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(54) **Title:** COMBINATIONS COMPRISING HCV PROTEASE INHIBITOR(S) AND HCV IRES INHIBITOR(S), AND METHODS OF TREATMENT RELATED THERETO

(57) **Abstract:** Disclosed are medicaments, pharmaceutical compositions, pharmaceutical kits, and methods based on combinations of: (a) at least one HCV IRES inhibitor; and (b) at least one HCV protease inhibitor; and optionally (c) at least one other therapeutic agent; for concurrent or consecutive administration in treating or ameliorating one or more symptoms of HCV, or disorders associated with HCV in a subject in need thereof.

COMBINATIONS COMPRISING HCV PROTEASE INHIBITOR(S) AND HCV IRES INHIBITOR(S), AND METHODS OF TREATMENT RELATED THERETO

FIELD OF THE INVENTION

The present invention relates to medicaments, pharmaceutical compositions, pharmaceutical kits, and methods based on combinations comprising, separately or together: (a) at least one hepatitis C virus (HCV) internal ribosomal entry site (IRES) inhibitor; (b) at least one HCV protease inhibitor; and optionally (c) at least one other therapeutic agent; for concurrent or consecutive administration in treating or ameliorating one or more symptoms of HCV, or disorders associated with HCV in a subject in need thereof.

BACKGROUND OF THE INVENTION

Citation of or reference to any application or publication in this Section or any Section of this application is not an admission that such document is available as prior art to the present 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 HCV include interferon-α (INF_α) and combination therapy with ribavirin and interferon. See, *e.g.*, Berenguer and Wright, *Proc Assoc Am Physicians*, **110(2)**:98-112 (1998). These therapies suffer from a low sustained response rate and frequent side effects. See, *e.g.*, Hoofnagle and di Bisceglie, *N*

Engl J Med, **336(5)**:347-356 (1997). Currently, no vaccine is available for HCV infection.

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, a HCV protease (NS3) necessary for polypeptide processing and viral replication has been identified, cloned and expressed; (see, *e.g.*, U.S. Patent No. 5,712,145). Translation of the HCV RNA genome produces an approximately 3000 amino acid polyprotein that 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 five 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.*, *Proc Natl Acad Sci (USA)*, **91(3)**:888-892 (1994), Failla *et al.*, *Fold Des*, **1(1)**:35-42 (1996), Wang *et al.*, *J Virol*, **78(2)**:700-709 (2004). The NS3/NS4a cleavage site is also more tolerant of mutagenesis than the other sites. See, *e.g.*, Kolykhalov *et al.*, *J Virol*, **68(11)**:7525-7533 (1994). 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.*, *J Virol*, **68(11)**:7351-7357 (1994).

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.*, *Biochemistry*, **36(31)**:9340-9348 (1997), Ingallinella *et al.*, *Biochemistry*, **37(25)**:8906-8914 (1998), Llinàs-Brunet *et al.*, *Bioorg Med Chem Lett*, **8(13)**:1713-1718 (1998)), inhibitors based on the 70-amino acid polypeptide eglin c (Martin *et al.*, *Biochemistry*, **37(33)**:11459-11468 (1998), inhibitors affinity selected from human pancreatic secretory trypsin inhibitor (hPSTI-C3) and minibody repertoires (MBip) (Dimasi *et al.*, *J Virol*, **71(10)**:7461-7469 (1997)), cV_HE2 (a "camelized" variable domain antibody fragment) (Martin *et al.*, *Protein Eng*, **10(5)**:607-614 (1997), and α1-antichymotrypsin (ACT) (Elzouki *et al.*, *J Hepat*, **27(1)**:42-48 (1997)). 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.). A ribozyme designed to selectively destroy HCV RNA has recently been disclosed (see, *BioWorld Today*, **9(217)**:4 (November 10, 1998)) as well.

The following U. S. patents and patent applications disclose various types of peptides and/or other compounds as NS-3 serine protease inhibitors of HCV: USP 6,846,802; USP 6,914,122; USP 6,838,475; USP 6,800,434; US2002/0160962;

US2004/0254117; WO03/062265; USP 6,838,466; US2005/0272663; US2006/0025441; US2005/0153900; US2005/0164921; US2005/0267043; US2005/0288233; US2005/0245458; US2005/0222047; WO2005/087731; US2005/0197301; US2005/0209164; and US2006/0046956.

An IRES is a nucleotide sequence that allows for translation initiation in the middle of a messenger RNA (mRNA) sequence as part of the greater process of protein synthesis. IRES is recognized by the 40S pre-initiation complex and mimics the 5' cap structure which is generally required in eukaryotes for the assembly of the initiation complex. IRES are located in the 5'UTR of RNA viruses and allow translation of the RNAs in a cap-independent manner. HCV-related IRESs directly bind 40S ribosomal subunit in such a way that their initiator codons are located in ribosomal P-site without mRNA scanning. These IRESs don't require eukaryotic initiation factors eIF1, 1A, 4A, 4B, and 4F.

The IRES is part of HCV that is found in different genotypes. It is an essential part of the replication process for the virus. It is believed that an IRES inhibitor will decrease the production of the virus. Thus, the conserved HCV IRES is a likely target for effective therapeutic intervention, see, *e.g.*, McCaffrey *et al., Hepatology*, **38(2)**:503-508 (2003) and references cited therein. McCaffrey *et al. supra* also disclose a morpholino antisense inhibitor as suited for targeting the HCV IRES.

U.S. 6,908,901 (Boehringer Ingelheim) and US20060046965 A1 (Boehringer Ingelheim) disclose certain HCV NS3 protease inhibitor peptide and dipeptide analogs respectively. Combining these analogs with an inhibitor of another target in the HCV life cycle including such as HCV polymerase inhibitors, NS3 helicase, N2/3 protease or IRES inhibitors as well as HIV and HBV inhibitors is generally described although no specific IRES inhibitors are mentioned, much less described.

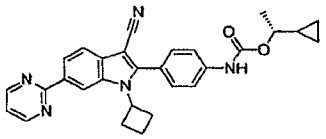
There remains a need for new treatments and therapies for HCV infection to treat, prevent or ameliorate of one or more symptoms of hepatitis C, methods for modulating the activity of serine proteases, particularly the HCV NS3/NS4a serine protease, and for methods of modulating the processing of the HCV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

It would also be desirable to modify the pharmacokinetic behavior of HCV treatments to enhance the efficacy and duration of action thereof.

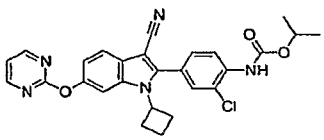
SUMMARY OF THE INVENTION

The present invention provides medicaments, pharmaceutical compositions, pharmaceutical kits, and methods based on combinations comprising, separately or together: (a) at least one anti-HCV agent which is an indole (*e.g.*, as described in WO 2006/019831) or a thienopyridine (*e.g.*, as described in WO 2006/019832); and (b) at least one HCV protease inhibitor which is a compound of Formula I to XXVI detailed below, or a pharmaceutically acceptable salt, solvate, or ester thereof; for concurrent or consecutive administration in treating or ameliorating one or more symptoms of HCV, or disorders associated with HCV in a subject in need thereof.

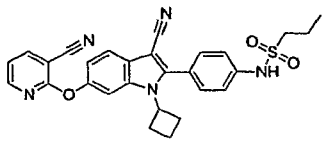
In one preferred embodiment, at least one anti-HCV agent is:



PS 102320 (a/k/a SCH 1385147),



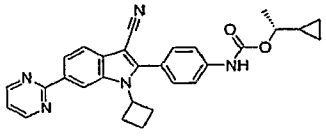
PS 102123 (a/k/a SCH 1383646),



PS 102283 (a/k/a SCH 1385145),

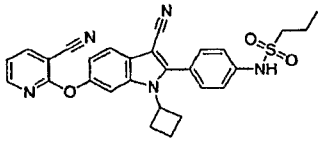
or a pharmaceutically acceptable salt, solvate, or ester thereof.

In another preferred embodiment, at least one anti-HCV agent is



SCH135147, or a pharmaceutically acceptable salt, solvate, or ester thereof.

In yet another preferred embodiment, at least one anti-HCV agent is



SCH1385145, or a pharmaceutically acceptable salt, solvate, or ester thereof.

The present invention also provides medicaments, pharmaceutical compositions, pharmaceutical kits, and methods based on combinations comprising, separately or together: (a) at least one hepatitis C virus (HCV) internal ribosomal entry site (IRES) inhibitor; and (b) at least one HCV protease inhibitor; for concurrent or consecutive administration in treating or ameliorating one or more symptoms of HCV, or disorders associated with HCV in a subject in need thereof.

According to certain preferred embodiments of the present invention, the HCV IRES inhibitor is selected from one or more of the thienopyridine or indole families of compounds disclosed in one or more of the following patent applications, the disclosure of each of which is incorporated herein its entirety by reference:

thienopyridine family: U.S. Patent Application No. 11/180,779 by Karp et al. published as US 2006/0019976 and International Patent Publication No. WO 2006/019831 (herein "WO '831); and

indole family: U.S. Patent Application No. 11/180,961 by Karp et al. published as US 2006/0223863 and International Patent Publication No. WO 2006/019832 (herein "WO '832); U.S. Patent Application No. 11/331,180 filed January 13, 206 by Karp et al.; U.S. Patent Application No. 11/653,435 filed January 13, 2007 by Karp et al.; U.S. Patent Application No. 11/653,450 filed January 16, 2007 by Karp et al., U.S. Patent Application No. 60/758,527 filed January 13, 2006 by Karp; U.S. Patent Application No. 11/653,436 filed January 13, 2007 by Karp; and U.S. Patent Application No. 11/653,448 filed January 16, 2007 by Karp.

In one preferred embodiment, at least one HCV IRES inhibitor is PS 102320 (a/k/a SCH 1385147, described above), PS 102123 (a/k/a SCH 1383646, described above), PS 102283 (a/k/a SCH 1385145, described above), or a pharmaceutically acceptable salt, solvate, or ester thereof. In another preferred embodiment, at least one HCV IRES inhibitor is SCH135147, or a pharmaceutically acceptable salt,

solvate, or ester thereof. In another preferred embodiment, at least one HCV IRES inhibitor is SCH1385145, or a pharmaceutically acceptable salt, solvate, or ester thereof.

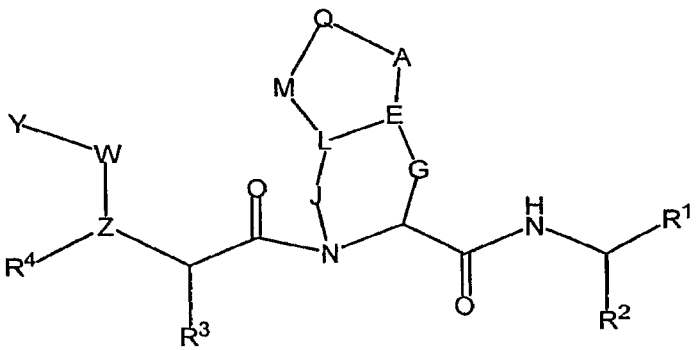
In one embodiment, at least one HCV IRES inhibitor is Heptazyme, I70® (OSI Pharmaceuticals Inc.), or RiboTargets RNA inhibitor. In one embodiment, at least one HCV IRES inhibitor is I70®.

In one embodiment, the medicament further comprises at least one other therapeutic agent. In a preferred embodiment, at least one other therapeutic agent is an interferon. In one embodiment, at least one other therapeutic agent is ribavirin, levovirin, VP 50406, ISIS 14803, VX 497, Thymosin, Maxamine, or mycophenolate mofetil.

In one embodiment wherein at least one other therapeutic agent is an interferon, the medicament further comprises ribavirin. In another embodiment, at least one other therapeutic agent is an interferon, and at least one other therapeutic agent is ribavirin, levovirin, VP 50406, ISIS 14803, VX 497, Thymosin, Maxamine, or mycophenolate mofetil.

In one embodiment, at least one HCV protease inhibitor is a compound of Formula I to XXVI detailed below or a pharmaceutically acceptable salt, solvate or ester thereof.

In one embodiment, at least one HCV protease inhibitor is a compound of structural Formula I:



or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula I:

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, wherein R^5 is COR^7 wherein R^7 is NHR^9 , wherein R^9 is selected from the group consisting of H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, cycloalkyl, arylalkyl, heteroarylalkyl, $[CH(R^{1'})]_pCOOR^{11}$,$[CH(R^{1'})]_pCONR^{12}R^{13}$,$[CH(R^{1'})]_pSO_2R^{11}$,$[CH(R^{1'})]_pCOR^{11}$,$[CH(R^{1'})]_pCH(OH)R^{11}$,$CH(R^{1'})CONHCH(R^2)COOR^{11}$,$CH(R^{1'})CONHCH(R^{2'})CONR^{12}R^{13}$,$CH(R^{1'})CONHCH(R^2)R'$,$CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})COOR^{11}$,$CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONR^{12}R^{13}$,$CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})COOR^{11}$,$CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONR^{12}R^{13}$,$CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONHCH(R^{5'})COOR^{11}andCH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONHCH(R^{5'})$ $CONR^{12}R^{13}$, 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

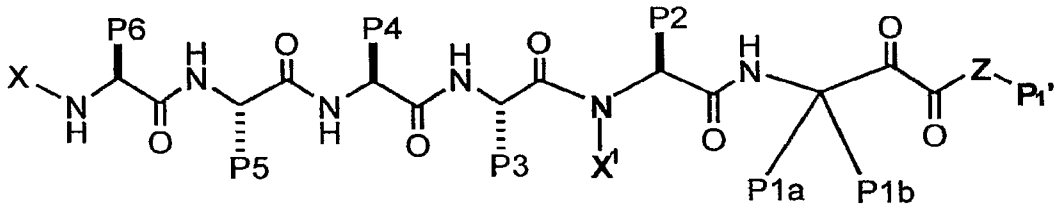
R, R', R^2, R^3 and R^4 are independently selected from the group consisting of H; C_1-C_{10} alkyl; C_2-C_{10} alkenyl; C_3-C_8 cycloalkyl; C_3-C_8 heterocycloalkyl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, halogen; (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, at least one HCV protease inhibitor is a compound of structural Formula II:



or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula II:

Z is NH;

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,

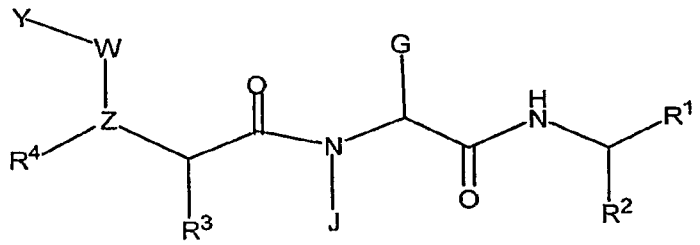
and aryl may be additionally optionally substituted with moieties independently selected from R^{13}.

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, at least one HCV protease inhibitor is a compound of structural Formula III:



or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula III:

G is carbonyl;

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 $C(OR)_2$, 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;

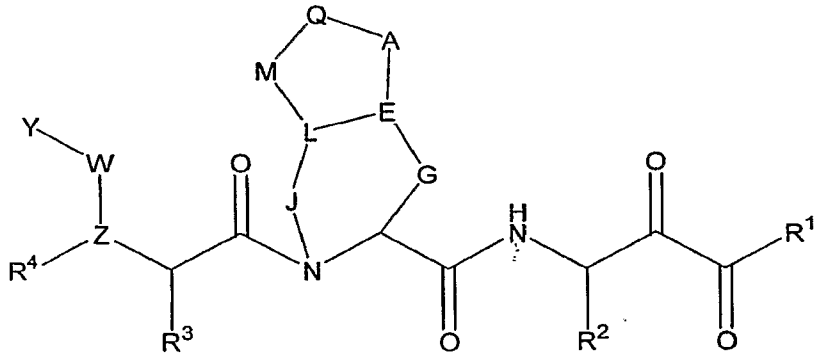
W maybe present or absent, and if W is present, W is selected from C=O, C=S, or SO_2; and

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, at least one HCV protease inhibitor is a compound of structural Formula IV:



or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula IV:

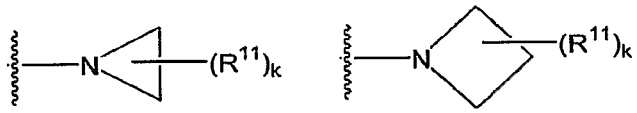
Y is selected from the group consisting of the following moieties: alkyl, alkyl-aryl, heteroalkyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyloxy, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocycloalkyloxy, cycloalkyloxy, alkylamino, arylamino, alkyl-arylamino, arylamino, heteroarylamino,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

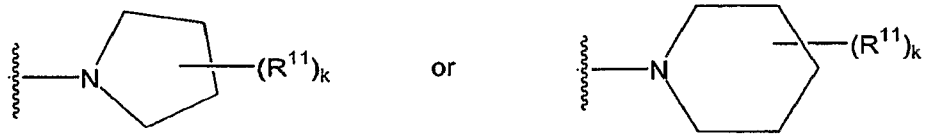
or X^{12};

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;

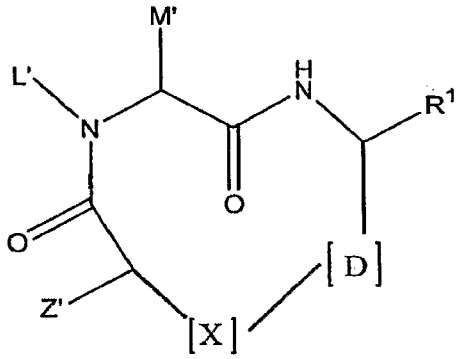
M may be present or absent, and when M is present, M is O, N(R), S, $S(O_2)$, $(CH_2)_p$, $(CHR)_p$ $(CHR\text{-}CHR')_p$, or $(CRR')_p$;

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, at least one HCV protease inhibitor is a compound of structural Formula V:



or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula V:

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

(2) R^5 is H, -OH, $-OR^8$, $-NR^9R^{10}$, $-C(O)OR^8$, $-C(O)NR^9R^{10}$, $-CF_3$, $-C_2F_5$, 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}, $-CH(R^{1'})CH(R^{1'})C(O)OR^{11}$,$[CH(R^{1'})]_pC(O)OR^{11}$,$-[CH(R^{1'})]_pC(O)NR^{12}R^{13}$,$-[CH(R^{1'})]_pS(O_2)R^{11}$,$-[CH(R^{1'})]_pC(O)R^{11}$,$-[CH(R^{1'})]_pS(O_2)NR^{12}R^{13}$, $CH(R^{1'})C(O)N(H)CH(R^{2'})(R')$, $CH(R^{1'})CH(R^{1'})C(O)NR^{12}R^{13}$, $-CH(R^{1'})CH(R^{1'})S(O_2)R^{11}$, $-CH(R^{1'})CH(R^{1'})S(O_2)NR^{12}R^{13}$, $-CH(R^{1'})CH(R^{1'})C(O)R^{11}$, $-[CH(R^{1'})]_pCH(OH)R^{11}$, $-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)OR^{11}$, $C(O)N(H)CH(R^{2'})C(O)OR^{11}$,$-C(O)N(H)CH(R^{2'})C(O)R^{11}$,$CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)NR^{12}R^{13}$,$-CH(R^{1'})C(O)N(H)CH(R^{2'})R'$,$CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)N(H)CH(R^{3'})C(O)OR^{11}$,$CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)CH(R^{3'})NR^{12}R^{13}$,$CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)N(H)CH(R^{3'})C(O)NR^{12}R^{13}$,$CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)N(H)CH(R^{3'})C(O)N($

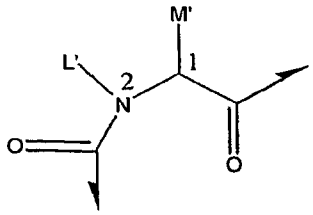
H)CH ($R^{4'}$)C(O)OR^{11},
H($R^{1'}$)C(O)N(H)CH($R^{2'}$)C(O)N(H)CH($R^{3'}$)C(O)N(H)CH($R^{4'}$)C(O)$NR^{12}R^{13}$,
CH($R^{1'}$)C(O)N(H)CH($R^{2'}$
)C(O)N(H)CH($R^{3'}$)C(O)N(H)CH($R^{4'}$)C(O)N(H)CH($R^{5'}$)C(O)OR^{11},
and CH($R^{1'}$)C(O)N(H)CH($R^{2'}$)C(O)N(H)CH($R^{3'}$)C(O)N(H)CH($R^{4'}$)C(O)N(H)CH($R^{5'}$)C(O)$NR^{12}R^{13}$;
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;

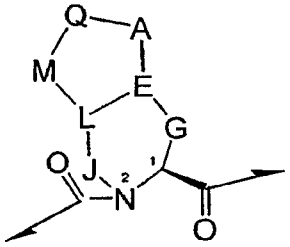
(6) L' is H, OH, alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, or heterocyclyl;

(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:



and wherein structural Formula 2 is represented by:



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;

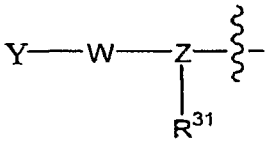
Q is present or absent, and when Q is present, Q is NR, PR, (CR=CR), $(CH_2)_p$, $(CHR)_p$, $(CRR')_p$, $(CHR\text{-}CHR')_p$, O, NR, S, SO, or SO_2; when Q is absent, M is (i) either directly linked to A or (ii) an independent substituent on L, said independent substituent bing selected from -OR, -CH(R)(R'), $S(O)_{0\text{-}2}R$ 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'), $S(O)_{0\text{-}2}R$ 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:



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,

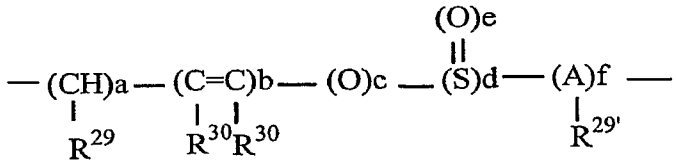
heterocycloalkyloxy, heteroalkyl-heteroaryl, cycloalkyloxy, alkylamino, arylamino, alkyl-arylamino, arylamino, heteroarylamino, cycloalkylamino or heterocycloalkylamino, and R^{31} is unsubstituted or optionally substituted with one or two substituents which are the same or different and are independently 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:



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;

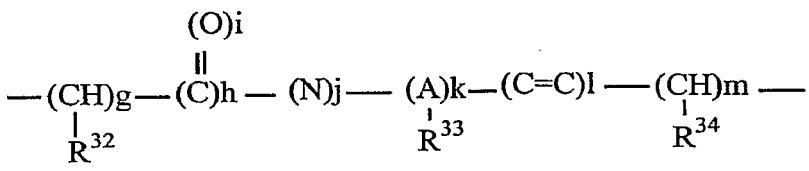
R^{29} and $R^{29'}$ are independently present or absent and if present can be the same or different, each being independently one or two substituents independently selected from the group consisting of: H, halo, alkyl, aryl, cycloalkyl, cycloalkylamino,

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:



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

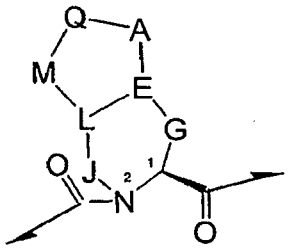
R^{32} and R^{34} are linked together such that the combination forms a portion of a cycloalkyl group;

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

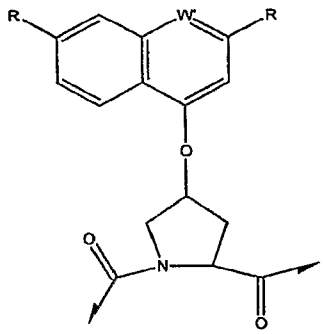
A is C, N, S or O,

(11) provided that when structural Formula 2:



Formula 2

is



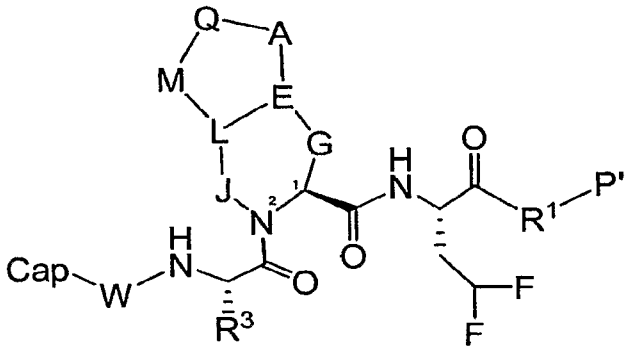
and

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, at least one HCV protease inhibitor is a compound of structural Formula VI:



or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula VI:

Cap is 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;

P' is –NHR;

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'), $-S(O)_{0\text{-}2}R$ or –NRR';

A is present or absent and if present A is –O-, -O(R) CH_2-, $-(CHR)_p$-, $-(CHR\text{-}CHR')_p$-, $(CRR')_p$, 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;

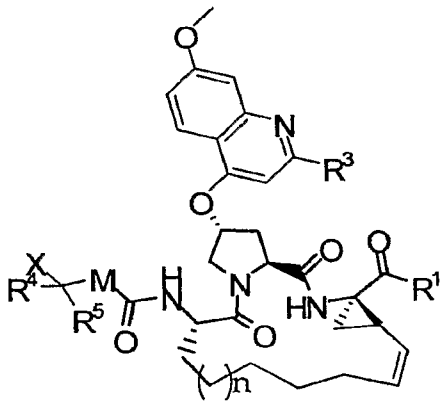
R, R' and R^3 can be the same or different, each being independently selected from the group consisting of: H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_3-C_8 cycloalkyl, C_3-C_8

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 carbonyl.

In another embodiment, at least one HCV protease inhibitor is a compound of structural Formula VII:

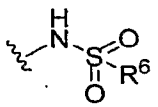


or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula VII:

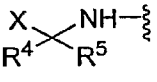
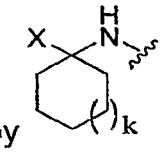
M is O, N(H), or CH_2;

n is 0-4;

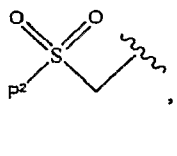
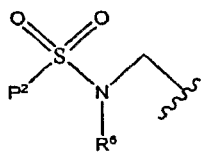
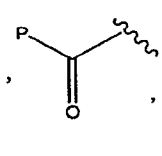
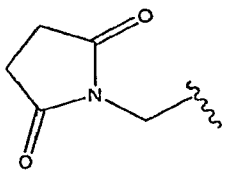
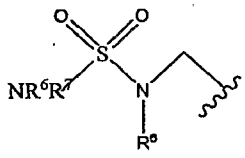
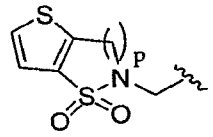
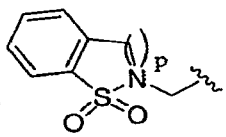
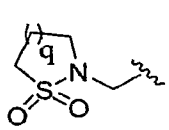
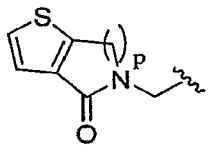
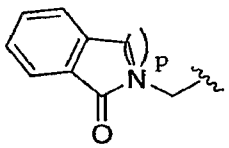
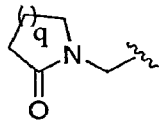
R^1 is $-OR^6$, $-NR^6R^7$ or  ;

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;

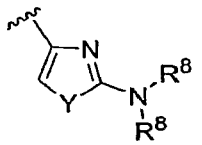
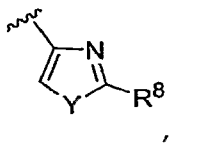
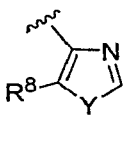
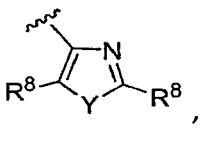
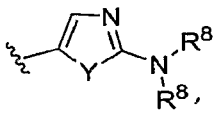
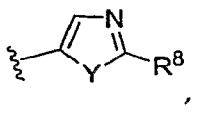
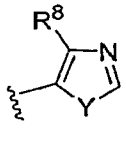
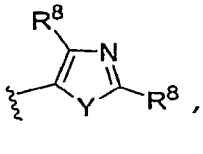
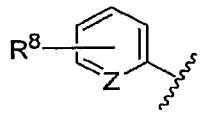
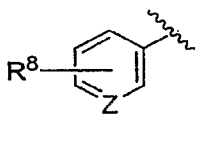
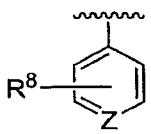
X is selected from the group consisting of:











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

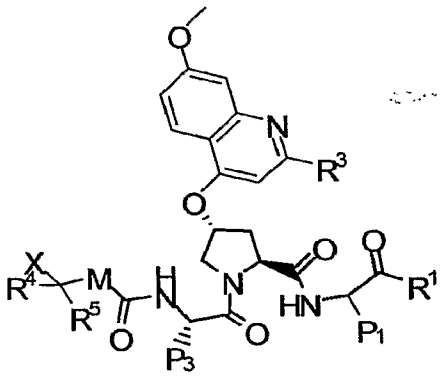
R^3 is selected from the group consisting of: aryl, heterocyclyl, heteroaryl,











and


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, at least one HCV protease inhibitor is a compound of structural Formula VIII:



or a pharmaceutically acceptable salt, solvate or ester thereof;

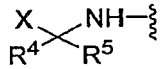
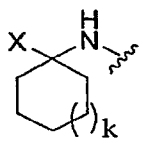
wherein in Formula VIII:

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

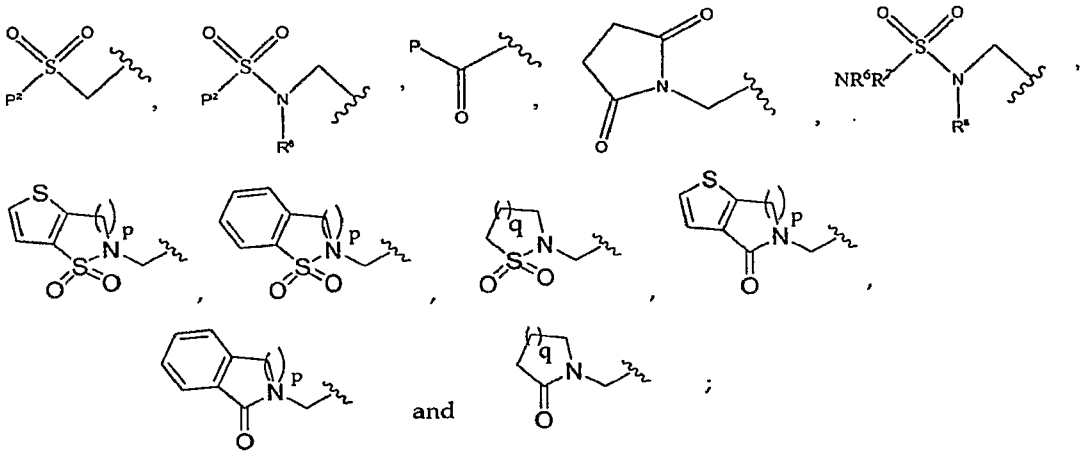
R^1 is $-C(O)NHR^6$, where R^6 is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, hydroxyl, amino, arylamino or alkylamino;

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;

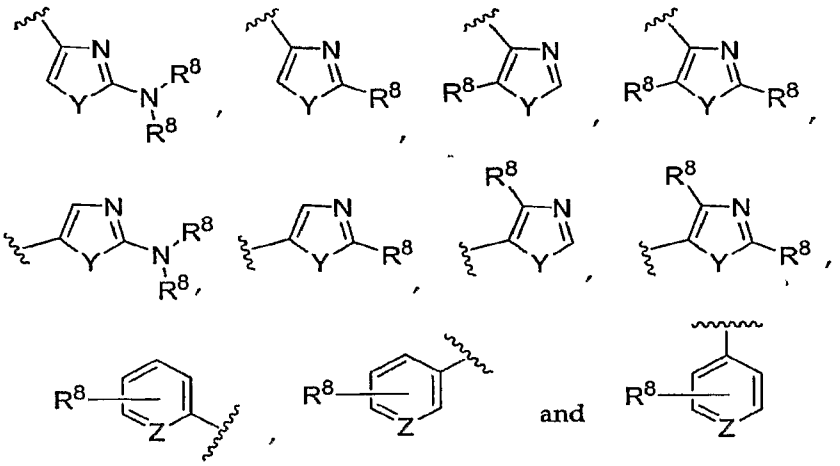
X is selected from the group consisting of:



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;

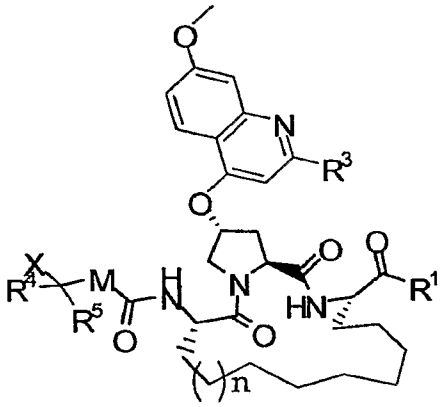
and

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, at least one HCV protease inhibitor is a compound of structural Formula IX:

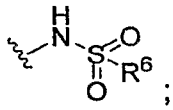


or a pharmaceutically acceptable salt, solvate or ester thereof;

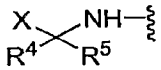
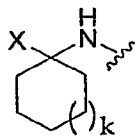
wherein in Formula IX:

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

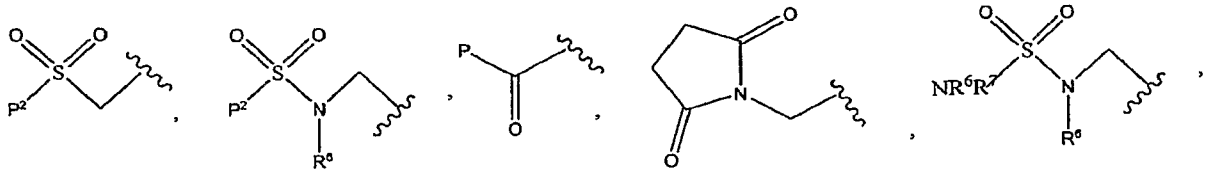
n is 0-4;

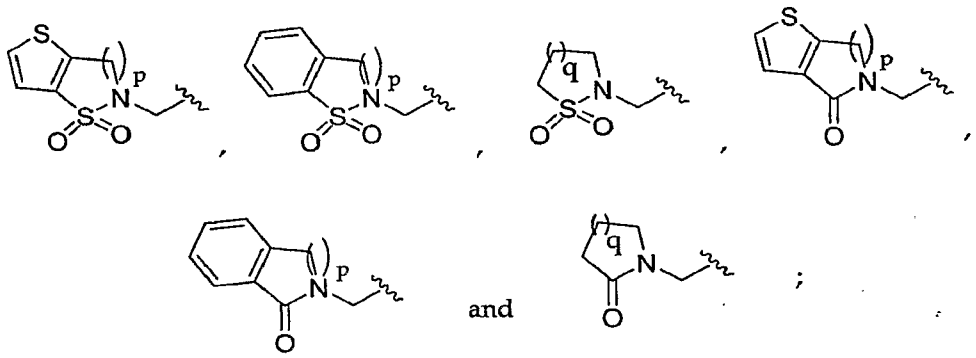
R^1 is $-OR^6$, $-NR^6R^7$ or ;

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:

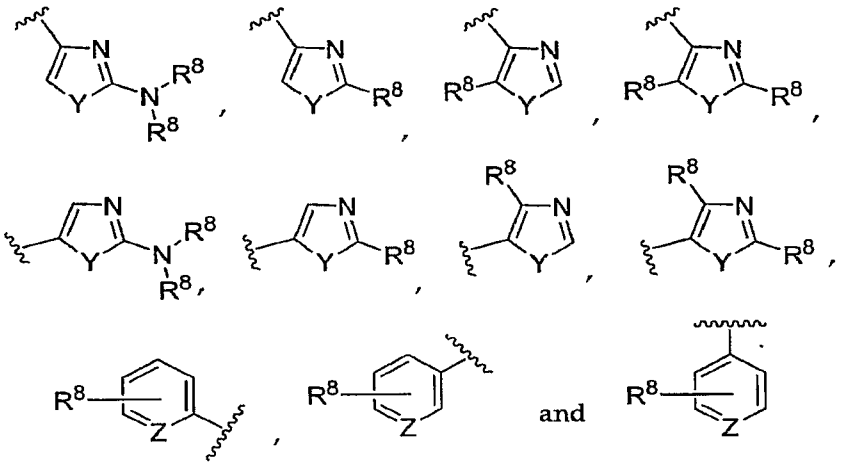




where p is 1 to 2, q is 1 to 3 and P^2 is alkyl, aryl, heteroaryl, heteroalkyl, cycloalkyl, dialkylamino, alkylamino, arylamino or cycloalkylamino;

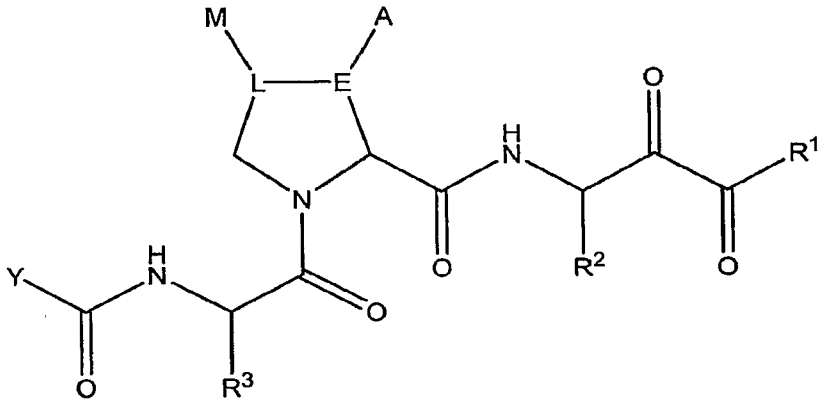
and

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, at least one HCV protease inhibitor is a compound of structural Formula X:

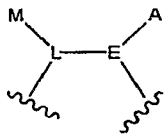


or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula X:

R^1 is NHR^9, wherein R^9 is H, alkyl-, alkenyl-, alkynyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, heterocyclyl-, arylalkyl-, or 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:



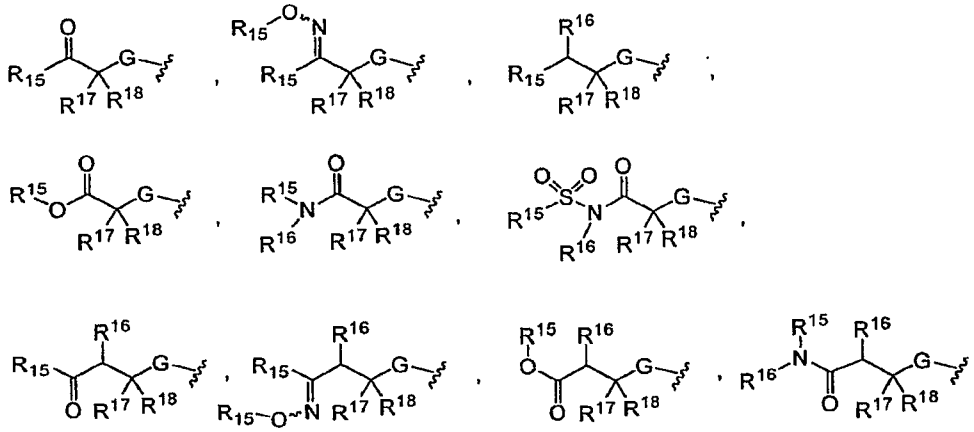
shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl;

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;

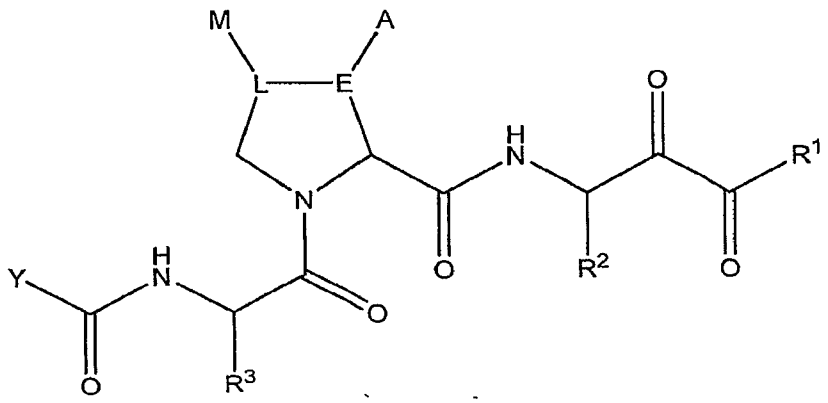
and Y is selected from the following moieties:



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, at least one HCV protease inhibitor is a compound of structural Formula XI:

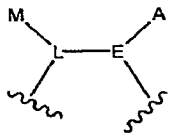


or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XI:

R^1 is NHR^9, wherein R^9 is H, alkyl-, alkenyl-, alkynyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, heterocyclyl-, arylalkyl-, or 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:



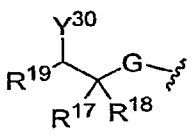
shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl;

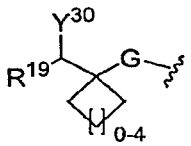
E is C(H) or C(R);

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

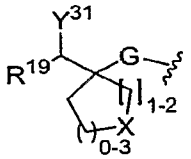
R, R', R^2, and R^3 can be the same or different, each being independently selected from the group consisting of H, alkyl-, alkenyl-, alkynyl-, cycloalkyl-, heteroalkyl-, heterocyclyl-, aryl-, heteroaryl-, (cycloalkyl)alkyl-, (heterocyclyl)alkyl-, aryl-alkyl-, and heteroaryl-alkyl-; or alternately R 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:

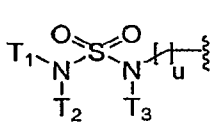




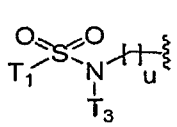
or



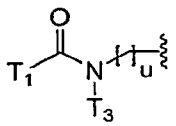
wherein Y^{30} and Y^{31} are selected from



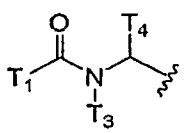
,



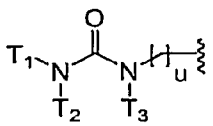
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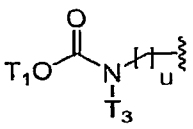
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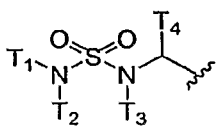
,



,



or



where u is a number 0-6;

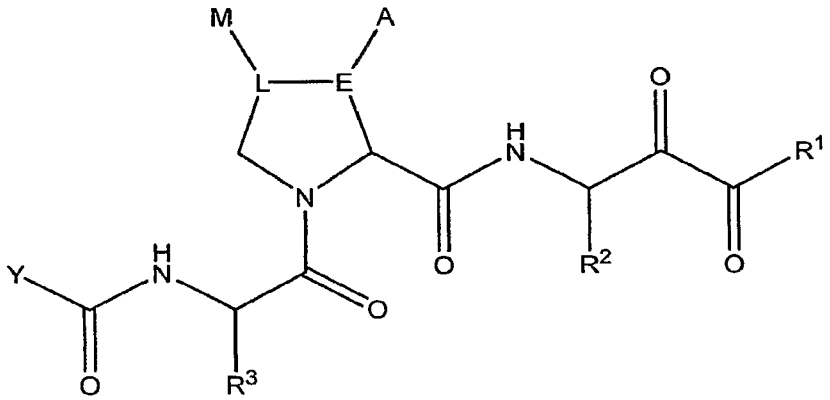
X is selected from O, NR^{15}, $NC(O)R^{16}$, S, S(O) and SO_2;

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, at least one HCV protease inhibitor is a compound of structural Formula XII:

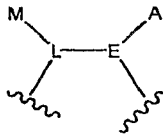


or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XII:

R^1 is NHR^9, wherein R^9 is H, alkyl-, alkenyl-, alkynyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, heterocyclyl-, arylalkyl-, or 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:



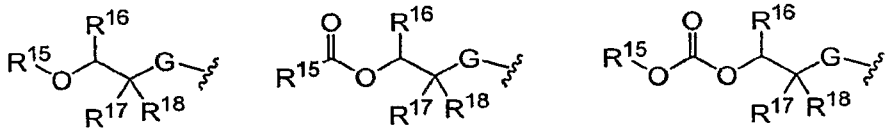
shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl;

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

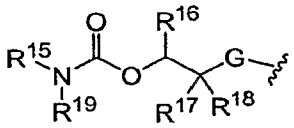
L is C(H), C(R), $CH_2C(R)$, or $C(R)CH_2$;

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

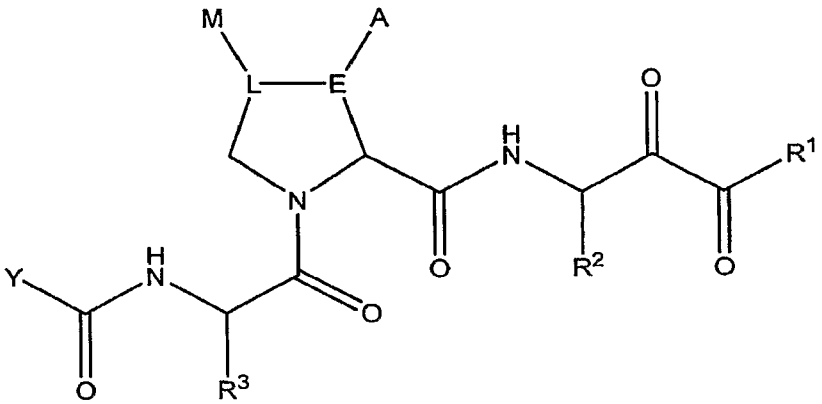


wherein G is NH or O; and R^{15}, R^{16}, R^{17}, R^{18}, and R^{19} can be the same or different, each being independently selected from the group consisting of H, alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, 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, at least one HCV protease inhibitor is a compound of structural Formula XIII:

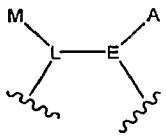


or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XIII:

R^1 is NHR^9, wherein R^9 is H, alkyl-, alkenyl-, alkynyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, heterocyclyl-, arylalkyl-, or heteroarylalkyl;

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



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

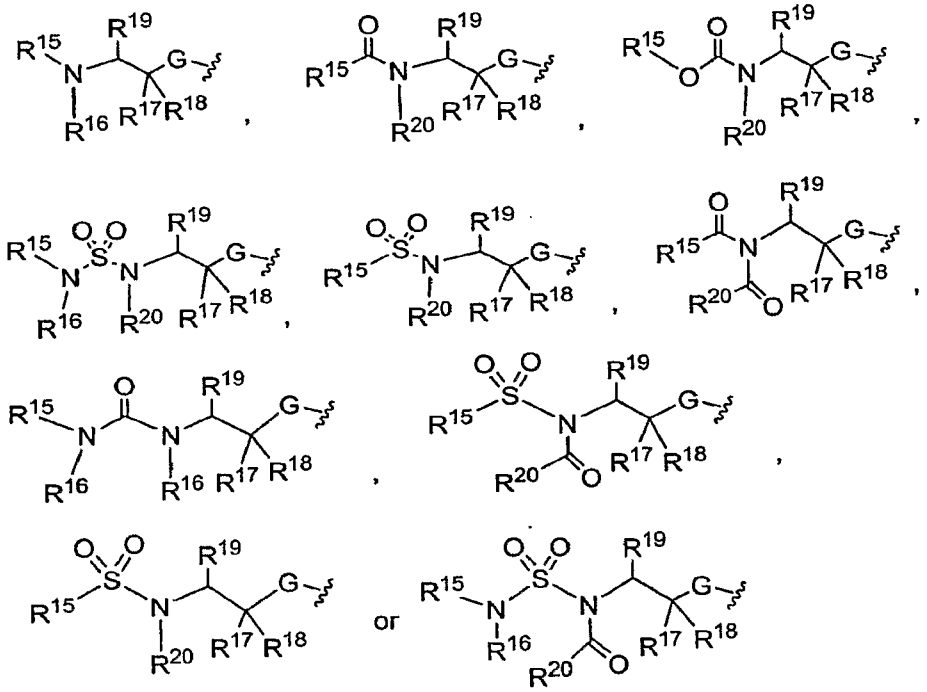
E is C(H) or C(R);

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

R, R', R^2, and R^3 can be the same or different, each being independently selected from the group consisting of H, alkyl-, alkenyl-, alkynyl-, cycloalkyl-, heteroalkyl-, heterocyclyl-, aryl-, heteroaryl-, (cycloalkyl)alkyl-, (heterocyclyl)alkyl-,

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

and Y is selected from the following moieties:

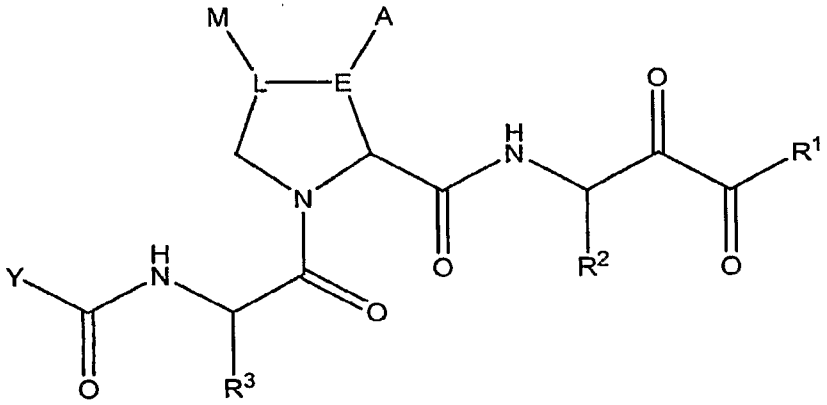


wherein G is NH or O, and R^{15}, R^{16}, R^{17} , R^{18}, R^{19} and R^{20} can be the same or different, each being independently selected from the group consisting of H, C_1-C_{10} alkyl, C_1-C_{10} heteroalkyl, C_2-C_{10} alkenyl, C_2-C_{10} heteroalkenyl, C_2-C_{10} alkynyl, C_2-C_{10} heteroalkynyl,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

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

cyano, and nitro.

In another embodiment, at least one HCV protease inhibitor is a compound of structural Formula XIV:



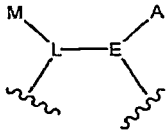
or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XIV:

R^1 is NHR^9, wherein R^9 is H, alkyl-, alkenyl-, alkynyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, heterocyclyl-, arylalkyl-, or 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:



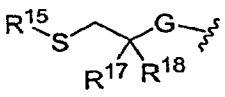
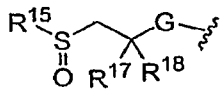
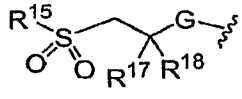
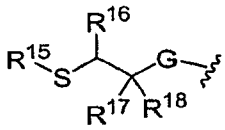
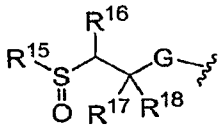
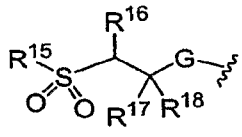
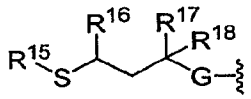
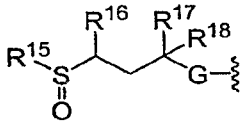
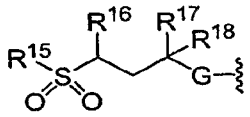
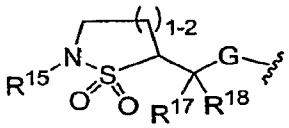
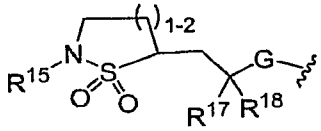
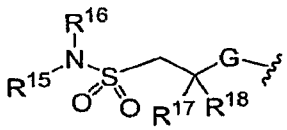
shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl;

E is C(H) or C=;

L is C(H), C=, CH_2C=, or C=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;

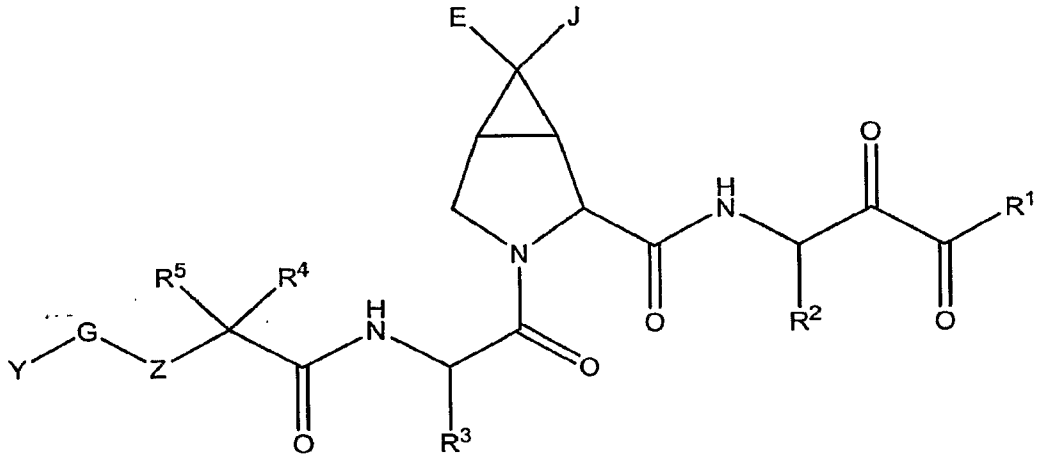
and Y is selected from the following moieties:


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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, at least one HCV protease inhibitor is a compound of structural Formula XV:



or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XV:

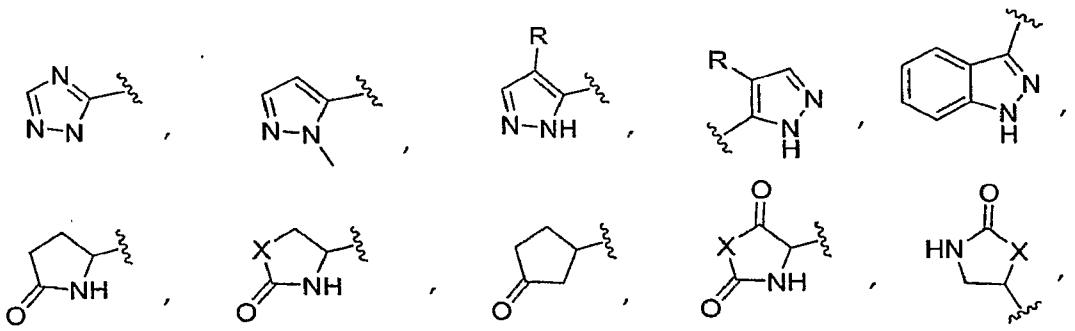
R^1 is NHR^9, wherein R^9 is H, alkyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, cycloalkyl-, arylalkyl-, or heteroarylalkyl;

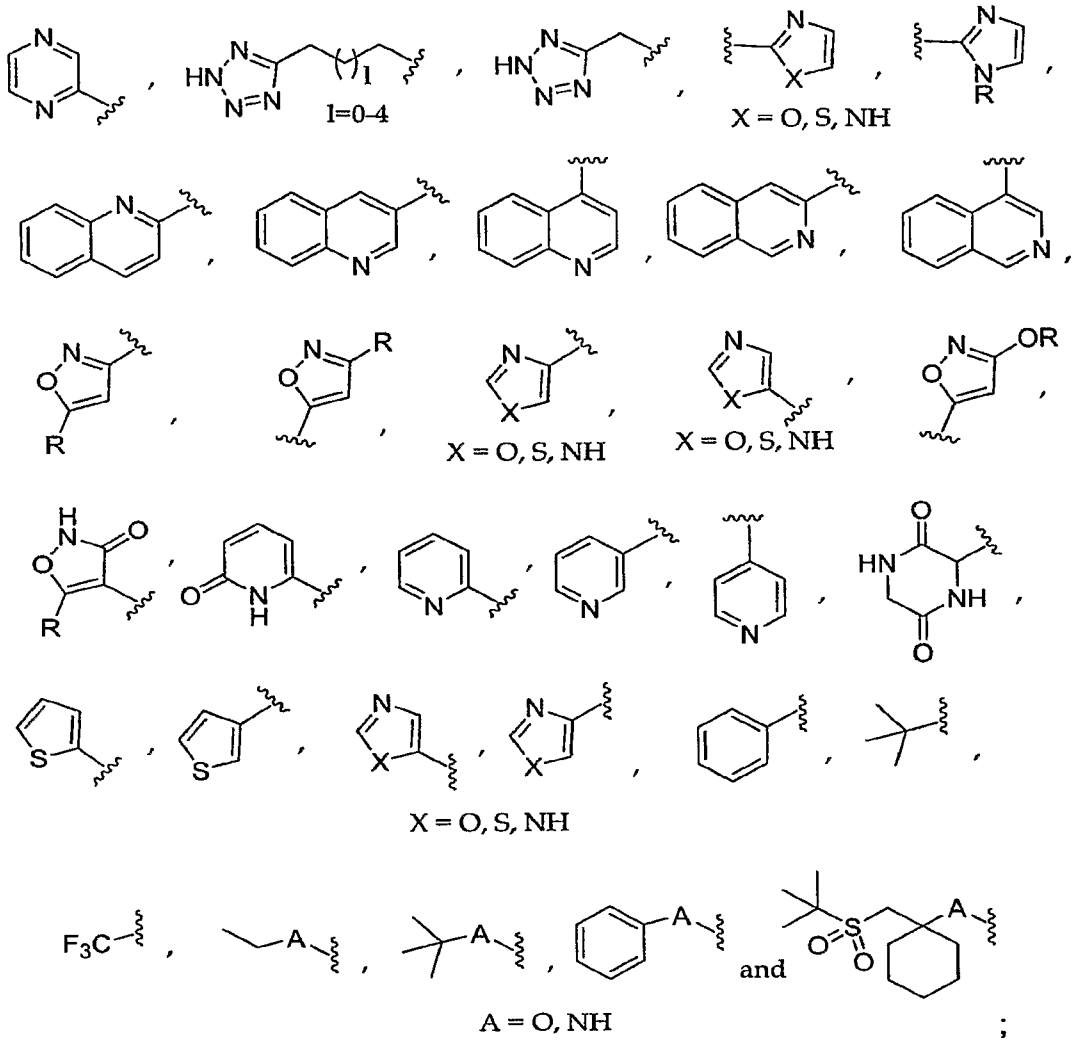
E and J can be the same or different, each being independently selected from the group consisting of R, OR, NHR, NRR^7, SR, halo, and $S(O_2)R$, or E and J can be directly connected to each other to form either a three to eight-membered cycloalkyl, or a three to eight-membered heterocyclyl moiety;

Z is N(H), N®, 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:





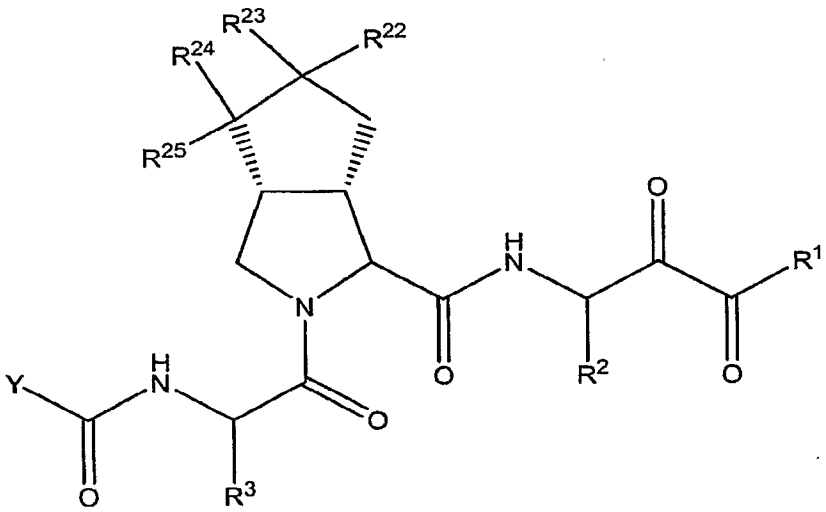
;

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, at least one HCV protease inhibitor is a compound of structural Formula XVI:



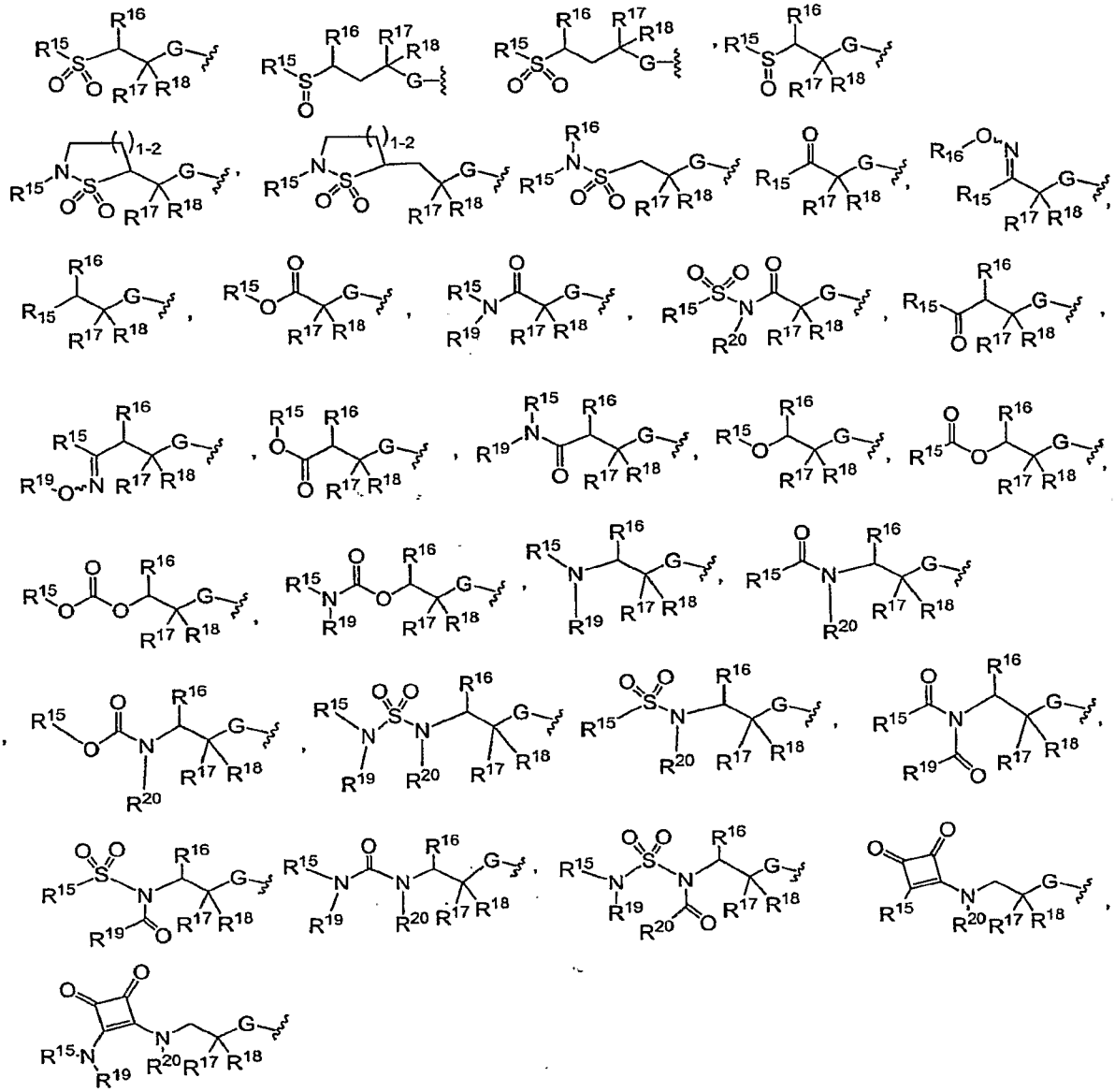
or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XVI:

R^1 is NHR^9, wherein R^9 is H, alkyl-, alkenyl-, alkynyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, heterocyclyl-, arylalkyl-, or heteroarylalkyl;

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:

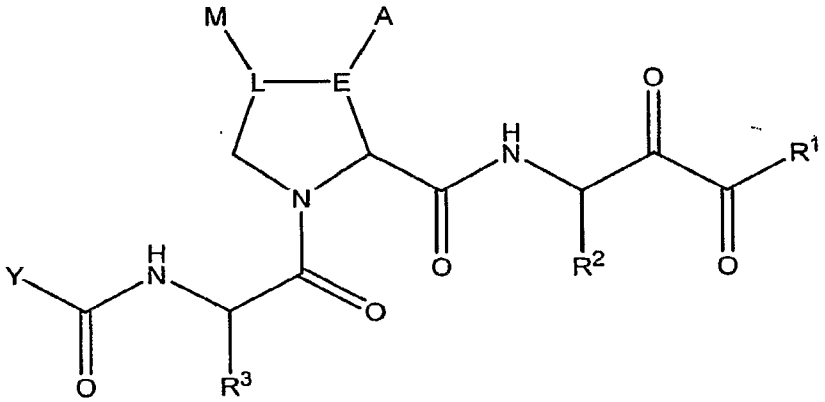


wherein G is NH or O; and R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24} and R^{25} can be the same or different, each being independently selected from the group consisting of H, alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, cycloalkyl, heterocyclyl, 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, at least one HCV protease inhibitor is a compound of structural Formula XVII:

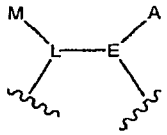


or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XVII:

R^1 is NHR^9, wherein R^9 is H, alkyl-, alkenyl-, alkynyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, heterocyclyl-, arylalkyl-, or 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

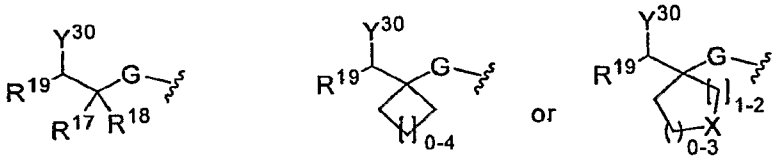
five to ten-membered heteroaryl;

E is C(H) or C=;

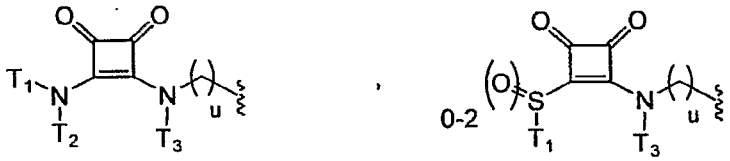
L is C(H), C=, CH_2C=, or C=CH_2;

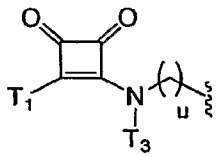
R, R', R^2, and R^3 can be the same or different, each being independently selected from the group consisting of H, alkyl-, alkenyl-, alkynyl-, cycloalkyl-, heteroalkyl-, heterocyclyl-, aryl-, heteroaryl-, (cycloalkyl)alkyl-, (heterocyclyl)alkyl-, aryl-alkyl-, and heteroaryl-alkyl-; or alternately R 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;

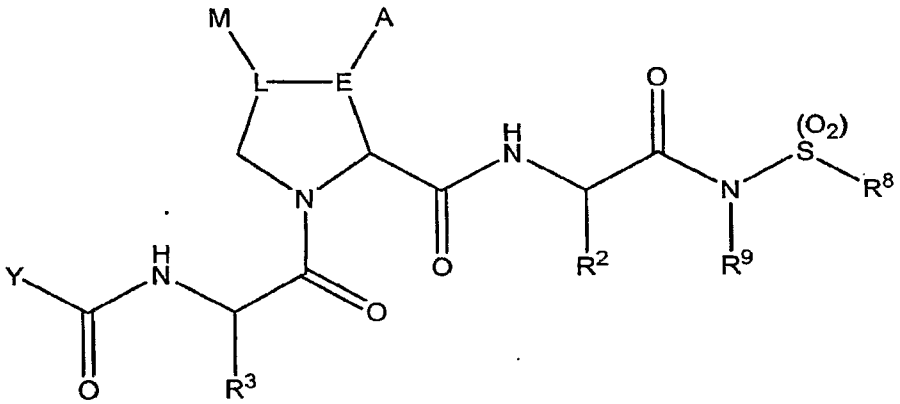
G is NH or O; and

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, at least one HCV protease inhibitor is a compound of structural Formula XVIII:



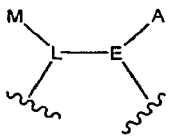
or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XVIII:

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);

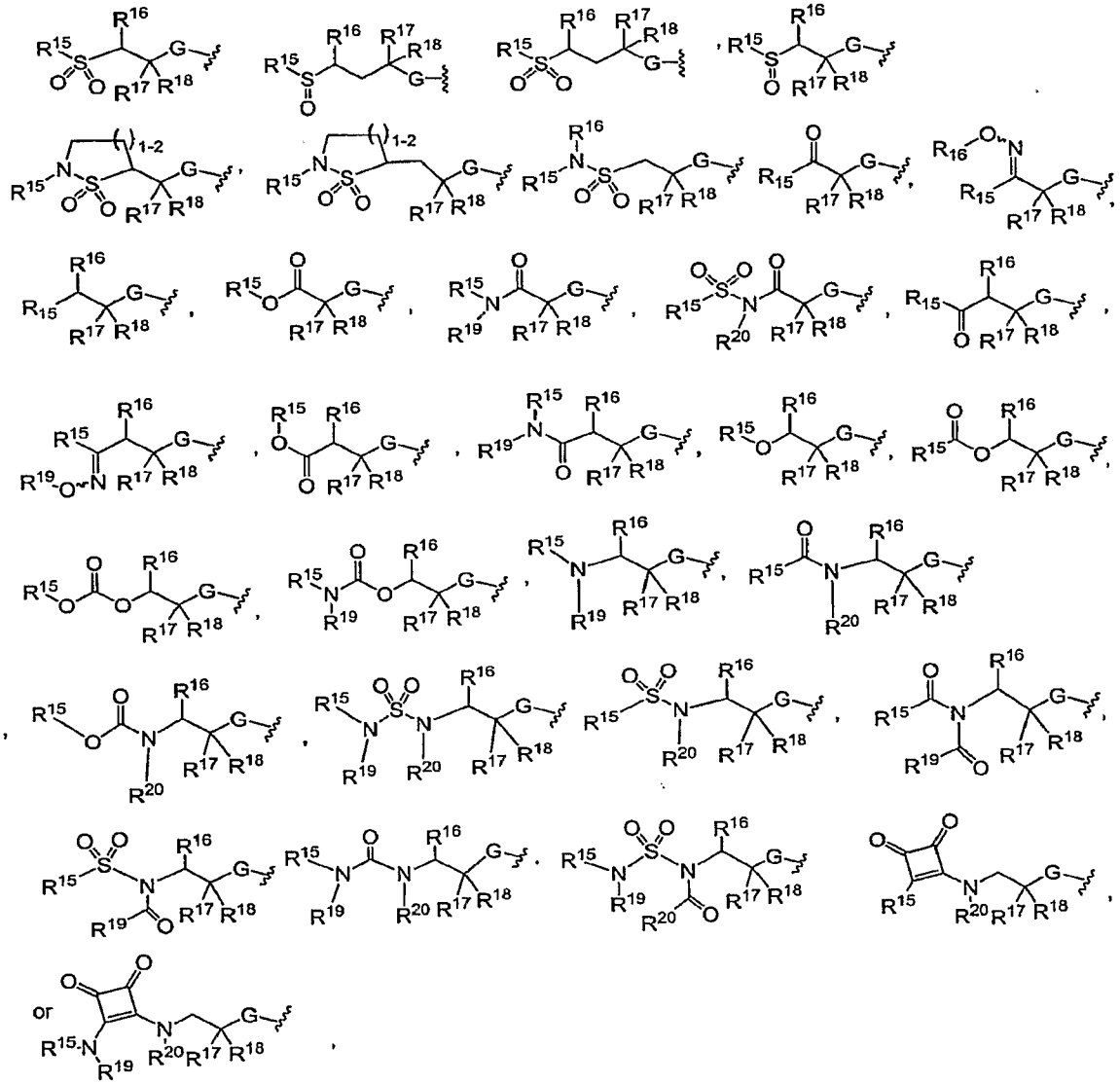
L is C(H), C(R), $CH_2C(R)$, or $C(R)CH_2$;

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:

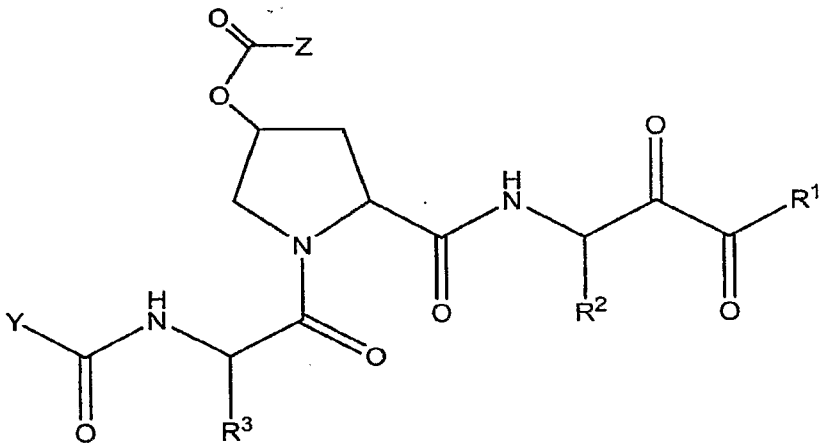


wherein G is NH or O; and R^{15}, R^{16}, R^{17}, R^{18}, R^{19} and R^{20} can be the same or different, each being independently selected from the group consisting of H, alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, cycloalkyl, heterocyclyl,

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, at least one HCV protease inhibitor is a compound of structural Formula XIX:



or a pharmaceutically acceptable salt, solvate or ester thereof;

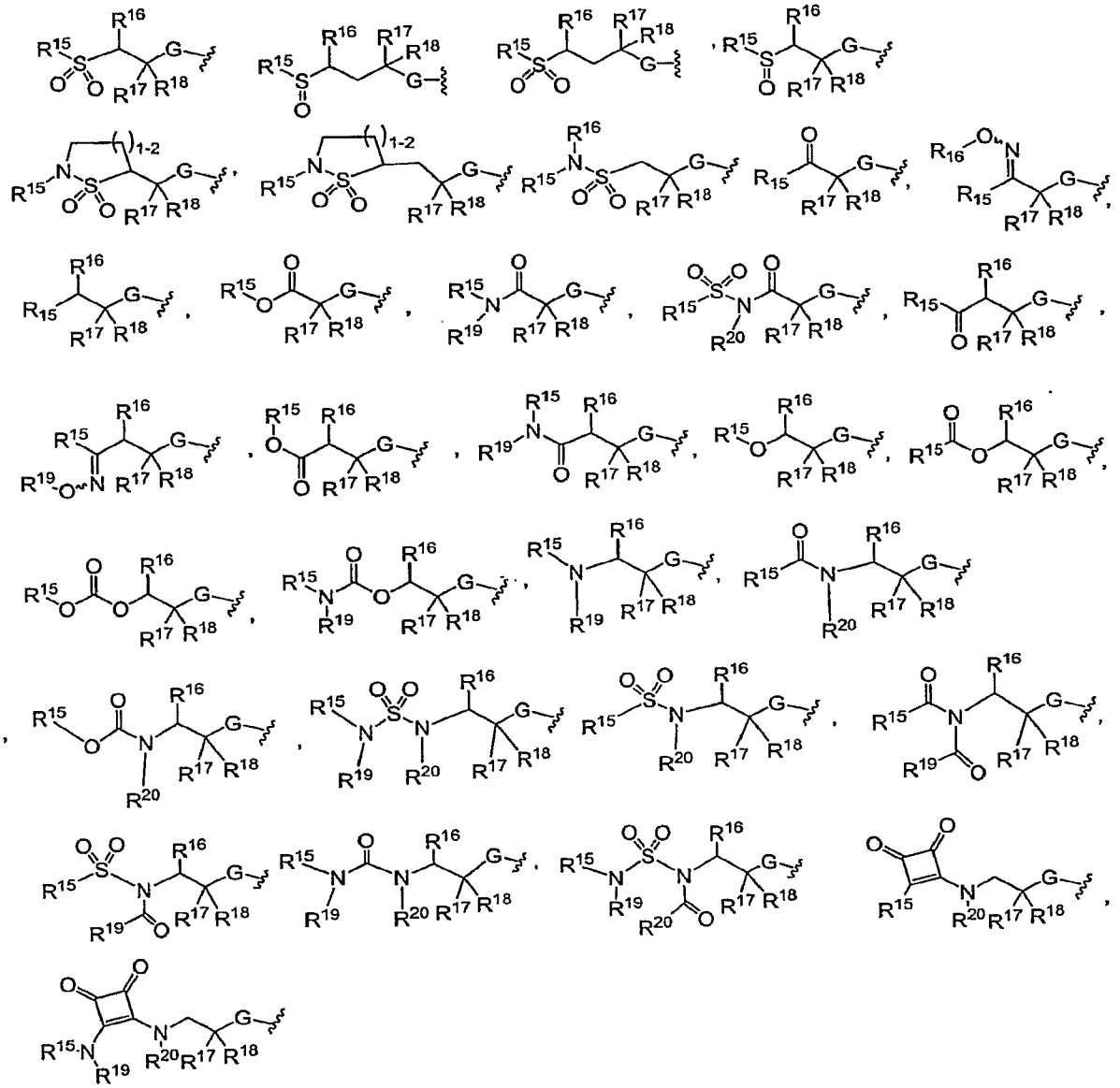
wherein in Formula XIX:

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 NHR^9, wherein R^9 is H, alkyl-, alkenyl-, alkynyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, heterocyclyl-, arylalkyl-, or heteroarylalkyl;

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:



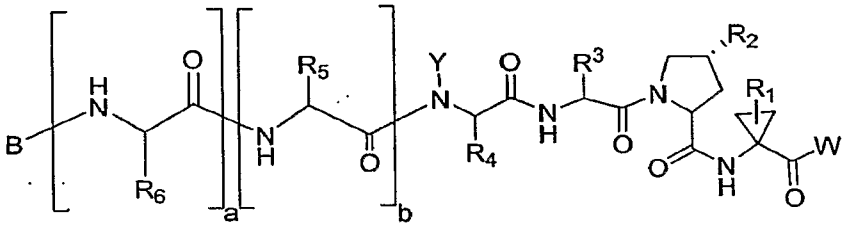
wherein G is NH or O; and R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20} and R^{21} can be the same or different, each being independently selected from the group consisting of H, alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, 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, at least one HCV protease inhibitor is a compound of structural Formula XX:

P6 P5 P4 P3 P2 P1



or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XX:

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; $N0_2$; 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};

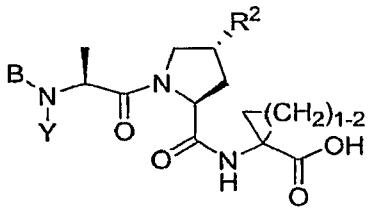
wherein R_{22} is C_{1-6}alkyl; C_{1-6} alkoxy; amino optionally mono- or di- substituted with C_{1-6} alkyl; sulfonyl; $N0_2$; OH; SH; halo; haloalkyl; carboxyl; amide or (lower alkyl)amide;

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 the above-shown structure of the compound of Formula XX, 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.

In another embodiment, at least one HCV protease inhibitor is a compound of structural Formula XXI:



or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XXI:

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},

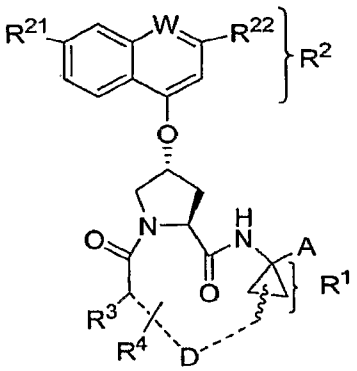
or R_{20} is Het or (lower alkyl)-Het, both optionally mono-, di- or tri- substituted with R_{21},

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} araikyl 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, at least one HCV protease inhibitor is a compound of structural Formula XXII:



or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XXII:

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;

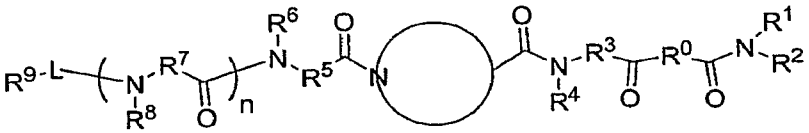
R^3 is hydroxy, NH_2, or a group of formula -NH-R^{31}, wherein R^{31} is $C_{6 \text{ or } 10}$ aryl, heteroaryl, -C(O)-R^{32}, -C(O)-NHR^{32} or -C(O)-OR^{32}, wherein R^{32} is C_{1-6} alkyl or C_{3-6} cycloalkyl;

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_{1-8} 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, at least one HCV protease inhibitor is a compound of structural Formula XXIII:



or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XXIII:

R^0 is a bond or difluoromethylene;

R^1 is hydrogen;

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:

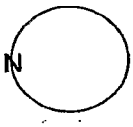
optionally substituted (1, 1- or 1,2-)cycloalkylene; or

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

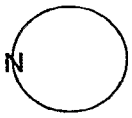
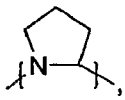
cyclic group or an optionally substituted aromatic group, and wherein the methylene or ethylene is further optionally substituted with an aliphatic group substituent; or;

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

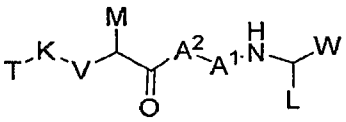


is substituted monocyclic azaheterocyclyl or optionally substituted multicyclic azaheterocyclyl, or optionally substituted multicyclic azaheterocyclenyl wherein the unsaturatation is in the ring distal to the ring bearing the R^9-L-(N(R^8)-R^7-C(O)-)$_n$N(R^6)-R^5-C(O)-N moiety and to which the –C(O)-N(R^4)-R^3-C(O)C(O)NR^2R^1 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.

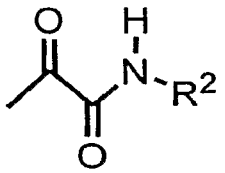
In another embodiment, at least one HCV protease inhibitor is a compound of structural Formula XXIV:



or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XXIV:

W is:



;

m is 0 or 1;

R^2 is hydrogen, alkyl, alkenyl, aryl, aralkyl, aralkenyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkenyl, heteroaryl, or heteroaralkyl; 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, carboxamidoaikyl, 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;

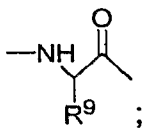
R^8 is hydrogen alkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, aralkanoyl, heterocyclanoyl, heteroaralkanoyl, $-C(O)R^{14}$, $-S0_2R^{14}$, or carboxamido, and is optionally substitituted with 1-3 J groups; or R^8 and Z, together with the atoms to which they are bound,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

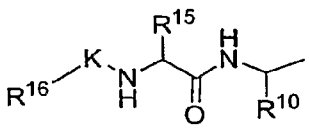
M is alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroaralkyl, optionally substituted by 1-3 J groups, wherein any alkyl carbon atom may be replaced by a heteroatom;

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



;

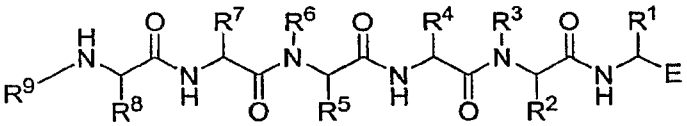
R^{12} is hydrogen, aryl, heteroaryl, cycloalkyl, heterocyclyl, cycloalkylidenyl, or heterocycloalkylidenyl, and is optionally substituted with 1-3 J groups, or a first R^{12} and a second R^{12}, together with the nitrogen to which they are bound, form a mono- or bicyclic ring system optionally substituted 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, at least one HCV protease inhibitor is a compound of structural Formula XXV:



or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XXV:

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;

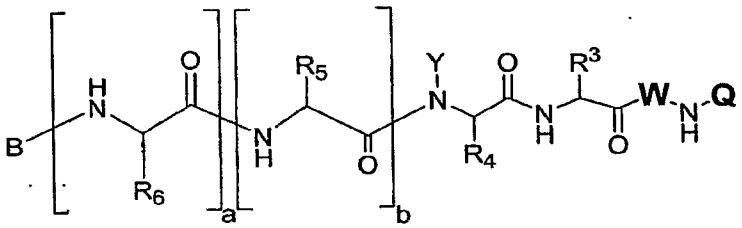
R^7 represent lower alkyl, hydroxydower alkyl, carboxylower alkyl, aryl-iower alkyl, lower cycloalkyl-lower alkyl or lower cycloalkyl;

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, at least one HCV protease inhibitor is a compound of structural Formula XXVI:

P6 P5 P4 P3 P2 P1



or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XXVI:

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;

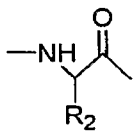
R_5, when present, is C_{1-6} alkyl, or carboxy(lower)alkyl;

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

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

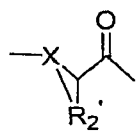
R_3 is C1-10 alkyl; C_{3-10} cycloalkyl;

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

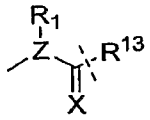
R_2' is C_{3-4} alkylene that joins X to form a 5- or 6-membered ring, said ring optionally substituted with OH; SH; NH2; carboxyl; R_{12}; OR_{12}, SR_{12}, NHR_{12} or $NR_{12}R_{12}$' wherein R_{12} and R_{12}' are independently:

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;

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

R_{13} is C0-NH-R_{14} wherein R_{14} is 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

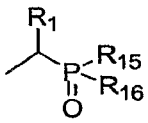
R_{14} is C_6 or C_{10} aryl or C_{7-16} aralkyl optionally substituted with C_{1-6} alkyl, NH_2, OH, SH, halo, carboxyl or carboxy(lower)alkyl or substituted with a further C_{3-7}

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;

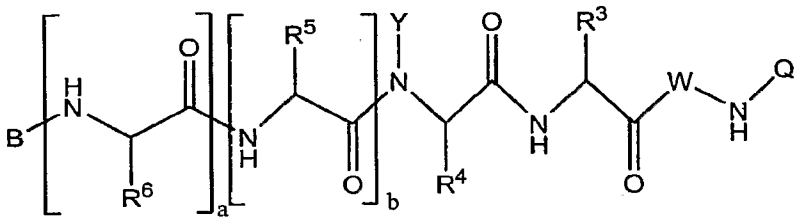
with the proviso that when Z is CH, then R_{13} is not an α-amino acid or an ester thereof;

Q is a phosphonate group of the formula:

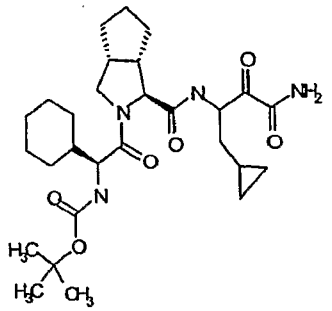
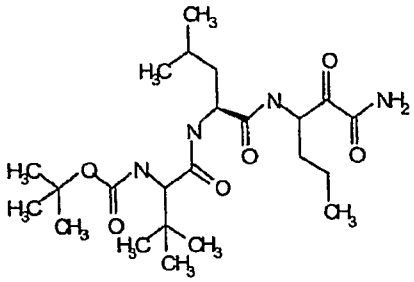
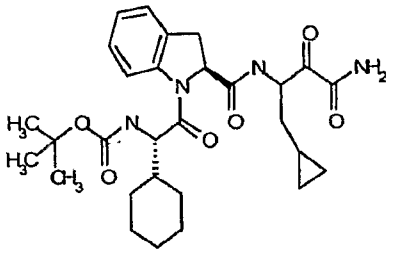
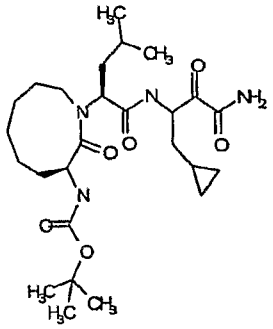
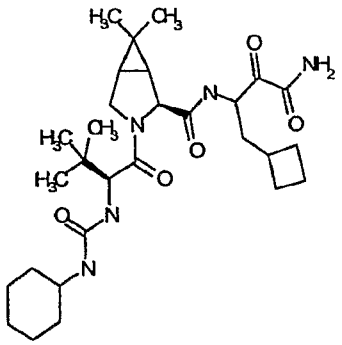
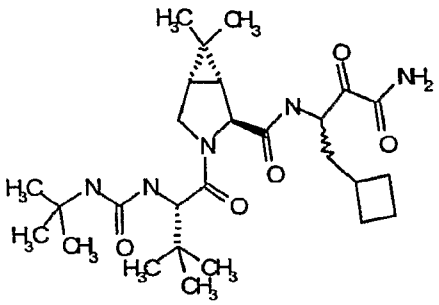
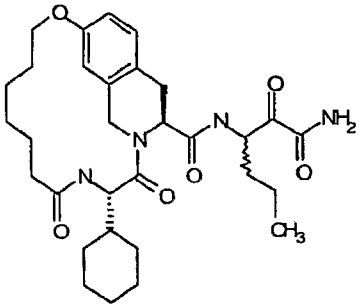
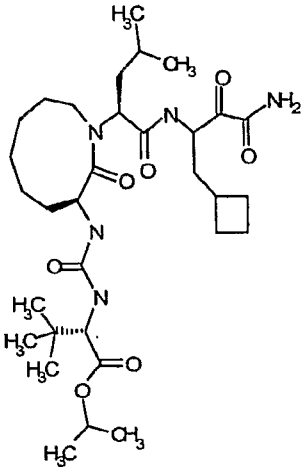
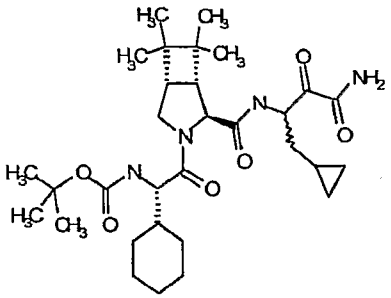
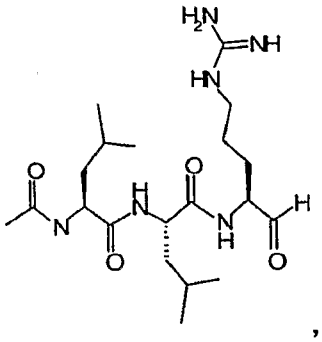
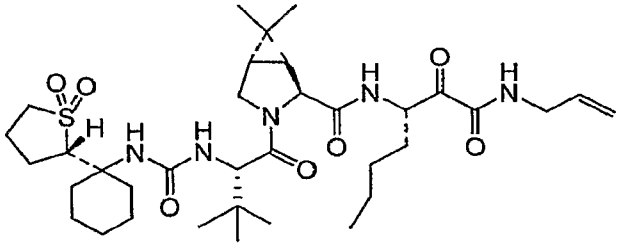


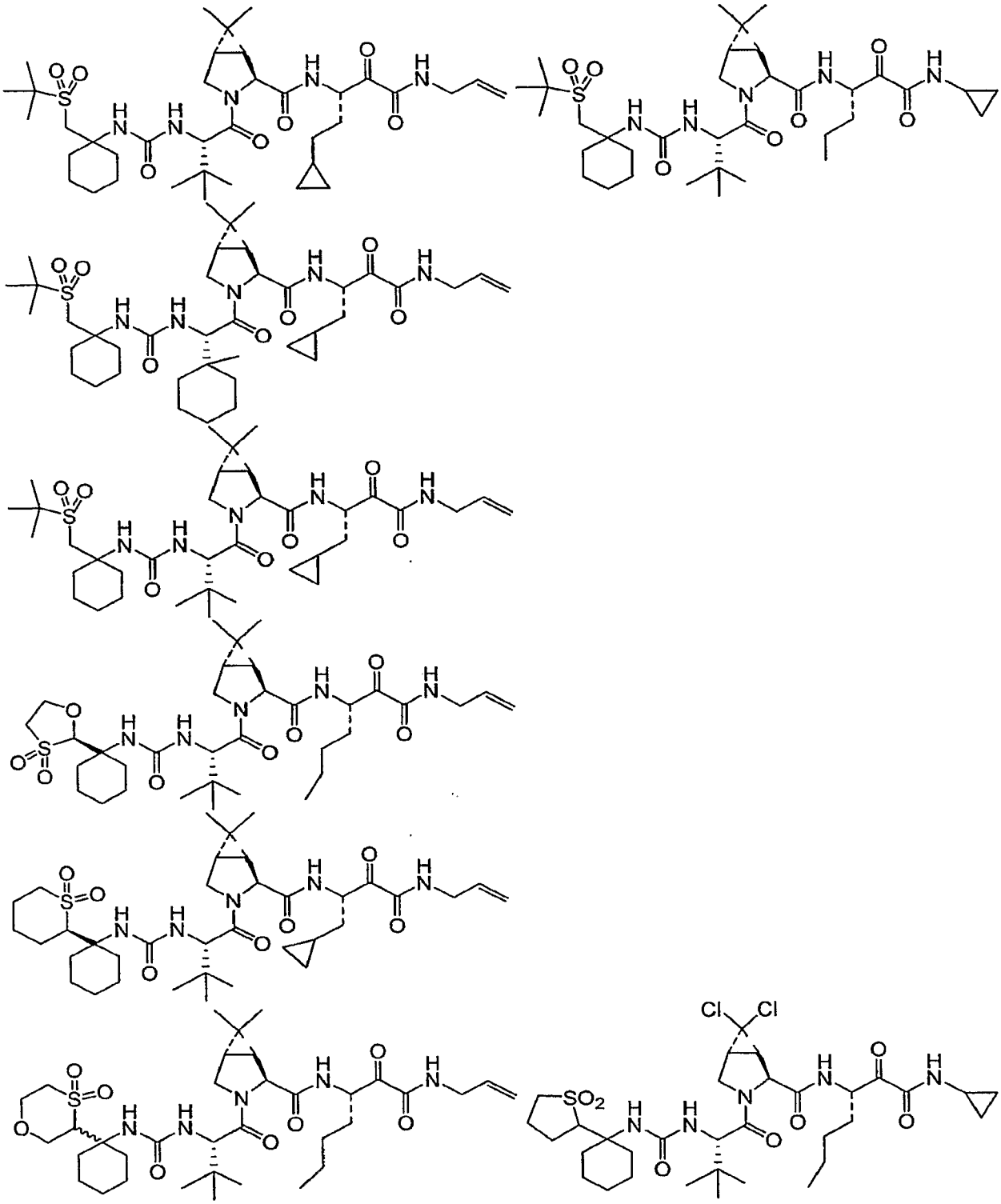
wherein R_{15} and R_{16} are independently C_{6-20} aryloxy; and R_1 is as defined above.

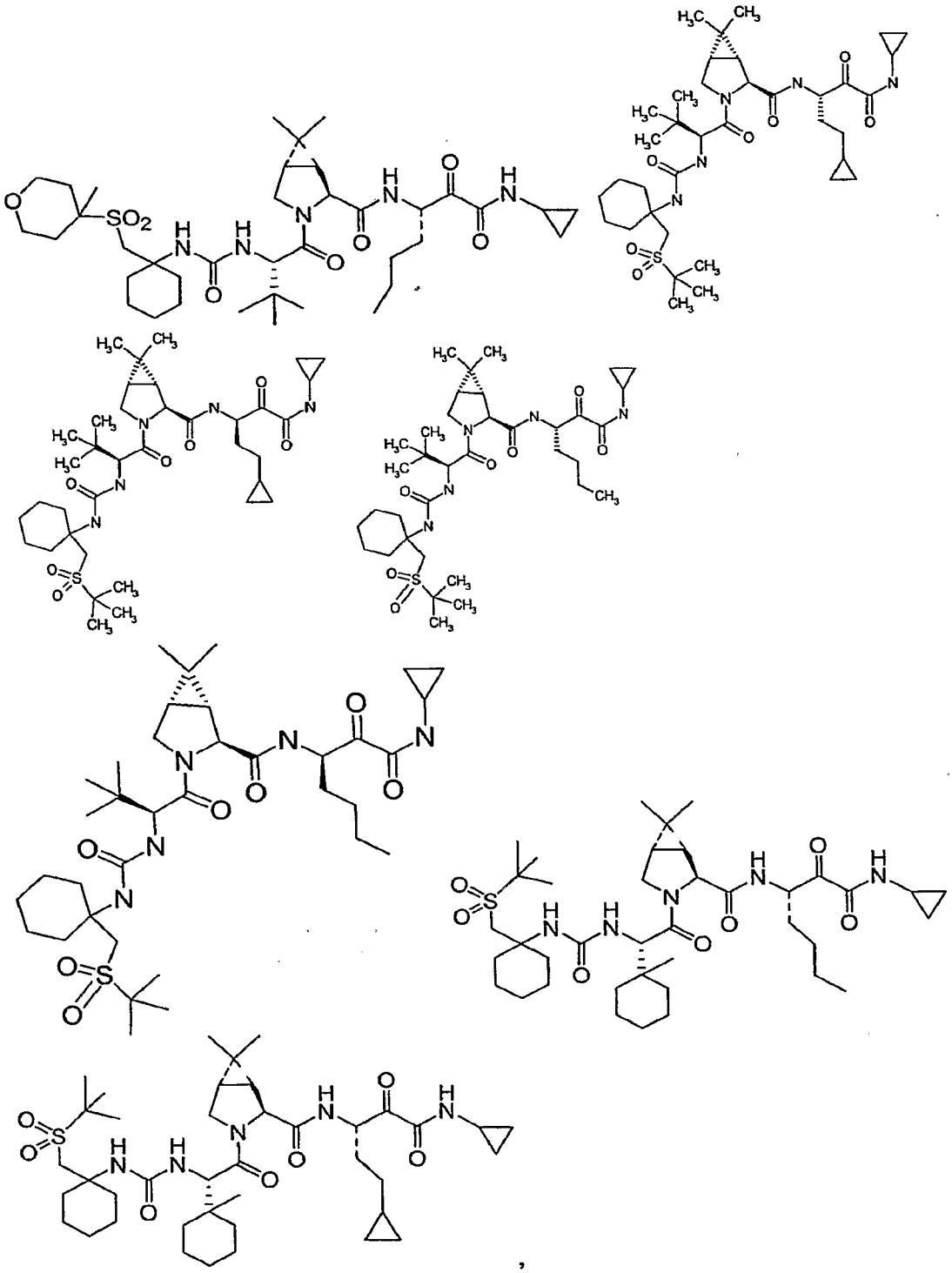
In the above-shown structure of the compound of Formula XXVI, the terms P6, P5, P4, P3, P2 and P1 denote the respective amino acid moieties as is conventionally known to those skilled in the art. Thus, the actual structure of the compound of Formula XXVI is:



In one preferred embodiment, at least one HCV protease inhibitor is selected from the group consisting of:


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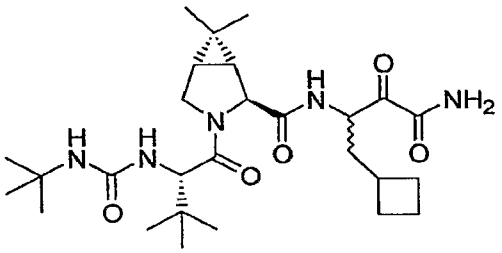


or a pharmaceutically acceptable salt, solvate or ester thereof.

In another preferred embodiment, the present invention provides medicaments and methods using the same comprising, separately or together:

(a) at least one HCV IRES inhibitor; and

(b) at least one HCV protease inhibitor, wherein at least one HCV protease inhibitor is

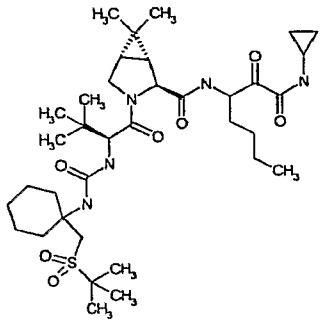


Formula Ia, or a pharmaceutically acceptable salt, solvate or ester thereof;
for concurrent or consecutive administration in treating or ameliorating one or more symptoms of HCV, or disorders associated with HCV in a subject in need thereof.

In yet another preferred embodiment, the present invention provides medicaments and methods using the same comprising, separately or together:

(a) at least one HCV IRES inhibitor; and

(b) at least one HCV protease inhibitor, wherein at least one HCV protease inhibitor is



or a pharmaceutically acceptable salt, solvate or ester thereof;
for concurrent or consecutive administration in treating or ameliorating one or more symptoms of HCV, or disorders associated with HCV in a subject in need thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing summary, as well as the following detailed description, is better understood when read in conjunction with the appended drawings. In the drawings:

FIG. 1 is a schematic illustration of one synthetic protocol for obtaining an exemplary indole containing compound, designated PS102320 (a/k/a SCH 1385147), having IRES inhibitor activity useful for the combinations of the present invention.

FIG. 2 is an alternative schematic illustration of one synthetic protocol for obtaining an exemplary indole containing compound, designated PS102320 (a/k/a SCH 1385147), having IRES inhibitor activity useful for the combinations of the present invention.

FIG. 3 is a schematic illustration of one synthetic protocol for obtaining an exemplary indole containing compound, designated PS102123 (a/k/a SCH 1383646), having IRES inhibitor activity useful for the combinations of the present invention.

FIG. 4 is a schematic illustration of one synthetic protocol for obtaining an exemplary indole containing compound, designated PS102283 (a/k/a SCH 1385145), having IRES inhibitor activity useful for the combinations of the present invention.

FIG. 5 is a graph of the relative inhibition of replicon RNA by HCV IRES inhibitor SCH 1383646 (at a concentration of 0, 0.05, 0.09, 0.187, 0.37, and 0.75 μM) in combination with Formula I (*i.e.*, SCH 446211 (SCH 6)) (at a concentration of 0, 0.09, 0.187, 0.37, 0.75, and 1.5 μM).

FIG. 6 is a graph of the relative inhibition of replicon RNA by Formula I (*i.e.*, SCH 446211 (SCH 6)) (at a concentration of 0, 0.09, 0.187, 0.37, 0.75, and 1.5 μM) in combination with HCV IRES inhibitor SCH 1383646 (at a concentration of 0, 0.05, 0.09, 0.187, 0.37, and 0.75 μM).

DETAILED DESCRIPTION

The present invention provides medicaments, pharmaceutical compositions, pharmaceutical kits, and methods based on combinations comprising, separately or together: (a) at least one HCV IRES inhibitor; (b) at least one HCV protease inhibitor; for concurrent or consecutive administration in treating or ameliorating one or more symptoms of HCV, or disorders associated with HCV in a subject in need thereof.

In one embodiment, the medicament further comprises at least one other therapeutic agent. In a preferred embodiment, at least one other therapeutic agent is an interferon. In one embodiment, at least one other therapeutic agent is ribavirin, levovirin, VP 50406, ISIS 14803, VX 497, Thymosin, Maxamine, or mycophenolate mofetil.

In one embodiment wherein at least one other therapeutic agent is an interferon, the medicament further comprises ribavirin. In another embodiment, at least one other therapeutic agent is an interferon, and at least one other therapeutic agent is ribavirin, levovirin, VP 50406, ISIS 14803, VX 497, Thymosin, Maxamine, or mycophenolate mofetil.

In one embodiment, the interferon is a pegylated interferon. Preferably, the interferon is selected from the group consisting of interferon-alpha, PEG-interferon alpha conjugates, interferon alpha fusion polypeptides, consensus interferon, or a mixture of two or more thereof. Preferably, the interferon is selected from the group consisting of Roferon™, Pegasys™, Intron™, PEG-Intron™, Berofor Alpha™, and Infergen™. In one embodiment, the interferon is administered concurrently or consecutively with at least one HCV IRES inhibitor and at least one HCV protease inhibitor.

HCV IRES Inhibitors:

Non-limiting examples of suitable HCV IRES inhibitors that can be used in the practice of the present invention are disclosed in the following publications and announcements, all the disclosures of which are incorporated herein by reference in their entirety.

Certain non-limiting specific examples of HCV IRES inhibitors useful in the practice of the present invention include: a compound known as I70® from OSI Pharmaceuticals, Heptazyme, the IRES inhibitor (RNA inhibitor) from RiboTargets, the IRES inhibitor from Anadys Pharmaceuticals, the IRES inhibitor from RiboGene (QuestCor) and the thienopyridines reported as possible IRES inhibitors in WO2006019832 A1 (PTC Therapeutics). In addition, McCaffrey *et al., Hepatology*, **38(2)**:503-508 (2003); Jubin, *Curr Opin Mo. Ther,* **3(3)**:278-287 (2001); Mounir, "Symposium on Emerging Therapies for Chronic Viral Hepatitis," October 2-4, 1998,

Montreal, Canada) disclose HCV IRES inhibitors. The disclosures of the above-noted publications are incorporated in their entirety by reference.

According to certain preferred embodiments of the present invention, the HCV IRES inhibitor is selected from one or more of the thienopyridine or indole families of compounds disclosed in one or more of the following patent applications, the disclosure of each of which is incorporated herein its entirety by reference:

thienopyridine family: U.S. Patent Application No. 11/180,779 by Karp et al. published as US 2006/0019976 and International Patent Publication No. WO 2006/019831 (herein "WO '831); and

indole family: U.S. Patent Application No. 11/180,961 by Karp et al. published as US 2006/0223863 and International Patent Publication No. WO 2006/019832 (herein "WO '832); U.S. Patent Application No. 11/331,180 filed January 13, 206 by Karp et al.; U.S. Patent Application No. 11/653,435 filed January 13, 2007 by Karp et al.; U.S. Patent Application No. 11/653,450 filed January 16, 2007 by Karp et al., U.S. Patent Application No. 60/758,527 filed January 13, 2006 by Karp; U.S. Patent Application No. 11/653,436 filed January 13, 2007 by Karp; and U.S. Patent Application No. 11/653,448 filed January 16, 2007 by Karp.

Techniques for preparing thienopyridine compounds useful for the present invention are provided by the synthetic schemes designated A-S shown in WO '832 and discussed on page 112 through 124 which pages are incorporated herein specifically by reference.

Techniques for preparing variously derivitized indole compounds useful for the present invention are provided in the schemes on pages 350 to 381 of WO '831 incorporated specifically by reference herein. In particular, Scheme K on page 359 of WO '831 shows methods for preparing suitable indole starting materials, for example Compound 1 of FIG. 1 herein. Scheme K of WO '831 in conjunction with procedures illustrated in Scheme D, page 352 of WO '831 and Scheme H5 → r 1x compound, page 356 of WO '831, illustrates procedure for preparing more complex indole precursors, for example Compound 4 of FIG. 2 herein.

FIGS. 1 and 2 of the present application provide detailed synthetic schemes for preparing a member of the indole family i.e., PS102320 (a/k/a SCH 1385147), presently preferred for use according to the present invention.

In one preferred embodiment, at least one HCV IRES inhibitor is PS 102320 (a/k/a SCH 1385147, described above), PS 102123 (a/k/a SCH 1383646, described above), PS 102283 (a/k/a SCH 1385145, described above), or a pharmaceutically acceptable salt, solvate, or ester thereof. In another preferred embodiment, at least one HCV IRES inhibitor is SCH135147, or a pharmaceutically acceptable salt, solvate, or ester thereof. In another preferred embodiment, at least one HCV IRES inhibitor is SCH1385145, or a pharmaceutically acceptable salt, solvate, or ester thereof.

In one embodiment, at least one HCV IRES inhibitor is, I70®, or RiboTargets RNA inhibitor. In one embodiment, at least one HCV IRES inhibitor is I70®.

A therapeutically effective amount of HCV IRES inhibitor is an amount effective to inhibit HCV translation. Similarly, a therapeutically effective amount of anti-HCV agent which is an indole (*e.g.*, as described in WO 2006/019831) or a thienopyridine (*e.g.*, as described in WO 2006/019832) is an amount effective against HCV to produce the desired therapeutic or ameliorative effect in a suitable human subject. The effect of such compound can be determined by analyzing (1) the presence of HCV-RNA; (2) the presence of anti-HCV antibodies; (3) the level of serum alanine amino transferase (ALT) and aspartate aminotransferase (AST) (ALT and AST are elevated in patients chronically infected with HCV); or (4) hepatocellular damage or any combination thereof. The precise effective amount for a subject will depend upon the subjects's body weight, size and health. Therapeutically effective amounts for a given patient can be determined by routine experimentation that is within the skill and judgment of the clinician.

For any compound, the therapeutically effective amount can be estimated initially either in cell culture assays or in relevant animal models, such as marmosets and tamarins. The animal model may also be used to determine the appropriate concentration range and route of administration. Such information can be then be used to determine useful doses and routes for administration in humans. Therapeutic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g. ED_{50} (the dose therapeutically effective in 50% of the population) and LD_{50} (the dose lethal to 50% of the population). The dose ratio between therapeutic and toxic effects is the

therapeutic index, and it can be expressed as the ratio, LD_{50}/ED_{50}. Pharmaceutical compositions that exhibit large therapeutic indices are preferred. The dosage contained in such compositions is preferably within a range of circulating concentrations that include an ED_{50} with little or no toxicity. The dosage may vary within this range depending upon the dosage from employed, sensitivity of the patient, and the route of administration.

More specifically, the concentration-biological effect relationships observed with regard to the compound(s) of the present invention indicate an initial target plasma concentration ranging from approximately 0.1 µg/mL to approximately 50 µg/mL, more preferably from approximately 5 µg/mL to approximately 50 µg/mL, even more preferably from approximately 10 µg/mL to approximately 25 µg/mL. To achieve such plasma concentrations, the compounds of the invention may be administered at doses that vary from 0.1 µg to 100,000 mg, depending upon the route of administration. Guidance as to particular dosages and methods of delivery is provided in the literature and is generally available to practitioners in the art. In general the dose will be in the range of about 1mg/day to about 10g/day, or about 0.1g to about 3g/day, or about 0.3g to about 3g/day, or about 0.5g to about 2g/day, in single, divided, or continuous doses for a patient weighing between about 40 to about 100 kg (which dose may be adjusted for patients above or below this weight range, particularly children under 40 kg).

The exact dosage will be determined by the practitioner, in light of factors related to the subject that requires treatment. Dosage and administration are adjusted to provide sufficient levels of the active agent(s) or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, general health of the subject, age, weight, and gender of the subject, diet, time, and frequency of administration, drug combination(s), reaction sensitivities, and tolerance/response to therapy. Long-acting pharmaceutical compositions may be administered every 3 to 4 days, every week, or once every two weeks depending on half-life and clearance rate of the particular formulation.

HCV Protease Inhibitors:

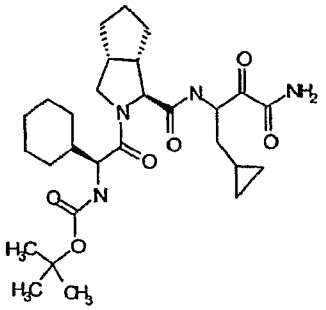
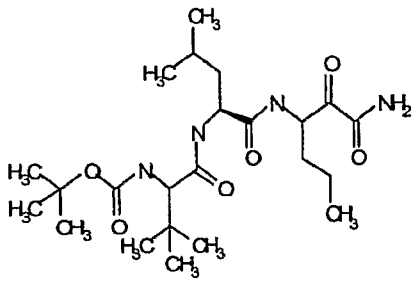
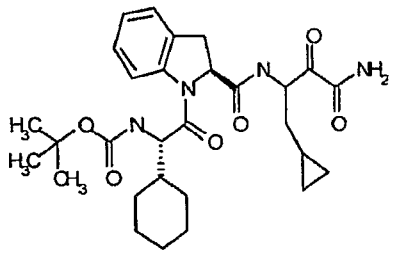
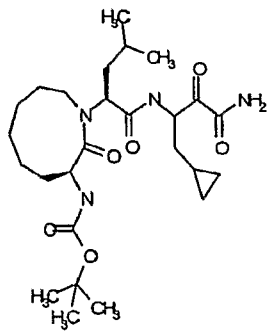
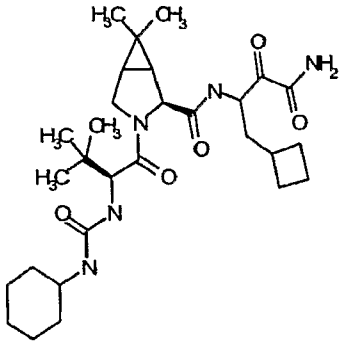
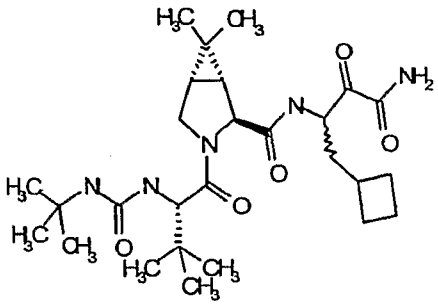
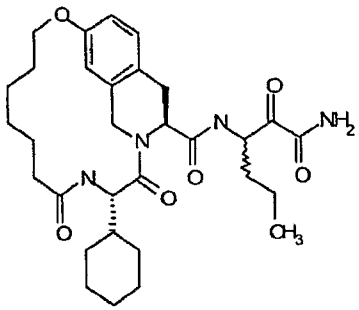
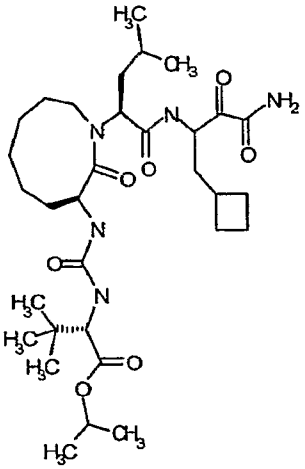
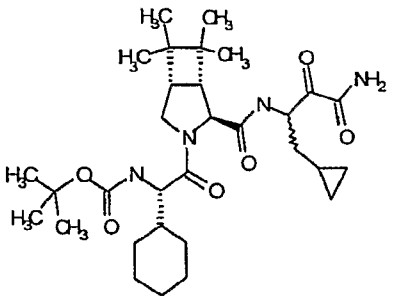
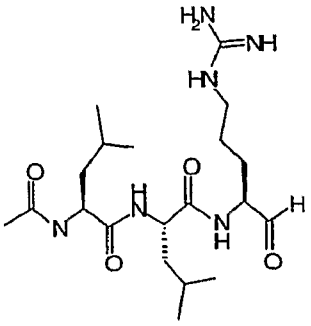
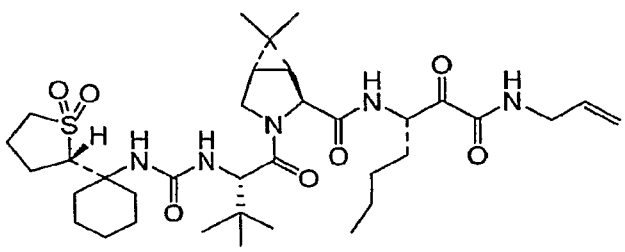
In one embodiment, at least one HCV protease inhibitor is selected from the group of HCV protease inhibitors referred to in the following documents (which are incorporated by reference herein): US20040048802A1, US20040043949A1, US20040001853A1, US20030008828A1, US20020182227A1, US20020177725A1, US20020150947A1, US20050267018A1, US20020034732A1, US20010034019A1, US20050153877A1, US20050074465A1, US20050053921A1, US20040253577A1, US20040229936A1, US20040229840A1, US20040077551A1, EP1408031A1, WO9837180A2, US6696281B1, JP11137252A, WO0111089A1, US6280940B1, EP1106702A1, US20050118603A1, JP2000007645A, WO0053740A1, WO0020400A1, WO2004013349A2, WO2005027871A2, WO2002100900A2, WO0155703A1, US20030125541A1, US20040039187A1, US6608027B1, US20030224977A1, WO2003010141A2, WO2003007945A1, WO2002052015A2, WO0248375A2, WO0066623A2, WO0009543A2, WO9907734A2, US6767991B1, US20030187018A1, US20030186895A1, WO2004087741A1, WO2004039970A1, WO2004039833A1, WO2004037855A1, WO2004030670A1, US20040229818A1, US20040224900A1, WO2005028501A1, WO2004103996A1, WO2004065367A1, WO2004064925A1, WO2004093915A1, WO2004009121A1, WO2003066103A1, WO2005034850A2, WO2004094452A2, WO2004015131A2, WO2003099316A1, WO2003099274A1, WO2003053349A2, WO2002060926A2, WO0040745A1, US6586615B1, WO2002061048A2, WO0248157A2, WO0248116A2, WO2005017125A2, WO0022160A1, US20060051745A1, WO2004021871A2, WO2004011647A1, WO9816657A1, US5371017A, WO9849190A2, US5807829A, WO0005243A2, WO0208251A2, WO2005067437A2, WO9918856A1, WO0004914A1, WO0212543A2, WO9845040A1, WO0140262A1, WO0102424A2, WO0196540A2, WO0164678A2, US5512391A, WO0218369A2, WO9846597A1, WO2005010029A1, WO2004113365A2, WO2004093798A2, WO2004072243A2, WO9822496A2, WO2004046159A1, JP11199509A, WO2005012288A1, WO2004108687A2, WO9740168A1, US20060110755A1, WO2002093519A2, US6187905B1, WO2003077729A2, WO9524414A1, WO2005009418A2, WO2004003000A2, US20050037018A1, WO9963998A1, WO0063444A2, WO9938888A2, WO9964442A1, WO0031129A1, WO0168818A2, WO9812308A1, WO9522985A1, WO0132691A1, WO9708304A2, WO2002079234A1,

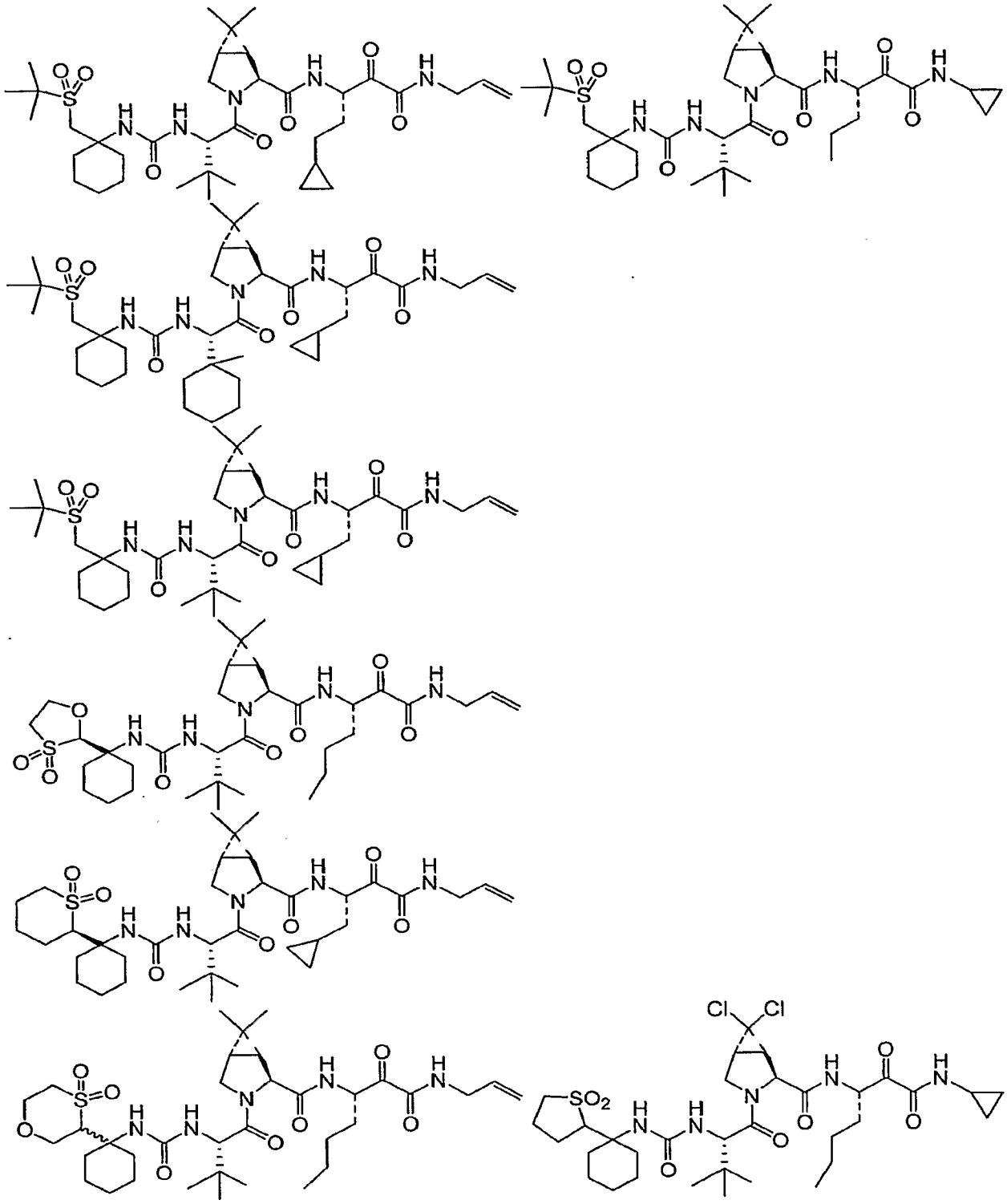
JP10298151A, JP09206076A, JP09009961A, JP2001103993A, JP11127861A, JP11124400A, JP11124398A, WO2003051910A2, WO2004021861A2, WO9800548A1, WO2004026896A2, WO0116379A1, US5861297A, WO2004007512A2, WO2004003138A2, WO2002057287A2, WO2004009020A2, WO2004000858A2, WO2003105770A2, WO0114517A1, WO9805333A1, US6280728B1, EP1443116A1, US20040063911A1, WO2003076466A1, WO2002087500A2, WO0190121A2, WO2004016222A2, WO9839030A1, WO9846630A1, WO0123331A1, WO9824766A1, US6168942B1, WO0188113A2, WO2005018330A1, WO2005003147A2, WO9115596A1, WO9719103A1, WO9708194A1, WO2002055693A2, WO2005030796A1, WO2005021584A2, WO2004113295A1, WO2004113294A1, WO2004113272A1, WO2003062228A1, WO0248172A2, WO0208198A2, WO0181325A2, WO0177113A2, WO0158929A1, WO9928482A2, WO9743310A1, WO9636702A2, WO9635806A1, WO9635717A2, US6326137B1, US6251583B1, US5990276A, US5759795A, US5714371A, US6524589B1, WO0208256A2, WO0208187A1, WO2003062265A2, US7012066B2, JP07184648A, JP06315377A, WO2002100851A2, WO2002100846A1, WO0039348A1, JP06319583A, JP11292840A, JP08205893A, WO0075338A2, WO0075337A1, WO2003059384A1, WO2002063035A2, WO2002070752A1, US6190920B1, WO2002068933A2, WO0122984A1, JP04320693A, JP2003064094A, WO0179849A2, WO0006710A1, WO0001718A2, WO0238799A2, WO2005037860A2, WO2005035525A2, WO2005025517A2, WO2005007681A2, WO2003035060A1, WO2003006490A1, WO0174768A2, WO0107027A2, WO0024725A1, WO0012727A1, WO9950230A1, WO9909148A1, WO9817679A1, WO9811134A1, WO9634976A1, WO2003087092A2, WO2005028502A1, WO 2004/052885 A1, US5837464A, DE20201549U1, WO2003090674A2, WO9727334A1, WO0034308A2, US6127116A, US20030054000A1, JP2001019699A, US6596545B1, US6329209B1, IT1299179, CA2370400, KR2002007244, KR165708, KR2000074387, KR2000033010, KR2000033011, KR2001107178, KR2001107179, ES2143918, KR2002014283, KR149198, KR2001068676.

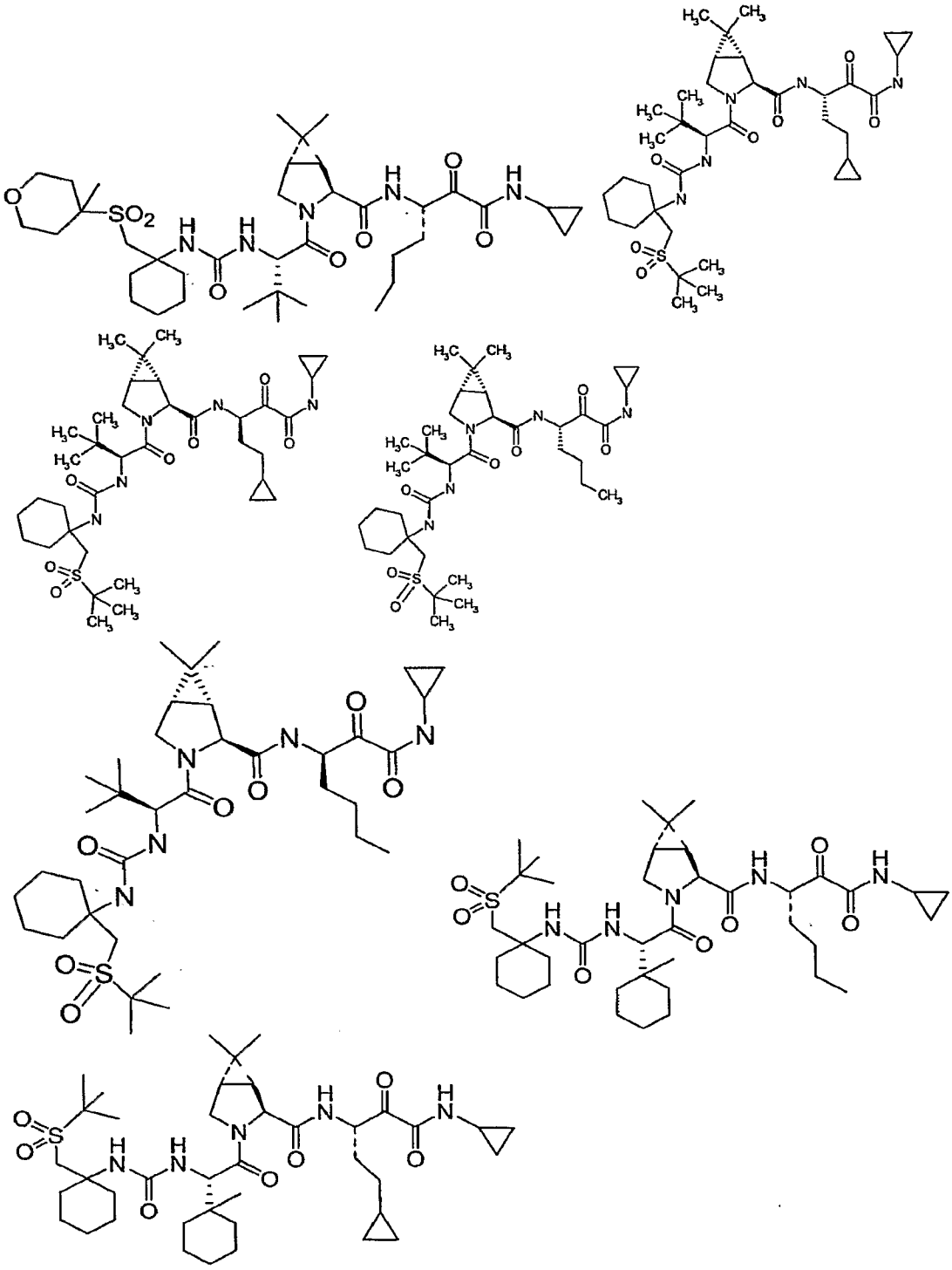
In one embodiment, at least one HCV protease inhibitor is selected from the group consisting of compounds of Formula I to XXVI detailed above or a

pharmaceutically acceptable salt, solvate or ester thereof.

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


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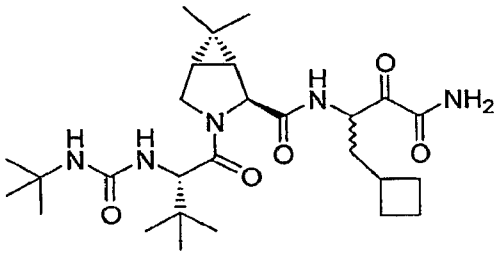
or a pharmaceutically acceptable salt, solvate or ester thereof.

In a preferred embodiment, at least one HCV protease inhibitor is a compound of Formula I, Formula XIV, or a pharmaceutically acceptable salt, solvate or ester thereof.

In a preferred embodiment, the present invention provides medicaments and methods using the same comprising, separately or together:

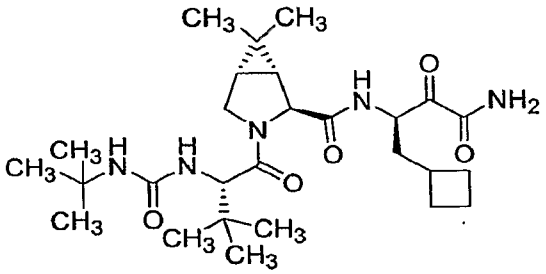
(a) at least one HCV IRES inhibitor; and

(b) at least one HCV protease inhibitor, wherein at least one HCV protease inhibitor is

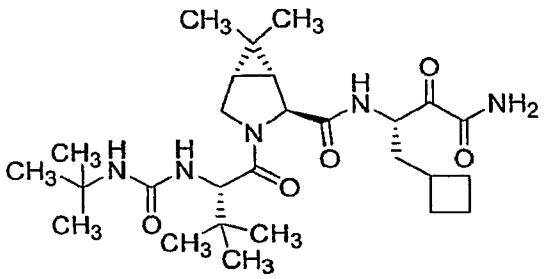


Formula Ia, or a pharmaceutically acceptable salt, solvate or ester thereof; for concurrent or consecutive administration in treating or ameliorating one or more symptoms of HCV, or disorders associated with HCV in a subject in need thereof.

In another preferred embodiment, the present invention provides at least one HCV protease inhibitor is



Formula Ib,



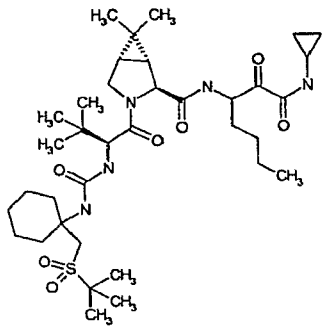
Formula Ic,

or a pharmaceutically acceptable salt, solvate or ester thereof.

In yet another embodiment, the present invention provides medicaments and methods using the same comprising, separately or together:

(a) at least one HCV IRES inhibitor; and

(b) at least one HCV protease inhibitor, wherein at least one HCV protease inhibitor is



or a pharmaceutically acceptable salt, solvate or ester thereof;

for concurrent or consecutive administration in treating or ameliorating one or more symptoms of HCV, or disorders associated with HCV in a subject in need thereof.

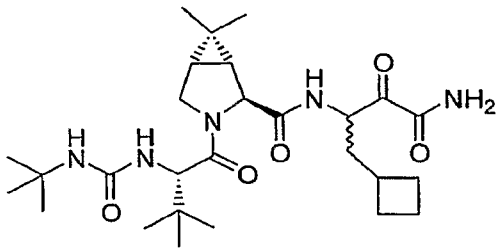
In one preferred embodiment, at least one HCV protease inhibitor is administered at a dosage range of about 100 to about 3600 mg per day (*e.g.*, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, 1000 mg, 1050 mg, 1100 mg, 1150 mg, 1200 mg, 1250 mg, 1300 mg, 1350 mg, 1400 mg, 1450 mg, 1500 mg, 1550 mg, 1600 mg, 1650 mg, 1700 mg, 1750 mg, 1800 mg, 1850 mg, 1900 mg, 1950 mg, 2000 mg, 2050 mg, 2100 mg, 2150 mg, 2200 mg, 2250 mg, 2300 mg, 2350 mg, 2400 mg, 2450 mg, 2500 mg, 2550 mg, 2600 mg, 2650 mg, 2700 mg, 2750 mg, 2800 mg, 2850 mg, 2900 mg, 2950 mg, 3000 mg, 3050 mg, 3100 mg, 3150 mg, 3200 mg, 3250 mg, 3300 mg, 3350 mg, 3400 mg,

3450 mg, 3500 mg, 3550 mg, 3600 mg per day). In one preferred embodiment, at least one HCV protease inhibitor is administered at a dosage range of about 400 mg to about 2500 mg per day. Note that the dosage of HCV protease inhibitor may be administered as a single dose (*i.e.*, QD) or divided over 2-4 doses (*i.e.*, BID, TID, or QID) per day. Preferably, at least one HCV protease inhibitor is administered orally.

In one embodiment, where at least one HCV protease inhibitor is selected from the group consisting of a compound of Formula Ia, Ib, or Ic, or a pharmaceutically acceptable salt, solvate, or ester thereof, the preferred dosage range is about 400 mg to 2400 mg per day. In one preferred embodiment, where at least one HCV protease inhibitor is selected from the group consisting of a compound of Formula Ia, Ib, or Ic, or a pharmaceutically acceptable salt, solvate, or ester thereof, the dosage is about 1200 mg per day administered as about 400 mg TID. In another preferred embodiment, where at least one HCV protease inhibitor is selected from the group consisting of a compound of Formula Ia, Ib, or Ic, or a pharmaceutically acceptable salt, solvate, or ester thereof, the dosage is about 800 mg, 1600 mg, or 2400 mg per day administered as about 800 mg QD, BID, or TID, respectively.

Non-limiting examples of suitable HCV protease inhibitors of Formula I and methods of making the same are disclosed in WO 2003/062265 at page 48 through page 75, incorporated herein by reference.

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

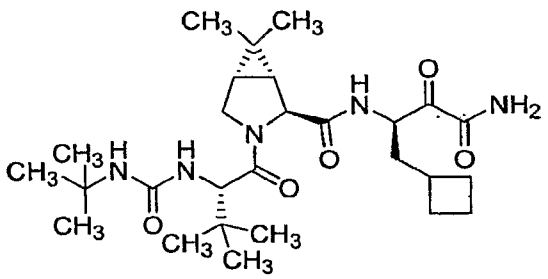


Formula Ia

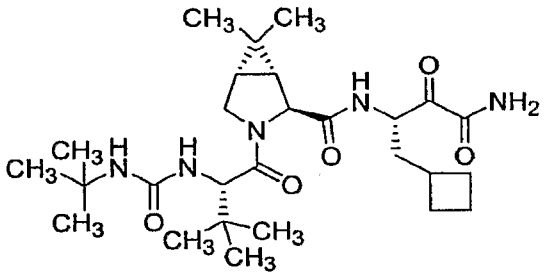
and pharmaceutically acceptable salts or solvates thereof, disclosed in U.S. Patent No. 7,012,066 as Example XXIV, on columns 448-451, which is incorporated herein by reference.

The compound of formula Ia has been separated into its isomer/diastereomers of Formulas Ib and Ic, as disclosed in US2005/0249702

published November 10, 2005. In one embodiment, at least one 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 U.S. Patent No. 6,894,072, granted May 17, 2005, col. 5, lines 54 through col. 49, line 48, at 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 Publication Ser. No. 2005/0119168, page 3, [0024], through page 215, paragraph [0833], incorporated herein by reference.

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.

Non-limiting examples of suitable compounds of Formula VII, VIII, and IX as well as methods of making the same are disclosed in International Patent Publication WO2005/051980 and in U.S. Patent Publication 2005/0164921 at page 3, paragraph [0026] through page 113, paragraph [0271], incorporated herein by reference.

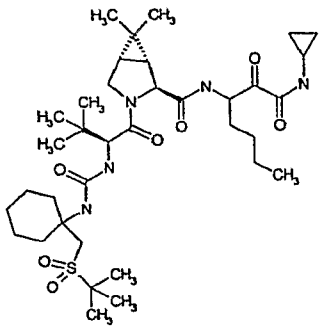
Non-limiting examples of suitable compounds of Formula X and methods of making the same are disclosed in International Patent Publication WO2005/085275 and in U.S. Patent Publication 2005/0267043 at page 4, paragraph [0026] through page 519, paragraph [0444], incorporated herein by reference.

Non-limiting examples of suitable compounds of Formula XI and methods of making the same are disclosed in International Patent Publication WO2005/087721 and in U.S. Patent Publication 2005/0288233 at page 3, paragraph [0026] through page 280, paragraph [0508], incorporated herein by reference.

Non-limiting examples of suitable compounds of Formula XII and methods of making the same are disclosed in International Patent Publication WO2005/087725 and in U.S. Patent Publication 2005/0245458 at page 4, paragraph [0026] through page 194, paragraph [0374], incorporated herein by reference.

Non-limiting examples of suitable compounds of Formula XIII and methods of making the same are disclosed in International Patent Publication WO2005/085242 and in U.S. Patent Publication 2005/0222047 at page 3, paragraph [0026] through page 209, paragraph [0460], incorporated herein by reference.

Non-limiting examples of suitable compounds of Formula XIV and methods of making the same are disclosed in International Patent Publication WO2005/087731 at page 8, line 20 through page 683, line 6, incorporated herein by reference. In particular, the preparation of such compounds including the following structure referred to in International Patent Publication WO2005/087731 as Compound 484



can be found on page 299, Example 792 to page 355, Example 833, incorporated herein by reference.

Non-limiting examples of suitable compounds of Formula XV and methods of making the same are disclosed in International Patent Publication WO2005/058821 and in U.S. Patent Publication 2005/0153900 at page 4, paragraph [0028] through page 83, paragraph [0279], incorporated herein by reference.

Non-limiting examples of suitable compounds of Formula XVI and methods of making the same are disclosed in International Patent Publication WO2005/087730 and in U.S. Patent Publication 2005/0197301 at page 3, paragraph [0026] through page 156, paragraph [0312], incorporated herein by reference.

Non-limiting examples of suitable compounds of Formula XVII and methods of making the same are disclosed in International Patent Publication WO2005/085197 and in U.S. Patent Publication 2005/0209164 at page 3, paragraph [0026] through page 87, paragraph [0354], incorporated herein by reference.

Non-limiting examples of suitable compounds of Formula XVIII and methods of making the same are disclosed in U.S. Patent Publication 2006/0046956, at page 4, paragraph [0024] through page 50, paragraph [0282], incorporated incorporated herein by reference.

Non-limiting examples of suitable compounds of Formula XIX and methods of making the same are disclosed in International Patent Publication WO2005/113581 and in U.S. Patent Publication 2005/0272663 at page 3, paragraph [0026] through page 76, incorporated herein by reference.

Non-limiting examples of suitable compounds of Formula XX and methods of making the same are disclosed in International Patent Publication WO 2000/09558 at page 4, line 17 through page 85, incorporated herein by reference.

Non-limiting examples of suitable compounds of Formula XXI and methods of

making the same are disclosed in International Patent Publication WO 2000/09543 at page 4, line 14 through page 124, incorporated herein by reference.

Non-limiting examples of suitable compounds of Formula XXII and methods of making the same are disclosed in International Patent Publication WO 2000/59929 and in U.S. Patent No. 6,608,027, at col. 65, line 65 through col. 141, line 20, each incorporated herein by reference.

Non-limiting examples of suitable compounds of Formula XXIII and methods of making the same are disclosed in International Patent Publication WO02/18369 at page 4, line 4 through page 311, incorporated herein by reference.

Non-limiting examples of suitable compounds of Formula XXIV and methods of making the same are disclosed in U.S. Patent Publication No. 2002/0032175, 2004/0266731 and U.S. Patent No. 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.

Non-limiting examples of suitable compounds of Formula XXV and methods of making the same are disclosed in International Patent Publication WO 1998/22496 at page 3 through page 122, incorporated herein by reference.

Non-limiting examples of suitable compounds of Formula XXVI and methods of making the same are disclosed in International Patent Publication WO 1998/17679 at page 5, line 20 through page 108, line 9, incorporated herein by reference.

Medicaments, compositions, and methods

The present invention also provides a pharmaceutical composition comprising a therapeutically effective amount of the medicament and a pharmaceutically acceptable carrier.

The present invention also provides pharmaceutical kits comprising the medicament, in combined or separate unit dosage forms, said forms being suitable for administration of (a) and (b) in effective amounts, and instructions for administering (a) and (b) to treat or ameliorate one or more symptoms associated with HCV infection.

The present invention also provides methods for treating or ameliorating one or more symptoms of HCV, or disorders associated with HCV in a subject in need thereof, comprising administering to the subject an effective amount of the

aforementioned medicament.

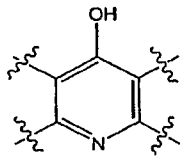
In one embodiment, the administering is oral, intravenous, intrathecal, parenteral, transdermal, or subcutaneous or a combination of two or more thereof.

In one embodiment, the subject is treatment naïve. In another embodiment, the subject is treatment experienced.

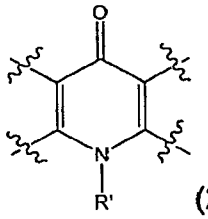
Isomers of the various compounds useful according to the present invention (where they exist), including enantiomers, stereoisomers, diastereomers, rotamers, tautomers and racemates are also contemplated as being part of this invention. The invention includes d and l isomers in both pure form and in 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 compounds of the present invention, whether crystalline or amorphous, also are contemplated as being part of this invention. The (+) isomers of the present compounds are preferred compounds of 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 compounds of this invention 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 compounds of the invention 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).

The compounds useful for the present invention 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 compounds of the various formulae of the present invention may be formed, for example, by reacting a compound of the present invention 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.

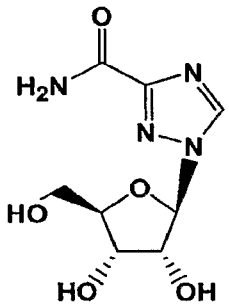
In such esters, unless otherwise specified, any alkyl moiety present preferably contains from 1 to 18 carbon atoms, particularly from 1 to 6 carbon atoms, more particularly from 1 to 4 carbon atoms. Any cycloalkyl moiety present in such esters preferably contains from 3 to 6 carbon atoms. Any aryl moiety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

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

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

In yet another embodiment, the compositions of the invention may be used for the treatment of HCV in humans in combination with one or more antiviral and/or immunomodulatory agents. Examples of such antiviral and/or immunomodulatory agents include intron, pegylated intron, ribavirin and the like. Illustrative examples include, but are not limited to, Ribavirin ((formula L, 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), 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).



Formula L

The HCV protease inhibitor and HCV protease inhibitor combination-comprising composition 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 in accordance with the methods of the present invention. 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 to15 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 compositions and combinations of the present invention can be useful for treating subjects of any HCV genotype. 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 r egions 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).

In one embodiment, a preferred dosage for the administration of a composition of the present invention is about 0.001 to 500 mg/kg of body weight/day of a composition of the present invention or a pharmaceutically acceptable salt or ester thereof. An especially preferred dosage is about 0.01 to 25 mg/kg of body weight/day of a composition of the present invention or a pharmaceutically acceptable salt or ester thereof.

"Effective amount" or "therapeutically effective amount" is meant to describe an amount of a medicament, pharmaceutical composition or combination of the invention effective against HCV to produce the desired therapeutic or ameliorative effect in a suitable human subject.

For administration of pharmaceutically acceptable salts of the compounds, the weights indicated above refer to the weight of the acid equivalent or the base equivalent of the therapeutic compound derived from the salt.

When administering a combination therapy to a patient in need of such administration, the therapeutic agents in the combination, or a pharmaceutical composition or compositions comprising the therapeutic agents, may be administered in any order such as, for example, sequentially, concurrently, together, simultaneously and the like. The amounts of the various actives in such combination therapy may be different amounts (different dosage amounts) or same amounts (same dosage amounts). Thus, for illustration purposes, a compound of the present invention and an additional therapeutic agent may be present in fixed amounts (dosage amounts) in a single dosage unit (e.g., a capsule, a tablet and the like).

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described herein and the other pharmaceutically active agent or treatment within its dosage range. Compounds of

the present invention may also be administered sequentially with known therapeutic agents when a combination formulation is inappropriate. The invention is not limited in the sequence of administration; compounds/compositions of the present invention may be administered either prior to or after administration of the known therapeutic agent. Such techniques are within the skills of persons skilled in the art as well as attending physicians.

The pharmacological properties of the compositions of this invention may be confirmed by a number of pharmacological assays for measuring HCV viral activity, such as are well know to those skilled in the art.

While it is possible for the active ingredient to be administered alone, it is preferable to present it as a pharmaceutical composition. The compositions of the present invention comprise at least one active ingredient, as defined above, together with one or more acceptable carriers, adjuvants or vehicles thereof and optionally other therapeutic agents. Each carrier, adjuvant or vehicle must be acceptable in the sense of being compatible with the other ingredients of the composition and not injurious to the mammal in need of treatment.

Accordingly, this invention also relates to pharmaceutical compositions comprising at least one compound utilized in the presently claimed methods, or a pharmaceutically acceptable salt or ester thereof and at least one pharmaceutically acceptable carrier, adjuvant or vehicle.

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

forms) and the like. Moreover, when desired or needed, suitable binders, lubricants, disintegrating agents and coloring agents may also be incorporated in the mixture. Powders and tablets may be comprised of from about 5 to about 95 percent inventive composition. Surfactants may be present in the pharmaceutical formulations of the present invention in an amount of about 0.1 to about 10% by weight or about 1 to about 5% by weight. Acidifying agents may be present 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.

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

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

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

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

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

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

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

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

Preferably the compound is administered orally, intravenously, intrathecally or subcutaneously, parenteraly, transdermally or any combination of such methods.

Preferably, the pharmaceutical preparation 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.

Some useful terms are described below:

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

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

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

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

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

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

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

more preferably from about 3 to about 10% by weight, even more preferably from about 3 to about 6% by weight.

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

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

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

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

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

For preparing pharmaceutical compositions from the combinations described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 95 percent active ingredient. Suitable solid carriers are known in the art, e.g., magnesium carbonate, magnesium stearate, talc, sugar or lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration. 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 term pharmaceutical composition is also intended to encompass both the bulk composition and individual dosage units comprised of more than one (e.g., two) pharmaceutically active agents such as, for example, a compound of the present invention and an additional agent selected from the lists of the additional agents described herein, along with any pharmaceutically inactive excipients. The bulk composition and each individual dosage unit can contain fixed amounts of the afore-said "more than one pharmaceutically active agents". 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, pills and the like. Similarly, the herein-described method of treating a subject by administering a pharmaceutical composition of the present invention is also intended to encompass the administration of the afore-said bulk composition and individual dosage units.

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. 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.

Preferably the composition is administered orally, intravenously or subcutaneously.

Preferably, the pharmaceutical preparation 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 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 composition(s) of the present invention preferably are administered in an amount effective to reduce the concentration of HCV RNA per milliliter of plasma to a level of less than about 29 IU/mL. The term "concentration of less than 29 International Units of HCV RNA per milliliter of plasma (29 IU/mL)" in the context of the present invention means that there are fewer than 29 IU/ml of HCV RNA, which translates into fewer than 100 copies of HCV-RNA per ml of plasma of the patient as measured by quantitative, multi-cycle reverse transcriptase PCR methodology. HCV-RNA is preferably measured in the present invention by research-based RT-PCR methodology well known to the skilled clinician. This methodology is referred to herein as HCV-RNA/qPCR. The lower limit of detection of HCV-RNA is 29 IU/ml or 100 copies/ml. Serum HCV-RNA/qPCR testing and HCV genotype testing will be performed by a central laboratory. See also J. G. McHutchinson et al. (N. Engl. J. Med., 1998, 339:1485-1492), and G. L. Davis et al. (N. Engl. J. Med. 339:1493-1499).

Assay for HCV Protease Inhibitory Activity:

Spectrophotometric Assay: Spectrophotometric assay for the HCV serine protease can be performed on the inventive compounds by following the procedure described by R. Zhang *et al*, *Analytical Biochemistry*, 270 (1999) 268-275, the disclosure of which is incorporated herein by reference. The assay based on the proteolysis of chromogenic ester substrates is suitable for the continuous monitoring of HCV NS3 protease activity. The substrates are derived from the P side of the NS5A-NS5B junction sequence (Ac-DTEDVVX(Nva), where X = A or P) whose C-terminal carboxyl groups are esterified with one of four different chromophoric alcohols (3- or

4-nitrophenol, 7-hydroxy-4-methyl-coumarin, or 4-phenylazophenol). Illustrated below are the synthesis, characterization and application of these novel spectrophotometric ester substrates to high throughput screening and detailed kinetic evaluation of HCV NS3 protease inhibitors.

Materials and Methods:

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

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

Substrate Synthesis and Purification: The synthesis of the substrates is done as reported by R. Zhang *et al*, (*ibid.*) and is initiated by anchoring Fmoc-Nva-OH to 2-chlorotrityl chloride resin using a standard protocol (K. Barlos *et al, Int. J. Pept. Protein Res.*, 37 (1991), 513-520). The peptides are subsequently assembled, using Fmoc chemistry, either manually or on an automatic ABI model 431 peptide synthesizer. The N-acetylated and fully protected peptide fragments are cleaved from the resin either by 10% acetic acid (HOAc) and 10% trifluoroethanol (TFE) in

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

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

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

Protease Assay: HCV protease assays are performed at 30°C using a 200 µl reaction mix in a 96-well microtiter plate. Assay buffer conditions (25 mM MOPS pH 6.5, 300 mM NaCl, 10% glycerol, 0.05% lauryl maltoside, 5 µM EDTA and 5 µM DTT) are optimized for the NS3/NS4A heterodimer (D. L. Sali *et al, ibid.*)). Typically, 150 µl mixtures of buffer, substrate and inhibitor are placed in wells (final concentration of DMSO ≤ 4 % v/v) and allowed to preincubate at 30 °C for

approximately 3 minutes. Fifty µls of prewarmed protease (12 nM, 30°C) in assay buffer, is then used to initiate the reaction (final volume 200 µl).The plates are monitored over the length of the assay (60 minutes) for change in absorbance at the appropriate wavelength (340 nm for 3-Np and HMC, 370 nm for PAP, and 400 nm for 4-Np) using a Spectromax Plus microtiter plate reader equipped with a monochrometer (acceptable results can be obtained with plate readers that utilize cutoff filters). Proteolytic cleavage of the ester linkage between the Nva and the chromophore is monitored at the appropriate wavelength against a no enzyme blank as a control for non-enzymatic hydrolysis. The evaluation of substrate kinetic parameters is performed over a 30-fold substrate concentration range (~6-200 µM). Initial velocities are determined using linear regression and kinetic constants are obtained by fitting the data to the Michaelis-Menten equation using non-linear regression analysis (Mac Curve Fit 1.1, K. Raner). Turnover numbers (k_{cat}) are calculated assuming the enzyme is fully active.

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

The following non-limiting Examples illustrate the present invention.

EXAMPLES

Combination of HCV Protease Inhibitor + HCV IRES Inhibitor

The effect on HCV replicon RNA after treatment with HCV protease inhibitor Formula I, *i.e.*, SCH 446211 (SCH 6), alone or in combination with HCV IRES inhibitor SCH 1383646 was examined.

Replicon RNA response to antiviral agent(s)

Replicon RNA response to antiviral agent(s) was examined using the HCV protease inhibitor Formula I, *i.e.*, SCH 446211 (SCH 6), alone or in combination with HCV IRES inhibitor SCH 1383646.

In brief, replicon cells were seeded at 4000 cells/well in 96-well collagen I-coated Biocoat plates (Becton Dickinson). At 24 hrs post-seeding, replicon cells were treated with the requisite anti-viral agent(s). The final concentration of DMSO was 0.5%, fetal bovine serum was 5%, and G418 (an aminoglycoside used as a selective agent) was 500 µg/ml. Media and anti-viral agent(s) were refreshed daily for 3 days, at which point the cells were washed with PBS and lysed in 1x cell lysis buffer (Ambion cat #8721). The replicon RNA level was measured using real time PCR (Taqman assay). The ampicon was located in NS5B. The PCR primers used were: 5B.2F, ATGGACAGGCGCCCTGA (SEQ ID NO: 1); 5B.2R, TTGATGGGCAGCTTGGTTTC (SEQ ID NO: 2); the probe sequence was FAM-labeled CACGCCATGCGCTGCGG (SEQ ID NO: 3). GAPDH RNA was used as endogenous control and was amplified in the same reaction as NS5B (multiplex PCR) using primers and VIC-labeled probe recommended by the manufacture (PE Applied Biosystem). The real-time RT-PCR reactions were run on ABI PRISM 7900HT Sequence Detection System using the following program: 48°C for 30 min, 95°C for 10 min, 40 cycles of 95°C for 15 sec, 60°C for 1 min. The ΔCT values (CT_{5B}-CT_{GAPDH}) were plotted against drug concentration and fitted to the sigmoid dose response model using SAS (SAS Institute Inc.) or Graphpad PRISM software(Graphpad Software Inc.). The IC_{50} is the drug dose necessary to achieve ΔCT= 1 over the projected baseline. IC_{90} is the drug dose necessary to achieve ΔCT= 3.2 over the baseline. Alternatively, to quantitate the absolute amount replicon RNA, a standard curve was established by including serially diluted T7 transcripts of replicon RNA in the Taqman assay. All Taqman reagents were from PE Applied Biosystem. See also, Malcolm *et al.*, "SCH 503034, a mechanism based inhibitor of hepatitis C virus NS3 protease, suppresses polyprotein maturation and enhances the antiviral activity of alpha interferon in replicon cells," *Antimicrob Agents and Chemother*, **50(3)**:1013-1020 (2006), incorporated herein by reference.

In particular, the relative inhibition of replicon RNA was examined using the following anti-viral agents:

- HCV IRES inhibitor SCH 1383646 (at a concentration of 0, 0.05, 0.09, 0.187, 0.37, and 0.75 μM) in combination with Formula I (*i.e.*, SCH 446211 (SCH 6)) (at a concentration of 0, 0.09, 0.187, 0.37, 0.75, and 1.5 μM).
- Formula I (*i.e.*, SCH 446211 (SCH 6)) (at a concentration of 0, 0.09, 0.187, 0.37, 0.75, and 1.5 μM) in combination with HCV IRES inhibitor SCH 1383646 (at a concentration of 0, 0.05, 0.09, 0.187, 0.37, and 0.75 μM).

The combination of HCV protease inhibitor of Formula I (*i.e.*, SCH 446211 (SCH 6)) with HCV IRES inhibitor SCH 1383646 was found to be more efficacious in inhibiting HCV RNA replication in replicon cells than either HCV IRES inhibitor SCH 1383646 alone (FIG. 5) or HCV protease inhibitor SCH 446211 (SCH 6) alone (FIG. 6).

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

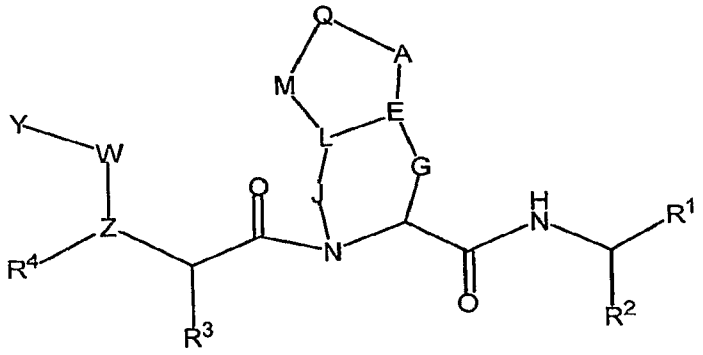
What is claimed is:

1. A medicament comprising, separately or together:

(a) at least one hepatitis C virus (HCV) internal ribosomal entry site (IRES) inhibitor; and

(b) at least one HCV protease inhibitor which is a compound of Formula I to XXVI below:

i.



Formula I

or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula I:

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, wherein R^5 is COR^7 wherein R^7 is NHR^9 , wherein R^9 is selected from the group consisting of H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, cycloalkyl, arylalkyl, heteroarylalkyl, $[CH(R^{1'})]_pCOOR^{11}$,$[CH(R^{1'})]_pCONR^{12}R^{13}$,$[CH(R^{1'})]_pSO_2R^{11}$,$[CH(R^{1'})]_pCOR^{11}$,$[CH(R^{1'})]_pCH(OH)R^{11}$,$CH(R^{1'})CONHCH(R^2)COOR^{11}$,$CH(R^{1'})CONHCH(R^{2'})CONR^{12}R^{13}$,$CH(R^{1'})CONHCH(R^2)R'$,$CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})COOR^{11}$,$CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONR^{12}R^{13}$,$CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})COOR^{11}$,$CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONR^{12}R^{13}$,$CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONHCH(R^{5'})COOR^{11}andCH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONHCH(R^{5'})$ $CONR^{12}R^{13}$, 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 may be 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

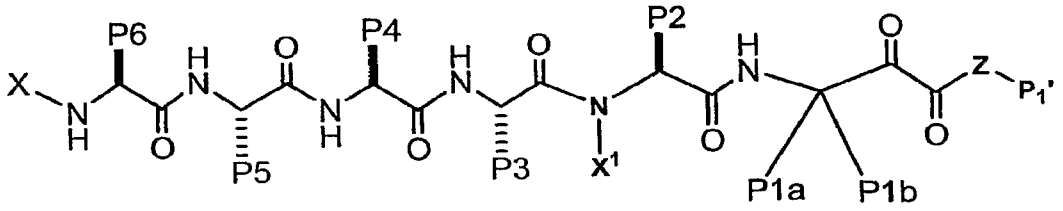
R, R', R^2, R^3 and R^4 are independently selected from the group consisting of H; C_1-C_{10} alkyl; C_2-C_{10} alkenyl; C_3-C_8 cycloalkyl; C_3-C_8 heterocycloalkyl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, halogen;

(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;

ii.



Formula II

or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula II:

Z is NH;

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}.

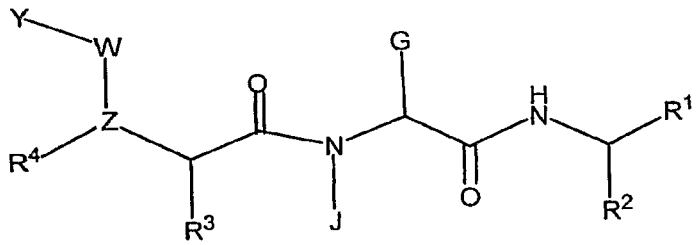
P1a, P1b, P2, P3, P4, P5, and P6 are independently: H; C1-C10 straight or branched chain alkyl; C2-C10 straight or branched chain alkenyl; C3-C8 cycloalkyl, C3-C8 heterocyclic; (cycloalkyl)alkyl or (heterocyclyl)alkyl , wherein said cycloalkyl is made up of 3 to 8 carbon atoms, and zero to 6 oxygen, 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};

iii.



Formula III

or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula III:

G is carbonyl;

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;

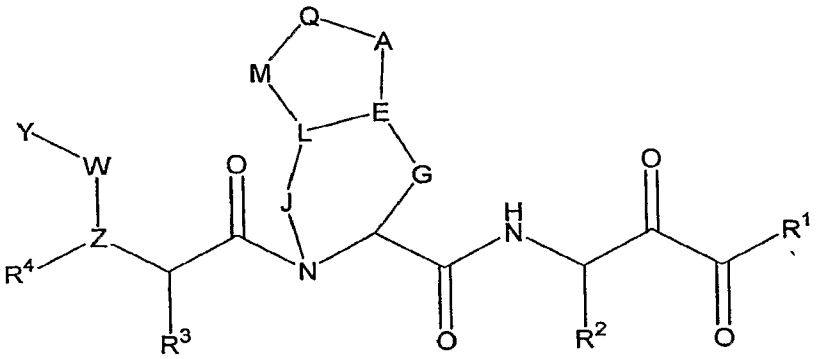
W maybe present or absent, and if W is present, W is selected from C=O, C=S, or SO_2; and

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;

iv.



Formula IV

or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula IV:

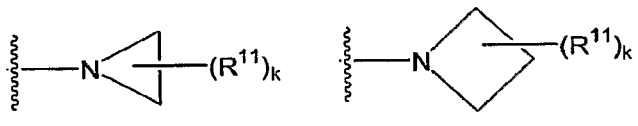
Y is selected from the group consisting of the following moieties: alkyl, alkyl-aryl, heteroalkyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyloxy, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocycloalkyloxy, cycloalkyloxy, alkylamino, arylamino, alkyl-arylamino, arylamino, heteroarylamino, cycloalkylamino and

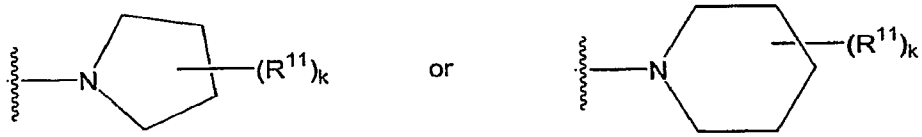
heterocycloalkylamino, with the proviso that Y maybe optionally substituted with X^{11} or X^{12};

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 $(CRR')_p$;

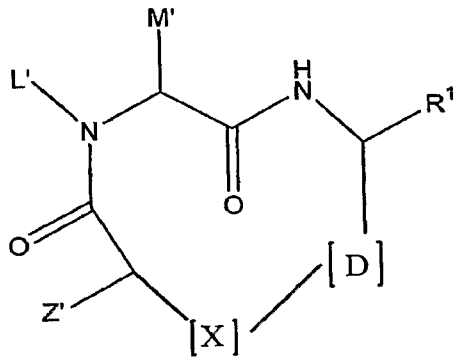
p is a number from 0 to 6; and

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;

v.



Formula V

or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula V:

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

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

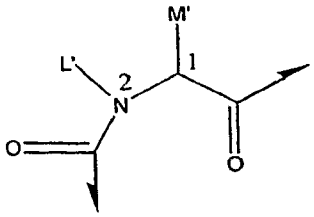
R^{14} is present or not and if present is selected from the group consisting of: H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, alkyl-aryl, allyl, alkyl-heteroaryl, alkoxy, aryl-alkyl, alkenyl, alkynyl and heteroaralkyl;

(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;

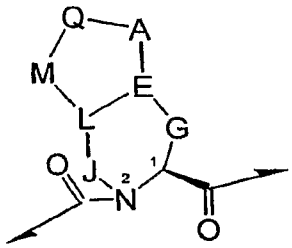
(6) L' is H, OH, alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, or heterocyclyl;

(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;

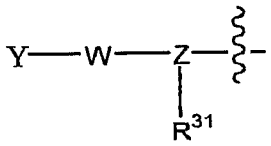
Q is present or absent, and when Q is present, Q is NR, PR, (CR=CR), $(CH_2)_p$, $(CHR)_p$, $(CRR')_p$, $(CHR\text{-}CHR')_p$, O, NR, S, SO, or SO_2; when Q is absent, M is (i) either directly linked to A or (ii) an independent substituent on L, said independent substituent bing selected from -OR, -CH(R)(R'), $S(O)_{0\text{-}2}R$ 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'), $S(O)_{0\text{-}2}R$ 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);

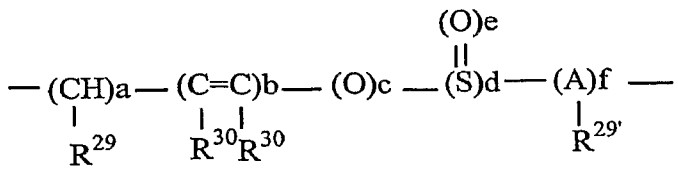
R^{31} is H, hydroxyl, aryl, alkyl, alkyl-aryl, heteroalkyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyloxy, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocycloalkyloxy, heteroalkyl-heteroaryl, cycloalkyloxy, alkylamino, arylamino, alkyl-arylamino, arylamino, heteroarylamino, cycloalkylamino 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;

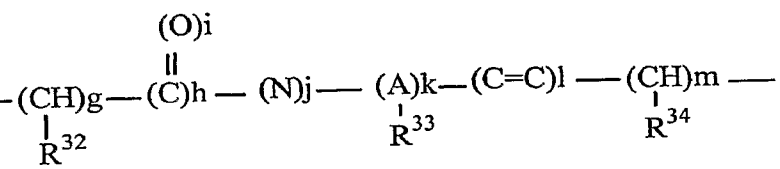
A is C, N, S or O;

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

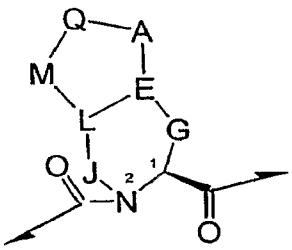
R^{32} and R^{34} are linked together such that the combination forms a portion of a cycloalkyl group;

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

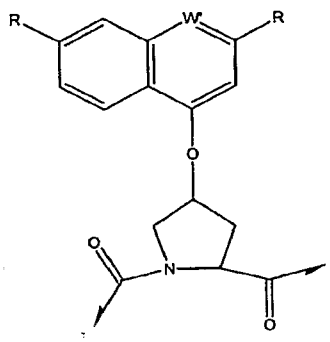
A is C, N, S or O,

(11) provided that when structural Formula 2:



Formula 2

is



and

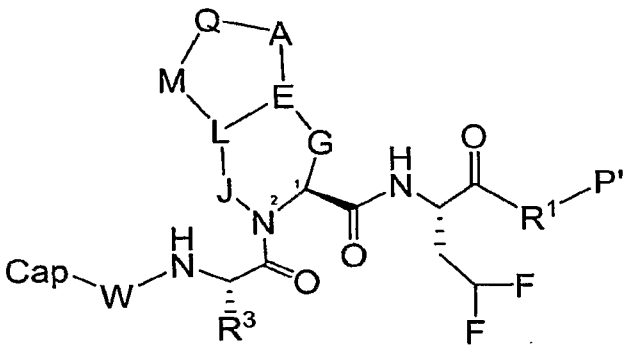
W' is CH or N, both the following conditional exclusions (i) and (ii) apply:

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;

vi.



Formula VI

or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula VI:

Cap is 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;

P' is –NHR;

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'), $-S(O)_{0\text{-}2}R$ or –NRR';

A is present or absent and if present A is –O-, -O(R) CH_2-, $-(CHR)_p$-, $-(CHR\text{-}CHR')_p$-, $(CRR')_p$, 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;

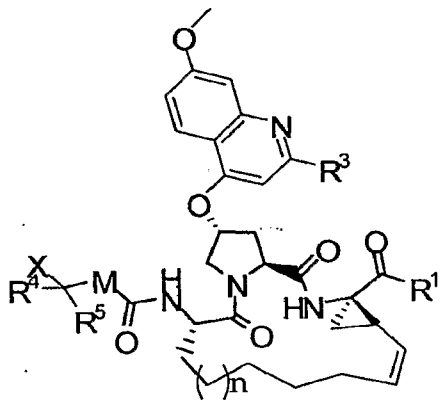
R, R' and R^3 can be the same or different, each being independently selected

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 carbonyl;

vii.



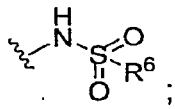
Formula VII

or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula VII:

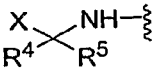
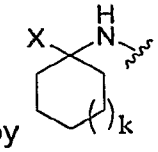
M is O, N(H), or CH_2;

n is 0-4;

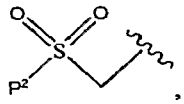
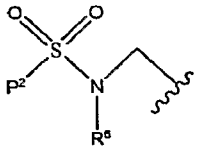
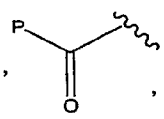
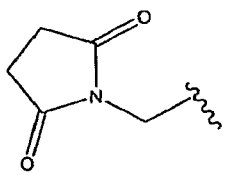
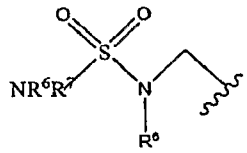
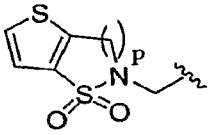
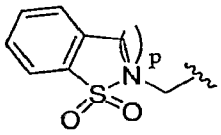
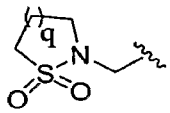
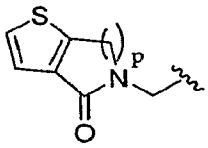
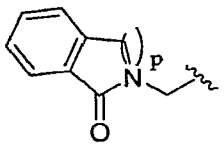
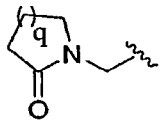
R^1 is $-OR^6$, $-NR^6R^7$ or ;

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;

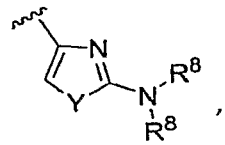
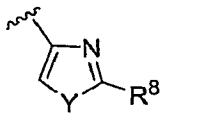
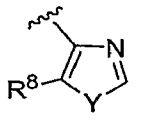
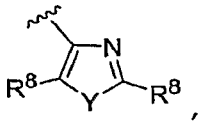
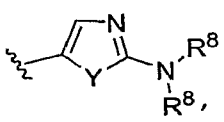
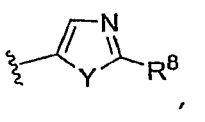
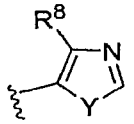
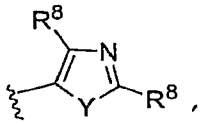
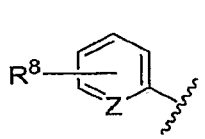
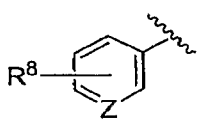
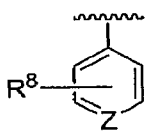
X is selected from the group consisting of:











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

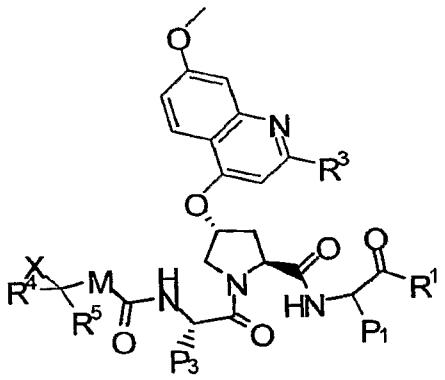
R^3 is selected from the group consisting of: aryl, heterocyclyl, heteroaryl,











and


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;

viii.



Formula VIII

or a pharmaceutically acceptable salt, solvate or ester thereof;

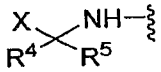
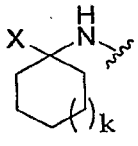
wherein in Formula VIII:

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

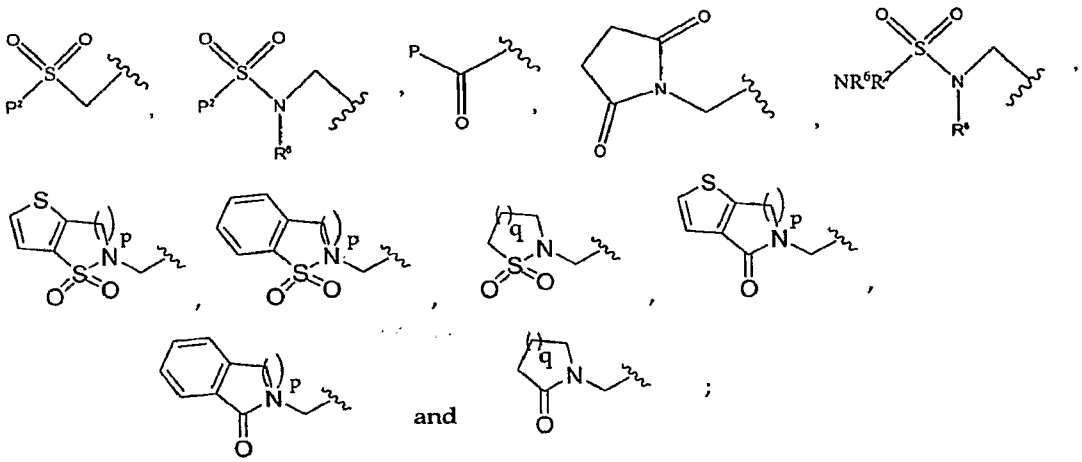
R^1 is $-C(O)NHR^6$, where R^6 is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, hydroxyl, amino, arylamino or alkylamino;

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;

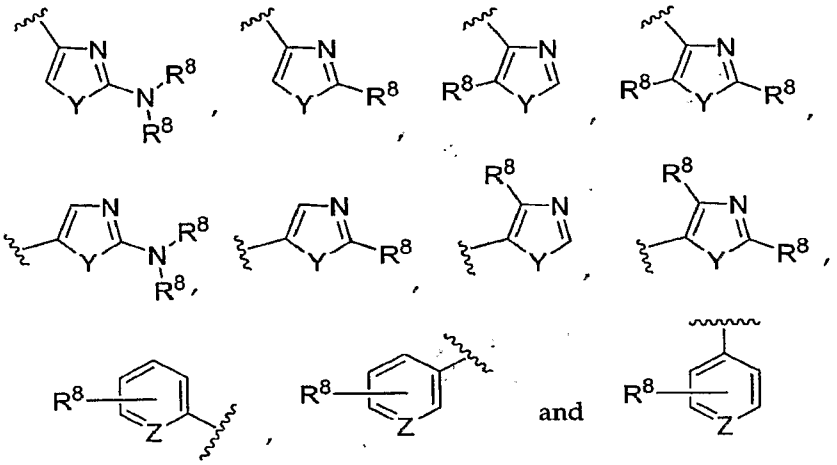
X is selected from the group consisting of:



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;

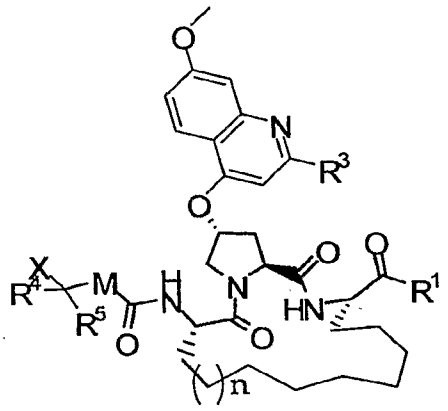
and

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;

ix.



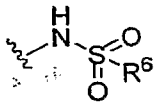
Formula IX

or a pharmaceutically acceptable salt, solvate or ester thereof;

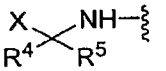
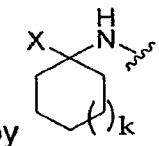
wherein in Formula IX:

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

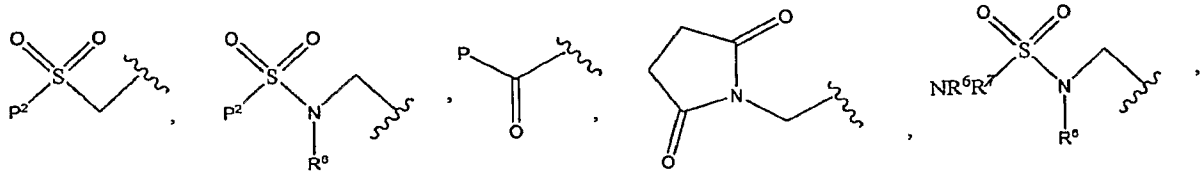
n is 0-4;

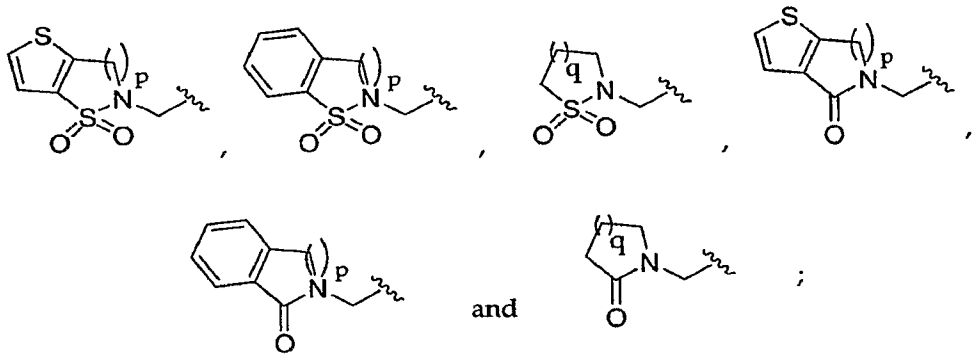
R^1 is $-OR^6$, $-NR^6R^7$, or ;

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:

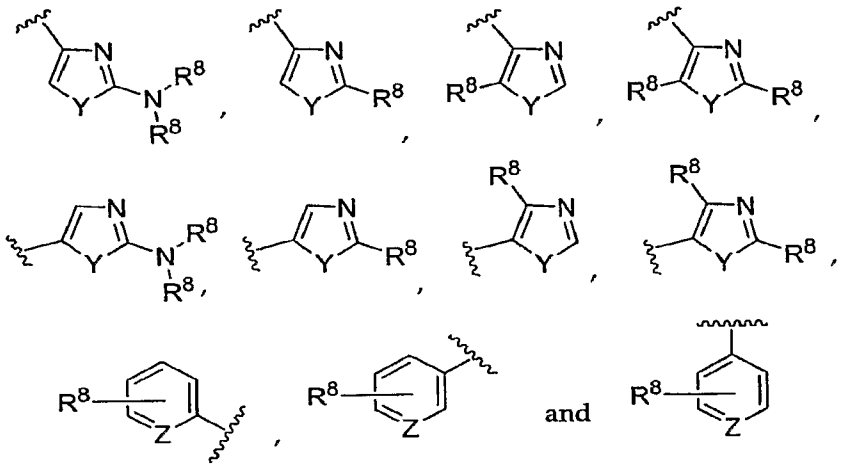




where p is 1 to 2, q is 1 to 3 and P^2 is alkyl, aryl, heteroaryl, heteroalkyl, cycloalkyl, dialkylamino, alkylamino, arylamino or cycloalkylamino;

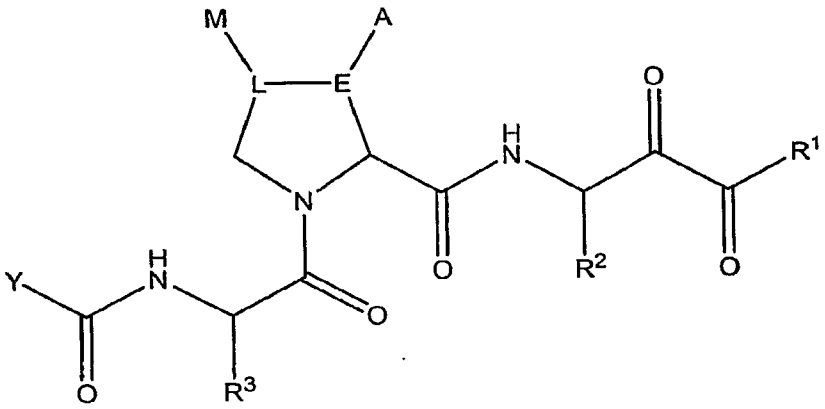
and

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;

x.



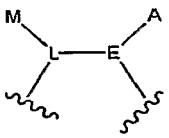
Formula X

or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula X:

R^1 is NHR^9, wherein R^9 is H, alkyl-, alkenyl-, alkynyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, heterocyclyl-, arylalkyl-, or 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:



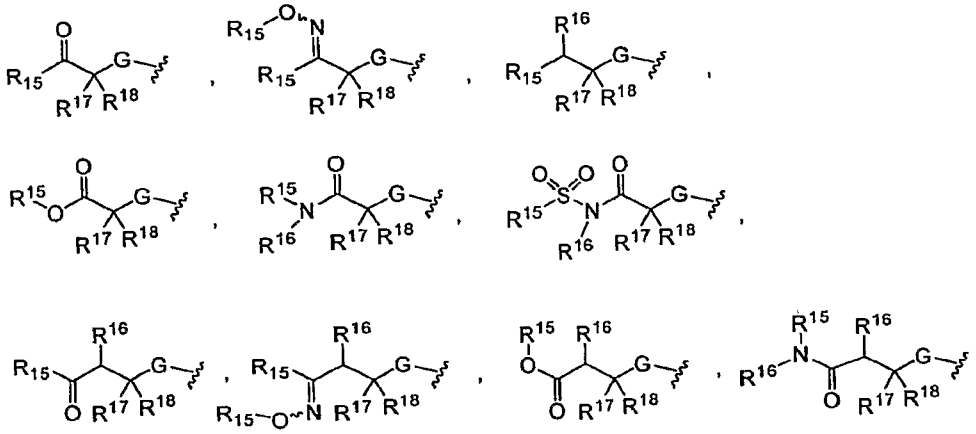
shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl;

E is C(H) or C=;

L is C(H), C=, CH_2C=, or C=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;

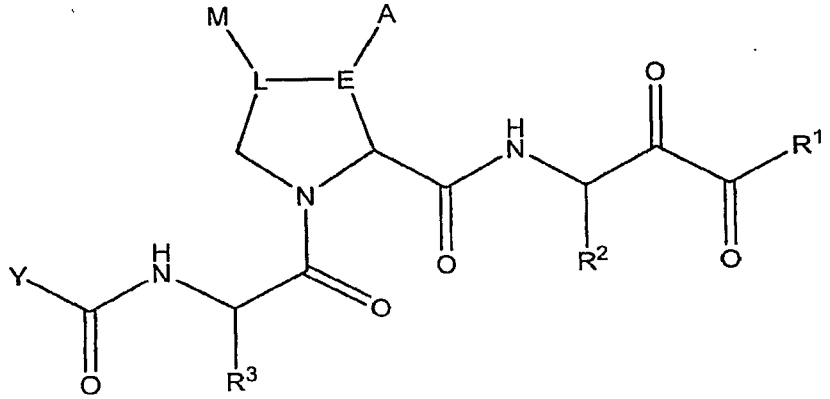
and Y is selected from the following moieties:



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;

xi.



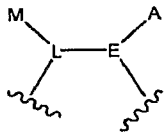
Formula XI

or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XI:

R^1 is NHR^9, wherein R^9 is H, alkyl-, alkenyl-, alkynyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, heterocyclyl-, arylalkyl-, or 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:



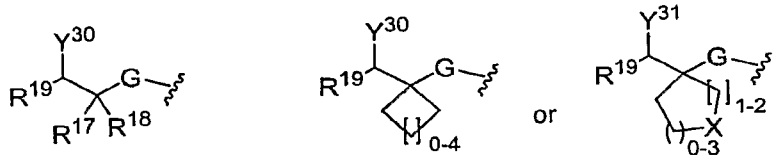
shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl;

E is C(H) or C=;

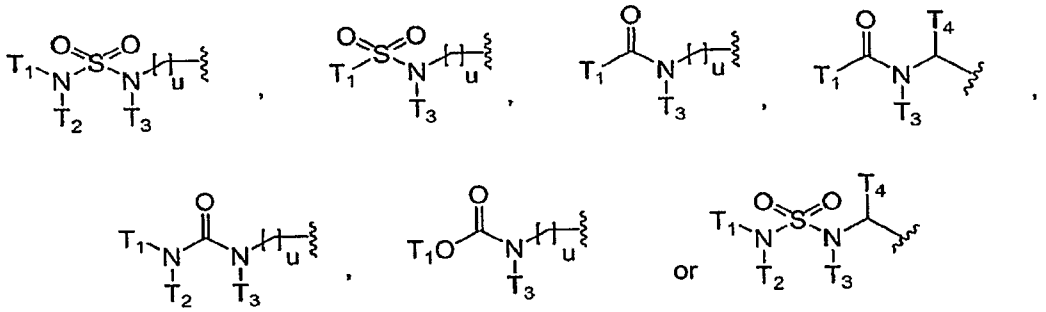
L is C(H), C=, CH_2C=, or C=CH_2;

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;

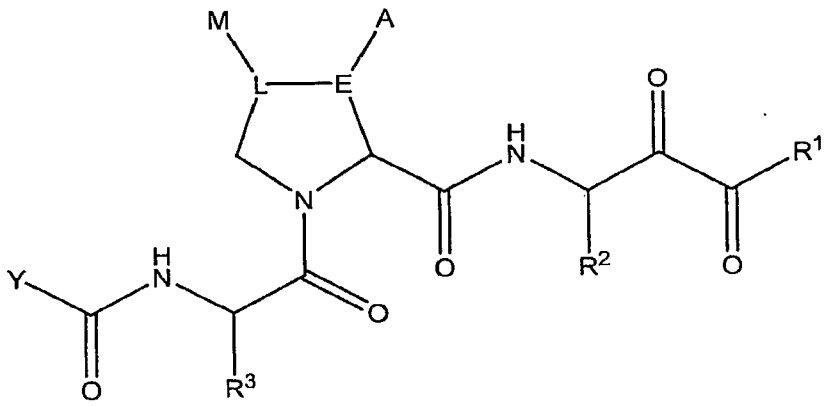
X is selected from O, NR^{15}, $NC(O)R^{16}$, S, S(O) and SO_2;

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;

xii.



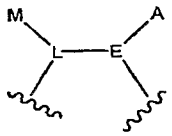
Formula XII

or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XII:

R^1 is NHR^9, wherein R^9 is H, alkyl-, alkenyl-, alkynyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, heterocyclyl-, arylalkyl-, or 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:



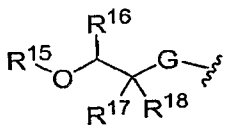
shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl;

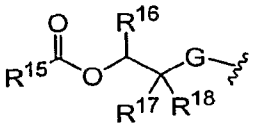
E is C(H) or C=;

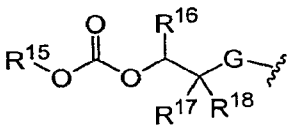
L is C(H), C=, CH_2C=, or C=CH_2;

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;

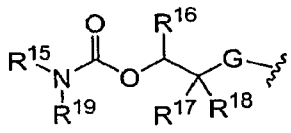
and Y is selected from the following moieties:







or

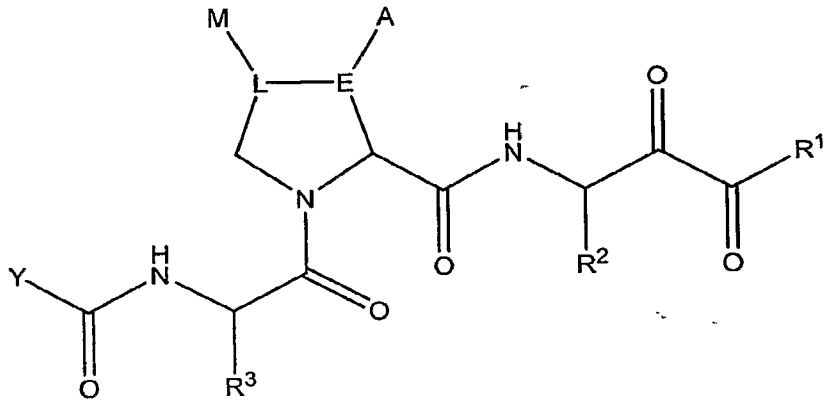


wherein G is NH or O; and R^{15}, R^{16}, R^{17}, R^{18}, and R^{19} can be the same or different, each being independently selected from the group consisting of H, alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl,

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: □ulfonam, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, amido, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, □ulfonamide, alkylsulfonamido, arylsulfonamido, alkyl, aryl, heteroaryl, keto, carboxy, carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyloxy, alkylureido, arylureido, halo, cyano, and nitro;

xiii.



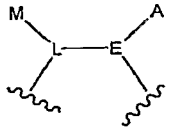
Formula XIII

or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XIII:

R^1 is NHR^9, wherein R^9 is H, alkyl-, alkenyl-, alkynyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, heterocyclyl-, arylalkyl-, or 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:



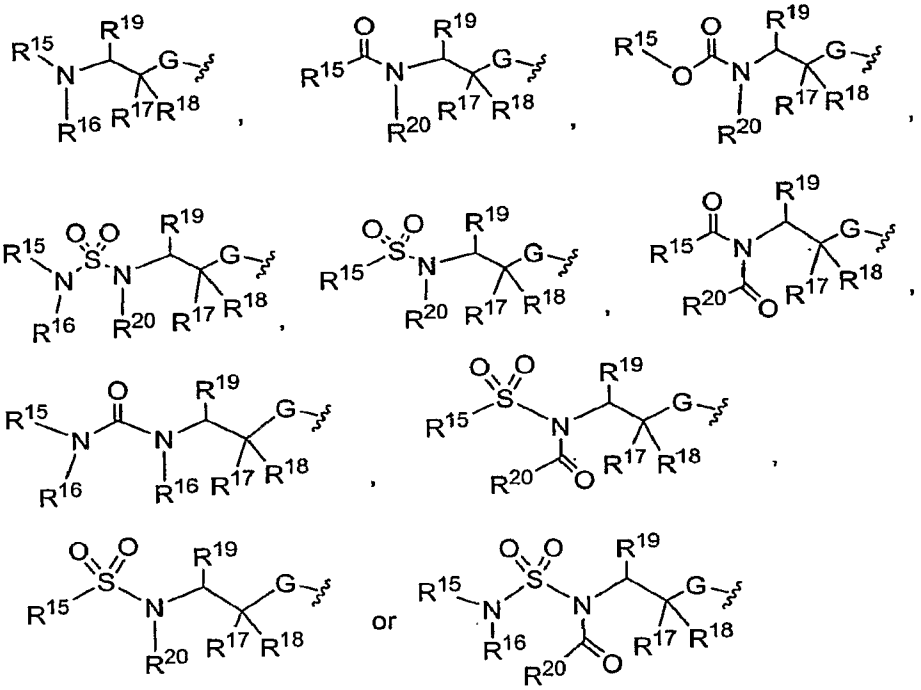
shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl;

E is C(H) or C=;

L is C(H), C=, CH_2C=, or C=CH_2;

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

and Y is selected from the following moieties:

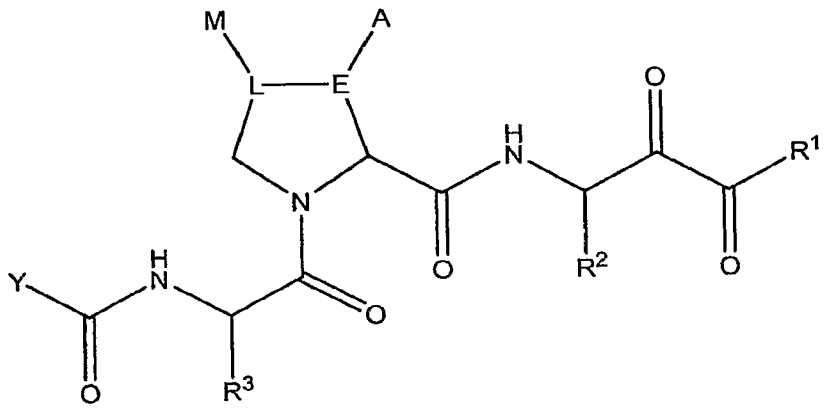


wherein G is NH or O, and R^{15}, R^{16}, R^{17} , R^{18}, R^{19} and R^{20} can be the same or different, each being independently selected from the group consisting of H, C_1-C_{10} alkyl, C_1-C_{10} heteroalkyl, C_2-C_{10} alkenyl, C_2-C_{10} heteroalkenyl, C_2-C_{10} alkynyl, C_2-C_{10} heteroalkynyl,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

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

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

xiv.



Formula XIV

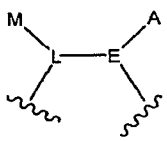
or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XIV:

R^1 is NHR^9, wherein R^9 is H, alkyl-, alkenyl-, alkynyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, heterocyclyl-, arylalkyl-, or 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:



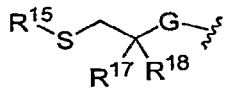
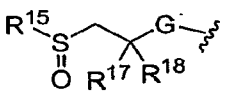
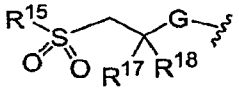
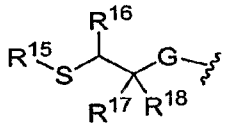
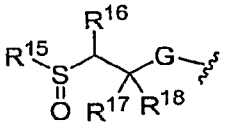
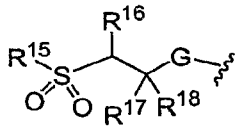
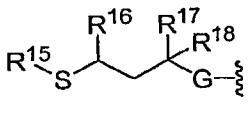
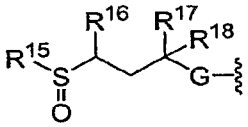
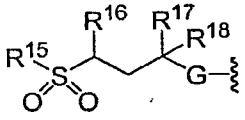
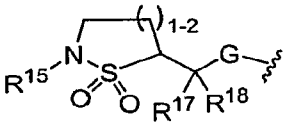
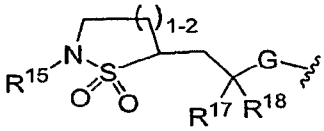
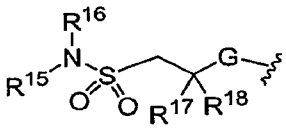
shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl;

E is C(H) or C=;

L is C(H), C=, CH_2C=, or C=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:

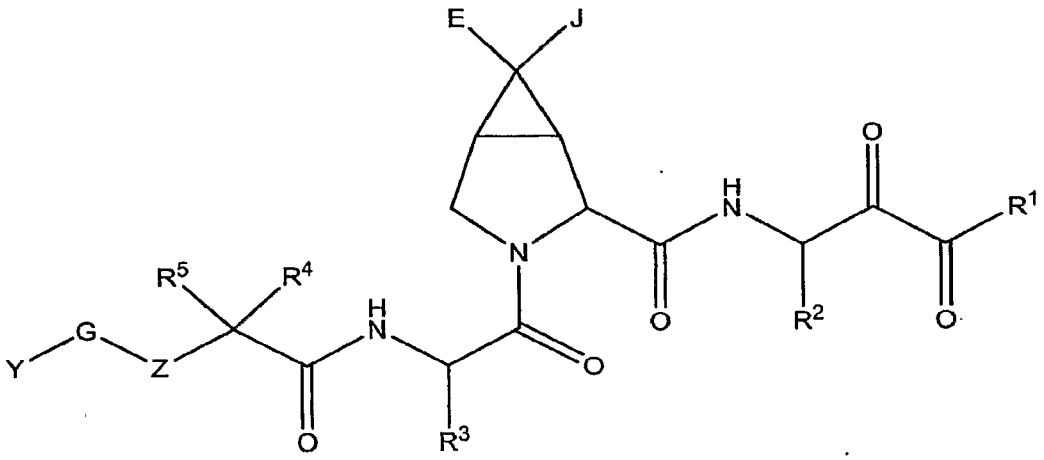

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and


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;

xv.



Formula XV

or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XV:

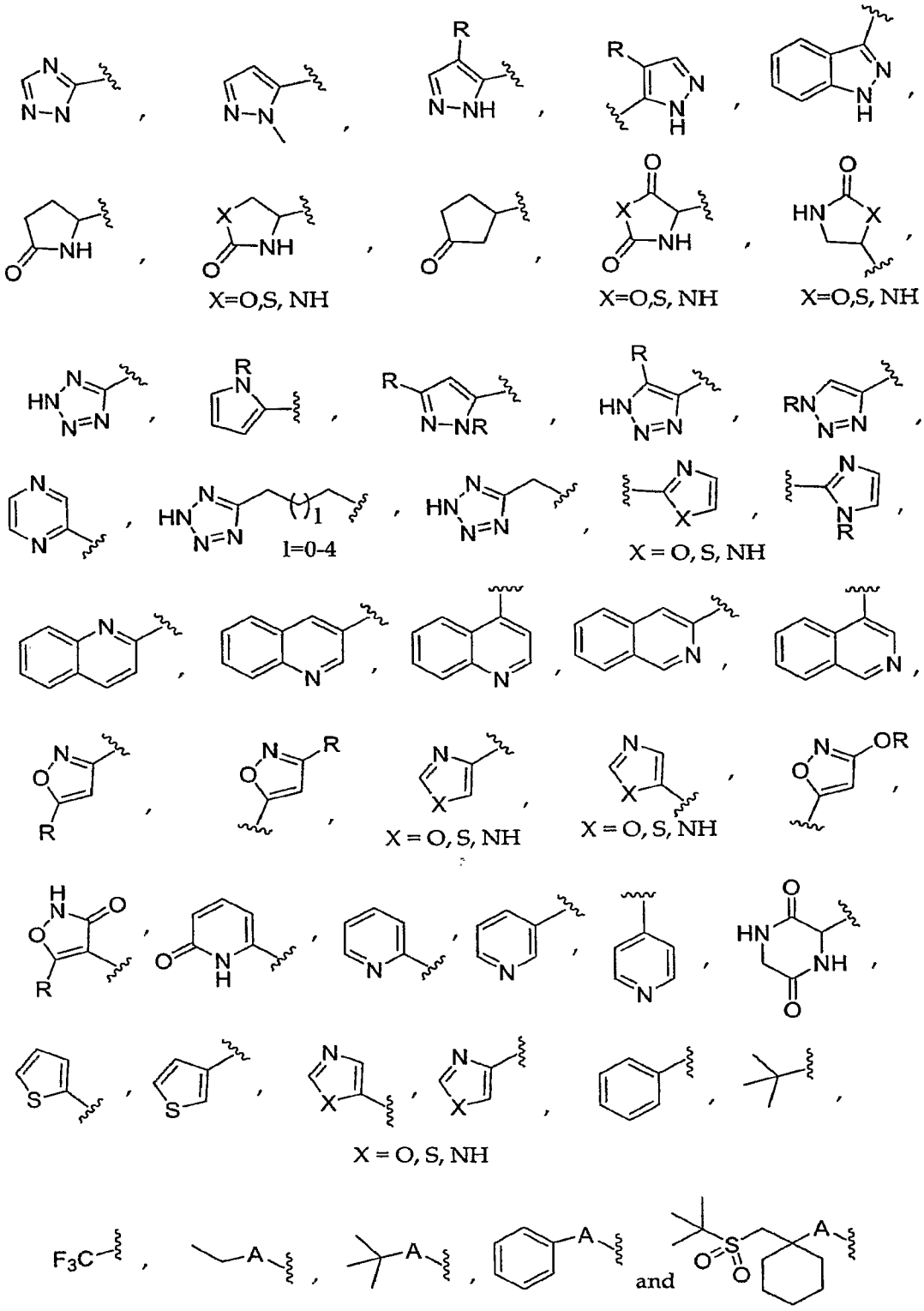
R^1 is NHR^9, wherein R^9 is H, alkyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, cycloalkyl-, arylalkyl-, or heteroarylalkyl;

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=, 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:

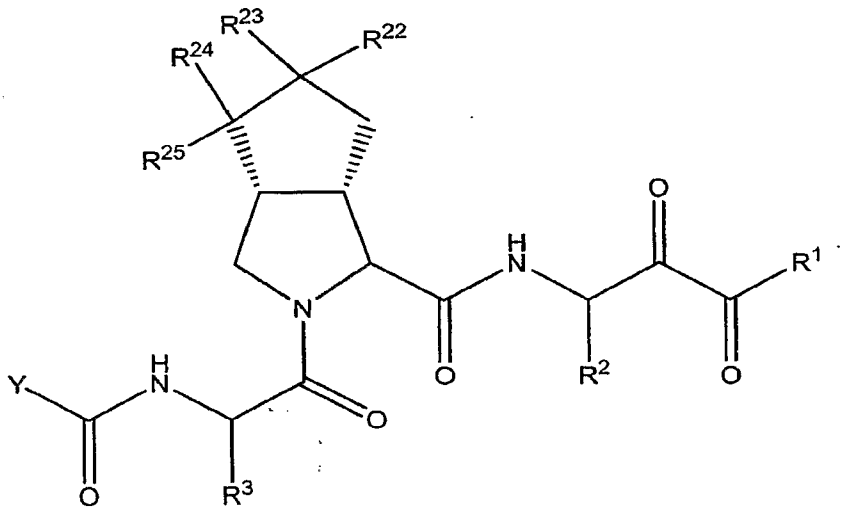

X=O,S, NH
X=O,S, NH
X=O,S, NH
l=0-4
X = O, S, NH
X = O, S, NH
X = O, S, NH
X = O, S, NH
and
A = O, NH

;

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;

xvi.



Formula XVI

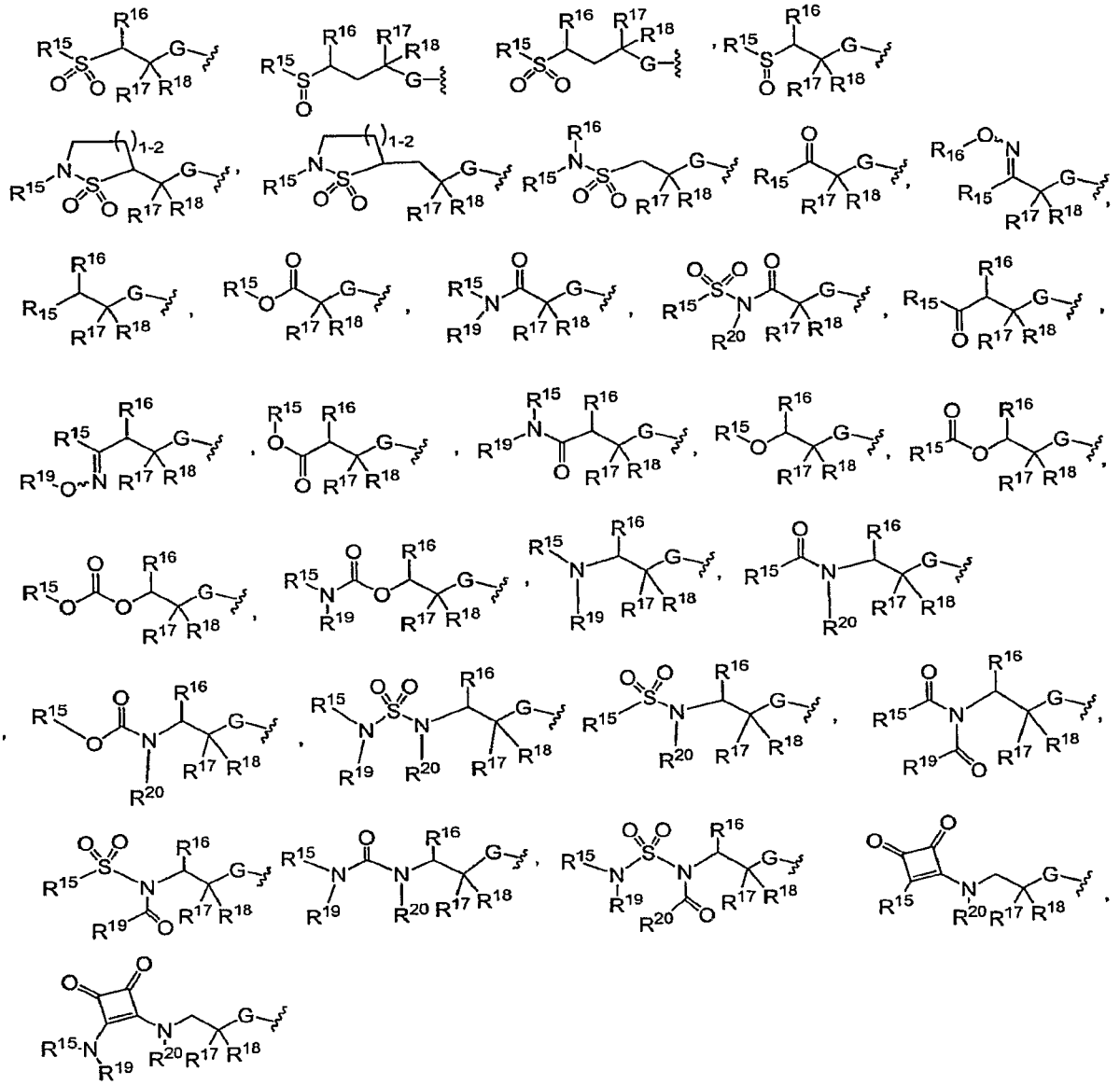
or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XVI:

R^1 is NHR^9, wherein R^9 is H, alkyl-, alkenyl-, alkynyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, heterocyclyl-, arylalkyl-, or heteroarylalkyl;

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:

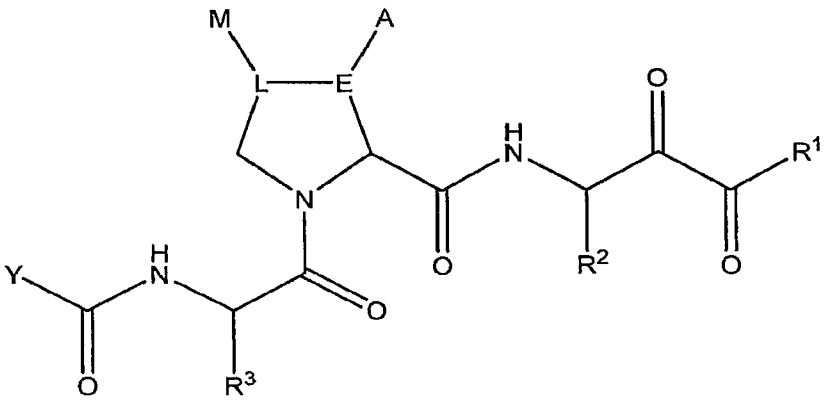


wherein G is NH or O; and R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24} and R^{25} can be the same or different, each being independently selected from the group consisting of H, alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, cycloalkyl, heterocyclyl,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

xvii.



Formula XVII

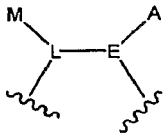
or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XVII:

R^1 is NHR^9, wherein R^9 is H, alkyl-, alkenyl-, alkynyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, heterocyclyl-, arylalkyl-, or 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:



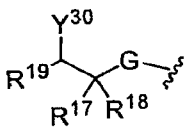
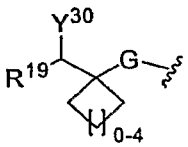
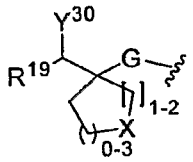
shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl;

E is C(H) or C=;

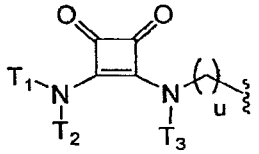
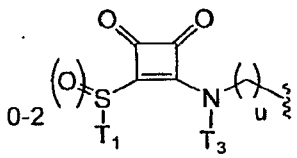
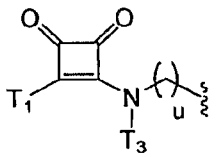
L is C(H), C=, CH_2C=, or C=CH_2;

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:



or


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;

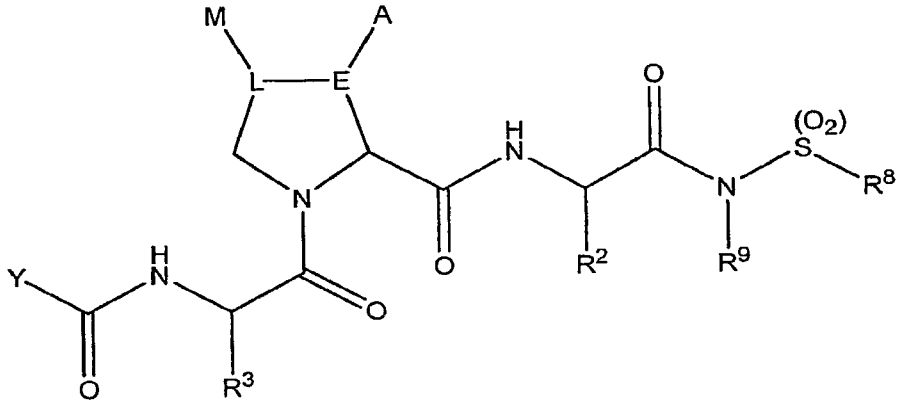
G is NH or O; and

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;

xviii.



Formula XVIII

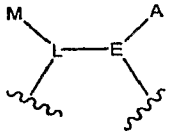
or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XVIII:

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;

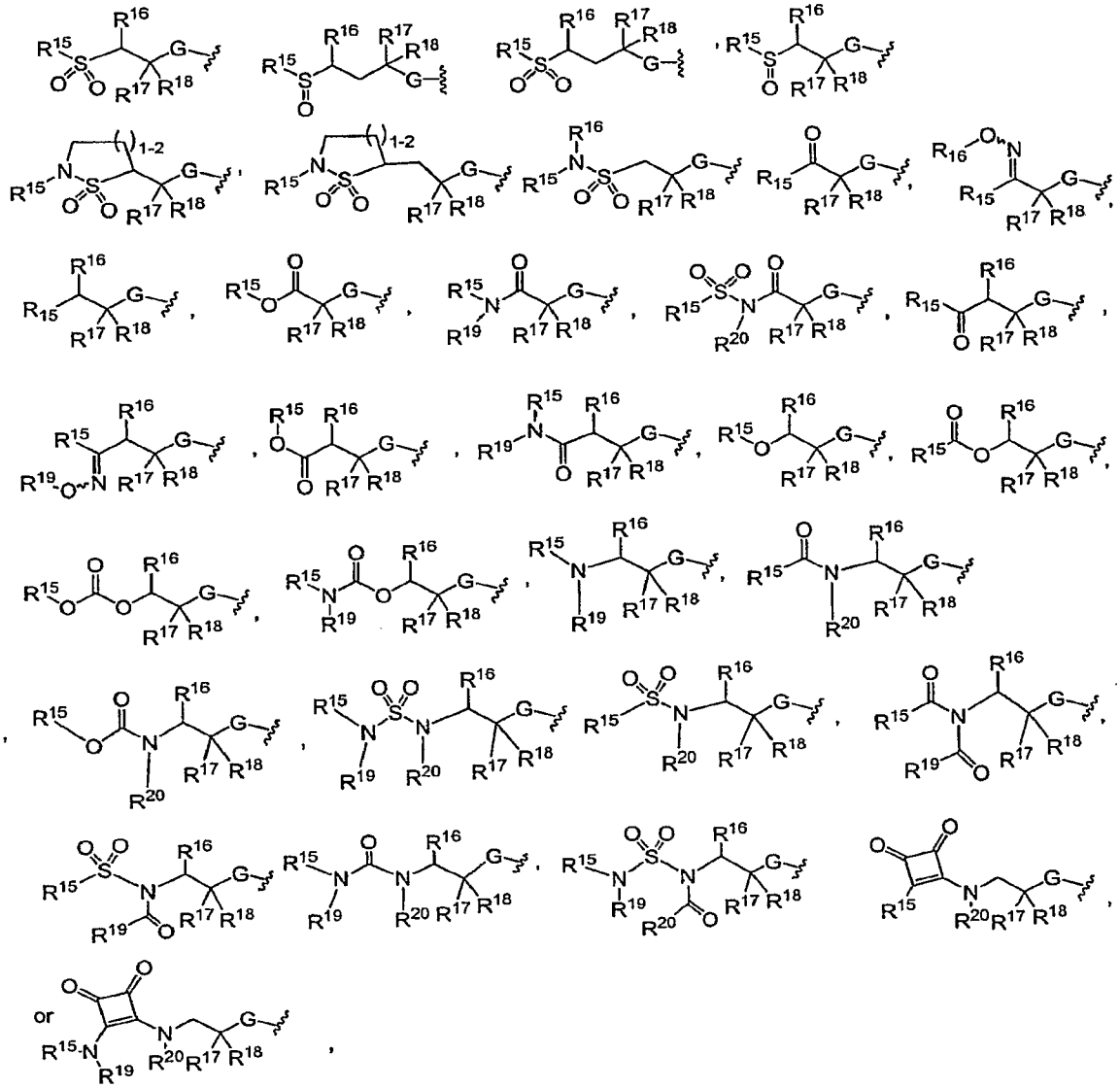
E is C(H) or C(R);

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;

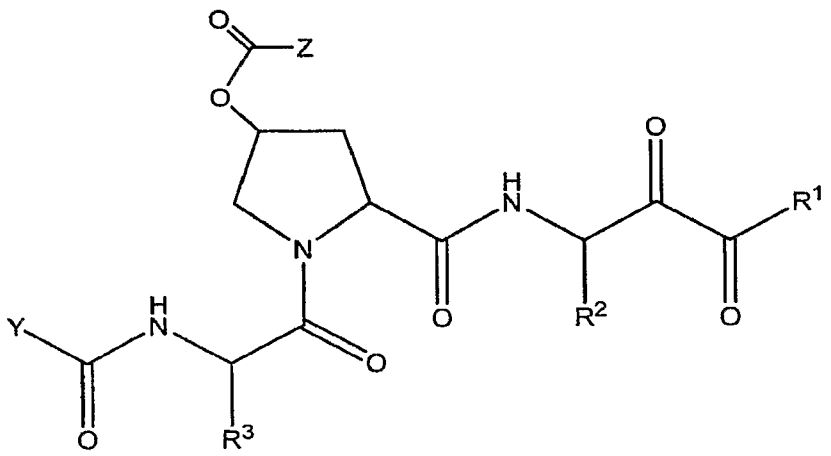
Y is selected from the following moieties:



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;

xix.



Formula XIX

or a pharmaceutically acceptable salt, solvate or ester thereof;

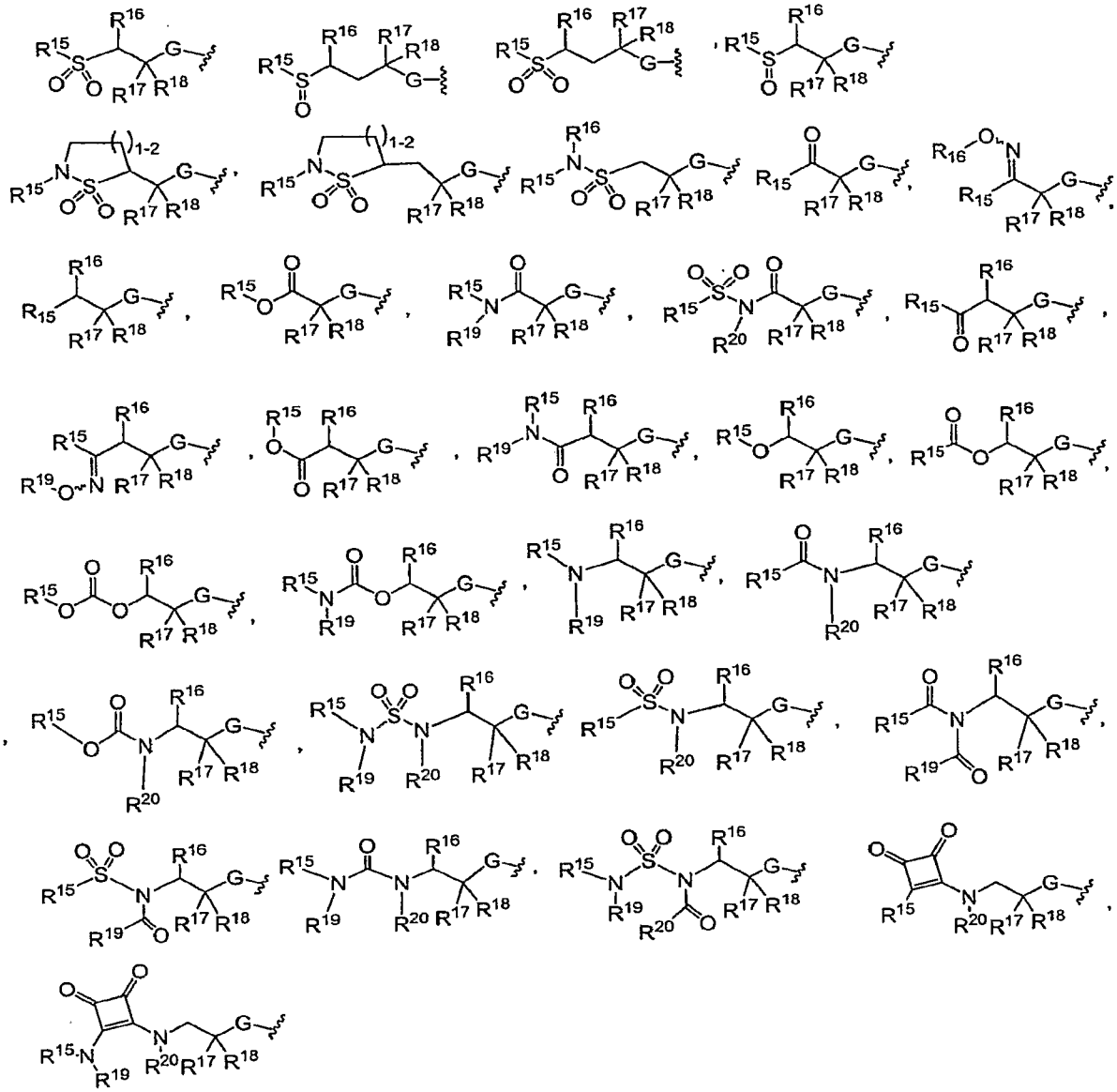
wherein in Formula XIX:

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 NHR^9, wherein R^9 is H, alkyl-, alkenyl-, alkynyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, heterocyclyl-, arylalkyl-, or heteroarylalkyl;

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:

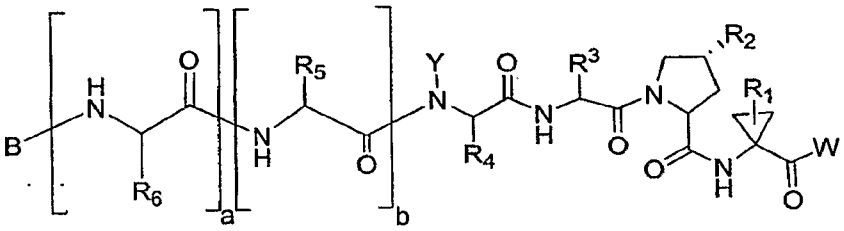


wherein G is NH or O; and R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20} and R^{21} can be the same or different, each being independently selected from the group consisting of H, alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl,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

xx.

P6 P5 P4 P3 P2 P1



Formula XX

or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XX:

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;

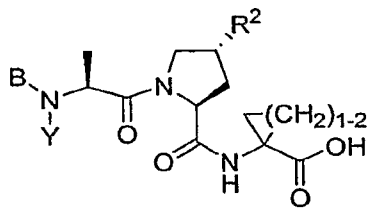
R_5, when present, is C_{1-6} alkyl optionally substituted with carboxyl;

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; $N0_2$; 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; $N0_2$; 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 the above-shown structure of the compound of Formula XX, 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;

xxi.



Formula XXI
or a pharmaceutically acceptable salt, solvate or ester thereof;
wherein in Formula XXI:
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},

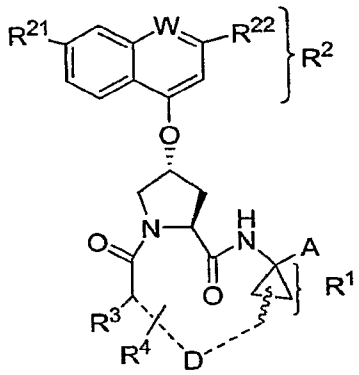
wherein each R_{21} is independently C_{1-6} alkyl; C_{1-6} alkoxy; lower thioalkyl; sulfonyl; NO_2; OH; SH; halo; haloalkyl; amino optionally mono- or di- substituted with C_{1-6} alkyl, C_6 or C_{10} aryl, C_{7-14} aralkyl, Het or (lower alkyl)-Het; amido optionally

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;

xxii.



Formula XXII

or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XXII:

W is CH or N,

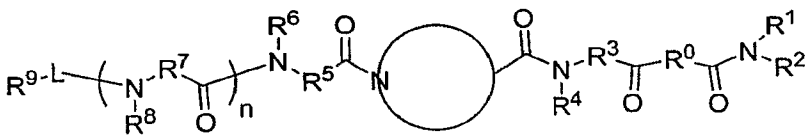
R^{21} is H, halo, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkoxy, hydroxy, or $N(R^{23})_2$, wherein each R^{23} is independently H, C_{1-6} alkyl or C_{3-6} cycloalkyl;

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;

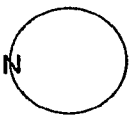
or R^{24} is NH-C(O)-OR^{26} wherein R^{26} is C_{1-6} alkyl or C_{3-6} cycloalkyl;
R^3 is hydroxy, NH_2 , or a group of formula -NH-R^{31} , wherein R^{31} is $C_{6 \text{ or } 10}$ aryl, heteroaryl, -C(O)-R^{32}, -C(O)-NHR^{32} or -C(O)-OR^{32} , wherein R^{32} is C_{1-6} alkyl or C_{3-6} cycloalkyl;
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_{1-8} alkyl, C_{3-6} cycloalkyl, $C_{6 \text{ or } 10}$ aryl and C_{7-16} aralkyl;
or A is a carboxylic acid;

xxiii.



Formula XXIII
or a pharmaceutically acceptable salt, solvate or ester thereof;
wherein in Formula XXIII:
R^0 is a bond or difluoromethylene;
R^1 is hydrogen;
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;

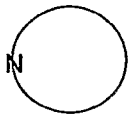
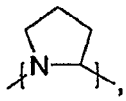


is substituted monocyclic azaheterocyclyl or optionally substituted multicyclic azaheterocyclyl, or optionally substituted multicyclic azaheterocyclenyl wherein the unsaturatation is in the ring distal to the ring bearing the R^9-L-($N(R^8)$-R^7-$C(O)$-)$_n$$N(R^6)$-$R^5$-C(O)-N moiety and to which the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

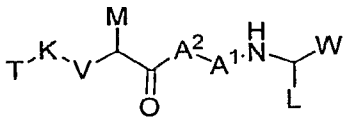
L is -C(O)-, -OC(O)-, -NR^{10}C(O)-, -$S(0)_2$-, or – $NR^{10}S(0)_2$-; and

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;

xxiv.

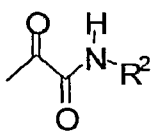


Formula XXIV

or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XXIV:

W is:



;

m is 0 or 1;

R^2 is independently hydrogen, alkyl, alkenyl, aryl, aralkyl, aralkenyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkenyl, heteroaryl, or heteroaralkyl, 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, carboxamidoaikyl, 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 substititued with 1-3 J groups;

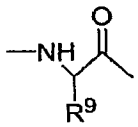
R^8 is hydrogen alkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, aralkanoyl, heterocyclanoyl, heteroaralkanoyl, $-C(O)R^{14}$, $-S0_2R^{14}$, or carboxamido, and is optionally substititued with 1-3 J groups; or R^8 and Z, together with the atoms to which they are bound,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

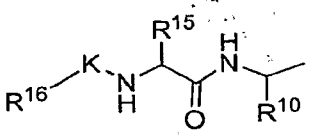
M is alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroaralkyl, optionally substituted by 1-3 J groups, wherein any alkyl carbon atom may be replaced by a heteroatom;

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



;

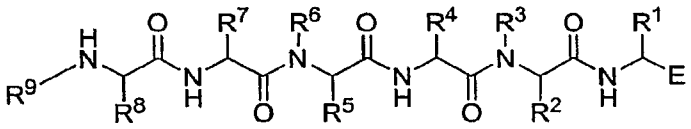
R^{12} is hydrogen, aryl, heteroaryl, cycloalkyl, heterocyclyl, cycloalkylidenyl, or heterocycloalkylidenyl, and is optionally substituted with 1-3 J groups, or a first R^{12} and a second R^{12}, together with the nitrogen to which they are bound, form a mono- or bicyclic ring system optionally substituted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

xxv.



Formula XXV

or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XXV:

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;

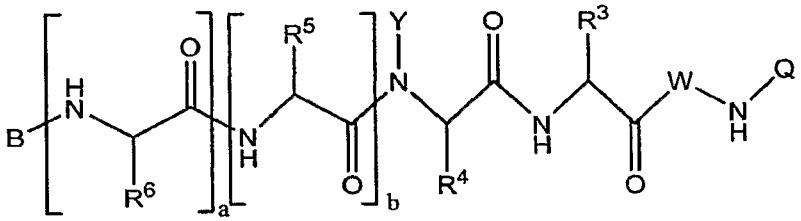
R^6 represents hydrogen or lower alkyl;

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

xxvi.



Formula XXVI

or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XXVI:

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;

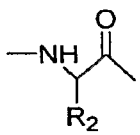
R_5, when present, is C_{1-6} alkyl, or carboxy(lower)alkyl;

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

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

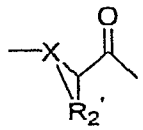
R_3 is C1-10 alkyl; C_{3-10} cycloalkyl;

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

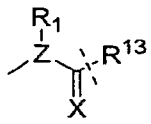
R_2' is C_{3-4} alkylene that joins X to form a 5- or 6-membered ring, said ring optionally substituted with OH; SH; NH2; carboxyl; R_{12}; OR_{12}, SR_{12}, NHR_{12} or $NR_{12}R_{12}$' wherein R_{12} and R_{12}' are independently:

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;

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

R_{13} is C0-NH-R_{14} wherein R_{14} is 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

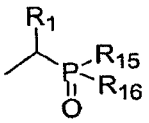
R_{14} is C_6 or C_{10} aryl or C_{7-16} aralkyl optionally substituted with C_{1-6} alkyl, NH_2, OH, SH, halo, carboxyl or carboxy(lower)alkyl or substituted with a further C_{3-7}

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;

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

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;

for concurrent or consecutive administration in treating or ameliorating one or more symptoms of HCV, or disorders associated with HCV in a subject in need thereof.

2. The medicament of claim 1, further comprising at least one other therapeutic agent.

3. The medicament of claim 2, wherein at least one other therapeutic agent is an interferon.

4. The medicament of claim 3, further comprising ribavirin.

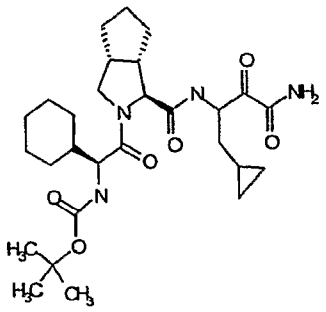
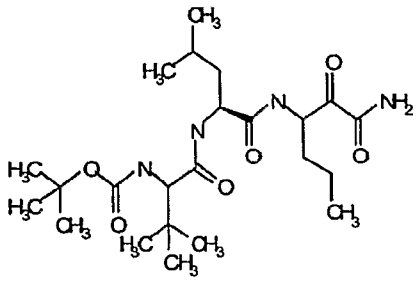
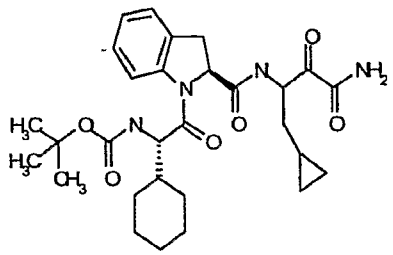
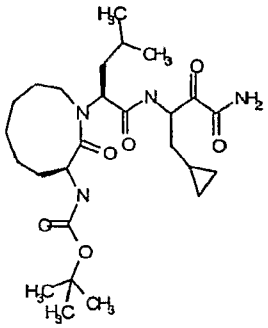
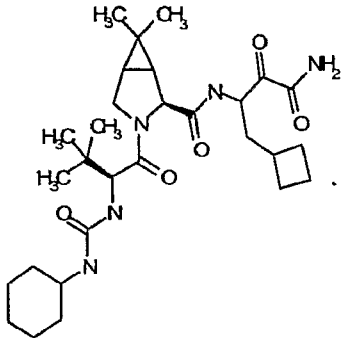
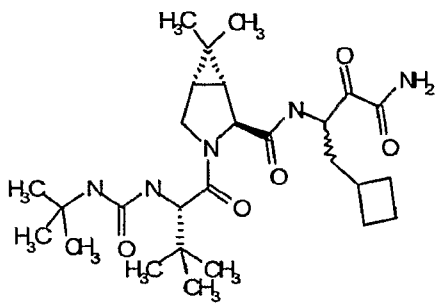
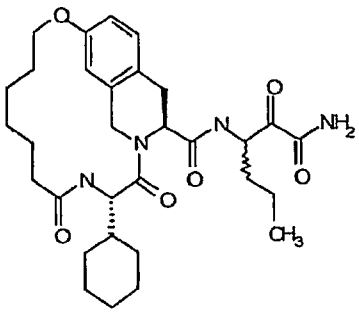
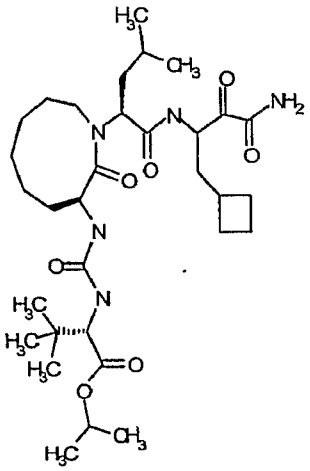
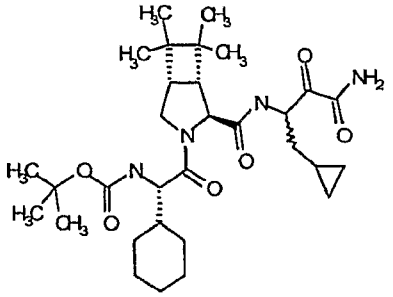
5. The medicament of claim 1 or 3, further comprising ribavirin, levovirin, VP 50406, ISIS 14803, VX 497, Thymosin, Maxamine, or mycophenolate mofetil.

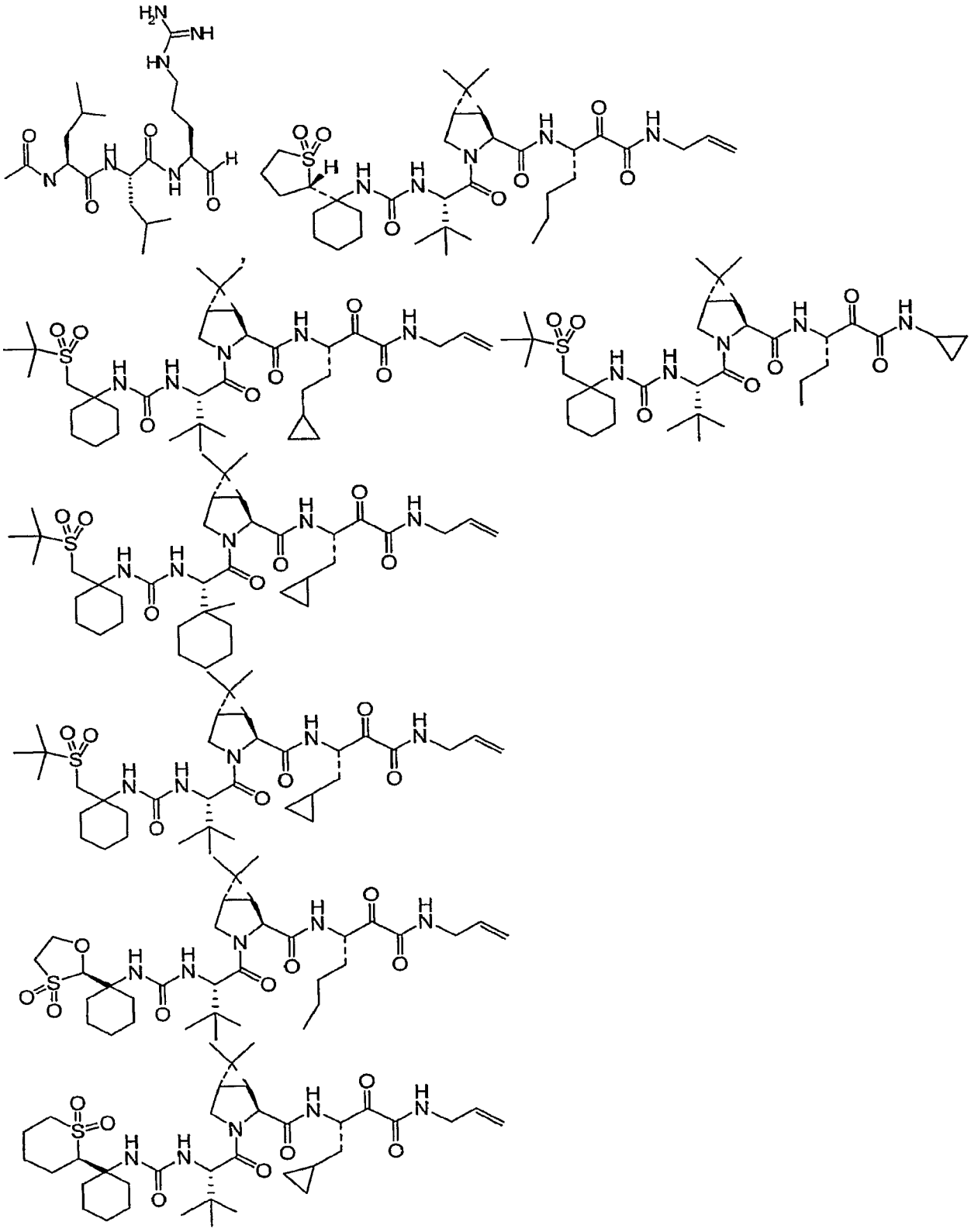
6. The medicament of claim 1, 2, 3, or 4, wherein at least one HCV IRES inhibitor is I70®, or RiboTargets RNA inhibitor.

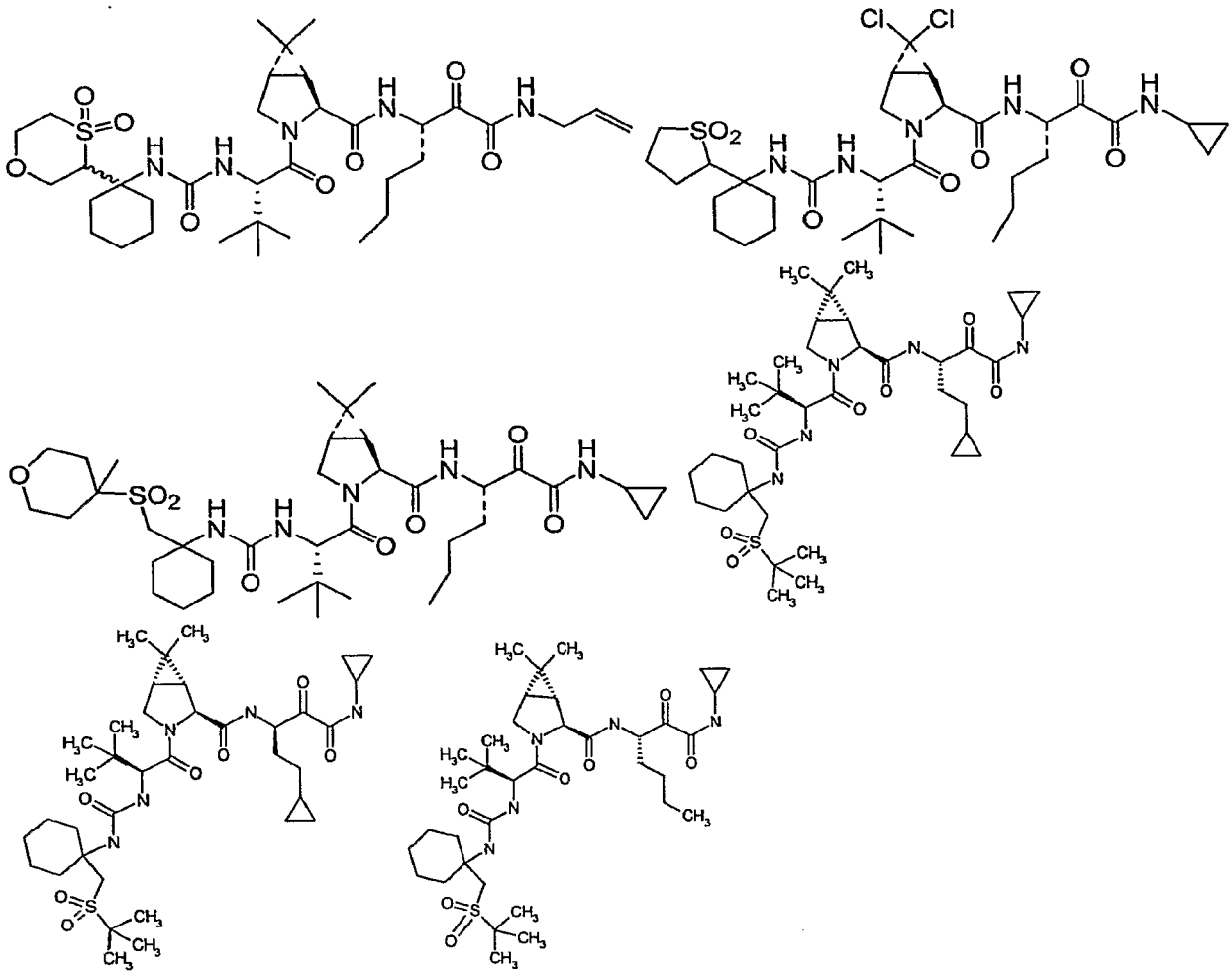
7. The medicament of claim 6, wherein at least one HCV IRES inhibitor is I70®.

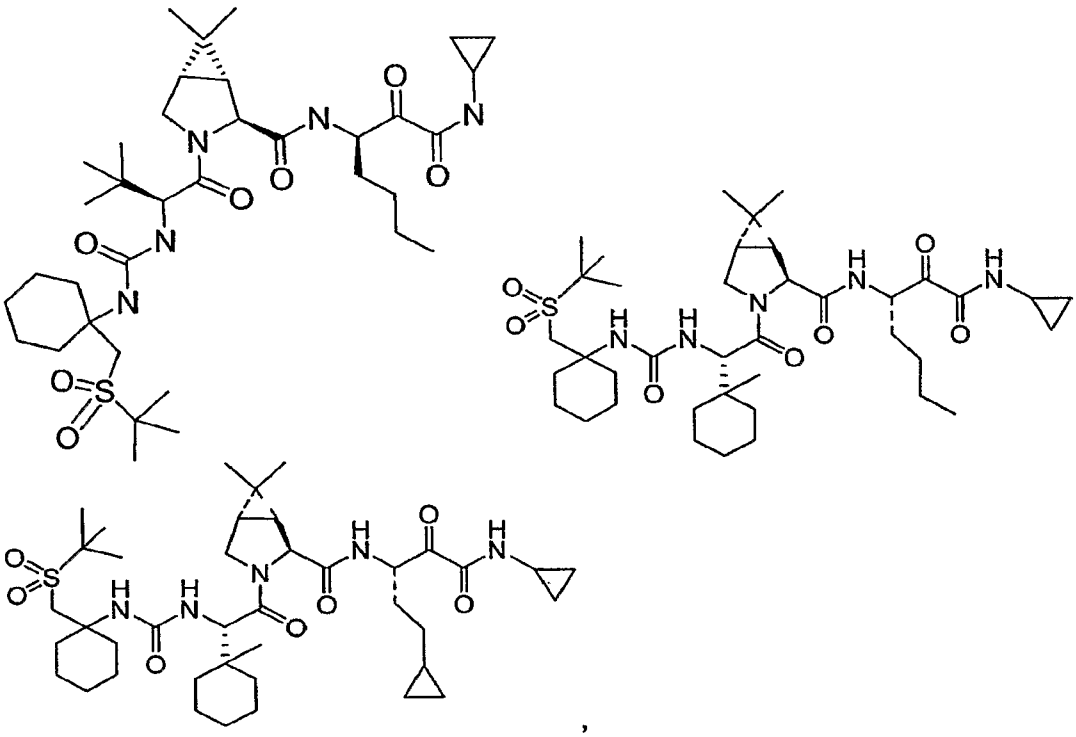
8. The medicament of claim 1, 2, 3 or 4, wherein at least one HCV protease inhibitor is administered in an amount ranging from about 100 to about 3600 mg per day.

9. The medicament of claim 1, 2, 3 or 4, wherein at least one HCV protease inhibitor is:


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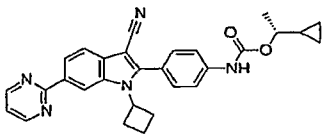




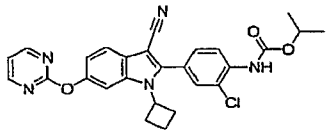
or a pharmaceutically acceptable salt, solvate or ester thereof and the IRES inhibitor is a thienopyridine or indole having anti-HCV activity.

10. The medicament of claim 1, 2, 3, or 4, wherein at least one HCV protease inhibitor is a compound of Formula I, Formula XIV, or a pharmaceutically acceptable salt, solvate or ester thereof.

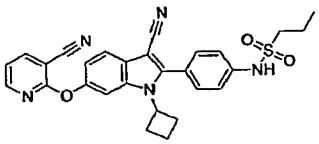
11. The medicament of claim 1, 2, 3, or 4, wherein at least one HCV IRES inhibitor is:



PS 102320 (a/k/a SCH 1385147),



PS 102123 (a/k/a SCH 1383646),



PS 102283 (a/k/a SCH 1385145),

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

12. The medicament of Claim 3, wherein the interferon is a pegylated interferon.

13. The medicament of Claim 3, wherein the interferon is selected from the group consisting of interferon-alpha, PEG-interferon alpha conjugates, interferon alpha fusion polypeptides, consensus interferon, or a mixture of two or more thereof.

14. The medicament of any of Claim 3, wherein the interferon is selected from the group consisting of Roferon™, Pegasys™, Intron™, PEG-Intron™, Berofor Alpha™, and Infergen™, or a mixture of two or more thereof.

15. The medicament of Claim 3, wherein the interferon is administered concurrently or consecutively with at least one HCV IRES inhibitor and at least one HCV protease inhibitor.

16. A pharmaceutical composition comprising a therapeutically effective amount of the medicament of Claim 1, and a pharmaceutically acceptable carrier.

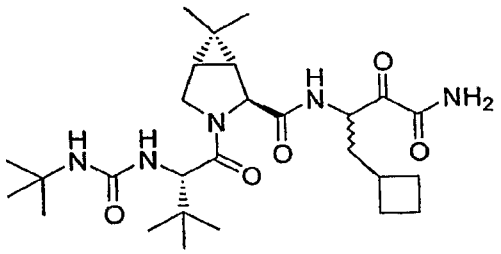
17. A pharmaceutical kit comprising (a) as defined in Claim 1, and (b) as defined in Claim 1, in separate unit dosage forms, said forms being suitable for administration of (a) and (b) in effective amounts, and instructions for administering (a) and (b) to treat or ameliorate one or more symptoms associated with HCV infection.

18. A medicament comprising

(a) at least one hepatitis C virus (HCV) internal ribosomal entry site (IRES)

inhibitor; and

(b) at least one HCV protease inhibitor, wherein at least one HCV protease inhibitor is:

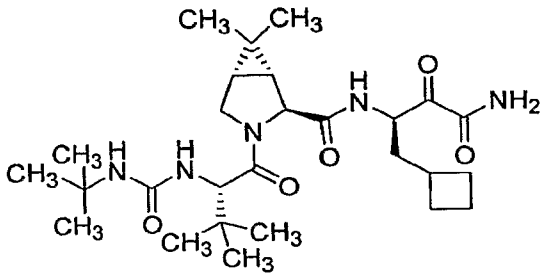


Formula Ia

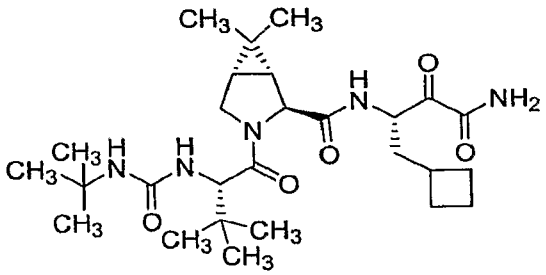
or a pharmaceutically acceptable salt, solvate or ester thereof;

for concurrent or consecutive administration in treating or ameliorating one or more symptoms of HCV, or disorders associated with HCV in a subject in need thereof.

19. The medicament of claim 18, wherein at least one HCV protease inhibitor is:



Formula Ib,



Formula Ic,

or a pharmaceutically acceptable salt, solvate or ester thereof.

20. The medicament of Claim 18, further comprising at least one other therapeutic agent.

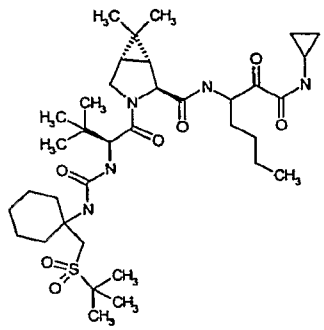
21. The medicament of Claim 20, wherein at least one other therapeutic agent is an interferon.

22. The medicament of Claim 21, further comprising ribavirin.

23. A medicament comprising, separately or together:

(a) at least one hepatitis C virus (HCV) internal ribosomal entry site (IRES) inhibitor; and

(b) at least one HCV protease inhibitor, wherein at least one HCV protease inhibitor is:



or a pharmaceutically acceptable salt, solvate or ester thereof;
for concurrent or consecutive administration in treating or ameliorating one or more symptoms of HCV, or disorders associated with HCV in a subject in need thereof.

24. The medicament of Claim 23, further comprising at least one other therapeutic agent.

25. The medicament of Claim 24, wherein at least one other therapeutic agent is an interferon.

26. The medicament of Claim 25, further comprising ribavirin.

27. The medicament of Claim 23, wherein at least one other therapeutic agent is ribavirin.

28. A method for treating or ameliorating one or more symptoms of HCV, or

disorders associated with HCV in a subject in need thereof, comprising the step of administering to the subject an effective amount of the medicament of Claim 1.

29. The method of Claim 28, wherein said administration is oral, intravenous, intrathecal, parenteral, transdermal, or subcutaneous or a combination of two or more thereof.

30. The method of Claim 28, wherein the subject is treatment naïve.

31. The method of Claim 28, wherein the subject is treatment experienced.

32. A method for treating or ameliorating one or more symptoms of HCV, or disorders associated with HCV in a subject in need thereof, comprising the step of administering to the subject an effective amount of the medicament of Claim 18.

33. The method of Claim 32, wherein said administration is oral, intravenous, intrathecal, parenteral, transdermal, or subcutaneous or a combination of two or more thereof.

34. The method of Claim 32, wherein the subject is treatment naïve.

35. The method of Claim 32, wherein the subject is treatment experienced.

36. A method for treating or ameliorating one or more symptoms of HCV, or disorders associated with HCV in a subject in need thereof, comprising the step of administering to the subject an effective amount of the medicament of Claim 23.

37. The method of Claim 36, wherein said administration is oral, intravenous, intrathecal, parenteral, transdermal, or subcutaneous or a combination of two or more thereof.

38. The method of Claim 36, wherein the subject is treatment naïve.

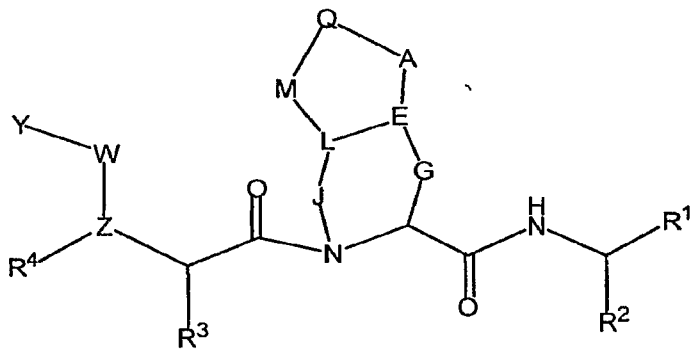
39. The method of Claim 36, wherein the subject is treatment experienced.

40. A medicament comprising, separately or together:

(a) at least one anti-HCV agent which is an indole or a thienopyridine; and

(b) at least one HCV protease inhibitor which is a compound of Formula I to XXVI below:

i.



Formula I

or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula I:

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, wherein R^5 is COR^7 wherein R^7 is NHR^9 , wherein R^9 is selected from the group consisting of H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, cycloalkyl, arylalkyl, heteroarylalkyl, $[CH(R^{1'})]_pCOOR^{11}$,$[CH(R^{1'})]_pCONR^{12}R^{13}$,$[CH(R^{1'})]_pSO_2R^{11}$,$[CH(R^{1'})]_pCOR^{11}$,$[CH(R^{1'})]_pCH(OH)R^{11}$,$CH(R^{1'})CONHCH(R^2)COOR^{11}$,$CH(R^{1'})CONHCH(R^{2'})CONR^{12}R^{13}$,$CH(R^{1'})CONHCH(R^2)R'$,$CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})COOR^{11}$,$CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONR^{12}R^{13}$,$CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})COOR^{11}$,$CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONR^{12}R^{13}$,$CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONHCH(R^{5'})COOR^{11}andCH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONHCH(R^{5'})$ $CONR^{12}R^{13}$, 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 may be 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

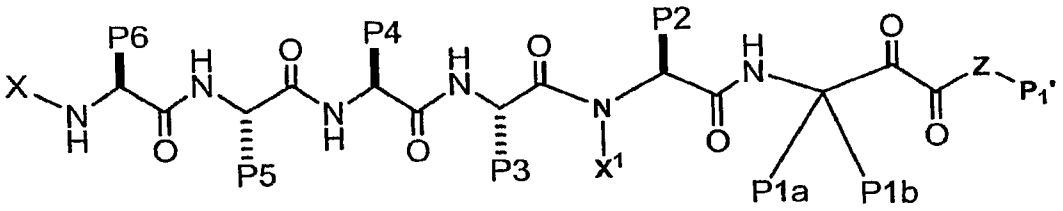
R, R', R^2, R^3 and R^4 are independently selected from the group consisting of H; C_1-C_{10} alkyl; C_2-C_{10} alkenyl; C_3-C_8 cycloalkyl; C_3-C_8 heterocycloalkyl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, halogen;

(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;

ii.



Formula II

or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula II:

Z is NH;

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}.

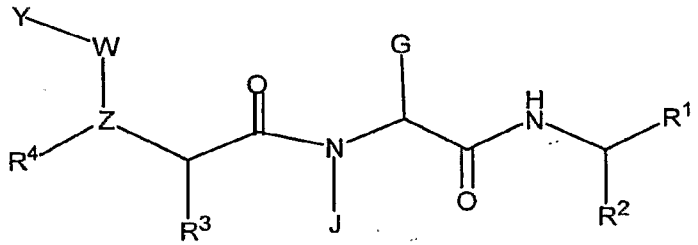
P1a, P1b, P2, P3, P4, P5, and P6 are independently: H; C1-C10 straight or branched chain alkyl; C2-C10 straight or branched chain alkenyl; C3-C8 cycloalkyl, C3-C8 heterocyclic; (cycloalkyl)alkyl or (heterocyclyl)alkyl , wherein said cycloalkyl is made up of 3 to 8 carbon atoms, and zero to 6 oxygen, 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};

iii.



Formula III

or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula III:

G is carbonyl;

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;

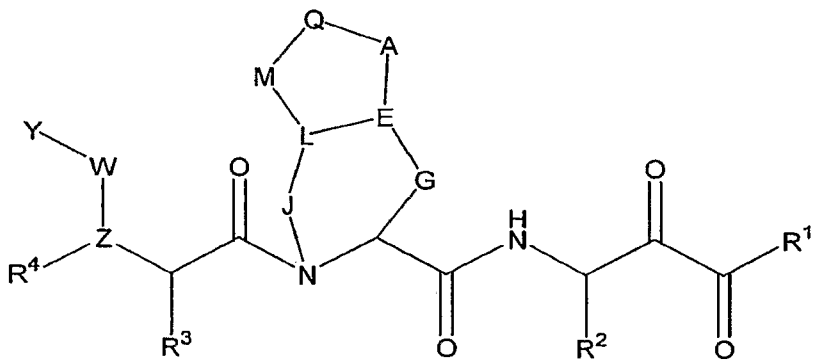
W maybe present or absent, and if W is present, W is selected from C=O, C=S, or SO_2; and

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;

iv.



Formula IV

or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula IV:

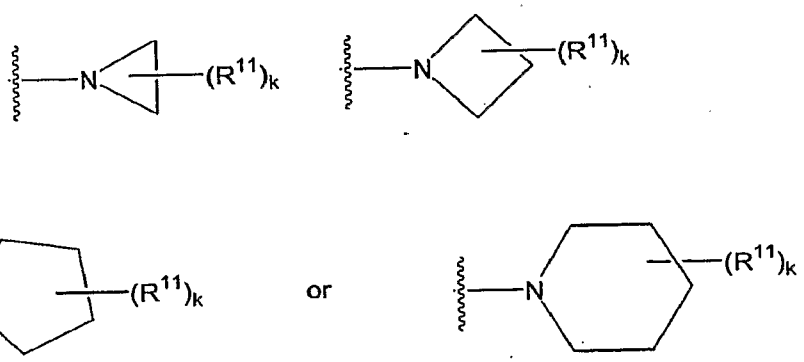
Y is selected from the group consisting of the following moieties: alkyl, alkyl-aryl, heteroalkyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyloxy, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocycloalkyloxy, cycloalkyloxy, alkylamino, arylamino, alkyl-arylamino, arylamino, heteroarylamino, 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 $(CRR')_p$;

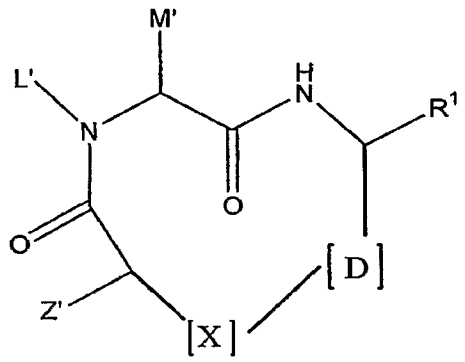
p is a number from 0 to 6; and

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;

v.



Formula V

or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula V:

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

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

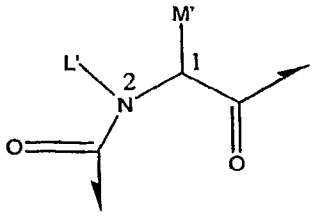
R^{14} is present or not and if present is selected from the group consisting of: H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, alkyl-aryl, allyl, alkyl-heteroaryl, alkoxy, aryl-alkyl, alkenyl, alkynyl and heteroaralkyl;

(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;

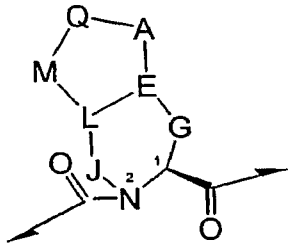
(6) L' is H, OH, alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, or heterocyclyl;

(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;

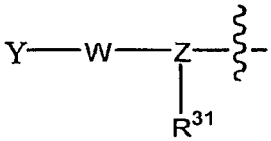
Q is present or absent, and when Q is present, Q is NR, PR, (CR=CR), $(CH_2)_p$, $(CHR)_p$, $(CRR')_p$, $(CHR\text{-}CHR')_p$, O, NR, S, SO, or SO_2; when Q is absent, M is (i) either directly linked to A or (ii) an independent substituent on L, said independent substituent bing selected from -OR, -CH(R)(R'), $S(O)_{0\text{-}2}R$ 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'), $S(O)_{0\text{-}2}R$ 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);

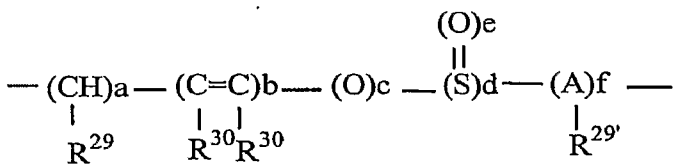
R^{31} is H, hydroxyl, aryl, alkyl, alkyl-aryl, heteroalkyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyloxy, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocycloalkyloxy, heteroalkyl-heteroaryl, cycloalkyloxy, alkylamino, arylamino, alkyl-arylamino, arylamino, heteroarylamino, cycloalkylamino 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;

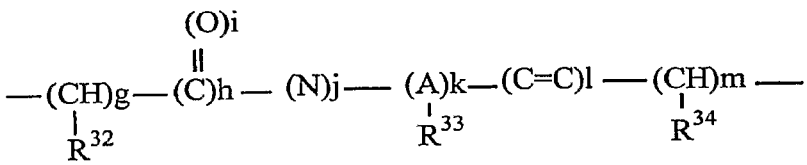
A is C, N, S or O;

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

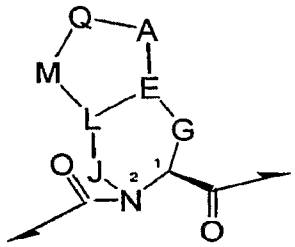
R^{32} and R^{34} are linked together such that the combination forms a portion of a cycloalkyl group;

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

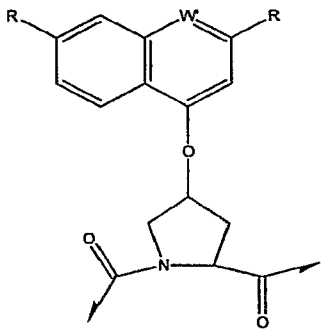
A is C, N, S or O,

(11) provided that when structural Formula 2:



Formula 2

is



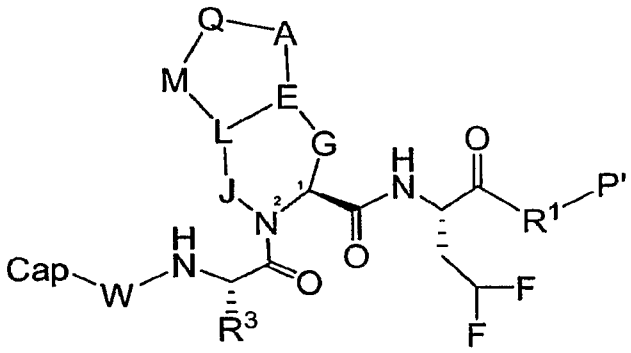
and

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;

vi.



Formula VI

or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula VI:

Cap is 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;

P' is –NHR;

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'), $-S(O)_{0\text{-}2}R$ or –NRR';

A is present or absent and if present A is –O-, -O(R) CH_2-, $-(CHR)_p$-, $-(CHR\text{-}CHR')_p$-, $(CRR')_p$, 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;

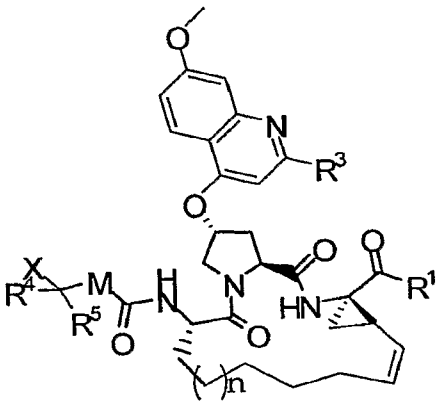
R, R' and R^3 can be the same or different, each being independently selected

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 carbonyl;

vii.



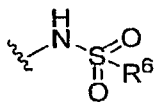
Formula VII

or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula VII:

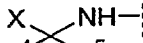
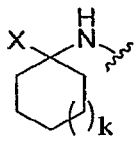
M is O, N(H), or CH_2;

n is 0-4;

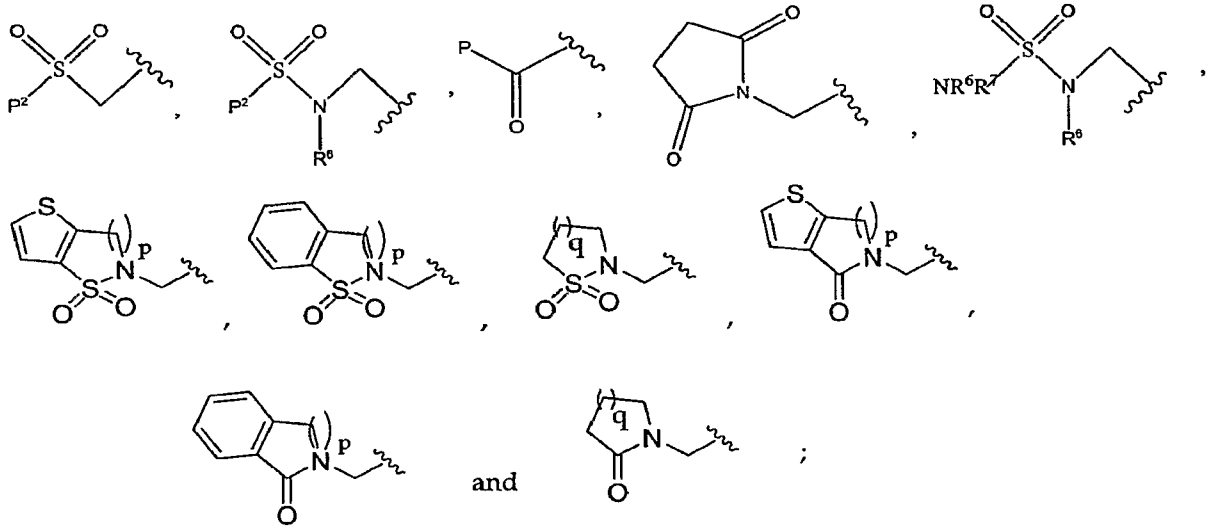
R^1 is $-OR^6$, $-NR^6R^7$ or ;

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;

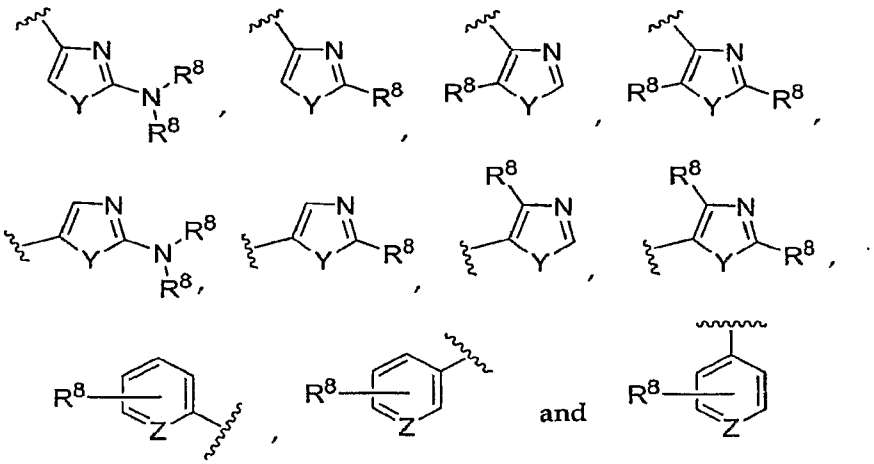
X is selected from the group consisting of:



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

and

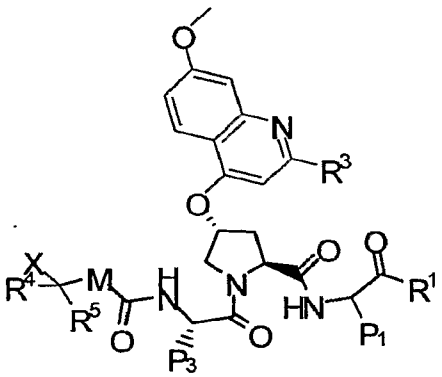
R^3 is selected from the group consisting of: aryl, heterocyclyl, heteroaryl,



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;

viii.



Formula VIII

or a pharmaceutically acceptable salt, solvate or ester thereof;

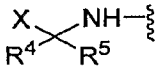
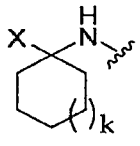
wherein in Formula VIII:

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

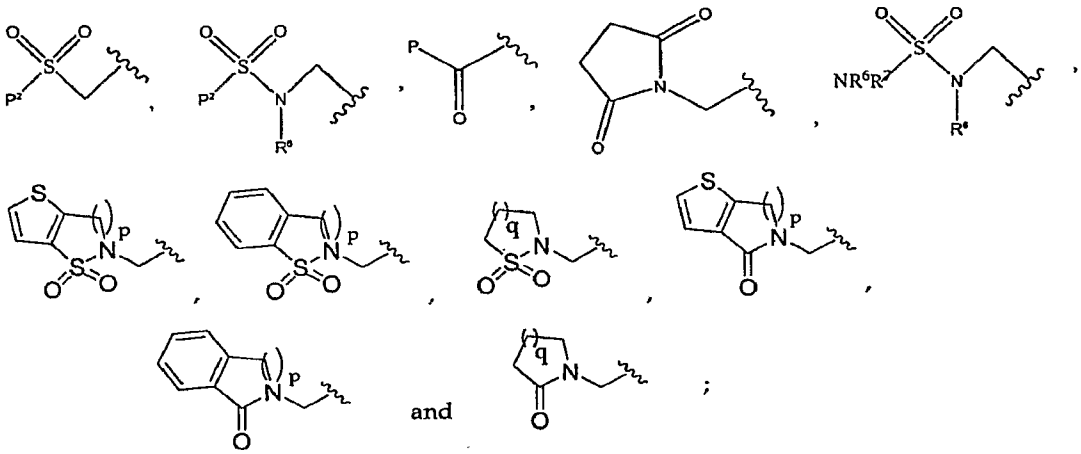
R^1 is $-C(O)NHR^6$, where R^6 is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, hydroxyl, amino, arylamino or alkylamino;

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;

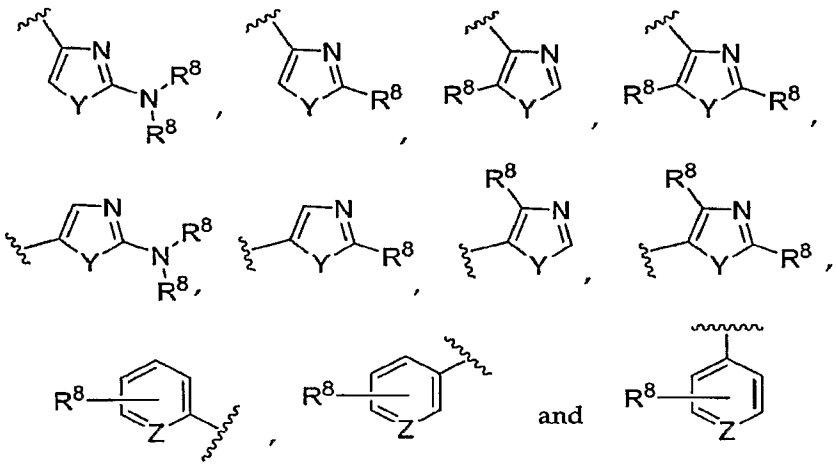
X is selected from the group consisting of:



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;

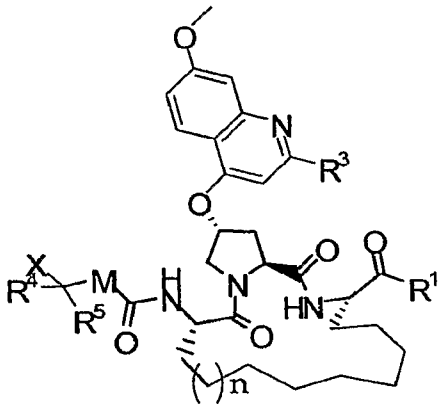
and

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;

ix.



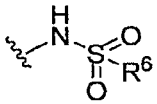
Formula IX

or a pharmaceutically acceptable salt, solvate or ester thereof;

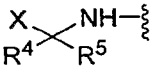
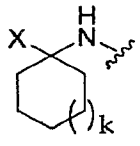
wherein in Formula IX:

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

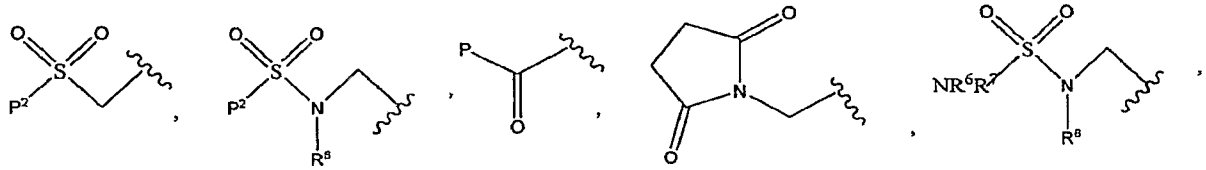
n is 0-4;

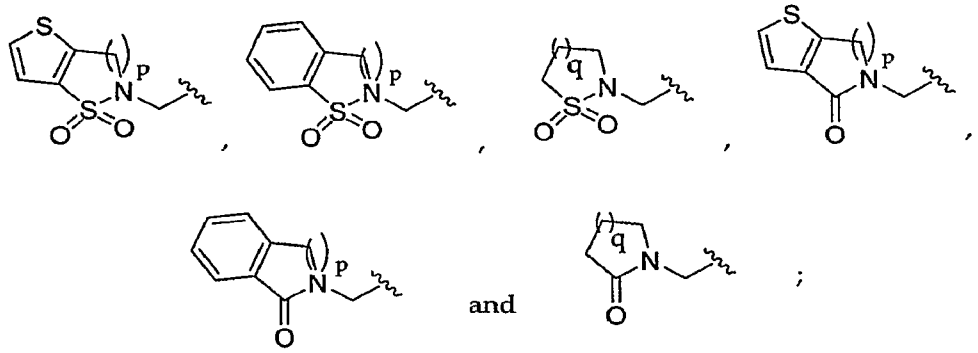
R^1 is $-OR^6$, $-NR^6R^7$ or ;

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:

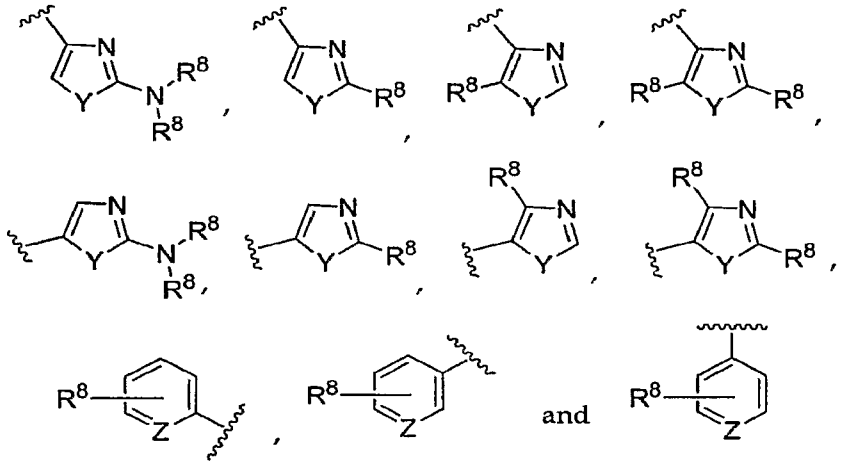




where p is 1 to 2, q is 1 to 3 and P^2 is alkyl, aryl, heteroaryl, heteroalkyl, cycloalkyl, dialkylamino, alkylamino, arylamino or cycloalkylamino;

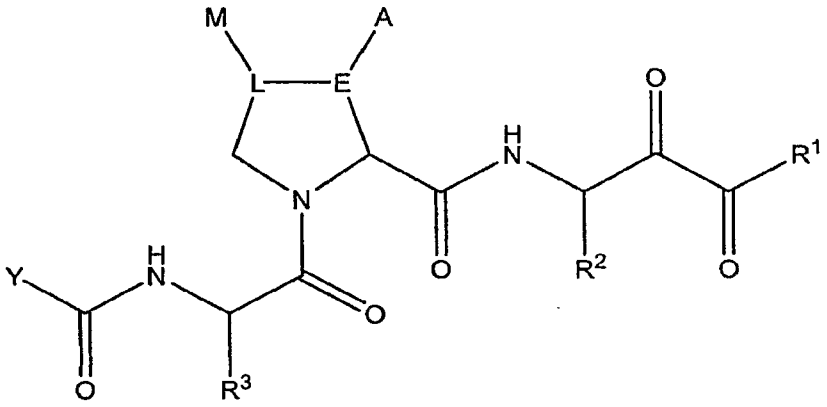
and

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;

x.



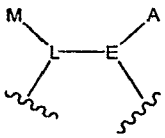
Formula X

or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula X:

R^1 is NHR^9, wherein R^9 is H, alkyl-, alkenyl-, alkynyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, heterocyclyl-, arylalkyl-, or 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:



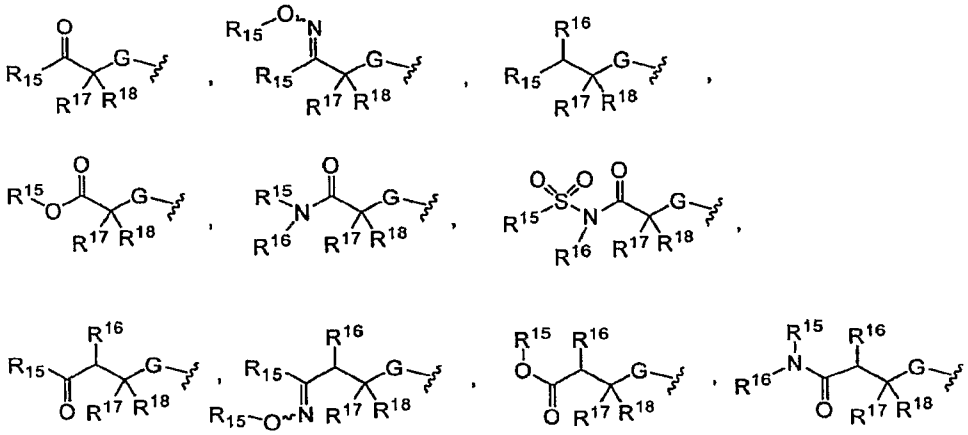
shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl;

E is C(H) or C=;

L is C(H), C=, CH_2C=, or C=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;

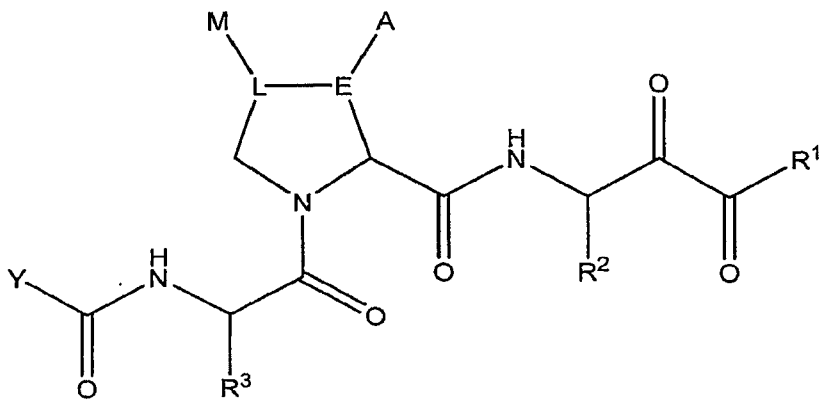
and Y is selected from the following moieties:



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;

xi.



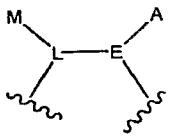
Formula XI

or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XI:

R^1 is NHR^9, wherein R^9 is H, alkyl-, alkenyl-, alkynyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, heterocyclyl-, arylalkyl-, or 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:



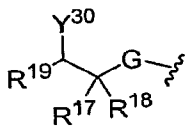
shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl;

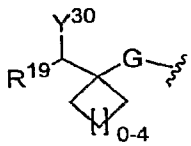
E is C(H) or C=;

L is C(H), C=, CH_2C=, or C=CH_2;

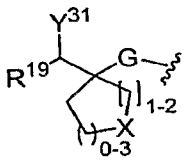
R, R', R^2, and R^3 can be the same or different, each being independently selected from the group consisting of H, alkyl-, alkenyl-, alkynyl-, cycloalkyl-, heteroalkyl-,heterocyclyl-, aryl-, heteroaryl-, (cycloalkyl)alkyl-, (heterocyclyl)alkyl-, aryl-alkyl-, and heteroaryl-alkyl-; or alternately R and 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:

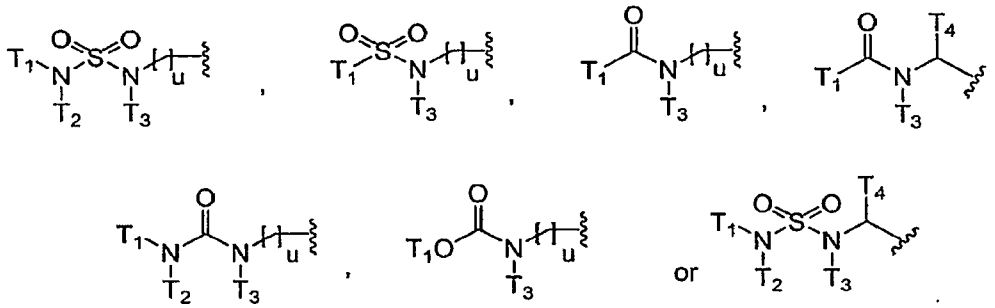




or



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



where u is a number 0-6;

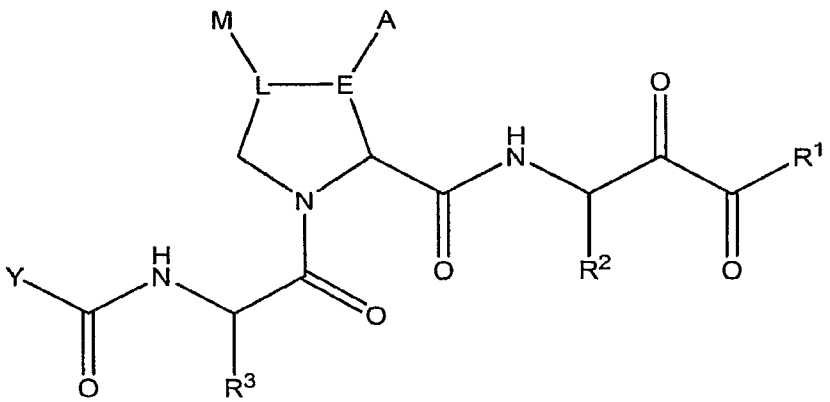
X is selected from O, NR^{15}, $NC(O)R^{16}$, S, S(O) and SO_2;

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;

xii.



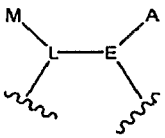
Formula XII

or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XII:

R^1 is NHR^9, wherein R^9 is H, alkyl-, alkenyl-, alkynyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, heterocyclyl-, arylalkyl-, or 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:



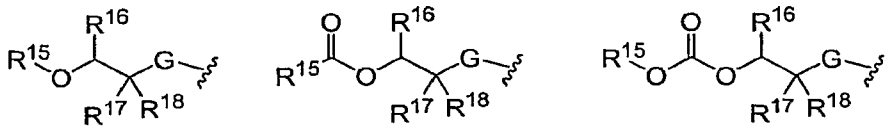
shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl;

E is C(H) or C=;

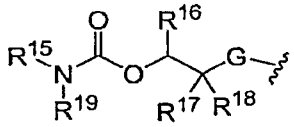
L is C(H), C=, CH_2C=, or C=CH_2;

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

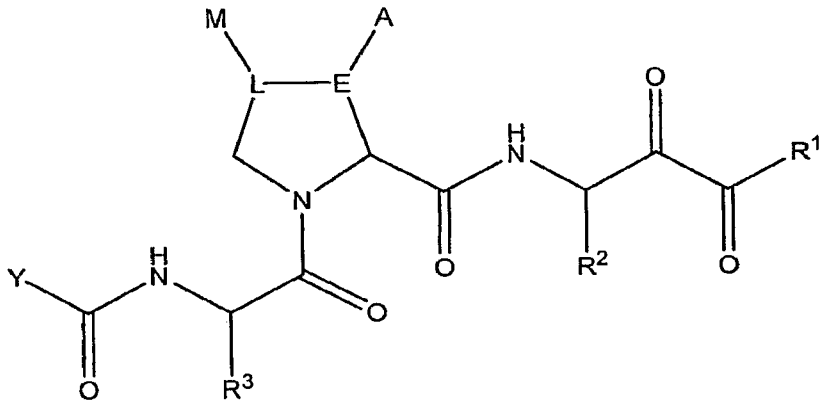


wherein G is NH or O; and R^{15}, R^{16}, R^{17}, R^{18}, and R^{19} can be the same or different, each being independently selected from the group consisting of H, alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl,

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: □ulfonam, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, amido, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, □ulfonamide, alkylsulfonamido, arylsulfonamido, alkyl, aryl, heteroaryl, keto, carboxy, carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyloxy, alkylureido, arylureido, halo, cyano, and nitro;

xiii.



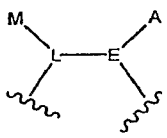
Formula XIII

or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XIII:

R^1 is NHR^9, wherein R^9 is H, alkyl-, alkenyl-, alkynyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, heterocyclyl-, arylalkyl-, or 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:



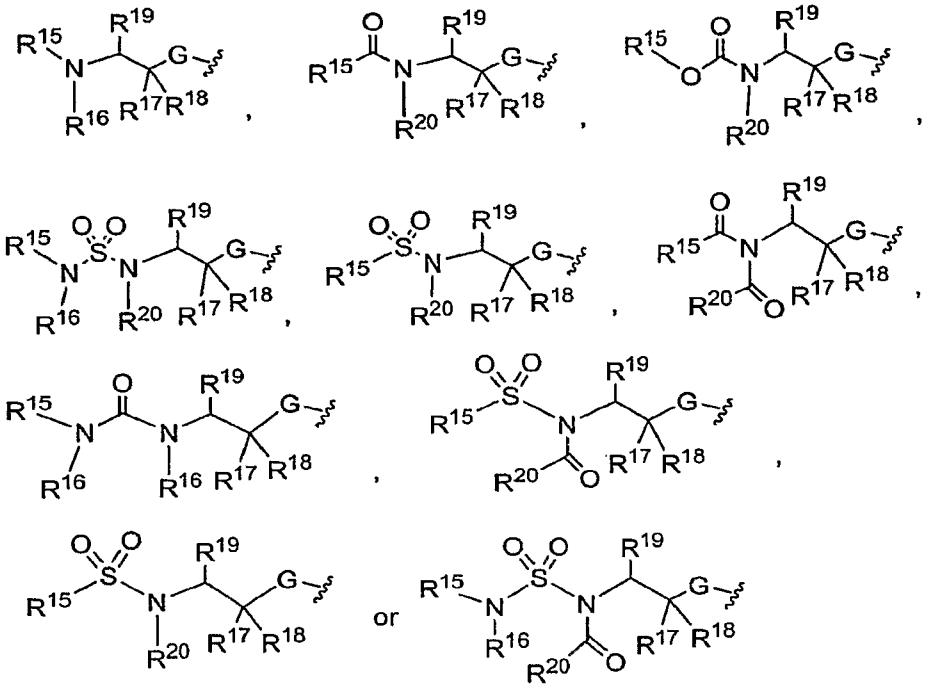
shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl;

E is C(H) or C=;

L is C(H), C=, CH_2C=, or C=CH_2;

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

and Y is selected from the following moieties:

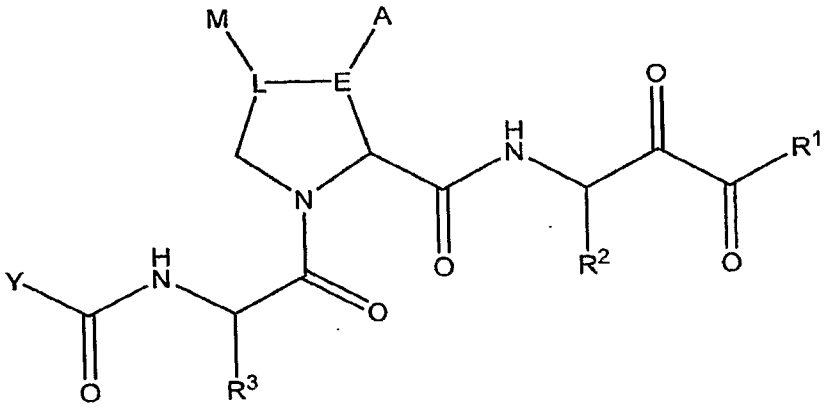


wherein G is NH or O, and R^{15}, R^{16}, R^{17} , R^{18}, R^{19} and R^{20} can be the same or different, each being independently selected from the group consisting of H, C_1-C_{10} alkyl, C_1-C_{10} heteroalkyl, C_2-C_{10} alkenyl, C_2-C_{10} heteroalkenyl, C_2-C_{10} alkynyl, C_2-C_{10} heteroalkynyl,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

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

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

xiv.



Formula XIV

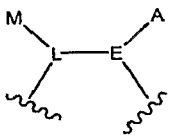
or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XIV:

R^1 is NHR^9, wherein R^9 is H, alkyl-, alkenyl-, alkynyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, heterocyclyl-, arylalkyl-, or 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:



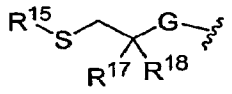
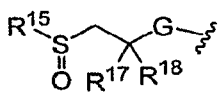
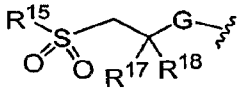
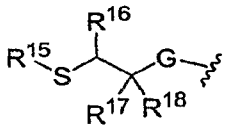
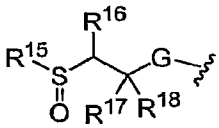
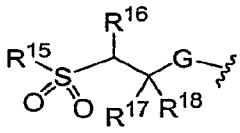
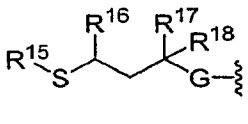
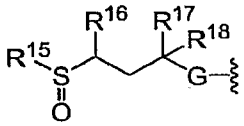
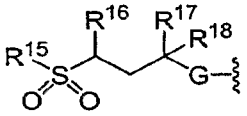
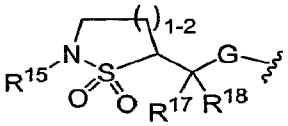
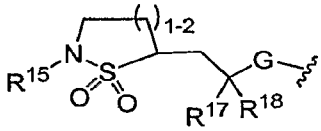
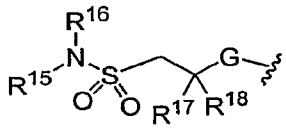
shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl;

E is C(H) or C=;

L is C(H), C=, CH_2C=, or C=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:

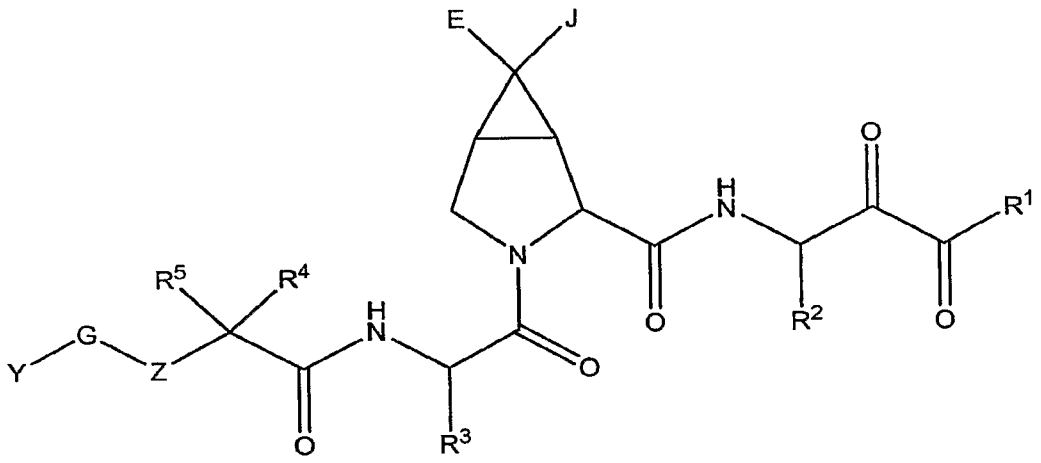

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and


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;

xv.



Formula XV

or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XV:

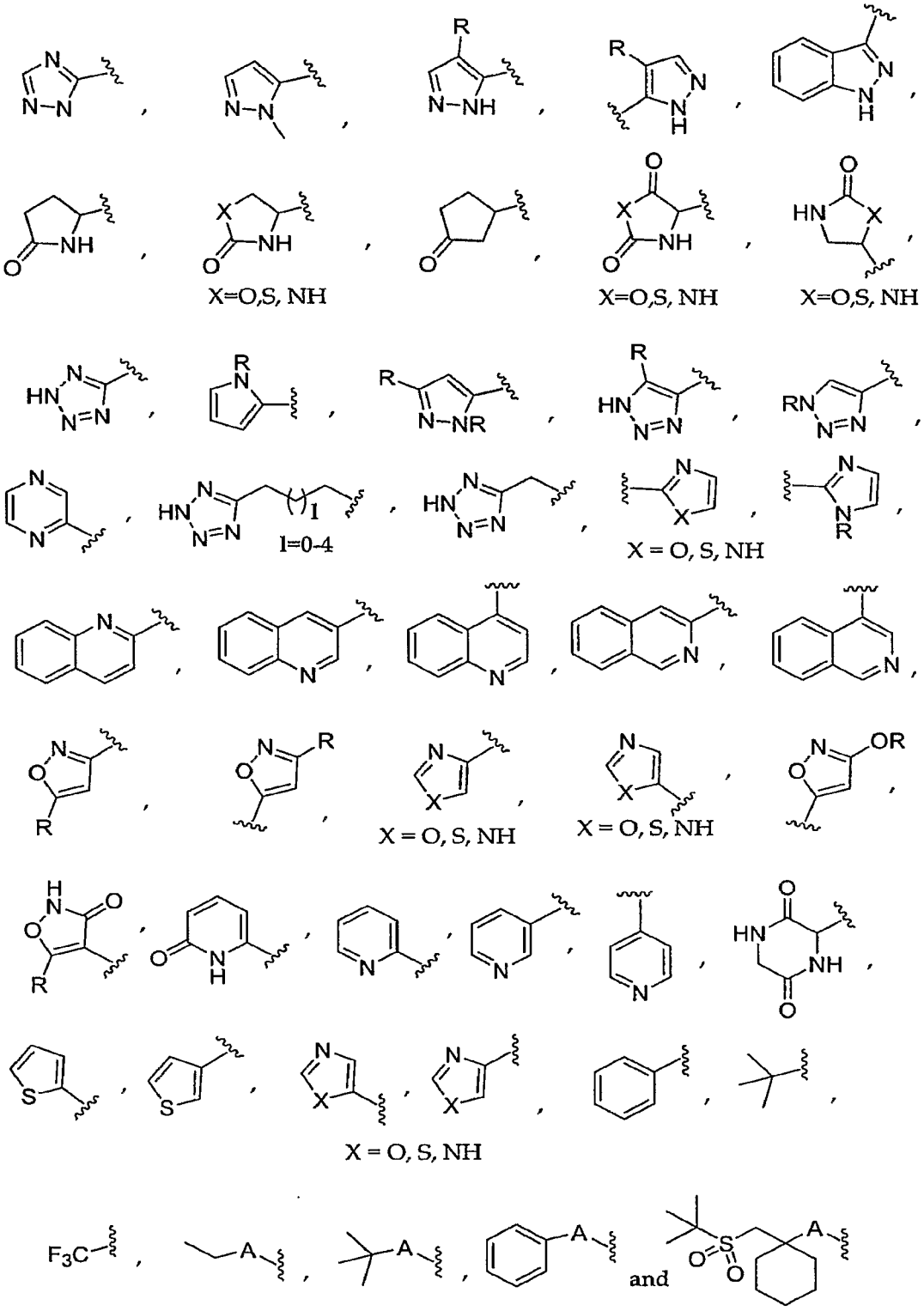
R^1 is NHR^9, wherein R^9 is H, alkyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, cycloalkyl-, arylalkyl-, or heteroarylalkyl;

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=, 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:

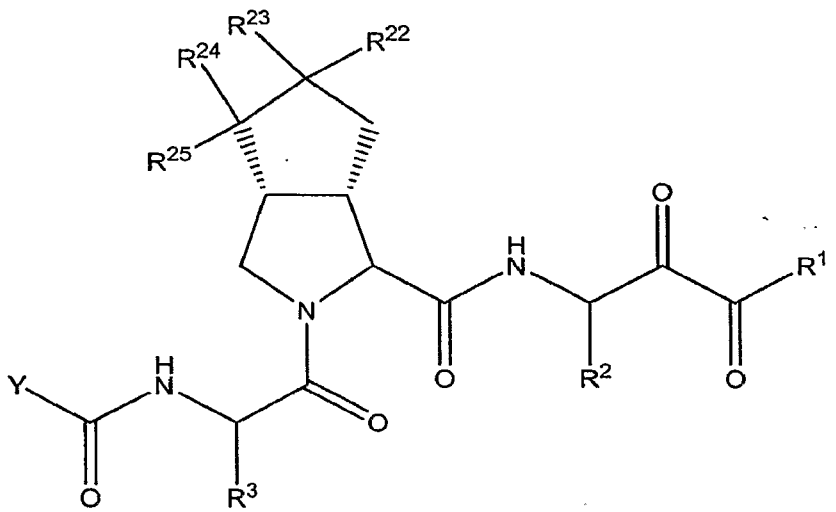

X=O,S, NH
X=O,S, NH
X=O,S, NH
l=0-4
X = O, S, NH
X = O, S, NH
X = O, S, NH
X = O, S, NH
and
A = O, NH

;

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;

xvi.



Formula XVI

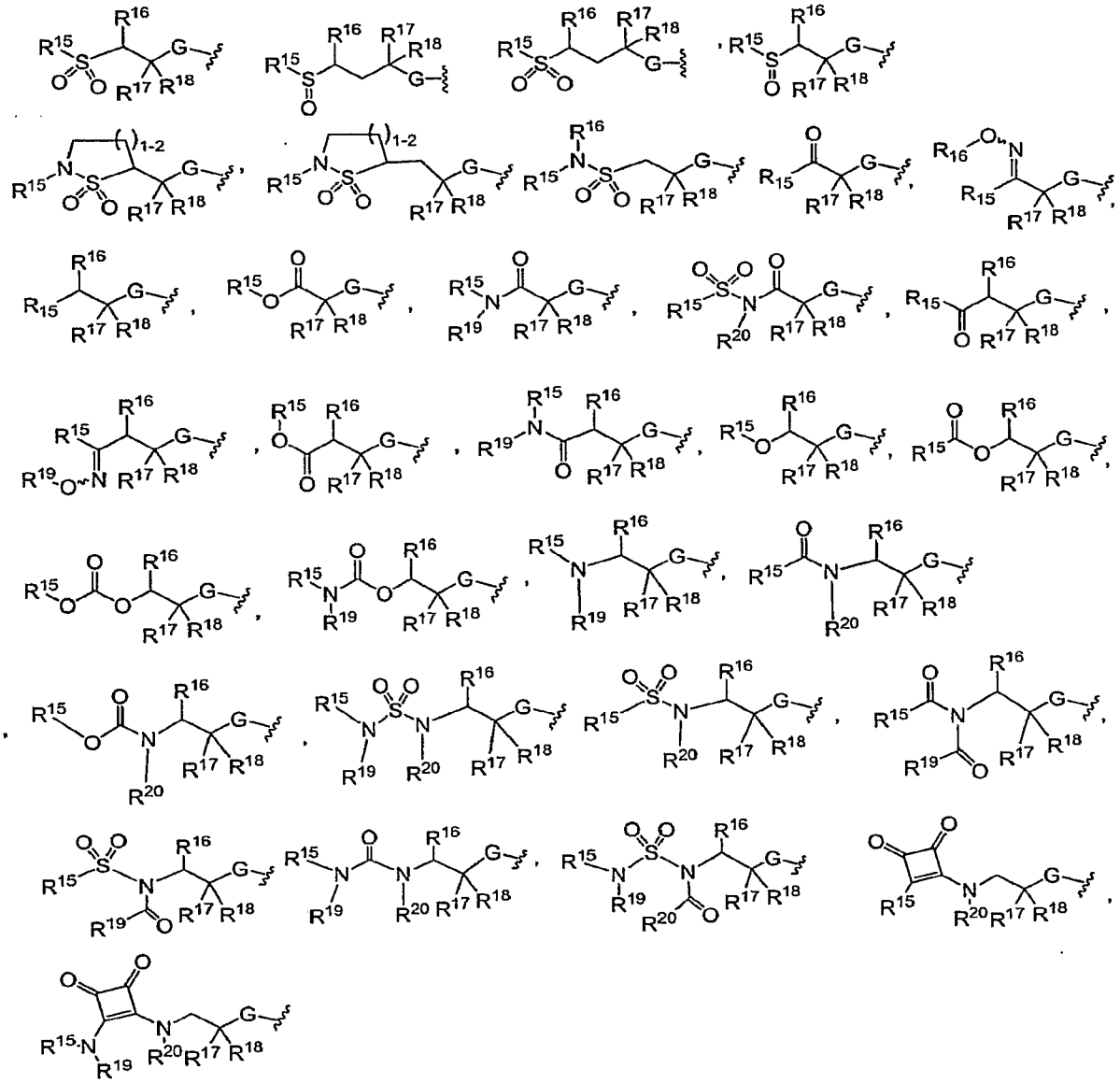
or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XVI:

R^1 is NHR^9, wherein R^9 is H, alkyl-, alkenyl-, alkynyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, heterocyclyl-, arylalkyl-, or heteroarylalkyl;

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:

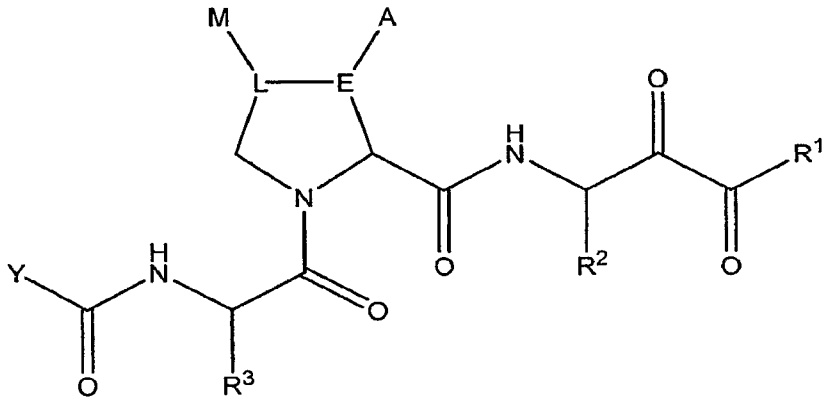


wherein G is NH or O; and R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24} and R^{25} can be the same or different, each being independently selected from the group consisting of H, alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, cycloalkyl, heterocyclyl,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

xvii.



Formula XVII

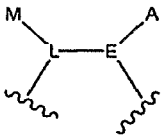
or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XVII:

R^1 is NHR^9, wherein R^9 is H, alkyl-, alkenyl-, alkynyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, heterocyclyl-, arylalkyl-, or 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:



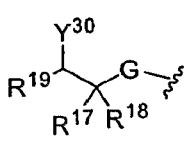
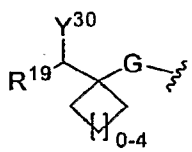
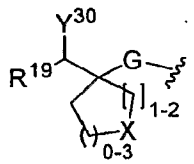
shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl;

E is C(H) or C=;

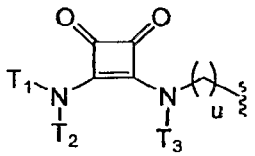
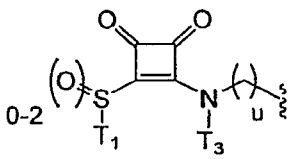
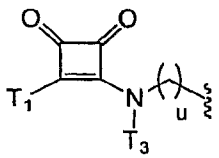
L is C(H), C=, CH_2C=, or C=CH_2;

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:



or


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;

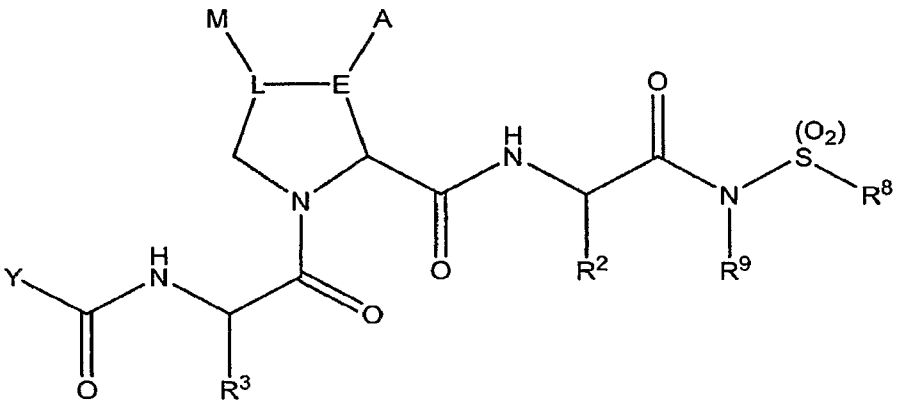
G is NH or O; and

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;

xviii.



Formula XVIII

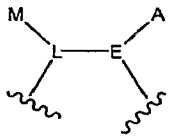
or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XVIII:

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;

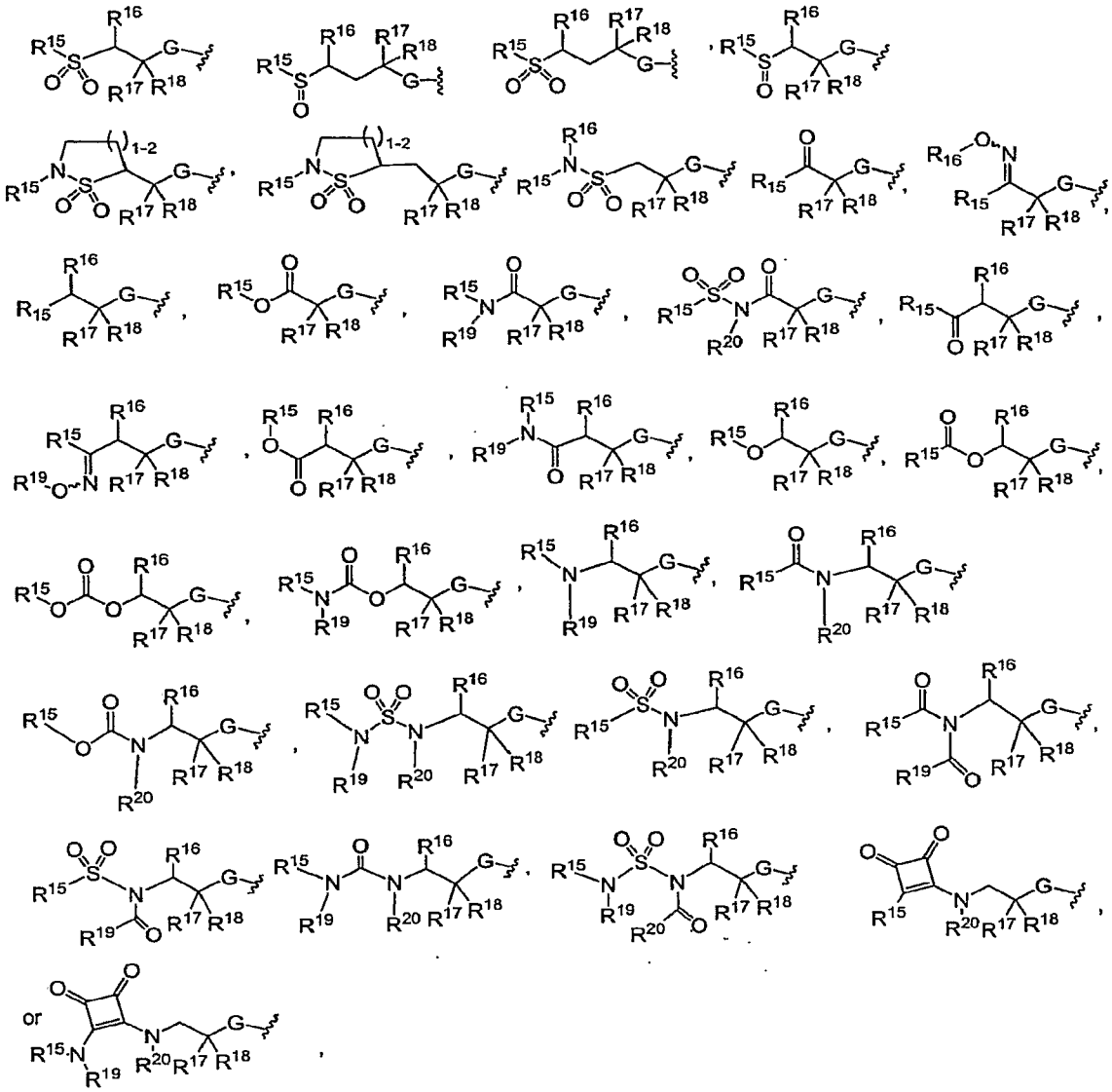
E is C(H) or C(R);

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;

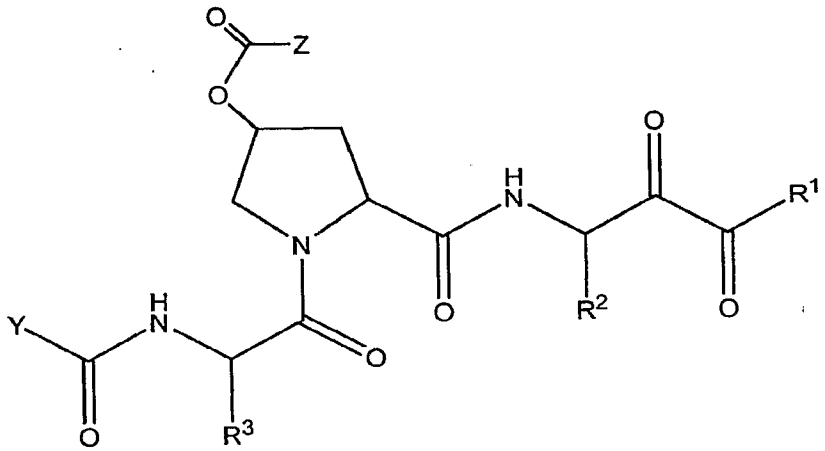
Y is selected from the following moieties:



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;

xix.



Formula XIX

or a pharmaceutically acceptable salt, solvate or ester thereof;

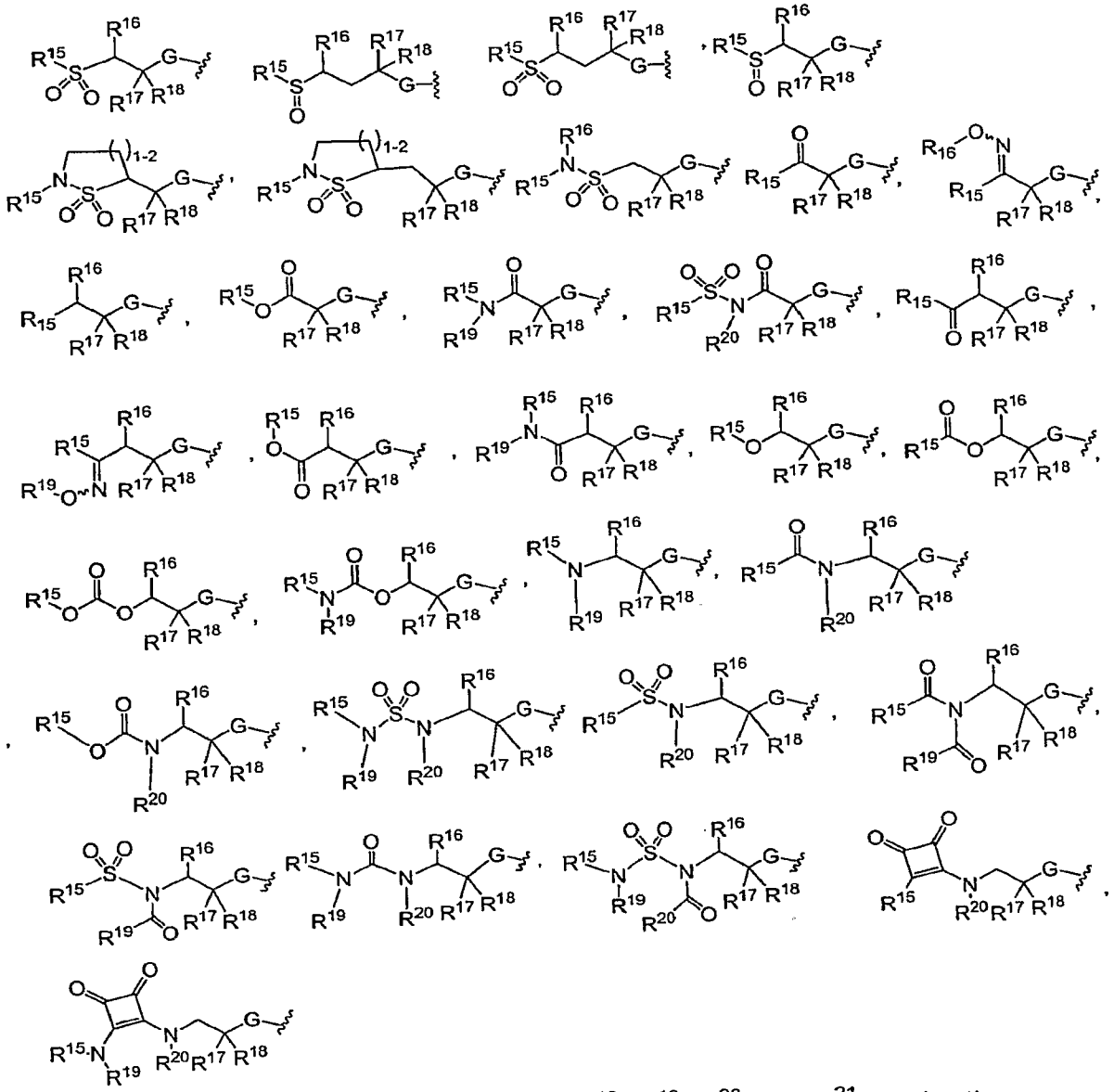
wherein in Formula XIX:

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 NHR^9, wherein R^9 is H, alkyl-, alkenyl-, alkynyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, heterocyclyl-, arylalkyl-, or heteroarylalkyl;

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;

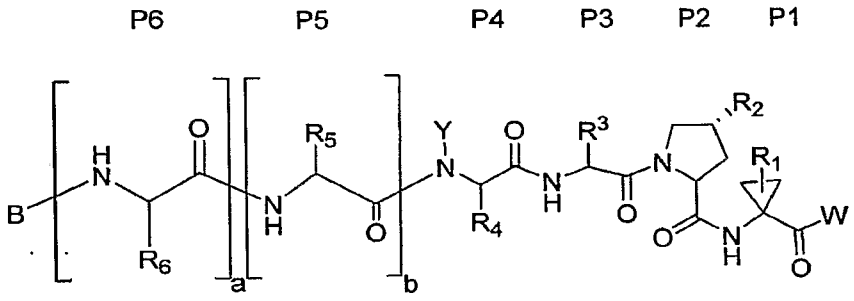
Y is selected from the following moieties:



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;

xx.



Formula XX

or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XX:

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;

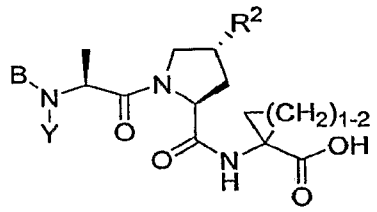
R_5, when present, is C_{1-6} alkyl optionally substituted with carboxyl;

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; $N0_2$; 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; $N0_2$; 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 the above-shown structure of the compound of Formula XX, 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;

xxi.



Formula XXI
or a pharmaceutically acceptable salt, solvate or ester thereof;
wherein in Formula XXI:
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},

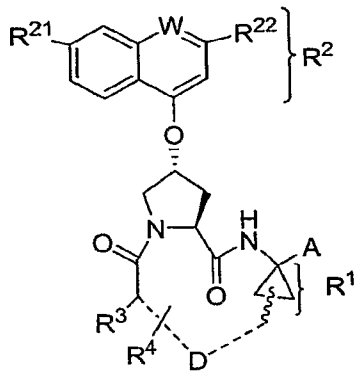
wherein each R_{21} is independently C_{1-6} alkyl; C_{1-6} alkoxy; lower thioalkyl; sulfonyl; NO_2; OH; SH; halo; haloalkyl; amino optionally mono- or di- substituted with C_{1-6} alkyl, C_6 or C_{10} aryl, C_{7-14} aralkyl, Het or (lower alkyl)-Het; amido optionally

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;

xxii.



Formula XXII

or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XXII:

W is CH or N,

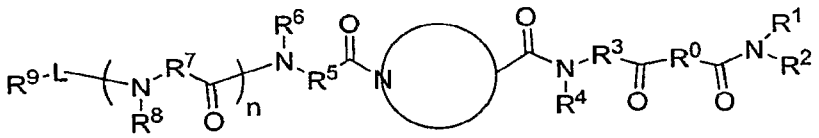
R^{21} is H, halo, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkoxy, hydroxy, or $N(R^{23})_2$, wherein each R^{23} is independently H, C_{1-6} alkyl or C_{3-6} cycloalkyl;

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;

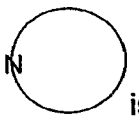
or R^{24} is NH-C(O)-OR^{26} wherein R^{26} is C_{1-6} alkyl or C_{3-6} cycloalkyl;
R^3 is hydroxy, NH_2 , or a group of formula -NH-R^{31} , wherein R^{31} is $C_{6 \text{ or } 10}$ aryl, heteroaryl, -C(O)-R^{32}, -C(O)-NHR^{32} or -C(O)-OR^{32} , wherein R^{32} is C_{1-6} alkyl or C_{3-6} cycloalkyl;
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_{1-8} alkyl, C_{3-6} cycloalkyl, $C_{6 \text{ or } 10}$ aryl and C_{7-16} aralkyl;
or A is a carboxylic acid;

xxiii.



Formula XXIII
or a pharmaceutically acceptable salt, solvate or ester thereof;
wherein in Formula XXIII:
R^0 is a bond or difluoromethylene;
R^1 is hydrogen;
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;

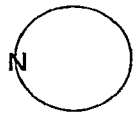
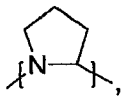


is substituted monocyclic azaheterocyclyl or optionally substituted multicyclic azaheterocyclyl, or optionally substituted multicyclic azaheterocyclenyl wherein the unsaturatation is in the ring distal to the ring bearing the R^9-L-(N(R^8)-R^7-C(O)-)$_n$N(R^6)-R^5-C(O)-N moiety and to which the –C(O)-N(R^4)-R^3-C(O)C(O)NR^2R^1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

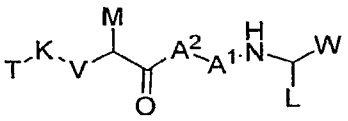
L is -C(O)-, -OC(O)-, -NR^{10}C(O)-, -S(0)$_2$-, or – NR^{10}S(0)$_2$-; and

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;

xxiv.

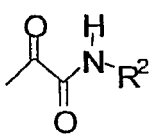


Formula XXIV

or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XXIV:

W is:



;

m is 0 or 1;

R^2 is independently hydrogen, alkyl, alkenyl, aryl, aralkyl, aralkenyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkenyl, heteroaryl, or heteroaralkyl, 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, carboxamidoaikyl, 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;

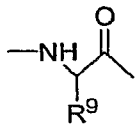
R^8 is hydrogen alkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, aralkanoyl, heterocyclanoyl, heteroaralkanoyl, $-C(O)R^{14}$, $-S0_2R^{14}$, or carboxamido, and is optionally substitititued with 1-3 J groups; or R^8 and Z, together with the atoms to which they are bound,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

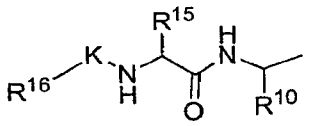
M is alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroaralkyl, optionally substituted by 1-3 J groups, wherein any alkyl carbon atom may be replaced by a heteroatom;

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



;

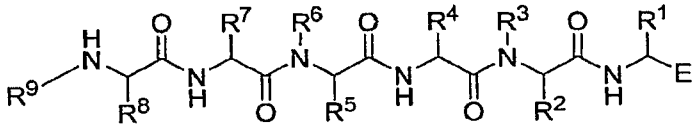
R^{12} is hydrogen, aryl, heteroaryl, cycloalkyl, heterocyclyl, cycloalkylidenyl, or heterocycloalkylidenyl, and is optionally substituted with 1-3 J groups, or a first R^{12} and a second R^{12}, together with the nitrogen to which they are bound, form a mono- or bicyclic ring system optionally substituted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

xxv.



Formula XXV

or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XXV:

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;

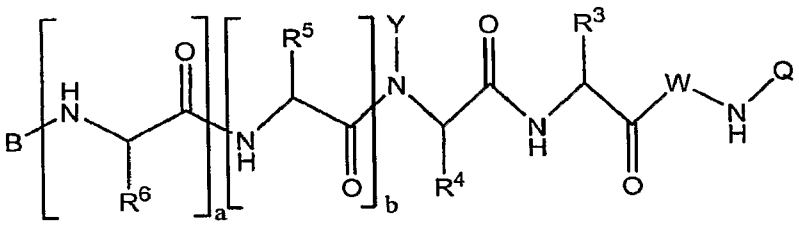
R^6 represents hydrogen or lower alkyl;

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

xxvi.



Formula XXVI

or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XXVI:

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;

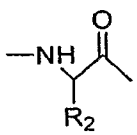
R_5, when present, is C_{1-6} alkyl, or carboxy(lower)alkyl;

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

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

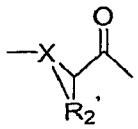
R_3 is C1-10 alkyl; C_{3-10} cycloalkyl;

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

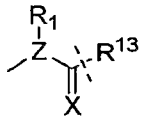
R_2' is C_{3-4} alkylene that joins X to form a 5- or 6-membered ring, said ring optionally substituted with OH; SH; NH2; carboxyl; R_{12}; OR_{12}, SR_{12}, NHR_{12} or $NR_{12}R_{12}$' wherein R_{12} and R_{12}' are independently:

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;

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

R_{13} is C0-NH-R_{14} wherein R_{14} is 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

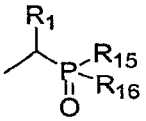
R_{14} is C_6 or C_{10} aryl or C_{7-16} aralkyl optionally substituted with C_{1-6} alkyl, NH_2, OH, SH, halo, carboxyl or carboxy(lower)alkyl or substituted with a further C_{3-7}

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;

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

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;

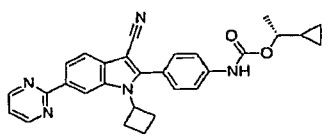
for concurrent or consecutive administration in treating or ameliorating one or more symptoms of HCV, or disorders associated with HCV in a subject in need thereof.

41. The medicament of claim 40, further comprising at least one other therapeutic agent.

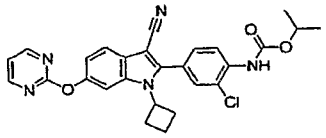
42. The medicament of claim 41, wherein at least one other therapeutic agent is an interferon.

43. The medicament of claim 42, further comprising ribavirin.

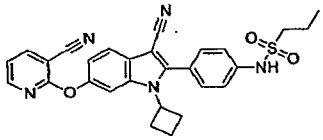
44. The medicament of claim 40, 41, 42, or 43, wherein at least one anti-HCV agent is:



PS 102320 (a/k/a SCH 1385147),



PS 102123 (a/k/a SCH 1383646),



PS 102283 (a/k/a SCH 1385145),

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

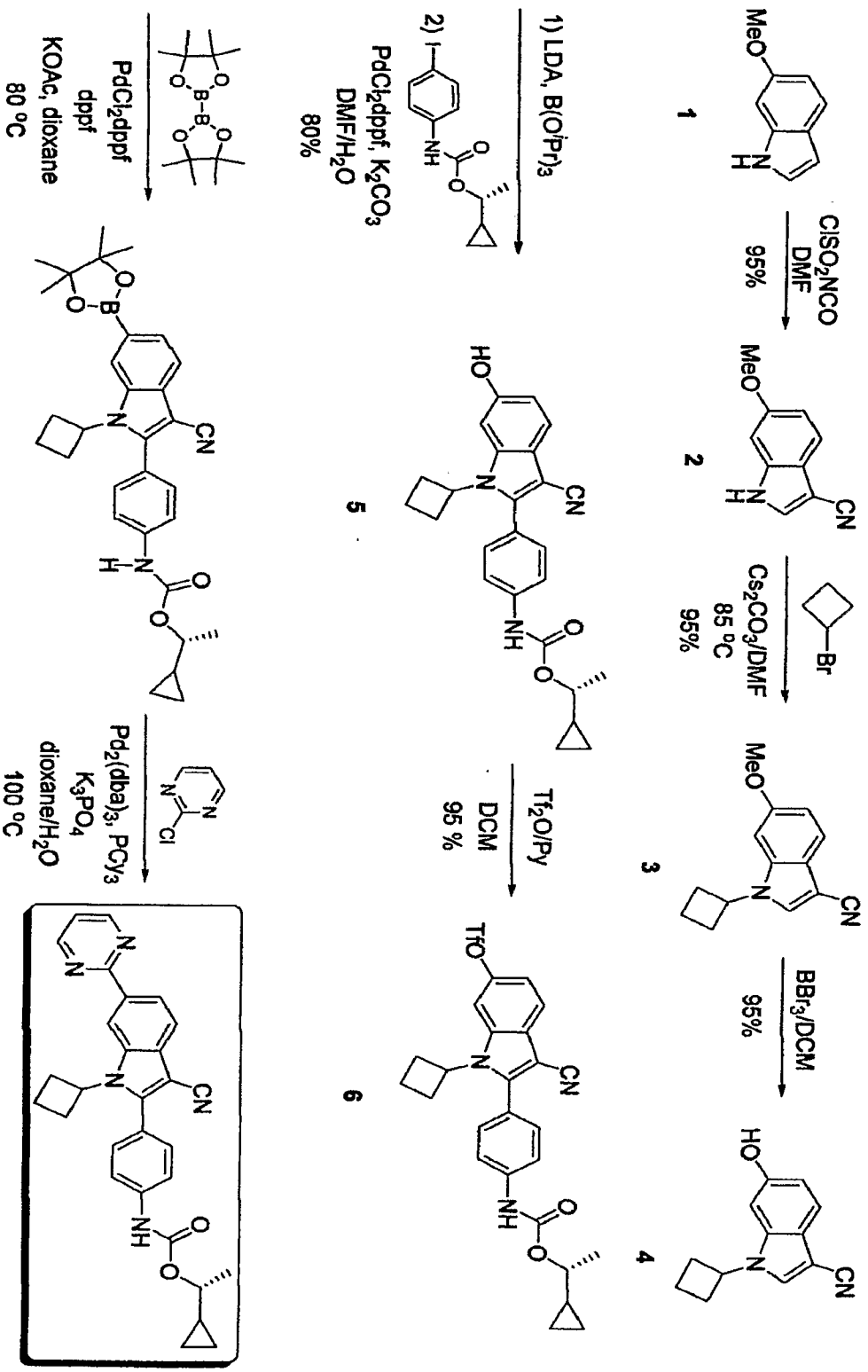

MeO
1
ClSO2NCO
DMF
95%
2
Cs2CO3/DMF
85 °C
95%
3
BBr3/DCM
95%
4
1) LDA, B(O'Pr)3
2)
PdCl2dppf, K2CO3
DMF/H2O
80%
5
Tf2O/Py
DCM
95 %
6
PdCl2dppf
dppf
KOAc, dioxane
80 °C
91%
7
Pd2(dba)3, PCy3
K3PO4
dioxane/H2O
100 °C
89%
PS102320

Figure 1

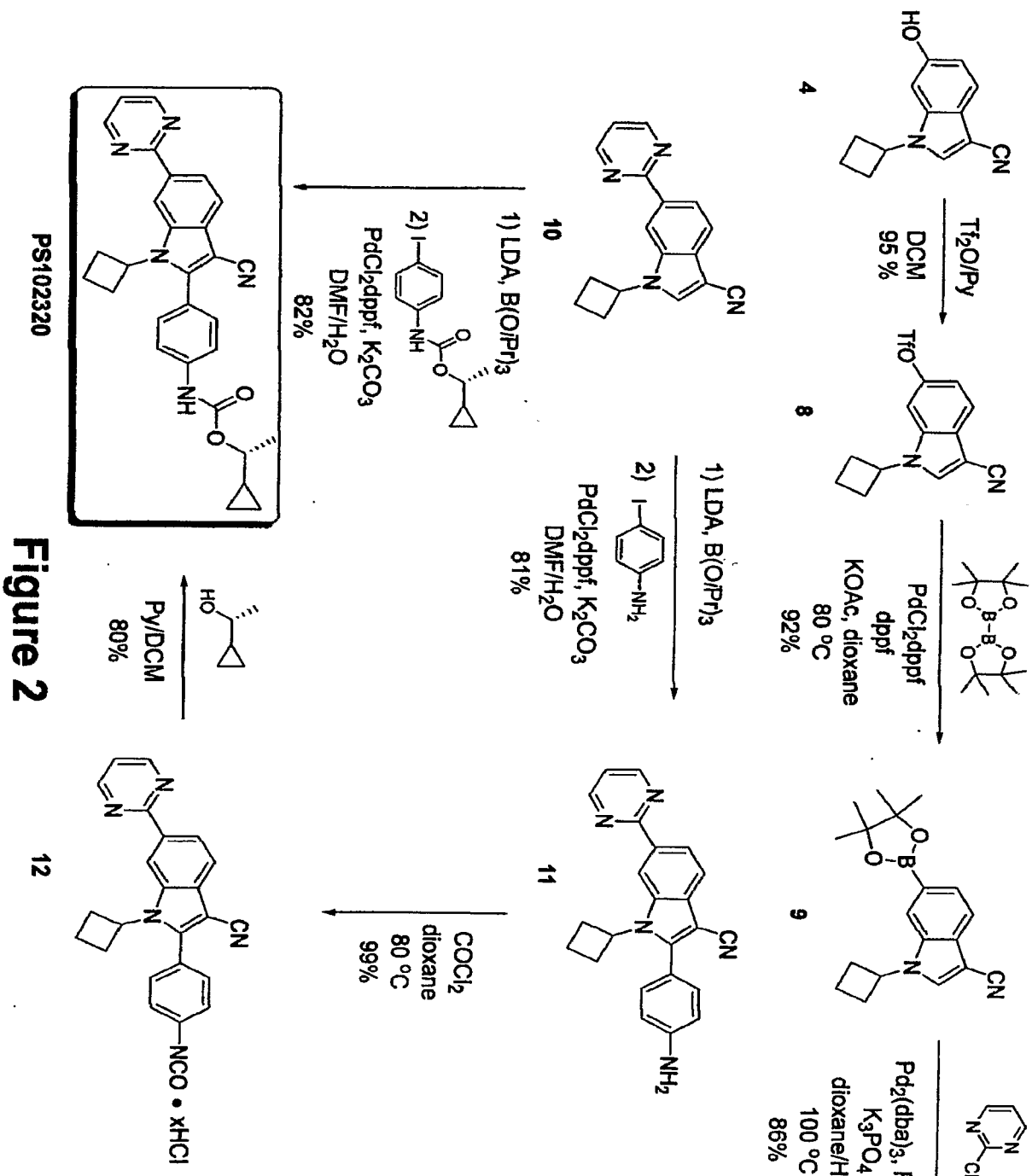

HO
CN
4
Tf2O/Py
DCM
95 %
TfO
CN
8
PdCl2dppf
dppf
KOAc, dioxane
80 °C
92%
O
B
B
O
O
O
CN
9
Pd2(dba)3, PCy3
K3PO4
dioxane/H2O
100 °C
86%
N
Cl
1) LDA, B(OiPr)3
2)
NH2
PdCl2dppf, K2CO3
DMF/H2O
81%
CN
10
NH2
COCl2
dioxane
80 °C
99%
CN
11
NCO • xHCl
CN
12
HO
Py/DCM
80%
1) LDA, B(OiPr)3
2)
I
NH
O
O
PdCl2dppf, K2CO3
DMF/H2O
82%
PS102320

Figure 2

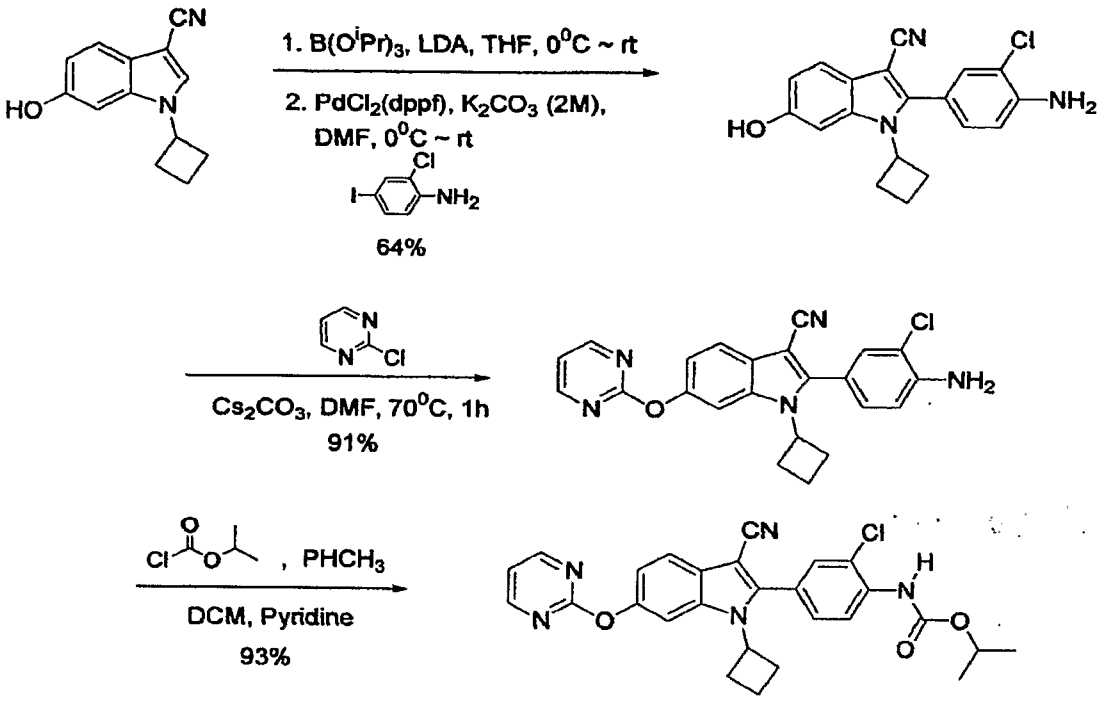

CN
HO
N
1. B(OiPr)3, LDA, THF, 0°C ~ rt
2. PdCl2(dppf), K2CO3 (2M),
DMF, 0°C ~ rt
Cl
I
NH2
64%
CN
Cl
HO
N
NH2
N
N
Cl
Cs2CO3, DMF, 70°C, 1h
91%
CN
Cl
N
N
O
N
NH2
O
Cl
O
, PHCH3
DCM, Pyridine
93%
CN
Cl
N
N
O
N
H
N
O
O

Figure 3

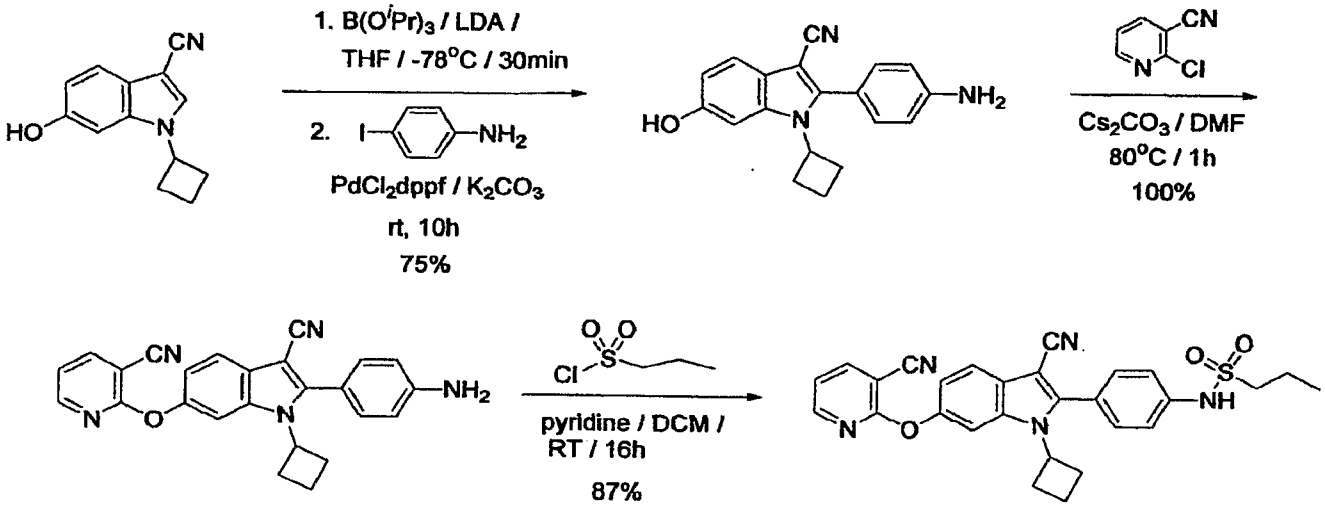

1. B(OiPr)3 / LDA /
THF / -78°C / 30min
2.
PdCl2dppf / K2CO3
rt, 10h
75%
Cs2CO3 / DMF
80°C / 1h
100%
pyridine / DCM /
RT / 16h
87%

Figure 4

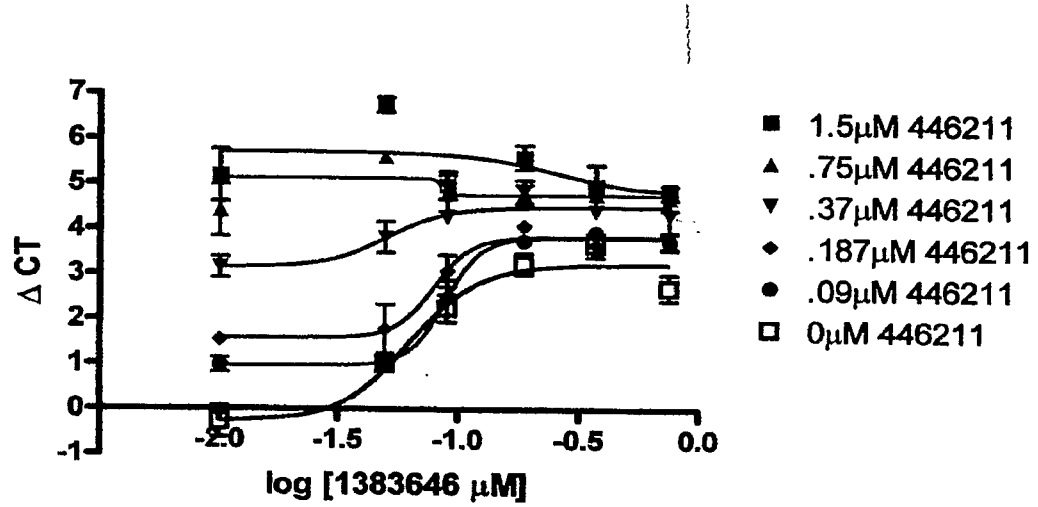

7
6
5
4
3
2
1
0
-1
ΔCT
-2.0
-1.5
-1.0
-0.5
0.0
log [1383646 μM]
1.5μM 446211
.75μM 446211
.37μM 446211
.187μM 446211
.09μM 446211
0μM 446211

Figure 5

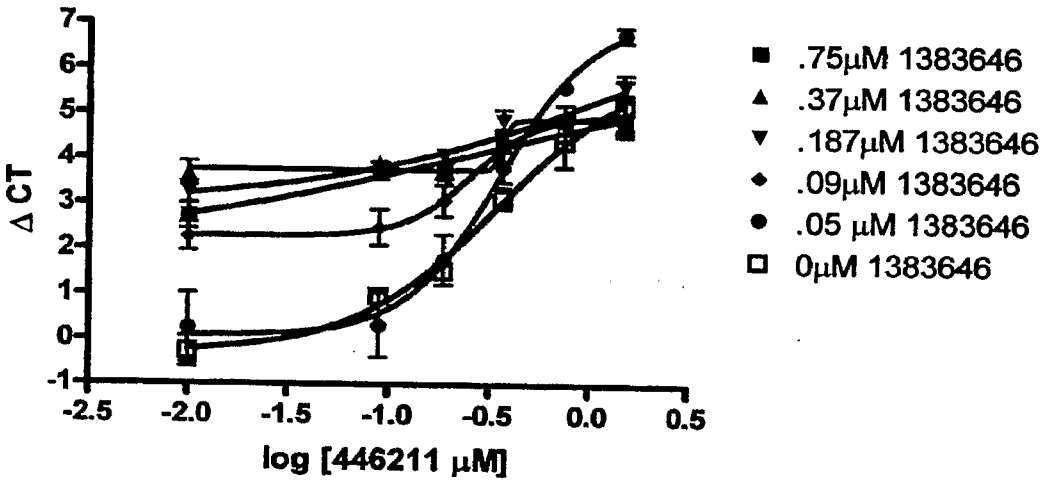

ΔCT
7
6
5
4
3
2
1
0
-1
-2.5
-2.0
-1.5
-1.0
-0.5
0.0
0.5
log [446211 μM]
.75μM 1383646
.37μM 1383646
.187μM 1383646
.09μM 1383646
.05 μM 1383646
0μM 1383646

Figure 6