

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 patent application Serial Number 60/548,251 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.

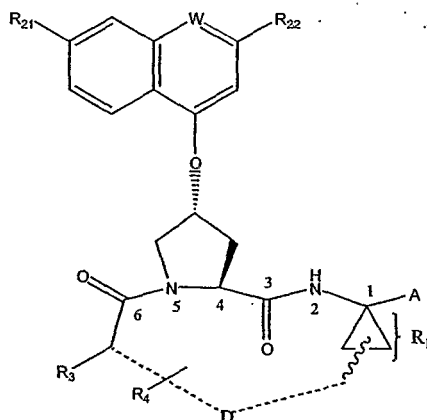
Inhibitors of HCV protease that have been reported include antioxidants (see, International Patent Application Publication No. WO 98/14181), certain peptides and peptide analogs (see, International Patent Application Publication No. WO 98/17679, Landro *et al.* (1997) Biochem. 36:9340-9348, Ingallinella *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)).

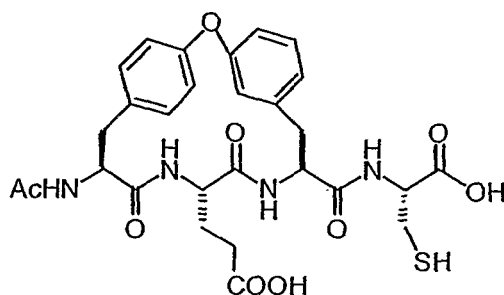
Reference is also made to the PCT Publications, No. WO 98/17679, published April 30, 1998 (Vertex Pharmaceuticals Incorporated); WO 98/22496, published May 28, 1998 (F. Hoffmann-La Roche AG); and WO 99/07734, published February 18, 1999 (Boehringer Ingelheim Canada Ltd.).

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:

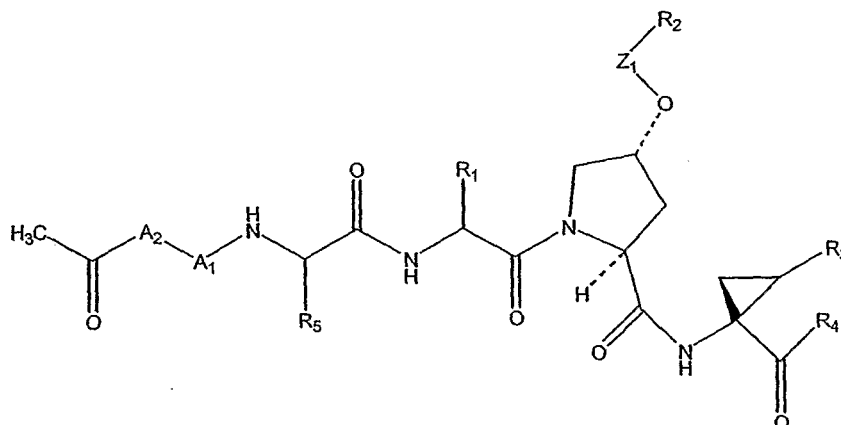


Reference is made to A. Marchetti *et al*, *Synlett*, S1, 1000-1002 (1999) describing the synthesis of bicyclic analogs of an inhibitor of HCV NS3 protease. A compound disclosed therein has the formula:

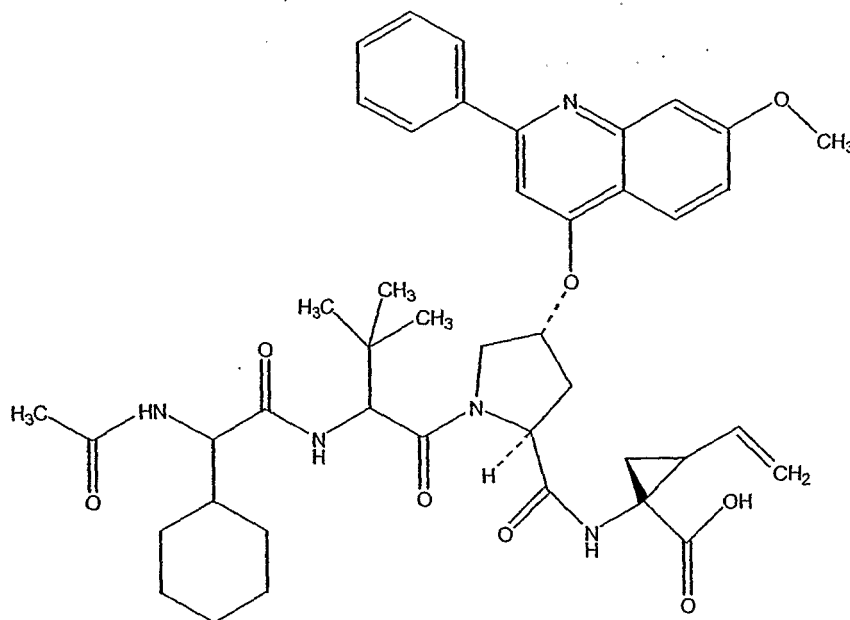


Reference is also made to W. Han *et al*, *Bioorganic & Medicinal Chem. Lett.* (2000) 10, 711-713, which describes the preparation of certain α -ketoamides, α -ketoesters and α -diketones containing allyl and ethyl functionalities.

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

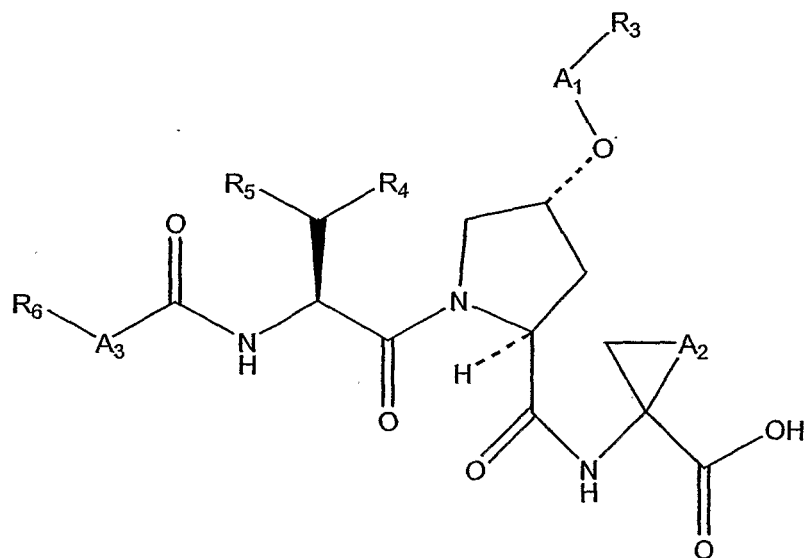


where the various elements are defined therein. An illustrative compound of that series is:

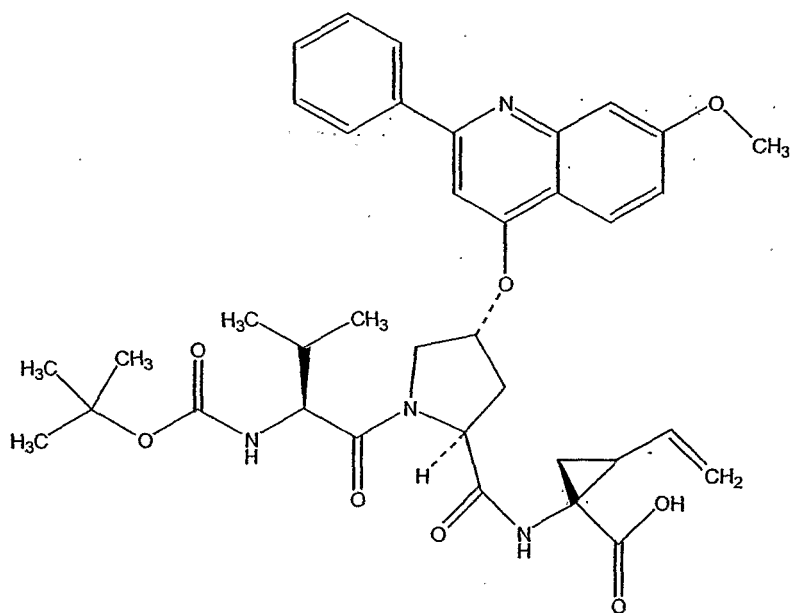


Reference is also made to WO 00/09543 (Assignee: Boehringer Ingelheim Limited; Published February 24, 2000) which discloses peptide derivatives of the formula:

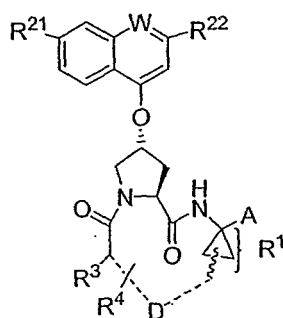
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where the various elements are defined therein. An illustrative compound of that series is:



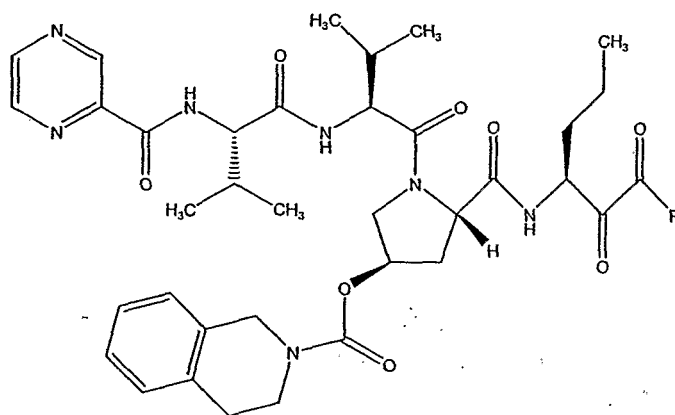
5 Reference is also made to U.S. 6,608,027 (Boehringer Ingelheim, Canada)
which discloses NS3 protease inhibitors of the type:



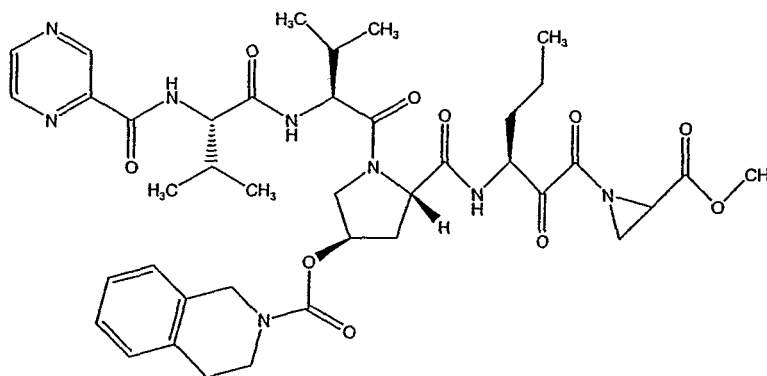
wherein the various moieties are defined therein.

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.

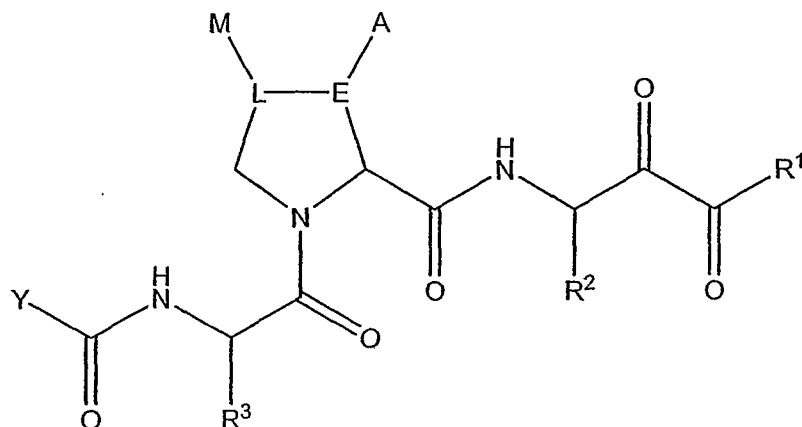
There is a need for methods of treatment or prevention or amelioration of one or more symptoms of hepatitis C.

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, or enantiomers, stereoisomers, rotamers, tautomers, diastereomers and racemates of said compounds, or a pharmaceutically acceptable salt, solvate or ester of said compounds, said compounds having the general structure having the general structure shown in structural Formula 1:

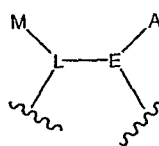


Formula I

wherein:

R^1 is H, OR^8 , NR^9R^{10} , or CHR^9R^{10} , wherein R^8 , R^9 and R^{10} can be the same or different, each being independently selected from the group consisting of H, alkyl-,
 5 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:



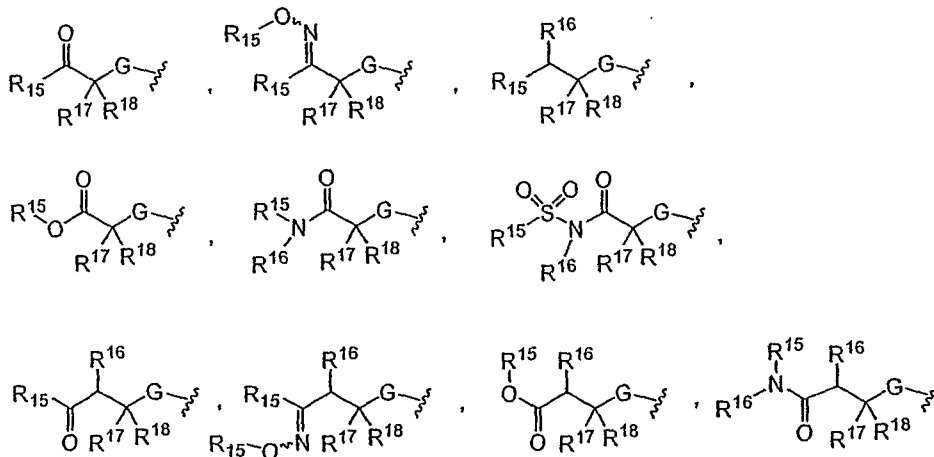
shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl;

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
 20 each other such that NRR' forms a four to eight-membered heterocyclyl;

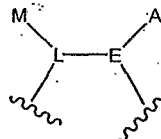
and Y is selected from the following moieties:



wherein G is NH or O; and R¹⁵, R¹⁶, R¹⁷ and R¹⁸ 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, R¹⁵ and R¹⁶ are connected to each other to form a four to eight-membered cycloalkyl, heteroaryl or heterocyclyl structure, and likewise, independently R¹⁷ and R¹⁸ are connected to each other to form a three to eight-membered cycloalkyl or heterocyclyl;

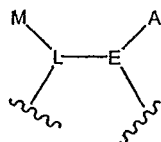
wherein each of said alkyl, aryl, heteroaryl, cycloalkyl or heterocyclyl can be unsubstituted or optionally independently substituted with one or more moieties selected from the group consisting of: hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, amido, alkylamino, arylamino, alkylsulfonyl,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

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



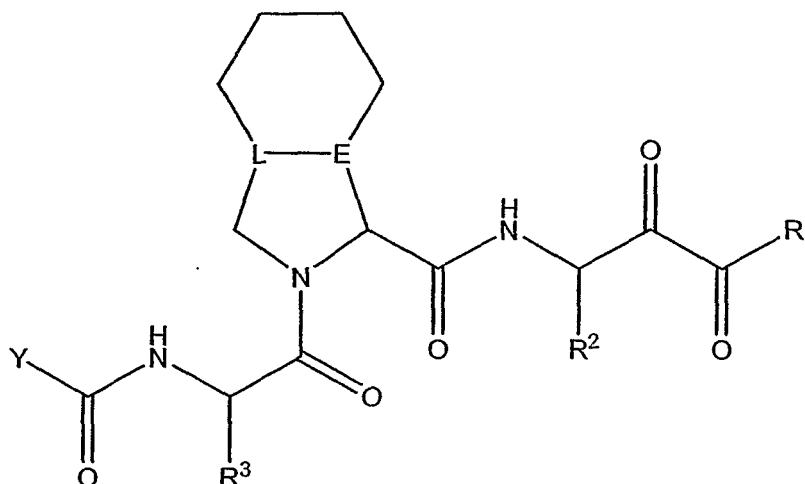
shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl" can be illustrated in a non-limiting matter as follows.

Thus, for example, in the case where A and M are connected such that the moiety:

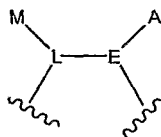


shown above in Formula I forms a six -membered cycloalkyl (cyclohexyl), Formula I can be depicted as:

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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:



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

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

The compounds represented by Formula I, by themselves or in combination with one or more other suitable agents disclosed herein, can be useful for treating diseases such as, for example, HCV, HIV, AIDS (Acquired Immune Deficiency

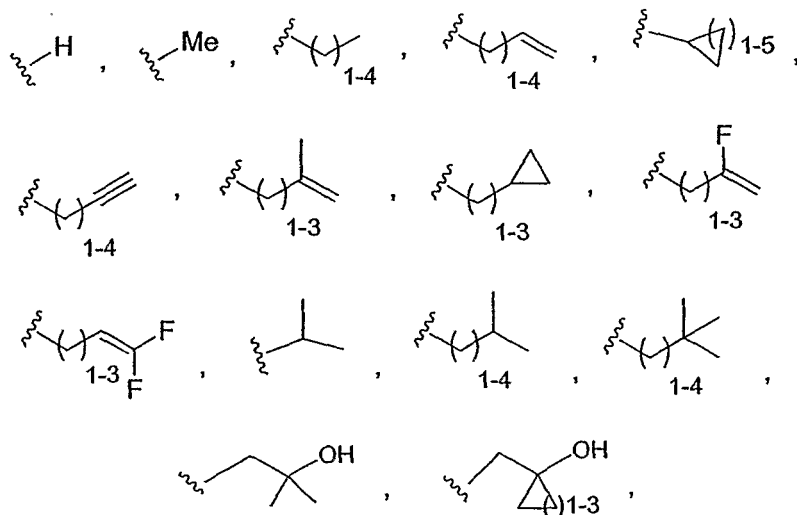
Syndrome), and related disorders, as well as for modulating the activity of hepatitis C virus (HCV) protease, preventing HCV, or ameliorating one or more symptoms of hepatitis C. Such modulation, treatment, prevention or amelioration can be done with the inventive compounds as well as with pharmaceutical compositions or formulations comprising such compounds. Without being limited to theory, it is believed that the HCV protease may be the NS3 or NS4a protease. The inventive compounds can inhibit such protease. They can also modulate the processing of hepatitis C virus (HCV) polypeptide.

Detailed Description

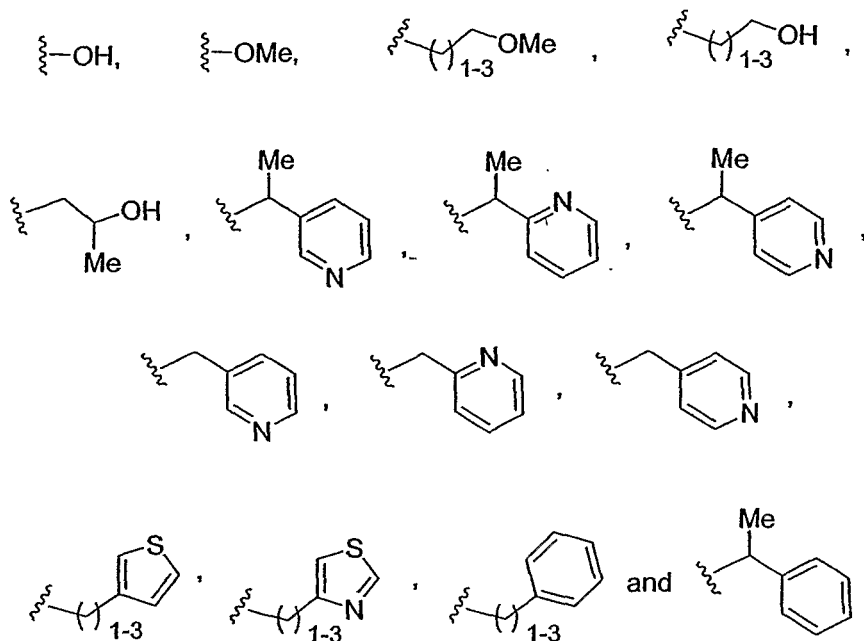
In an embodiment, the present invention discloses compounds which are represented by structural Formula 1 or a pharmaceutically acceptable salt, solvate or ester thereof, wherein the various moieties are as defined above.

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

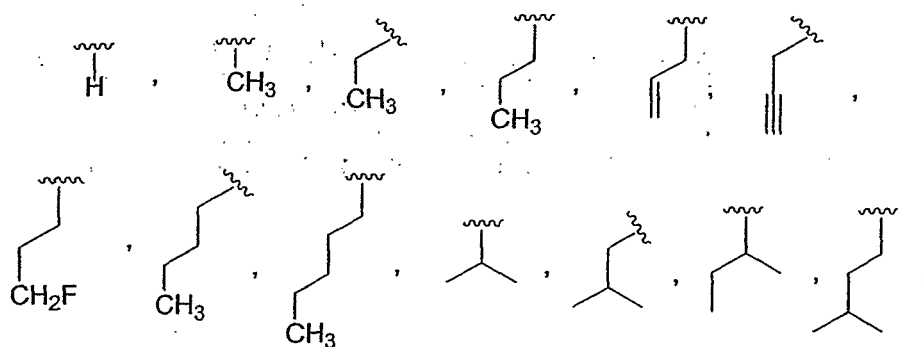
In another embodiment, R^{14} is selected from the group consisting of:



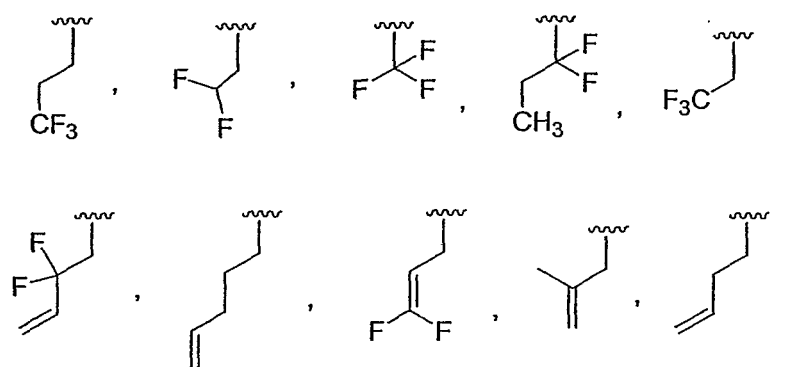
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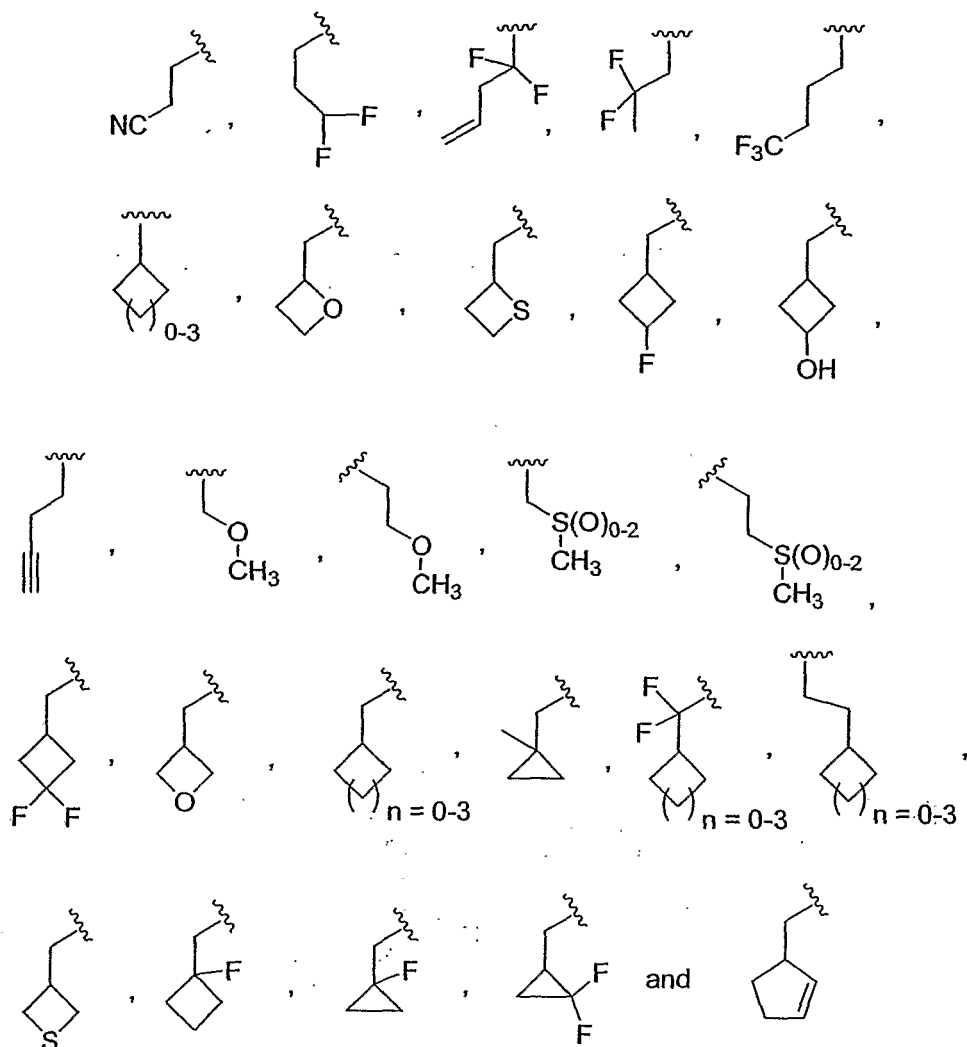
In another embodiment, R^2 is selected from the group consisting of the following moieties:



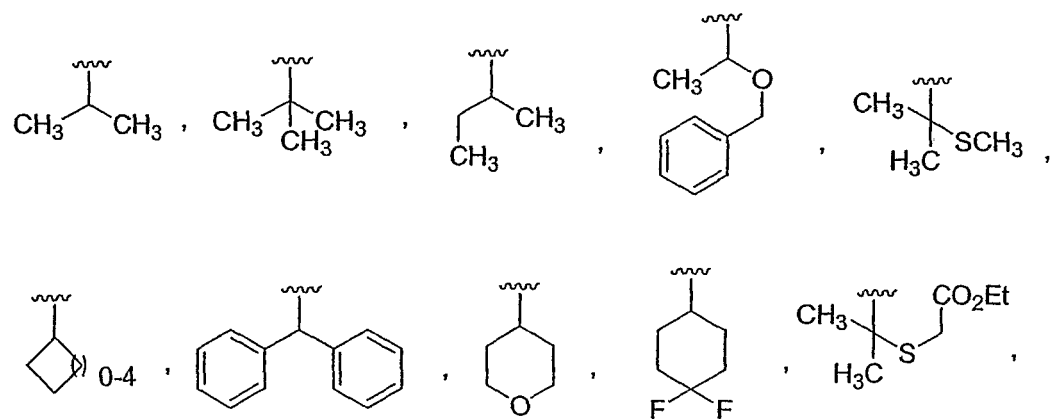
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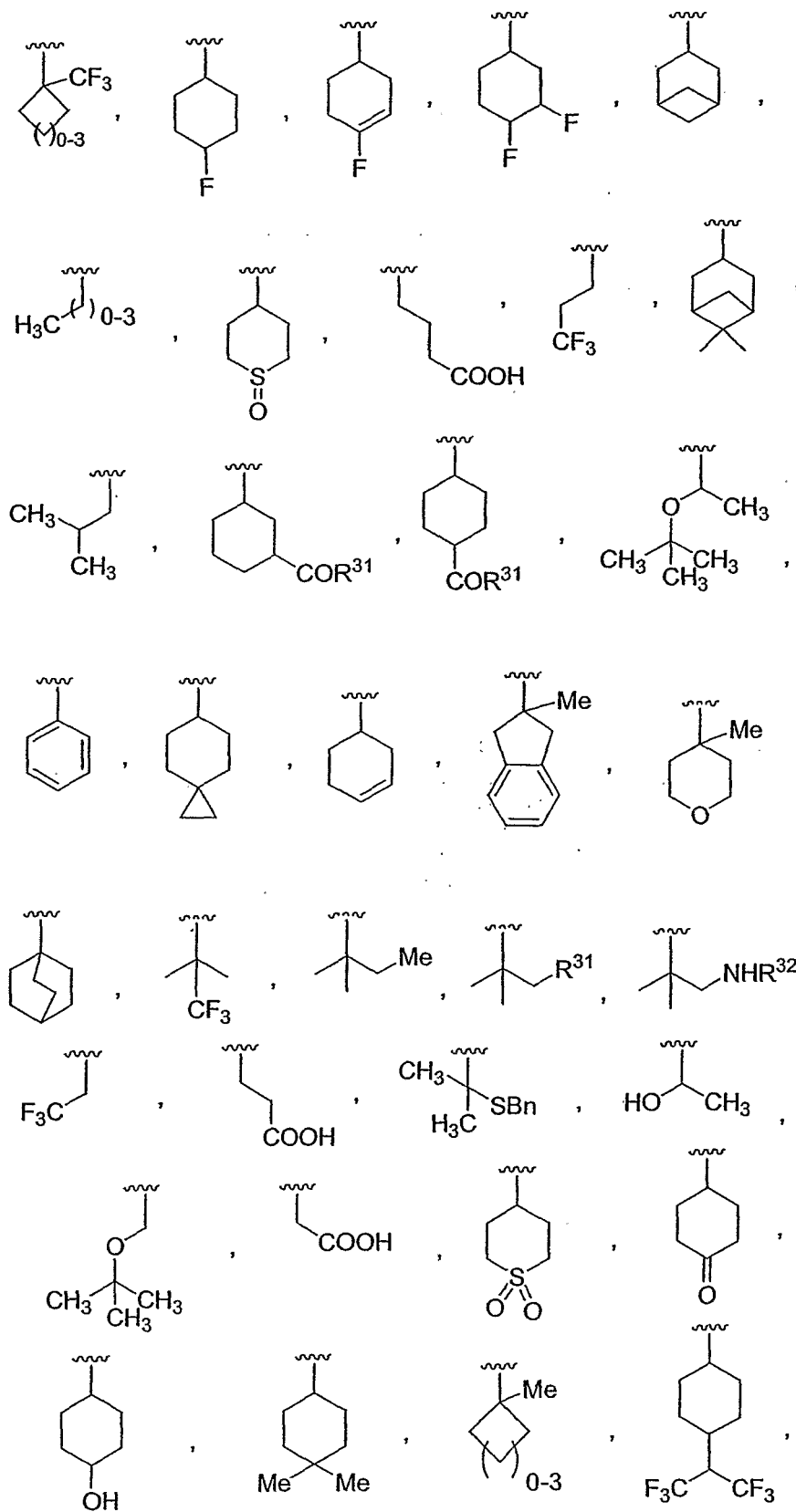
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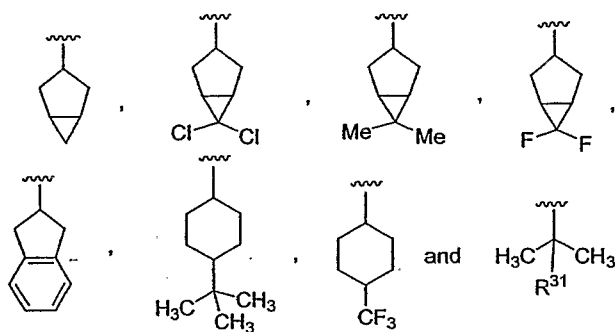
In another embodiment, R^3 is selected from the group consisting of:



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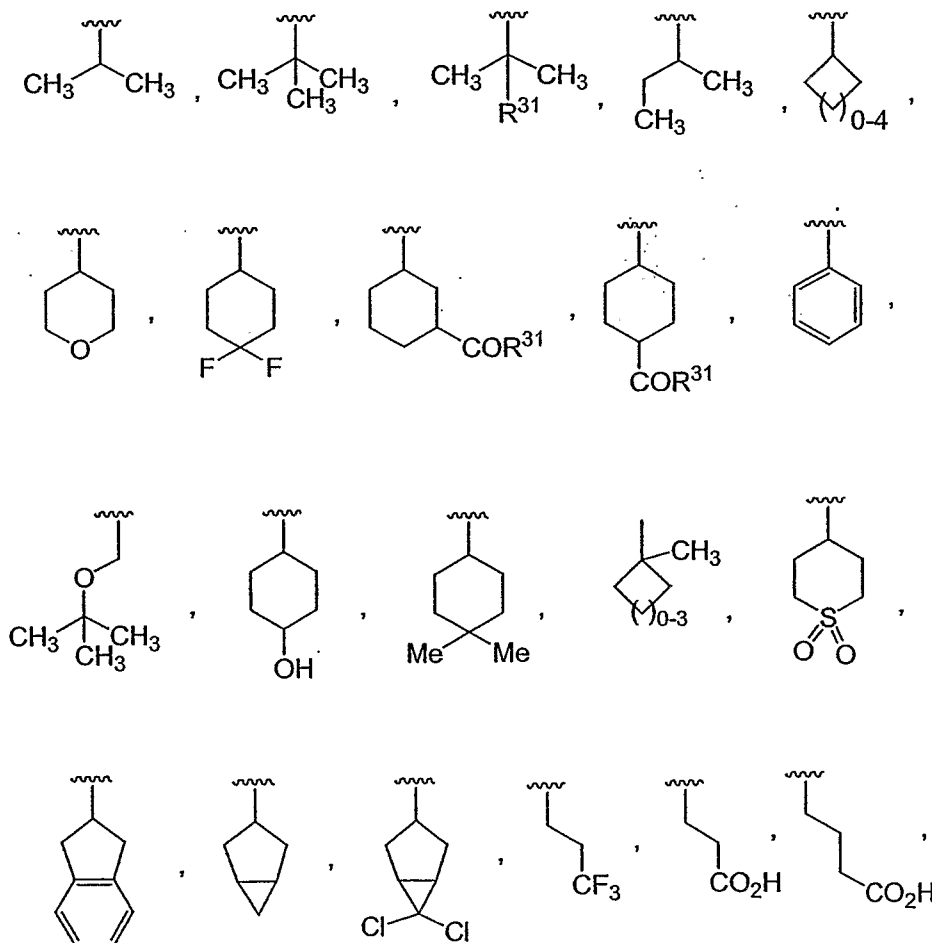
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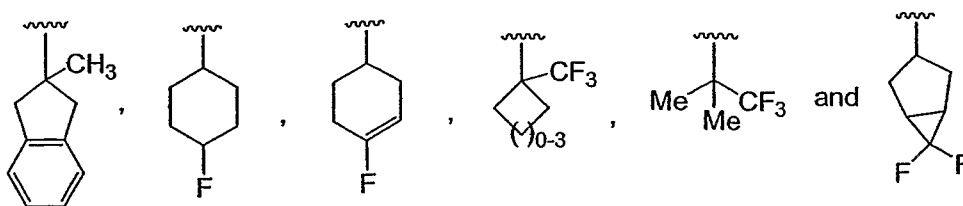
wherein R^{31} is OH or O-alkyl; and

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

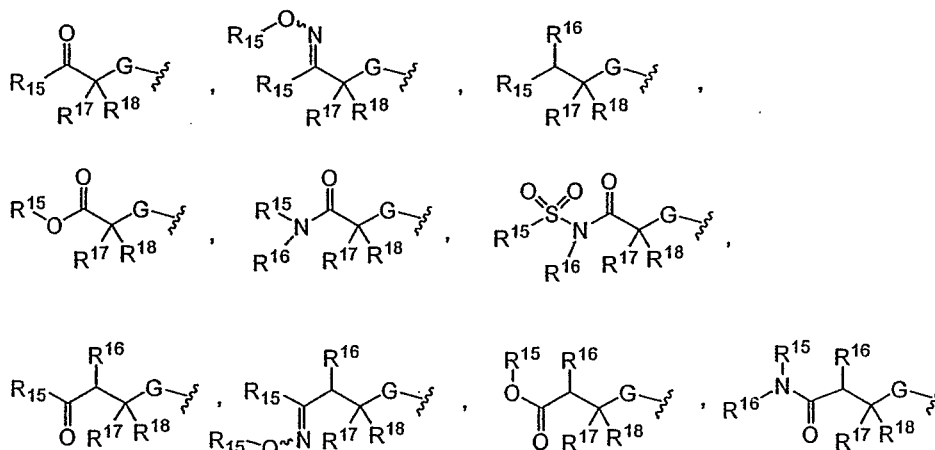
- 5 In an additional embodiment, R^3 is selected from the group consisting of the following moieties:



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



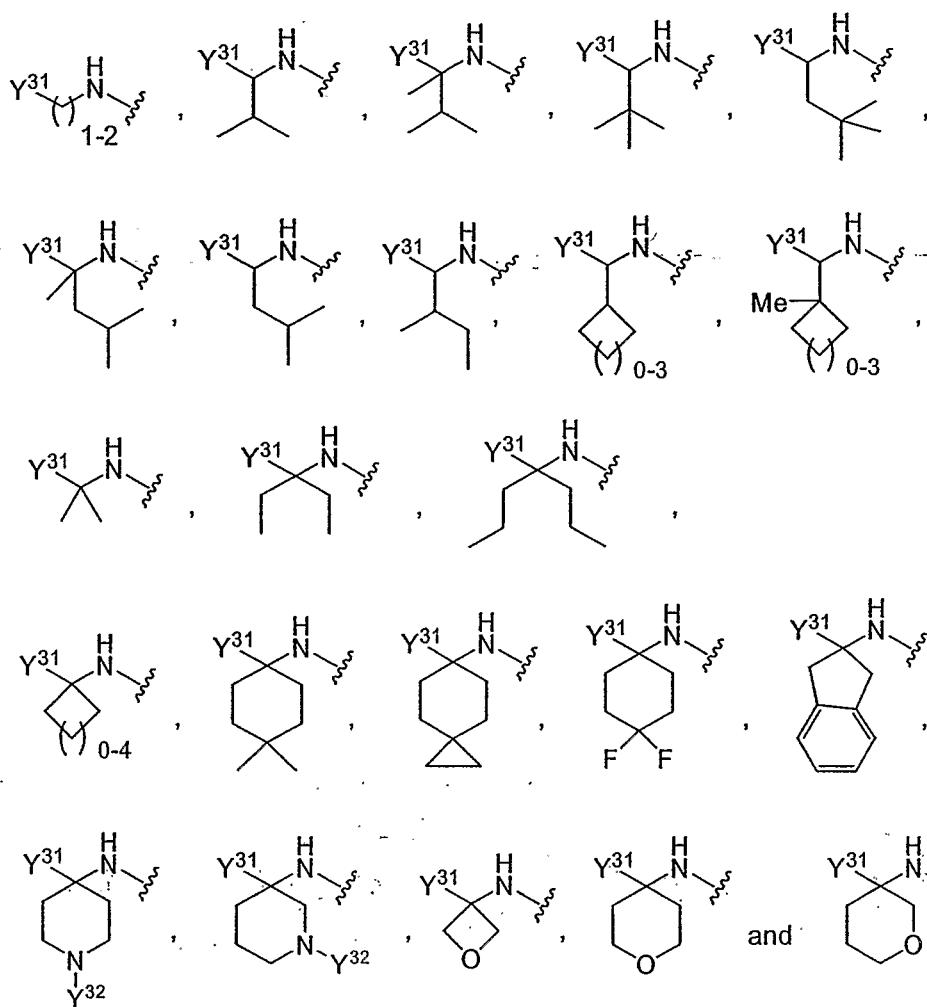
wherein G is NH or O; and R^{15} , R^{16} , R^{17} and R^{18} can be the same or different, each
 5 being independently selected from the group consisting of H, alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, or alternately, R^{15} and R^{16} are connected to each other to form a four to eight-membered cycloalkyl, heteroaryl or heterocyclyl structure, and likewise, independently R^{17} and R^{18} are connected to each other to form a three
 10 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, alkyl,
 15 aryl, heteroaryl, alkylsulfonamido, arylsulfonamido, keto, carboxy, carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyloxy, alkylureido, arylureido, halo, cyano, and nitro.

In an additional embodiment, G is NH.

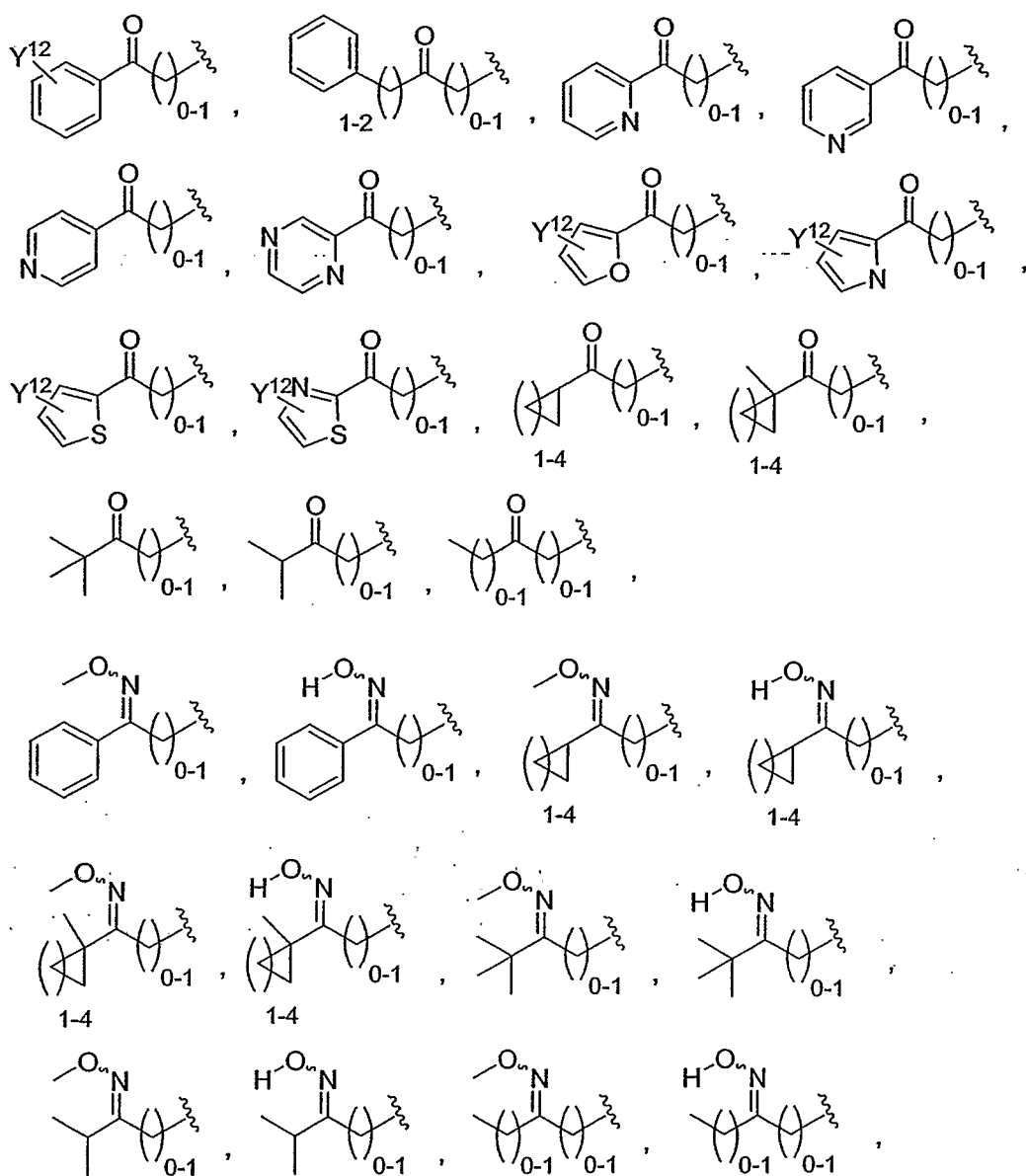
In an additional embodiment, Y is selected from the group consisting of:

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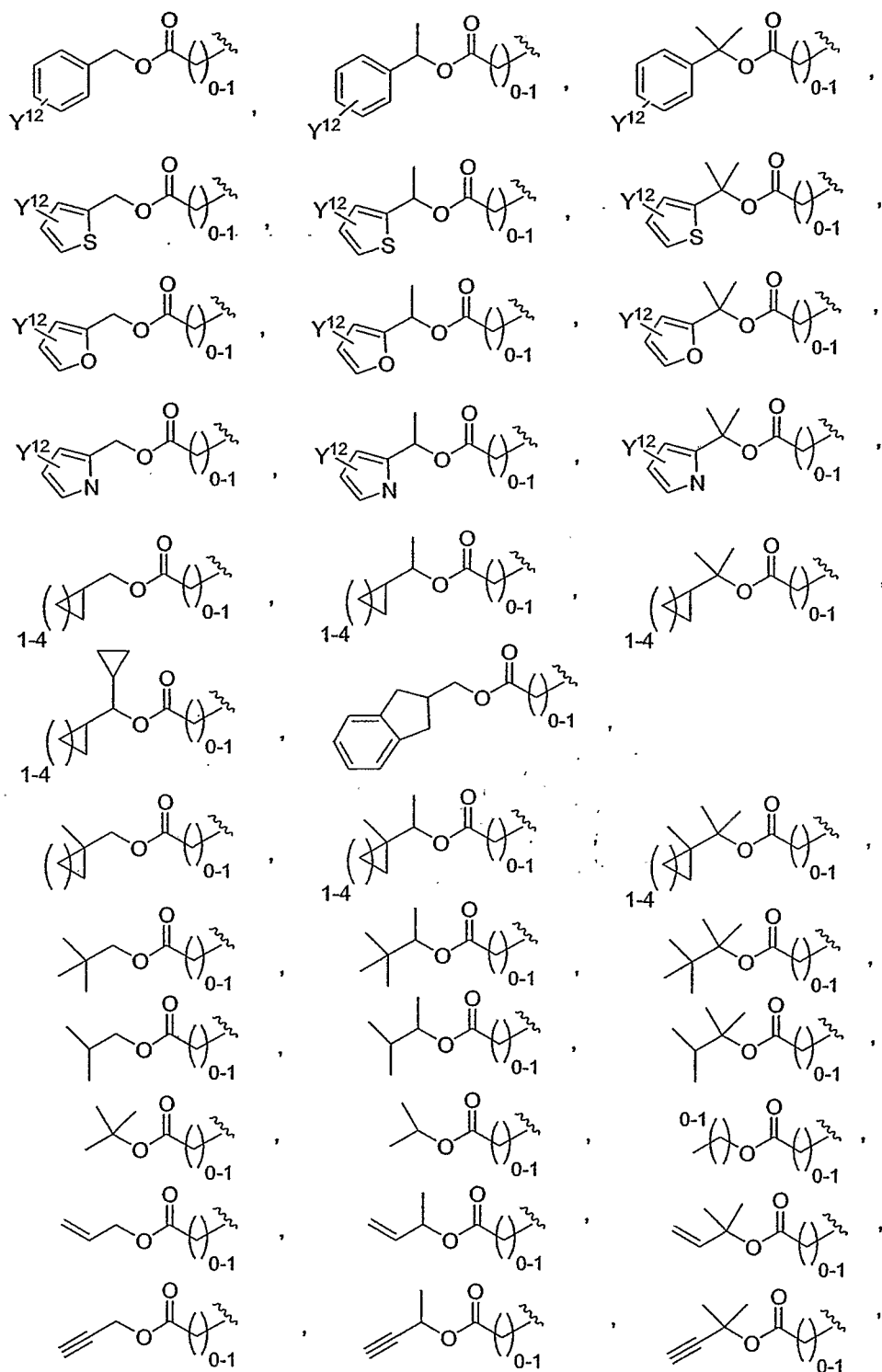


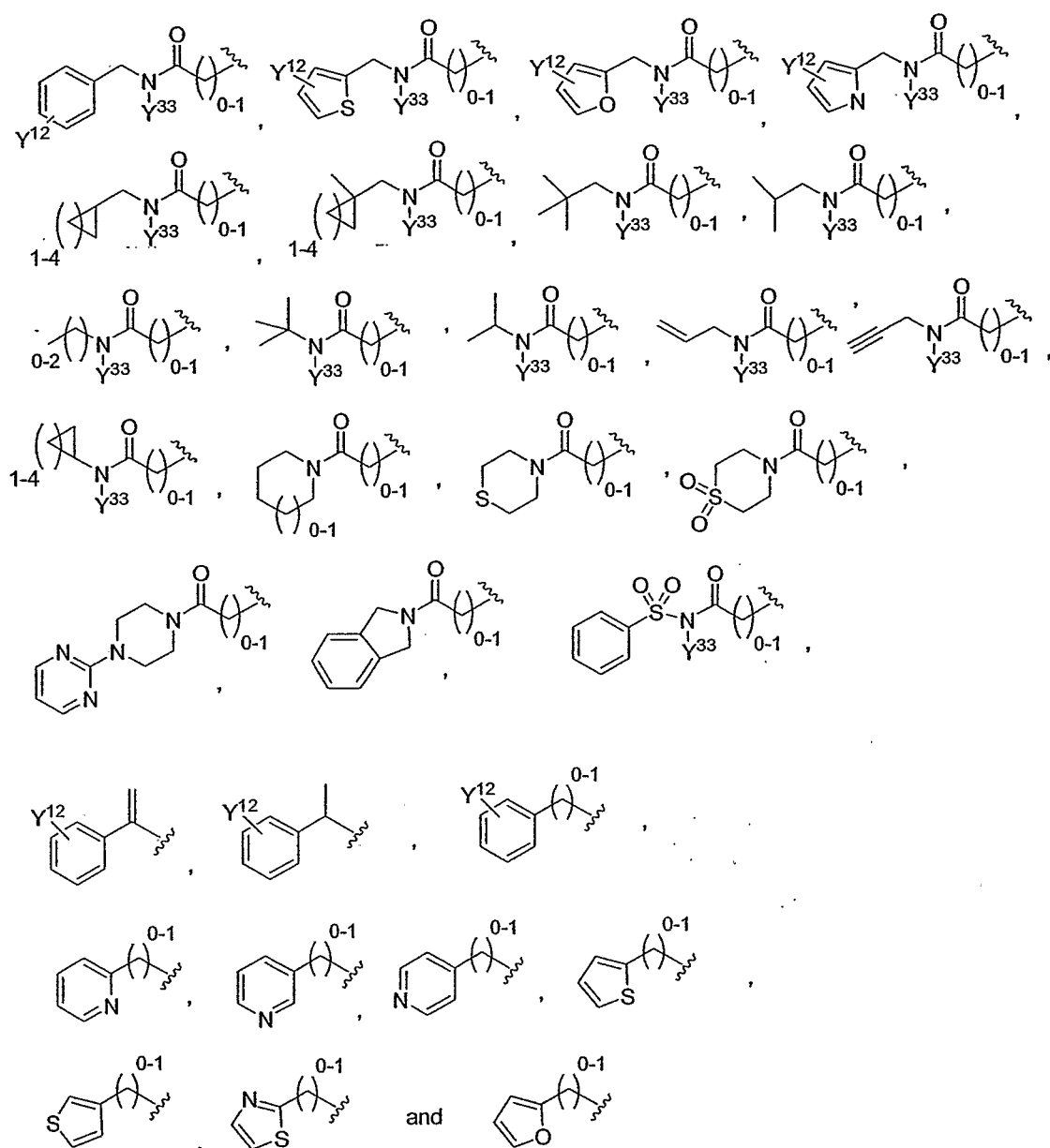
wherein Y^{31} is selected from the group consisting of:

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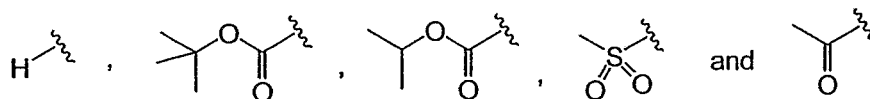


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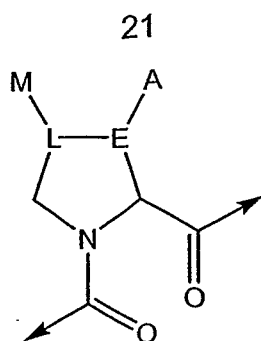
Y^{32} is selected from the group consisting of:



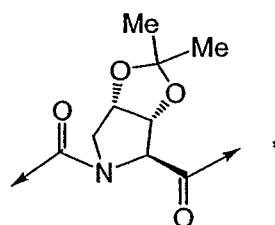
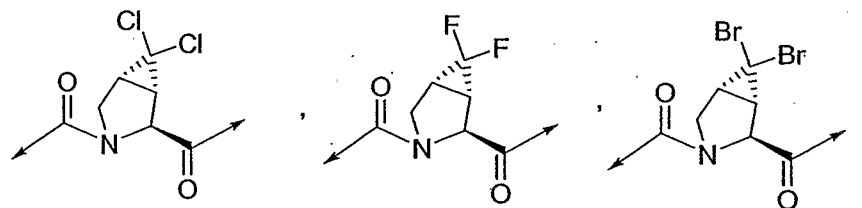
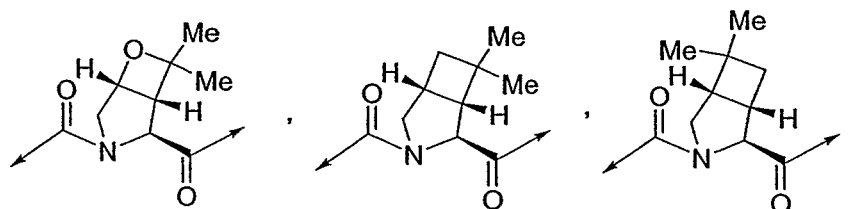
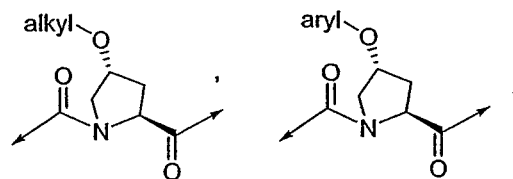
and Y^{12} is selected from the group consisting of H, CO_2H , CO_2Me , OMe, F, Cl, Br, NH_2 , $N(H)S(O_2)CH_3$, $N(H)C(O)CH_3$, NO_2 , NMe_2 , $S(O_2)NH_2$, CF_3 , Me, OH, OCF_3 , and $C(O)NH_2$ and Y^{33} is selected from the group consisting of:



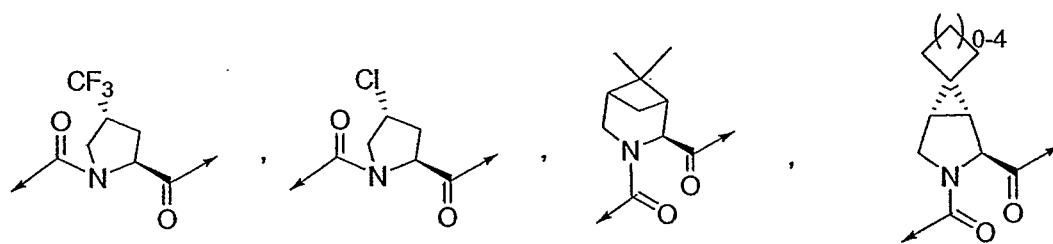
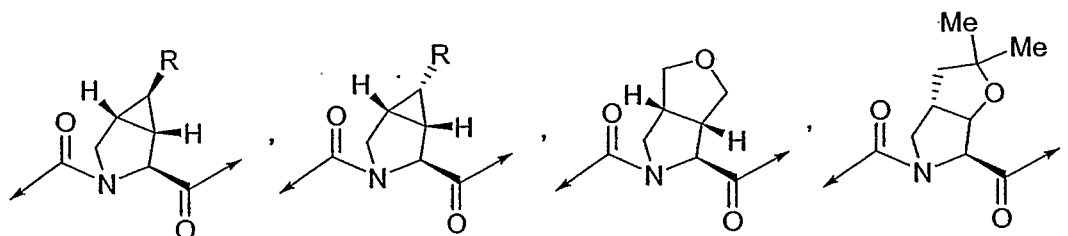
In another embodiment, the moiety:



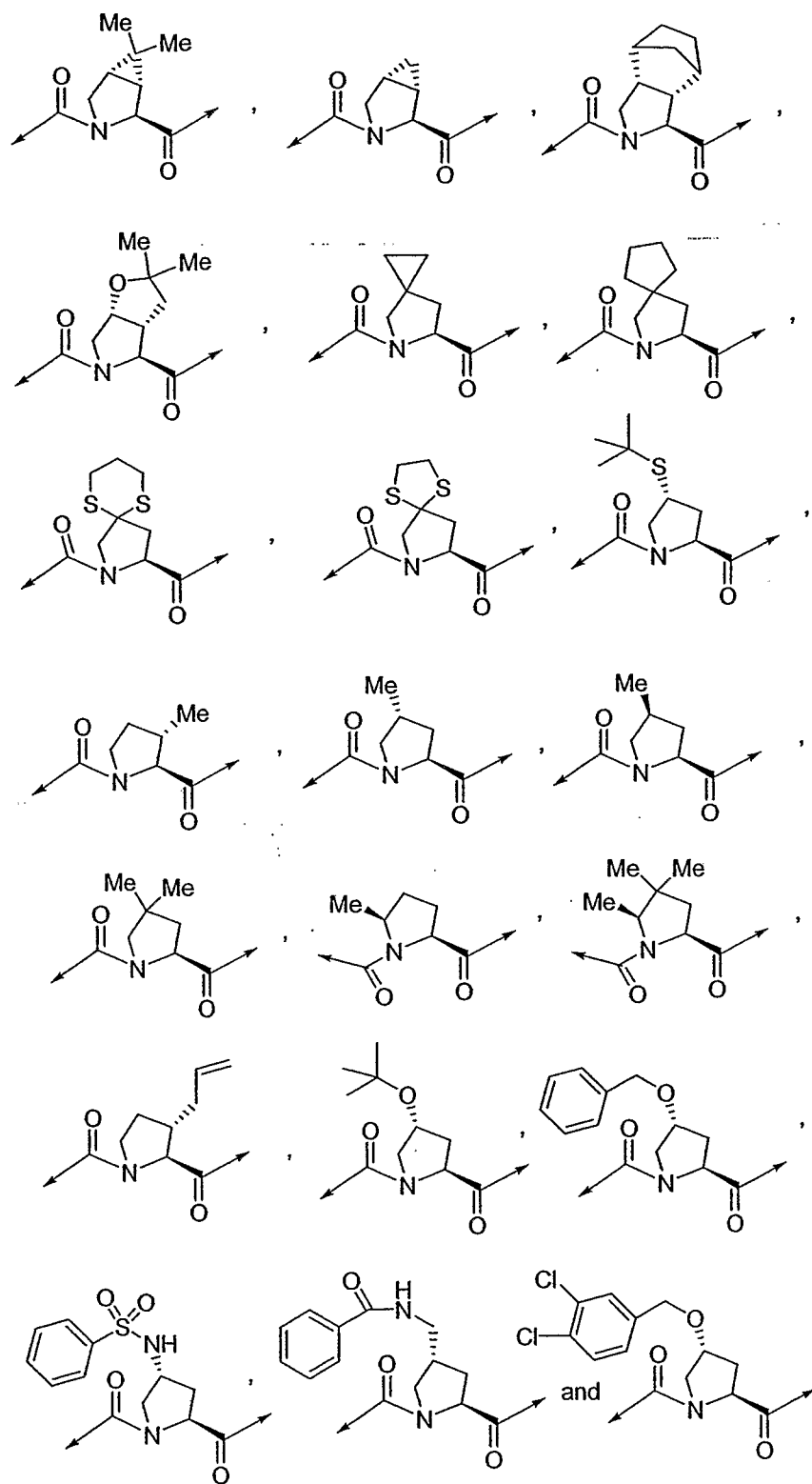
is selected from the following structures:



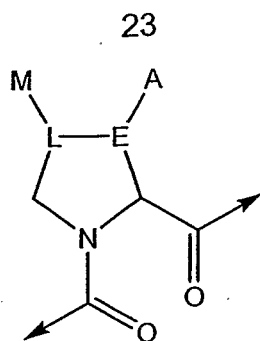
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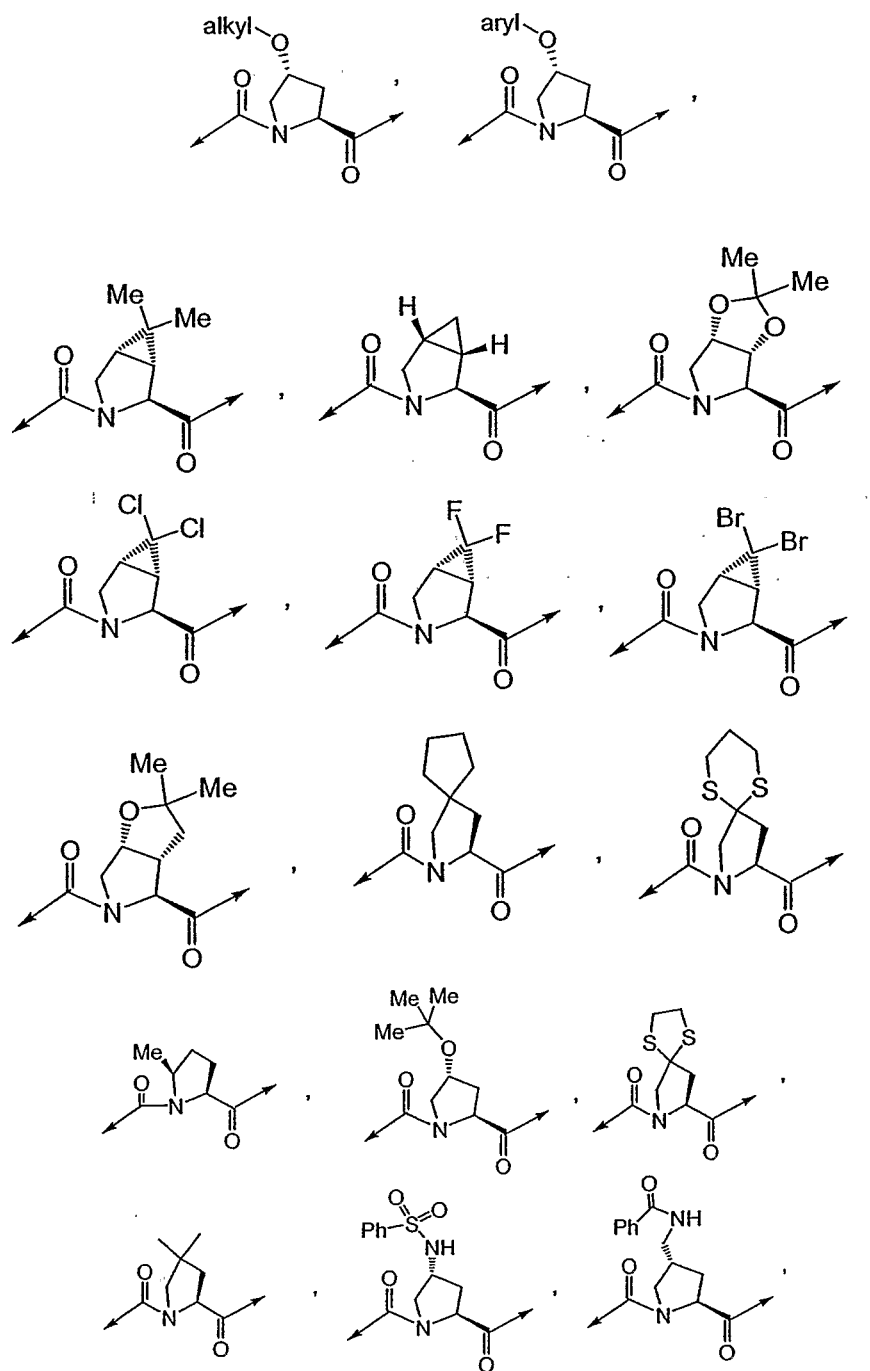
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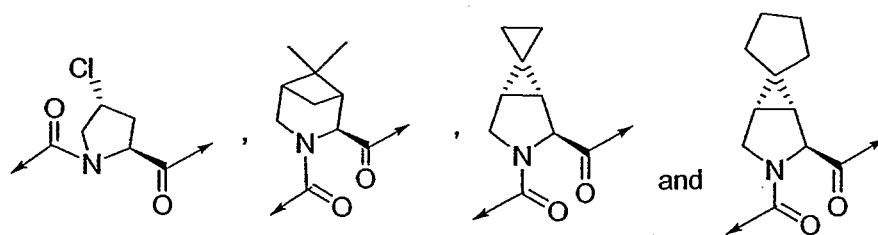
In an additional embodiment, the moiety:



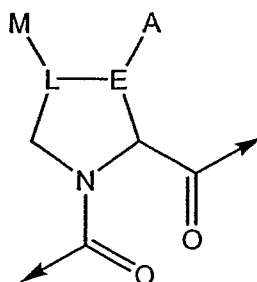
is selected from the following structures:



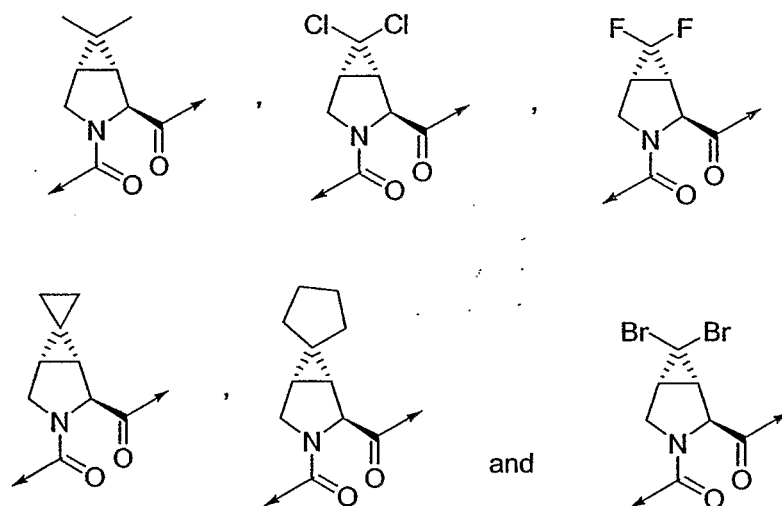
24



In a still additional embodiment, the moiety:

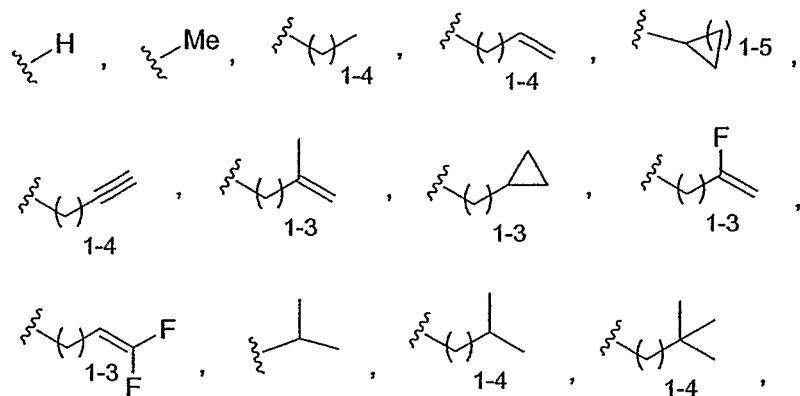


is selected from the following structures:

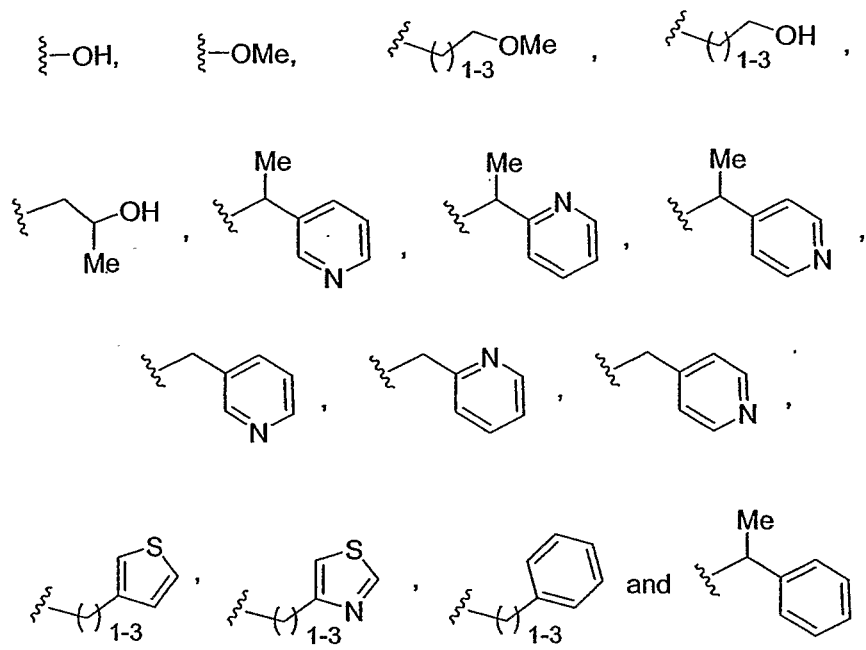


5

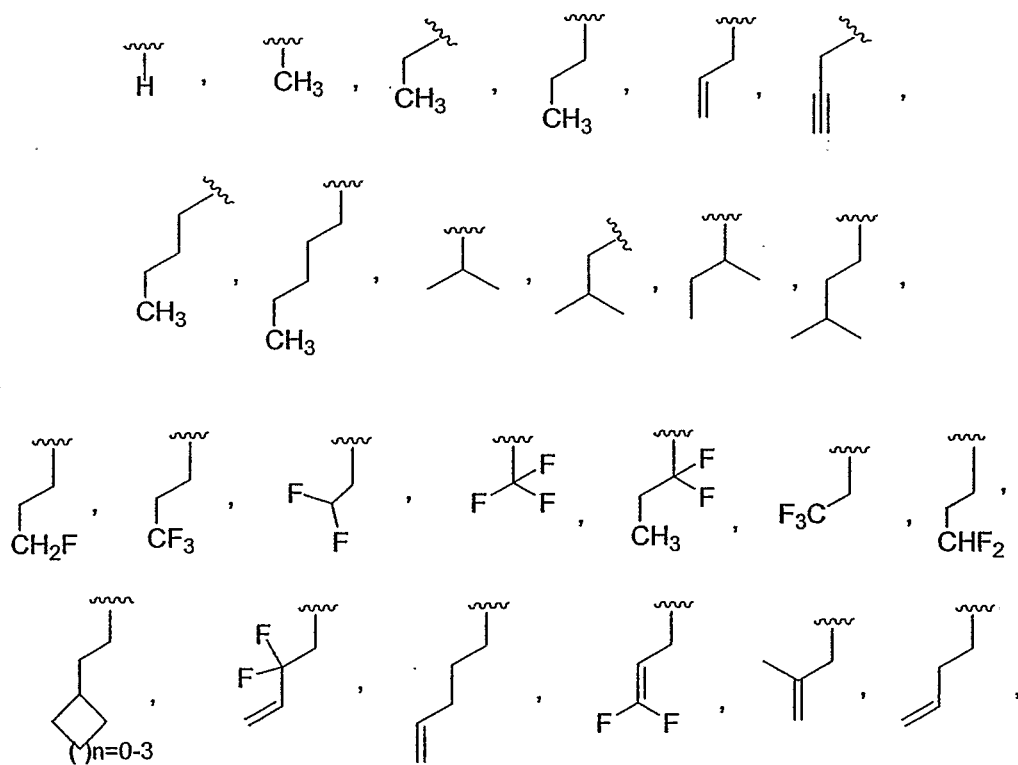
In a further additional embodiment, R^1 is NHR^{14} , where R^{14} is selected from the group consisting of:



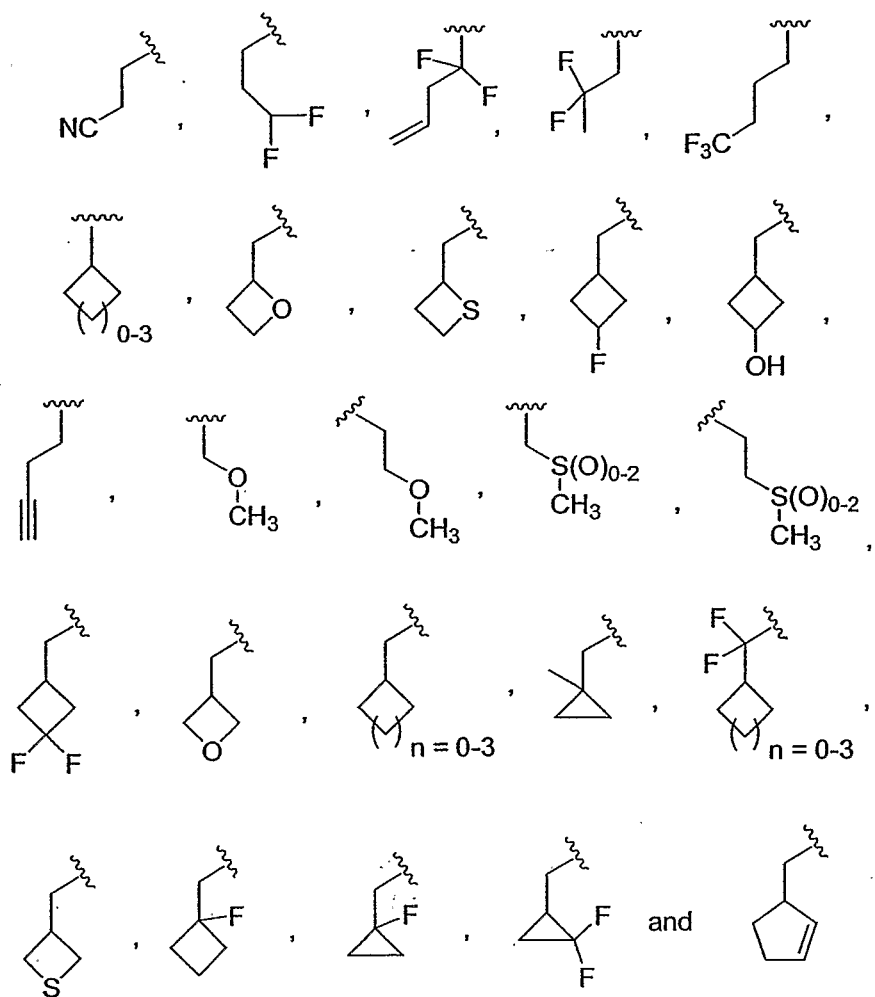
25



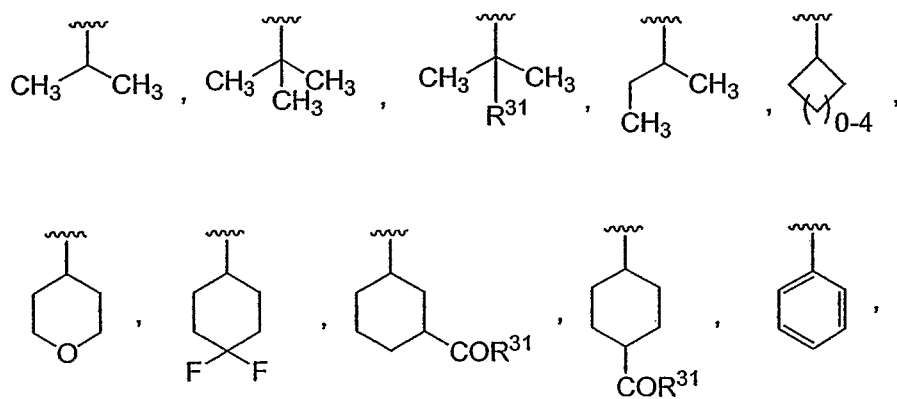
R^2 is selected from the group consisting of the following moieties:



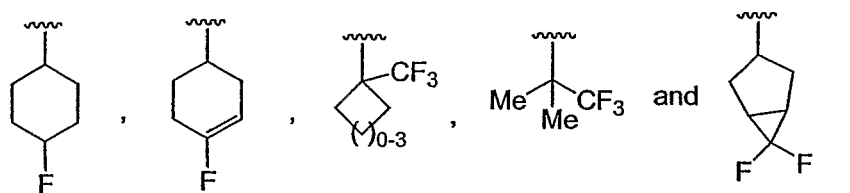
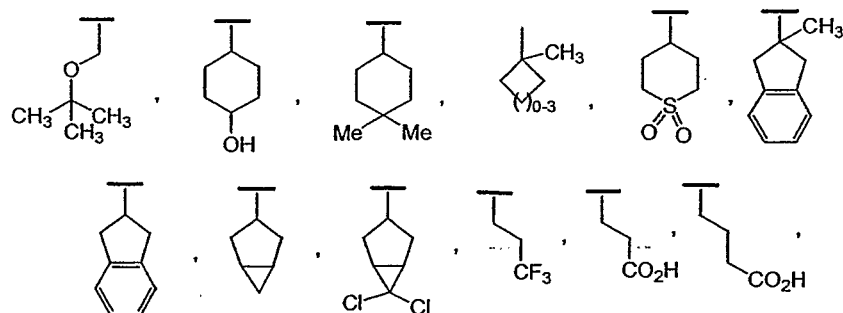
26



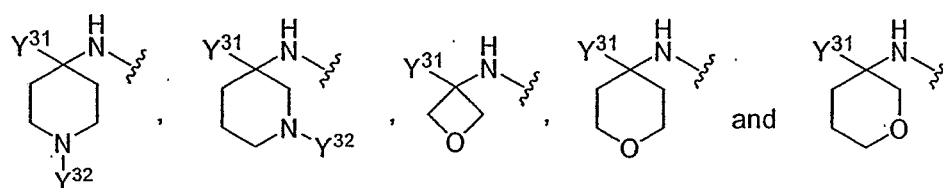
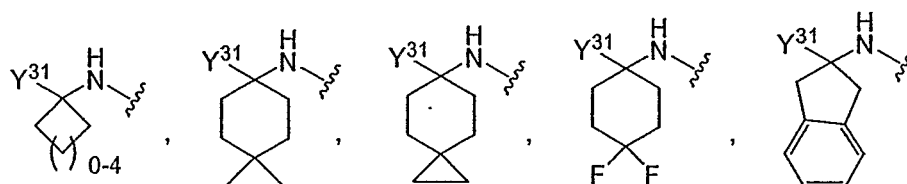
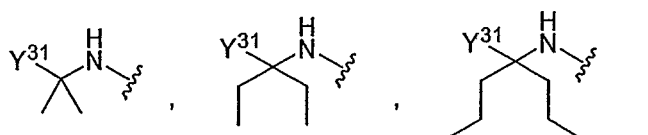
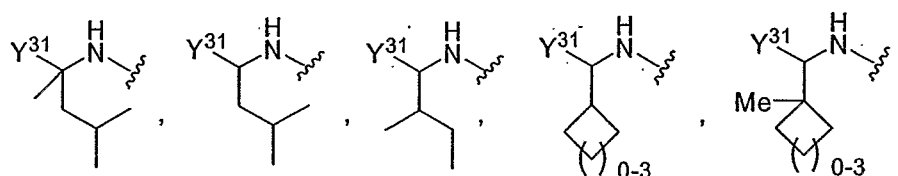
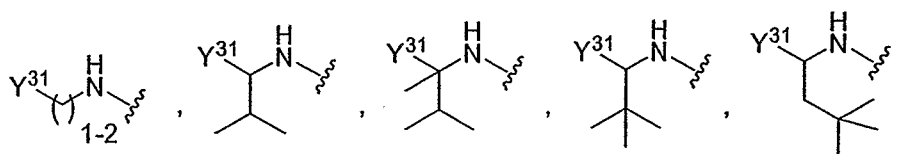
R^3 is selected from the group consisting of the following moieties:



27

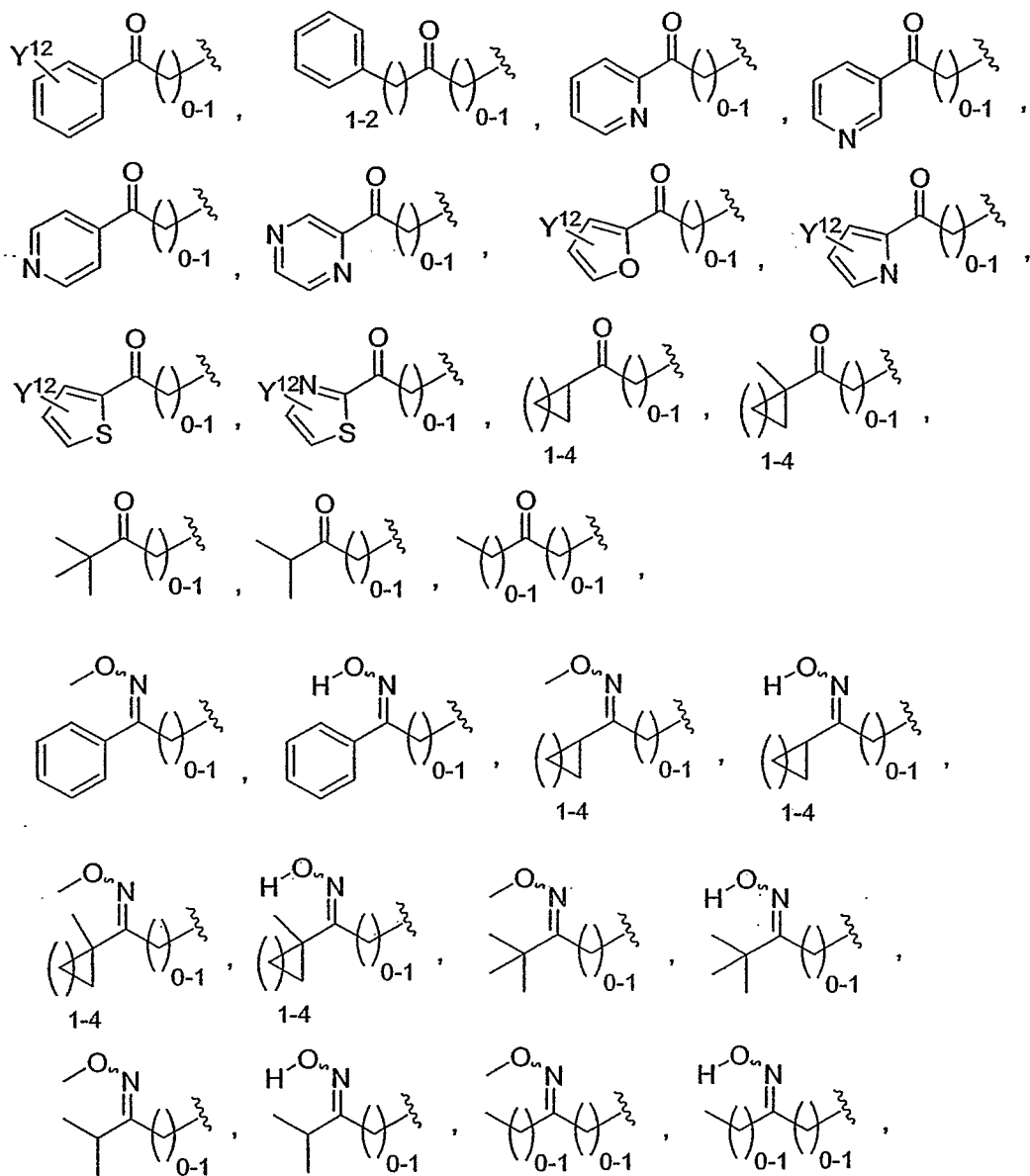


Y is selected from the group consisting of:

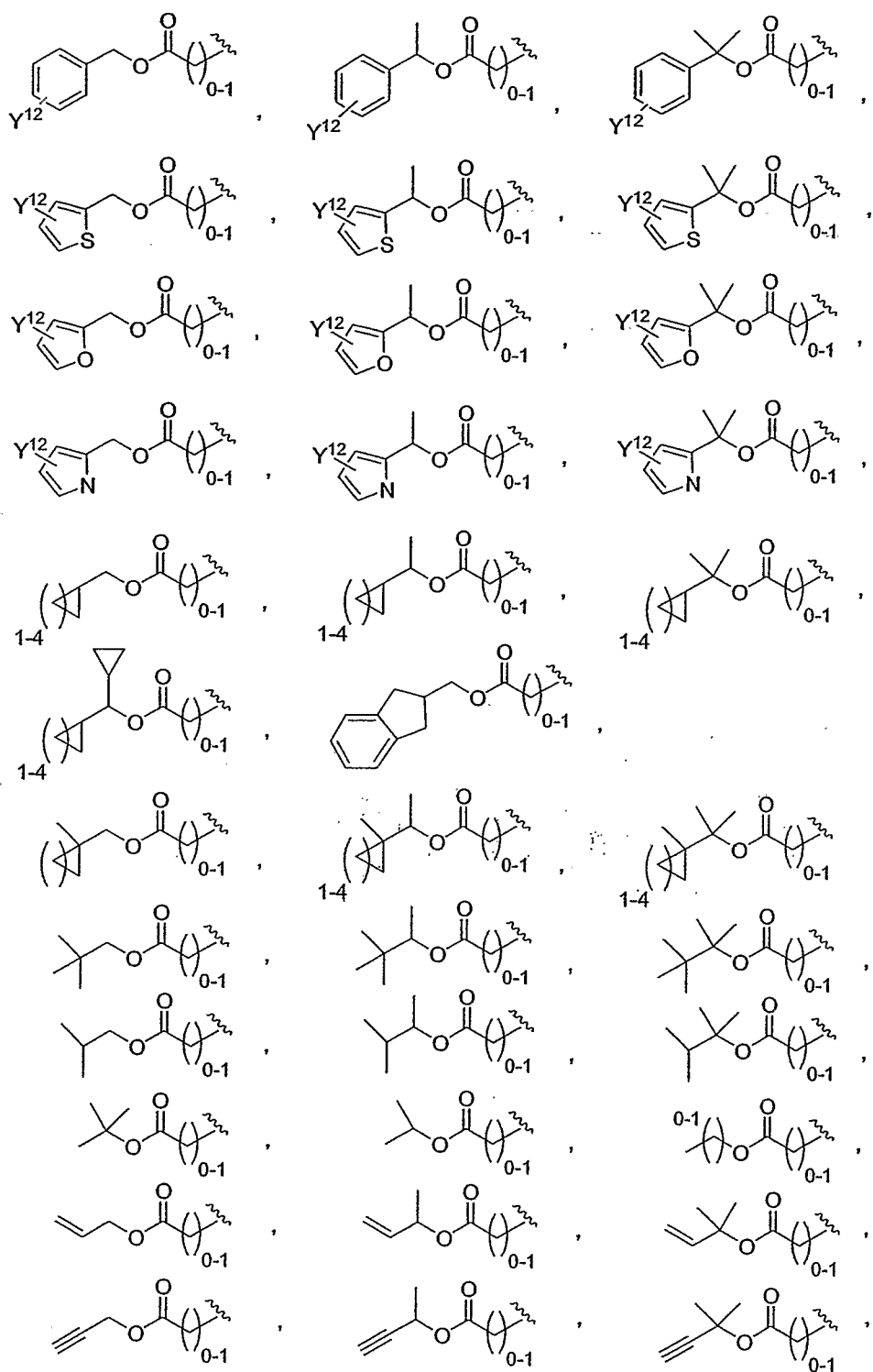


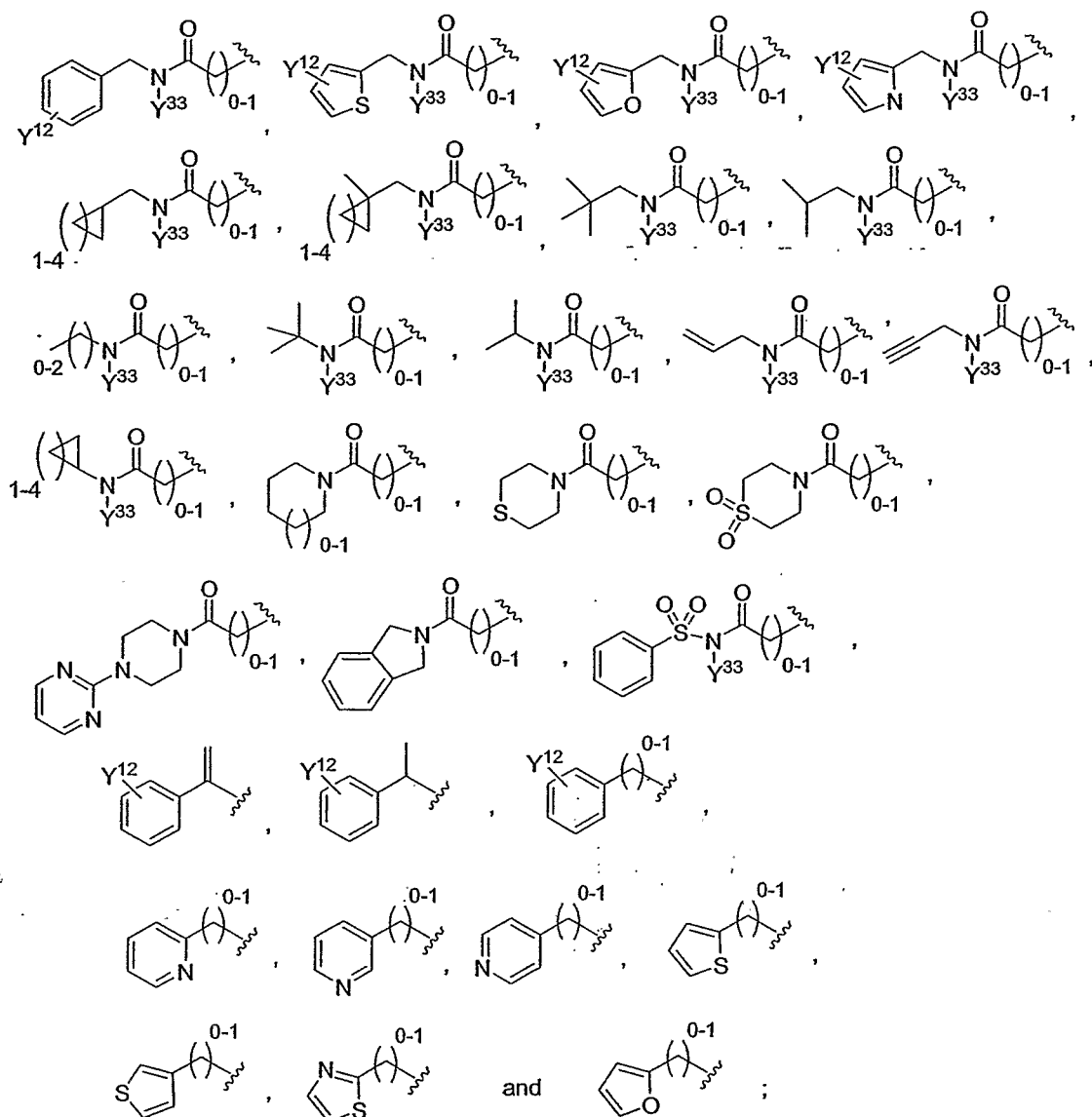
5

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

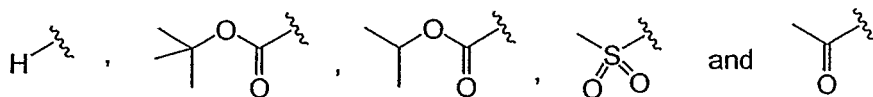


29

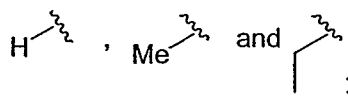




Y^{32} is selected from the group consisting of:

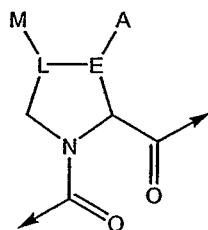


5 and Y^{12} is selected from the group consisting of H, CO_2H , CO_2Me , OMe, F, Cl, Br, NH_2 , $N(H)S(O_2)CH_3$, $N(H)C(O)CH_3$, NO_2 , NMe_2 , $S(O_2)NH_2$, CF_3 , Me, OH, OCF_3 , and $C(O)NH_2$ and Y^{33} is selected from the group consisting of:

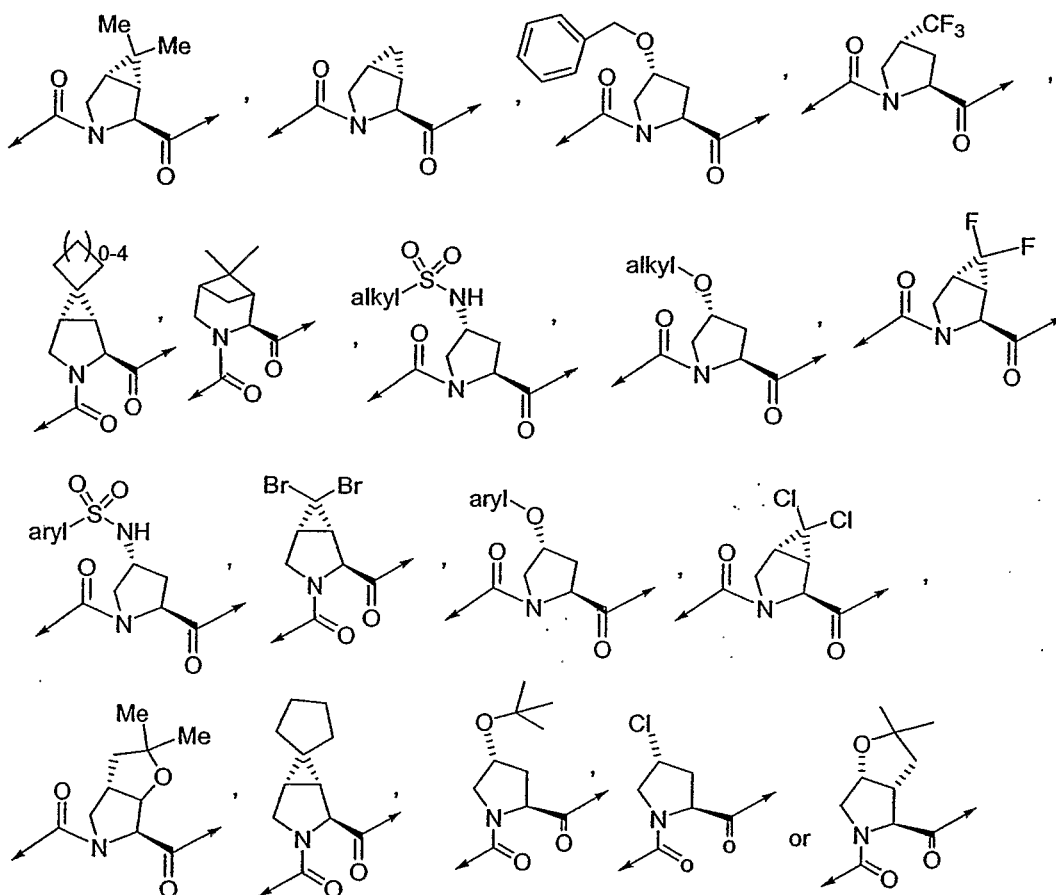


and the moiety:

31



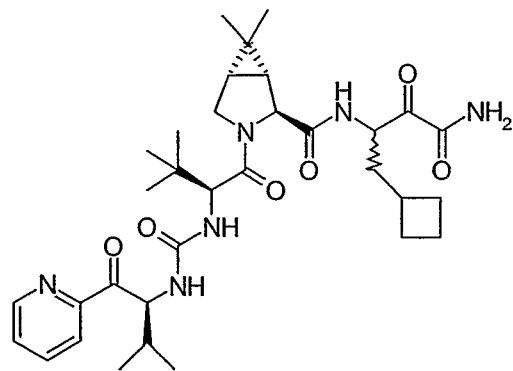
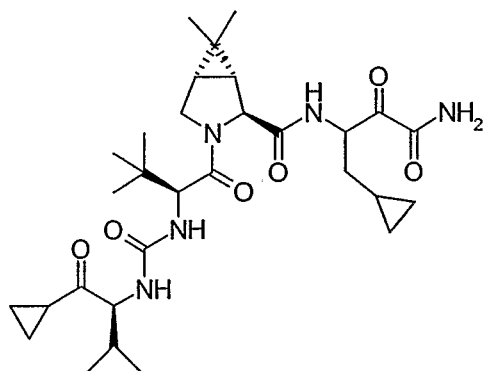
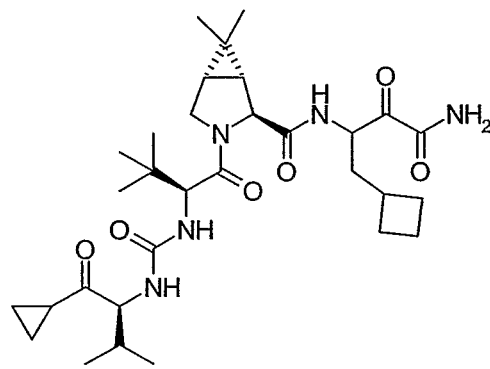
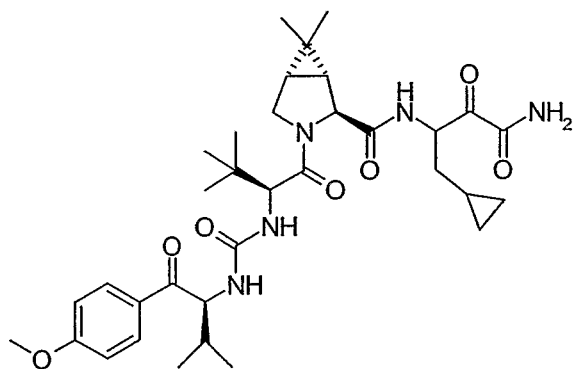
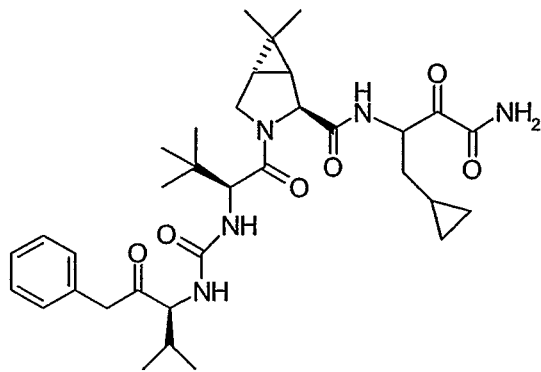
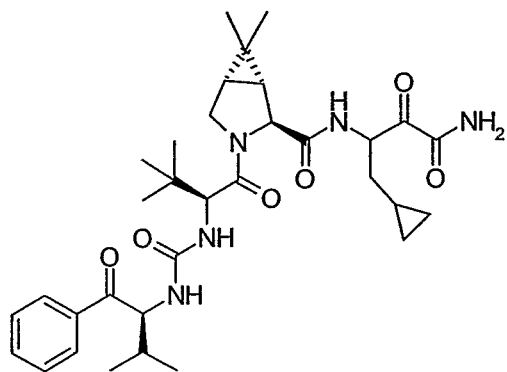
is:

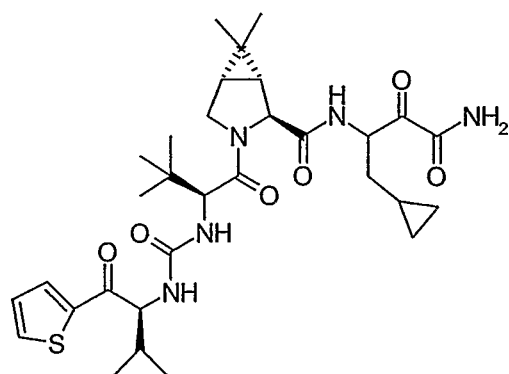
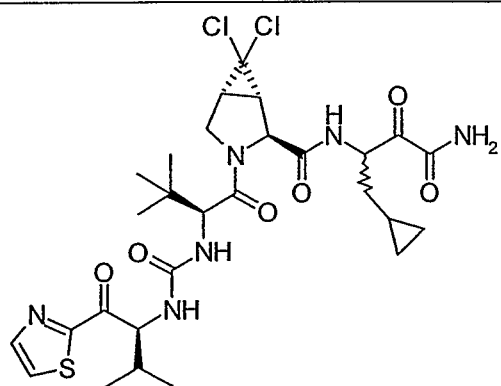
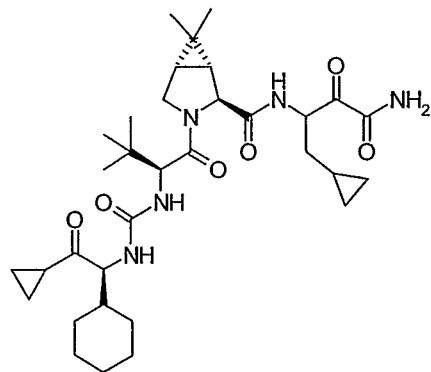
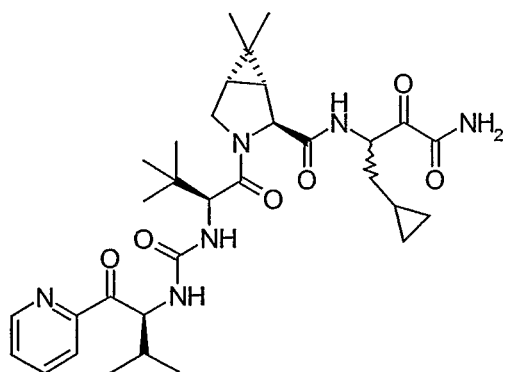
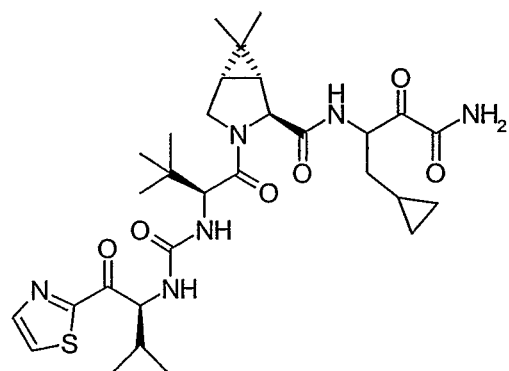
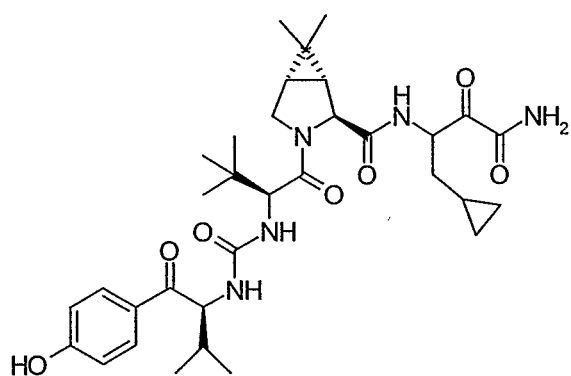
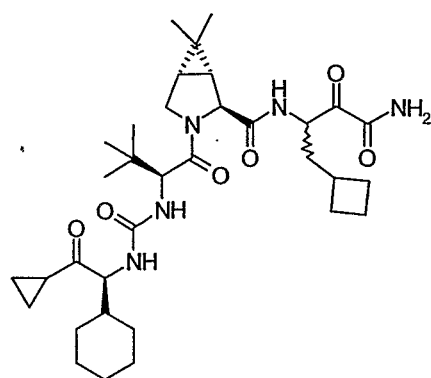
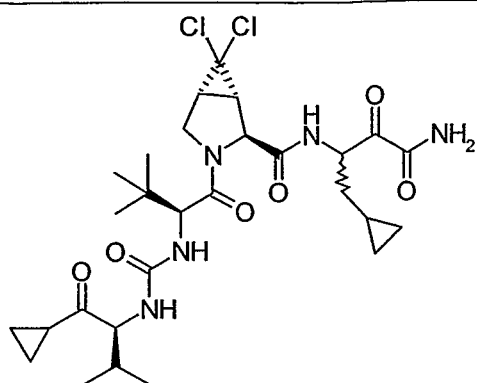


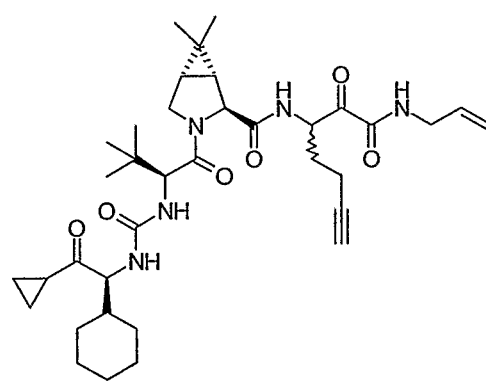
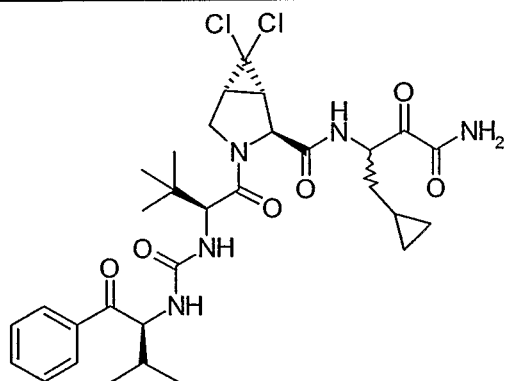
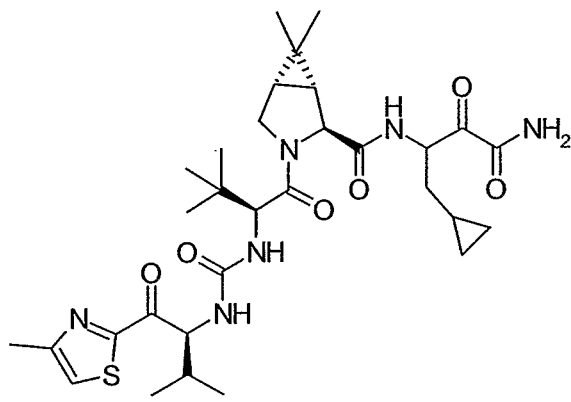
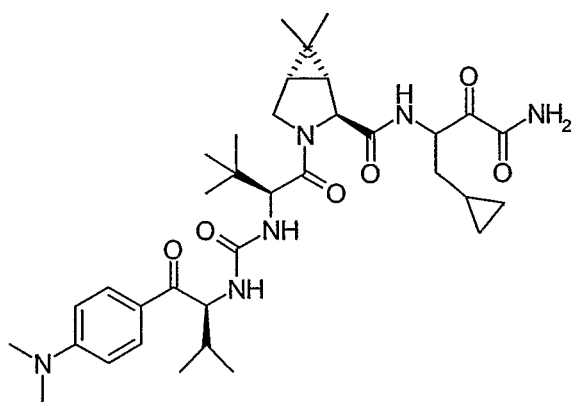
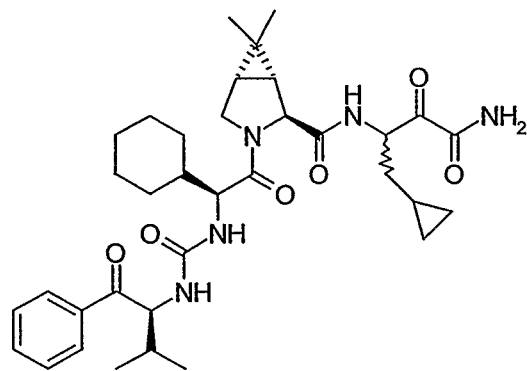
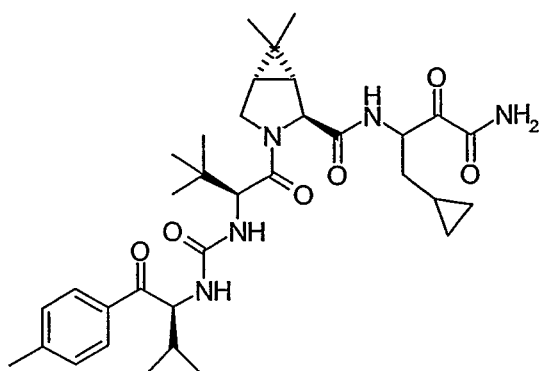
In a still additional embodiment, the present invention discloses compounds shown in **Table 1**, **Table 2**, **Table 3**, **Table 4**, **Table 5** and **Table 6** later in this specification. Also shown in the **Tables** are the biological activities of several inventive compounds (as K_i^* values). The range of K_i^* in **Tables 1-6** is defined as follows: A: <75nM (nanomolar); B: 76-250 nM; and C: >250 nM.

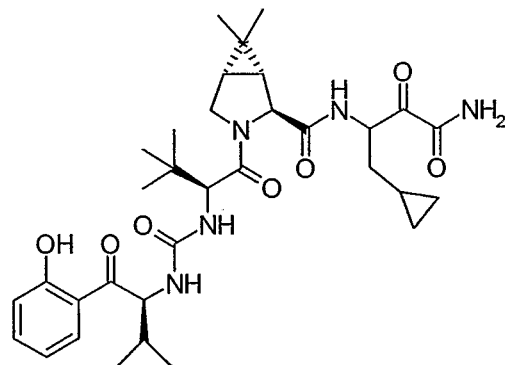
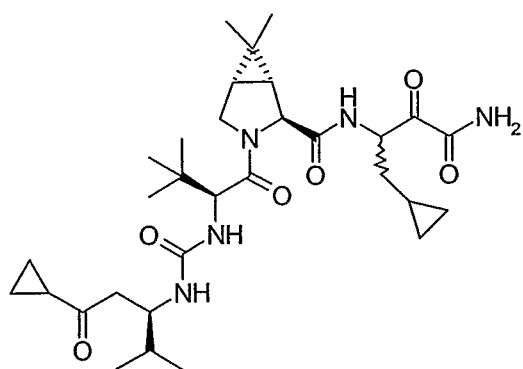
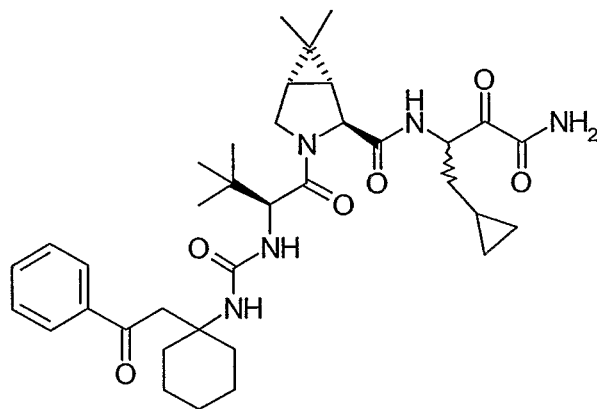
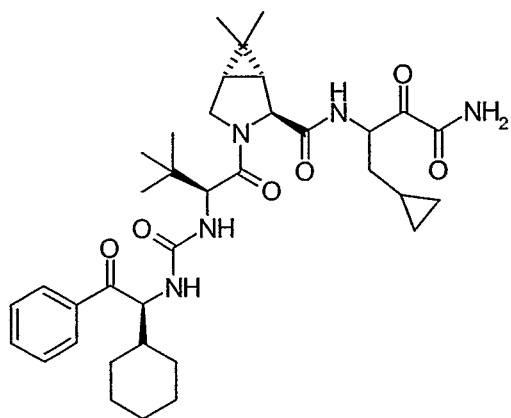
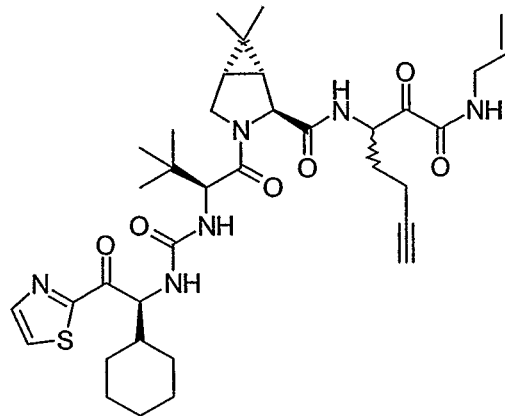
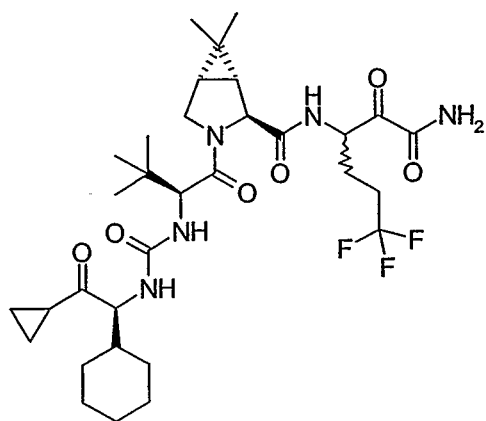
Yet another embodiment of the invention discloses compounds in **Table 7**:

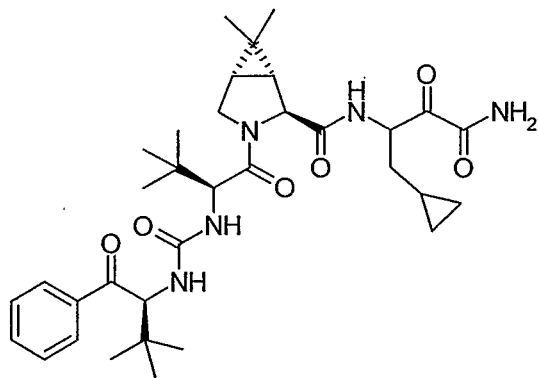
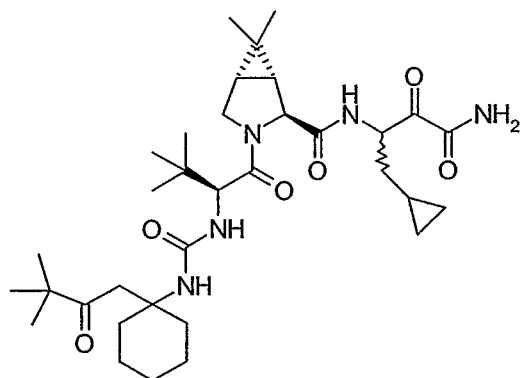
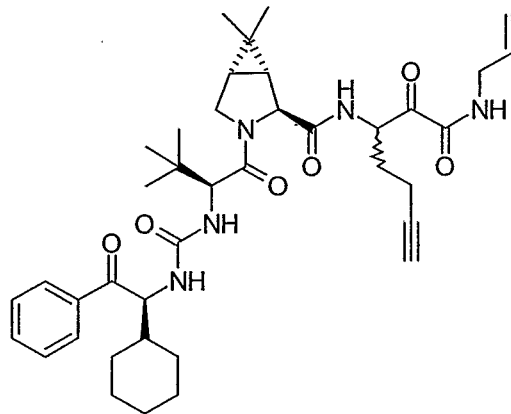
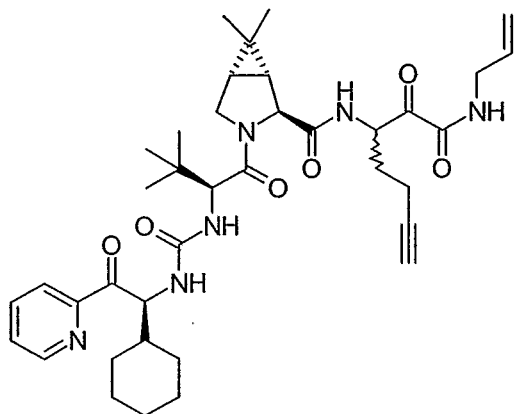
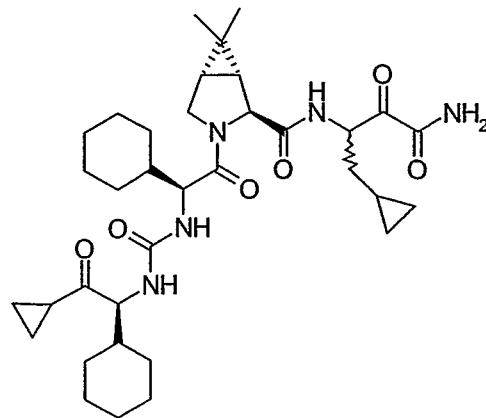
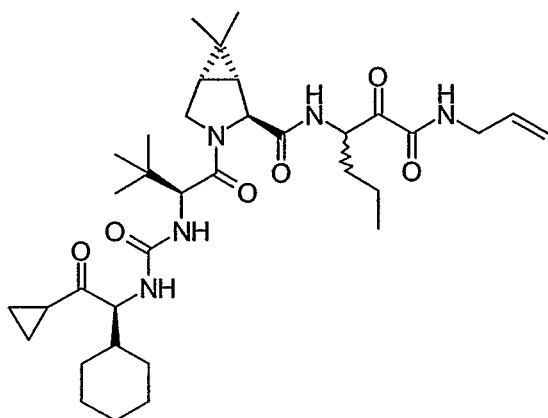
TABLE 7

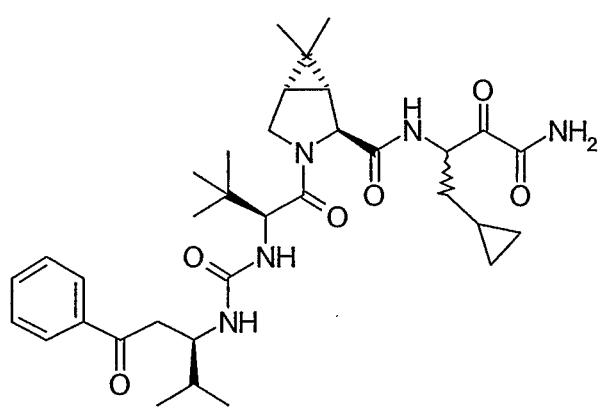
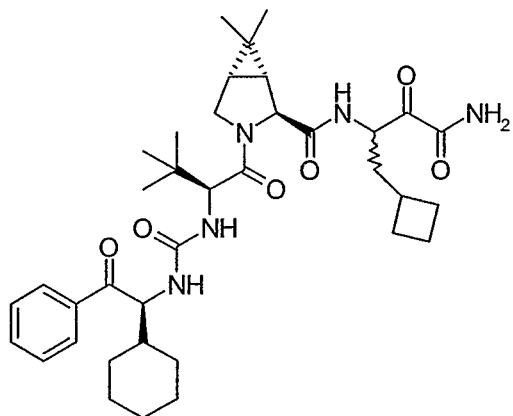
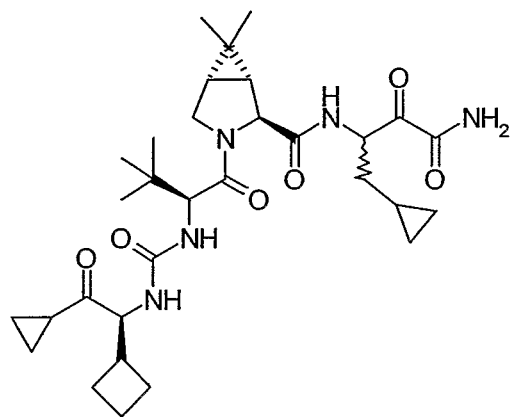
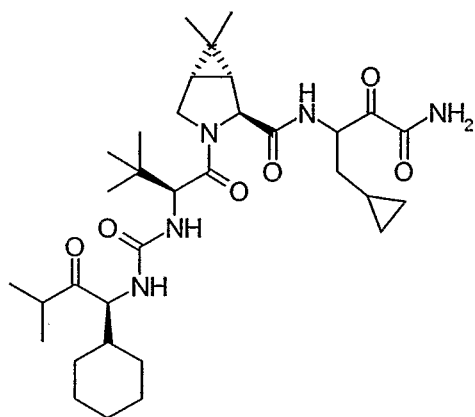
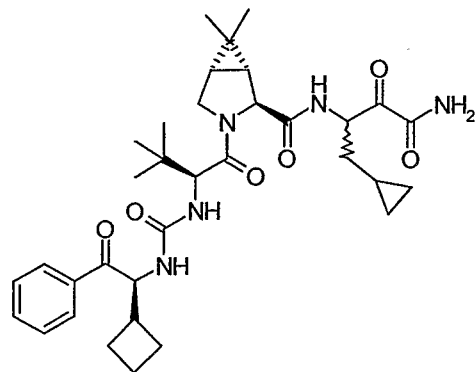
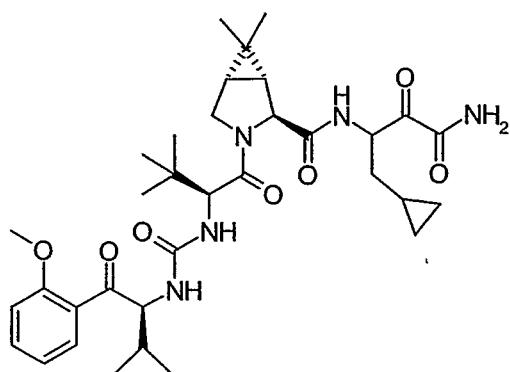


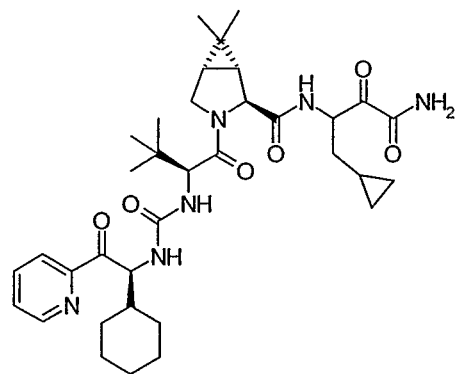
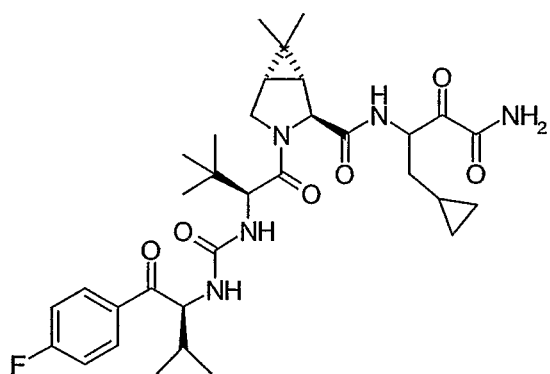
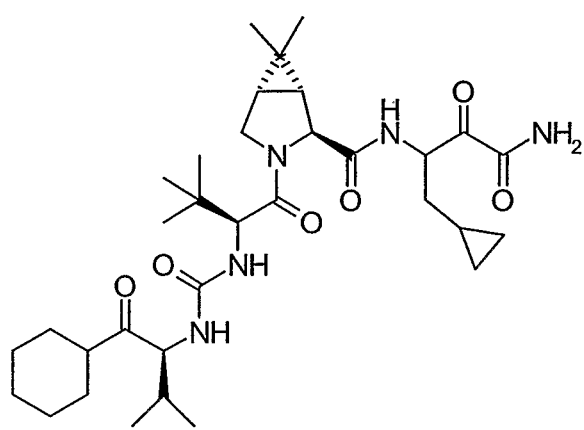
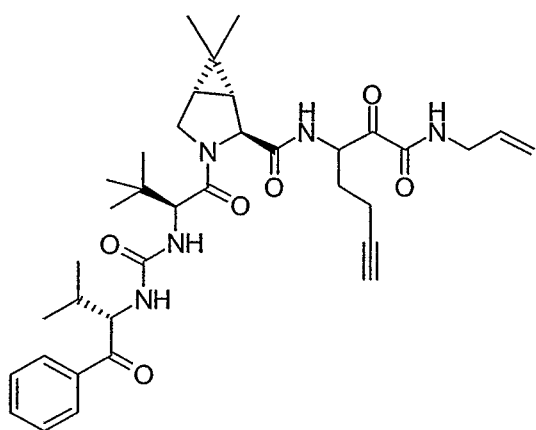
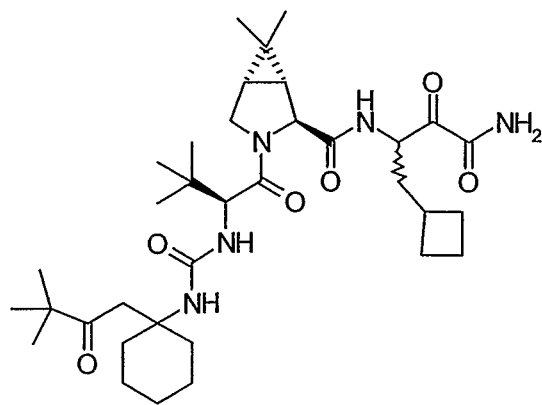
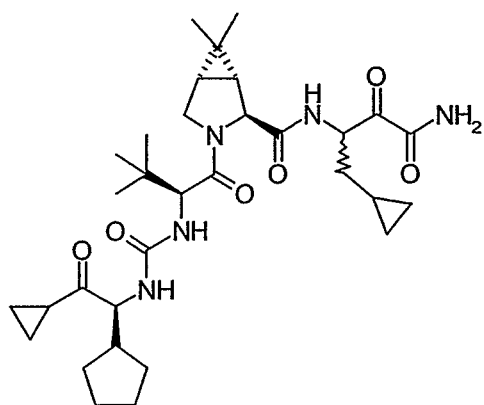


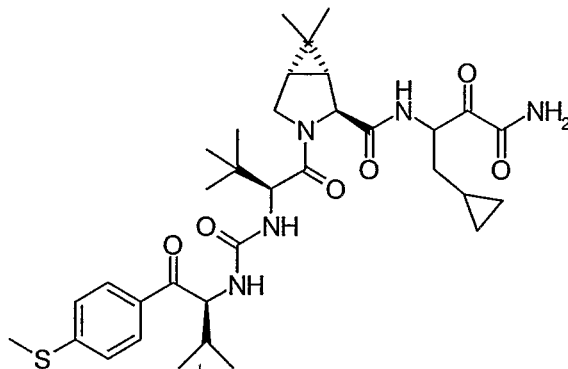
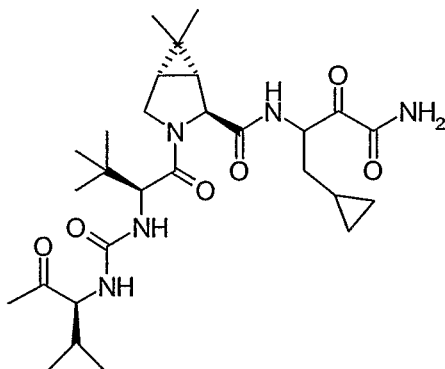
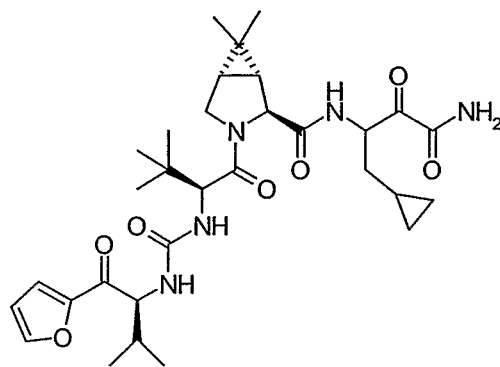
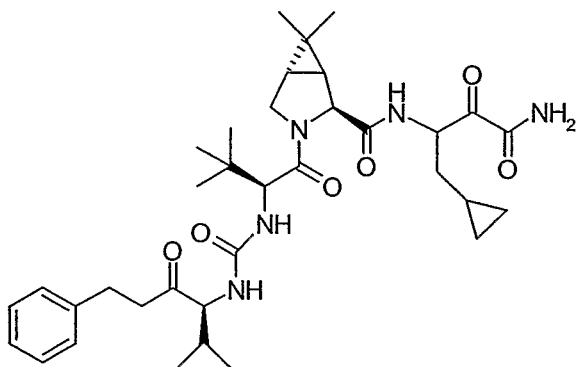
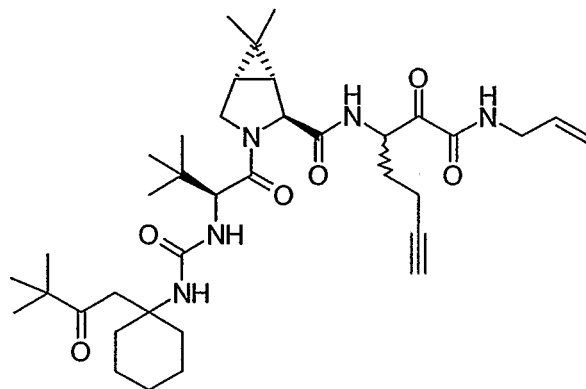
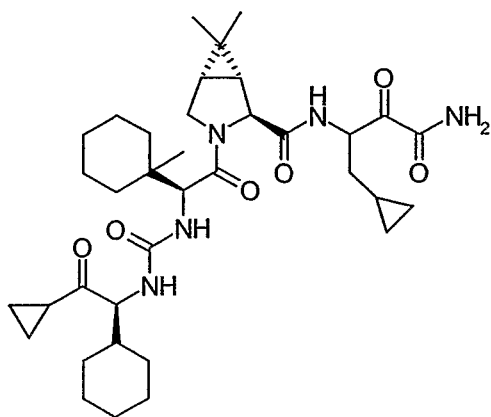


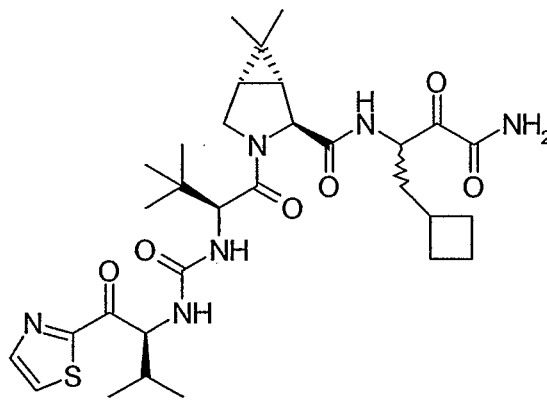
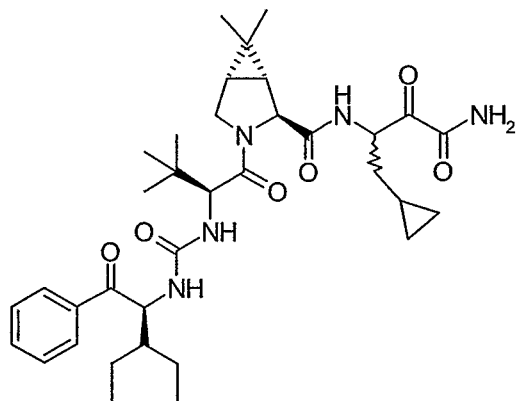
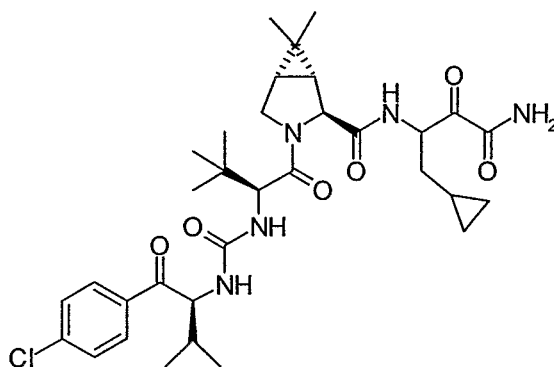
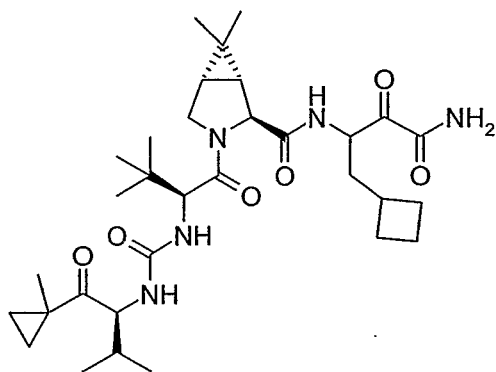
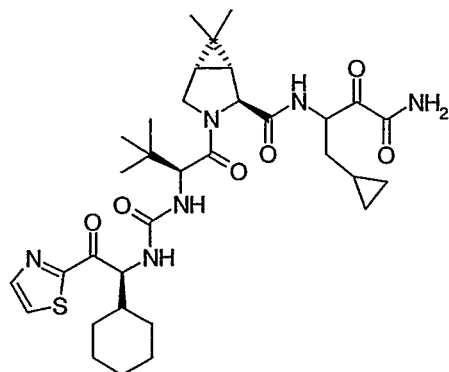
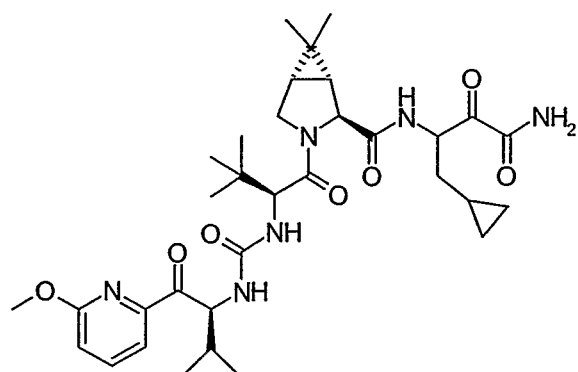


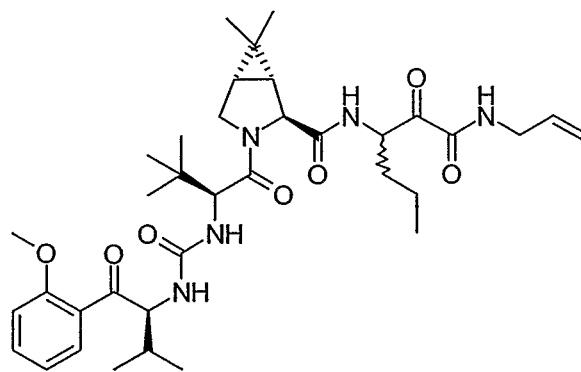
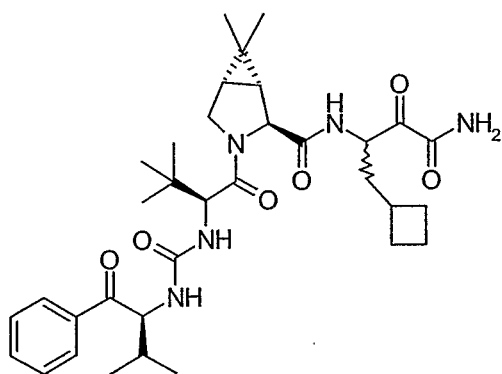
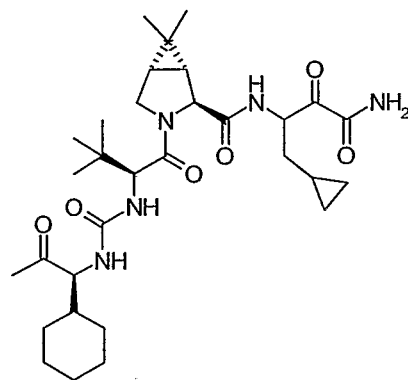
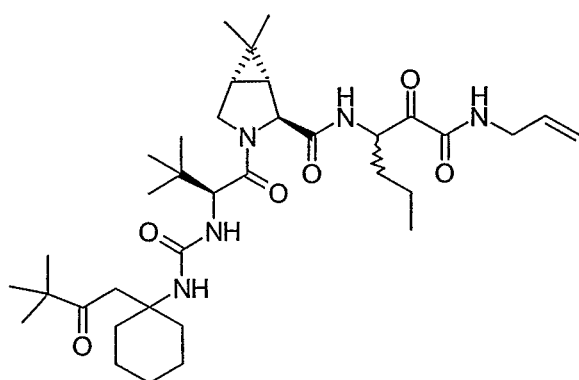
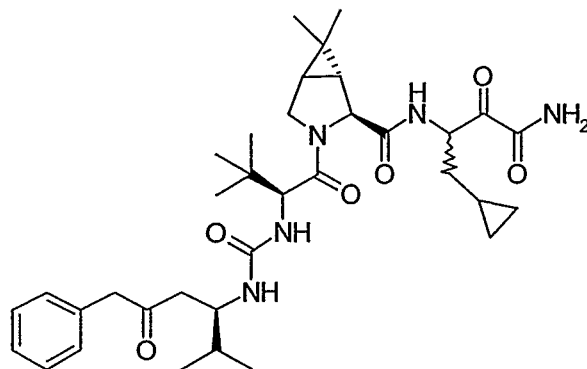
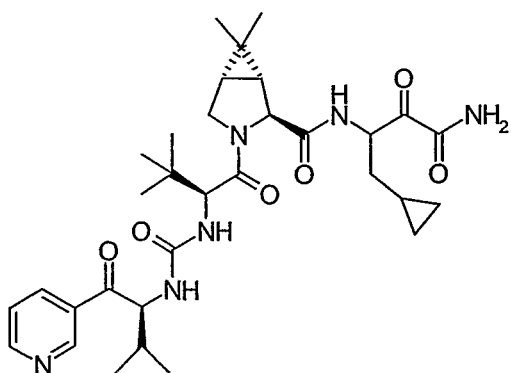


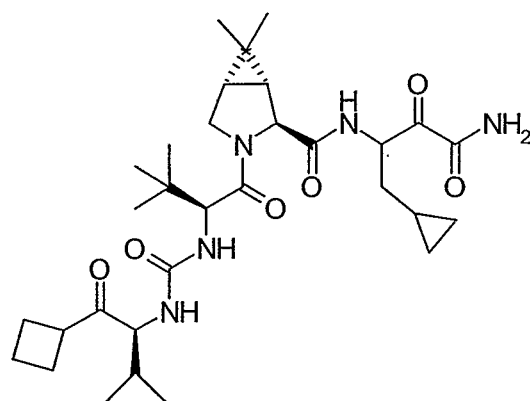
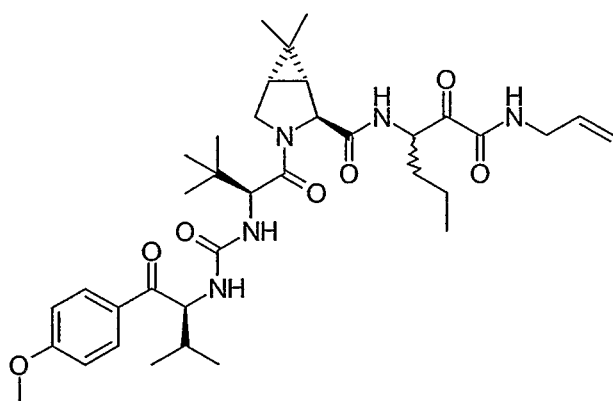
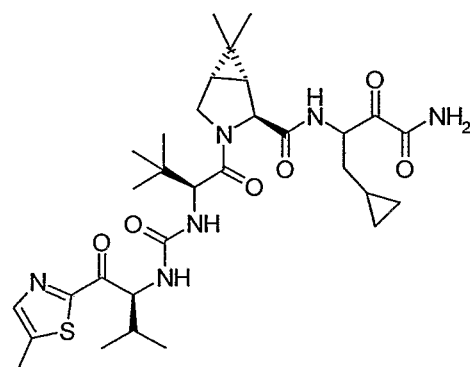
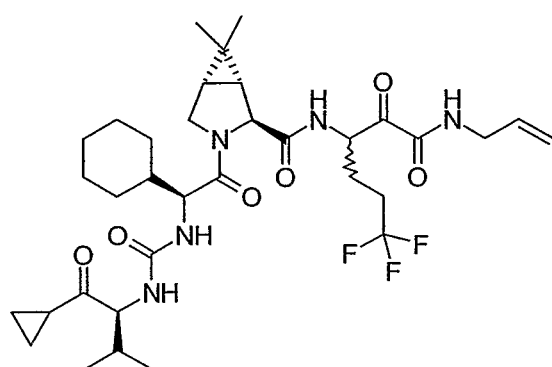
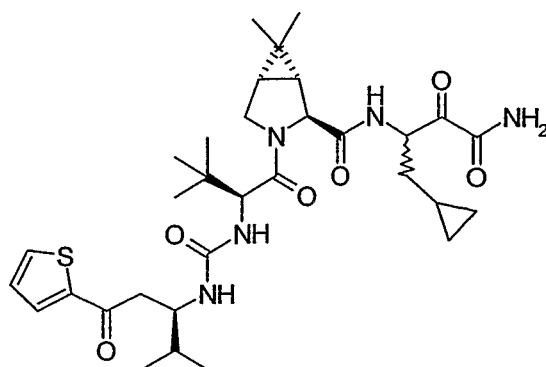
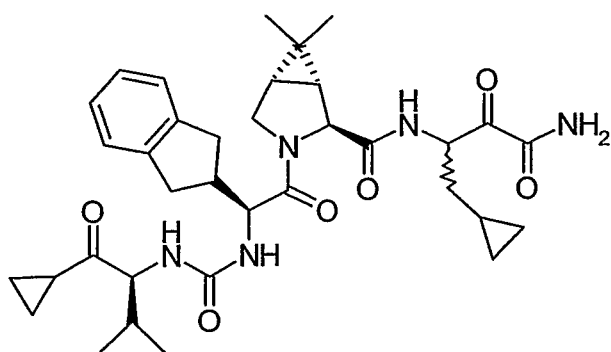


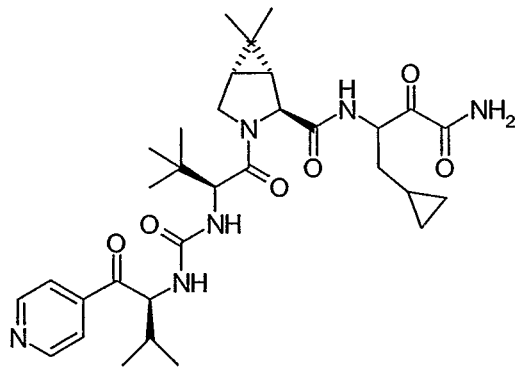
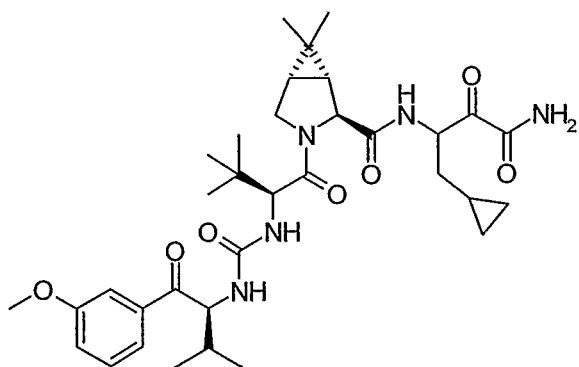
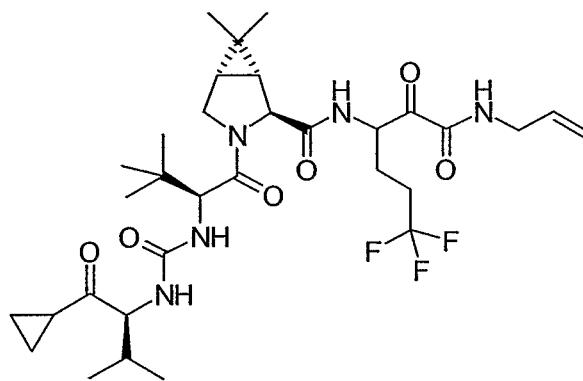
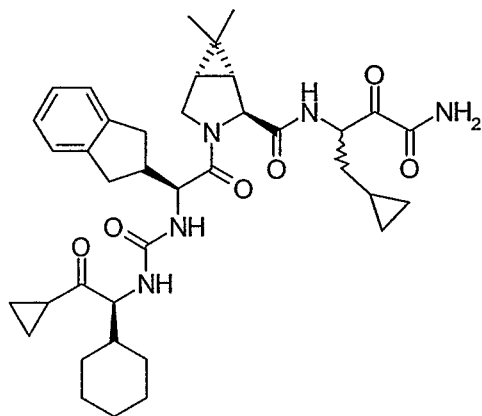
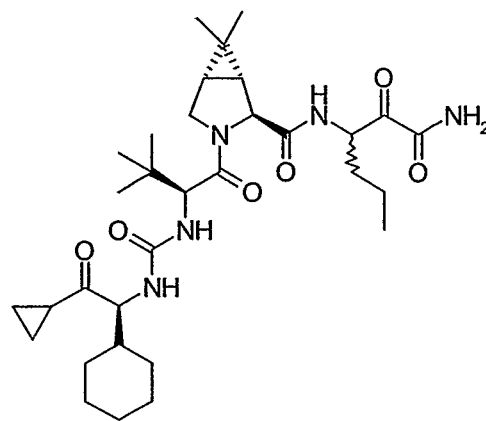
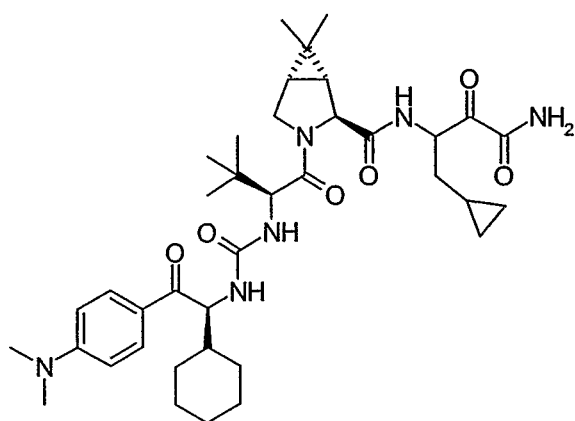


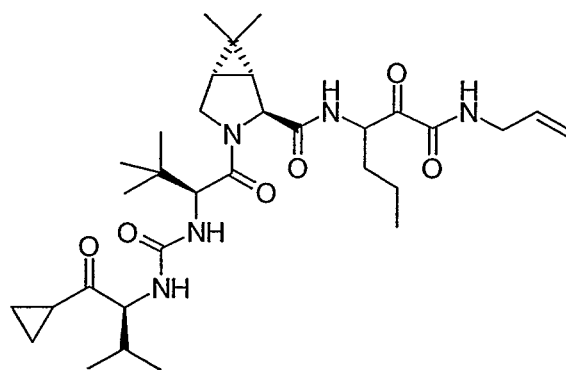
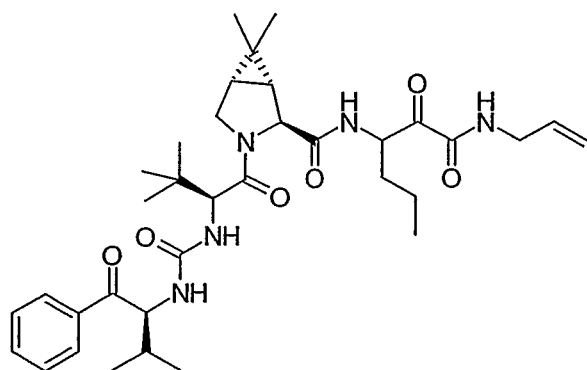
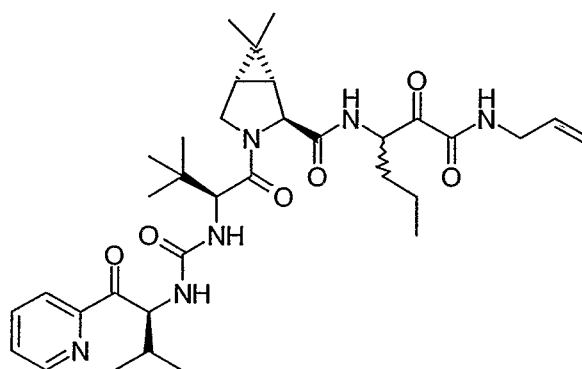
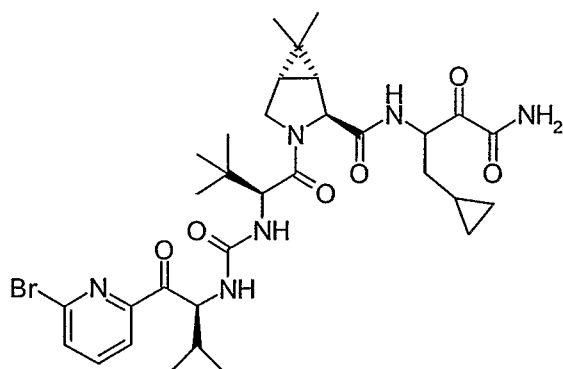
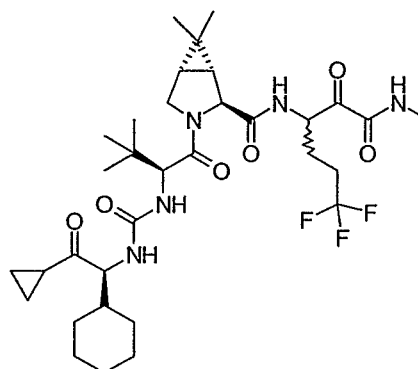
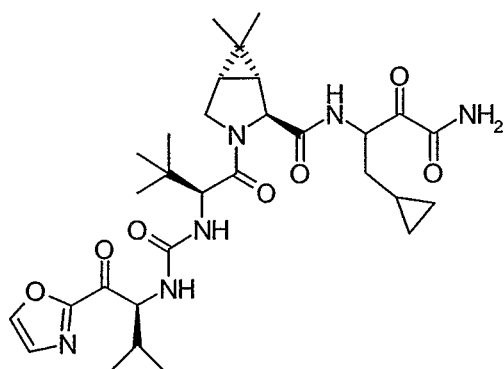
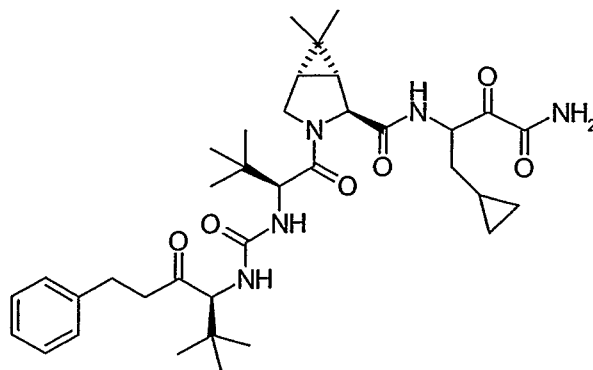
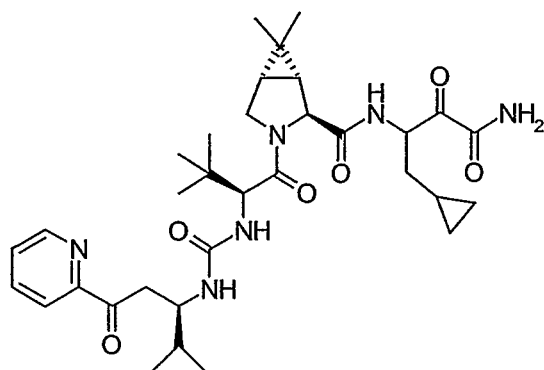


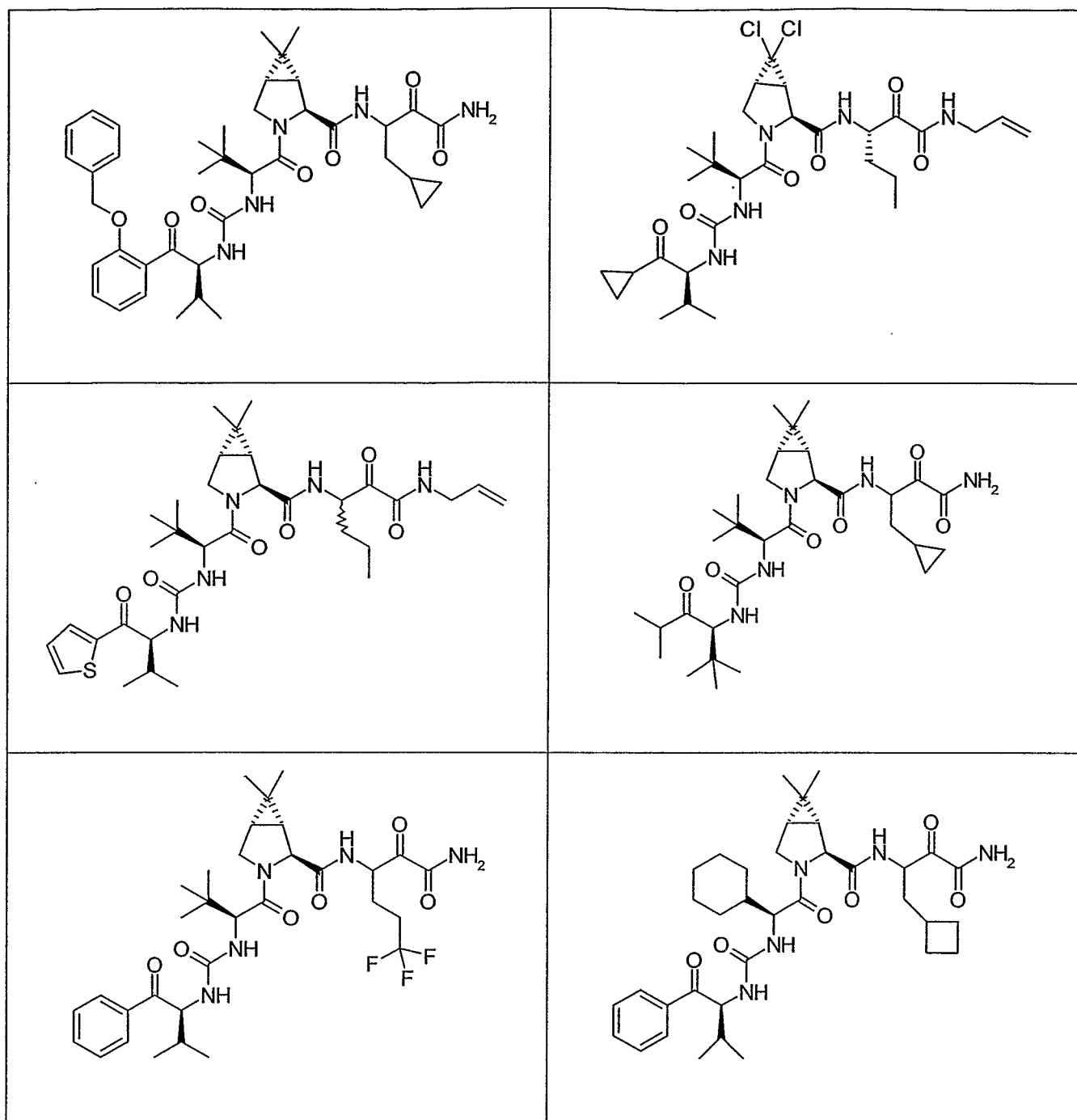


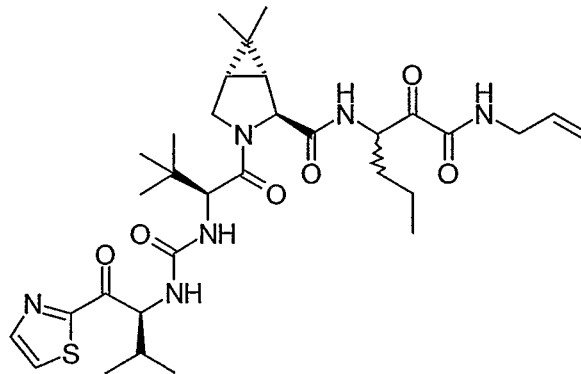
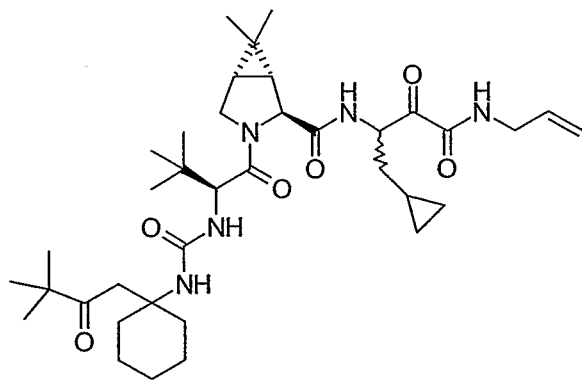
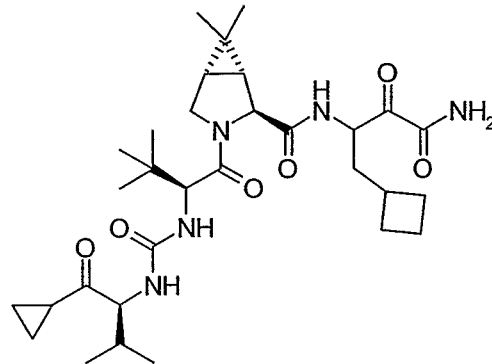
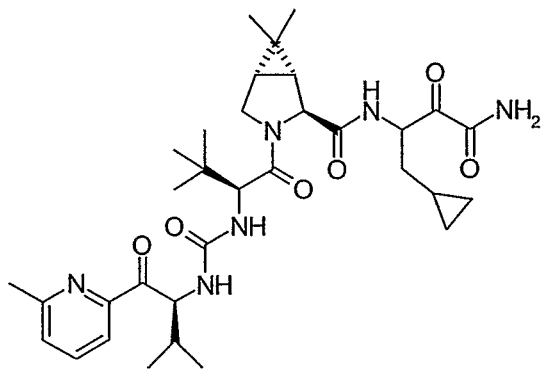
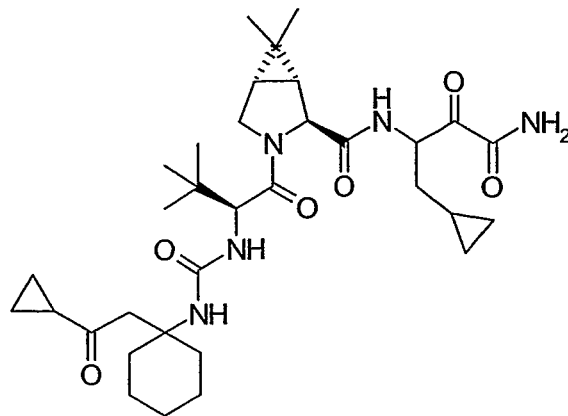
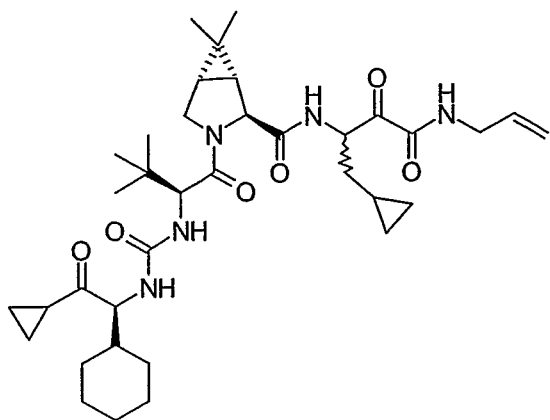


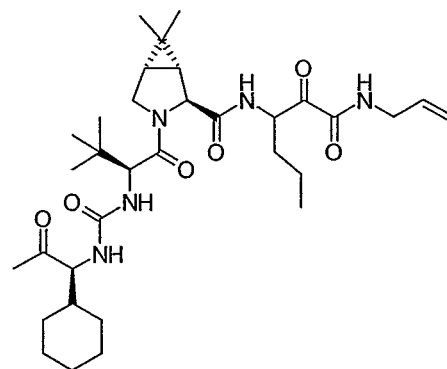
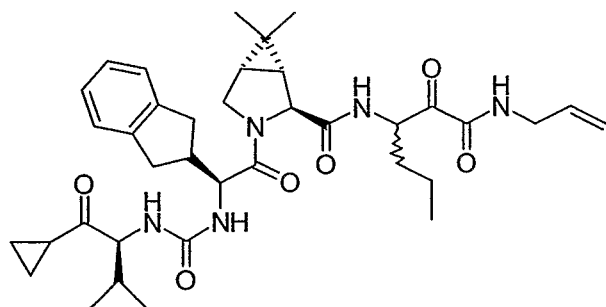
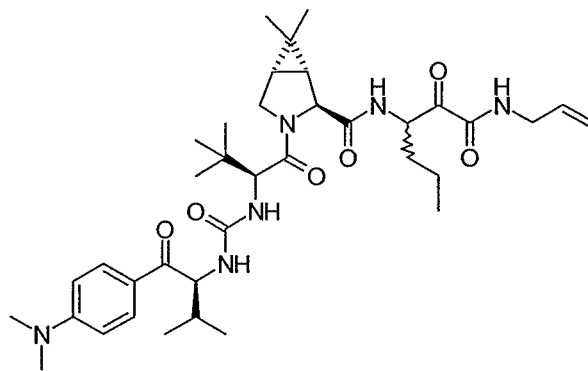
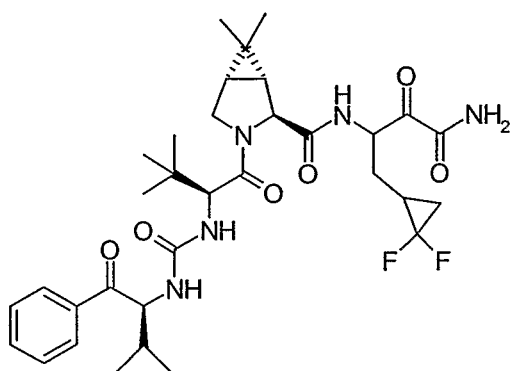
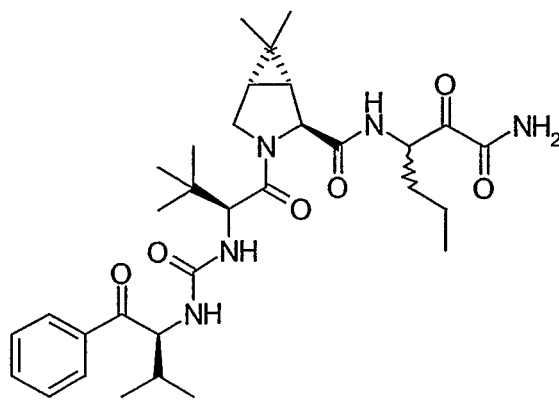
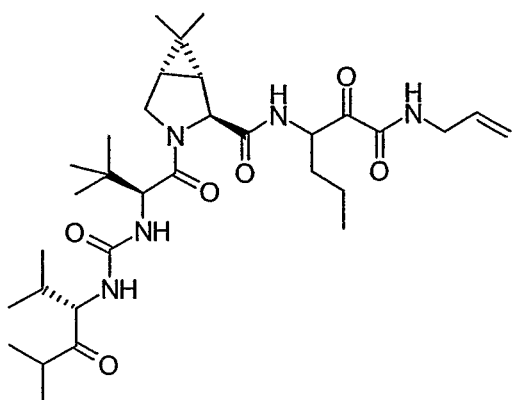


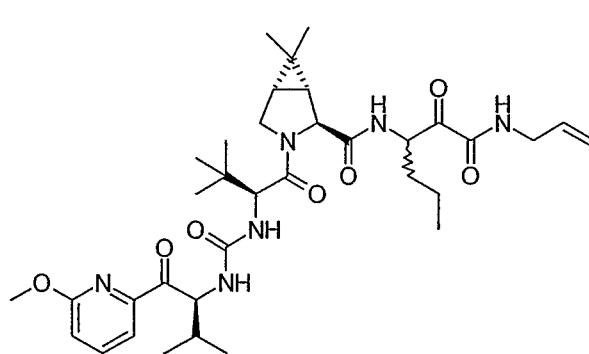
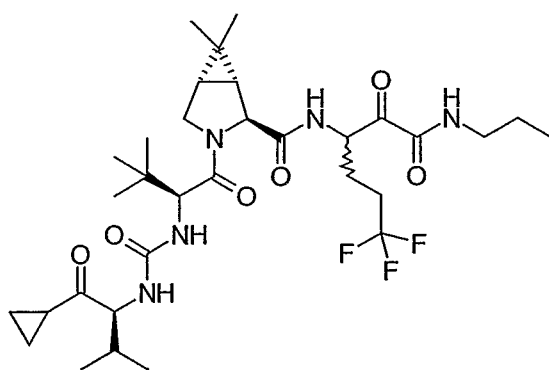
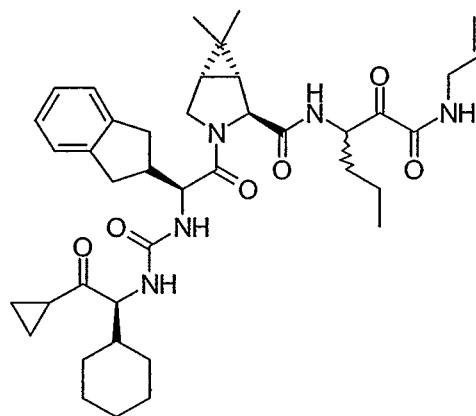
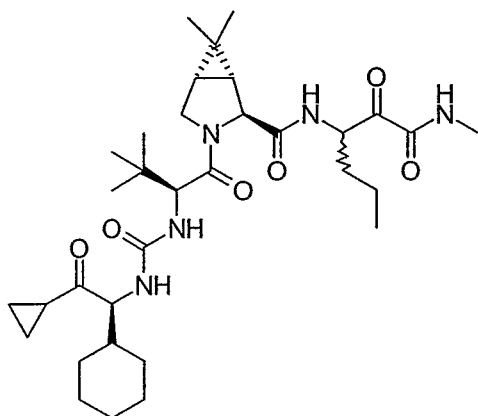
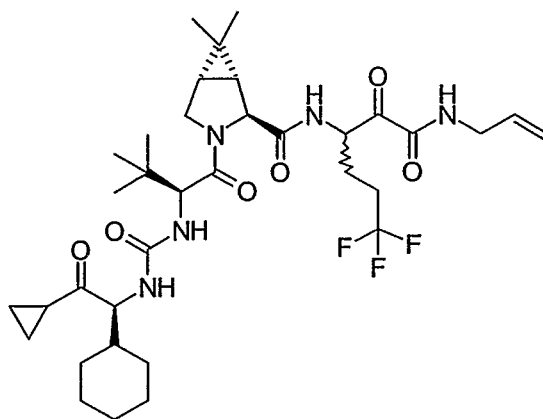
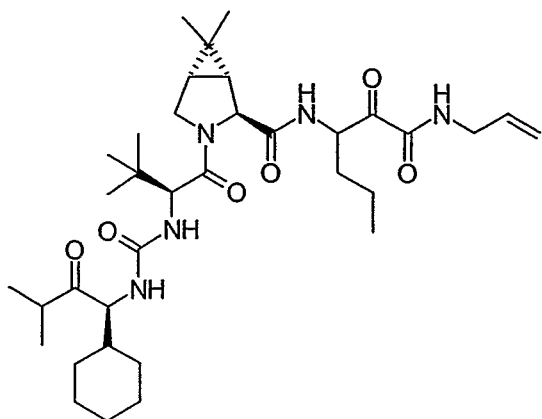


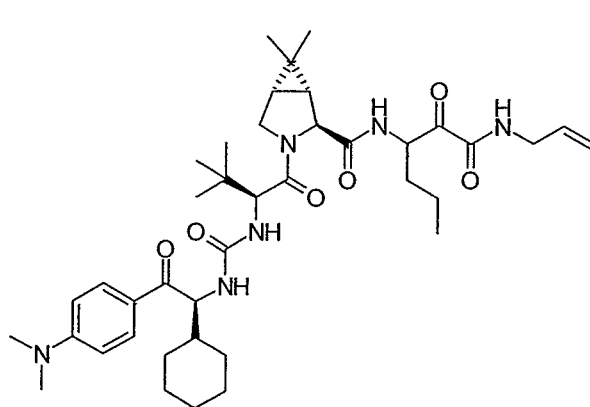
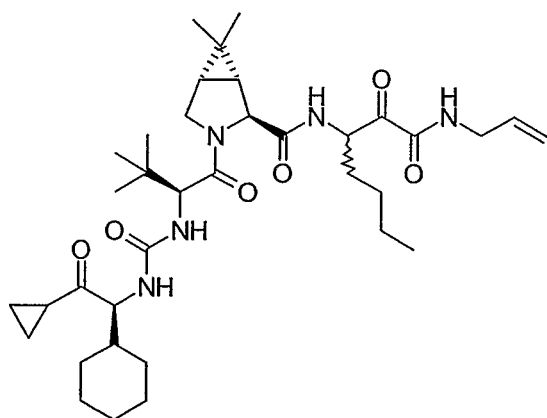
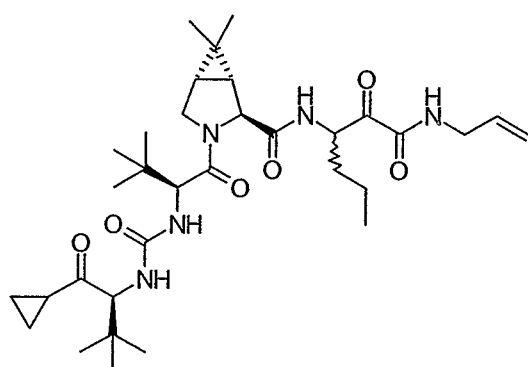
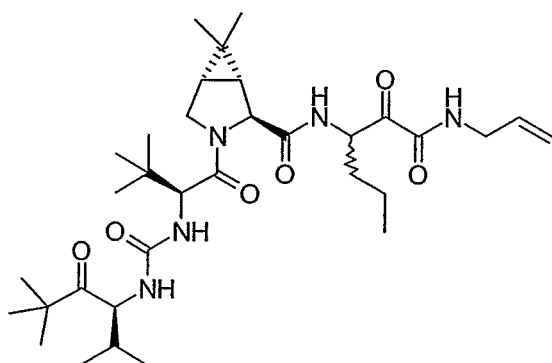
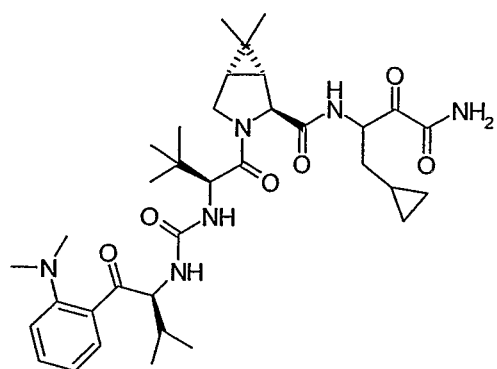
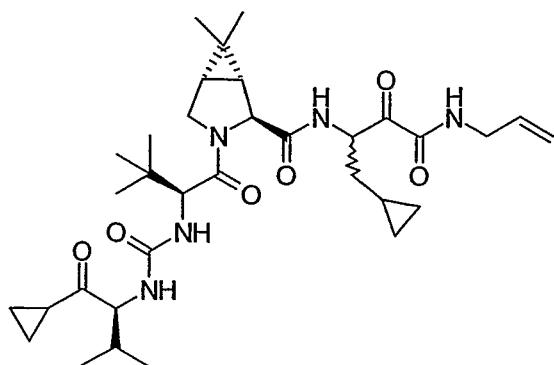


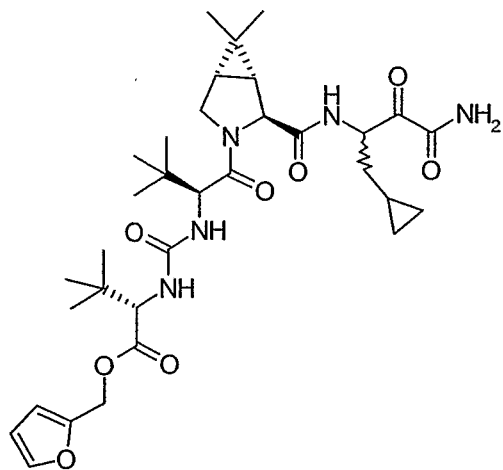
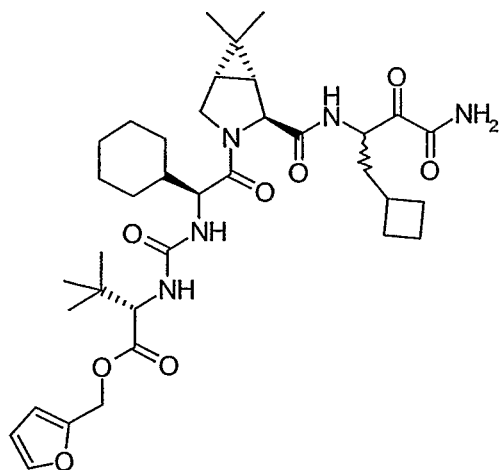
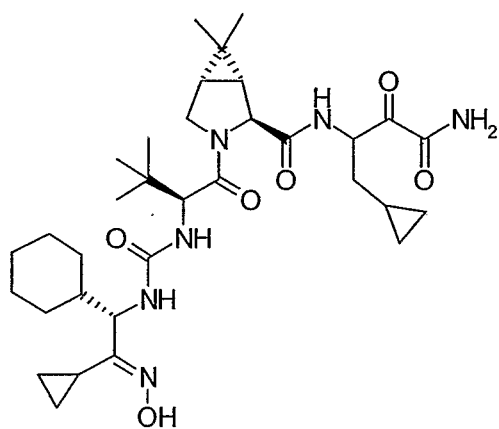
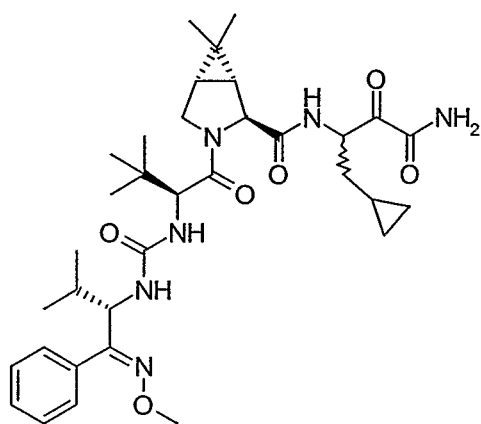
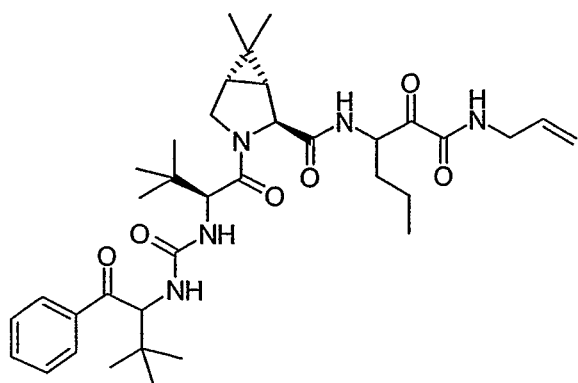


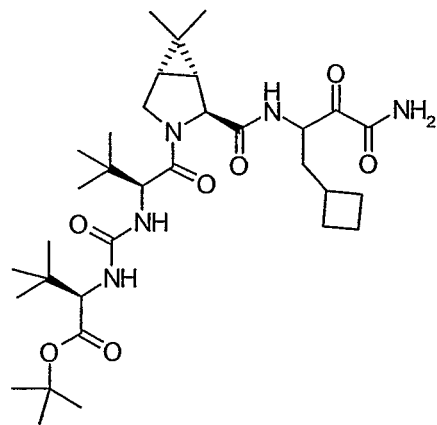
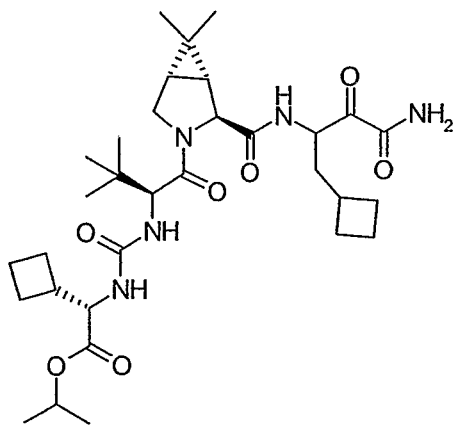
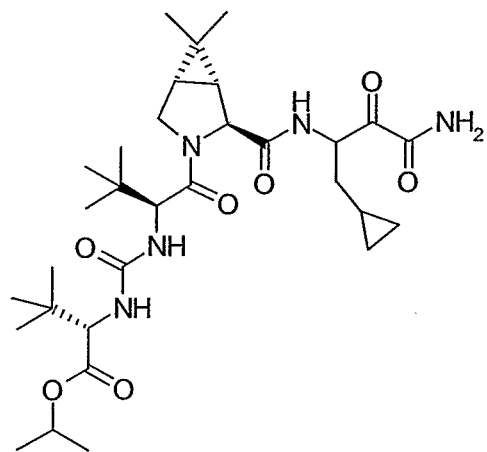
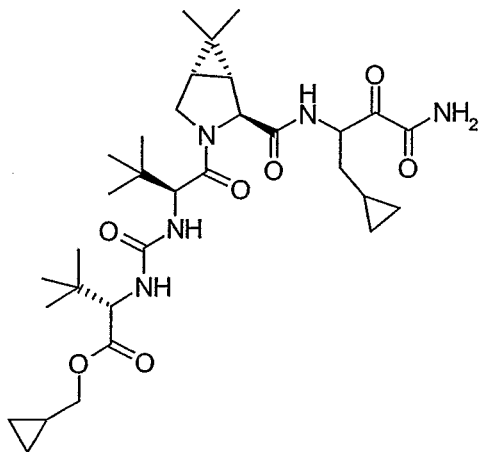
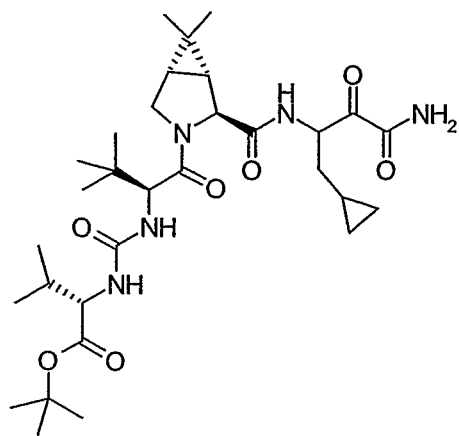
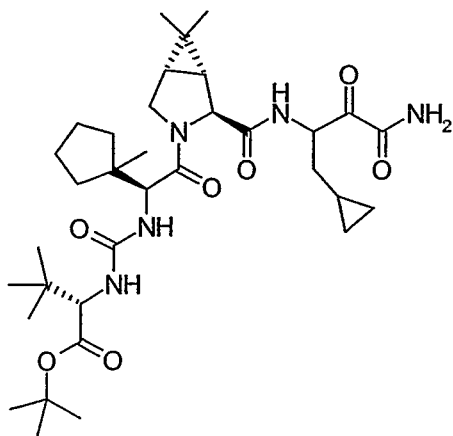


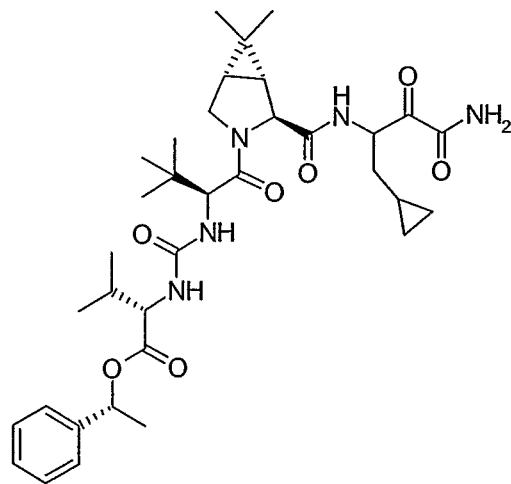
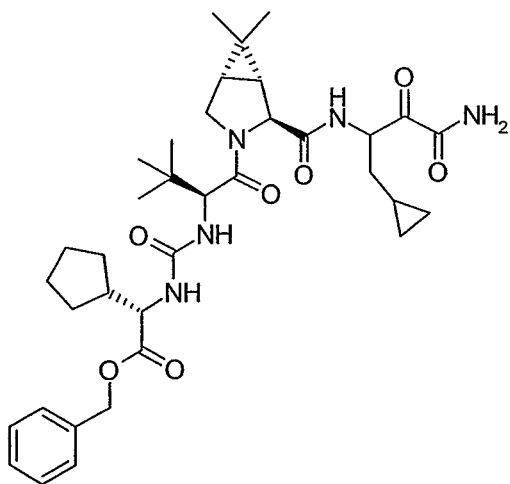
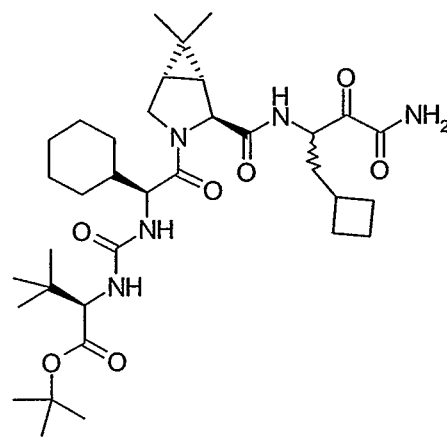
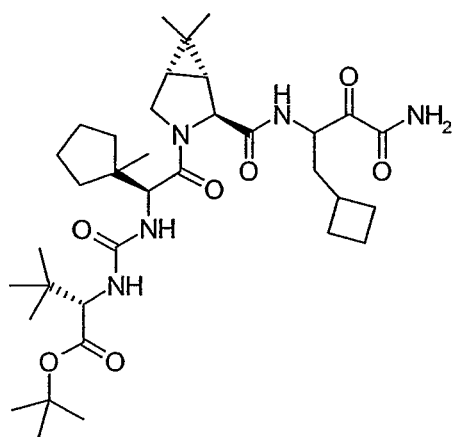
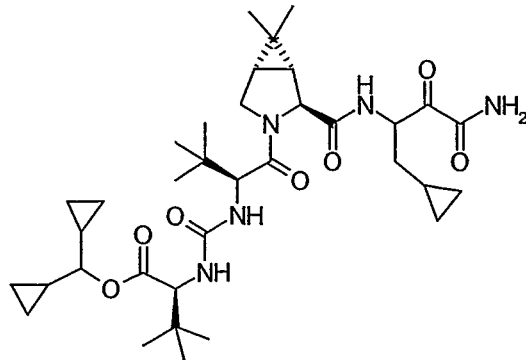
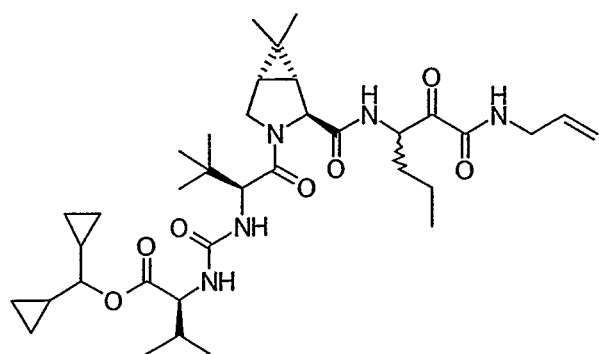


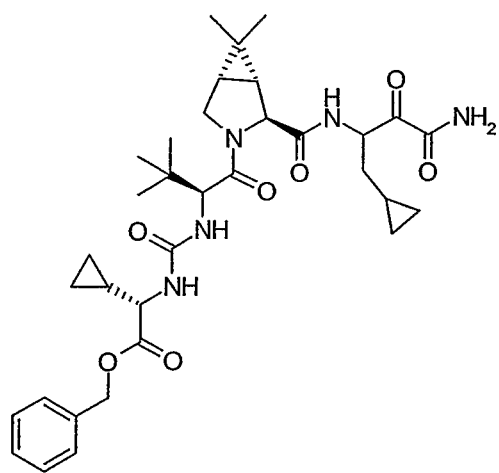
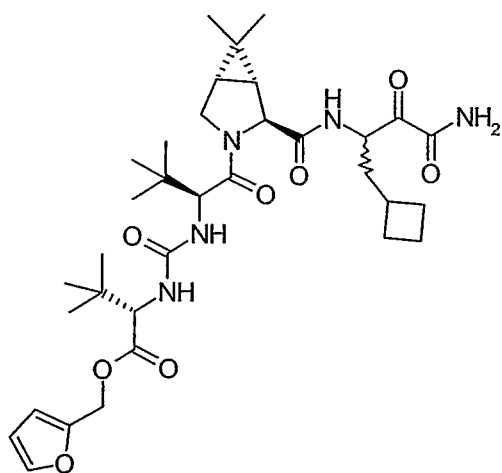
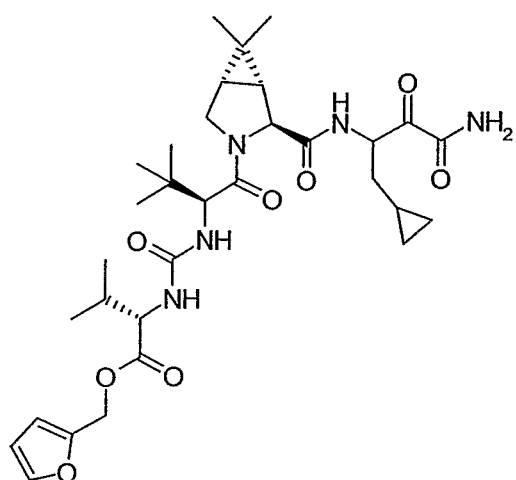
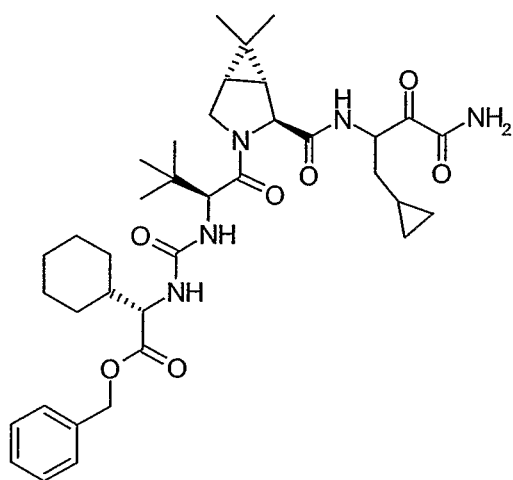
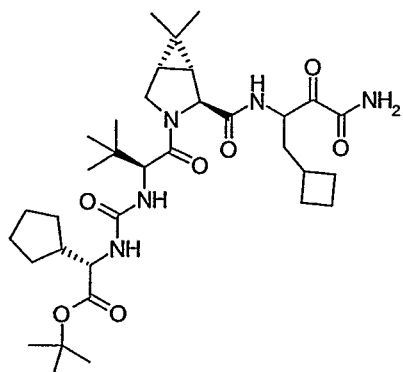
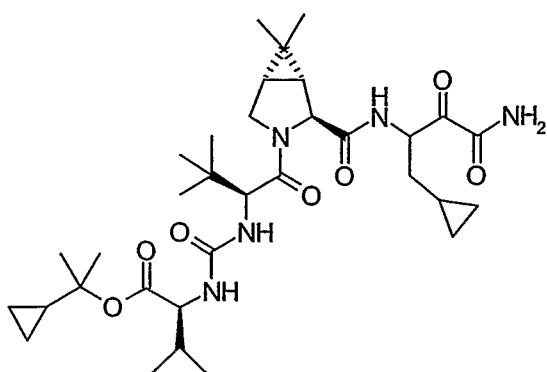


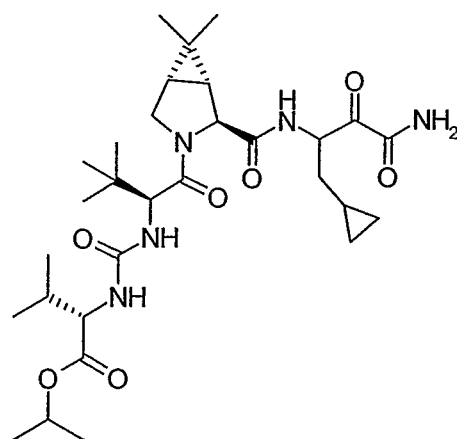
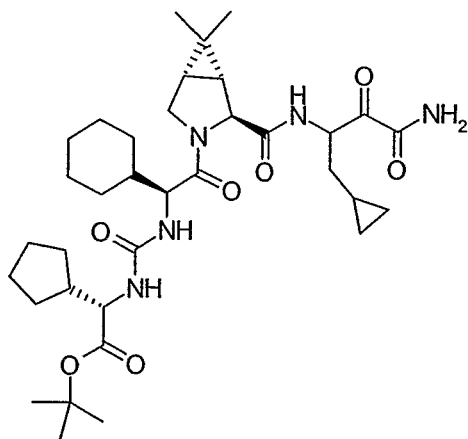
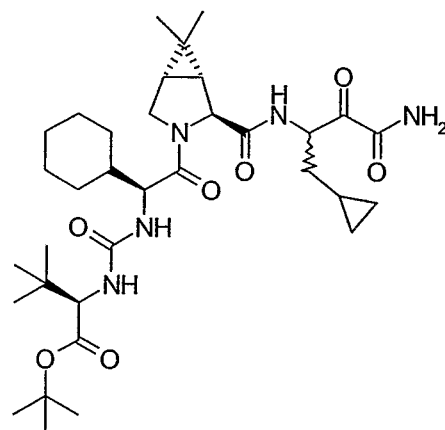
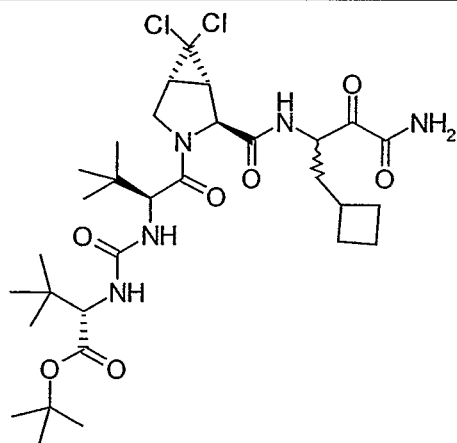
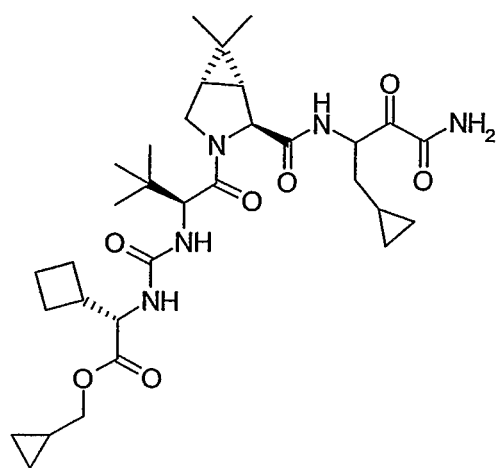
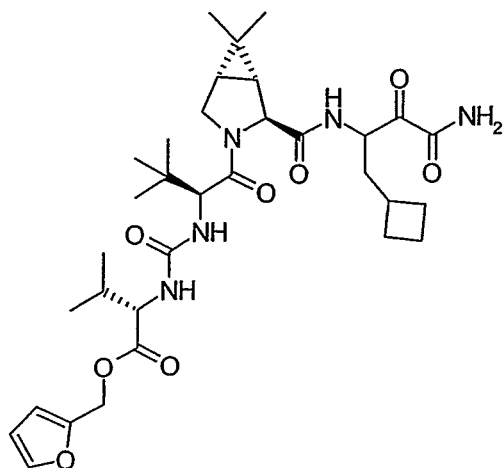


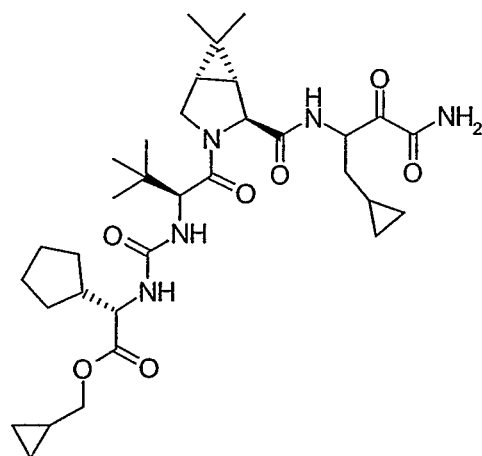
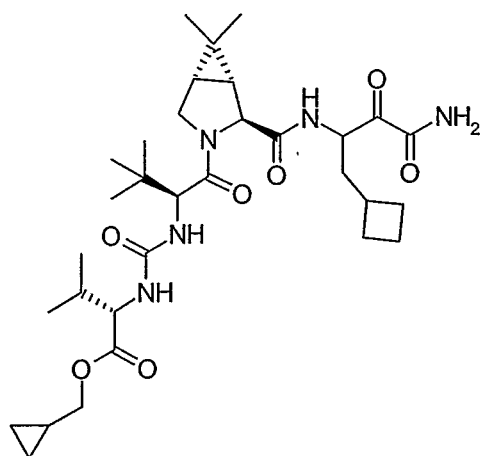
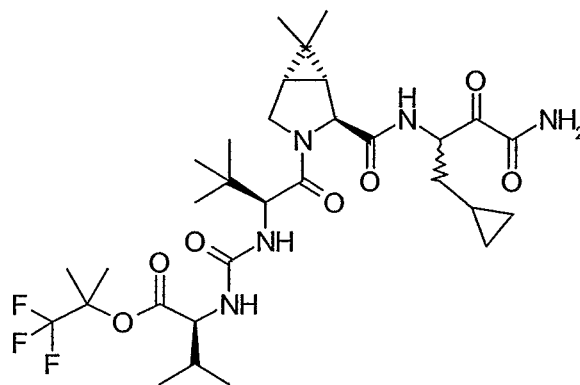
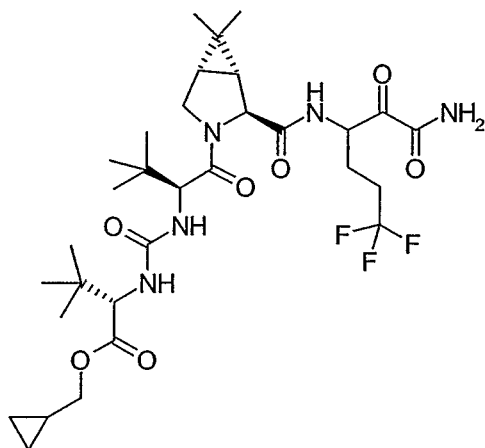
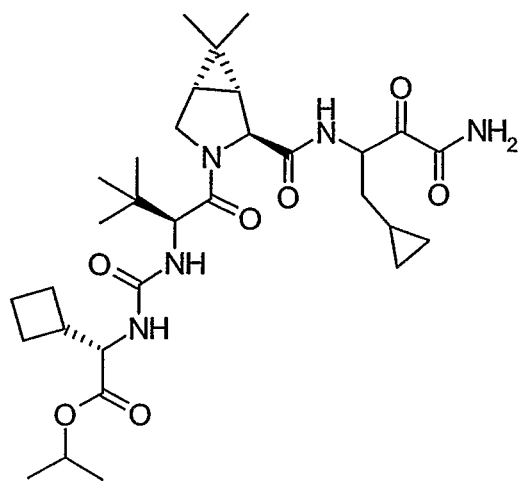
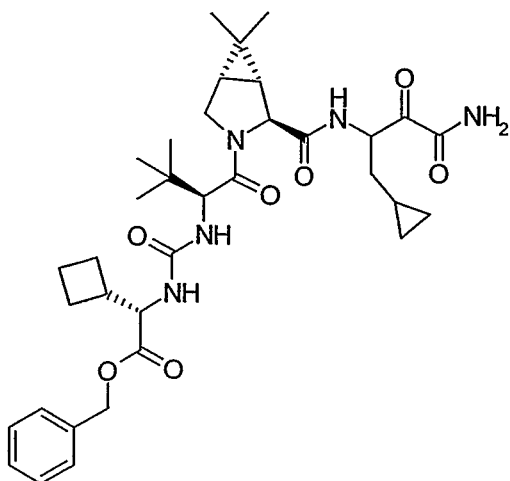


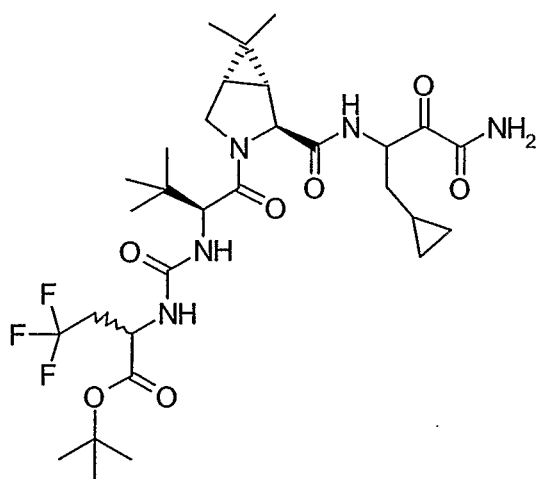
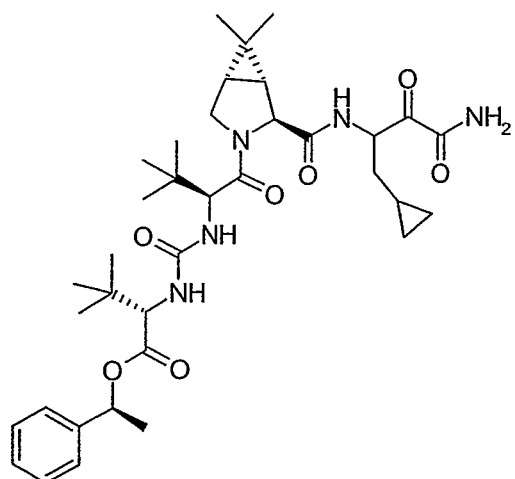
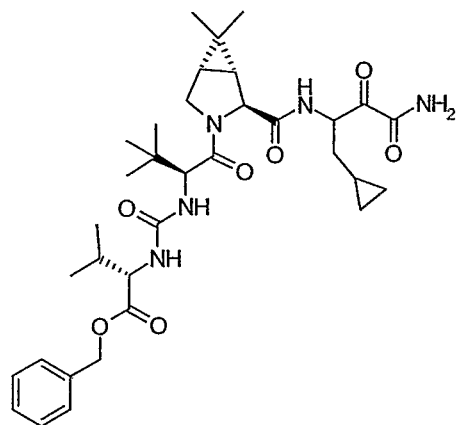
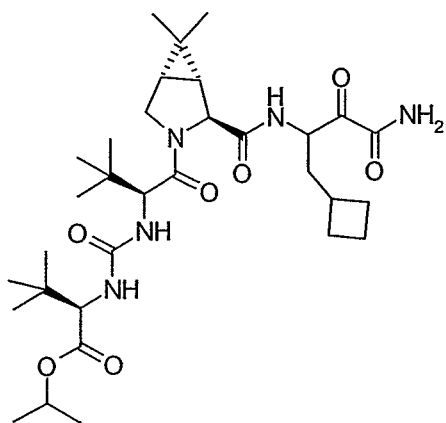
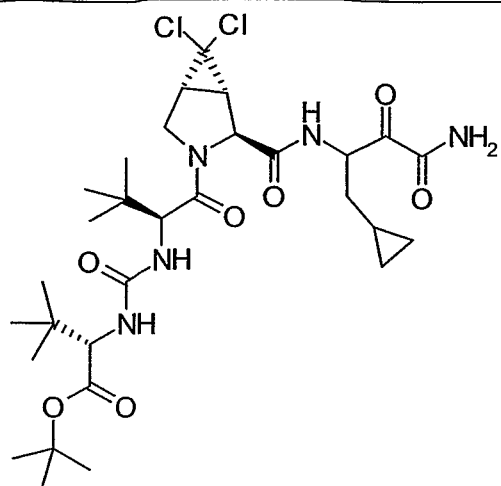
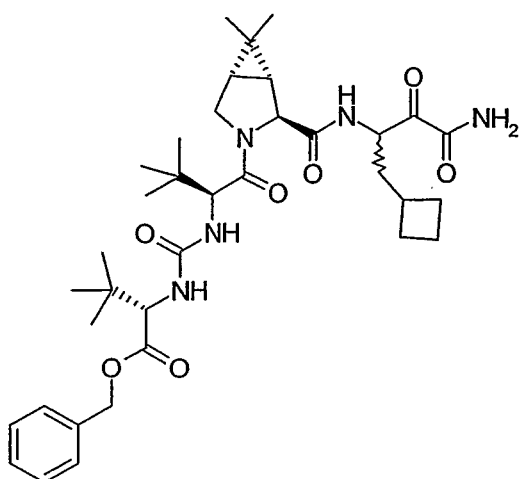


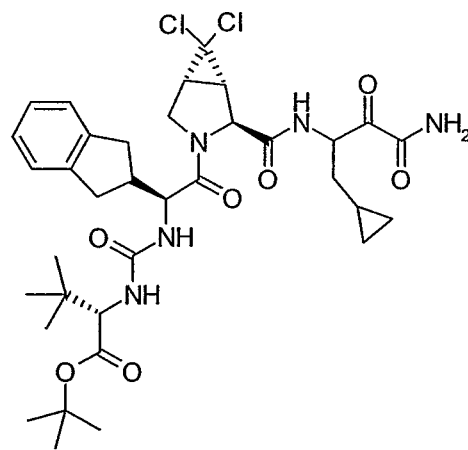
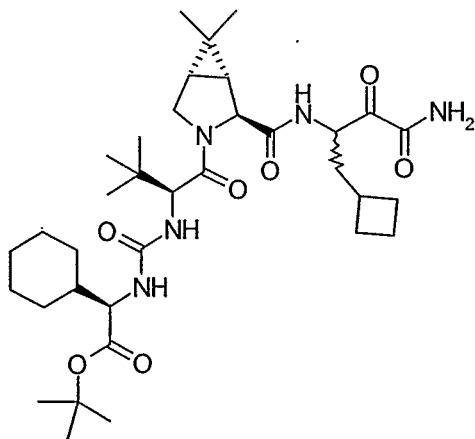
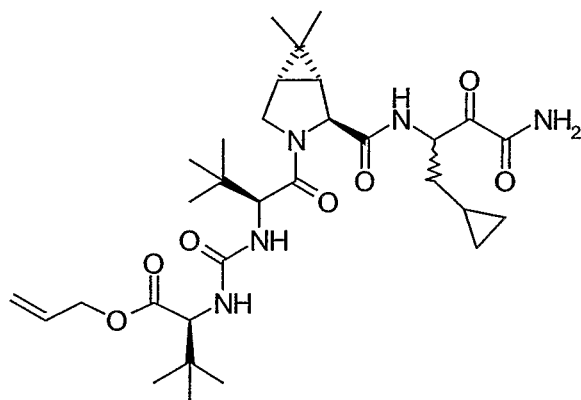
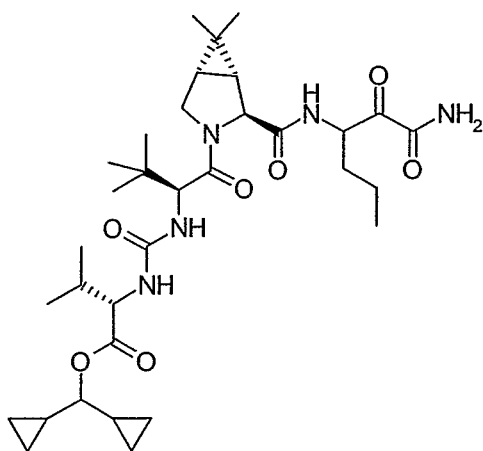
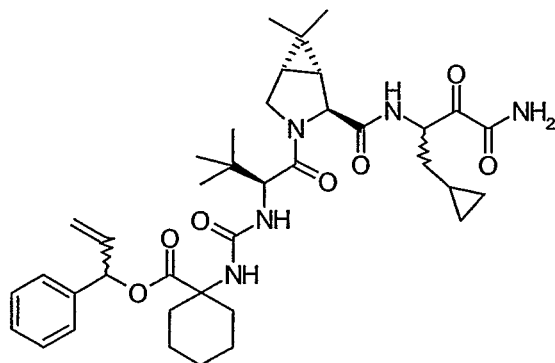
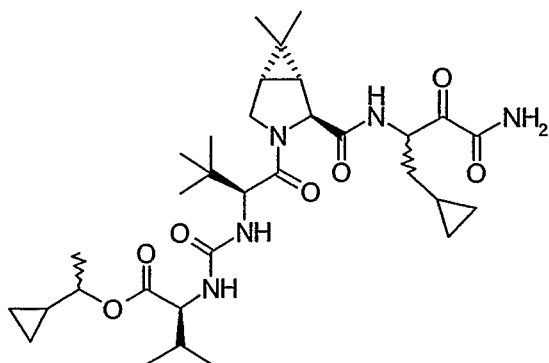


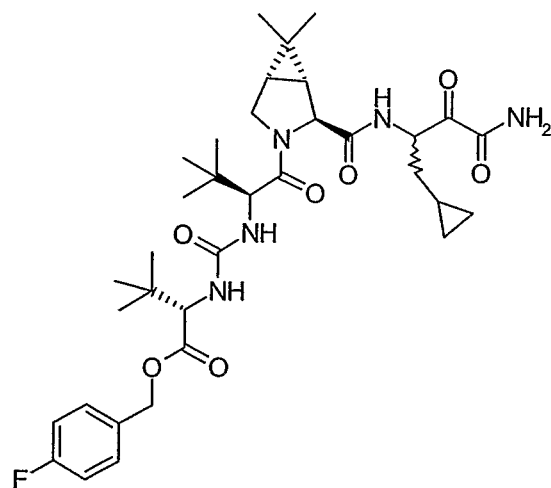
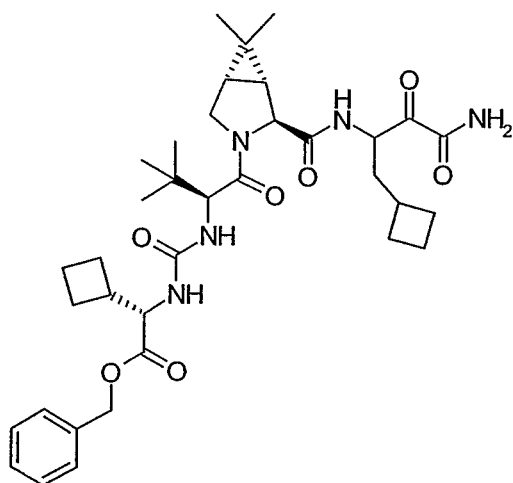
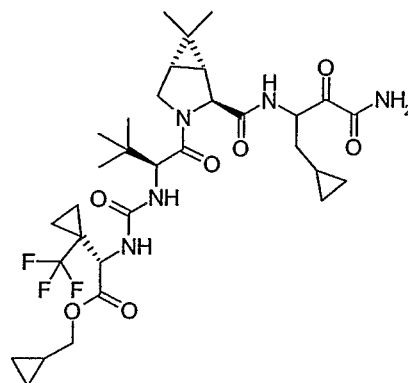
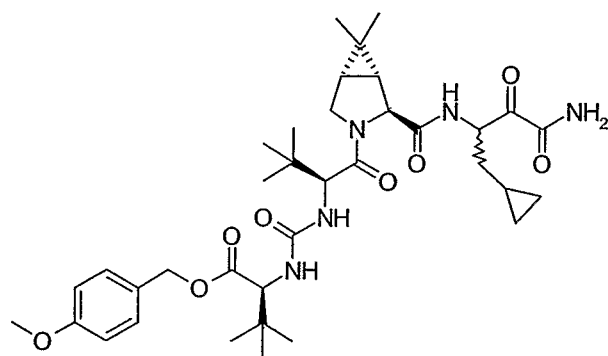
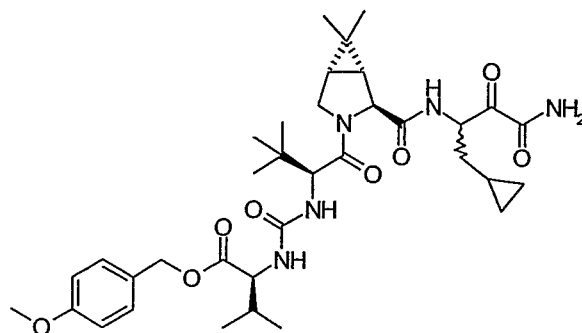
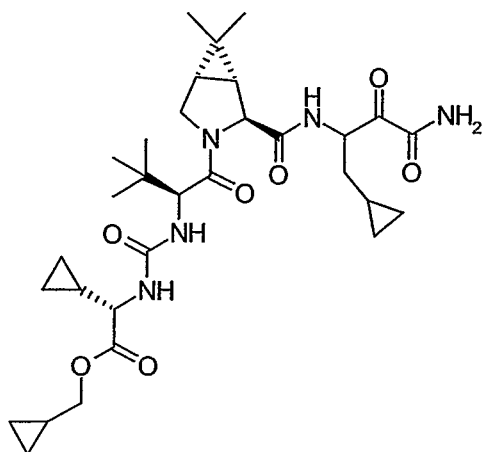


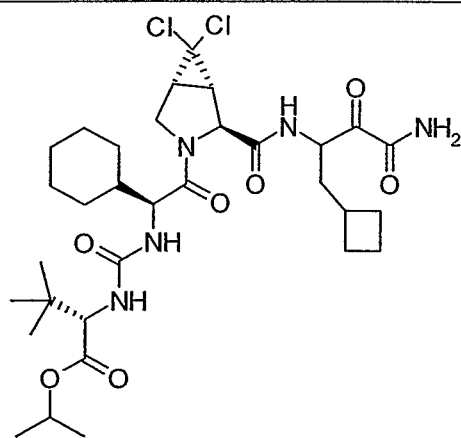
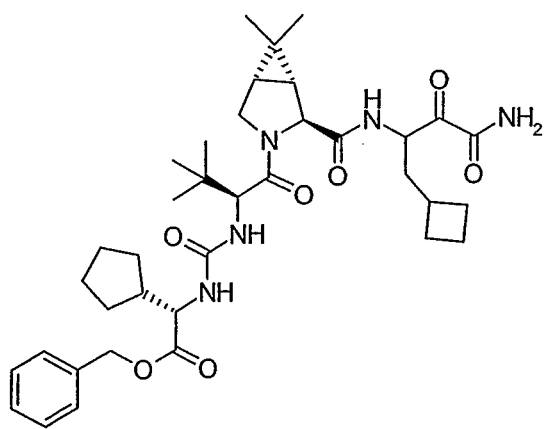
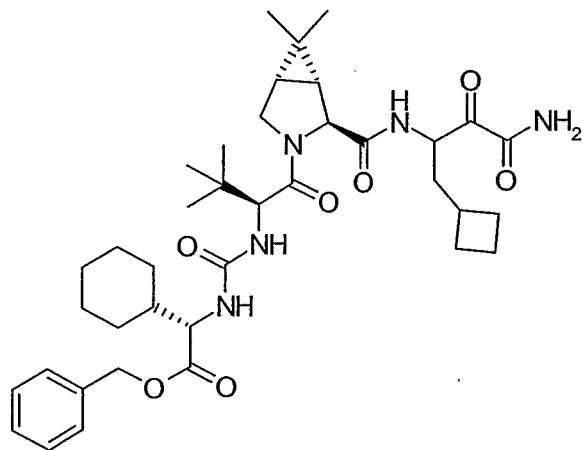
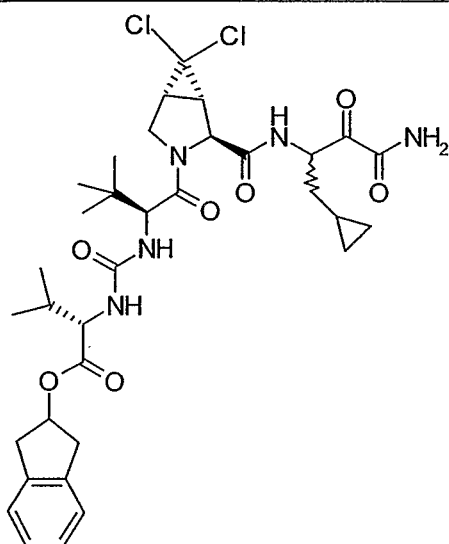
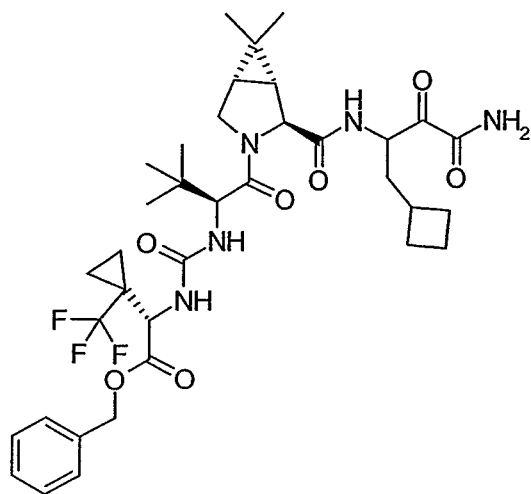
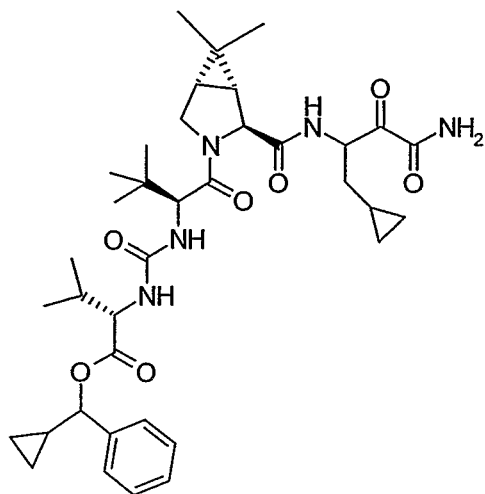


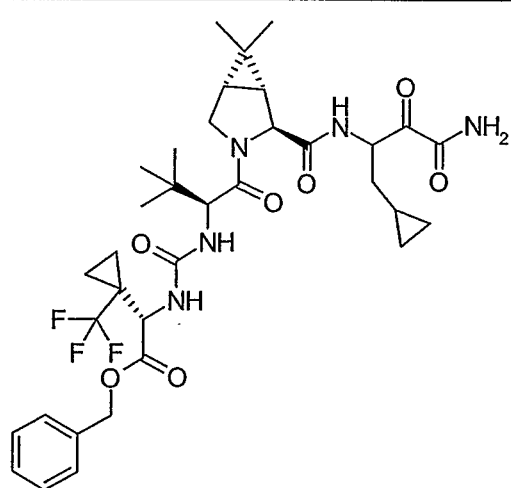
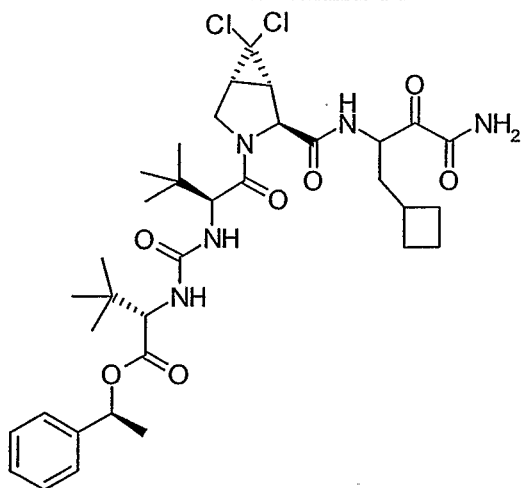
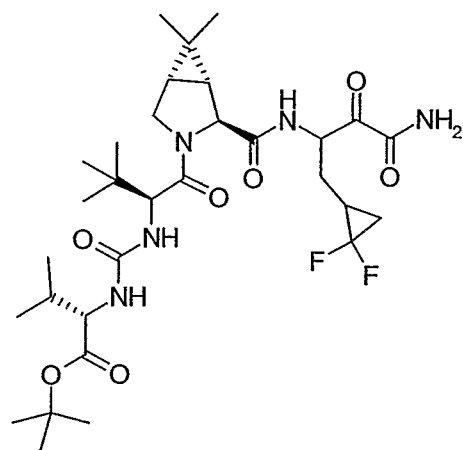
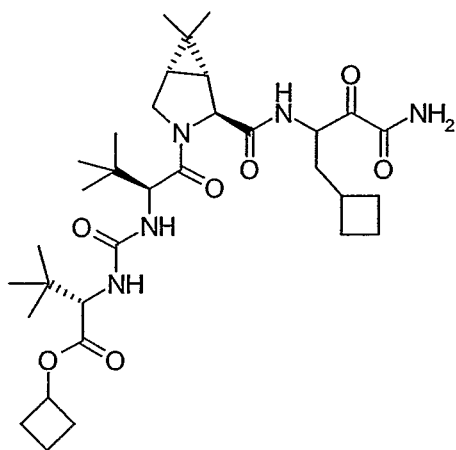
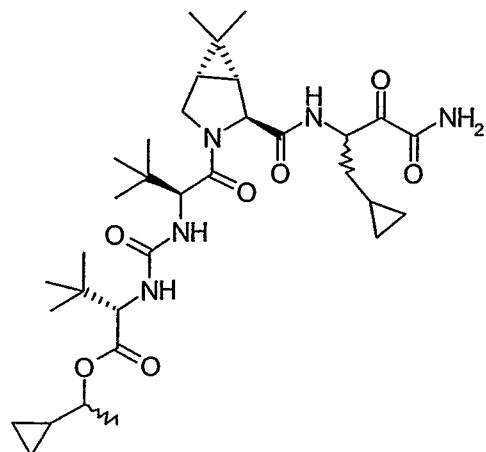
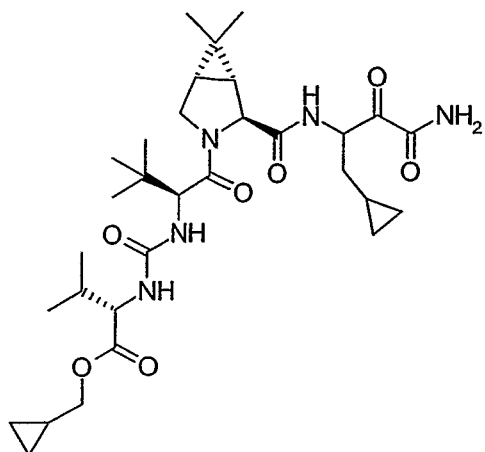


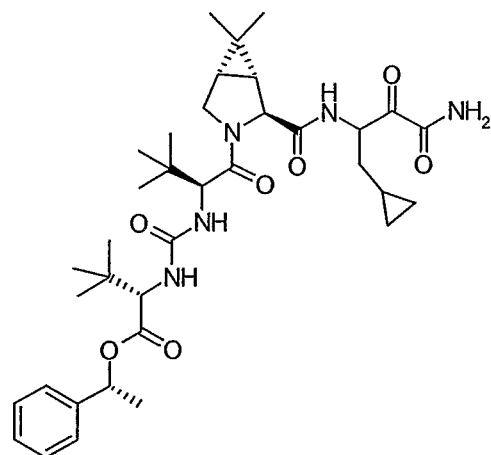
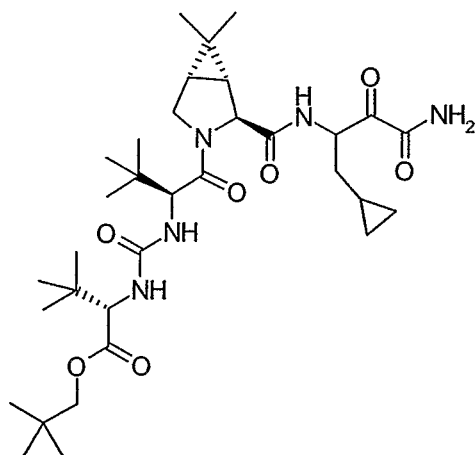
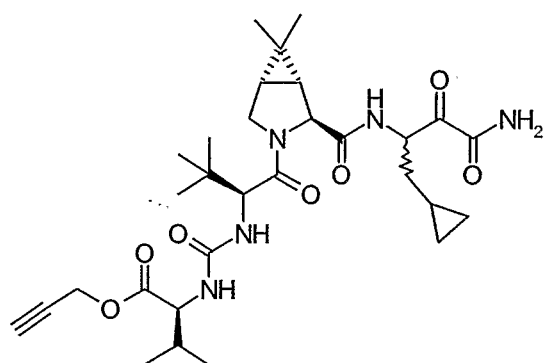
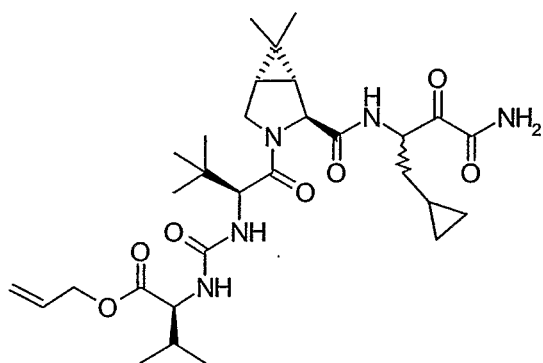
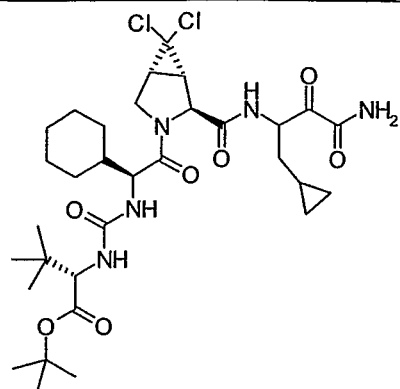
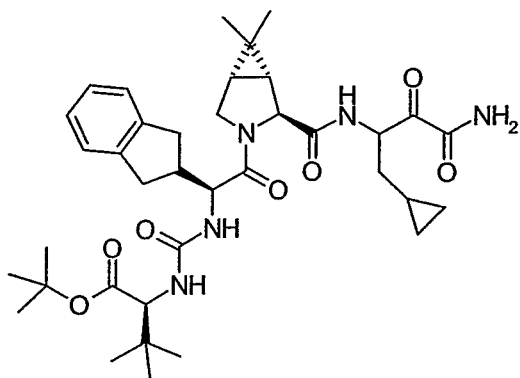


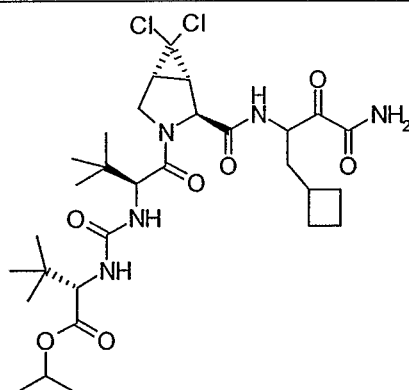
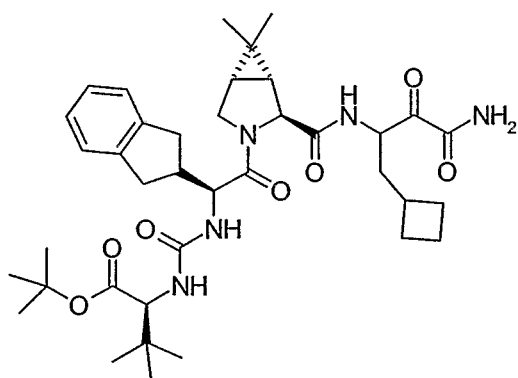
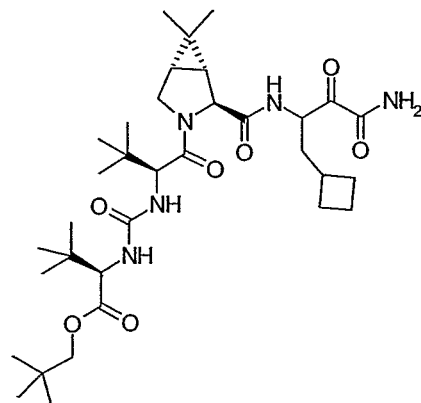
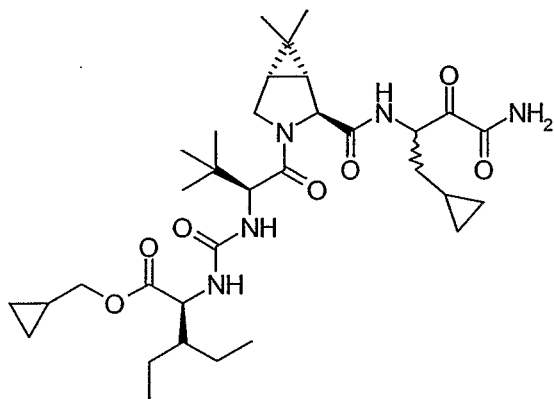
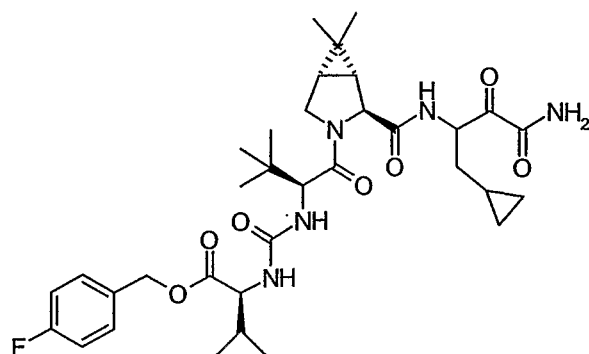
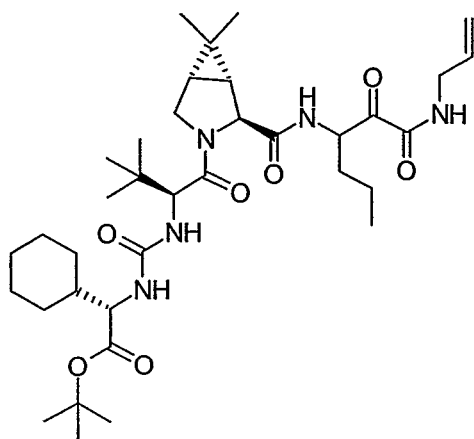


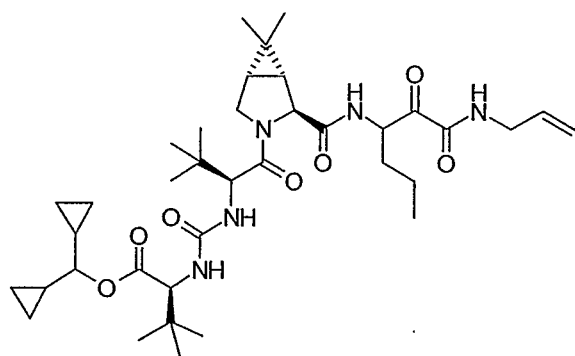
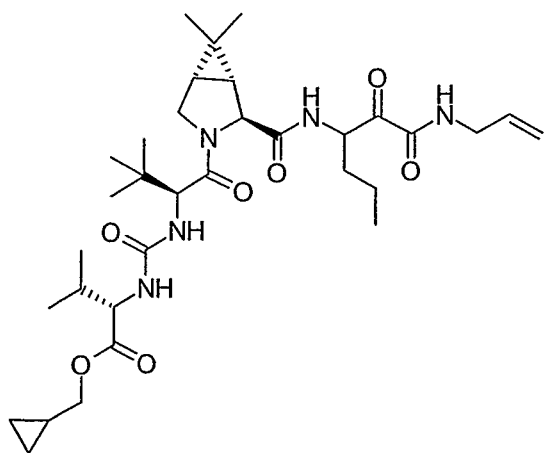
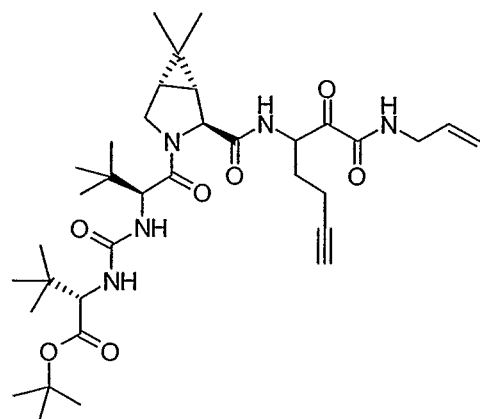
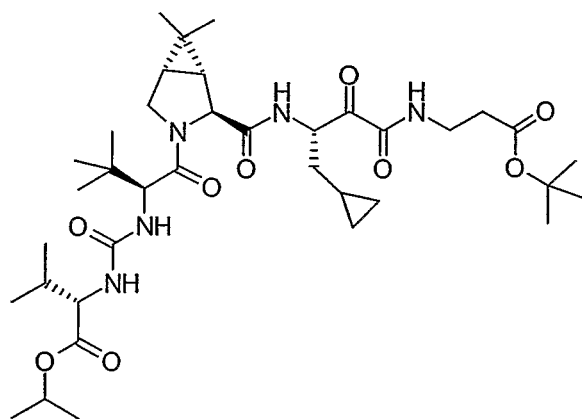
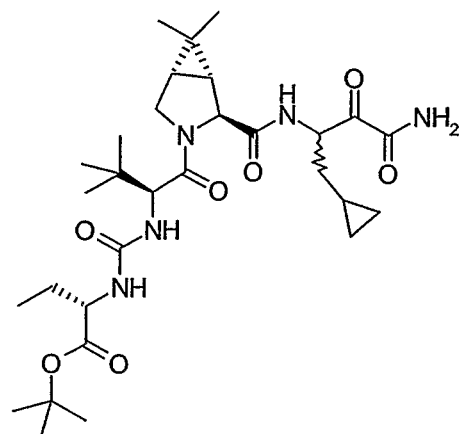
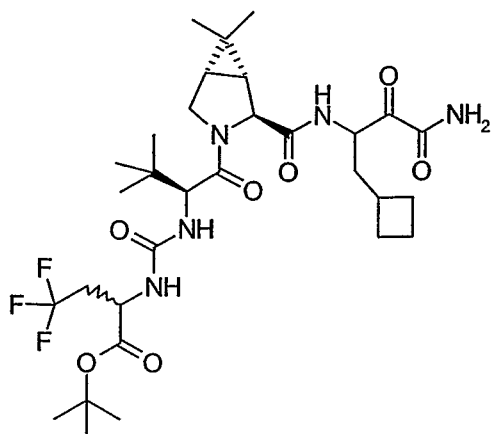


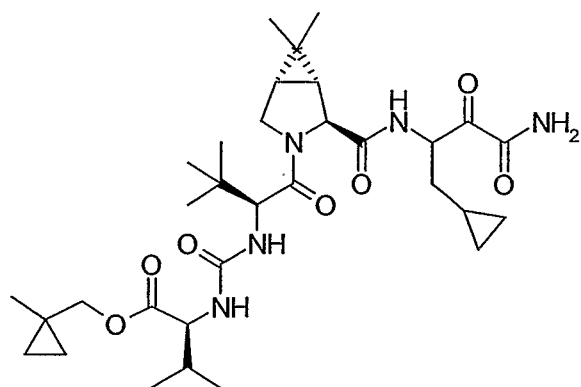
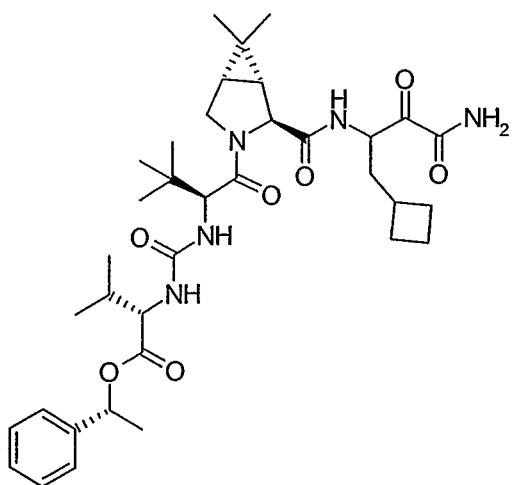
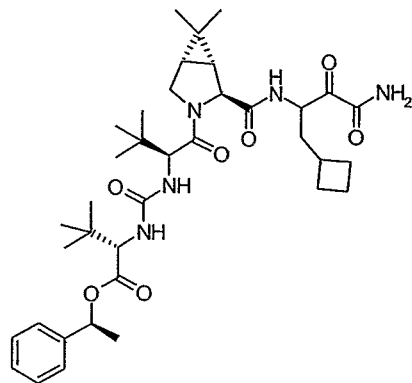
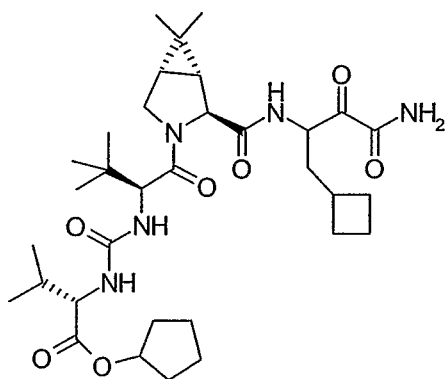
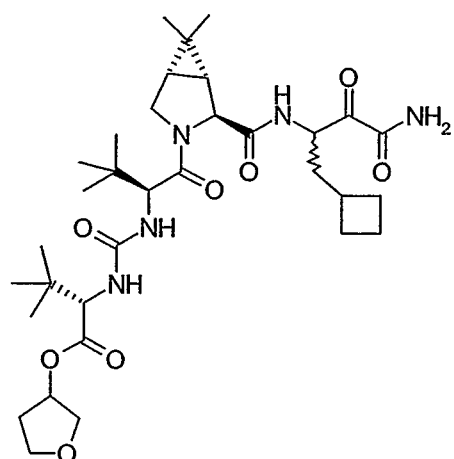
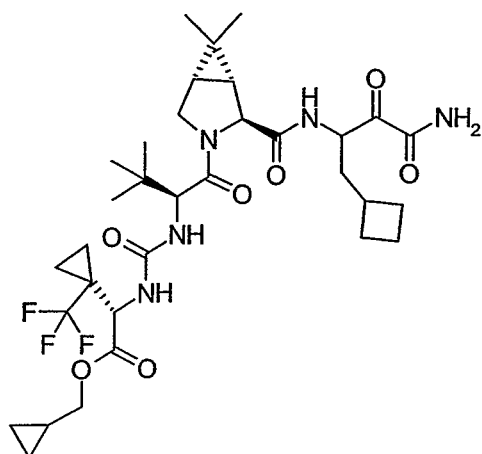


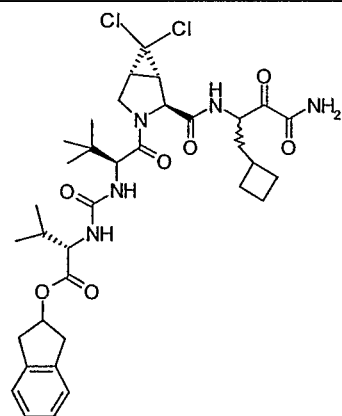
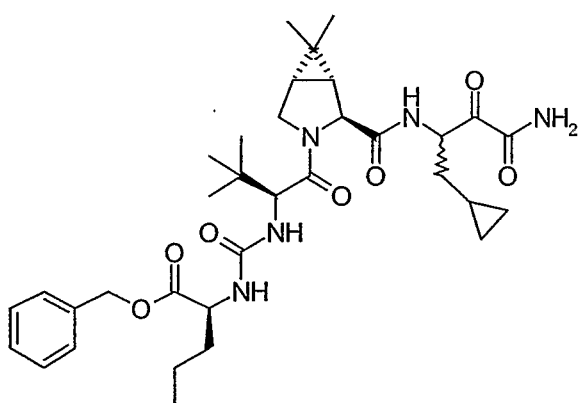
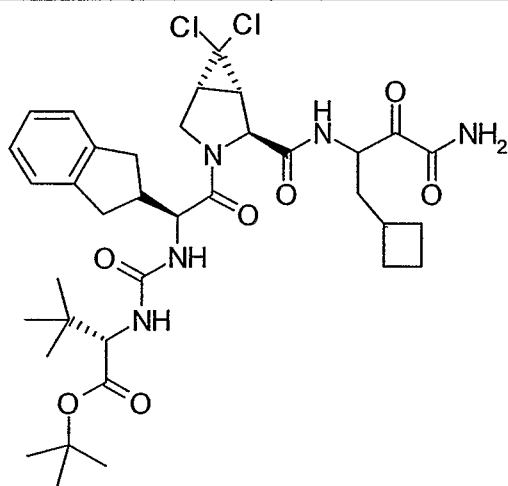
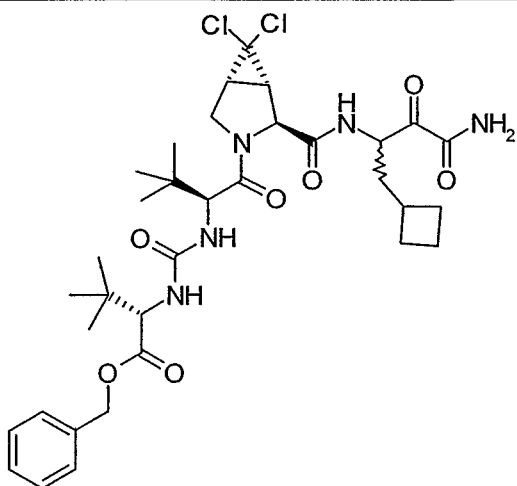
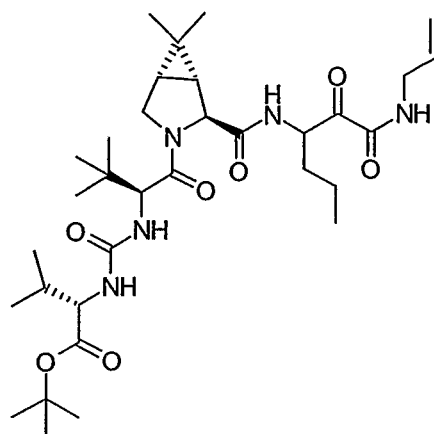
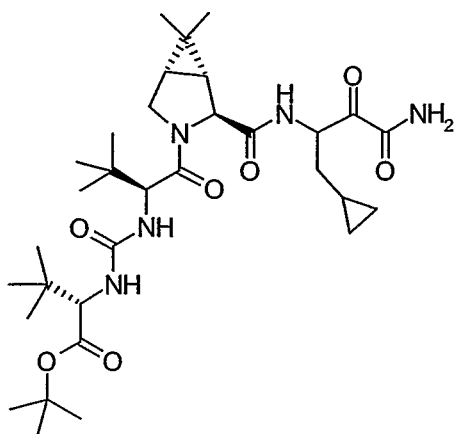


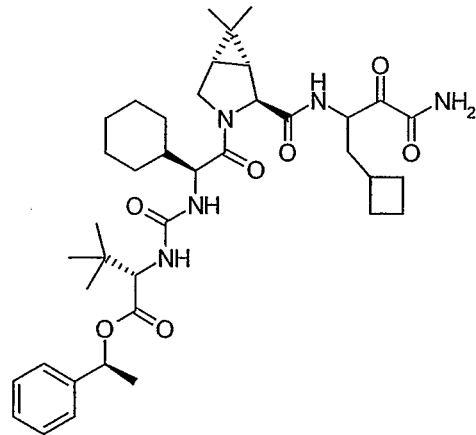
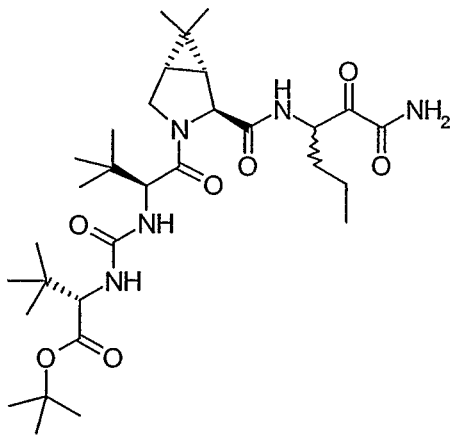
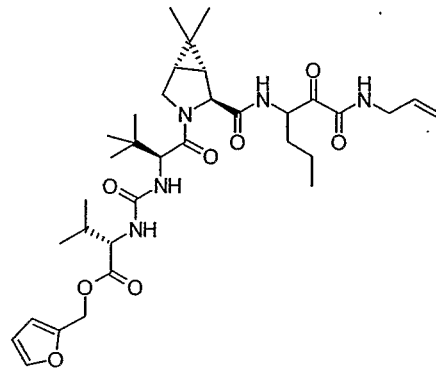
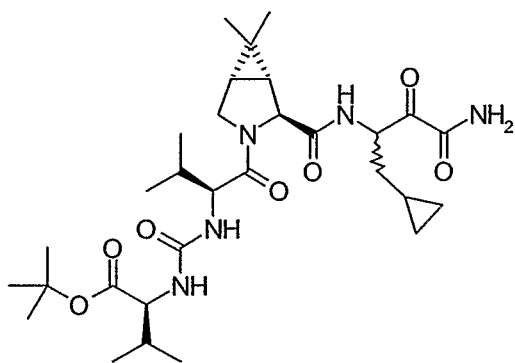
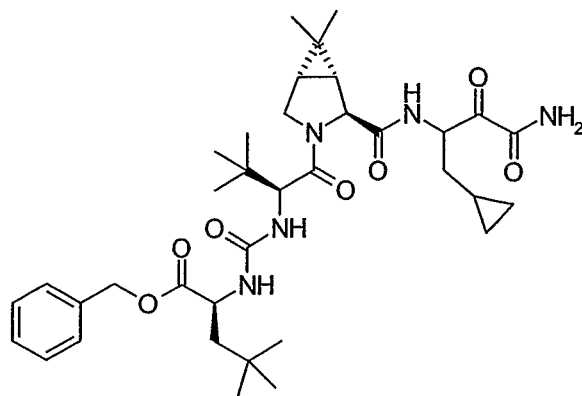
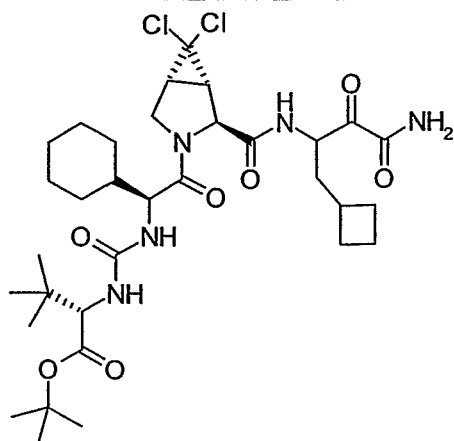


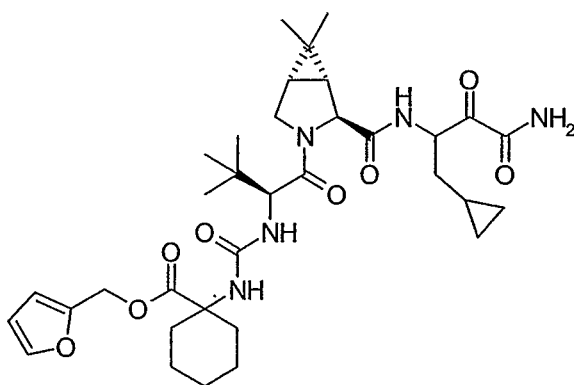
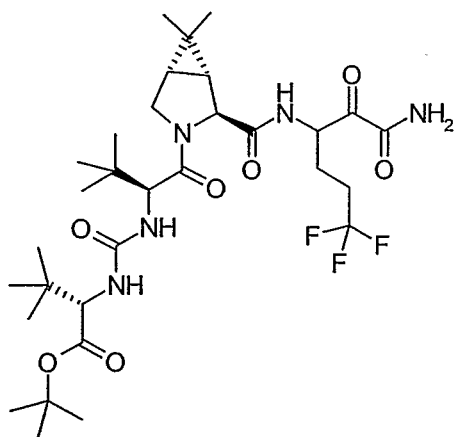
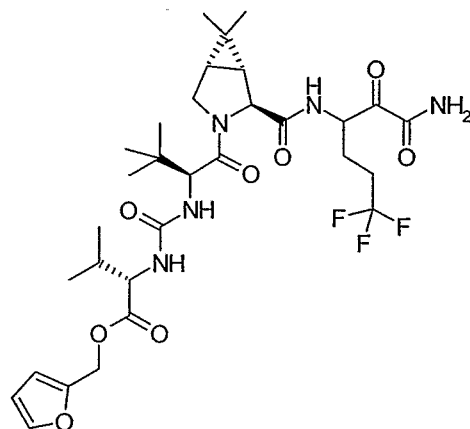
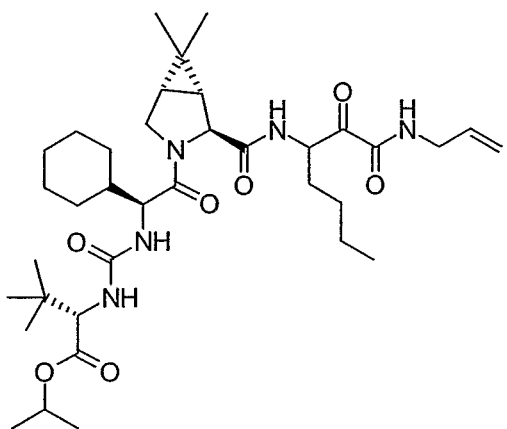
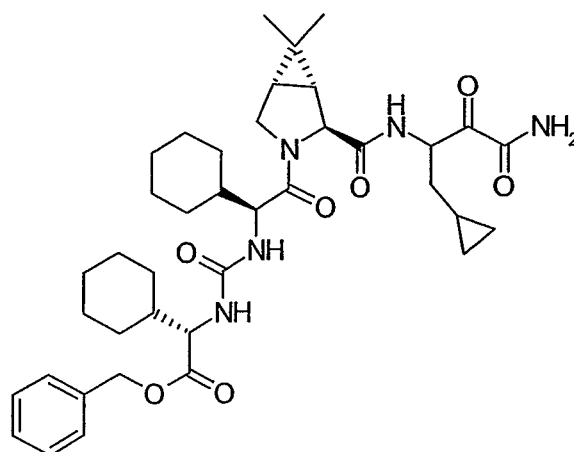
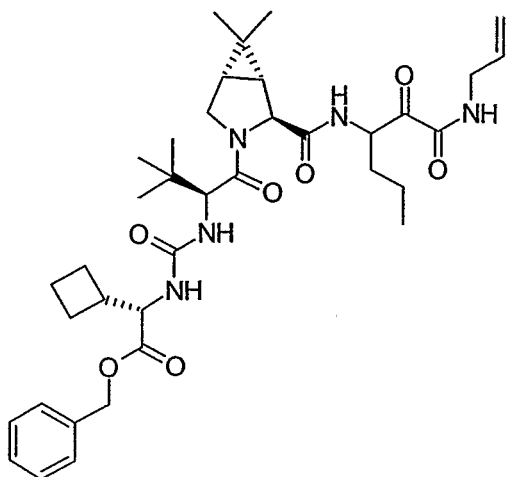


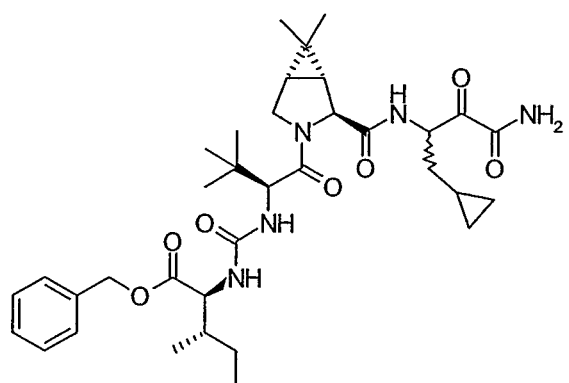
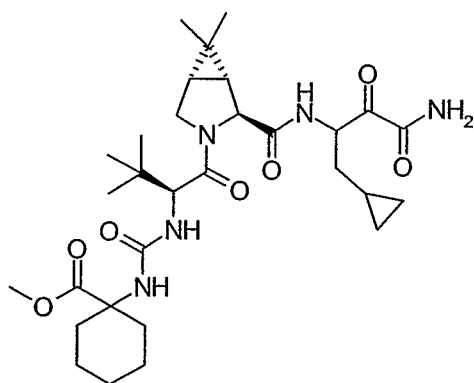
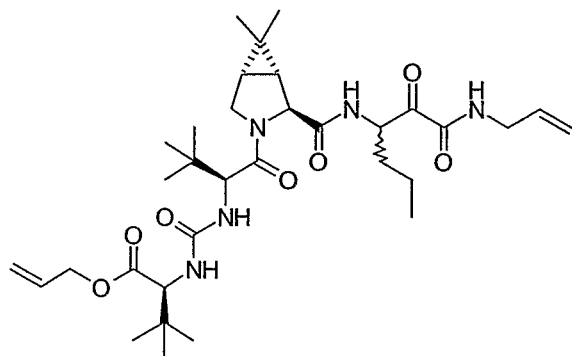
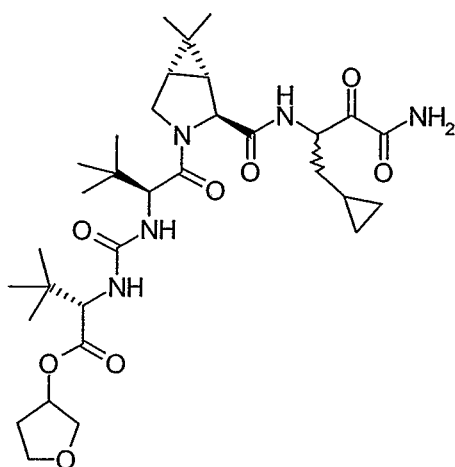
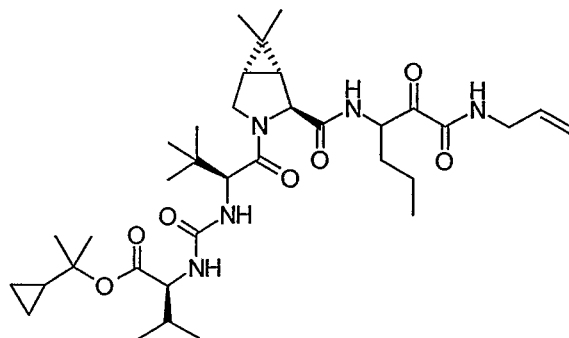
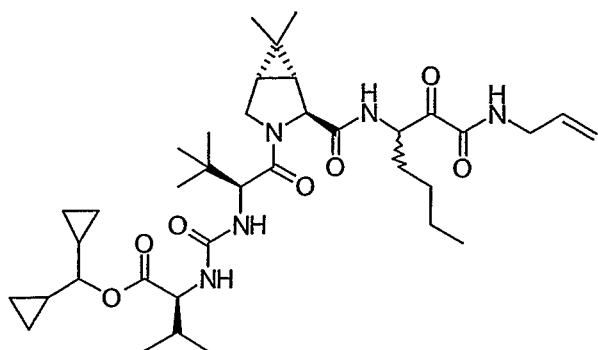


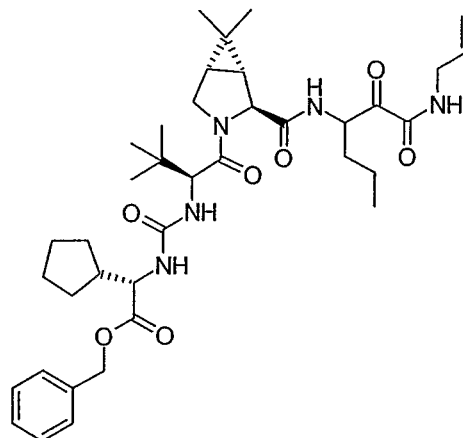
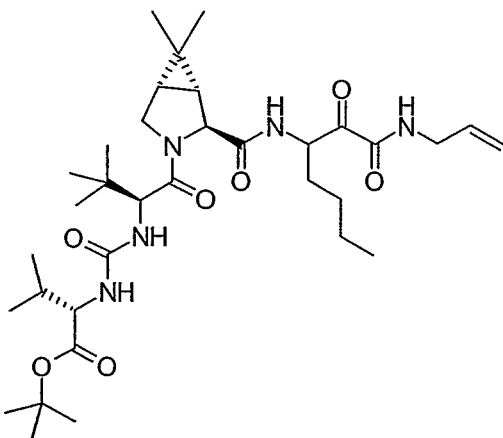
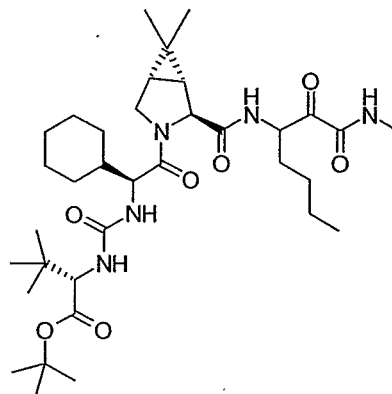
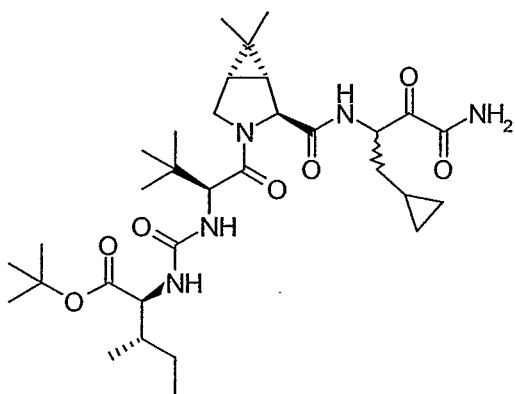
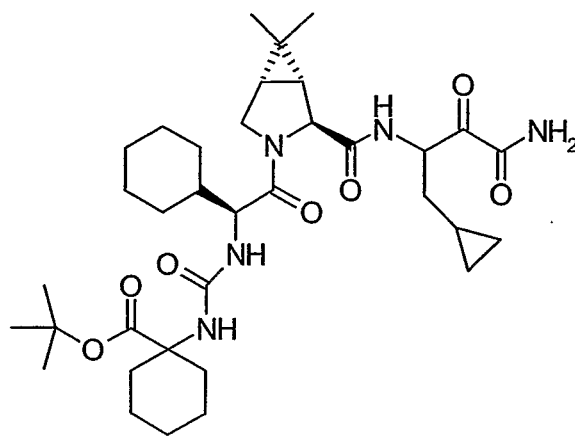
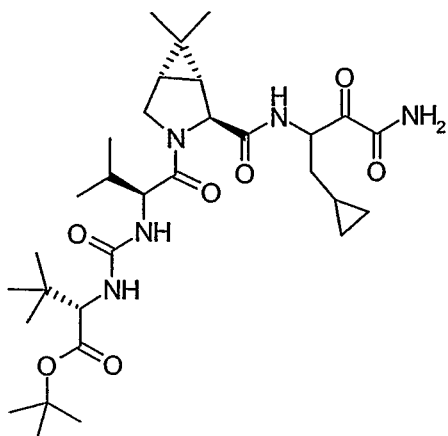


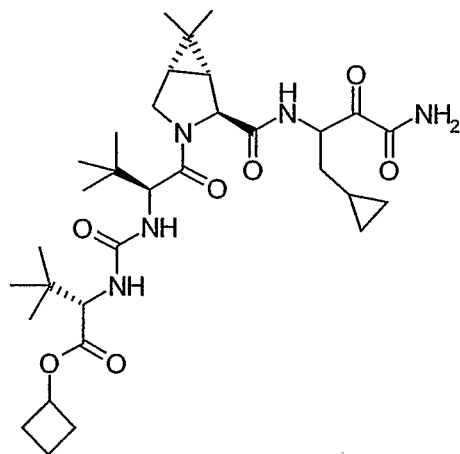
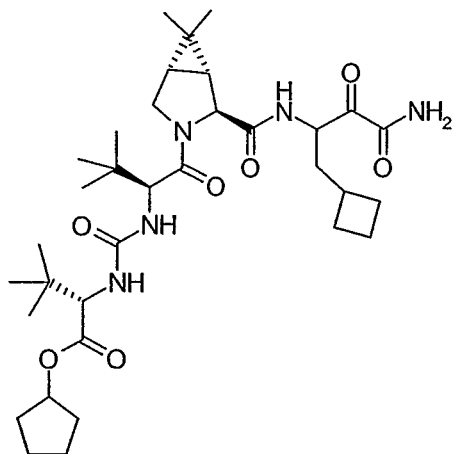
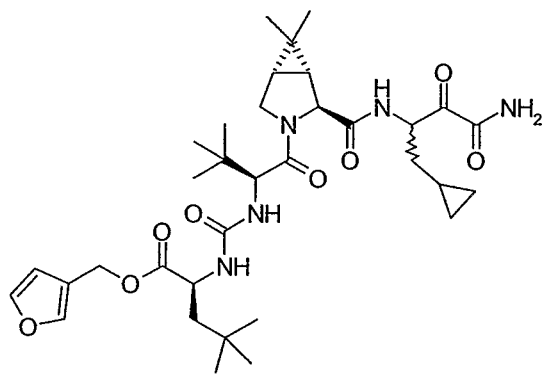
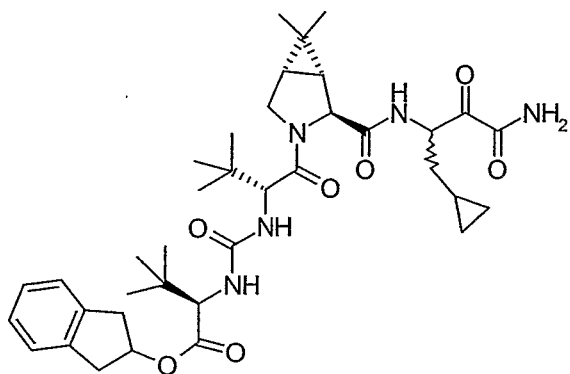
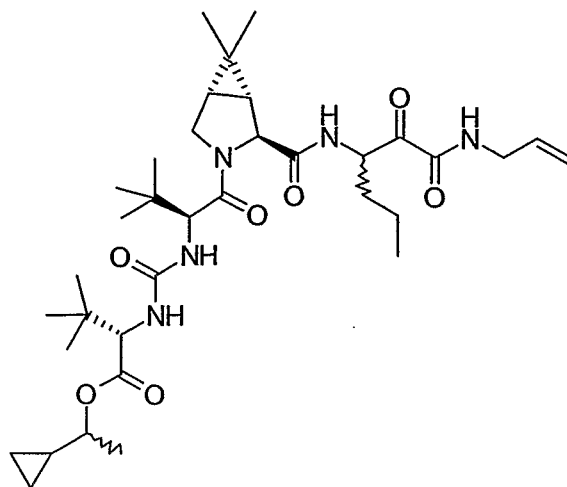
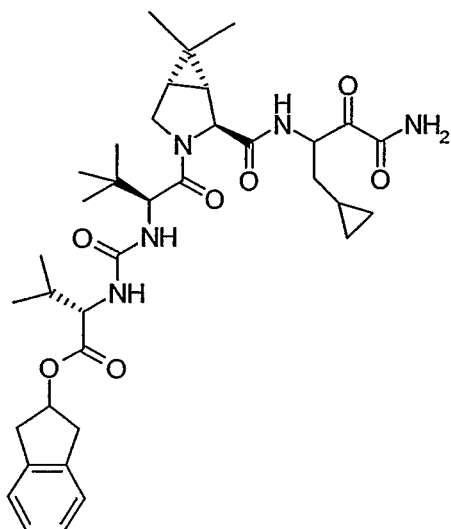


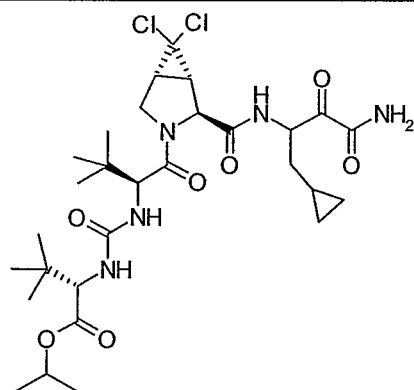
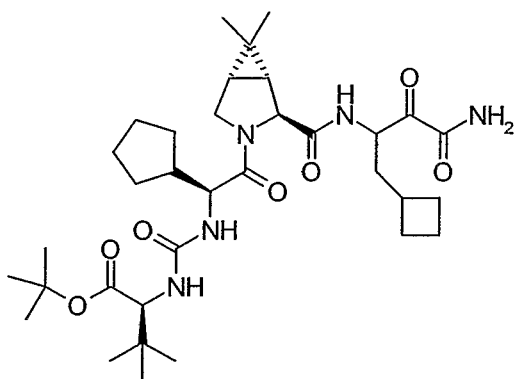
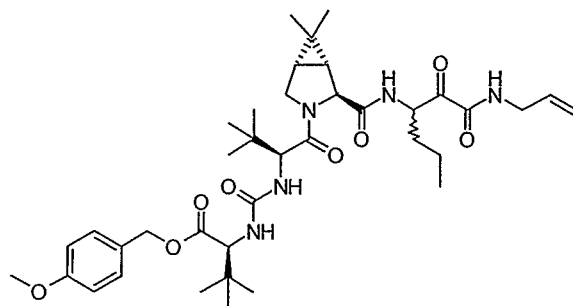
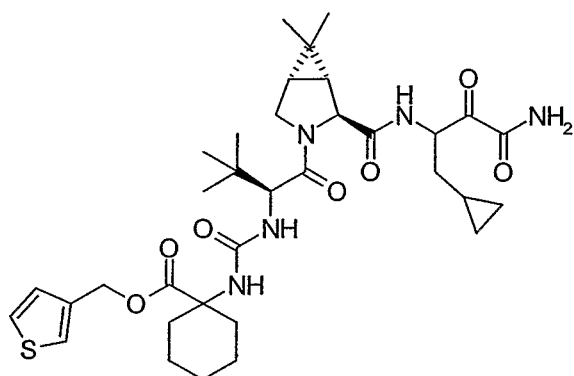
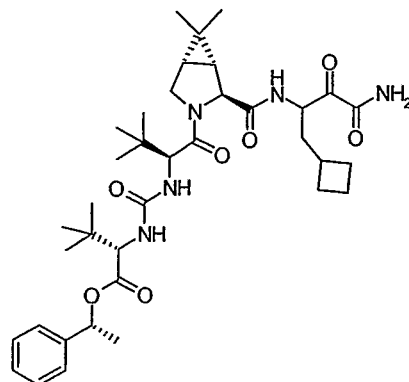
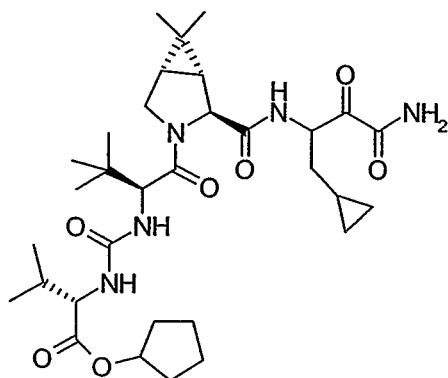


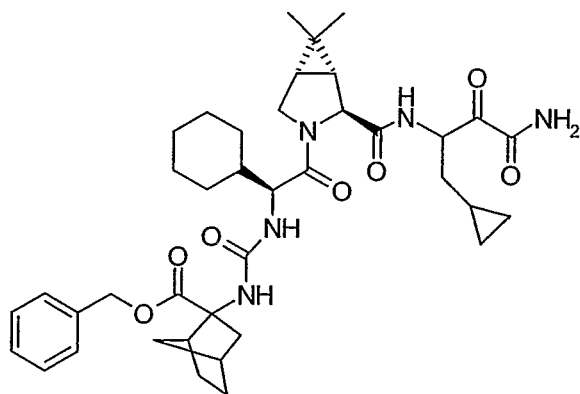
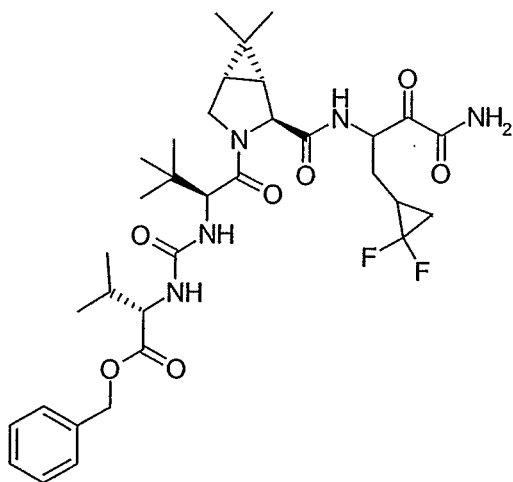
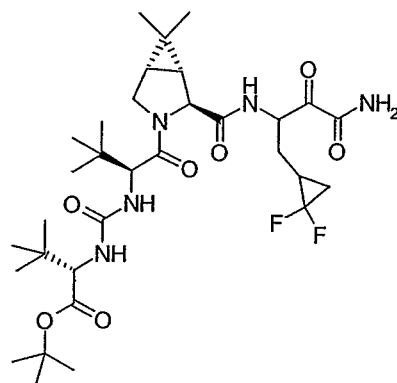
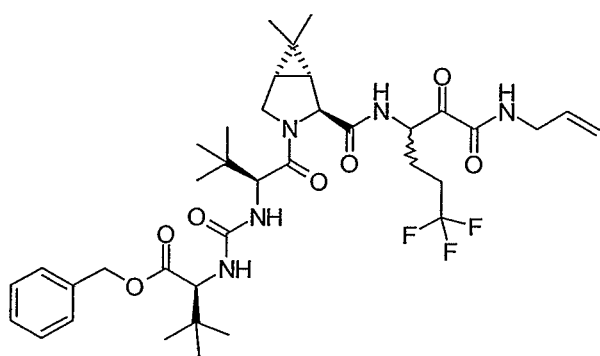
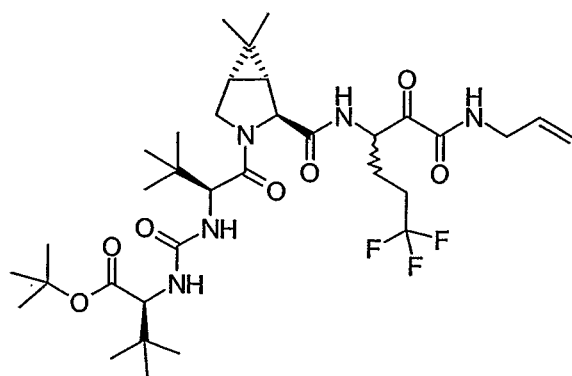
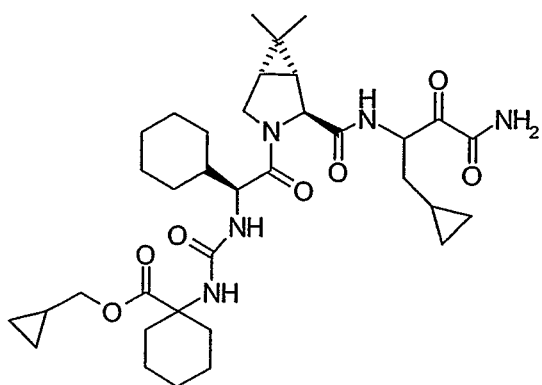


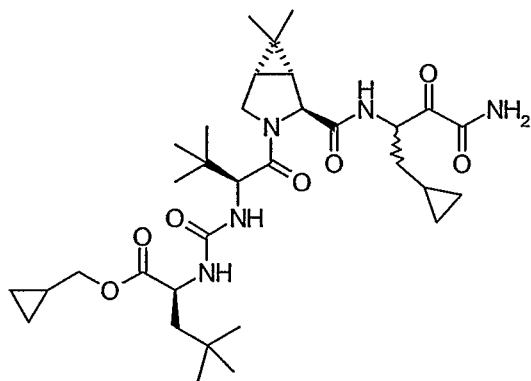
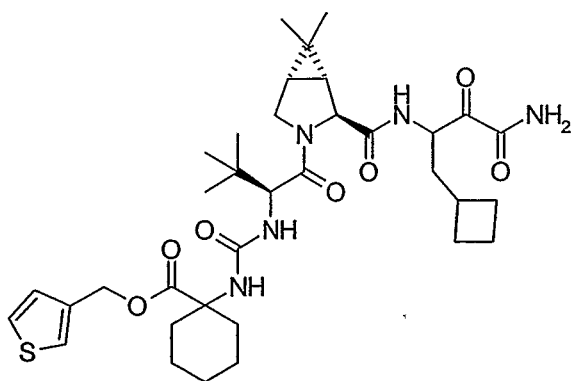
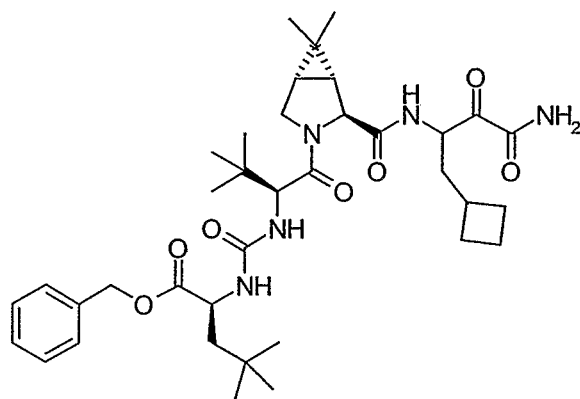
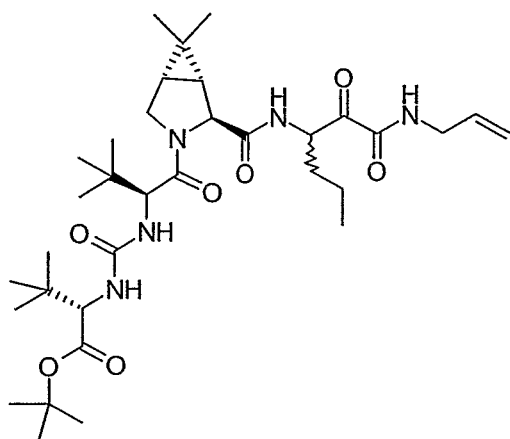
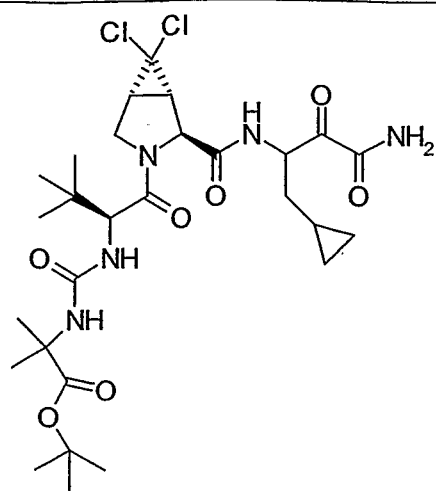
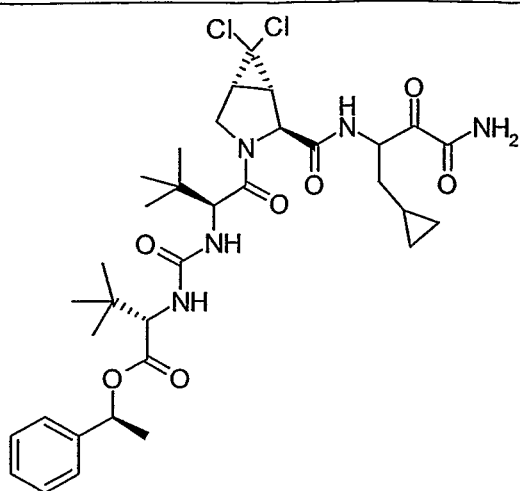


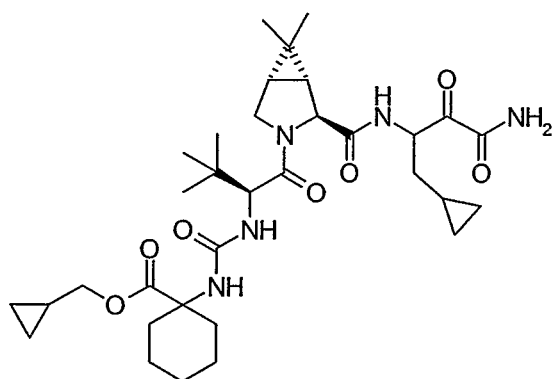
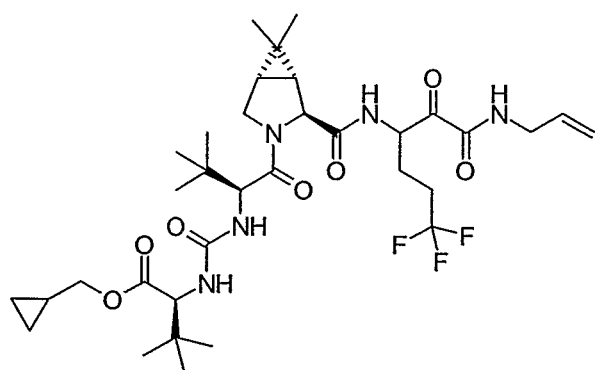
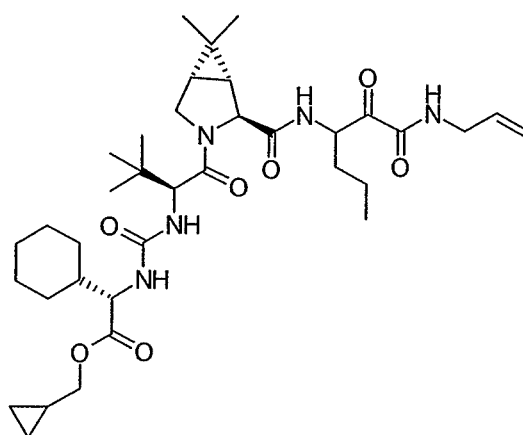
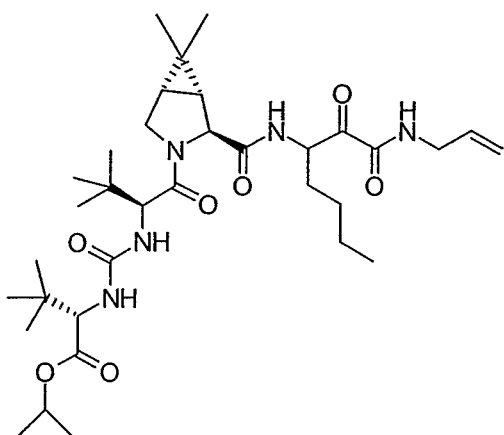
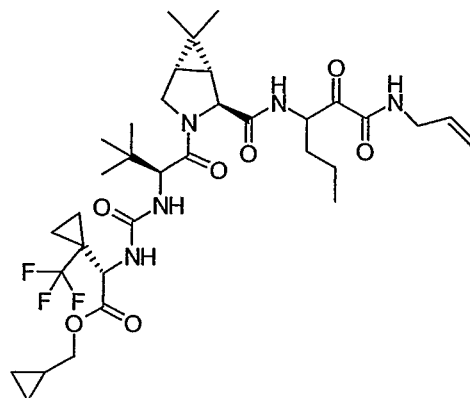
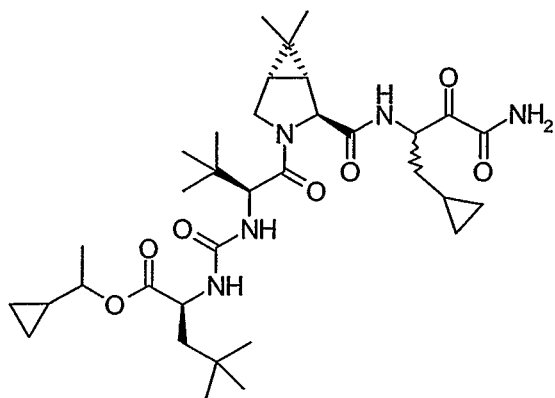


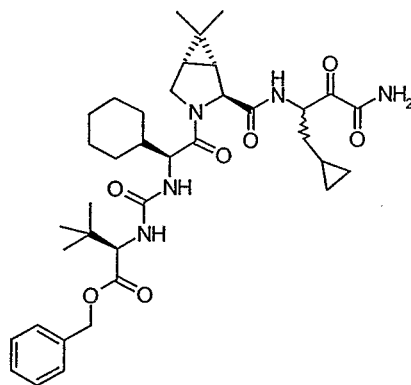
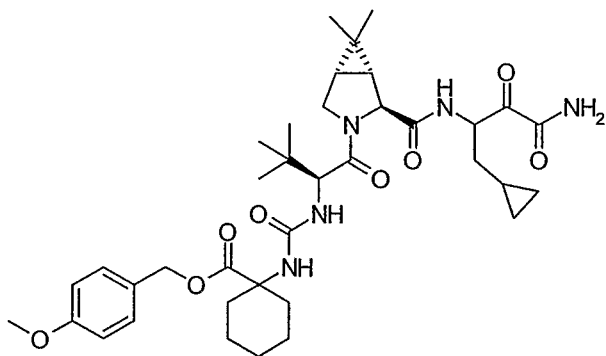
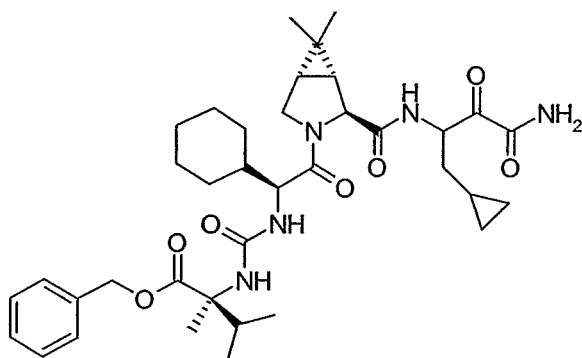
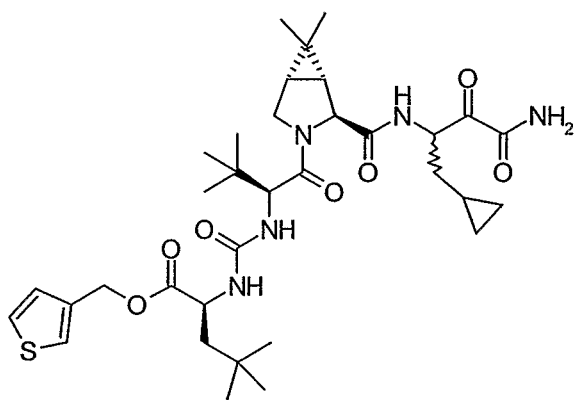
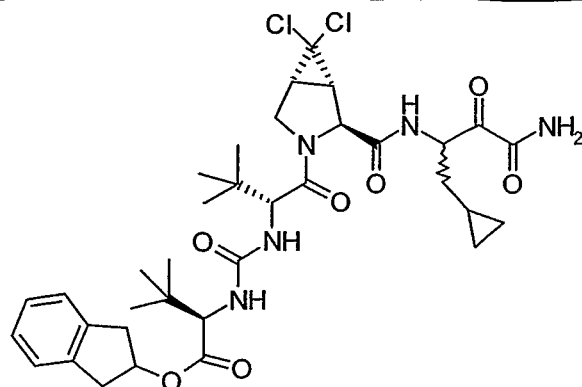
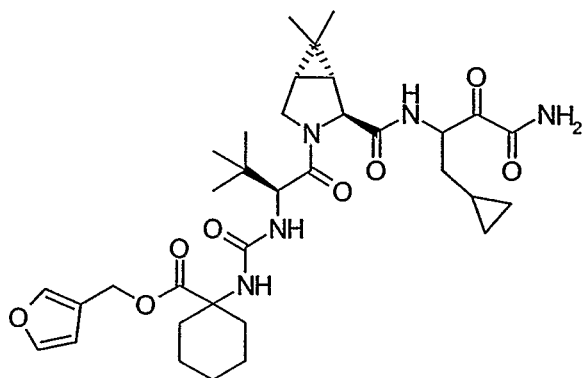


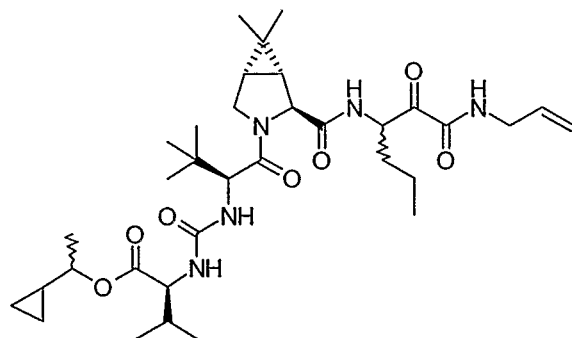
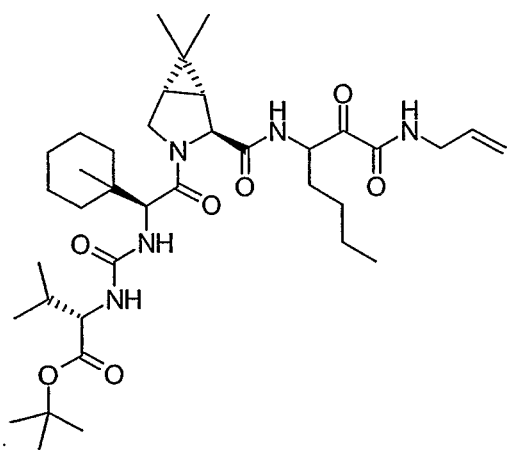
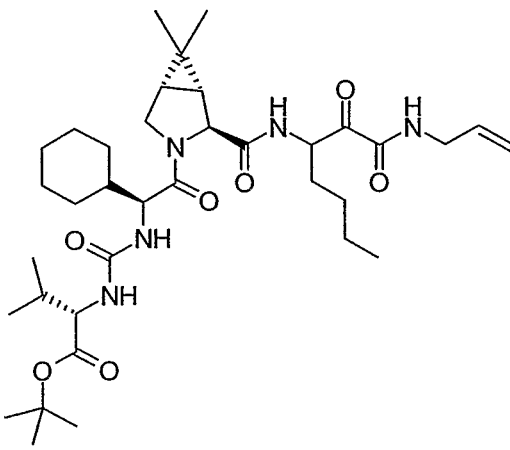
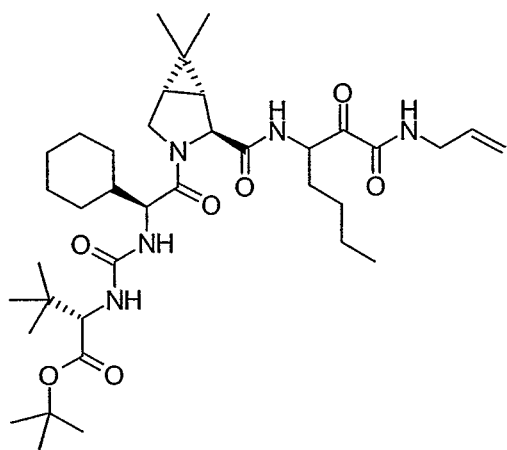
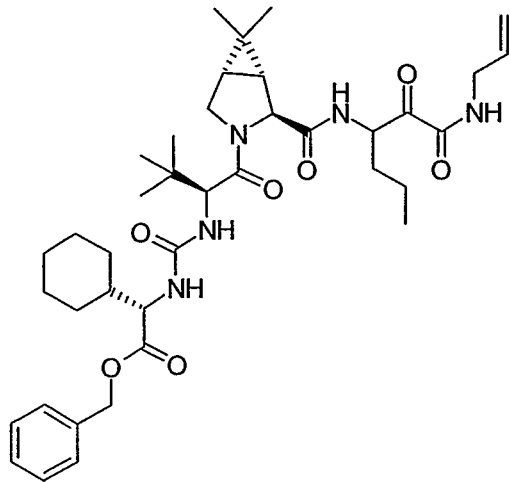
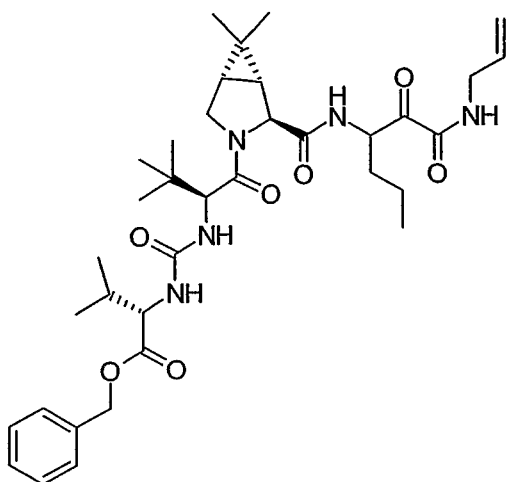


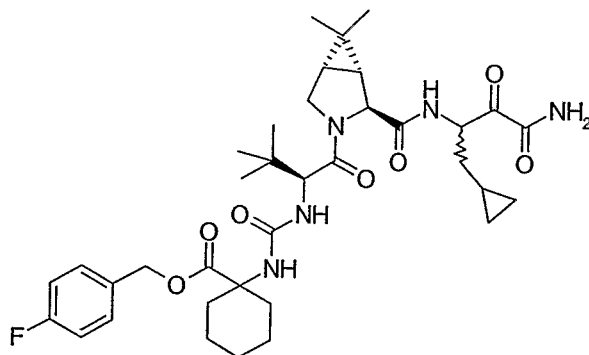
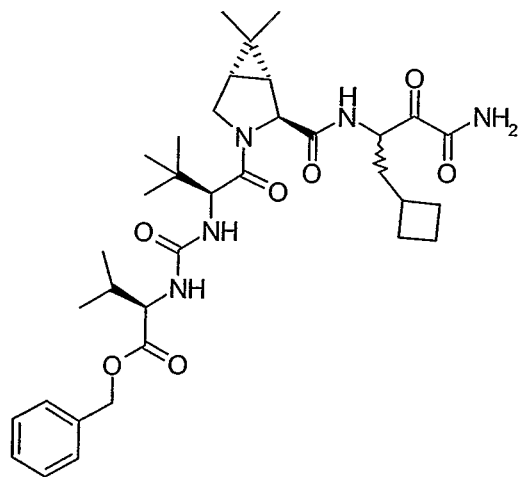
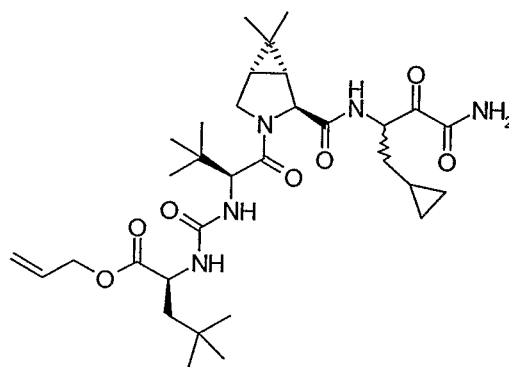
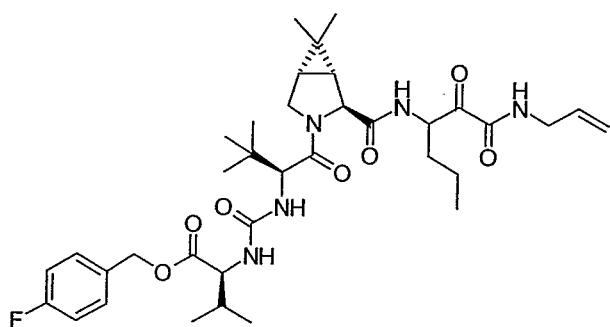
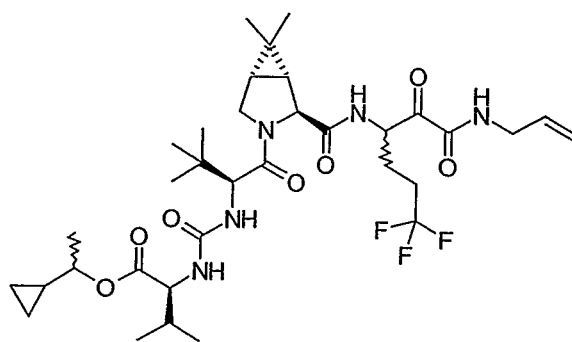
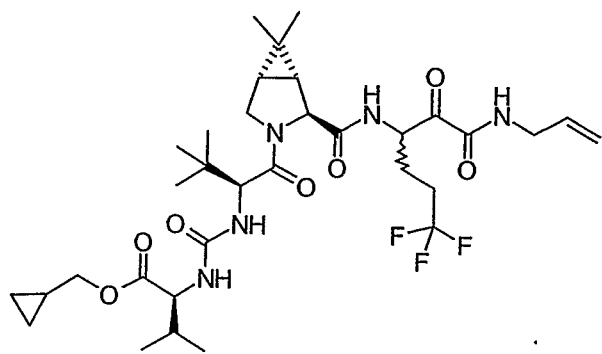


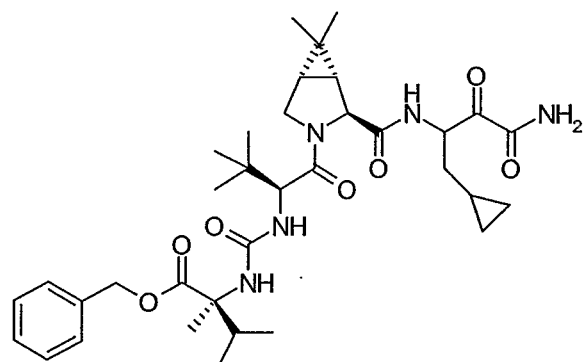
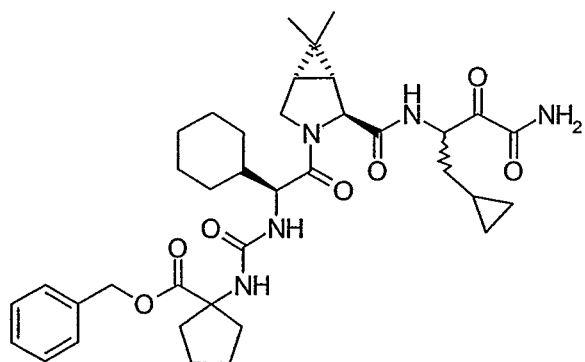
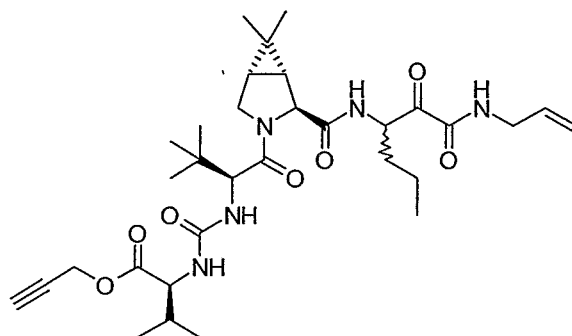
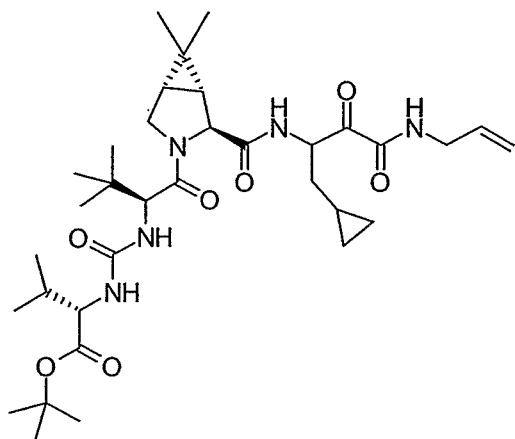
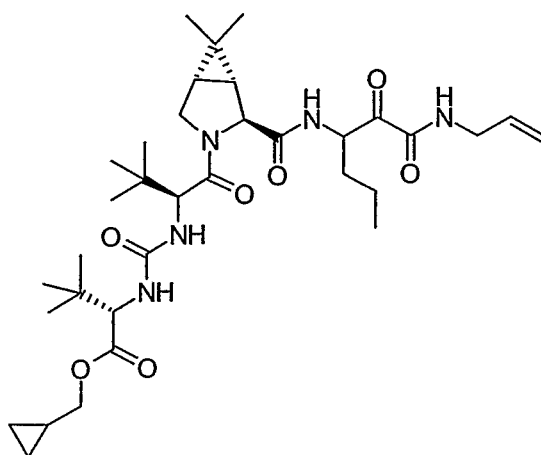
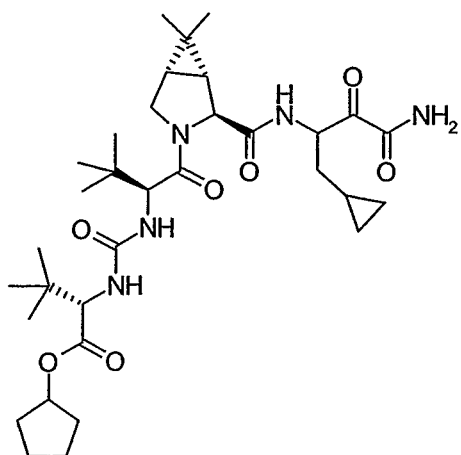


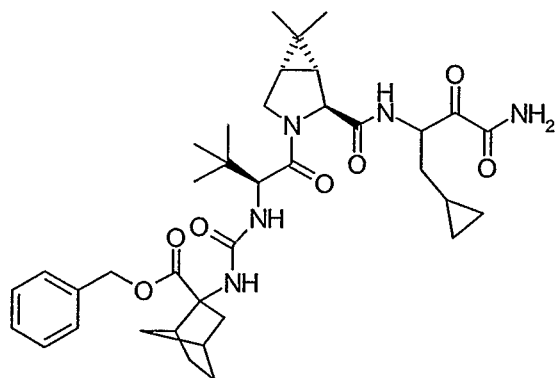
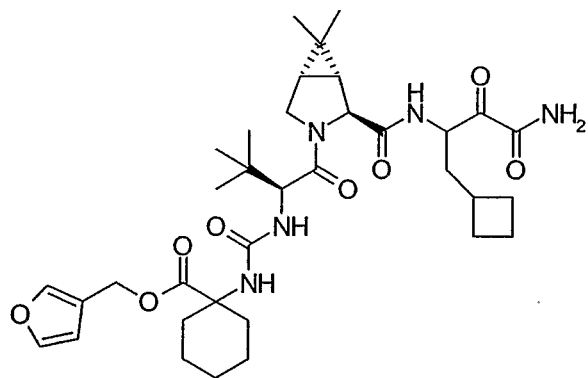
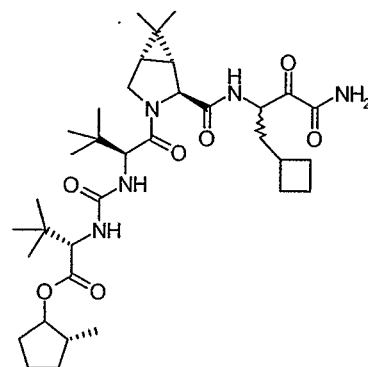
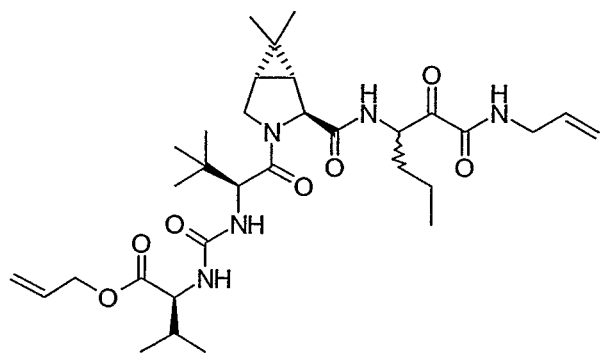
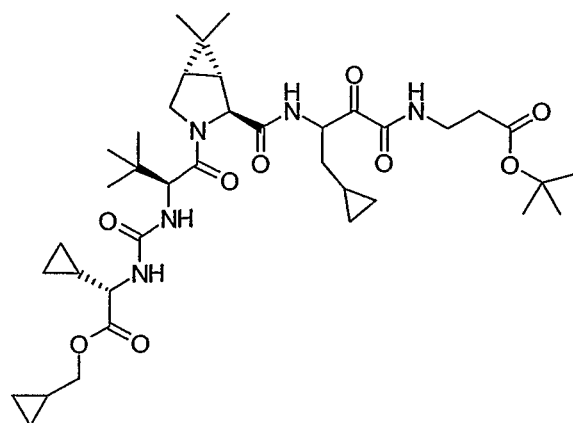
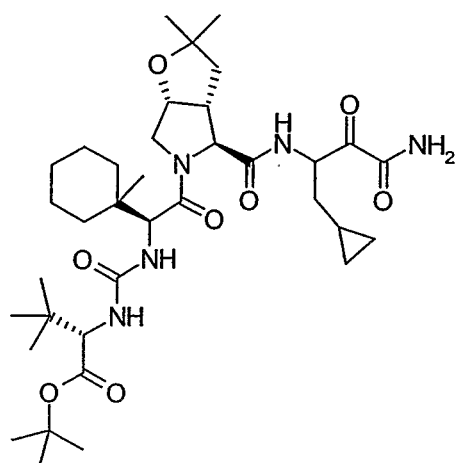


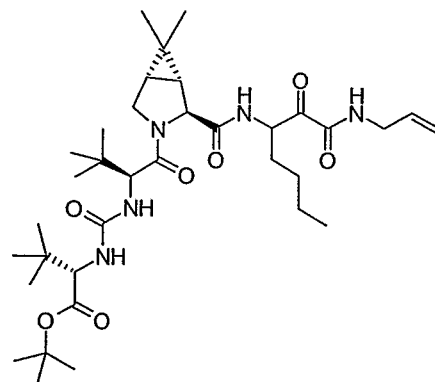
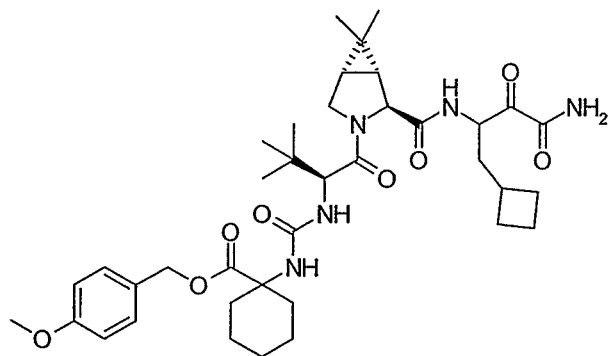
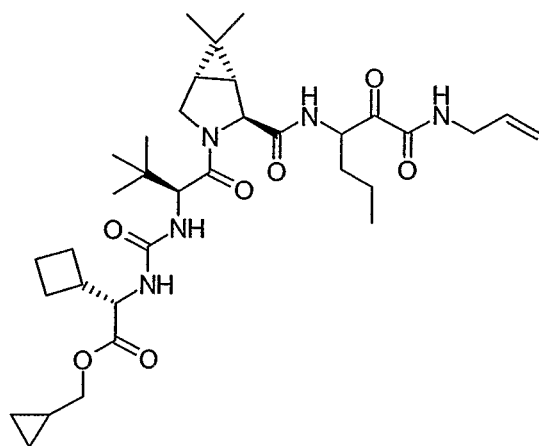
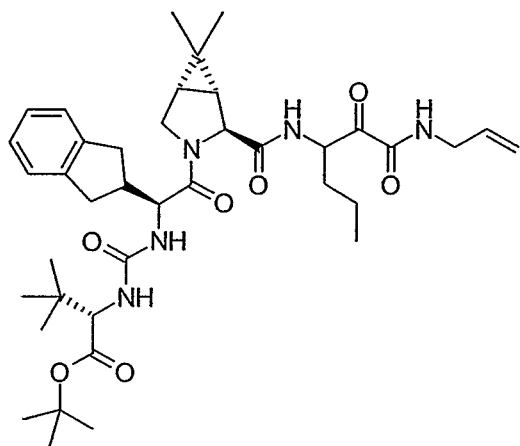
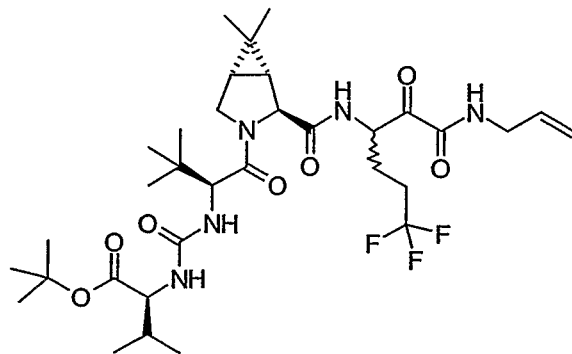
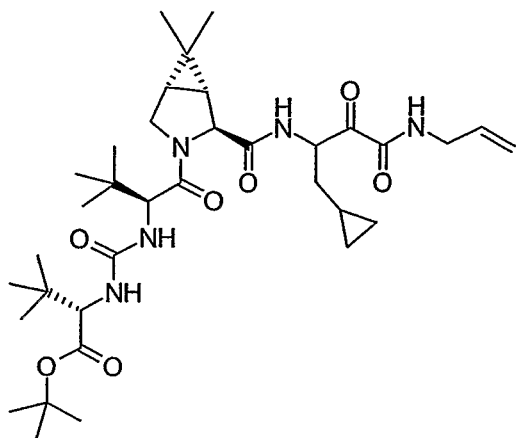


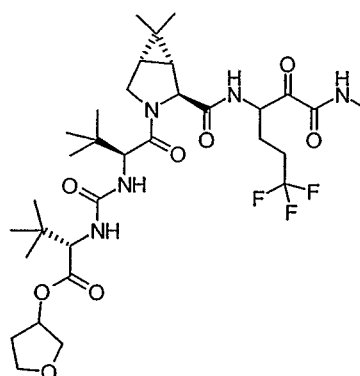
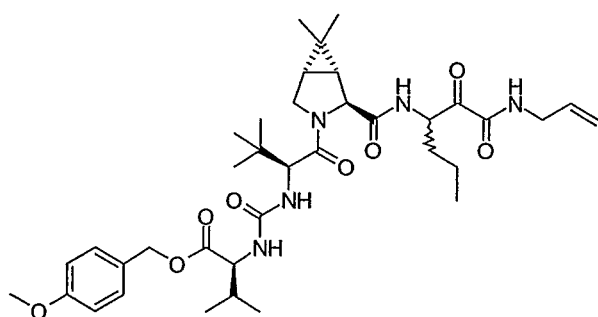
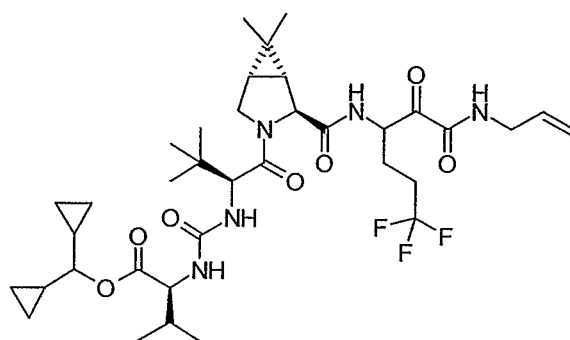
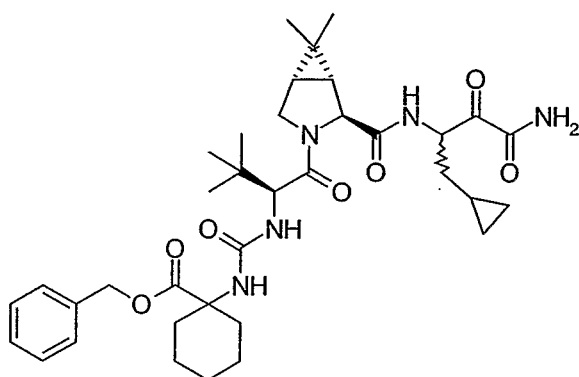
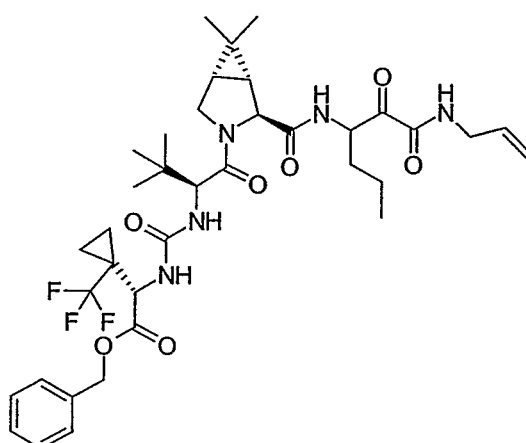
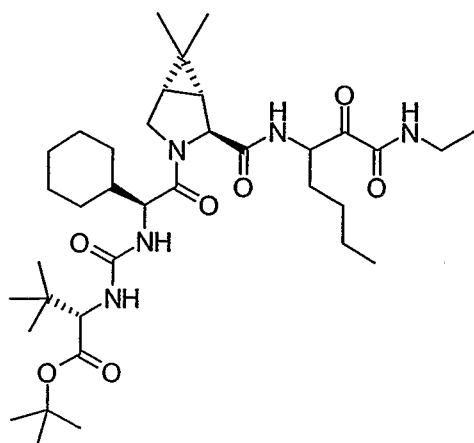


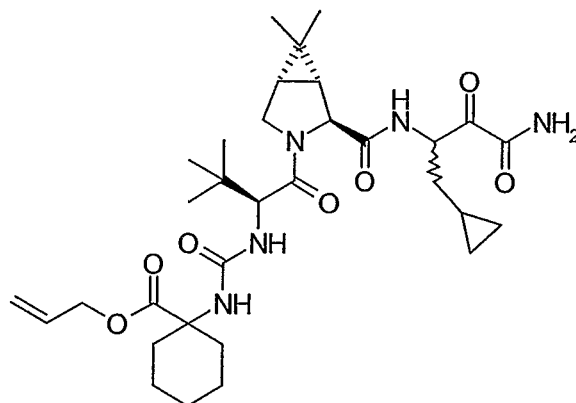
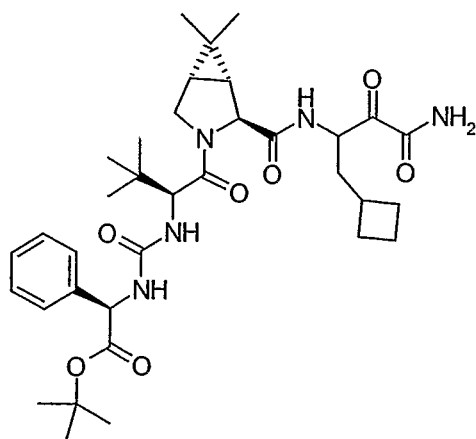
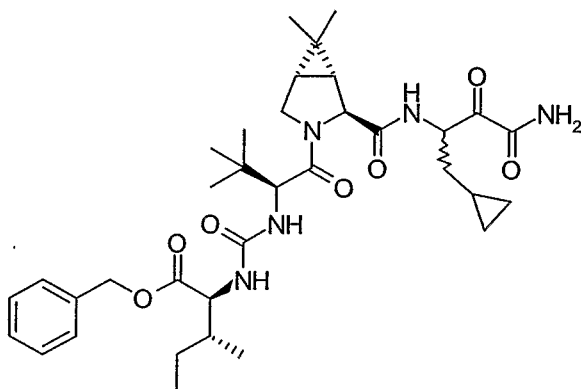
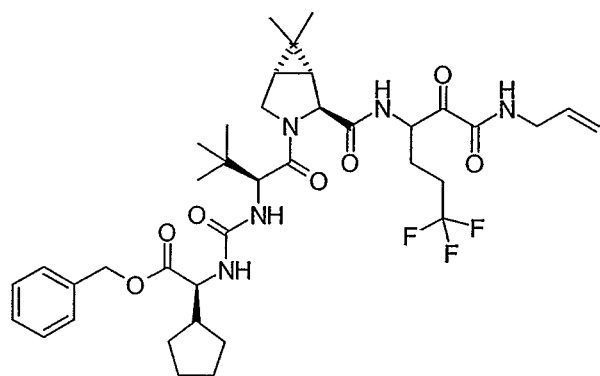
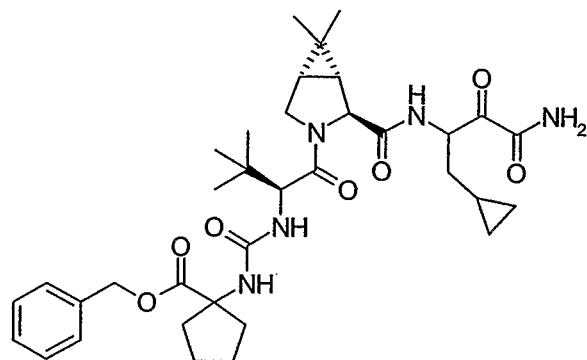
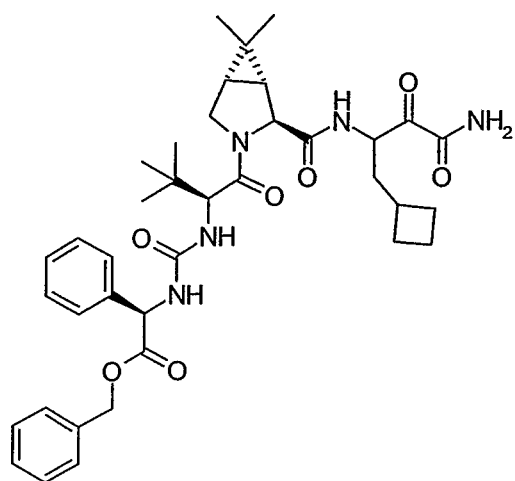


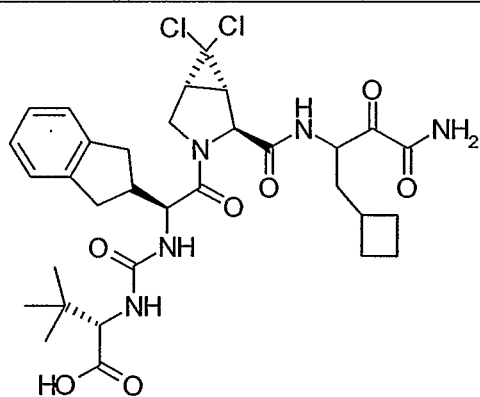
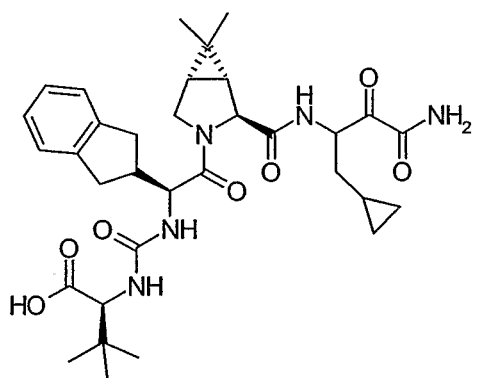
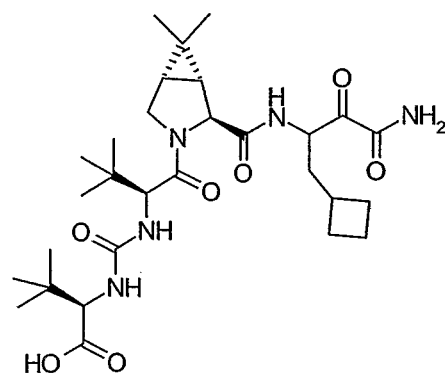
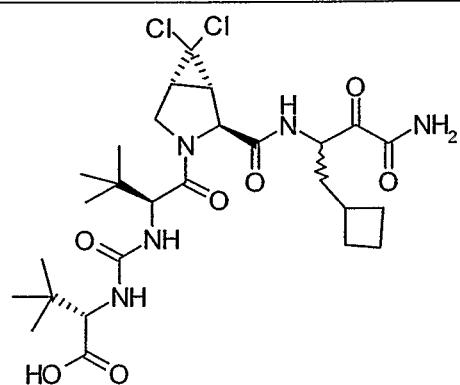
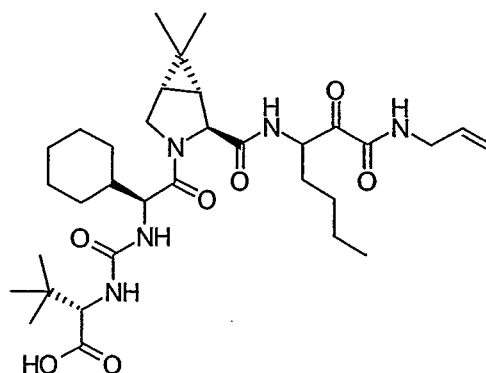
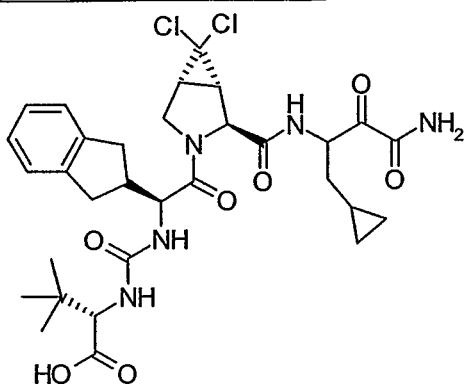


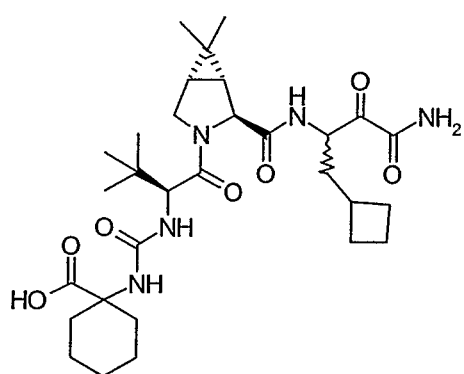
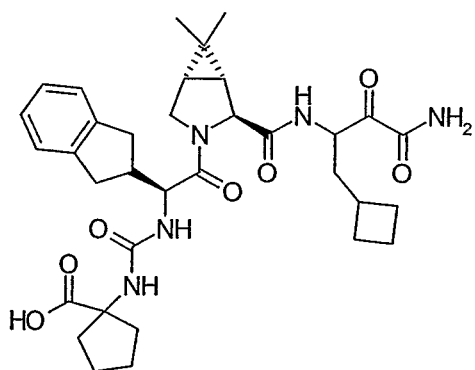
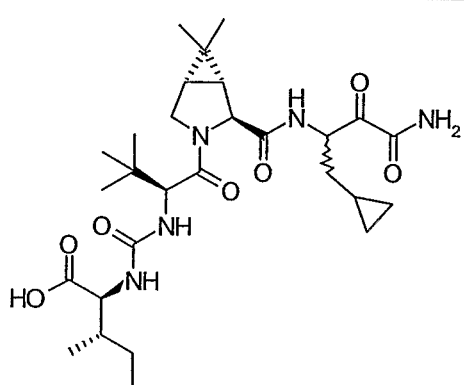
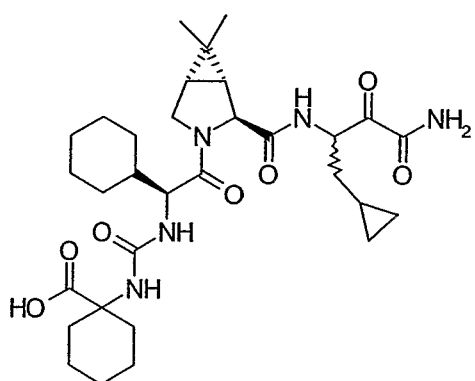
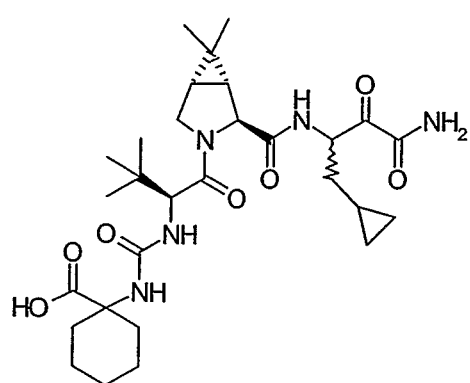
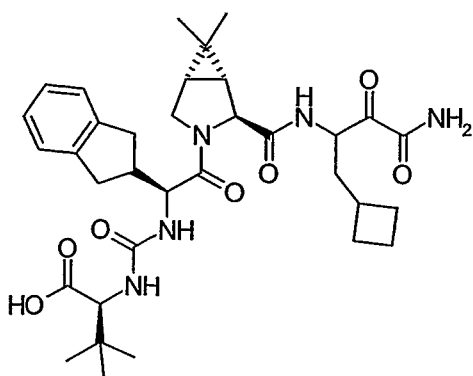


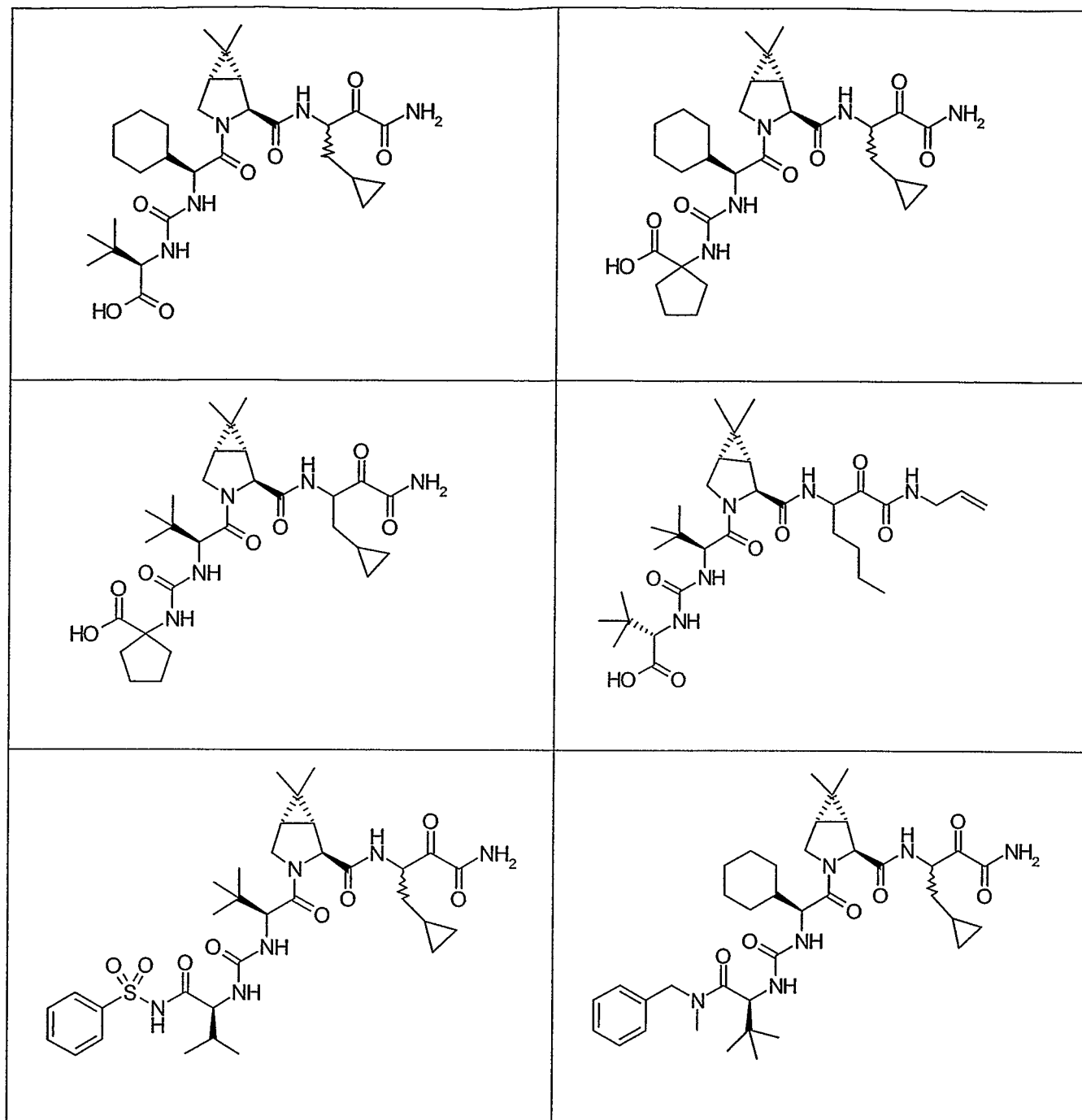


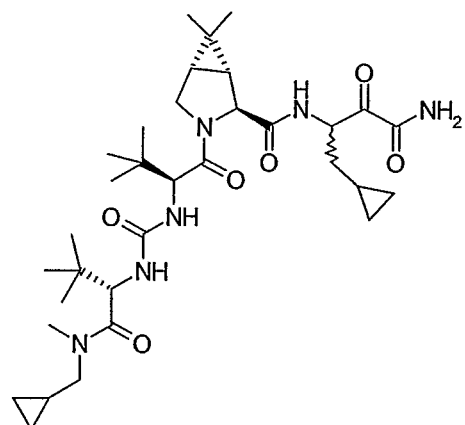
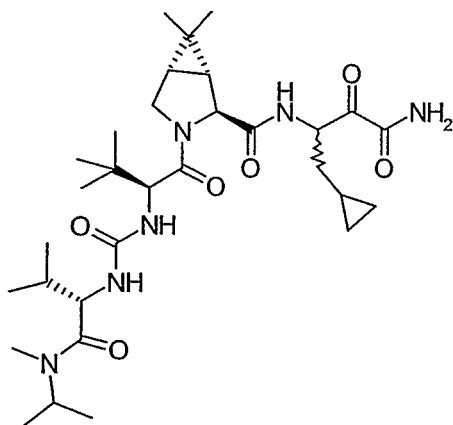
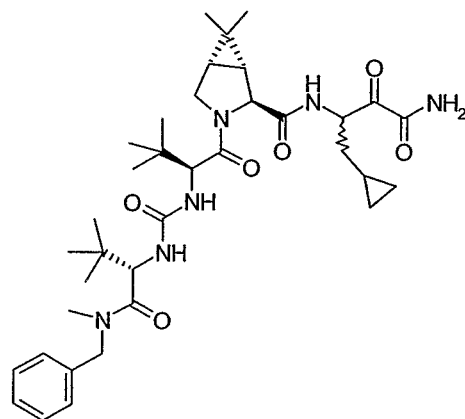
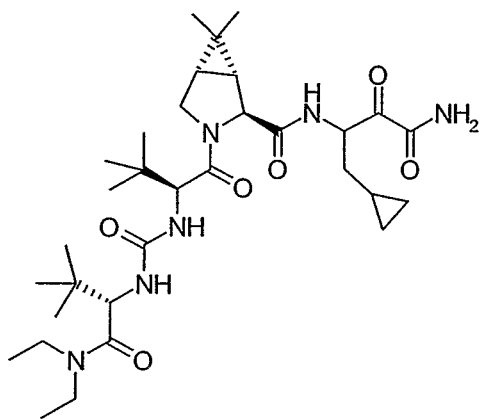
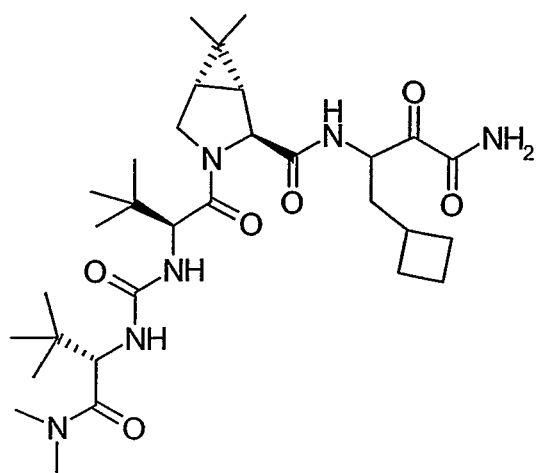
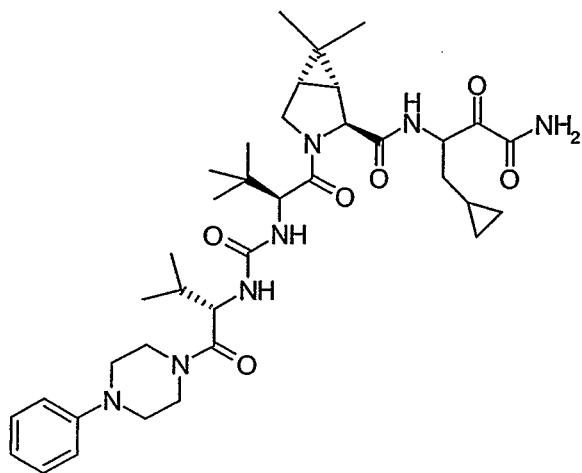


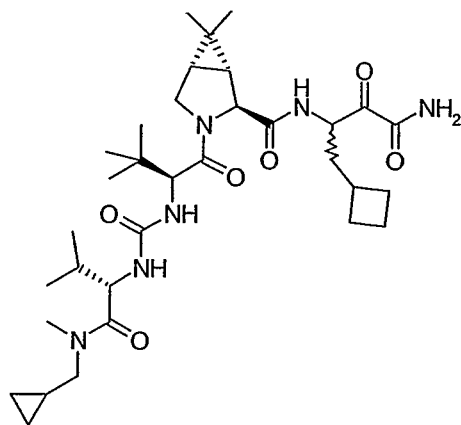
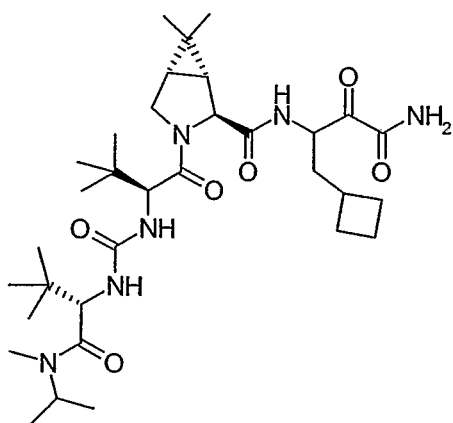
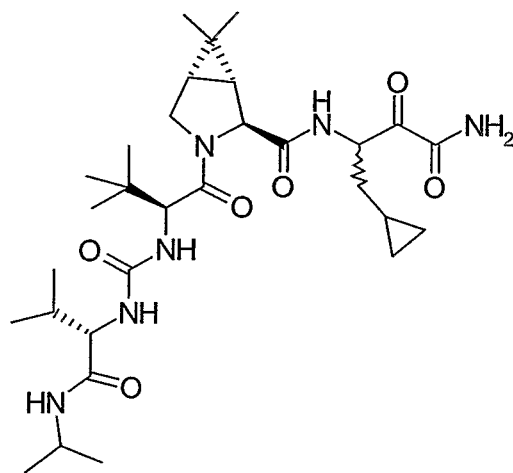
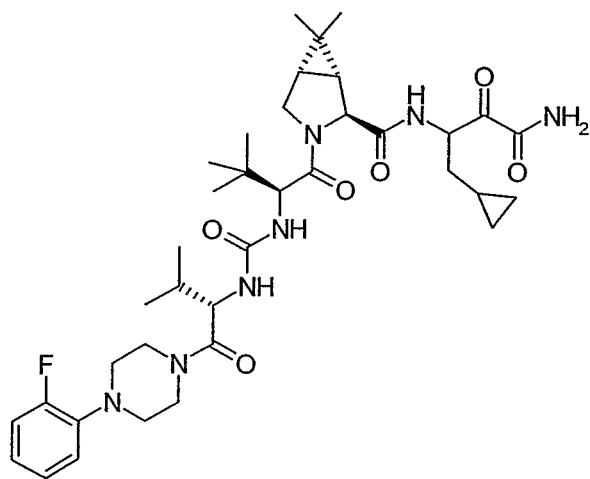
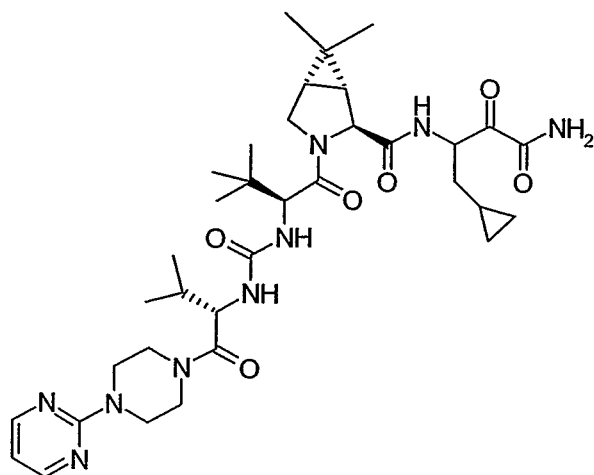
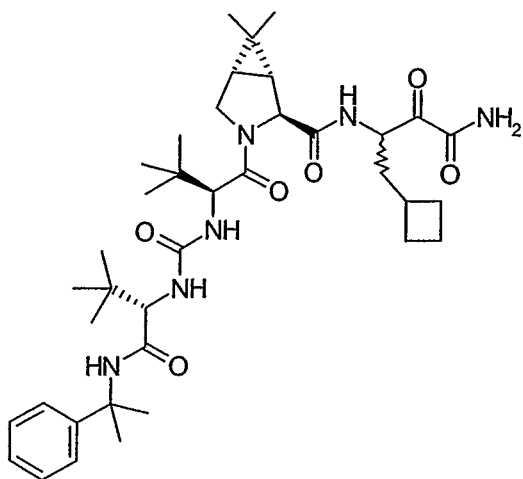


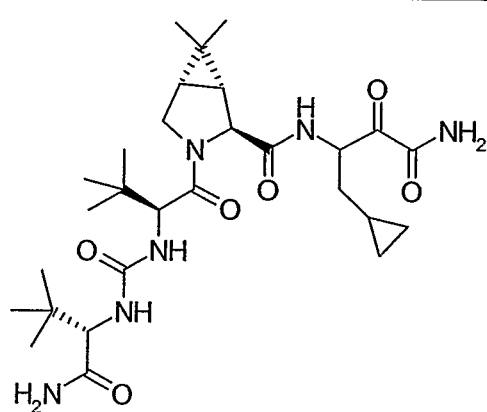
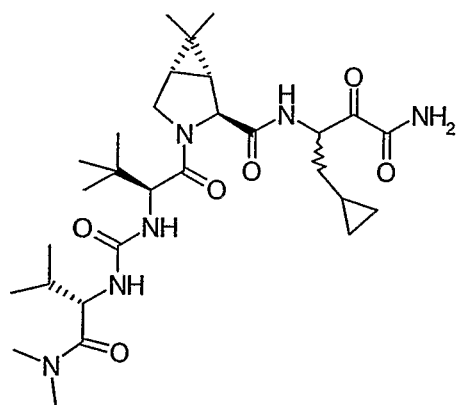
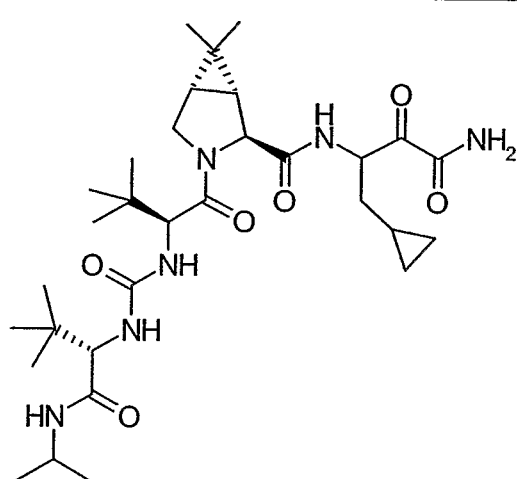
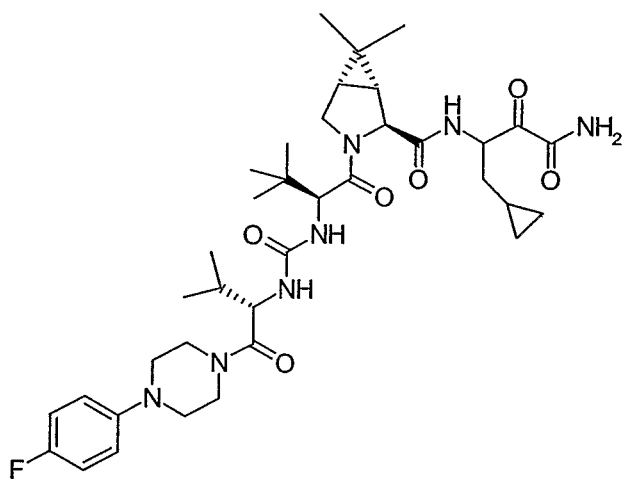
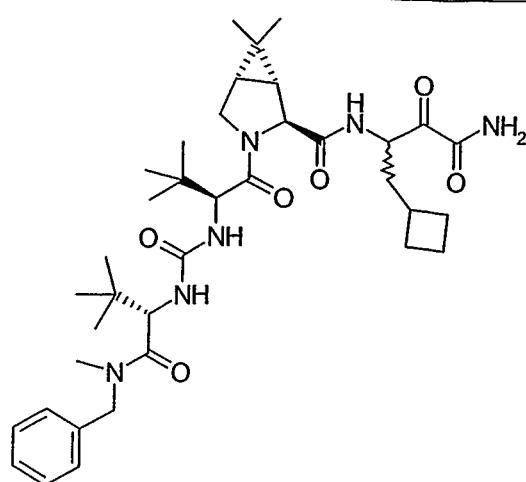
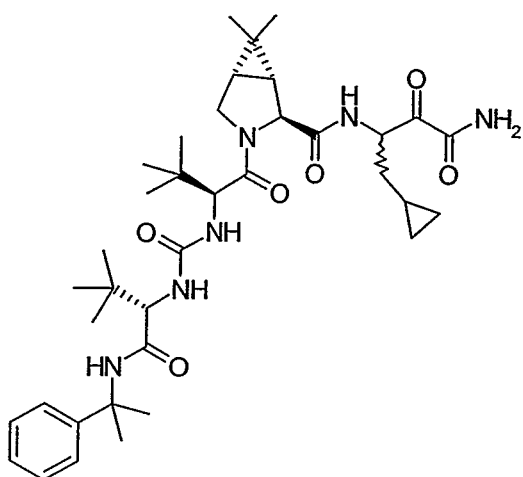


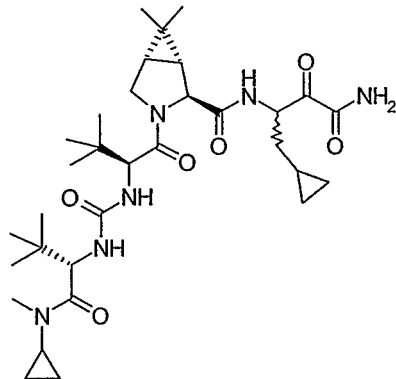
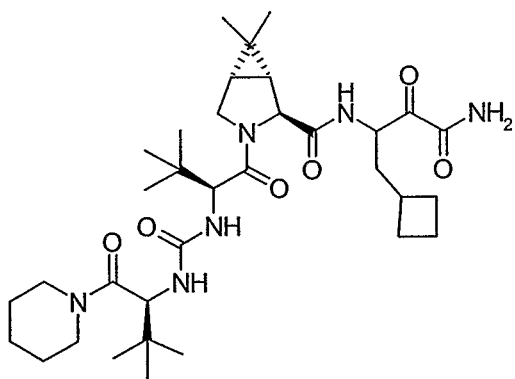
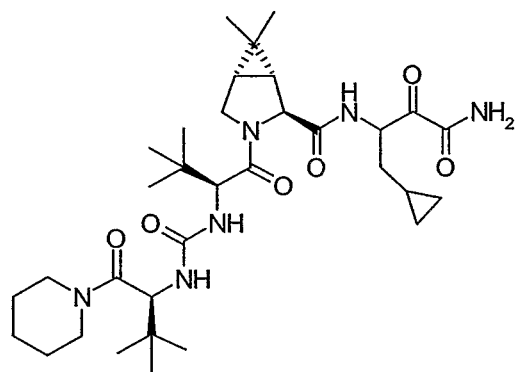
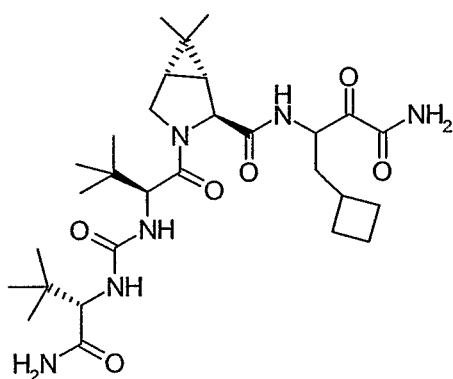
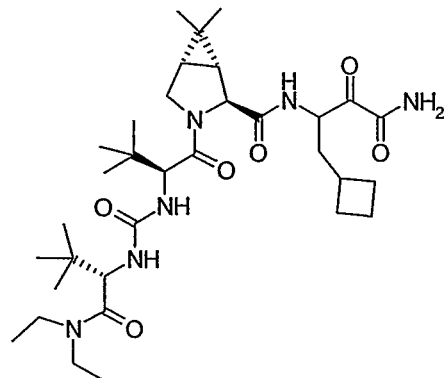
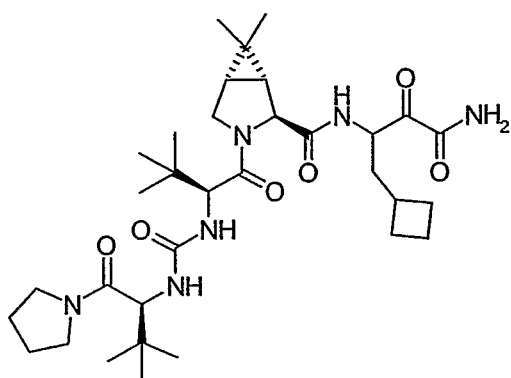


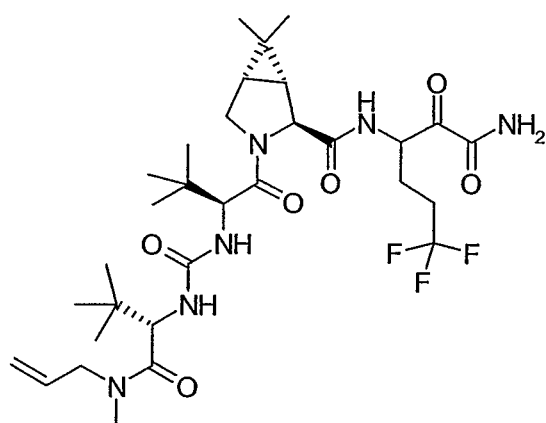
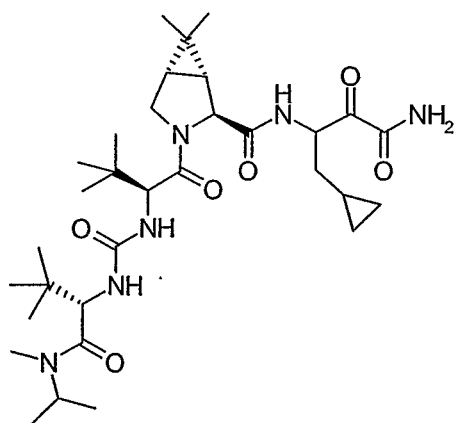
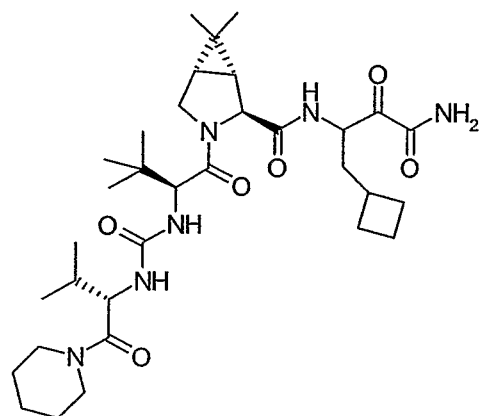
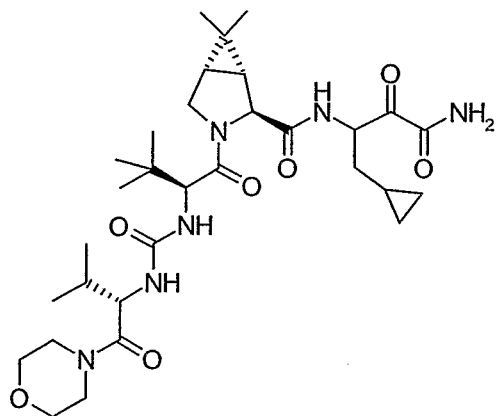
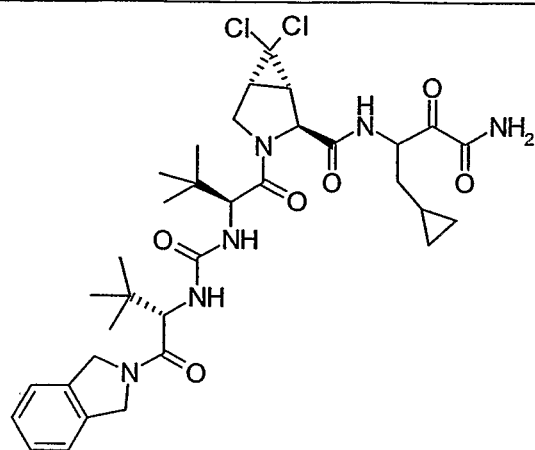
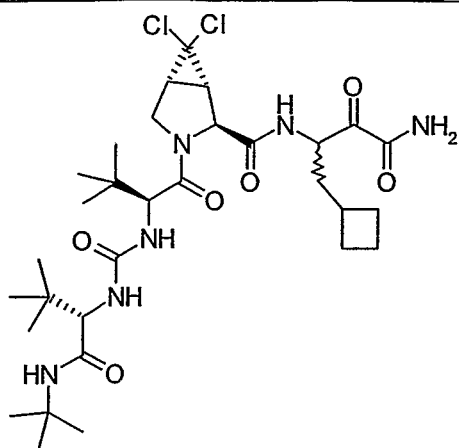


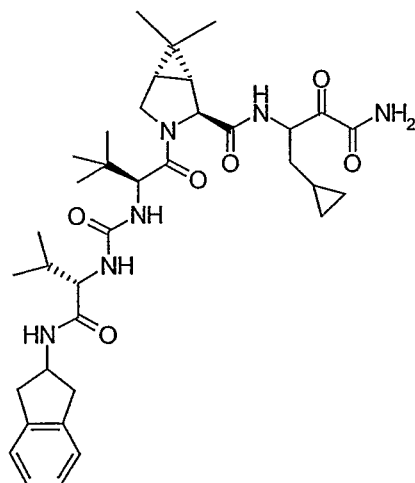
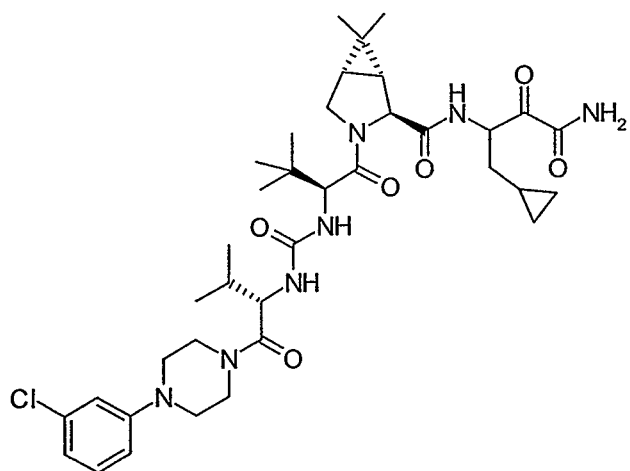
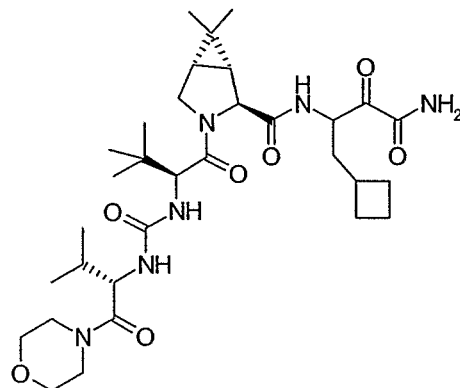
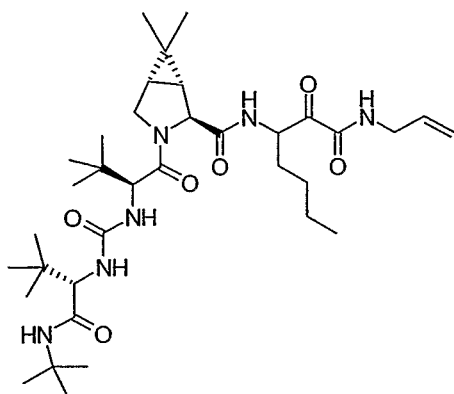
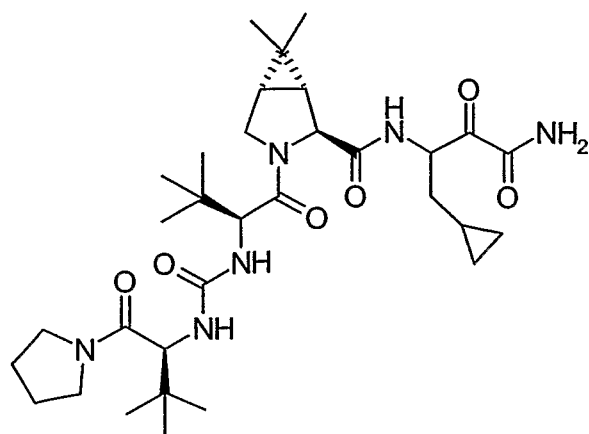
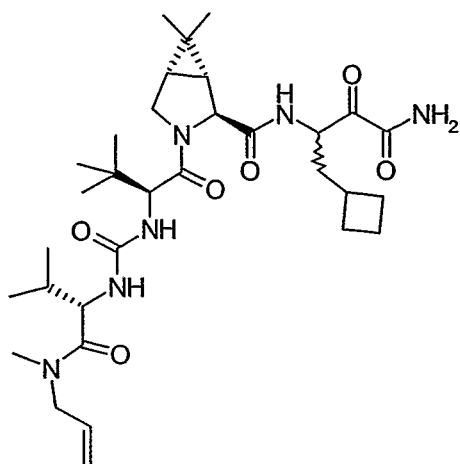


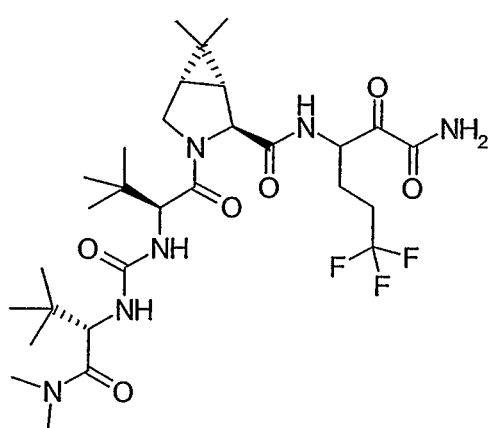
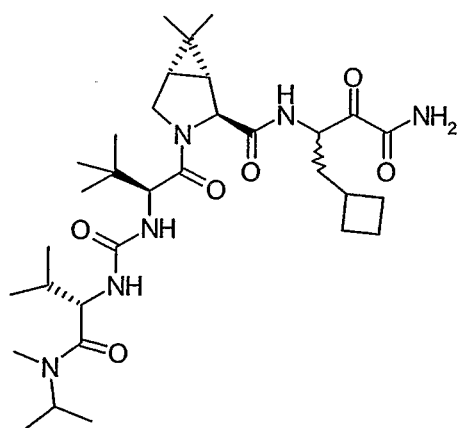
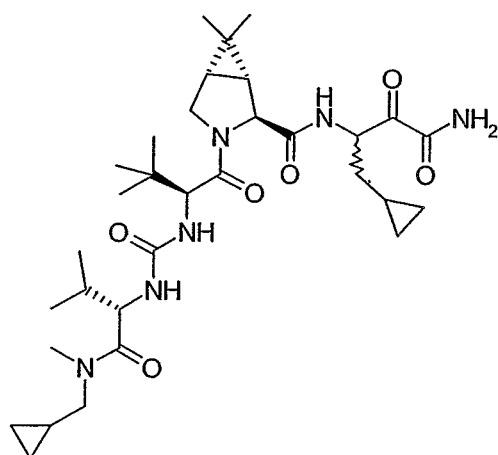
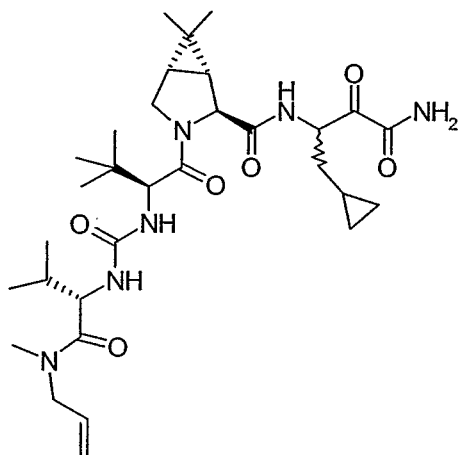
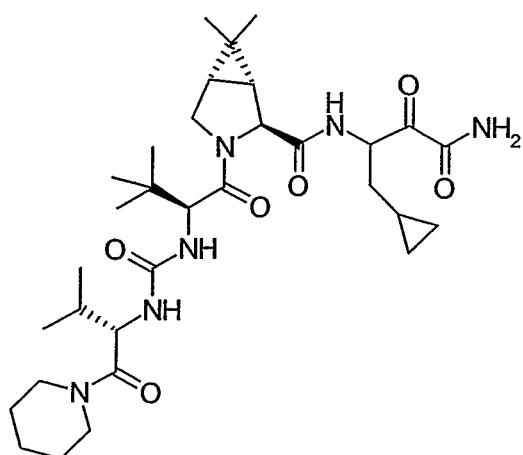
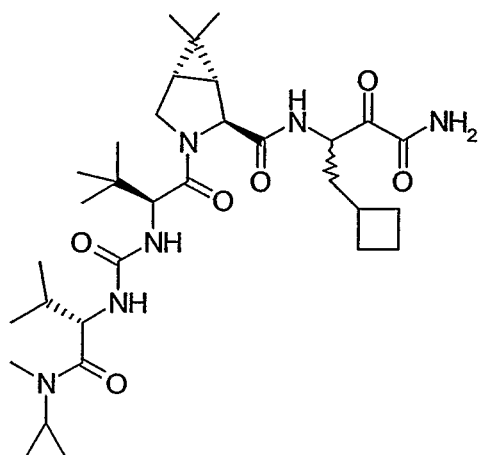


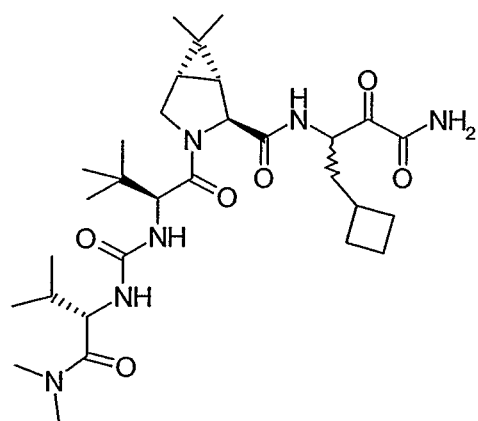
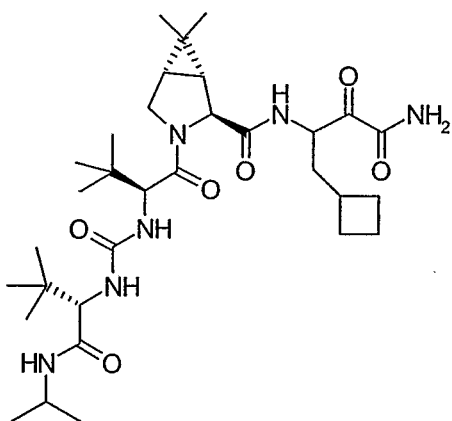
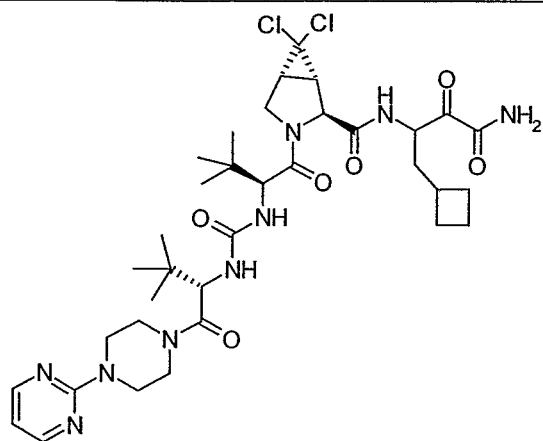
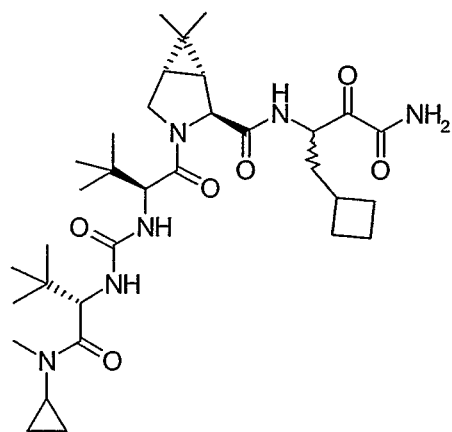
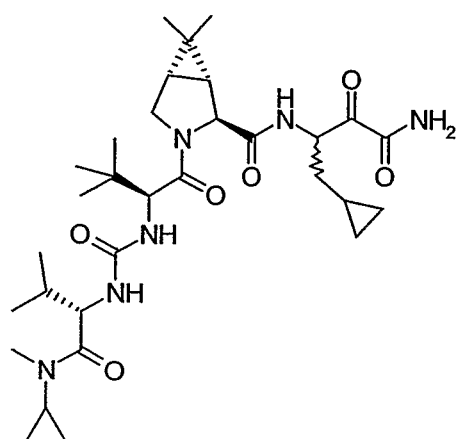
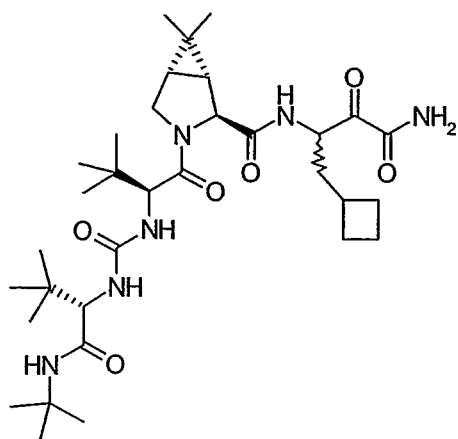


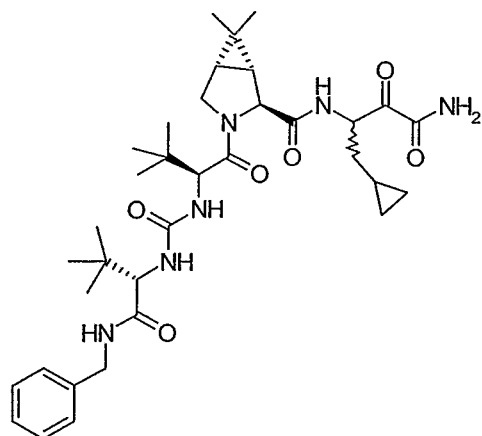
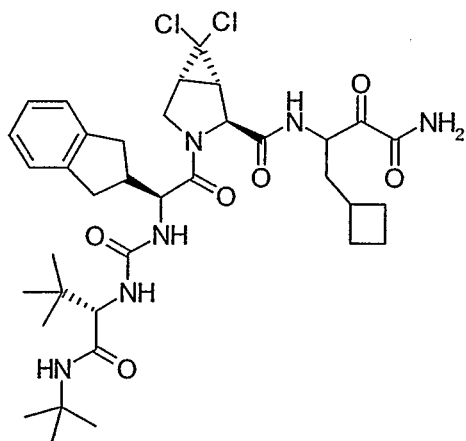
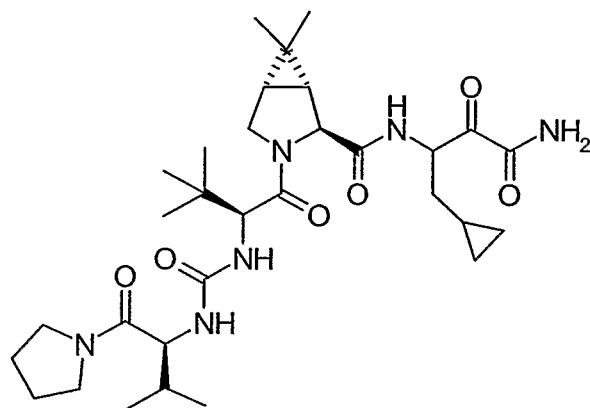
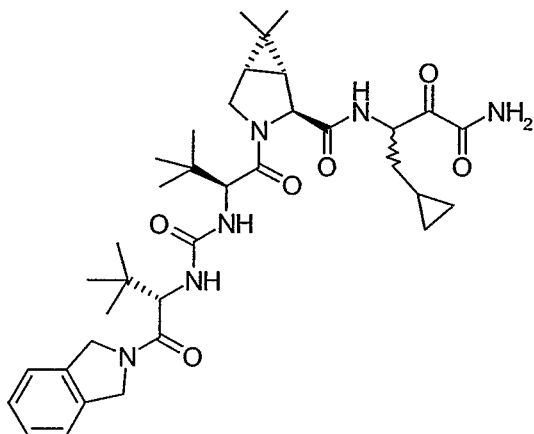
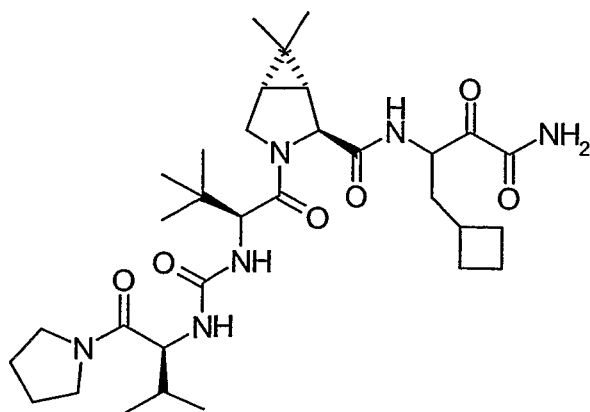
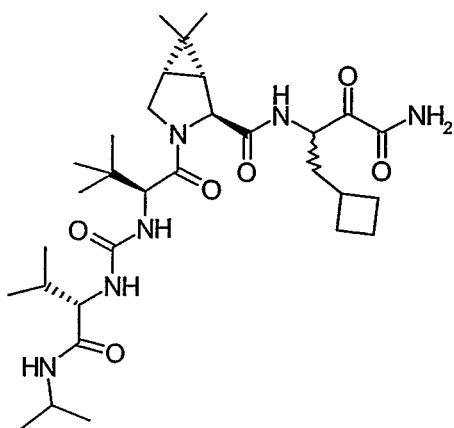


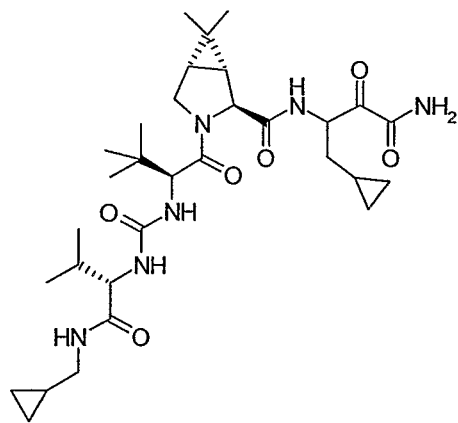
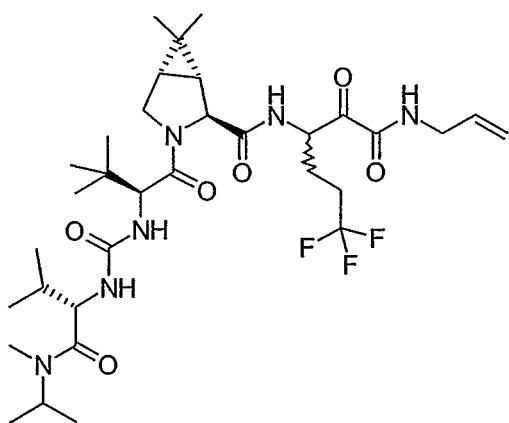
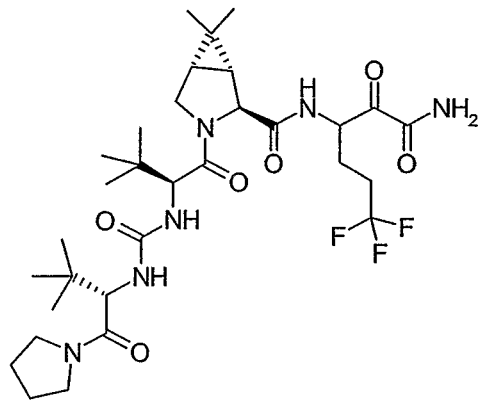
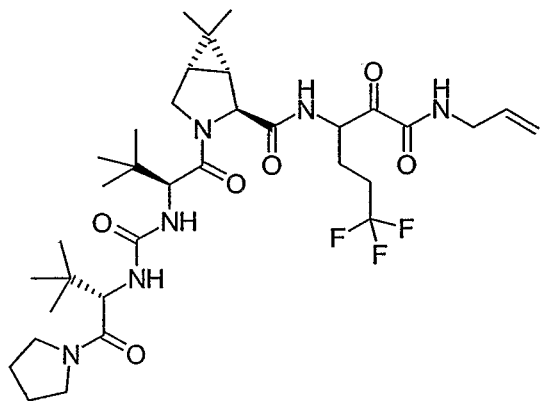
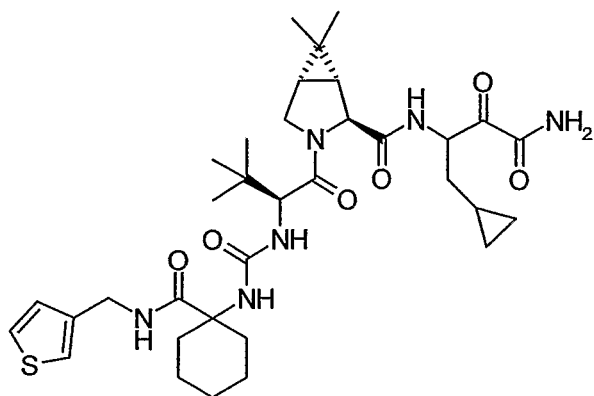
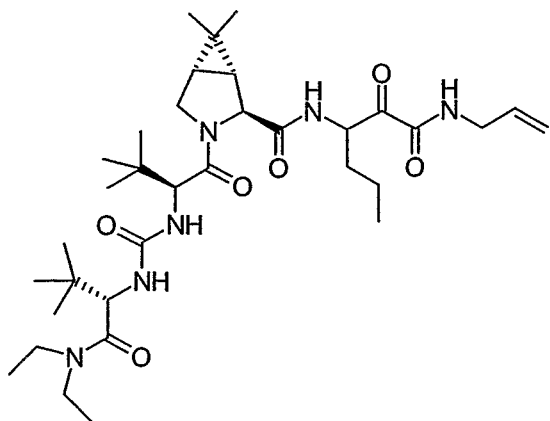


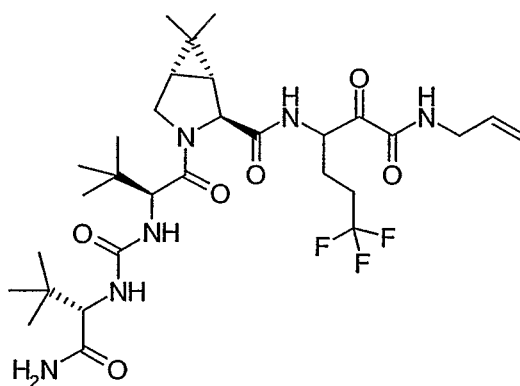
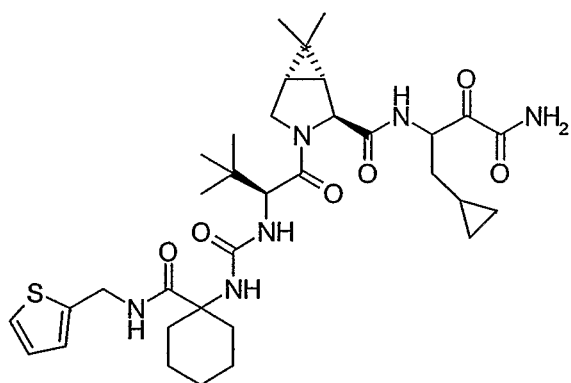
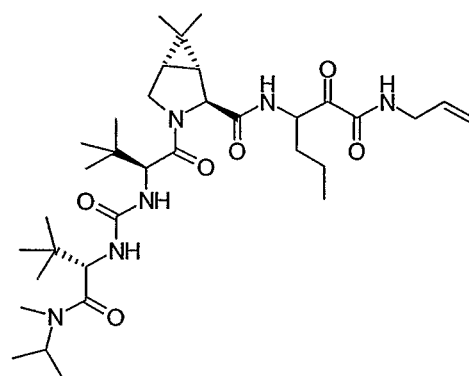
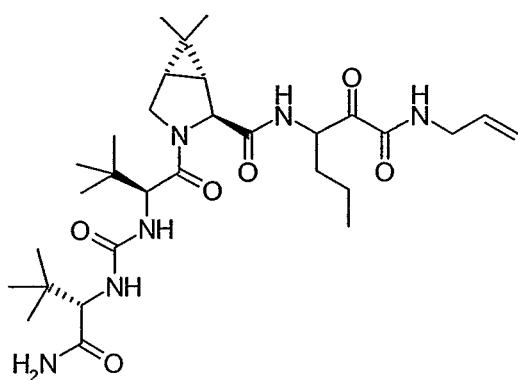
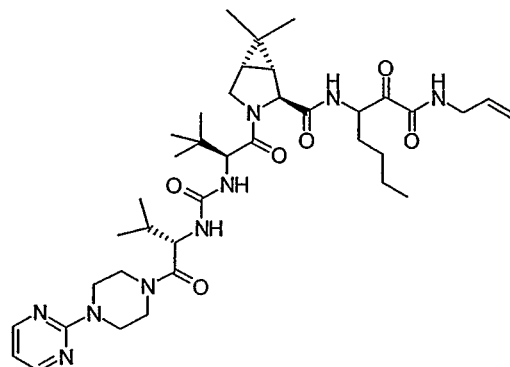
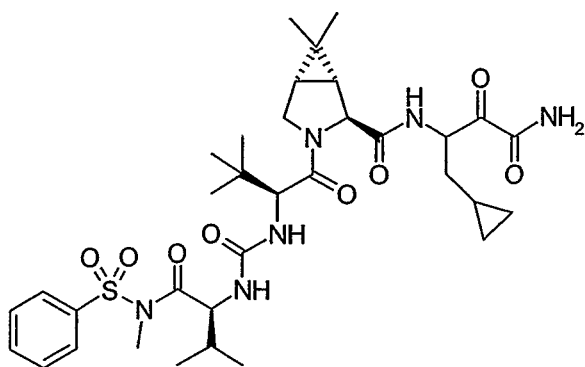


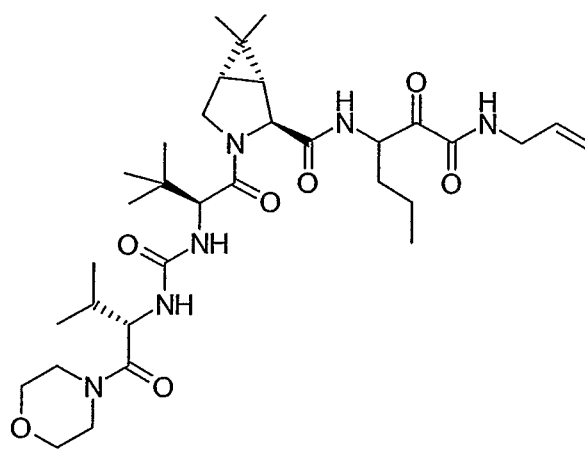
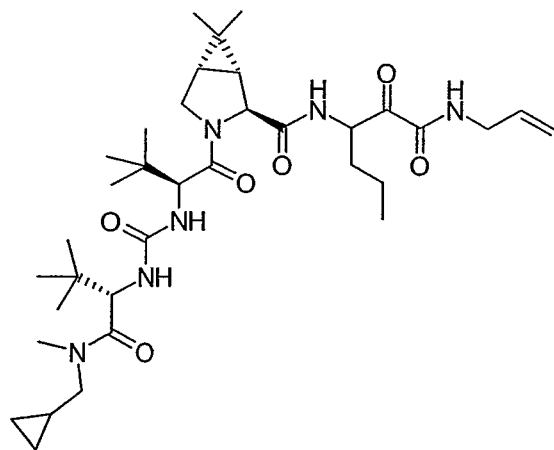
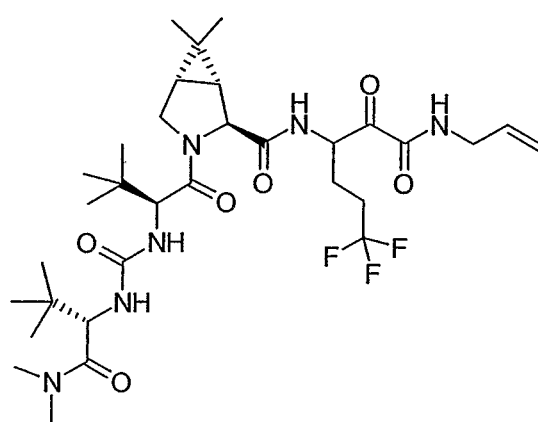
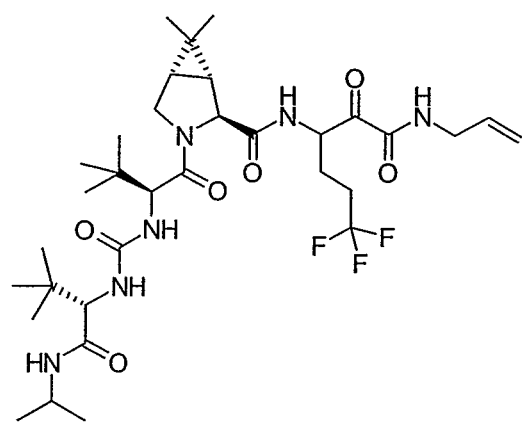
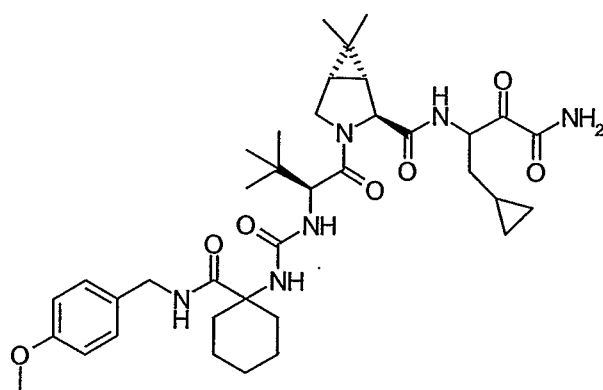
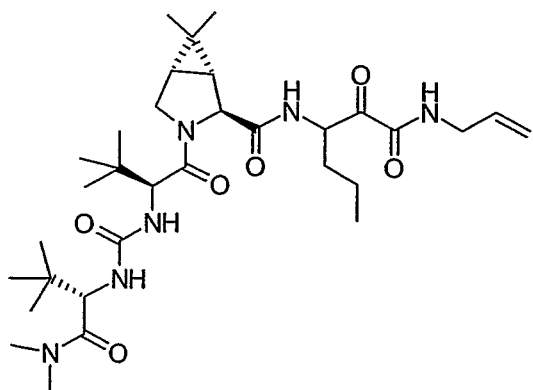


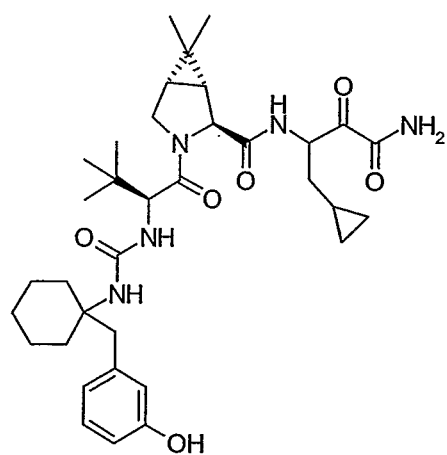
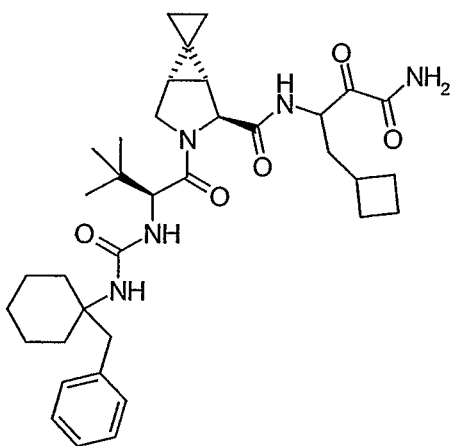
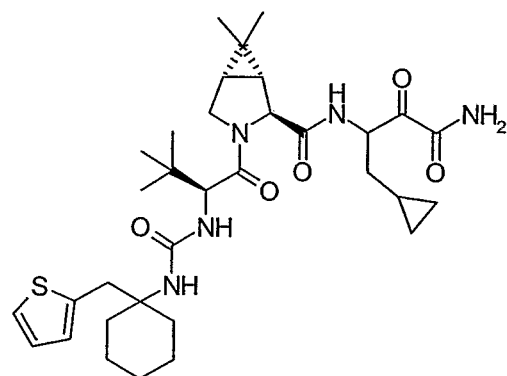
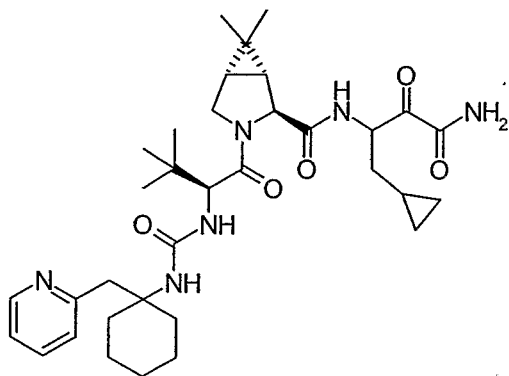
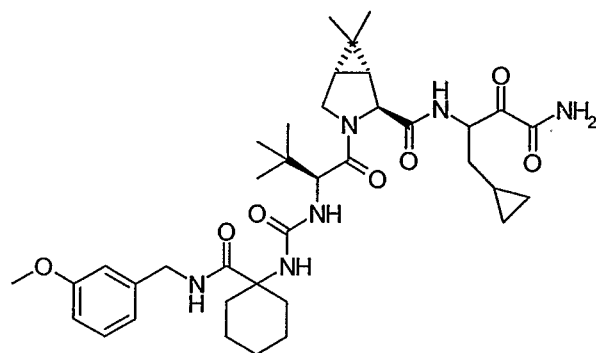
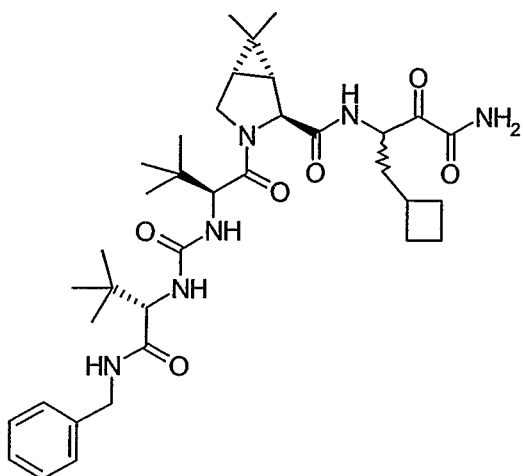


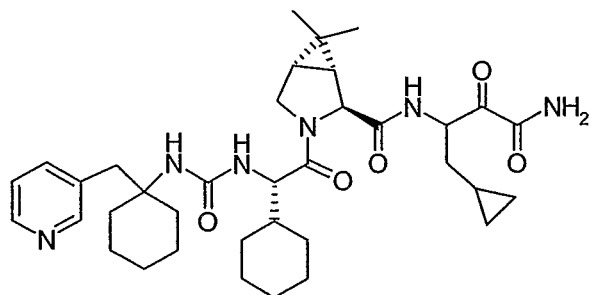
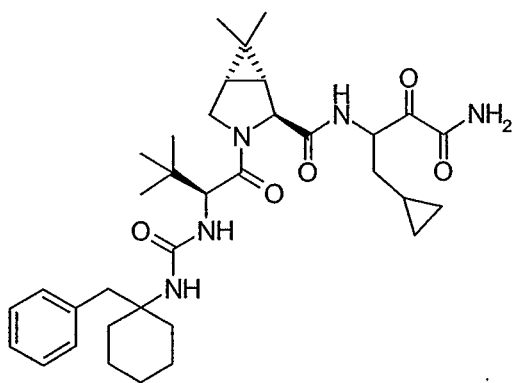
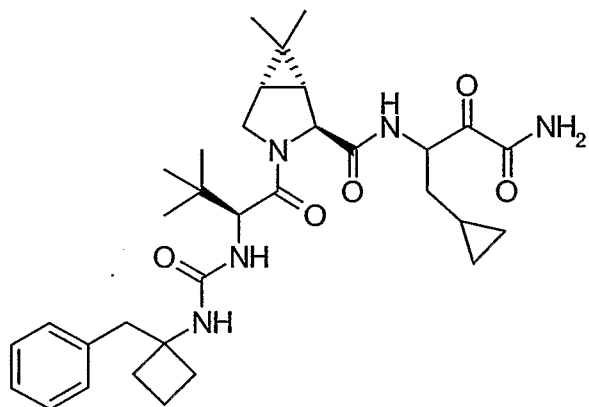
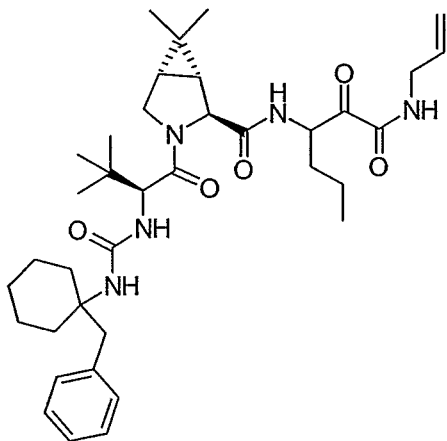
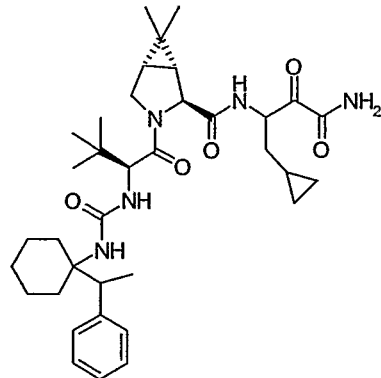
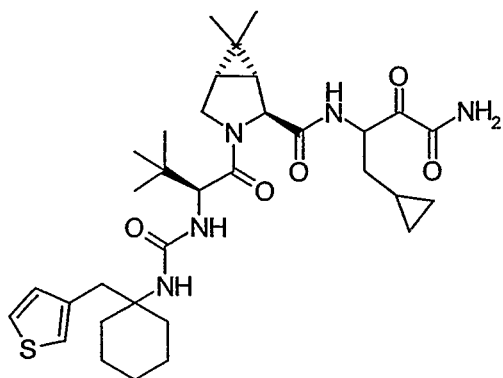


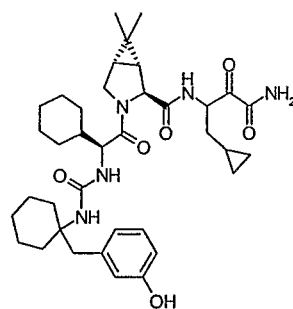
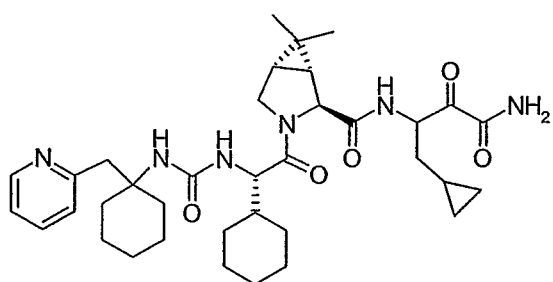
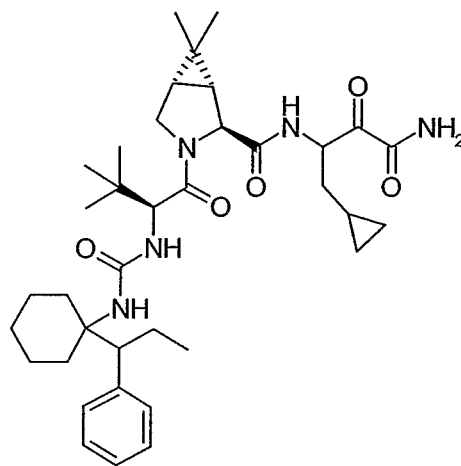
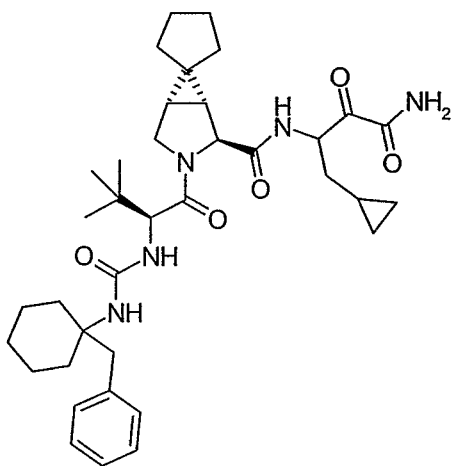
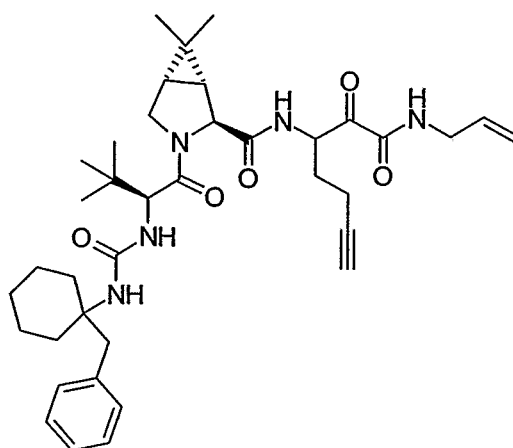
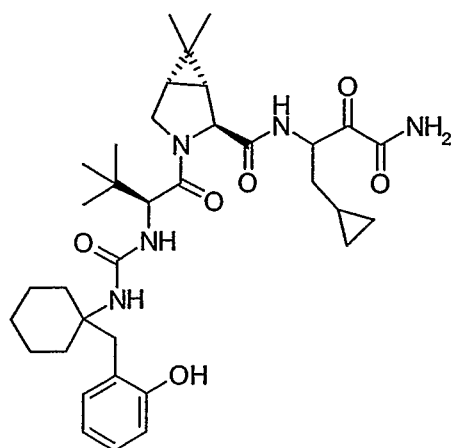


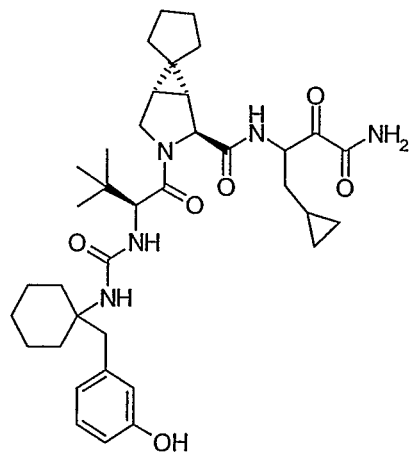
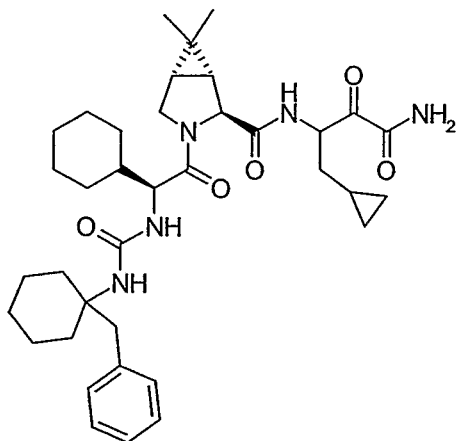
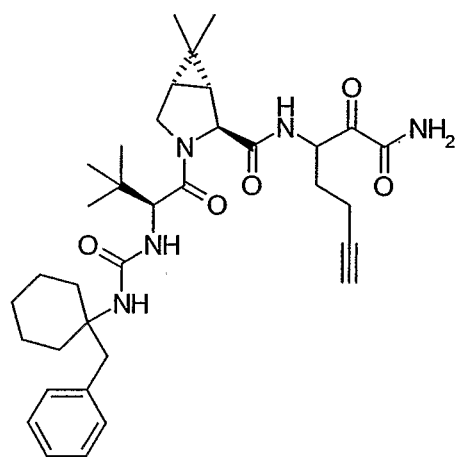
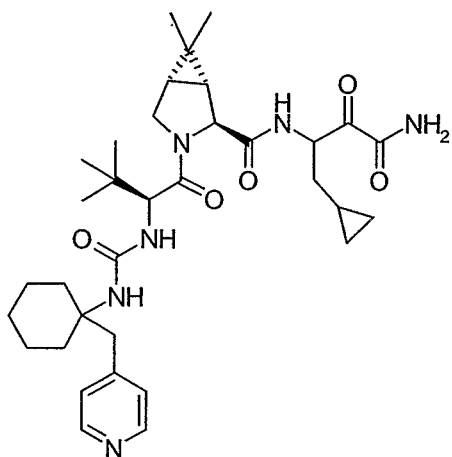
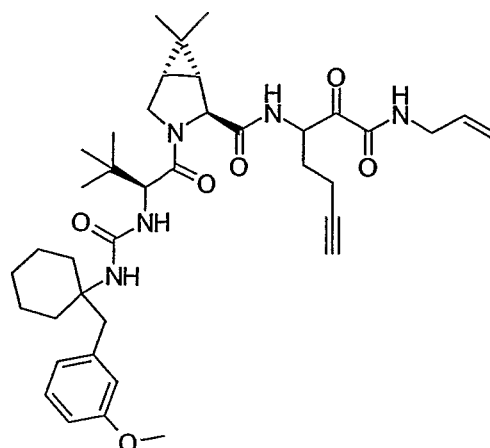
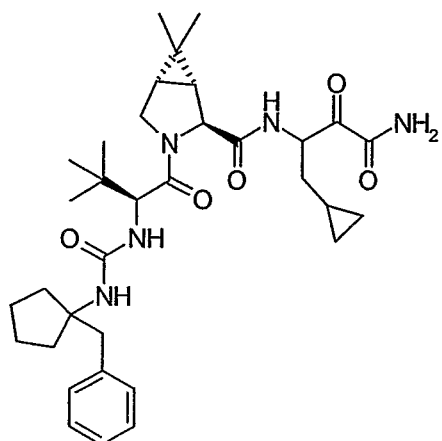


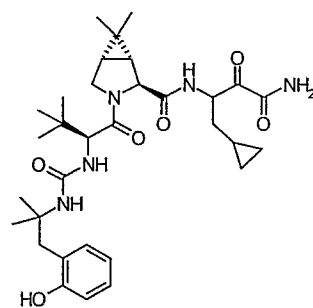
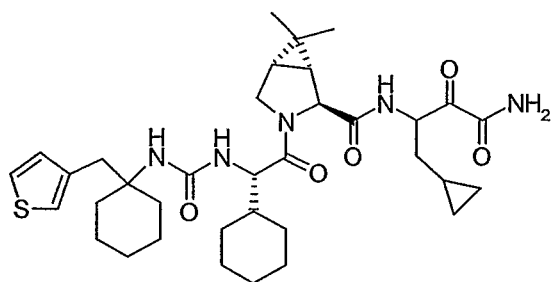
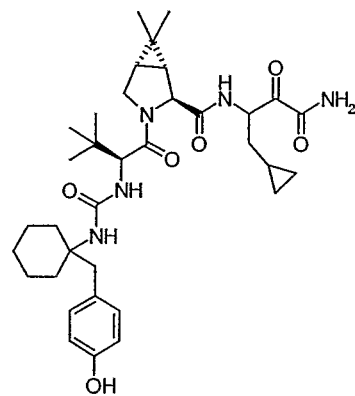
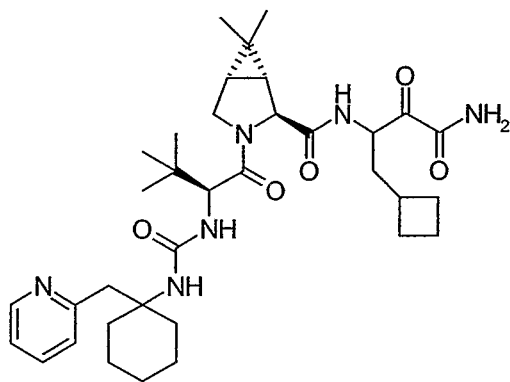
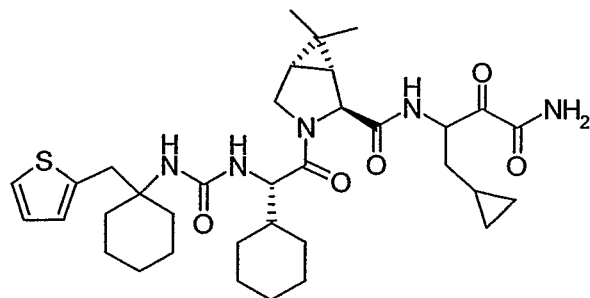
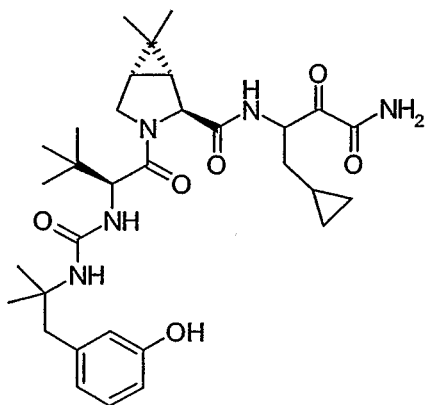


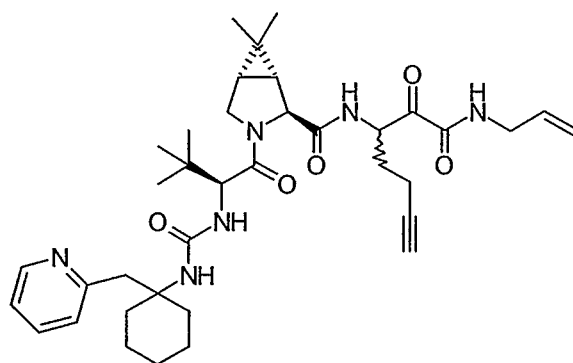
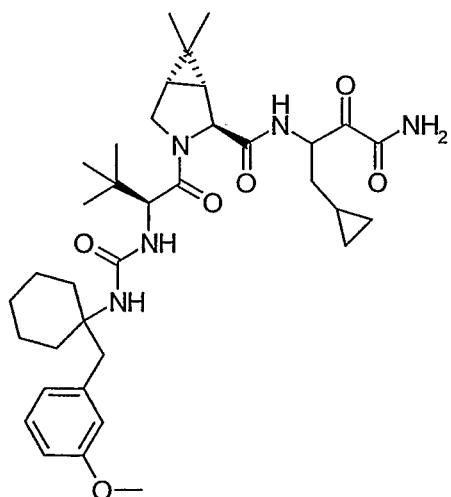
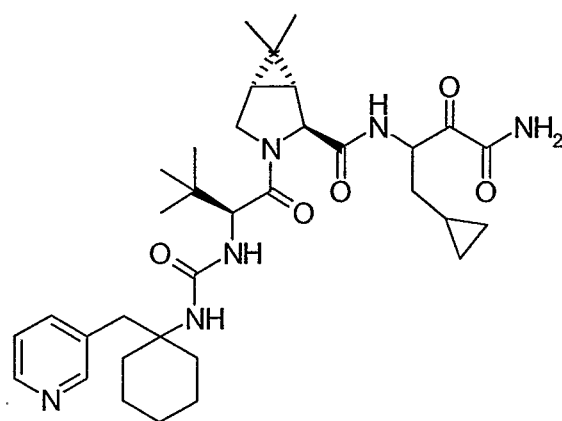
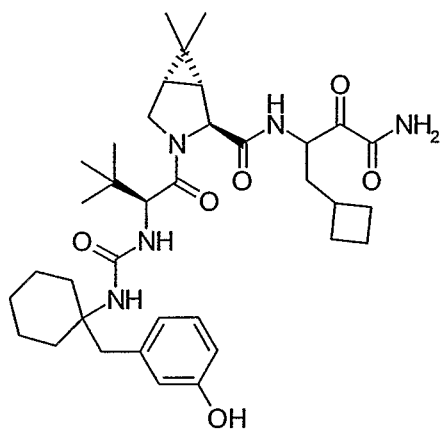
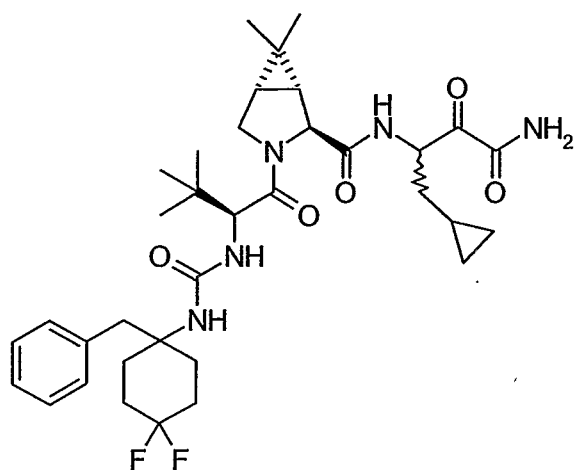
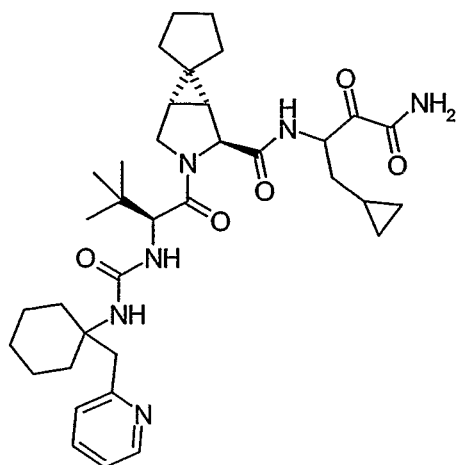


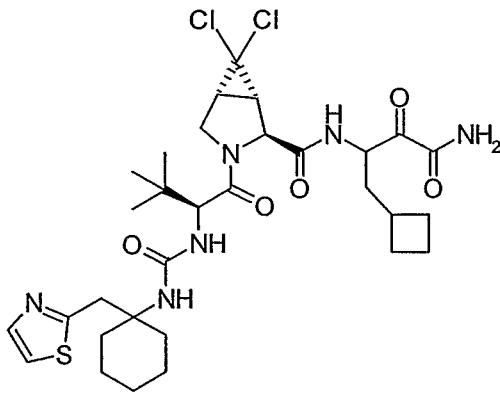
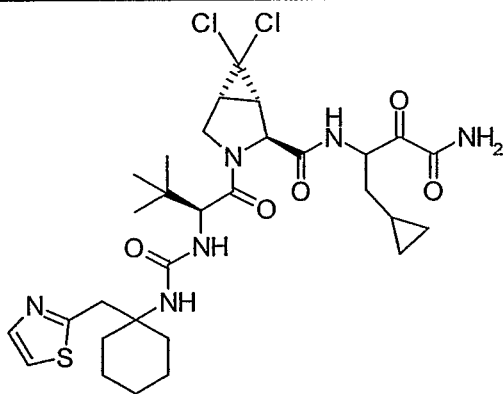
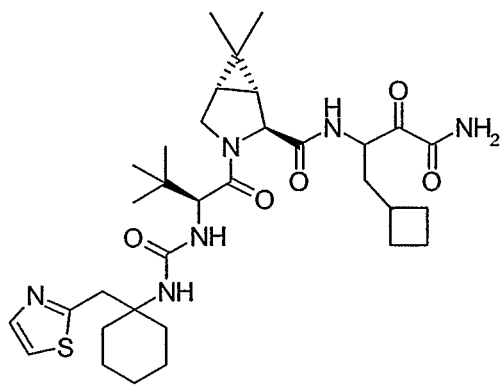
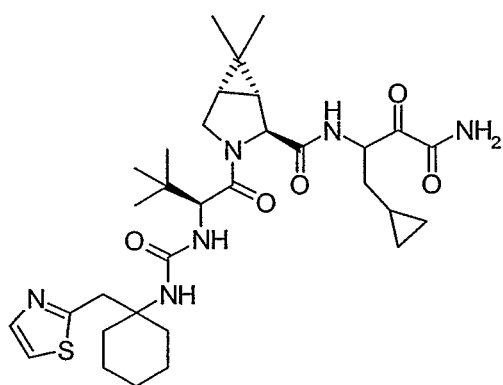


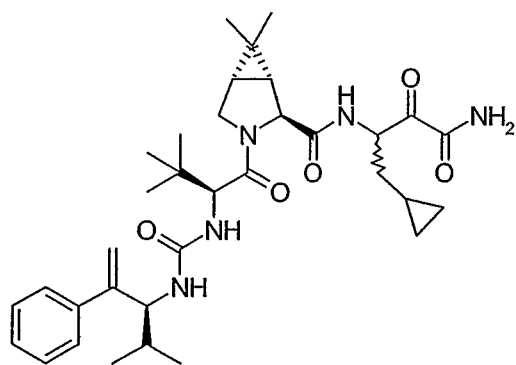
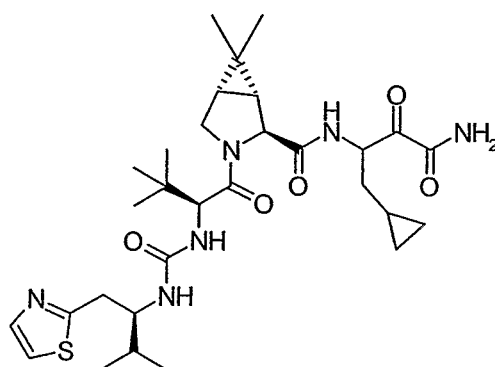
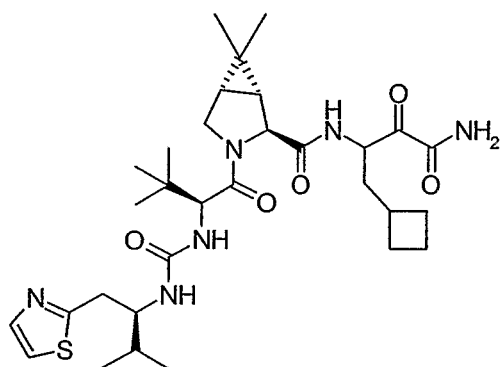
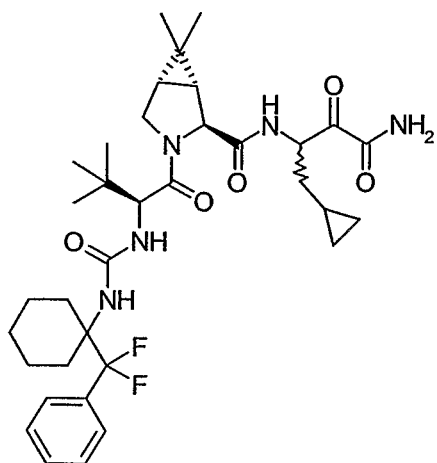




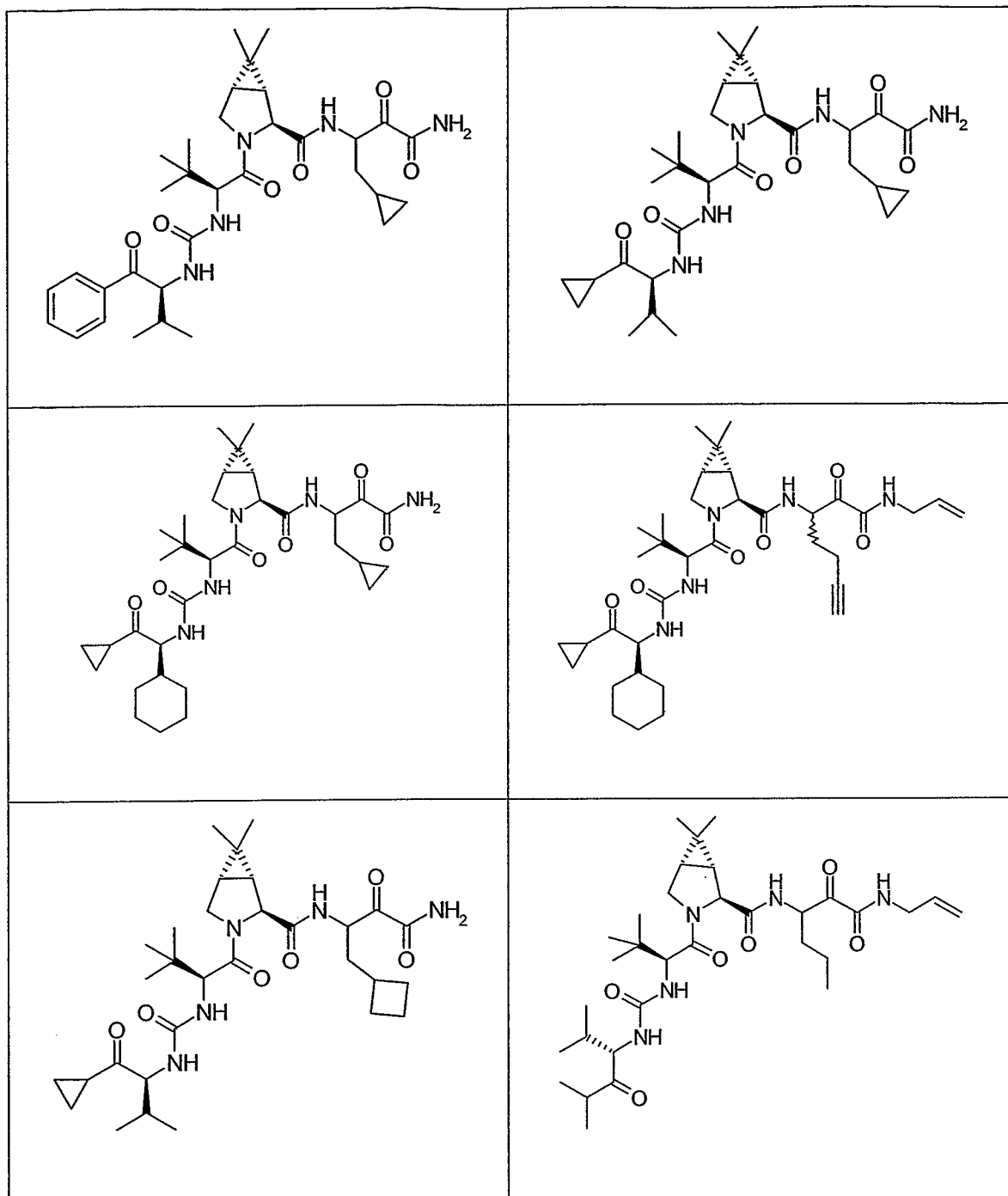


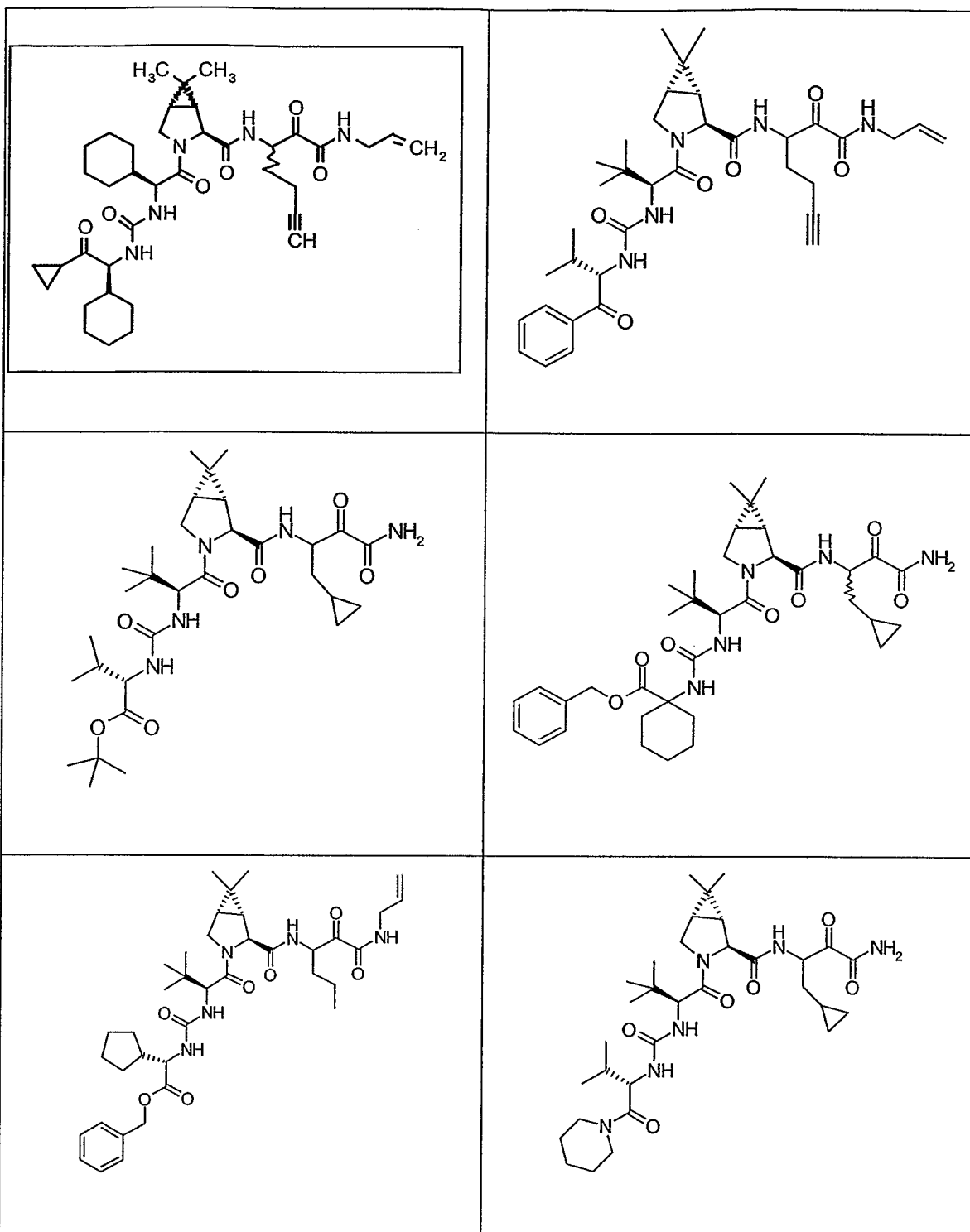


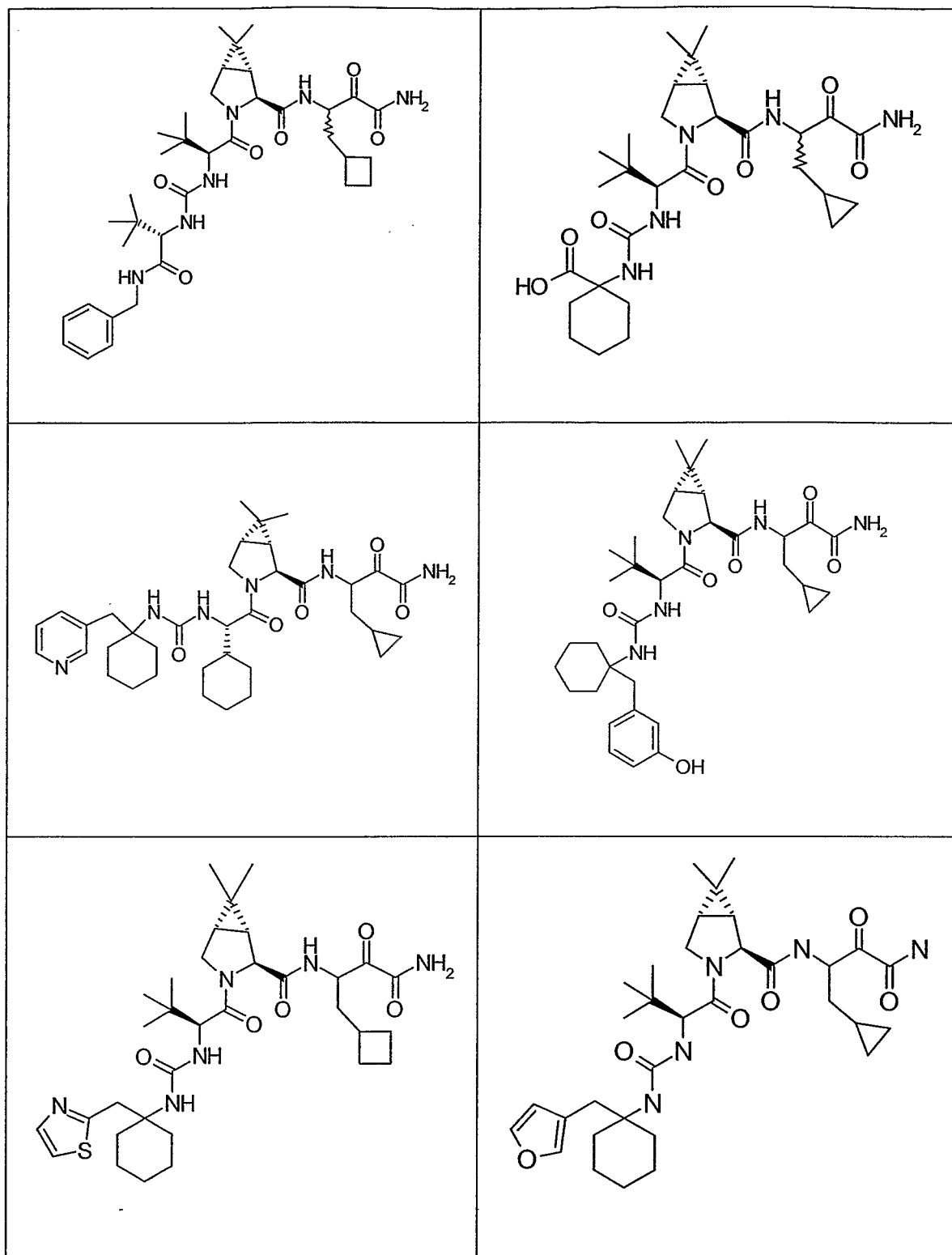




In an additional embodiment, this invention discloses the following compounds:

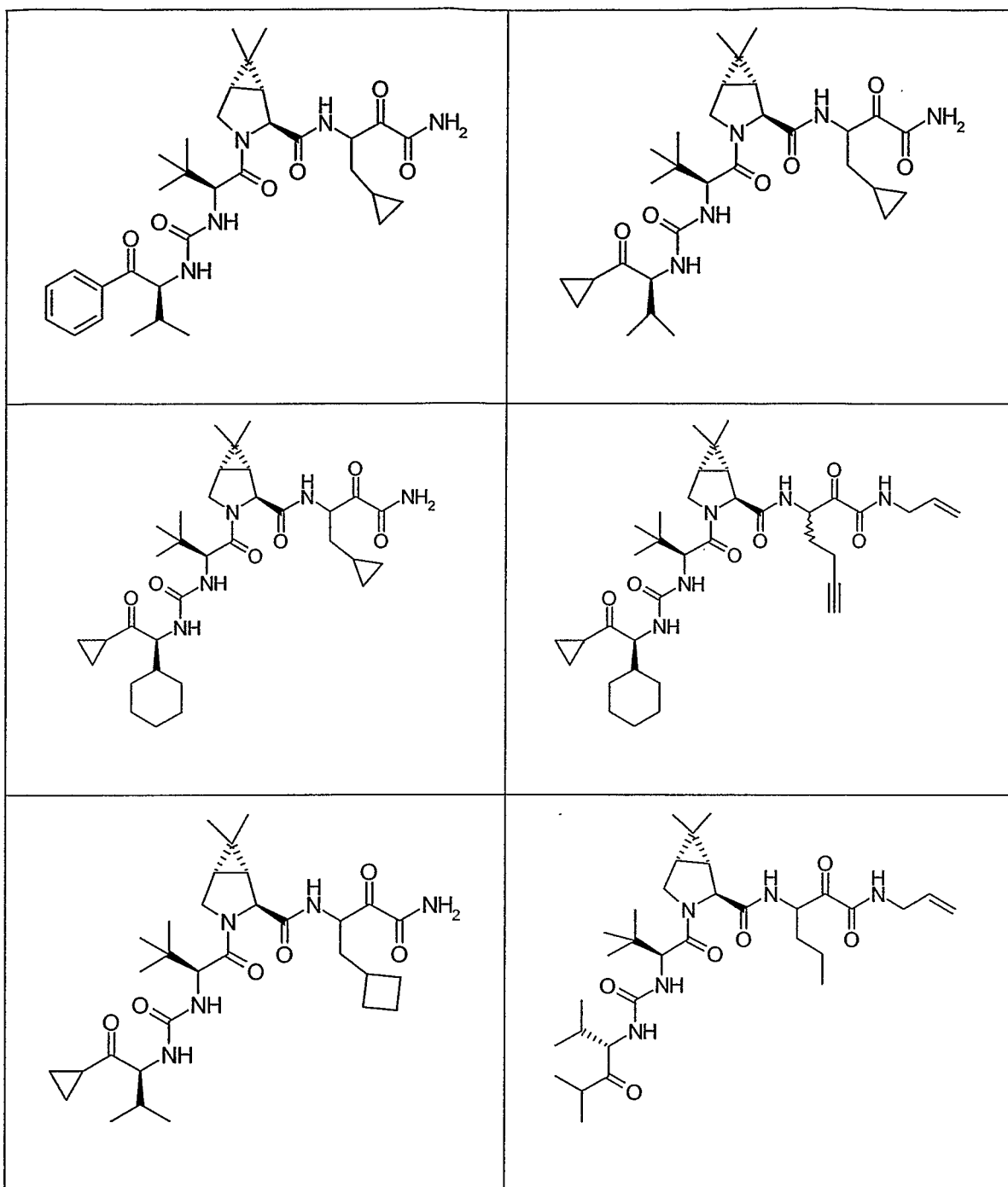


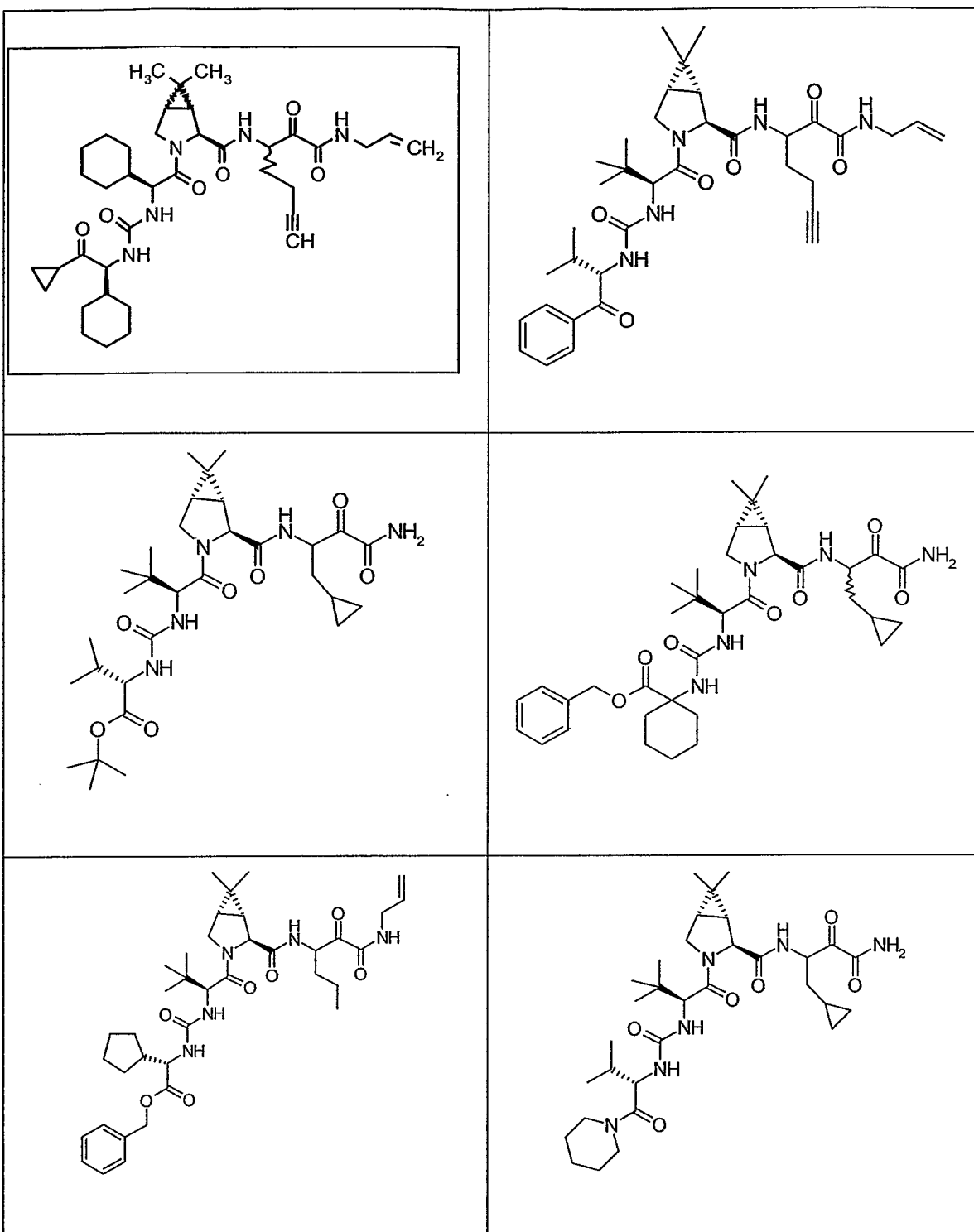


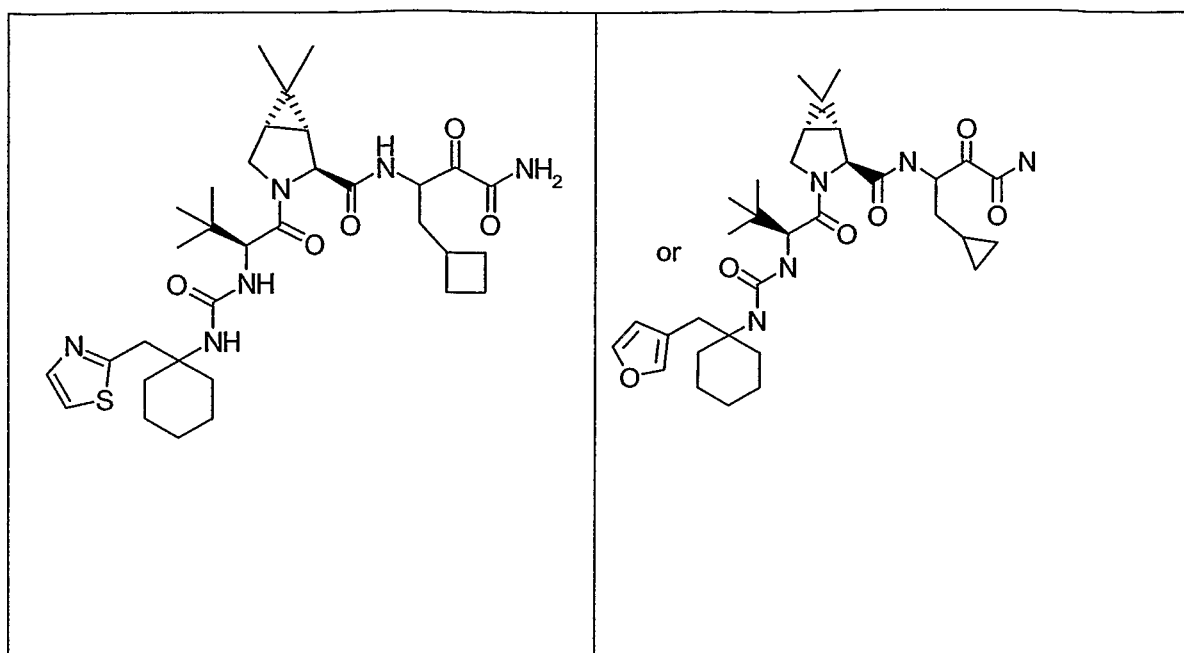


A still additional embodiment discloses the compounds in **Table 8**:

Table 8







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.

5 "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
10 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
15 group consisting of halo, alkyl, aryl, cycloalkyl, cyano, hydroxy, alkoxy, alkylthio, amino, -NH(alkyl), -NH(cycloalkyl), -N(alkyl)₂, -N(cycloalkyl)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
20 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
5 "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.

10 "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
15 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-butyne 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
20 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"
25 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
30 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, quinoxaliny, phthalazinyl, oxindolyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinoliny, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinoliny, 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.

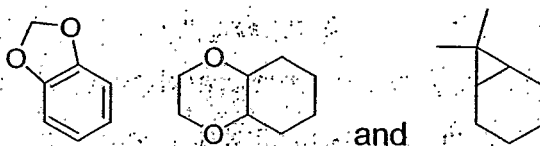
"Alkylaryl" means an alkyl-aryl- group in which the alkyl and aryl are as previously described. Preferred alkylaryls comprise a lower alkyl group. Non-limiting example of a suitable alkylaryl group is tolyl. The bond to the parent moiety is through the aryl.

"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.

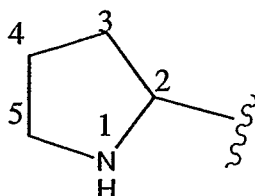
"Ring system substituent" means a substituent attached to an aromatic or non-aromatic ring system which, for example, replaces an available hydrogen on the ring

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:



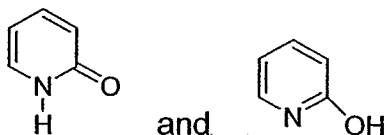
"Heterocyclyl" means a non-aromatic saturated monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur, alone 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.

5 "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
10 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.

15 "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
20 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.

25 "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.

30 "Alkylsulfonyl" means an alkyl-S(O₂)- 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(O₂)- 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, R², etc.) occurs more than one time in any constituent or in Formula 1, its definition on each occurrence is independent of its definition at every other occurrence.

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

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

"Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanlates, methanlates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H₂O.

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

The compounds of Formula 1 can form salts which are also within the scope of this invention. Reference to a compound of Formula 1 herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed

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

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

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

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

5 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
10 example, benzyl), aryloxyalkyl (for example, phenoxyethyl), aryl (for example, phenyl optionally substituted with, for example, halogen, C₁₋₄alkyl, or C₁₋₄alkoxy 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
15 may be further esterified by, for example, a C₁₋₂₀ alcohol or reactive derivative thereof, or by a 2,3-di-(C₆₋₂₄)acyl glycerol.

Compounds of Formula 1, and salts, solvates, esters and prodrugs thereof, may exist in their tautomeric form (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present invention.

20 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, solvates and esters 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),
25 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
30 present invention can have the S or R configuration as defined by the IUPAC 1974 Recommendations. The use of the terms "salt", "solvate" "prodrug" and the like, is intended to equally apply to the salt, solvate and prodrug of enantiomers,

stereoisomers, rotamers, tautomers, positional isomers, racemates or prodrugs of the inventive compounds.

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

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

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

The compounds of Formula 1 may be used for the manufacture of a medicament to treat disorders associated with the HCV protease, for example, the method comprising bringing into intimate contact a compound of Formula 1 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 hydrophilic 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 LevovirinTM (from ICN Pharmaceuticals, Costa Mesa, California), VP 50406TM (from Viropharma, Incorporated, Exton, Pennsylvania), ISIS 14803TM (from ISIS Pharmaceuticals, Carlsbad, California), HeptazymeTM (from Ribozyme Pharmaceuticals, Boulder, Colorado), VX 497TM (from Vertex Pharmaceuticals, Cambridge, Massachusetts), ThymosinTM (from SciClone Pharmaceuticals, San Mateo, California), MaxamineTM (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 (RoferonTM, from Hoffman La-Roche, Nutley, New Jersey) in the form of pegylated interferon alpha-2a (e.g., as sold under the trade name PegasysTM), interferon alpha-2b (IntronTM, from Schering-Plough Corporation) in the form of pegylated interferon alpha-2b (e.g., as sold under the trade name PEG-

IntronTM), interferon alpha-2c (Berofer AlphaTM, from Boehringer Ingelheim, Ingelheim, Germany) or consensus interferon as defined by determination of a consensus sequence of naturally occurring interferon alphas (InfergenTM, from Amgen, Thousand Oaks, California).

5 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
10 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.

15 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.

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

THF: Tetrahydrofuran

DMF: N,N-Dimethylformamide

EtOAc: Ethyl acetate

AcOH: Acetic acid

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

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

NMM: N-Methylmorpholine

ADDP: 1,1'-(Azodicarbonyl)dipiperidine

DEAD: Diethylazodicarboxylate

30 MeOH: Methanol

EtOH: Ethanol

Et₂O: Diethyl ether

DMSO: Dimethylsulfoxide

HOBt: N-Hydroxybenzotriazole

PyBrOP: Bromo-tris-pyrrolidinophosphonium hexafluorophosphate

DCM: Dichloromethane

DCC: 1,3-Dicyclohexylcarbodiimide

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

Phg: Phenylglycine

Chg: Cyclohexylglycine

Bn: Benzyl

Bzl: Benzyl

10 Et: Ethyl

Ph: Phenyl

iBoc: isobutoxycarbonyl

iPr: isopropyl

^tBu or Bu^t: tert-Butyl

15 Boc: tert-Butyloxycarbonyl

Cbz: Benzyloxycarbonyl

Cp: Cyclopentylidienyl

Ts: p-toluenesulfonyl

Me: Methyl

20 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)

25 NaHMDS: Sodium Hexamethyldisilazide or Sodium bis(trimethylsilylamide)

LiHMDS: Lithium Hexamethyldisilazide or Lithium bis(trimethylsilylamide)

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

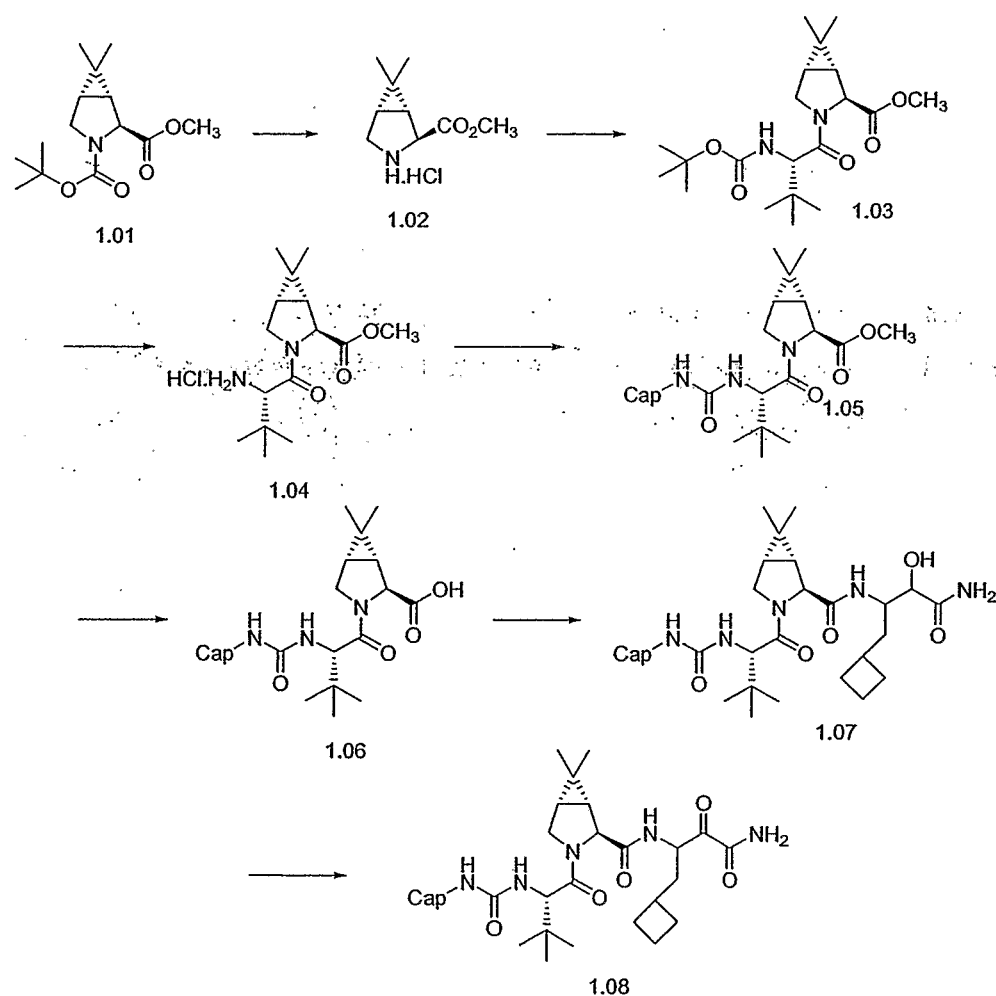
TG: Thioglycerol

30 **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

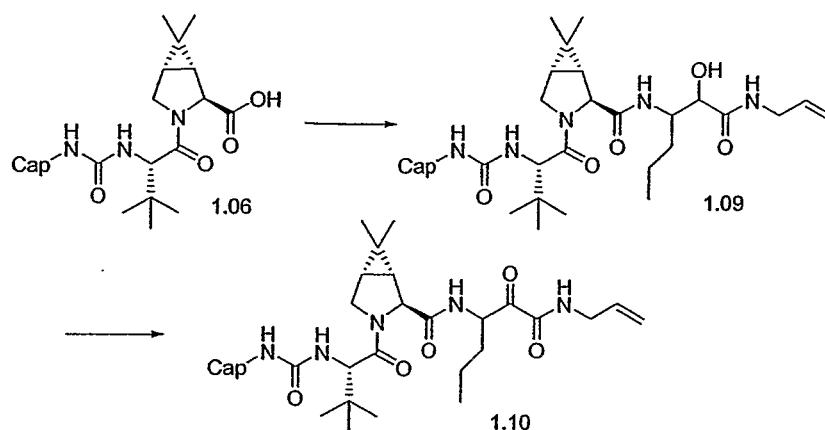
Deprotection of the N-Boc functionality of 1.01 under acidic conditions provided the hydrochloride salt 1.02 which was subsequently coupled with N-Boc-tert-leucine under peptide coupling methodology to afford 1.03. N-Boc deprotection followed by treatment with appropriate isocyanate gave the urea 1.05. Hydrolysis of the methyl ester provided the acid 1.06. Peptide coupling of the acid 1.06 with the appropriate P₁-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

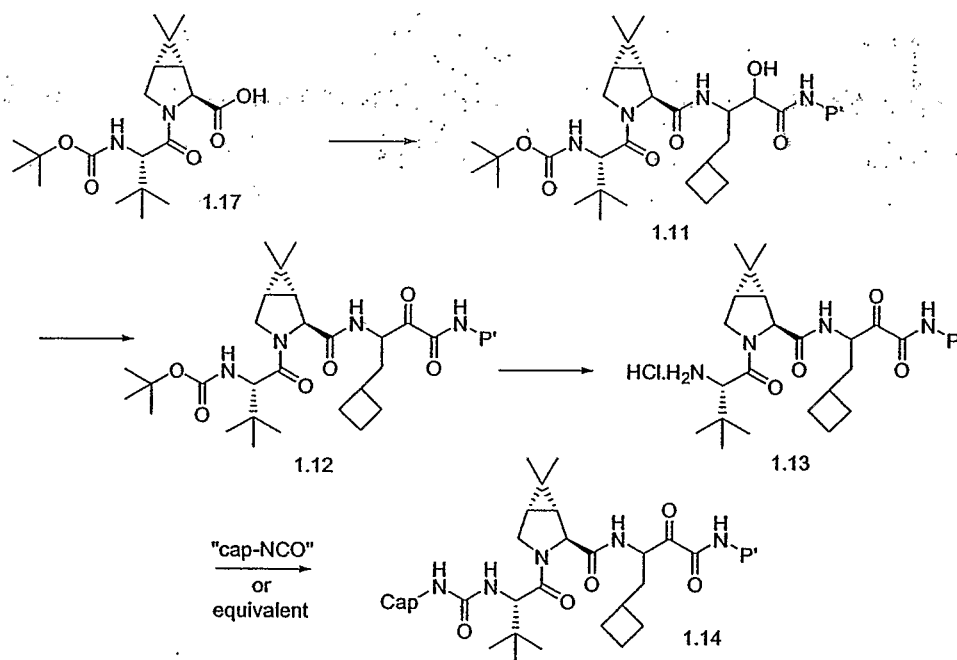
Peptide coupling of the acid 1.06 with the appropriate P₁-P' secondary amide moiety afforded the hydroxyl amide 1.09. Oxidation (Moffatt or Dess-Martin's) resulted in the target compound 1.10.

133



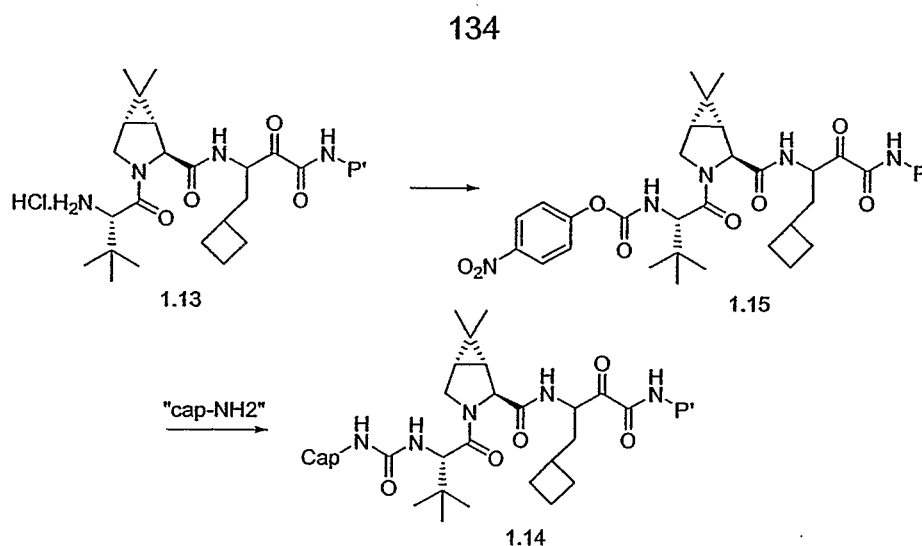
Method C

In another variation, peptide coupling of the N-Boc-P₂-P₃-acid 1.17 with the appropriate P₁-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.



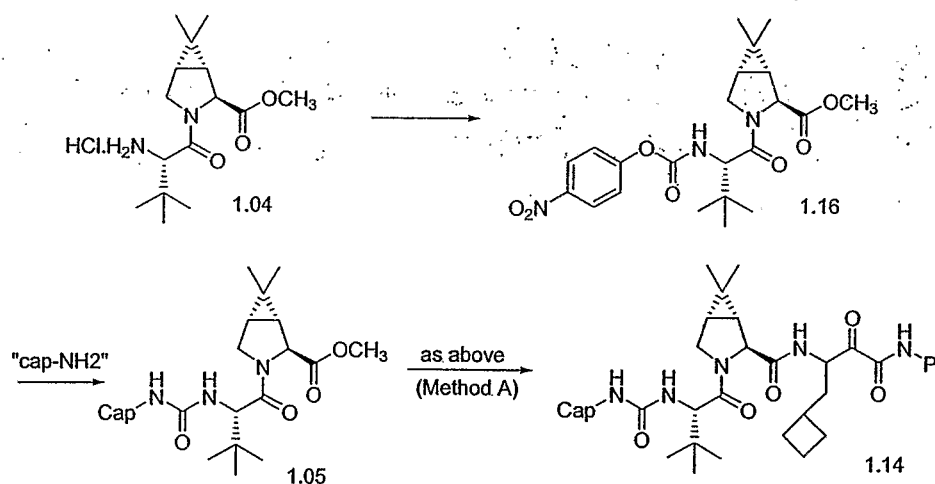
Method D

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

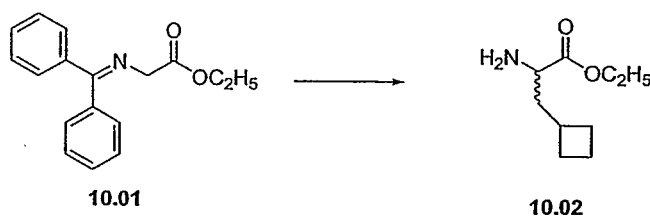
In yet another variation, the dipeptide hydrochloride salt 1.03 was converted to the 4-nitrophenyl carbamate as described above. Treatment with an amine (or amine hydrochloride salt) of choice provided the urea derivative 1.05. Hydrolysis and further elaboration as described in Methods A/B provided the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



Preparation of P1-P' moieties

Preparation of Intermediates 10.11 and 10.12

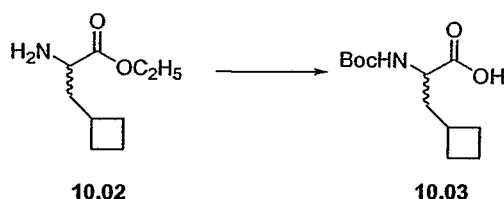
Step 1.



A stirred solution of ketimine **10.01** (50 g, 187.1 mmol) under N_2 in dry THF (400 mL) was cooled to -78°C and treated with 1 M solution of K^tBuO (220 mL, 1.15 equiv.) in THF. The reaction mixture was warmed to 0°C and stirred for 1 h and

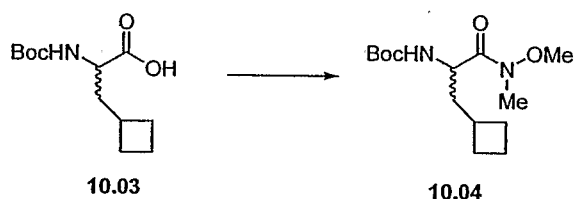
treated with bromomethyl cyclobutane (28 mL, 249 mmol). The reaction mixture was stirred at room temperature for 48 h and concentrated *in vacuo*. The residue was dissolved in Et₂O (300 mL) and treated with aq. HCl (2 M, 300 mL). The resulting solution was stirred at room temperature for 5 h and extracted with Et₂O (1 L). The aqueous layer was made basic to pH ~12-14 with NaOH (50 % aq.) and extracted with CH₂Cl₂ (3x300 mL). The combined organic layers were dried (MgSO₄), filtered, and concentrated to give the pure amine (**10.02**, 18 g) as a colorless oil.

Step 2.



A solution of the amine **10.02** (18g, 105.2 mmol) at 0 °C in CH₂Cl₂ (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/H₂O (200 ml, 1:1) and treated with LiOH•H₂O (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 Et₂O. The aqueous layer was acidified with conc. HCl to pH~1-2 and extracted with CH₂Cl₂. The combined organic layers were dried (MgSO₄), 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.

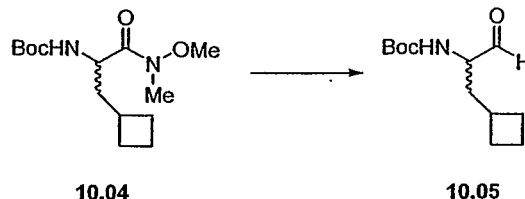
Step 3.



A solution of the acid **10.03** (15.0 g, 62 mmol) in CH₂Cl₂ (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 CH₂Cl₂ (3x300 ml). The combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo* and purified by

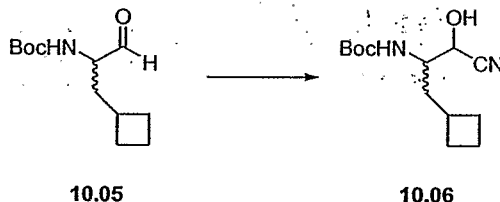
chromatography (SiO₂, EtOAc/Hex 2:3) to yield the amide **10.04** (15.0 g) as a colorless solid.

Step 4.



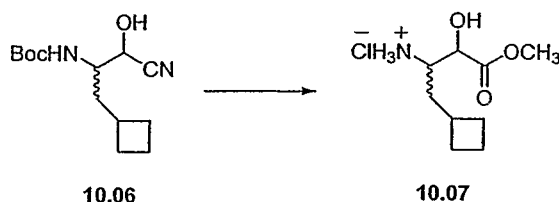
- 5 A solution of the amide **10.04** (15 g, 52.1 mmol) in dry THF (200 mL) was treated dropwise with a solution of LiAlH₄ (1M, 93 mL, 93 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h and carefully quenched at 0 °C with a solution of KHSO₄ (10% aq.) and stirred for 0.5 h. The reaction mixture was diluted with aq. HCl (1 M, 150 mL) and extracted with CH₂Cl₂ (3x200 mL). The combined
- 10 organic layers were washed with aq. HCl (1 M), saturated NaHCO₃, brine, and dried (MgSO₄). The mixture was filtered and concentrated *in vacuo* to yield **10.05** as a viscous colorless oil (14 g).

Step 5:



- 15 A solution of the aldehyde **10.05** (14 g, 61.6 mmol) in CH₂Cl₂ (50 mL), was treated with Et₃N (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 CH₂Cl₂ (3x200 mL). The combined organic layer were washed with H₂O, brine, dried
- 20 (MgSO₄), filtered, concentrated *in vacuo* and purified by chromatography (SiO₂, EtOAc/Hex 1:4) to yield **10.06** (10.3 g) as a colorless liquid

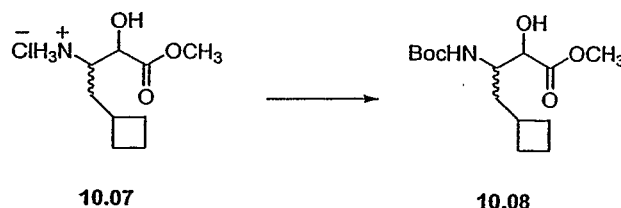
Step 6.



Methanol saturated with HCl*, prepared by bubbling HCl gas through CH₃OH (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.

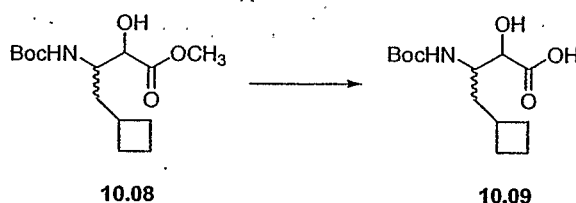
* Alternatively 6M HCl prepared by addition of AcCl to dry methanol can also be used.

Step 7.



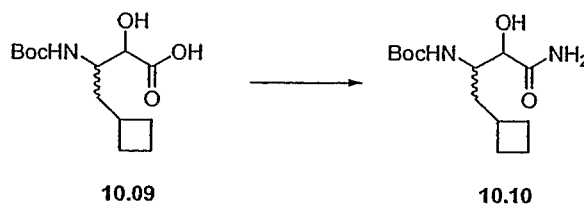
A solution of the amine hydrochloride **10.07** in CH₂Cl₂ (200 mL) was treated with Et₃N (45.0 mL, 315 mmol) and Boc₂O (45.7g, 209 mmol) at -78 °C. The reaction mixture was then stirred at room temperature overnight and diluted with HCl (2 M, 200 mL) and extracted into CH₂Cl₂. The combined organic layers were dried (MgSO₄) filtered, concentrated *in vacuo* and purified by chromatography (EtOAc/Hex 1:4) to yield hydroxy ester **10.08**.

Step 8.



A solution of methyl ester **10.08** (3g, 10.5 mmol) in THF/H₂O (1:1) was treated with LiOH•H₂O (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.

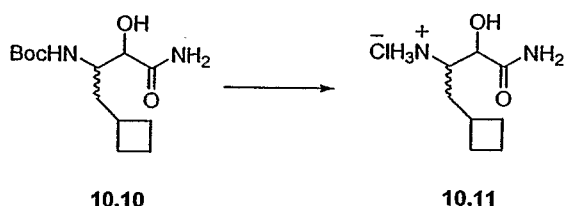
Step 9



A solution of the acid **10.09** (from above) in CH₂Cl₂ (50 mL) and DMF (25 mL) was treated with NH₄Cl (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 CH₂Cl₂. The combined organic layers were washed with aq. saturated NaHCO₃, dried (MgSO₄) 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. H₂O₂ (10 mL), LiOH•H₂O (820 mg, 20.8 mmol) at 0 °C in 50 mL of CH₃OH for 0.5 h.).

Step 10.



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.

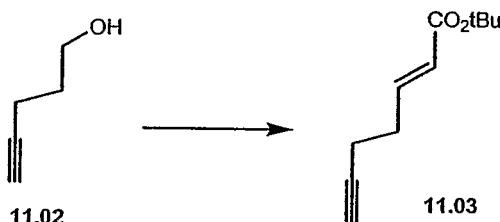
Step 11.



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**

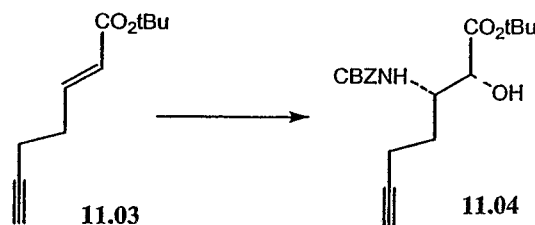
Step 1.



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

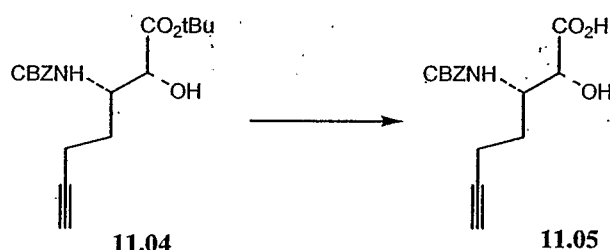
chromatography using 1% EtOAc in hexanes as eluent to give the desired compound, **11.03** (3.92g). Some impure fractions were also obtained but set aside at this time.

Step 2



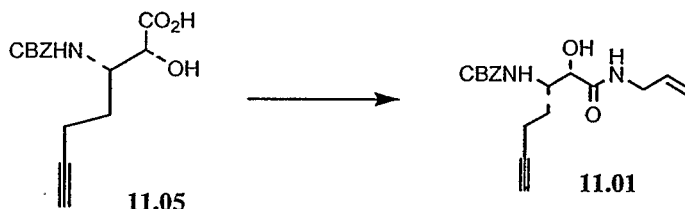
Using the alkene **11.03** (1.9g) in n-propanol (20ml; Aldrich), benzyl carbamate (4.95g; Aldrich) in n-propanol (40ml), NaOH (1.29g) in water (79ml), tert-butyl hypochlorite (3.7ml), (DHQ)2PHAL (0.423g; Aldrich) in n-propanol (37.5ml), and potassium osmate:dehydrate (0.1544g; Aldrich) and the procedure 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.

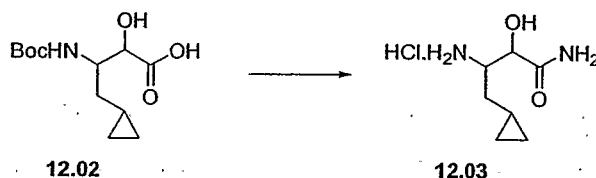
5 Preparation of Intermediates 12.03 and 12.04

Step 1



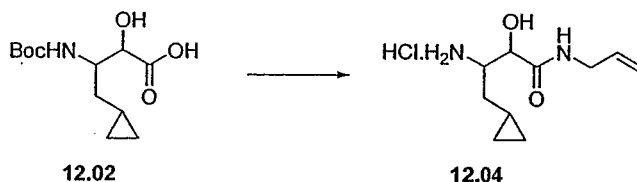
Compound **12.01** was converted to the required material **12.02** using essentially the procedures described for Intermediate **10.11**, Steps 3-8.

10 Step 2



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

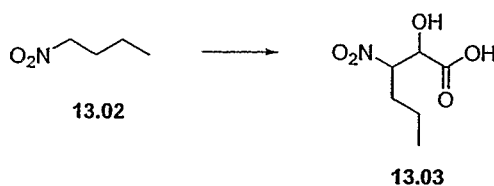
Step 3



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

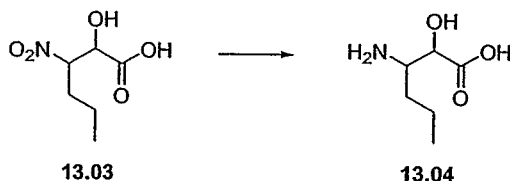
Step 1



To a stirred solution of 1-nitrobutane, **13.02** (16.5 g, 0.16 mol) and glyoxylic acid in H₂O (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.

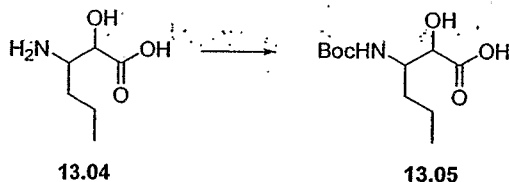
temperature, stirred overnight and concentrated to dryness to give an oil. The oil was then dissolved in H₂O and acidified to pH =1 with 10% HCl, followed by extraction with EtOAc. The combined organic solution was washed with brine, dried over Na₂SO₄, filtered and concentrated to dryness to give the product **13.03** (28.1 g, 99% yield).

Step 2



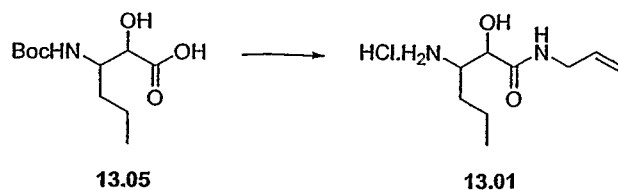
To a stirred solution of compound **13.03** (240 g, 1.35 mol) in acetic acid (1.25 L) was added 10% Pd/C (37 g). The resulting solution was hydrogenated at 59 psi for 3 hrs and then at 60 psi overnight. The acetic acid was then evaporated and azeotroped 3 times with toluene, then triturated with MeOH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

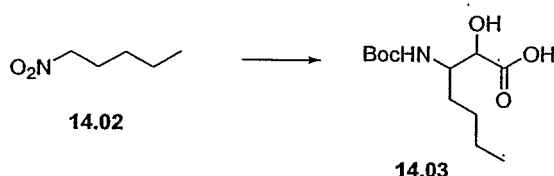


To a stirred solution of the amino acid **13.04** (2.0 g, 13.6 mmol) in dioxane (10 mL) and H₂O (5mL) at 0°C, was added 1N NaOH solution (4.3 mL, 14.0 mmol). The resulting solution was stirred for 10 minutes, followed by addition of di-*t*-butyldicarbonate (0.110 g, 14.0 mmol) and stirred at 0°C for 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 KHSO₄ (3.36 g) and H₂O (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 Na₂SO₄, filtered and concentrated to dryness to give the product **13.05** as a clear gum (3.0 g, 89% yield).

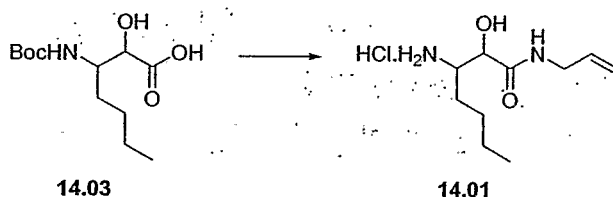
142

Step 4:

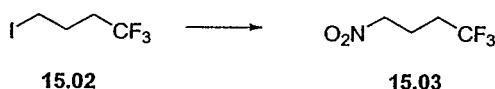
Compound **13.05** was converted to the required intermediate **13.01** using essentially the procedures described for Intermediate **10.12**, Step 11.

Preparation of Intermediate 14.01**Step 1**

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

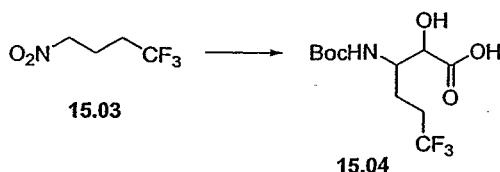
Step 2

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

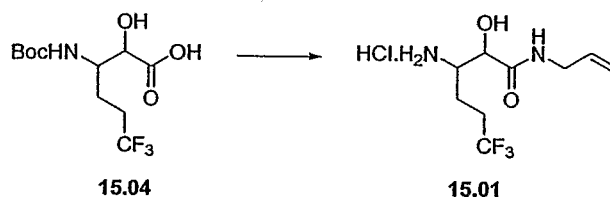
Preparation of Intermediate 15.01**Step 1**

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.

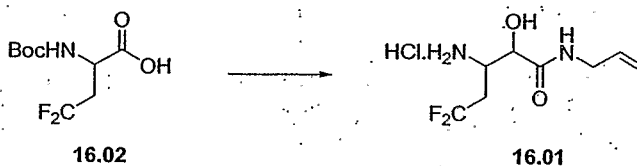
143

Step 2

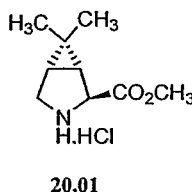
Compound **15.03** was converted to the required material **15.04** using essentially the procedures described for Intermediate **13.01**, Steps 1-3.

Step 3

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

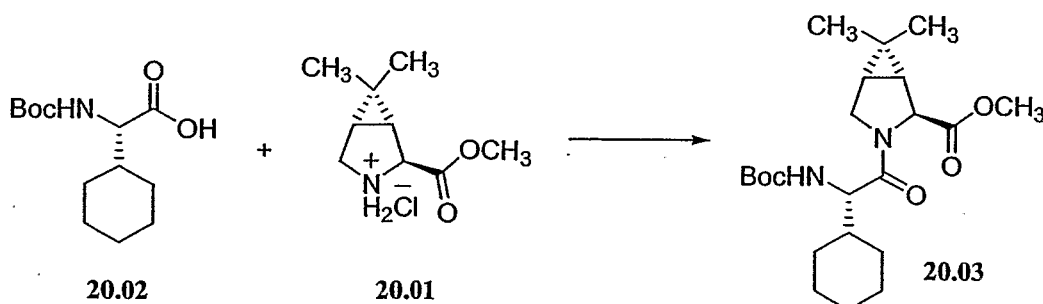
Preparation of Intermediate 16.01

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**.

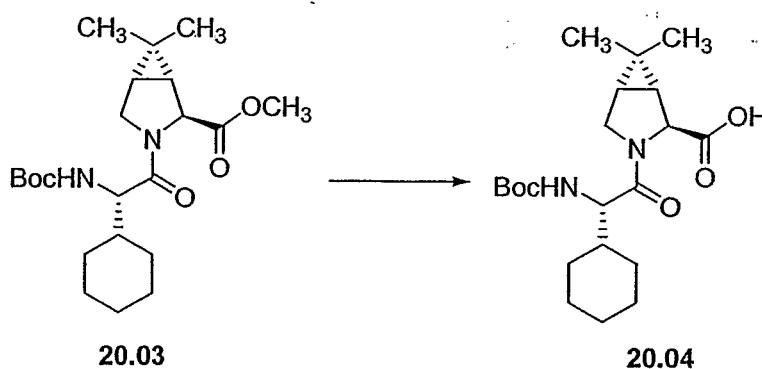
PREPARATION OF P2 / P3-P2 MOIETIES**Preparation of Intermediate 20.01**

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

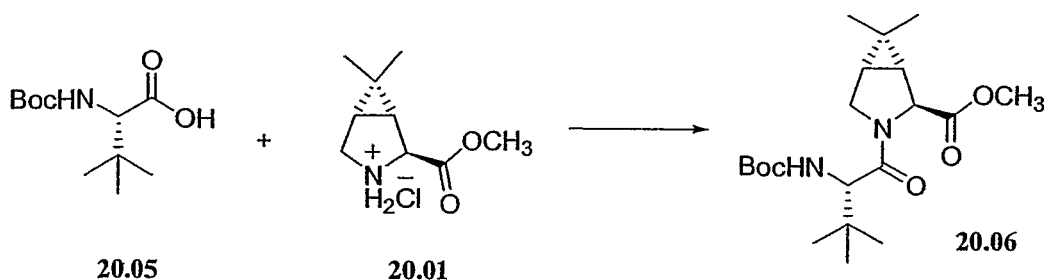
A solution of commercial amino acid Boc-Chg-OH, **20.02** (Senn chemicals, 6.64 g, 24.1 mmol) and amine hydrochloride **20.01** (4.5 g, 22 mmol) in CH₂Cl₂ (100 mL) at 0 °C was treated with BOP reagent and stirred at rt. for 15 h. The reaction mixture was concentrated *in vacuo*, then it was diluted with aq. 1 M HCl and extracted into EtOAc (3x200 mL). The combined organic layers were washed with saturated NaHCO₃ (200 mL), dried (MgSO₄), filtered and concentrated *in vacuo*, and chromatographed (SiO₂, EtOAc/Hex 3:7) to obtain **20.03** (6.0 g) as a colorless solid.

Step 2:

A solution of methyl ester **20.03** (4.0 g, 9.79 mmol) in THF/H₂O (1:1) was treated with LiOH•H₂O (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**.

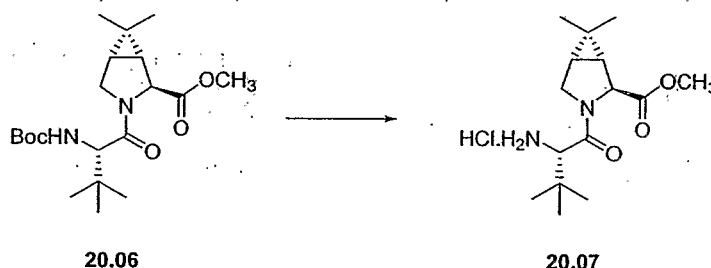
Preparation of Intermediate 20.07Step 1

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A solution of Boc-tert-Leu **20.05** (Fluka, 5.0 g 21.6 mmol) in dry $\text{CH}_2\text{Cl}_2/\text{DMF}$ (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 (SiO_2 , Acetone/Hexane 1:5) to yield **20.06** as a colorless solid.

Step 2



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 **21.01**:

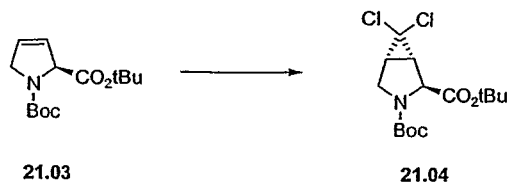
Step 1:



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

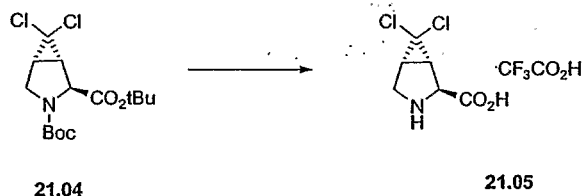
chromatography eluting with 10-25% EtOAc/hexane to give the product **21.03** as a pale yellow oil (5.29 g, 84%).

Step 2:



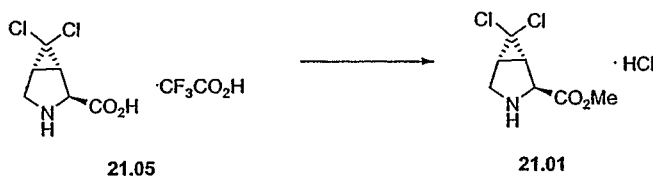
To a stirred solution of the dehydropyrrolidine derivative **21.03** (10.1 g, 37.4 mmol), benzyltriethylammonium chloride (1.60 g, 7.02 mmol) in chloroform (120 mL) at room temperature was added 50% aqueous sodium hydroxide (120 g). After vigorously stirred at this temperature for 24 h, the dark mixture was diluted with CH_2Cl_2 (200 mL) and diethyl ether (600 mL). After the layers were separated, the aqueous solution was extracted with $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ (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:



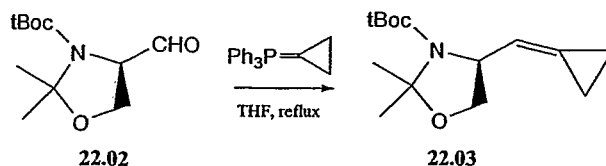
The solution of **21.04** (9.34 g, 26.5 mmol) in CH_2Cl_2 (25 mL) and $\text{CF}_3\text{CO}_2\text{H}$ (50 mL) was stirred at room temperature for 4.5 h before it was concentrated *in vacuo* to give a brown residue, **21.05** which was used in Step 4 without further purification.

Step 4

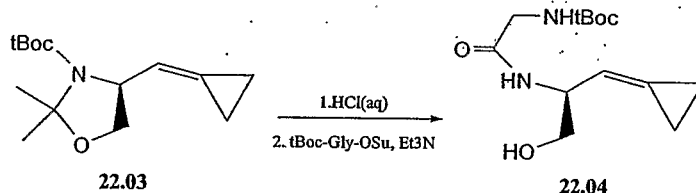


Concentrated hydrochloric acid (4.5 mL) was added to a solution of the residue **21.05** from Step 3 in methanol (70 mL) and the resulting mixture was warmed to 65°C in an oil bath. After 18 h, the mixture was concentrated *in vacuo* to give a brown oil **21.01**, which was used further without purification.

Preparation of Intermediate 22.01

Step 1

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

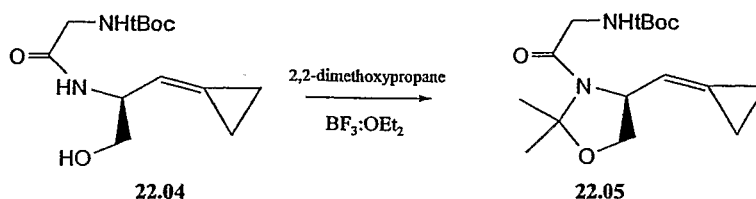
A solution of 1M HCl in MeOH/MeOAc was prepared by adding 14.2ml of acetyl chloride dropwise into cold methanol and diluting the resulting solution to 200ml at room temperature.

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

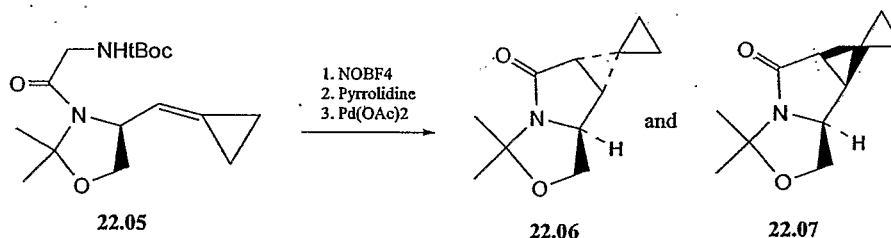
volatiles were removed under reduced pressure and the residue was purified by silica gel column chromatography using methanol (1-3%) in dichloromethane providing the desired amide **22.04** (9.09g).

Step 3.



The alcohol **22.04** (9.09g; 33.6mmol) was dissolved in acetone (118.5ml) and treated with 2,2-dimethoxypropane (37.4ml; 304 mmol) and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (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

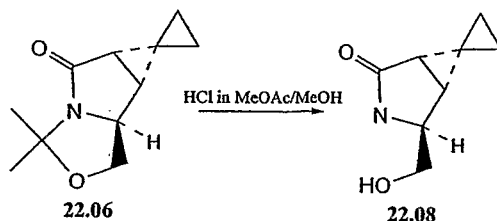


The carbamate **22.05** (8.81g; 28.4mmol) was dissolved in acetonitrile (45ml) and the solution was cooled to -40°C under an atmosphere of nitrogen. Pyridine (6.9ml; 85.3mmol) followed by nitrosium tetrafluoroborate (6.63g; 56.8mmol) were added and the resulting reaction mixture maintained below 0°C 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

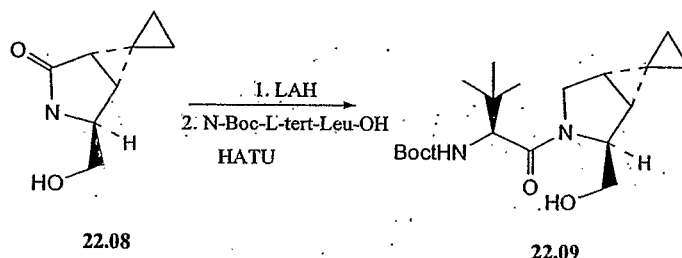
column chromatography using EtOAc-hexane (1:4) to provide the i) the trans-pyrrolidinone **22.06** (1.94g) followed by ii) the cis-pyrrolidinone **22.07** (1.97g).

Step 5



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

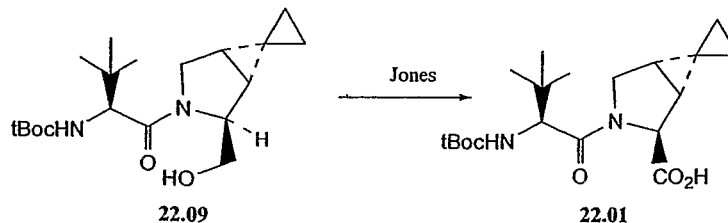


To a solution of the lactam **22.08** (1.29g; 8.44mmol) in anhydrous tetrahydrofuran (55ml) was added lithium aluminum hydride (2.40g; 63.2mmol) and the resulting mixture was refluxed for 8h. After cooling, water, followed by 15% aq. NaOH were added and the resulting mixture was filtered through celite 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).

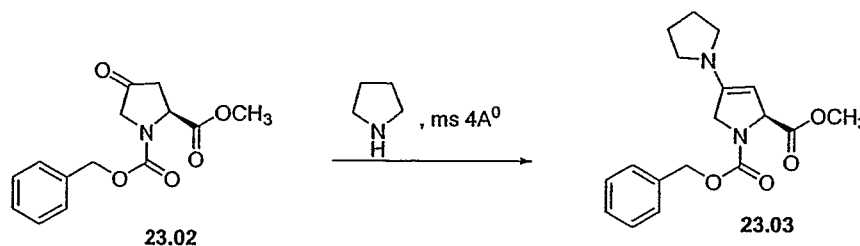
Step 7



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**

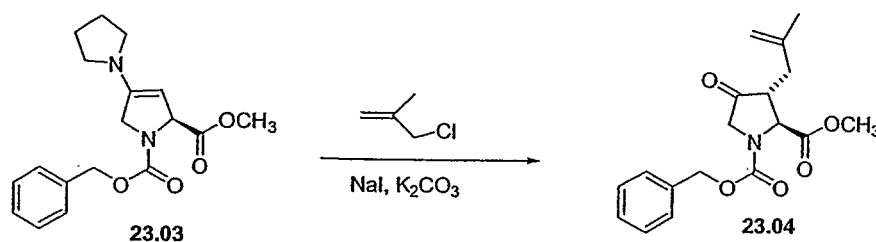
Step 1:



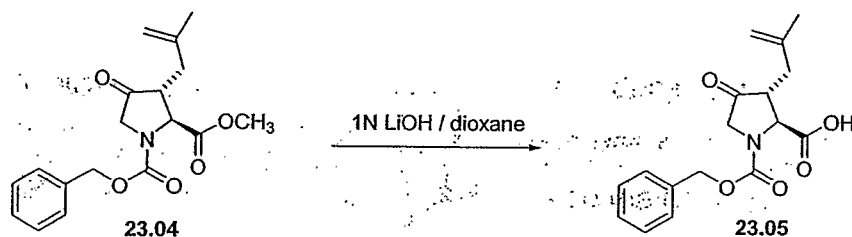
To the mixture of ester **23.02** (6.0g) and molecular sieve (5.2g) in anhydrous methylene chloride (35 mL) was added pyrrolidine (5.7 mL, 66.36 mmol). The resulting brown slurry was stirred at room temperature under N₂ for 24 h, filtered and washed with anhydrous CH₃CN. The combined filtrate was concentrated to yield the desired product, **23.03**.

Step 2:

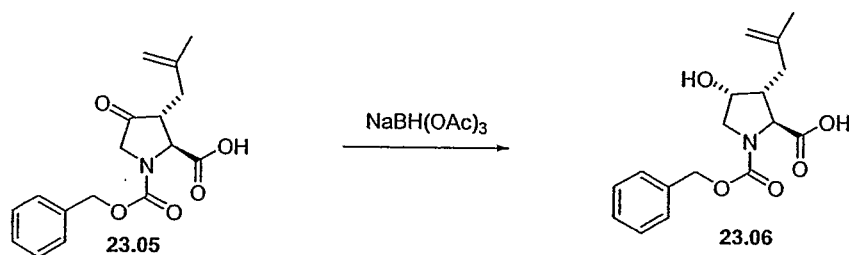
151



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:

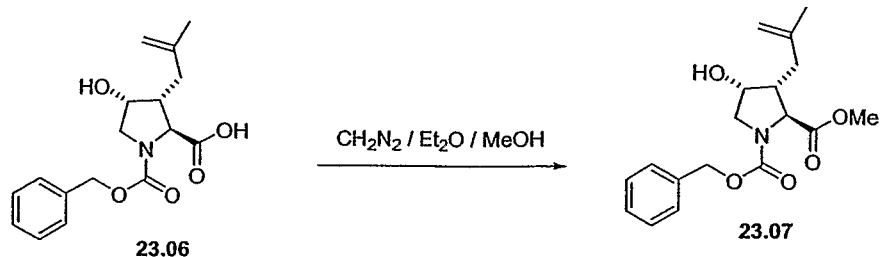
The product **23.04** from the preceding step (2.7 g, 8.16 mmol) was dissolved in dioxane (20 mL) and treated with freshly prepared 1N LiOH (9 mL). The reaction mixture was stirred at ambient temperature under N_2 for 20 h. The reaction mixture was taken in EtOAc and washed with H_2O . The combined aqueous phase was cooled to 0°C 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:

To a suspension of $\text{NaBH}(\text{OAc})_3$ (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

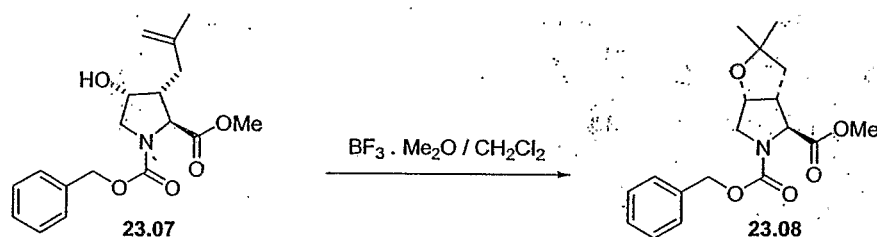
cold water (100 mL) was added to the slurry and stirred for 1/2 hr. Organic layer was separated, filtered, dried and evaporated to yield the desired product, **23.06**.

Step 5:



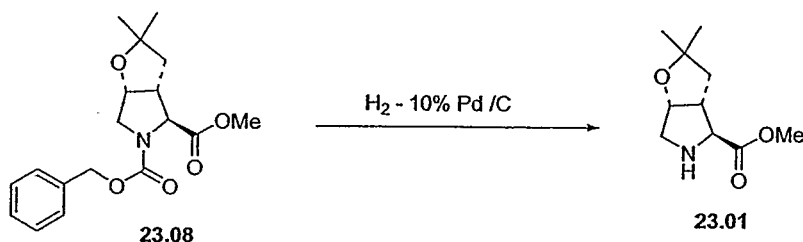
To a solution of the product **23.06** from preceding step (1.9g) in MeOH (40 mL) was treated with excess of CH_2N_2 / Et_2O solution and stirred for overnight. The reaction mixture was concentrated to dryness to yield a crude residue. The residue was chromatographed on silica gel, eluting with a gradient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

Step 6:



To a solution of product **23.07** from preceding step (1.36 g) in anhydrous CH_2Cl_2 (40 mL) was treated with $\text{BF}_3 \cdot \text{Me}_2\text{O}$ (0.7 mL). The reaction mixture was stirred at ambient temperature for 20 h and quenched with sat. NaHCO_3 (30 mL) and 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:



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

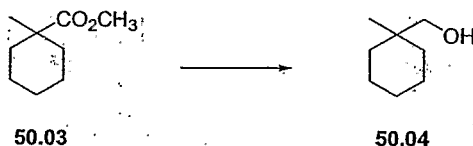
Preparation of Intermediate 50.01

Step 1



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



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.

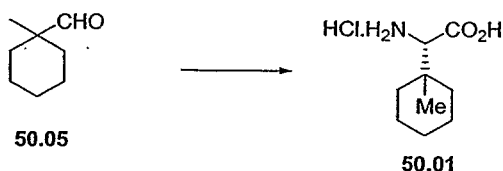
Step 3



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.

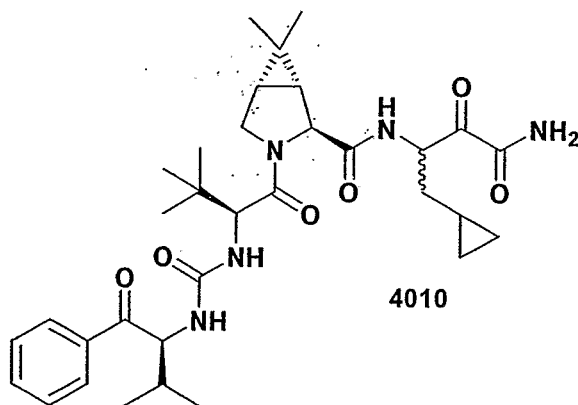
Step 4



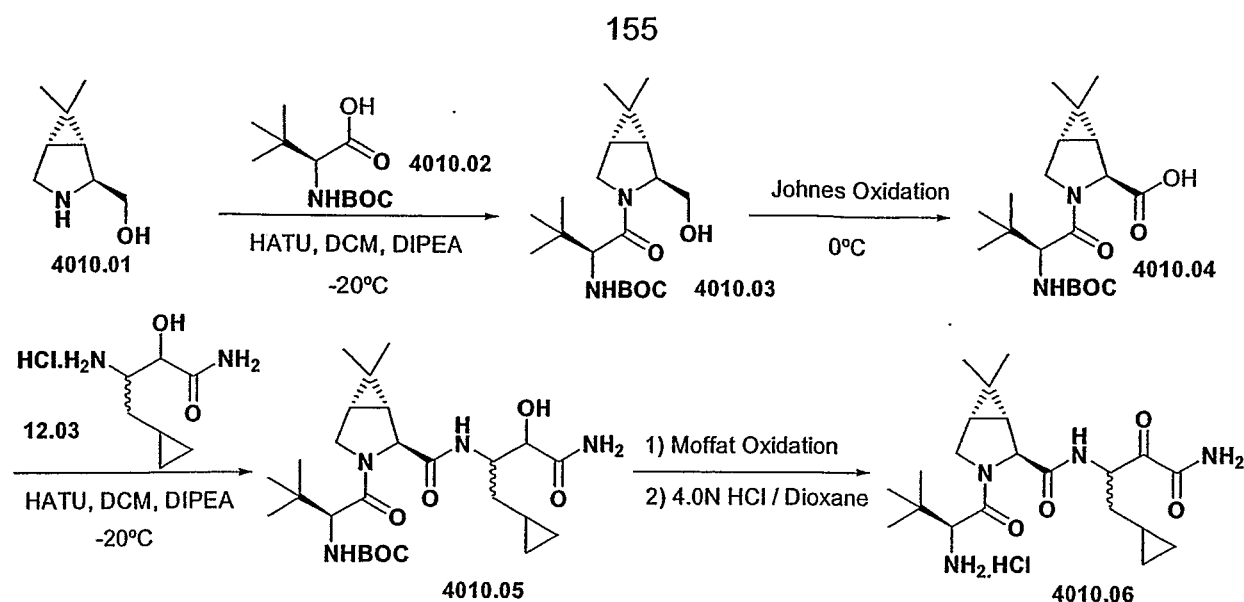
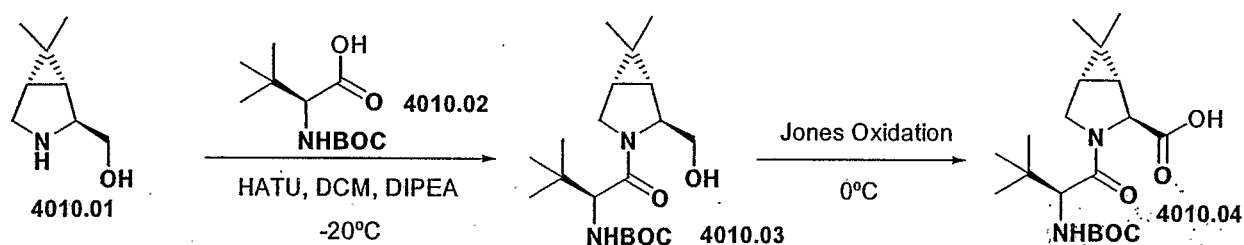
The aldehyde **50.05** from above was converted to the desired material **50.01** using essentially the method of Chakraborty *et. al* (Tetrahedron, **1995**, 51(33), 9179-90).

PREPARATION OF SPECIFIC EXAMPLES from Table 1

Example I: Preparation of Compound of Formula 4010



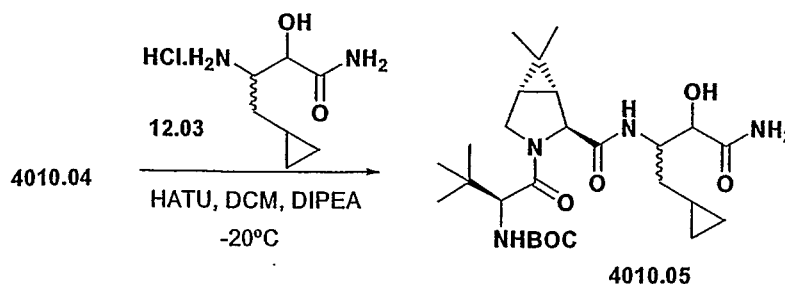
Part I: Preparation of intermediate 4010.06

**Step1:**

To a -20°C solution of Amine **4010.01** (10g, 72mmol) prepared following the method of R. Zhang and J. S. Madalengoitia (*J. Org. Chem.* **1999**, *64*, 330) in DCM (200mL) was added HATU (1.05equiv, 28.8g), Boc-L-Tert Leucine (Aldrich Chemical Co., Milwaukee, Wisconsin, 1.1 equiv, 79.2 mmol, 18.3g) and DIPEA (0.2 mol, 40 mL). Reaction was stirred for 24h then was diluted with EtOAc and washed with NaHCO_3 . Organic layer was washed with citric acid then brine. Organic layer was dried over MgSO_4 , filtered and concentrated under vacuo. The residue **4010.03** (72 mmol) was dissolved in Acetone (1.2 L) at 0°C . Then, 5equiv of Jones reagent (138 mL, 360 mmol, prepared by dissolving 91g of Chromium trioxide in 70 mL of conc, H_2SO_4 and diluted to 300 mL) were added. After 45 min, no starting material was detected by TLC. Isopropanol (40 mL) was added and 500 mL of EtOAc. The green solution was filtered off through a pad of celite and the filtrate concentrated to dryness. The residue was diluted with 10% sodium carbonate and extracted with Et_2O . The aqueous layer was then acidified to pH=2 with HCl 3.0N and extracted with EtOAc (3 times 200 mL). Organic layer was dried over MgSO_4 , filtered and concentrated under vacuo. to yield 21.55 g of intermediate **4010.04**.

Step2:

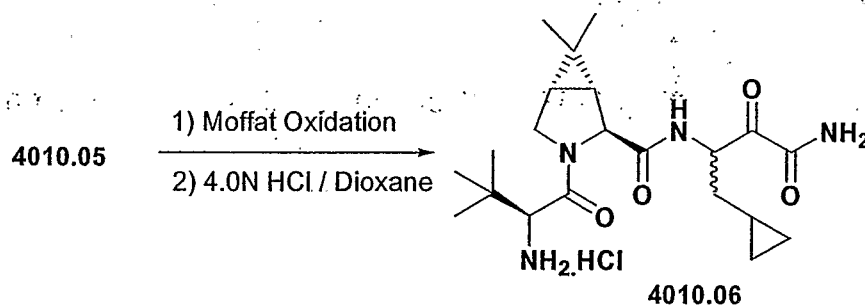
156



To a -20°C solution **4010.04** (10.4g, 28mmol) in DCM (300 mL) was added HATU (1.05 equiv, 29.4mmol, 11.2g), amine salt **12.03** (1.0equiv, 28mmol, 5.48g, prepared as described in Preparation of intermediates, preparation of P1-P' moieties). After 10 min at -20°C, DIPEA (3.6equiv, 100 mmol, 17.4mL) was added. Reaction was stirred at this temp for 16 h. After 16, the reaction was diluted with EtOAc and washed successively with NaHCO₃, citric acid (10% w/w) and brine. Organic layer was dried over MgSO₄, filtered and concentrated under vacuo. to yield: 14 g of intermediate

4010.05.

Step3:

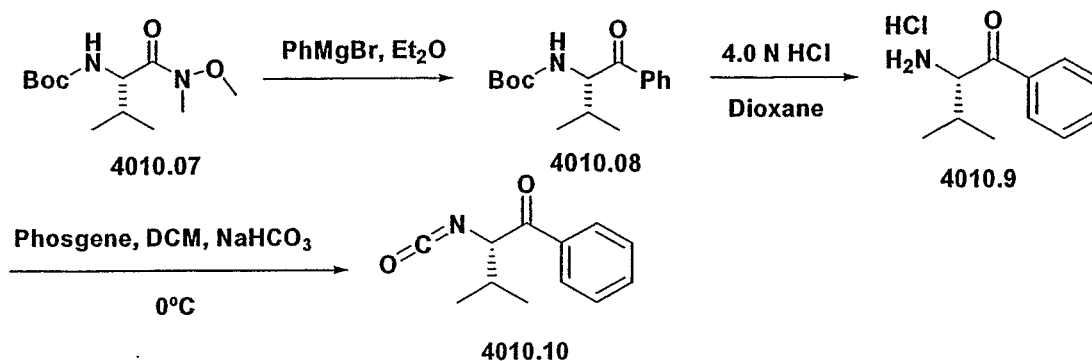


Et₃N (3 equiv., 5.2 mmol, 0.72 mL) is added to a mixture of crude **4010.05** (1.06g, 1.73 mmol theoretical) and EDCI (4equiv., 6.92 mmol, 1.33g) in EtOAc (12 mL) at RT. After addition, DMSO (4.5 mL) was slowly charged. This was followed by addition of methanesulfonic acid (3.6equiv, 6.22 mmol, 0.4 mL) with temperature between 20 and 30°C. The reaction was agitated for 1h. After 1h, TLC shows reaction completed. At 0°C, a chilled mixture of EtOAc (12 mL) and iced water (2 mL) was added. After 2 minutes, the biphasic mixture was allowed to settle and the layers were separated. The upper organic layer was washed with H₂O and brine. Organic layer was dried over MgSO₄, filtered and concentrated under vacuo. The residue was purified by HPFC, 25+M, 15% to 60% (EtOAc) in Hexanes. Purification provided (0.6g) of ketoamide. To a RT solution ketoamide (0.6g) was added 25mL of a 4.0 N HCl solution in Dioxane. Reaction was stirred at RT for 1h to observe completion then

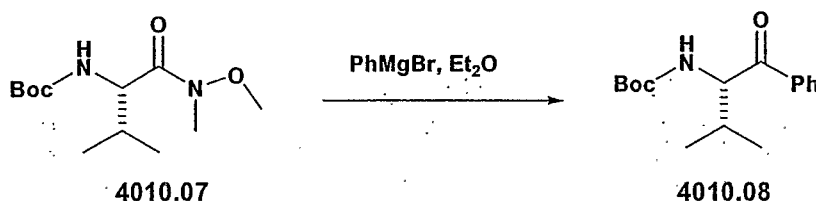
concentrated to about 5 mL and diluted with Heptanes and Ether.(10 mL each). The resulting white precipitate was filtered off and dried under a N₂ flow to provide 0.49 g (81% yield) of intermediate **4010.06**.

Part II: Preparation of intermediate 4010.10

5

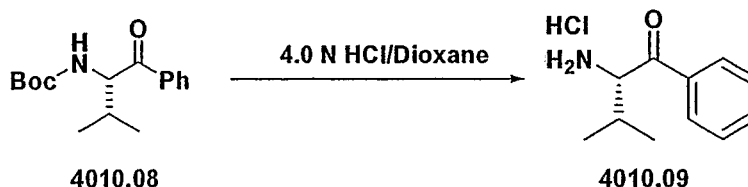


Step1:



PhMgBr (2.5 equiv, 40 mL) was added @ -78°C to a Et₂O (200mL) solution of commercially available Weinreb amide **4010.07** (Aldrich Chemical Co., Milwaukee, Wisconsin, USA, 12g, 46 mmol). After 2 h, reaction was quenched by addition of HCl 1.0 N, diluted with EtOAc and washed with brine, dried over MgSO₄, filtered and concentrated under vacuo. The residue was purified by HPFC Biotage 75+S, 2% (EtOAc) to 8% (EtOAc) in Hexane. 3.76g of **4010.08** were obtained.

Step2:

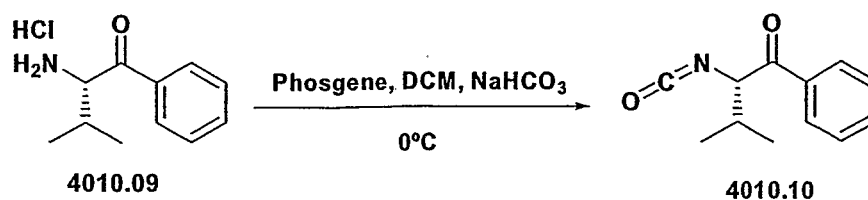


To **4010.08** (1.93g, 6.9 mmol) was added 5 mL of 4M HCl (in Dioxane). The reaction was stirred at RT for 50min and concentrated to dryness to get 1.29g of product **4010.09**.

Step3:

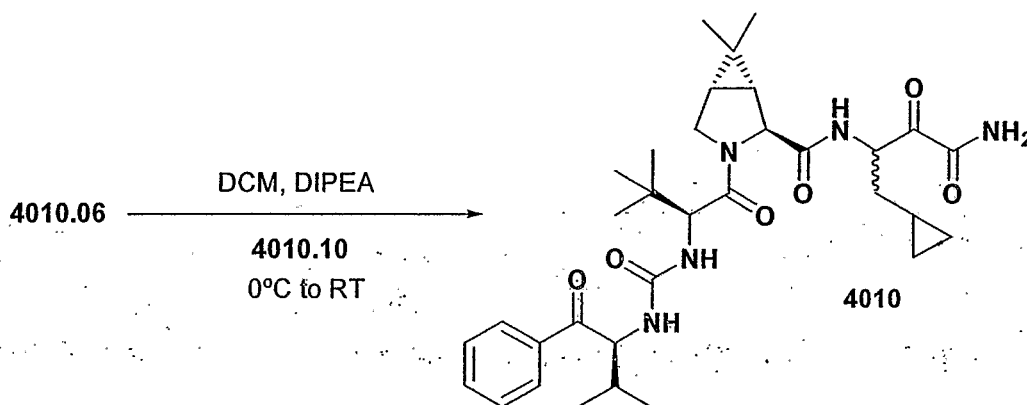
20

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To a 0°C solution of phosgene (6.3 mL) in CH₂Cl₂ (50 mL) and NaHCO₃ (sat.) (50 mL) was added **4010.09** (1.29g, 6 mmol). The mixture was stirred at RT for 2.5h then separated. Organic layer was dried over Na₂SO₄ (anhydrous) and concentrated under vacuum to half volume with cooling bath. Diluted it to 20mL with CH₂Cl₂ to get **4010.10** as a 0.3M solution in CH₂Cl₂.

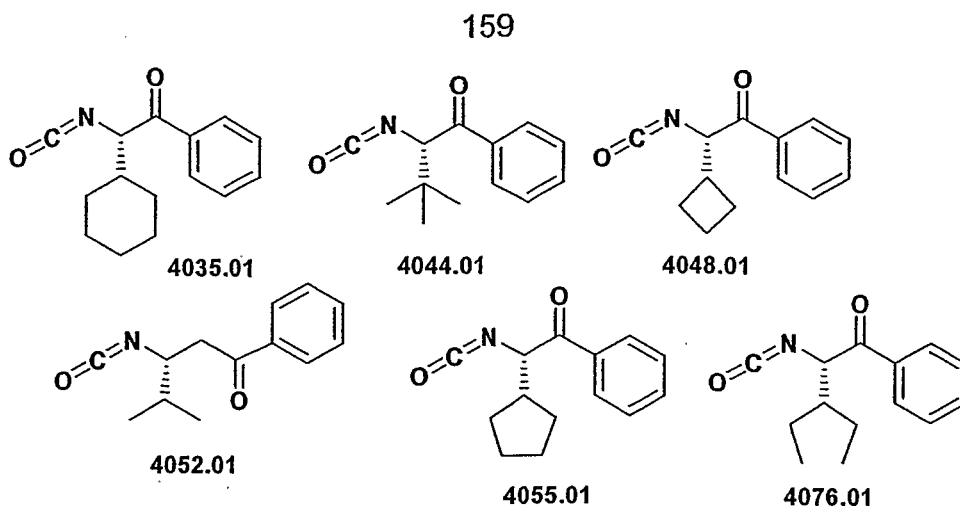
Part III: Preparation of Compound of Formula 4010 of Table 1



Following general **method C**: To a 0°C solution of amine **4010.06** (20 mg, 0.045 mmol) in CH₂Cl₂ (2 mL) was added isocyanate **4010.10** (2 equiv., 0.3 mL) then DIPEA (0.035 mmol, 0.06 mL). The reaction was stirred at RT for 1.2 hrs then diluted with EtOAc and washed with sat. NH₄Cl and Brine. Organic layer was dried over MgSO₄, filtered and concentrated to dryness. Residue was purified by plate with 40% acetone in hexane to get 12.7mg of product **4010** (46% yield); LCMS : (610.1 : M+1), (632 : M+Na).

HCV inhibitors **4028**, **4031**, **4062**, **4082**, **4102**, **4109**, **4110**, **4119**, **4120**, **4151**, **4152**, **4153**, **4154**, **4163**, **4165**, **4176**, **4184** and **4201** described in **Table 1** were prepared using intermediate **4010.10**.

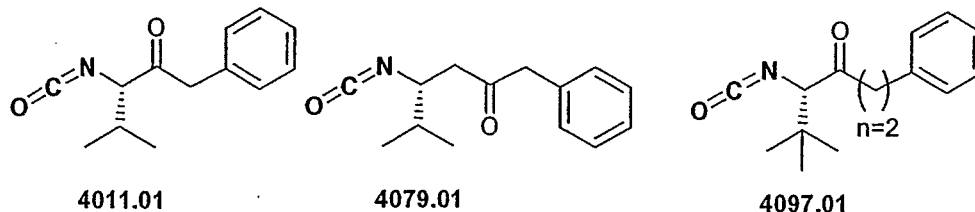
Example II: Preparation of Intermediate of Formula 4035.01, 4044.01, 4048.01, 4052.01, 4055.01, and 4076.01:



Isocyanates **4035.01**, **4044.01**, **4055.01**, **4048.01** and **4076.01** were prepared according the procedure outlined in preparative example I by replacing in **step1** the commercially available (L)-Valine N,O-Dimethylhydroxyl amide with the corresponding *tert*-Leucine, cyclohexylglycine, spirocyclohexylglycine, cyclobutylglycine, homovaline, cyclopentylglycine respectively. N,O-Dimethylhydroxyl amide were prepared from commercially N-Boc amino acids following the procedure outlined in **step1** of preparative example of compound of formula **4032**.

HCV inhibitors **4035**, **4042**, **4044**, **4048**, **4051**, **4052**, **4055**, **4076**, **4126**, **4141** and **4147** described in **Table 1** were prepared using intermediates **4005.01**, **4035.01**, **4048.01**, **4052.01**, **4055.01**, and **4076.01** according to the general procedures described before.

Example III: Preparation of Intermediate of Formula 4011.01, 4079.01 and 4097.01

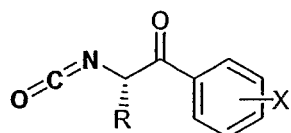


Isocyanates **4011.01**, **4079.01** and **4097.01** were prepared according the procedure outlined in preparative example I by replacing in **step1** the Phenylmagnesium bromide by the commercially available Benzylmagnesium chloride and Phenethylmagnesium chloride with (L)-Valine N,O-Dimethylhydroxyl amide or (L)-

Homovaline N,O-Dimethylhydroxyl amide or *tert*-Leucine N,O-Dimethylhydroxyl amide.

HCV inhibitors **4011**, **4068**, **4079** and **4097** described in **Table 1** were prepared using intermediates **4011.01**, **4079.01** and **4097.01** according to the general procedures described before.

Example IV: Preparation of Intermediates of Formula 4012.01



4012.01

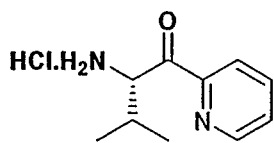
X= F, Cl, Br, CF₃, OMe, OPh, OCH₂Ph, Me, NMe₂, SMe
ortho, meta and para position

R= (L)-Valine, (L)-*tert*-Leucine, (L)-Cyclohexylglycine

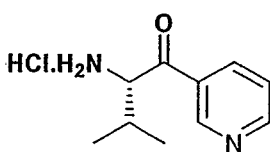
Isocyanates of type **4012.01** were prepared according the procedure outlined in preparative example I by replacing in **step1** the Phenylmagnesium bromide by the corresponding commercially available ortho, meta or para-substituted Phenyl Grignard reagents (as an example but not limited to: X= F, Cl, Br, CF₃, OMe, OPh, OCH₂Ph, Me, NMe₂, SMe) with (L)-Valine N,O-Dimethylhydroxyl amide or with the corresponding *tert*-Leucine and cyclohexylglycine N,O-Dimethylhydroxyl amide.

HCV inhibitors **4012**, **4027**, **4029**, **4045**, **4064**, **4071**, **4075**, **4083**, **4088**, **4090**, **4094**, **4100**, **4104**, **4113**, **4121**, **4122**, **4130**, **4136**, **4140**, **4157**, **4160** and **4177** described in **Table 1** were prepared using intermediates **4012.01** according to the general procedures described before.

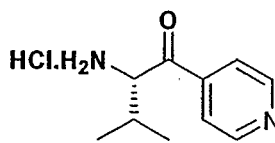
Example V: Preparation of Intermediate of Formula 4017.01, 4078.01, 4095.01, 4041.01, 4175.01 and 4190.01



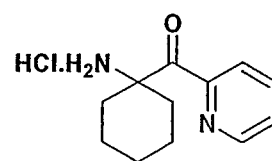
4017.01



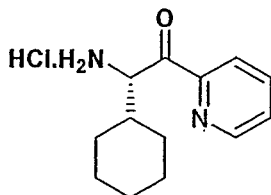
4078.01



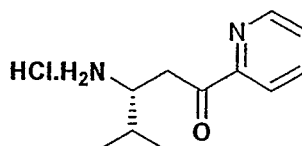
4095.01



4190.01



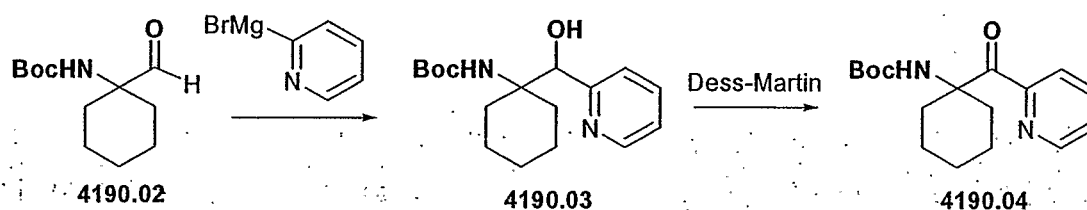
4041.01



4175.01

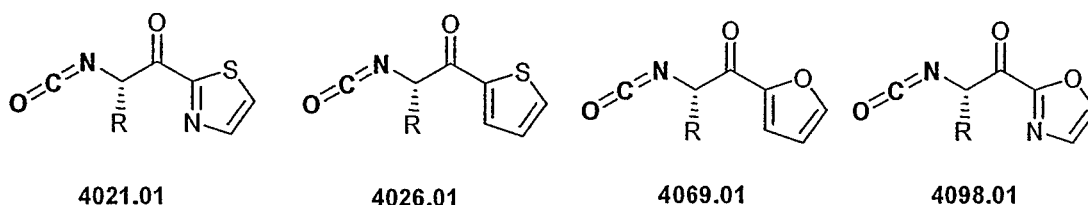
Amine salts **4017.01**, **4041.01**, **4078.01**, **4095.01** and **4175.01** were prepared according the procedure outlined in preparative example I **step1** and **step2** by replacing in **step1** the Phenylmagnesium bromide by the corresponding Magnesium bromide Pyridine that were reacted with the corresponding (L)-Valine N,O-Dimethylhydroxyl amide or (L)-Homovaline N,O-Dimethylhydroxyl amide or (L)-*tert*-Leucine N,O-Dimethylhydroxyl amide or (L)-Cyclohexylglycine N,O-Dimethylhydroxyl amide. The corresponding 2, 3 and 4 Magnesium bromide Pyridine were prepared according Queguiner and all, *Tetrahedron*, **2000**, 56, 1349-1360. For the amine salt **4190.01**, 2 magnesium bromide pyridine was reacted with aldehyde **4190.02** and alcohol **4190.03** was oxidized to pyridine ketone **4190.04** according **scheme 4190.01**.

Scheme 4190.01: Preparation of intermediate 4190.04



HCV inhibitors **4017**, **4022**, **4041**, **4065**, **4078**, **4095**, **4096**, **4101**, **4168**, **4170**, **4172**, **4176**, **4190**, **4199** and **4205** described in Table 1 were prepared using amine salts **4017.01**, **4041.01**, **4078.01**, **4095.01**, **4175.01** and **4190.01** and corresponding isocyanates or 4-nitrophenyl carbamate following **method D** of General Schemes for Preparation of Target Compounds.

Example VI: Preparation of Intermediates of Formula 4021.01, 4026.01, 4069.01 and 4098.01



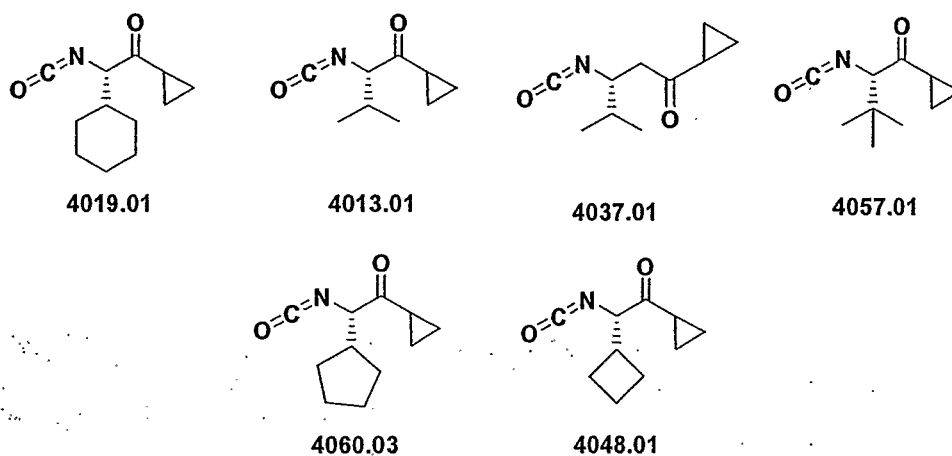
R= (L)-Valine, (L)-*tert*-Leucine, (L)-Cyclhoexylglycine

Isocyanates of type **4021.01**, **4026.01**, **4069.01** and **4098.01** were prepared according the procedure outlined in preparative example I by replacing in **step1** the Phenylmagnesium bromide by the known lithio-furan, thiazole, thiophene and oxazole that were reacted with the corresponding (L)-Valine N,O-Dimethylhydroxyl amide or

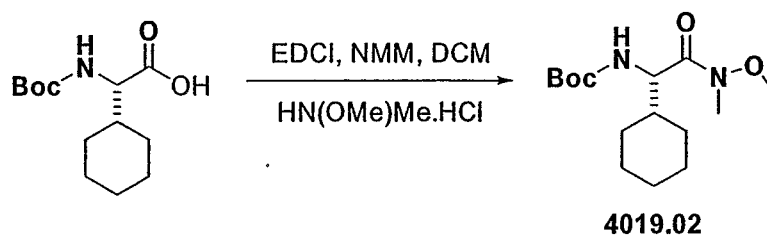
(L)-Homovaline N,O-Dimethylhydroxyl amide or (L)-*tert*-Leucine N,O-Dimethylhydroxyl amide or (L)-Cyclohexylglycine N,O-Dimethylhydroxyl amide.

HCV inhibitors **4021**, **4024**, **4026**, **4034**, **4069**, **4073**, **4077**, **4098**, **4106**, **4117**, **4148**, **4158**, **4159**, **4171**, **4174**, **4181**, **4185**, **4189**, **4191**, **4208** and **4209** described in Table 1 were prepared using intermediates of formula **4021.01**, **4026.01**, **4069.01** and **4098.01** according to the general procedures described before.

SCHEME VII: Preparation of Compound of Formula 4019.01, 4013.01, 4037.01, 4057.01, 4060.01 and 4048.01

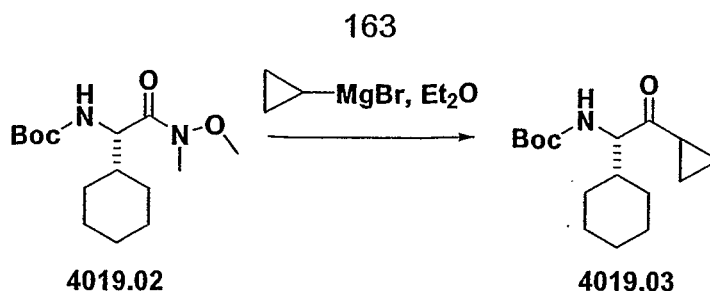


Step1:



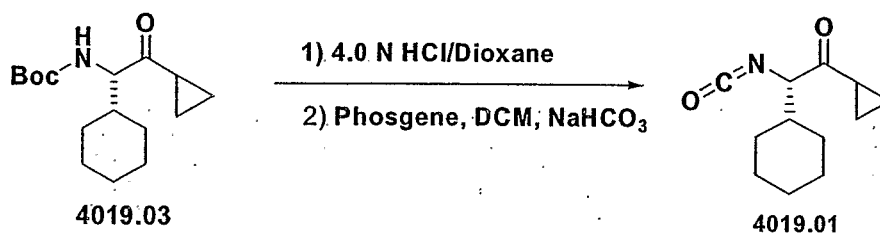
To a -10°C solution of BocCyclohexylGlycine (10g, 36 mmol) in DCM (130 mL) was added N,O-Dimethylhydroxylamine hydrochloride (3.7g, 37.8 mmol), NMM (4.2 mL, 37.8 mmol) and EDCI (7.3g, 37.8 mmol) portionwise in 15 minutes. The reaction was stirred at this temperature for 1h then HCl (1N, 55 mL) was added. Reaction was extracted with DCM (2 times 50 mL) and combined organic layers was washed with NaHCO_3 sat then brine. Organic layer was dried over MgSO_4 , filtered and concentrated to dryness to provide **4019.02** as a viscous oil (10.8g).

Step2:



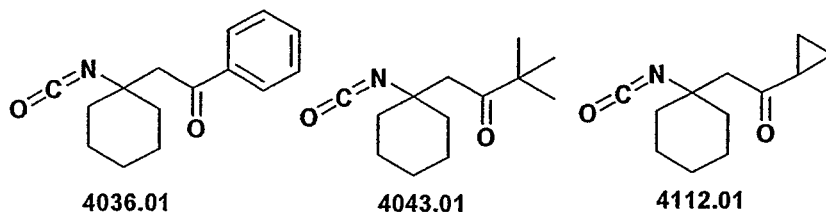
To **4019.02** (1.1g, 3.66 mmol) in Ether (40 mL) was added Cyclopropylmagnesium Bromide (22 mL, 3 equiv, 0.5M in THF) at 0°C . The reaction was warmed up to RT after 5min was stirred at RT for when the reaction was
 5 quenched by the addition of 1N HCl. Reaction was diluted with EtOAc and washed with brine. The organic layer was dried over MgSO₄ filtered and concentrated to dryness. The residue was purified by HPFC Biotage 25+S, 3% (EtOAc) to 13% EtOAc in Hexane to get **4019.03** (0.676g, 66% yield).

Step3:



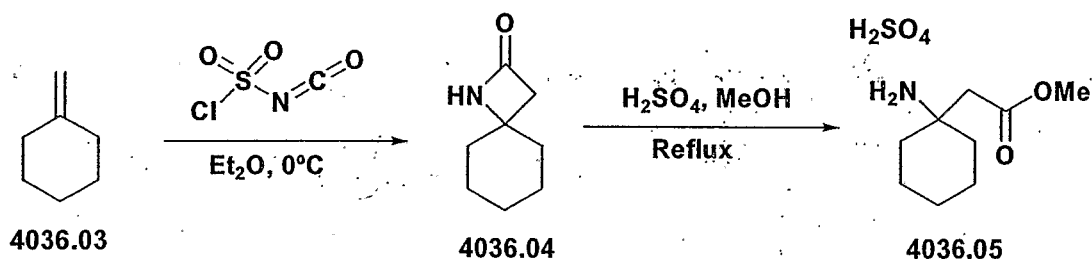
Isocyanate **4019.01** was prepared following **steps 2 and 3** of preparative example I. Isocyanates of Formula **4013.01**, **4037.01**, **4057.01**, **4060.01** and **4048.01** were prepared as described above by replacing in **step2** (L)-Cyclohexylglycine N,O-Dimethylhydroxyl amide by (L)-Valine N,O-Dimethylhydroxyl amide or (L)-Homovaline N,O-Dimethylhydroxyl amide or (L)-*tert*-Leucine N,O-Dimethylhydroxyl amide or (L)-Cyclopentylglycine N,O-Dimethylhydroxyl amide or (L)-Cyclobutylglycine N,O-Dimethylhydroxyl amide,
 HCV inhibitors **4013**, **4016**, **4018**, **4019**, **4023**, **4032**, **4033**, **4037**, **4039**, **4040**, **4048**,
 20 **4057**, **4060**, **4066**, **4074**, **4084**, **4086**, **4091**, **4092**, **4093**, **4099**, **4103**, **4105**, **4111**, **4114**, **4123**, **4129**, **4131**, **4132**, **4133**, **4135**, **4138**, **4139**, **4144**, **4149**, **4150**, **4155**, **4156**, **4161**, **4164**, **4167**, **4169**, **4173**, **4186**, **4187**, **4192**, **4193**, **4195**, **4197**, **4200**, **4204**, **4206** and **4207** described in **Table 1** were prepared using intermediates of formula **4019.01**, **4013.01**, **4037.01**, **4057.01**, **4060.01** and **4048.01** according to the
 25 general procedures described before.

Example VIII: Preparation of Intermediates of Formula 4036.01, 4043.01 and 4112.01



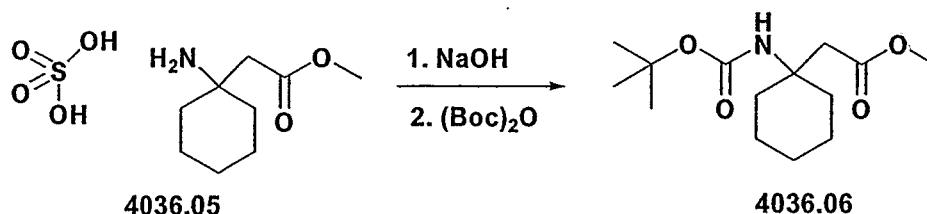
Isocyanates of Formula **4036.01**, **4043.01** and **4112.01** were prepared according the procedure outlined in preparative example I with Phenylmagnesium bromide, *tert*-Butyl lithium and Cyclopropylmagnesium bromide by replacing in **step1** the (L)-Valine N,O-Dimethylhydroxyl amide by the prepared homo-spirocyclohexylglycine N,O-Dimethylhydroxyl amide **4036.02** prepared as follow:

Step1:



Ester **4036.05** was prepared according T. Suzuki, *Chem.Pharm. Bull.* **46(7)** 1116-1124 (1998) from methylenecyclohexane **4036.03** (3.5g, 36.4 mmol) and chlorosulfonyl isocyanate (1.03 equiv, 37.625 mmol, 3.3mL) followed by treatment with sulfuric acid. 4.7g of colorless oil **4036.04** were obtained.

Step2:

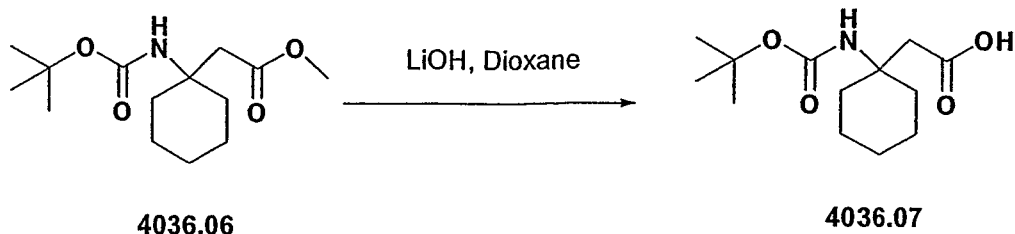


To a RT solution of **4036.05** (1g, 3.71 mmol) in dioxane (10 mL) was added (Boc)₂O (1.1 equiv, 4 mmol, 0.9g) then NaHCO₃sat followed by K₂CO₃ to reach Ph= 9 .After 18h, reaction was extracted with Et₂O. Organic layer was washed with successively

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with citric acid (10% w/w) and brine. Organic layer was dried over MgSO_4 , filtered and concentrated under vacuo. to provide 1 g of **4036.06**.

Step3:

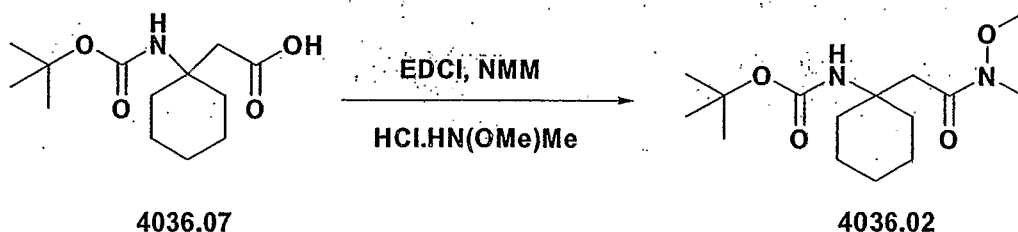


5

To a RT solution of **4036.06** (5g, 18.4 mmol) in Dioxane (30 mL) was added 30mL (1.5 equiv) of 1.0 LiOH. After 5h, reaction was diluted with Et_2O and extracted. H_2O layer was acidified to $\text{pH}=1.5$ with 1 N HCl and extracted with EtOAc . Organic layer was washed with brine and dried over MgSO_4 , filtered and concentrated under vacuo. to provide 4.75g of **4036.07**.

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Step4:



To a 0°C solution of **4036.07** (12.6 mmol, 3.25g) in DCM 35mL was added HCl.

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HN(OMe)Me (1.05 equiv, 13.23 mmol, 1.27g) and NMM (1.05 equiv, 13.23 mmol, 1.5 mL). EDCI was added portionwise (1.05 equiv, 13.23 mmol, 2.54 g) over 10 min.

When reaction completed, HCl 1.5 N was added (50 mL) and reaction was extracted with EtOAc , washed with Brine, dried over MgSO_4 , filtered and concentrated under vacuo to yield: 3.5g of **4036.02**.

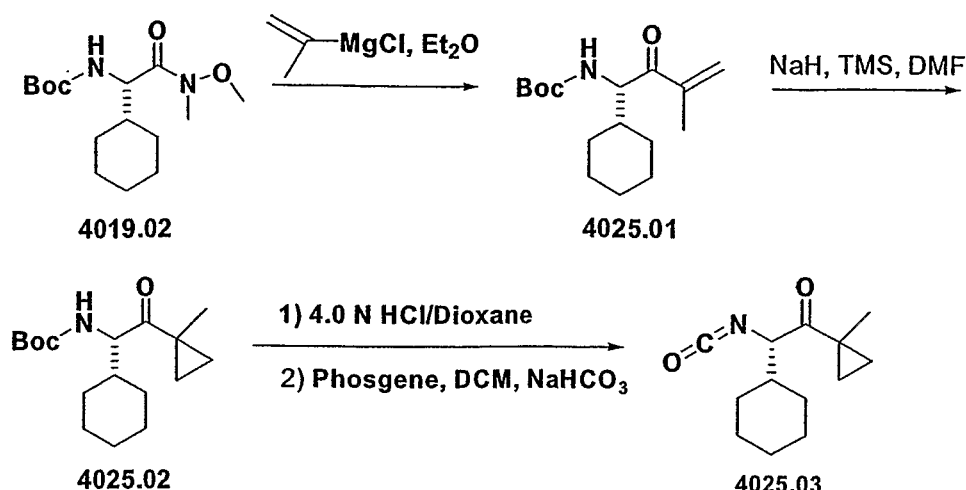
20

HCV inhibitors **4036**, **4043**, **4061**, **4067**, **4080**, **4112** and **4115** described in Table 1 were prepared using intermediates of formula **4036.01**, **4043.01** and **4112.01** according to the general procedures described before.

Example IX: Preparation of compound of Formula 4025

Scheme IX

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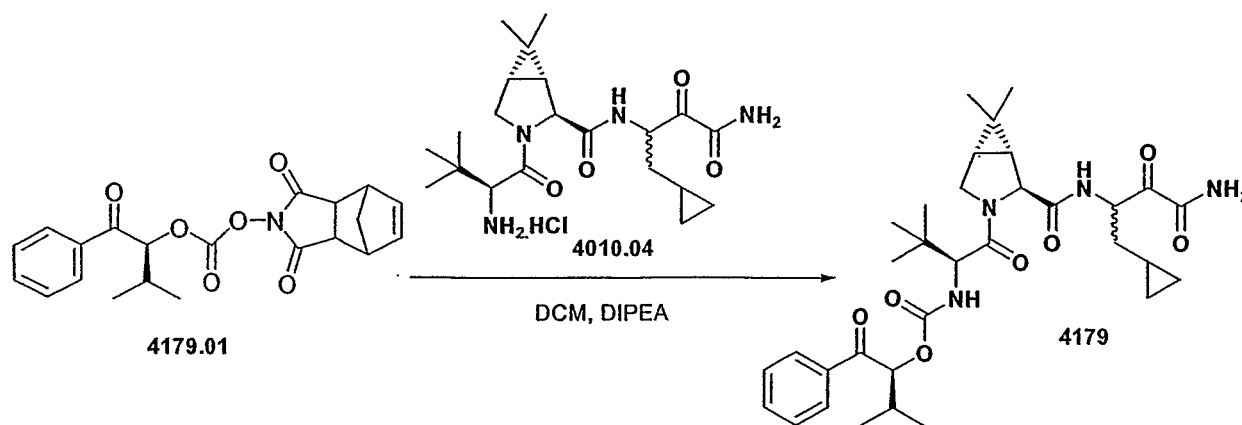
To amide **4019.02** (0.8g, 2.66 mmol) in ether (50 mL) was added isopropenylmagnesium Bromide (Aldrich Chemical Co., Milwaukee, Wisconsin, USA 19 mL, 9.5 mmol, 3.6 equiv) at 0°C. The reaction was warmed up to RT after 5min and stirred at RT for 3hrs then quenched by the addition of 1N HCl. reaction was diluted with EtOAc and washed with brine. The organic layer was dried over MgSO₄ filtered and concentrated down. The residue was purified it by HPFC with 10% EtOAc in hexane to get 0.304g of product **4025.01** (Yield= 40.6%).

Trimethylsulfoxonium iodide (237 mg, 1.08 mmol) was added in one portion to a suspension of NaH (43 mg, 1.08 mmol, 60% in oil) in DMF at RT and stirred for 30min under N₂. The reaction mixture was cooled to -30°C. A solution of ketone **4025.01** (304 mg, 1.08 mmol) in 1mL DMF was added dropwise to the mixture and stirred at -30°C ~ 0°C for 2hrs then 3mL of H₂O was added dropwise at -20°C to the reaction mixture. Reaction was diluted with EtOAc. and organic layer was washed with aq. NH₄Cl, H₂O and brine. Organic layer was dried over MgSO₄, filtered and concentrated down. The residue was purified it by HPFC with 0~1% EtOAc in CH₂Cl₂ to give 176mg of ketone **4025** (Yield= 54%). Optical Rotation: [α]_D²⁰=+87.12 (c=7.5mg/2mL, 20°C, CHCl₃).

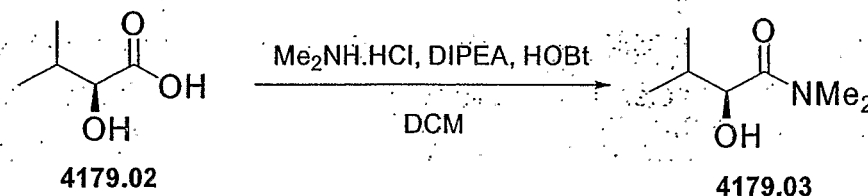
Isocyanate **4025.03** was prepared according the procedure described in step3 of Preparative Example VII (scheme VII).

HCV inhibitors **4025**, **4053** and **4127** described in **Table 1** were prepared using intermediate of formula **4025.03** according to the general procedures described before.

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Example X: Preparation of compound of Formula 4179**Scheme X**

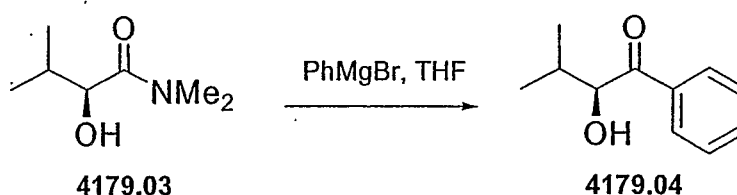
- 5 HCV inhibitors **4179** described in **Table 1** was prepared according the **Scheme X** above using intermediate of formula **4179.01** prepared according the procedure describe below.

Step1:

10

- To a mixture of (S)-hydroxyisovaleric acid (4.4g, 37 mmol), dimethylamine hydrochloride (3.0g, 37 mmol), and 1-hydroxy-1H-benzotriazole (5g, 37 mmol) in THF (20 mL) was added diisopropylethylamine (6.4 mL, 37 mmol) dropwise at -20°C then dicyclohexylcarbodiimide (8g, 39 mmol) was added at once, and the mixture was stirred at RT overnight. After 18 hours, the formed precipitate was filtered off and washed with EtOAc. the combined filtrates were concentrated in vacuo and residue was purified by biotage 75+S column (35% EtOAc/Hex). to yield 5.3 g of amide **4179.03**.

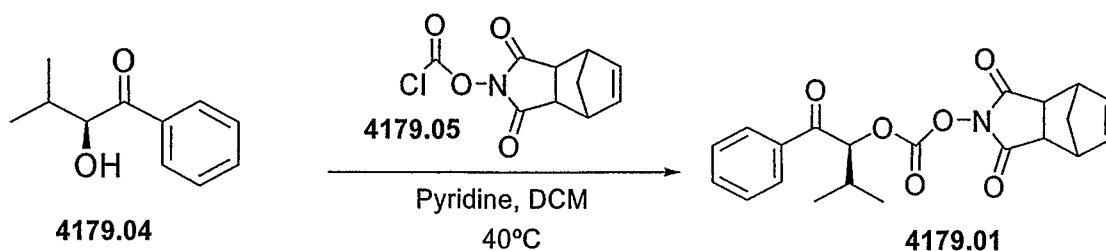
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Step2:

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To **4179.03** (1.5g, 10 mmol) in dry THF (30 mL) was added phenylmagnesium bromide (10 mL, 3.0M in Ether) at 0C. The reaction was warmed up to RT gradually. and stirred at RT overnight then was quenched by the addition of 1N HCl, diluted with EtOAc and washed with brine. The organic layer was dried over MgSO₄. purified by
 5 HPFC biotage 25+M with 15-25% EtOAc in Hex. to yield 1.6 g of **4179.04**.

Step3:



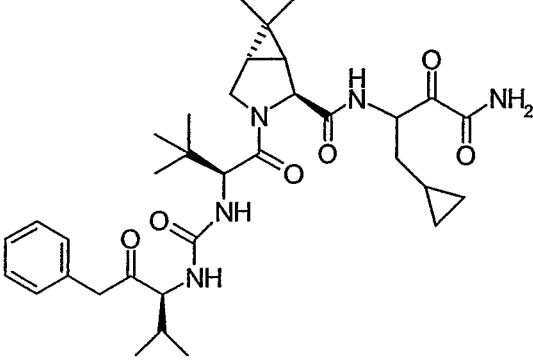
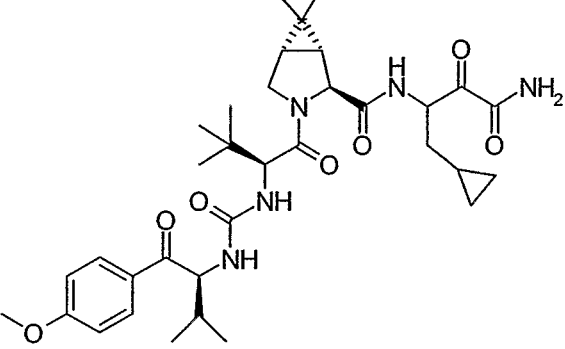
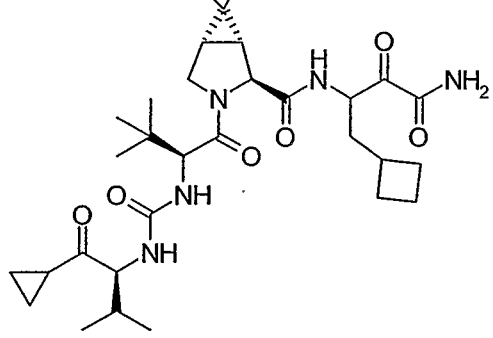
To chloroformate **4179.05** in CH₂Cl₂ at 0C was added dropwise a solution of **4179.04**
 10 (0.8g, 4.5 mmol) and pyridine (0.5 mL). The reaction was warmed up to 40C with hot water and stirred for 1.5 hr then diluted with EtOAc, washed with sat. NaHCO₃, CuSO₄, and brine. dried over MgSO₄, filtered, concentrated and purified by column biotage 25+S (40-60% EtOAc/Hex.) to yield 580 mg of **4179.01**.

All other HCV inhibitors reported in **Table 1** can be prepared according procedures
 15 described above in examples **I** to **VIII**.

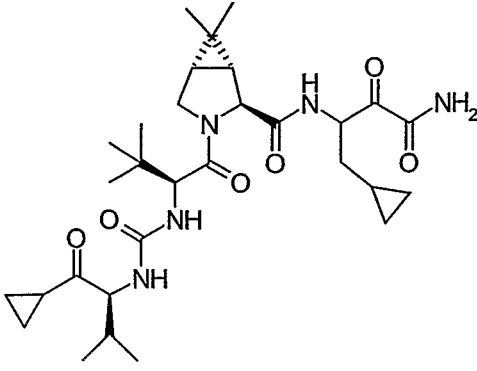
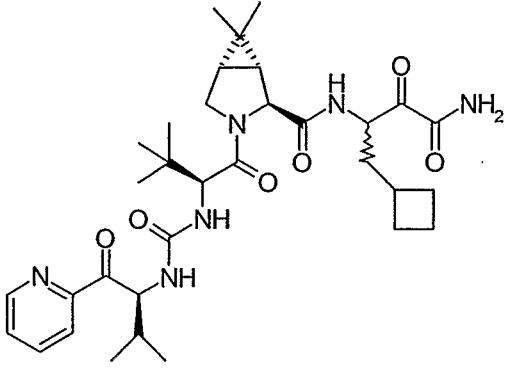
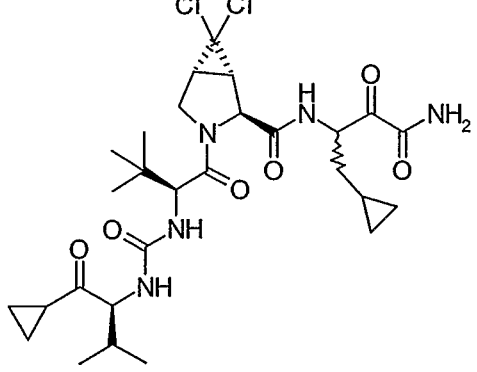
TABLE 1: KETONES

Cmpd #	Table 1 : Ketones	MW	Ki* Range
4010		610	A

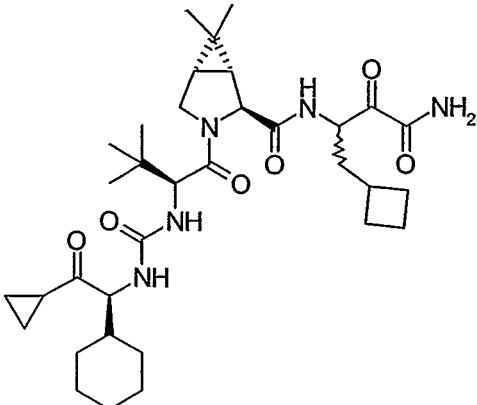
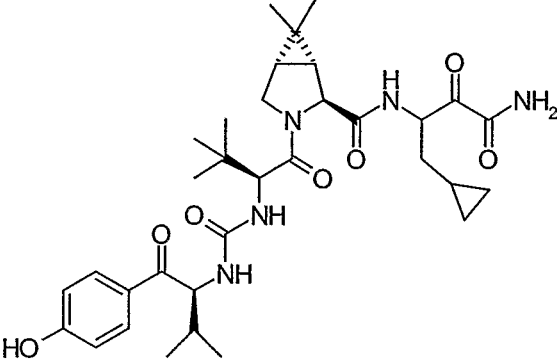
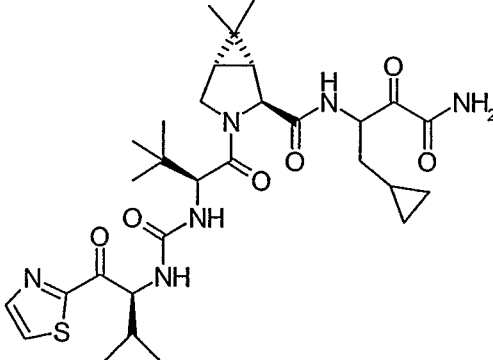
169

Cmpd #	Table 1 : Ketones	MW	Ki* Range
4011		624	A
4012		640	A
4013		588	A

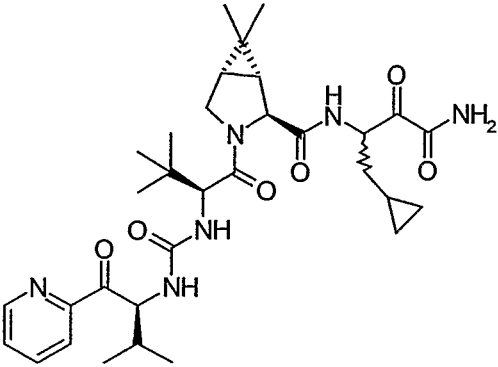
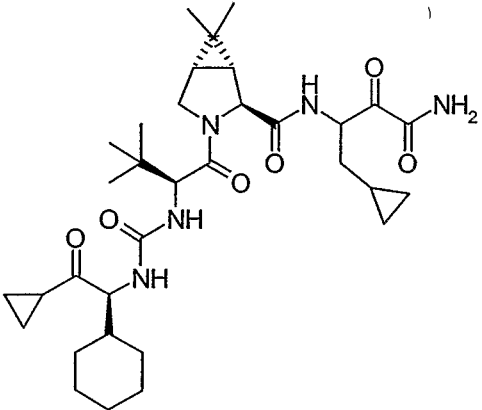
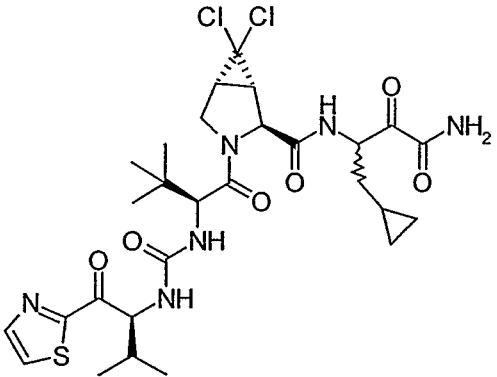
170

Cmpd #	Table 1 : Ketones	MW	Ki* Range
4016		574	A
4017		625	A
4018		615	A

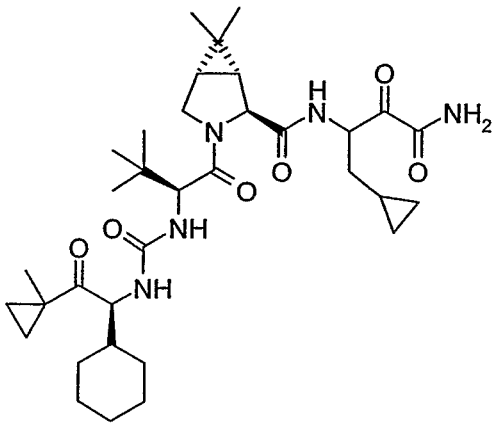
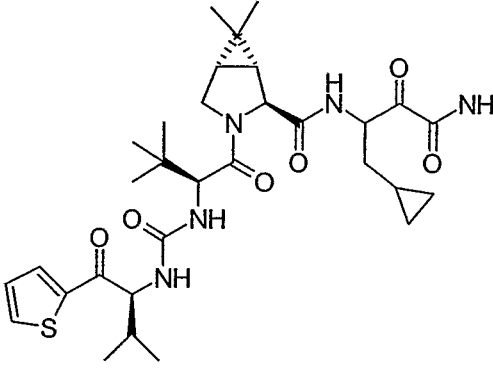
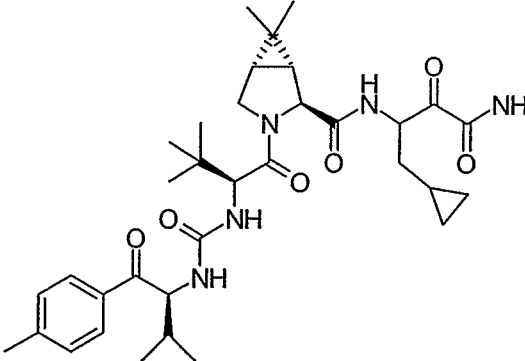
171

Cmpd #	Table 1 : Ketones	MW	Ki* Range
4019		628	A
4020		626	A
4021		617	A

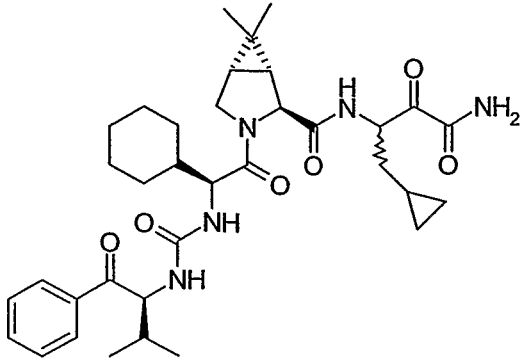
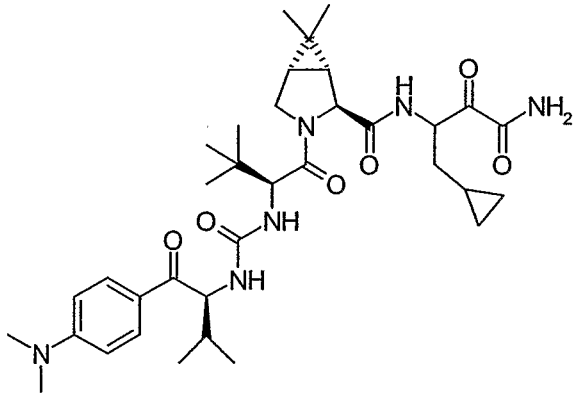
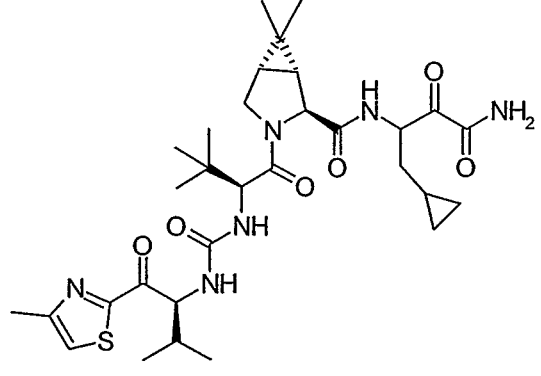
172

Cmpd #	Table 1 : Ketones	MW	Ki* Range
4022		611	A
4023		614	A
4024		658	A

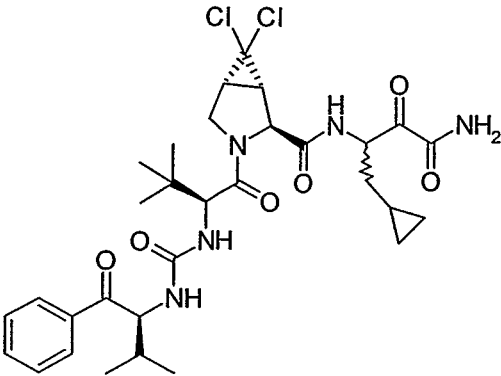
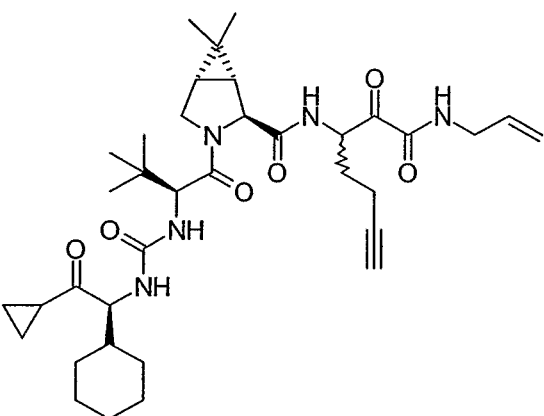
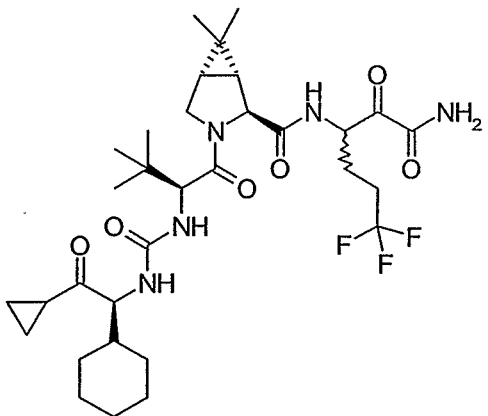
173

Cmpd #	Table 1 : Ketones	MW	Ki* Range
4025		628	A
4026		616	A
4027		624	A

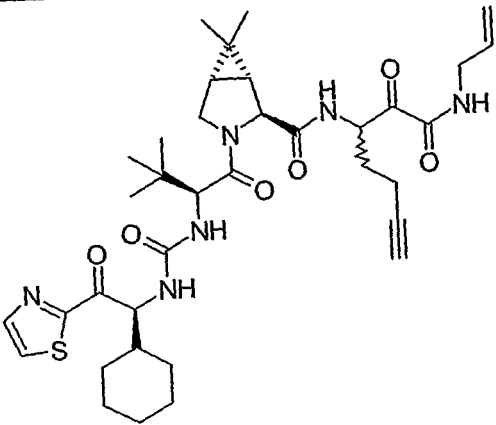
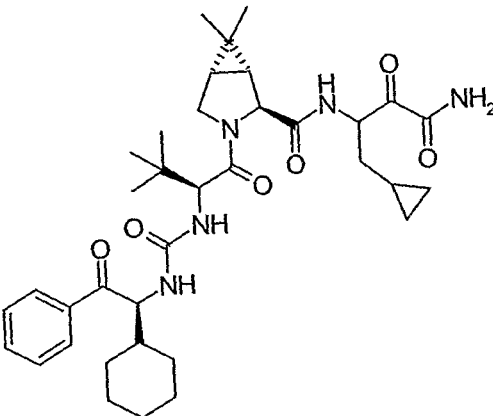
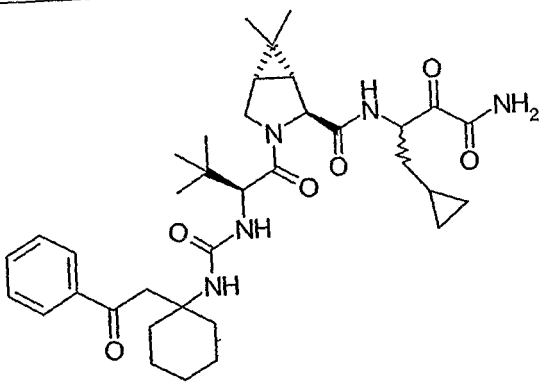
174

Cmpd #	Table 1 : Ketones	MW	Ki* Range
4028	 Chemical structure of compound 4028: A complex molecule featuring a central pyrrolidine ring substituted with a cyclohexyl group, a dimethylamino group, and a carbonyl group. This central moiety is linked via amide bonds to a benzamide derivative and a cyclopropylcarbamoyl group.	636	A
4029	 Chemical structure of compound 4029: Similar to 4028, but the benzamide group is replaced by a 4-(dimethylamino)benzamide derivative.	653	A
4030	 Chemical structure of compound 4030: Similar to 4028, but the benzamide group is replaced by a thiazole-2-carboxamide derivative.	631	A

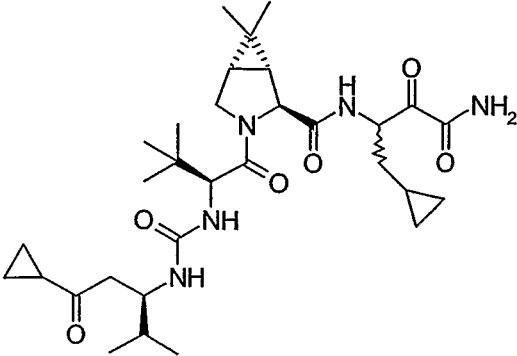
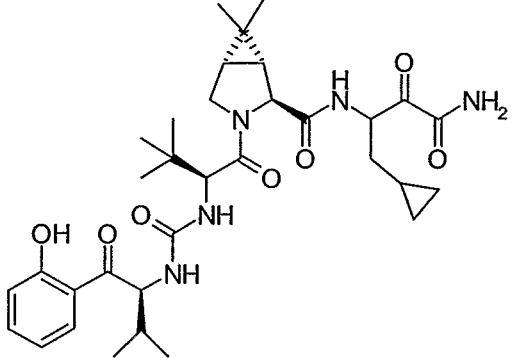
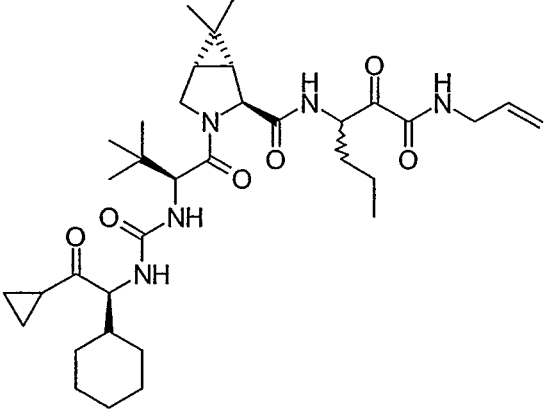
175

Cmpd #	Table 1 : Ketones	MW	Ki* Range
4031		651	A
4032		652	A
4033		656	A

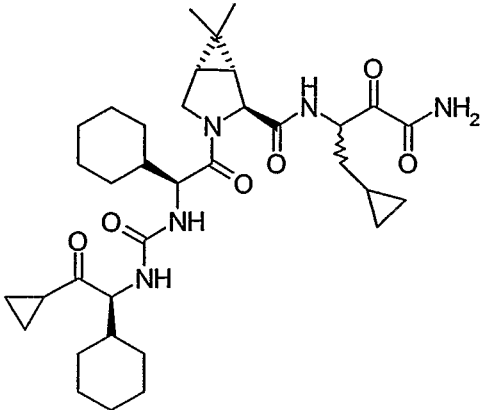
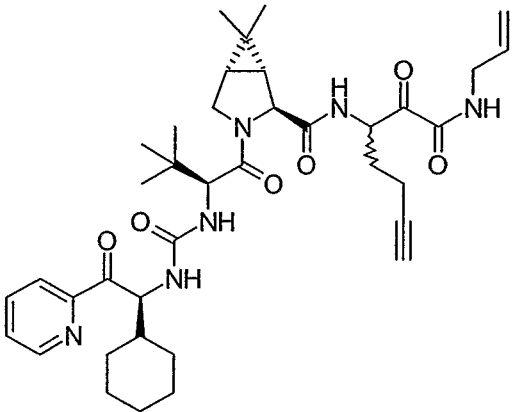
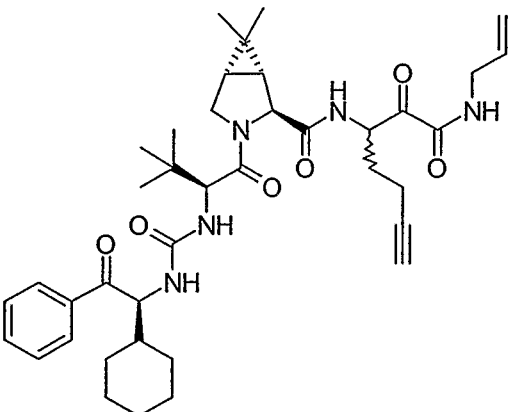
176

Cmpd #	Table 1 : Ketones	MW	Ki* Range
4034		695	A
4035		650	A
4036		650	A

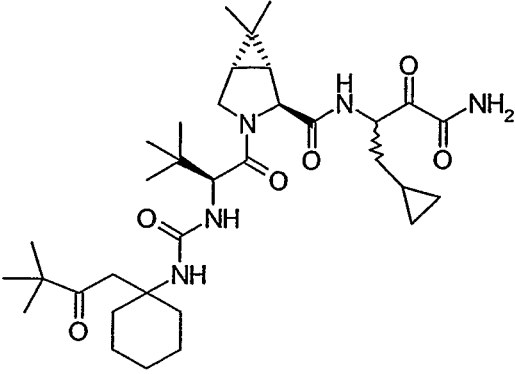
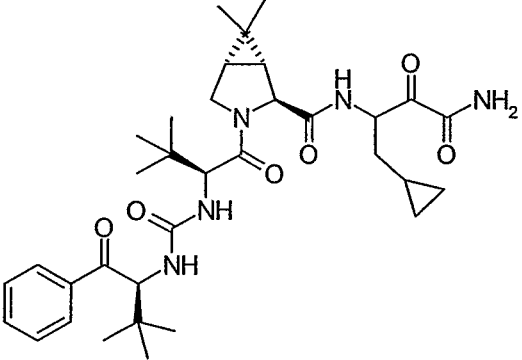
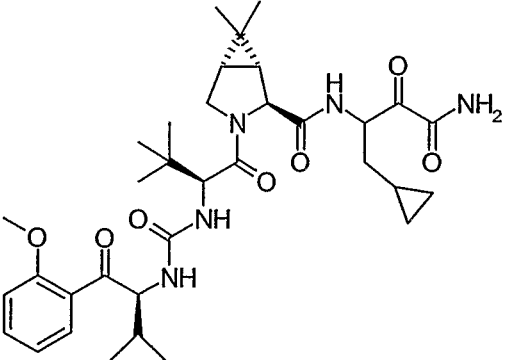
177

Cmpd #	Table 1 : Ketones	MW	Ki* Range
4037		588	A
4038		626	A
4039		642	A

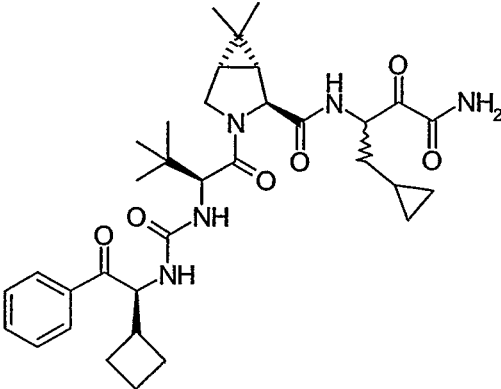
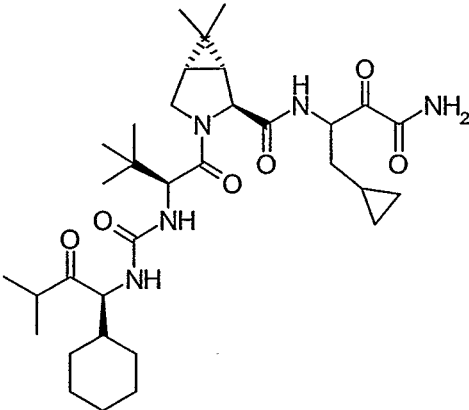
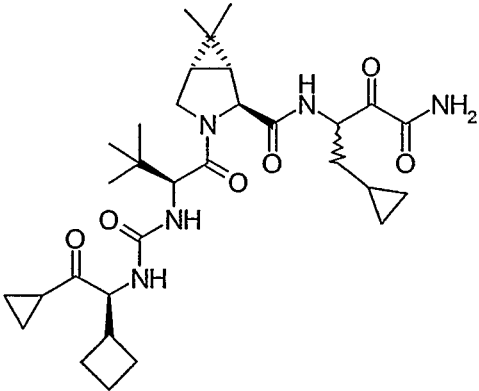
178

Cmpd #	Table 1 : Ketones	MW	Ki* Range
4040	 Chemical structure of compound 4040: A complex molecule featuring a central pyrrolidine ring substituted with a tert-butyl group and a carbonyl group. This central ring is linked via amide bonds to various side chains, including a cyclohexylmethyl group, a cyclopropylmethyl group, and a cyclohexylmethyl group attached to a carbonyl. The molecule also contains a cyclopropylmethyl ketone and a cyclohexylmethyl ketone.	640	A
4041	 Chemical structure of compound 4041: A complex molecule featuring a central pyrrolidine ring substituted with a tert-butyl group and a carbonyl group. This central ring is linked via amide bonds to various side chains, including a cyclohexylmethyl group, a cyclopropylmethyl group, and a cyclohexylmethyl group attached to a carbonyl. The molecule also contains a cyclopropylmethyl ketone and a cyclohexylmethyl ketone.	689	A
4042	 Chemical structure of compound 4042: A complex molecule featuring a central pyrrolidine ring substituted with a tert-butyl group and a carbonyl group. This central ring is linked via amide bonds to various side chains, including a cyclohexylmethyl group, a cyclopropylmethyl group, and a cyclohexylmethyl group attached to a carbonyl. The molecule also contains a cyclopropylmethyl ketone and a cyclohexylmethyl ketone.	688	A

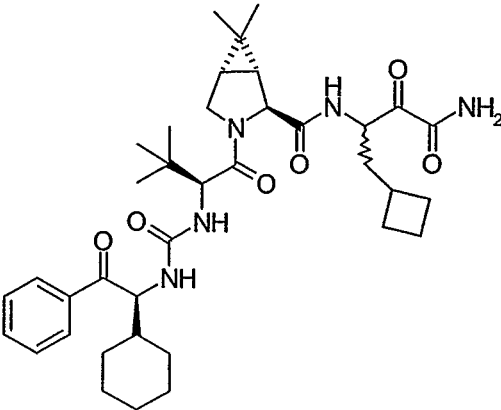
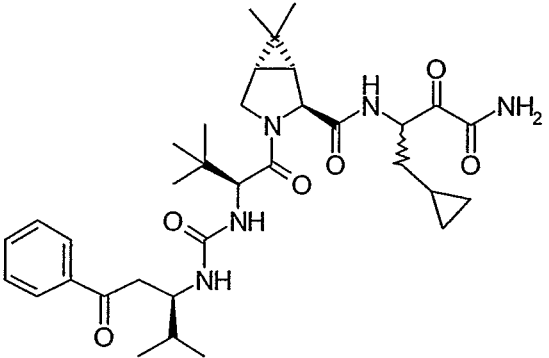
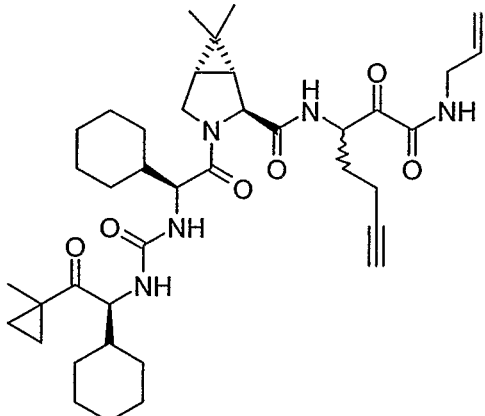
179

Cmpd #	Table 1 : Ketones	MW	Ki* Range
4043		630	A
4044		624	A
4045		640	A

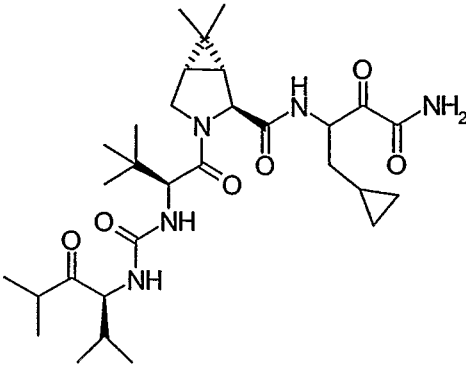
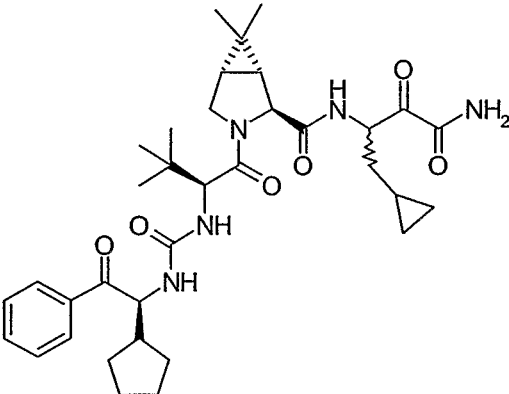
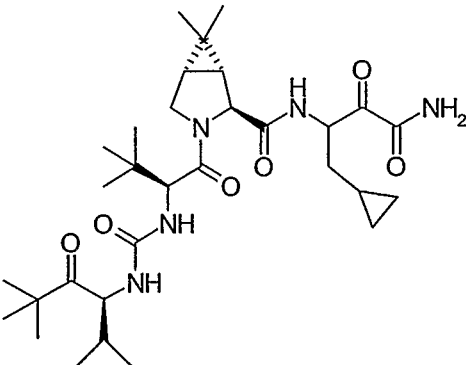
180

Cmpd #	Table 1 : Ketones	MW	Ki* Range
4046		622	A
4047		616	A
4048		586	A

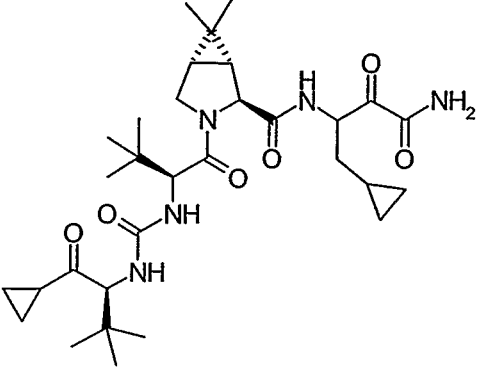
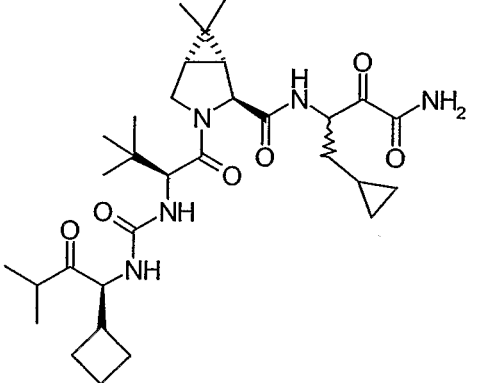
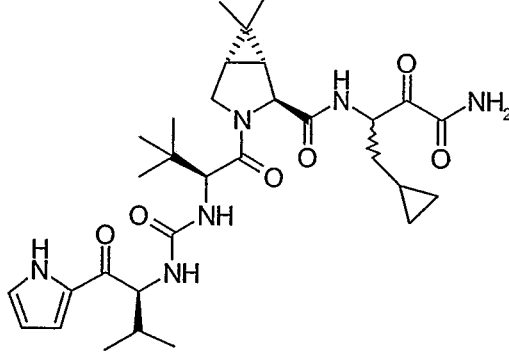
181

Cmpd #	Table 1 : Ketones	MW	Ki* Range
4051		664	A
4052		624	A
4053		692	A

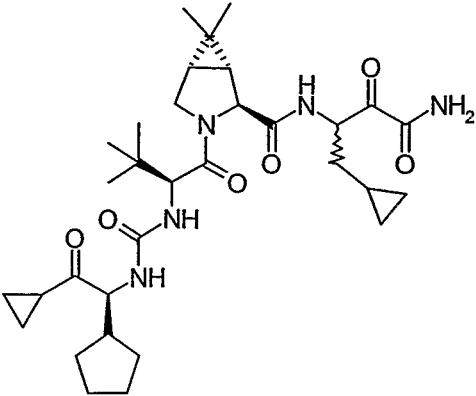
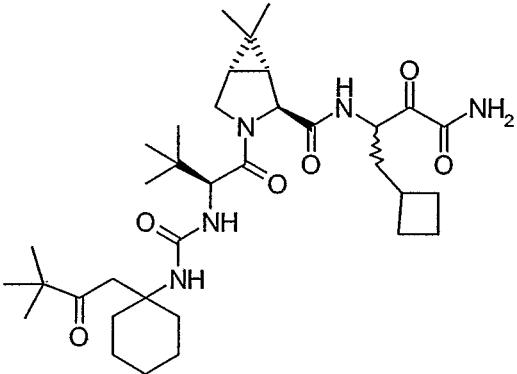
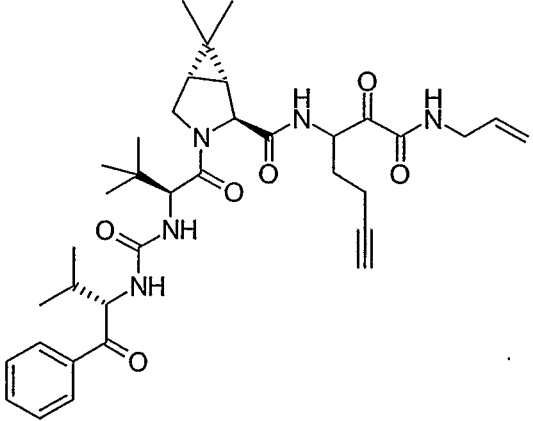
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Cmpd #	Table 1 : Ketones	MW	Ki* Range
4054		576	A
4055		636	A
4056		590	A

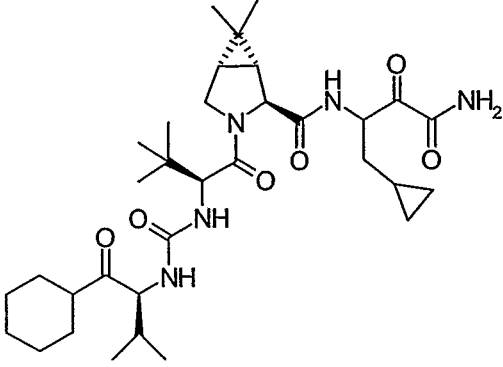
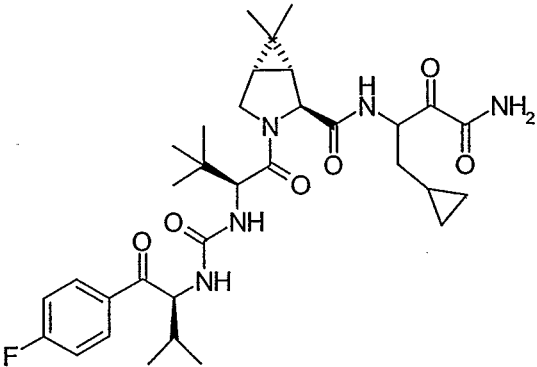
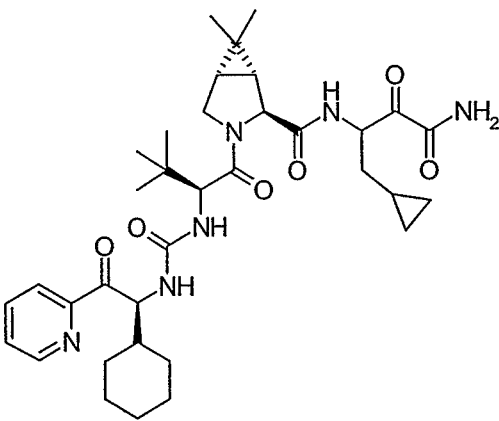
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Cmpd #	Table 1 : Ketones	MW	Ki* Range
4057		588	A
4058		588	A
4059		599	A

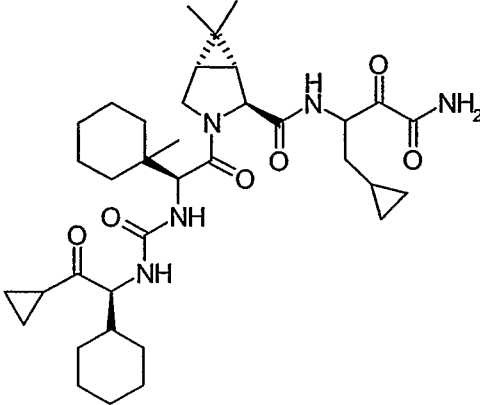
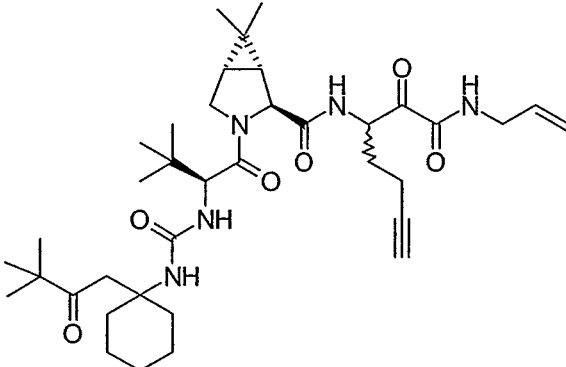
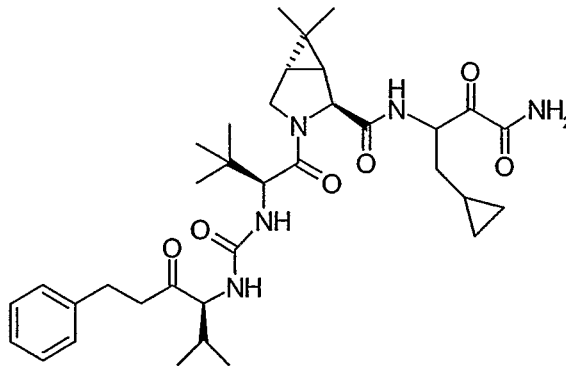
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Cmpd #	Table 1 : Ketones	MW	Ki* Range
4060		600	A
4061		644	A
4062		648	A

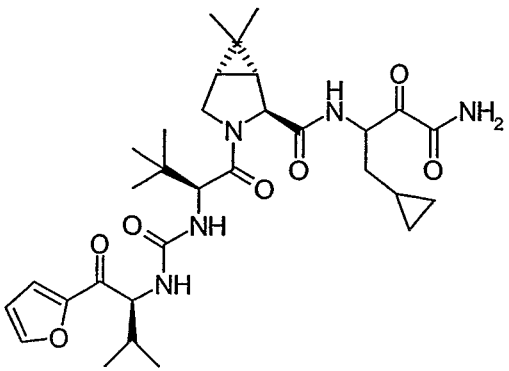
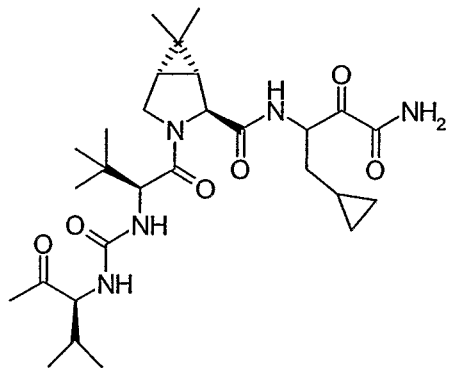
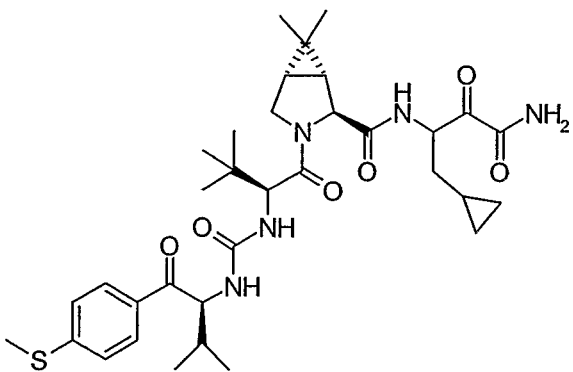
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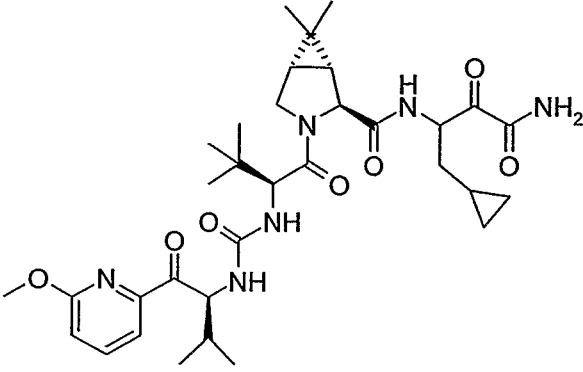
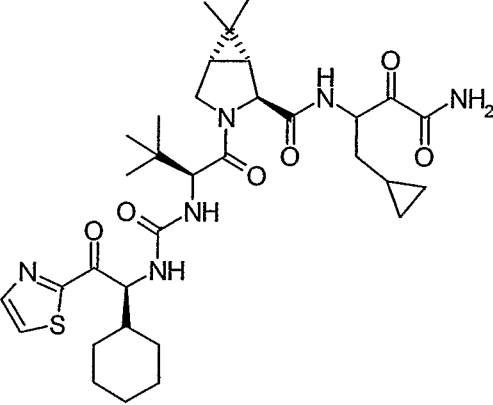
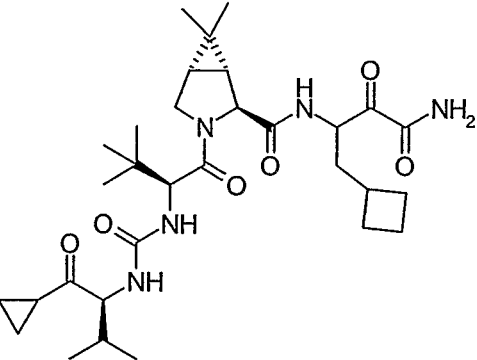
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4063		616	A
4064		628	A
4065		651	A

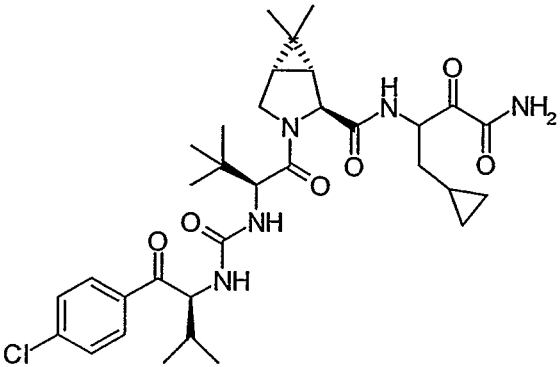
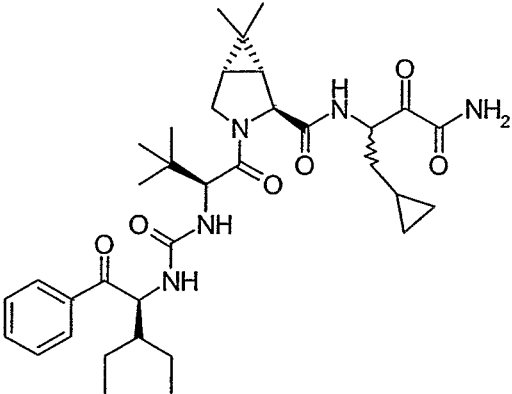
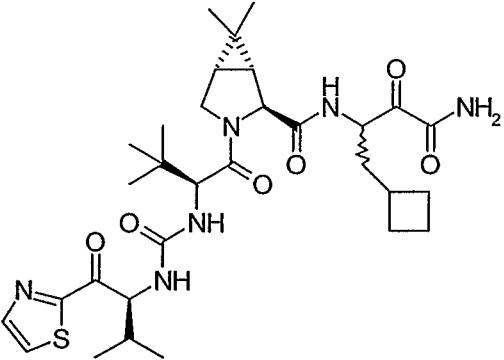
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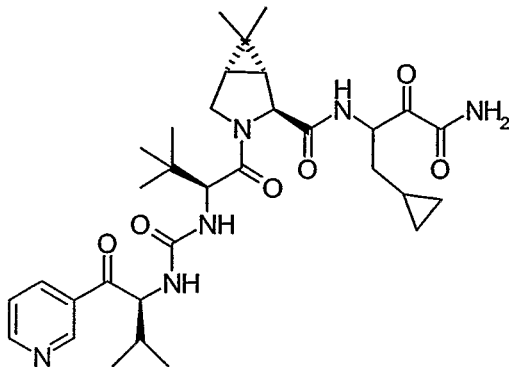
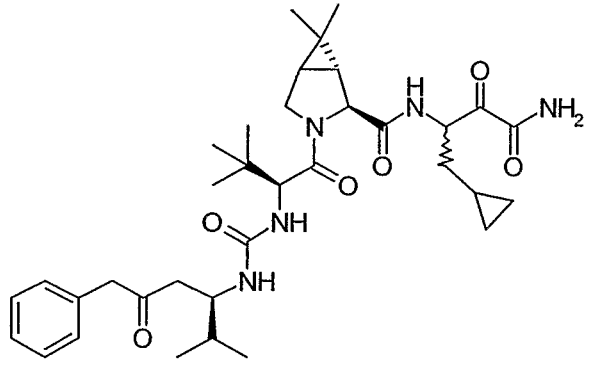
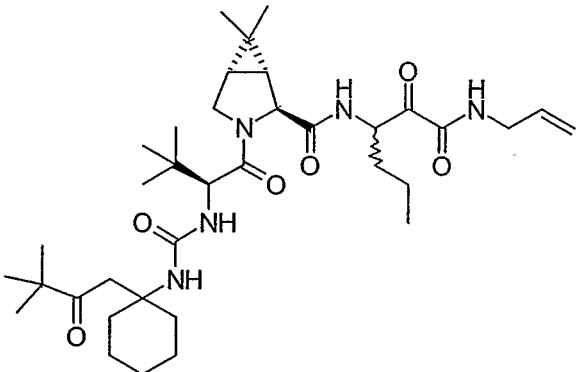
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4066		654	A
4067		668	A
4068		638	A

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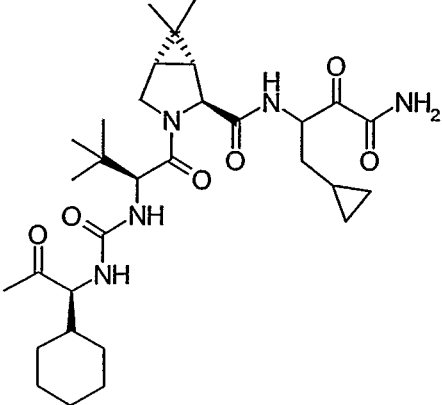
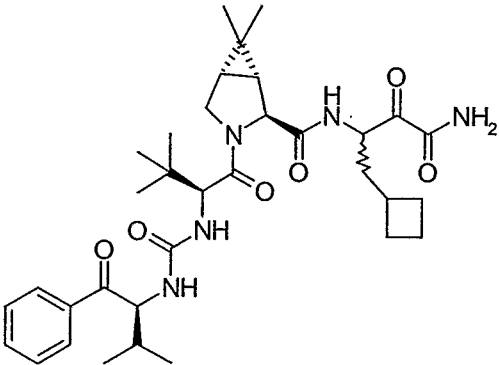
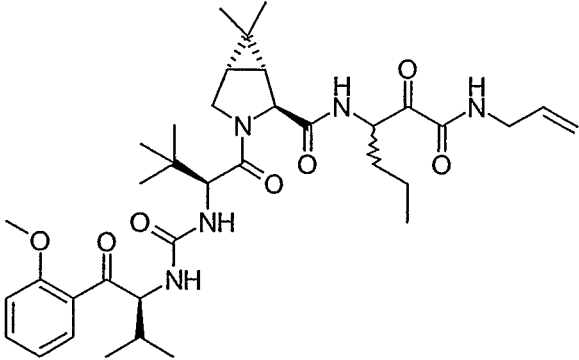
Cmpd #	Table 1 : Ketones	MW	Ki* Range
4069		600	A
4070		548	A
4071		656	A

Cmpd #	Table 1 : Ketones	MW	Ki* Range
4072	 Chemical structure of compound 4072: A complex molecule featuring a central pyrrolidine ring substituted with a tert-butyl group and a dimethylamino group. It is linked via amide bonds to a cyclopropylmethyl group, a 4-aminobutyl group, and a 2-methoxy-5-pyridylmethyl group.	641	A
4073	 Chemical structure of compound 4073: Similar to 4072, but the 2-methoxy-5-pyridylmethyl group is replaced by a 2-thiazolylmethyl group attached to a cyclohexyl ring.	657	A
4074	 Chemical structure of compound 4074: Similar to 4072, but the 2-methoxy-5-pyridylmethyl group is replaced by a cyclopropylmethyl group.	588	A

Cmpd #	Table 1 : Ketones	MW	Ki* Range
4075		644	A
4076		638	A
4077		631	A

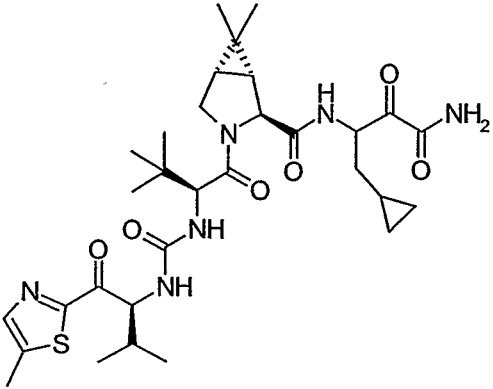
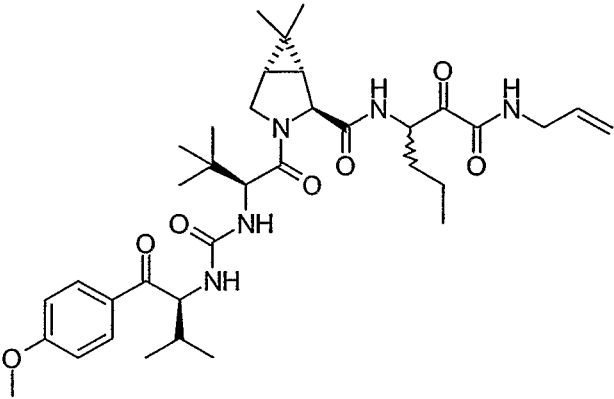
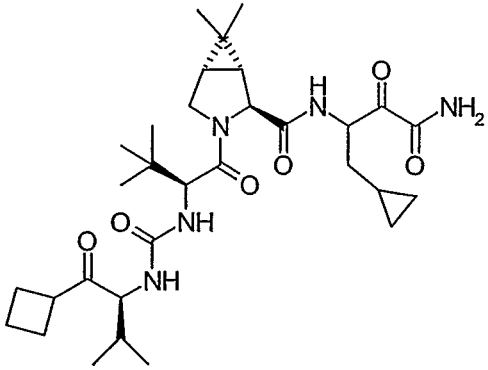
Cmpd #	Table 1 : Ketones	MW	Ki* Range
4078		611	A
4079		638	A
4080		658	A

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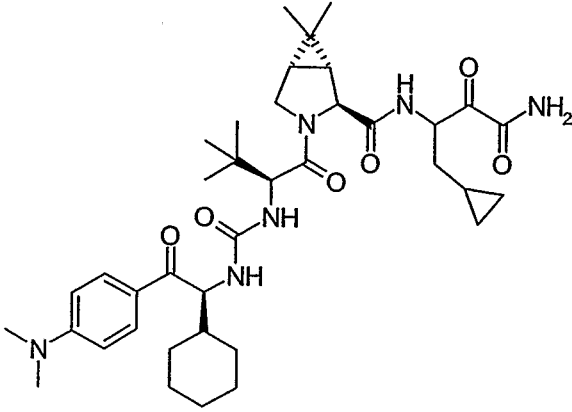
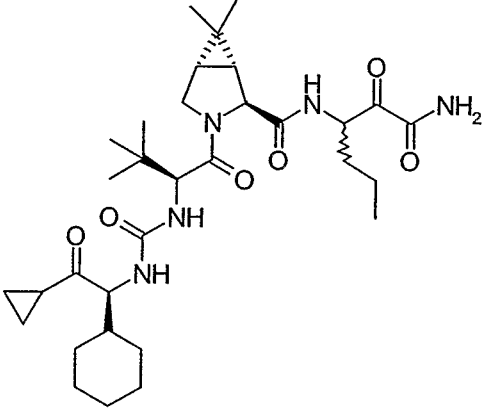
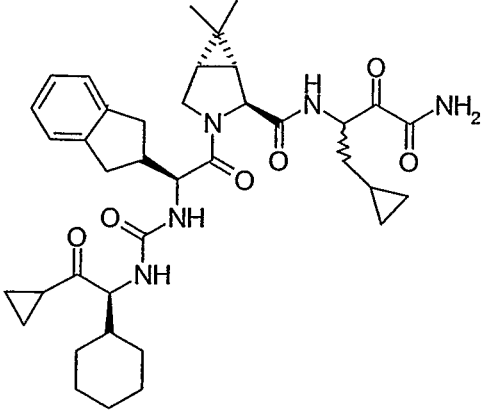
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4081		588	A
4082		624	A
4083		668	A

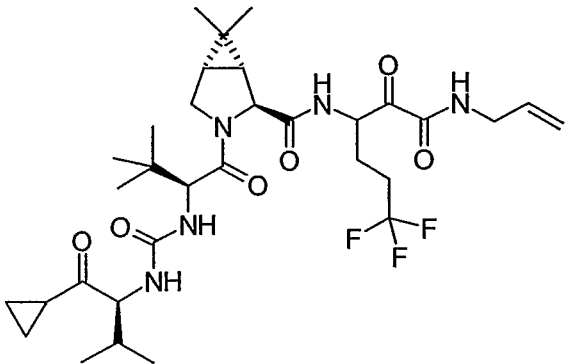
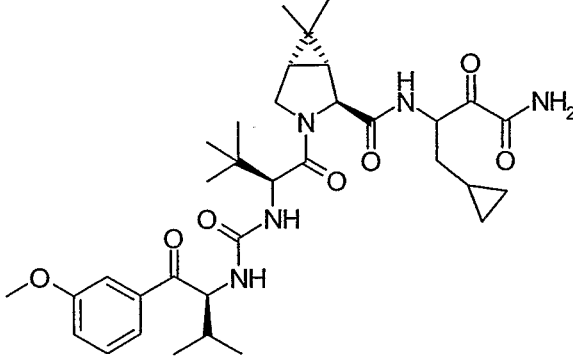
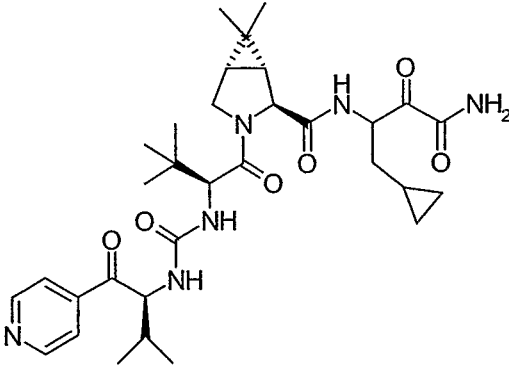
Cmpd #	Table 1 : Ketones	MW	Ki* Range
4084		634	A
4085		630	A
4086		682	A

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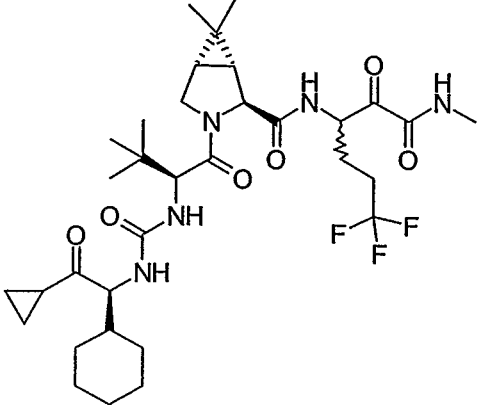
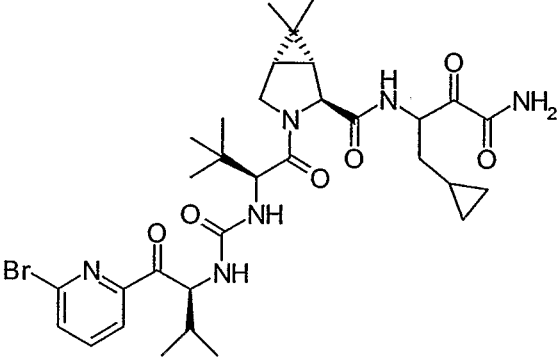
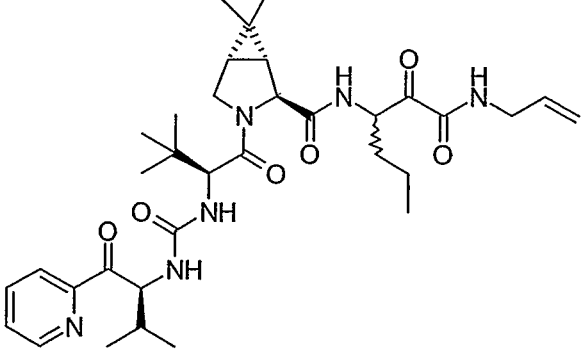
Cmpd #	Table 1 : Ketones	MW	Ki* Range
4087		631	A
4088		668	A
4089		588	A

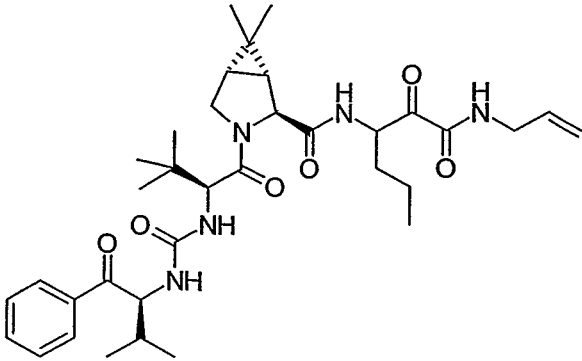
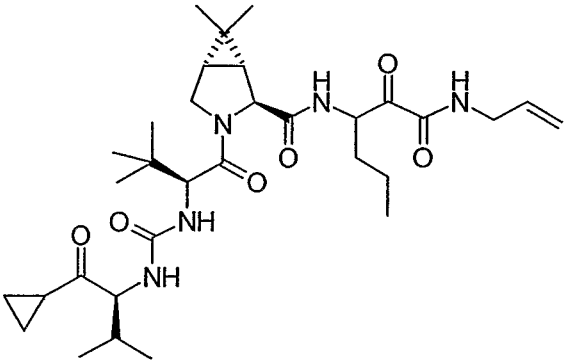
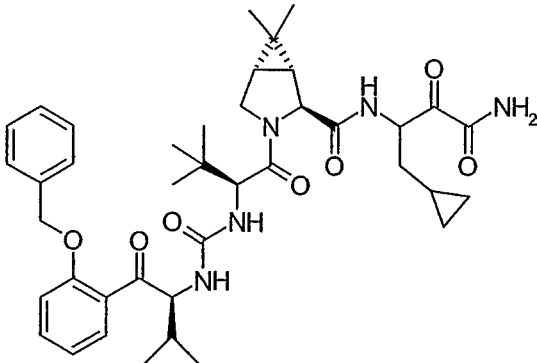
194

Cmpd #	Table 1 : Ketones	MW	Ki* Range
4090	 Chemical structure of compound 4090: A complex molecule featuring a central pyrrolidine ring substituted with a tert-butyl group and a dimethylamino group. It is linked via amide bonds to a cyclohexyl ring (which is further substituted with a cyclopropyl ketone and a dimethylaminophenyl ketone) and a 2-amino-3-cyclopropylpropanoate moiety.	693	A
4091	 Chemical structure of compound 4091: Similar to 4090, but the dimethylaminophenyl ketone is replaced by a cyclopropyl ketone, and the cyclopropyl group on the propanoate chain is replaced by an ethyl group.	602	A
4092	 Chemical structure of compound 4092: Similar to 4090, but the dimethylaminophenyl ketone is replaced by an indan-1-yl ketone, and the cyclopropyl group on the propanoate chain is replaced by an ethyl group.	674	A

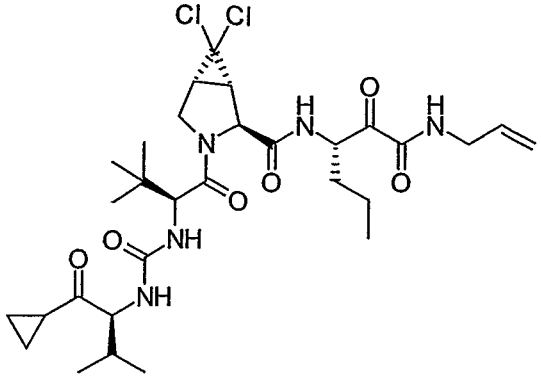
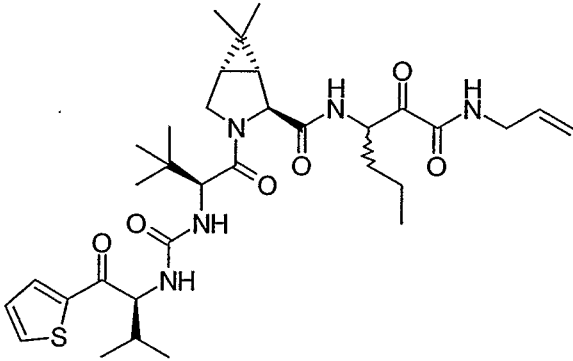
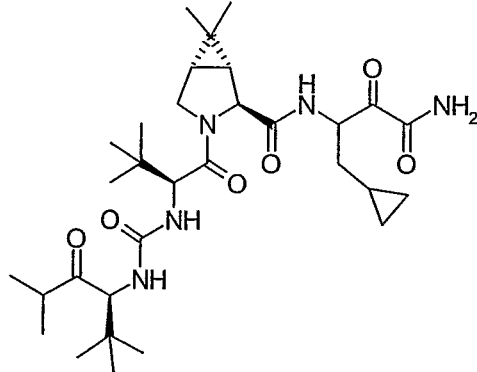
Cmpd #	Table 1 : Ketones	MW	Ki* Range
4093		656	A
4094		640	A
4095		611	A

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Cmpd #	Table 1 : Ketones	MW	Ki* Range
4099	 Chemical structure of compound 4099: A complex molecule featuring a central pyrrolidine ring substituted with a tert-butyl group and a carbonyl group. This pyrrolidine is linked via an amide bond to a side chain containing a 2,2,2-trifluoroethyl group and a methylamino group. Another amide branch connects the side chain to a cyclohexylmethyl group, which is further substituted with a cyclopropylmethyl ketone.	670	A
4100	 Chemical structure of compound 4100: Similar to 4099, but the side chain amide is linked to a cyclopropylmethyl ketone instead of a trifluoroethyl group. The other amide branch remains linked to a cyclohexylmethyl ketone substituted with a cyclopropylmethyl group.	690	A
4101	 Chemical structure of compound 4101: Similar to 4100, but the side chain amide is linked to a 2-propenyl (allyl) group instead of a cyclopropylmethyl ketone. The other amide branch remains linked to a cyclohexylmethyl ketone substituted with a cyclopropylmethyl group.	639	A

Cmpd #	Table 1 : Ketones	MW	Ki* Range
4102		638	A
4103		602	A
4104		716	A

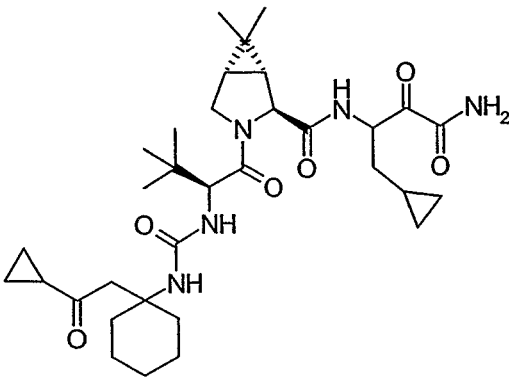
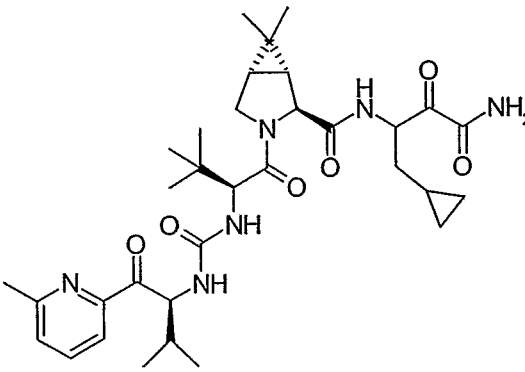
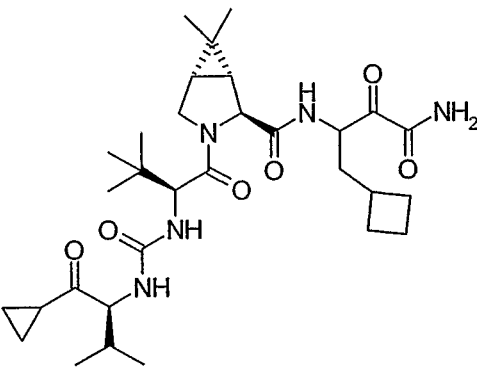
199

Cmpd #	Table 1 : Ketones	MW	Ki* Range
4105		643	A
4106		644	A
4108		590	A

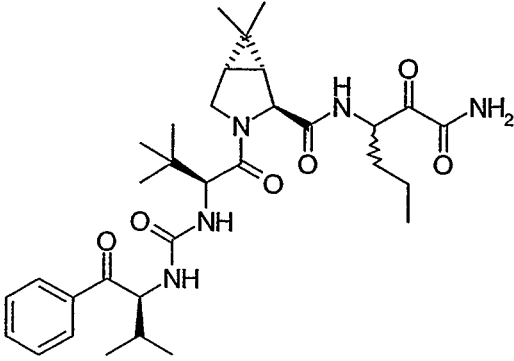
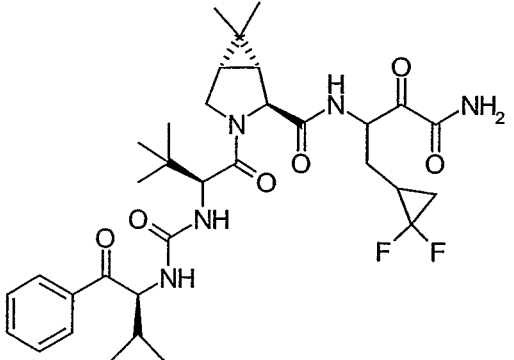
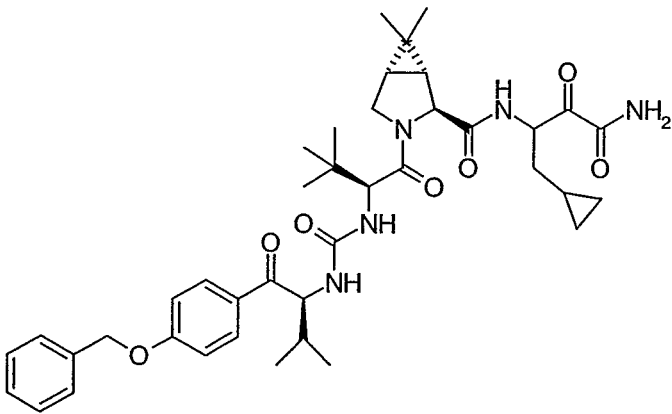
200

Cmpd #	Table 1 : Ketones	MW	Ki* Range
4109		652	A
4110		650	A
4111		654	A

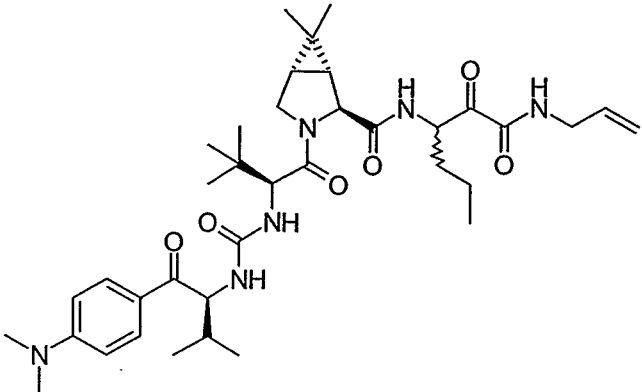
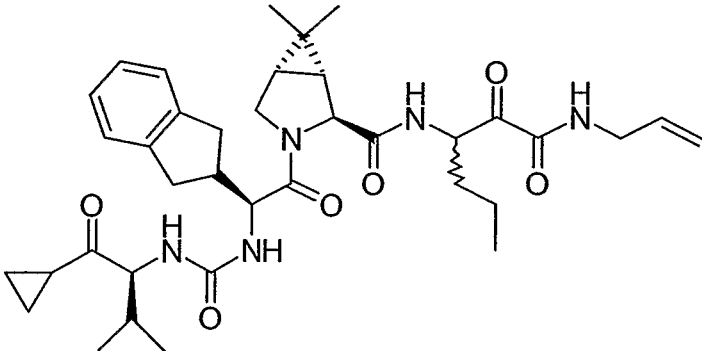
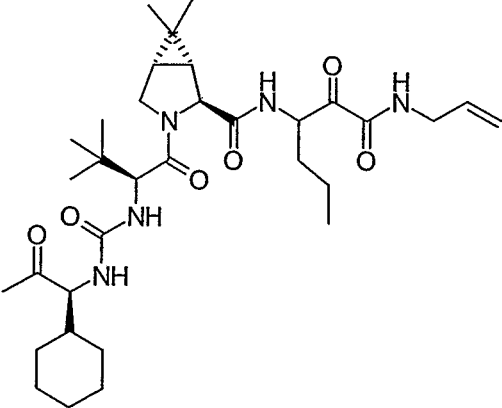
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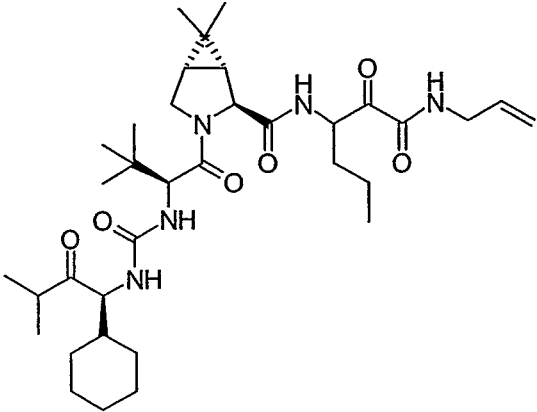
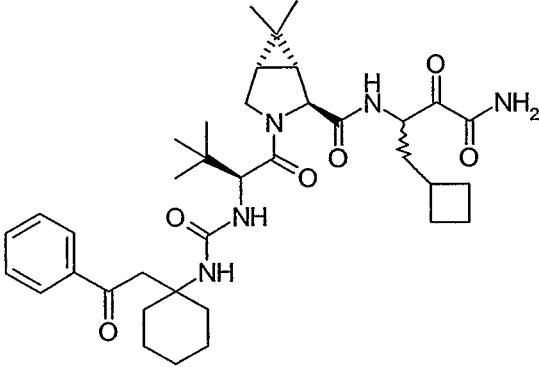
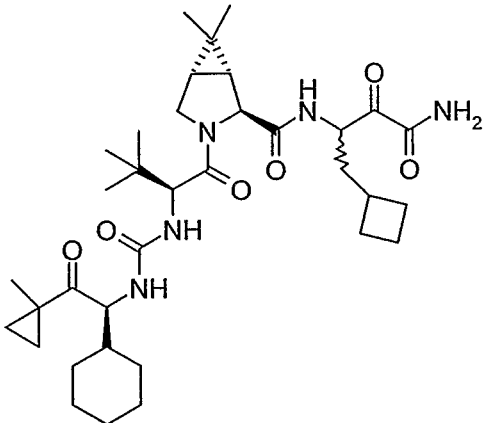
Cmpd #	Table 1 : Ketones	MW	Ki* Range
4112		614	A
4113		625	A
4114		588	A

Cmpd #	Table 1 : Ketones	MW	Ki* Range
4115		670	A
4117		645	A
4118		604	A

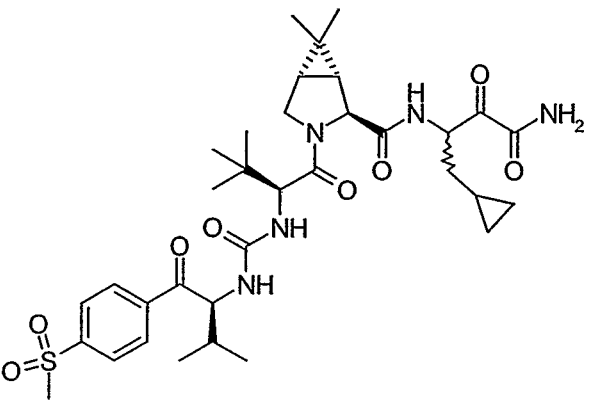
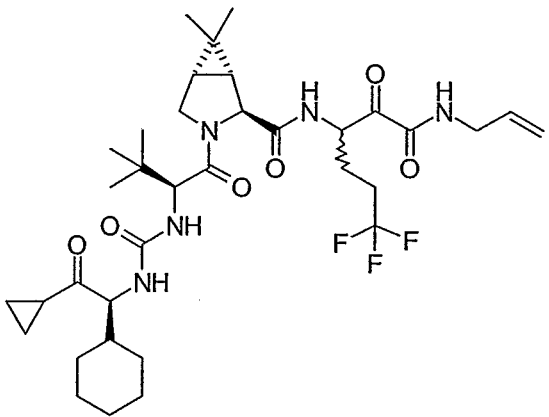
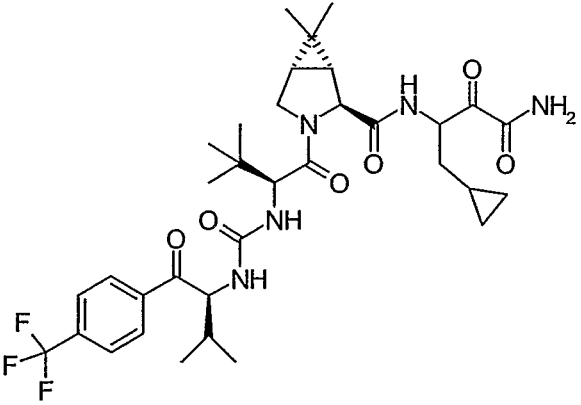
Cmpd #	Table 1 : Ketones	MW	Ki* Range
4119		598	A
4120		646	A
4121		716	A

204

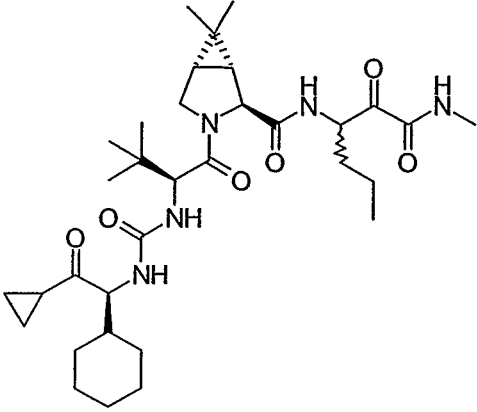
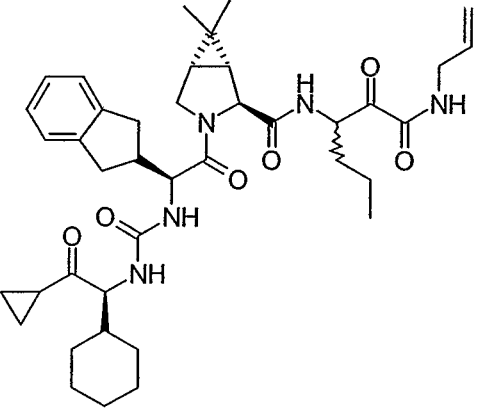
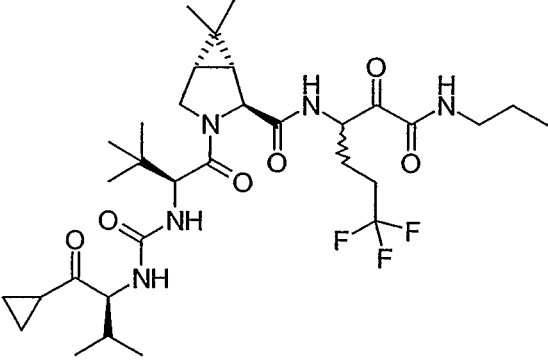
Cmpd #	Table 1 : Ketones	MW	Ki* Range
4122	 Chemical structure of compound 4122: A complex molecule featuring a central pyrrolidine ring substituted with a tert-butyl group and a carbonyl group. This pyrrolidine is linked via an amide bond to a side chain containing a chiral center, a ketone, and a terminal allyl group. Another amide branch connects the pyrrolidine to a chiral center which is further substituted with a benzyl group and a dimethylaminophenyl ketone.	681	A
4123	 Chemical structure of compound 4123: Similar to 4122, but the benzyl group is replaced by a 1-phenyl-2-cyclopropyl-1-ethyl group, and the dimethylaminophenyl ketone is replaced by a cyclopropyl ketone.	662	A
4124	 Chemical structure of compound 4124: Similar to 4122, but the benzyl group is replaced by a cyclohexyl ketone, and the dimethylaminophenyl ketone is replaced by a cyclohexyl ketone.	616	A

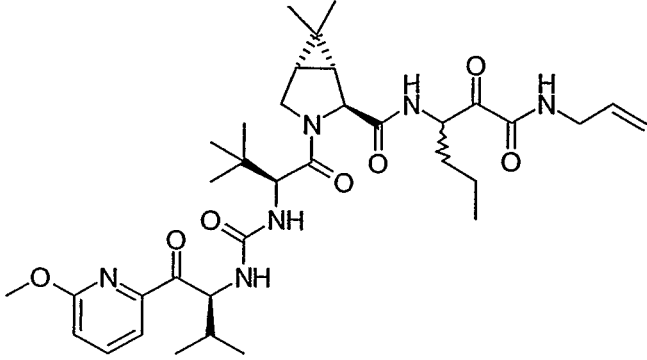
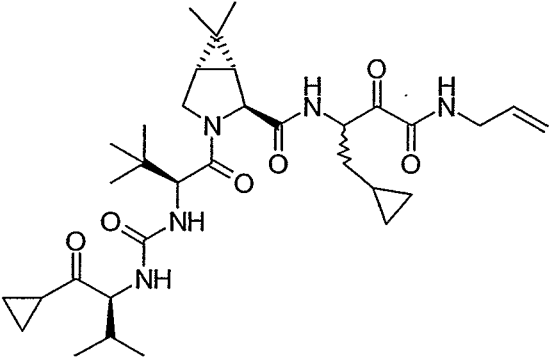
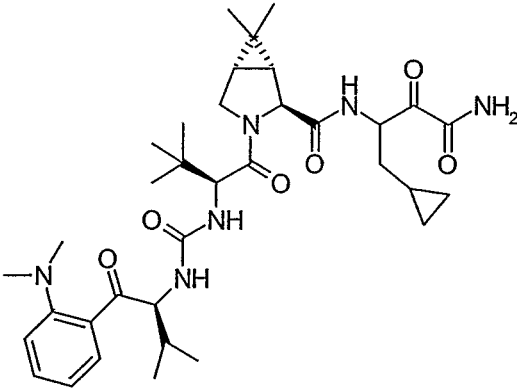
Cmpd #	Table 1 : Ketones	MW	Ki* Range
4125		644	A
4126		664	A
4127		642	A

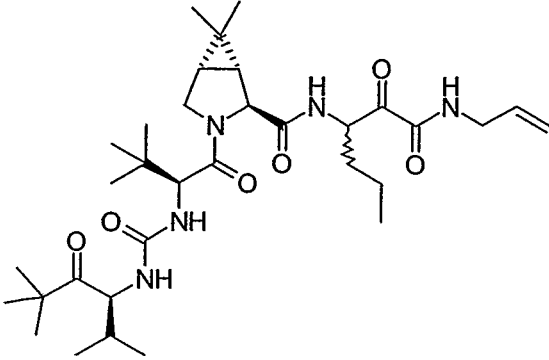
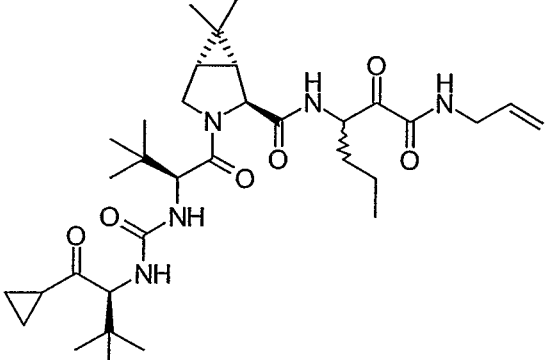
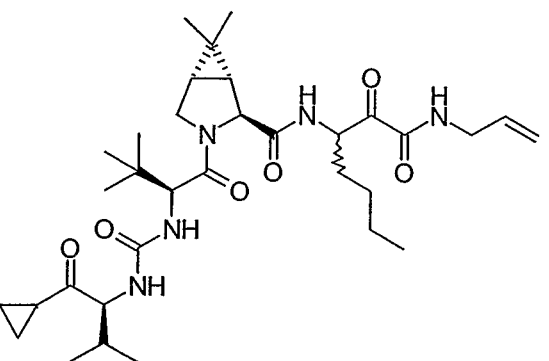
206

Cmpd #	Table 1 : Ketones	MW	Ki* Range
4128		688	A
4129		696	A
4130		678	A

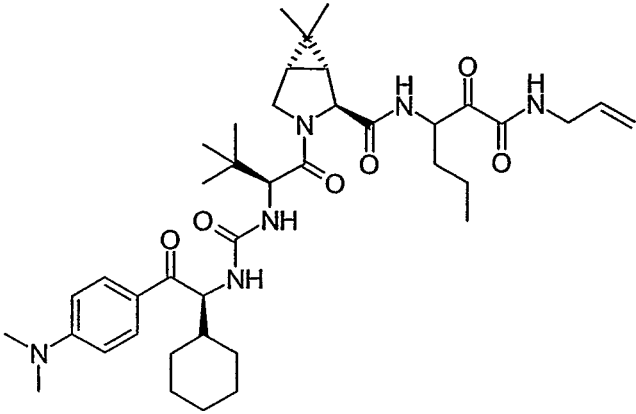
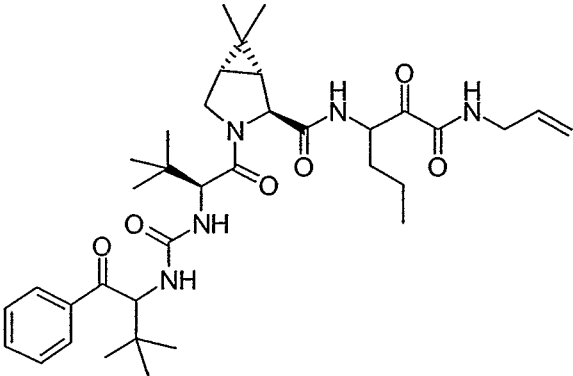
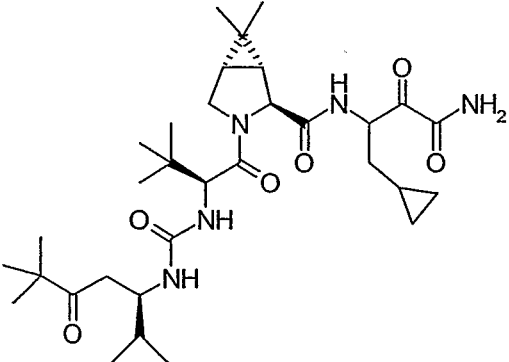
207

Cmpd #	Table 1 : Ketones	MW	Ki* Range
4131		616	A
4132		702	A
4133		658	A

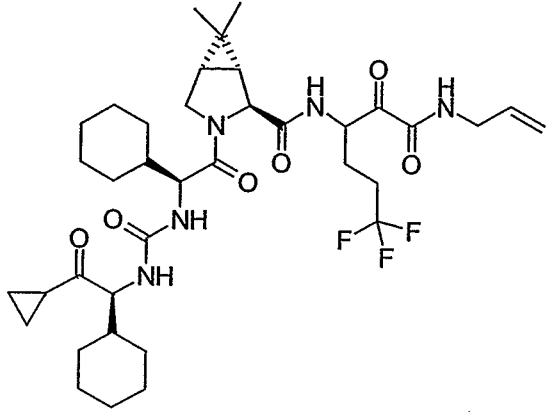
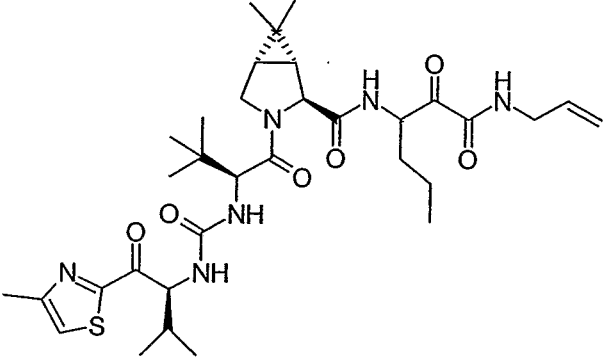
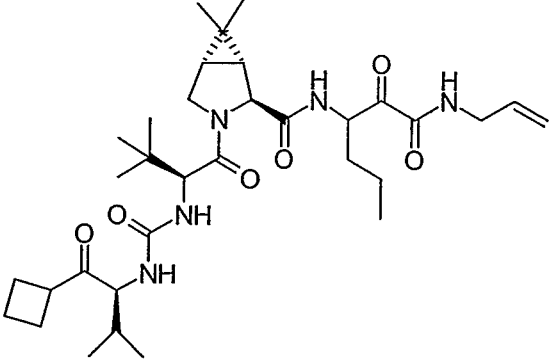
Cmpd #	Table 1 : Ketones	MW	Ki* Range
4134	 <chem>CCOC1=CC=C(C=C1)C(=O)C(C)C(=O)NC(=O)C(C)(C)C(=O)N[C@@H]2C[C@H](C(C)(C)C)C[C@H]2C(=O)NC(=O)C(CC)C(=O)NC(=O)CC=C</chem>	669	A
4135	 <chem>CC1(C)C(=O)NC(=O)C(C)C(=O)N[C@@H]2C[C@H](C(C)(C)C)C[C@H]2C(=O)NC(=O)C(C1)C(=O)NC(=O)CC=C</chem>	614	A
4136	 <chem>CC1(C)C(=O)NC(=O)C(C)C(=O)N[C@@H]2C[C@H](C(C)(C)C)C[C@H]2C(=O)NC(=O)C(C1)C(=O)NC(=O)N</chem>	653	A

Cmpd #	Table 1 : Ketones	MW	Ki* Range
4137		618	A
4138		616	A
4139		656	A

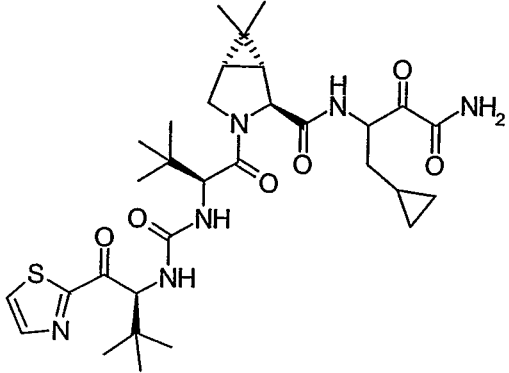
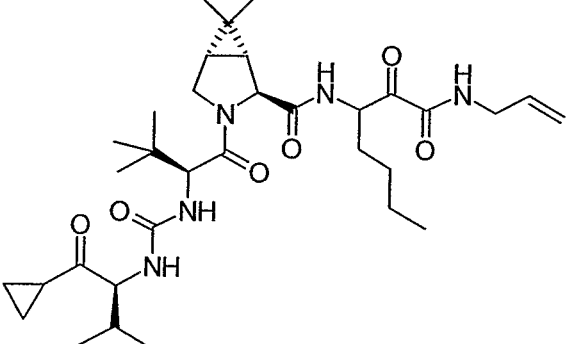
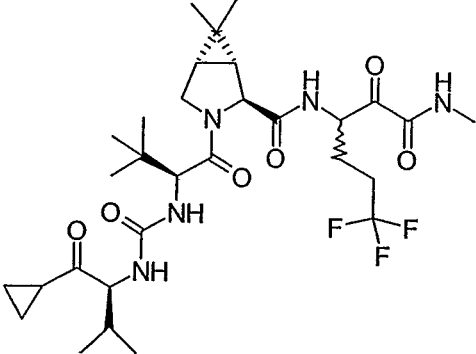
210

Cmpd #	Table 1 : Ketones	MW	Ki* Range
4140		721	A
4141		652	A
4143		604	A

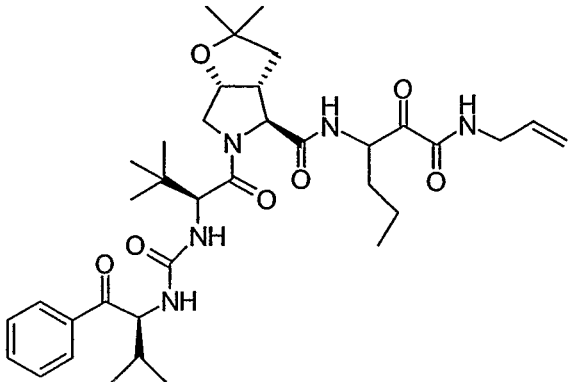
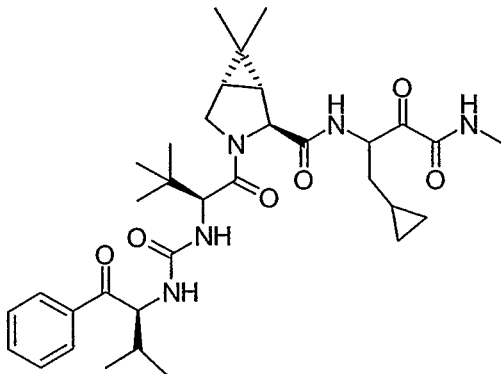
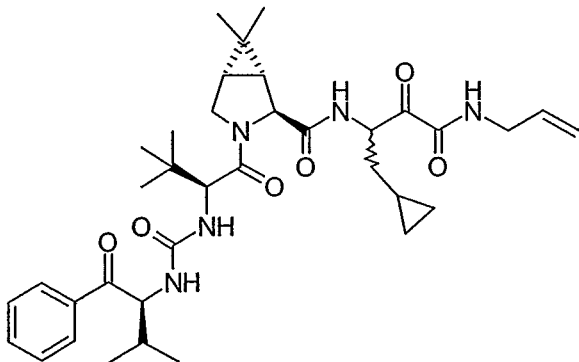
211

Cmpd #	Table 1 : Ketones	MW	Ki* Range
4144		722	A
4145		659	A
4146		616	A

212

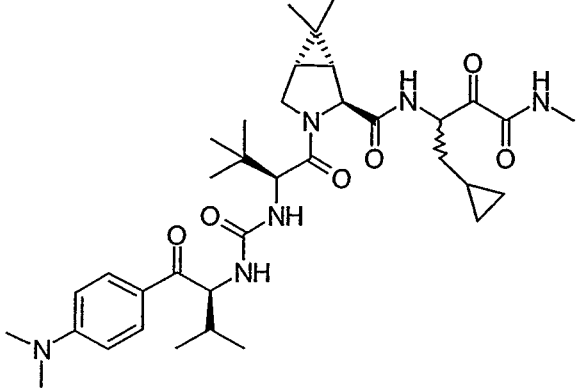
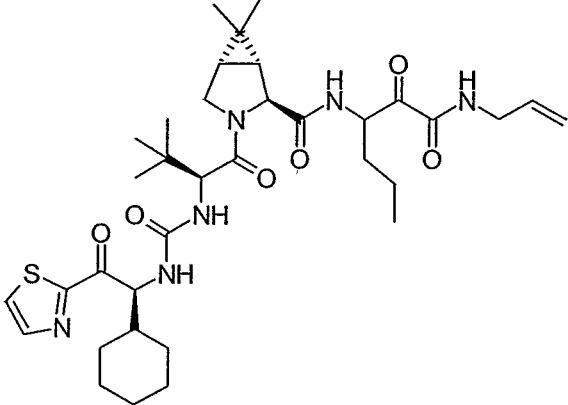
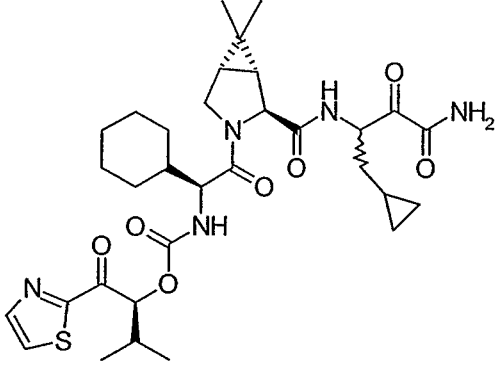
Cmpd #	Table 1 : Ketones	MW	Ki* Range
4148		631	A
4149		616	A
4150		630	A

213

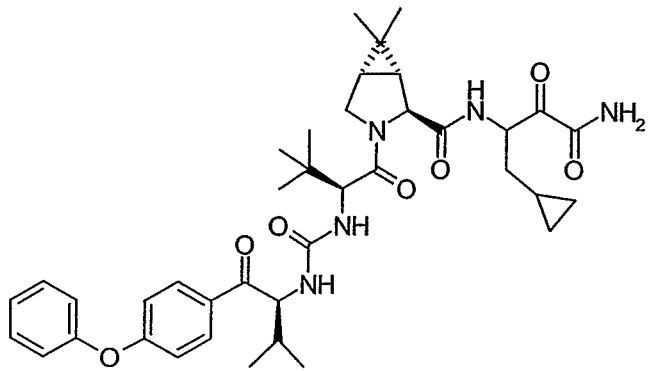
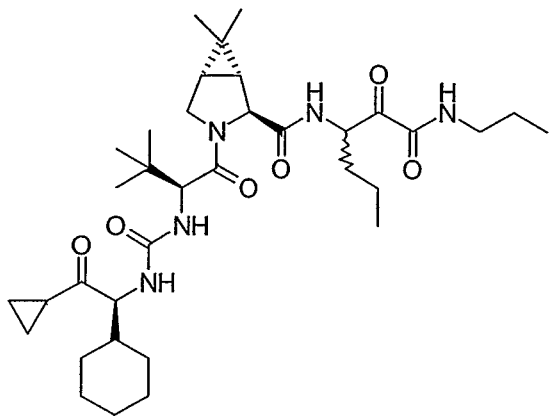
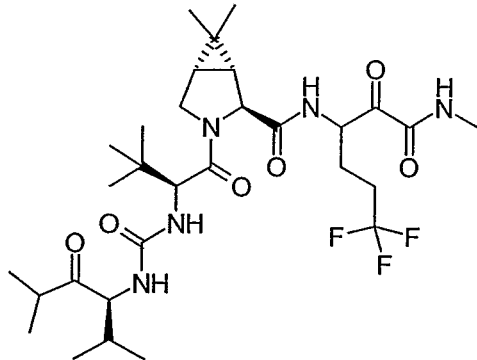
Cmpd #	Table 1 : Ketones	MW	Ki* Range
4151		668	A
4152		624	A
4153		650	A

[illegible]

215

Cmpd #	Table 1 : Ketones	MW	Ki* Range
4157		667	A
4158		685	A
4159		644	A

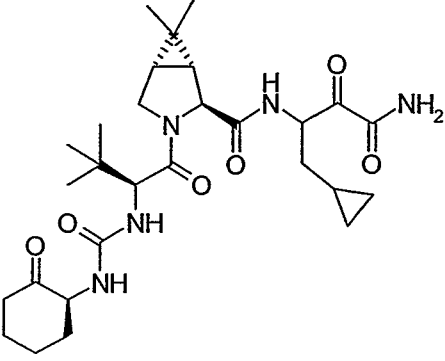
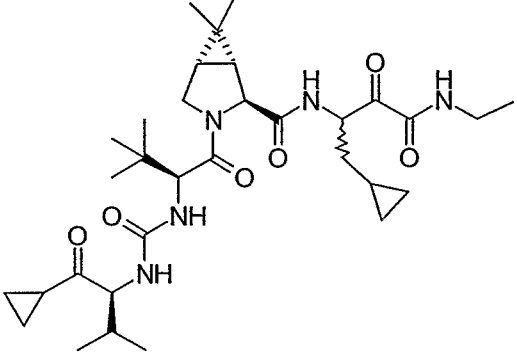
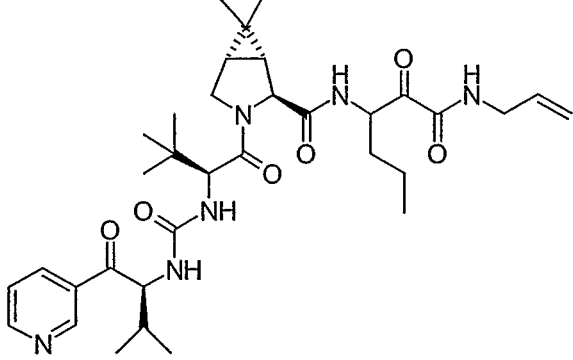
216

Cmpd #	Table 1 : Ketones	MW	Ki* Range
4160		702	A
4161		644	A
4162		632	A

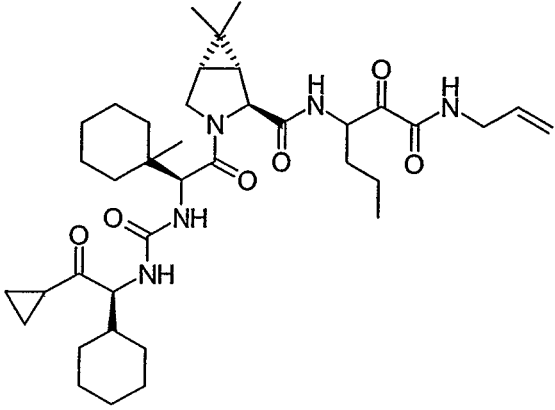
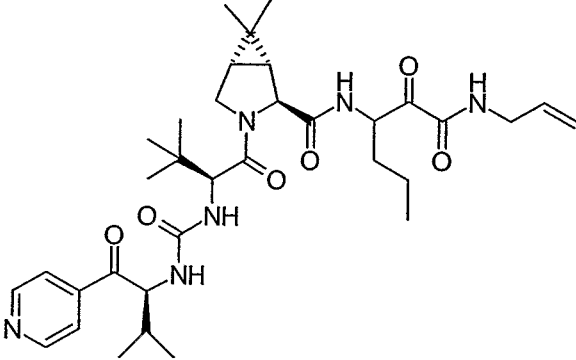
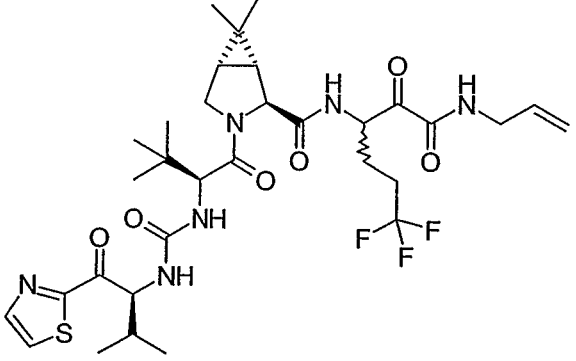
217

Cmpd #	Table 1 : Ketones	MW	Ki* Range
4163		637	A
4164		660	A
4165		662	A

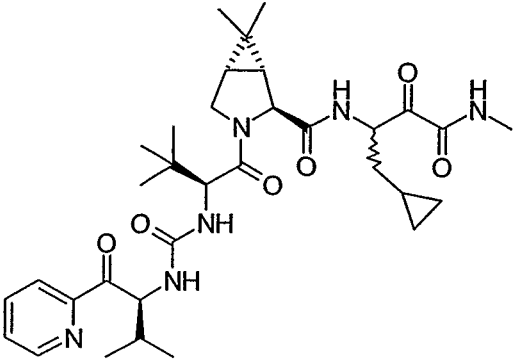
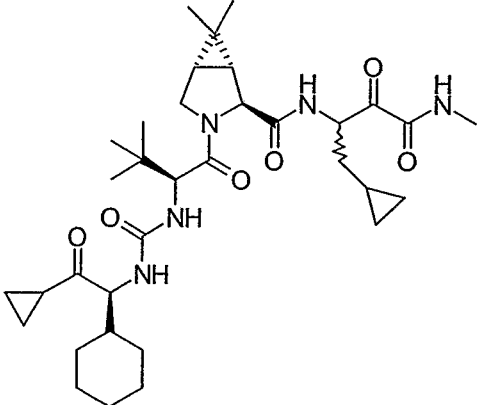
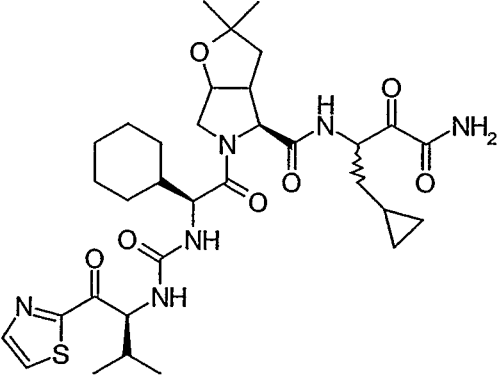
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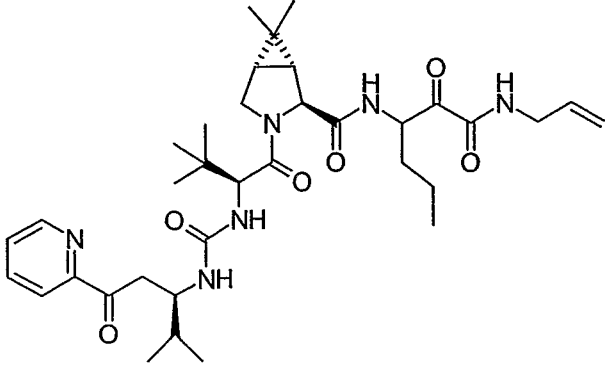
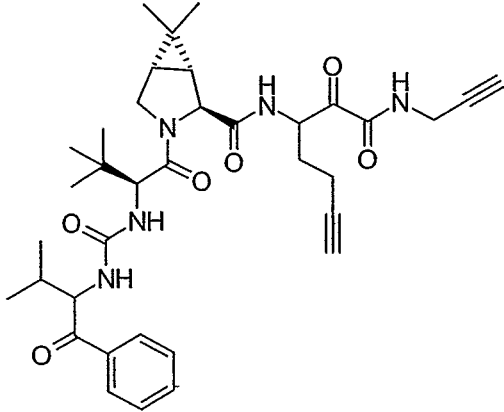
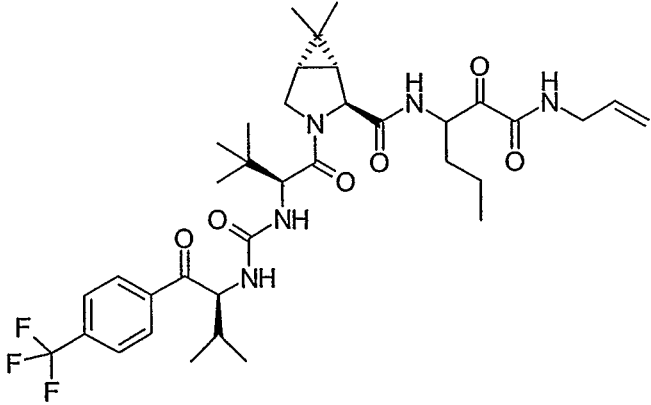
Cmpd #	Table 1 : Ketones	MW	Ki* Range
4166		546	A
4167		602	A
4168		639	A

219

Cmpd #	Table 1 : Ketones	MW	Ki* Range
4169		682	A
4170		639	A
4171		699	A

220

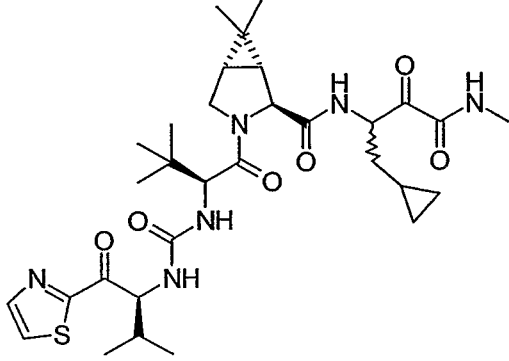
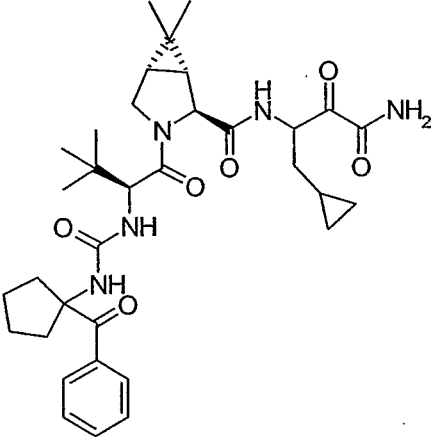
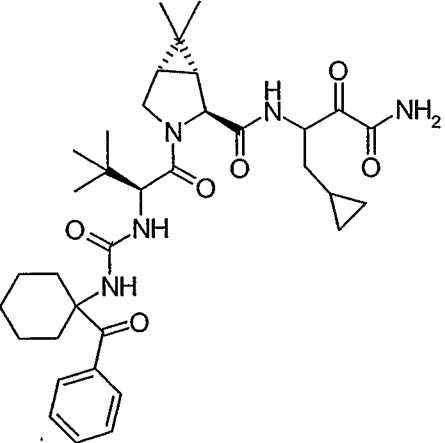
Cmpd #	Table 1 : Ketones	MW	Ki* Range
4172	 Chemical structure of compound 4172: A complex molecule featuring a pyridine ring connected to a carbonyl group, which is linked to a chiral center. This chiral center is further connected to a chain containing a pyrrolidine ring, a carbonyl group, and a cyclopropylmethyl group. The molecule also includes a secondary amide and a tertiary amide.	625	A
4173	 Chemical structure of compound 4173: A complex molecule featuring a cyclohexane ring connected to a carbonyl group, which is linked to a chiral center. This chiral center is further connected to a chain containing a pyrrolidine ring, a carbonyl group, and a cyclopropylmethyl group. The molecule also includes a secondary amide and a tertiary amide.	628	B
4174	 Chemical structure of compound 4174: A complex molecule featuring a thiophene ring connected to a carbonyl group, which is linked to a chiral center. This chiral center is further connected to a chain containing a pyrrolidine ring, a carbonyl group, and a cyclopropylmethyl group. The molecule also includes a secondary amide and a tertiary amide.	673	B

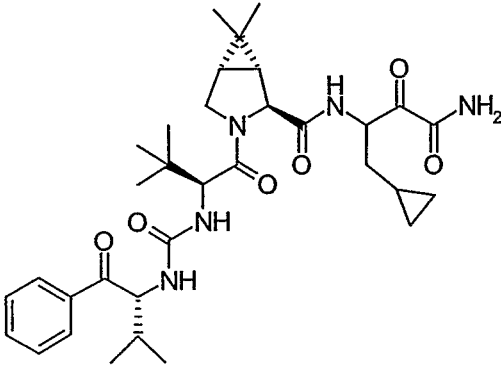
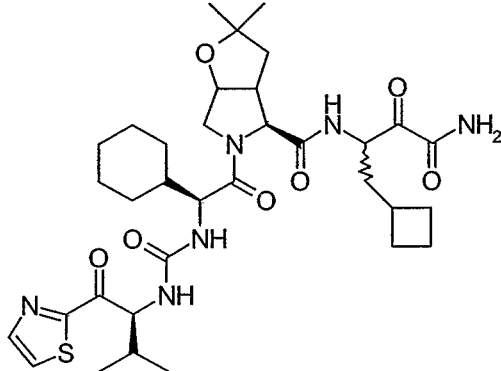
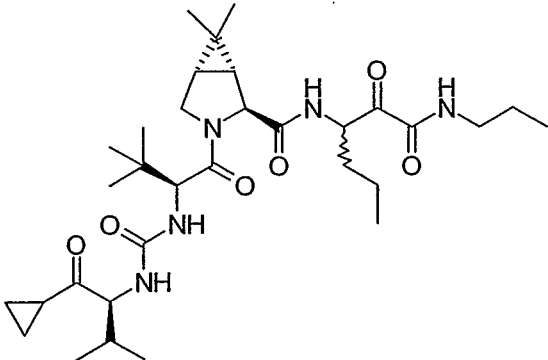
Cmpd #	Table 1 : Ketones	MW	Ki* Range
4175		653	B
4176		646	B
4177		706	B

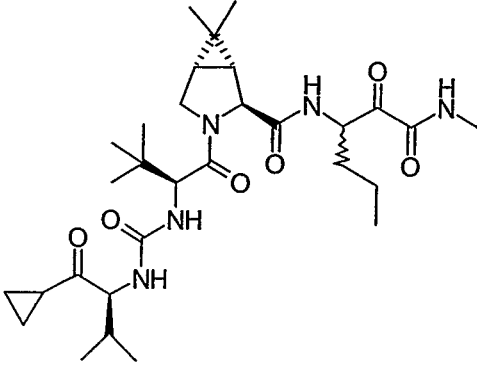
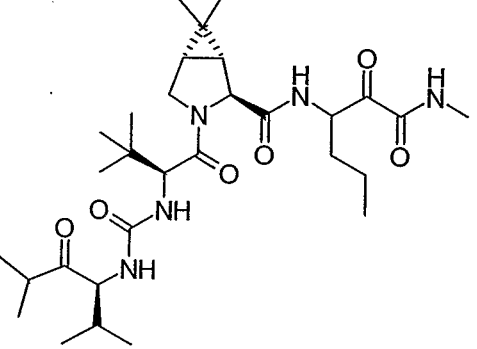
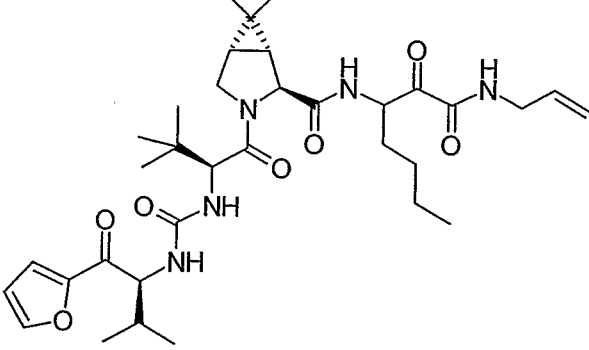
222

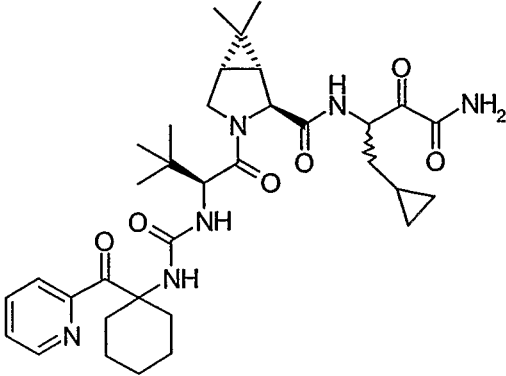
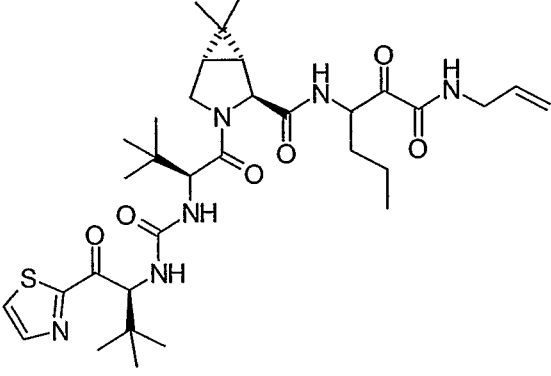
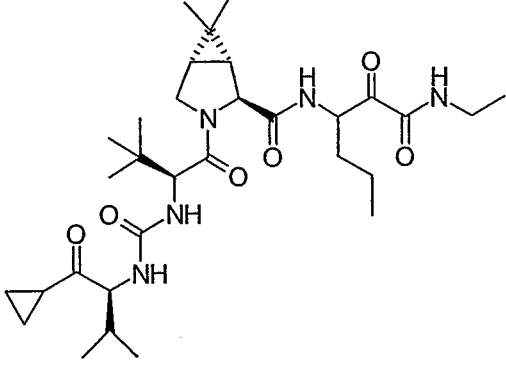
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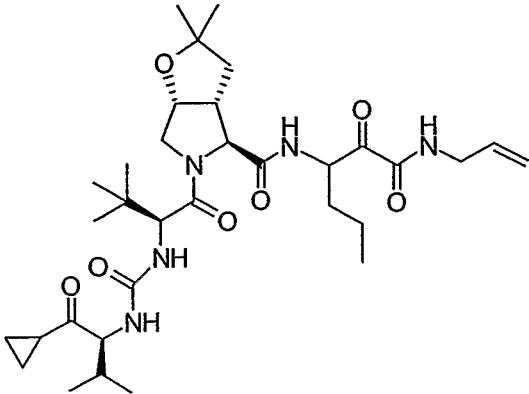
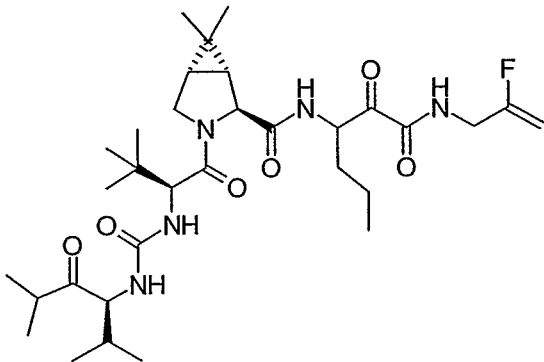
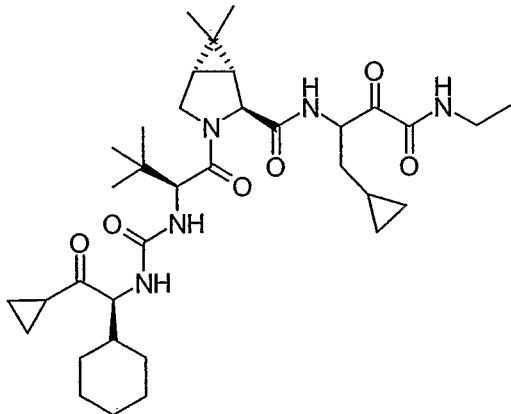
223

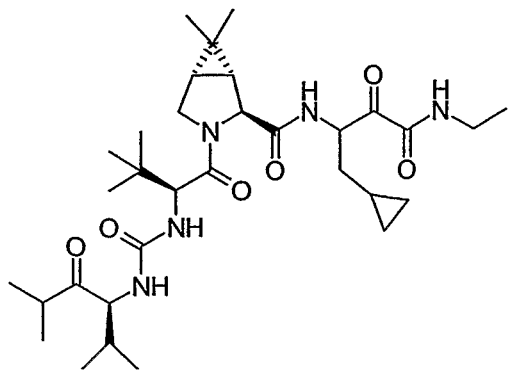
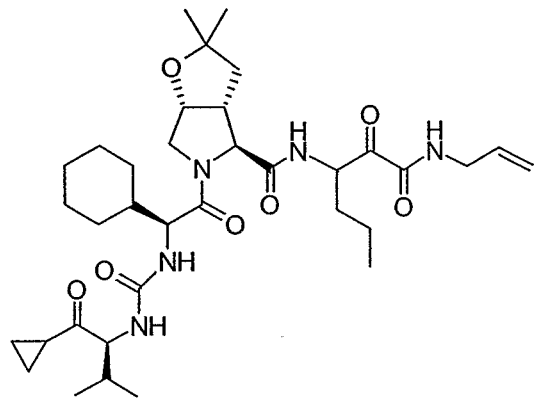
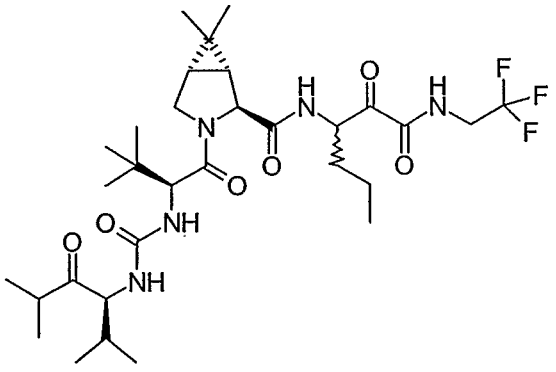
Cmpd #	Table 1 : Ketones	MW	Ki* Range
4181		631	B
4182		622	B
4183		636	B

Cmpd #	Table 1 : Ketones	MW	Ki* Range
4184		610	B
4185		687	B
4186		604	B

Cmpd #	Table 1 : Ketones	MW	Ki* Range
4187		576	B
4188		578	B
4189		642	B

Cmpd #	Table 1 : Ketones	MW	Ki* Range
4190		637	B
4191		659	B
4192		590	B

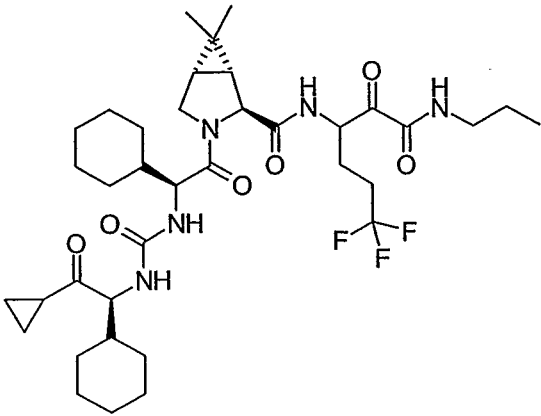
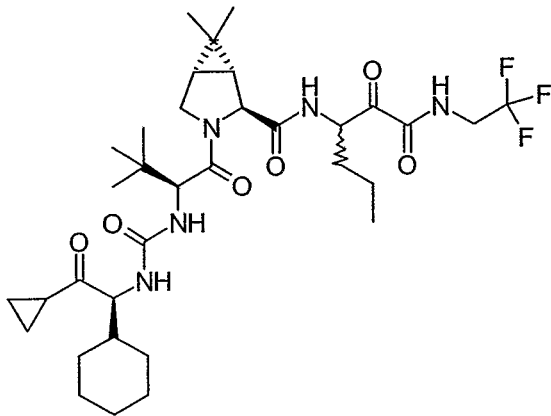
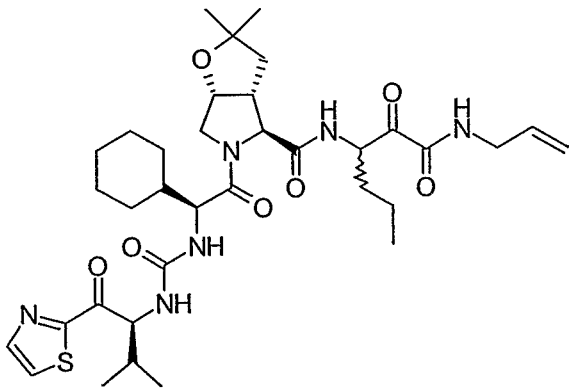
Cmpd #	Table 1 : Ketones	MW	Ki* Range
4193		632	B
4194		622	B
4195		642	B

Cmpd #	Table 1 : Ketones	MW	Ki* Range
4196		604	B
4197		658	B
4198		646	B

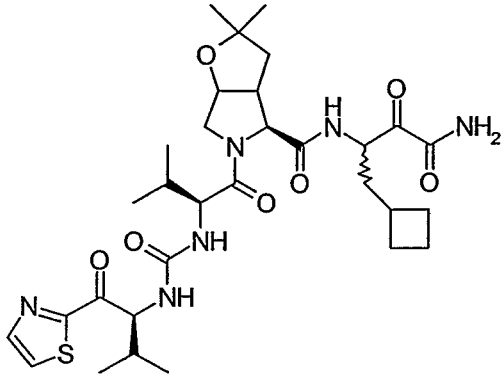
Cmpd #	Table 1 : Ketones	MW	Ki* Range
4199		657	B
4200		698	B
4201		662	B

Cmpd #	Table 1 : Ketones	MW	Ki* Range
4203		660	C
4204		620	C
4205		665	C

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Cmpd #	Table 1 : Ketones	MW	Ki* Range
4206		724	C
4207		684	C
4208		701	C

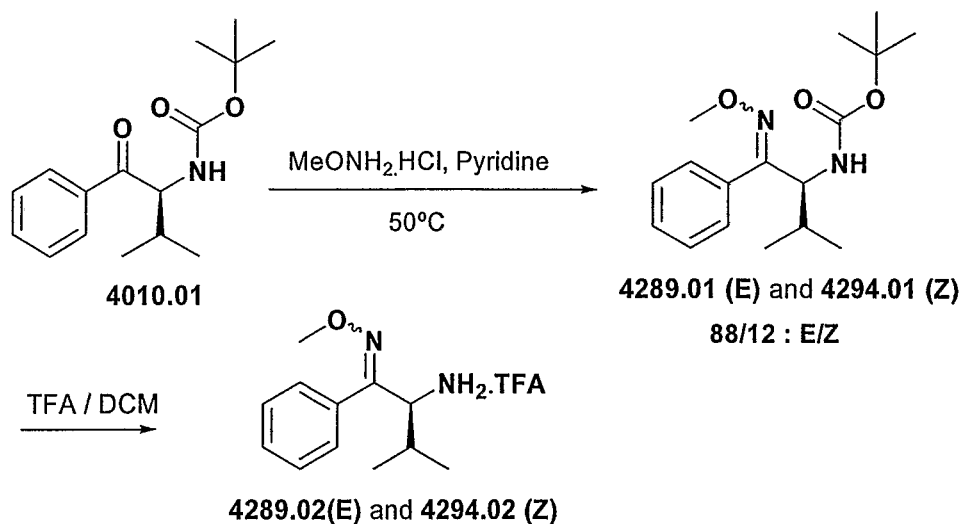
232

Cmpd #	Table 1 : Ketones	MW	Ki* Range
4209		647	C

PREPARATION OF SPECIFIC EXAMPLES from Table 2

Example XI: Preparation of Compound of Formula 4289 and 4294

5



Step1:

To a RT solution of Ketone **4010.01** prepared in **step 1** of preparative example III (2 mmol, 554 mg) in Pyridine (10 mL) was added O-methylhydroxylamine hydrochloride (2equiv, 4 mmol, 334 mg). The resulting mixture was heated to 50°C for 18 hr. After 18 h, TLC showed no starting material and a slightly less polar product and the reaction was concentrated under vacuo to remove pyridine. The resulting white slurry was dissolved in DCM and washed with HCl 1.0 N (10 mL). DCM layer was then

10

washed with aqueous CuSO₄sat and brine. Organic layer was dried over MgSO₄, filtered and concentrated under vacuo. The residue was purified by HPFC Biotage 25+ M. HPFC, 3%(EtOAc) to 12%(EtOAc) in Hexane, Purification provided 2 isomers **4289.01** and **4294.01** in a 80/20 E/Z ratio.

Step2

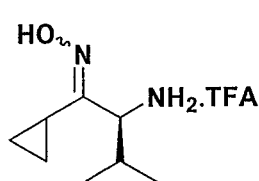
To **4294.01**(60 mg) in CH₂Cl₂ (3 mL) under N₂ was added TFA (1 mL) at RT. The reaction was stirred at RT for 20min and was concentrated to dryness and placed under high vacuum overnight. 40mg of product **4294.02** was obtained.

Identical procedure was applied to the other isomer **4289.01** to produce amine salt **4289.02**.

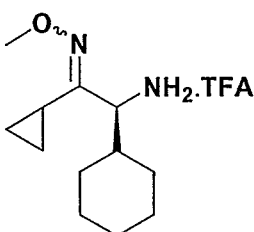
Step3:

HCV inhibitors **4294** and **4289** in **table 2** were prepared using amine salts **4294.02** and **4289.02** and corresponding isocyanates or 4-nitrophenyl carbamate following **method D** of General Schemes for Preparation of Target Compounds.

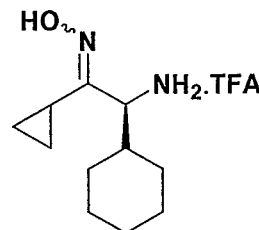
Example XII: Preparation of Compound of Formula 4291.02, 4297.02 and 4290.02



4291.02 (E and Z)



4297.02 (E and Z)



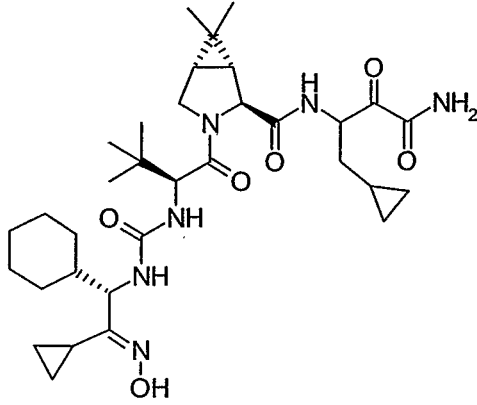
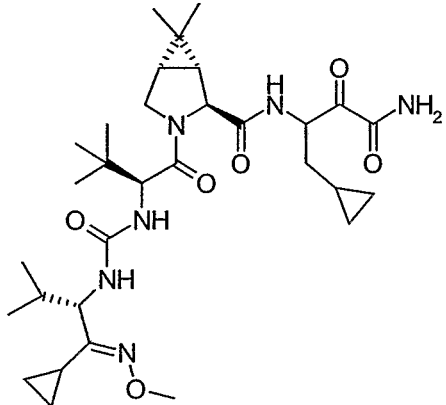
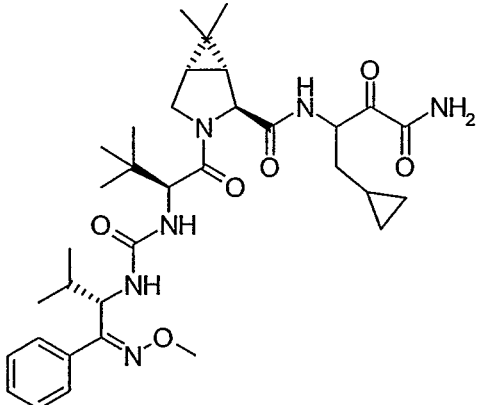
4290.02 (E and Z)

Amines salts of Formula **4291.02**, **4297.02** and **4290.02** were prepared according **step 1** and **2** of preparative example **XI** by replacing O-methylhydroxylamine hydrochloride by methylhydroxylamine hydrochloride and ketone **4010.01** by the corresponding (L) Cyclohexylglycine ketone **4019.03** of preparative example **VII** and the corresponding (L) Valine ketone.

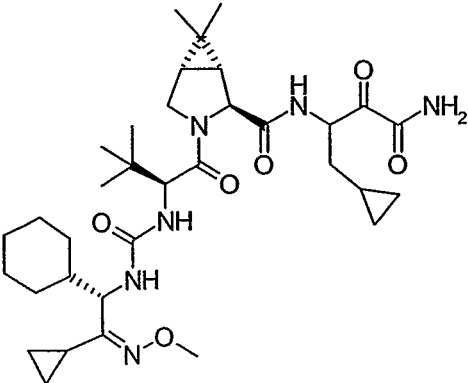
HCV inhibitors **4290**, **4291**, **4292**, **4293**, **4295**, **4297** and **4298** in **table 2** were prepared using amine salts **4291.02**, **4297.02** and **4290.02** and the corresponding isocyanates or 4-nitrophenyl carbamate following **method D** of General Schemes for Preparation of Target Compounds.

Cmpd #	Table 2: Oximes	MW	Ki* Range
4289		639	A
4290		629	A
4291		589	B

235

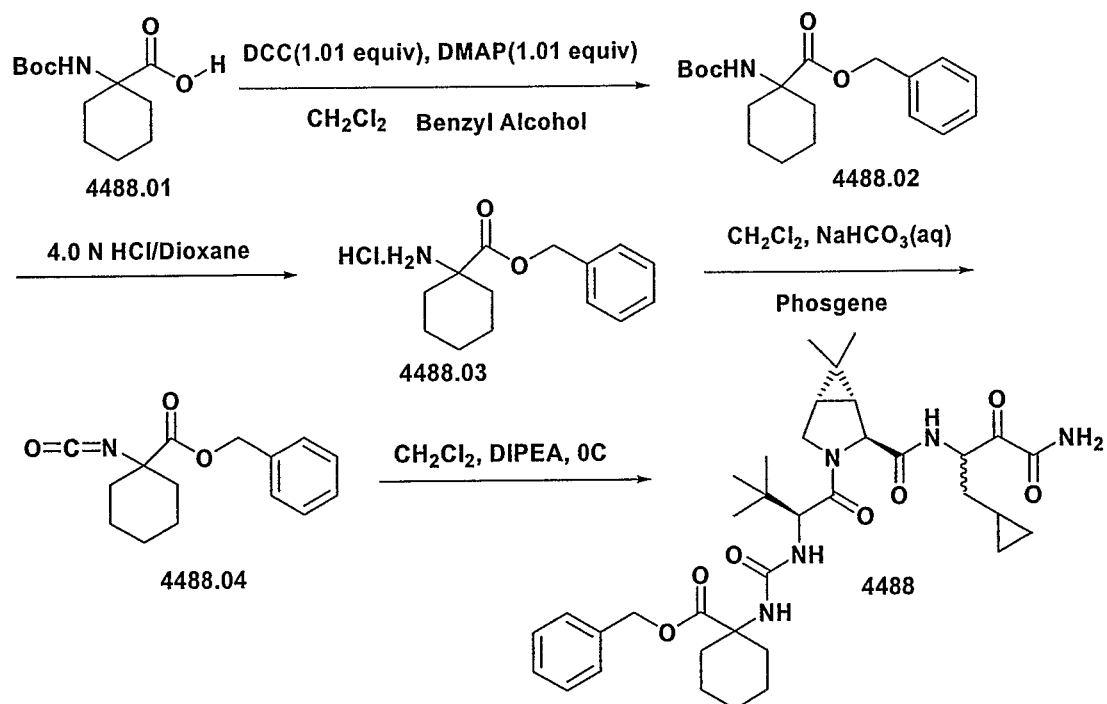
Cmpd #	Table 2: Oximes	MW	Ki* Range
4292		629	B
4293		603	B
4294		639	B

Cmpd #	Table 2: Oximes	MW	Ki* Range
4295		603	B
4296		667	B
4297		643	B

Cmpd #	Table 2: Oximes	MW	Ki* Range
4298		643	B

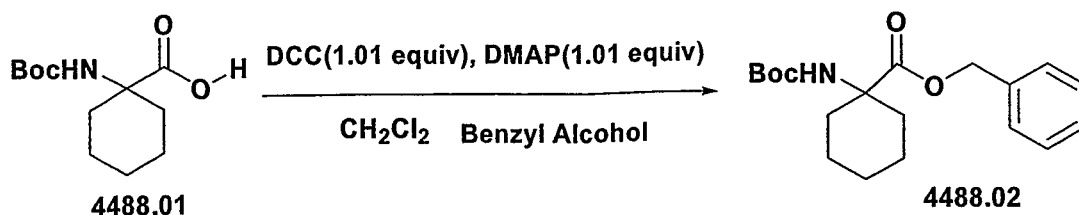
PREPARATION OF SPECIFIC EXAMPLES from Table 3

Example XIII: Preparation of Compound of Formula 4488:

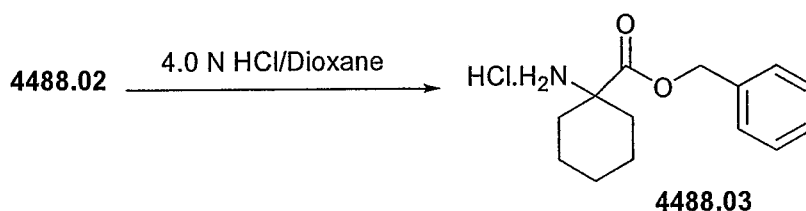


Step1:

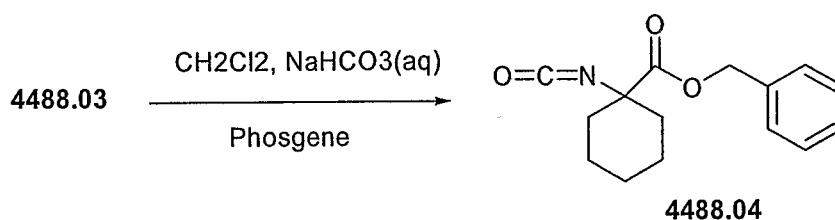
238



To a RT solution of Boc-1-amino-cyclohexanecarboxylic acid **4488.01** (3g, 13.38 mmol) in CH_2Cl_2 (30 mL) was added Benzyl alcohol (3equiv, 4 mL), DMAP (1.01 equiv, 1.65g) and DCC (1.0 M solution in DCM, 1.01 equiv, 13.5mL). The reaction was stirred at RT for 48h. The insoluble material was removed by filtration and crude was concentrated to dryness. The residue was purified by flash chromatography (5% to 10% EtOAc in Hexanes, Biotage 40M). Purification furnished **4488.02** (3.64 g). (M+H)= 334.

Step2:

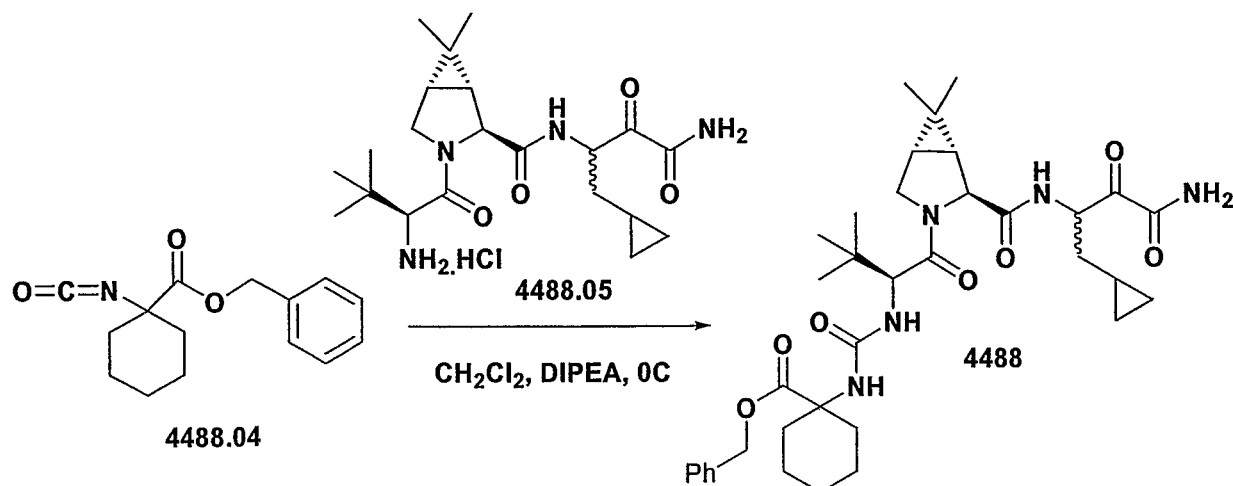
To a RT solution of **4488.02** (3.6g, 10.8 mmol) was added 100 mL of a 4.0 N HCl solution in Dioxane. Reaction was stirred at RT for 1h then 18 h to observe completion. After 18 h, reaction was diluted with Heptanes and Et₂O and the precipitate was filtered off and rinsed with Et₂O and dried under a N₂ flow. Reaction yielded 2.6 g of **4488.03** as a white powder.

Step3:

To a 0°C solution of **4488.03** (2.5 mmol, 666 mg) in CH_2Cl_2 (25 ml) and NaHCO_3 sat (20 mL) was added Phosgene (2 equiv, 20% in PhMe, 2.5 mL). The reaction was warmed-up to RT and stirred for 2 hours. The organic phase was separated and was then dried over anhydrous MgSO_4 and concentrated to half volume under vacuum with cooling bath. The solution was then diluted to 25 mL and used as a 0.1 M solution of **4488.04**.

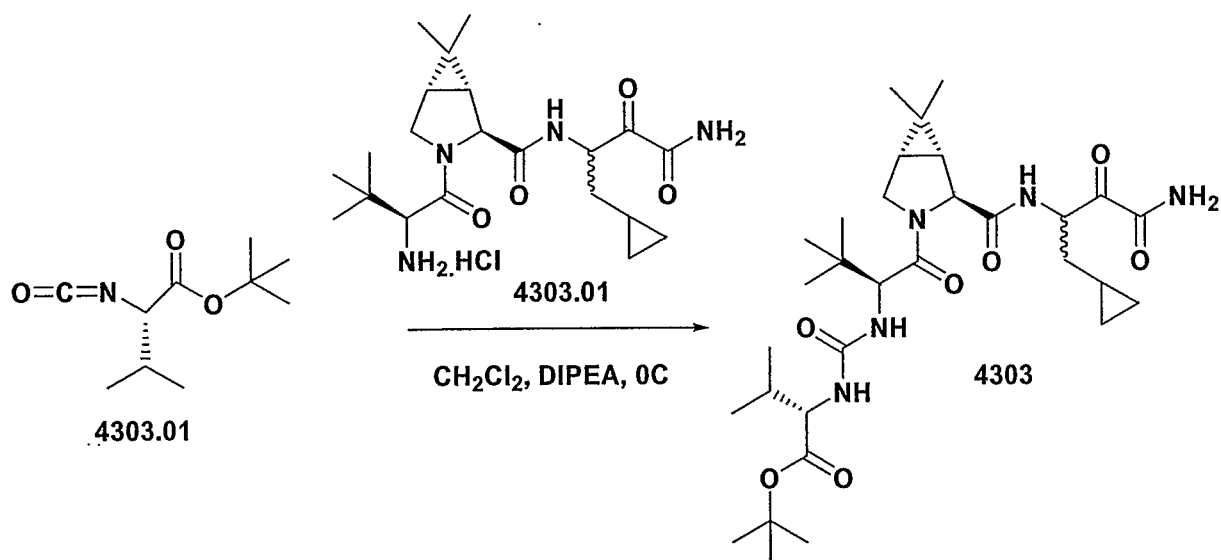
Step4:

239



To a 0°C solution of amine **4488.05** prepared following general **method C** (60mg, 0.135 mmol) in CH_2Cl_2 (5ml) was added DIPEA (8equiv., 1.08 mmol, 0.2 mL) and isocyanate **4488.04** (3equiv., 0.406 mmol, 4 mL). The reaction was warmed-up to RT and stirred for 2 hours. Reaction was diluted with EtOAc and washed successively with citric acid (10% w/w) and brine. Organic layer was dried over MgSO_4 , filtered and concentrated under vacuo. The residue was purified by preparative plate using 40% Acetone in Hexane as eluant. Purification furnished 32 mg of product HCV inhibitor **4488**. (M+H)= 667.

Example XIV: Preparation of Compound of Formula 4303

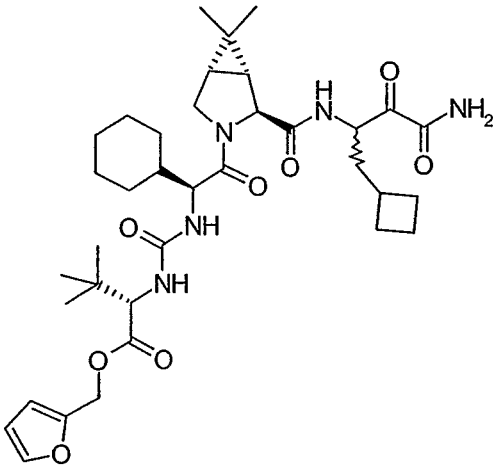
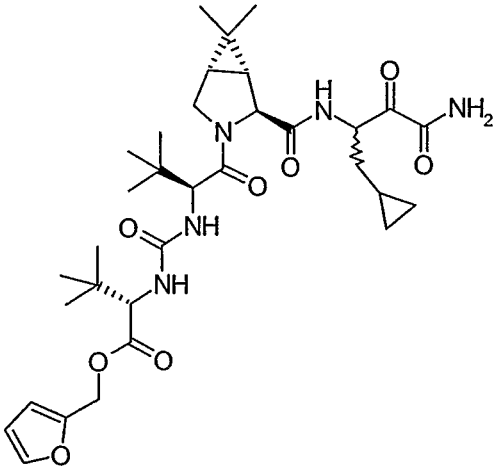


All *tert*-Butyl esters included in **Table 3** were prepared according the following procedure. Commercially available amino *tert*-Butyl ester hydrochloride like (but not limited to) (L)-cyclohexylglycine, (L)-Valine, (L)-*tert*-Leucine *tert*-Butyl ester hydrochloride were reacted with phosgene as outlined in **step 3** of preparative

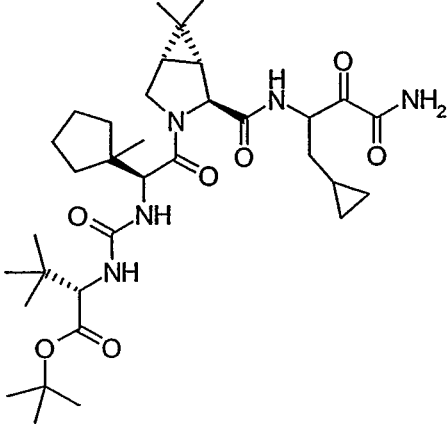
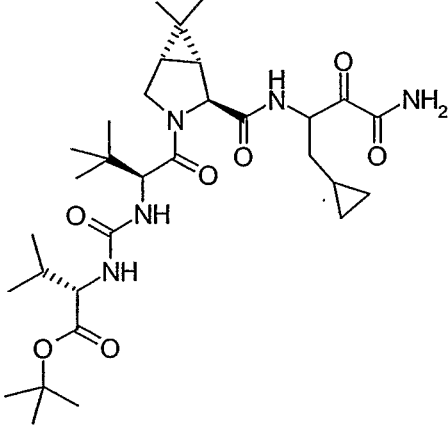
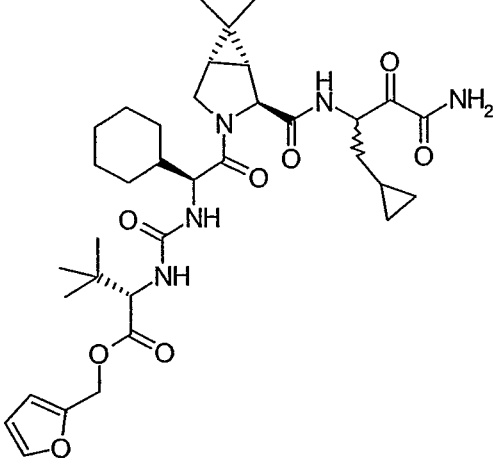
example **XIII** to produce the corresponding isocyanate (**4303.01** was prepared from commercially available (L)-Valine *tert*-Butyl ester hydrochloride). Isocyanates were reacted with various amines like **4303.01** prepared following general **method C** to produce HCV inhibitors like **4303** listed in **Table 3**.

- 5 All other HCV inhibitors listed in **Table 3** were prepared according procedure described in Preparative Example **XIII** by replacing in **step 1** benzyl alcohol with other commercially available alcohols (primary, secondary and tertiary) and Boc-1-amino-cyclohexanecarboxylic acid **4488.01** with other commercially amino acid like (but not limited to) (L)-cyclohexylglycine, (L)-Valine or (L)-*tert*-Leucine.

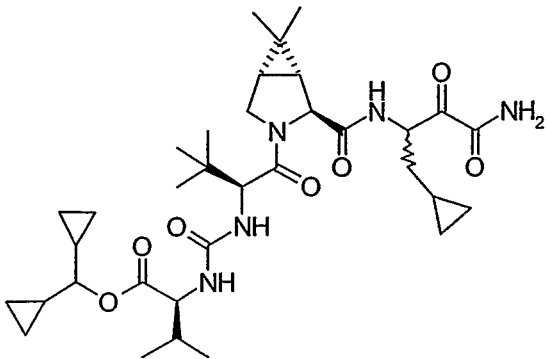
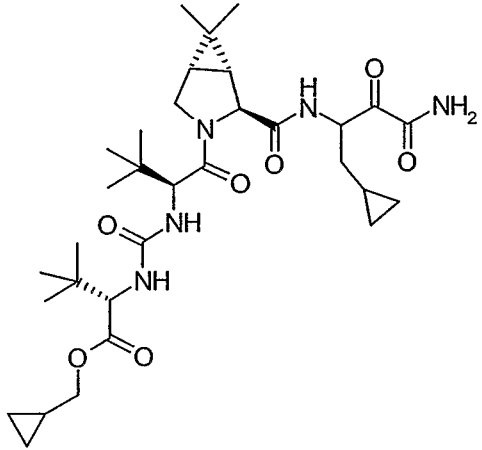
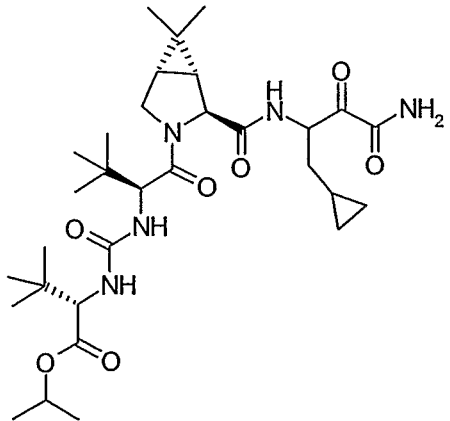
10

Cmpd #	Table 3: Esters	MW	Ki* Range
4300		684	A
4301		644	A

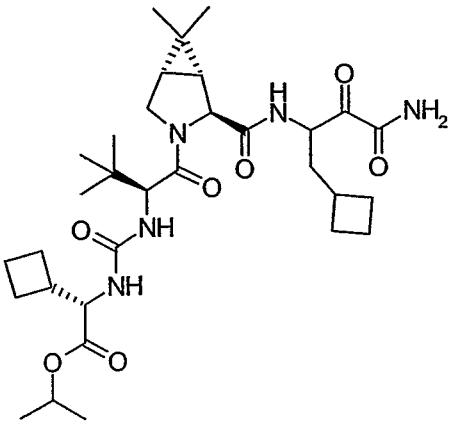
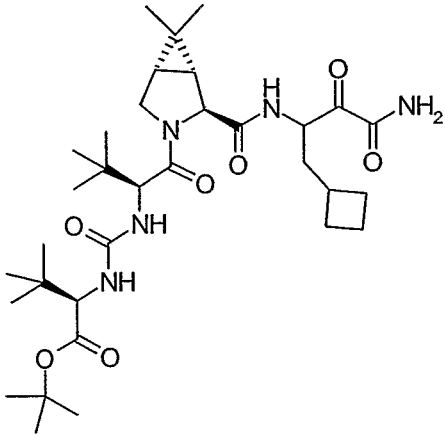
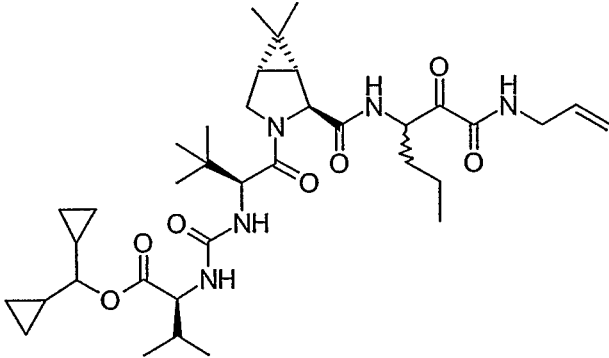
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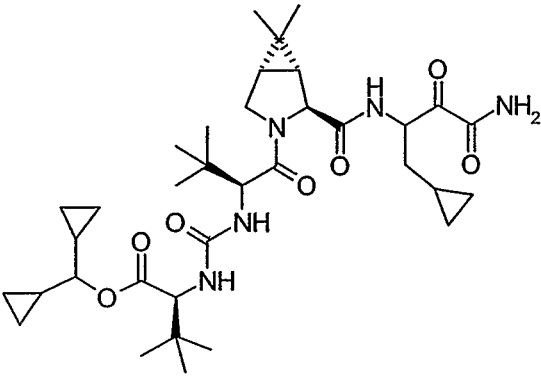
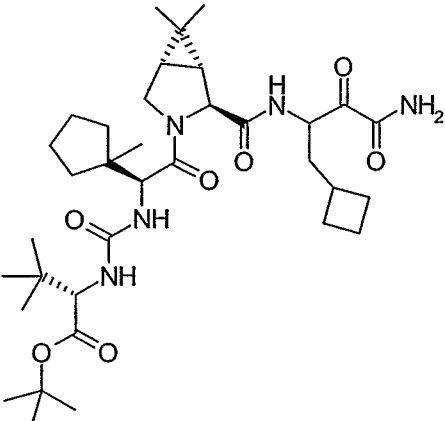
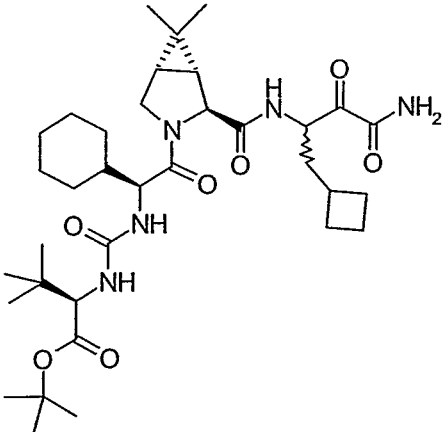
Cmpd #	Table 3: Esters	MW	Ki* Range
4302		646	A
4303		606	A
4304		670	A

242

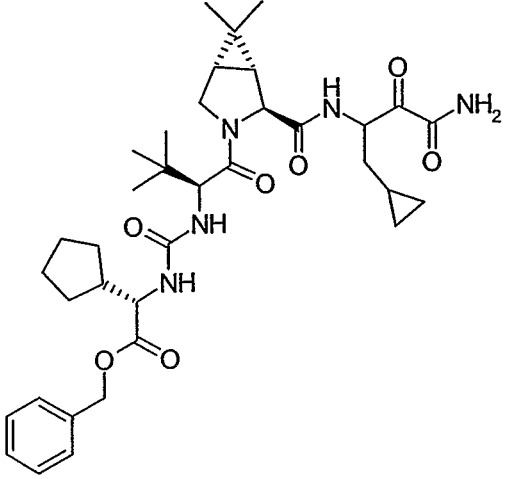
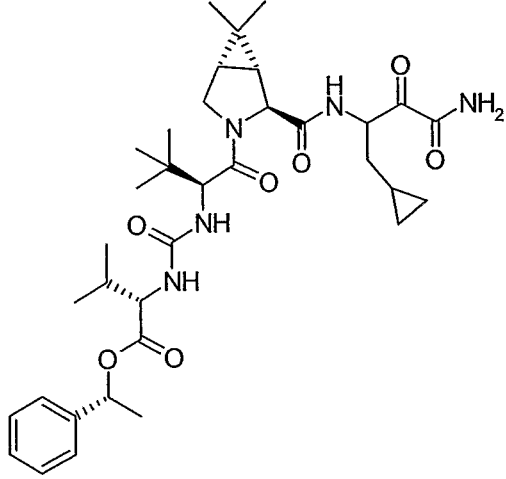
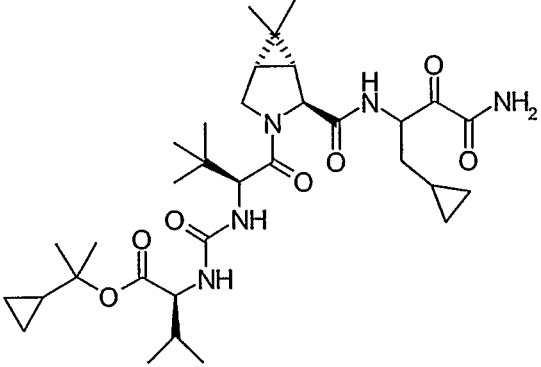
Cmpd #	Table 3: Esters	MW	K _i * Range
4305		644	A
4306		618	A
4307		606	A

243

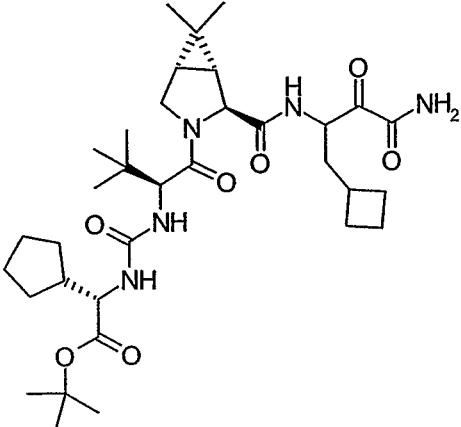
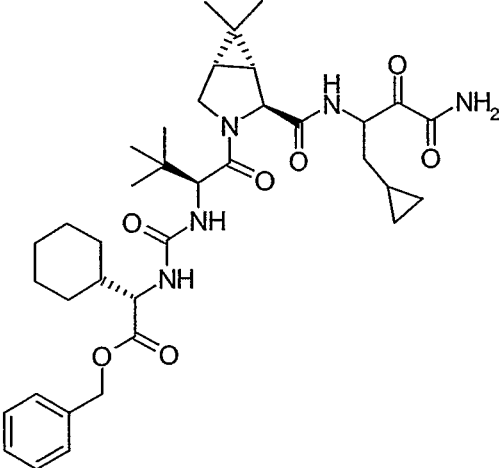
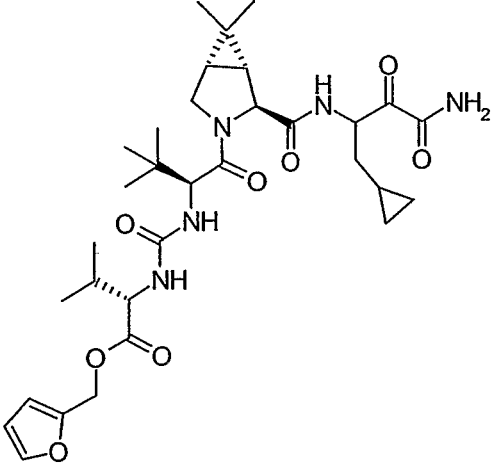
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4308		618	A
4309		634	A
4310		672	A

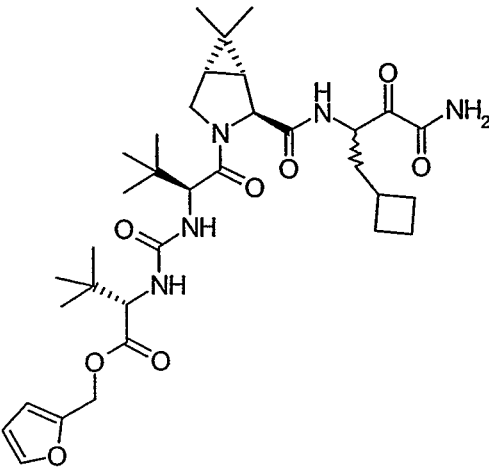
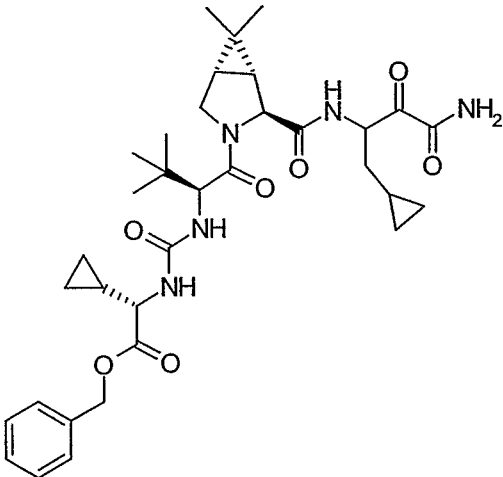
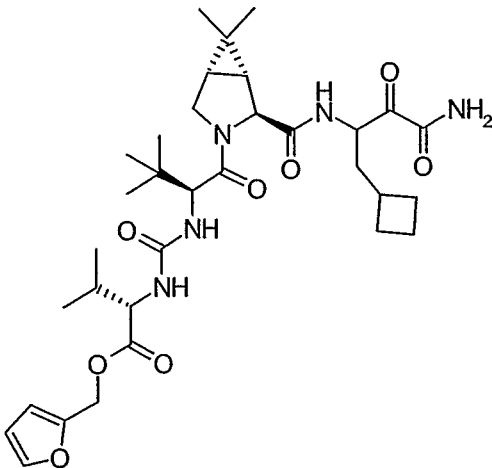
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4311		658	A
4312		660	A
4313		660	A

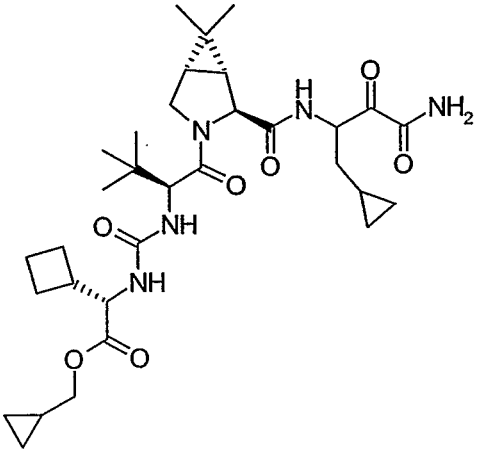
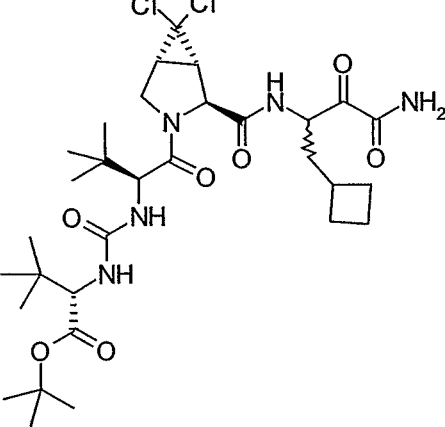
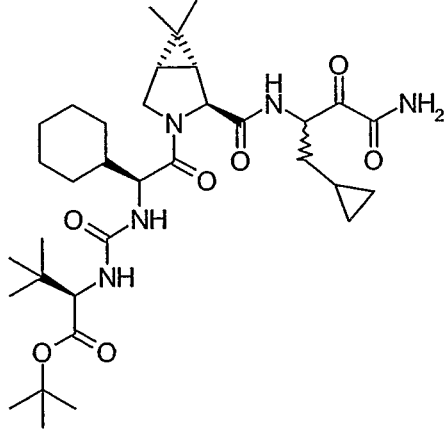
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Cmpd #	Table 3: Esters	MW	Ki* Range
4314		666	A
4315		654	A
4316		632	A

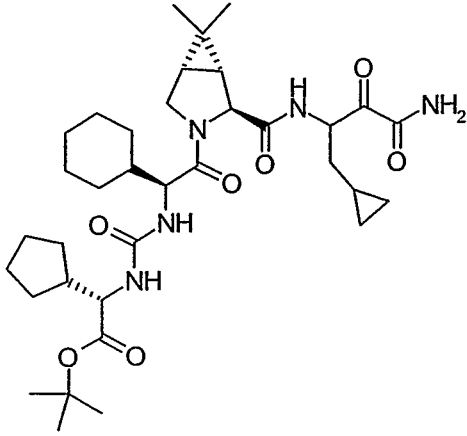
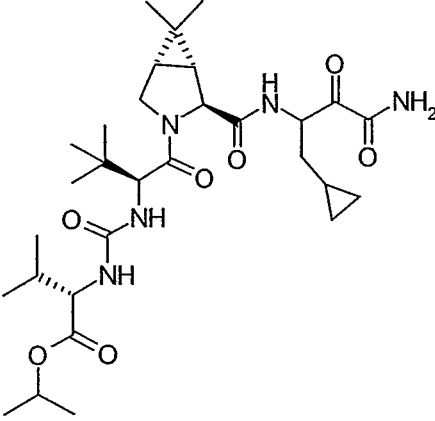
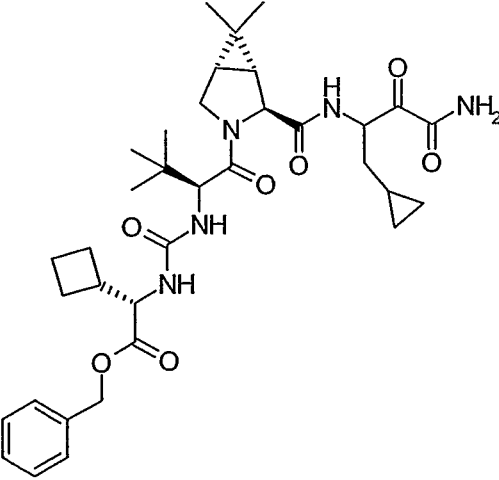
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Cmpd #	Table 3: Esters	MW	Ki* Range
4317		646	A
4318		680	A
4319		630	A

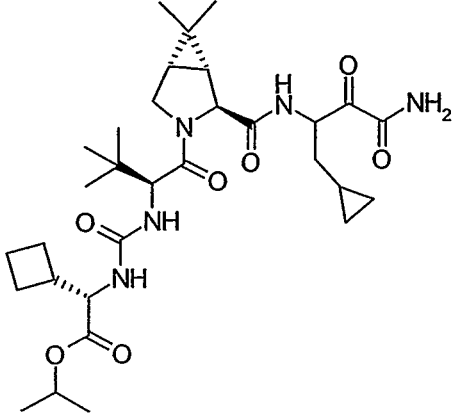
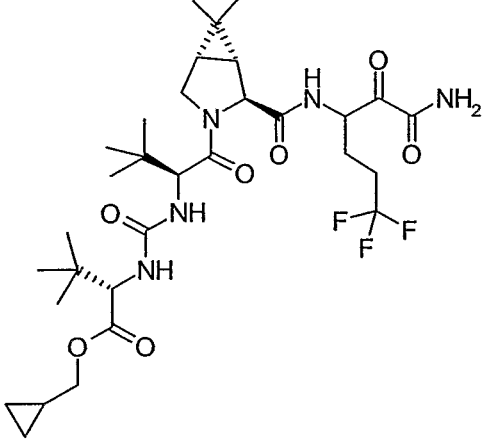
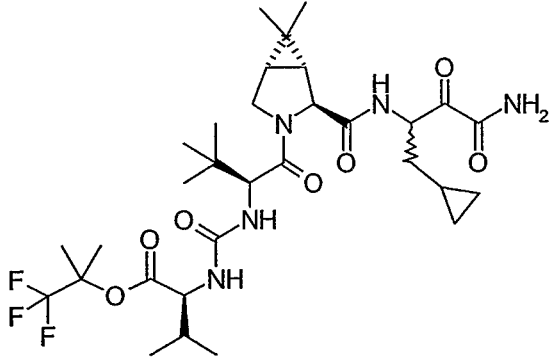
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4320		658	A
4321		638	A
4322		644	A

Cmpd #	Table 3: Esters	MW	Ki* Range
4323		616	A
4324		675	A
4325		646	A

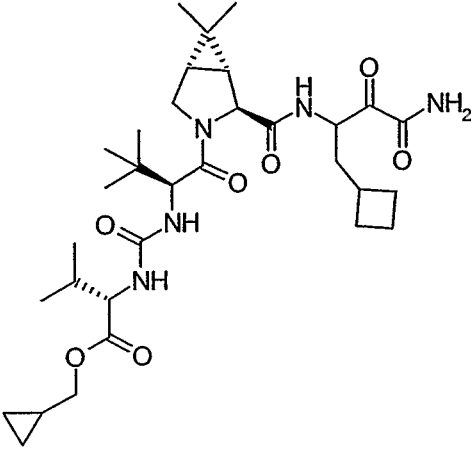
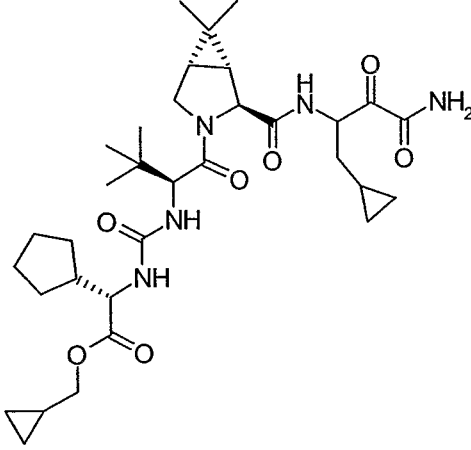
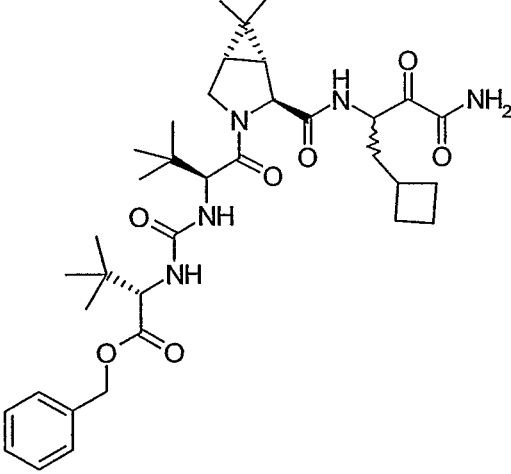
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Cmpd #	Table 3: Esters	MW	Ki* Range
4326		658	A
4327		592	A
4328		652	A

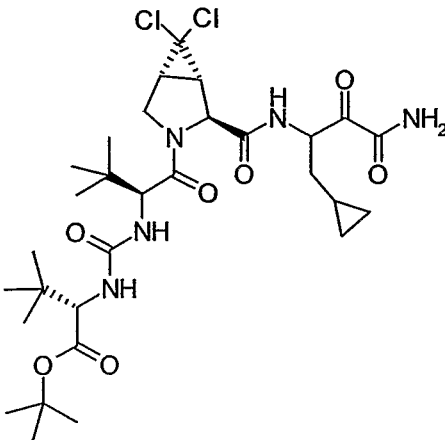
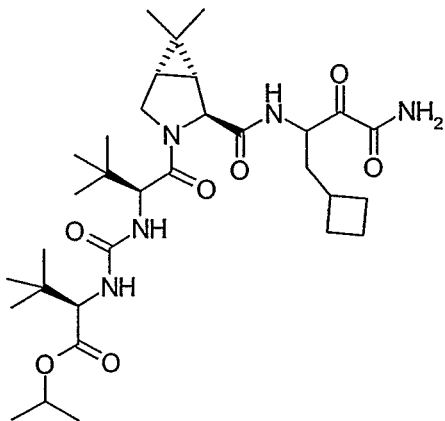
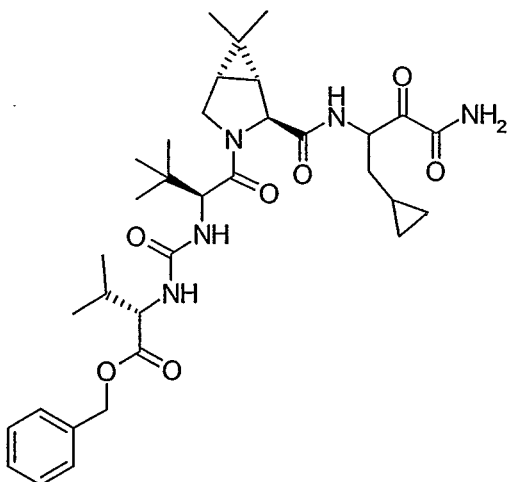
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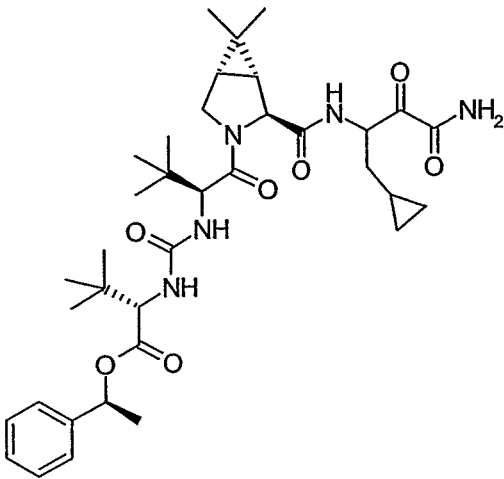
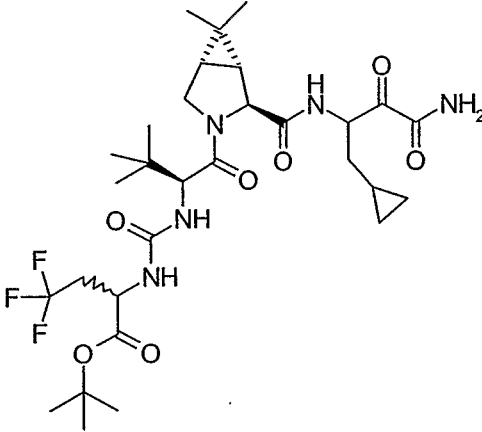
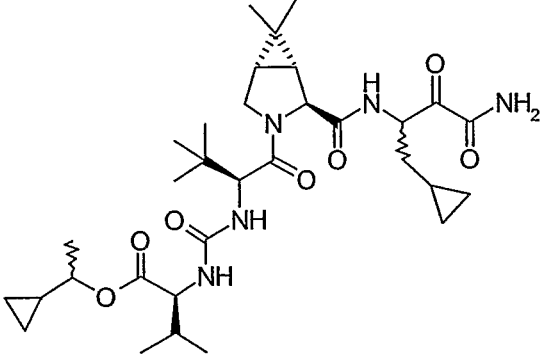
Cmpd #	Table 3: Esters	MW	Ki* Range
4329		604	A
4330		660	A
4331		660	A

251

Cmpd #	Table 3: Esters	MW	Ki* Range
4332		618	A
4333		630	A
4334		668	A

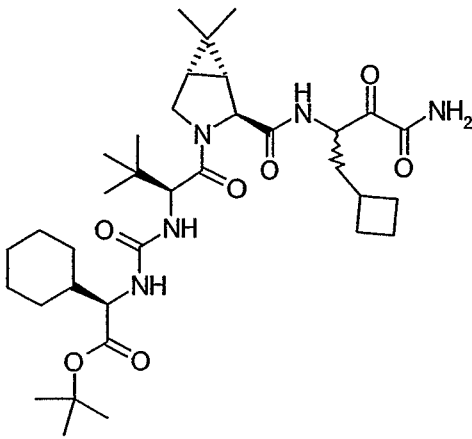
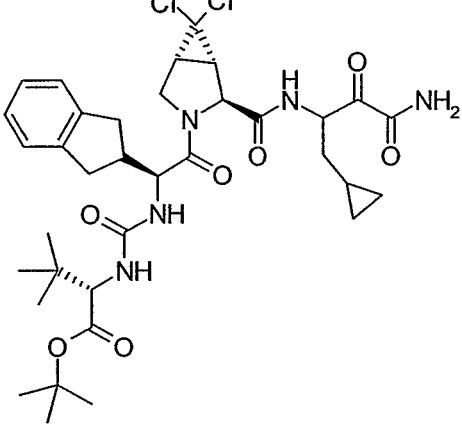
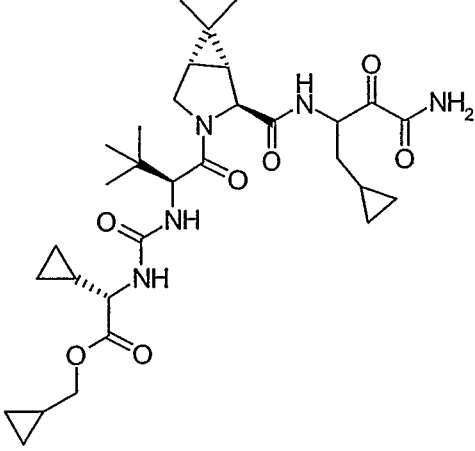
252

Cmpd #	Table 3: Esters	MW	Ki* Range
4335		661	A
4336		620	A
4337		640	A

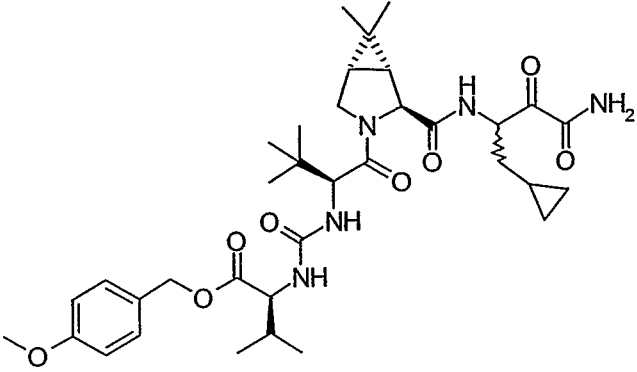
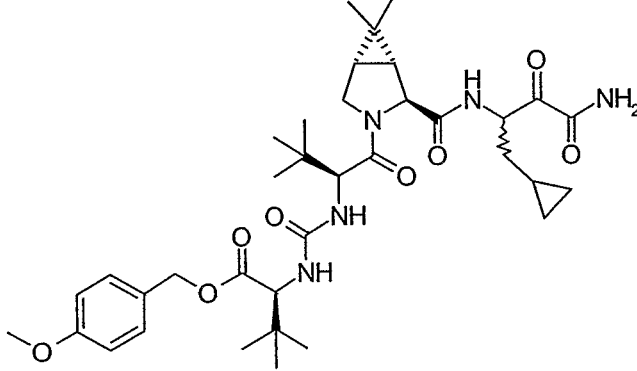
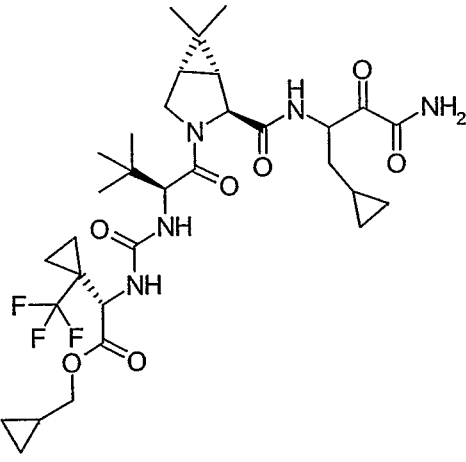
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4338		668	A
4339		646	A
4340		618	A

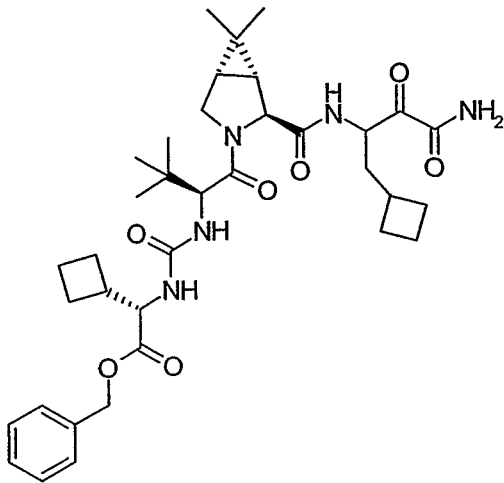
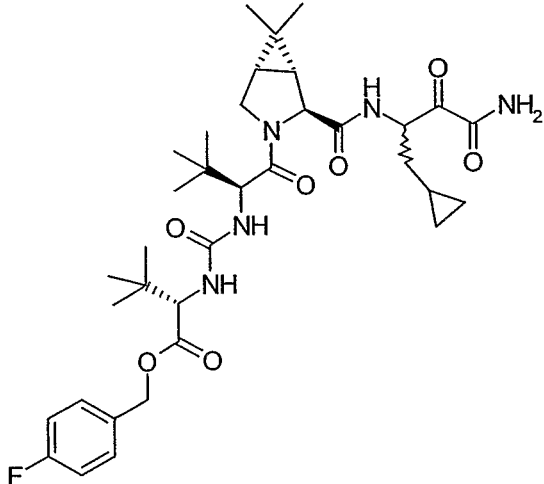
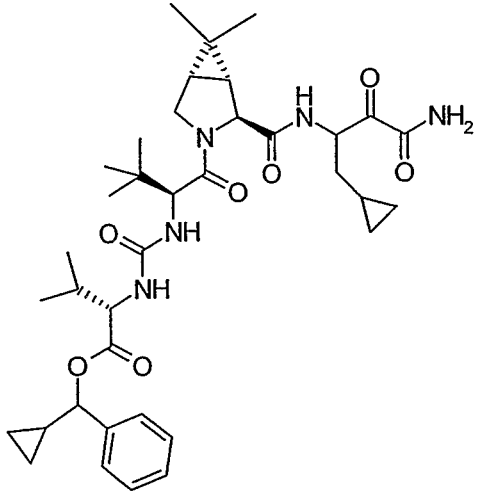
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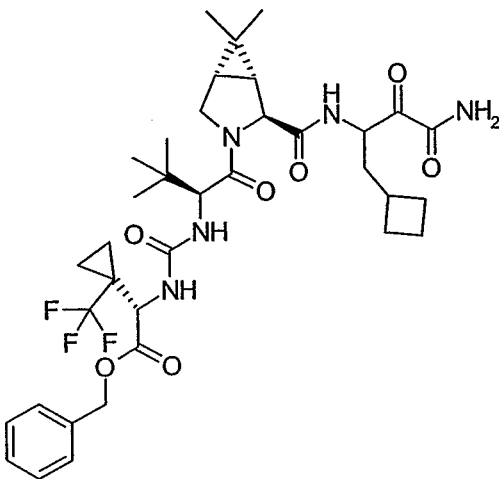
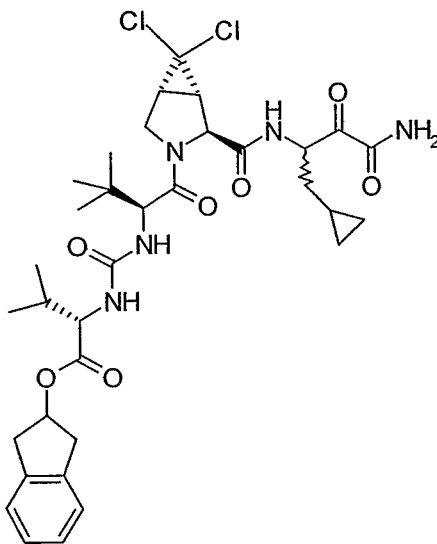
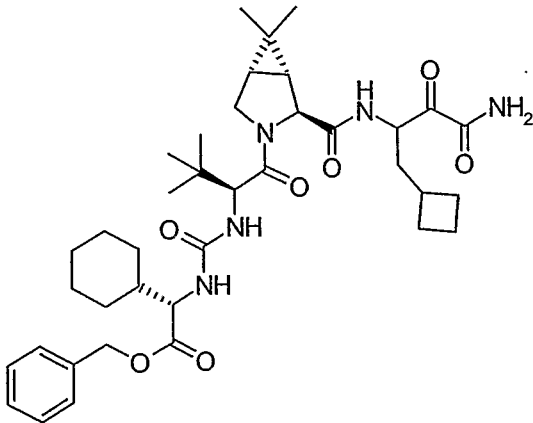
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4345		721	A
4346		602	A

256

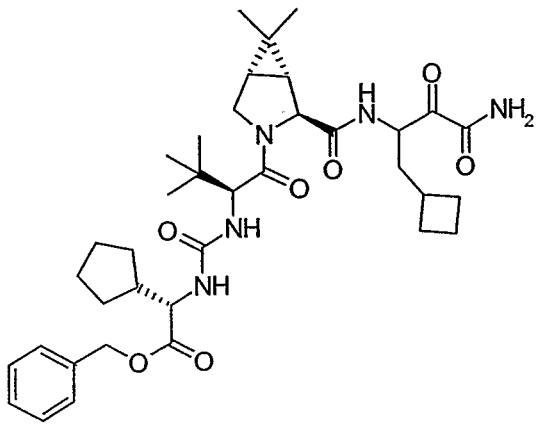
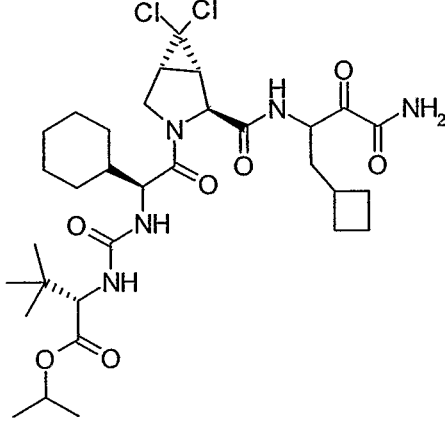
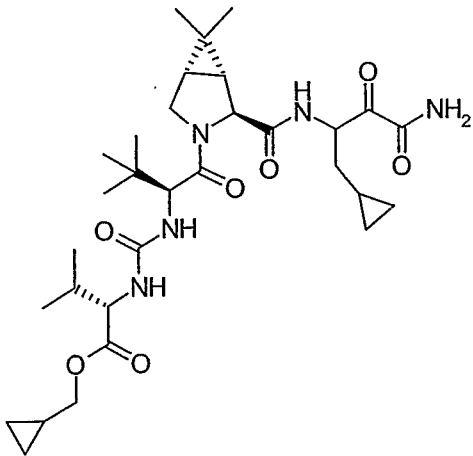
Cmpd #	Table 3: Esters	MW	Ki* Range
4347		670	A
4348		684	A
4349		670	A

Cmpd #	Table 3: Esters	MW	Ki* Range
4350		666	A
4351		672	A
4352		680	A

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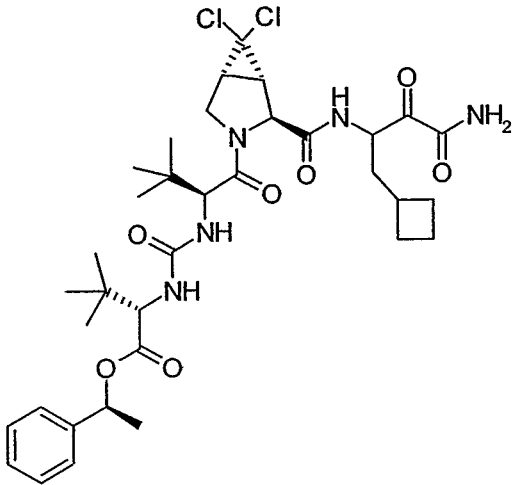
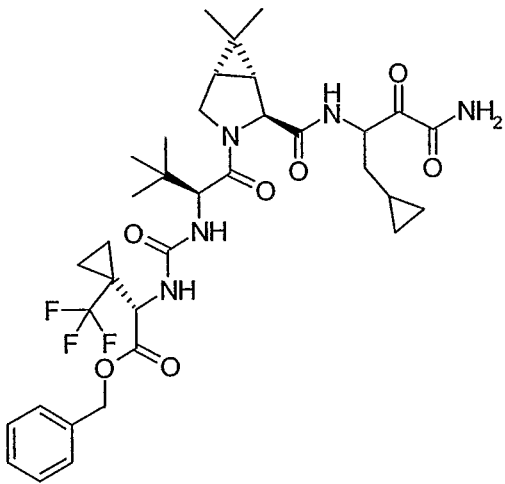
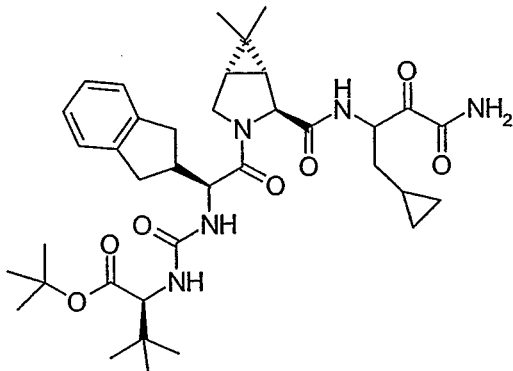
Cmpd #	Table 3: Esters	MW	Ki* Range
4353		720	A
4354		707	A
4355		694	A

259

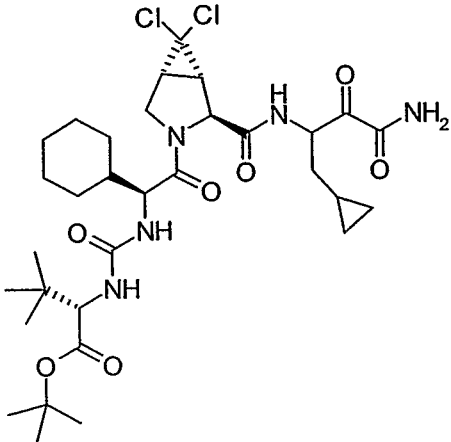
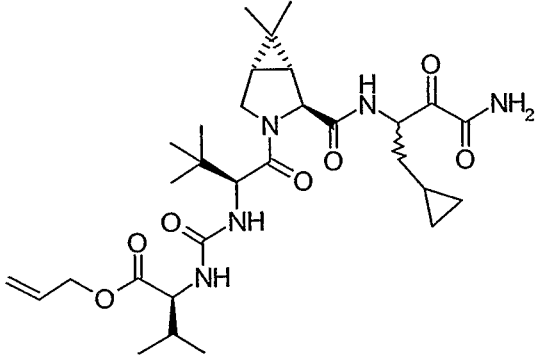
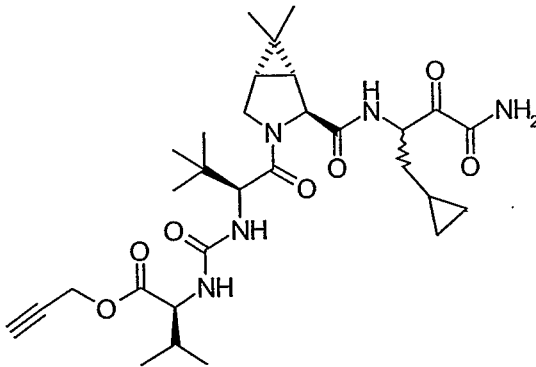
Cmpd #	Table 3: Esters	MW	Ki* Range
4356		680	A
4357		687	A
4358		604	A

Cmpd #	Table 3: Esters	MW	Ki* Range
4359		632	A
4360		632	A
4361		642	A

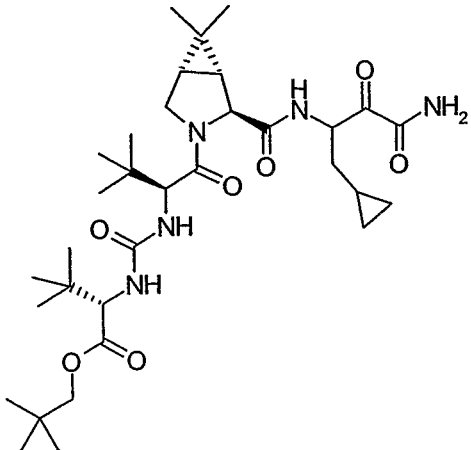
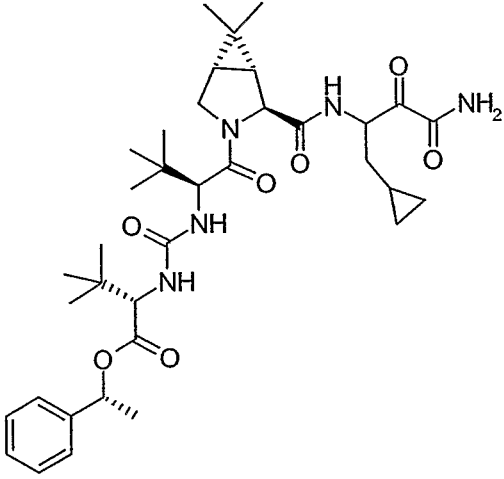
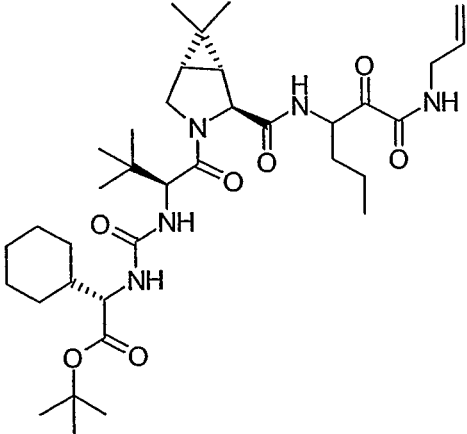
261

Cmpd #	Table 3: Esters	MW	Ki* Range
4362		723	A
4363		706	A
4364		680	A

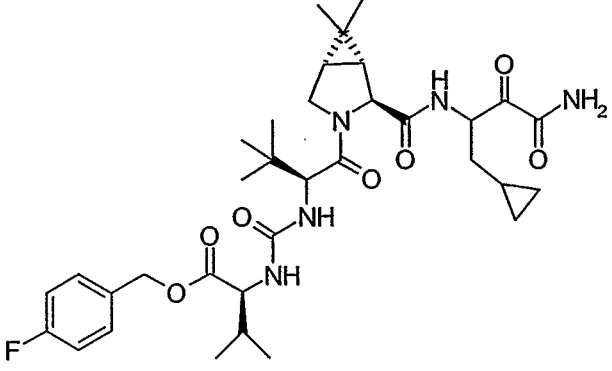
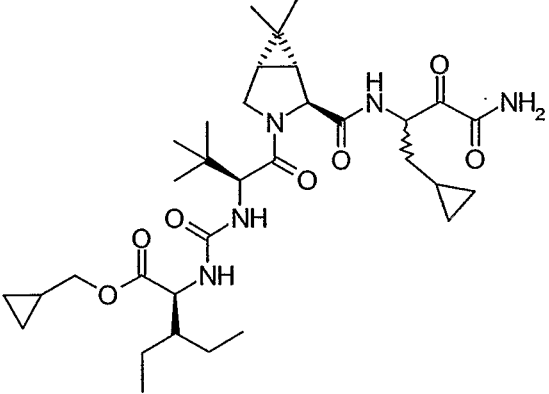
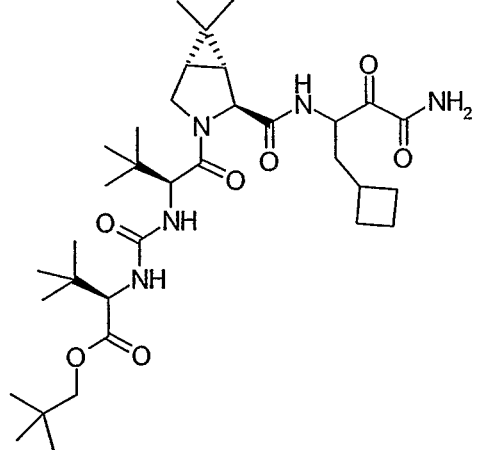
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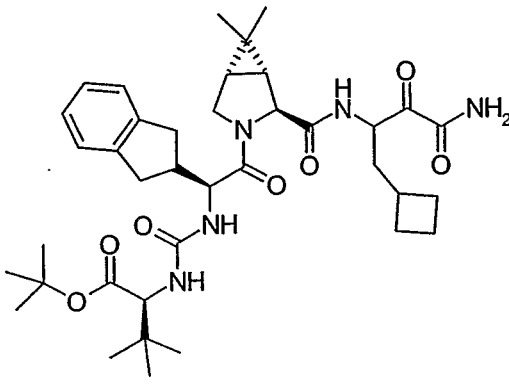
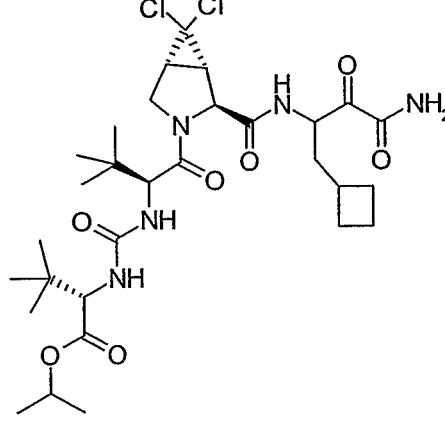
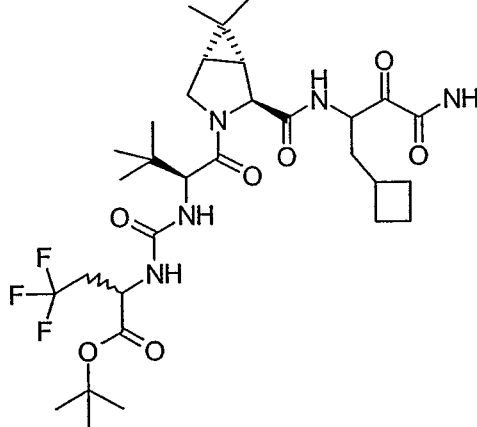
Cmpd #	Table 3: Esters	MW	Ki* Range
4365		687	A
4366		590	A
4367		588	A

263

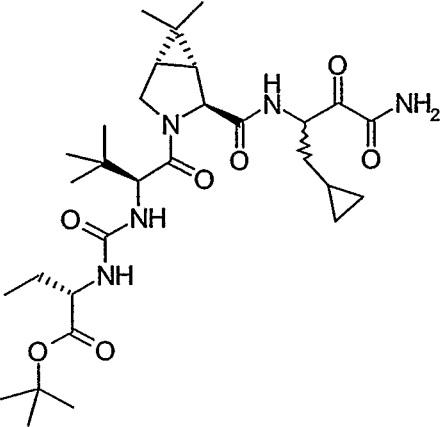
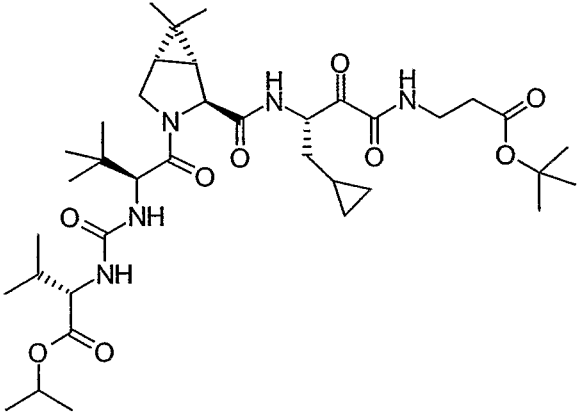
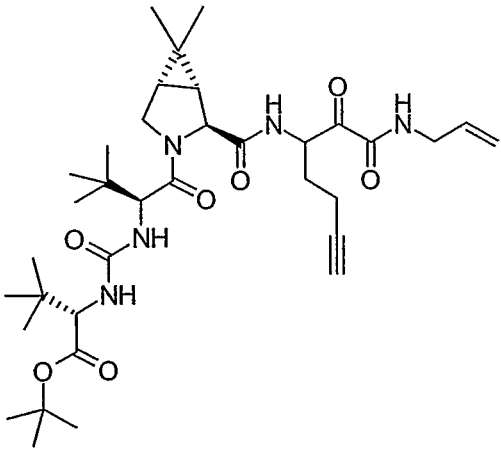
Cmpd #	Table 3: Esters	MW	Ki* Range
4368		634	A
4369		668	A
4370		674	A

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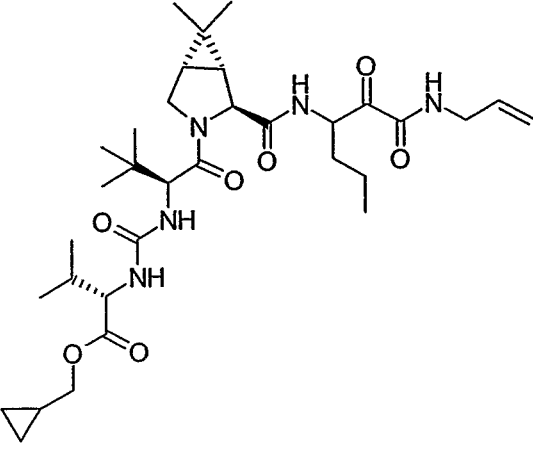
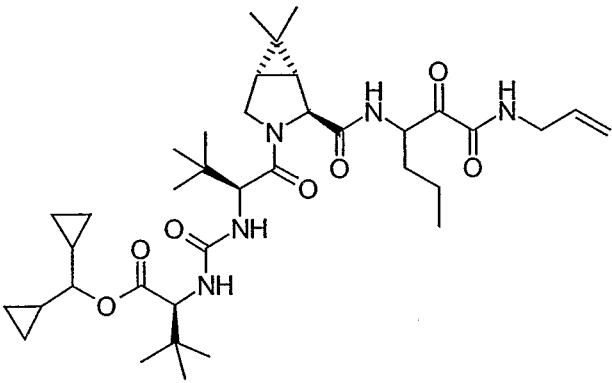
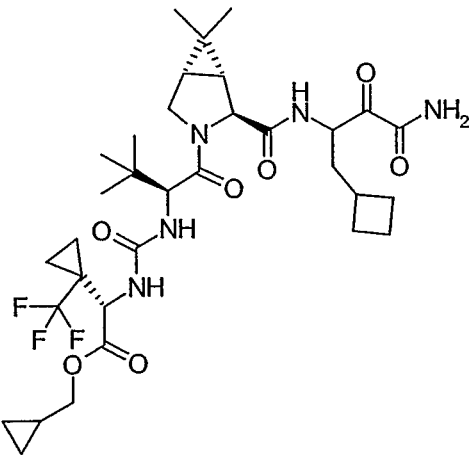
Cmpd #	Table 3: Esters	MW	Ki* Range
4371		658	A
4372		632	A
4373		648	A

Cmpd #	Table 3: Esters	MW	Ki* Range
4374		694	A
4375		661	A
4376		660	A

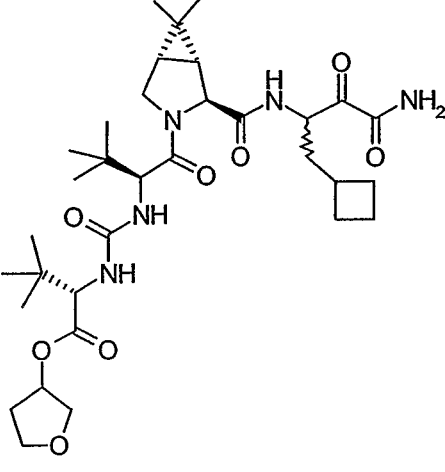
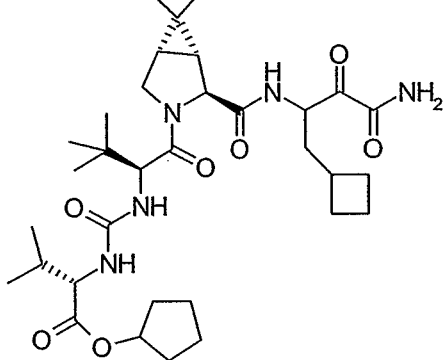
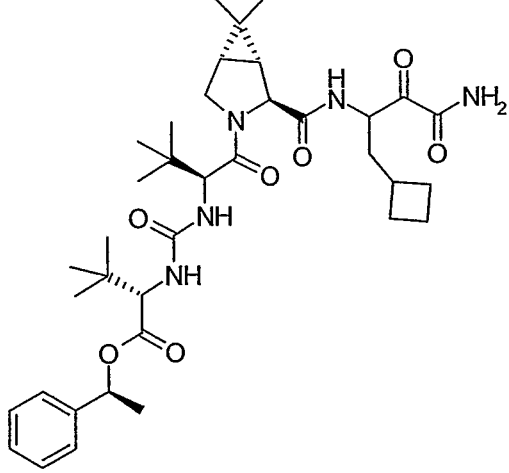
266

Cmpd #	Table 3: Esters	MW	Ki* Range
4377		592	A
4378		720	A
4379		658	A

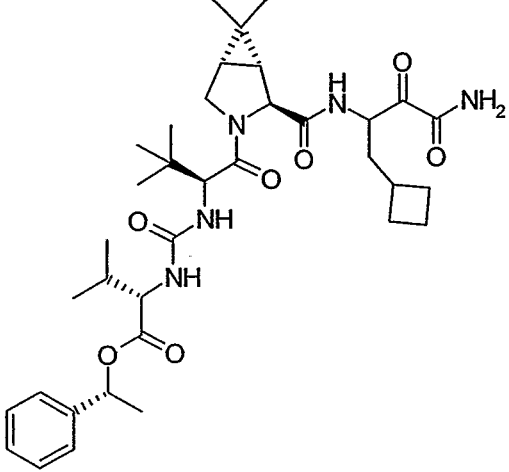
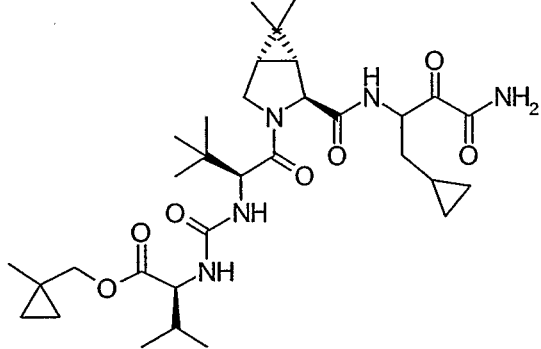
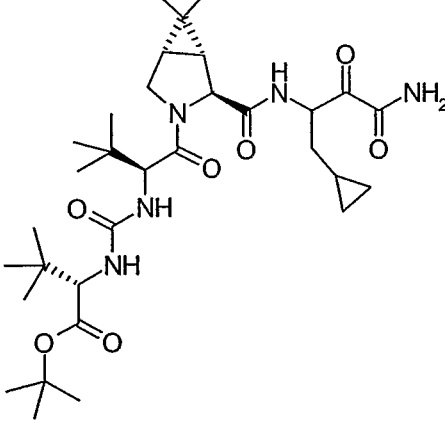
267

Cmpd #	Table 3: Esters	MW	Ki* Range
4380		632	A
4381		686	A
4382		684	A

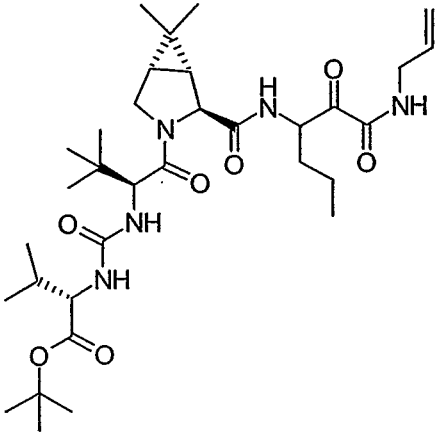
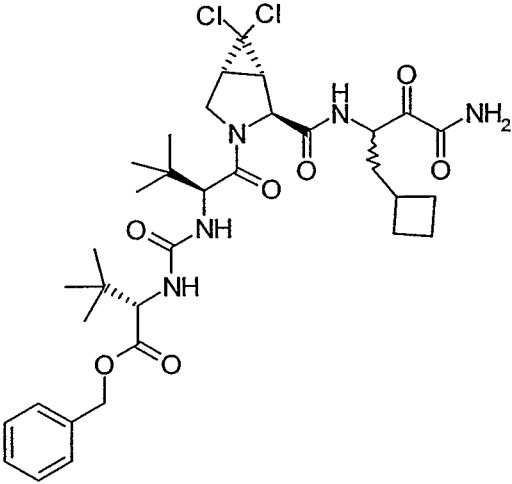
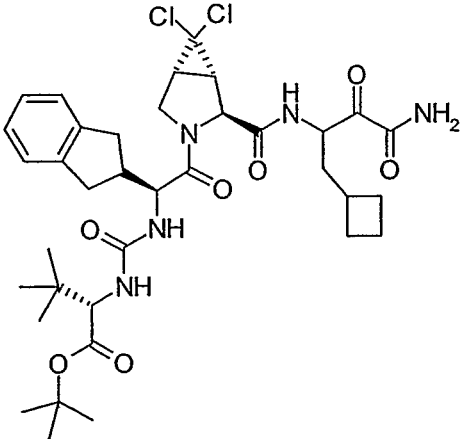
268

Cmpd #	Table 3: Esters	MW	Ki* Range
4383		648	A
4384		632	A
4385		682	A

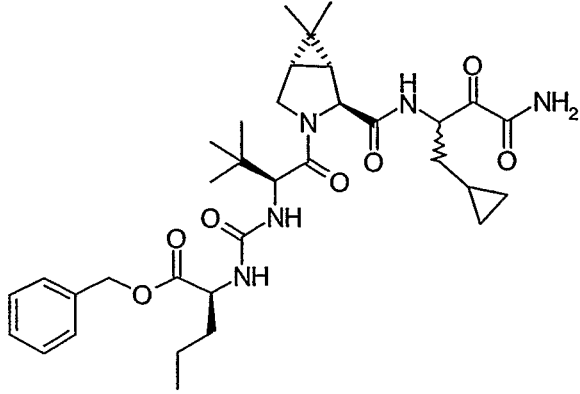
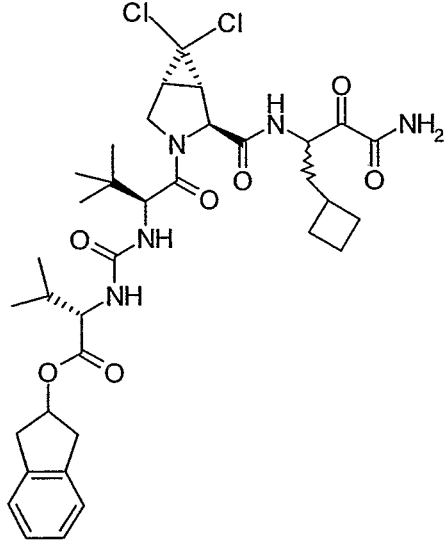
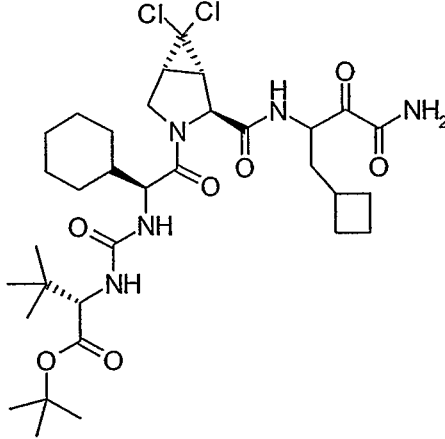
269

Cmpd #	Table 3: Esters	MW	Ki* Range
4386		668	A
4387		618	A
4388		620	A

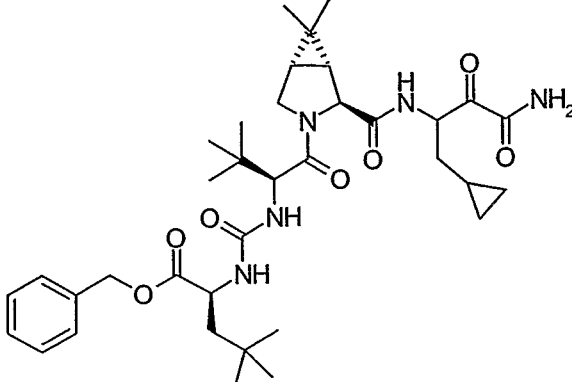
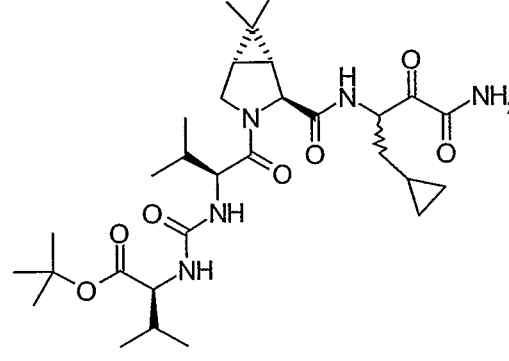
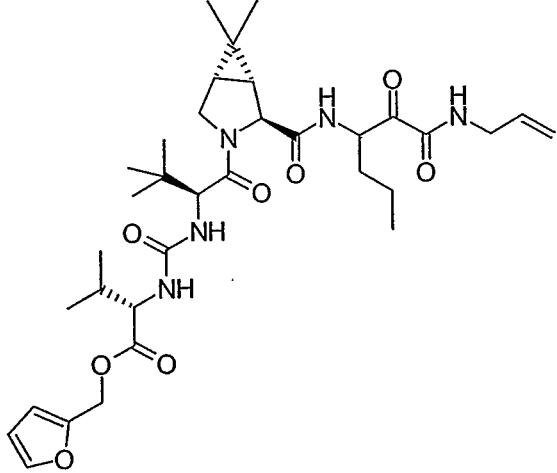
270

Cmpd #	Table 3: Esters	MW	Ki* Range
4389		634	A
4390		709	A
4391		735	A

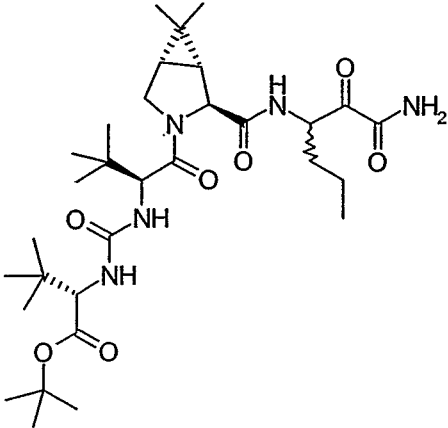
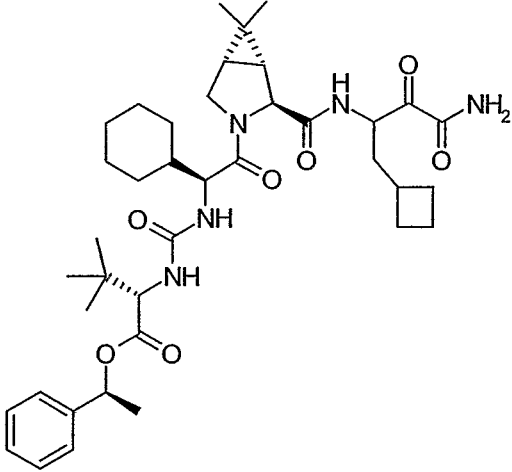
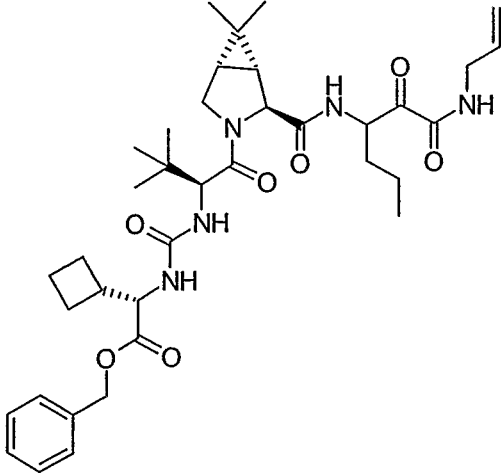
271

Cmpd #	Table 3: Esters	MW	Ki* Range
4392		640	A
4393		721	A
4394		701	A

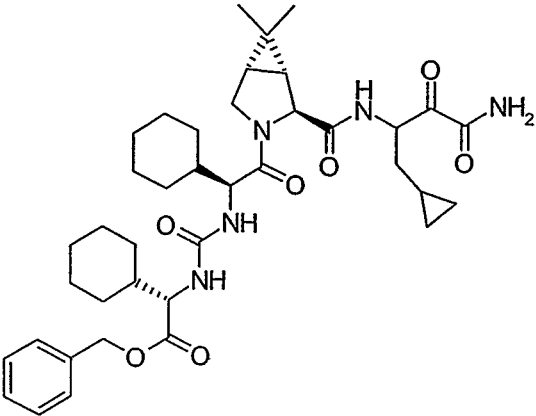
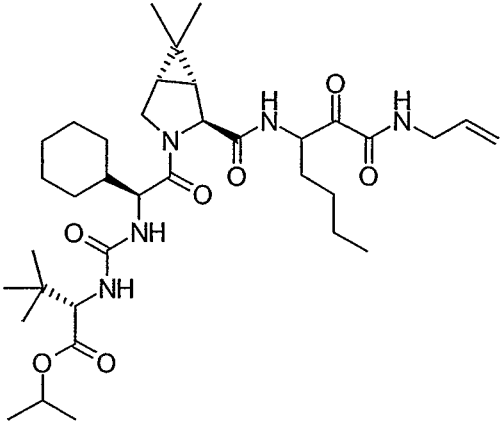
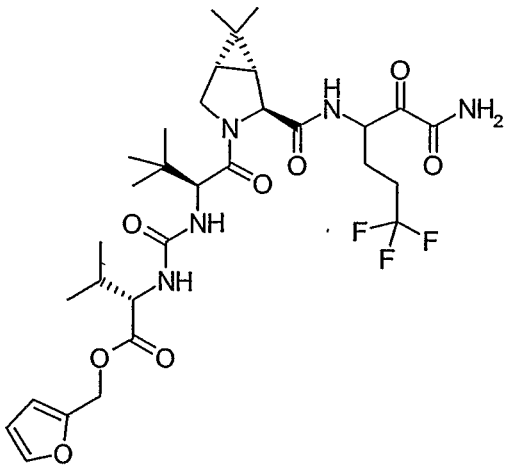
272

Cmpd #	Table 3: Esters	MW	Ki* Range
4395		668	A
4396		592	A
4397		658	A

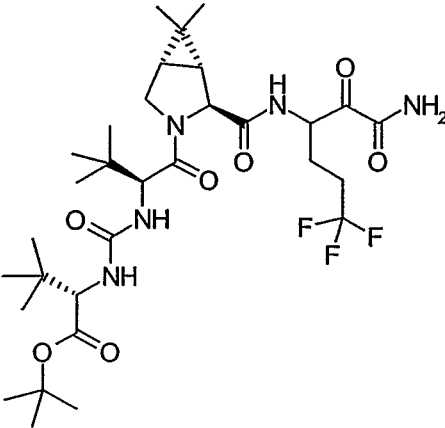
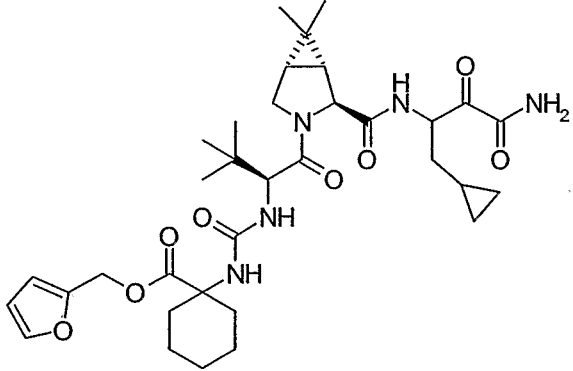
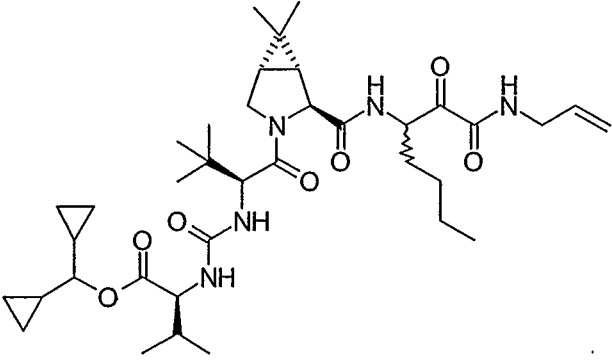
273

Cmpd #	Table 3: Esters	MW	Ki* Range
4398		608	A
4399		708	A
4400		680	A

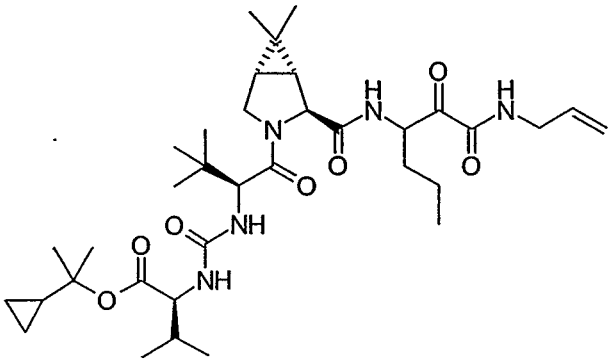
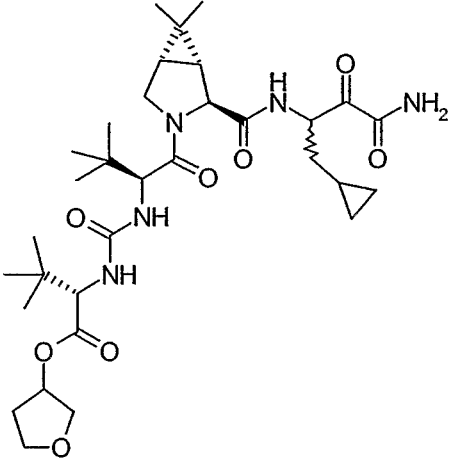
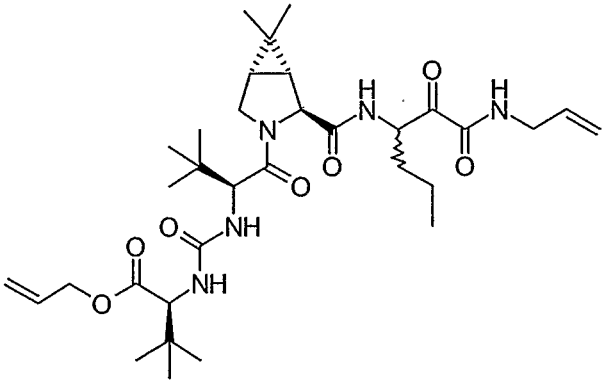
274

Cmpd #	Table 3: Esters	MW	Ki* Range
4401	 Chemical structure of compound 4401: A complex molecule featuring a central pyrrolidine ring substituted with a cyclohexyl group, a tert-butyl group, and a carbamate linkage. The carbamate is connected to a chain containing a cyclopropyl group, an amide, and a primary amide. Another branch from the central carbon contains a cyclohexyl group and a carbamate linked to a benzyl ester.	706	A
4402	 Chemical structure of compound 4402: A complex molecule featuring a central pyrrolidine ring substituted with a cyclohexyl group, a tert-butyl group, and a carbamate linkage. The carbamate is connected to a chain containing a propyl group, an amide, and a vinyl group. Another branch from the central carbon contains a cyclohexyl group and a carbamate linked to an isopropyl ester.	674	A
4403	 Chemical structure of compound 4403: A complex molecule featuring a central pyrrolidine ring substituted with a cyclohexyl group, a tert-butyl group, and a carbamate linkage. The carbamate is connected to a chain containing a trifluoromethyl group, an amide, and a primary amide. Another branch from the central carbon contains a cyclohexyl group and a carbamate linked to a furan-2-ylmethyl ester.	672	A

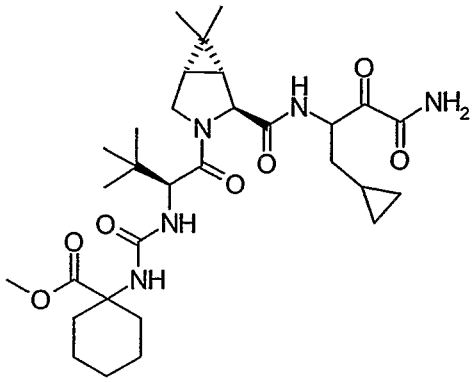
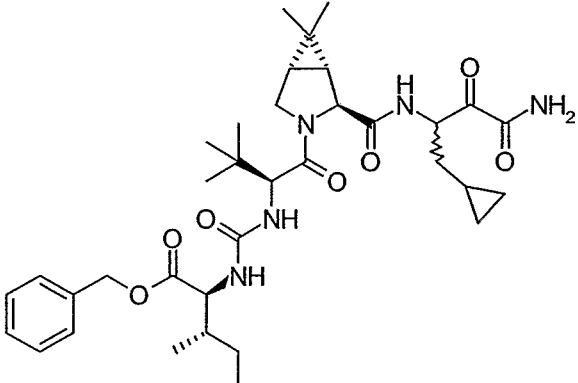
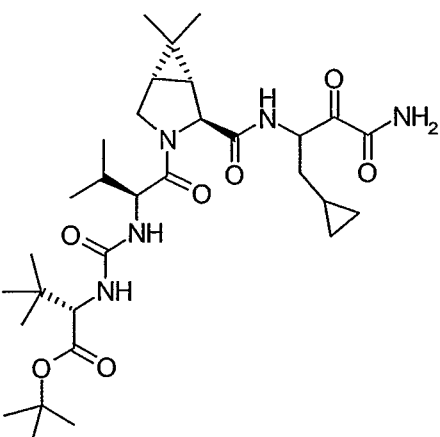
275

Cmpd #	Table 3: Esters	MW	Ki* Range
4404		662	A
4405		656	A
4406		686	A

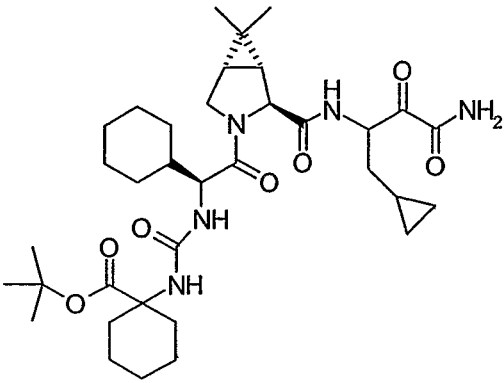
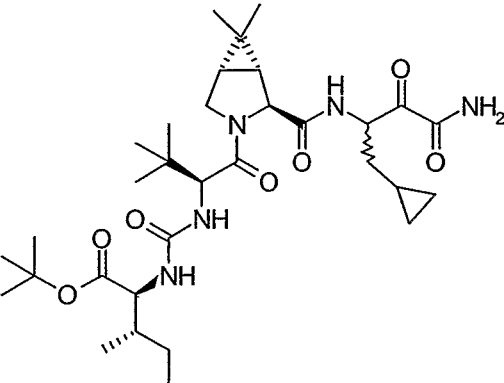
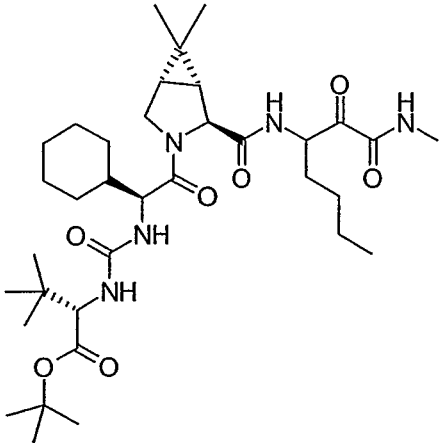
276

Cmpd #	Table 3: Esters	MW	Ki* Range
4407		660	A
4408		634	A
4409		632	A

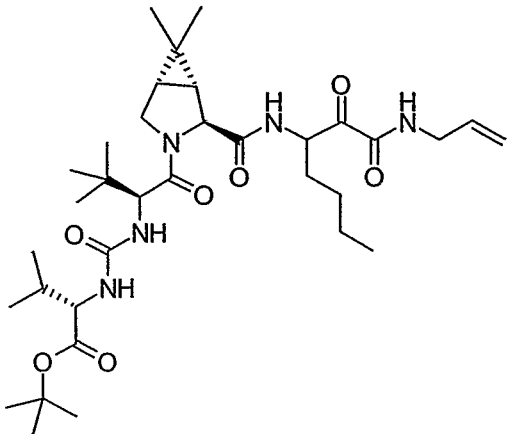
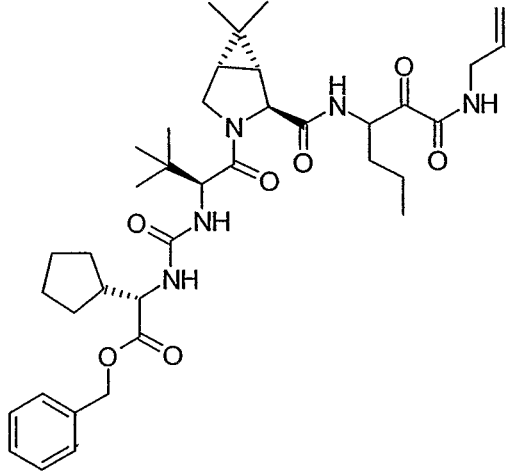
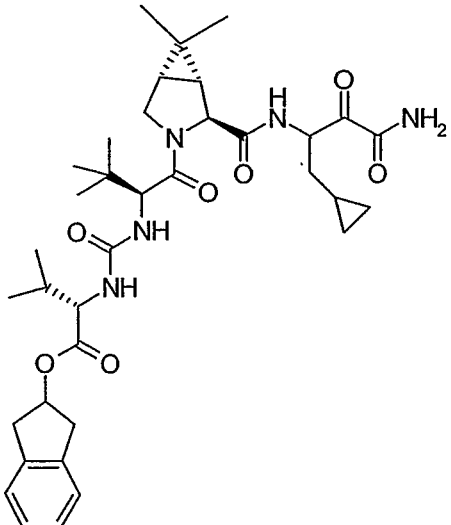
277

Cmpd #	Table 3: Esters	MW	Ki* Range
4410		590	A
4411		654	A
4412		606	A

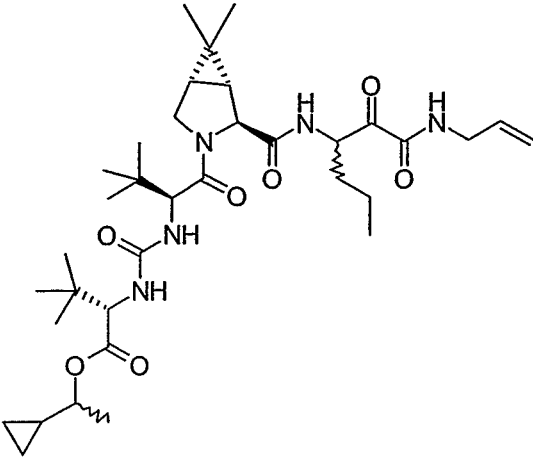
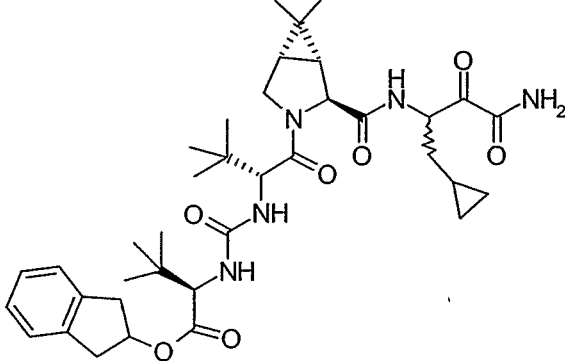
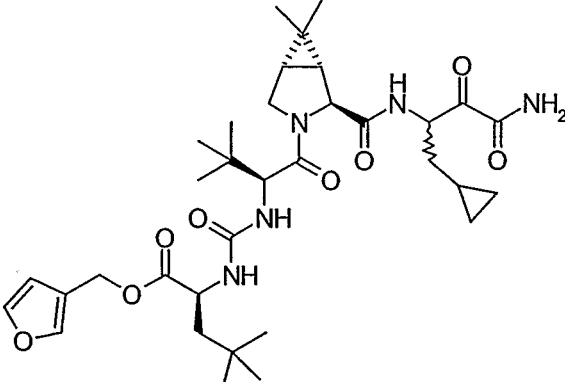
278

Cmpd #	Table 3: Esters	MW	Ki* Range
4413		658	A
4414		620	A
4415		662	A

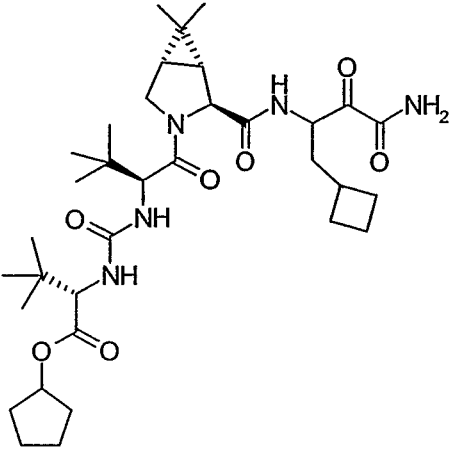
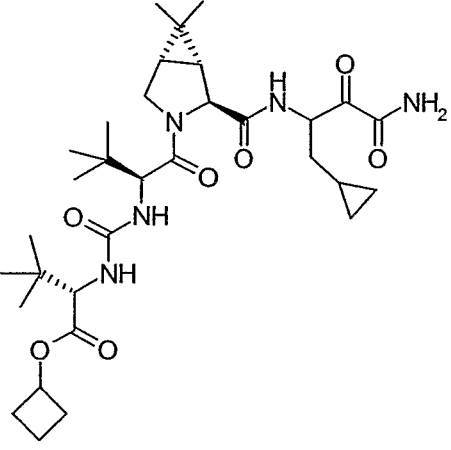
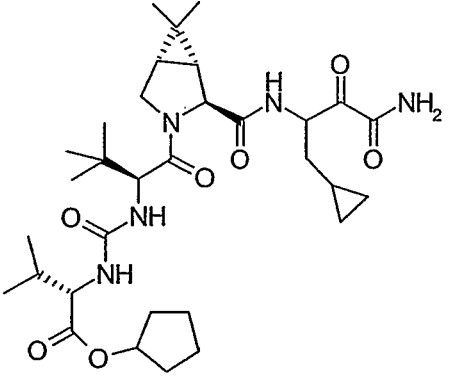
279

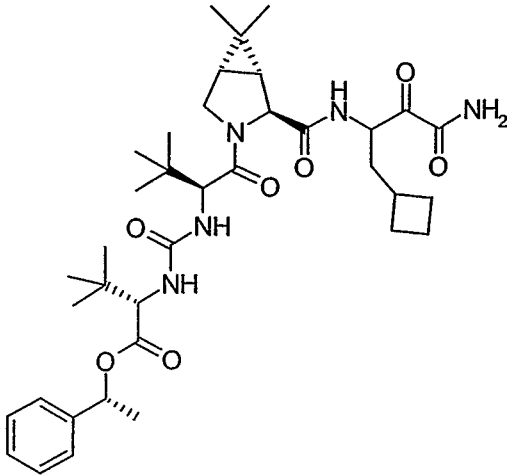
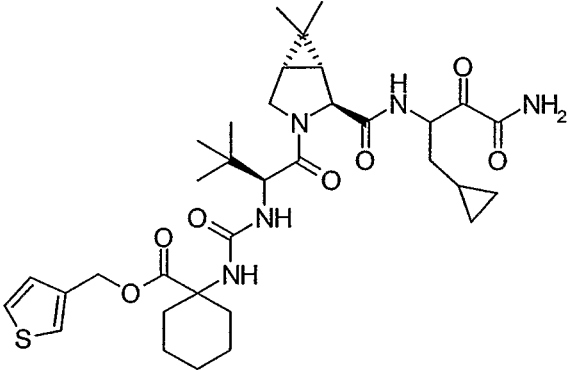
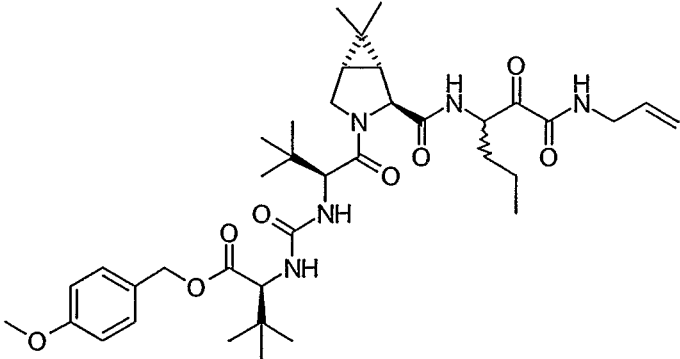
Cmpd #	Table 3: Esters	MW	Ki* Range
4416		648	A
4417		694	A
4418		666	A

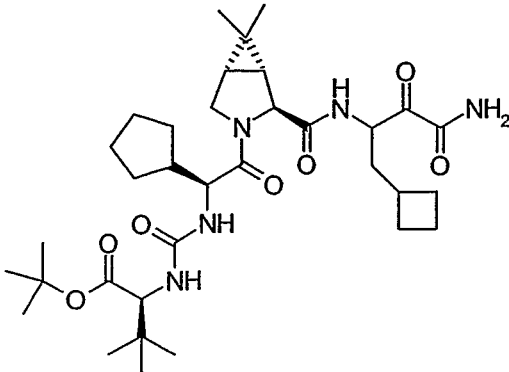
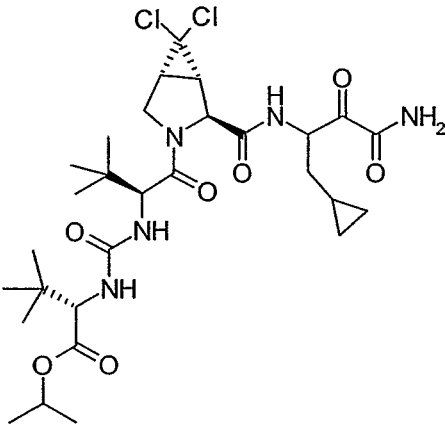
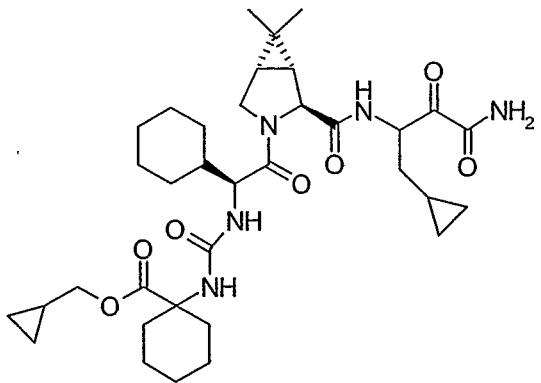
280

Cmpd #	Table 3: Esters	MW	Ki* Range
4419		660	A
4420		680	A
4421		658	A

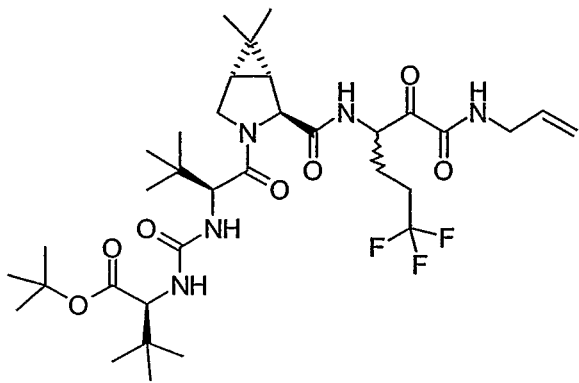
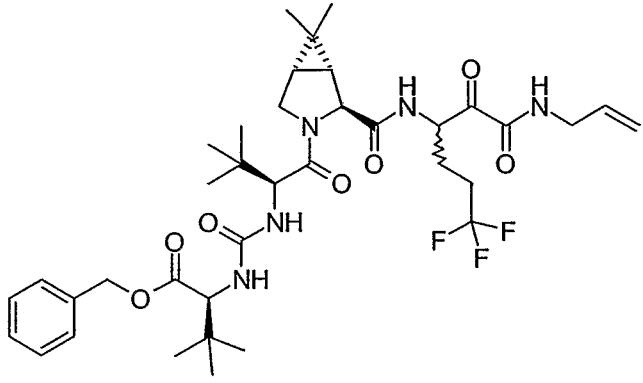
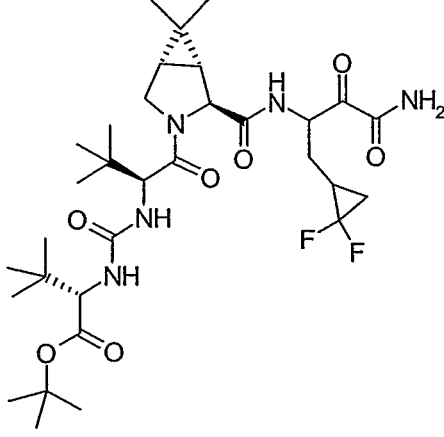
281

Cmpd #	Table 3: Esters	MW	Ki* Range
4422		646	A
4423		618	A
4424		618	A

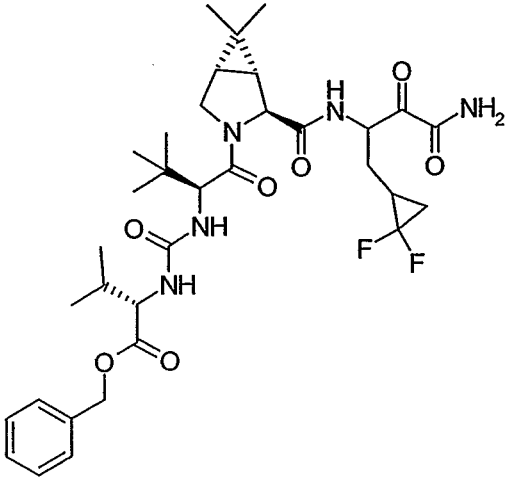
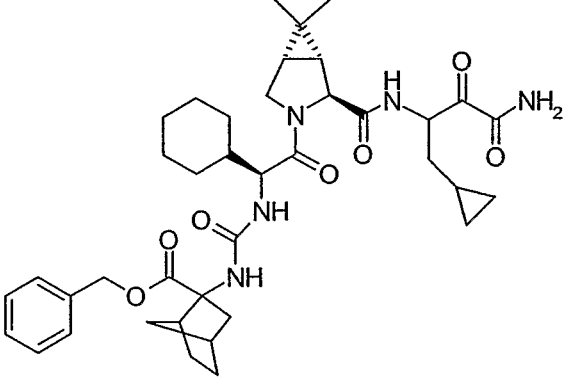
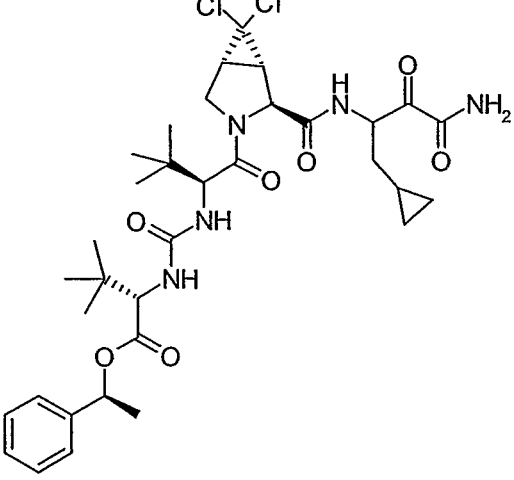
Cmpd #	Table 3: Esters	MW	Ki* Range
4425		682	A
4426		672	A
4427		712	A

Cmpd #	Table 3: Esters	MW	Ki* Range
4428		646	A
4429		647	A
4430		656	A

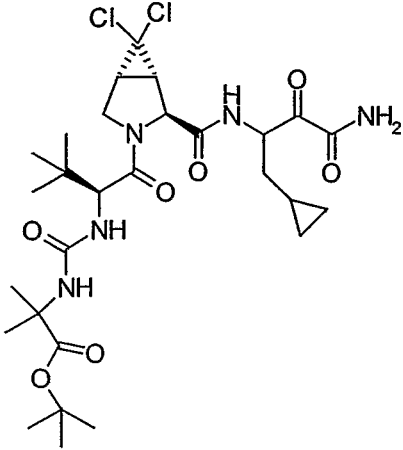
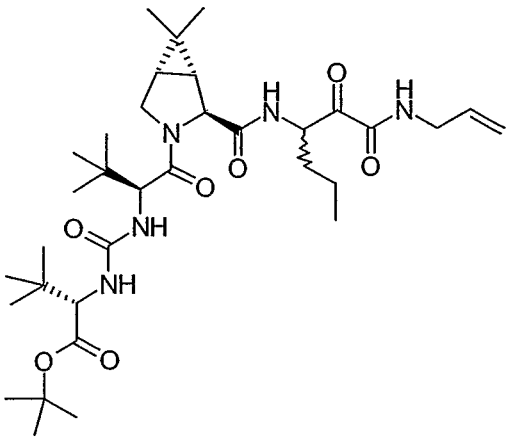
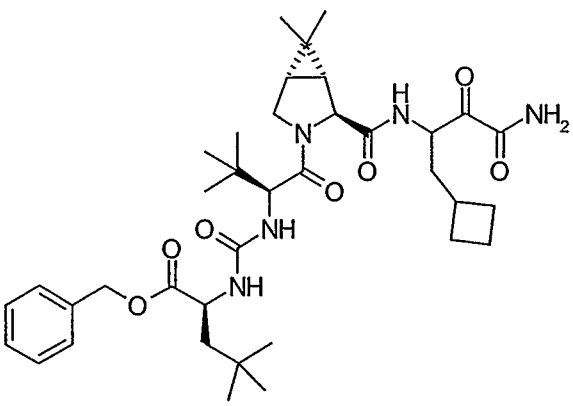
284

Cmpd #	Table 3: Esters	MW	Ki* Range
4431		702	A
4432		736	A
4433		656	A

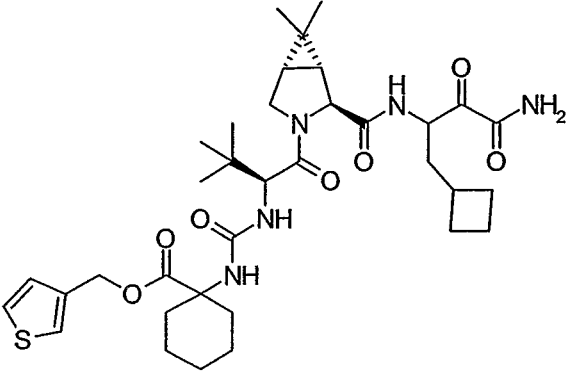
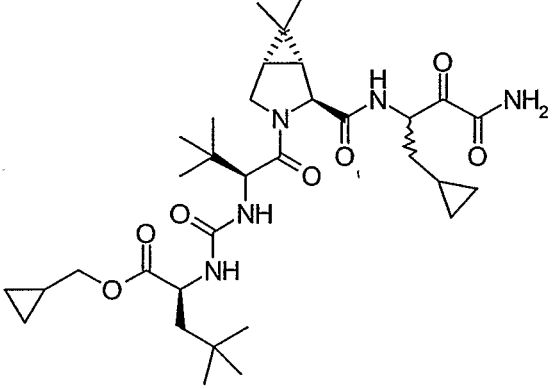
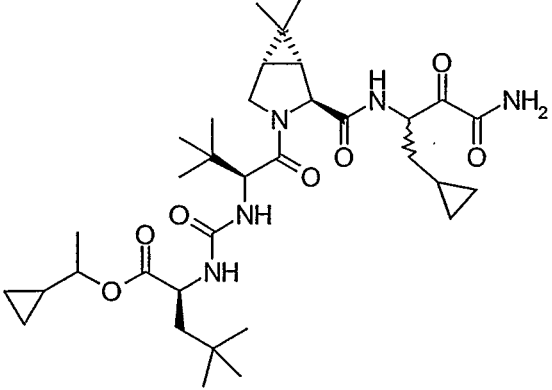
285

Cmpd #	Table 3: Esters	MW	Ki* Range
4434		676	A
4435		704	A
4436		709	A

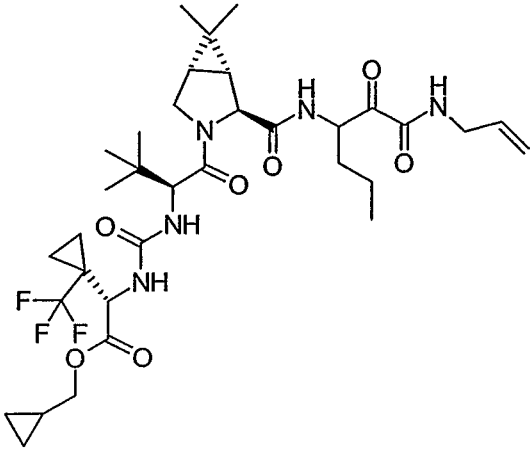
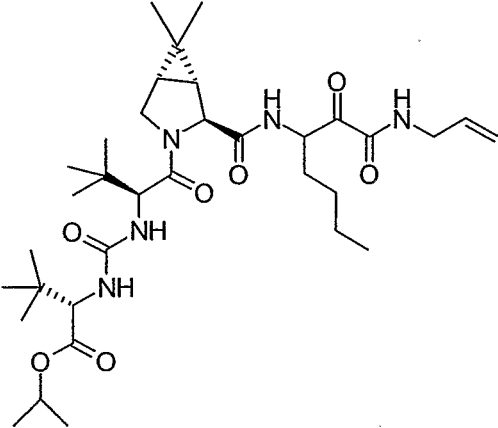
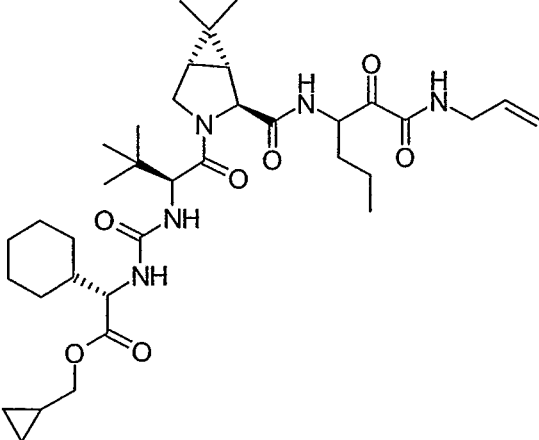
286

Cmpd #	Table 3: Esters	MW	Ki* Range
4437		633	A
4438		648	A
4439		682	A

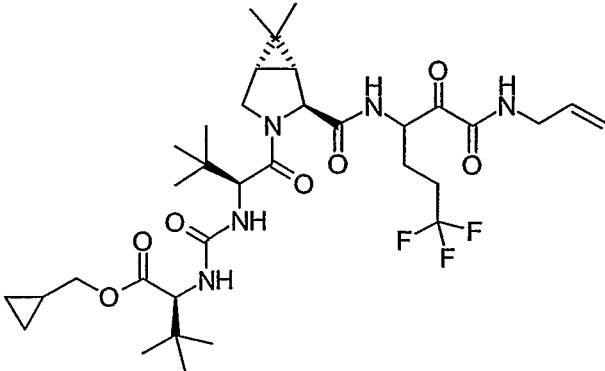
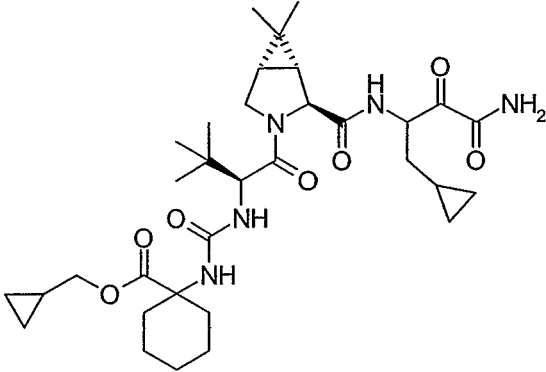
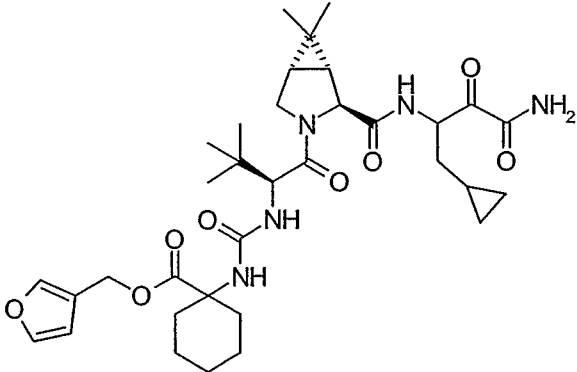
287

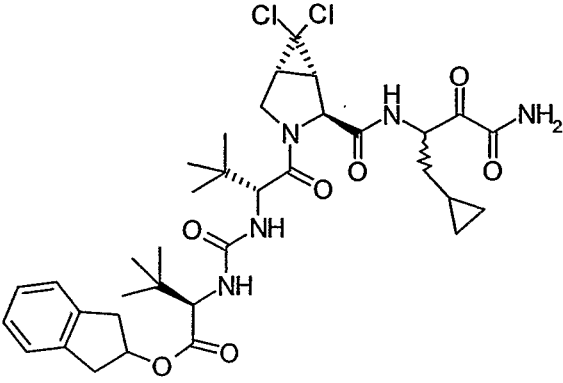
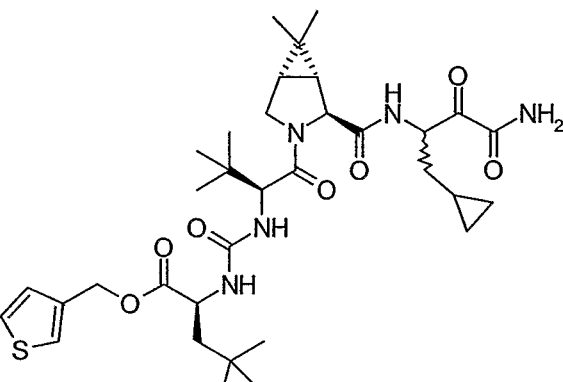
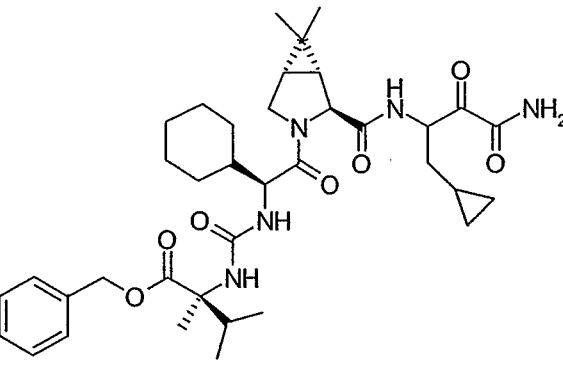
Cmpd #	Table 3: Esters	MW	Ki* Range
4440	 <chem>CC(C)[C@H](NC(=O)NCC1CCCC1C(=O)N)C(=O)NCC2CCCCC2C(=O)OCC3=CC=CS3</chem>	686	A
4441	 <chem>CC(C)[C@H](NC(=O)NCC1CCC1C(=O)N)C(=O)NCC2CCCCC2C(=O)OCC3CC3</chem>	632	A
4442	 <chem>CC(C)[C@H](NC(=O)NCC1CCC1C(=O)N)C(=O)NCC2CCCCC2C(=O)OC(C)C</chem>	646	A

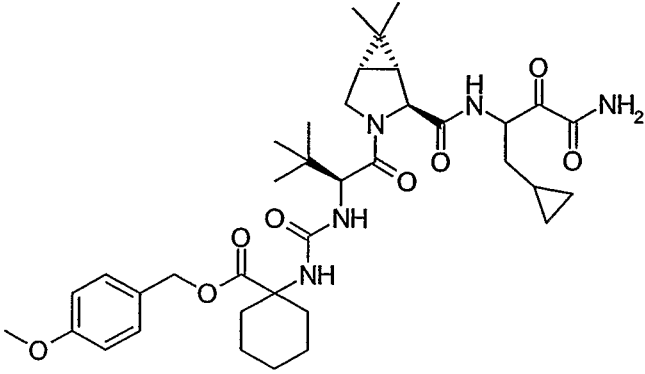
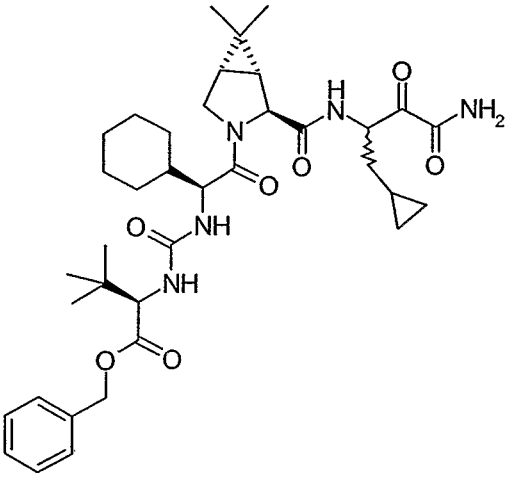
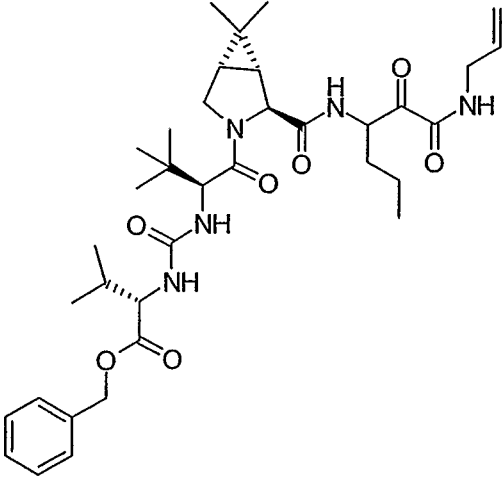
288

Cmpd #	Table 3: Esters	MW	Ki* Range
4443		698	A
4444		648	A
4445		672	A

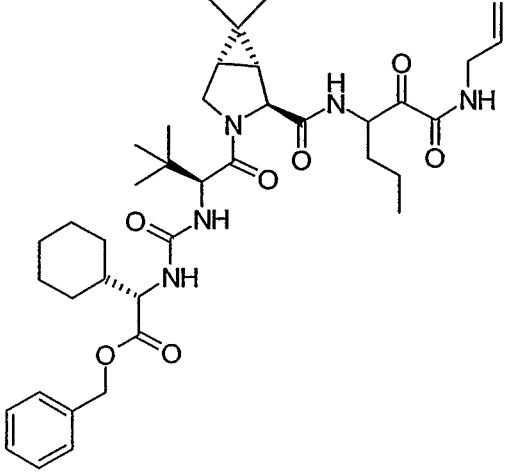
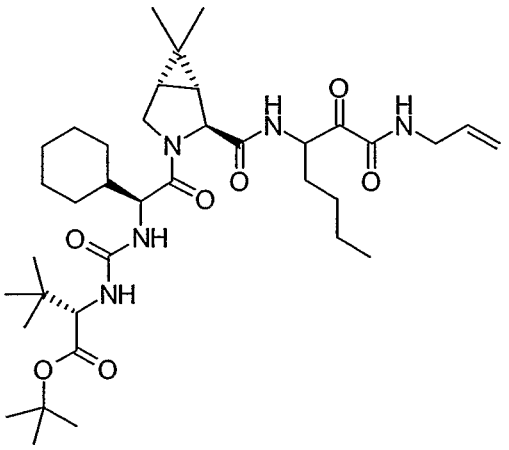
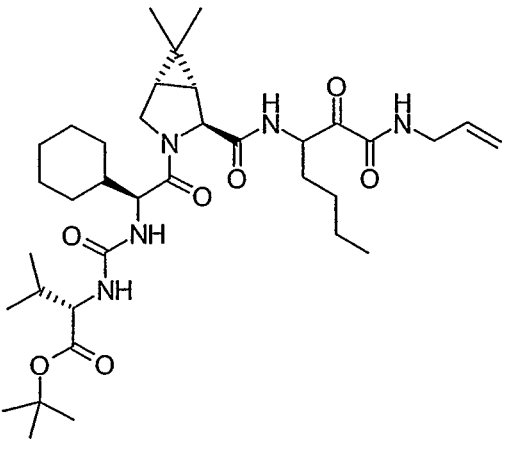
289

Cmpd #	Table 3: Esters	MW	Ki* Range
4446		700	A
4447		630	A
4448		656	A

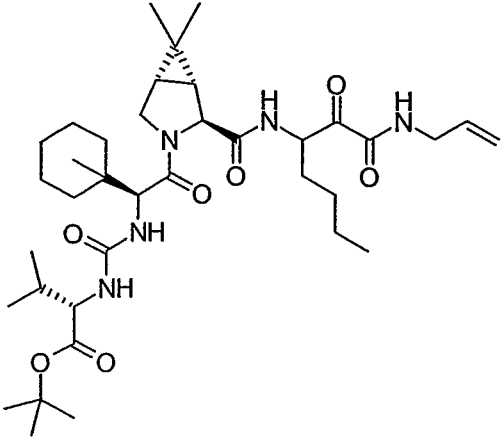
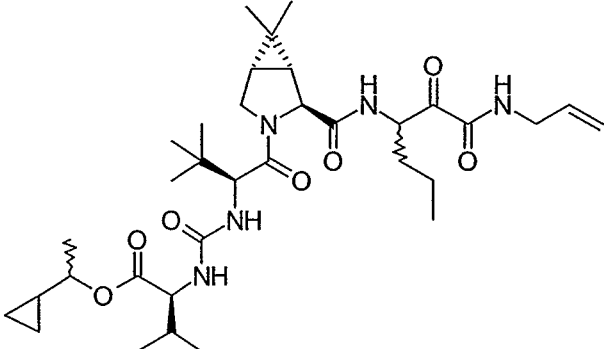
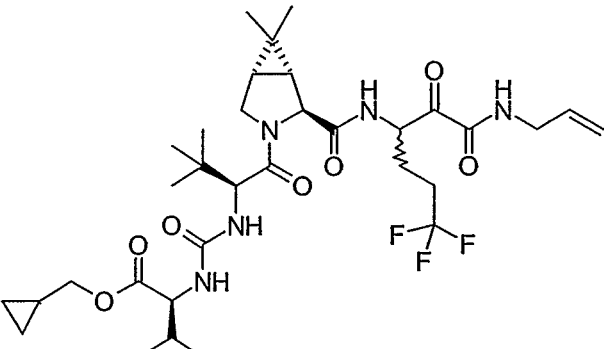
Cmpd #	Table 3: Esters	MW	Ki* Range
4449		721	A
4450		674	A
4451		680	A

Cmpd #	Table 3: Esters	MW	Ki* Range
4452		696	A
4453		680	A
4454		668	A

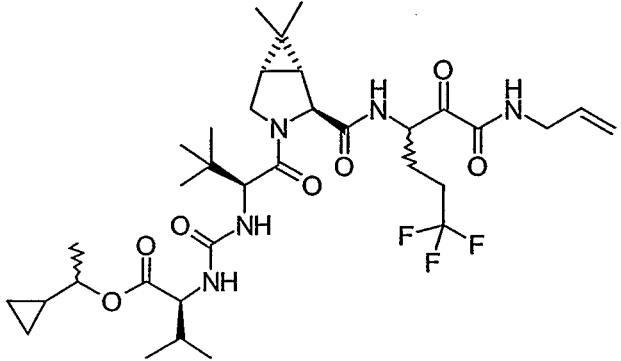
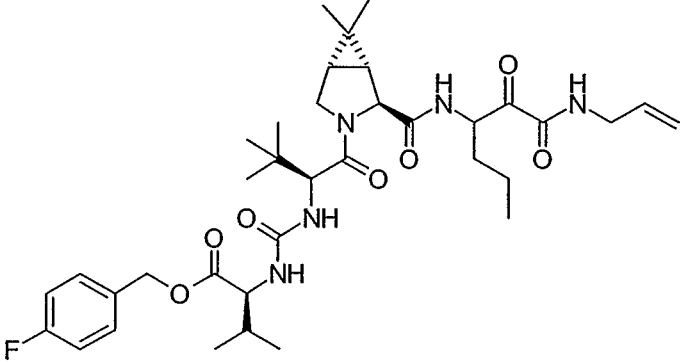
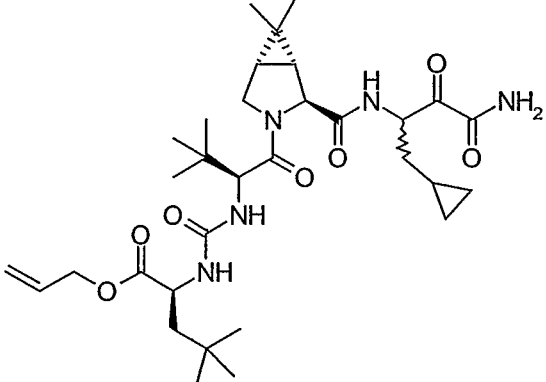
292

Cmpd #	Table 3: Esters	MW	Ki* Range
4455		708	A
4456		688	A
4457		674	A

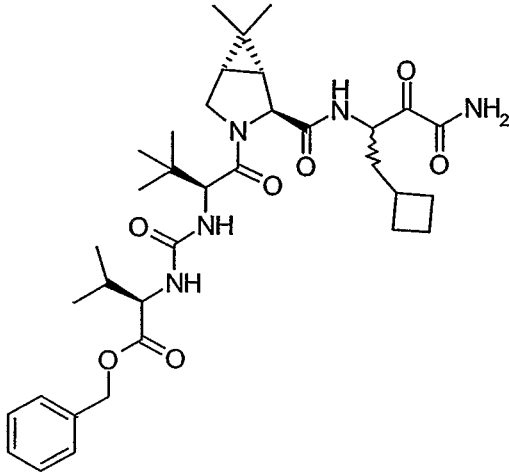
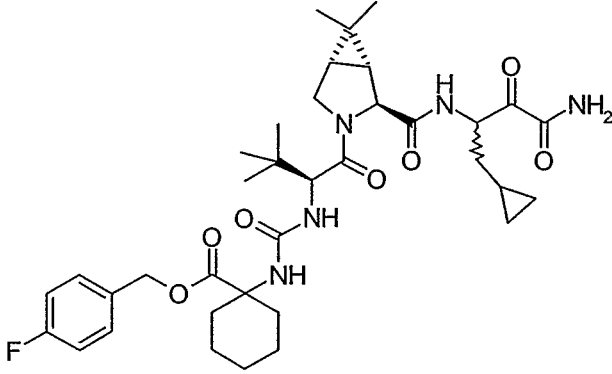
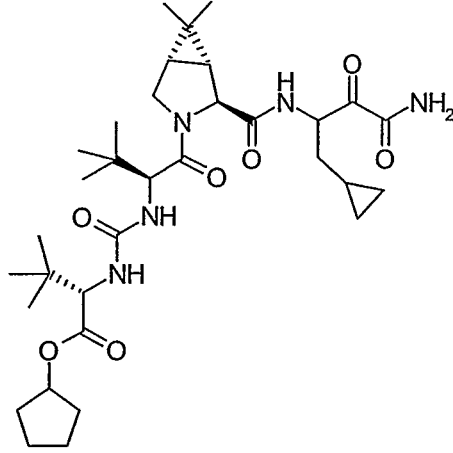
293

Cmpd #	Table 3: Esters	MW	Ki* Range
4458		688	A
4459		646	A
4460		686	A

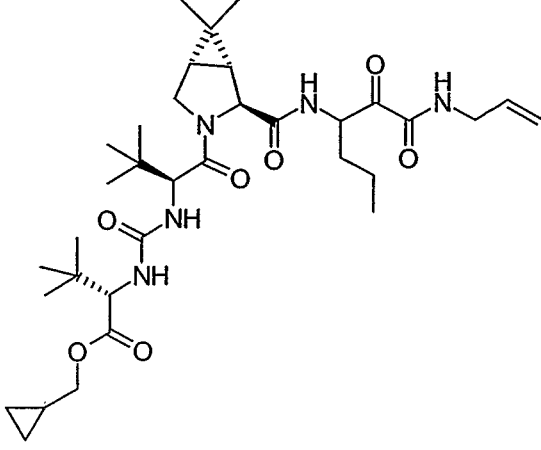
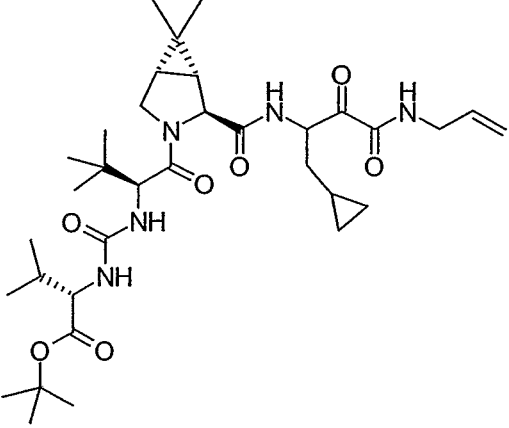
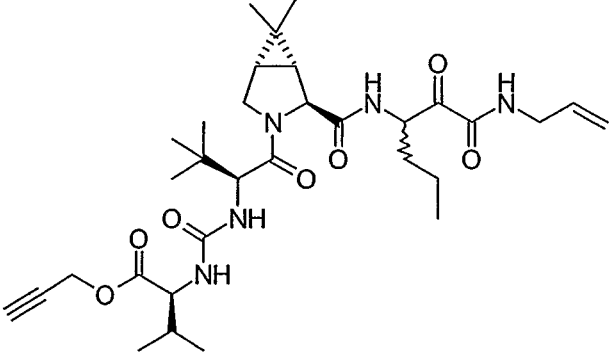
294

Cmpd #	Table 3: Esters	MW	Ki* Range
4461		700	A
4462		686	A
4463		618	A

295

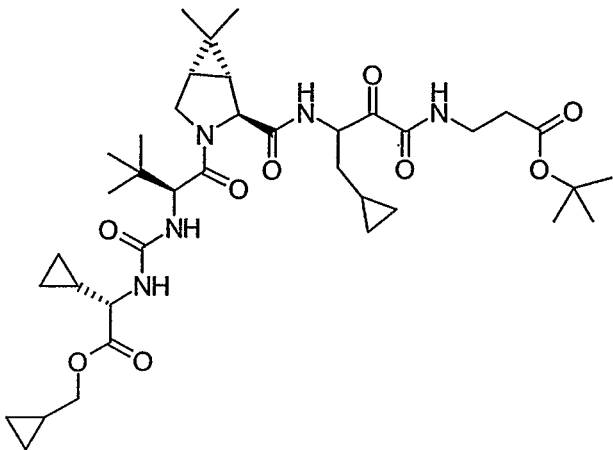
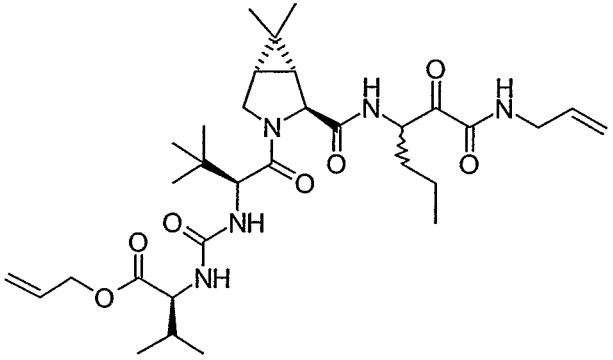
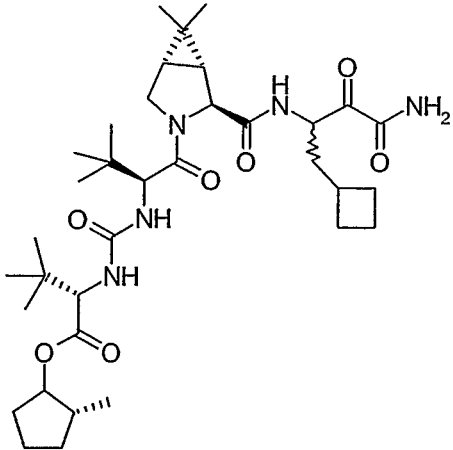
Cmpd #	Table 3: Esters	MW	Ki* Range
4464		654	A
4465		684	A
4466		632	A

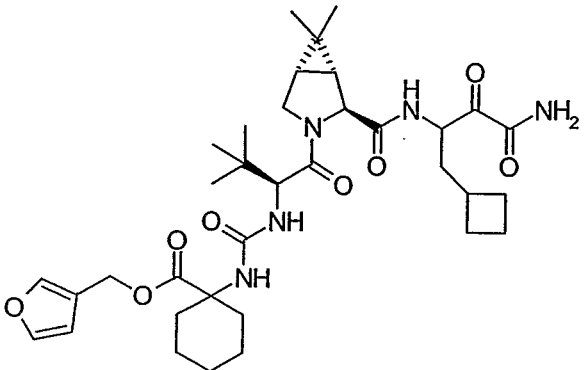
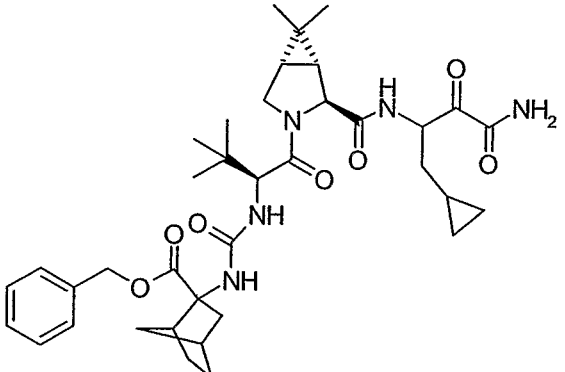
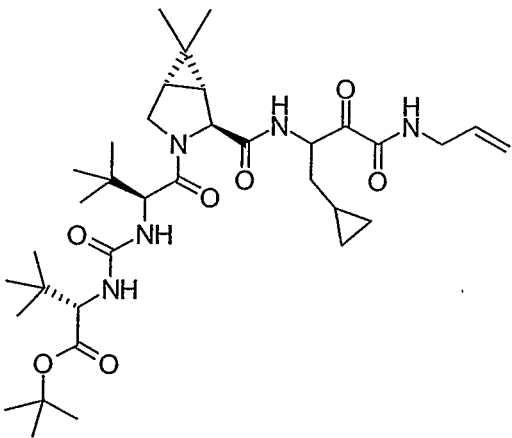
296

Cmpd #	Table 3: Esters	MW	Ki* Range
4467		646	A
4468		646	A
4469		616	A

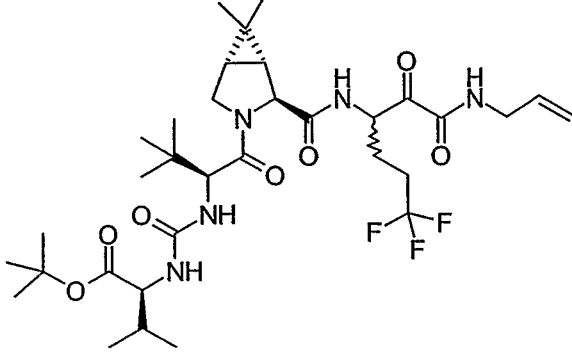
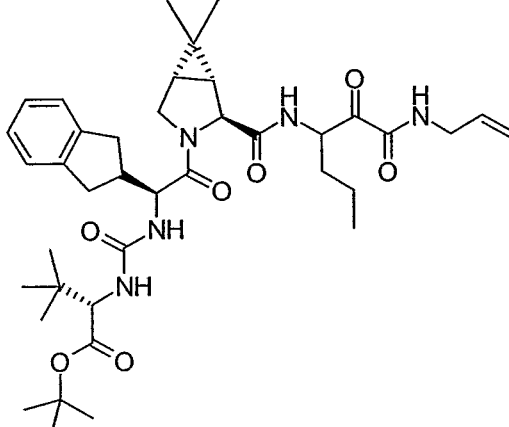
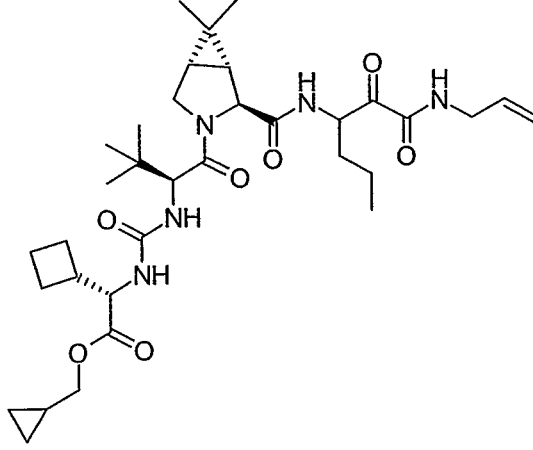
Cmpd #	Table 3: Esters	MW	Ki* Range
4470		678	A
4471		654	A
4472		690	A

298

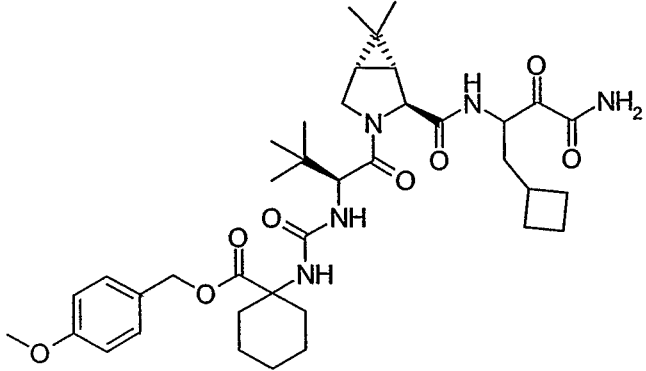
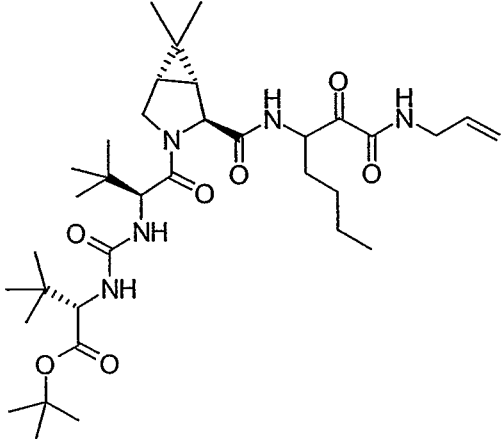
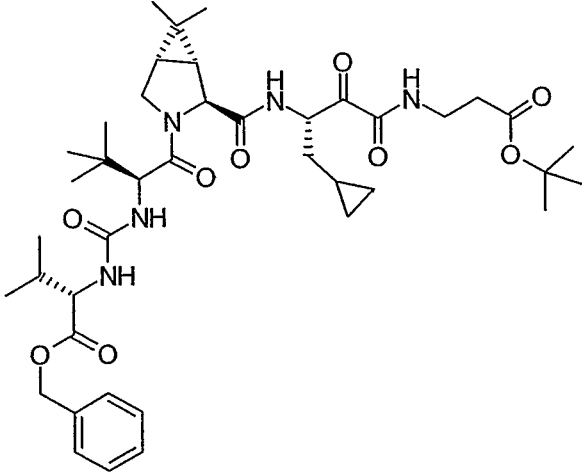
Cmpd #	Table 3: Esters	MW	Ki* Range
4473		730	A
4474		618	A
4475		660	A

Cmpd #	Table 3: Esters	MW	Ki* Range
4476		670	A
4477		678	A
4478		660	A

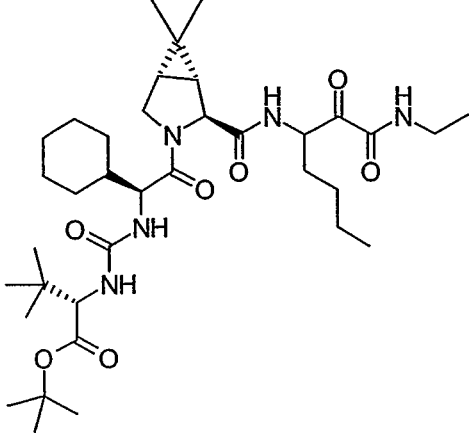
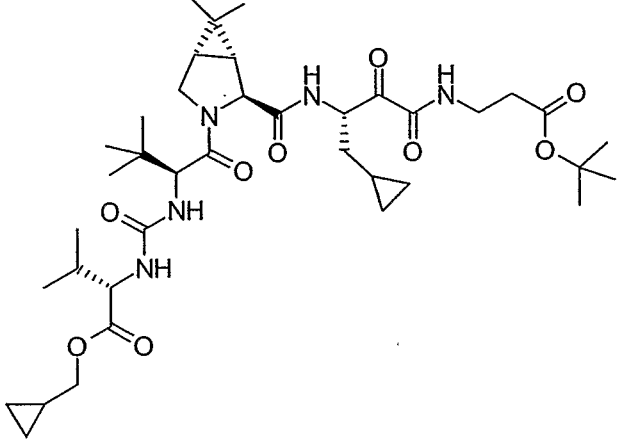
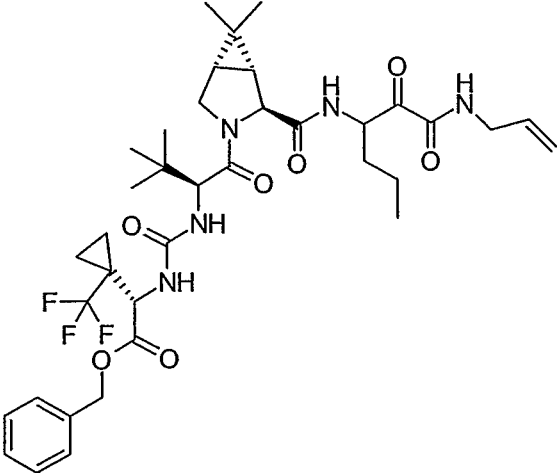
300

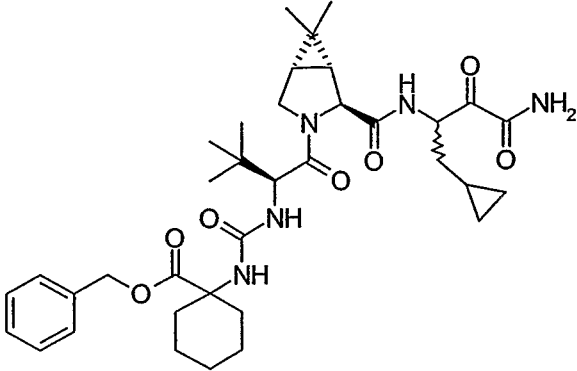
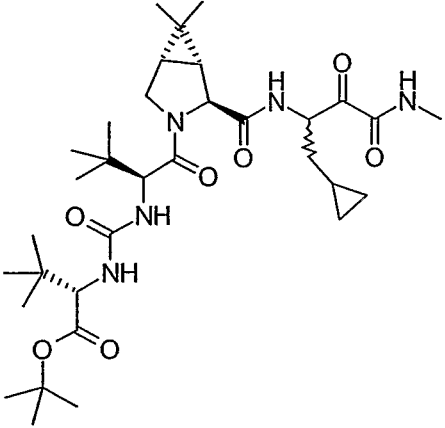
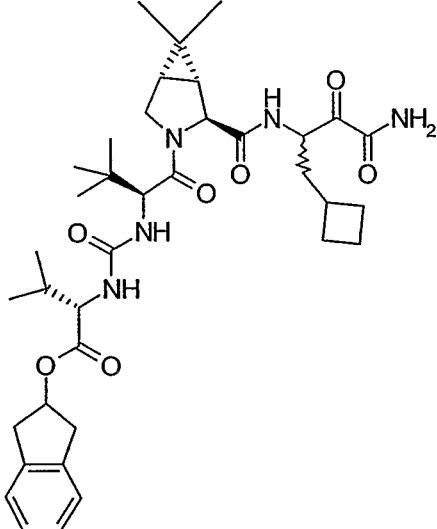
Cmpd #	Table 3: Esters	MW	Ki* Range
4479		688	A
4480		708	A
4481		644	A

301

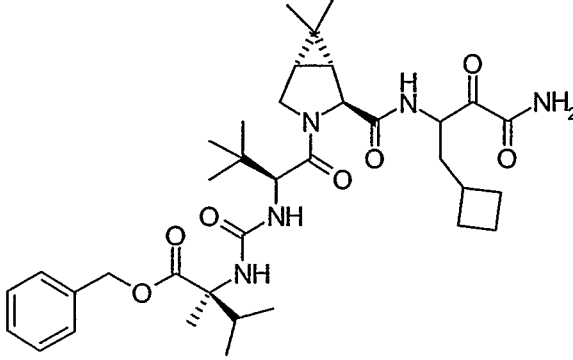
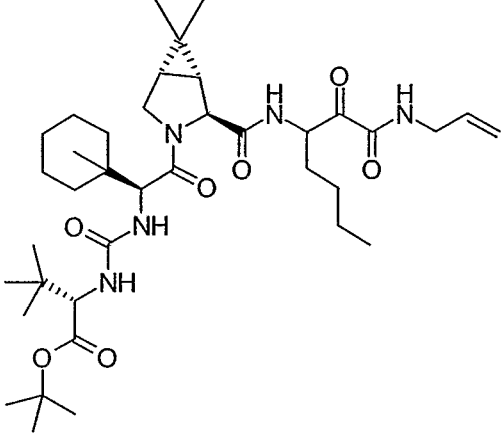
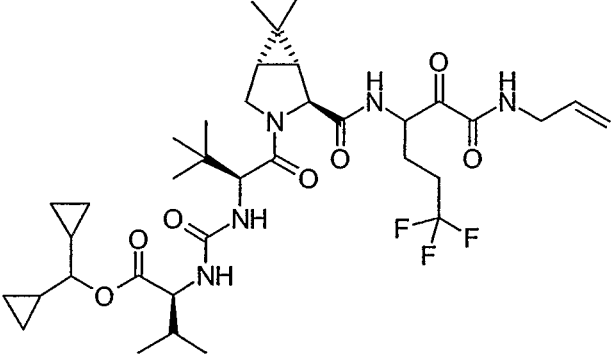
Cmpd #	Table 3: Esters	MW	Ki* Range
4482		710	A
4483		662	A
4484		768	A

302

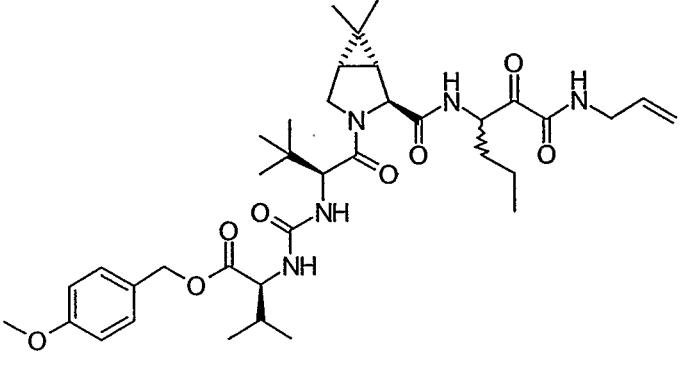
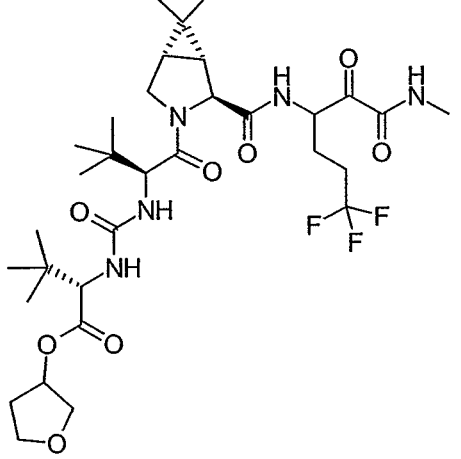
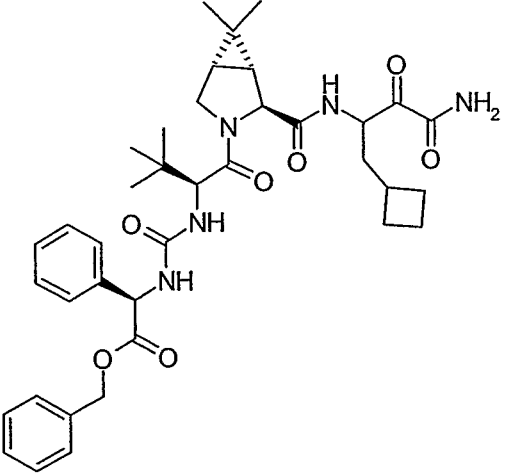
Cmpd #	Table 3: Esters	MW	Ki* Range
4485		676	A
4486		732	A
4487		734	A

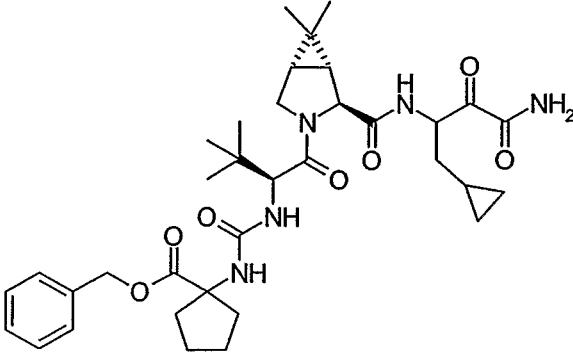
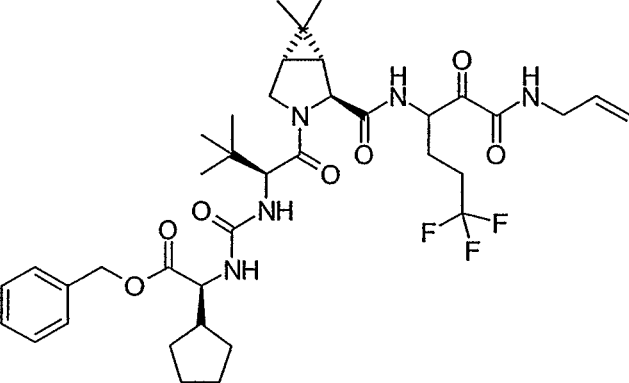
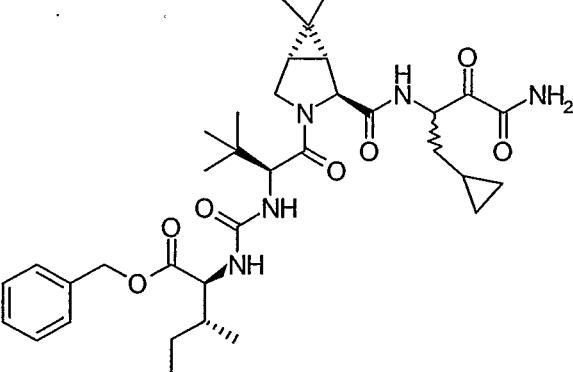
Cmpd #	Table 3: Esters	MW	Ki* Range
4488		666	A
4489		634	A
4490		680	A

304

Cmpd #	Table 3: Esters	MW	Ki* Range
4491		668	A
4492		702	A
4493		726	A

305

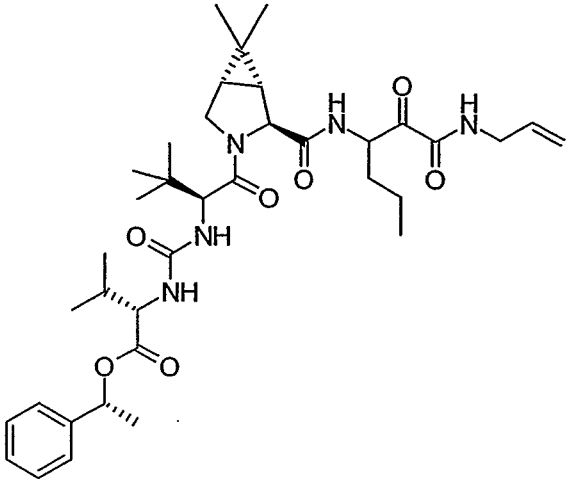
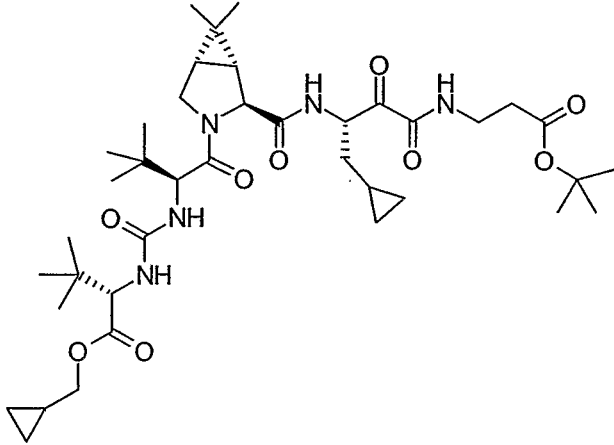
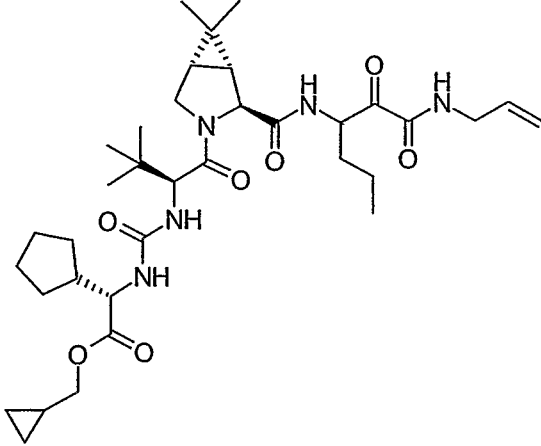
Cmpd #	Table 3: Esters	MW	Ki* Range
4494		698	A
4495		690	A
4496		688	A

Cmpd #	Table 3: Esters	MW	Ki* Range
4497		652	A
4498		748	A
4499		654	A

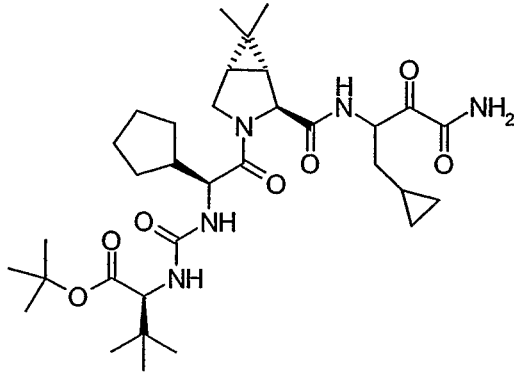
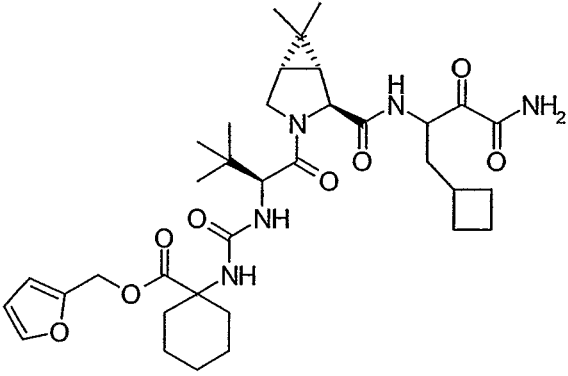
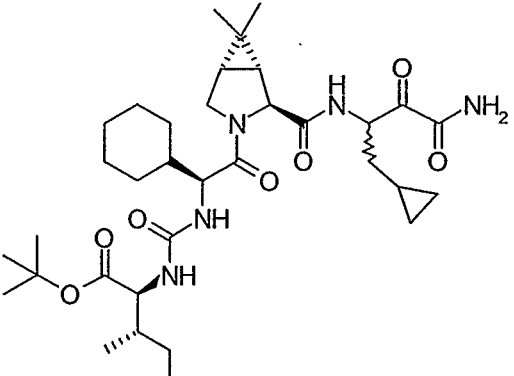
307

Cmpd #	Table 3: Esters	MW	Ki* Range
4500		654	A
4501		616	A
4502		692	A

308

Cmpd #	Table 3: Esters	MW	Ki* Range
4503		682	A
4504		746	A
4505		658	A

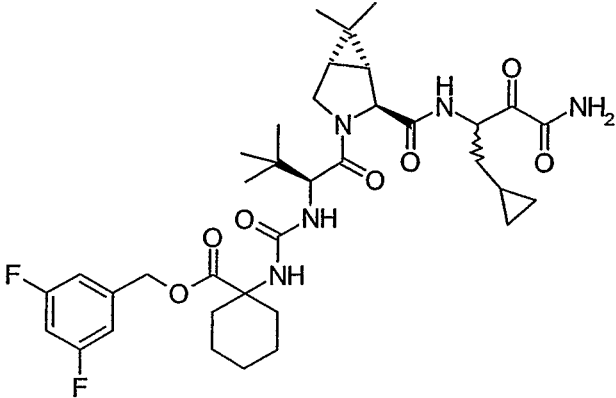
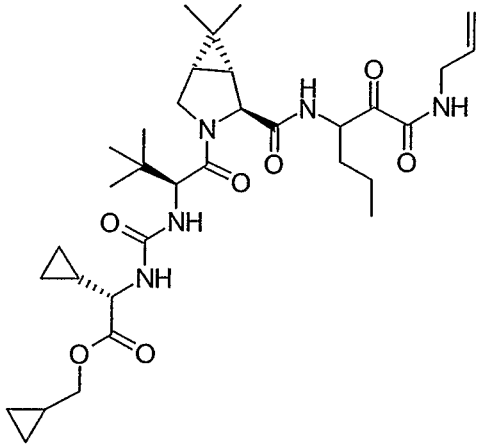
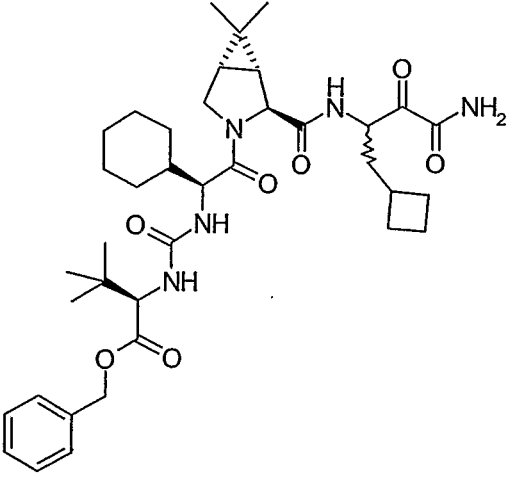
309

Cmpd #	Table 3: Esters	MW	Ki* Range
4506		632	A
4507		670	A
4508		646	A

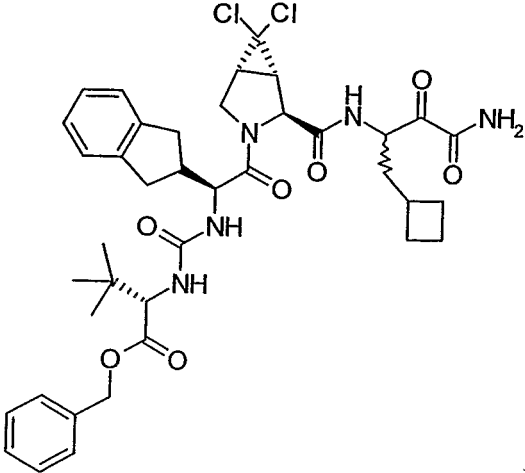
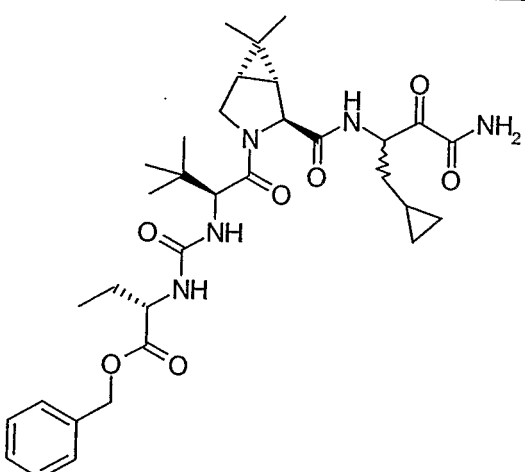
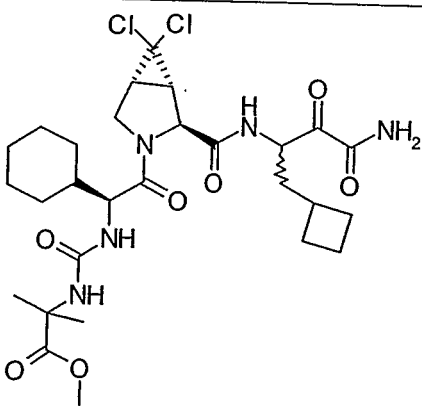
310

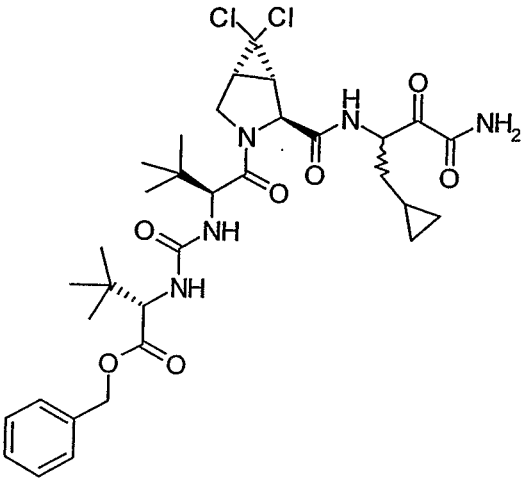
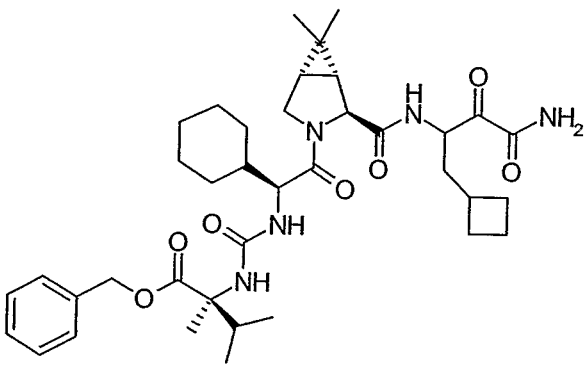
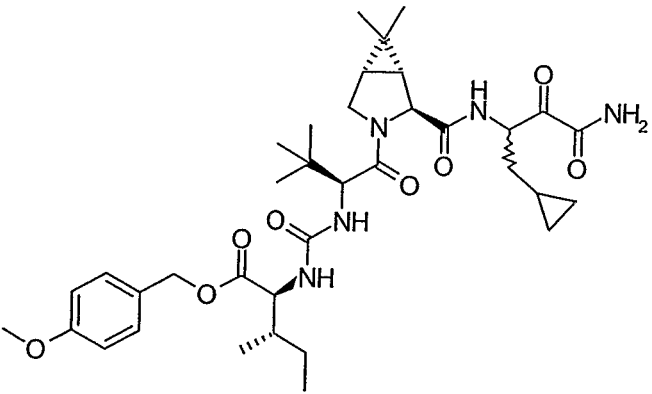
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311

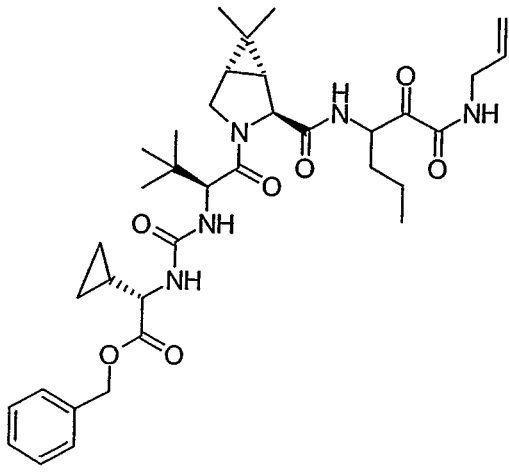
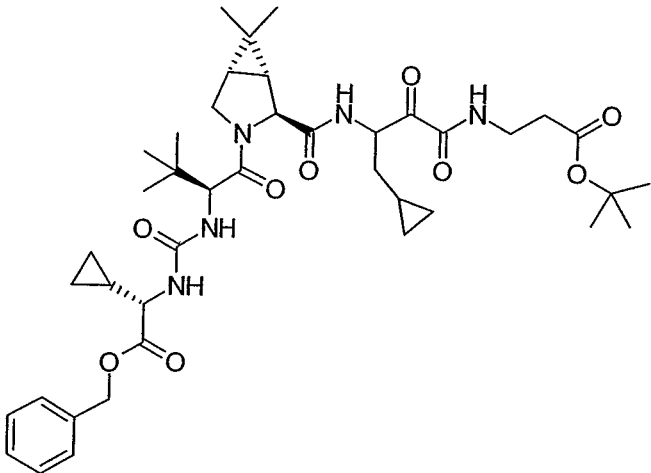
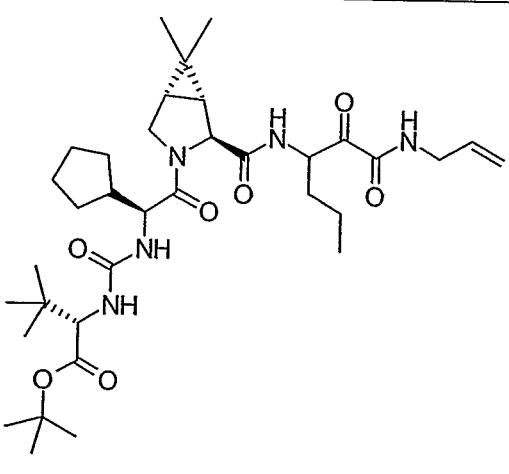
Cmpd #	Table 3: Esters	MW	Ki* Range
4512		702	A
4513		630	A
4514		694	A

312

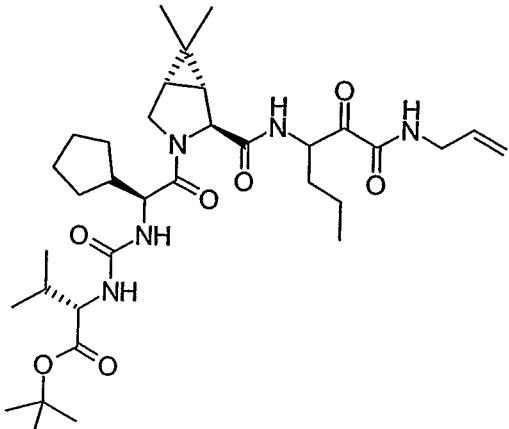
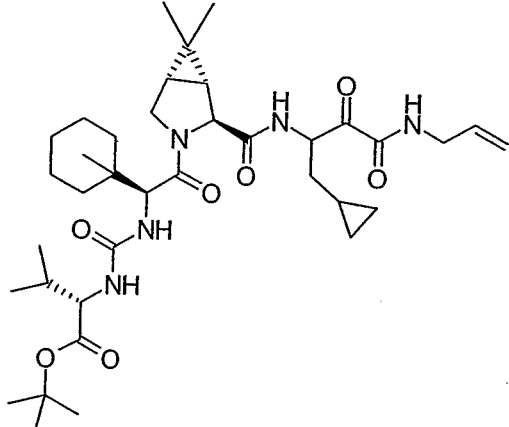
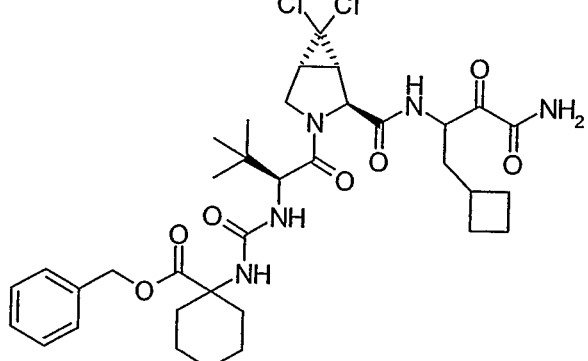
Cmpd #	Table 3: Esters	MW	Ki* Range
4515		769	A
4516		626	A
4517		631	A

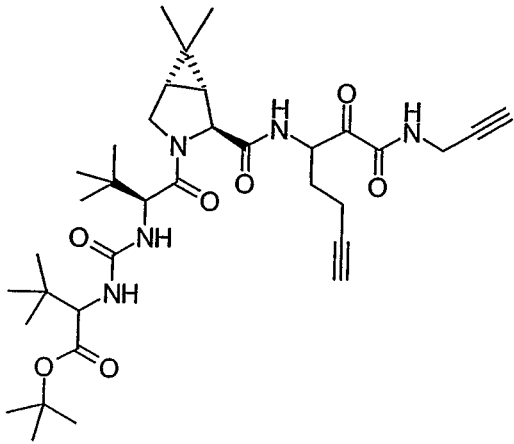
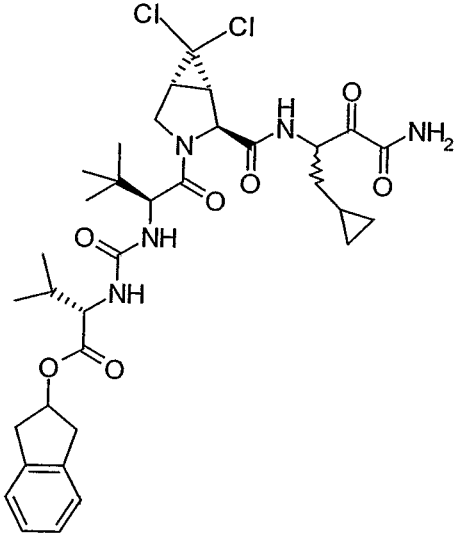
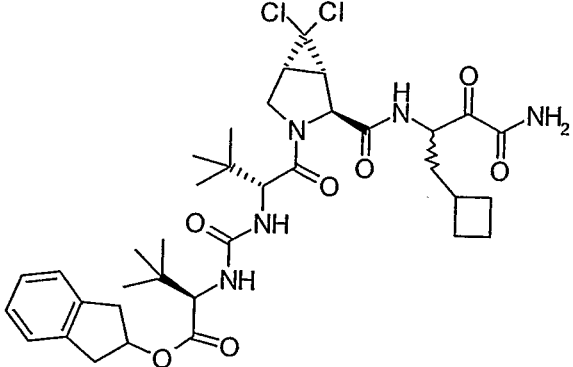
Cmpd #	Table 3: Esters	MW	Ki* Range
4518		695	A
4519		694	A
4520		684	A

314

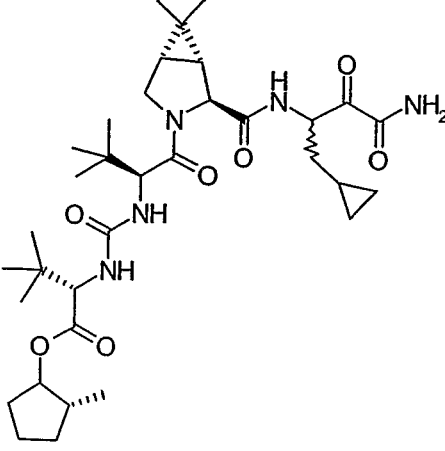
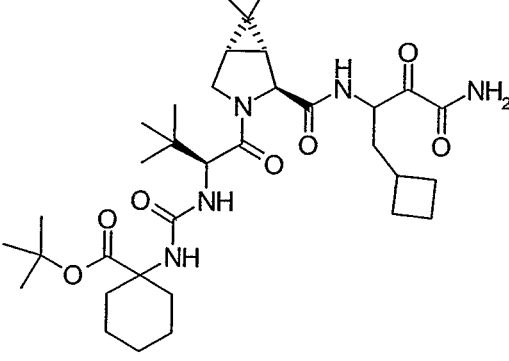
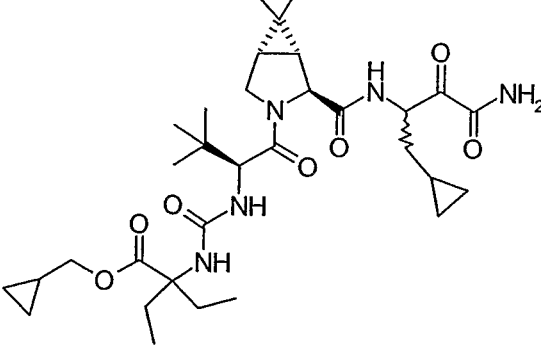
Cmpd #	Table 3: Esters	MW	Ki* Range
4522		666	A
4523		766	A
4524		660	A

315

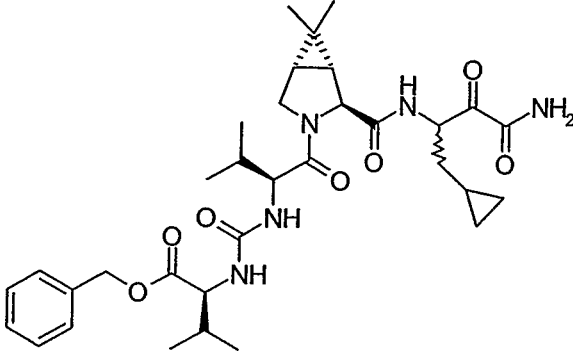
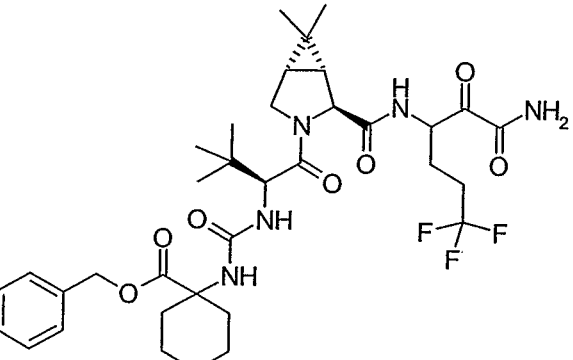
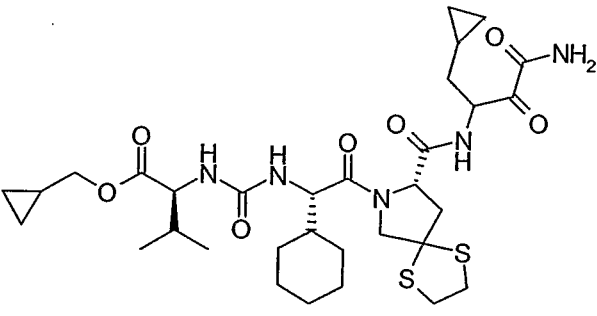
Cmpd #	Table 3: Esters	MW	Ki* Range
4525		646	A
4526		686	A
4527		721	A

Cmpd #	Table 3: Esters	MW	Ki* Range
4528		656	A
4529		707	A
4530		735	A

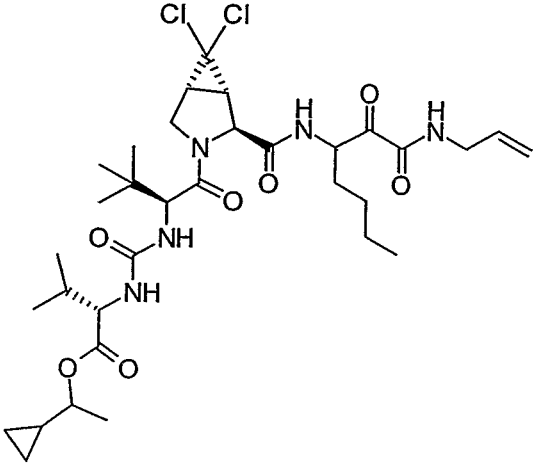
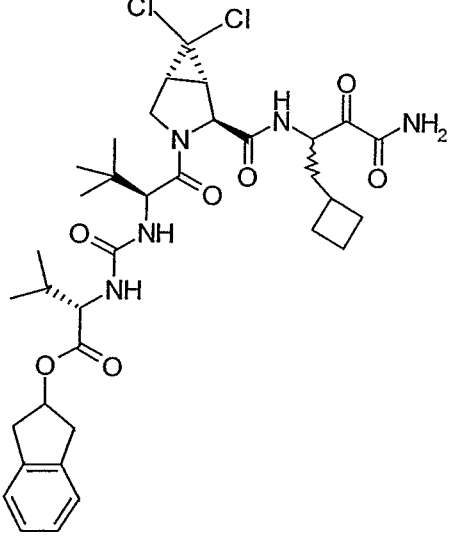
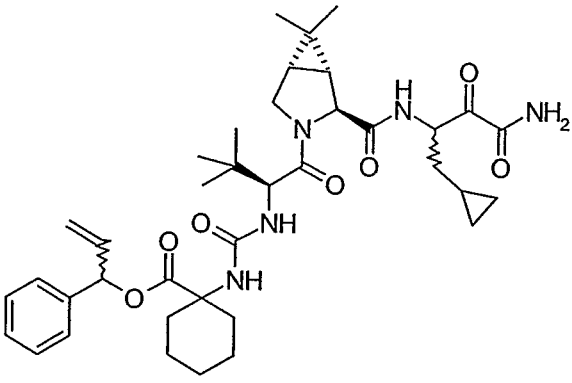
317

Cmpd #	Table 3: Esters	MW	Ki* Range
4531		646	A
4532		646	A
4533		618	A

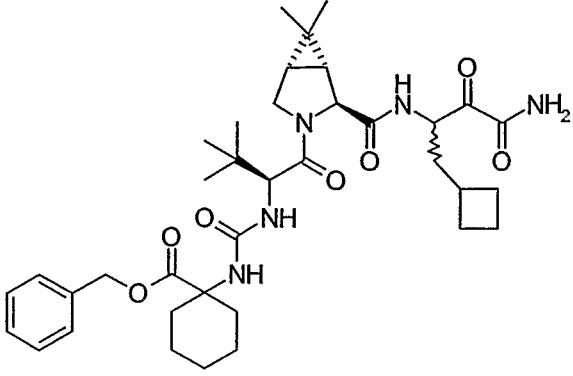
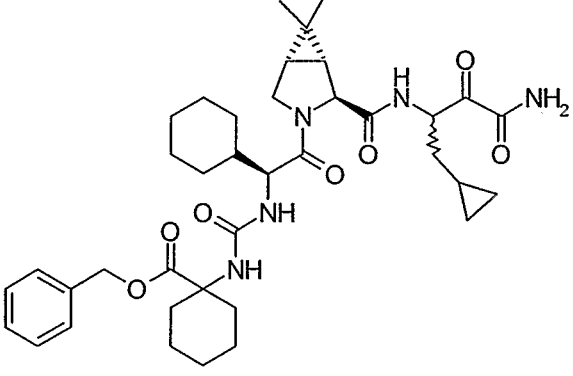
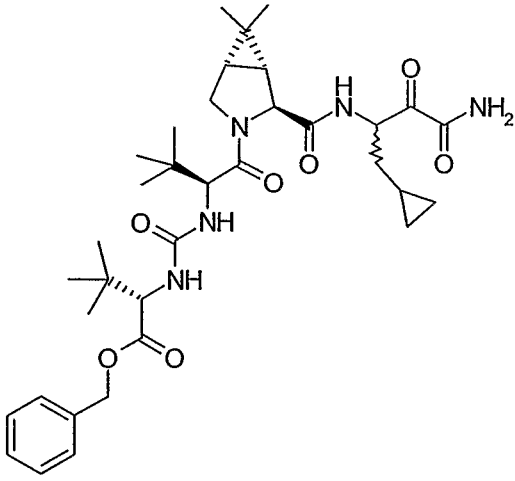
318

Cmpd #	Table 3: Esters	MW	Ki* Range
4534		626	A
4535		708	A
4536		680	A

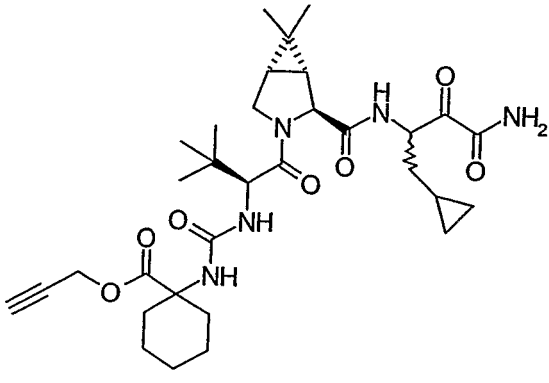
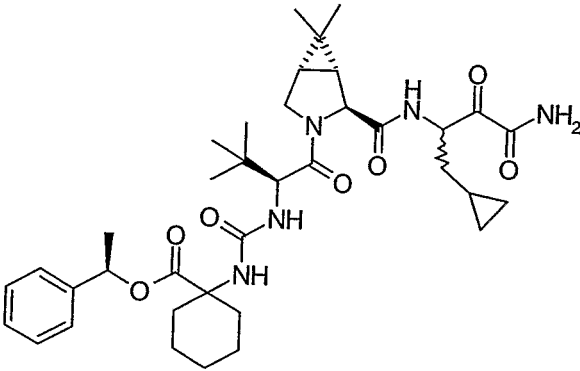
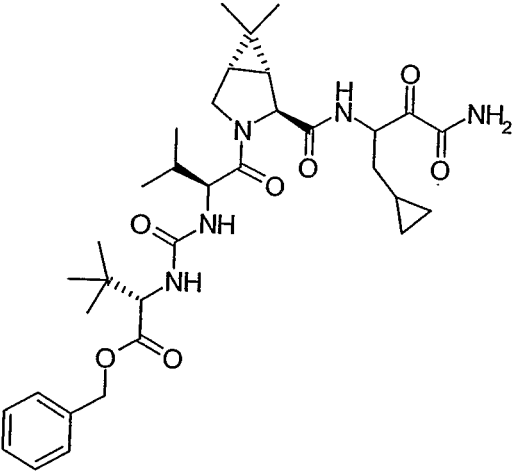
319

Cmpd #	Table 3: Esters	MW	Ki* Range
4537		701	A
4538		721	A
4539		692	B

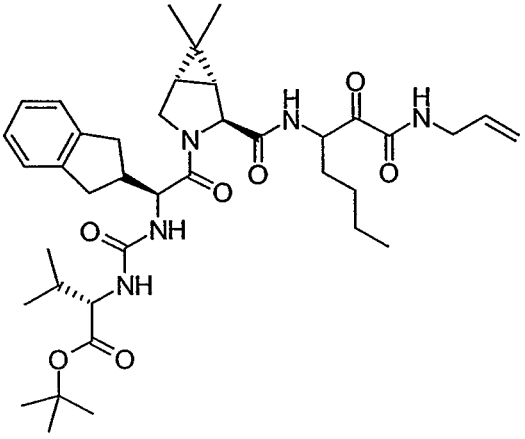
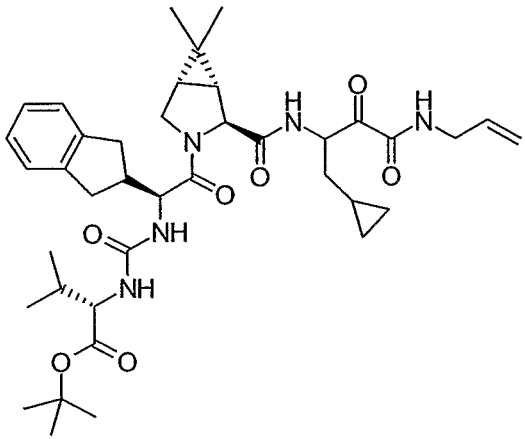
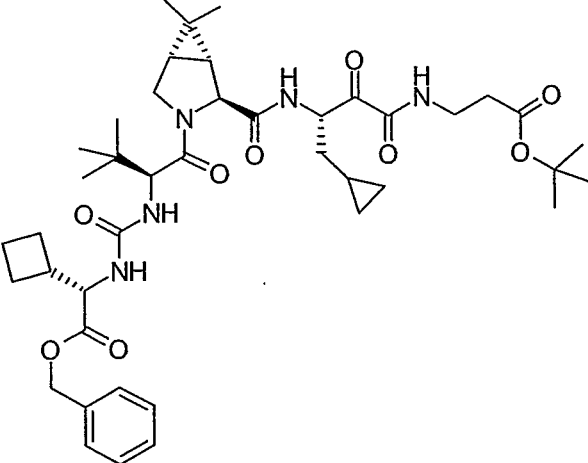
320

Cmpd #	Table 3: Esters	MW	Ki* Range
4540		680	B
4541		692	B
4542		654	B

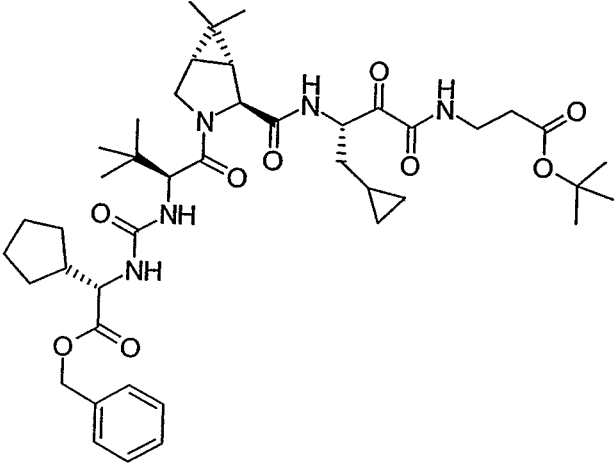
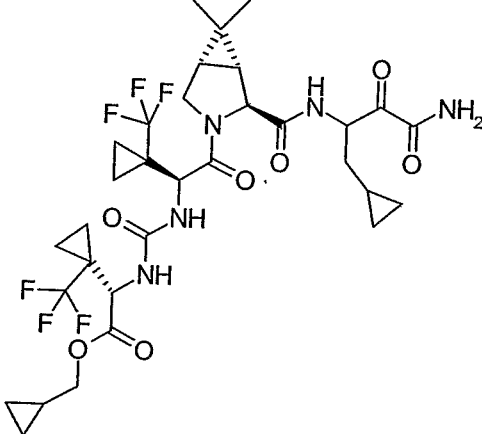
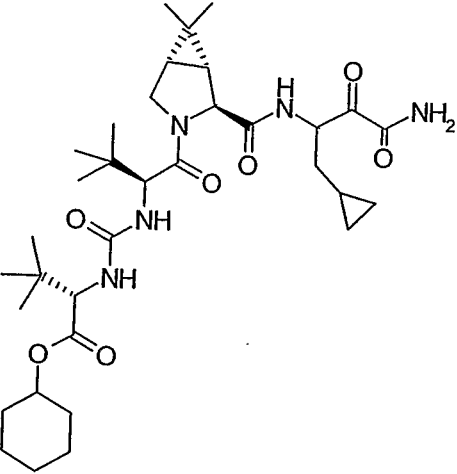
321

Cmpd #	Table 3: Esters	MW	Ki* Range
4543		614	B
4544		680	B
4545		640	B

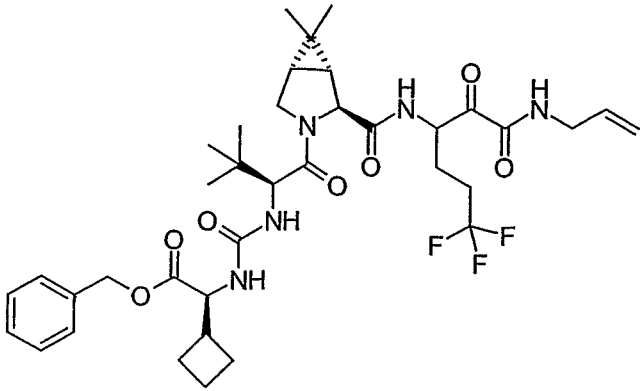
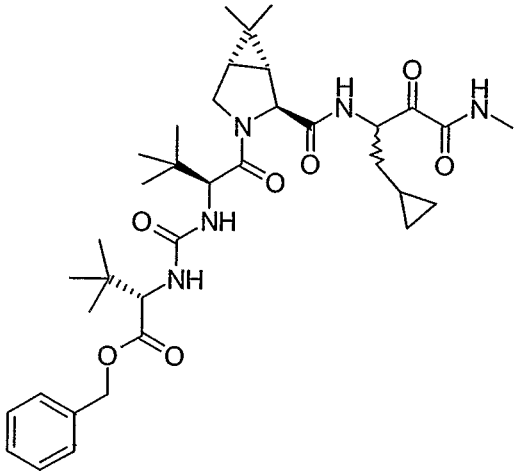
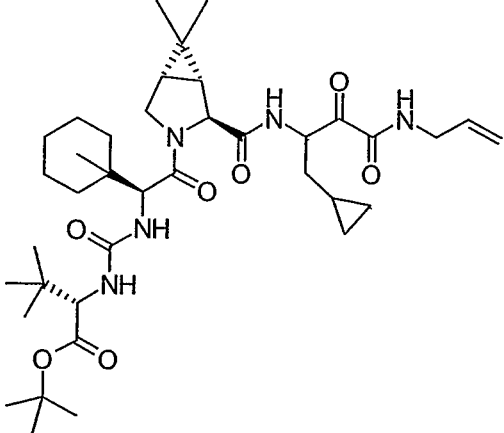
322

Cmpd #	Table 3: Esters	MW	Ki* Range
4546		708	B
4547		706	B
4548		780	B

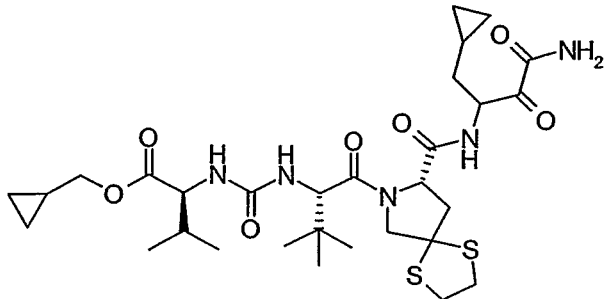
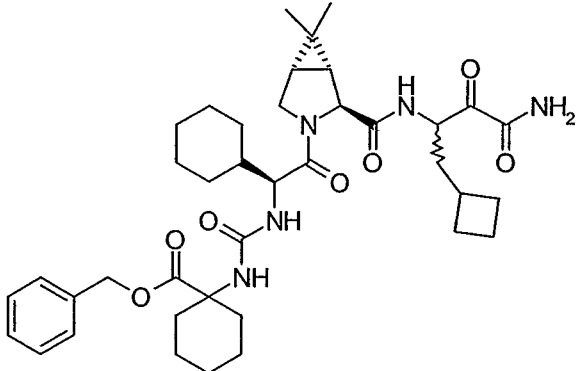
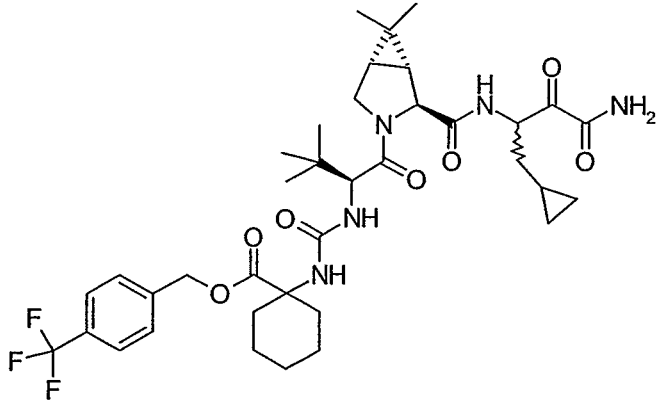
323

Cmpd #	Table 3: Esters	MW	Ki* Range
4549		794	B
4550		722	B
4551		646	B

324

Cmpd #	Table 3: Esters	MW	Ki* Range
4552		734	B
4553		668	B
4554		700	B

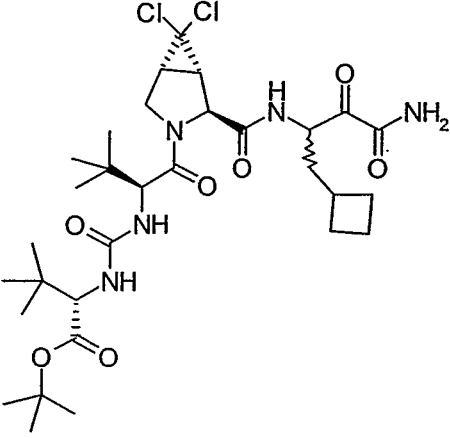
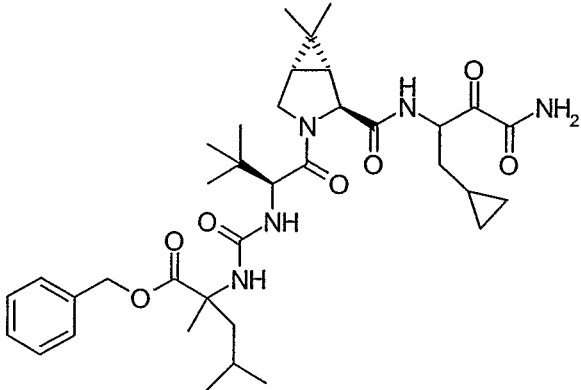
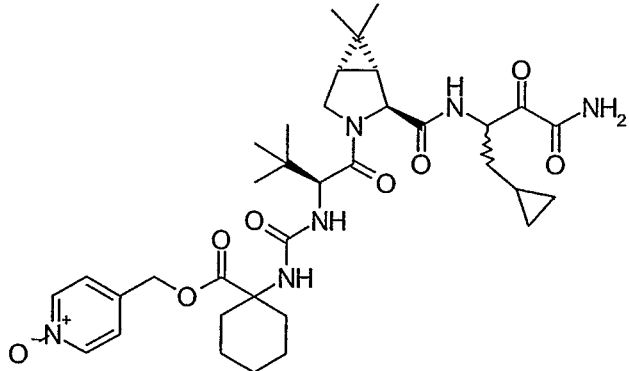
325

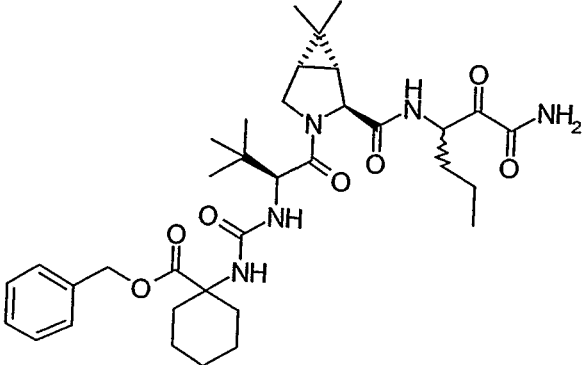
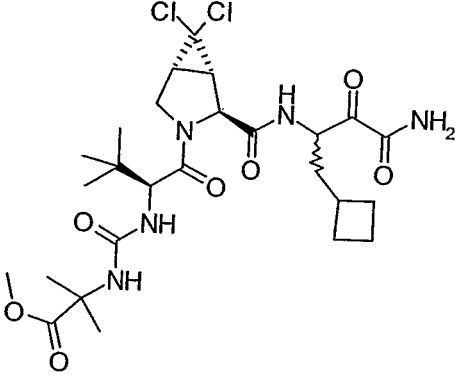
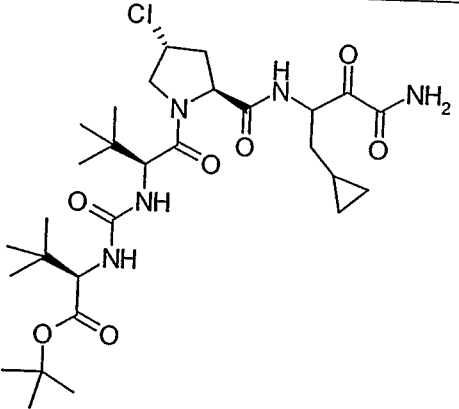
Cmpd #	Table 3: Esters	MW	Ki* Range
4555		654	B
4556		706	B
4557		734	B

326

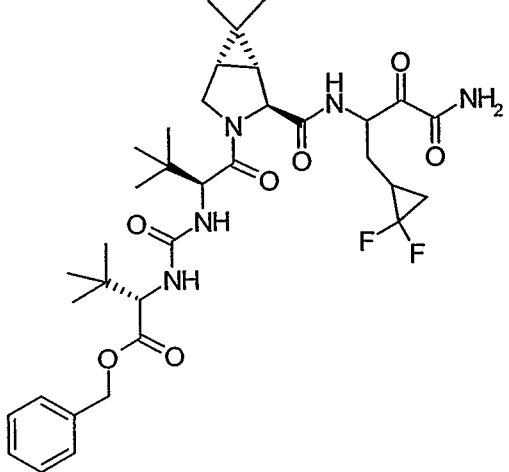
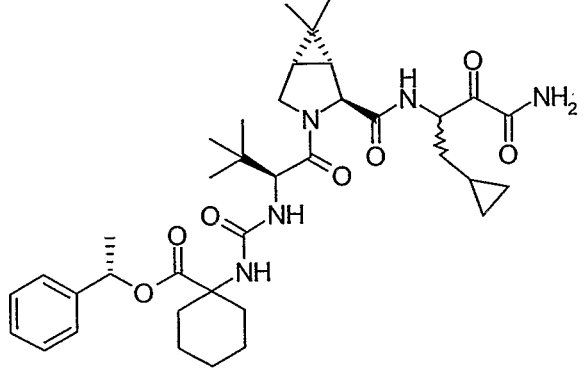
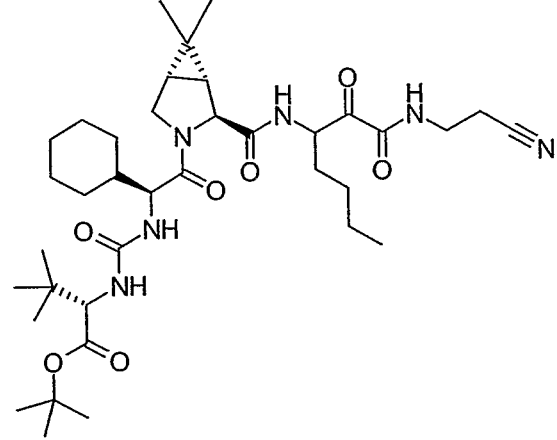
[illegible]

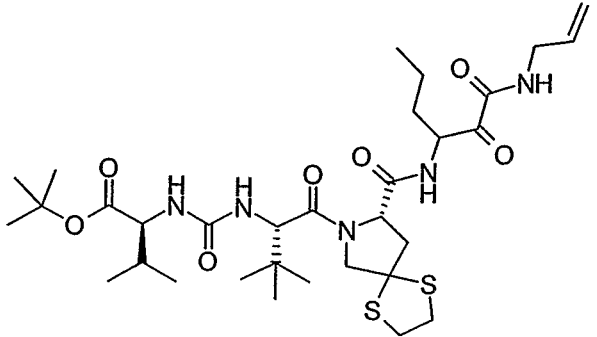
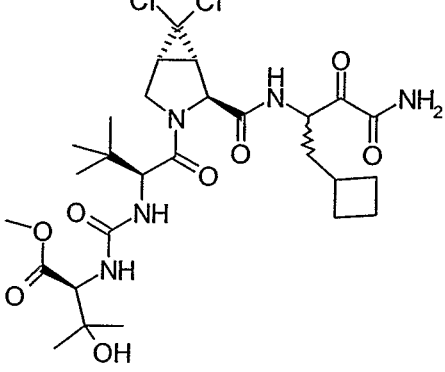
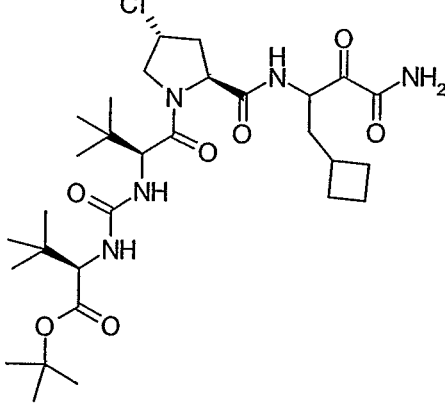
327

Cmpd #	Table 3: Esters	MW	Ki* Range
4561		675	B
4562		668	B
4563		683	B

Cmpd #	Table 3: Esters	MW	Ki* Range
4564		654	B
4565		605	B
4566		614	B

329

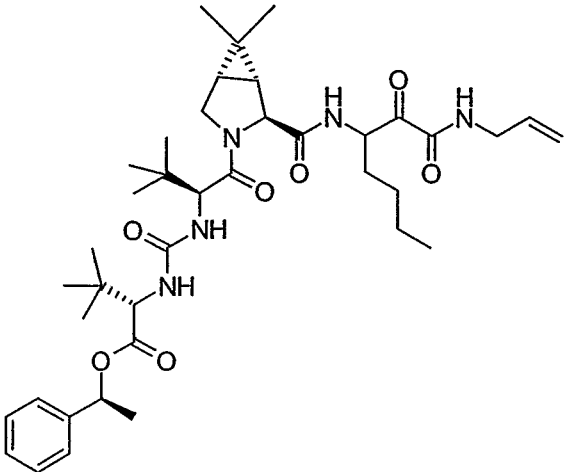
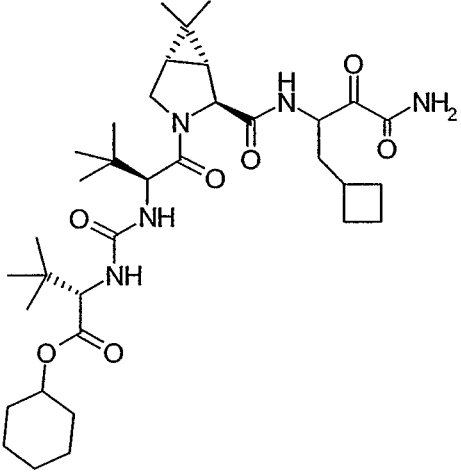
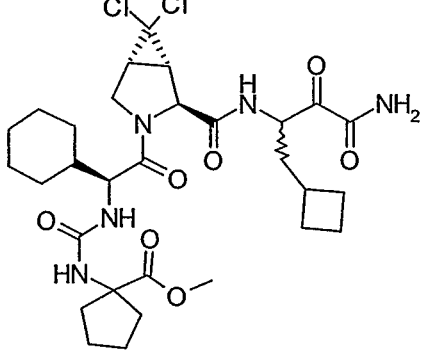
Cmpd #	Table 3: Esters	MW	Ki* Range
4567		690	B
4568		680	B
4569		701	B

Cmpd #	Table 3: Esters	MW	Ki* Range
4570		684	B
4571		635	B
4572		628	B

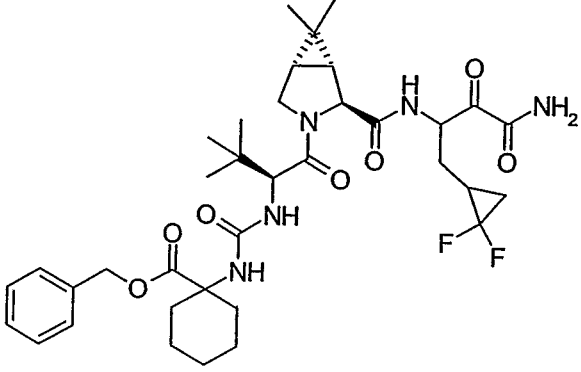
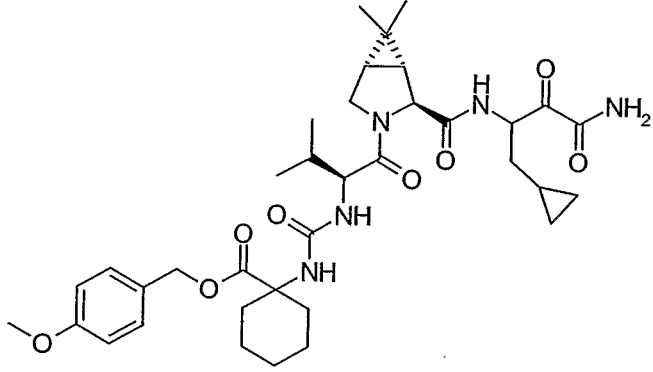
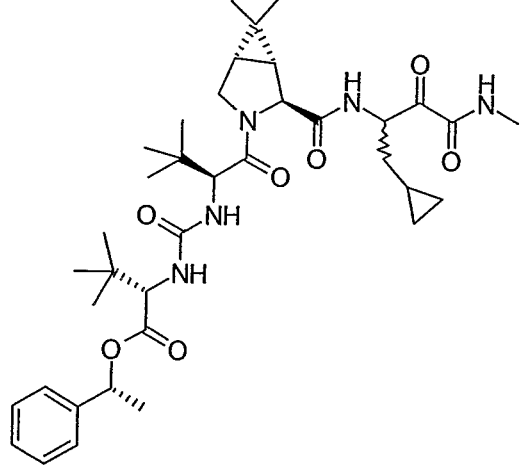
331

Cmpd #	Table 3: Esters	MW	Ki* Range
4573		682	B
4574		724	B
4575		710	B

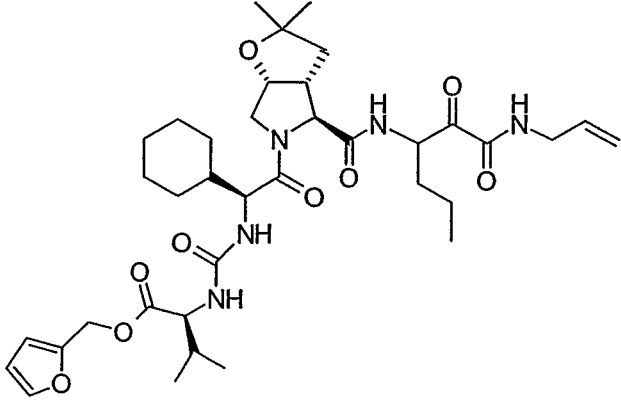
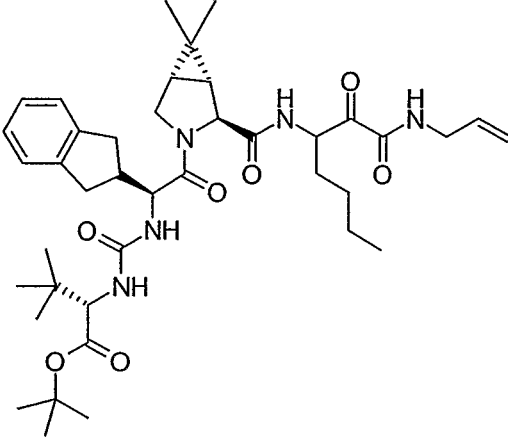
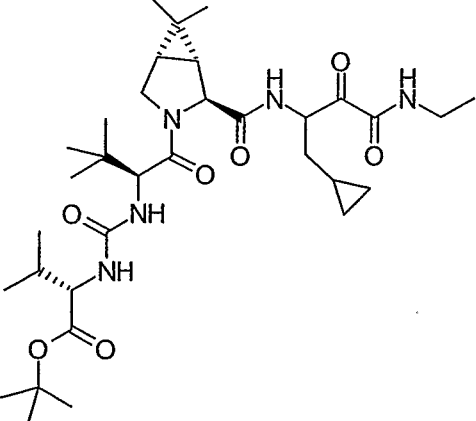
333

Cmpd #	Table 3: Esters	MW	Ki* Range
4579		710	B
4580		660	B
4581		657	B

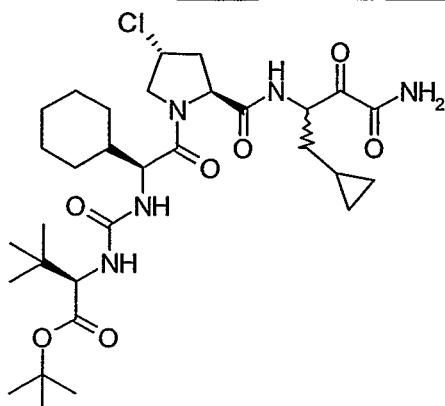
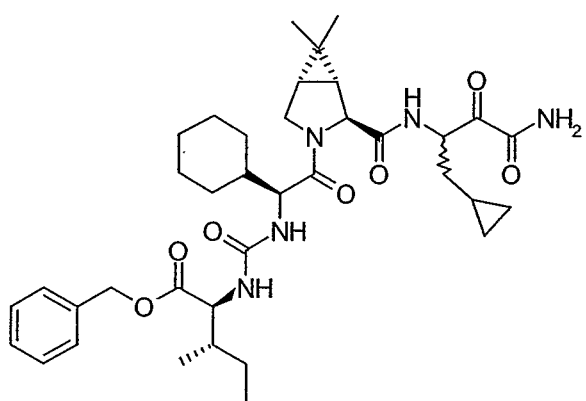
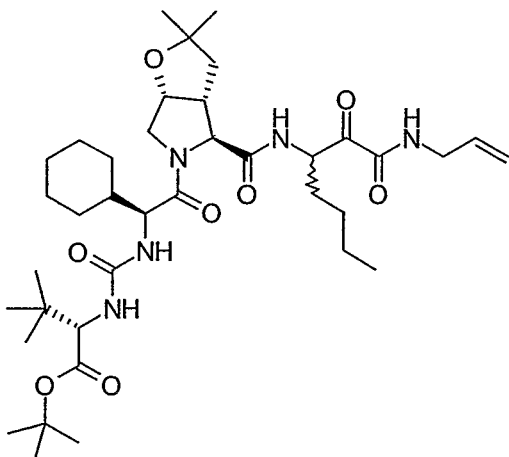
334

Cmpd #	Table 3: Esters	MW	Ki* Range
4582		702	B
4583		682	B
4584		682	B

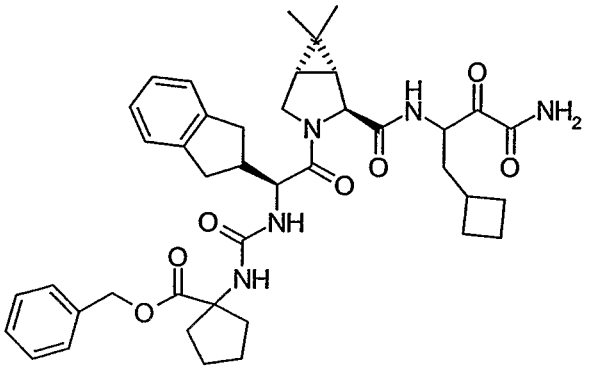
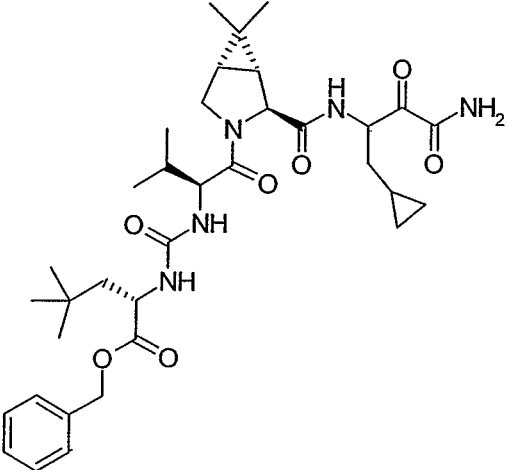
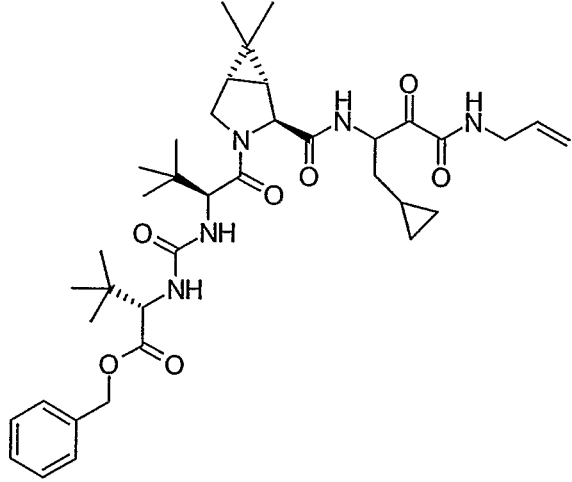
335

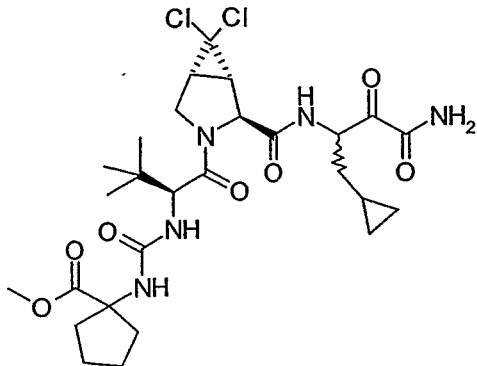
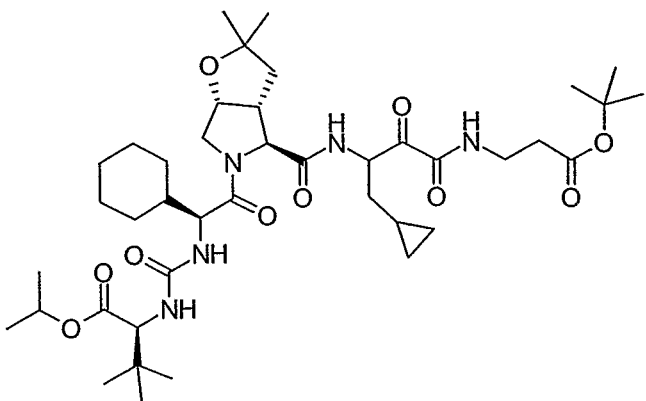
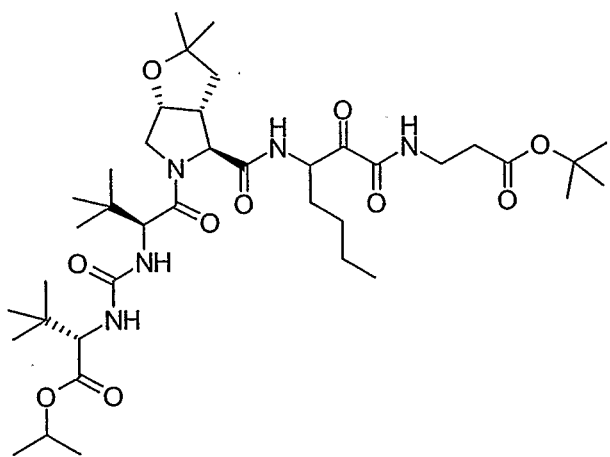
Cmpd #	Table 3: Esters	MW	Ki* Range
4585		714	B
4586		722	B
4587		634	B

336

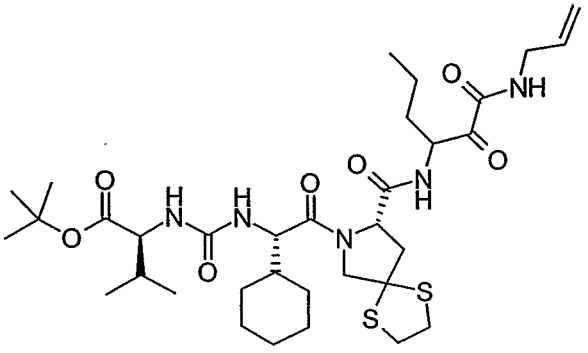
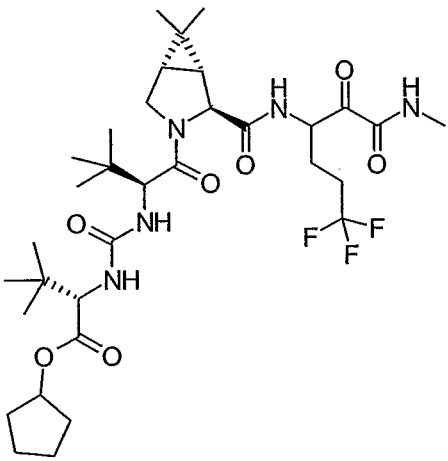
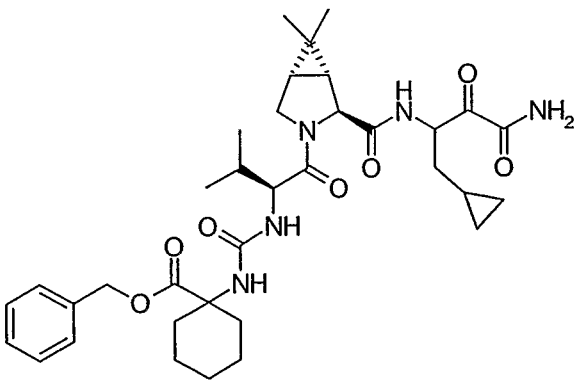
Cmpd #	Table 3: Esters	MW	Ki* Range
4588		640	B
4589		680	B
4590		718	B

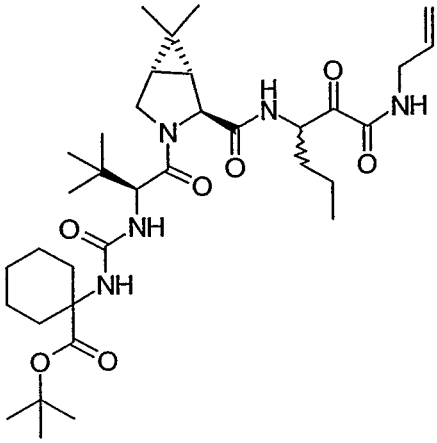
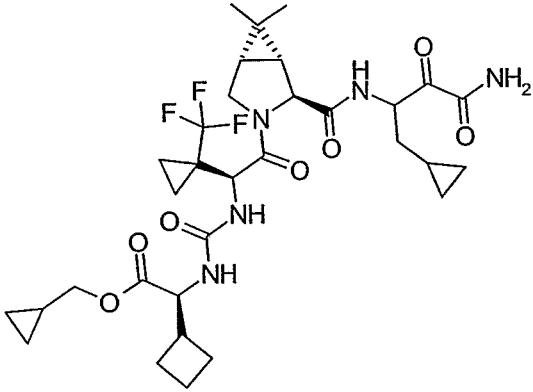
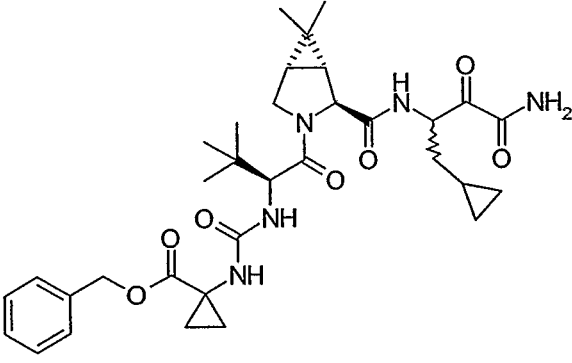
337

Cmpd #	Table 3: Esters	MW	Ki* Range
4591		726	B
4592		654	B
4593		694	B

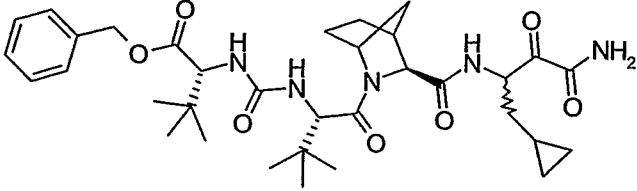
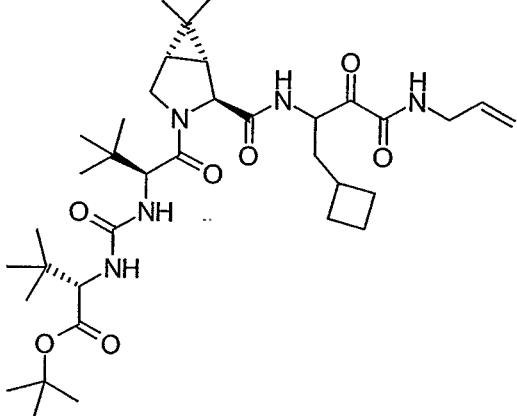
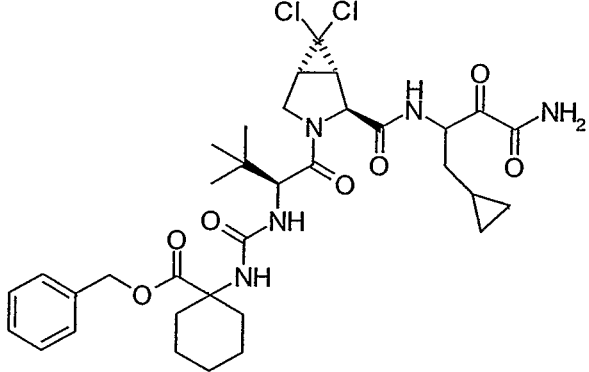
Cmpd #	Table 3: Esters	MW	Ki* Range
4594		617	B
4595		790	B
4596		766	B

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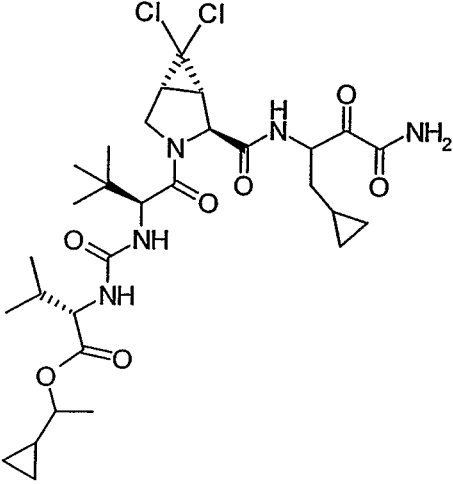
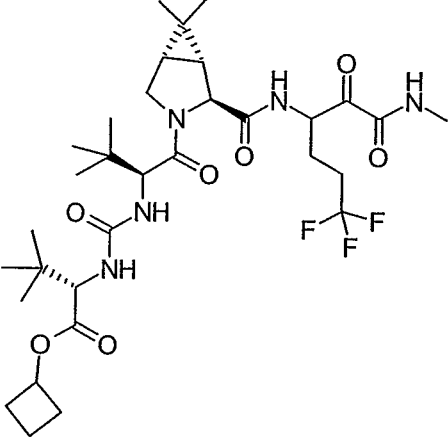
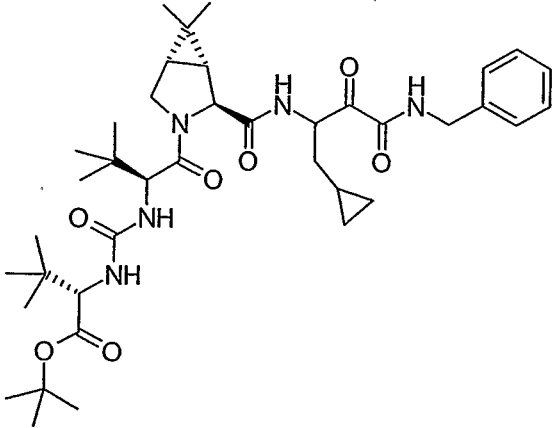
Cmpd #	Table 3: Esters	MW	Ki* Range
4597		710	B
4598		688	B
4599		652	B

Cmpd #	Table 3: Esters	MW	Ki* Range
4600		660	B
4601		668	B
4602		624	B

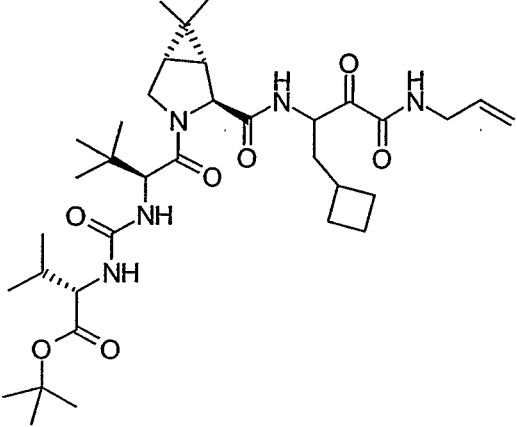
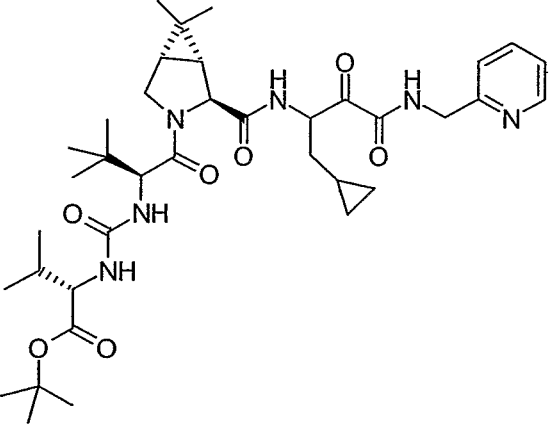
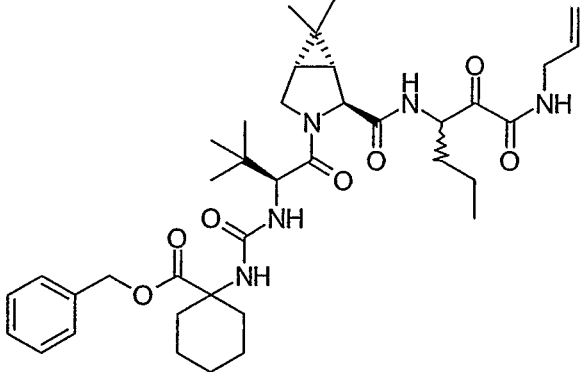
341

Cmpd #	Table 3: Esters	MW	Ki* Range
4603		640	B
4604		674	B
4605		707	B

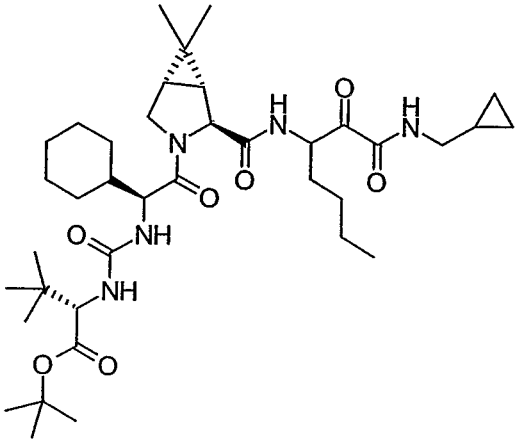
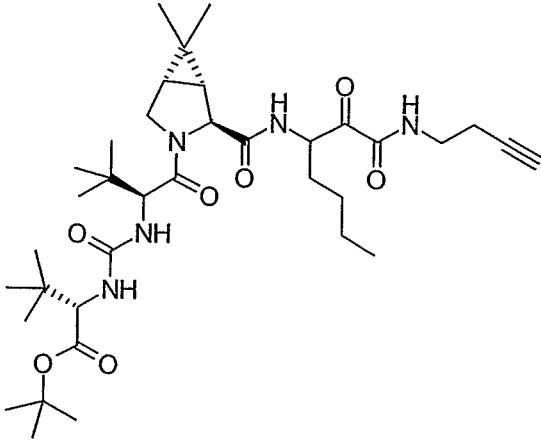
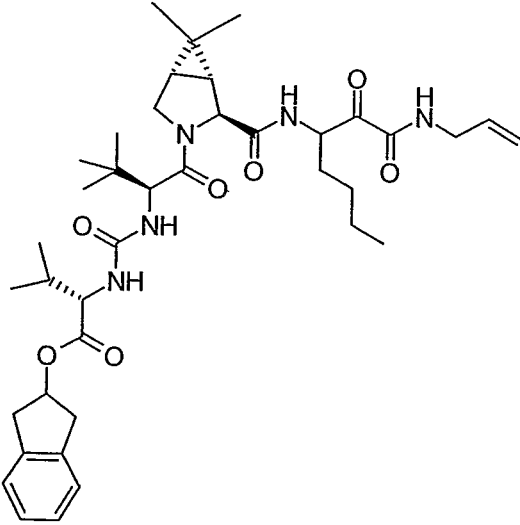
342

Cmpd #	Table 3: Esters	MW	Ki* Range
4606		659	B
4607		674	B
4608		710	B

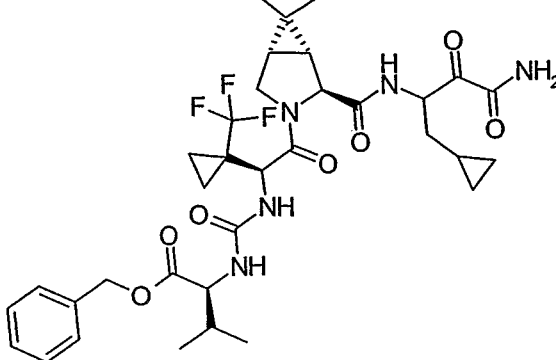
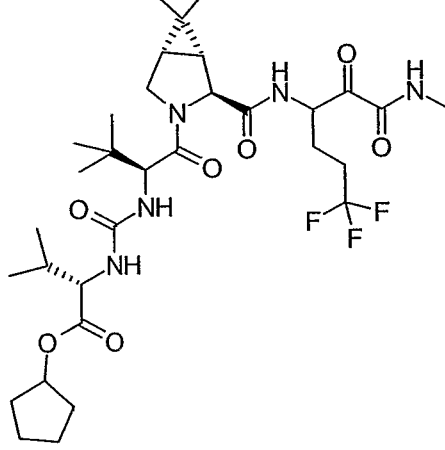
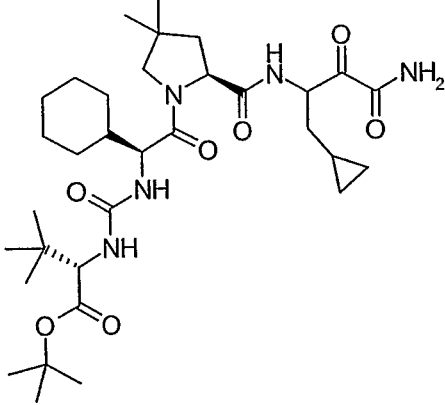
343

Cmpd #	Table 3: Esters	MW	Ki* Range
4609		660	B
4610		697	B
4611		694	B

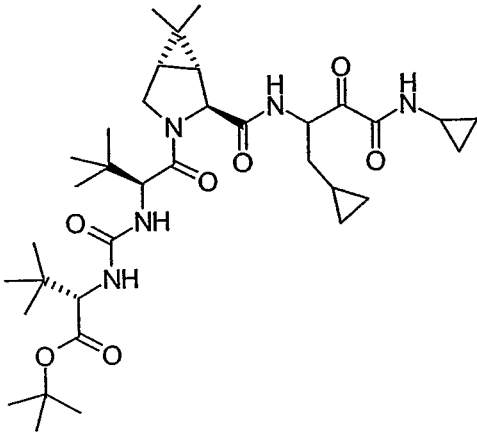
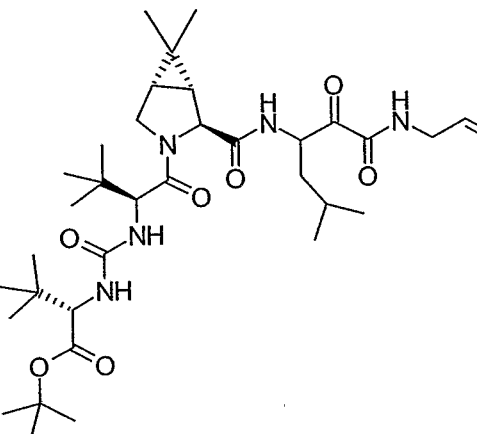
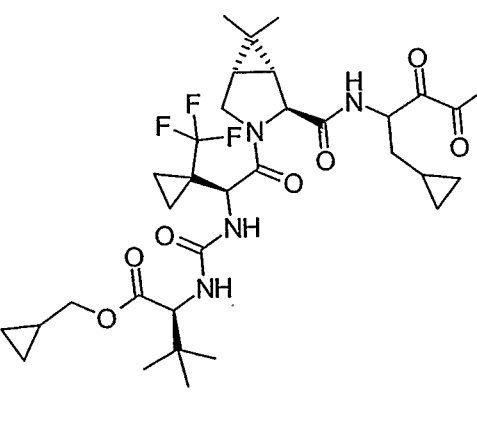
344

Cmpd #	Table 3: Esters	MW	Ki* Range
4612	 Chemical structure of compound 4612: A complex molecule featuring a central pyrrolidine ring. The pyrrolidine ring is substituted with a tert-butyl group (wedge), a cyclohexyl group (dash), and a carbonyl group. The carbonyl group is part of an amide linkage to a side chain containing a cyclopropyl group. Another amide linkage connects the pyrrolidine ring to a side chain containing a tert-butyl group and a carbonyl group. The side chain also contains a cyclopropyl group.	702	B
4613	 Chemical structure of compound 4613: A complex molecule featuring a central pyrrolidine ring. The pyrrolidine ring is substituted with a tert-butyl group (wedge), a cyclohexyl group (dash), and a carbonyl group. The carbonyl group is part of an amide linkage to a side chain containing a cyclopropyl group. Another amide linkage connects the pyrrolidine ring to a side chain containing a tert-butyl group and a carbonyl group. The side chain also contains a cyclopropyl group.	674	B
4614	 Chemical structure of compound 4614: A complex molecule featuring a central pyrrolidine ring. The pyrrolidine ring is substituted with a tert-butyl group (wedge), a cyclohexyl group (dash), and a carbonyl group. The carbonyl group is part of an amide linkage to a side chain containing a cyclopropyl group. Another amide linkage connects the pyrrolidine ring to a side chain containing a tert-butyl group and a carbonyl group. The side chain also contains a cyclopropyl group.	708	B

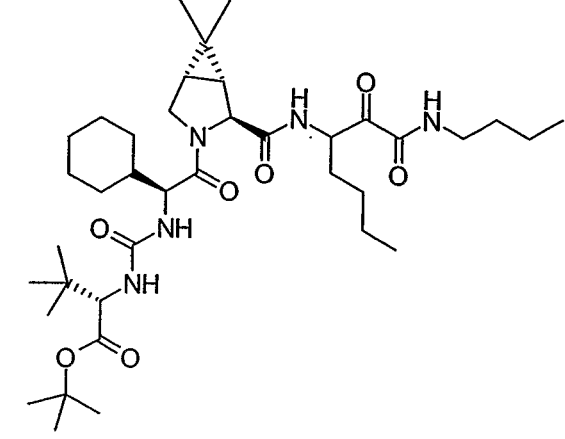
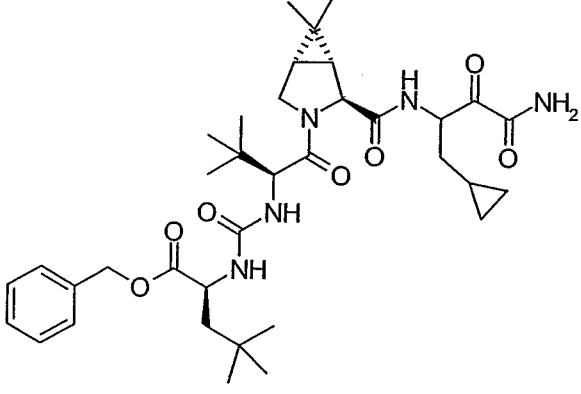
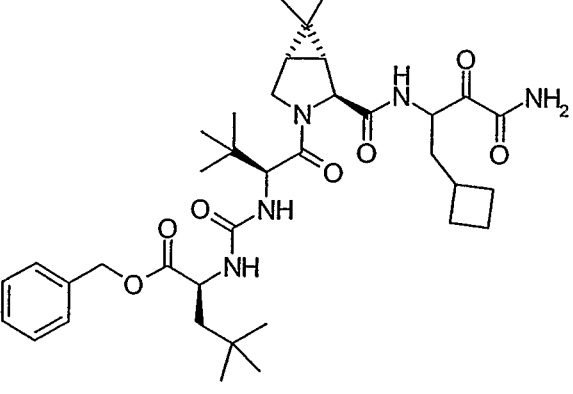
345

Cmpd #	Table 3: Esters	MW	Ki* Range
4615		692	B
4616		674	B
4617		634	B

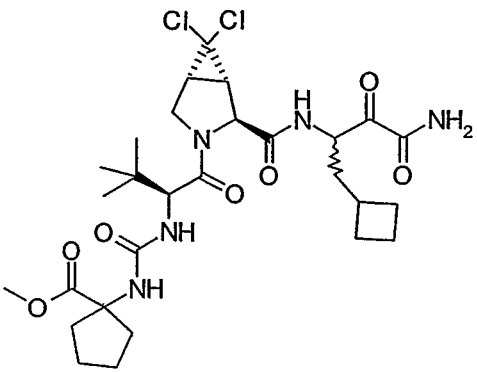
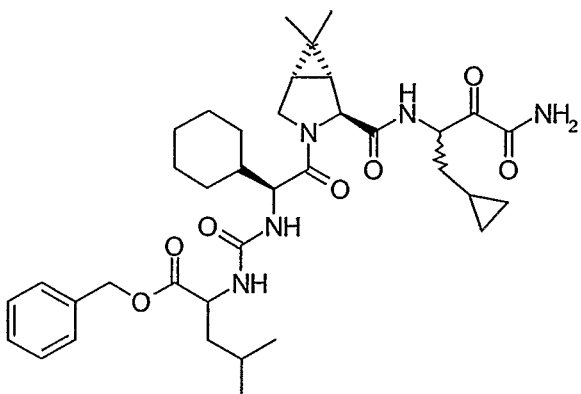
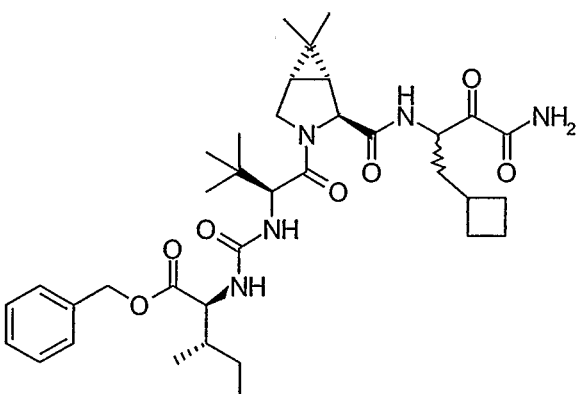
346

Cmpd #	Table 3: Esters	MW	Ki* Range
4618		660	B
4619		662	B
4620		670	B

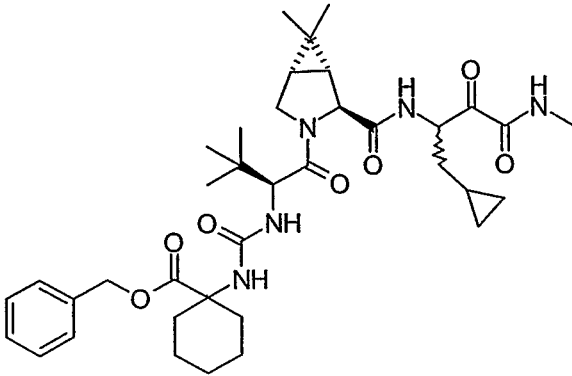
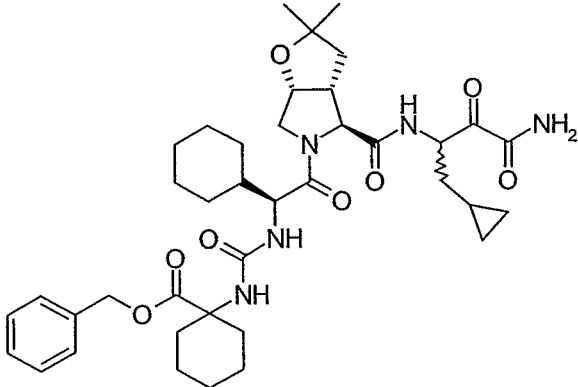
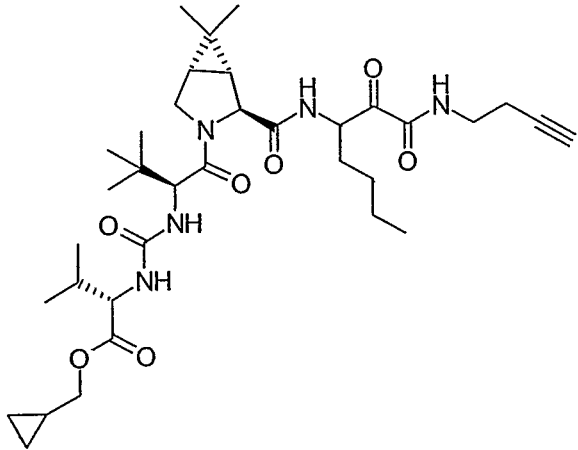
347

Cmpd #	Table 3: Esters	MW	Ki* Range
4621		704	B
4622		668	B
4623		682	B

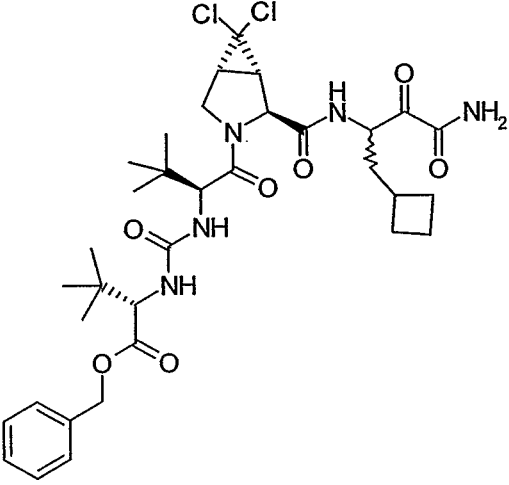
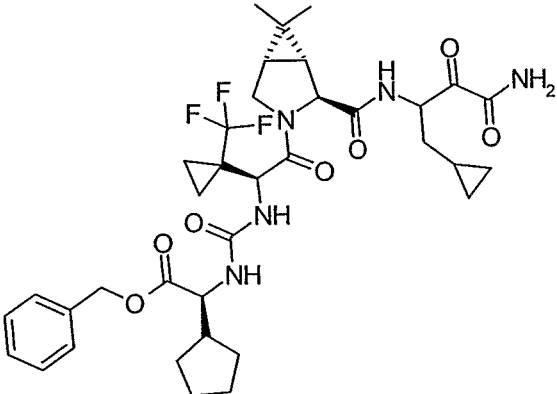
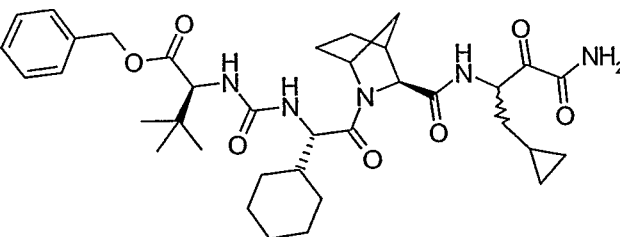
348

Cmpd #	Table 3: Esters	MW	Ki* Range
4624		631	B
4625		680	B
4626		668	B

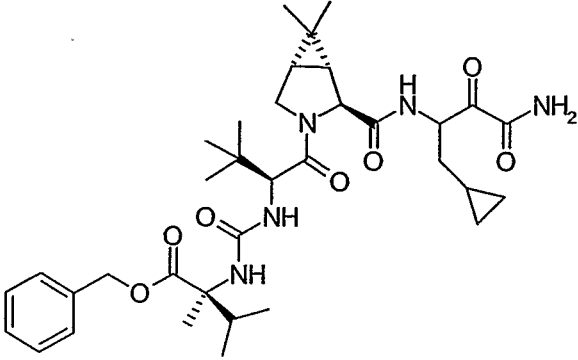
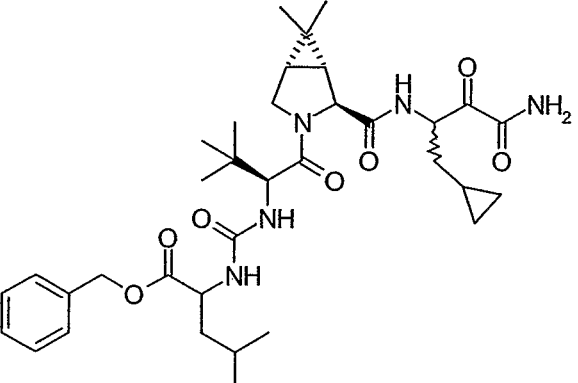
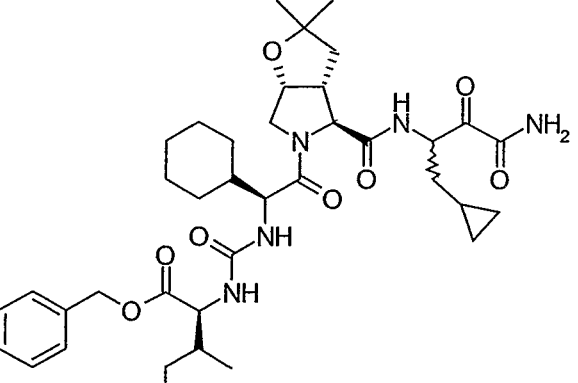
349

Cmpd #	Table 3: Esters	MW	Ki* Range
4627		680	B
4628		722	B
4629		658	B

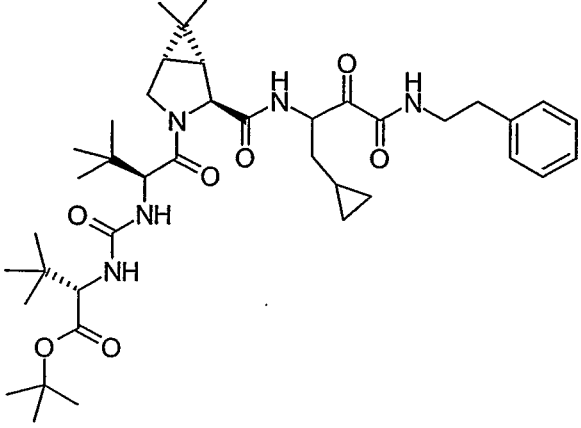
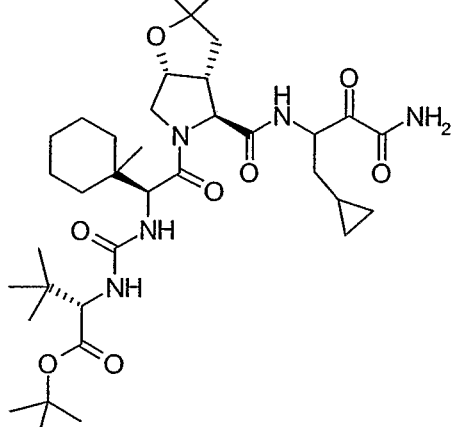
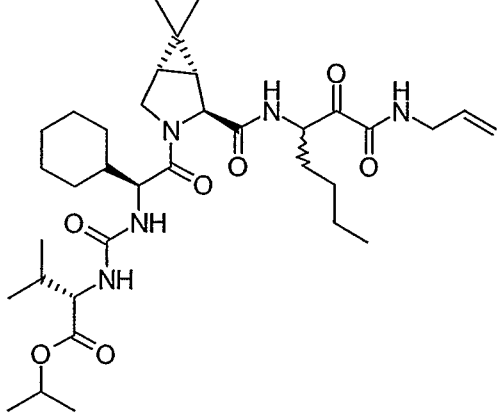
350

Cmpd #	Table 3: Esters	MW	Ki* Range
4630		709	C
4631		718	C
4632		666	C

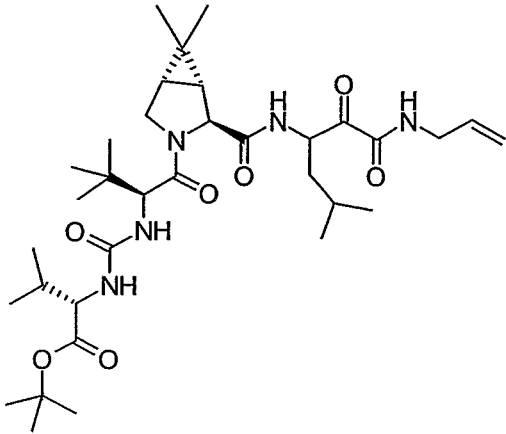
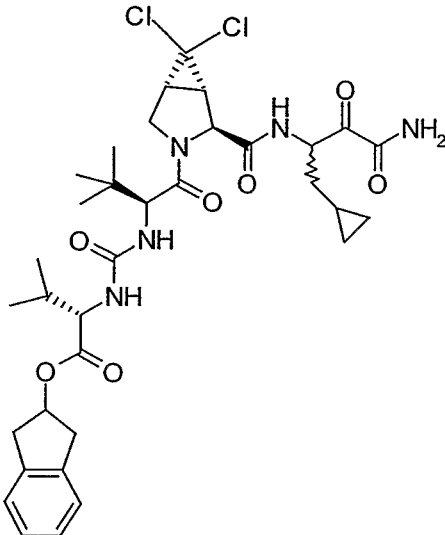
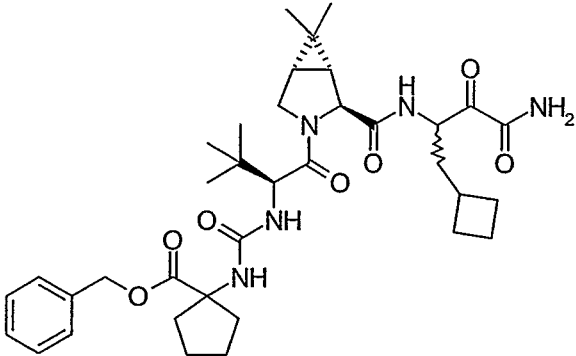
351

Cmpd #	Table 3: Esters	MW	Ki* Range
4633		654	C
4634		654	C
4635		710	C

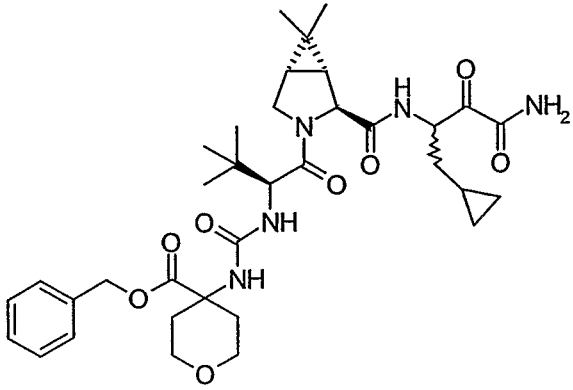
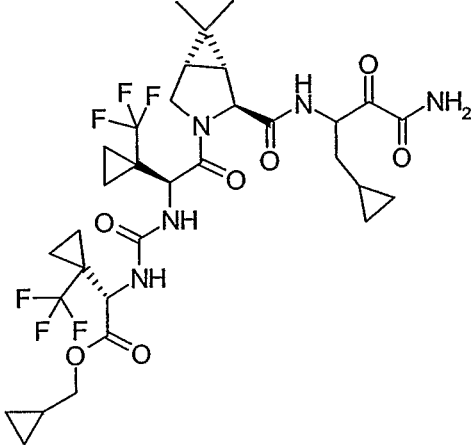
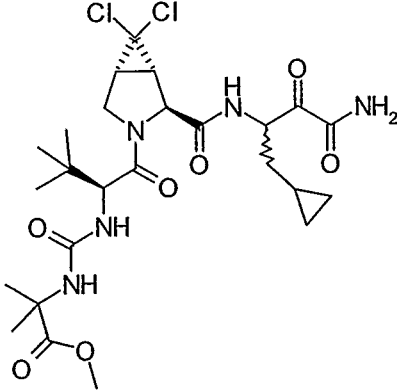
352

Cmpd #	Table 3: Esters	MW	Ki* Range
4636		724	C
4637		690	C
4638		660	C

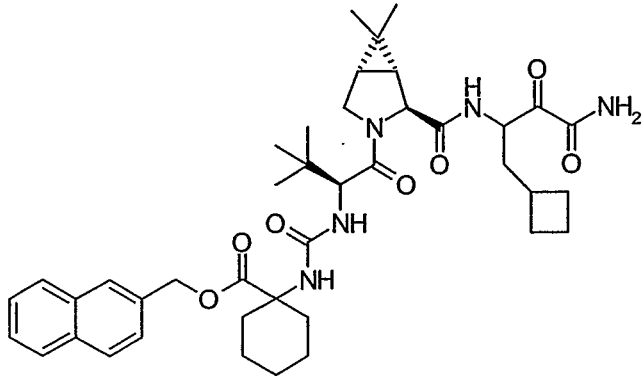
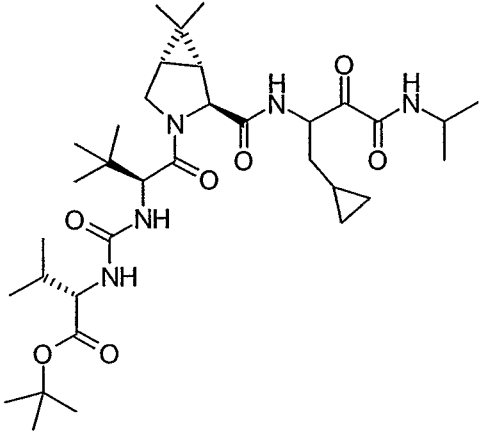
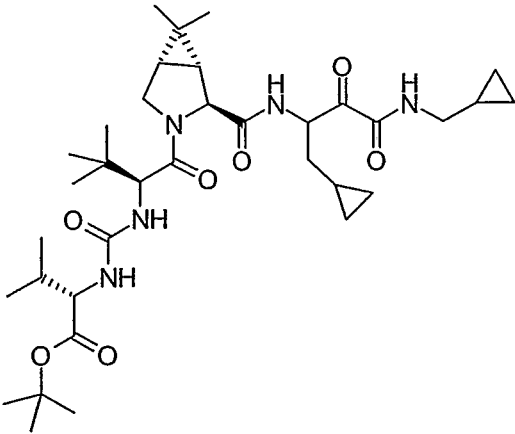
353

Cmpd #	Table 3: Esters	MW	Ki* Range
4639		648	C
4640		707	C
4641		666	C

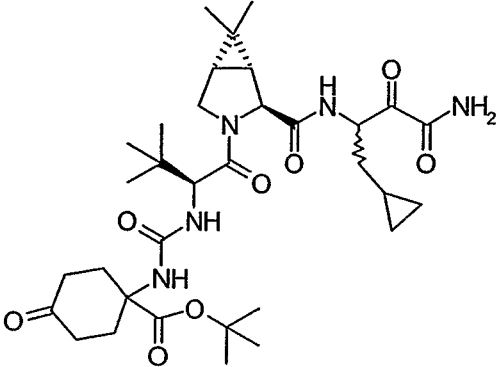
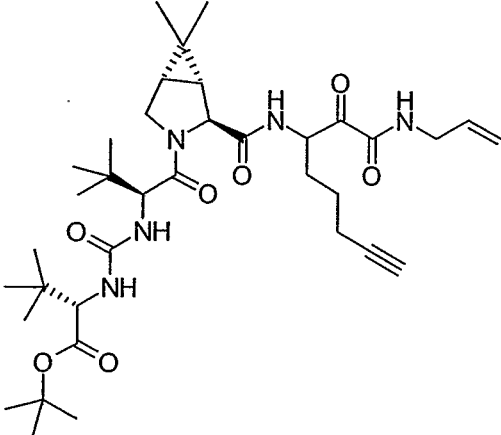
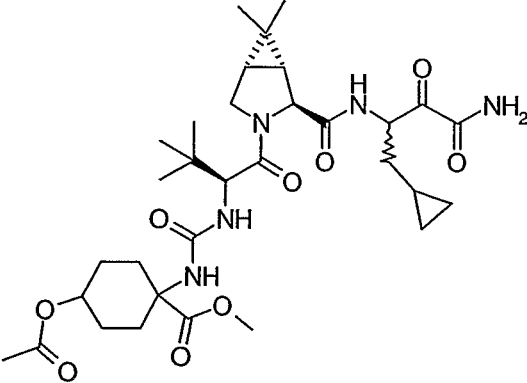
354

Cmpd #	Table 3: Esters	MW	Ki* Range
4642		668	C
4643		722	C
4644		591	C

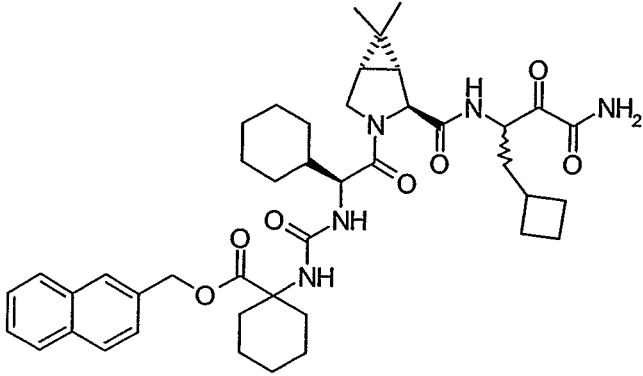
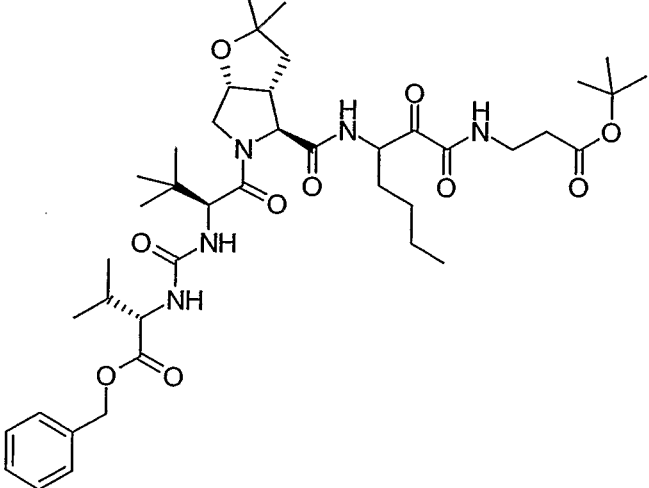
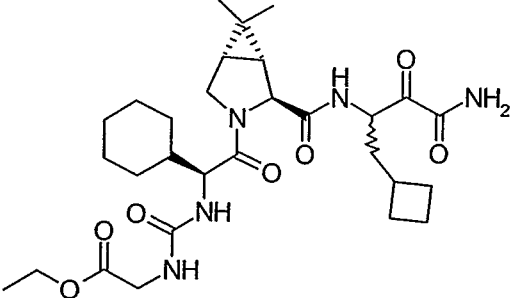
355

Cmpd #	Table 3: Esters	MW	Ki* Range
4645		730	C
4646		648	C
4647		660	C

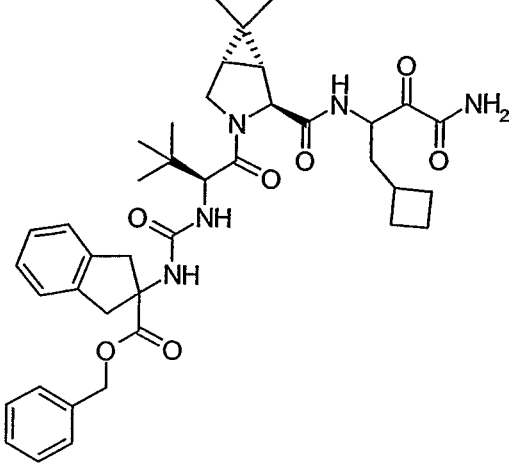
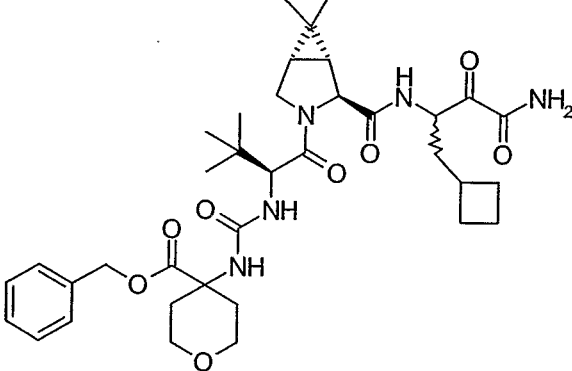
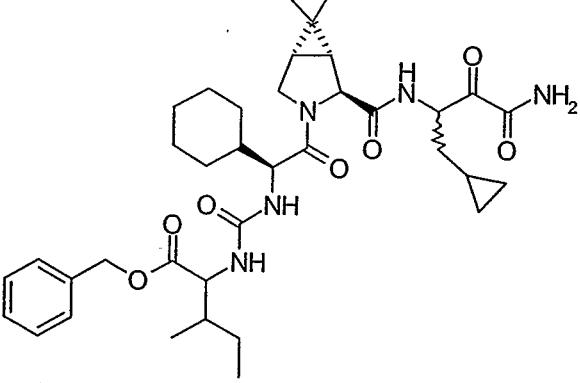
356

Cmpd #	Table 3: Esters	MW	Ki* Range
4648		646	C
4649		672	C
4650		648	C

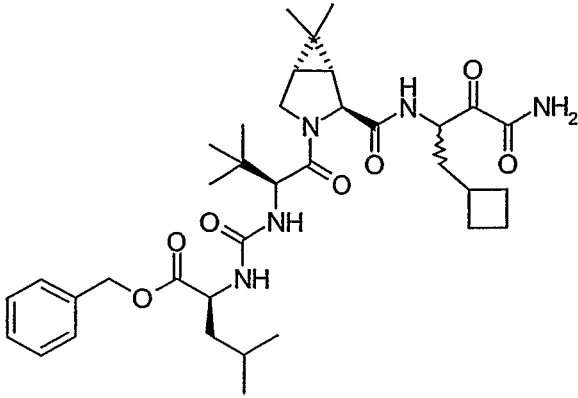
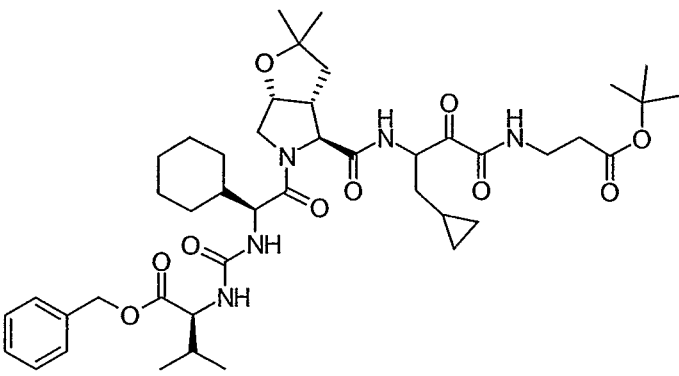
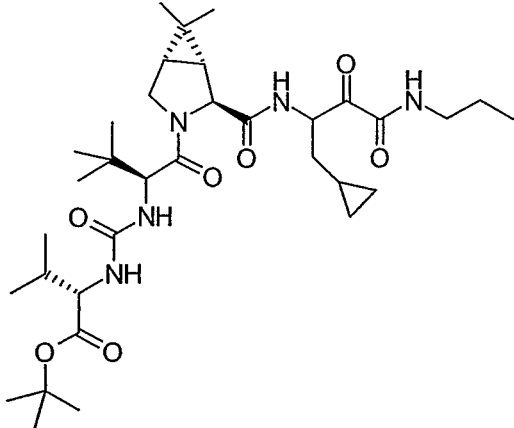
357

Cmpd #	Table 3: Esters	MW	Ki* Range
4651		756	C
4652		800	C
4653		576	C

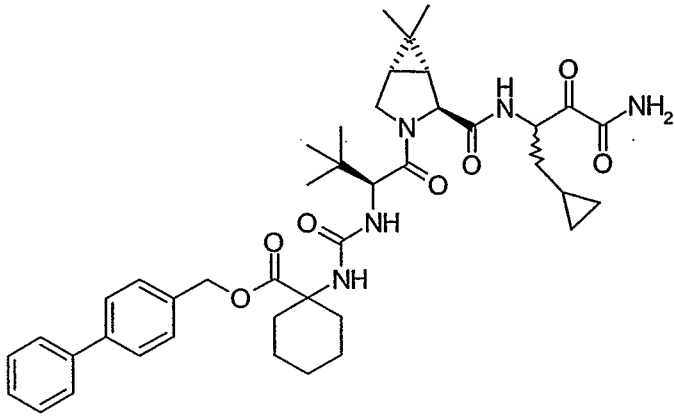
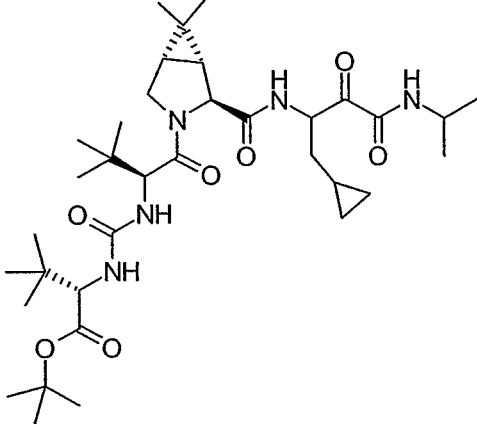
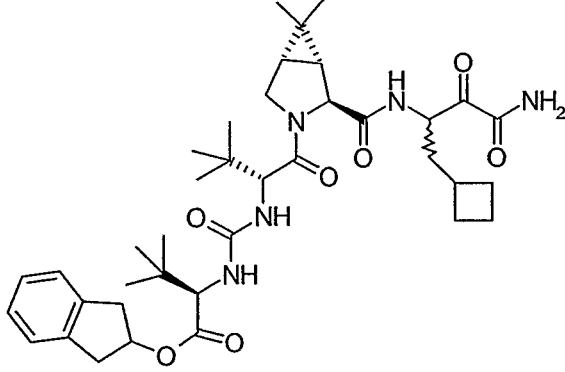
358

Cmpd #	Table 3: Esters	MW	Ki* Range
4654		714	C
4655		682	C
4657		680	C

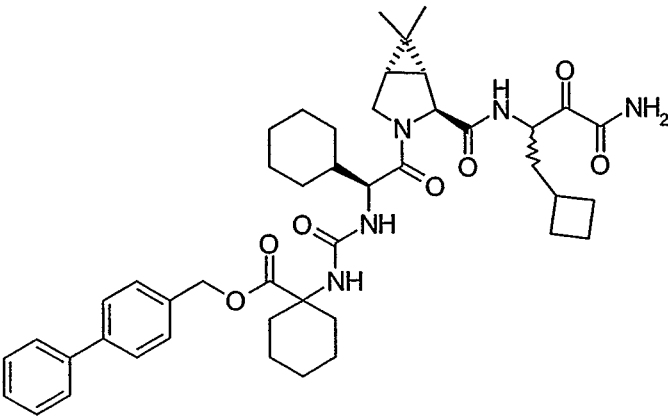
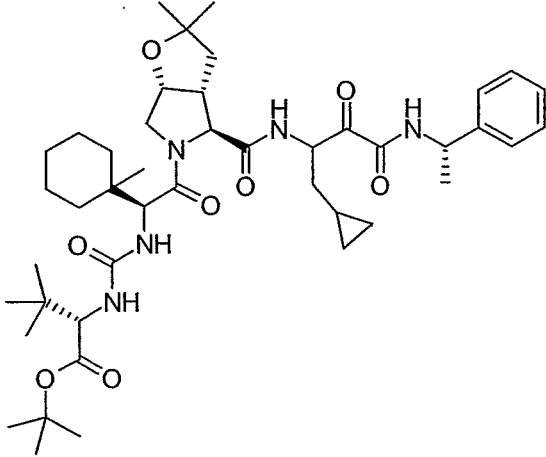
359

Cmpd #	Table 3: Esters	MW	Ki* Range
4658		668	C
4659		824	C
4660		648	C

360

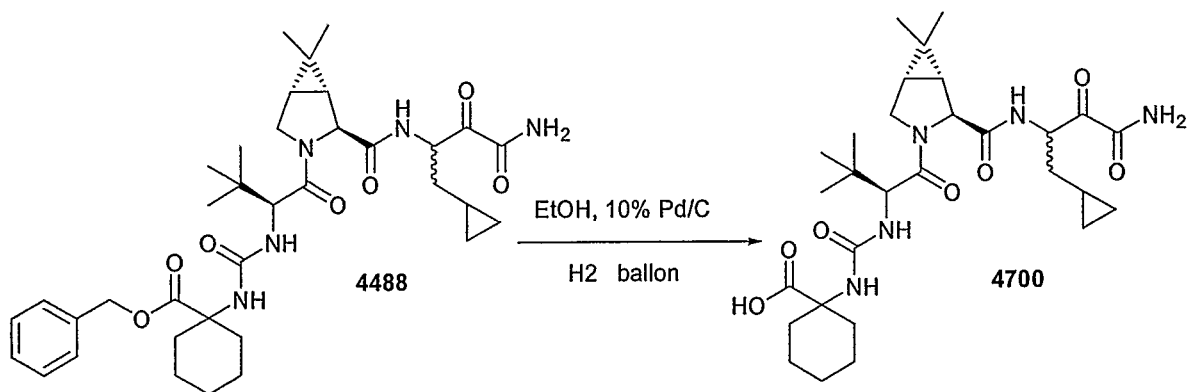
Cmpd #	Table 3: Esters	MW	Ki* Range
4661		742	C
4662		662	C
4663		694	C

361

Cmpd #	Table 3: Esters	MW	Ki* Range
4665		782	C
4666		626	C

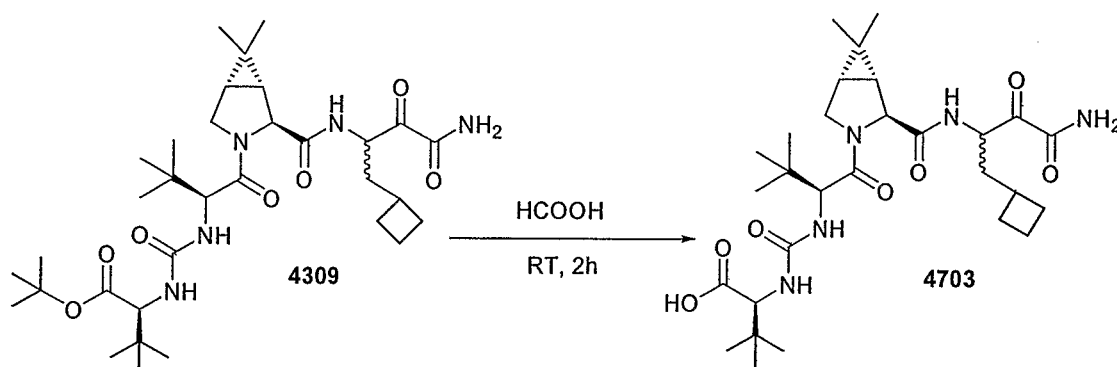
PREPARATION OF SPECIFIC EXAMPLES from Table 4

Example XV: Preparation of Compound of Formula 4700:



To a solution of ester **4488** of **table 3** (28 mg, 0.042 mmol) in ethanol (5 ml) was added 10% Pd/C catalyst (20% w/w, 6 mg). The resulting suspension was hydrogenated until thin layer chromatography indicated complete consumption of the starting material (~3 hrs). The catalyst was removed by filtration through a pad of celite and washed with EtOAc. The combined filtrate and washings were evaporated under vacuum to dryness to provide the desired product **4700** (25 mg). (M+H)= 576.

Example XVI: Preparation of Compound of Formula 4703

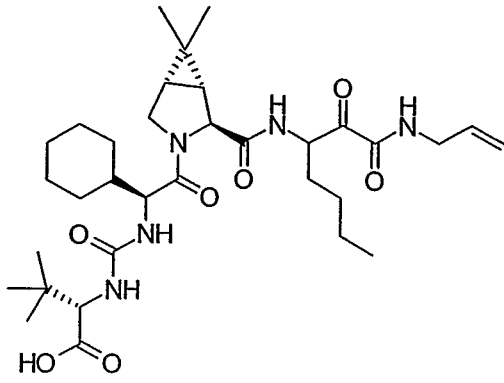
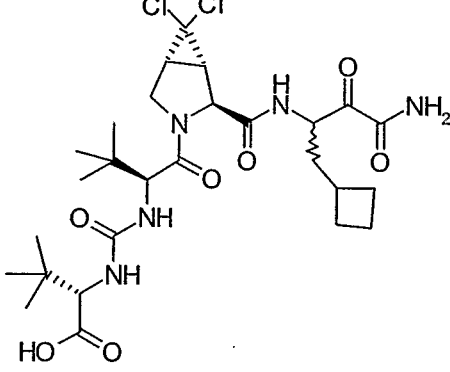
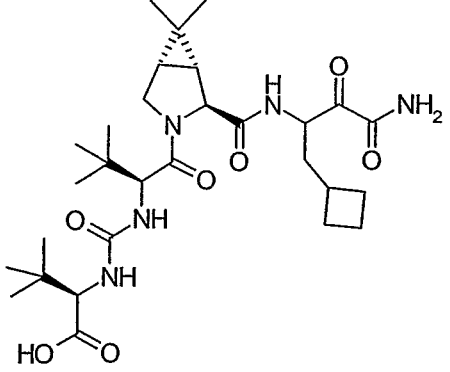


To ester **4309** of **table 3** (70 mg) was 5 mL of HCOOH (98%). The reaction was stirred at RT until thin layer chromatography indicated complete consumption of the starting material (~2 hrs). The volatiles were evaporated under vacuum to dryness to provide the desired product **4703** (62 mg). (M+H)= 578.

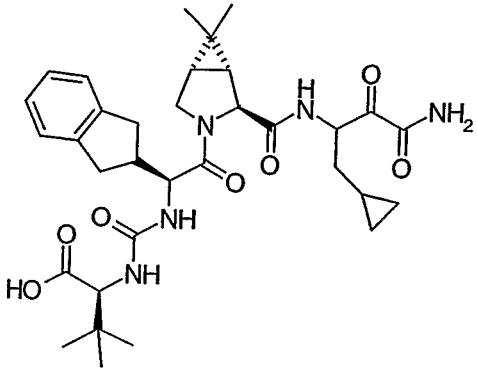
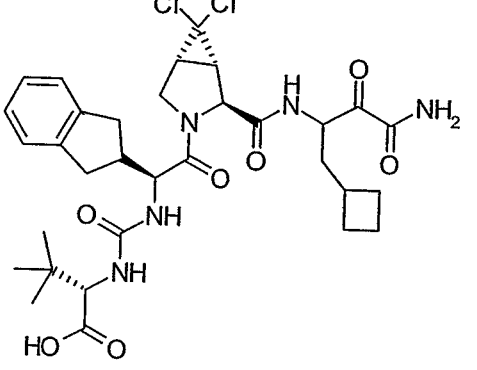
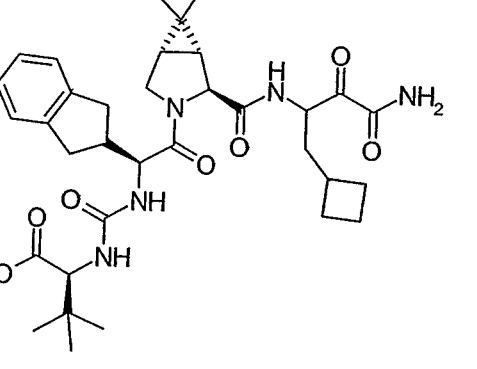
All other **HCV inhibitors of Table 4** were prepared according procedure described in preparative examples **XV** and **XVI** above.

Cmpd #	Table 4: Carboxylic Acids	MW	Ki* Range
4700		576	A

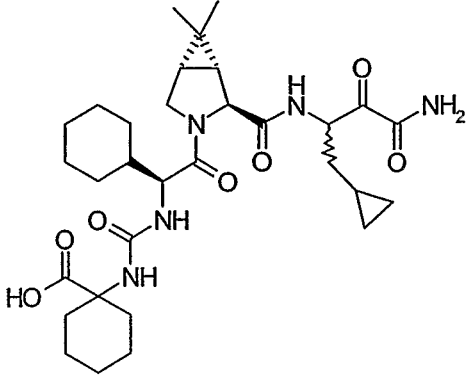
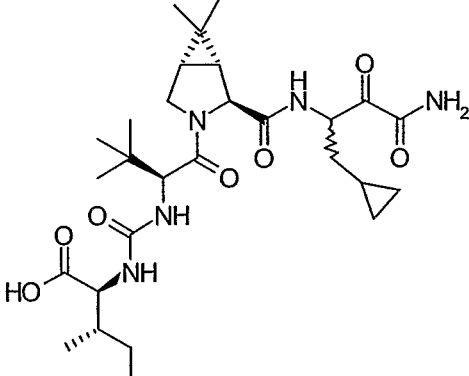
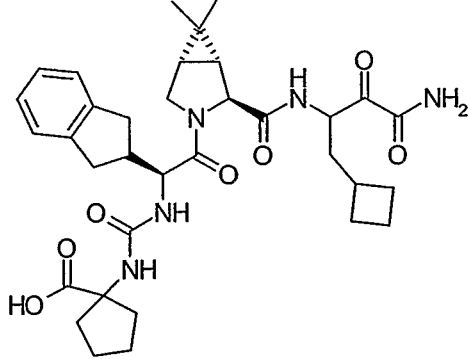
363

Cmpd #	Table 4: Carboxylic Acids	MW	Ki* Range
4701		632	A
4702		619	A
4703		577	A

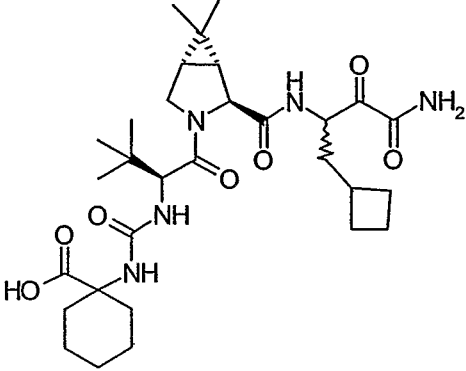
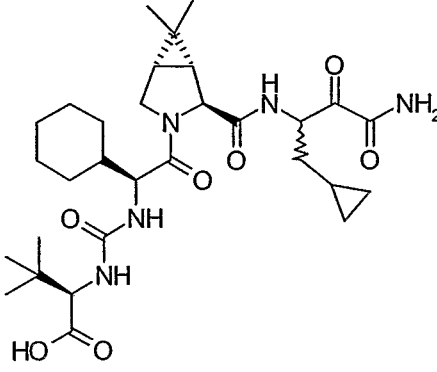
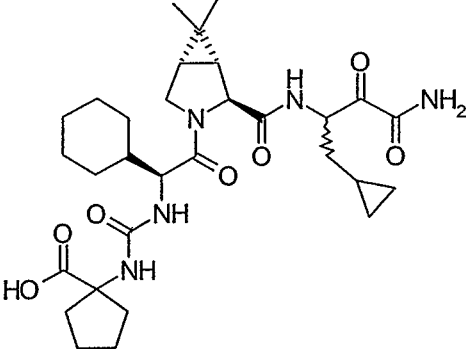
364

Cmpd #	Table 4: Carboxylic Acids	MW	Ki* Range
4704		624	A
4705		679	A
4706		638	A

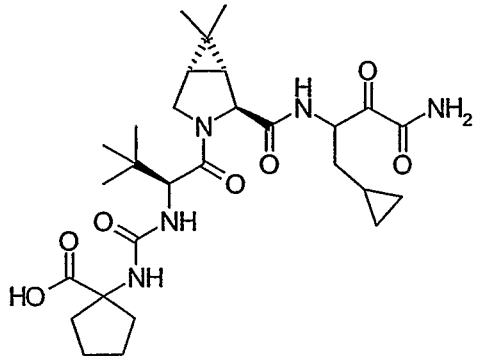
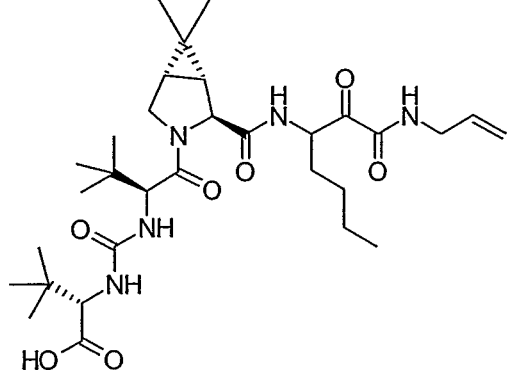
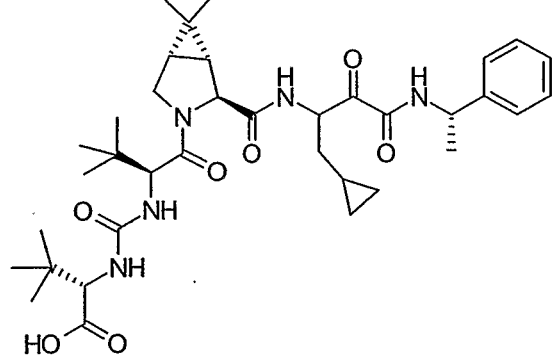
365

Cmpd #	Table 4: Carboxylic Acids	MW	Ki* Range
4707		602	A
4708		564	A
4709		636	A

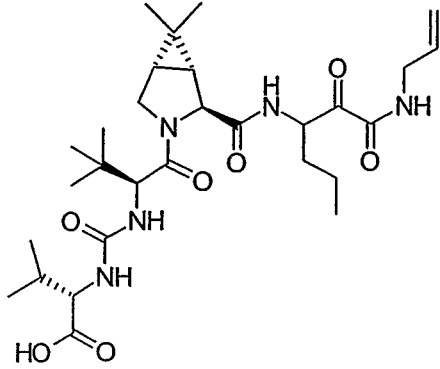
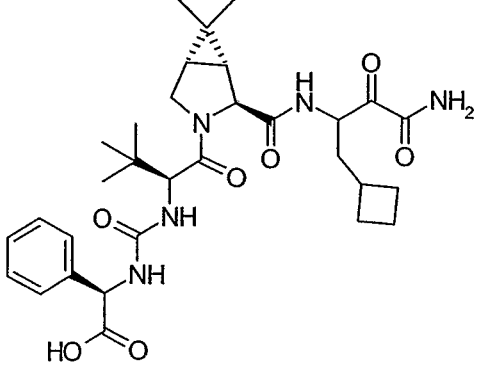
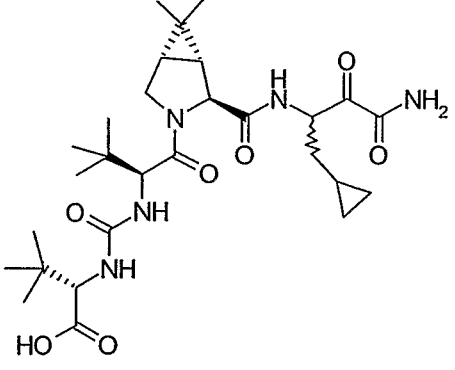
366

Cmpd #	Table 4: Carboxylic Acids	MW	Ki* Range
4710		590	A
4711		590	A
4712		588	A

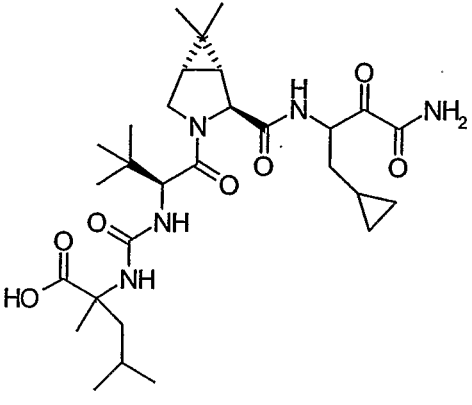
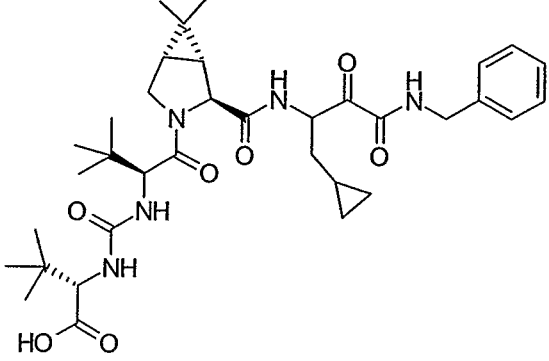
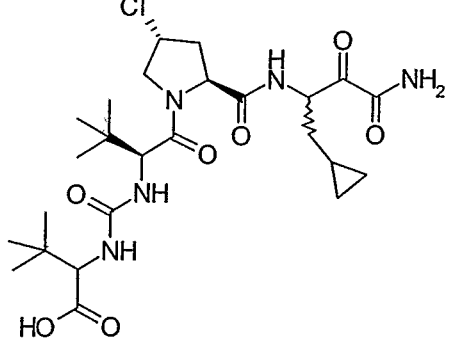
367

Cmpd #	Table 4: Carboxylic Acids	MW	Ki* Range
4713		562	A
4714		606	A
4715		668	A

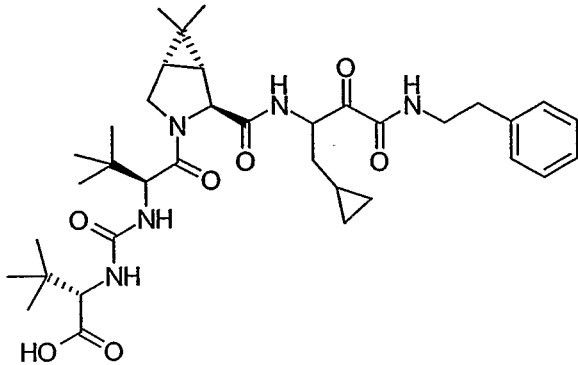
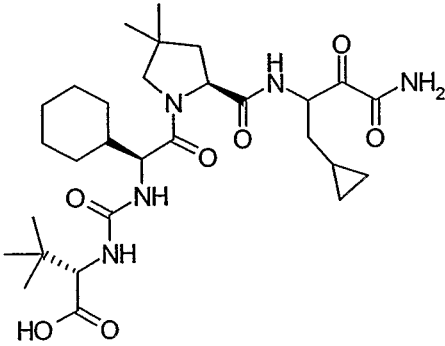
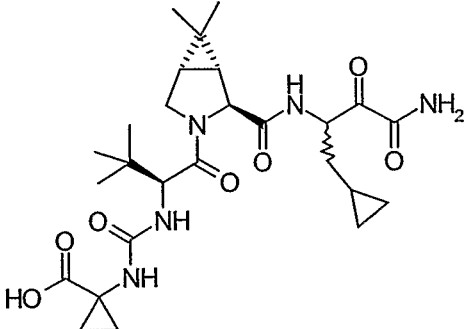
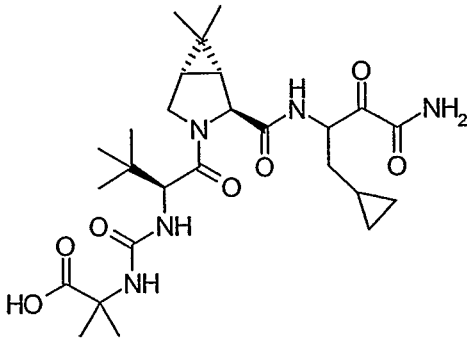
368

Cmpd #	Table 4: Carboxylic Acids	MW	Ki* Range
4716		578	A
4717		598	A
4718		564	A

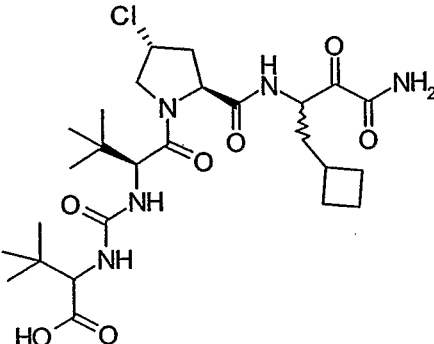
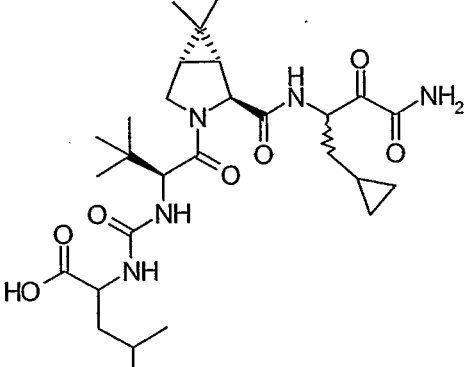
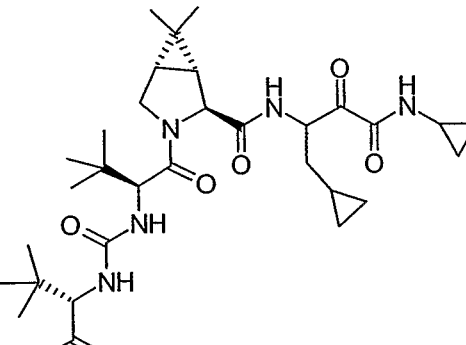
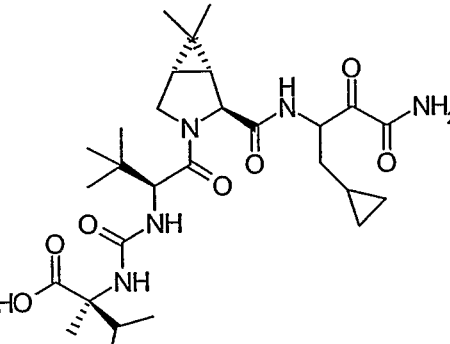
369

Cmpd #	Table 4: Carboxylic Acids	MW	Ki* Range
4719		578	A
4720		654	A
4721		558	A

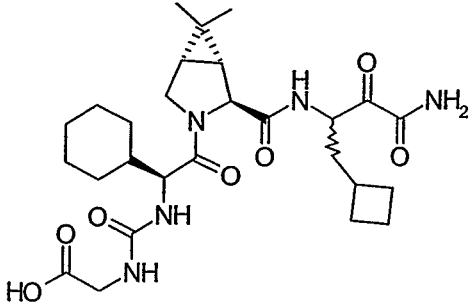
370

Cmpd #	Table 4: Carboxylic Acids	MW	Ki* Range
4722		668	A
4723		578	B
4724		534	B
4725		536	B

371

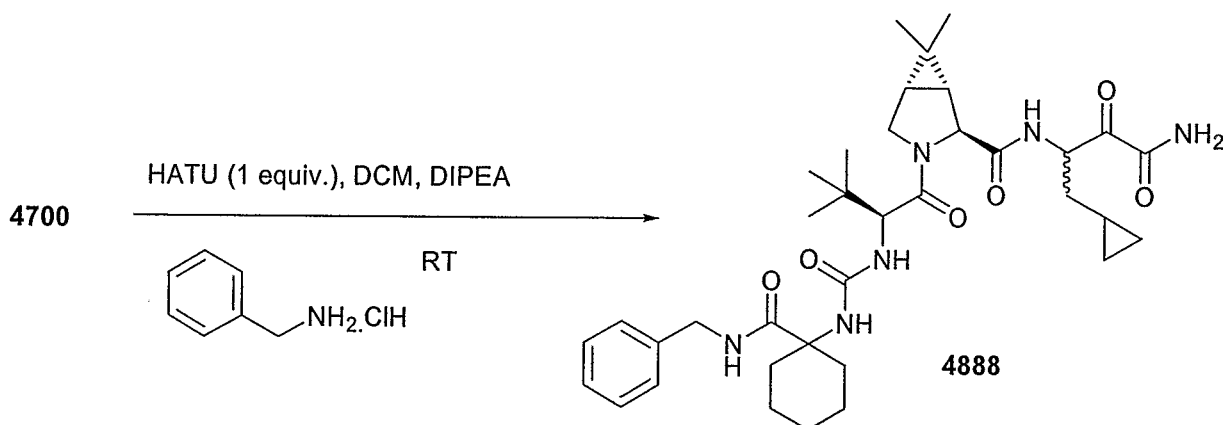
Cmpd #	Table 4: Carboxylic Acids	MW	Ki* Range
4726		572	B
4727		564	B
4728		604	B
4729		564	B

372

Cmpd #	Table 4: Carboxylic Acids	MW	Ki* Range
4730		548	C

PREPARATION OF SPECIFIC EXAMPLES from Table 5

Example XVII: Preparation of Compound of Formula 4888



5

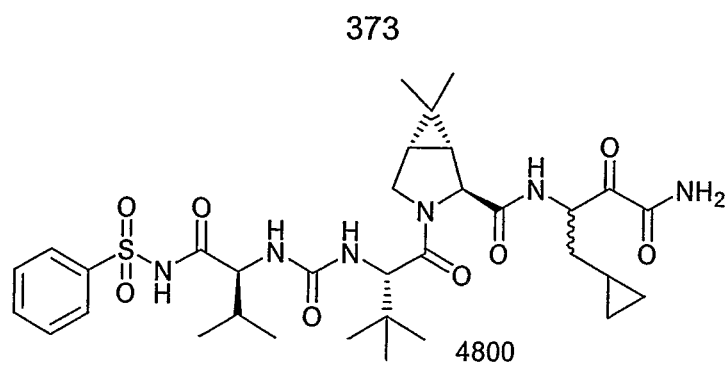
To a RT solution of **4700** (Table 4) of preparative example **XV** (0.02 g, 0.035 mmol) in CH₂Cl₂ (2 mL) was added Benzylamine. HCl (1.2 equiv, 0.042 mmol, 6 mg), HATU (1.2 equiv, 0.042 mmol, 16 mg) then DIPEA (5 equiv, 0.175 mmol, 0.031 mL). The reaction was stirred RT for 2 hours then was diluted with EtOAc and washed successively with citric acid (10% w/w), NaHCO₃ and brine. Organic layer was dried over MgSO₄, filtered and concentrated under vacuo. The residue was purified by preparative plate using 40% Acetone in Hexane as eluant. 4mg of desired product **4888** were obtained. (M+H)=665.

10

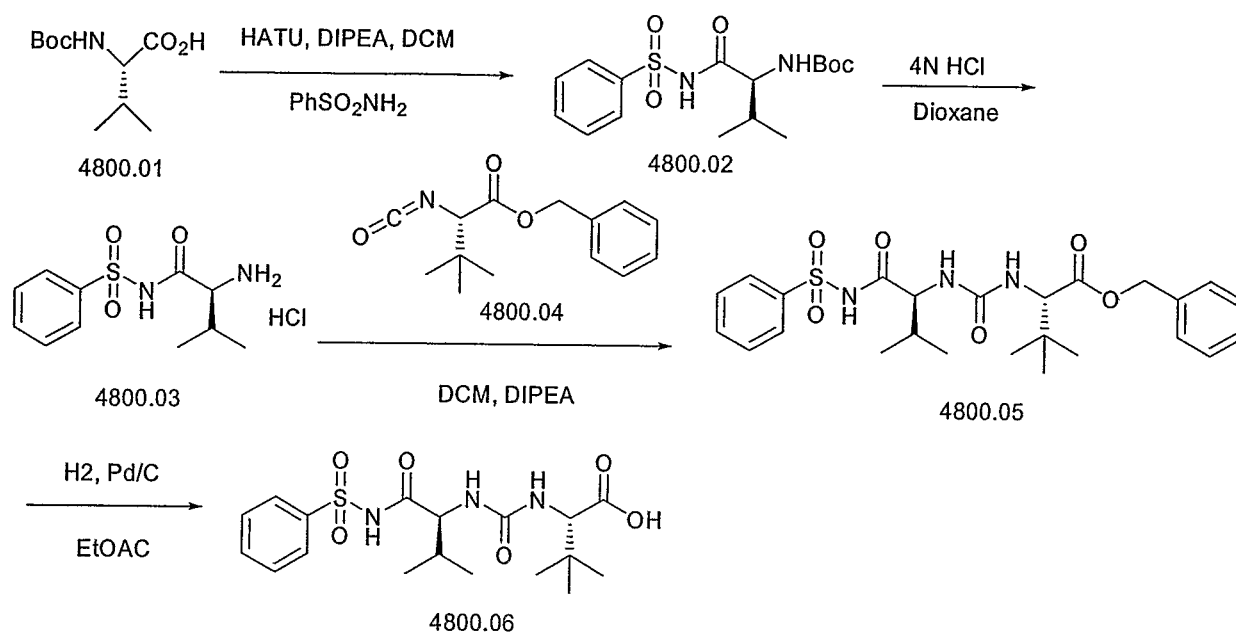
HCV inhibitors **4801** to **4917** of Table 5 have been prepared using the procedure described in example **XVII**.

15

Example XVIII: Preparation of Compound of Formula 4800



Part I: Preparation of intermediate of formula 4800.05



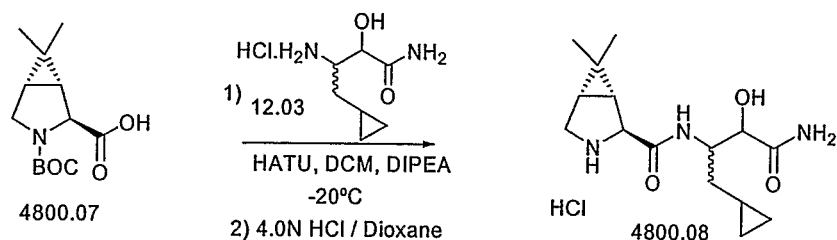
To a -20°C solution of Boc-L-Valine **4800.01** (1.1 g, 5mmol) in DCM (20 mL) was added HATU (1.2 equiv, 6mmol, 2.3g), DIPEA (5equiv, 25 mmol, 4.4mL) then Benzene sulfonamide (1.1 equiv, 5.5 mmol, 0.86g). Reaction was stirred at this temp for 48 h. The reaction was diluted with EtOAc and washed successively with citric acid (10% w/w), NaHCO₃ and brine. Organic layer was dried over MgSO₄, filtered and concentrated under vacuo. Recrystallization occurred with a mixture on DCM and MeOH. 600 mg of white crystals (**4800.02**) were obtained with 1.5g of oily residue. The 600 mg were used in the next step.

4.0 N HCl Dioxane (25 mL) was added to **4800.02** (600mg). Reaction was stirred at RT until no starting material was detected by TLC (2 h). Then, Et₂O was added and the resulting white powder was filtered off and dried under a N₂ flow to yield= 0.46g (1.57 mmol) of **4800.03**.

To a 0°C solution of isocyanate **4800.04** (prepared as described in **step3** of preparative example **XIII** by replacing Boc-1-amino-cyclohexanecarboxylic acid **4488.01** of **step1** by Boc-L-Tert-Leucine, 0.7 mmol, 3.5 mL) in CH₂Cl₂ (2ml) was added **4800.03** (180mg, 0.61 mmol) then DIPEA (1.1equiv., 0.7mmol, 0.122 mL). The reaction was warmed-up to RT and stirred over the week-end. After 48h, reaction was concentrated to dryness and the oily residue was purified by HPFC Biotage 25+S, 50% to 100% EtOAc in Hexane. Purification provided 110 mg of **4800.05**.

To a solution of **4800.05** (0.11g, 0.219mmol) in EtOAc (5ml) was added 10% Pd/C catalyst (15% w/w, 16mg). The resulting suspension was hydrogenated until thin layer chromatography indicated complete consumption of the starting material (~3 hrs). The catalyst was removed by filtration through a pad of celite and washed with EtOAc. The combined filtrate and washings were evaporated under vacuum to dryness to provide the desired product **4800.06** (85mg).

Part II: Preparation of intermediate of formula **4800.08**

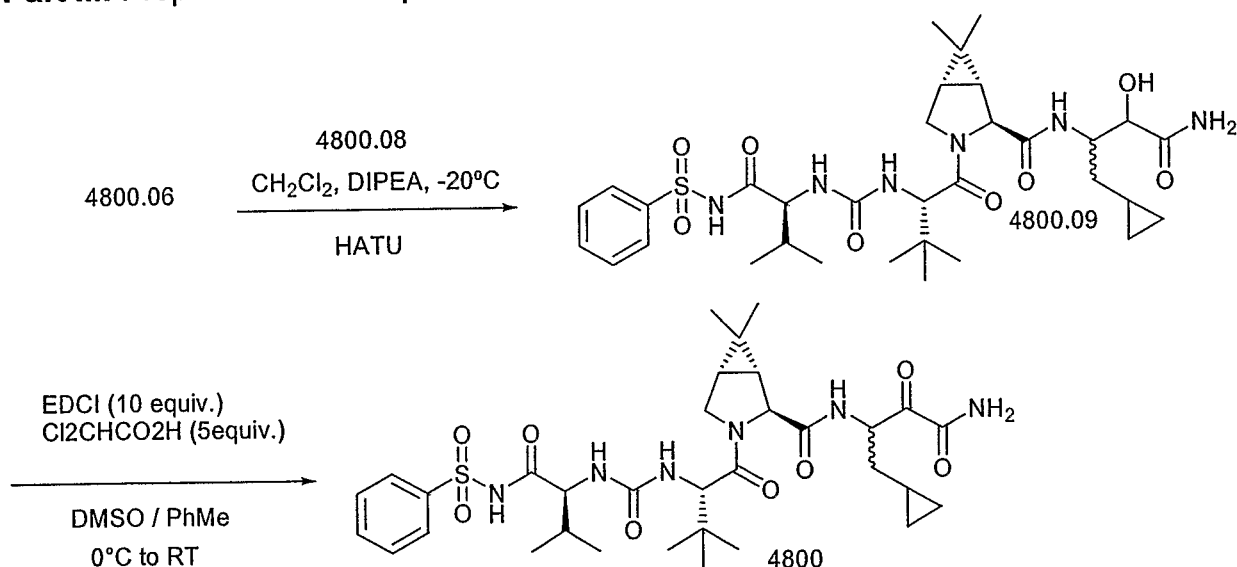


To a -20°C solution of acid **4800.07** (prepared following the method of R. Zhang and J. S. Madalengoitia (*J. Org. Chem.* **1999**, *64*, 330), 5.1g, 20mmol) in DCM (200 mL) was added HATU (1.05 equiv, 21mmol, 8g), amine salt **12.03** (prepared as described

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in Preparation of intermediates, preparation of P1-P' moieties, 1.0equiv, 20mmol, 3.893g). After 10 min at -20°C, DIPEA (5equiv, 100 mmol, 17.4mL) was added. and reaction was stirred at this temp for 16 hrs then the reaction was diluted with EtOAc and washed successively with NaHCO₃, citric acid (10% w/w) and brine. Organic layer was dried over MgSO₄, filtered and concentrated under vacuo. Purification Biotage 75+M (3.5 l of 1/1 Hex/EtOAc) then 100% EtOAc. provided 12g of a light brown oil that was used directly in the following step. To a RT solution of this crude oil (12g) was added 100 mL of a 4.0 N HCl solution in Dioxane. Reaction was stirred at RT for 1h to observe completion then diluted with Heptanes and concentrated to dryness under vacuo to furnish 10.4 g of dark brown oil **4800.08** that was used directly for the preparation of compound of formula **4800.09**.

Part III: Preparation of Compound of Formula 4800:



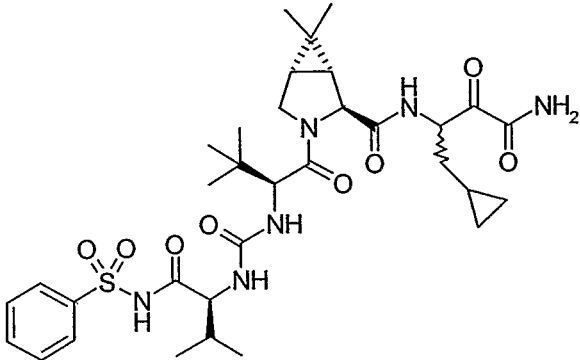
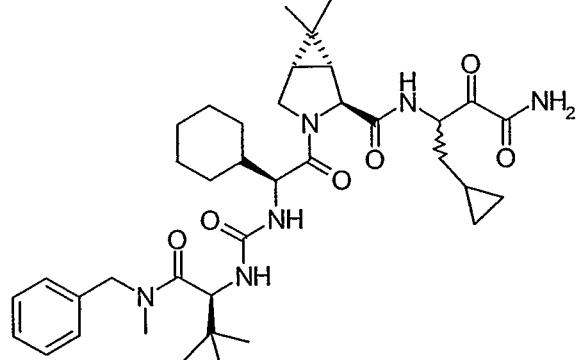
To a -20°C solution of **4800.06** (85 mg, 0.2 mmol) in DCM (50 mL) was added HATU (1.2 equiv, 0.24mmol, 92 mg), crude amine salt **4800.08** (1.2 equiv, 0.24 mmol, 80 mg). After 10 min at -20°C, DIPEA (5equiv, 1 mmol, 0.22mL) was added. Reaction was stirred at this temperature for 18 h then reaction was diluted with EtOAc and washed successively with citric acid (10% w/w) and brine. Organic layer was dried over MgSO₄, filtered and concentrated under vacuo. 250 mg of crude **4800.09** were obtained. (M+H)= 691.

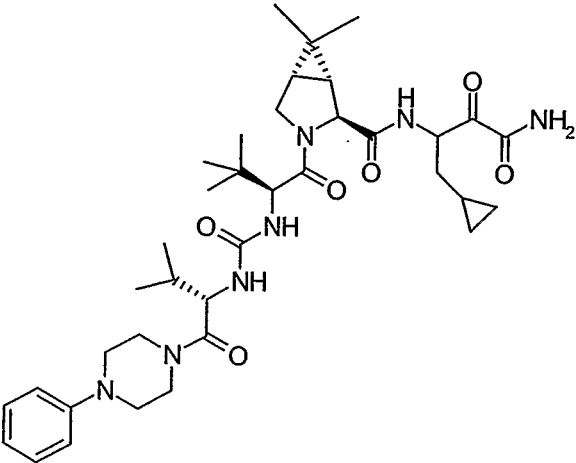
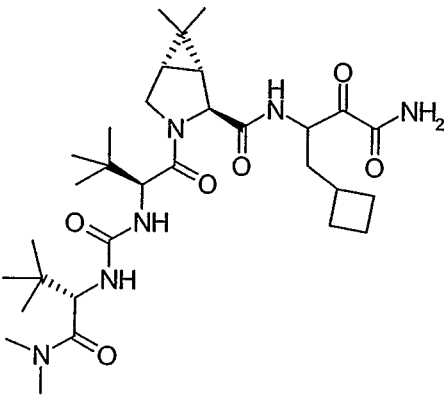
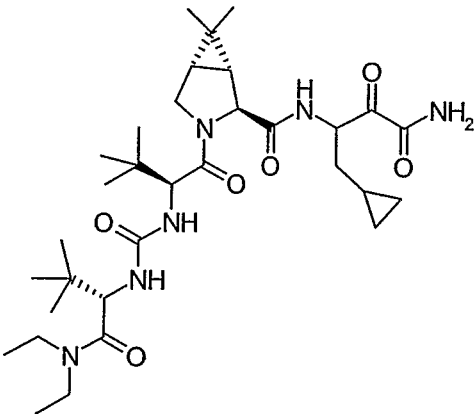
To a 0°C solution of crude **4800.09** (0.25g, 0.2mmol) in DMSO/PhMe (12 mL) was added EDCI (10 equiv, 1mmol, 400mg) and Dichloroacetic acid (5equiv, 1mmol, 0.08mL). The reaction was warmed-up to RT gradually and stirred at this temperature. After 4h, reaction was diluted with water and the 2 phases were separated. Organic

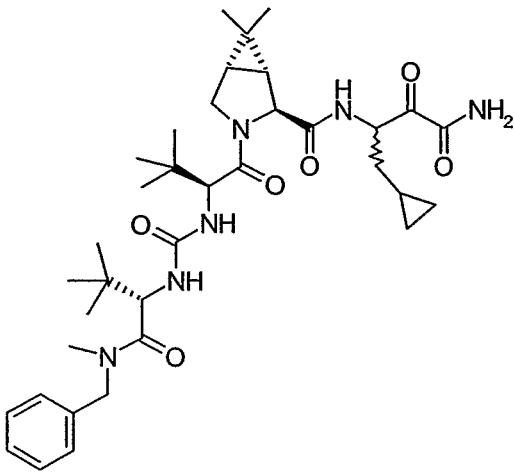
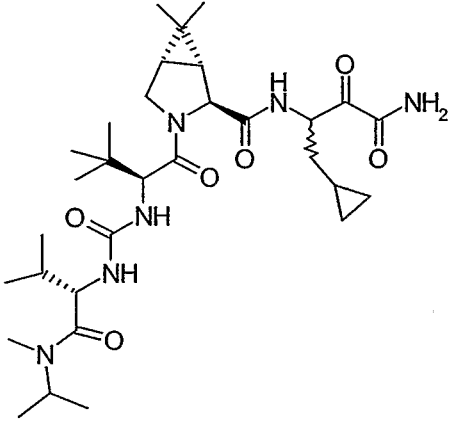
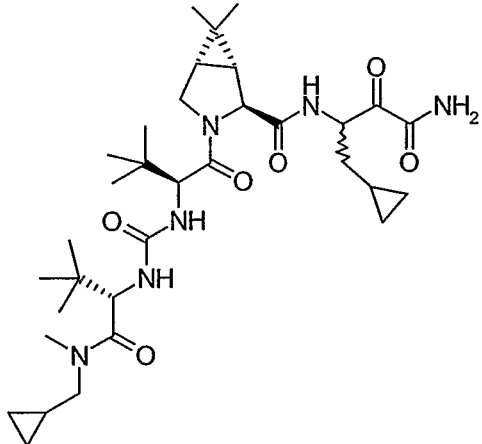
376

layer was washed with sat. Na₂S₂O₃ (2 TIMES) , NaHCO₃ and brine. Organic layer was dried over MgSO₄, filtered and concentrated under vacuo. The residue was purified by HPFC Biotage 12 S, 2% to 6% MeOH in DCM. Purification furnished 35 mg of compound of formula **4800**.

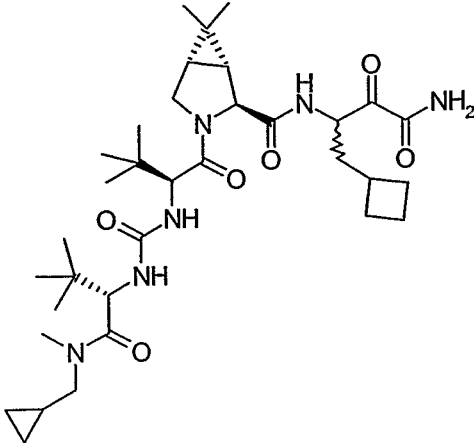
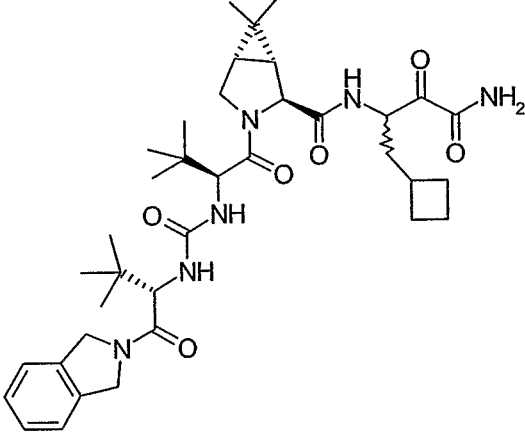
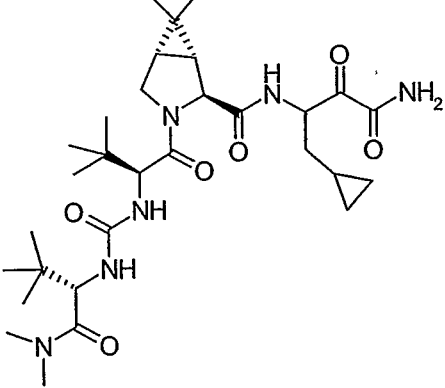
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Cmpd #	Table 5: Amides	MW	Ki* Range
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4801		693	A

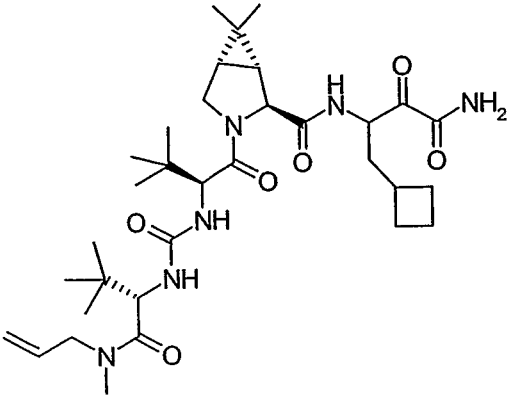
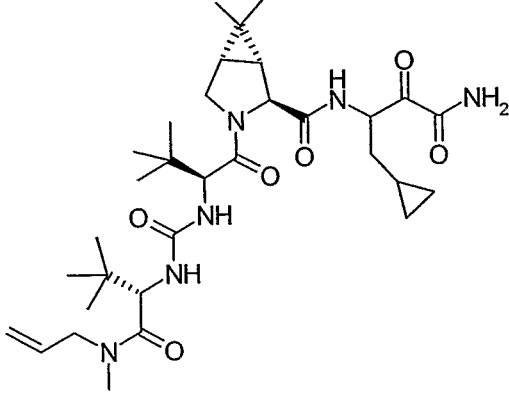
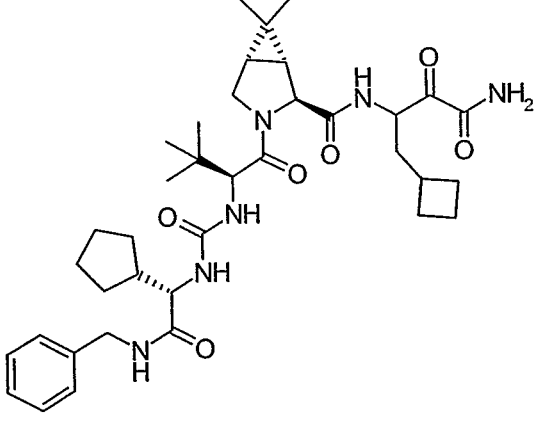
Cmpd #	Table 5: Amides	MW	Ki* Range
4802		694	A
4803		605	A
4804		619	A

Cmpd #	Table 5: Amides	MW	Ki* Range
4805		667	A
4806		605	A
4807		631	A

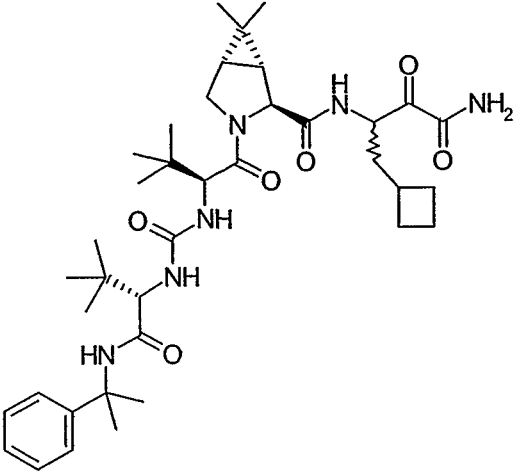
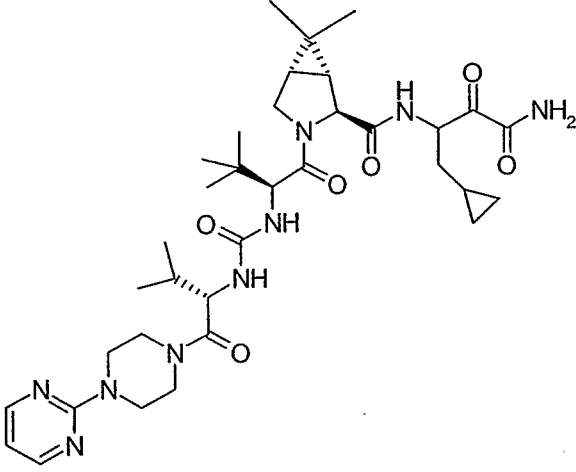
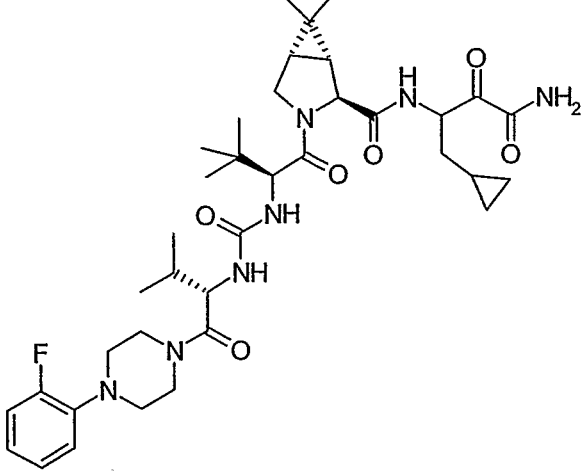
379

Cmpd #	Table 5: Amides	MW	Ki* Range
4808		645	A
4809		679	A
4810		591	A

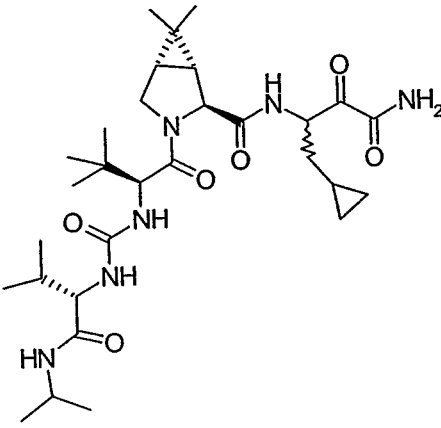
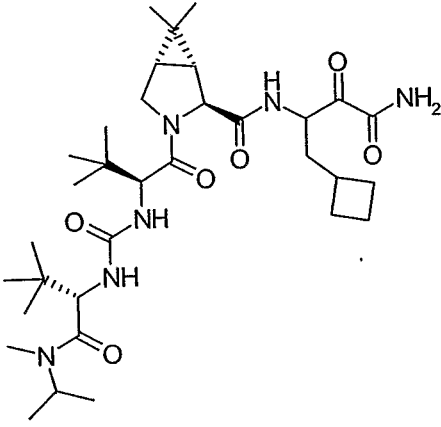
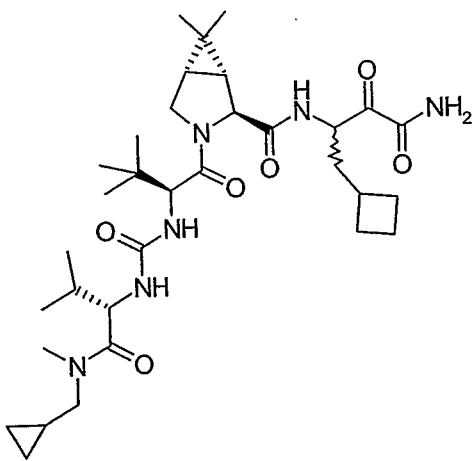
380

Cmpd #	Table 5: Amides	MW	Ki* Range
4811		631	A
4812		617	A
4813		679	A

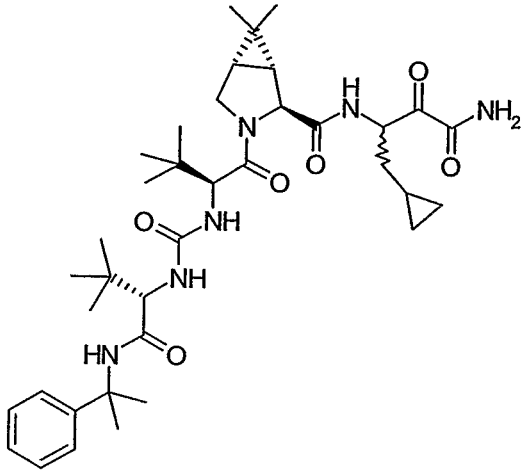
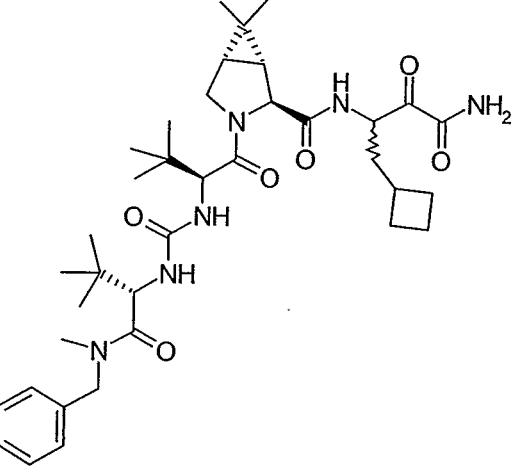
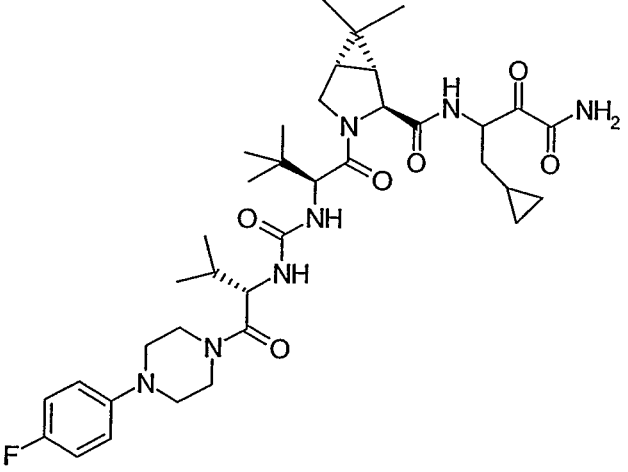
381

Cmpd #	Table 5: Amides	MW	Ki* Range
4814		695	A
4815		696	A
4816		712	A

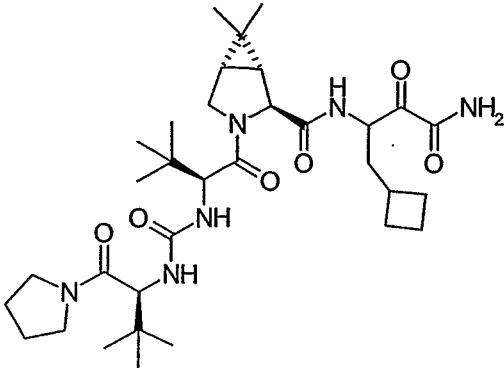
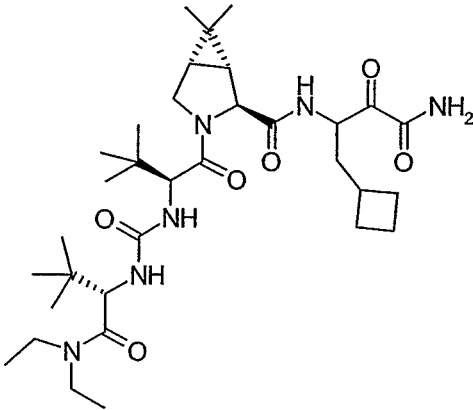
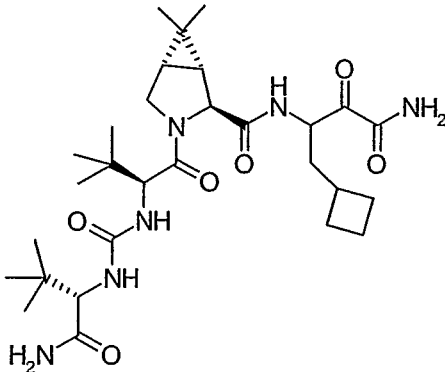
382

Cmpd #	Table 5: Amides	MW	Ki* Range
4817		591	A
4818		633	A
4819		631	A

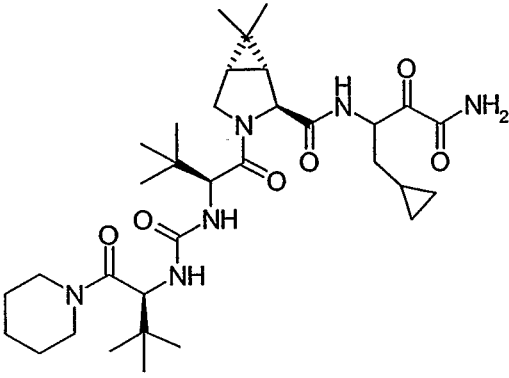
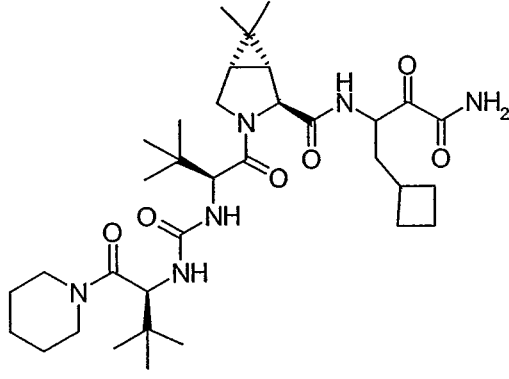
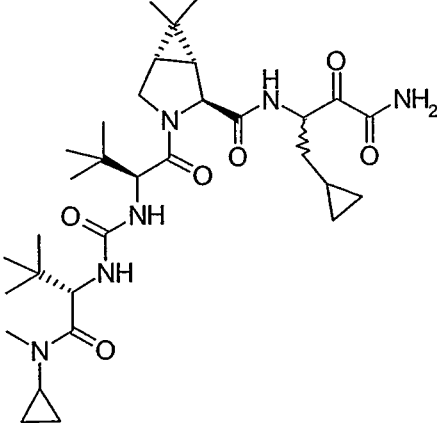
383

Cmpd #	Table 5: Amides	MW	Ki* Range
4820		681	A
4821		681	A
4822		712	A

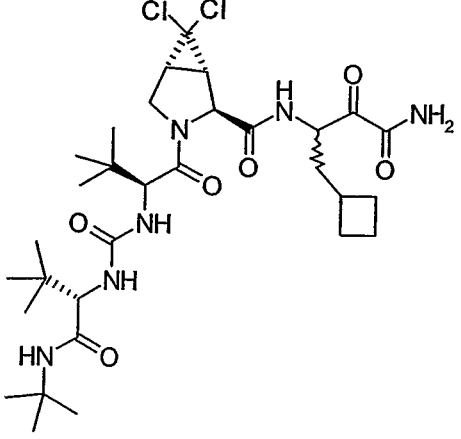
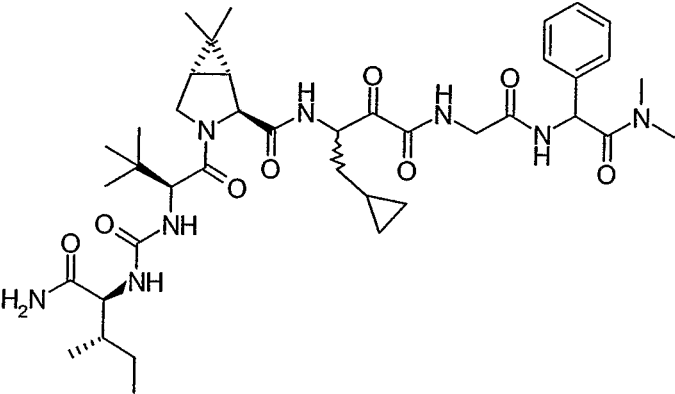
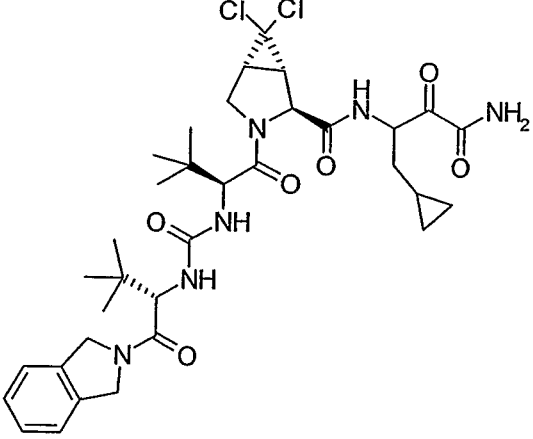
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Cmpd #	Table 5: Amides	MW	Ki* Range
4826		631	A
4827		633	A
4828		577	A

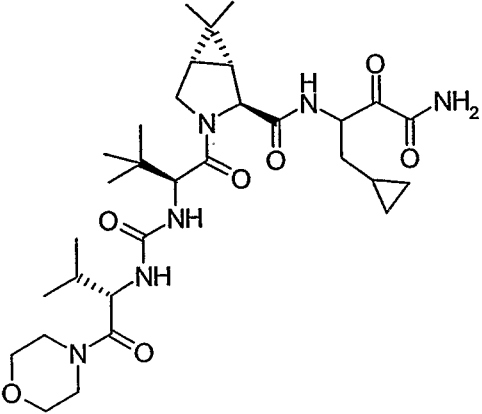
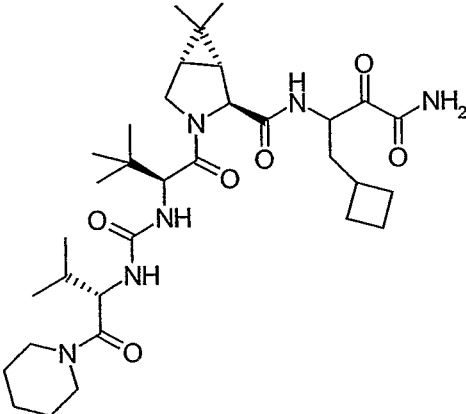
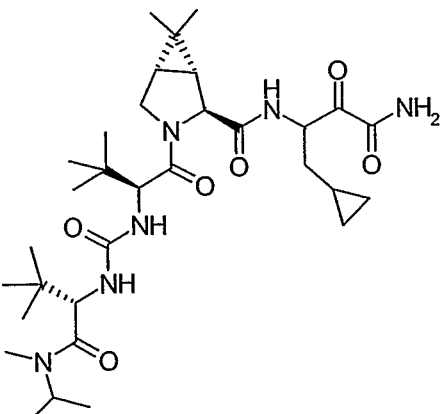
386

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4829		631	A
4830		645	A
4831		617	A

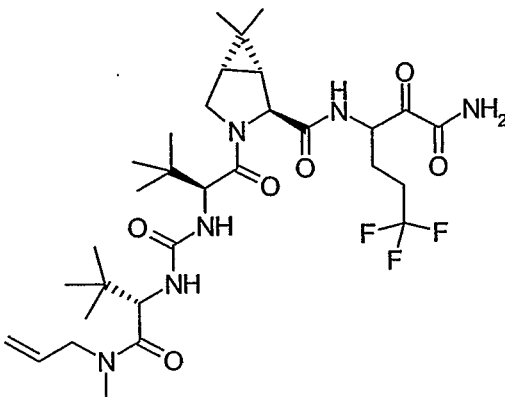
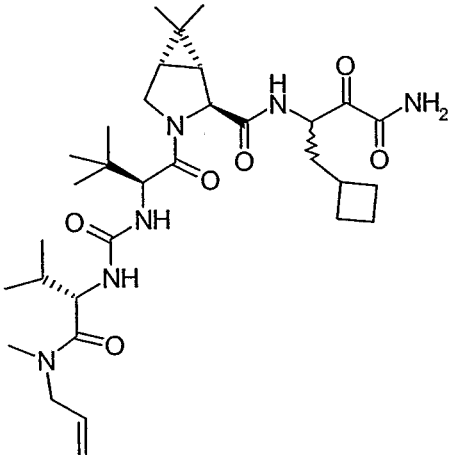
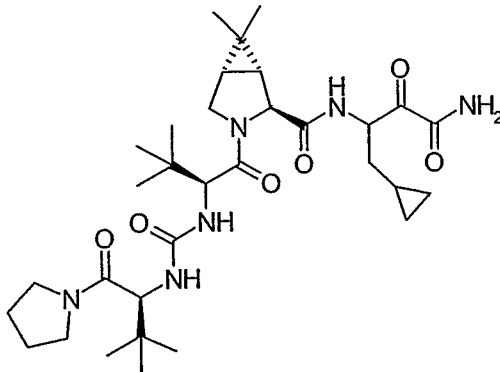
387

Cmpd #	Table 5: Amides	MW	Ki* Range
4832		674	A
4833		781	A
4834		706	A

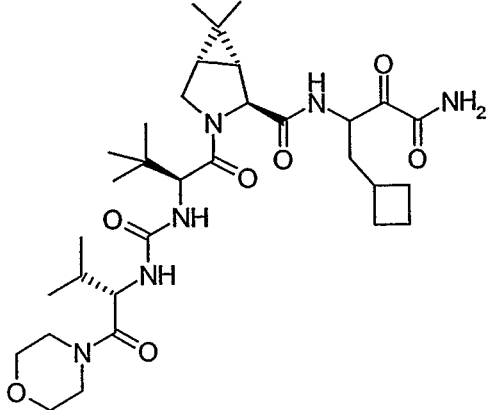
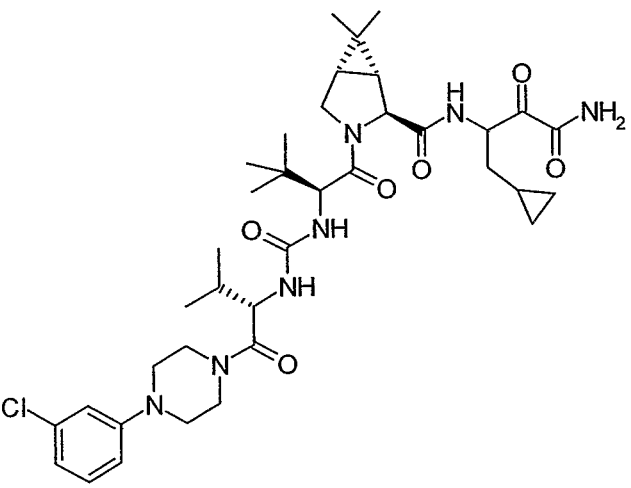
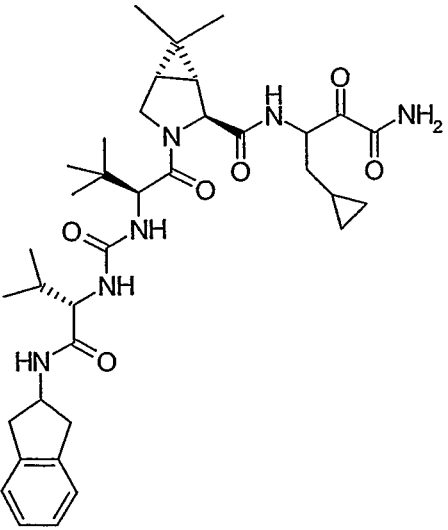
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Cmpd #	Table 5: Amides	MW	Ki* Range
4835		619	A
4836		631	A
4837		619	A

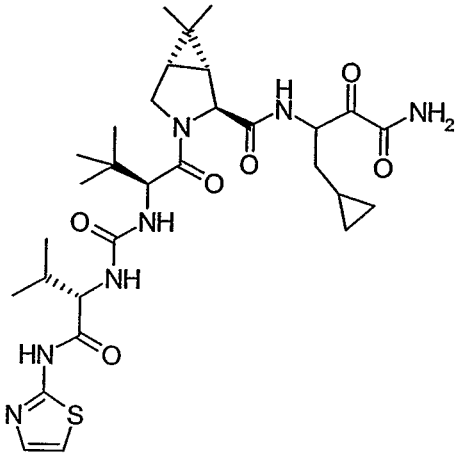
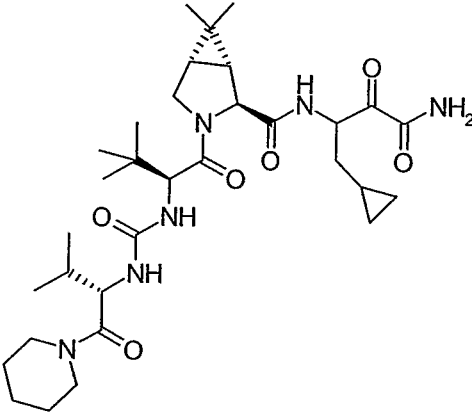
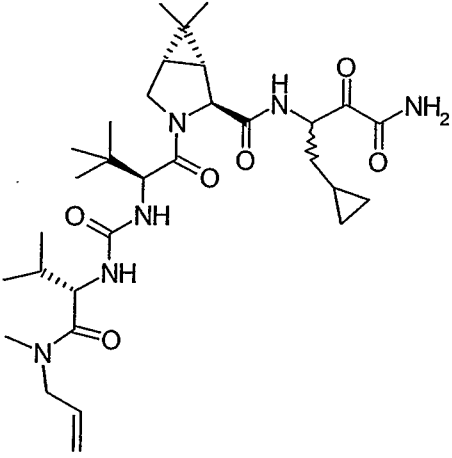
389

Cmpd #	Table 5: Amides	MW	Ki* Range
4838		659	A
4839		617	A
4840		617	A

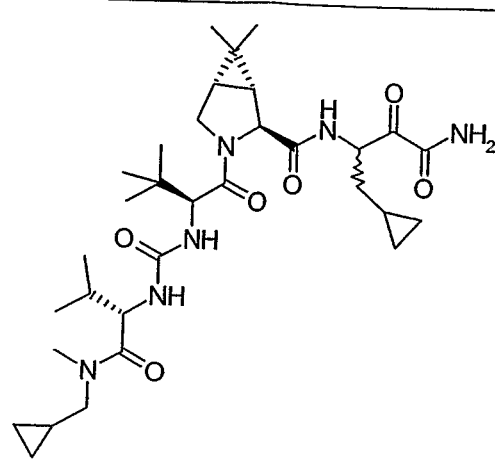
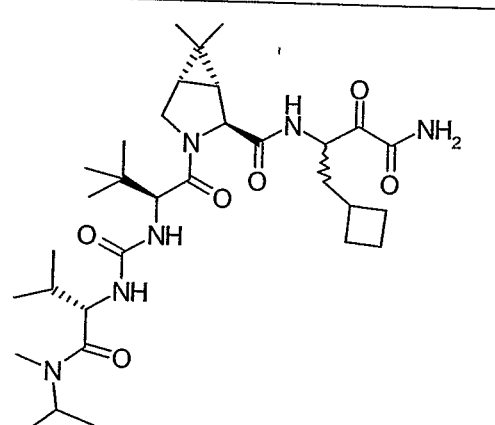
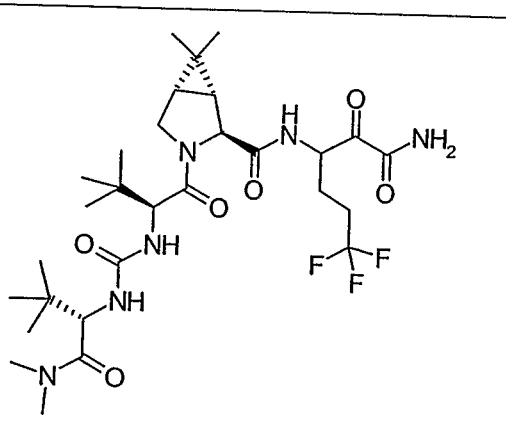
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Cmpd #	Table 5: Amides	MW	Ki* Range
4842		633	A
4843		728	A
4844		665	A

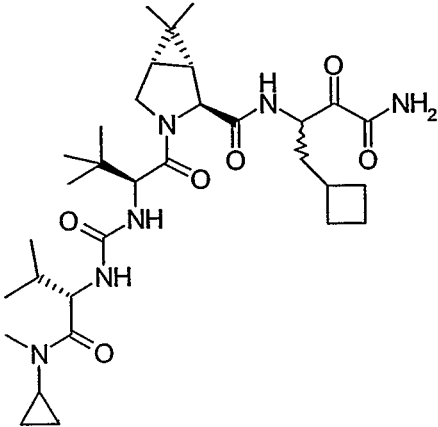
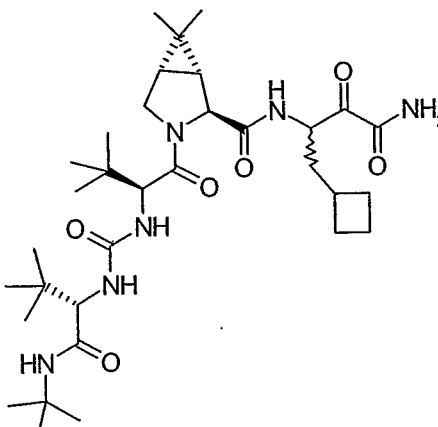
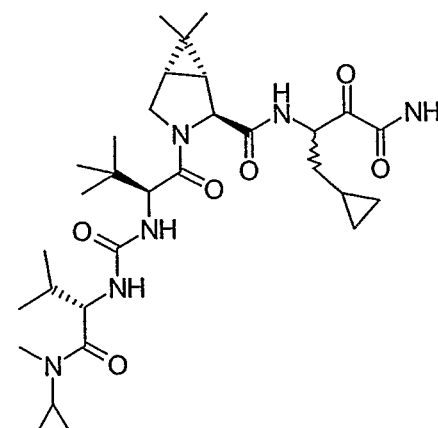
391

Cmpd #	Table 5: Amides	MW	Ki* Range
4845		632	A
4846		617	A
4847		603	A

392

Cmpd #	Table 5: Amides	MW	Ki* Range
4848		617	A
4849		619	A
4850		633	A

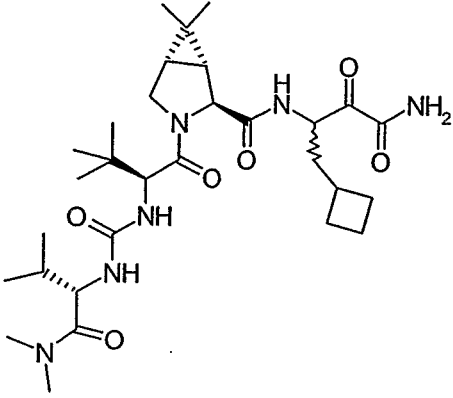
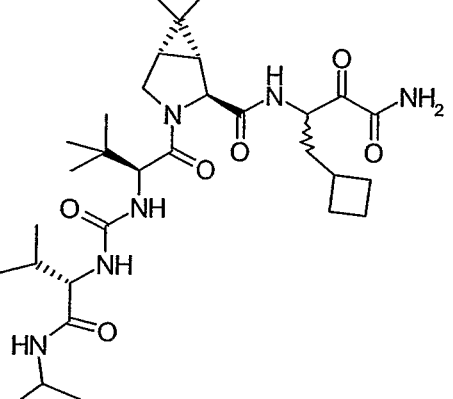
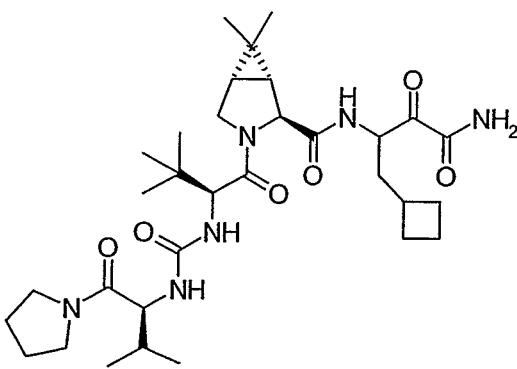
393

Cmpd #	Table 5: Amides	MW	Ki* Range
4851		617	A
4852		633	A
4853		603	A

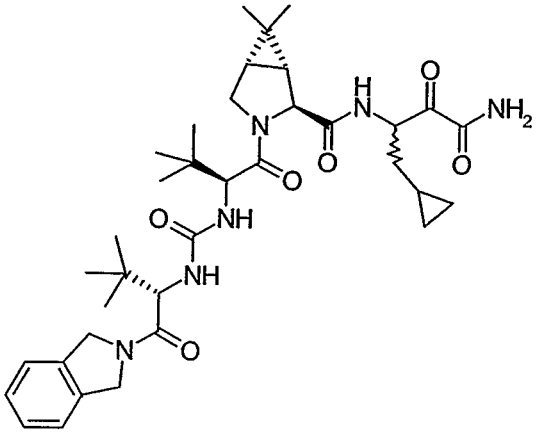
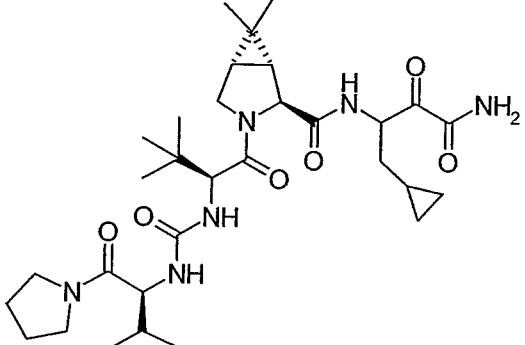
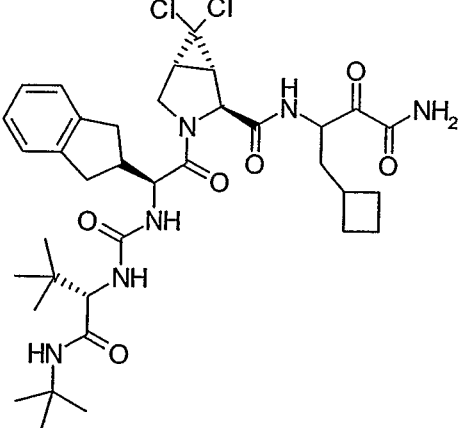
394

Cmpd #	Table 5: Amides	MW	Ki* Range
4854		631	A
4855		765	A
4856		619	A

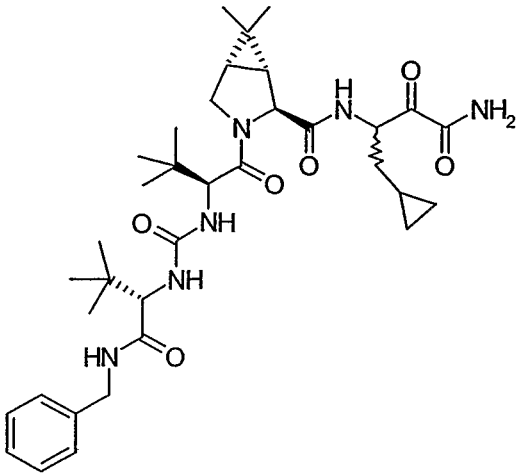
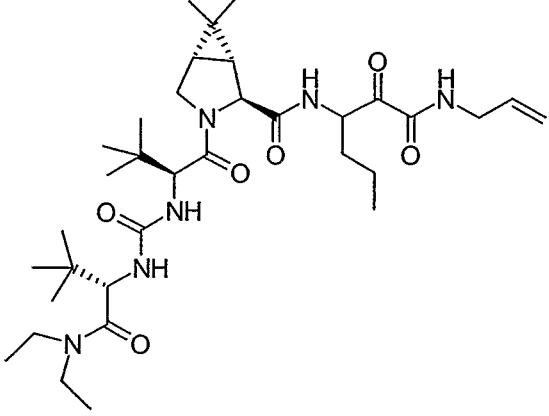
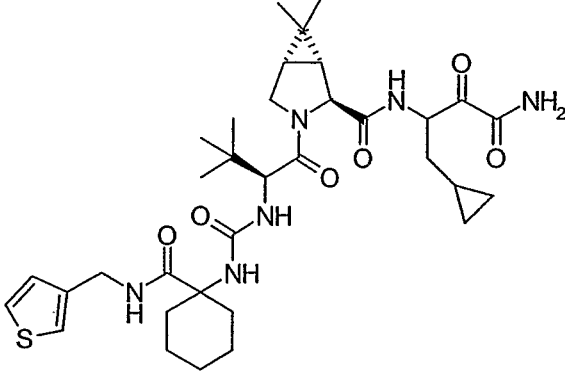
395

Cmpd #	Table 5: Amides	MW	Ki* Range
4857		591	A
4858		605	A
4859		617	A

396

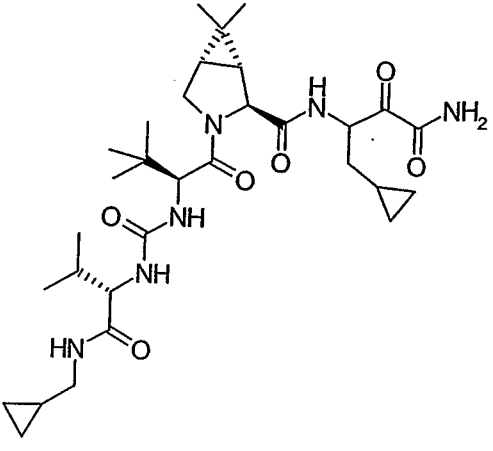
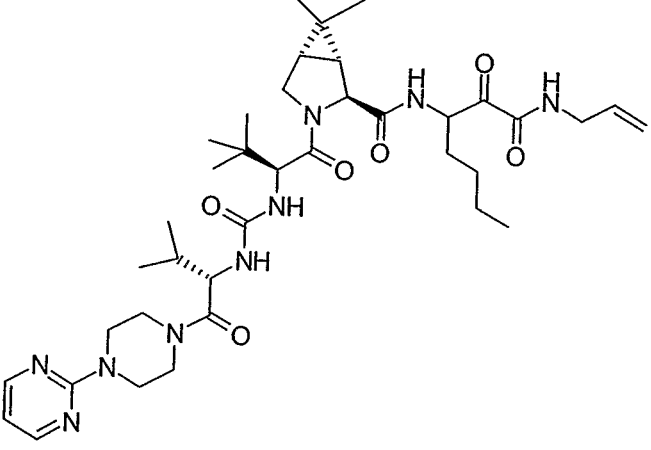
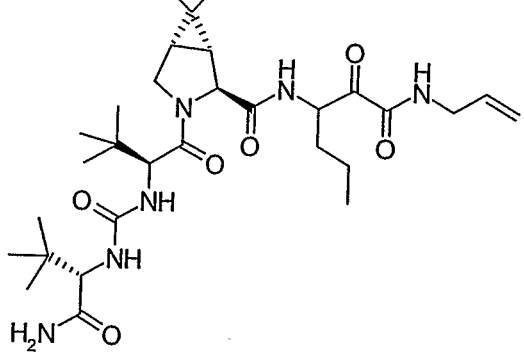
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4861		603	A
4862		734	A

397

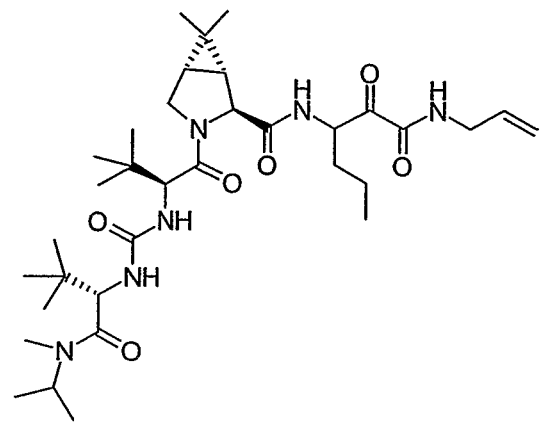
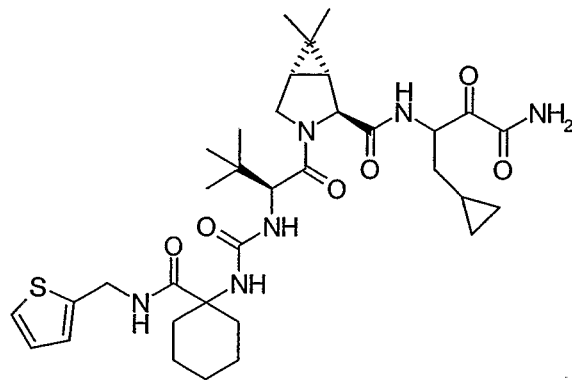
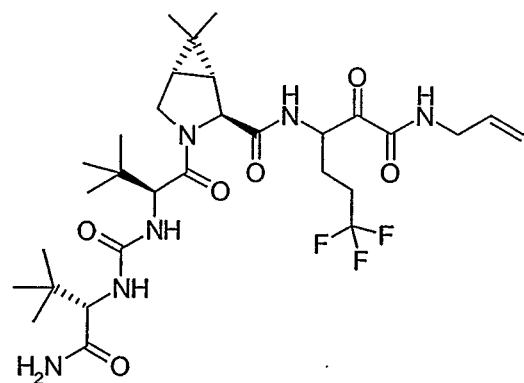
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4864		647	A
4865		671	A

Cmpd #	Table 5: Amides	MW	Ki* Range
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4867		659	A
4868		687	A

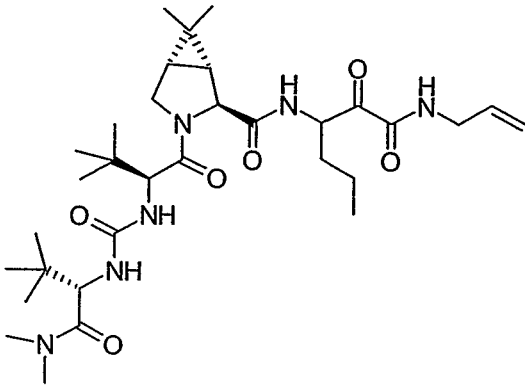
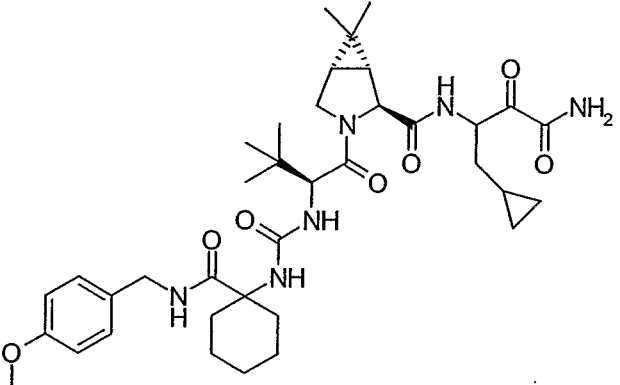
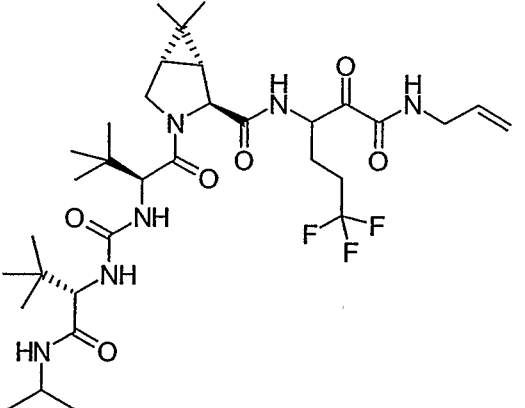
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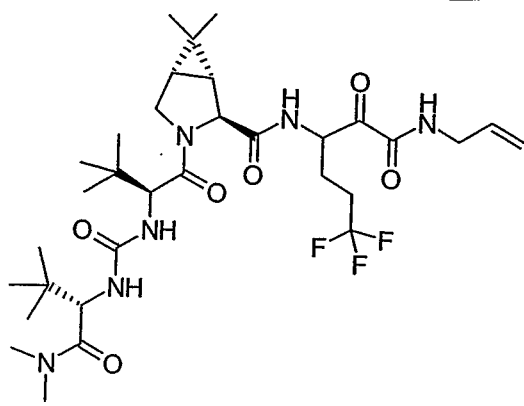
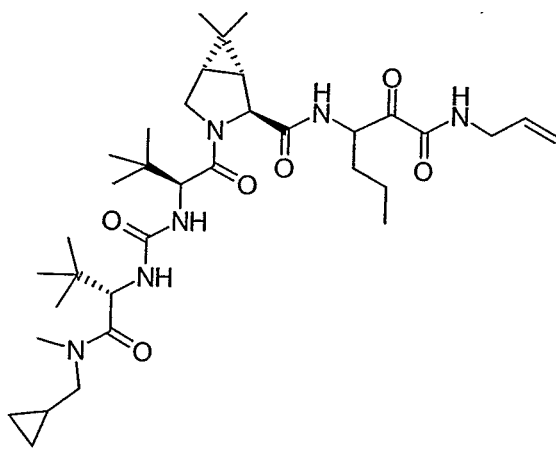
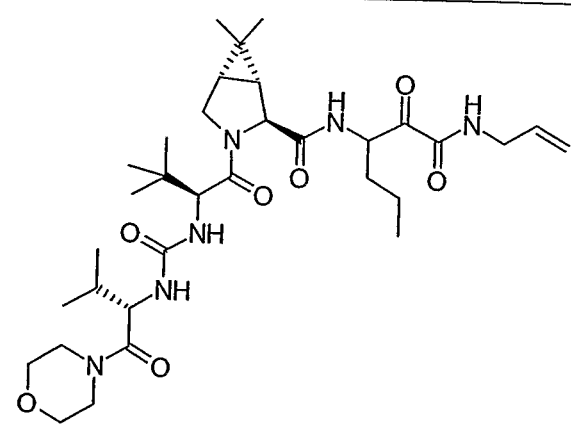
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4871		738	A
4872		591	A

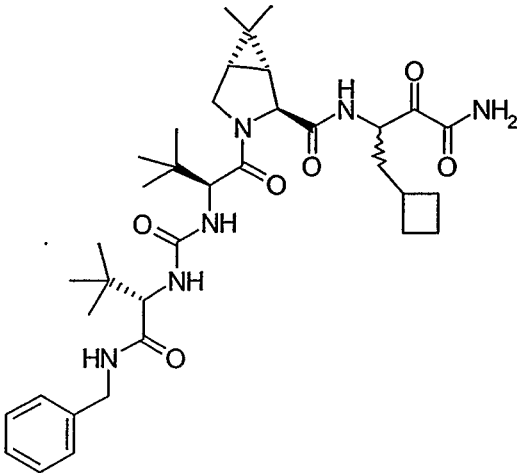
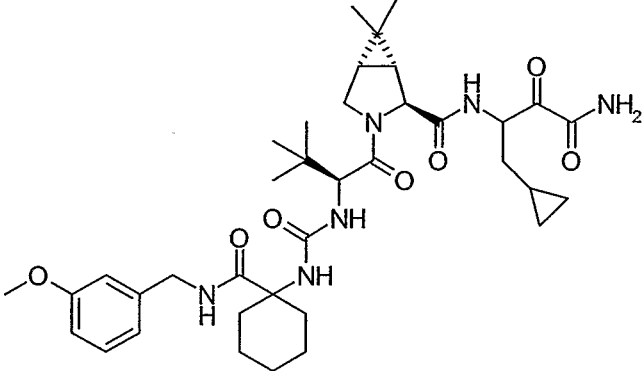
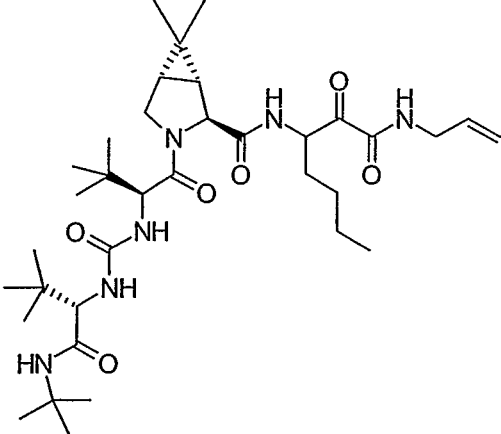
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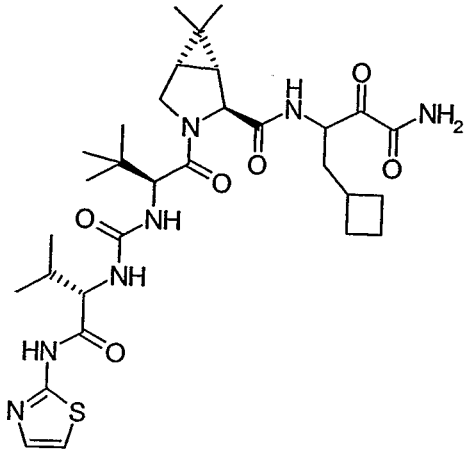
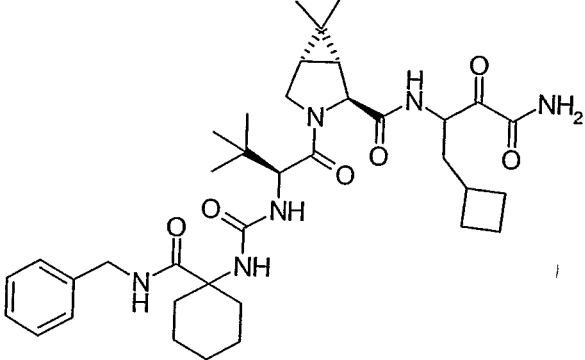
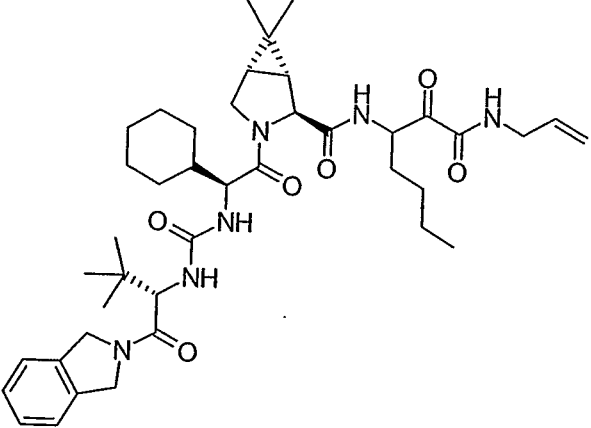
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4875		645	A

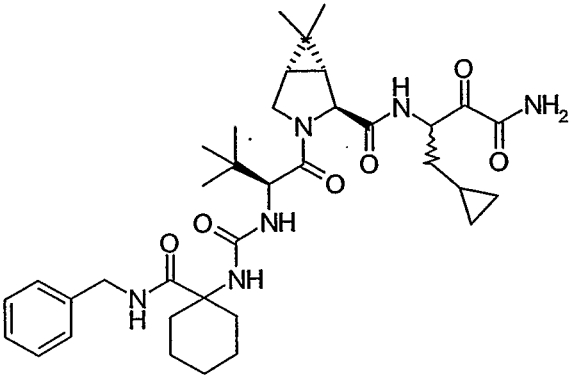
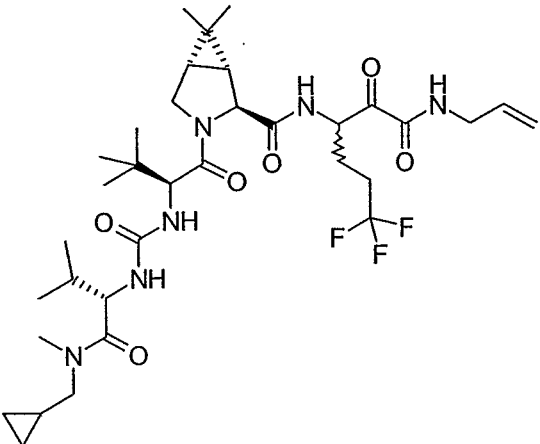
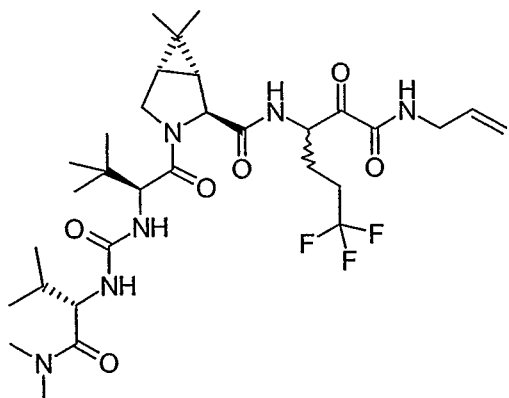
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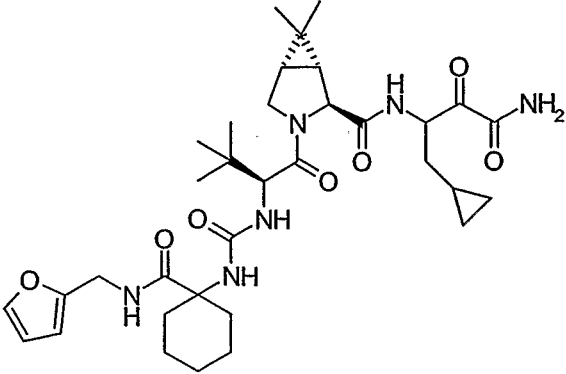
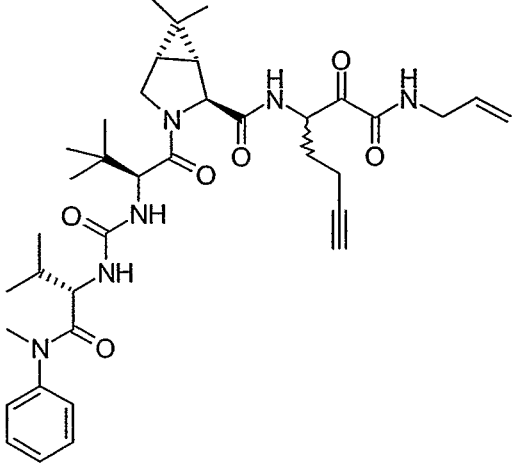
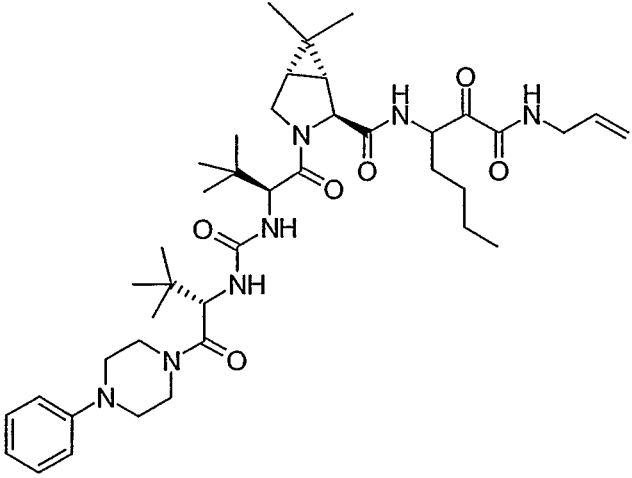
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4877		695	A
4878		687	A

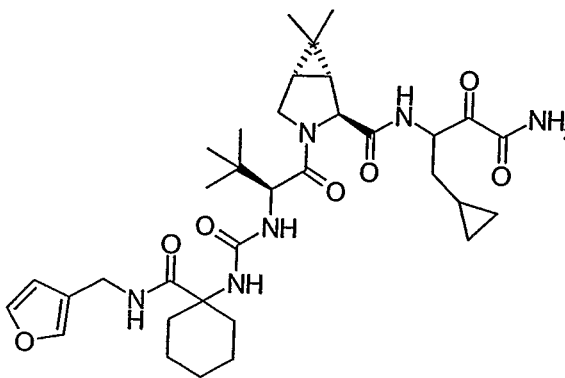
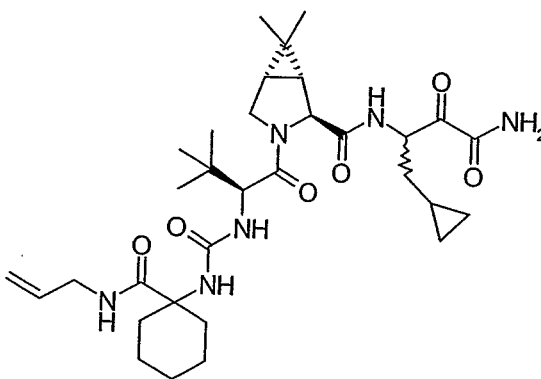
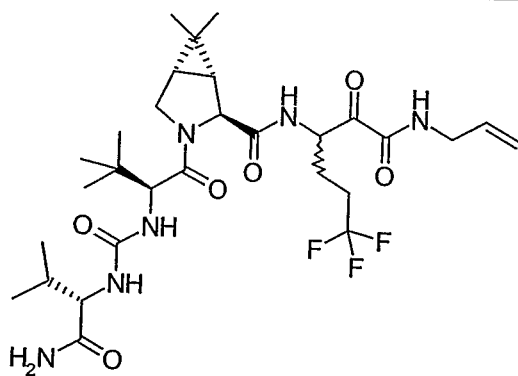
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4880		659	A
4881		647	A

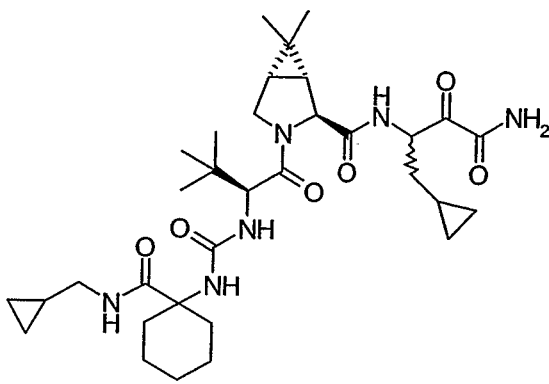
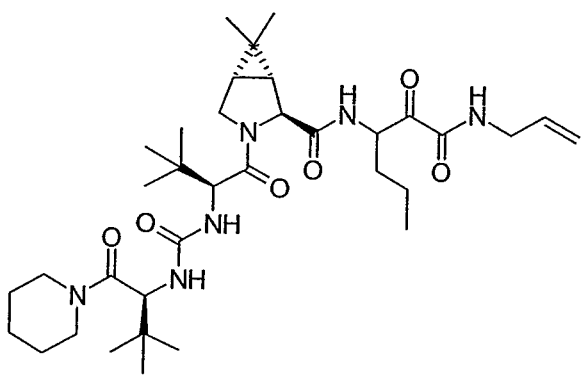
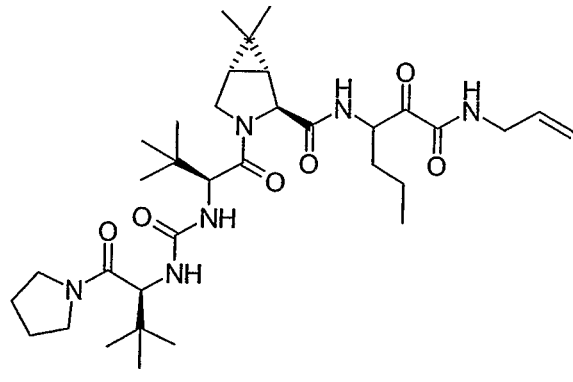
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4882		667	A
4883		695	A
4884		661	A

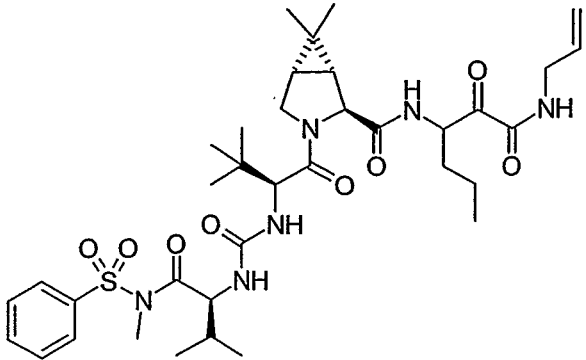
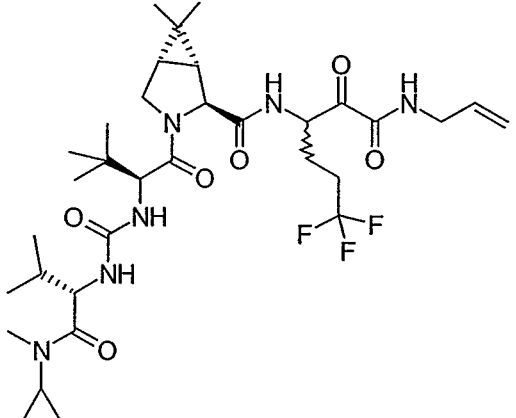
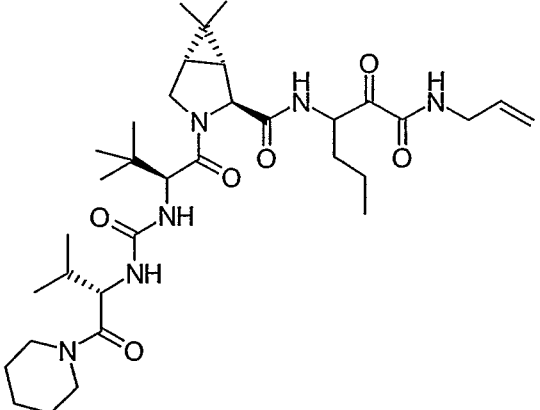
Cmpd #	Table 5: Amides	MW	Ki* Range
4885		646	A
4886		679	A
4887		733	A

Cmpd #	Table 5: Amides	MW	Ki* Range
4888		665	A
4889		699	A
4890		659	A

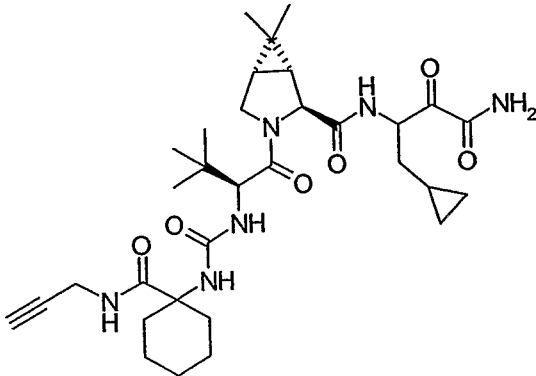
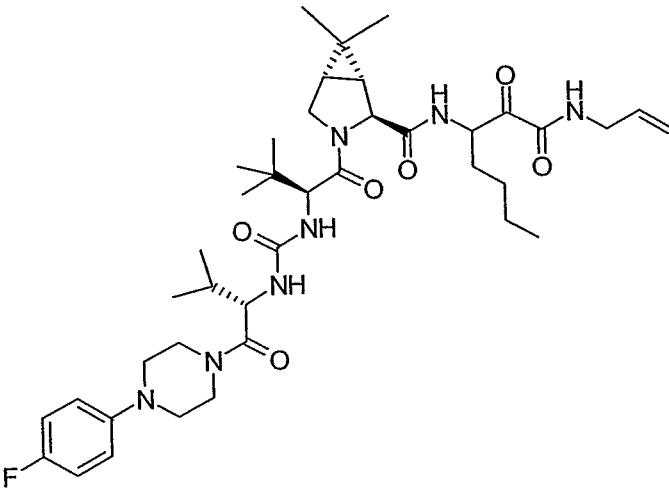
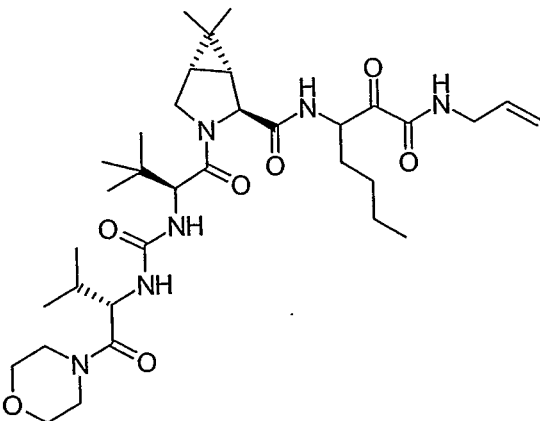
Cmpd #	Table 5: Amides	MW	Ki* Range
4891		655	A
4892		677	A
4893		750	A

Cmpd #	Table 5: Amides	MW	Ki* Range
4894		655	A
4895		615	A
4896		631	A

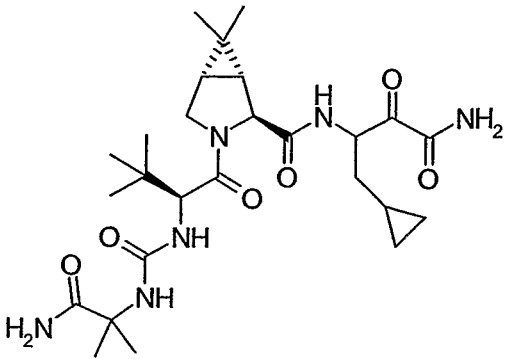
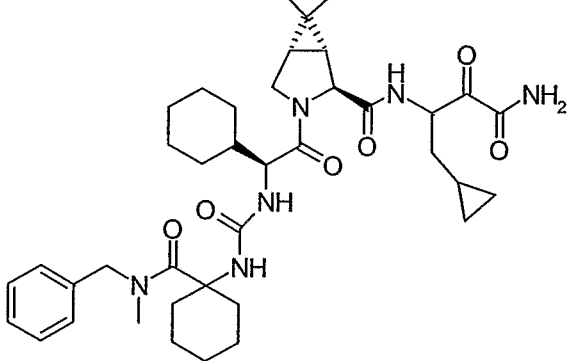
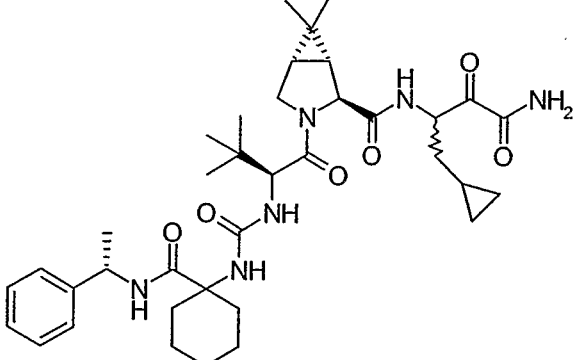
Cmpd #	Table 5: Amides	MW	Ki* Range
4897		629	A
4898		659	A
4899		645	A

Cmpd #	Table 5: Amides	MW	Ki* Range
4900		731	A
4901		685	A
4902		645	A

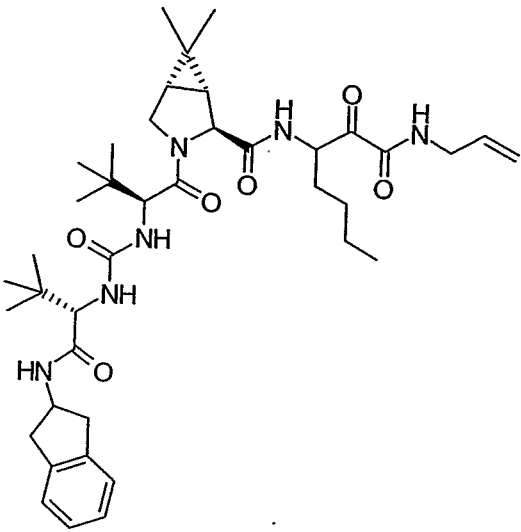
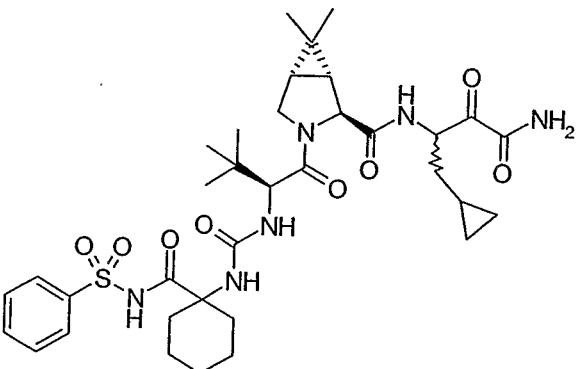
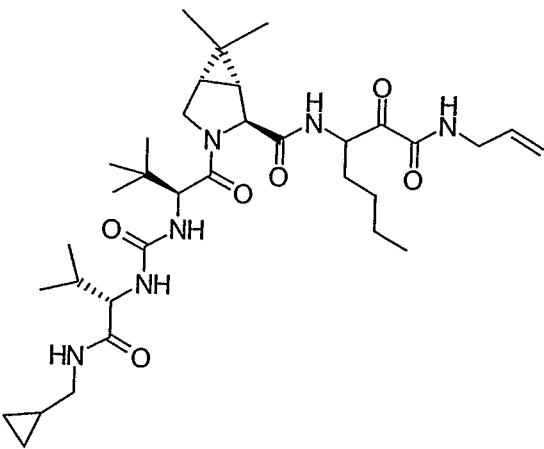
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Cmpd #	Table 5: Amides	MW	Ki* Range
4903		613	A
4904		754	B
4905		661	B

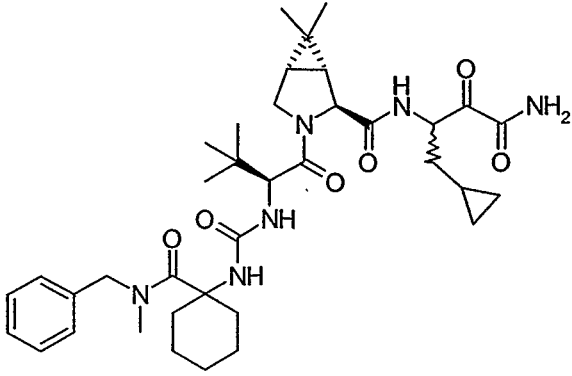
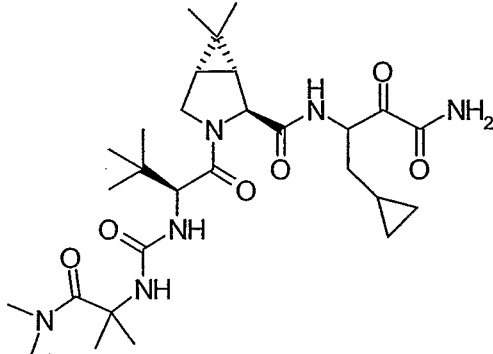
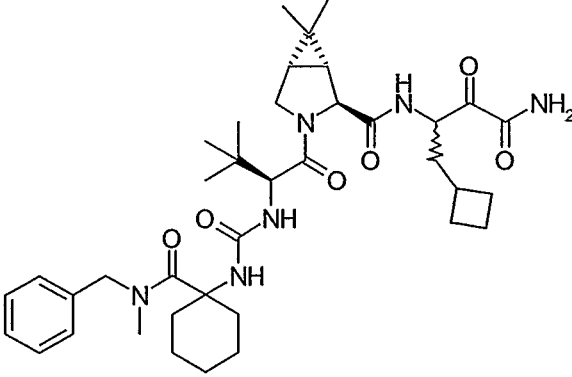
411

Cmpd #	Table 5: Amides	MW	Ki* Range
4906		535	B
4907		705	B
4908		679	B

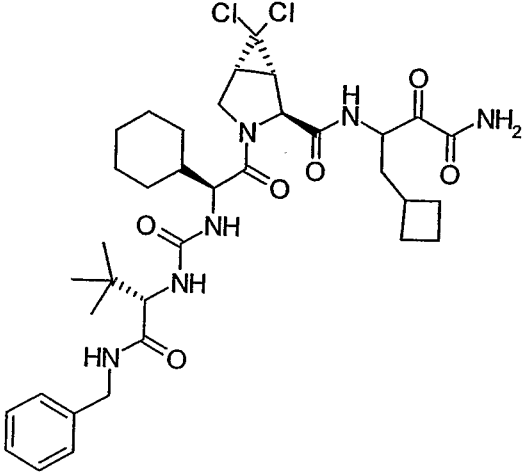
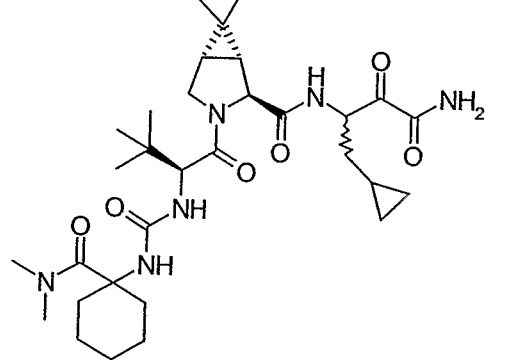
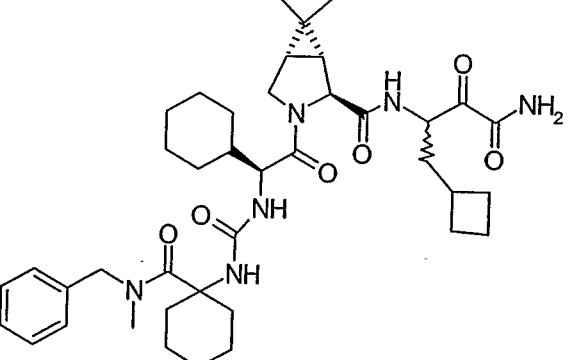
412

Cmpd #	Table 5: Amides	MW	Ki* Range
4909		721	B
4910		715	B
4911		645	B

413

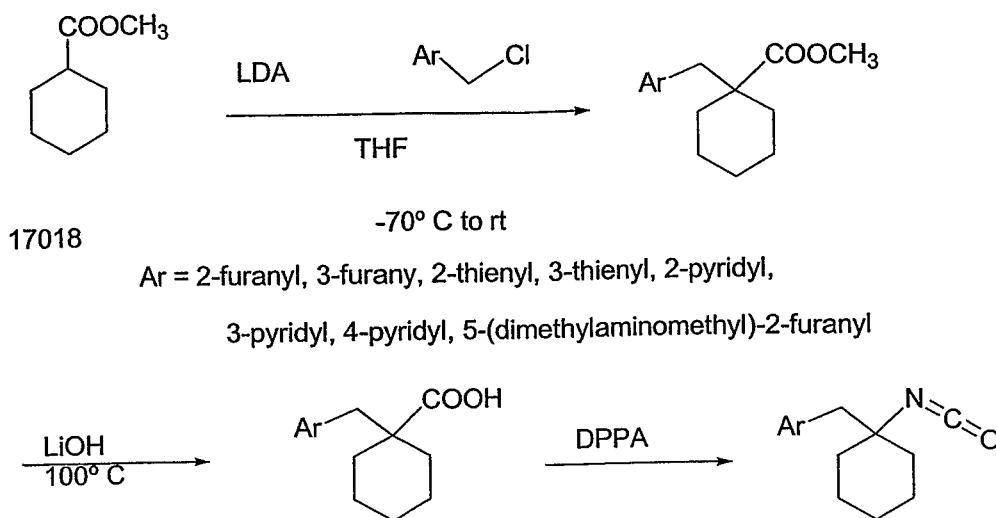
Cmpd #	Table 5: Amides	MW	Ki* Range
4912	 Chemical structure of compound 4912: A complex molecule featuring a cyclohexane ring substituted with a benzyl group and a dimethylamino group. This ring is linked via an amide bond to a side chain containing a pyrrolidine ring, a tert-butyl group, and a cyclopropylmethyl group, which is further substituted with a primary amide group.	679	B
4913	 Chemical structure of compound 4913: Similar to 4912, but the cyclohexane ring is substituted with a dimethylamino group and a dimethylamino group. The side chain is identical to 4912, featuring a pyrrolidine ring, a tert-butyl group, and a cyclopropylmethyl group, with a primary amide group.	563	B
4914	 Chemical structure of compound 4914: Similar to 4912, but the cyclohexane ring is substituted with a benzyl group and a dimethylamino group. The side chain is identical to 4912, featuring a pyrrolidine ring, a tert-butyl group, and a cyclobutylmethyl group, with a primary amide group.	693	C

414

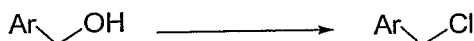
Cmpd #	Table 5: Amides	MW	Ki* Range
4915		734	C
4916		603	C
4917		719	C

Example XIX: Preparation of General Intermediates of Tables 6.1, 6.2 and 6.3

415



Part I: Preparation of Intermediate of Table 6.1



(HETEROCYCLYL)METHYL CHLORIDES:

5-(Dimethylaminomethyl)furfuryl chloride was prepared from commercially available 5-(dimethylaminomethyl)furfuryl alcohol (Aldrich Chemical Co., Milwaukee, Wisconsin, USA) as reported (Il Farmaco, *Ed. Sci.*, **1982**, 37, 398).

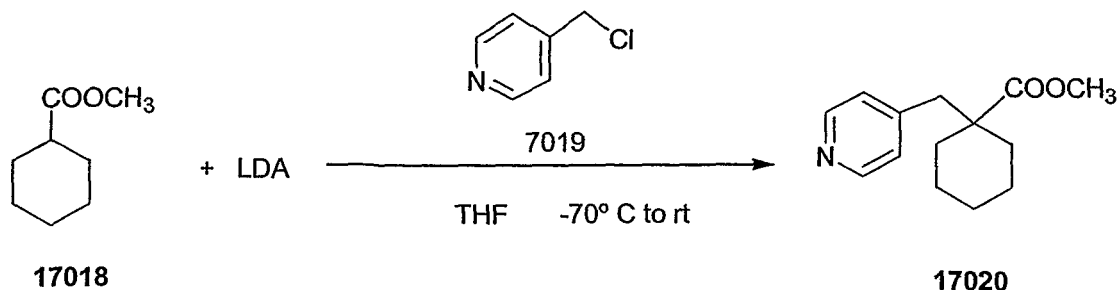
2-, 3-, And 4-picolyl chlorides were prepared from the commercially available hydrochloride salts (Aldrich Chemical Co., Milwaukee, Wisconsin, USA) by partitioning them with cold 2.5 N NaOH and ether, drying the ether extract with MgSO₄, and concentrating the solution in a 15° C water bath, all immediately before use.

2-Chloromethylfuran was prepared from SOCl₂ in Et₂O as reported (JACS, (1928), 50, 1955). 3-chloromethylfuran was prepared similarly, except a solution of alcohol and pyridine was added to a solution of SOCl₂ to prevent excessive formation of sulfonate diester. In both cases distillation was necessary to effect rearrangement of the initial chlorosulfonate isolate. Both distilled halides were immediately stored in ether (~1 M) with a little solid K₂CO₃ at -20° C. These solutions were stable for at least 24 hours.

2- And 3-chloromethylthiophene were prepared using the same procedures as for 2- and 3-chloromethylfuran, except distillation was not necessary, since the chlorosulfonates transformed spontaneously under the reaction conditions. The dried extract solutions were rapidly suction-filtered through silica gel pads to effect sufficient

purification. The filtrates were stored cold, and concentrated carefully immediately before use.

METHYL [2-(4-PYRIDYLMETHYL)CYCLOHEXANE]CARBOXYLATE



A solution of 20 mL of 2 M LDA / THF-heptane (Acros Chemical Co.) in 50 mL of THF was cooled to -70°C , and 6 g of methyl cyclohexanecarboxylate **17018** was added drop wise at $< -60^\circ \text{C}$. After an additional 0.5 hr stirring at -70°C , 5.1 g of 4-picolyl chloride in 40 mL ether was added drop wise at $< -60^\circ \text{C}$. The temperature was then allowed to rise slowly to room temperature over 2 hr, and stirred an additional 2 hr. The reaction was quenched in a cold mixture of 200 mL 20% aqueous KH_2PO_4 and 5 mL 12 N HCl, the mixture was extracted with EtOAc, the extract was washed with brine, and then dried with MgSO_4 . The mixture was filtered, the filtrate was evaporated, the residue was evaporated twice from xylene, and the final residue was chromatographed on silica gel (1:4 $\text{Et}_2\text{O}-\text{CH}_2\text{Cl}_2$) to obtain 3.0 g of an amber oil **17020** (30%): ^1H -NMR (CDCl_3) δ 8.46 (d, 2H, $\Delta v=6.0$), 6.98 (d, 2H, $\Delta v=6.0$), 3.62 (s, 3H), 2.79 (s, 2H), 2.05 (m, 2H), 1.7-1.2 (mm, 8H).

METHYL [2-(HETEROARYLMETHYL)CYCLOHEXANE]CARBOXYLATES

The procedure of the preceding example was applied to the aryl methyl chlorides to afford the corresponding substituted cyclohexanecarboxylates as summarized in the following Table 6.1.

TABLE 6.1

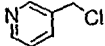
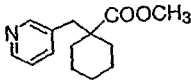
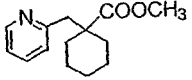
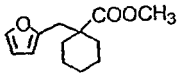
Starting halide	Chromatography system	Yield	Product	Product ^1H -NMR (CDCl ₃) δ (Δv in Hz)
 17021	1:3 Et ₂ O-CH ₂ Cl ₂ to 1:1 acetone-CH ₂ Cl ₂	31	 17028	8.45 (d of d, 1H, $\Delta v_1=4.8$, $\Delta v_2=1.8$), 7.35 (d of t, 1H, $\Delta v_1=7.8$, $\Delta v_2=1.8$), 7.18 (d of d, 1H, $\Delta v_1=7.8$, $\Delta v_2=4.8$), 3.62(s, 3H), 2.79 (s, 2H), 2.1 (m, 2H), 1.7-1.2 (mm, 8H)
 17022	1:3 Et ₂ O-CH ₂ Cl ₂ to 1:1 acetone-CH ₂ Cl ₂	58	 17029	8.50 (br d, 1H, $\Delta v=4.5$), 7.55 (t+, 1H, $\Delta v_1=7.6$, $\Delta v_2=1.8$), 7.10 (d of d+, $\Delta v_1=7.6$, $\Delta v_2=4.5$, $\Delta v_3=nd$), 7.01 (d, $\Delta v=7.6$), 3.64 (s, 3H), 2.98 (s, 2H), 2.1 (m, 2H), 1.7-1.2 (mm, 8H)
 17023	Rapid silica pad filtration in 1:1 hexane-toluene	52	 17030	7.28 (br d, 1H, $\Delta v=1.8$), 6.26 (d of d, 1H, $\Delta v_1=3.0$, $\Delta v_2=1.8$), 5.97 (d, 1H, $\Delta v=3.0$), 3.66 (s, 3H), 2.83 (s, 2H), 2.05 (m, 2H), 1.7-1.2 (mm, 8H)

TABLE 6.1

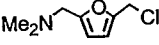
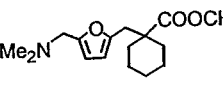
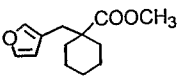
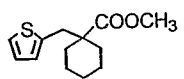
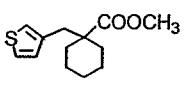
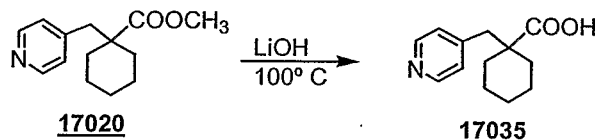
Starting halide	Chromatography system	Yield	Product	Product H ¹ -NMR (CDCl ₃) δ (Δv in Hz)
 17024	Short column, EtOAc to acetone None: extracted at pH 5.0 after saturating aqueous with NaCl	30	 17031	6.05 (d, 1H, $\Delta v=3.0$), 5.89 (d, 1H), 3.66 (s, 3H), 3.40 (s, 2H), 2.81 (s, 2H), 2.23 (s, 6H), 2.05 (m, 2H), 1.7-1.2 (mm, 8H)
 17025	Rapid silica pad filtration in 1:1 hexane-toluene	81	 17032	7.34 (m, 1H), 7.18 (br s, 1H), 6.17 (br s, 1H), 3.65 (s 3H), 2.62 (s, 2H), 2.1 (m, 2H), 1.7-1.2 (mm, 8H)
 17026	4:96 Et ₂ O-hexane	75	 17033	7.11 (d+, 1H, $\Delta v=5.1$), 6.91 (d of d, 1H, $\Delta_1 v=5.1$, $\Delta v_2=3.6$), 6.72 (d of d, 1H, $\Delta_1 v=3.6$, $\Delta v_2=0.9$), 3.67 (s 3H), 3.04 (s, 2H), 2.1 (m, 2H), 1.7-1.2 (mm, 8H)

TABLE 6.1				
Starting halide	Chromatography system	Yield	Product	Product H ¹ -NMR (CDCL ₃) δ (Δv in Hz)
 17027	3:97 Et ₂ O-hexane	53	 17034	7.20 (d of d, 1H, $\Delta v_1=5.0$, $\Delta v_2=3.0$), 6.89 (br s, 1H), 6.80 (d of d, 1H, $\Delta v_1=5.0$, $\Delta v_2=1.5$), 3.63 (s 3H), 2.83 (s, 2H), 2.1 (m, 2H), 1.7-1.2 (mm, 8H)

Part II: Preparation of Intermediates of Table 6.2:

Preparative example **17035** : Preparation of Intermediate of Formula **17035**

[2-(4-PYRIDYLMETHYL)CYCLOHEXANE]CARBOXYLIC ACID

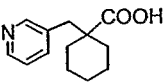
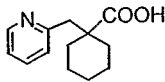
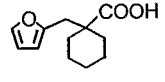
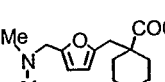


A solution of 3.4 g ester **17020** of the previous example in 20 mL of dioxane was treated with 30 mL of 1 N aqueous LiOH, and the mixture was stirred at 100° C for 6 hr. The mixture was quenched in ice-water, extracted with ether, and the cold aqueous was slowly acidified to pH 4 with 3 N HCl. The precipitate was filtered, washed with water, and dried to leave 2.8 g (58%) product acid **17035**: H¹ -NMR (DMSO-d₆) δ 8.42 (d, 2H), 7.08 (d, 2H), 2.73 (s, 2H), 1.9-1.1 (mm, 10H). A portion was crystallized from EtOH: mp: 240-242° C; elemental analysis confirmed: CHN. Same procedure was applied for the preparation of intermediates **17036** and **17037** of table 6.2.

[1-(HETEROARYLMETHYL)CYCLOHEXANE]CARBOXYLIC ACIDS

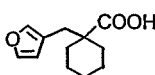
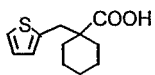
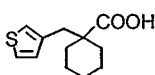
The procedure of the preceding example was applied to the esters (**17038**, **17039**, **17040**, **17041**, **17042**) from Table 6.2 except that the acidified aqueous extract (pH 3.5-4.0) was extracted with EtOAc, after saturating with NaCl in the case of the two pyridyl products **17036** and **17037**. The extract was evaporated to leave

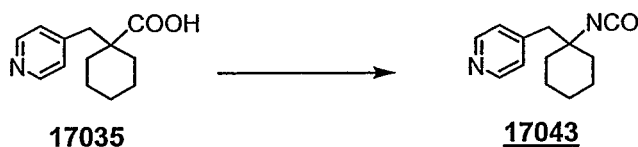
the product acids. Portions were crystallized for analysis as summarized in the following Table 6.2.

TABLE 6.2						
Starting ester	Product	Yield %	Product H^1 -NMR (CDCL ₃) δ ((ppm); Δv in Hz	crystallization solvent	mp (°C)	Elem anal
17028	 17036	31	8.42 (br s, 2H), 7.57 (d+, 1H, $\Delta v_1=7.5$, $\Delta v_2=1.8$), 7.27 (d of d, 1H, $\Delta v_1=7.5$, $\Delta v_2=2.7$), 2.83 (s, 2H), 2.1 (m, 2H), 1.7-1.2 (mm, 8H)	CH ₃ CCl ₃ -cyclohexane	155-7	CHN
17029	 17037	58	8.62 (d, 1H, $\Delta v=5.1$), 7.70 (t+, 1H, $\Delta v_1=7.5$, $\Delta v_2=1.8$), 7.22 (m, 2H), 3.10 (s, 2H), 2.1 (m, 2H), 1.6-1.3 (mm, 8H)	EtOH-(i-Pr) ₂ O	137-8	CHN
17030	 17038	52	7.29 (br s, 1H), 6.27 (d of d, 1H, $\Delta v_1=3.0$, $\Delta v_2=1.8$), 6.05 (d, 1H, $\Delta v=3.0$), 2.90 (s, 2H), 2.0 (m, 2H), 1.7-1.2 (mm, 8H)	na	oil	CH
17031	 17039	30	6.47 (d, 1H, $\Delta v=3.0$), 6.08 (d, 1H, $\Delta v=3.0$), 4.14 (s, 2H), 2.84 (s, 2H), 2.77 (s, 6H), 2.1 (m, 2H), 1.7-1.1 (mm, 8H)	CH ₃ CCl ₃ -cyclohexane	133-5	na

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TABLE 6.2

Starting ester	Product	Yield %	Product H^1 -NMR (CDCL ₃) δ ((ppm); Δv in Hz	crystallization solvent	mp (°C)	Elem anal
17032	 17040	81	7.34 (br s, 1H), 7.22 (br s, 1H), 6.22 (br s, 1H), 2.67 (s, 2H), 2.0 (m, 2H), 1.7-1.2 (mm, 8H)	na	oil	CH
17033	 17041	75	7.14 (d of d, 1H, $\Delta v_1=5.2$, $\Delta v_2=1.0$), 6.93 (d of d, 1H, $\Delta v_1=5.2$, $\Delta v_2=3.6$), 6.80 (d+, 1H, $\Delta v_1=3.6$, $\Delta v_2=\text{nod}^2$), 3.08 ³ (2H), 2.1 (m, 2H), 1.7-1.2 (mm, 8H)	cyclohexane-hexane/ -10°C	64-7 ¹	CH
17034	 17042	53	7.22 (d of d, 1H, $\Delta v_1=5.0$, $\Delta v_2=2.5$), 6.96 (d+, 1H, $\Delta v_1=2.5$, $\Delta v_2=\text{nod}$), 6.89 (d of d, 1H, $\Delta v_1=5.0$, $\Delta v_2=1.2$), 2.89 (2H)	cyclohexane	72-74	CH
Note 1: lit. value = 71-73° C (<i>J. Chem. Res. Miniprint</i>, 1981, 4, 1043-1056). Note 2: nd = not determined; insufficient resolution. Note 3: lit. value = δ 3.08 (v.s.).						

Part III: Preparation of Intermediates of Table 6.3:**Preparative example 17043 : Preparation of Intermediate of Formula 17043****1-(4-PYRIDYLMETHYL)CYCLOHEXYL ISOCYANATE**

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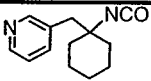
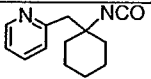
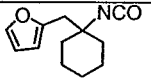
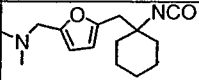
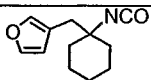
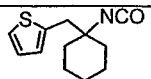
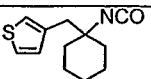
A mixture of 0.5 g of the carboxylic acid **17035** described above, 0.5 mL diphenylphosphoryl azide, and 25 mL toluene was heated at 110° C for 0.75 hr. The

cooled mixture was placed on a column of silica gel and rapidly eluted with EtOAc-hexane (2:3) to afford 0.39 g of the title compound as an oil, which was used soon after preparation. The product **17043** was stored in 1 M CH₂Cl₂ solution for brief periods. ¹H-NMR (CDCl₃) δ 8.3 (br s, 2H), 7.17 (d, J=5.4, 2H), 2.78 (s, 2H), 1.8-1.1 (m, 10H).

General Example Table 6.3

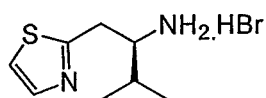
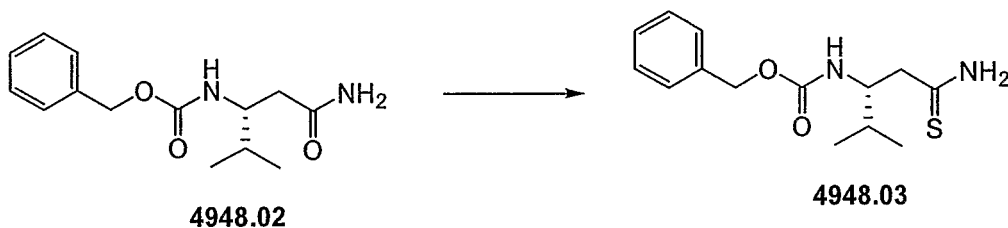
1-(HETEROARYLMETHYL)CYCLOHEXYL ISOCYANATES

The procedure of the preceding example **17043** was applied to the acids of Table 6.2 to obtain the isocyanates **17048**, **17049**, **17050**, **17051**, **17052**, **17053** and **17054** shown in Table 6.3.

TABLE 6.3			
Starting acid	Isocyanate Product	Yield %	chromatography solvent
17036	 17048	75	EtOAc-hexane (2:3)
17037	 17049	82	EtOAc-hexane (2:3)
17038	 17050	68	Et ₂ O-hexane (1:9)
17039	 17051	29	not chromatographed
17040	 17052	21	Et ₂ O-hexane (1:9)
17041	 17053	78	Et ₂ O-hexane (1:9)
17042	 17054	74	Et ₂ O-hexane (1:9)

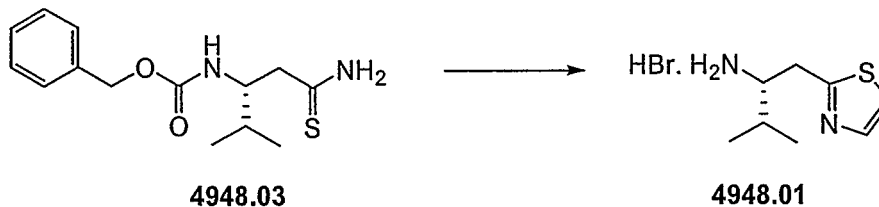
HCV inhibitors **4921, 4922, 4923, 4927, 4933, 4938, 4939, 4940, 4941, 4944, 4946, 4947, 4955, 4962, 4965, 4966** of **Table 6** were prepared using isocyanates **17043, 17048, 17049, 17050, 17051, 17052, 17053** and **17054** shown in **table 6.3** according the general procedure described before.

Example XX: Preparation of General Intermediates **4948.01** used in the preparation of HCV inhibitor **4948, 4949, 4972, 4973** of **table 6** according the general procedure describe before.

**4948.01****Step 1**

Step1: Compound **4948.02** (2.5g, 10 mmol) was taken in dioxane (30 mL).

Lawesson's reagent (2.23g, 5.5 mmol, STENCH) was added and the reaction mixture was heated at 60°C for 2 hrs under nitrogen atmosphere. The reaction mixture was allowed to cool to room temperature over 3.5 hr period, while stirring. The reaction mixture was then concentrated. Saturated sodium bicarbonate solution (50 mL) was added to the residue and extracted with chloroform (2 x). The combined chloroform layer was concentrated to afford 2.8 g of **4948.03** which was used without any purification.

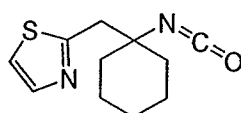


Step2: Preparation of bromoacetaldehyde: Bromoacetaldehyde diethylacetal (2 mL) was added to concentrated HCl (2.4 mL) and heated at 60°C for 30 min. This mixture was then cooled to 10°C. DMF (30 mL) was added followed by powdered molecular

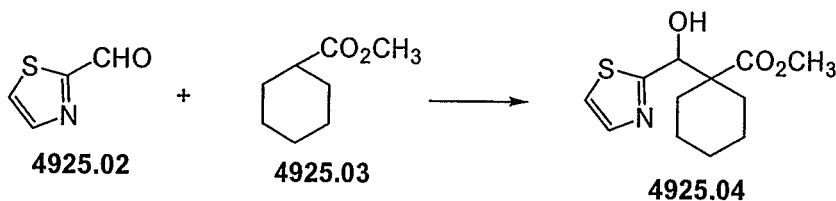
sieves (one spatula). The solution was decanted and used immediately as described below.

A solution of bromoacetaldehyde in DMF prepared as above was added to **4948.03** (1.4 g, from Step 1) and heated at 60°C for 5 hrs. At this time the reaction mixture was cooled to room temperature, diluted with ethyl acetate (50 mL) and washed with saturated sodium bicarbonate (100 mL). The organic layer was separated and the aqueous layer was further extracted with ethyl acetate (50 mL). The combined organic layer was washed with water (100 mL), brine (100 mL), dried (Na₂SO₄) and concentrated. The residue was purified by flash chromatography using 12/88 EtOAc/hexanes which afforded 964 mg of intermediate that was taken up in 33% hydrogen bromide in acetic acid (10 mL). This mixture was stirred at room temperature for 1 hr. Diethyl ether (100 mL) was added which resulted in a white precipitate. Filtration followed by washing with diethyl ether (2 x) provided **4948.01** as a white solid in quantitative yield.

Example XXI: Preparation of General Intermediates **4925.01** used in the preparation of HCV inhibitor **4925**, **4926**, **4928**, **4929**, **4952**, **4959**, **4968** of Table 6 according the general procedure describe before.

**4925.01**

Step1

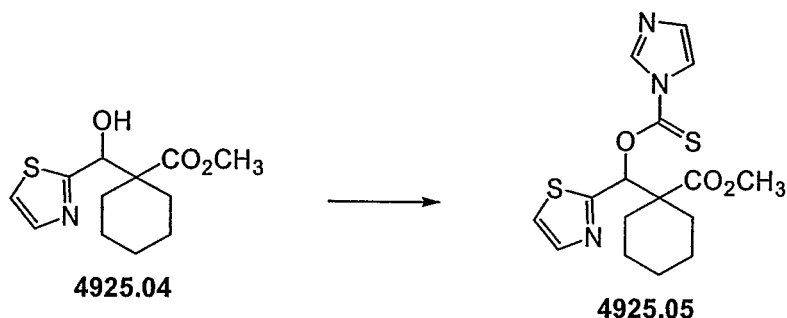


To a solution of methylcyclohexanecarboxylate **4925.03** (2.54 mL, 17.68 mmol) in THF (100 mL) at -78°C was added LDA (2.0M in hexanes/THF/ethylbenzene, 17.68 mL, 35.36 mmol) under nitrogen atmosphere. The reaction mixture was maintained at that temperature for 30 min. Then a solution of the aldehyde **4925.02** (2.0 g, 17.68 mmol) in THF (10 mL) was added dropwise. The temperature was slowly brought to 10°C over 1.5 hr. TLC indicated complete consumption of starting materials. The reaction was quenched with saturated ammonium chloride solution/brine (200 mL)

425

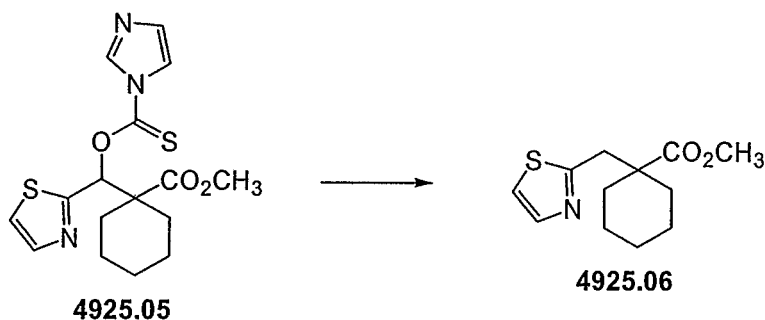
and extracted with diethyl ether (2 x). The combined ether layer was dried (Na_2SO_4) and concentrated. Purification of the residue by flash chromatography using 23/77 EtOAc/hexanes afforded 2.72 g of the required material, **4925.04**.

Step 2



To a solution of **4925.04** (1.02 g, 4.0 mmol) in THF (30 mL) was added thiocarbonyl diimidazole (1.78 g, 10.0 mmol). The mixture was refluxed under nitrogen atmosphere for 5 hrs. The reaction mixture was cooled to room temperature, diluted with diethyl ether, washed with saturated ammonium chloride solution, dried (Na_2SO_4) and concentrated. Purification of the residue by flash chromatography using 20/80 to 30/70 EtOAc/dichloromethane afforded 1.3 g of the required material, **4925.05**.

Step 3



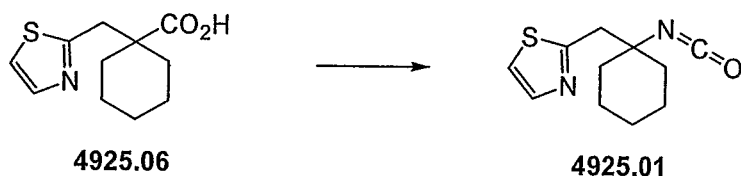
Compound **4925.05** (1.27 g, 3.48 mmol) was taken in toluene (40 mL). To this were added AIBN (2,2'-Azobisisobutyronitrile, 57 mg, 0.348 mmol) and TBTH (tri-n-butyl tin hydride, 1.87 mL, 6.96 mmol) under nitrogen atmosphere. The mixture was refluxed overnight (16 hrs). At this time the reaction mixture was cooled to room temperature, and quenched with aqueous 1N HCl (100 mL). It was then extracted with diethyl ether (100 mL). The organic layer was washed with 1N HCl (100 mL), dried (Na_2SO_4) and concentrated. Purification of the residue by flash chromatography using 8/92 EtOAc/dichloromethane afforded 400 mg of the required material, **4925.05**.

Step 4



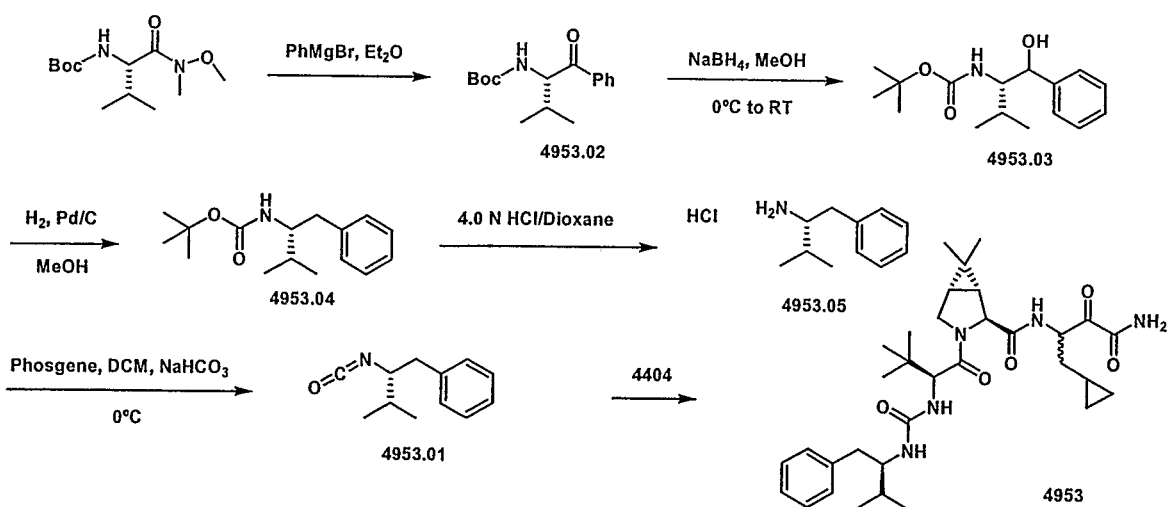
To a mixture of compound **4925.05** (478 mg, 2.0 mmol) in dioxane (5 mL) and water (5 mL) was added solid potassium hydroxide (336 mg, 6 mmol). The reaction mixture was heated at 80°C for 2 hrs and 100°C for 3 hrs. The reaction mixture was cooled to room temperature, concentrated and quenched with aqueous 1N HCl. The aqueous layer was extracted with dichloromethane, dried (Na₂SO₄) and concentrated to afford 390 mg of the required material, **4925.06** LC-MS: 226 (M+H).

Step 5



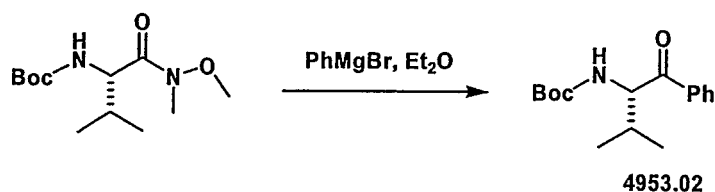
The acid **4925.06** (390 mg, 1.73 mmol) was taken in toluene (10 mL). Triethylamine (0.27 mL, 1.9 mmol) and DPPA (Diphenylphosphoryl azide, 0.42 mL, 1.94 mmol) were then added. The reaction mixture was refluxed for 5 hrs and cooled to room temperature. This resulted in the formation of the isocyanate **4925.01** which was used further as a 0.173 M solution in toluene.

Example XXII: Preparation of isocyanate **4953.01** used in the preparation of HCV inhibitor **4953** of Table 6.



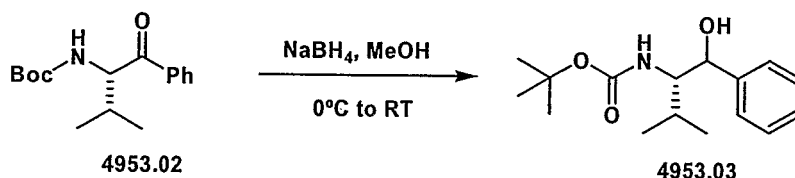
Step1

427



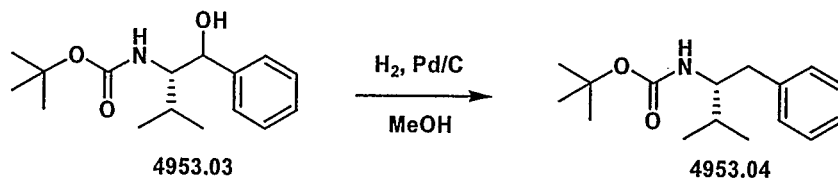
PhMgBr (2.5 equiv, 40 mL) was added @ -78°C to a Et₂O (200mL) solution of commercially available Weinreb amide (Aldrich Chemical Co., Milwaukee, Wisconsin, USA, 12g, 46 mmol). After 2 h, reaction was quenched by addition of HCl 1.0 N, diluted with EtOAc and washed with brine, dried over MgSO₄, filtered and concentrated under vacuo. The residue was purified by HPFC Biotage 75+S, Seg1: 2%B to 2%B, Linear, 320mL / Seg2: 2%B to 8%B, Linear, 3200 mL / Seg3: Hold 8% for 5CV(1600 mL). 3.76g of **4953.02** were obtained.

Step2



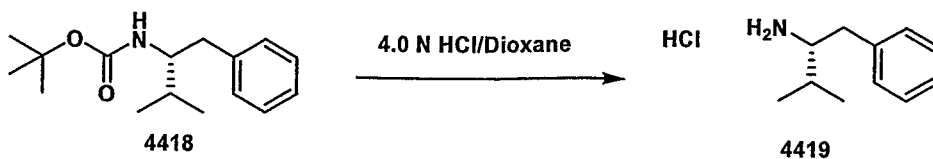
To a 0°C solution of **4953.02** (1.5 g, 5.4mmol) in MeOH (100 mL) was added NaBH₄ (5 equiv, 27 mmol, 1.02 g). Reaction was warmed-up to RT and stirred until thin layer chromatography indicated complete consumption of the starting material (~0.5 hr). Reaction was stopped by addition of HCl 1.0 N and extracted with EtOAc. Organic layer was dried over MgSO₄, filtered and concentrated under vacuo. The residue was purified by HPFC Biotage 25+S, Seg1: 3%B, Linear, 120mL / Seg2: 3%B to 12%B, Linear, 1200mL / Seg3: Hold 10% for 240 mL. Purification furnished 1.35g of **4953.03**.

Step 3

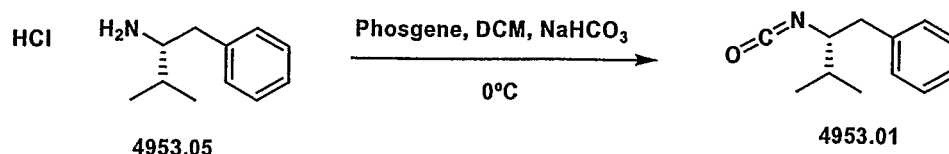


To a solution of N₂ flushed solution of **4953.03** (1.35g, 4.8mmol) in MeOH (50ml) was added 10% Pd/C catalyst (0.5g). The resulting suspension was hydrogenated for 18h. The catalyst was removed by filtration through a pad of celite and washed with EtOAc. The combined filtrate and washings were evaporated under vacuum to dryness to provide after purification the desired product **4418** (85mg) and recovered **4953.04**.

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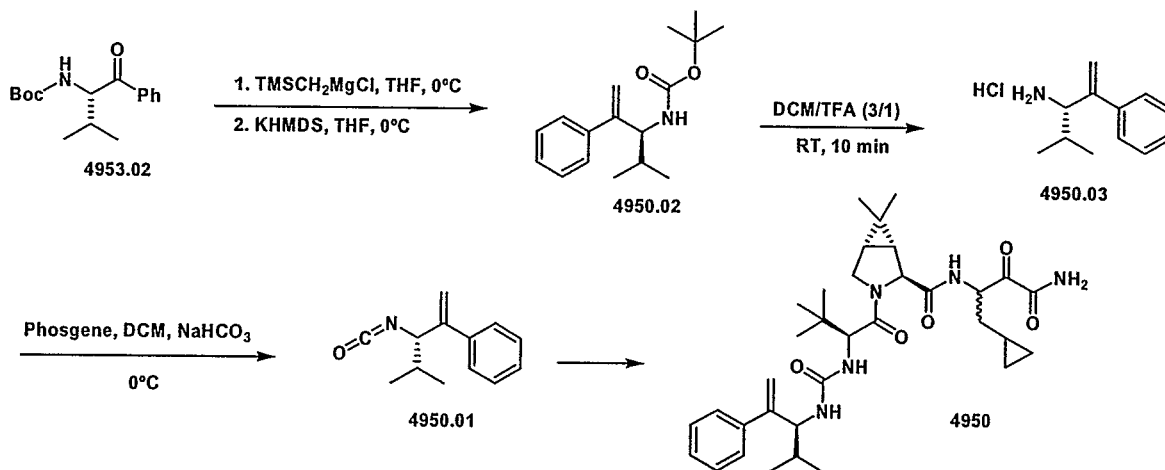
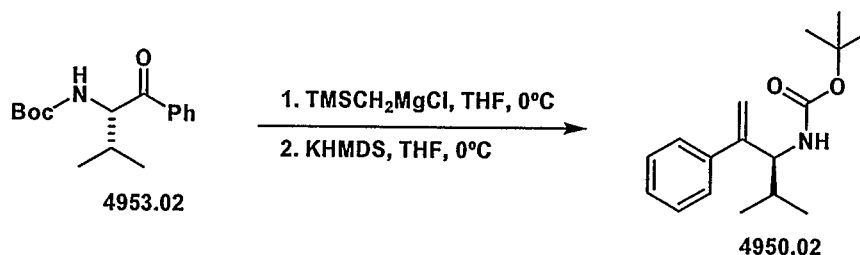
Step 4

4953.04 (28 mg, 0.10 mmol) was treated with 4.0 N HCl solution in Dioxane described previously to deliver quantitatively **4953.05**.

5 **Step5**

4953.05 (28 mg, 0.10 mmol) was treated with phosgene as described previously to deliver **4953.01** that was used as described before to prepare HCV inhibitor **4953** of Table 6.

10 **Example XXIII:** Preparation of isocyanate **4950.01** used in the preparation of HCV inhibitor **4950** of Table 6.

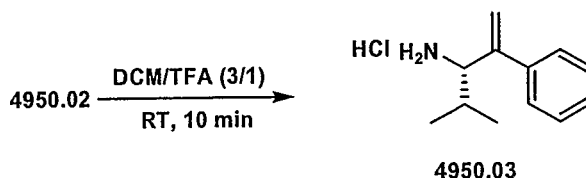
**Step1**

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To a -25°C solution of ketone **4953.02** prepared in step 1 of preparative example XXII (2.77g, 10mmol) in THF (50 mL) was added TMSCH₂MgCl (1.0M in Et₂O, 2equiv, 20 mmol, 20 mL). The temperature was slowly raised to 0°C and stirred for 1 h, quenched

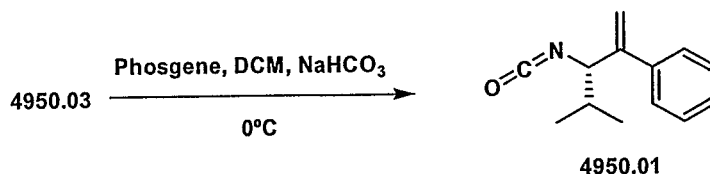
with H₂O (5 mL) and diluted with EtOAc. The reaction mixture was washed with NH₄Cl sat and brine. Organic layer was dried over MgSO₄, filtered and concentrated under vacuo. To a 0°C solution of the above crude in THF (50 mL) was added KHMDs (2.7 equiv, 0.5M in PhMe, mmol, 54 mL). The mixture was stirred at 0°C for 1.5h then RT for 3 hr then quenched with saturated NH₄Cl and diluted with EtOAc. The organic layer was washed with brine, dried over MgSO₄, filtered and concentrated under vacuo. purification via HPFC, 40+S, Seg1: Hold 2%B, Linear, 60mL / Seg2: 2%B to 8%B, Linear, 600mL / Seg3: Hold 8%B, Linear, 300mL. 0.5g of **4950.02** were isolated.

Step2



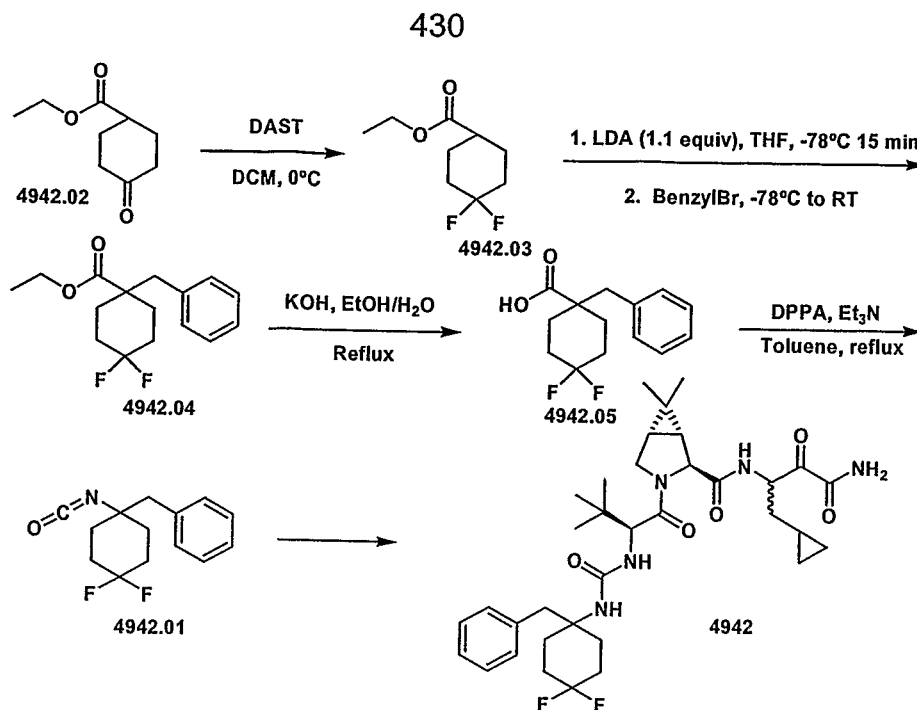
To a rt solution of **4950.02** (100 mg, 0.36 mmol) in DCM 3 mL was added 1 mL of TFA. Reaction turned yellow immediately. After 10 min, TLC showed no starting material and reaction was diluted with Hexanes and concentrated to dryness. The resulting yellow oil was placed under high vacuum overnight and analyzed by NMR. 109 mg of **4950.03** were obtained.

Step3

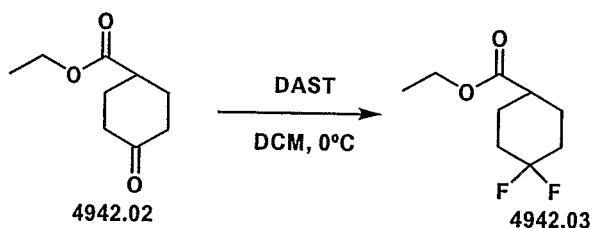


A DCM (5mL) solution of TFA salt **4950.03** (109 mg, 0.36 mmol) was added to a 0°C solution of saturated aqueous NaHCO₃ (5mL) and Phosgene (2equiv, 0.72 mmol, 0.36mL). Rapid stirring was set immediately and the ice-cooled reaction mixture was stirred for 2 hours at high speed. After 2 hours, the organic phase (lower) was separated and was then dried over anhydrous MgSO₄ and concentrated to half volume under vacuum with cooling bath. Dilute to 3.6 mL (0.1M solution in DCM of **4950.01**) that was used as described before to prepare HCV inhibitor **4950** of Table 6.

Example XXIV: Preparation of isocyanate **4942.01** used in the preparation of HCV inhibitor **4942** of Table 6.

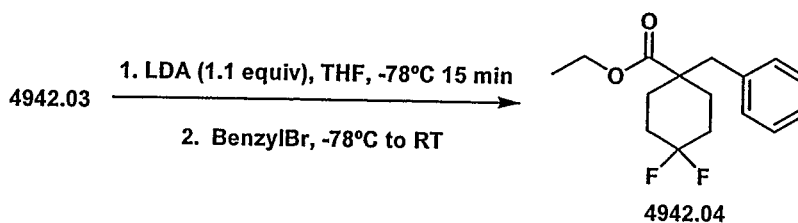


Step1



- 5 To a 0°C solution of DAST (2equiv, 40 mL) in DCM (290mL) was added a solution 4-cyclohexanone carboxylic Acid Ethyl Ester **4942.02** (25g, 147 mmol) in DCM (100 mL) dropwise over 20 min. the mixture was allowed to stir at RT overnight. H₂O (50 ml) was then added carefully (CAUTION: STRONG EXOTHERM). The mixture was basified to PH 5 (takes a great amount of time, watch out for violent acid-base reaction) with saturated NaHCO₃. Finally, aqueous layer was removed by extraction and organic layer was washed with saturated NaHCO₃ without any problem. Aqueous layer was back extracted with EtOAc and both combined organic layers were dried over MgSO₄, filtered and the solvent removed by evaporation under reduced pressure to yield crude **4942.03** (29.33 g) as a dark red oil.

Step2

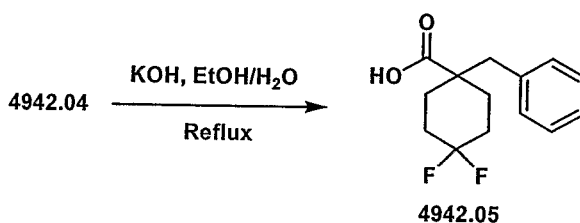


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To a -78°C solution of ethyl ester **4942.03** (20 mmol, 3.84g) in THF (25 mL) was added 1.0 equiv of LDA (10mL). Addition of LDA produced a light yellow color. After 15 min, Benzyl bromide (1.1 equiv, 22 mmol, 2.61 mL) was added dropwise. Reaction color turned gold immediately. Reaction was then gradually warmed-up to rt overnight.

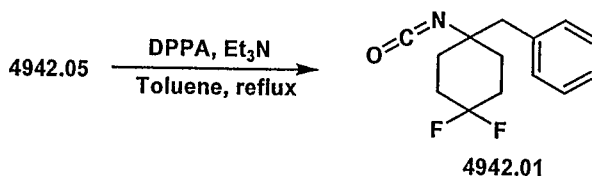
5 Reaction was stopped by addition of Sat. aqueous NH_4Cl . Reaction was diluted with EtOAc and layers were separated. Washed with NaHCO_3 , then brine. Organic layer was dried over MgSO_4 , filtered and concentrated under vacuo. Purification via HPFC, 40+S, Seg1: Hold 5%B, Linear, 60mL / Seg2: 5%B to 20%B, Linear, 600mL / Seg3: Hold 20%B, Linear, 300mL. 0.915 g of **4942.04** was isolated.

10 **Step3**



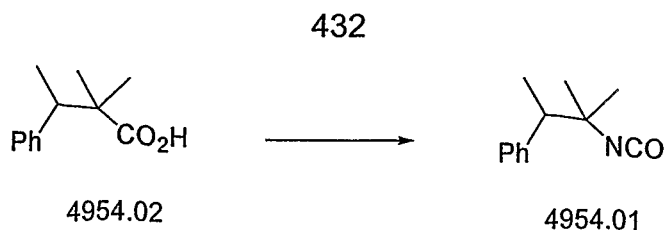
To a solution of **4942.04** (0.8g, 2.8 mmol) in EtOH / H_2O (36 mL / 4 mL) was added KOH (10 equiv, 28 mmol, 1.57 g). The reaction was brought to reflux until completion. 48h reflux was necessary to observe completion. Diluted with Et_2O and basified to $\text{Ph}=9$ with saturated NaHCO_3 . Et_2O layer was discarded to remove non carboxylic acid material. Aqueous layer was acidified to $\text{Ph}=1$ with HCl 1.0N and extracted with EtOAc. The organic layer was washed with brine, dried over MgSO_4 , filtered and concentrated under vacuo. 535 mg of a light orange solid were isolated as **4942.05**.

15 **Step4**



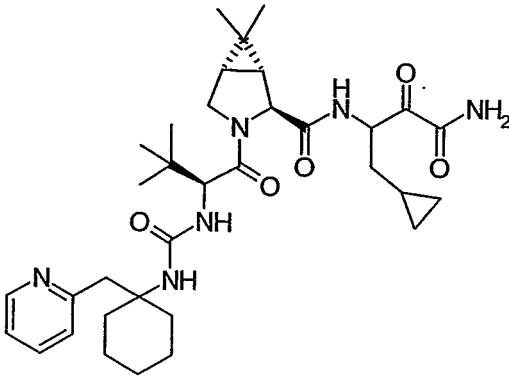
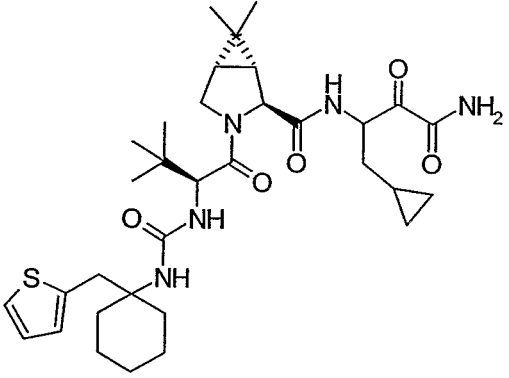
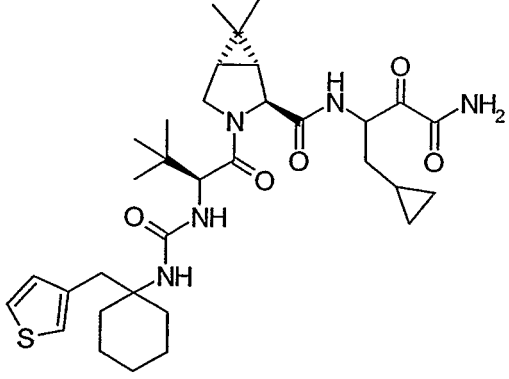
20 Acid **4942.05** (335mg, 1.314 mmol) in Toluene (10 mL) was treated as described previously to afford isocyanate **4942.01** that was used as described before to prepare HCV inhibitor **4942** of Table 6.

25 **Example XXV:** Preparation of isocyanate **4954.01** used in the preparation of HCV inhibitor **4954** of Table 6.

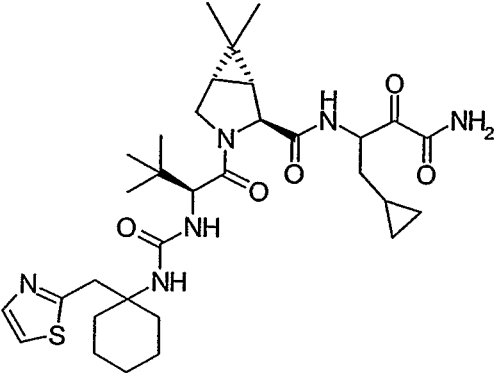
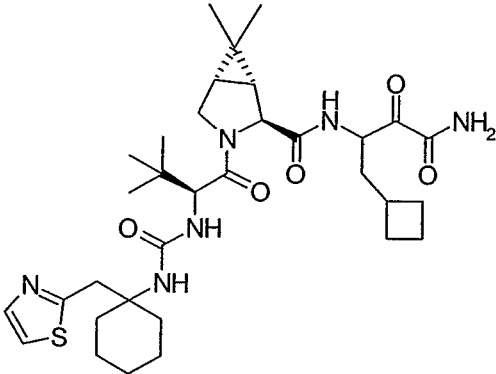
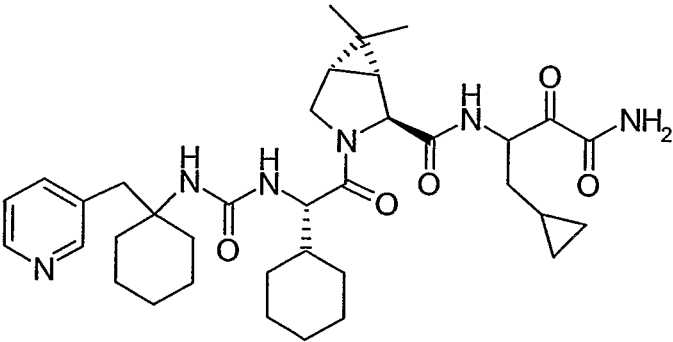


To a solution of 50.2 mg of compound **4954.02** (Adam, Waldemar; Baeza, Jaime; Liu, Ju-Chao, *Journal of the American Chemical Society* (1972), 94(6), 2000-6) in toluene (4.0 mL) was added DPPA (0.06 mL) and Et₃N (0.037mL). The reaction mixture was
5 heated at 110 °C for 40 min, cooled and washed with Satd. NaHCO₃, dried over MgSO₄, filtered and concentrated to afford isocyanate **4954.01**. The crude obtained was used without purification to prepare as described before HCV inhibitor **4954** of Table 6.

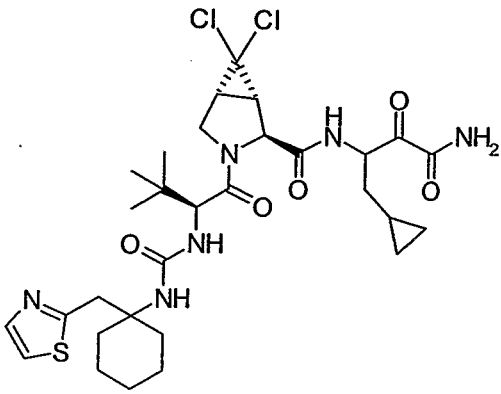
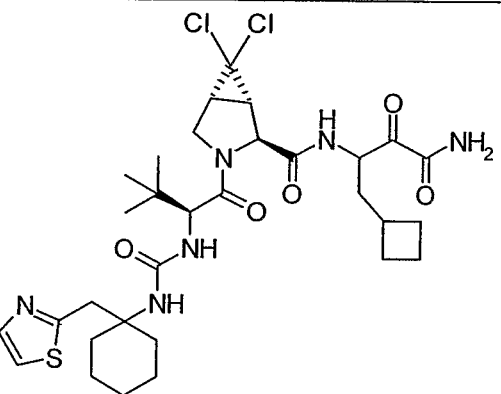
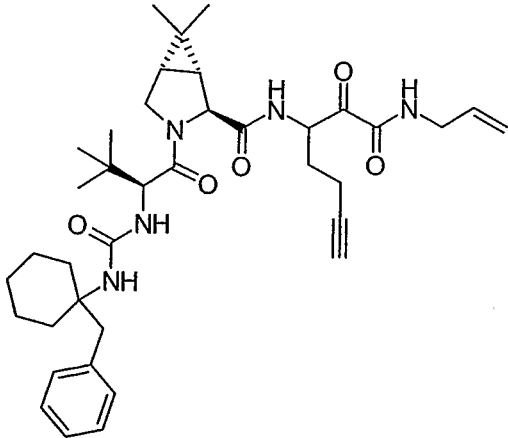
433

cmpd#	Table 6	MW	Ki* range
4921		623	A
4922		628	A
4923		628	A

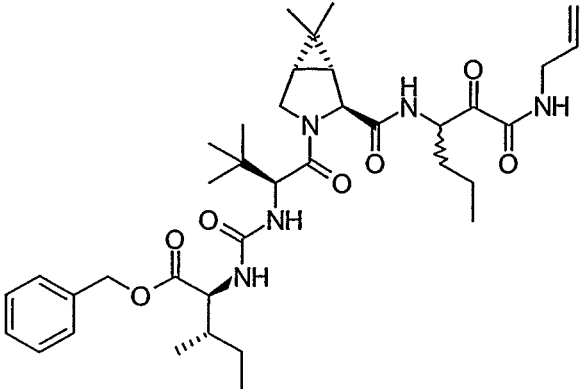
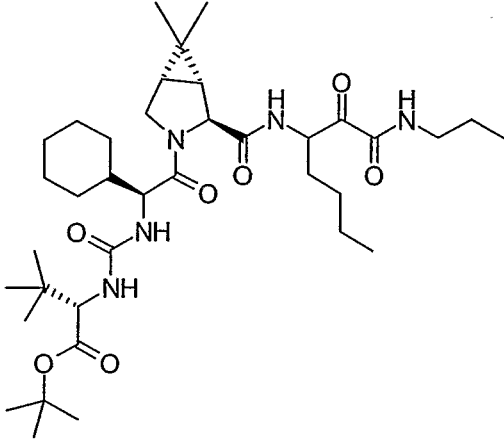
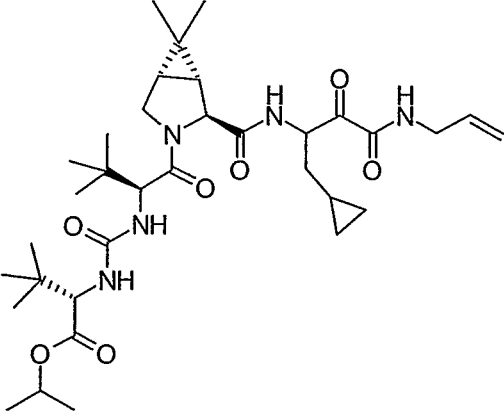
434

cmpd#	Table 6	MW	Ki* range
4925		629	A
4926		643	A
4927		649	A

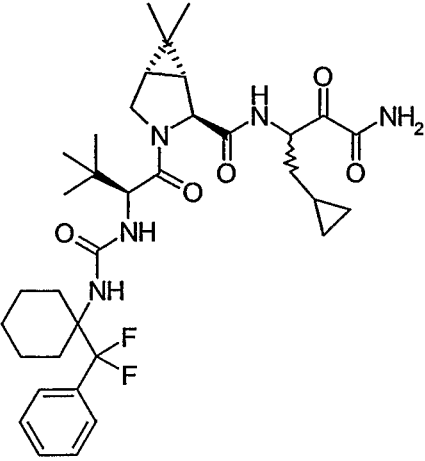
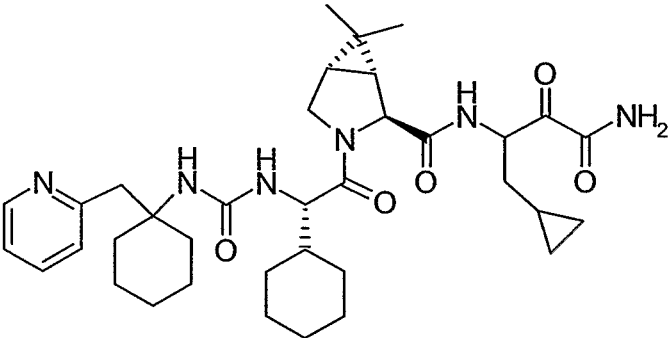
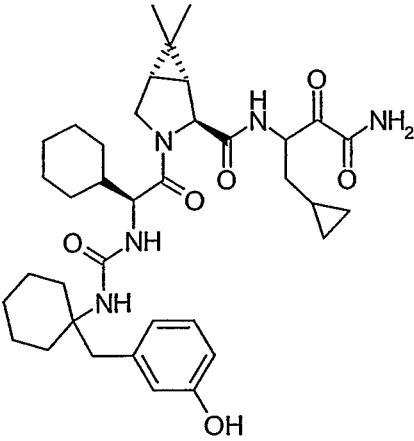
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cmpd#	Table 6	MW	Ki* range
4928		670	A
4929		684	A
4930		660	A

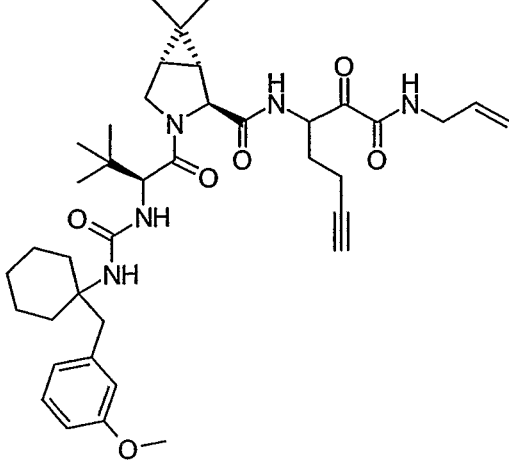
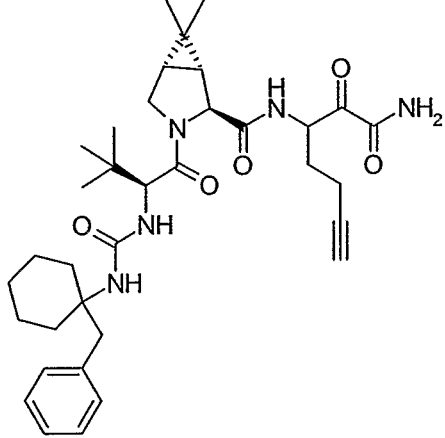
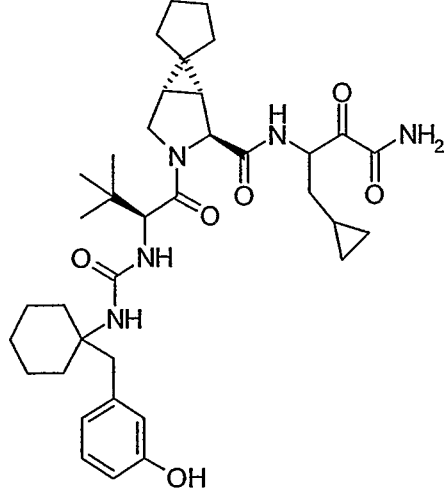
332

Cmpd #	Table 3: Esters	MW	Ki* Range
4576		682	B
4577		690	B
4578		646	B

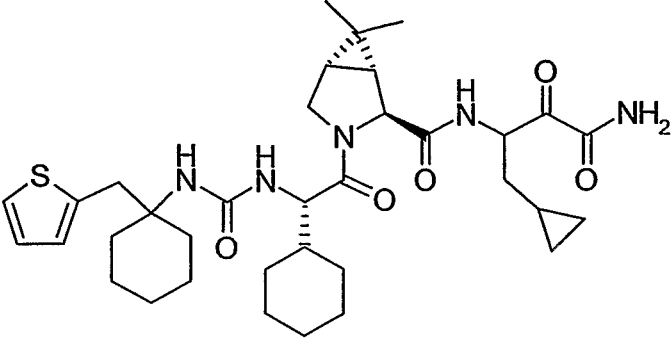
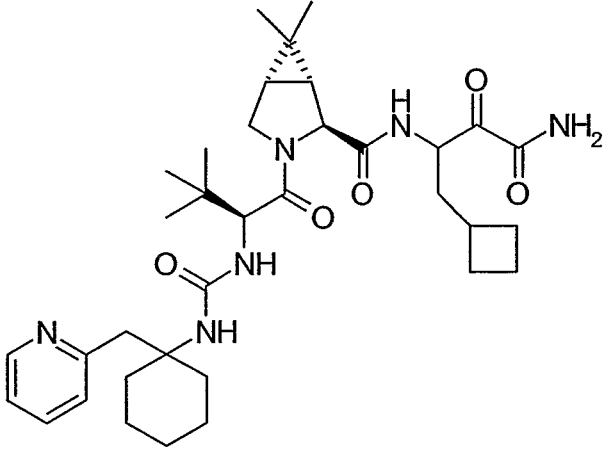
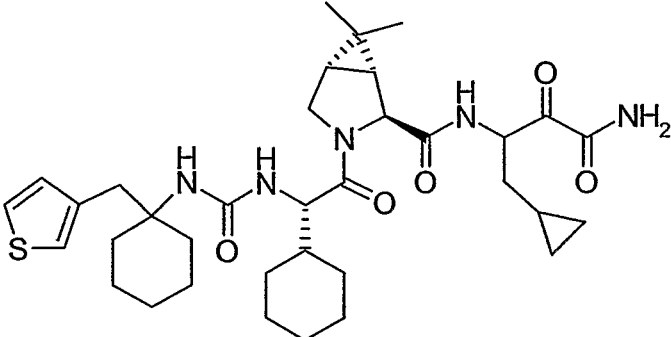
436

cmpd#	Table 6	MW	Ki* range
4931	 Chemical structure of compound 4931: A complex molecule featuring a central pyrrolidine ring. The pyrrolidine ring is substituted with a tert-butyl group at the 2-position, a carbonyl group at the 3-position, and a carbonyl group at the 4-position. The carbonyl at the 3-position is linked to a chain containing a cyclopropyl group and a primary amide group. The carbonyl at the 4-position is linked to a chain containing a cyclohexyl group, a carbonyl group, and a primary amide group. The cyclohexyl group is further substituted with a phenyl ring and two fluorine atoms.	658	A
4933	 Chemical structure of compound 4933: A complex molecule featuring a central pyrrolidine ring. The pyrrolidine ring is substituted with a tert-butyl group at the 2-position, a carbonyl group at the 3-position, and a carbonyl group at the 4-position. The carbonyl at the 3-position is linked to a chain containing a cyclopropyl group and a primary amide group. The carbonyl at the 4-position is linked to a chain containing a cyclohexyl group, a carbonyl group, and a primary amide group. The cyclohexyl group is further substituted with a pyridine ring.	649	A
4934	 Chemical structure of compound 4934: A complex molecule featuring a central pyrrolidine ring. The pyrrolidine ring is substituted with a tert-butyl group at the 2-position, a carbonyl group at the 3-position, and a carbonyl group at the 4-position. The carbonyl at the 3-position is linked to a chain containing a cyclopropyl group and a primary amide group. The carbonyl at the 4-position is linked to a chain containing a cyclohexyl group, a carbonyl group, and a primary amide group. The cyclohexyl group is further substituted with a phenyl ring and a hydroxyl group.	664	A

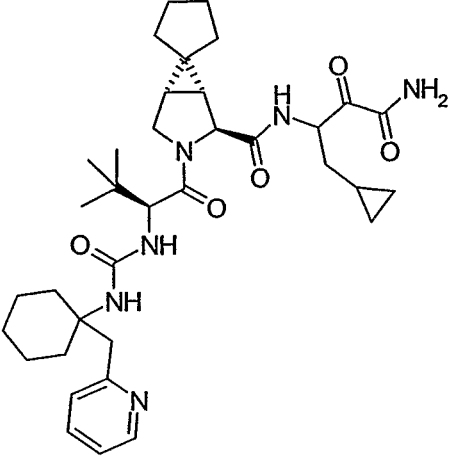
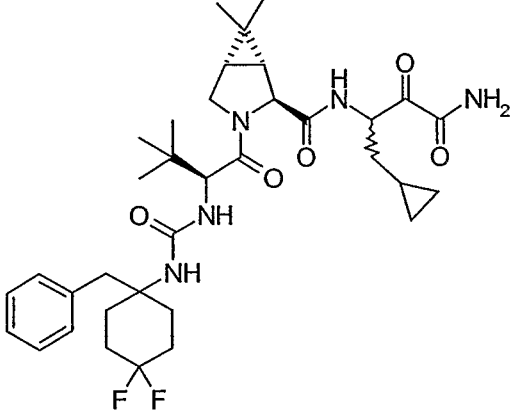
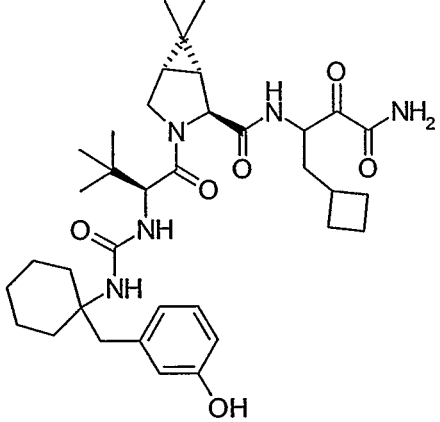
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cmpd#	Table 6	MW	Ki* range
4935		690	A
4936		620	A
4937		664	A

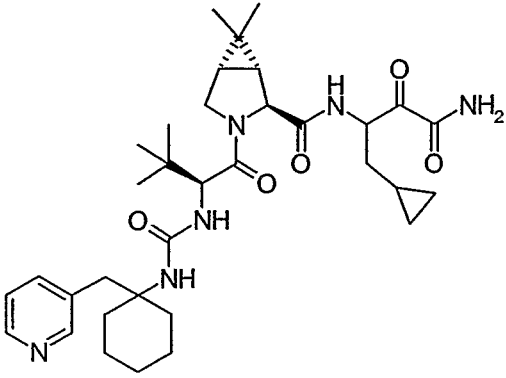
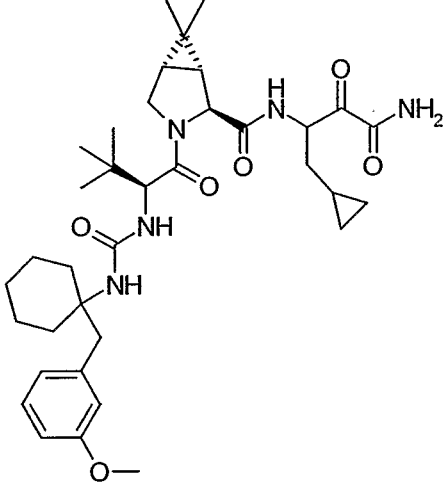
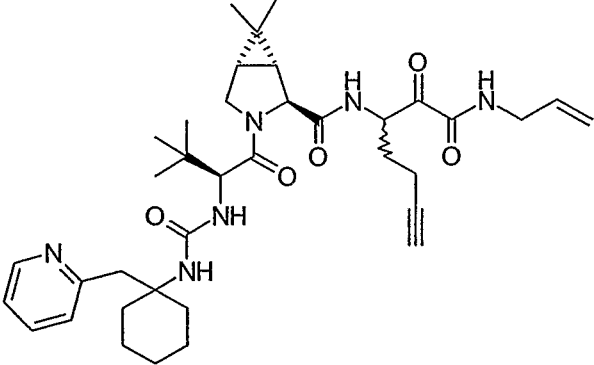
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cmpd#	Table 6	MW	Ki* range
4938		654	A
4939		637	A
4940		654	A

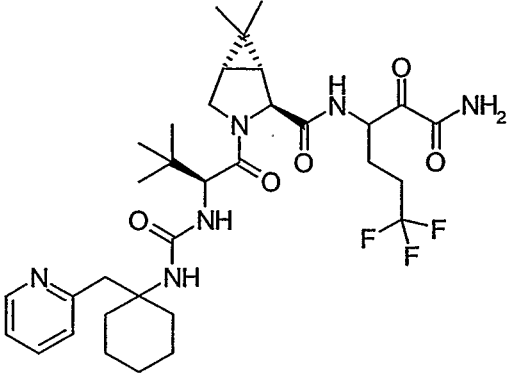
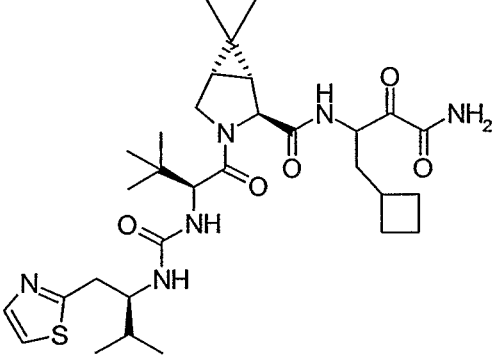
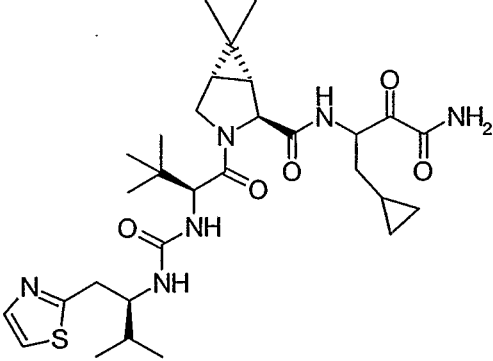
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cmpd#	Table 6	MW	Ki* range
4941		649	A
4942		658	A
4943		652	A

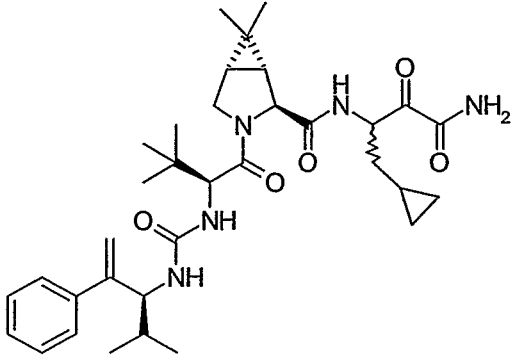
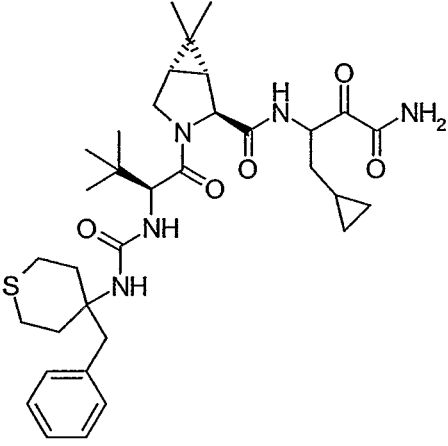
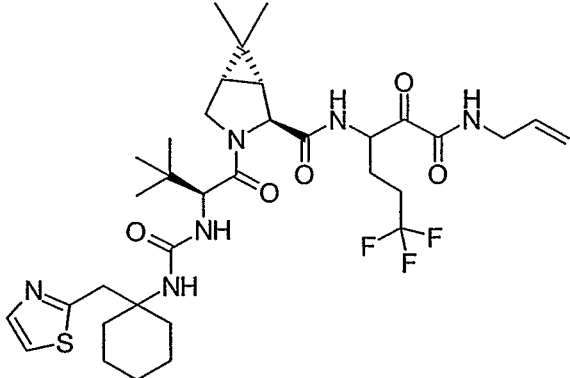
440

cmpd#	Table 6	MW	Ki* range
4944	 Chemical structure of compound 4944: A complex molecule featuring a central pyrrolidine ring substituted with a tert-butyl group and a dimethylamino group. It is linked via amide bonds to a cyclopropylmethyl group, a 2,2,4,4-tetramethyl-5-oxopentyl group, and a 2-((cyclohexylmethyl)(pyridin-2-yl)amino)ethyl group.	623	A
4945	 Chemical structure of compound 4945: Similar to 4944, but the side chain is a 2-((4-methoxyphenyl)methyl)(cyclohexylmethyl)amino group.	652	A
4946	 Chemical structure of compound 4946: Similar to 4944, but the side chain is a 2-((cyclohexylmethyl)(pyridin-2-yl)amino)ethyl group, and the central pyrrolidine ring is substituted with a tert-butyl group and a dimethylamino group. The molecule also features a 2-((cyclohexylmethyl)(pyridin-2-yl)amino)ethyl group and a 2,2,4,4-tetramethyl-5-oxopentyl group.	661	A

441

cmpd#	Table 6	MW	Ki* range
4947	 Chemical structure of compound 4947: A complex molecule featuring a central pyrrolidine ring substituted with a tert-butyl group and a dimethylamino group. It is linked via amide bonds to a side chain containing a 2,2,2-trifluoroethyl group and a carboxamide group. Another amide branch connects to a 1-(cyclohexylmethyl)pyrrolidine moiety.	665	A
4948	 Chemical structure of compound 4948: Similar to 4947, but the side chain contains a cyclobutyl group instead of a trifluoroethyl group. The other amide branch connects to a 1-(2-methyl-1H-thiazol-4-ylmethyl)pyrrolidine moiety.	617	A
4949	 Chemical structure of compound 4949: Similar to 4948, but the side chain contains a cyclopropyl group instead of a cyclobutyl group. The other amide branch connects to a 1-(2-methyl-1H-thiazol-4-ylmethyl)pyrrolidine moiety.	603	A

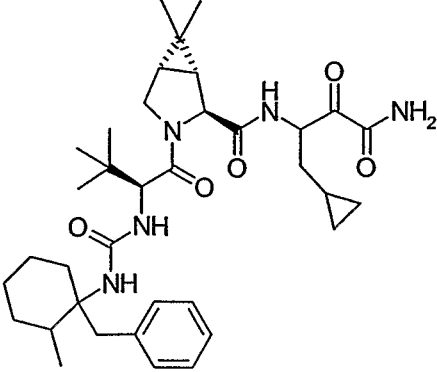
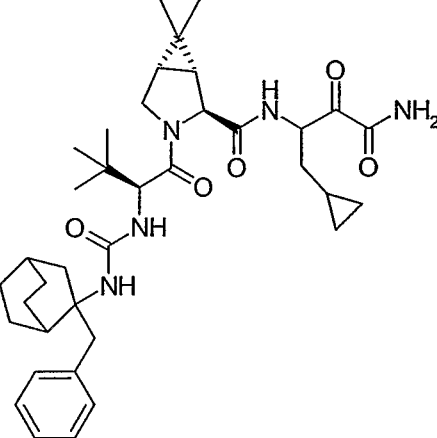
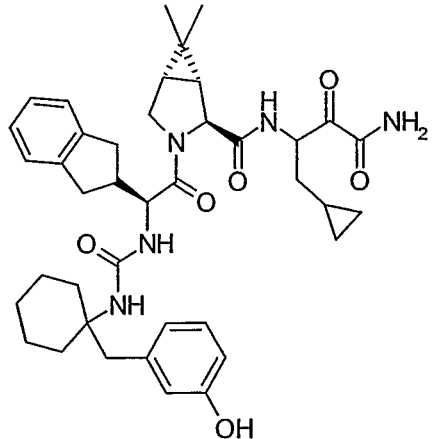
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cmpd#	Table 6	MW	Ki* range
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4951		640	A
4952		711	A

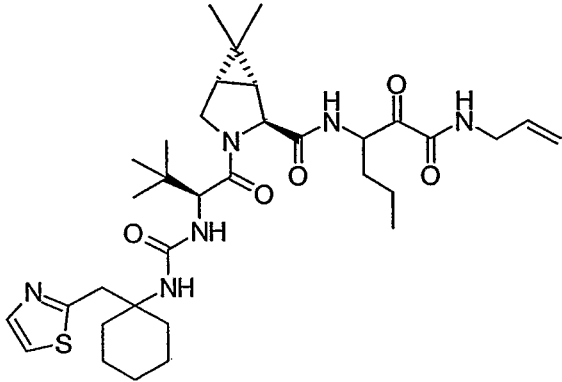
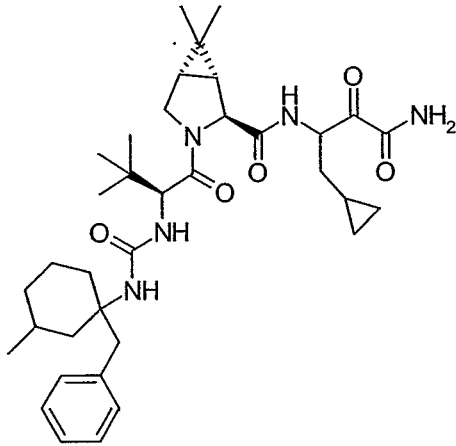
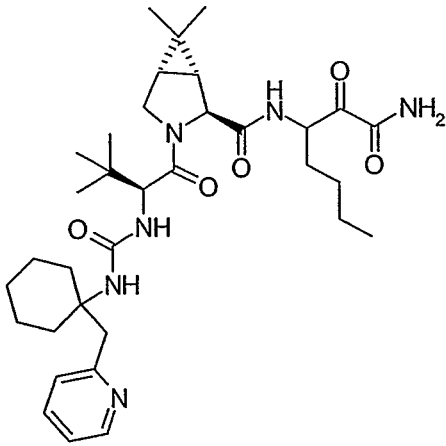
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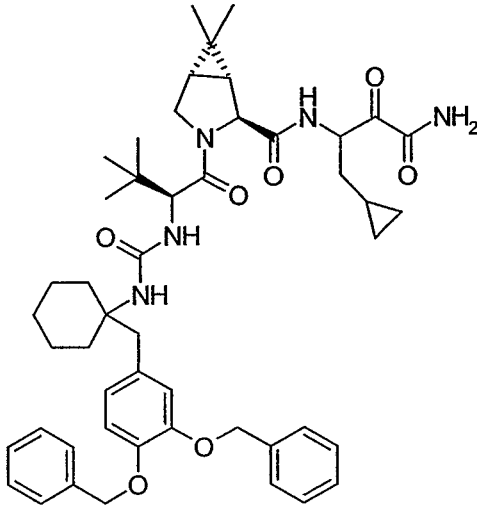
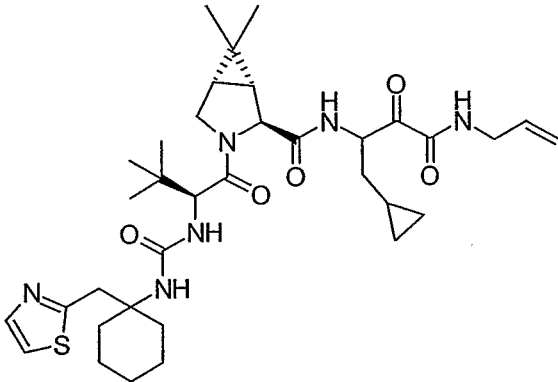
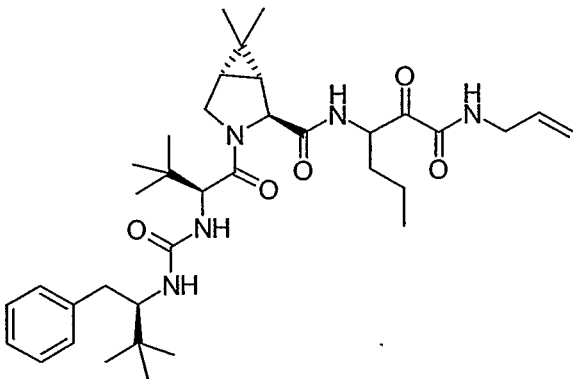
cmpd#	Table 6	MW	Ki* range
4953	 <chem>CC(C)(C)N1C(=O)C(C(=O)NCC2CC2)C(=O)N1C(=O)NCC(C)Cc3ccccc3</chem>	596	A
4954	 <chem>CC(C)(C)N1C(=O)C(C(=O)NCC2CC2)C(=O)N1C(=O)NCC(C)Cc3ccccc3</chem>	596	A
4955	 <chem>CC(C)(C)N1C(=O)C(C(=O)NCC2CC2)C(=O)N1C(=O)NCC3CCCCC3</chem>	649	A

444

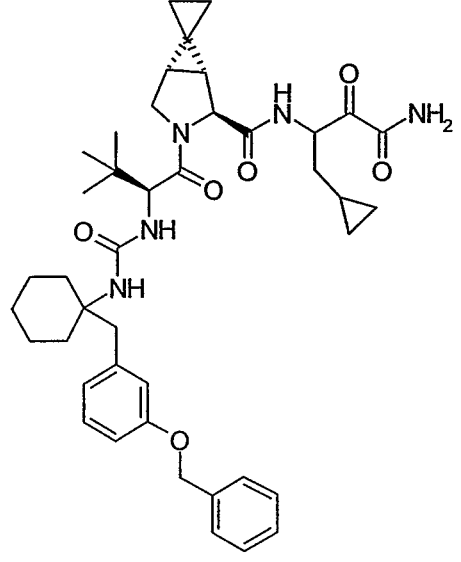
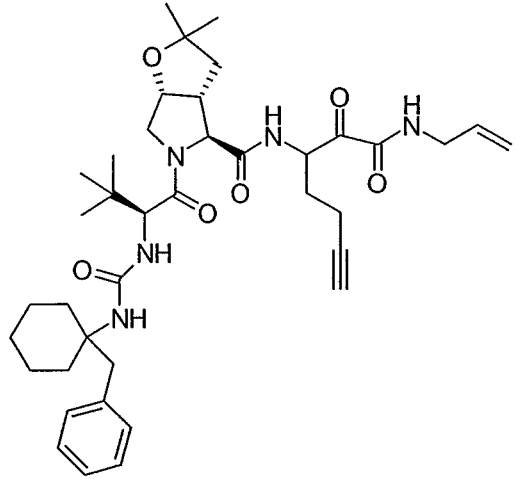
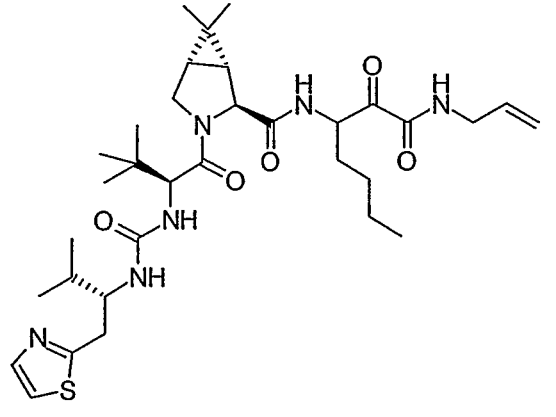
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4956		636	A
4957		648	A
4958		698	A

445

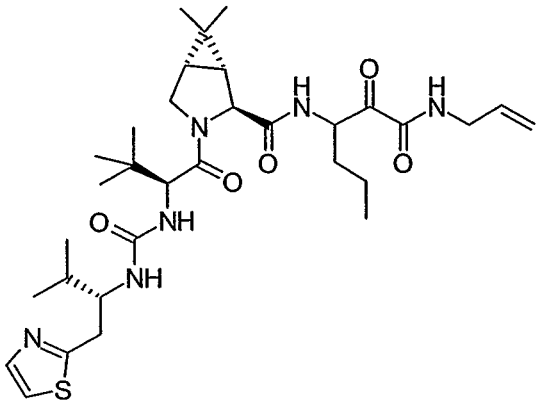
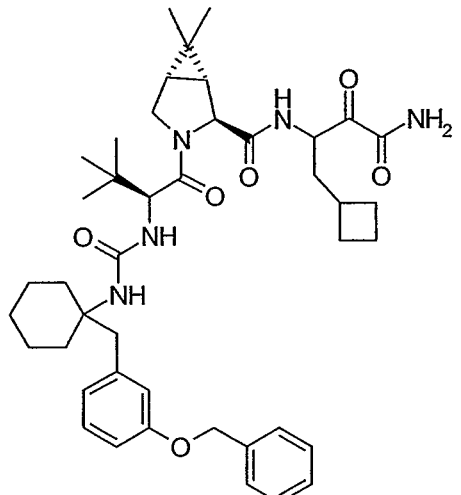
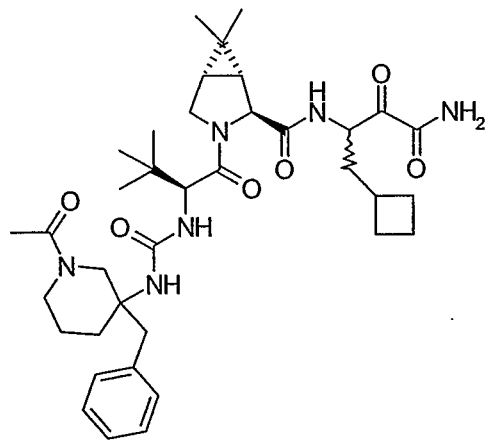
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4959		657	A
4960		636	A
4962		625	B

cmpd#	Table 6	MW	Ki* range
4967		834	B
4968		669	B
4969		638	B

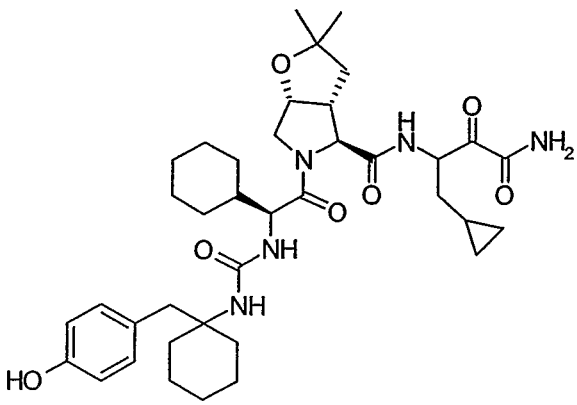
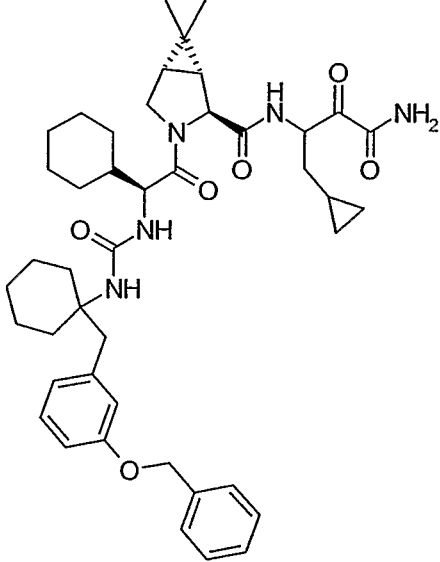
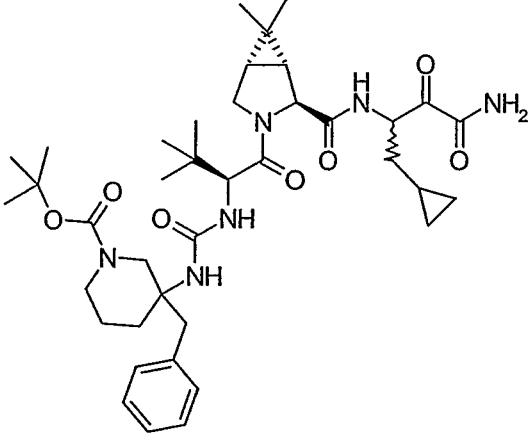
448

cmpd#	Table 6	MW	Ki* range
4970	 Chemical structure of compound 4970: A complex molecule featuring a cyclohexane ring substituted with a benzyl group and a benzyl ether group. The benzyl group is further substituted with a cyclopropylmethyl group. The benzyl ether group is further substituted with a cyclopropylmethyl group. The molecule also contains a pyrrolidine ring, a carbamate group, and a primary amide group.	726	B
4971	 Chemical structure of compound 4971: A complex molecule featuring a cyclohexane ring substituted with a benzyl group and a benzyl ether group. The benzyl group is further substituted with a cyclopropylmethyl group. The benzyl ether group is further substituted with a cyclopropylmethyl group. The molecule also contains a pyrrolidine ring, a carbamate group, and a primary amide group.	690	B
4972	 Chemical structure of compound 4972: A complex molecule featuring a cyclohexane ring substituted with a benzyl group and a benzyl ether group. The benzyl group is further substituted with a cyclopropylmethyl group. The benzyl ether group is further substituted with a cyclopropylmethyl group. The molecule also contains a pyrrolidine ring, a carbamate group, and a primary amide group.	645	B

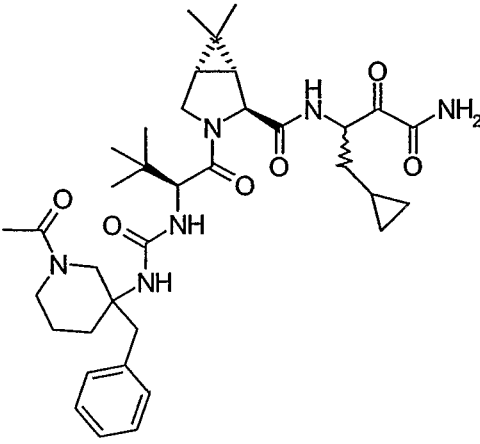
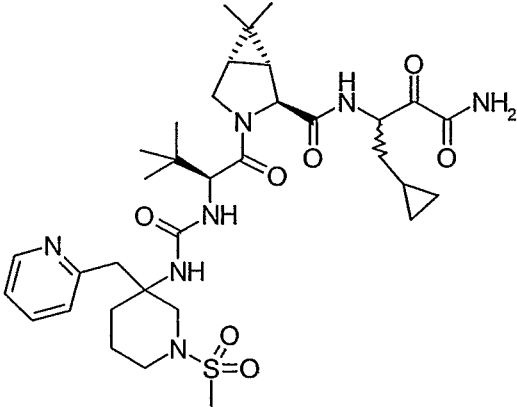
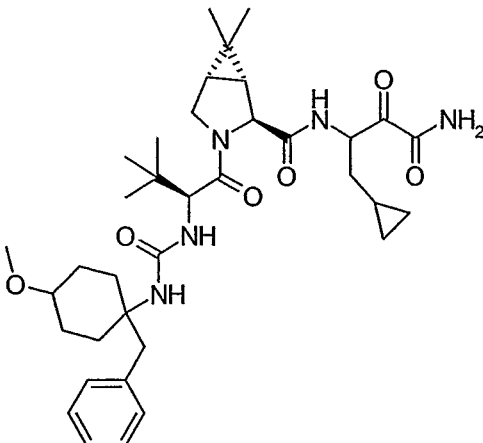
449

cmpd#	Table 6	MW	Ki* range
4973		631	B
4974		742	B
4975		679	B

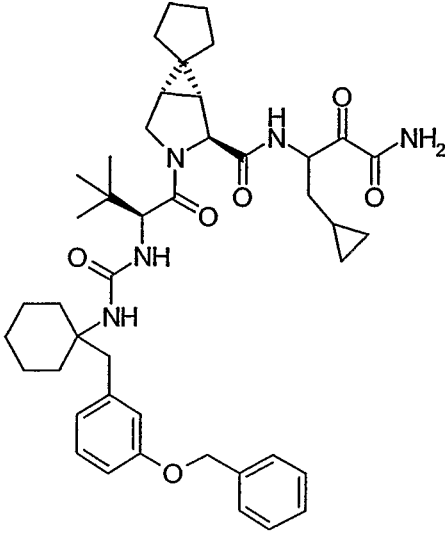
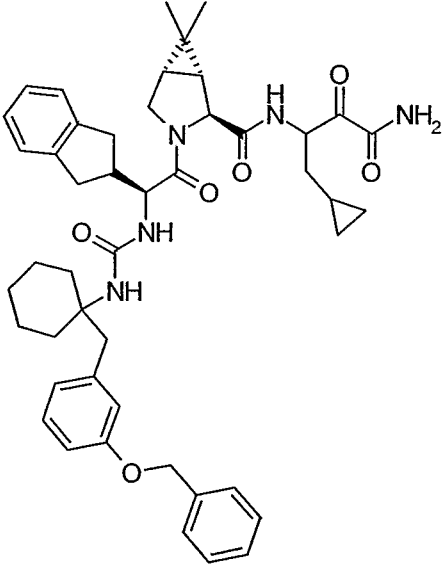
450

cmpd#	Table 6	MW	Ki* range
4976	 Chemical structure of compound 4976: A complex molecule featuring a central pyrrolidine ring. The pyrrolidine ring is substituted with a tert-butyl group, a cyclohexylmethyl group, and a carbonyl group. The carbonyl group is part of an amide linkage to a cyclopropylmethyl group, which is further substituted with a carboxamide group. Another amide linkage connects the pyrrolidine ring to a cyclohexylmethyl group, which is substituted with a 4-hydroxyphenyl group.	694	B
4977	 Chemical structure of compound 4977: A complex molecule featuring a central pyrrolidine ring. The pyrrolidine ring is substituted with a tert-butyl group, a cyclohexylmethyl group, and a carbonyl group. The carbonyl group is part of an amide linkage to a cyclopropylmethyl group, which is further substituted with a carboxamide group. Another amide linkage connects the pyrrolidine ring to a cyclohexylmethyl group, which is substituted with a 4-(benzyloxy)phenyl group.	754	B
4978	 Chemical structure of compound 4978: A complex molecule featuring a central pyrrolidine ring. The pyrrolidine ring is substituted with a tert-butyl group, a cyclohexylmethyl group, and a carbonyl group. The carbonyl group is part of an amide linkage to a cyclopropylmethyl group, which is further substituted with a carboxamide group. Another amide linkage connects the pyrrolidine ring to a cyclohexylmethyl group, which is substituted with a 4-(benzyloxy)phenyl group.	723	B

451

cmpd#	Table 6	MW	Ki* range
4979		665	B
4980		702	B
4981		652	B

452

cmpd#	Table 6	MW	Ki* range
4982		754	B
4983		788	B

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.

5 **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 monochromator 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 μ M EDTA and 5 μ M 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 Na₂CO₃ solution) to remove the acid used in cleavage. The DCM phase is dried over Na₂SO₄ 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).

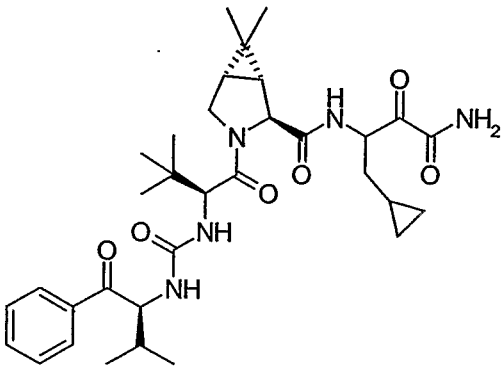
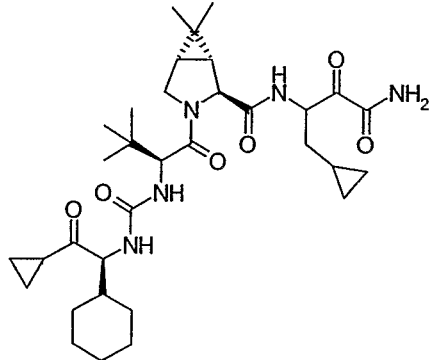
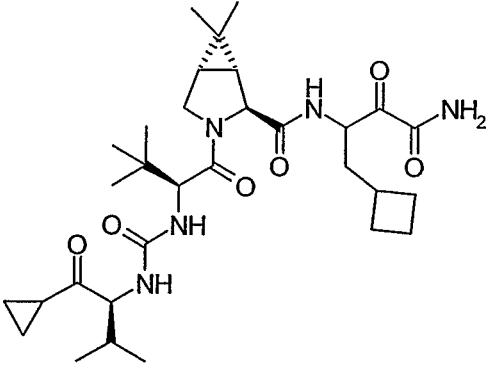
Protease Assay: HCV protease assays are performed at 30°C using a 200 µl reaction mix in a 96-well microtiter plate. Assay buffer conditions (25 mM MOPS pH 6.5, 300 mM NaCl, 10% glycerol, 0.05% lauryl maltoside, 5 µM EDTA and 5 µM DTT) are

optimized for the NS3/NS4A heterodimer (D. L. Sali *et al, ibid.*). Typically, 150 μ l 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 μ l of prewarmed protease (12 nM, 30°C) in assay buffer, is then used to initiate the reaction (final volume 200 μ l). 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 monochromator (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 μ M). 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.

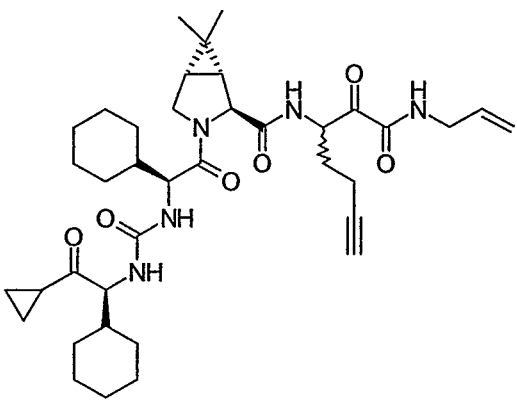
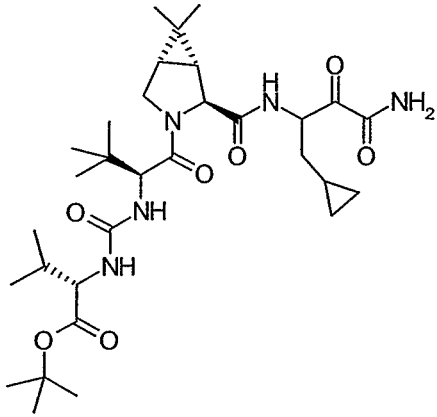
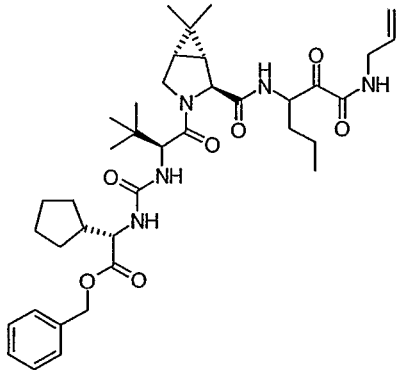
Evaluation of Inhibitors and Inactivators: The inhibition constants (K_i) for the competitive inhibitors Ac-D-(D-Gla)-L-I-(Cha)-C-OH (27), Ac-DTEDVVA(Nva)-OH and Ac-DTEDVVP(Nva)-OH are determined experimentally at fixed concentrations of enzyme and substrate by plotting v_0/v_i vs. inhibitor concentration ($[I]_0$) according to the rearranged Michaelis-Menten equation for competitive inhibition kinetics: $v_0/v_i = 1 + [I]_0 / (K_i (1 + [S]_0 / K_M))$, where v_0 is the uninhibited initial velocity, v_i is the initial velocity in the presence of inhibitor at any given inhibitor concentration ($[I]_0$) and $[S]_0$ is the substrate concentration used. The resulting data are fitted using linear regression and the resulting slope, $1/(K_i(1+[S]_0/K_M))$, is used to calculate the K_i value. The K_i^* values of some of the inventive compounds are shown in **Table 8**:

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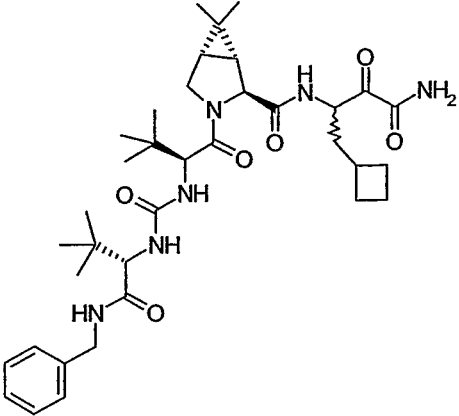
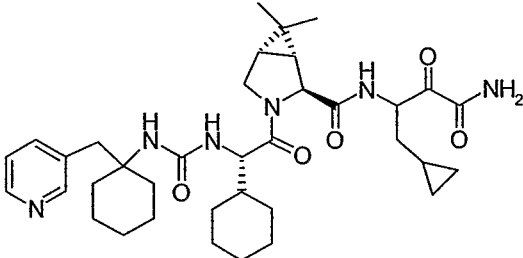
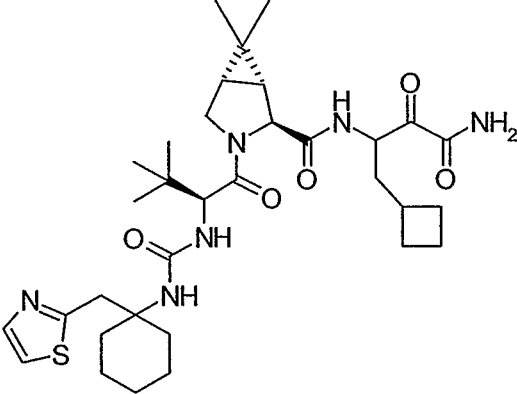
Table 8

structure	Ki* (nM)
	5
	8
	15

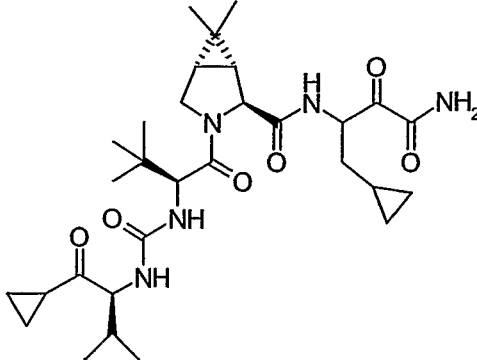
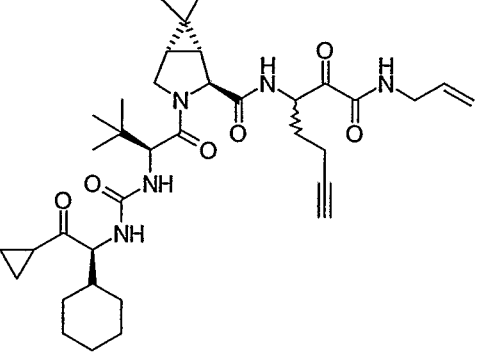
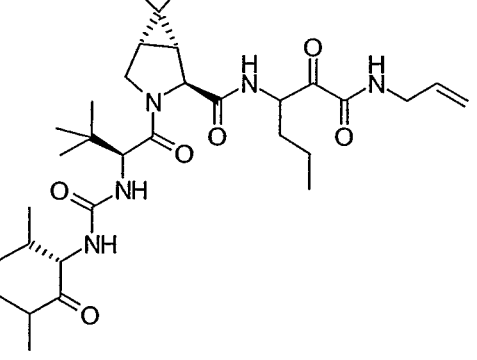
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	13
	22
	30

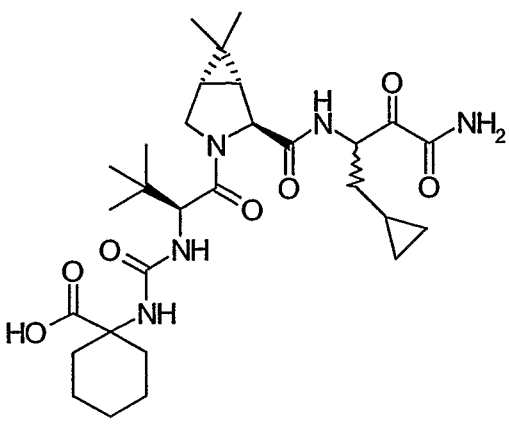
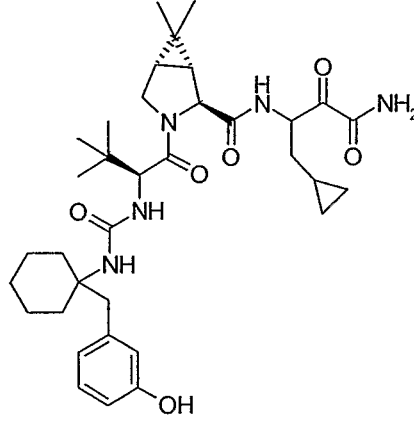
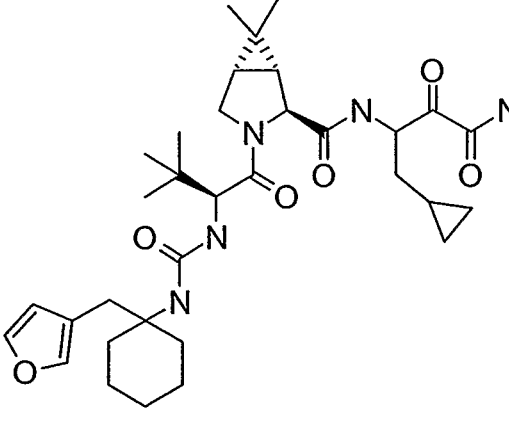
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	40
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	9
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	4.3

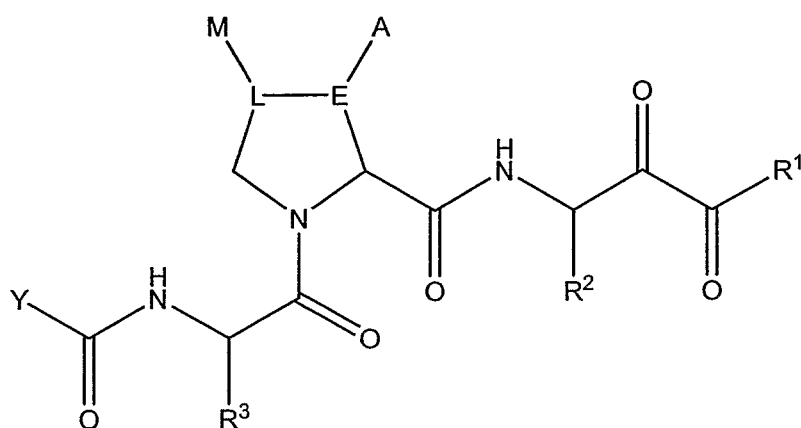
While the present invention has been described with in conjunction with the specific embodiments set forth above, many alternatives, modifications and other variations thereof will be apparent to those of ordinary skill in the art. All such

5 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,
 5 diastereomers and racemates of said compound, or a pharmaceutically acceptable salt, solvate or ester of said compound, said compound having the general structure shown in Formula I:

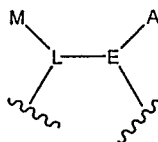


Formula I

10 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;

15 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:



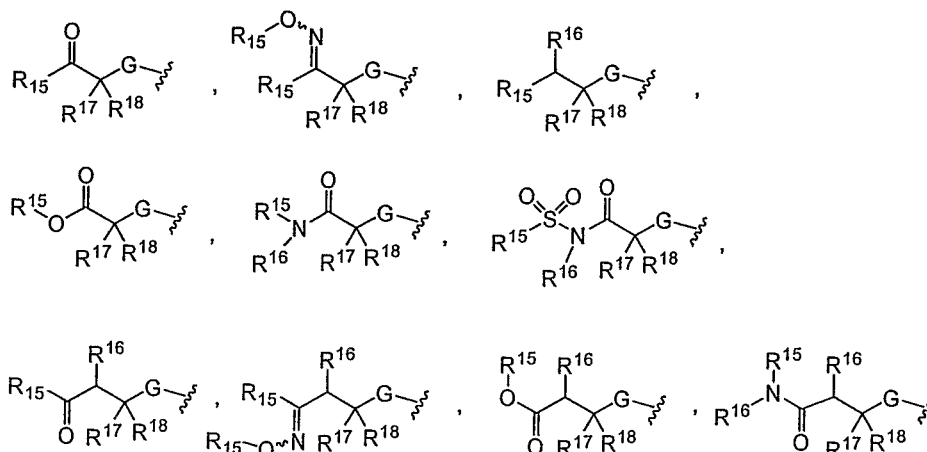
20 shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl;

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

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

R, R', R², and R³ 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
 5 each other such that NRR' forms a four to eight-membered heterocyclyl;

and Y is selected from the following moieties:



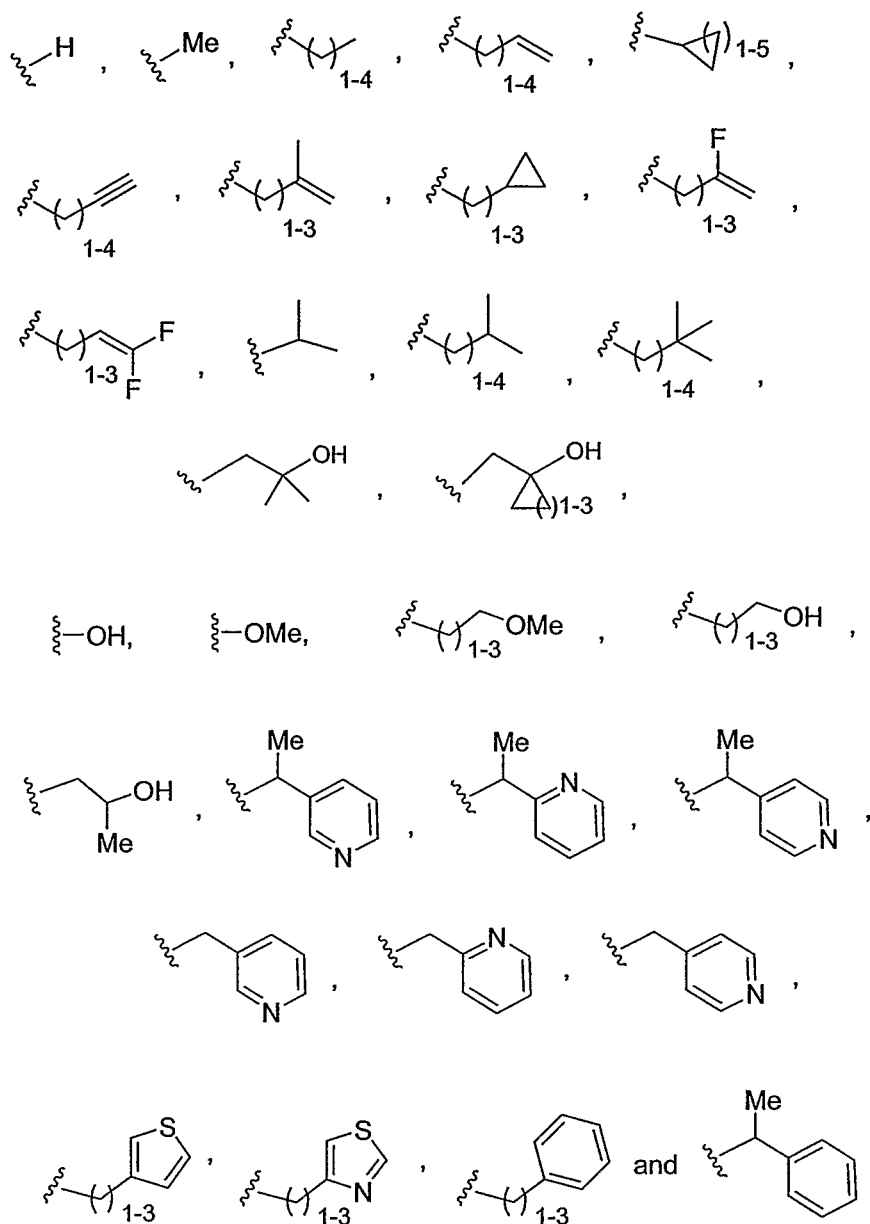
wherein G is NH or O; and R¹⁵, R¹⁶, R¹⁷ and R¹⁸ can be the same or different, each being independently selected from the group consisting of H, alkyl, heteroalkyl,
 10 alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, or alternately, R¹⁵ and R¹⁶ are connected to each other to form a four to eight-membered cycloalkyl, heteroaryl or heterocyclyl structure, and likewise, independently R¹⁷ and R¹⁸ are connected to each other to form a three to eight-membered cycloalkyl or heterocyclyl;

15 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, alkyl, aryl, heteroaryl, alkylsulfonamido, arylsulfonamido, keto, carboxy, carbalkoxy,
 20 carboxamido, alkoxycarbonylamino, alkoxycarbonyloxy, alkylureido, arylureido, halo, cyano, and nitro.

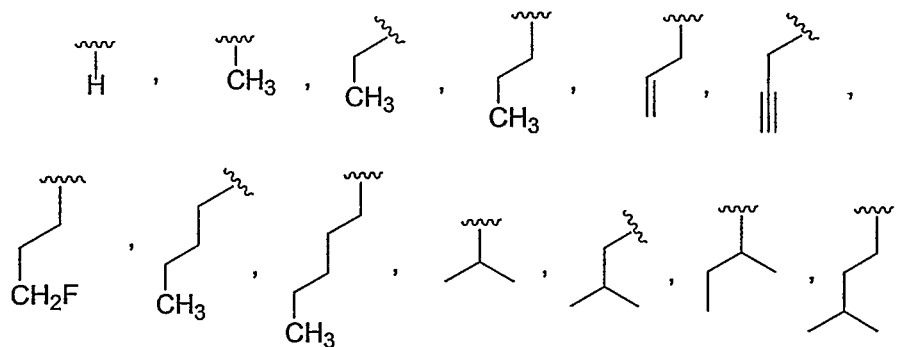
2. The compound of claim 1, wherein R¹ is NR⁹R¹⁰, and R⁹ is H, R¹⁰ is H, or R¹⁴ wherein R¹⁴ is H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, alkyl-aryl, alkyl-heteroaryl, aryl-alkyl, alkenyl, alkynyl or heteroaryl-alkyl.

3. The compound of claim 2, wherein R¹⁴ is selected from the group consisting of:

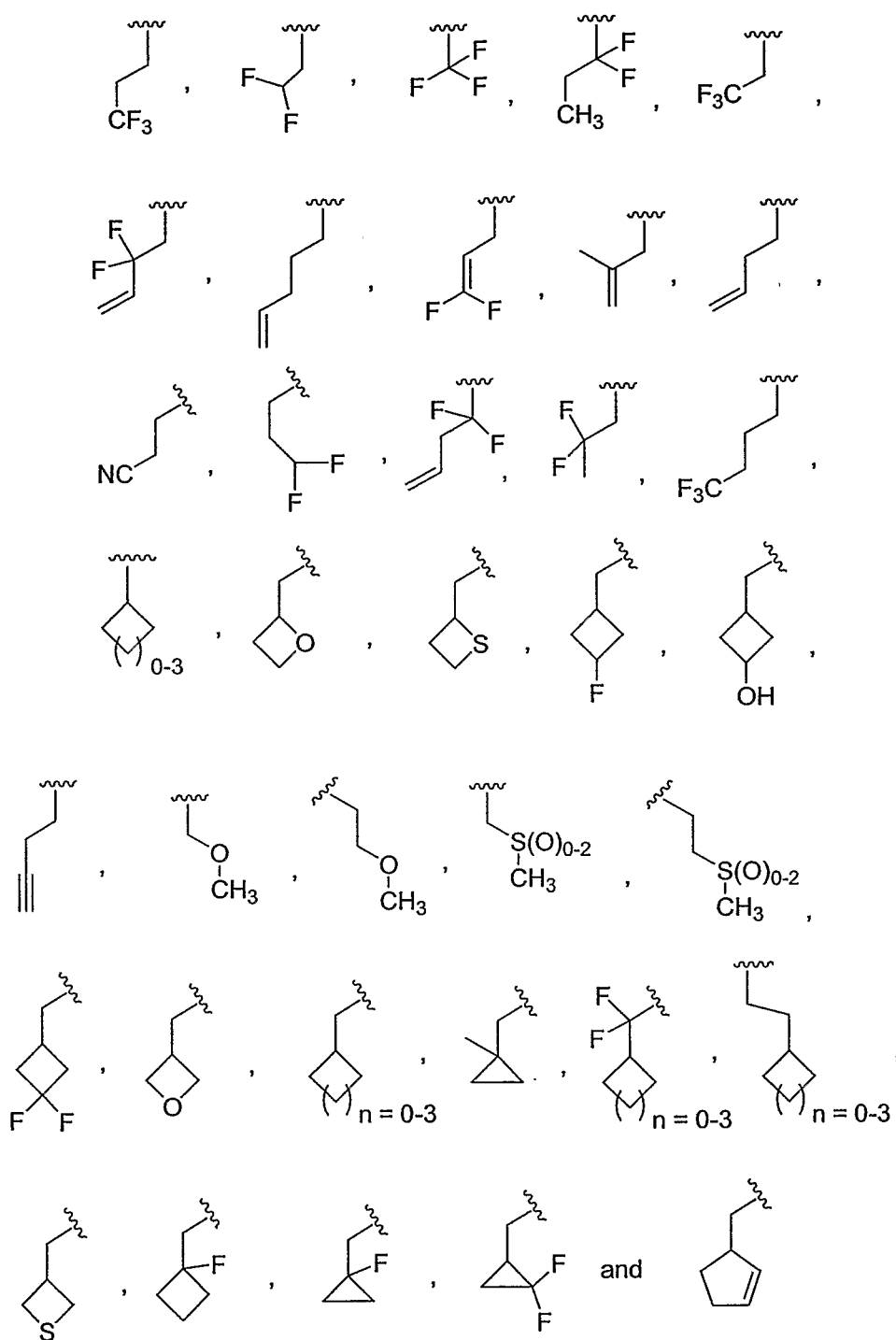
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4. The compound of claim 1, wherein R^2 is selected from the group consisting of the following moieties:

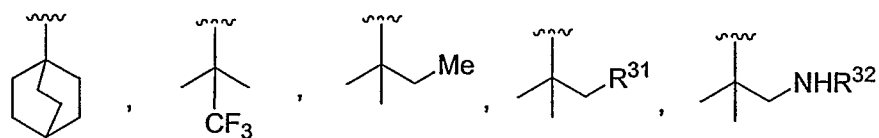
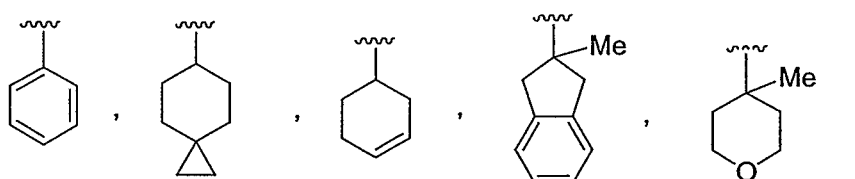
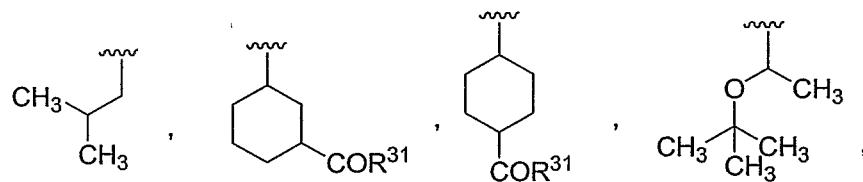
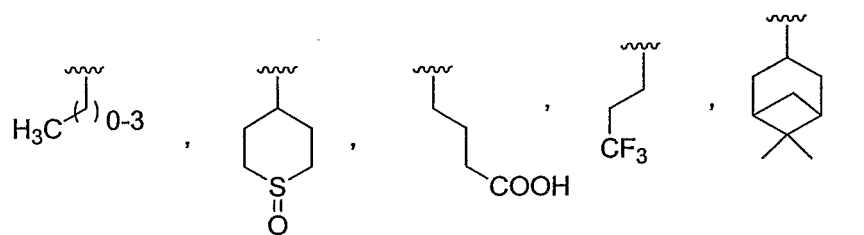
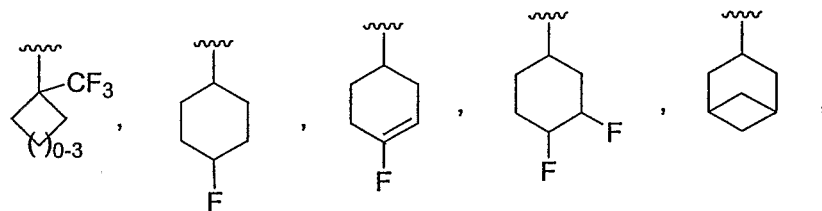
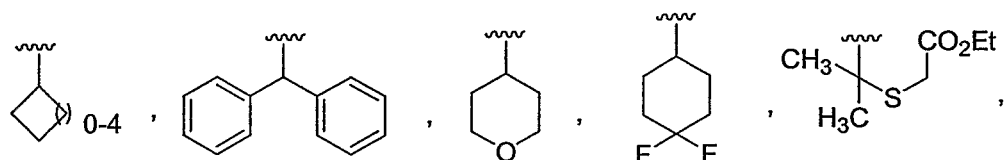
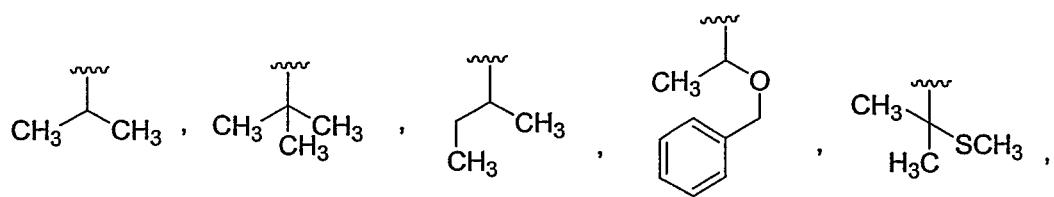


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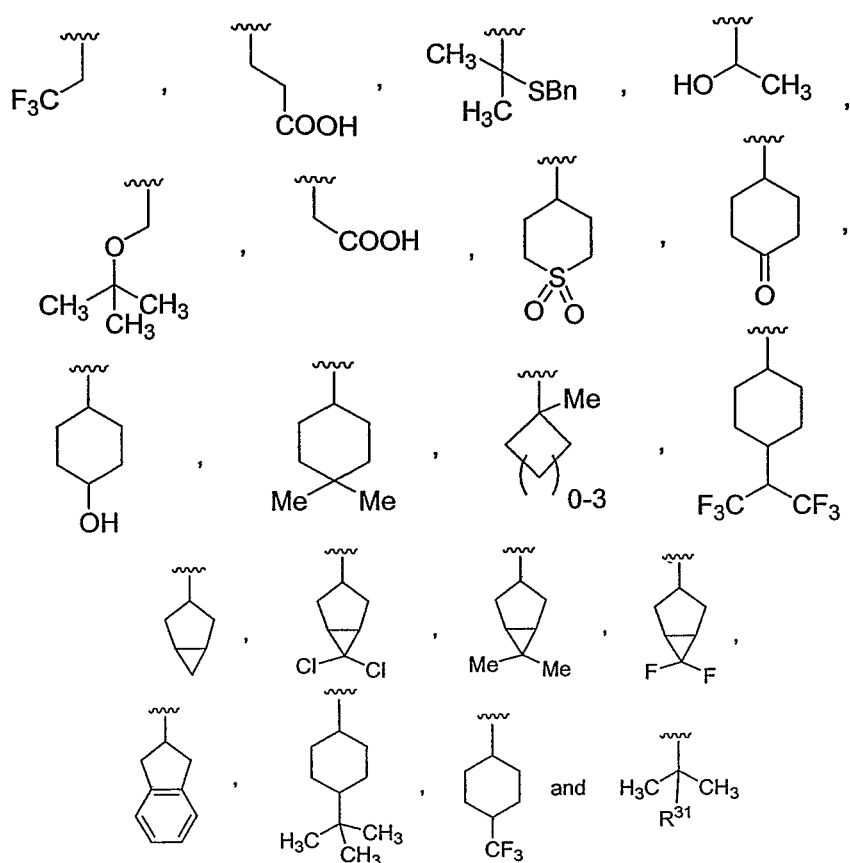


5. The compound of claim 1, wherein R^3 is selected from the group consisting of:

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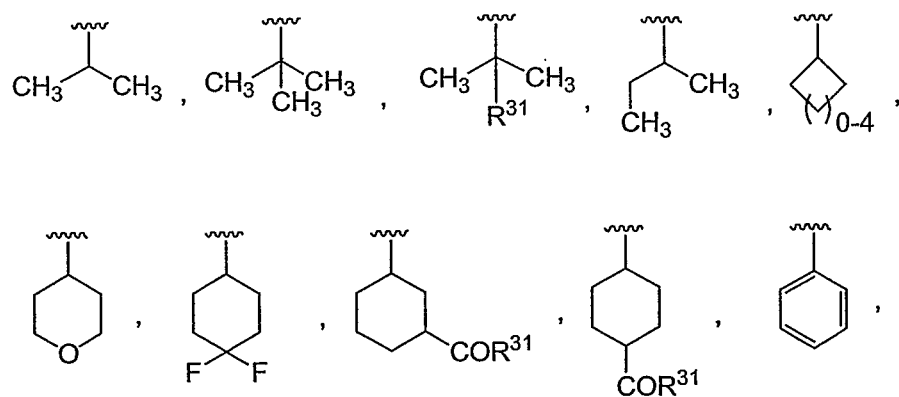


wherein R^{31} is OH or O-alkyl; and

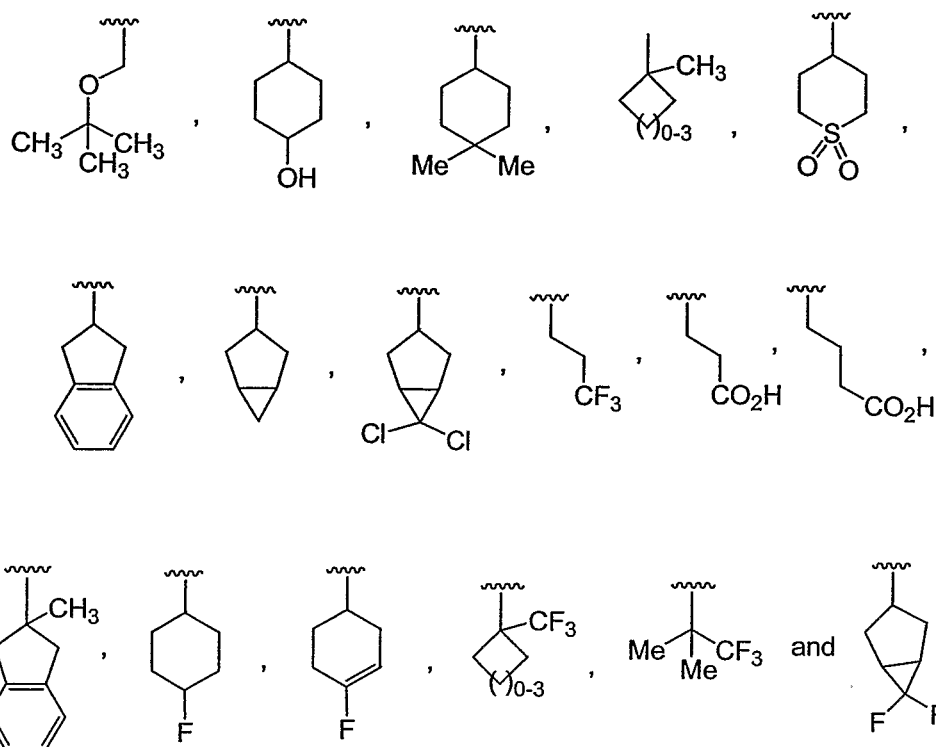
R^{32} is H, $C(O)CH_3$, $C(O)OtBu$ or $C(O)N(H)tBu$.

5

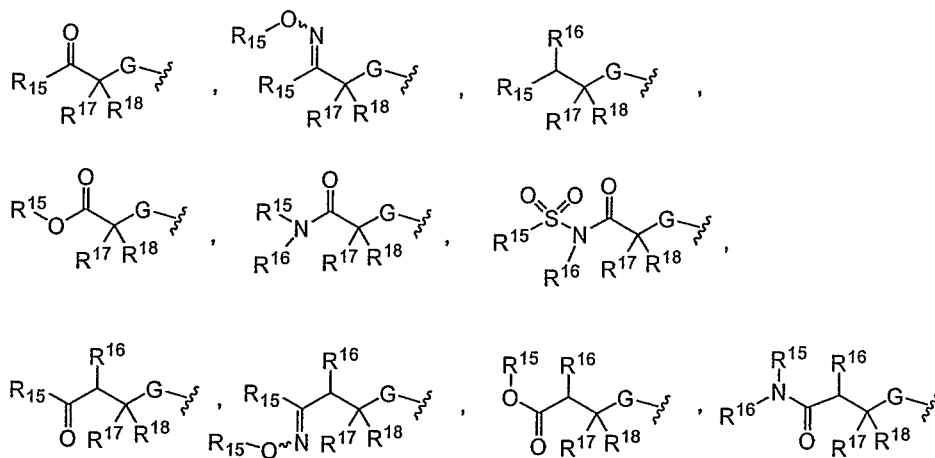
6. The compound of claim 1, wherein R^3 is selected from the group consisting of the following moieties:



468



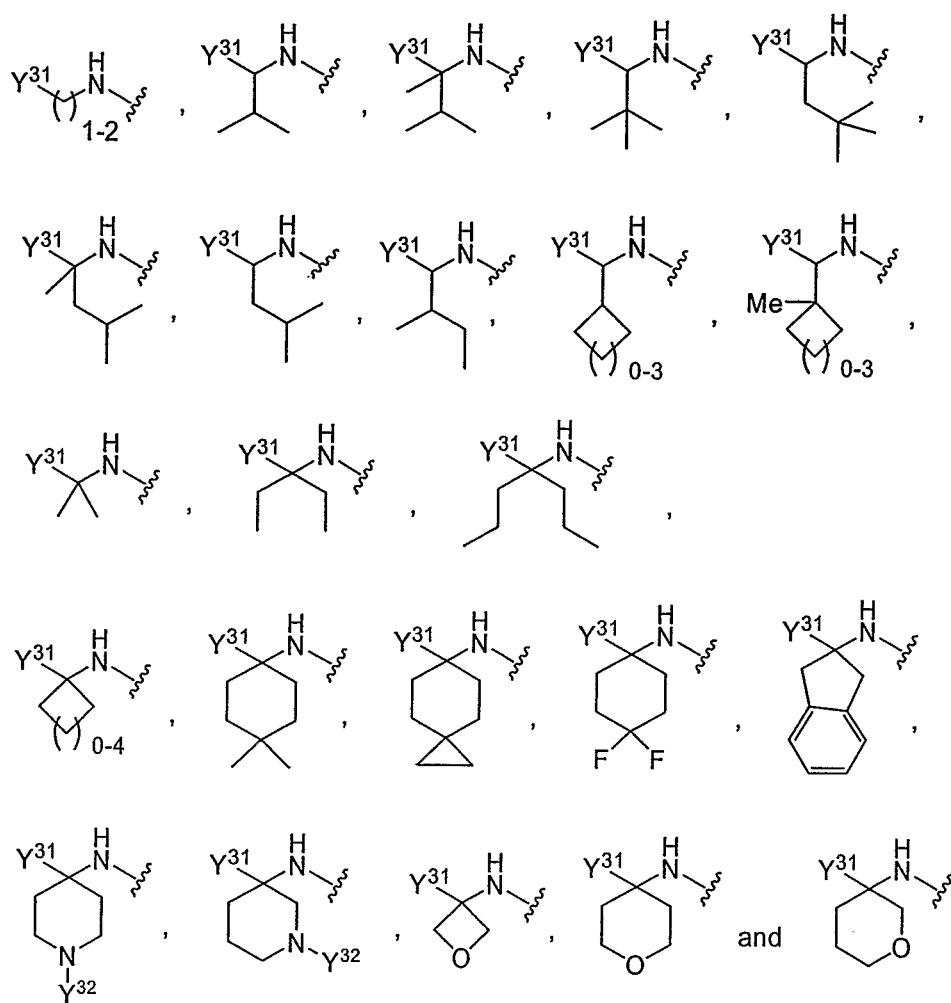
7. The compound of claim 1, wherein Y is selected from the following moieties:



wherein G is NH; and R^{15} , R^{16} , R^{17} and R^{18} are as defined in claim 1.

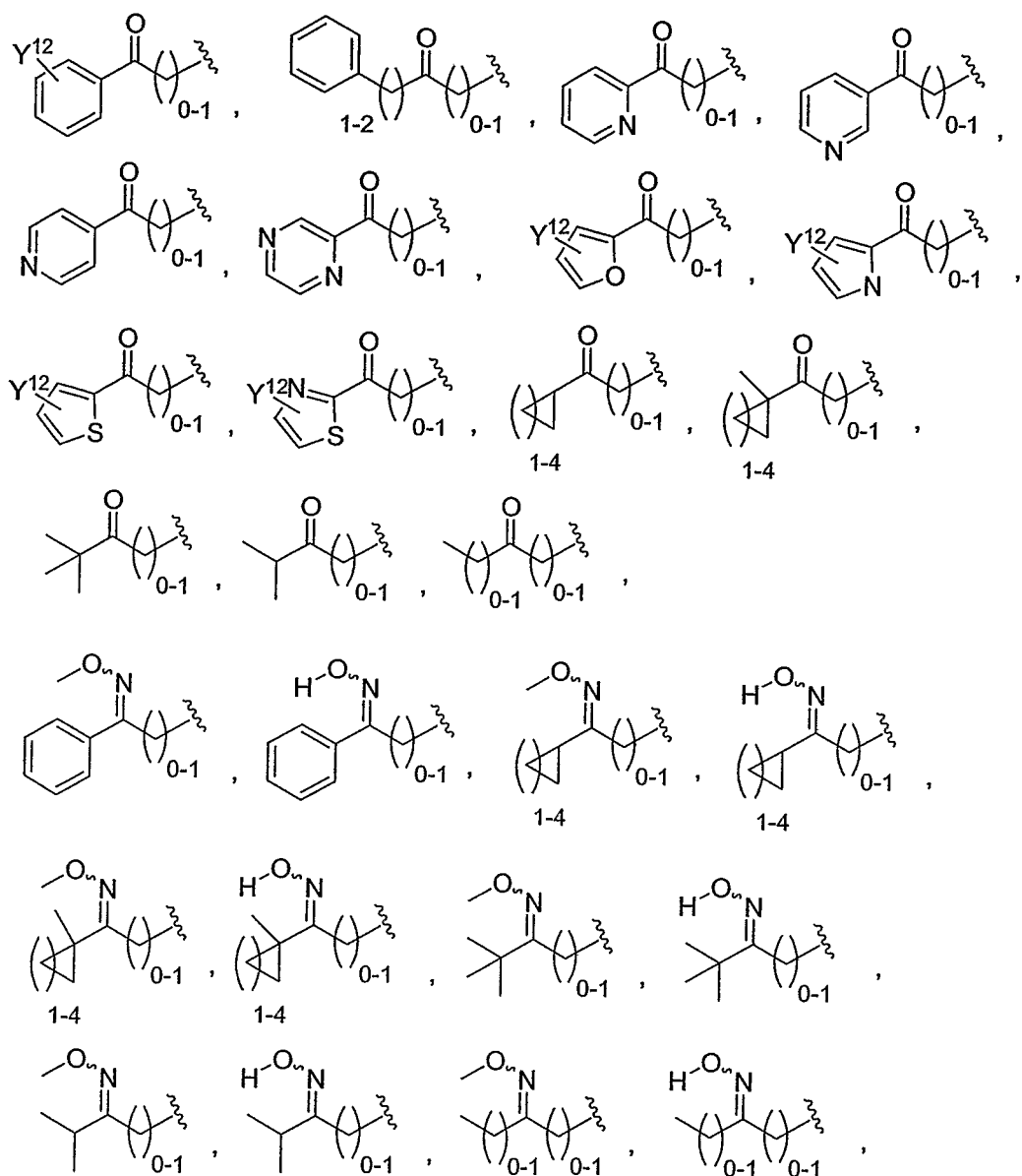
8. The compound of claim 7, wherein Y is selected from the group consisting of:

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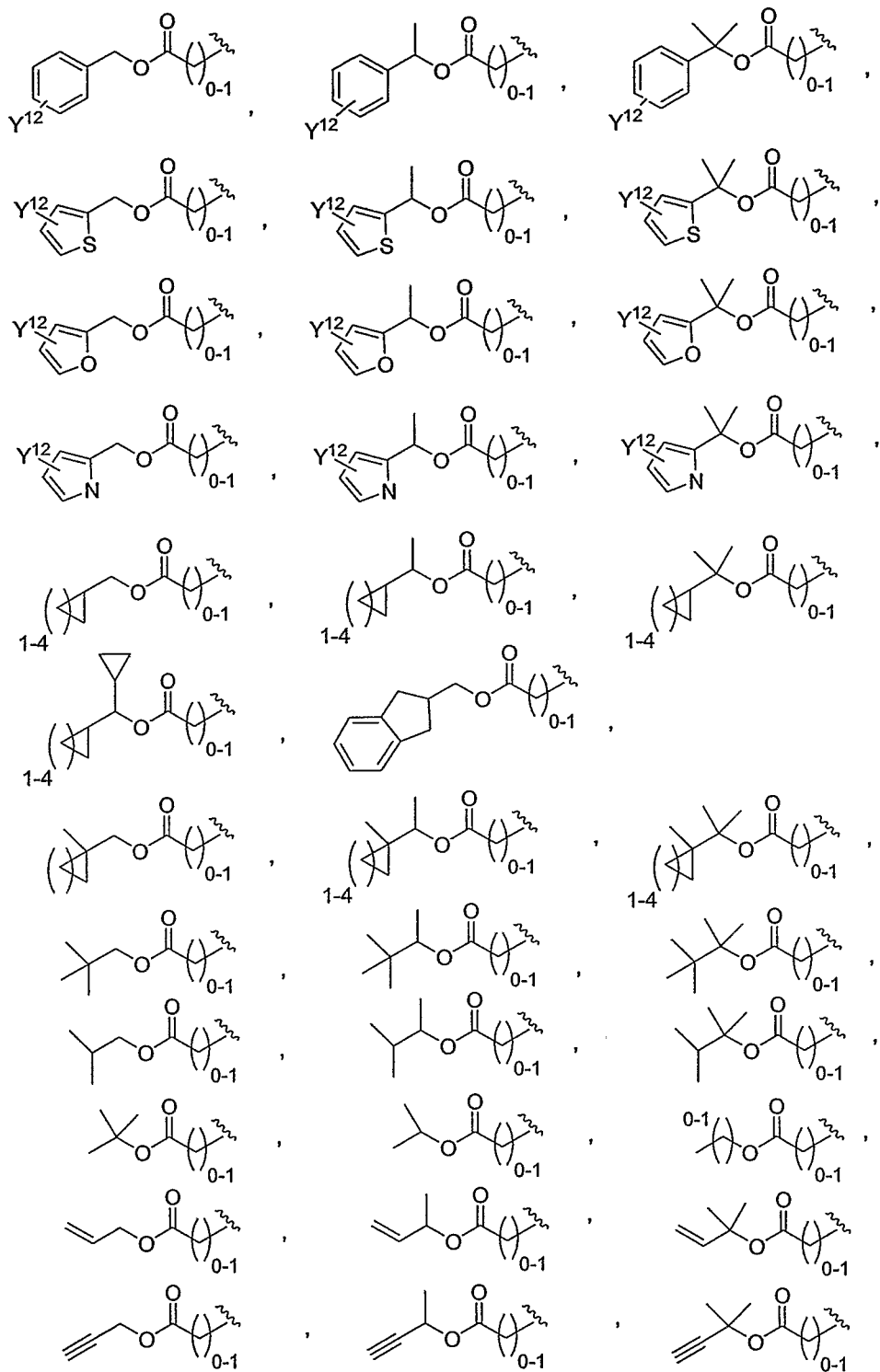


wherein Y³¹ is selected from the group consisting of:

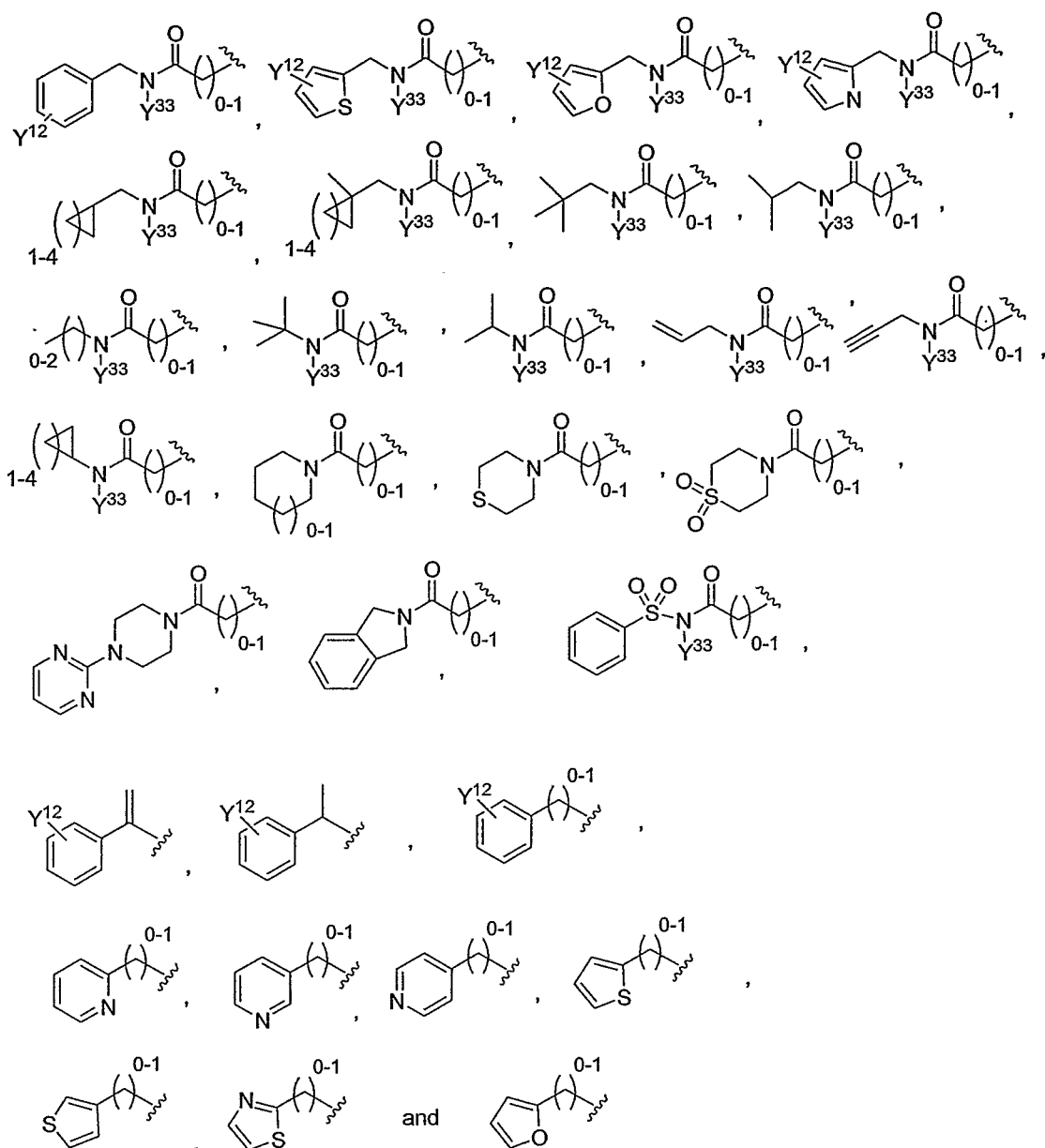
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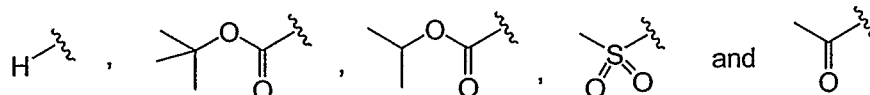
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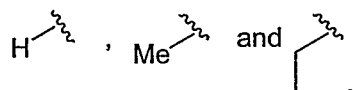
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Y^{32} is selected from the group consisting of:

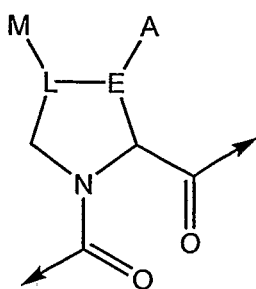


and Y^{12} is selected from the group consisting of H, CO_2H , CO_2Me , OMe , F, Cl, Br, NH_2 , $N(H)S(O_2)CH_3$, $N(H)C(O)CH_3$, NO_2 , NMe_2 , $S(O_2)NH_2$, CF_3 , Me, OH, OCF_3 , and $C(O)NH_2$ and Y^{33} is selected from the group consisting of:

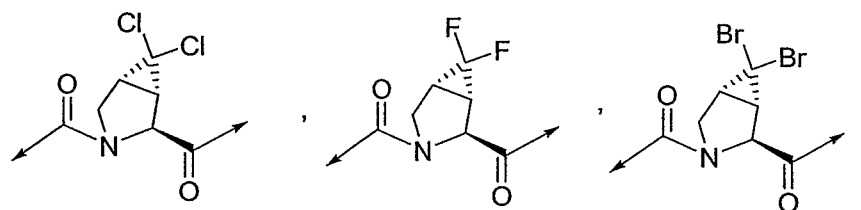
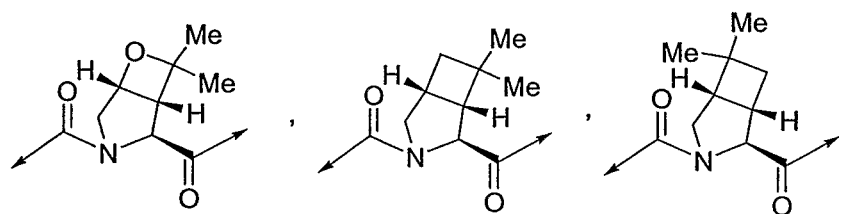
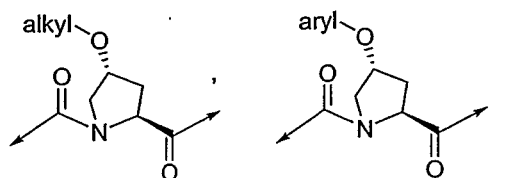


9. The compound of claim 1, wherein the moiety:

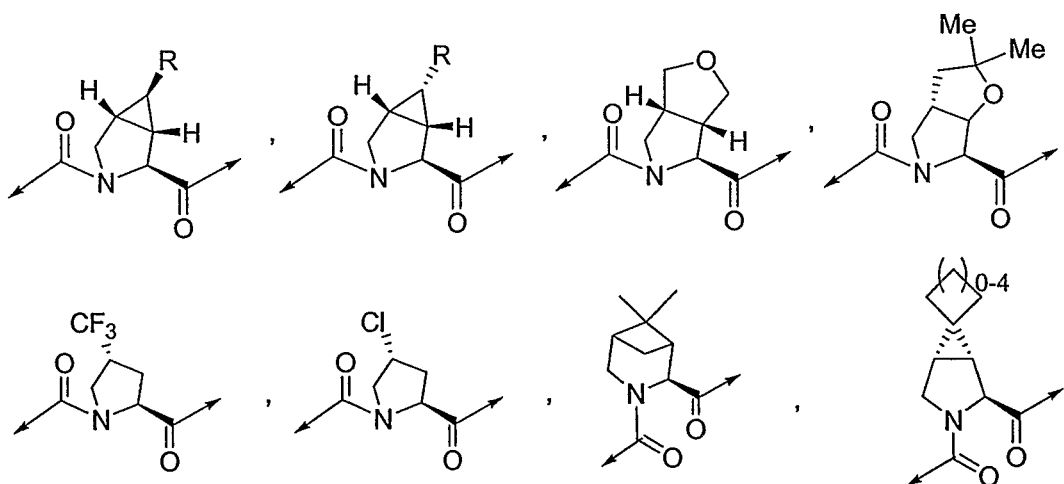
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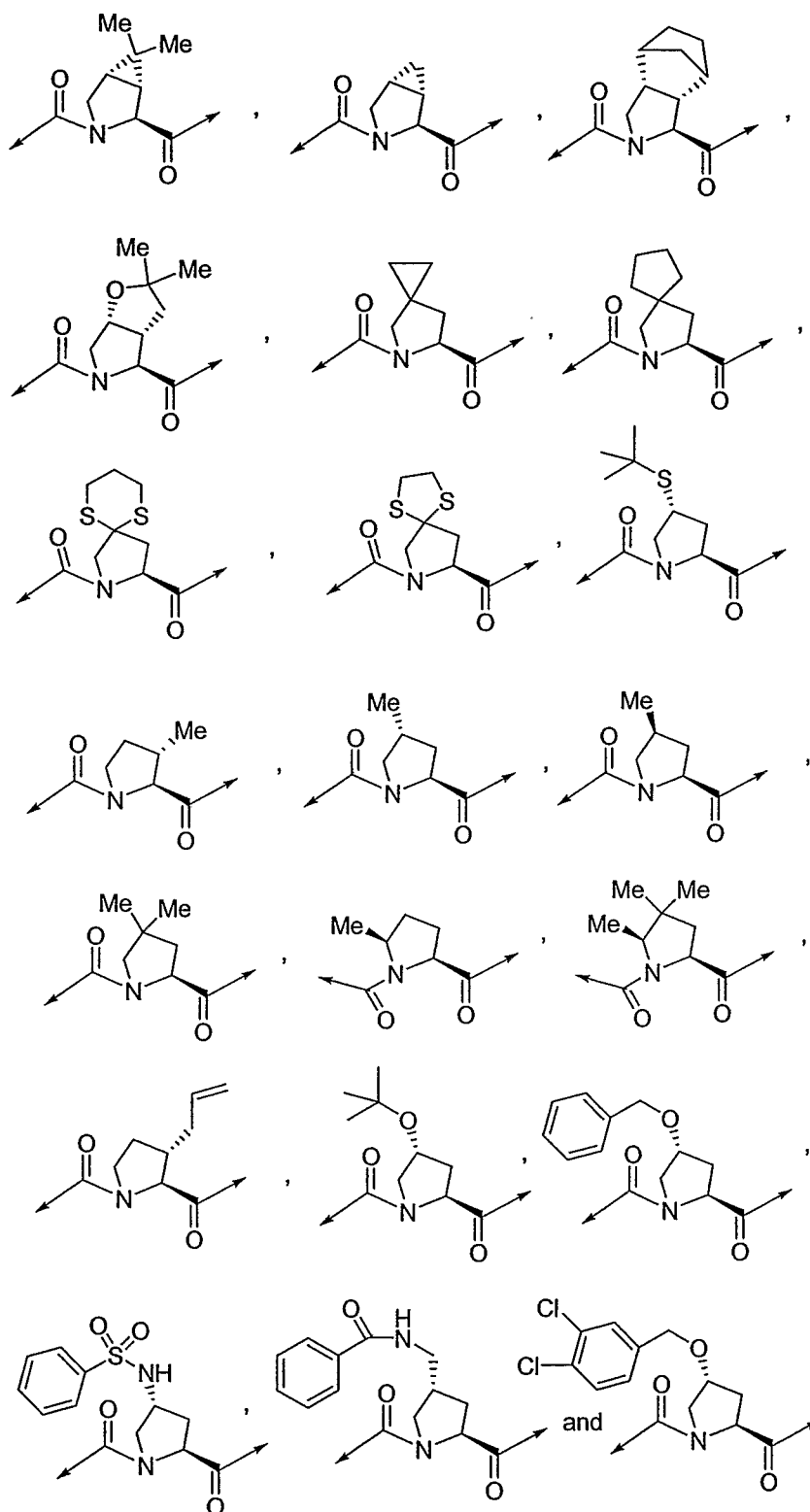
is selected from the following structures:



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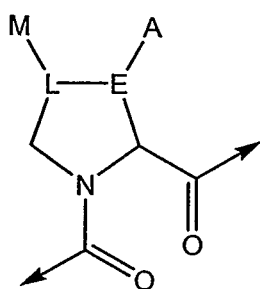


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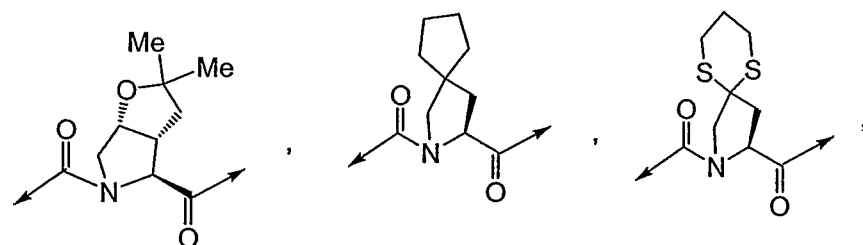
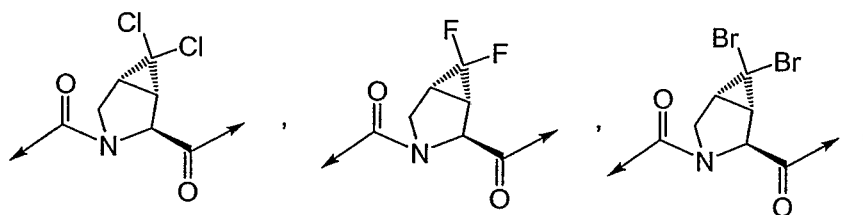
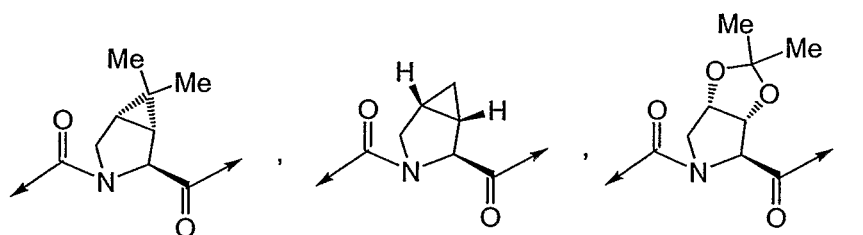
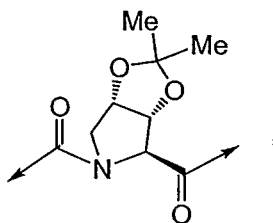
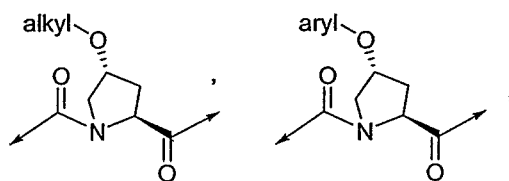


10. The compound of claim 9, wherein the moiety:

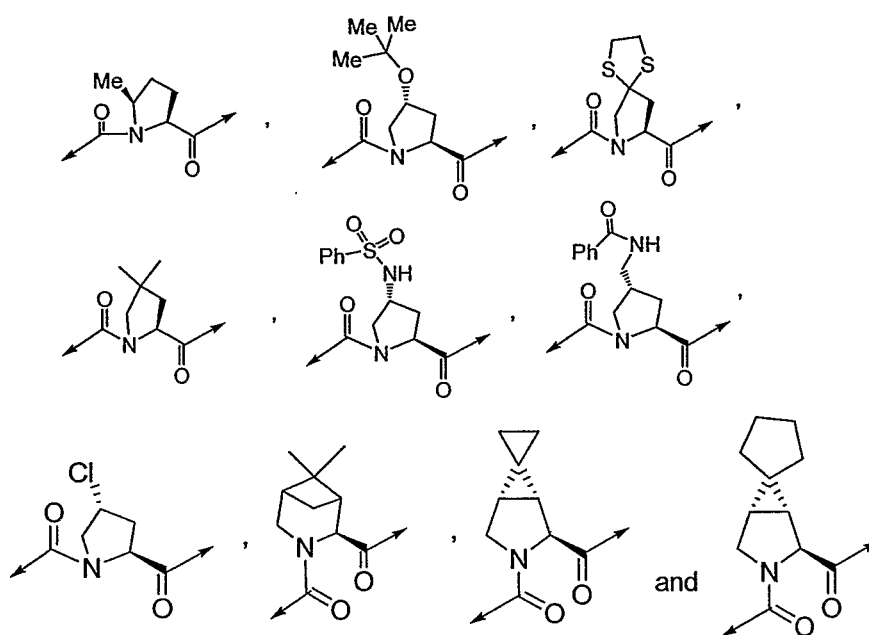
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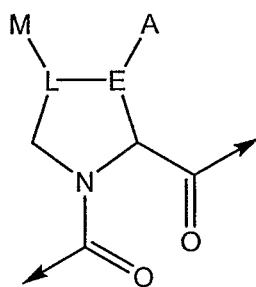
is selected from the following structures:



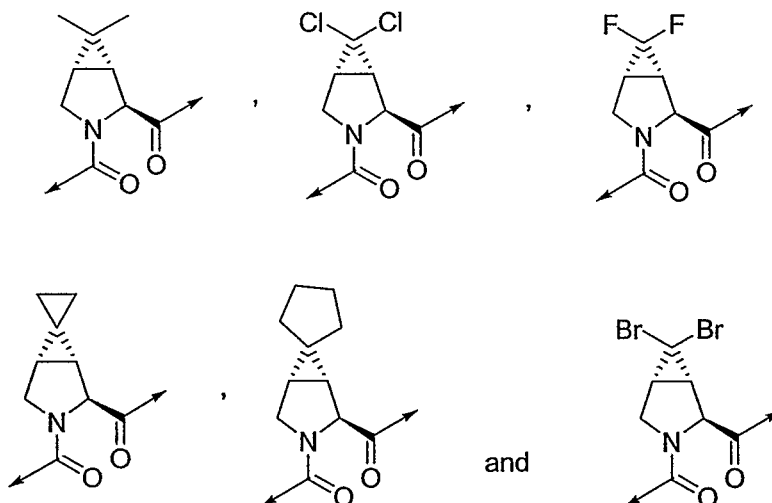
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11. The compound of claim 10, wherein the moiety:

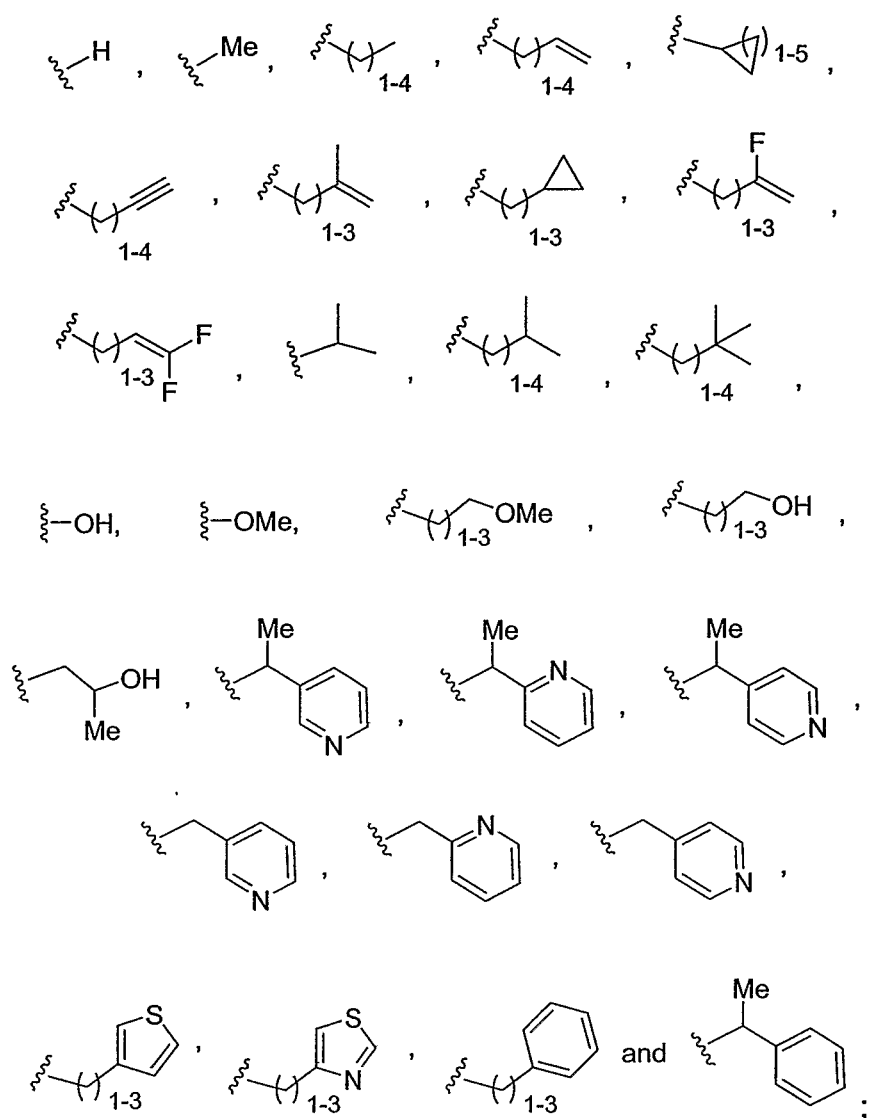


5 is selected from the following structures:

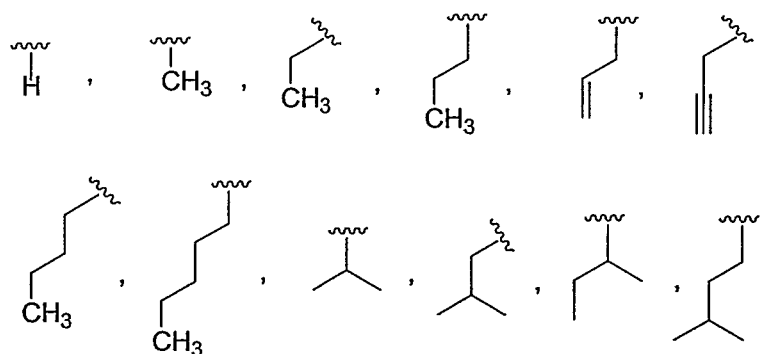


12. The compound of claim 1, R^1 is NHR^{14} , where R^{14} is selected from the group consisting of:

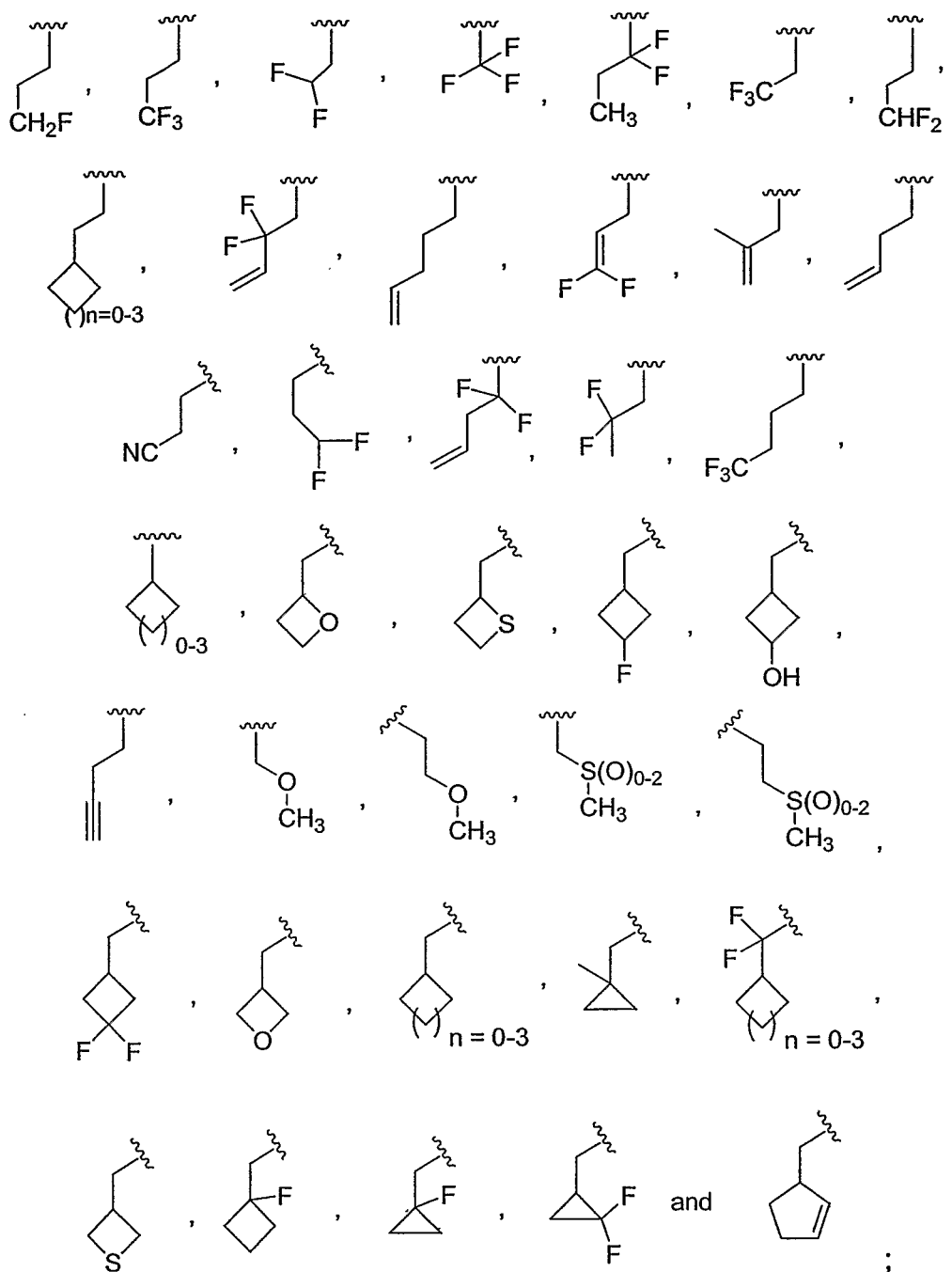
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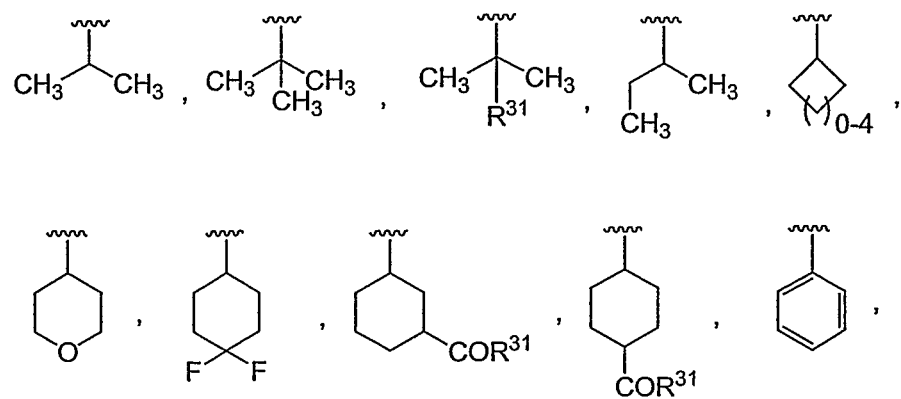
R^2 is selected from the group consisting of the following moieties:

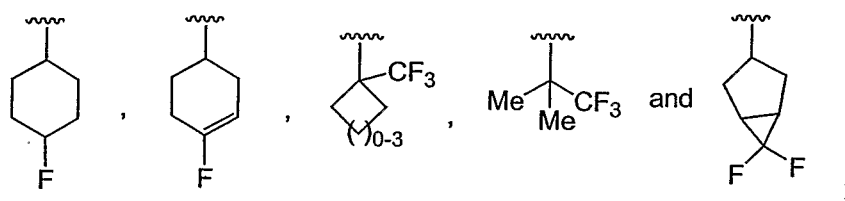
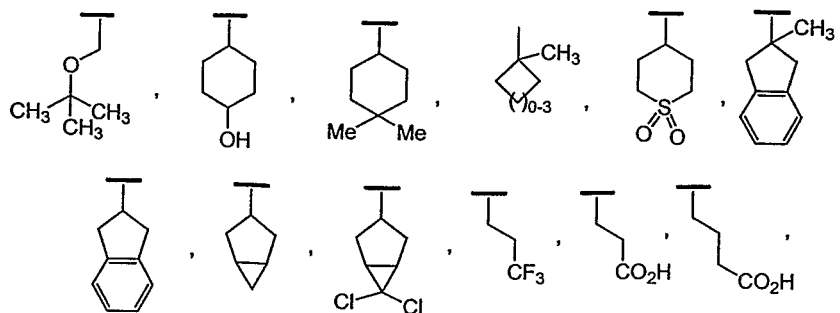


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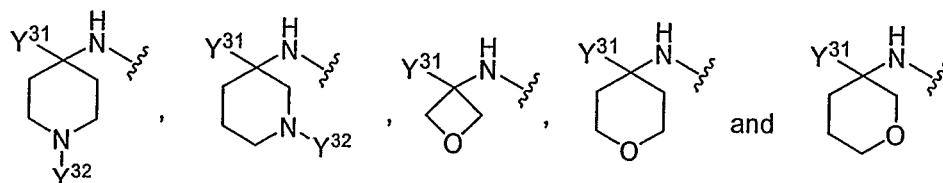
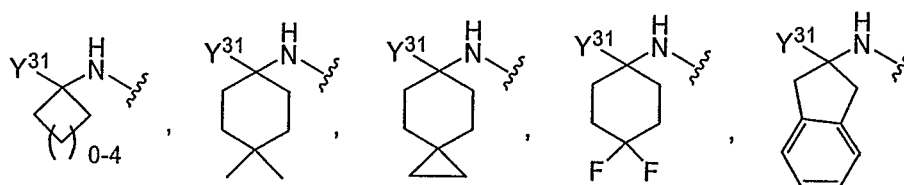
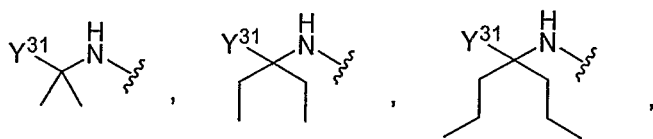
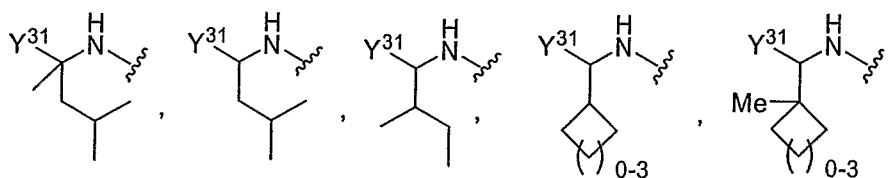
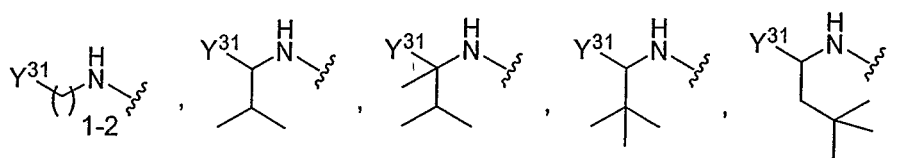


R³ is selected from the group consisting of the following moieties:



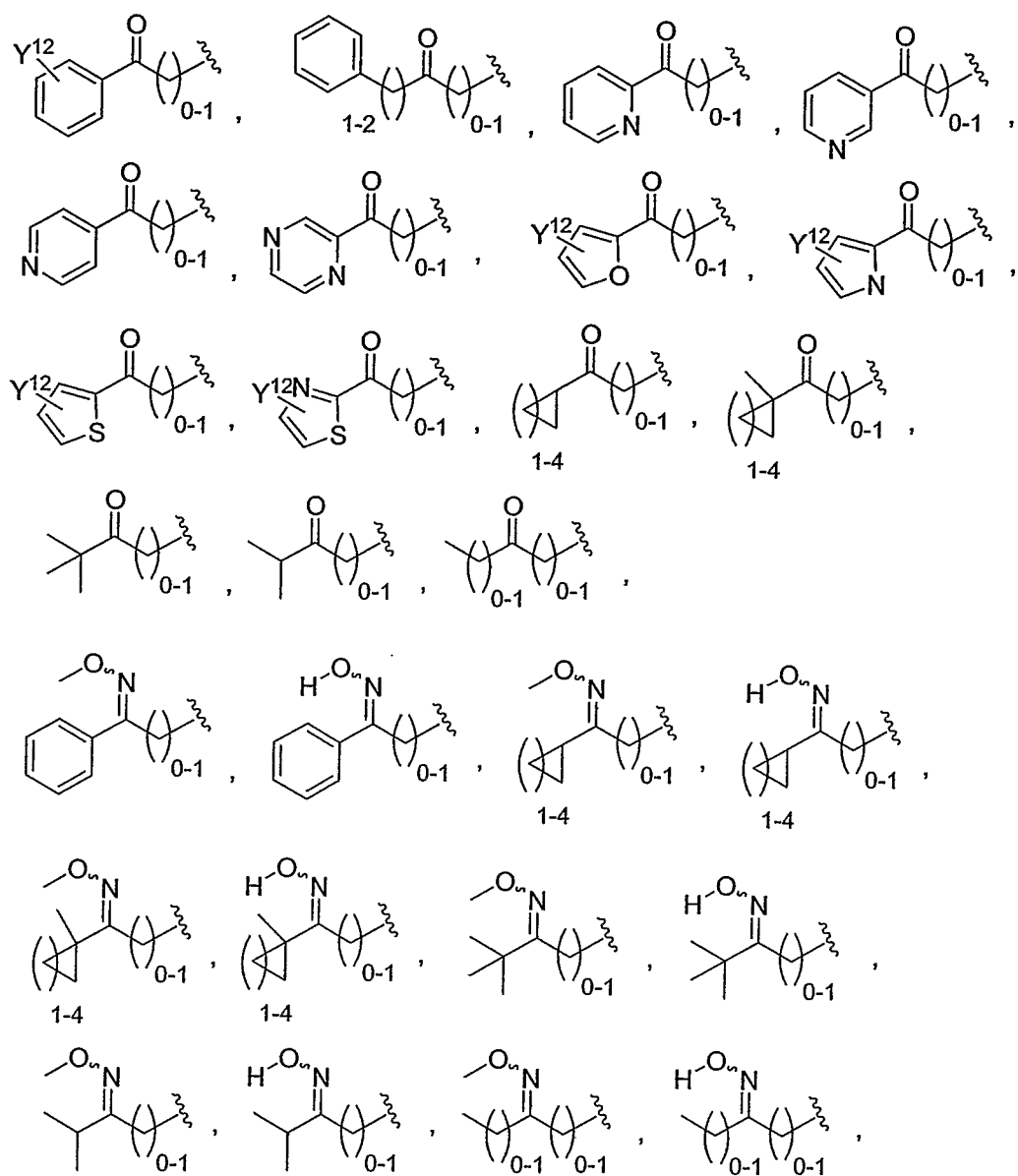


5 Y is selected from the group consisting of:

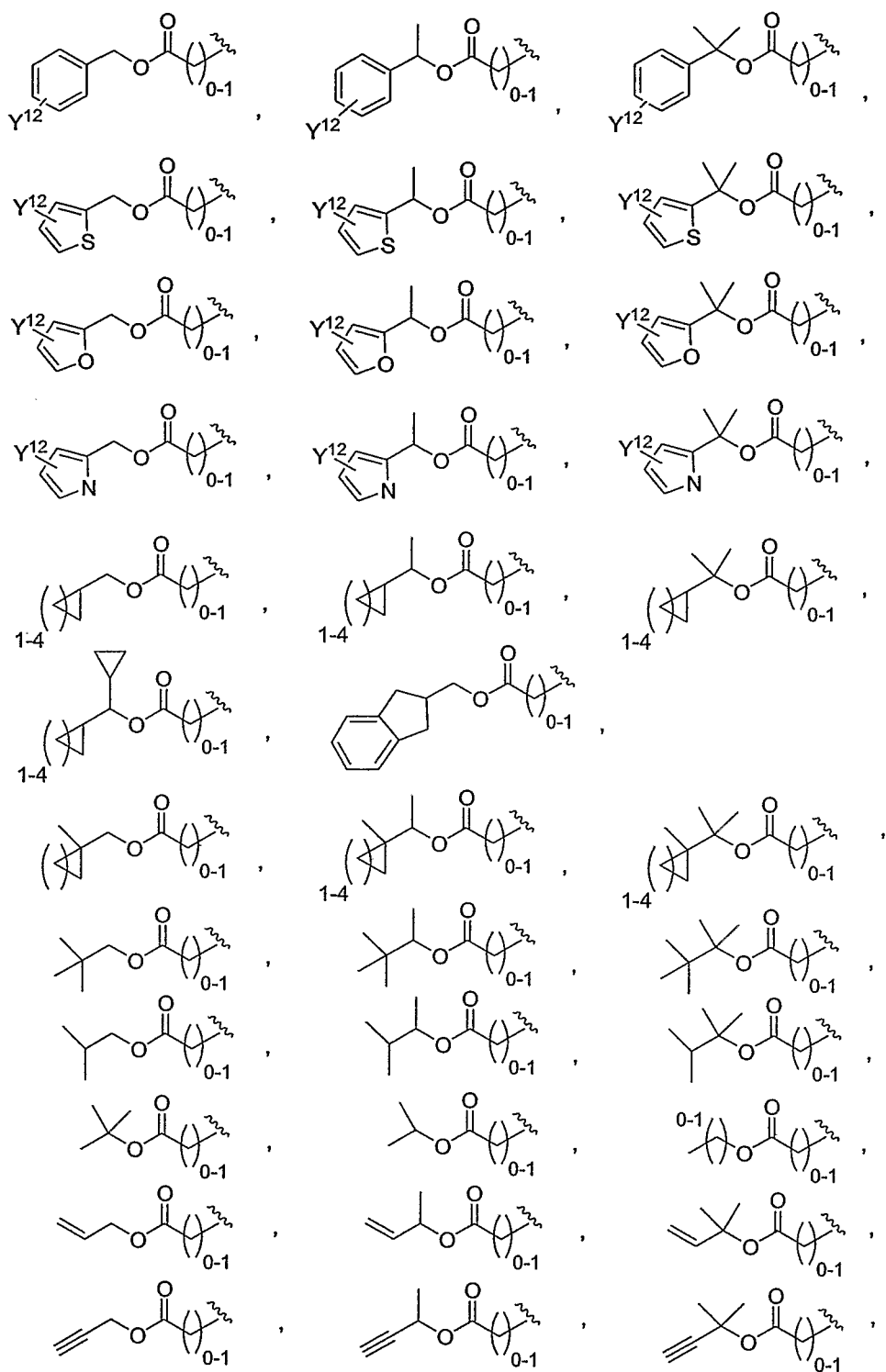


wherein Y³¹ is selected from the group consisting of:

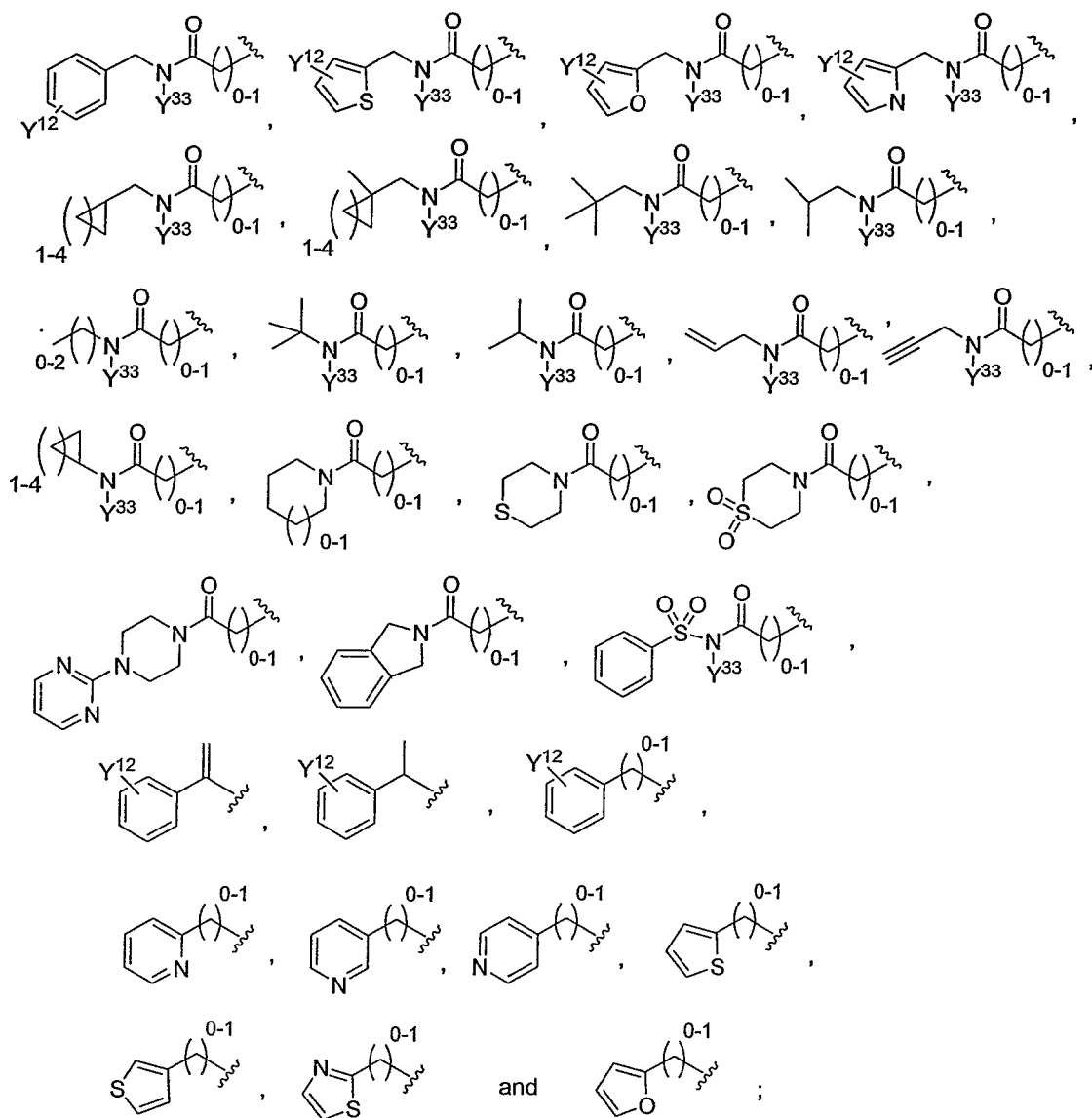
480



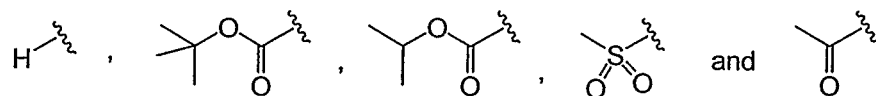
481



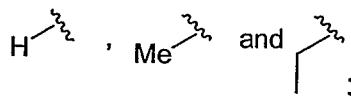
482



Y³² is selected from the group consisting of:

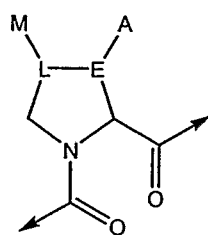


- 5 and Y¹² is selected from the group consisting of H, CO₂H, CO₂Me, OMe, F, Cl, Br, NH₂, N(H)S(O₂)CH₃, N(H)C(O)CH₃, NO₂, NMe₂, S(O₂)NH₂, CF₃, Me, OH, OCF₃, and C(O)NH₂ and Y³³ is selected from the group consisting of:

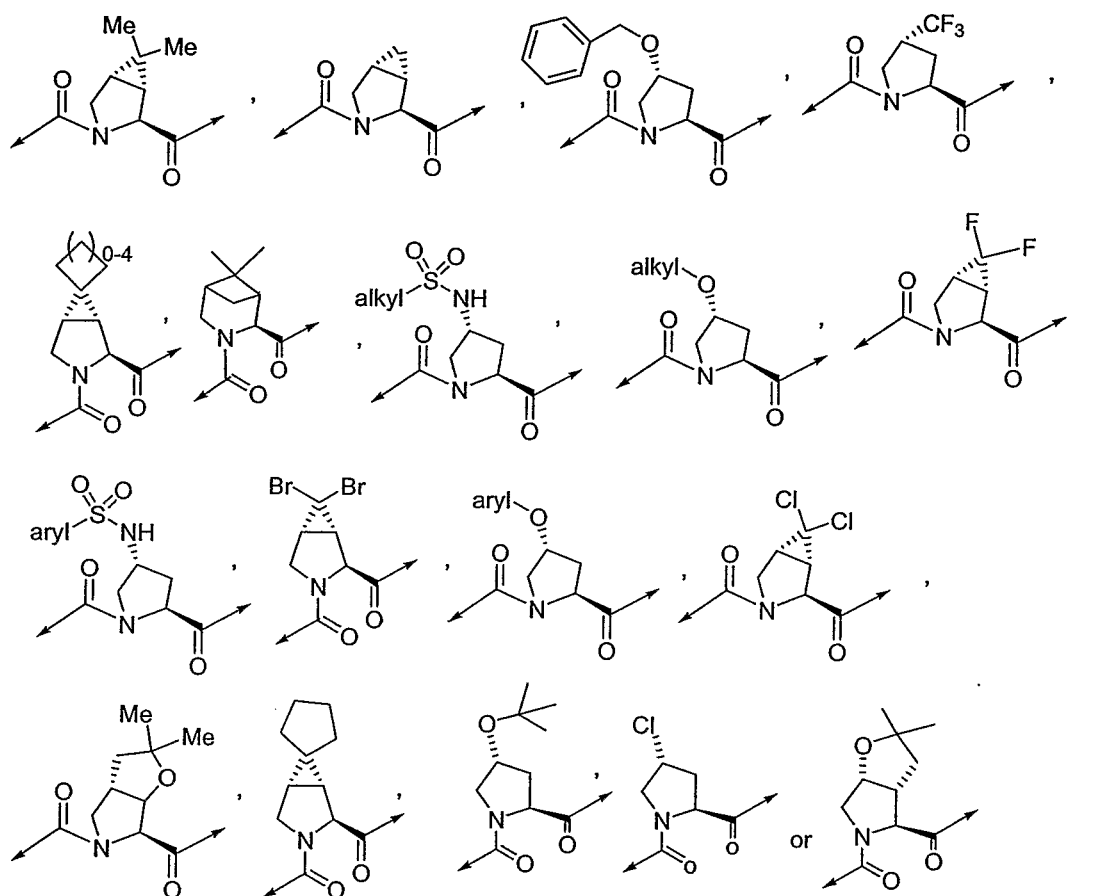


and the moiety:

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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 14 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, 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.

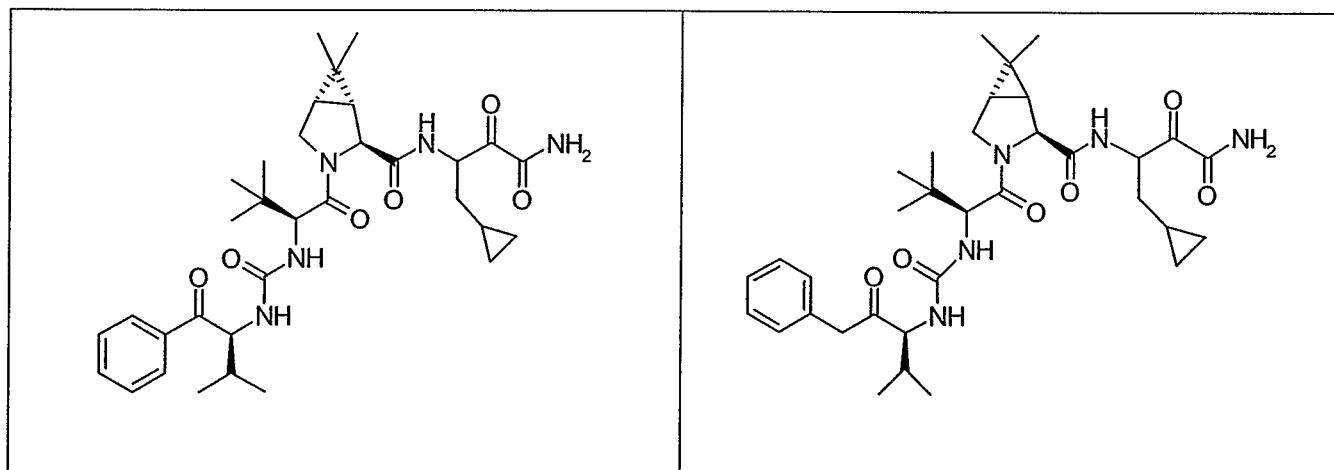
19. A method of treating disorders associated with the HCV, said method comprising administering to a patient in need of such treatment a pharmaceutical composition which comprises therapeutically effective amounts of at least one compound of claim 1.

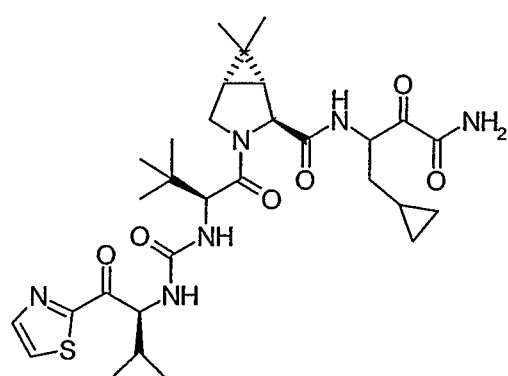
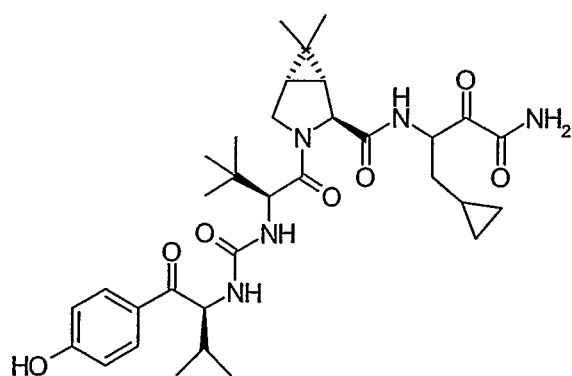
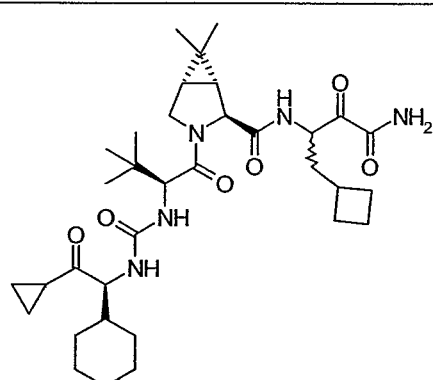
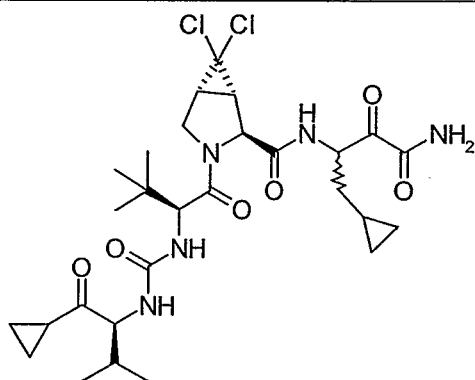
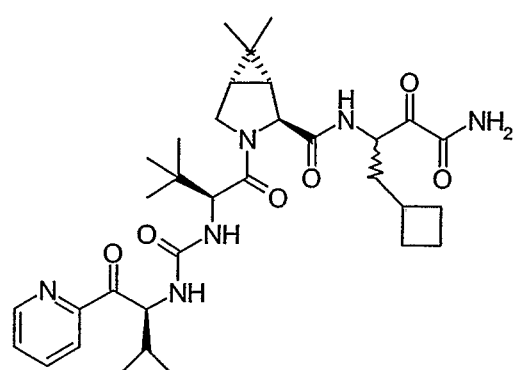
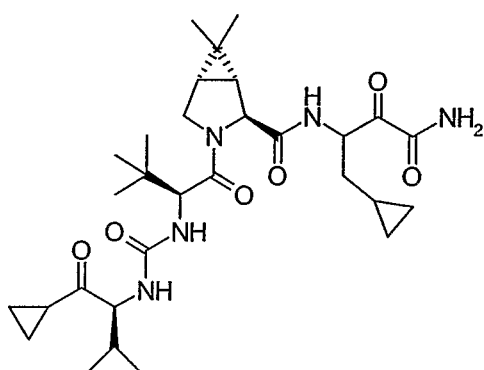
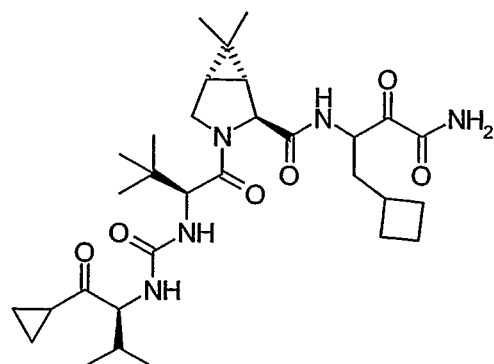
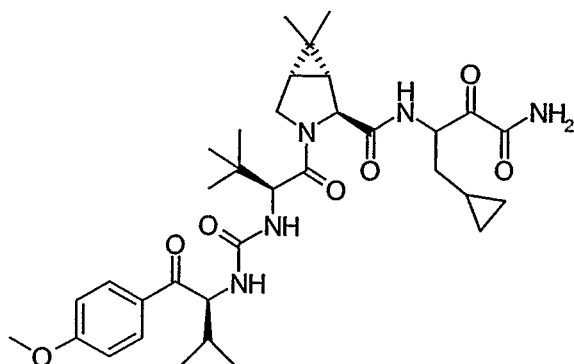
20. The method of claim 19, wherein said administration is oral or subcutaneous.

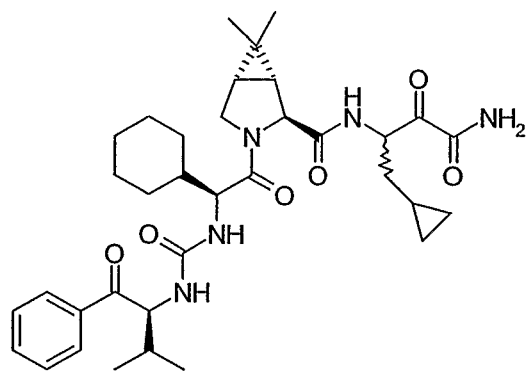
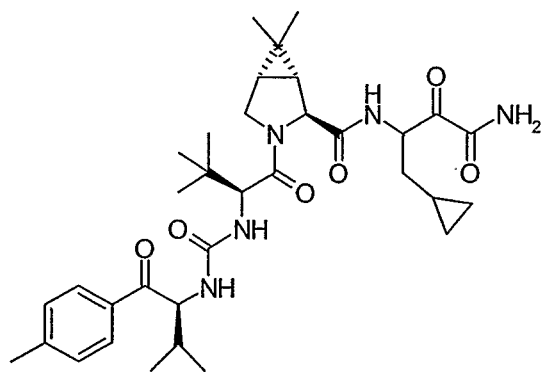
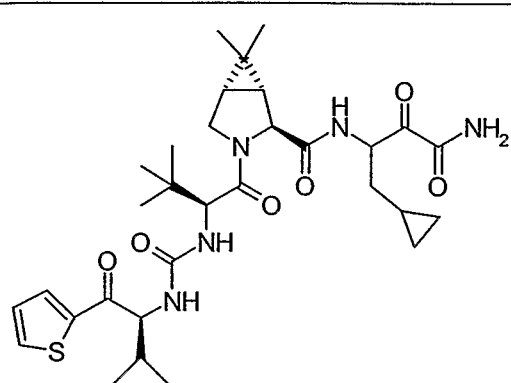
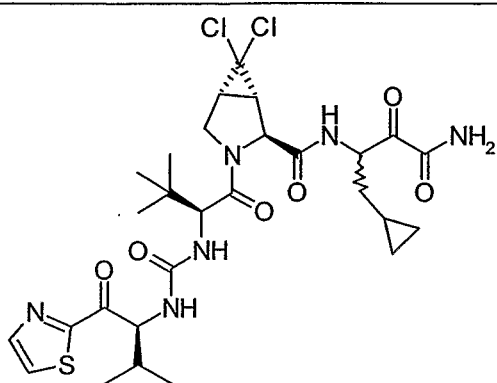
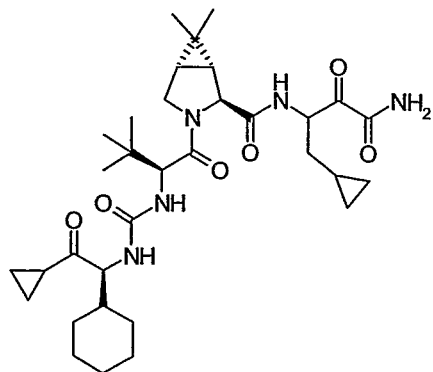
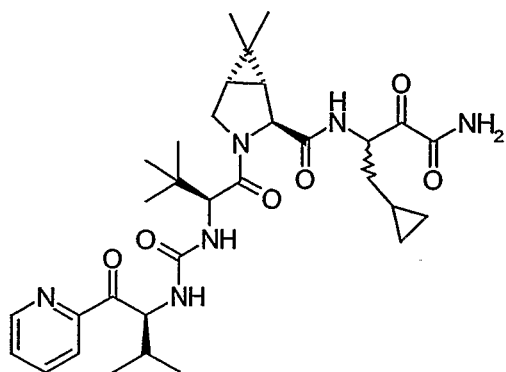
21. The use of a compound of claim 1 for the manufacture of a medicament to treat disorders associated with the HCV.

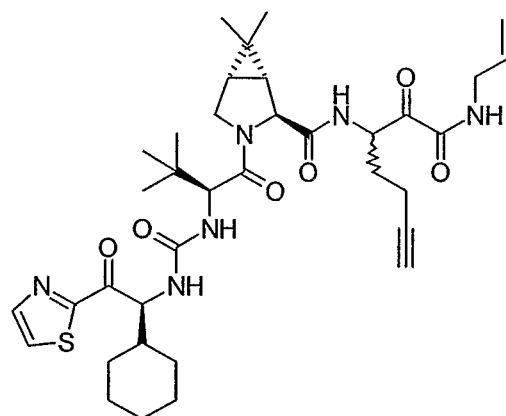
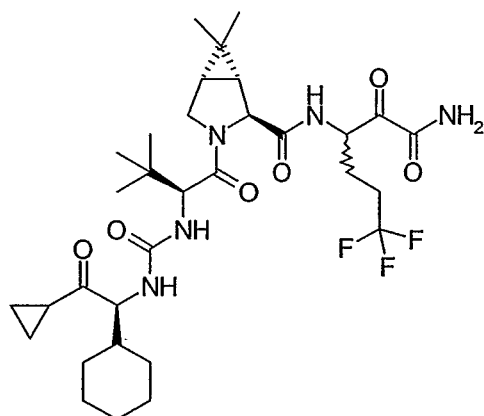
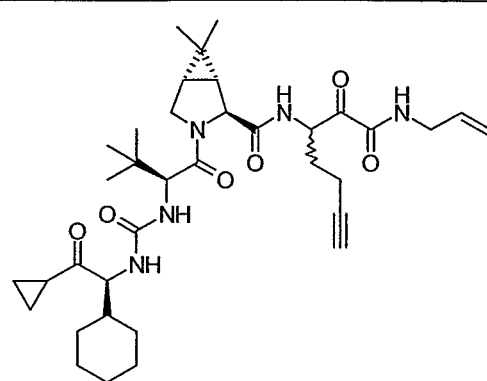
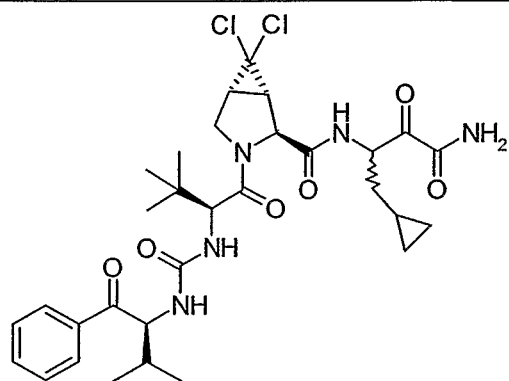
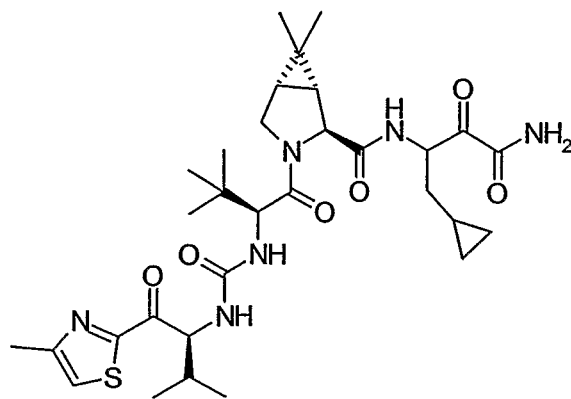
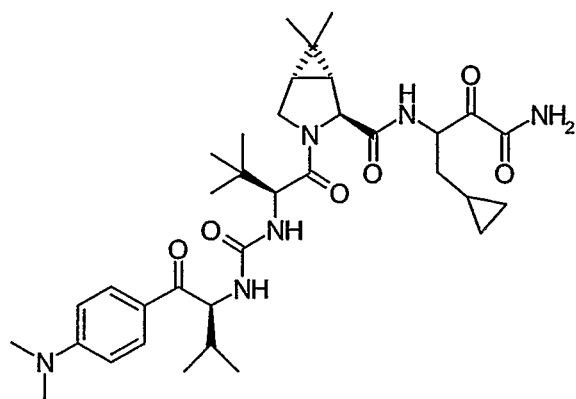
22. A method of preparing a pharmaceutical composition for treating the disorders associated with the HCV, said method comprising bringing into intimate physical contact at least one compound of claim 1 and at least one pharmaceutically acceptable carrier.

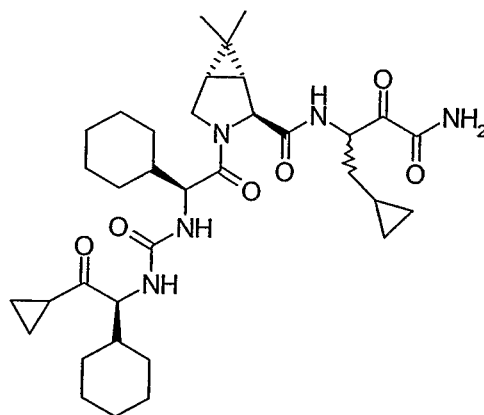
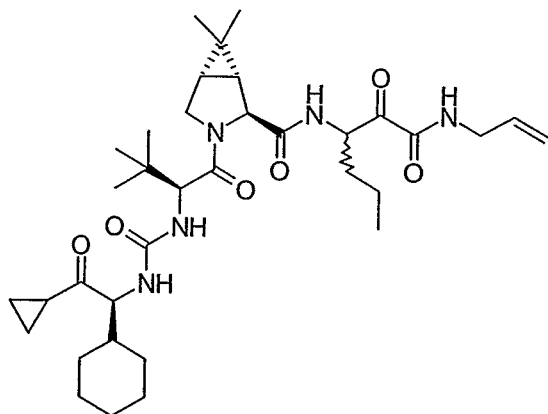
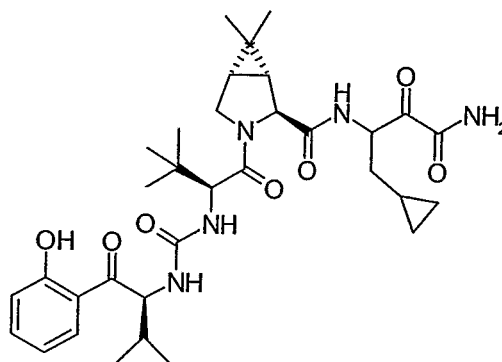
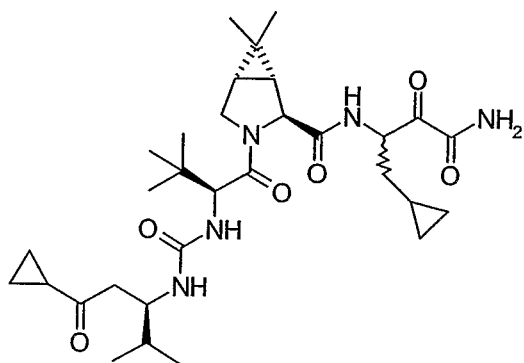
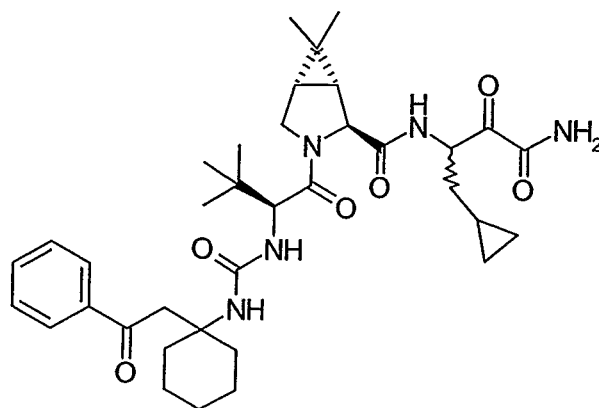
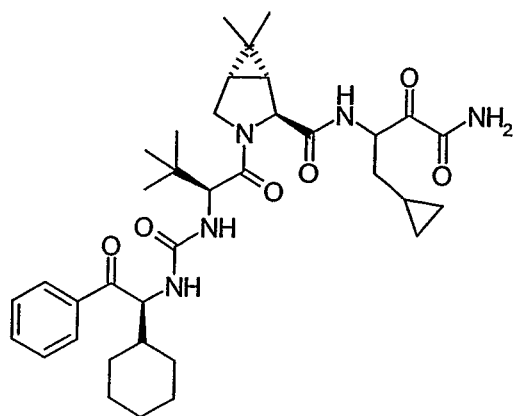
23. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, diastereomers and racemates of said compound, or a pharmaceutically acceptable salt, solvate or ester of said compound, said compound being selected from the compounds of structures listed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

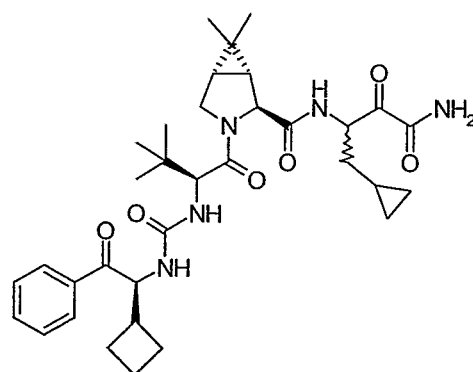
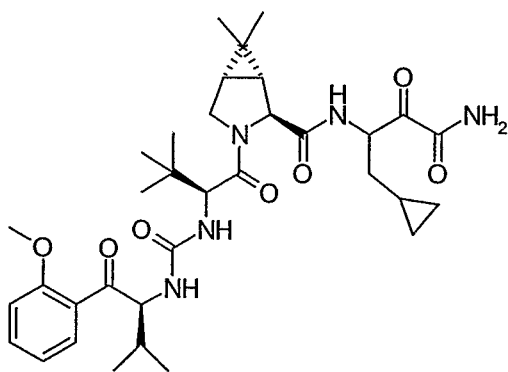
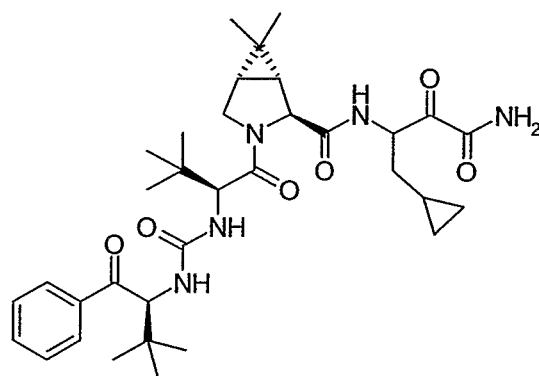
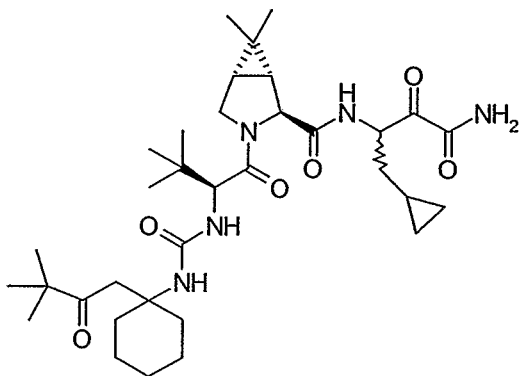
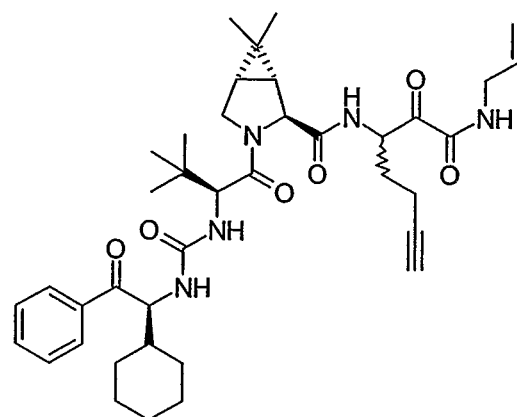
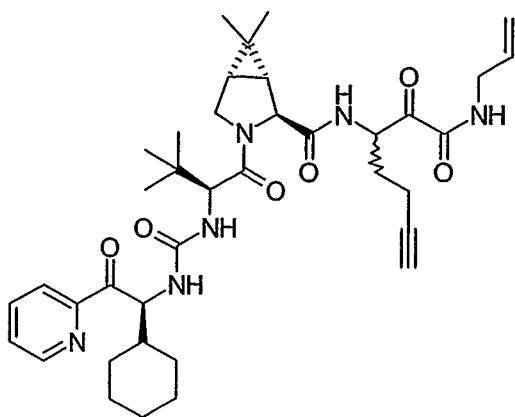


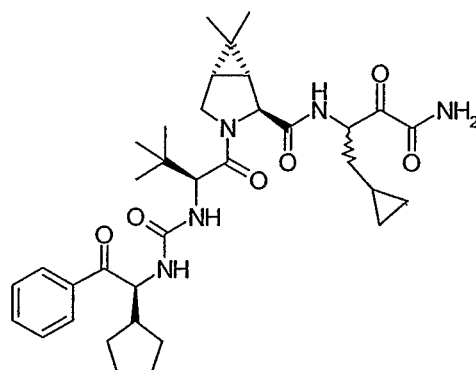
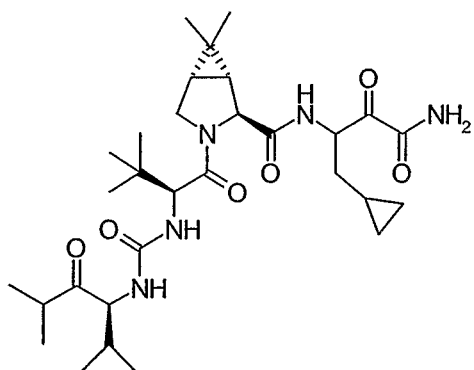
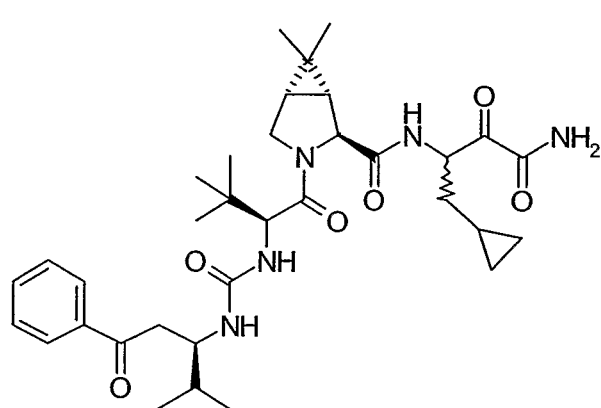
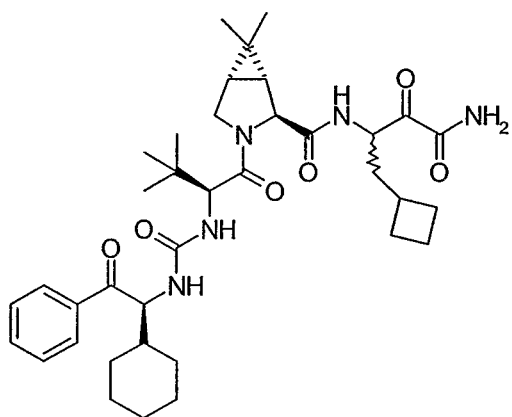
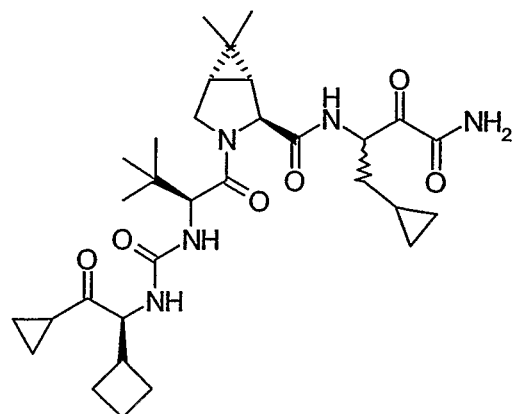
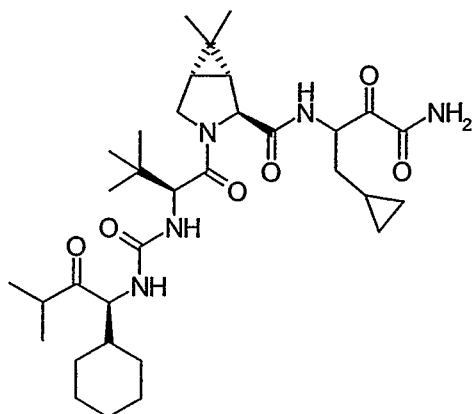


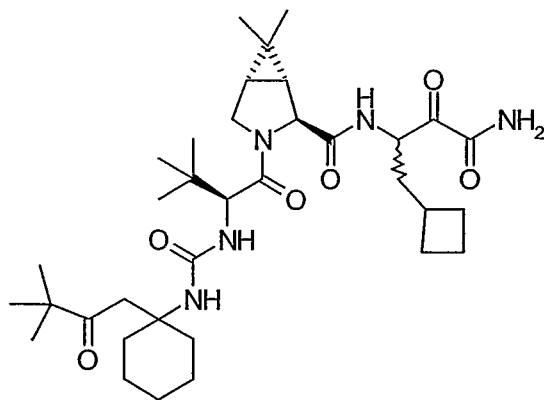
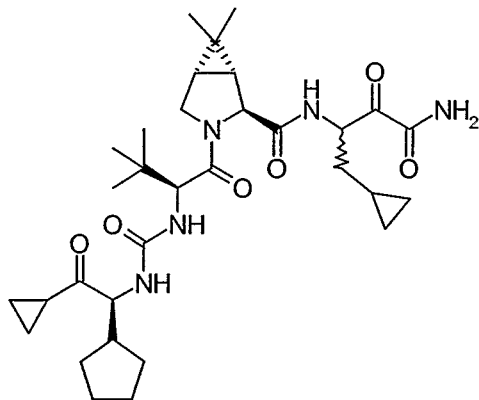
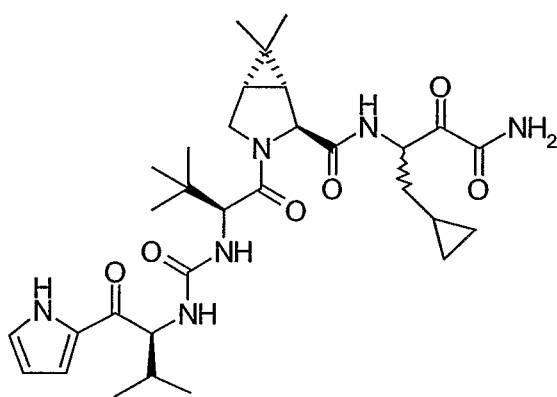
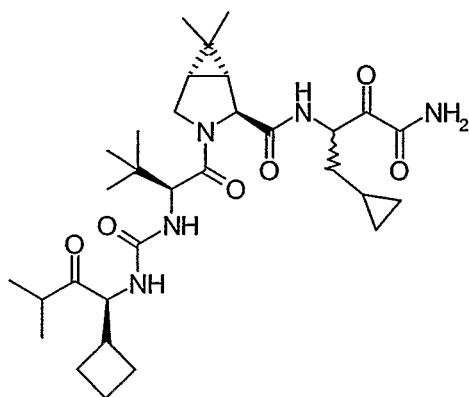
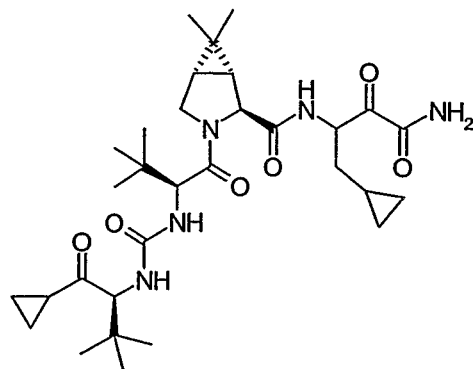
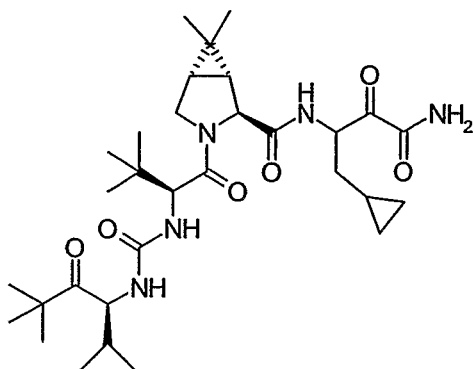


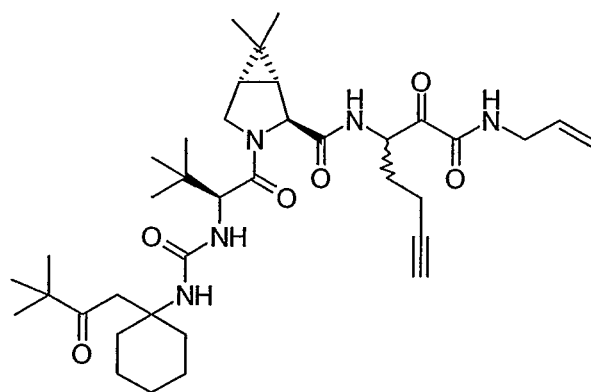
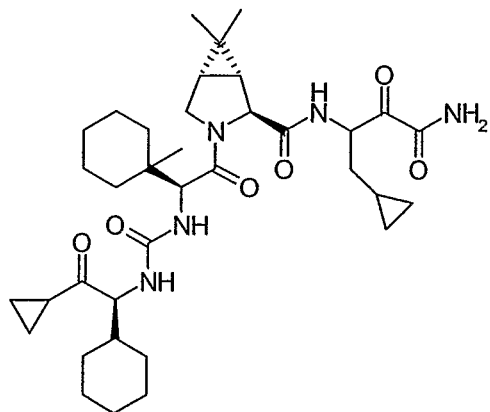
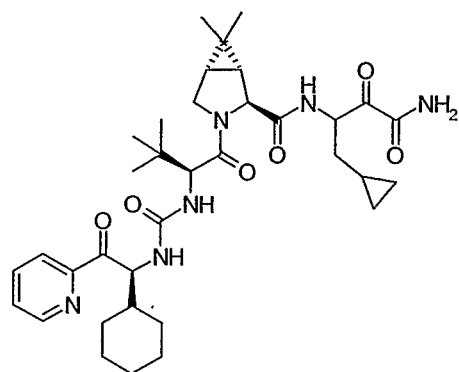
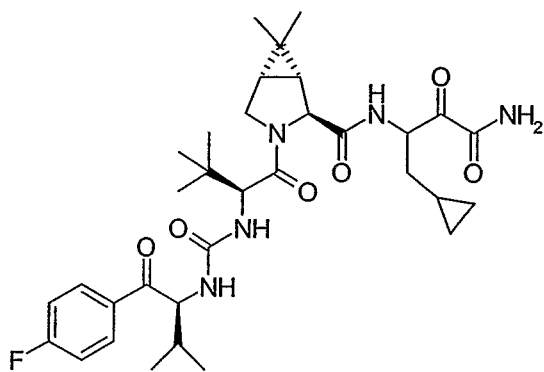
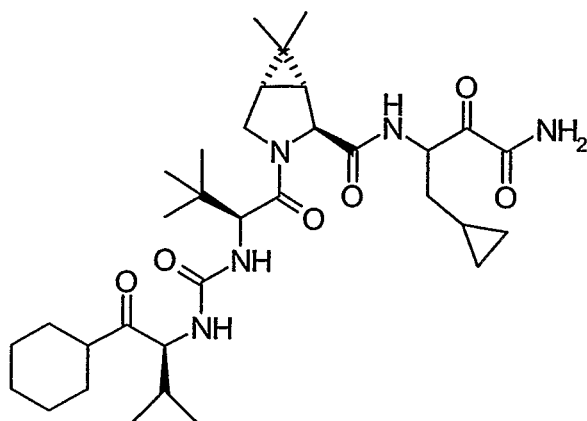
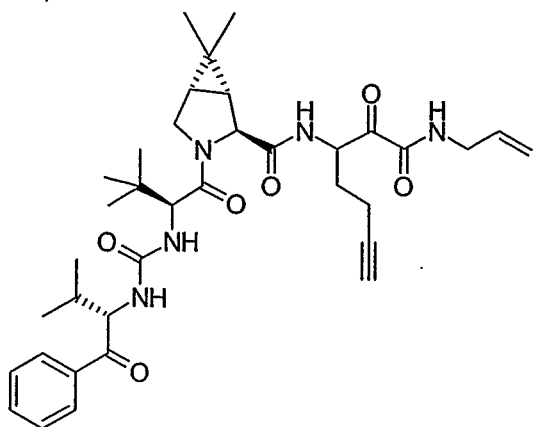


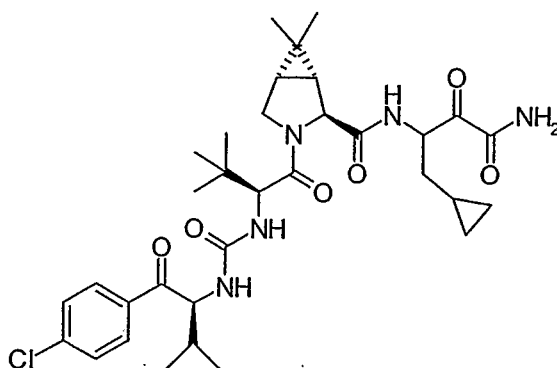
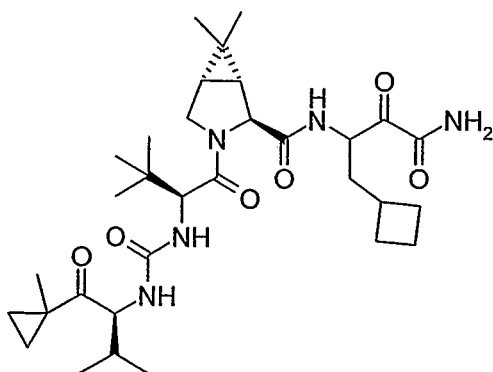
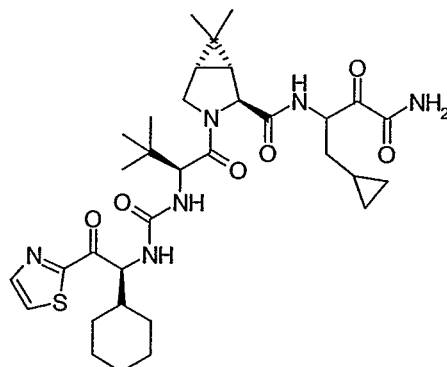
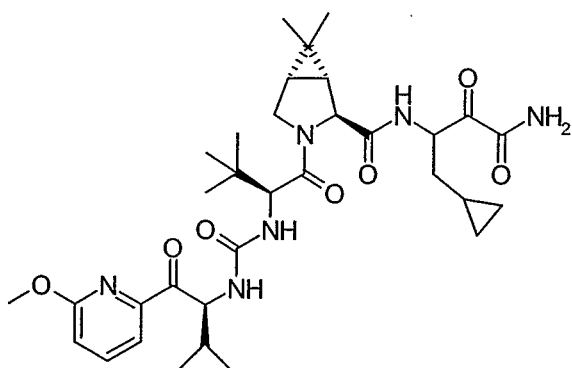
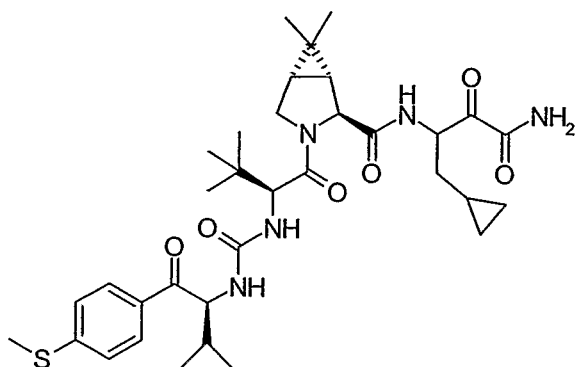
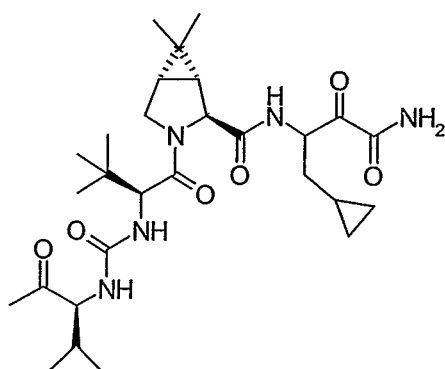
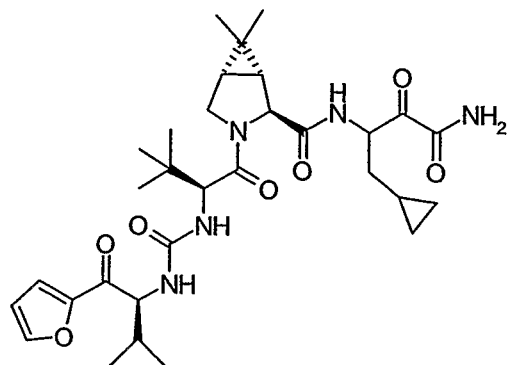
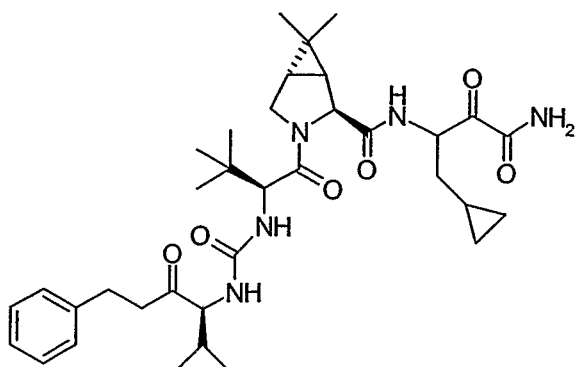


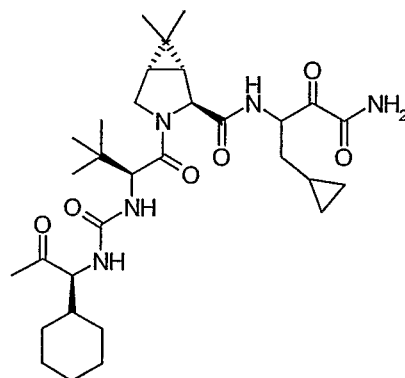
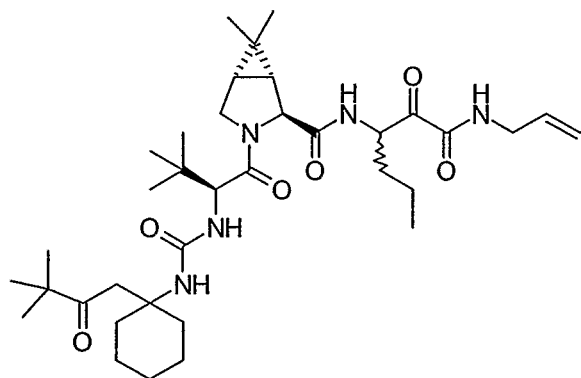
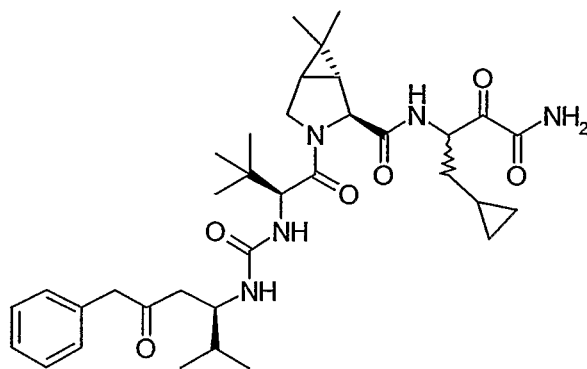
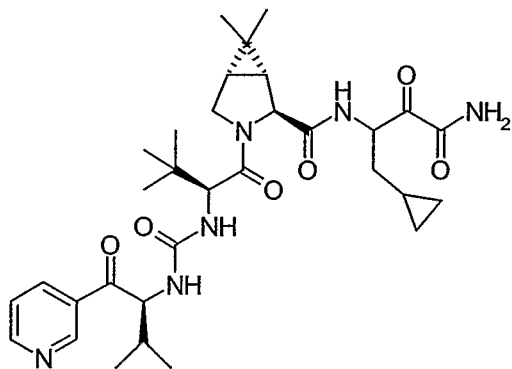
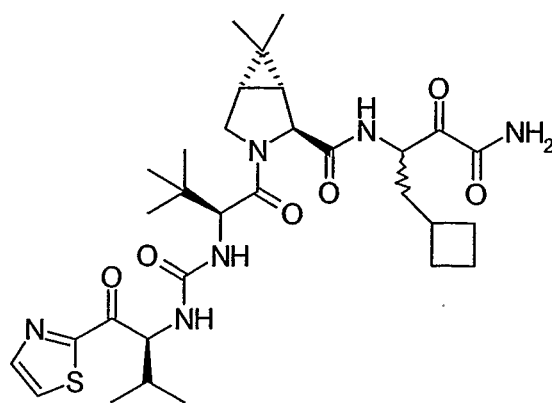
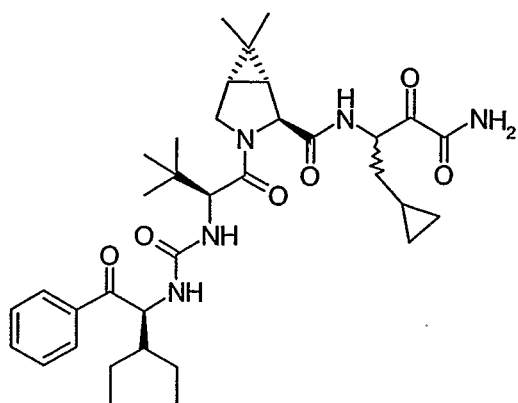


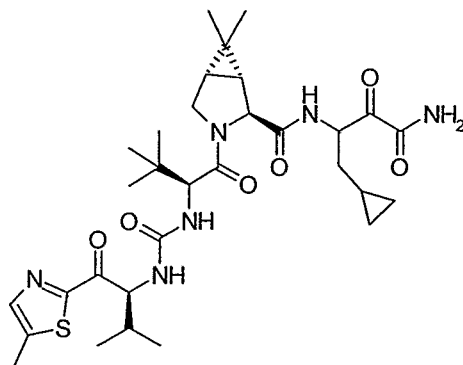
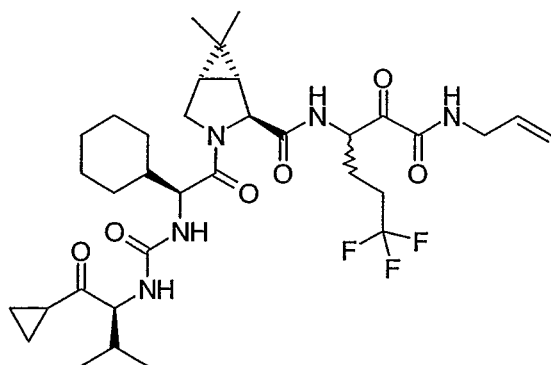
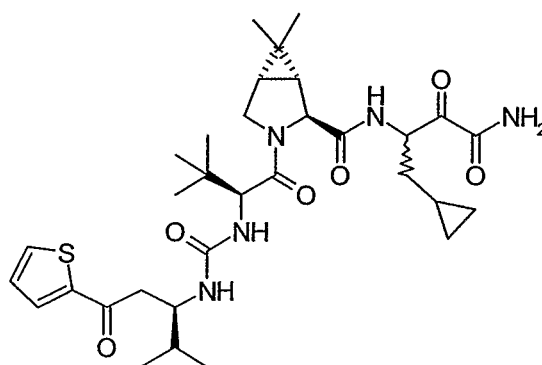
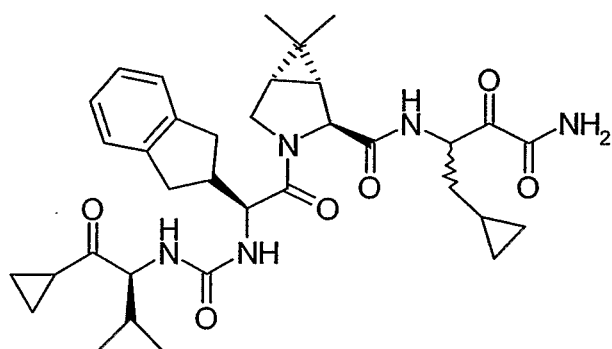
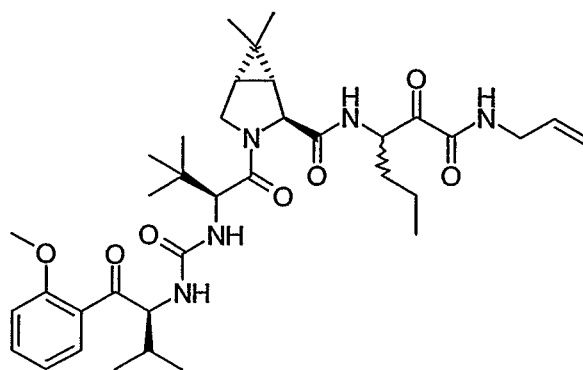
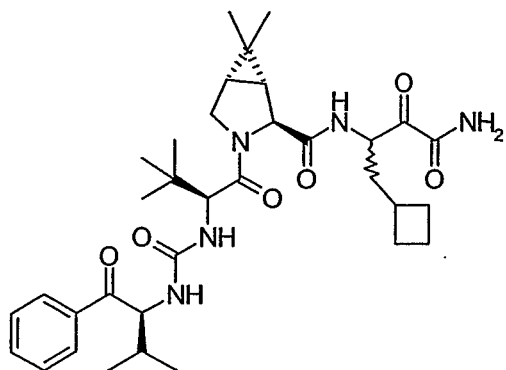


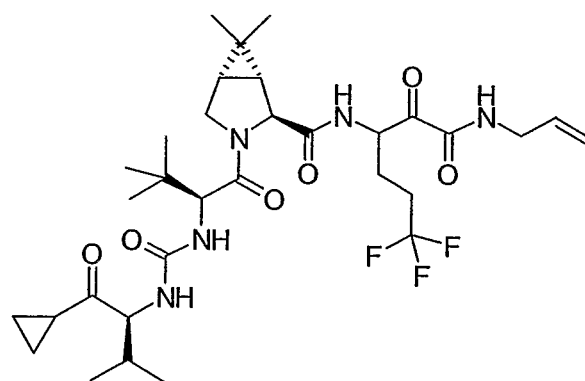
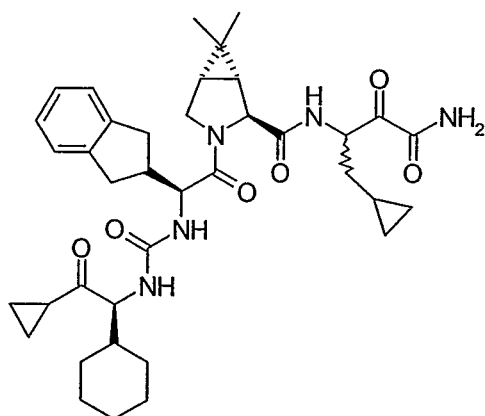
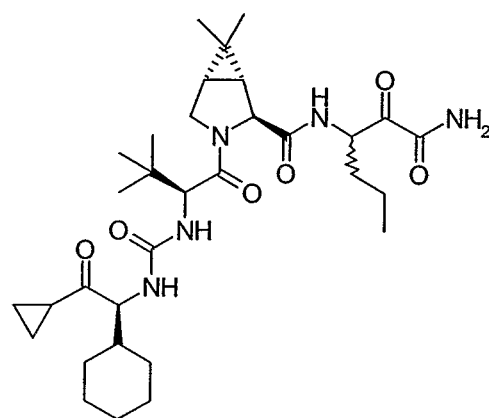
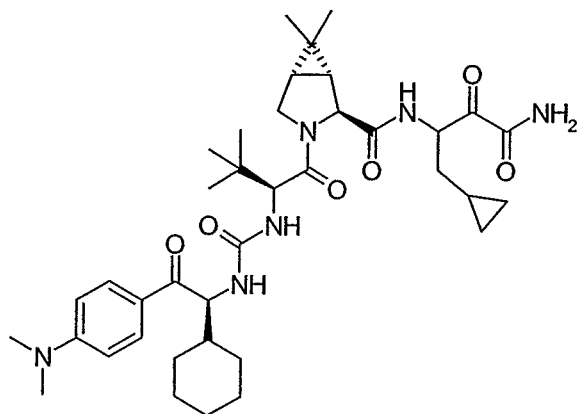
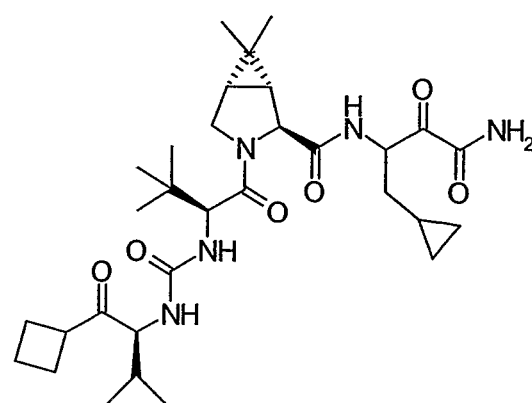
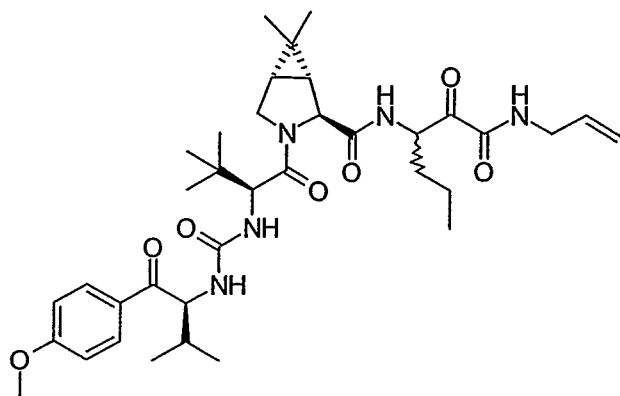


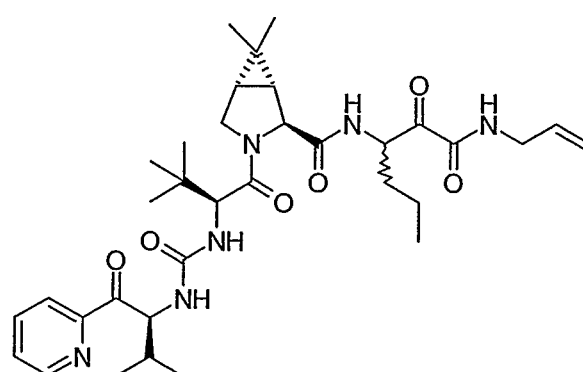
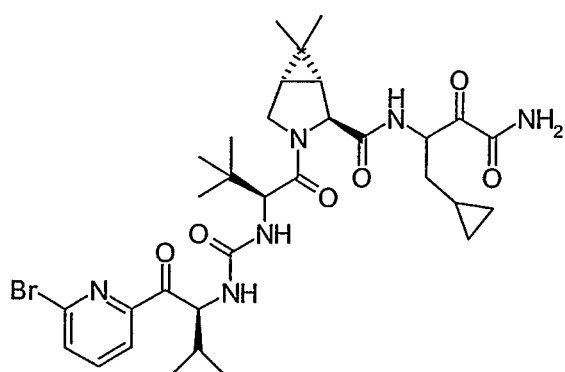
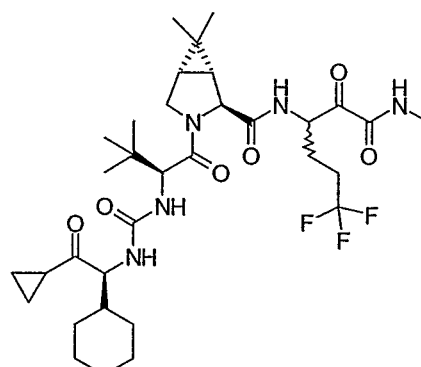
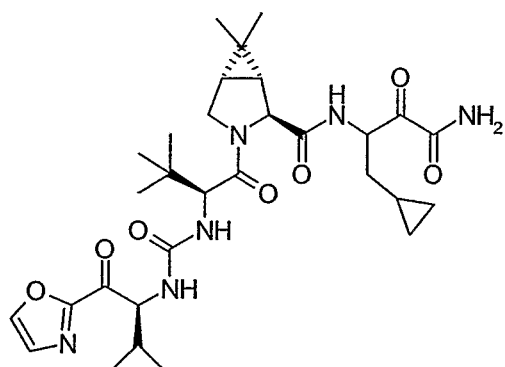
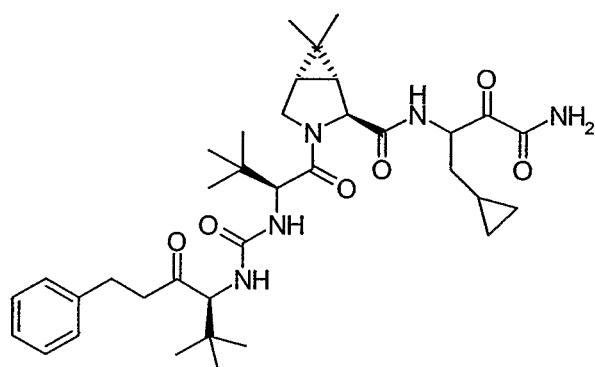
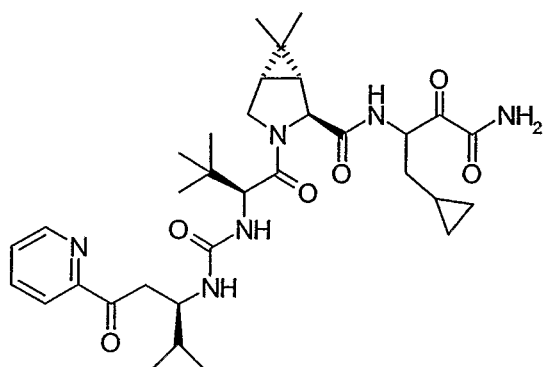
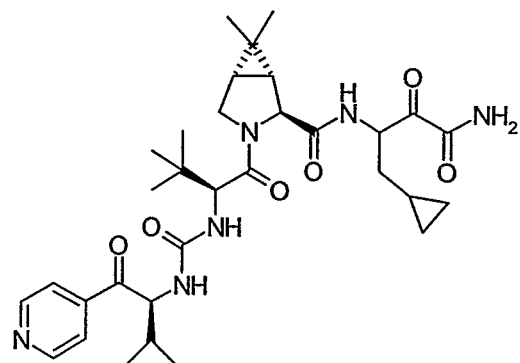
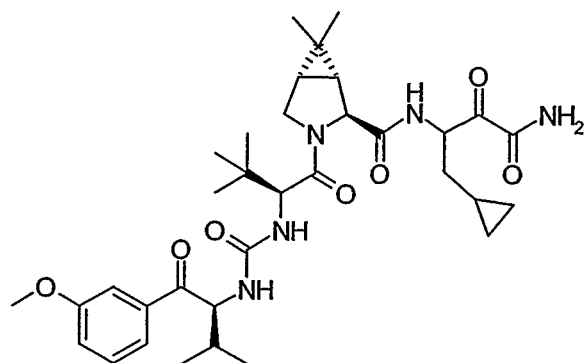


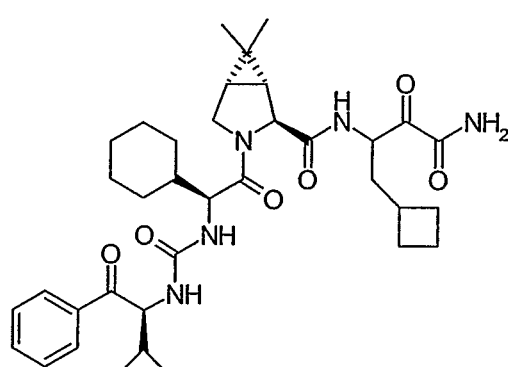
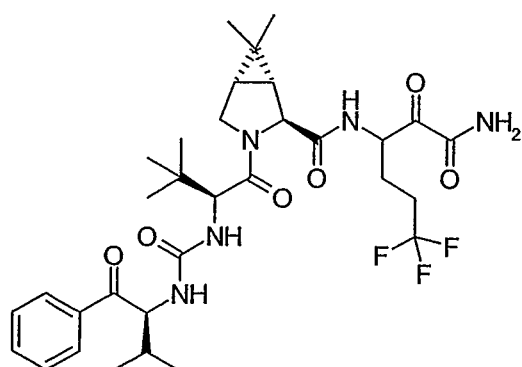
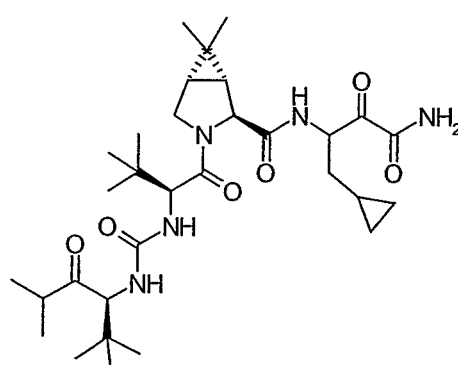
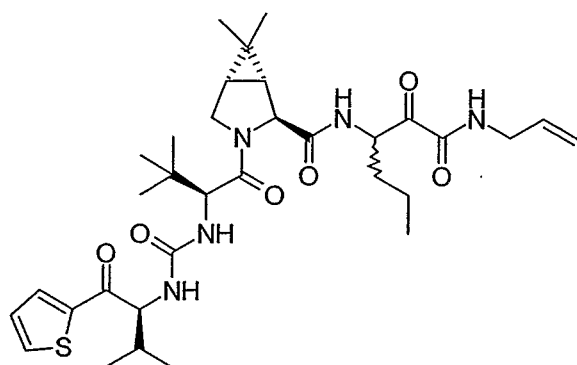
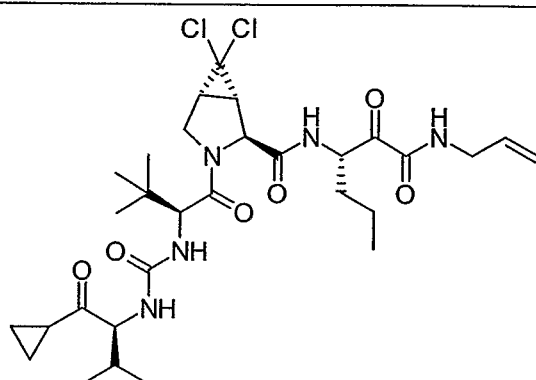
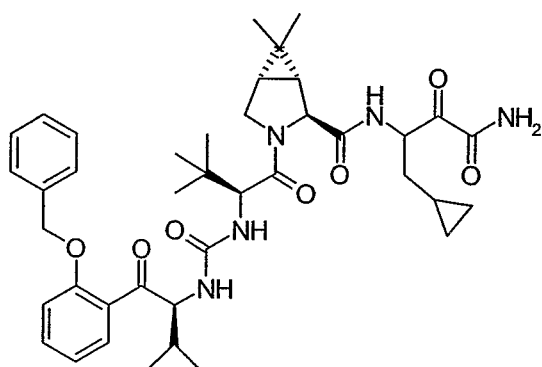
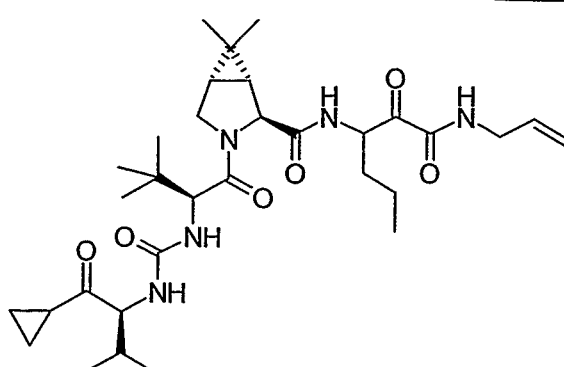
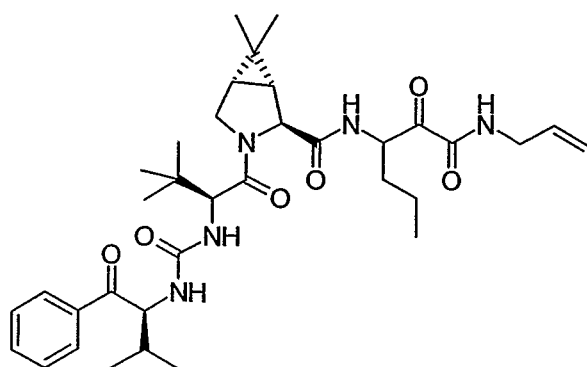


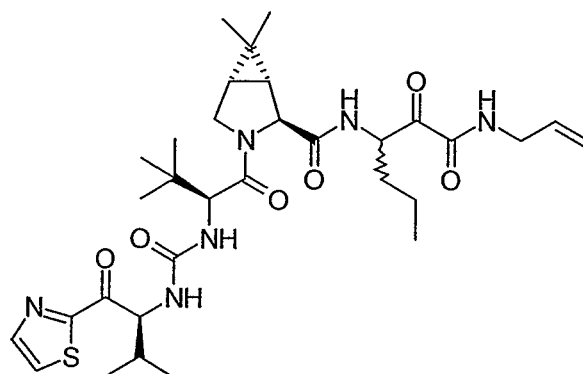
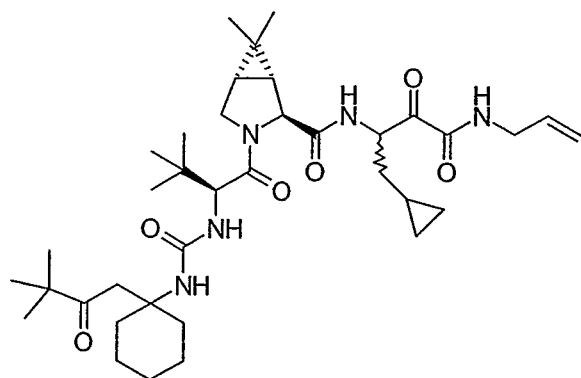
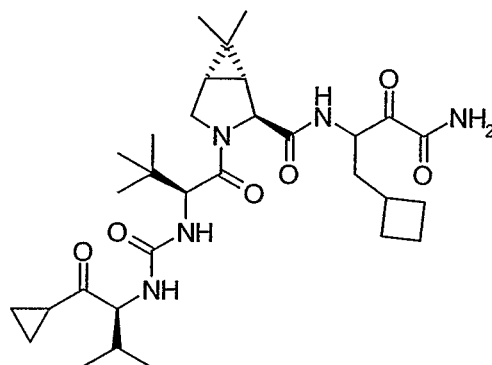
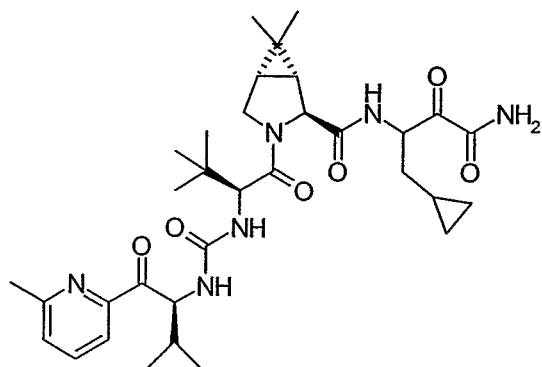
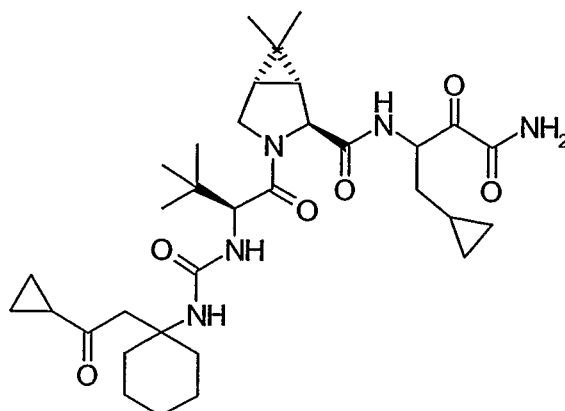
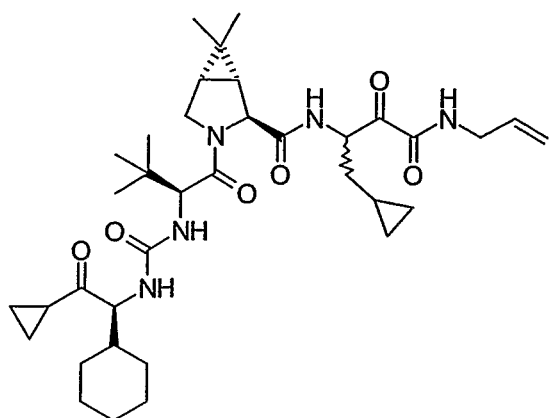


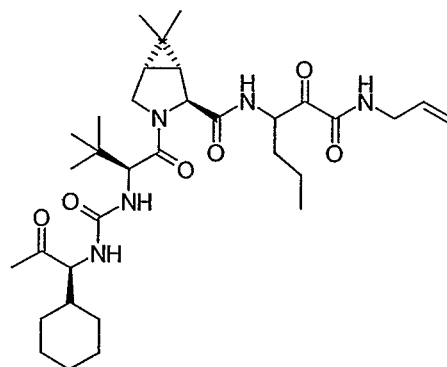
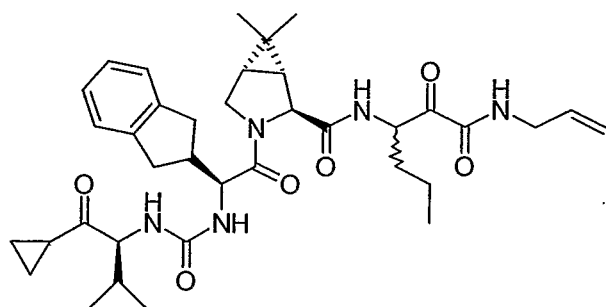
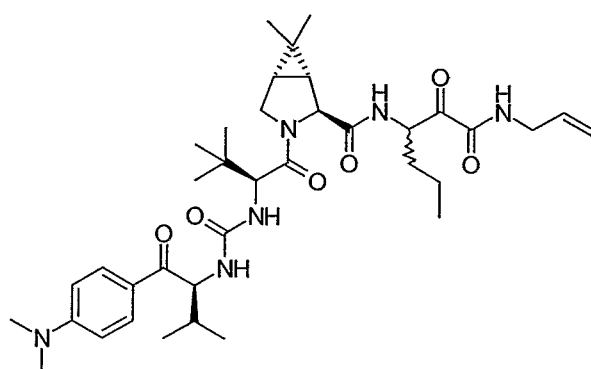
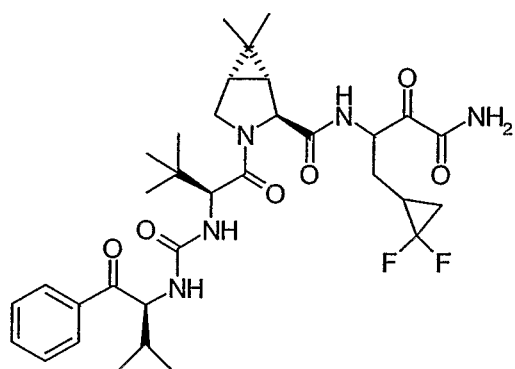
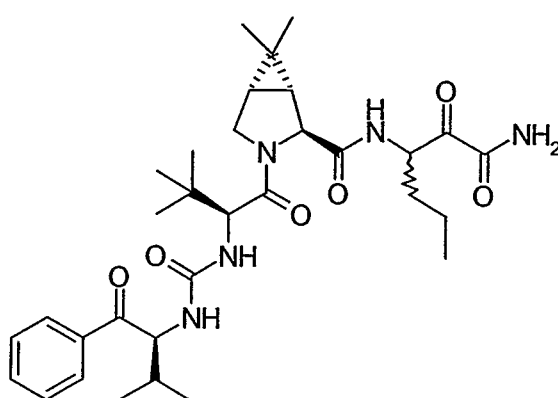
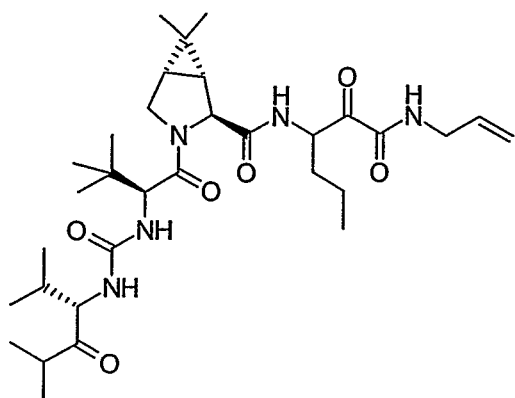




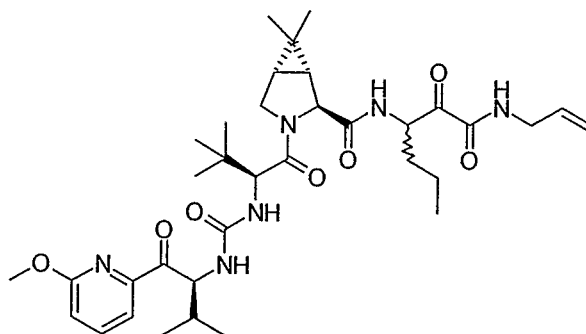
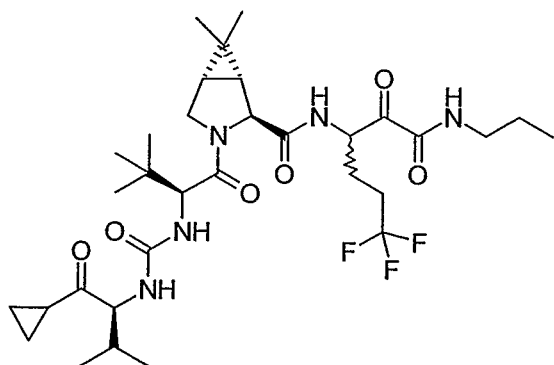
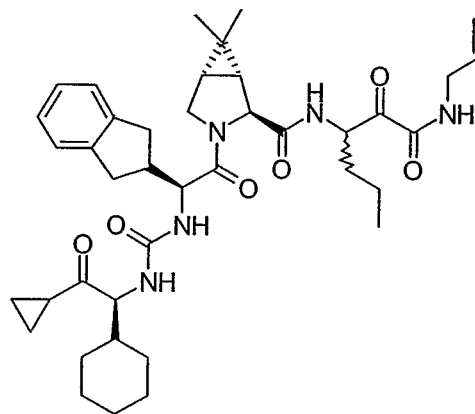
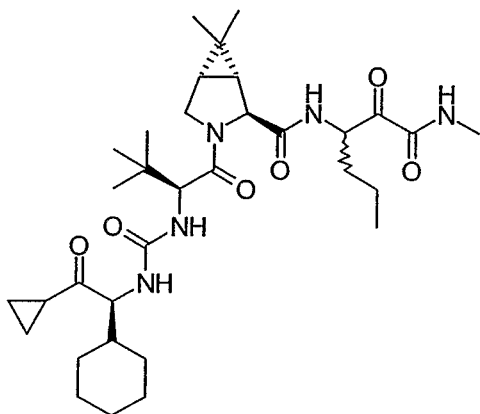
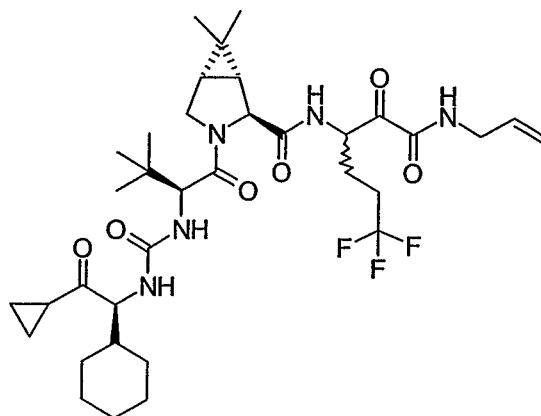
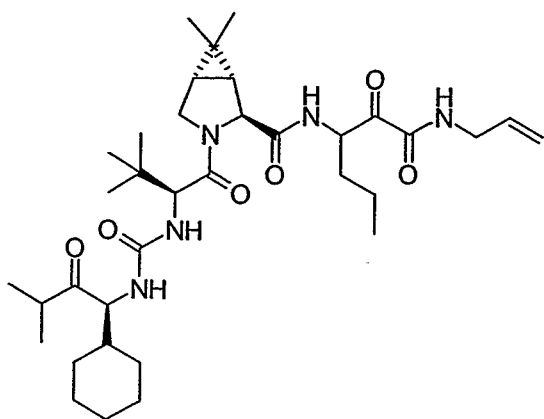


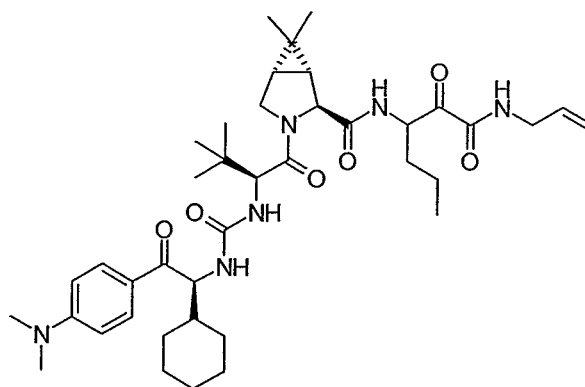
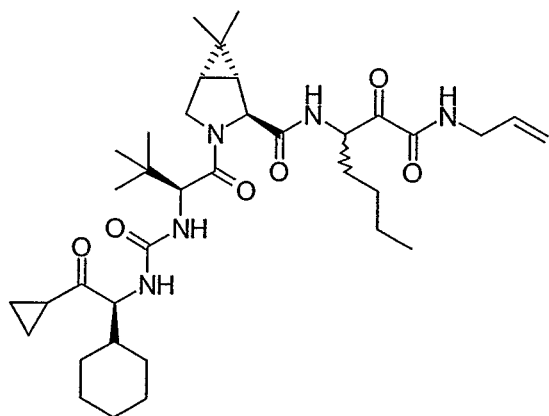
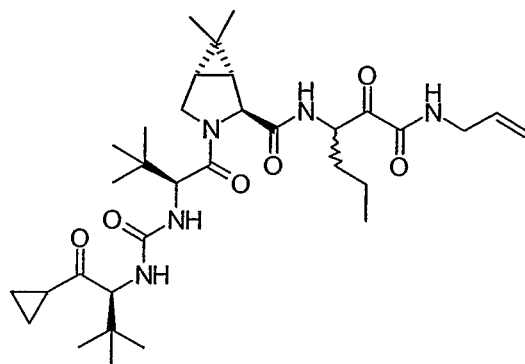
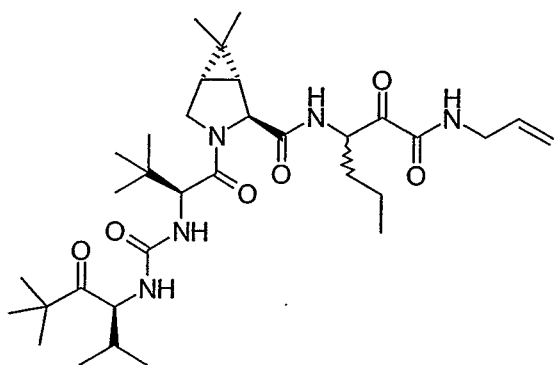
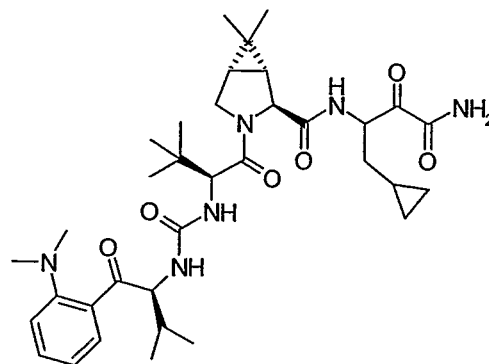
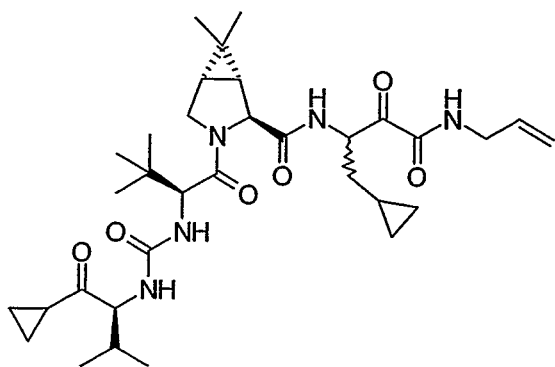


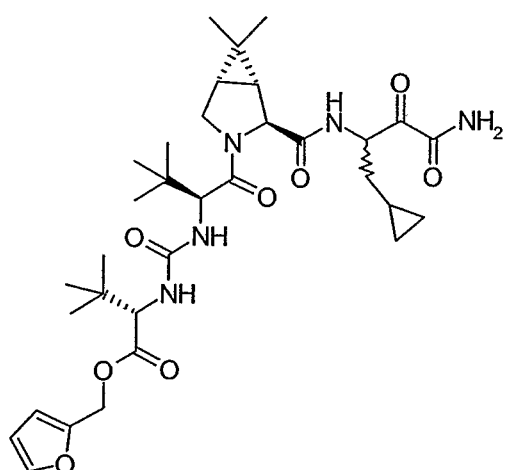
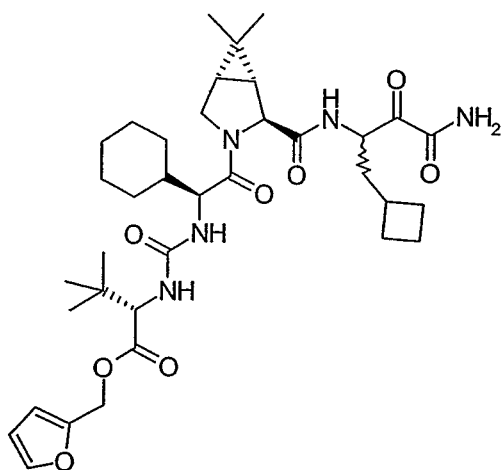
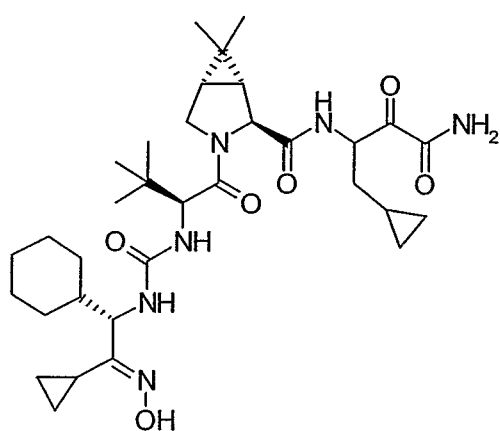
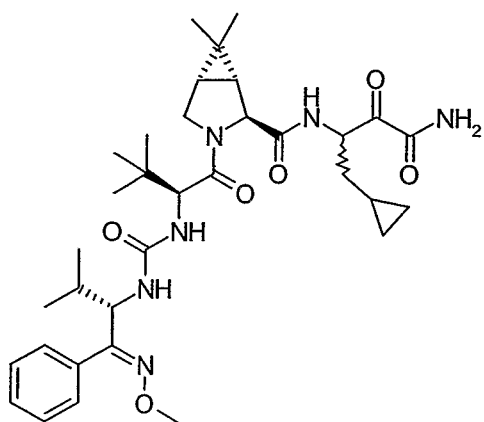
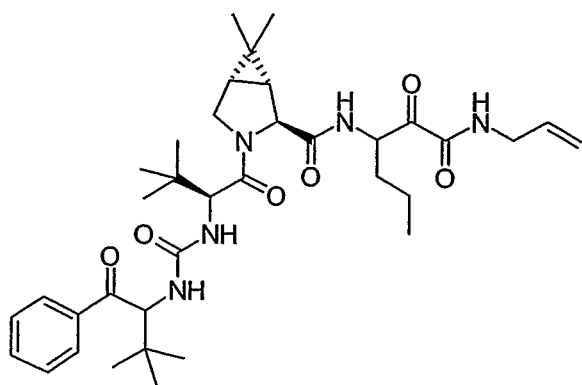


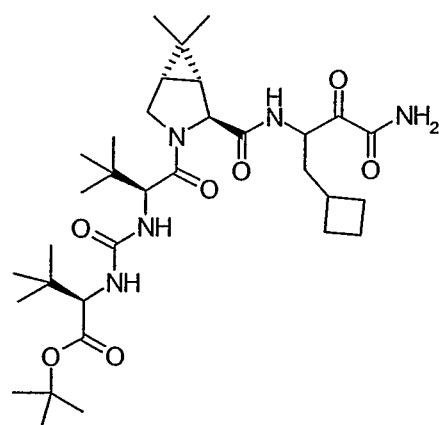
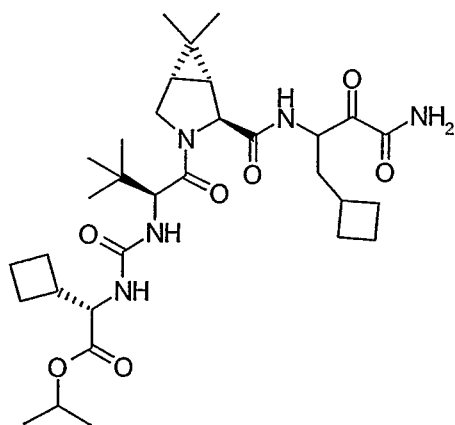
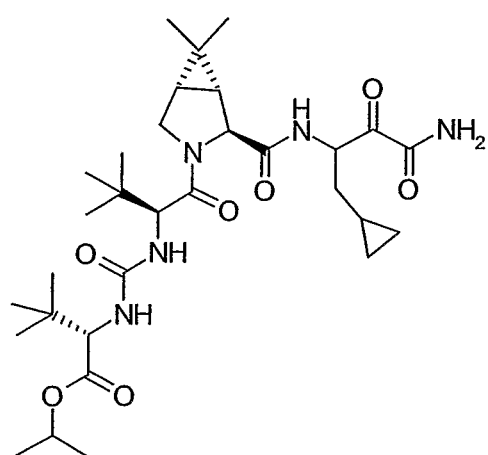
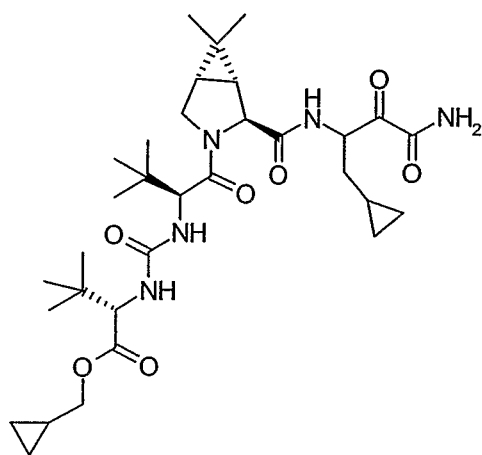
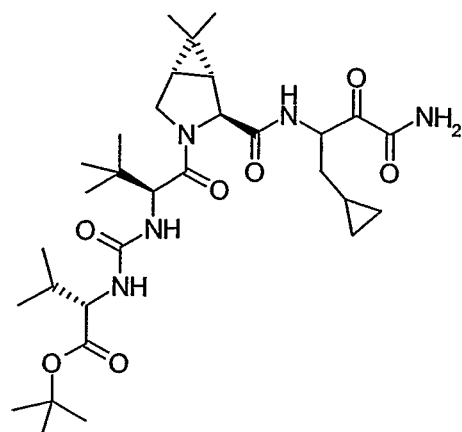
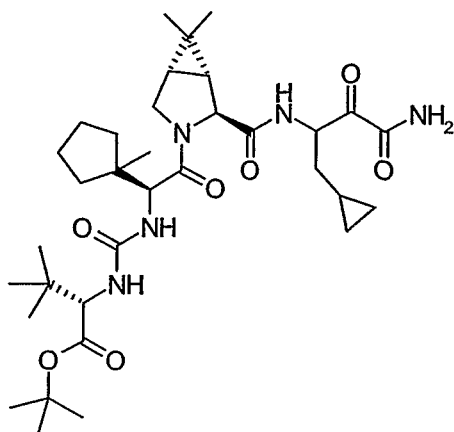


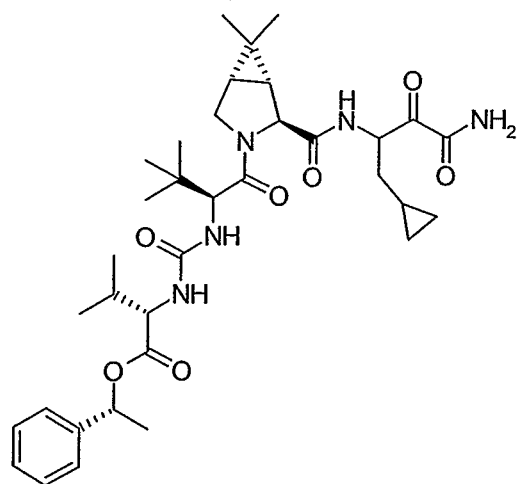
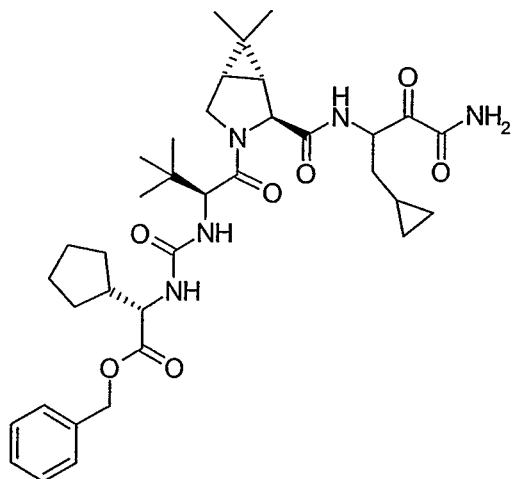
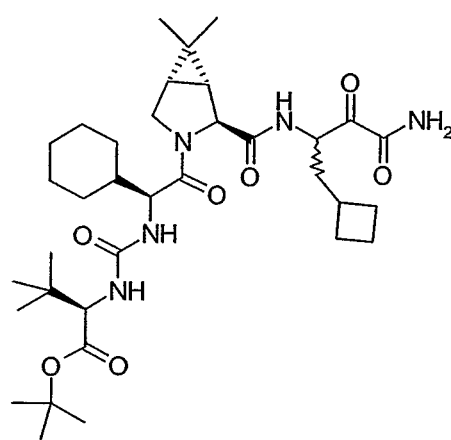
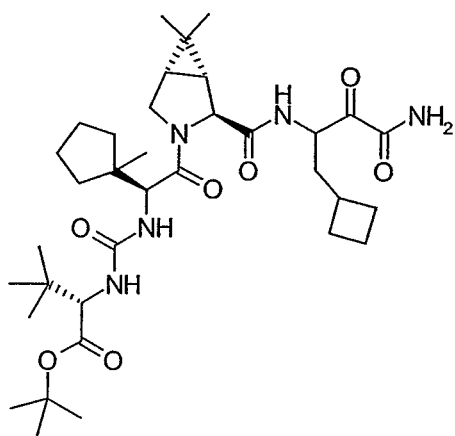
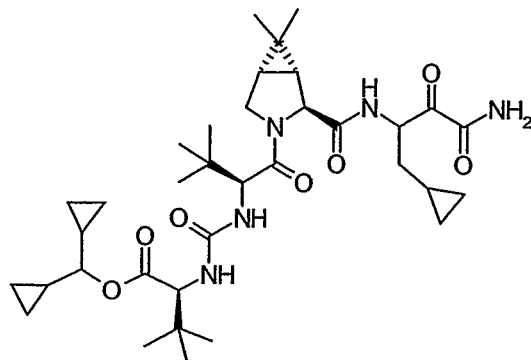
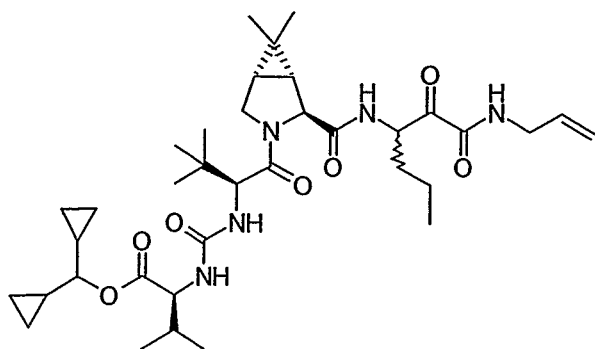
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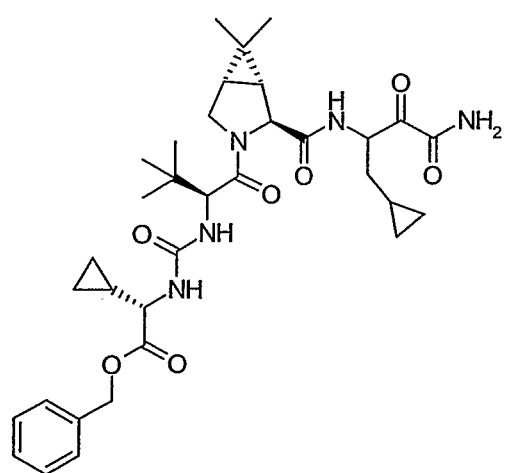
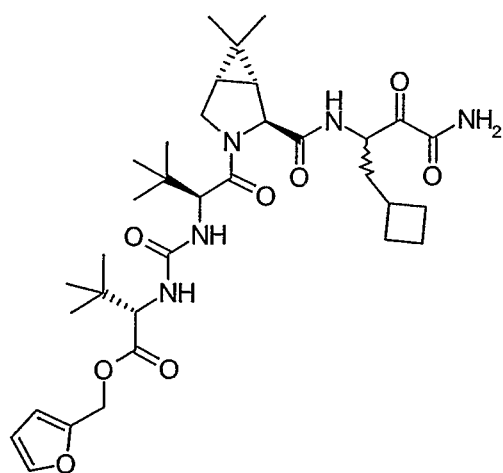
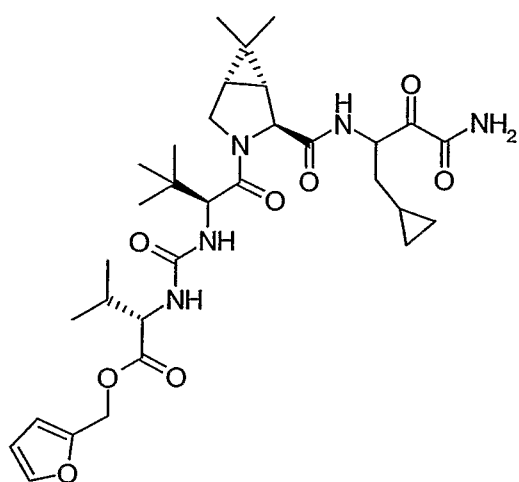
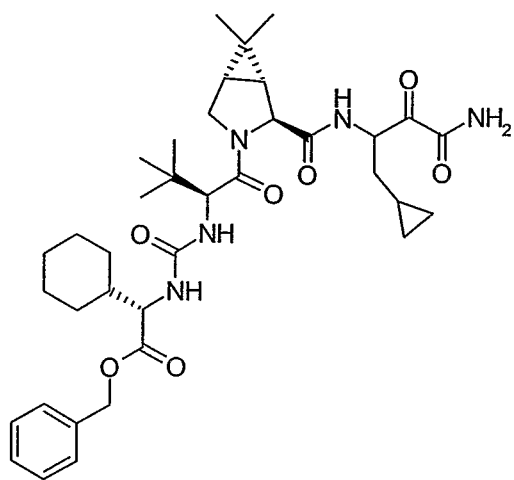
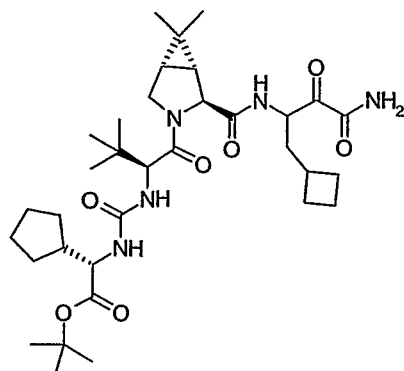
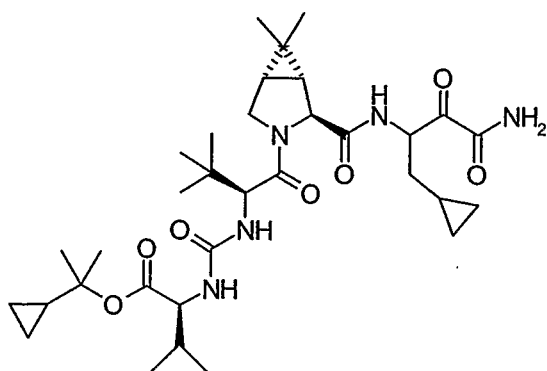


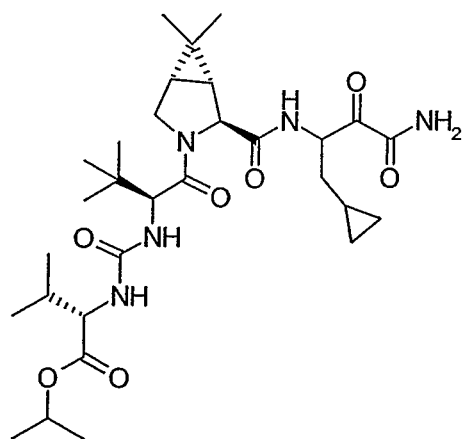
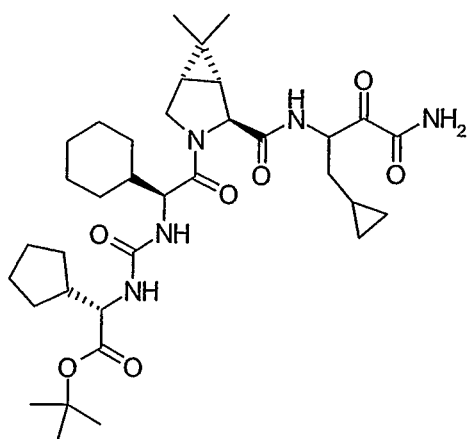
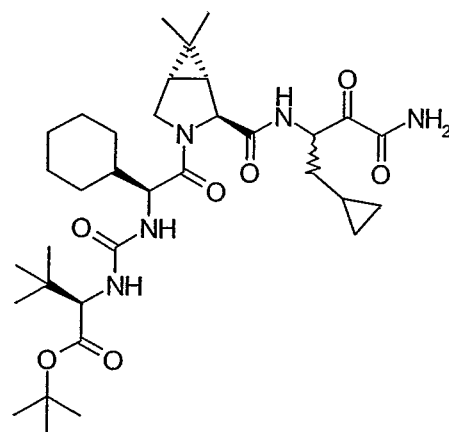
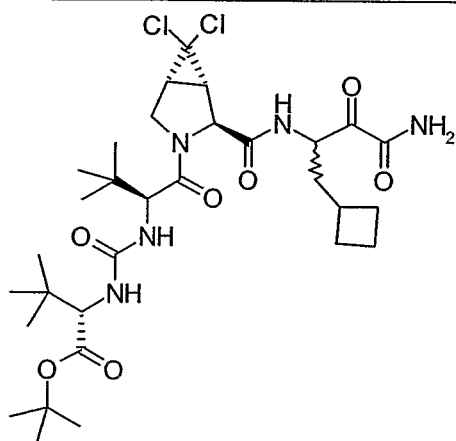
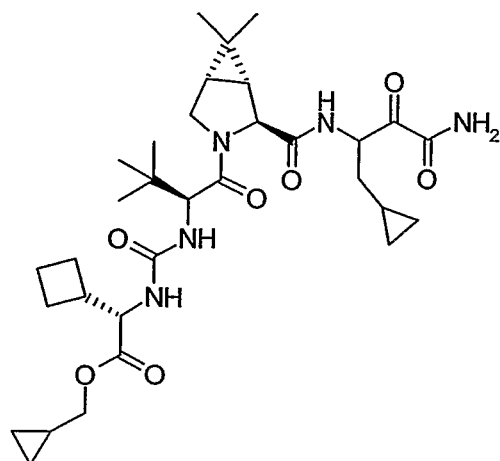
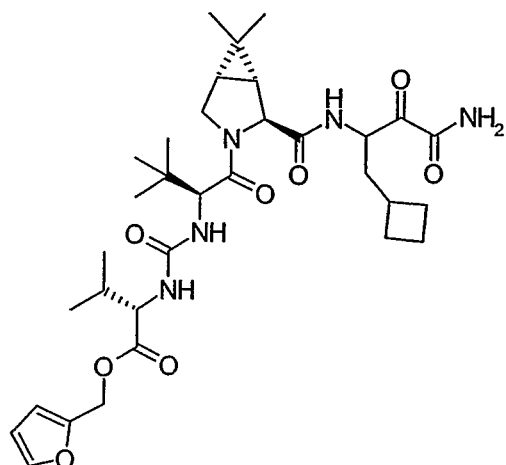


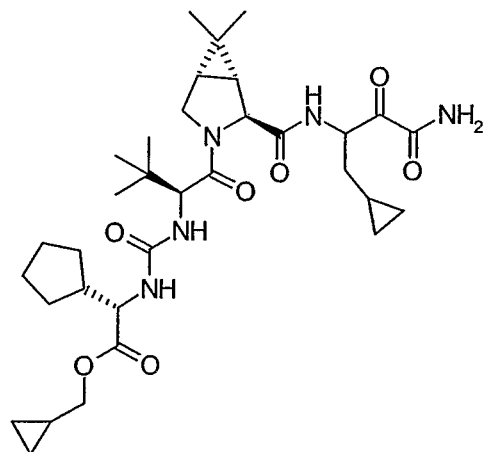
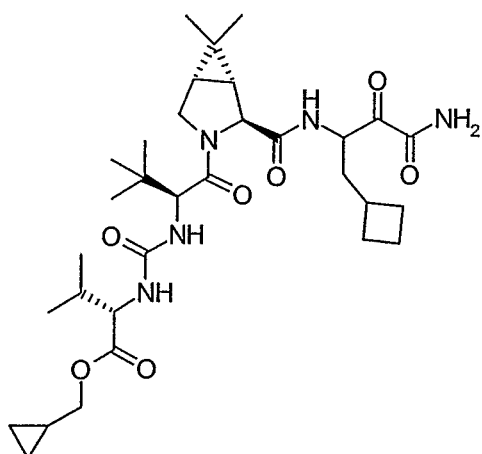
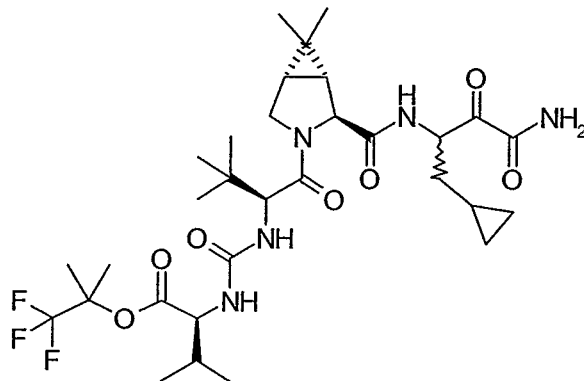
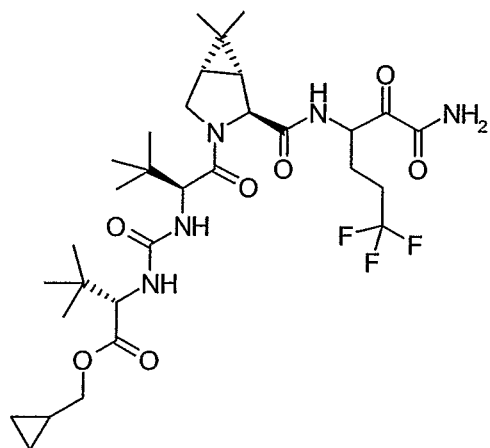
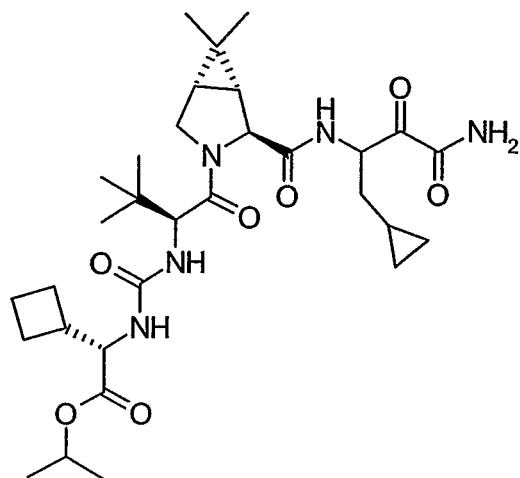
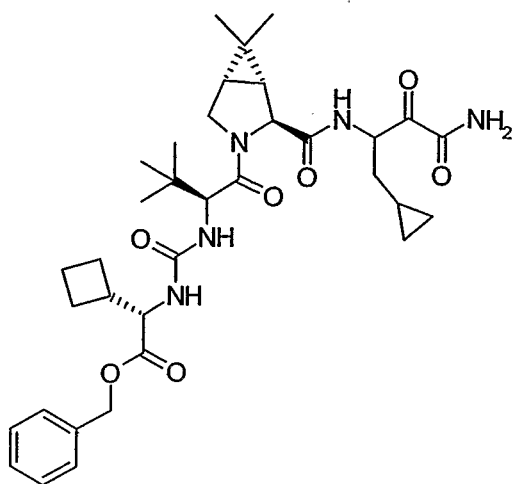


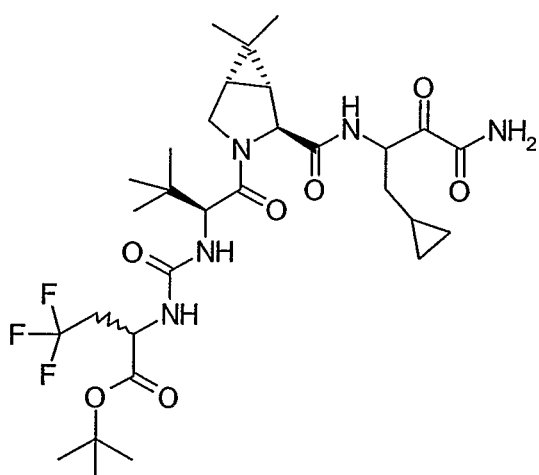
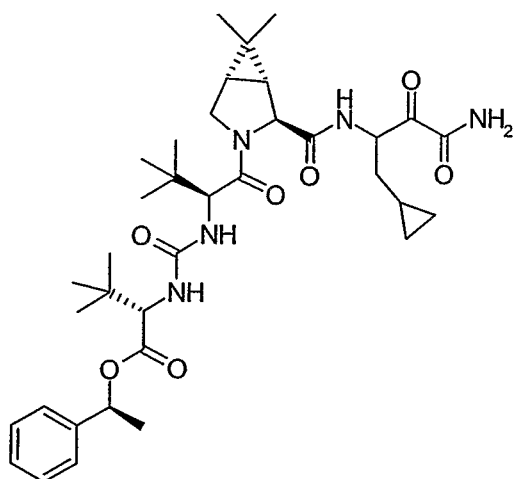
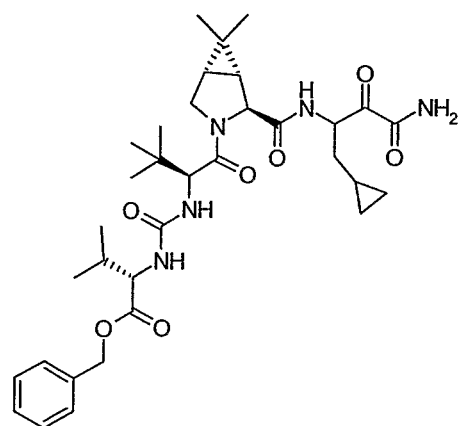
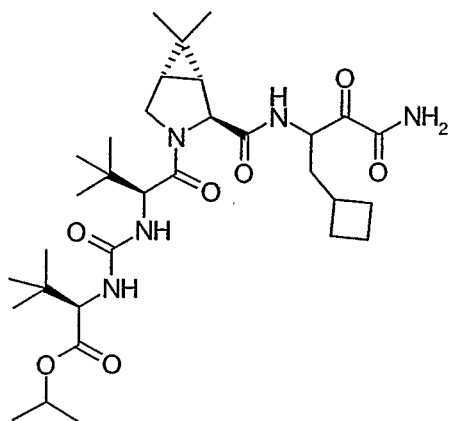
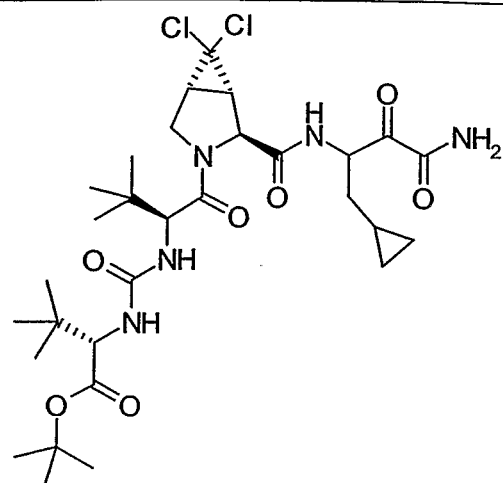
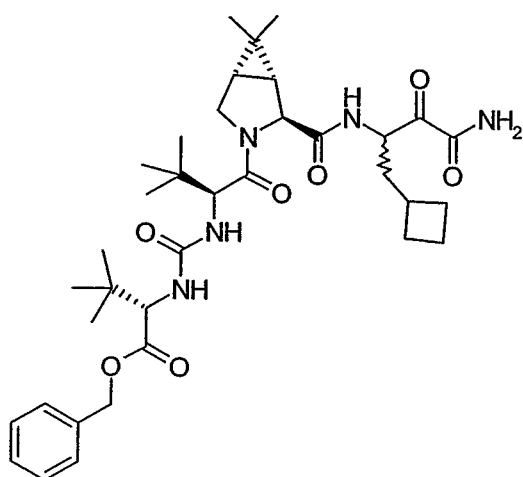


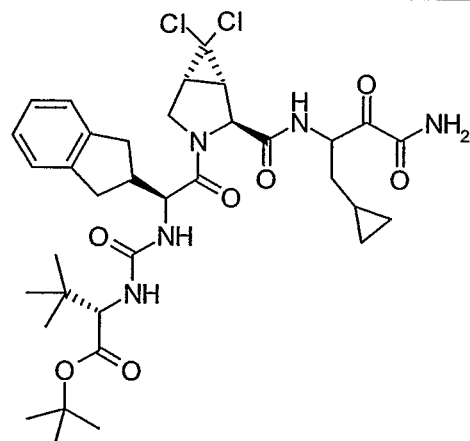
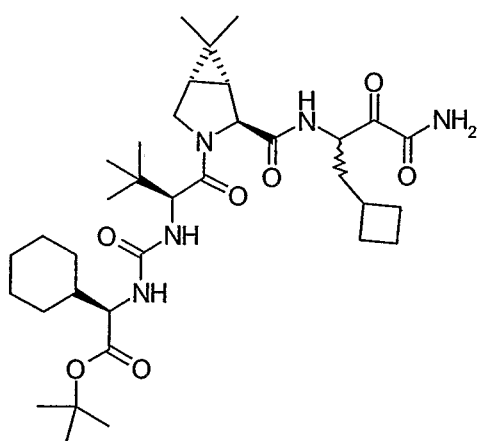
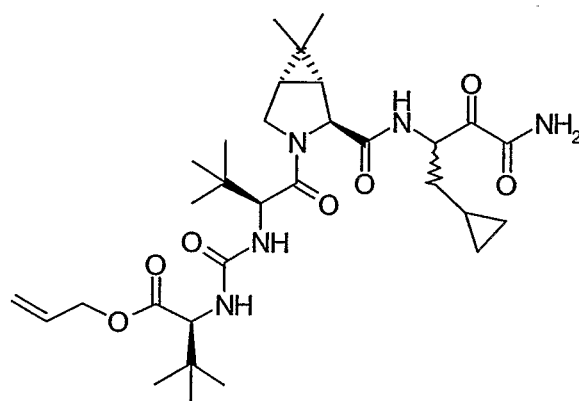
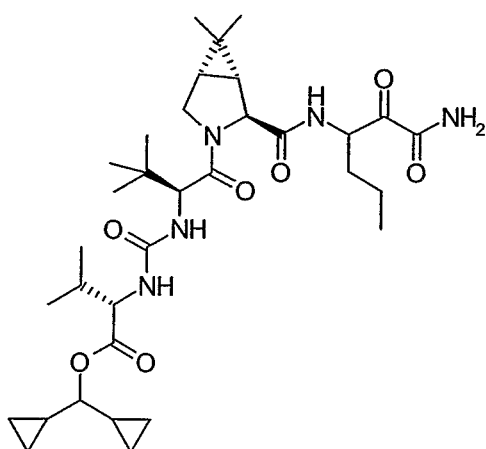
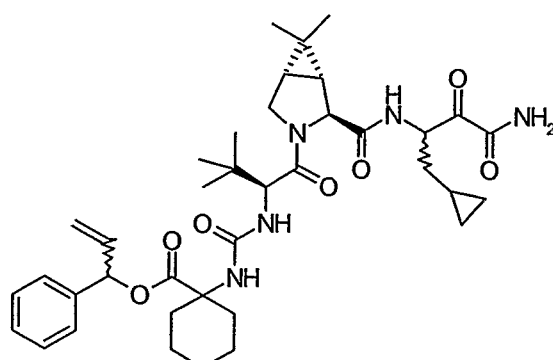
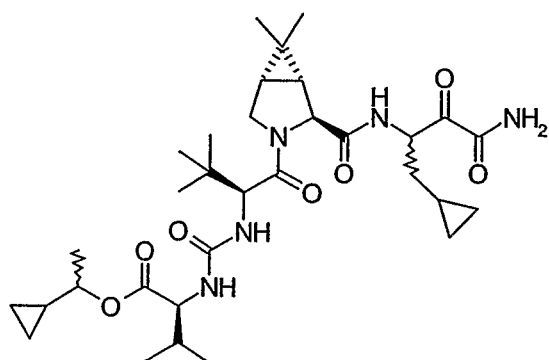




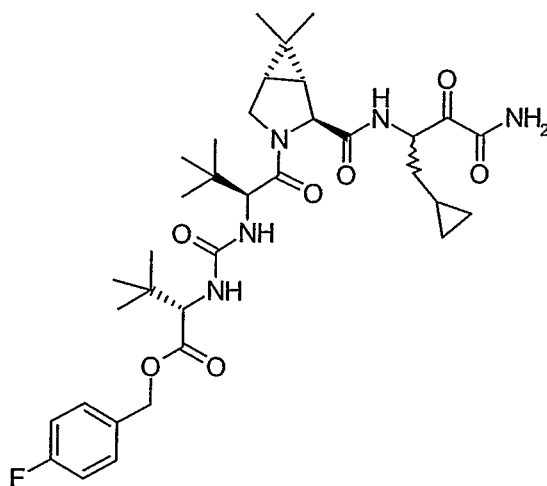
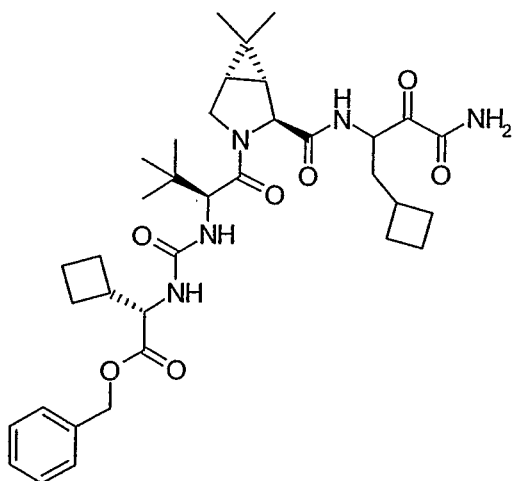
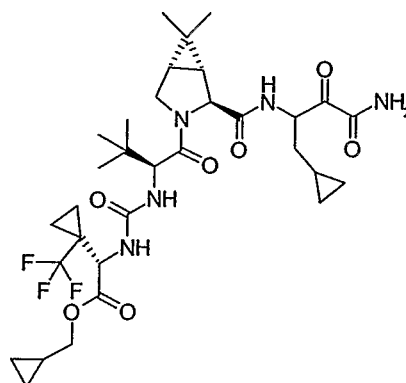
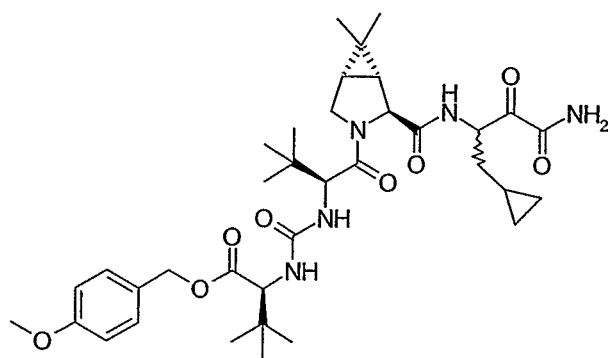
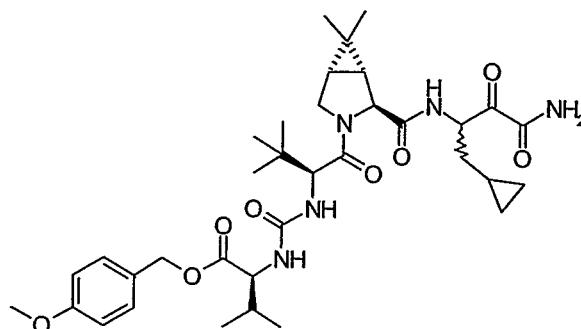
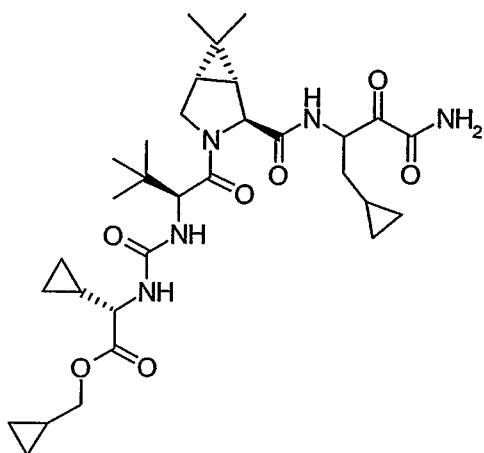


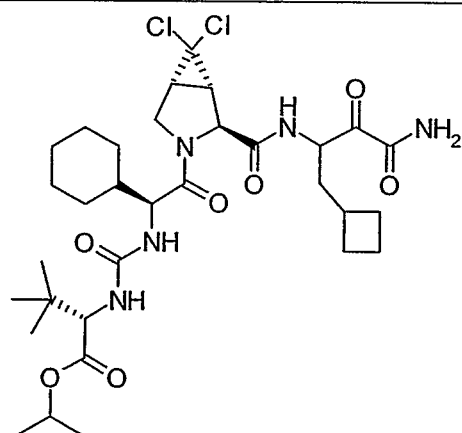
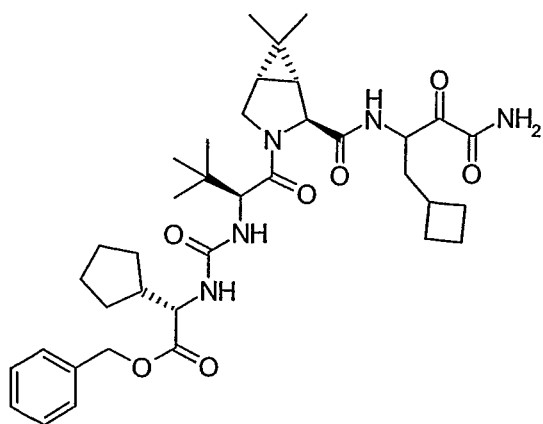
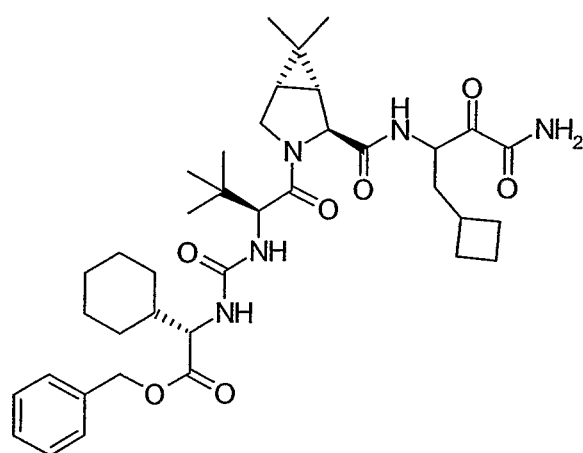
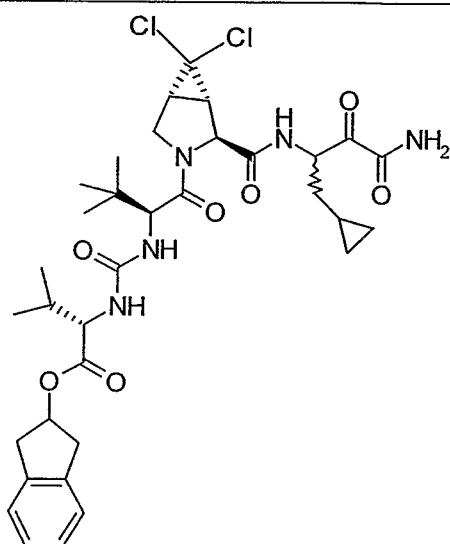
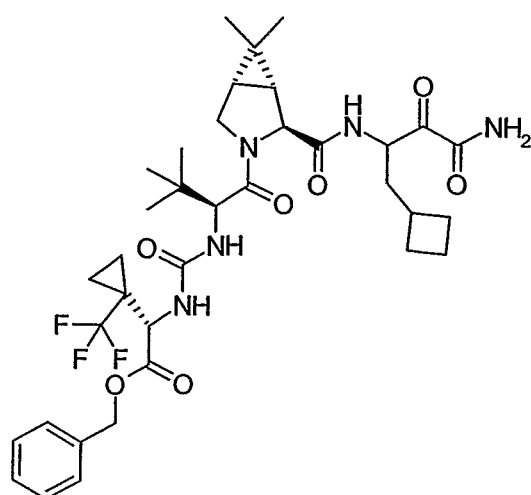
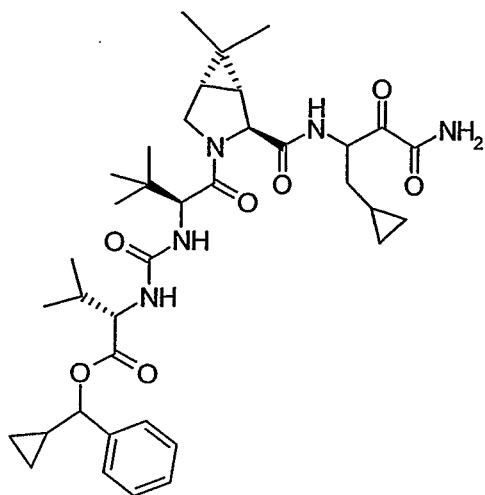


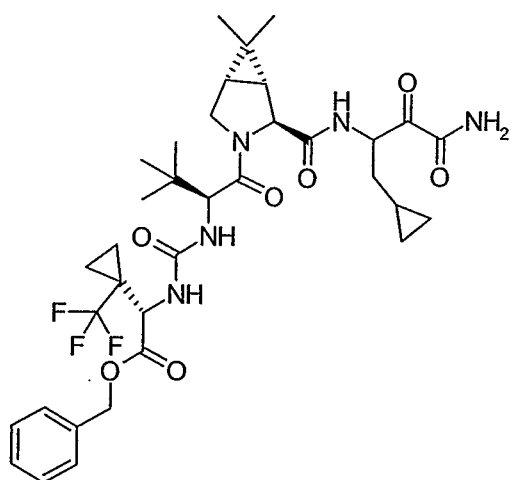
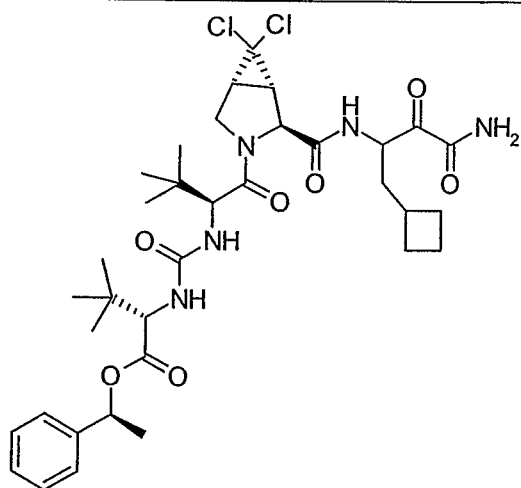
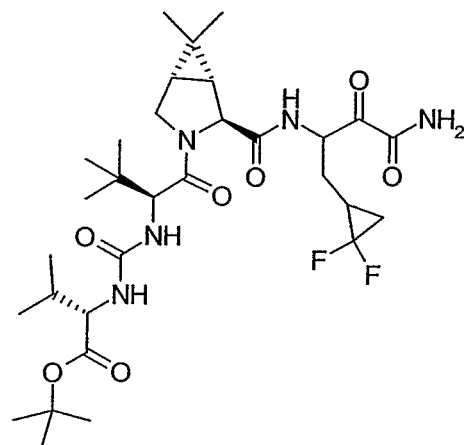
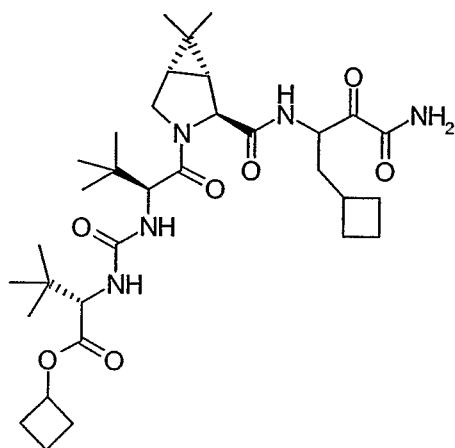
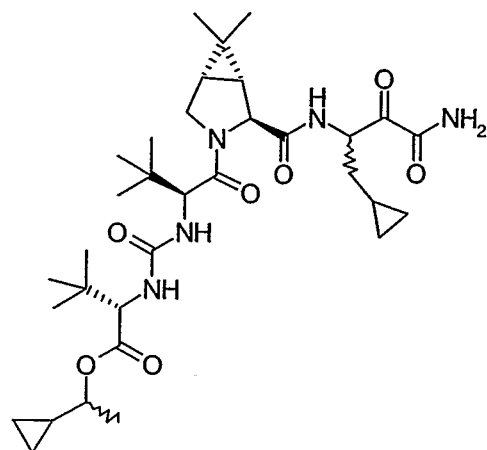
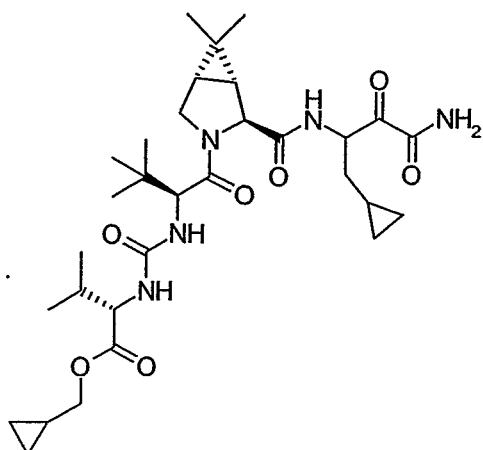


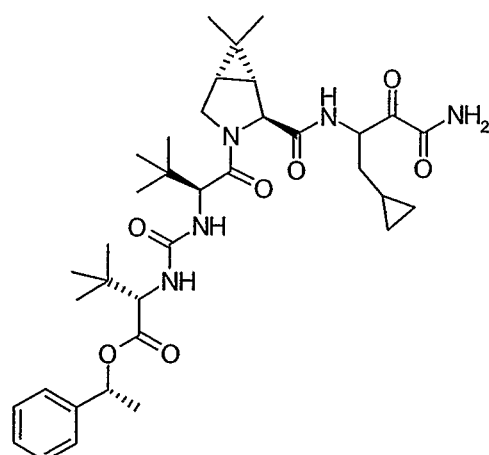
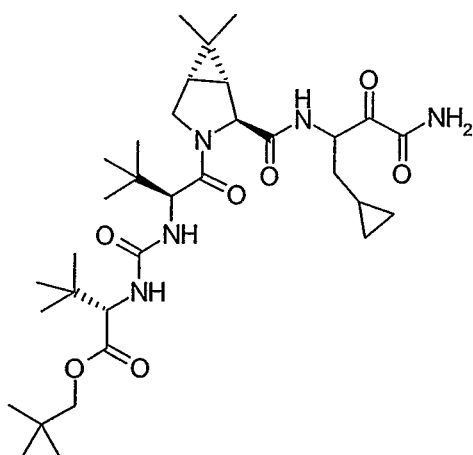
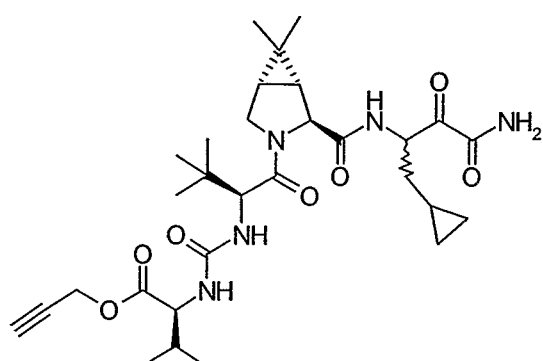
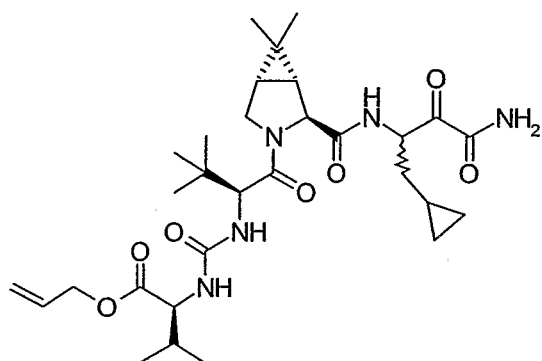
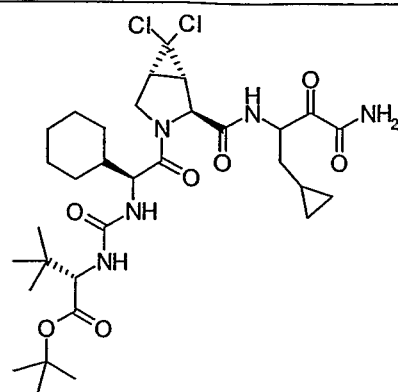
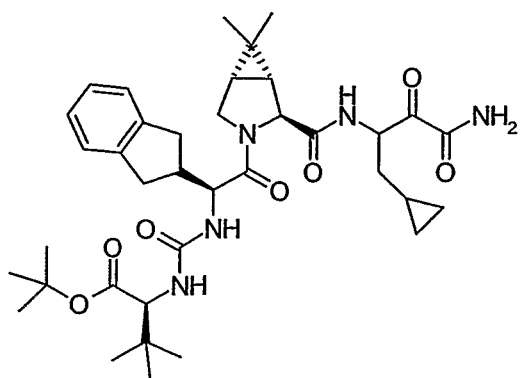


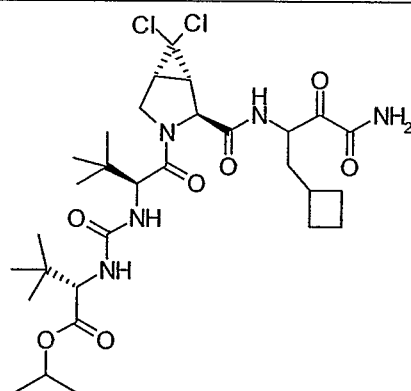
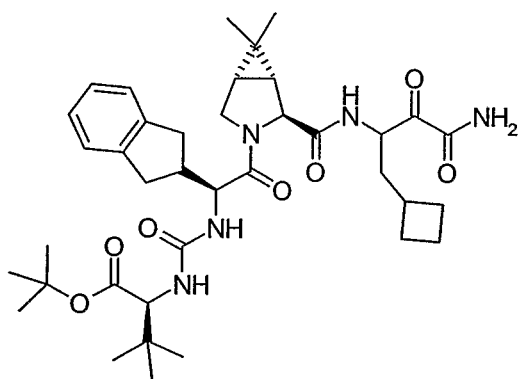
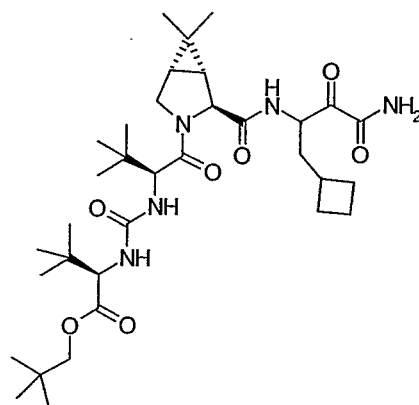
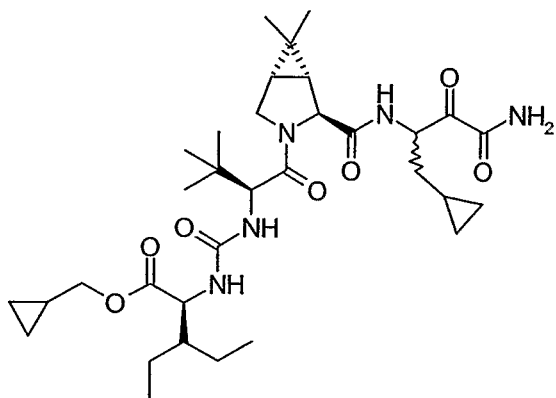
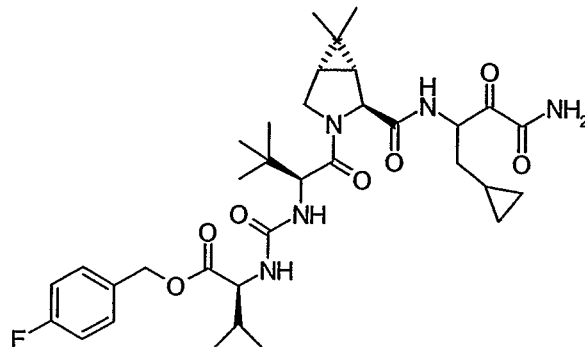
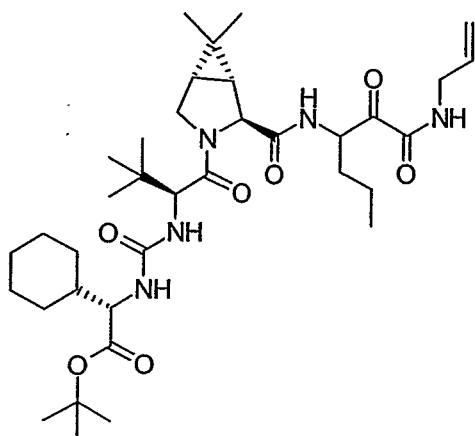
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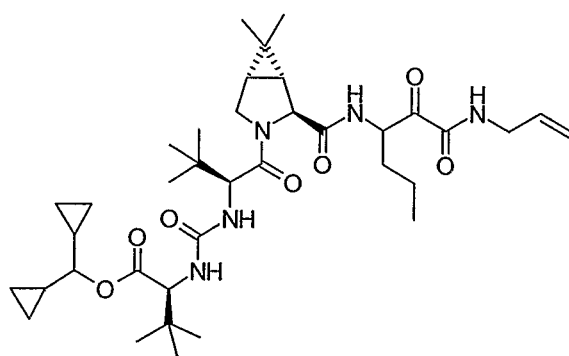
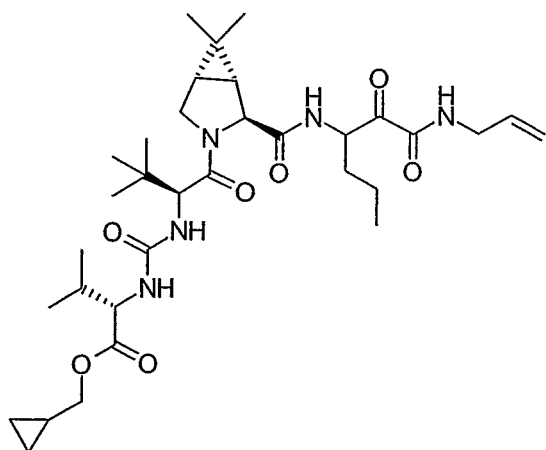
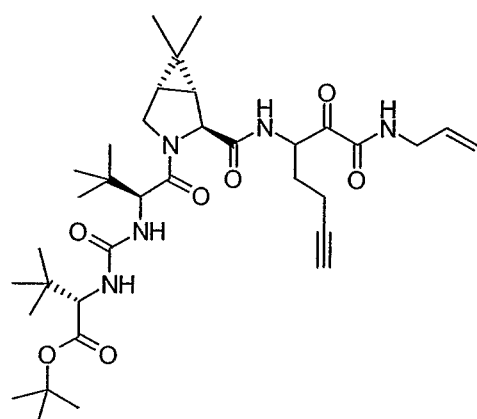
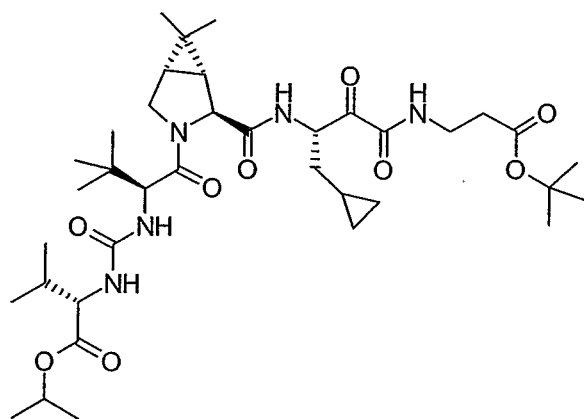
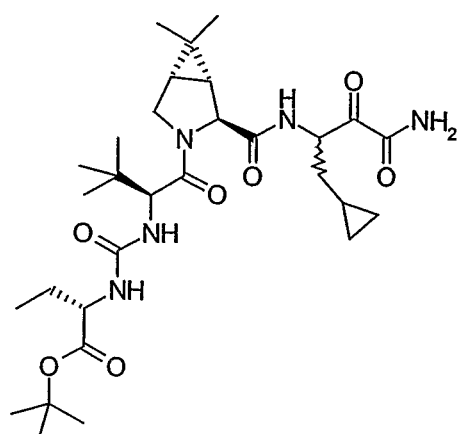
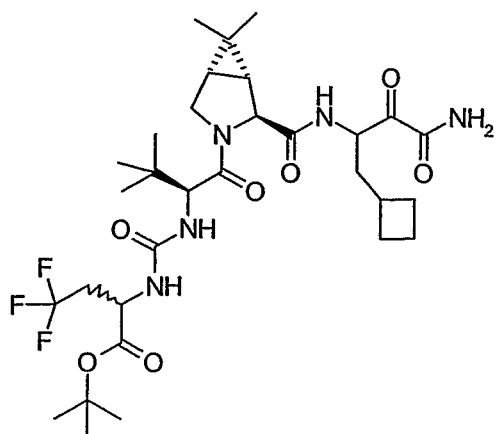


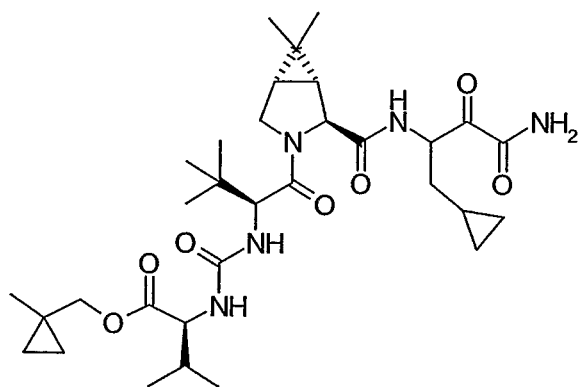
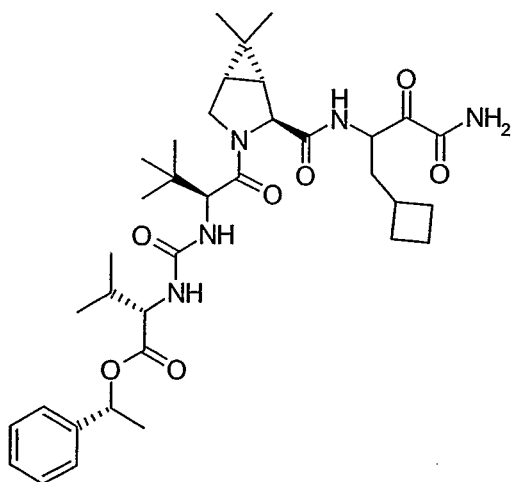
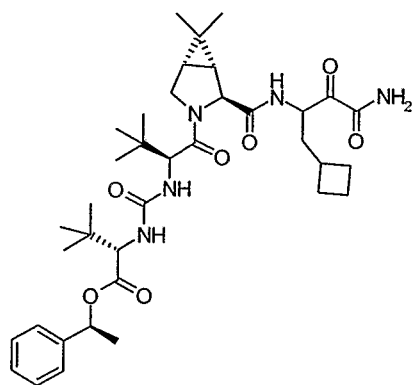
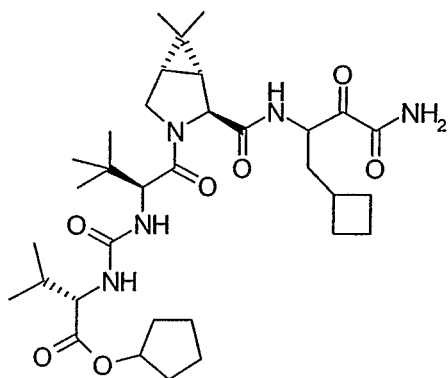
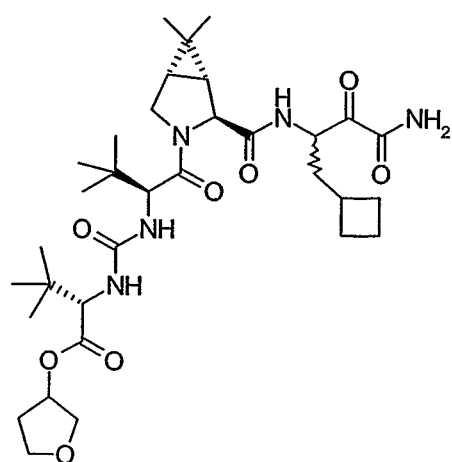
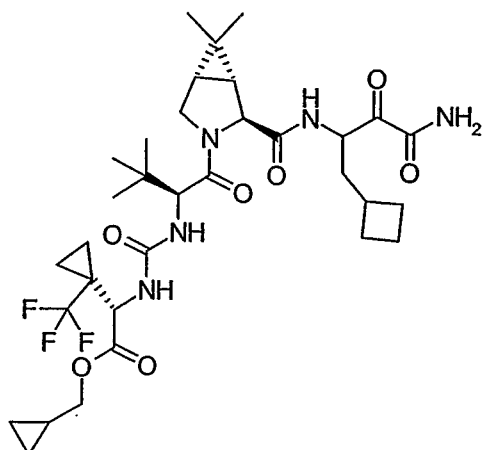


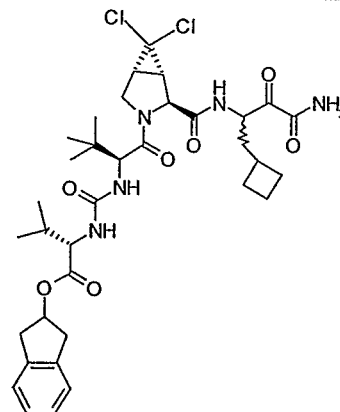
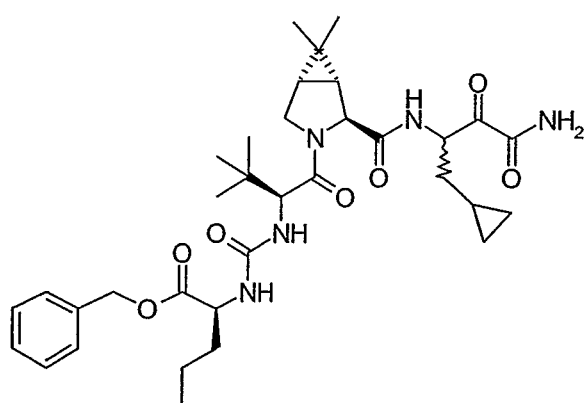
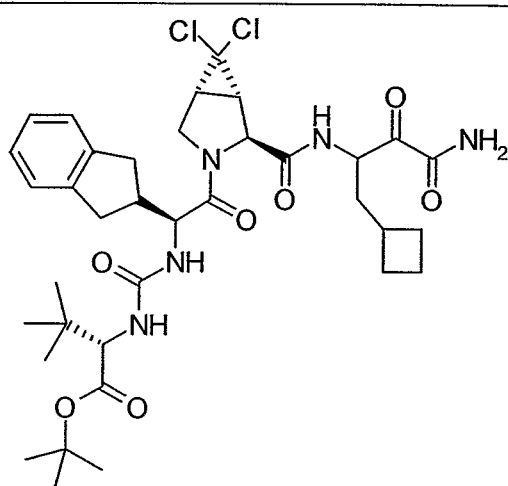
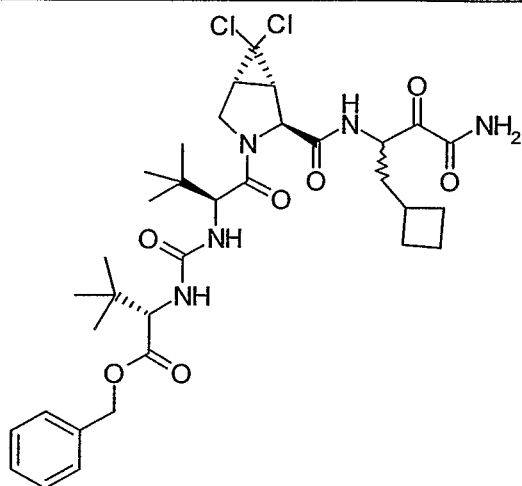
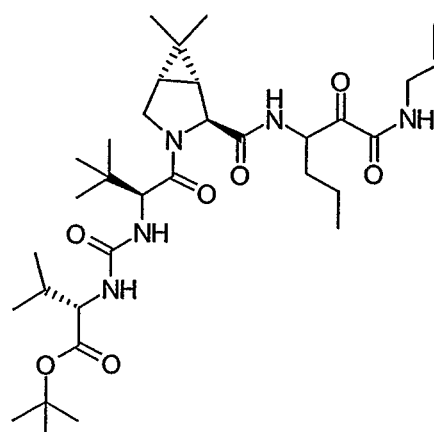
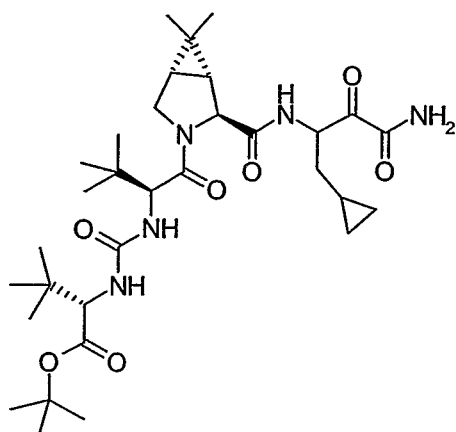


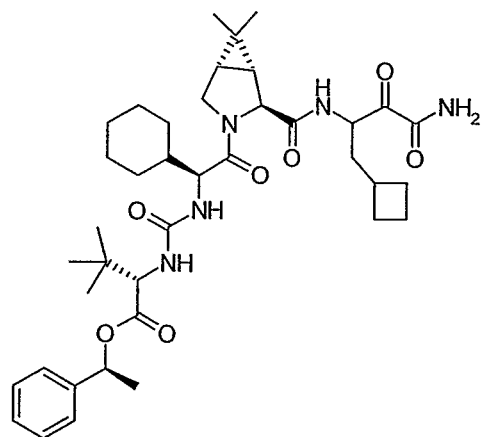
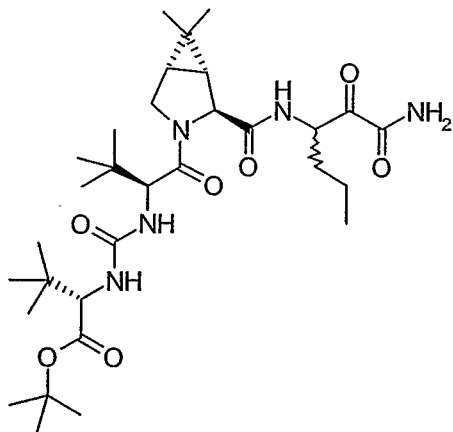
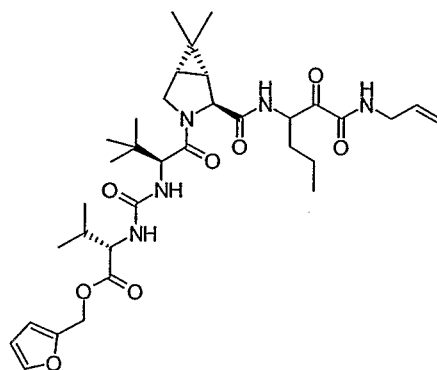
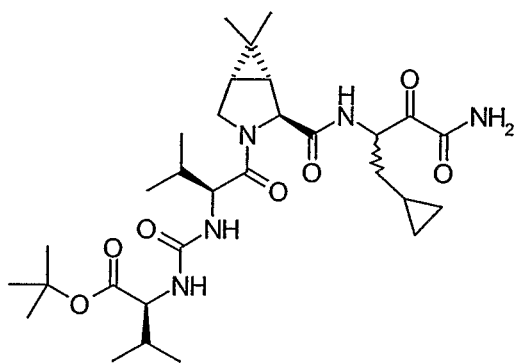
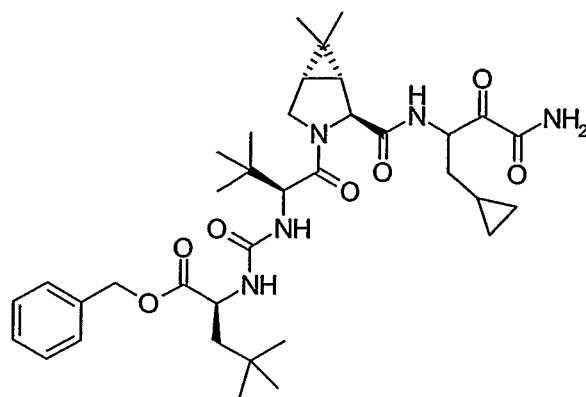
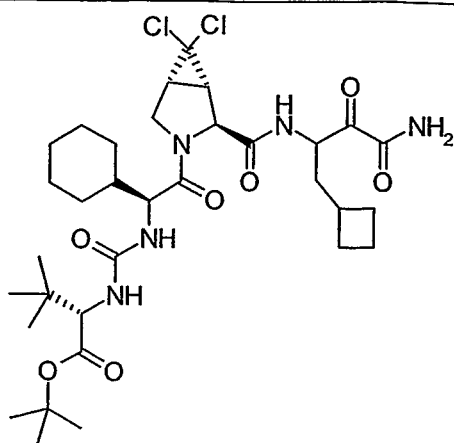


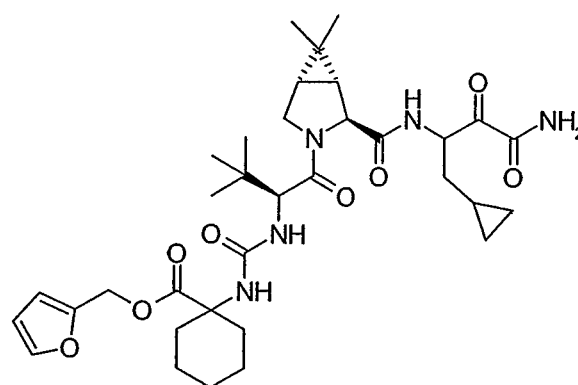
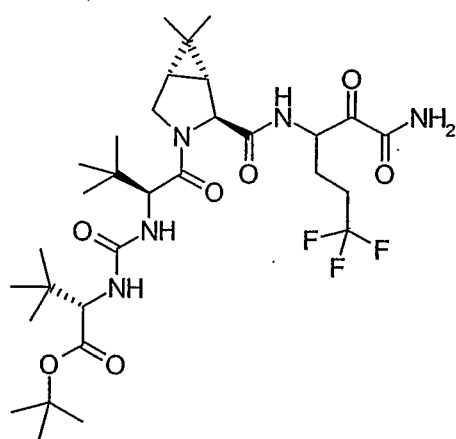
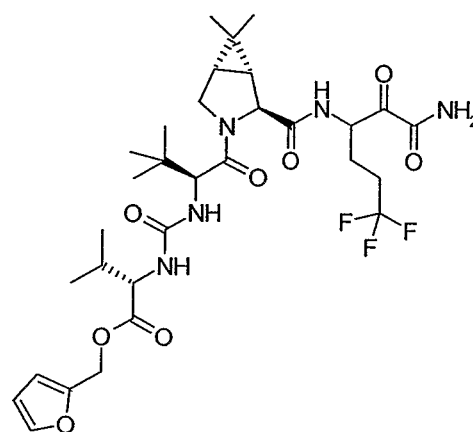
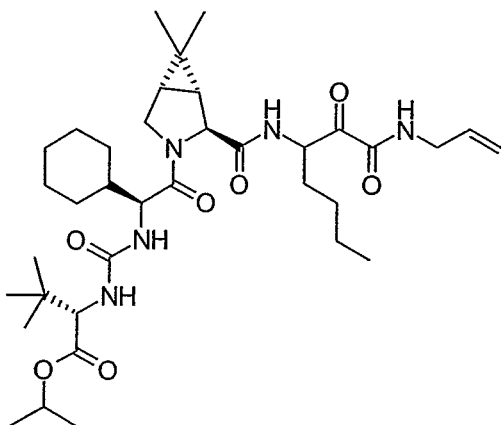
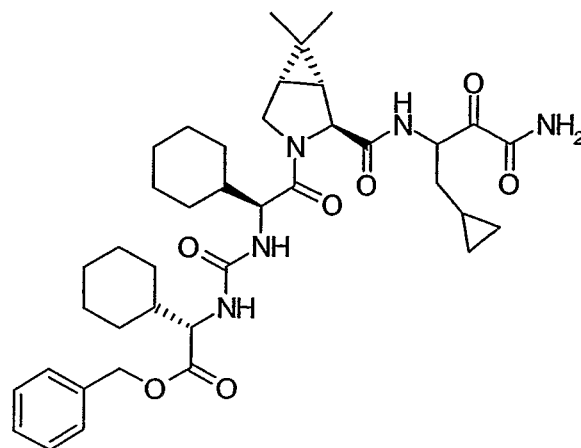
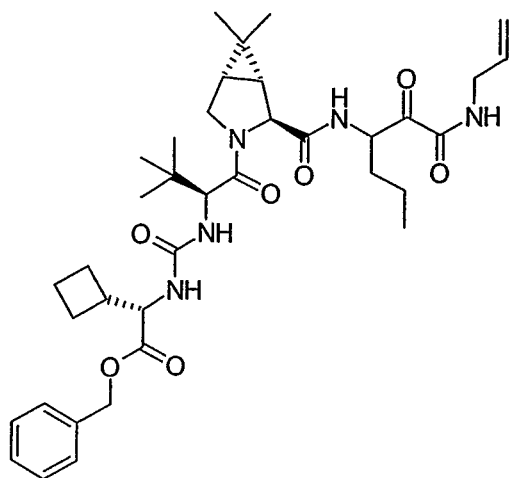


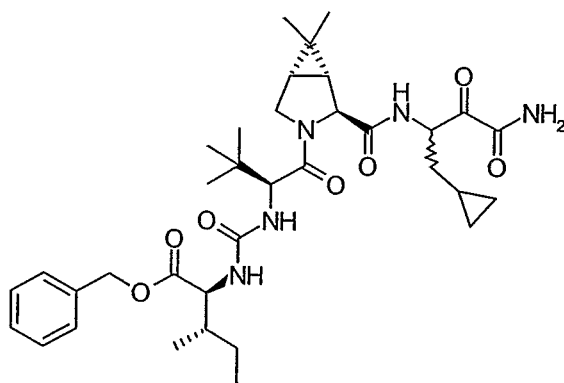
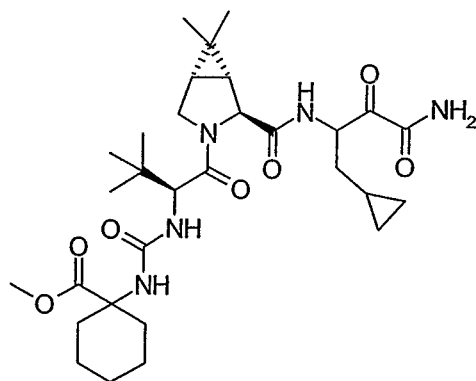
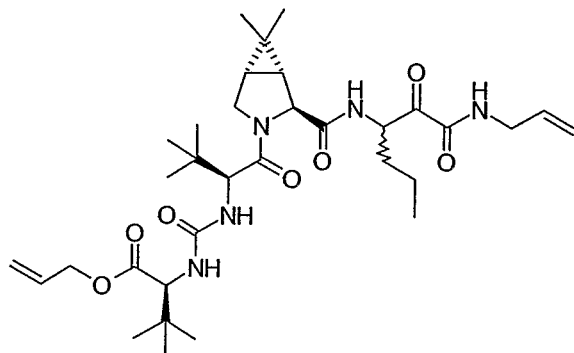
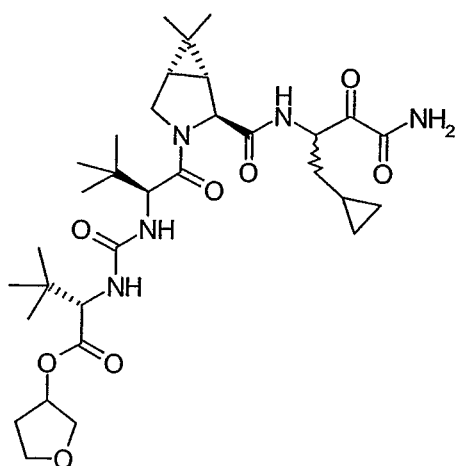
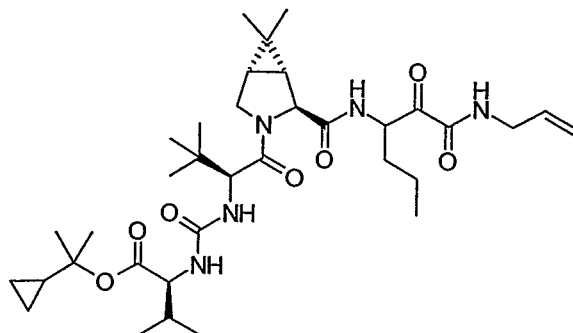
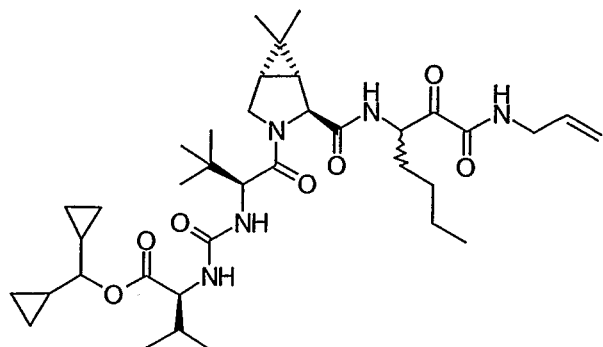


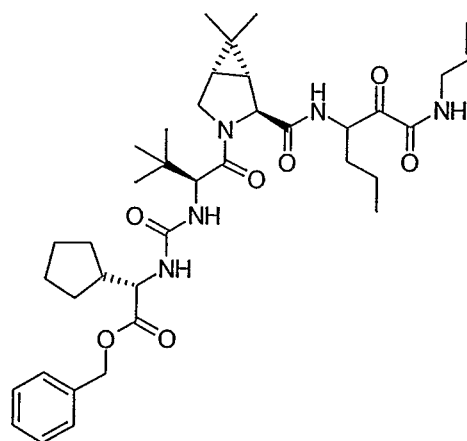
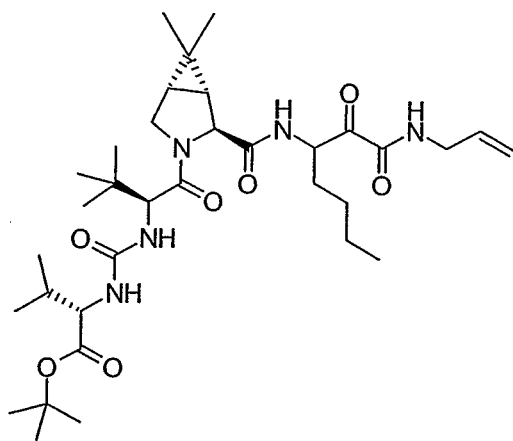
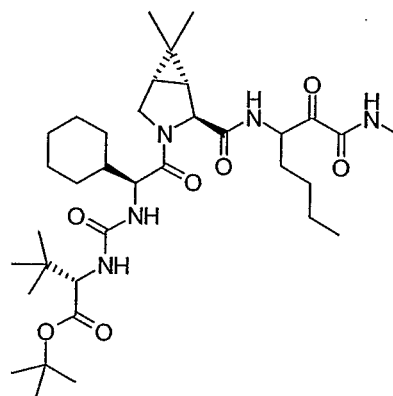
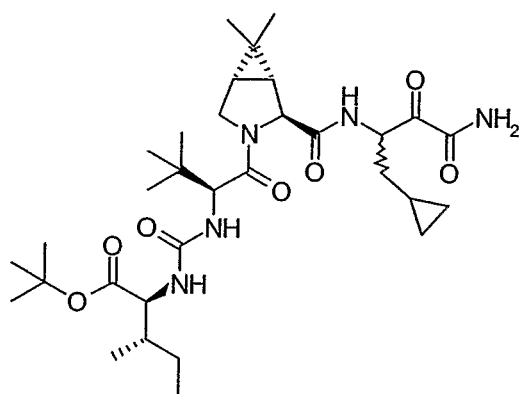
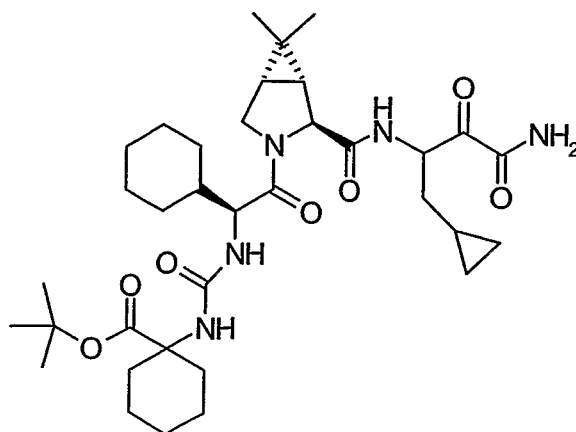
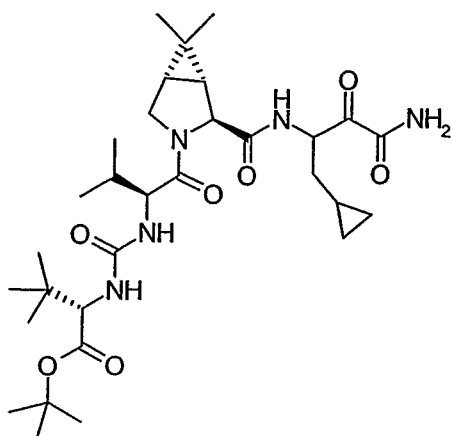


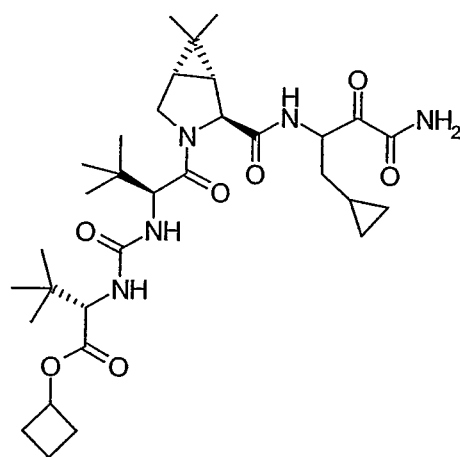
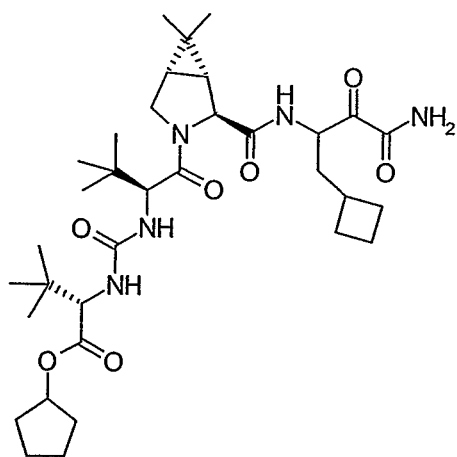
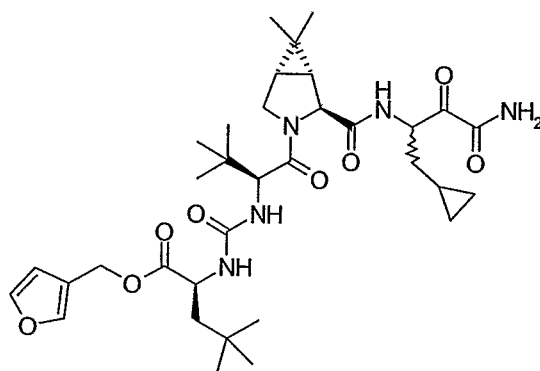
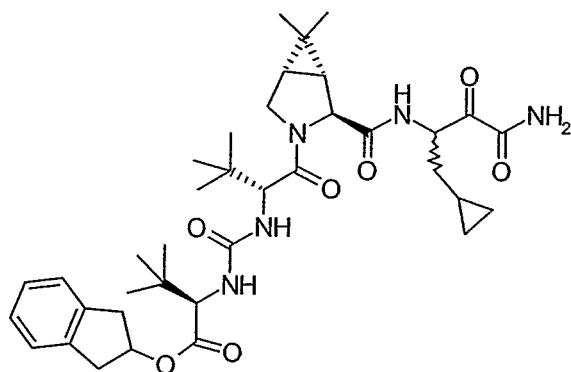
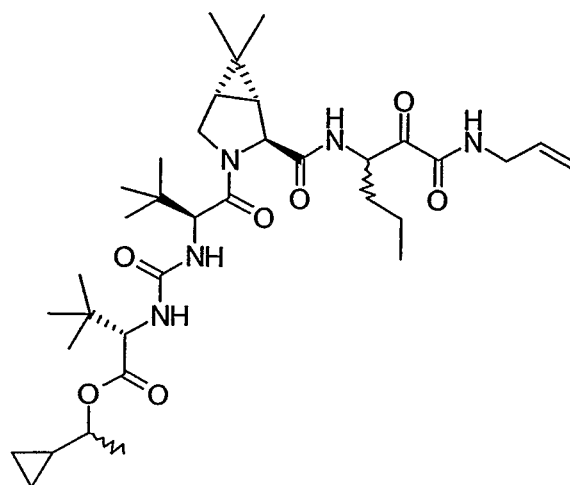
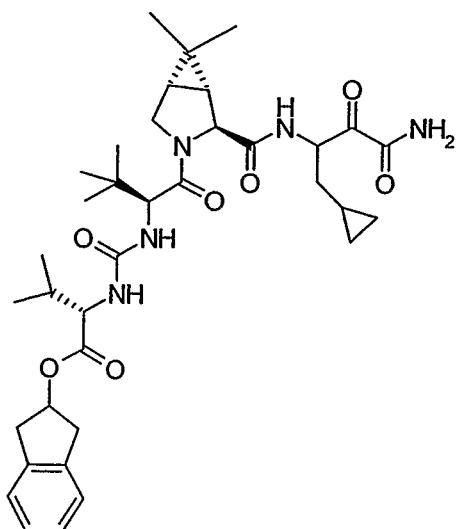


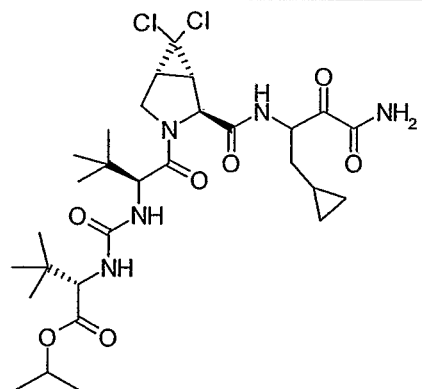
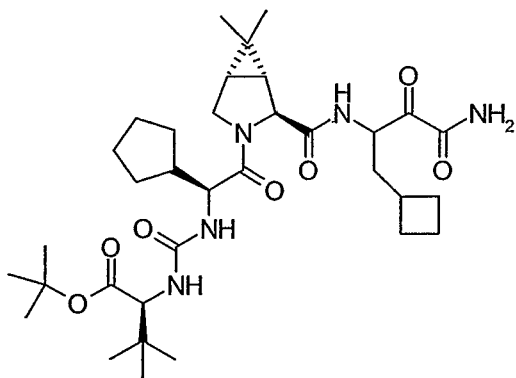
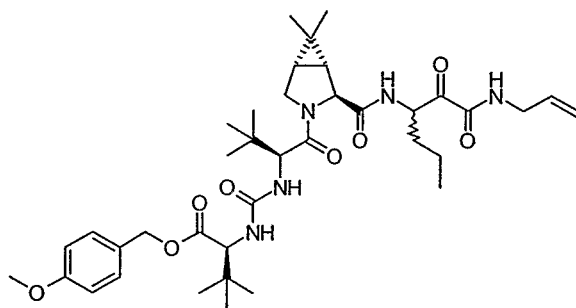
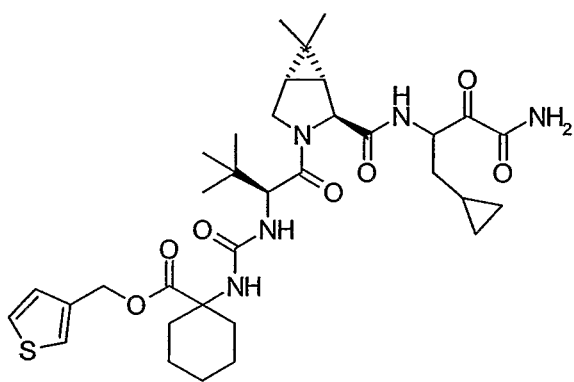
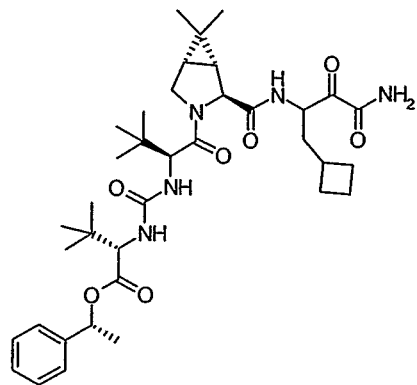
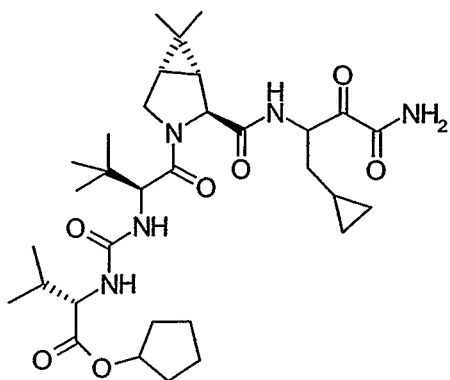


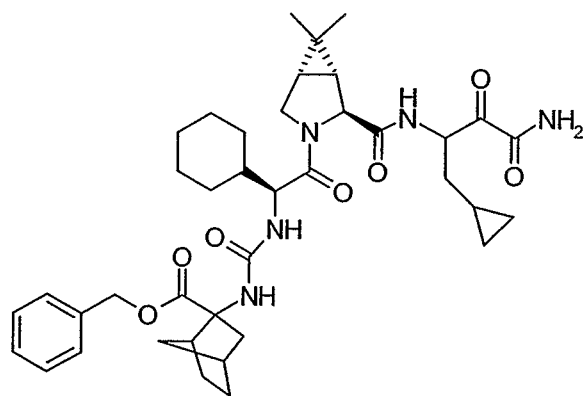
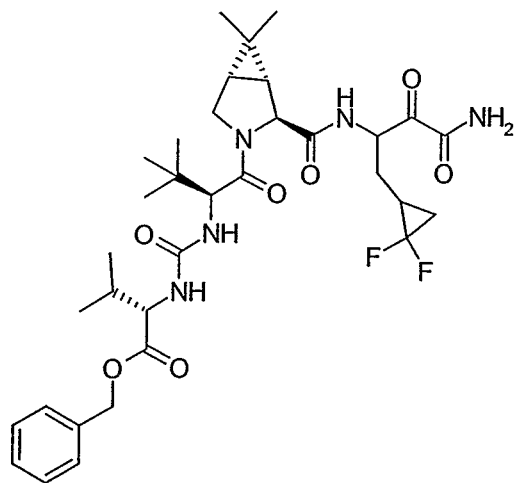
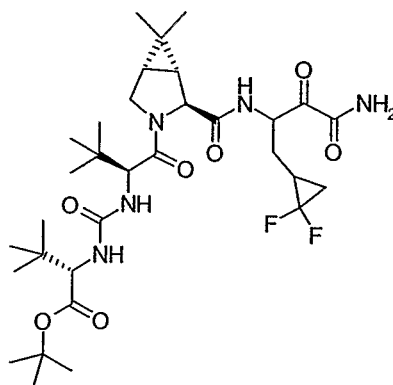
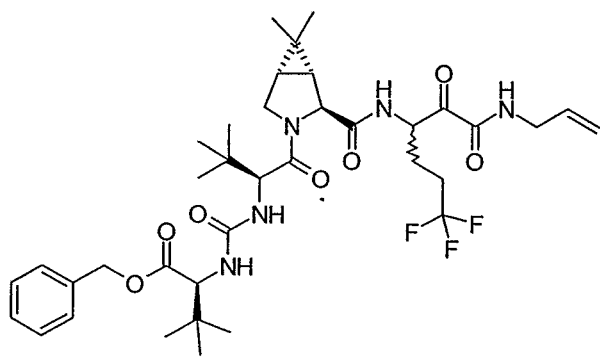
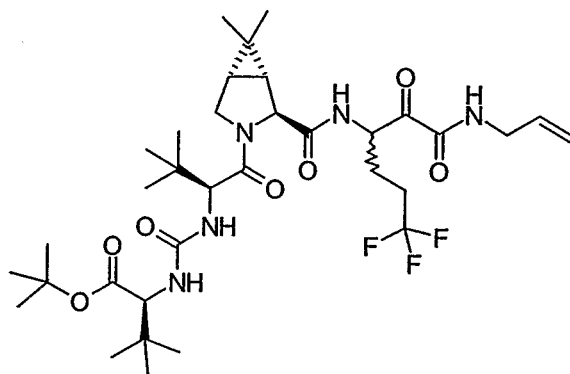
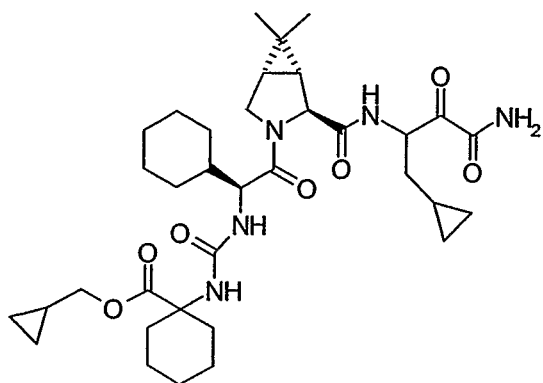


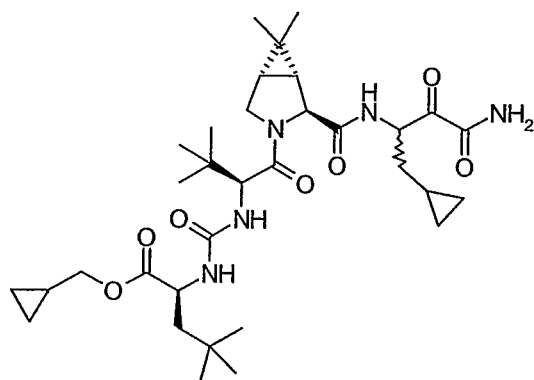
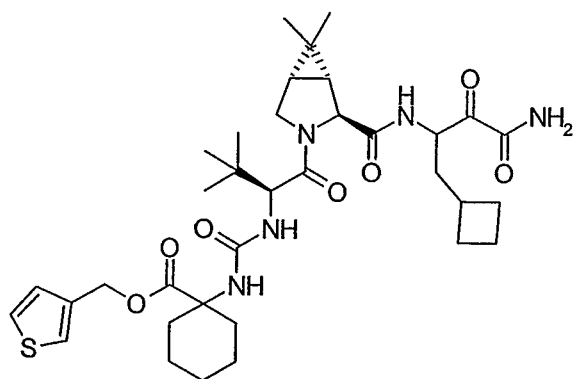
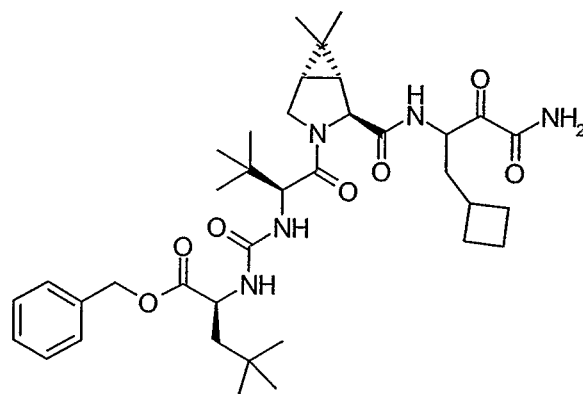
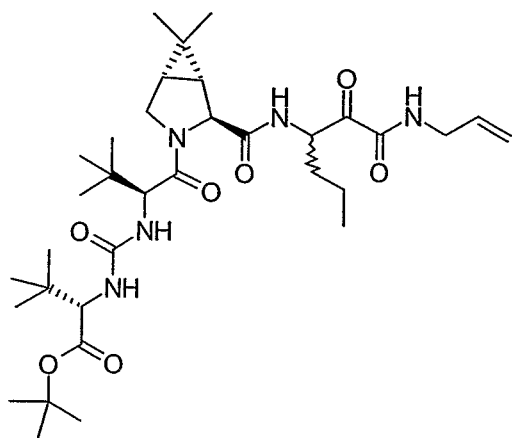
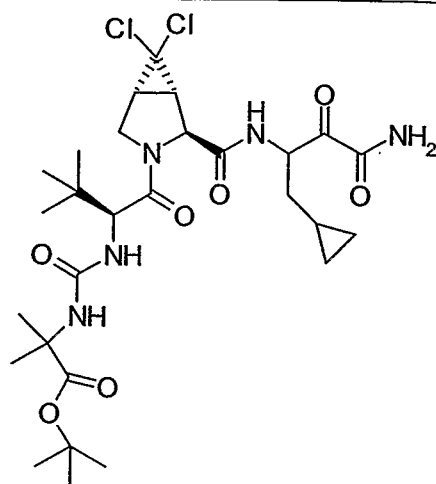
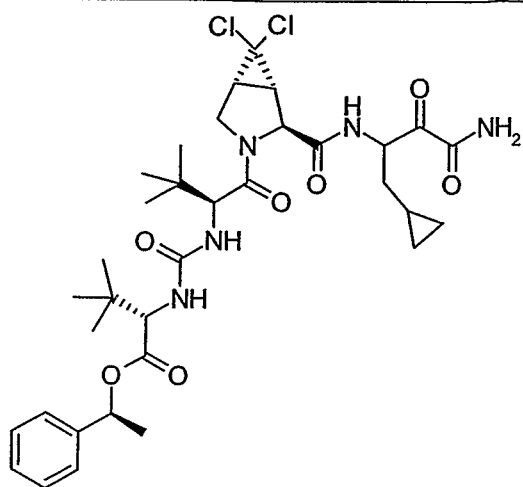


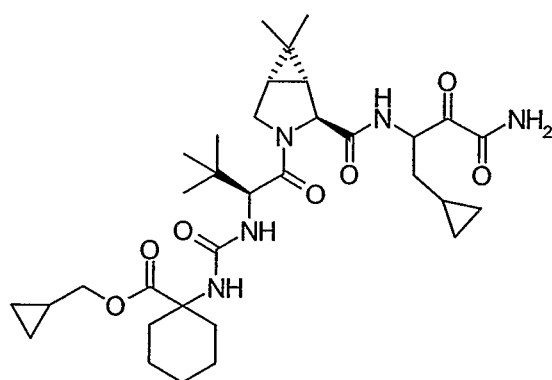
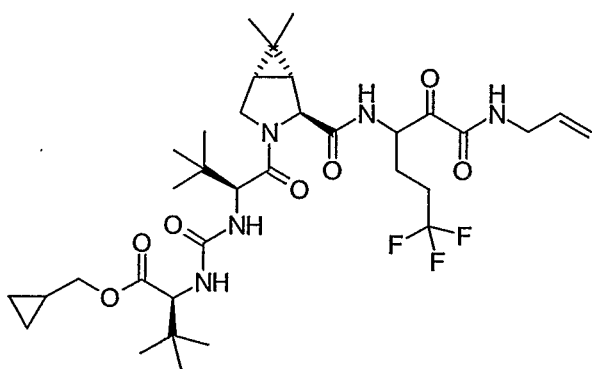
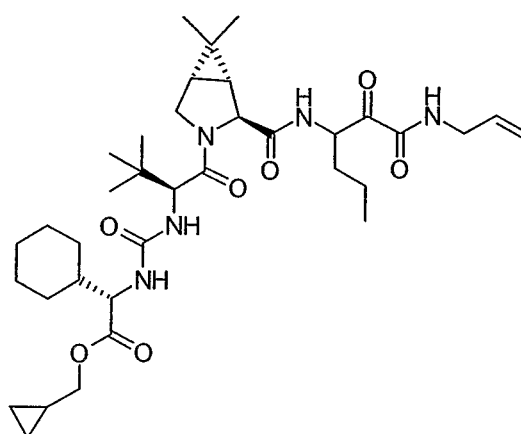
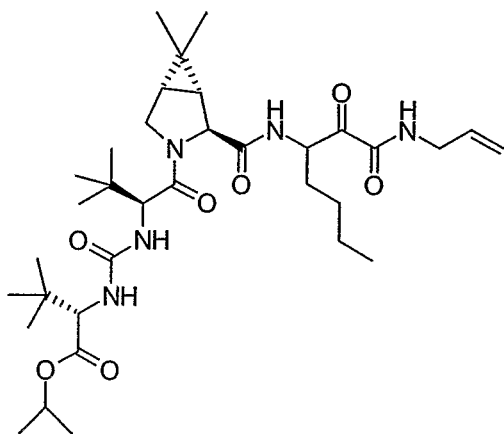
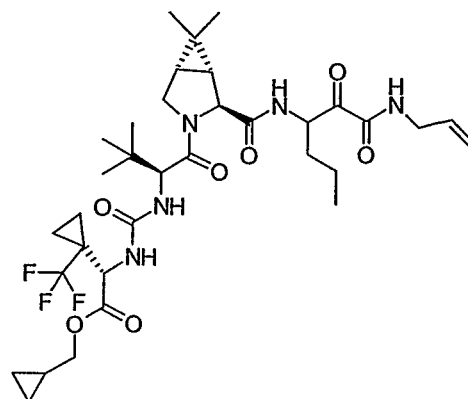
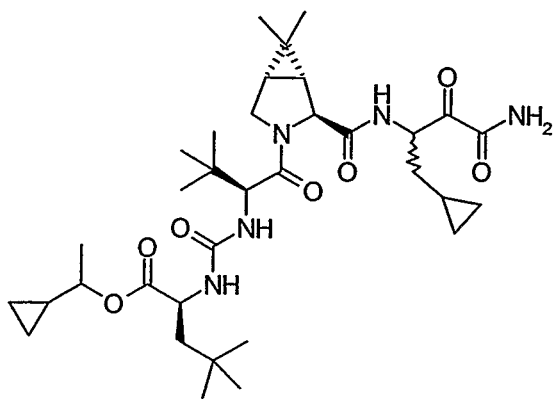


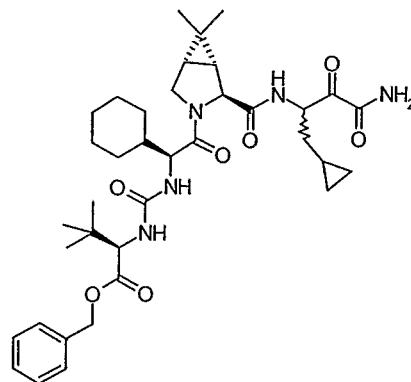
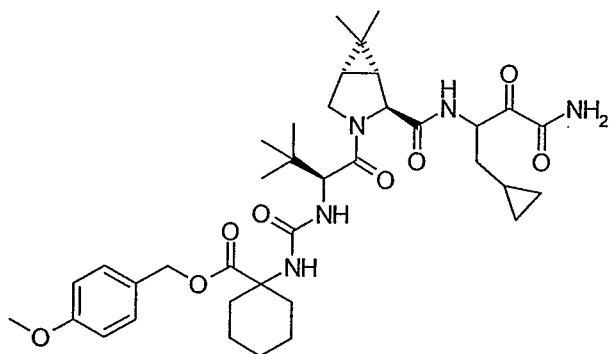
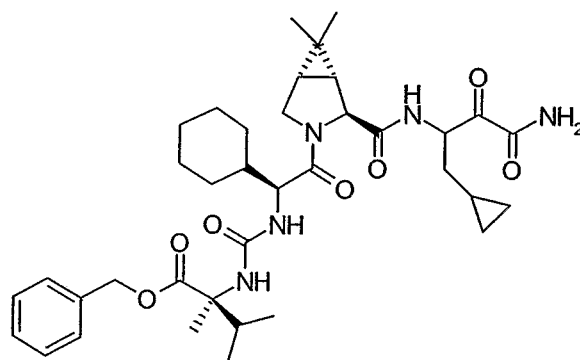
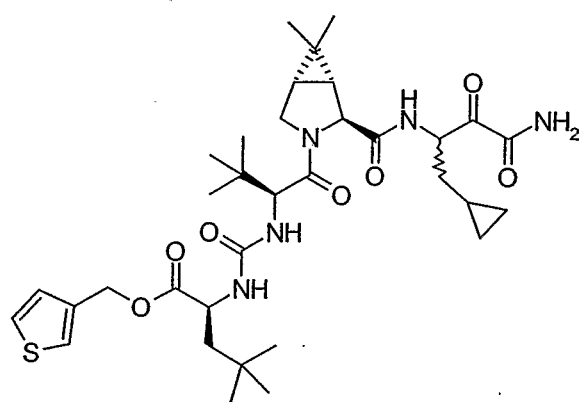
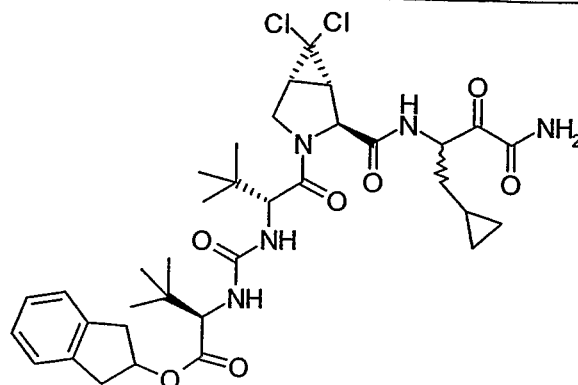
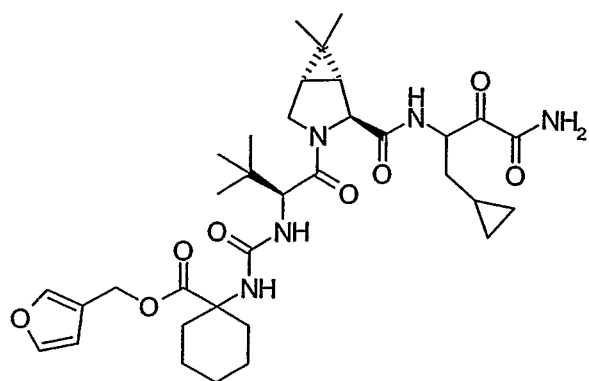


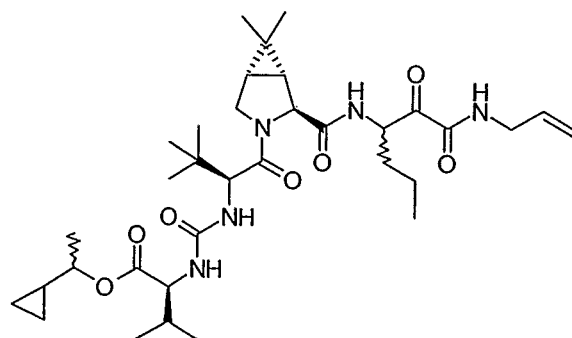
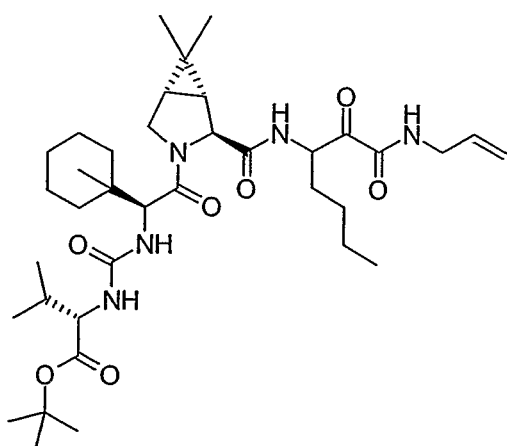
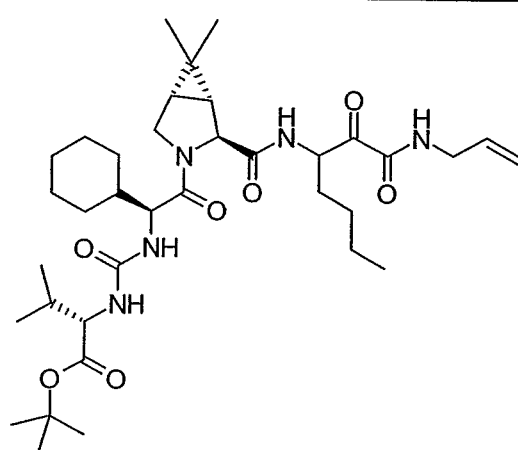
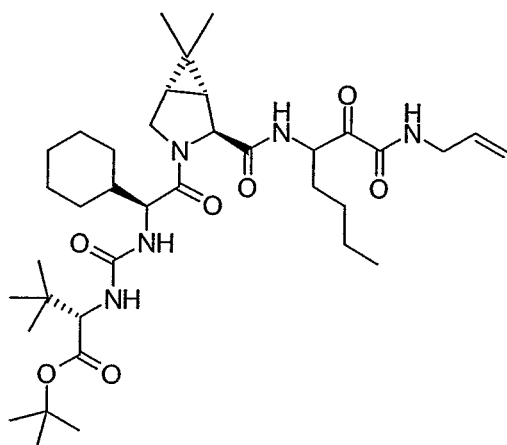
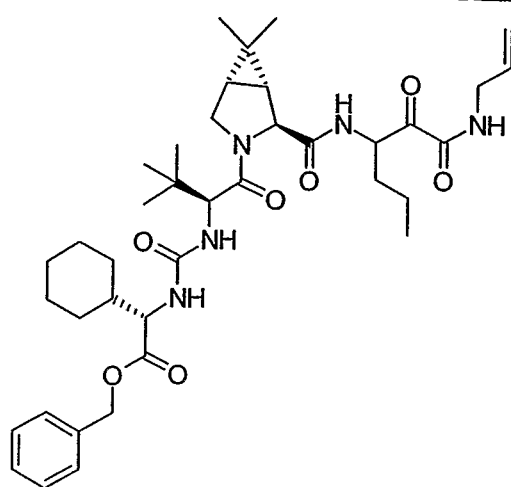
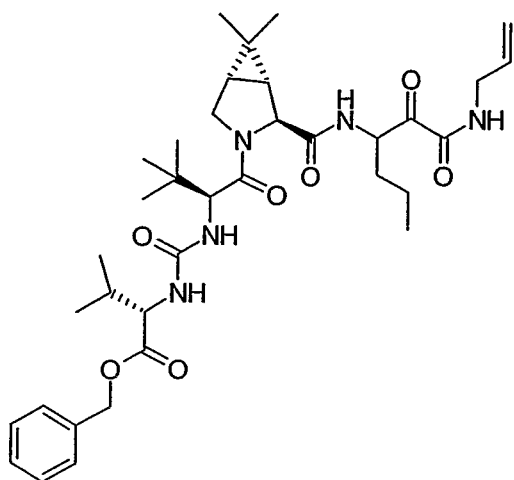


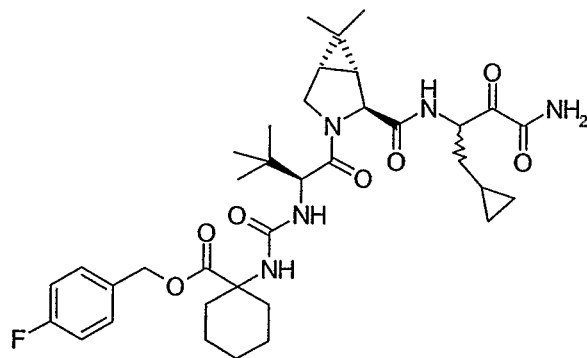
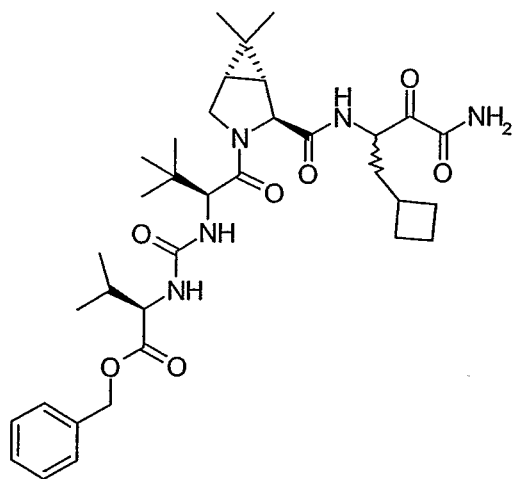
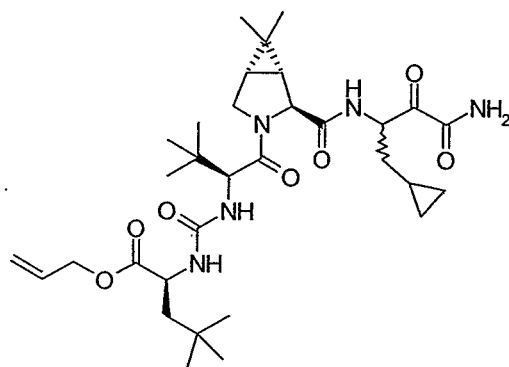
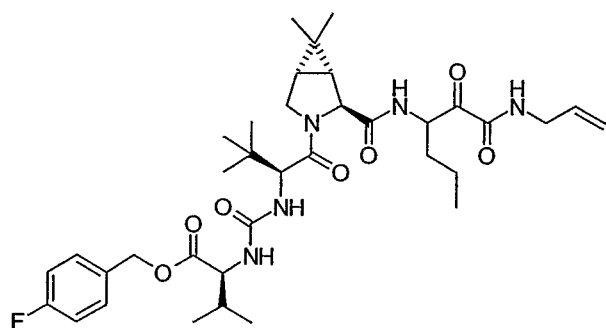
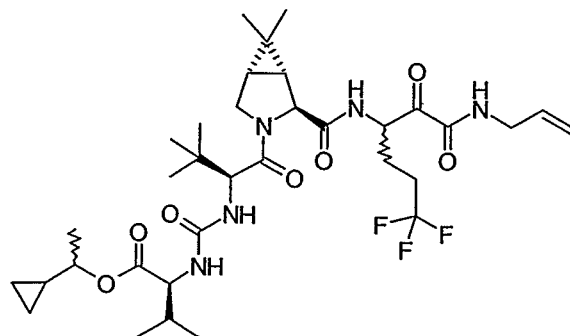
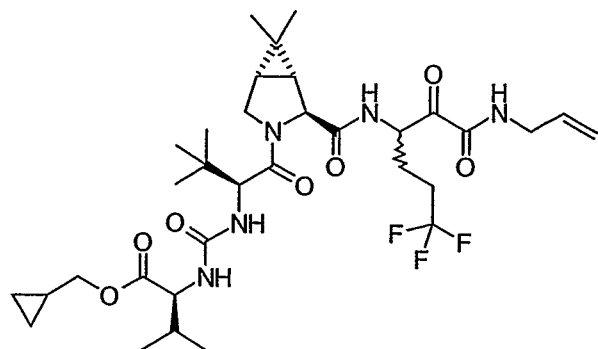


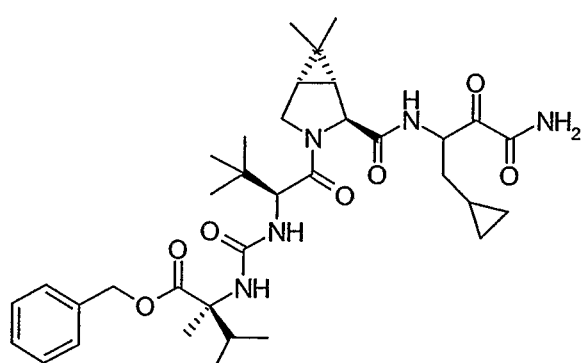
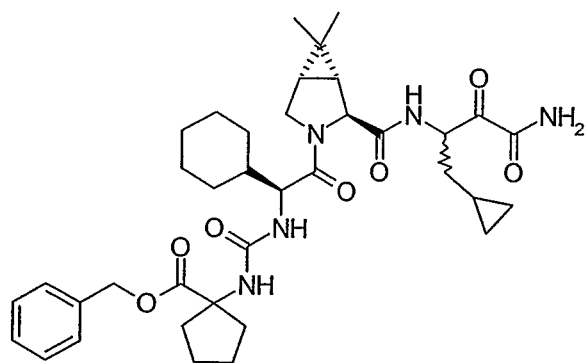
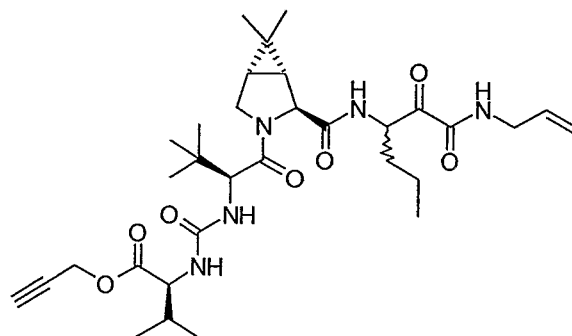
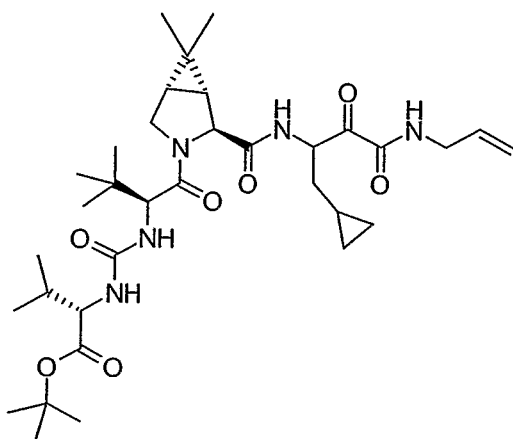
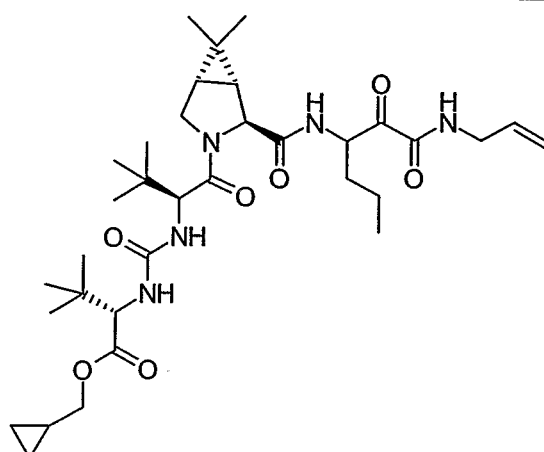
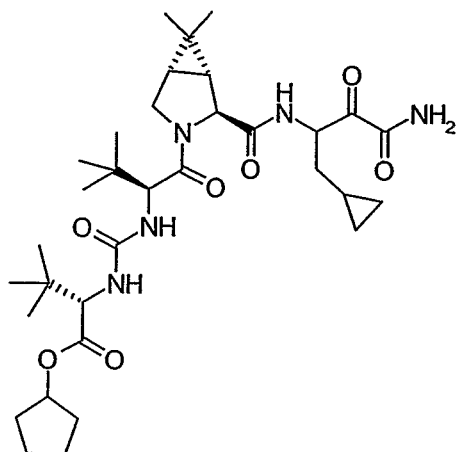


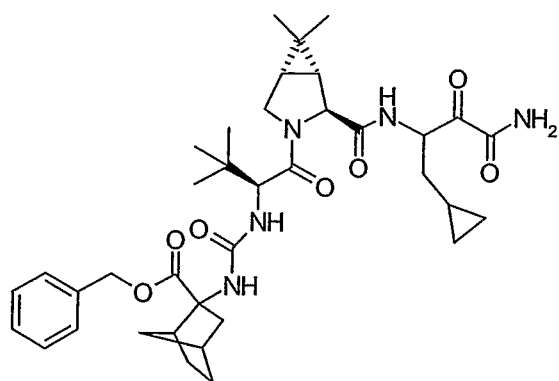
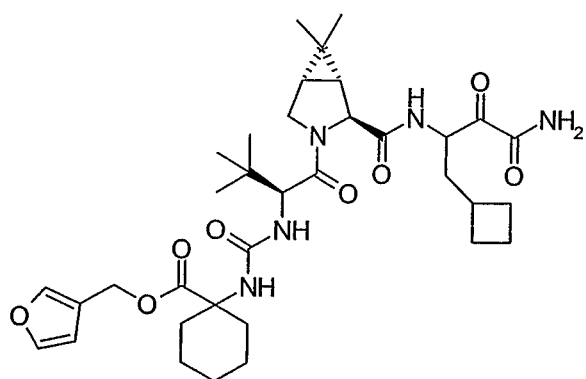
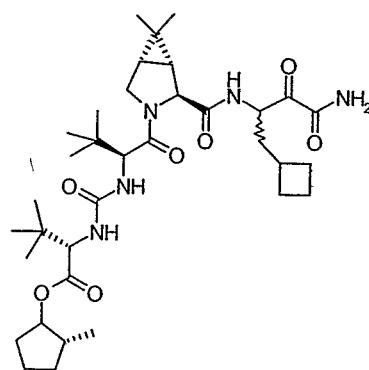
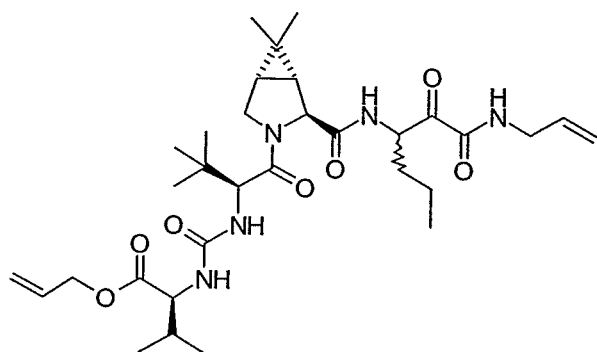
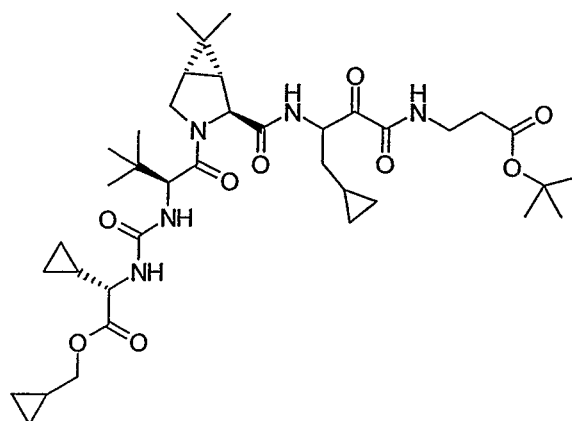
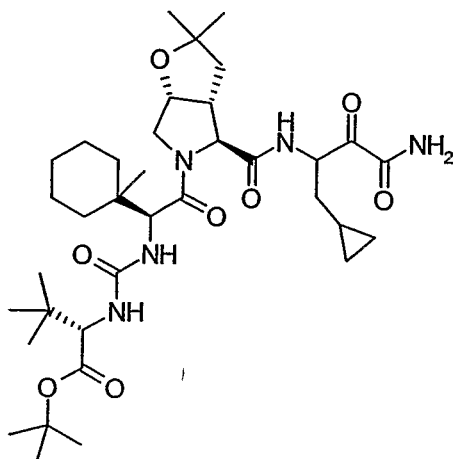


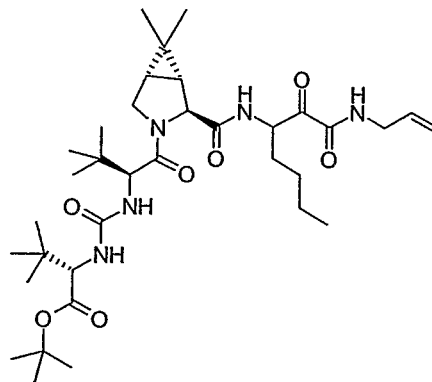
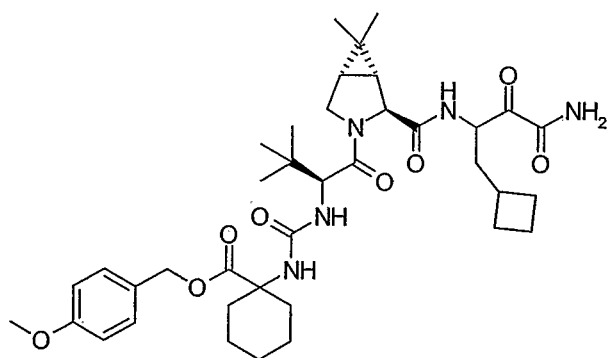
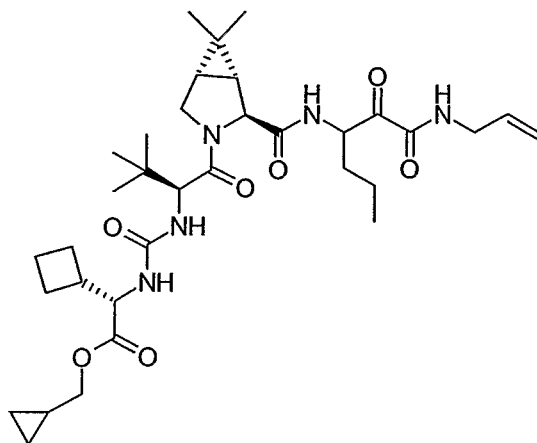
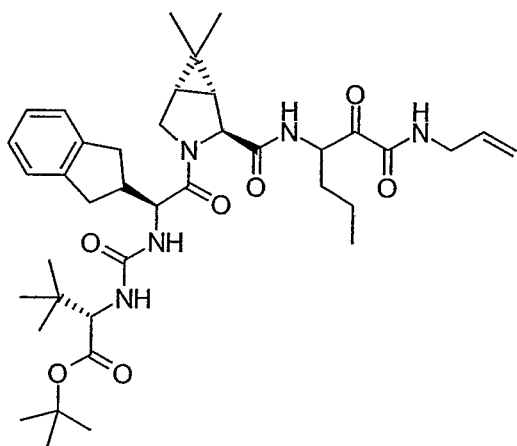
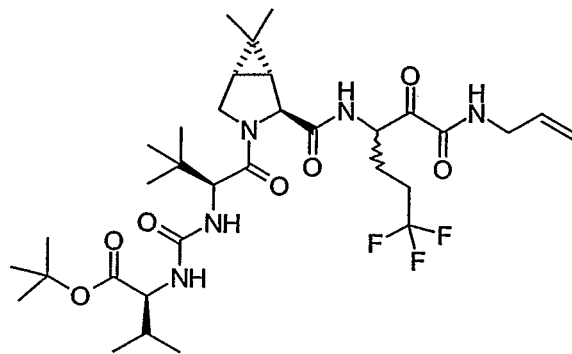
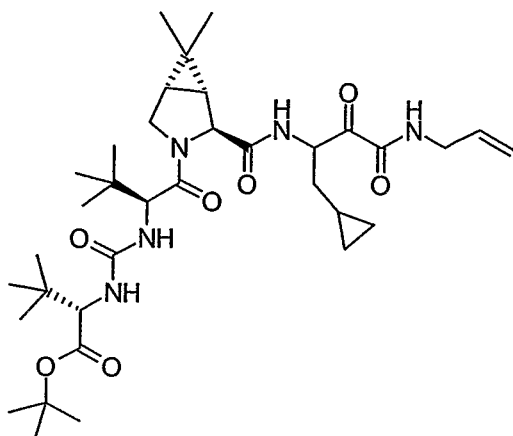


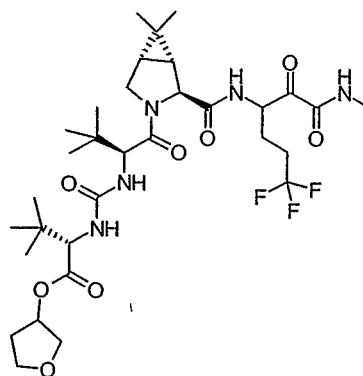
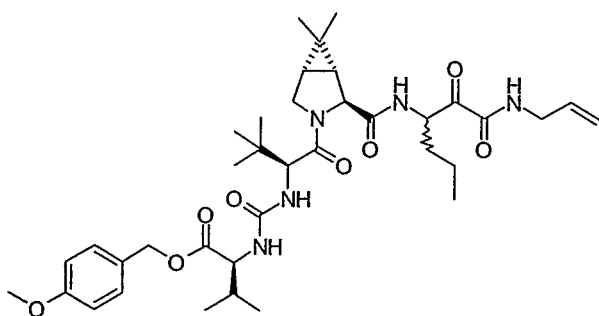
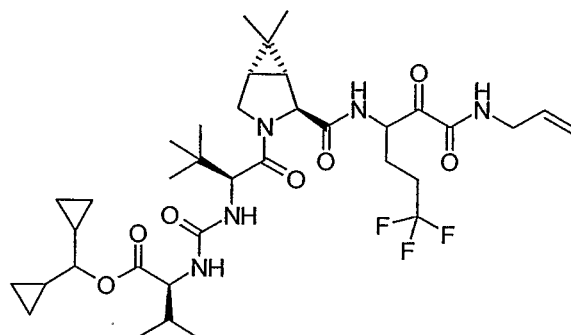
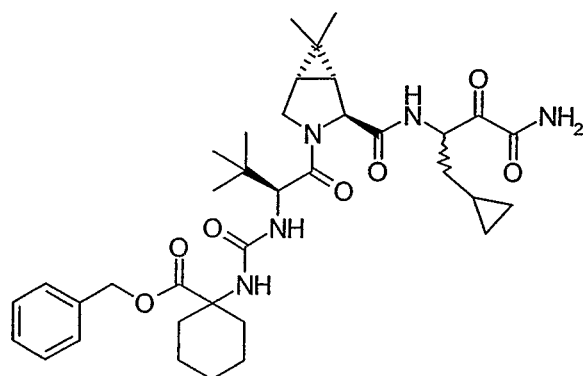
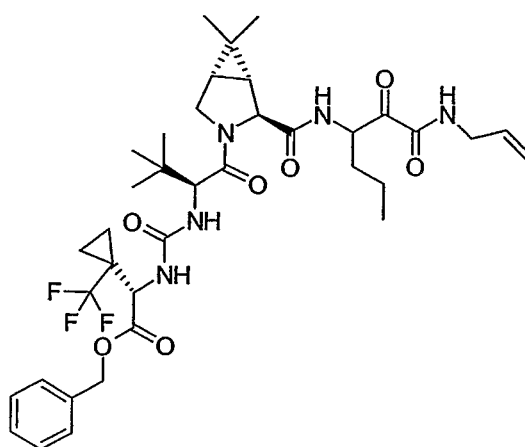
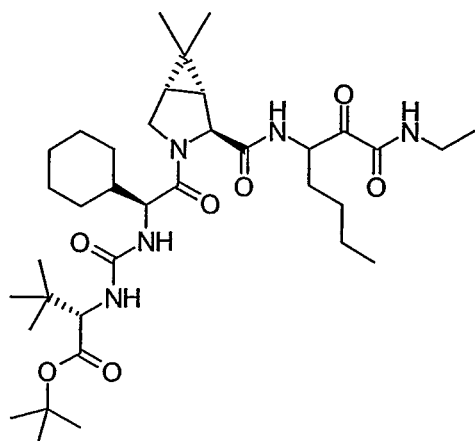


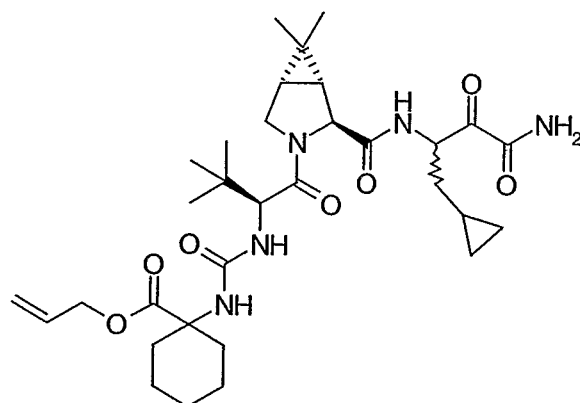
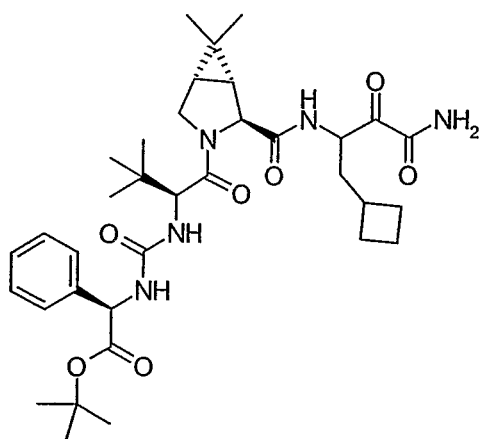
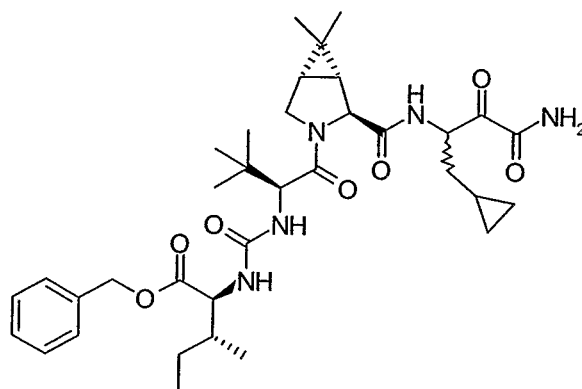
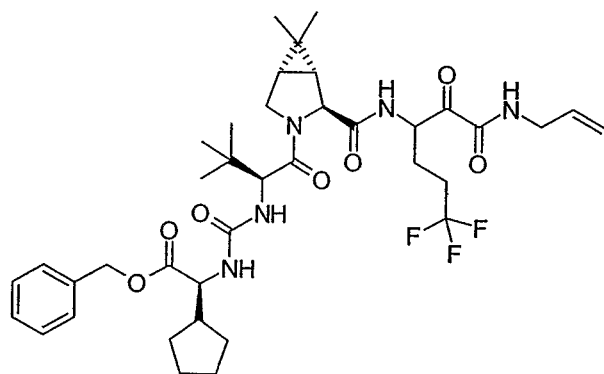
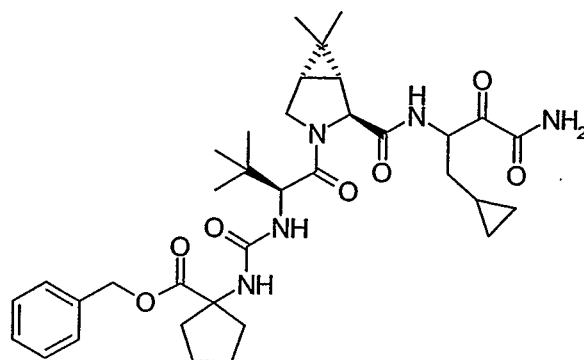
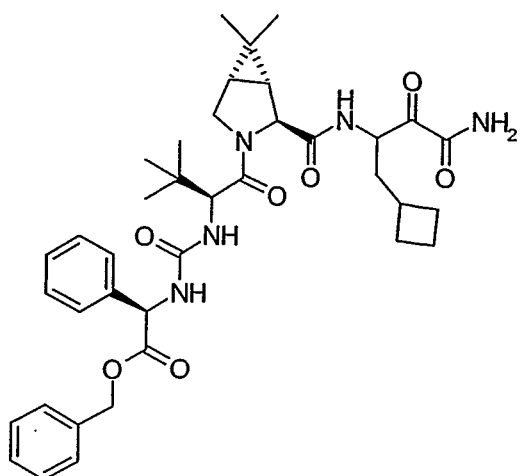


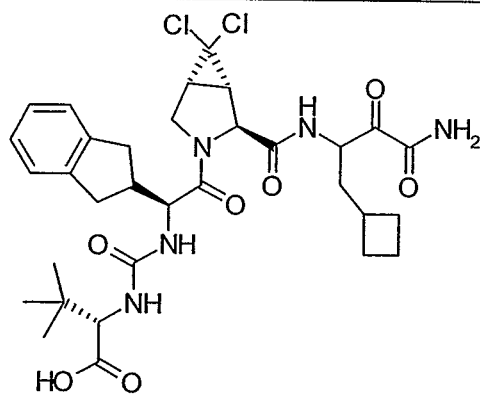
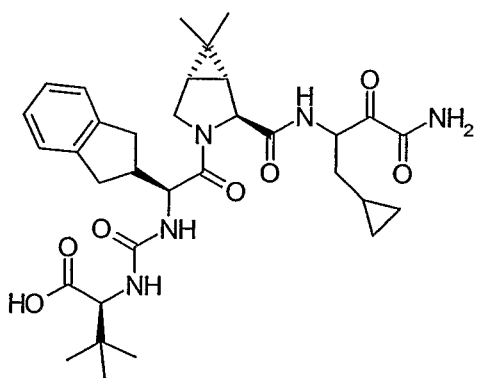
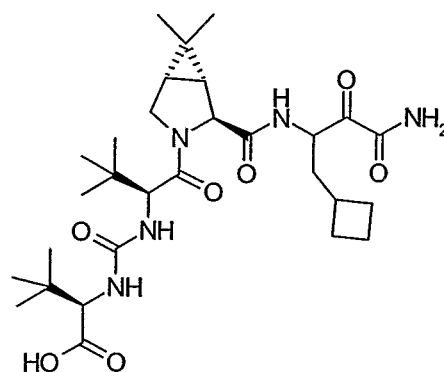
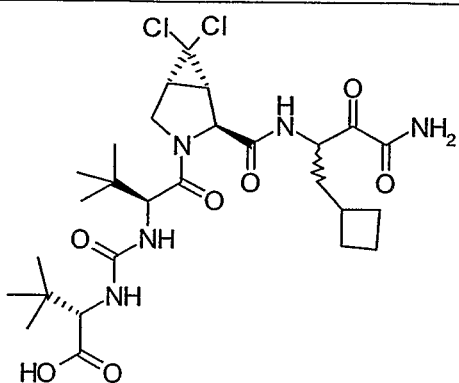
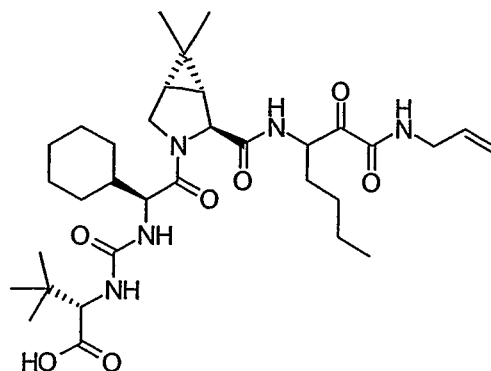
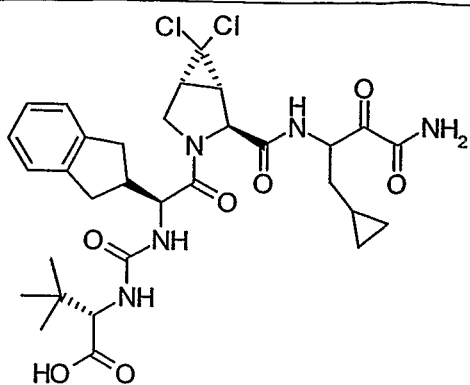


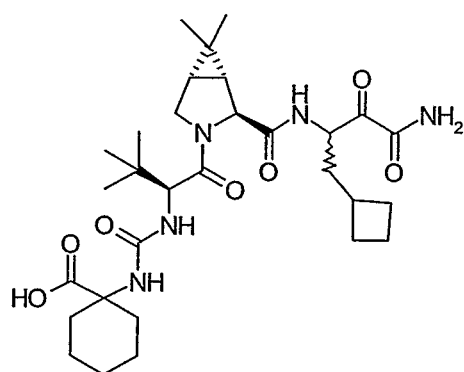
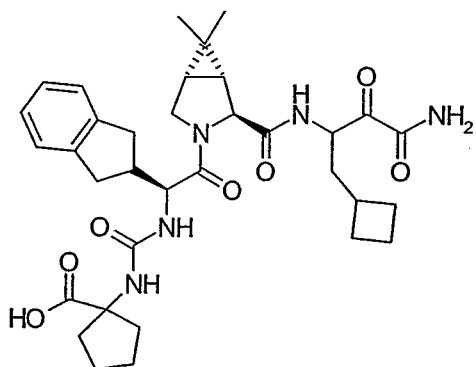
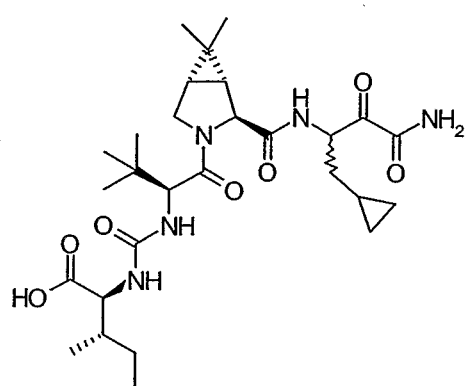
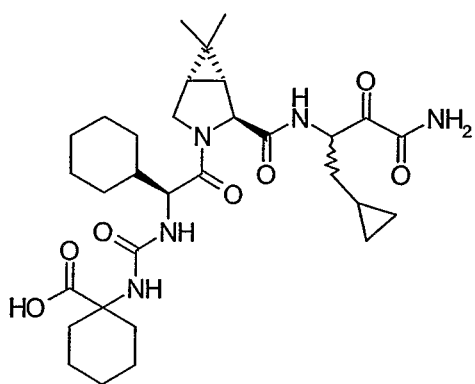
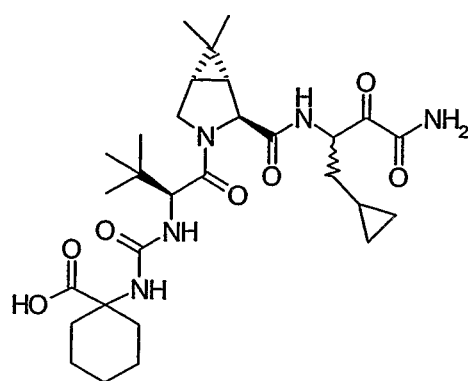
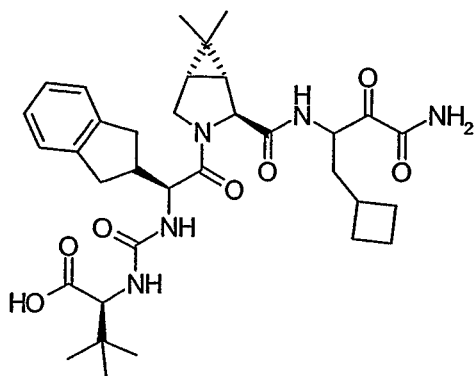


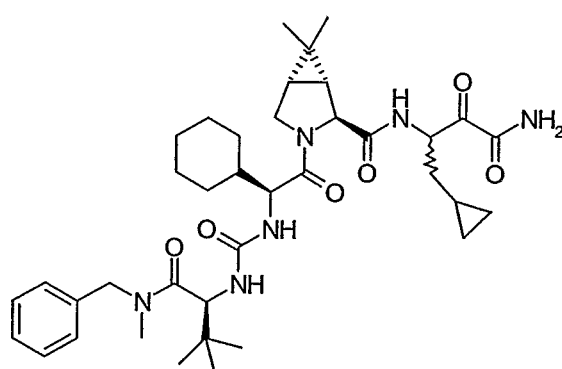
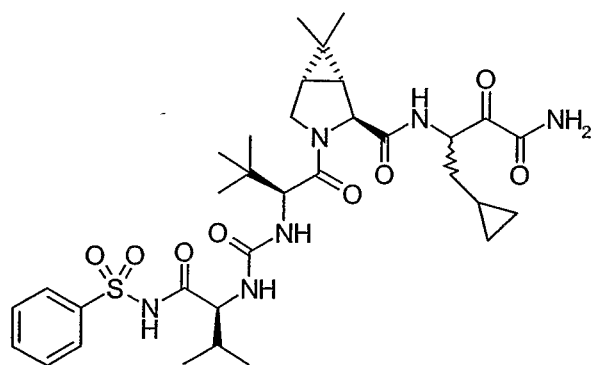
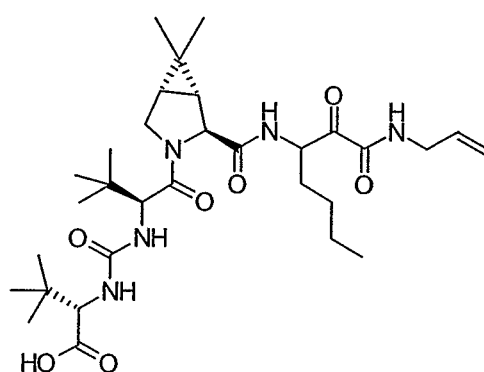
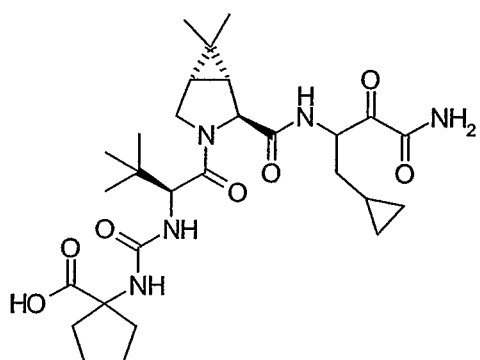
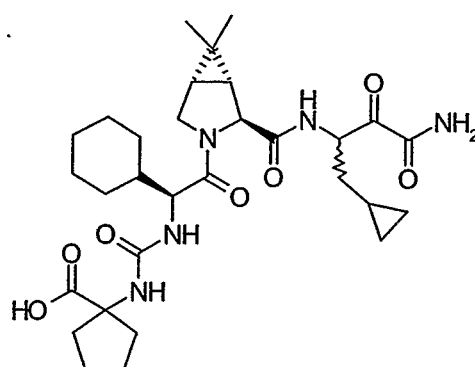
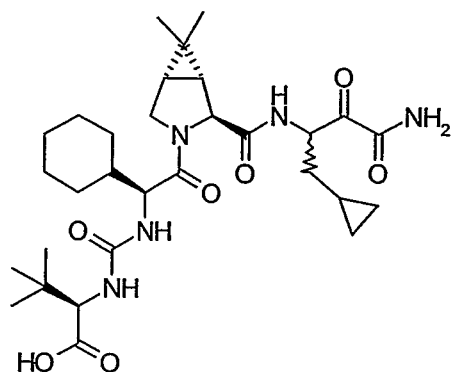


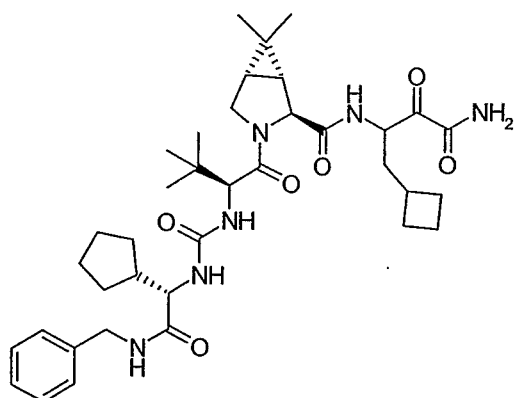
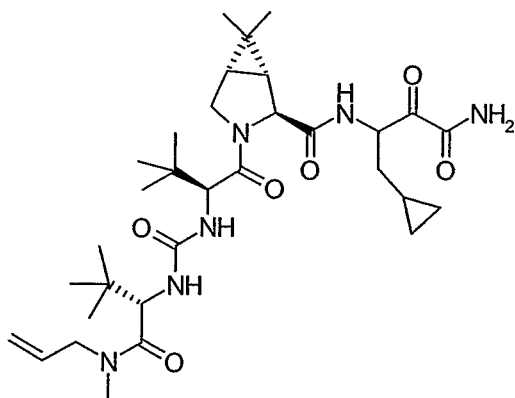
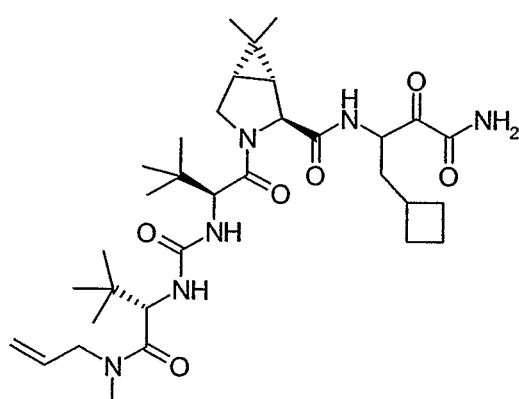
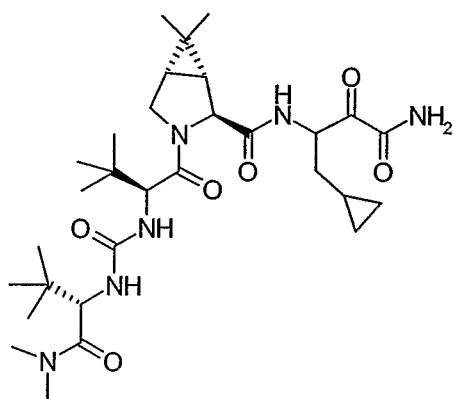
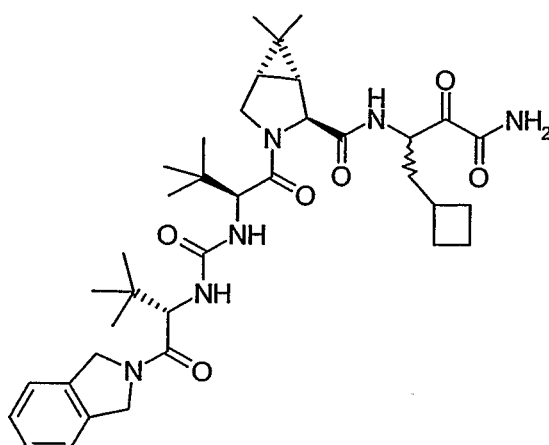
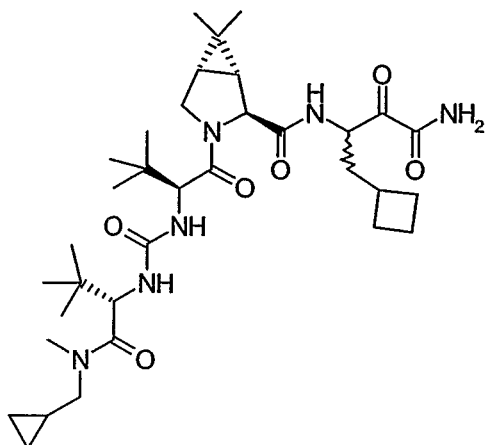


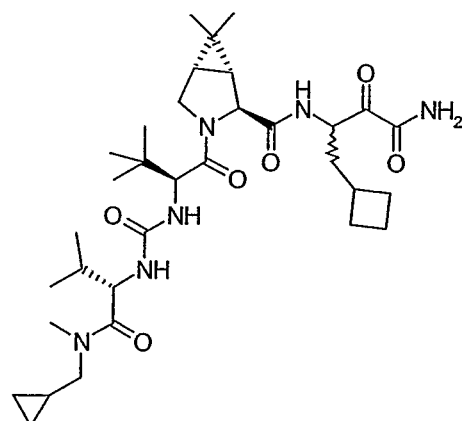
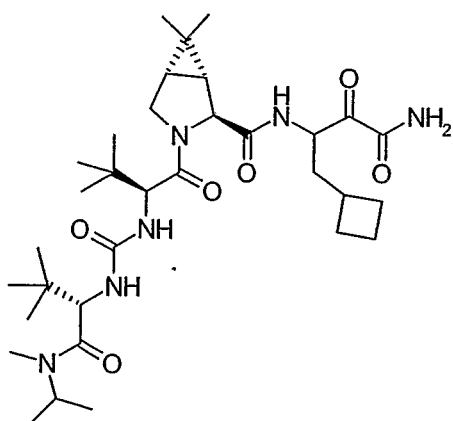
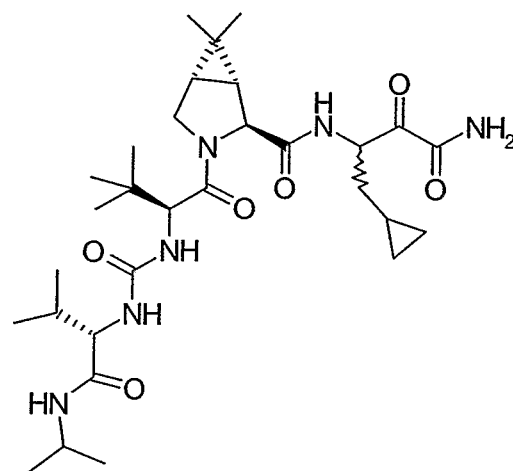
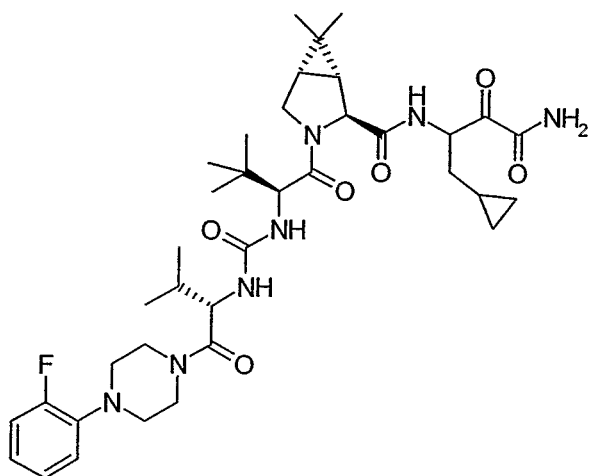
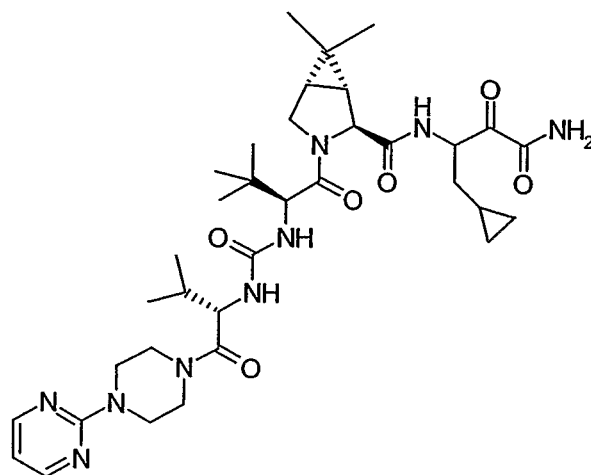
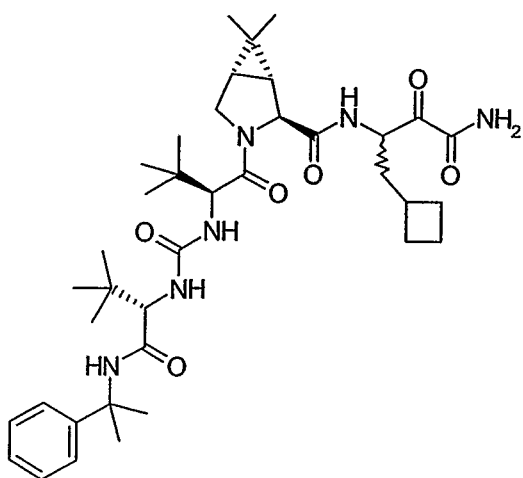


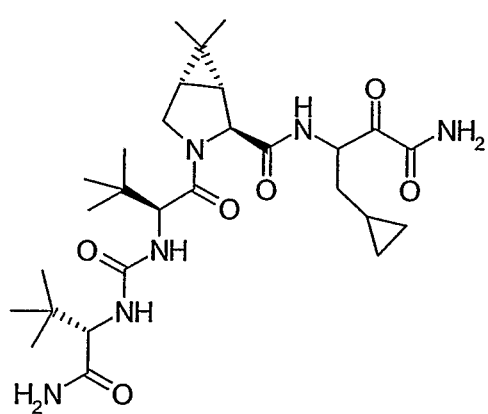
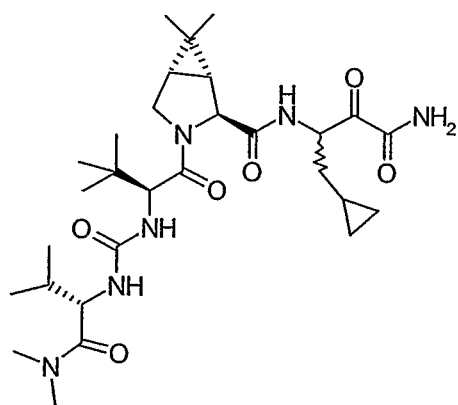
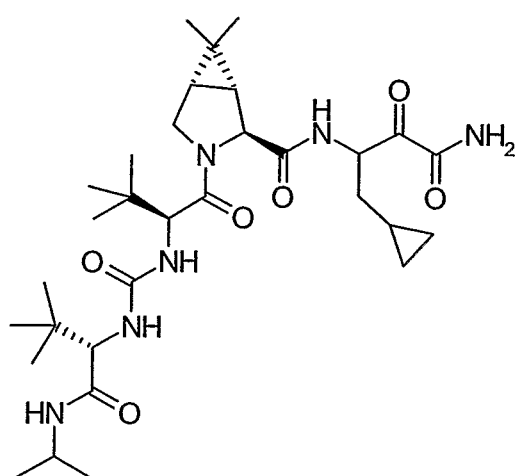
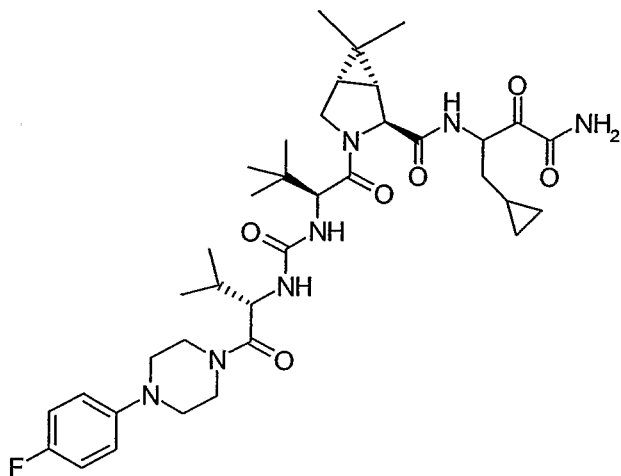
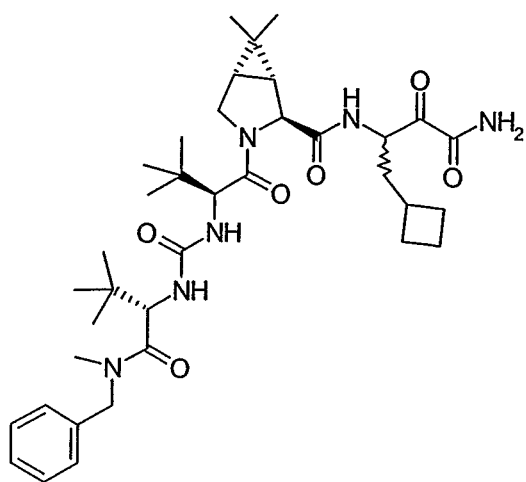
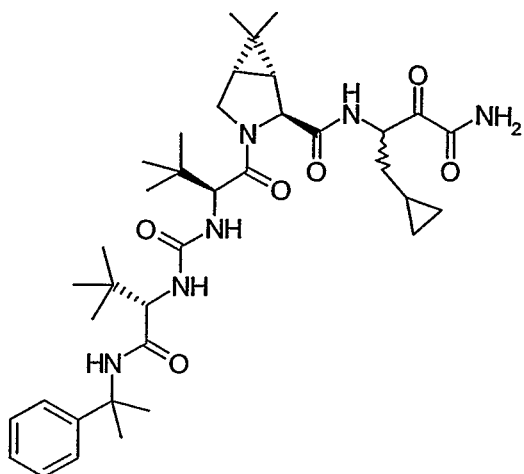


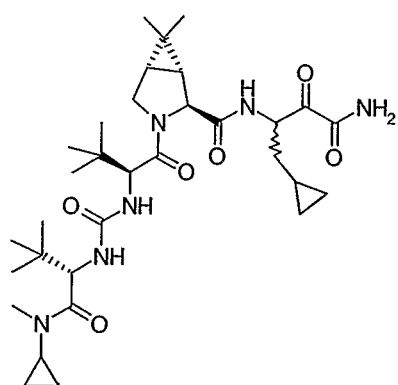
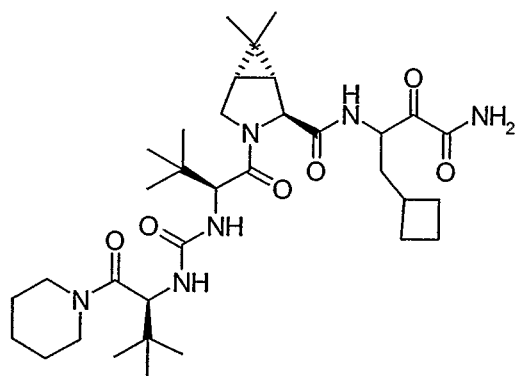
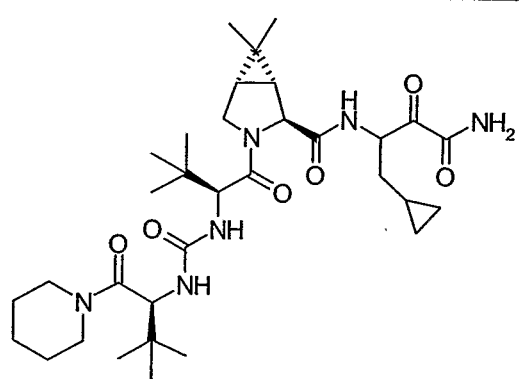
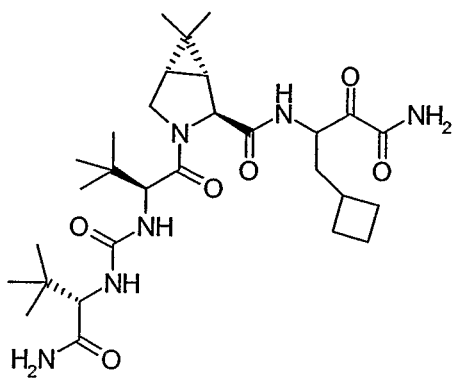
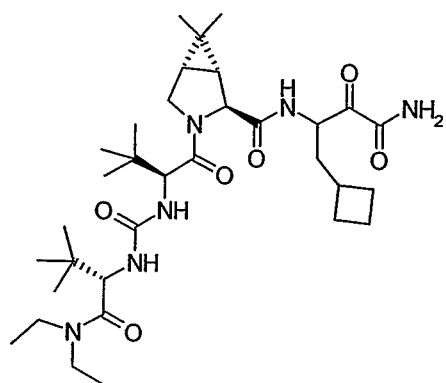
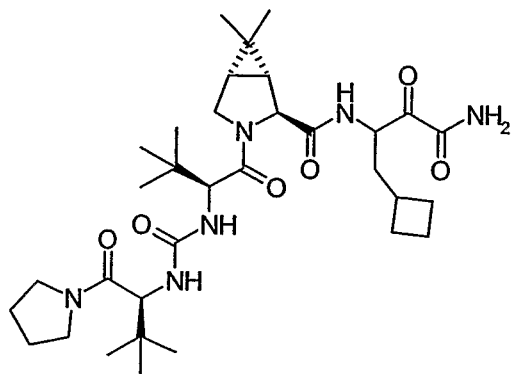


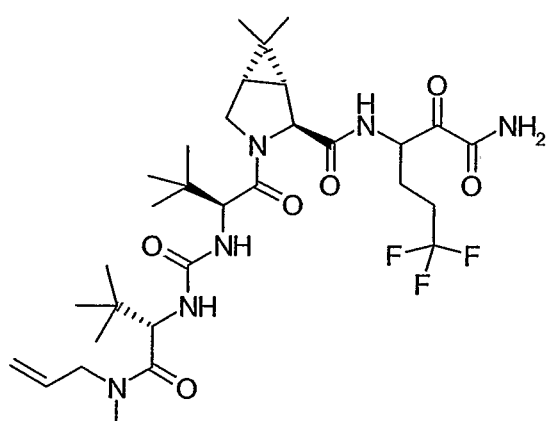
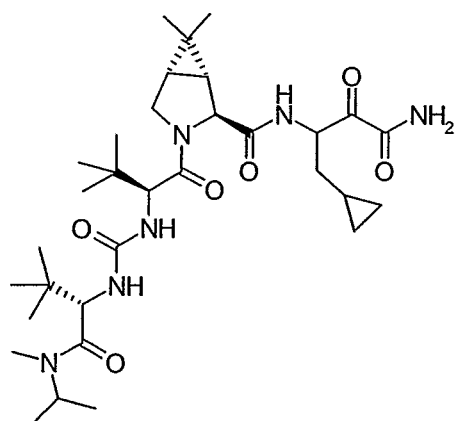
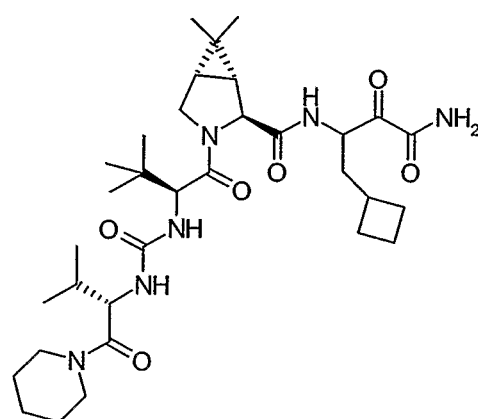
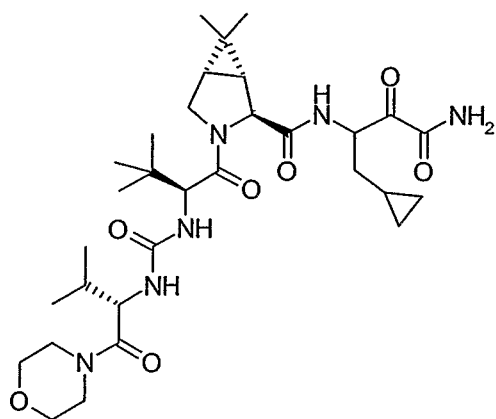
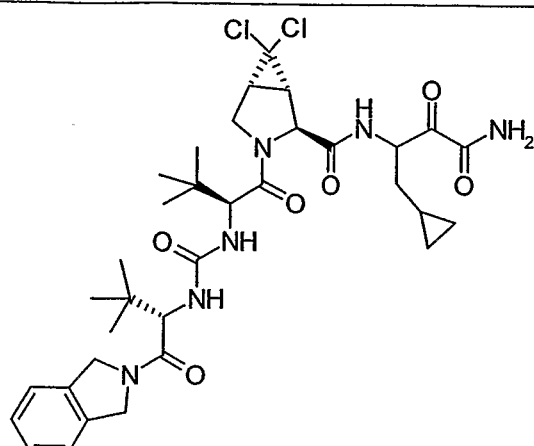
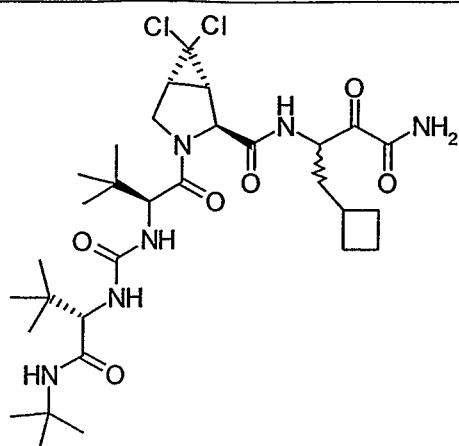


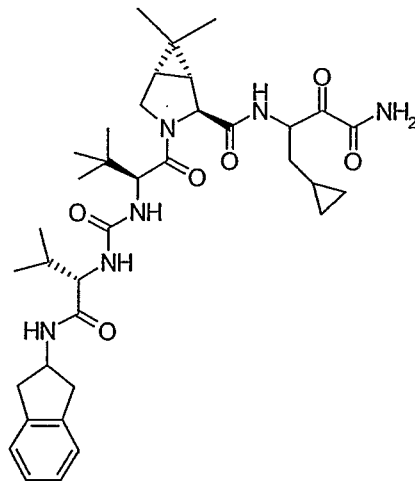
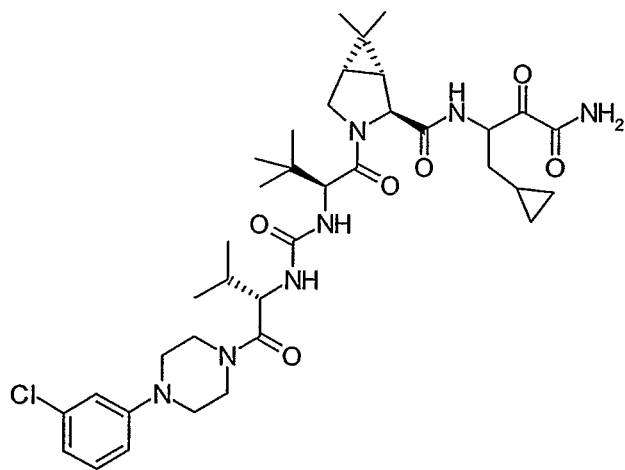
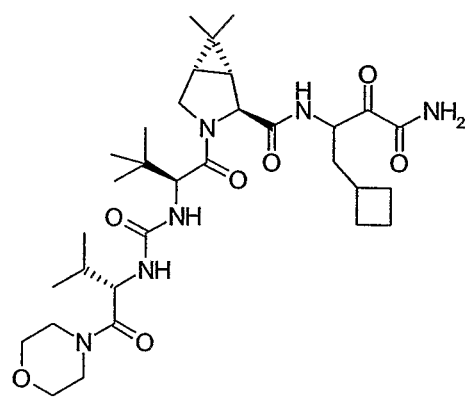
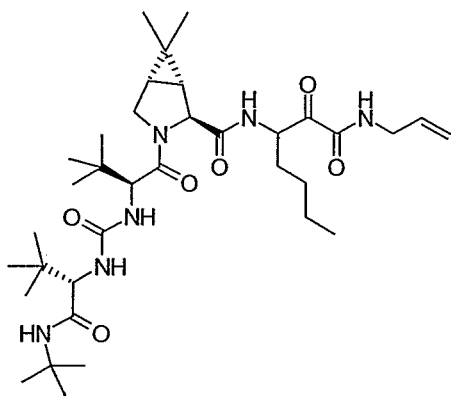
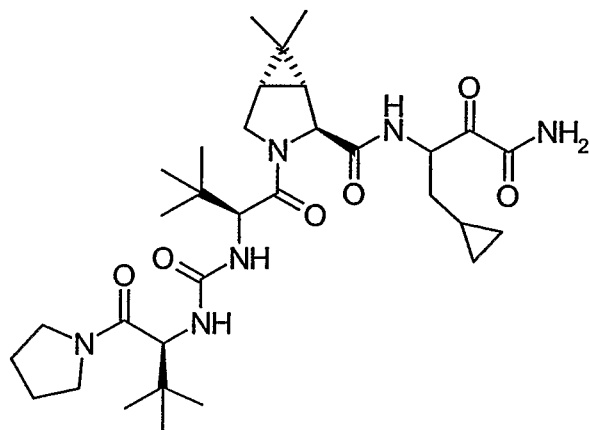
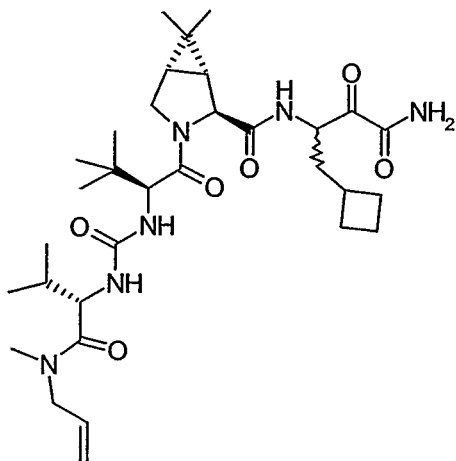


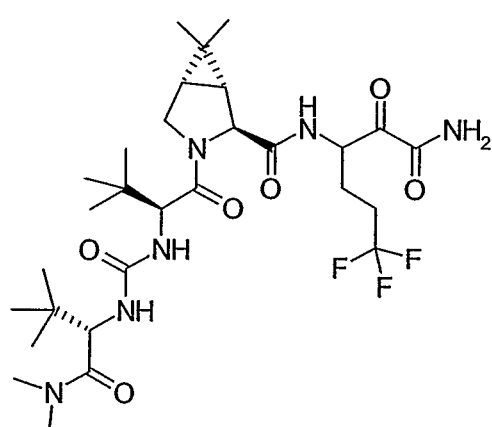
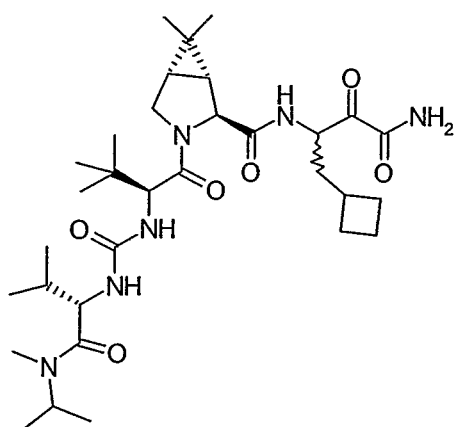
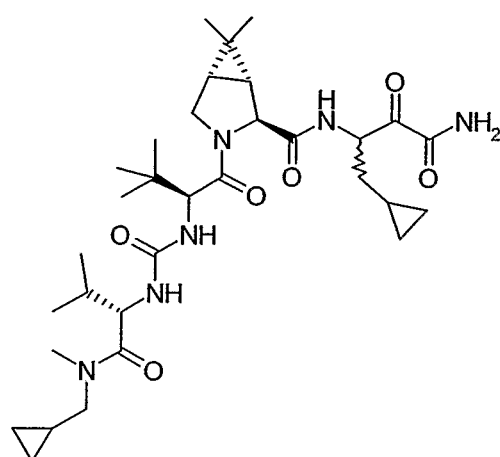
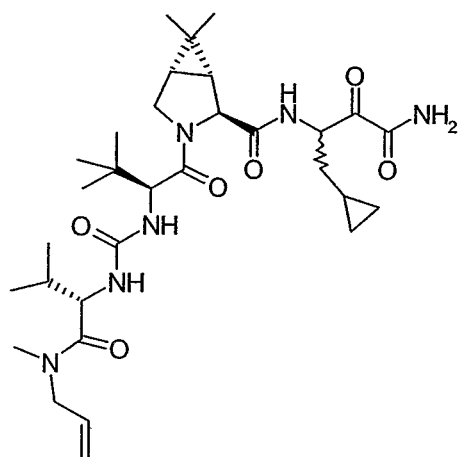
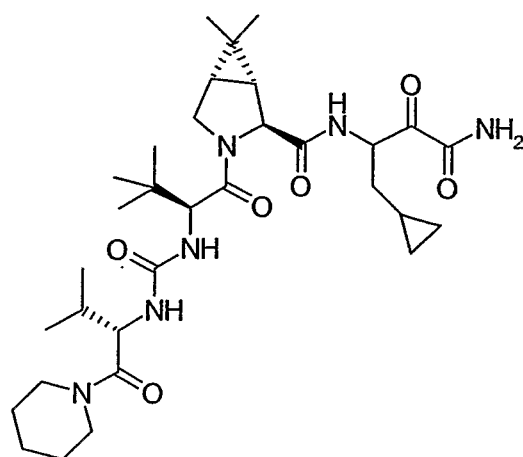
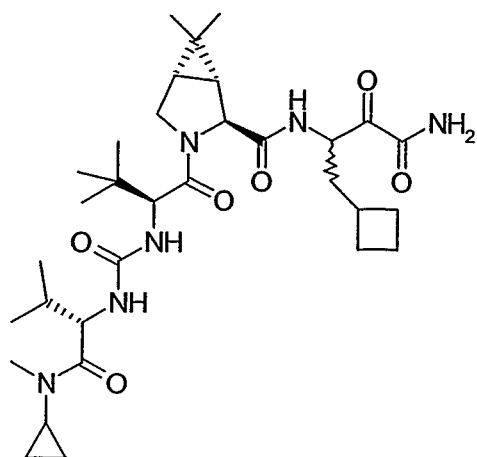


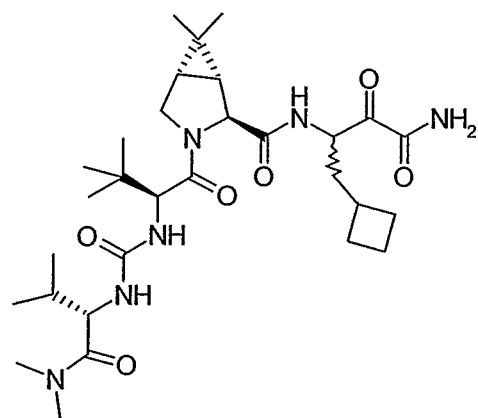
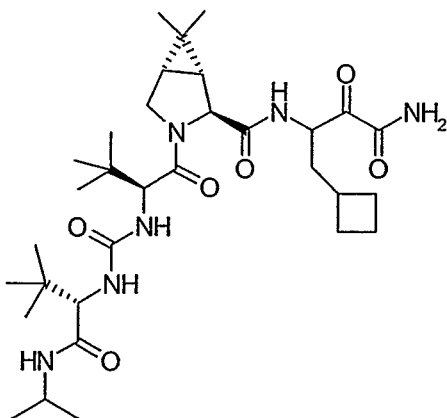
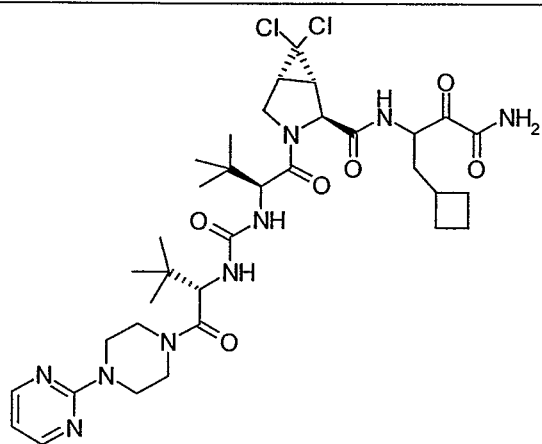
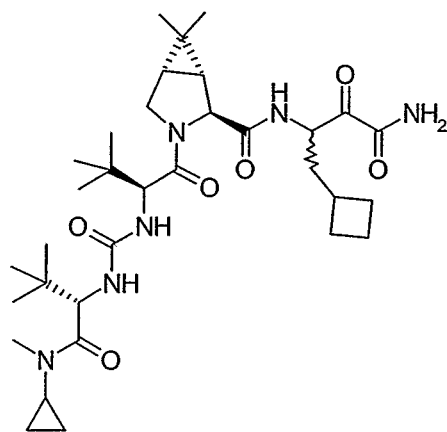
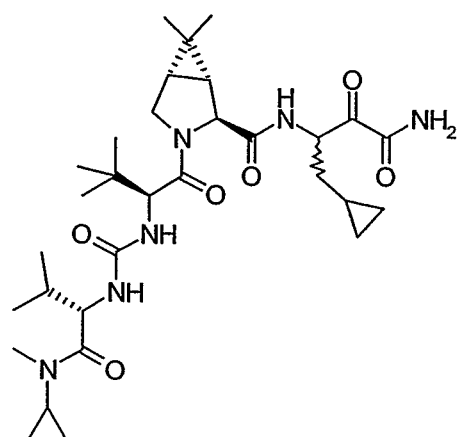
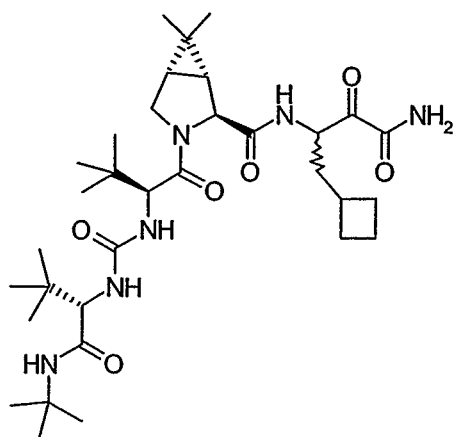


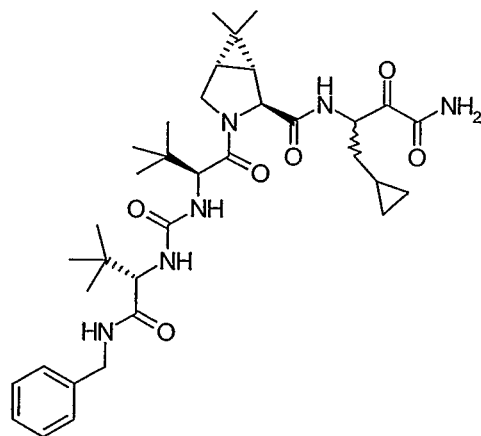
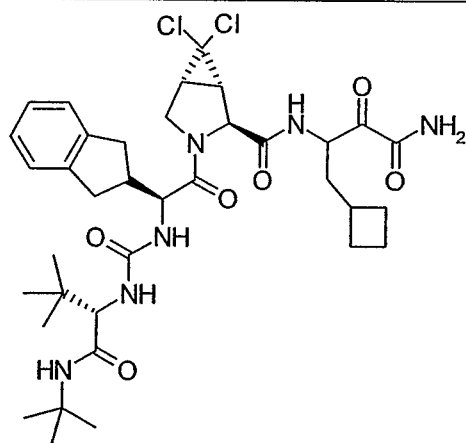
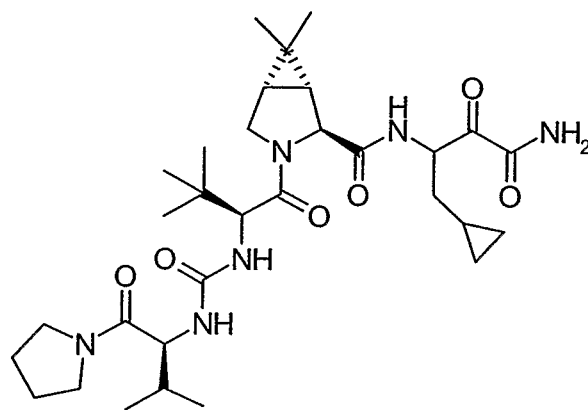
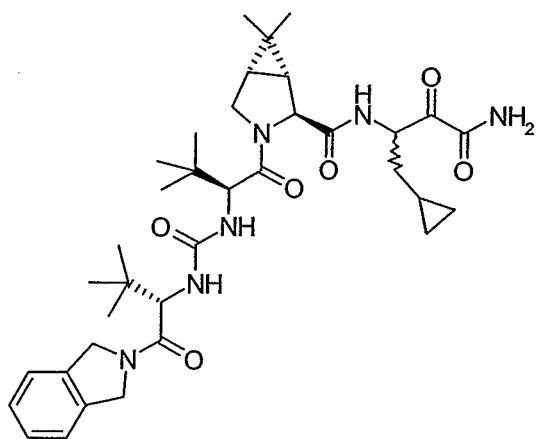
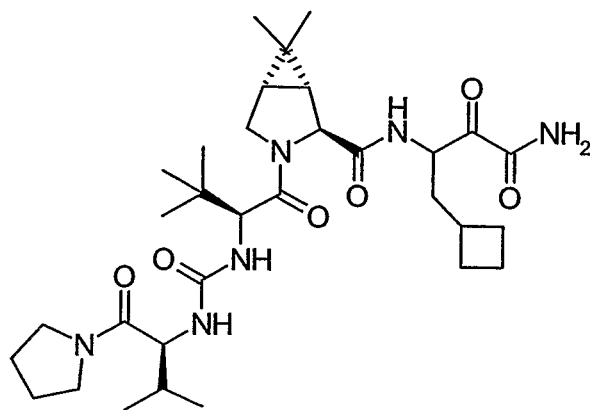
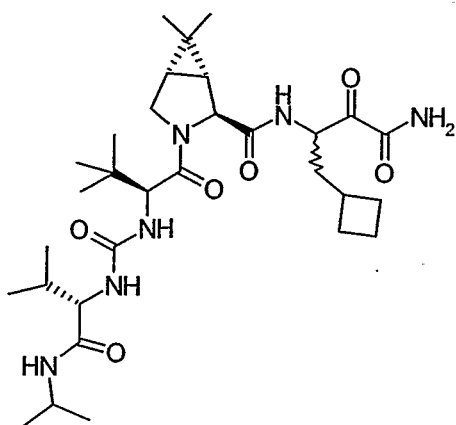


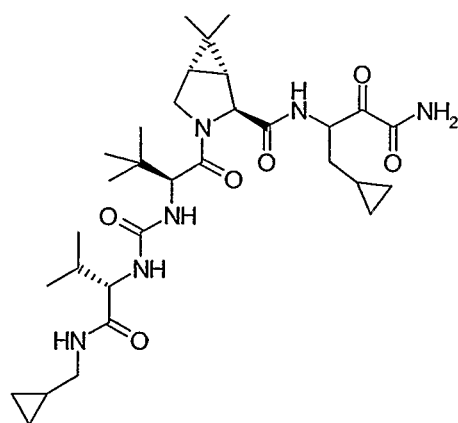
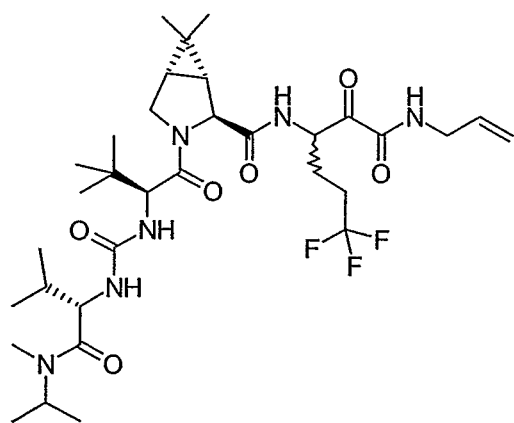
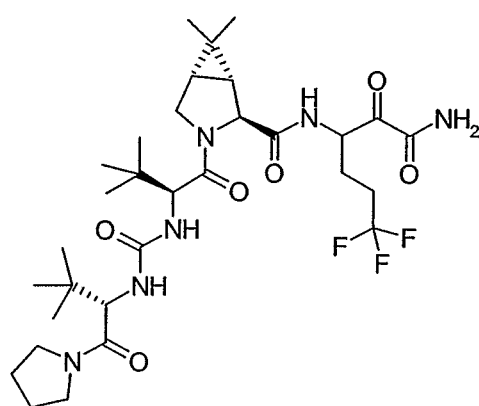
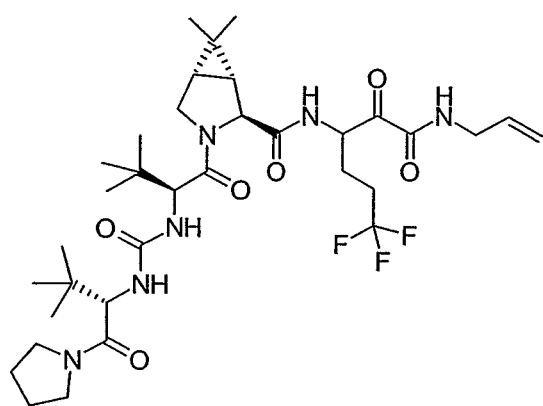
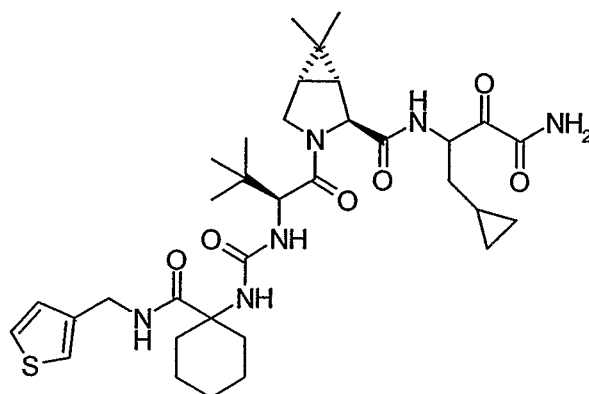
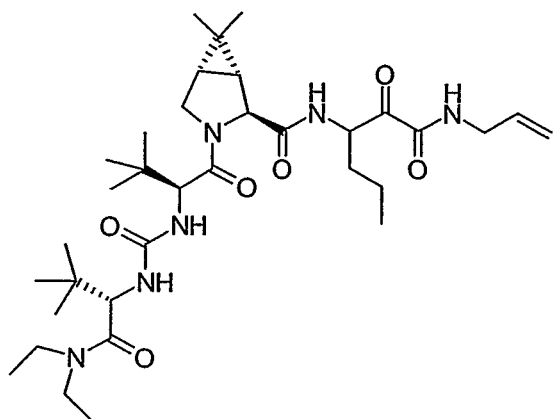


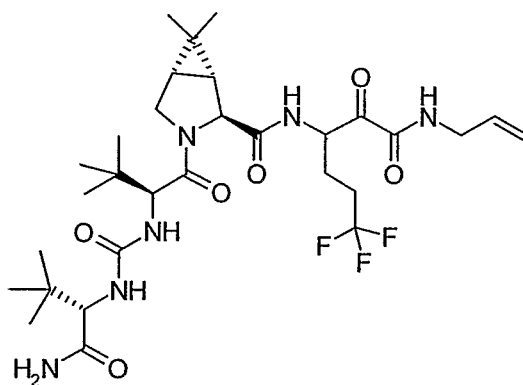
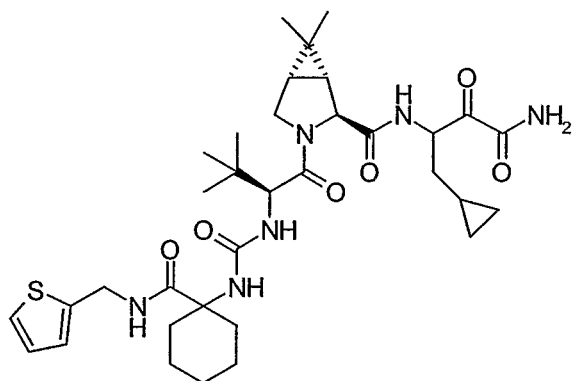
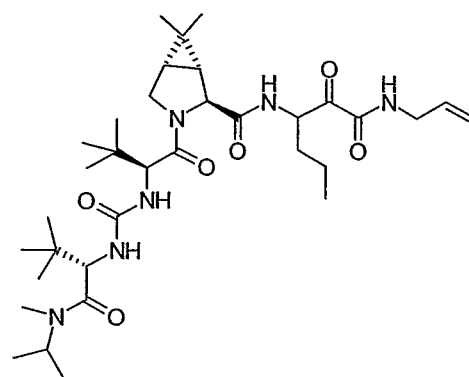
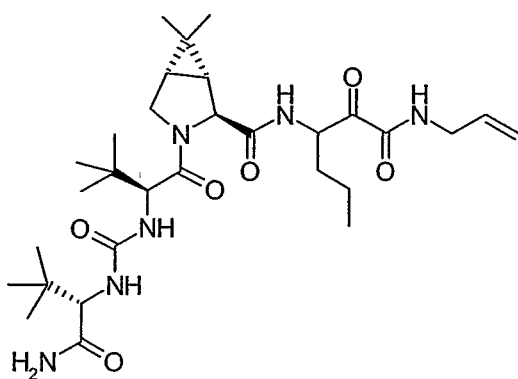
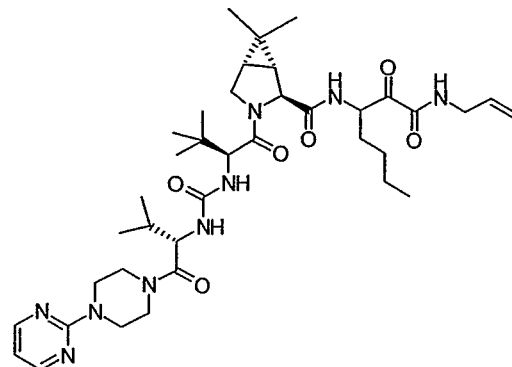
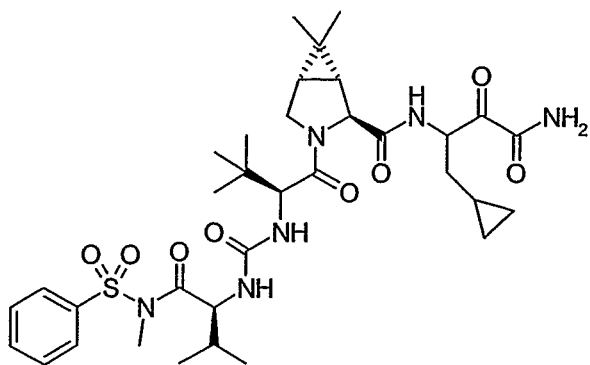


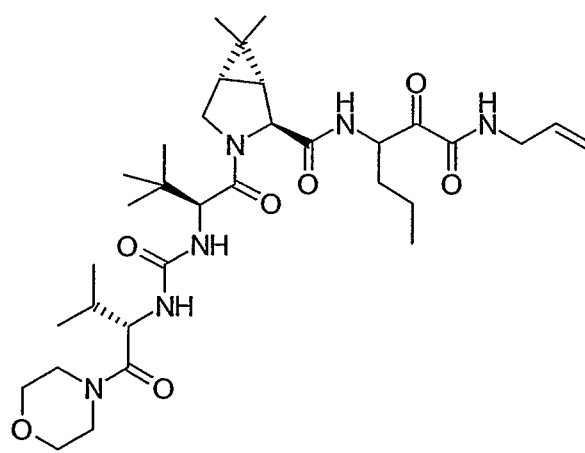
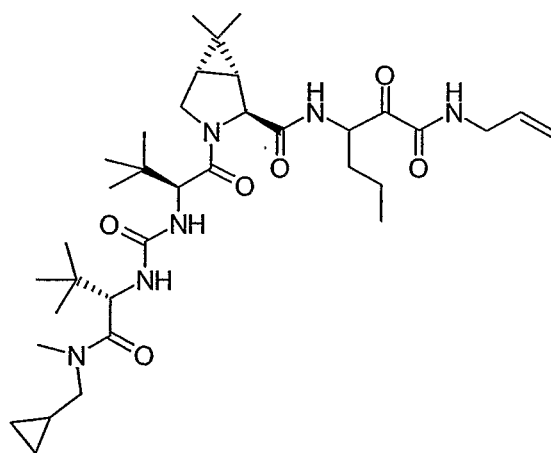
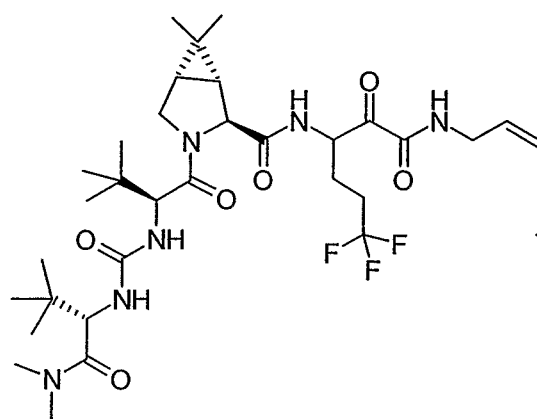
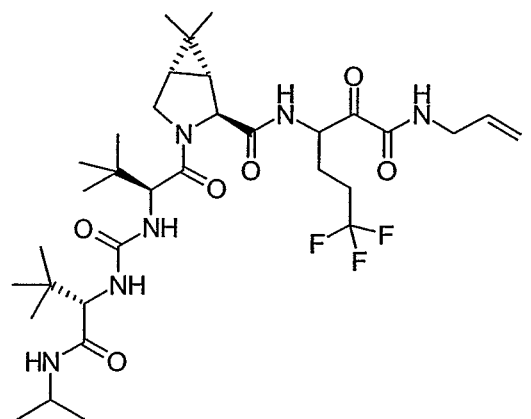
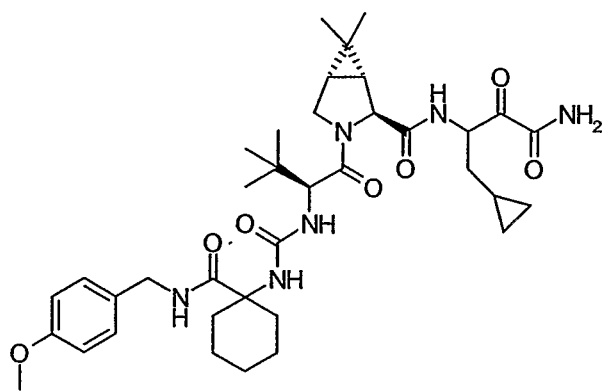
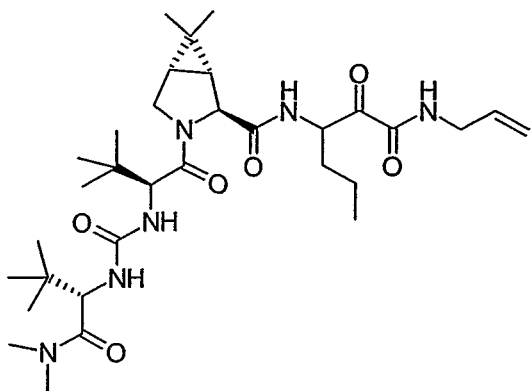


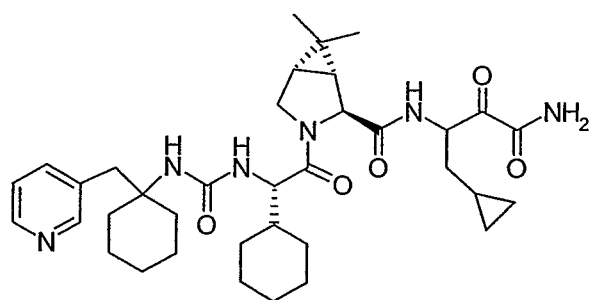
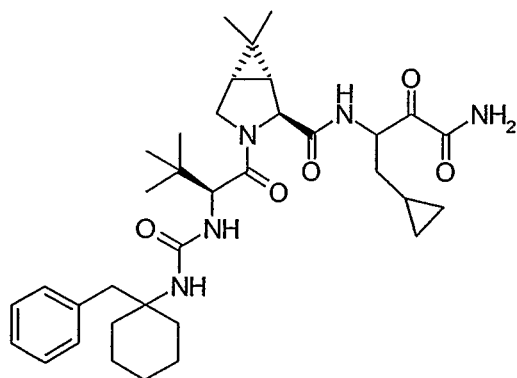
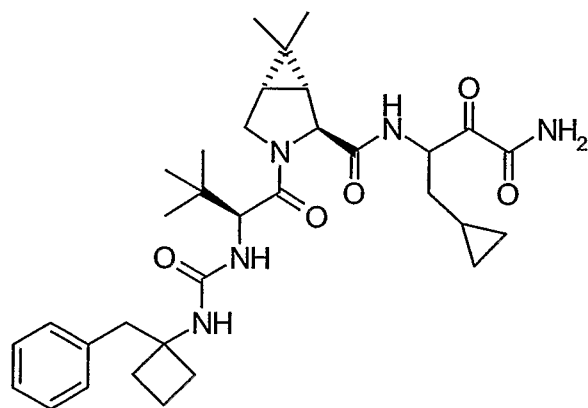
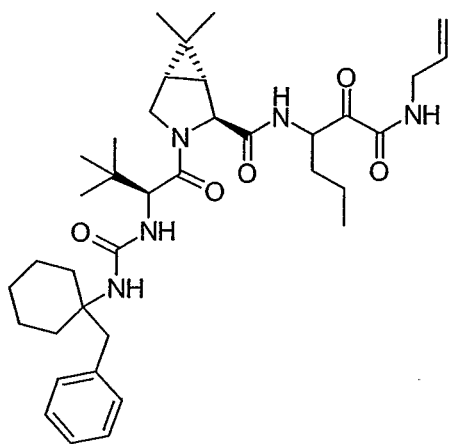
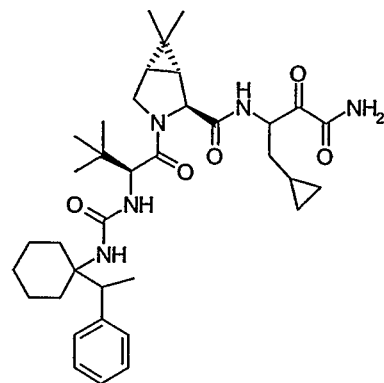
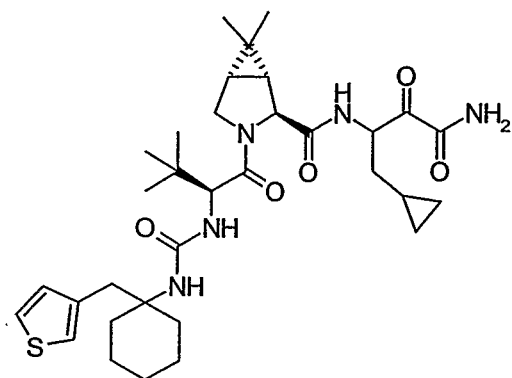


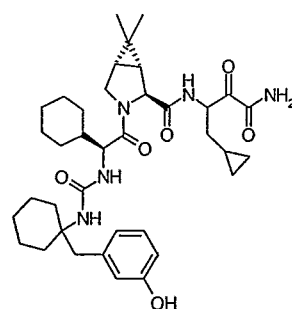
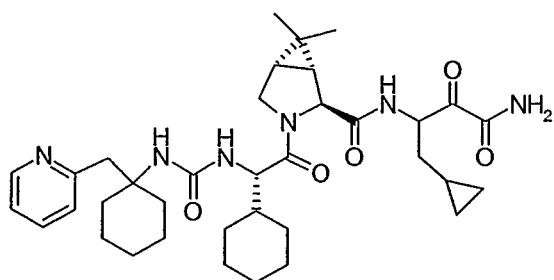
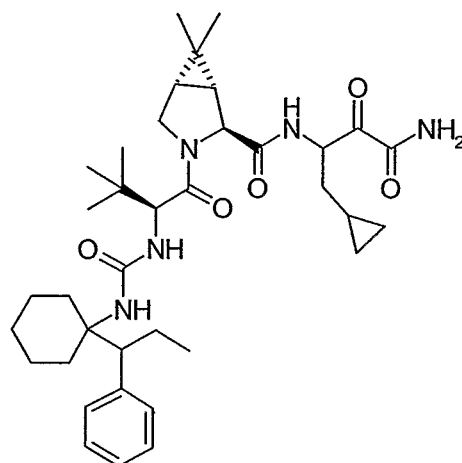
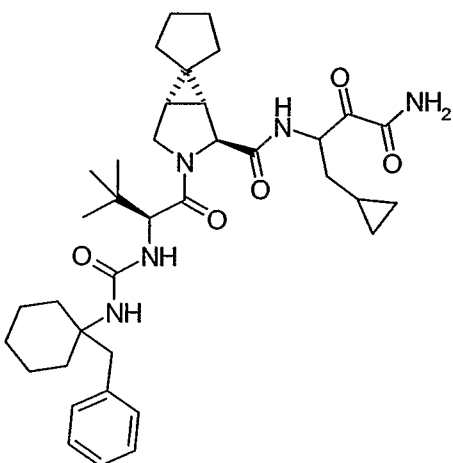
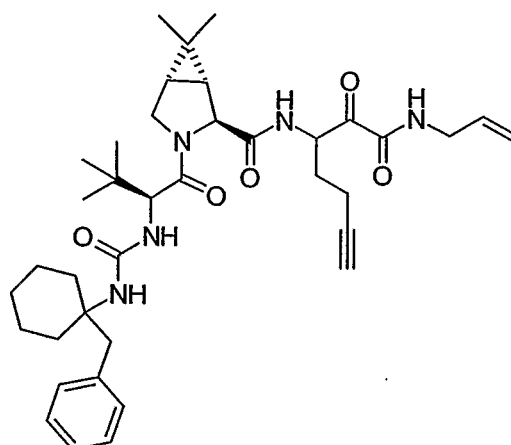
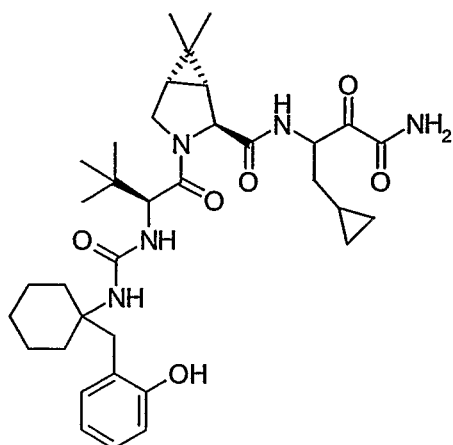


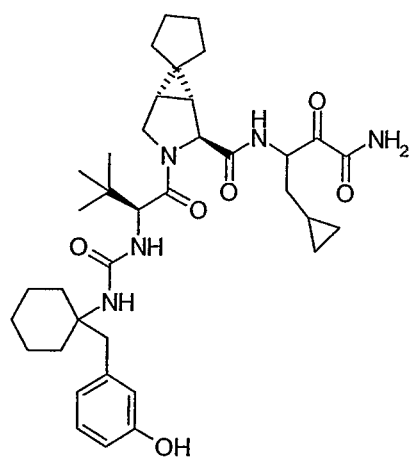
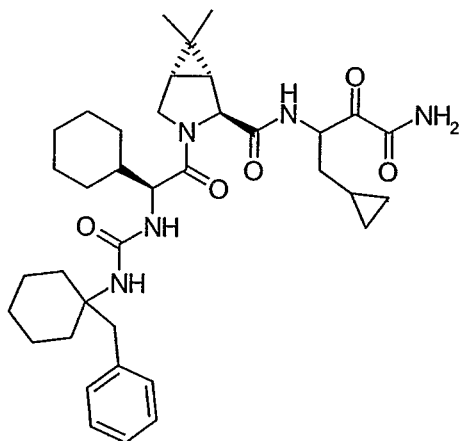
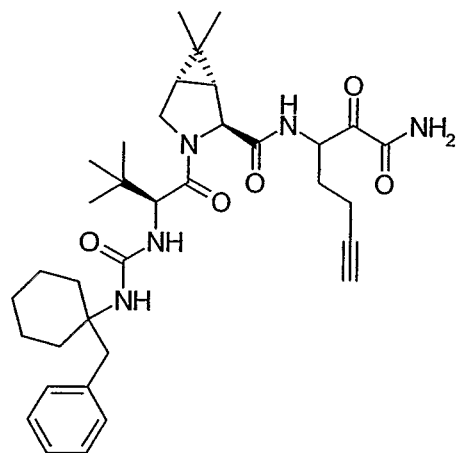
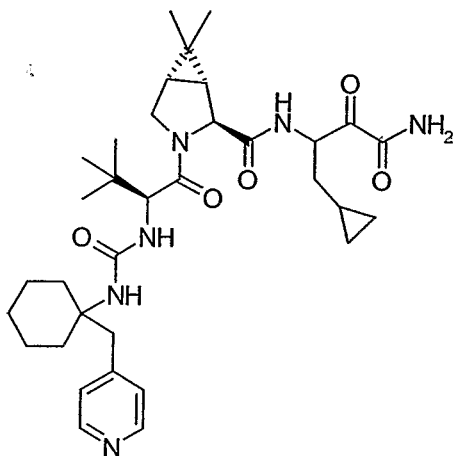
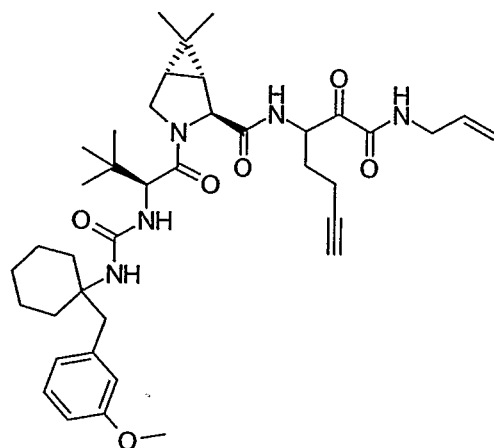
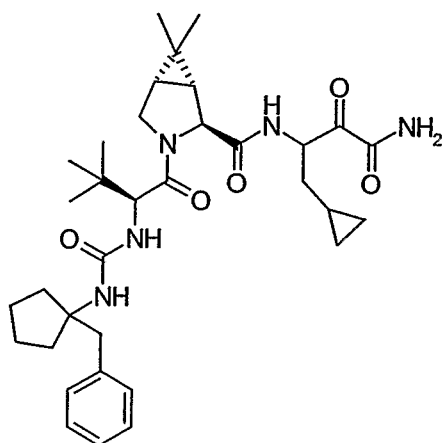


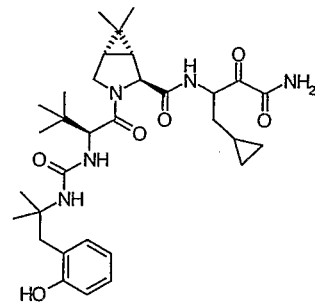
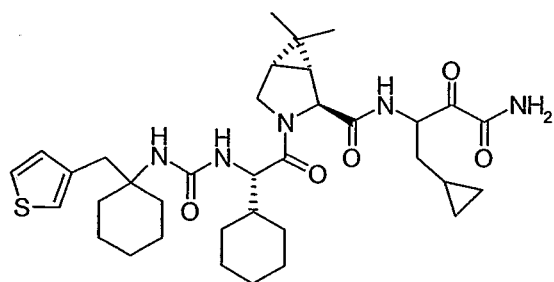
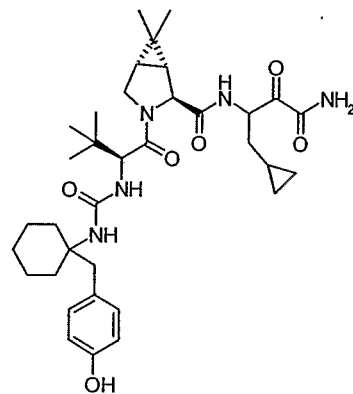
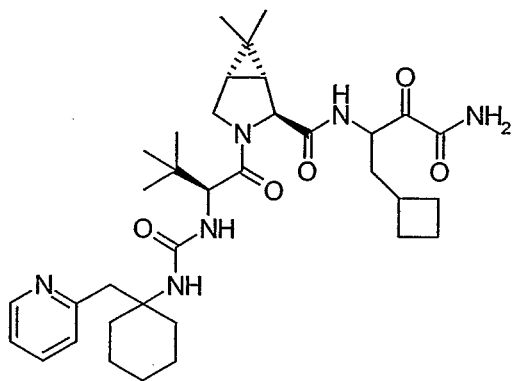
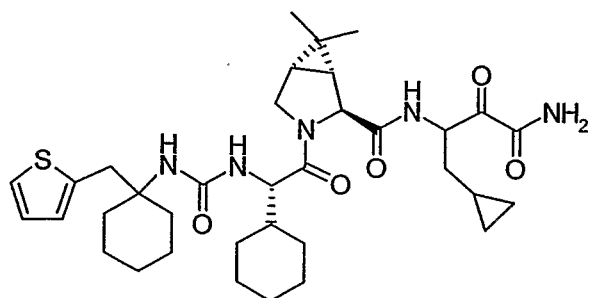
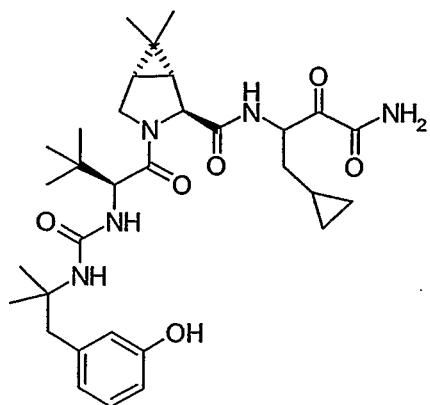


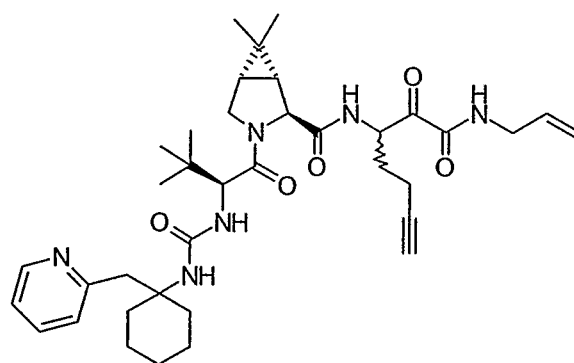
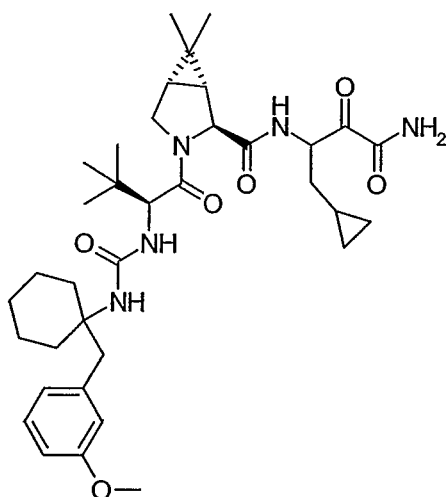
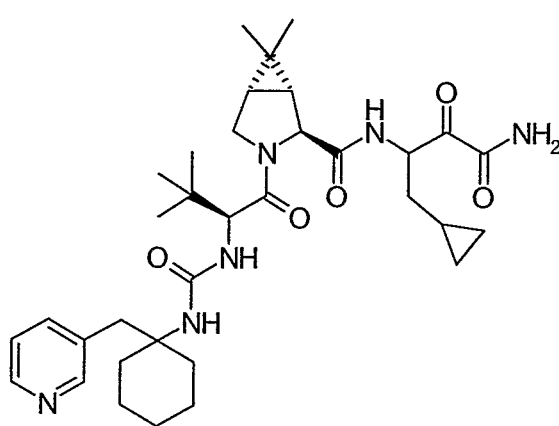
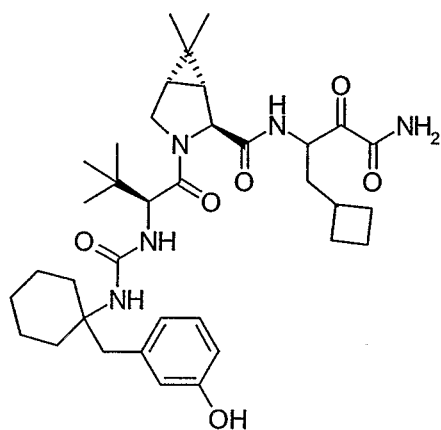
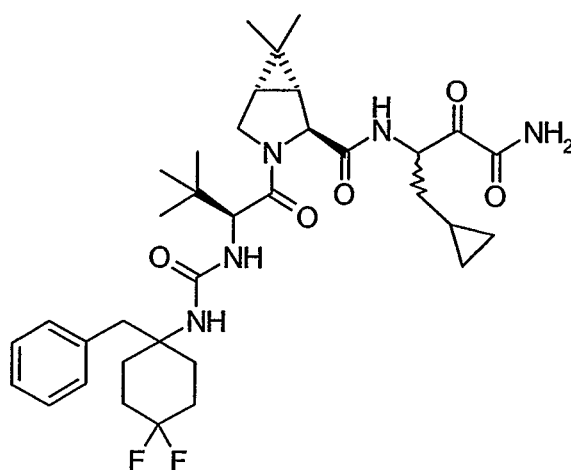
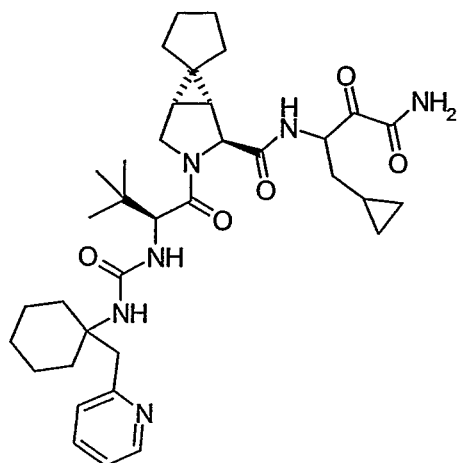


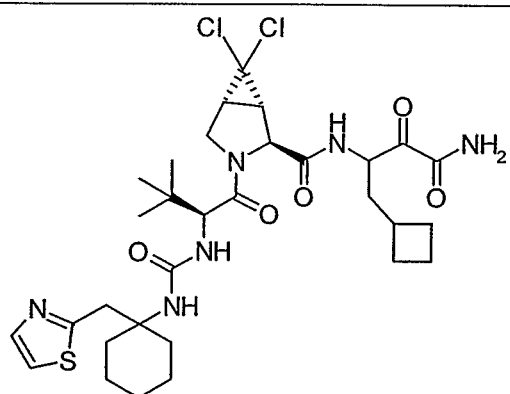
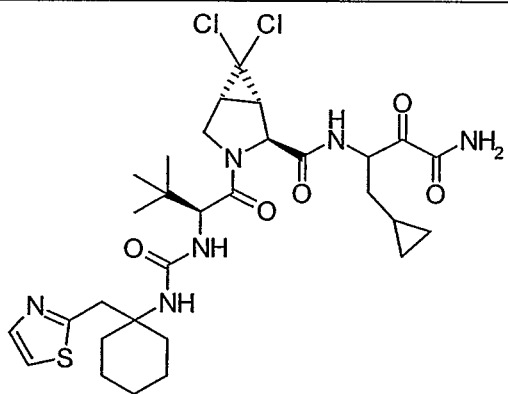
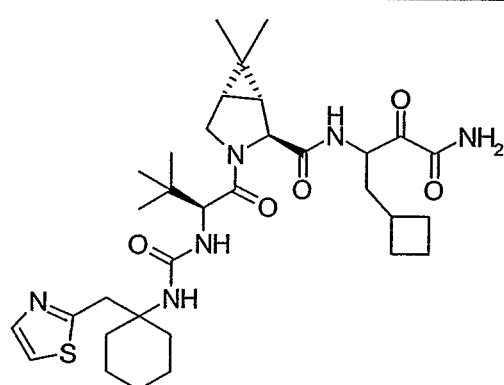
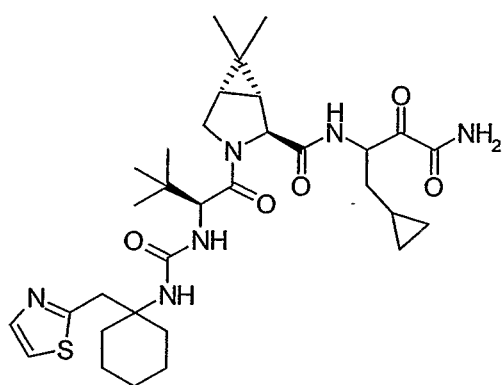


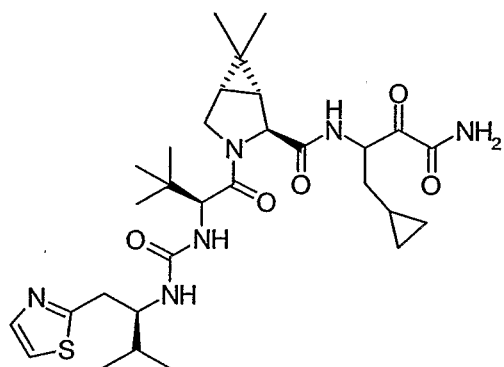
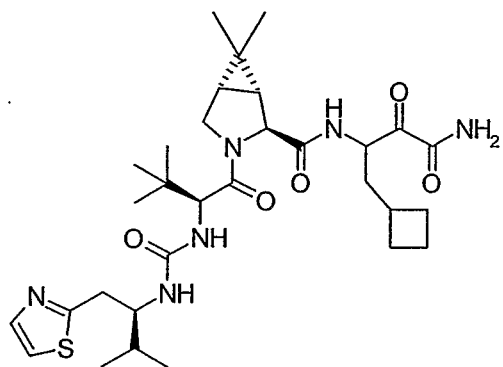
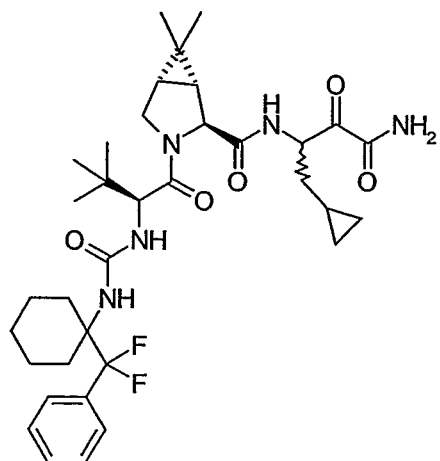


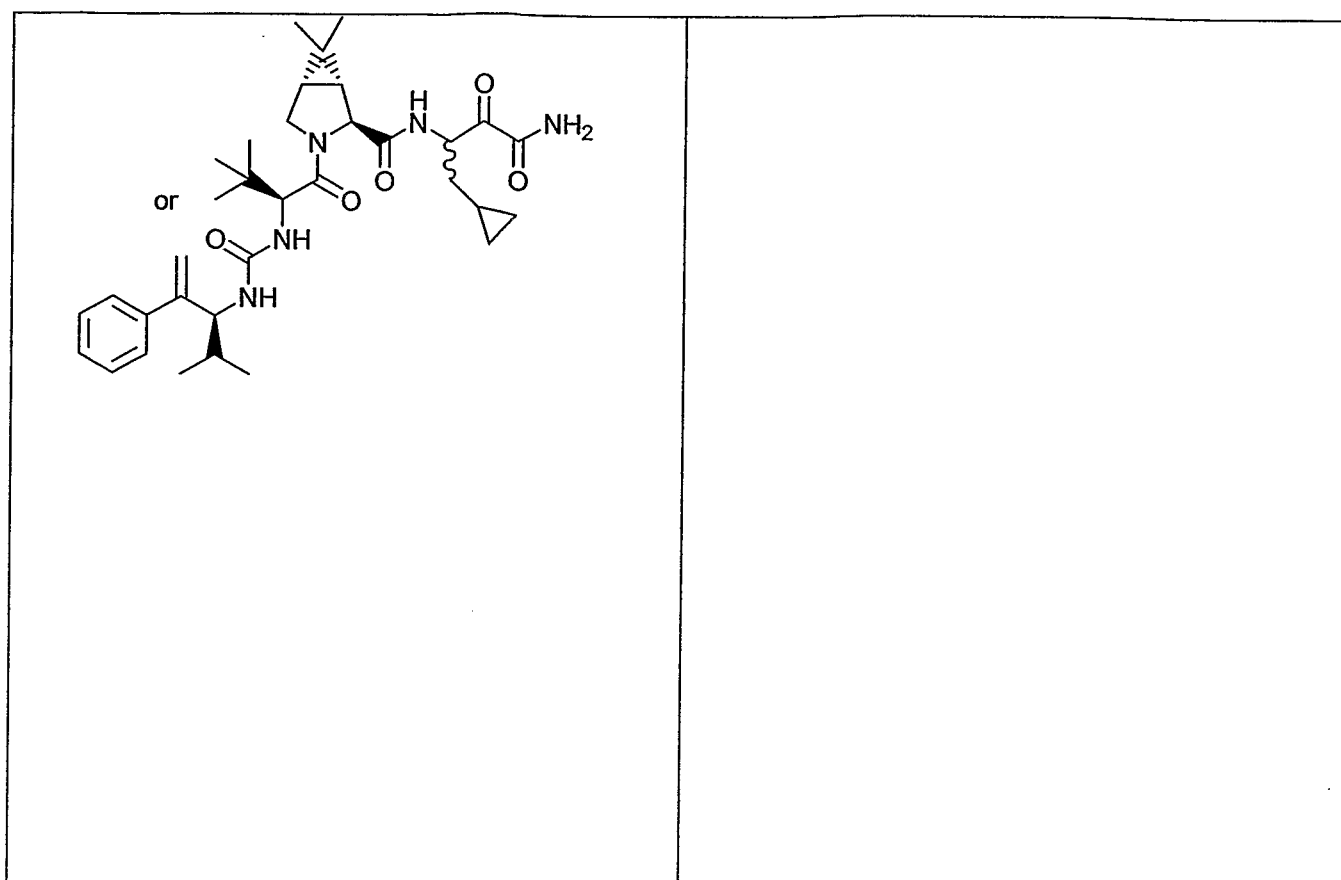












24. A pharmaceutical composition for treating disorders associated with the HCV, said composition comprising therapeutically effective amount of one or more compounds in claim 23 and a pharmaceutically acceptable carrier.

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

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

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

28. A method of treatment of a hepatitis C virus associated disorder, comprising administering an effective amount of one or more compounds of claim 23.

29. A method of modulating the activity of hepatitis C virus (HCV) protease, comprising contacting HCV protease with one or more compounds of claim 23.

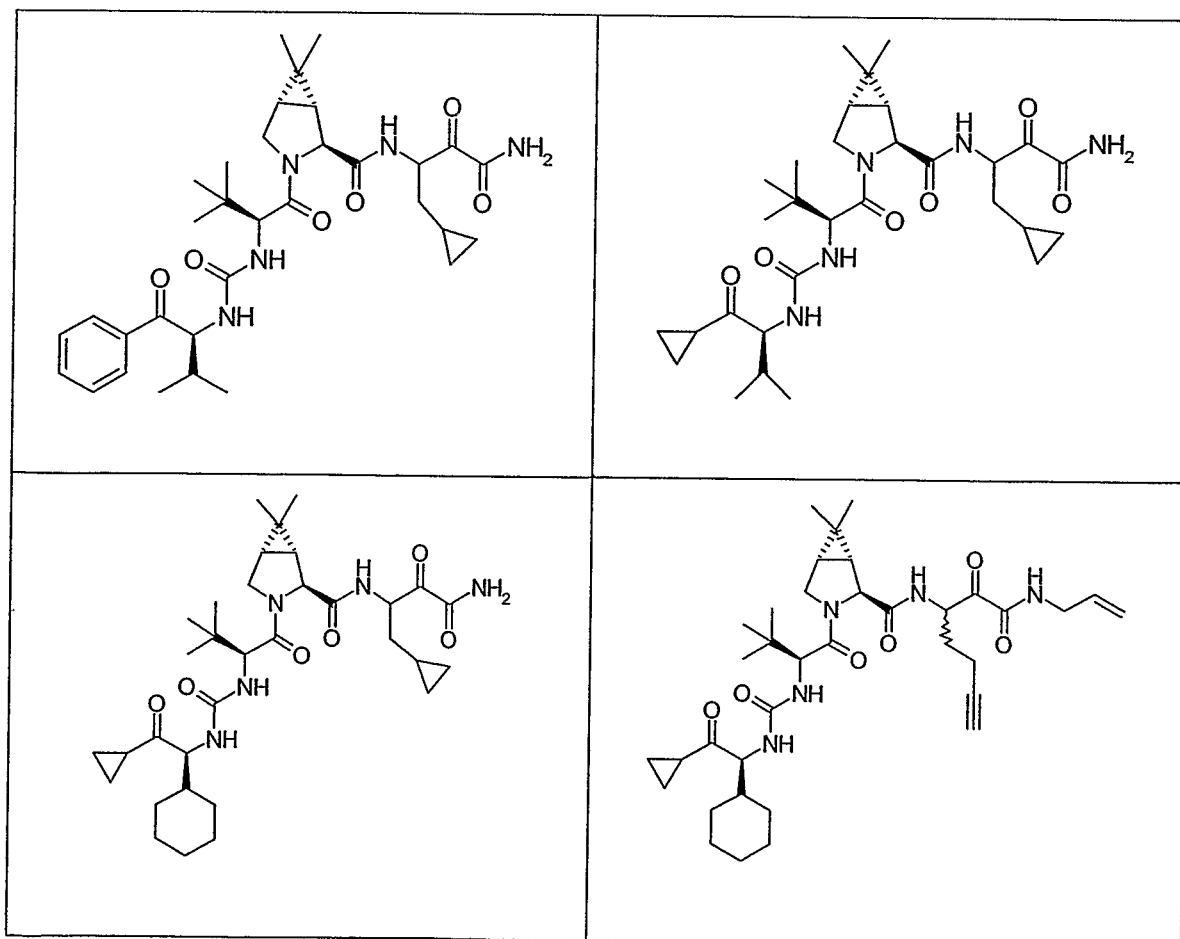
30. A method of treating, preventing, or ameliorating one or more symptoms of hepatitis C, comprising administering a therapeutically effective amount of one or more compounds of claim 23.

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

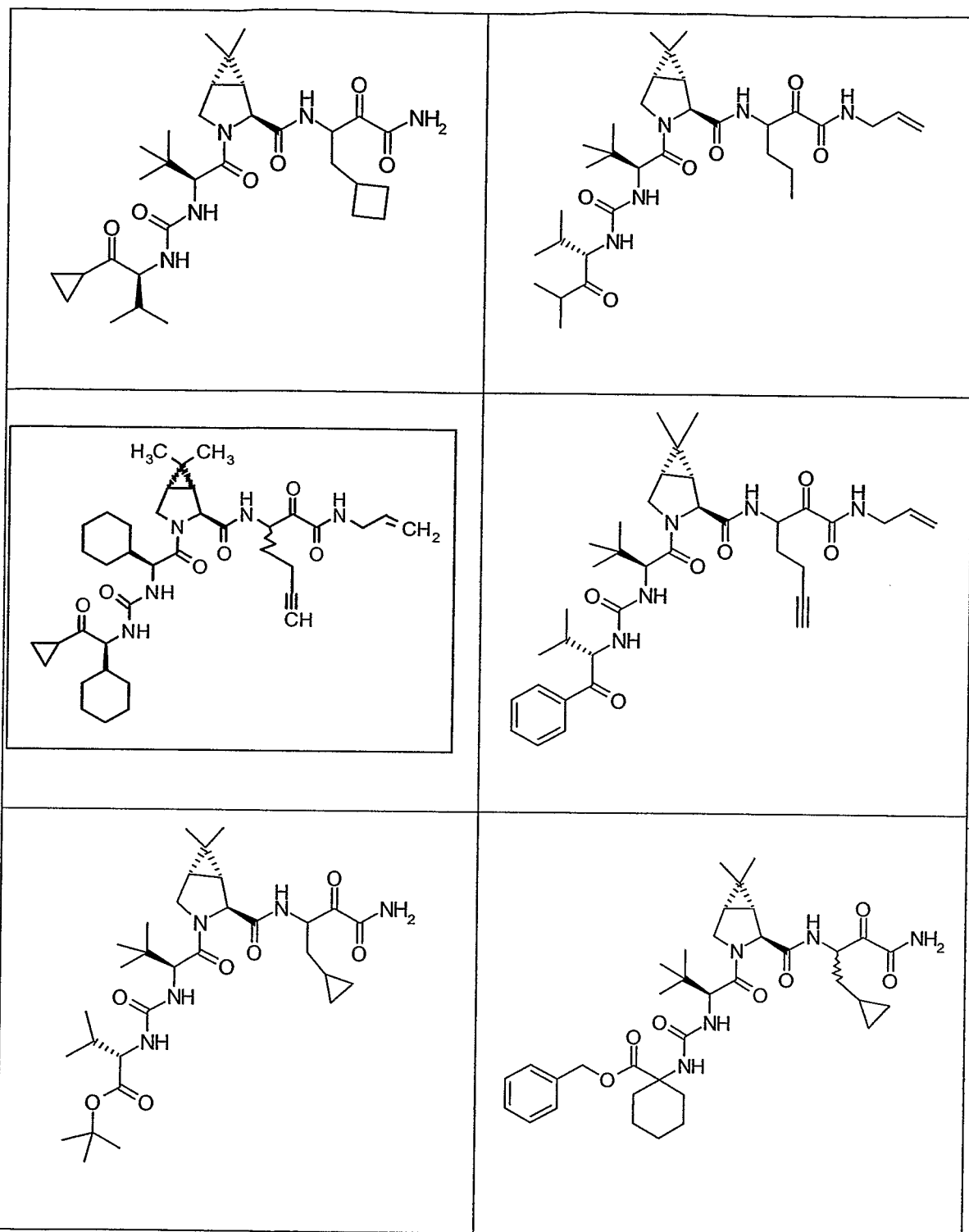
32. The method of claim 31, wherein the compound or compounds inhibit HCV NS3/NS4a protease.

33. 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 23.

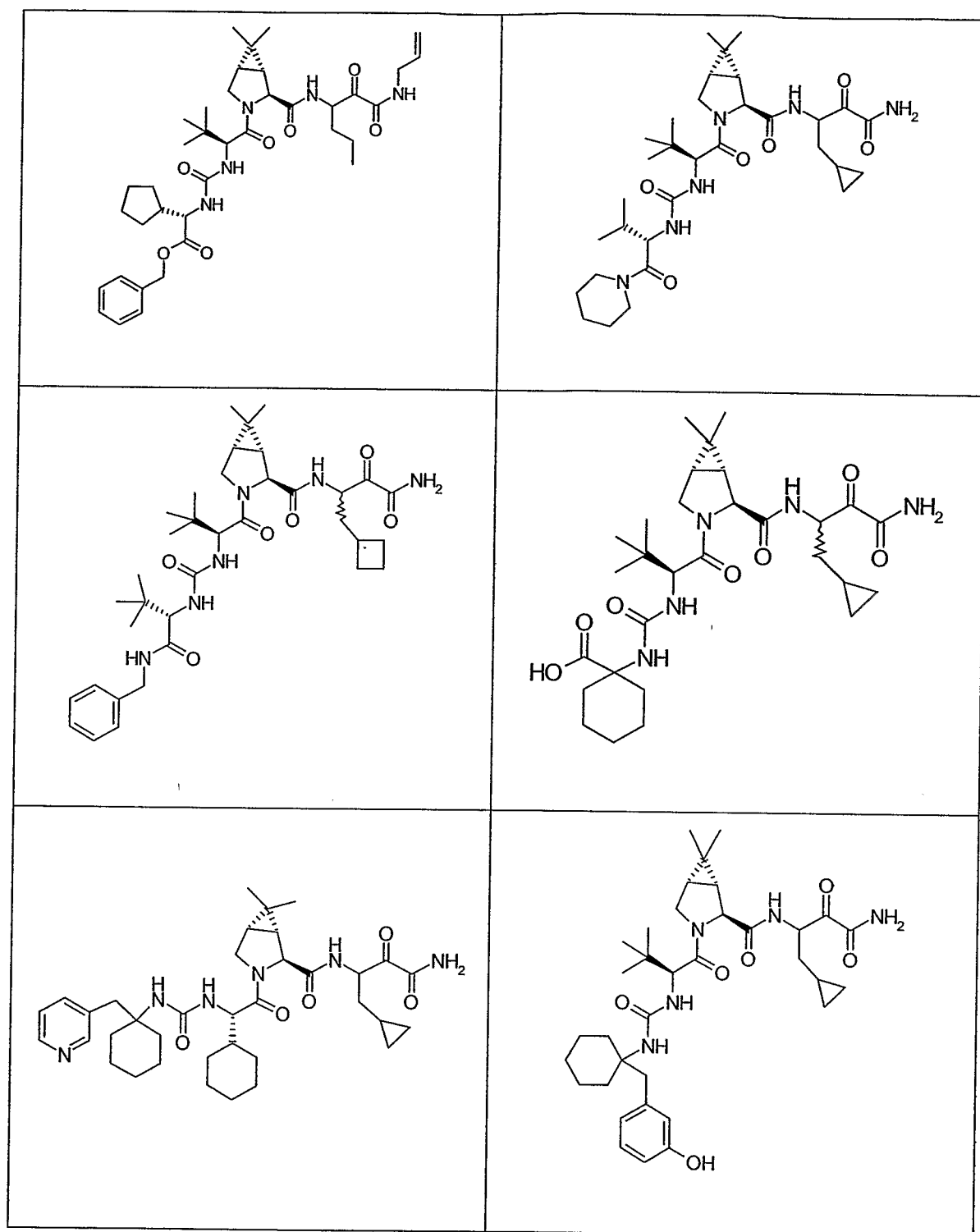
34. A method of treating disorders associated with the HCV, said method comprising administering to a patient in need of such treatment, a pharmaceutical composition which comprises therapeutically effective amounts of at least one compound, or enantiomers, stereoisomers, rotamers, tautomers, diastereomers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



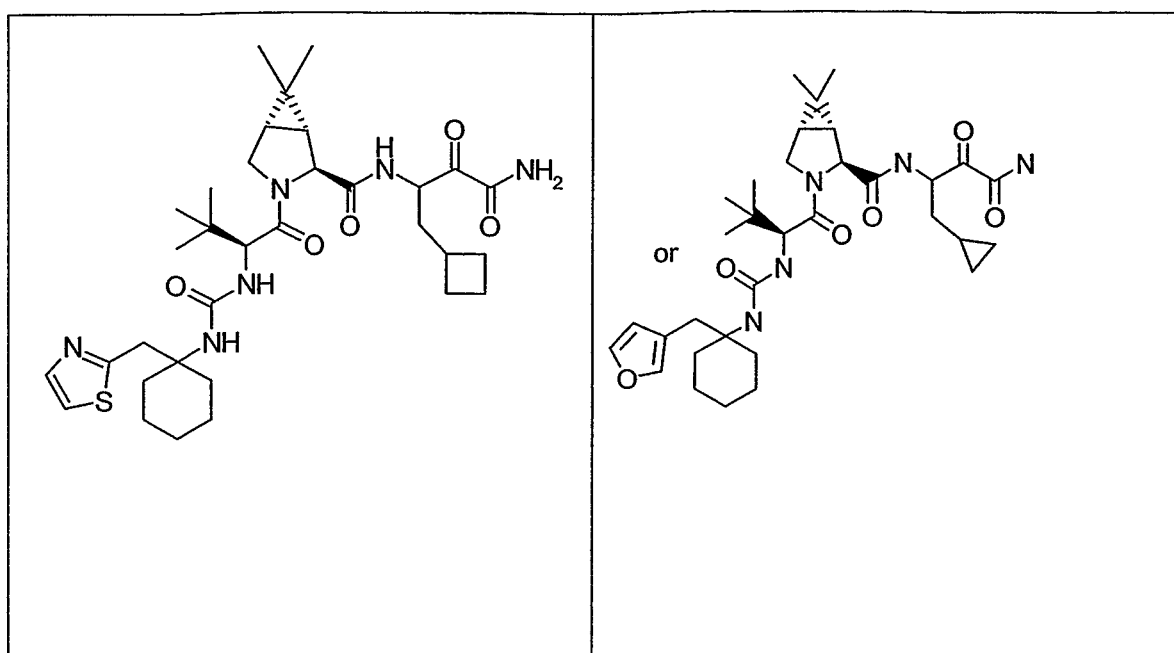
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35. A compound of claim 1 in purified form.