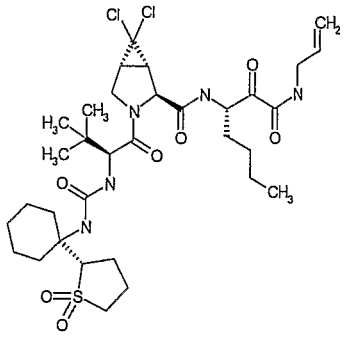
803		705.9649		A
804		720.9796		A

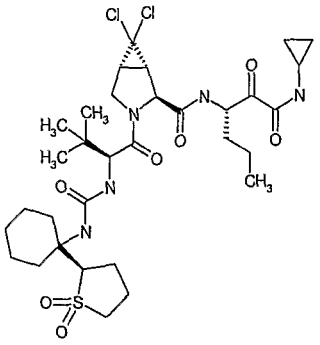
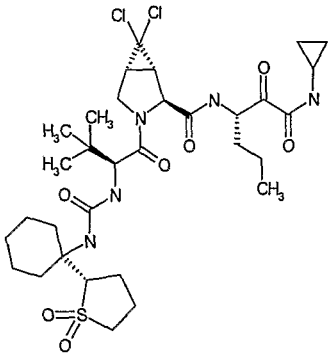
805		720.9796		A
806		790.0838		A

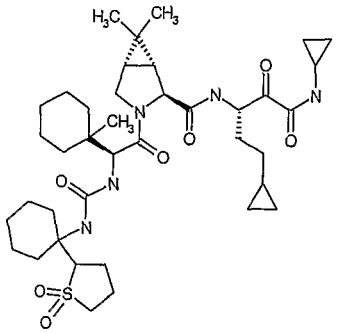
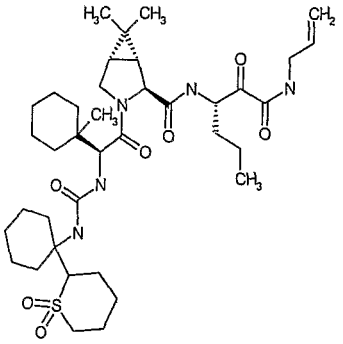
807		778.0727		A
808		723.9803		A

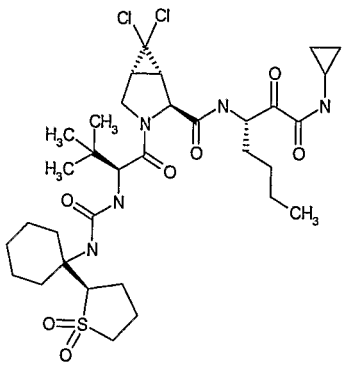
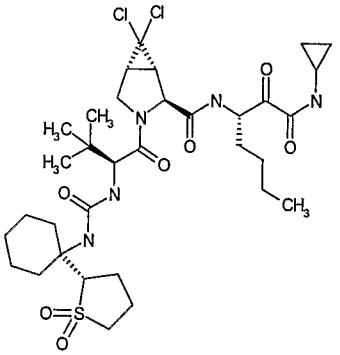
809		764.0456		A
810		705.9649	706.4	A

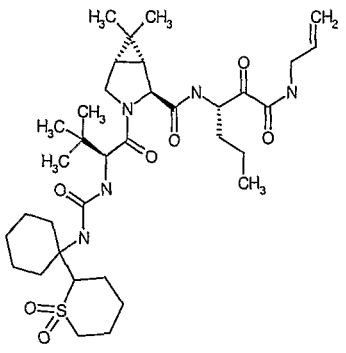
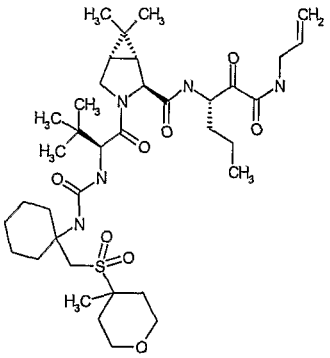
811		776.0568		A
812		798.1471	798.4	A

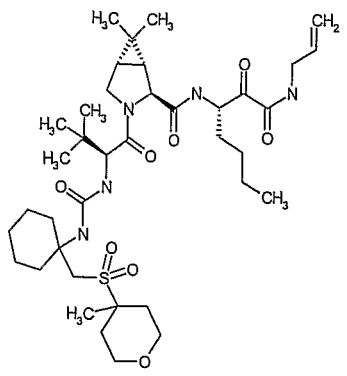
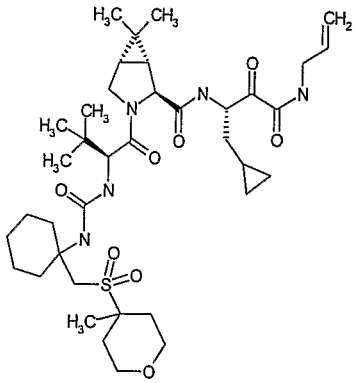
813		732.7737	732.1	A
814		732.7737	732.1	A

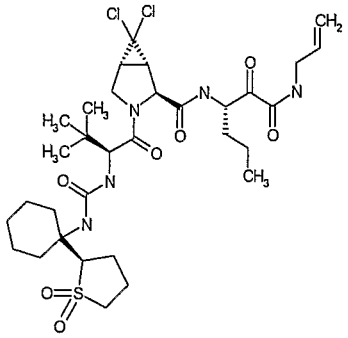
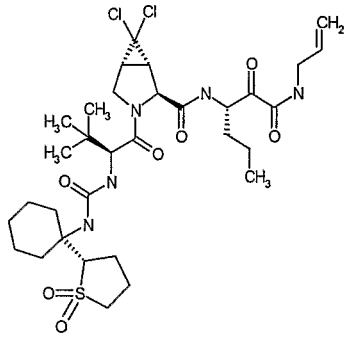
815		718.7466	718.1	A
816		718.7466	718.1	A

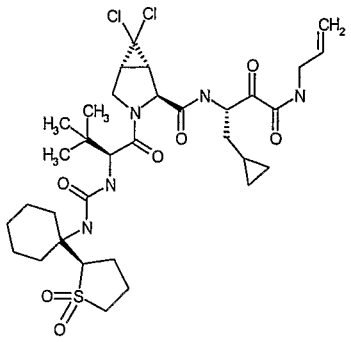
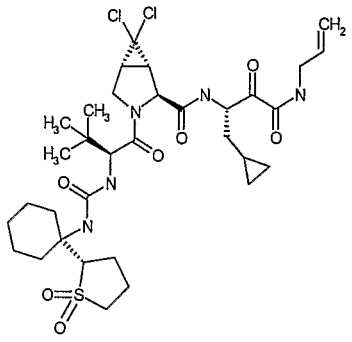
817		744.0143	744.1	A
818		732.0032	732.1	A

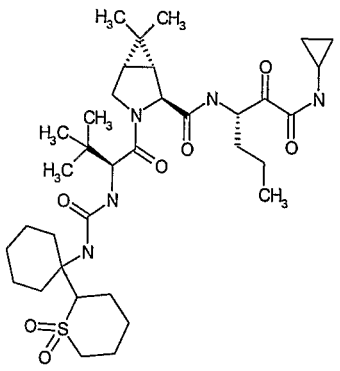
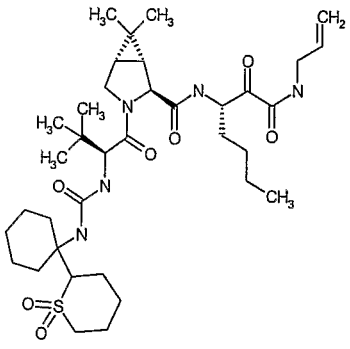
819		732.7737	732.1	A
820		732.7737	732.1	A

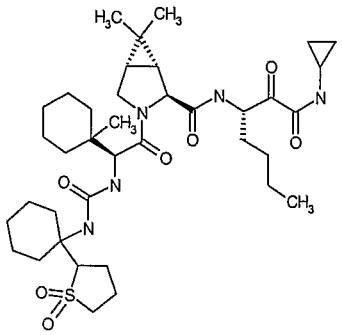
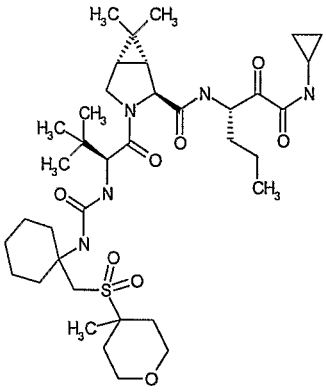
821		691.9378	692.1	A
822		735.9914	736.1	A

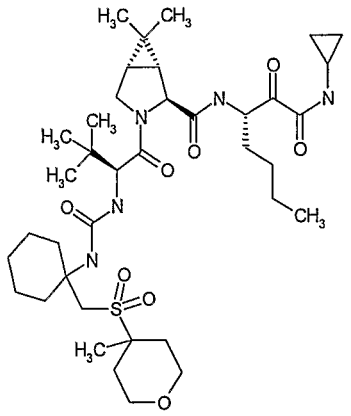
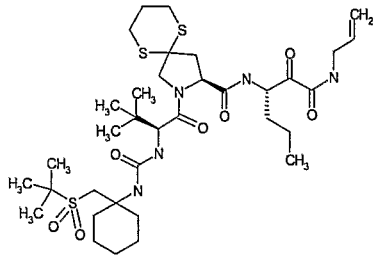
823		750.0185	750.1	A
824		748.0026	748.1	A

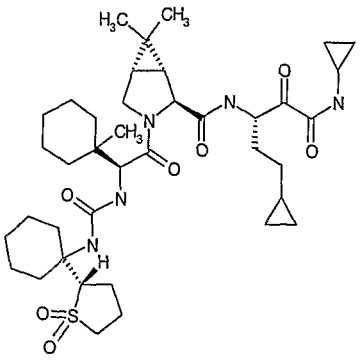
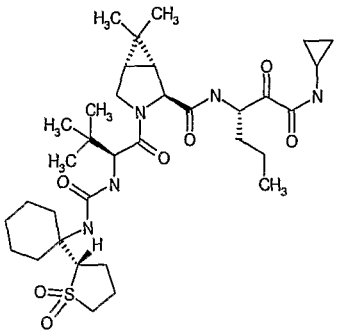
825		718.7466	718.2	A
826		718.7466	718.2	A

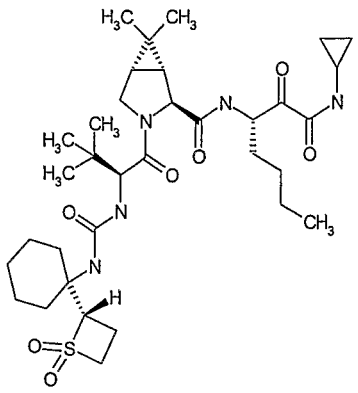
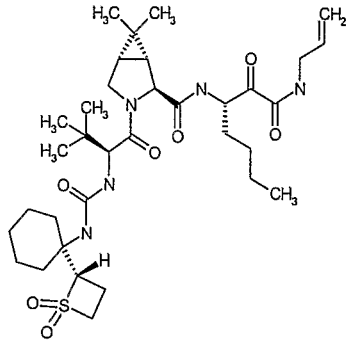
827		730.7578	730.2	A
828		730.7578	730.2	A

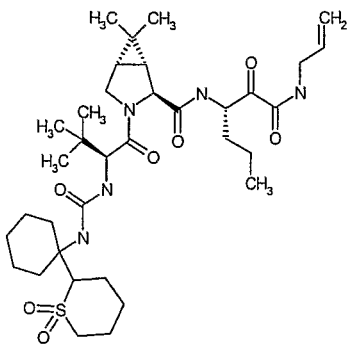
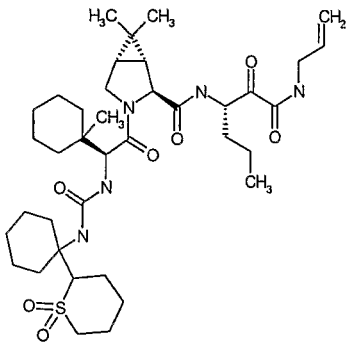
829		691.9378		A
830		705.9649	706.1	A

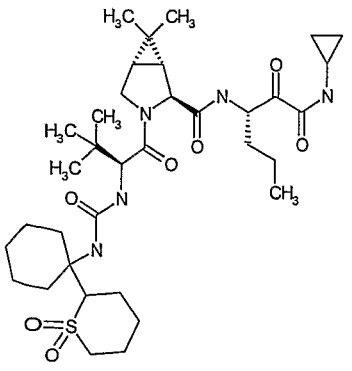
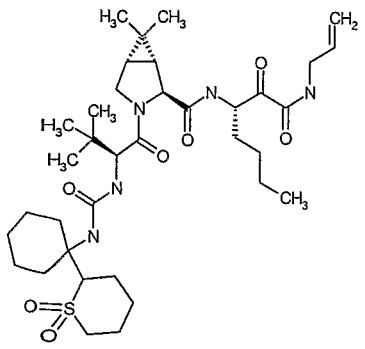
831		732.0032	732.2	A
832		735.9914	736.1	A

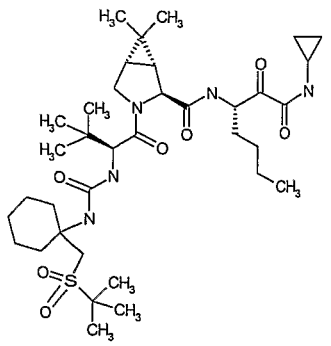
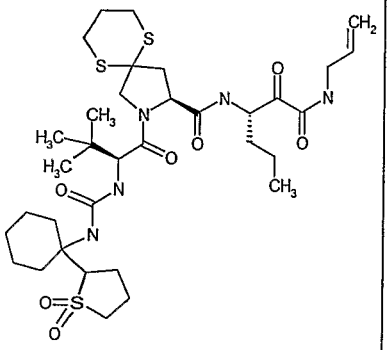
833		750.0185	750.1	A
834		758.0818	758.2	A

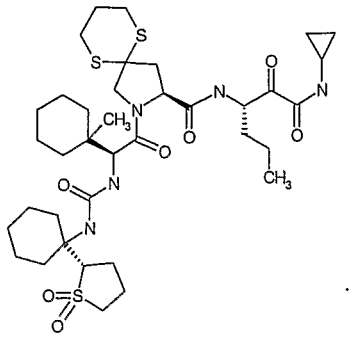
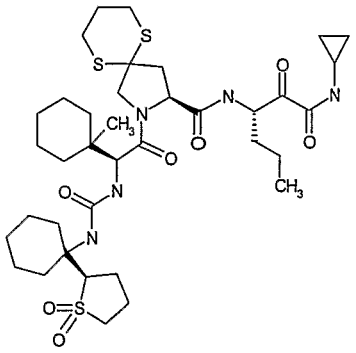
835		744.0143	744.1	A
836		677.9108		A

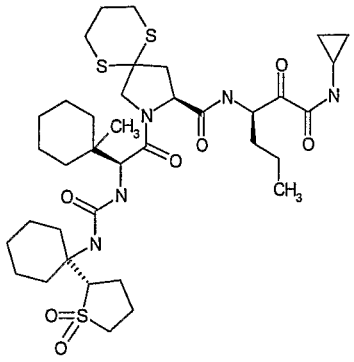
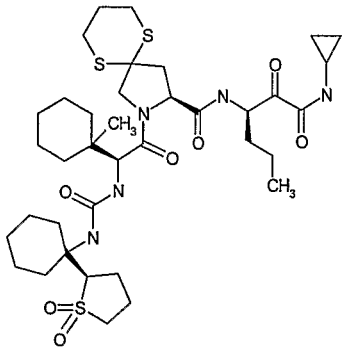
837		677.9108	678.3	A
838		677.9108	678.3	A

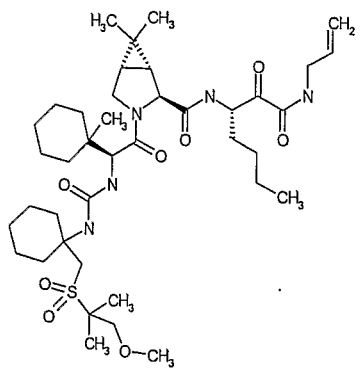
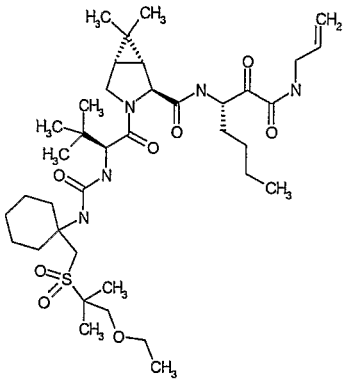
839		691.9378		A
840		732.0032		A

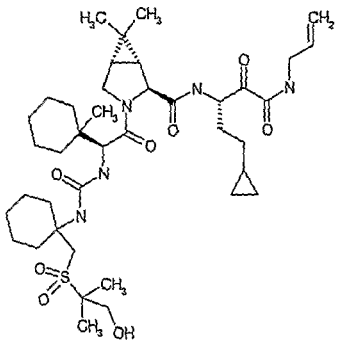
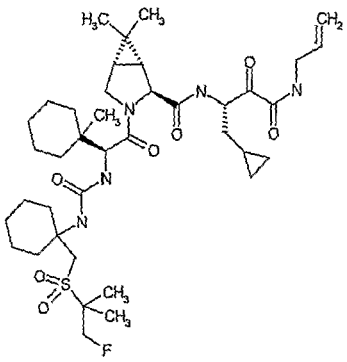
841		691.9378		A
842		705.9649		A

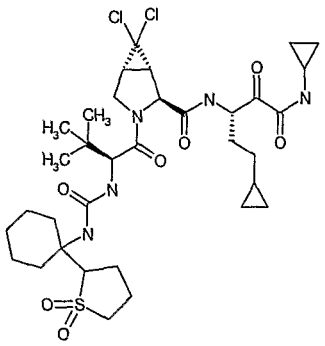
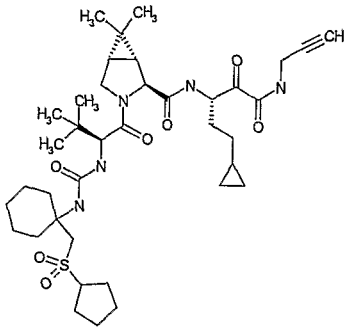
843		707.9809	708.4	11
845		742.0388	742.4	A

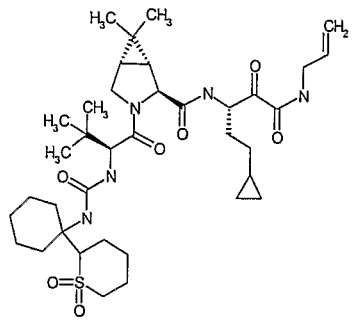
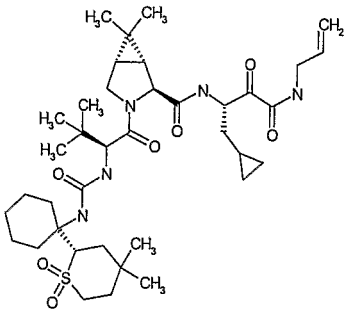
846		782.1041	782.4	A
847		782.1041	782.4	A

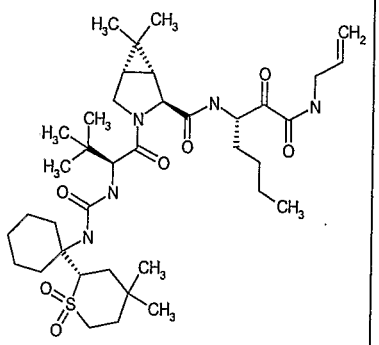
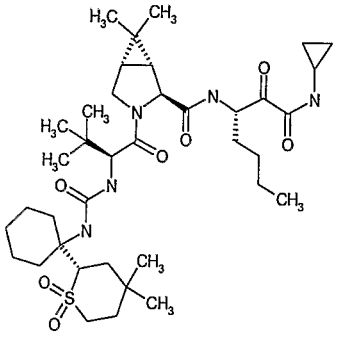
848		782.1041	782.4	B
849		782.1041	782.4	B

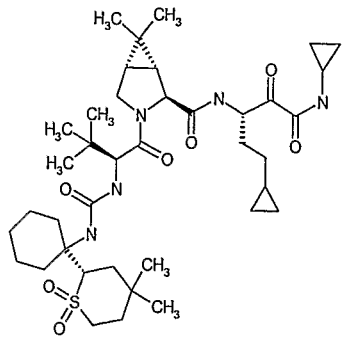
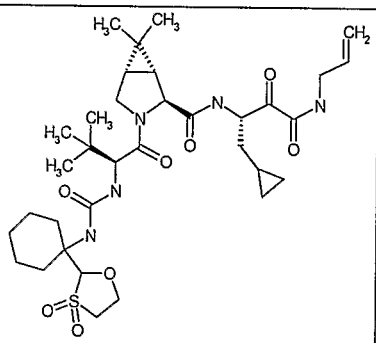
850		778.0727		A
851		752.0345		A

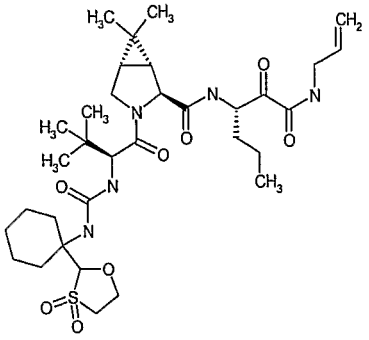
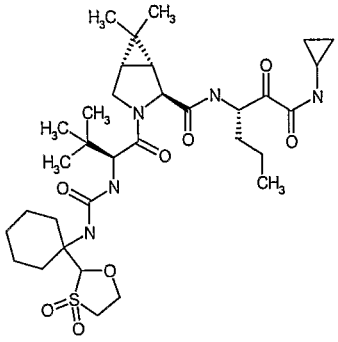
852		776.0568		A
853		764.0207		A

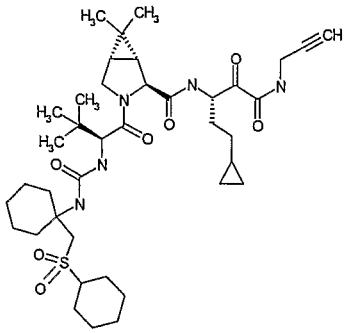
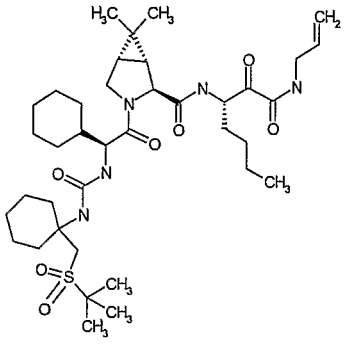
854		744.7849	744.4	A
855		729.9872	730.2	A

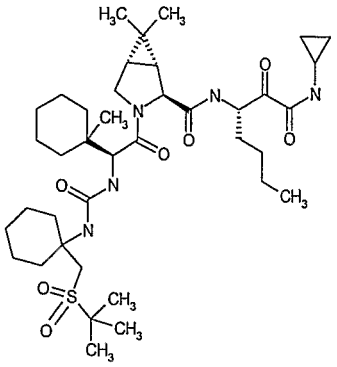
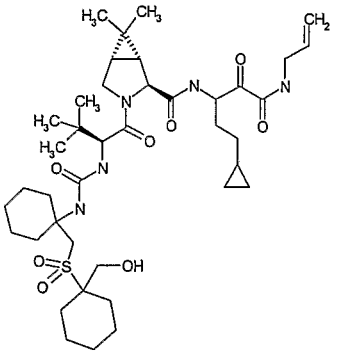
856		717.9761		5
857		732.0032	732.4	A

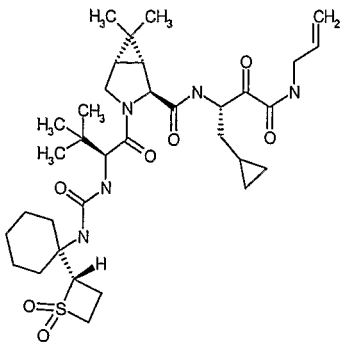
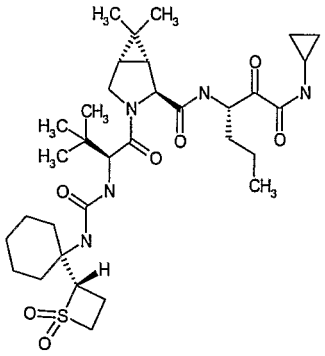
858		734.0191	734.4	A
859		734.0191	734.41	A

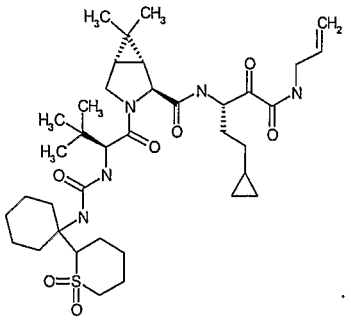
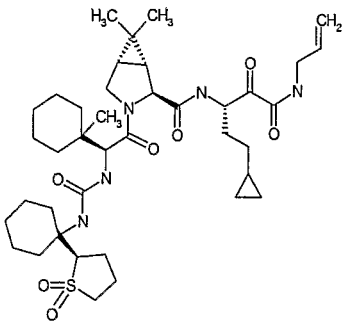
860		746.0303	746.5	A
861		691.8942	692.4	A

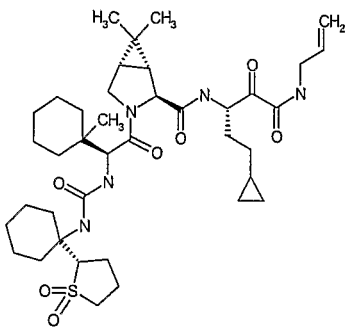
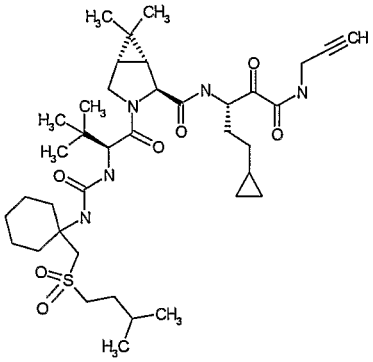
862		679.8831	680.38	A
863		679.8831	680.4	A

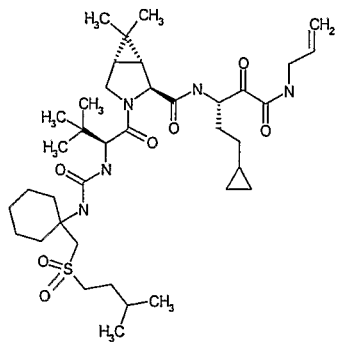
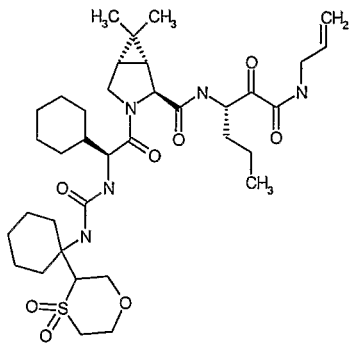
864		744.0143	744.1	A
865		734.0191	734.4	A

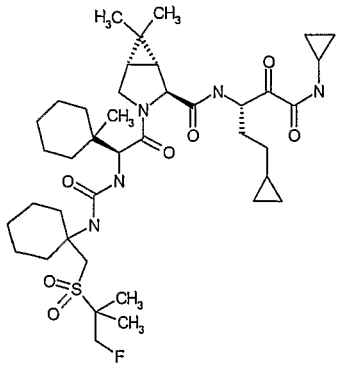
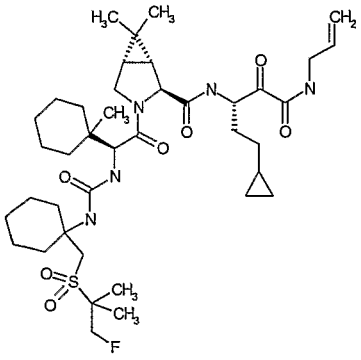
866		748.0462	748.4	A
867		776.0568		A

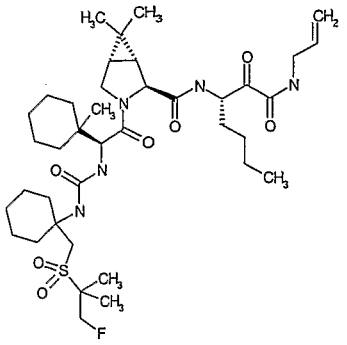
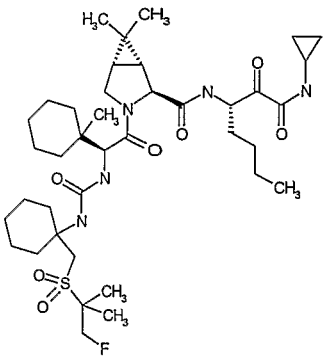
868		675.8948		A
869		663.8837		A

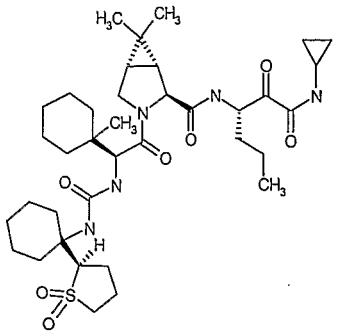
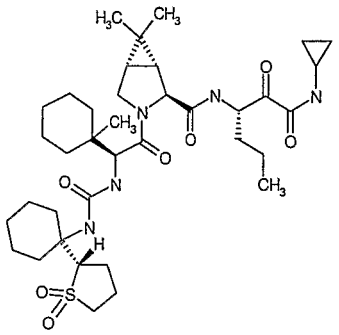
870		717.9761		A
871		744.0143		A

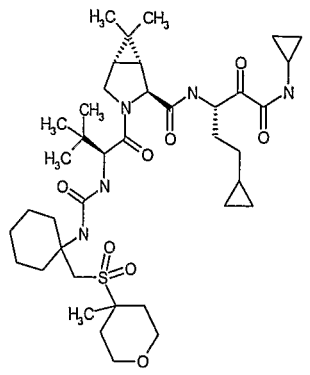
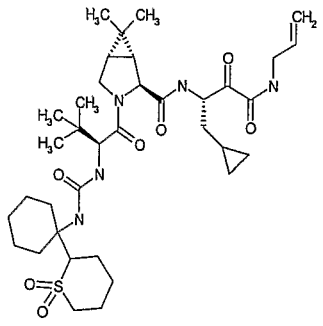
872		744.0143		A
873		732.0032	732.1	A

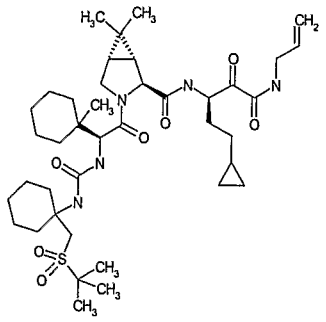
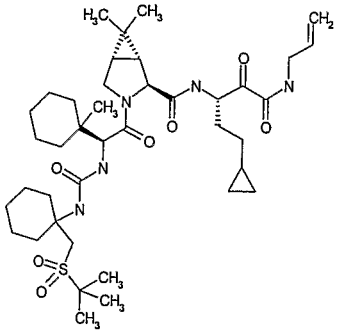
874		734.0191	734.1	A
875		719.9484		A

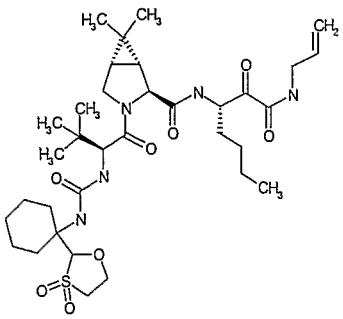
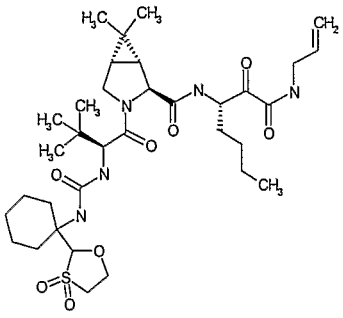
876		778.0478		A
877		778.0478		A

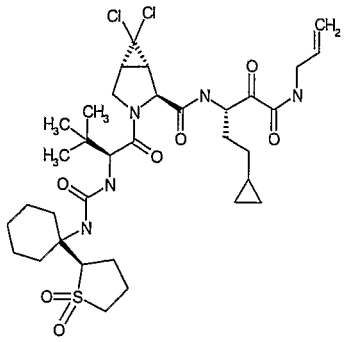
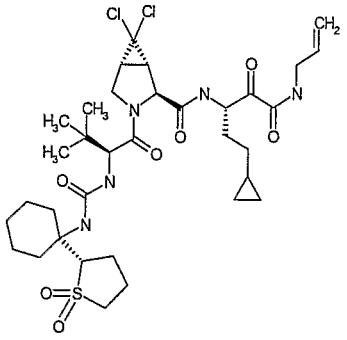
878		766.0366		A
879		766.0366		A

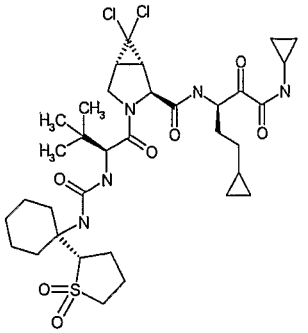
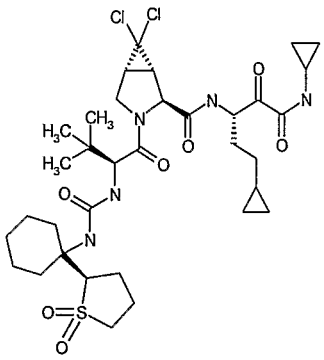
880		717.9761	718.1	A
881		717.9761	718.1	A

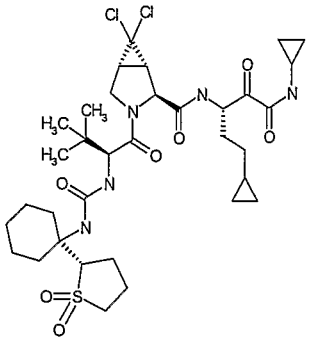
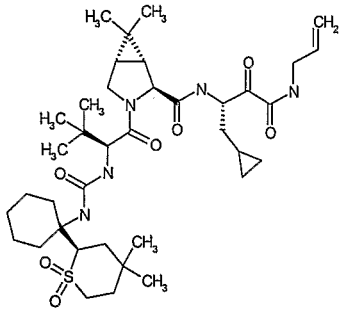
882		762.0297	762.1	A
883		703.949	704.1	A

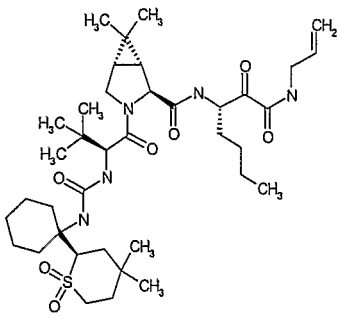
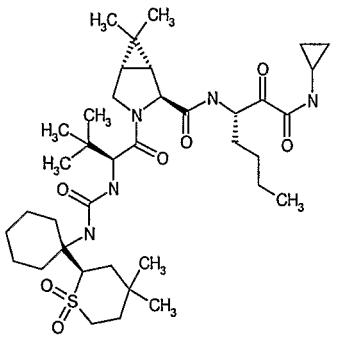
883-a		760.0574		B
883-b		760.0574		A

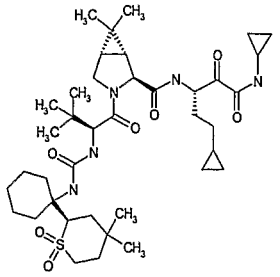
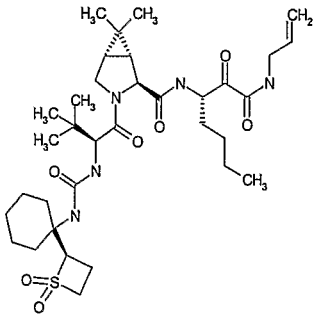
883-c		693.9102		3
883-d		693.9102		A

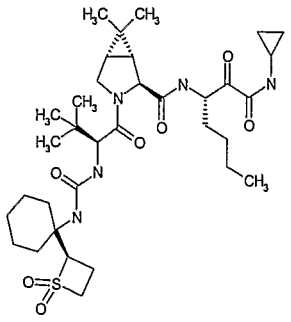
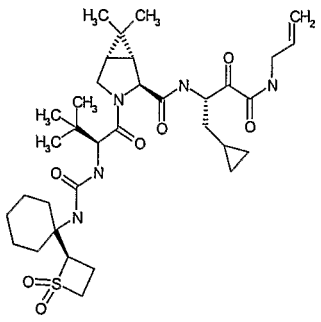
883-e		744.7849		A
883-f		744.7849		A

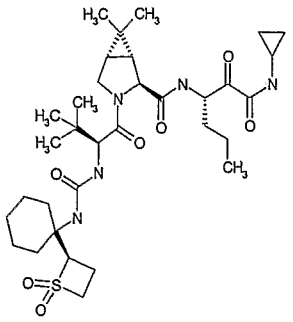
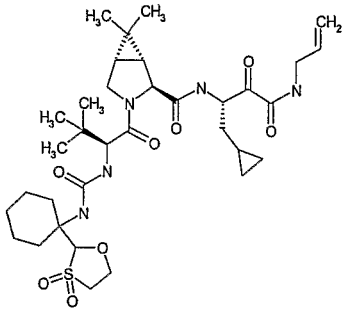
883-fa		744.7849		A
883-g		744.7849		A

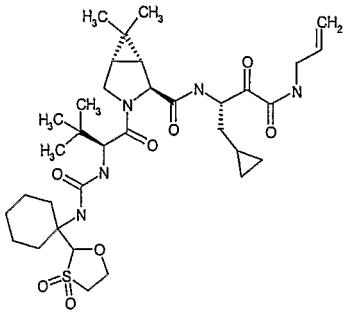
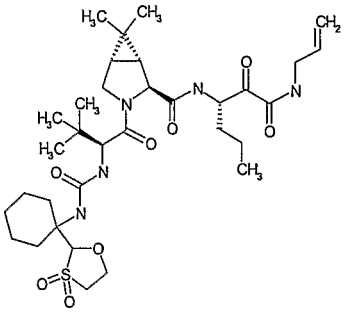
883-h		744.7849		A
883-i		732.0032		A

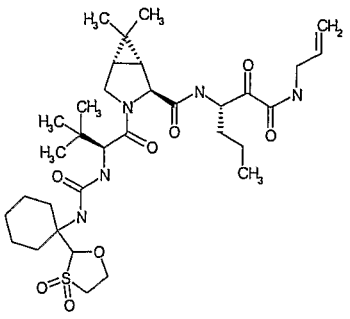
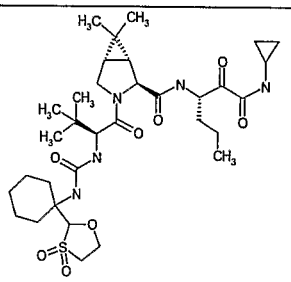
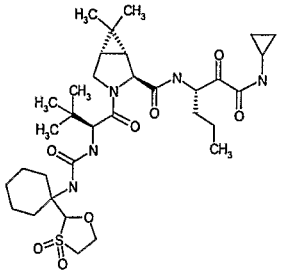
883-j		734.0191		A
883-k		734.0191		A

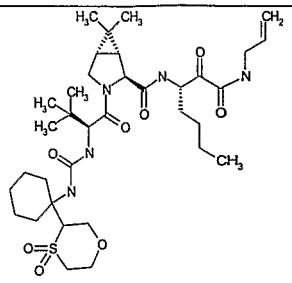
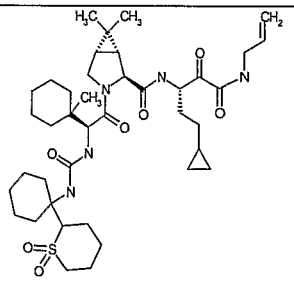
883-l		746.0303		A
883-m		677.9108		A

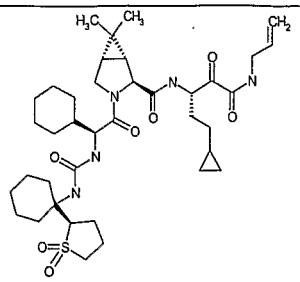
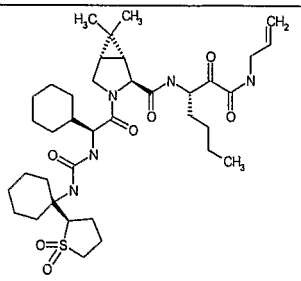
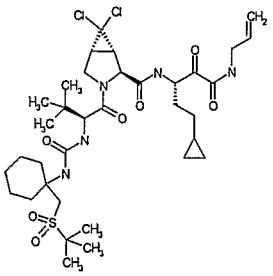
883-n		677.9108		A
883-o		675.8948		A

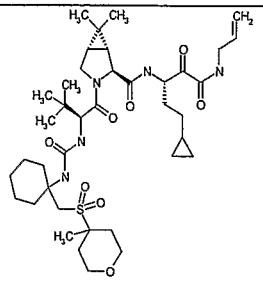
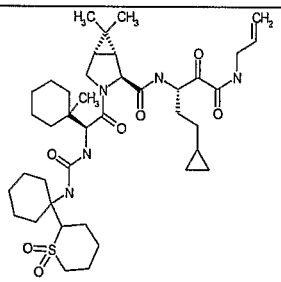
883-p		663.8837		A
883-q		691.8942		A

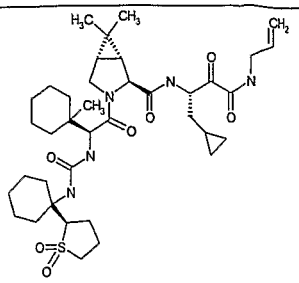
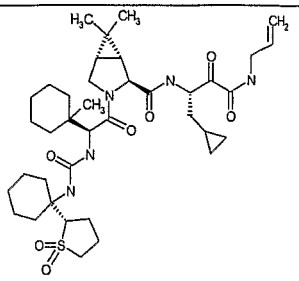
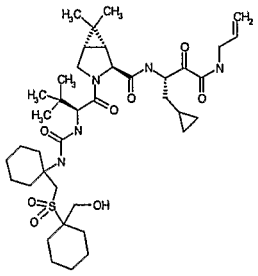
883-r		691.8942		A
883-s		679.8831		A

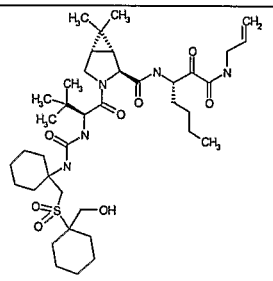
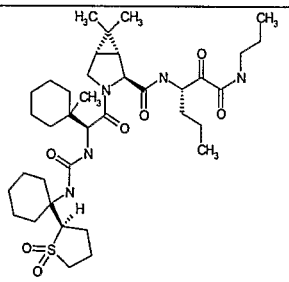
883-t		679.8831		A
883-u		679.8831		A
883-v		679.8831		A

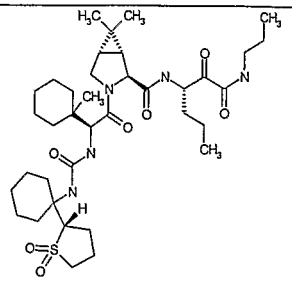
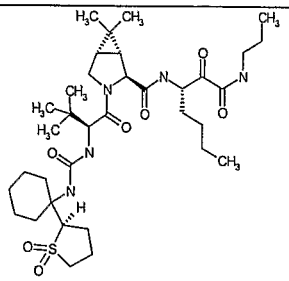
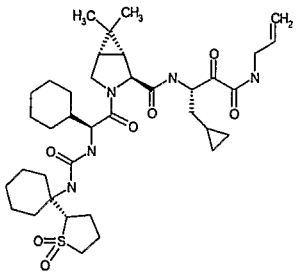
883-w		707.9372		3
883-x		758.0414		A

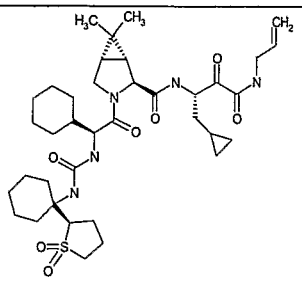
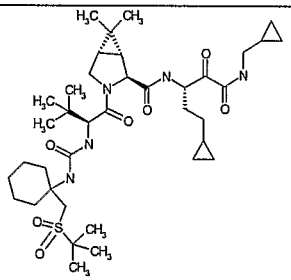
883-y		729.9872		A
883-z		717.9761		A
883-aa		760.8279		A

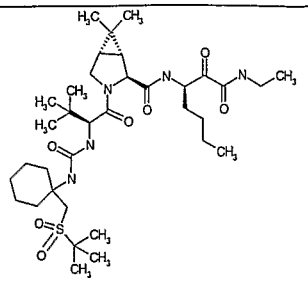
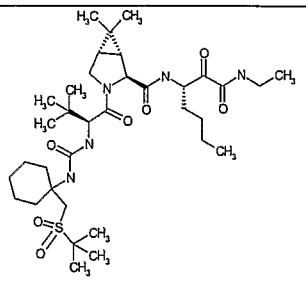
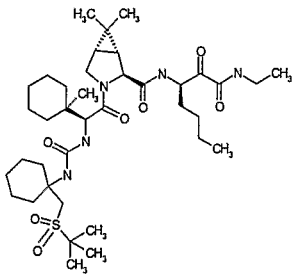
883-ab		762.0297		A
883-ac		758.0414		A

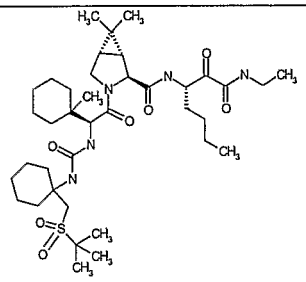
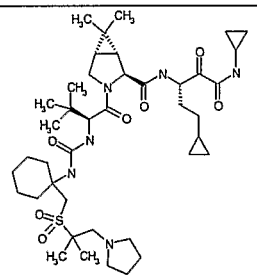
883-ad		729.9872		A
883-ae		729.9872		A
883-af		762.0297		A

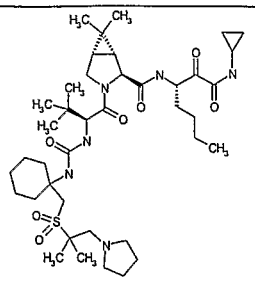
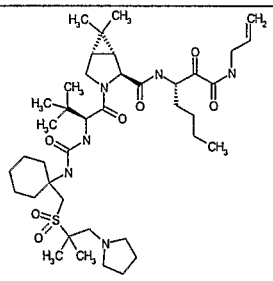
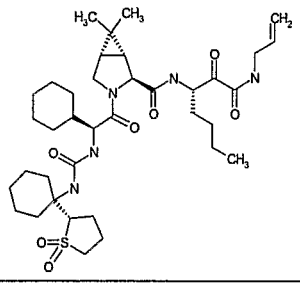
883-ag		764.0456		A
883-ah		719.992		A

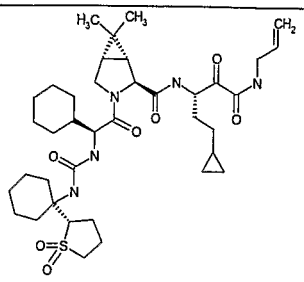
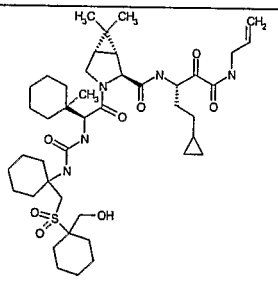
883-ai		719.992		A
883-aj		693.9538		A
883-ak		715.9601		A

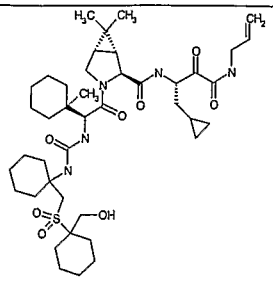
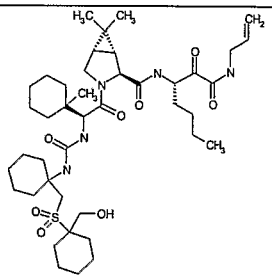
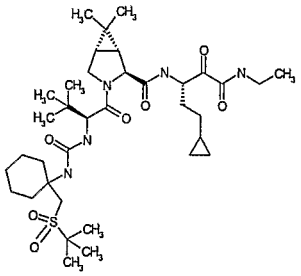
883-al		715.9601		A
883-am		734.0191		A

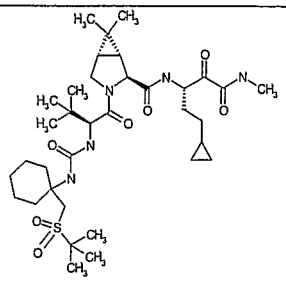
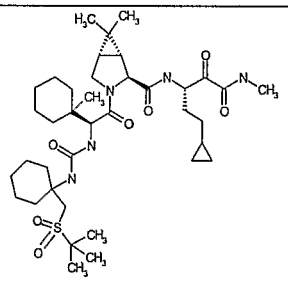
883-an		695.9697		C
883-ao		695.9697		A
883-ap		736.0351		B

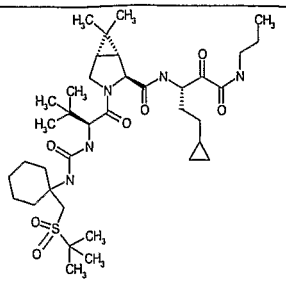
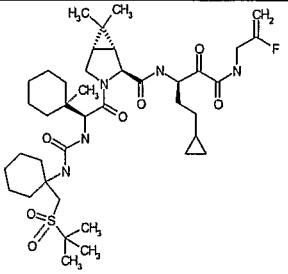
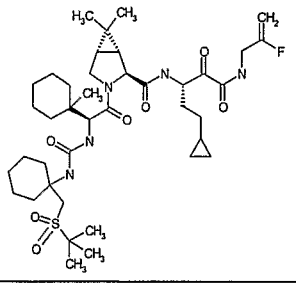
883-aq		736.0351		A
883-ar		789.0991		A

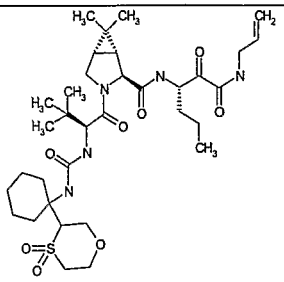
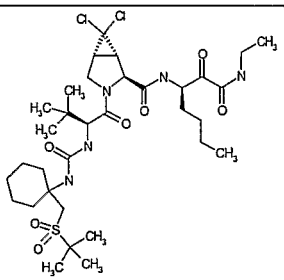
883-as		777.088		A
883-at		777.088		A
883-au		717.9761		A

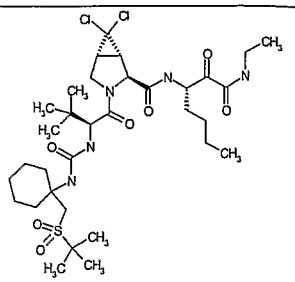
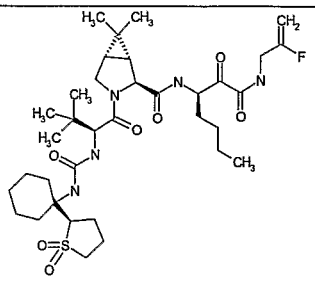
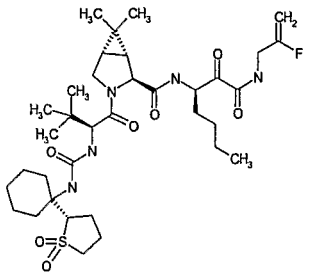
883-av		729.9872		A
883-aw		816.1221		A

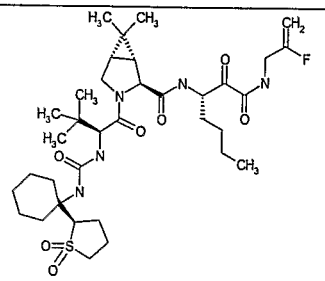
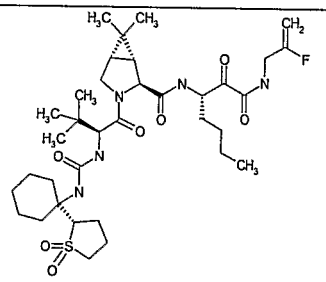
883-ax		802.095		A
883-ay		804.1109		A
883-az		707.9809		A

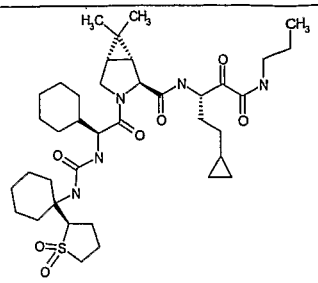
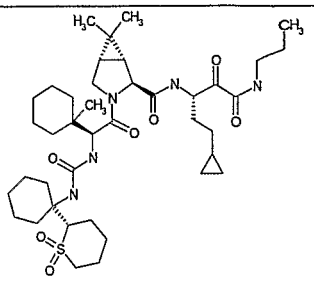
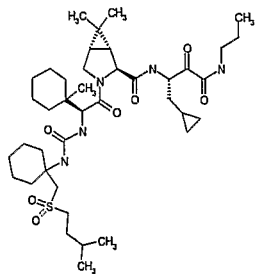
883-ba		693.9538		A
883-bb		734.0191		A

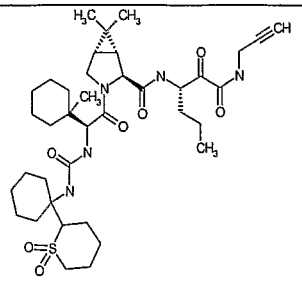
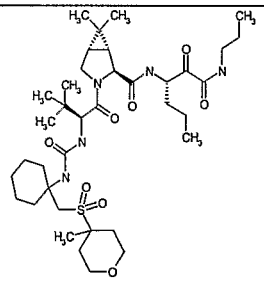
883-bc		722.008		A
883-bd		778.0478		b
883-be		778.0478		A

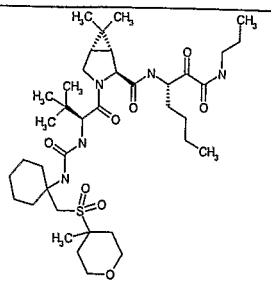
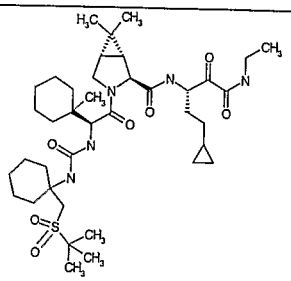
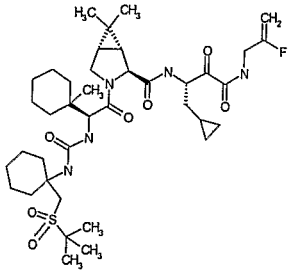
883-bf		693.9102		A
883-bg		736.8056		B

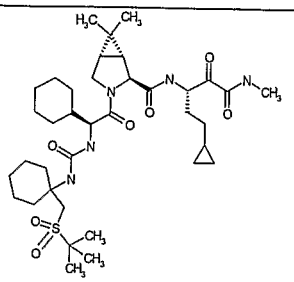
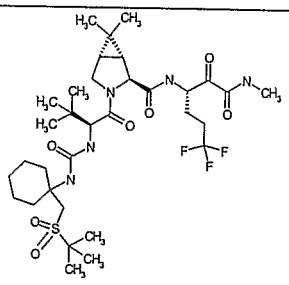
883-bh		736.8056		A
883-bi		709.9283		B
883-bj		709.9283		B

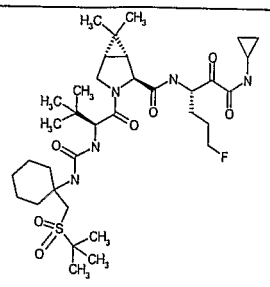
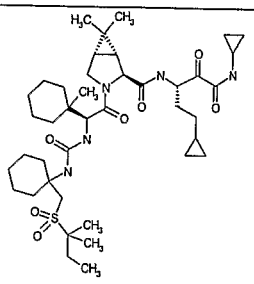
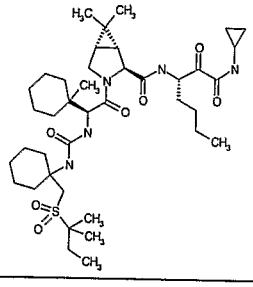
883-bk		709.9283		A
883-bl		709.9283		A

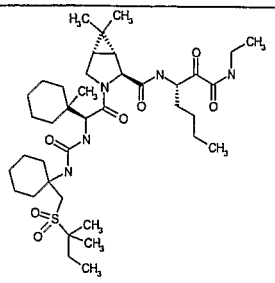
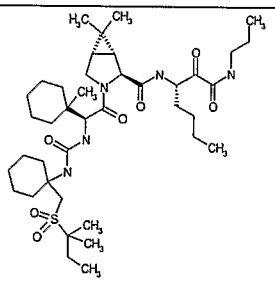
883-bm		732.0032		A
883-bn		760.0574		A
883-bo		762.0733		A

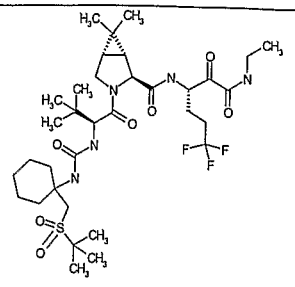
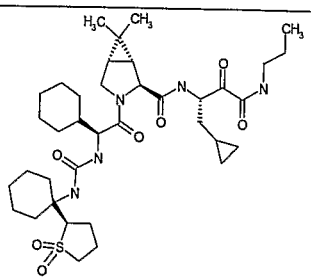
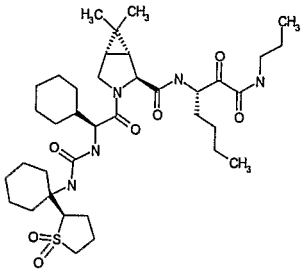
883-bp		729.9872		A
883-bq		738.0074		A

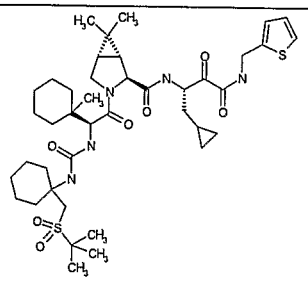
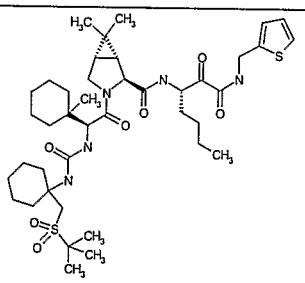
883-br		752.0345		A
883-bs		748.0462		A
883-bt		764.0207		A

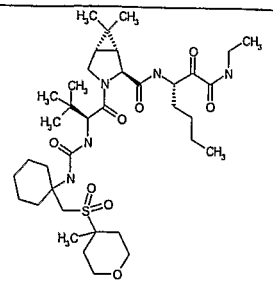
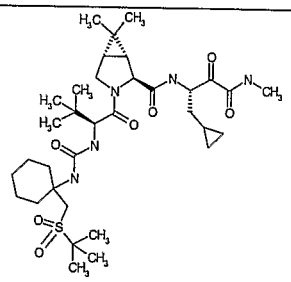
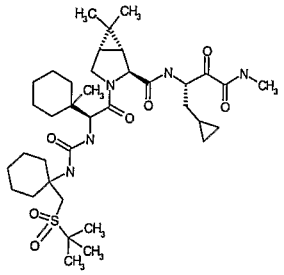
883-bu		719.992		A
883-bv		721.8868		A

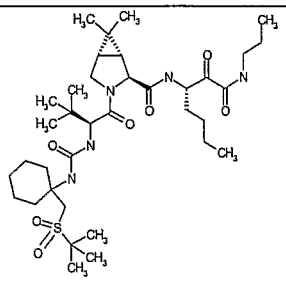
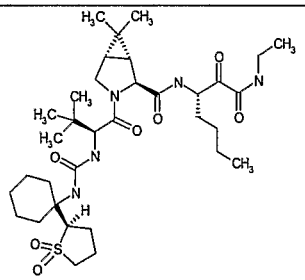
883-bw		711.9442		A
883-bx		774.0844		A
883-by		762.0733		A

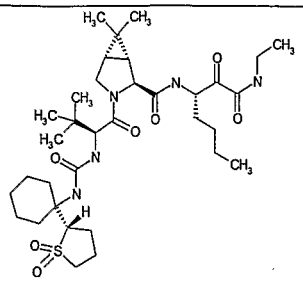
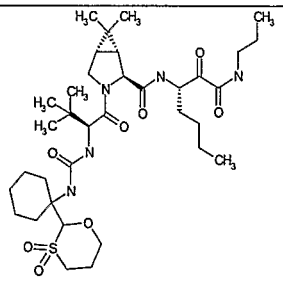
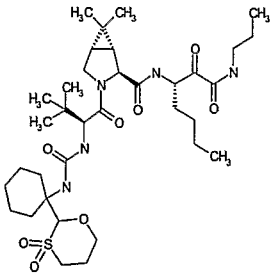
883-bz		750.0621		A
883-ca		764.0892		A

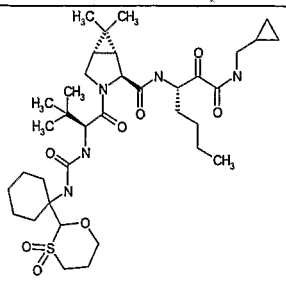
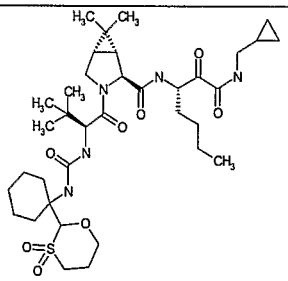
883-cb		735.9139		A
883-cc		717.9761		A
883-cd		719.992		A

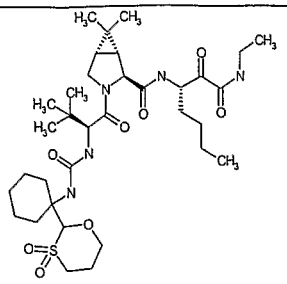
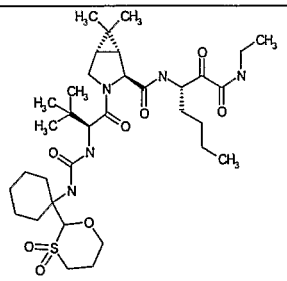
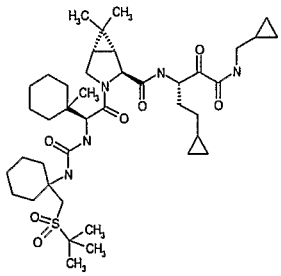
883-ce		802.1166		A
883-cf		804.1325		A

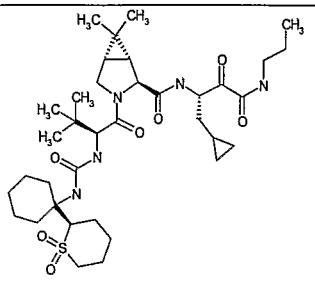
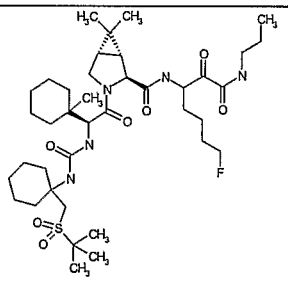
883-cg		738.0074		A
883-ch		679.9267		A
883-ci		719.992		A

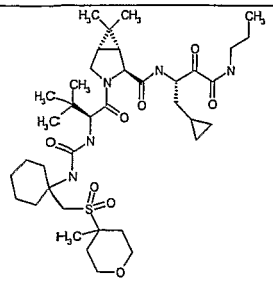
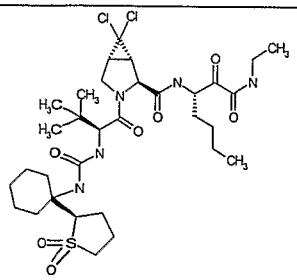
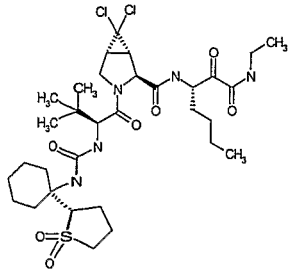
883-cj		709.9968		A
883-ck		679.9267		A

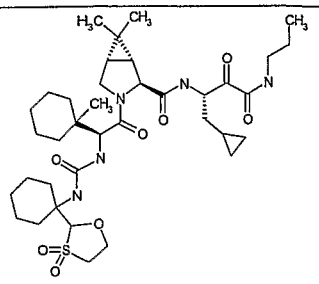
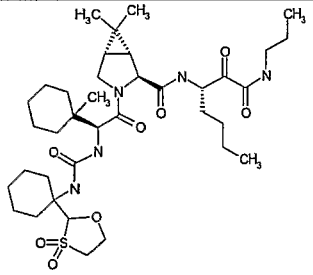
883-cl		679.9267		A
883-cm		709.9532		A
883-cn		709.9532		A

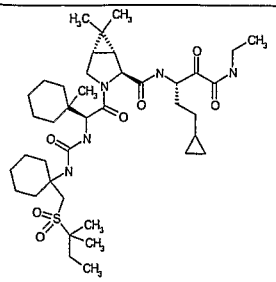
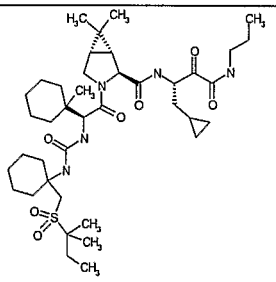
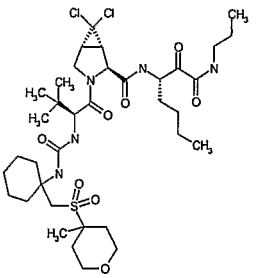
883-co		721.9643		A
883-cp		721.9643		A

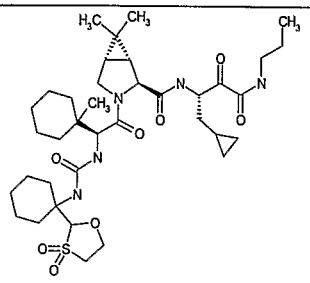
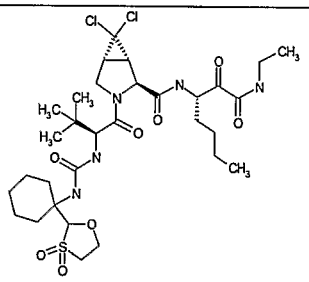
883-cq		695.9261		A
883-cr		695.9261		B
883-cs		774.0844		A

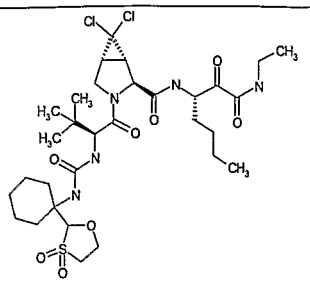
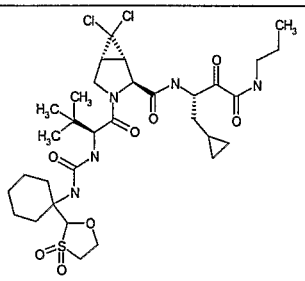
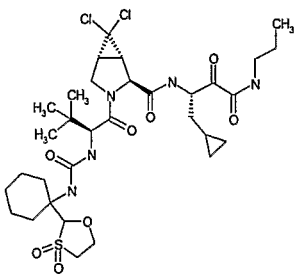
883-ct		705.9649		A
883-cu		768.0526		A

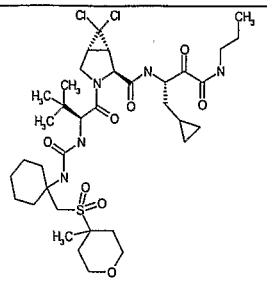
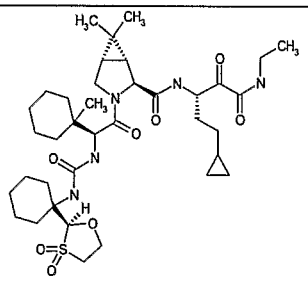
883-cv		750.0185		A
883-cw		720.7626		A
883-cx		720.7626		A

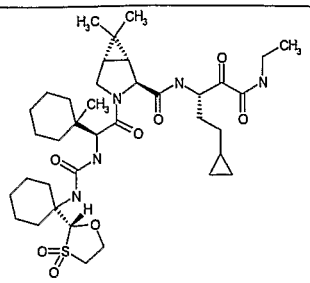
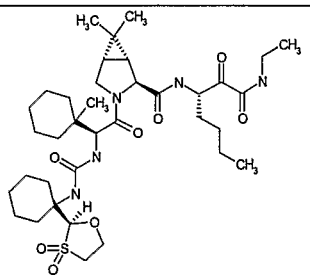
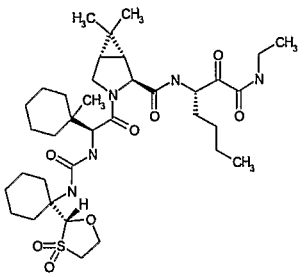
883-cy		733.9755		A
883-cz		735.9914		A

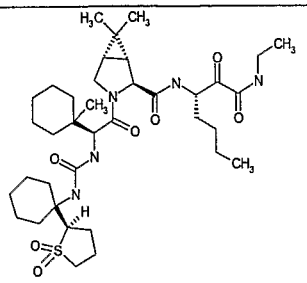
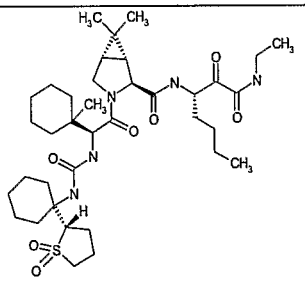
883-da		762.0733		A
883-db		762.0733		A
883-dc		792.8703		A

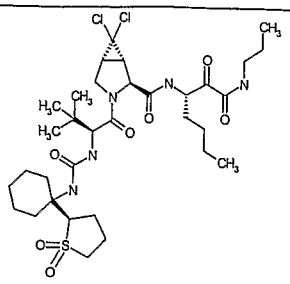
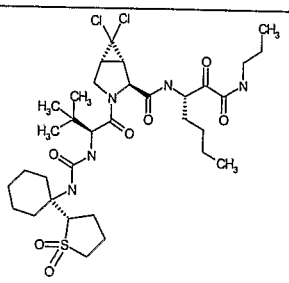
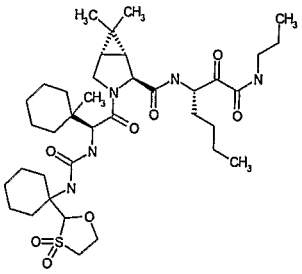
883-dd		733.9755		A
883-de		722.7349		A

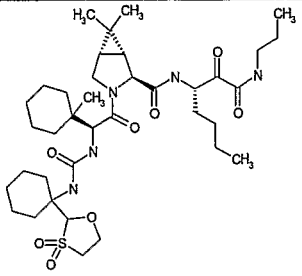
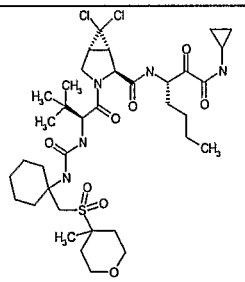
883-df		722.7349		A
883-dg		734.746		A
883-dh		734.746		A

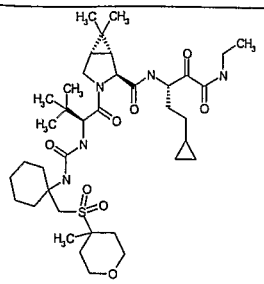
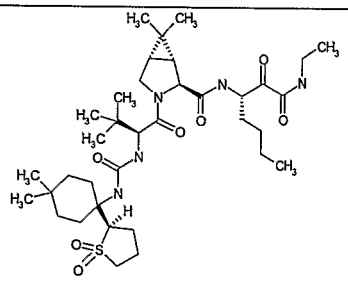
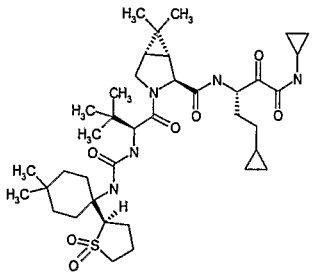
883-di		790.8544		A
883-dj		733.9755		A

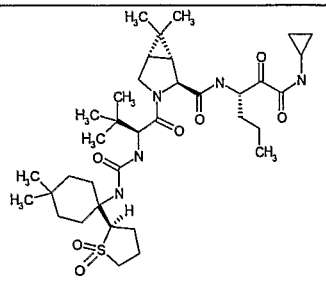
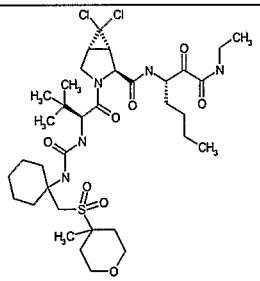
883-dk		733.9755		A
883-dl		721.9643		A
883-dm		721.9643		A

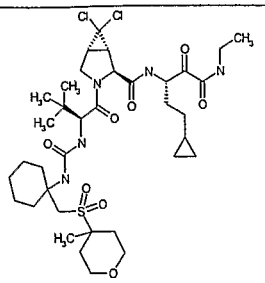
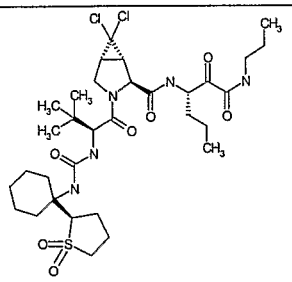
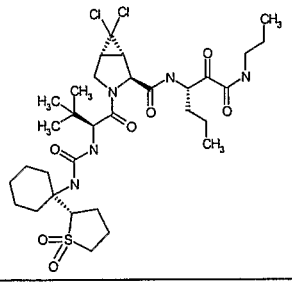
883-dn		719.992		A
883-do		719.992		A

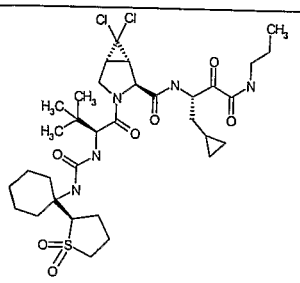
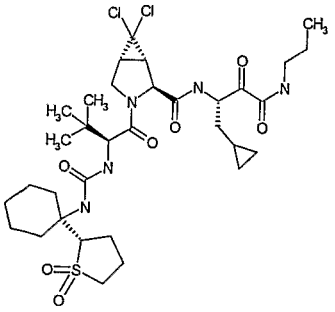
883-dp		734.7897		A
883-dq		734.7897		A
883-dr		735.9914		A

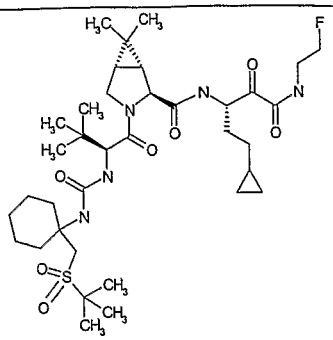
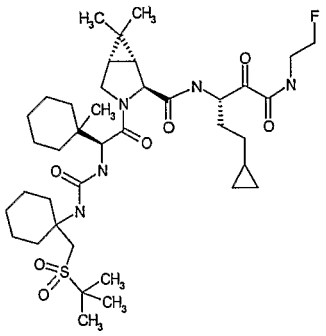
883-ds		735.9914		A
883-dt		790.8544		A

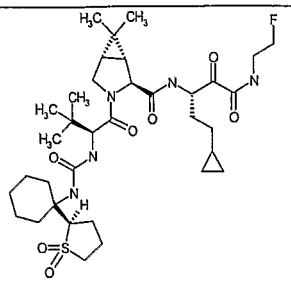
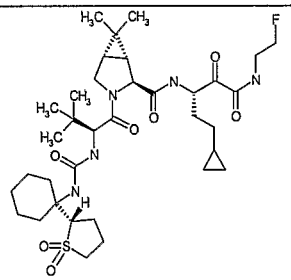
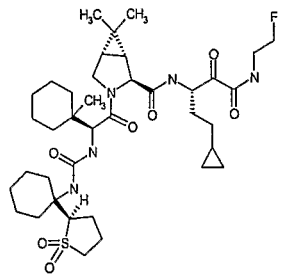
883-du		750.0185		A
883-dv		707.9809		A
883-dw		732.0032		A

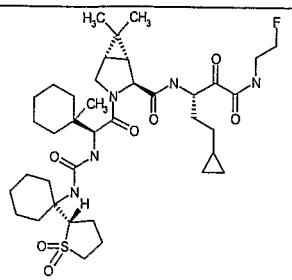
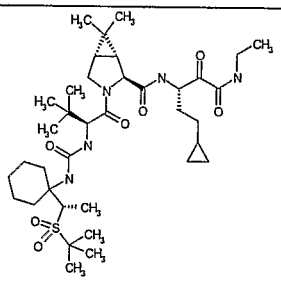
883-dx		705.9649		A
883-dy		778.8432		A

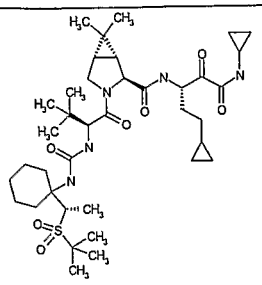
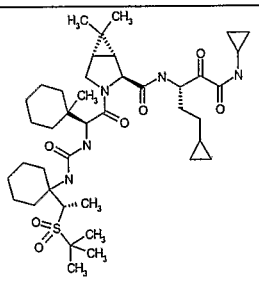
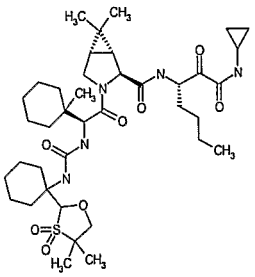
883-dz		790.8544		A
883-ea		720.7626		A
883-eb		720.7626		A

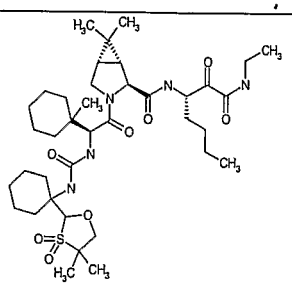
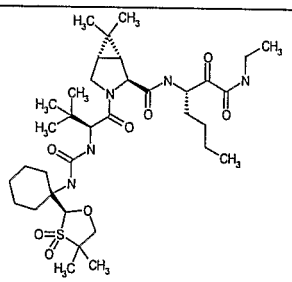
883-ec		732.7737		A
883-ed		732.7737		A

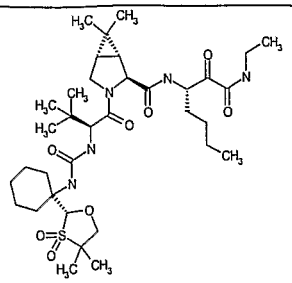
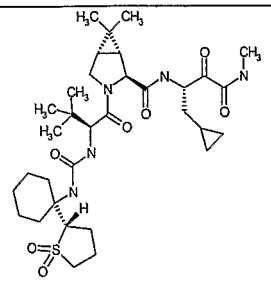
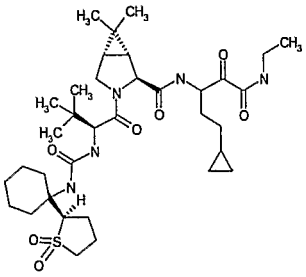
883-ee		725.9713		A
883-ef		766.0366		A

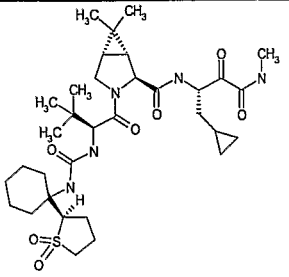
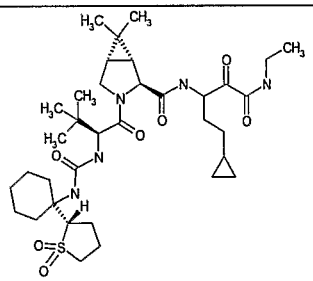
883-eg		709.9283		A
883-eh		709.9283		A
883-ei		749.9936		A

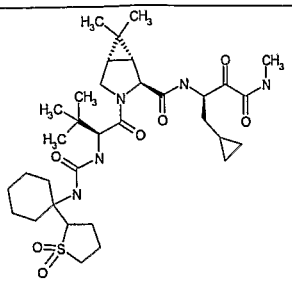
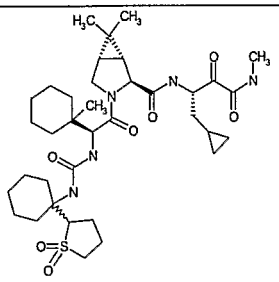
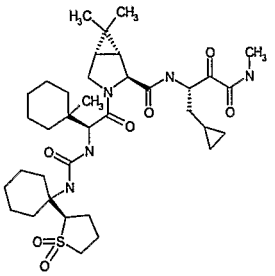
883-ej		749.9936		A
883-ek		722.008		A

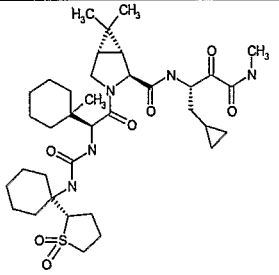
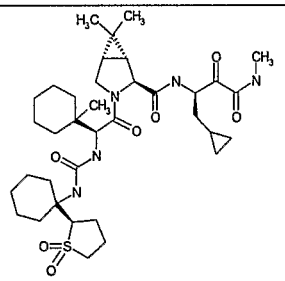
883-el		734.0191		A
883-em		774.0844		A
883-en		762.0297		A

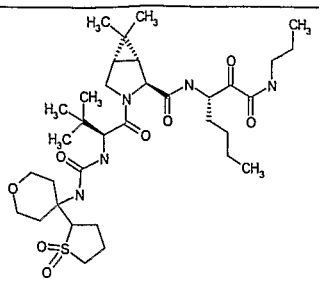
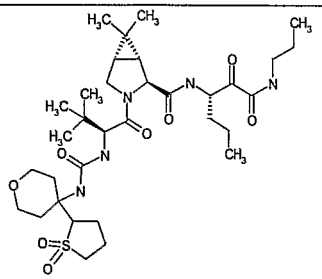
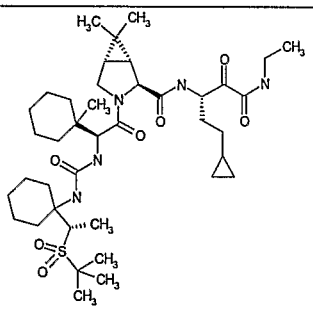
883-eo		750.0185		A
883-ep		709.9532		A

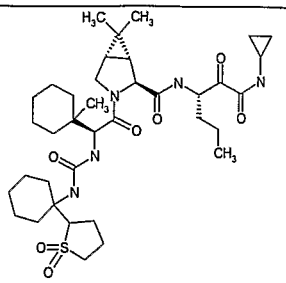
883-eq		709.9532		A
883-er		663.8837		A
883-es		691.9378		A

883-et		663.8837		A
883-eu		691.9378		A

883-ev		663.8837		A
883-ew		703.949		A
883-ex		703.949		A

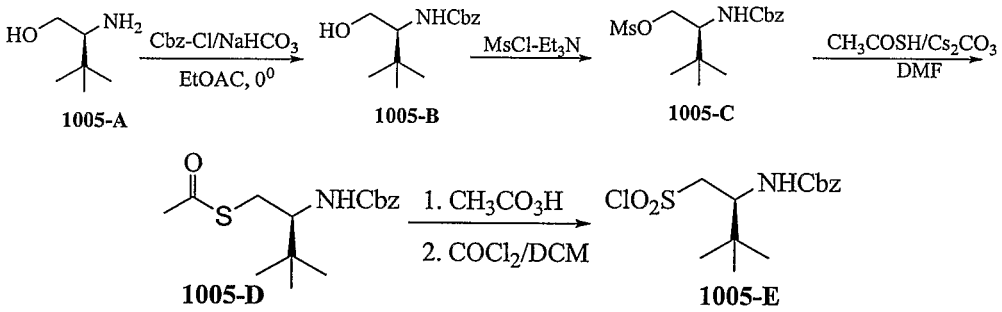
883-ey		703.949		A
883-ez		703.949		A

883-fa		695.9261		B
883-fb		681.899		A
883-fc		762.0733		A

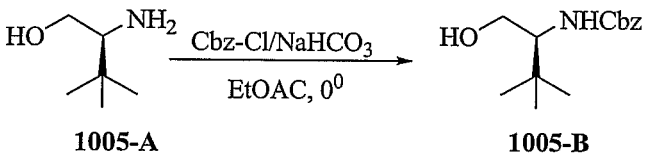
883-fd		717.9761		A

Also disclosed are the following compounds in **Table 4** and **Table 4A.** The preparation of the compounds in **Table 4** and **Table 4A** is described below:

EXAMPLE 1005:



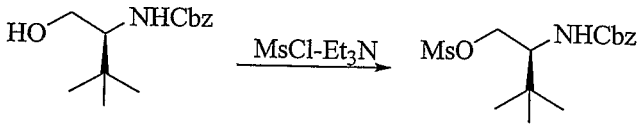
STEP 1



To a solution of 5g of **1005-A** (commercially available from Aldrich) in 100 ml of EtOAc at 0^0C were added 40 ml of saturated $NaHCO_3$ solution followed by 6.5 ml of Cbz-Cl in one portion. The resulting mixture was stirred for 2h and layers were separated. The aqueous layer was back extracted with

50 ml of EtOAc. The combined organic layer was washed once with brine, dried over $MgSO_4$ and concentrated to a colorless liquid which solidified on standing. 10.7g of **1005-B** as white solids were obtained.
MS: 274 $[M+Na]^+$.

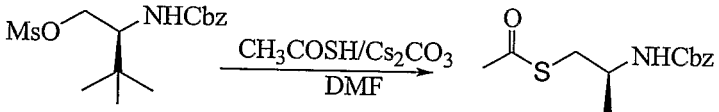
STEP 2



1005-B **1005-C**

To a solution of 10.7g of **1005-B** in 120 ml of DCM at 0^0C were added 7.04 ml of triethylamine and 4.05 ml of methanesulfonyl chloride. The mixture was stirred at 0^0C for 10 minutes and 1.5h at room temperature. The mixture was washed with 1M $KHSO_4$ solution, water, brine and dried over $MgSO_4$. Concentration of solvent gave the crude product which was purified on silica gel column eluted with DCM. 13g of **1005-C** were obtained as colorless thick oil. MS: 352 $[M+Na]^+$.

STEP 3

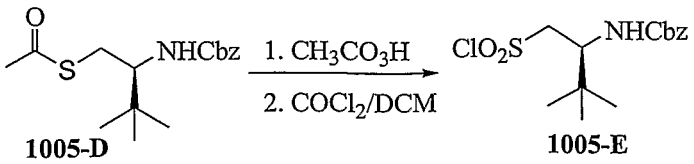


1005-C **1005-D**

To a suspension of 8.3g of Cs_2CO_3 in 100 ml of anhydrous DMF were added 3.3 ml of thioacetic acid. To the dark brown slurry was added a solution of 12.97g of **1005-C** in 30 ml of anhydrous DMF. The resulting mixture was stirred overnight at room temperature, diluted with 300 ml of ice-water and extracted with 2x250 ml of EtOAc. The combined organic layer was washed with water, brine and dried over $MgSO_4$. Evaporation of solvent gave ~10g of the crude product which was purified over silica gel column with 10% EtOAc in hexane. 4.8g of **1005-D** as white solids were obtained. MS: 310 $[M+H]^+$,

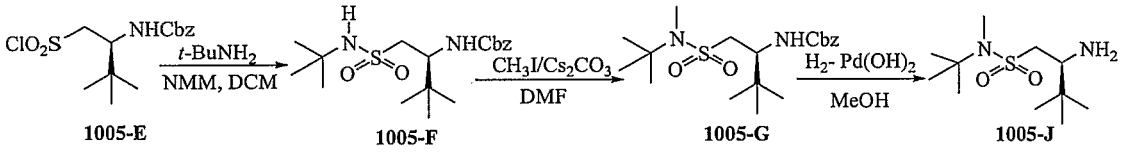
332 $[M+Na]^+$.

STEP 4



1005-D **1005-E**

To a solution of 4.4g of **1005-D** in 15 ml of AcOH was added a solution of 15 ml of 30% H_2O_2 and 30 ml of AcOH. The resulting solution was stirred at room temperature for 20 h. 75 mg of 10% Pd/C were added and the mixture was stirred for 1h, filtered through a celite pad and rinsed with MeOH. The combined filtrate was concentrated and co-evaporated with 3x100 ml of toluene to give solids. 90 ml of anhydrous DCM were added to dissolve solids and to the solution was added 15 ml of 20% phosgene in toluene (Fluka) followed by 1.8 ml of anhydrous DMF. Gas evolved and the mixture was stirred at room temperature for 2 h and concentrated to yield solid residue. Purification on silica gel eluted with DCM gave 3.94 g of **1005-E** as solids. MS: 356, 358 $[M+Na]^+$.



1005-E **1005-F** **1005-G** **1005-J**

STEP 5

A mixture of 900 mg of **1005-E**, 1.0 ml of t-Butylamine and 0.4 ml of NMM in 40 ml of DCM was stirred at room temperature for 0.5 h, washed with 1M KHSO4 solution, brine and dried over $MgSO_4$. Evaporation of solvent gave 445 mg of the crude product which was purified on silica gel with DCM and 5% EtOAc in DCM. 617 mg of **1005-F** were obtained. MS: 379 $[M+Na]^+$.

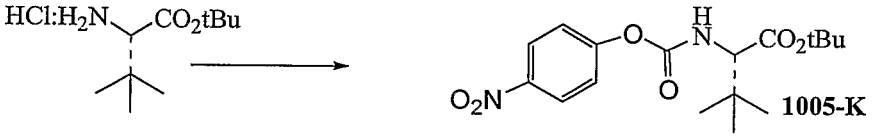
STEP 6

A mixture of 600 mg of **1005-F**, 2.64 g of cesium carbonate and 0.5 ml methyl iodide in 10 ml of anhydrous DMF was stirred at room temperature

overnight, diluted with 50 ml of ice-cold water and extracted with 2x50 ml EtOAc. The combined organic solution was washed twice with water, once with brine, dried over MgSO4. Removal of solvent under vacuum gave 620 mg of **1005-G** as white solids. MS: 385 $[M+H]^+$.

STEP 7

A solution of **1005-G** (600 mg) and $Pd(OH)_2$ (70mg) in MeOH was placed under an atmosphere of hydrogen overnight. The solids were filtered and washed thoroughly with MeOH. The volatiles were removed under reduced pressure to give the amine (**1005-J**; 380mg). MS: 251 $[M+H]^+$.

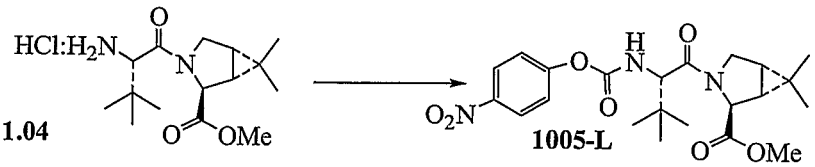


1005-K

STEP 8

To a solution of the of the hydrochloride salt (Bachem; 2.24g) in dichloromethane (50ml) was added NMM (2.6ml) followed by the p-nitrophenyl chloroformate (2.42g) and the resulting mixture was stirred at room temperature overnight. The reaction mixture was washed with cold aq. 1N HCl, sat aq. sodium bicarbonate, dried and the volatiles were removed under reduced pressure. The crude reaction product by silica gel chromatography using EtOAc:hexanes (1:10) as eluent to give the carbamate (**1005-K**; 2.97g).

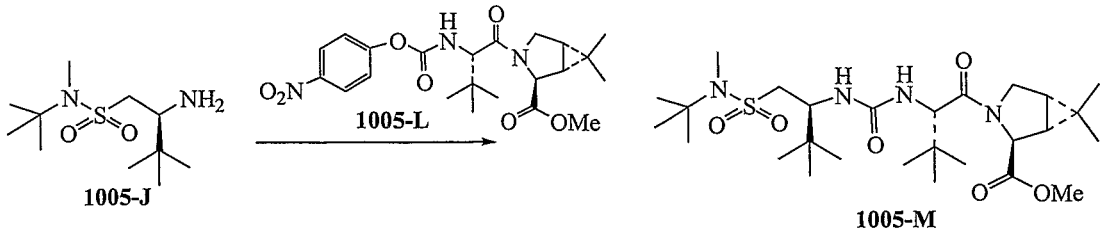
STEP 9



1.04 **1005-L**

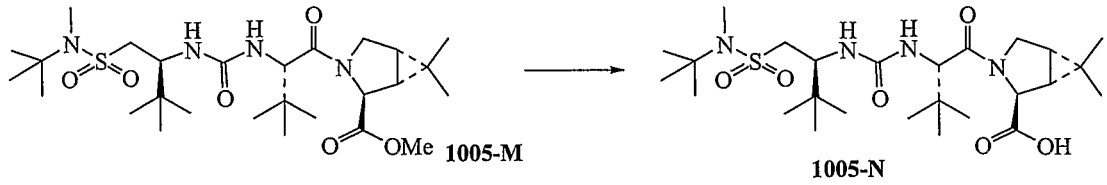
Using the procedure set forth in **STEP 8** the carbamate **1005-L** was prepared from the amine-hydrochloride salt **1.04**.

STEP 10



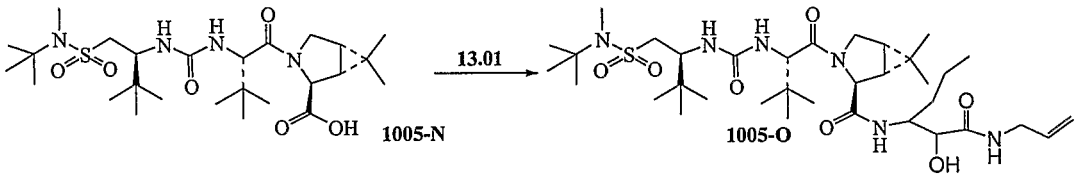
NMM (0.12ml) was added to a mixture of the amine (**1005-J**; 0.20g) and the carbamate (**1005-L**; 0.375g) in acetonitrile (15ml) and the resulting mixture was stirred at room temperature, under an atmosphere of nitrogen, overnight. The volatiles were removed under reduced pressure and the residue was partitioned between EtOAc and water. The organic phase was separated, dried and concentrated. The crude reaction product was purified by silica gel column chromatography using EtOAc: Hexanes (2:3) as eluent, providing the desired urea (**1005-M**; 0.43g). MS: 559.28 $[M+H]^+$.

STEP 11



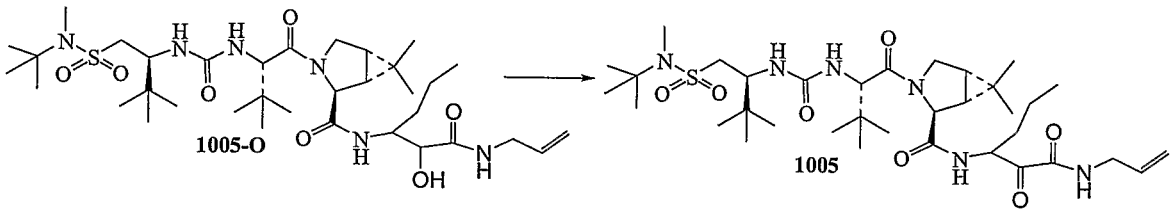
Lithium hydroxide (0.020g) in water (2ml) was added to a solution of the methyl ester (1005-M; 0.41g) in dioxane (15ml) and the resulting mixture was stirred at room temperature overnight. Aqueous HCl (0.01N) was added and the organics were extracted into EtOAc. The organic phase was separated, dried and concentrated to yield the carboxylic acid (**1005-N**; 0.395g). MS: 545.32 $[M+H]^+$.

STEP 12



Hunigs base (0.050ml) was added to a mixture of the carboxylic acid (**1005-N**; 0.030g) and the hydrochloride salt (**13.01**; 0.015g) in dichloromethane (5ml) at -20C, under an atmosphere of nitrogen. The reaction was maintained at this temperature for a period of 20h. Aqueous work-up gave a crude reaction product (**1005-O**) which was used in **STEP12**, below.

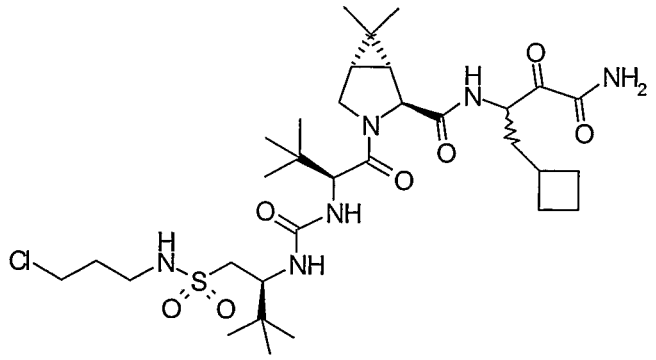
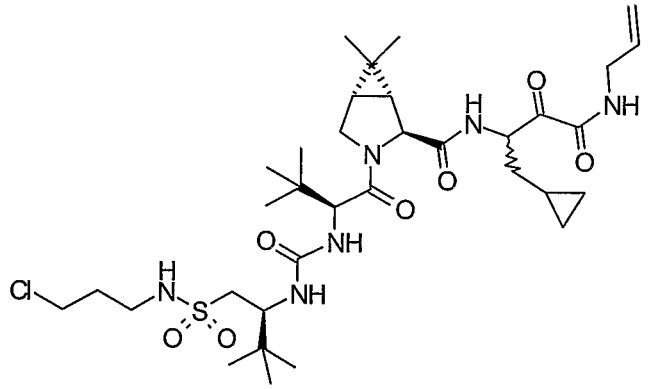
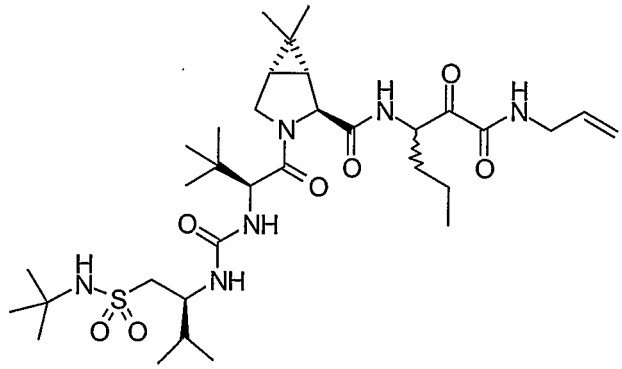
STEP 13

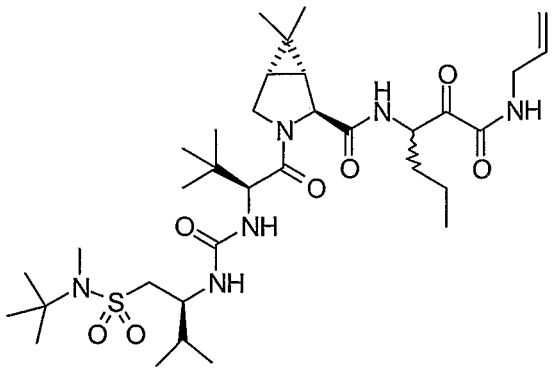
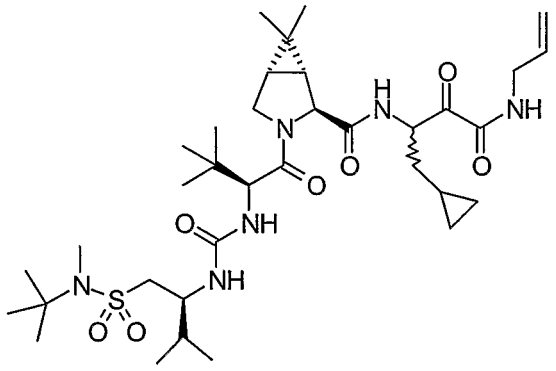
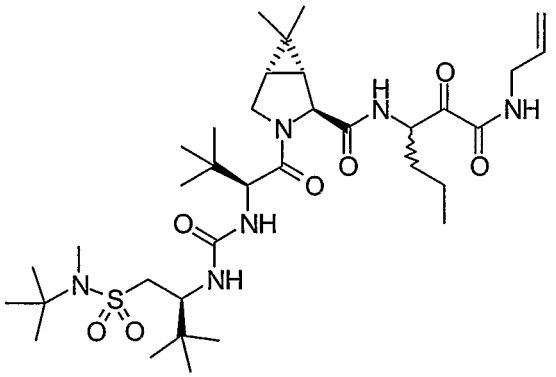


To crude (**1005-O**; above in **STEP 11**) in dichloromethane (3ml) was added Dess-Martin periodinane (0.050g) and the resulting mixture was stirred at room temperature for a period of 24h. Aqueous work-up and silica gel plate chromatography using dichloromethane:methanol (20:1) as eluent gave the desired α-keto-amide (0.0282g), as a white solid. Ki* ranges are: A = <75 nM; B = 75 - 250 nM; C = >250 nM.

Table 4

Prep. Ex.	COMPOUND	FABMS: MH+	Ki* range

1000		703.7	A
1001		729.7	B
1002		683.3	C

1003		697.3	A
1004		709.3	A
1005		711.3	B

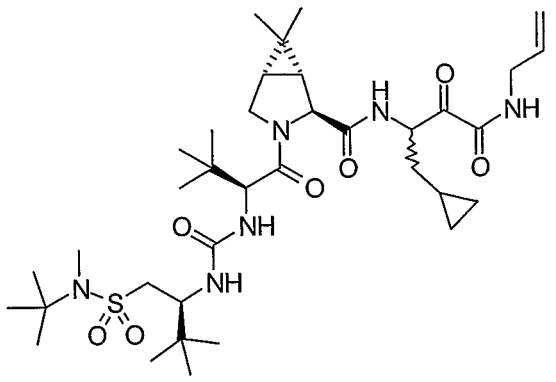
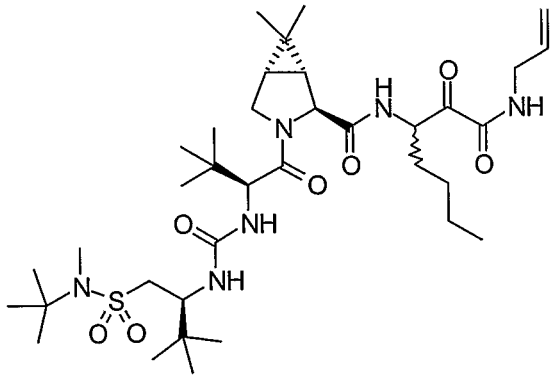
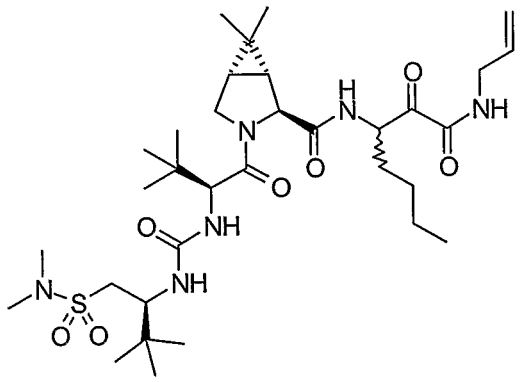
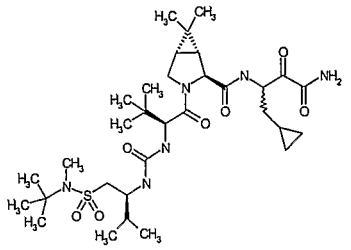
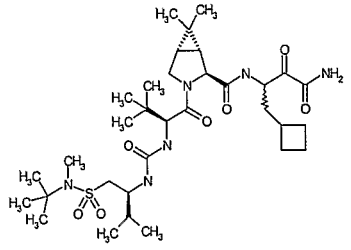
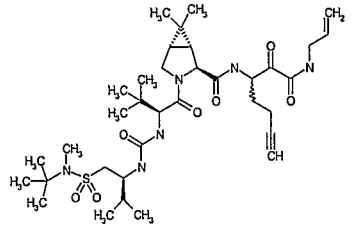
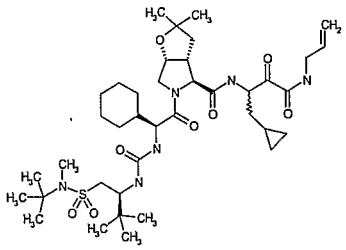
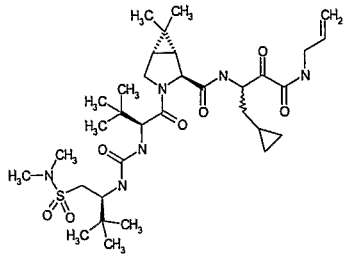
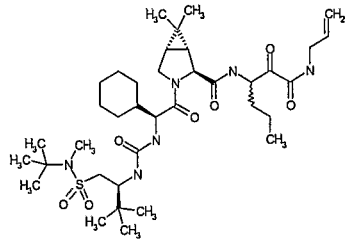
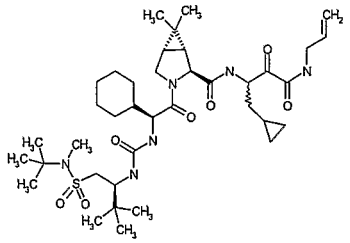
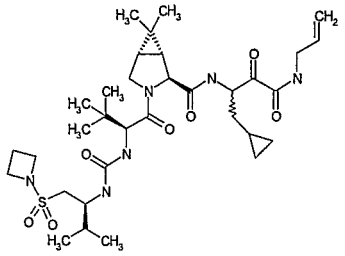
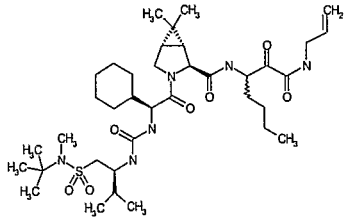
1006		723.3	B
1007		725.3	B
1008		683.3	B

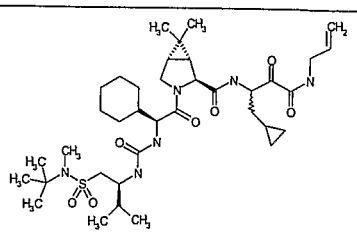
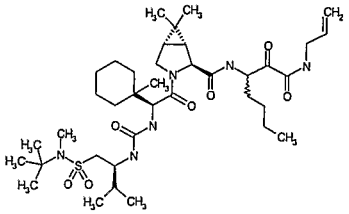
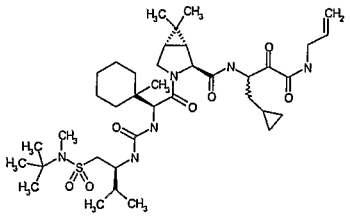
Table 4A lists still additional compounds representing the present invention:

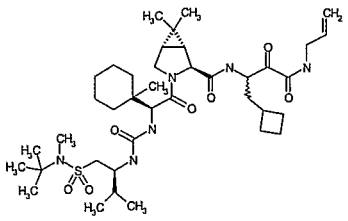
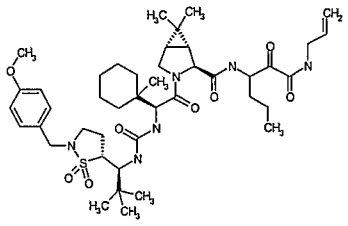
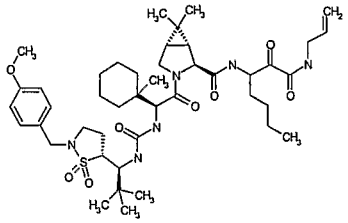
Table 4A

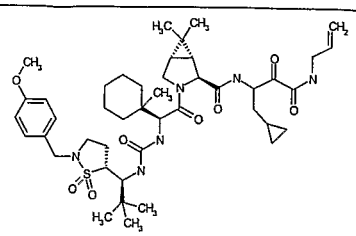
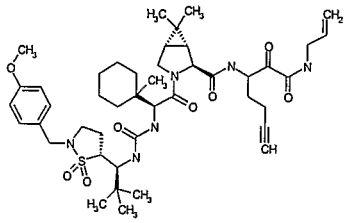
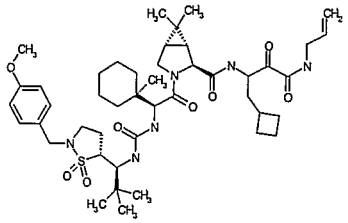
Prep. Ex.	Compound	Select Mass Spectra Data	Ki* Range
1100			A
1101			A
1102			A

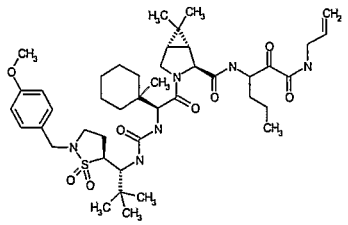
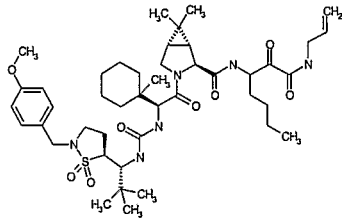
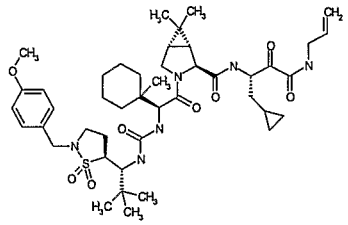
1103			B
1104			B
1105			B

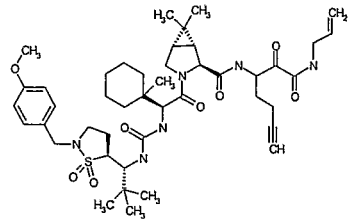
1106			B
1107			A
1108			A

1109			B
1110			A
1111			C

1112			A
1113			C
1114			C

1115			C
1116			C
1117			C

1118			C
1119			C
1120			

1121			C

The present invention relates to novel HCV protease inhibitors. This utility can be manifested in their ability to inhibit the HCV NS2/NS4a serine protease. A general procedure for such demonstration is illustrated by the following *in vitro* assay.

Assay for HCV Protease Inhibitory Activity:

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

Materials and Methods:

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

Enzyme Preparation: Recombinant heterodimeric HCV NS3/NS4A protease (strain 1a) is prepared by using the procedures published previously (D. L. Sali *et al*, *Biochemistry*, 37 (1998) 3392-3401). Protein concentrations are determined by the Biorad dye method using recombinant HCV protease standards previously quantified by amino acid analysis. Prior to assay initiation, the enzyme storage buffer (50 mM sodium phosphate pH 8.0, 300 mM NaCl, 10% glycerol, 0.05% lauryl maltoside and 10 mM DTT) is exchanged for the assay buffer (25 mM MOPS pH 6.5, 300 mM NaCl, 10% glycerol, 0.05% lauryl maltoside, 5 µM EDTA and 5 µM DTT) utilizing a Biorad Bio-Spin P-6 prepacked column.

Substrate Synthesis and Purification: The synthesis of the substrates is done as reported by R. Zhang *et al*, (*ibid.*) and is initiated by anchoring Fmoc-Nva-OH to 2-chlorotrityl chloride resin using a standard protocol (K. Barlos *et al, Int. J. Pept. Protein Res.*, 37 (1991), 513-520). The peptides are subsequently assembled, using Fmoc chemistry, either manually or on an automatic ABI model 431 peptide synthesizer. The N-acetylated and fully protected peptide

fragments are cleaved from the resin either by 10% acetic acid (HOAc) and 10% trifluoroethanol (TFE) in dichloromethane (DCM) for 30 min, or by 2% trifluoroacetic acid (TFA) in DCM for 10 min. The combined filtrate and DCM wash is evaporated azeotropically (or repeatedly extracted by aqueous Na_2CO_3 solution) to remove the acid used in cleavage. The DCM phase is dried over Na_2SO_4 and evaporated.

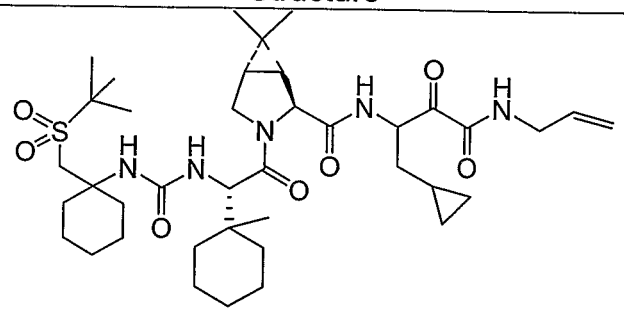
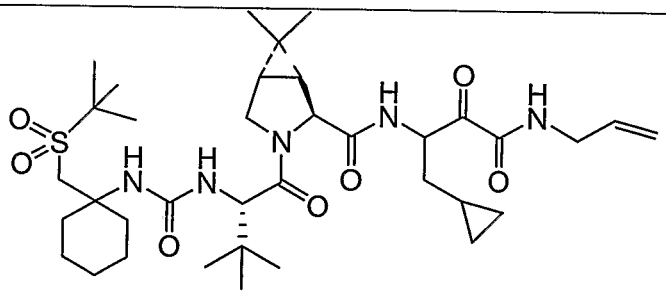
The ester substrates are assembled using standard acid-alcohol coupling procedures (K. Holmber *et al, Acta Chem. Scand.*, B33 (1979) 410-412). Peptide fragments are dissolved in anhydrous pyridine (30-60 mg/ml) to which 10 molar equivalents of chromophore and a catalytic amount (0.1 eq.) of para-toluenesulfonic acid (pTSA) were added. Dicyclohexylcarbodiimide (DCC, 3 eq.) is added to initiate the coupling reactions. Product formation is monitored by HPLC and can be found to be complete following 12-72 hour reaction at room temperature. Pyridine solvent is evaporated under vacuum and further removed by azeotropic evaporation with toluene. The peptide ester is deprotected with 95% TFA in DCM for two hours and extracted three times with anhydrous ethyl ether to remove excess chromophore. The deprotected substrate is purified by reversed phase HPLC on a C3 or C8 column with a 30% to 60% acetonitrile gradient (using six column volumes). The overall yield following HPLC purification can be approximately 20-30%. The molecular mass can be confirmed by electrospray ionization mass spectroscopy. The substrates are stored in dry powder form under desiccation.

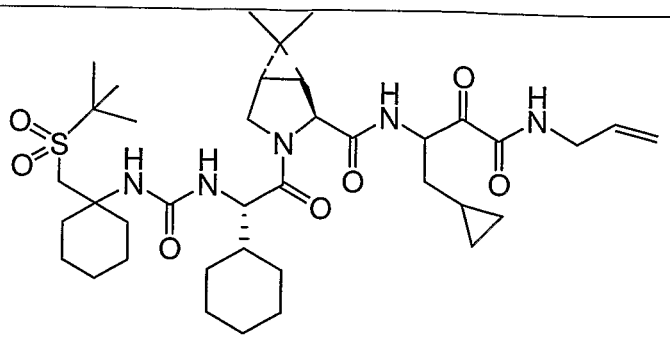
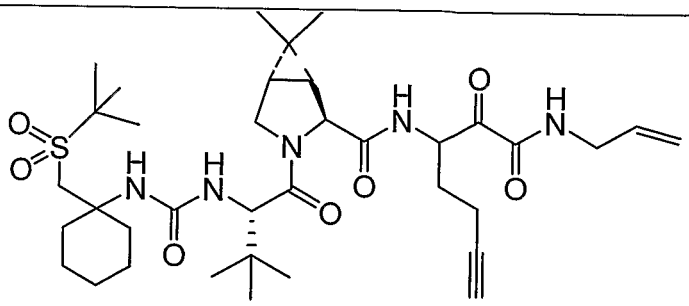
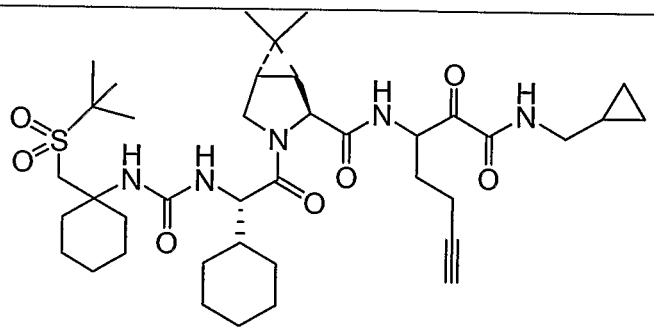
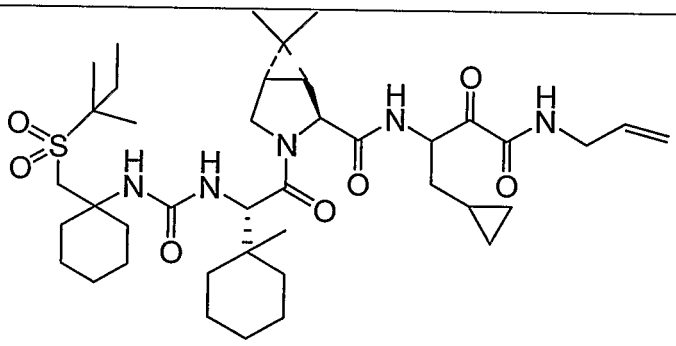
Spectra of Substrates and Products: Spectra of substrates and the corresponding chromophore products are obtained in the pH 6.5 assay buffer. Extinction coefficients are determined at the optimal off-peak wavelength in 1-cm cuvettes (340 nm for 3-Np and HMC, 370 nm for PAP and 400 nm for 4-Np) using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

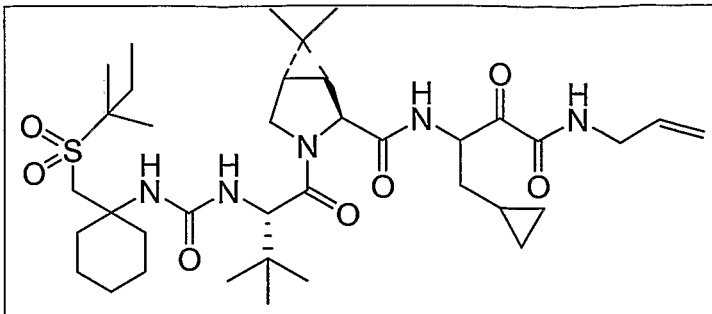
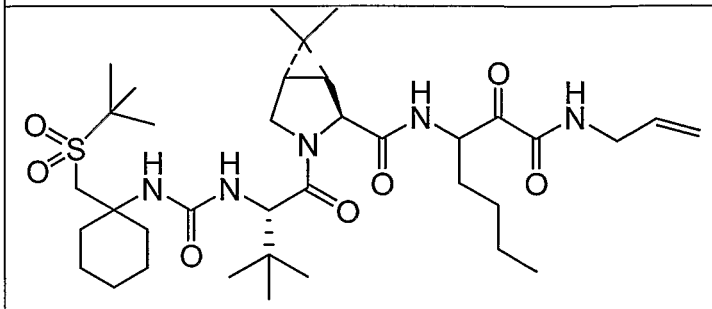
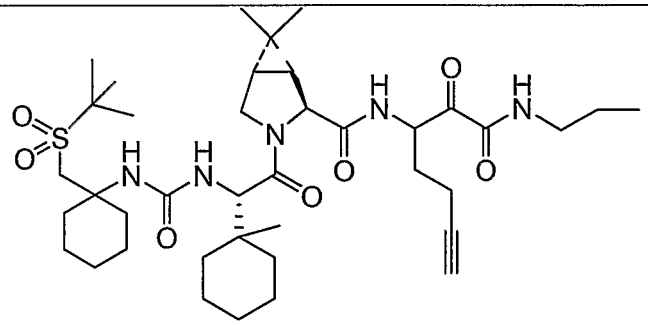
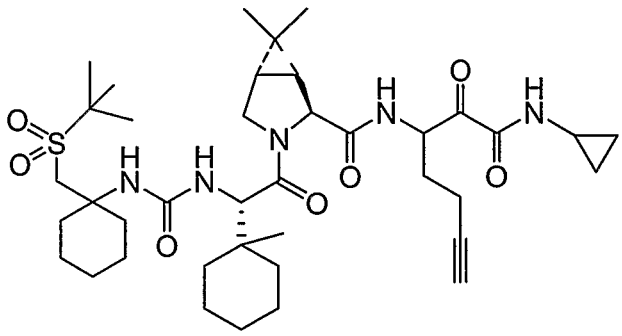
that wavelength yielding the maximum fractional difference in absorbance between substrate and product (product OD - substrate OD)/substrate OD). Protease Assay: HCV protease assays are performed at 30°C using a 200 µl reaction mix in a 96-well microtiter plate. Assay buffer conditions (25 mM MOPS pH 6.5, 300 mM NaCl, 10% glycerol, 0.05% lauryl maltoside, 5 µM EDTA and 5 µM DTT) are optimized for the NS3/NS4A heterodimer (D. L. Sali *et al, ibid.*)). Typically, 150 µl mixtures of buffer, substrate and inhibitor are placed in wells (final concentration of DMSO ≤4 % v/v) and allowed to preincubate at 30 °C for approximately 3 minutes. Fifty µls of prewarmed protease (12 nM, 30°C) in assay buffer, is then used to initiate the reaction (final volume 200 µl).The plates are monitored over the length of the assay (60 minutes) for change in absorbance at the appropriate wavelength (340 nm for 3-Np and HMC, 370 nm for PAP, and 400 nm for 4-Np) using a Spectromax Plus microtiter plate reader equipped with a monochrometer (acceptable results can be obtained with plate readers that utilize cutoff filters). Proteolytic cleavage of the ester linkage between the Nva and the chromophore is monitored at the appropriate wavelength against a no enzyme blank as a control for non-enzymatic hydrolysis. The evaluation of substrate kinetic parameters is performed over a 30-fold substrate concentration range (~6-200 µM). Initial velocities are determined using linear regression and kinetic constants are obtained by fitting the data to the Michaelis-Menten equation using non-linear regression analysis (Mac Curve Fit 1.1, K. Raner). Turnover numbers (k_{cat}) are calculated assuming the enzyme is fully active. Evaluation of Inhibitors and Inactivators: The inhibition constants (K_i) for the competitive inhibitors Ac-D-(D-Gla)-L-I-(Cha)-C-OH (27), Ac-DTEDVVA(Nva)-OH and Ac-DTEDVVP(Nva)-OH are determined experimentally at fixed concentrations of enzyme and substrate by plotting v_o/v_i vs. inhibitor

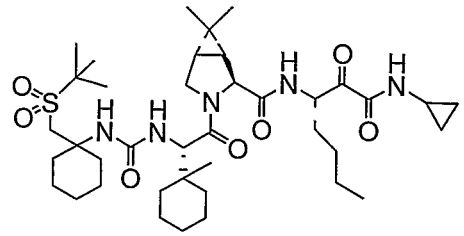
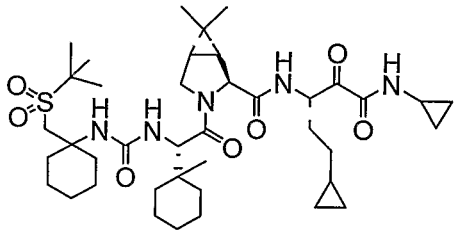
concentration ($[I]_o$) according to the rearranged Michaelis-Menten equation for competitive inhibition kinetics: $v_o/v_i = 1 + [I]_o/(K_i (1 + [S]_o/K_m))$, where v_o is the uninhibited initial velocity, v_i is the initial velocity in the presence of inhibitor at any given inhibitor concentration ($[I]_o$) and $[S]_o$ is the substrate concentration used. The resulting data are fitted using linear regression and the resulting slope, $1/(K_i(1+[S]_o/K_m)$, is used to calculate the K_i value. The following **Table 5** lists the obtained Ki* values (in nanoMolar) for some of the inventive compounds. Several others are noted in the **Tables** on earlier pages.

Table 5

Structure	Ki* (nM)
	10
	14

	4.1
	2
	19
	9

	14
	11
	4
	6

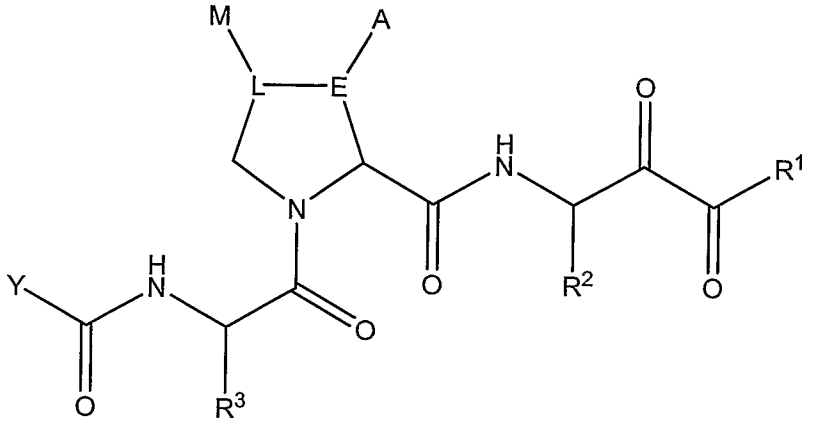
	5
	3

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

CLAIMS

What is claimed is:

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



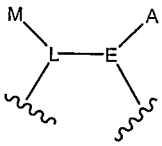
Formula I

wherein:

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

A and M can be the same or different, each being independently selected from R, OR, NHR, NRR', SR, SO_2R, and halo;

or A and M are connected to each other such that the moiety:



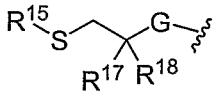
shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl;

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

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

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

and Y is selected from the following moieties: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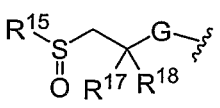
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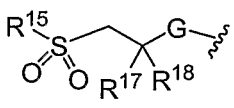
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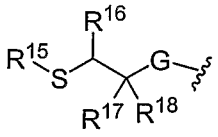
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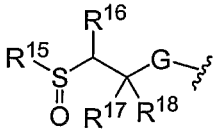
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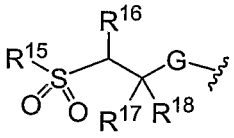
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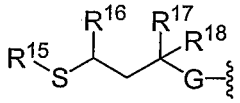
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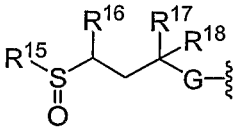
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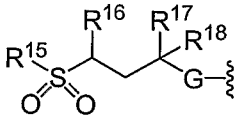
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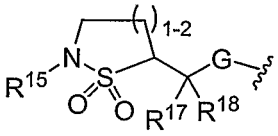
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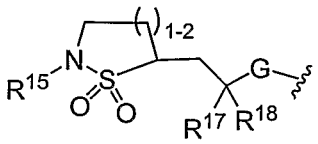
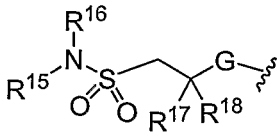

and


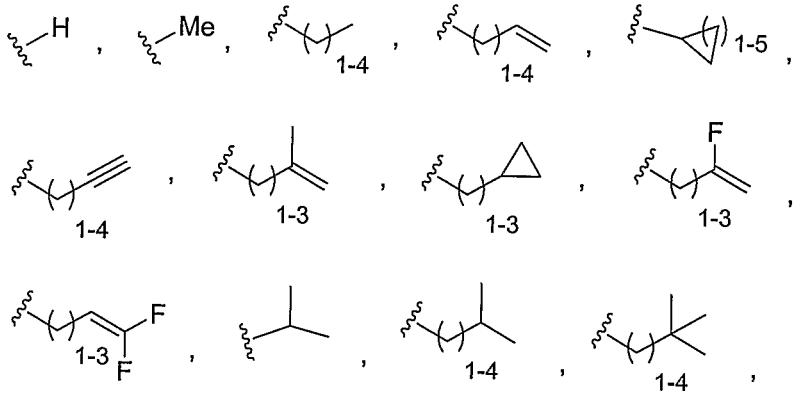
wherein G is NH or O; and R^{15}, R^{16}, R^{17} and R^{18} can be the same or different, each being independently selected from the group consisting of H, alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, cycloalkyl,

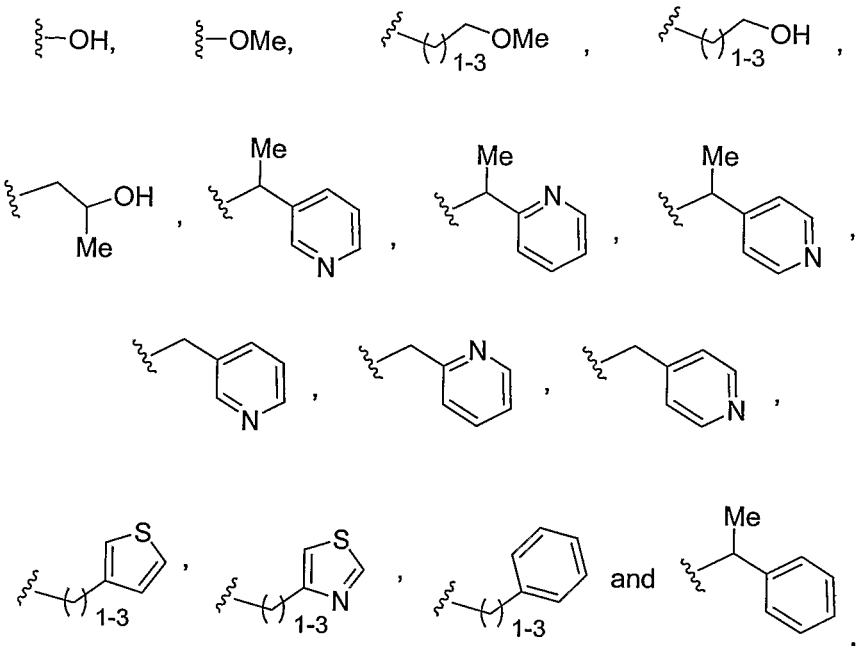
heterocyclyl, aryl, and heteroaryl, or alternately, (i) R^{15} and R^{16} are connected to each other to form a four to eight-membered cyclic structure, and (ii) likewise, independently R^{17} and R^{18} are connected to each other to form a three to eight-membered cycloalkyl or heterocyclyl;

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

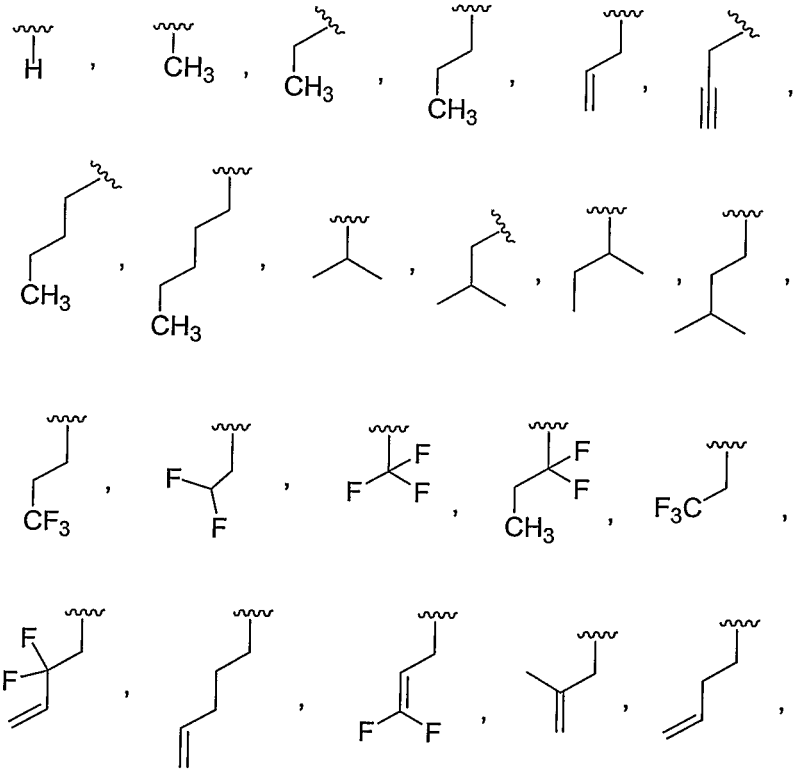
2. The compound of claim 1, wherein R^1 is NR^9R^{10}, and R^9 is H, R^{10} is H, or R^{14} wherein R^{14} is H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, alkyl-aryl, alkyl-heteroaryl, aryl-alkyl, alkenyl, alkynyl or heteroaryl-alkyl.

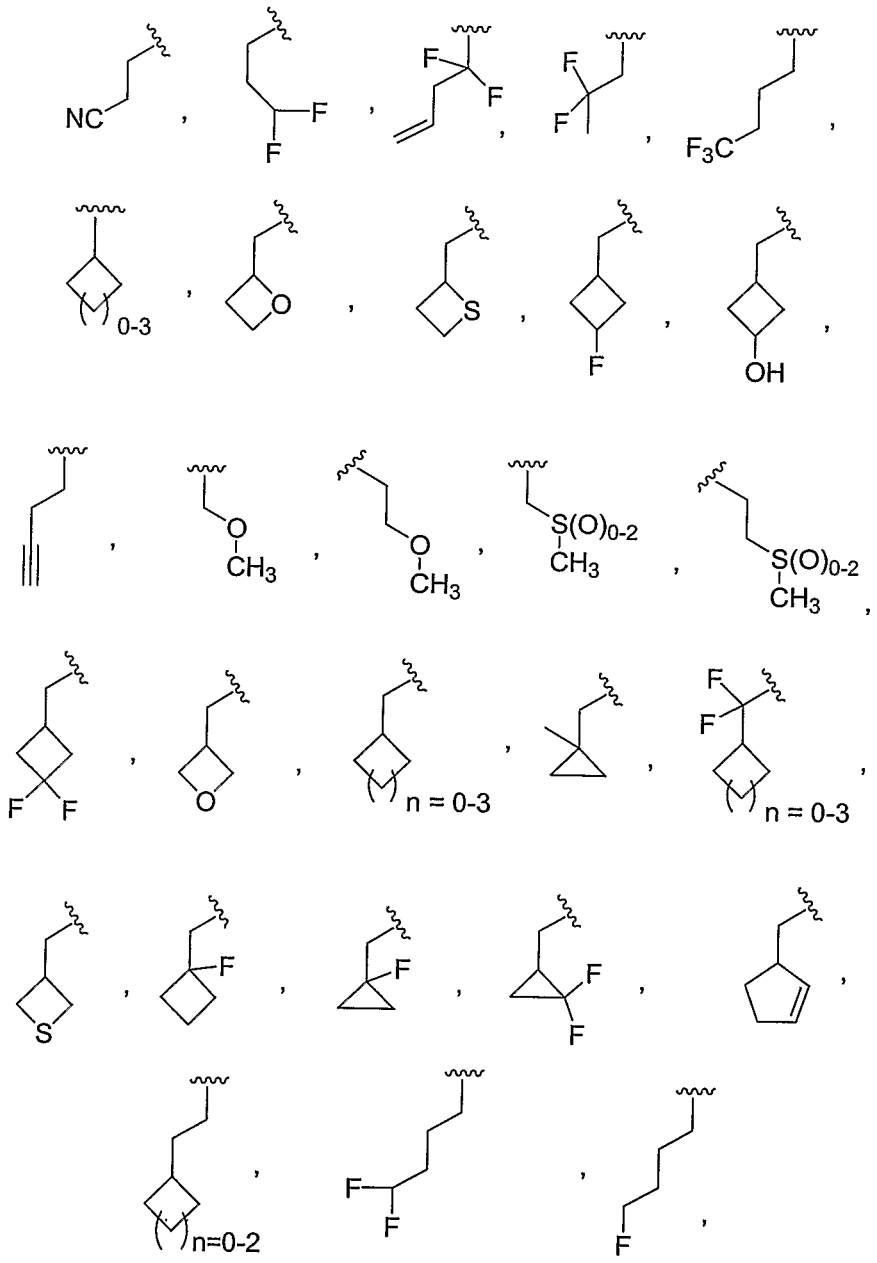
3. The compound of claim 2, wherein R^{14} is selected from the group consisting of:



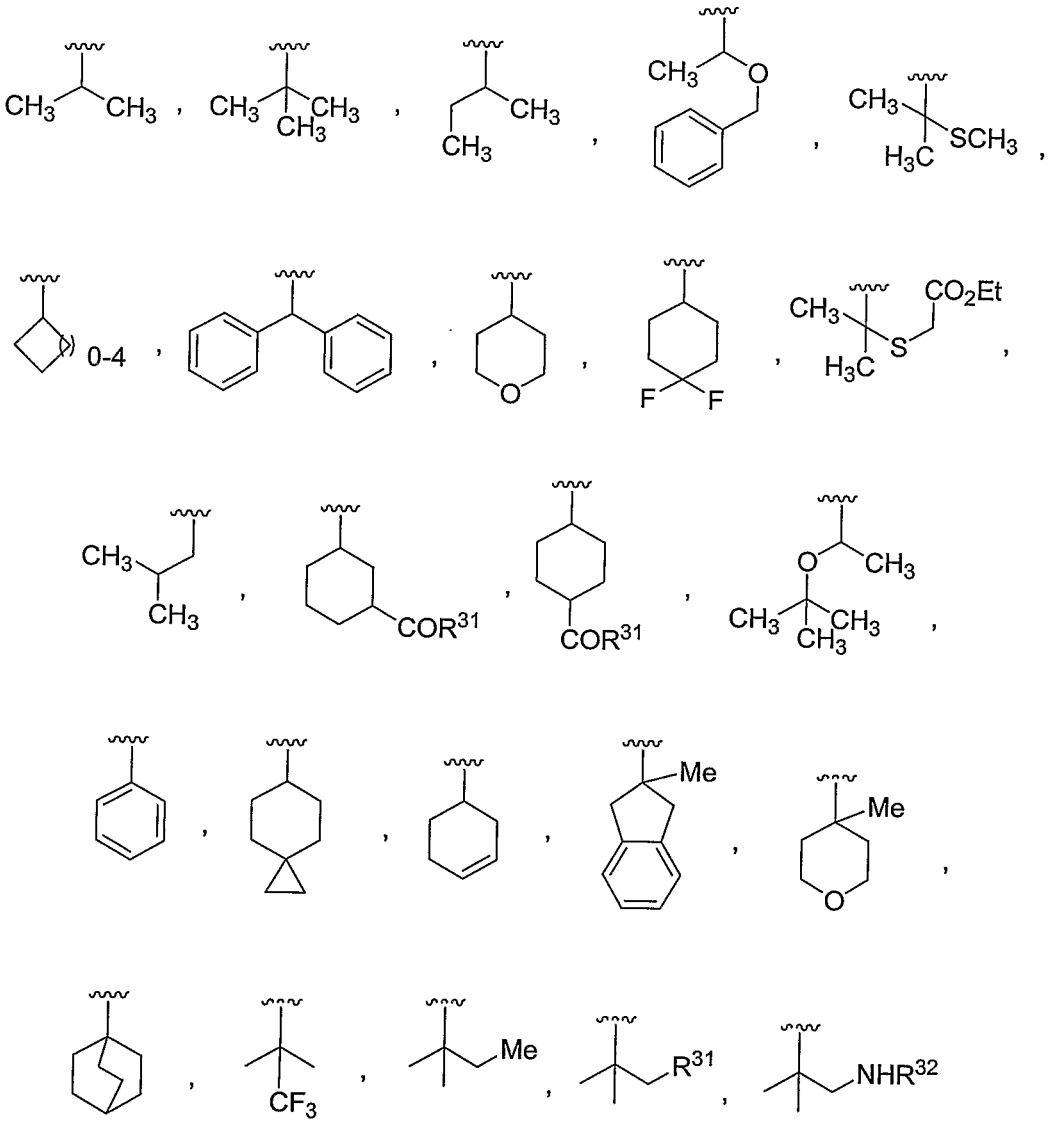


4. The compound of claim 1, wherein R^2 is selected from the group consisting of the following moieties:





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


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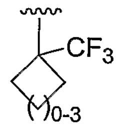
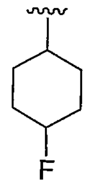
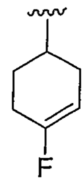
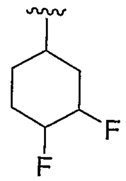
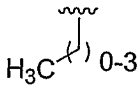
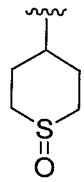
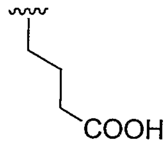
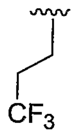
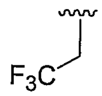
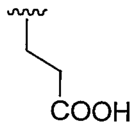
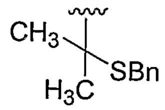
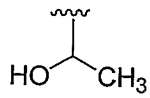
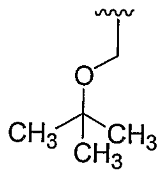
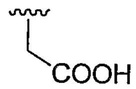
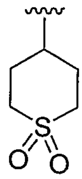
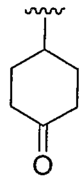
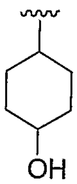
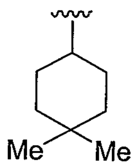
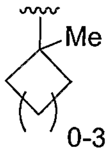
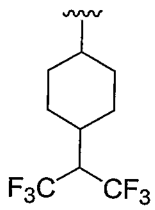
O
CF3
Me
R31
NHR32

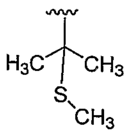
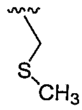
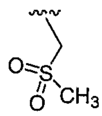
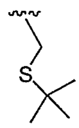
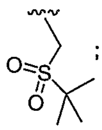
 ,  ,  ,  ,

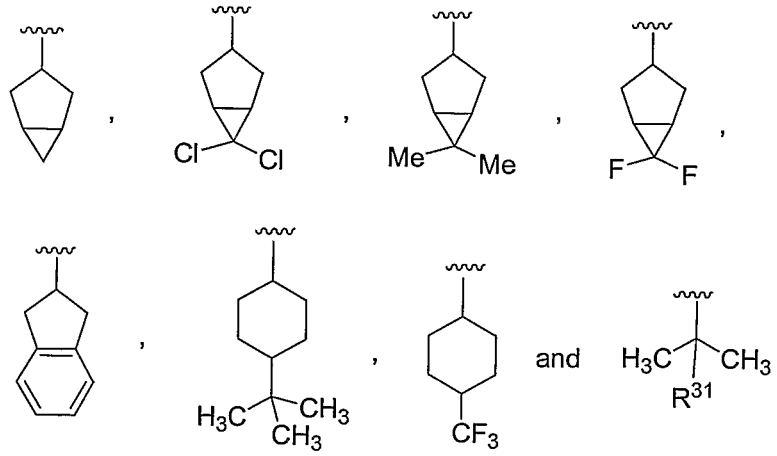
 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,  ,

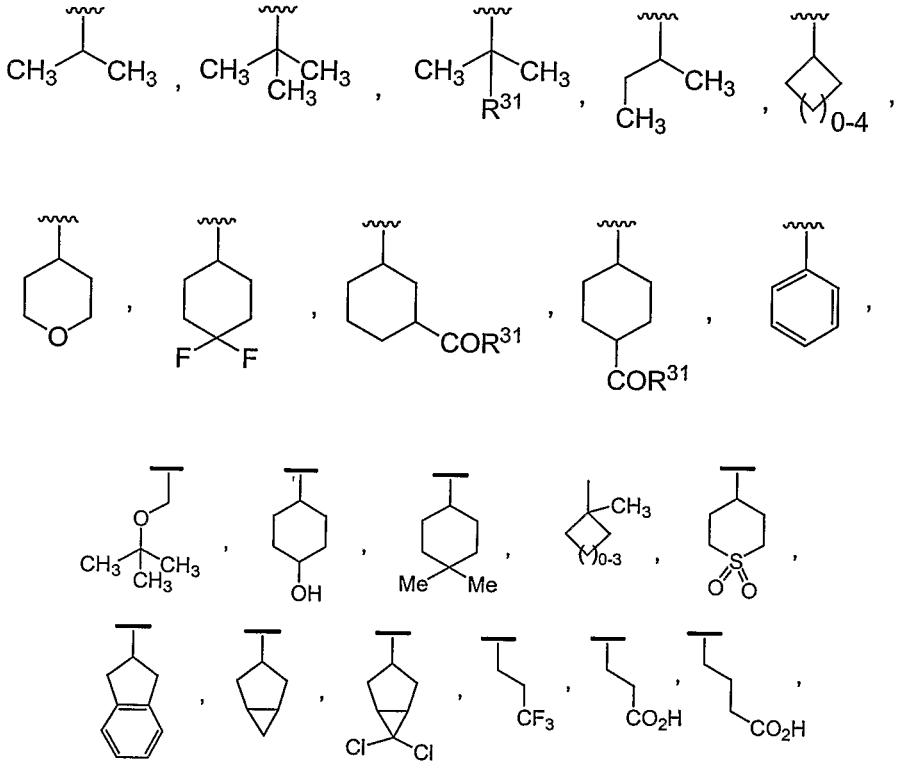
 ,  ,  ,  and  ;

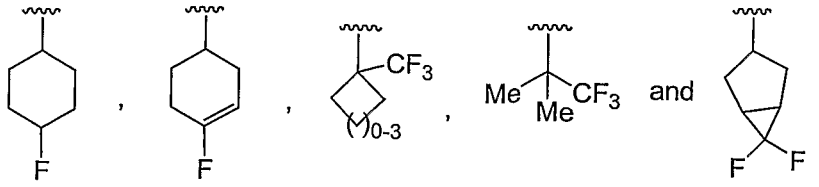


wherein R^{31} is OH or O-alkyl; and

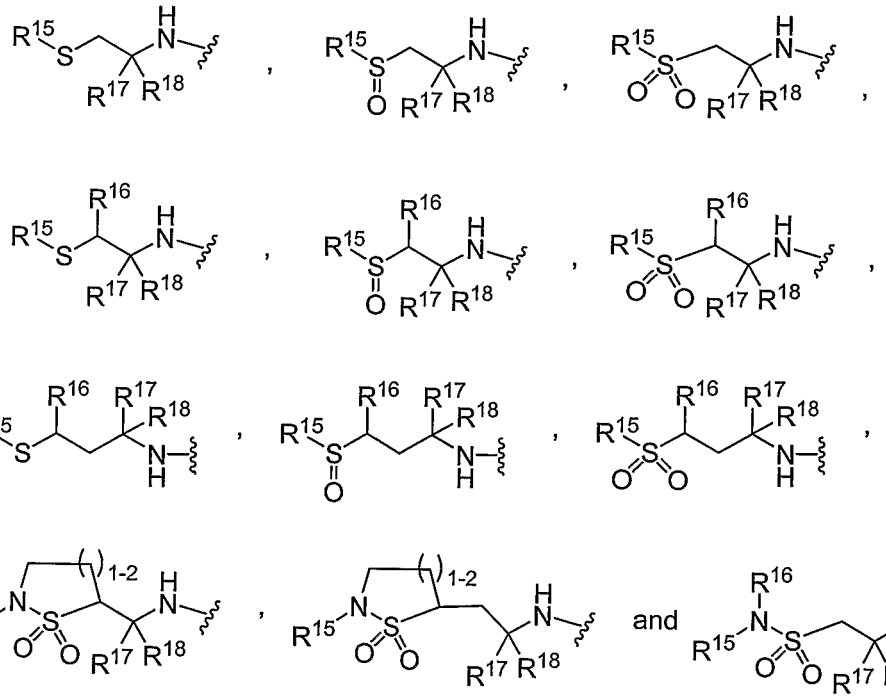
R^{32} is H, $C(O)CH_3$, C(O)OtBu or C(O)N(H)tBu.

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





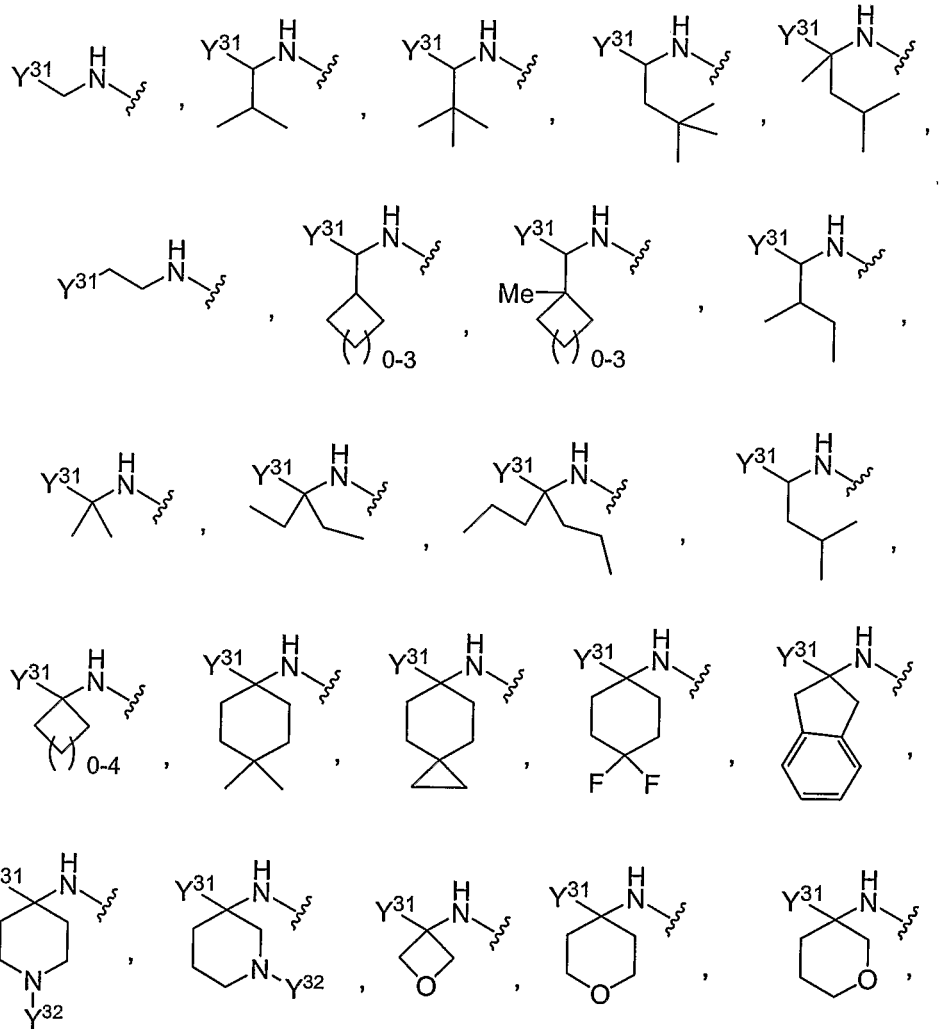
7. The compound of claim 1, wherein Y is selected from the following moieties:

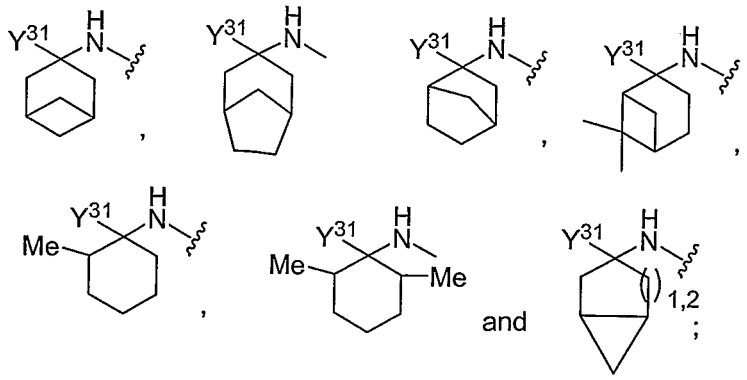


wherein R^{15}, R^{16}, R^{17} and R^{18} can be the same or different, each being independently selected from the group consisting of H, alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, or alternately, R^{15} and R^{16} are connected to each other to form a four to eight-membered cycloalkyl or heterocyclic structure; R^{17} and R^{18} are connected to each other to form a three to eight-membered cycloalkyl or heterocyclyl, wherein each of said aryl, heteroaryl, cycloalkyl or heterocyclyl can be unsubstituted or optionally

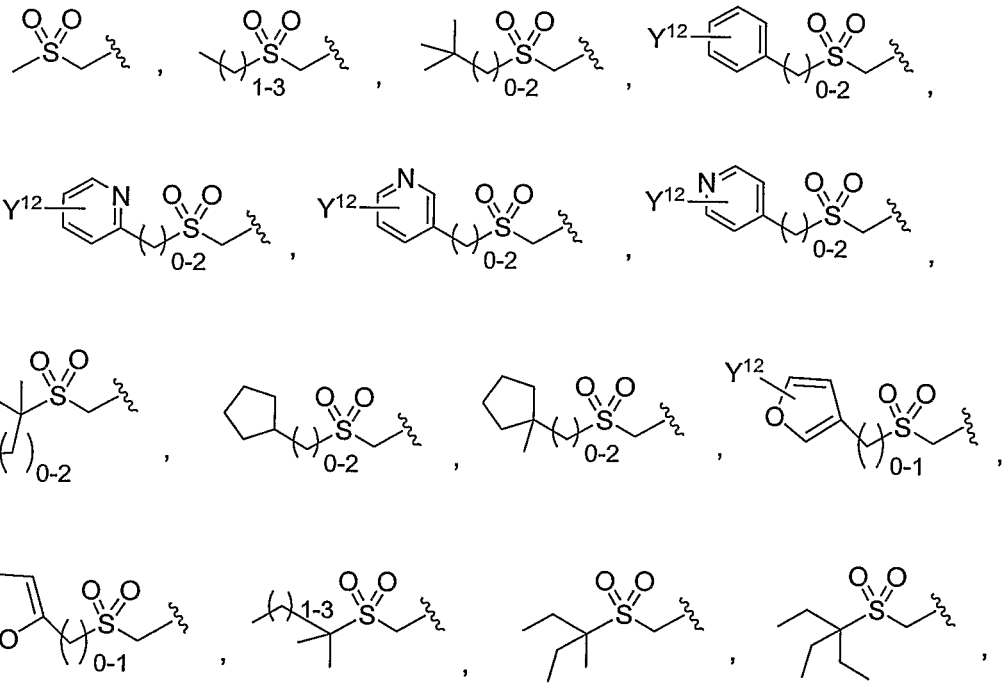
independently substituted with one or more moieties selected from the group consisting of: hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, amido, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, sulfonamido, alkylsulfonamido, arylsulfonamido, alkyl, aryl, heteroaryl, carboxy, carbalkoxy,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

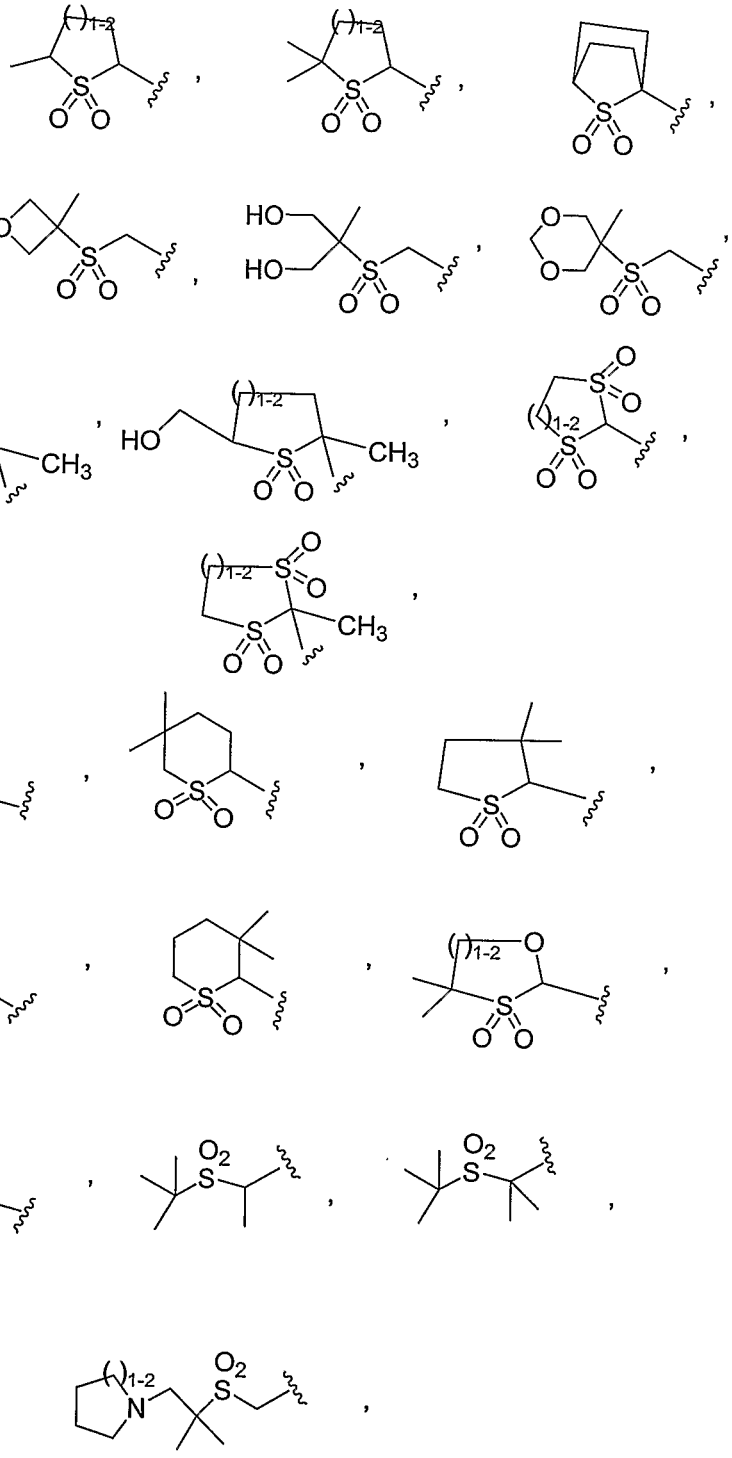
8. The compound of claim 7, Y is selected from the group consisting of:

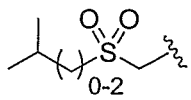




wherein Y^{31} is selected from the group consisting of:



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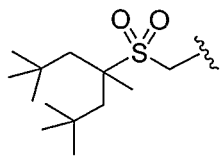
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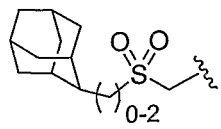
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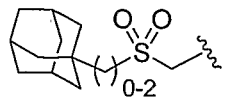
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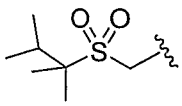
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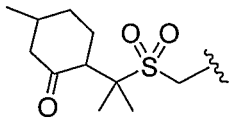
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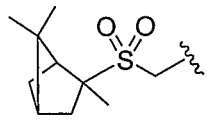
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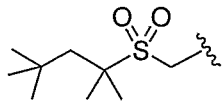
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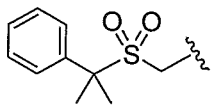
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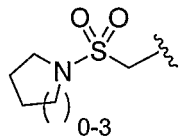
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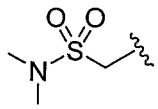
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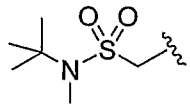
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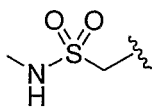
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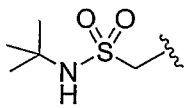
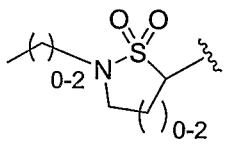
S
N
H
,

O
O
S
N
H
,

O
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S
N
0-2
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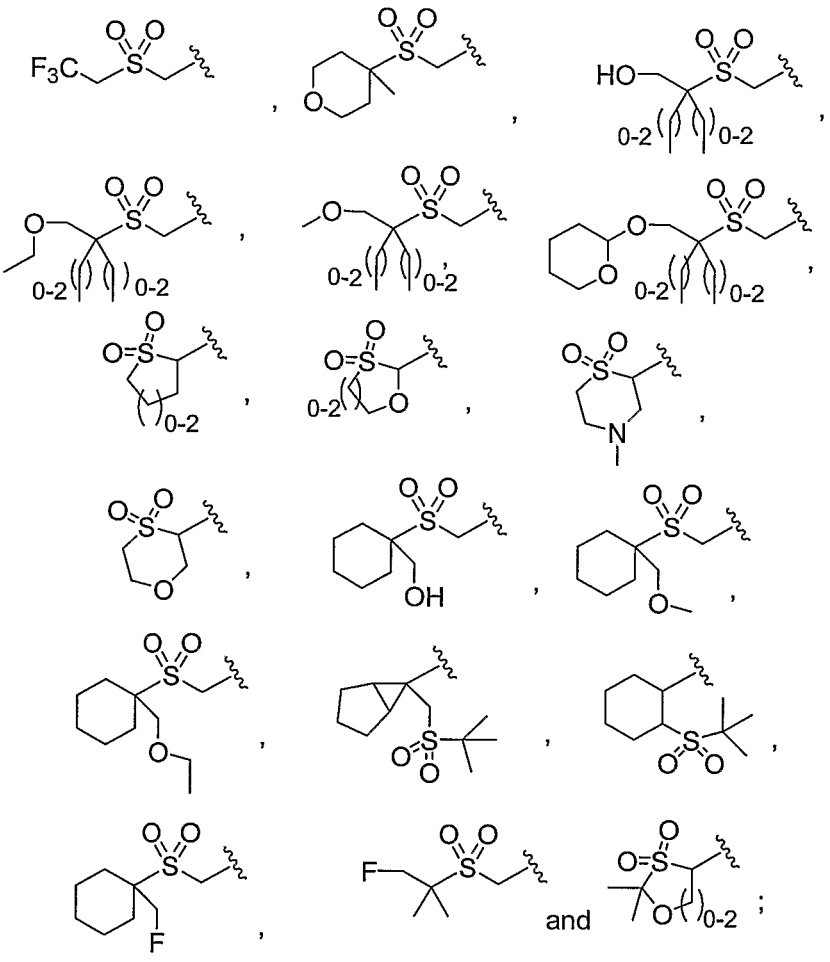
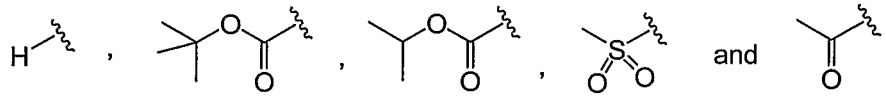
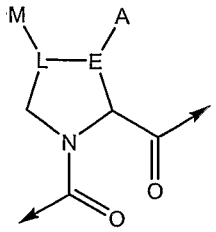


Y^{32} is selected from the group consisting of:

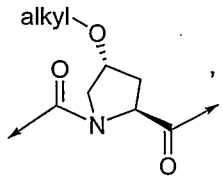


and Y^{12} is selected from the group consisting of H, CO_2H, CO_2Me, OMe, F, Cl, Br, NH_2, $N(H)S(O_2)CH_3$, $N(H)C(O)CH_3$, NO_2, $S(O_2)NH_2$, CF_3, Me, OH, OCF_3, and $C(O)NH_2$.

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



is selected from the following structures: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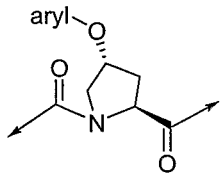
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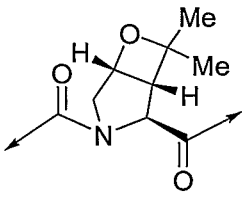
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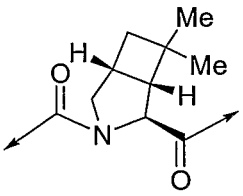
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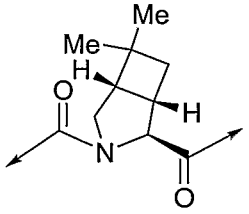
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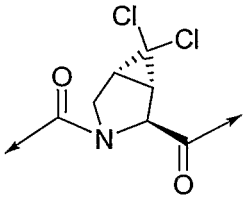
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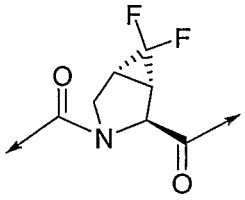
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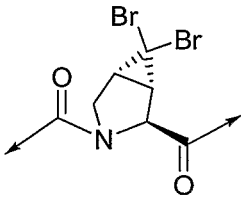
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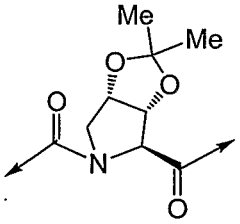
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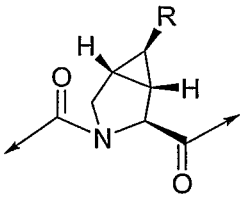
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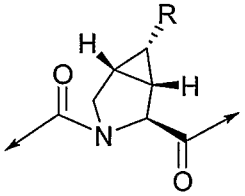
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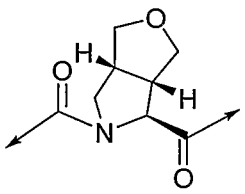
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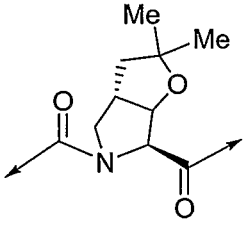
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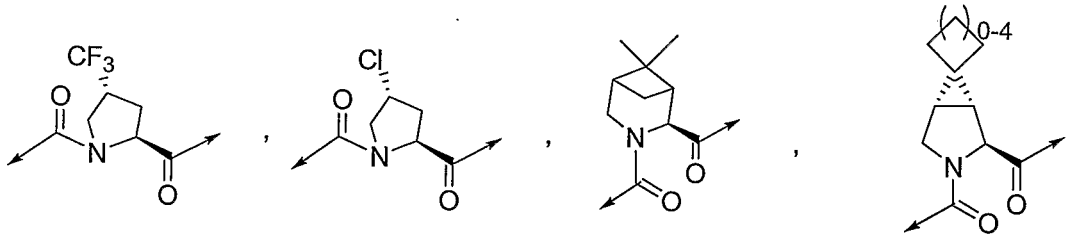
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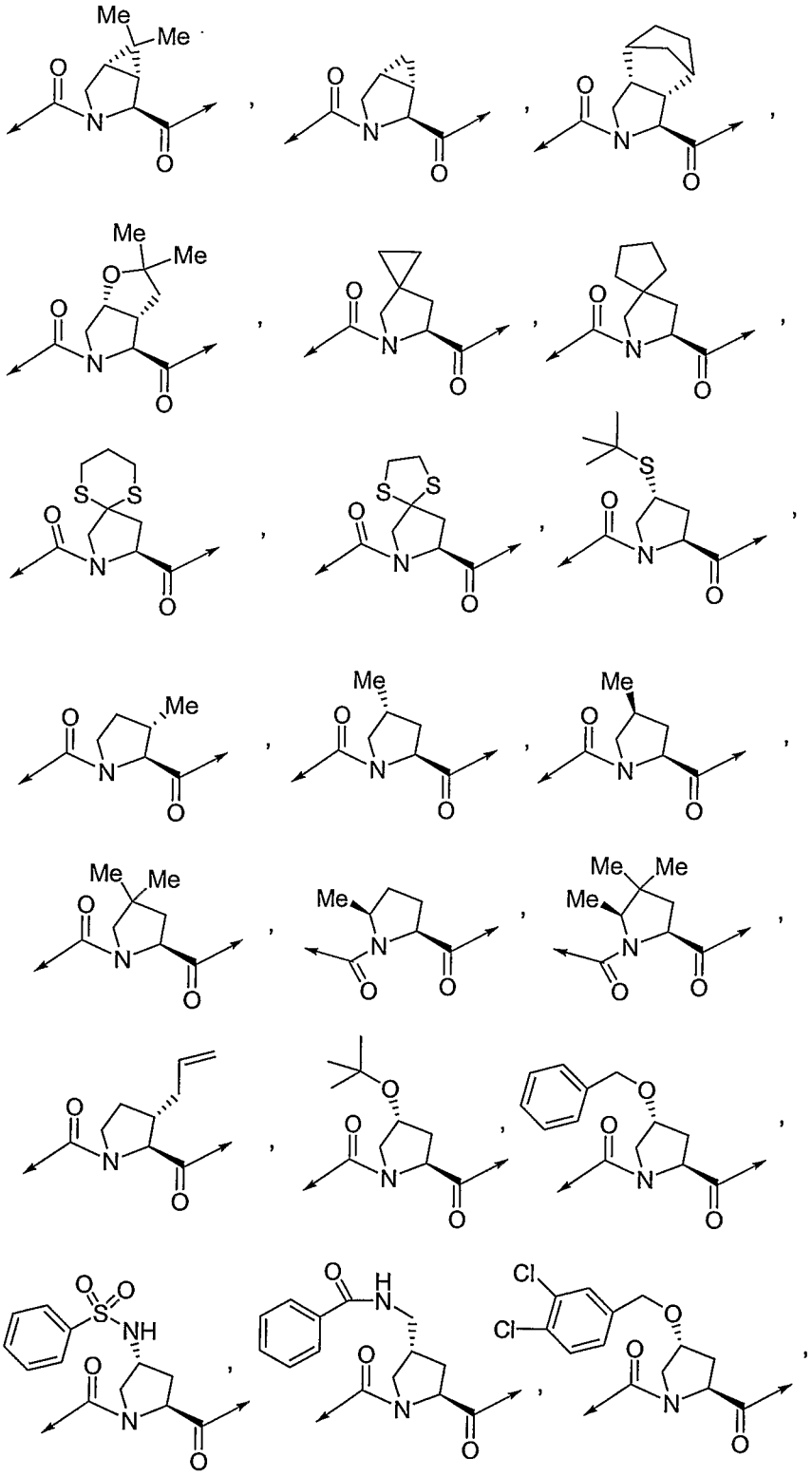
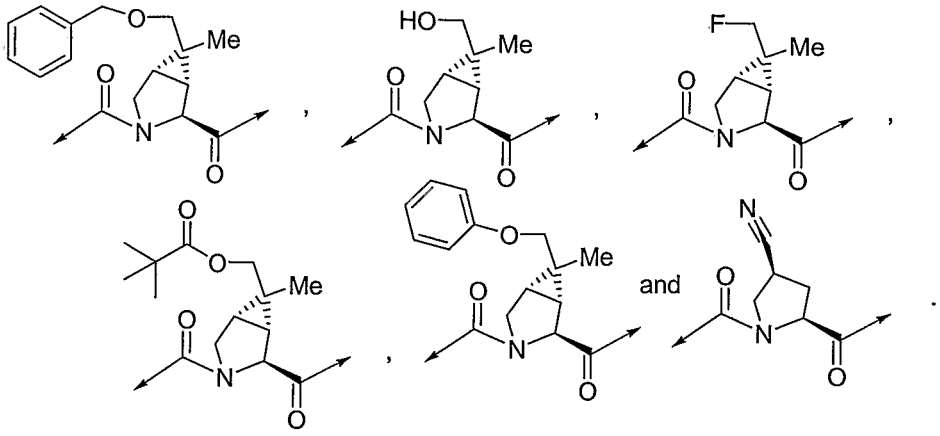
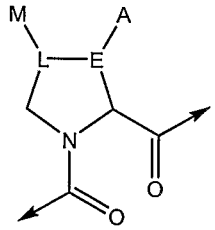
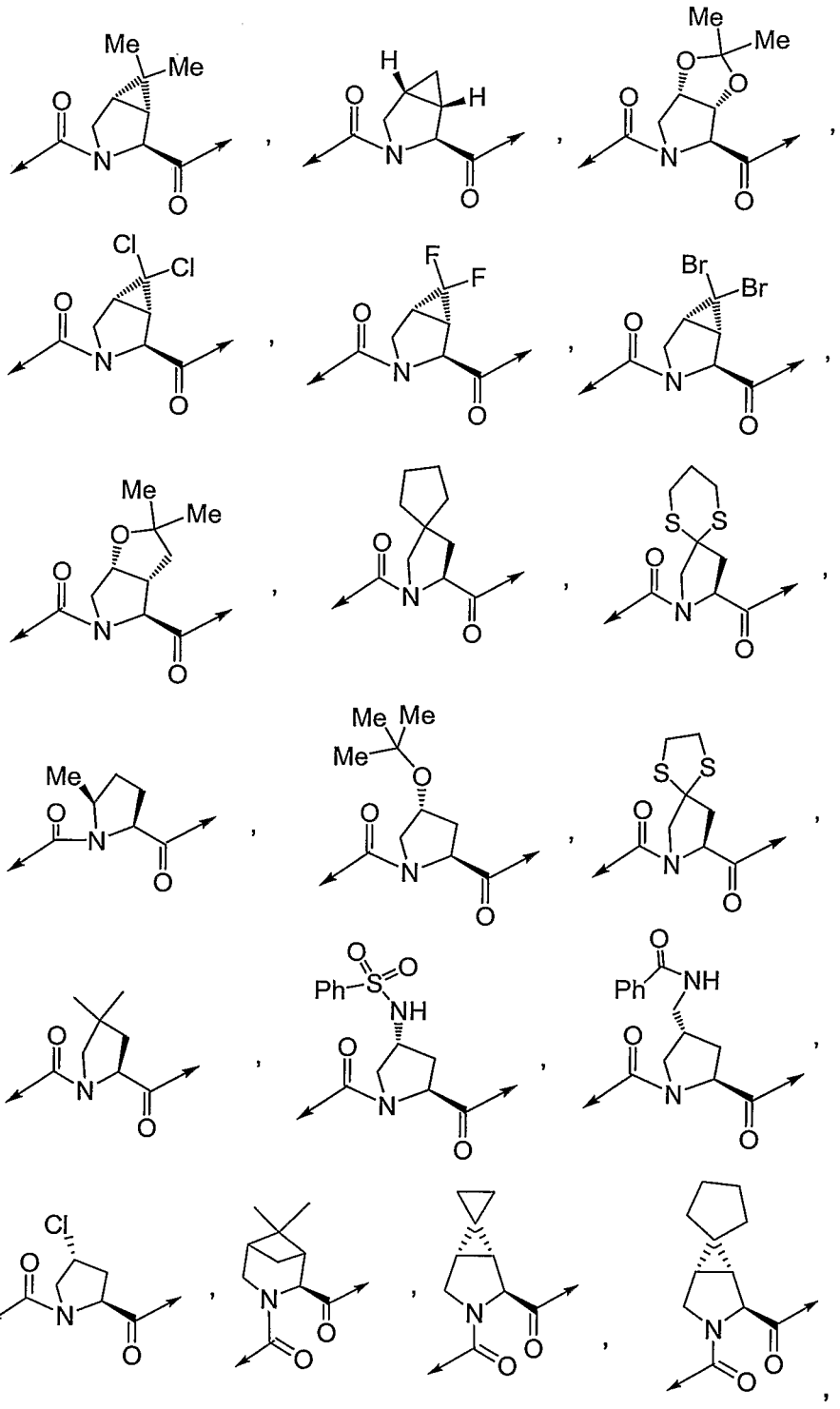


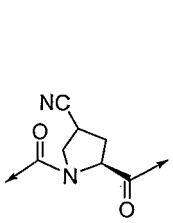
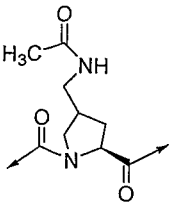


10. The compound of claim 9, wherein the moiety:



is selected from the following structures:




and

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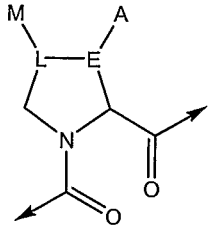
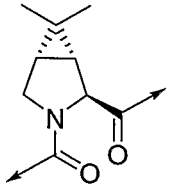
11. The compound of claim 10, wherein the moiety:



is selected from the following structures: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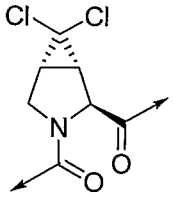
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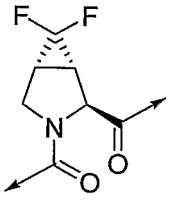

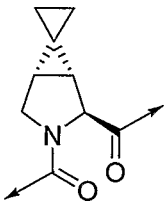
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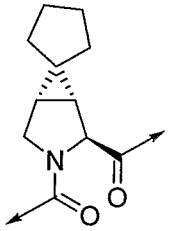
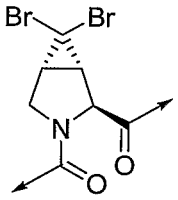

and

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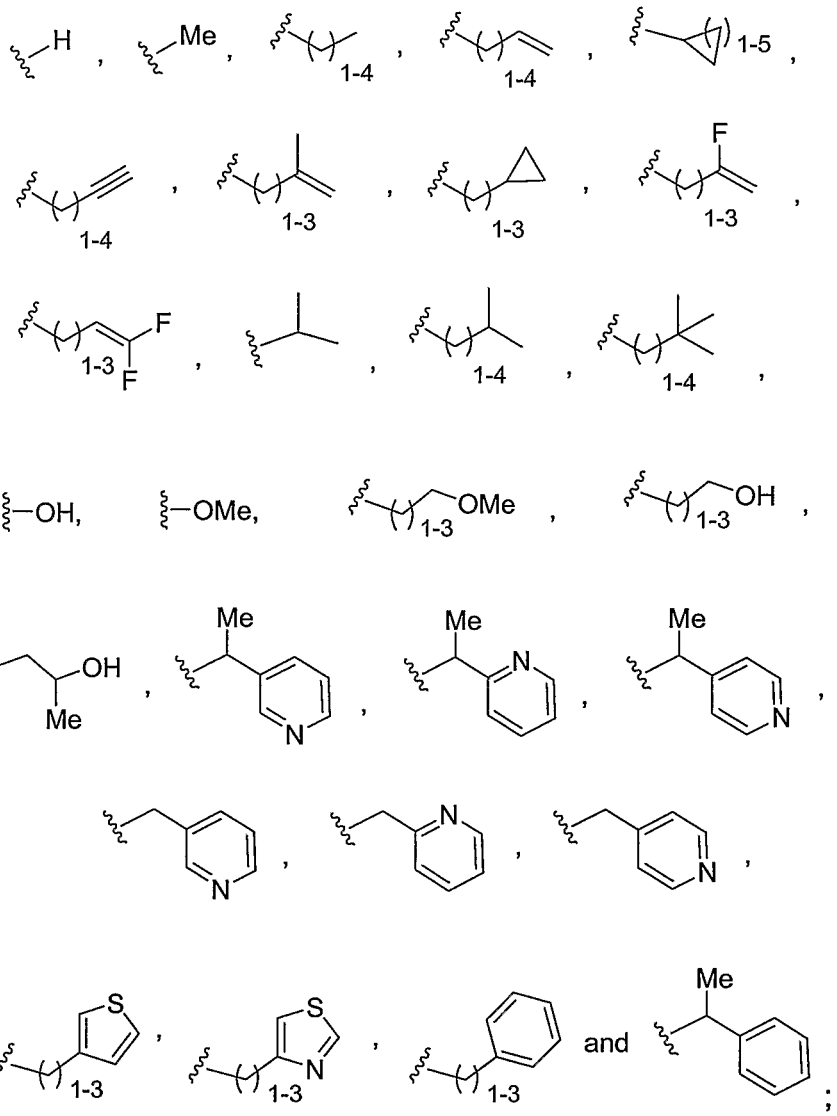
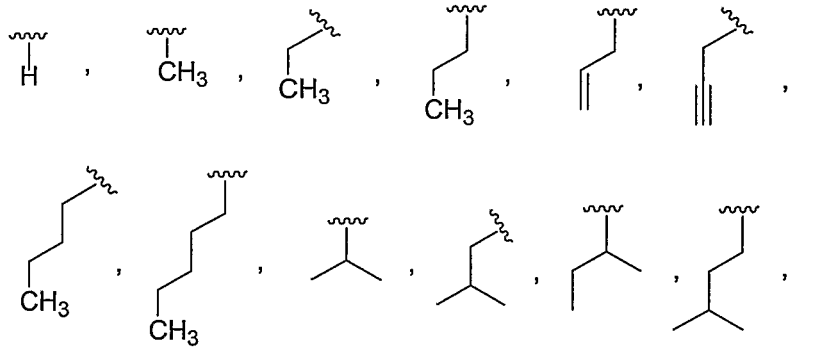
12. The compound of claim 1, wherein:

R^1 is NHR^{14}, where R^{14} is selected from the group consisting of:



;

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



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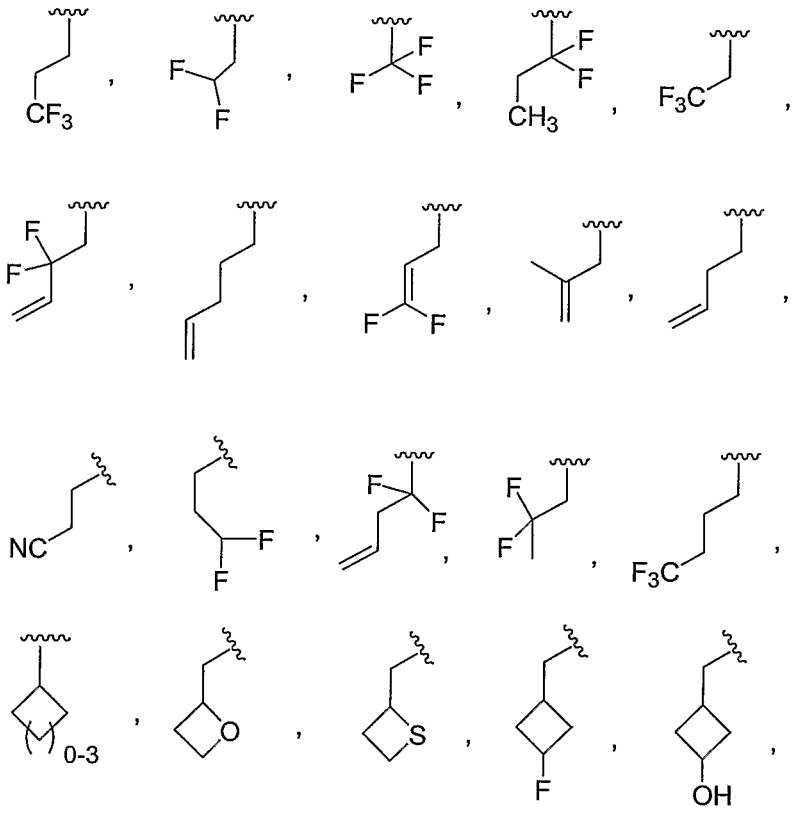
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F
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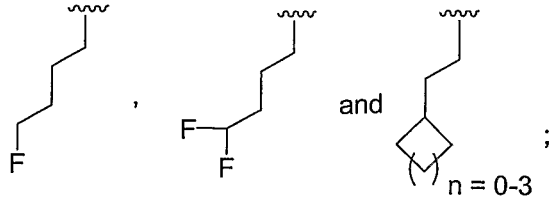
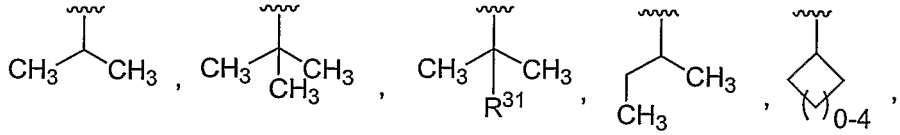
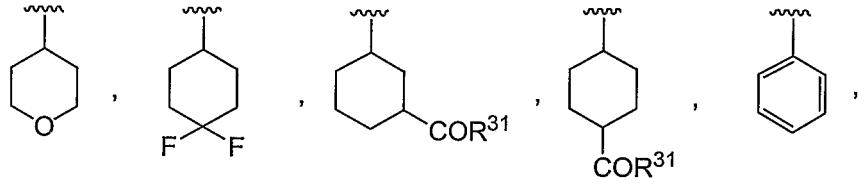
CH3
F3C
F
F
F
F
NC
F
F
F
F
F
F3C
0-3
O
S
F
OH
O
CH3
O
CH3
S(O)0-2
CH3
S(O)0-2
CH3
F
F
O
n = 0-3
n = 0-3
F
F
S
F
F
F

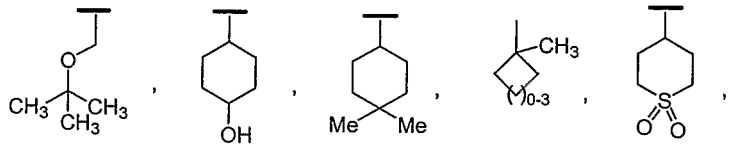


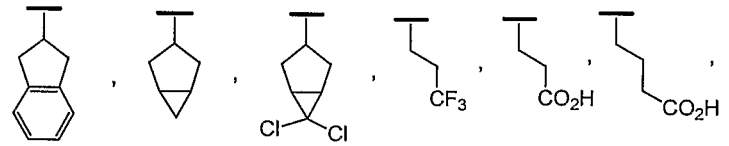
;

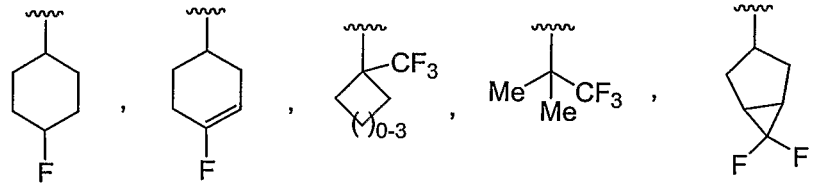
R^3 is selected from the group consisting of the following moieties:





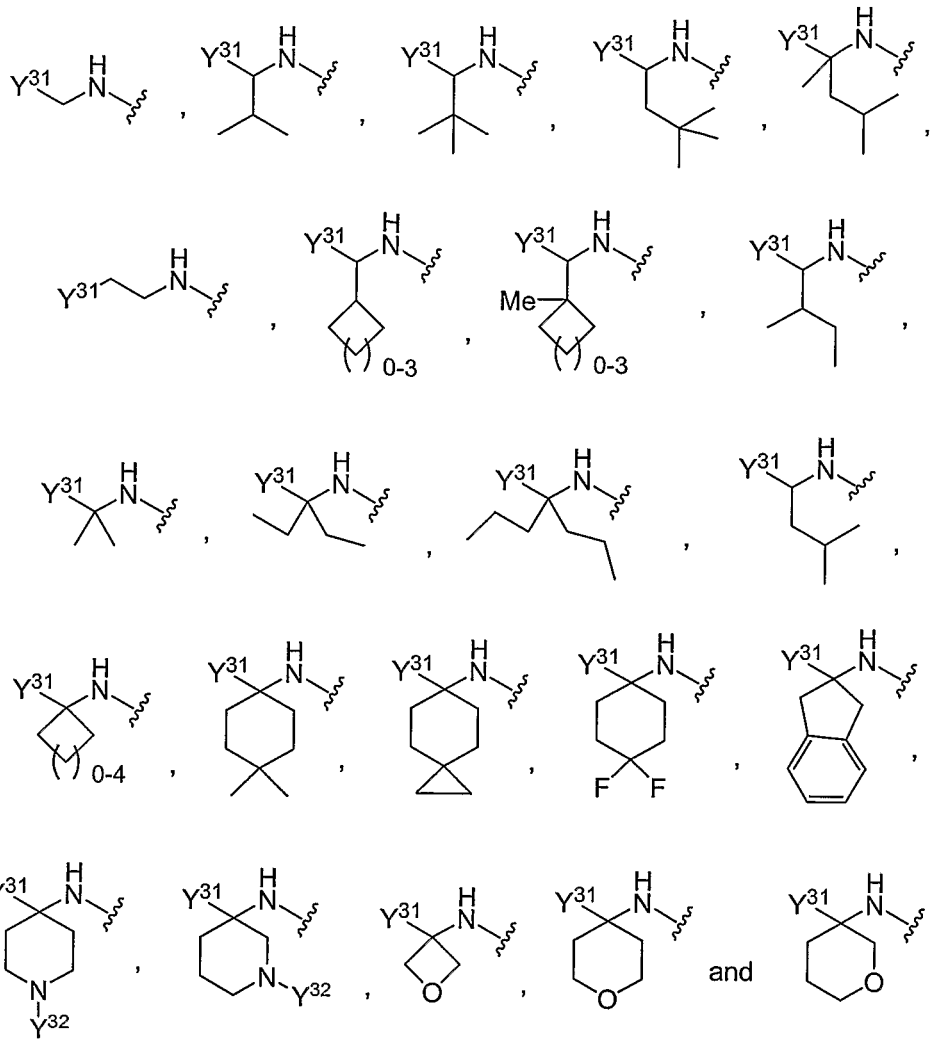




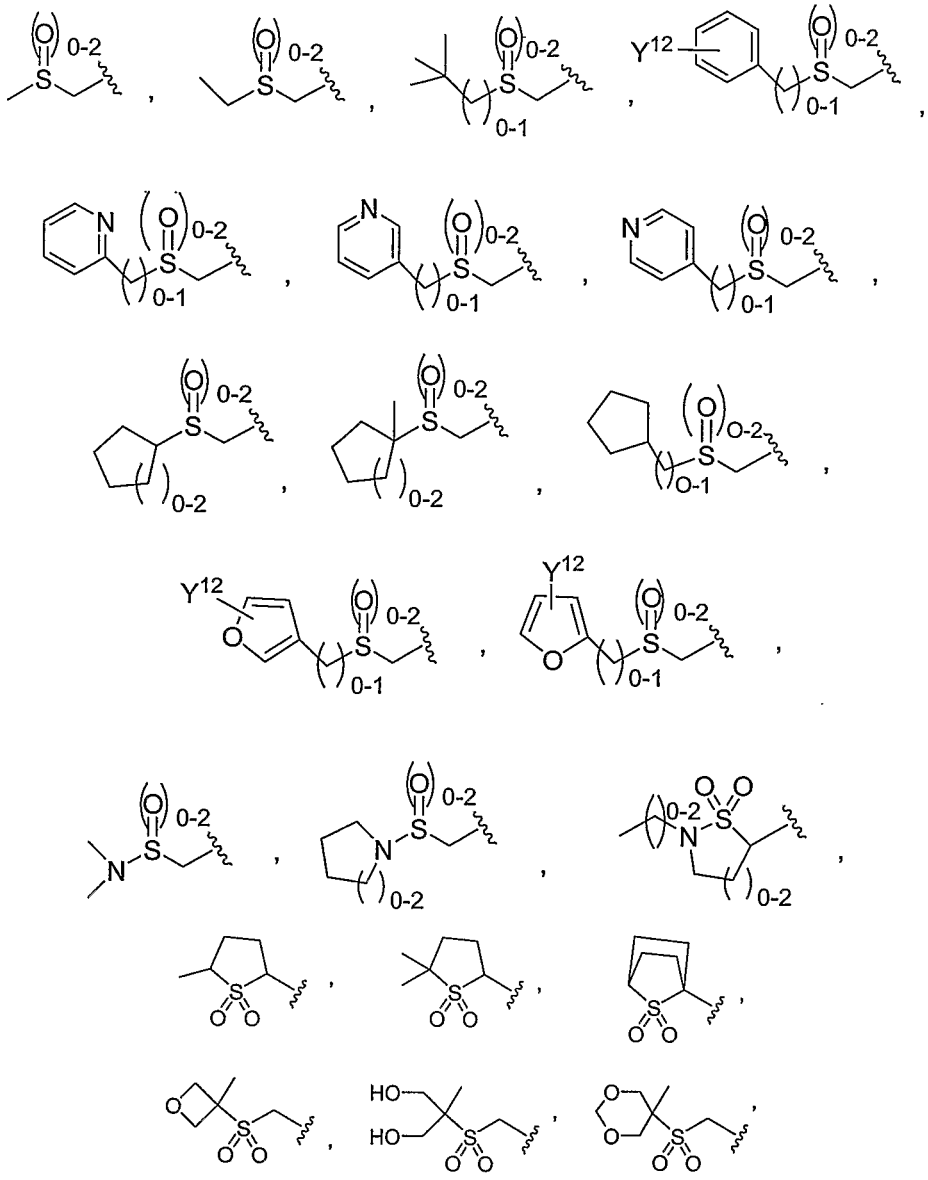


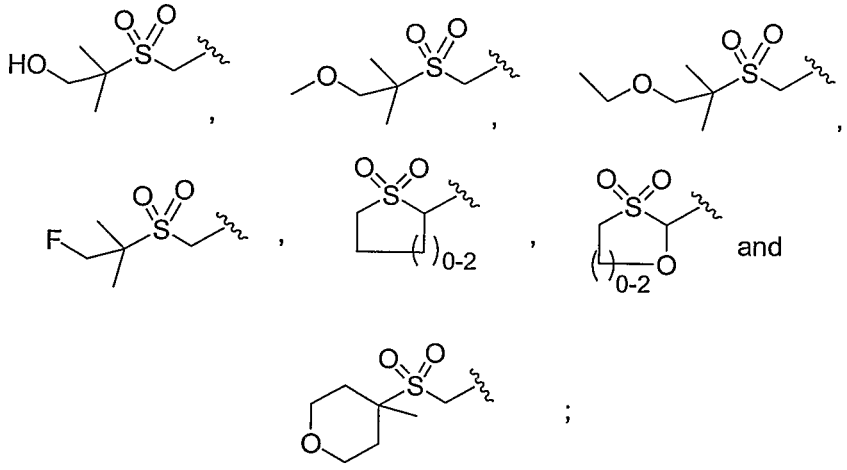
;

Y is selected from the group consisting of:



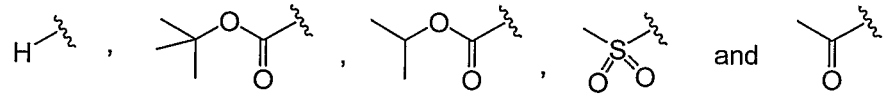
wherein Y^{31} is selected from the group consisting of:



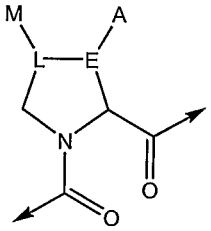


;

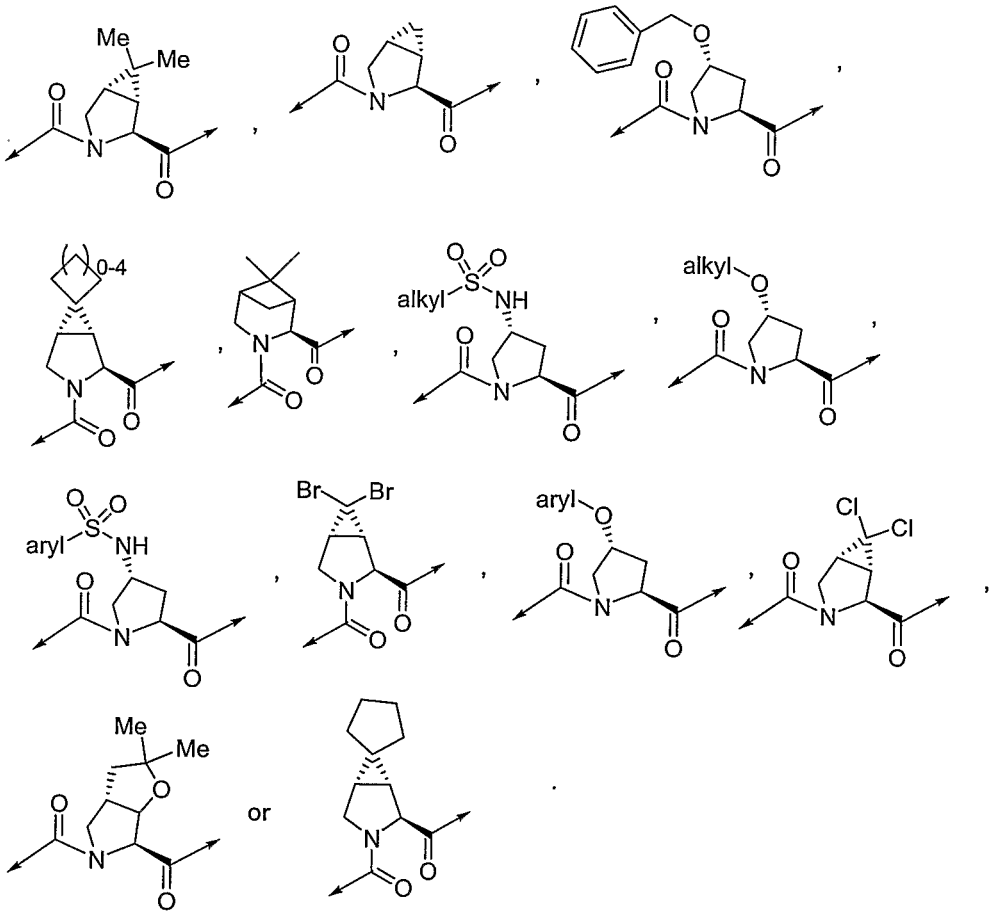
Y^{32} is selected from the group consisting of:



and Y^{12} is selected from the group consisting of H, CO_2H, CO_2Me, OMe, F, Cl, Br, NH_2, $N(H)S(O_2)CH_3$, $N(H)C(O)CH_3$, NO_2, $S(O_2)NH_2$, CF_3, Me, OH, OCF_3, and $C(O)NH_2$; and the moiety:



is:



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

14. The pharmaceutical composition of claim 13 for use in treating disorders associated with HCV.

15. The pharmaceutical composition of claim 13 additionally comprising at least one pharmaceutically acceptable carrier.

16. The pharmaceutical composition of claim 15, additionally containing at least one antiviral agent.

17. The pharmaceutical composition of claim 16, still additionally containing at least one interferon.

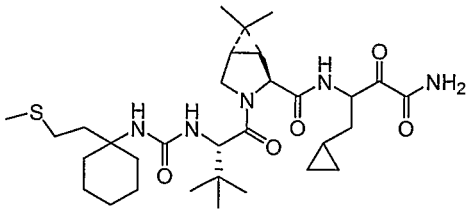
18. The pharmaceutical composition of claim 17, wherein said at least one antiviral agent is ribavirin and said at least one interferon is α-interferon or pegylated interferon.

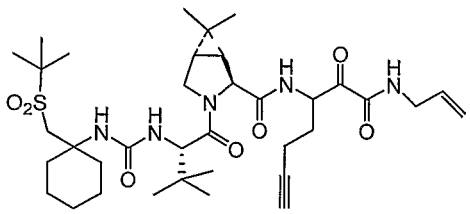
19. A method of treating disorders associated with the HCV, said method comprising administering to a patient in need of such treatment a pharmaceutical composition which comprises therapeutically effective amounts of at least one compound of claim 1.

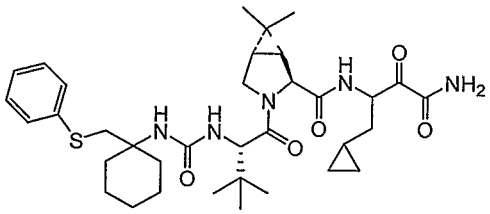
20. The method of claim 19, wherein said administration is oral or subcutaneous.

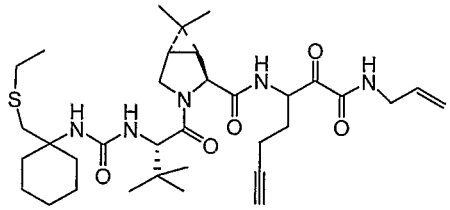
21. A method of preparing a pharmaceutical composition for treating the disorders associated with the HCV, said method comprising bringing into intimate contact at least one compound of claim 1 and at least one pharmaceutically acceptable carrier.

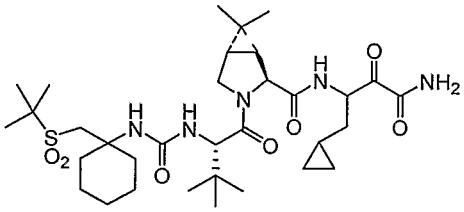
22. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, and racemates of said compound, or a pharmaceutically acceptable salt or solvate or ester of said compound, said compound being selected from the compounds of structures listed below:

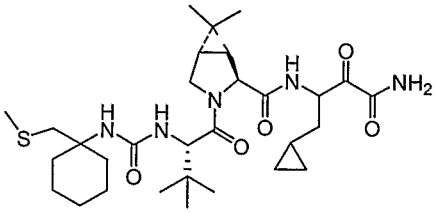


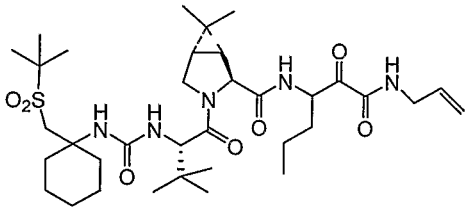


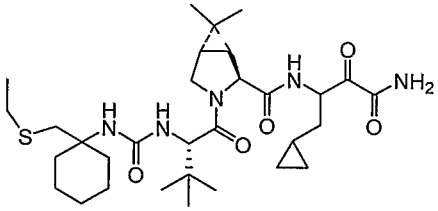


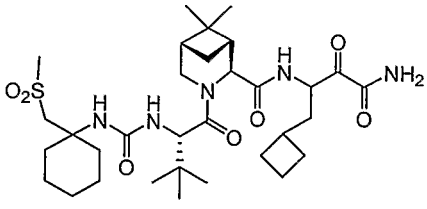


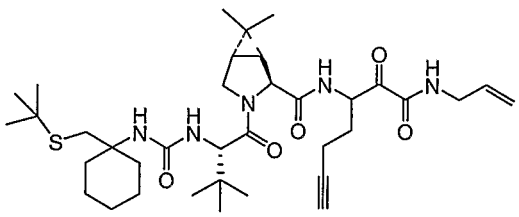


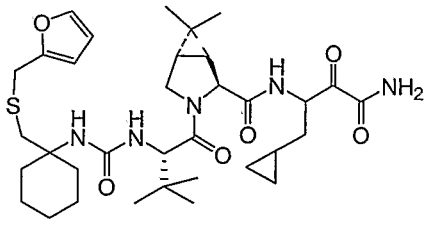


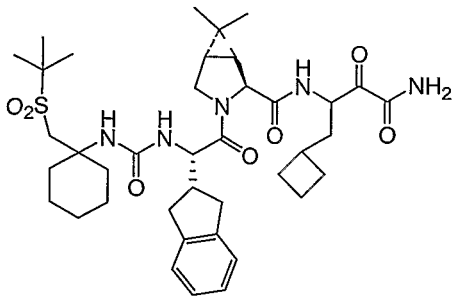


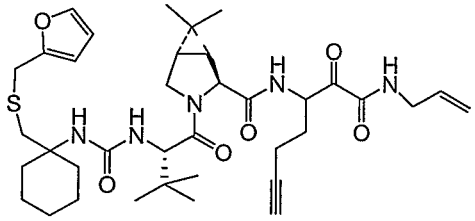


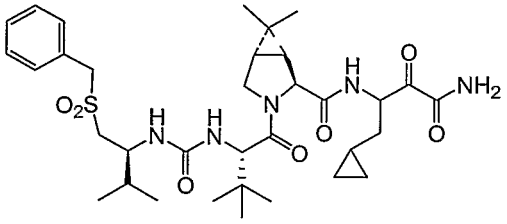


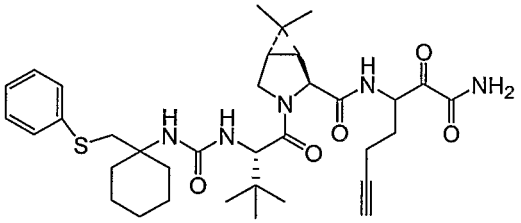


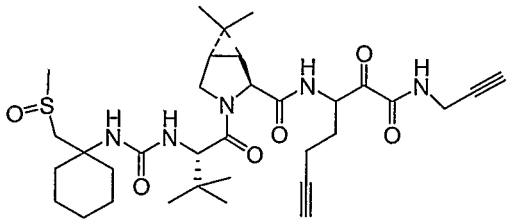


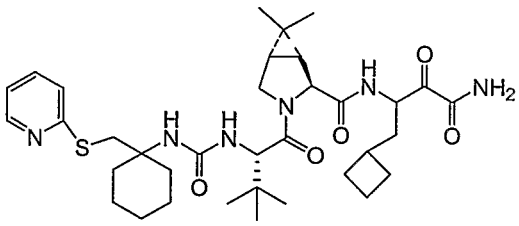


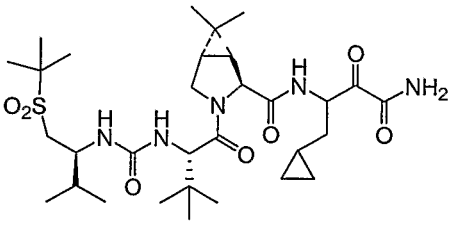


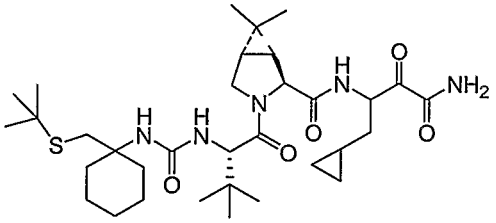


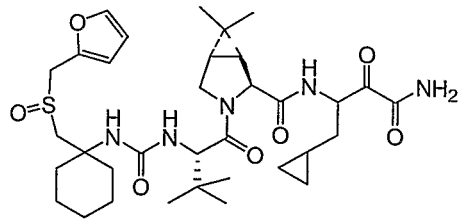


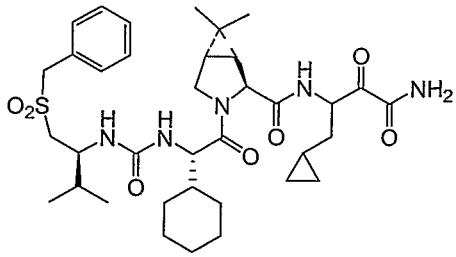


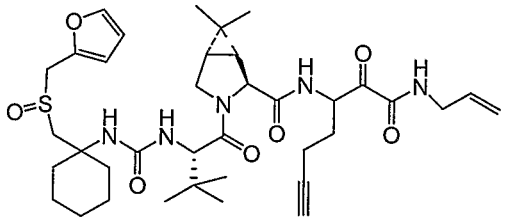


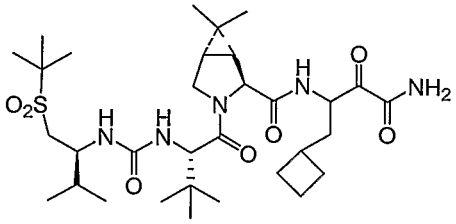


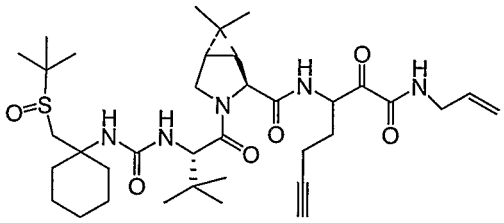


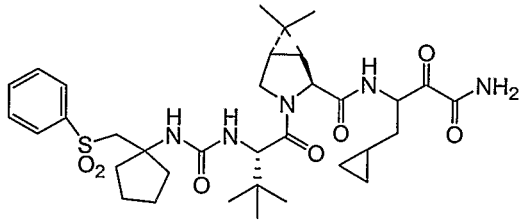


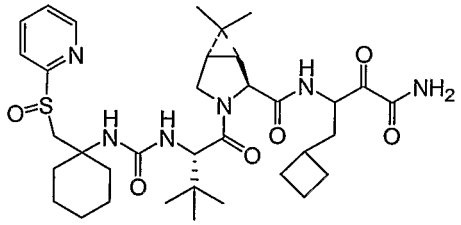


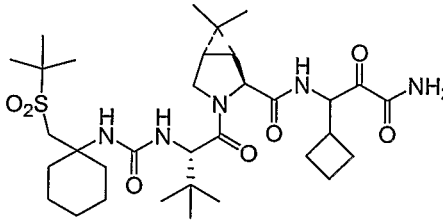


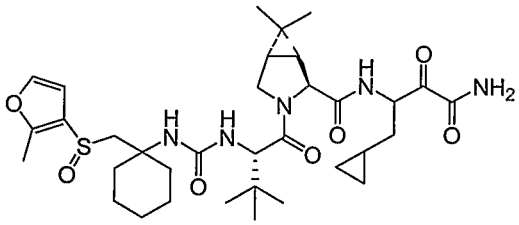


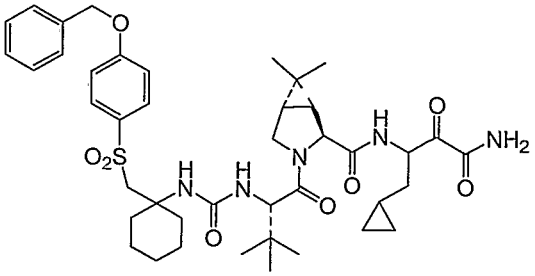


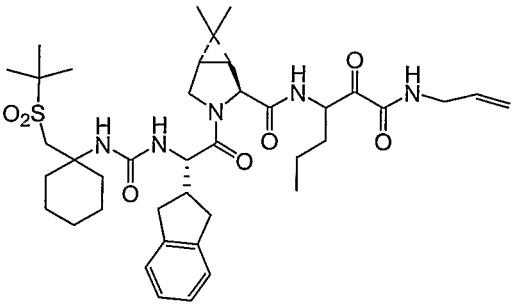


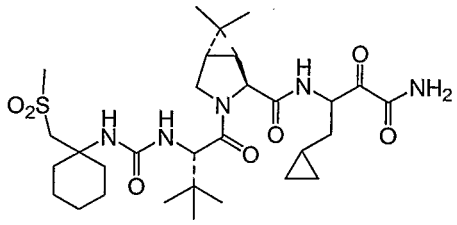


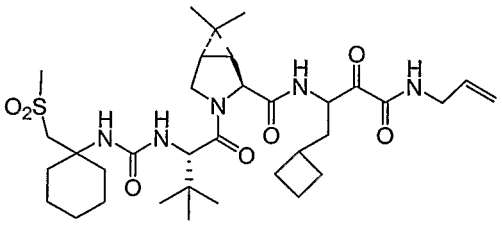


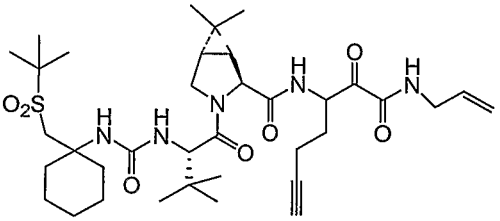


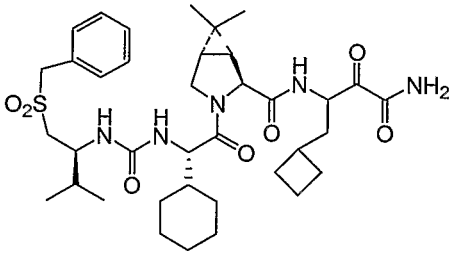


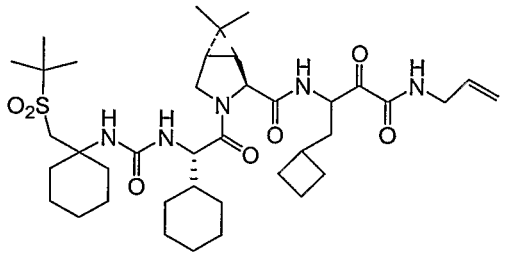


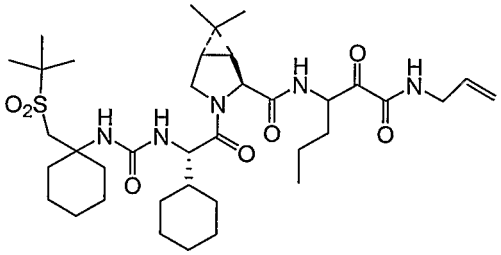


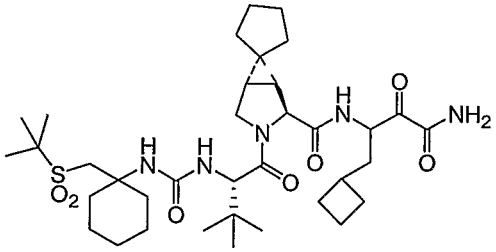


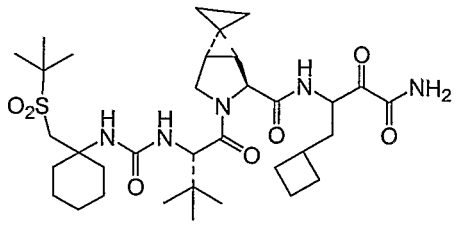


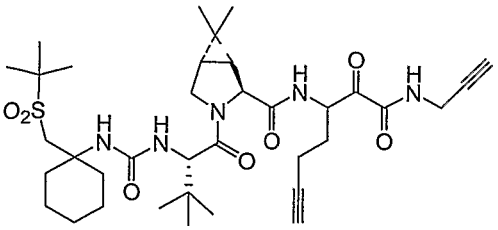


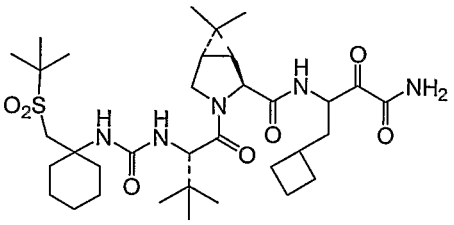


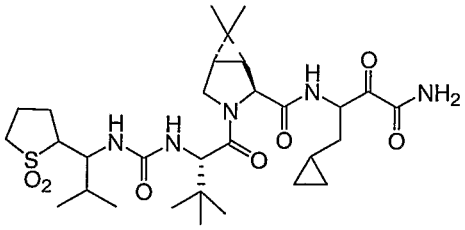


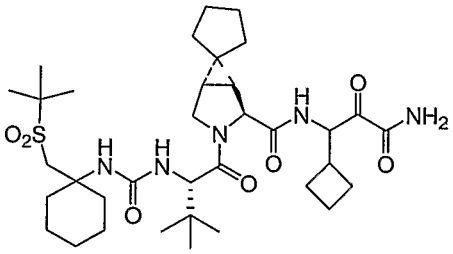


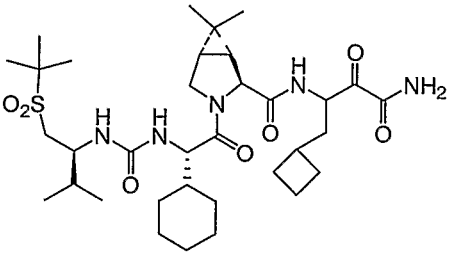


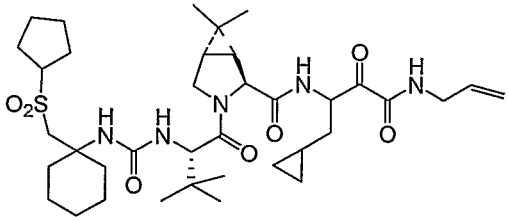


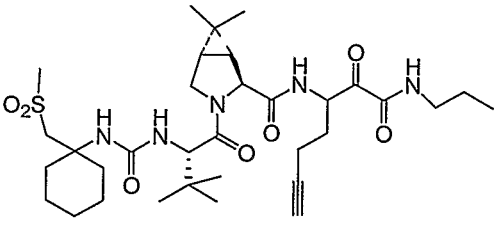


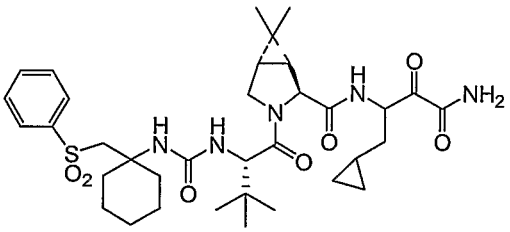


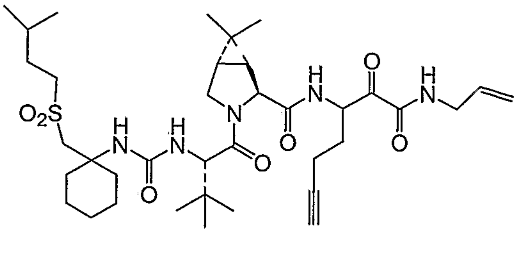












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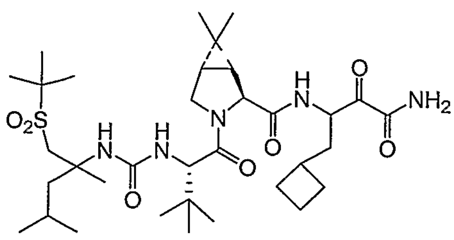

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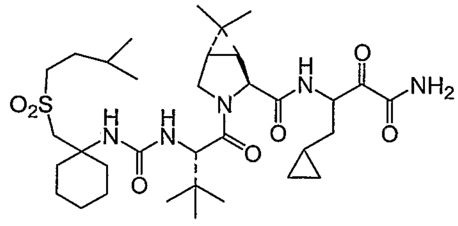

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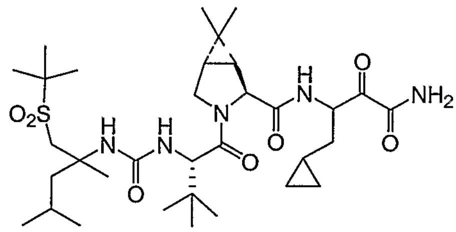

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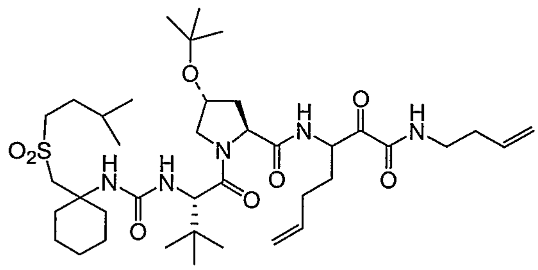

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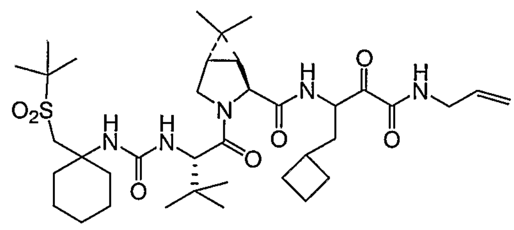

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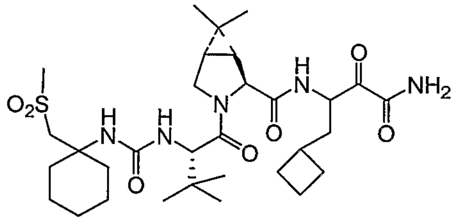

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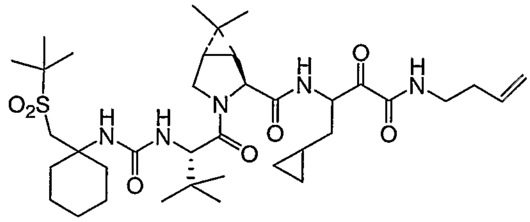

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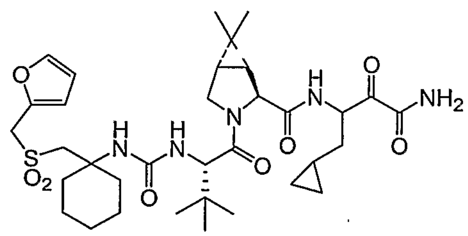

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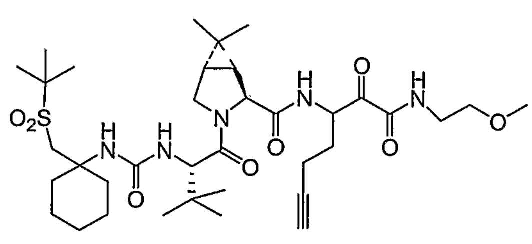

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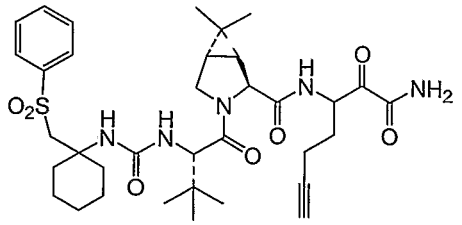

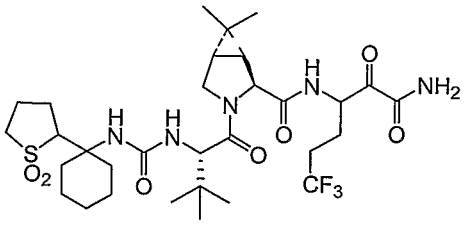

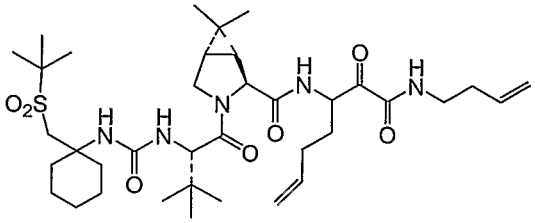

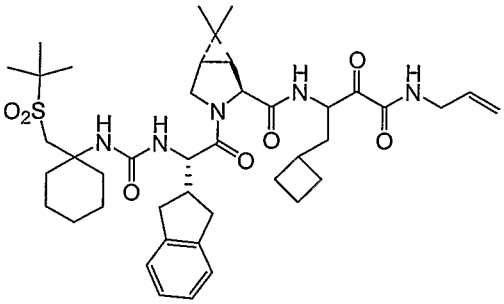

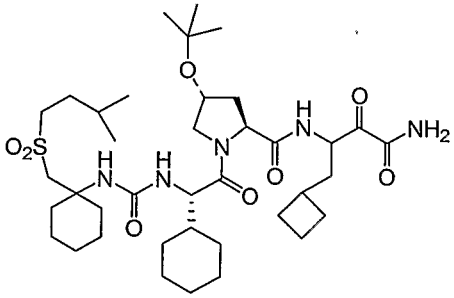

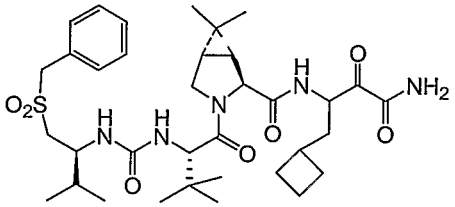

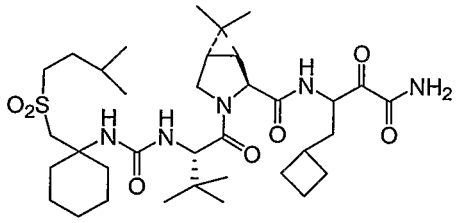

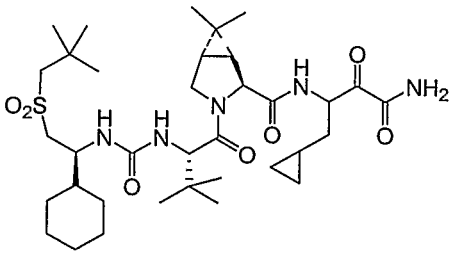

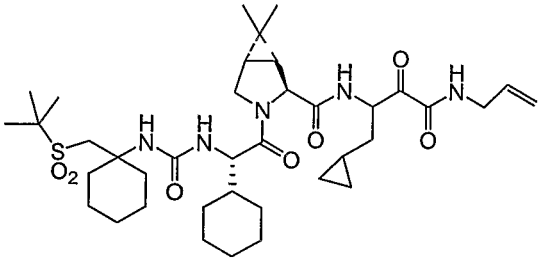

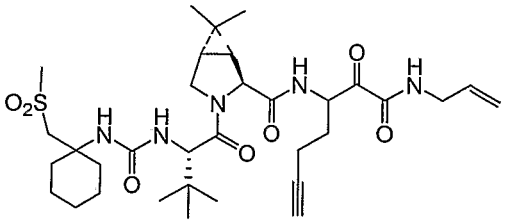

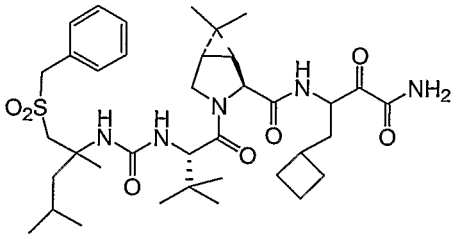

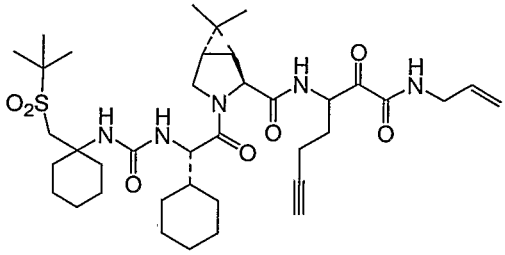

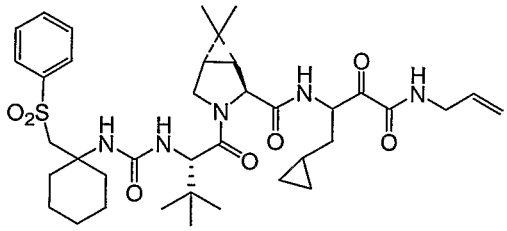

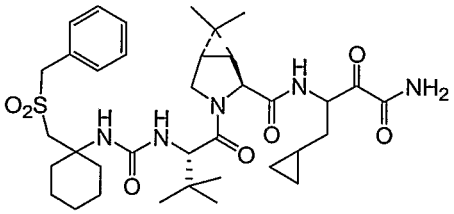

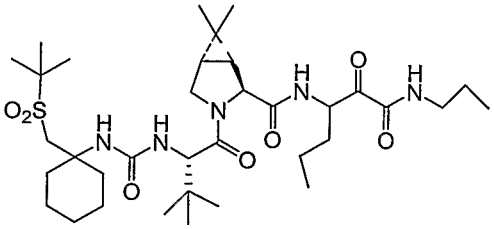

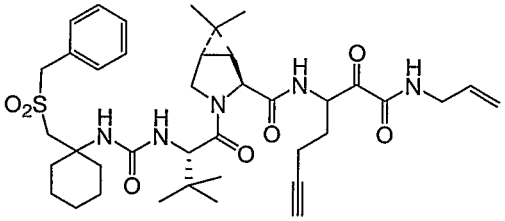

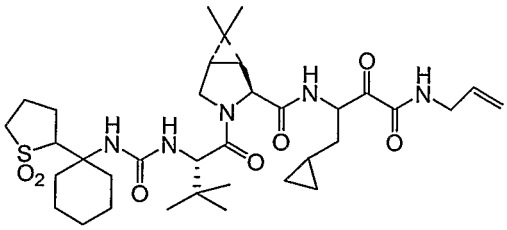

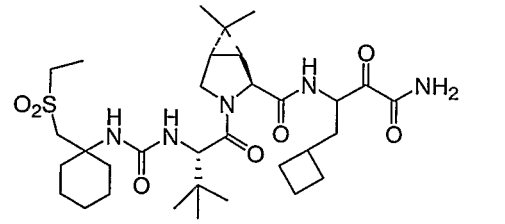

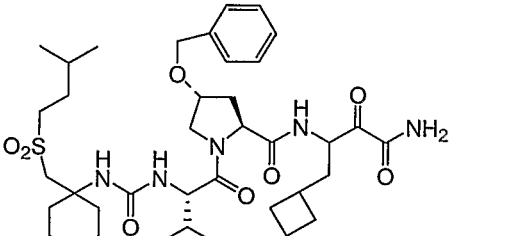

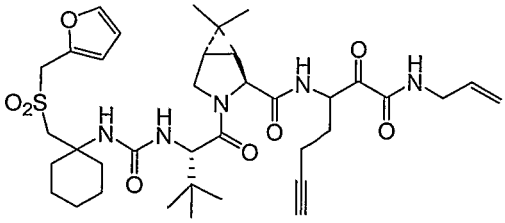

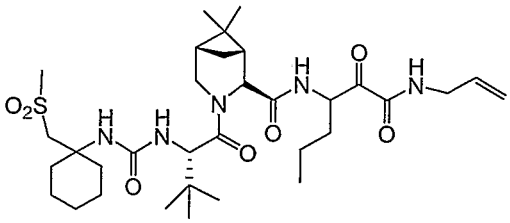

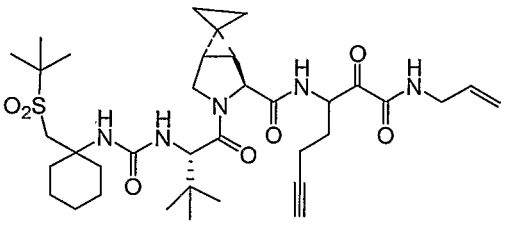

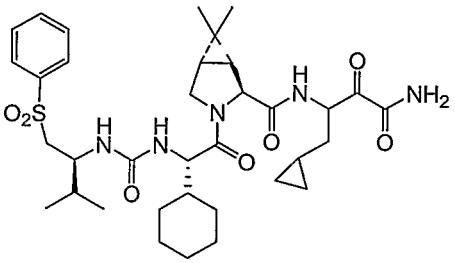

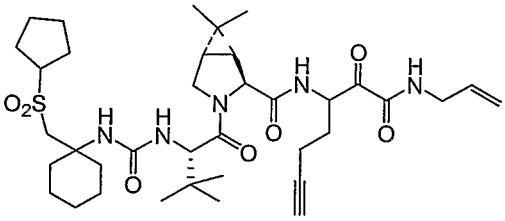

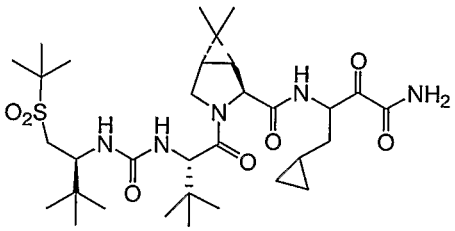

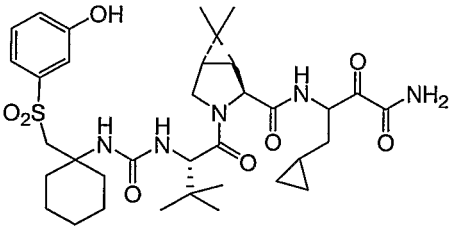

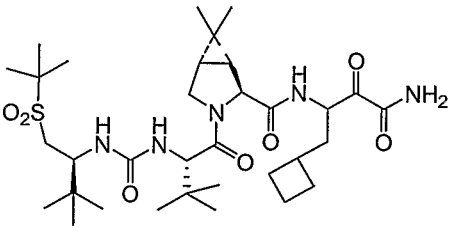

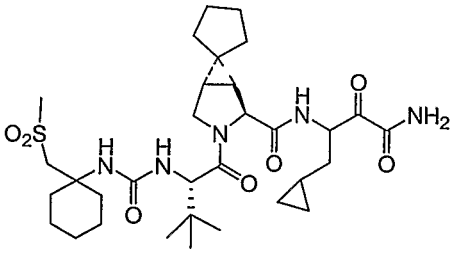

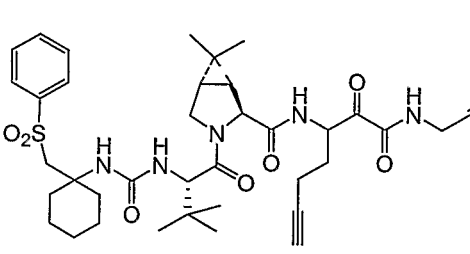

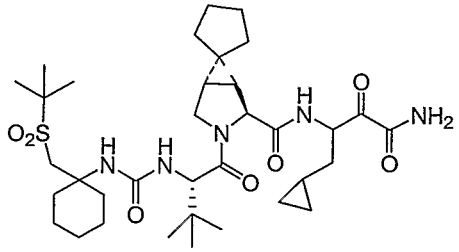

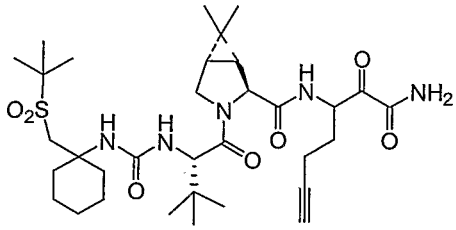

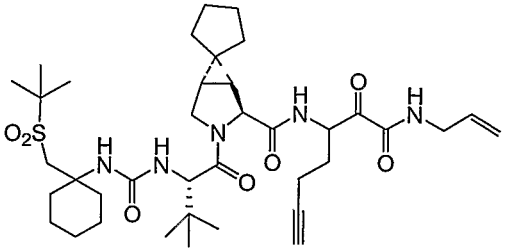

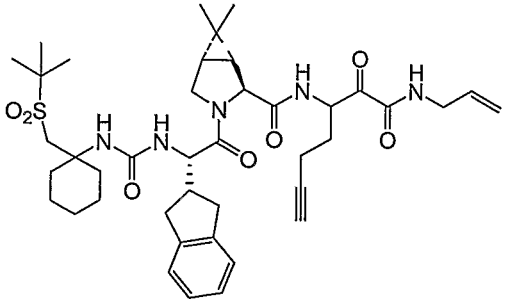

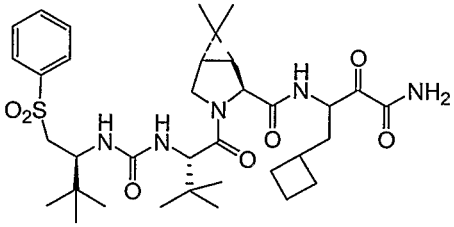

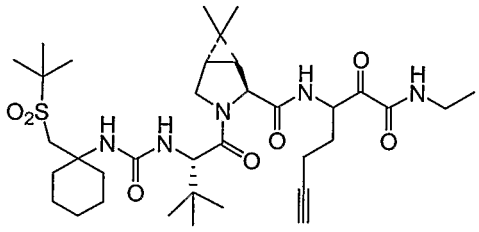

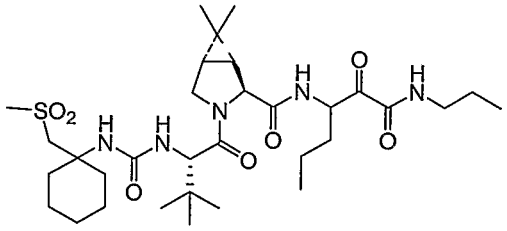

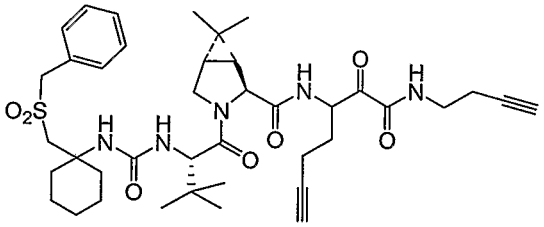

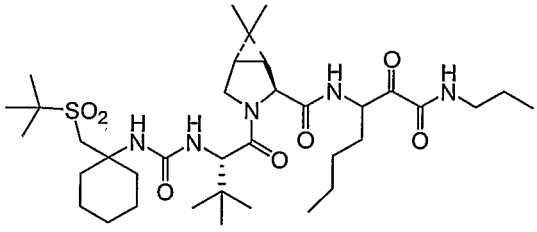

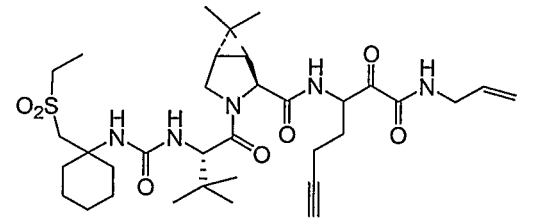

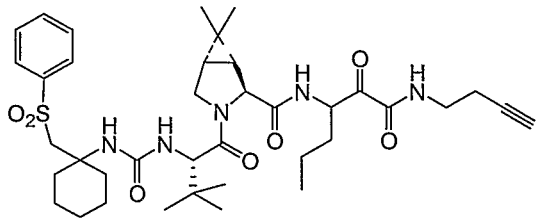

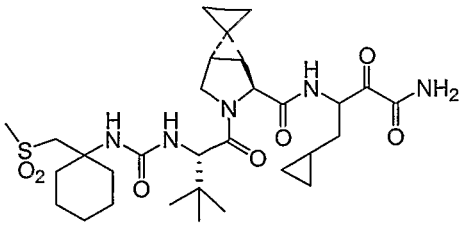

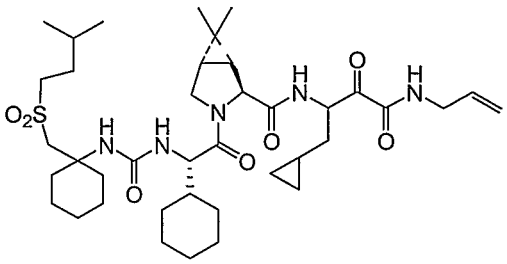

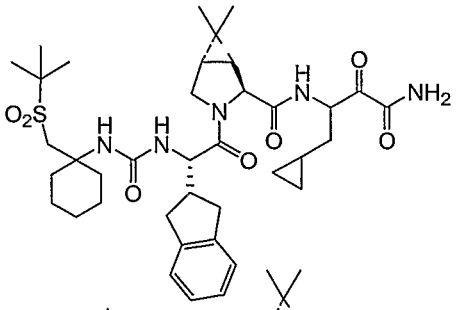

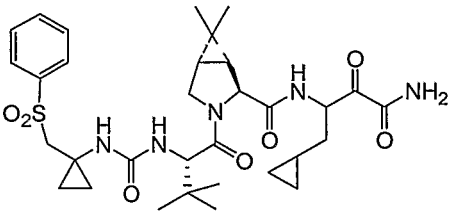

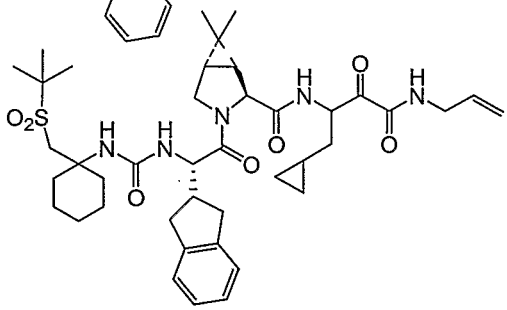

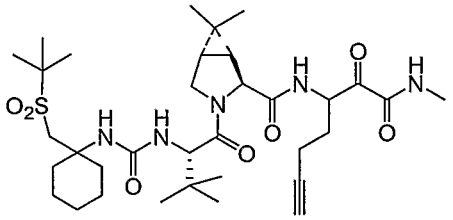

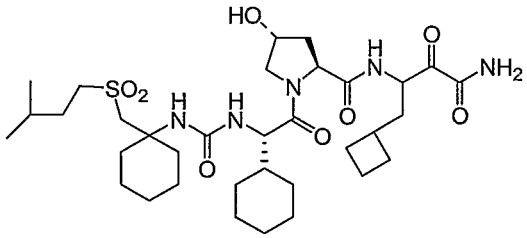

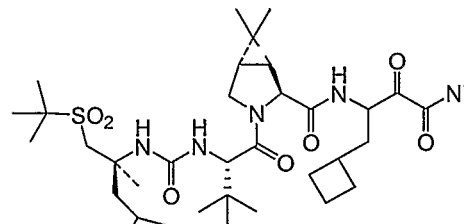

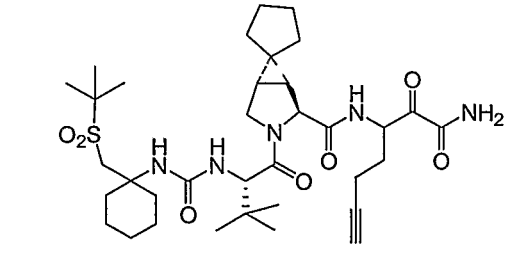

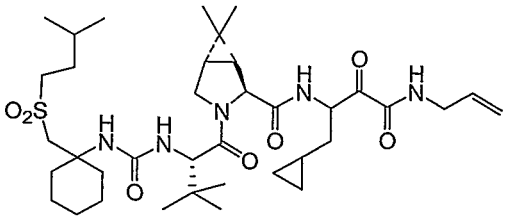

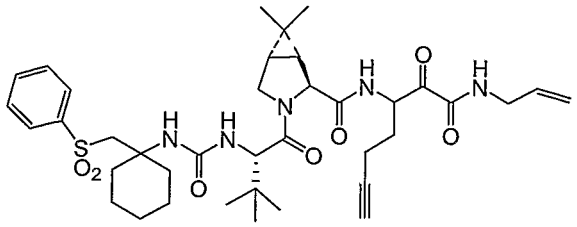

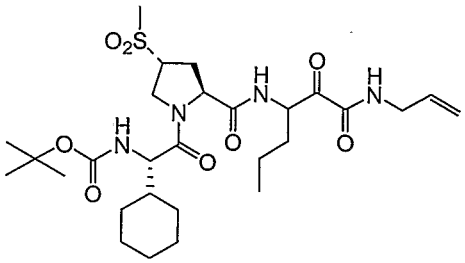

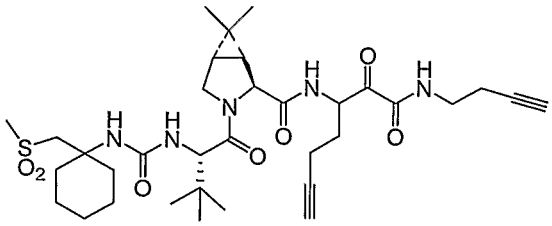

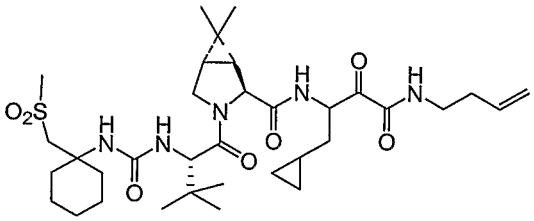

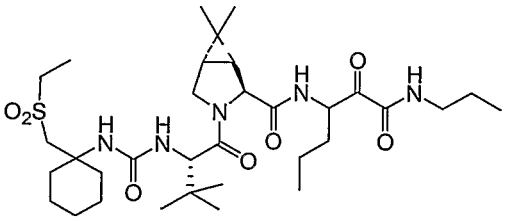

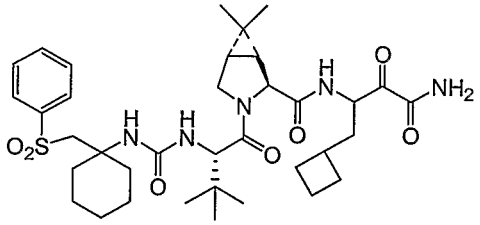

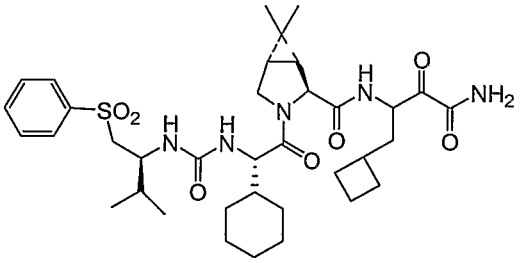

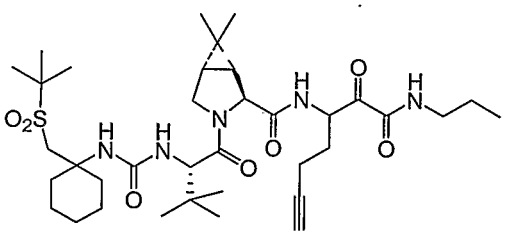

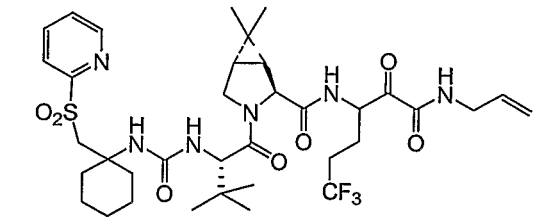

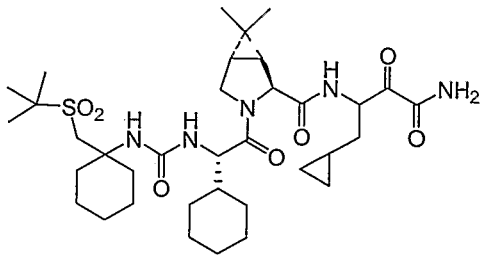

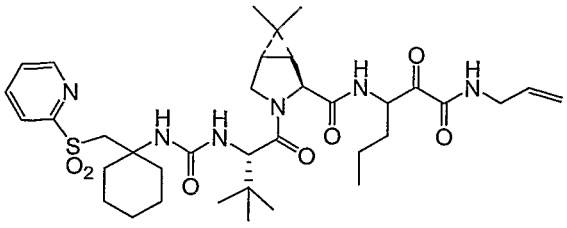

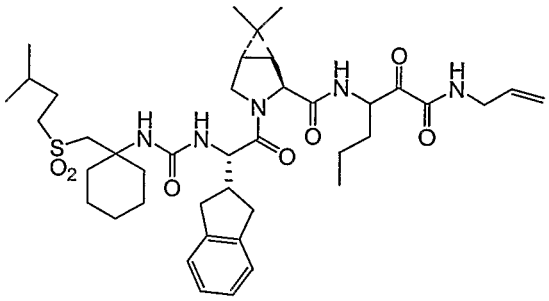

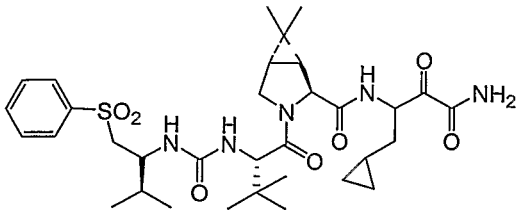

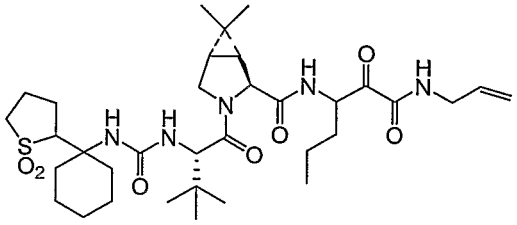

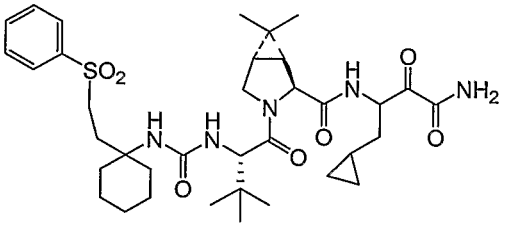

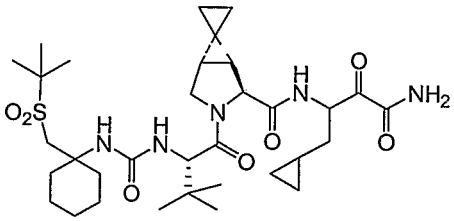

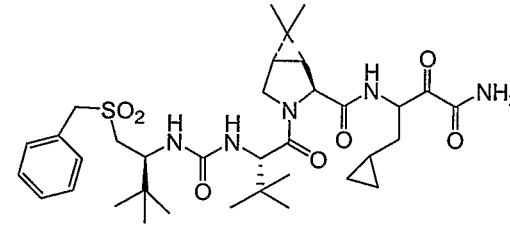

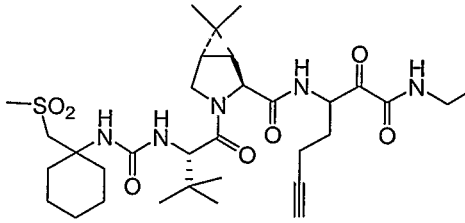

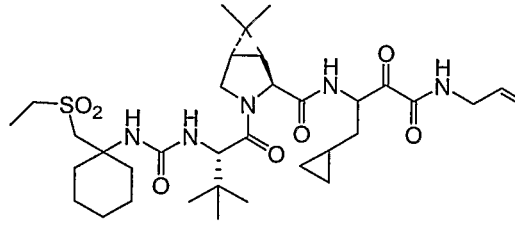

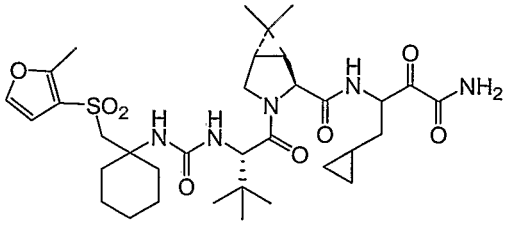

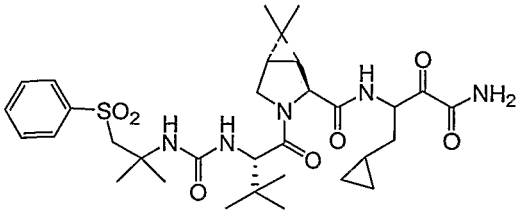

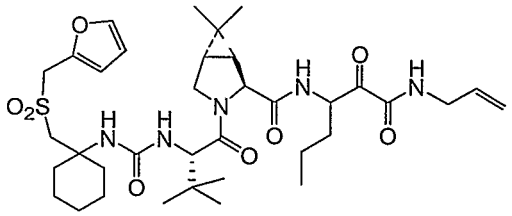

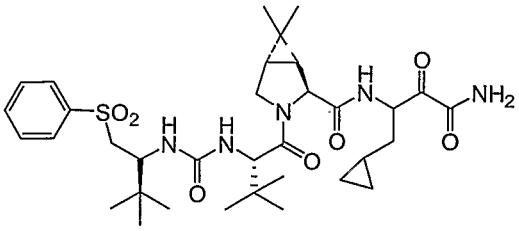

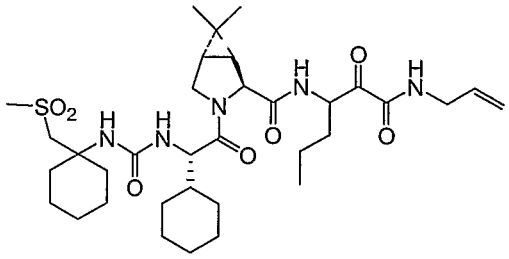

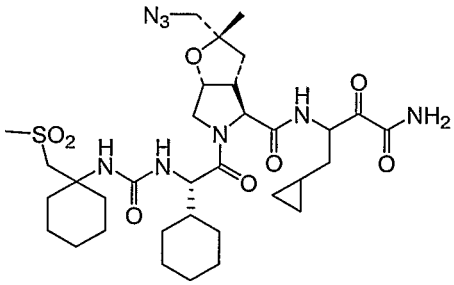

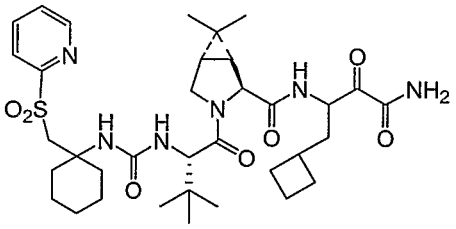

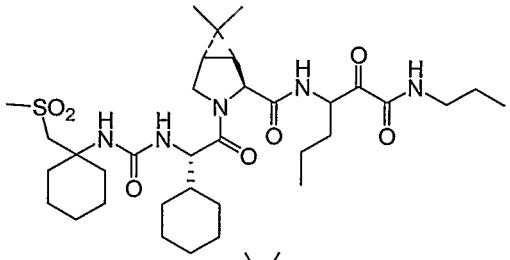

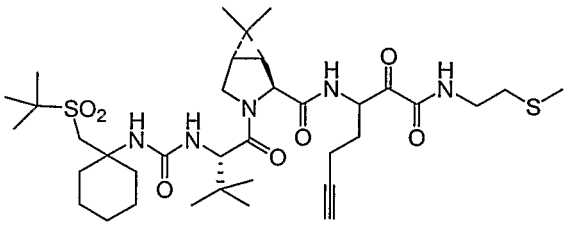

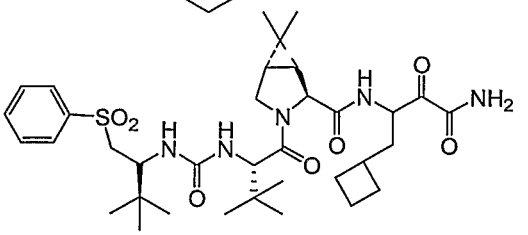

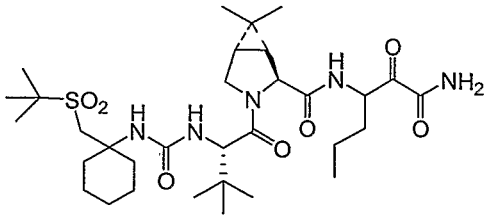

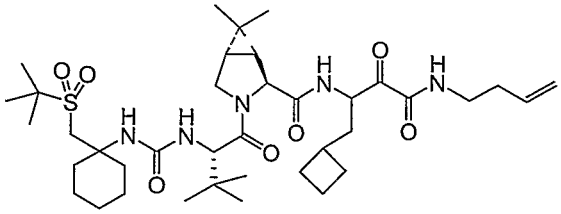

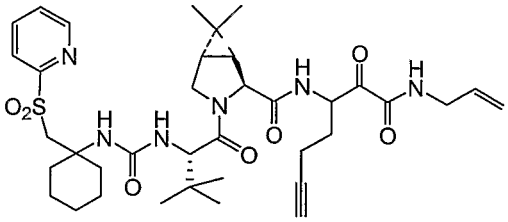

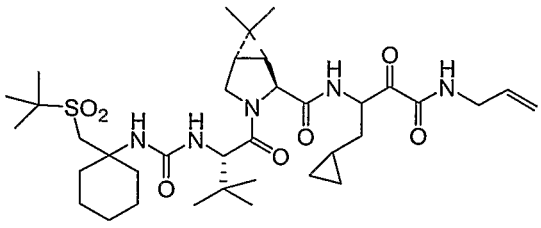

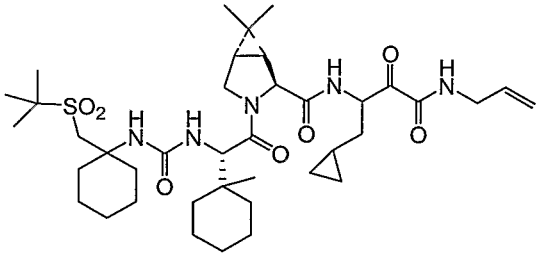

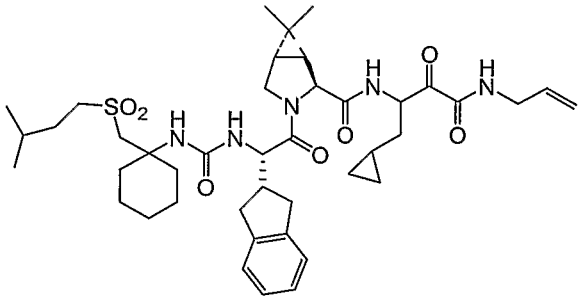

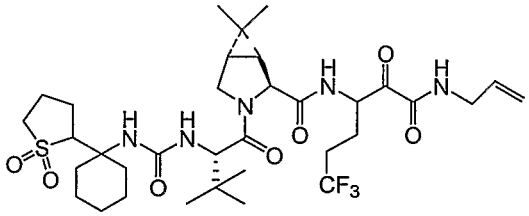

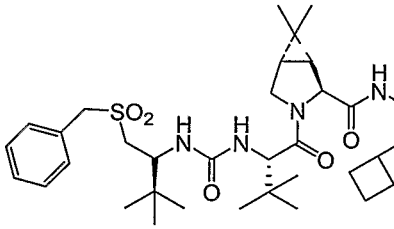

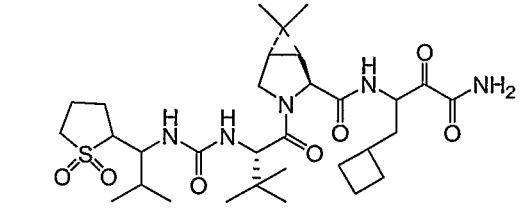

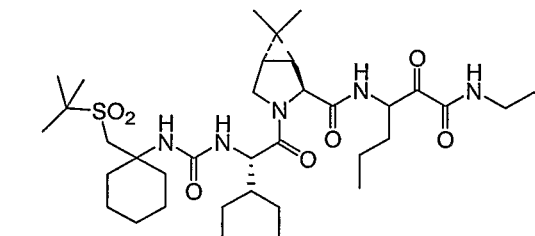

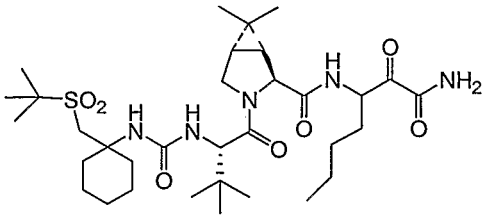

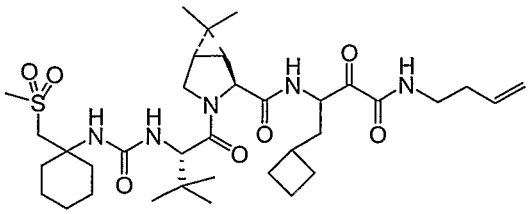

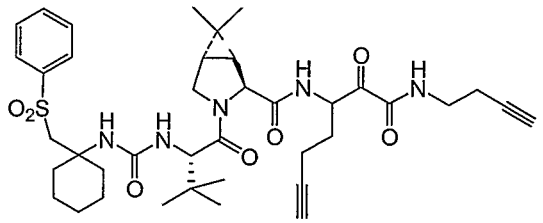

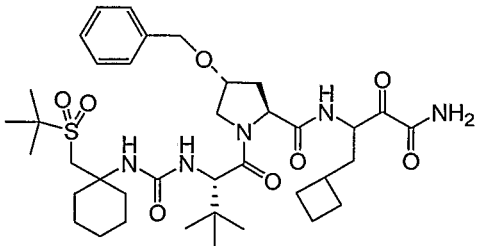

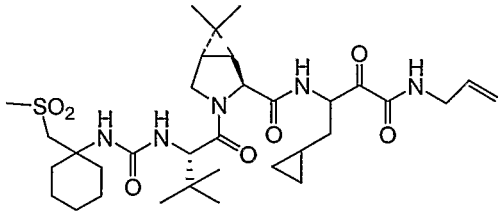

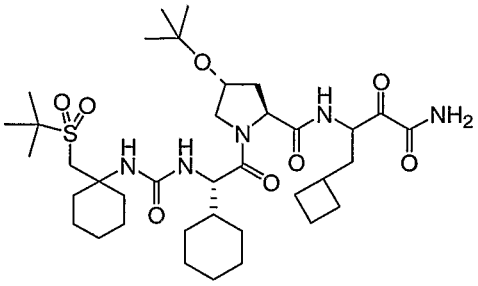

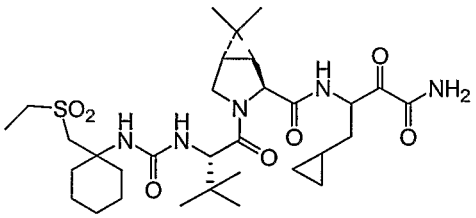

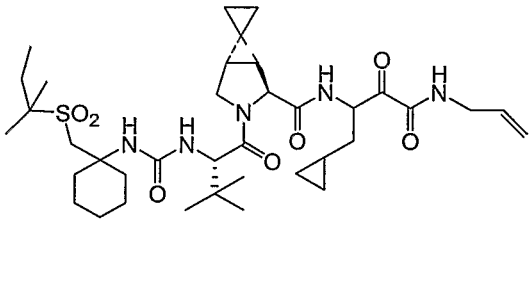

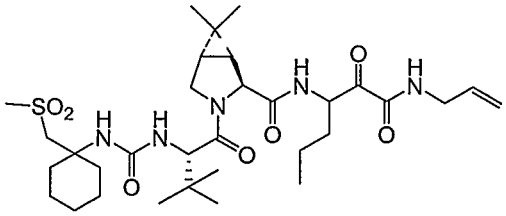

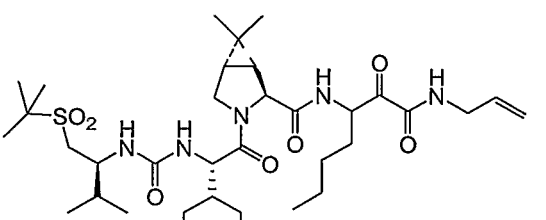

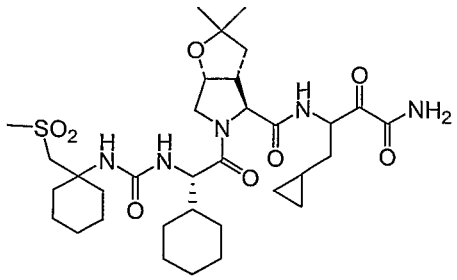

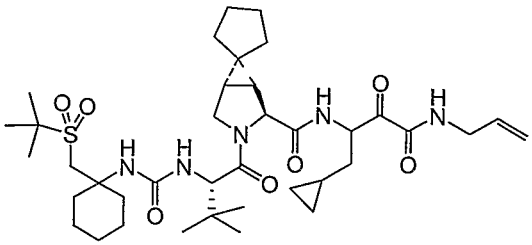

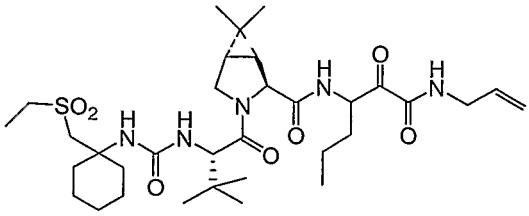

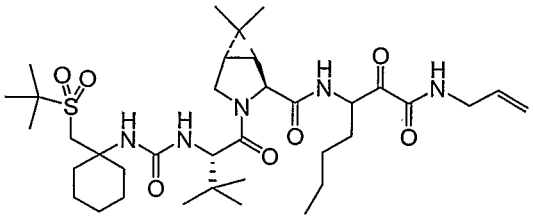

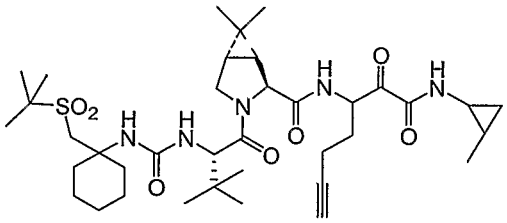

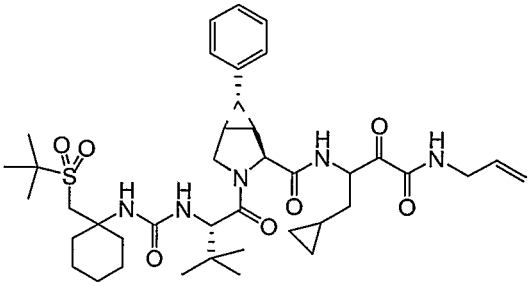

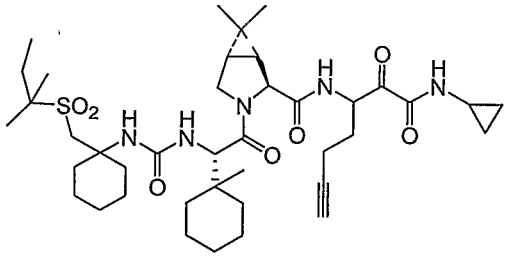

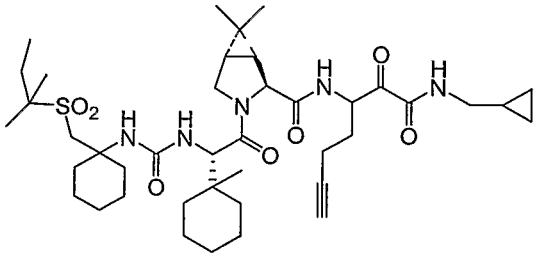

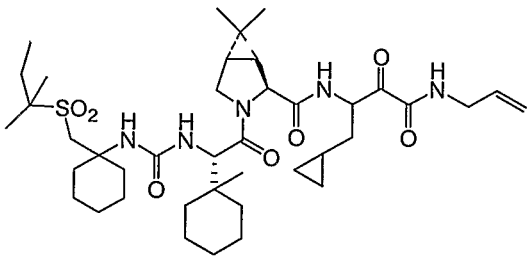

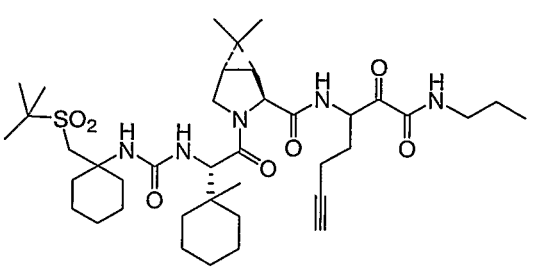

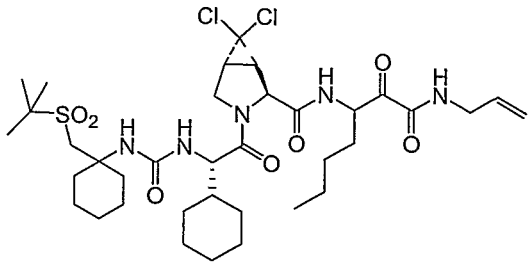

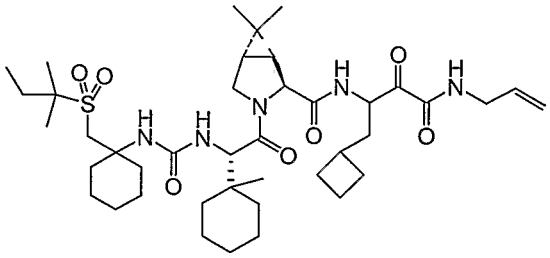

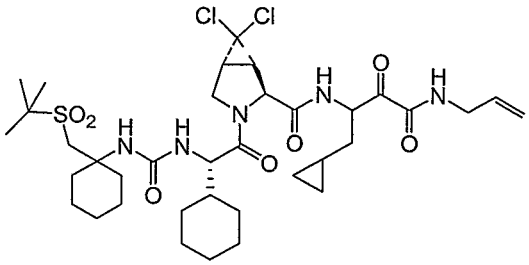

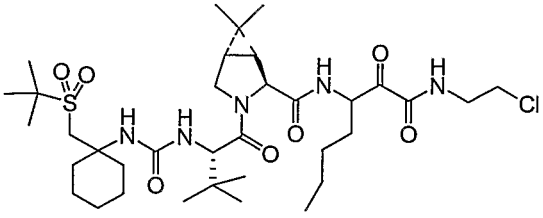

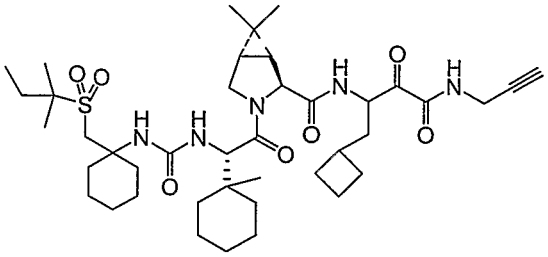

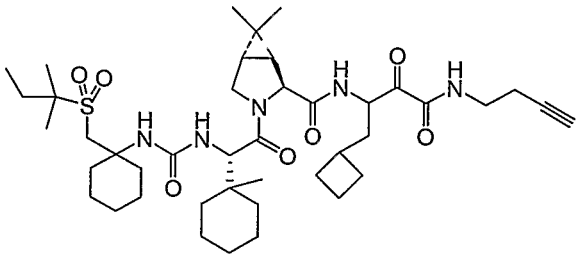

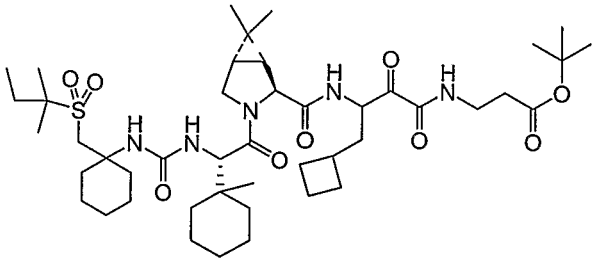

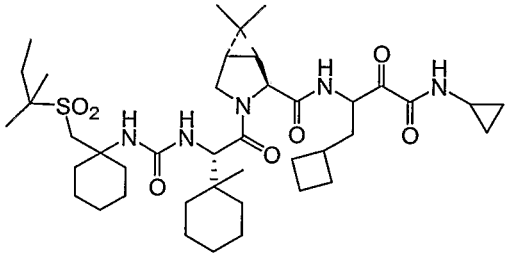

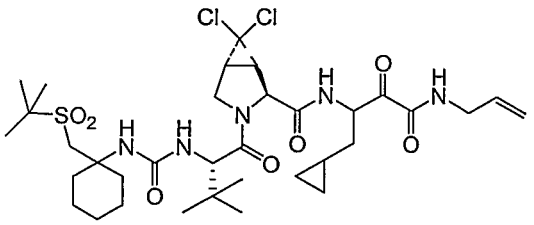

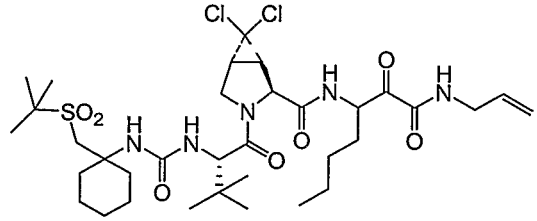

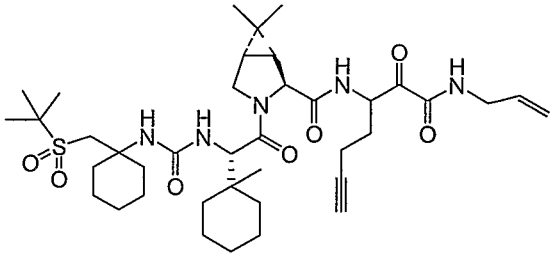

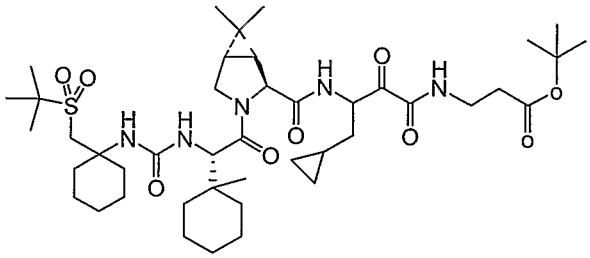

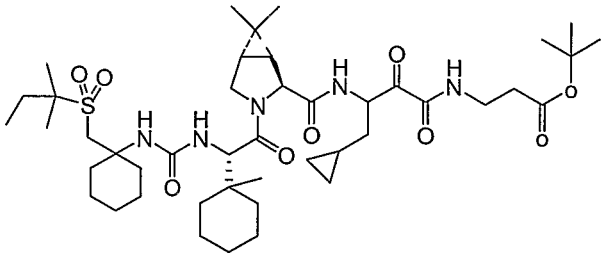

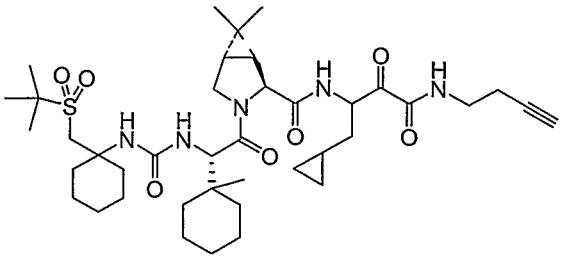

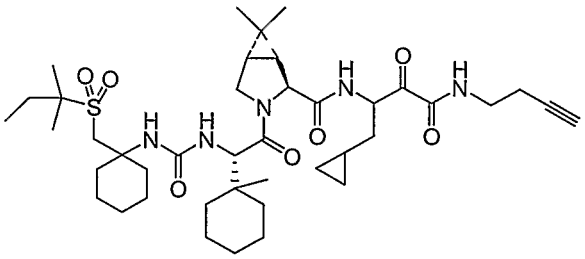

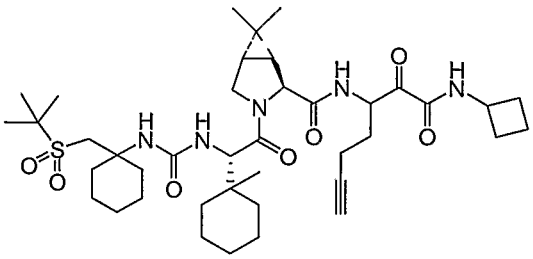

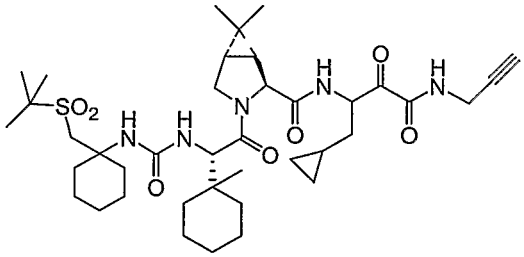

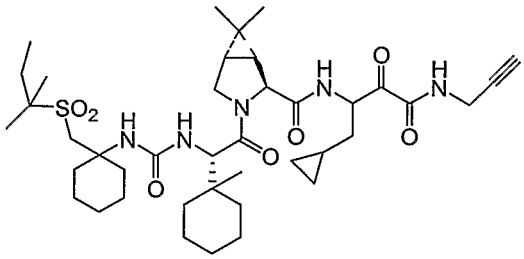

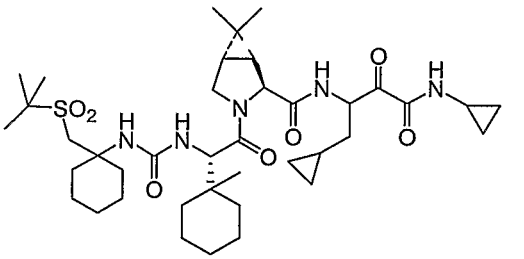

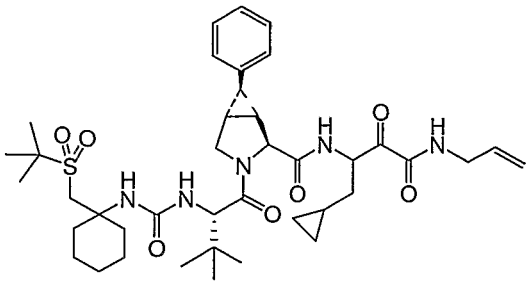

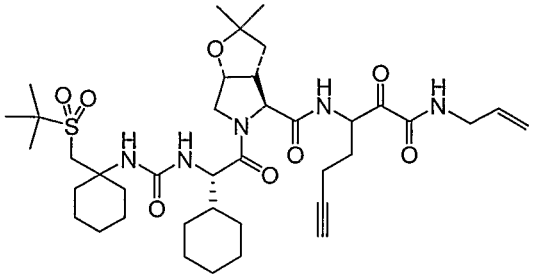

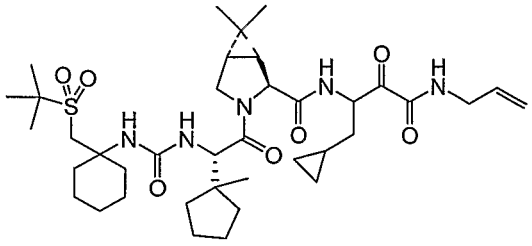

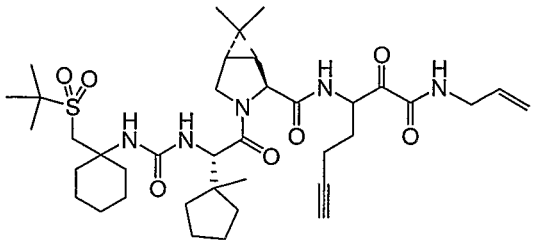

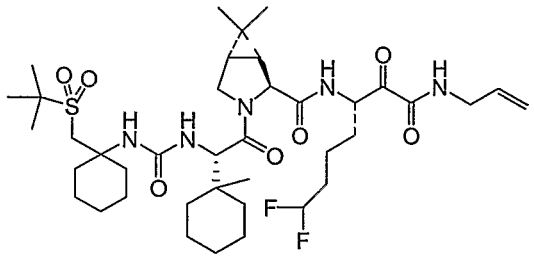

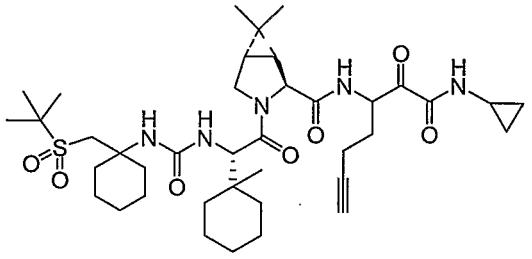

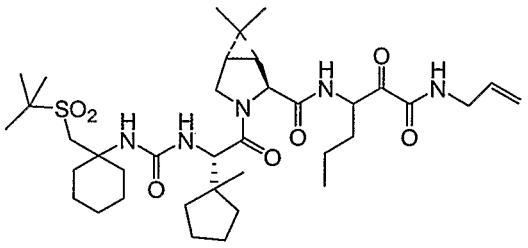

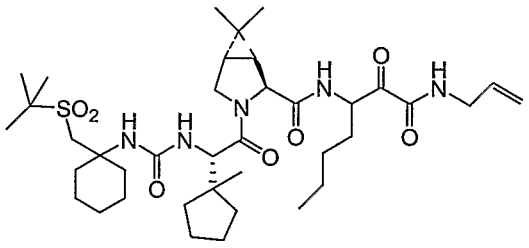

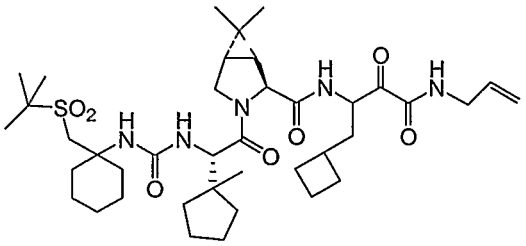

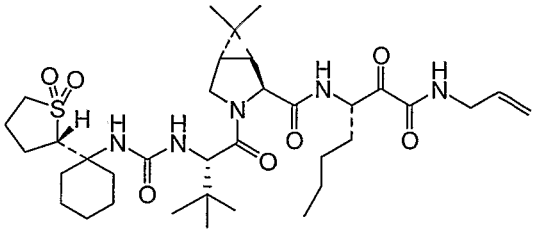

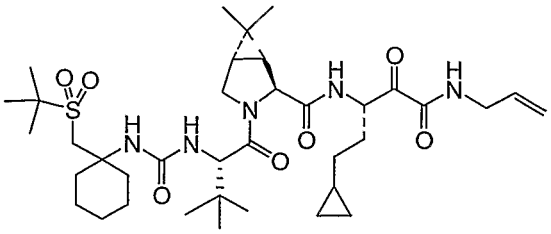

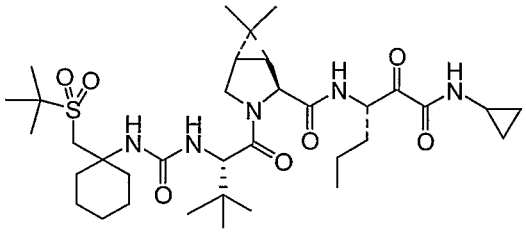

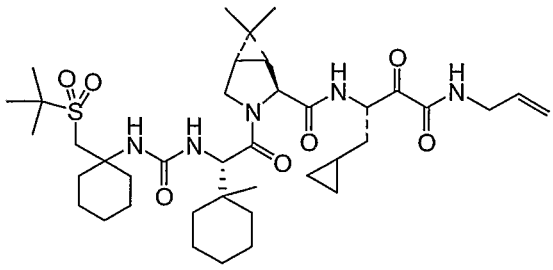

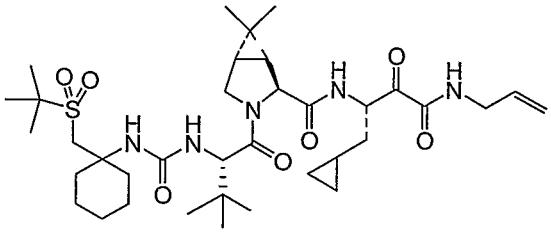

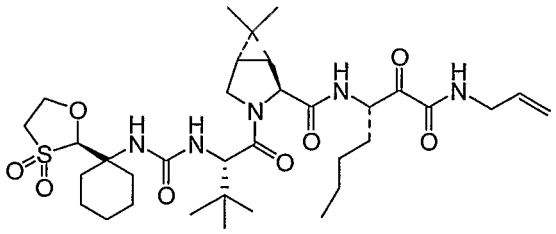

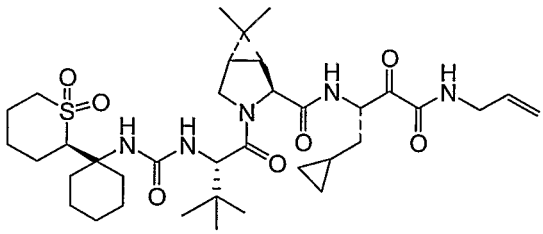

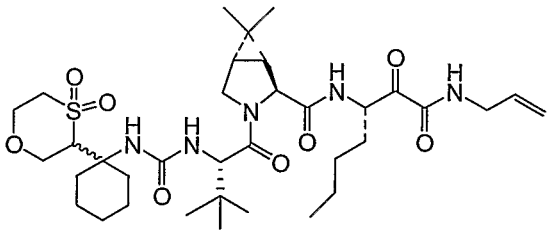

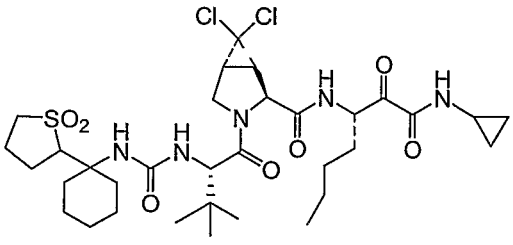

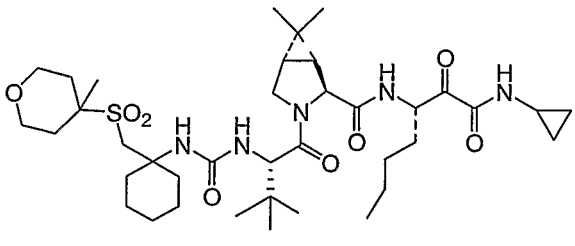

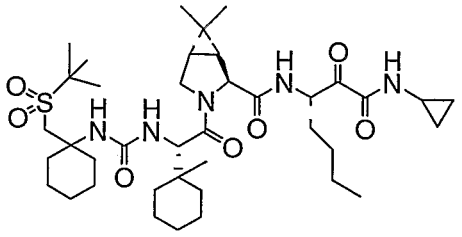
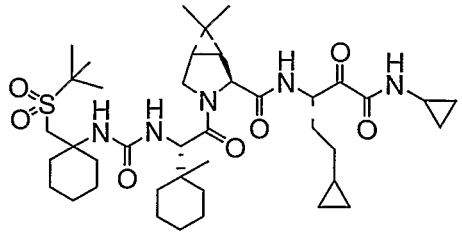
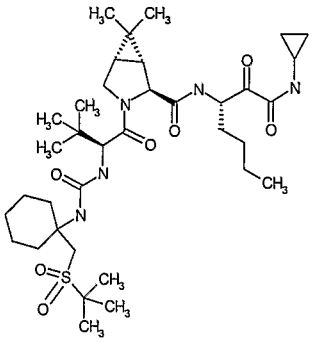
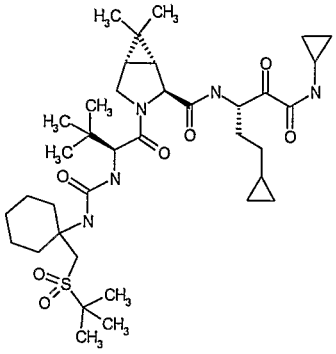
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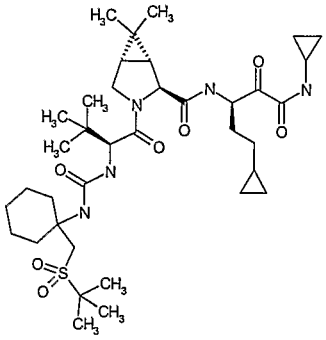


23. A pharmaceutical composition for treating disorders associated with the HCV, said composition comprising therapeutically effective amount of one or more compounds in claim 22 and a pharmaceutically acceptable carrier.

24. The pharmaceutical composition of claim 23, additionally containing at least one antiviral agent.

25. The pharmaceutical composition of claim 24, still additionally containing at least one interferon or PEG-interferon alpha conjugate.

26. The pharmaceutical composition of claim 25, wherein said at least one antiviral agent is ribavirin and said at least one interferon is α-interferon or pegylated interferon.

27. A method of treatment of a hepatitis C virus associated disorder, comprising administering an effective amount of one or more compounds of claim 22.

28. A method of modulating the activity of hepatitis C virus (HCV) protease, comprising contacting HCV protease with one or more compounds of claim 22.

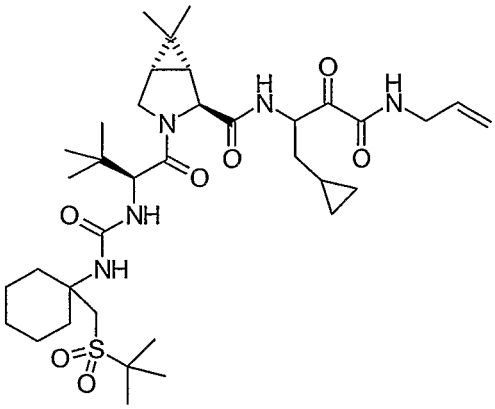
29 A method of treating, preventing, or ameliorating one or more symptoms of hepatitis C, comprising administering a therapeutically effective amount of one or more compounds of claim 22.

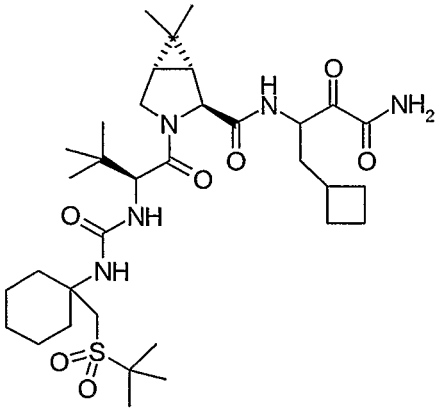
30. The method of claim 29, wherein the HCV protease is the NS3/NS4a protease.

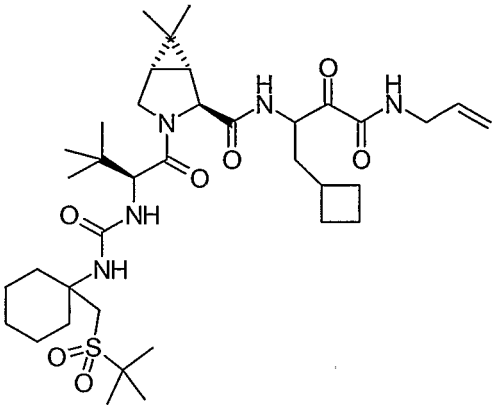
31. The method of claim 30, wherein the compound or compounds inhibit HCV NS3/NS4a protease.

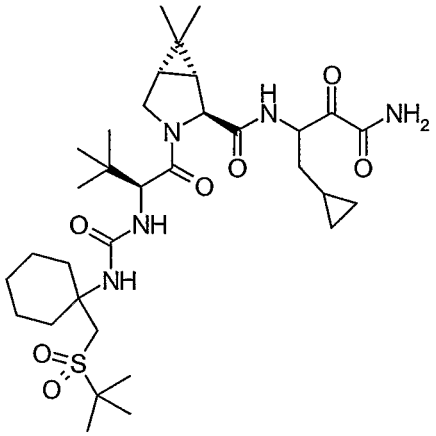
32. A method of modulating the processing of hepatitis C virus (HCV) polypeptide, comprising contacting a composition containing the HCV polypeptide under conditions in which said polypeptide is processed with one or more compounds of claim 22.

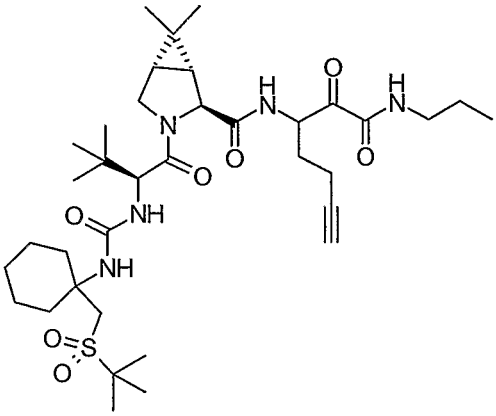
33. A method of treating disorders associated with the HCV, said method comprising administering to a patient in need of such treatment, a pharmaceutical composition which comprises therapeutically effective amounts of at least one compound, or enantiomers, stereoisomers, rotamers, tautomers, and racemates of said compound, or a pharmaceutically acceptable salt or solvate or ester of said compound, said compound being selected from the following:

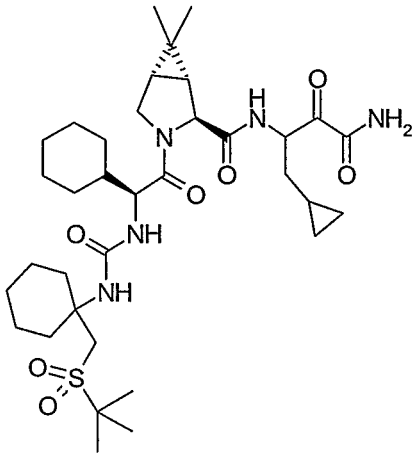


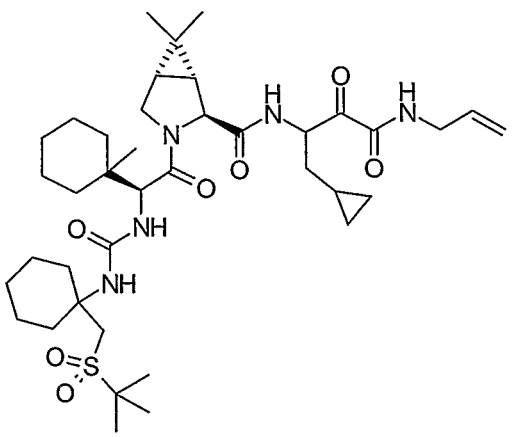


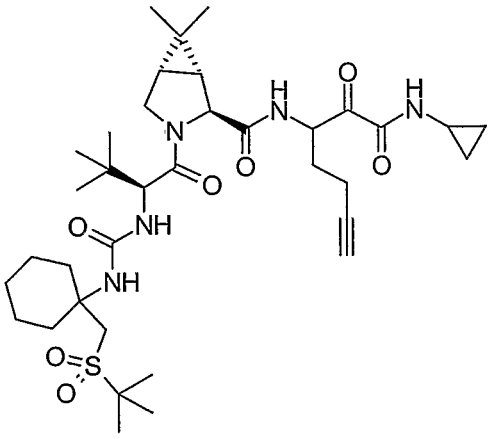


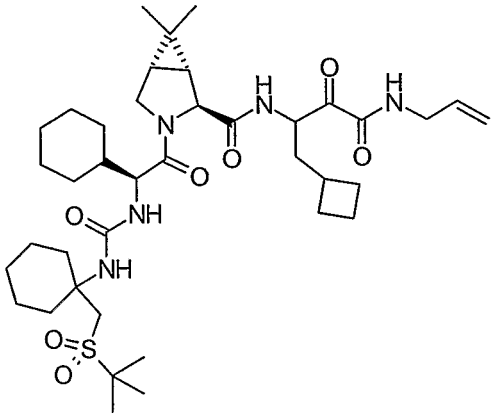


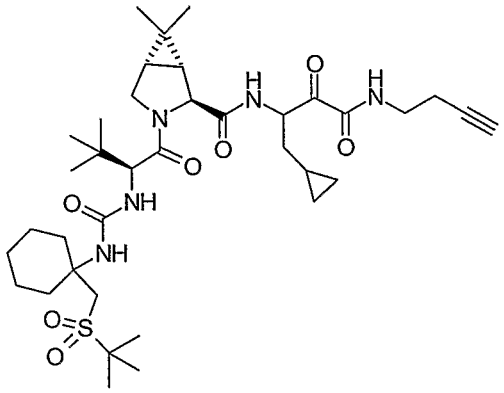


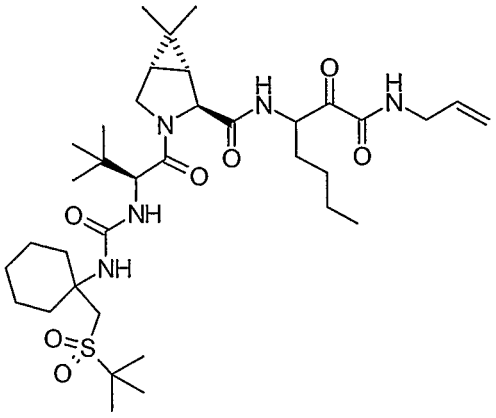


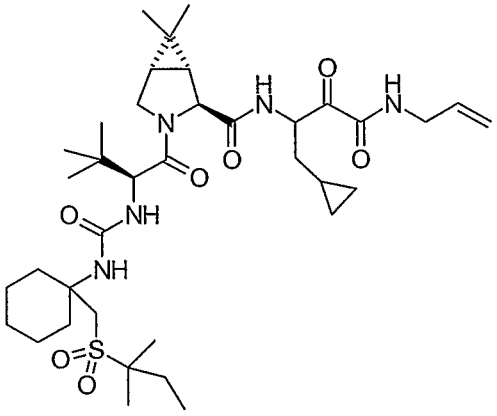


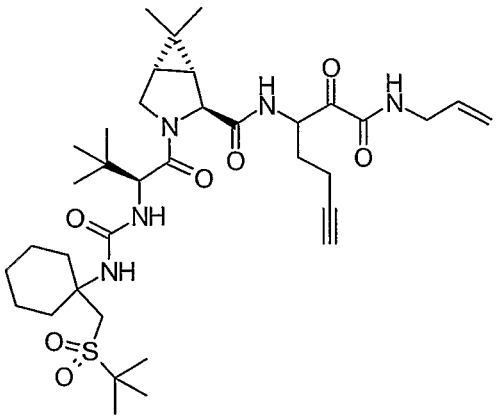


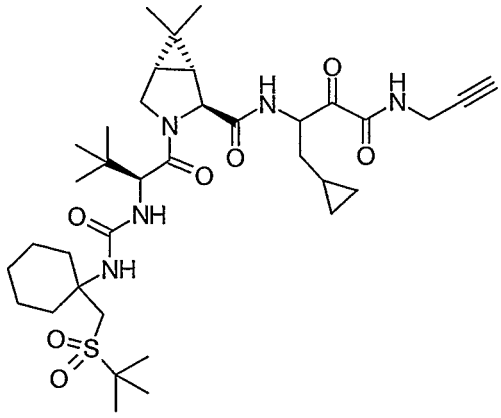


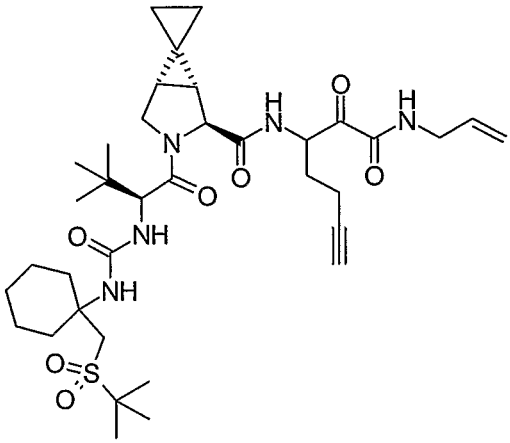


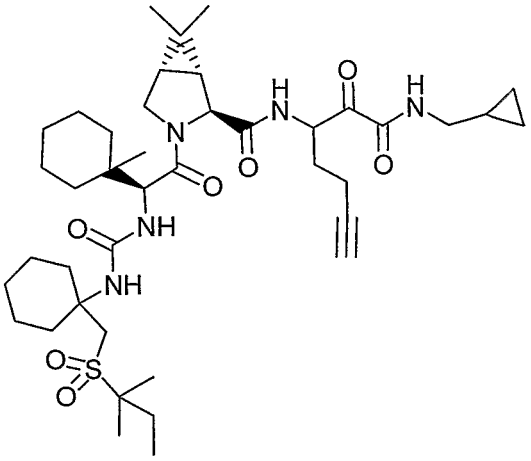


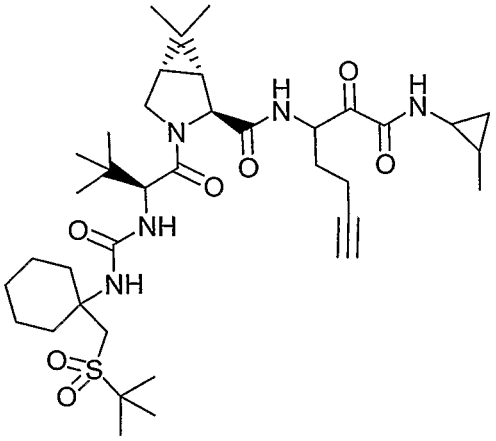


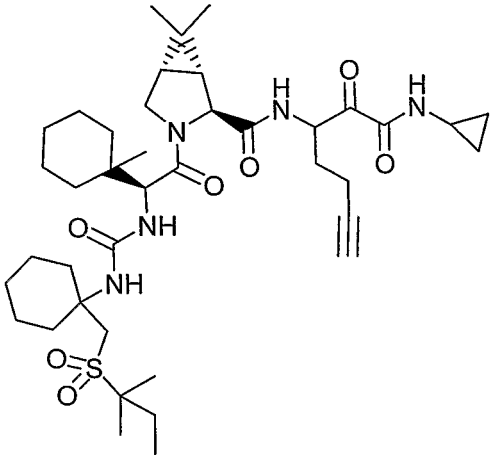


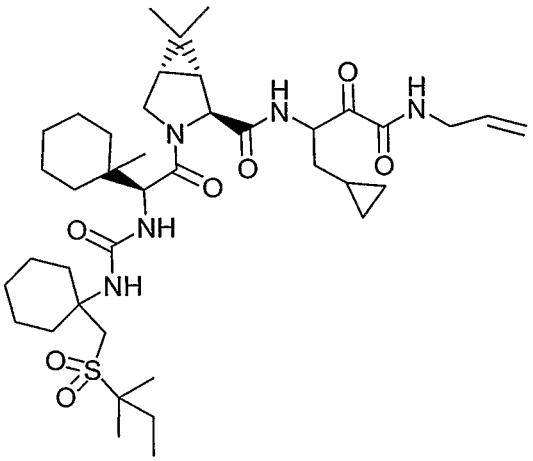


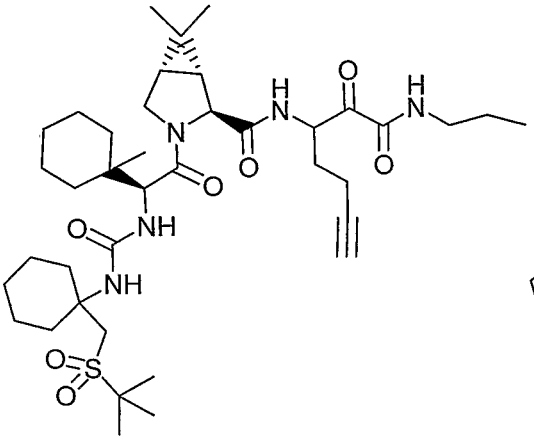


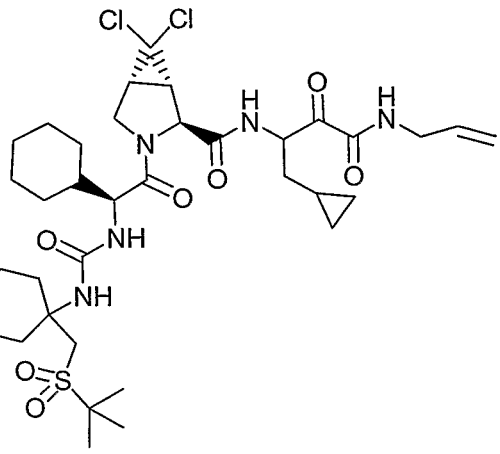


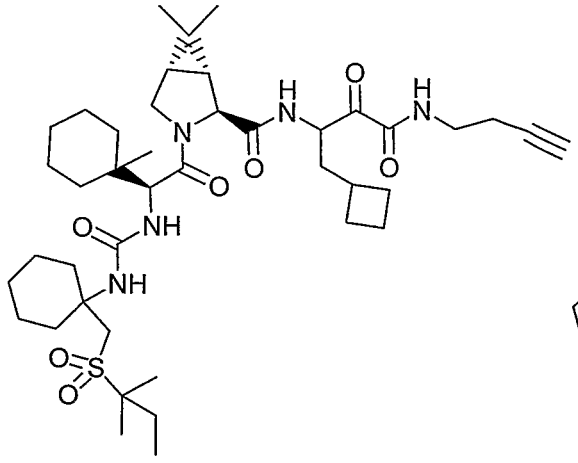


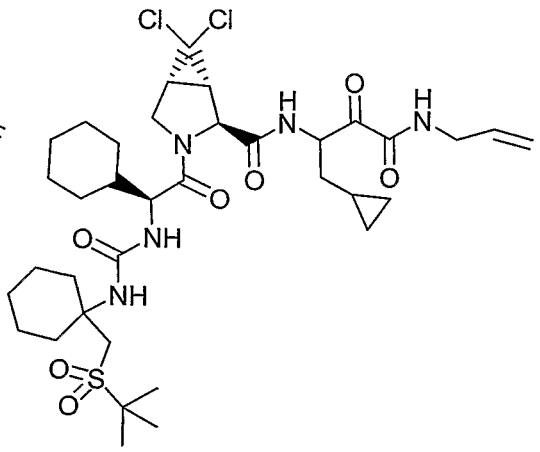


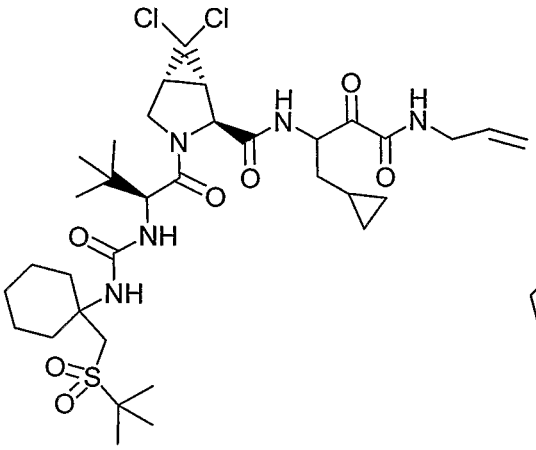


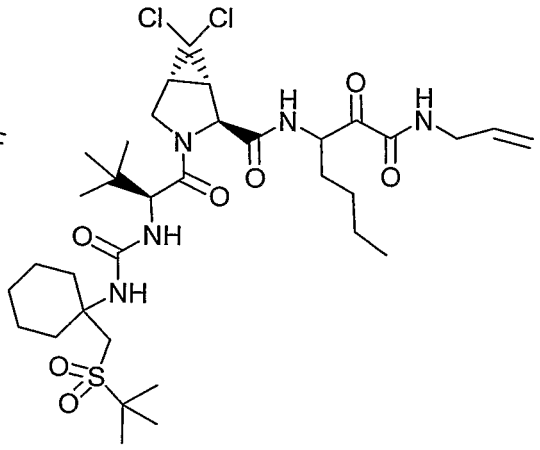


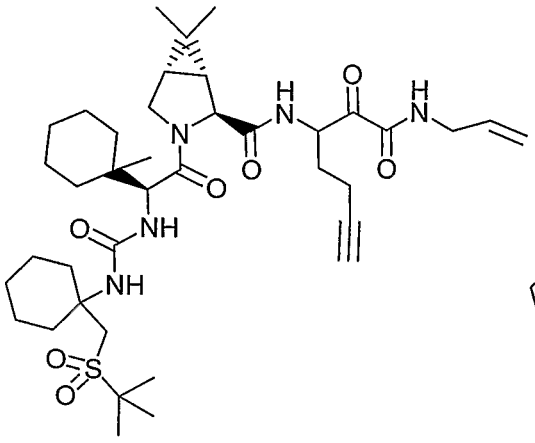


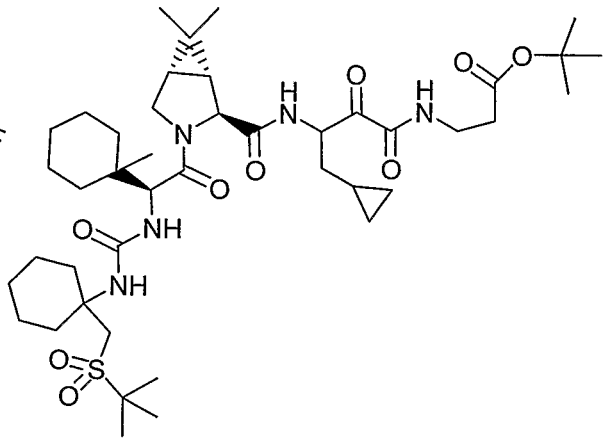


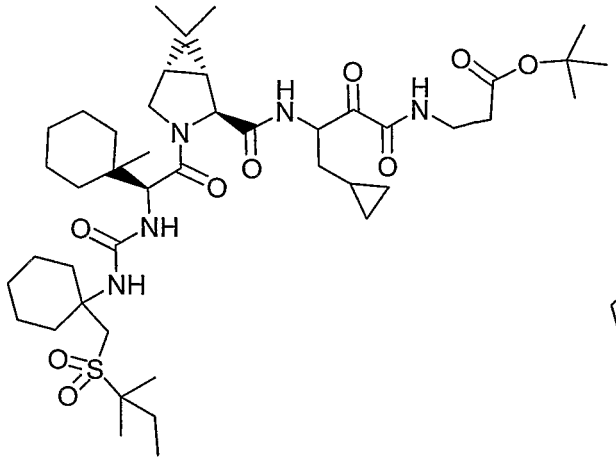


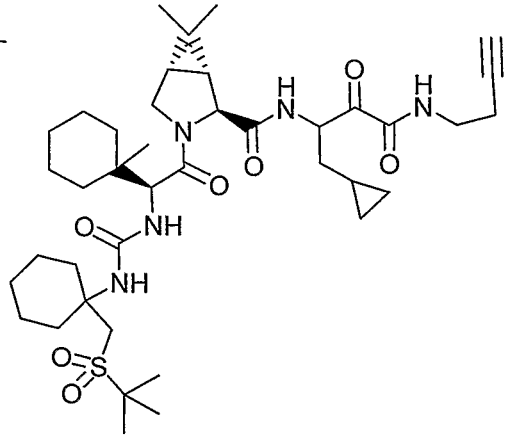


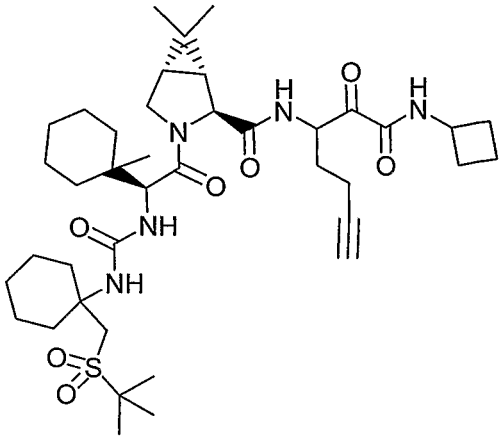


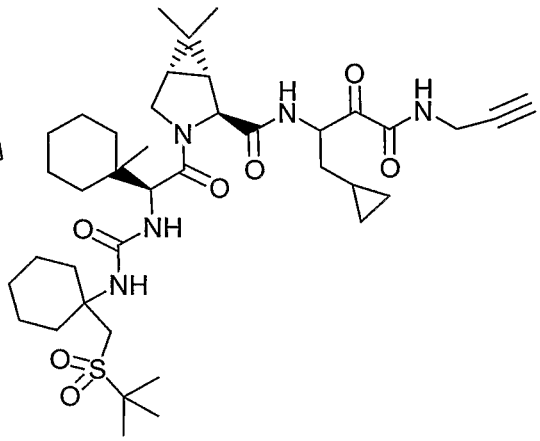


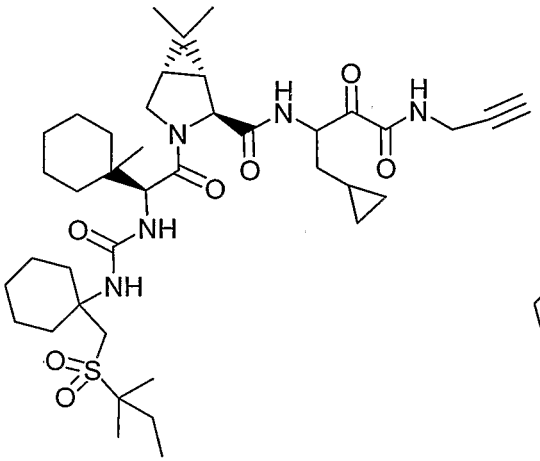


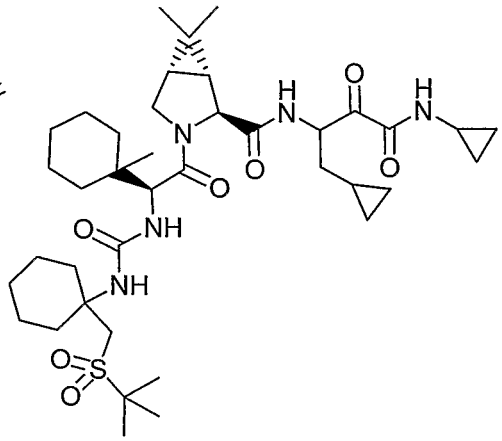


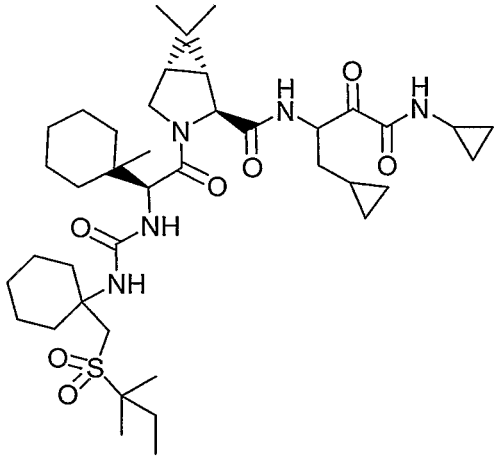


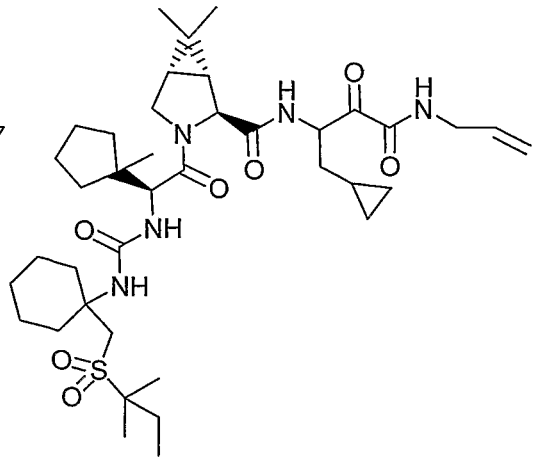


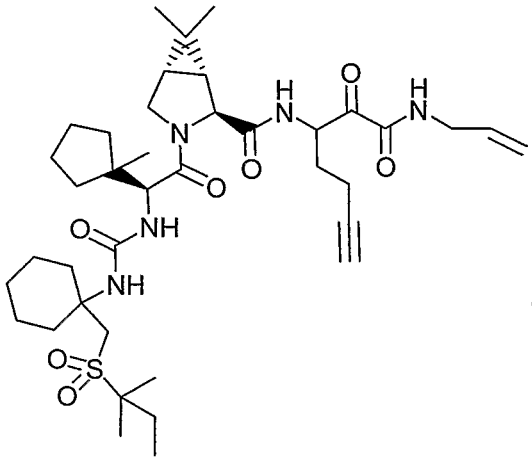


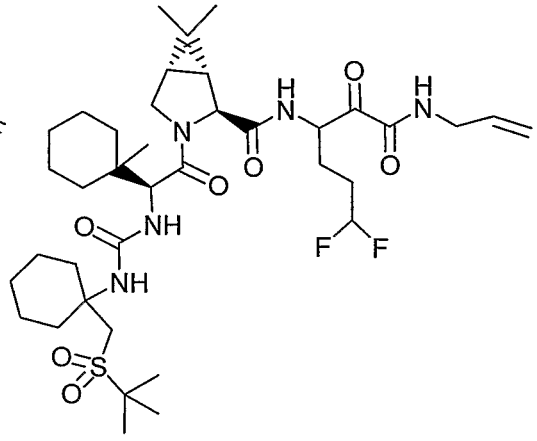


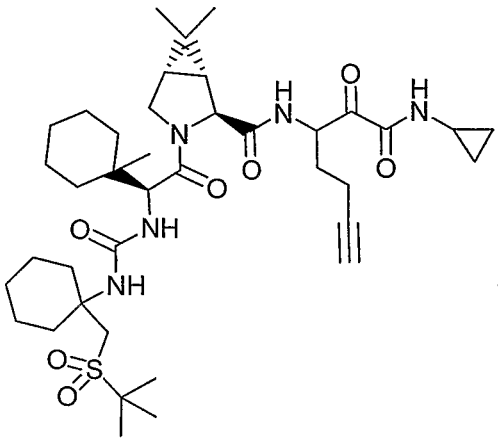


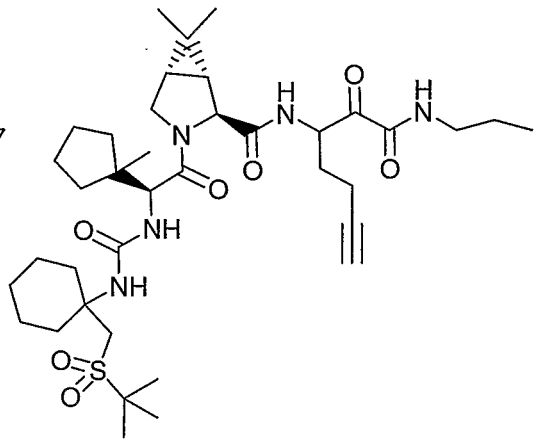


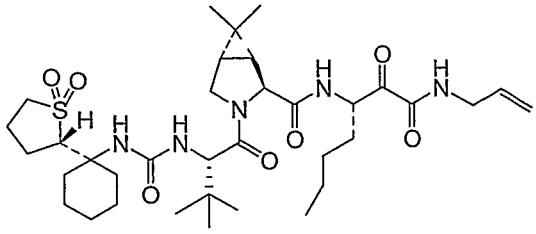


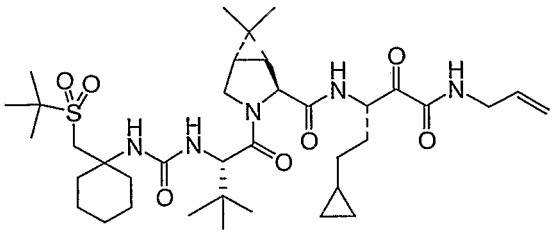


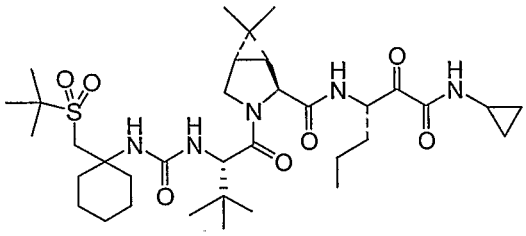


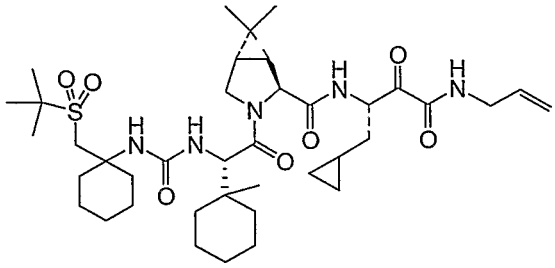


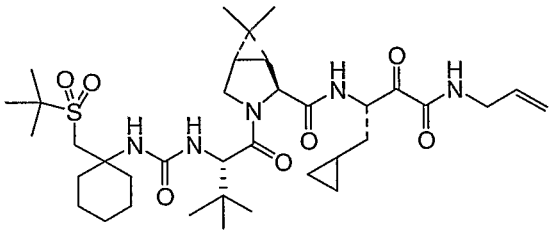


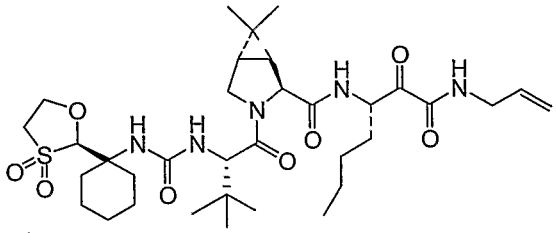


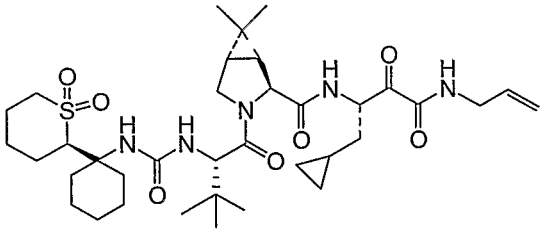


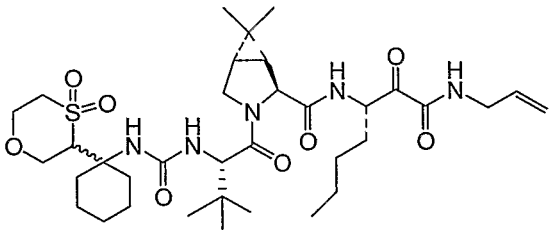


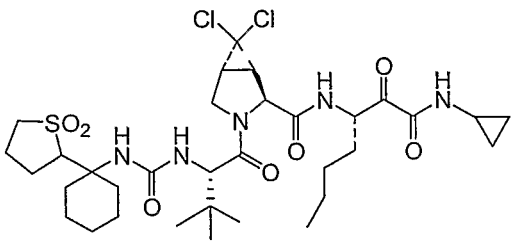


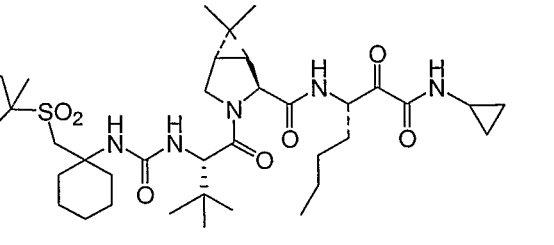




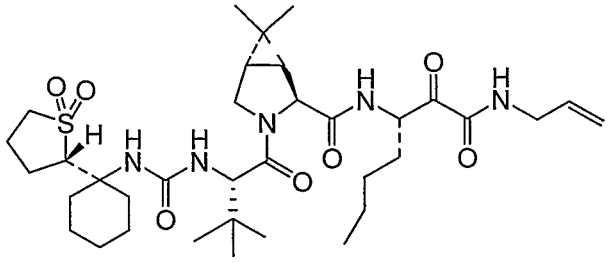




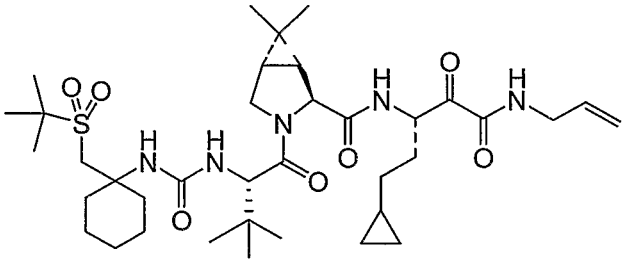




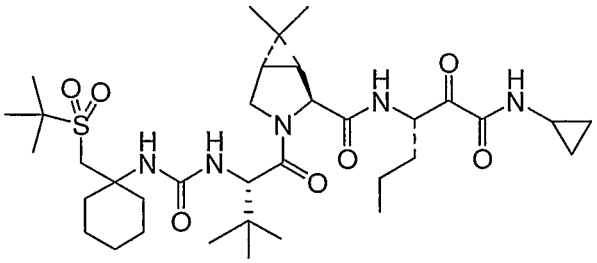
34. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, and racemates of said compound, or a pharmaceutically acceptable salt or solvate or ester of said compound, said compound having the structure:



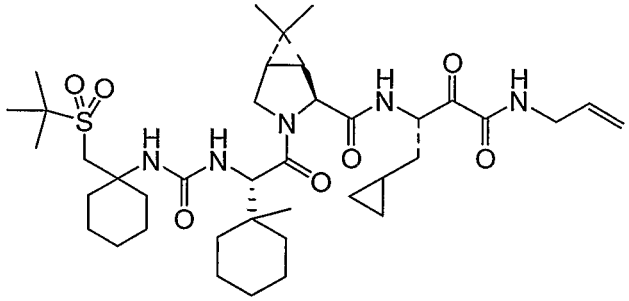
35. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, and racemates of said compound, or a pharmaceutically acceptable salt or solvate or ester of said compound, said compound having the structure:



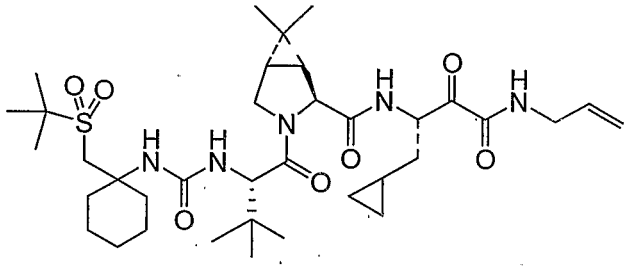
36. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, and racemates of said compound, or a pharmaceutically acceptable salt or solvate or ester of said compound, said compound having the structure:



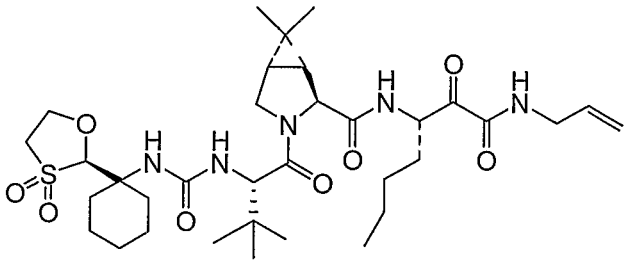
37. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, and racemates of said compound, or a pharmaceutically acceptable salt or solvate or ester of said compound, said compound having the structure:



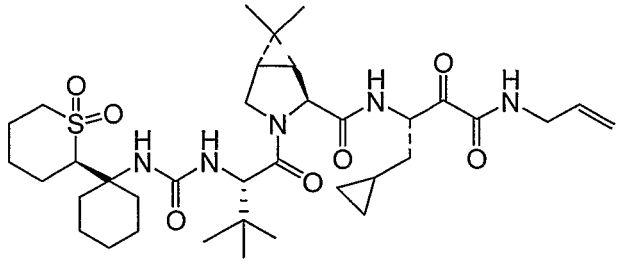
38. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, and racemates of said compound, or a pharmaceutically acceptable salt or solvate or ester of said compound, said compound having the structure:



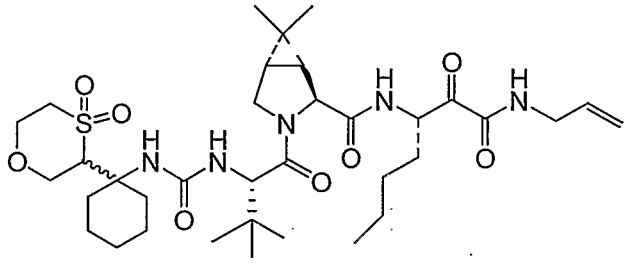
39. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, and racemates of said compound, or a pharmaceutically acceptable salt or solvate or ester of said compound, said compound having the structure:



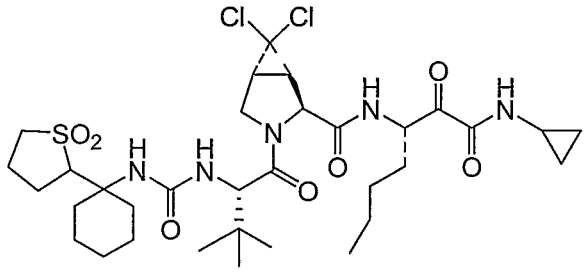
40. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, and racemates of said compound, or a pharmaceutically acceptable salt or solvate or ester of said compound, said compound having the structure:



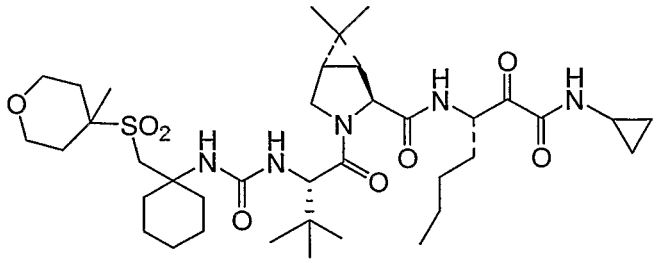
41. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, and racemates of said compound, or a pharmaceutically acceptable salt or solvate or ester of said compound, said compound having the structure:



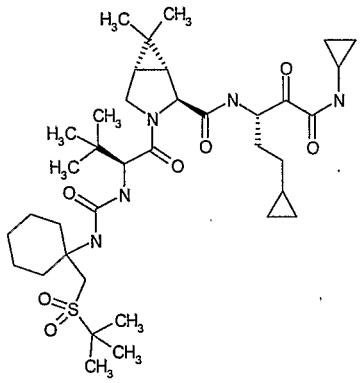
42. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, and racemates of said compound, or a pharmaceutically acceptable salt or solvate or ester of said compound, said compound having the structure:



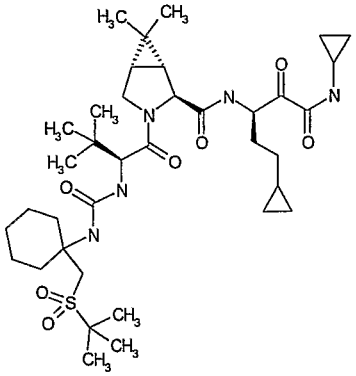
43. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, and racemates of said compound, or a pharmaceutically acceptable salt or solvate or ester of said compound, said compound having the structure:



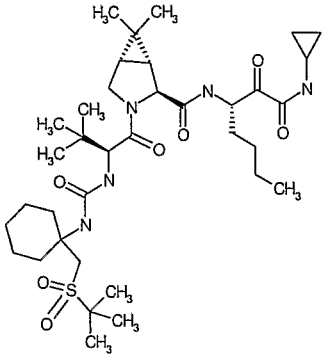
44. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, and racemates of said compound, or a pharmaceutically acceptable salt or solvate or ester of said compound, said compound having the structure:



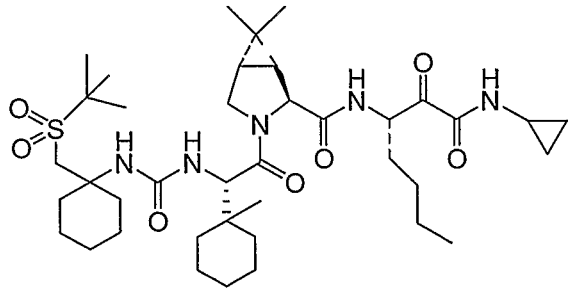
45. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, and racemates of said compound, or a pharmaceutically acceptable salt or solvate or ester of said compound, said compound having the structure:



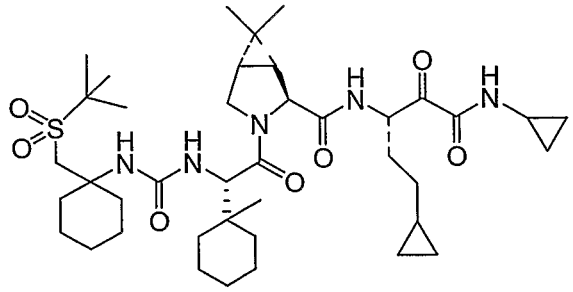
46. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, and racemates of said compound, or a pharmaceutically acceptable salt or solvate or ester of said compound, said compound having the structure:



47. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, and racemates of said compound, or a pharmaceutically acceptable salt or solvate or ester of said compound, said compound having the structure:



48. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, and racemates of said compound, or a pharmaceutically acceptable salt or solvate or ester of said compound, said compound having the structure:



49. A compound of claim 1 in purified form.