PHARMACEUTICAL FORMULATIONS AND METHODS OF TREATMENT USING THE SAME

Field of the Invention

The present invention relates to pharmaceutical formulations that are useful for treating a wide variety of diseases or disorders associated with hepatitis C virus ("HCV") by inhibiting HCV protease (for example HCV NS3/NS4a serine protease), and/or diseases or disorders associated with cathepsin activity and inhibiting cathepsin activity.

BACKGROUND OF THE INVENTION

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

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

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.

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.).

Pending and copending U. S. patent applications, Serial No. 60/194,607, filed April 5, 2000, and Serial No. 60/198,204, filed April 19, 2000, Serial No. 60/220,110, filed July 21, 2000, Serial No. 60/220,109, filed July 21, 2000, Serial No. 60/220,107, filed July 21, 2000, Serial No. 60/254,869, filed December 12, 2000, Serial No. 60/220,101, filed July 21, 2000, Serial No. 60/568,721 filed May 6, 2004, and WO 2003/062265, disclose various types of peptides and/or other compounds as NS-3 serine protease inhibitors of hepatitis C virus.

There is a need for new treatments and therapies for HCV infection to treat or prevent or ameliorate of one or more symptoms of hepatitis C, methods for modulating the activity of serine proteases, particularly the HCV NS3/NS4a serine protease, and methods of modulating the processing of the HCV polypeptide using the compounds provided herein.

Another aspect of the present invention is directed to inhibiting cathepsin activity. Cathepsins (Cats) belong to the papain superfamily of lysosomal cysteine proteases. Cathepsins are involved in the normal proteolysis and turnover of target

proteins and tissues as well as in initiating proteolytic cascades by proenzyme activation and in participating in MHC class II molecule expression. Baldwin (1993) Proc. Natl. Acad. Sci., 90: 6796-6800; Mixuochi (1994) Immunol. Lett., 43:189-193.

However, aberrant cathepsin expression has also been implicated in several serious human disease states. Cathepsins have been shown to be abundantly expressed in cancer cells, including breast, lung, prostate, glioblastoma and head/neck cancer cells, (Kos et al. (1998) Oncol. Rep., 5:1349-1361; Yan et al. (1998) Biol. Chem., 379:113-123; Mort et al. (1997) Int. J Biochem. Cell Biol., 29: 715-720; Friedrick et al. (1999) Eur. J Cancer, 35:138-144) and are associated with poor treatment outcome of patients with breast cancer, lung cancer, brain tumor and head/neck cancer. Kos et al, supra. Additionally, aberrant expression of cathepsin is evident in several inflammatory disease states, including rheumatoid arthritis and osteoarthritis. Keyszer (1995) Arthritis Rheum., 38:976-984.

The molecular mechanisms of cathepsin activity are not completely understood. Recently, it was shown that forced expression of cathepsin B rescued cells from serum deprivation-induced apoptotic death (Shibata et al. (1998) Biochem. Biophys. Res. Commun., 251: 199-203) and that treatment of cells with antisense oligonucleotides of cathepsin B induced apoptosis. Isahara et at. (1999) Neuroscience, 91:233-249. These reports suggest an anti-apoptotic role for the cathepsins that is contrary to earlier reports that cathepsins are mediators of apoptosis. Roberts et al (1997) Gastroenterology, 113: 1714-1726; Jones et al. (1998) Am. J Physiol., 275: G723-730.

Cathepsin K is a member of the family of enzymes which are part of the papain superfamily of cysteine proteases. Cathepsins B, H, L, N and S have been described in the literature. Recently, cathepsin K polypeptide and the cDNA encoding such polypeptide were disclosed in U.S. Pat. No. 5, 501,969 (called cathepsin O therein). Cathepsin K has been recently expressed, purified, and characterized. Bossard, M. J., et al., (1996) *J Biol. Chem* . 271, 12517-12524; Drake, F. H., et al., (1996) *J. Biol. Chem* . 271, 12511-12516; Bromme, D., et al., (1996) *J. Biol. Chem* . 271, 2126-2132.

Cathepsin K has been variously denoted as cathepsin O, cathepsin X or cathepsin O2 in the literature. The designation cathepsin K is considered to be the more appropriate one (name assigned by Nomenclature Committee of the International Union of Biochemistry and Molecular Biology).

Cathepsins of the papain superfamily of cysteine proteases function in the normal physiological process of protein degradation in animals, including humans, e.g., in the degradation of connective tissue. However, elevated levels of these enzymes in the body can result in pathological conditions leading to disease. Thus, cathepsins have been implicated in various disease states, including but not limited to, infections by pneumocystis carinii, trypsanoma cruzi, trypsanoma brucei brucei, and Crithidia fusiculata; as well as in schistosomiasis malaria, tumor metastasis, metachromatic leukodystrophy, muscular dystrophy, amytrophy, and the like. See International Publication Number WO 94/04172, published on Mar. 3, 1994, and references cited therein. See also European Patent Application EP 0 603 873 A1, and references cited therein. Two bacterial cysteine proteases from *P. gingivallis* , called gingipains, have been implicated in the pathogenesis of gingivitis. Potempa, J., et al. (1994) *Perspectives in Drug Discovery and Design* , 2, 445-458.

Cathepsin K is believed to play a causative role in diseases of excessive bone or cartilage loss. Bone is composed of a protein matrix in which spindle- or plate-shaped crystals of hydroxyapatite are incorporated. Type I Collagen represents the major structural protein of bone comprising approximately 90% of the structural protein. The remaining 10% of matrix is composed of a number of non-collagenous proteins, including osteocalcin, proteoglycans, osteopontin, osteonectin, thrombospondin, fibronectin, and bone sialoprotein. Skeletal bone undergoes remodeling at discrete foci throughout life. These foci, or remodeling units, undergo a cycle consisting of a bone resorption phase followed by a phase of bone replacement. Bone resorption is carried out by osteoclasts, which are multinuclear cells of hematopoietic lineage. In several disease states, such as osteoporosis and Paget's disease, the normal balance between bone resorption and formation is disrupted, and there is a net loss of bone at each cycle. Ultimately, this leads to weakening of the bone and may result in increased fracture risk with minimal trauma.

The abundant selective expression of cathepsin K in osteoclasts strongly suggests that this enzyme is essential for bone resorption. Thus, selective inhibition of cathepsin K may provide an effective treatment for diseases of excessive bone loss, including, but not limited to, osteoporosis, gingival diseases such as gingivitis and periodontitis, Paget's disease, hypercalcemia of malignancy, and metabolic bone disease. Cathepsin K levels have also been demonstrated to be elevated in chondroclasts of osteoarthritic synovium. Thus, selective inhibition of cathepsin K may also be useful for treating diseases of excessive cartilage or matrix degradation, including, but not limited to, osteoarthritis and rheumatoid arthritis. Metastatic neoplastic cells also typically express high levels of proteolytic enzymes that degrade the surrounding matrix. Thus, selective inhibition of cathepsin K may also be useful for treating certain neoplastic diseases.

There are reports in the literature of the expression of Cathepsin B and L antigen and that activity is associated with early colorectal cancer progression. Troy et al., (2004) Eur J Cancer, 40(10):1610-6. The findings suggest that cysteine proteases play an important role in colorectal cancer progression.

Cathepsin L has been shown to be an important protein mediating the malignancy of gliomas and it has been suggested that its inhibition may diminish their invasion and lead to increased tumor cell apoptosis by reducing apoptotic threshold. Levicar et al., (2003) Cancer Gene Ther., 10(2): 141-51.

Katunama et al., (2002) Arch Biochem Biophys., 397(2):305-11 reports on antihypercalcemic and antimetastatic effects of CLIK-148 in vivo, which is a specific inhibitor of cathepsin L. This reference also reports that CLIK-148 treatment reduced distant bone metastasis to the femur and tibia of melanoma A375 tumors implanted into the left ventricle of the heart.

Rousselet et al., (2004) Cancer Res., 64(1): 146-51 reports that anti-cathepsin L single chain variable fragment (ScFv) could be used to inhibit the tumorigenic and metastatic phenotype of human melanoma, depending on procathepsin L secretion, and the possible use of anti-cathepsin L ScFv as a molecular tool in a therapeutic cellular approach.

Colella et al., (2003) Biotech Histochem., 78(2):101-8 reports that the cysteine proteinases cathepsin L and B participate in the invasive ability of the PC3 prostrate cancer cell line, and the potential of using cystein protease inhibitiors such as cystatins as anti-metastatic agents.

Krueger et al., (2001) Cancer Gene Ther., 8(7):522-8 reports that in human osteosarcoma cell line MNNG/HOS, cathepsin L influences cellular malignancy by promoting migration and basement membrane degradation..

Frohlich et al., (2204) Arch Dermatol Res., 295(10):411-21 reports that cathepsins B and L are involved in invasion of basal cell carcinoma (BCC) cells.

U.S. Provisional Patent Application Serial No. Not Yet Assigned, entitled "Compounds for Inhibiting Cathepsin Activity", filed April 20, 2005, discloses various types of peptides and/or other compounds as inhibitors of cathepsin.

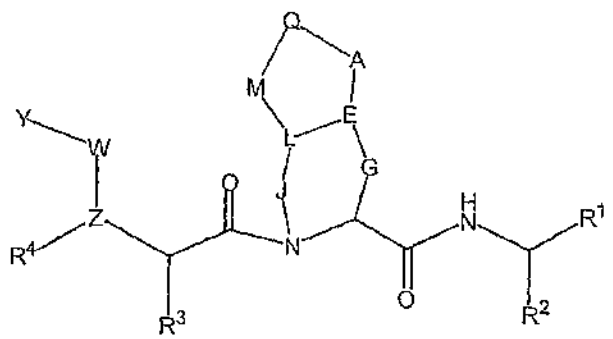
Cathepsins therefore are attractive targets for the discovery of novel chemotherapeutics and methods of treatment effective against a variety of diseases. There is a need for compounds and associated formulations useful in the inhibition of cathepsin activity and in the treatment of these disorders.

There is a need for pharmacuetical formulations inlcuding inhibitors of HCV protease or cathepsin having good dissolution to facilitate absorption of the inhibitor.

SUMMARY OF THE INVENTION

The present invention provides pharmaceutical formulations comprising (i) at least one surfactant and (ii) at least one compound of Formulae I-XXVI.

In one embodiment, the compound is a compound of structural Formula I



Formula I

or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein:

Y is selected from the group consisting of the following moieties: alkyl, alkyl-aryl, heteroalkyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyloxy, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocycloalkyloxy, cycloalkyloxy, alkylamino, arylamino, alkyl-arylamino, arylamino, heteroarylamino, cycloalkylamino and heterocycloalkylamino, with the proviso that Y maybe optionally substituted with X^{11} or X^{12};

X^{11} is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, heteroaryl, alkylheteroaryl, or heteroarylalkyl, with the proviso that X^{11} may be additionally optionally substituted with X^{12};

X^{12} is hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyloxy, alkylureido, arylureido, halogen, cyano, or nitro, with the proviso that said alkyl, alkoxy, and aryl may be additionally optionally substituted with moieties independently selected from X^{12};

R^1 is COR^5 or $B(OR)_2$, wherein R^5 is H, OH, OR^8, NR^9R^{10}, CF_3, C_2F_5, C_3F_7, CF_2R^6, R^6, or COR^7 wherein R^7 is H, OH, OR^8, CHR^9R^{10}, or NR^9R^{10} , wherein R^6, R^8, R^9 and R^{10} are independently selected from the group consisting of H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, cycloalkyl, arylalkyl, heteroarylalkyl, $[CH(R^{1'})]_pCOOR^{11}$, $[CH(R^{1'})]_pCONR^{12}R^{13}$, $[CH(R^{1'})]_pSO_2R^{11}$, $[CH(R^{1'})]_pCOR^{11}$, $[CH(R^{1'})]_pCH(OH)RCH(R^{1'})CONHCH(R^{2'})COO\ R^{11}$, $CH(R^{1'})CONHCH(R^{2'})CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})R'$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})COO\ R^{11}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})\ CONHCH(R^{4'})COO\ R^{11}$, $CH(R^{1'})CONHCH(R^{2'})\ CONHCH(R^{3'})CONHCH(R^{4'})CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONHCH(R^{5'})COO\ R^{11}$ and $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONHCH(R^{5'})\ CONR^{12}R^{13}$, wherein $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, R^{11}, R^{12}, R^{13}, and R' are independently selected from the group consisting of H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, alkyl-aryl, alkyl-heteroaryl, aryl-alkyl

and heteroaralkyl;

Z is selected from O, N, CH or CR;

W maybe present or absent, and if W is present, W is selected from C=O, C=S, C(=N-CN), or SO_2;

Q maybe present or absent, and when Q is present, Q is CH, N, P, $(CH_2)_p$, $(CHR)_p$, $(CRR')_p$, O, NR, S, or SO_2; and when Q is absent, M may be present or absent; when Q and M are absent, A is directly linked to L;

A is O, CH_2, $(CHR)_p$, $(CHR\text{-}CHR')_p$, $(CRR')_p$, NR, S, SO_2 or a bond;

E is CH, N, CR, or a double bond towards A, L or G;

G may be present or absent, and when G is present, G is $(CH_2)_p$, $(CHR)_p$, or $(CRR')_p$; and when G is absent, J is present and E is directly connected to the carbon atom in Formula I as G is linked to;

J maybe present or absent, and when J is present, J is $(CH_2)_p$, $(CHR)_p$, or $(CRR')_p$, SO_2, NH, NR or O; and when J is absent, G is present and E is directly linked to N shown in Formula I as linked to J;

L may be present or absent, and when L is present, L is CH, CR, O, S or NR; and when L is absent, then M may be present or absent; and if M is present with L being absent, then M is directly and independently linked to E, and J is directly and independently linked to E;

M may be present or absent, and when M is present, M is O, NR, S, SO_2, $(CH_2)_p$, $(CHR)_p$ $(CHR\text{-}CHR')_p$, or $(CRR')_p$;

p is a number from 0 to 6; and

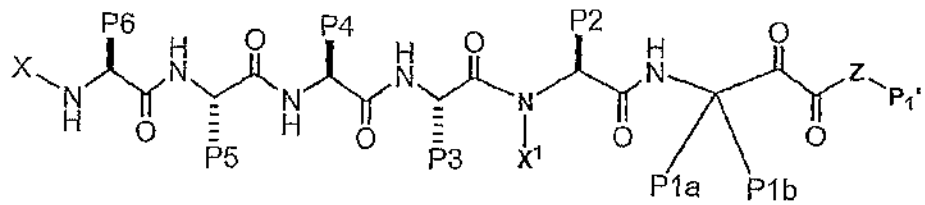
R, R', R^2, R^3 and R^4 are independently selected from the group consisting of H; C_1-C_{10} alkyl; C_2-C_{10} alkenyl; C_3-C_8 cycloalkyl; C_3-C_8 heterocycloalkyl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, halogen; (cycloalkyl)alkyl and (heterocycloalkyl)alkyl, wherein said cycloalkyl is made of three to eight carbon atoms, and zero to six oxygen, nitrogen, sulfur, or phosphorus atoms, and said alkyl is of one to six carbon atoms; aryl; heteroaryl; alkyl-aryl; and alkyl-heteroaryl;

wherein said alkyl, heteroalkyl, alkenyl, heteroalkenyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl moieties may be optionally and chemically-suitably substituted, with said term "substituted" referring to optional and chemically-suitable substitution with

one or more moieties selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, heterocyclic, halogen, hydroxy, thio, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, sulfonamido, sulfoxide, sulfone, sulfonyl urea, hydrazide, and hydroxamate;

further wherein said unit N-C-G-E-L-J-N represents a five-membered or six-membered cyclic ring structure with the proviso that when said unit N-C-G-E-L-J-N represents a five-membered cyclic ring structure, or when the bicyclic ring structure in Formula I comprising N, C, G, E, L, J, N, A, Q, and M represents a five-membered cyclic ring structure, then said five-membered cyclic ring structure lacks a carbonyl group as part of the cyclic ring.

In another embodiment, the compound is a compound of Formula II:



Formula II

or a pharmaceutically acceptable salt, solvate or ester thereof; wherein:

Z is O, NH or NR^{12};

X is alkylsulfonyl, heterocyclylsulfonyl, heterocyclylalkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylcarbonyl, heterocyclylcarbonyl, heterocyclylalkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, heterocyclyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkyaminocarbonyl, heterocyclylaminocarbonyl, arylaminocarbonyl, or heteroarylaminocarbonyl moiety, with the proviso that X may be additionally optionally substituted with R^{12} or R^{13};

X^1 is H; C_1-C_4 straight chain alkyl; C_1-C_4 branched alkyl or ; CH_2-aryl (substituted or unsubstituted);

R^{12} is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, heteroaryl, alkylheteroaryl, or heteroarylalkyl moiety, with the proviso that R^{12} may be additionally optionally substituted with R^{13}.

R^{13} is hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyloxy, alkylureido, arylureido, halogen, cyano, or nitro moiety, with the proviso that the alkyl, alkoxy, and aryl may be additionally optionally substituted with moieties independently selected from R^{13}.

P1a, P1b, P2, P3, P4, P5, and P6 are independently:

H; C1-C10 straight or branched chain alkyl; C2-C10 straight or branched chain alkenyl;

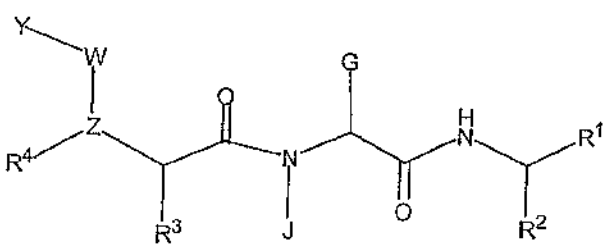
C3-C8 cycloalkyl, C3-C8 heterocyclic; (cycloalkyl)alkyl or (heterocyclyl)alkyl , wherein said cycloalkyl is made up of 3 to 8 carbon atoms, and zero to 6 oxygen, nitrogen, sulfur, or phosphorus atoms, and said alkyl is of 1 to 6 carbon atoms;

aryl, heteroaryl, arylalkyl, or heteroarylalkyl, wherein said alkyl is of 1 to 6 carbon atoms;

wherein said alkyl, alkenyl, cycloalkyl, heterocyclyl; (cycloalkyl)alkyl and (heterocyclyl)alkyl moieties may be optionally substituted with R^{13}, and further wherein said P1a and P1b may optionally be joined to each other to form a spirocyclic or spiroheterocyclic ring, with said spirocyclic or spiroheterocyclic ring containing zero to six oxygen, nitrogen, sulfur, or phosphorus atoms, and may be additionally optionally substituted with R^{13}; and

P1' is H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclyl-alkyl, aryl, aryl-alkyl, heteroaryl, or heteroaryl-alkyl; with the proviso that said P1' may be additionally optionally substituted with R^{13}.

In another embodiment, the compound is a compound of Formula III



Formula III

or a pharmaceutically acceptable salt, solvate or ester thereof; wherein:

G, J and Y may be the same or different and are independently selected from the group consisting of the moieties: H, alkyl, alkyl-aryl, heteroalkyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyloxy, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocycloalkyloxy, cycloalkyloxy, alkylamino, arylamino, alkyl-arylamino, arylamino, heteroarylamino, cycloalkylamino and heterocycloalkylamino, with the proviso that Y maybe additionally optionally substituted with X^{11} or X^{12};

X^{11} is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, heteroaryl, alkylheteroaryl, or heteroarylalkyl moiety, with the proviso that X^{11} may be additionally optionally substituted with X^{12};

X^{12} is hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyloxy, alkylureido, arylureido, halogen, cyano, or nitro, with the proviso that said alkyl, alkoxy, and aryl may be additionally optionally substituted with moieties independently selected from X^{12};

R^1 is COR^5 or $B(OR)_2$, wherein R^5 is selected from the group consisting of H, OH, OR^8, NR^9R^{10}, CF_3, C_2F_5, C_3F_7, CF_2R^6, R^6 and COR^7 wherein R^7 is selected from the group consisting of H, OH, OR^8, CHR^9R^{10}, and NR^9R^{10} , wherein R^6, R^8, R^9 and R^{10} may be the same or different and are independently selected from the group consisting of H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, cycloalkyl, arylalkyl, heteroarylalkyl, $CH(R^{1'})COOR^{11}$,$CH(R^{1'})CONR^{12}R^{13}$,$CH(R^{1'})CONHCH(R^{2'})COOR^{11}$, $CH(R^{1'})CONHCH(R^{2'})CONR^{12}R^{13}$,$CH(R^{1'})CONHCH(R^{2'})R'$,$CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})COOR^{11}$,$CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})COOR^{11}$,$CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONR^{12}R^{13}$,$CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONHCH(R^{5'})COOR^{11}$,and$CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONHCH(R^{5'})CONR^{12}R^{13}$, wherein $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, R^{11}, R^{12}, R^{13}, and R' may be the same or different and are independently selected from a group consisting of H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, alkyl-aryl, alkyl-heteroaryl, aryl-alkyl and heteroaralkyl;

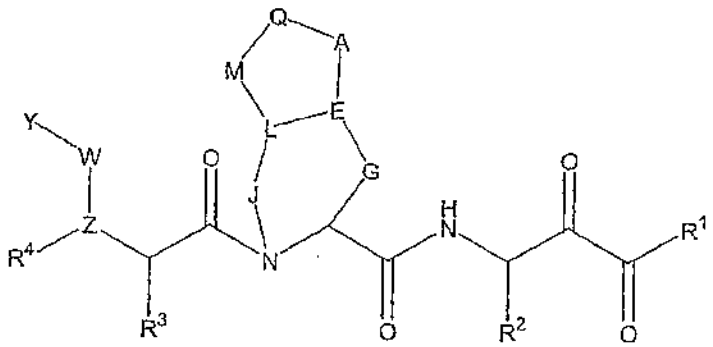
Z is selected from O, N, or CH;

W maybe present or absent, and if W is present, W is selected from C=O, C=S, or SO_2; and

R, R', R^2, R^3 and R^4 are independently selected from the group consisting of H; C1-C10 alkyl; C2-C10 alkenyl; C3-C8 cycloalkyl; C3-C8 heterocycloalkyl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro; oxygen, nitrogen, sulfur, or phosphorus atoms (with said oxygen, nitrogen, sulfur, or phosphorus atoms numbering zero to six); (cycloalkyl)alkyl and (heterocycloalkyl)alkyl, wherein said cycloalkyl is made of three to eight carbon atoms, and zero to six oxygen, nitrogen, sulfur, or phosphorus atoms, and said alkyl is of one to six carbon atoms; aryl; heteroaryl; alkyl-aryl; and alkyl-heteroaryl;

wherein said alkyl, heteroalkyl, alkenyl, heteroalkenyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl moieties may be optionally substituted, with said term "substituted" referring to optional and chemically-suitable substitution with one or more moieties selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, heterocyclic, halogen, hydroxy, thio, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, sulfonamide, sulfoxide, sulfone, sulfonylurea, hydrazide, and hydroxamate.

In another embodiment, the compound is a compound of Formula IV



Formula IV

or a pharmaceutically acceptable salt, solvate or ester thereof; wherein:

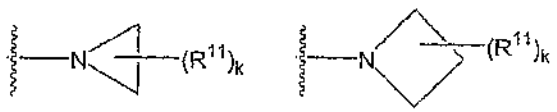
Y is selected from the group consisting of the following moieties: alkyl, alkyl-aryl, heteroalkyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyloxy, alkyl-

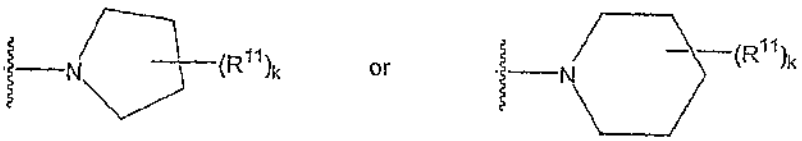
aryloxy, aryloxy, heteroaryloxy, heterocycloalkyloxy, cycloalkyloxy, alkylamino, arylamino, alkyl-arylamino, arylamino, heteroarylamino, cycloalkylamino and heterocycloalkylamino, with the proviso that Y maybe optionally substituted with X^{11} or X^{12};

X^{11} is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, heteroaryl, alkylheteroaryl, or heteroarylalkyl, with the proviso that X^{11} may be additionally optionally substituted with X^{12};

X^{12} is hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxyl, carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyloxy, alkylureido, arylureido, halogen, cyano, or nitro, with the proviso that said alkyl, alkoxy, and aryl may be additionally optionally substituted with moieties independently selected from X^{12};

R^1 is selected from the following structures:





wherein k is a number from 0 to 5, which can be the same or different, R^{11} denotes optional substituents, with each of said substituents being independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, cycloalkyl, alkyl-aryl, heteroalkyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, alkyloxy, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocycloalkyloxy, cycloalkyloxy, alkylamino, arylamino, alkyl-arylamino, arylamino, heteroarylamino, cycloalkylamino, heterocycloalkylamino, hydroxy, thio, alkylthio, arylthio, amino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxyl, carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyloxy, alkylureido, arylureido, halogen, cyano, and nitro, with the proviso that R^{11} (when $R^{11} \neq H$) maybe optionally substituted with X^{11} or X^{12};

Z is selected from O, N, CH or CR;

W may be present or absent, and if W is present, W is selected from C=O, C=S, C(=N-CN), or $S(O_2)$;

Q may be present or absent, and when Q is present, Q is CH, N, P, $(CH_2)_p$, $(CHR)_p$, $(CRR')_p$, O, N(R), S, or $S(O_2)$; and when Q is absent, M may be present or absent;

when Q and M are absent, A is directly linked to L;

A is O, CH_2, $(CHR)_p$, $(CHR\text{-}CHR')_p$, $(CRR')_p$, N(R), S, $S(O_2)$ or a bond;

E is CH, N, CR, or a double bond towards A, L or G;

G may be present or absent, and when G is present, G is $(CH_2)_p$, $(CHR)_p$, or $(CRR')_p$; and when G is absent, J is present and E is directly connected to the carbon atom in Formula I as G is linked to;

J may be present or absent, and when J is present, J is $(CH_2)_p$, $(CHR)_p$, or $(CRR')_p$, $S(O_2)$, NH, N(R) or O; and when J is absent, G is present and E is directly linked to N shown in Formula I as linked to J;

L may be present or absent, and when L is present, L is CH, C(R), O, S or N(R); and when L is absent, then M may be present or absent; and if M is present with L being absent, then M is directly and independently linked to E, and J is directly and independently linked to E;

M may be present or absent, and when M is present, M is O, N(R), S, $S(O_2)$, $(CH_2)_p$, $(CHR)_p$ $(CHR\text{-}CHR')_p$, or $(CRR')_p$;

p is a number from 0 to 6; and

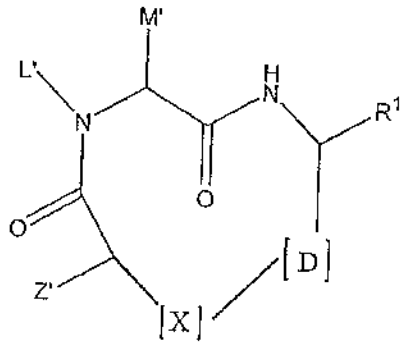
R, R', R^2, R^3 and R^4 can be the same or different, each being independently selected from the group consisting of H; C_1-C_{10} alkyl; C_2-C_{10} alkenyl; C_3-C_8 cycloalkyl; C_3-C_8 heterocycloalkyl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, halogen, (cycloalkyl)alkyl and (heterocycloalkyl)alkyl, wherein said cycloalkyl is made of three to eight carbon atoms, and zero to six oxygen, nitrogen, sulfur, or phosphorus atoms, and said alkyl is of one to six carbon atoms; aryl; heteroaryl; alkyl-aryl; and alkyl-heteroaryl;

wherein said alkyl, heteroalkyl, alkenyl, heteroalkenyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl moieties may be optionally substituted, with said term "substituted" referring to substitution with one or more moieties which can be the same or different, each being independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, heterocyclic, halogen, hydroxy, thio, alkoxy,

aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, sulfonamido, sulfoxide, sulfone, sulfonyl urea, hydrazide, and hydroxamate;

further wherein said unit N-C-G-E-L-J-N represents a five-membered cyclic ring structure or six-membered cyclic ring structure with the proviso that when said unit N-C-G-E-L-J-N represents a five-membered cyclic ring structure, or when the bicyclic ring structure in Formula I comprising N, C, G, E, L, J, N, A, Q, and M represents a five-membered cyclic ring structure, then said five-membered cyclic ring structure lacks a carbonyl group as part of said five-membered cyclic ring.

In another embodiment, the compound is a compound of Formula V



Formula V

or a pharmaceutically acceptable salt, solvate or ester of said compound wherein:

(1) R^1 is $-C(O)R^5$ or $-B(OR)_2$;

(2) R^5 is H, -OH, $-OR^6$, $-NR^9R^{10}$, $-C(O)OR^8$, $-C(O)NR^9R^{10}$, $-CF_3$, $-C_2F_5$, C_3F_7, $-CF_2R^6$, $-R^6$, $-C(O)R^7$ or $NR^7SO_2R^8$;

(3) R^7 is H, -OH, $-OR^8$,or $-CHR^9R^{10}$;

(4) R^6, R^8, R^9 and R^{10} are independently selected from the group consisting of H: alkyl, alkenyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, arylalkyl, heteroarylalkyl, R^{14}, $-CH(R^{1'})CH(R^{1'})C(O)OR^{11}$,$[CH(R^{1'})]_pC(O)OR^{11}$,$-[CH(R^{1'})]_pC(O)NR^{12}R^{13}$,$-[CH(R^{1'})]_pS(O_2)R^{11}$,$-[CH(R^{1'})]_pC(O)R^{11}$,$-[CH(R^{1'})]_pS(O_2)NR^{12}R^{13}$, $CH(R^{1'})C(O)N(H)CH(R^{2'})(R')$, $CH(R^{1'})CH(R^{1'})C(O)NR^{12}R^{13}$, $-CH(R^{1'})CH(R^{1'})S(O_2)R^{11}$, $-CH(R^{1'})CH(R^{1'})S(O_2)NR^{12}R^{13}$, $-CH(R^{1'})CH(R^{1'})C(O)R^{11}$, $-[CH(R^{1'})]_pCH(OH)R^{11}$, $-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)OR^{11}$, $C(O)N(H)CH(R^{2'})C(O)OR^{11}$,$-C(O)N(H)CH(R^{2'})C(O)R^{11}$,$CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)NR^{12}R^{13}$,$-CH(R^{1'})C(O)N(H)CH(R^{2'})R'$,$CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)N(H)$

$CH(R^{3'})C(O)OR^{11}$,$CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)CH(R^{3'})NR^{12}R^{13}$,$CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)N(H)CH(R^{3'})C(O)NR^{12}R^{13}$,$CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)N(H)CH(R^{3'})C(O)N(H)CH(R^{4'})C(O)OR^{11}$,

$H(R^{1'})C(O)N(H)CH(R^{2'})C(O)N(H)CH(R^{3'})C(O)N(H)CH(R^{4'})C(O)NR^{12}R^{13}$,

$CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)N(H)CH(R^{3'})C(O)N(H)CH(R^{4'})C(O)N(H)CH(R^{5'})C(O)OR^{11}$,

and$CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)N(H)CH(R^{3'})C(O)N(H)CH(R^{4'})C(O)N(H)CH(R^{5'})C(O)NR^{12}R^{13}$;

wherein $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, R^{11}, $R^{12}$and R^{13} can be the same or different, each being independently selected from the group consisting of: H, halogen, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, alkoxy, aryloxy, alkenyl, alkynyl, alkyl-aryl, alkyl-heteroaryl, heterocycloalkyl, aryl-alkyl and heteroaralkyl;

or

R^{12} and R^{13} are linked together wherein the combination is cycloalkyl, heterocycloalkyl, ary or heteroaryl;

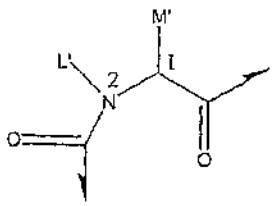
R^{14} is present or not and if present is selected from the group consisting of: H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, alkyl-aryl, allyl, alkyl-heteroaryl, alkoxy, aryl-alkyl, alkenyl, alkynyl and heteroaralkyl;

(5) R and R' are present or not and if present can be the same or different, each being independently selected from the group consisting of: H, OH, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_3-C_8 cycloalkyl, C_3-C_8 heterocycloalkyl, alkoxy, aryloxy, alkylthio, arylthio, alkylamino, arylamino, amino, amido, arylthioamino, arylcarbonylamino, arylaminocarboxy, alkylaminocarboxy, heteroalkyl, alkenyl, alkynyl, (aryl)alkyl, heteroarylalkyl, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, halogen, (cycloalkyl)alkyl, aryl, heteroaryl, (alkyl)aryl, alkylheteroaryl, alkyl-heteroaryl and (heterocycloalkyl)alkyl, wherein said cycloalkyl is made of three to eight carbon atoms, and zero to six oxygen, nitrogen, sulfur, or phosphorus atoms, and said alkyl is of one to six carbon atoms;

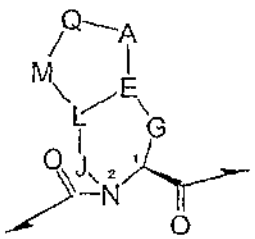
(6) L' is H, OH, alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, or heterocyclyl;

(7) M' is H, alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, arylalkyl, heterocyclyl or an amino acid side chain;

or L' and M' are linked together to form a ring structure wherein the portion of structural Formula 1 represented by



is represented by structural Formula 2:



Formula 2

wherein in Formula 2:

E is present or absent and if present is C, CH, N or C(R);

J is present or absent, and when J is present, J is $(CH_2)_p$, $(CHR\text{-}CHR')_p$, $(CHR)_p$, $(CRR')_p$, $S(O_2)$, N(H), N(R) or O; when J is absent and G is present, L is directly linked to the nitrogen atom marked position 2;

p is a number from 0 to 6;

L is present or absent, and when L is present, L is C(H) or C(R); when L is absent, M is present or absent; if M is present with L being absent, then M is directly and independently linked to E, and J is directly and independently linked to E;

G is present or absent, and when G is present, G is $(CH_2)_p$, $(CHR)_p$, $(CHR\text{-}CHR')_p$ or $(CRR')_p$; when G is absent, J is present and E is directly connected to the carbon atom marked position 1;

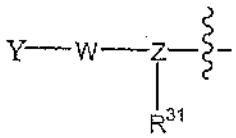
Q is present or absent, and when Q is present, Q is NR, PR, (CR=CR), $(CH_2)_p$, $(CHR)_p$, $(CRR')_p$, $(CHR\text{-}CHR')_p$, O, NR, S, SO, or SO_2; when Q is absent, M is (i) either directly linked to A or (ii) an independent substituent on L, said

independent substituent bing selected from -OR, -CH(R)(R'), $S(O)_{0-2}R$ or –NRR' or (iii) absent; when both Q and M are absent, A is either directly linked to L, or A is an independent substituent on E, said independent substituent bing selected from -OR, -CH(R)(R'), $S(O)_{0-2}R$ or –NRR' or A is absent;

A is present or absent and if present A is O, O(R), $(CH_2)_p$, $(CHR)_p$, $(CHR\text{-}CHR')_p$, $(CRR')_p$, N(R), NRR', S, $S(O_2)$, -OR, CH(R)(R') or NRR'; or A is linked to M to form an alicyclic, aliphatic or heteroalicyclic bridge;

M is present or absent, and when M is present, M is halogen, O, OR, N(R), S, $S(O_2)$, $(CH_2)_p$, $(CHR)_p$ $(CHR\text{-}CHR')_p$, or $(CRR')_p$; or M is linked to A to form an alicyclic, aliphatic or heteroalicyclic bridge;

(8) Z' is represented by the structural Formula 3:



Formula 3

wherein in Formula 3, Y is selected from the group consisting of: H, aryl, alkyl, alkyl-aryl, heteroalkyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyloxy, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocycloalkyloxy, heteroalkyl-heteroaryl, heteroalkyl-heterocycloalkyl, cycloalkyloxy, alkylamino, arylamino, alkyl-arylamino, arylamino, heteroarylamino, cycloalkylamino and heterocycloalkylamino, and Y is unsubstituted or optionally substituted with one or two substituents which are the same or different and are independently selected from X^{11} or X^{12};

X^{11} is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, heteroaryl, alkylheteroaryl, or heteroarylalkyl, and X^{11} is unsubstituted or optionally substituted with one or more of X^{12} moieties which are the same or different and are independently selected;

X^{12} is hydroxy, alkoxy, alkyl, alkenyl, alkynyl, aryl, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkylcarbonyl, arylcarbonyl, heteroalkylcarbonyl, heteroarylcarbonyl, sulfonylurea, cycloalkylsulfonamido, heteroaryl-cycloalkylsulfonamido, heteroaryl-sulfonamido, alkoxycarbonylamino,

alkoxycarbonyloxy, alkylureido, arylureido, halogen, cyano, or nitro, and said alkyl, alkoxy, and aryl are unsubstituted or optionally independently substituted with one or more moieties which are the same or different and are independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, heteroaryl, alkylheteroaryl, or heteroarylalkyl;

Z is O, N, C(H) or C(R);

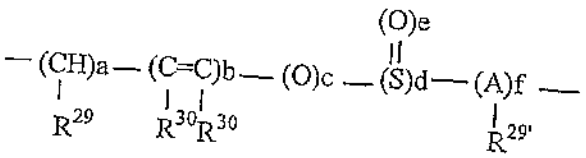
R^{31} is H, hydroxyl, aryl, alkyl, alkyl-aryl, heteroalkyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyloxy, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocycloalkyloxy, heteroalkyl-heteroaryl, cycloalkyloxy, alkylamino, arylamino, alkyl-arylamino, arylamino, heteroarylamino, cycloalkylamino or heterocycloalkylamino, and R^{31} is unsubstituted or optionally substituted with one or two substituents which are the same or different and are independently selected from X^{13} or X^{14};

X^{13} is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, heteroaryl, alkylheteroaryl, or heteroarylalkyl, and X^{13} is unsubstituted or optionally substituted with one or more of X^{14} moieties which are the same or different and are independently selected;

X^{14} is hydroxy, alkoxy, alkyl, alkenyl, alkynyl, aryl, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkylcarbonyl, arylcarbonyl, heteroalkylcarbonyl, heteroarylcarbonyl, cycloalkylsulfonamido, heteroaryl-cycloalkylsulfonamido, heteroarylsulfonamido, alkoxycarbonylamino, alkoxycarbonyloxy, alkylureido, arylureido, halogen, cyano, or nitro, and said alkyl, alkoxy, and aryl are unsubstiuted or optionally independently substituted with one or more moieties which are the same or different and are independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, heteroaryl, alkylheteroaryl, or heteroarylalkyl;

W may be present or absent, and if W is present, W is C(=O), C(=S), C(=N-CN), or $S(O_2)$;

(9) X is represented by structural Formula 4:



Formula 4

wherein in Formula 4, a is 2, 3, 4, 5, 6, 7, 8 or 9;

b, c, d, e and f are 0, 1, 2, 3, 4 or 5;

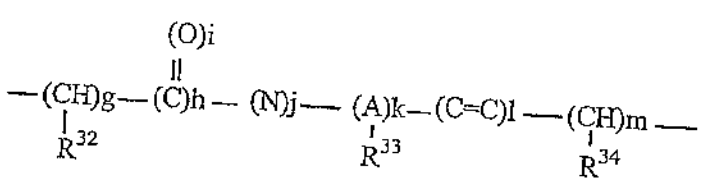
A is C, N, S or O;

R^{29} and $R^{29'}$ are independently present or absent and if present can be the same or different, each being independently one or two substituents independently selected from the group consisting of: H, halo, alkyl, aryl, cycloalkyl, cycloalkylamino, cycloalkylaminocarbonyl, cyano, hydroxy, alkoxy, alkylthio, amino, -NH(alkyl), -NH(cycloalkyl), $-N(alkyl)_2$, carboxyl, C(O)O-alkyl, heteroaryl, aralkyl, alkylaryl, aralkenyl, heteroaralkyl, alkylheteroaryl, heteroaralkenyl, hydroxyalkyl, aryloxy, aralkoxy, acyl, aroyl, nitro, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, arylsulfinyl, heteroarylsulfinyl, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkenyl, heterocyclyl, heterocyclenyl, Y_1Y_2N-alkyl-, $Y_1Y_2NC(O)$- and $Y_1Y_2NSO_2$-, wherein Y_1 and Y_2 can be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, and aralkyl; or

R^{29} and $R^{29'}$ are linked together such that the combination is an aliphatic or heteroaliphatic chain of 0 to 6 carbons;

R^{30} is present or absent and if present is one or two substituents independently selected from the group consisting of: H, alkyl, aryl, heteroaryl and cylcoalkyl;

(10) D is represented by structural Formula 5:



Formula 5

wherein in Formula 5, R^{32}, R^{33} and R^{34} are present or absent and if present are independently one or two substituents independently selected from the group consisting of: H, halo, alkyl, aryl, cycloalkyl, cycloalkylamino, spiroalkyl, cycloalkylaminocarbonyl, cyano, hydroxy, alkoxy, alkylthio, amino, -NH(alkyl), -NH(cycloalkyl), -N(alkyl)$_2$, carboxyl, –C(O)O-alkyl, heteroaryl, aralkyl, alkylaryl, aralkenyl, heteroaralkyl, alkylheteroaryl, heteroaralkenyl, hydroxyalkyl, aryloxy, aralkoxy, acyl, aroyl, nitro, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, arylsulfinyl, heteroarylsulfinyl, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkenyl, heterocyclyl, heterocyclenyl, Y_1Y_2N-alkyl-, $Y_1Y_2NC(O)$- and $Y_1Y_2NSO_2$-, wherein Y_1 and Y_2 can be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, and aralkyl; or

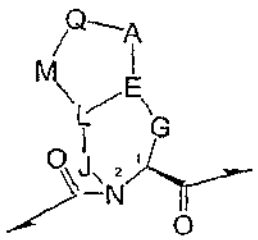
R^{32} and R^{34} are linked together such that the combination forms a portion of a cycloalkyl group;

g is 1, 2, 3, 4, 5, 6, 7, 8 or 9;

h, i, j, k, l and m are 0, 1, 2, 3, 4 or 5; and

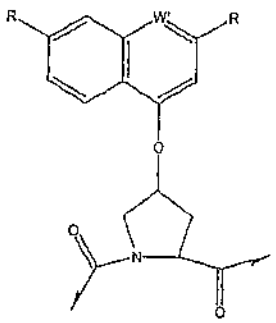
A is C, N, S or O,

(11) provided that when structural Formula 2:



Formula 2

is



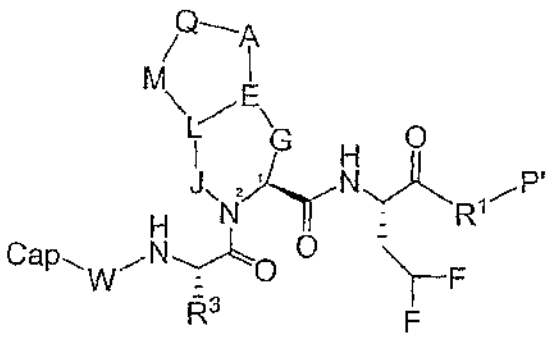
and

W' is CH or N, both the following conditional exclusions (i) and (ii) apply:

conditional exclusion (i): Z' is not –NH–R^{36}, wherein R^{36} is H, $C_{6 \text{ or } 10}$ aryl, heteroaryl, –C(O)–R^{37}, –C(O)–OR^{37} or –C(O)–NHR^{37}, wherein R^{37} is C_{1-6} alkyl or C_{3-6} cycloalkyl; and

conditional exclusion (ii): R^1 is not –C(O)OH, a pharmaceutically acceptable salt of –C(O)OH, an ester of –C(O)OH or –C(O)NHR^{38} wherein R^{38} is selected from the group consisting of C_{1-8} alkyl, C_{3-6} cycloalkyl, $C_{6 \text{ to } 10}$ aryl or C_{7-16} aralkyl.

In another embodiment, the compound is a compound of Formula VI



Formula VI

or a pharmaceutically acceptable salt, solvate or ester of said compound, wherein:

Cap and P' are independently H, alkyl, alkyl-aryl, heteroalkyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyloxy, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocyclyloxy, cycloalkyloxy, amino, alkylamino, arylamino, alkyl-arylamino, arylamino, heteroarylamino, cycloalkylamino, carboxyalkylamino, arlylalkyloxy or heterocyclylamino, wherein each of said alkyl, alkyl-aryl, heteroalkyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyloxy, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocyclyloxy, cycloalkyloxy, amino, alkylamino, arylamino, alkyl-arylamino, arylamino, heteroarylamino, cycloalkylamino, carboxyalkylamino, arlylalkyloxy or

heterocyclylamino can be unsubstituted or optionally independently substituted with one or two substituents which can be the same or different and are independently selected from X^1 and X^2;

X^1 is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, arylheteroaryl, heteroaryl, heterocyclylamino, alkylheteroaryl, or heteroarylalkyl, and X^1 can be unsubstituted or optionally independently substituted with one or more of X^2 moieties which can be the same or different and are independently selected;

X^2 is hydroxy, alkyl, aryl, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyloxy, alkylureido, arylureido, halogen, cyano, keto, ester or nitro, wherein each of said alkyl, alkoxy, and aryl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different and are independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, arylheteroaryl, heteroaryl, heterocyclylamino, alkylheteroaryl and heteroarylalkyl;

W may be present or absent, and when W is present W is C(=O), C(=S), C(=NH), C(=N-OH), C(=N-CN), S(O) or $S(O_2)$;

Q maybe present or absent, and when Q is present, Q is N(R), P(R), CR=CR', $(CH_2)_p$, $(CHR)_p$, $(CRR')_p$, $(CHR\text{-}CHR')_p$, O, S, S(O) or $S(O_2)$; when Q is absent, M is (i) either directly linked to A or (ii) M is an independent substituent on L and A is an independent substituent on E, with said independent substituent being selected from –OR, -CH(R') , $S(O)_{0\text{-}2}R$ or –NRR'; when both Q and M are absent, A is either directly linked to L, or A is an independent substituent on E, selected from –OR, CH(R)(R'), $\text{-}S(O)_{0\text{-}2}R$ or –NRR';

A is present or absent and if present A is –O-, -O(R) CH_2-, $\text{-}(CHR)_p$-, $\text{-}(CHR\text{-}CHR')_p$-, $(CRR')_p$, N(R), NRR', S, or $S(O_2)$, and when Q is absent, A is –OR, -CH(R)(R') or –NRR' ; and when A is absent, either Q and E are connected by a bond or Q is an independent substituent on M;

E is present or absent and if present E is CH, N, C(R);

G may be present or absent, and when G is present, G is $(CH_2)_p$, $(CHR)_p$, or

$(CRR')_p$; when G is absent, J is present and E is directly connected to the carbon atom marked position 1;

J may be present or absent, and when J is present, J is $(CH_2)_p$, $(CHR\text{-}CHR')_p$, $(CHR)_p$, $(CRR')_p$, $S(O_2)$, N(H), N(R) or O; when J is absent and G is present, L is directly linked to the nitrogen atom marked position 2;

L may be present or absent, and when L is present, L is CH, N, or CR; when L is absent, M is present or absent; if M is present with L being absent, then M is directly and independently linked to E, and J is directly and independently linked to E;

M may be present or absent, and when M is present, M is O, N(R), S, $S(O_2)$, $(CH_2)_p$, $(CHR)_p$, $(CHR\text{-}CHR')_p$, or $(CRR')_p$;

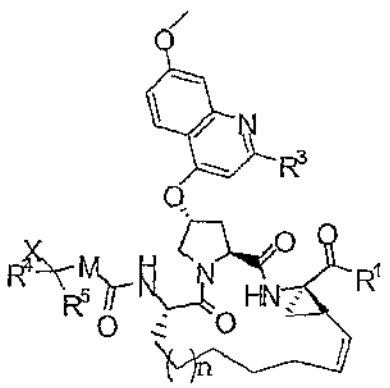
p is a number from 0 to 6;

R, R' and R^3 can be the same or different, each being independently selected from the group consisting of: H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_3-C_8 cycloalkyl, C_3-C_8 heterocyclyl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, arylthioamino, arylcarbonylamino, arylaminocarboxy, alkylaminocarboxy, heteroalkyl, heteroalkenyl, alkenyl, alkynyl, aryl-alkyl, heteroarylalkyl, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, halogen, (cycloalkyl)alkyl, aryl, heteroaryl, alkyl-aryl, alkylheteroaryl, alkyl-heteroaryl and (heterocyclyl)alkyl;

R and R' in (CRR') can be linked together such that the combination forms a cycloalkyl or heterocyclyl moiety; and

R^1 is N(R) or O.

In another embodiment, the compound is a compound of Formula VII

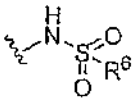


Formula VII

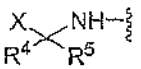
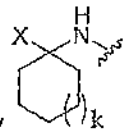
or a pharmaceutically acceptable salt, solvate or ester thereof, wherein,

M is O, N(H), or CH_2;

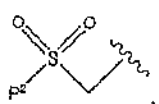
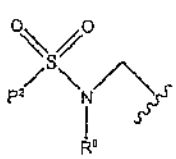
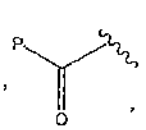
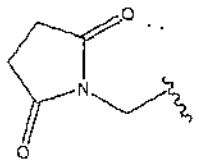
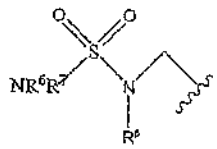
n is 0-4;

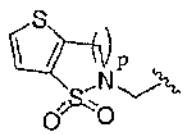
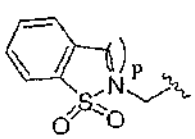
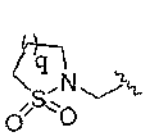
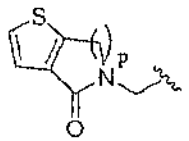
R^1 is $-OR^6$, $-NR^6R^7$ or ;

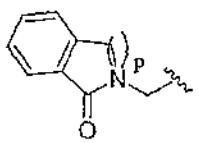
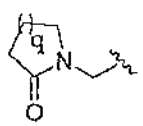
where R^6 and R^7 can be the same or different, each being independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, hydroxyl, amino, arylamino and alkylamino;

R^4 and R^5 can be the same or different, each being independently selected from the group consisting of H, alkyl, aryl and cycloalkyl; or alternatively R^4 and R^5 together form part of a cyclic 5- to 7- membered ring such that the moiety  is represented by  where k is 0 to 2;

X is selected from the group consisting of:

, , , , ,

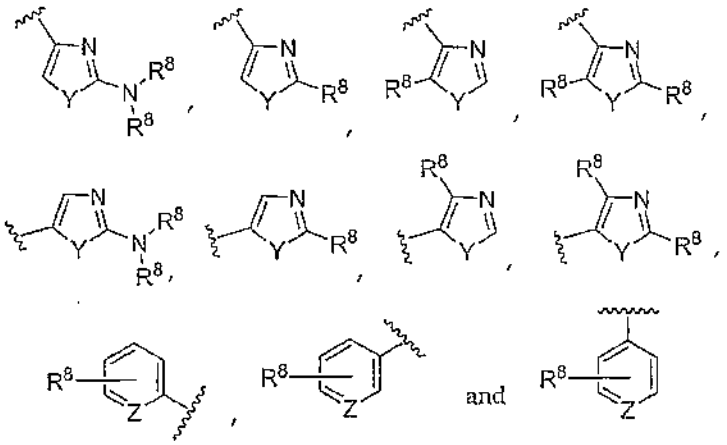
, , , ,

 and ;

where p is 1 to 2, q is 1-3 and P^2 is alkyl, aryl, heteroaryl, heteroalkyl, cycloalkyl, dialkylamino, alkylamino, arylamino or cycloalkylamino;

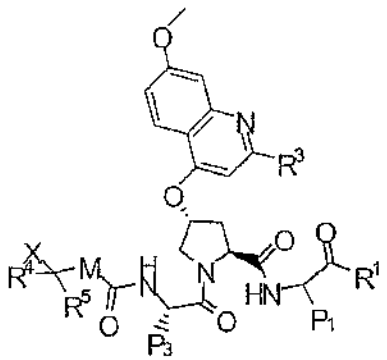
and

R^3 is selected from the group consisting of: aryl, heterocyclyl, heteroaryl,



where Y is O, S or NH, and Z is CH or N, and the R^8 moieties can be the same or different, each R^8 being independently selected from the group consisting of hydrogen, alkyl, heteroalkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, hydroxyl, amino, arylamino, alkylamino, dialkylamino, halo, alkylthio, arylthio and alkyloxy.

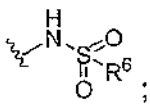
In another embodiment, the compound is a compound of Formula VIII:



Formula VIII

or a pharmaceutically acceptable salt, solvate or ester thereof, wherein,

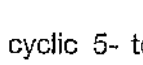
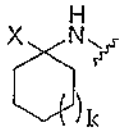
M is O, N(H), or CH_2;

R^1 is $-OR^6$, $-NR^6R^7$ or ;

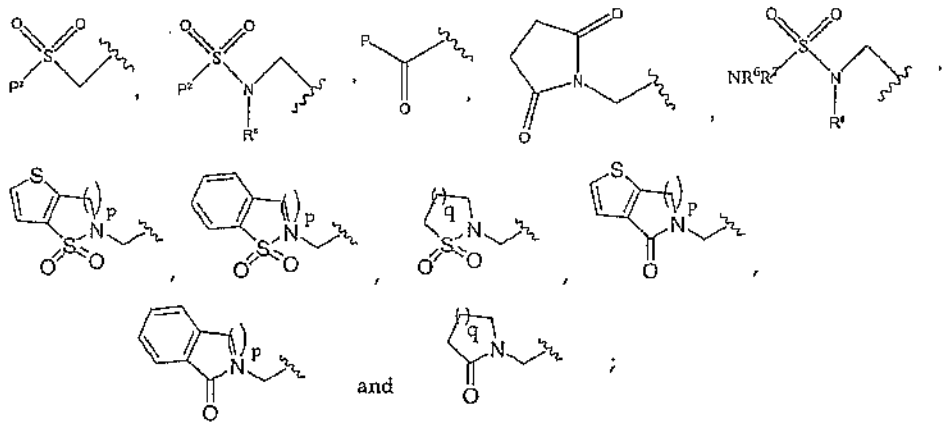
where R^6 and R^7 can be the same or different, each being independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, hydroxyl, amino, arylamino and alkylamino;

P_1 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl haloalkyl;

P_3 is selected from the group consisting of alkyl, cycloalkyl, aryl and cycloalkyl fused with aryl;

R^4 and R^5 can be the same or different, each being independently selected from the group consisting of H, alkyl, aryl and cycloalkyl; or alternatively R^4 and R^5 together form part of a cyclic 5- to 7- membered ring such that the moiety  is represented by  where k is 0 to 2;

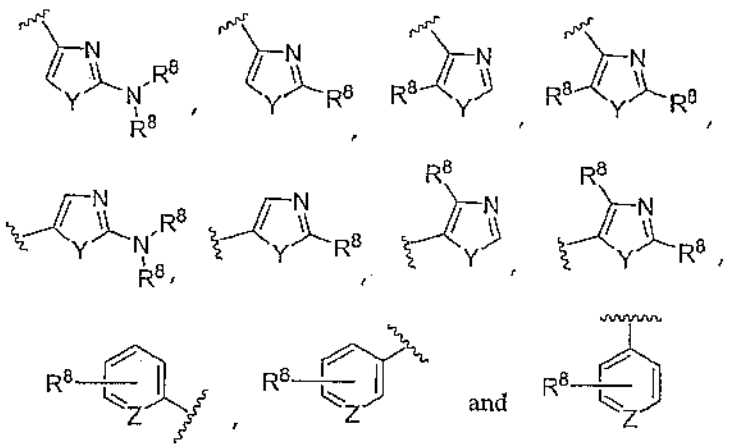
X is selected from the group consisting of:



where p is 1 to 2, q is 1 to 3 and P^2 is alkyl, aryl, heteroaryl, heteroalkyl, cycloalkyl, dialkylamino, alkylamino, arylamino or cycloalkylamino;

and

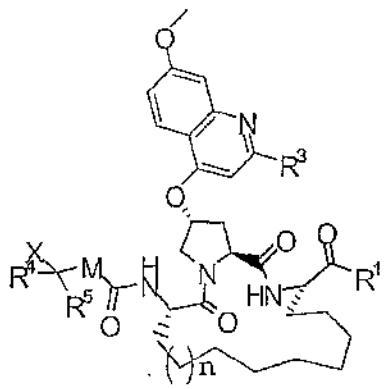
R^3 is selected from the group consisting of: aryl, heterocyclyl, heteroaryl,



where Y is O, S or NH, and Z is CH or N, and the R^8 moieties can be the same or

different, each R^8 being independently selected from the group consisting of hydrogen, alkyl, heteroalkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, hydroxyl, amino, arylamino, alkylamino, dialkylamino, halo, alkylthio, arylthio and alkyloxy.

In another embodiment, the compound is a compound of Formula IX:

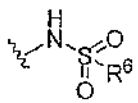


Formula IX

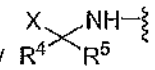
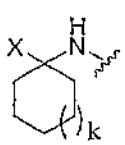
or a pharmaceutically acceptable salt, solvate or ester thereof, wherein,

M is O, N(H), or CH_2;

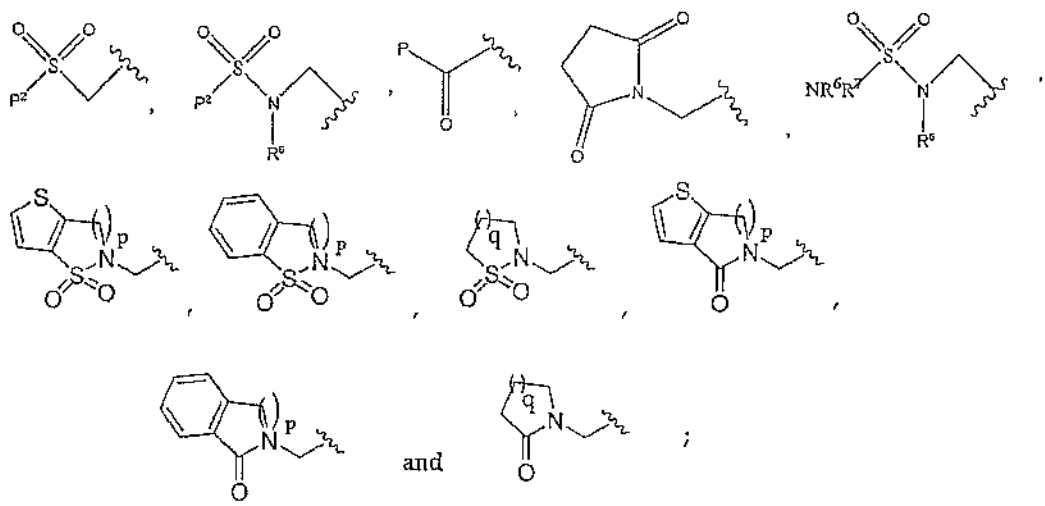
n is 0-4;

R^1 is $-OR^6$, $-NR^6R^7$ or ;

where R^6 and R^7 can be the same or different, each being independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, hydroxyl, amino, arylamino and alkylamino;

R^4 and R^5 can be the same or different, each being independently selected from the group consisting of H, alkyl, aryl and cycloalkyl; or alternatively R^4 and R^5 together form part of a cyclic 5- to 7- membered ring such that the moiety  is represented by  where k is 0 to 2;

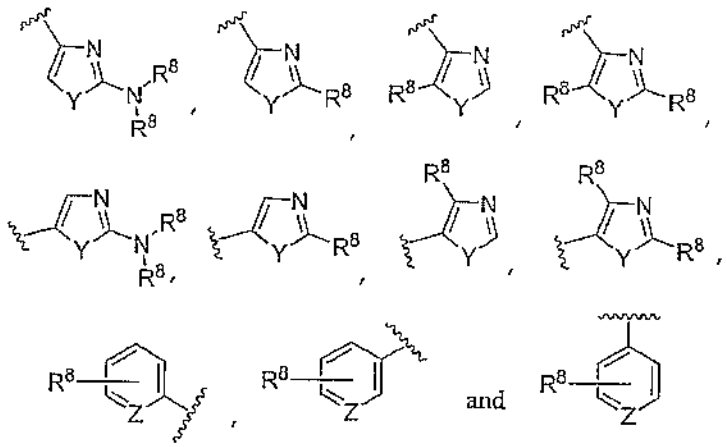
X is selected from the group consisting of:



where p is 1 to 2, q is 1 to 3 and P^2 is alkyl, aryl, heteroaryl, heteroalkyl, cycloalkyl, dialkylamino, alkylamino, arylamino or cycloalkylamino;

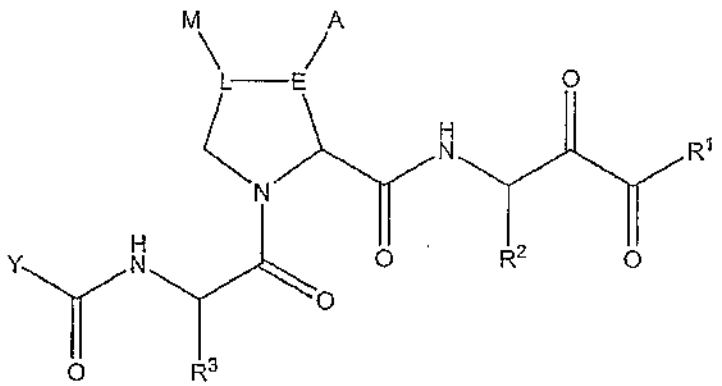
and

R^3 is selected from the group consisting of: aryl, heterocyclyl, heteroaryl,



where Y is O, S or NH, and Z is CH or N, and the R^8 moieties can be the same or different, each R^8 being independently selected from the group consisting of hydrogen, alkyl, heteroalkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, hydroxyl, amino, arylamino, alkylamino, dialkylamino, halo, alkylthio, arylthio and alkyloxy.

In another embodiment, the compound is a compound of Formula X:

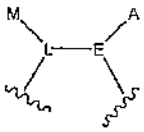


Formula X

or a pharmaceutically acceptable salt, solvate or ester thereof; wherein:

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

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



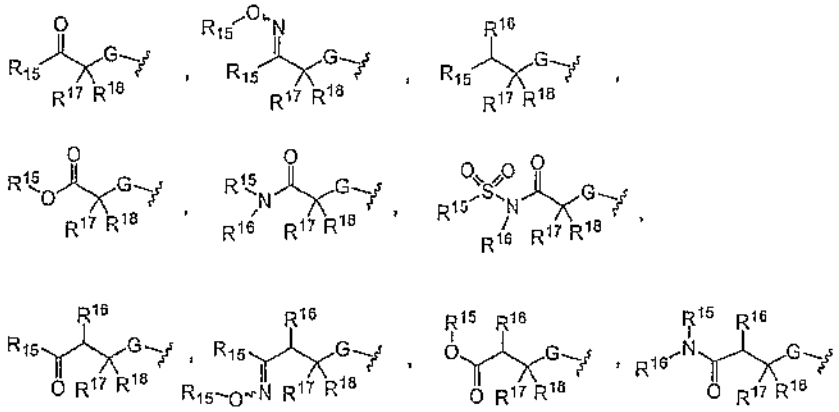
shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl;

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

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

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

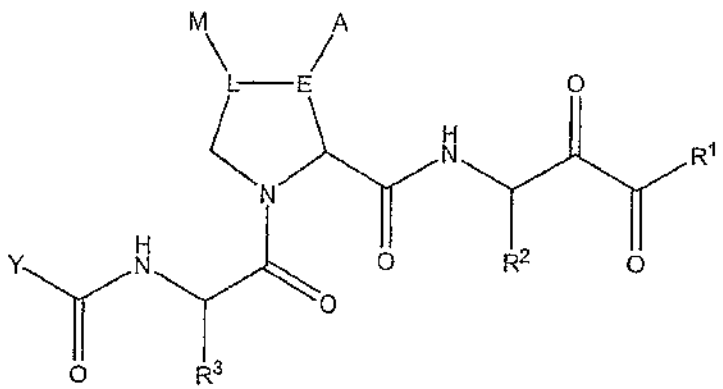
and Y is selected from the following moieties:



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

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.

In one embodiment, the compound is a compound of Formula XI:

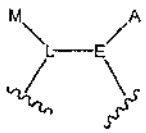


Formula XI

or a pharmaceutically acceptable salt, solvate or ester thereof; wherein:

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

A and M can be the same or different, each being independently selected from R, NR^9R^{10}, SR, SO_2R, and halo; or A and M are connected to each other (in other words, A-E-L-M taken together) such that the moiety:



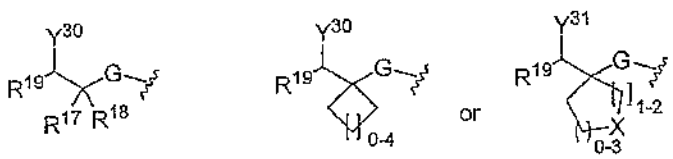
shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl;

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

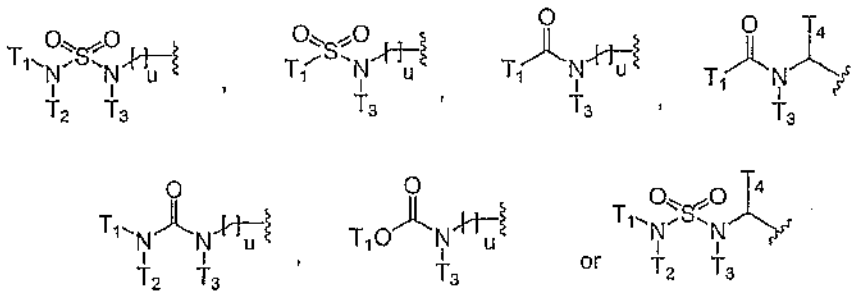
L is C(H), C(R), $CH_2C(R)$, or $C(R)CH_2$;

R, R', R^2, and R^3 can be the same or different, each being independently selected from the group consisting of H, alkyl-, alkenyl-, alkynyl-, cycloalkyl-, heteroalkyl-, heterocyclyl-, aryl-, heteroaryl-, (cycloalkyl)alkyl-, (heterocyclyl)alkyl-, aryl-alkyl-, and heteroaryl-alkyl-; or alternately R and R' in NRR' are connected to each other such that NR^9R^{10} forms a four to eight-membered heterocyclyl;

Y is selected from the following moieties:



wherein Y^{30} and $Y^{31}$are selected from



where u is a number 0-6;

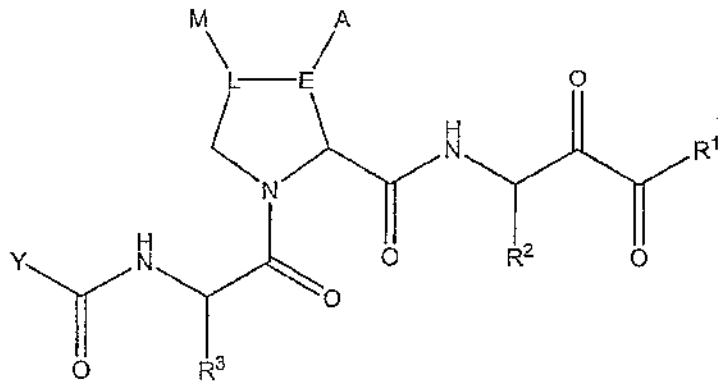
X is selected from O, NR^{15}, $NC(O)R^{16}$, S, S(O) and SO_2;

G is NH or O; and

R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, T_1, T_2, T_3 and T_4 can be the same or different, each being independently selected from the group consisting of H, alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, or alternately, R^{17} and R^{18} are connected to each other to form a three to eight-membered cycloalkyl or heterocyclyl;

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

In another embodiment, the compound is a compound of Formula XII:

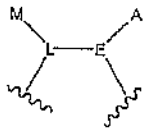


Formula XII

or a pharmaceutically acceptable salt, solvate or ester thereof; wherein:

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

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



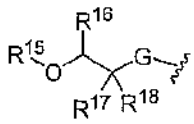
shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl;

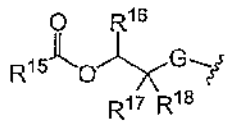
E is C(H) or C(R);

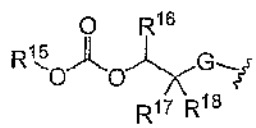
L is C(H), C(R), $CH_2C(R)$, or $C(R)CH_2$;

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

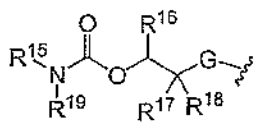
and Y is selected from the following moieties:







or

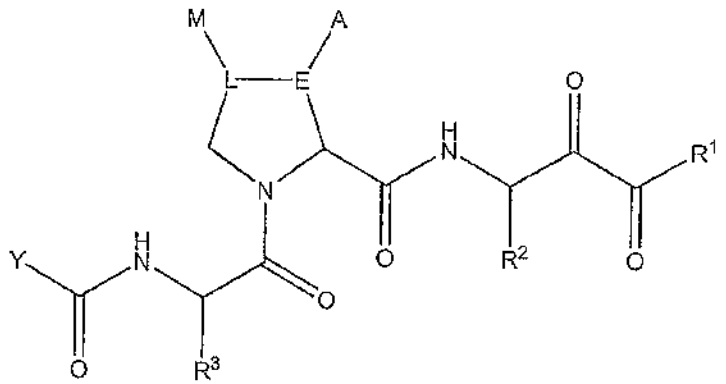


wherein G is NH or O; and R^{15}, R^{16}, R^{17}, R^{18}, and R^{19} can be the same or different, each being independently selected from the group consisting of H, alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, or alternately, (i) either R^{15} and R^{16} are connected to

each other to form a four to eight-membered cyclic structure, or R^{15} and R^{19} are connected to each other to form a four to eight-membered cyclic structure, and (ii) likewise, independently, R^{17} and R^{18} are connected to each other to form a three to eight-membered cycloalkyl or heterocyclyl;

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

In another embodiment, the compound is a compound of Formula XIII:

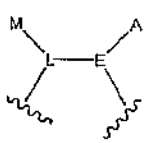


Formula XIII

or a pharmaceutically acceptable salt, solvate or ester thereof; wherein:

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

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



shown above in Formula I forms either a three, four, six, seven or eight-membered

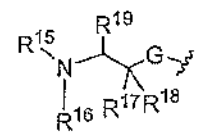
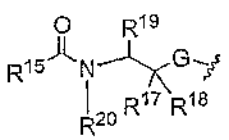
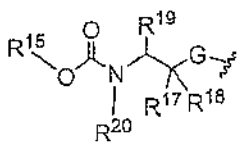
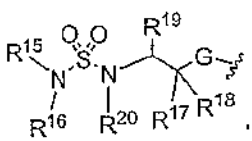
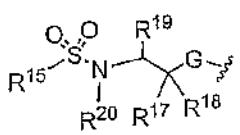
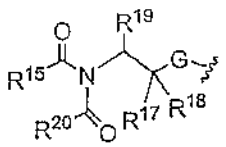
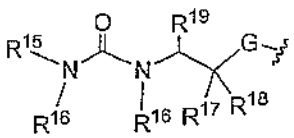
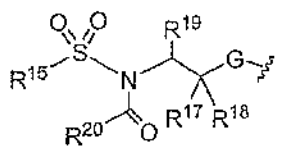
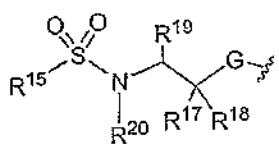
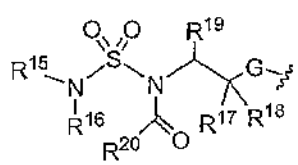
cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl;

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

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

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

and Y is selected from the following moieties:

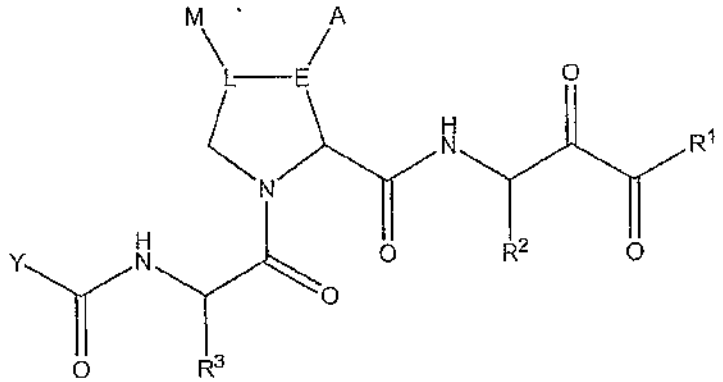

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or


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

membered cycloalkyl or heterocyclyl,

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

In another embodiment, the compound is a compound of Formula XIV:



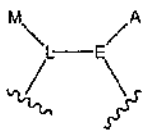
Formula XIV

or a pharmaceutically acceptable salt, solvate or ester thereof; wherein:

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

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

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



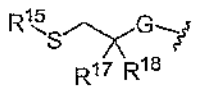
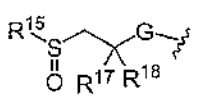
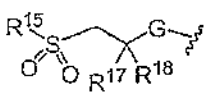
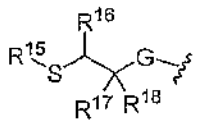
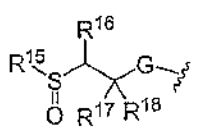
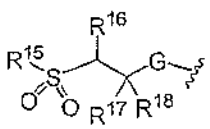
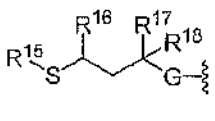
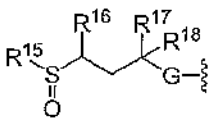
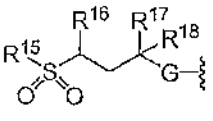
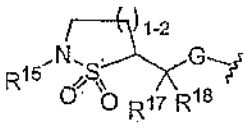
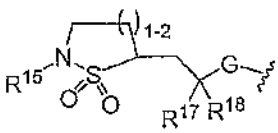
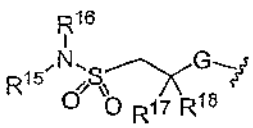
shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl;

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

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

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

and Y is selected from the following moieties:

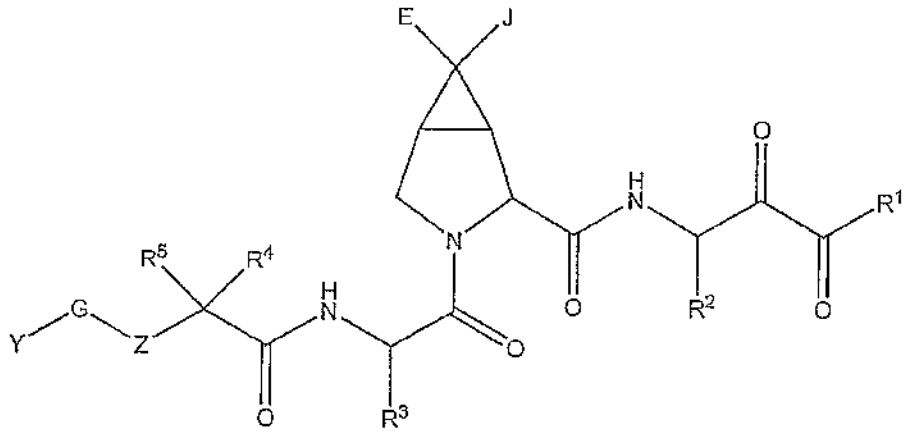

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and


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

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

carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyloxy, alkylureido, arylureido, halo, cyano, and nitro.

In another embodiment, the compound is a compound of Formula XV:



Formula XV

or a pharmaceutically acceptable salt, solvate or ester thereof; wherein:

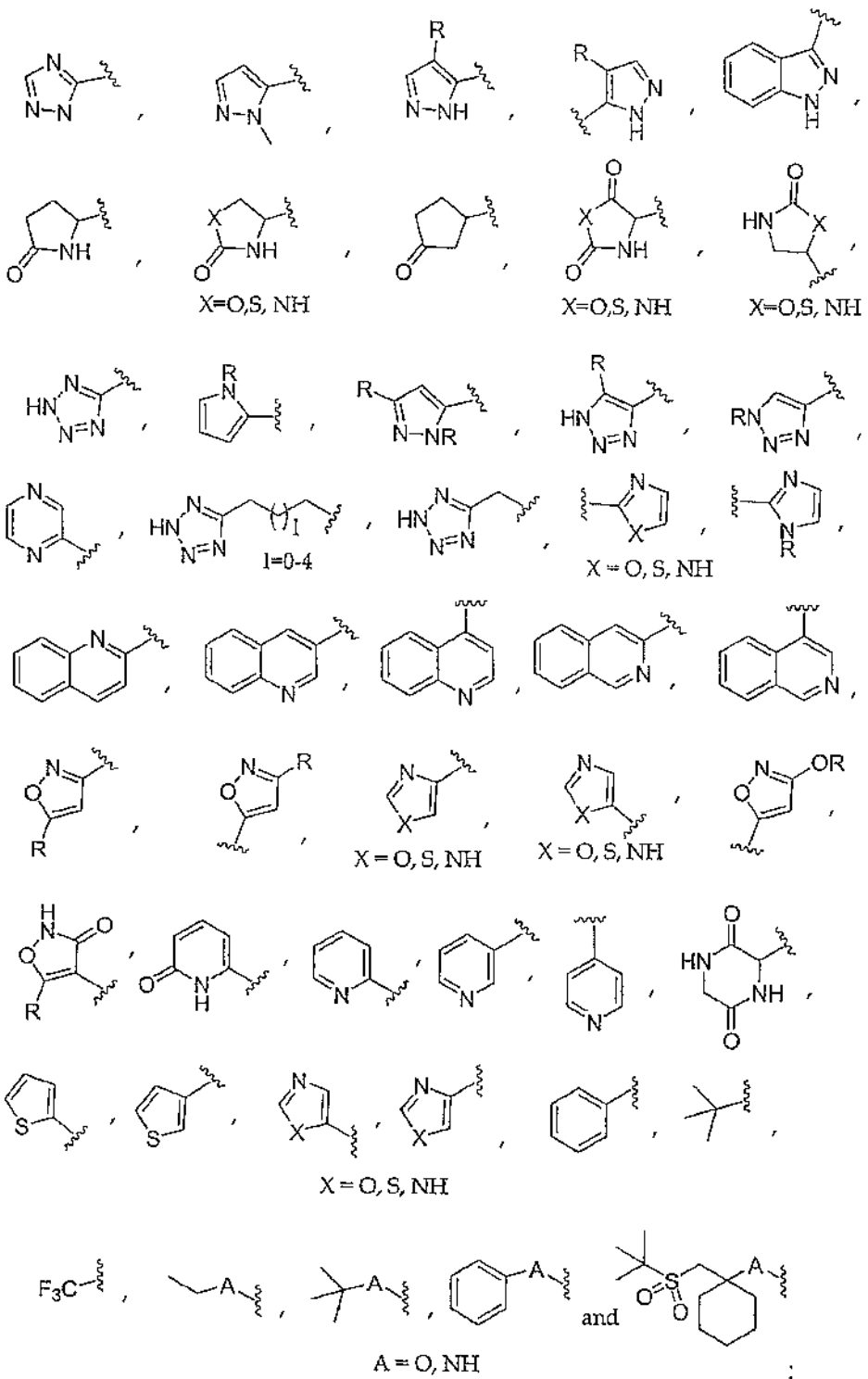
R^1 is H, OR^8, NR^9R^{10}, or CHR^9R^{10}, wherein R^8, R^9 and R^{10} can be the same or different, each being independently selected from the group consisting of H, alkyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, cycloalkyl-, arylalkyl-, and heteroarylalkyl;

E and J can be the same or different, each being independently selected from the group consisting of R, OR, NHR, NRR^7, SR, halo, and $S(O_2)R$, or E and J can be directly connected to each other to form either a three to eight-membered cycloalkyl, or a three to eight-membered heterocyclyl moiety;

Z is N(H), N(R), or O, with the proviso that when Z is O, G is present or absent and if G is present with Z being O, then G is C(=O);

G maybe present or absent, and if G is present, G is C(=O) or $S(O_2)$, and when G is absent, Z is directly connected to Y;

Y is selected from the group consisting of:

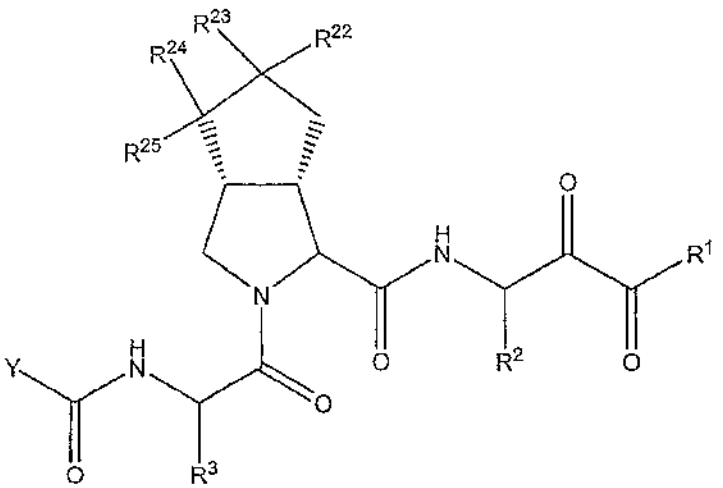

X=O,S, NH
X=O,S, NH
X=O,S, NH
I=0-4
X = O, S, NH
X = O, S, NH
X = O, S, NH
X = O, S, NH
A = O, NH
and

;

R, R^7, R^2, R^3, R^4 and R^5 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-, wherein each of said heteroalkyl, heteroaryl and heterocyclyl independently has one to six oxygen, nitrogen, sulfur, or phosphorus atoms;

wherein each of said alkyl, heteroalkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl and heterocyclyl moieties can be unsubstituted or optionally independently substituted with one or more moieties selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, heterocyclyl, halo, hydroxy, thio, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, sulfonamido, sulfoxide, sulfone, sulfonyl urea, hydrazide, and hydroxamate.

In another embodiment, the compound is a compound of Formula XVI:



Formula XVI

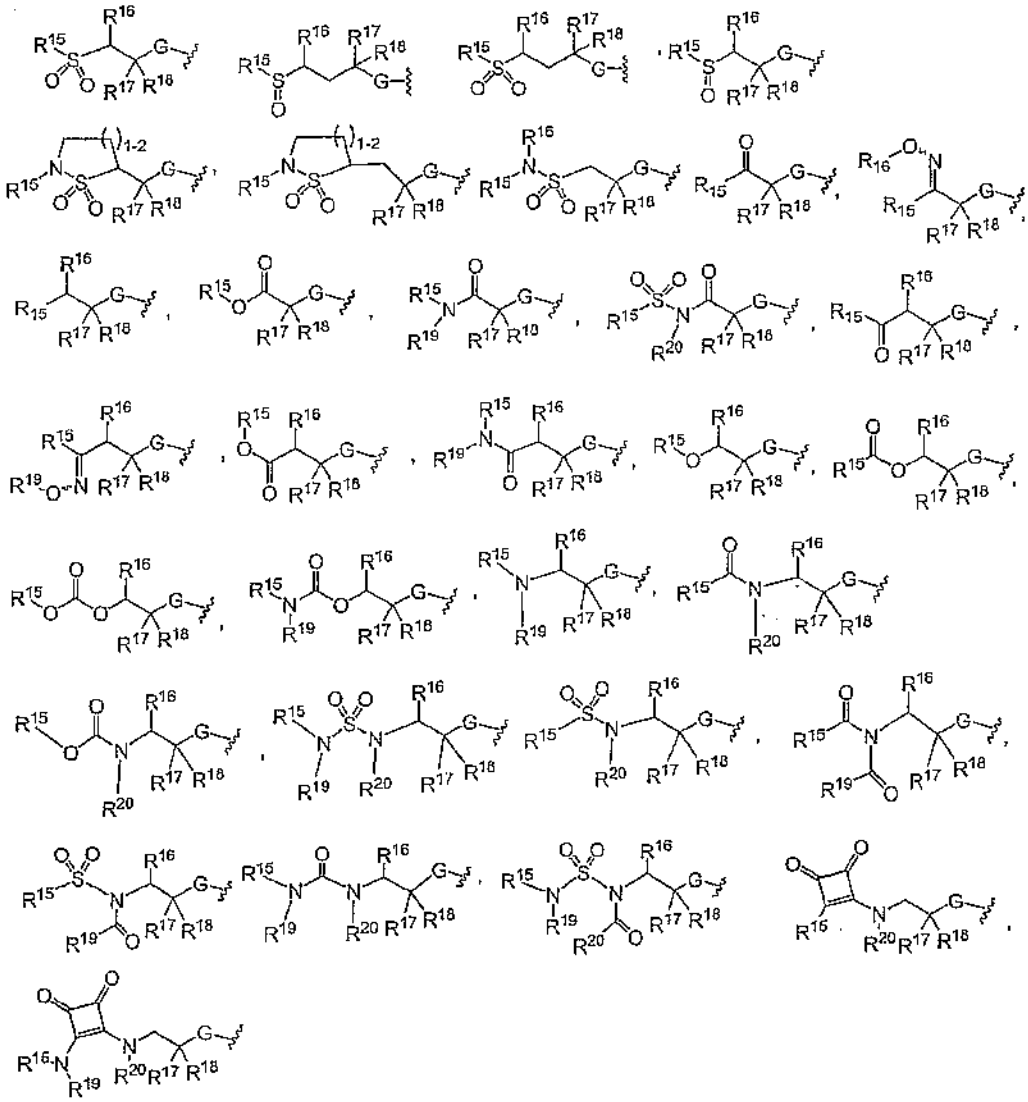
or a pharmaceutically acceptable salt, solvate or ester thereof; wherein:

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, or alternately R^9 and R^{10} in NR^9R^{10} are connected to each other such that NR^9R^{10} forms a four to eight-membered heterocyclyl, and likewise

independently alternately R^9 and R^{10} in CHR^9R^{10} are connected to each other such that CHR^9R^{10} forms a four to eight-membered cycloalkyl;

R^2 and R^3 can be the same or different, each being independently selected from the group consisting of H, alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl;

Y is selected from the following moieties:

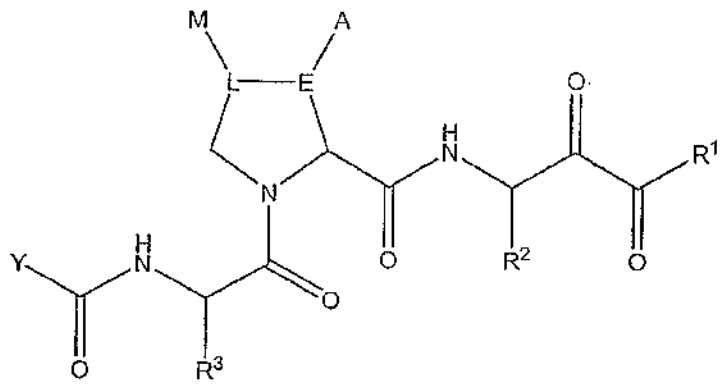


wherein G is NH or O; and R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24} and R^{25} can be the same or different, each being independently selected from the group consisting of H, alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, or alternately

(i) R^{17} and R^{18} are independently connected to each other to form a three to eight-membered cycloalkyl or heterocyclyl; (ii) likewise independently R^{15} and R^{19} are connected to each other to form a four to eight-membered heterocyclyl; (iii) likewise independently R^{15} and R^{16} are connected to each other to form a four to eight-membered heterocyclyl; (iv) likewise independently R^{15} and R^{20} are connected to each other to form a four to eight-membered heterocyclyl; (v) likewise independently R^{22} and R^{23} are connected to each other to form a three to eight-membered cycloalkyl or a four to eight-membered heterocyclyl; and (vi) likewise independently R^{24} and R^{25} are connected to each other to form a three to eight-membered cycloalkyl or a four to eight-membered 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.

In another embodiment, the compound is a compound of Formula XVII:

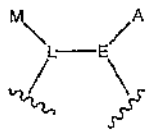


Formula XVII

or a pharmaceutically acceptable salt, solvate or ester thereof; wherein:

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

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



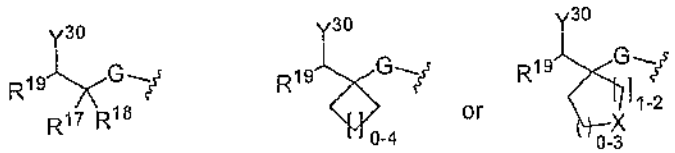
shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl;

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

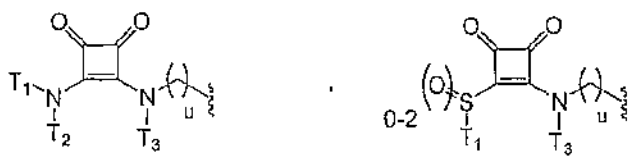
L is C(H), C(R), $CH_2C(R)$, or $C(R)CH_2$;

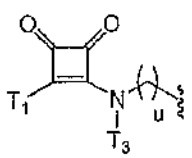
R, R', R^2, and R^3 can be the same or different, each being independently selected from the group consisting of H, alkyl-, alkenyl-, alkynyl-, cycloalkyl-, heteroalkyl-, heterocyclyl-, aryl-, heteroaryl-, (cycloalkyl)alkyl-, (heterocyclyl)alkyl-, aryl-alkyl-, and heteroaryl-alkyl-; or alternately R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

Y is selected from the following moieties:



wherein Y^{30} is selected from





where u is a number 0-1;

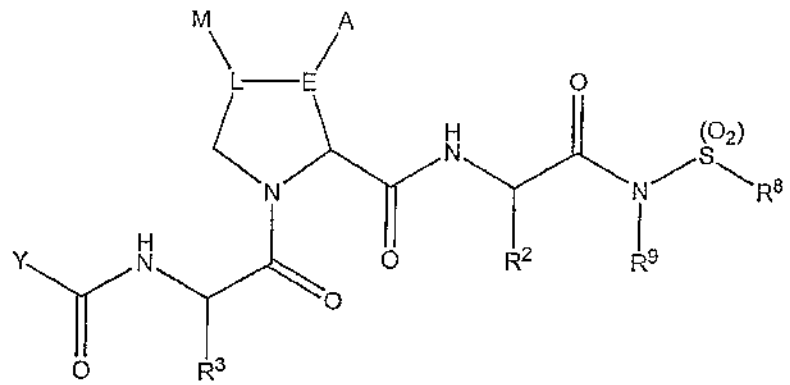
X is selected from O, NR^{15}, $NC(O)R^{16}$, S, S(O) and SO_2;

G is NH or O; and

R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, T_1, T_2, and T_3 can be the same or different, each being independently selected from the group consisting of H, alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, or alternately, R^{17} and R^{18} are connected to each other to form a three to eight-membered cycloalkyl or heterocyclyl;

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

In another embodiment, the compound is a compound of Formula XVIII:



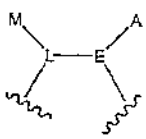
Formula XVIII

or a pharmaceutically acceptable salt, solvate or ester thereof, wherein:

R^8 is selected from the group consisting of alkyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, heterocyclyl-, arylalkyl-, heteroarylalkyl- , and heterocyclylalkyl;

R^9 is selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl and cycloalkyl;

A and M can be the same or different, each being independently selected from R, OR, N(H)R, N(RR'), SR, $S(O_2)R$, and halo; or A and M are connected to each other (in other words, A-E-L-M taken together) such that the moiety:



shown above in Formula I forms either a three, four, five, 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;

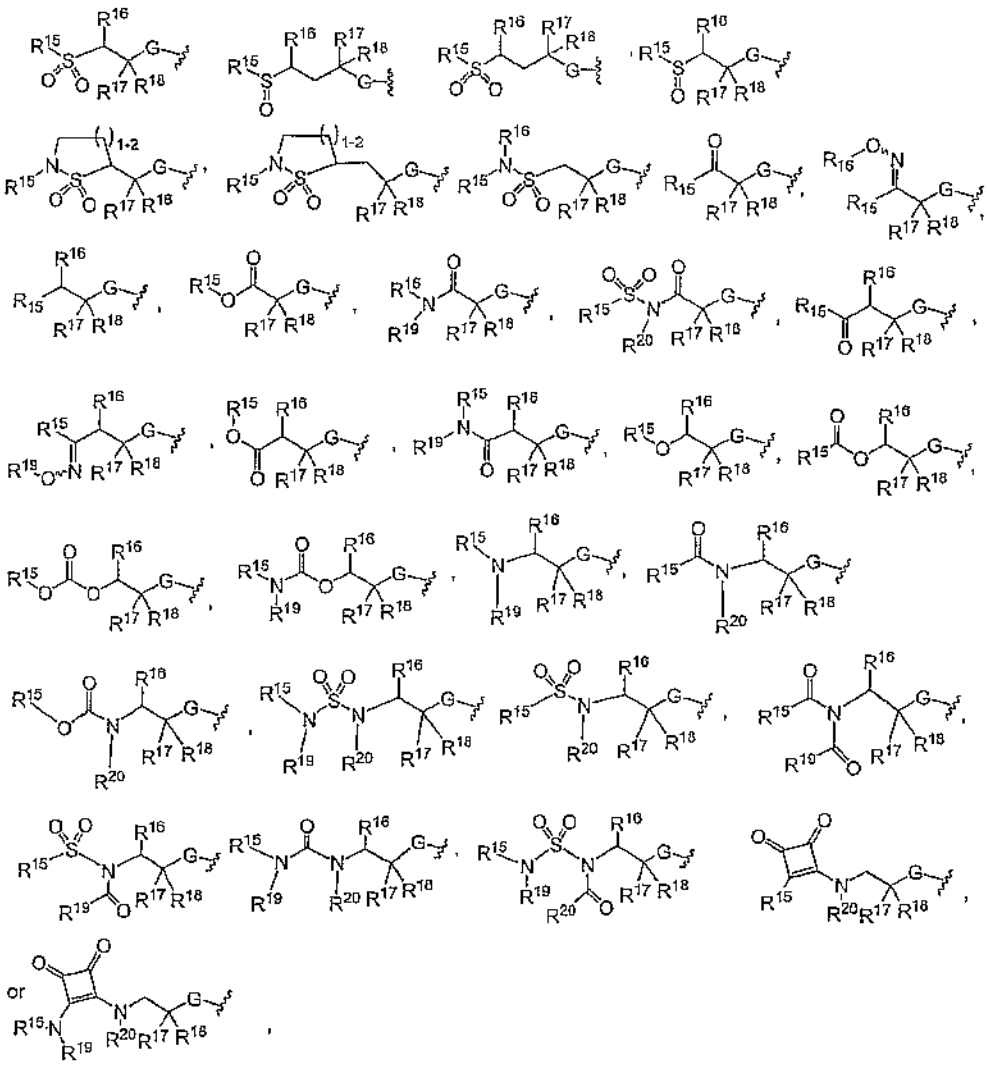
E is C(H) or C(R);

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

R and R' 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 N(RR') are connected to each other such that N(RR') forms a four to eight-membered heterocyclyl;

R^2 and R^3 can be the same or different, each being independently selected from the group consisting of H, alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, cycloalkyl, spiro-linked cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl;

Y is selected from the following moieties:

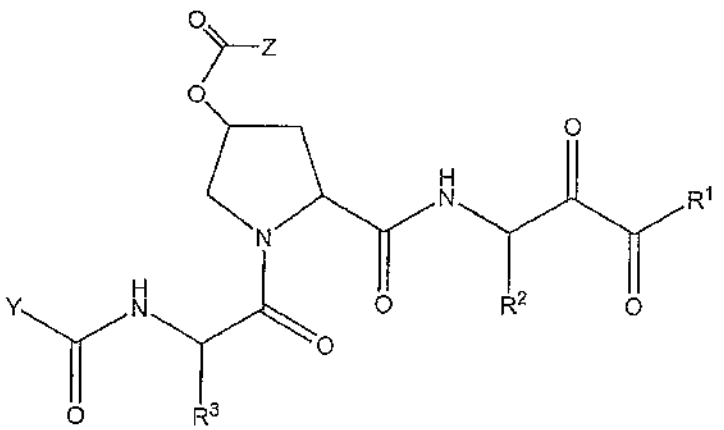


wherein G is NH or O; and R^{15}, R^{16}, R^{17}, R^{18}, R^{19} and R^{20} can be the same or different, each being independently selected from the group consisting of H, alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl,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

wherein each of said alkyl, aryl, heteroaryl, cycloalkyl, spiro-linked cycloalkyl, and

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

In another embodiment, the compound is a compound of Formula XIX:



Formula XIX

wherein:

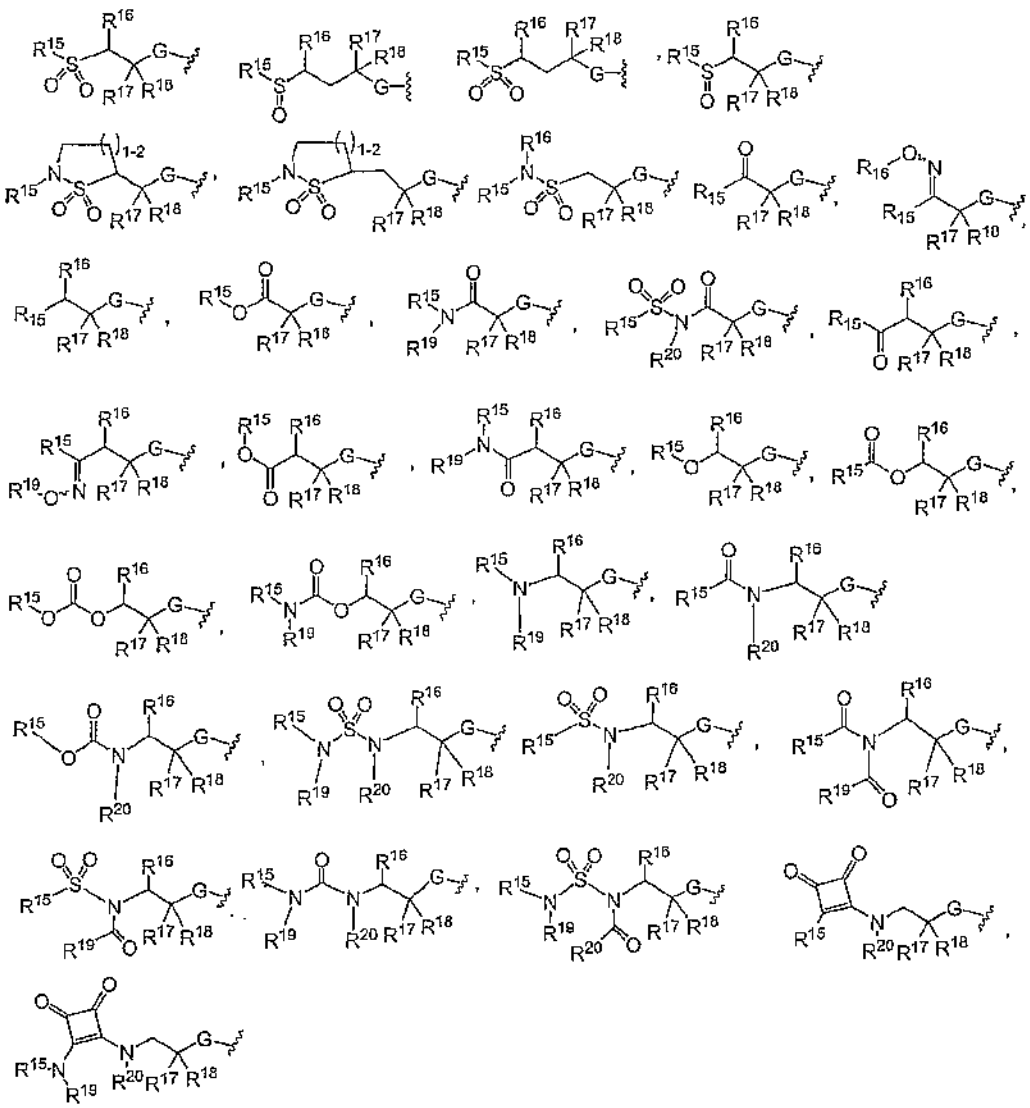
Z is selected from the group consisting of a heterocyclyl moiety,

N(H)(alkyl), -N(alkyl)$_2$, -N(H)(cycloalkyl), -N(cycloalkyl)$_2$, -N(H)(aryl, -N(aryl)$_2$, -N(H)(heterocyclyl), -N(heterocyclyl)$_2$, -N(H)(heteroaryl), and -N(heteroaryl)$_2$;

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, or alternately R^9 and R^{10} in NR^9R^{10} are connected to each other such that NR^9R^{10} forms a four to eight-membered heterocyclyl, and likewise independently alternately R^9 and R^{10} in CHR^9R^{10} are connected to each other such that CHR^9R^{10} forms a four to eight-membered cycloalkyl;

R^2 and R^3 can be the same or different, each being independently selected from the group consisting of H, alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl;

Y is selected from the following moieties:

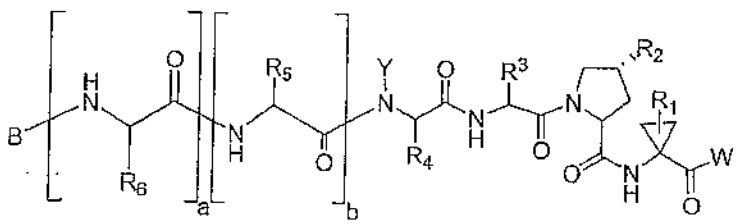


wherein G is NH or O; and R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20} and R^{21} can be the same or different, each being independently selected from the group consisting of H, alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, or alternately (i) R^{17} and R^{18} are independently connected to each other to form a three to eight-membered cycloalkyl or heterocyclyl; (ii) likewise independently R^{15} and R^{19} are connected to each other to form a four to eight-membered heterocyclyl; (iii) likewise independently R^{15} and R^{16} are connected to each other to form a four to eight-membered heterocyclyl; and (iv) likewise independently R^{15} and R^{20} are connected to each other to form a four to eight-membered 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.

In another embodiment, the compound is a compound of formula XX

P6 P5 P4 P3 P2 P1



Formula XX

or a pharmaceutically acceptable salt, solvate or ester thereof; wherein: a is 0 or 1; b is 0 or 1; Y is H or C_{1-6} alkyl;

B is H, an acyl derivative of formula R_7-C(O)- or a sulfonyl of formula R_7-SO2 wherein

R7 is (i) C_{1-10} alkyl optionally substituted with carboxyl, C_{1-6} alkanoyloxy or C_{1-6} alkoxy;

(ii) C_{3-7} cycloalkyl optionally substituted with carboxyl, (C_{1-6} alkoxy)carbonyl or phenylmethoxycarbonyl;

(iii) C_6 or C_{10} aryl or C_{7-16} aralkyl optionally substituted with C_{1-6} alkyl, hydroxy, or amino optionally substituted with C_{1-6} alkyl; or

(iv) Het optionally substituted with C_{1-6} alkyl, hydroxy, amino optionally substituted with C_{1-6} alkyl, or amido optionally substituted with C_{1-6} alkyl;

R_6, when present, is C_{1-6} alkyl substituted with carboxyl;

R_5, when present, is C_{1-6} alkyl optionally substituted with carboxyl;

R_4 is C_{1-10} alkyl, C_{3-7} cycloalkyl or C_{4-10} (alkylcycloalkyl);

R_3 is C_{1-10} alkyl, C_{3-7} cycloalkyl or C_{4-10} (alkylcycloalkyl);

R_2 is CH_2-R_{20}, NH-R_{20}, 0-R_{20} or S-R_{20}, wherein R_{20} is a saturated or unsaturated C_{3-7}

cycloalkyl or C_{4-10} (alkyl cycloalkyl) being optionally mono-, di- or tri-substituted with R_{21}, or R_{20} is a C_6 or C_{10} aryl or C_{7-16} aralkyl optionally mono-, di- or tri- substituted with R_{21},

or R_{20} is Het or (lower alkyl)-Het optionally mono-, di- or tri- substituted with R_{21},

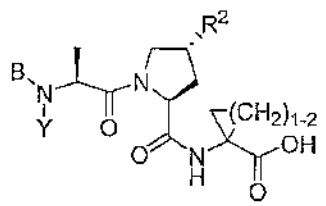
wherein each R_{21} is independently C_{1-6} alkyl; C_{1-6}alkoxy; amino optionally mono- or di-substituted with C_{1-6} alkyl; sulfonyl; NO_2; OH; SH; halo; haloalkyl; amido optionally mono-substituted with C_{1-6} alkyl, C_6 or C_{10} aryl, C_{7-16} aralkyl, Het or (lower alkyl)-Het; carboxyl; carboxy(lower alkyl); C_6 or C_{10} aryl, C_{7-16} aralkyl or Het, said aryl, aralkyl or Het being optionally substituted with R_{22};

wherein R_{22} is C_{1-6}alkyl; C_{1-6} alkoxy; amino optionally mono- or di- substituted with C_{1-6} alkyl; sulfonyl; NO_2; OH; SH; halo; haloalkyl; carboxyl; amide or (lower alkyl)amide;

R_1 is C_{1-6} alkyl or C_{2-6} alkenyl optionally substituted with halogen; and

W is hydroxy or a N-substituted amino.

In another embodiment, the compound is a compound of Formula XXI



Formula XXI

or a pharmaceutically acceptable salt, solvate or ester thereof; wherein:

B is H, a C_6 or C_{10} aryl, C_{7-16} aralkyl; Het or (lower alkyl)- Het, all of which optionally substituted with C_{1-6} alkyl; C_{1-6} alkoxy; C_{1-6} alkanoyl; hydroxy; hydroxyalkyl; halo; haloalkyl; nitro; cyano; cyanoalkyl; amino optionally substituted with C_{1-6} alkyl; amido; or (lower alkyl)amide;

or B is an acyl derivative of formula R_4-C(O)-; a carboxyl of formula R_4-0-C(O)-; an amide of formula R_4-N(R_5)-C(O)-; a thioamide of formula R_4-N(R_5)-C(S)-; or a sulfonyl of formula R_4-SO2 wherein

R_4 is (i) C_{1-10} alkyl optionally substituted with carboxyl, C_{1-6} alkanoyl, hydroxy, C_{1-6} alkoxy, amino optionally mono- or di-substituted with C_{1-6} alkyl, amido, or (lower alkyl) amide;

(ii) C_{3-7} cycloalkyl, C_{3-7} cycloalkoxy, or C_{4-10} alkylcycloalkyl, all optionally substituted with hydroxy, carboxyl, (C_{1-6} alkoxy)carbonyl, amino optionally mono- or di-substituted with C_{1-6} alkyl, amido, or (lower alkyl) amide;

(iii) amino optionally mono- or di-substituted with C_{1-6} alkyl; amido; or (lower alkyl)amide;

(iv) C_6 or C_{10} aryl or C_{7-16} aralkyl, all optionally substituted with C_{1-6} alkyl, hydroxy, amido, (lower alkyl)amide, or amino optionally mono- or di- substituted with C_{1-6} alkyl; or

(v) Het or (lower alkyl)-Het, both optionally substituted with C_{1-6} alkyl, hydroxy, amido, (lower alkyl) amide, or amino optionally mono- or di-substituted with C_{1-6} alkyl;

R_5 is H or C_{1-6} alkyl;

with the proviso that when R_4 is an amide or a thioamide, R_4 is not (ii) a cycloalkoxy;

Y is H or C_{1-6} alkyl;

R_3 is C_{1-8} alkyl, C_{3-7} cycloalkyl, or C_{4-10} alkylcycloalkyl, all optionally substituted with hydroxy, C_{1-6} alkoxy, C_{1-6} thioalkyl, amido, (lower alkyl)amido, C_6 or C_{10} aryl, or C_{7-16} aralkyl;

R_2 is CH_2-R_{20}, NH-R_{20}, O-R_{20} or S-R_{20}, wherein R_{20} is a saturated or unsaturated C_{3-7} cycloalkyl or C_{4-10} (alkylcycloalkyl), all of which being optionally mono-, di- or tri-substituted with R_{21}, or R_{20} is a C_6 or C_{10} aryl or C_{7-14} aralkyl, all optionally mono-, di- or tri-substituted with R_{21},

or R_{20} is Het or (lower alkyl)-Het, both optionally mono-, di- or tri- substituted with R_{21},

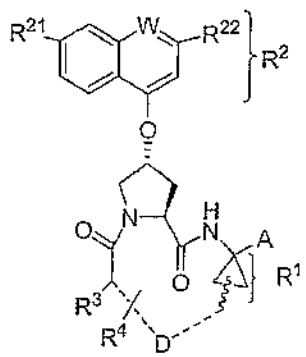
wherein each R_{21} is independently C_{1-6} alkyl; C_{1-6} alkoxy; lower thioalkyl; sulfonyl; NO_2; OH; SH; halo; haloalkyl; amino optionally mono- or di- substituted with C_{1-6} alkyl, C_6 or C_{10} aryl, C_{7-14} aralkyl, Het or (lower alkyl)-Het; amido optionally mono-substituted with C_{1-6} alkyl, C_6 or C_{10} aryl, C_{7-14} aralkyl, Het or (lower alkyl)-Het;

carboxyl; carboxy(lower alkyl); C_6 or C_{10} aryl, C_{7-14} aralkyl or Het, said aryl, aralkyl or Het being optionally substituted with R_{22};

wherein R_{22} is C_{1-6} alkyl; C_{3-7} cycloalkyl; C_{1-6} alkoxy; amino optionally mono- or di-substituted with C_{1-6} alkyl; sulfonyl; (lower alkyl)sulfonyl; NO_2; OH; SH; halo; haloalkyl; carboxyl; amide; (lower alkyl)amide; or Het optionally substituted with C_{1-6} alkyl;

R1 is H; C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, all optionally substituted with halogen.

In another embodiment, the compound is a compound of Formula XXII



Formula XXII

or a pharmaceutically acceptable salt, solvate or ester thereof; wherein

W is CH or N,

R^{21} is H, halo, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkoxy, hydroxy, or $N(R^{23})_2$, wherein each R^{23} is independently H, C_{1-6} alkyl or C_{3-6} cycloalkyl;

R^{22} is H, halo, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} thioalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkoxy, C_{2-7} alkoxyalkyl, C_{3-6} cycloalkyl, $C_{6 \text{ or } 10}$ aryl or Het, wherein Het is a five-, six-, or seven-membered saturated or unsaturated heterocycle containing from one to four heteroatoms selected from nitrogen, oxygen and sulfur;

said cycloalkyl, aryl or Het being substituted with R^{24} , wherein R^{24} is H, halo, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkoxy, NO_2 , $N(R^{25})_2$, NH-C(O)-R^{25} or NH-C(O)-NH-R^{25}, wherein each R^{25} is independently: H, C_{1-6} alkyl or C_{3-6} cycloalkyl;

or R^{24} is NH-C(O)-OR^{26} wherein R^{26} is C_{1-6} alkyl or C_{3-6} cycloalkyl;

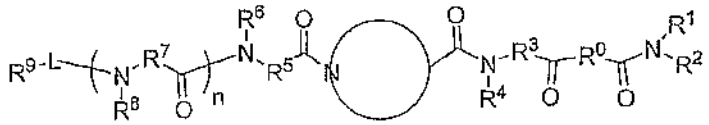
R^3 is hydroxy, NH_2 , or a group of formula -NH-R^{31} , wherein R^{31} is $C_{6 \text{ or } 10}$ aryl, heteroaryl, -C(O)-R^{32}, -C(O)-NHR^{32} or -C(O)-OR^{32} , wherein R^{32} is C_{1-6} alkyl or C_{3-6} cycloalkyl;

D is a 5 to 10-atom saturated or unsaturated alkylene chain optionally containing one to three heteroatoms independently selected from: O, S, or N-R^{41} , wherein R^{41} is H, C_{1-6} alkyl, C_{3-6} cycloalkyl or -C(O)-R^{42} , wherein R^{42} is C_{1-6} alkyl, C_{3-6} cycloalkyl or $C_{6 \text{ or } 10}$ aryl; R^4 is H or from one to three substituents at any carbon atom of said chain D, said substituent independently selected from the group consisting of: C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, hydroxy, halo, amino, oxo, thio and C 1-6 thioalkyl, and

A is an amide of formula -C(O)-NH-R^5 , wherein R^5 is selected from the group consisting of: C_{1-6} alkyl, C_{3-6} cycloalkyl, $C_{6 \text{ or } 10}$ aryl and C_{7-16} aralkyl;

or A is a carboxylic acid.

In another embodiment, the compound is a compound of Formula XXIII



Formula XXIII

a pharmaceutically acceptable salt, solvate or ester thereof; wherein:

R^0 is a bond or difluoromethylene;

R^1 is hydrogen, optionally substituted aliphatic group, optionally substituted cyclic group or optionally substituted aromatic group;

R^2 and R^9 are each independently optionally substituted aliphatic group, optionally substituted cyclic group or optionally substituted aromatic group;

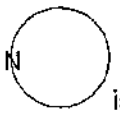
R3, R5 and R7 are each independently:

optionally substituted (1, 1- or 1,2-)cycloalkylene; or

optionally substituted (1,1- or 1,2-) heterocyclylene; or

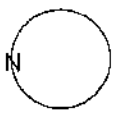
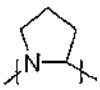
methylene or ethylene), substituted with one substituent selected from the group consisting of an optionally substituted aliphatic group, an optionally substituted cyclic group or an optionally substituted aromatic group, and wherein the methylene or ethylene is further optionally substituted with an aliphatic group substituent; or;

R4, R 6, R8 and R^{10} are each independently hydrogen or optionally substituted aliphatic group;

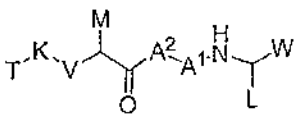


is substituted monocyclic azaheterocyclyl or optionally substituted multicyclic azaheterocyclyl, or optionally substituted multicyclic azaheterocyclenyl wherein the unsaturatation is in the ring distal to the ring bearing the R^9-L-(N(R^8)-R^7-C(O)-)$_n$N(R^6)-R^5-C(O)-N moiety and to which the –C(O)-N(R^4)-R^3-C(O)C(O)NR^2R^1 moiety is attached; L is -C(O)-, -OC(O)-, -NR^{10}C(O)-, -S(0)$_2$-, or – NR^{10}S(0)$_2$-; and n is 0 or 1,

provided

when  is substituted , then L is -OC(O)- and R^9 is optionally substituted aliphatic; or at least one of R^3, R^5 and R^7 is ethylene, substituted with one substituent selected from the group consisting of an optionally substituted aliphatic group, an optionally substituted cyclic group or an optionally substituted aromatic group and wherein the ethylene is further optionally substituted with an aliphatic group substituent; or R^4 is optionally substituted aliphatic.

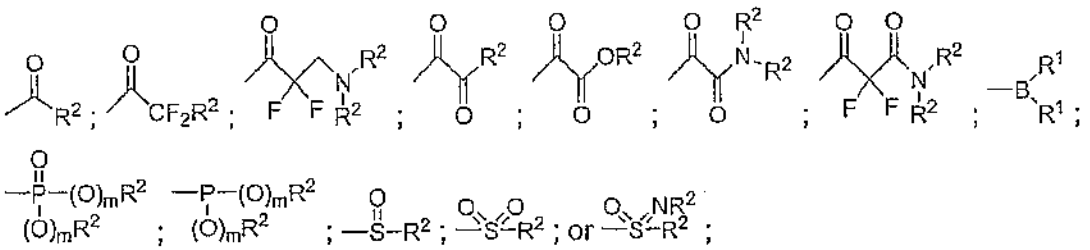
In another embodiment, the compound is a compound of Formula XXIV



Formula XXIV

or a pharmaceutically acceptable salt, solvate or ester thereof; wherein:

W is:



m is 0 or 1;

each R^1 is hydroxy, alkoxy, or aryloxy, or each R^1 is an oxygen atom and together with the boron, to which they are each bound, form a 5-7 membered ring, wherein the ring atoms are carbon, nitrogen, or oxygen;

each R^2 is independently hydrogen, alkyl, alkenyl, aryl, aralkyl, aralkenyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkenyl, heteroaryl, or heteroaralkyl, or two R^2 groups, which are bound to the same nitrogen atom, form together with that nitrogen atom, a 5-7 membered monocyclic heterocyclic ring system; wherein any R^2 carbon atom is optionally substituted with J;

J is alkyl, aryl, aralkyl, alkoxy, aryloxy, aralkoxy, cycloalkyl, cycloalkoxy, heterocyclyl, heterocyclyloxy, heterocyclylalkyl, keto, hydroxy, amino, alkylamino, alkanoylamino, aroylamino, aralkanoylamino, carboxy, carboxyalkyl, carboxamidoalkyl, halo, cyano, nitro, formyl, acyl, sulfonyl, or sulfonamido and is optionally substituted with 1-3 J^1 groups;

J^1 is alkyl, aryl, aralkyl, alkoxy, aryloxy, heterocyclyl, heterocyclyloxy, keto, hydroxy, amino, alkanoylamino, aroylamino, carboxy, carboxyalkyl, carboxamidoalkyl, halo, cyano, nitro, formyl, sulfonyl, or sulfonamido;

L is alkyl, alkenyl, or alkynyl, wherein any hydrogen is optionally substituted with halogen, and wherein any hydrogen or halogen atom bound to any terminal carbon atom is optionally substituted with sulfhydryl or hydroxy;

A^1 is a bond;

R^4 is alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, carboxyalkyl, or carboxamidoalkyl, and is optionally substituted with 1-3 J groups;

R^5 and R^6 are independently hydrogen, alkyl, alkenyl, aryl, aralkyl, aralkenyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroaralkyl, and is optionally substituted with 1-3 J groups;

X is a bond, -C(H)(R7)-, -0-, - S-, or -N(R8)-;

R^7 is hydrogen, alkyl, alkenyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroaralkyl, and is optionally substitituted with 1-3 J groups;

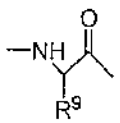
R^8 is hydrogen alkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, aralkanoyl, heterocyclanoyl, heteroaralkanoyl, $-C(O)R^{14}$, $-S0_2R^{14}$, or carboxamido, and is optionally substitituted with 1-3 J groups; or R^8 and Z, together with the atoms to which they are bound, form a nitrogen containing mono- or bicyclic ring system optionally substituted with 1-3 J groups;

R^{14} is alkyl, aryl, aralkyl, heterocyclyl, heterocyclyalkyl, heteroaryl, or heteroaralkyl;

Y is a bond, $-CH_2-$, -C(O)-, -C(O)C(O)-, - S(O)-, $-S(0)_2-$, or $-S(O)(NR^7)-$, wherein R^7 is as defined above;

Z is alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, $-OR^2$, or $-N(R^2)_2$, wherein any carbon atom is optionally substituted with J, wherein R^2 is as defined above;

A^2 is a bond or



R^9 is alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, carboxyalkyl, or carboxamidoalkyl, and is optionally substituted with 1-3 J groups;

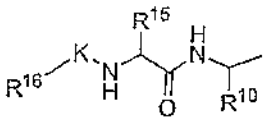
M is alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroaralkyl, optionally substituted by 1-3 J groups, wherein any alkyl carbon atom may be replaced by a heteroatom;

V is a bond, $-CH_2-$, $-C(H)(R^{11})-$, -0-, -S-, or $-N(R^{11})-$;

R^{11} is hydrogen or C_{1-3} alkyl;

K is a bond, -0-, -S-, -C(O)-, -S(O)-, $-S(0)_2-$, or $-S(O)(NR^{11})-$, wherein R^{11} is as defined above;

T is -R^{12}, -alkyl-R^{12}, -alkenyl-R^{12}, - alkynyl-R^{12}, -OR^{12}, -$N(R^{12})2$, -$C(O)R^{12}$, -$C(=NOalkyl)R^{12}$, or



;

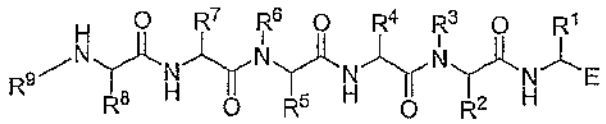
R^{12} is hydrogen, aryl, heteroaryl, cycloalkyl, heterocyclyl, cycloalkylidenyl, or heterocycloalkylidenyl, and is optionally substituted with 1-3 J groups, or a first R^{12} and a second R^{12}, together with the nitrogen to which they are bound, form a mono- or bicyclic ring system optionally substituted by 1-3 J groups;

R^{10} is alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, carboxyalkyl, or carboxamidoalkyl, and is optionally substituted with 1-3 hydrogens J groups;

R^{15} is alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, carboxyalkyl, or carboxamidoalkyl, and is optionally substituted with 1-3 J groups; and

R^{16} is hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, or heterocyclyl.

In another embodiment, the compound is a compound of Formula XXV



Formula XXV

or a pharmaceutically acceptable salt, solvate or ester thereof;
wherein

E represents CHO or $B(OH)_2$;

R^1 represents lower alkyl, halo-lower alkyl, cyano-lower alkyl, lower alkylthio-lower alkyl, aryl-lower alkylthio-lower alkyl, aryl-lower alkyl, heteroaryllower alkyl, lower alkenyl or lower alkynyl;

R^2 represents lower alkyl, hydroxy-lower alkyl, carboxylower alkyl, aryl- lower alkyl, aminocarbonyl-lower alkyl or lower cycloalkyl-lower alkyl; and

R^3 represents hydrogen or lower alkyl;

or R^2 and R^3 together represent di- or trimethylene optionally substituted by hydroxy;

R^4 represents lower alkyl, hydroxy-lower alkyl, lower cycloalkyl-lower alkyl, carboxy-lower alkyl, aryllower alkyl, lower alkylthio-lower alkyl, cyano-lower alkylthio-lower alkyl, aryl-lower alkylthio-lower alkyl, lower alkenyl, aryl or lower cycloalkyl;

R^5 represents lower alkyl, hydroxy-lower alkyl, lower alkylthio-lower alkyl, aryl-lower alkyl, aryl-lower alkylthio-lower alkyl, cyano-lower alkylthio-lower alkyl or lower cycloalkyl;

R^6 represents hydrogen or lower alkyl;

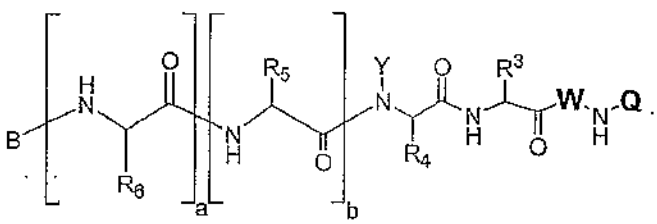
R^7 represent lower alkyl, hydroxydower alkyl, carboxylower alkyl, aryl-lower alkyl, lower cycloalkyl-lower alkyl or lower cycloalkyl;

R^8 represents lower alkyl, hydroxy-lower alkyl, carboxylower alkyl or aryl-lower alkyl; and

R^9 represents lower alkylcarbonyl, carboxy-lower alkylcarbonyl, arylcarbonyl, lower alkylsulphonyl, arylsulphonyl, lower alkoxycarbonyl or aryl-lower alkoxycarbonyl.

In another embodiment, the compound is a compound of Formula XXVI

P6 P5 P4 P3 P2 P1



Formula XXVI

or a pharmaceutically acceptable salt, solvate or ester thereof; wherein

B is an acyl derivative of formula R_{11}-C(O)- wherein R_{11} is Cl-10 alkyl optionally substituted with carboxyl; or R_{11} is C_6 or C_{10} aryl or C_{7-16} aralkyl optionally substituted with a C_{1-6} alkyl;

a is 0 or 1;

R_6, when present, is carboxy(lower)alkyl;

b is 0 or 1;

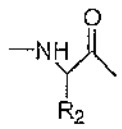
R_5, when present, is C_{1-6} alkyl, or carboxy(lower)alkyl;

Y is H or C_{1-6} alkyl;

R_4 is C_{1-10} alkyl; C_{3-10} cycloalkyl;

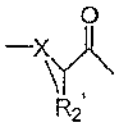
R_3 is C1-10 alkyl; C_{3-10} cycloalkyl;

W is a group of formula:



wherein R_2 is C_{1-10} alkyl or C_{3-7} cycloalkyl optionally substituted with carboxyl; C_6 or C_{10} aryl; or C_{7-16} aralkyl; or

W is a group of formula:



wherein X is CH or N; and

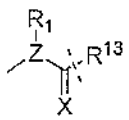
R_2' is C_{3-4} alkylene that joins X to form a 5- or 6-membered ring, said ring optionally substituted with OH; SH; NH2; carboxyl; R_{12}; OR_{12}, SR_{12}, NHR_{12} or $NR_{12}R_{12}$' wherein R_{12} and R_{12}' are independently:

cyclic C_{3-16} alkyl or acyclic C_{1-16} alkyl or cyclic C_{3-16} alkenyl or acyclic C_{2-16} alkenyl, said alkyl or alkenyl optionally substituted with NH_2, OH, SH, halo, or carboxyl; said alkyl or alkenyl optionally containing at least one heteroatom selected independently from the group consisting of: 0, S, and N; or

R_{12} and R_{12}' are independently C_6 or C_{10} aryl or C_{7-16} aralkyl optionally substituted with C_{1-6} alkyl, NH_2, OH, SH, halo, carboxyl or carboxy(lower)alkyl; said aryl or aralkyl optionally containing at least one heteroatom selected independently from the group consisting of: 0, S, and N;

said cyclic alkyl, cyclic alkenyl, aryl or aralkyl being optionally fused with a second 5-, 6-, or 7-membered ring to form a cyclic system or heterocycle, said second ring being optionally substituted with NH_2. OH, SH, halo, carboxyl or carboxy(lower)alkyl; C_6 or C_{10} aryl, or heterocycle; said second ring optionally containing at least one heteroatom selected independently from the group consisting of: 0, S, and N;

Q is a group of the formula:



wherein Z is CH or N;

X is 0 or S;

R_1 is H, C_{1-6} alkyl or C_{1-6} alkenyl both optionally substituted with thio or halo; and

when Z is CH, then R_{13} is H; CF_3; CF_2CF_3; CH_2-R_{14}; CH(F)-R_{14}; CF_2-R_{14}; $NR_{14}R_{14}$'; S-R_{14}; or C0-NH-R_{14} wherein R_{14} and R_{14}' are independently hydrogen, cyclic C_{3-10} alkyl or acyclic C_{1-10} alkyl or cyclic C_{3-10} alkenyl or acyclic C_{2-10} alkenyl, said alkyl or alkenyl optionally substituted with NH_2, OH, SH, halo or carboxyl; said alkyl or alkenyl optionally containing at least one heteroatom selected independently from the group consisting of: 0, S, and N; or

R_{14} and R_{14}' are independently C_6 or C_{10} aryl or C_{7-16} aralkyl optionally substituted with C_{1-6} alkyl, NH_2, OH, SH, halo, carboxyl or carboxy(lower)alkyl or substituted with a further C_{3-7} cycloalkyl, C_6 or C_{10} aryl, or heterocycle; said aryl or aralkyl optionally containing at least one heteroatom selected independently from the group consisting of: 0, S, and N;

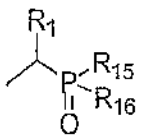
said cyclic alkyl, cyclic alkenyl, aryl or aralkyl being optionally fused with a second 5-, 6-, or 7-membered ring to form a cyclic system or heterocycle, said second ring being optionally substituted with NH_2, OH, SH, halo, carboxyl or carboxy(lower)alkyl or substituted with a further C_{3-7} cycloalkyl, C_6 or C_{10} aryl, or heterocycle; said second ring optionally containing at least one heteroatom selected independently from the group consisting of: 0, S, and N;

or R_{14} and R_{14}' are independently C_{1-4} alkyl which when joined together with N form a 3 to 6-membered nitrogen-containing ring which is optionally fused with a further C_{3-7} cycloalkyl, C_6 or C_{10} aryl or heterocycle;

with the proviso that when Z is CH, then R_{13} is not an α-amino acid or an ester thereof;

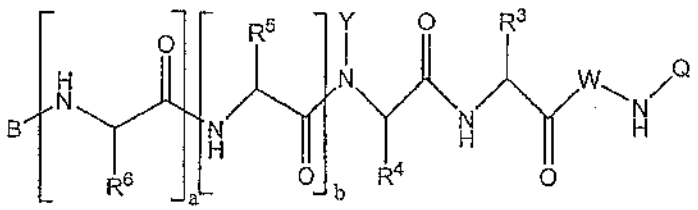
when Z is N, then R_{13} is H; carboxy; C_{1-6} alkyl optionally substituted with carboxy; CH_2-R_{14}; $CHR_{14}R_{14}$'; CH(F)-R_{14}; O-R_{14}; $NR_{14}R_{14}$' or S-R_{14} wherein R_{14} and R_{14}' are as defined above; or

Q is a phosphonate group of the formula:

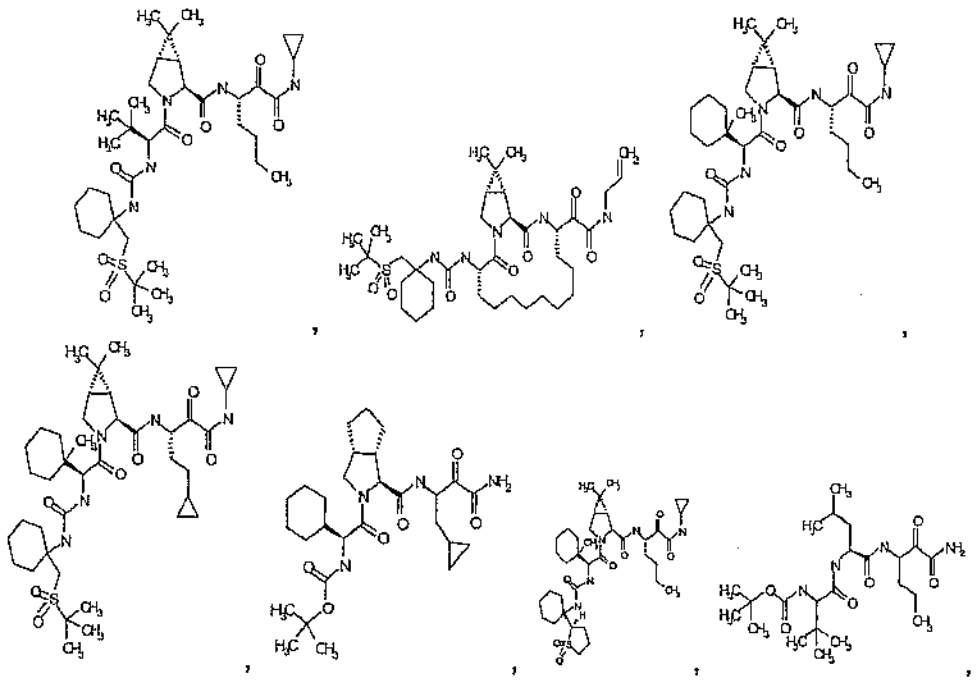


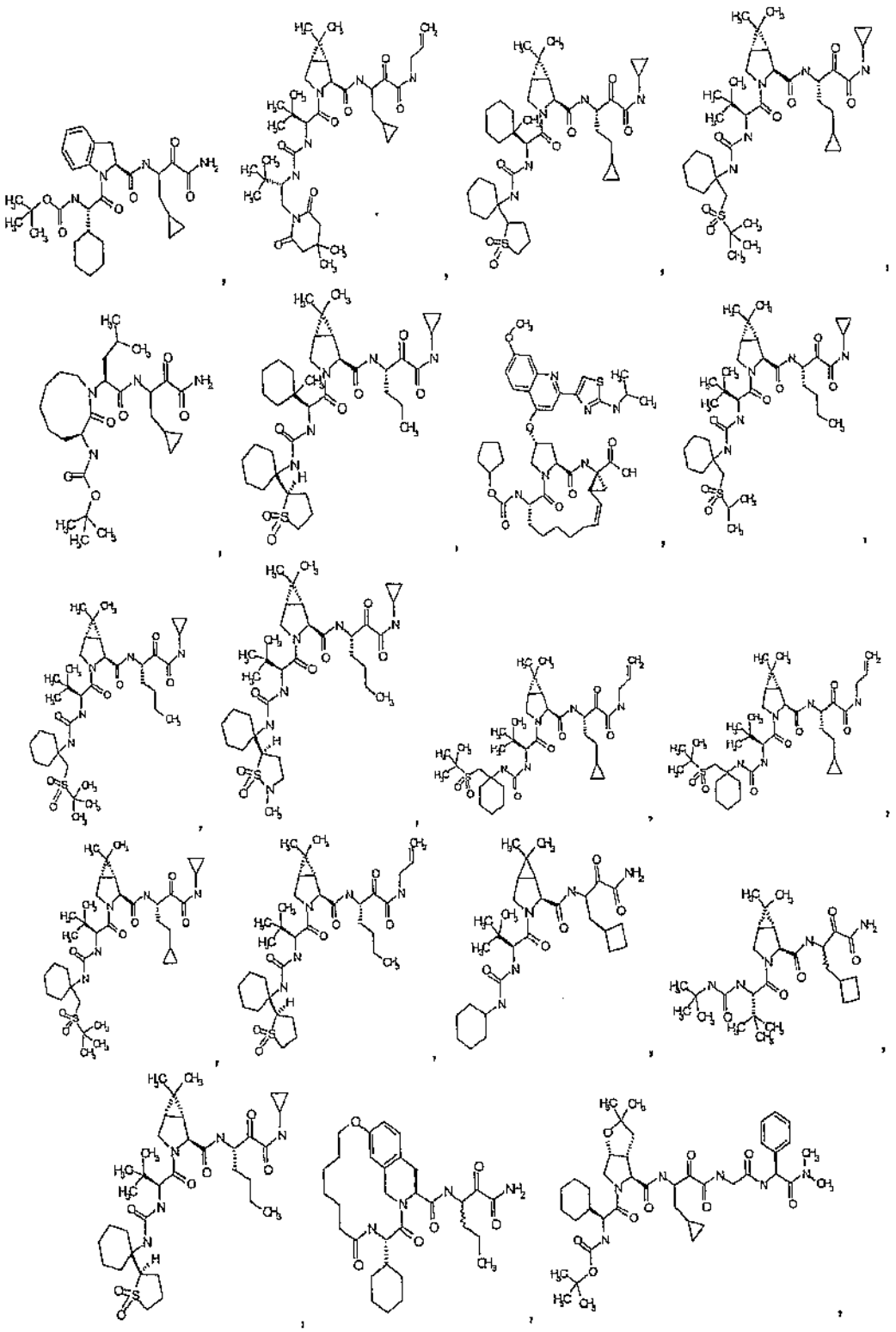
wherein R_{15} and R_{16} are independently C_{6-20} aryloxy; and R_1 is as defined above.

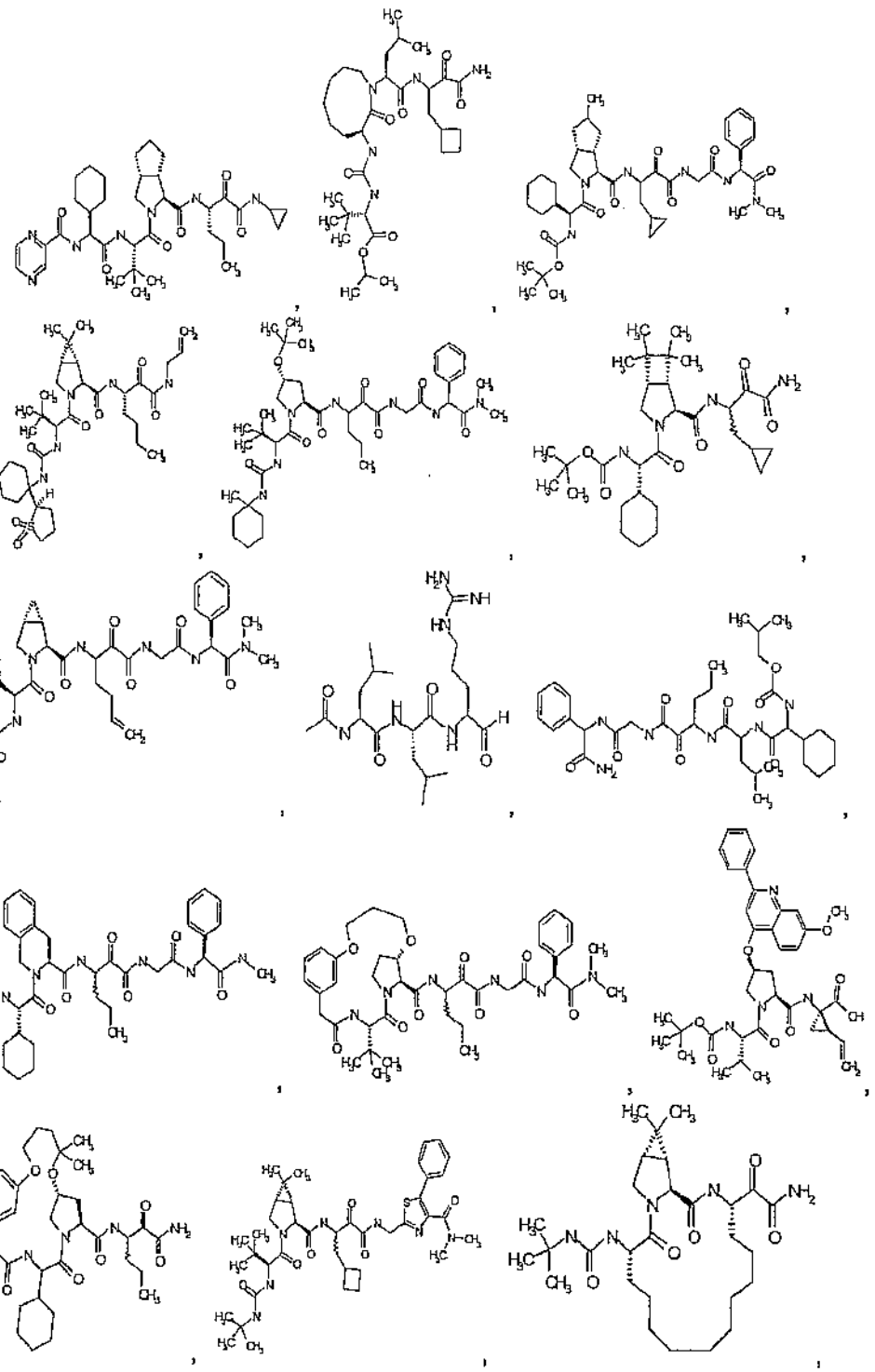
In the above-shown structure of the compound of Formula XXVI, the terms P6, P5, P4, P3, P2 and P1 denote the respective amino acid moieties as is conventionally known to those skilled in the art. Thus, the actual structure of the compound of Formula XXVI is:



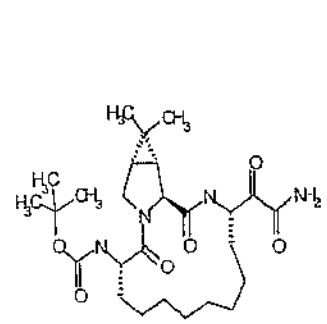
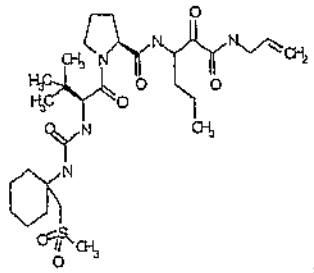
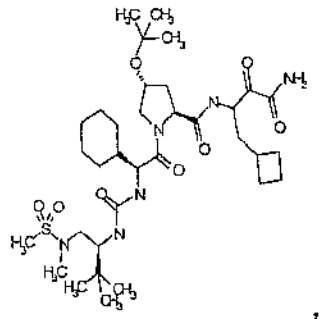
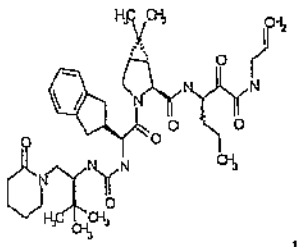
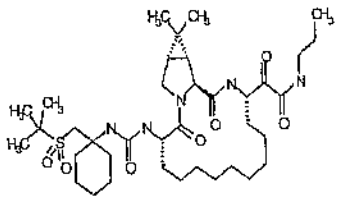
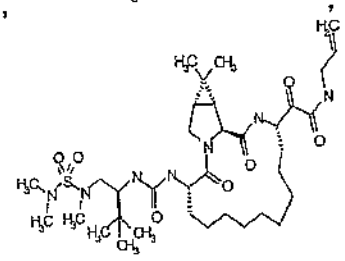
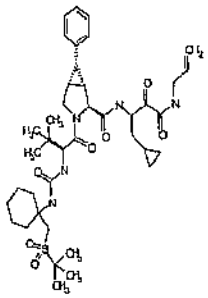
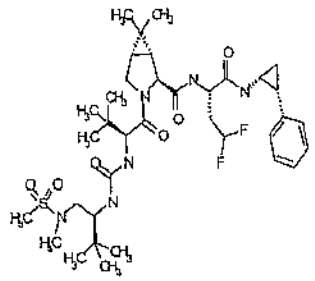
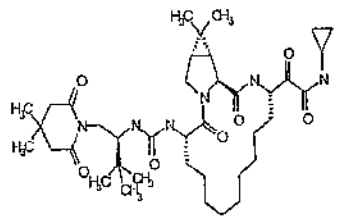
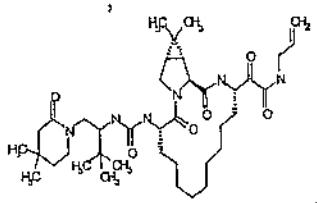
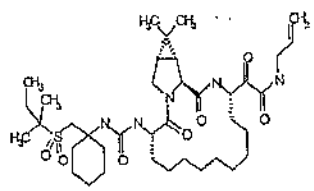
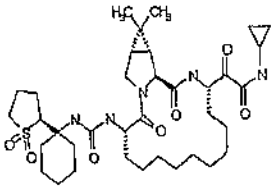
In another embodiment, the compound is selected from the group consisting of:







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,

or a pharmaceutically acceptable salt, solvate or ester thereof.

The surfactant in the pharmaceutical formulations of the present invention enhances wetting of the present compounds by aqueous systems (as in a mammal) and improves the dissolution rate of the compounds to render a greater quantity of the compound available for absorption than is available in a formulation of the present compounds that does not include a surfactant. Any pharmaceutically

acceptable surfactant that improves wetting of the present compounds may be used. Non-limiting examples of suitable surfactants include sodium lauryl sulfate, stearic acid, monoethanolamine, docusate sodium, sorbitan fatty acid esters, polyoxyethylene sorbitan fatty acid esters, ethoxylated aliphatic alcohols, propylene glycol monocaprylate, glycerol monostearate, medium chain triglycerides, polyoxyethylene alkyl ethers, and polyoxyethylene stearates. Additional suitable surfactants are discussed later.

The pharmaceutical formulations of the present invention may be used in treating HCV and other diseases/disorders, including those associated with cathepsin activity and/or for inhibiting cathepsin activity in a subject. One example of such disorders is proliferative diseases, such as cancer, autoimmune diseases, viral diseases, fungal diseases, neurological/neurodegenerative disorders, arthritis, inflammation, anti-proliferative (e.g., ocular retinopathy), neuronal, alopecia and cardiovascular disease. Many of these diseases and disorders are listed in U.S. 6,413,974, the disclosure of which is incorporated herein.

Another example of a disease that can be treated using the pharmaceutical formulations of the present invention is an inflammatory disease, such as organ transplant rejection, graft v. host disease, arthritis, rheumatoid arthritis, inflammatory bowel disease, atopic dermatitis, psoriasis, asthma, allergies, multiple sclerosis, fixed drug eruptions, cutaneous delayed-type hypersentitivity responses, tuberculoid leprosy, type I diabetes, and viral meningitis. Another example of a disease that can be treated using the pharmaceutical formulations of the present invention is a cardiovascular disease. Another example of a disease that can be treated using the pharmaceutical formulations of the present invention is a central nervous system disease, such as depression, cognitive function disease, neurodegenerative disease such as Parkinson's disease, senile dementia such as Alzheimer's disease, and psychosis of organic origin.

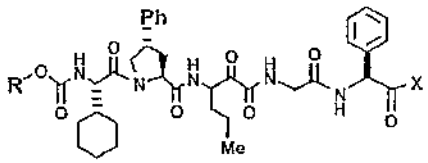
Other examples of diseases that can be treated using the pharmaceutical formulations of the present invention are diseases characterized by bone loss, such as osteoporosis; gingival diseases, such as gingivitis and periodontitis; and diseases characterized by excessive cartilage or matrix degradation, such as osteoarthritis and rheumatoid arthritis.

Other than in the operating examples, or where otherwise indicated, all numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about."

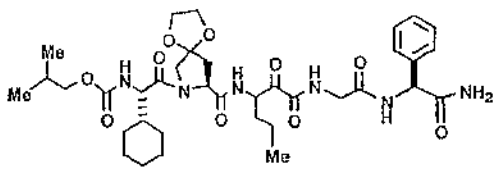
DETAILED DESCRIPTION

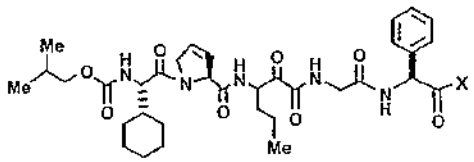
The present invention provides pharmaceutical formulations comprising at least one (one or more) compound of Formulae I-XXVI and at least one surfactant. Such formulations can be useful for inhibiting HCV protease and/or capthesin activity and have good dissolution characteristics to facilitate absorption of the compounds of Formulae I-XXVI.

Suitable compounds of formula I are disclosed in PCT International publication WO03/062265 published July 31, 2003. Non-limiting examples of certain compounds disclosed in this publication include:

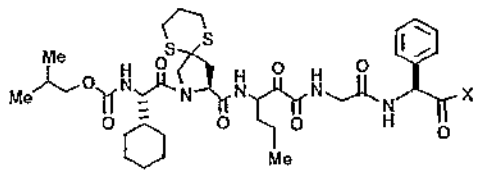


(R = t-butyl, X = NH_2)
(R = Isobutyl, X = NH_2)
(R = t-butyl, X = OH)
(R = Trichloroethyl, X = OH)

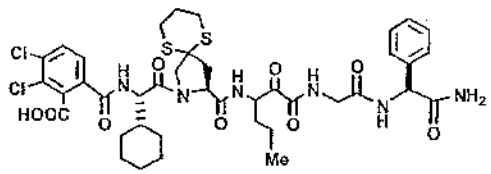


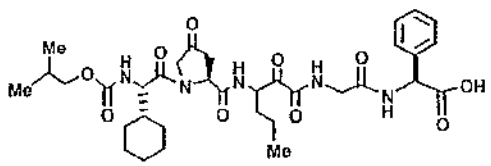


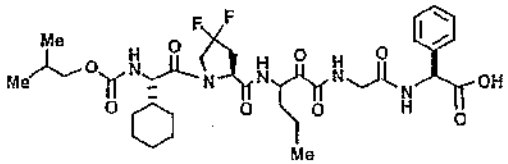
(X = O^{t}Bu)
(X = OH)

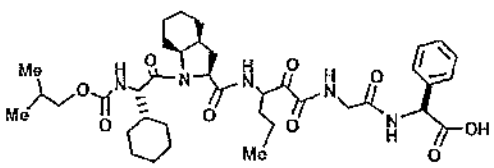


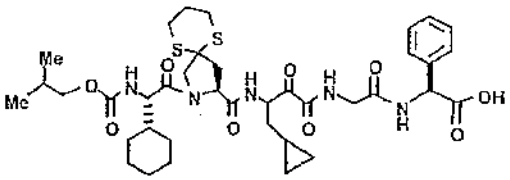
(X = OH)
(X = O^{t}Bu)
(X = NH_2)
(X = NHMe)
(X = NMe_2)

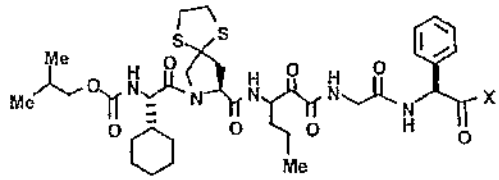




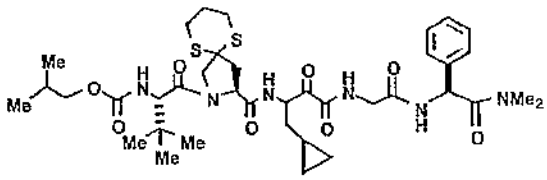


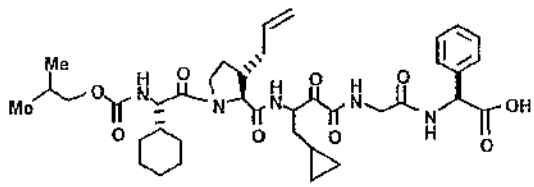


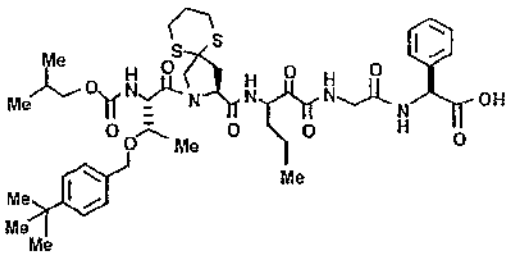


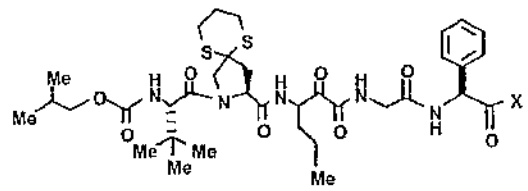


(X = NH_2)
(X = NMe_2)
(X = NHMe)
(X = OH)

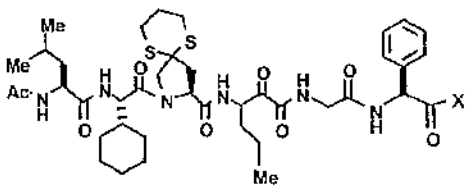




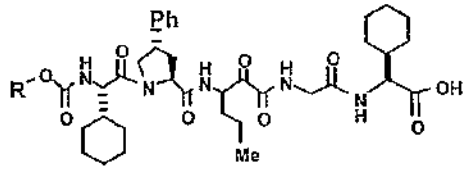




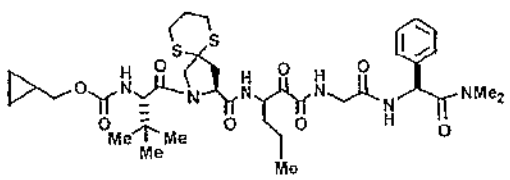
(X = O^tBu)
(X = OH)
(X = NH_2)
(X = NMe_2)

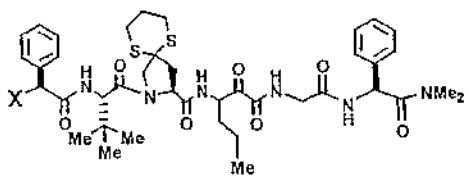


(X = O^tBu)
(X = OH)
(X = NH_2)
(X = NMe_2)
(X = NMeOMe)

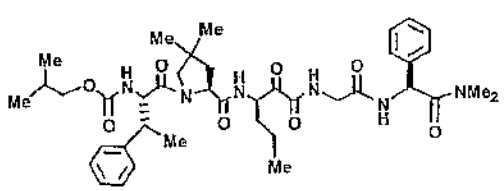


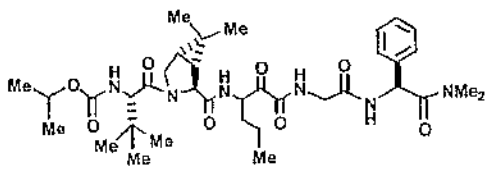
(R = t-butyl)
(R = Isobutyl)

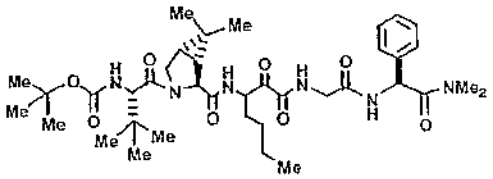


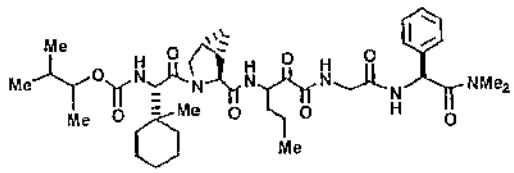


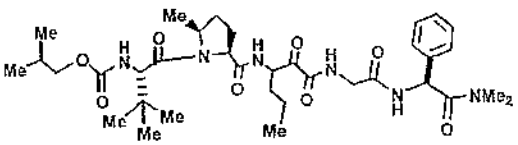
(X = Me, Y = CH_2Me)
(X = OAc, Y = Me)

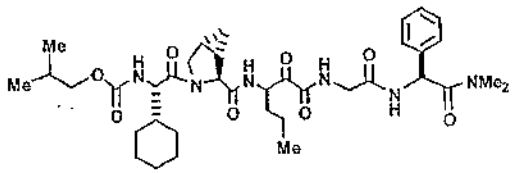


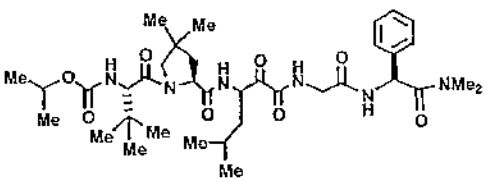


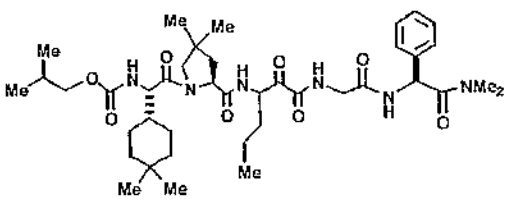


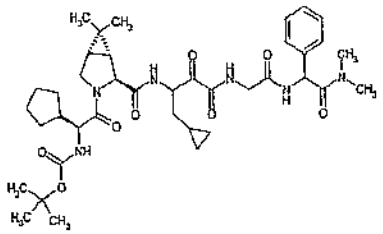


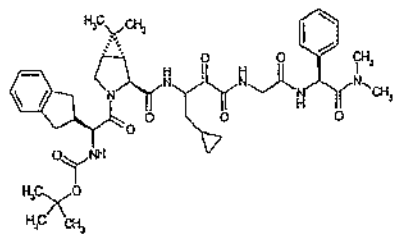


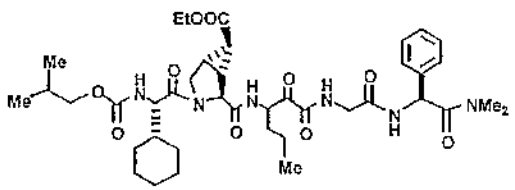


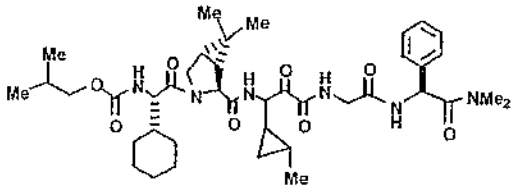


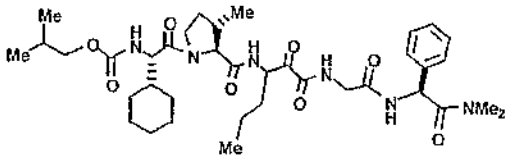


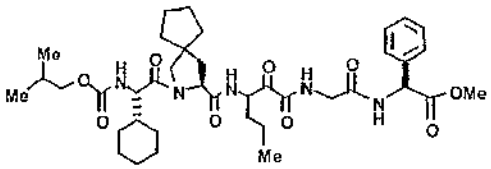


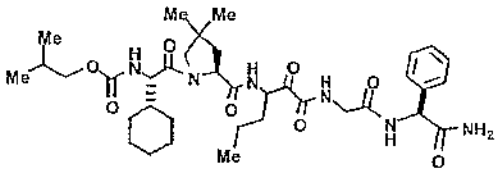


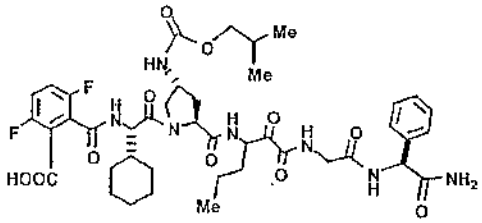


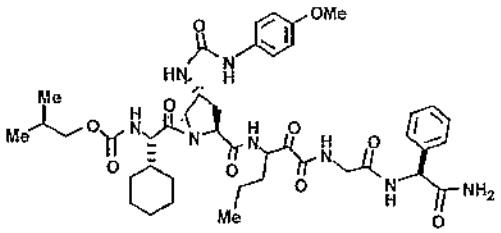


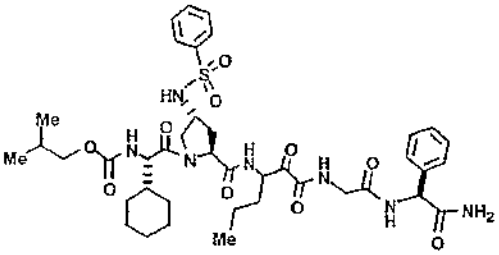


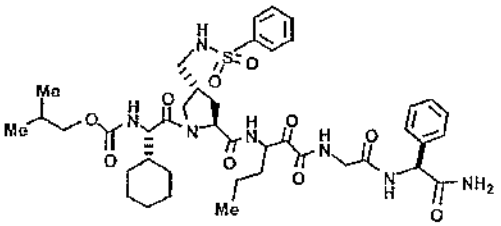


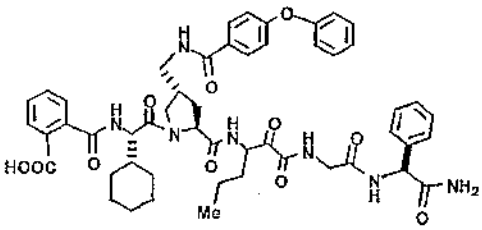


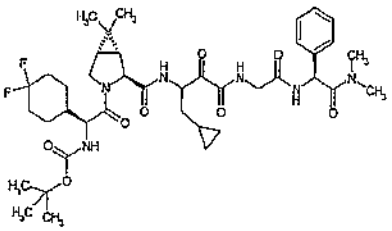


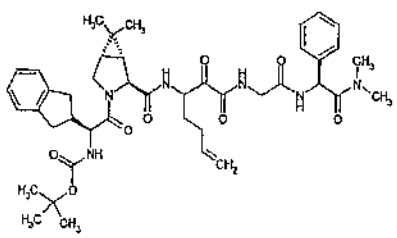


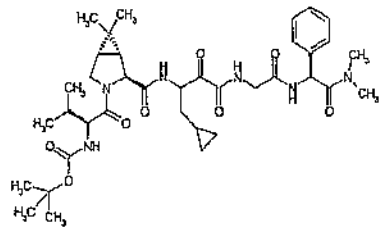
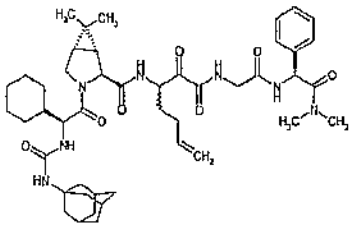
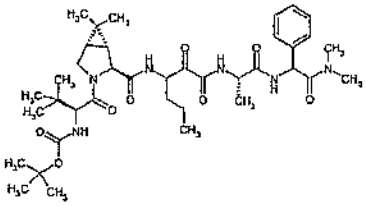
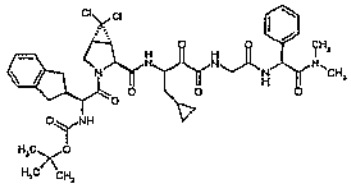
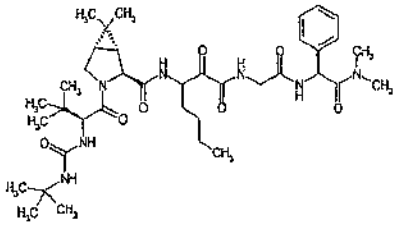
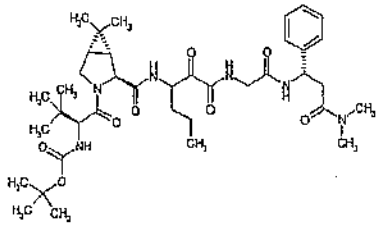
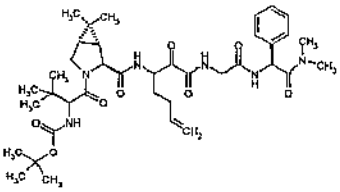
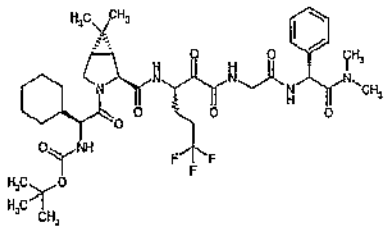
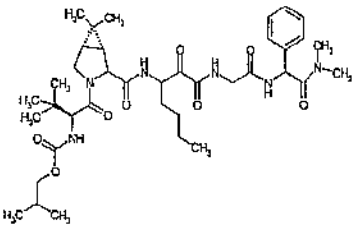
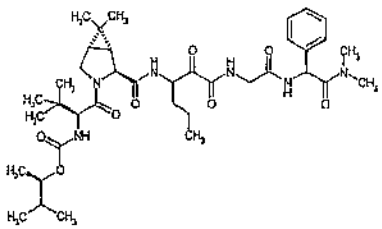
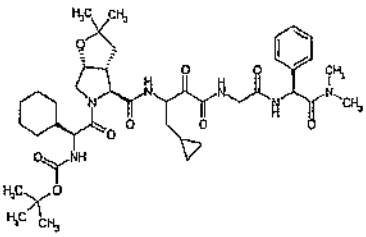
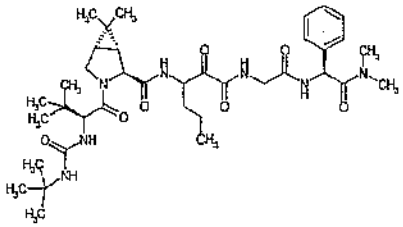
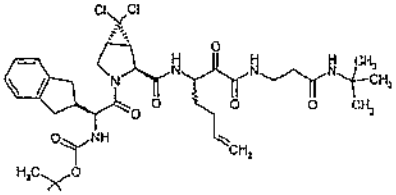
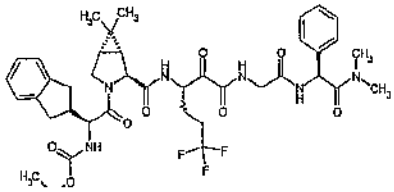


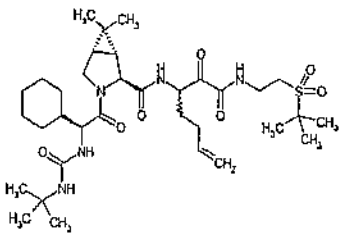


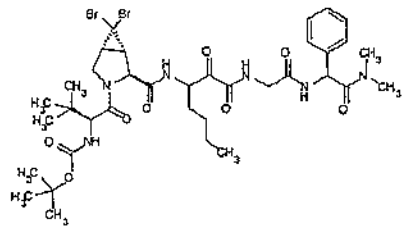


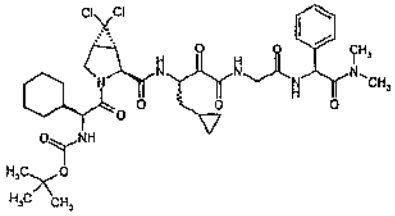


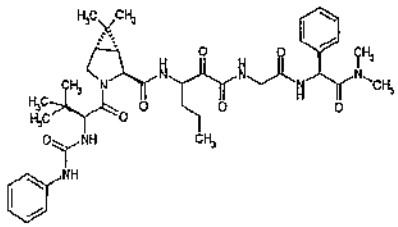


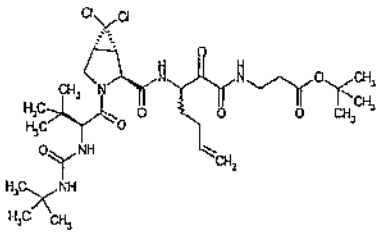















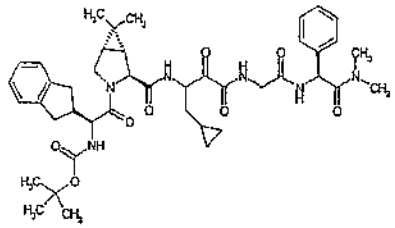


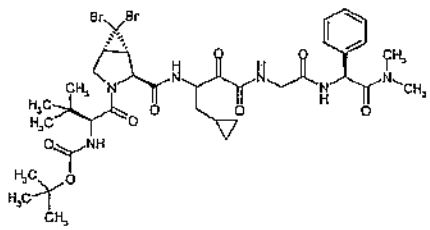


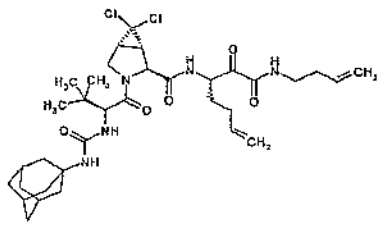


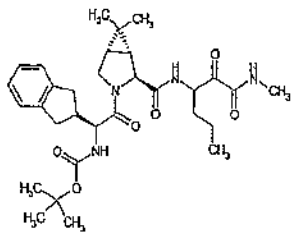


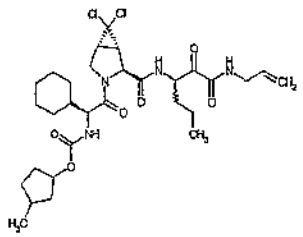


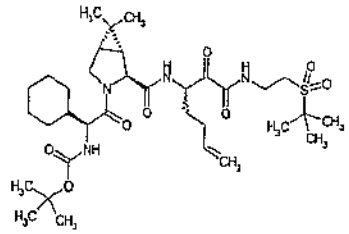


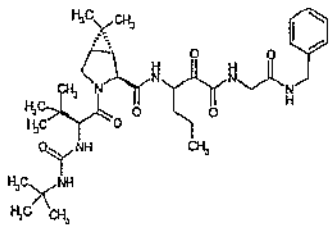


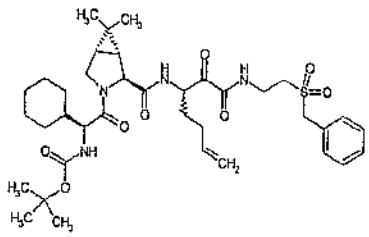


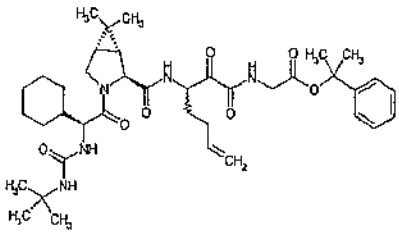


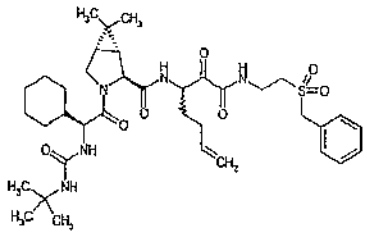


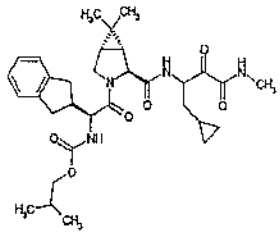


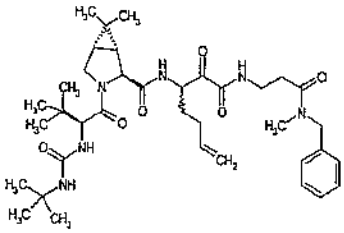


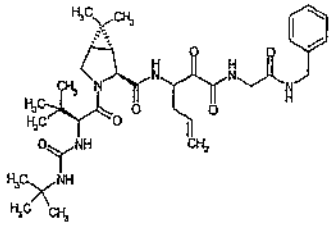


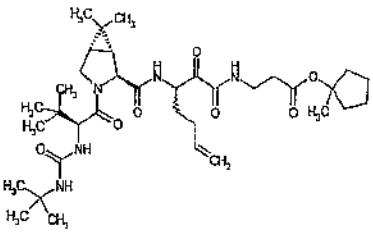


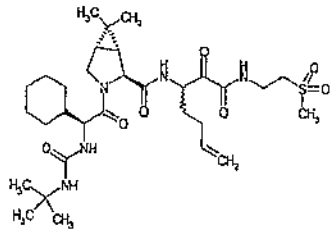


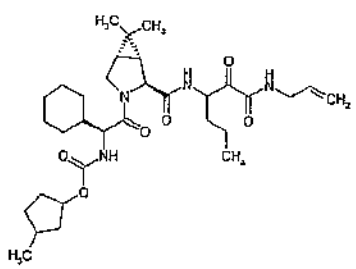


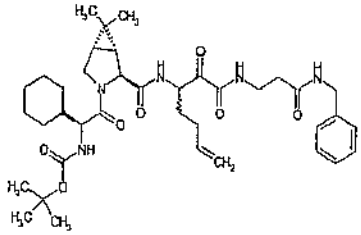


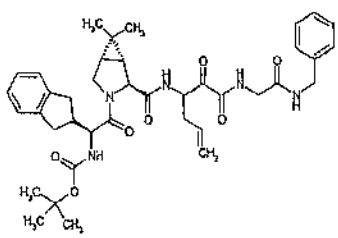


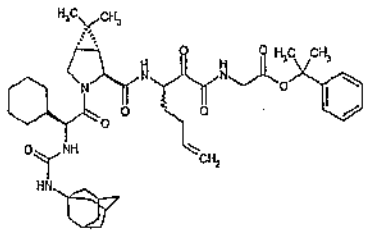


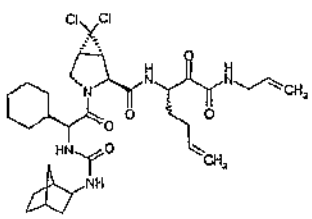


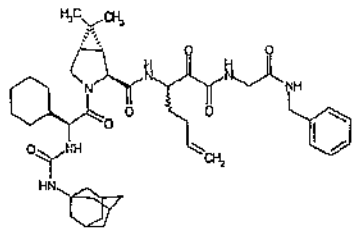


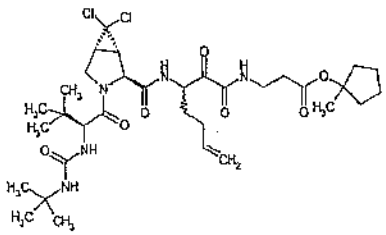


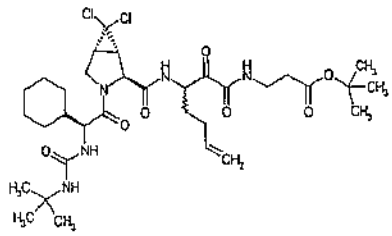


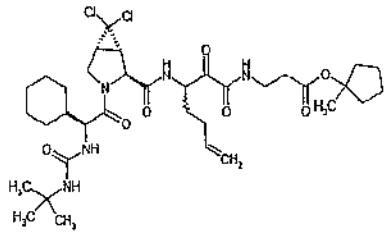


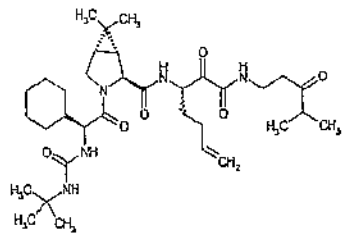


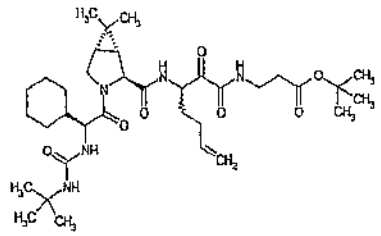


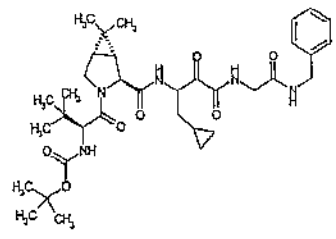


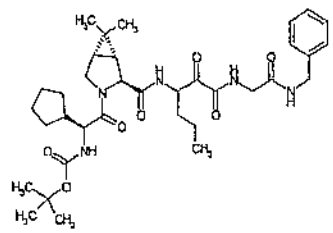


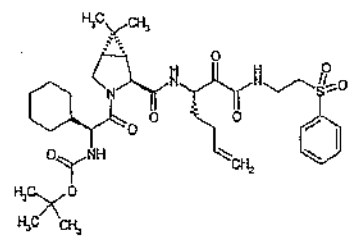


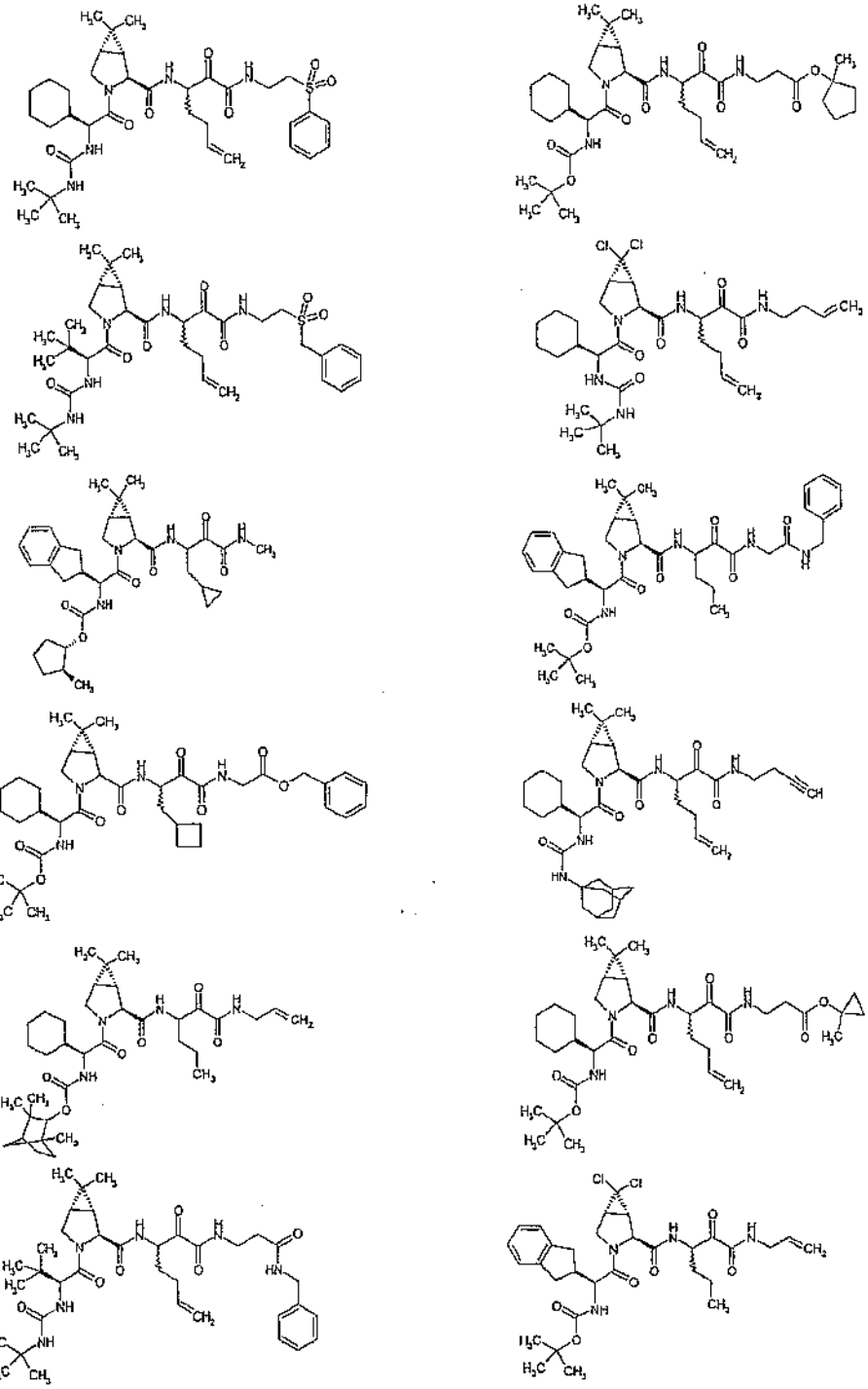


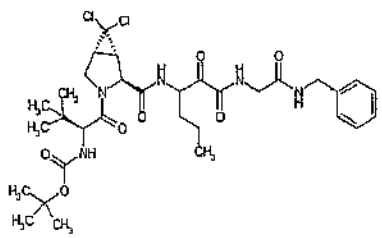
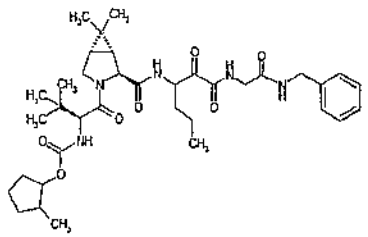
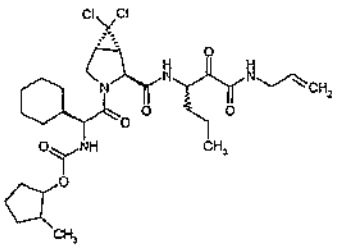
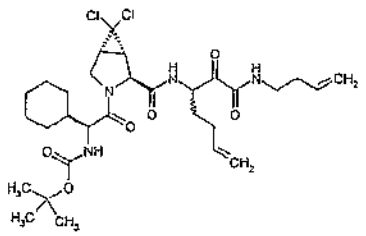
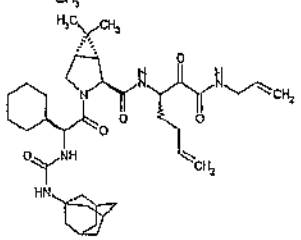
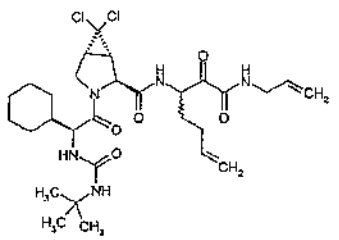
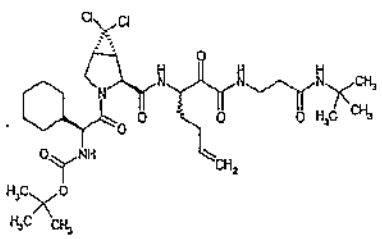
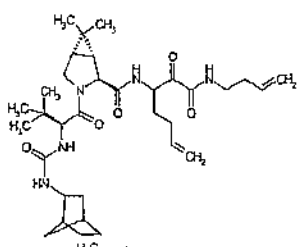
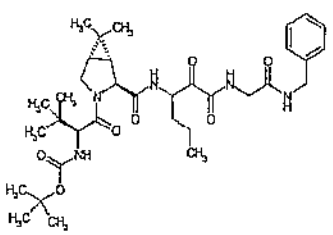
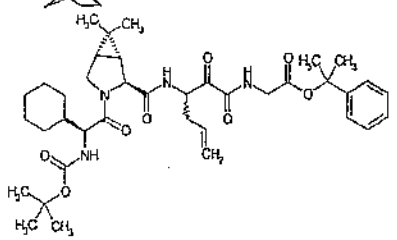
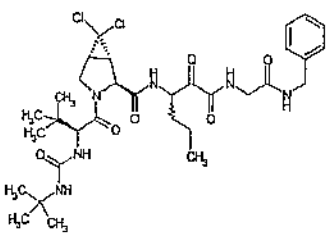
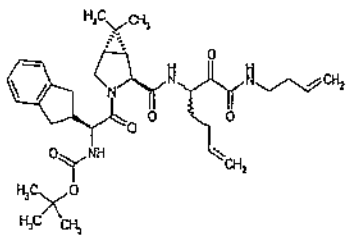


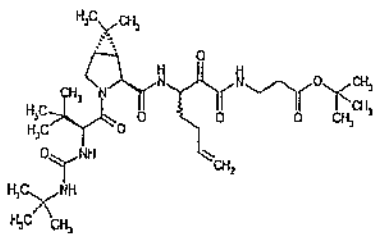
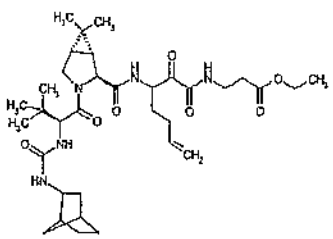
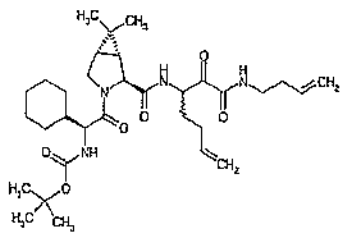
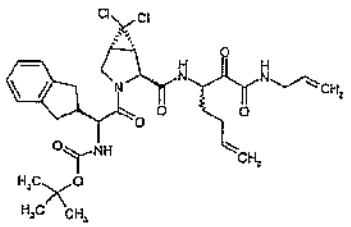
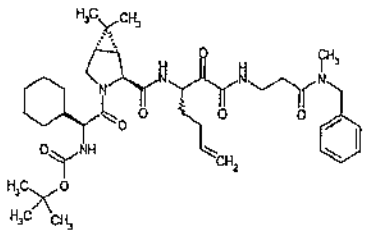
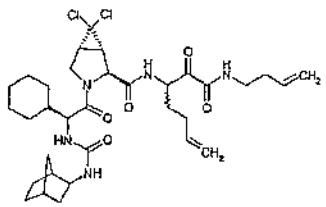
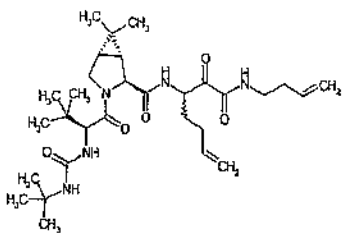
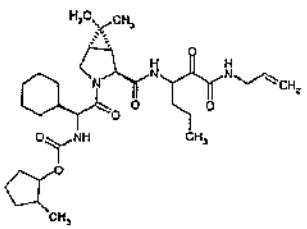
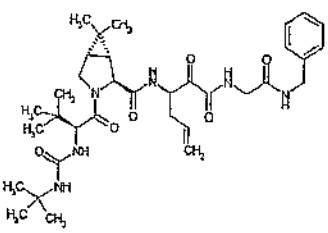
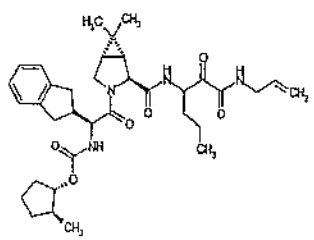
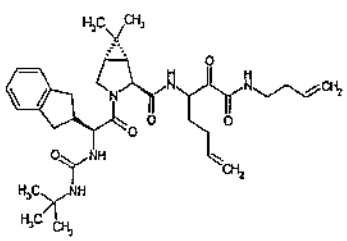
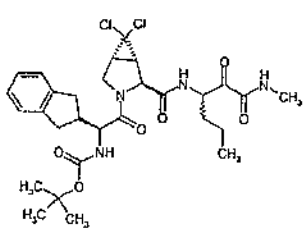


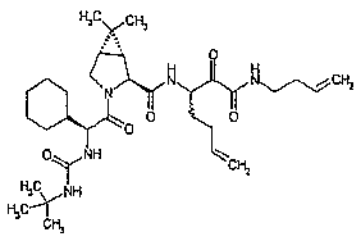
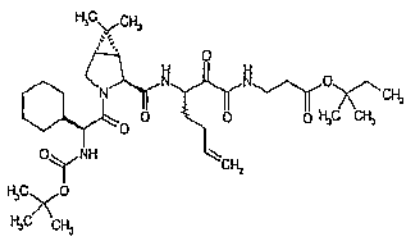
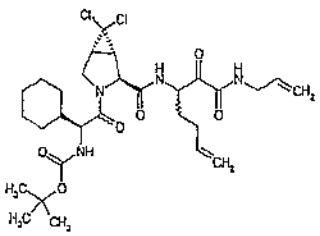
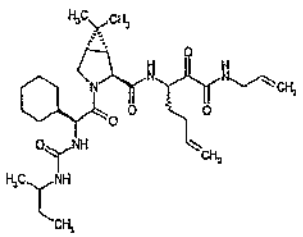
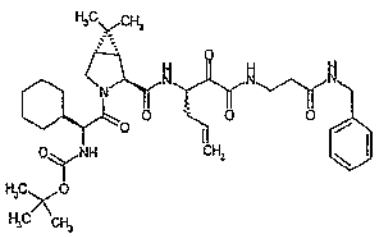
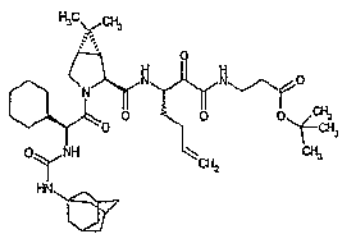
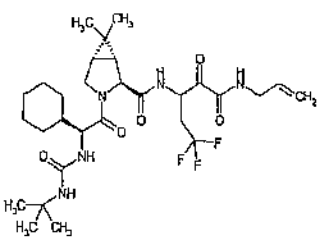
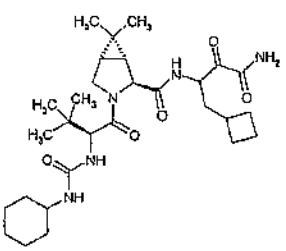
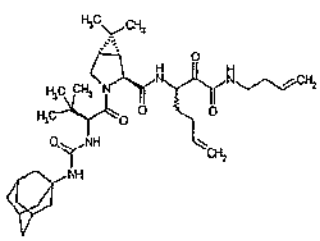
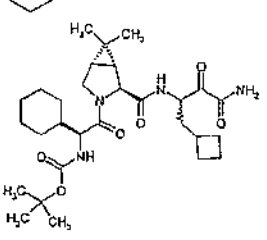
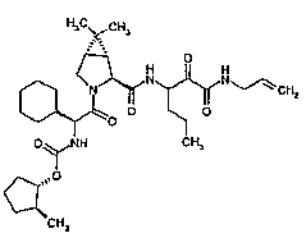
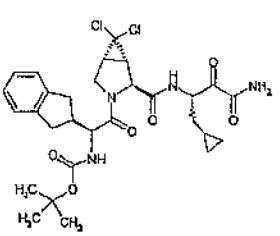


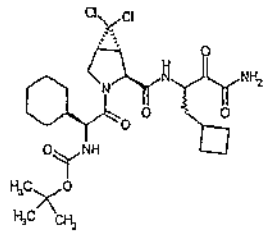


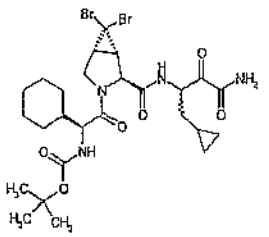


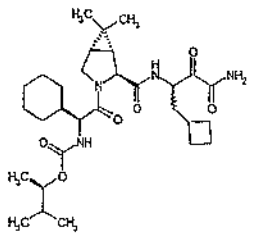













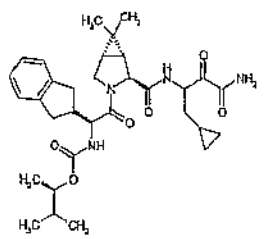













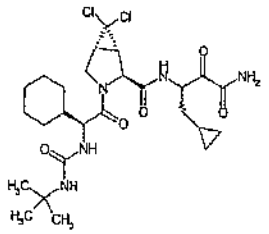













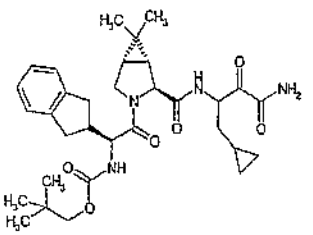


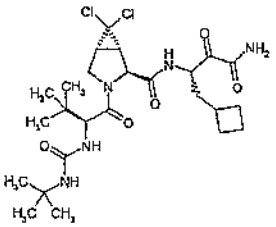


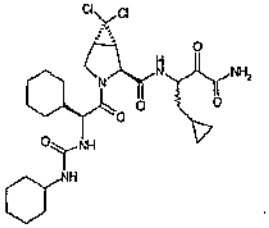


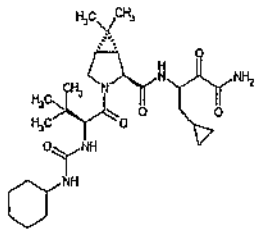


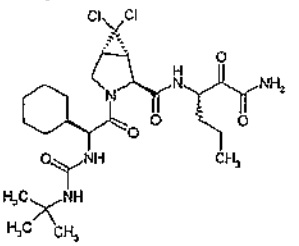


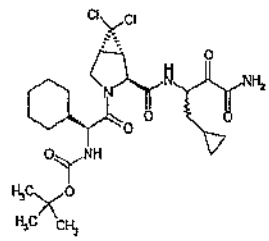


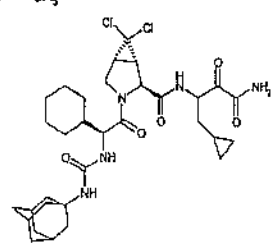




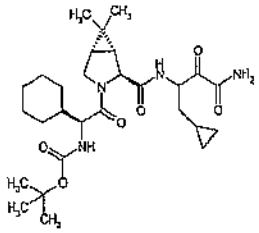


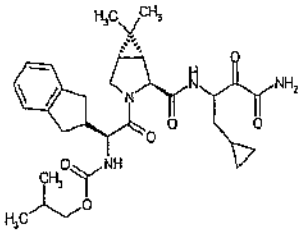


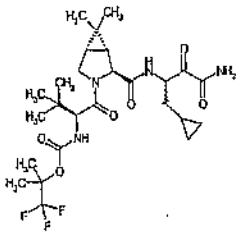


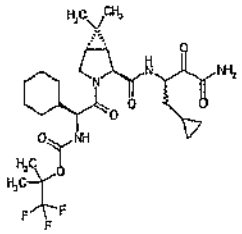


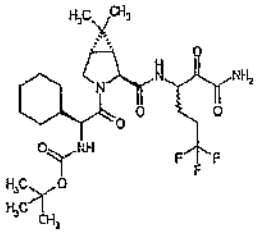
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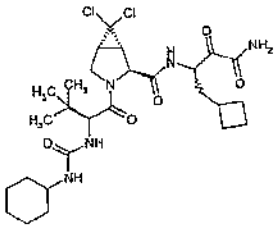


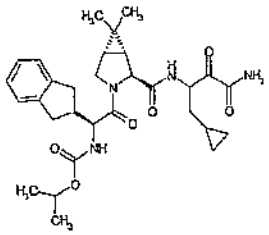


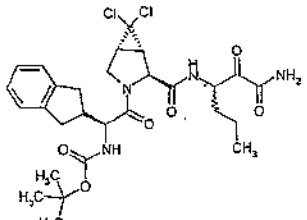


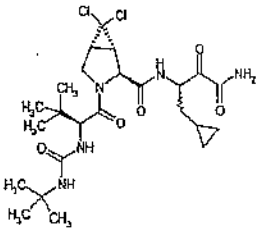


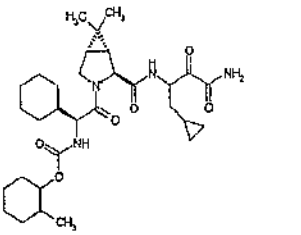


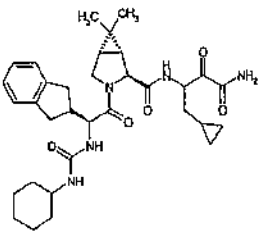


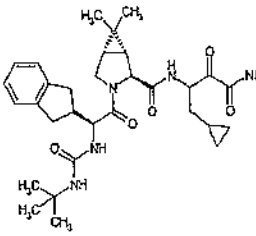


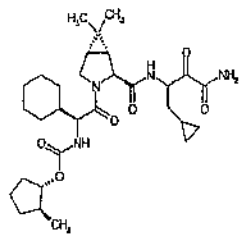
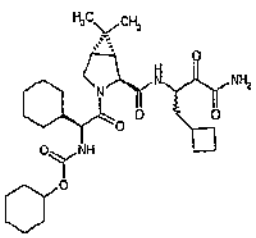
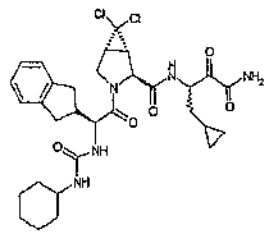
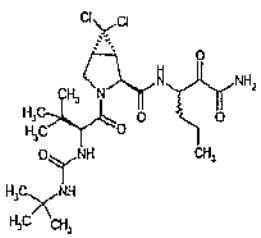
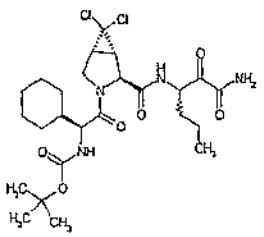
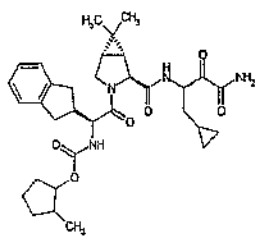
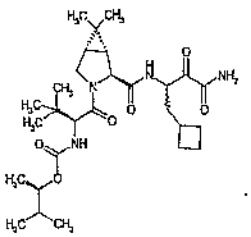
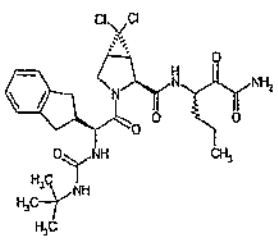
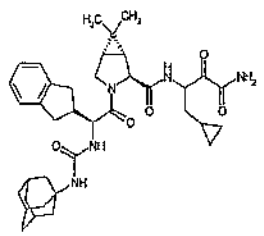
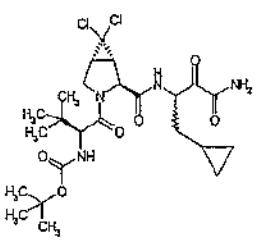
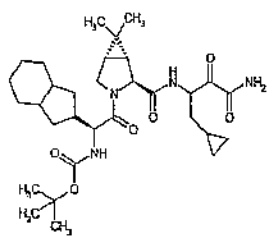
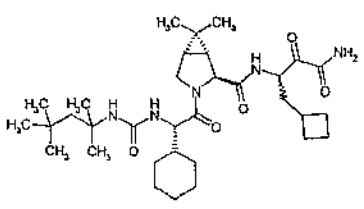


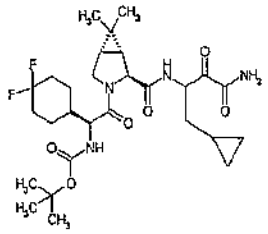


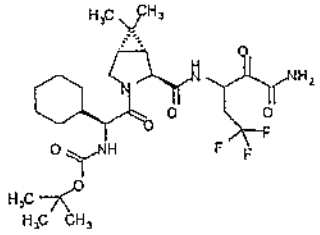


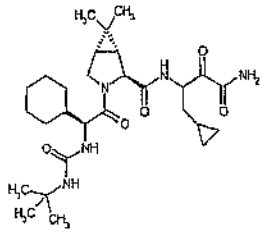


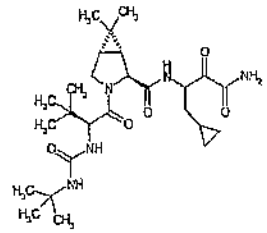


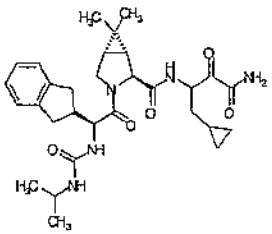













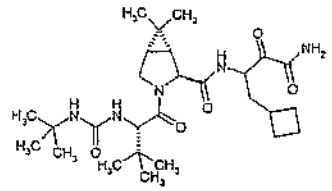


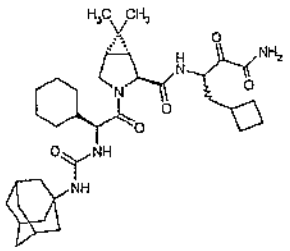


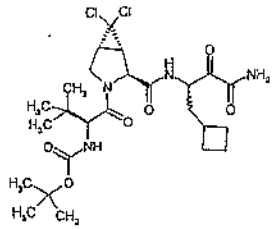


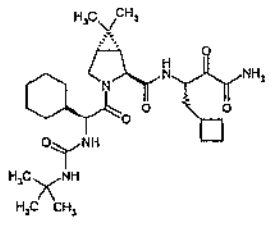


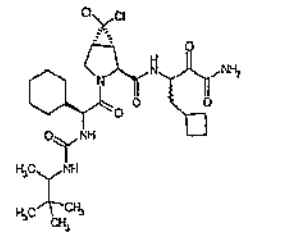


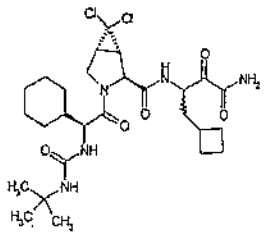


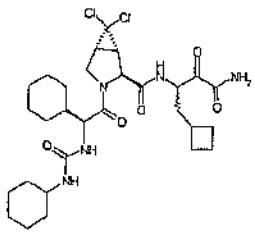


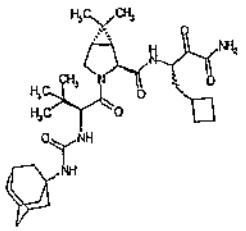


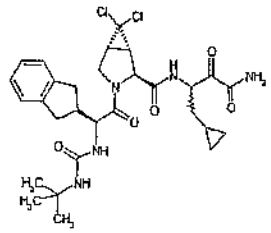


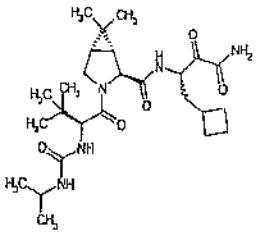


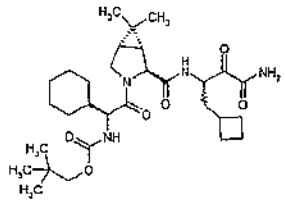


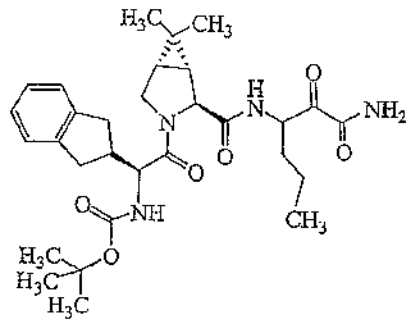


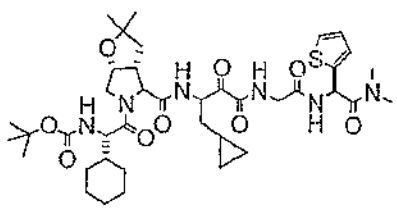


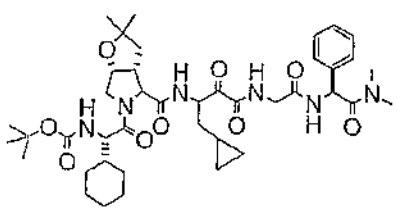


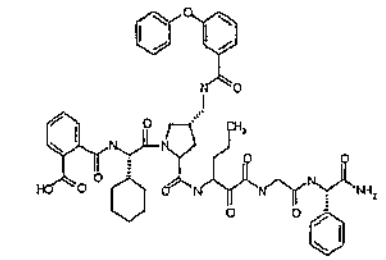


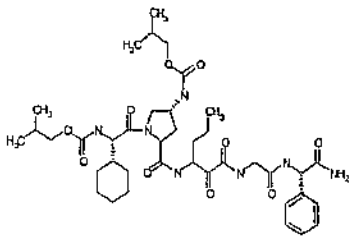


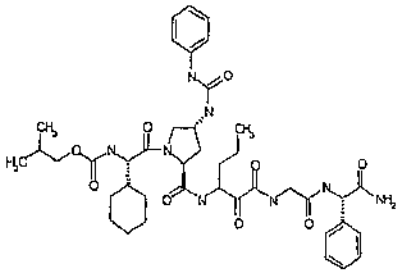


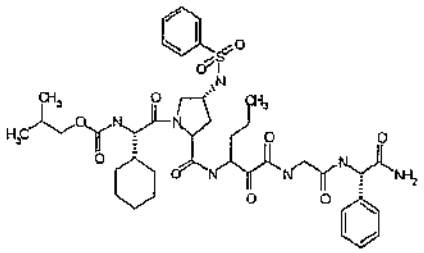


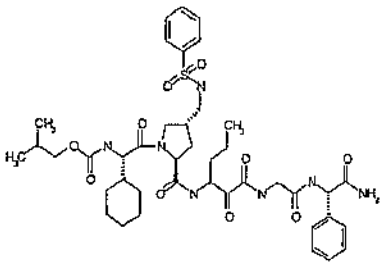


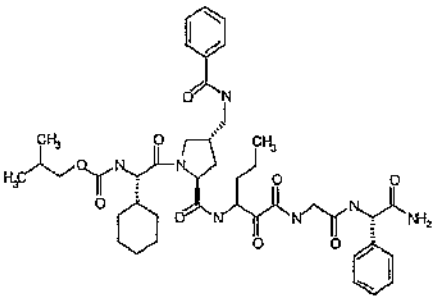


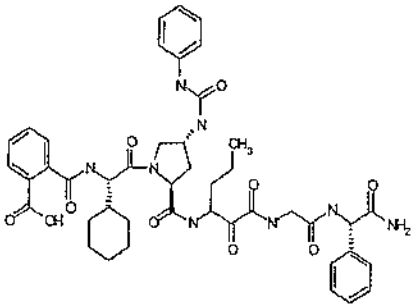


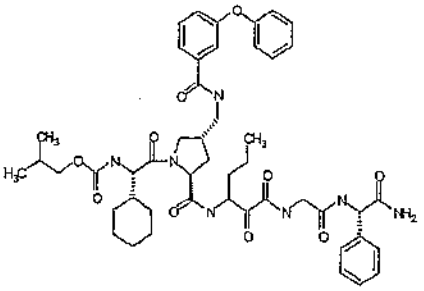




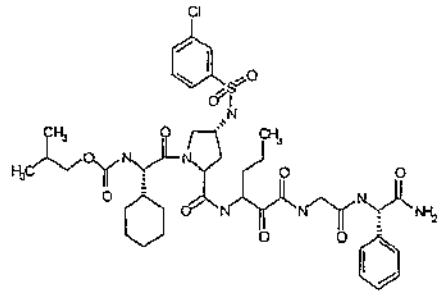


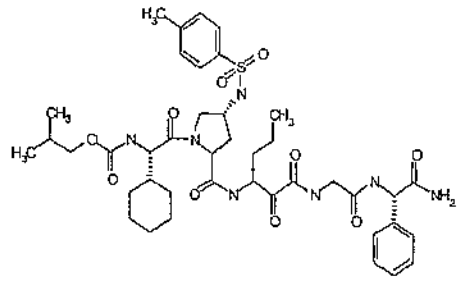


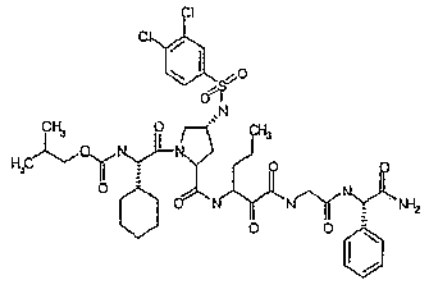


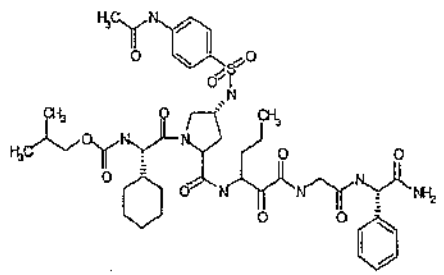


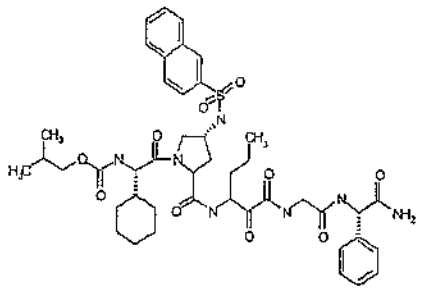
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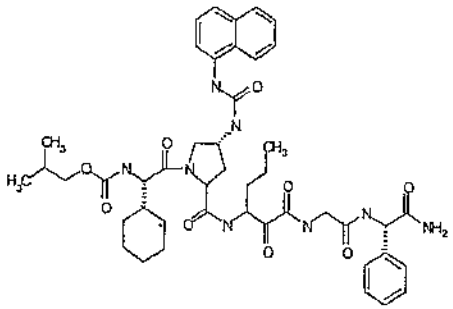


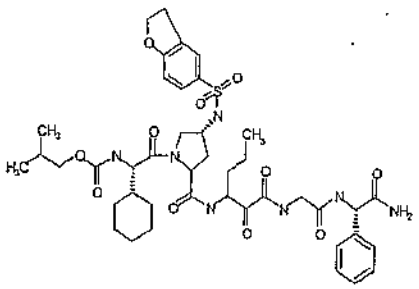


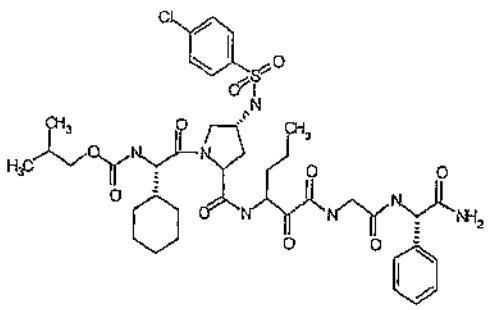


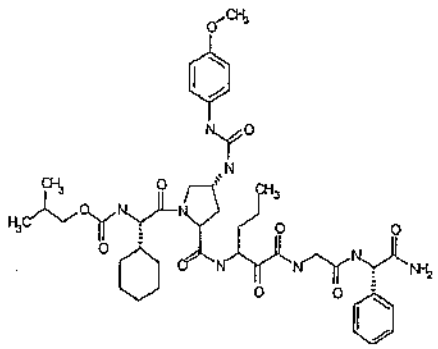


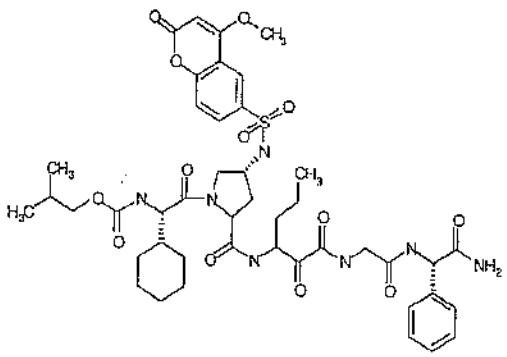


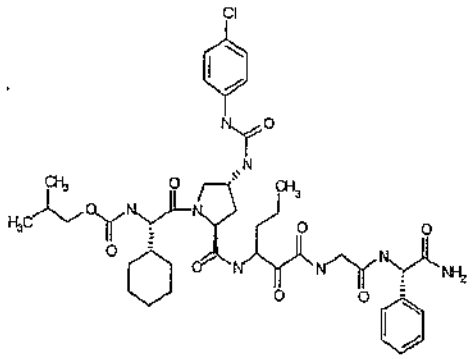


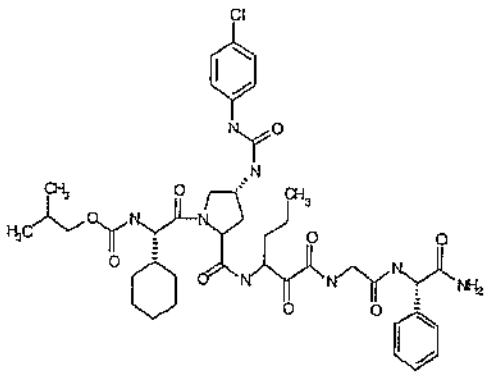


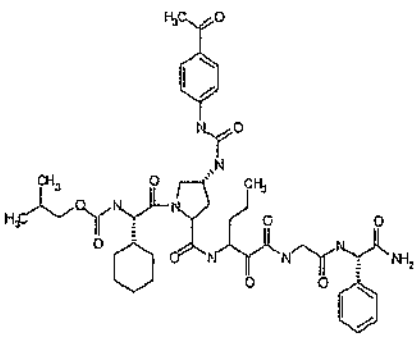


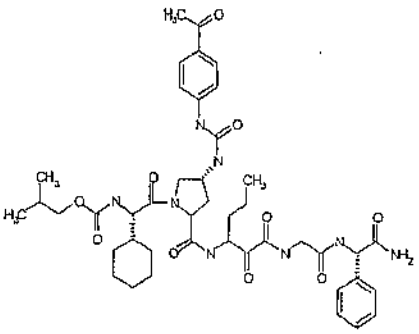


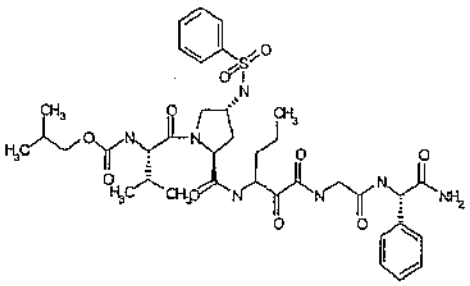


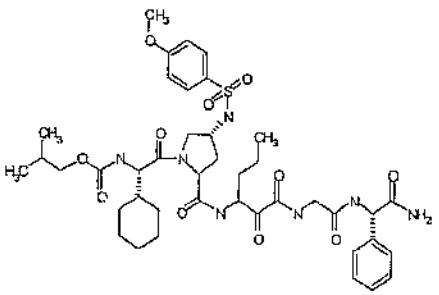


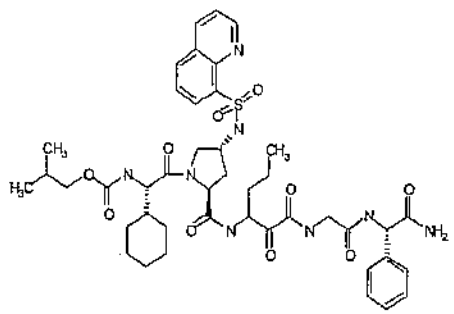


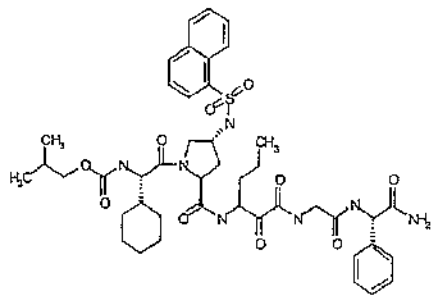


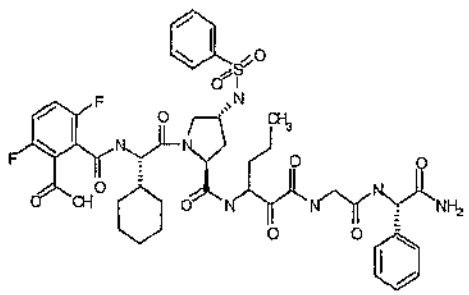


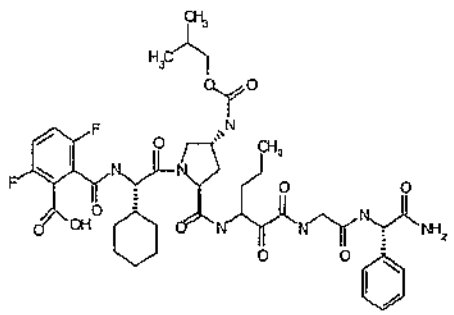




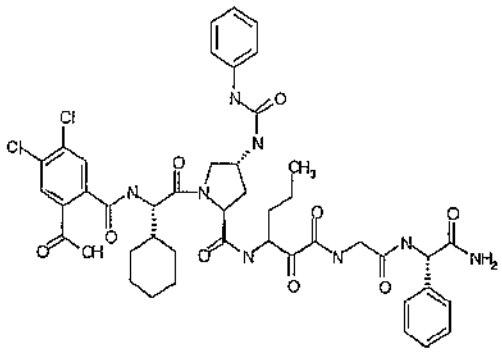


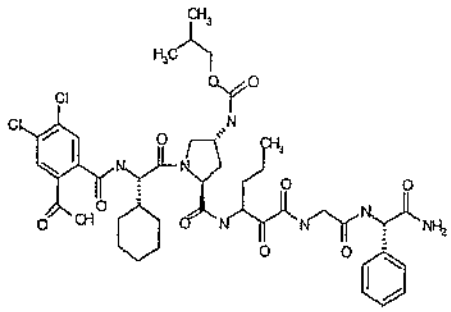


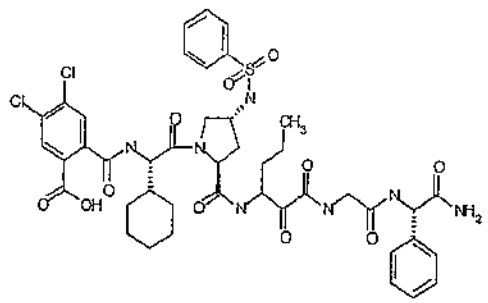


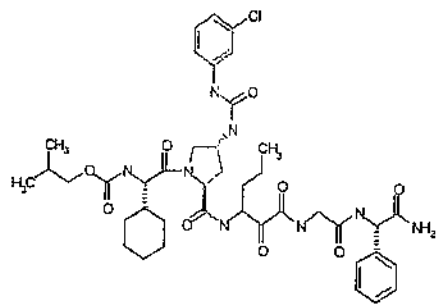


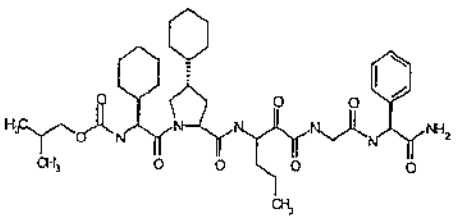
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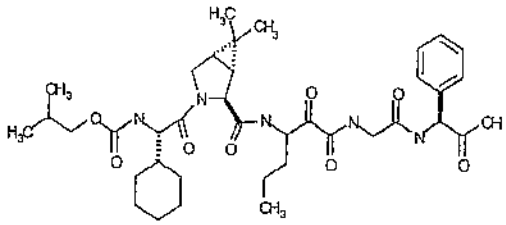


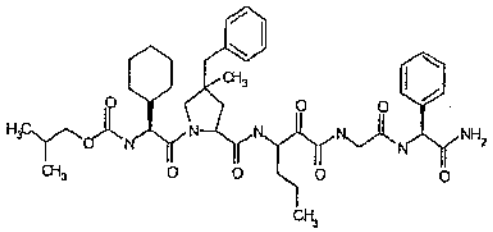


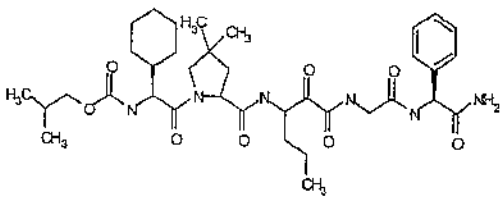


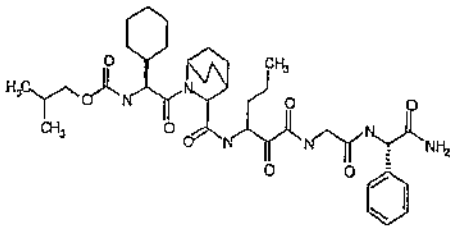


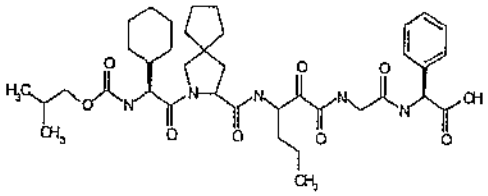




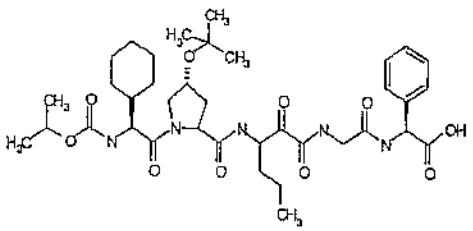


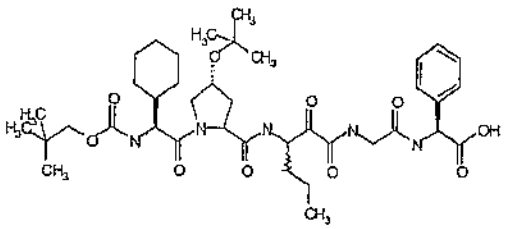


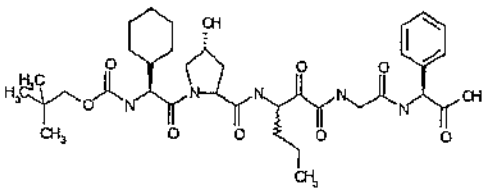


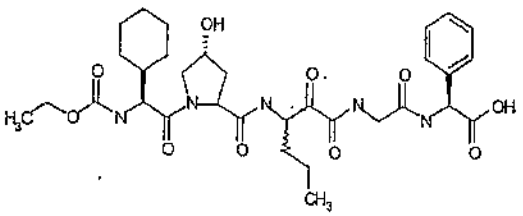


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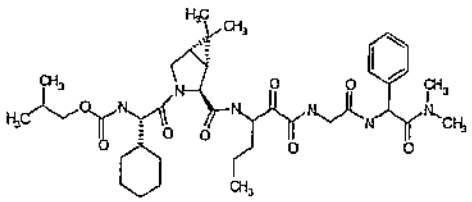


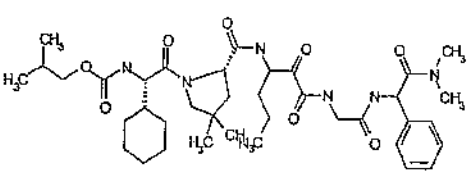


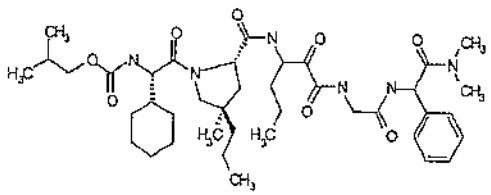


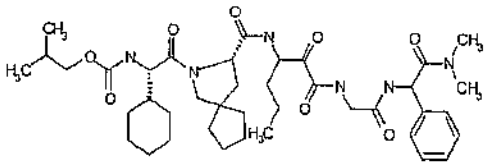


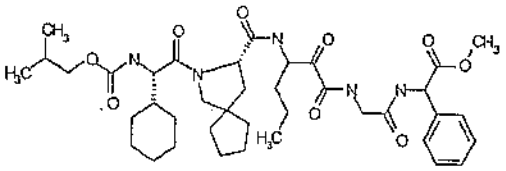
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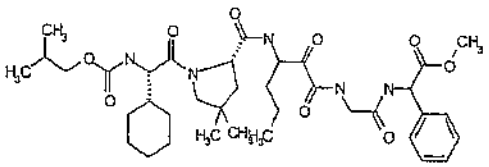


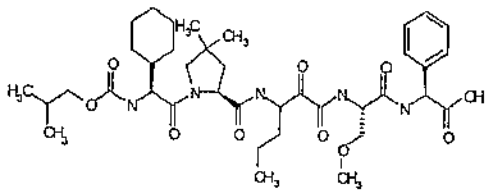




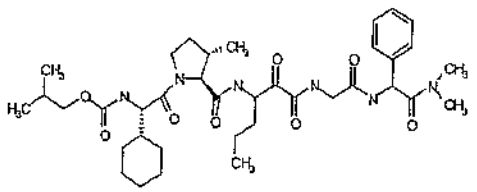


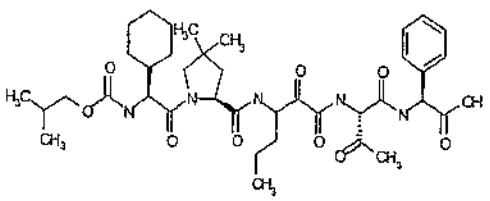


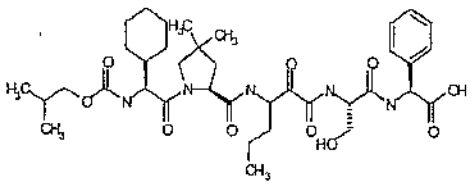


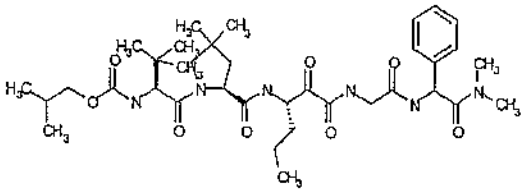


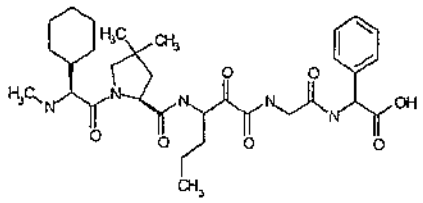
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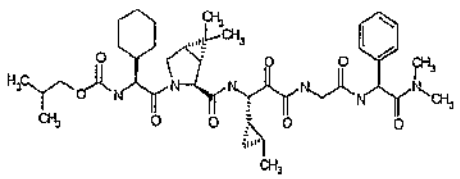


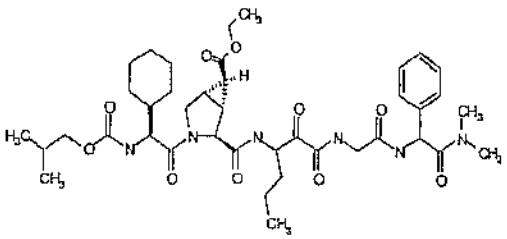


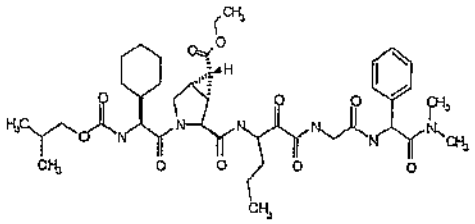




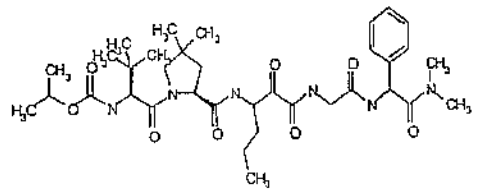


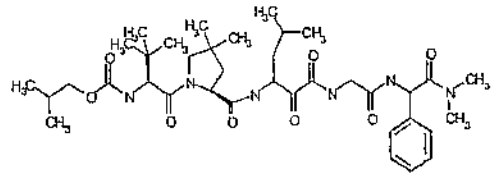


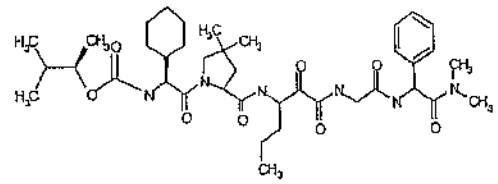


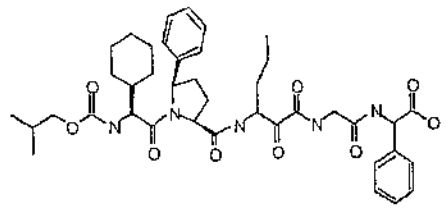


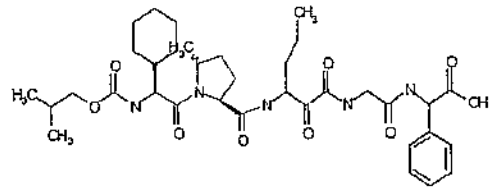
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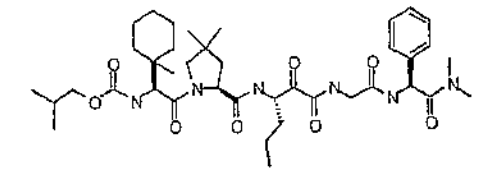


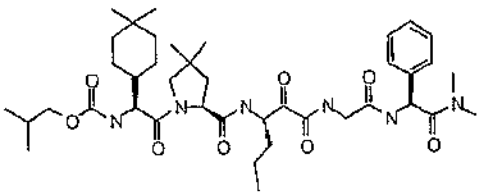


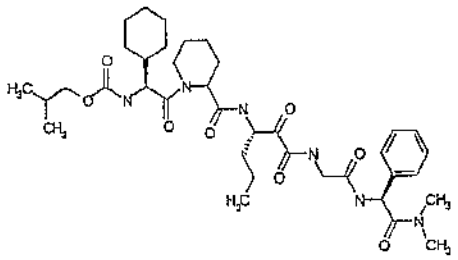


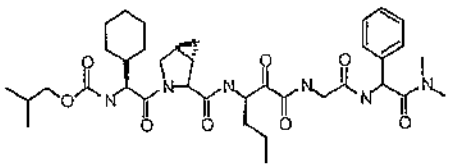


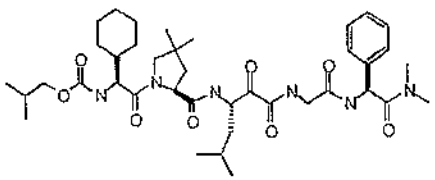


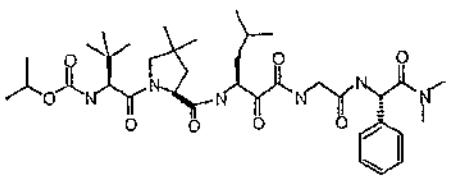


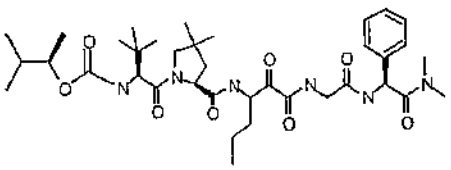


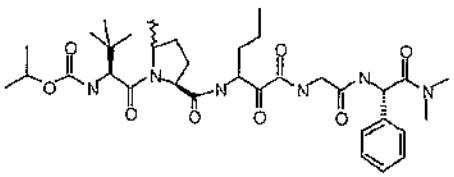


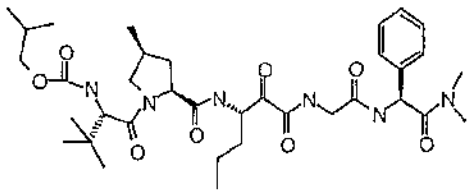


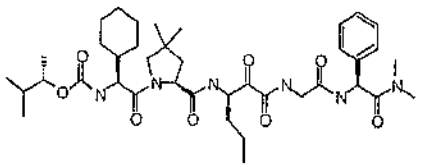


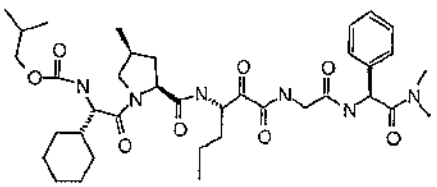


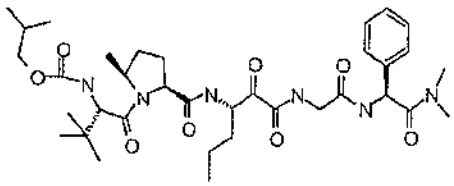




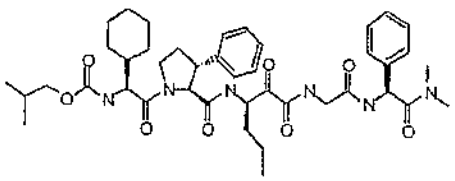


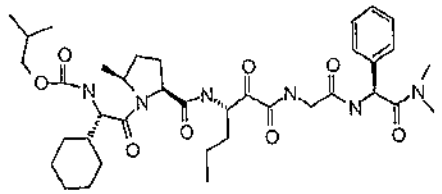


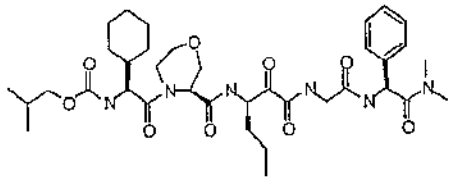


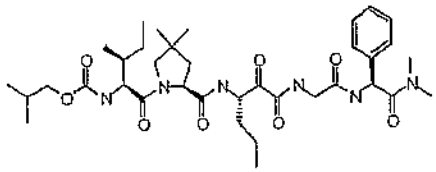


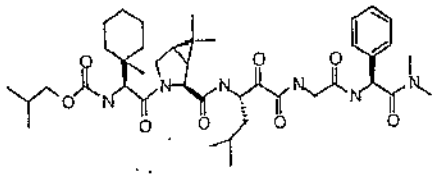
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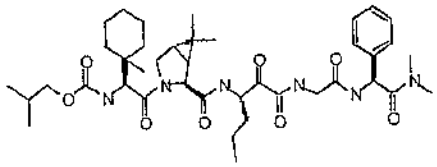


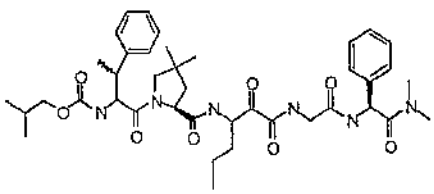


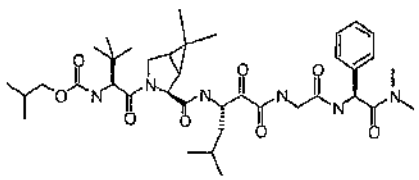


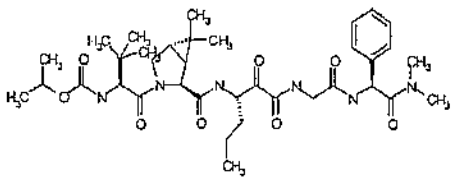


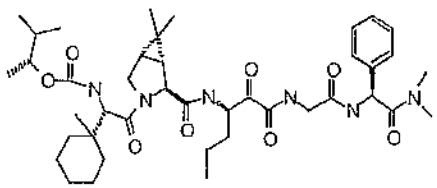


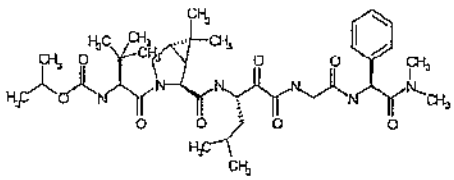


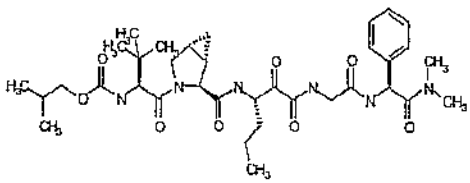




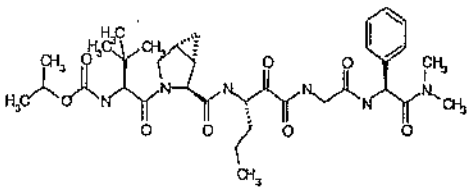


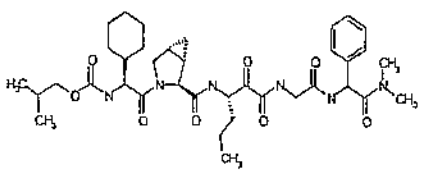


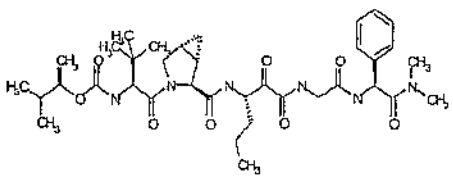


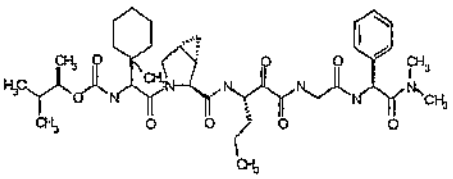


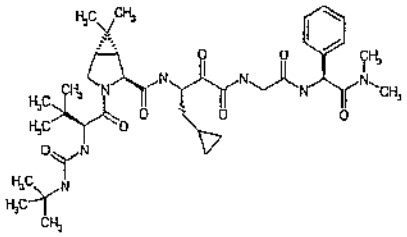
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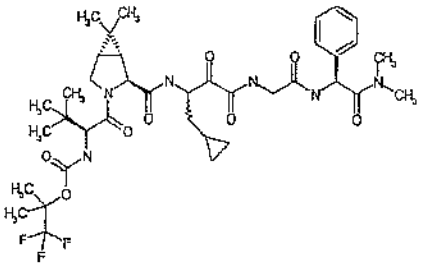




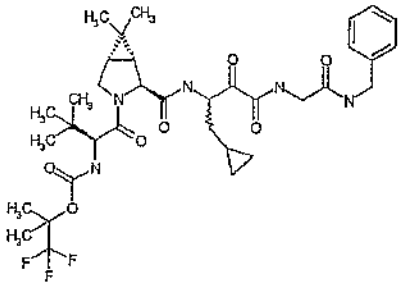


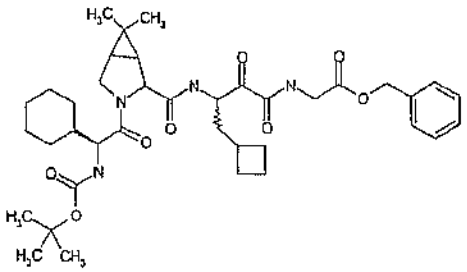


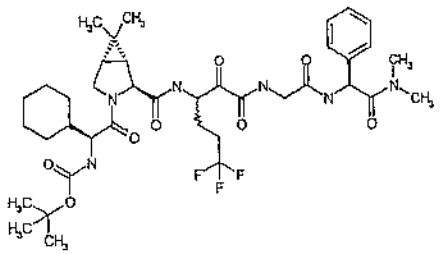


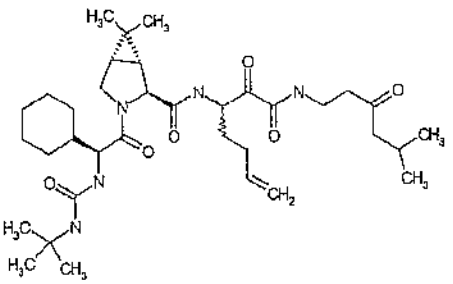


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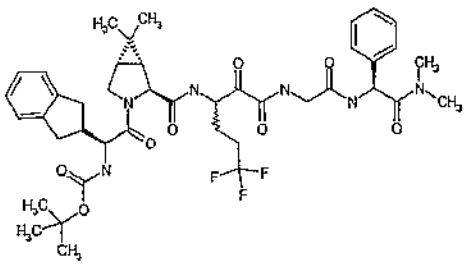


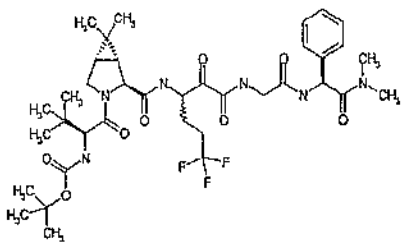


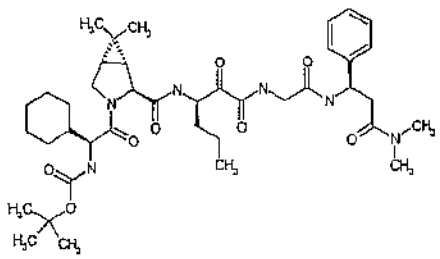


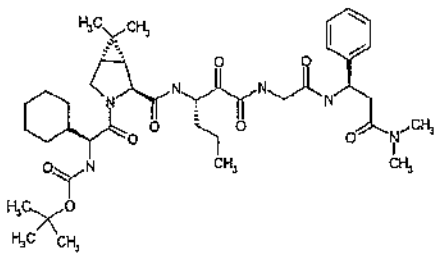


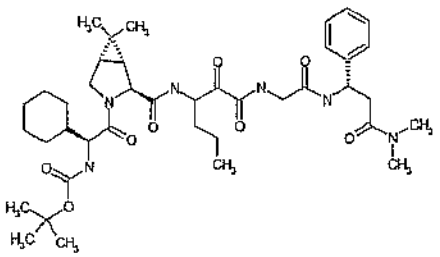
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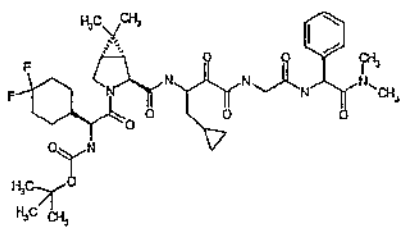


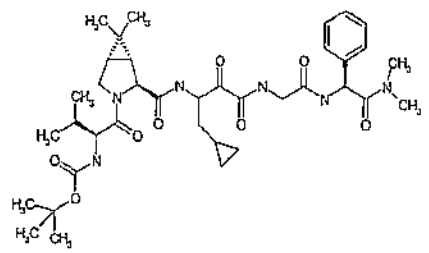




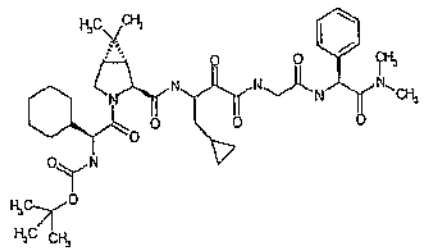


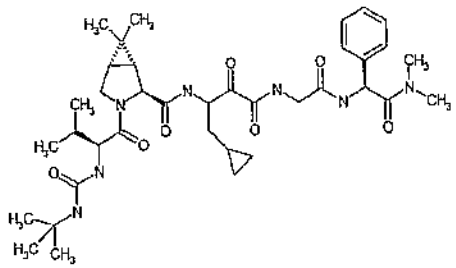




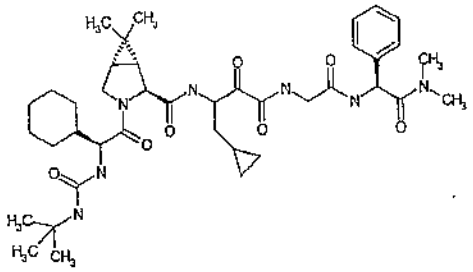


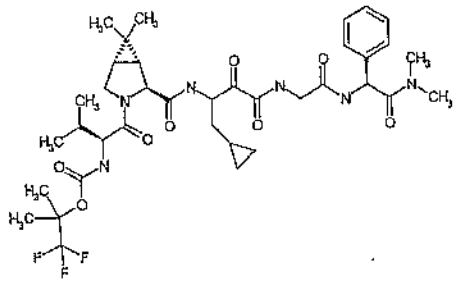
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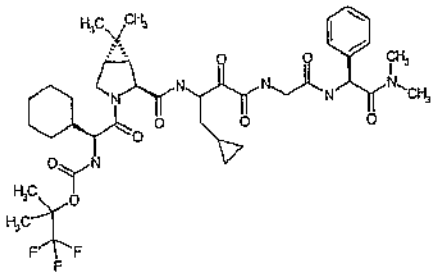


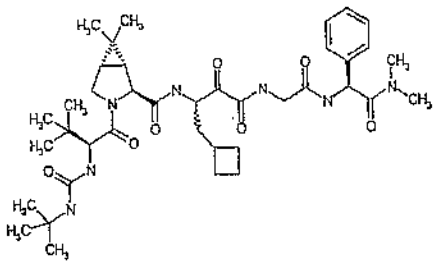


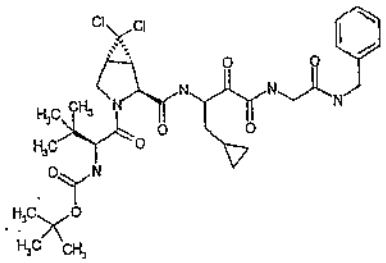
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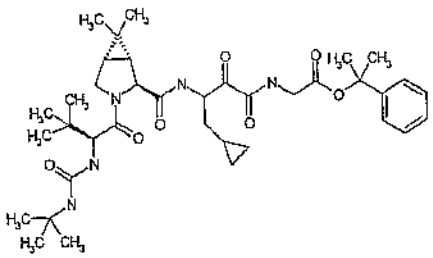


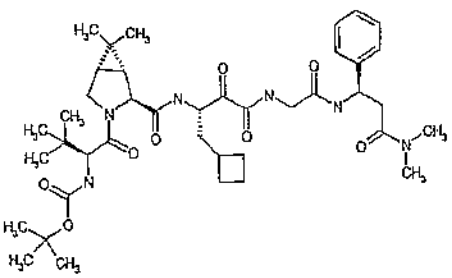


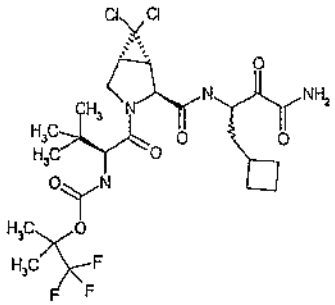


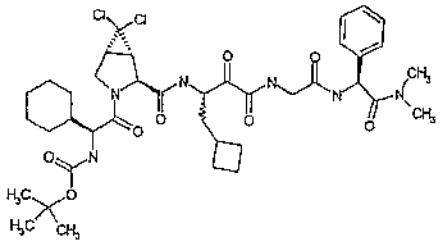




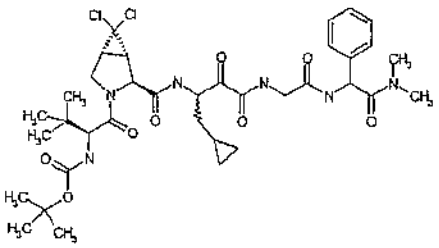


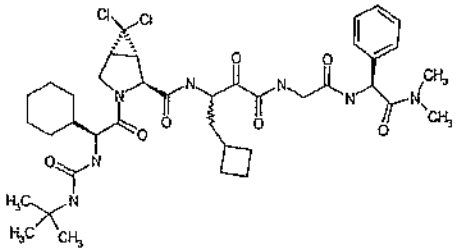


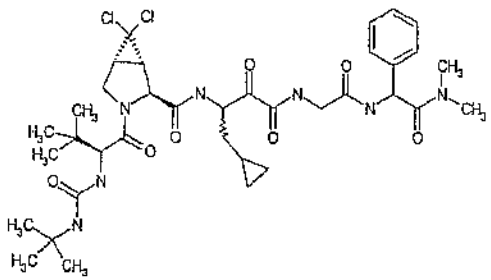


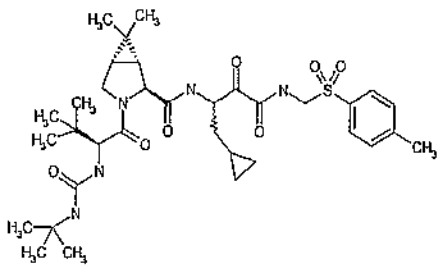


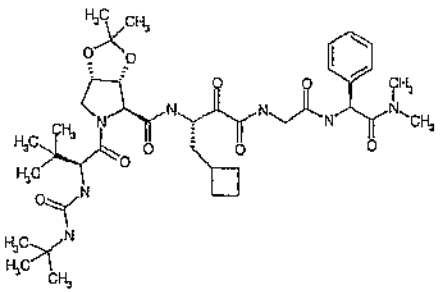
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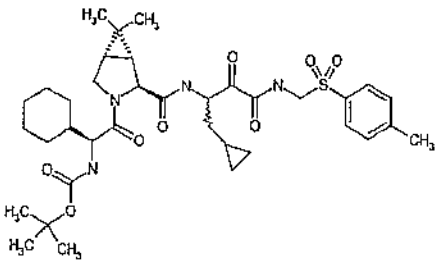


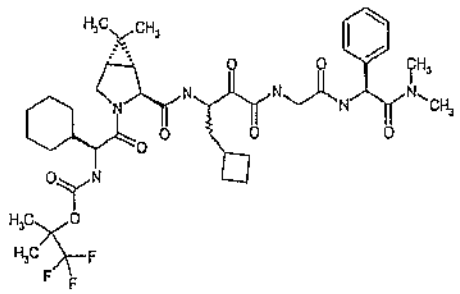


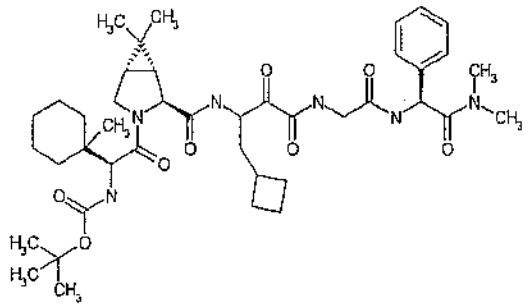


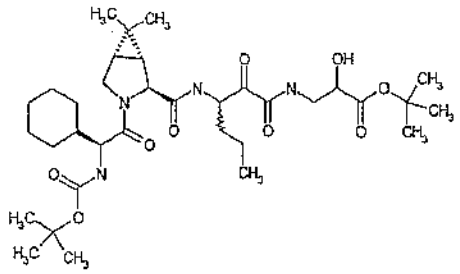


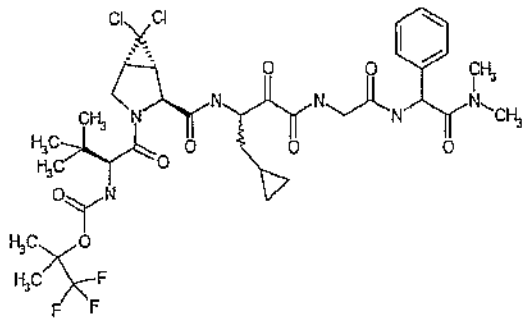
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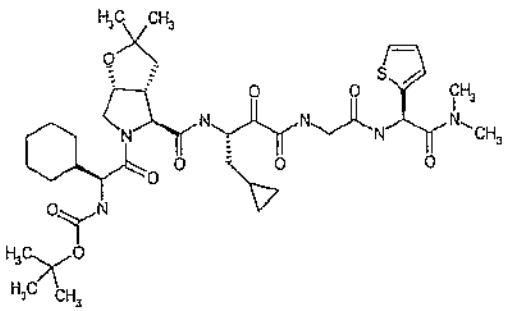


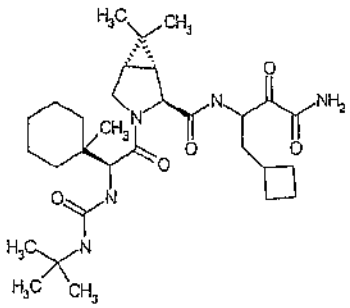


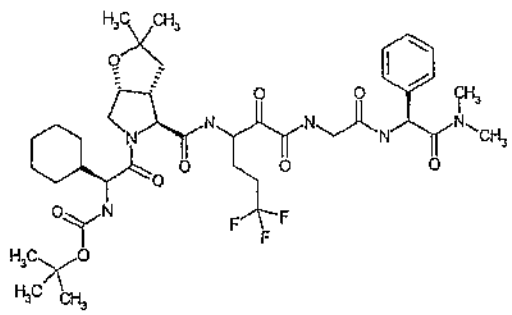




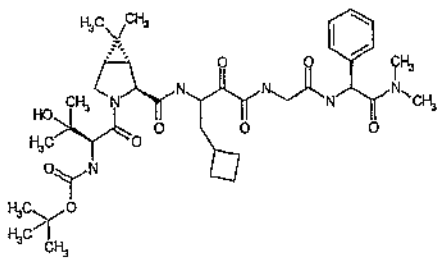


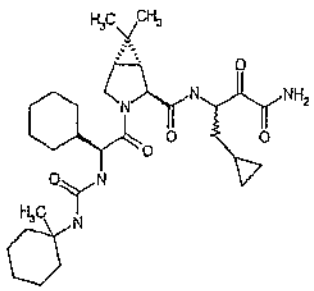


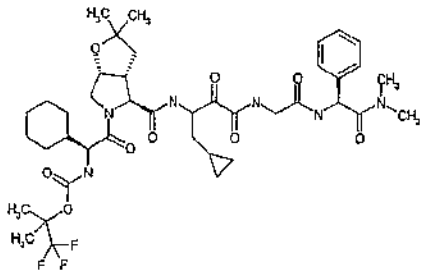


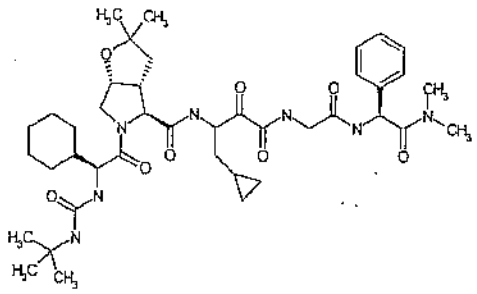


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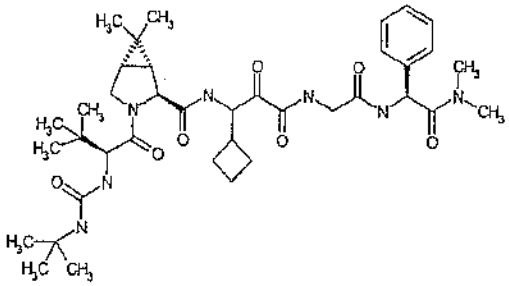


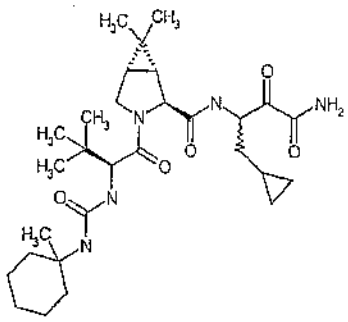


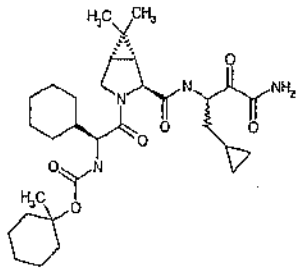


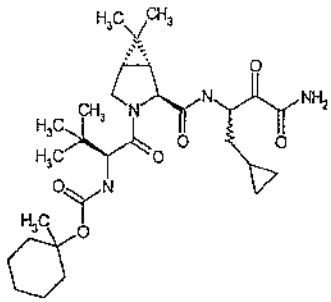


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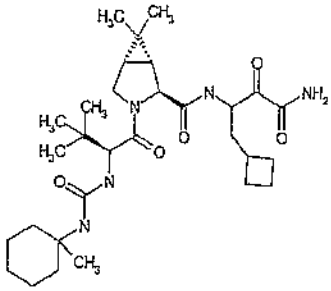


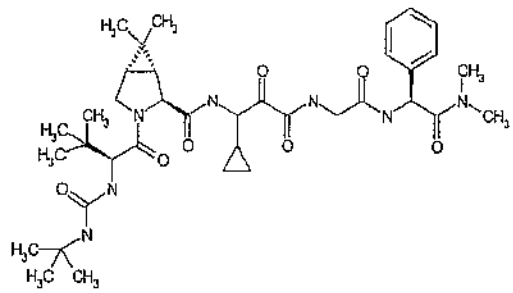


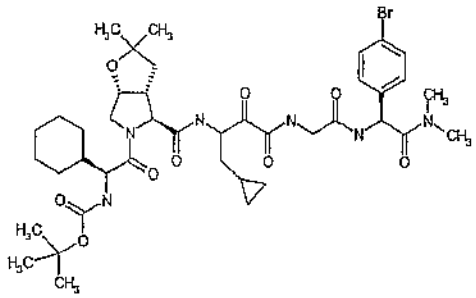


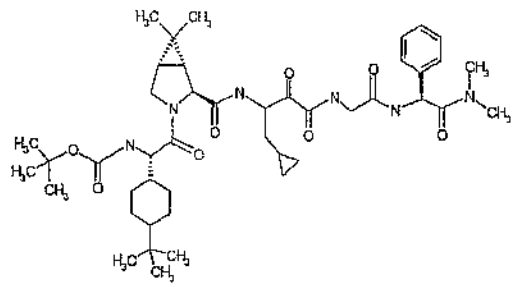


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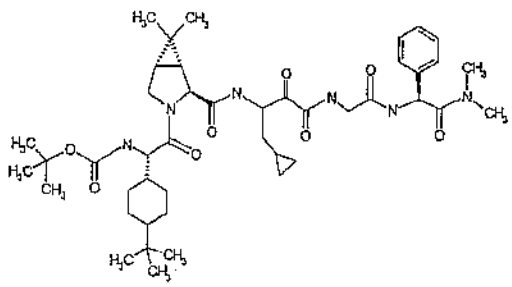


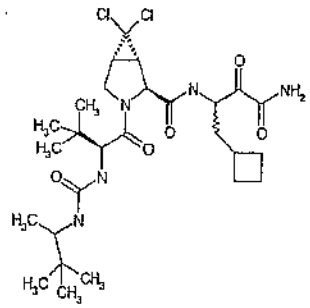


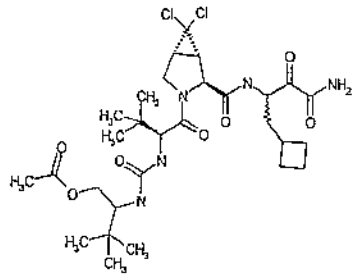


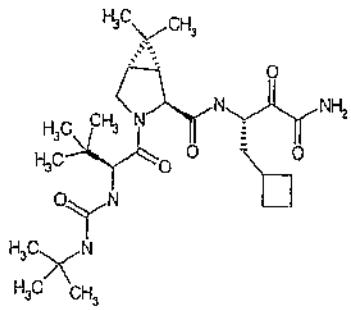


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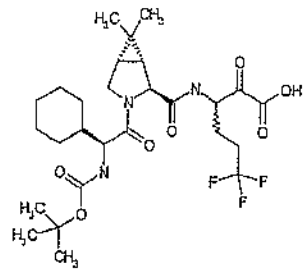


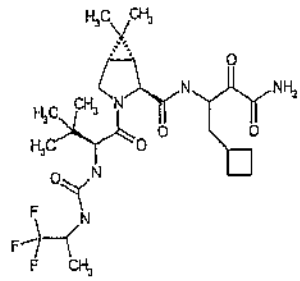


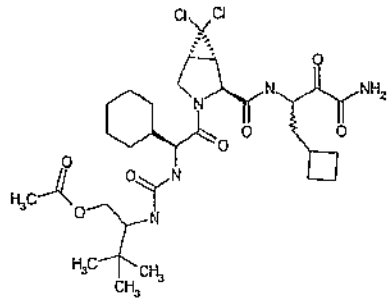


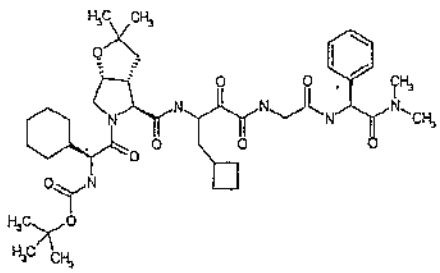


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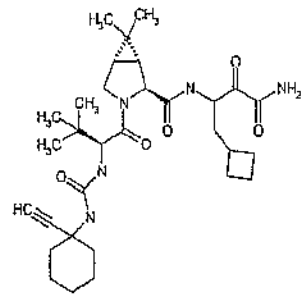


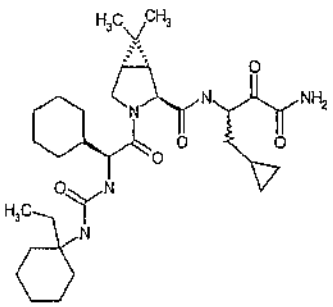


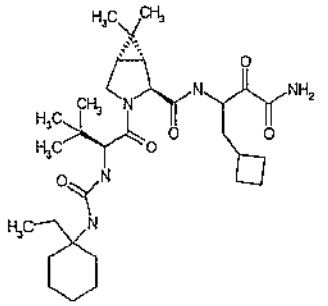


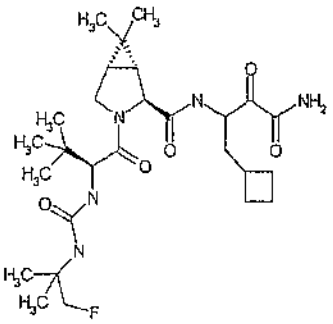


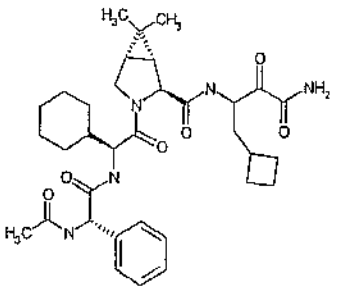
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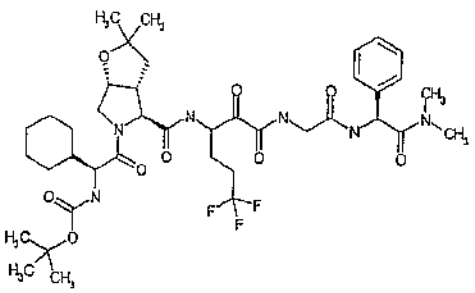


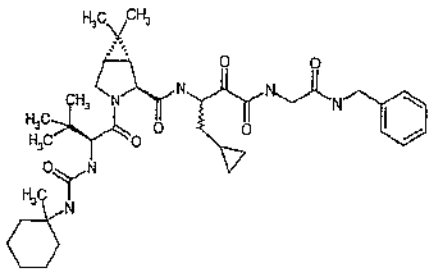


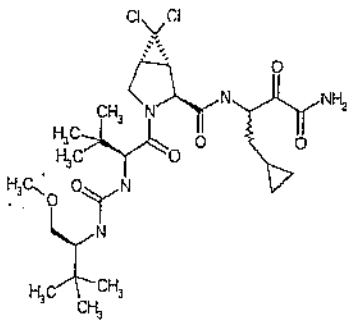


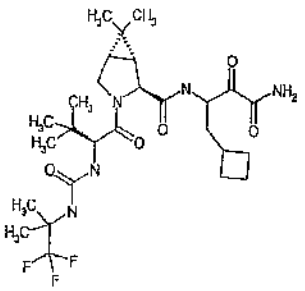


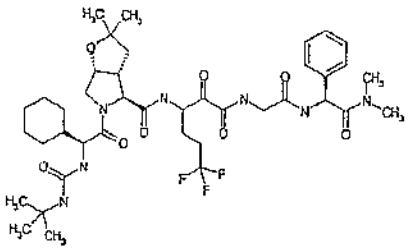


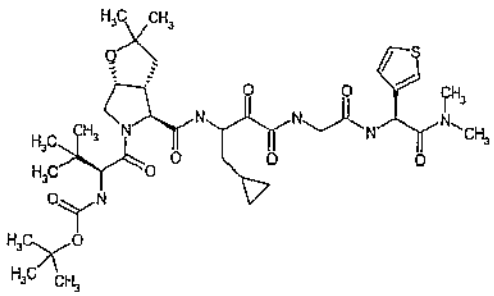


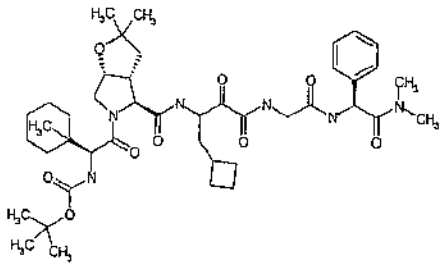


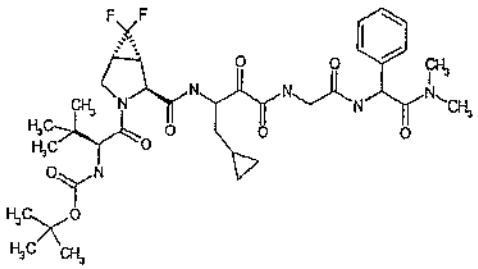


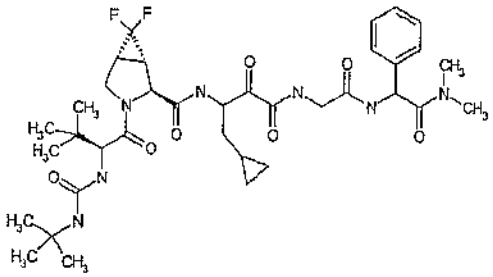


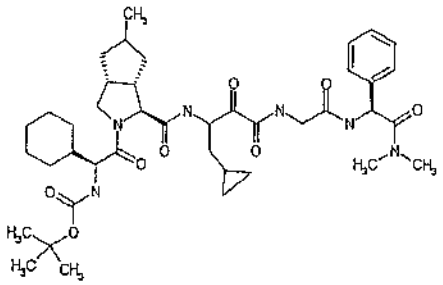


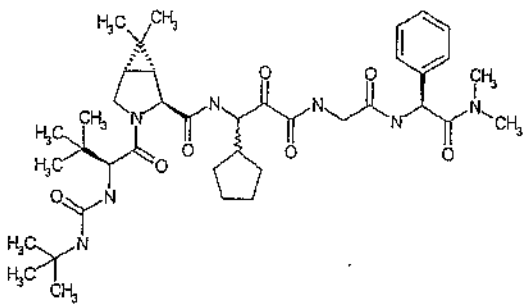


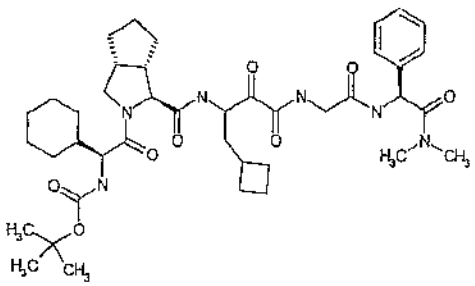


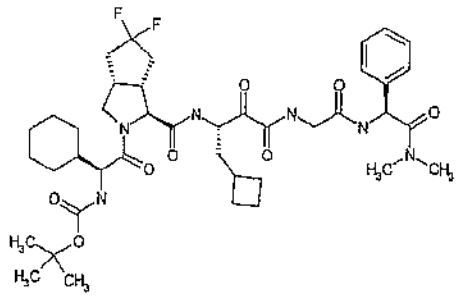


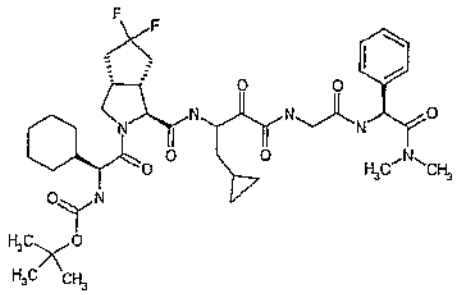


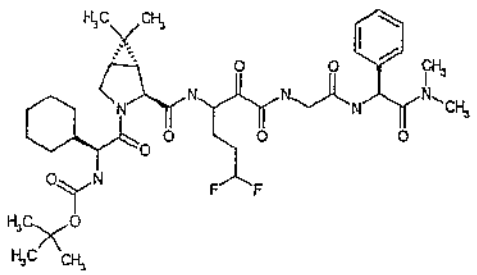


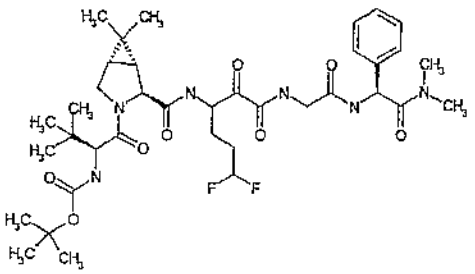


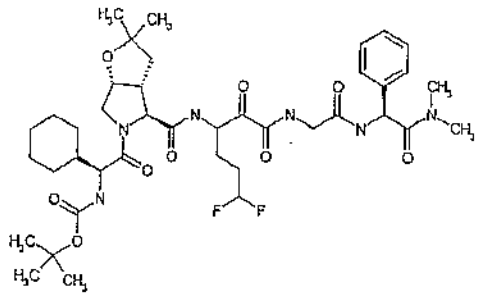


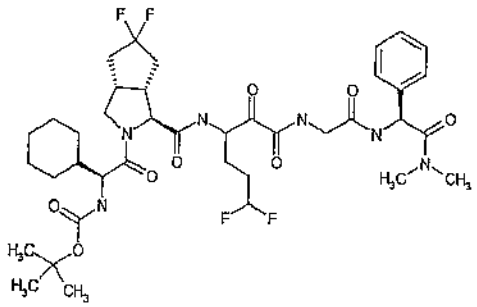


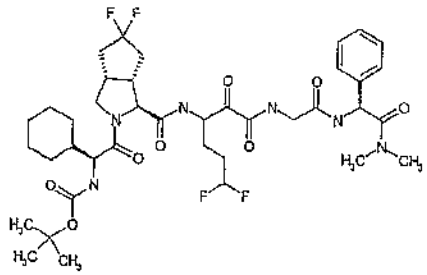


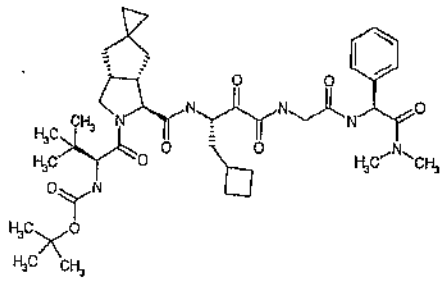


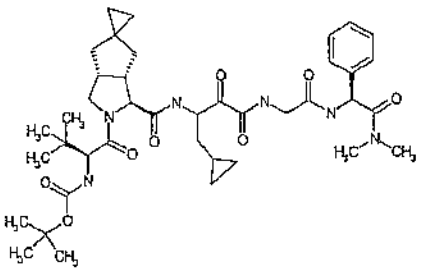


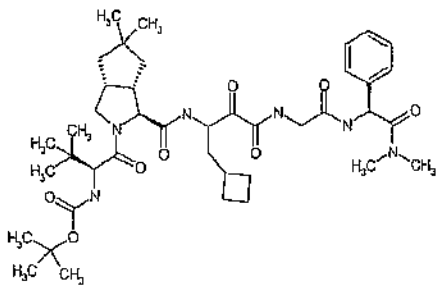


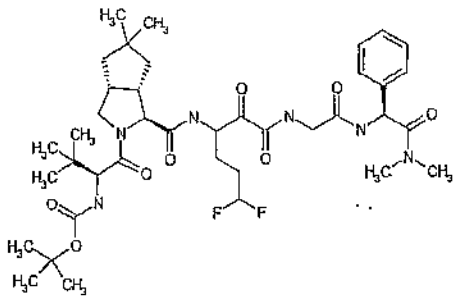


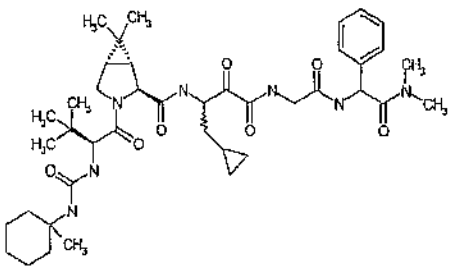


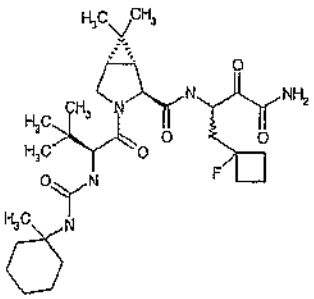


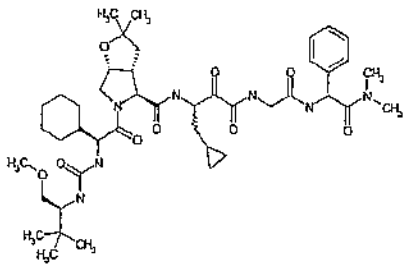


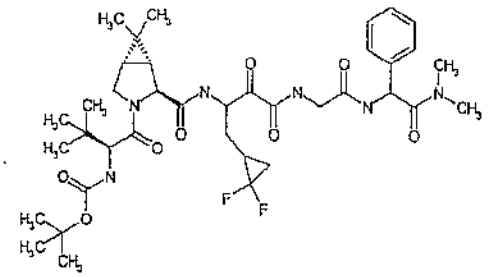




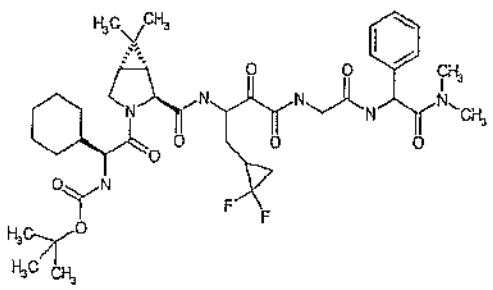


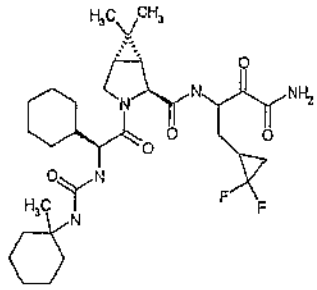


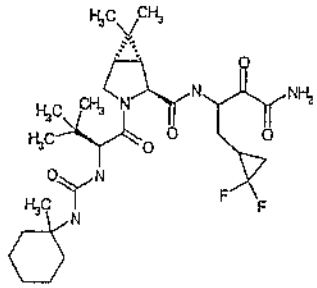


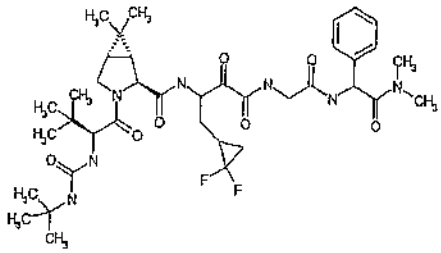


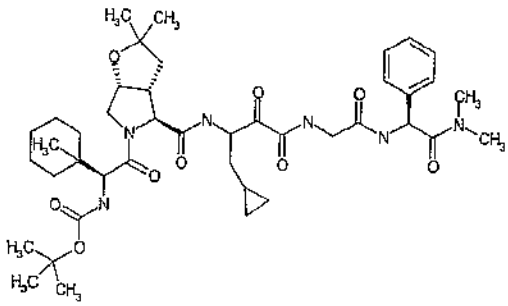
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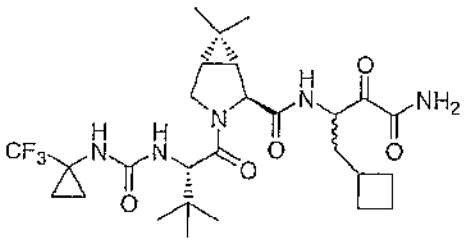






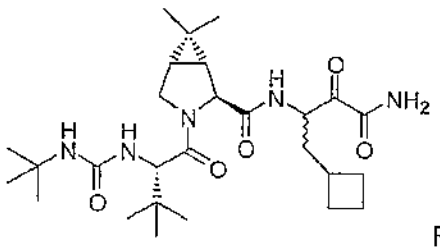






or a pharmaceutically acceptable salt, solvate or ester thereof.

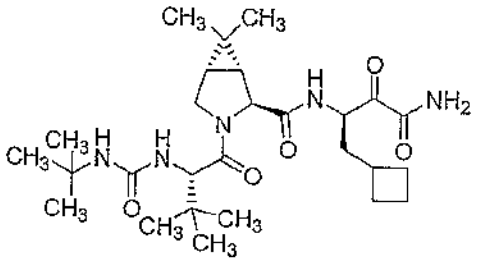
In one embodiment, the HCV protease inhibitor is selected from the group consisting of



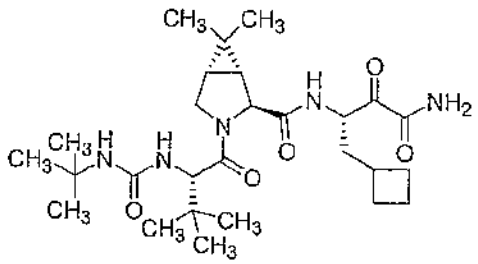
Formula Ia

and pharmaceutically acceptable salts or solvates thereof.

The compound of formula Ia has recently been separated into its isomer/diastereomers of Formulas Ib and Ic. In one embodiment, the HCV protease inhibitor is selected from the group consisting of the compound of Formula Ic and pharmaceutically acceptable salts or solvates thereof as a potent inhibitor of HCV NS3 serine protease.



Formula Ib



Formula Ic

The chemical name of the compound of Formula Ic is (1R,2S,5S)-N-[(1S)-3-amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[(2S)-2-[[[(1,1-dimethylethyl)amino]carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide.

Processes for making compounds of Formula I are disclosed in U.S. Patent Publication Nos. 2005/0059648, 2005/0020689 and 2005/0059800, incorporated by

reference herein.

Non-limiting examples of suitable compounds of formula II and methods of making the same are disclosed in WO02/08256 and in U.S. Patent No. 6,800,434, at col. 5 through col. 247, incorporated herein by reference.

Non-limiting examples of suitable compounds of formula III and methods of making the same are disclosed in International Patent Publication WO02/08187 and in U.S. Patent Publication 2002/0160962 at page 3, paragraph 22 through page 132, incorporated herein by reference.

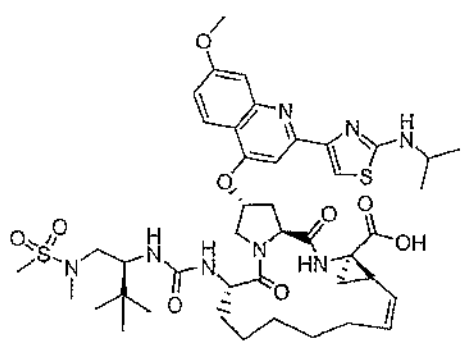
Non-limiting examples of suitable compounds of formula IV and methods of making the same are disclosed in International Patent Publication WO03/062228 and in U.S. Patent Publication 2003/0207861 at page 3, paragraph 25 through page 26, incorporated herein by reference.

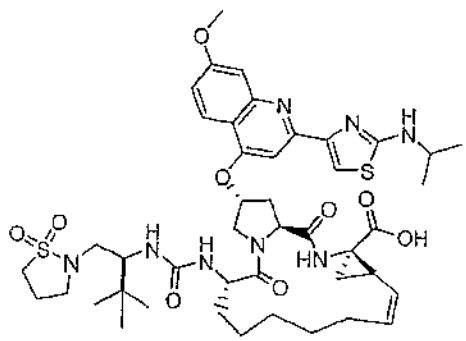
Non-limiting examples of suitable compounds of formula V and methods of making the same are disclosed in U.S. Patent Application No. 10/948,367 filed September 23, 2004, and the preparation of the compounds are detailed in the experimental section of this application set forth hereinbelow.

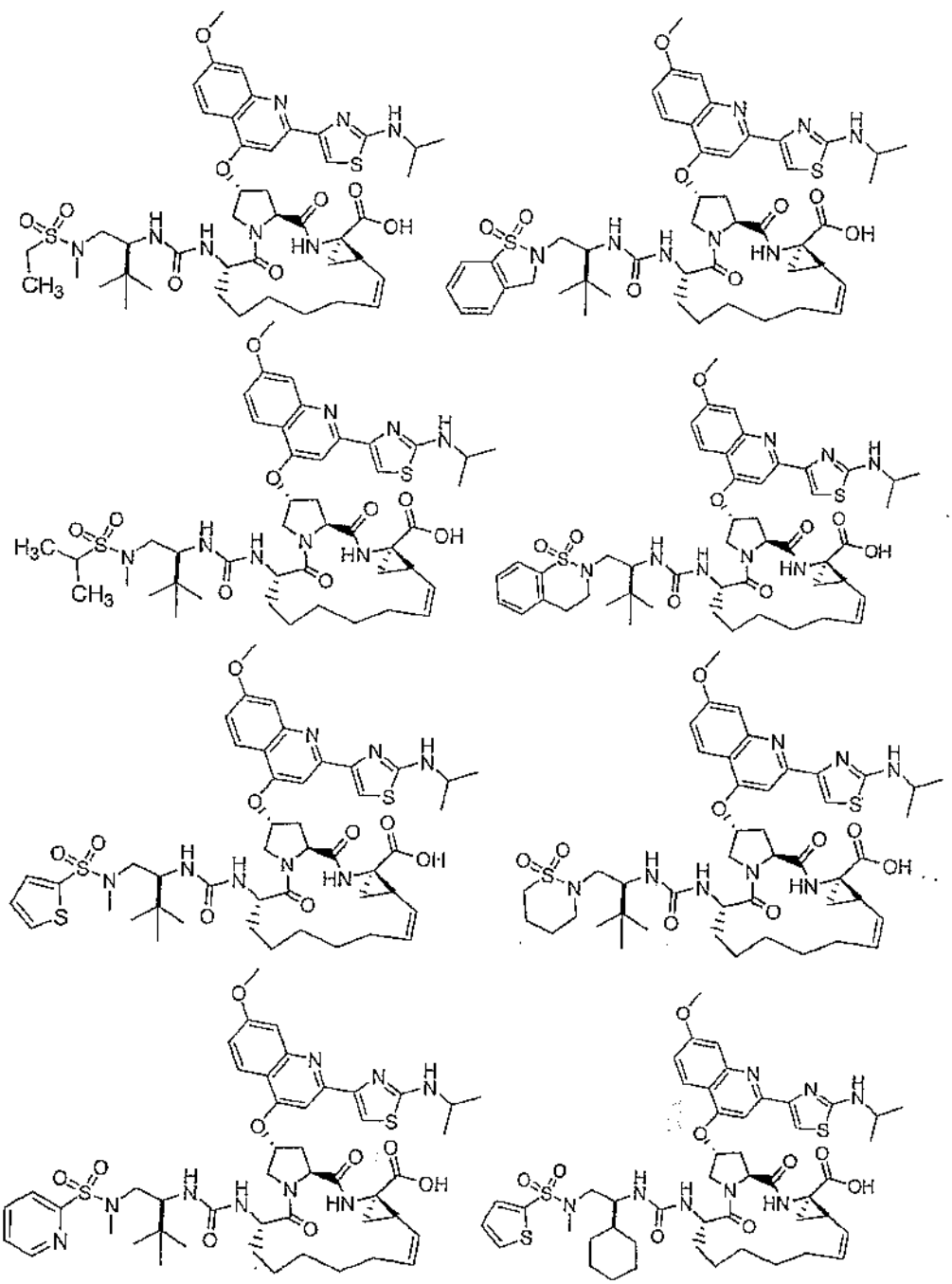
Non-limiting examples of suitable compounds of formula VI and methods of making the same are disclosed in U.S. Patent Publication Ser. No. 2005/0085425 at page 3, paragraph 0023 through page 139, incorporated herein by reference.

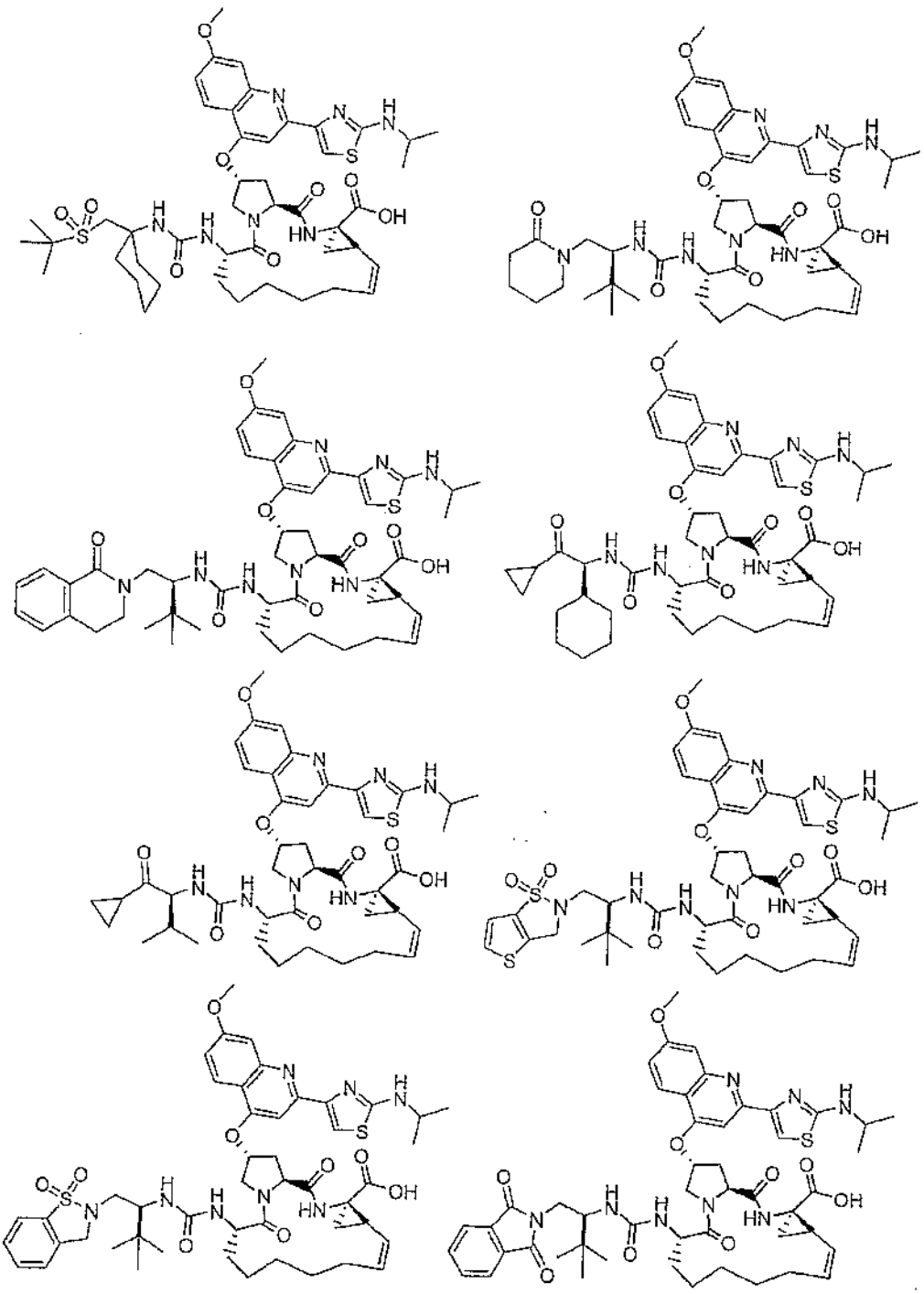
Compounds of formula VII-IX are disclosed in U.S. Patent Application Ser. No. 10/993,394 filed November 19, 2004, and the preparation of the compounds are detailed in the experimental section of this application set forth hereinbelow.

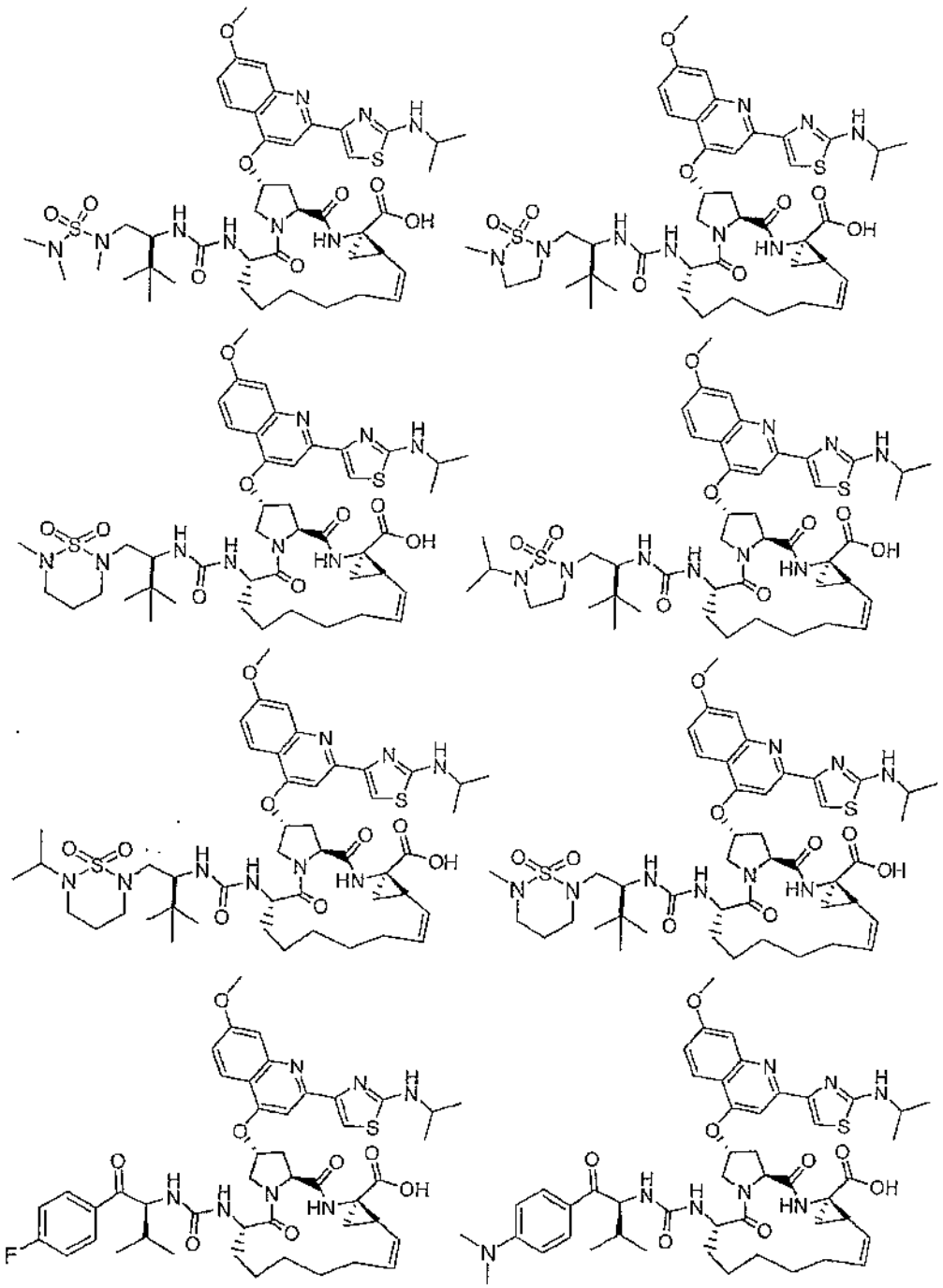
Non-limiting examples of certain compounds of formula VII disclosed in U.S. Patent Application Ser. No. 10/993,394 are:

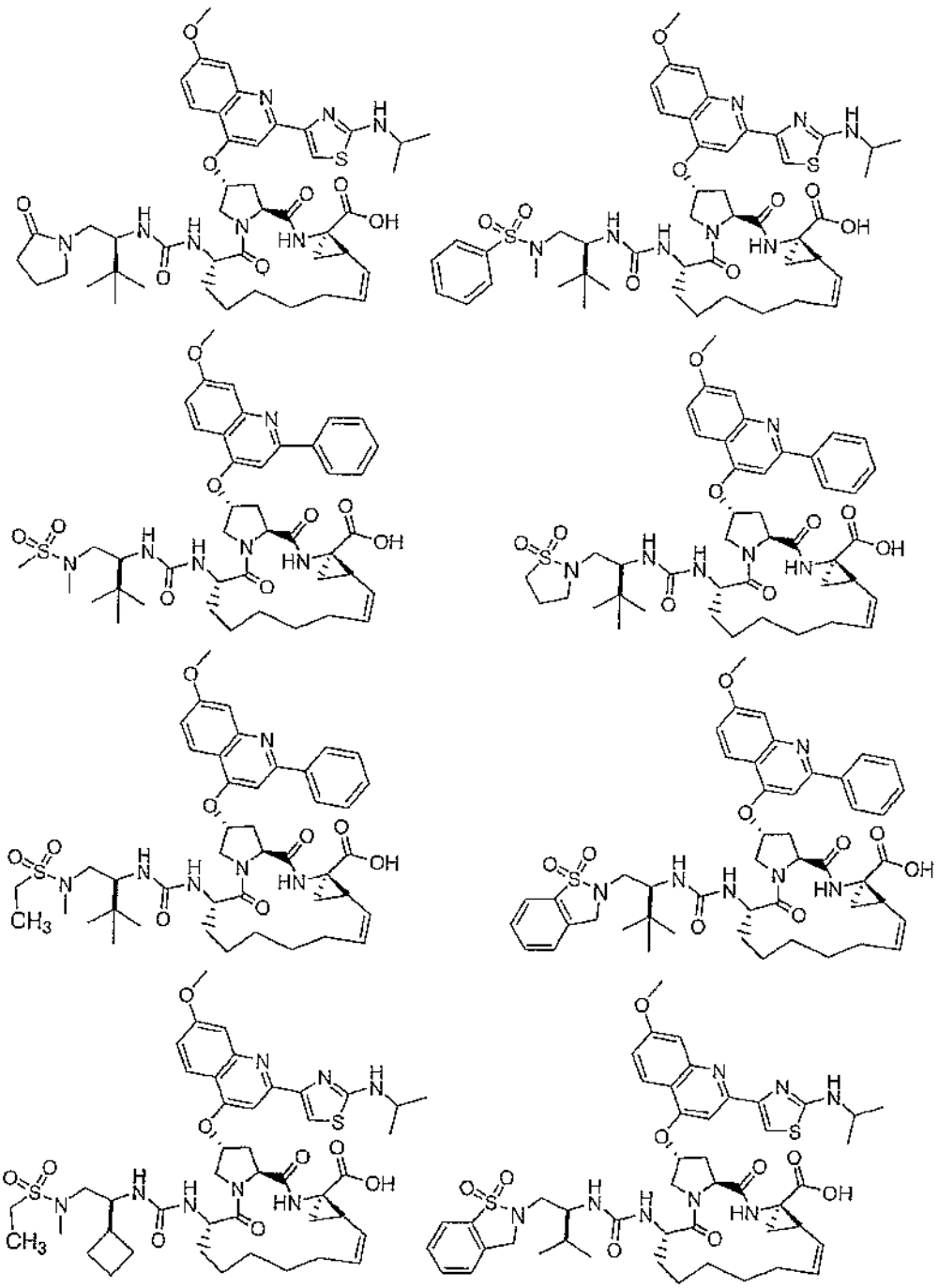


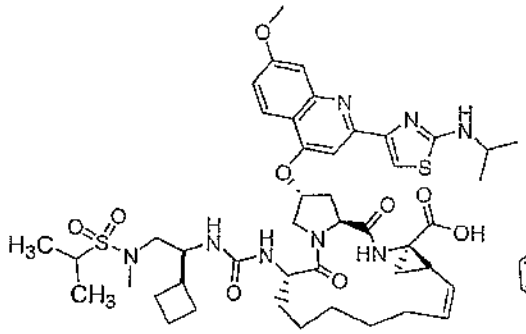


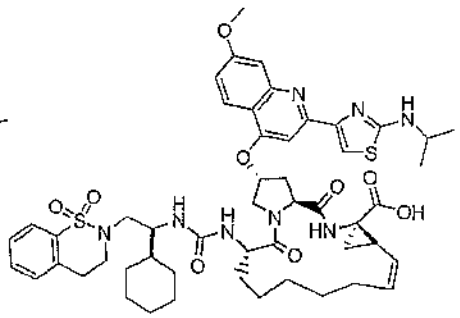


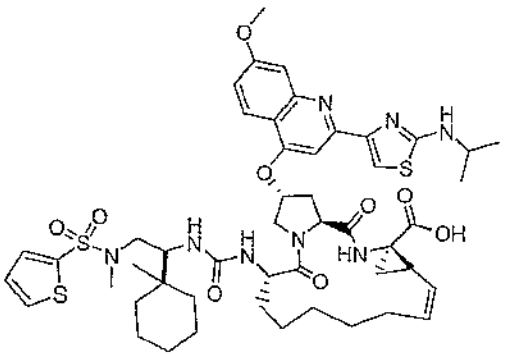


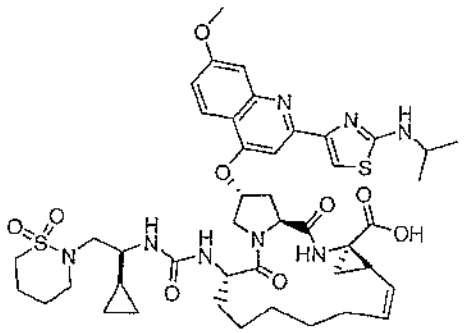


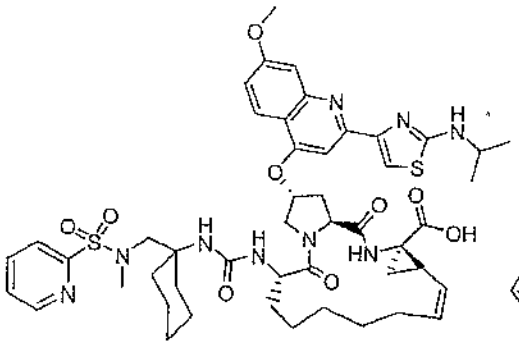


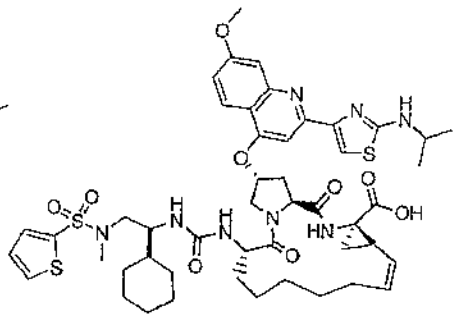


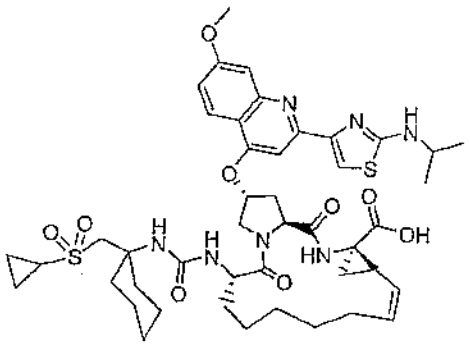


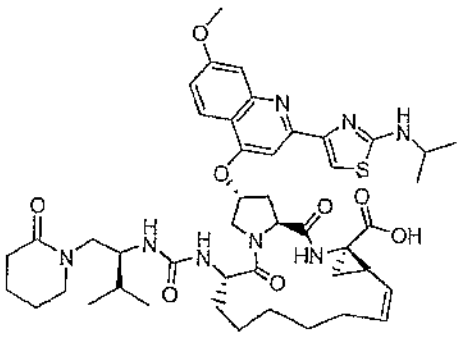


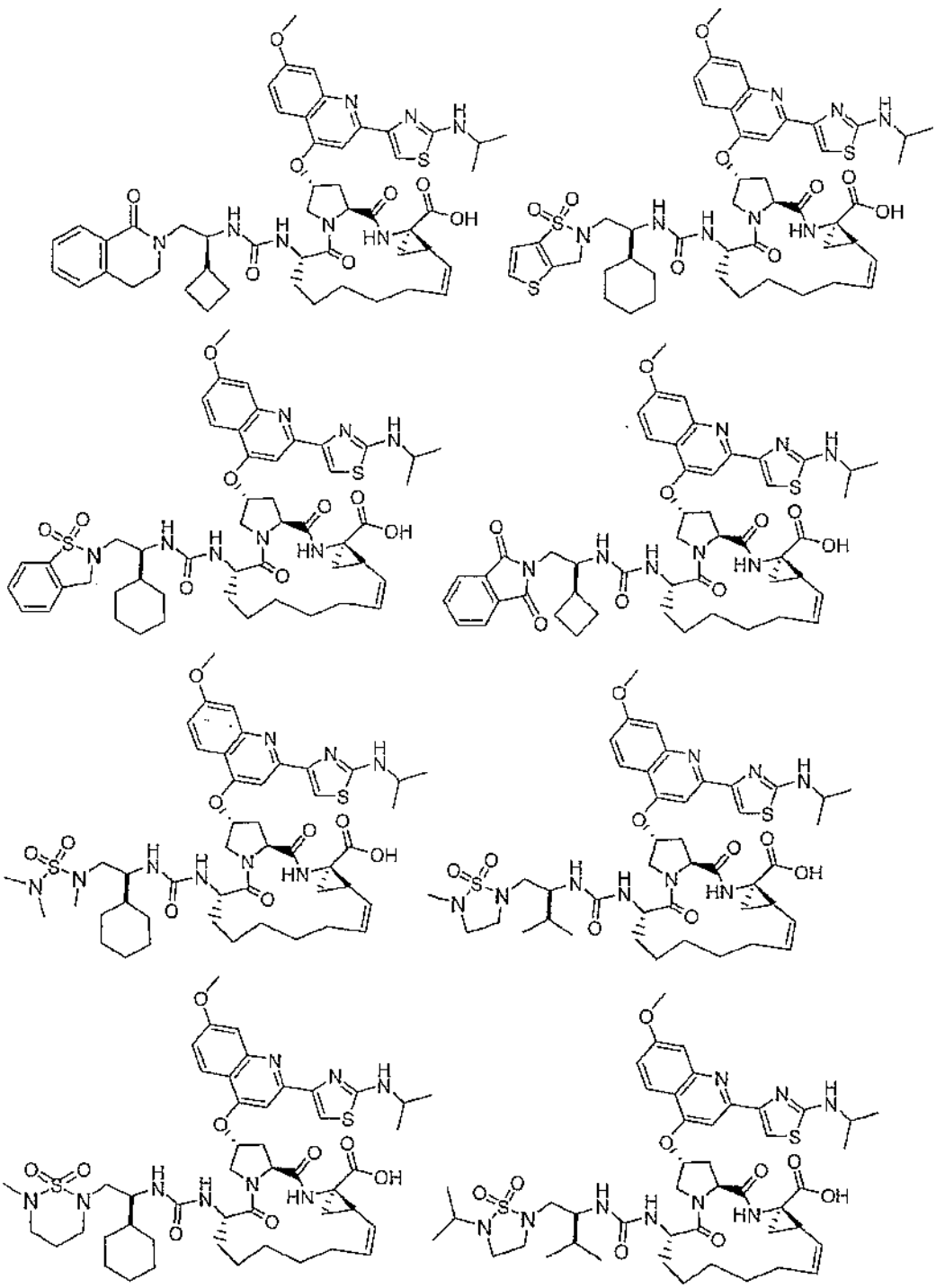


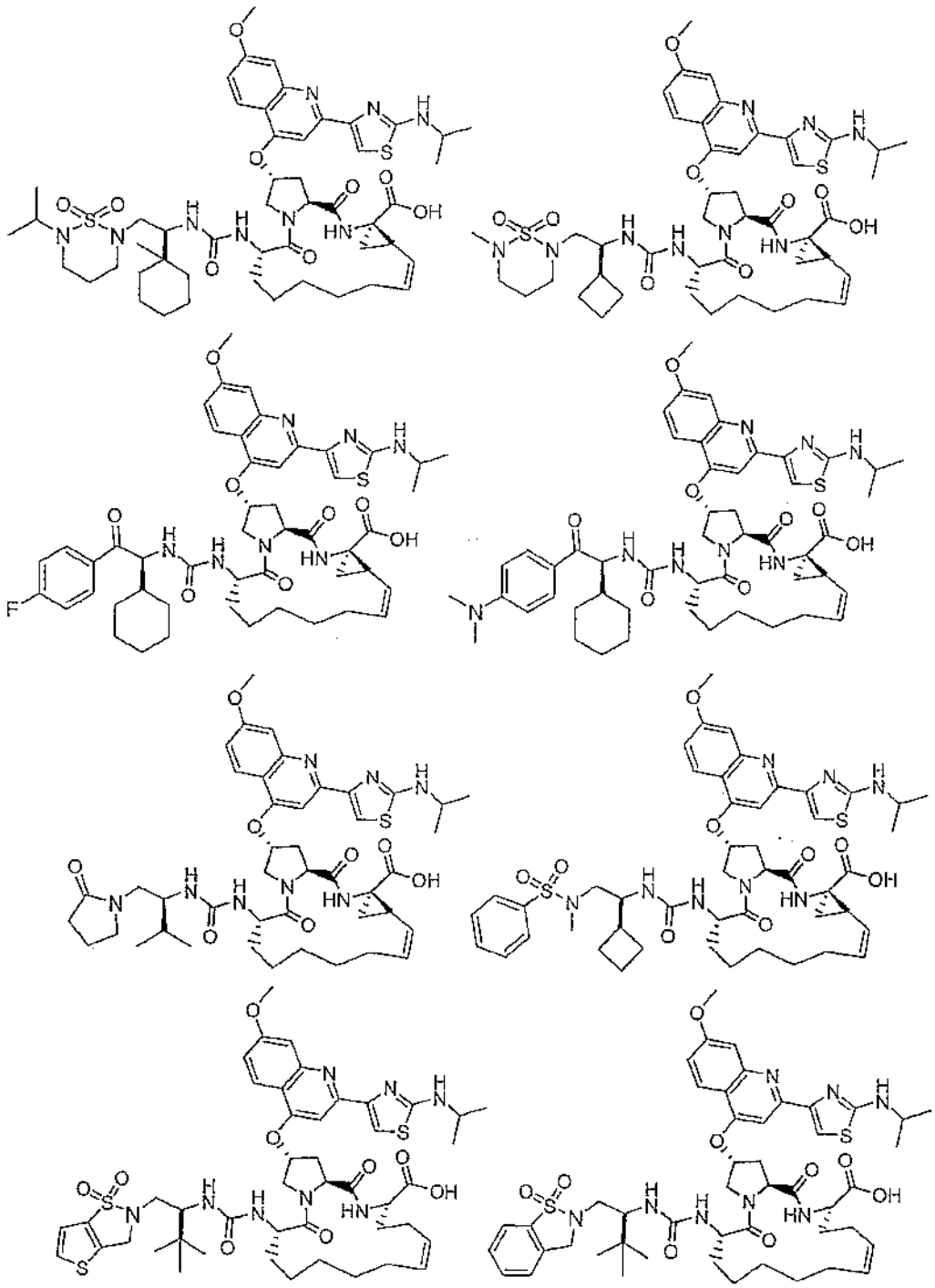


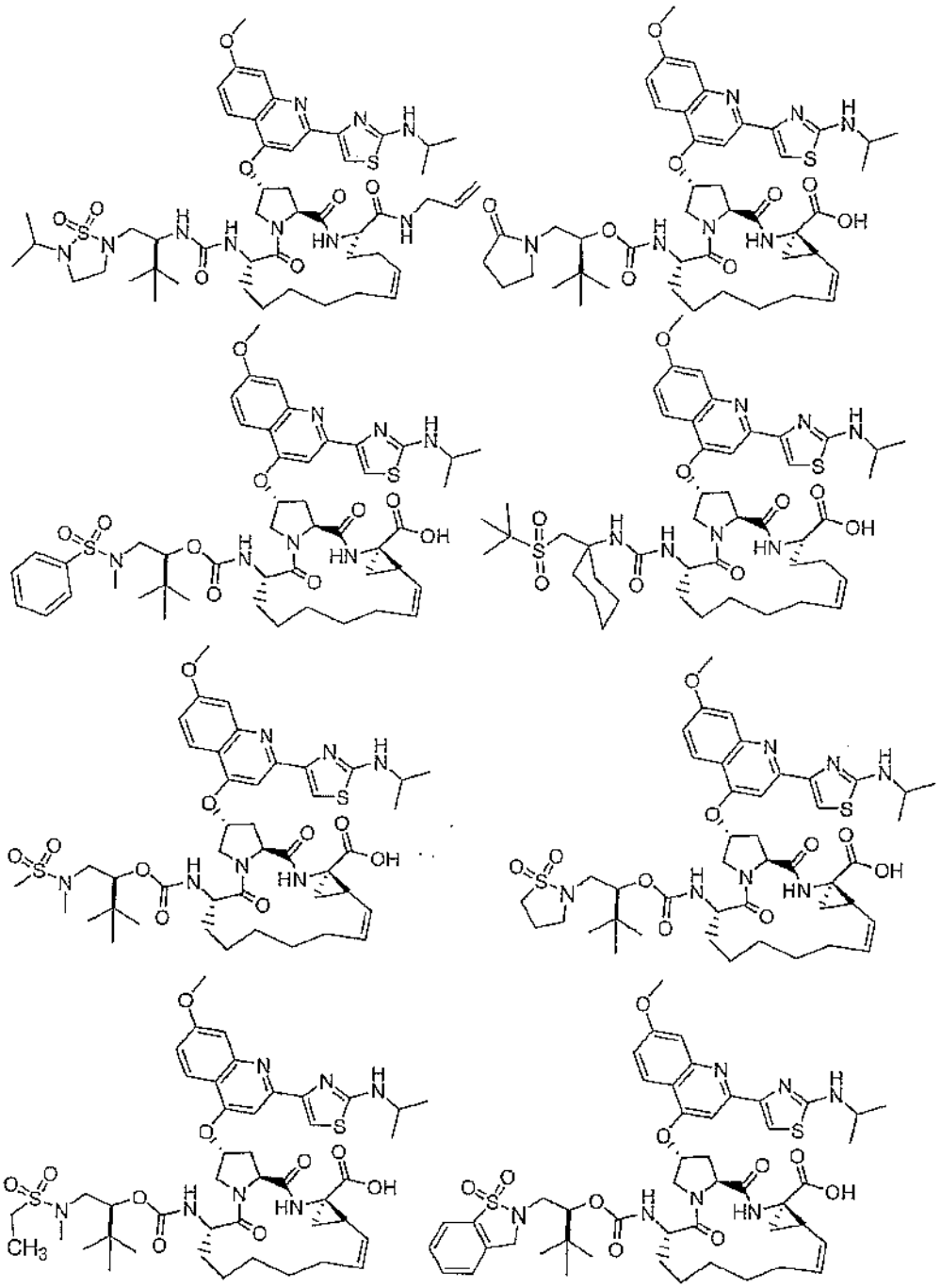


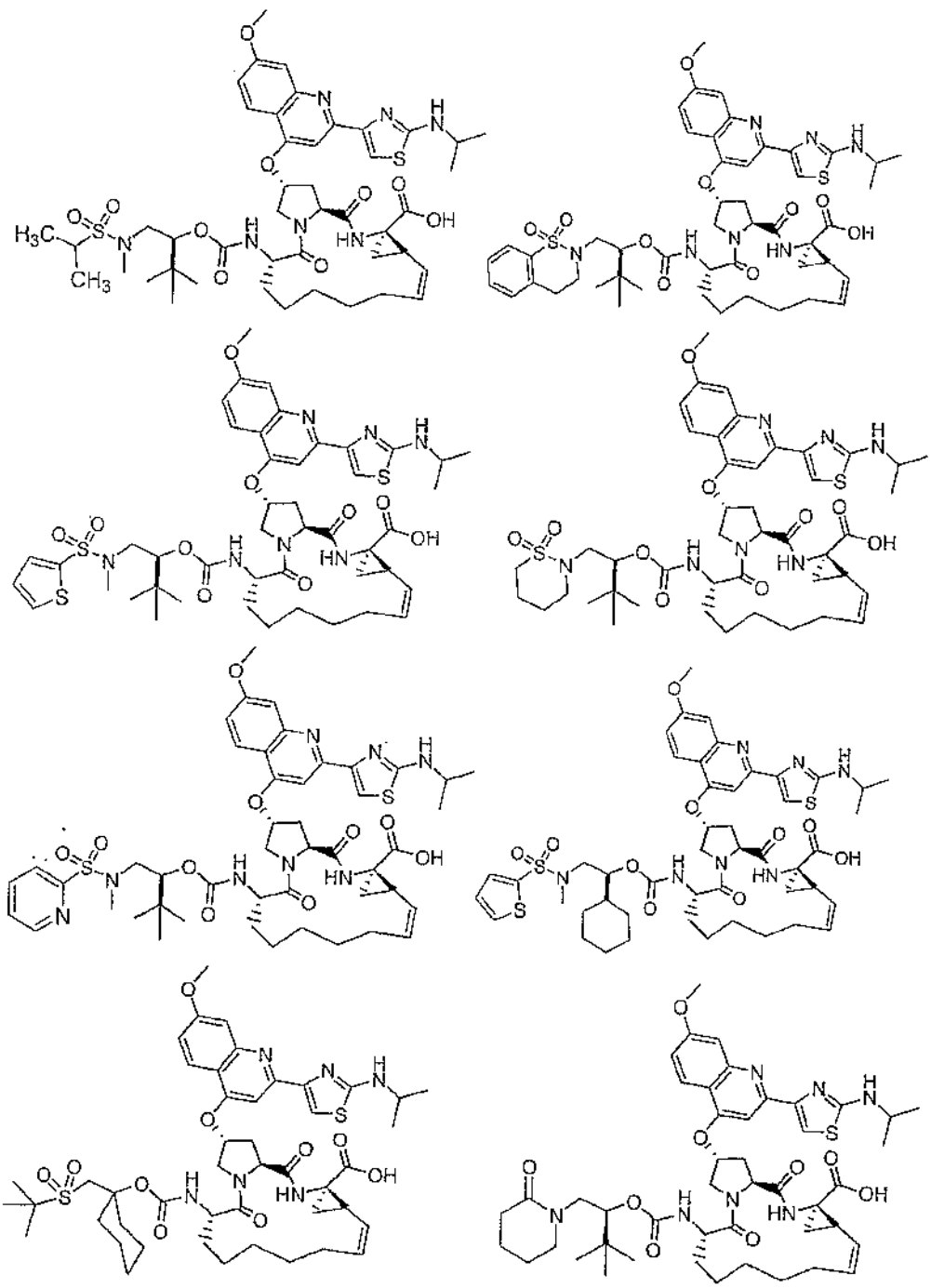


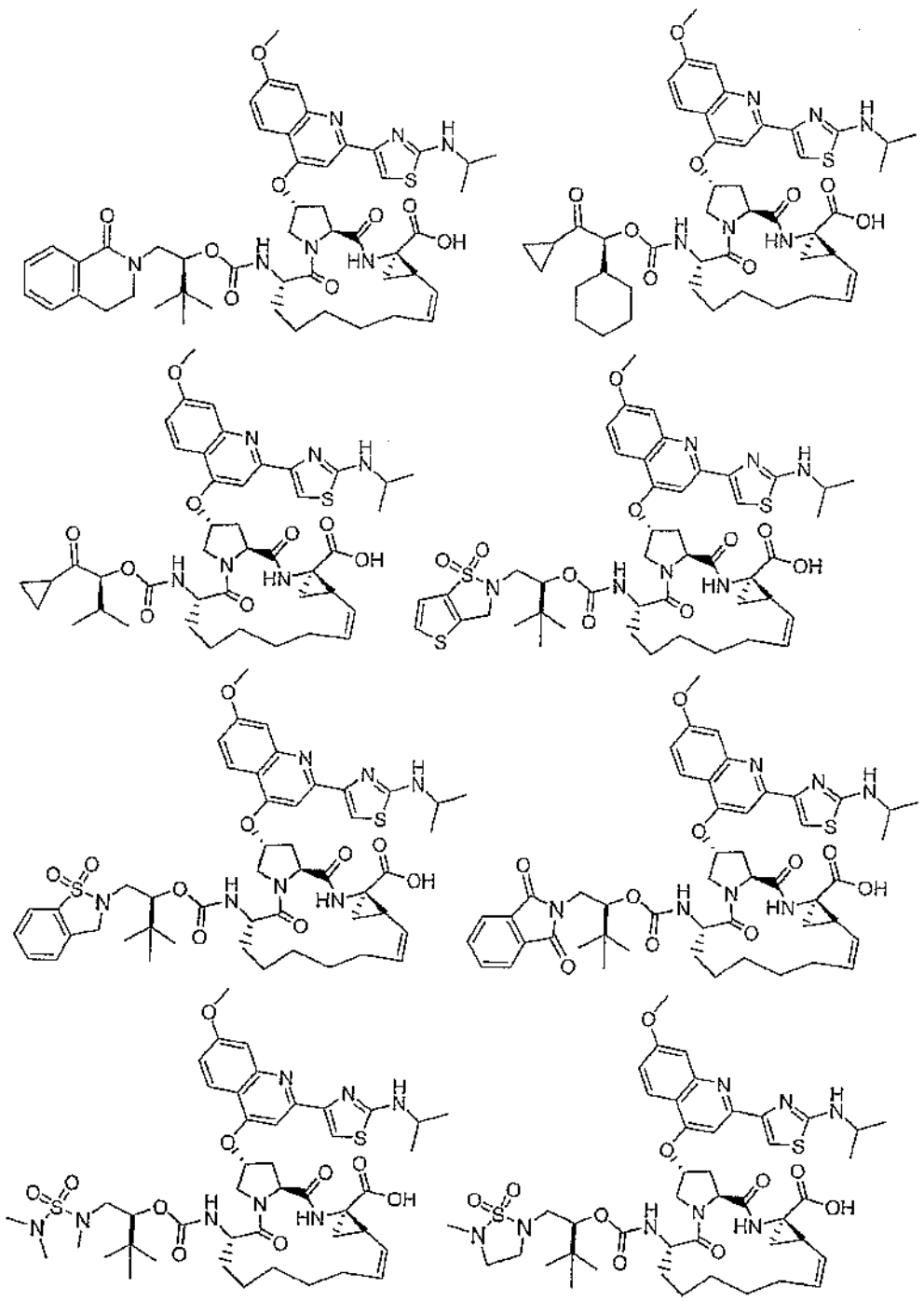


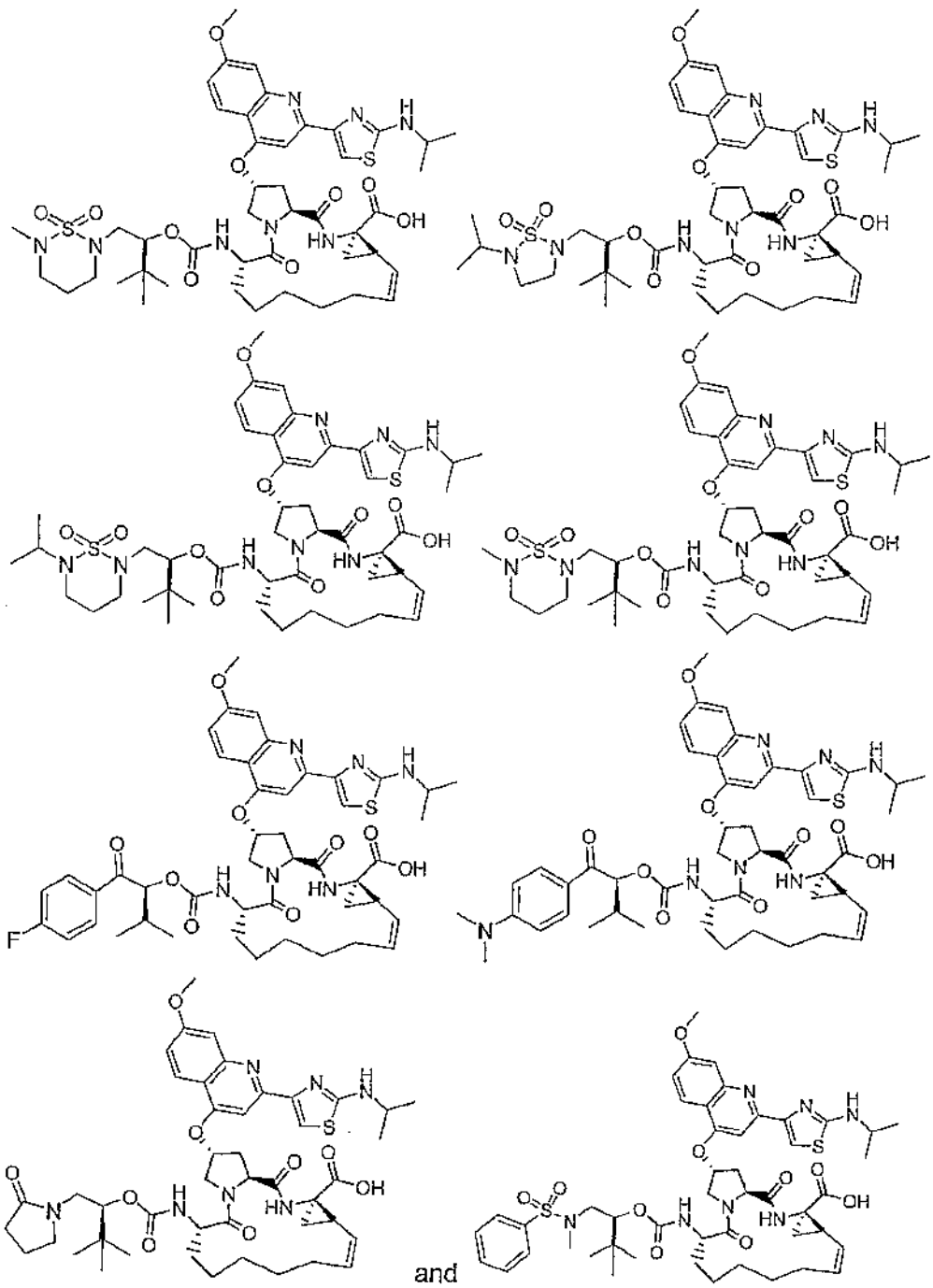








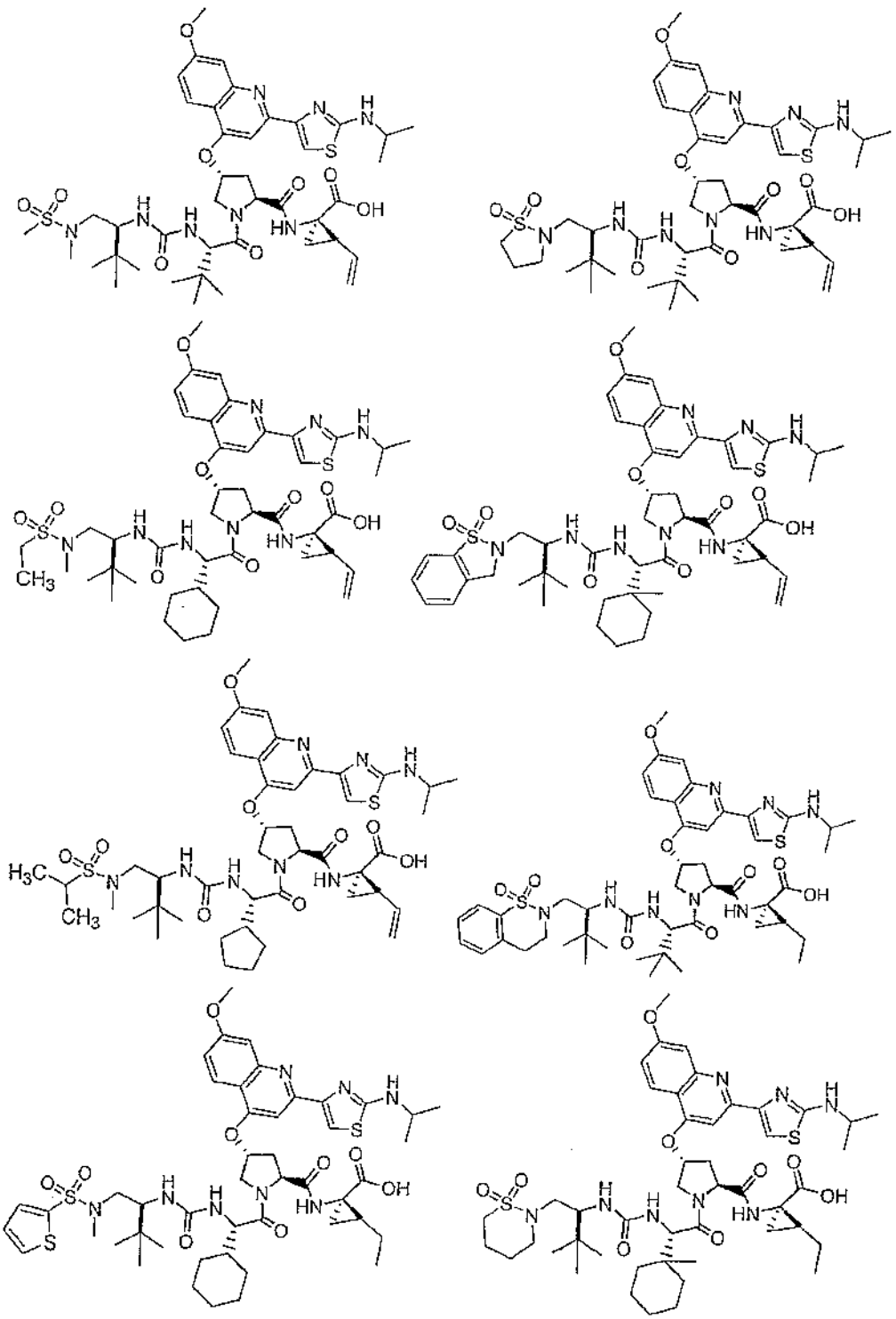


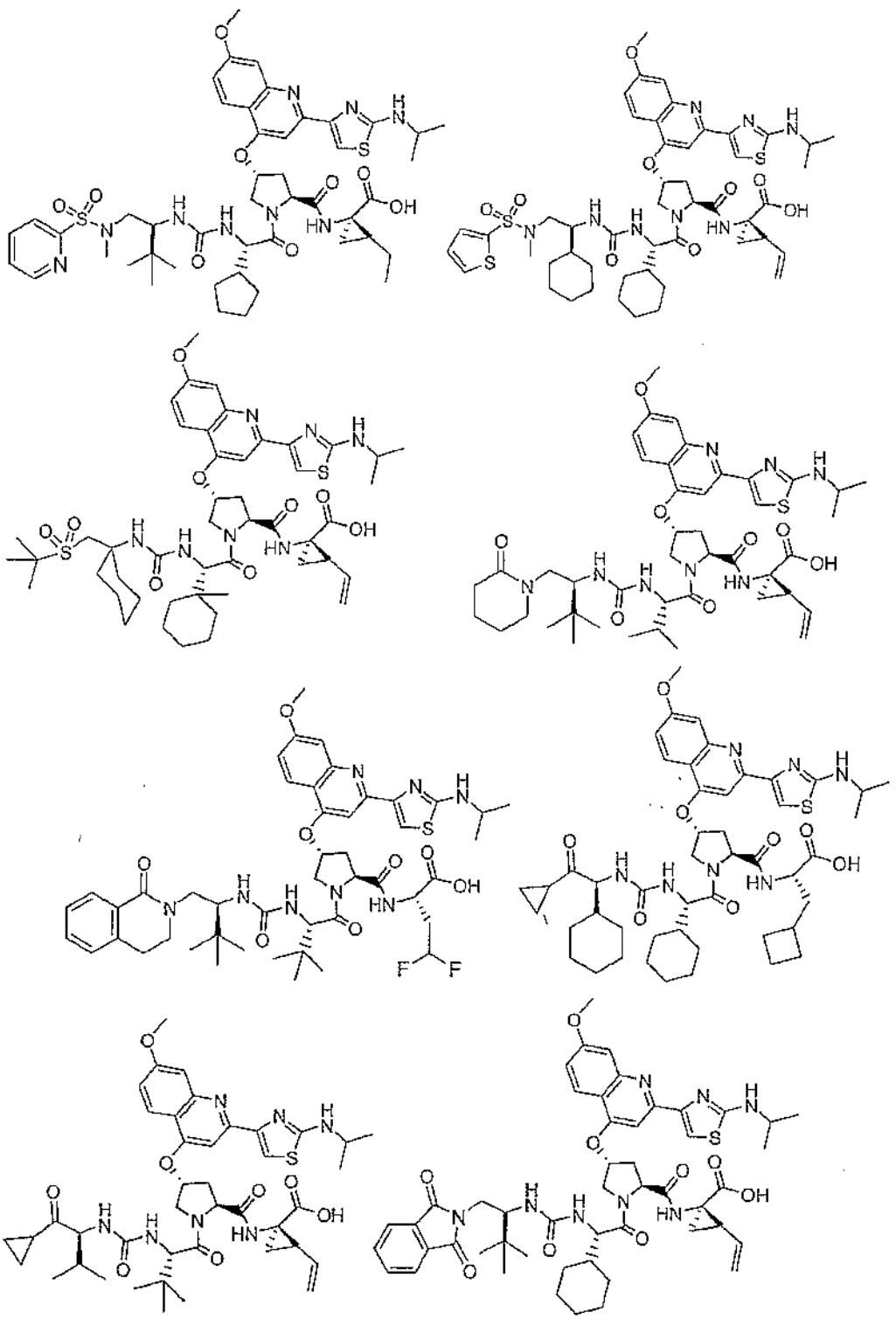


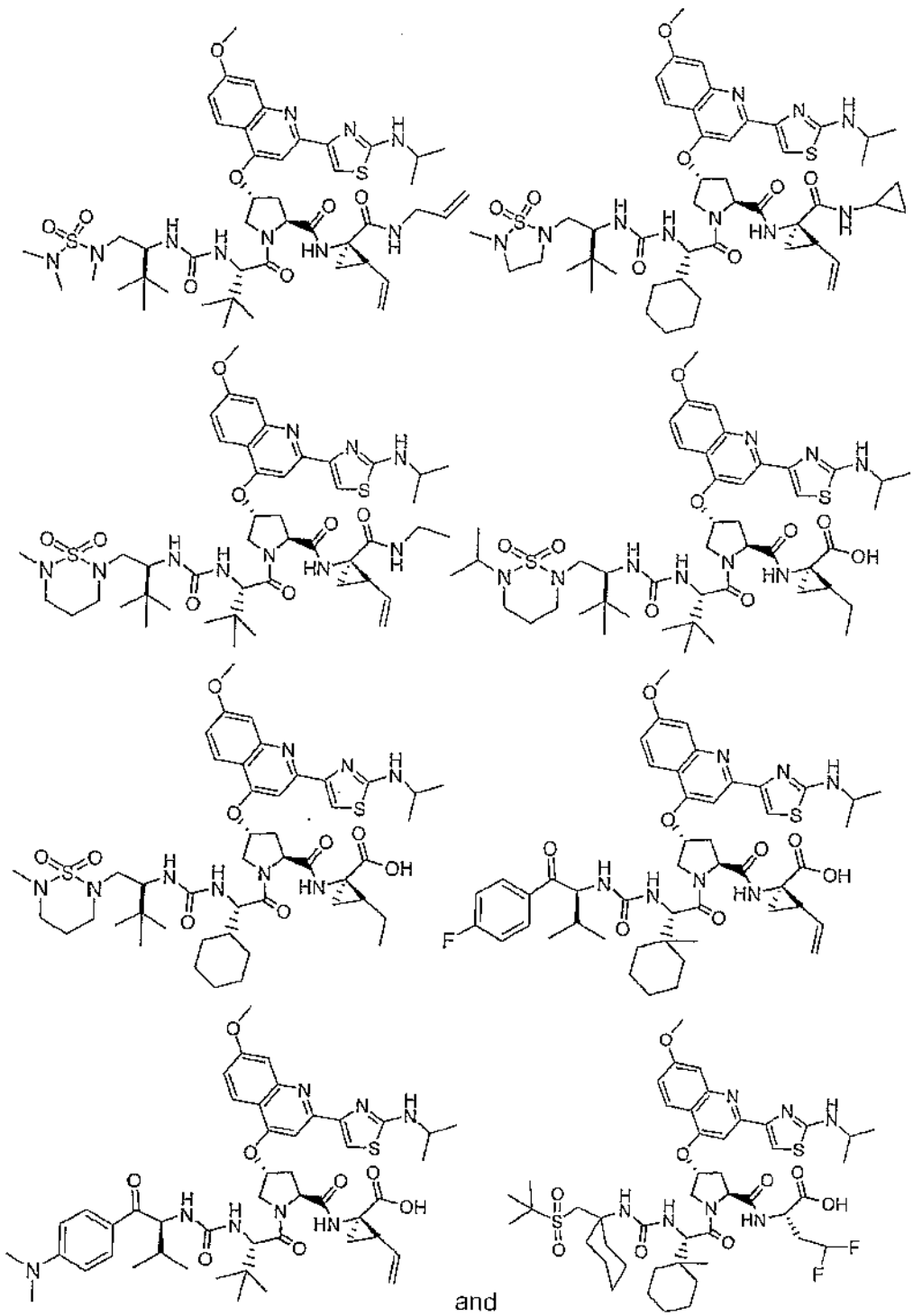
and

or a pharmaceutically acceptable salt, solvate or ester thereof.

Nonlimiting examples of certain compounds of formula VIII disclosed in U.S. Patent Application Ser. No. 10/993,394 are:



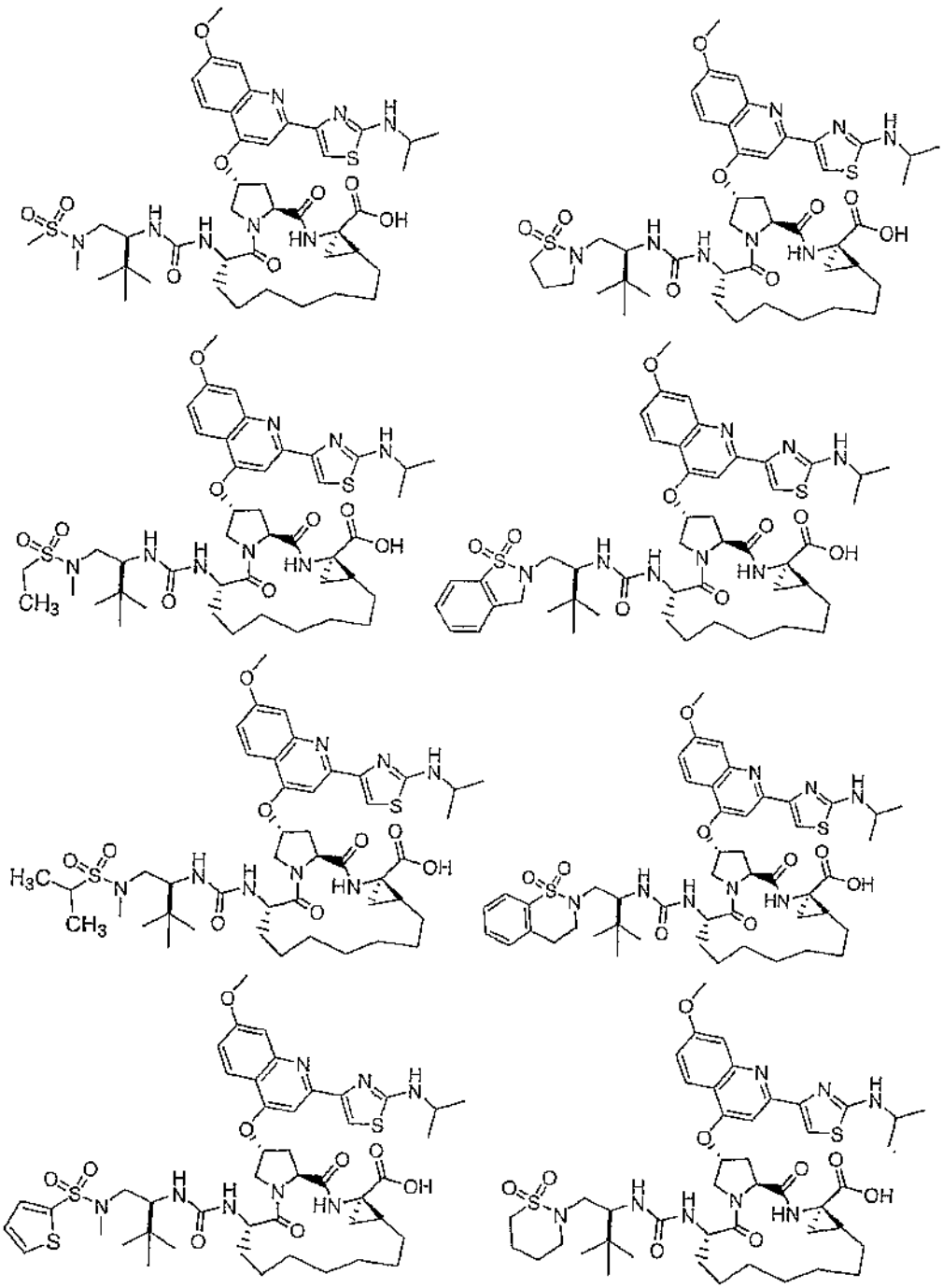


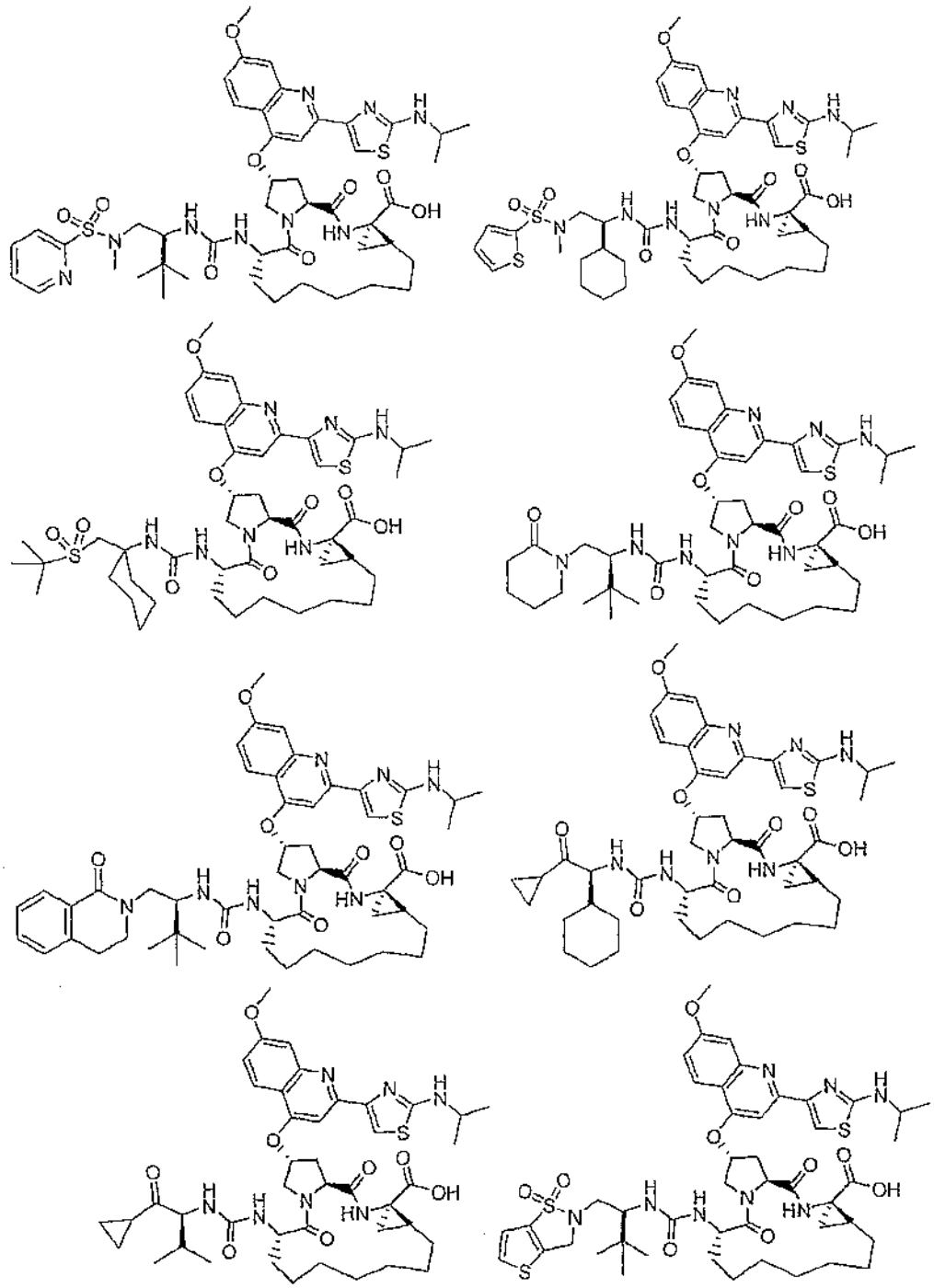


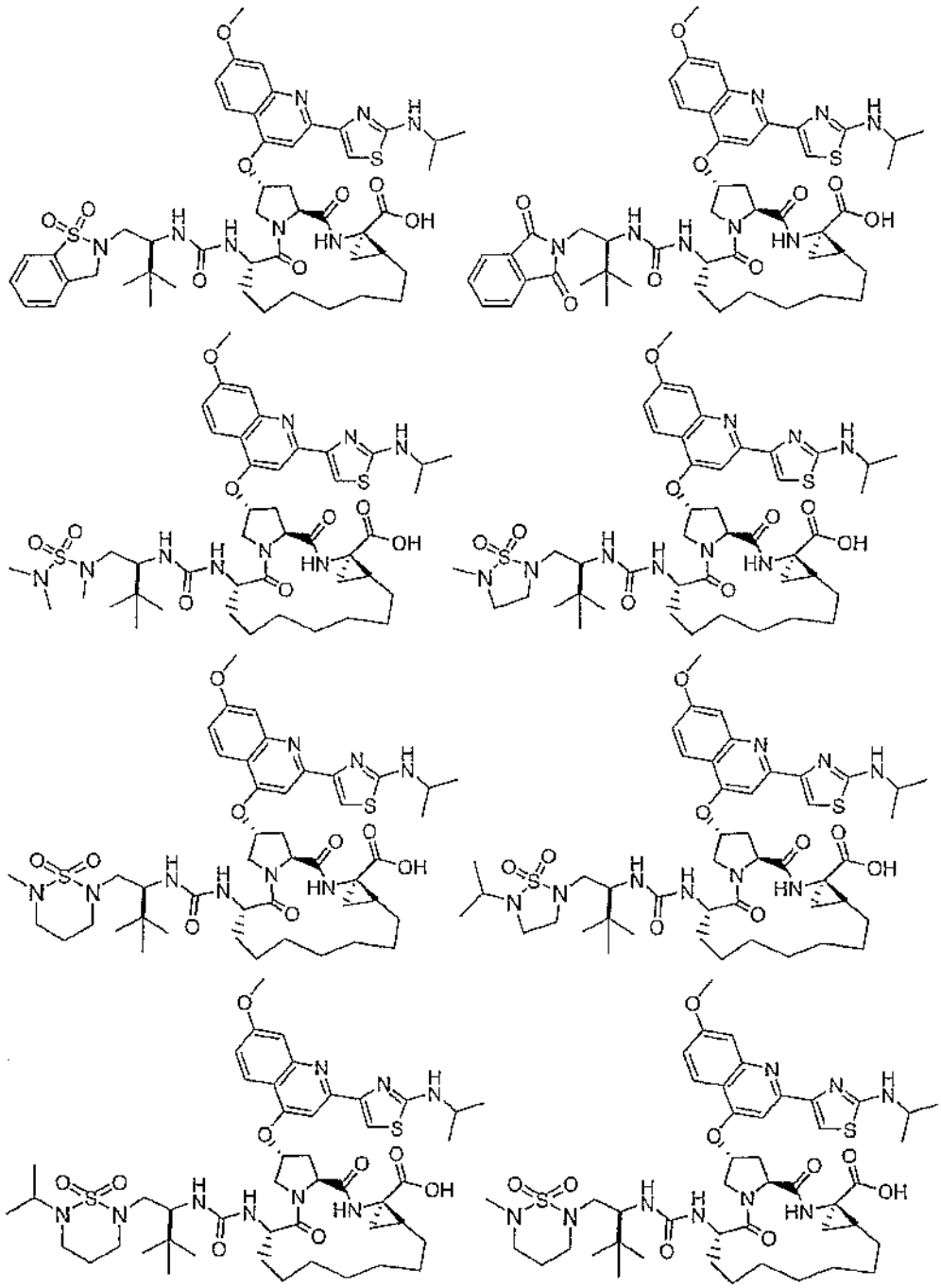
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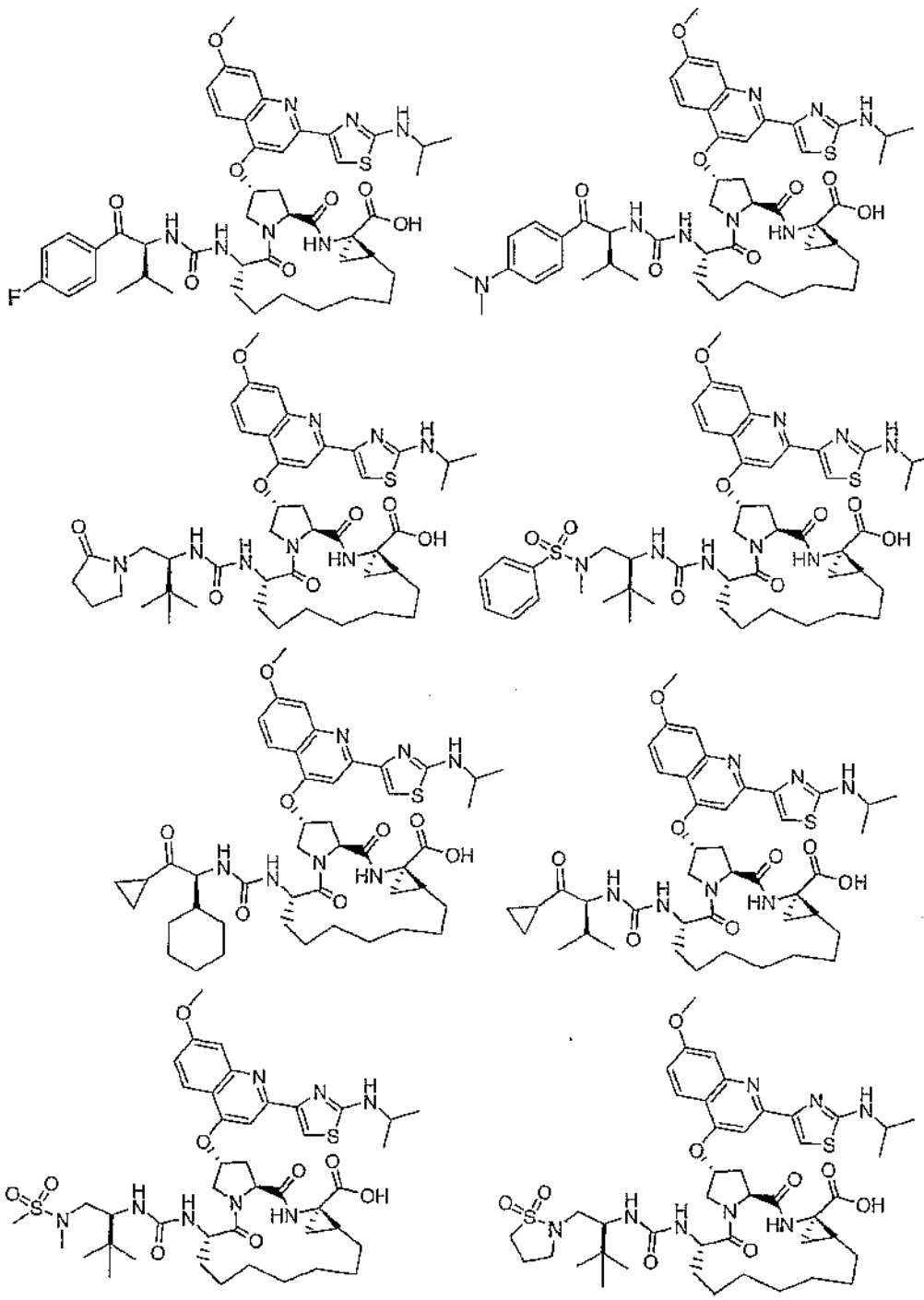
or a pharmaceutically acceptable salt, solvate or ester thereof.

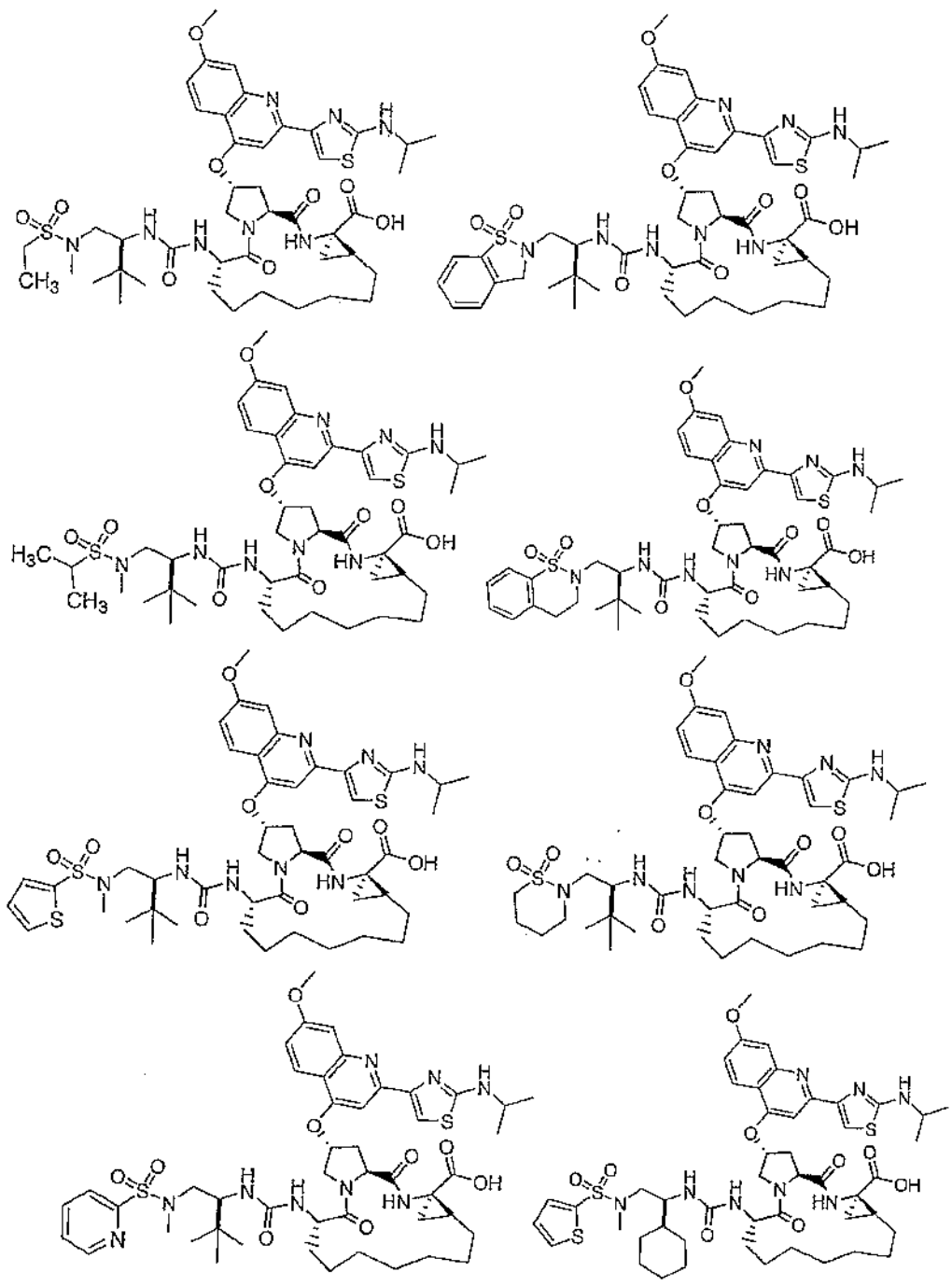
Nonlimiting examples of certain compounds of formula IX disclosed in U.S. Patent Application Ser. No. 10/993,394 are:

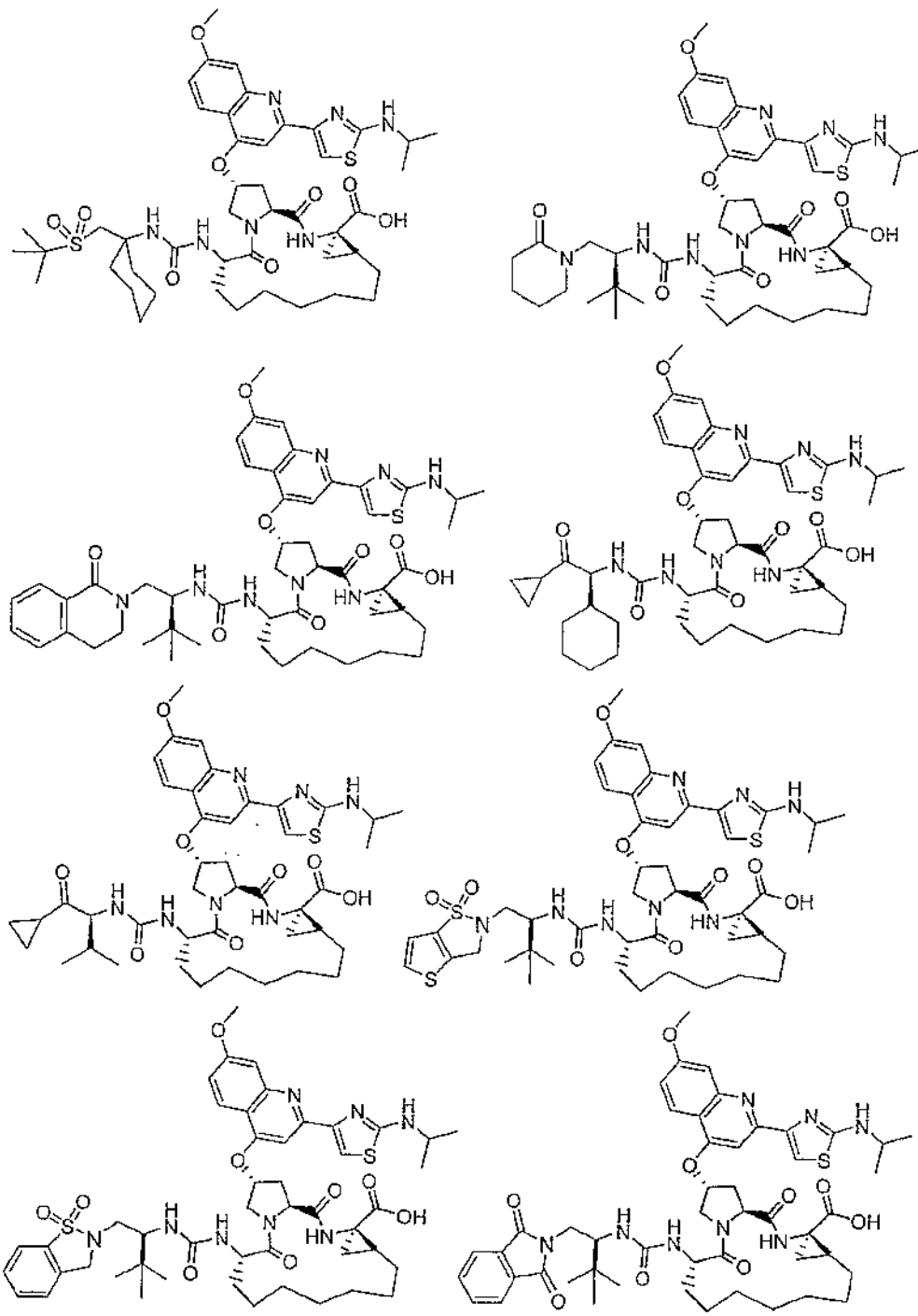


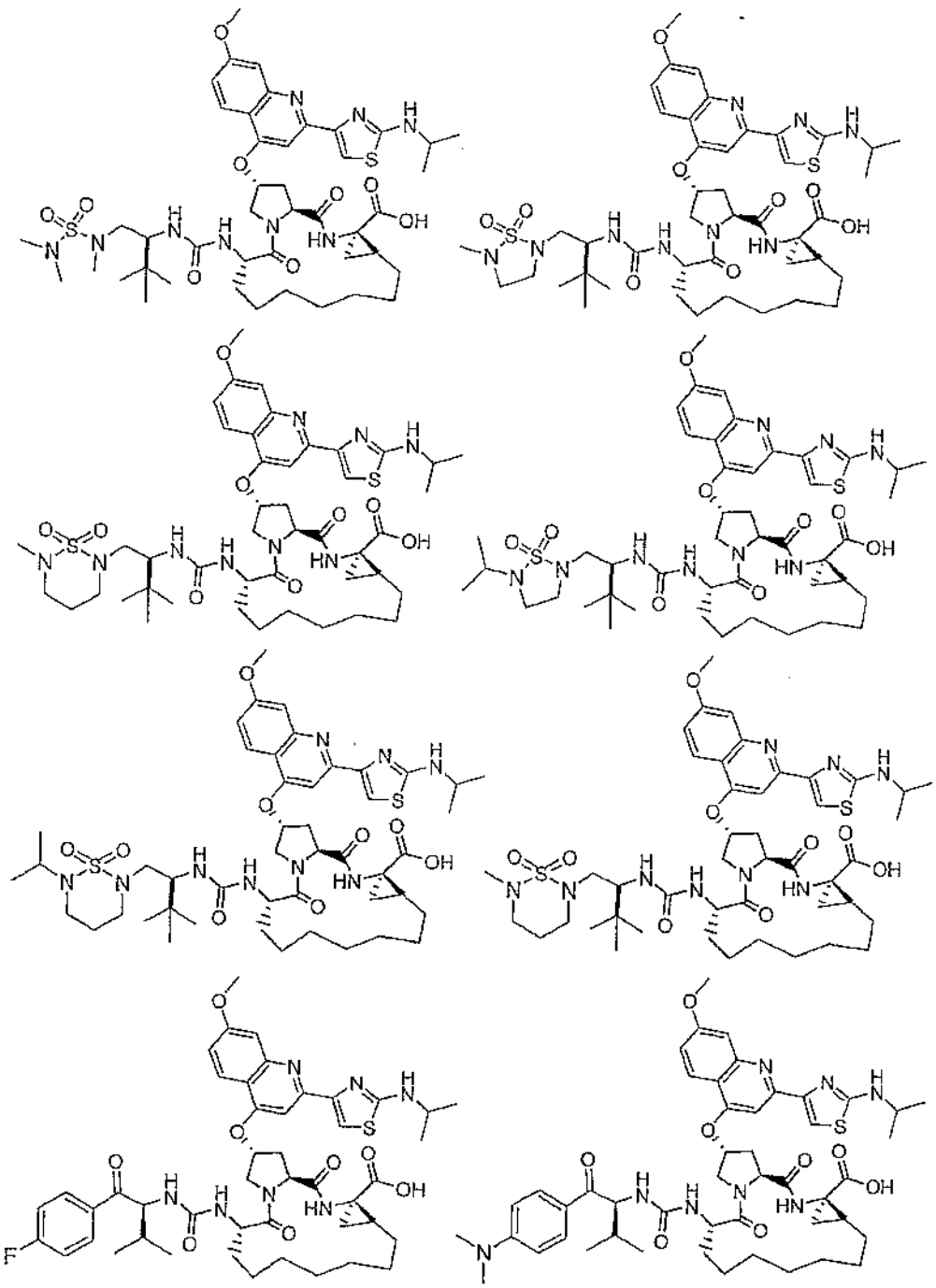


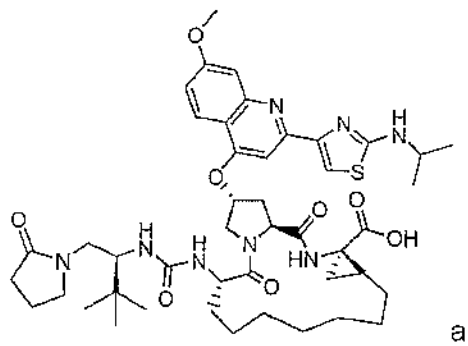




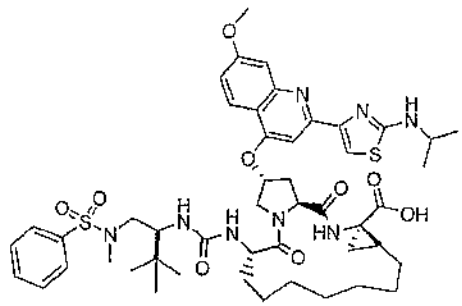








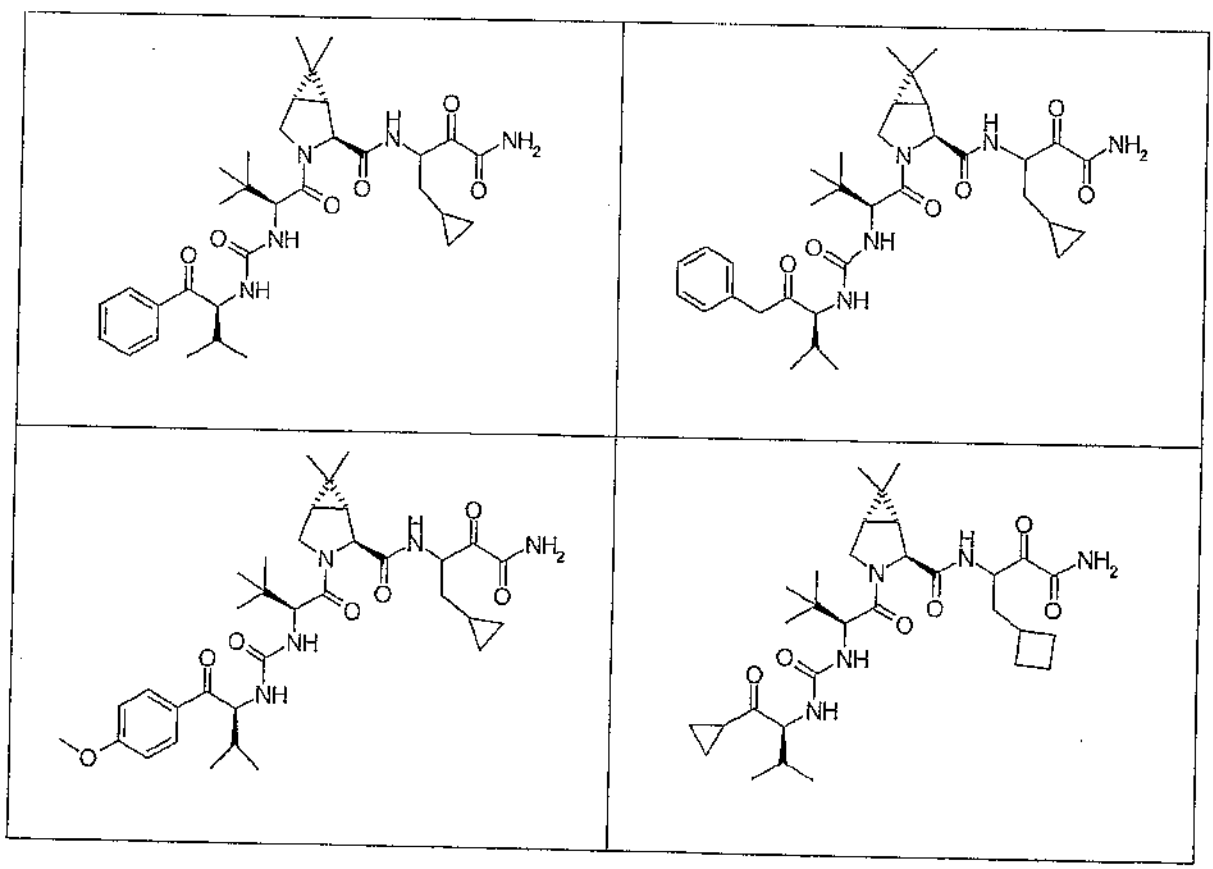
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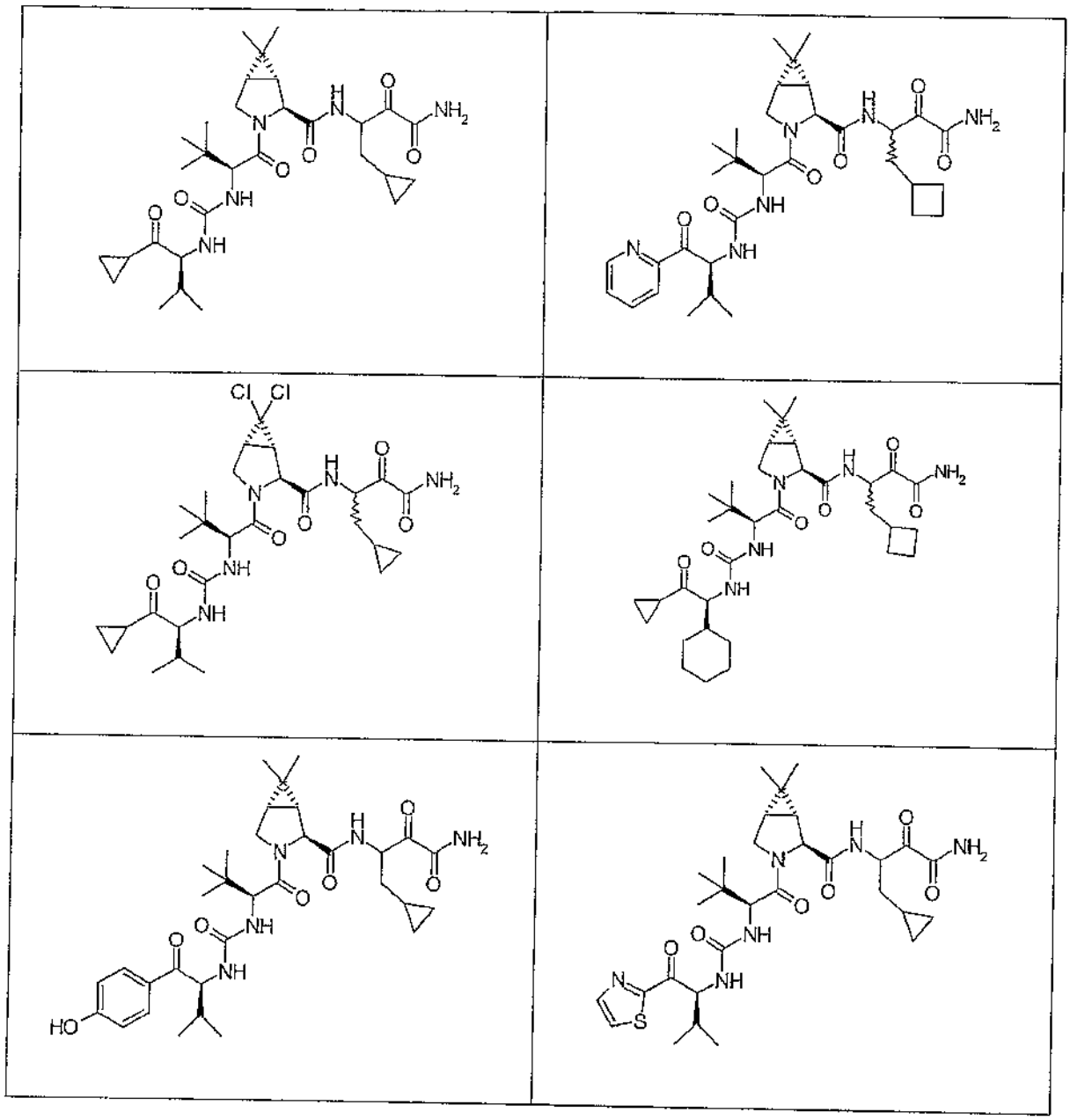


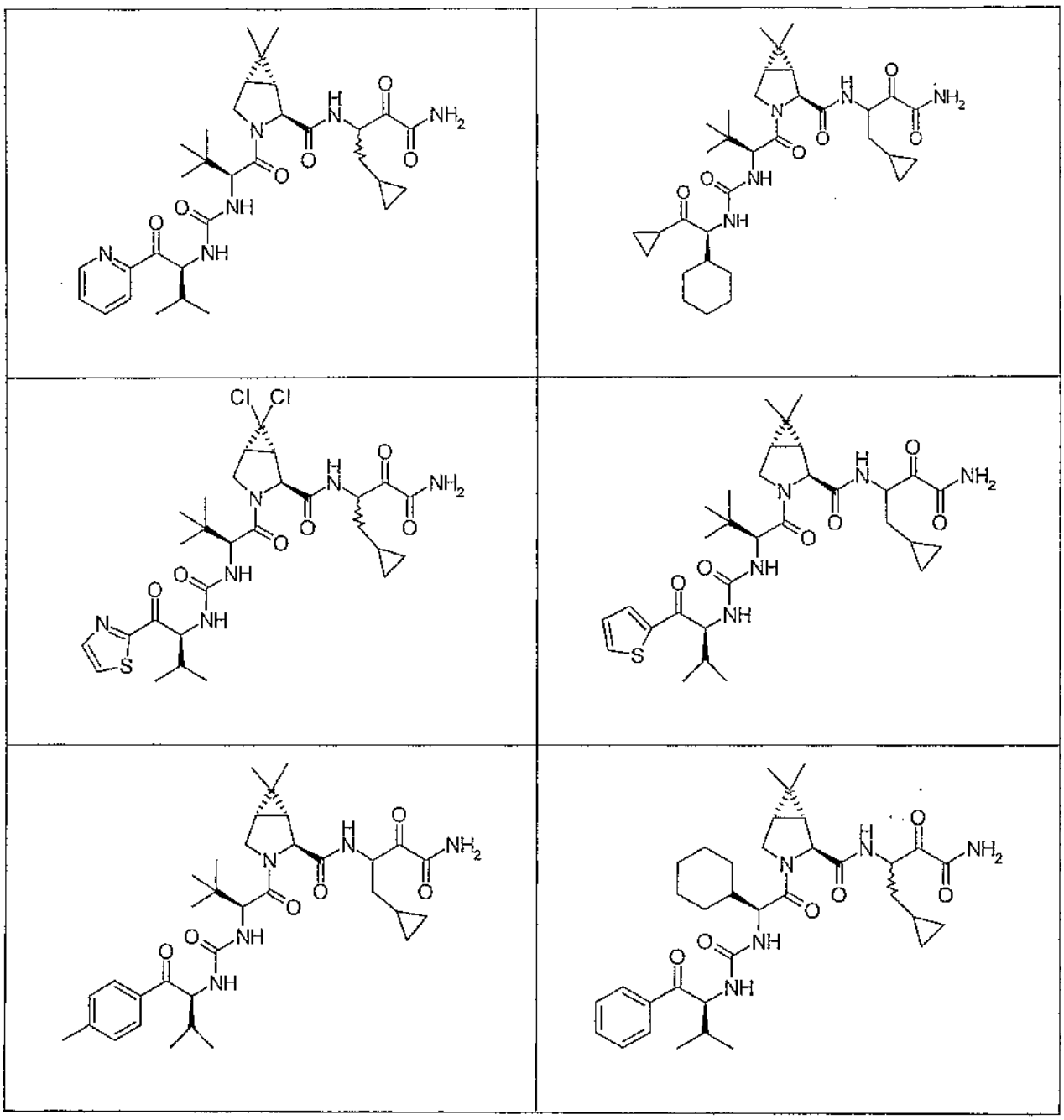
or a pharmaceutically acceptable salt, solvate or ester thereof.

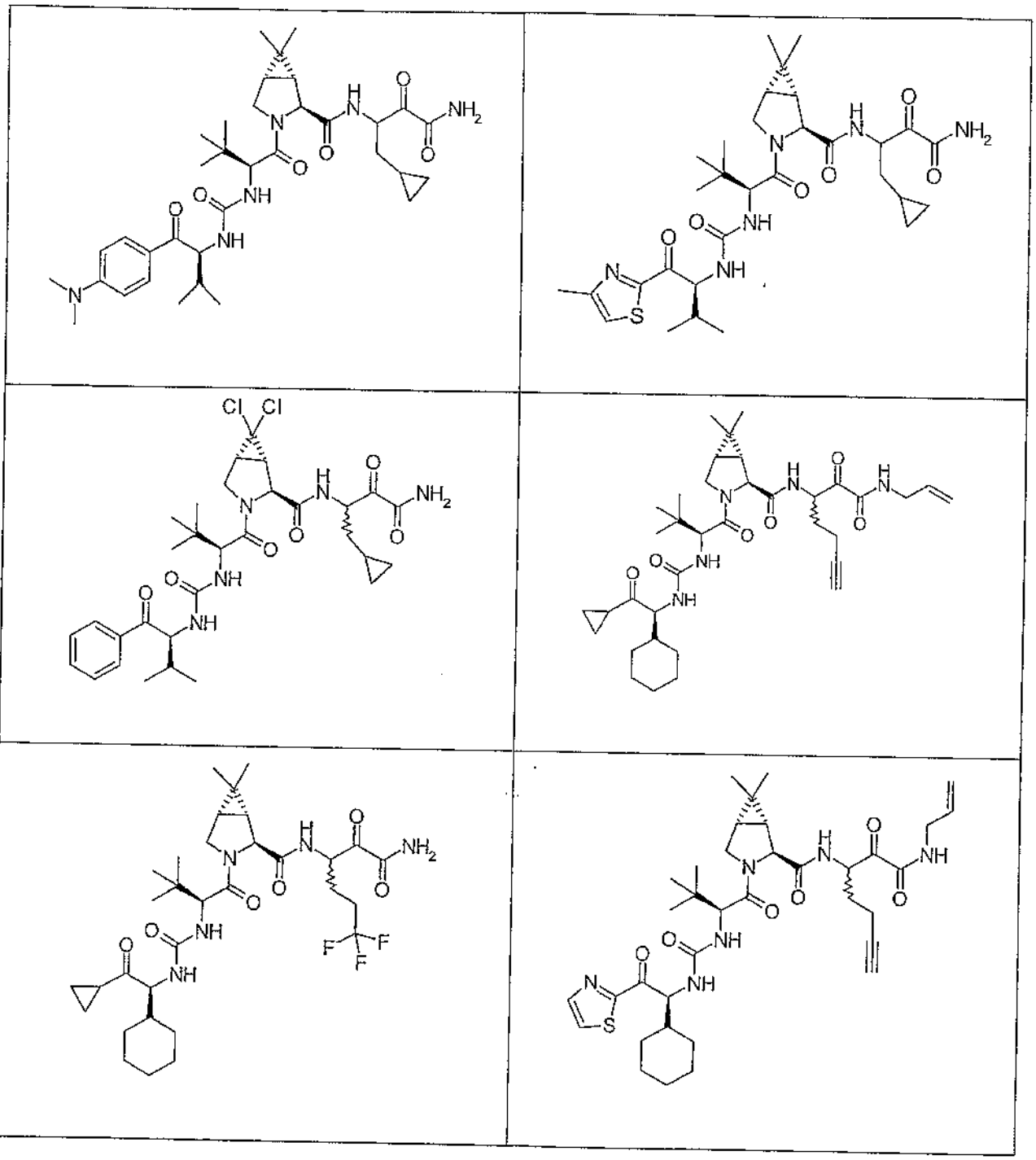
Compounds of formula X are disclosed in U.S. Patent Application Ser. No. 11/065,572 filed February 24, 2005 and the preparation of the compounds are detailed in the experimental section of this application set forth hereinbelow.

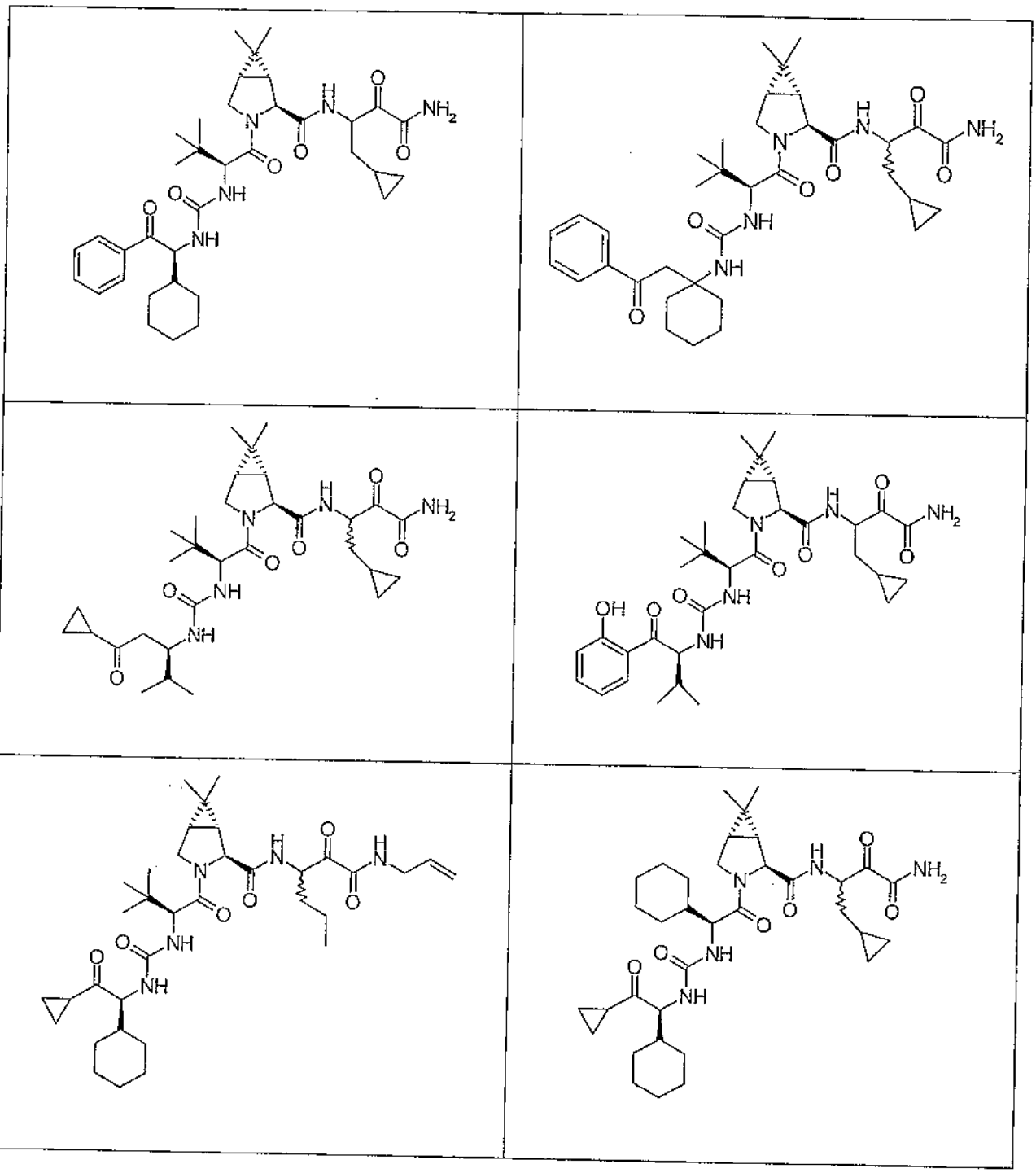
Non-limiting examples of certain compounds disclosed in U.S. Patent Application Ser. No. 11/065,572 filed February 24, 2005 are:

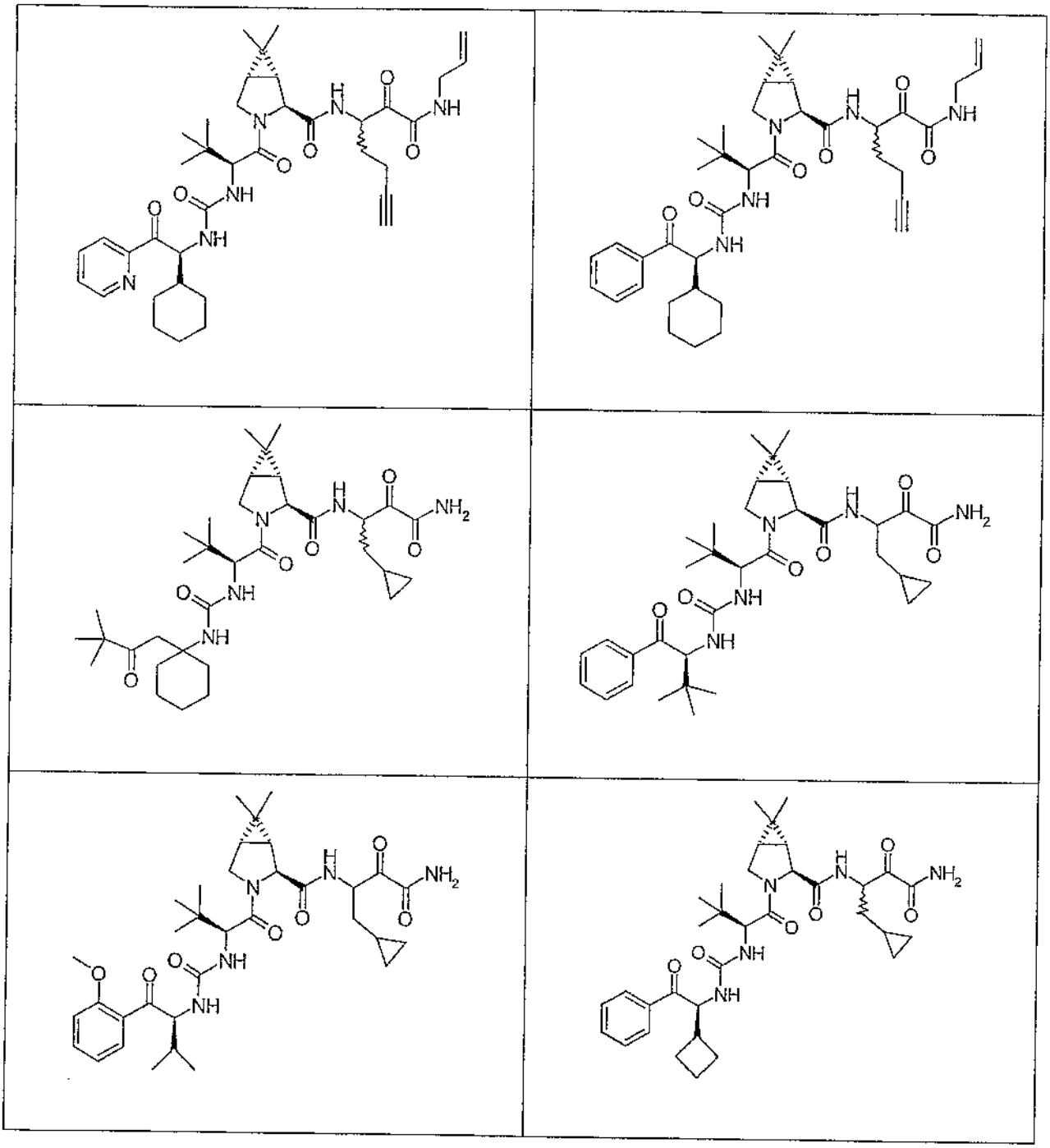


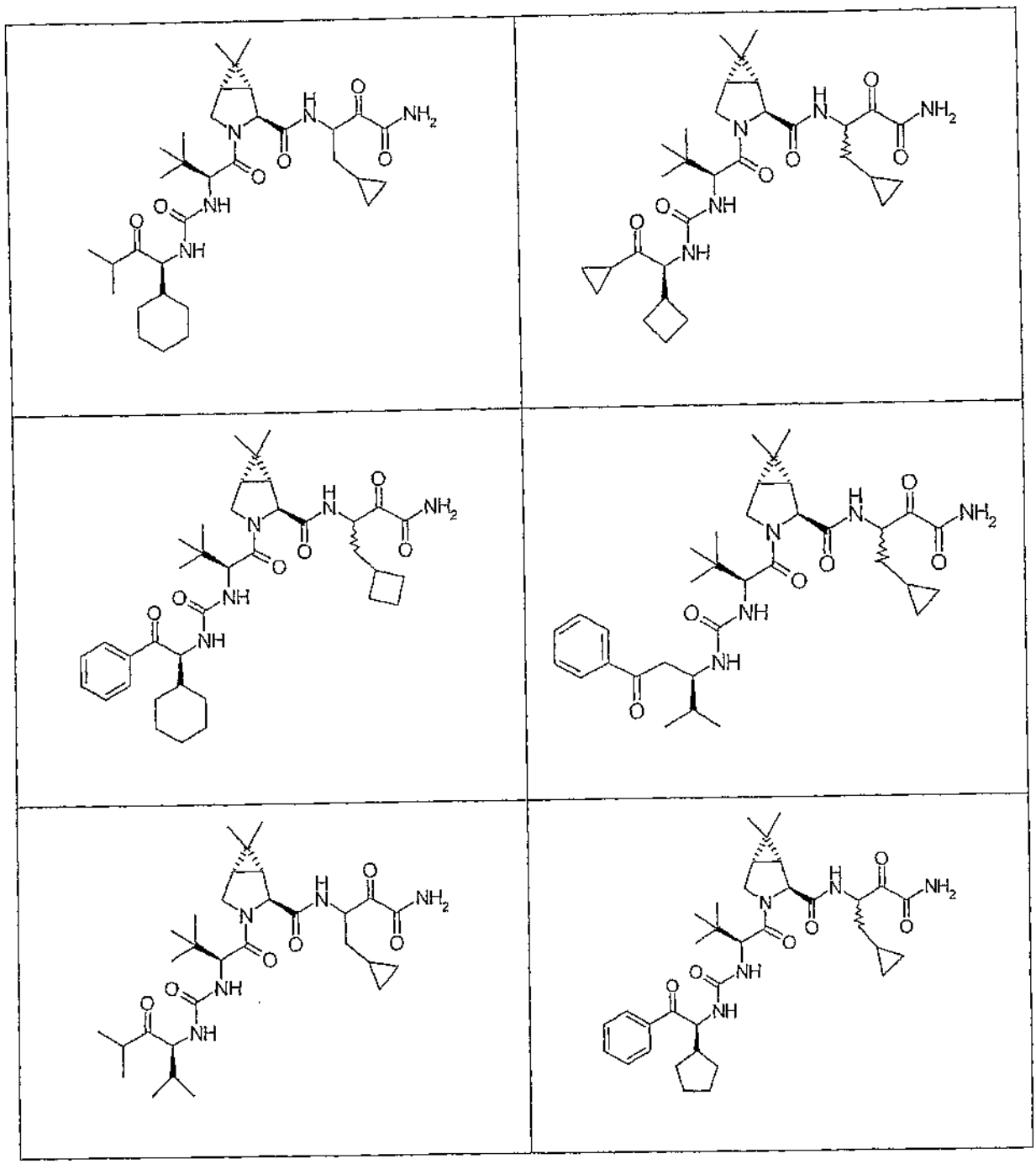


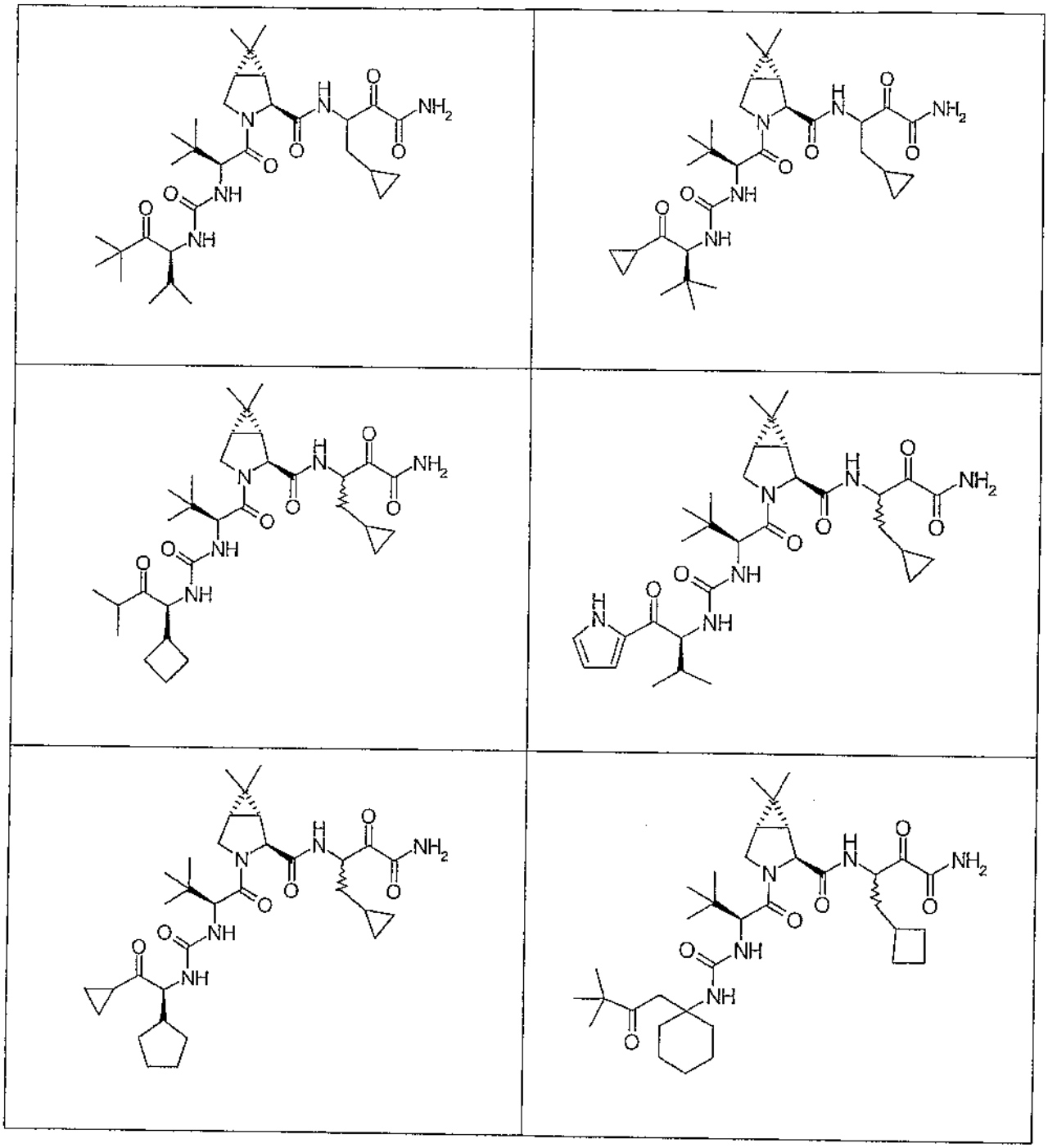


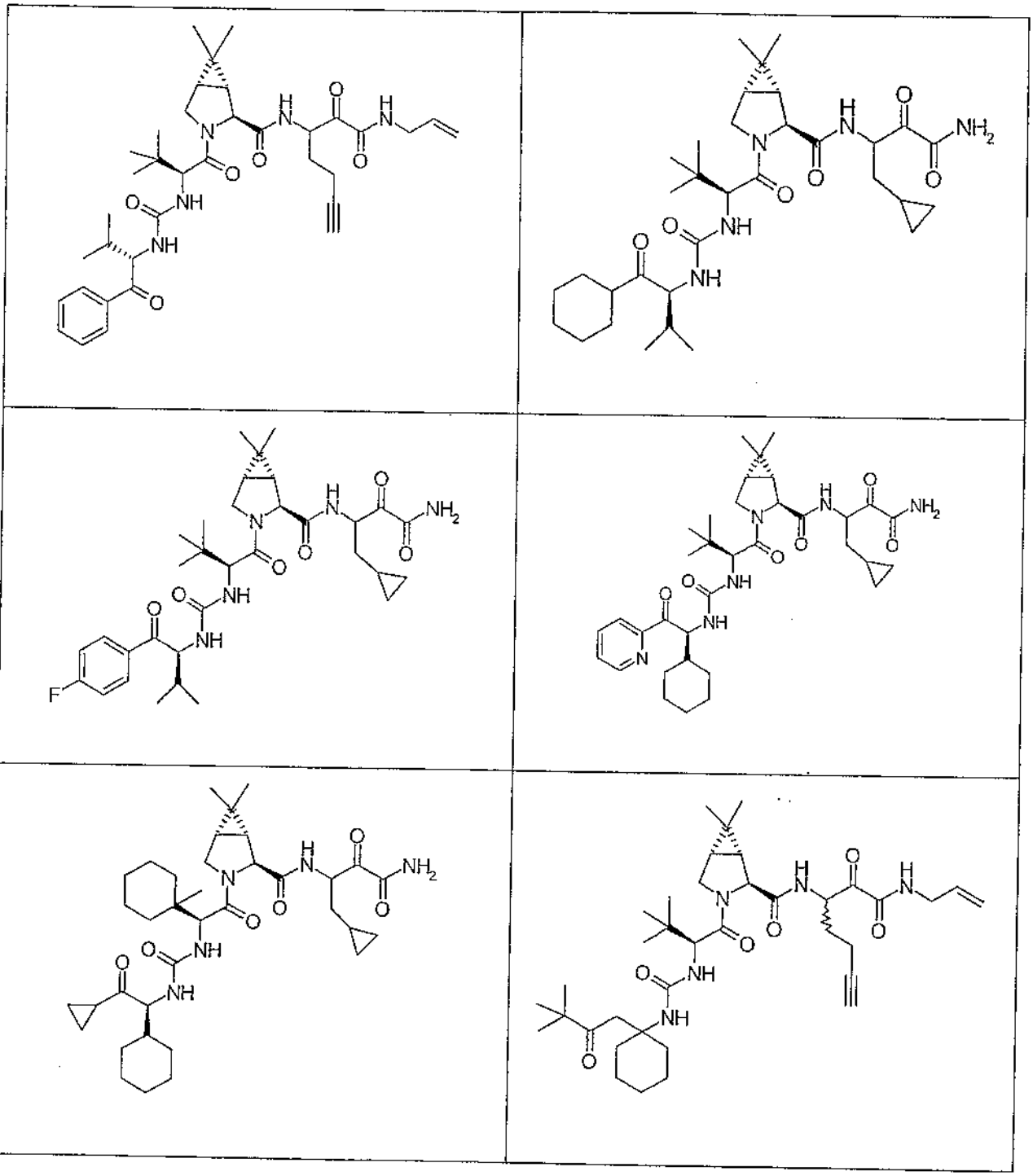


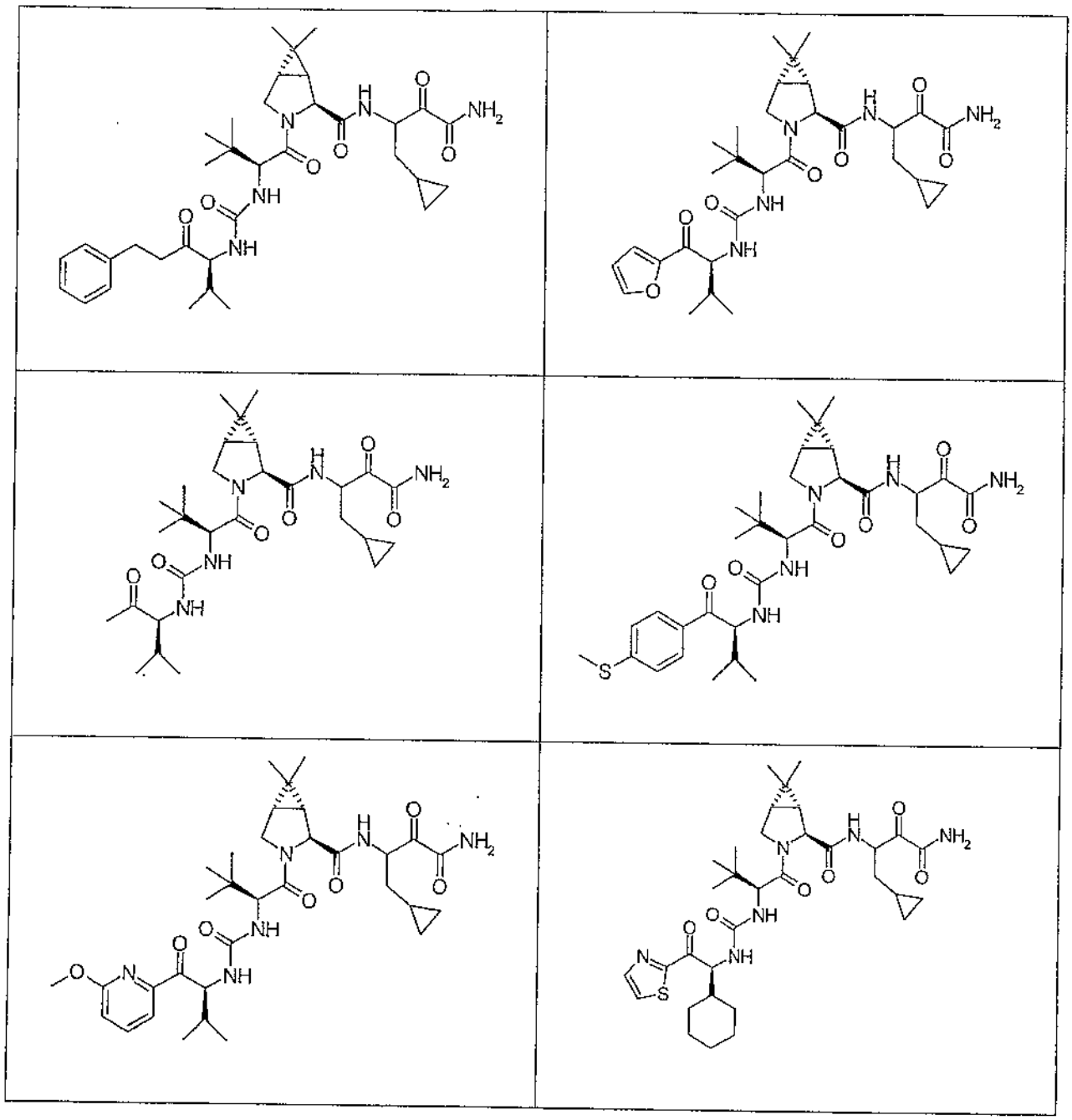


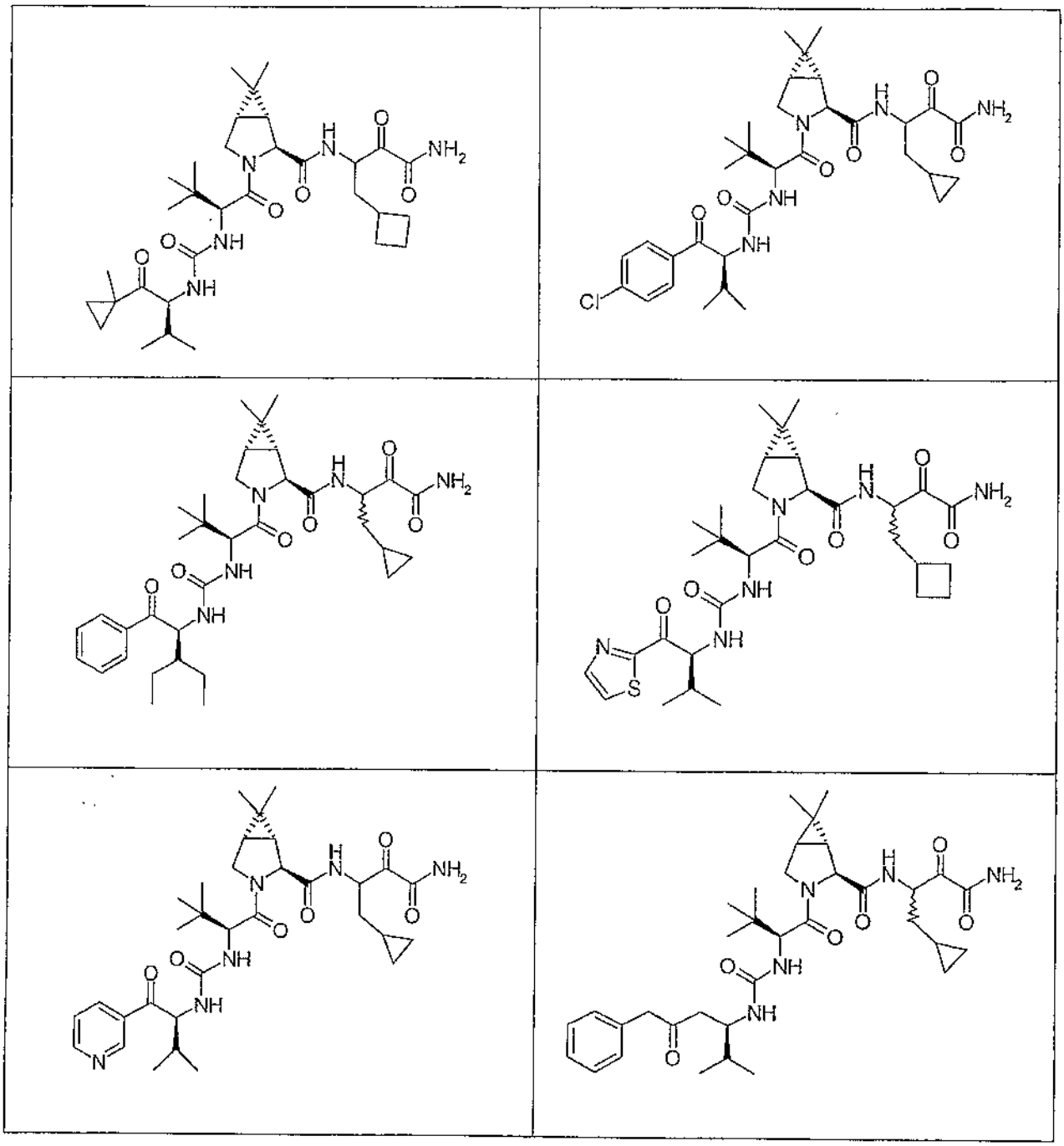


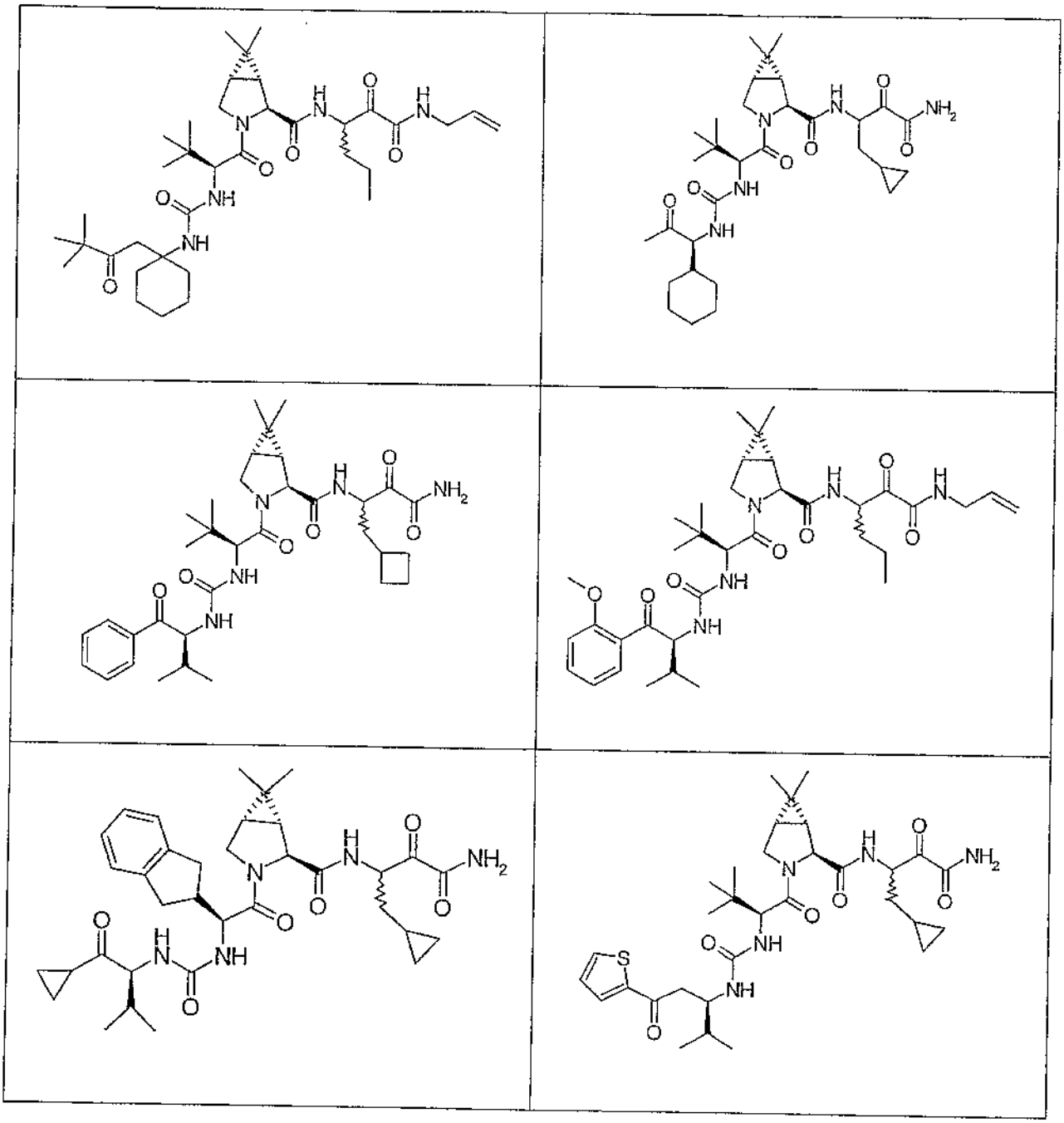


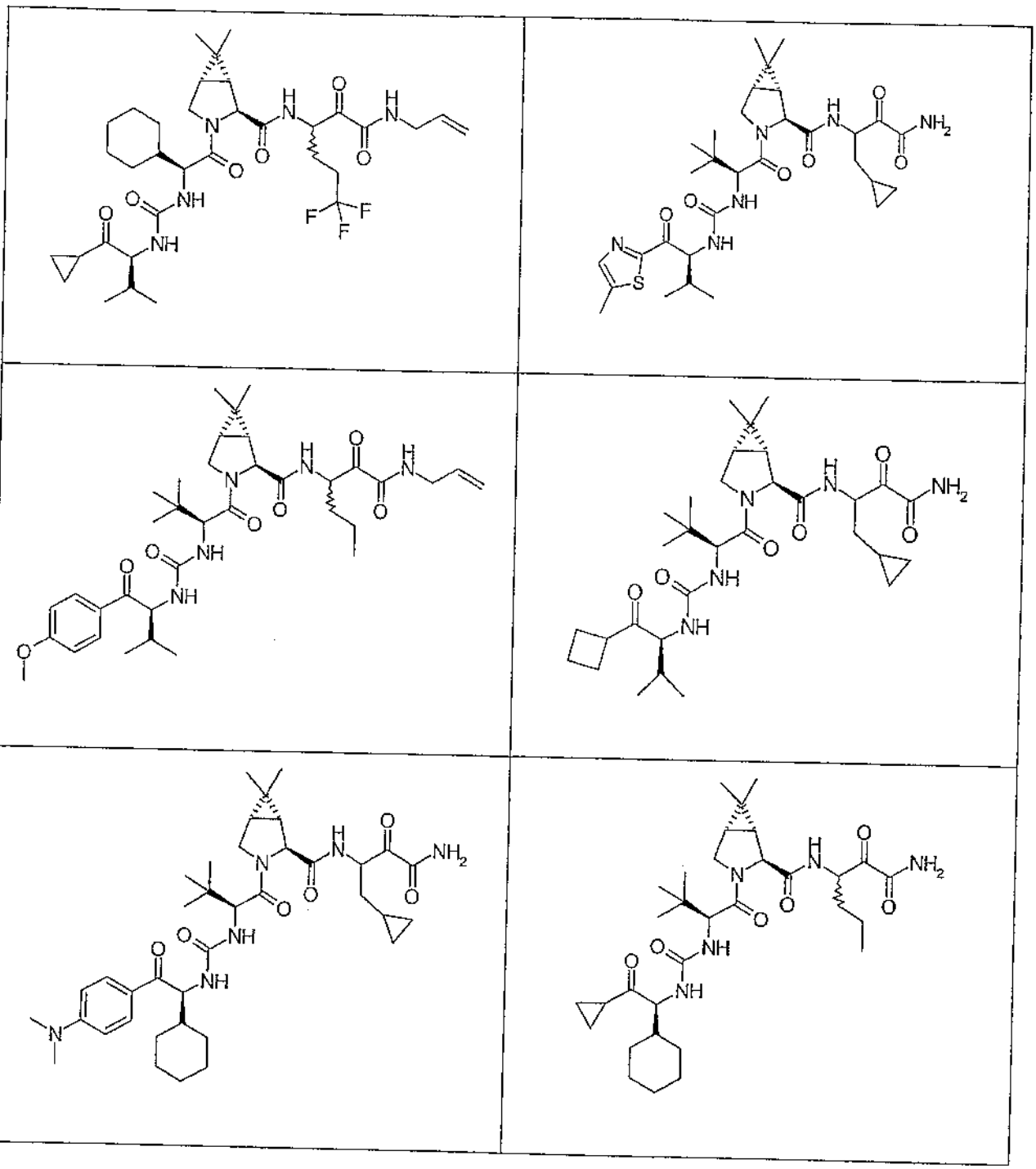


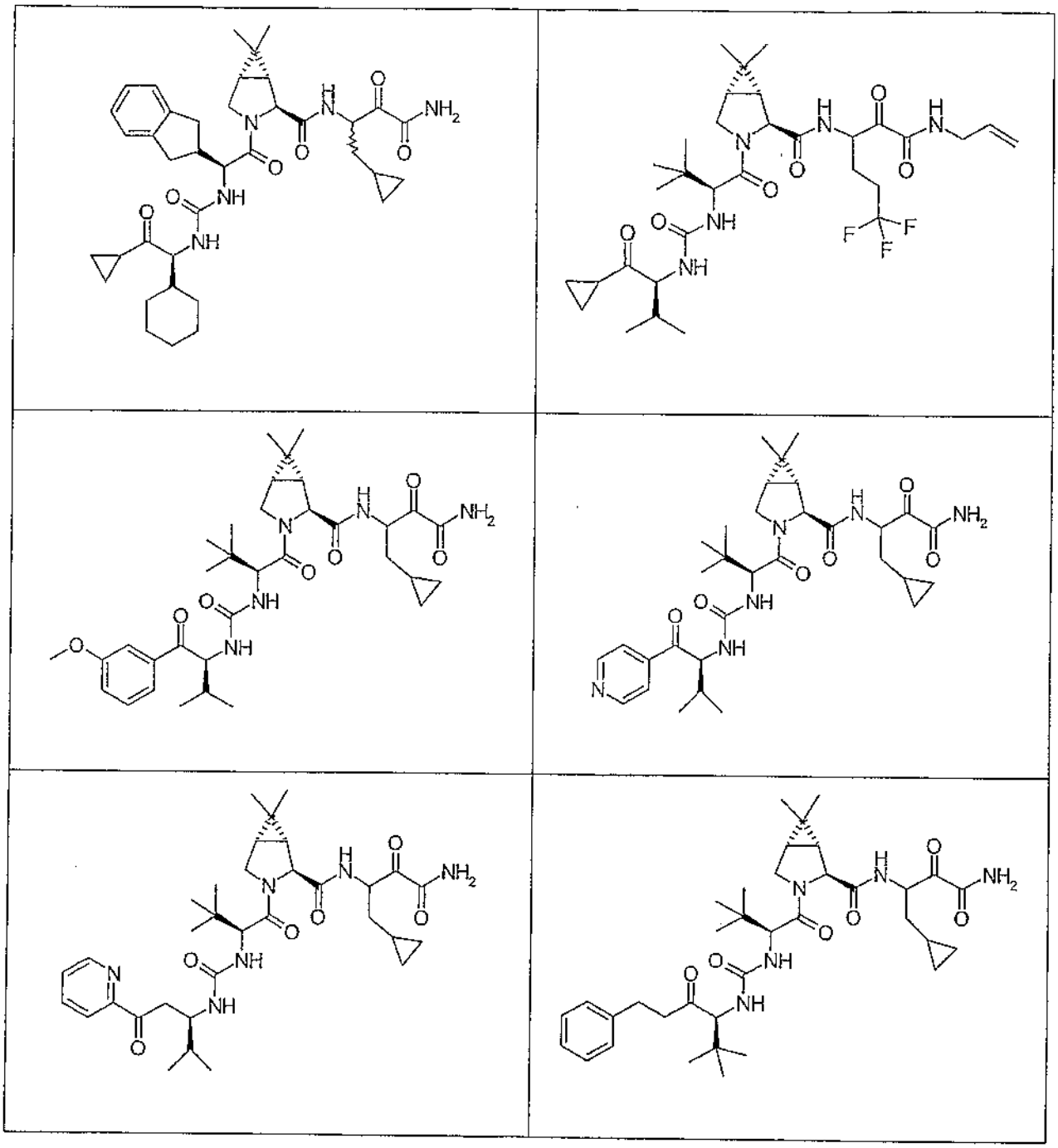


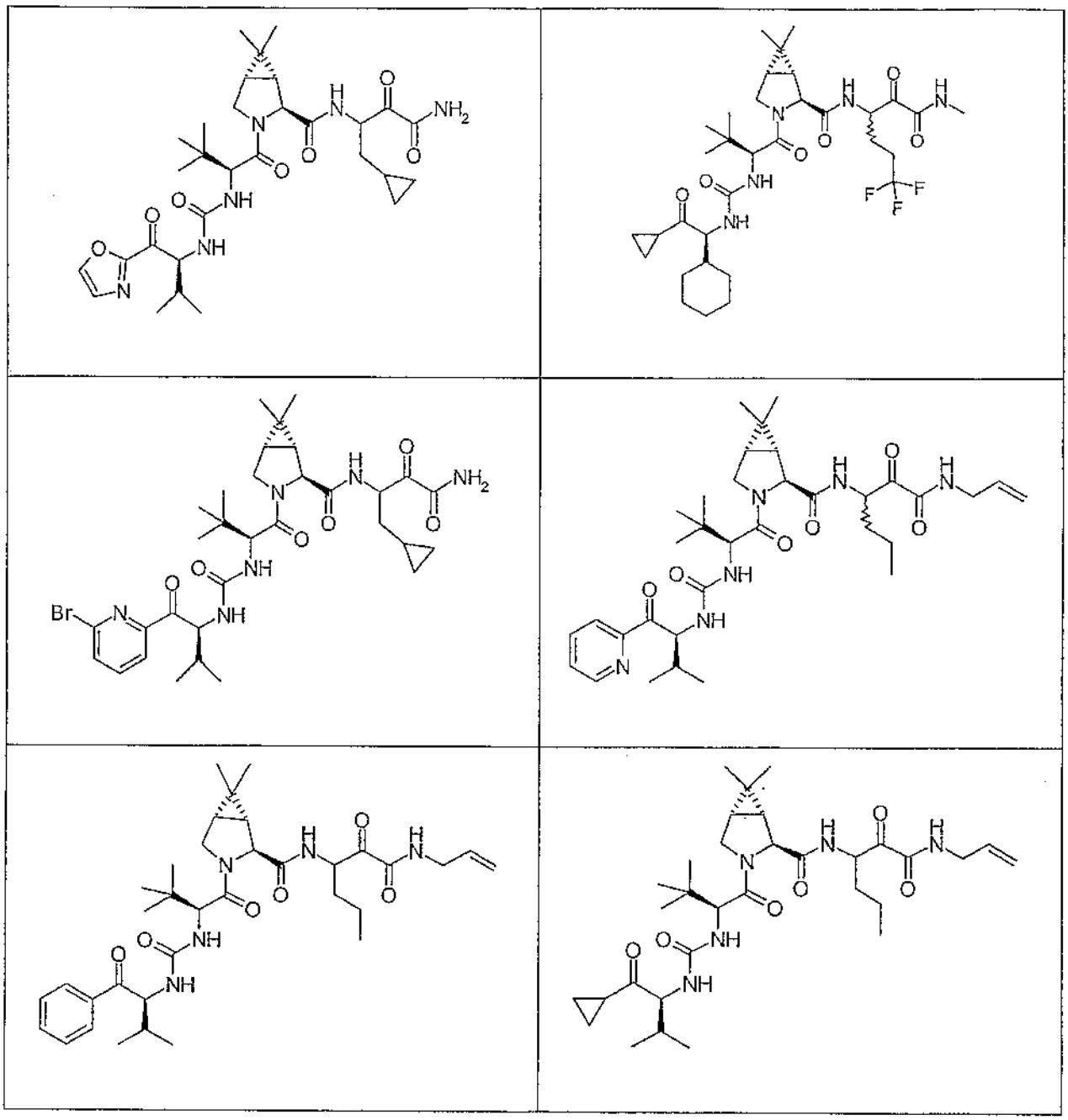


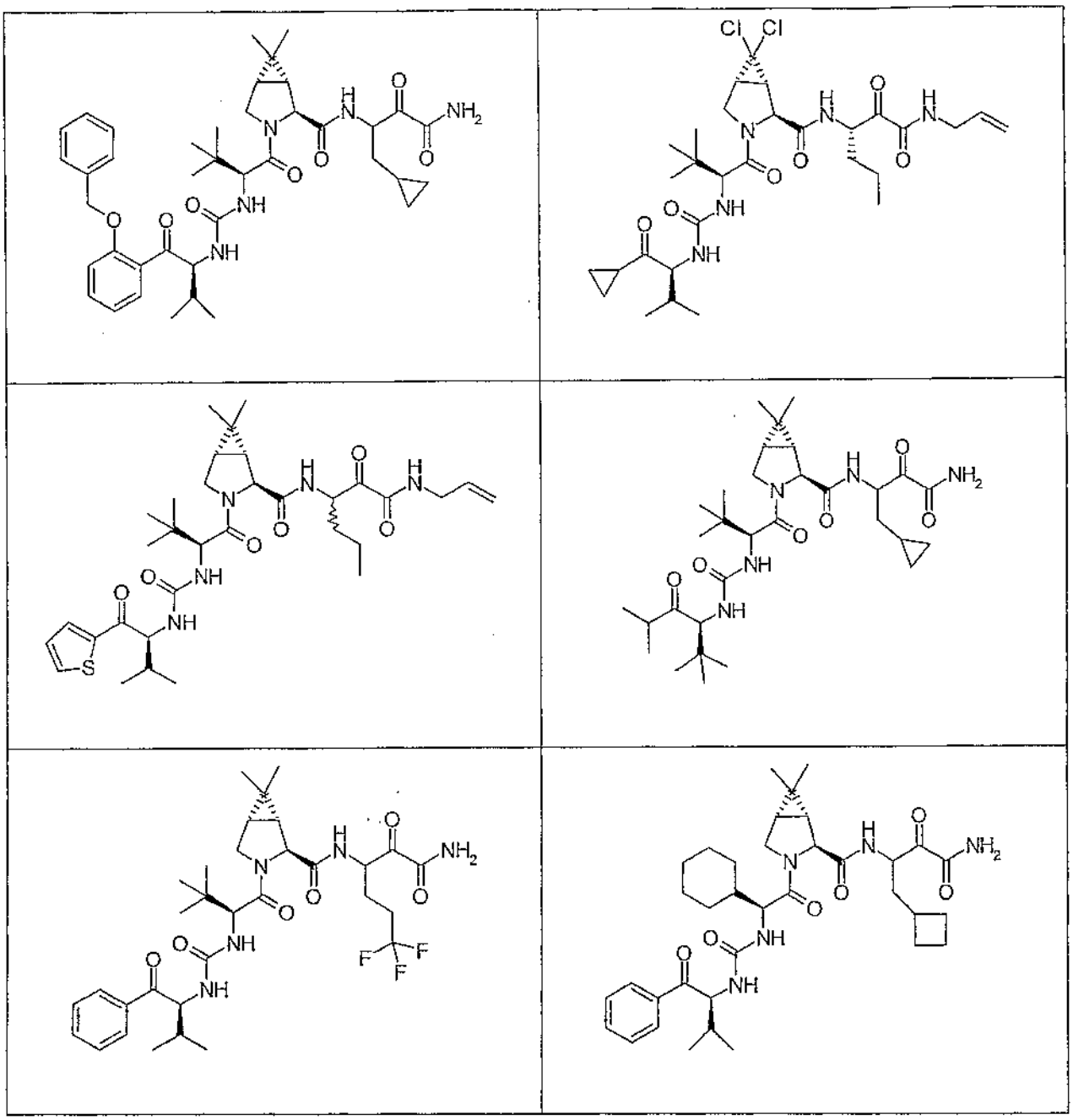


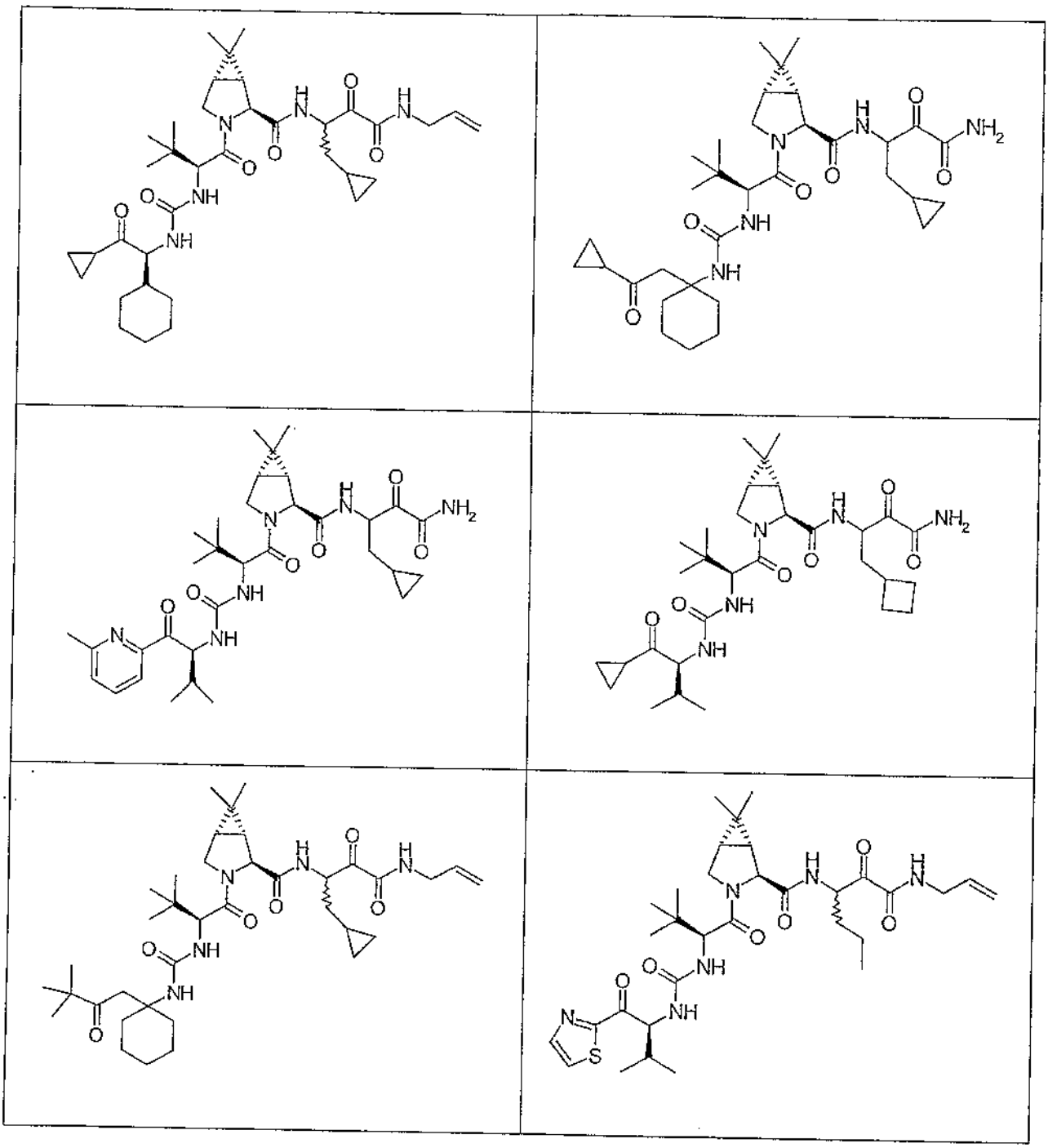


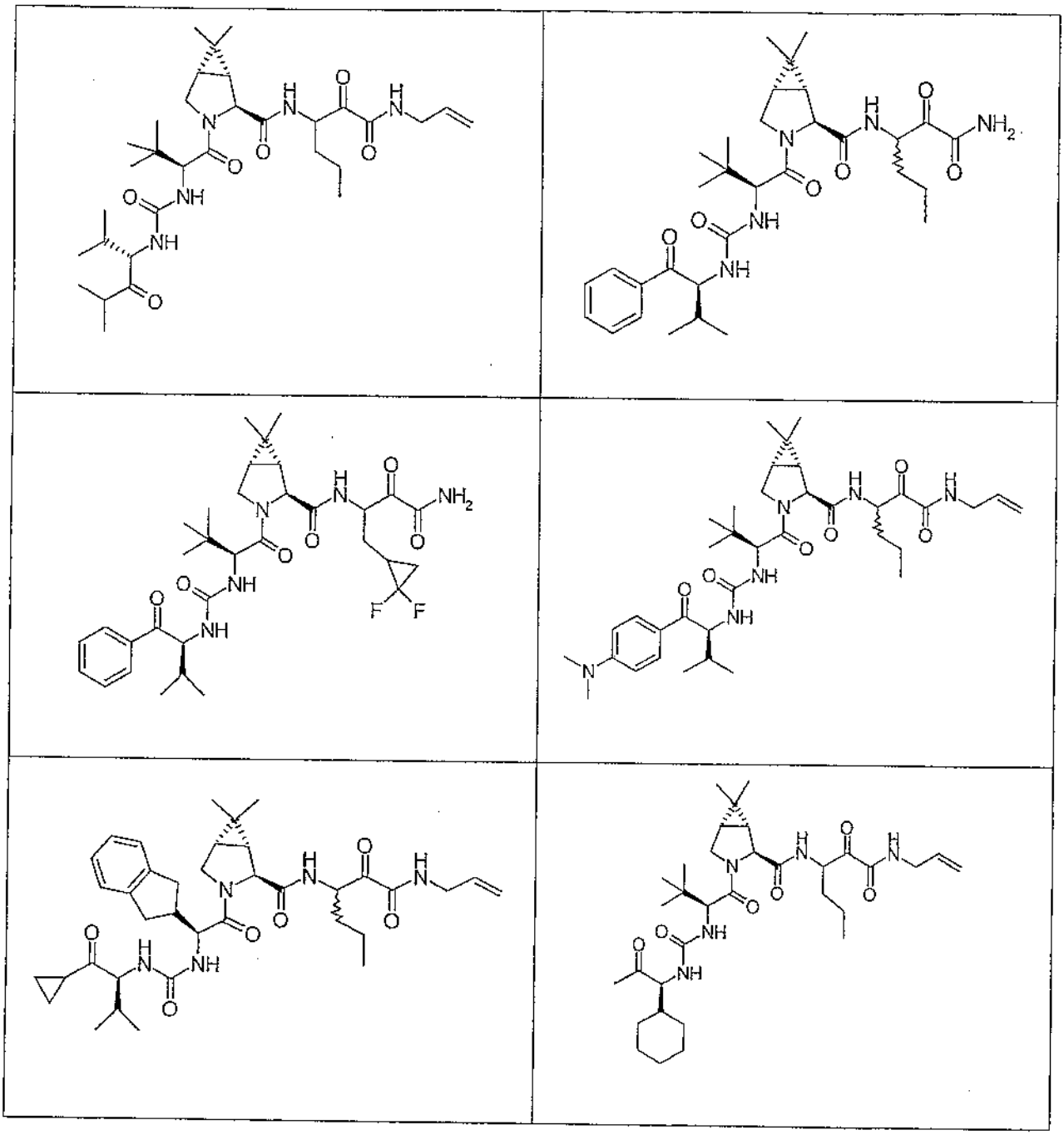


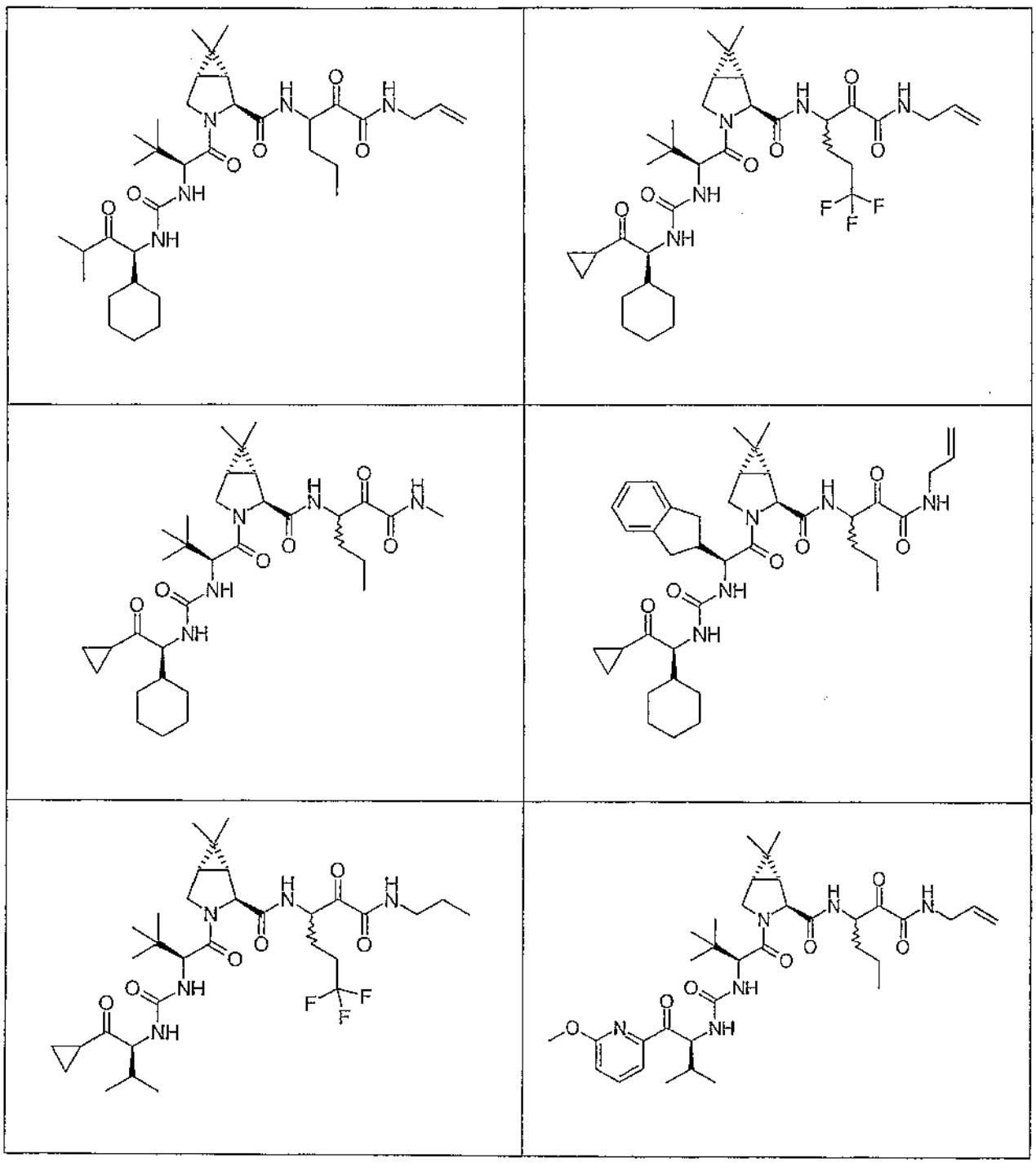


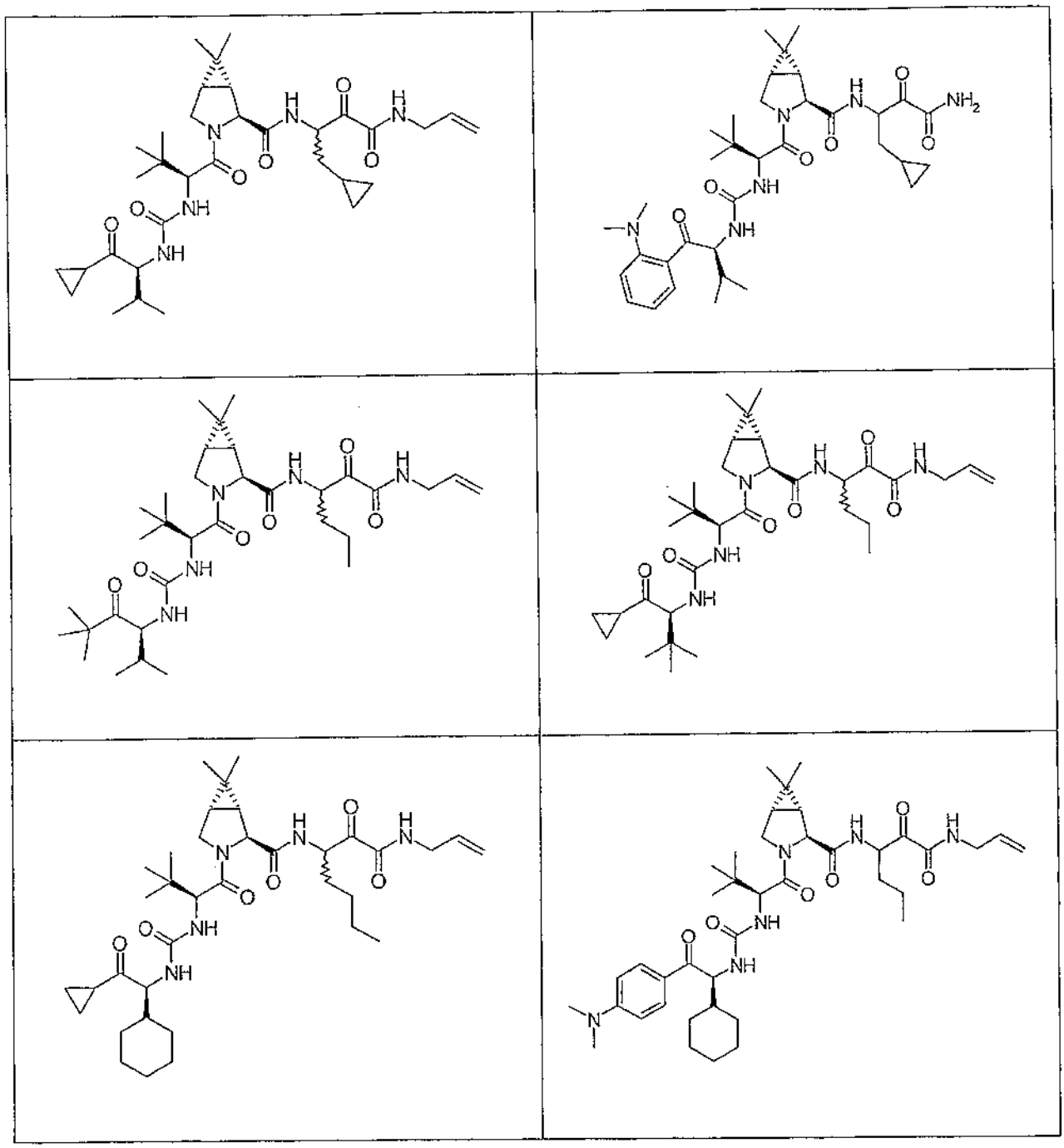


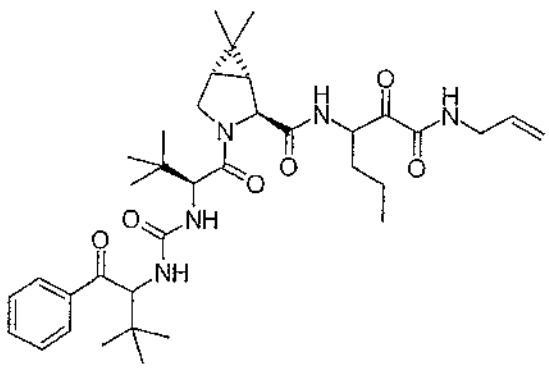


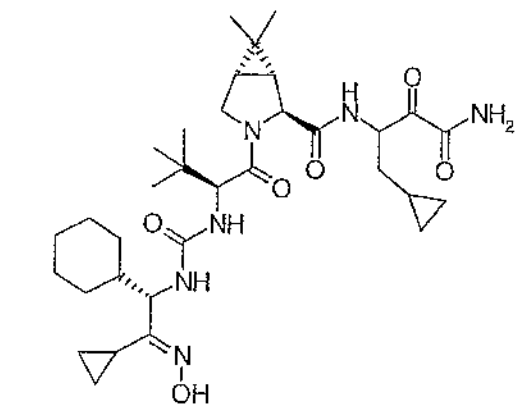


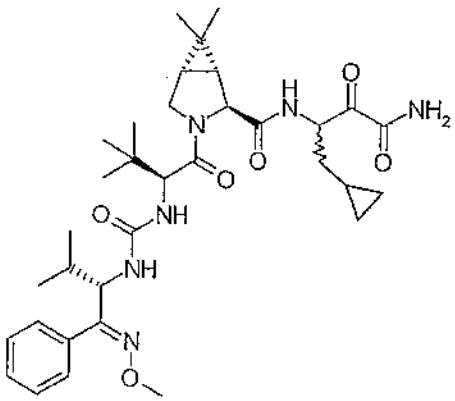


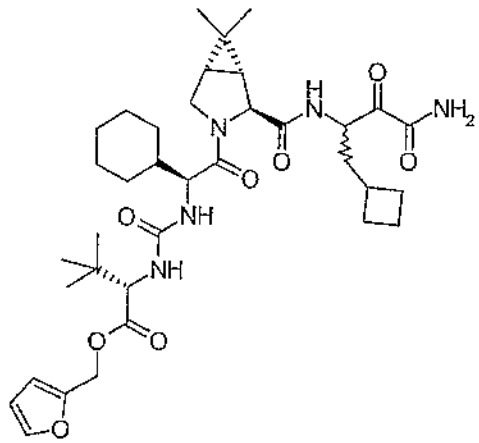


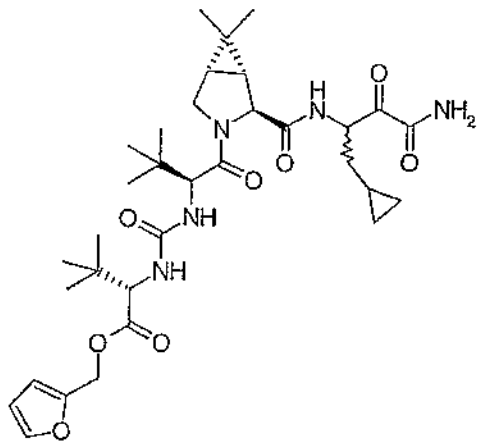


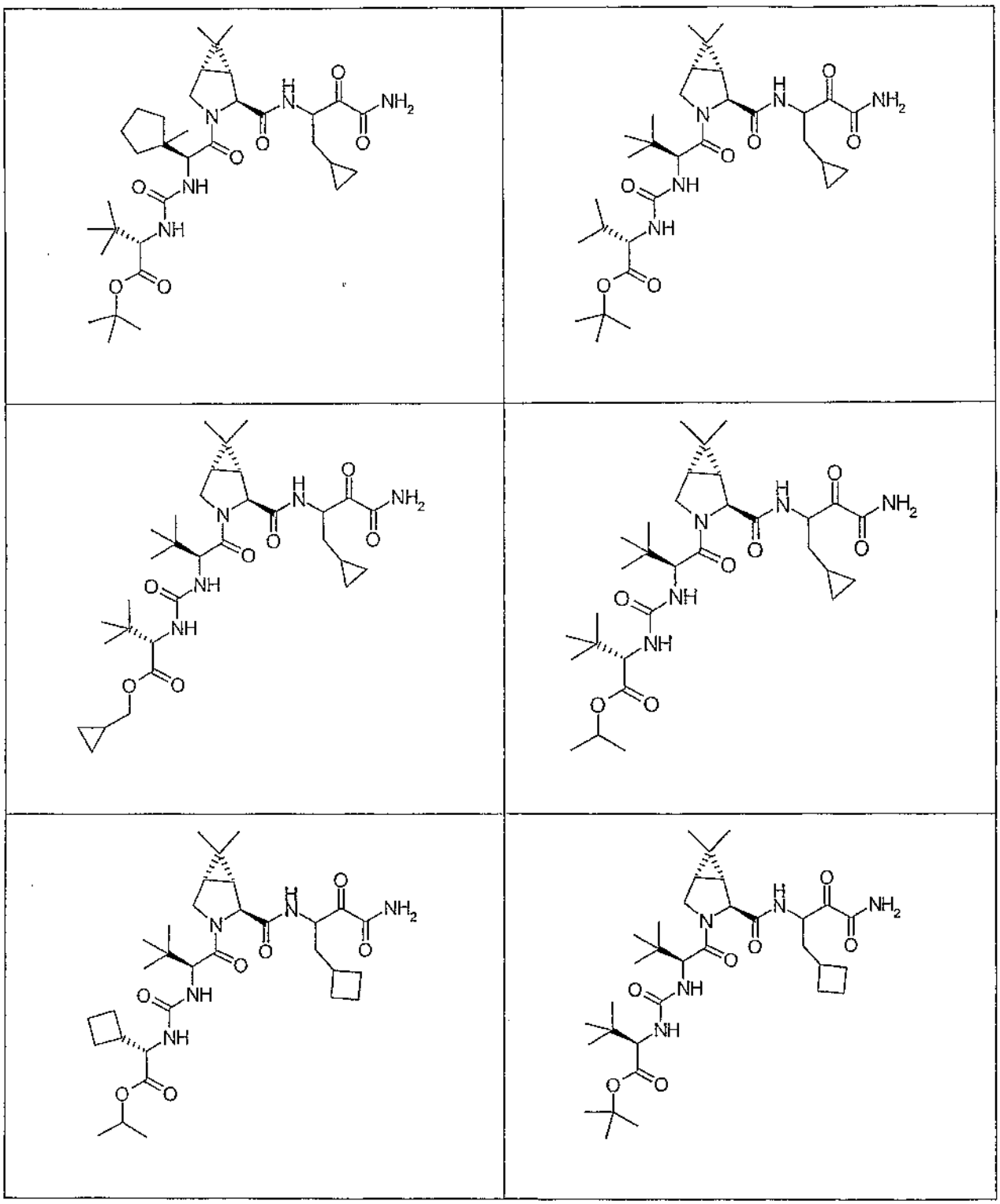


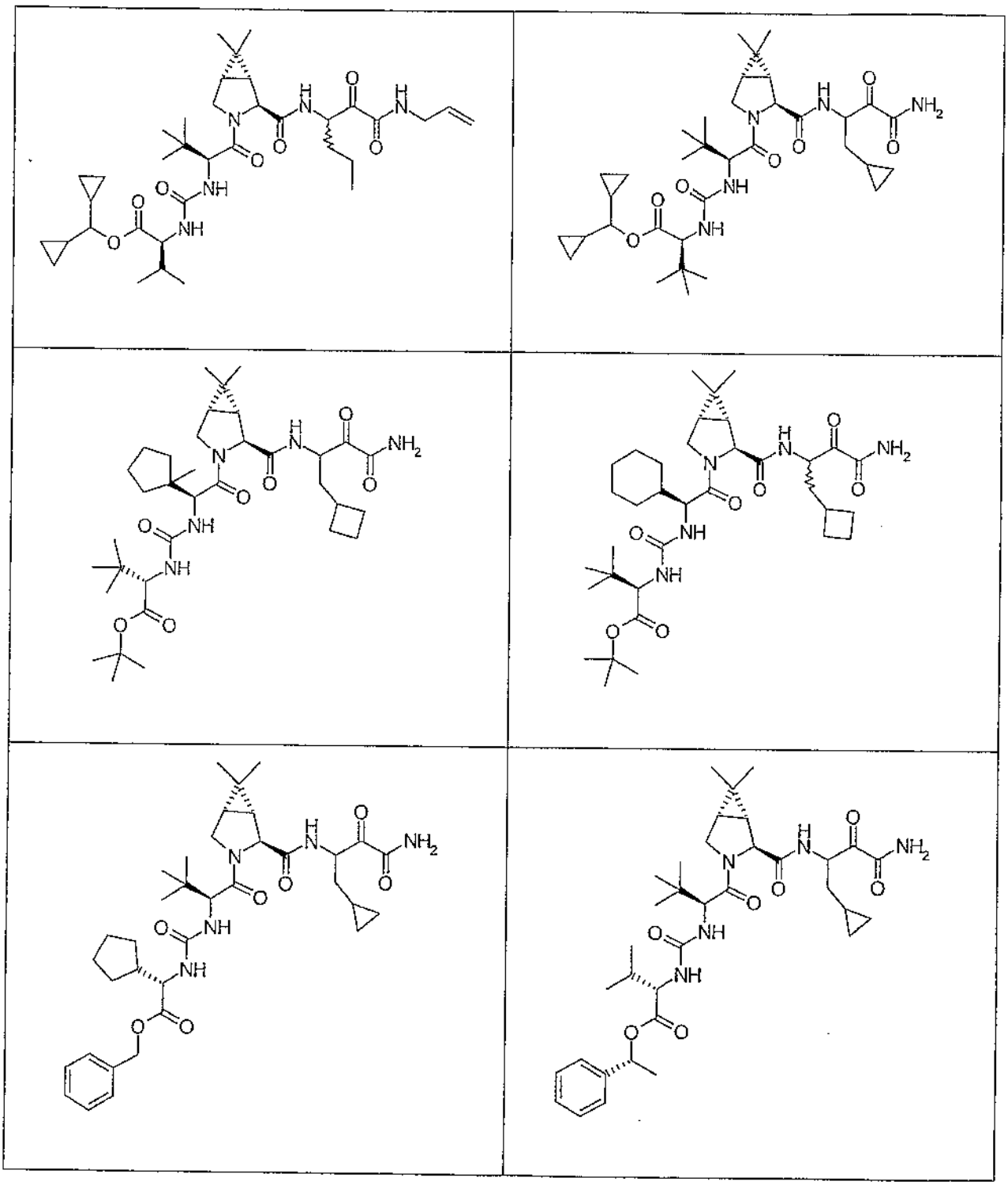


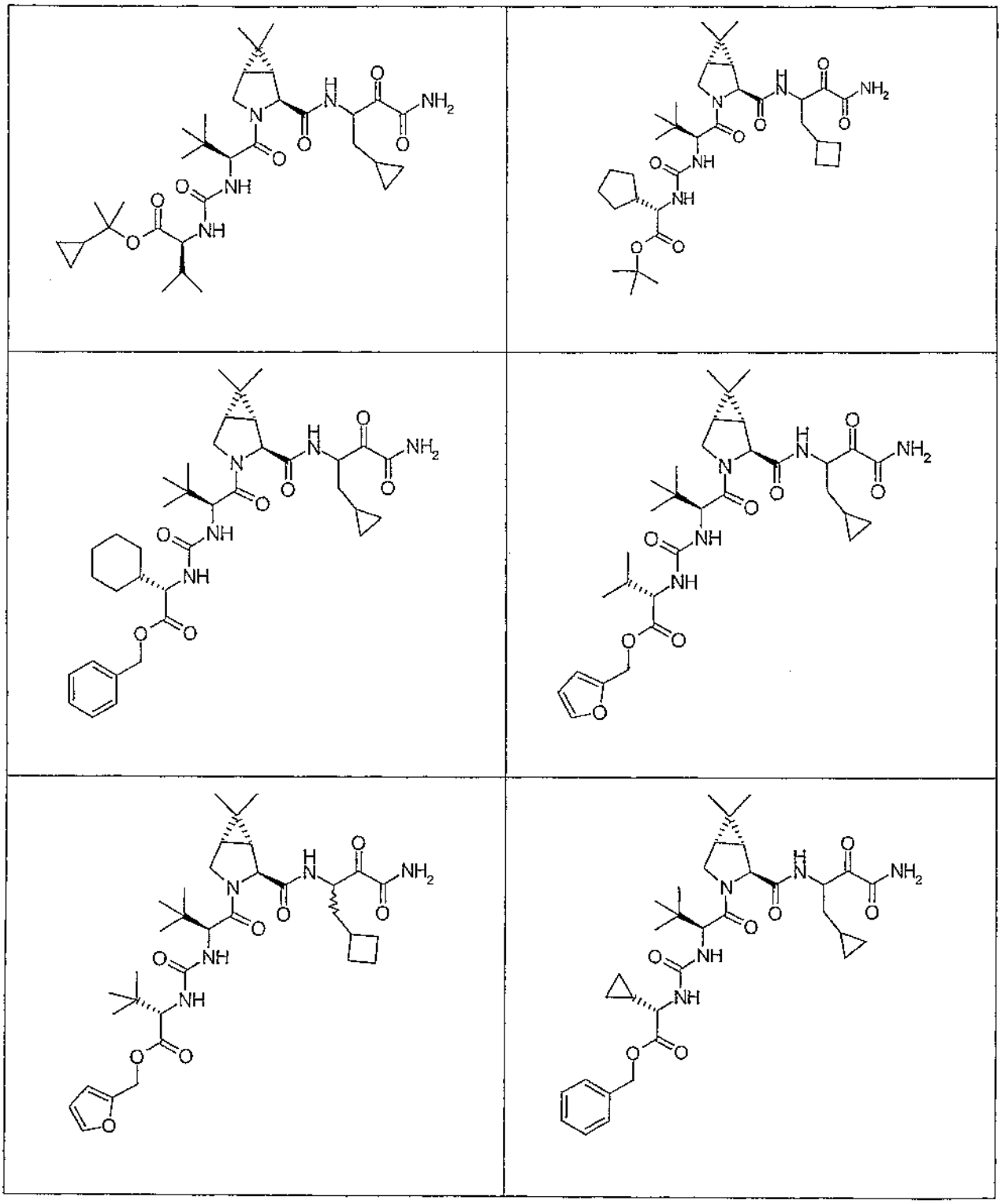


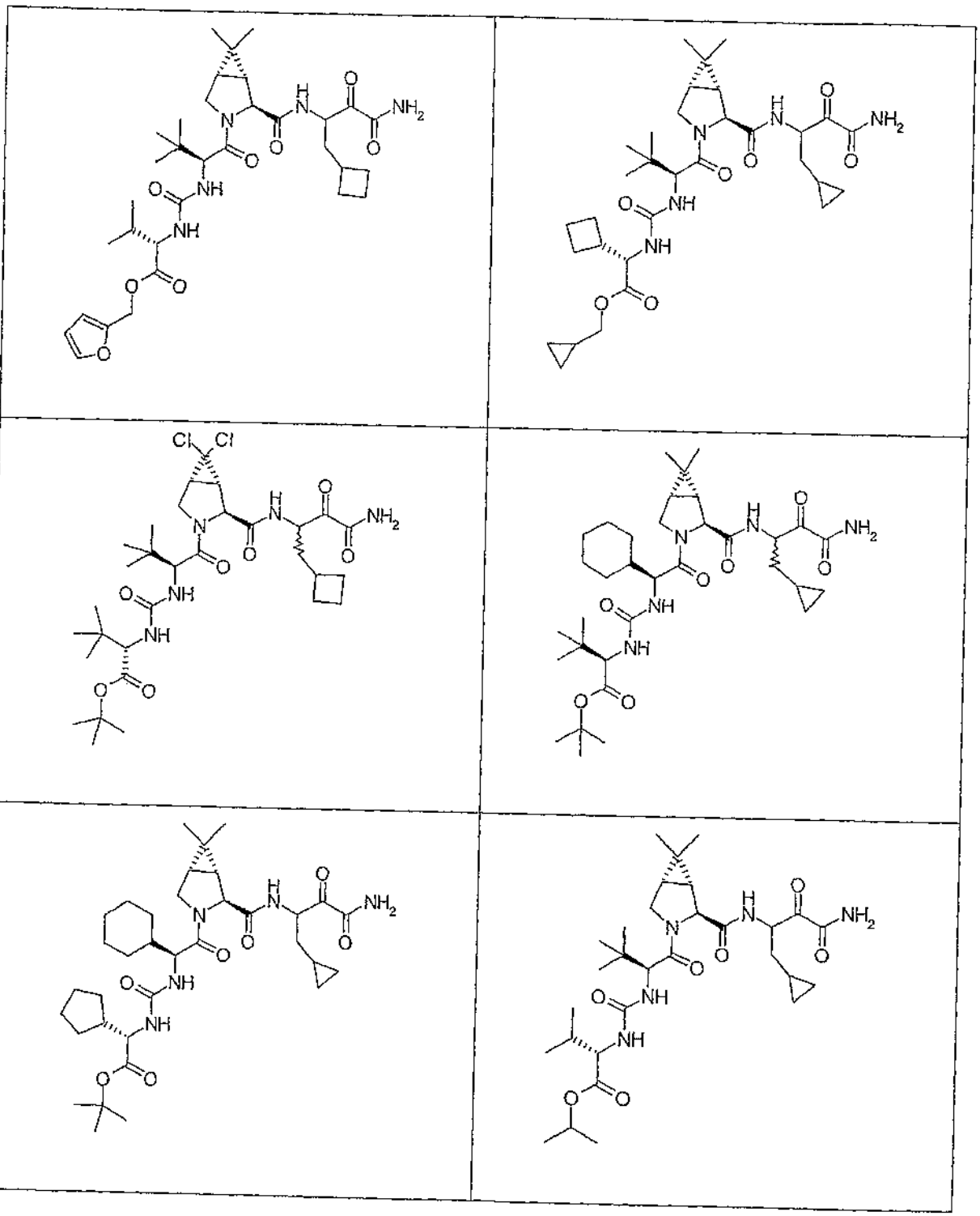


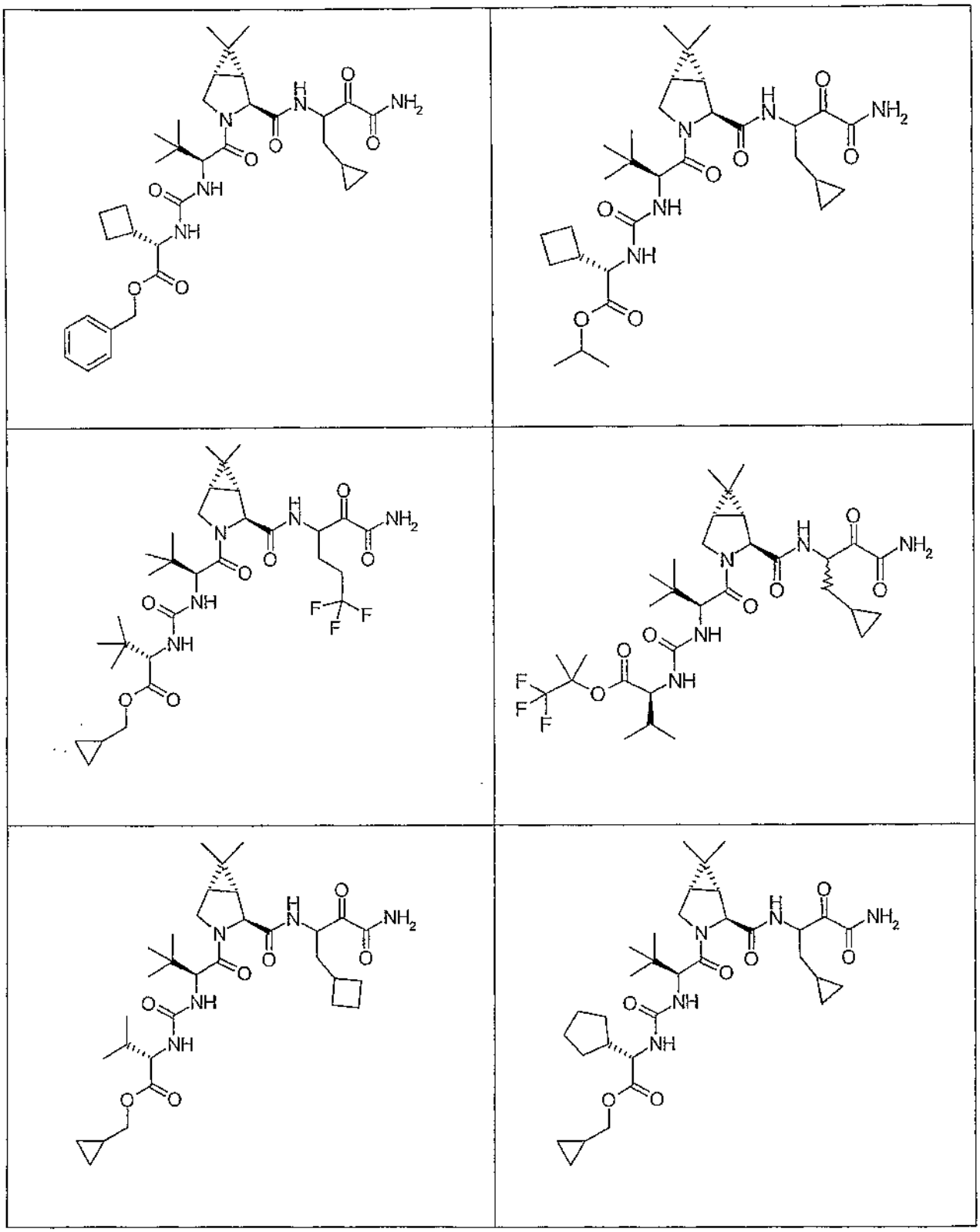


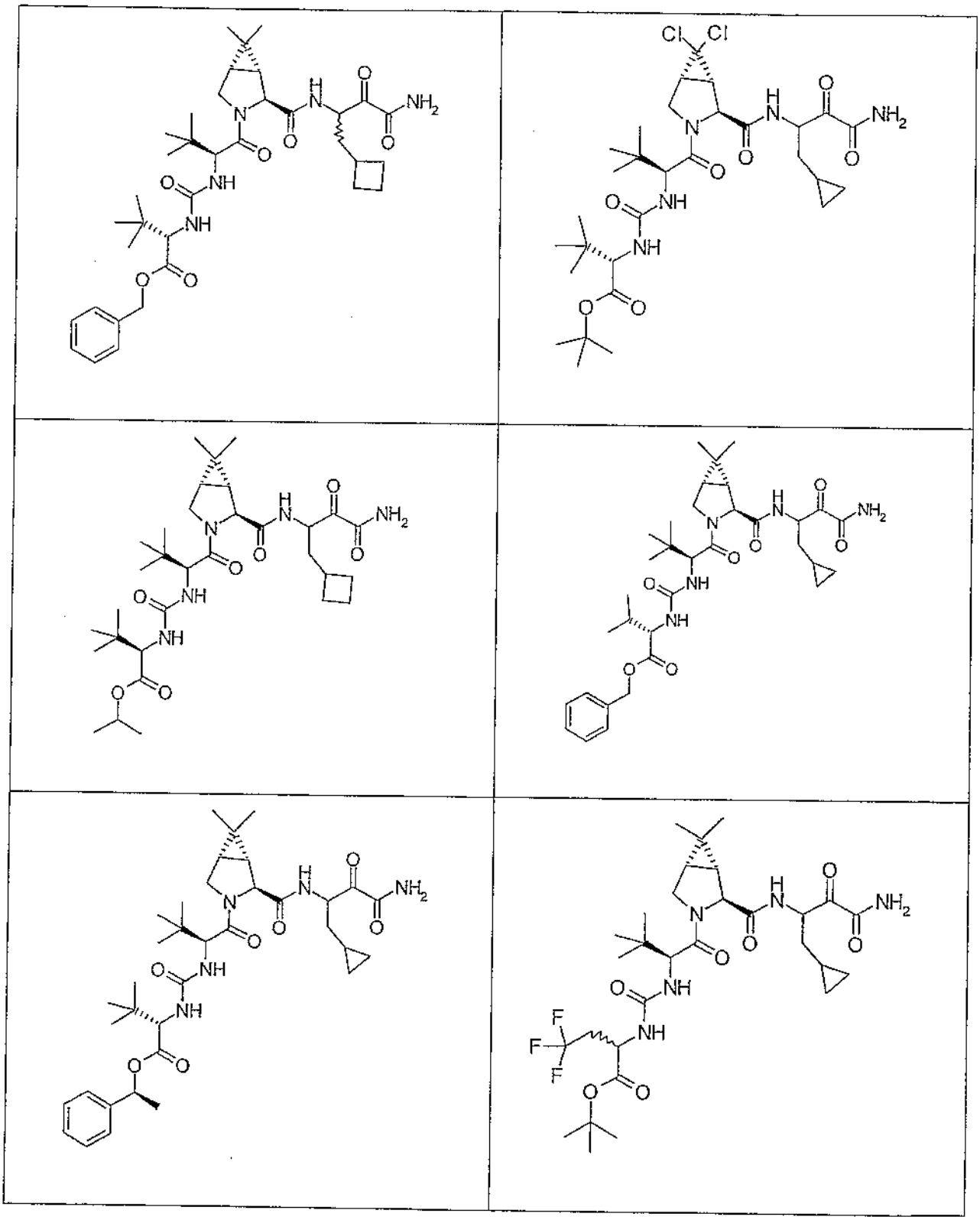


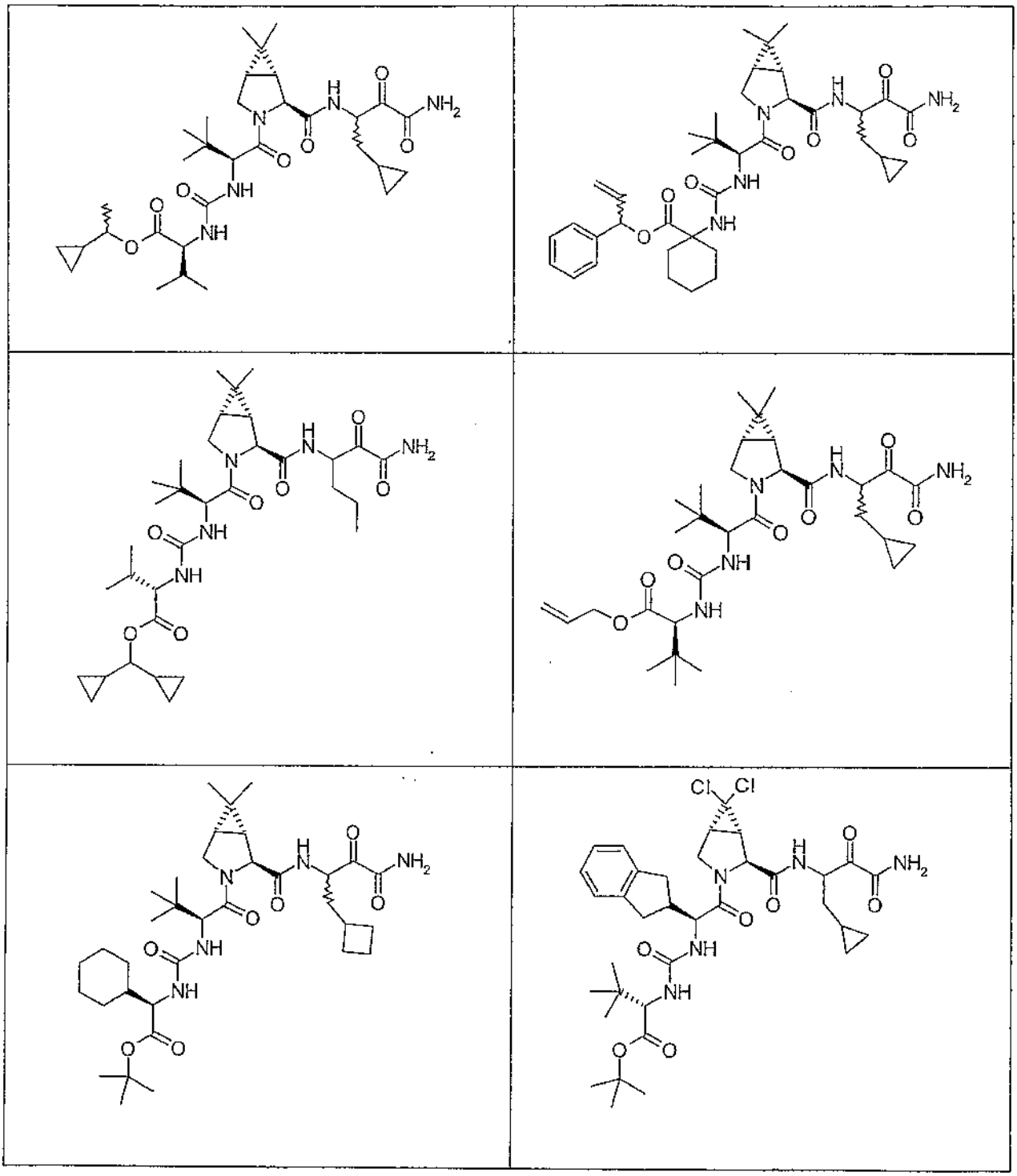


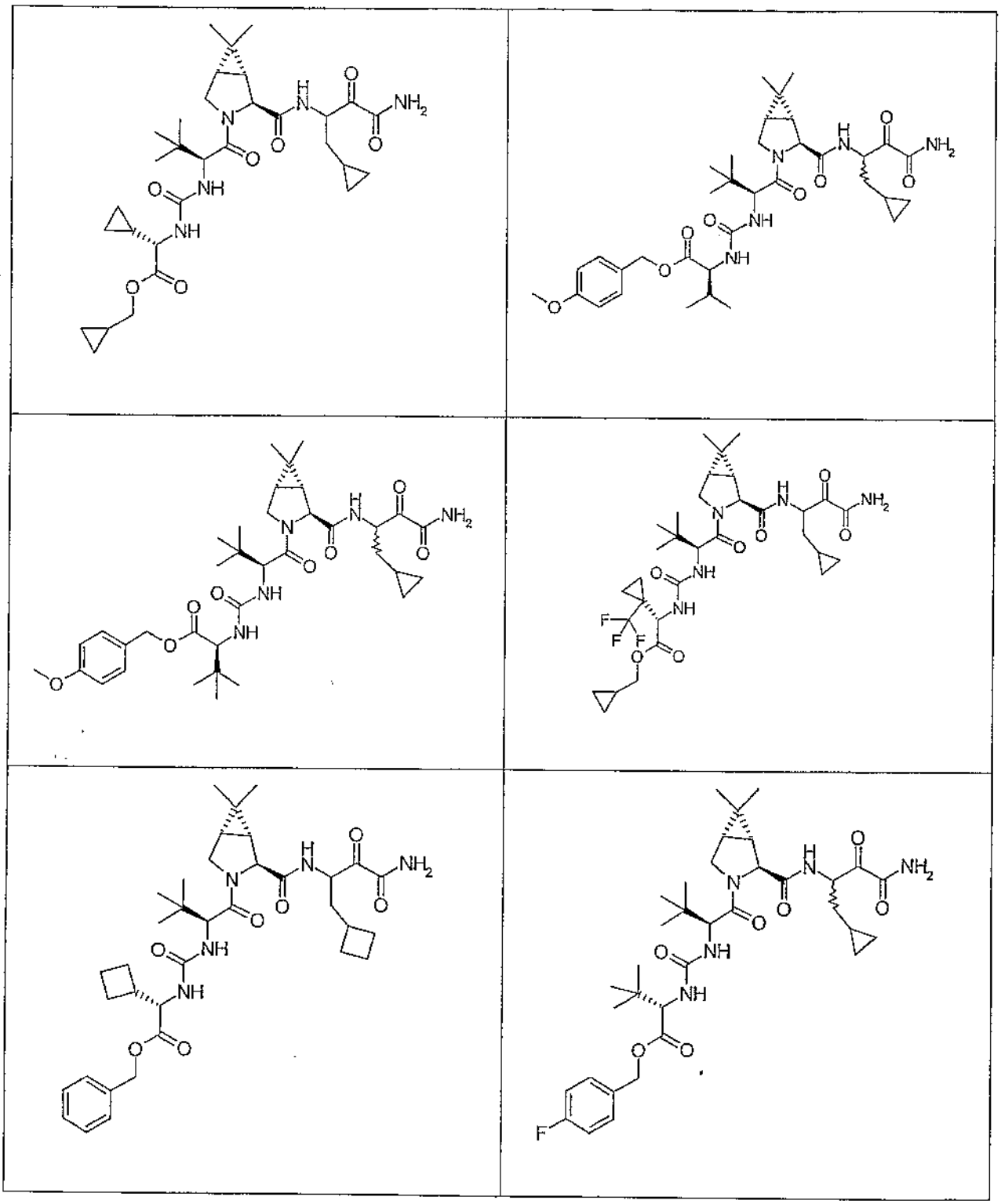


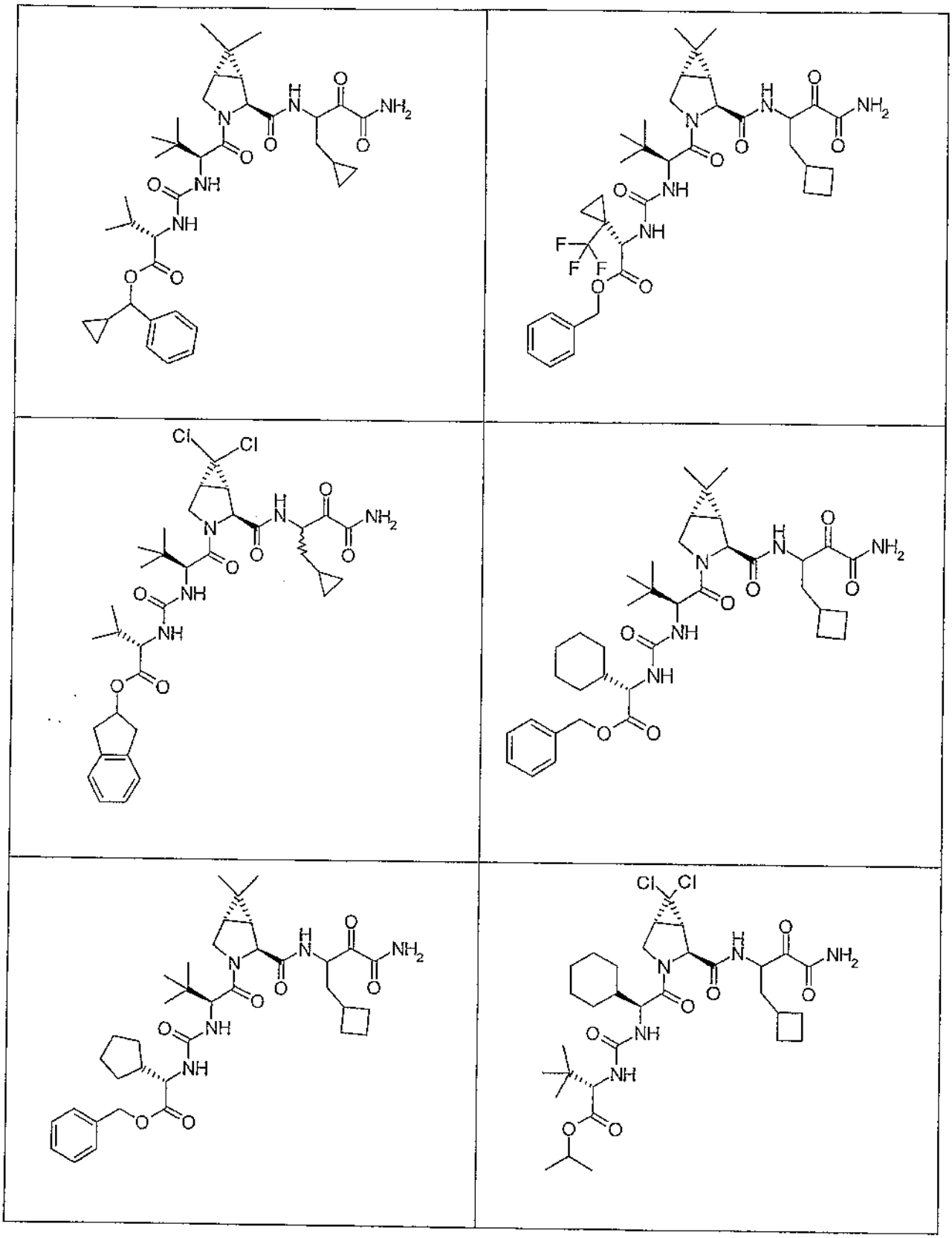


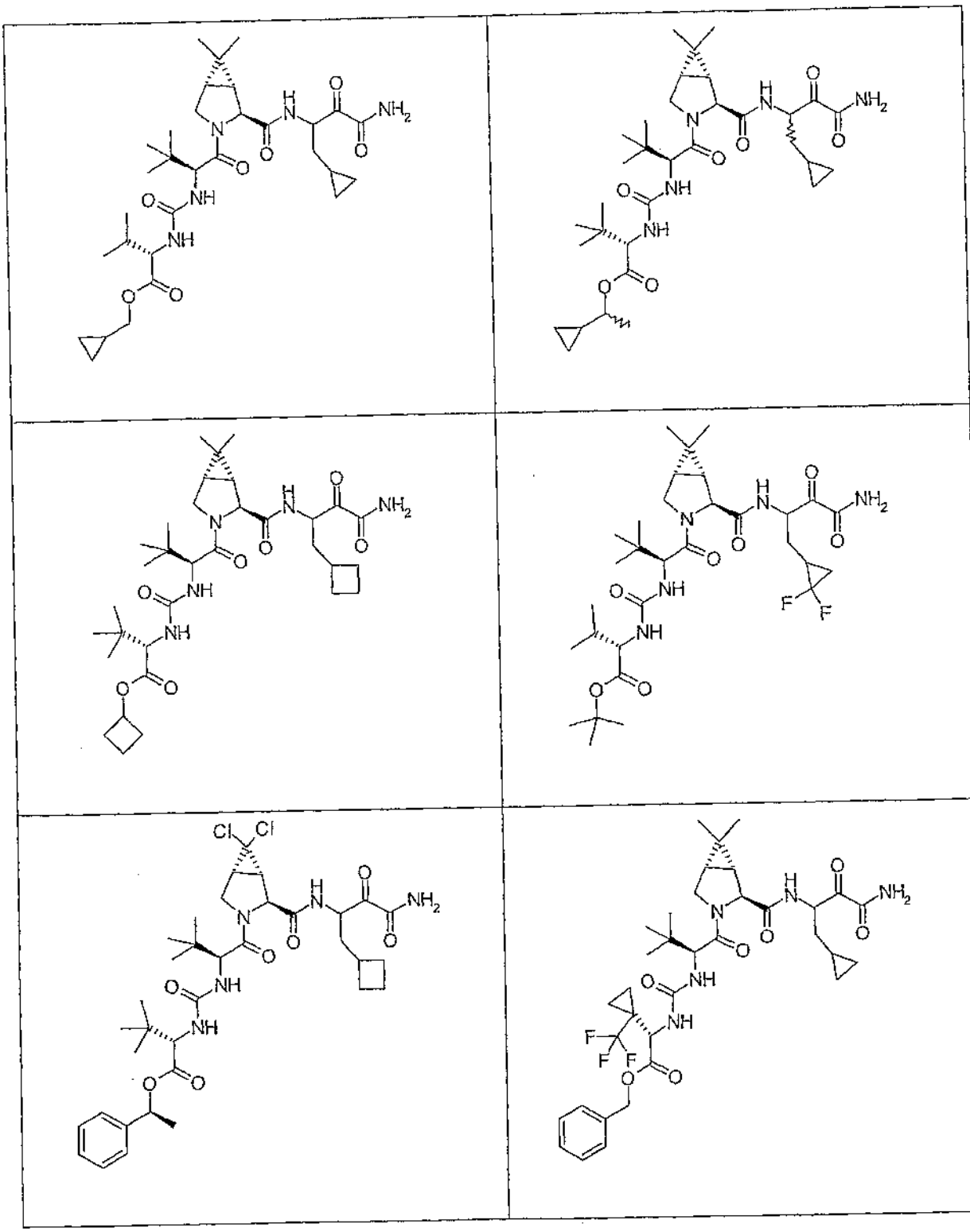


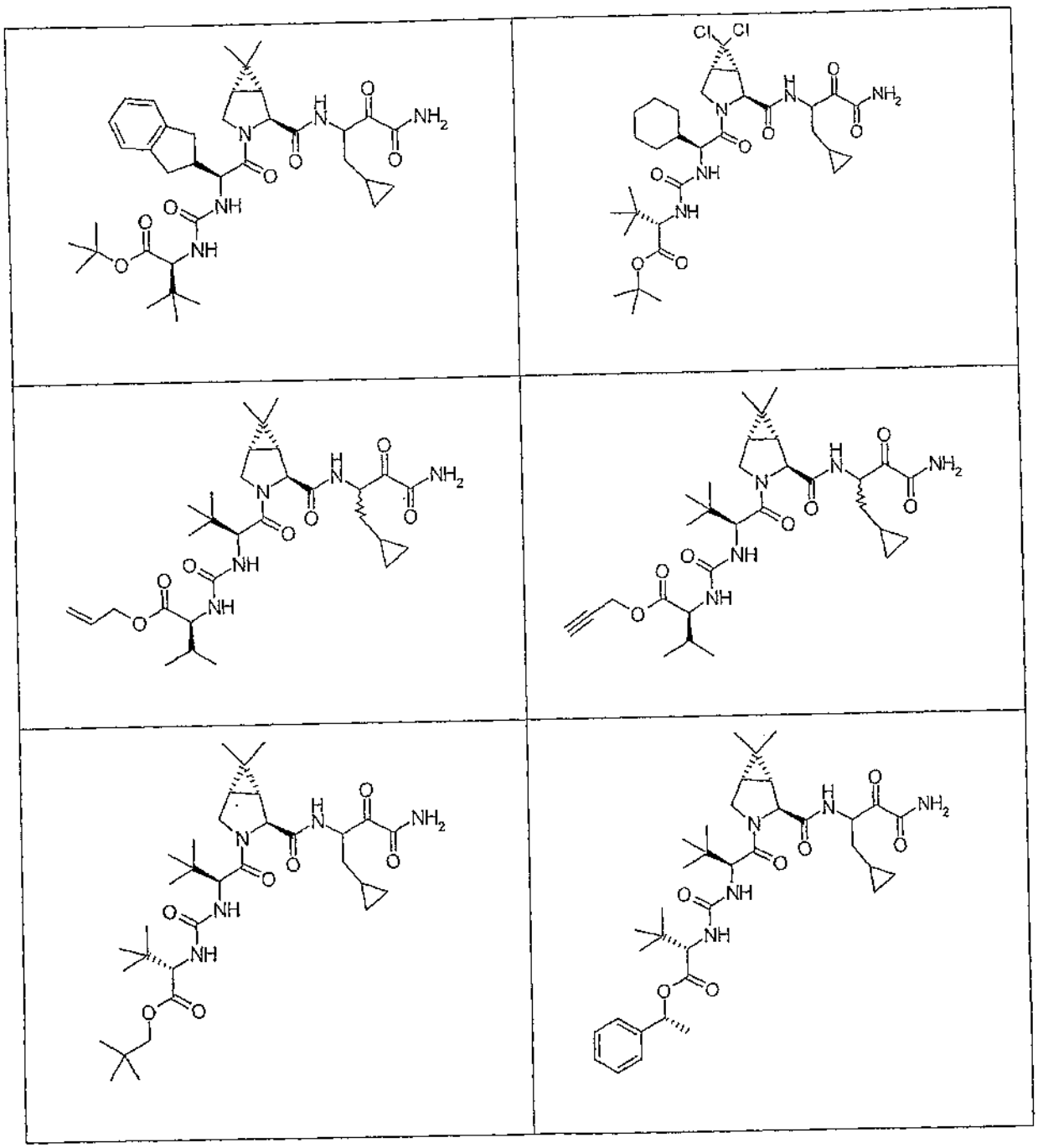


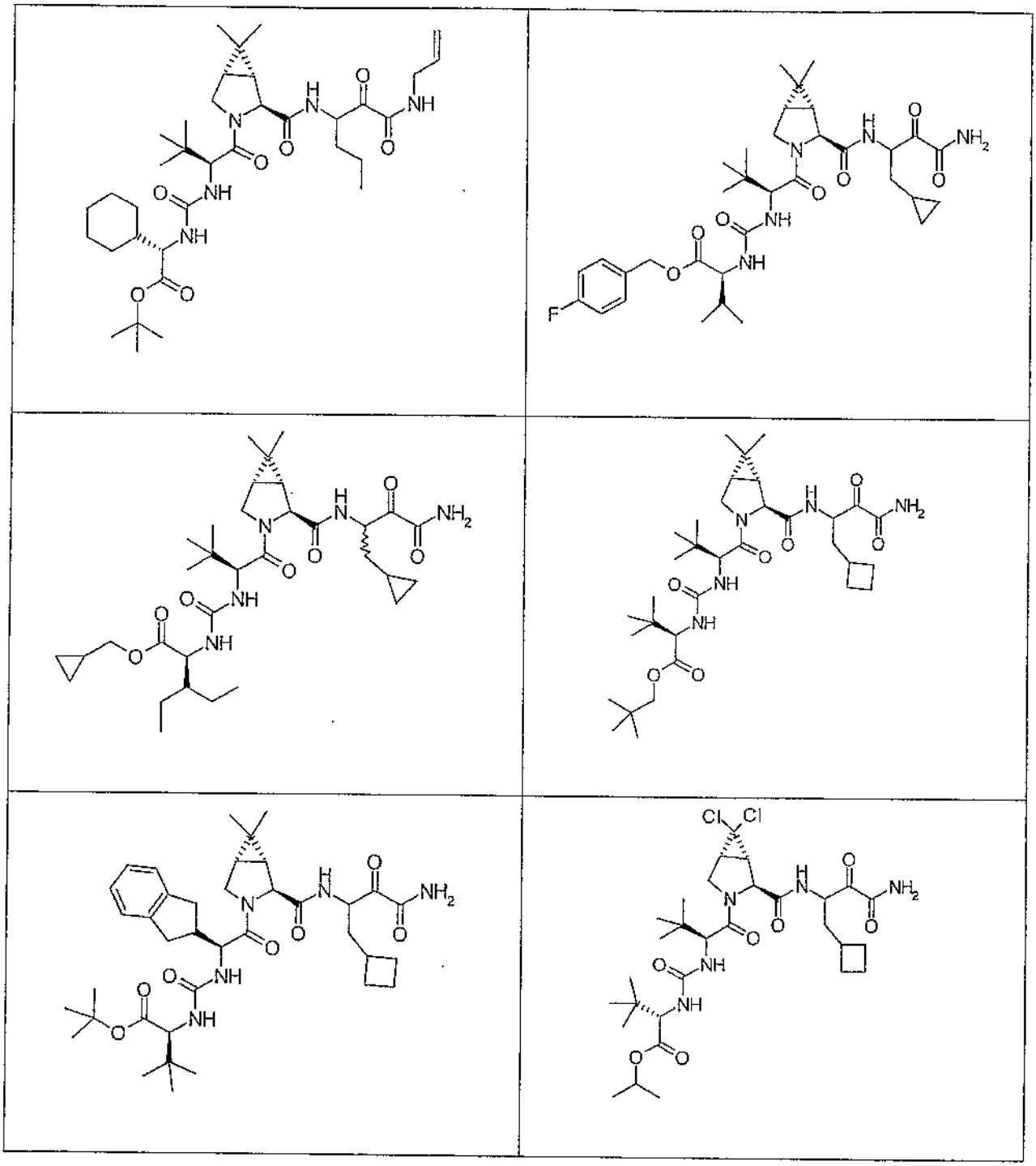


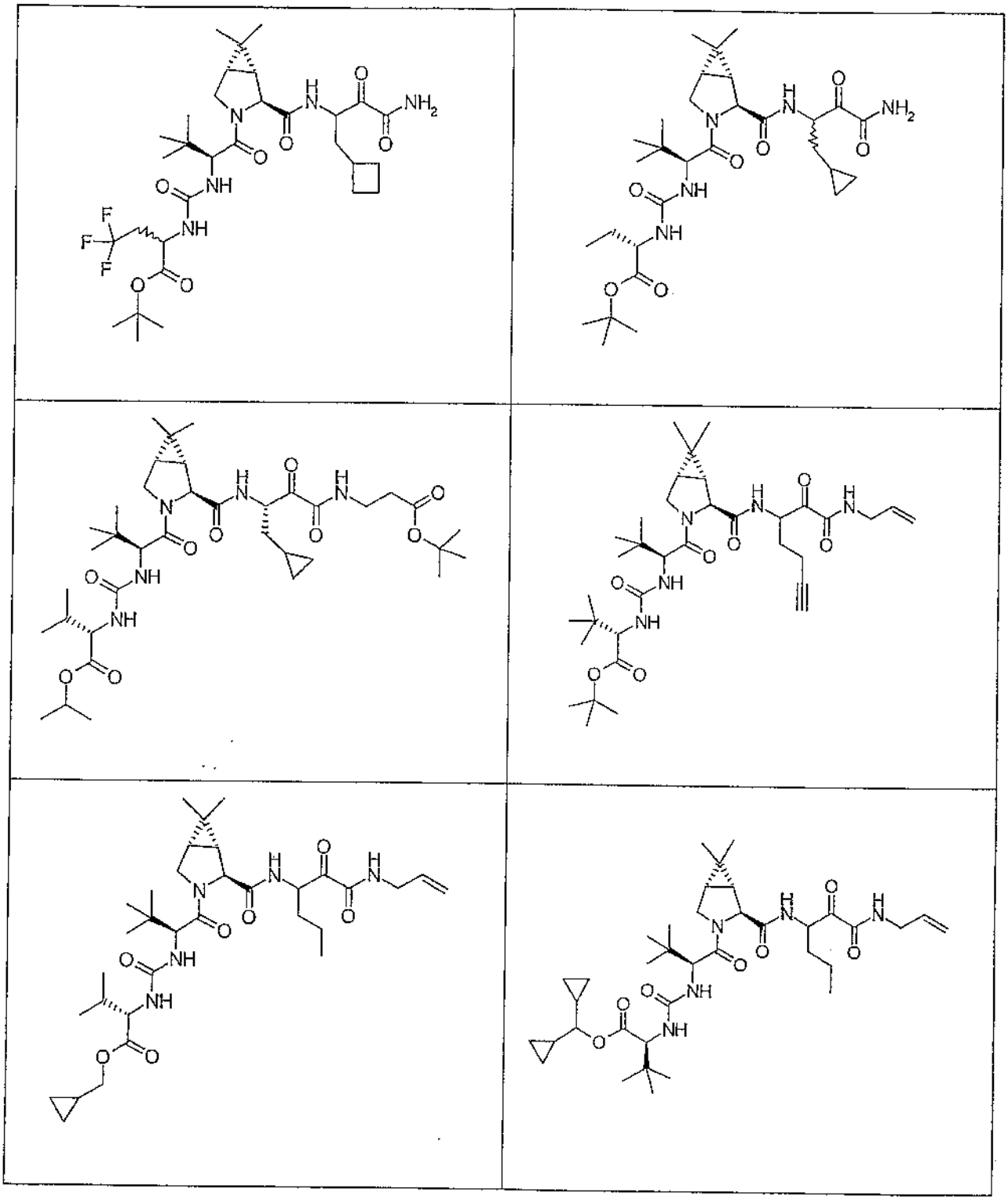


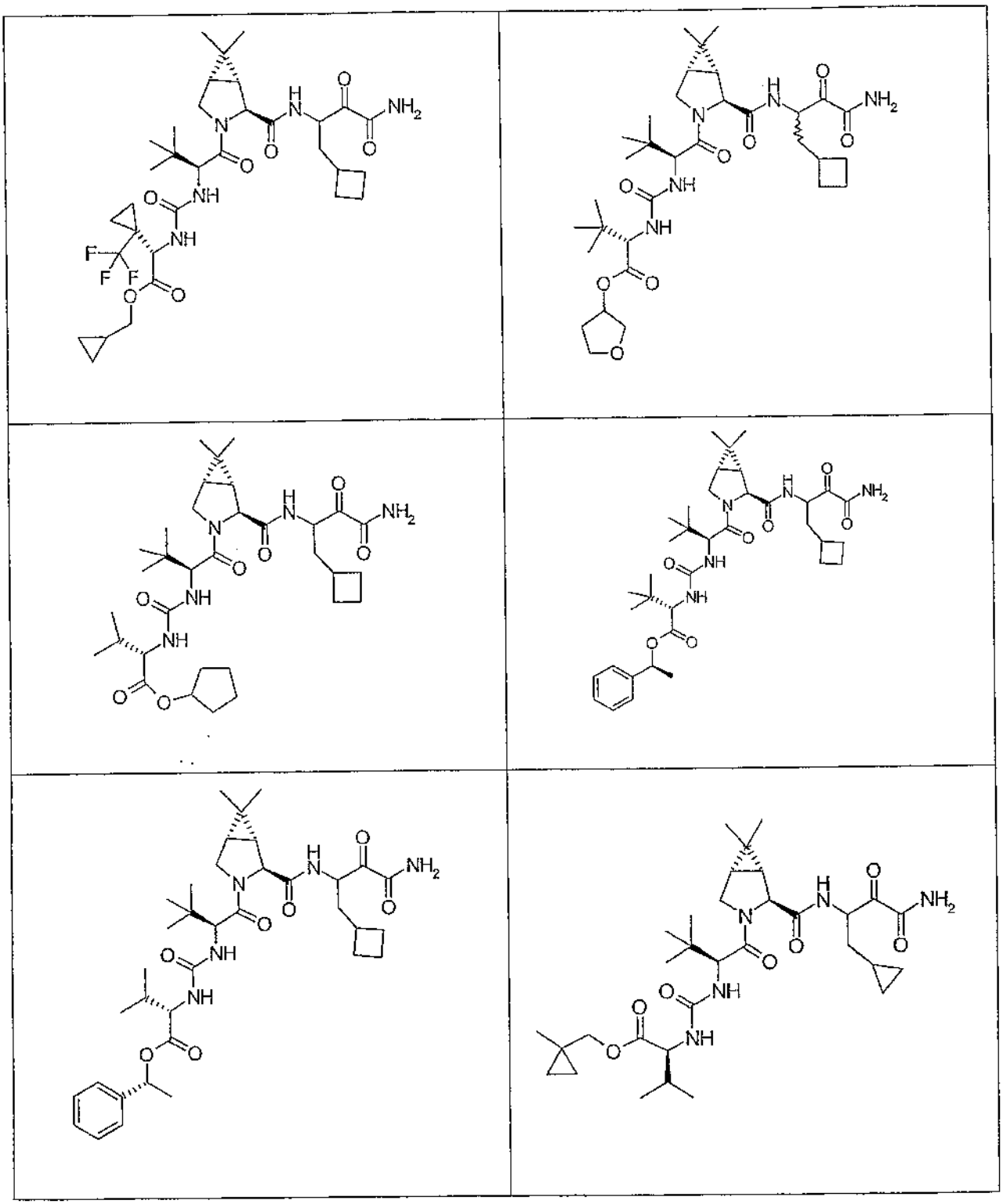


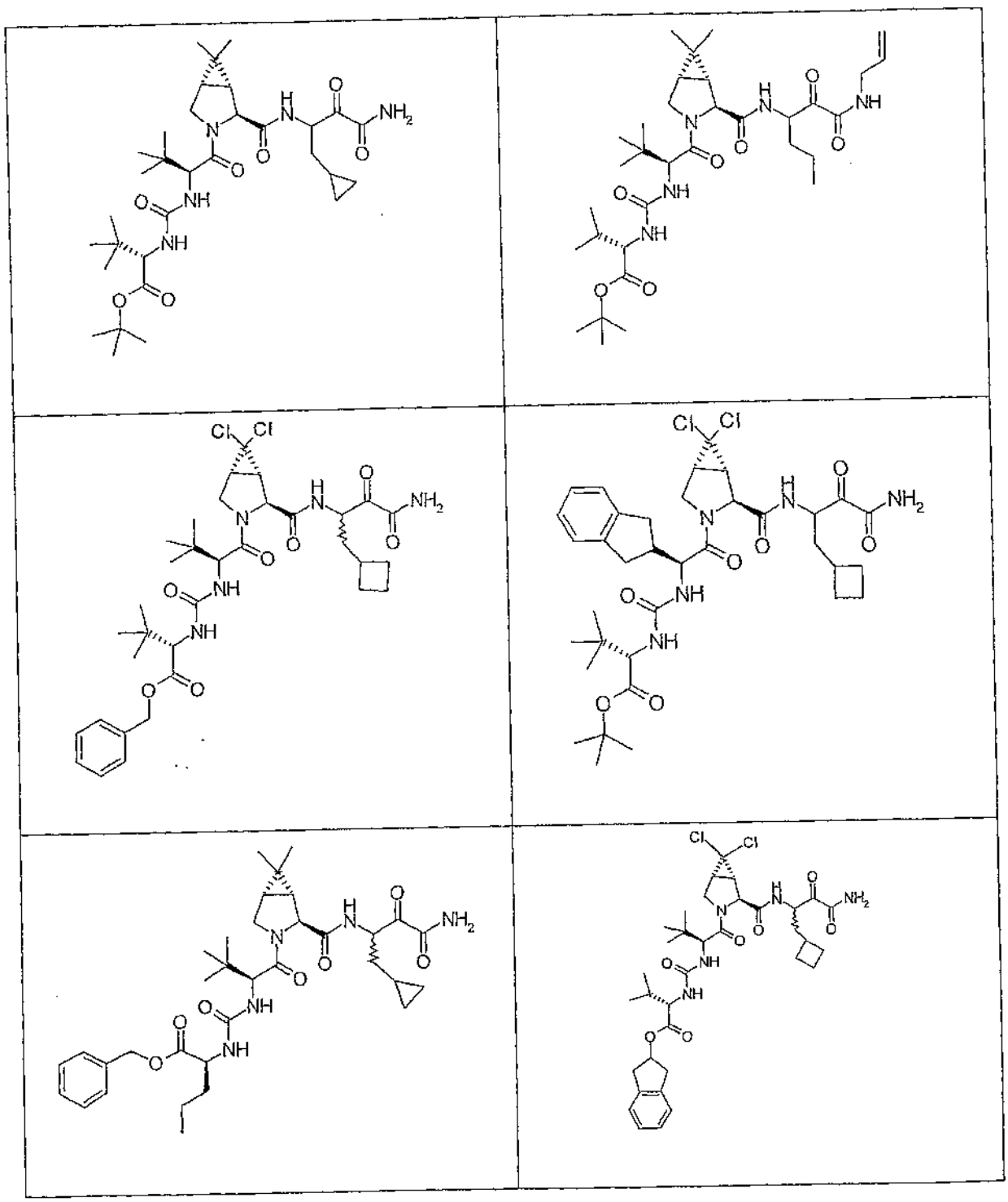


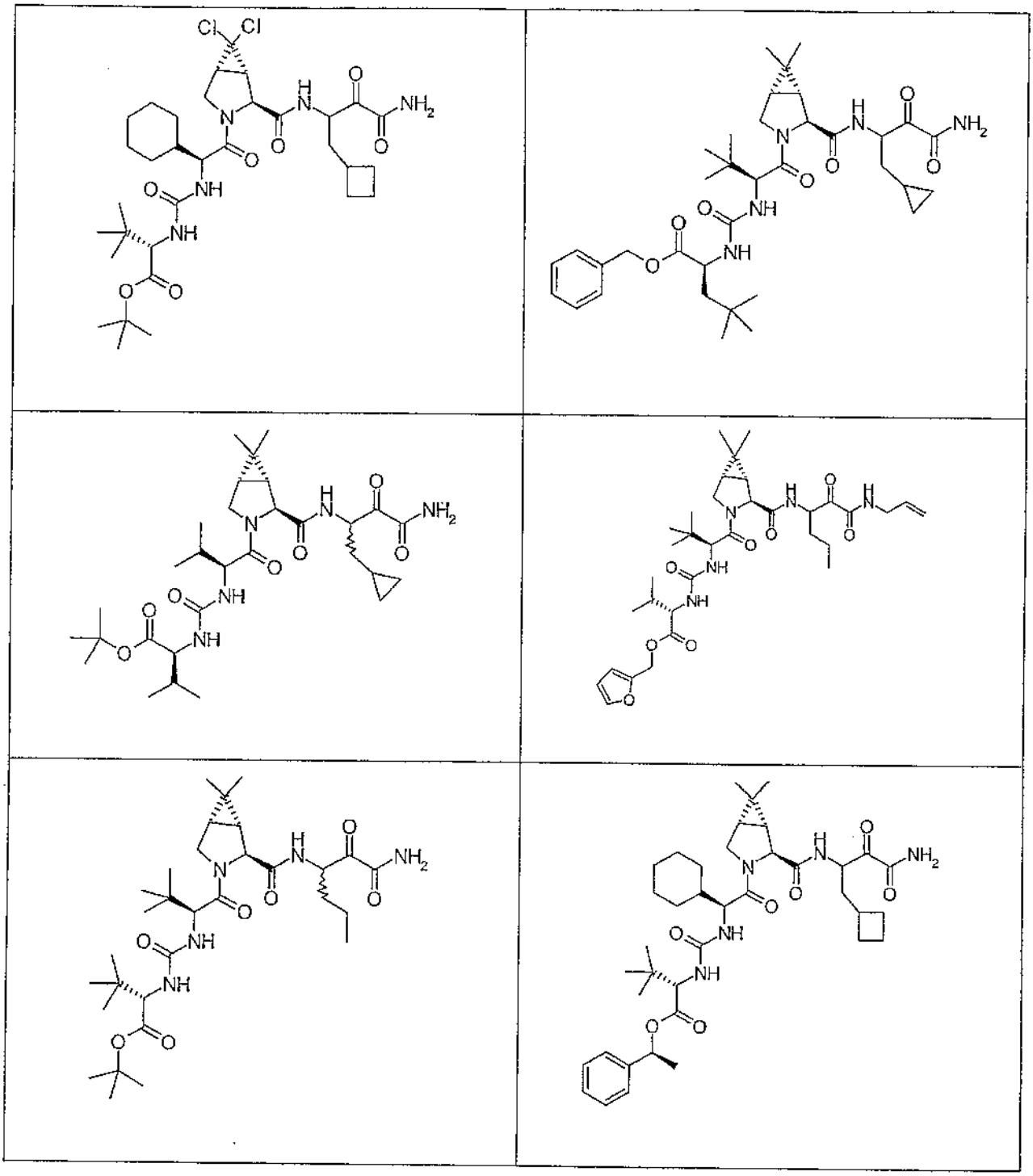


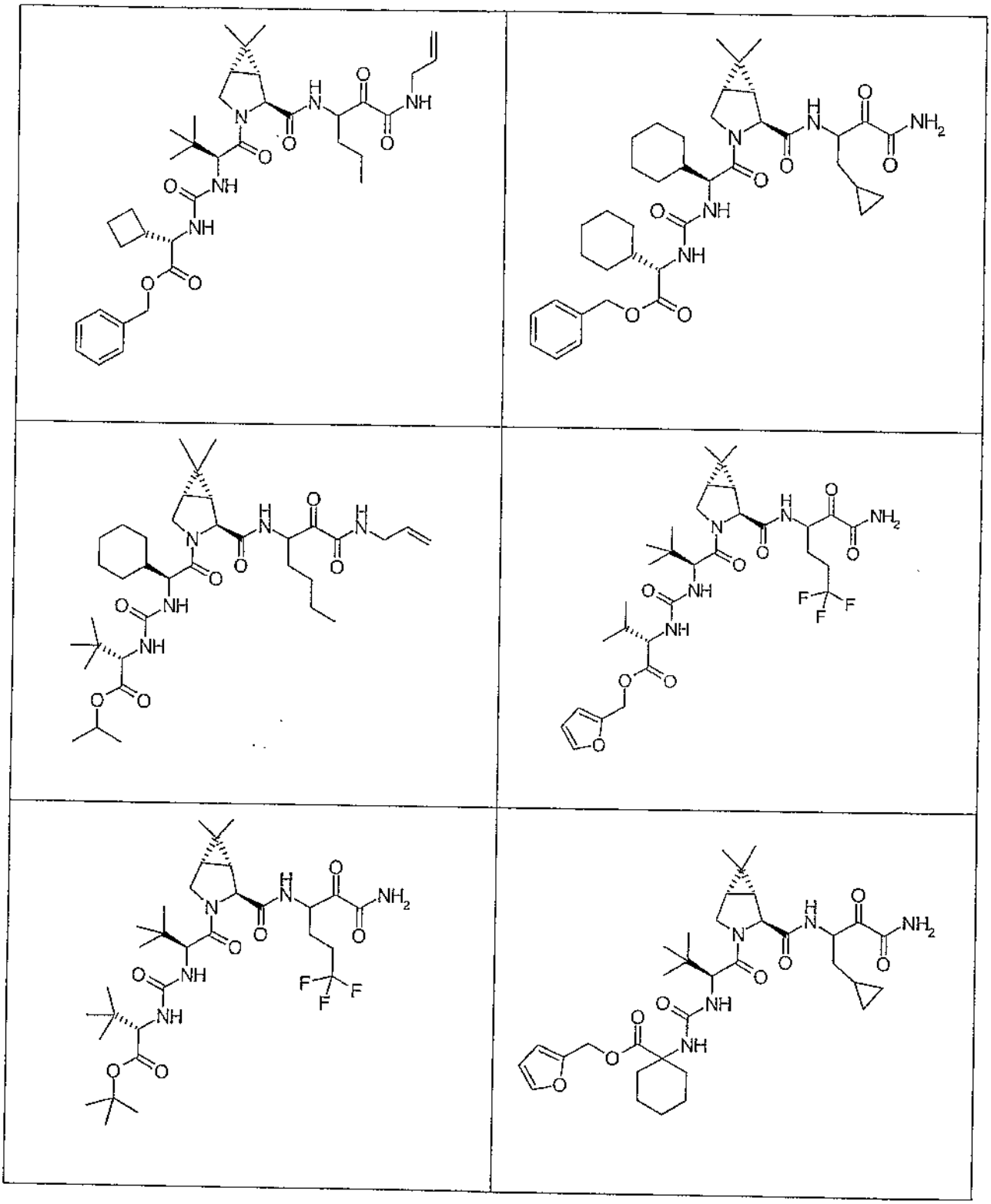


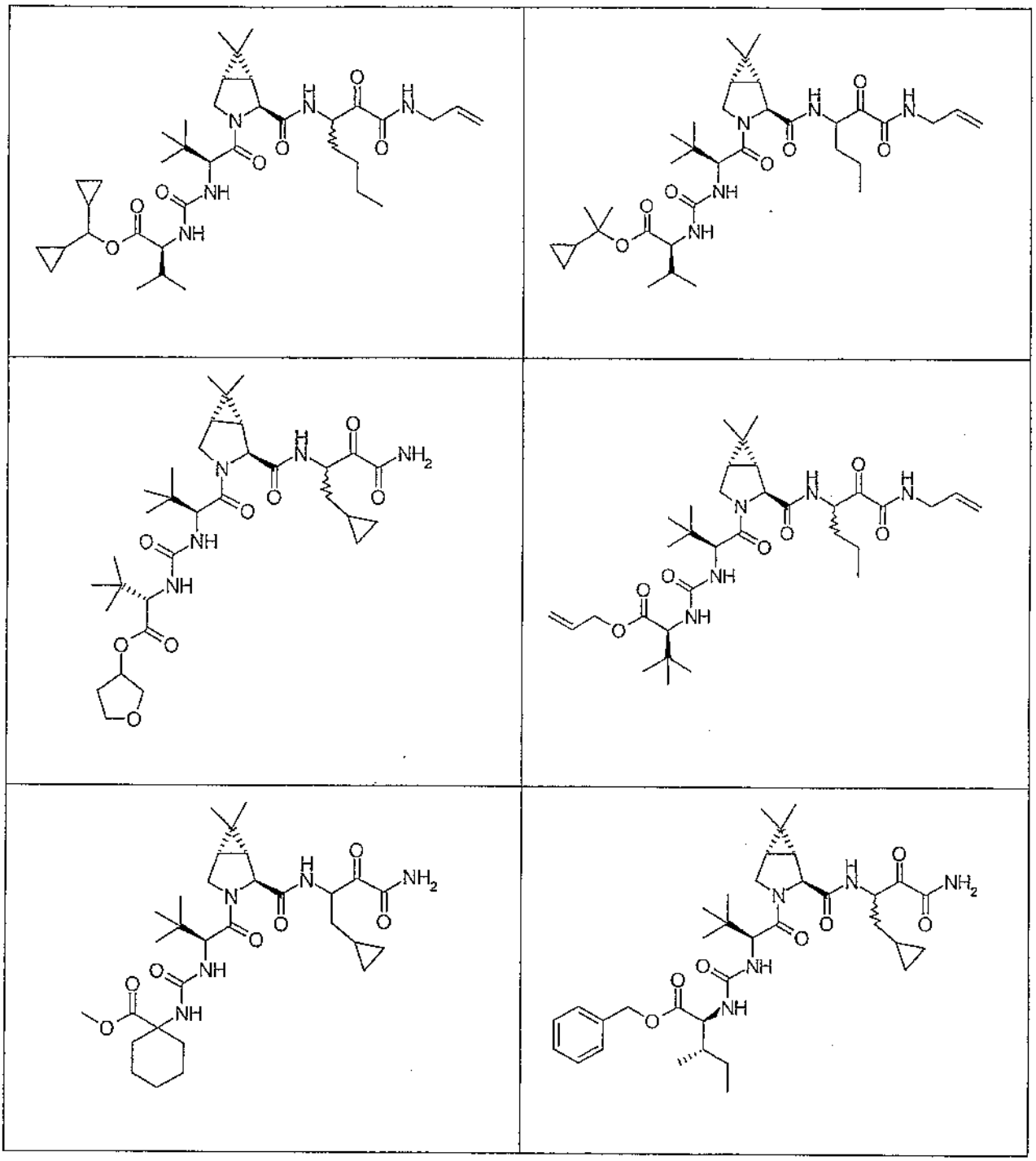


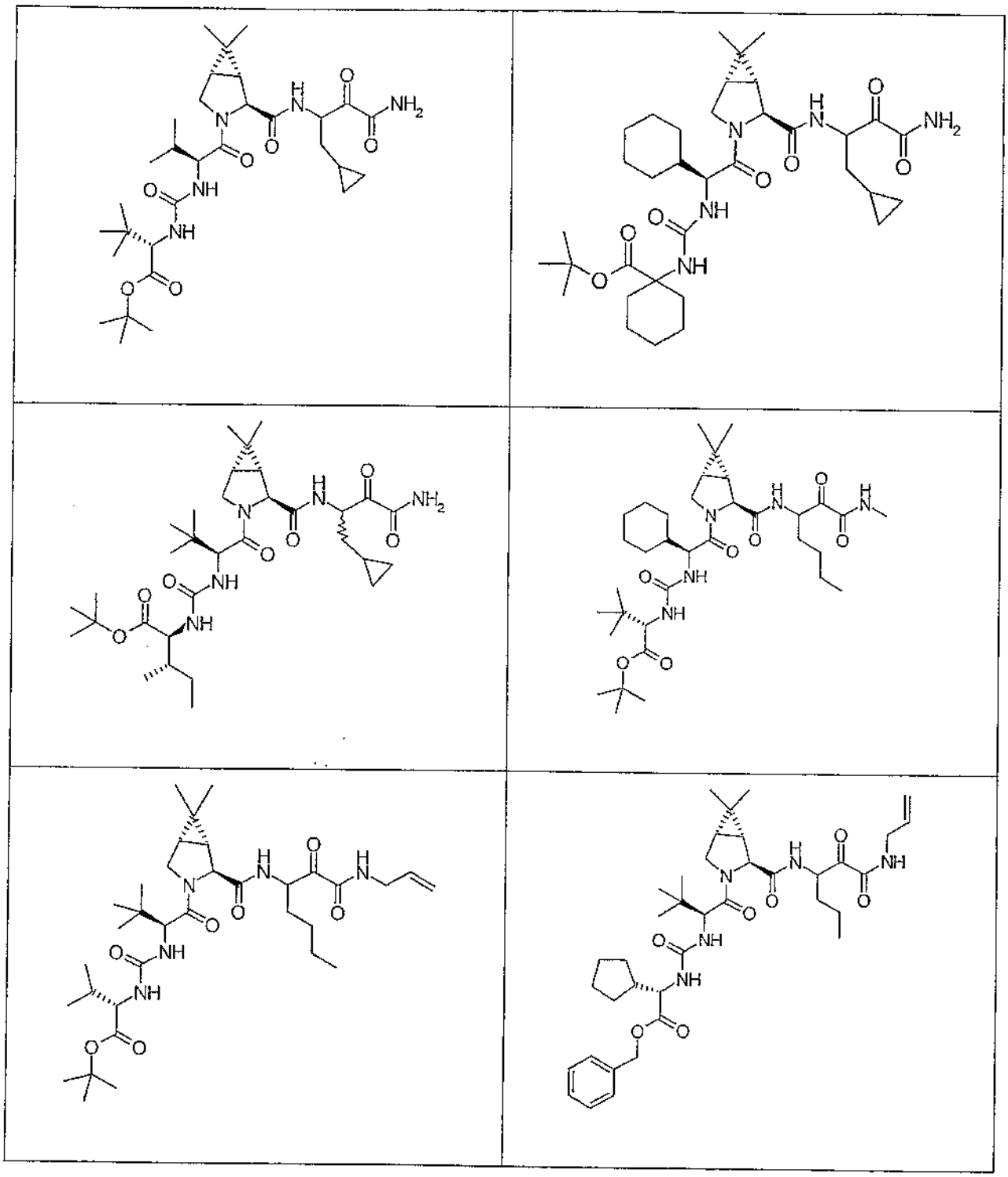


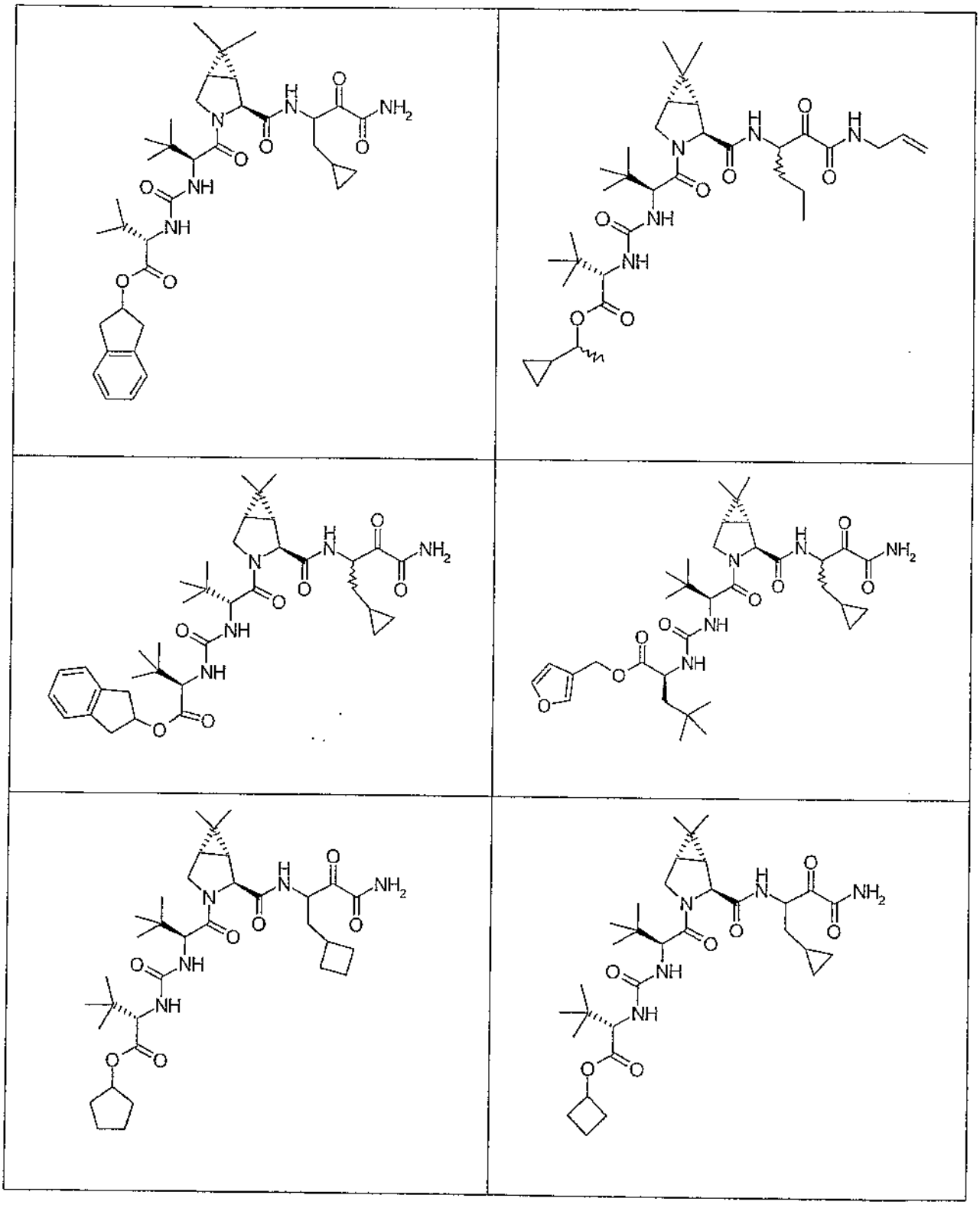


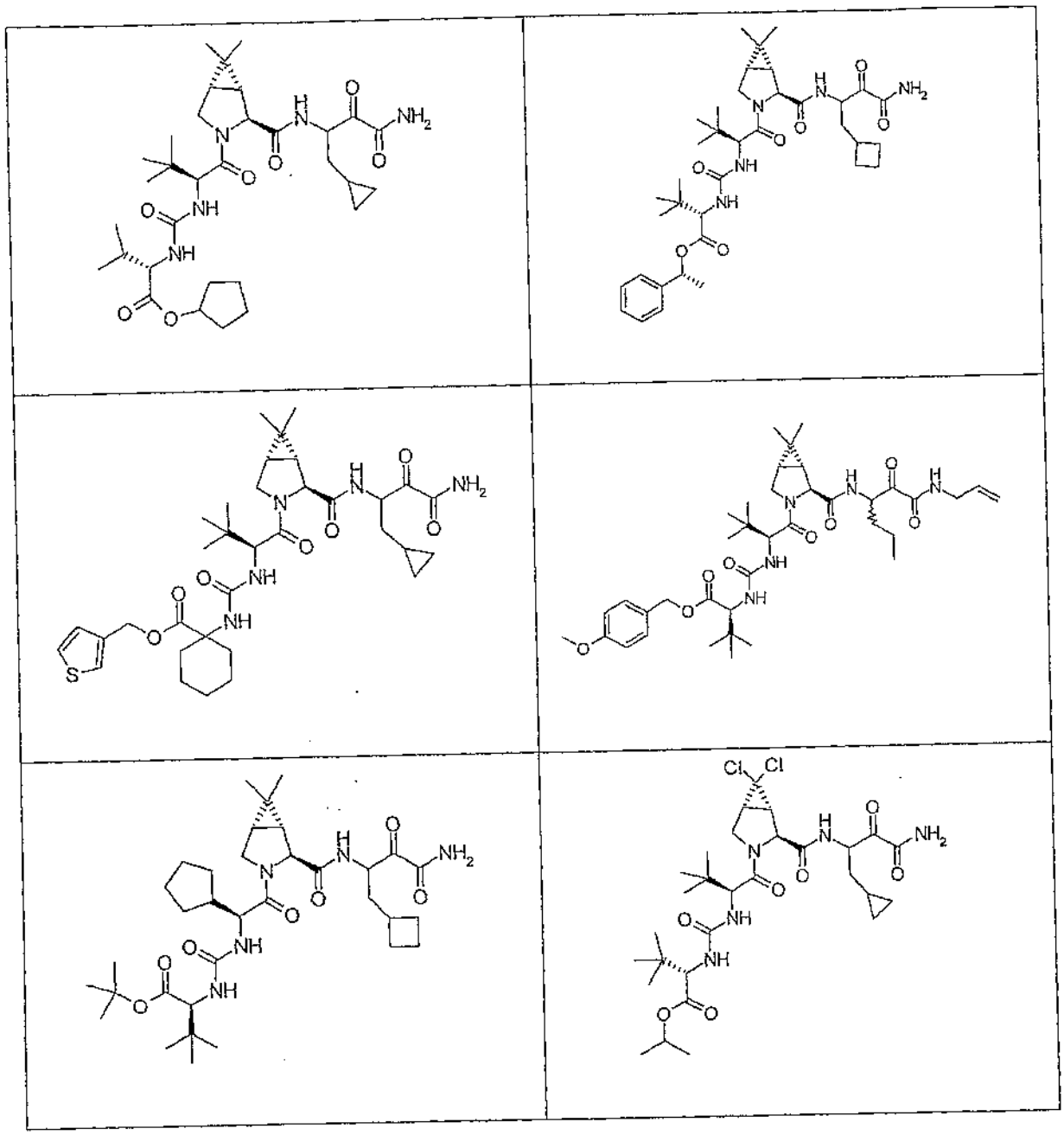


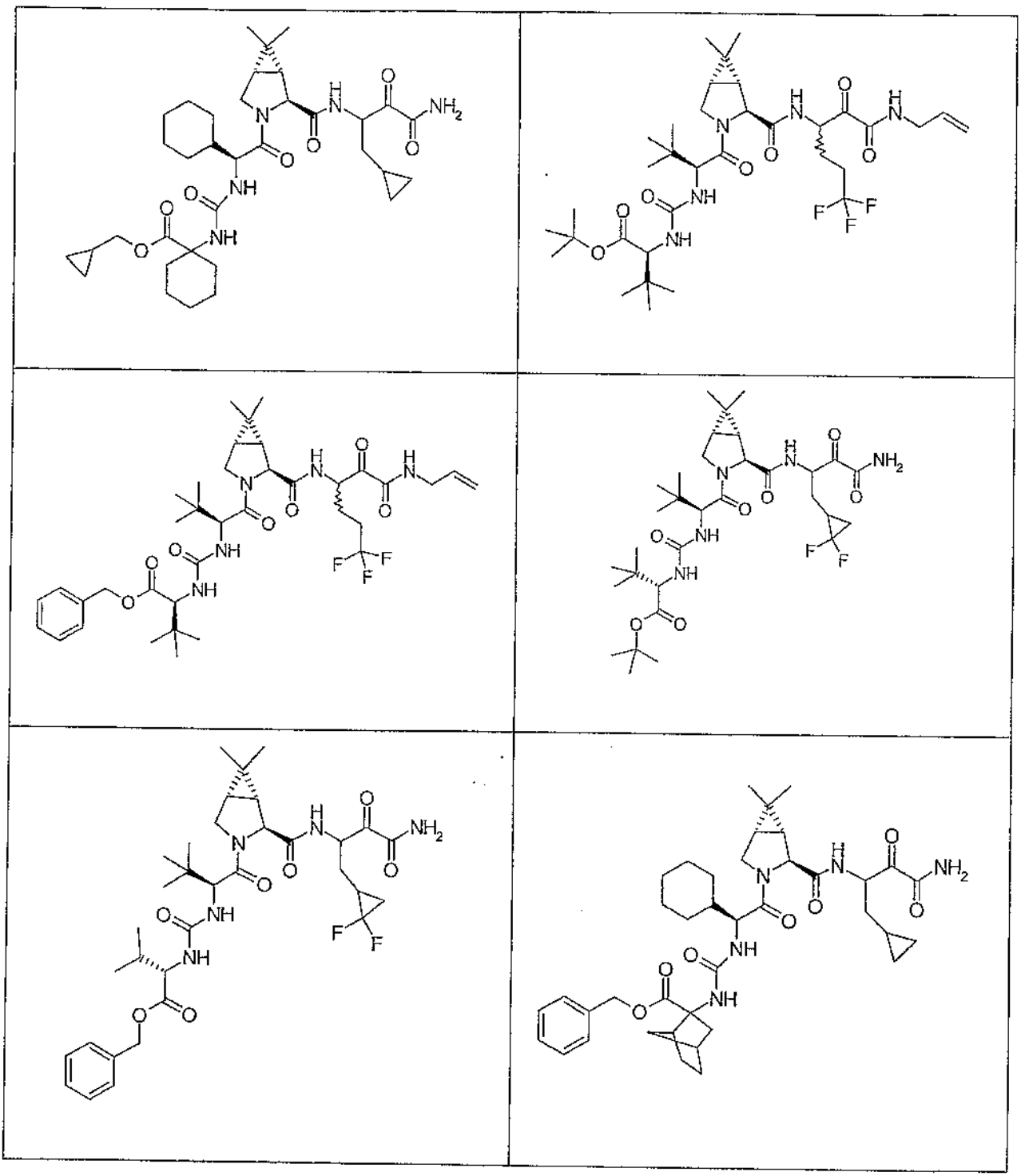


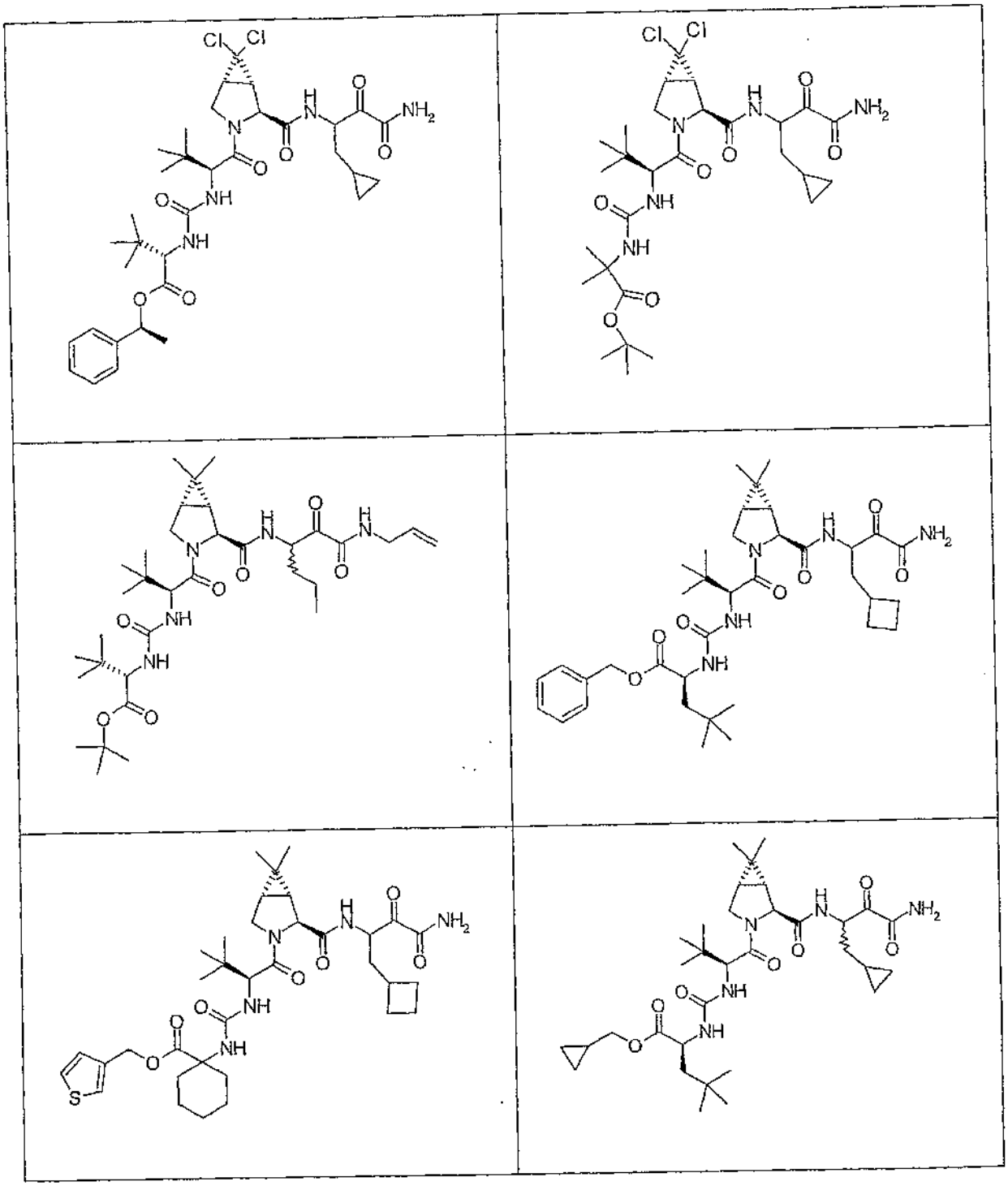


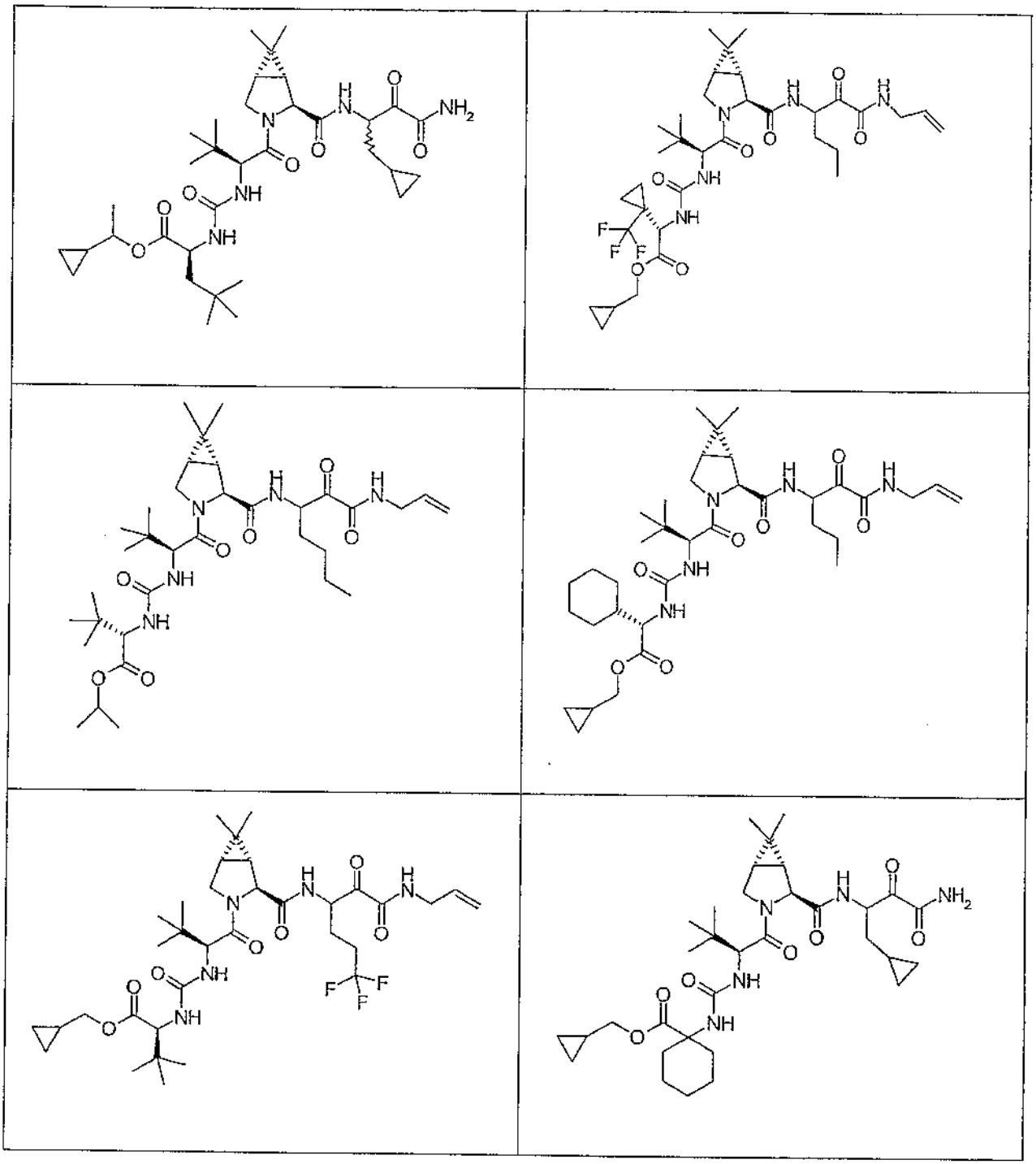


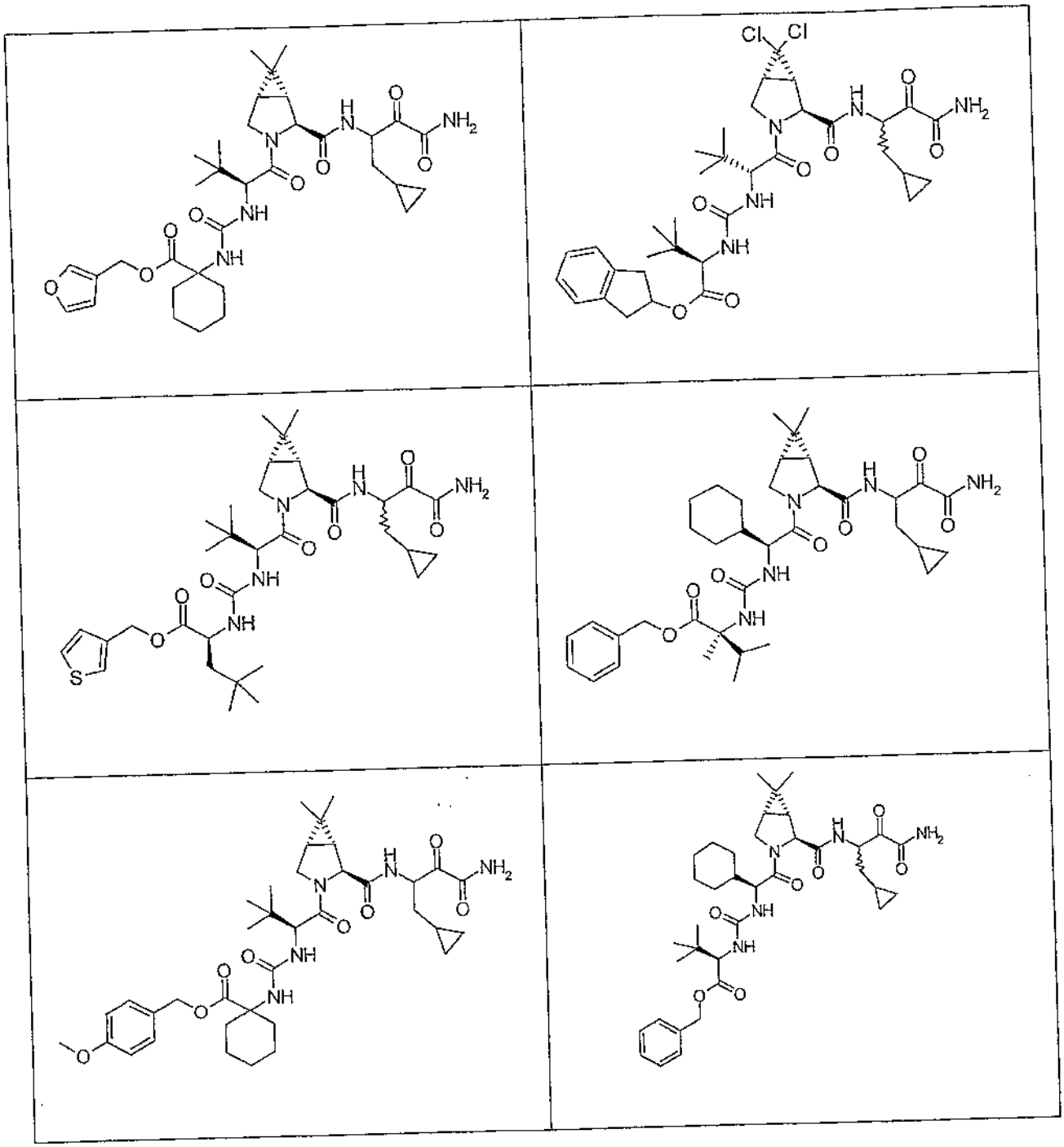


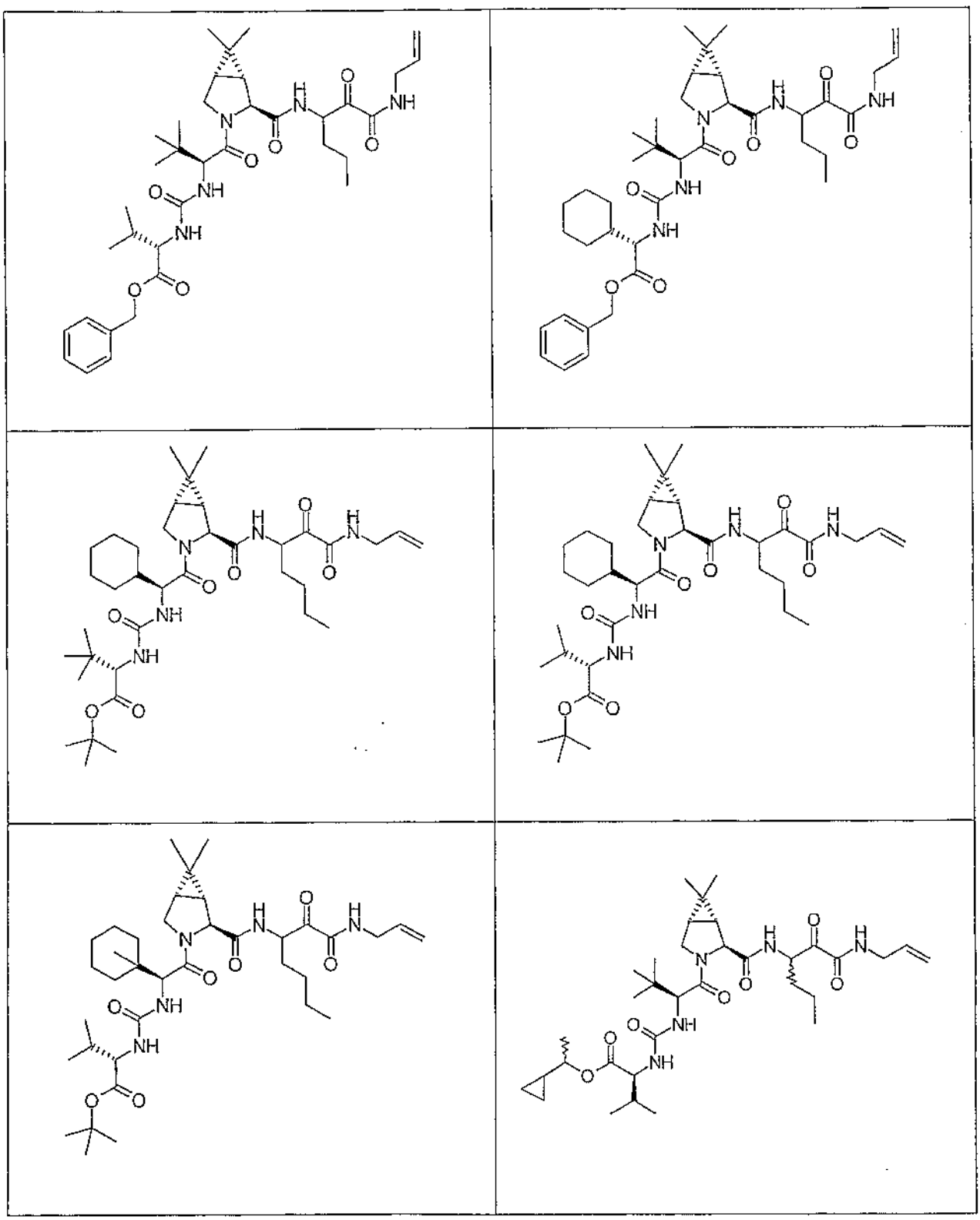


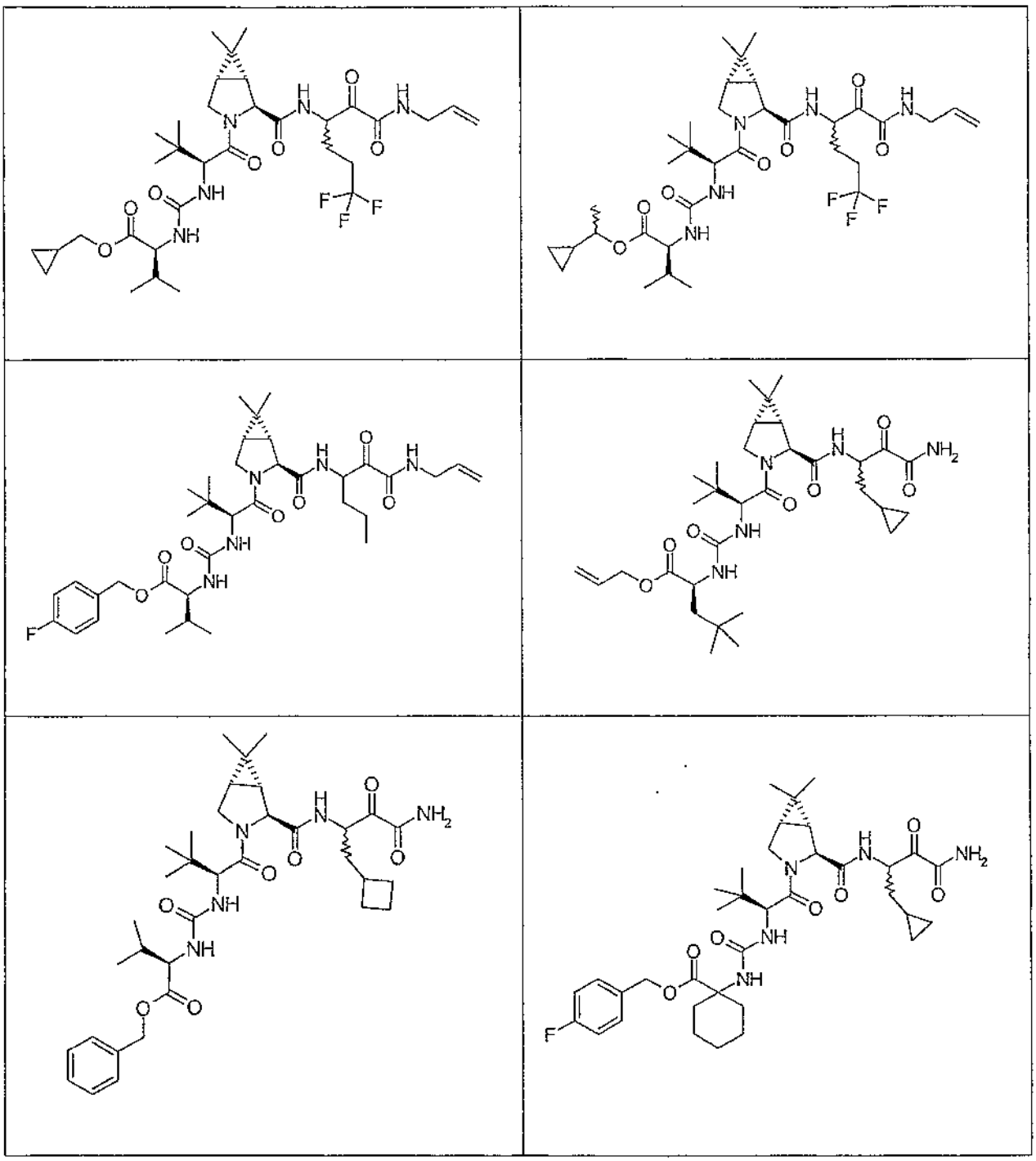


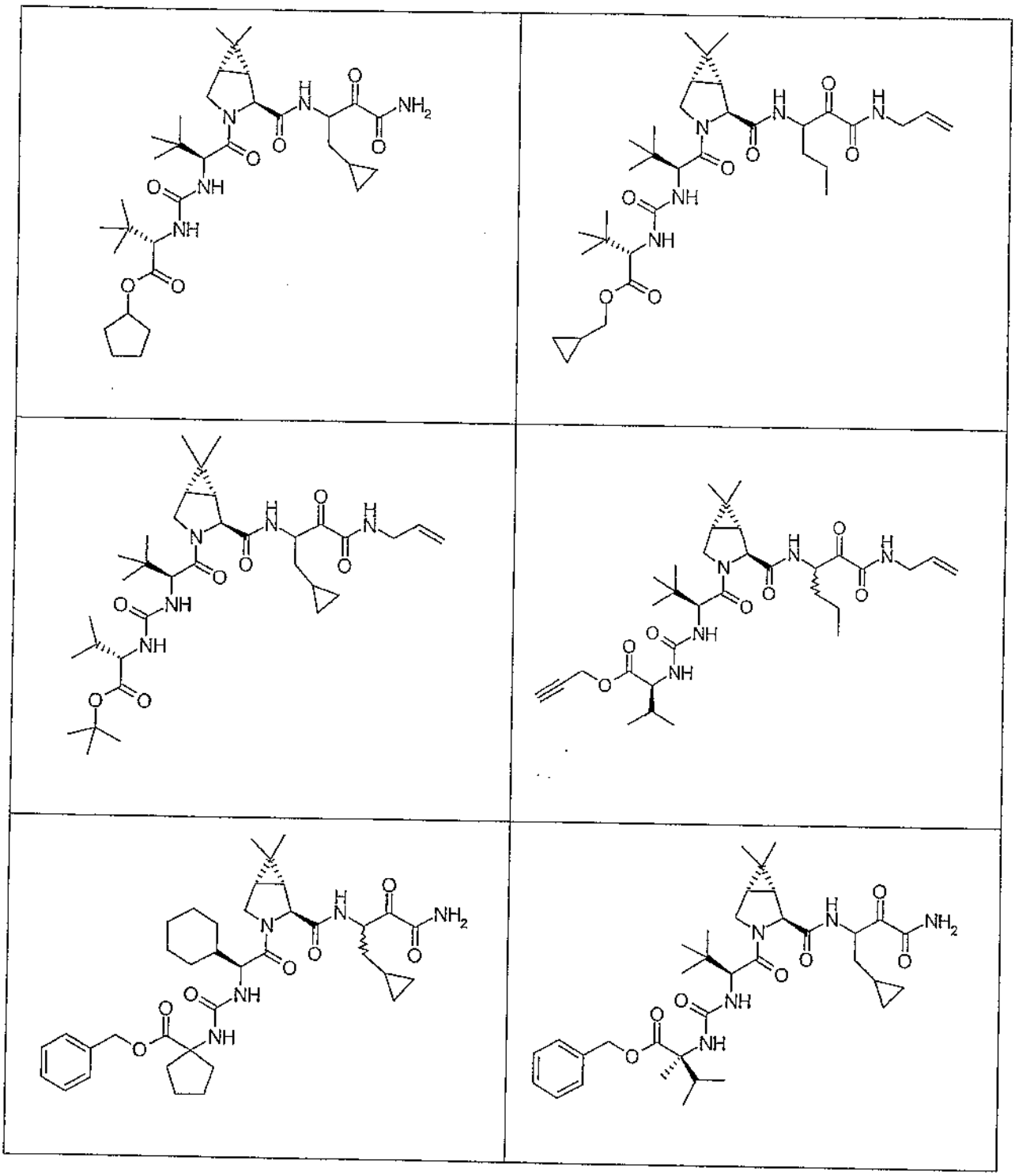


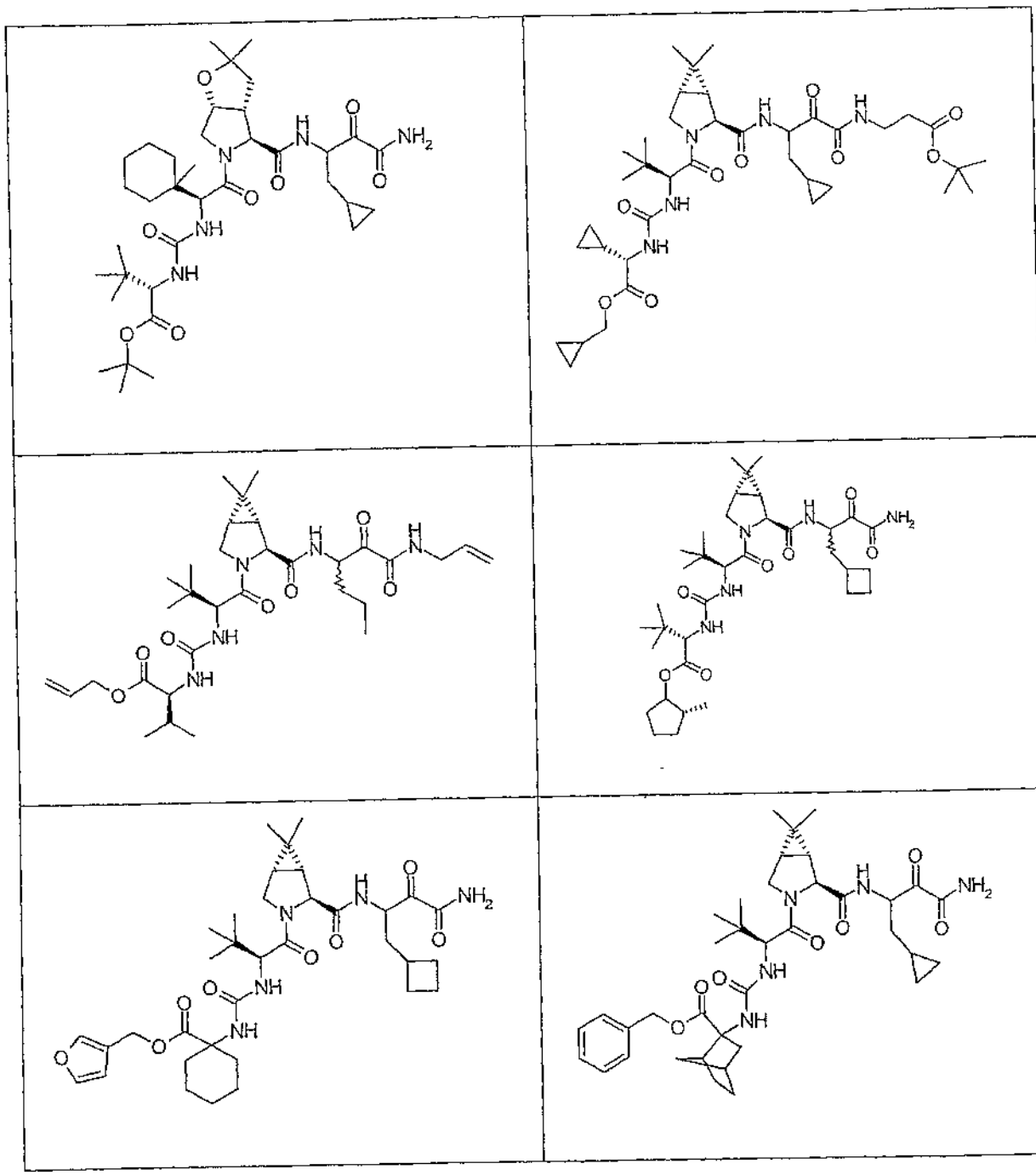


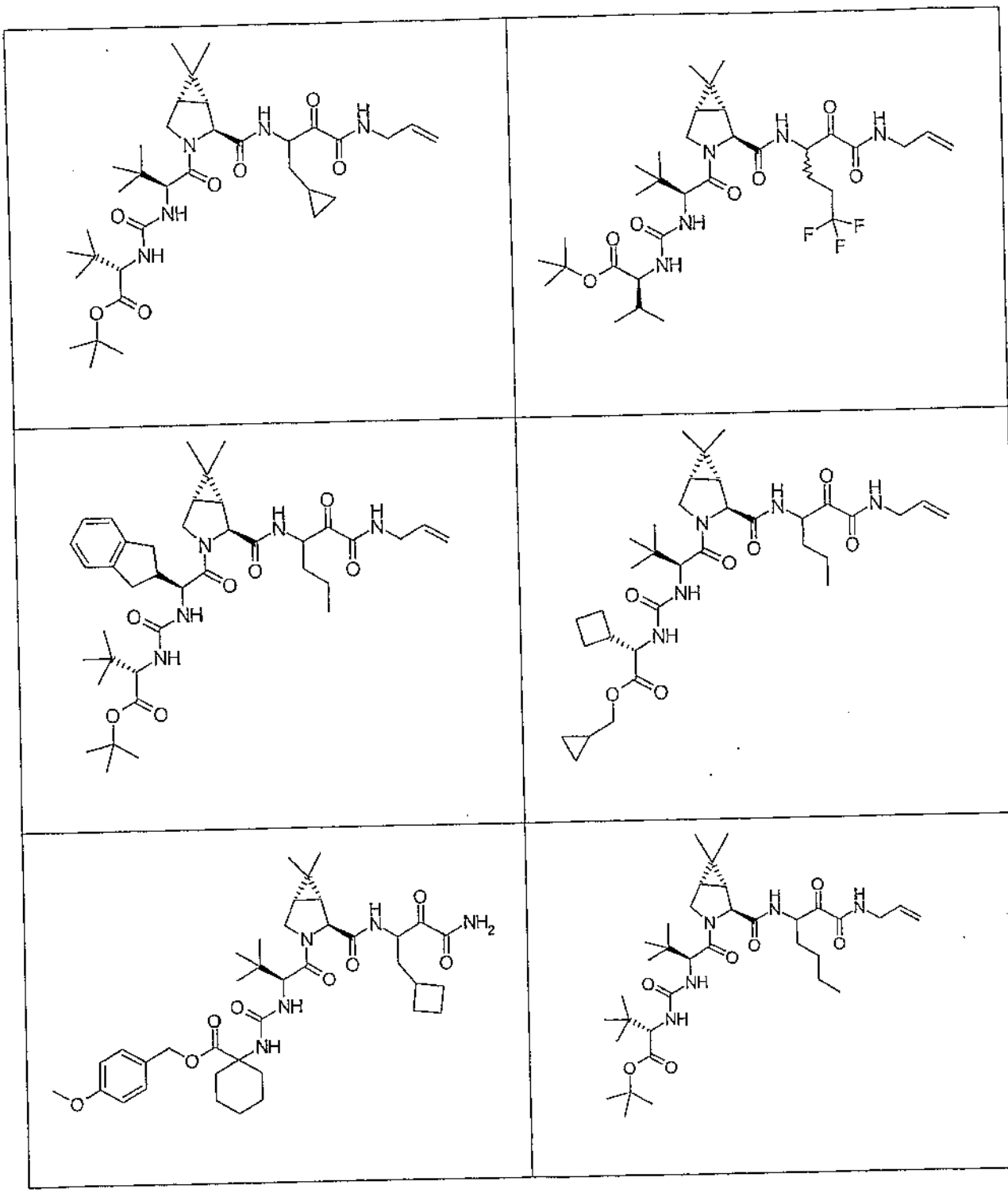


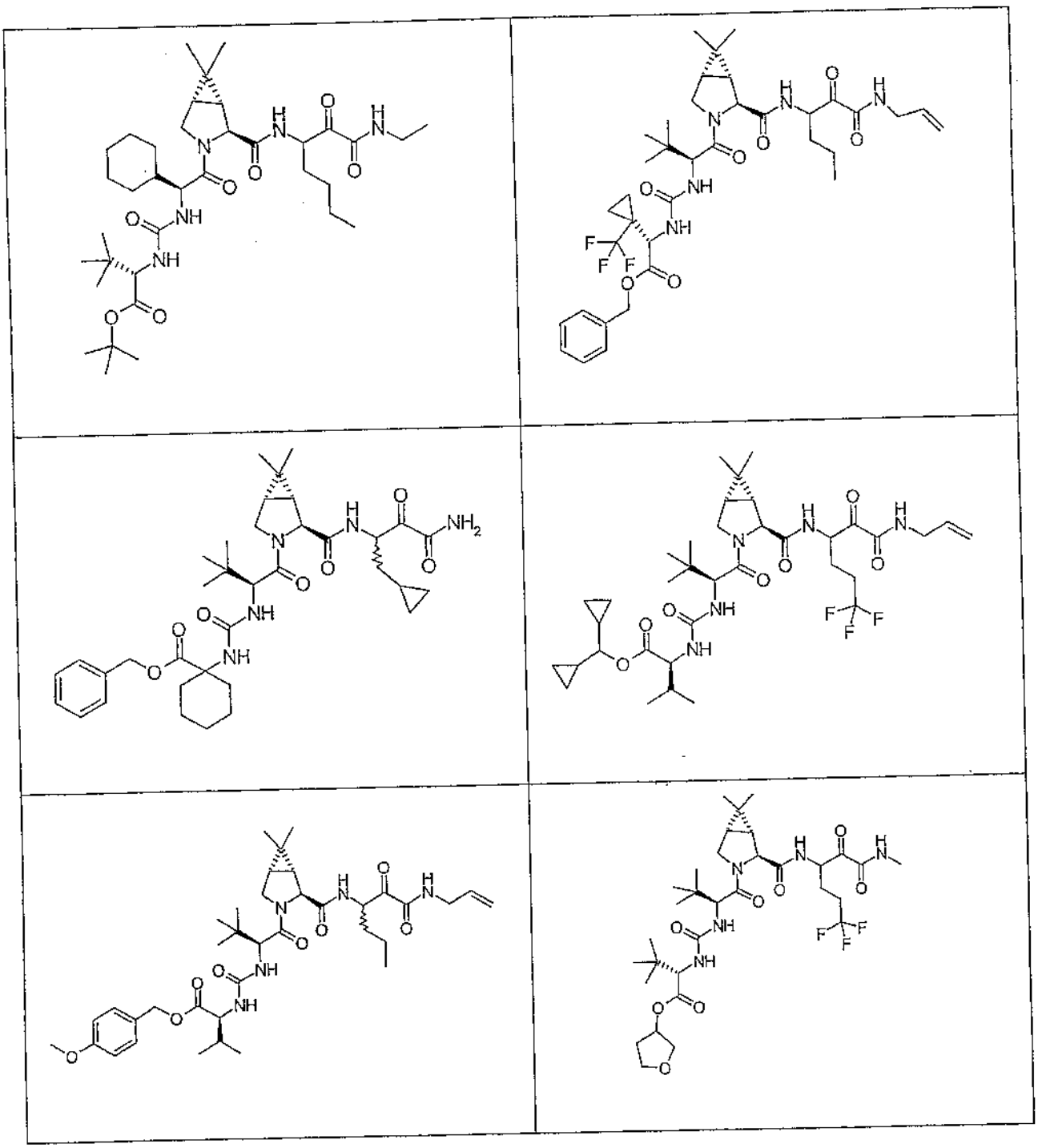


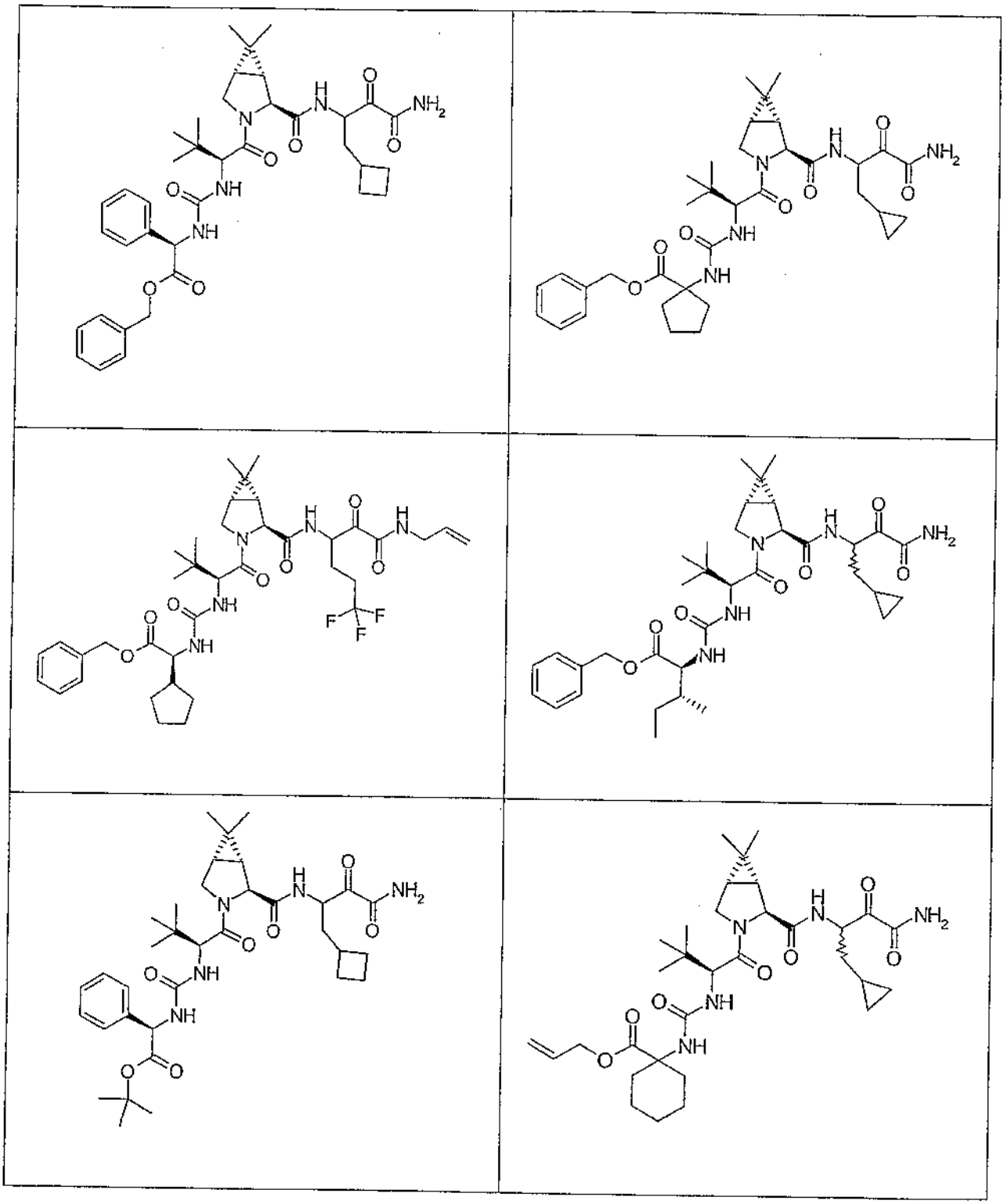


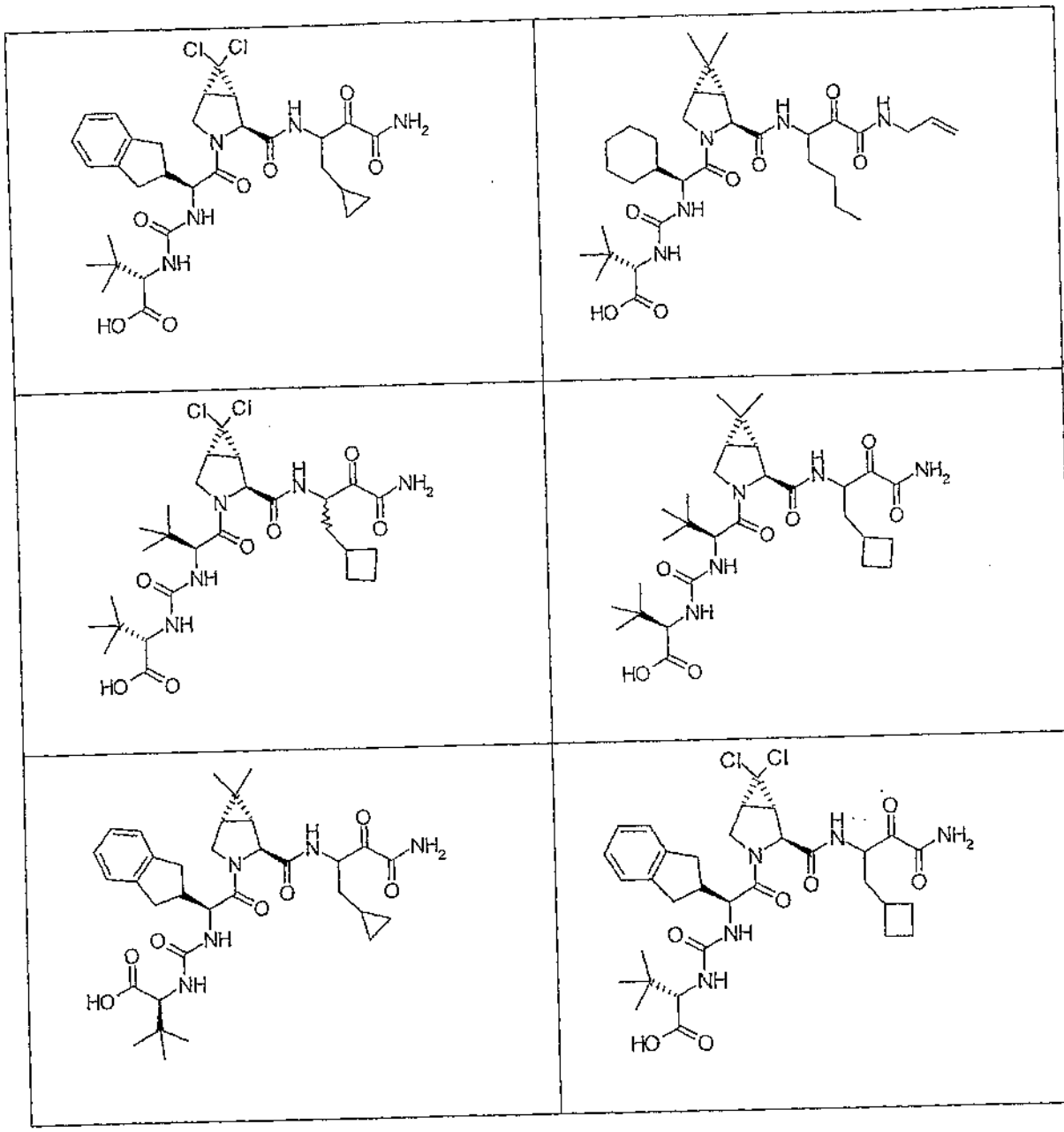


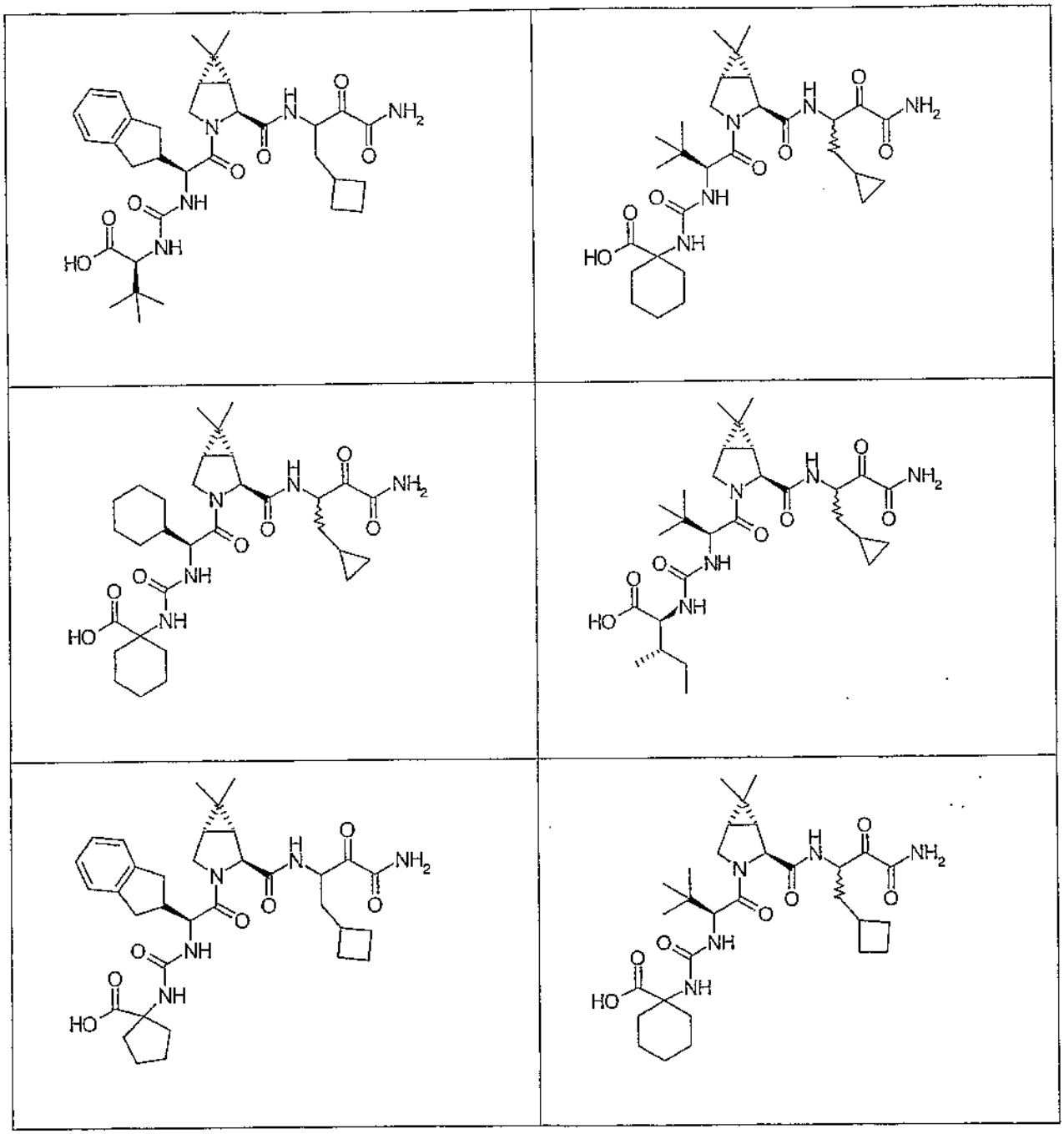


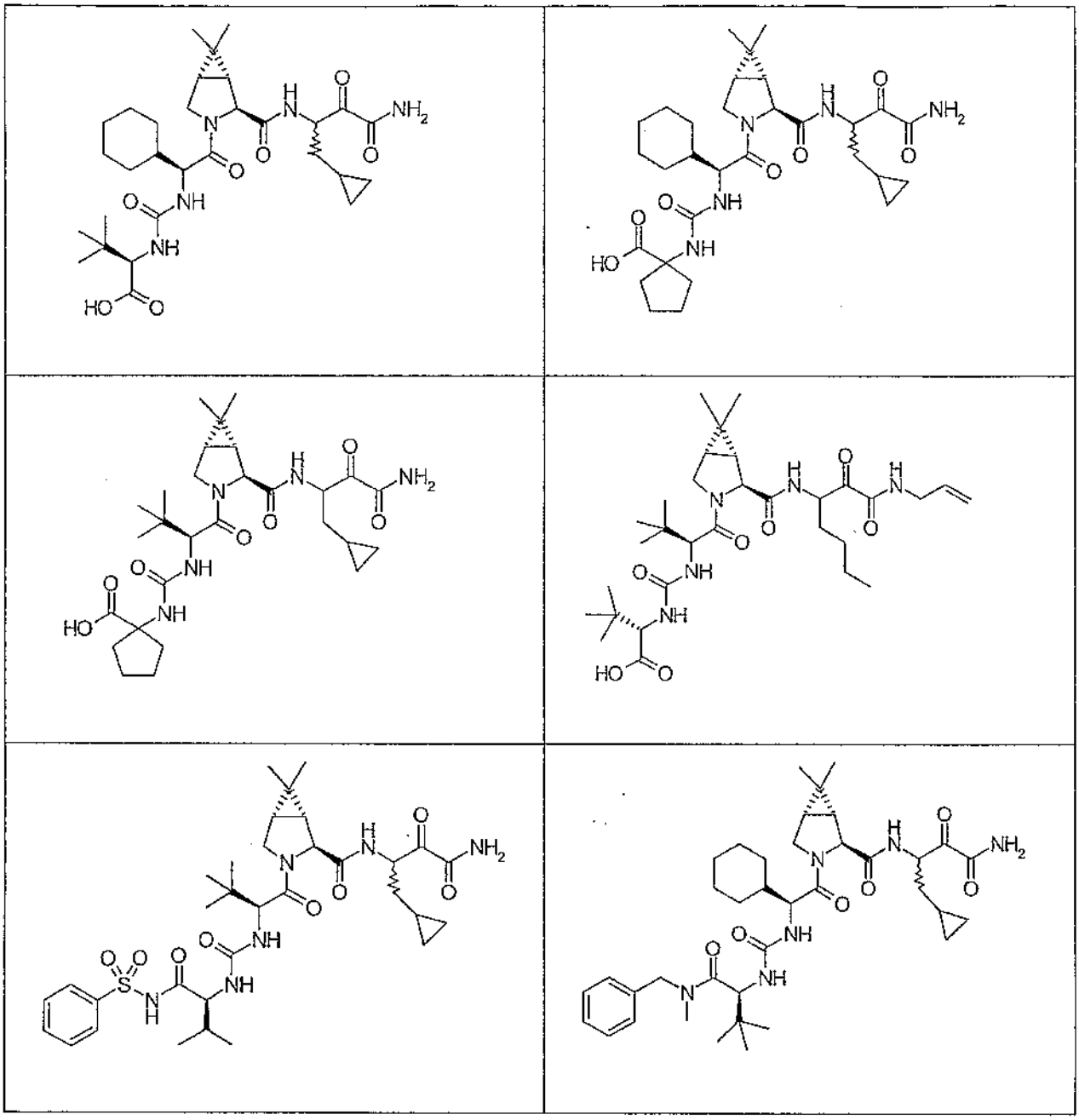


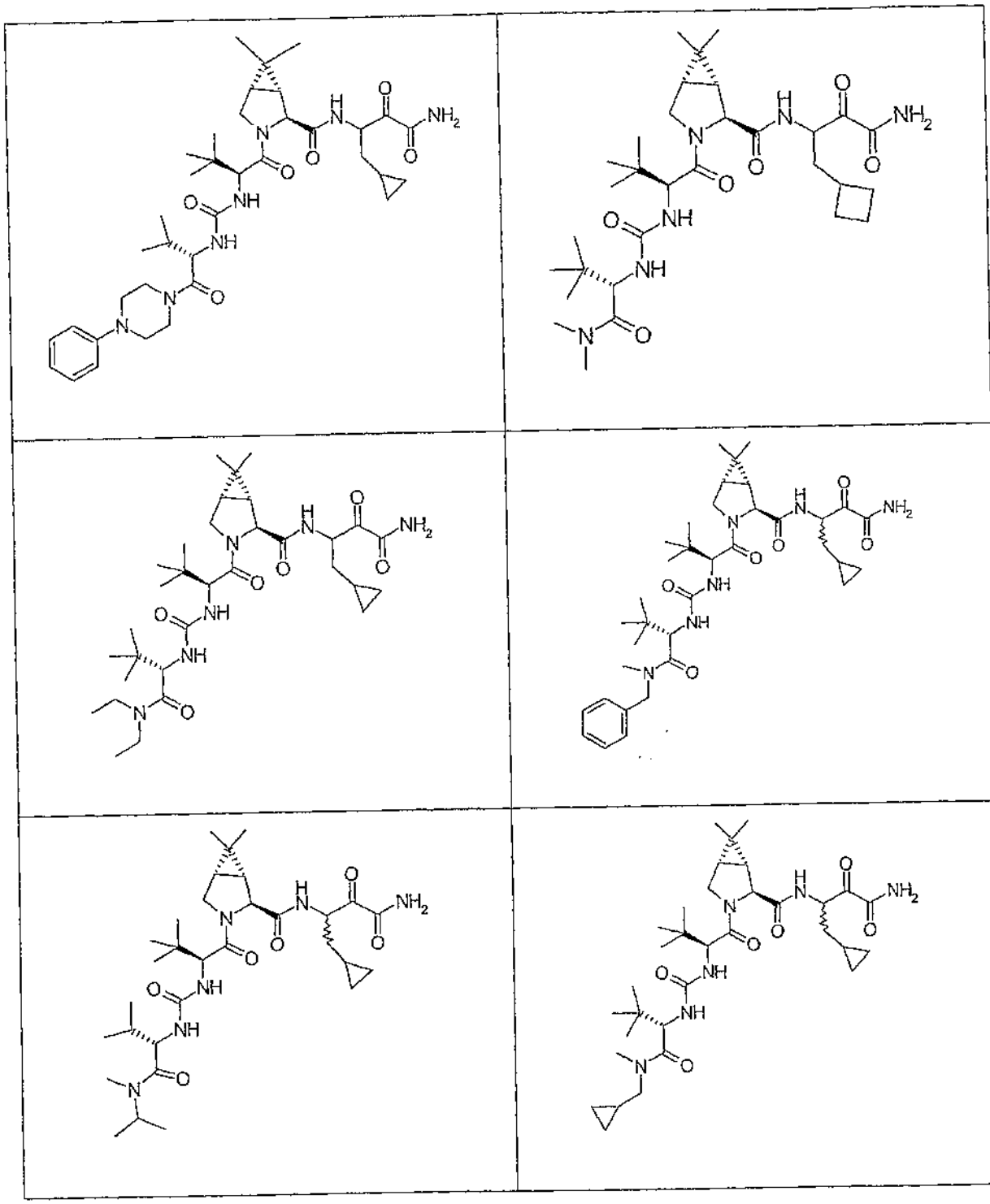


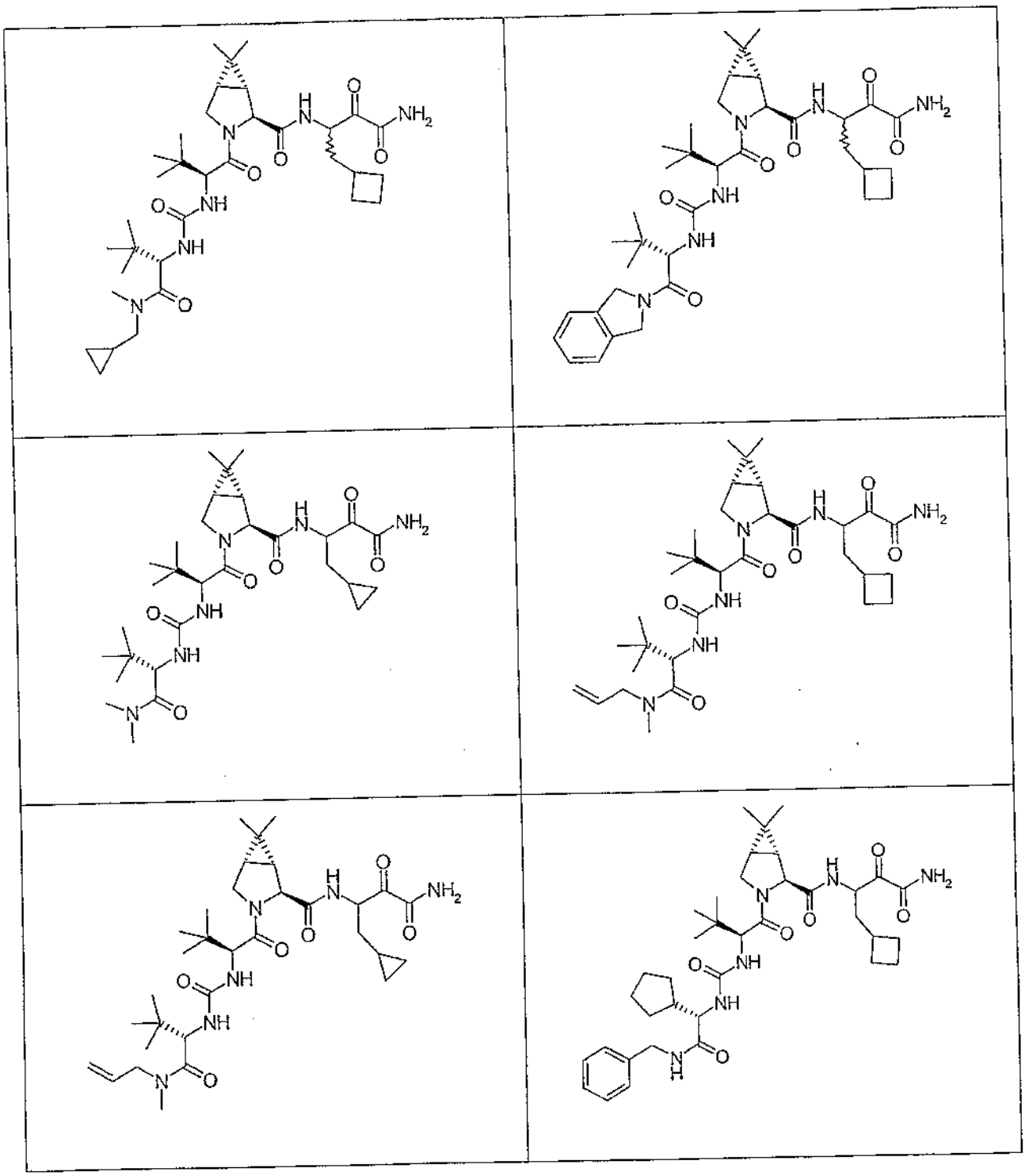


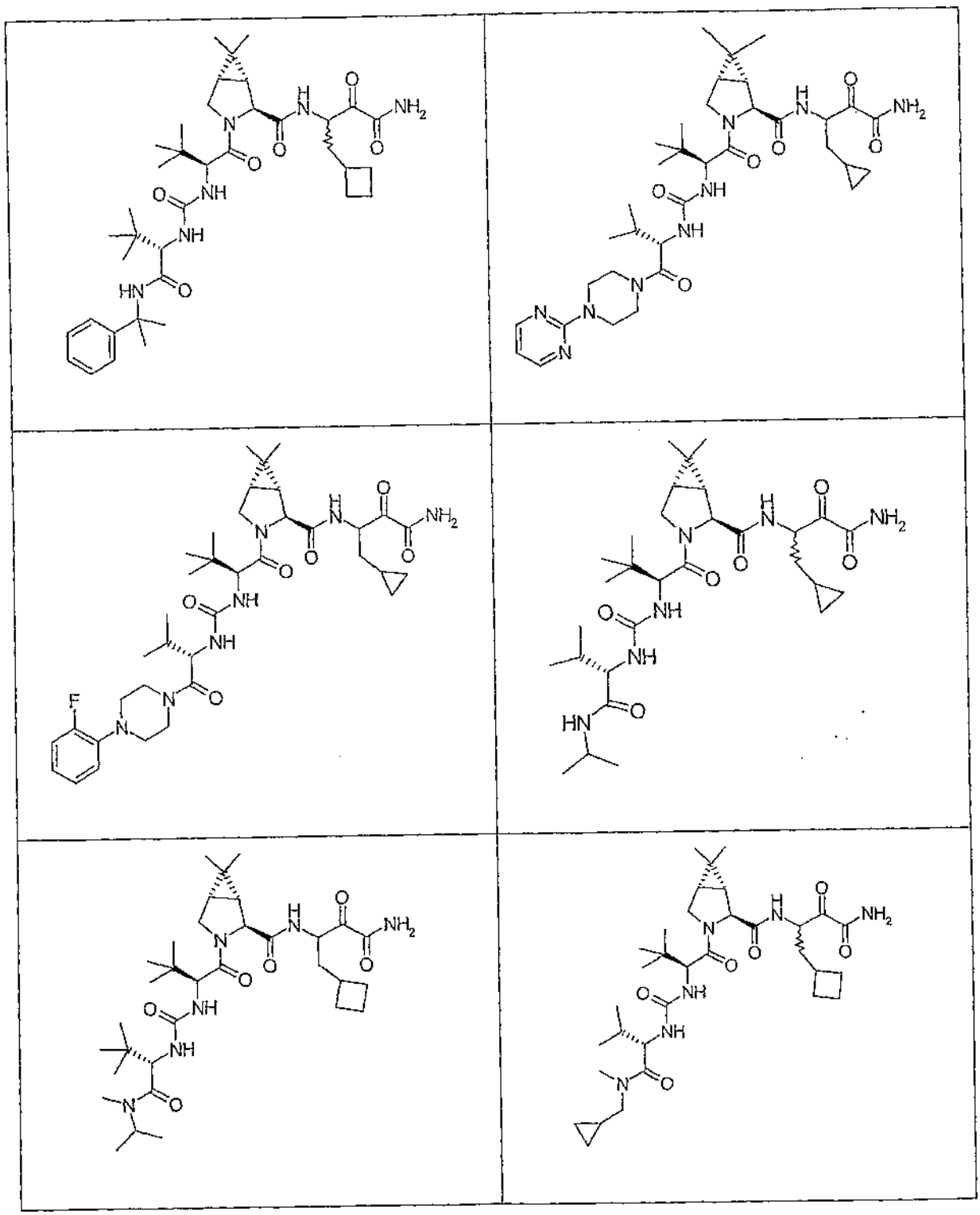


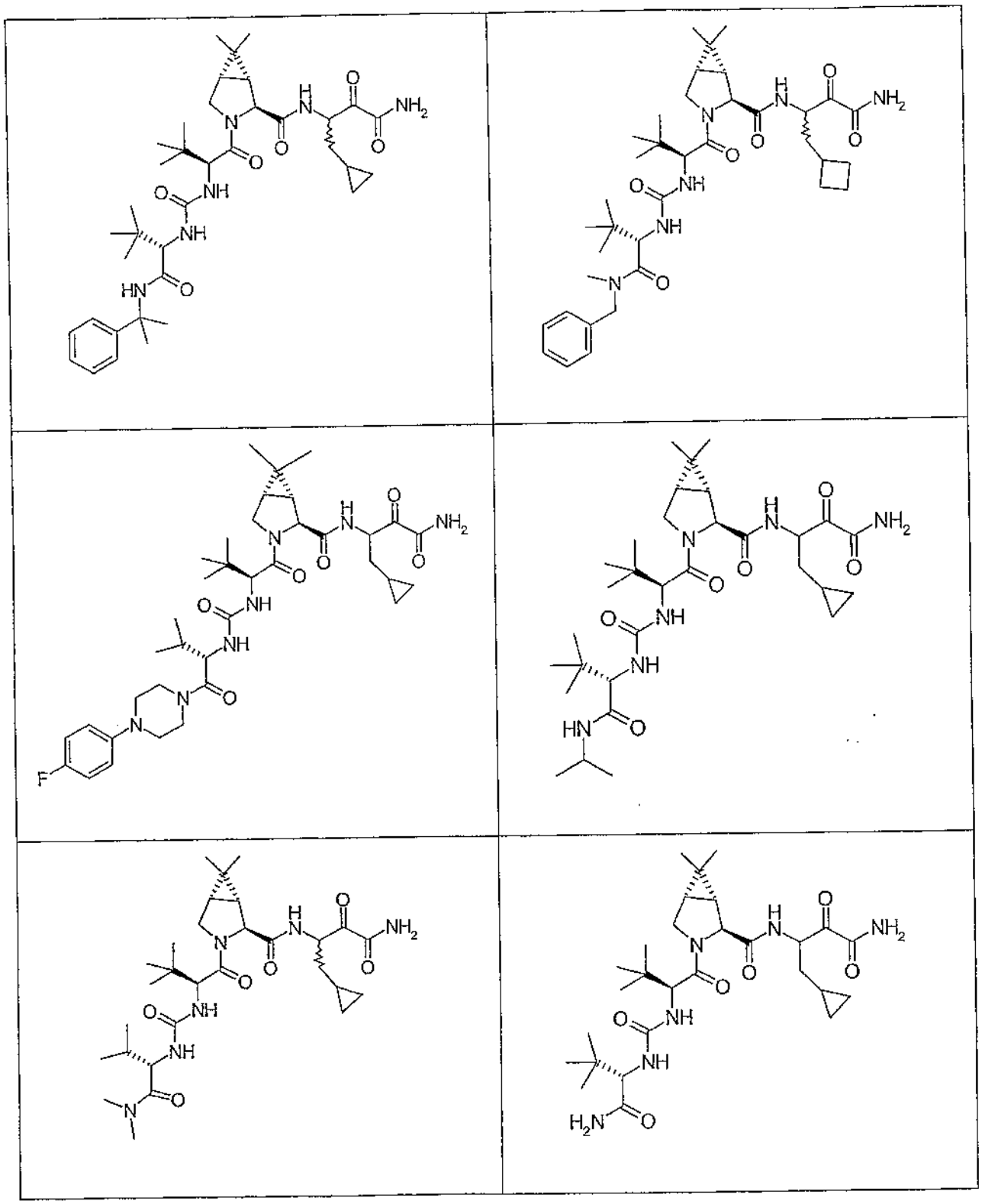


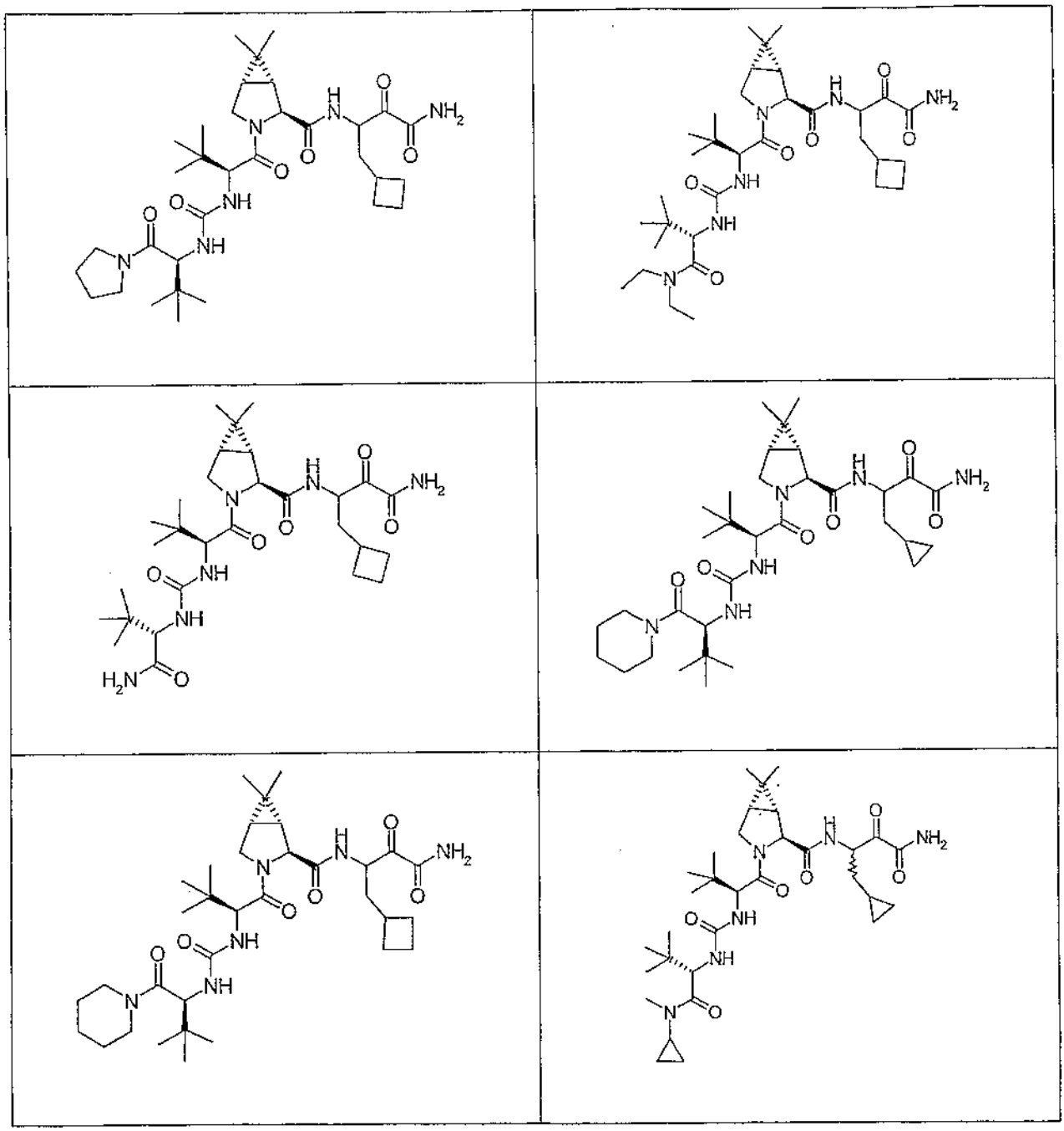


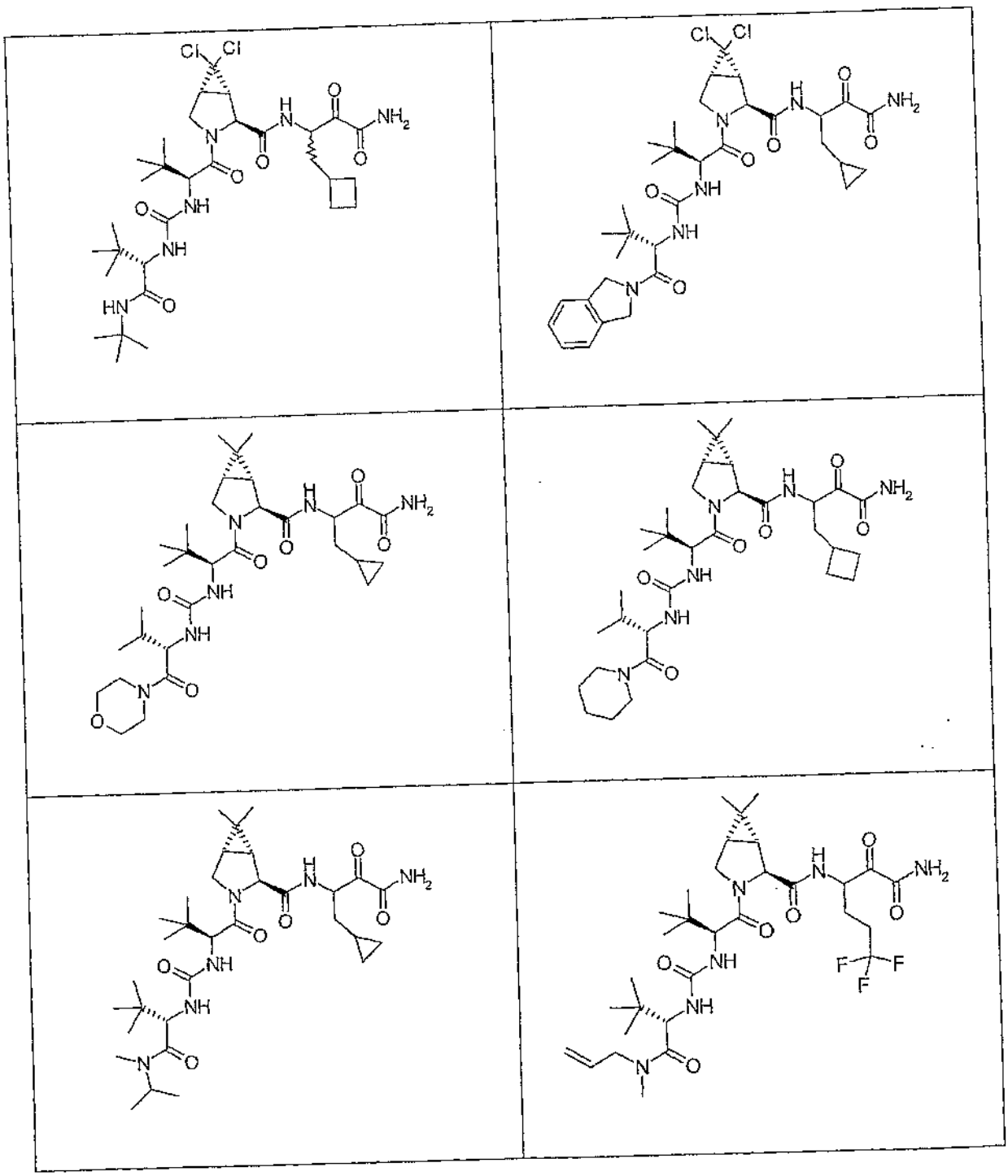


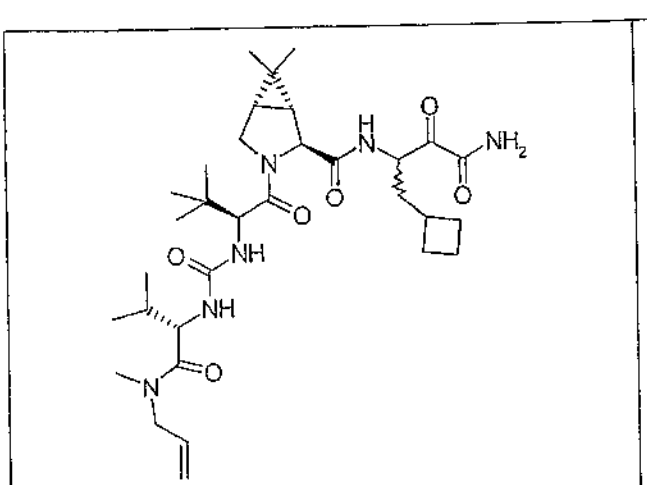


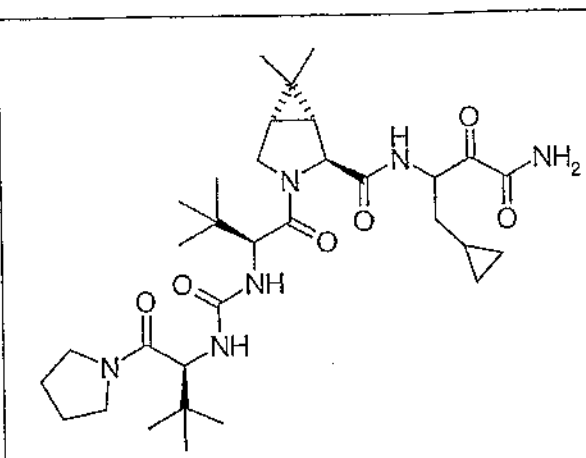


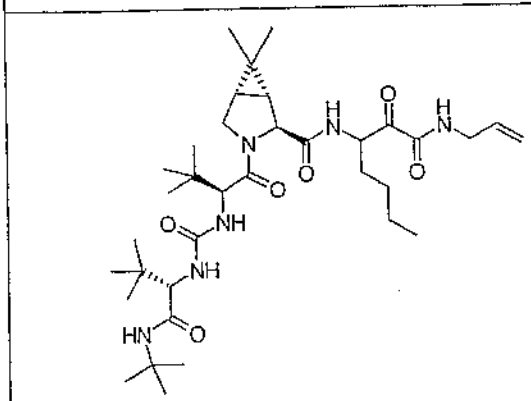


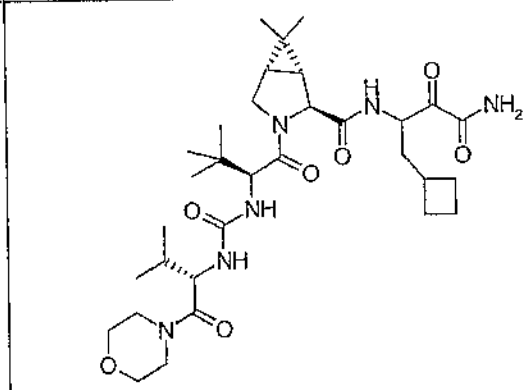


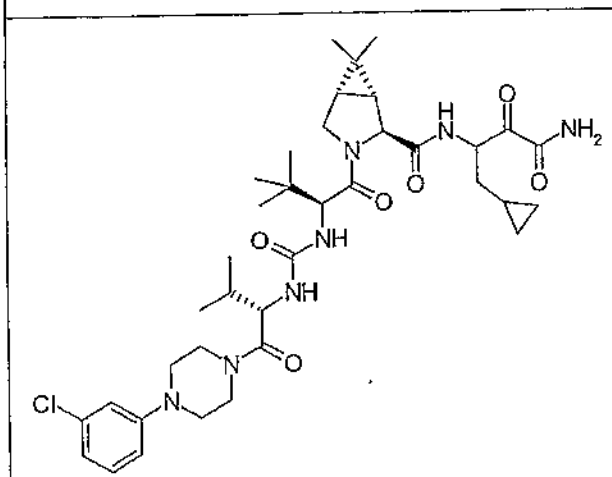


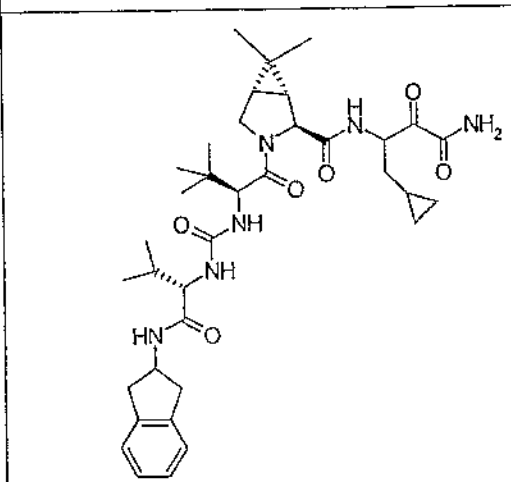


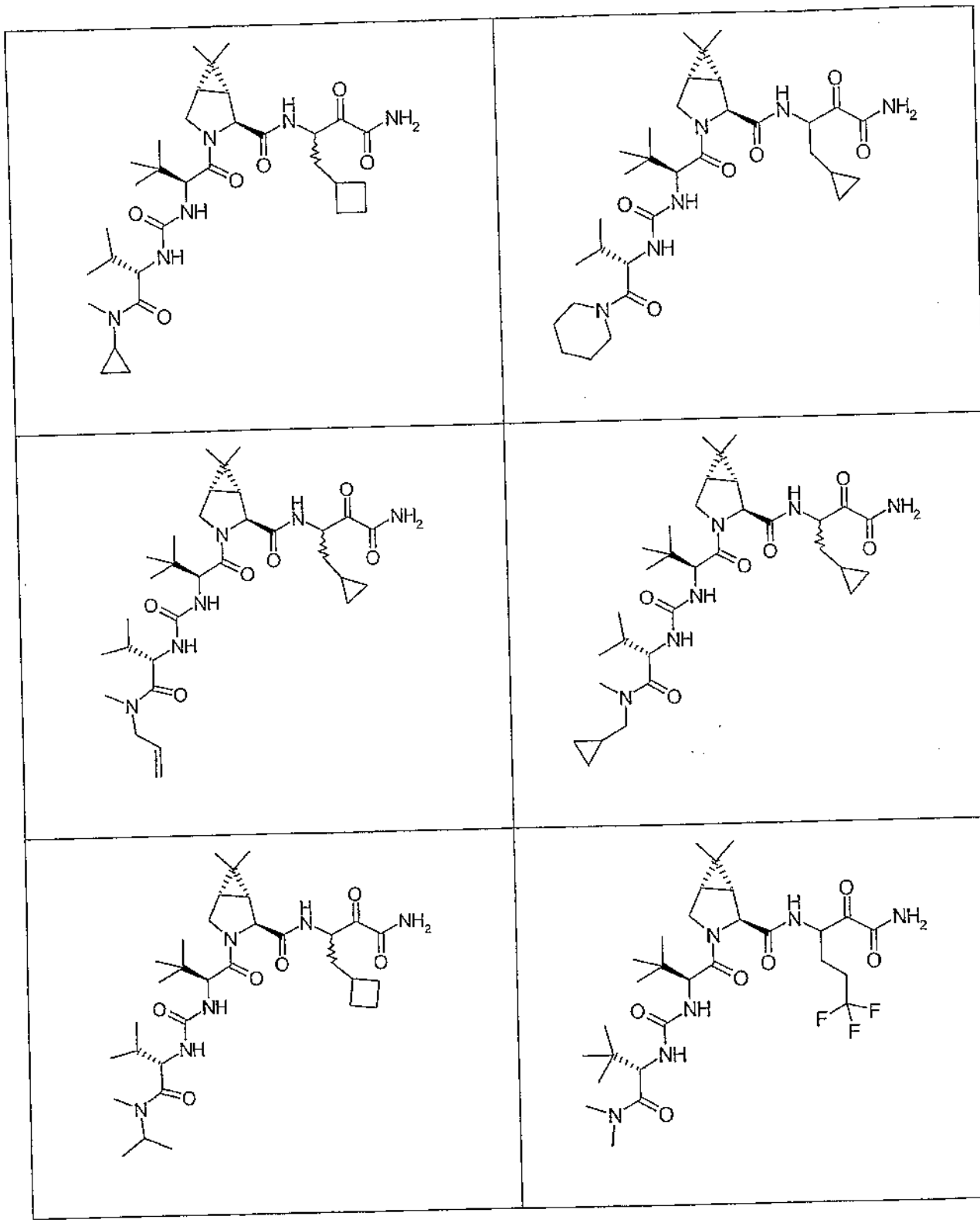


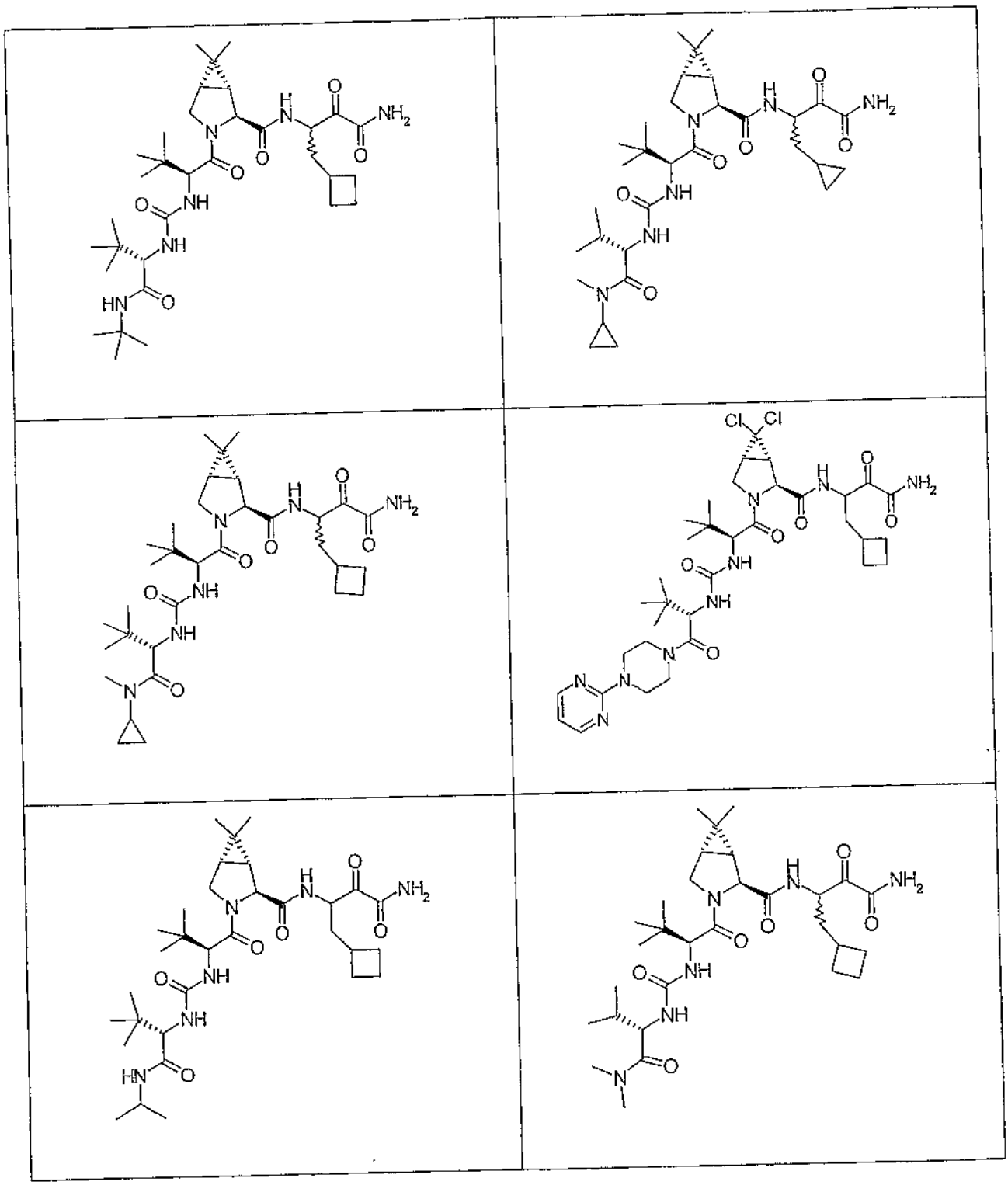


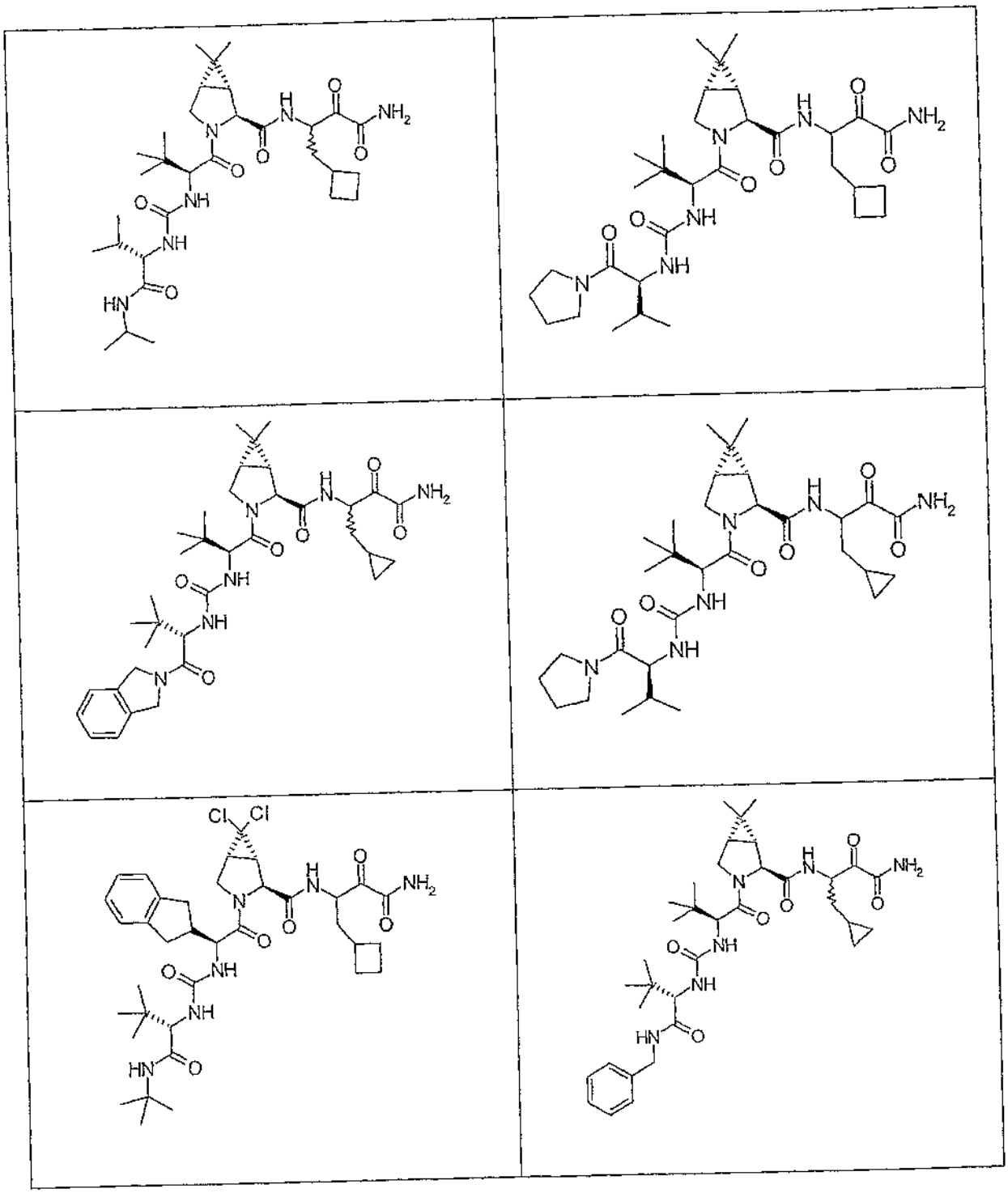


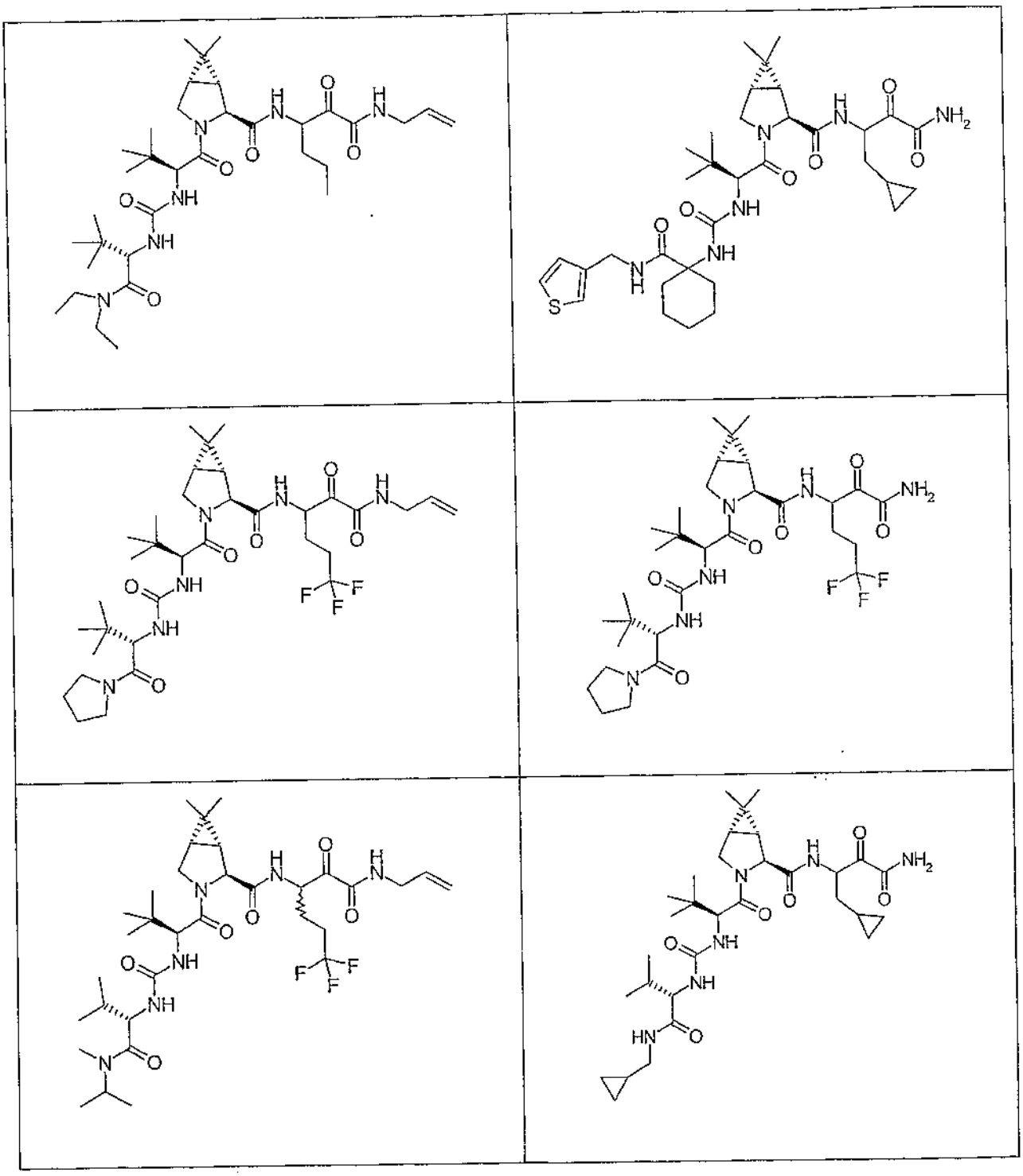


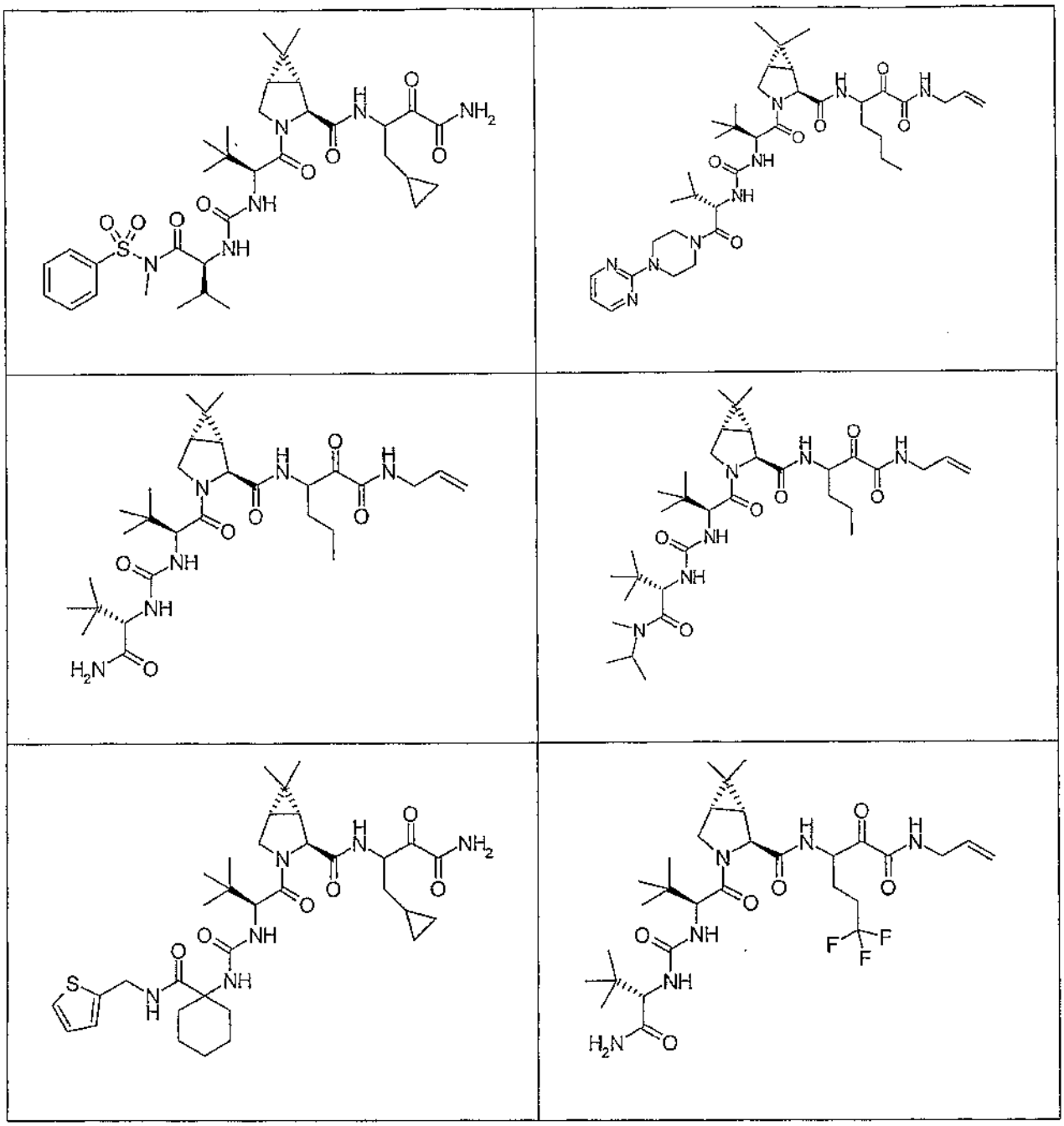


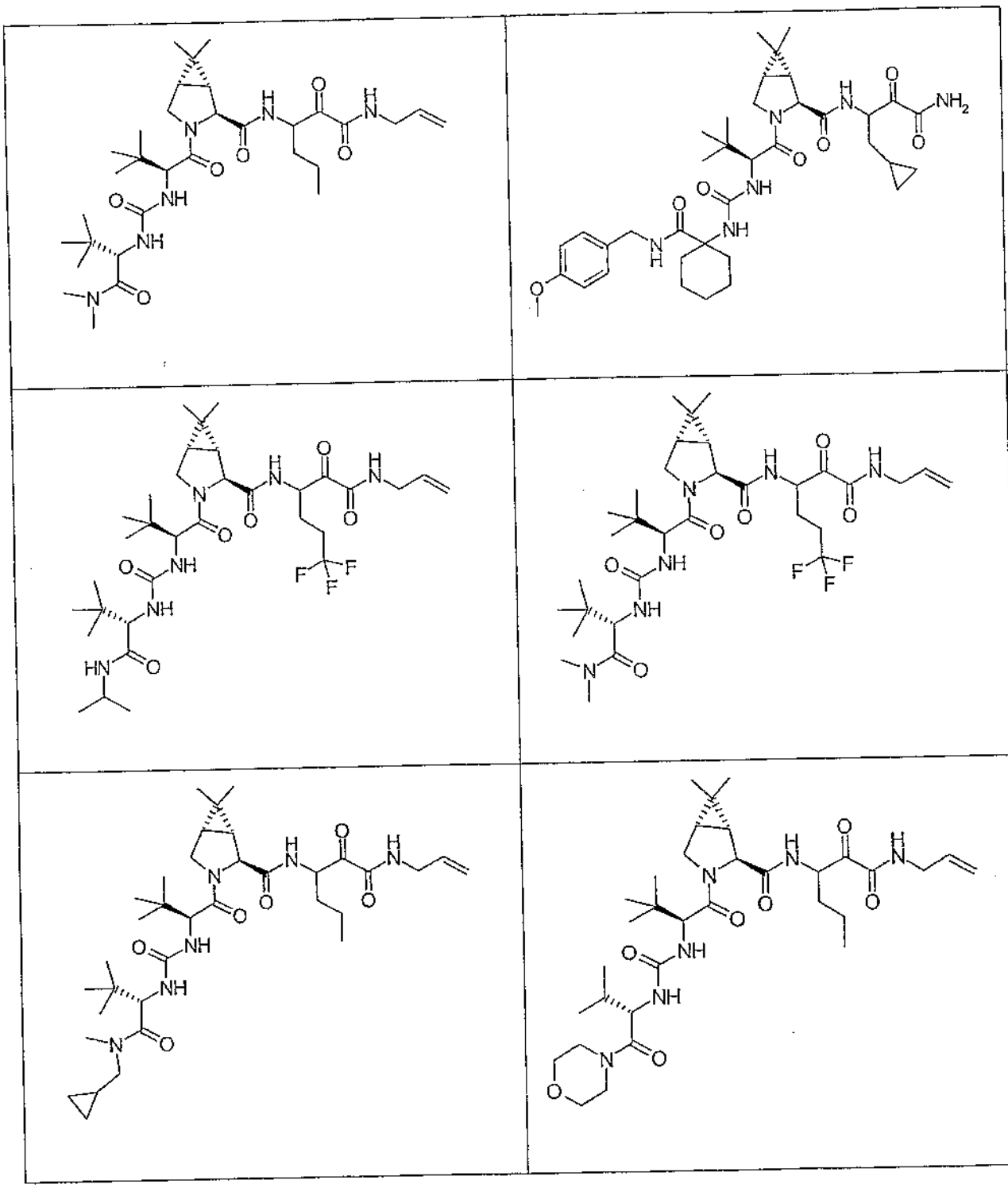


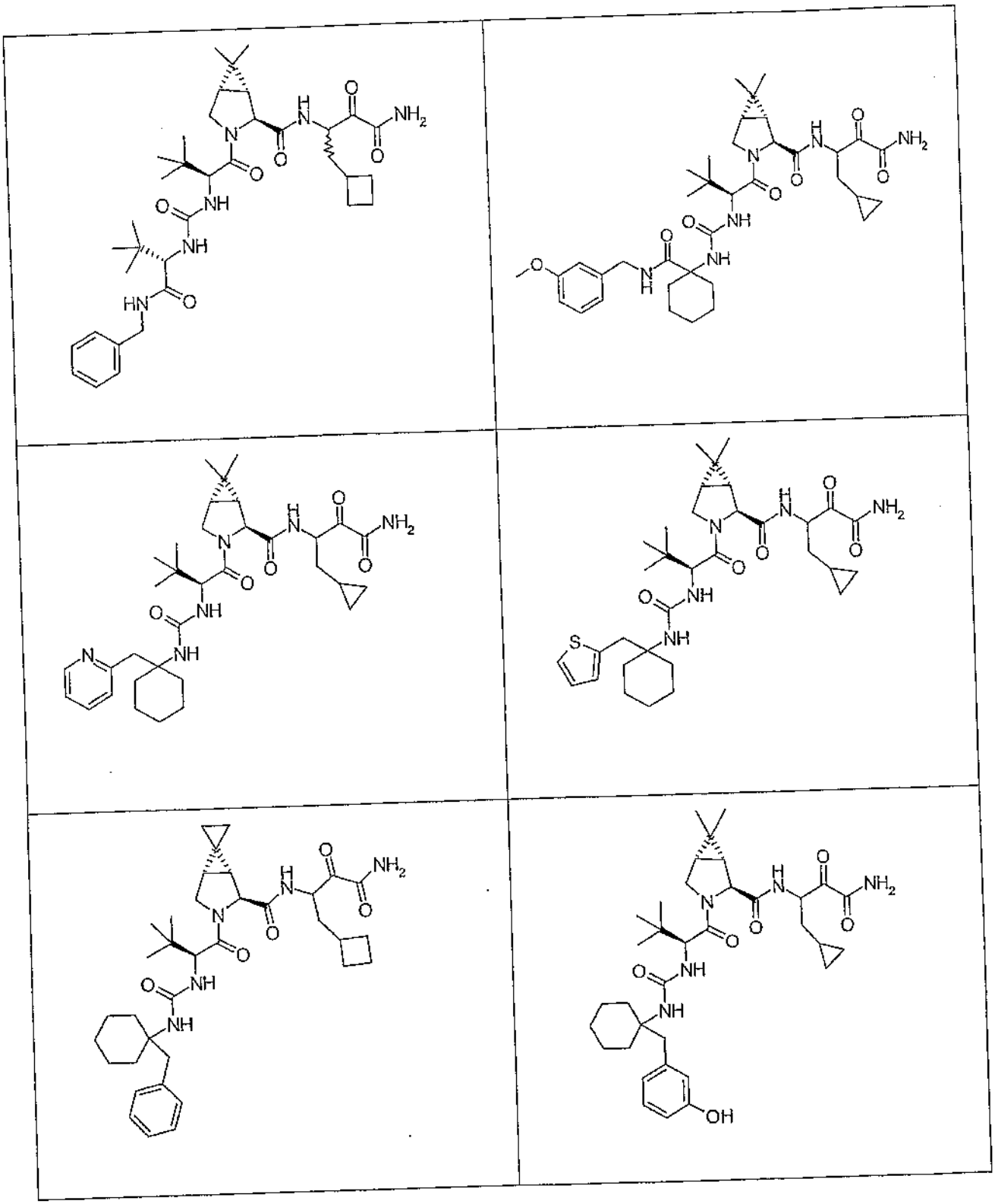


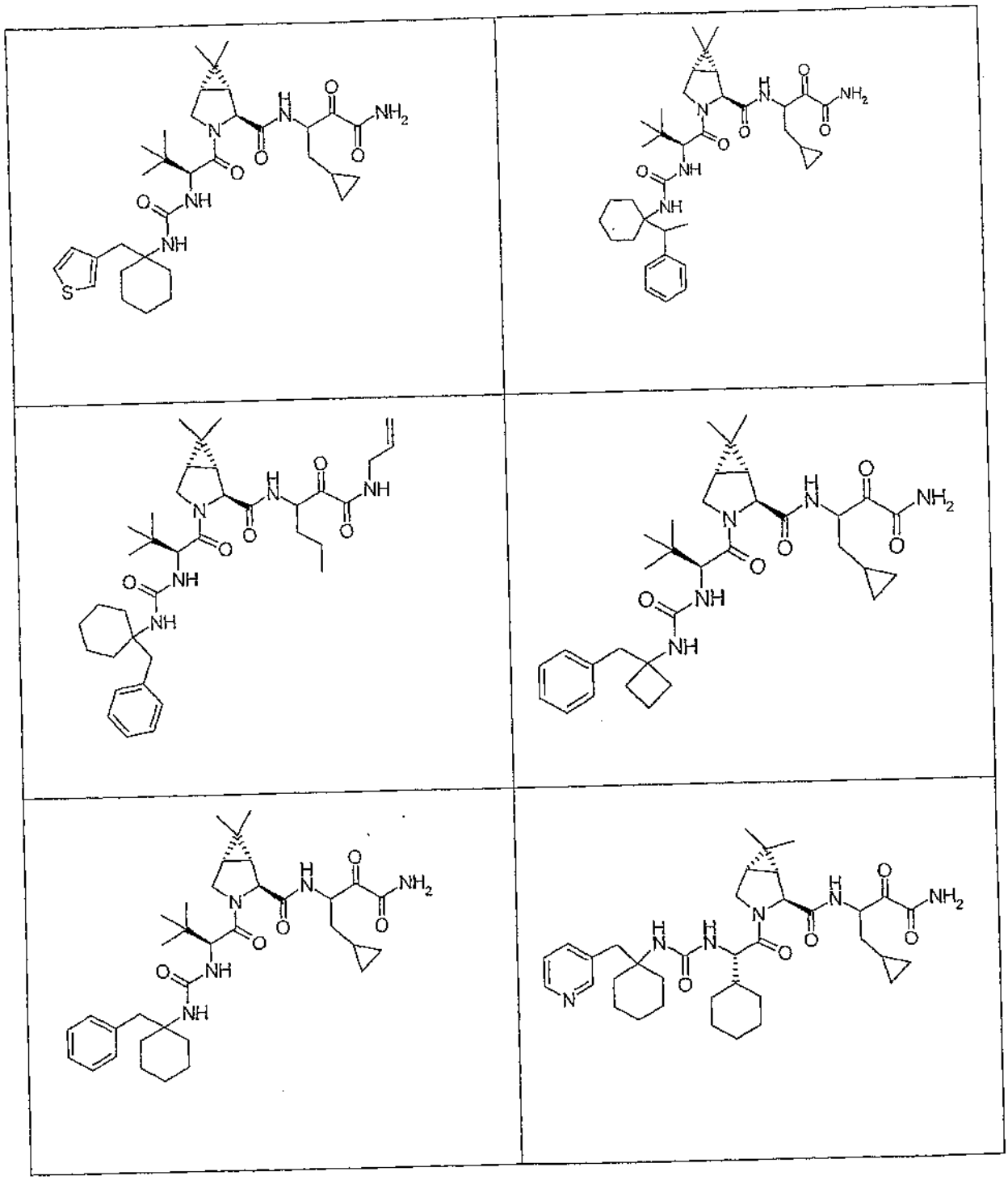


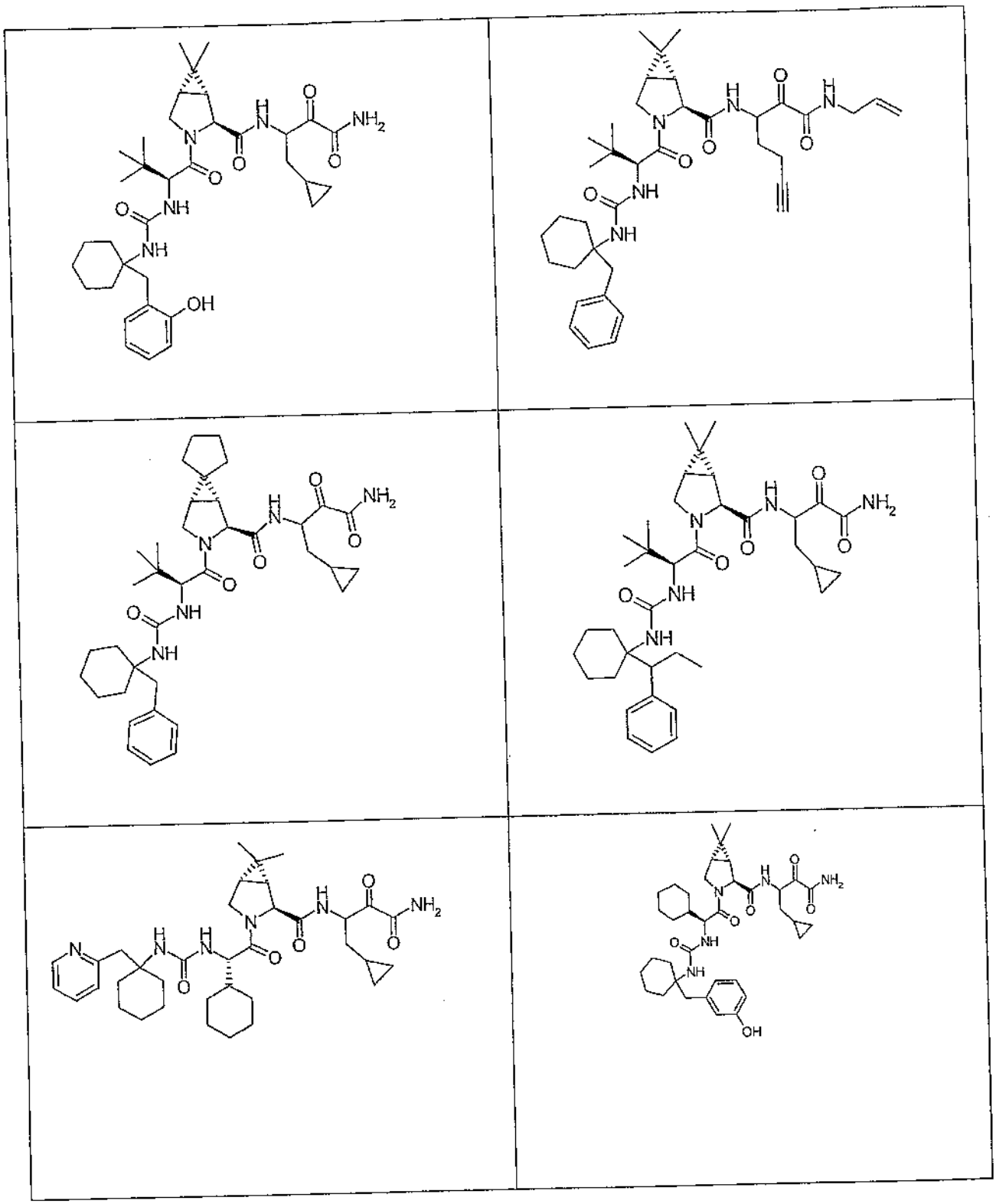


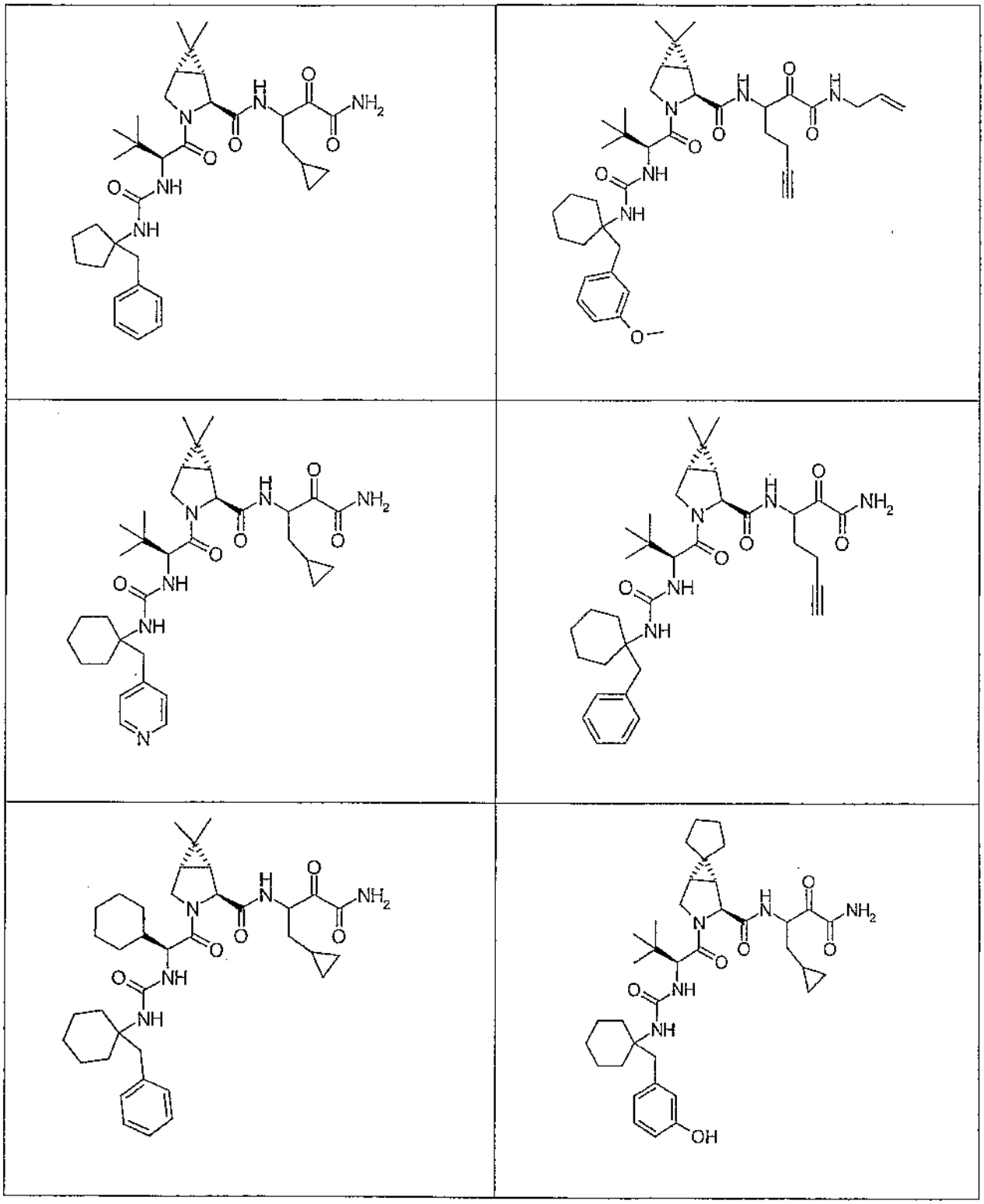


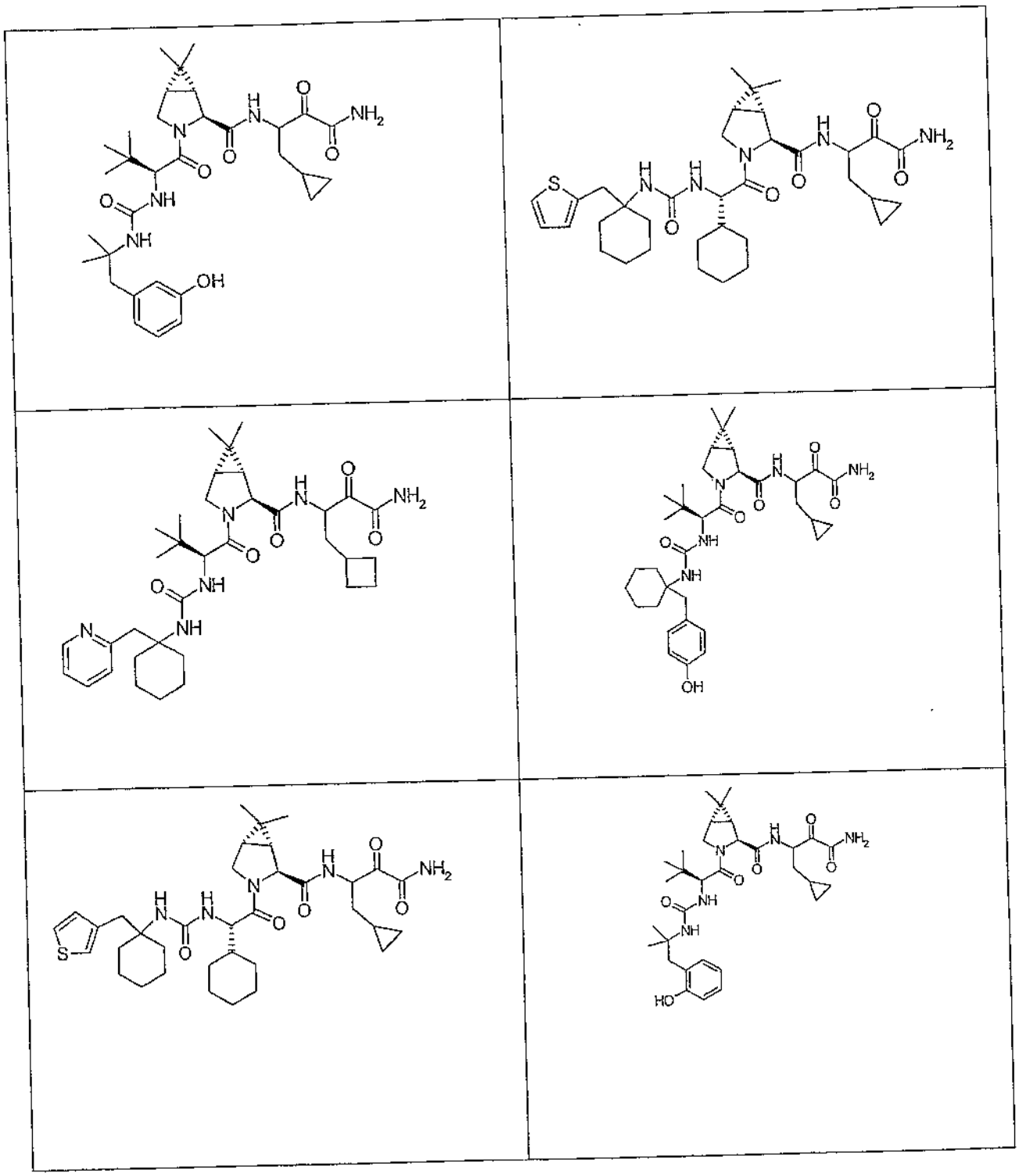


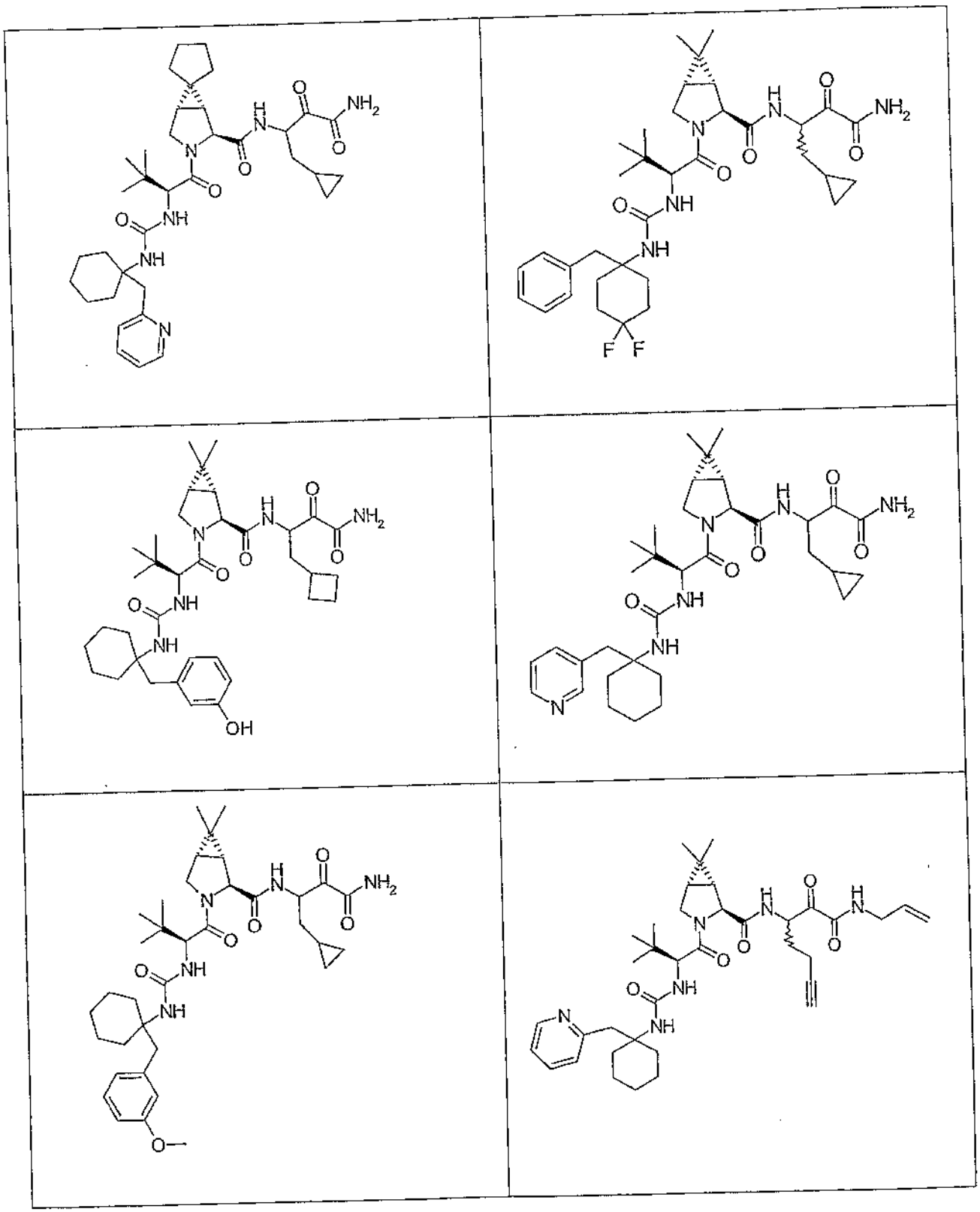


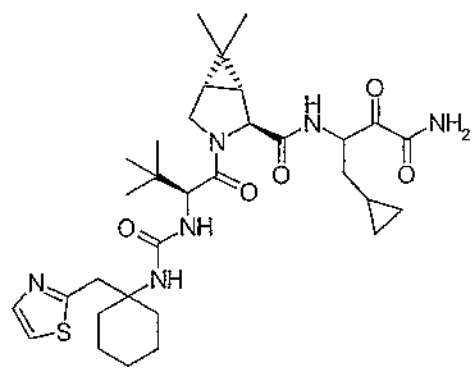
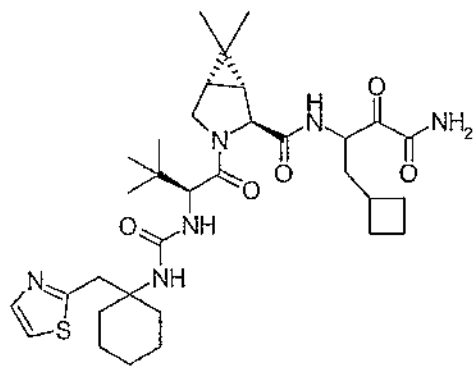
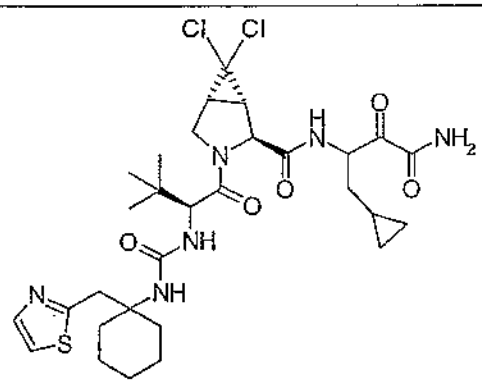
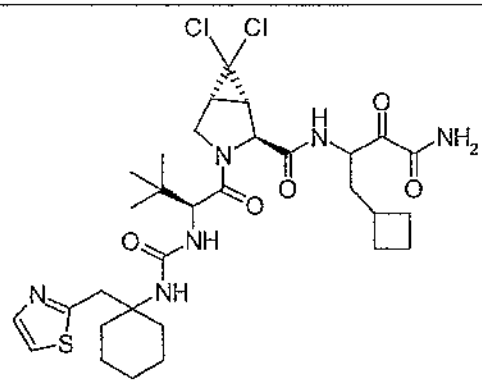


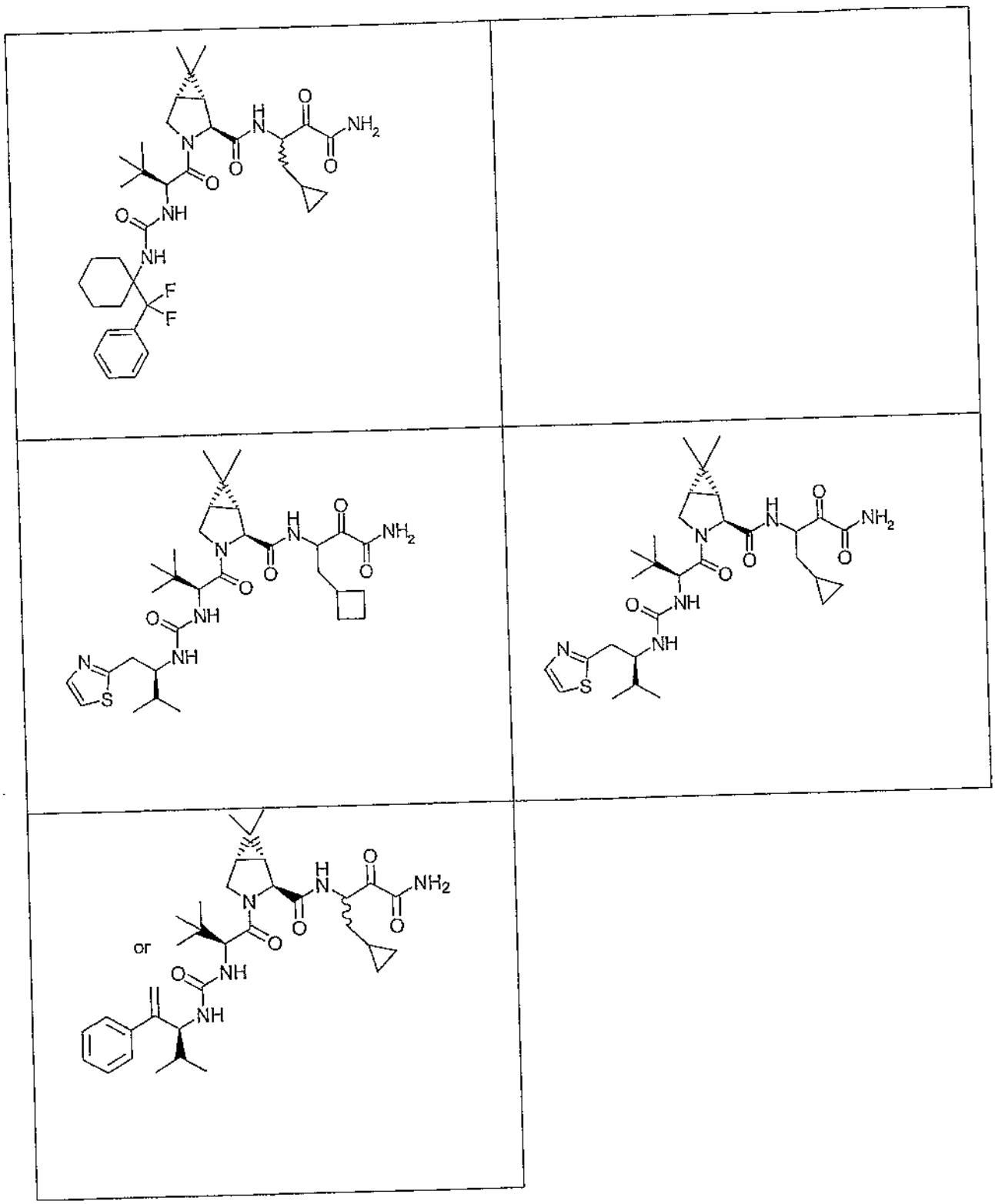








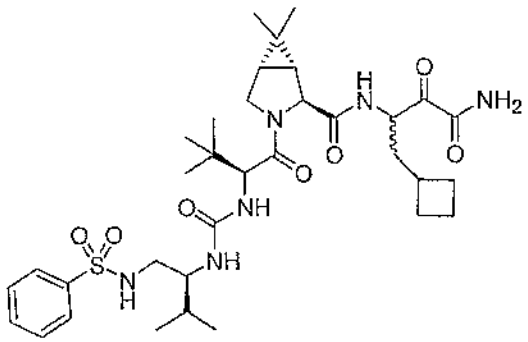


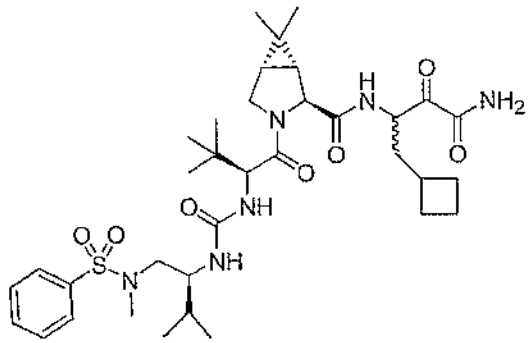
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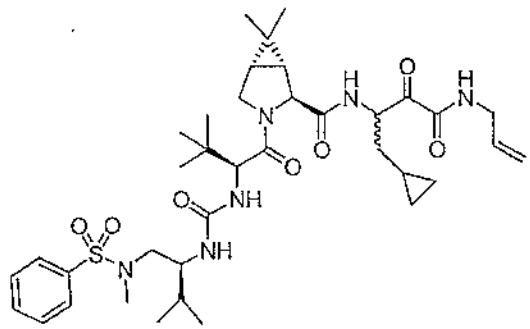
Compounds of formula XI are disclosed in U.S. Application Ser. No. 11/065,509 filed February 24, 2005. The preparation of these compounds is

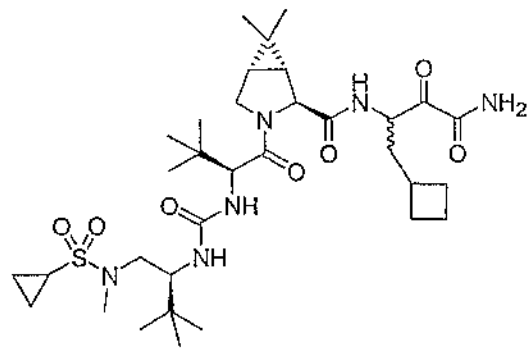
disclosed in the experimental section of this application set forth hereinbelow.

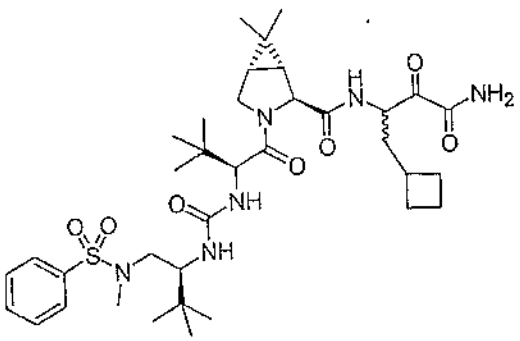
Non-limiting examples of certain compounds disclosed in U.S. Application Ser. No. 11/065,509 are:

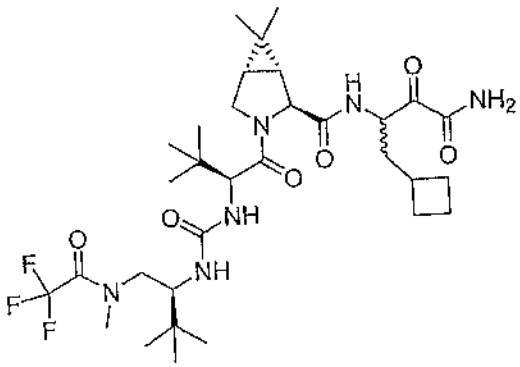


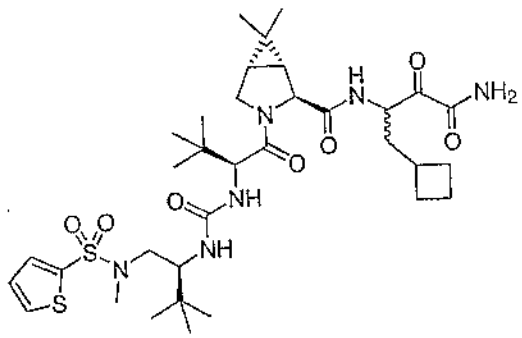


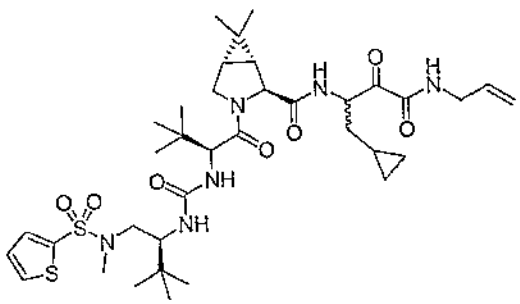


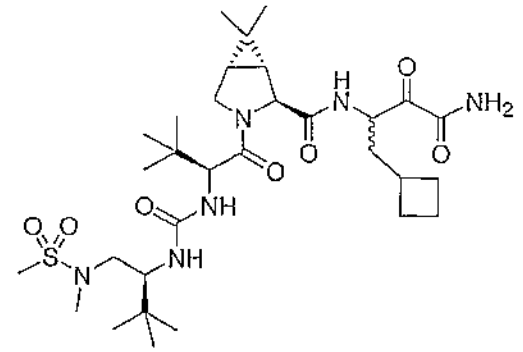


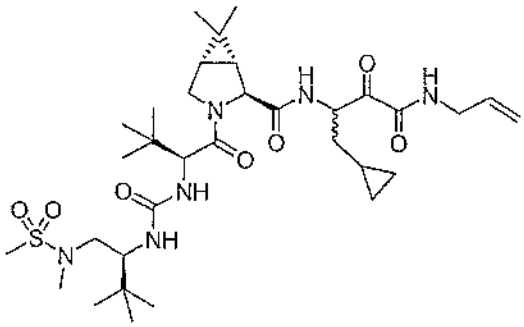


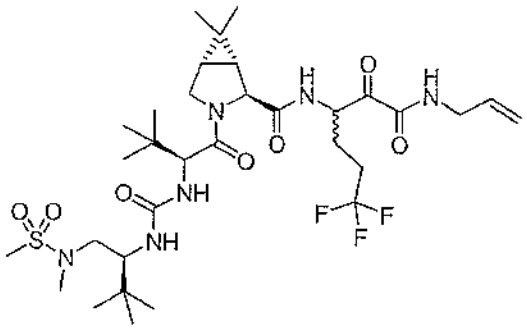


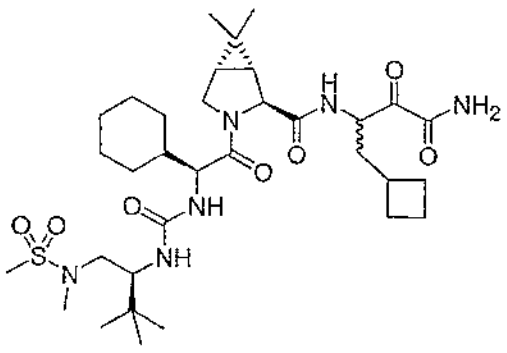


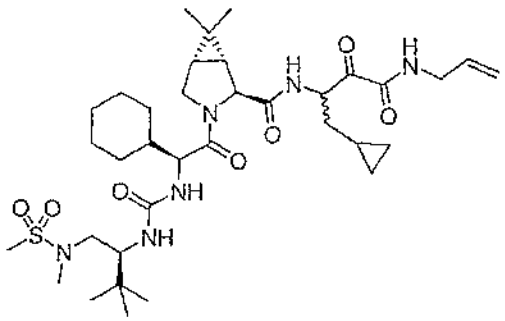


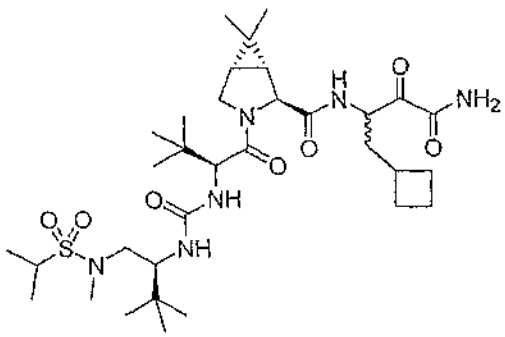


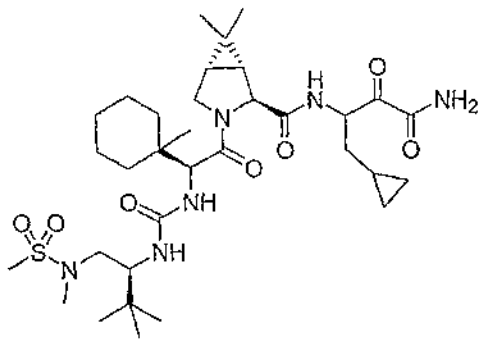


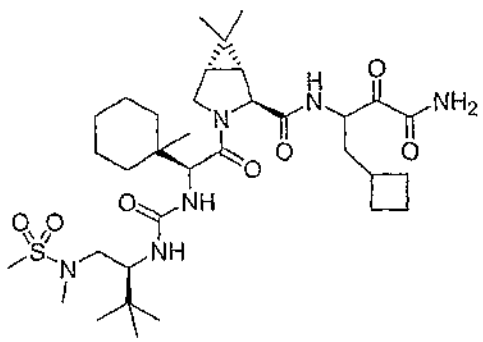


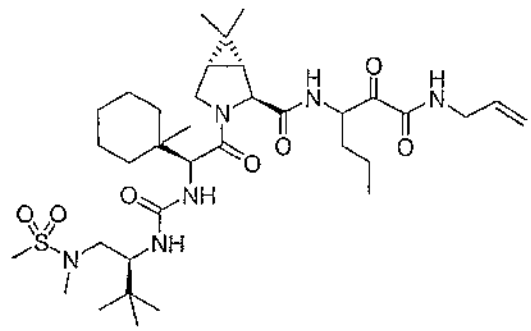


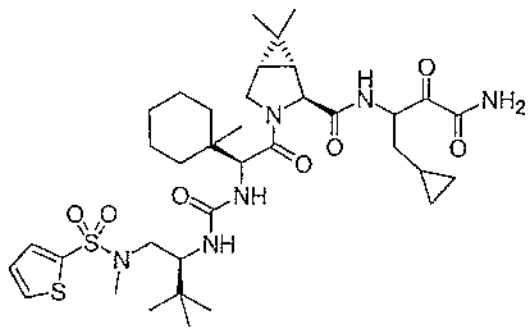


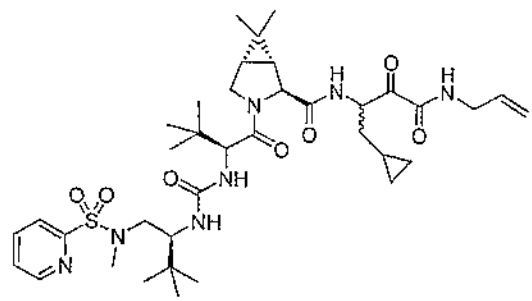


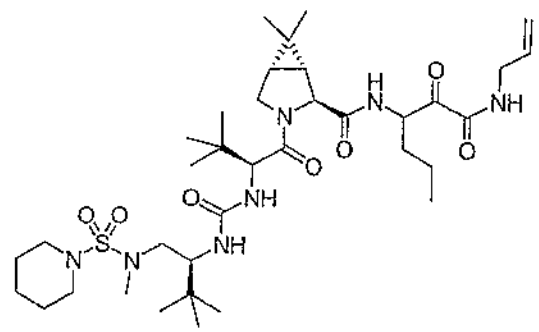


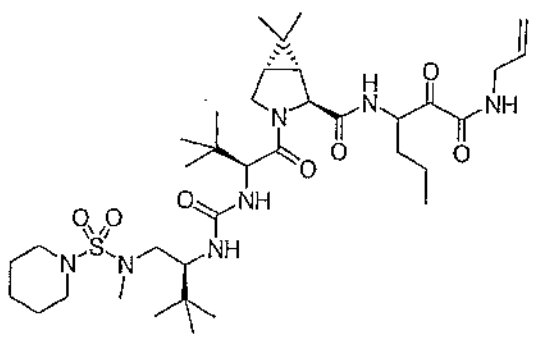




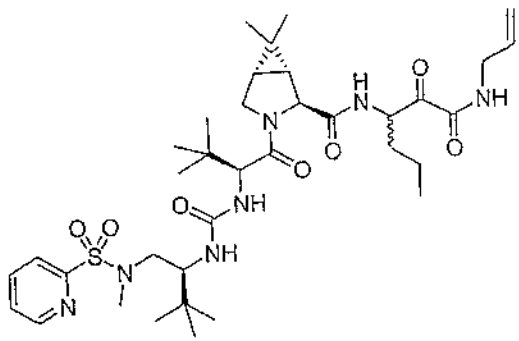


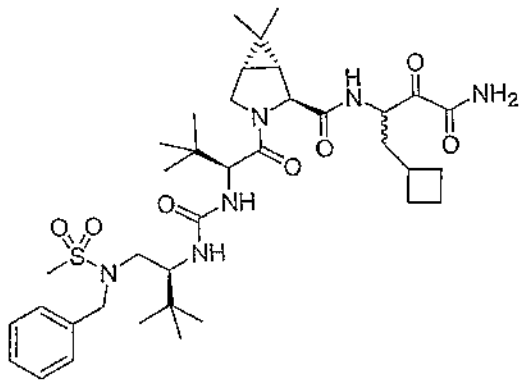


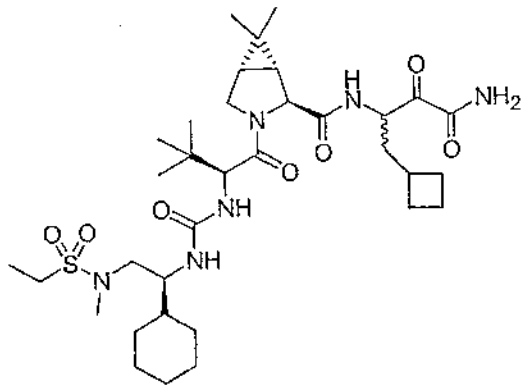


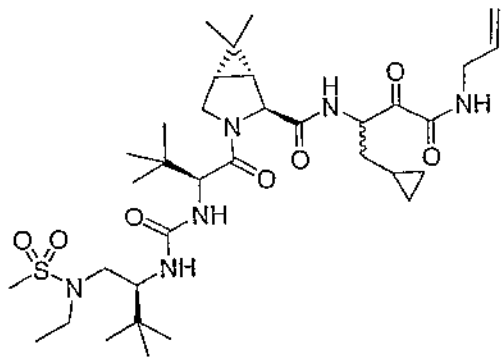


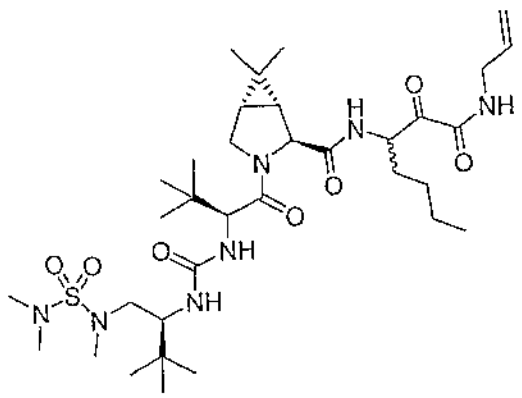
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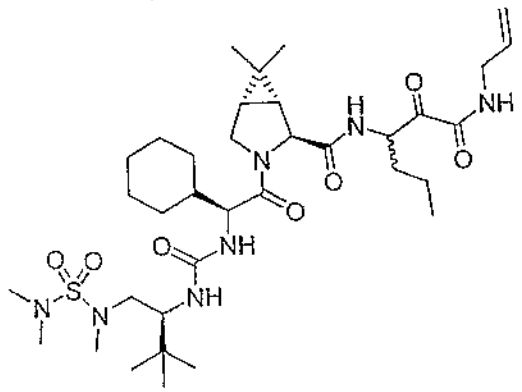


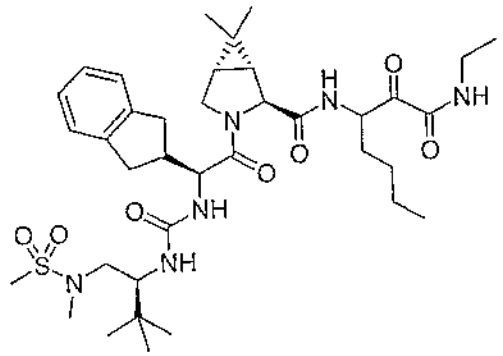


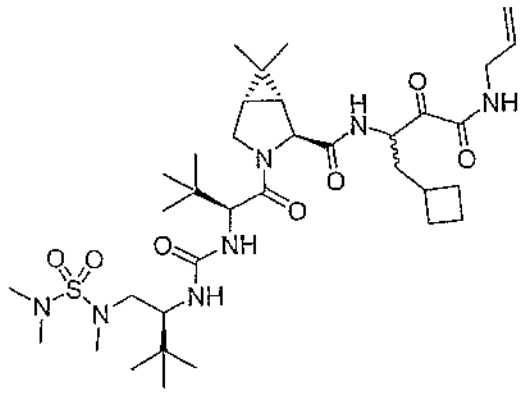


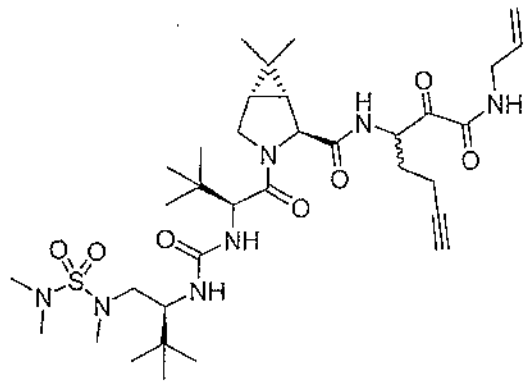


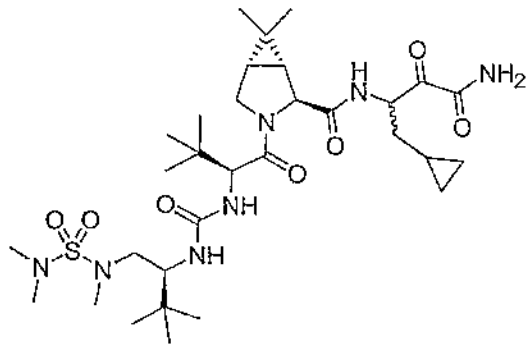


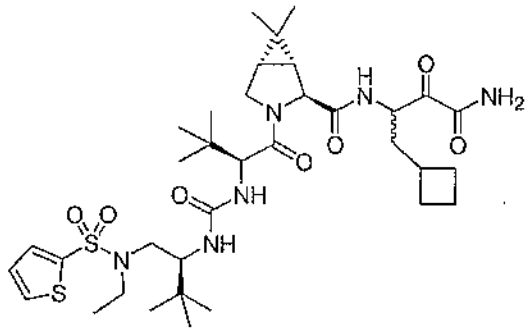


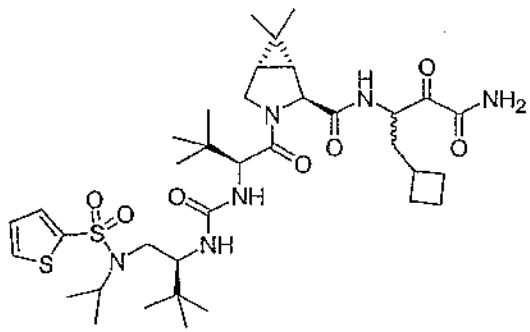


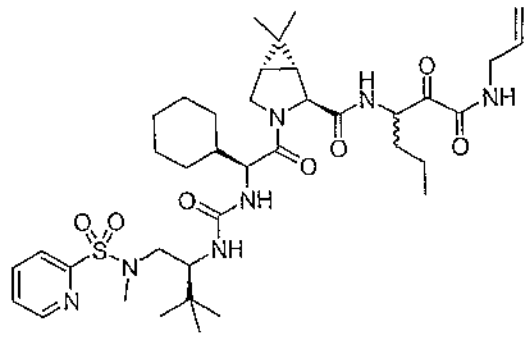


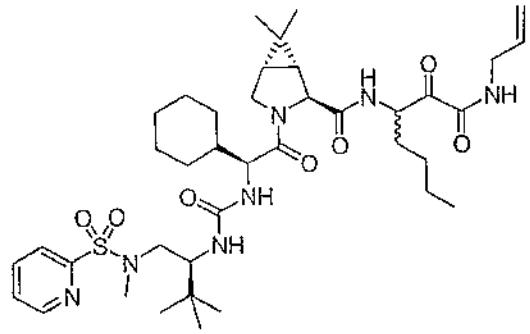


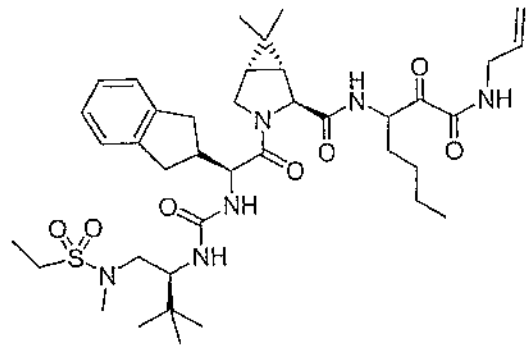


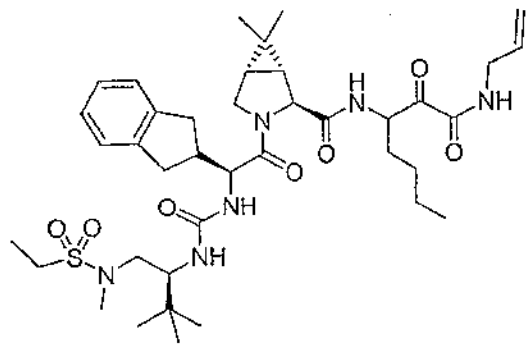


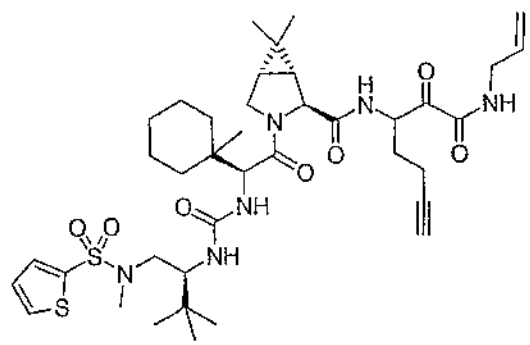




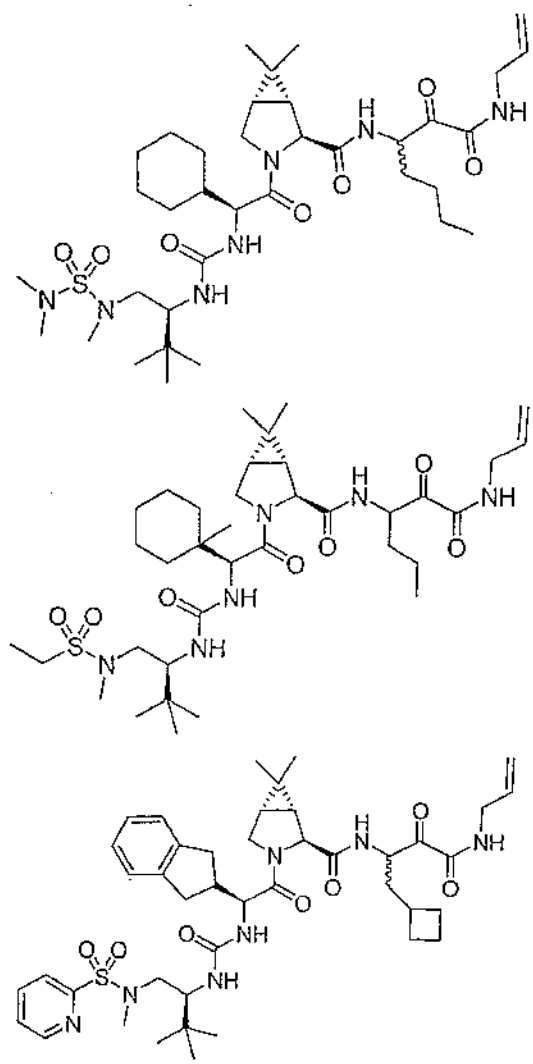


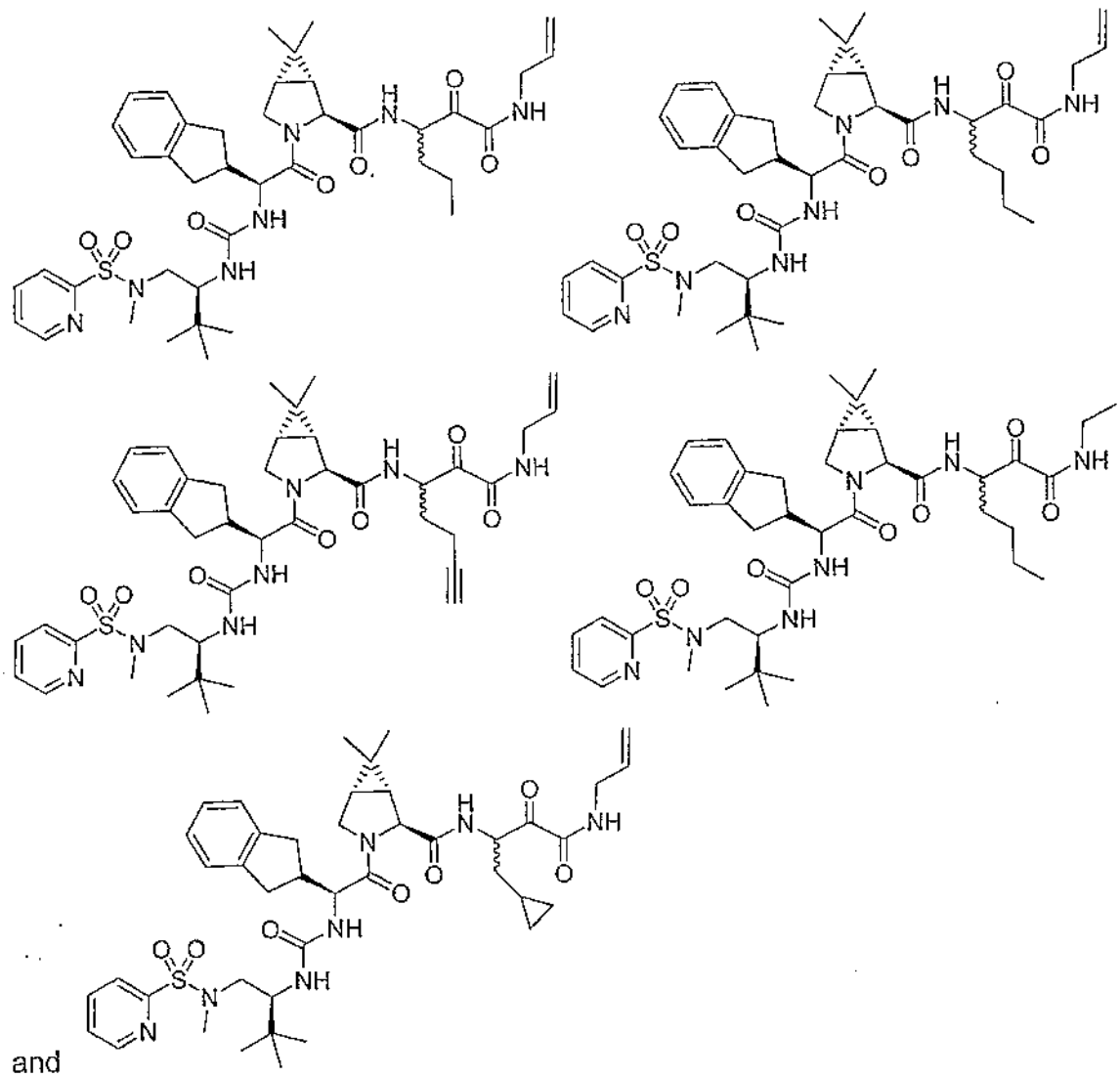






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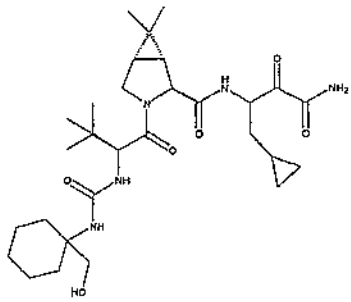


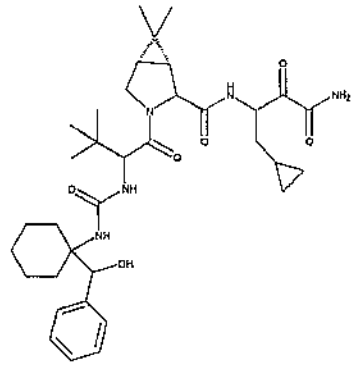
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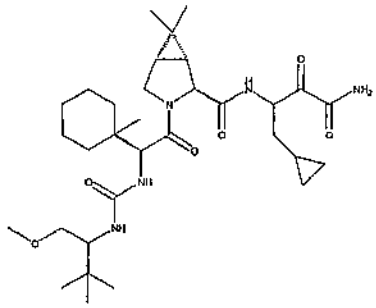
or a pharmaceutically acceptable salt, solvate or ester thereof.

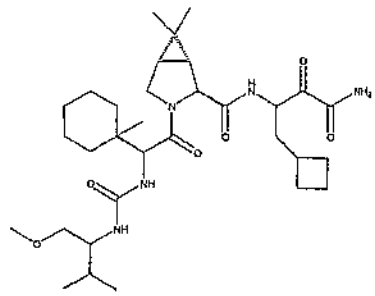
Compounds of formula XII are disclosed in U.S. Patent Application Ser. No. 11/065,531 filed February 24, 2005. The preparation of these compounds is disclosed in the experimental section of this application set forth hereinbelow.

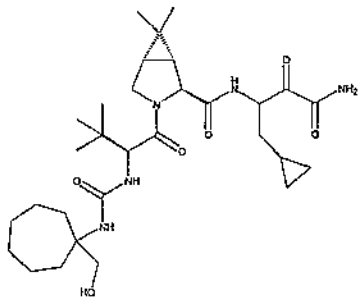
Non-limiting examples of certain compounds disclosed in U.S. Patent Application Ser. No. 11/065,531 are:

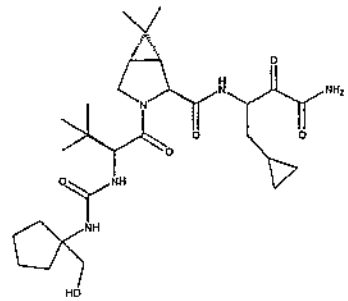


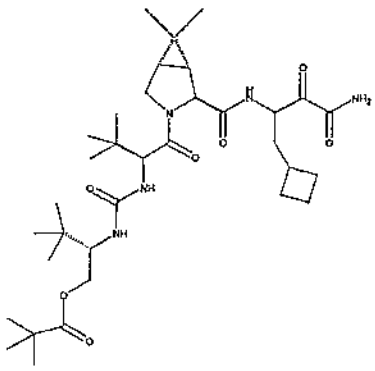


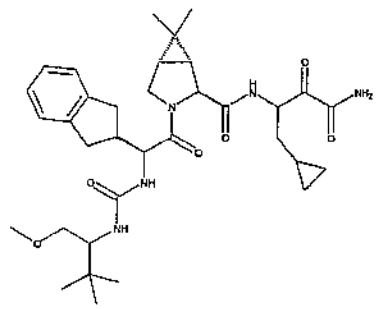


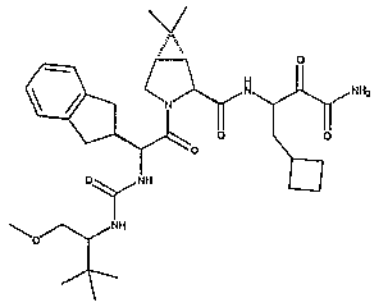


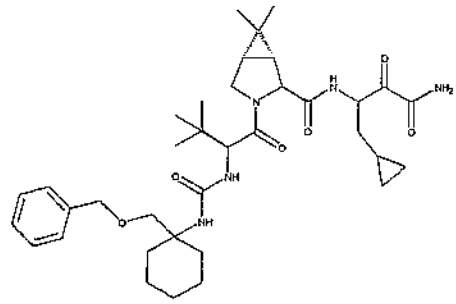


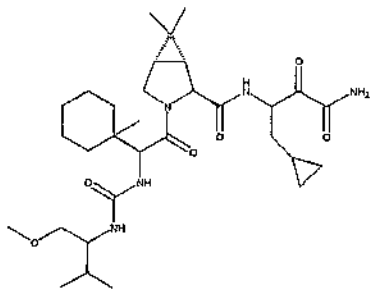


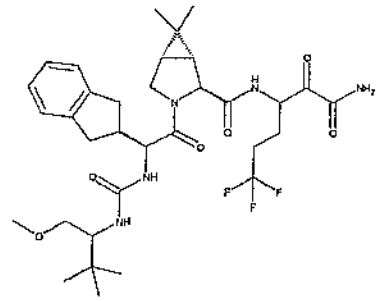


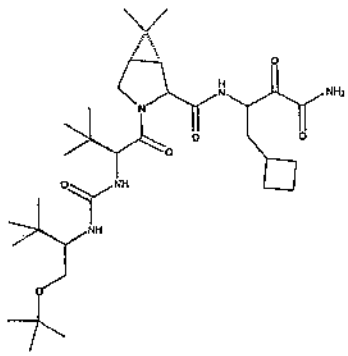


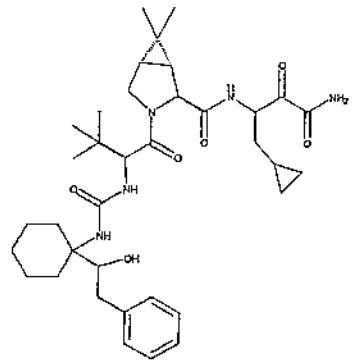


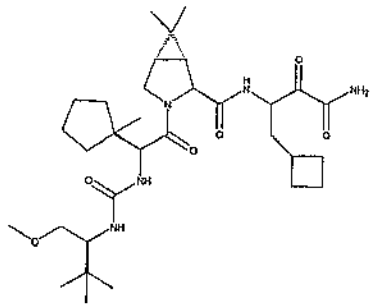


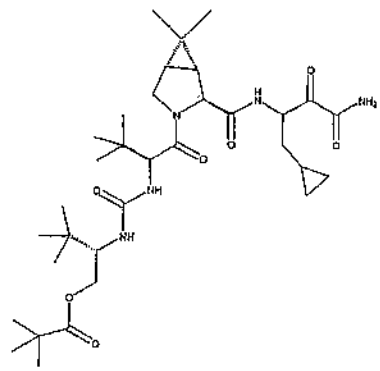


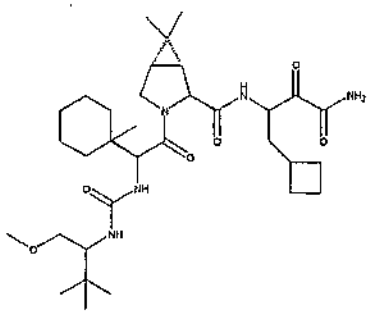


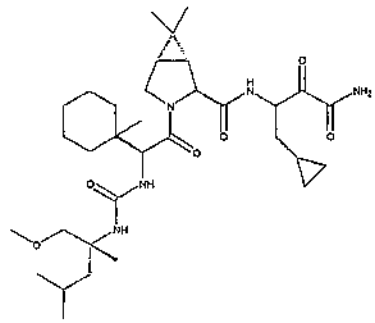


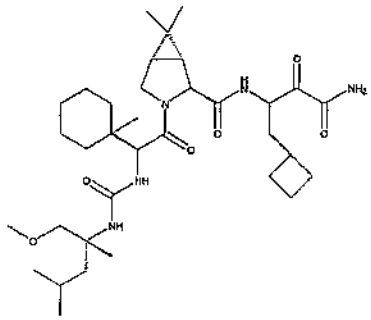


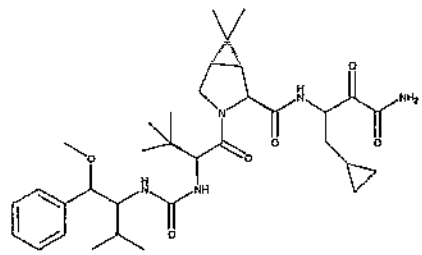


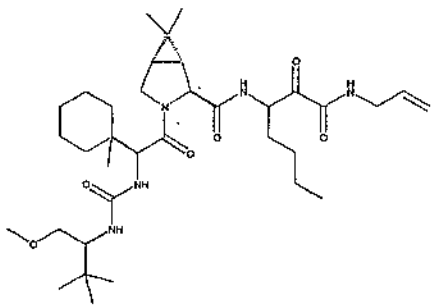


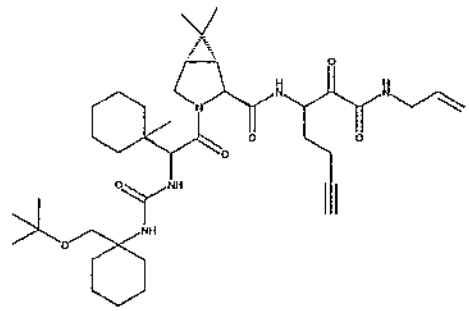


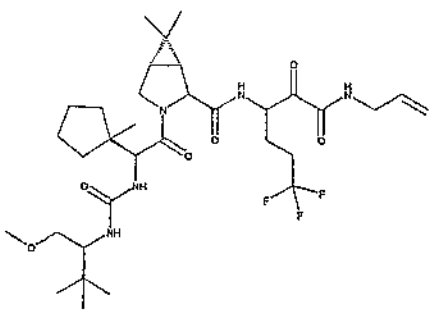


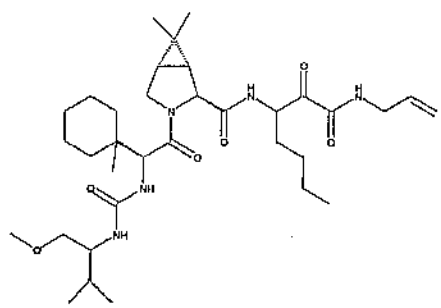


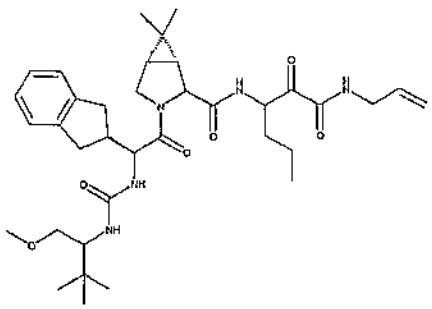


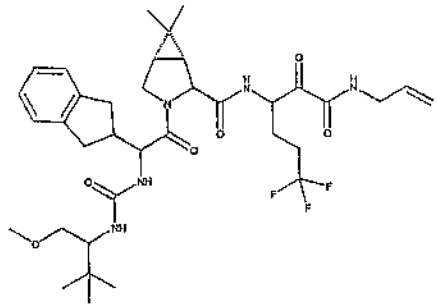


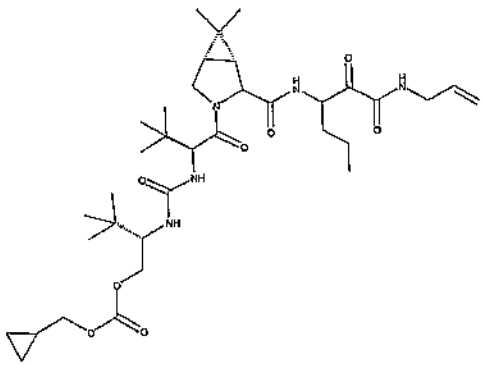


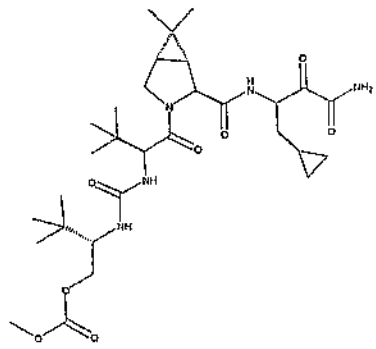


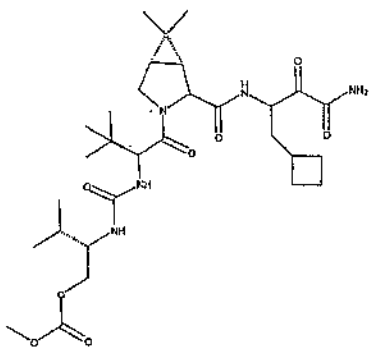


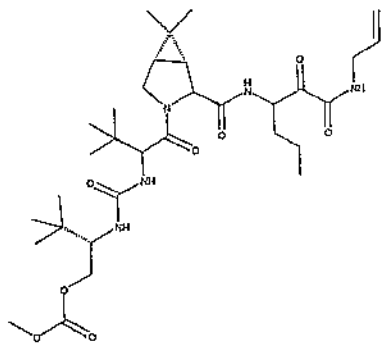


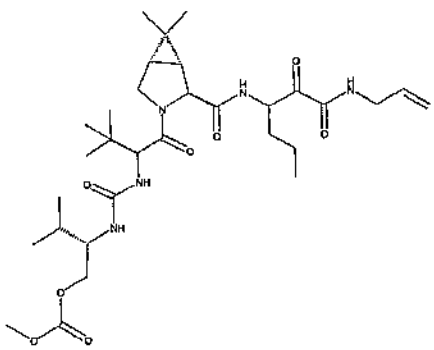


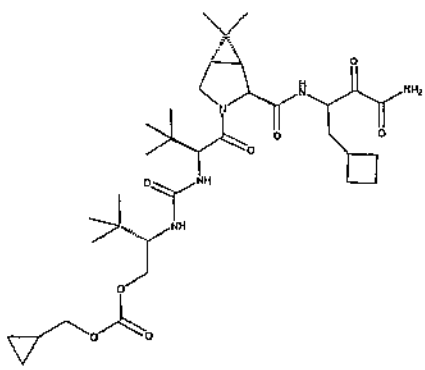


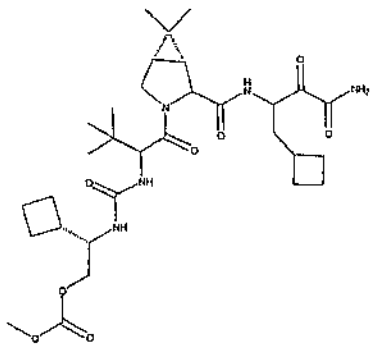


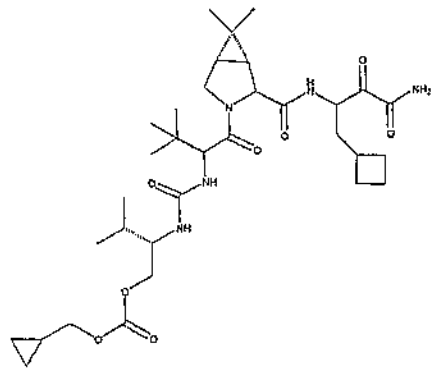


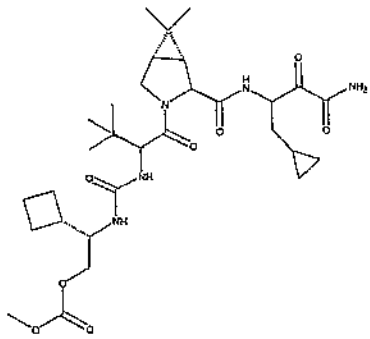


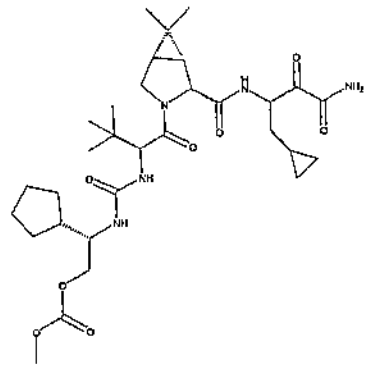


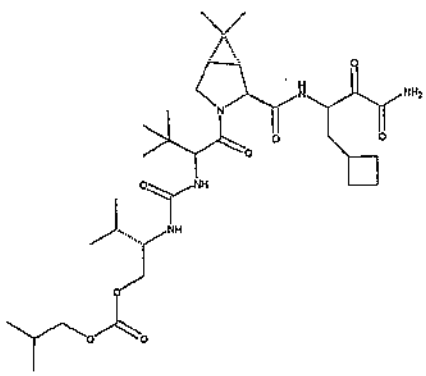


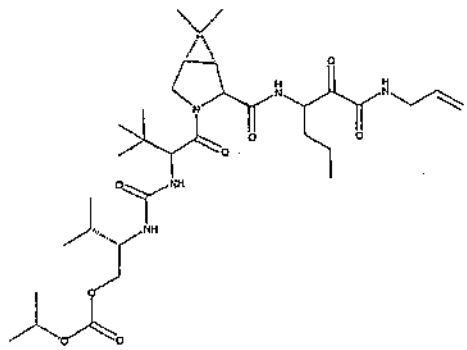


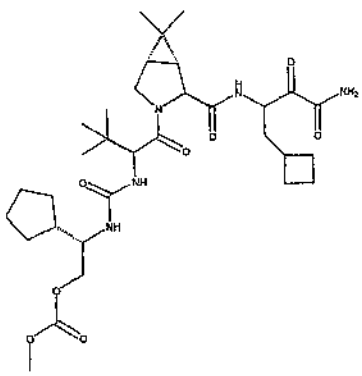


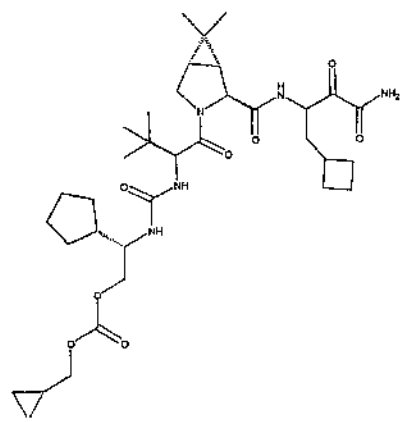


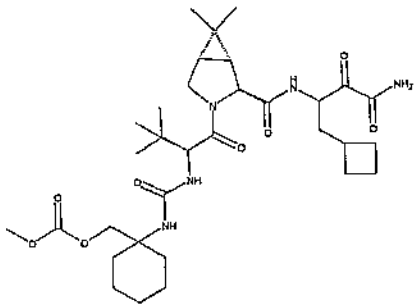


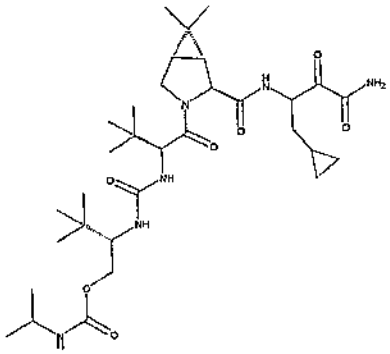


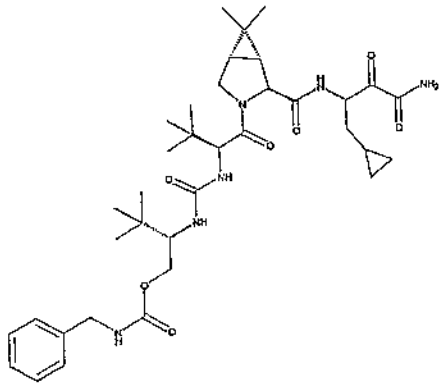


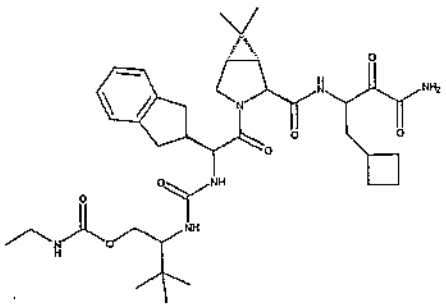


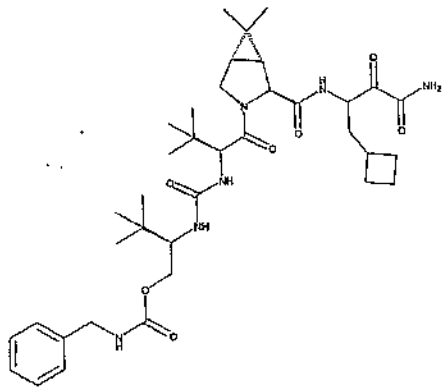


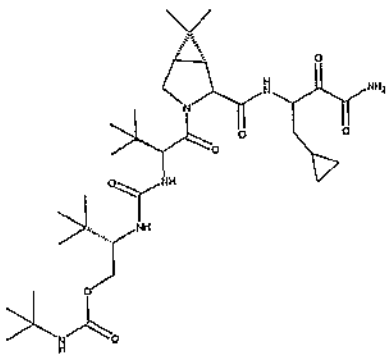


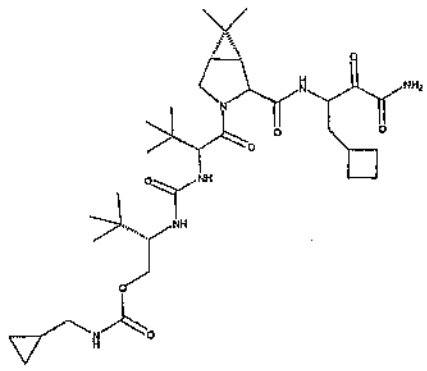


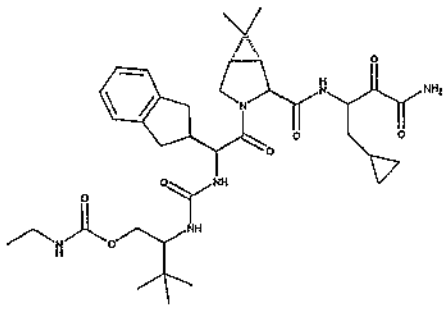


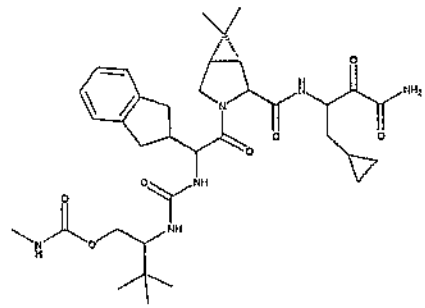


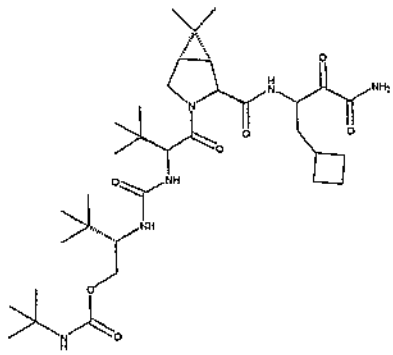


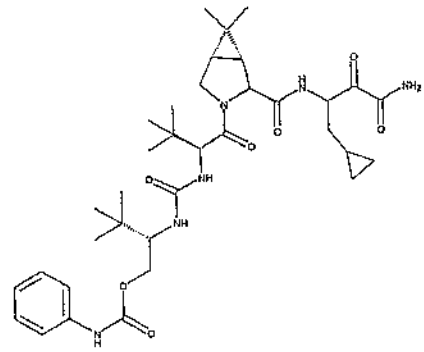


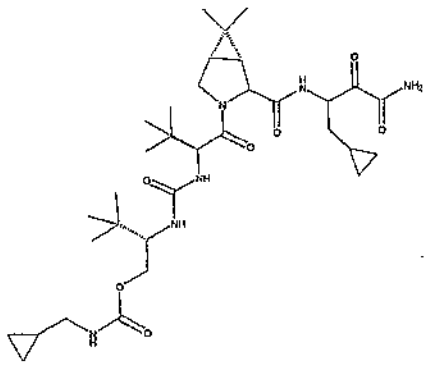


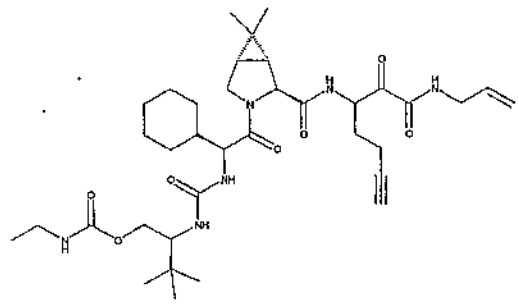


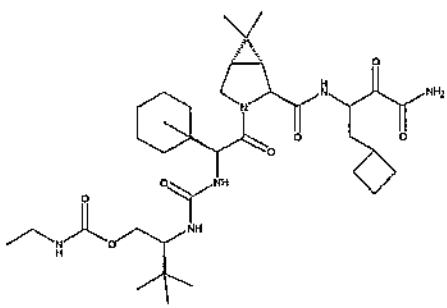


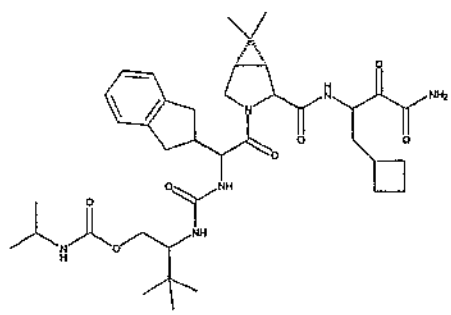


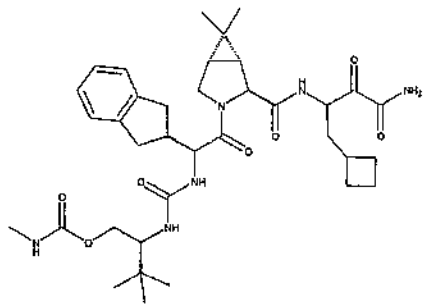


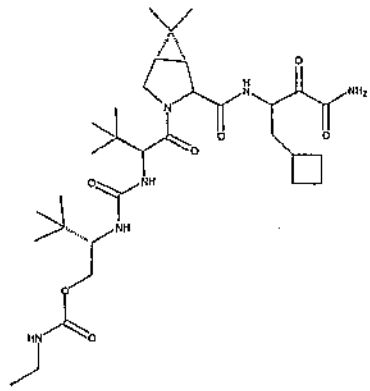


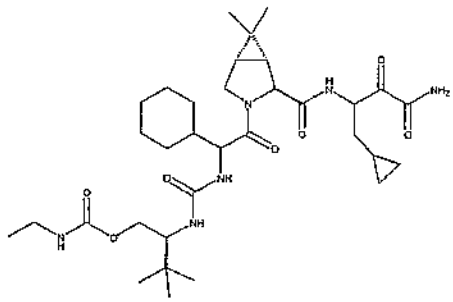


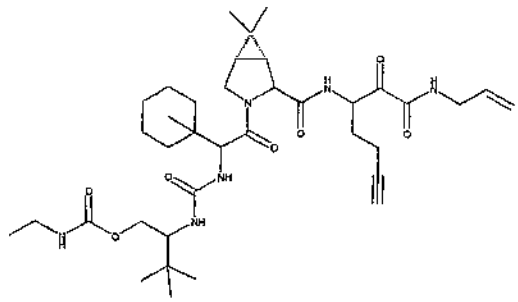


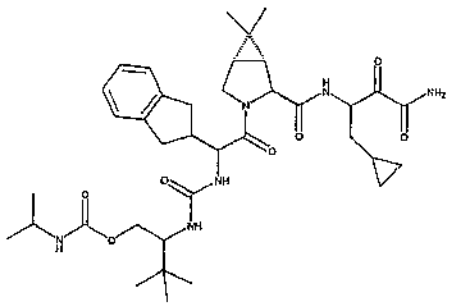


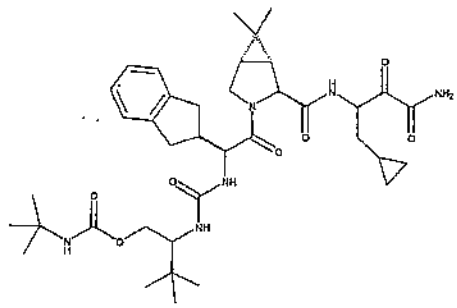


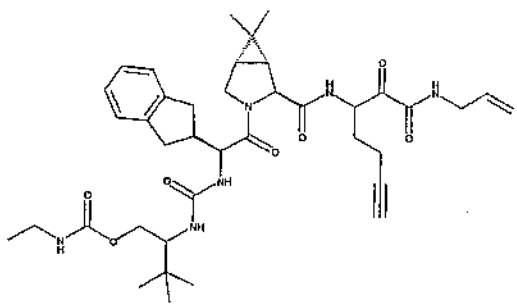


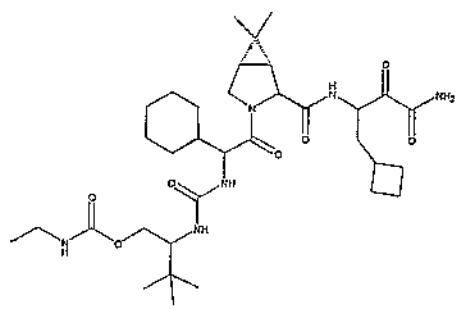


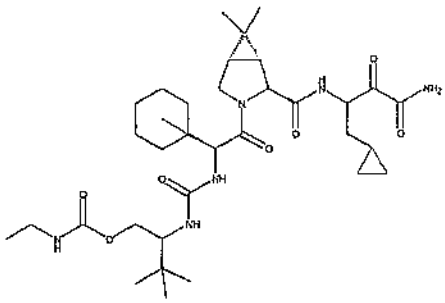


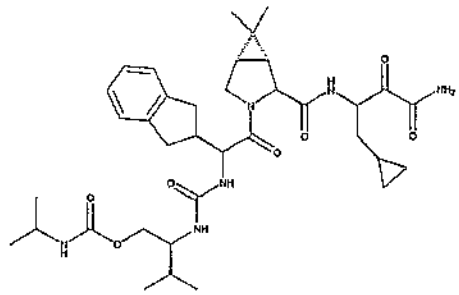


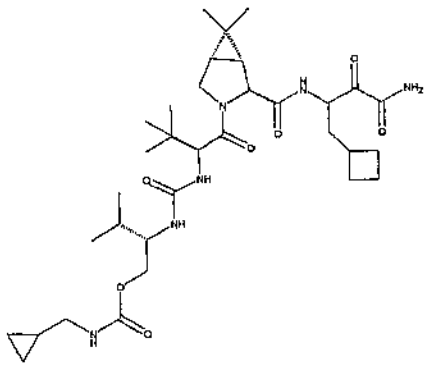


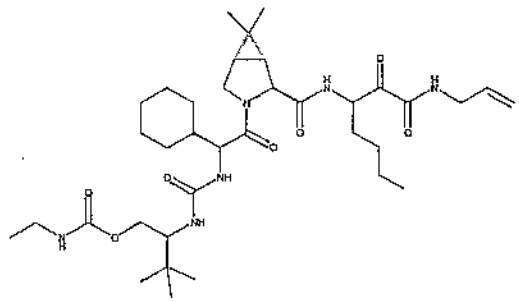


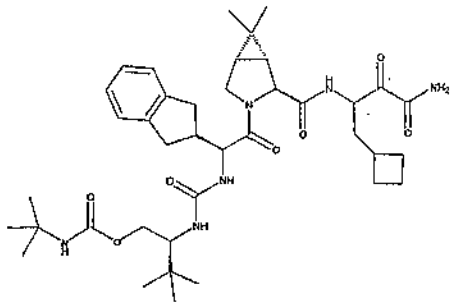


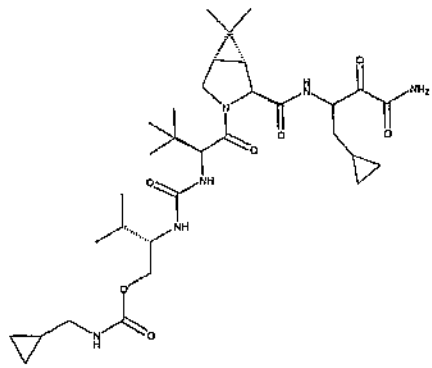


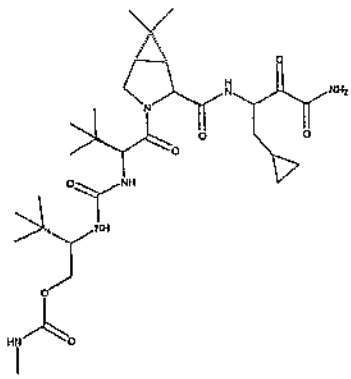


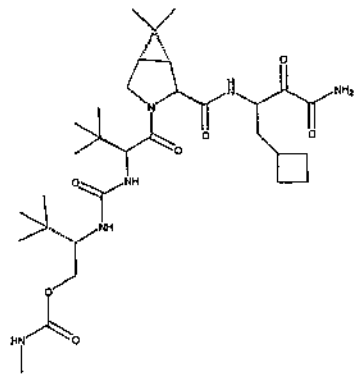


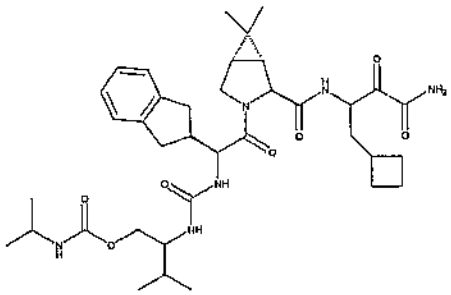


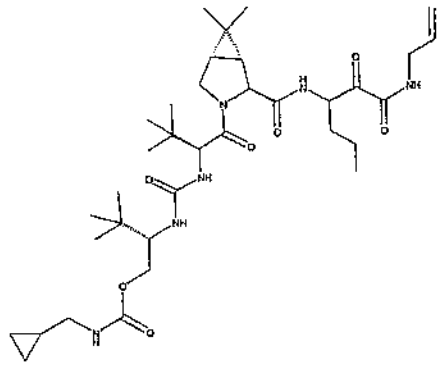


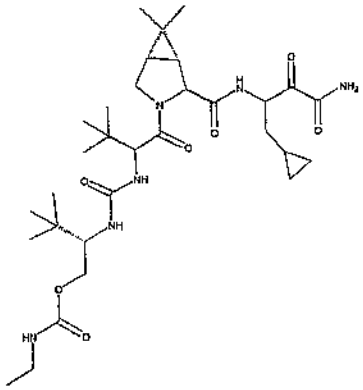


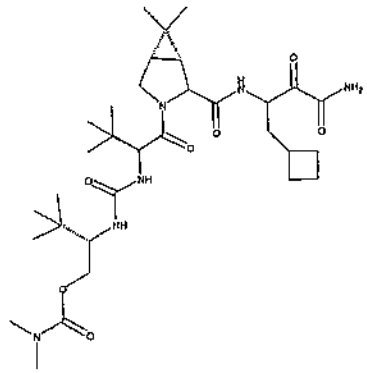


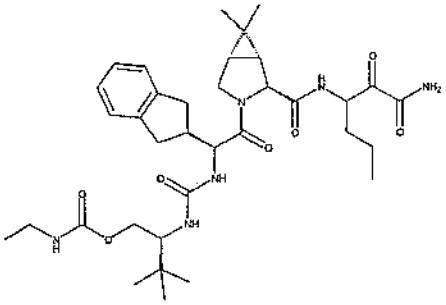


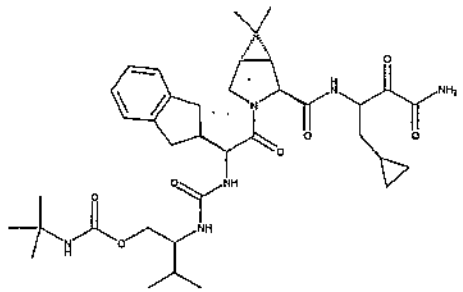


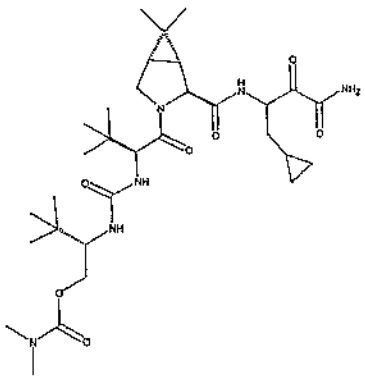


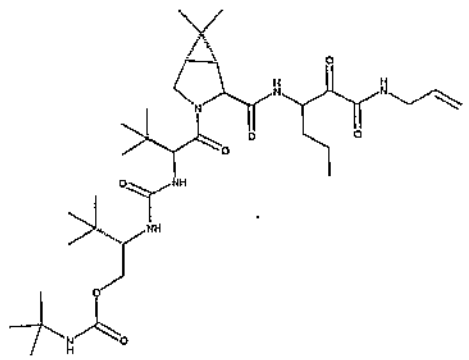


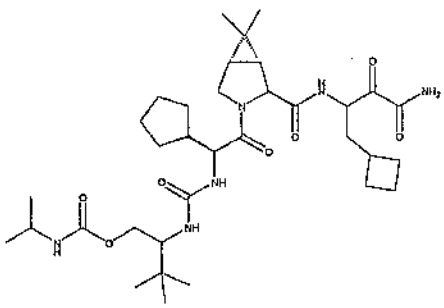


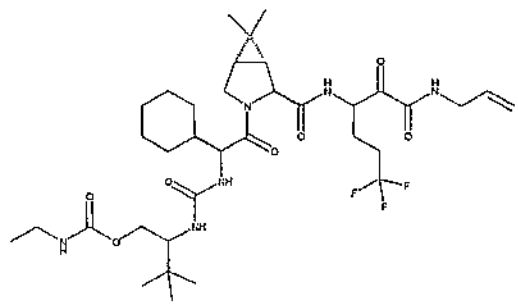


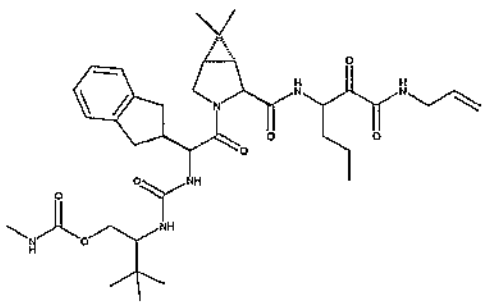


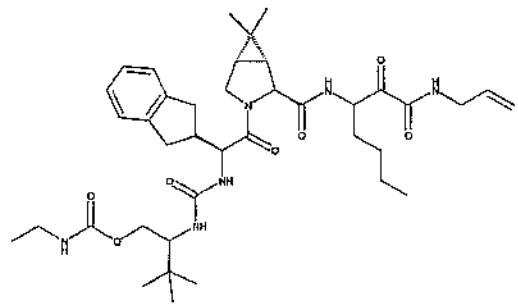


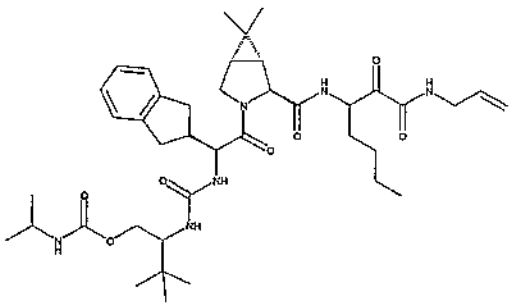


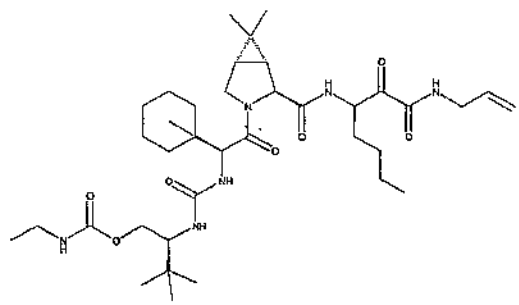


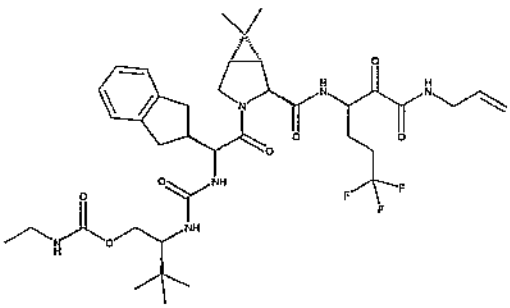


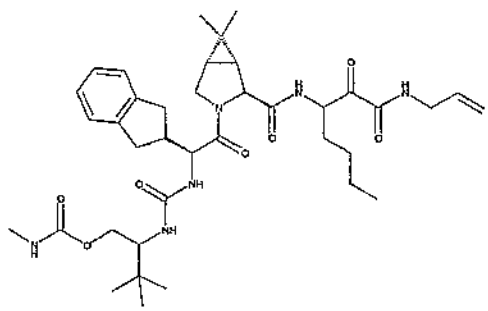


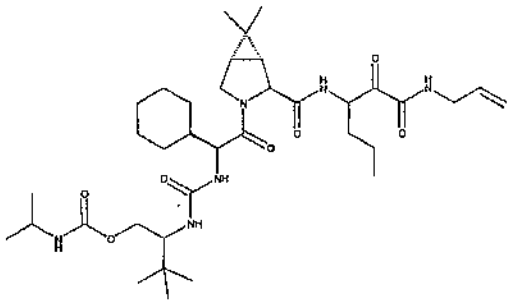


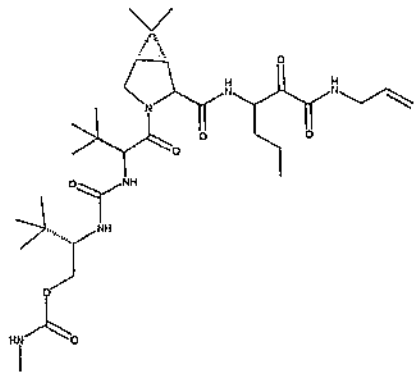


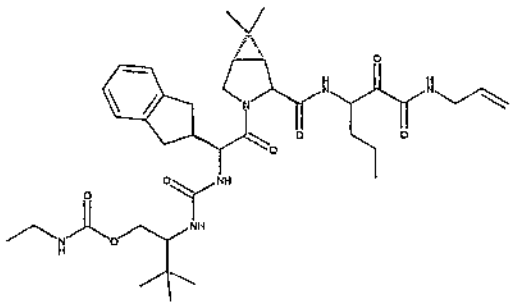


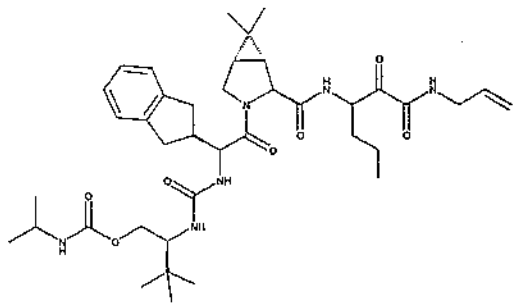


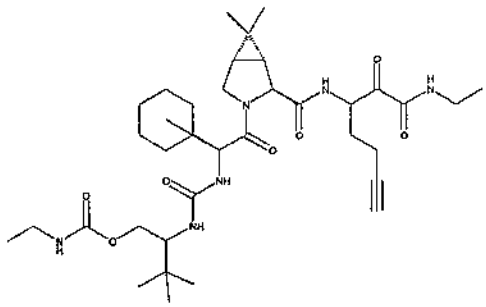


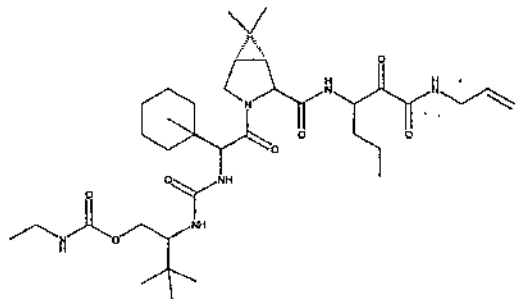


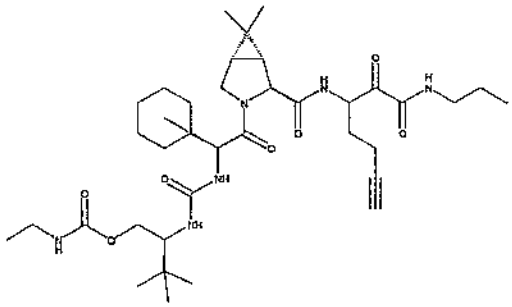


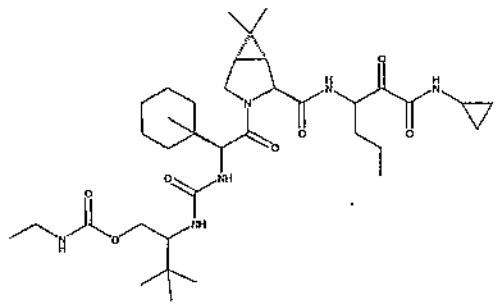


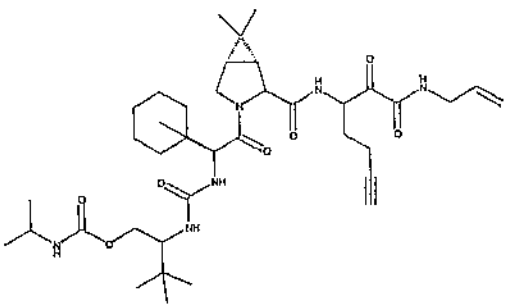


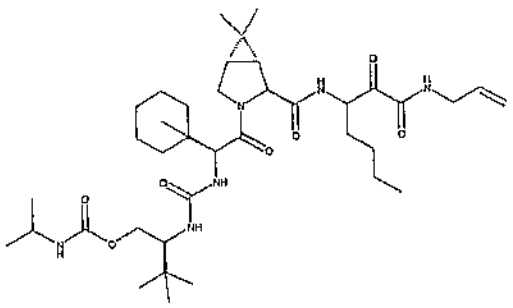


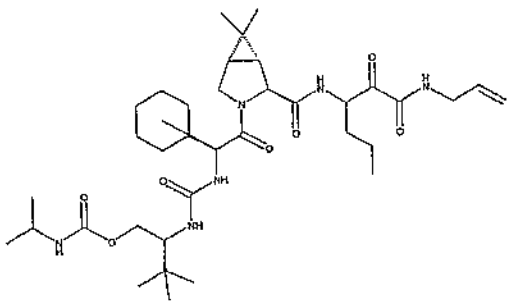


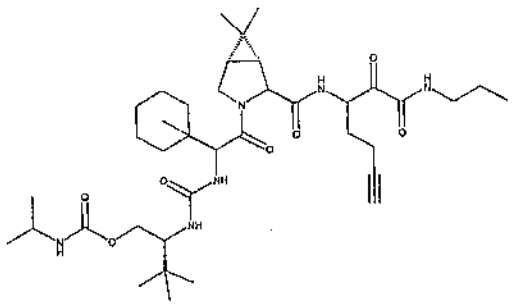


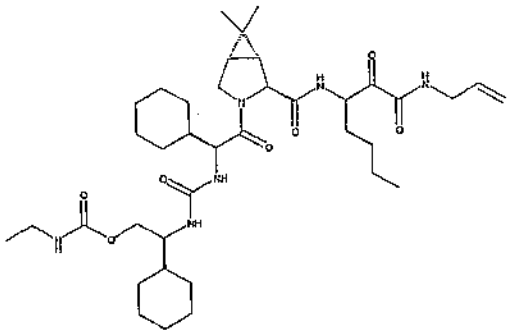


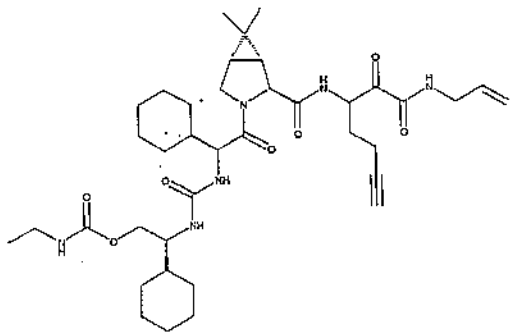


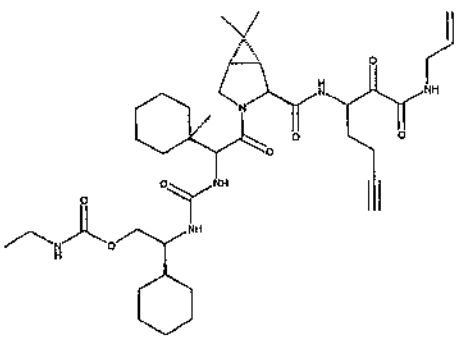


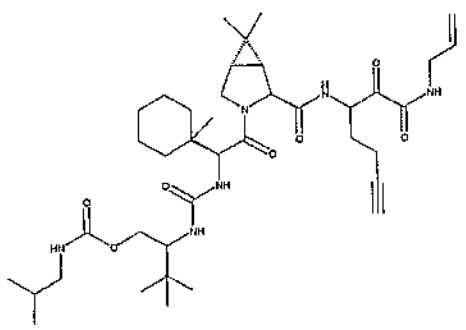


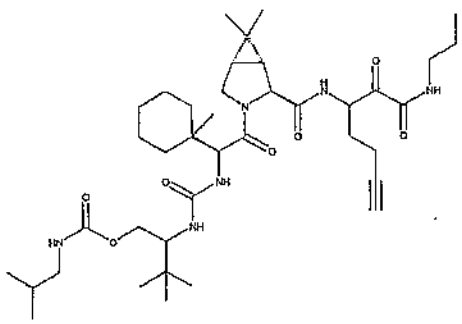
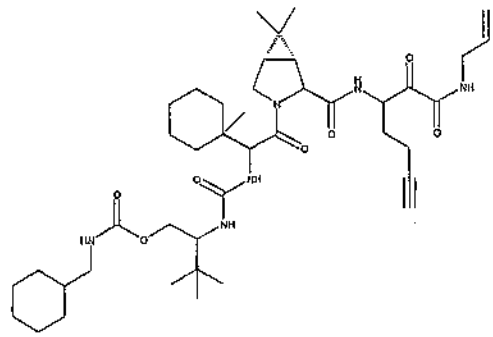
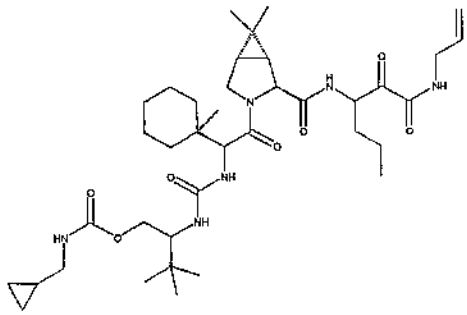
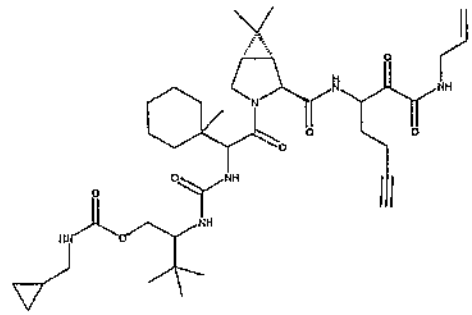
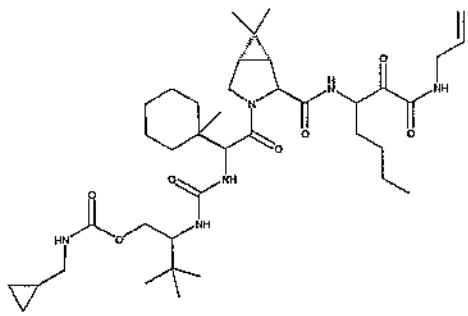
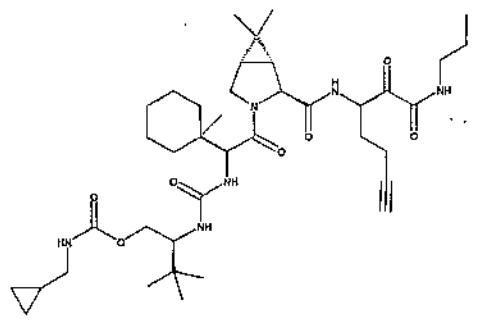
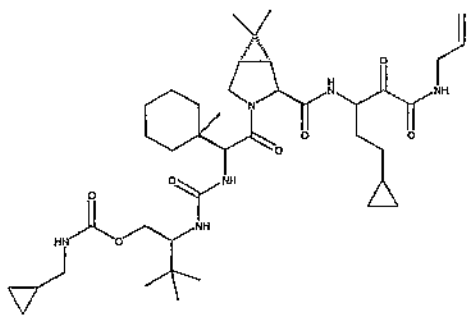
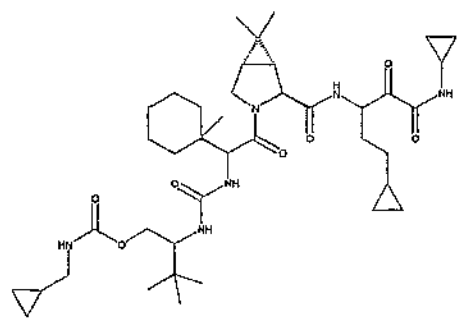








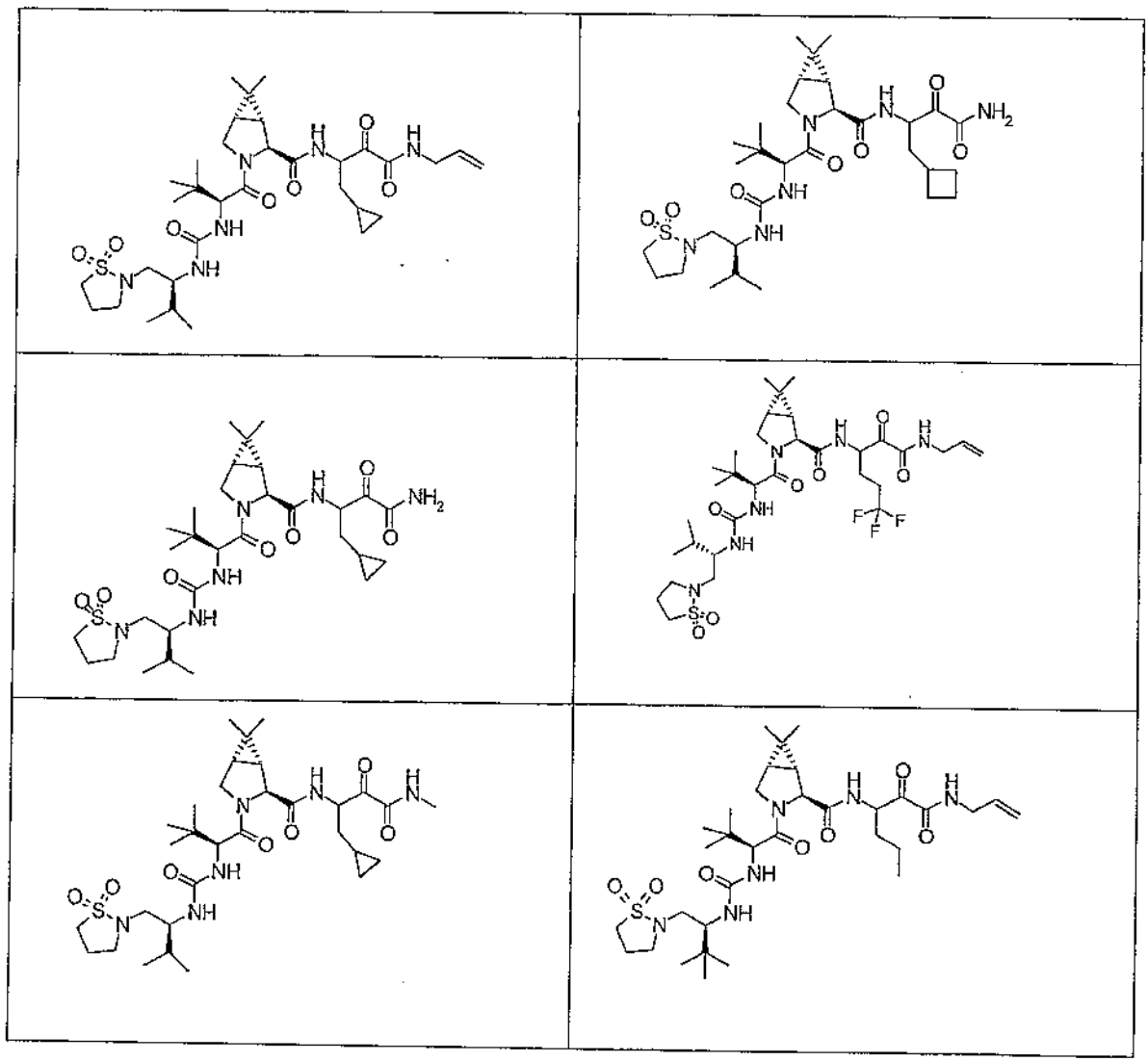


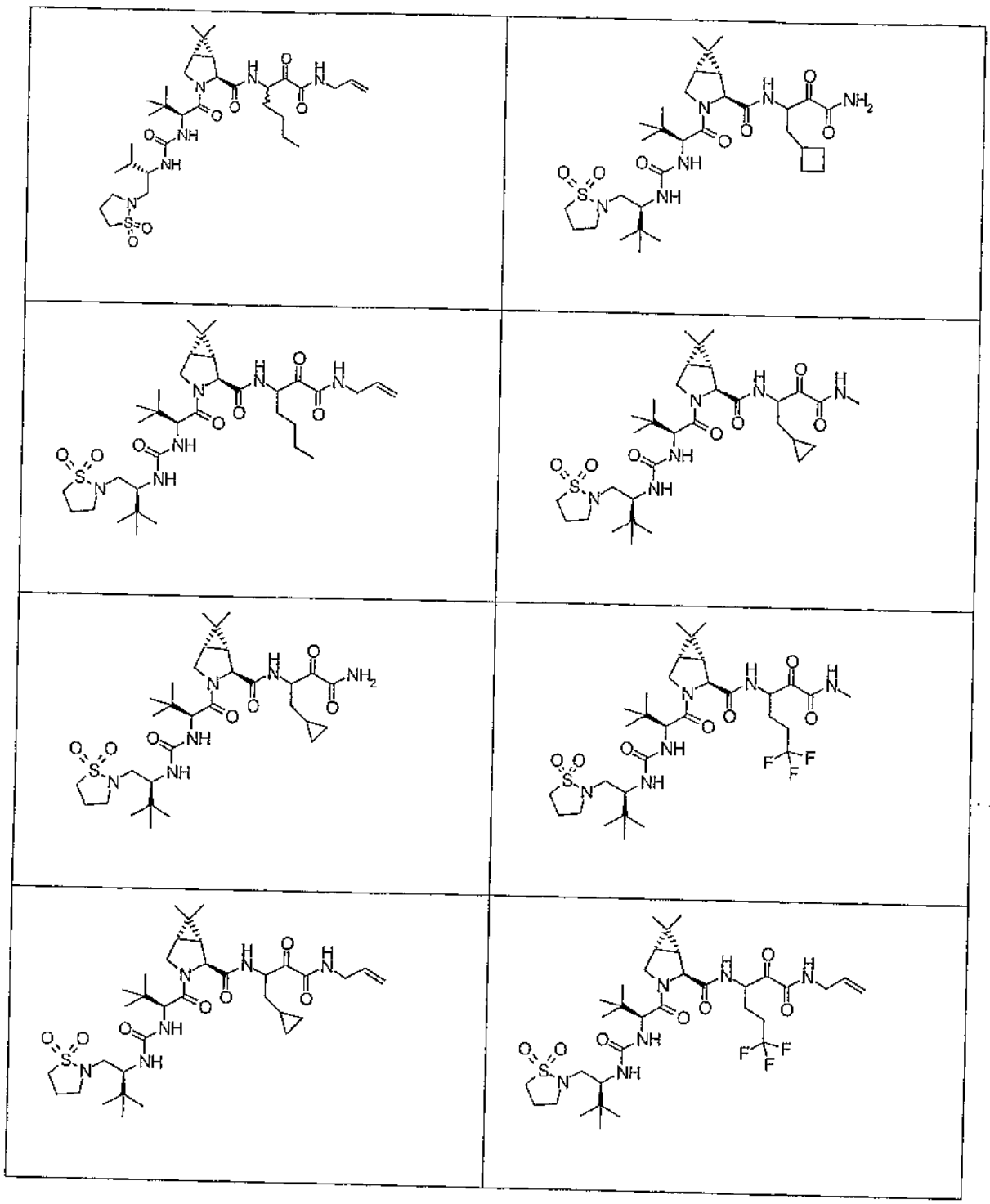









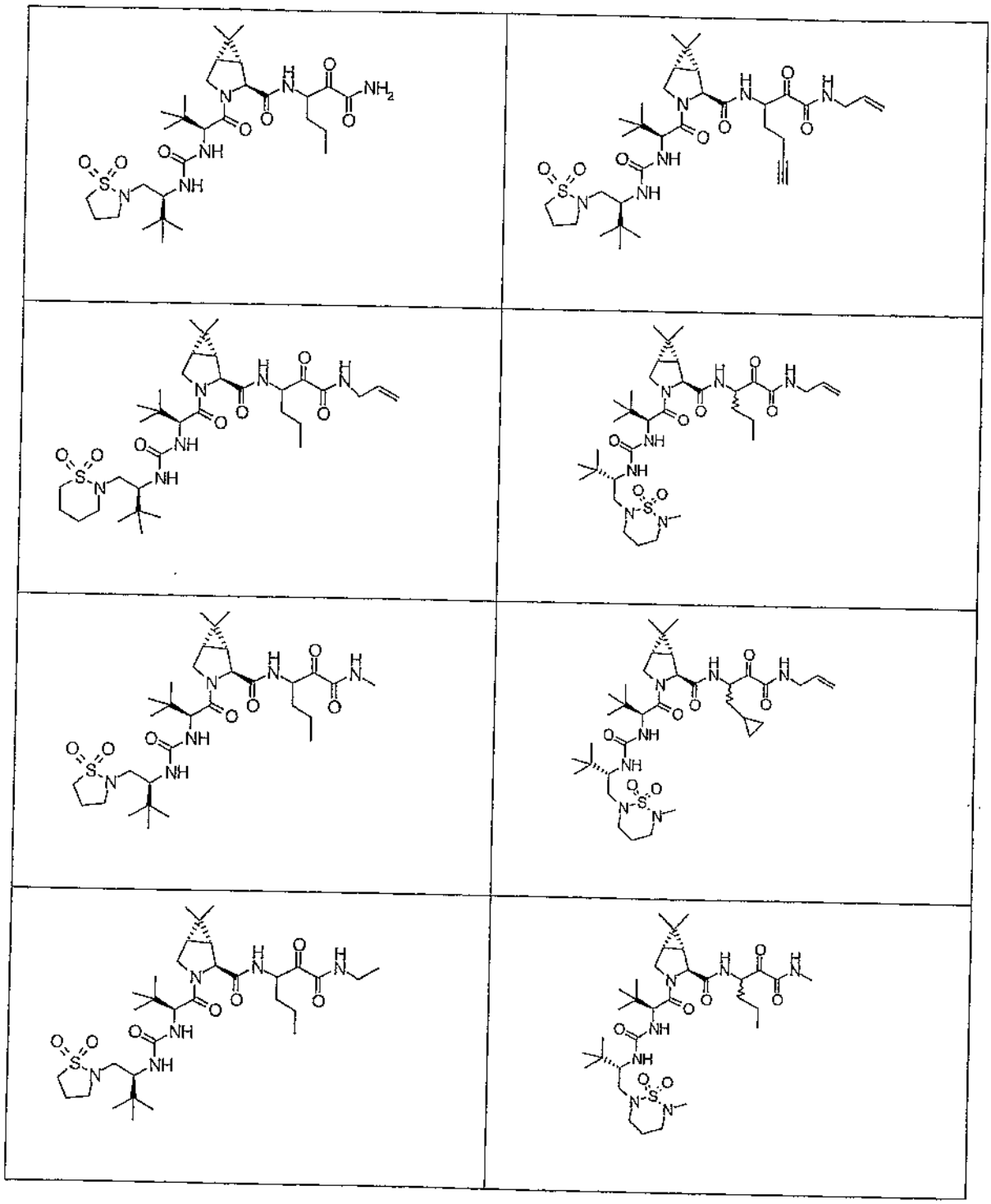
or a pharmaceutically acceptable salt, solvate or ester thereof.

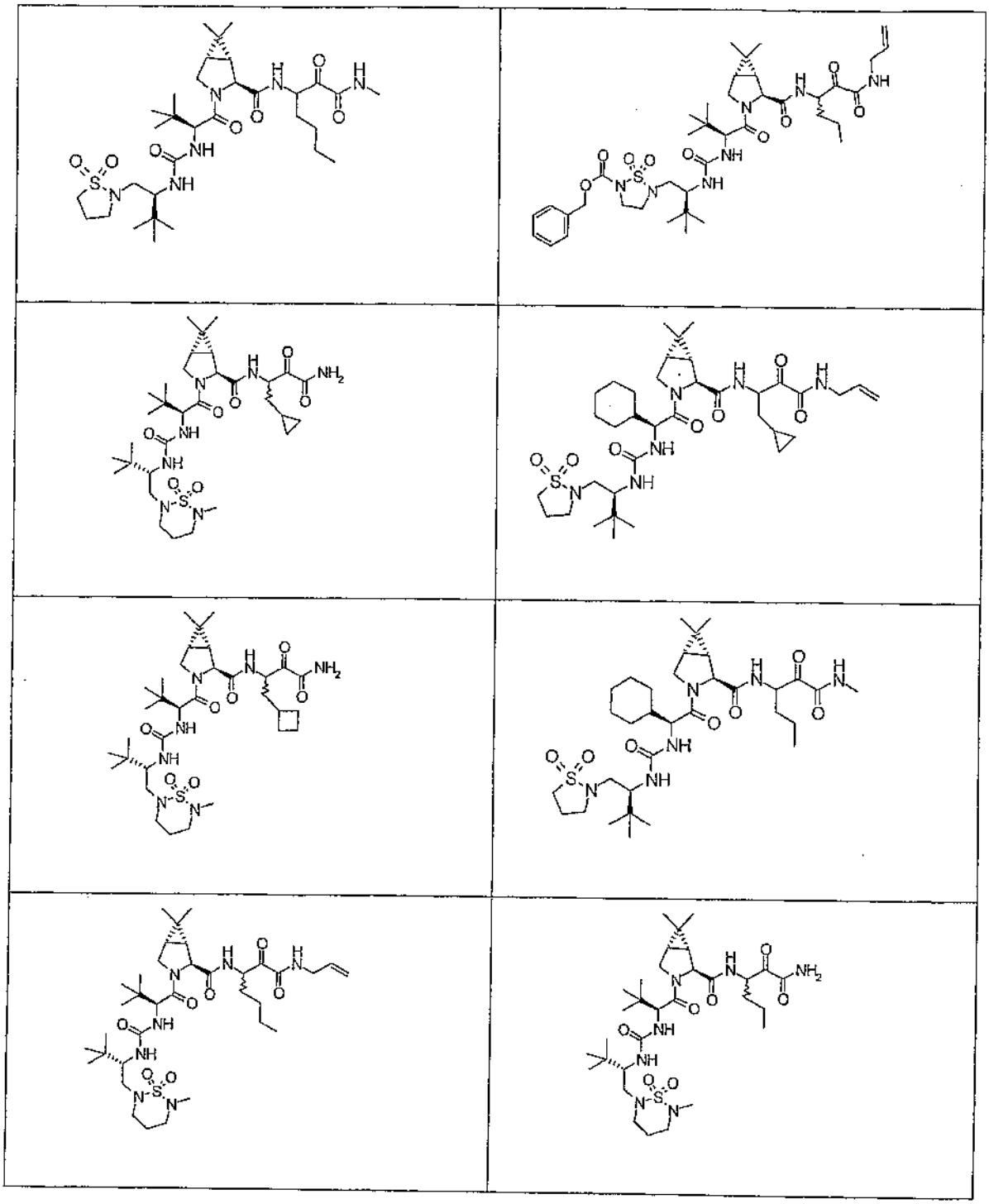
Compounds of formula XIII are disclosed in U.S. Patent Application Ser. No. 11/065,647 filed February 24, 2005. The preparation of these compounds is disclosed in the experimental section of this application set forth hereinbelow.

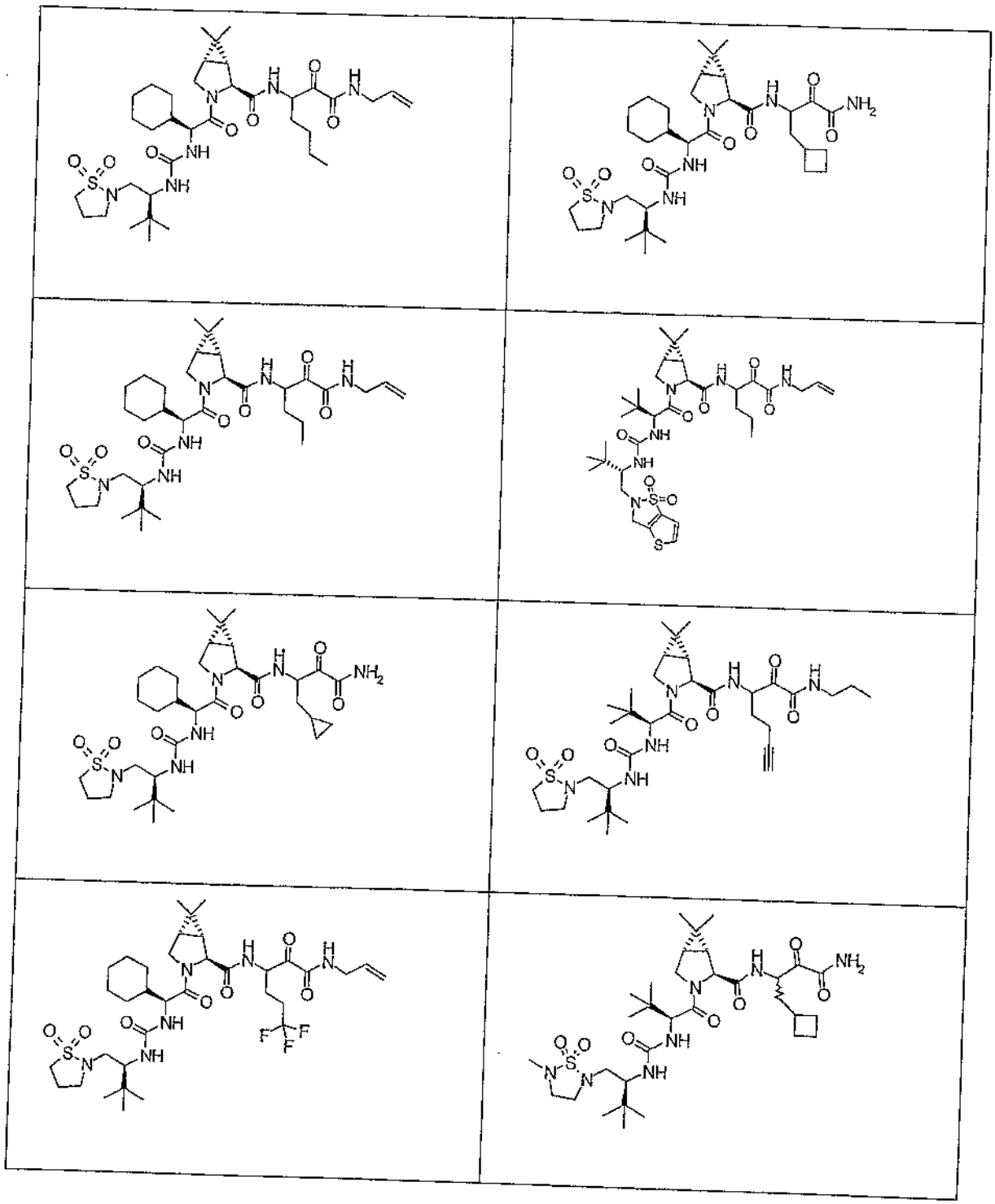
Non-limiting examples of certain compounds disclosed in U.S. Patent Application Ser. No. 11/065,647 are:

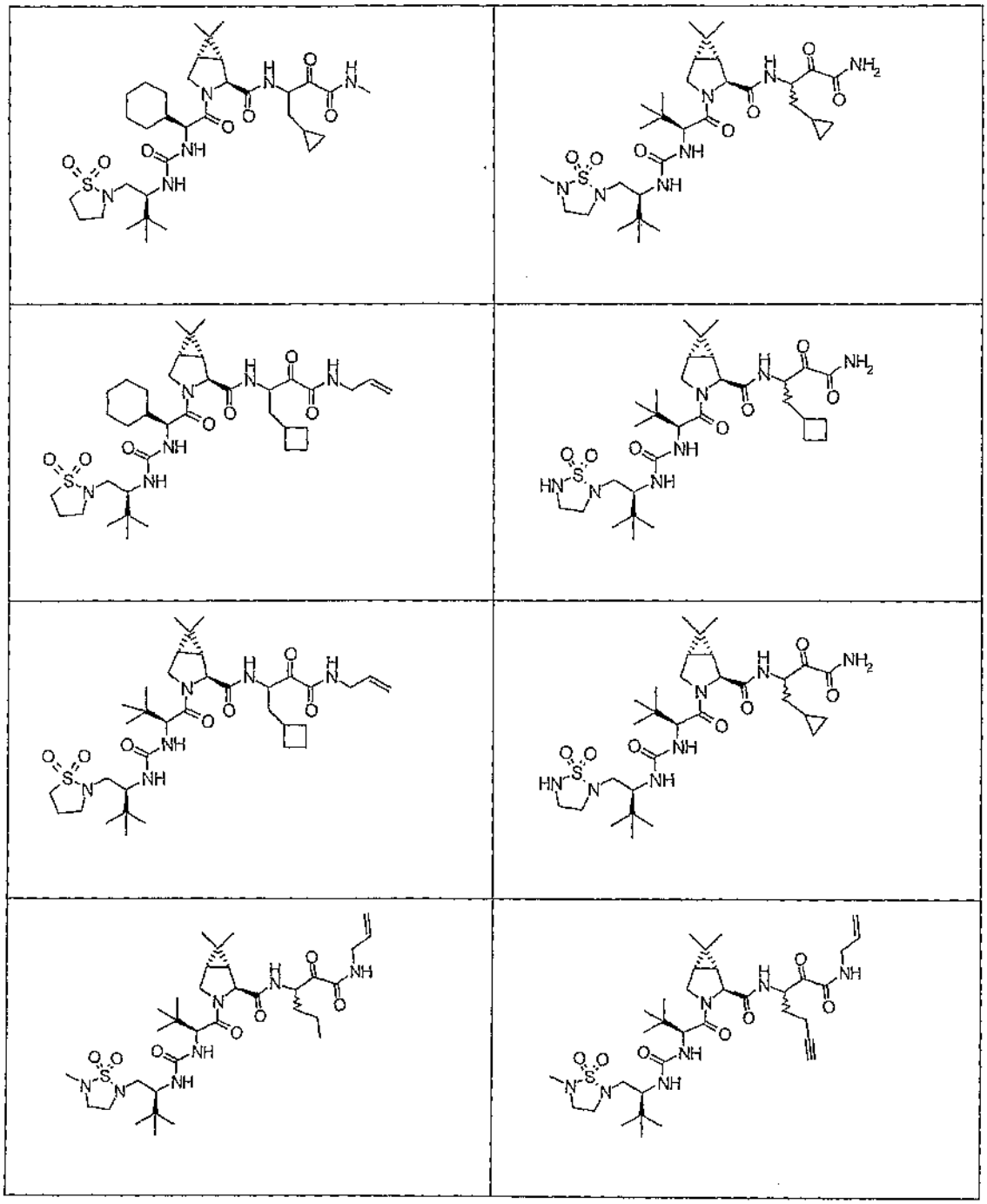


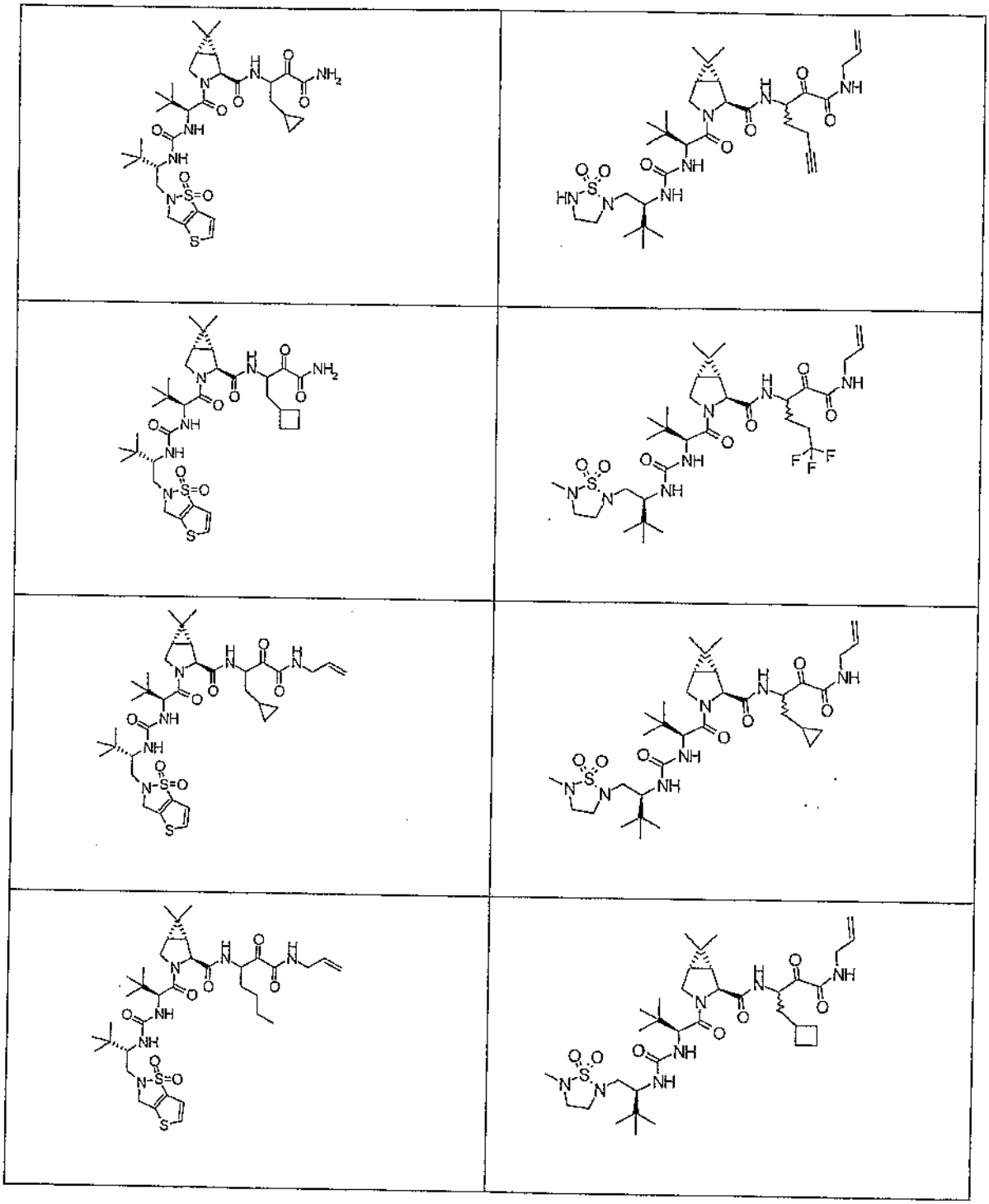


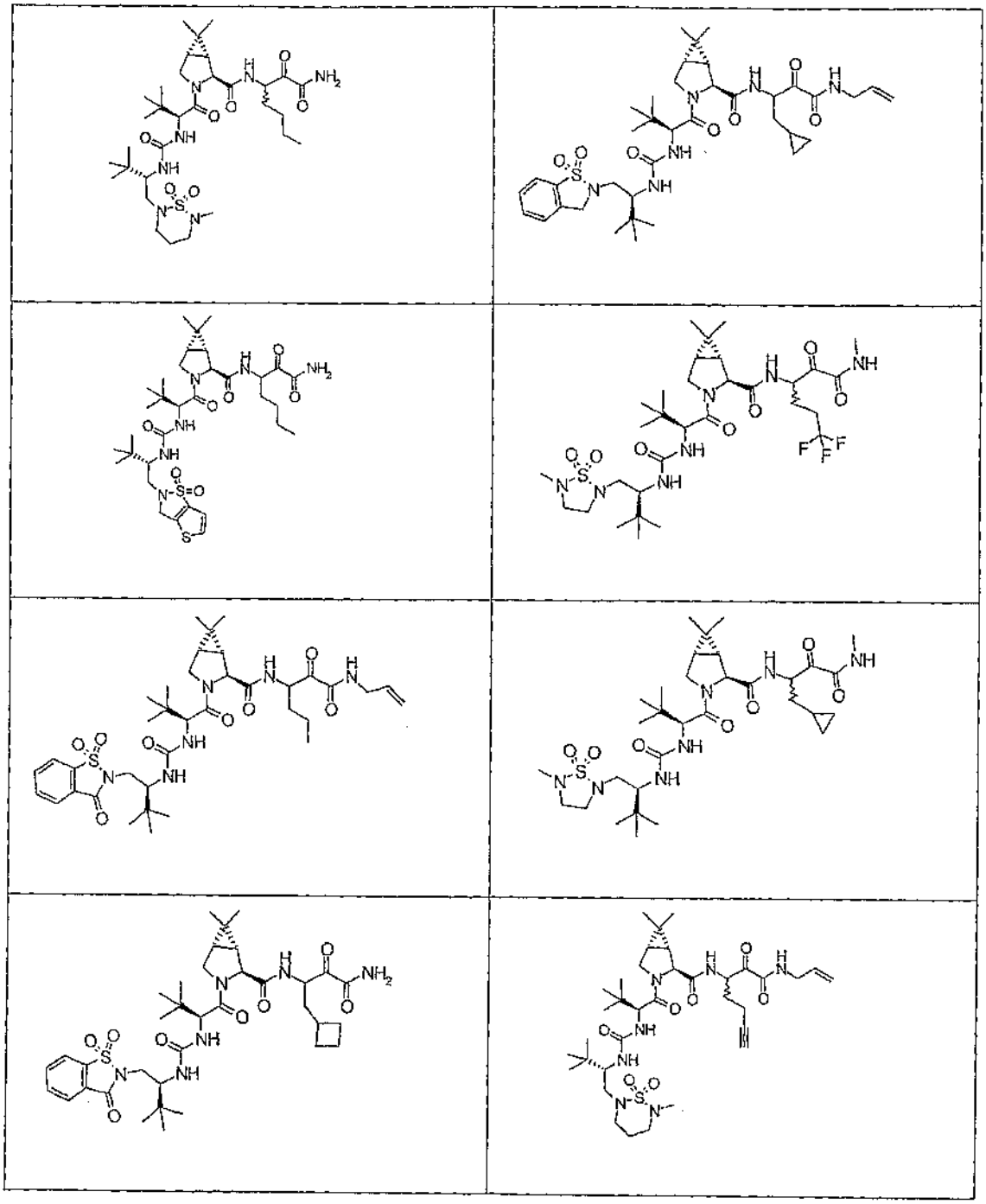


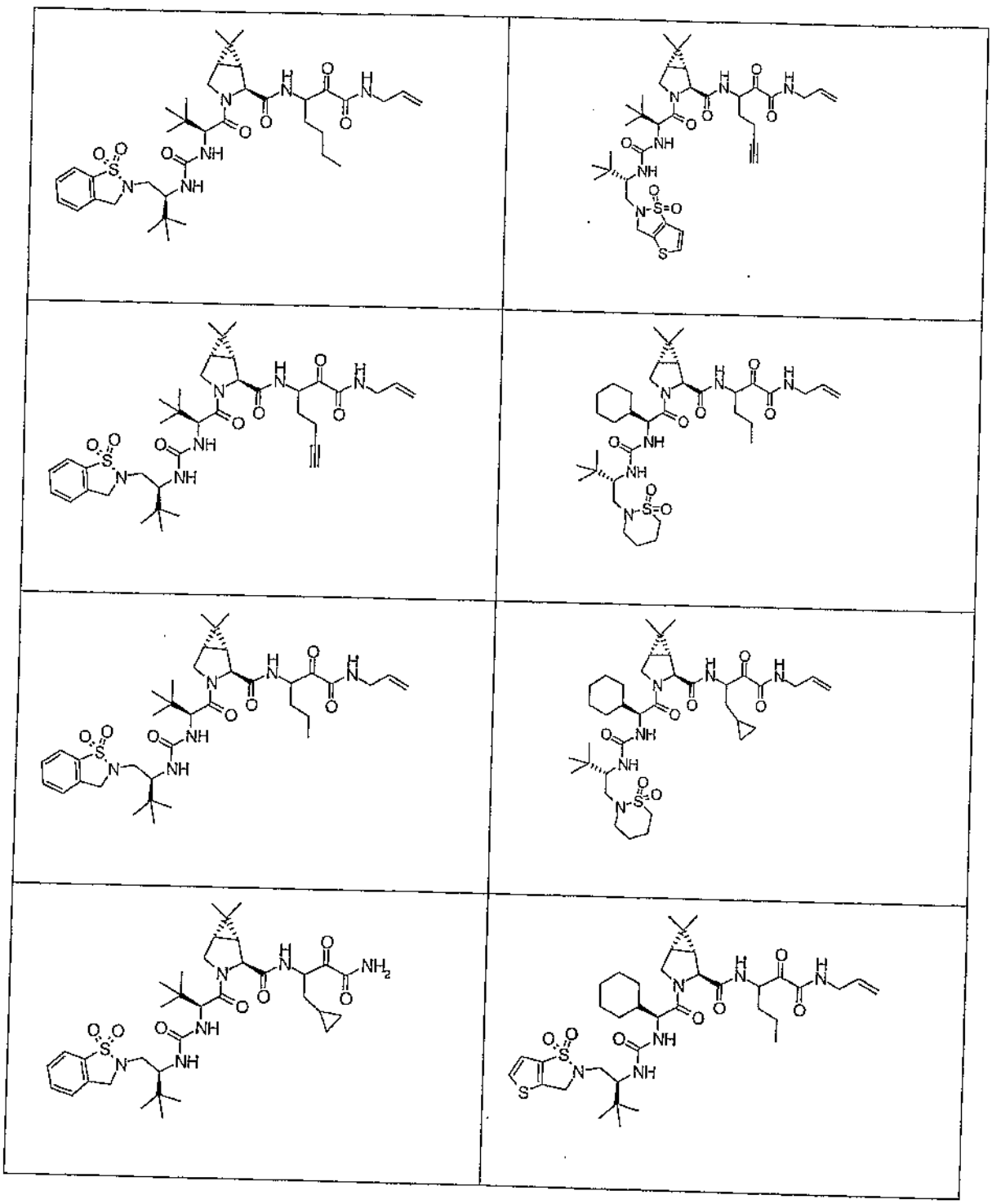


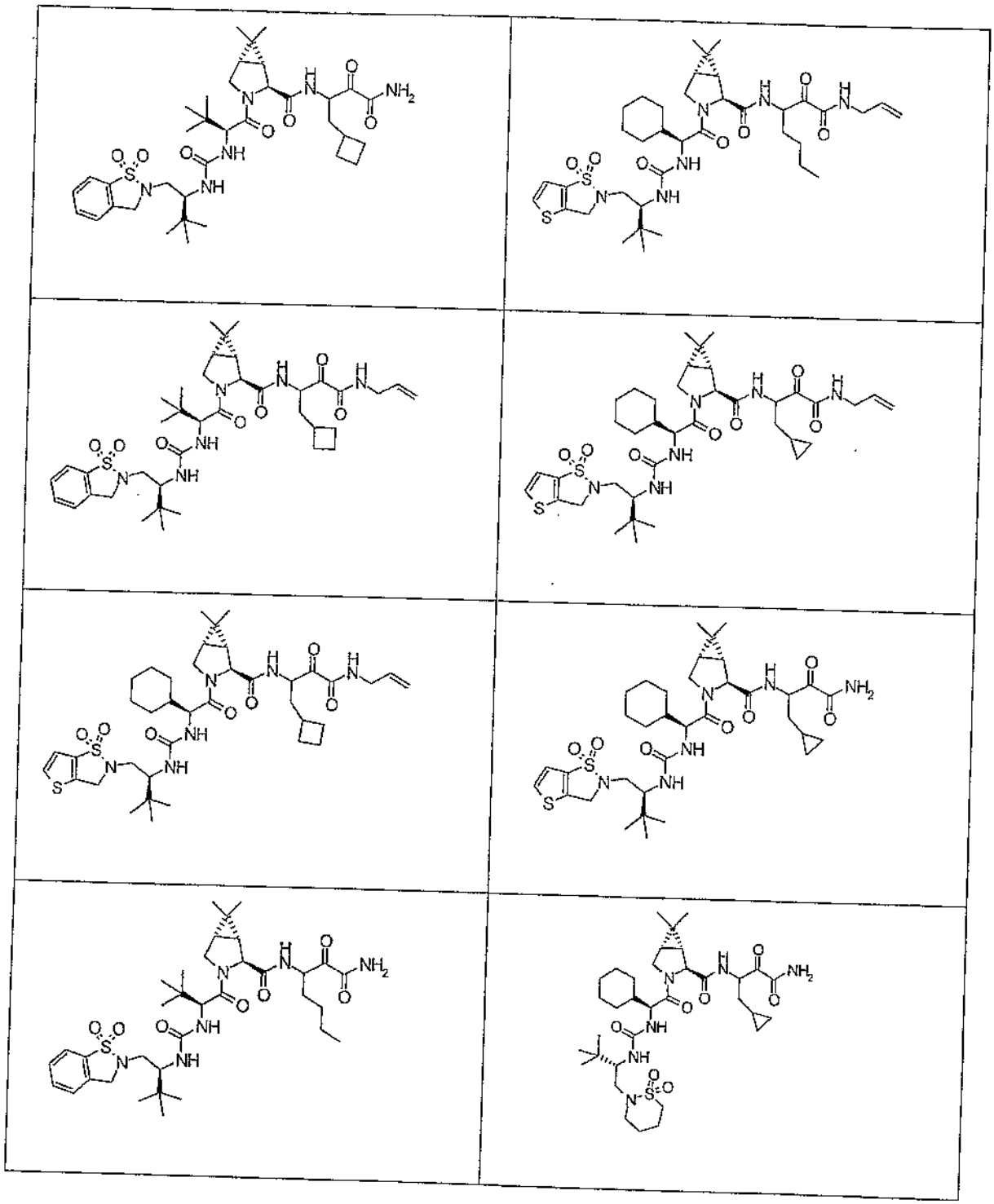


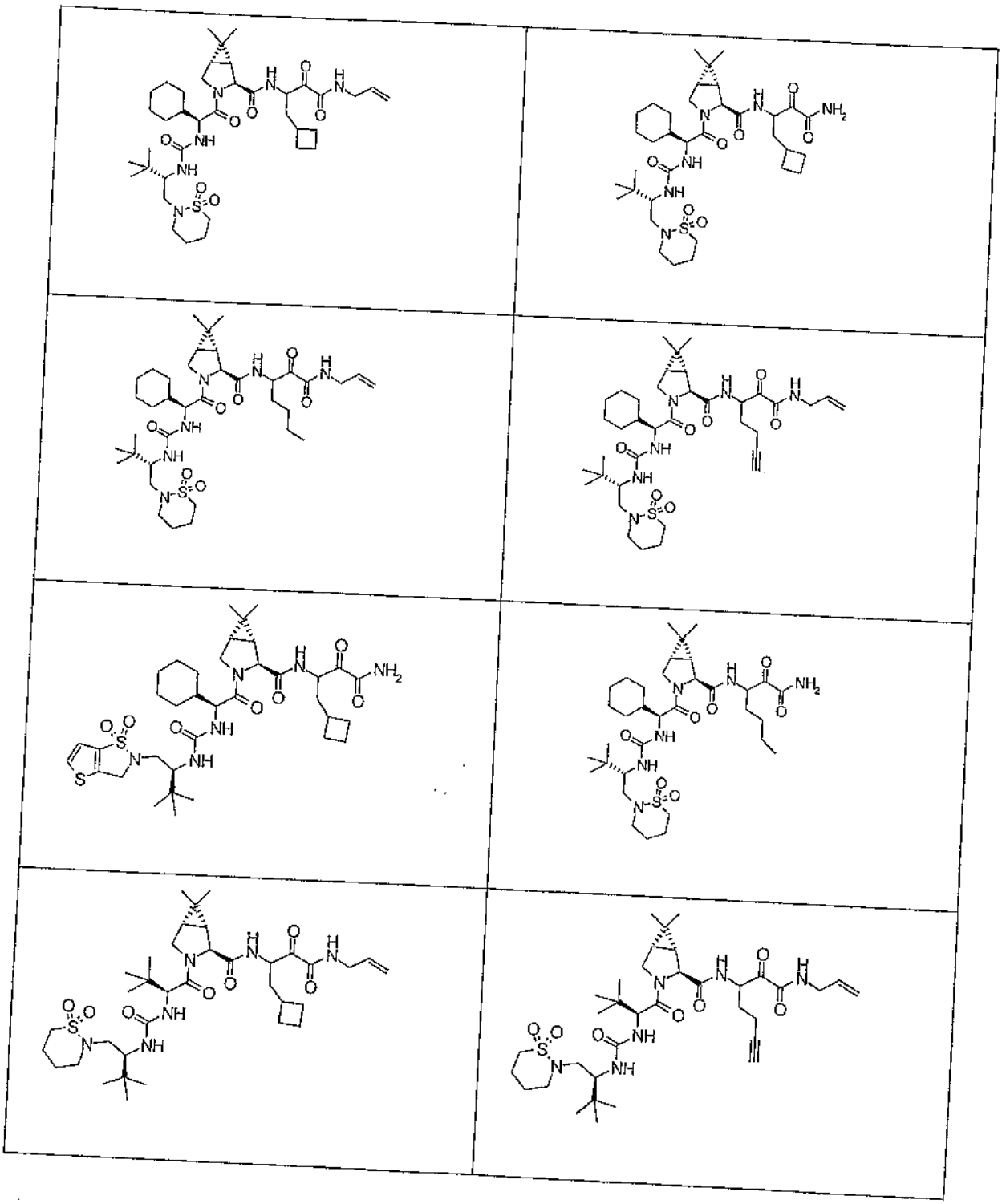


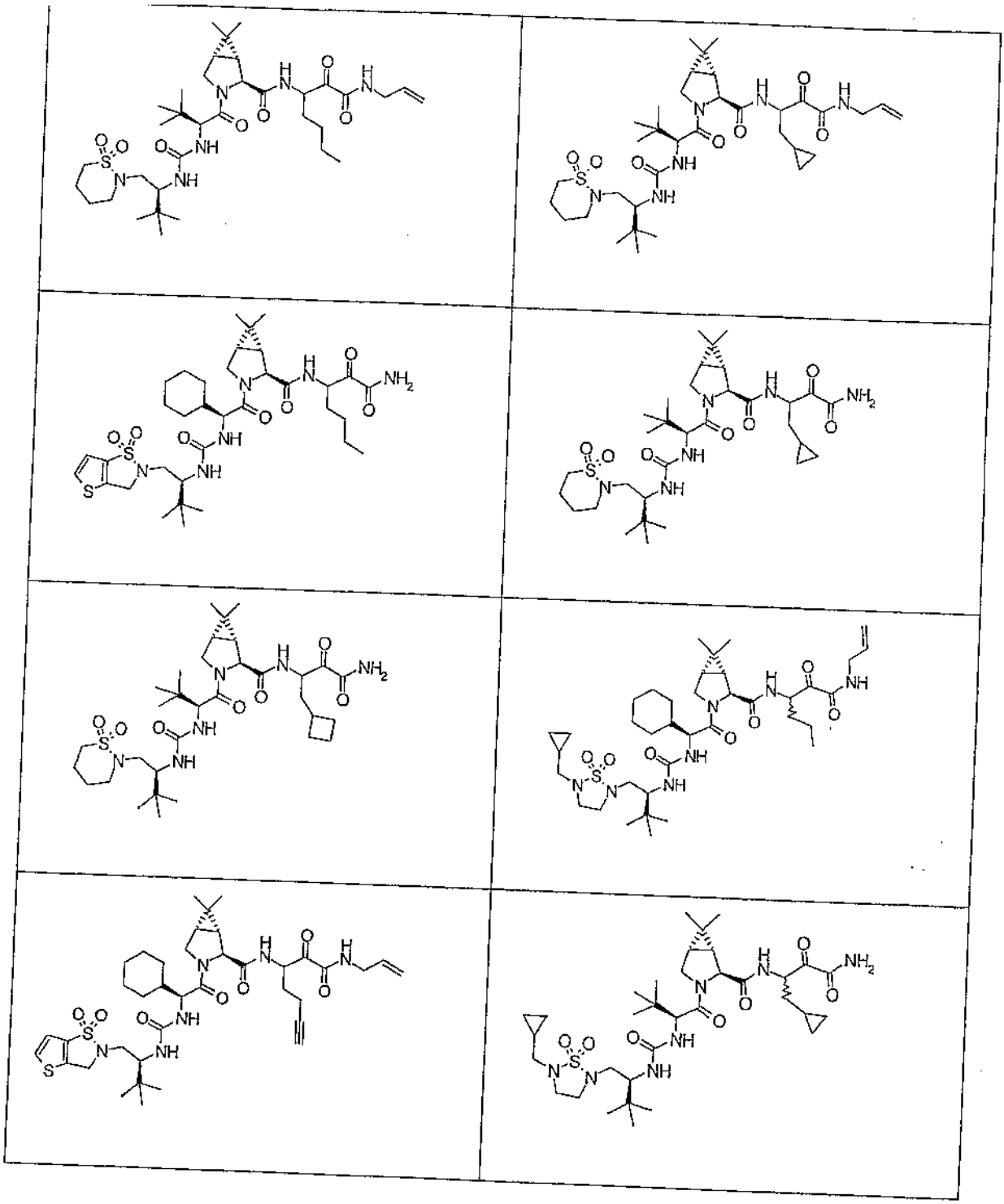


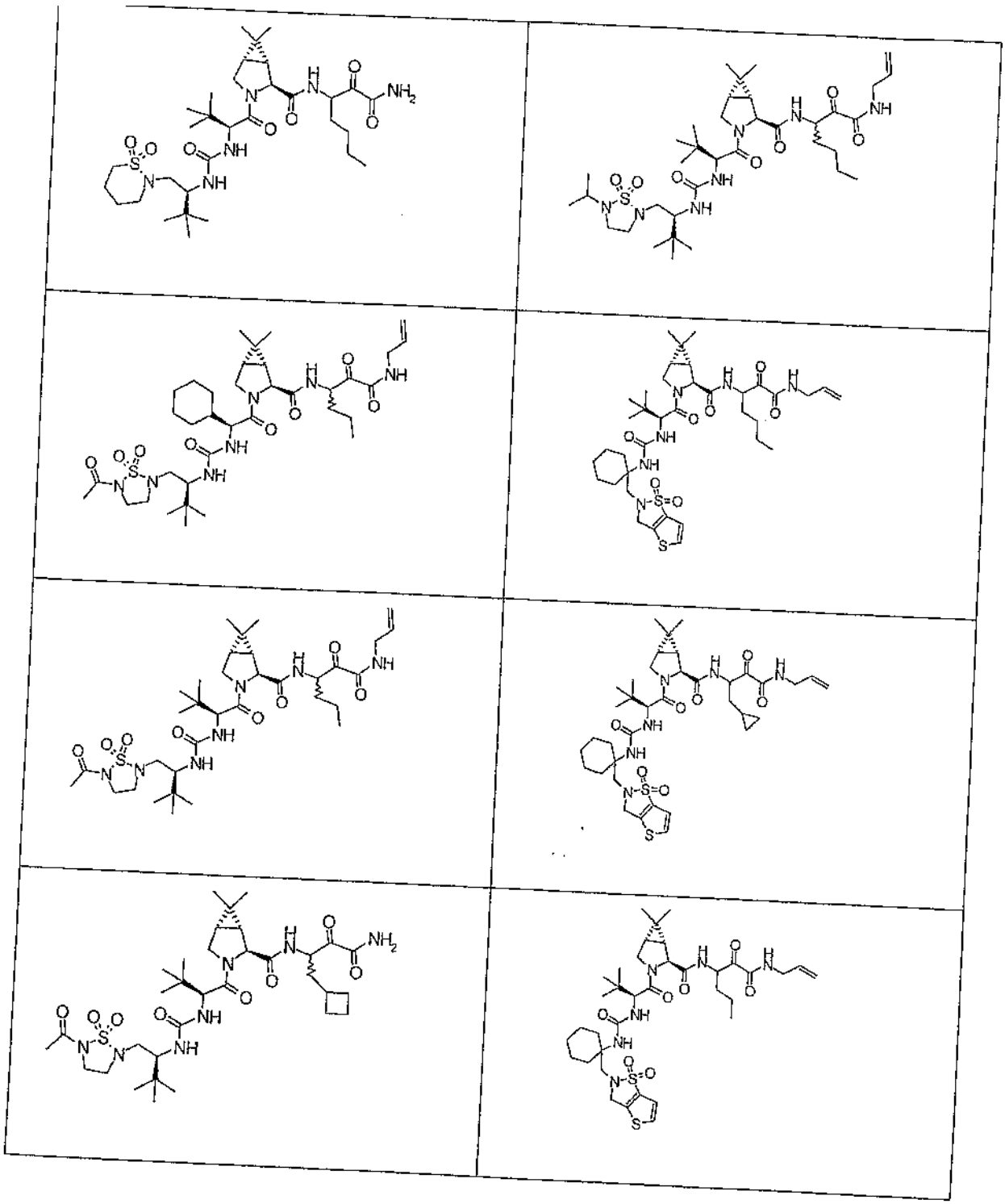


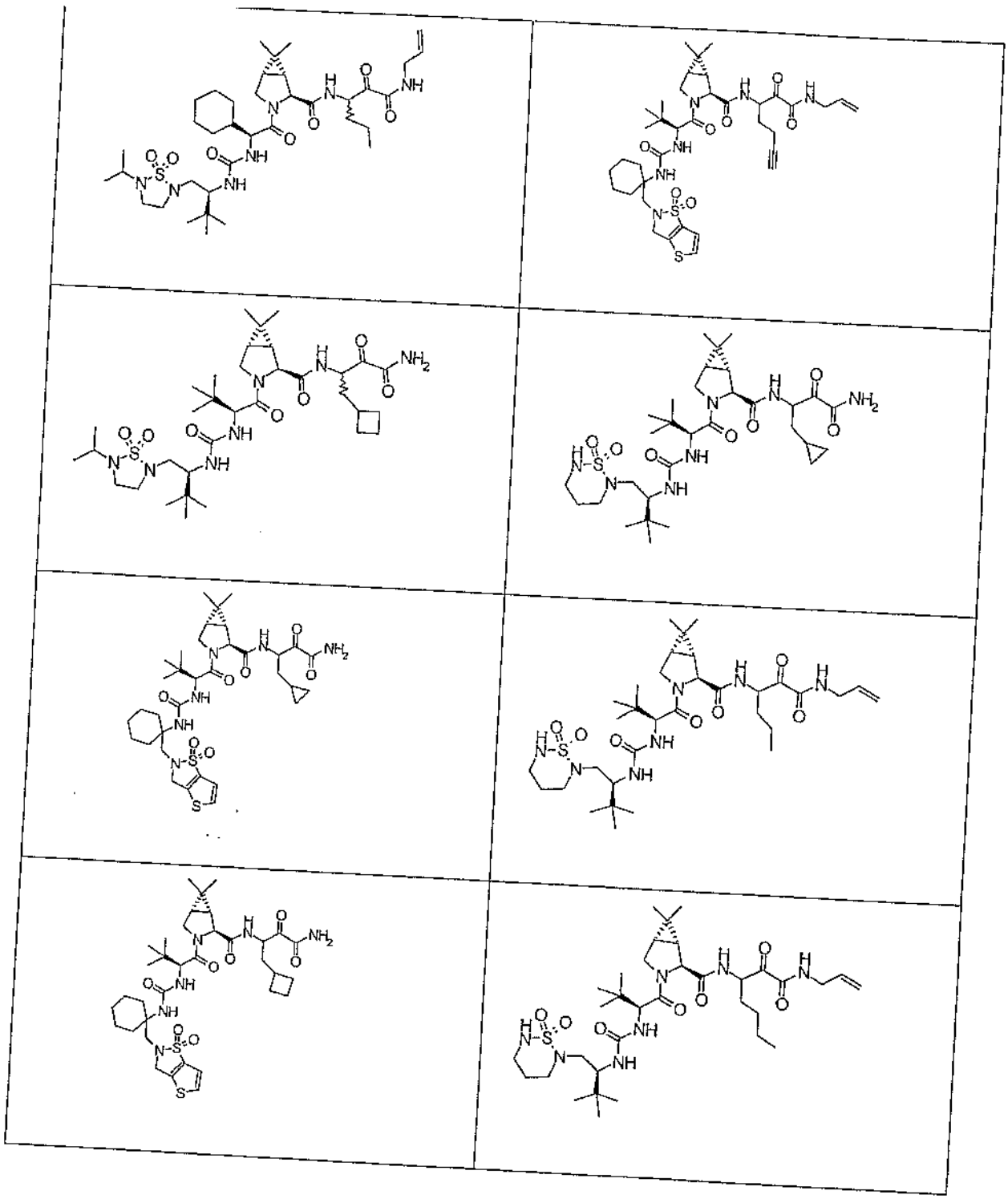


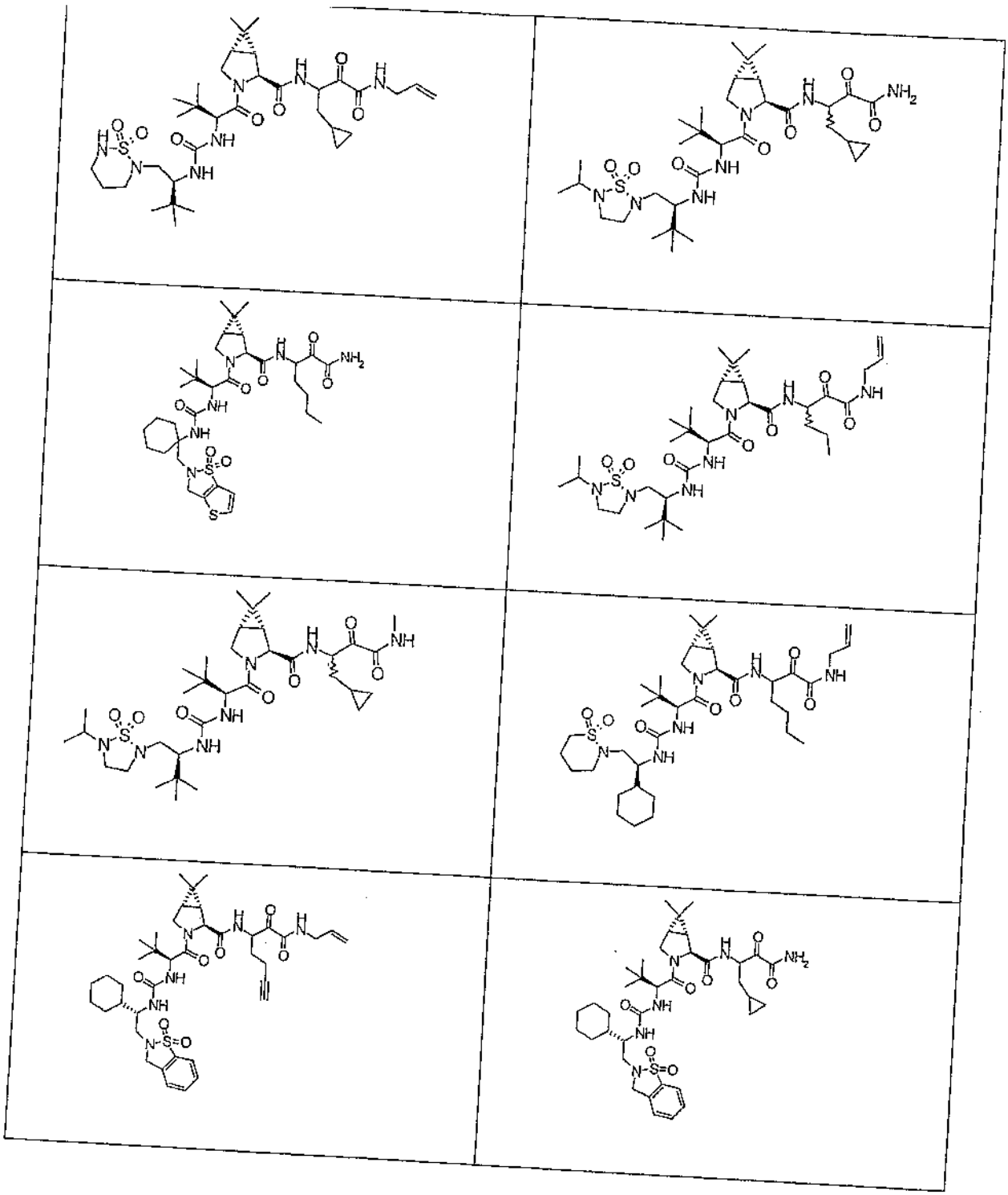


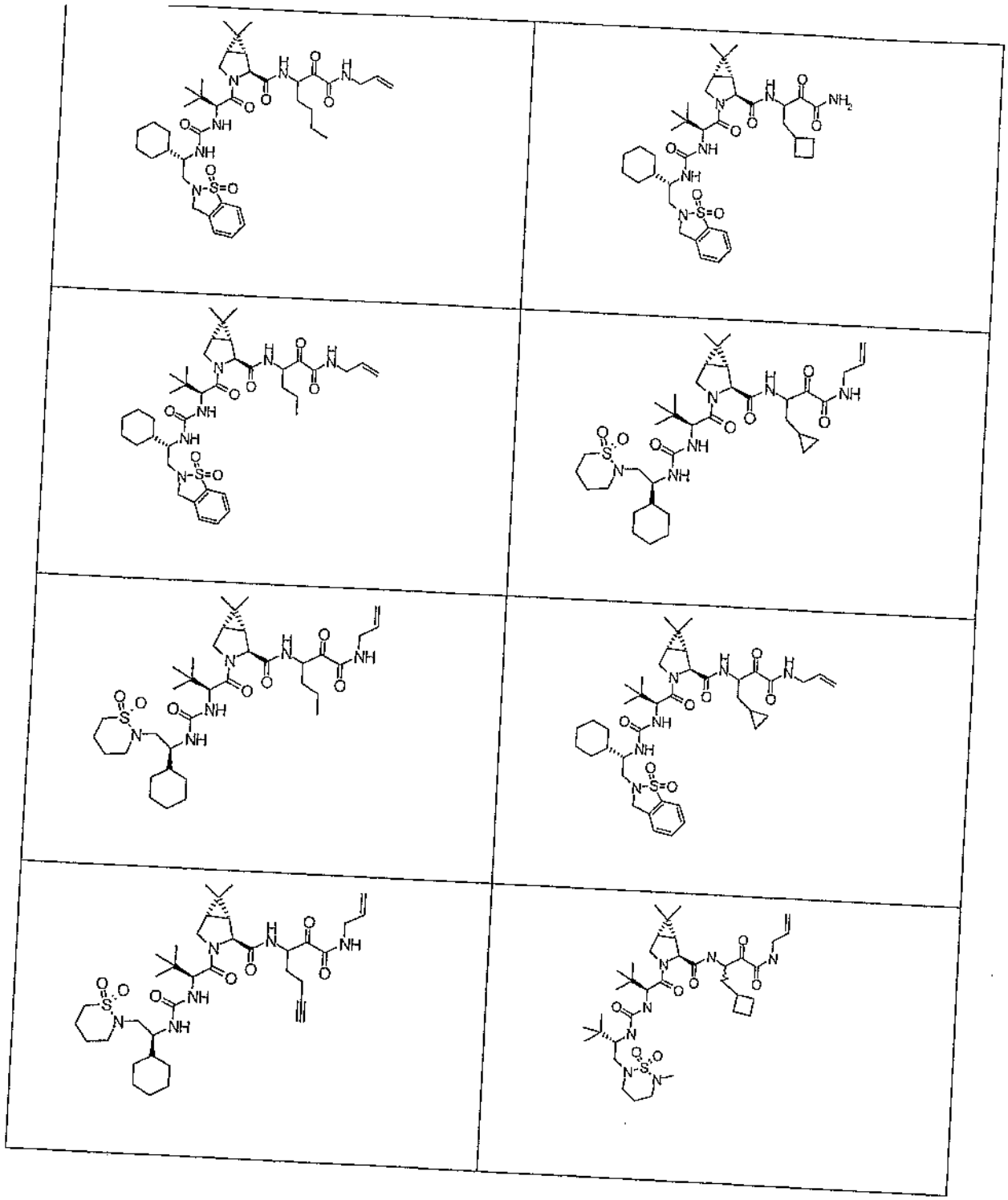


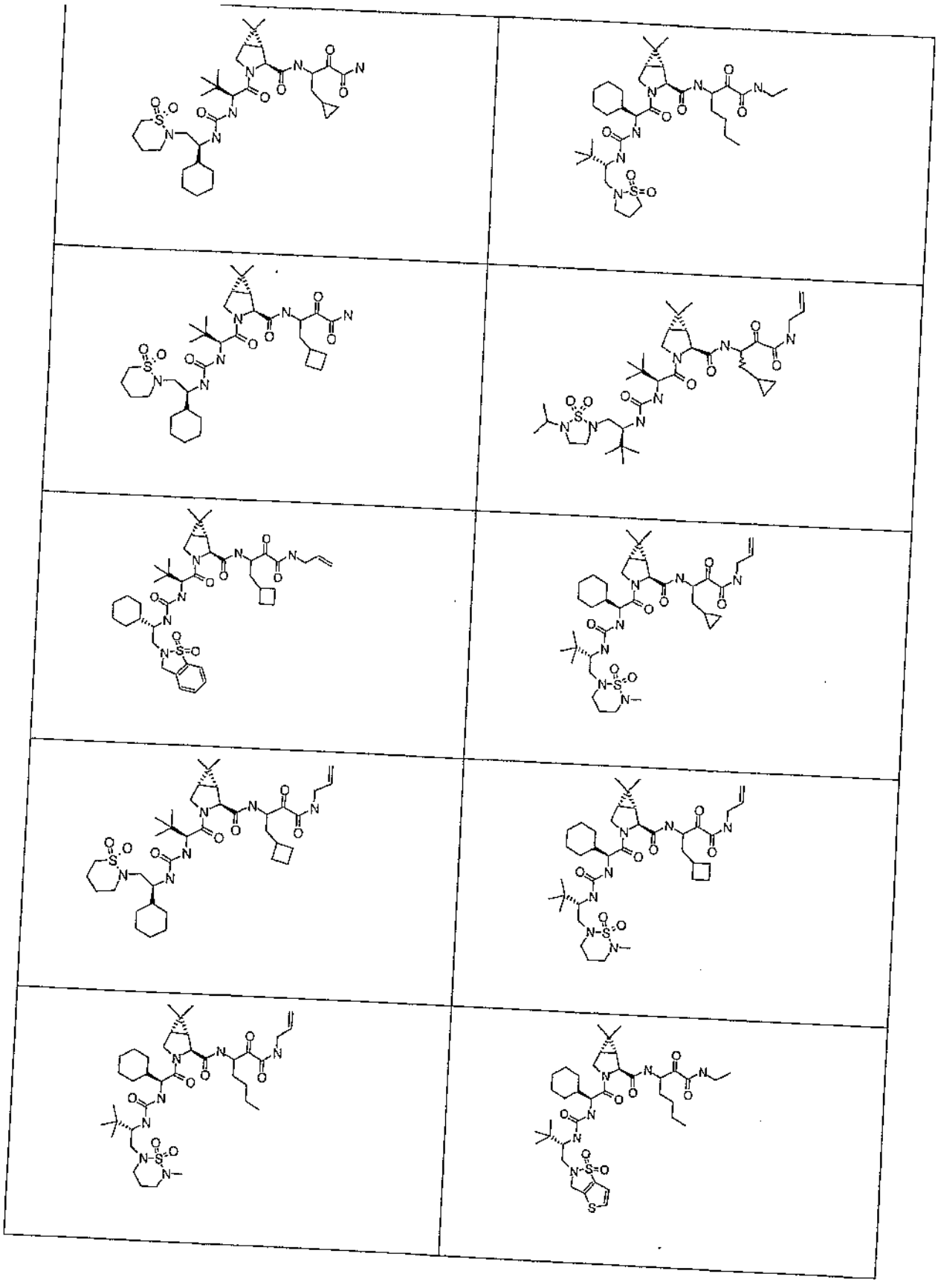


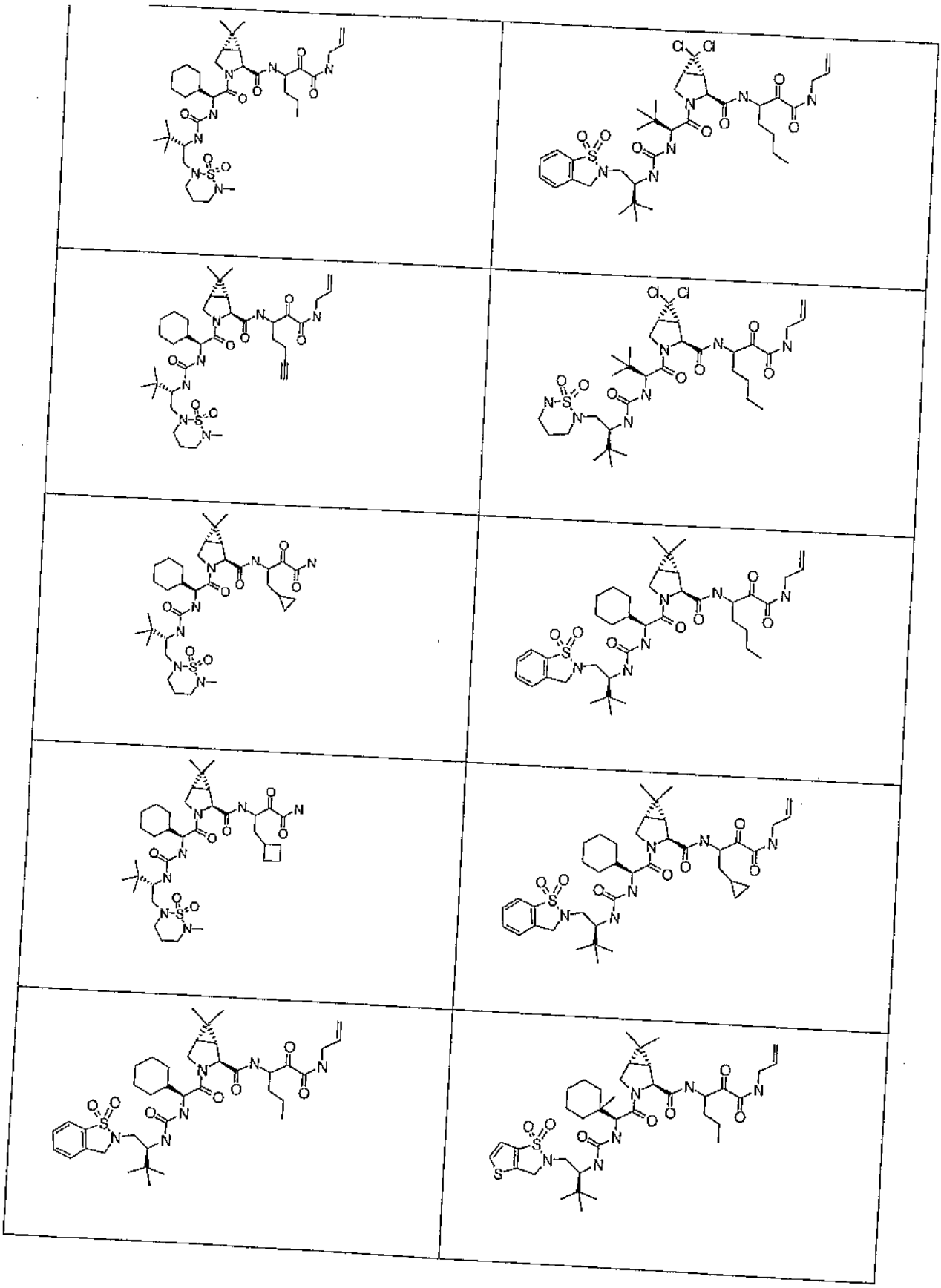


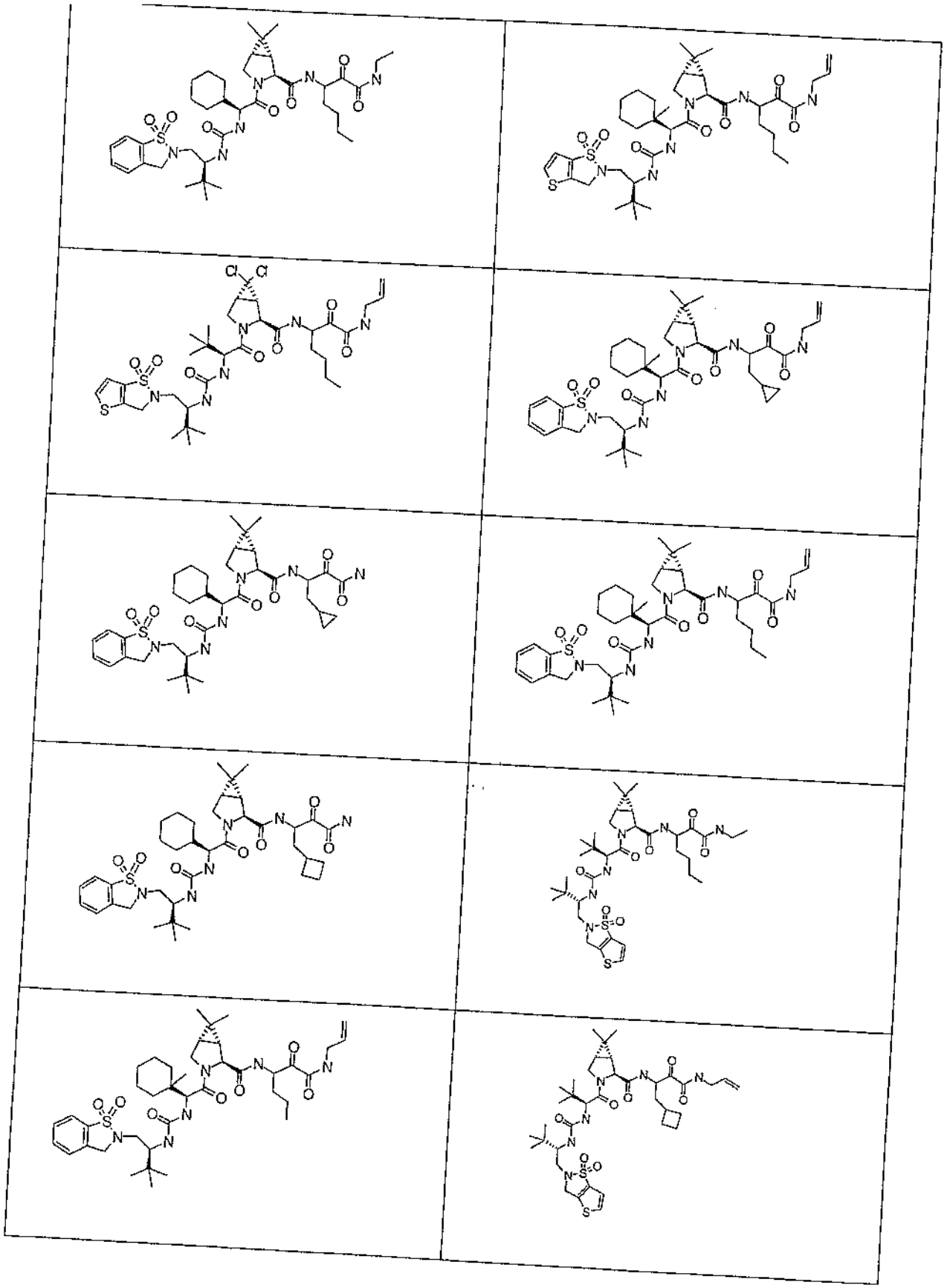


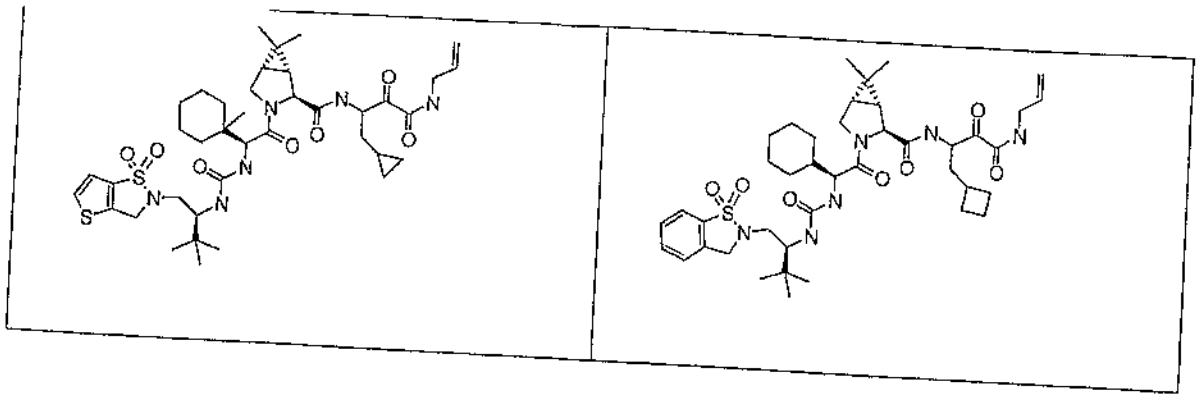


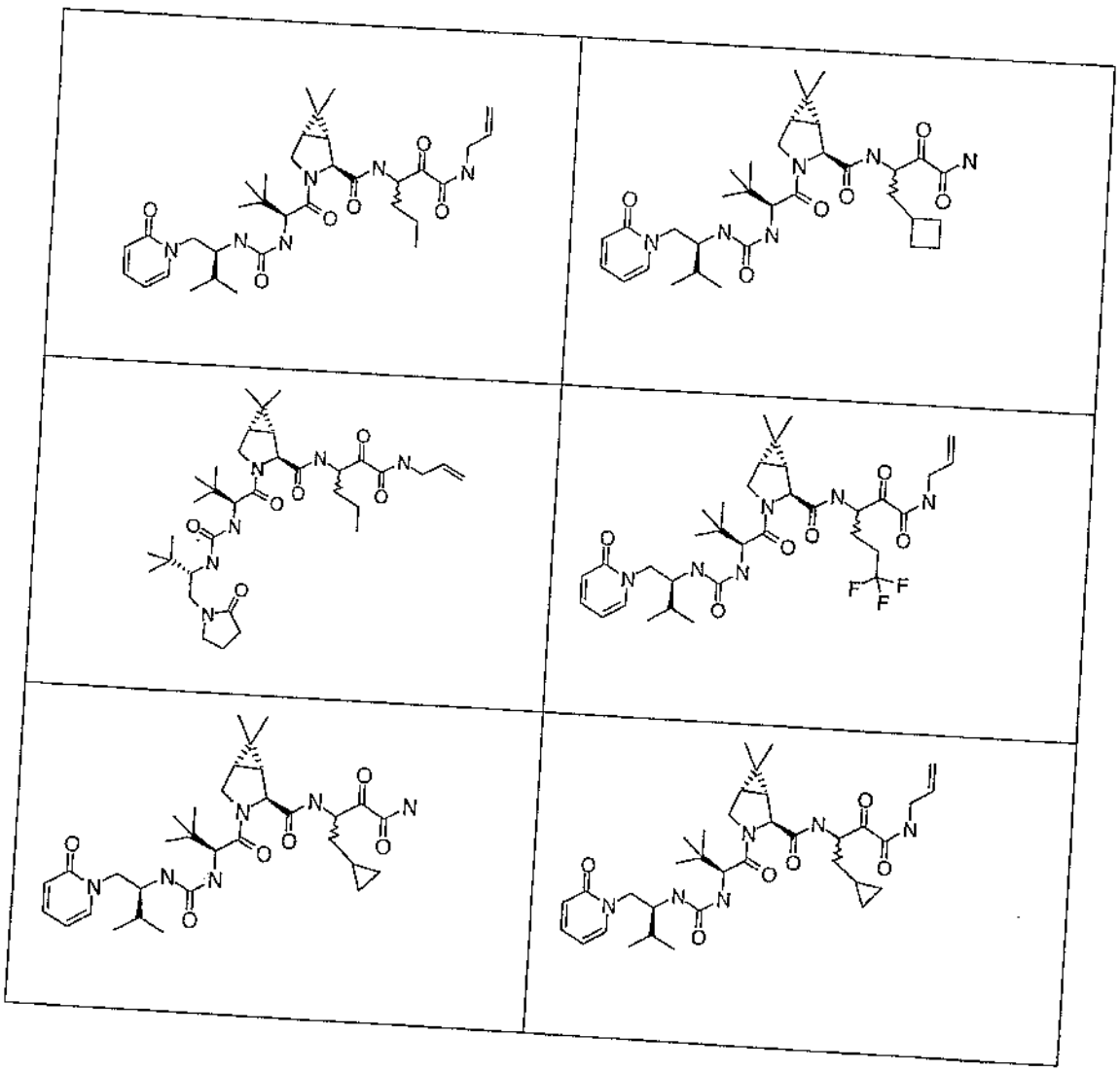


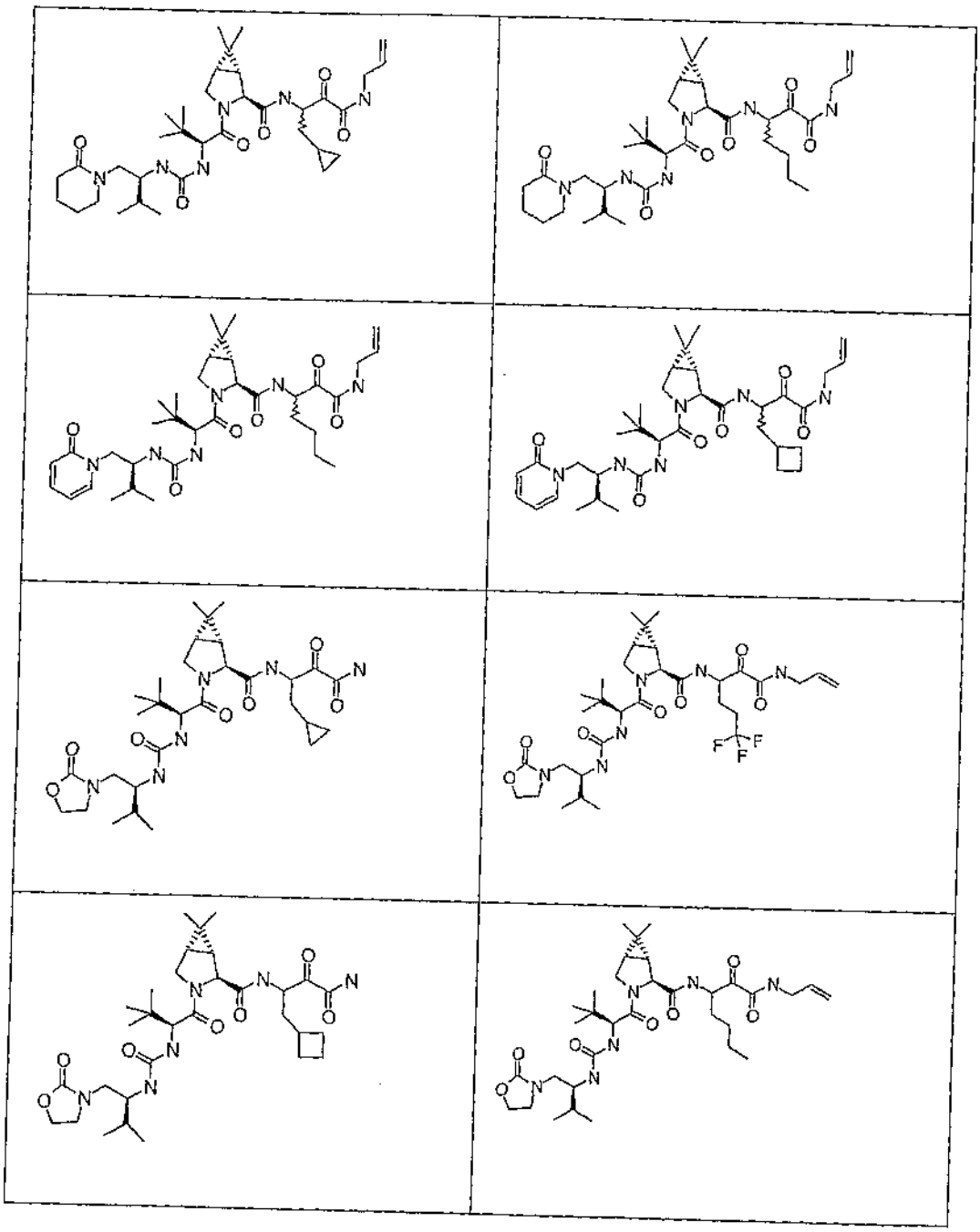


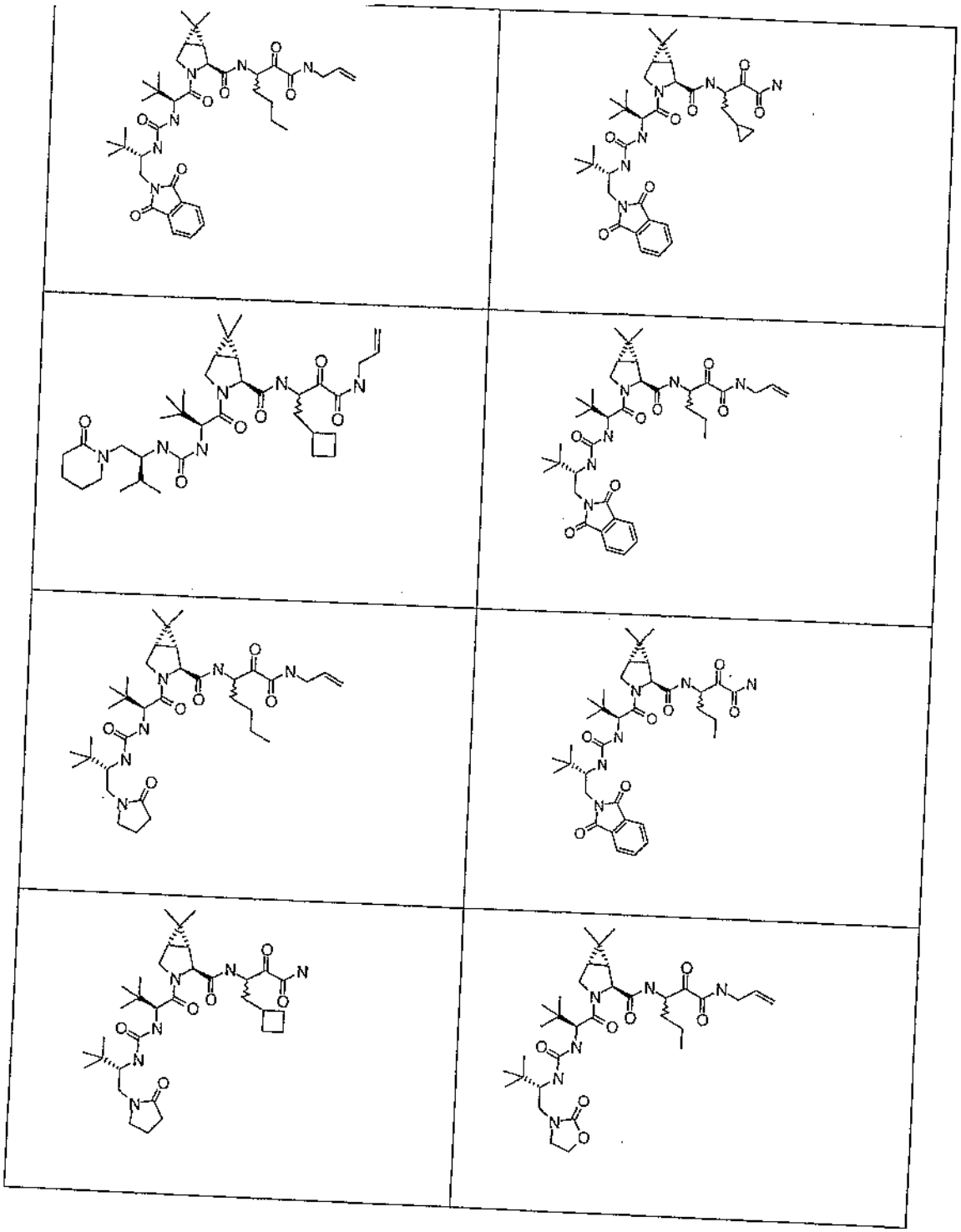


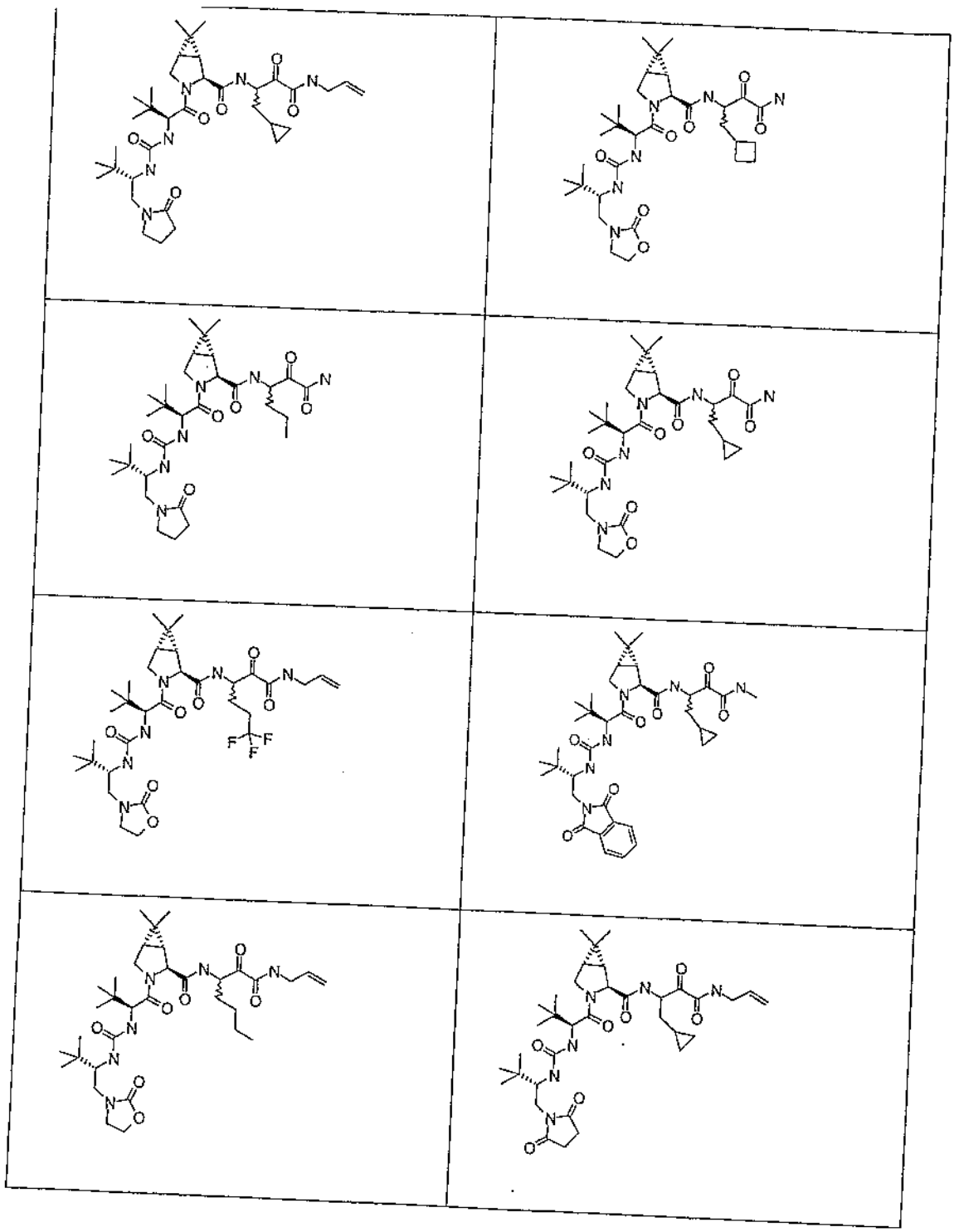


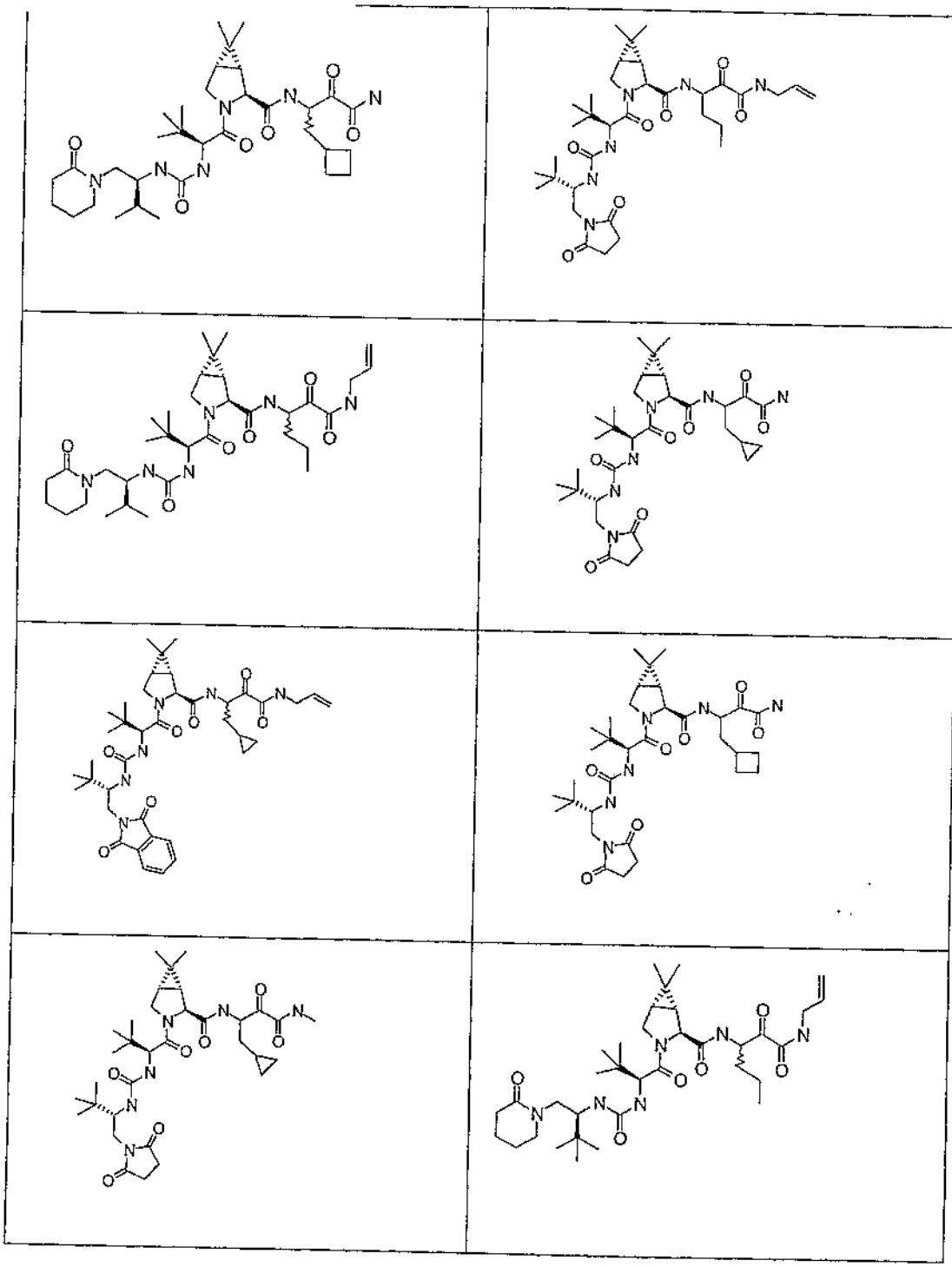


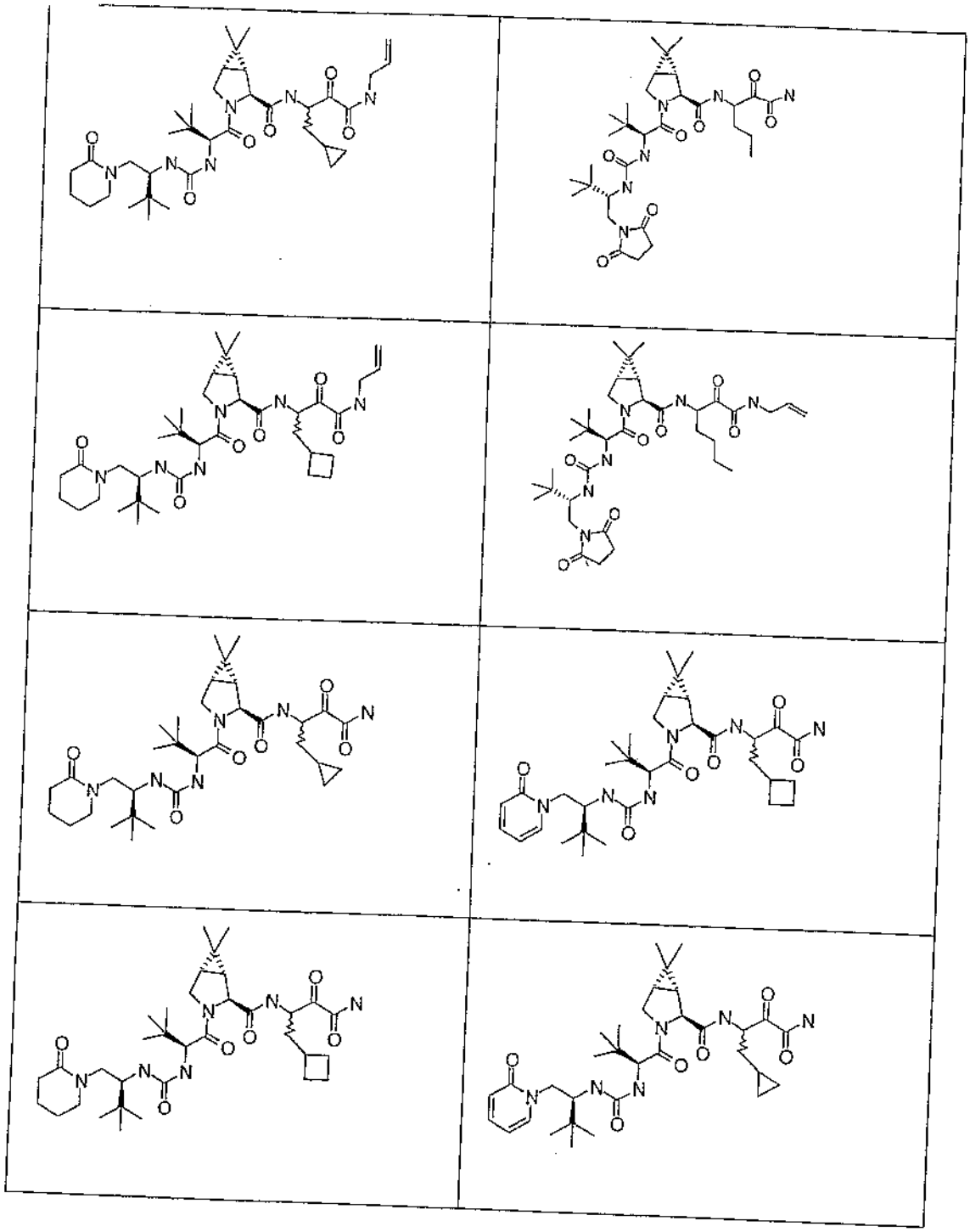


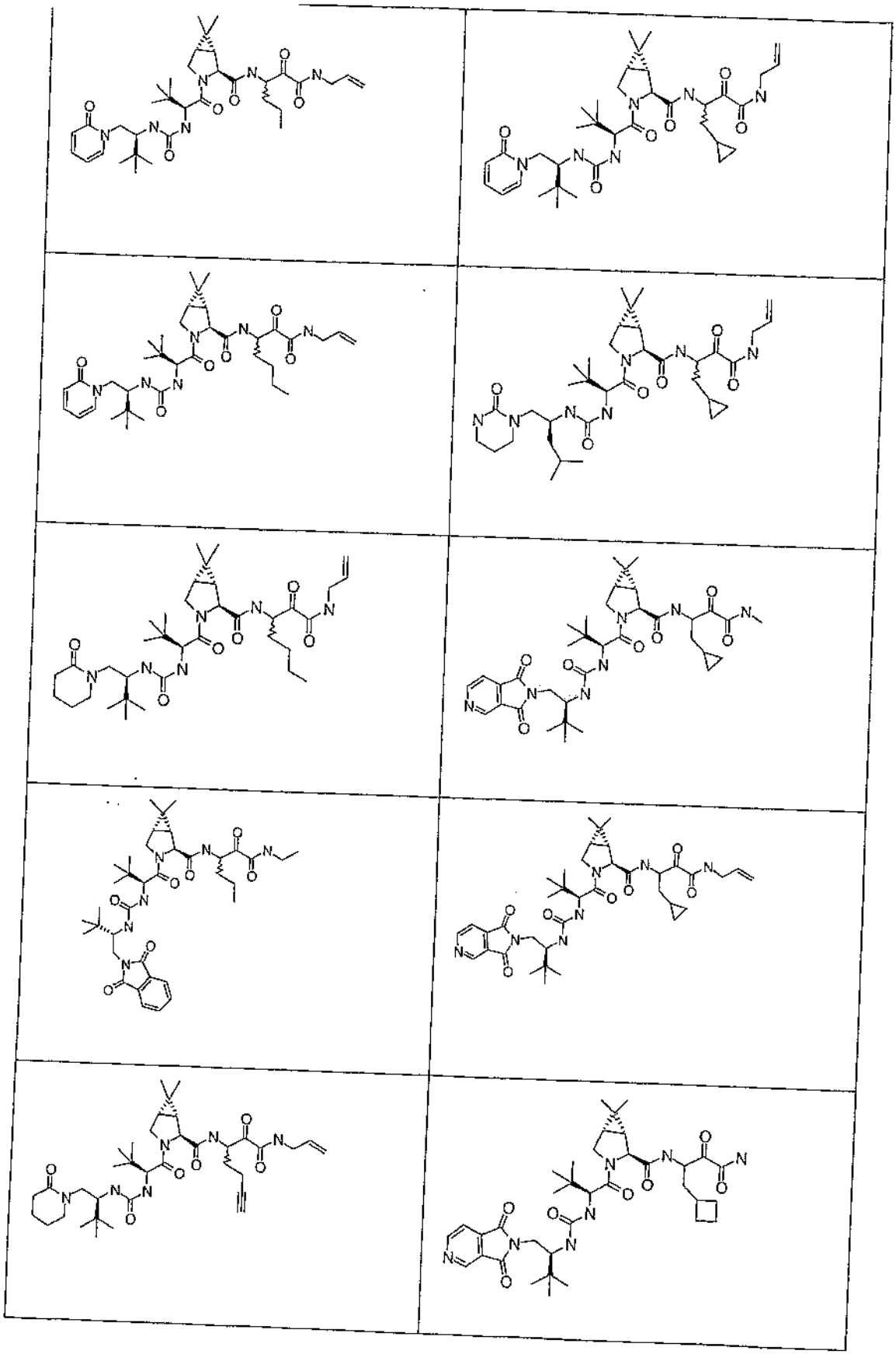


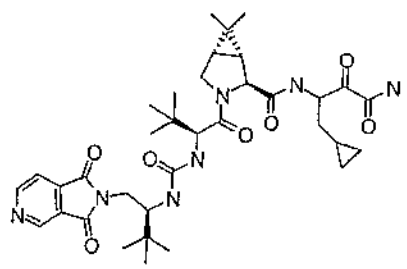
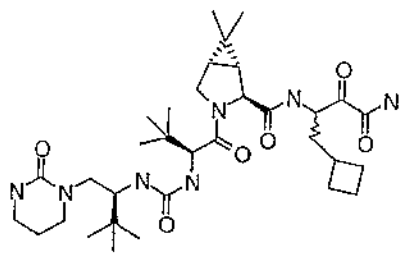
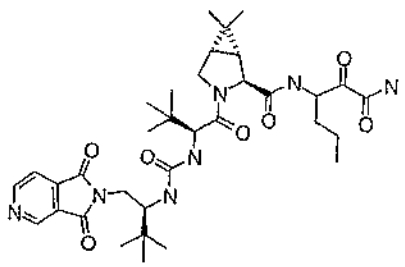
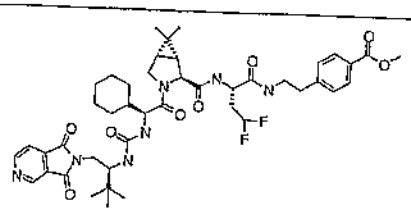
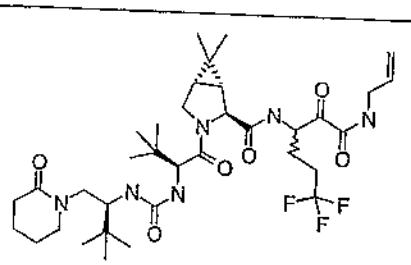
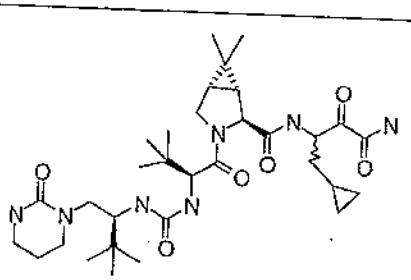
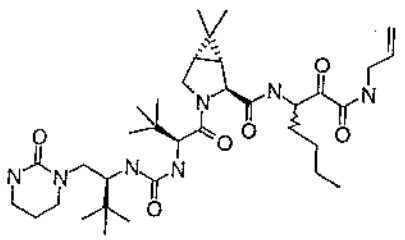
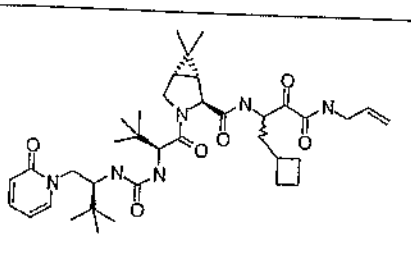


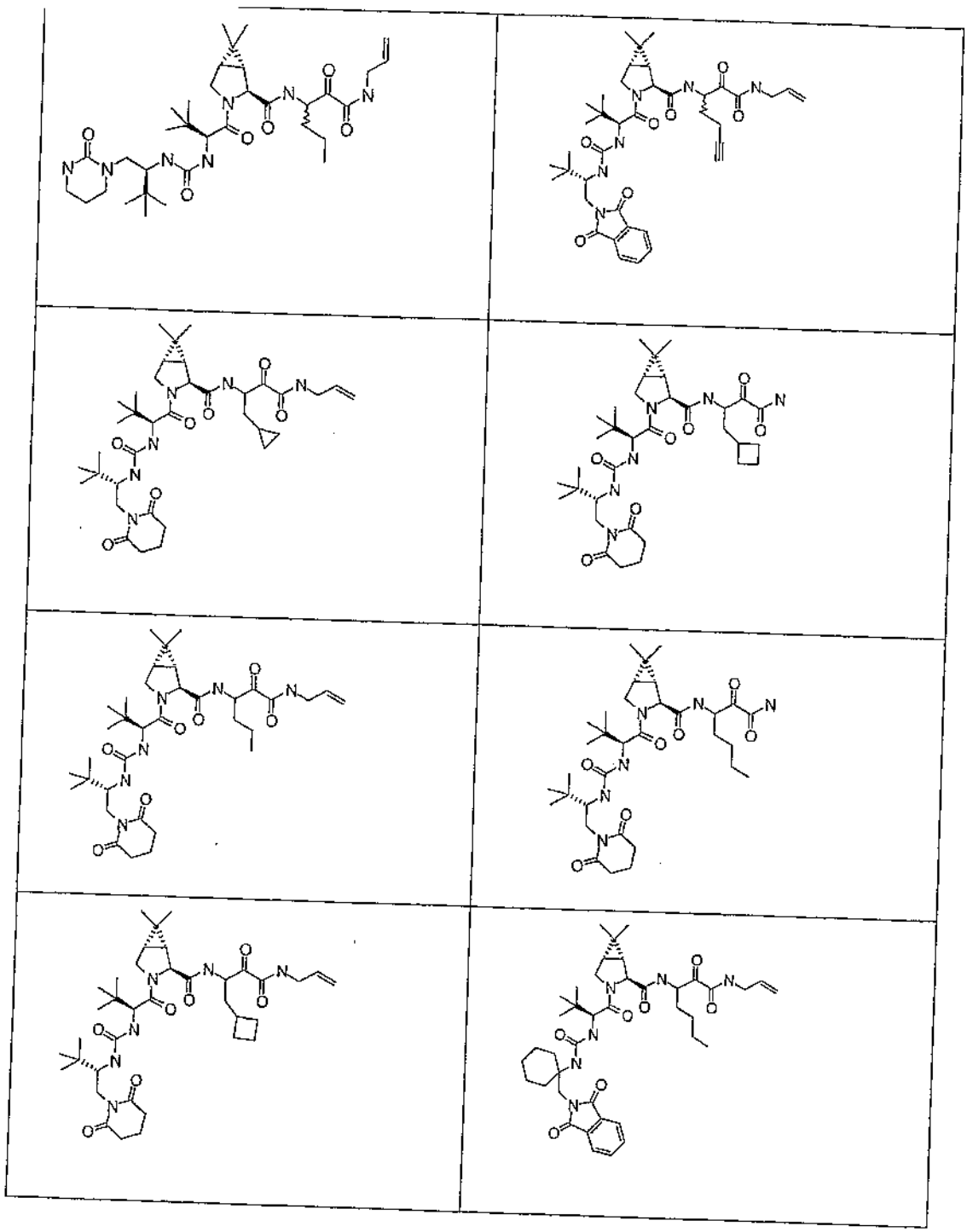


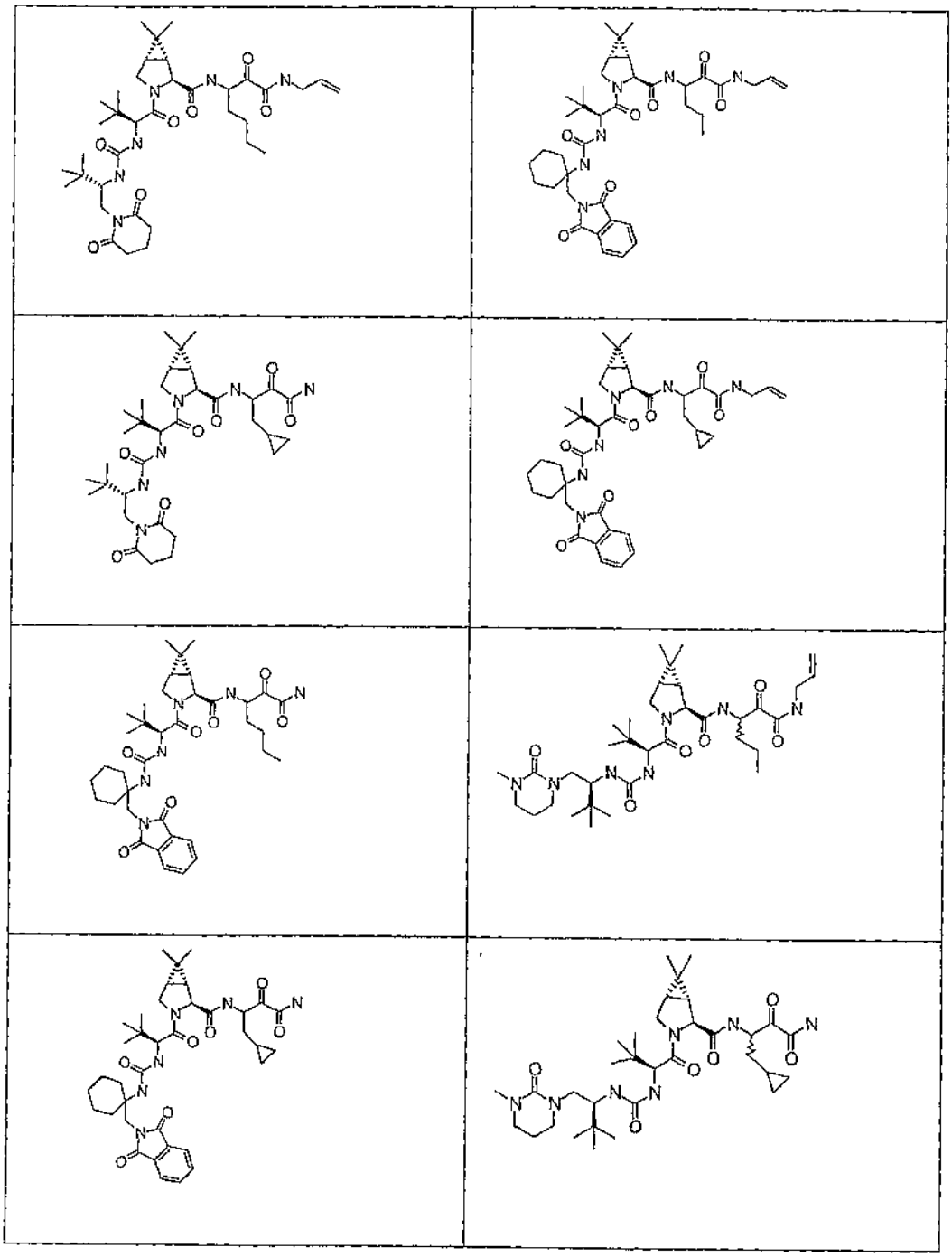


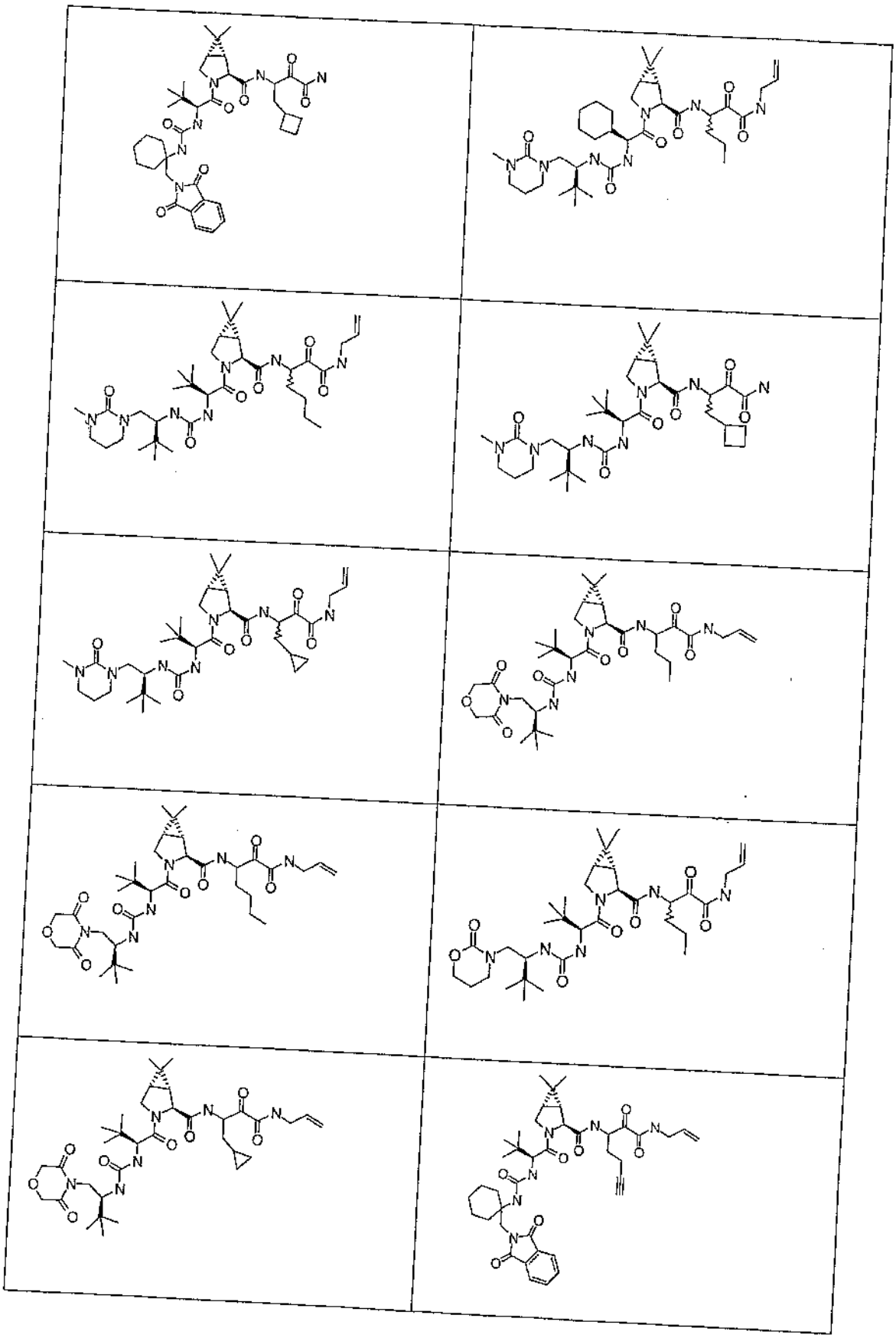


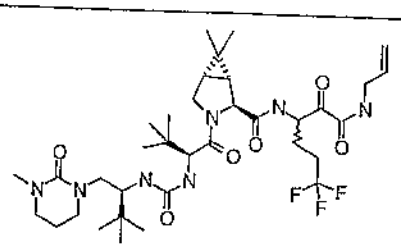
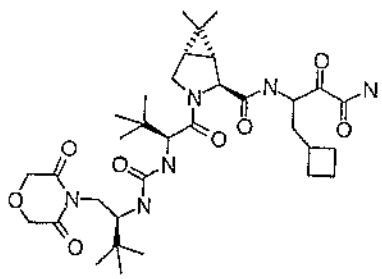
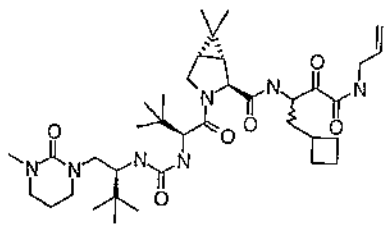
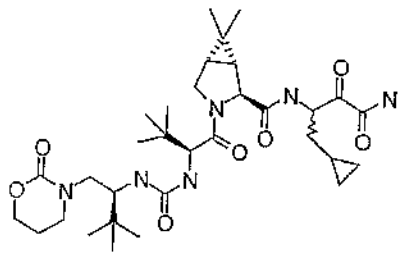
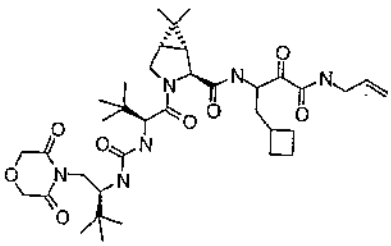
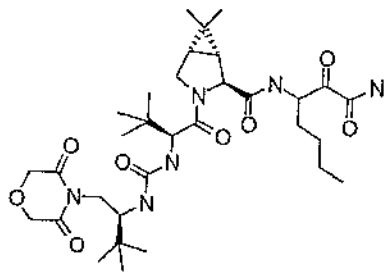


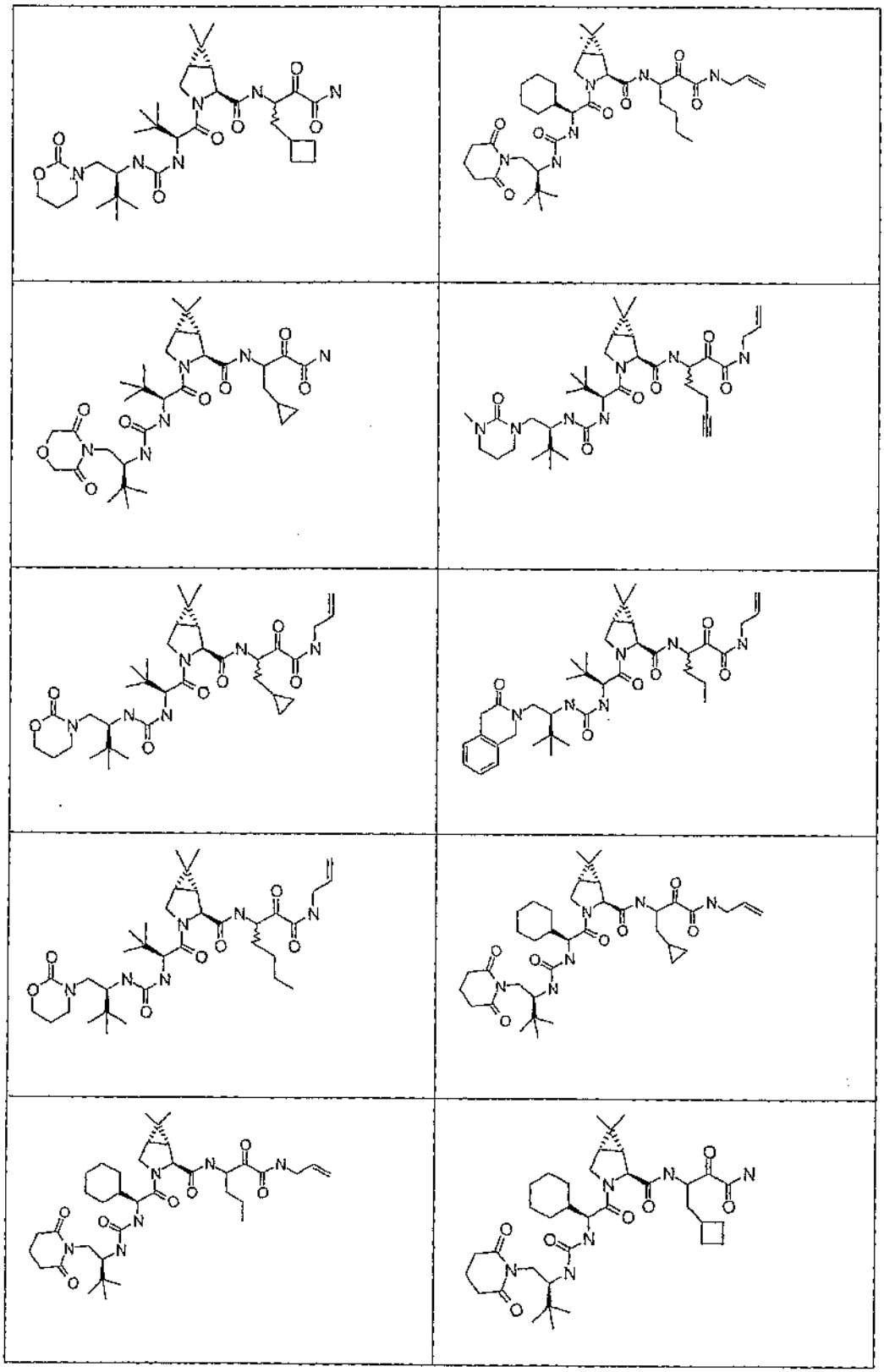
	
	
	
	

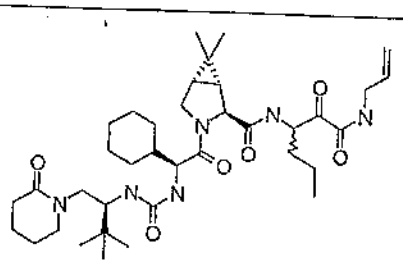
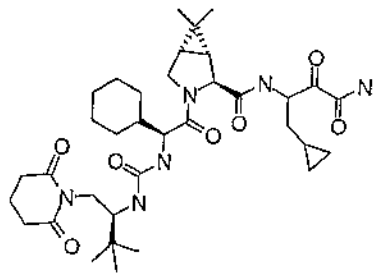
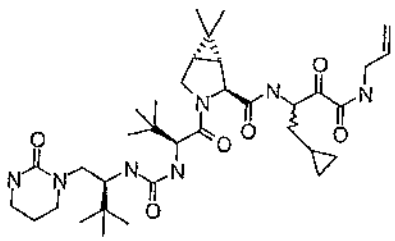
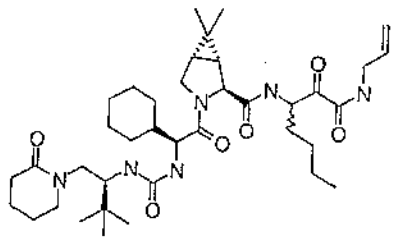
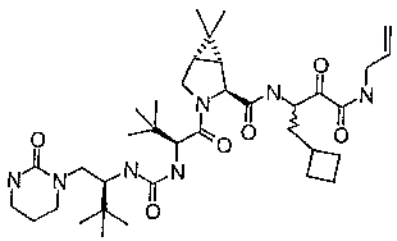
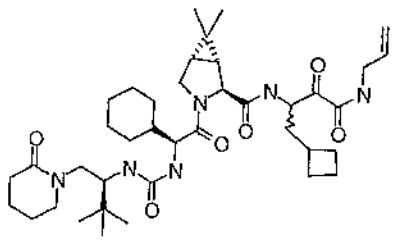
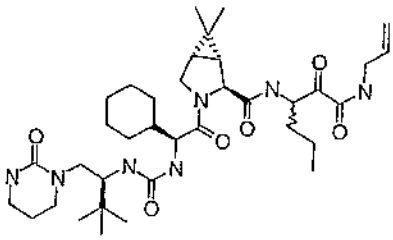
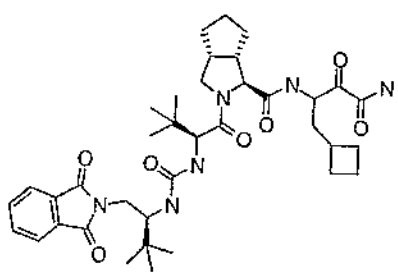


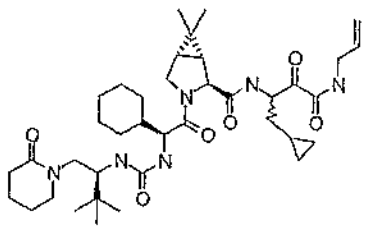
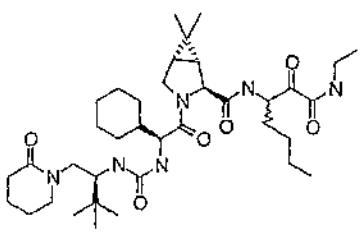
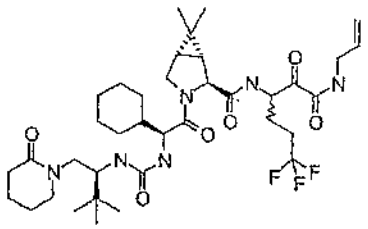
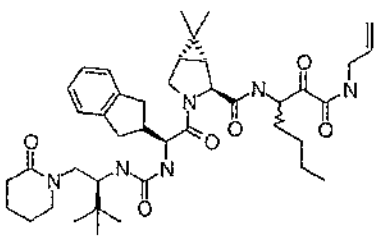
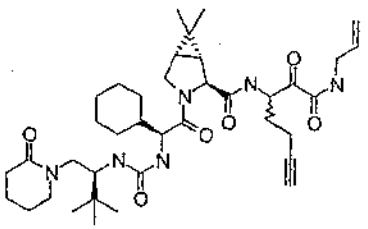
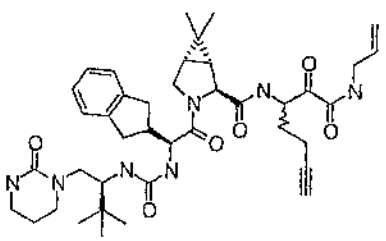
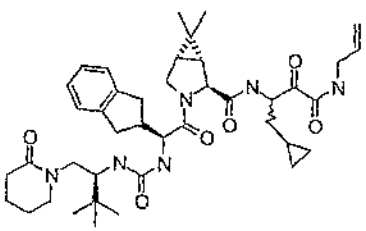
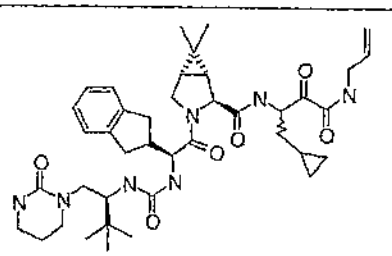


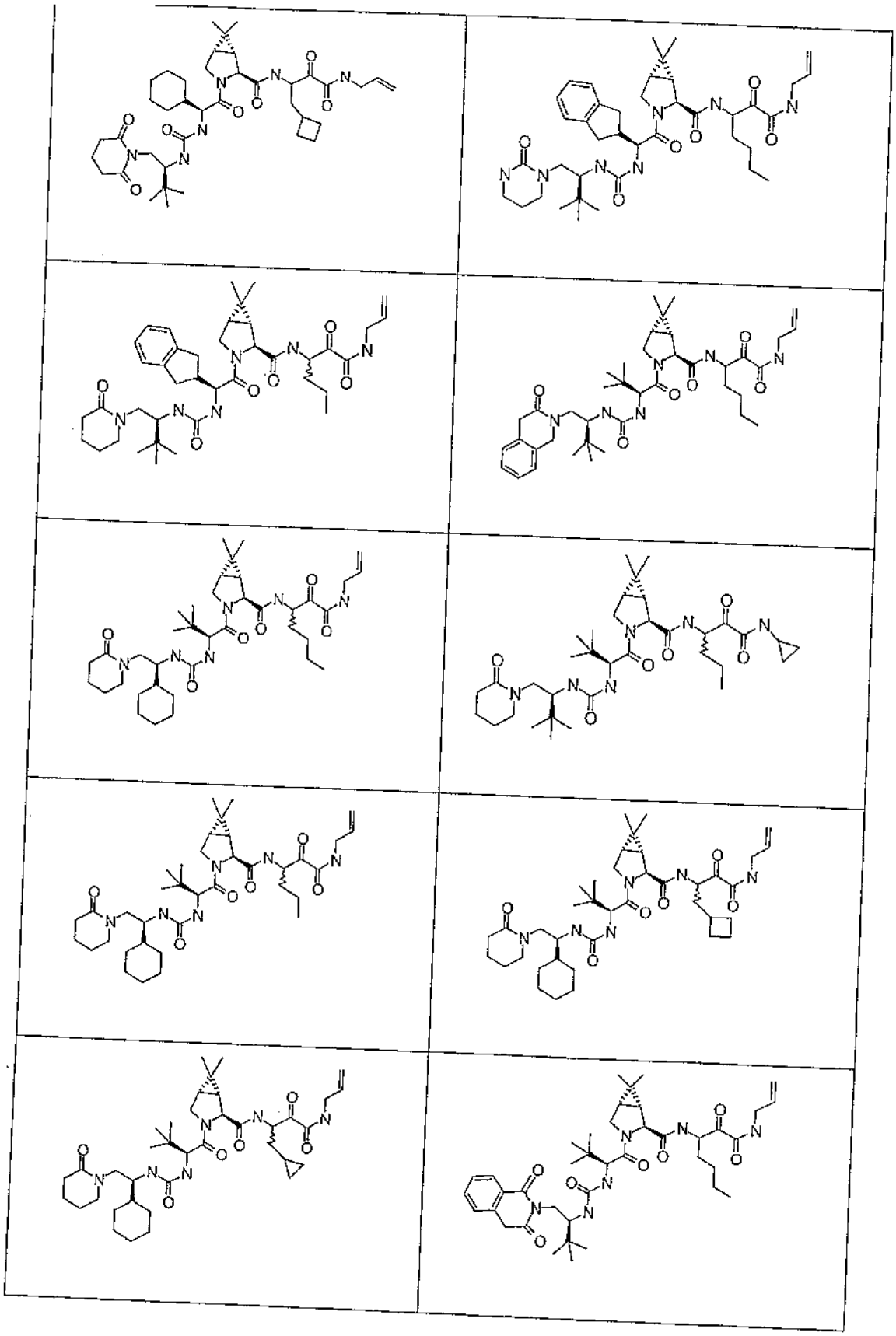


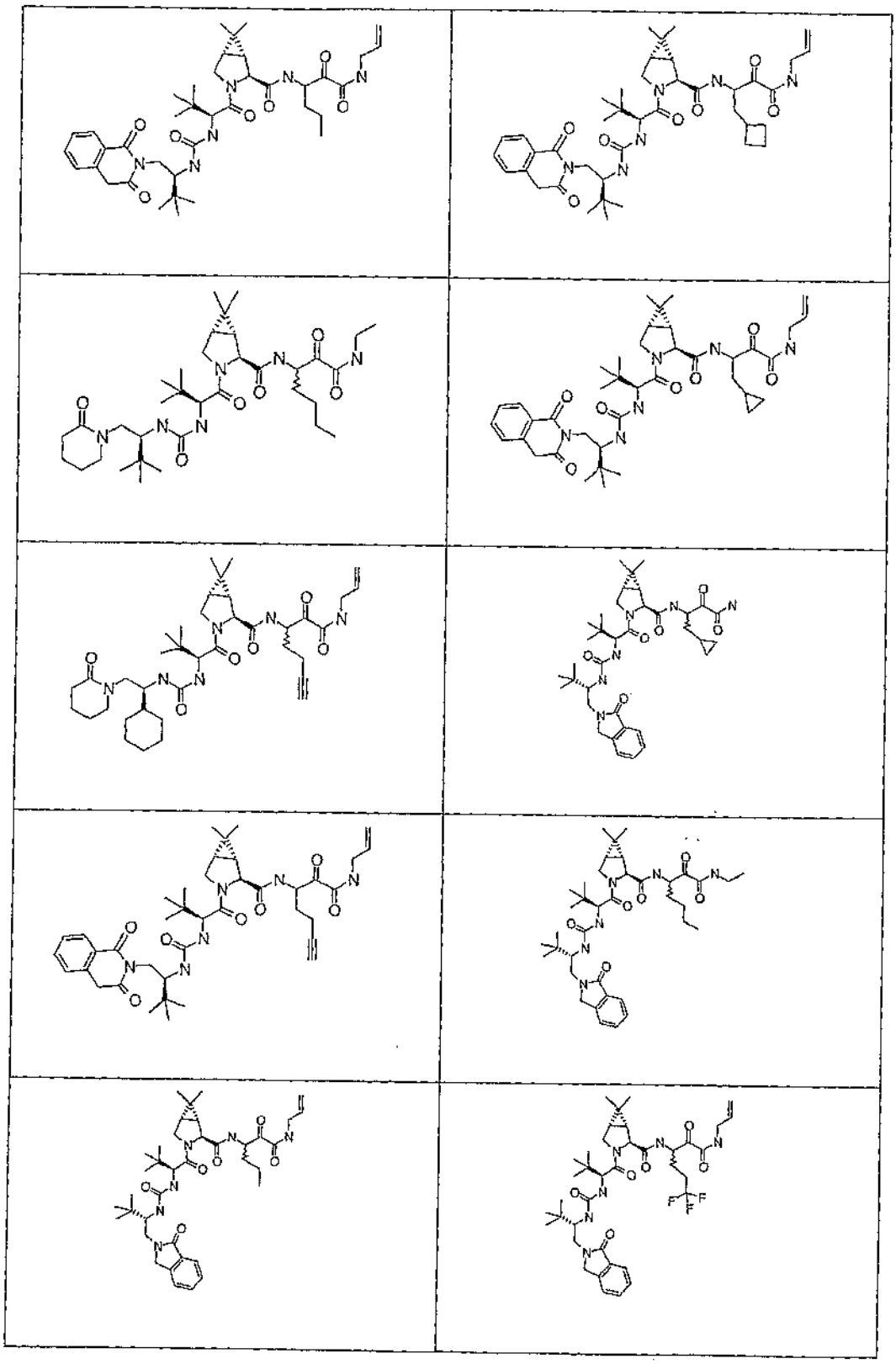
	
	
	

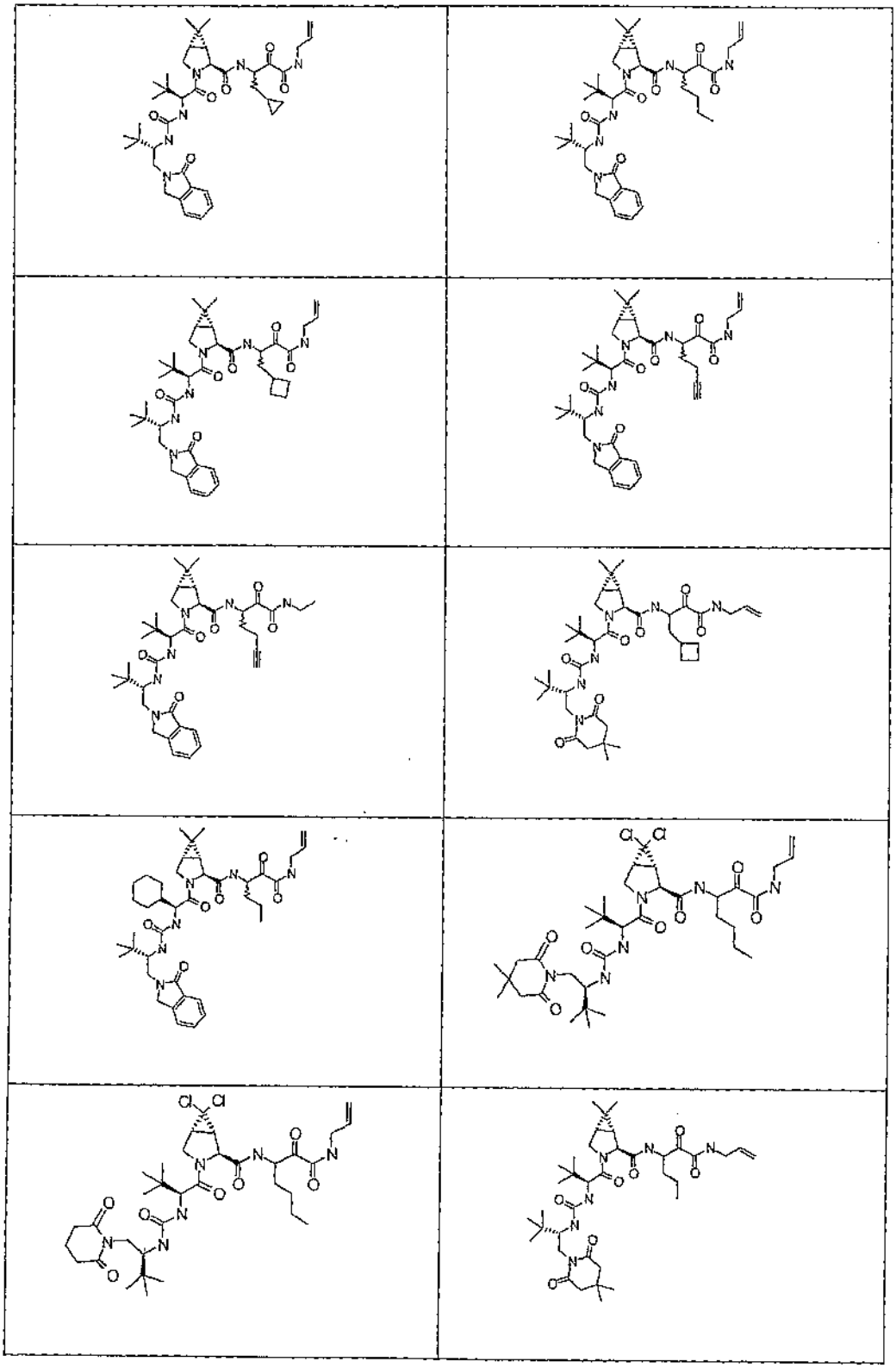


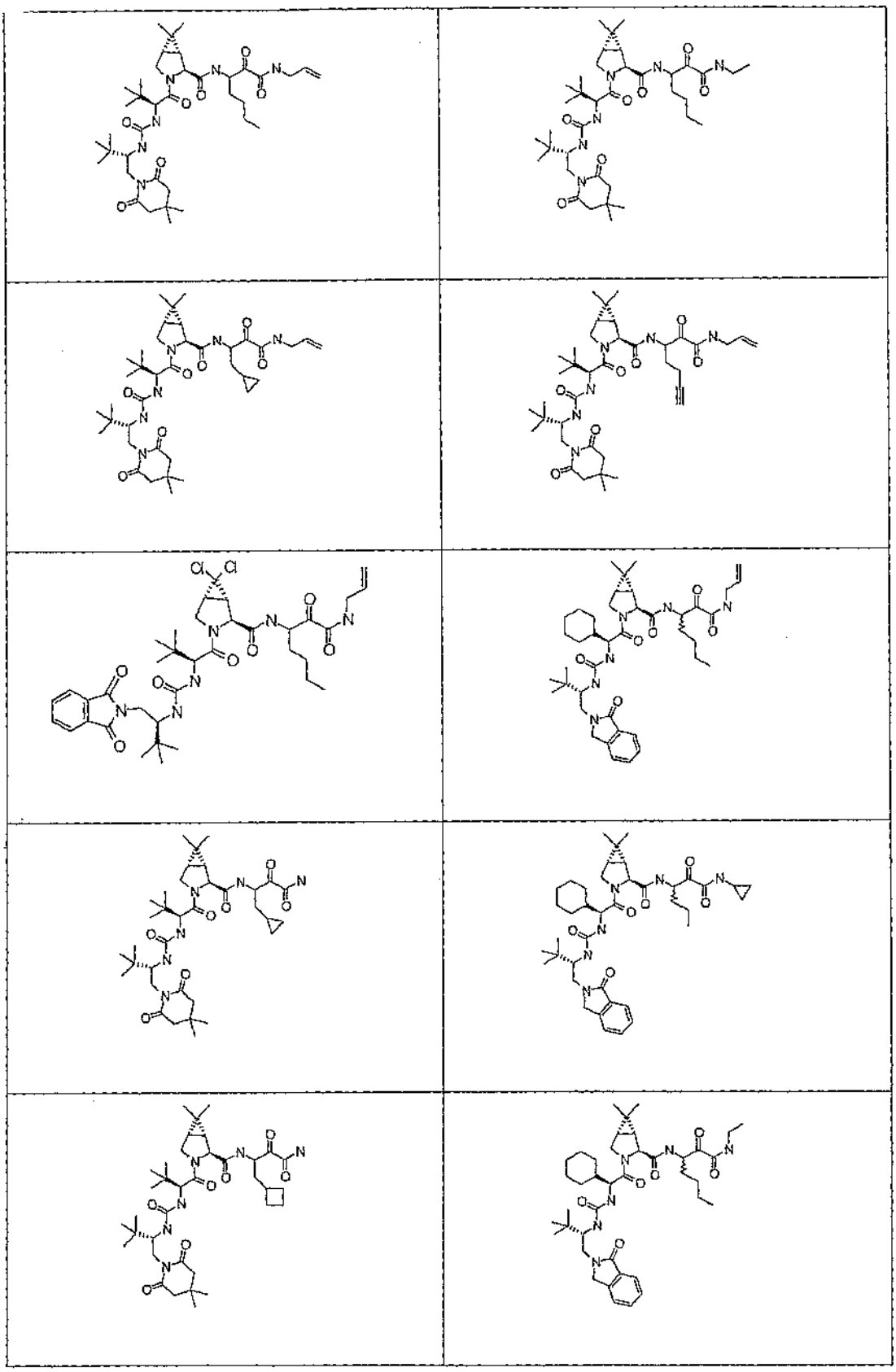
	
	
	
	

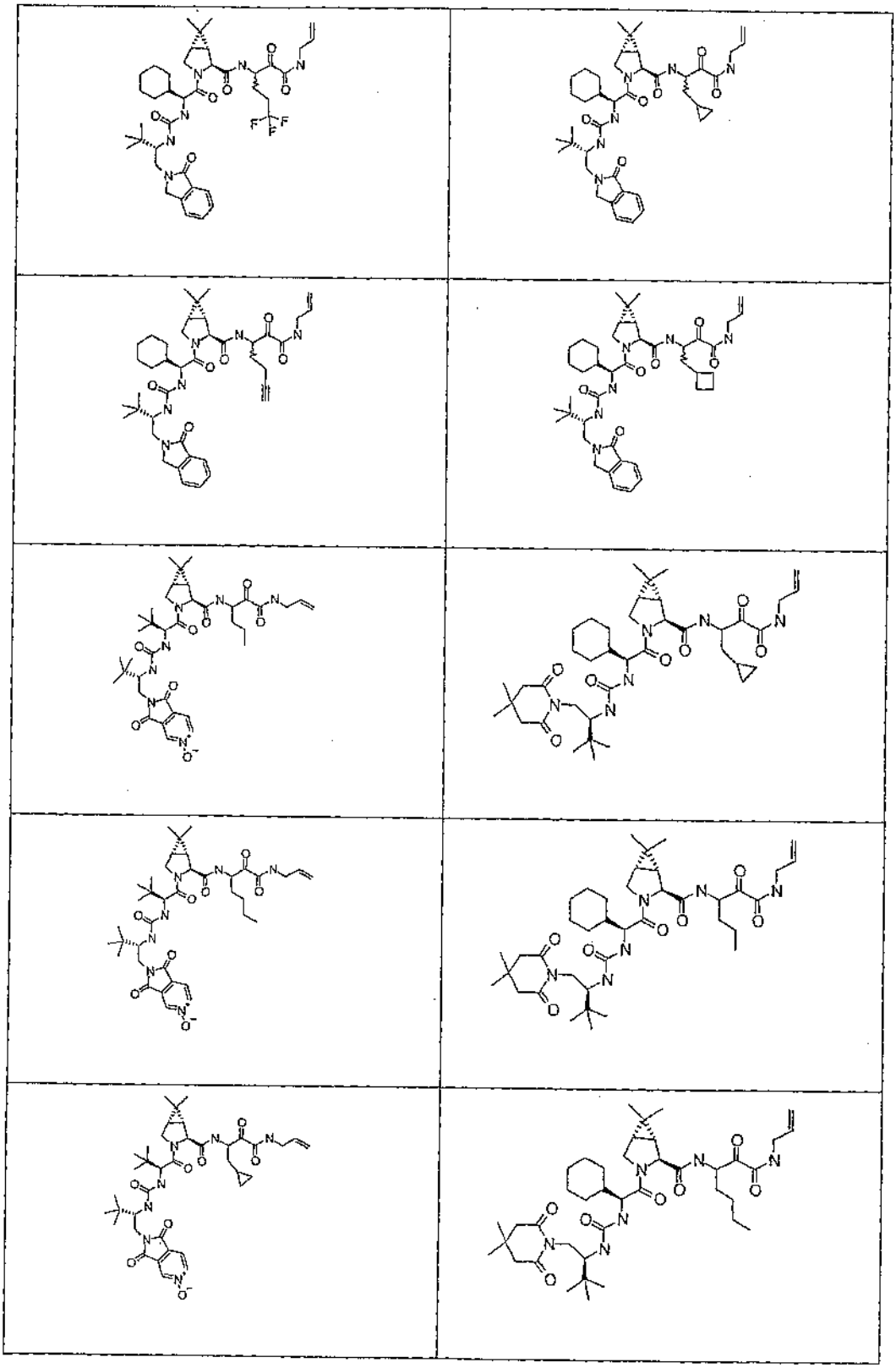
	
	
	
	

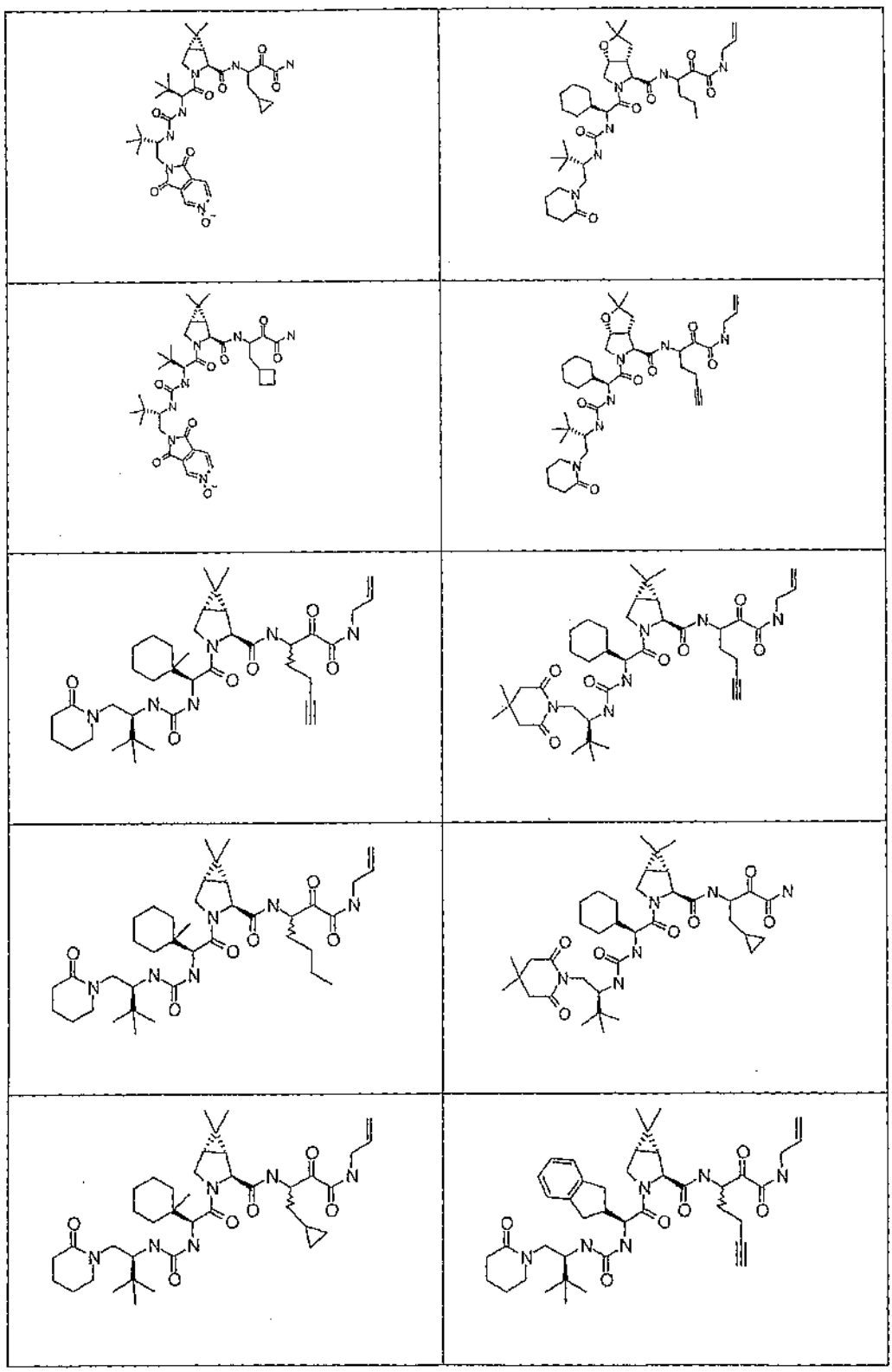


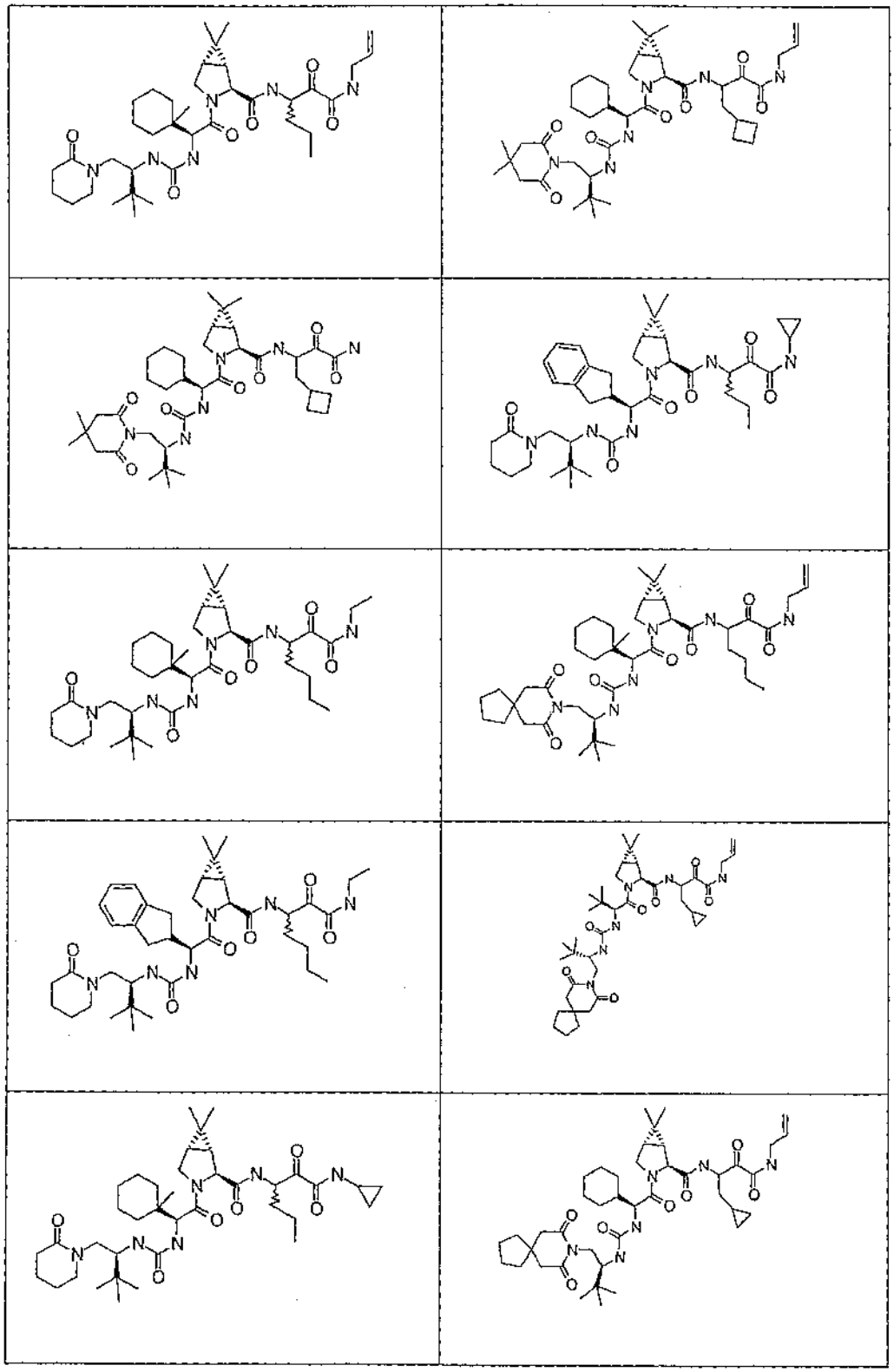


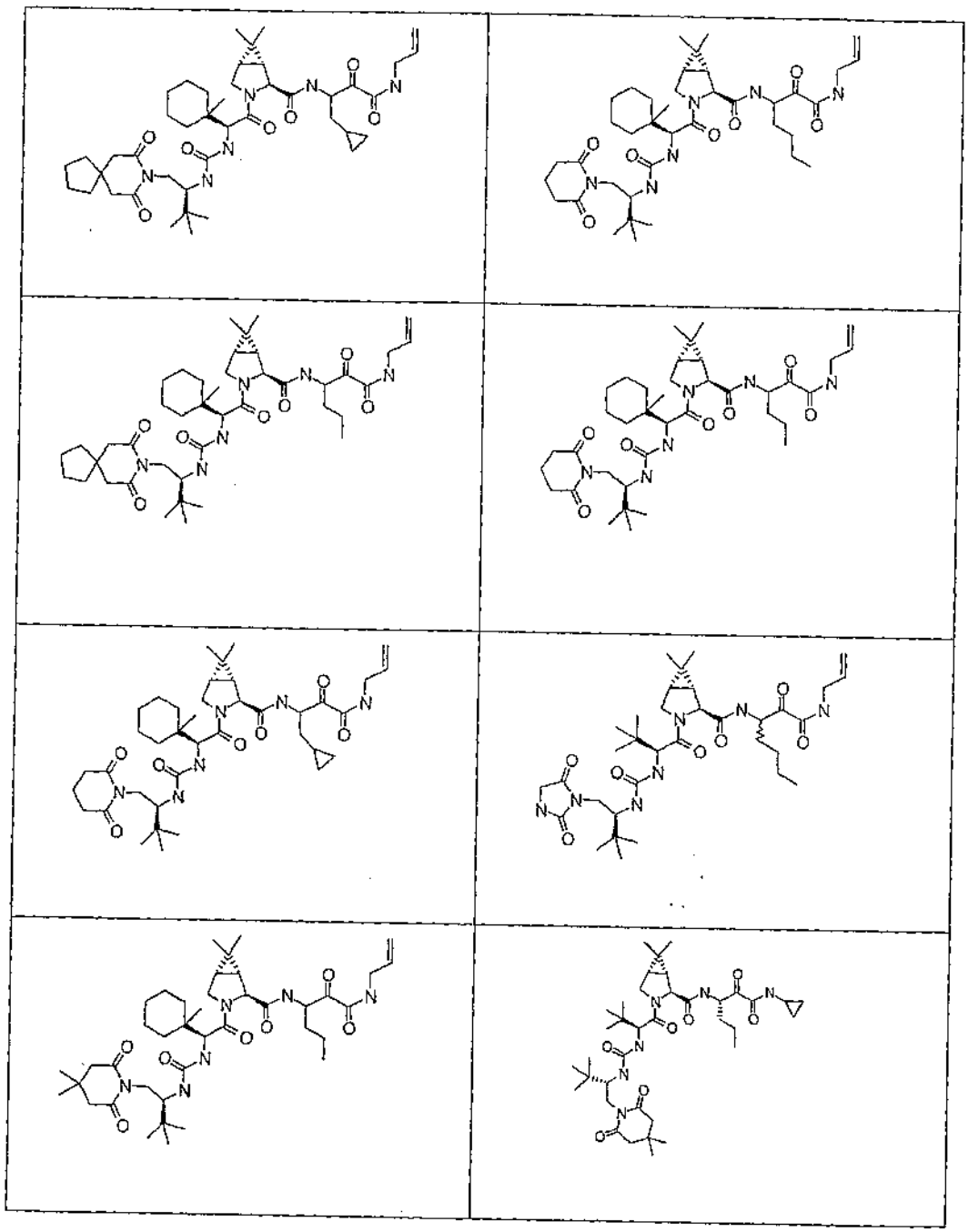


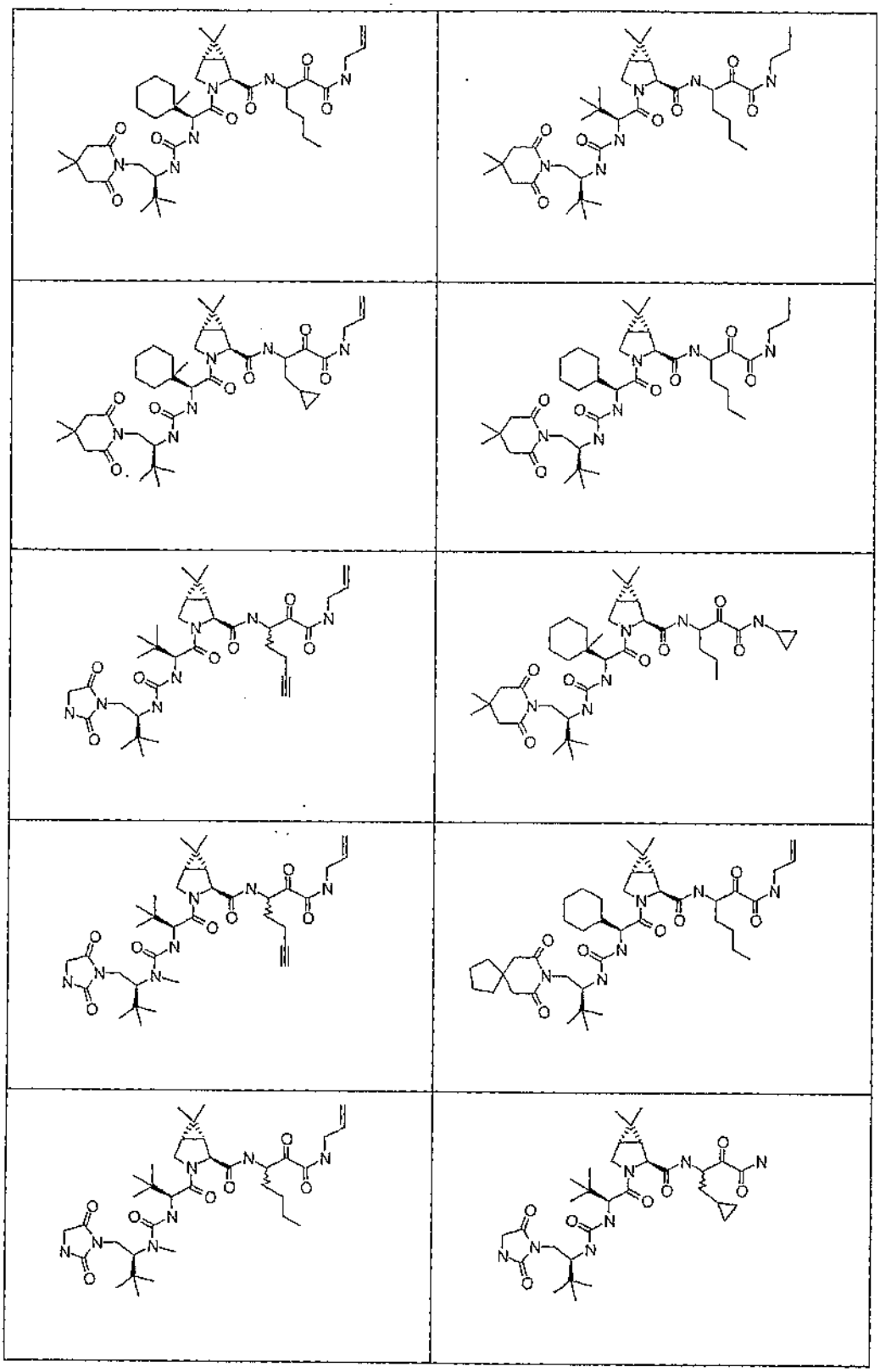


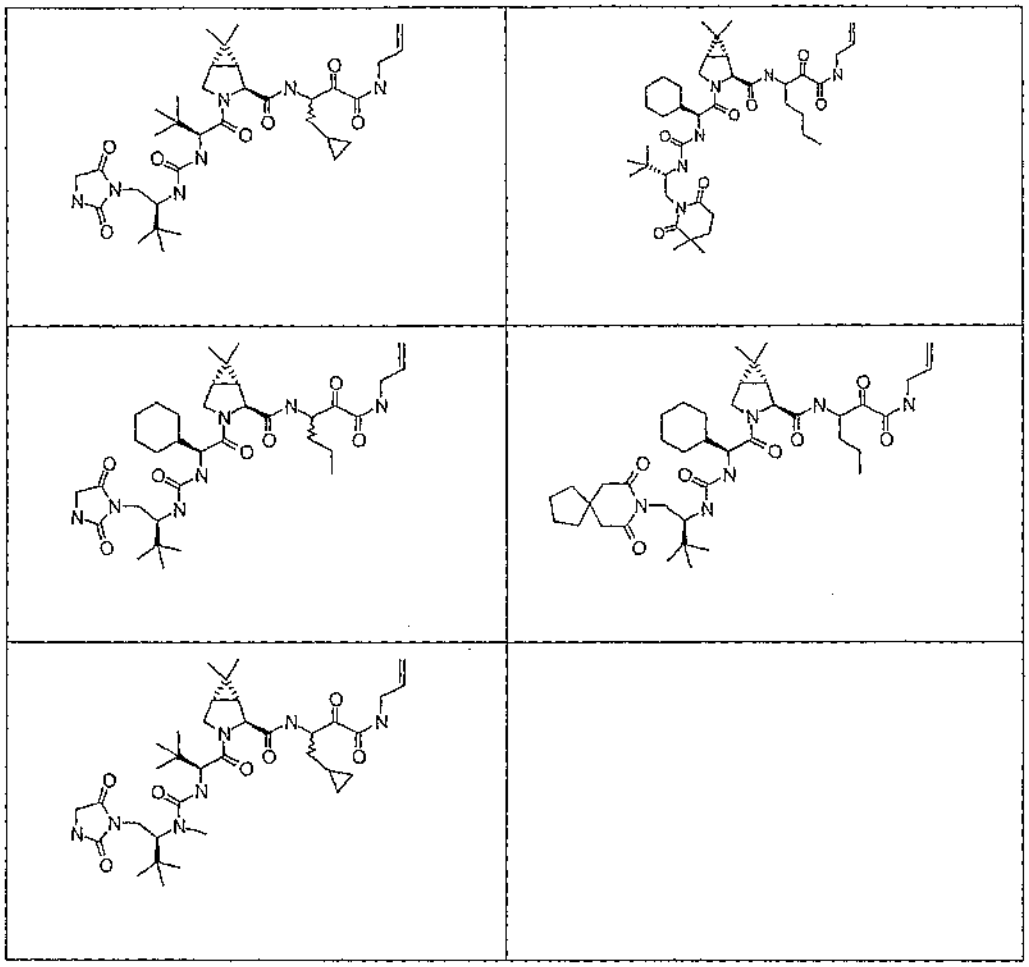








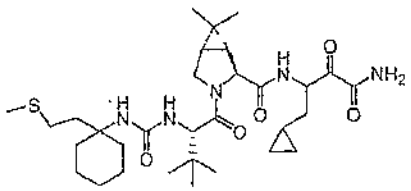


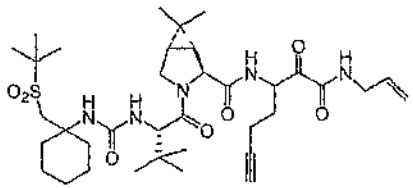


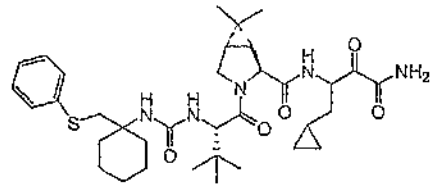
or a pharmaceutically acceptable salt, solvate or ester thereof.

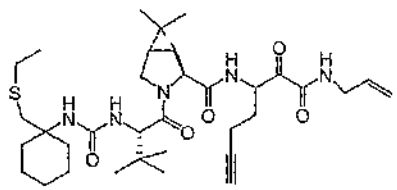
Compounds of formula XIV are disclosed in U.S. Patent Application Ser. No. 11/064,673 filed February 24, 2005. The preparation of these compounds is disclosed in the experimental section of this application set forth hereinbelow.

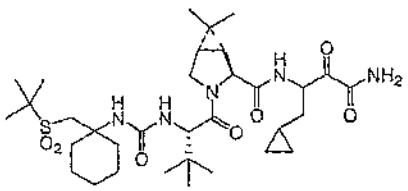
Non-limiting examples of certain compounds disclosed in U.S. Patent Application Ser. No. 11/064,673 are:

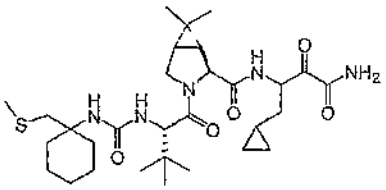


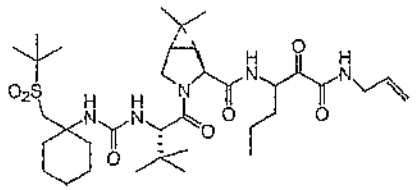


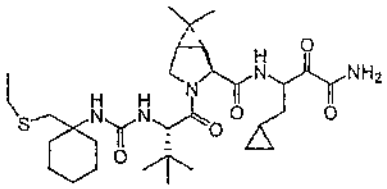


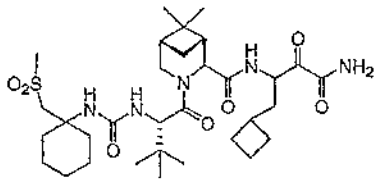


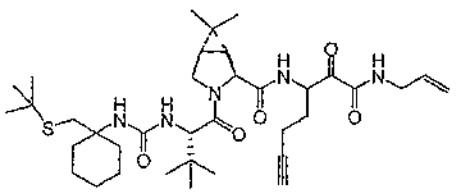


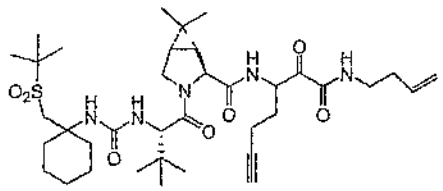


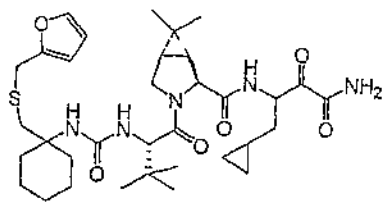


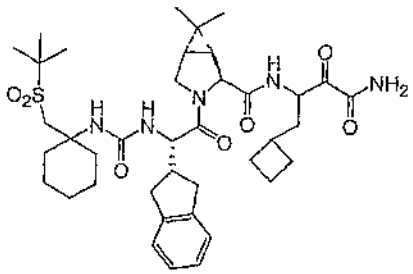


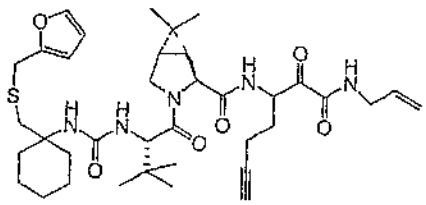


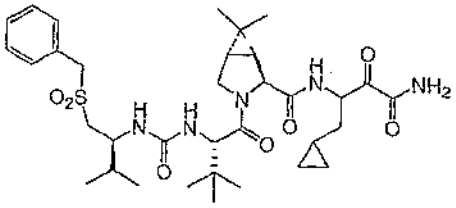


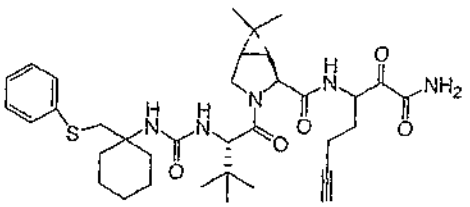


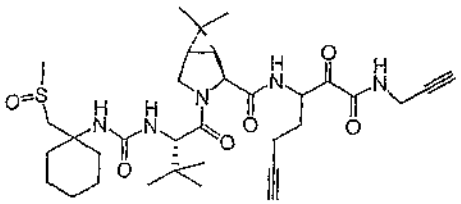


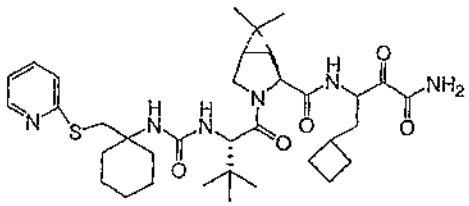


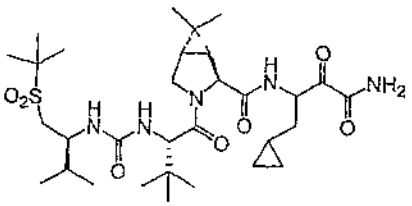


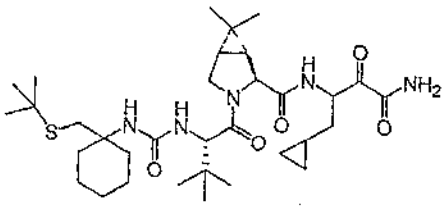


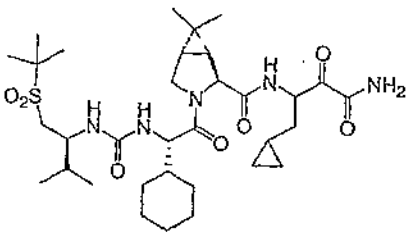


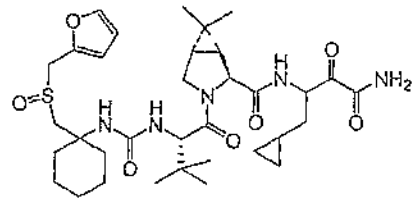


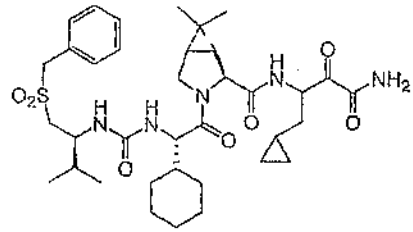


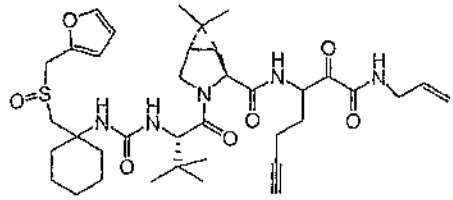


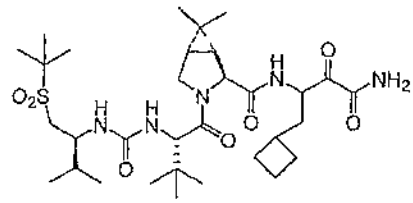


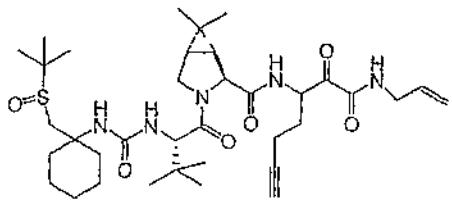


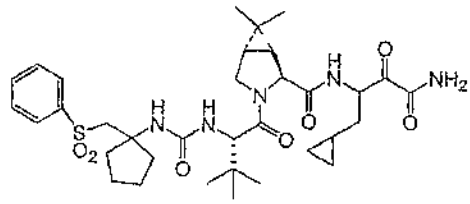


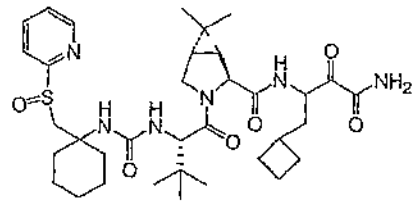


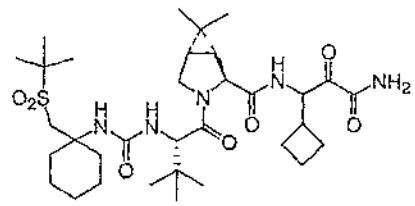


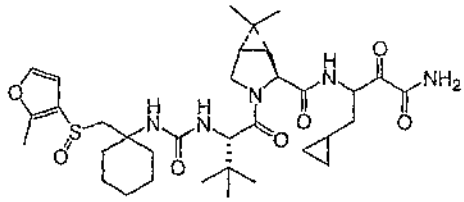


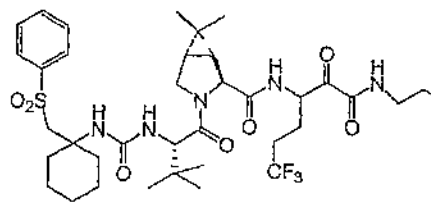


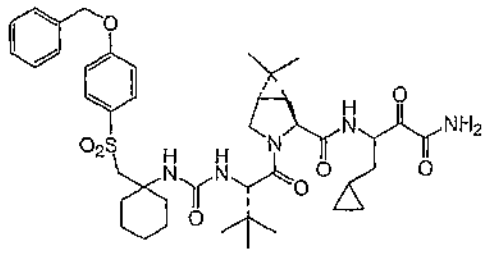


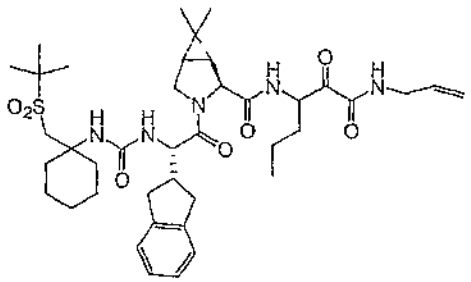


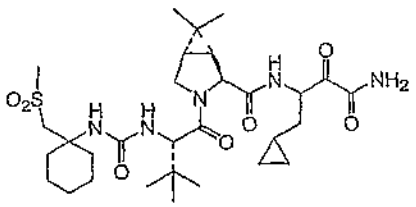


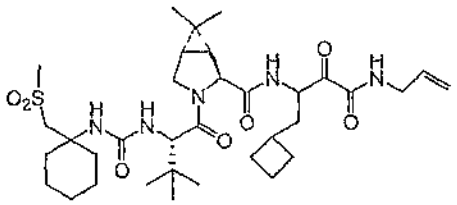


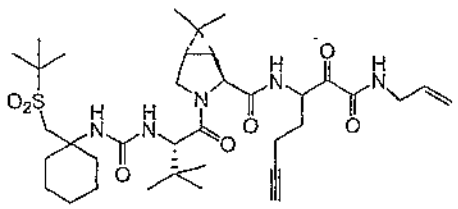


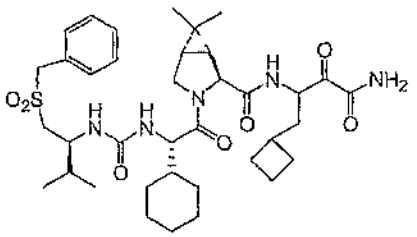


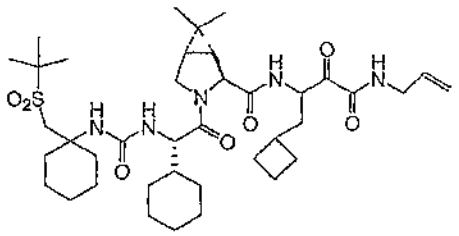


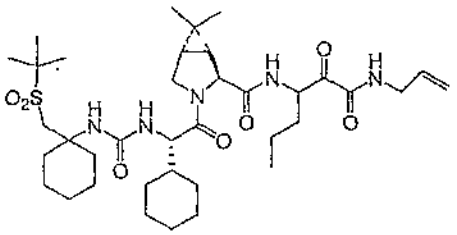


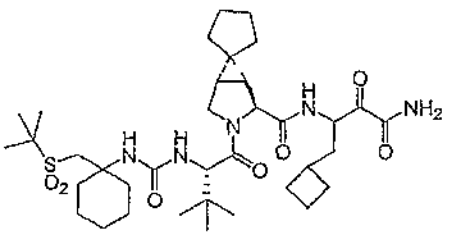


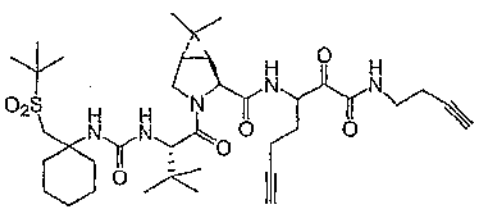


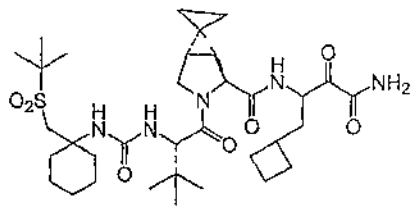


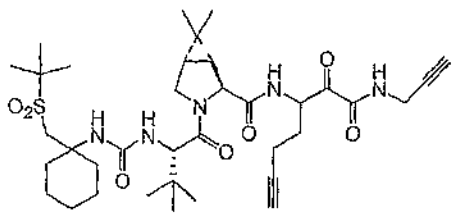


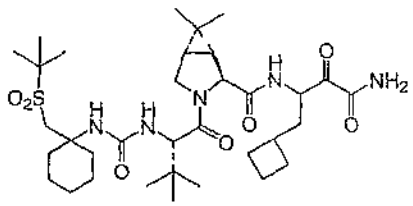


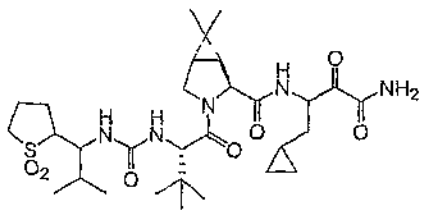


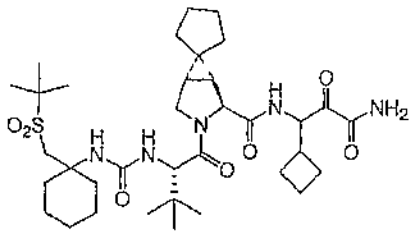


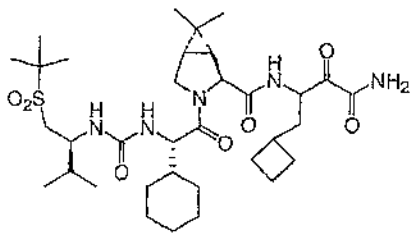


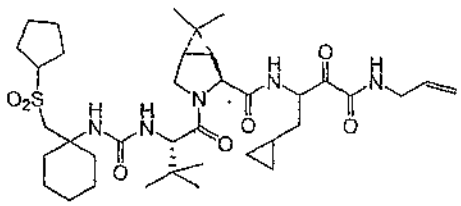


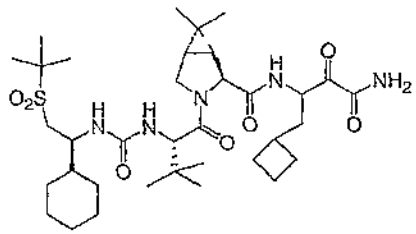


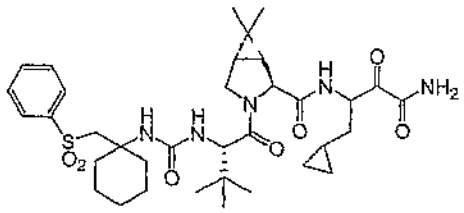


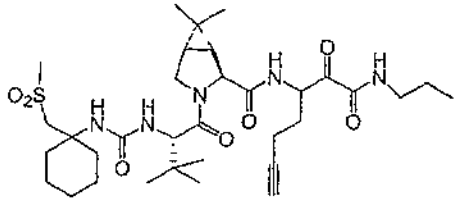


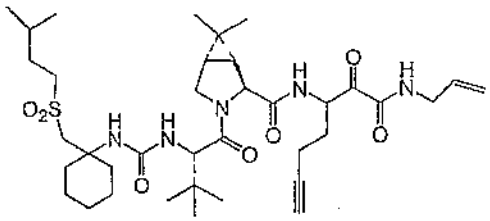


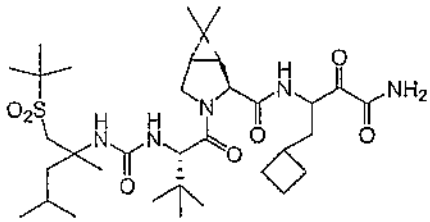


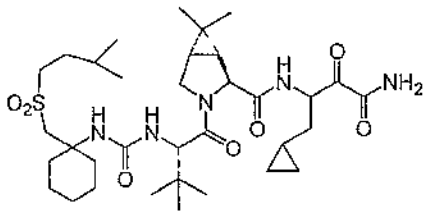


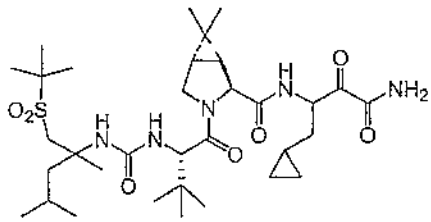


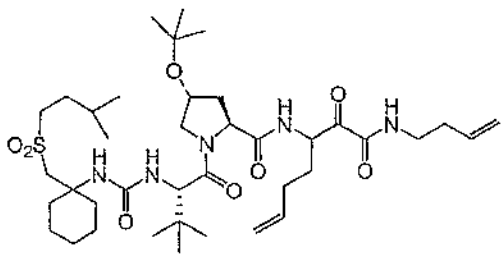


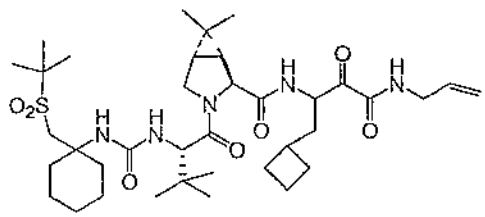


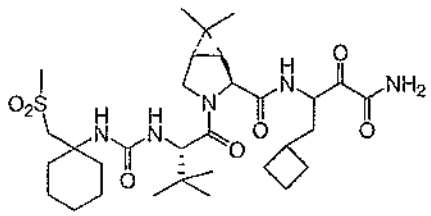


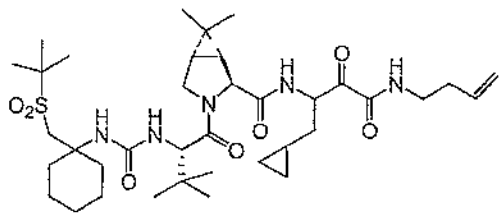


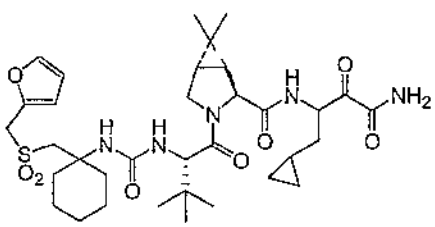


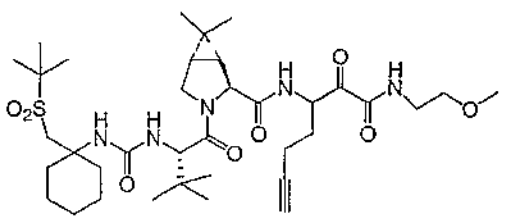


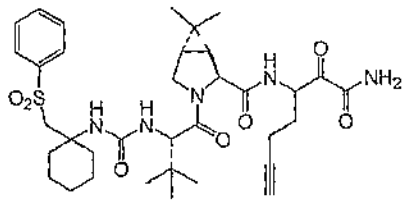


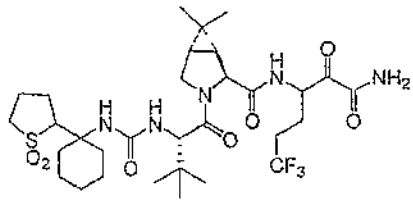


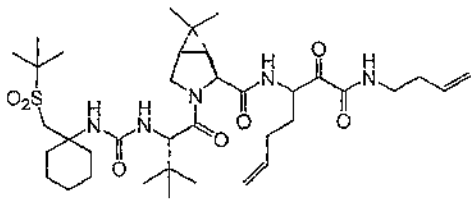


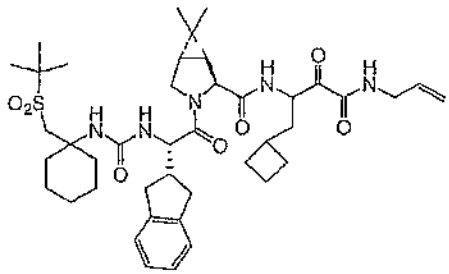


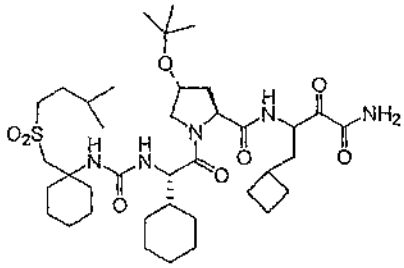


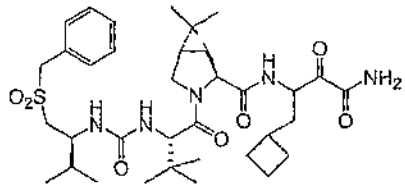


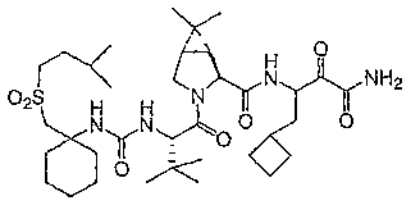


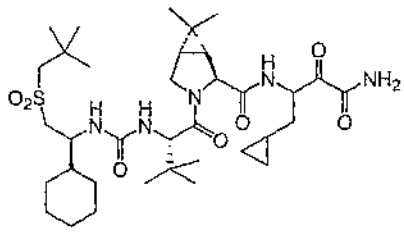


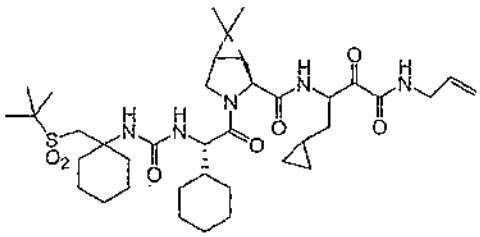


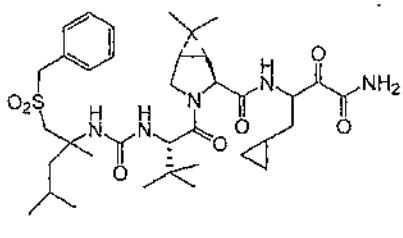


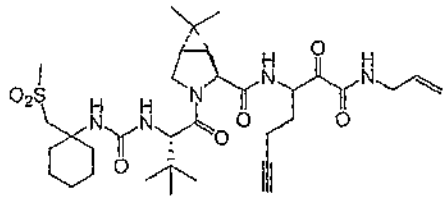


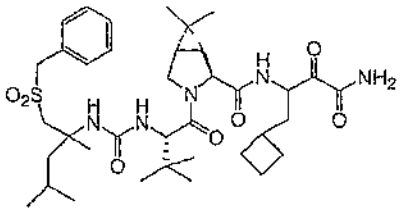


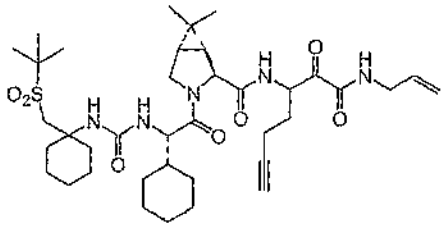


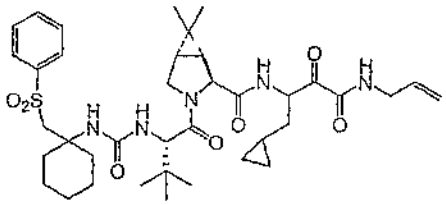


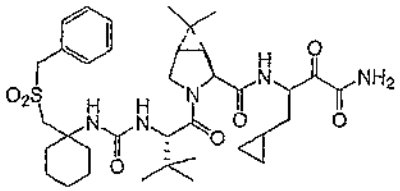


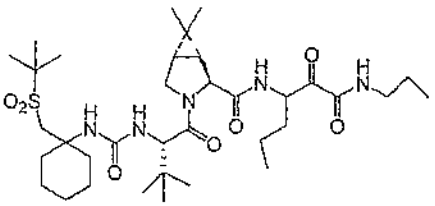


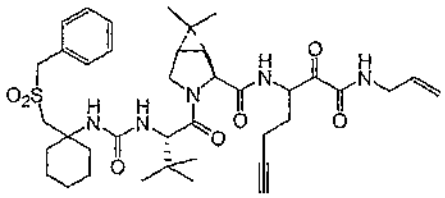


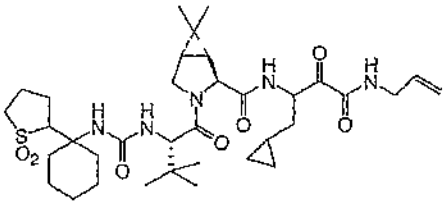


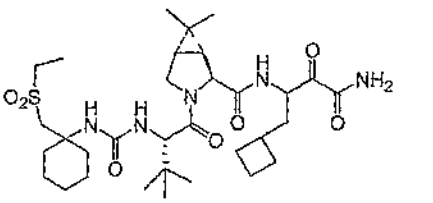


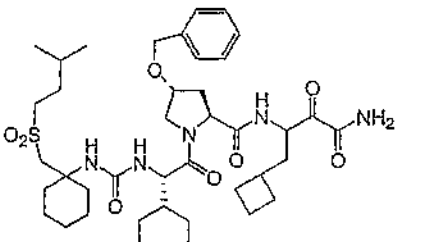


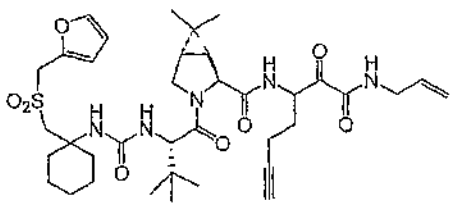


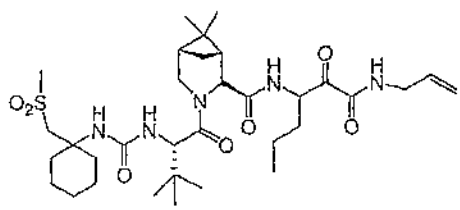


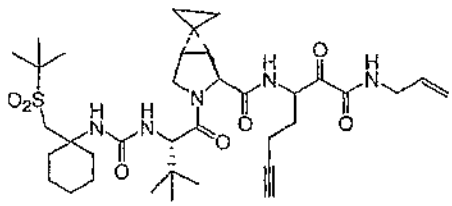


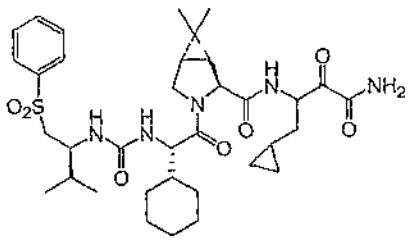


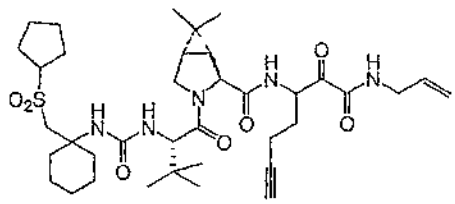


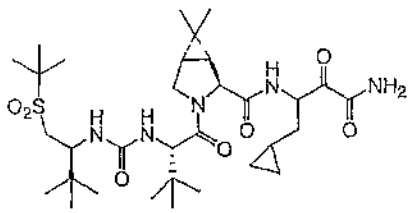


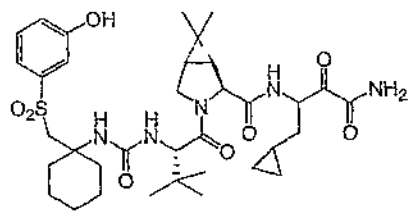


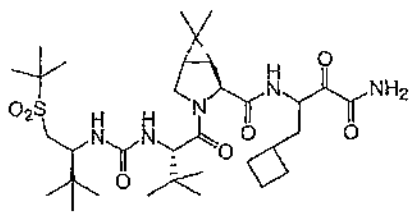


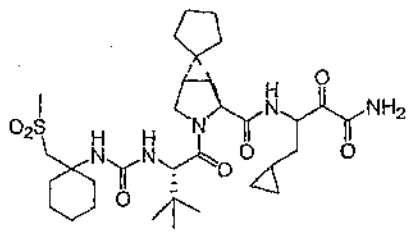


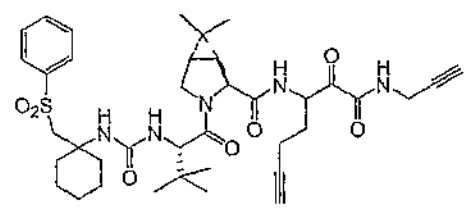


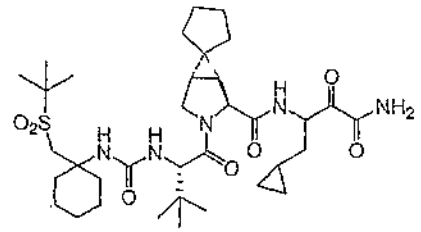


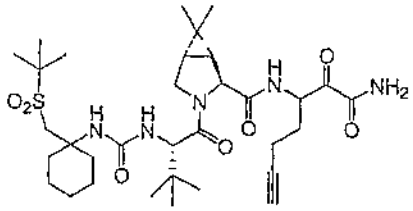


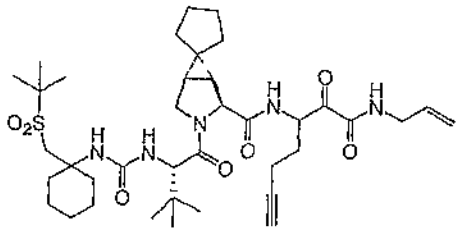


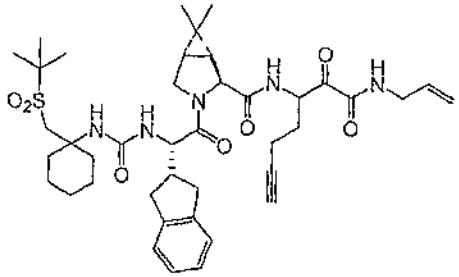


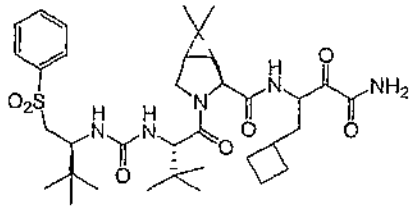


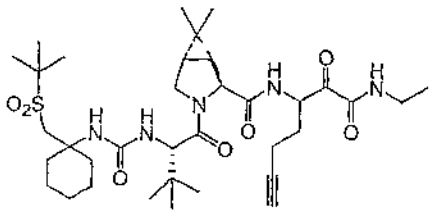


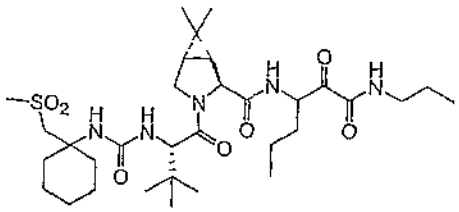


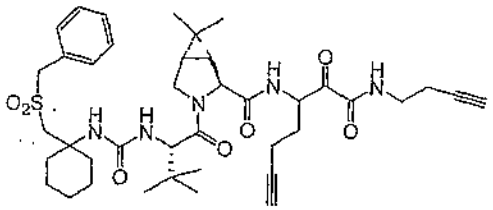


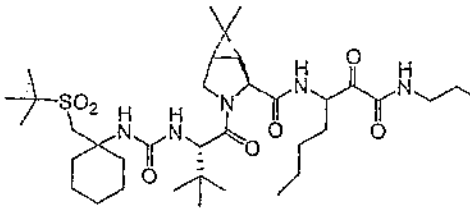


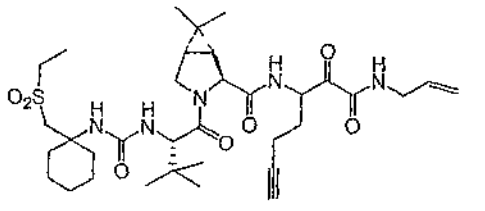


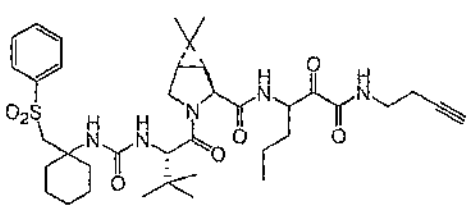


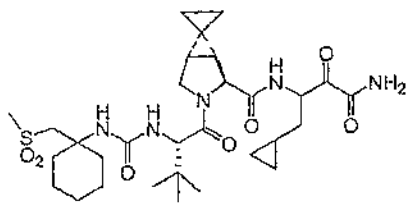


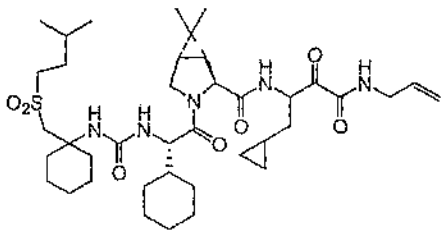


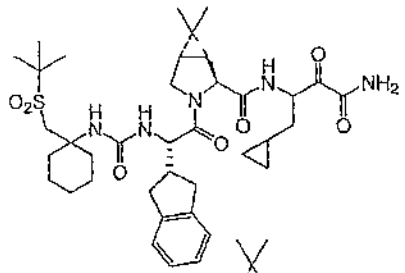


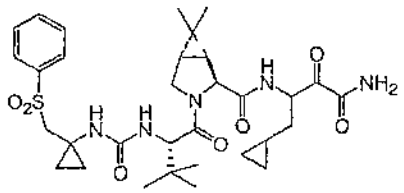


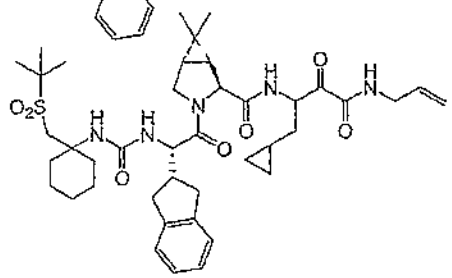


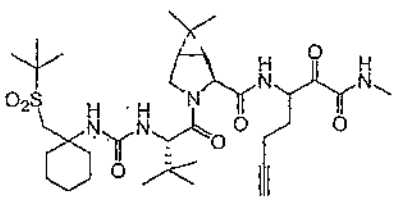


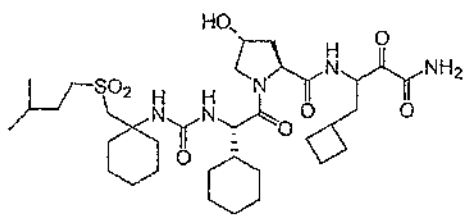


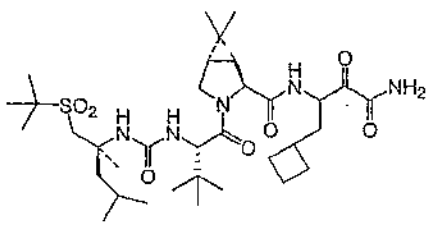


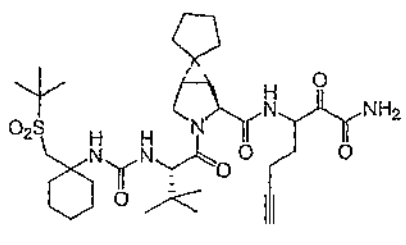


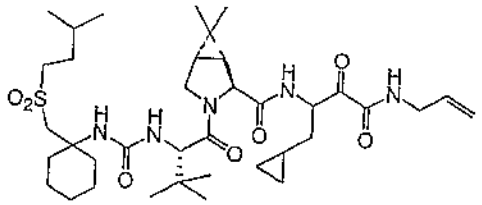


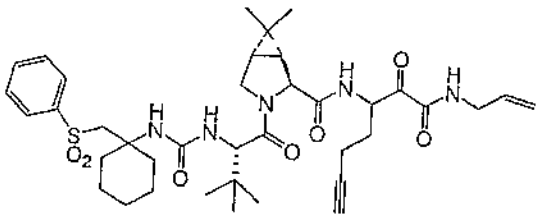


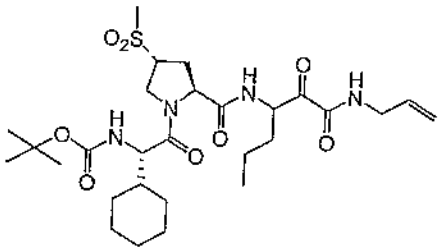


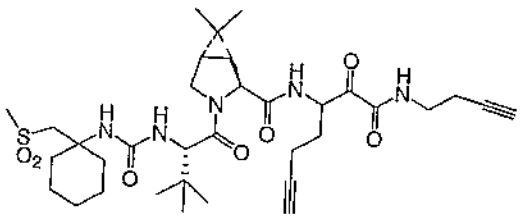


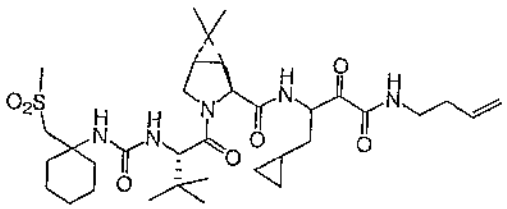


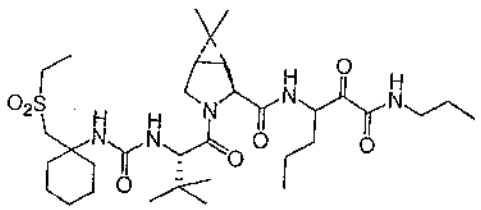


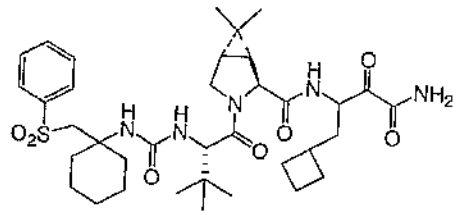


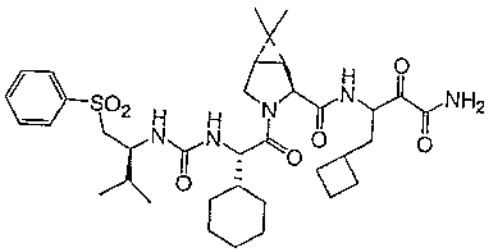


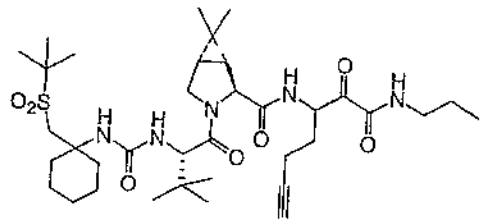


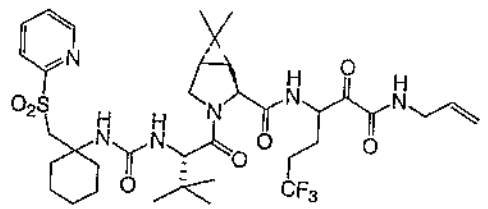


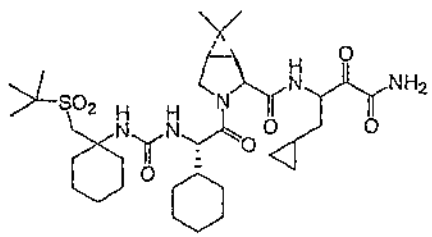


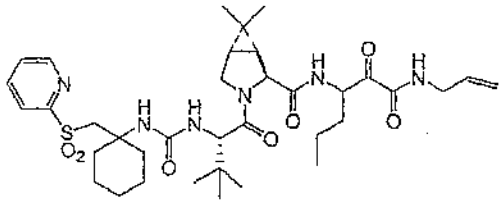


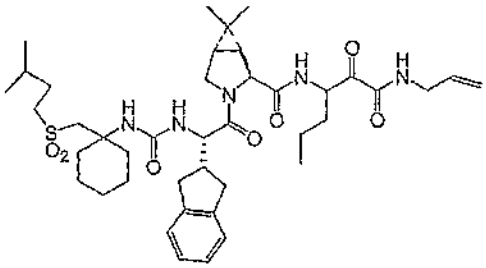


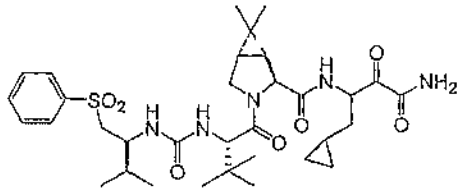


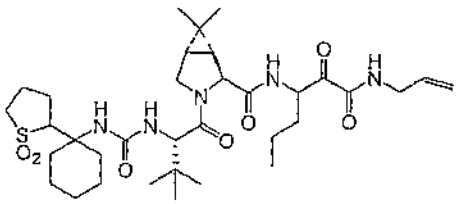


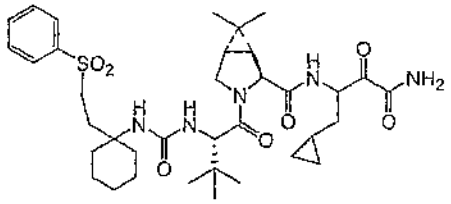


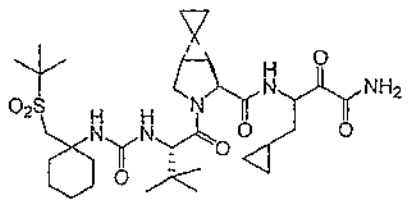


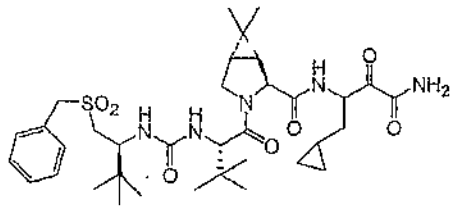


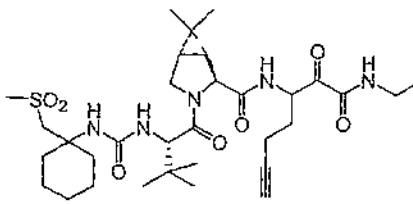


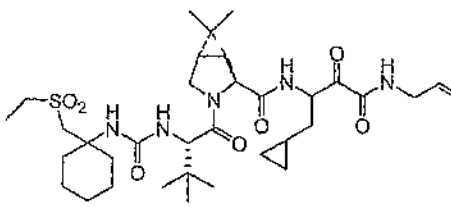


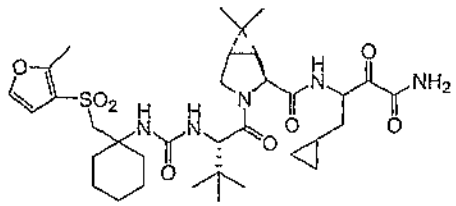


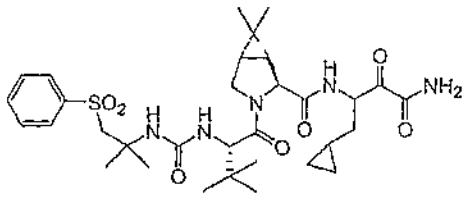


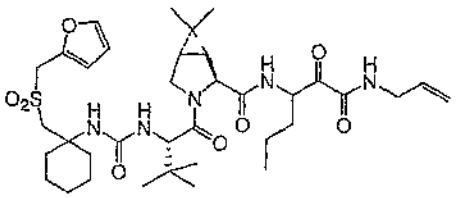


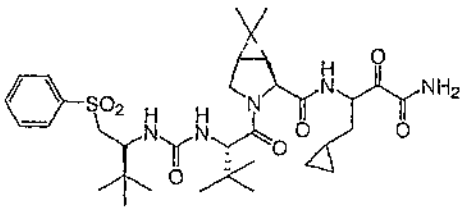


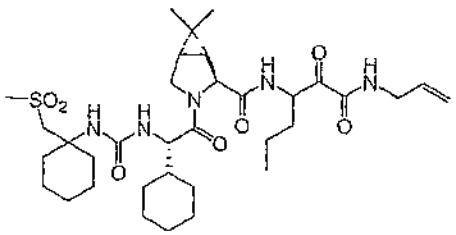


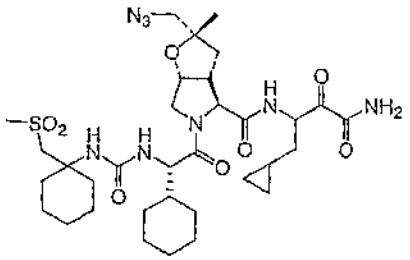


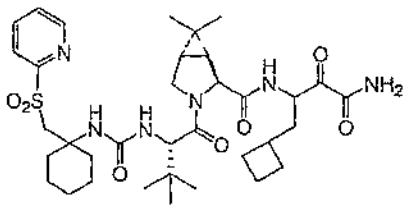


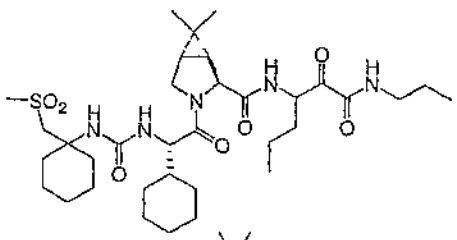


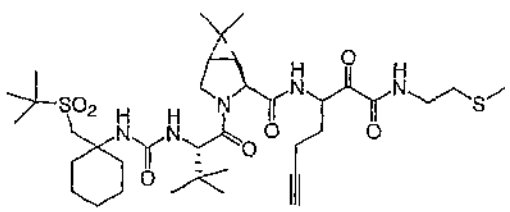


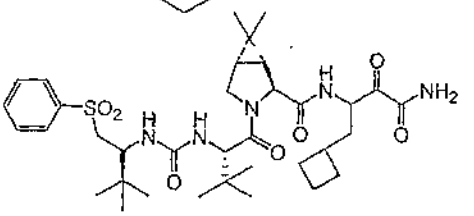


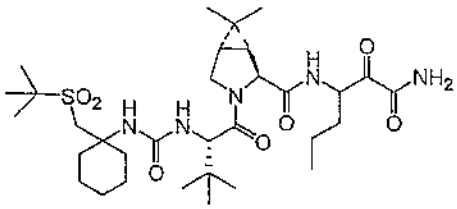


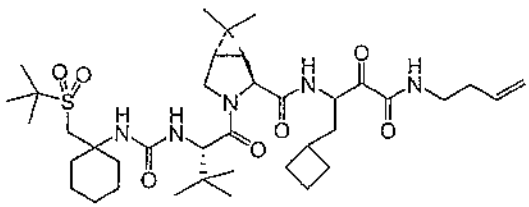


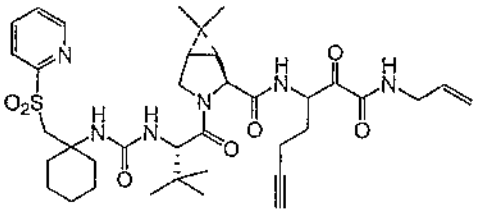


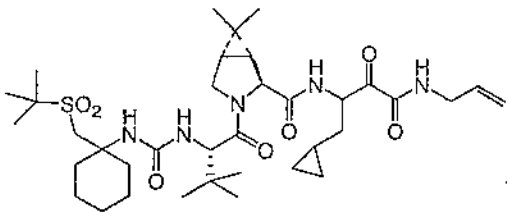


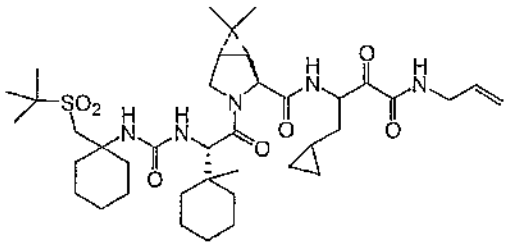


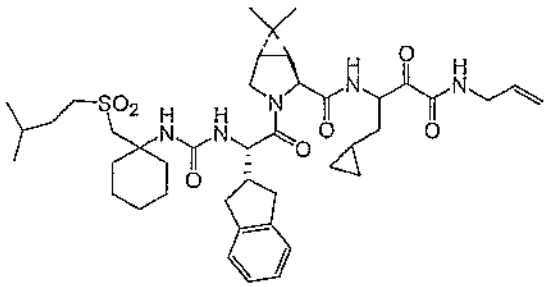


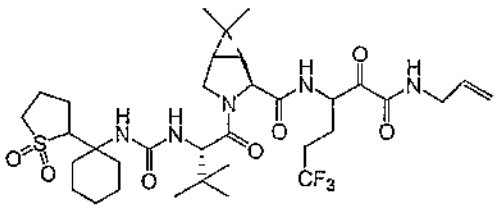


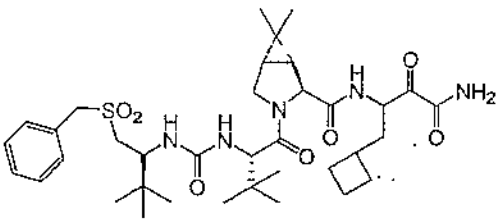


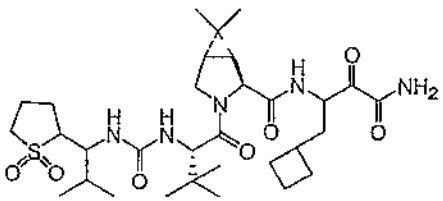


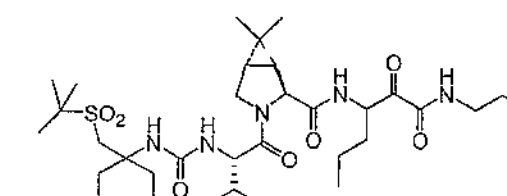


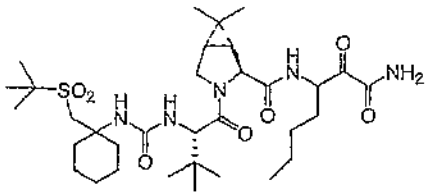


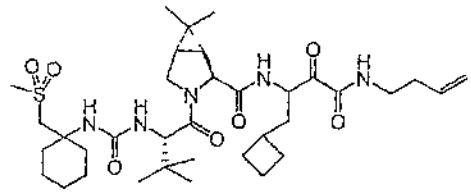


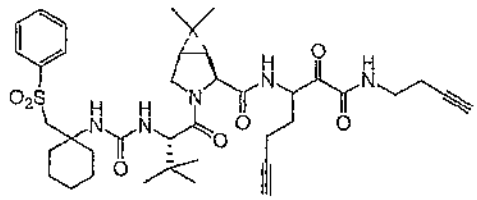


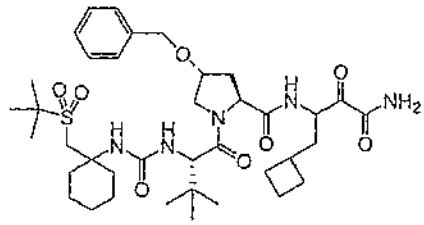


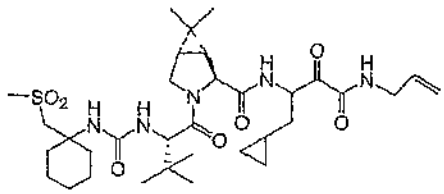


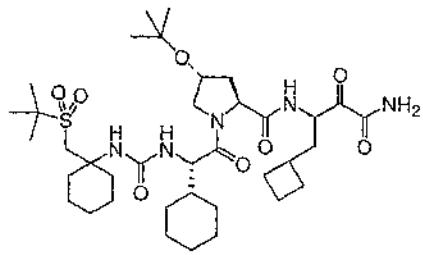


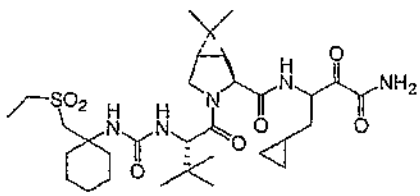


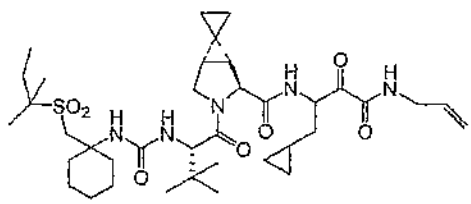


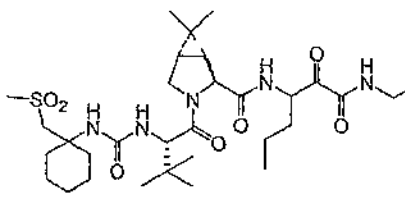


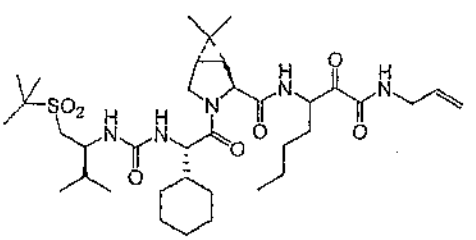


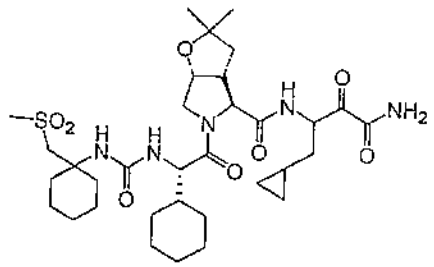


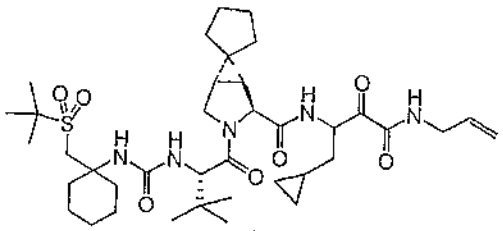


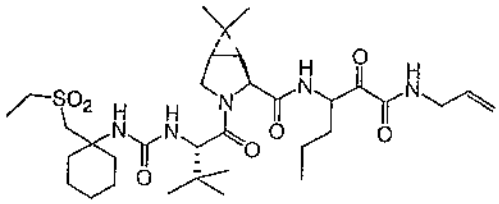


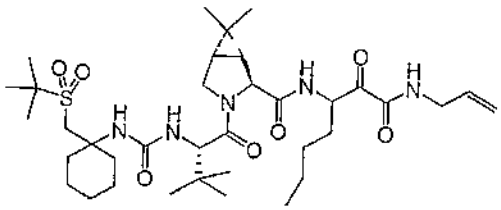


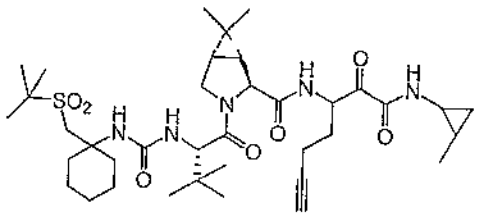


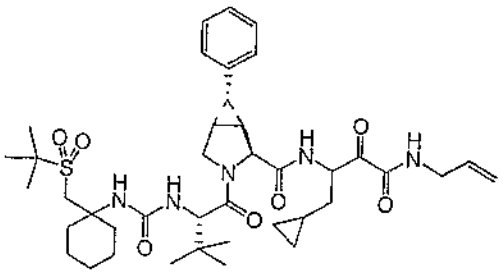


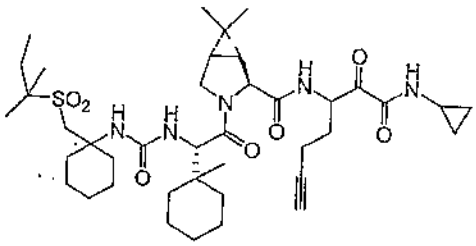


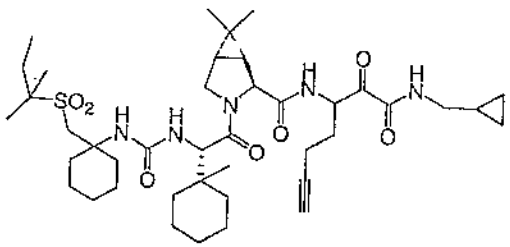


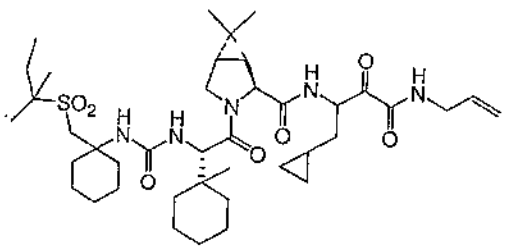


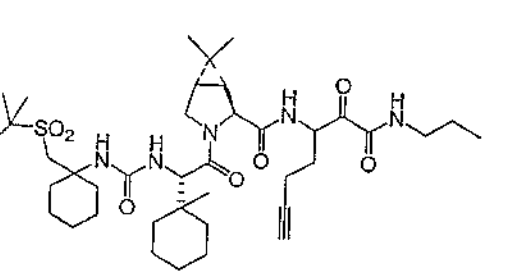


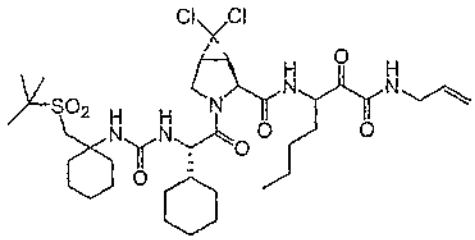


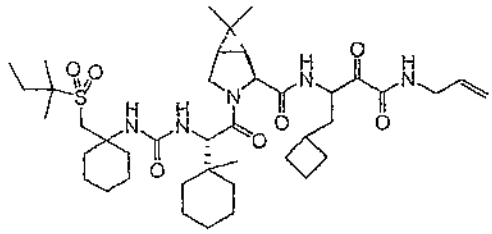


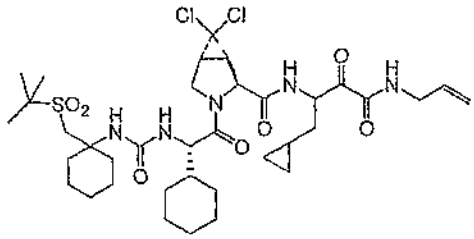


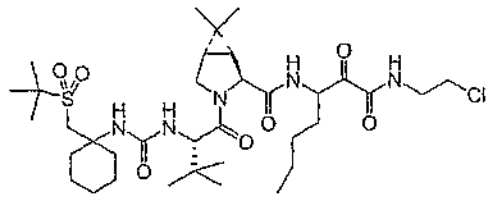


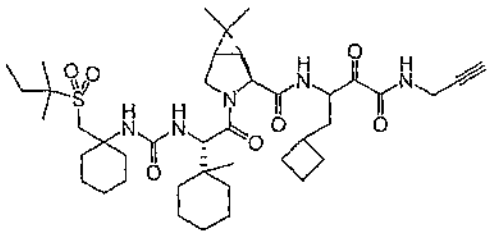


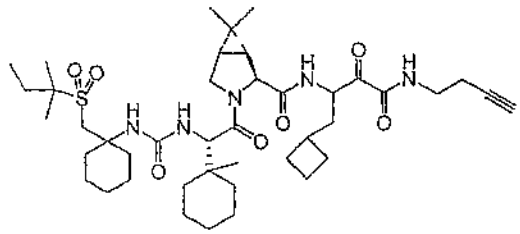


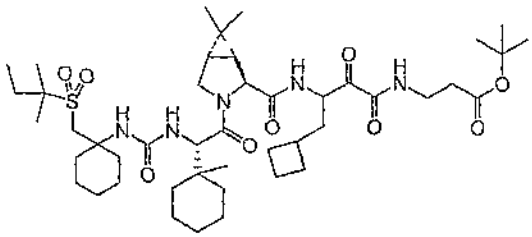


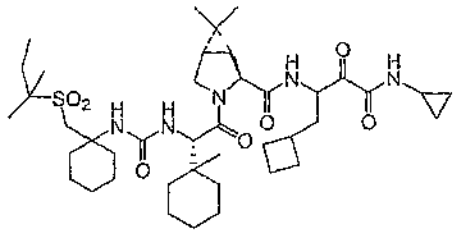


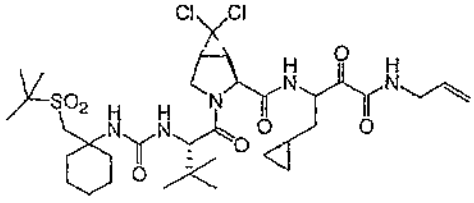


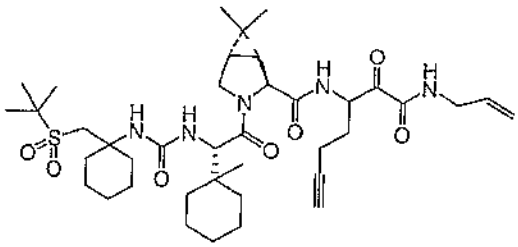


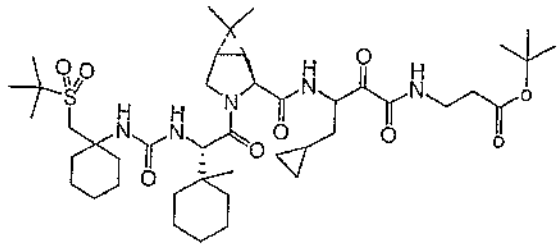


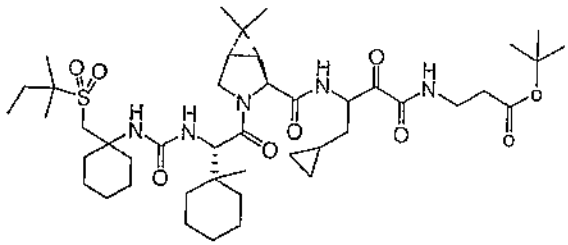


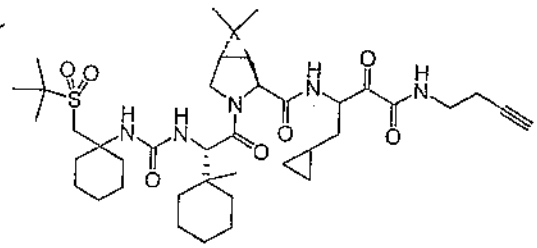


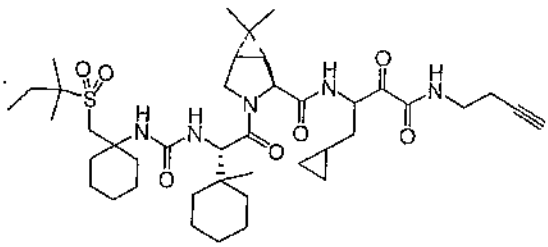


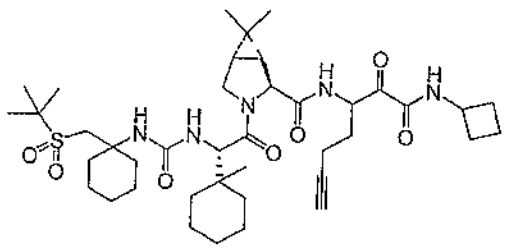


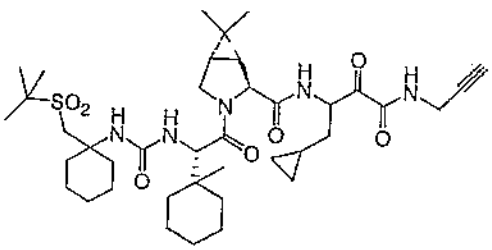


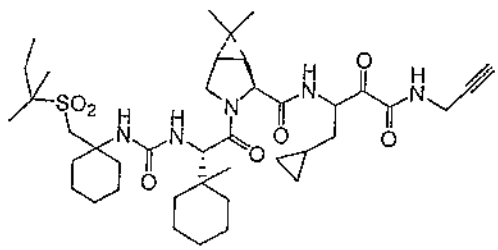


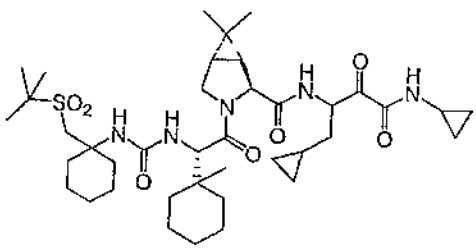


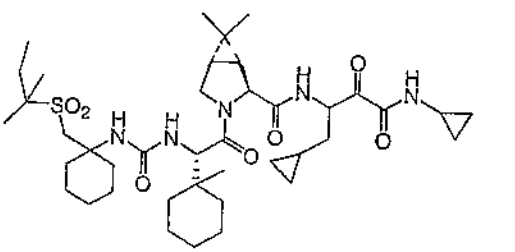


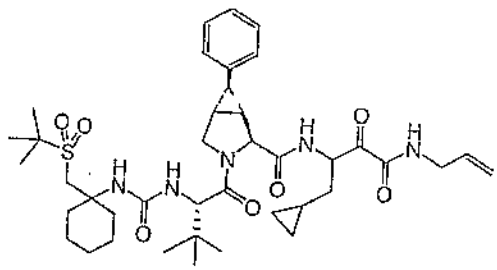


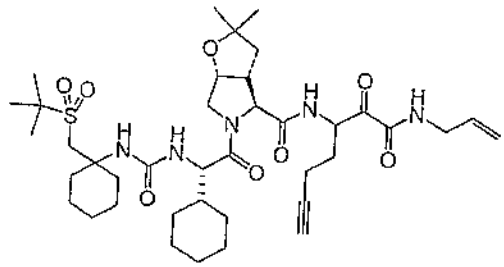


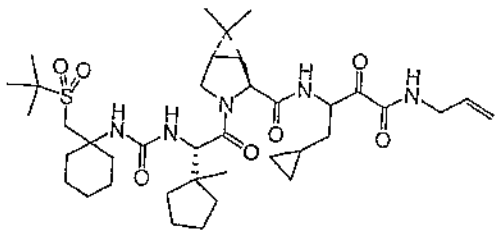


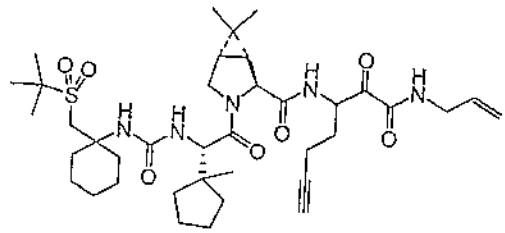


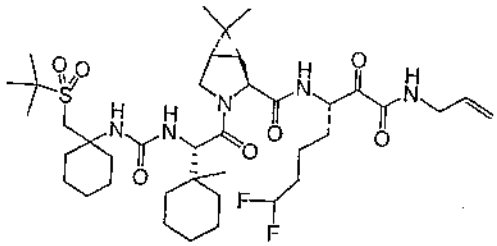


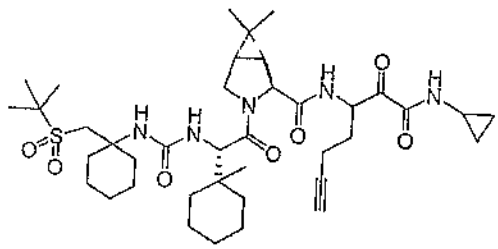


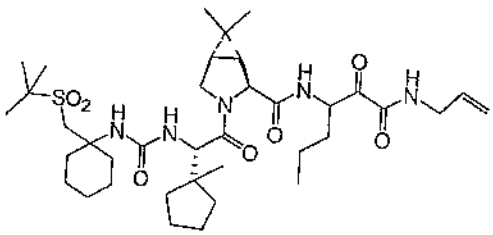


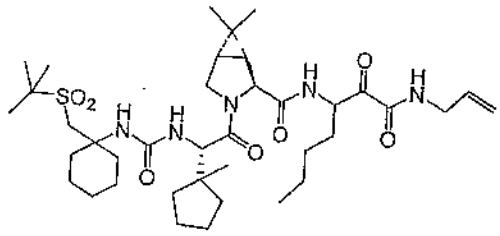


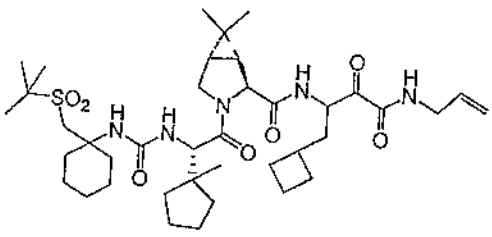


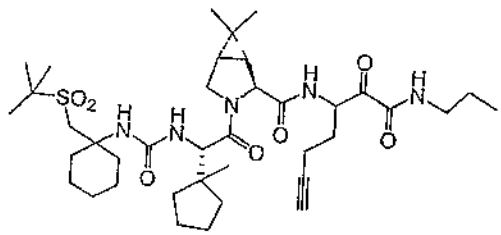


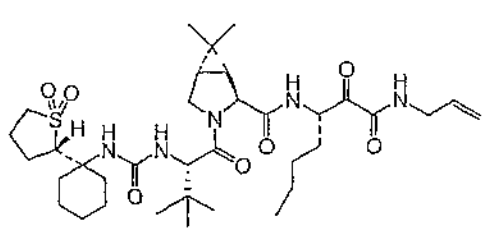


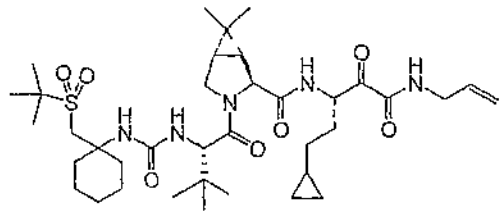


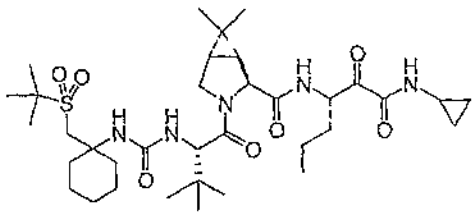


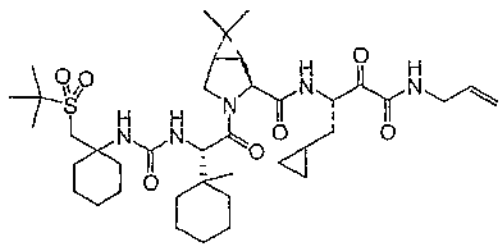


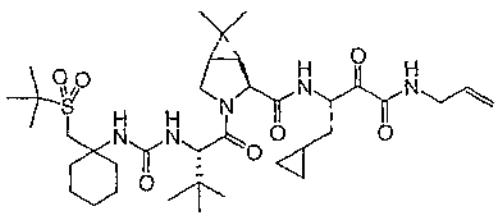


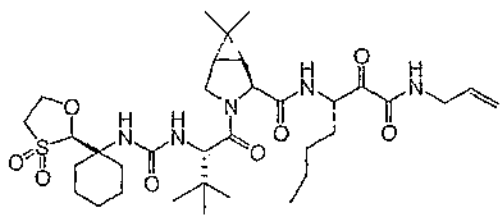


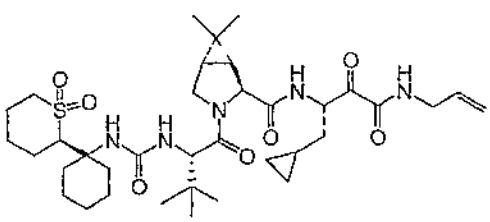


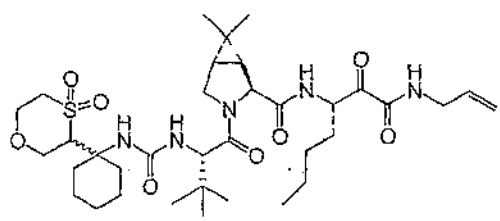


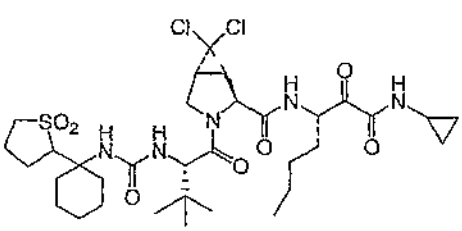


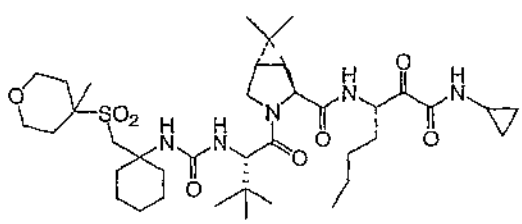


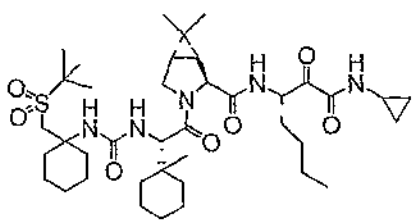


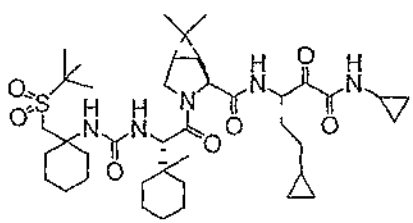


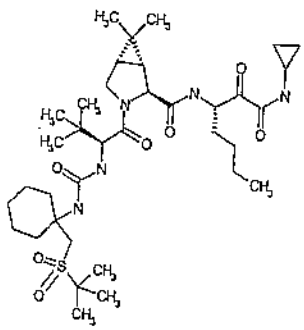
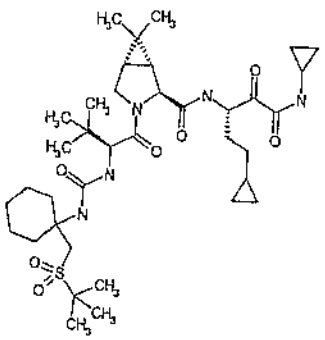
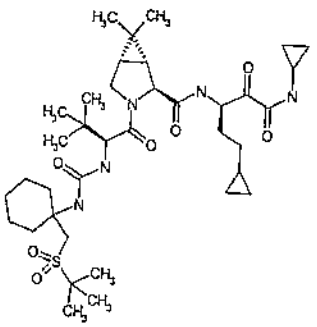






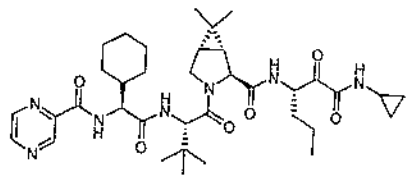
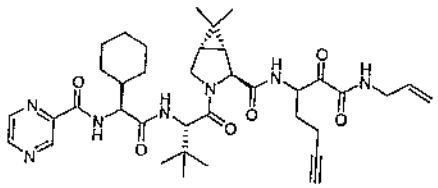
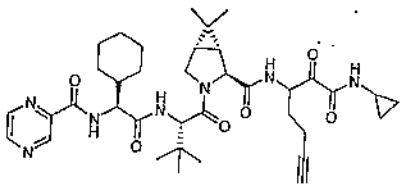
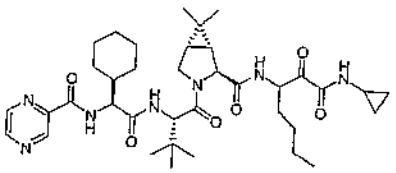
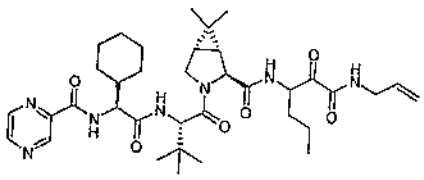
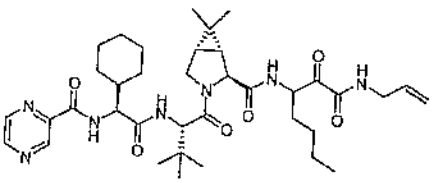
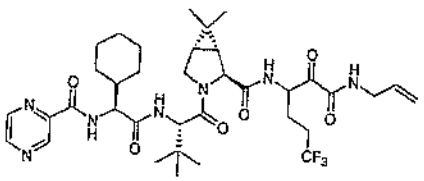
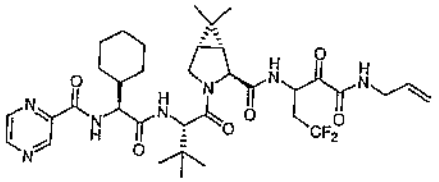


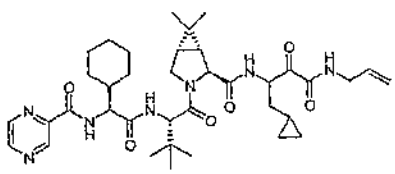
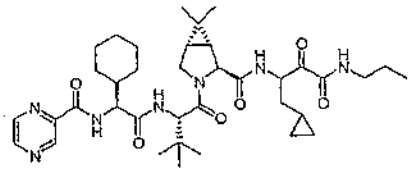
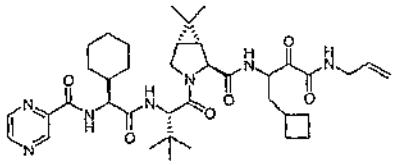
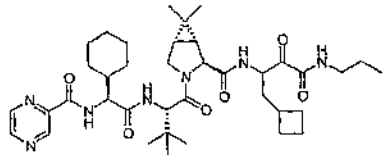
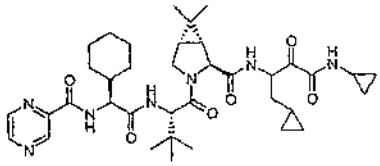
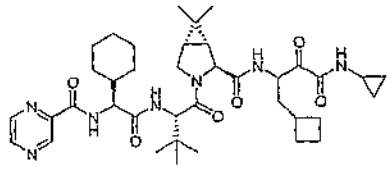
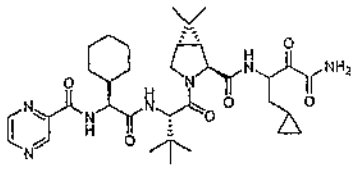
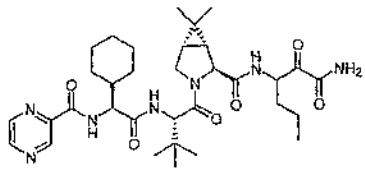
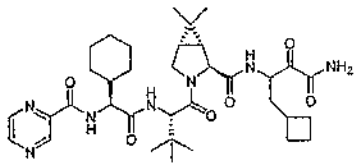
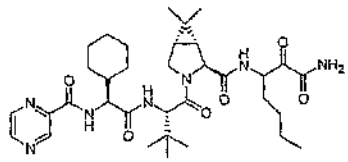
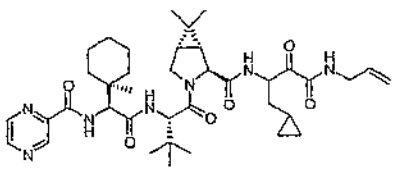
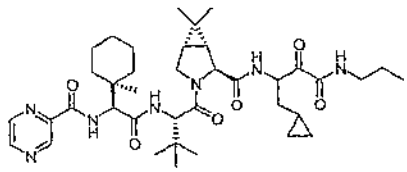
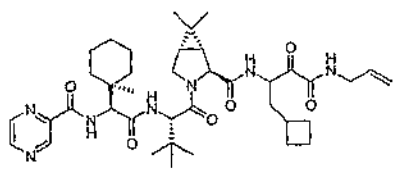
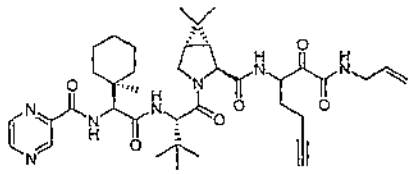


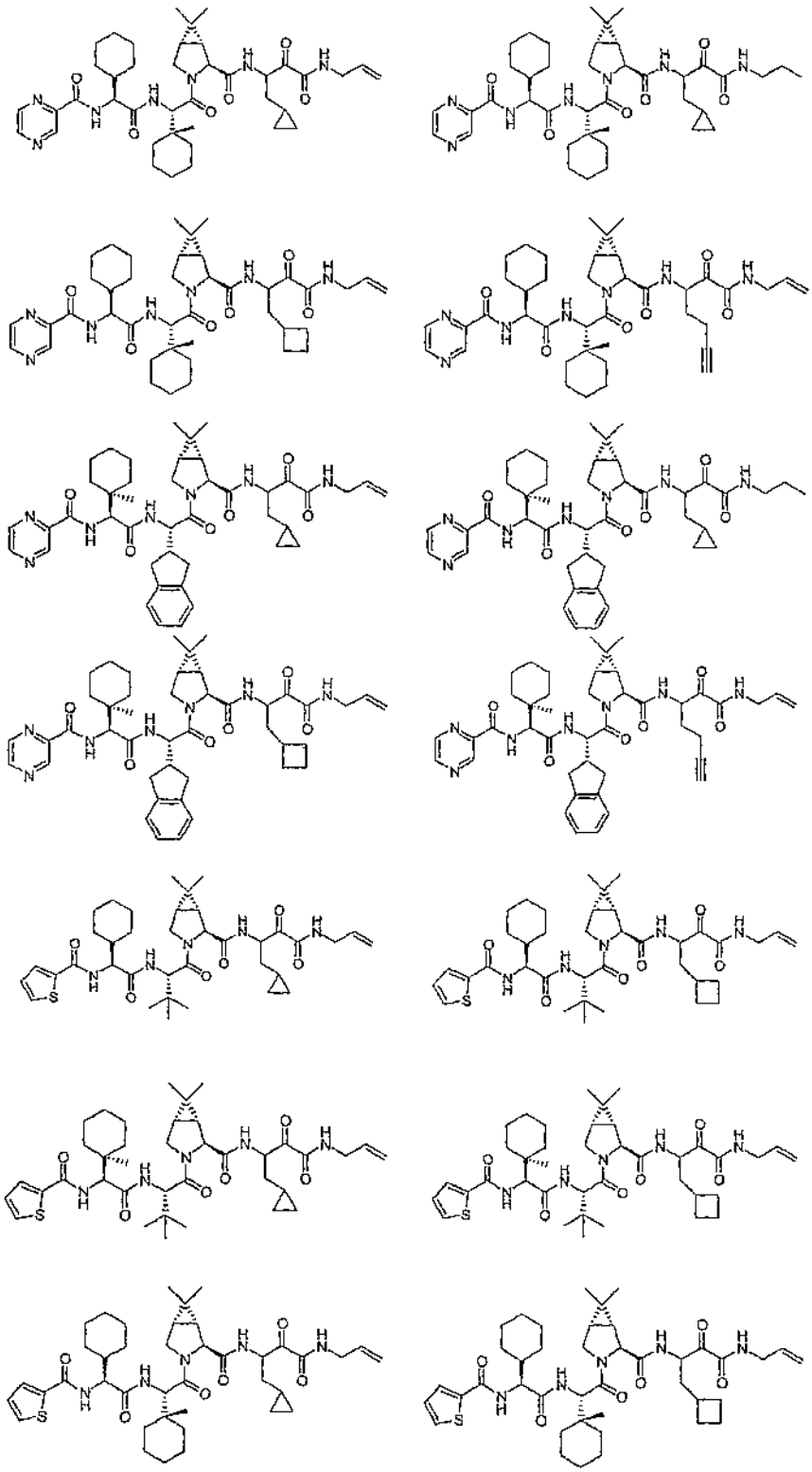


and

; or a pharmaceutically acceptable salt, solvate or ester thereof.

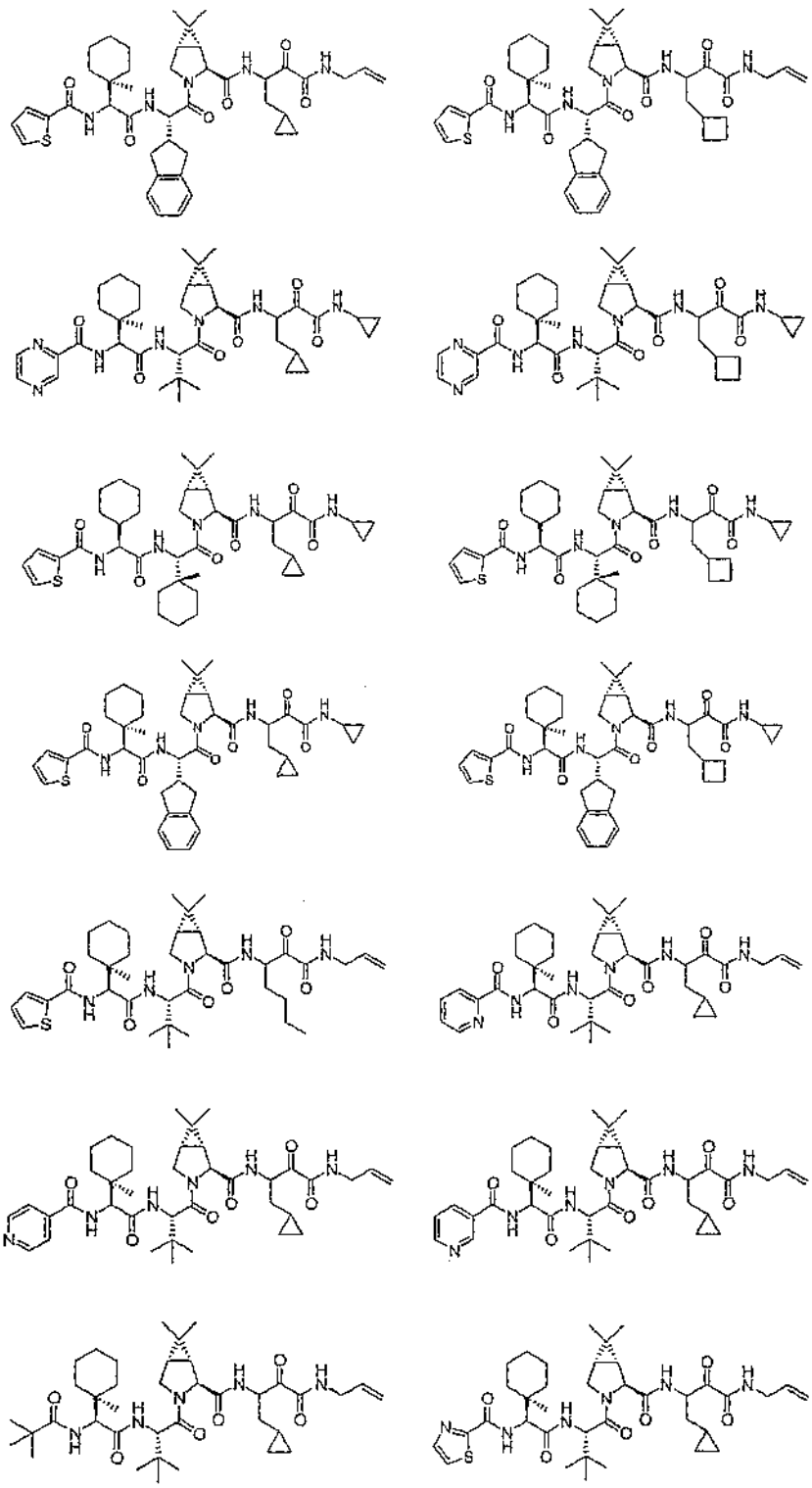
Compounds of formula XV are disclosed in U.S. Patent Application Ser. No. 11/007,910 filed December 9, 2004. The preparation of these compounds is disclosed in the experimental section of this application set forth hereinbelow.

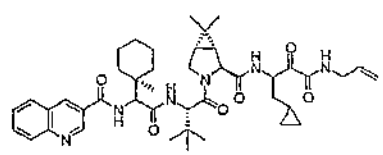
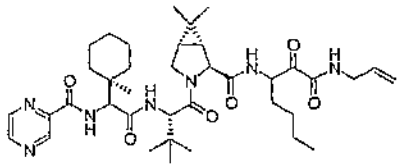
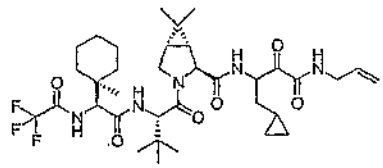
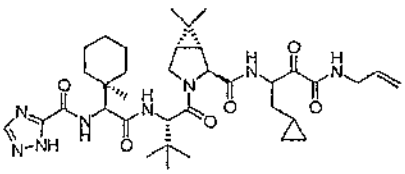
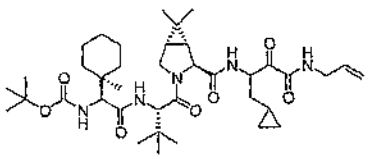
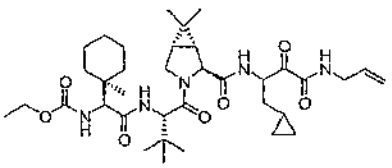
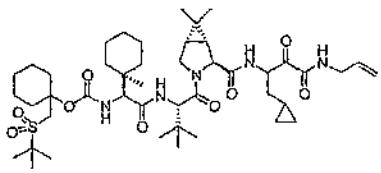
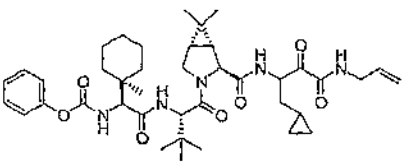
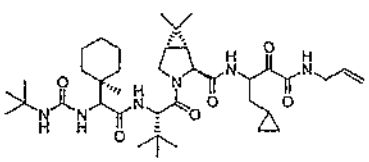
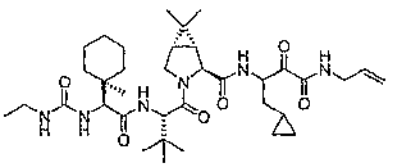
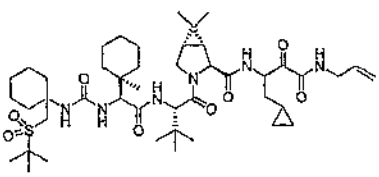
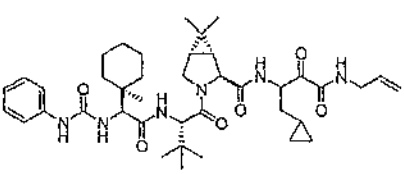
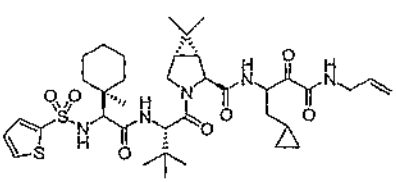
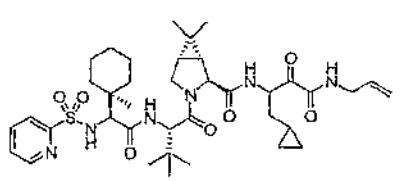
Non-limiting examples of certain compounds disclosed in U.S. Patent Application Ser. No. 11/007,910 are:

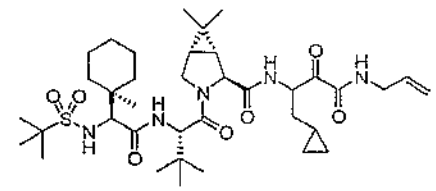
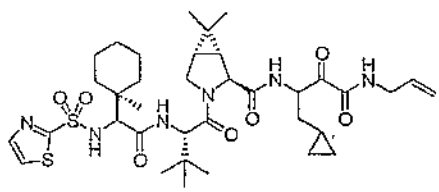
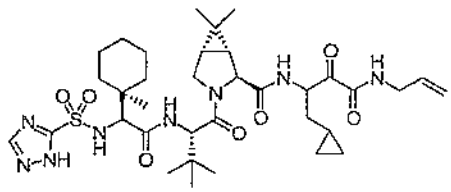
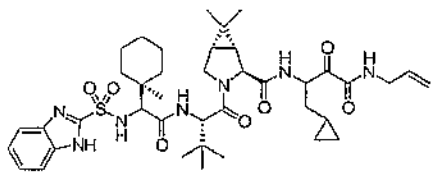
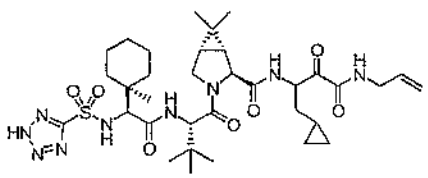
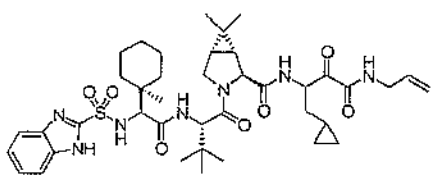
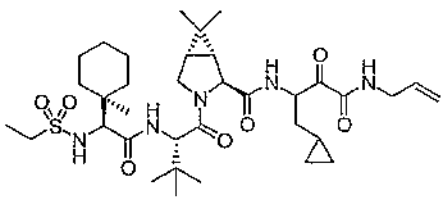
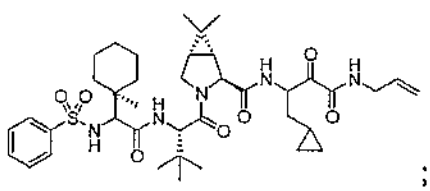













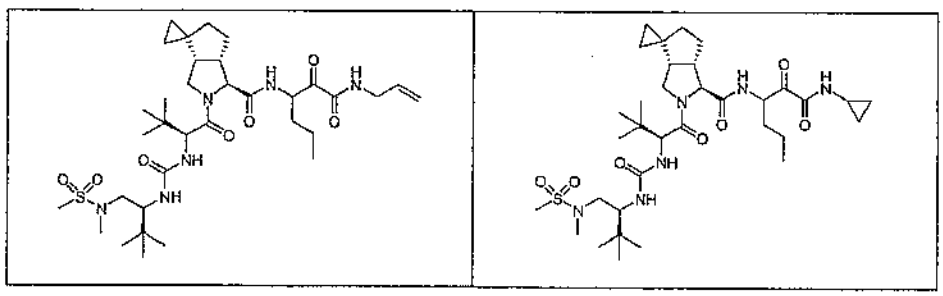















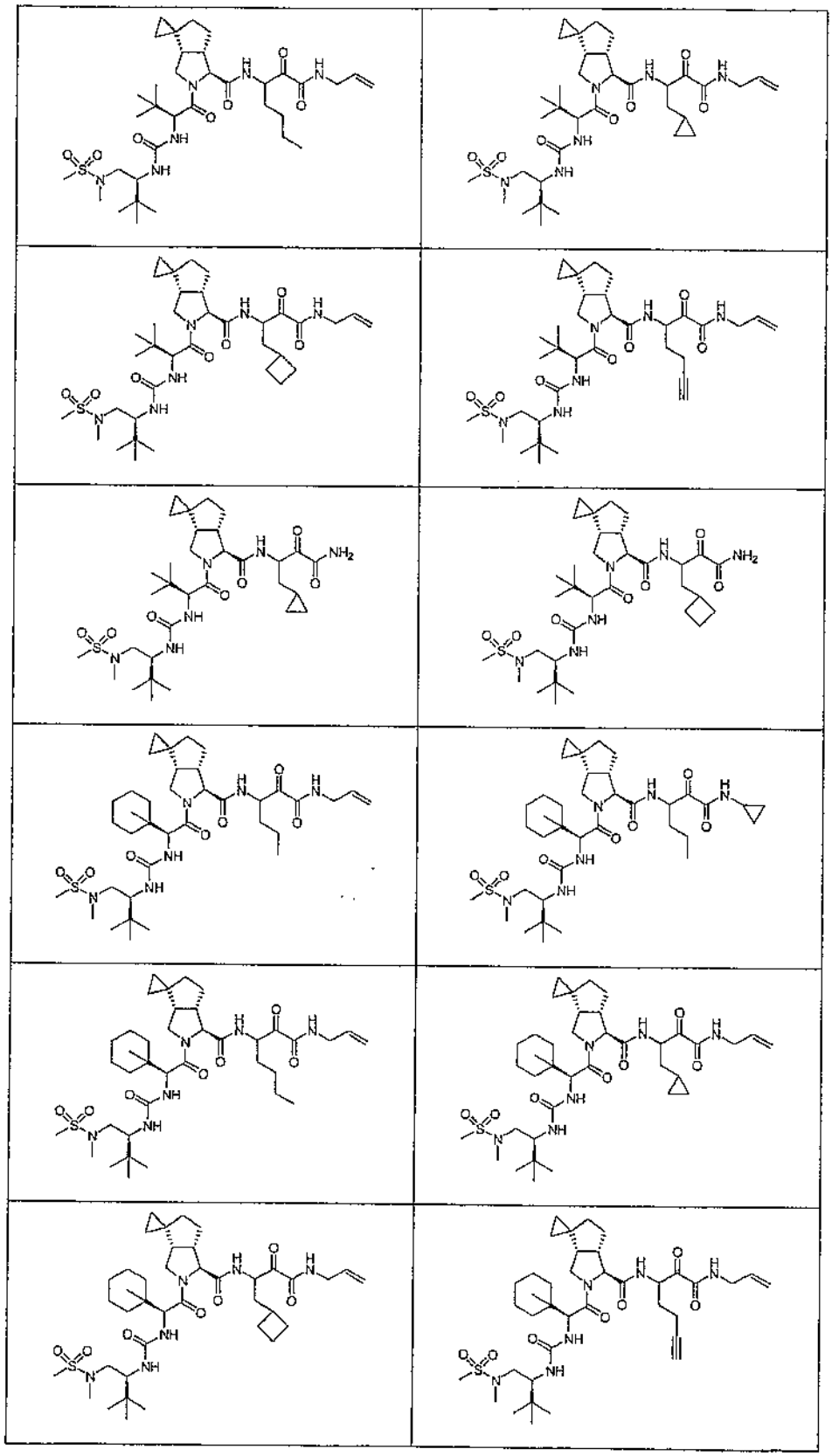







and

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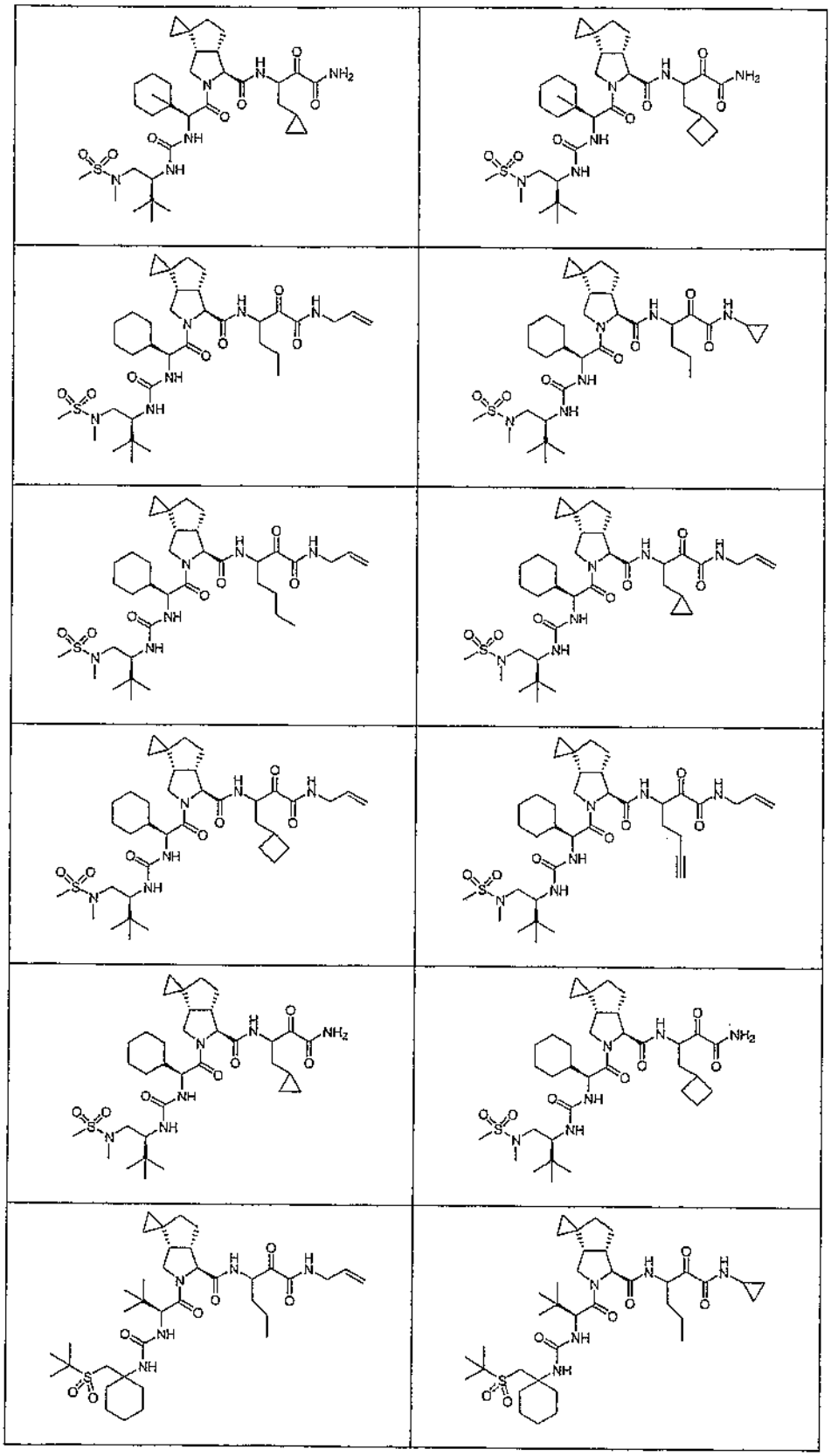
or a pharmaceutically acceptable salt, solvate or ester thereof.

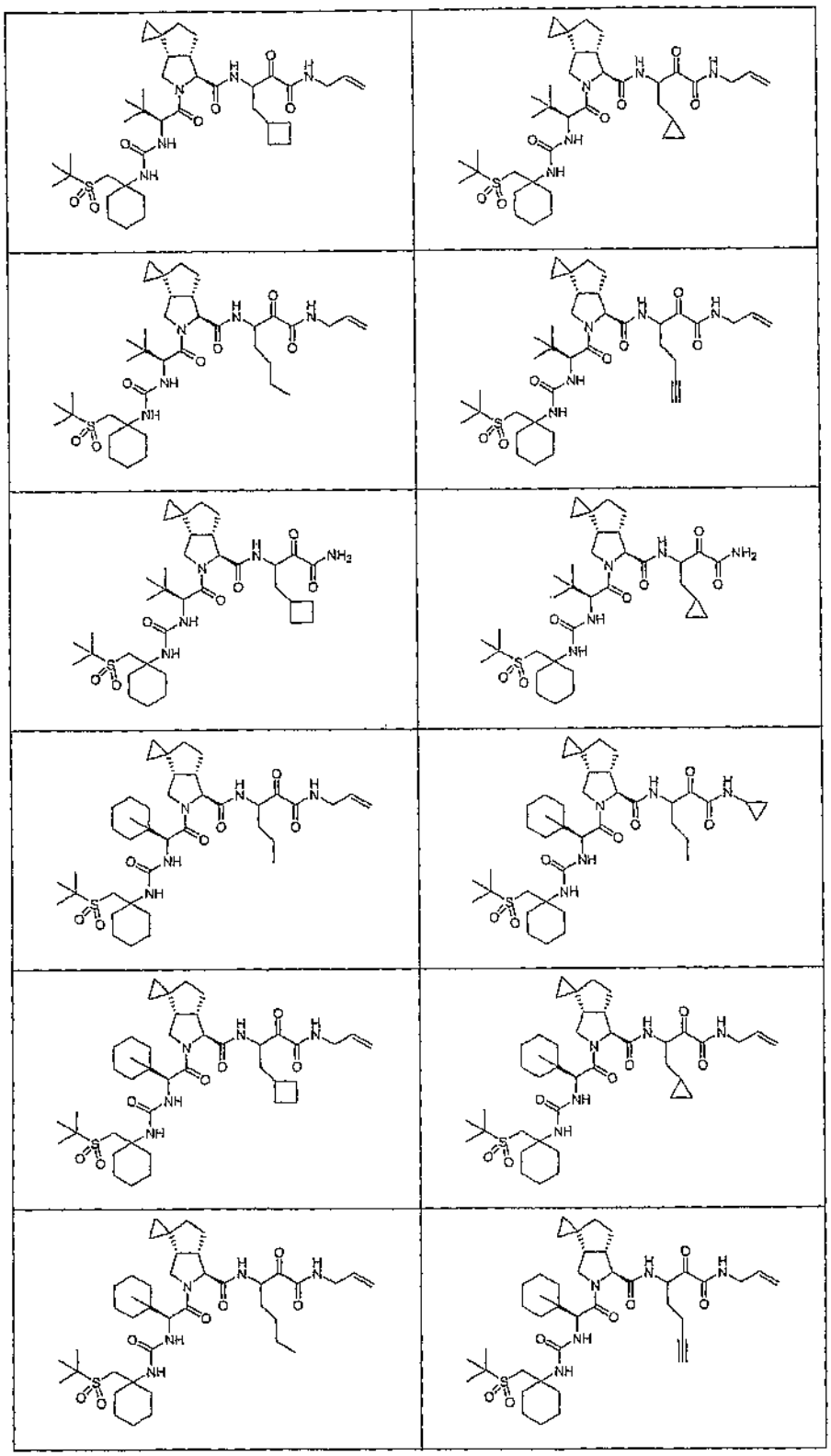
Compounds of formula XVI are disclosed in U.S. Patent Application Ser. No. 11/064,757 filed February 24, 2005. The preparation of these compounds is disclosed in the experimental section of this application set forth hereinbelow.

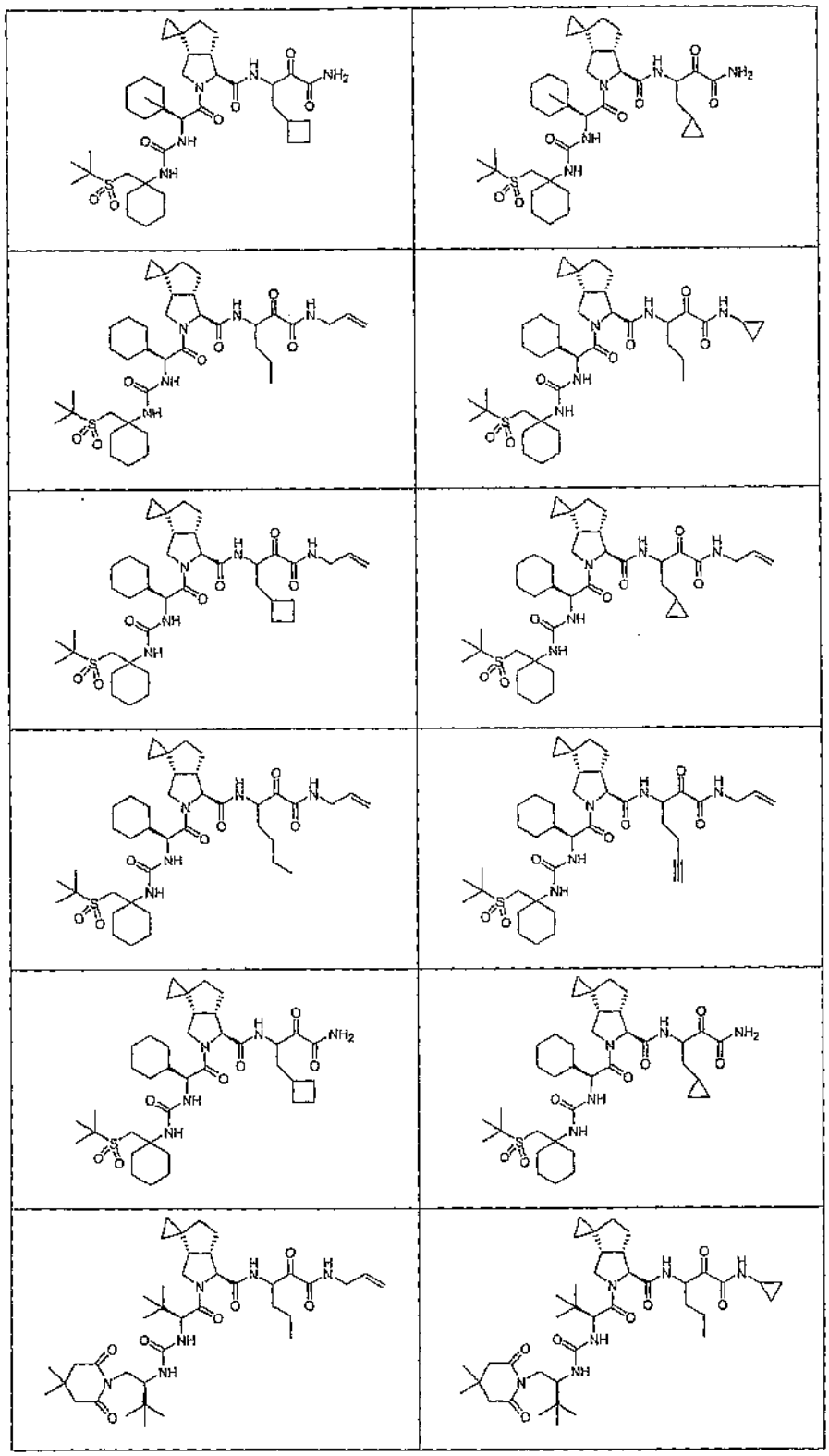
Non-limiting examples of certain compounds disclosed in U.S. Patent Application Ser. No. 11/064,757 are:

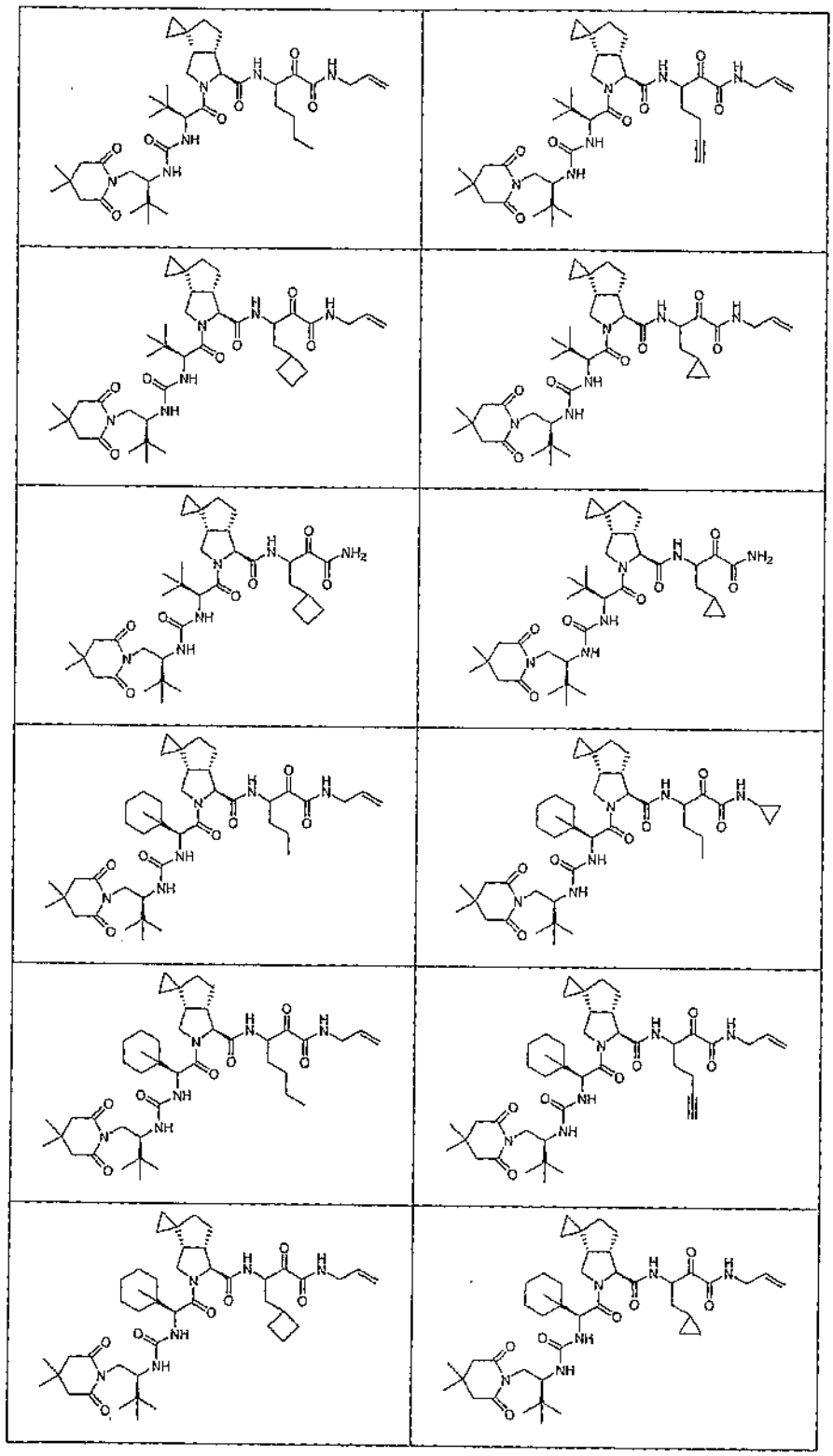


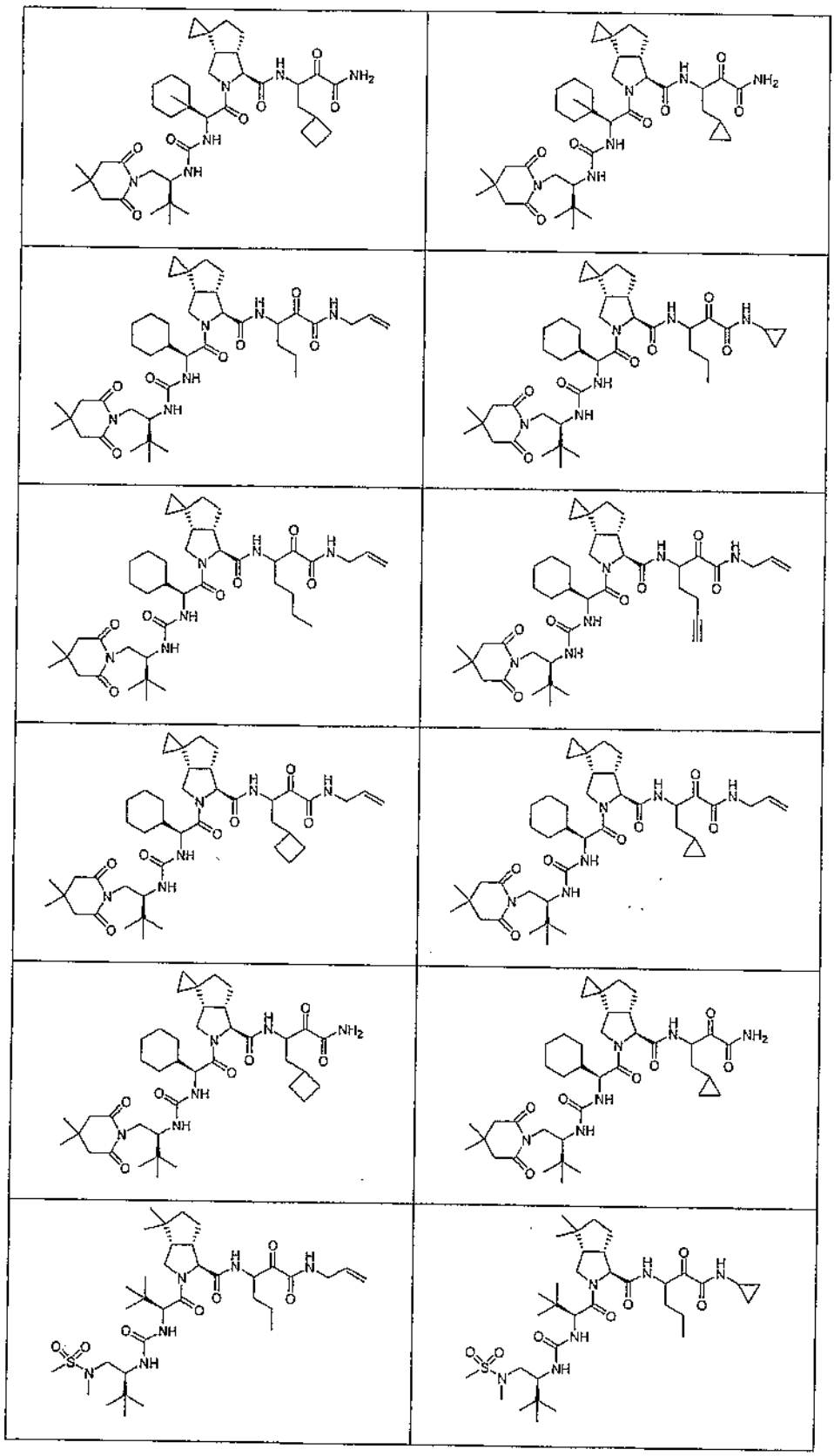


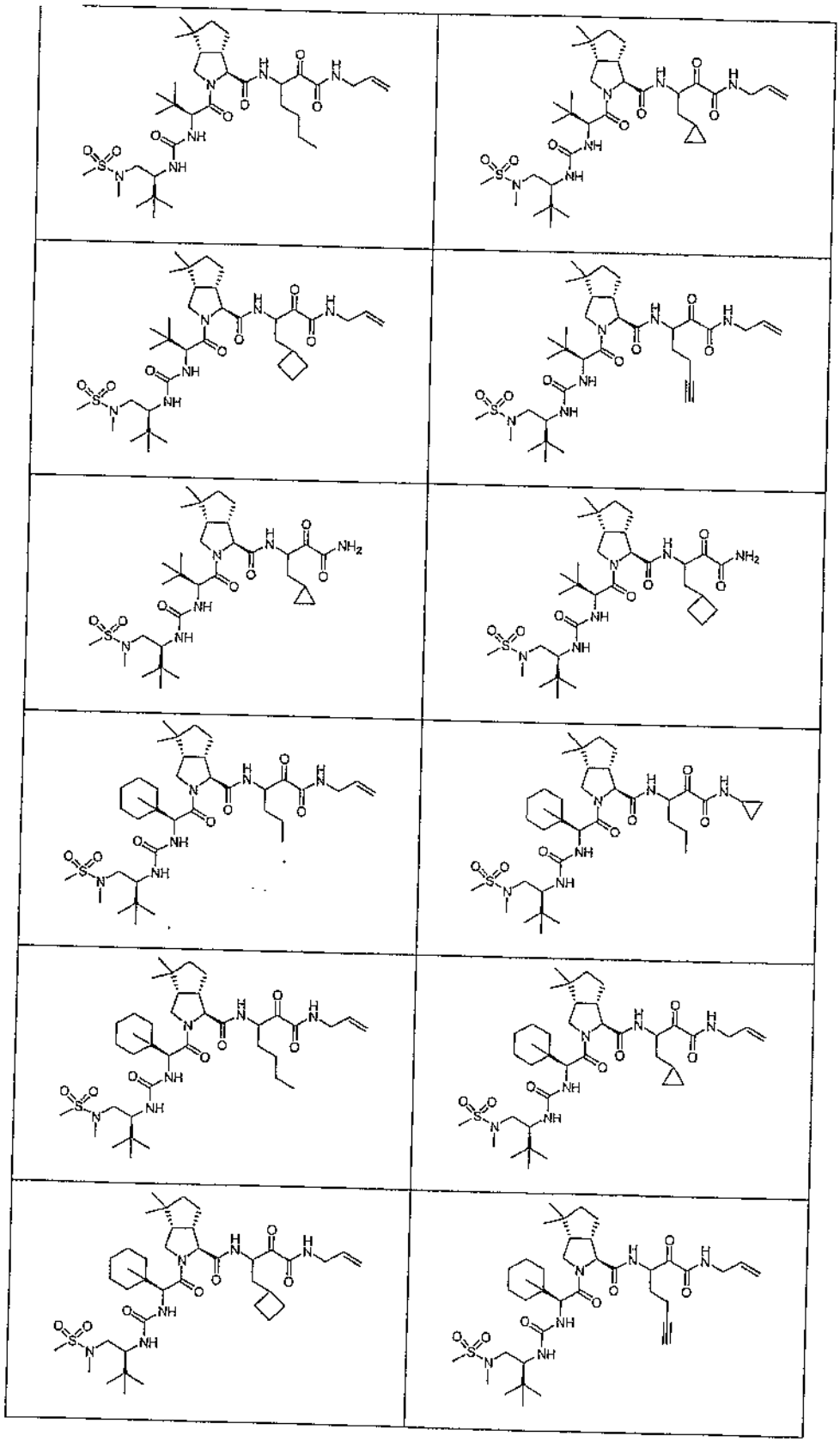


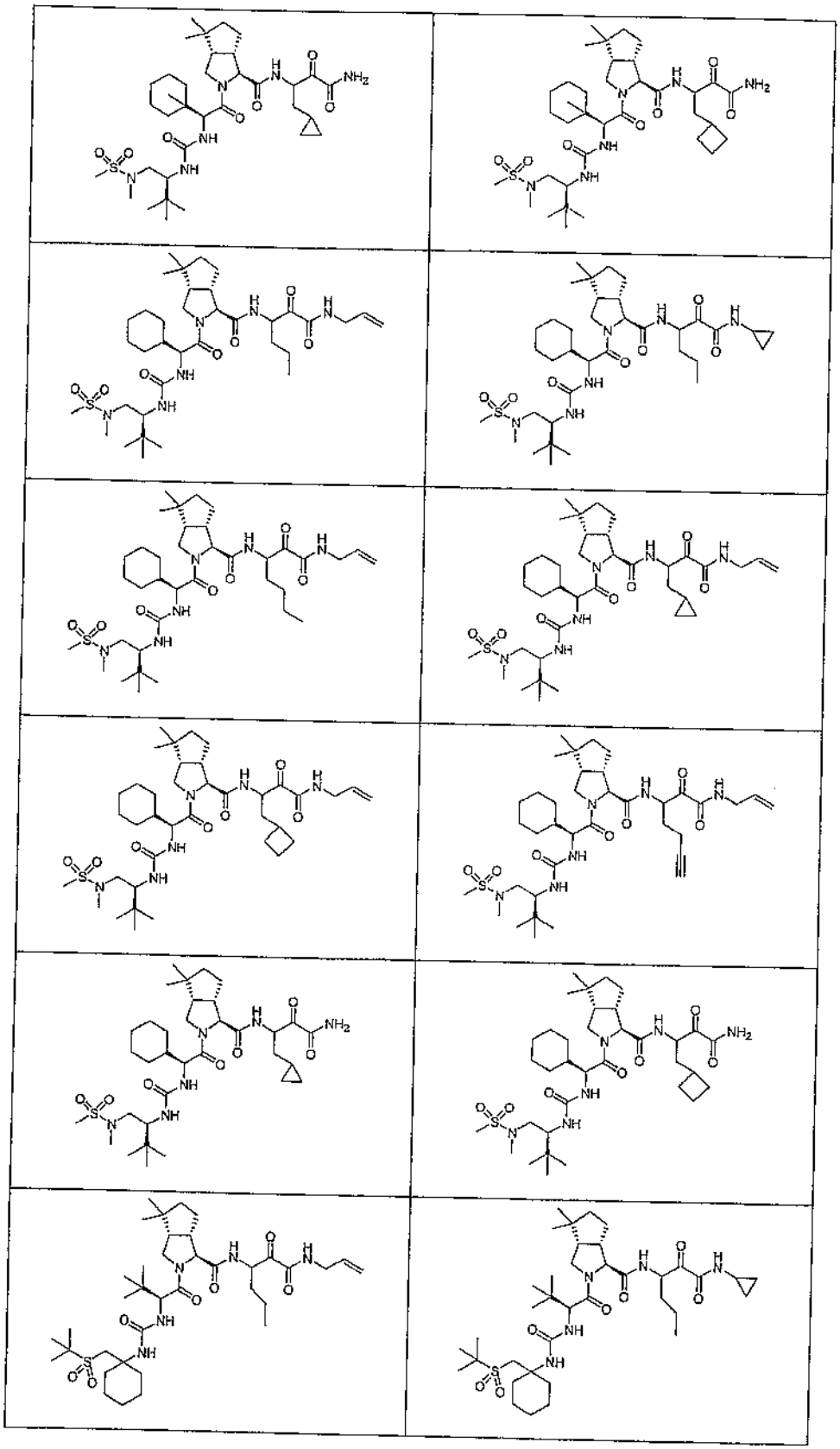


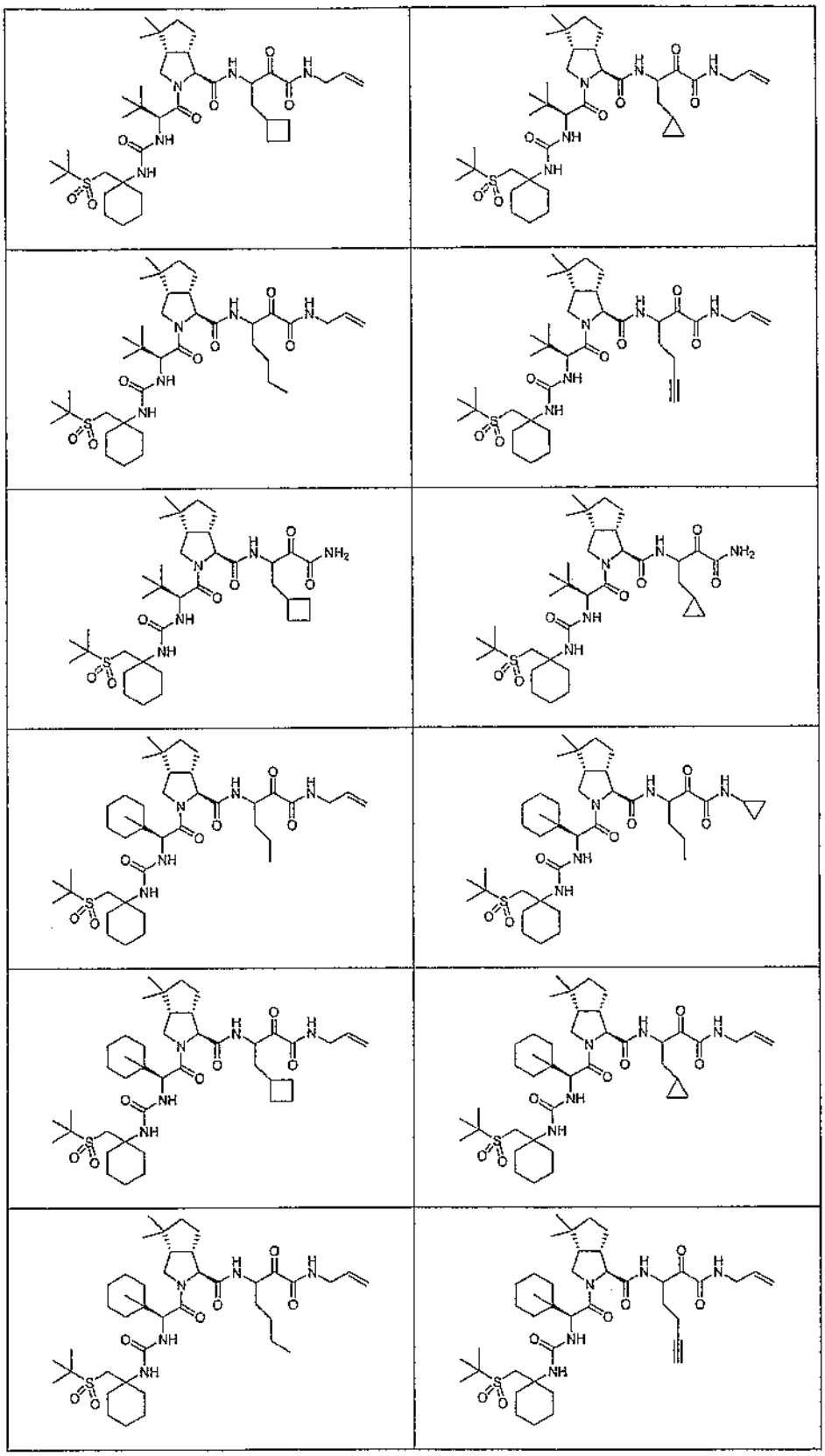


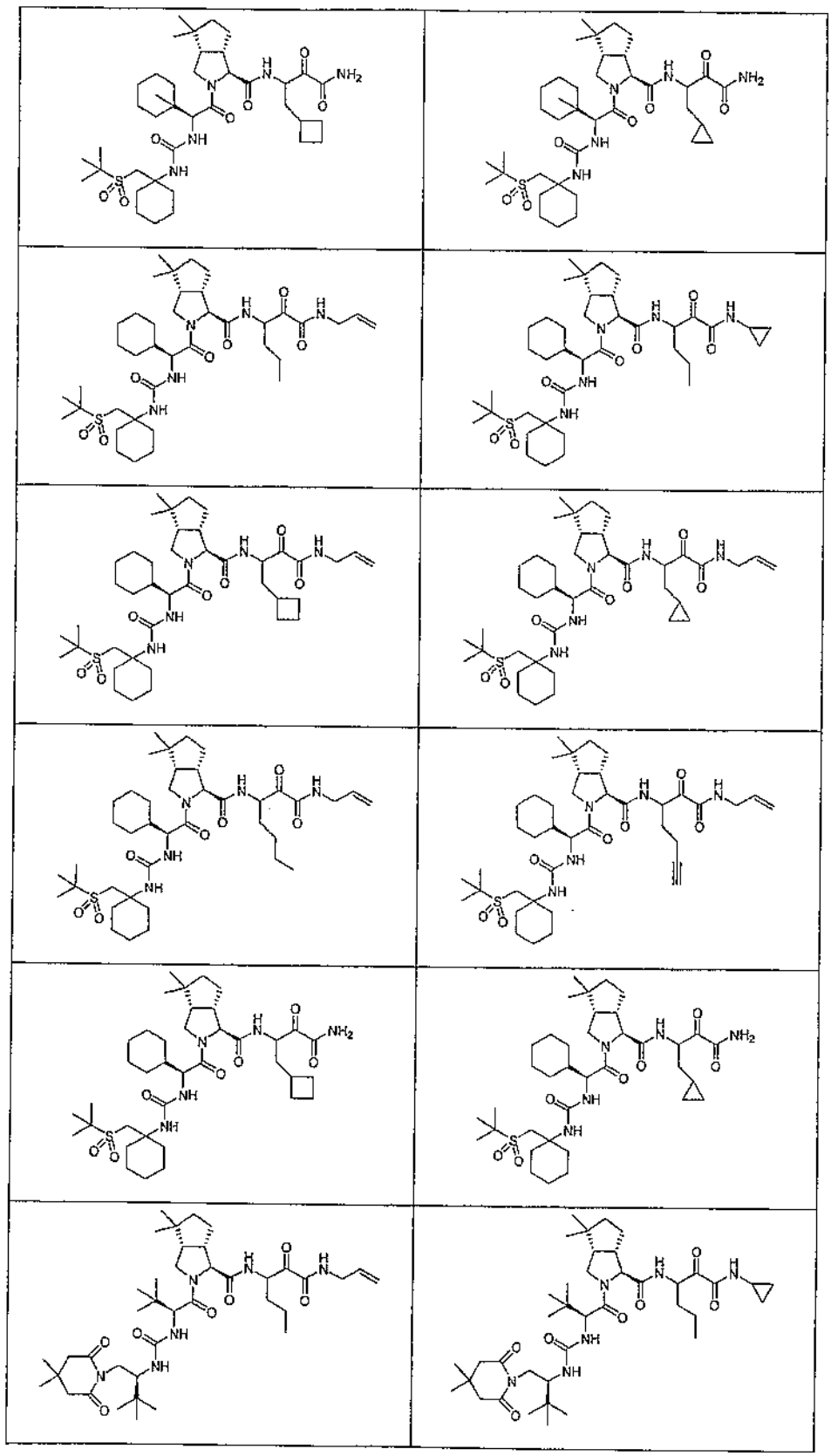


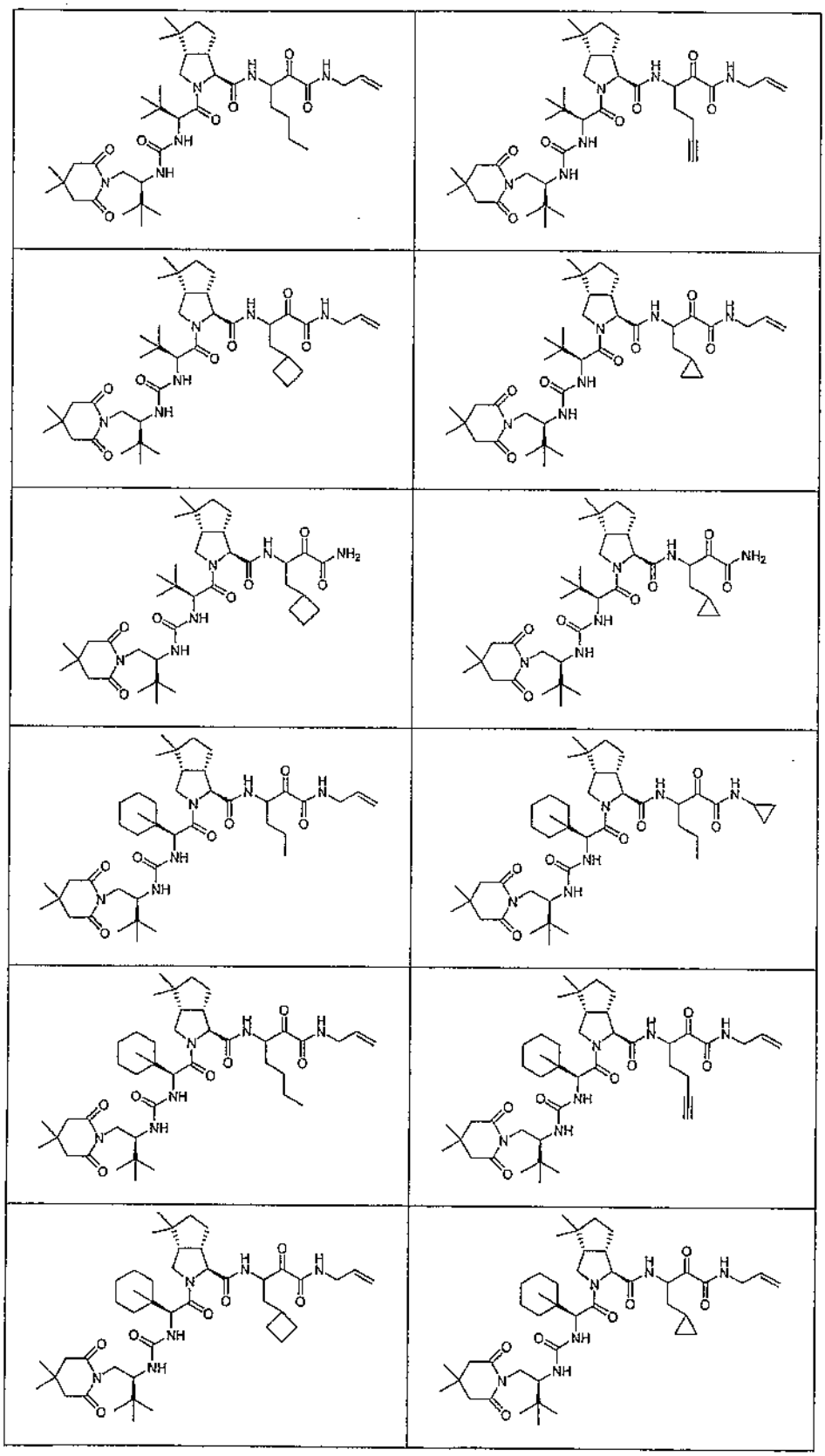


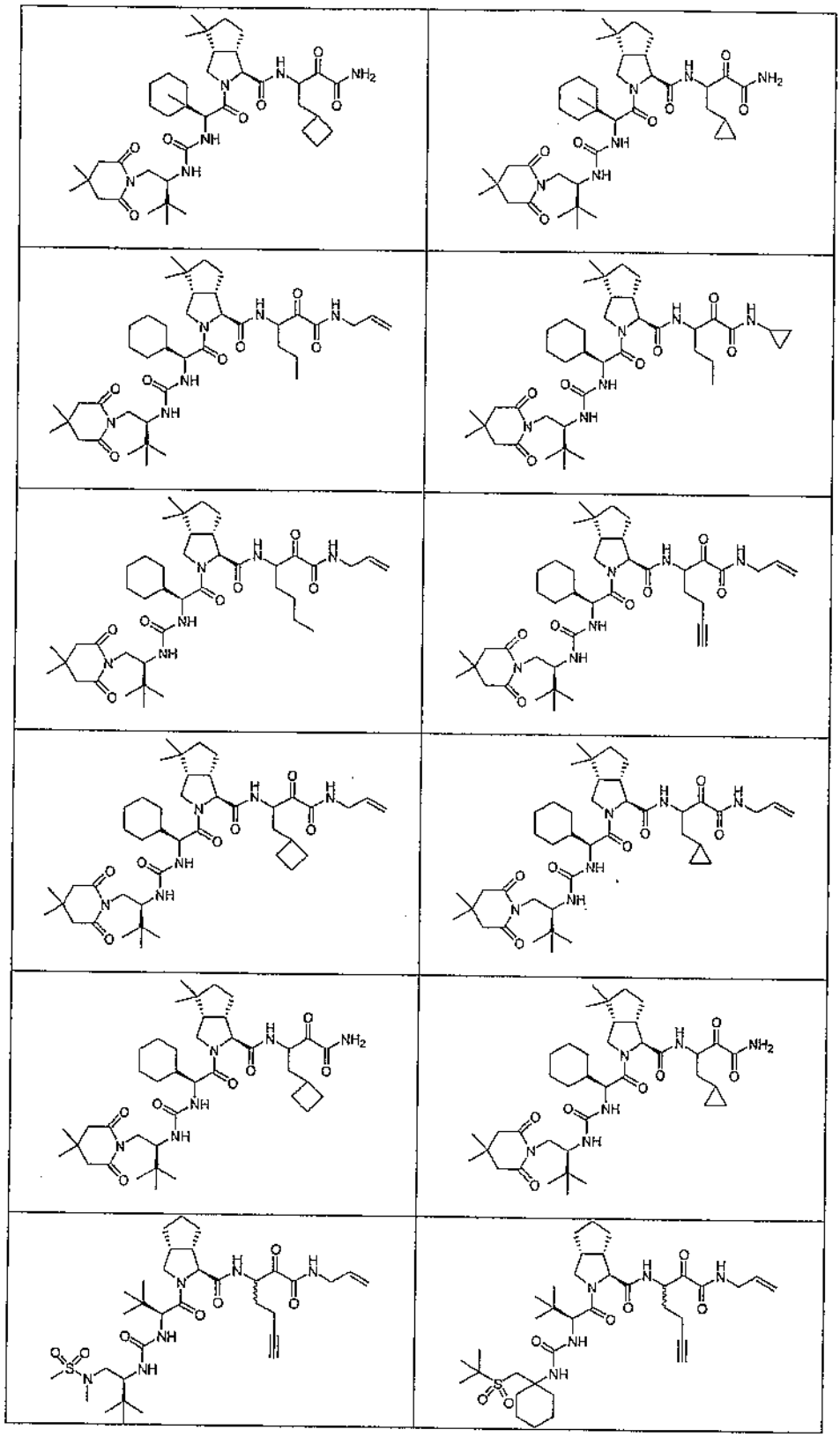


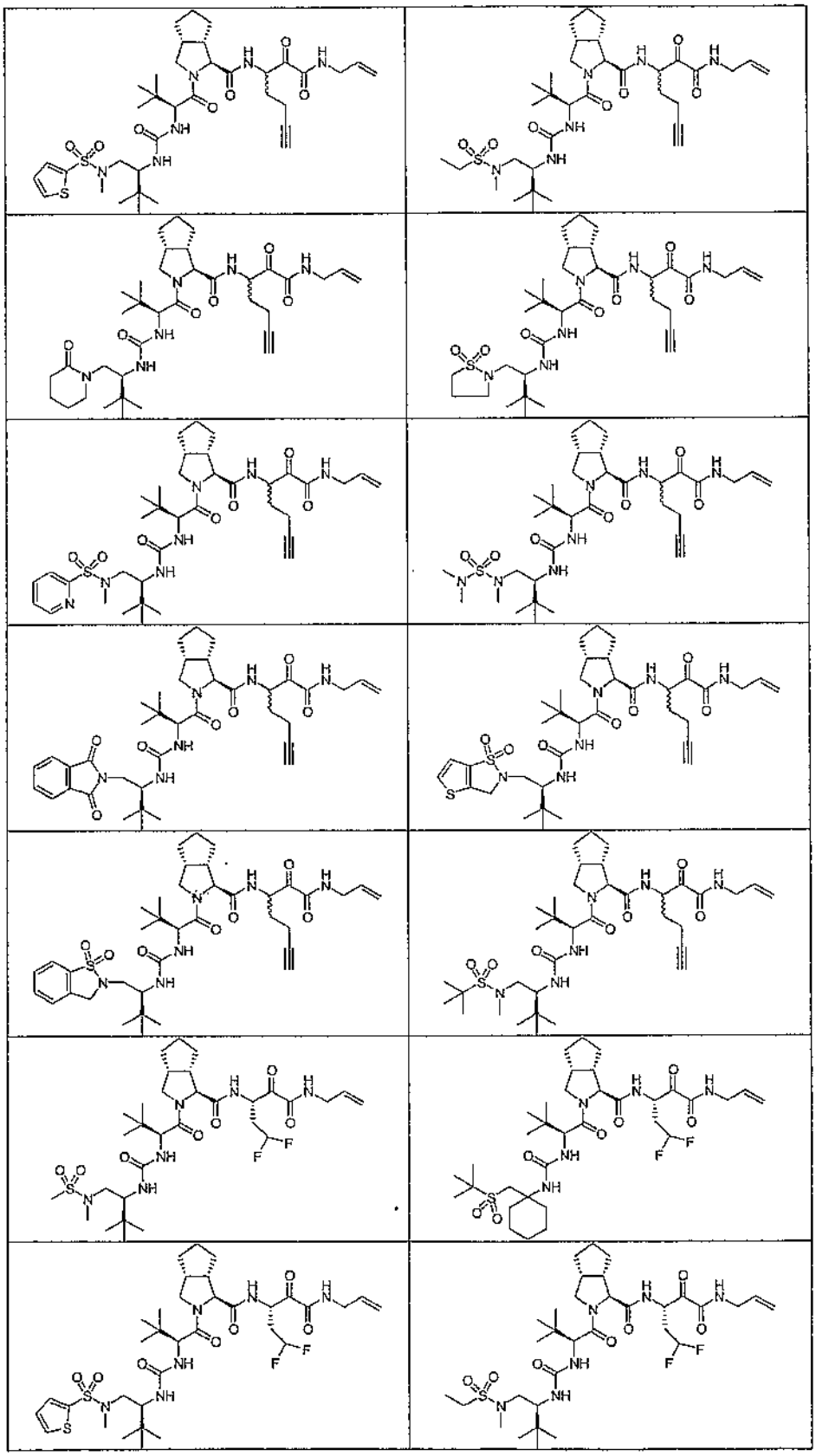


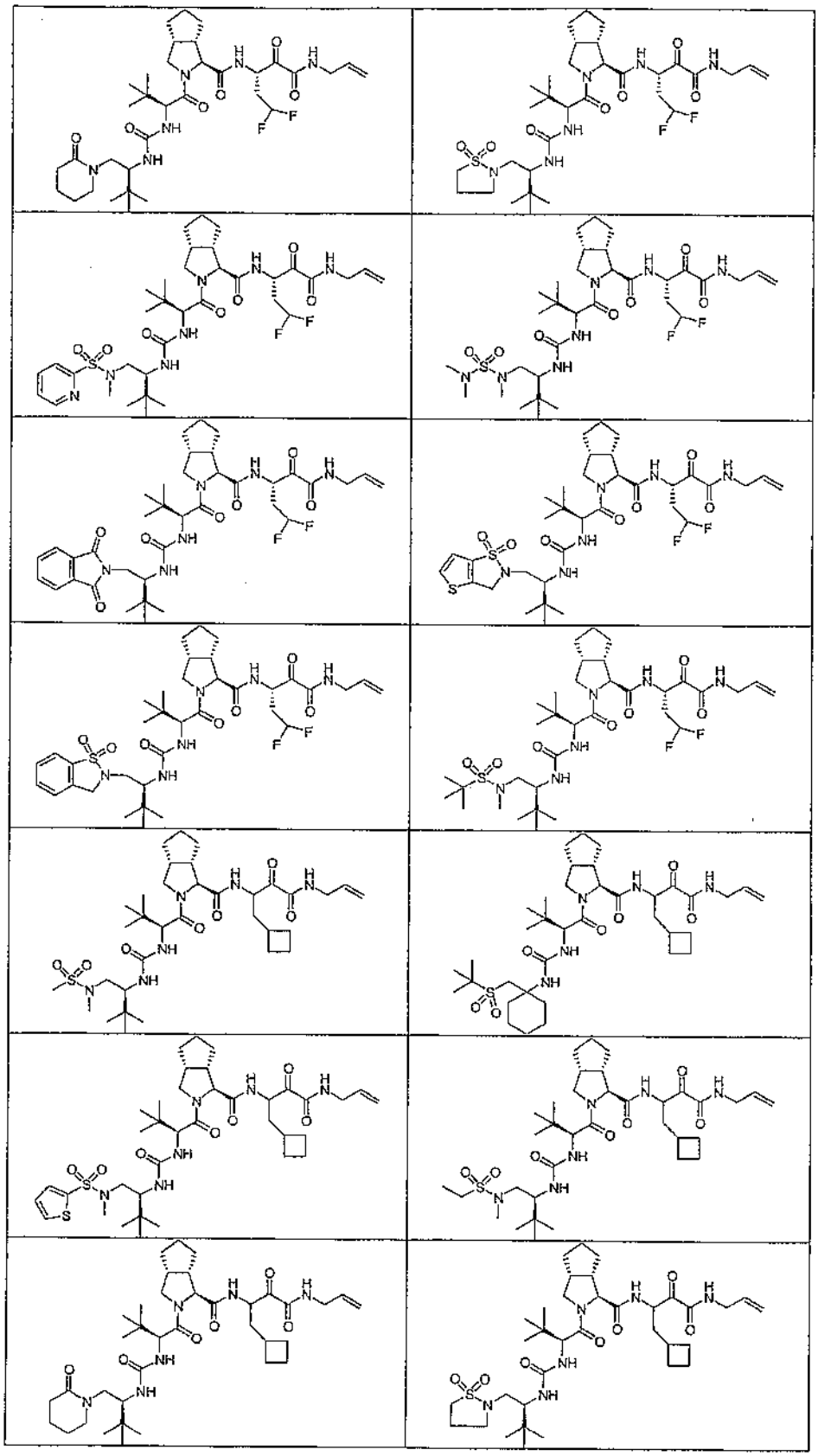


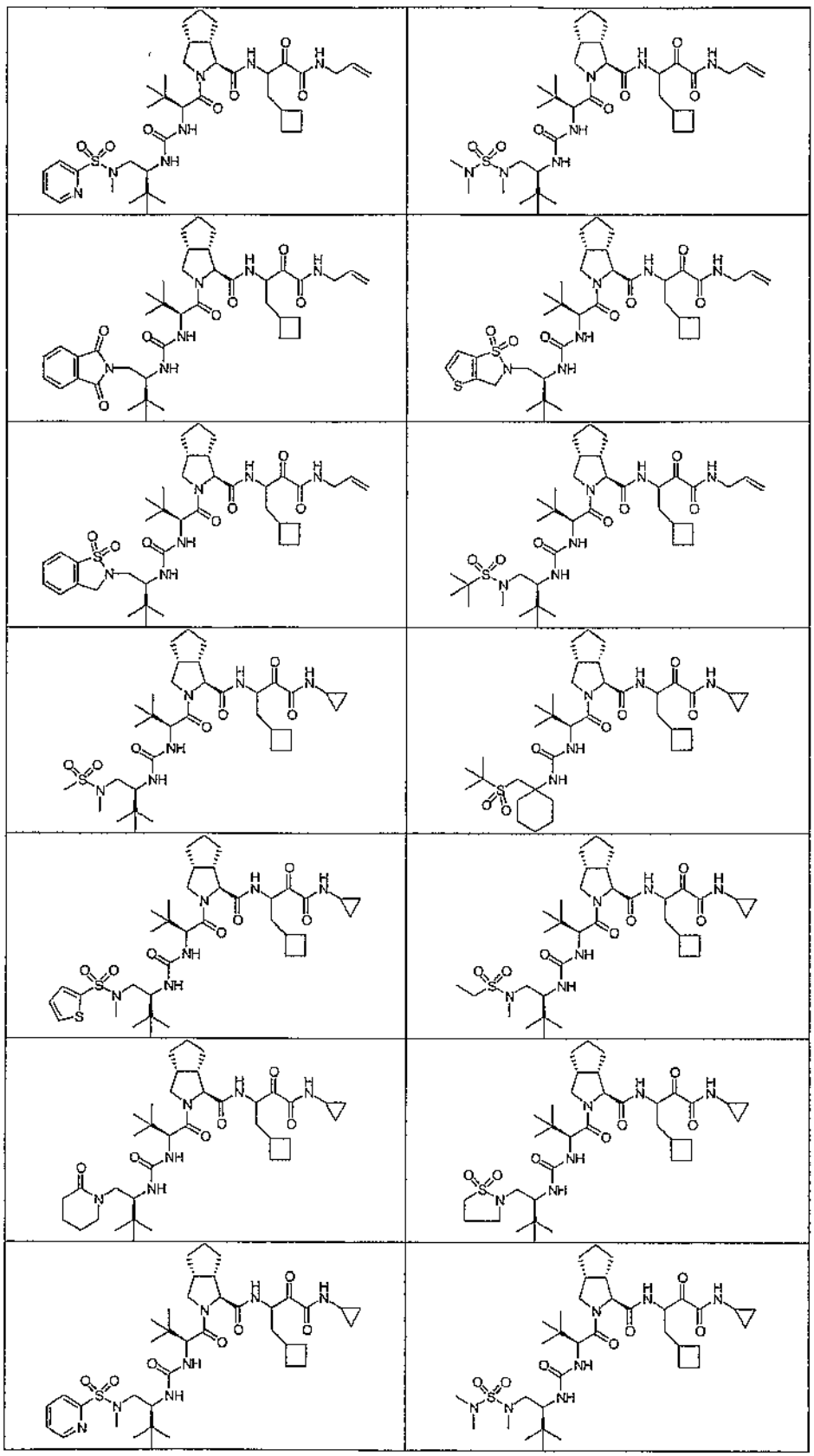


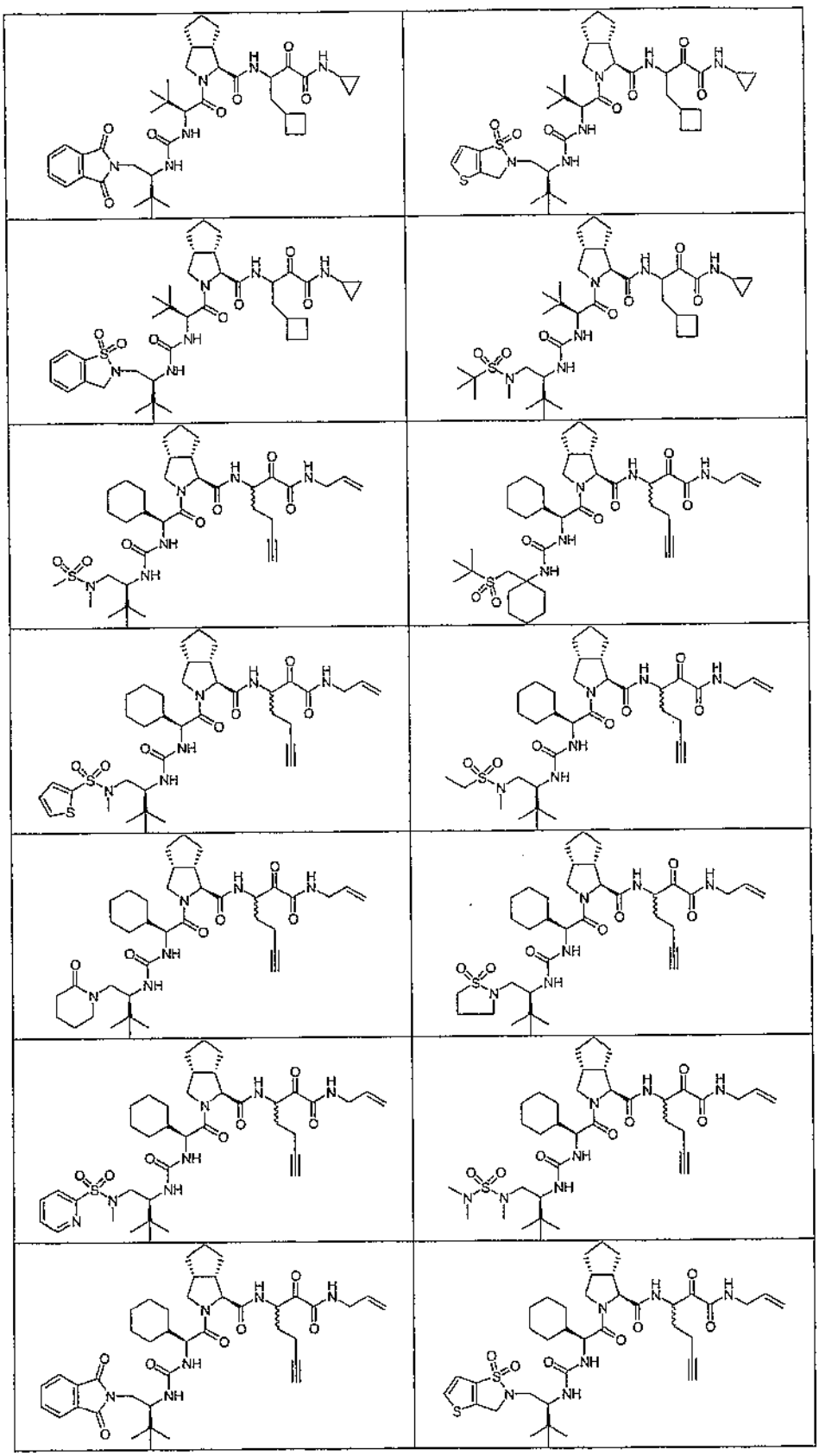


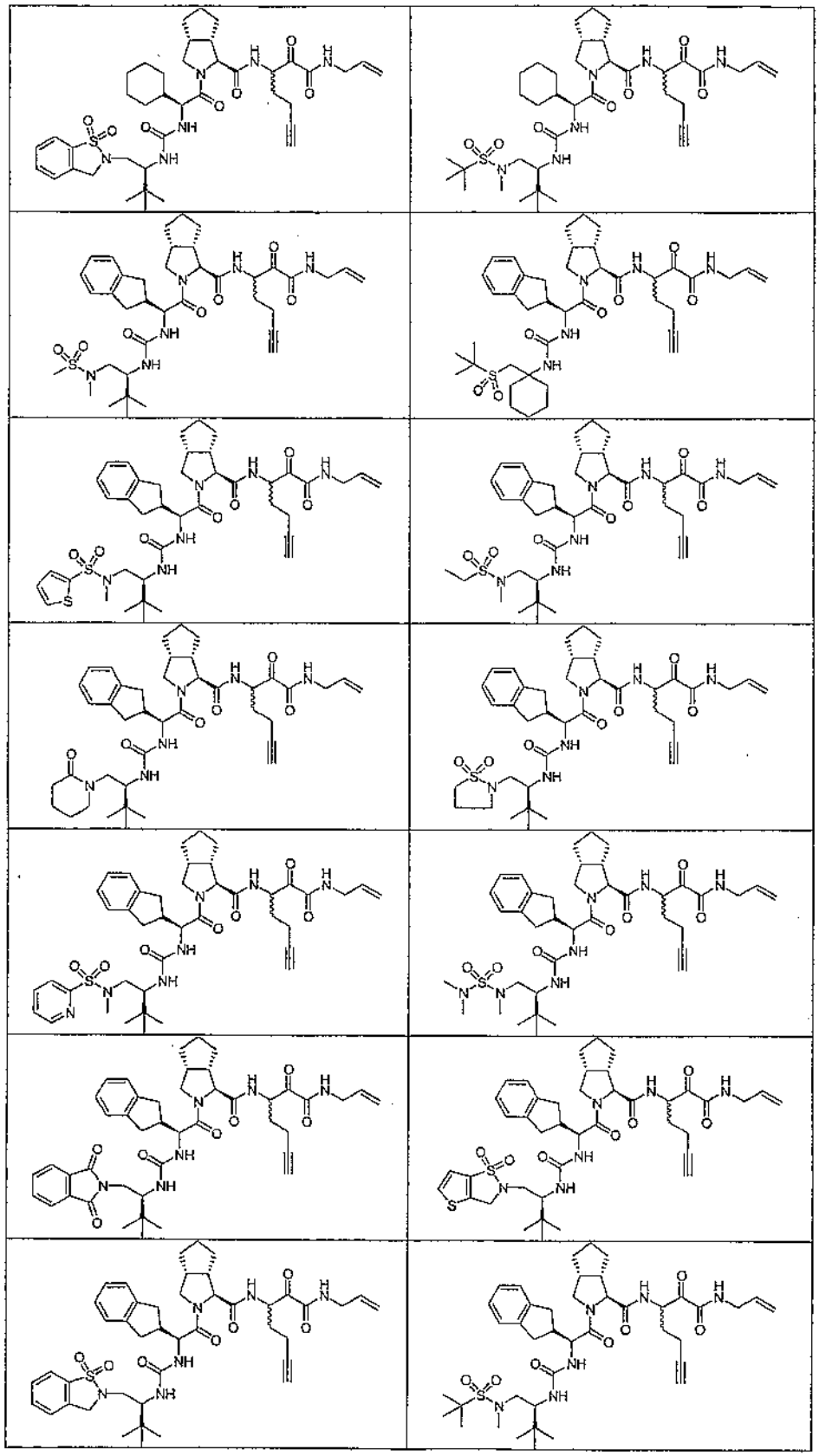


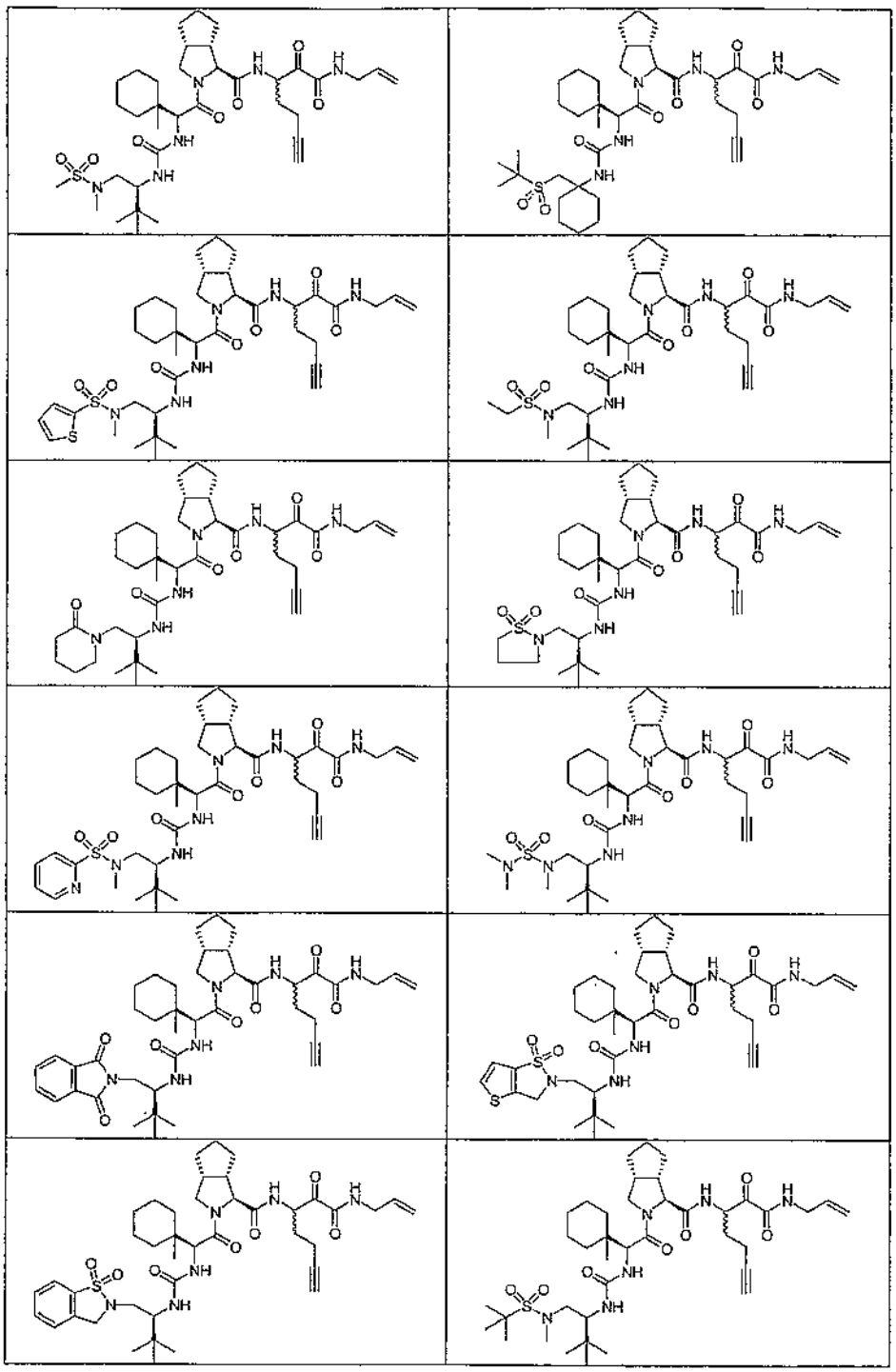








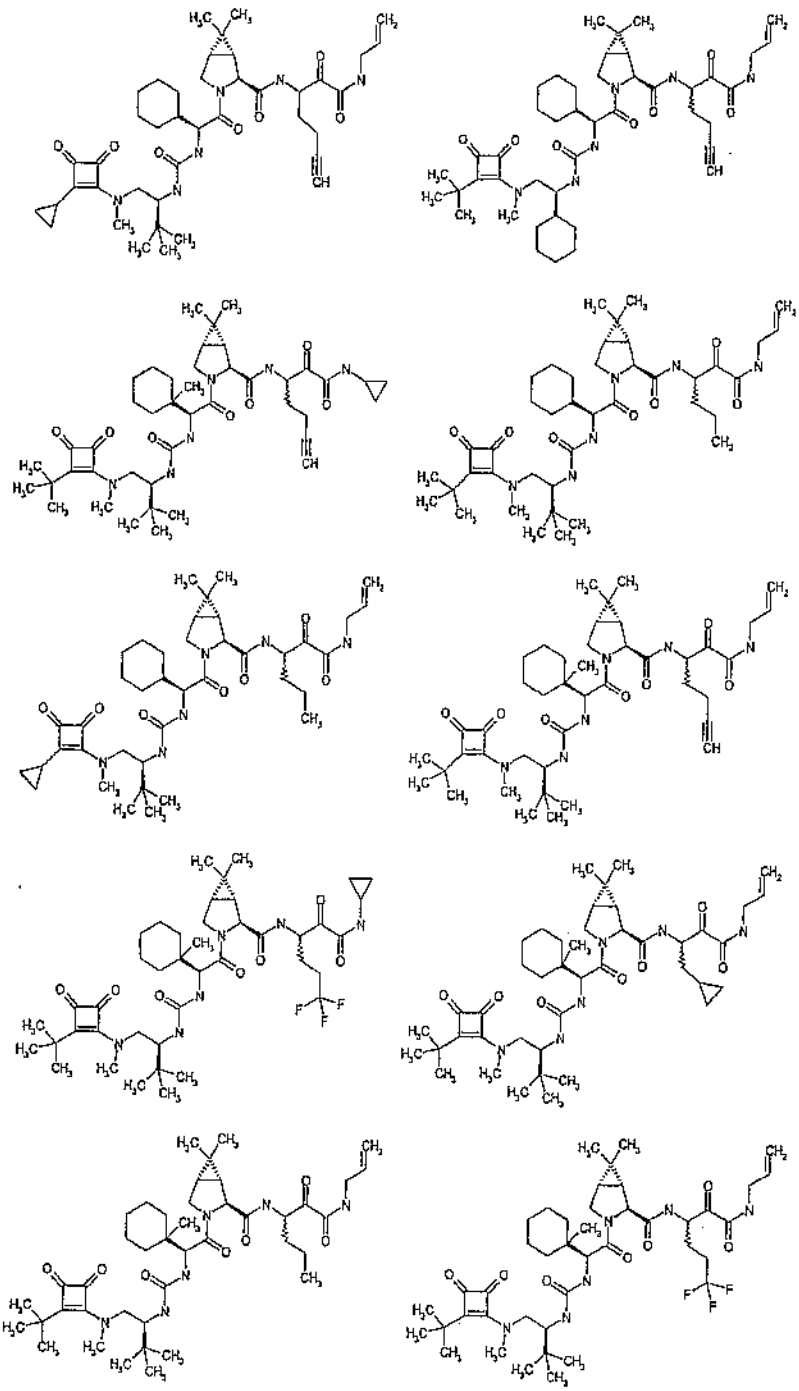


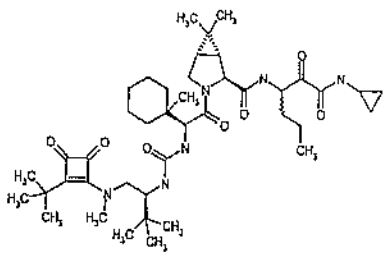


or a pharmaceutically acceptable salt, solvate or ester thereof.

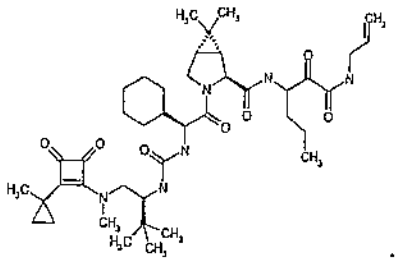
Compounds of formula XVII are disclosed in U.S. Patent Application Ser. No. 11/064,574 filed February 24, 2005. The preparation of these compounds is disclosed in the experimental section of this application set forth hereinbelow.

Non-limiting examples of certain compounds disclosed in U.S. Patent Application Ser. No. 11/064,574 are:





and

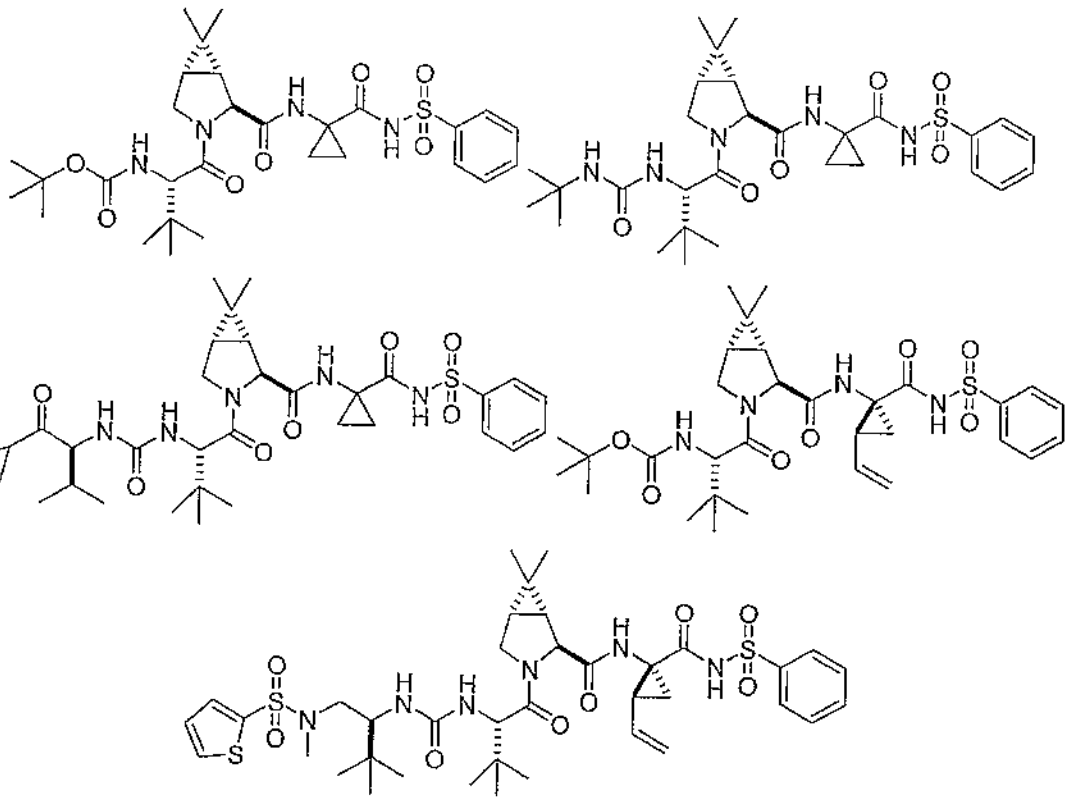


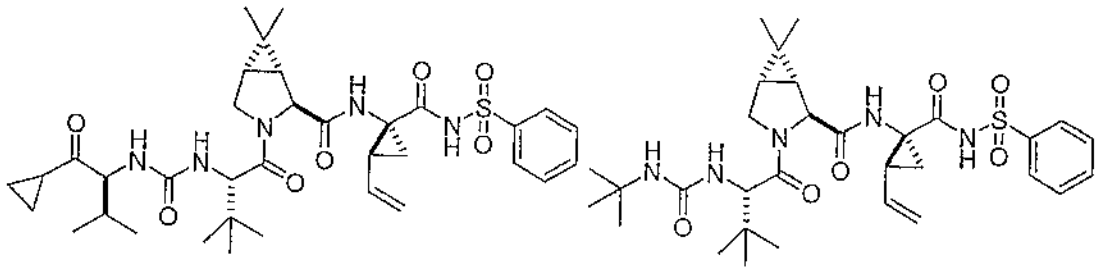
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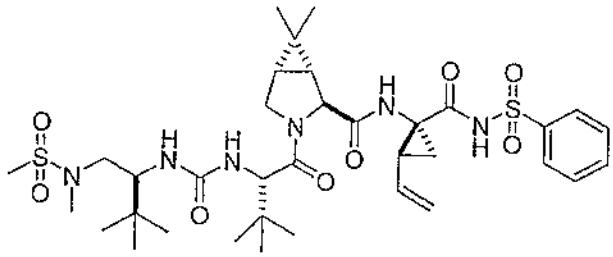
or a pharmaceutically acceptable salt, solvate or ester thereof.

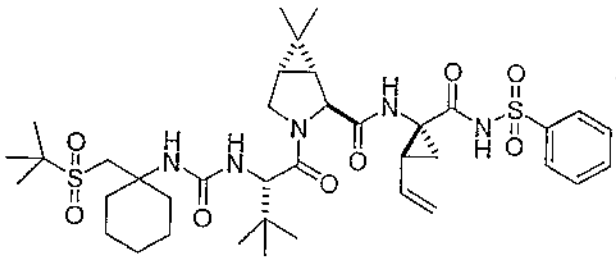
Compounds of formula XVIII are disclosed in U.S. Provisional Patent Application Ser. No. 60/605,234 filed August 27, 2004. The preparation of these compounds is disclosed in the experimental section of this application set forth hereinbelow.

Non-limiting examples of certain compounds disclosed in U.S. Provisional Patent Application Ser. No. 60/605,234 are:

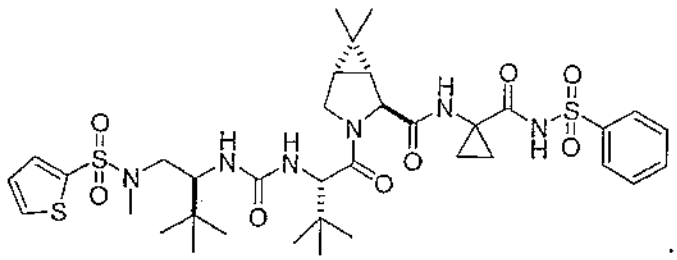








and

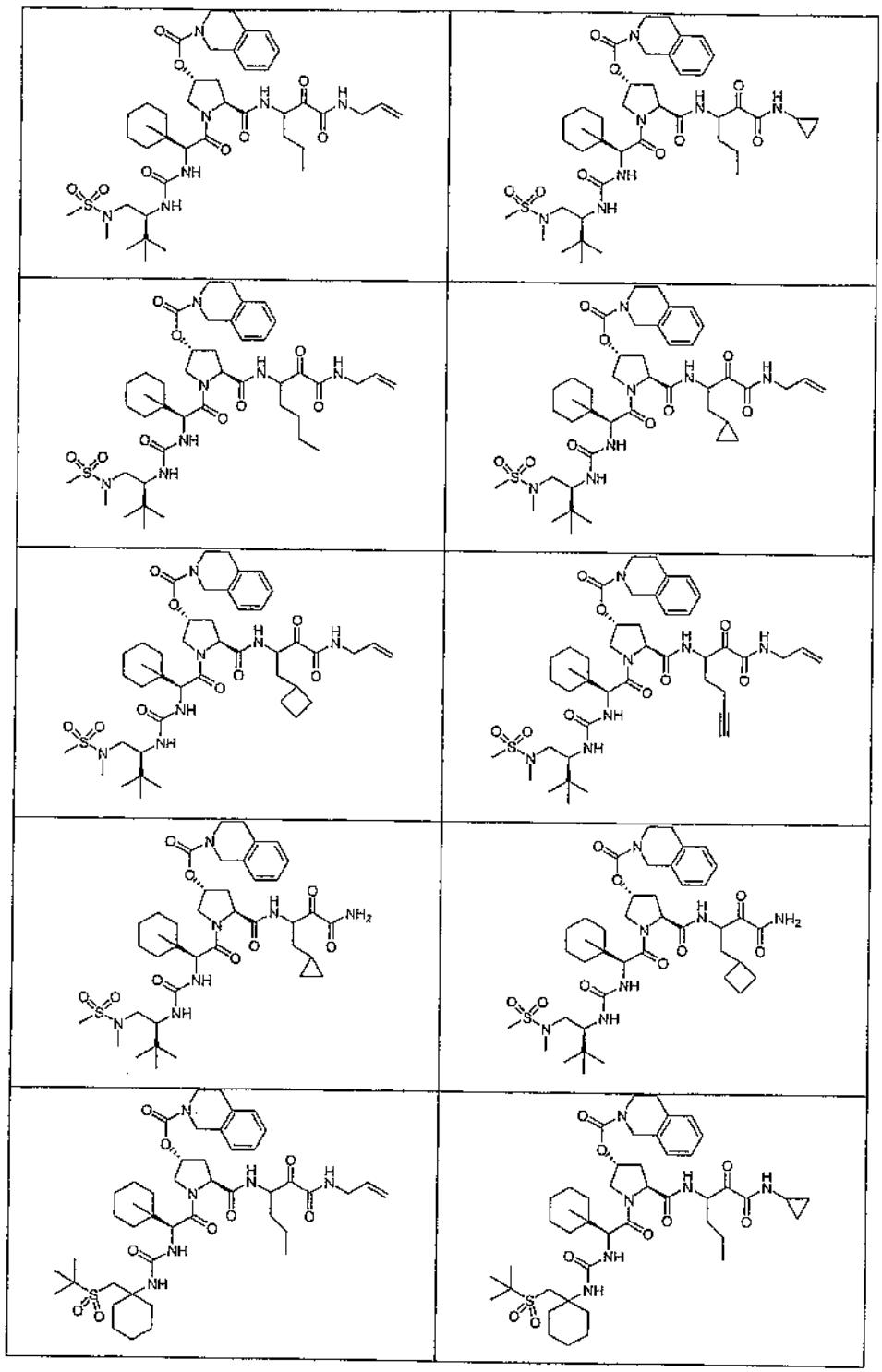


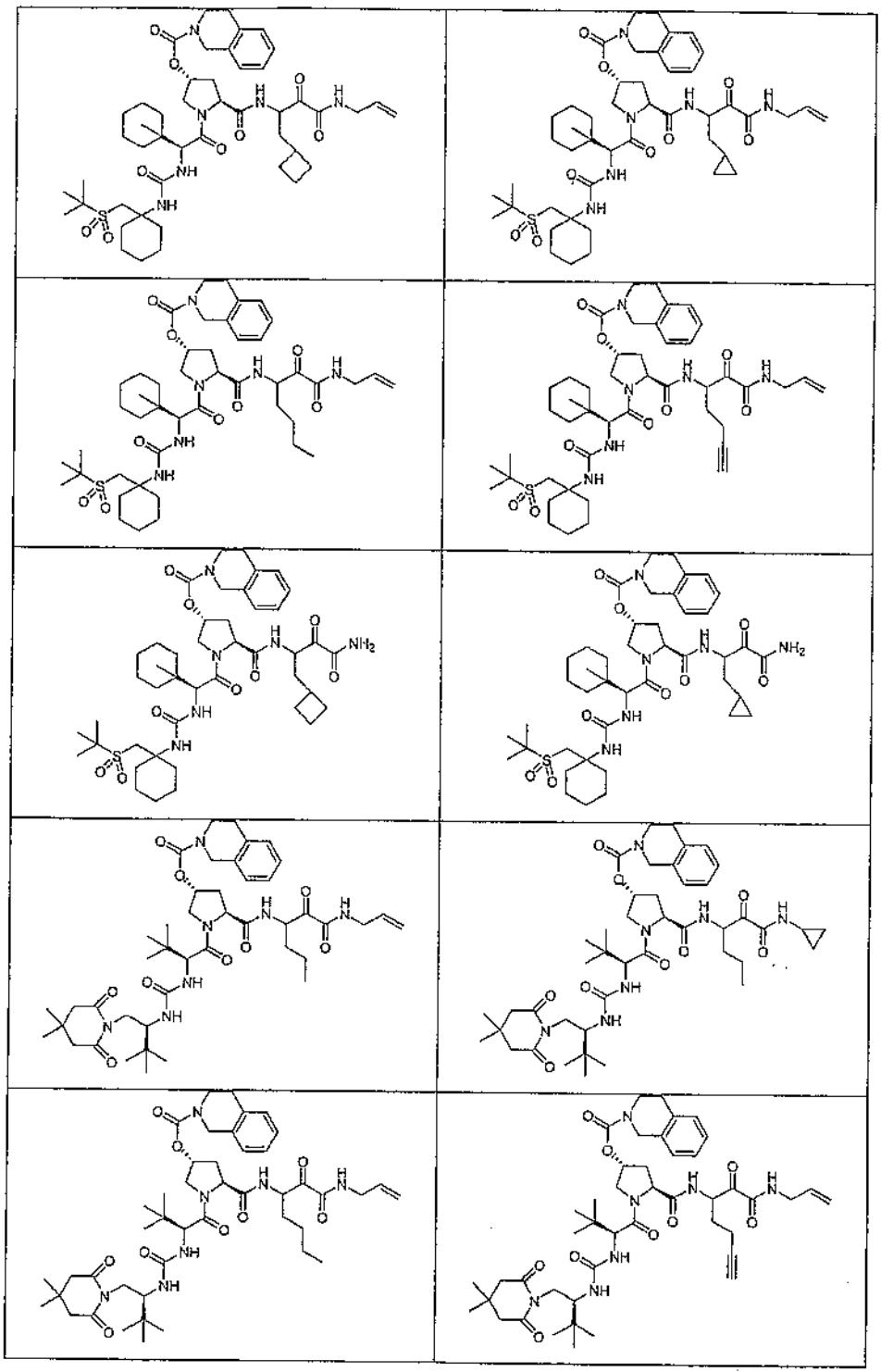
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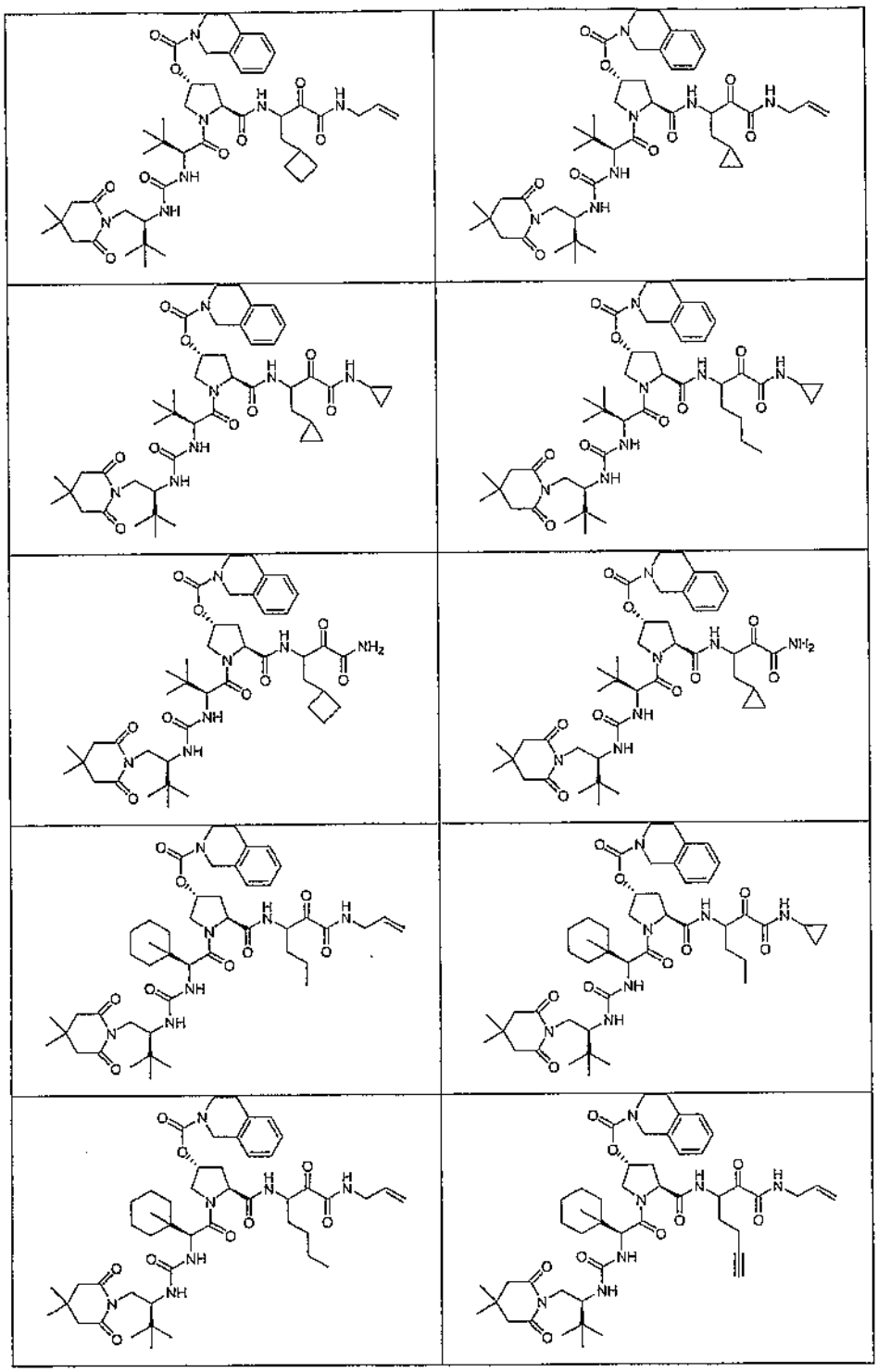
or a pharmaceutically acceptable salt, solvate or ester thereof.

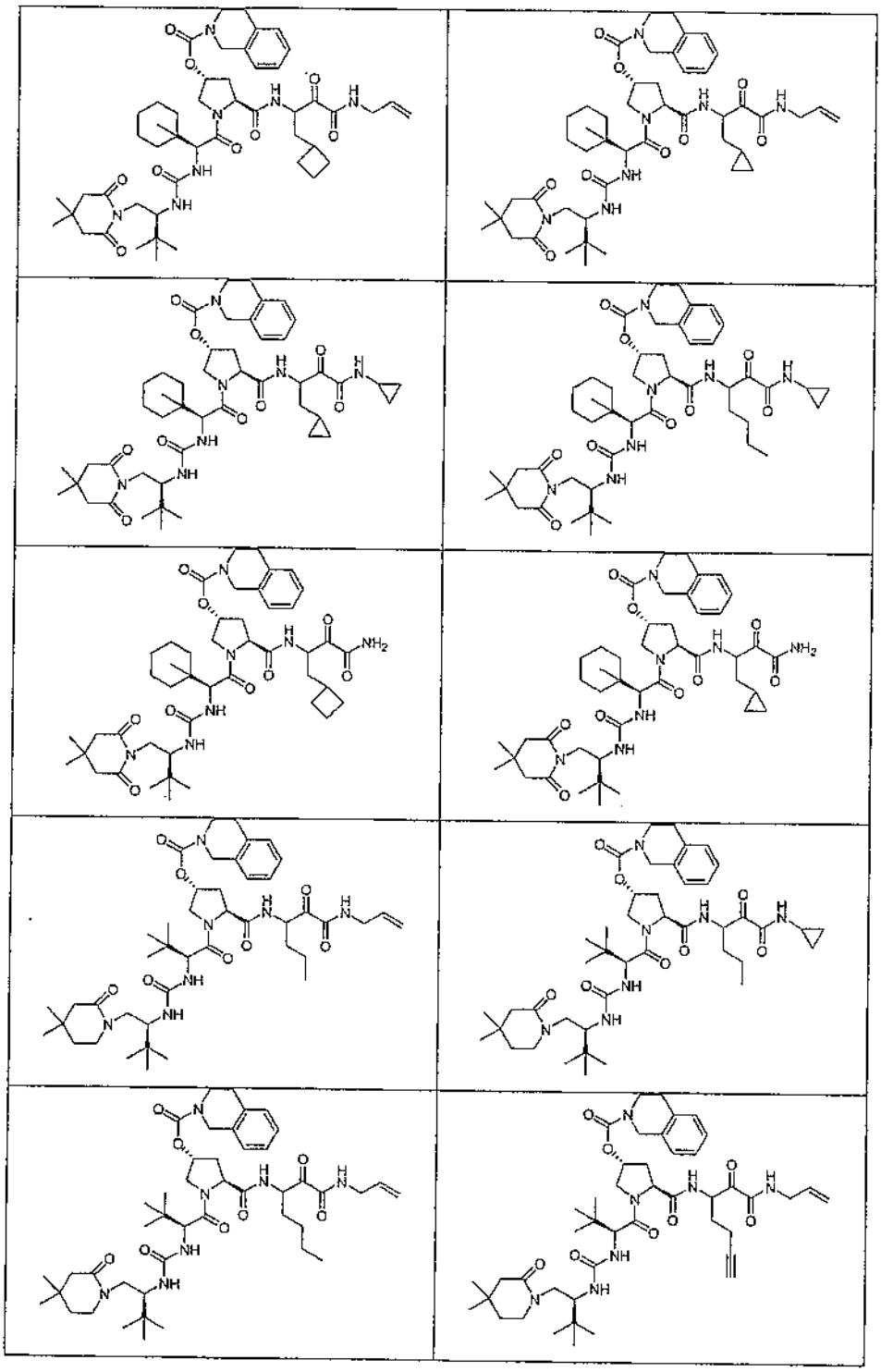
Compounds of formula XIX are disclosed in U.S. Provisional Patent Application Ser. No. 60/573,191 filed May 20, 2004. The preparation of these compounds is disclosed in the experimental section of this application set forth hereinbelow.

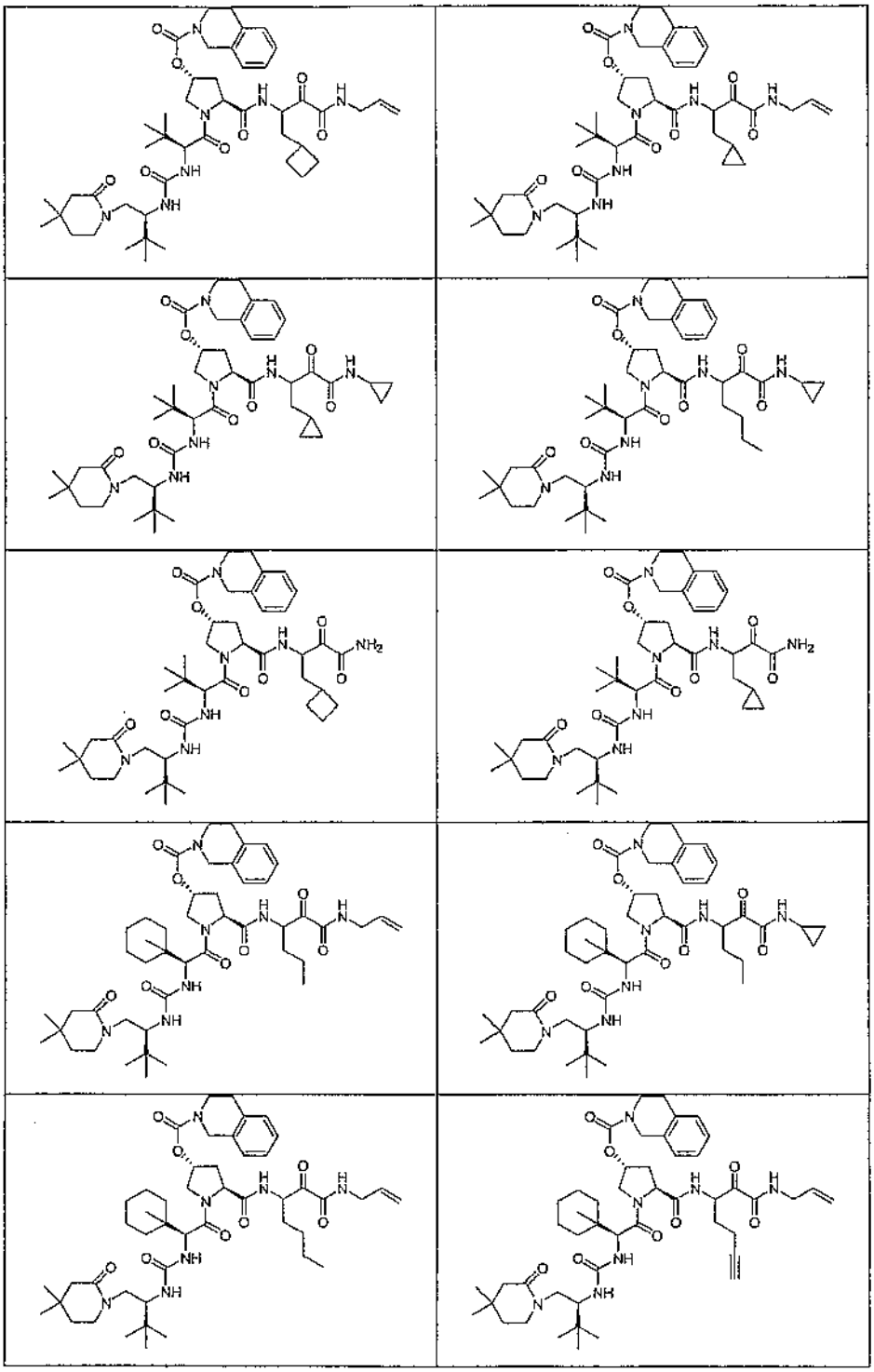
Non-limiting examples of certain compounds disclosed in U.S. Provisional Patent Application Ser. No. 60/573,191 are:

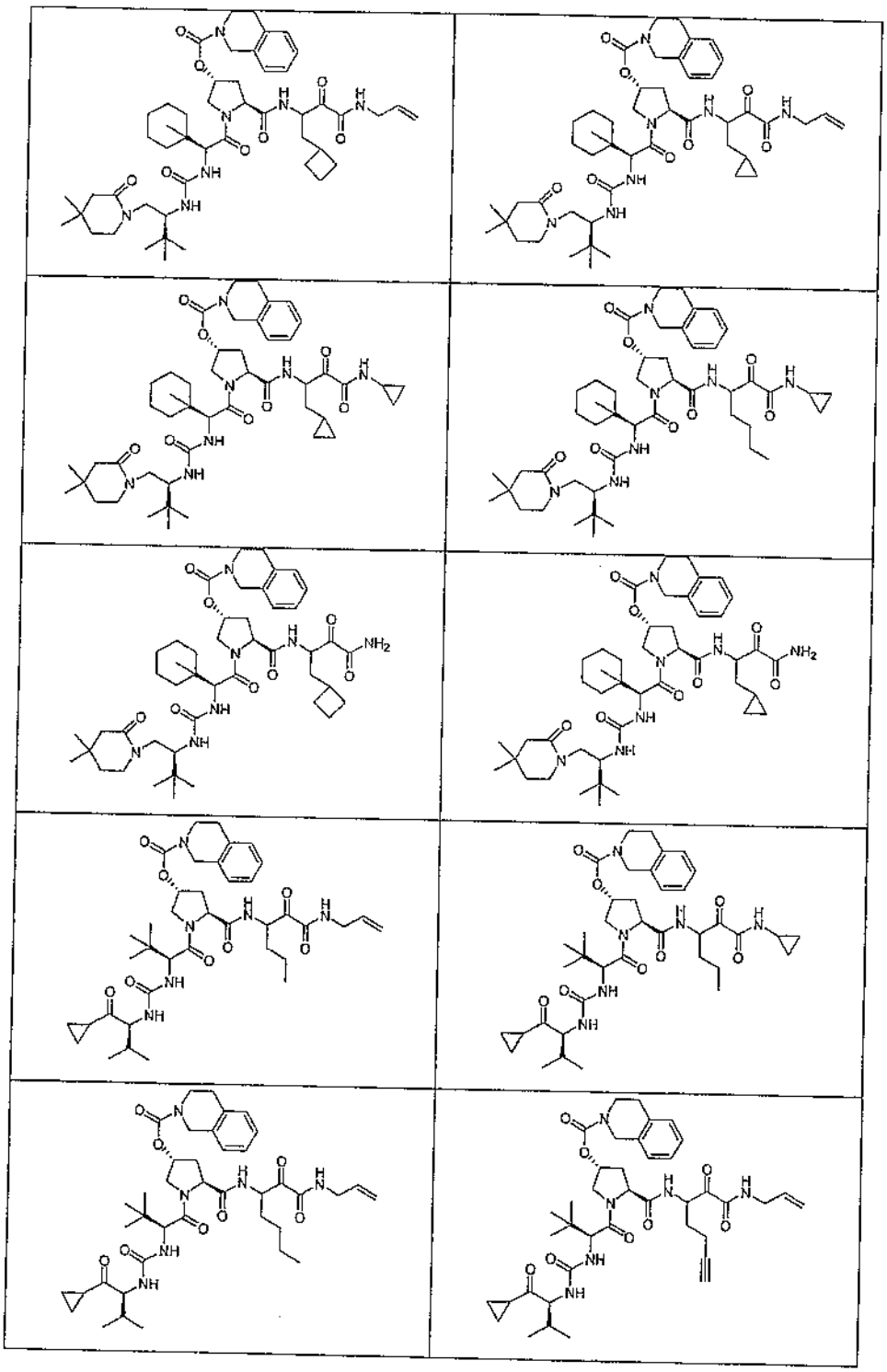


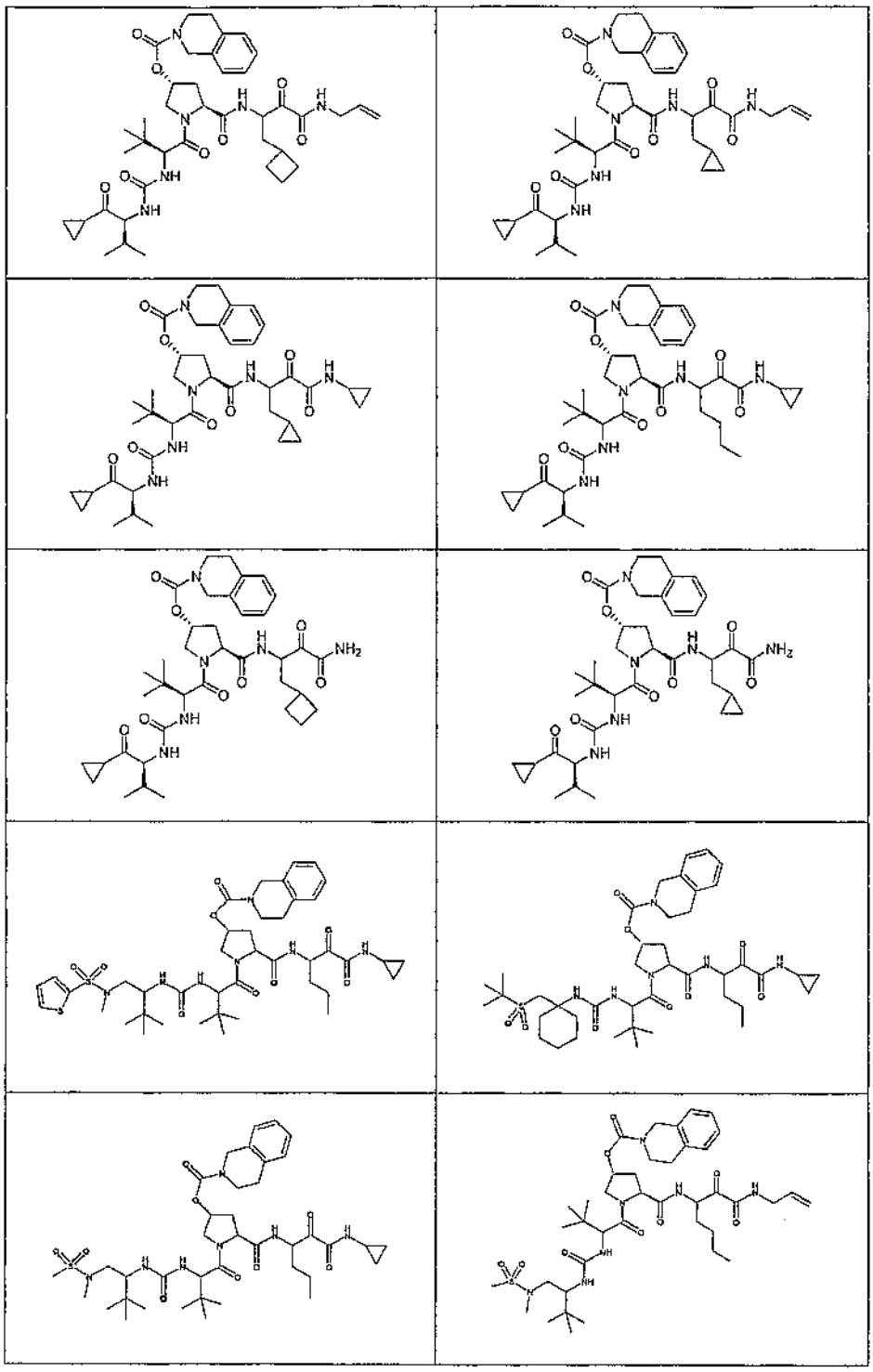


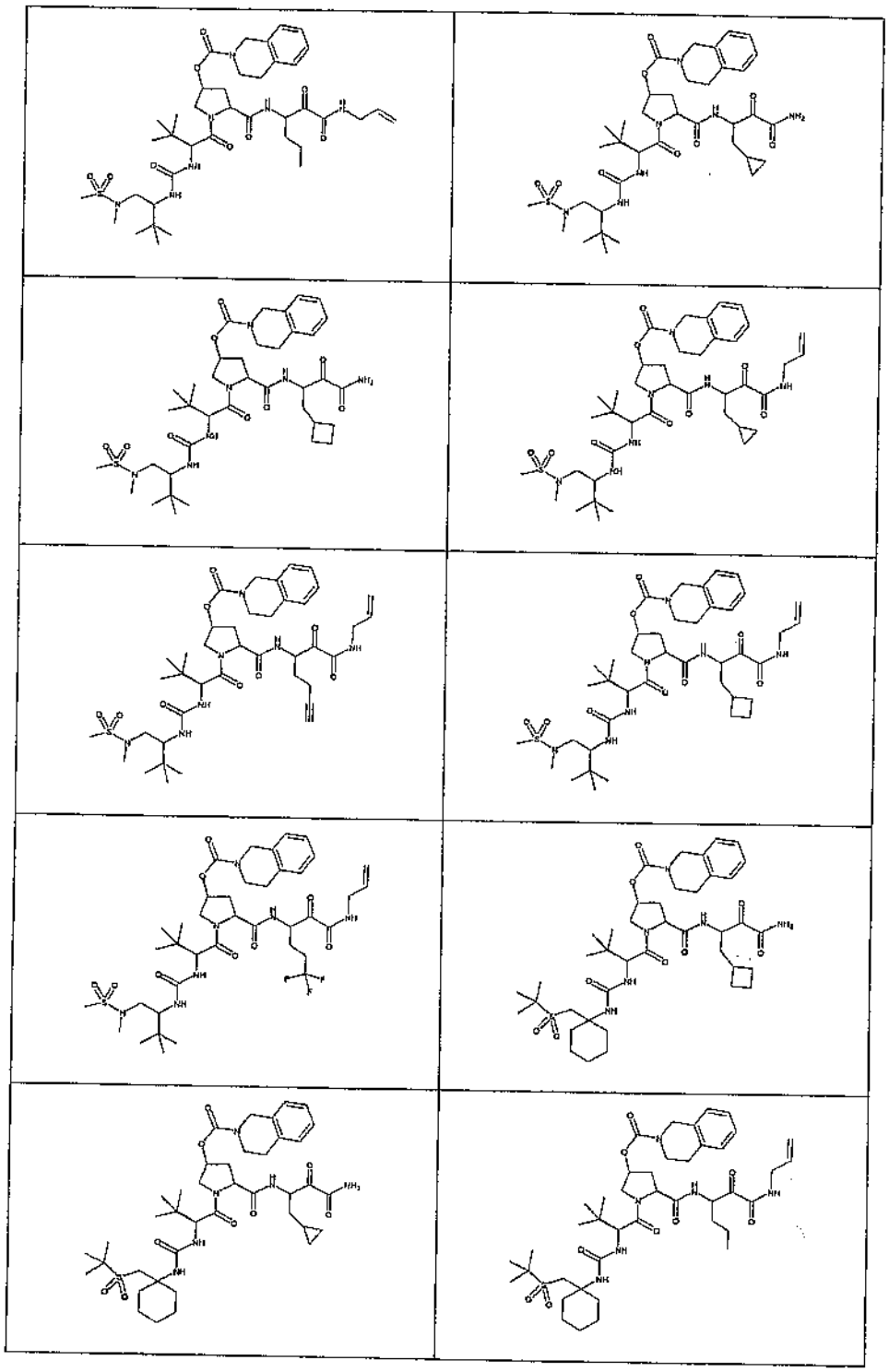


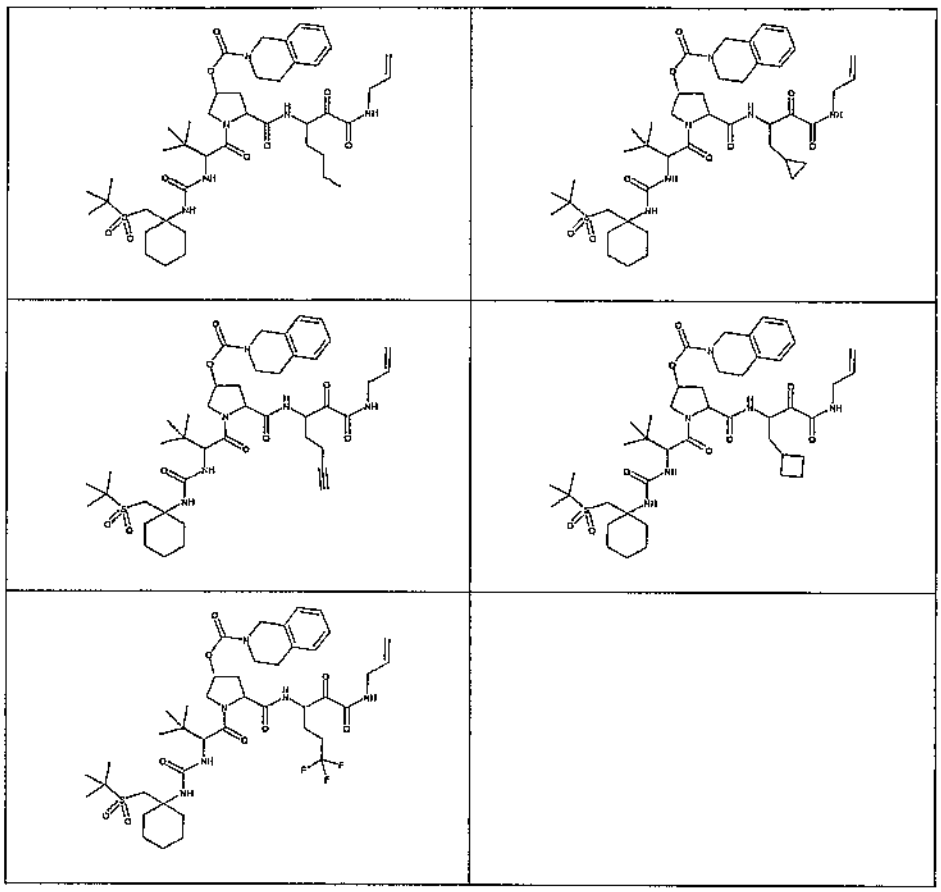












or a pharmaceutically acceptable salt, solvate or ester thereof.

Compounds of formula (XX) have been disclosed in U.S. Patent No. 6,767,991 at col. 3, line 48 through col. 147, incorporated herein by reference.

Compounds of formula (XXI) have been disclosed in U.S. Patent Publication Nos. 2002/0016442, 2002/0037998 and U.S. Patent Nos. 6,268,207, 6,323,180 at col. 3, line 28 through col. 141, line 60, 6,329,379 at col. 3, line 28 through col. 147, line 27, 6,329,417 at col. 3, line 25 through col. 147, line 30, 6,410,531 at col. 3, line 28 through col. 141, 6,534,523 at col. 3, line 34 through col. 139, line 29, and 6,420,380 at col. 3, line 28 through col. 141, line 65, each incorporated herein by reference.

Compounds of formula (XXII) have been disclosed in PCT International Patent Publication WO00/59929 published on October 12, 2000, U.S. Patent Publication No. 2004/0002448 and U.S. Patent No. 6,608,027 at col. 4 through col. 137, incorporated herein by reference.

Compounds of formula (XXIII) have been disclosed in PCT International

Patent Publication WO02/18369 published on March 7, 2002.

Compounds of formula (XXIV) have been disclosed U.S. Patent Publication Nos. 2002/0032175, 2004/0266731 and U.S. Patent Nos. 6,265,380 at col. 3, line 35 through col. 121 and 6,617,309 at col. 3, line 40 through col. 121, each incorporated herein by reference.

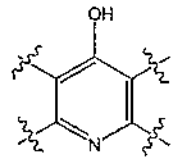
Compounds of formula (XXV) have been disclosed U.S. Patent Nos. 5,866,684 at col. 1 through col. 72 and 6,018,020 at col. 1 through col. 73, each incorporated herein by reference.

Compounds of formula (XXVI) have been disclosed in U.S. Patent No. 6,143,715 at col. 3, line 6 through col. 62, line 20, incorporated herein by reference.

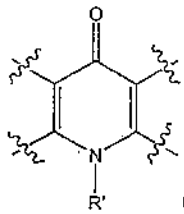
Isomers of the various present compounds (where they exist), including enantiomers, stereoisomers, rotamers, tautomers and racemates are also contemplated as being part of this invention. The invention includes d and l isomers in both pure form and in admixture, including racemic mixtures. Isomers can be prepared using conventional techniques, either by reacting optically pure or optically enriched starting materials or by separating isomers of a compound of the present invention. Isomers may also include geometric isomers, e.g., when a double bond is present. Polymorphous forms of the present compounds, whether crystalline or amorphous, also are contemplated as being part of this invention. The (+) isomers of the present compounds are preferred compounds used in the present invention.

Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are also within the scope of this invention.

It will be apparent to one skilled in the art that certain of the present compounds may exist in alternative tautomeric forms. All such tautomeric forms of the present compounds are within the scope of the invention. Unless otherwise indicated, the representation of either tautomer is meant to include the other. For example, both isomers (1) and (2) are contemplated:



(1)



(2) wherein R' is H or C_{1-6} unsubstituted alkyl.

Prodrugs and solvates of the compounds of the invention are also contemplated herein. 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. The term "prodrug" means a compound (e.g, a drug precursor) that is transformed *in vivo* to yield a compound of Formula (I) or a pharmaceutically acceptable salt, hydrate or solvate of the compound. The transformation may occur by various mechanisms (e.g., by metabolic or chemical processes), such as, for example, through hydrolysis in blood. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

For example, if a compound of Formula (I) or a pharmaceutically acceptable salt, hydrate or solvate of the compound contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as, for example, (C_1–C_8)alkyl, (C_2-C_{12})alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-

crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C_1-C_2)alkylamino(C_2-C_3)alkyl (such as β-dimethylaminoethyl), carbamoyl-(C_1-C_2)alkyl, N,N-di (C_1-C_2)alkylcarbamoyl-(C1-C2)alkyl and piperidino-, pyrrolidino- or morpholino(C_2-C_3)alkyl, and the like.

Similarly, if a compound of Formula (I) contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as, for example, (C_1-C_6)alkanoyloxymethyl, 1-((C_1-C_6)alkanoyloxy)ethyl, 1-methyl-1-((C_1-C_6)alkanoyloxy)ethyl, (C_1-C_6)alkoxycarbonyloxymethyl, N-(C_1-C_6)alkoxycarbonylaminomethyl, succinoyl, (C_1-C_6)alkanoyl, α-amino(C_1-C_4)alkanyl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, $P(O)(OH)_2$, $-P(O)(O(C_1-C_6)alkyl)_2$ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate), and the like.

If a compound of Formula (I) incorporates an amine functional group, a prodrug can be formed by the replacement of a hydrogen atom in the amine group with a group such as, for example, R-carbonyl, RO-carbonyl, NRR'-carbonyl where R and R' are each independently (C_1-C_{10})alkyl, (C_3-C_7) cycloalkyl, benzyl, or R-carbonyl is a natural α-aminoacyl or natural α-aminoacyl, —C(OH)C(O)OY^1 wherein Y^1 is H, (C_1-C_6)alkyl or benzyl, —$C(OY^2)Y^3$ wherein Y^2 is (C_1-C_4) alkyl and Y^3 is (C_1-C_6)alkyl, carboxy (C_1-C_6)alkyl, amino(C_1-C_4)alkyl or mono-N—or di-N,N-(C_1-C_6)alkylaminoalkyl, —$C(Y^4)Y^5$ wherein Y^4 is H or methyl and Y^5 is mono-N— or di-N,N-(C_1-C_6)alkylamino morpholino, piperidin-1-yl or pyrrolidin-1-yl, and the like.

"Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H_2O.

One or more of the present compounds may also exist as, or optionally converted to, a solvate. Preparation of solvates is generally known. Thus, for example, M. Caira *et al*, *J. Pharmaceutical Sci.*, 93(3), 601-611 (2004) describe the preparation of the solvates of the antifungal fluconazole in ethyl acetate as well as from water. Similar preparations of solvates, hemisolvate, hydrates and the like are described by E. C. van Tonder *et al*, *AAPS PharmSciTech.*, 5(1), article 12 (2004); and A. L. Bingham *et al*, *Chem. Commun.*, 603-604 (2001). A typical, non-limiting, process involves dissolving a compound in desired amounts of the desired solvent (organic or water or mixtures thereof) at a higher than ambient temperature, and cooling the solution at a rate sufficient to form crystals which are then isolated by standard methods. Analytical techniques such as, for example I. R. spectroscopy, show the presence of the solvent (or water) in the crystals as a solvate (or hydrate).

"Effective amount" or "therapeutically effective amount" is meant to describe an amount of a compound or a composition used in the present invention effective in inhibiting HCV protease and/or cathepsins, and thus producing the desired therapeutic, ameliorative, inhibitory or preventative effect in a suitable subject.

The present compounds form salts that are also within the scope of this invention. Reference to a compound of the present invention herein is understood to include reference to salts, esters and solvates thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of formula I contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful. Salts of the present compounds of the various formulae disclosed herein may be formed, for example, by reacting the present compounds 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. Acids (and bases) which are generally considered suitable for the formation of pharmaceutically useful salts from basic (or acidic) pharmaceutical compounds are discussed, for

example, by 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; in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website); and P. Heinrich Stahl, Camille G. Wermuth (Eds.), *Handbook of Pharmaceutical Salts: Properties, Selection, and Use*, (2002) Int'l. Union of Pure and Applied Chemistry, pp. 330-331. These disclosures are incorporated herein by reference thereto.

Exemplary acid addition salts include acetates, adipates, alginates, ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, cyclopentanepropionates, digluconates, dodecylsulfates, ethanesulfonates, fumarates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, hydrochlorides, hydrobromides, hydroiodides, 2-hydroxyethanesulfonates, lactates, maleates, methanesulfonates, methyl sulfates, 2-naphthalenesulfonates, nicotinates, nitrates, oxalates, pamoates, pectinates, persulfates, 3-phenylpropionates, phosphates, picrates, pivalates, propionates, salicylates, succinates, sulfates, sulfonates (such as those mentioned herein), tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) undecanoates, and the like.

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, aluminum salts, zinc salts, salts with organic bases (for example, organic amines) such as benzathines, diethylamine, dicyclohexylamines, hydrabamines (formed with N,N-bis(dehydroabietyl) ethylenediamine), N-methyl-D-glucamines, N-methyl-D-glucamides, t-butyl amines, piperazine, phenylcyclohexylamine, choline, tromethamine, 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, propyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (e.g. decyl, lauryl, myristyl 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. All acid and base salts, as well as esters and solvates, are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

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

In such esters, unless otherwise specified, any alkyl moiety present preferably contains from 1 to 18 carbon atoms, particularly from 1 to 6 carbon atoms, more particularly from 1 to 4 carbon atoms. Any cycloalkyl moiety present in such esters preferably contains from 3 to 6 carbon atoms. Any aryl moiety present in such esters preferably comprises a phenyl group.

The compounds of Formulae I-XXVI can exhibit HCV inhibitory activity and/or capthesin inhibitory activity. Pharmaceutical formulations containing these compounds can possess utility in treating hepatitis C and related disorders and/or capthesin-associated disorders and may be used by administering a therapeutically effective amount of the inventive pharmaceutical formulation to a patient having such a disease or diseases and in need of such a treatment.

The pharmaceutical formulations of the present invention are suited for treatment of infection by any of the genotypes of HCV. HCV types and subtypes may differ in their antigenicity, level of viremia, severity of disease produced, and response to interferon therapy. (Holland, J. et al., "Hepatitis C genotyping by direct sequencing of the product from the Roche Amplicor Test: methodology and

application to a South Australian population," Pathology, 30:192-195, 1998). The nomenclature of Simmonds, P. et al. ("Classification of hepatitis C virus into six major genotypes and a series of subtypes by phylogenetic analysis of the NS-5 region," J. Gen. Virol., 74:2391-9, 1993) is widely used and classifies isolates into six major genotypes, 1 through 6, with two or more related subtypes, e.g., 1a, 1b. Additional genotypes 7-10 and 11 have been proposed, however the phylogenetic basis on which this classification is based has been questioned, and thus types 7, 8, 9 and 11 isolates have been reassigned as type 6, and type 10 isolates as type 3. (Lamballerie, X. et al., "Classification of hepatitis C variants in six major types based on analysis of the envelope 1 and nonstructural 5B genome regions and complete polyprotein sequences," J. Gen. Virol., 78:45-51, 1997). The major genotypes have been defined as having sequence similarities of between 55 and 72% (mean 64.5%), and subtypes within types as having 75%-86% similarity (mean 80%) when sequenced in the NS-5 region. (Simmonds, P. et al., "Identification of genotypes of hepatitis C by sequence comparisons in the core, E1 and NS-5 regions," J. Gen. Virol., 75:1053-61, 1994).

The formulations of the invention may be used for the treatment of HCV in humans in monotherapy mode or in a combination therapy (e.g., dual combination, triple combination etc.) mode such as, for example, in combination with antiviral and/or immunomodulatory agents. Examples of such antiviral and/or immunomodulatory agents include Ribavirin (from Schering-Plough Corporation, Madison, New Jersey) and Levovirin™ (from ICN Pharmaceuticals, Costa Mesa, California), VP 50406™ (from Viropharma, Incorporated, Exton, Pennsylvania), ISIS 14803™ (from ISIS Pharmaceuticals, Carlsbad, California), Heptazyme™ (from Ribozyme Pharmaceuticals, Boulder, Colorado), VX 497™ (from Vertex Pharmaceuticals, Cambridge, Massachusetts), Thymosin™ (from SciClone Pharmaceuticals, San Mateo, California), Maxamine™ (Maxim Pharmaceuticals, San Diego, California), mycophenolate mofetil (from Hoffman-LaRoche, Nutley, New Jersey), interferon (such as, for example, interferon-alpha, PEG-interferon alpha conjugates) and the like. "PEG-interferon alpha conjugates" are interferon alpha molecules covalently attached to a PEG molecule. Illustrative PEG-interferon alpha conjugates include interferon alpha-2a (Roferon™, from Hoffman La-Roche, Nutley,

New Jersey) in the form of pegylated interferon alpha-2a (e.g., as sold under the trade name Pegasys™), interferon alpha-2b (Intron™, from Schering-Plough Corporation) in the form of pegylated interferon alpha-2b (e.g., as sold under the trade name PEG-Intron™), interferon alpha-2c (Berofor Alpha™, from Boehringer Ingelheim, Ingelheim, Germany) or consensus interferon as defined by determination of a consensus sequence of naturally occurring interferon alphas (Infergen™, from Amgen, Thousand Oaks, California).

The formulations of the present invention can be administered in combination with interferon alpha, PEG-interferon alpha conjugates or consensus interferon concurrently or consecutively at recommended dosages for the duration of HCV treatment. The commercially available forms of interferon alpha include interferon alpha 2a and interferon alpha 2b and also pegylated forms of both aforementioned interferon alphas. The recommended dosage of INTRON-A interferon alpha 2b (commercially available from Schering-Plough Corp.) as administered by subcutaneous injection at 3MIU(12 mcg)/0.5mL/TIW is for 24 weeks or 48 weeks for first time treatment. The recommended dosage of PEG-INTRON interferon alpha 2b pegylated (commercially available from Schering-Plough Corp.) as administered by subcutaneous injection at 1.5 mcg/kg/week, within a range of 40 to 150 mcg/week, is for at least 24 weeks. The recommended dosage of ROFERON A inteferon alpha 2a (commercially available from Hoffmann-La Roche) as administered by subcutaneous or intramuscular injection at 3MIU(11.1 mcg/mL)/TIW is for at least 48 to 52 weeks, or alternatively 6MIU/TIW for 12 weeks followed by 3MIU/TIW for 36 weeks. The recommended dosage of PEGASUS interferon alpha 2a pegylated (commercially available from Hoffmann-La Roche) as administered by subcutaneous injection at 180mcg/1mL or 180mcg/0.5mL is once a week for at least 24 weeks. The recommended dosage of INFERGEN interferon alphacon-1 (commercially available from Amgen) as administered by subcutaneous injection at 9mcg/TIW is for 24 weeks for first time treatment and up to 15 mcg/TIW for 24 weeks for non-responsive or relapse treatment. Optionally, Ribavirin, a synthetic nucleoside analogue with activity against a broad spectrum of viruses including HCV, can be included in combination with the interferon and the HCV protease inhibitor. The recommended dosage of ribavirin is in a range from 600 to 1400 mg per day for at least 24 weeks

(commercially available as REBETOL ribavirin from Schering-Plough or COPEGUS ribavirin from Hoffmann-La Roche).

The formulations of the present invention comprise at least one compound of Formulae I-XXVI, as defined above, together with one or more surfactant. The formulation can further comprises one or more pharmaceutically acceptable adjuvants and optionally other therapeutic agents and pharmaceutically acceptable carriers and excipients. Each excipient must be acceptable in the sense of being compatible with the other ingredients of the formulation and not injurious to the mammal in need of treatment.

In one embodiment, the adjuvant is at least one pharmaceutically acceptable surfactant or at least one acidifying agent or both. When desired or needed, suitable carriers and other excipients (such as binders, glidents, lubricants, and disintegrants) may also be incorporated in the formulation. These adjuvants, carriers and excipients as well as others are described hereinafter.

"Surfactant", as used herein, refers to an adjuvant material that reduces the contact angle between the active drug component and the environment of its use in a mammal and may also be referred to as a wetting agent. Treatment of diseases requiring high dosages of the present compounds, such as HCV, is enhanced by improving the absorption rate of the compounds thereby improving the extent of absorption of the compounds in a mammal. The surfactant in the pharmaceutical formulations of the present invention enhances wetting of the present compounds by aqueous systems (as in a mammal) and improves the dissolution rate of the compounds to render a greater quantity of the compound available for absorption than is available in a formulation of the present compounds that does not include a surfactant. Any pharmaceutically acceptable surfactant that improves wetting of the present compounds may be used. Particularly suitable surfactants include sodium lauryl sulfate, stearic acid, monoethanolamine, docusate sodium, sorbitan fatty acid esters, polyoxyethylene sorbitan fatty acid esters, ethoxylated aliphatic alcohols, propylene glycol monocaprylate, glycerol monostearate, medium chain triglycerides, polyoxyethylene alkyl ethers, and polyoxyethylene stearates. In one embodiment, the surfactant is sodium lauryl sulfate. In another embodiment, the surfactant is a polyoxyethylene sorbitan fatty acid ester. In yet another embodiment, the surfactant

is PEG-1-PEG-9-lauryl glycol ether. These surfactants may be used alone in or combination in the pharmaceutical formulations of the present invention in a total amount of about 0.1 to about 10% by weight or about 1 to about 5% by weight.

Acidifying agent refers to an adjuvant material that lowers the pH of the formulation. An acidic pH environment may improve the stability of the present compounds. Any pharmaceutically acceptable acidifying agent that improves stability of the present compounds may be used. Particularly suitable acidifying agents include tartaric acid, ascorbic acid, citric acid, malic acid, lactic acid and succinic acid. In one embodiment, the acidifying agent is tartaric acid. These acidifying agents may be used alone in or combination in the pharmaceutical formulations of the present invention in a total amount of about 0.1 to about 10% by weight or about 1 to 5% by weight.

Carrier refers to a substance that usually makes up the major portion of the composition or dosage form. Suitable carriers include celluloses such as microcrystalline cellulose; sugars such as lactose, sucrose, mannitol and sorbitol; and starches such as are derived from wheat, corn, rice and potato. The amount of carrier in the formulation can range from about 10 to about 90% by weight of the total formulation, or about 25 to about 75% by weight, or about 30 to about 60% by weight, or about 12 to about 60% by weight. In one embodiment, the carrier is microcrystalline cellulose.

Binders 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 lactose, sucrose and corn sweeteners; 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; polyethylene glycol; waxes and inorganics such as magnesium aluminum silicate. The amount of binder in the formulation can range from about 10 to about 90% by weight of the total formulation, or about 25 to about 75% by weight, or about 30 to about 60% by weight, or about

12 to about 60% by weight. In one embodiment, the binder is anhydrous lactose.

Glidents refers to material that prevents caking and improves 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 formulation can range from about 0.1% to about 5% by weight of the total formulation, or from about 0.5 to about 3% by weight.

Lubricants are substances 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 boric acid sodium chloride, sodium benzoate, sodium acetate, sodium chloride 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 formulation can range from about 0.1 to about 10% by weight of the formulation, or from about 0.5 to about 5% by weight.

Disintegrant refers to materials added to the formulation to help it break apart (disintegrate) and release the drug. Suitable disintegrants include starches; "cold water soluble" modified starches such as sodium carboxymethyl starch; natural and synthetic gums such as locust bean, karaya, guar gum, 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 formulation, or from about 2 to about 10% by weight.

Coloring agents provide coloration to the formulation 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 formulation, or from about 0.1 to about 1%.

Sweetening agents, flavoring agents, stabilizers, antioxidants and preservatives may also be included where appropriate.

The term pharmaceutical formulation encompasses both the bulk formulation and individual unit dosage forms. The bulk composition is material that has not yet been formed into individual dosage units. An illustrative dosage unit is an oral dosage unit such as tablets, capsules and the like.

The formulations of the present invention may be administered orally, intravenously, subcutaneously, or transdermally. Preferably, the pharmaceutical formulation is 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. Suitable unit dosage forms are solids, gels, or fluids including elixirs, dispersible granules, syrups, suspensions. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories.

The powders, tablets and capsules may be comprised of from about 5 to about 95 percent active ingredient. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration. Other examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions may be found in A. Gennaro (ed.), *Remington's Pharmaceutical Sciences,* 18th Edition, (1990), Mack Publishing Co., Easton, Pennsylvania. The formulations of the present invention may be produced via a dry blend processor a wet granulation process and filled or compressed into capsules or tablets.

Capsules (either solid-filled, semi-solid filled or liquid filled) are special containers or enclosures, often made of methyl cellulose, polyvinyl alcohols, or denatured gelatins or starch for holding or containing the pharmaceutical formulation. (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 pharmaceutical formulation. The tablet can be prepared by compression of mixtures or granulations obtained by wet granulation, dry granulation or by compaction.

A gel, such as an oral gel refers to the formulations dispersed or solubilized in

a hydrophillic semi-solid matrix.

Suppositories containing the formulations of the present invention may be prepared by melting a low melting wax such as a mixture of fatty acid glycerides such as cocoa butter, and dispersing the components of the formulations homogeneously therein by stirring or similar mixing. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

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.

Fluid forms may be liquids including solutions, suspensions and emulsions containing the formulations. Non-limiting examples include 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.

Also included are aerosol preparations of the present invention that are suitable for inhalation. Aerosols 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.

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. Alternatively, the formulations of the present invention may be prepared in powder blends that can be suspended in water or juices.

Transdermal formulations 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.

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.

The present invention discloses methods for preparing the pharmaceutical formulations of the present invention. Conventional methods for preparing tablets and capsules 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. In one embodiment, a capsule containing the pharmaceutical formulation of the present invention is produced by blending the active drug component with some excipients, compacting the mixture such as with a roller compactor, milling the compacted mixture, blending the milled material with any remaining excipients and filling the final blend into capsules.

In one embodiment, the pharmaceutical formulation of the present is administered orally and is in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

The amount and frequency of administration of the formulations of the present invention will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended daily dosage regimen for oral administration can range from about 50 mg/day to about 3000 mg/day, in two to four divided doses.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 1 mg to about 1000 mg, or from about 50 mg to about 800 mg, or from about 50 mg to about 600 mg, or from about 50 mg to about 400 mg, or from about 50 mg to about 200 mg according to the particular application. In one embodiment, the dosage form contains about 200 mg of the active compound. In another embodiment, the dosage form contains about 200 mg of the active compound.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage regimen for a particular situation is within the

skill of the art. For convenience, the total daily dosage may be divided and administered in portions during the day as required.

The following formulations exemplify some of the dosage forms of the present invention. In the formulation, the "Active Compound" designates any of the compounds of Formulae I-XXVI, as defined above, or a pharmaceutically acceptable sale, solvate or ester thereof.

EXAMPLE 1: Dry Blend

Ingredient	Amount
Active Compound	200 mg
Microcrystalline cellulose	0-60 wt.%
Lactose, anhydrous	0-60 wt.%
Sodium croscarmellose	2-10 wt.%
Sodium lauryl sulfate	0-10 wt.%
Tartaric acid	0-10 wt.%
Silicon dioxide	0-3 wt.%
Magnesium stearate	1-10 wt.%
Capsule shell	1 unit
TOTAL FILL WEIGHT	350-500 mg

In one embodiment, the powdery Active Compound can be blended with some of the ingredients and compacted with a roller compactor to densify the powder. The resulting compact is milled, and the milled compact is blended with the remaining ingredients and filled into a capsule or pressed into a tablet.

EXAMPLE 2: Wet Blend

Ingredient	Amount
Active Compound	200 mg
Microcrystalline cellulose	0-60 wt.%
Lactose, anhydrous	0-60 wt.%
Sodium croscarmellose	2-10 wt.%
Sodium lauryl sulfate	0-10 wt.%
Tartaric acid	0-10 wt.%
Pregelatinized starch	0-15 wt.%
Hydroxypropylmethylcellulose	0-6 wt.%
Magnesium stearate	1-10 wt.%
Capsule shell	1 unit
TOTAL FILL WEIGHT	350-500 mg

In one embodiment, the powdery Active Compound can be blended with some of the ingredients, granulated with a solution of binders and dried. The dry

granules are milled and blended with the remaining ingredients and filled into a capsule or pressed into a tablet.

The following experimental section applies for the preparation of the compounds of Formula XI:

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

THF: Tetrahydrofuran

DMF: N,N-Dimethylformamide

EtOAc: Ethyl acetate

AcOH: Acetic acid

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

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

NMM: N-Methylmorpholine

ADDP: 1,1'-(Azodicarbobyl)dipiperidine

DEAD: Diethylazodicarboxylate

MeOH: Methanol

EtOH: Ethanol

Et_2O: Diethyl ether

DMSO: Dimethylsulfoxide

HOBt: N-Hydroxybenzotriazole

PyBrOP: Bromo-tris-pyrrolidinophosphonium hexafluorophosphate

DCM: Dichloromethane

DCC: 1,3-Dicyclohexylcarbodiimide

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

Phg: Phenylglycine

Chg: Cyclohexylglycine

Bn: Benzyl

Bzl: Benzyl

Et: Ethyl

Ph: Phenyl

iBoc: isobutoxycarbonyl

iPr: isopropyl

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

Boc: *tert*-Butyloxycarbonyl

Cbz: Benzyloxycarbonyl

Cp: Cylcopentyldienyl

Ts: p-toluenesulfonyl

MCPBA: 3-chloroperbenzoic acid.

Me: Methyl

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

DMAP: 4-N,N-Dimethylaminopyridine

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

PCC: Pyridiniumchlorochromate

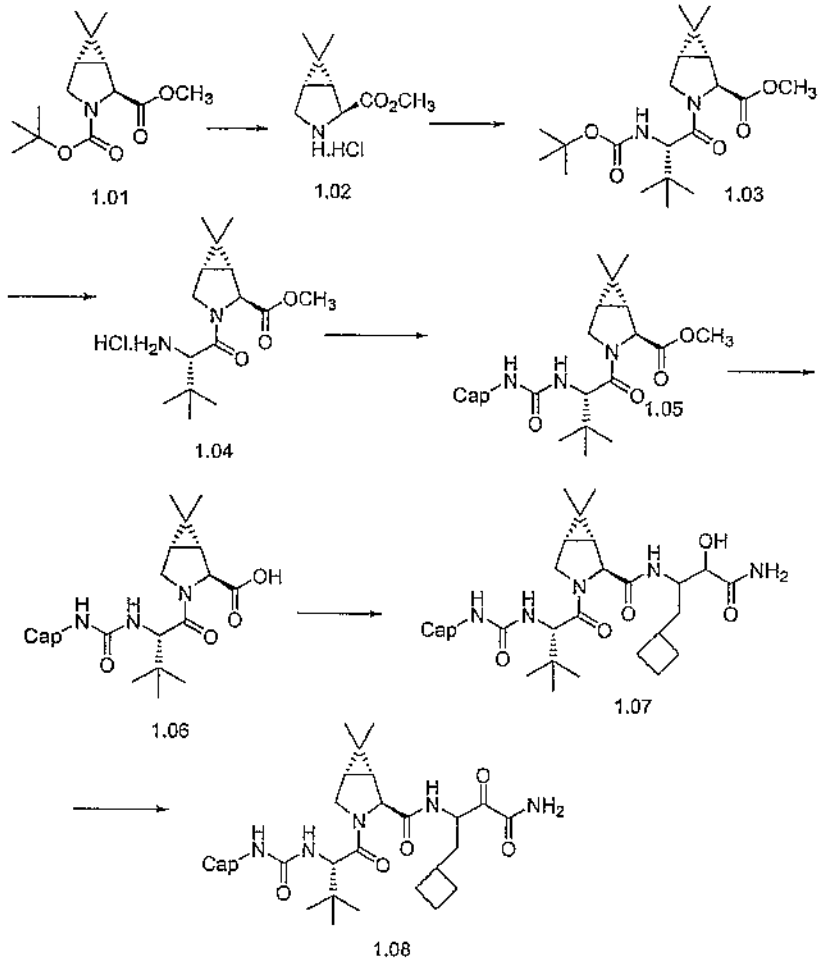
Other abbreviations are commonly used abbreviations Such as according to the guidelines published by *Journal of Organic Chemistry.*

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 (Louis A Carpino *et al.* "Preparation of uronium and immonium salts for peptide coupling", WO 2002094822, pp. 76) to afford 1.03. N-Boc deprotection followed by treatment with appropriate isocyanate gave the urea 1.05. Hydrolysis of the methyl ester provided the acid 1.06. Peptide coupling of the acid 1.06 with the appropriate P_1-P' primary amide moiety afforded the hydroxyl amide 1.07. Oxidation (Moffatt, or Dess-Martin's) resulted in the target compound 1.08.

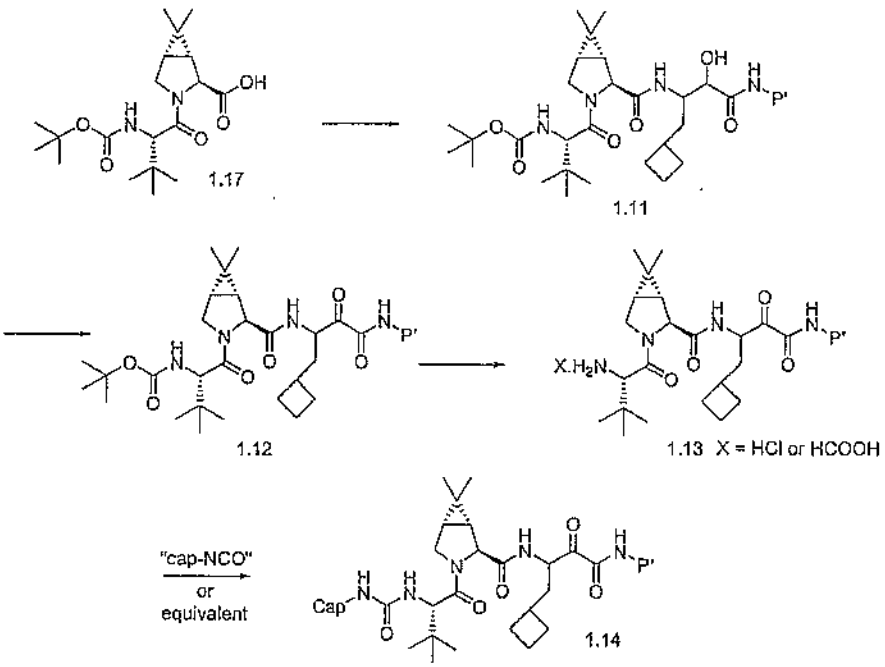


Method B

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

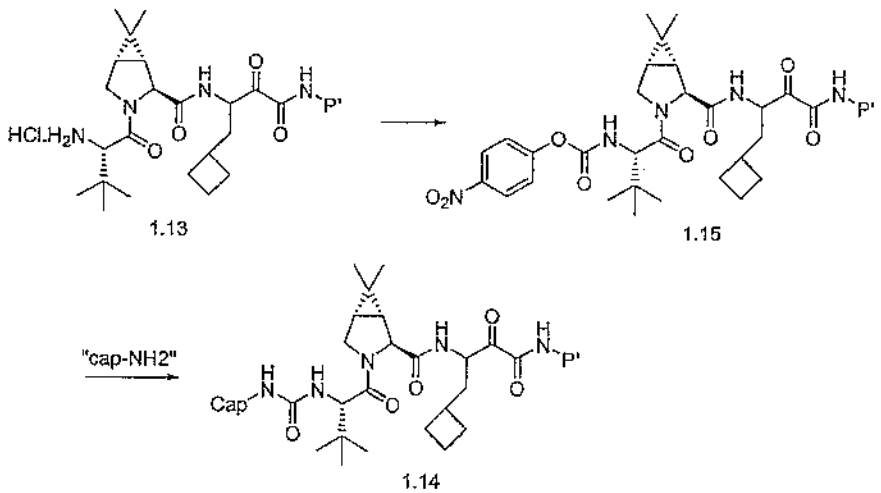
Method C

In another variation, peptide coupling of the N-Boc-P2-P_3-acid 1.03 with the appropriate P_1-P' amide moiety afforded the hydroxyl amide 1.11. Oxidation (Moffatt or Dess-Martin's) resulted in the keto-amide 1.12. Deprotection of the N-Boc using either formic acid or 4 M HCl in dioxane gave the formate or hydrochloride salt 1.13. Treatment with a suitable isocyanate (or isocyanate equivalent) resulted in the target compound 1.14.



Method D

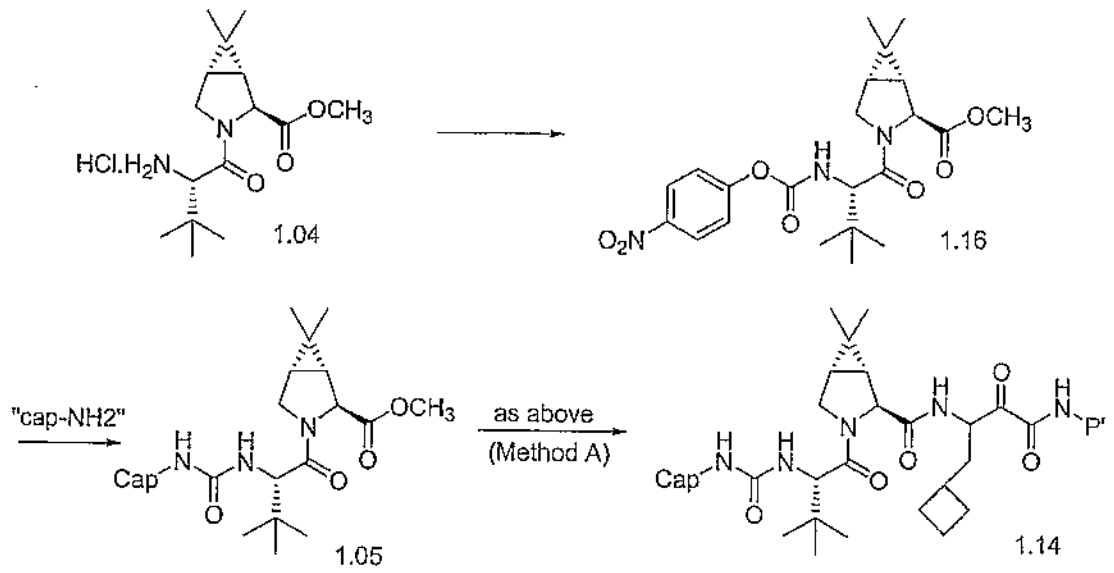
In yet another variation, the hydrochloride salt 1.13 was converted to the 4-nitrophenyl carbamate 1.15 by reaction with 4-nitrophenyl chloroformate. Subsequent treatment with an amine (or amine hydrochloride salt) of choice provided the target compound 1.14.



Method E

In yet another variation, the dipeptide hydrochloride salt 1.04 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.



The following experimental section applies for the preparation of the compounds of Formula XII:

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

THF: Tetrahydrofuran

DMF: N,N-Dimethylformamide

EtOAc: Ethyl acetate

AcOH: Acetic acid

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

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

NMM: N-Methylmorpholine

ADDP: 1,1'-(Azodicarbobyl)dipiperidine

DEAD: Diethylazodicarboxylate

MeOH: Methanol

EtOH: Ethanol

Et_2O: Diethyl ether

DMSO: Dimethylsulfoxide

HOBt: N-Hydroxybenzotriazole

PyBrOP: Bromo-tris-pyrrolidinophosphonium hexafluorophosphate

DCM: Dichloromethane

DCC: 1,3-Dicyclohexylcarbodiimide

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

Phg: Phenylglycine

Chg: Cyclohexylglycine

Bn: Benzyl

Bzl: Benzyl

Et: Ethyl

Ph: Phenyl

iBoc: isobutoxycarbonyl

iPr: isopropyl

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

Boc: tert-Butyloxycarbonyl

Cbz: Benzyloxycarbonyl

Cp: Cylcopentyldienyl

Ts: p-toluenesulfonyl

Me: Methyl

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

DMAP: 4-N,N-Dimethylaminopyridine

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

PCC: Pyridiniumchlorochromate

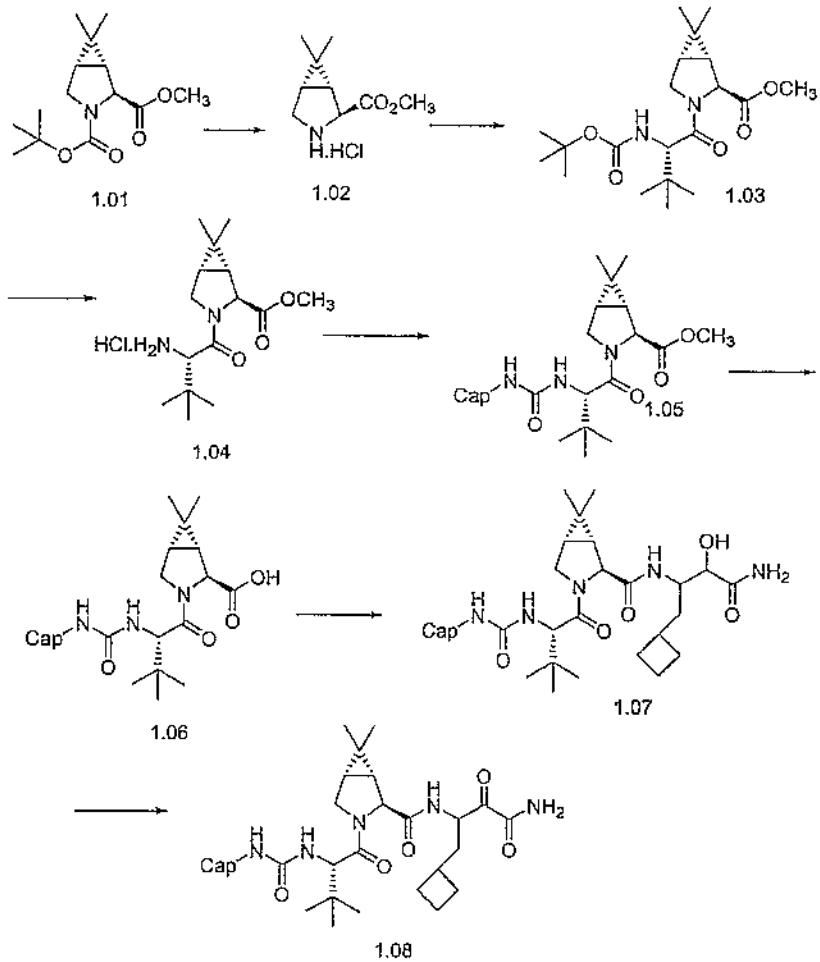
General Schemes for Preparation of Target Compounds

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

Method A:

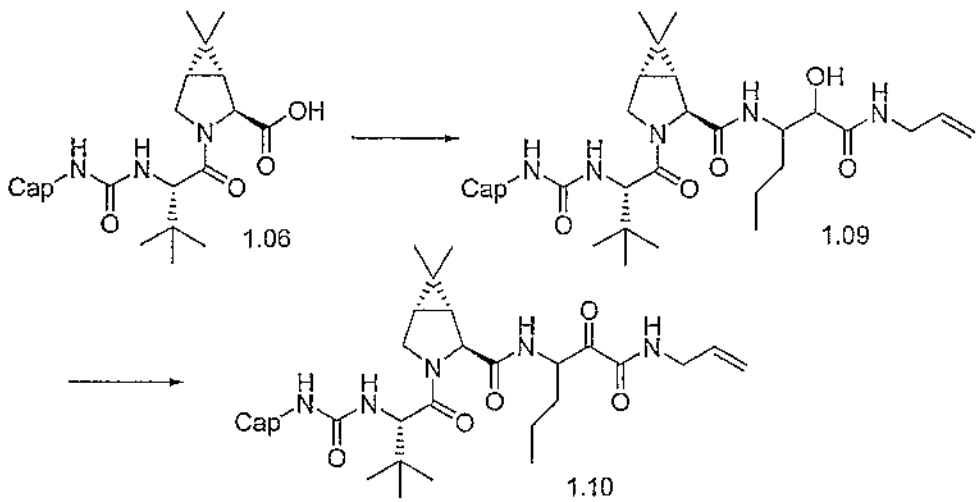
Deprotection of the N-Boc functionality of 1.01 under acidic conditions provided the hydrochloride salt 1.02 which was subsequently coupled with N-Boc-tert-leucine under peptide coupling methodology to afford 1.03. N-Boc deprotection followed by treatment with appropriate isocyanate gave the urea 1.05.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

ester provided the acid 1.06. Peptide coupling of the acid 1.06 with the appropriate P_1-P' primary amide moiety afforded the hydroxyl amide 1.07. Oxidation (Moffatt or related process - T.T.Tidwell, *Synthesis*, **1990**, 857; or Dess-Martin's – *J. Org. Chem.*, **1983**, *48*, 4155) resulted in the target compound 1.08.



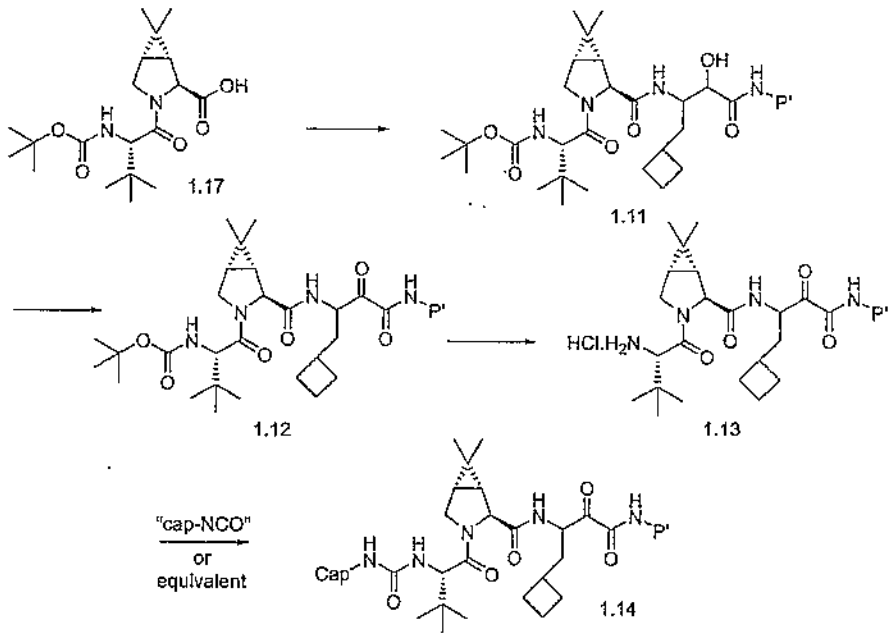
Method B

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



Method C

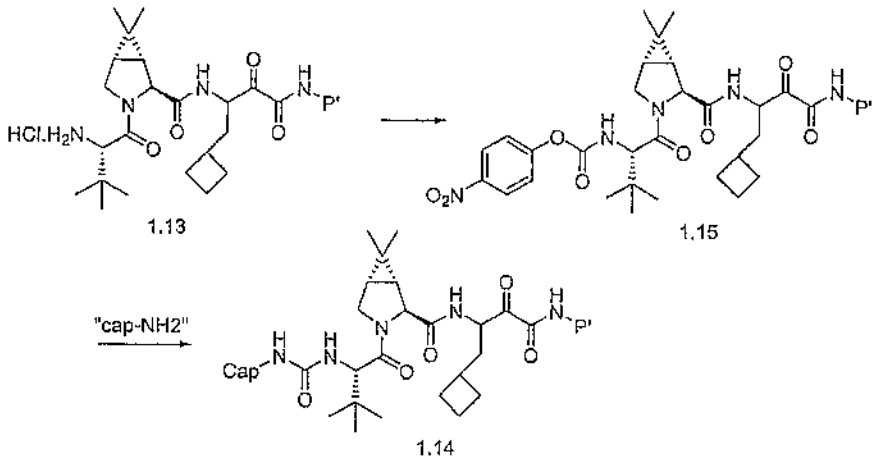
In another variation, peptide coupling of the N-Boc-P_2-P_3-acid 1.17 with the appropriate P_1-P' amide moiety afforded the hydroxyl amide 1.11. Oxidation (Moffatt or Dess-Martin's) resulted in the keto amide 1.12. Deprotection of the N-Boc functionality gave the hydrochloride salt 1.13. Treatment with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



Method D

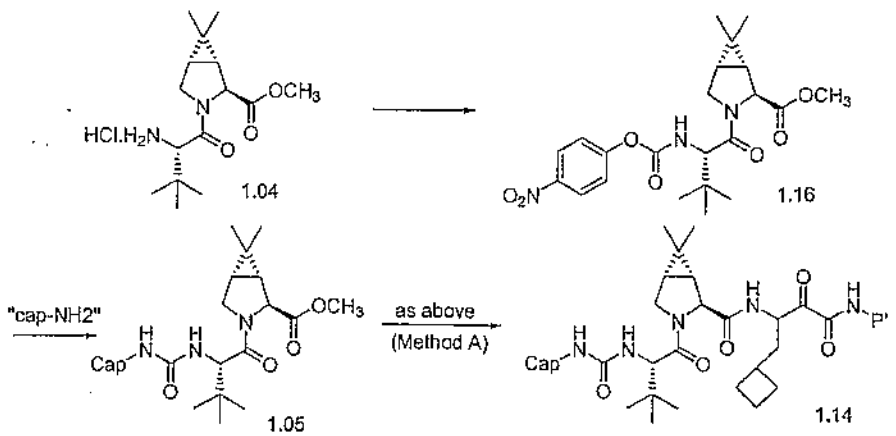
In yet another variation, the hydrochloride salt 1.13 was converted to the 4-nitrophenyl carbamate 1.15 by reaction with 4-nitrophenyl chloroformate.

Subsequent treatment with an amine (or amine hydrochloride salt) of choice provided the target compound 1.14.



Method E

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



The following experimental section applies for the preparation of the compounds of Formula XIII:

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

THF: Tetrahydrofuran

DMF: N,N-Dimethylformamide

EtOAc: Ethyl acetate

AcOH: Acetic acid

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

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

NMM: N-Methylmorpholine

ADDP: 1,1'-(Azodicarbobyl)dipiperidine

DEAD: Diethylazodicarboxylate

DIAD: Diisopropylazodicarboxylate

MeOH: Methanol

EtOH: Ethanol

Et_2O: Diethyl ether

DMSO: Dimethylsulfoxide

HOBt: N-Hydroxybenzotriazole

PyBrOP: Bromo-tris-pyrrolidinophosphonium hexafluorophosphate

DCM: Dichloromethane

DCC: 1,3-Dicyclohexylcarbodiimide

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

Phg: Phenylglycine

Chg: Cyclohexylglycine

Bn: Benzyl

Bz: Benzyl

Et: Ethyl

Ph: Phenyl

iBoc: isobutoxycarbonyl

iPr: isopropyl

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

Boc: tert-Butyloxycarbonyl

Cbz: Benzyloxycarbonyl

Cp: Cylcopentyldienyl

Ts: p-toluenesulfonyl

Me: Methyl

Ms or Mesyl: Methane sulfonyl

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

DMAP: 4-N,N-Dimethylaminopyridine

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

PCC: Pyridiniumchlorochromate

DIBAL-H: diisopropyl aluminum hydride

rt or RT: Room temperature

quant.: Quantitative yield

h or hr: hour

min: minute

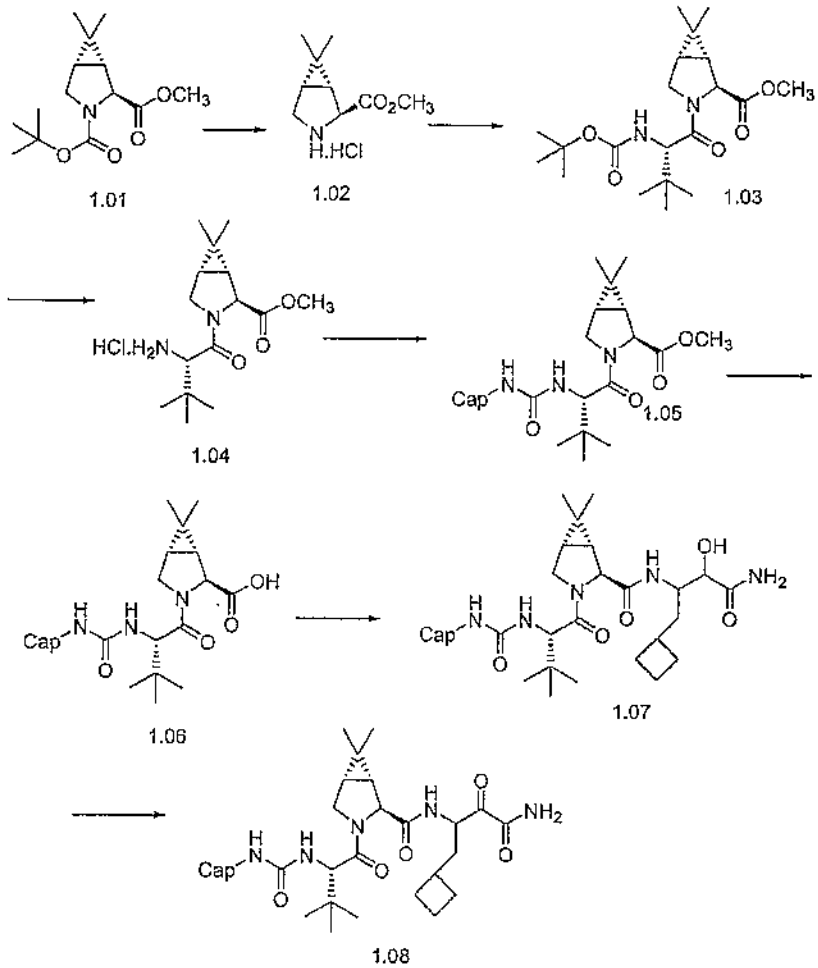
TFA: Trifluoroacetic acid

General Schemes for Preparation of Target Compounds

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

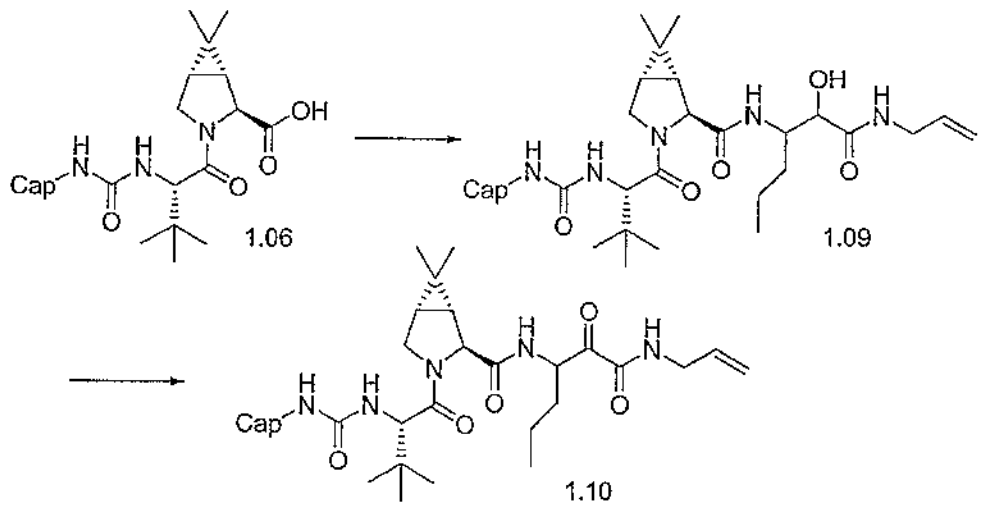
Method A

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



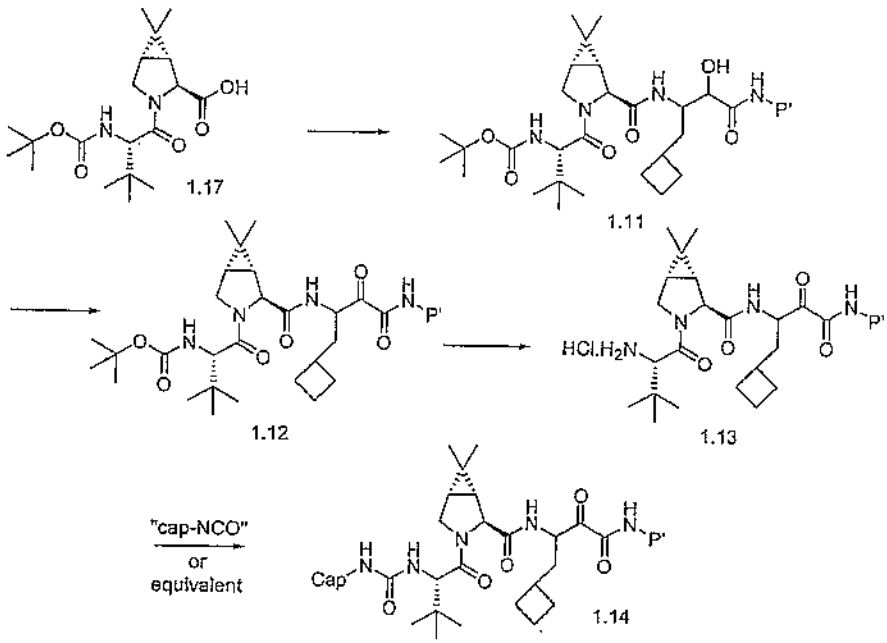
Method B

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



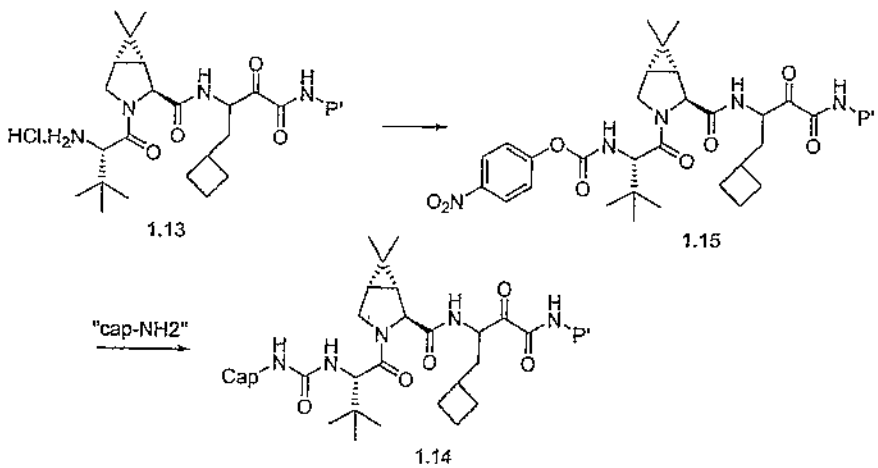
Method C

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



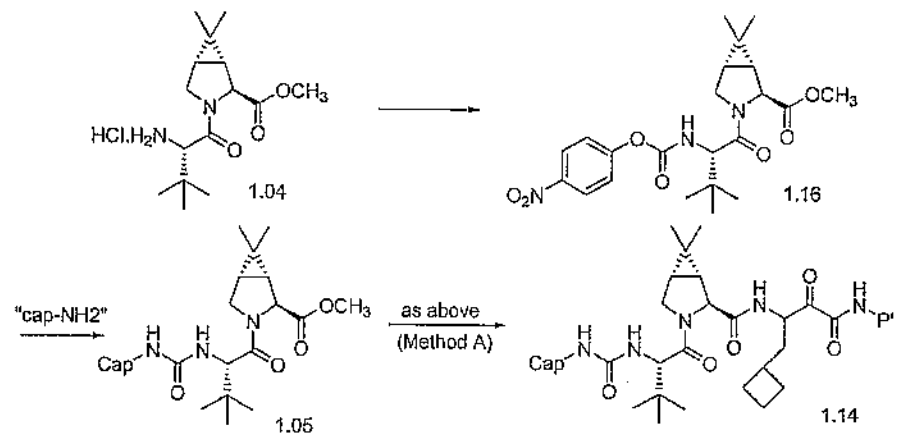
Method D

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



Method E

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



The following experimental section applies for the preparation of the compounds of Formula XIV:

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

THF: Tetrahydrofuran

DMF: N,N-Dimethylformamide

EtOAc: Ethyl acetate

AcOH: Acetic acid

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

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

NMM: N-Methylmorpholine

ADDP: 1,1'-(Azodicarbobyl)dipiperidine

DEAD: Diethylazodicarboxylate

MeOH: Methanol

EtOH: Ethanol

Et2O: Diethyl ether

DMSO: Dimethylsulfoxide

HOBt: N-Hydroxybenzotriazole

PyBrOP: Bromo-tris-pyrrolidinophosphonium hexafluorophosphate

DCM: Dichloromethane

DCC: 1,3-Dicyclohexylcarbodiimide

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

Phg: Phenylglycine

Chg: Cyclohexylglycine

Bn: Benzyl

Bzl: Benzyl

Et: Ethyl

Ph: Phenyl

DMF-DMA: N,N-Dimethylformamide-dimethylacetal

iBoc: isobutoxycarbonyl

iPr: isopropyl

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

Boc: tert-Butyloxycarbonyl

Cbz: Benzyloxycarbonyl

Cp: Cylcopentyldienyl

Ts: p-toluenesulfonyl

Me: Methyl

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

DMAP: 4-N,N-Dimethylaminopyridine

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

PCC: Pyridiniumchlorochromate

KHMDS: Potassium Hexamethyldisilazide or Potassium bis(trimethylsilylamide)

NaHMDS: Sodium Hexamethyldisilazide or Sodium bis(trimethylsilylamide)

LiHMDS: Lithium Hexamethyldisilazide or Lithium bis(trimethylsilylamide)

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

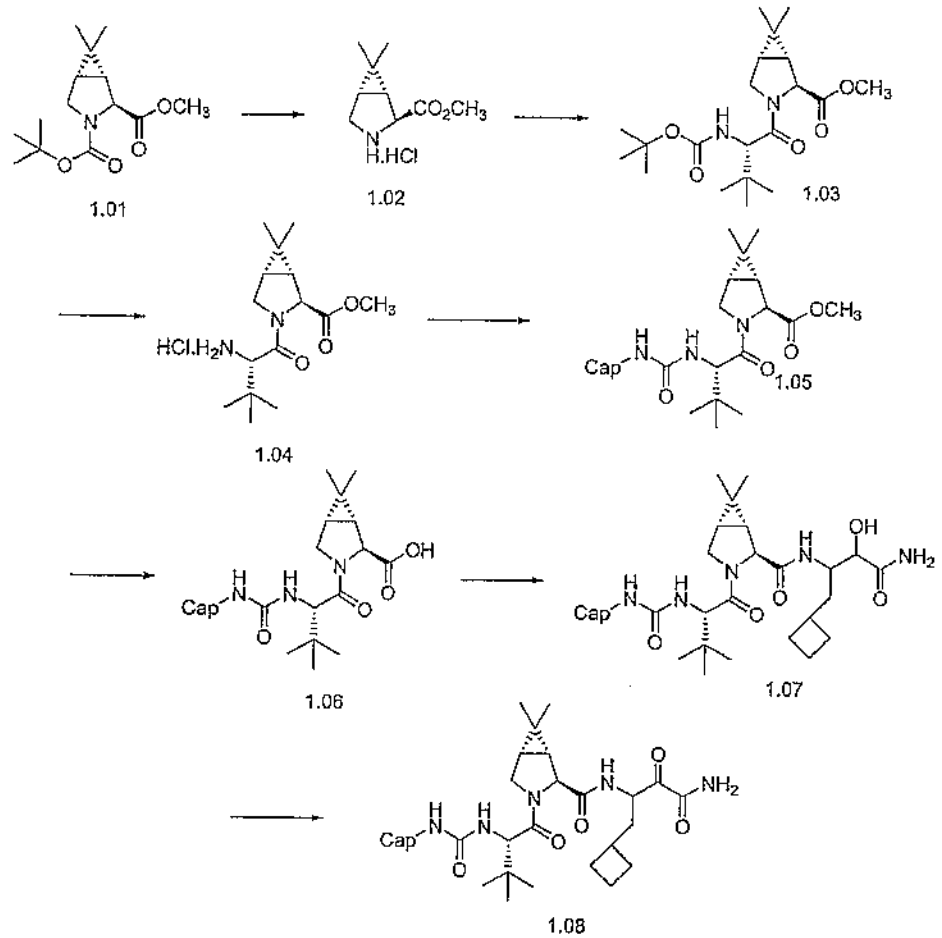
TG: Thioglycerol

General Schemes for Preparation of Target Compounds

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

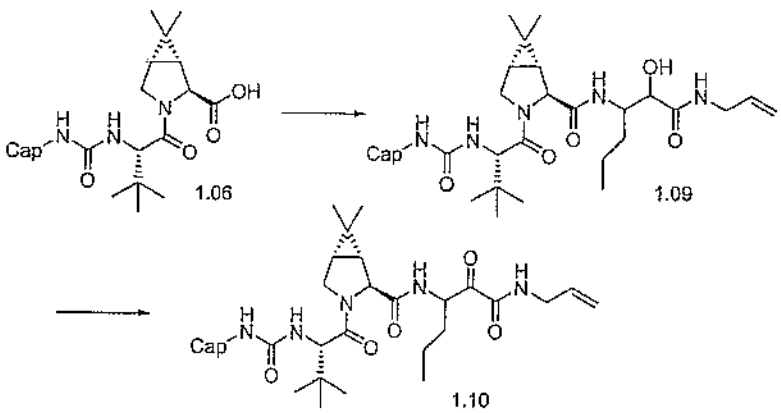
Method A

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



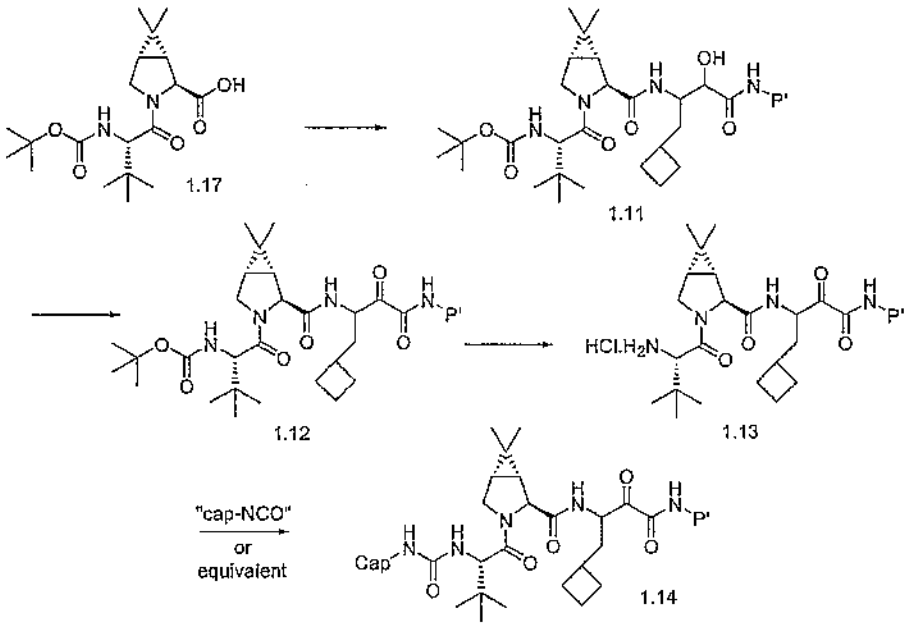
Method B

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


Cap
OH
1.06
1.09
1.10

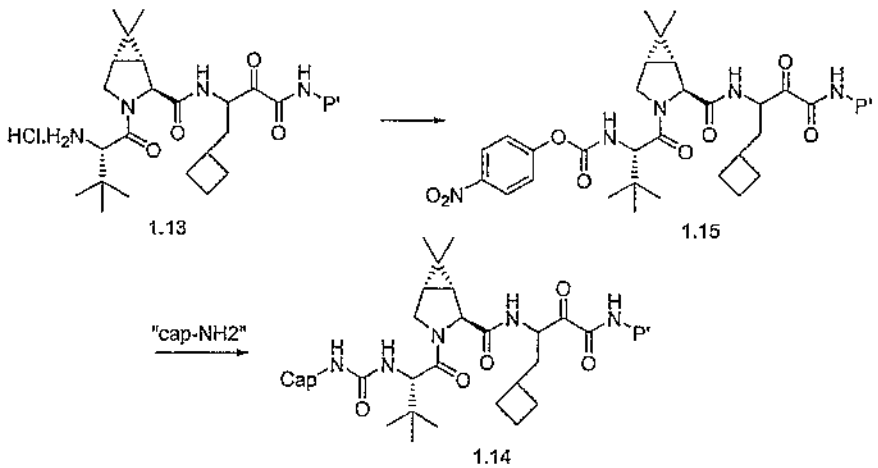
Method C

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



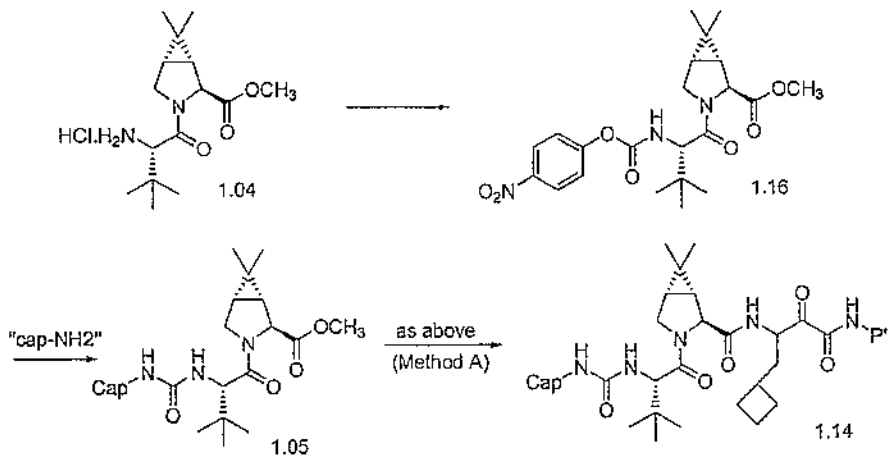
Method D

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



Method E

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



The following experimental section applies for the preparation of the compounds of Formula XV:

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

THF: Tetrahydrofuran

DMF: N,N-Dimethylformamide

EtOAc: Ethyl acetate

AcOH: Acetic acid

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

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

NMM: N-Methylmorpholine

ADDP: 1,1'-(Azodicarbobyl)dipiperidine

DEAD: Diethylazodicarboxylate

MeOH: Methanol

EtOH: Ethanol

Et2O: Diethyl ether

DMSO: Dimethylsulfoxide

HOBt: N-Hydroxybenzotriazole

PyBrOP: Bromo-tris-pyrrolidinophosphonium hexafluorophosphate

DCM: Dichloromethane

DCC: 1,3-Dicyclohexylcarbodiimide

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

Phg: Phenylglycine

Chg: Cyclohexylglycine

Bn: Benzyl

Bzl: Benzyl

Et: Ethyl

Ph: Phenyl

iBoc: isobutoxycarbonyl

iPr: isopropyl

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

Boc: tert-Butyloxycarbonyl

Cbz: Benzyloxycarbonyl

Cp: Cylcopentyldienyl

Ts: p-toluenesulfonyl

Me: Methyl

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

DMAP: 4-N,N-Dimethylaminopyridine

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

PCC: Pyridiniumchlorochromate

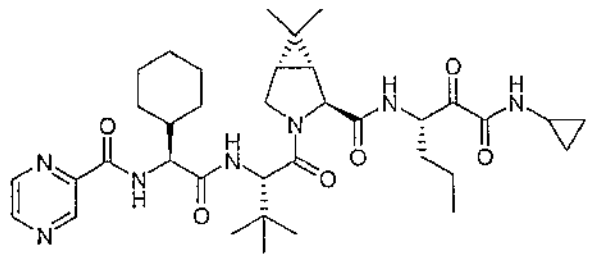
KHMDS: Potassium Hexamethyldisilazide or Potassium bis(trimethylsilylamide)

NaHMDS: Sodium Hexamethyldisilazide or Sodium bis(trimethylsilylamide)

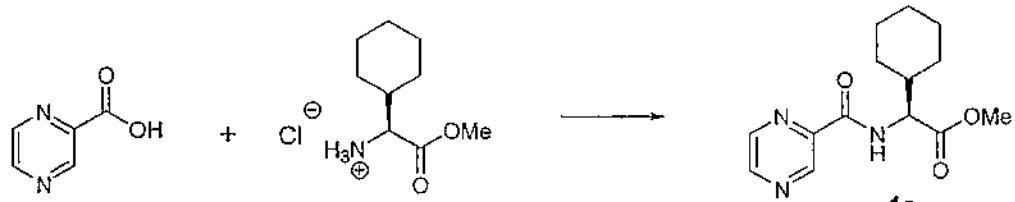
LiHMDS: Lithium Hexamethyldisilazide or Lithium bis(trimethylsilylamide)

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

Preparative Example 1:



Step A



1a 1b 1c

A solution of pyrazinecarboxylic acid **1a** (3 g) in 150 mL of dry dichloromethane and 150 mL of dry DMF was stirred at 0 °C and treated with HATU (1.4 eq, 6.03 g). L-cyclohexylglycine hydrochloride **1b** (1.2 eq, 6.03 g) was added in small portions. Then, N-methylmorpholine (4 eq, 10 mL, d 0.920) was added dropwise. The reaction mixture was gradually warmed to room temperature and stirred for 20 h. All the volatiles were removed under vacuum and the residue was dissolved in 500 mL of ethyl acetate. The organic layer was washed with water (100 mL), aqueous 1N HCl (100 mL), aqueous saturated sodium bicarbonate solution (100 mL), and brine (100 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 5:95 to 3:7) to afford the product **1c** as a white solid.

Step B

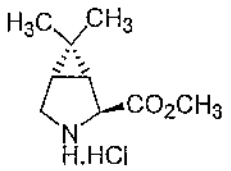


1c 1d

A solution of methyl ester **1c** (6.5 g) in 270 mL of a 1:1:1 mixture of THF/MeOH/water was cooled to 0 °C and treated with lithium hydroxide monohydrate (2.5 eq, 2.45 g). The mixture was stirred and monitored by TLC (acetone/hexanes; 2:8). When all the starting material had been consumed, the

reaction mixture was treated with 100 mL of aqueous 1N HCl and the mixture was concentrated on the rotavap. Dichloromethane (250 mL) was added and layers separated. The aqueous layer was extracted with dichloromethane (3 x 80 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated to afford the product **1d** as a white solid.

Step C

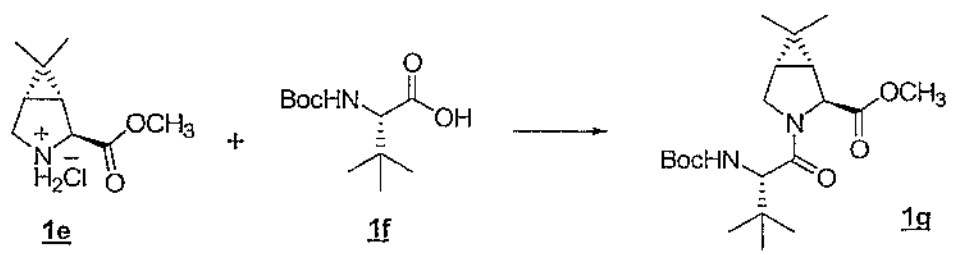


1e

The amino ester **1e** was prepared following the method of R. Zhang and J. S. Madalengoitia (*J. Org. Chem.* **1999**, *64*, 330), with the exception that the Boc group was cleaved by the reaction of the Boc-protected amino acid with methanolic HCl (4M HCl in dioxane was also employed for the deprotection).

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

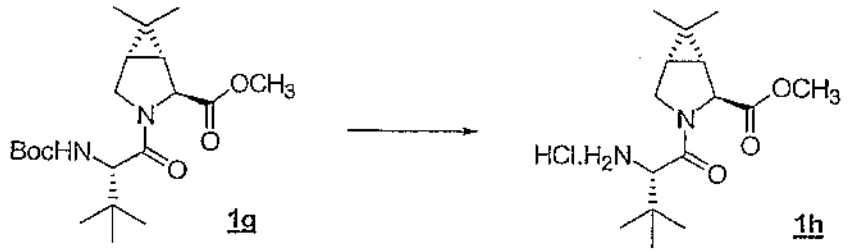
Step D



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

A solution of Boc-tert-Leu **1f** (Fluka, 5.0 g, 21.6 mmol) in dry CH_2Cl_2/DMF (50 mL, 1:1) was cooled to 0°C and treated with the amine hydrochloride **1e** (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 aqueous HCl (1 M) and extracted with CH_2Cl_2. The combined organic layers were washed with aqueous 1M HCl, saturated $NaHCO_3$, brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* and purified by chromatography (SiO_2, Acetone/Hexane 1:5) to yield **1g** as a colorless solid.

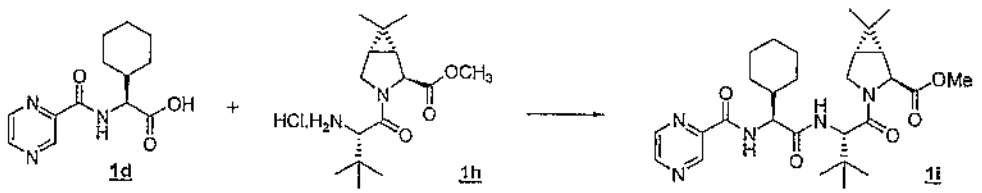
Step E



1g 1h

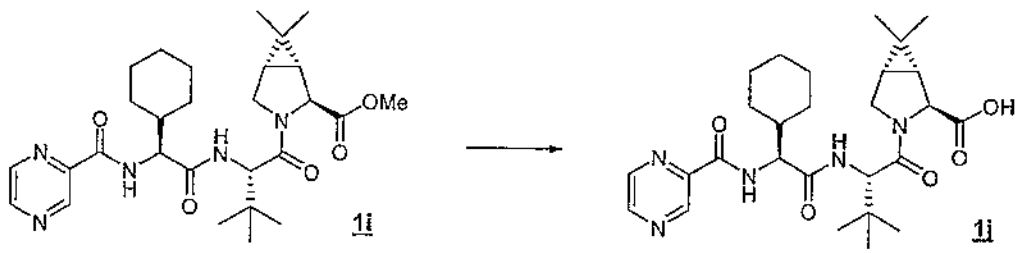
A solution of methyl ester **1g** (4.0 g, 10.46 mmol) was dissolved in 4M HCl in dioxane and stirred at rt. for 3 h. The reaction mixture was concentrated in *vacuo* to obtain the amine hydrochloride salt, **1h** which was used without purification.

Step F



1d 1h 1i

A solution of acid **1d** (100 mg) in 5 mL of dry dichloromethane and 5 mL of dry DMF was stirred at 0°C and treated with HATU (1.4 eq, 202 mg). The amine hydrochloride **1h** (1.2 eq, 146 mg) was added. Then, N-methylmorpholine (4 eq, 0.17 mL, d 0.920) was also added. The reaction mixture was stirred at 0 °C overnight. All the volatiles were removed under vacuum and the residue was dissolved in 80 mL of ethyl acetate. The organic layer was washed with water (10 mL), aqueous 1N HCl (10 mL), aqueous saturated sodium bicarbonate solution (10 mL), and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 1:9 to 4:6) to afford the product **1i** as a white solid.



1i 1j

A solution of methyl ester **1i** (180 mg) in 9 mL of a 1:1:1 mixture of THF/MeOH/water was cooled to 0°C and treated with lithium hydroxide monohydrate

(2.5 eq, 35 mg). The mixture was stirred and monitored by TLC (acetone/hexanes; 3:7). When all the starting material had been consumed, the reaction mixture was treated with 50 mL of aqueous 1N HCl and the mixture was concentrated on the rotavap. Dichloromethane (80 mL) was added and layers separated. The aqueous layer was extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated to afford the product **1j** as a white solid.

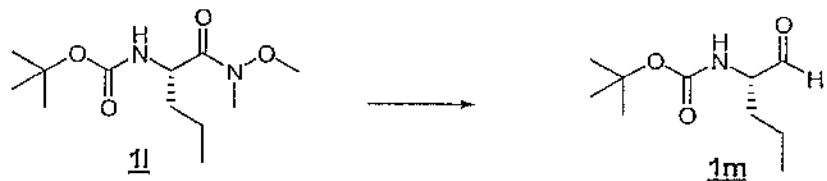
Step H



1k **1l**

A solution of acid **1k** (2 g) in 100 mL of dry dichloromethane and 5 mL of DMF was treated with N,O-dimethylhydroxylamine hydrochloride (1.1 eq, 986 mg), BOP reagent (1.1 eq, 4.47 g), and N-methylmorpholine (3.3 eq, 3.3 mL, d 0.920) in that order. The mixture was heated to 50 °C overnight. The reaction mixture was concentrated to half its volume and diluted with 400 mL of ethyl acetate. The organic layer was washed with water (80 mL), aqueous 1M HCl (80 mL), aqueous saturated sodium bicarbonate solution (80 mL), and brine (80 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 5:95 to 3:7) to afford the product **1l** as a clear oil.

Step I

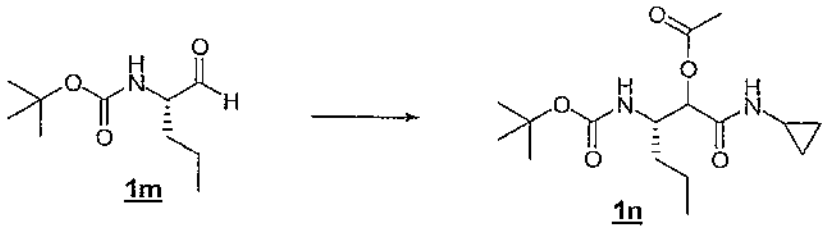


1l **1m**

A solution of amide **1l** (2.2 g) in 100 mL of dry THF was cooled to °C. Lithium aluminum hydride solution (1.3 eq) was added dropwise. The cooling bath was removed after 5 min and the mixture was allowed to reach room temperature. TLC analysis (ethyl acetate/hexanes; 2:8) showed that all the starting material had been consumed. The excess LAH was carefully quenched by addition of drops of aqueous saturated sodium hydrogen sulfate. The mixture was diluted with 200 mL of ether

and aqueous saturated sodium hydrogen sulfate was added in small portions until a white solid precipitated. The mixture was filtered thru celite and the filtrate was washed with 50 mL of brine. The organic layer was dried over magnesium sulfate, filtered and concentrated. The residue was chromatographed on silica gel (gradient: ethyl acetate/hexanes; 5:95 to 4:6) to afford the aldehyde product **1m** as a colorless oil.

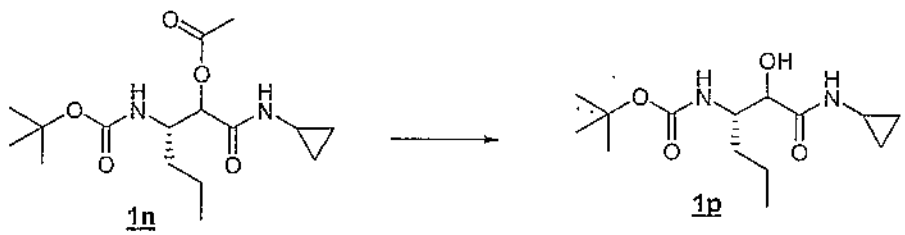
Step J



1m **1n**

A solution of aldehyde **1m** (1.8 g) in 100 mL of dry dichloromethane was treated with isonitrile (1.1 eq, 680 mg) and acetic acid (2 eq, 1.02 mL, d 1.0149). The mixture was stirred overnight. All the volatiles were removed under vacuum and the residue was chromatographed on silica gel (gradient: ethyl acetate/hexanes; 2:8 to 6:4) to afford the product **1n** as a white solid.

Step K



1n **1p**

A solution of acetate **1n** (1.6 g) in 60 mL of a 1:1:1 mixture of THF/MeOH/water was treated with lithium hydroxide monohydrate and stirred for approximately 1 h until all the starting material had been consumed as determined by TLC analysis (ethyl acetate/hexanes; 1:1). The volatiles were removed in rotavap and the residue was diluted with dichloromethane (150 mL). The layers were separated and the aqueous layer was diluted with 30 mL of aqueous saturated sodium bicarbonate solution and extracted with dichloromethane (3 x 80 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated to afford the product **1p** as a white solid.

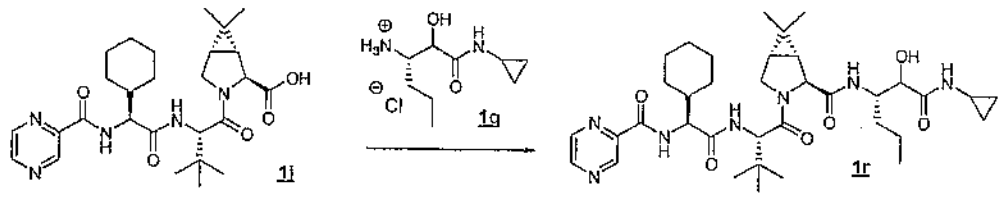
Step L



1p 1q

The N-Boc protected amine **1p** (1.5 g) was dissolved in 20 mL of 4M HCl in dioxane. The reaction mixture was stirred for about 1 h until all the starting material had been consumed. All the volatiles were removed under vacuum to afford the product **1q** as a white solid.

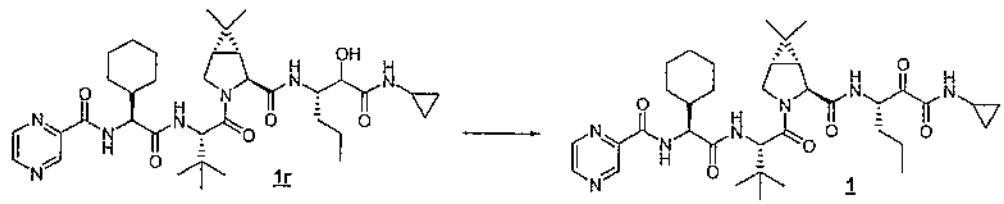
Step M



1j 1q 1r

A solution of acid **1j** (50 mg) in 2 mL of dry dichloromethane and 2 mL of dry DMF was stirred at 0°C and treated with HATU (1.4 eq, 52 mg). The amine hydrochloride **1q** (1.2 eq, 26 mg) was added. Then, N-methylmorpholine (4 eq, 0.042 mL, d 0.920) was also added. The reaction mixture was stirred at 0 °C overnight. All the volatiles were removed under vacuum and the residue was dissolved in 80 mL of ethyl acetate. The organic layer was washed with water (10 mL), aqueous 1N HCl (10 mL), aqueous saturated sodium bicarbonate solution (10 mL), and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The product **1r** was used without further purification.

Step N



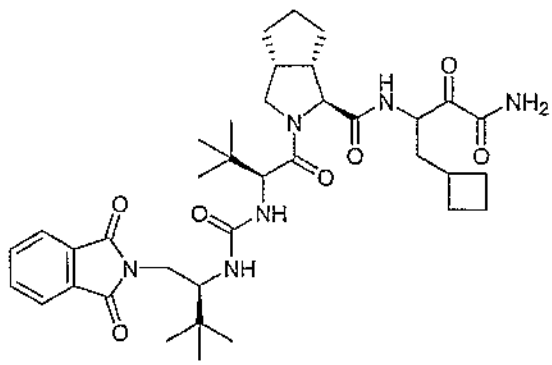
1r 1

A solution of alcohol **1r** (65 mg) in 5 mL of dry dichloromethane was treated with Dess-Martin periodinane (3 eq, 121 mg). Reaction mixture was stirred at room temperature for 45 min. The mixture was treated with aqueous 1M sodium thiosulfate solution (10 mL) and aqueous saturated sodium bicarbonate solution (10 mL) and stirred for 15 min. The mixture was extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 2:8 to 5:5) to afford the product **1** as a white solid.

One skilled in the art would understand that other suitable compounds of Formula XV can be prepared in a similar manner to that disclosed above.

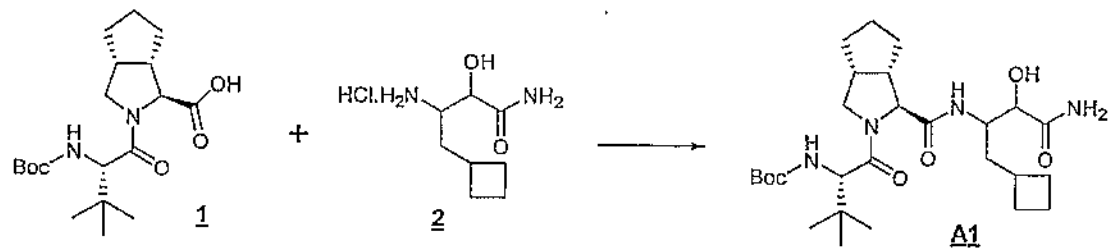
The following experimental section applies for the preparation of the compounds of Formula XVI:

Preparative Example A



A

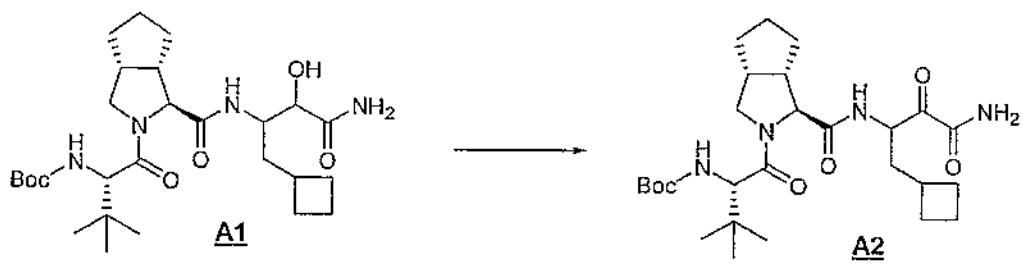
Step 1



1 2 A1

A solution of acid **1** (255 mg) in 5 mL of dry dichloromethane and 5 mL of dry DMF was stirred at 0°C and treated with HATU (368 mg). The amine hydrochloride **2** (201 mg) was added followed by addition of N-methylmorpholine (0.42 mL). The reaction mixture was gradually warmed to room temperature and stirred overnight. All the volatiles were removed under vacuum and the residue was taken into 100 mL of ethyl acetate. The organic layer was washed with aqueous 1N HCl (15 mL), aqueous saturated NaHCO3 (15 mL), water (15 mL), brine (15 mL), dried over MgSO4, filtered, and concentrated under reduced pressure to afford the desired product **A1**. No further purification was carried out for the product.

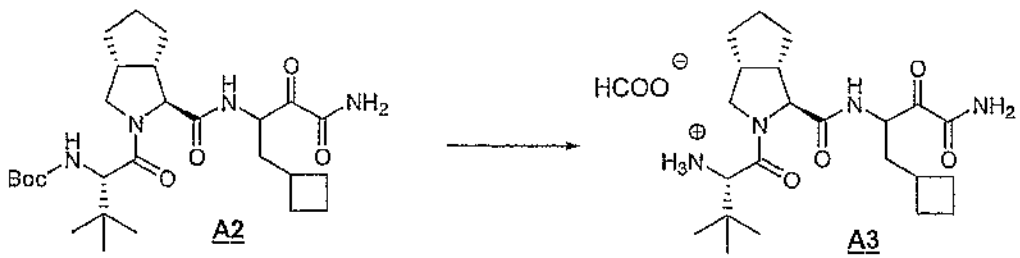
Step 2



A1 A2

A solution of **A1** (360 mg) in 20 mL of a 1:1 mixture of toluene/DMSO was treated with EDCI (1.3 g) and dichloroacetic acid (0.42 mL, d 1.563). Reaction mixture was stirred at room temperature for about 3 h. The reaction mixture was diluted with dichloromethane (100 mL) and washed with aqueous saturated $NaHCO_3$ (15 mL), aqueous 1N HCl (15 mL), and brine (15 mL). The organic layer was dried over magnesium sulfate, filtrated, and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient: acetone/hexanes; 2:8 to 5:5) to afford the product **A2** in 84% yield.

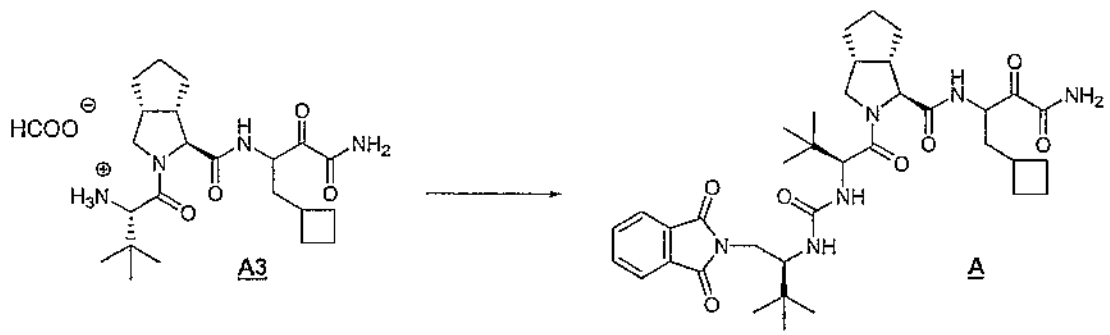
Step 3



A2 A3

The N-Boc protected amine **A2** was treated with 10 mL of formic acid. The resulting solution was stirred for 2 h. All the volatiles were removed under reduced pressure. No further purification was done for the product **A3**.

Step 4



A3 A

To a solution of the amine salt **A3** in 1 mL of dry methylene chloride was added N-methylmorpholine (0.037 mL, d 0.920). The resulting solution was cooled in an ice-water bath and a solution of isocyanate in toluene (2.5 mL of a 0.135M soln) was slowly added. The mixture was stirred for 2 h (temp 0 to 25°C). The reaction mixture was diluted with 60 mL of dichloromethane and washed with 15 mL of aqueous 1N HCl. Aqueous layer was back extracted with dichloromethane (2 x 20 mL). Combined organic layers were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on Silica gel (gradient: acetone/hexanes; 1:9 to 6:4) to give the product **A** (15 mg) as a white solid in 20% yield. HRMS (FAB) calcd for $C_{37}H_{53}N_6O_7$ [M+H] 693.3976; found 693.3987.

One skilled in the art would understand that other suitable compounds of Formula XVI can be prepared in a similar manner to that disclosed above.

The following experimental section applies for the preparation of the compounds of Formula XVII:

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

THF: Tetrahydrofuran

DMF: N,N-Dimethylformamide

EtOAc: Ethyl acetate

AcOH: Acetic acid

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

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

NMM: N-Methylmorpholine

ADDP: 1,1'-(Azodicarbobyl)dipiperidine

DEAD: Diethylazodicarboxylate

MeOH: Methanol

EtOH: Ethanol

Et2O: Diethyl ether

DMSO: Dimethylsulfoxide

HOBt: N-Hydroxybenzotriazole

PyBrOP: Bromo-tris-pyrrolidinophosphonium hexafluorophosphate

DCM: Dichloromethane

DCC: 1,3-Dicyclohexylcarbodiimide

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

Phg: Phenylglycine

Chg: Cyclohexylglycine

Bn: Benzyl

Bzl: Benzyl

Et: Ethyl

Ph: Phenyl

iBoc: isobutoxycarbonyl

iPr: isopropyl

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

Boc: tert-Butyloxycarbonyl

Cbz: Benzyloxycarbonyl

Cp: Cylcopentyldienyl

Ts: p-toluenesulfonyl

Me: Methyl

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

DMAP: 4-N,N-Dimethylaminopyridine

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

PCC: Pyridiniumchlorochromate

KHMDS: Potassium Hexamethyldisilazide or Potassium bis(trimethylsilylamide)

NaHMDS: Sodium Hexamethyldisilazide or Sodium bis(trimethylsilylamide)

LiHMDS: Lithium Hexamethyldisilazide or Lithium bis(trimethylsilylamide)

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

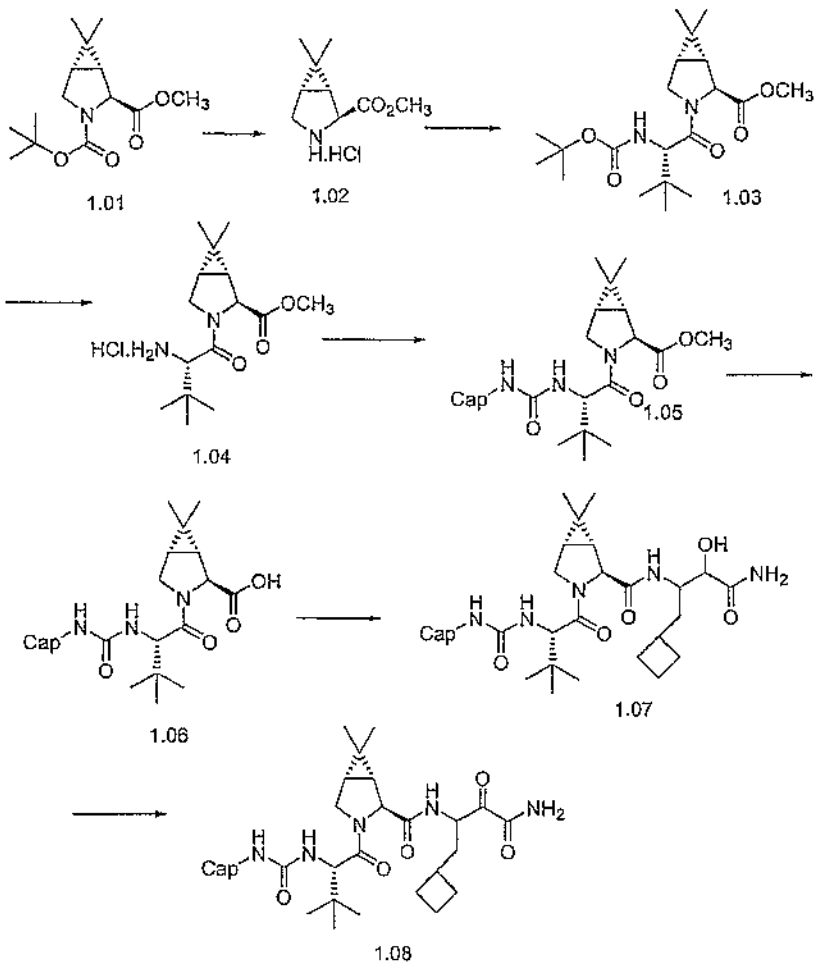
TG: Thioglycerol

General Schemes for Preparation of Target Compounds

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

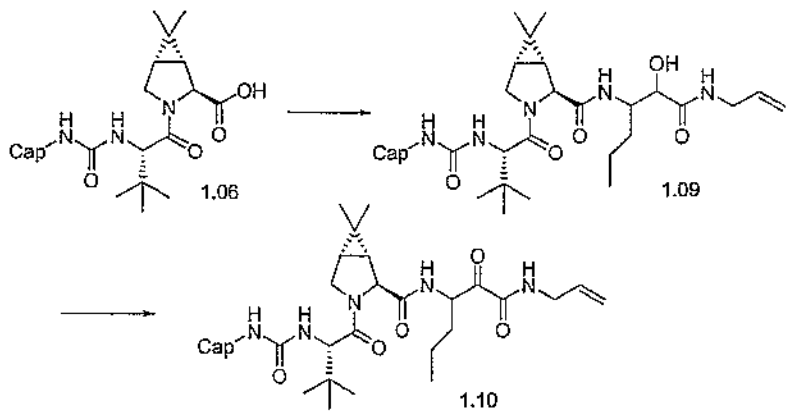
Method A

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



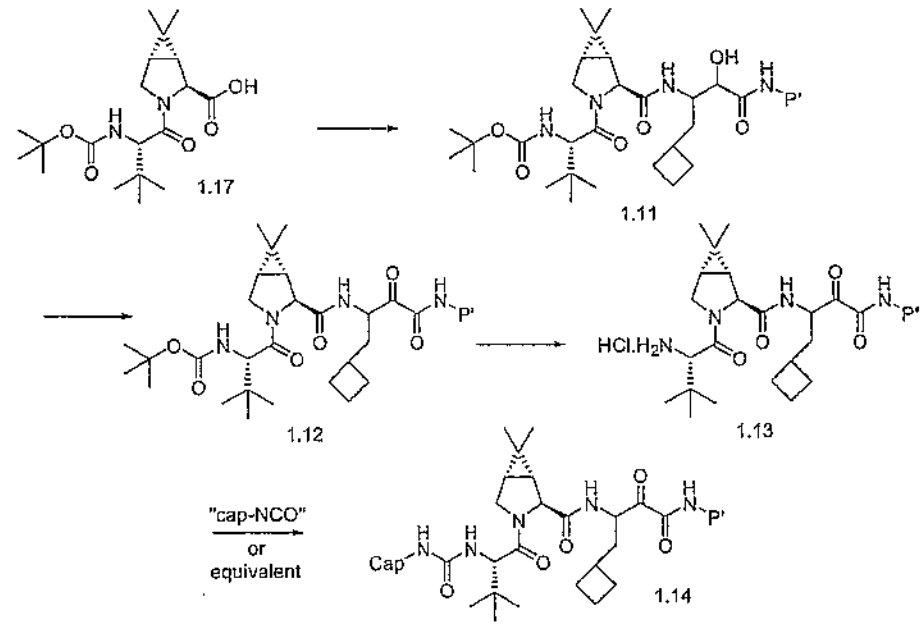
Method B

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



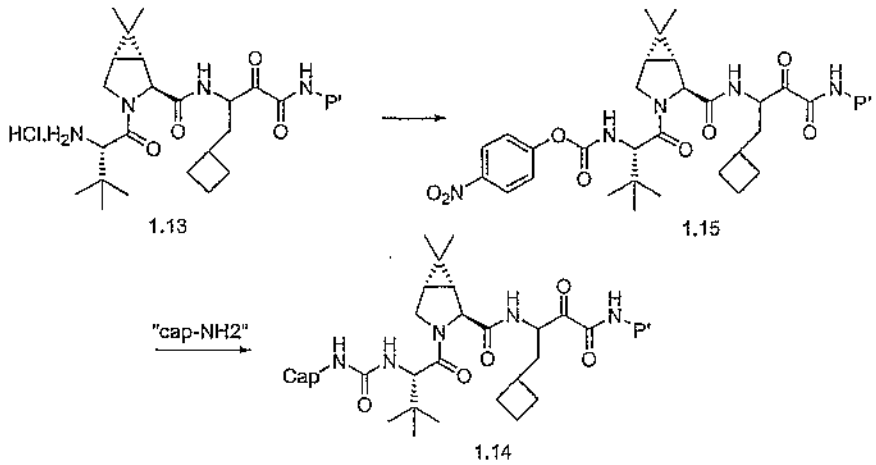
Method C

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



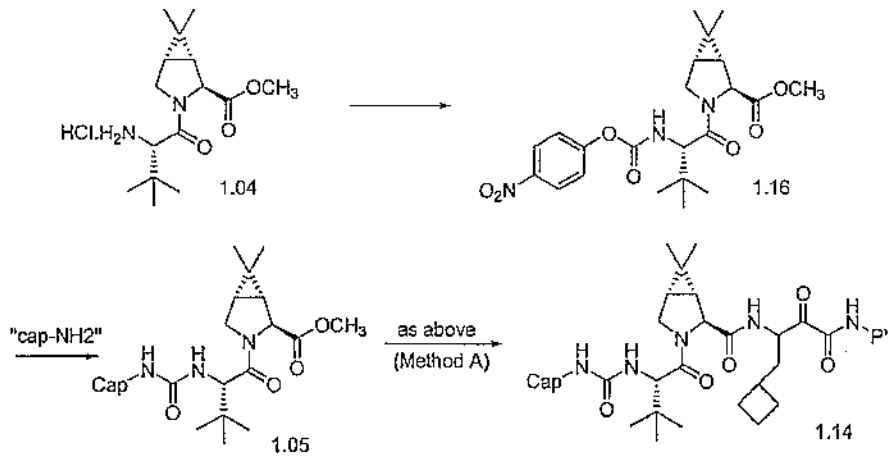
Method D

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



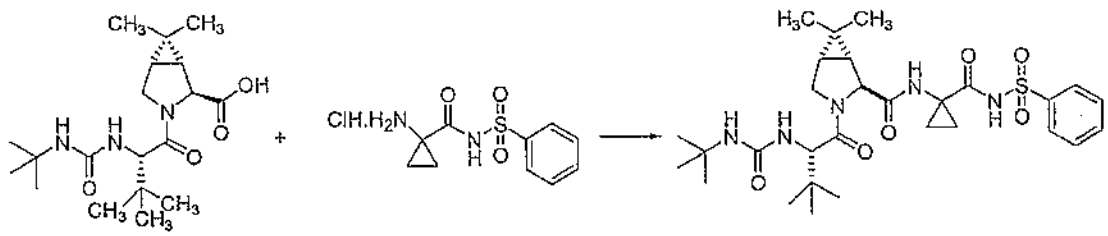
Method E

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



The following experimental section applies for the preparation of the compounds of Formula XVIII:

Example 3 Preparation of Compound of Formula 3



1.06 1.09 3

To a cooled solution (0 °C) of the intermediates **1.06** (75.0 mg, 0.2 mmol) and **1.09** (100.0 mg, 0.36 mmol) in DMF (5.0 mL) was added HATU (Aldrich, 76.05 mg, 0.20 mmol), followed by DIPEA (0.102 mL, 6 mmol). The reaction mixture was stirred for two days then warmed up to room temperature, diluted with ethyl acetate (40.0 mL), washed with 5% KH_2PO_4 containing 0.05 vol. of 1M H_3PO_4 and brine. Organic layer was dried over $MgSO_4$, filtered and concentrated to dryness. Residue was purified over silica gel using acetone–CH_2Cl_2 (1:9 to 1:1) to get 8.0 mg of product of formula **3** (6.5% yield) ; LCMS : (590.1).

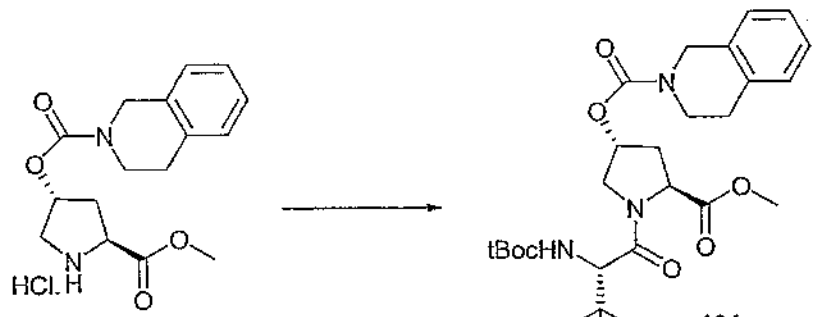
One skilled in the art would understand that other suitable compounds of Formula XVIII can be prepared in a similar manner to that disclosed above.

The following experimental section applies for the preparation of the compounds of Formula XIX:

Synthesis of Preparative Examples

Synthesis of Example **101**

Step1

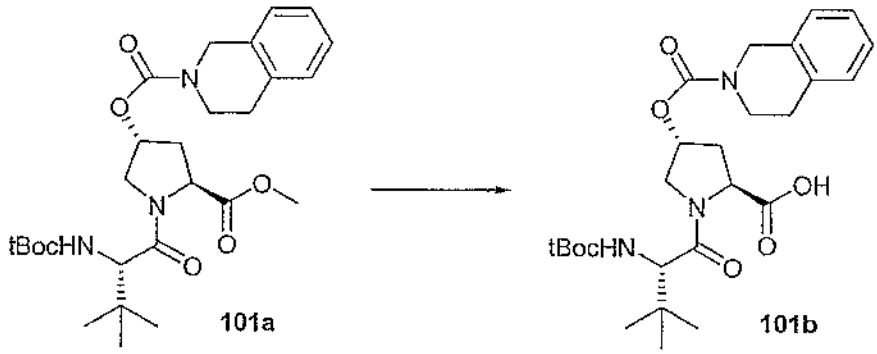


1.01 101a

To a stirred solution of the proline derivative **1.01** (3.66 mmol, prepared as described above) in dichloromethane (20 mL) and DMF (15 mL) at 0°C was added L-boc-tert-leucine (930 mg, 4.03 mmol), DIPEA (2.02 mL, 10.98 mmol) and HATU (1.8 g, 4.76 mmol). After 15 minutes at that temperature, the reaction flask was stored in the

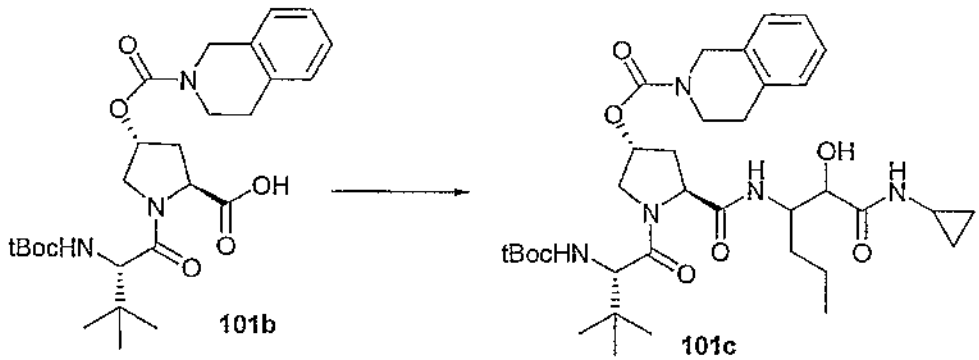
freezer (-20°C), overnight (16 hr). The reaction mixture was diluted with dichloromethane (80 mL) and washed with saturated sodium bicarbonate solution (80 mL), 10% aq. citric acid solution (80 mL), brine (80 mL), dried (Na_2SO_4), filtered and concentrated. The crude material was purified by silica chromatography using 25/75 to 50/50 EtOAc/hexanes to provide 1.77 g of the required material, **101a**. LC-MS: 518.1 $(M+H)^+$.

Step 2



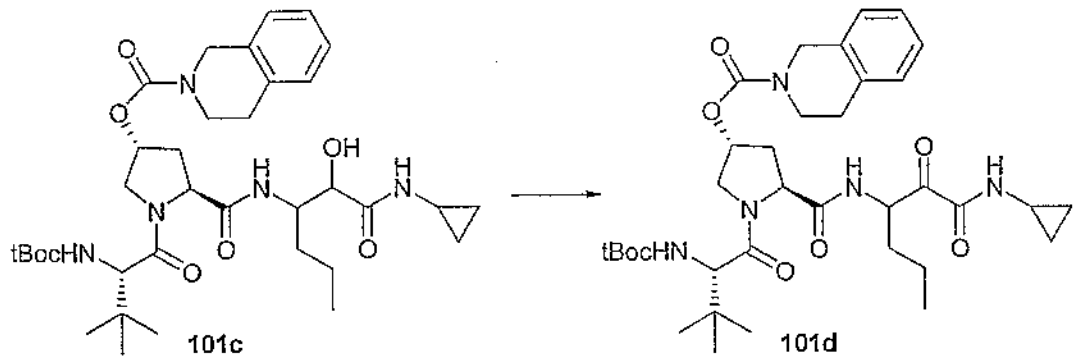
To a solution of the methyl ester **101a** (1.21 g, 2.34 mmol) in THF (10 mL) and MeOH (5 mL) was added aq. 1M LiOH solution (5 mL). The reaction mixture was stirred at RT for 4 h. It was then concentrated, diluted with water (50 mL) and acidified with solid citric acid (pH approximately 3) when white solid material crashed out. This solid was filtered off, washed with water and dried *in vacuo* to afford 970 mg of **101b**. LC-MS: 504.1 $(M+H)^+$.

Step 3



The acid **101b** (503 mg, 1 mmol) was coupled with intermediate **13.06** (334 mg, 1.5 mmol) using essentially procedure described above (Step 1, preparation of **101a**) to provide **101c** which was used without purification. MS: 672.37 $(M+H)^+$.

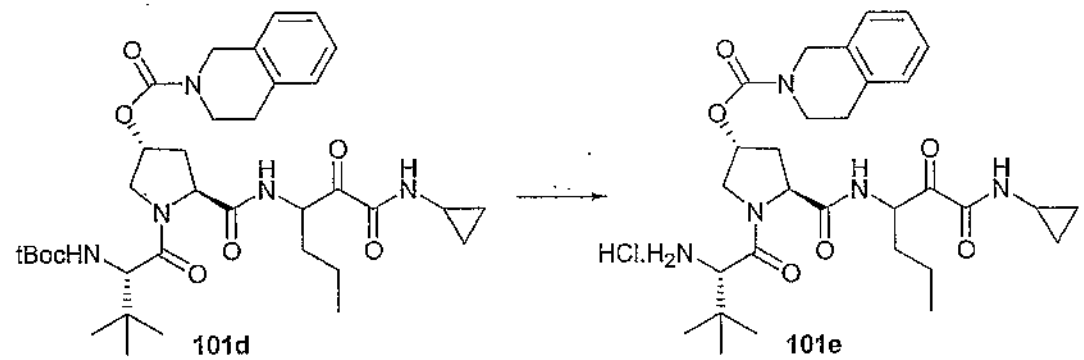
Step 4



101c **101d**

To a solution of the hydroxyl compound **101c** from above in dichloromethane (15 mL) was added Dess-Martin's periodinane (848 mg, 2 mmol) and the reaction mixture was stirred at RT for 5 h. At this time, the reaction mixture was diluted with dichloromethane (30 mL) and washed with 1:1 mixture of aq. 10% sodium thiosulfate solution and saturated sodium bicarbonate solution (2 x 25 mL each), brine (50 mL), dried (Na_2SO_4), filtered and concentrated. The crude material was purified by silica chromatography using 15/85 to 50/50 acetone/hexanes to provide 410 mg of the required material, **101d**. LC-MS: 670.2 $(M+H)^+$.

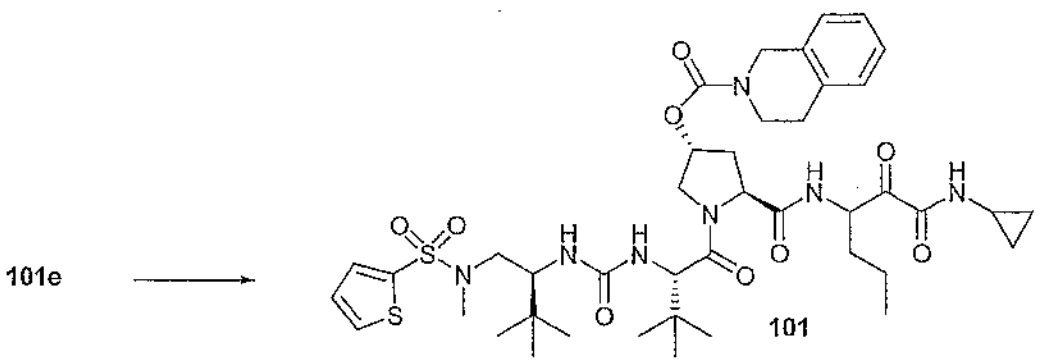
Step 5



101d **101e**

Deprotection of the N-boc functionality of **101d** to provide the required material **101e** was carried out as described for intermediate **1.01**, Step 3 (reaction time = 2 h). LC-MS: 570.1 $(M+H)^+$.

Step 6



To a solution of the amine salt **101e** (60 mg, 0.1 mmol) in dichloromethane (2 mL) at 0°C was added DIPEA (0.06 mL, 0.3 mmol) followed by the isocyanate intermediate **65.01** (0.25 M solution in toluene, 0.8 mL, 0.2 mmol). After 15 minutes at that temperature, the reaction flask was stored in the freezer (-20°C), overnight (16 hr). The reaction mixture was diluted with dichloromethane (20 mL) and washed with saturated ammonium chloride solution (20 mL), brine (20 mL), dried (Na_2SO_4), filtered and concentrated. The crude material was purified by silica chromatography using 15/85 to 50/50 acetone/hexanes to provide the required compound **101** (53 mg); LC-MS: 872.2 $(M+H)^+$.

One skilled in the art would understand that other suitable compounds of Formula XIX can be prepared in a similar manner to that disclosed above.

The following experimental section applies for the preparation of the compounds of Formulae Ia, Ib and Ic:

Abbreviations:

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

THF: Tetrahydrofuran

DMF: N,N-Dimethylformamide

EtOAc: Ethyl acetate

AcOH: Acetic acid

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

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

NMM: N-Methylmorpholine

MeOH: Methanol

EtOH: Ethanol

Et2O: Diethyl ether

DMSO: Dimethylsulfoxide

K^{t}BuO: Potassium tert-butoxide

DCM: Dichloromethane

Chg: Cyclohexylglycine

Bn: Benzyl

Et: Ethyl

Ph: Phenyl

iPr: isopropyl

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

Boc: tert-Butyloxycarbonyl

Cbz: Benzyloxycarbonyl

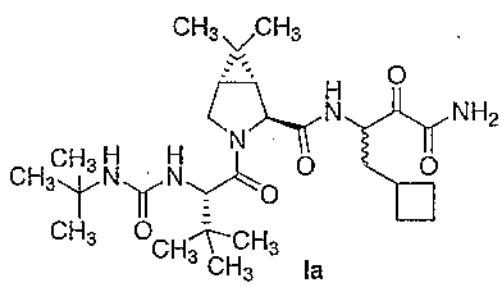
HATU: O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate

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

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

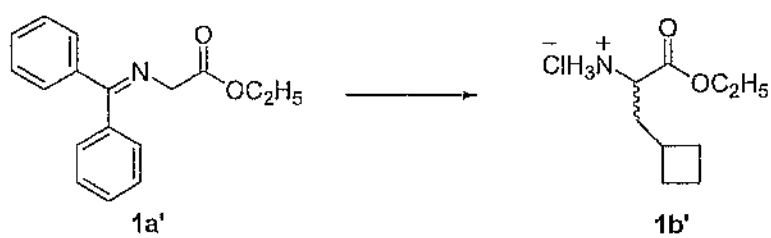
Example:

Synthesis of (1R,5S)-N-[3-Amino-1-(Cyclobutylmethyl)-2,3-Dioxopropyl]-3-[2(S)-[[[(1,1-Dimethylethyl)Amino]Carbonyl]Amino]-3,3-Dimethyl-1-Oxobutyl]-6,6-Dimethyl-3-Azabicyclo[3.1.0]Hexan-2(S)-Carboxamide (Structure Ia):



Ia

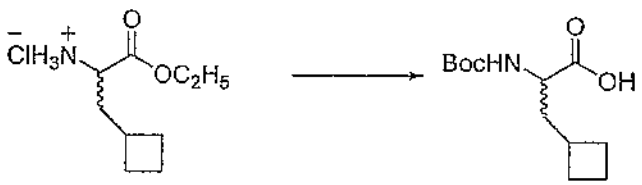
Step 1.



1a' 1b'

A stirred solution of the ketimime **1a'** (50 g, 187.1 mmol, available from Aldrich Chemical Company, Milwaukee, Wisconsin) under N_2 in dry THF (400 mL) was cooled to –78^0 C and treated with 1 M solution of K-^{t}BuO (220 mL, 1.15 equiv.) in THF. The reaction mixture was warmed to 0^0 C and stirred for 1 h and treated with bromomethylcyclobutane (28 mL, 249 mmol). The reaction mixture was stirred at room temperature for 48 h and concentrated *in vacuo*. The residue was dissolved in Et_2O (300 mL) and treated with aq. HCl (2 M, 300 mL) The resulting solution was stirred at room temperature for 5 h and extracted with Et_2O (1 L). The aqueous layer was made basic to pH ~12-14 with aq. NaOH (50 %) and extracted with CH_2Cl_2 (3x300 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give pure amine (**1b'**, 18 g) as a colorless oil.

Step 2.



1b' **1c'**

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

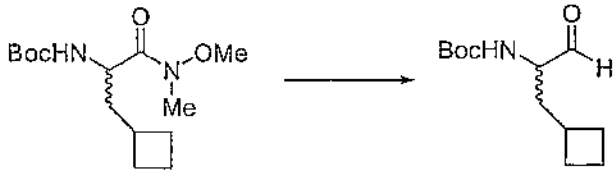
Step 3.



1c' **1d**

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

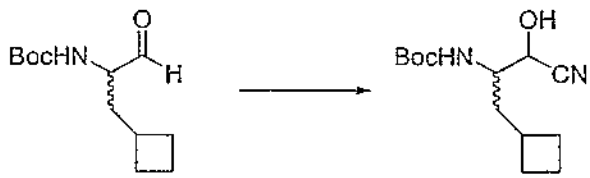
Step 4.



1d **1e**

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

Step 5.

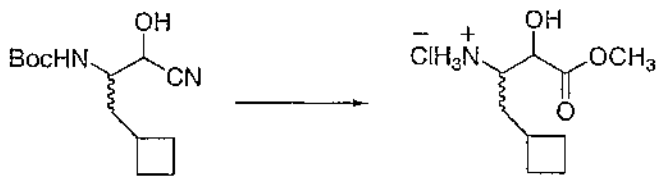


1e **1f**

A solution of the aldehyde **1e** (14 g, 61.6 mmol) in CH_2Cl_2 (50 mL), was treated with Et_3N (10.73 mL, 74.4 mmol), and acetone cyanohydrin (10.86 g, 127.57 mmol) and stirred at room temperature for 24 hrs. The reaction mixture was concentrated *in vacuo* and diluted with aq. HCl (1 M, 200 mL) and extracted into CH_2Cl_2 (3x200 mL). The combined organic layer were washed with H_2O, brine, dried

($MgSO_4$), filtered, concentrated *in vacuo* and purified by chromatography (SiO_2, EtOAc/Hex 1:4) to yield **1f** (10.3 g) as a colorless liquid as a mixture of diastereomers.

Step 6.

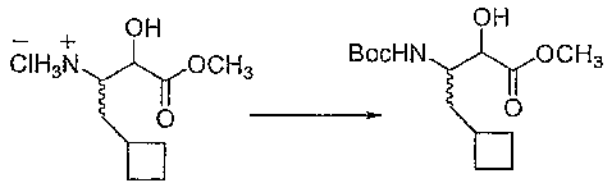


1f **1g**

Methanol saturated with HCl*, prepared by bubbling HCl gas to CH_3OH (700 ml) at 0 °C, was treated with cyanohydrin **1f** and heated to reflux for 24 h. The reaction was concentrated *in vacuo* to yield **1g**, which was used in the next step without purification.

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

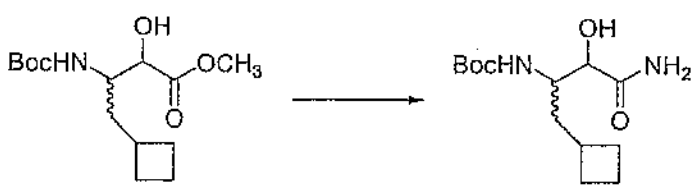
Step 7.



1g **1h**

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

Step 8.



1h **1i**

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

A solution of the acid in CH_2Cl_2 (50 mL) and DMF (25 mL) was treated with NH_4Cl (2.94 g, 5.5 mmol), EDCI (3.15 g, 16.5 mmol), HOOBt (2.69 g, 16.5 mmol), and NMM (4.4 g, 44 mmol). The reaction mixture was stirred at room temperature for 3 d. The solvents were removed under *vacuo* and the residue was diluted with aq. HCl (250 mL) and extracted with CH_2Cl_2. The combined organic layers were washed with aq. saturated $NaHCO_3$, dried ($MgSO_4$) filtered concentrated *in* vacuo to obtain **1i**, which was used as it is in the following steps. (Alternatively **1i** can also be obtained directly by the reaction of **1f** (4.5 g, 17.7 mmol) with aq. H_2O_2 (10 mL), LiOH•H_2O (820 mg, 20.8 mmol) at 0 °C in 50 mL of CH_3OH for 0.5 h.)

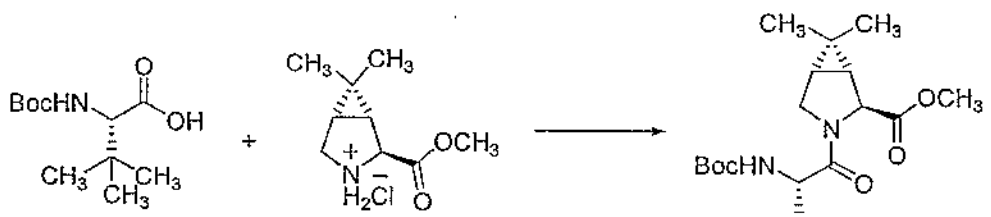
Step 9.



1i **1j**

A solution of **1i** 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 **1j** as a solid, which was used without further purification.

Step 10.

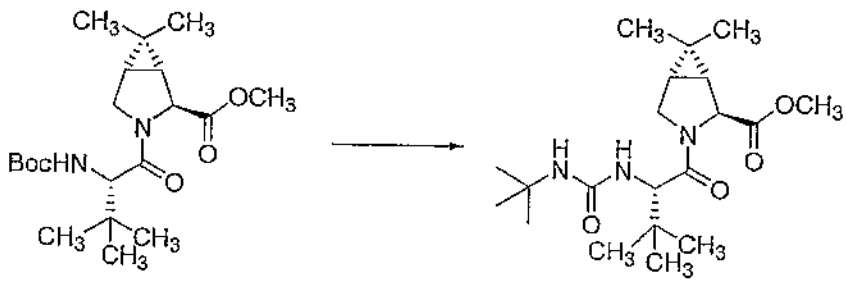


1k **1l** **1m**

The amino ester **1l** 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.

A solution of Boc-tert-Lue **1k** (Fluka, 5.0 g 21.6 mmol) in dry CH_2Cl_2/DMF (50 mL, 1:1) was cooled to 0° C and treated with the amine **1l** (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 24 hrs, 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 **1m** as a colorless solid.

Step 11.

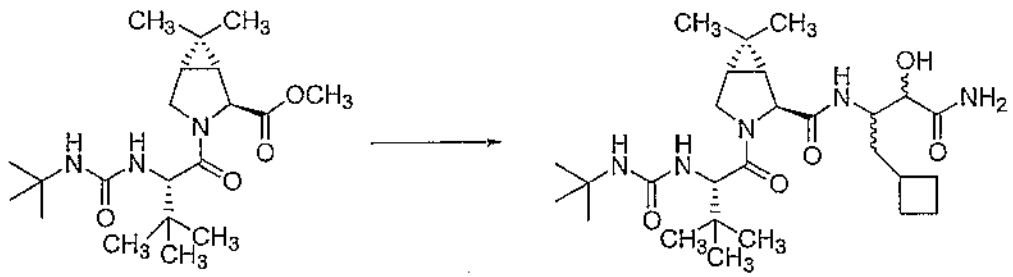


1m **1n**

A solution of methyl ester **1m** (4.0 g, 10.46 mmol) was dissolved in HCl (4 M solution in dioxane) and stirred at rt. for 3 h. The reaction mixture was concentrated *in vacuo* to obtain the amine hydrochloride salt used in the next step without further purification.

A solution of the amine hydrochloride salt (397 mg, 1.24 mmol) in CH_2Cl_2 (10 mL) was cooled to –78 °C and treated with *tert*-butyl isocyanate (250 mg, 2.5 mmol) and stirred at rt. overnight. The reaction mixture was concentrated *in* vacuo and the residue was diluted with aq. HCl (1M) and extracted with CH_2Cl_2. The combined organic layers were washed with aq. HCl (1M), saturated $NaHCO_3$ and brine. The organic layers were dried, filtered and concentrated *in vacuo* and the residue was purified by chromatography (SiO_2, acetone/Hex 1:4) to yield **1n** as a colorless solid.

Step 12.

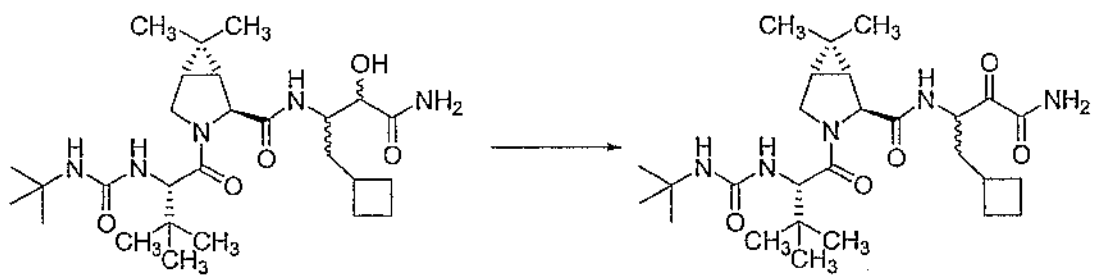


1n 1o

A solution of methyl ester **1n** (381 mg, 1.0 mmol) in THF/H_2O (1:1, 5 mL) was treated with LiOH•H_2O (62 mg, 1.5 mmol) and stirred at rt. for 3 h. The reaction mixture was acidified with aq. HCl and concentrated *in vacuo* to obtain the free acid.

A solution of acid (254.9 mg, 0.69 mmol) in DMF/CH_2Cl_2 (1:1, 5.0 mL) was treated with amine **1j** (159 mg, 0.763 mmol), EDCI (199 mg, 1.04 mmol), HOOBt (169.5 mg, 1.04 mmol) and NMM (280 mg, 2.77 mmol) at –20 °C. The reaction mixture was stirred at –20 °C for 48 h and concentrated in *vacuo*. The residue was diluted with aq. 1M HCl and extracted with EtOAc, The combined organic layers were extracted with aq. $NaHCO_3$, aq. HCl, brine, dried ($MgSO_4$) filtered, concentrated in *vacuo* to obtain **1o** (470 mg) as a tan colored solid that was used in the next reaction without further purification.

Step 13.

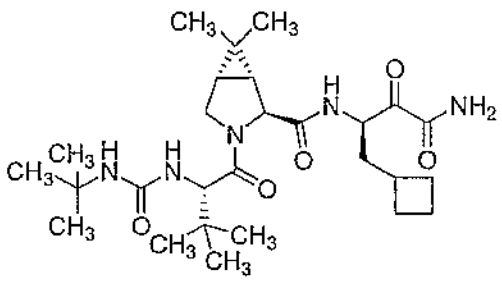


1o 1a

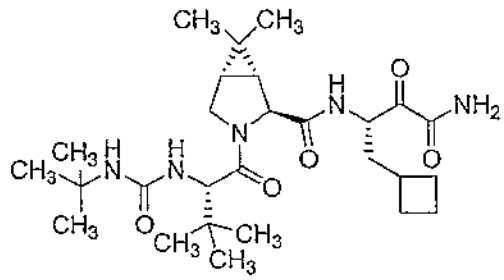
A solution of amide **1o** (470 mg, 0.9 mmol) in toluene and DMSO (1:1 20 mL) at 0 °C was treated with EDCI (1.72 g, 9.0 mmol) and dichloroacetic acid (0.37 mL, 4.5 mmol) and stirred at 0 °C for 4 hrs. The reaction mixture was diluted with CH_2Cl_2, and washed with saturated $NaHCO_3$, and brine. The organic layer was dried

($MgSO_4$), filtered, concentrated, *in vacuo* and purified by chromatography (SiO_2, acetone/hexanes 3:7) to yield **1a** as a colorless solid.

Separation of the Compound of Formula 1 into diastereomers of Formulas Ib and Ic:



Ib



Ic

Preparative HPLC condition for separation

COLUMN USED:	*NORMAL PHASE YMC DIOL-NP COLUMN* 120 Å, S-10/20; 50 mm x 500 mm I.D/length
SOLVENT A:	Hexanes
SOLVENT B:	To make 4 L of solvent (1.7 L Isopropanol + 300 mL of CH_3CN+ 2 L of CH_2Cl_2)
HPLC CONDITIONS:	12% of Solvent B/88% of Solvent A
FLOW:	120 mL/min

Procedure: 1 g of compound **1a** was dissolved in 10 mL of CH_2Cl_2/25 mL of Hexanes and injected into the column. It was eluted with 120 mL/min and two peaks were independently collected and concentrated. The solid residue was further dried in high vacuum and analyzed by analytical HPLC. Since the polar (second isomer) contained 2.6% of nonpolar diastereomer (First isomer), it was purified once more to isolate the pure diastereomers.

Analytical conditions for analysis of diastereomeric purity

COLUMN USED:	*NORMAL PHASE YMC DIOL-NP COLUMN* 200 Å, S-5 □M; 150 mm x 3 mm length/I.D
SOLVENT A:	Hexanes
SOLVENT B:	To make 4 L of solvent (1.7 L Isopropanol + 300 mL of CH_3CN+ 2 L of CH_2Cl_2)
HPLC CONDITIONS:	8.5% of Solvent B/91.5% of Solvent A
FLOW:	0.7 mL/min
Rt	Nonpolar isomer (**compound Ib**) =13.2 min

Polar isomer (**compound Ic**) =16.1 min

2.5 mg of compound in 1 mL was used and 20 μL was injected and analyzed with a U.V detector at □=254 nm.

Analytical data for compounds 2 and 3.

Compound 3 [Polar diastereomer]

^{1}H NMR (d_6-dmso, 500 MHz): □ 8.26 (d, 1 H, *J*= 7.0 Hz), 8.00 (s, 1 H), 7.75 (s, 1 H), 5.96 (s, 1 H), 5.84 (d, 1 H, *J*=10 Hz), 4.96 (m, 1 H), 4.28 (s, 1H), 4.11 (d, 1 H, *J*=11 Hz), 3.94 (d, 1H, *J*=10 Hz), 3.73 (dd, 1 H, J= 10 & 5 Hz), 2.48 (m, 1 H), 1.95 (m, 2 H), 1.61 (m, 1 H), 1.59 (m, 1 H), 1.77(m, 1 H), 1.57 (m, 1 H), 1.74 (m, 2 H), 1.42 (dd, 1 H, *J*=7.5 & 5 Hz), 1.28 (d, 1 H, *J*=7.5 Hz), 1.17 (s, 9 H), 1.01 (s, 3 H), 0.90 (s, 9 H), 0.85 (s, 3 H). ^{13}C NMR (d_6-dmso, 125 MHζ): □ 197.8, 170.9, 170.8, 162.8, 157.4, 59.1, 56.8, 51.8, 48.9, 47.4, 36.7, 34.0, 32.0, 30.6, 29.1, 27.8, 27.3, 27.1, 26.4, 26.1, 18.5, 17.7, 12.5. MS [FAB] 520 (55), 421 (100), 308 (75), 213 (90). HRMS calcd for $C_{27}H_{46}O_5N_5$ $[M+1]^+$ 520.3499; observed: 520.3505.

Compound 2 [Non-polar diastereomer]

^{1}H NMR (d_6-dmso, 500 MHz): □ 8.15 (d, 1 H, *J*= 7.0 Hz), 7.96 (s, 1 H), 7.74 (s, 1 H), 5.96 (s, 1 H), 5.86 (d, 1 H, *J*=10 Hz), 4.85 (m, 1 H), 4.27 (s, 1H), 4.13 (d, 1 H, *J*=11.0 Hz), 3.97 (d, 1H, *J*=10 Hz), 3.76 (dd, 1 H, J= 10 & 5 Hz), 2.36 (m, 1 H), 1.97 (m, 2 H), 1.60 (m, 2 H), 1.78 (m, 1 H), 1.64 (m, 1 H), 1.75 (m, 2 H), 1.44 (dd, 1 H, *J*=7.5 & 5 Hz), 1.27 (d, 1 H, *J*=7.5 Hz), 1.17 (s, 9 H), 1.00 (s, 3 H), 0.89 (s, 9 H), 0.82 (s, 3 H). ^{13}C NMR (d_6-dmso125 MHζ): δ 197.1, 171.1, 170.7, 163.0, 157.3, 59.4, 56.9, 52.1, 48.9, 47.4, 36.6, 34.0, 32.1, 30.5, 29.1, 27.9, 27.4, 26.8, 26.4, 26.1, 18.5, 17.8, 12.4. MS [FAB] 520 (40), 421 (100), 308 (60), 213 (65). HRMS calcd. for $C_{27}H_{46}O_5N_5$ $[M+1]^+$ 520.3499; observed: 520.3514.

It will be appreciated by those skilled in the art that changes could be made to the embodiments described above without departing from the broad inventive concept thereof. It is understood, therefore, that this invention is not limited to the particular embodiments disclosed, but it is intended to cover modifications that are within the spirit and scope of the invention, as defined by the appended claims.

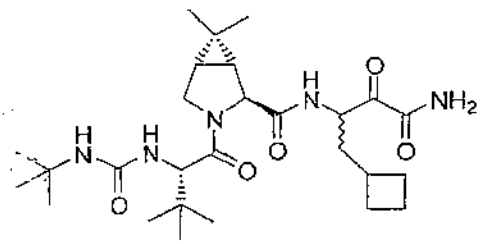
Each document (including granted patents, published patent applications, and nonpatent publications such as journal articles) referred to in this application is incorporated in its entirety by reference for all purposes.

CLAIMS

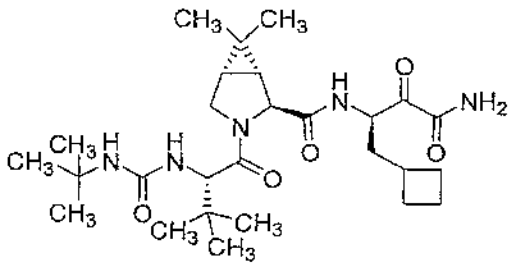
1. A pharmaceutical formulation comprising:

(a) at least one surfactant; and

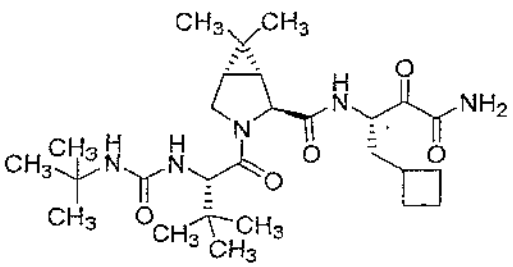
(b) at least one compound which is:

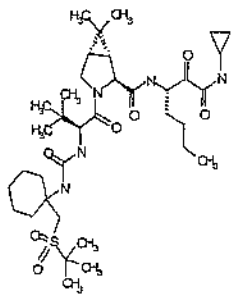


Formula Ia



Formula 1b





Formula Ic

or a pharmaceutically acceptable salt thereof

, wherein said at least one surfactant is selected from the group consisting of sodium lauryl sulfate, monoethanolamine, docusate sodium, poloxamer, lecithin, sorbitan fatty acid esters, polyoxyethylene sorbitan fatty acid esters, ethoxylated aliphatic alcohols, propylene glycol monocaprylate, glycerol monostearate, medium chain triglycerides, polyoxyethylene alkyl ethers, and polyoxyethylene stearates.

2. The pharmaceutical formulation of claim 1 wherein said at least one surfactant comprises sodium lauryl sulfate.

3. The pharmaceutical formulation of claim 1 wherein said formulation is in capsule form.

4. The pharmaceutical formulation of claim 1 wherein said at least one surfactant is present in an amount of about 0.1 to about 10% by weight.

5. The pharmaceutical formulation of claim 1 wherein said at least one compound is present in an amount of about 50 to about 1000 mg.

6. A compound of claim 1, for use in the treatment of HCV infection.

7. A compound of claim 1, for use in the treatment of a capthesin-associated disorder.

8. The pharmaceutical formulation of Claim 2 further comprising 0.1 to 15% by weight of a lubricant.

9. The pharmaceutical formulation of Claim 8 wherein the lubricant is magnesium stearate.

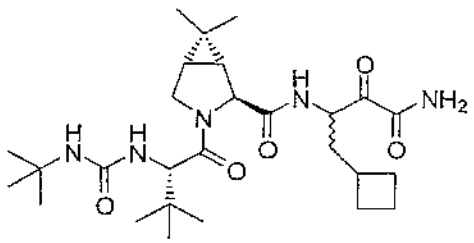
10. The pharmaceutical formulation of Claim 1 further comprising one or more carriers, binders or disintegrants, or a mixture of two or more thereof.

11. The pharmaceutical formulation of Claim 2, further comprising magnesium stearate and one or more carriers, binders or disintegrants, or a mixture of two or more thereof.

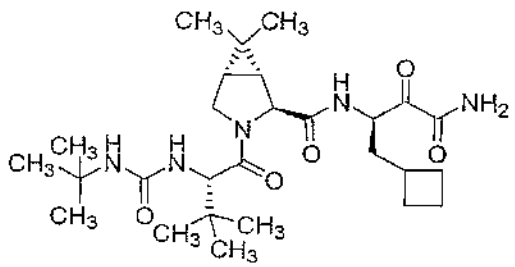
12. A pharmaceutical formulation, compirisng;

(a) a surfactant which is sodium lauryl sulfate and

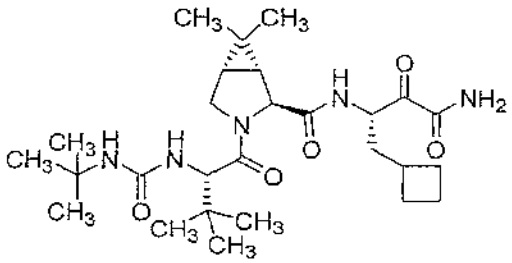
(b) at least one compound which is:



Formula Ia



Formula 1b



Formula Ic

or a pharmaceutically acceptable salt thereof.