



US 20070274951A1

(19) United States

(12) Patent Application Publication

Tong et al.

(10) Pub. No.: US 2007/0274951 A1

(43) Pub. Date: Nov. 29, 2007

- (54) COMBINATIONS COMPRISING HCV PROTEASE INHIBITOR(S) AND HCV POLYMERASE INHIBITOR(S), AND METHODS OF TREATMENT RELATED THERETO

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**PATENT DEPARTMENT (K-6-1, 1990)**  
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(21) Appl. No.: 11/705,087

(22) Filed: Feb. 9, 2007

**Related U.S. Application Data**

- (60) Provisional application No. 60/771,927, filed on Feb. 9, 2006. Provisional application No. 60/841,298, filed on Aug. 30, 2006.

**Publication Classification**

(51) Int. Cl.

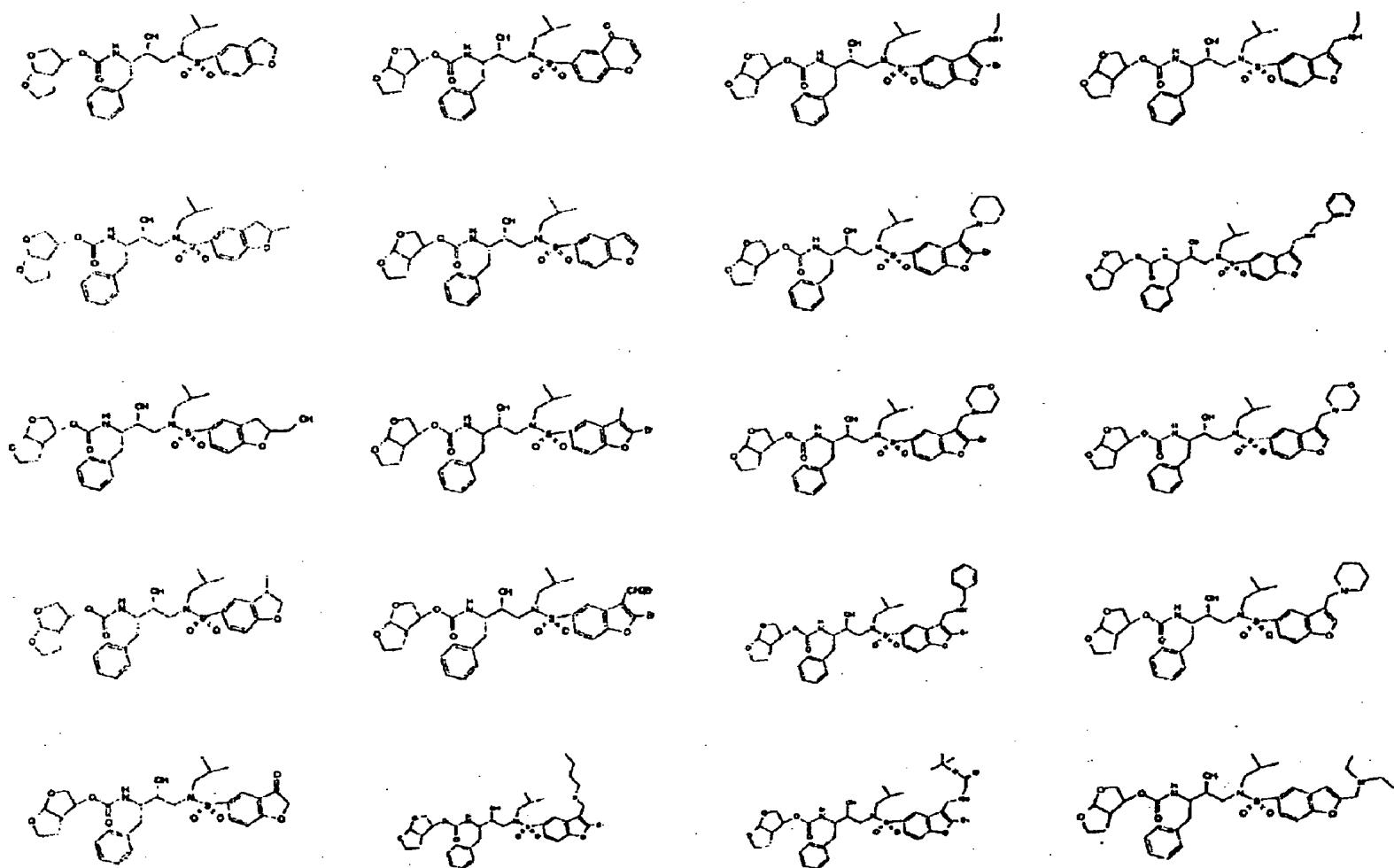
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*A61K 31/16* (2006.01)  
*A61K 31/40* (2006.01)  
*A61K 31/44* (2006.01)  
*A61K 31/445* (2006.01)  
*A61K 31/47* (2006.01)  
*A61P 31/12* (2006.01)  
*A61K 31/535* (2006.01)  
*A61K 31/54* (2006.01)  
*A61K 31/555* (2006.01)  
*A61K 31/70* (2006.01)

- (52) U.S. Cl. .... 424/85.7; 424/85.4; 514/183; 514/223.2; 514/235.2; 514/299; 514/309; 514/319; 514/410; 514/412; 514/416; 514/423; 514/424; 514/428; 514/43; 514/45; 514/46; 514/626

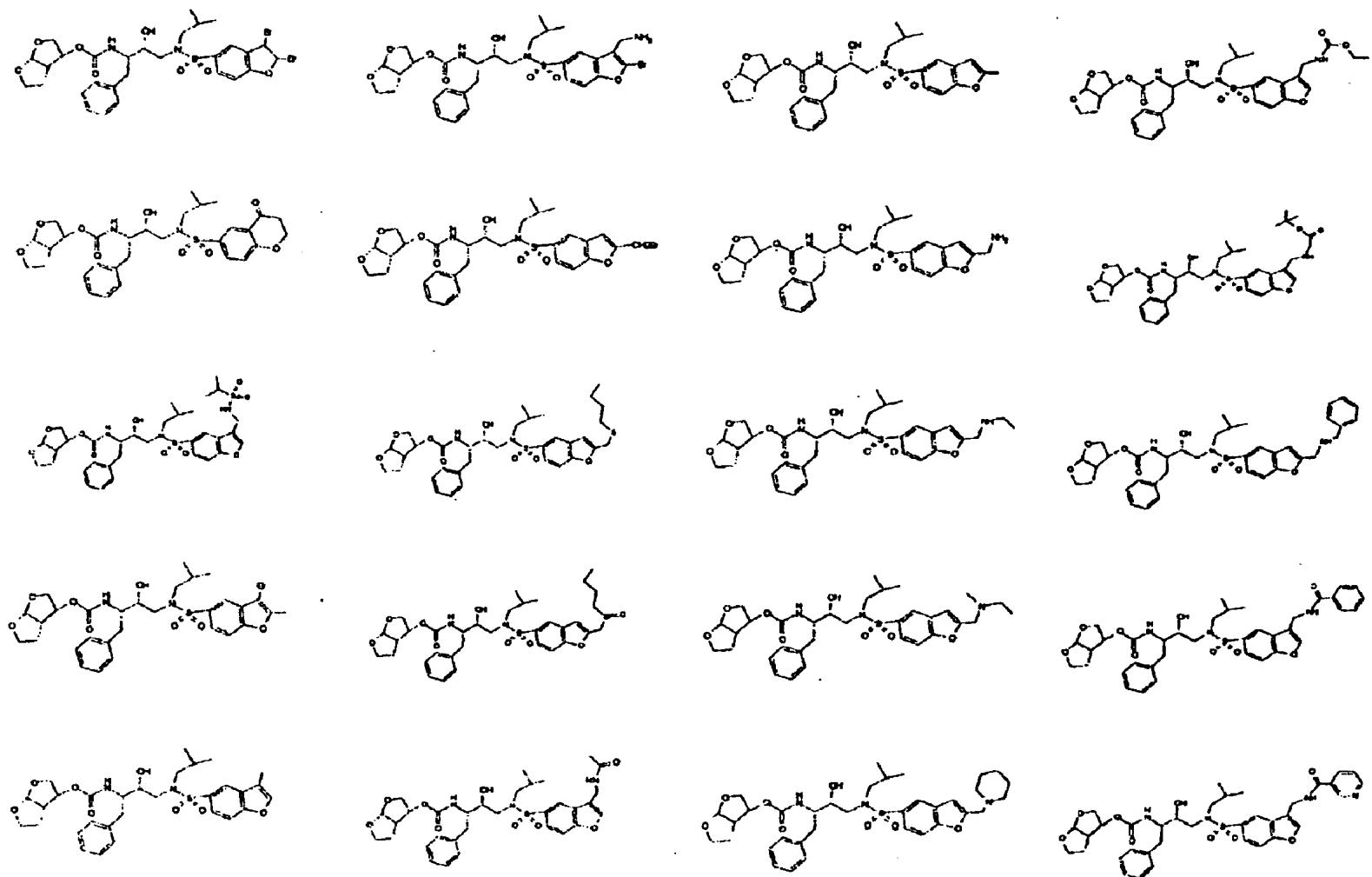
(57) **ABSTRACT**

Disclosed are medicaments, pharmaceutical compositions, pharmaceutical kits, and methods based on combinations of at least one HCV protease inhibitor and at least one HCV polymerase inhibitor but not HCV-796; 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.

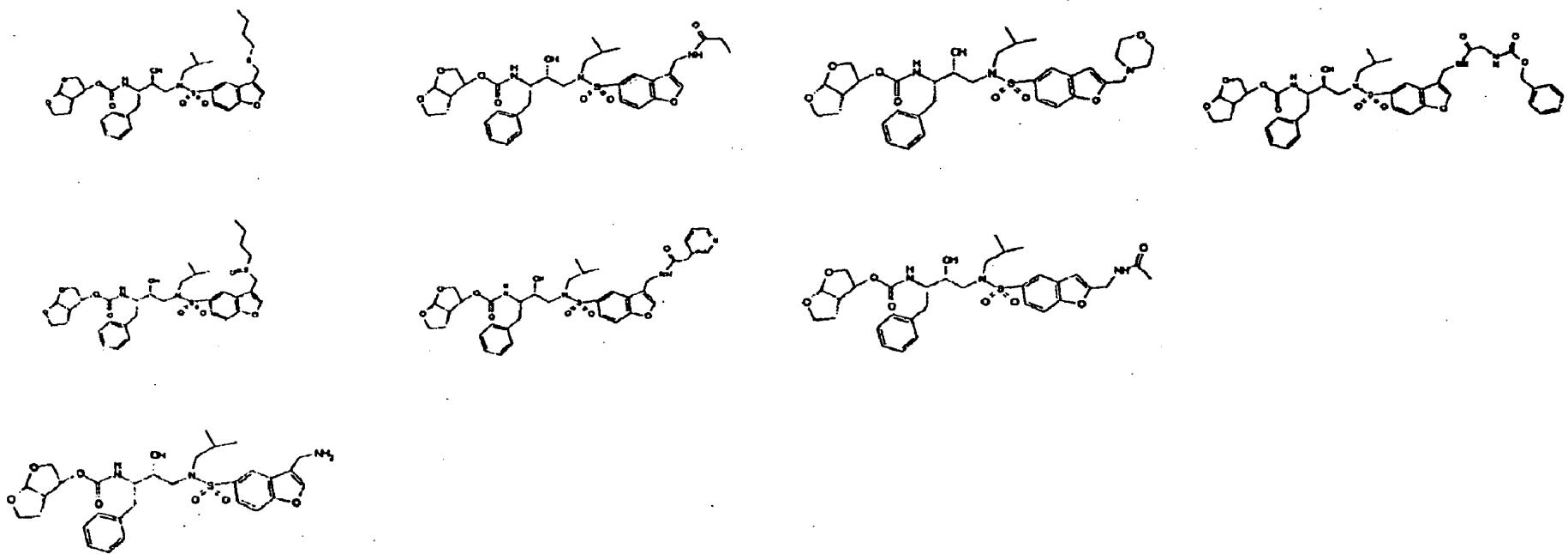




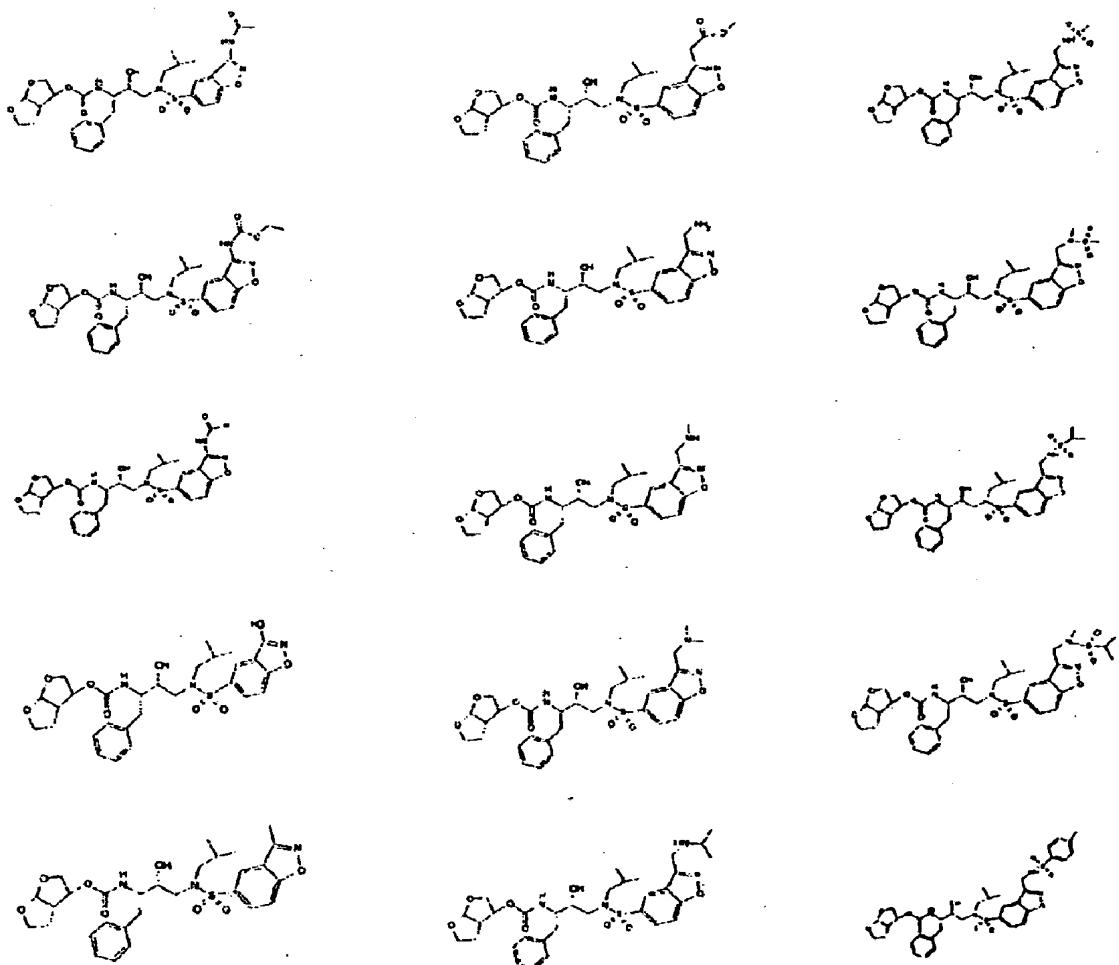
**Figure 1A**



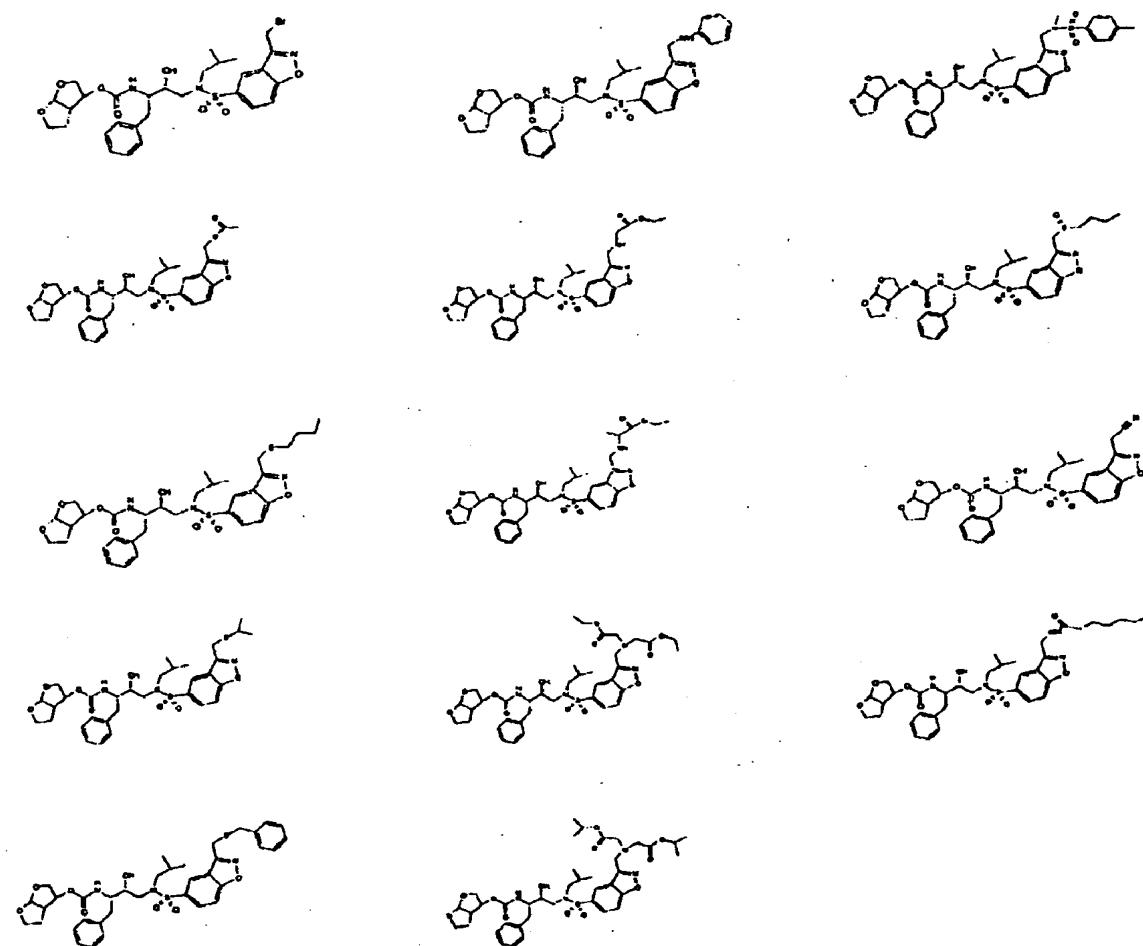
**Figure 1B**



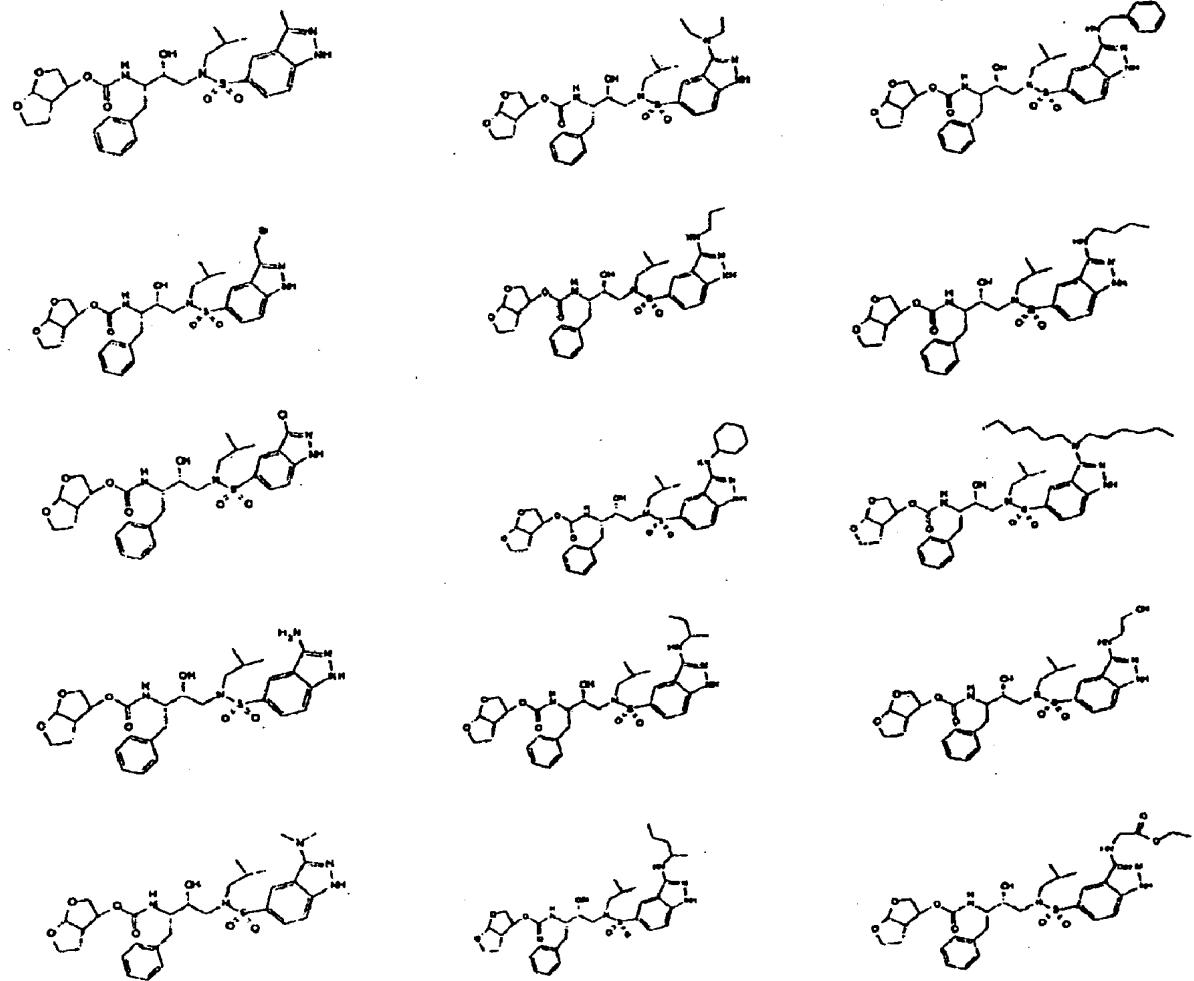
**Figure 1C**



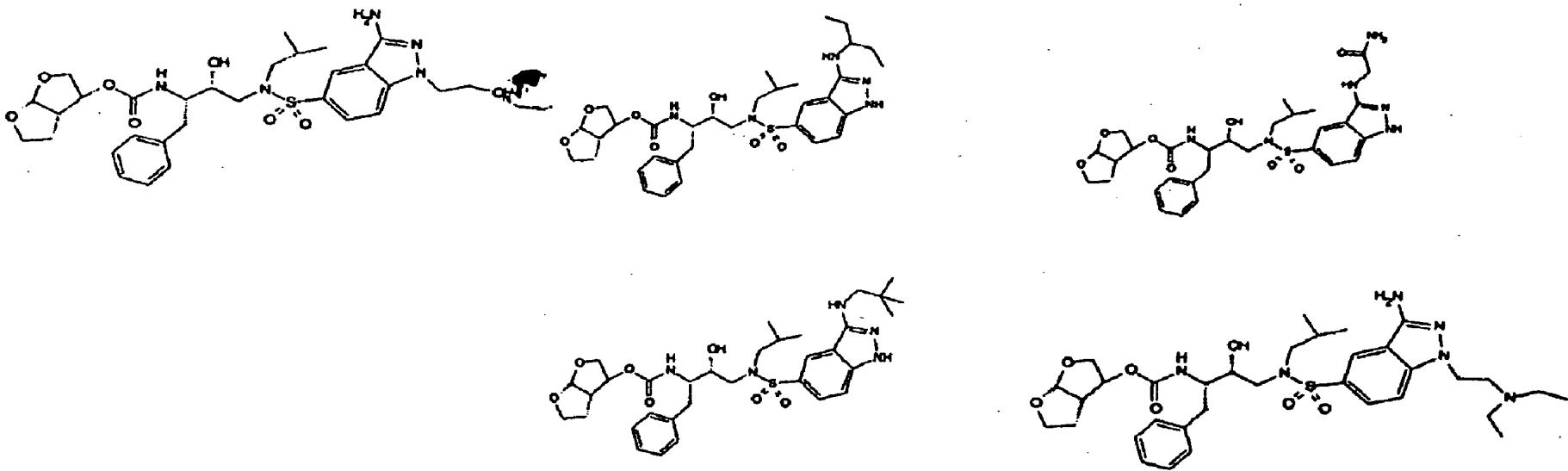
**Figure 1D**



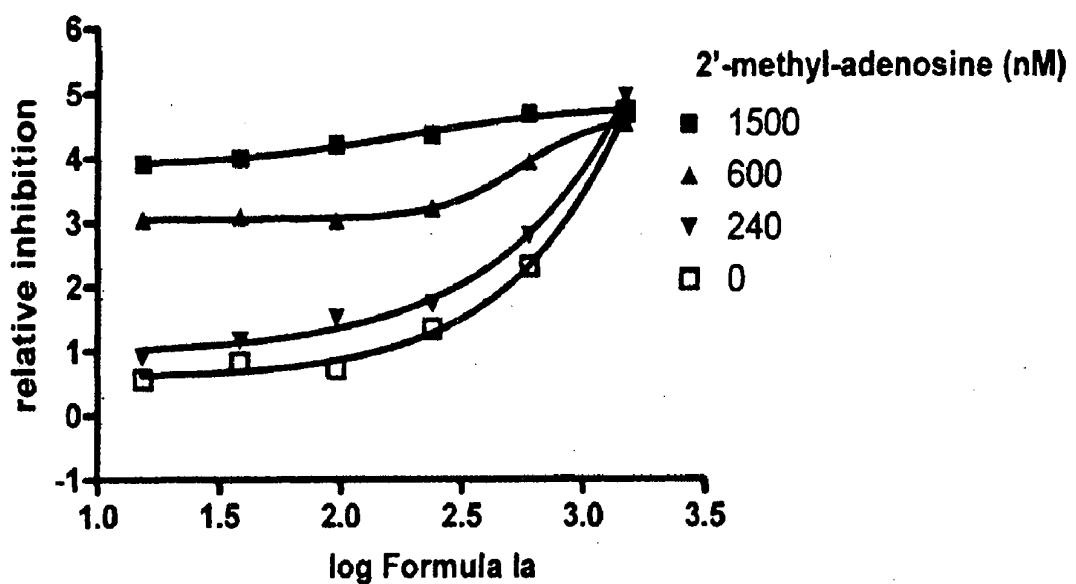
**Figure 1E**



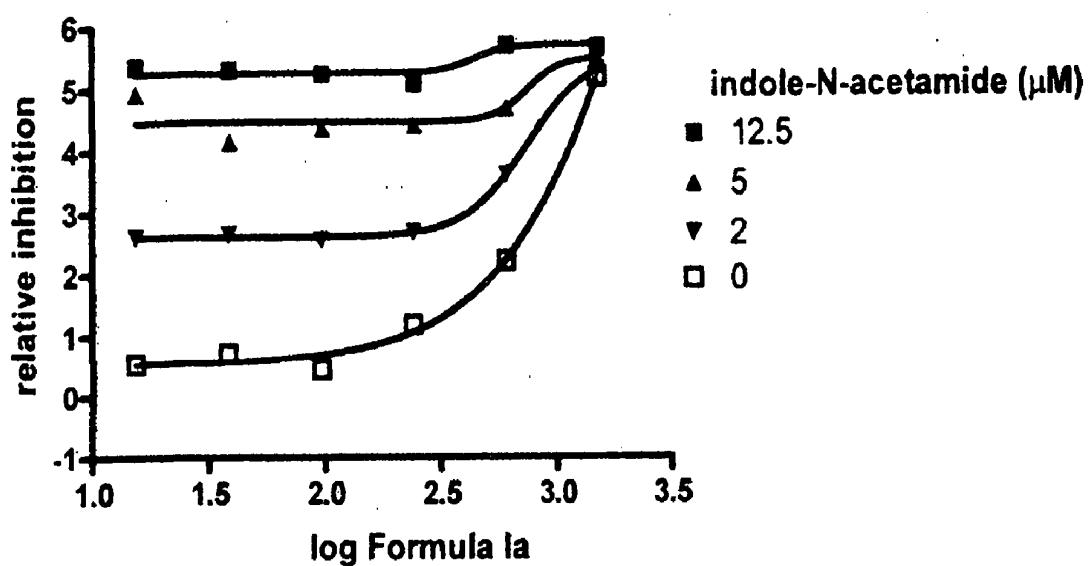
**Figure 1F**



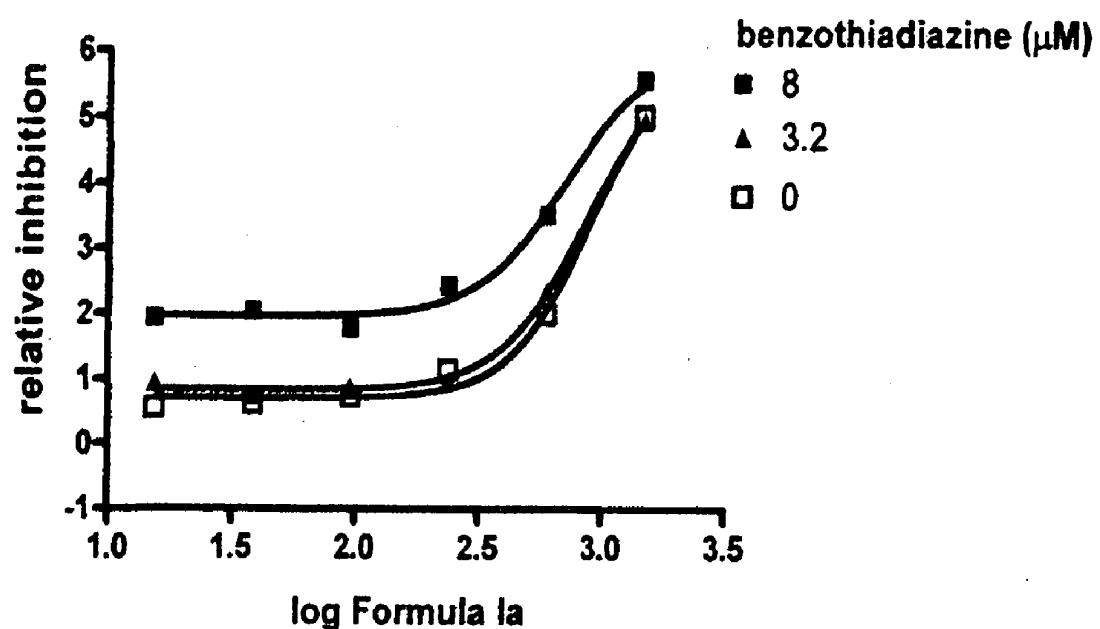
**Figure 1G**



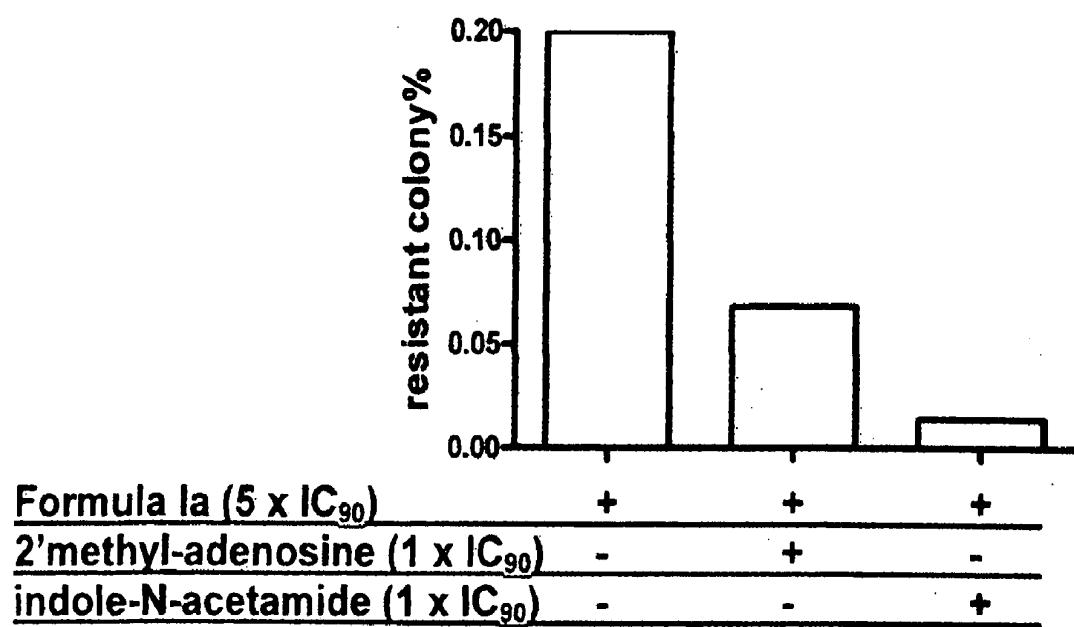
**Figure 2**



**Figure 3**



**Figure 4**



**Figure 5**

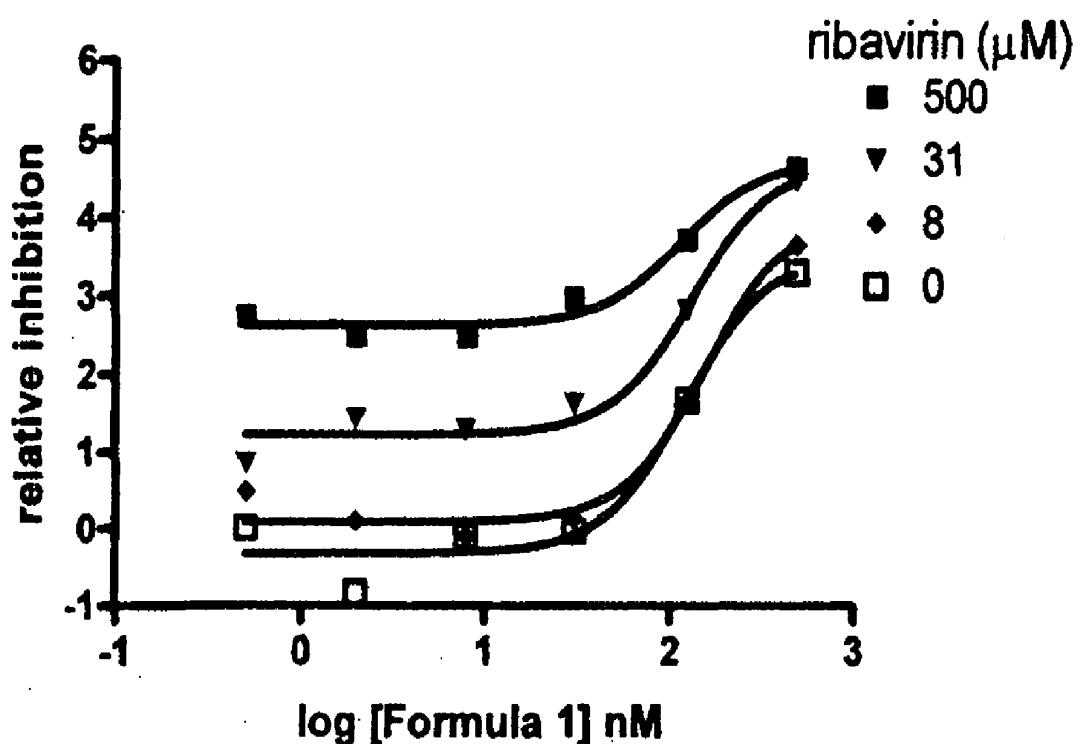


Figure 6

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

**REFERENCE TO RELATED APPLICATIONS**

[0001] This application claims priority under 35 U.S.C. §119(e) to U.S. Provisional Patent Application 60/771,927 filed Feb. 9, 2006 incorporated by reference herein and 60/841,298 filed Aug. 30, 2006.

**FIELD OF THE INVENTION**

[0002] 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) protease inhibitor; and (b) at least one HCV polymerase inhibitor but not HCV-796; 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**

[0003] 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%.

[0004] Current therapies for HCV include interferon- $\alpha$  (INF- $\alpha$ ) 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.

[0005] 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 biliary cirrhosis.

[0006] Recently, a HCV protease necessary for polypeptide processing and viral replication has been identified, cloned and expressed; (see, e.g., U.S. Pat. No. 5,712,145). This approximately 3000 amino acid polyprotein contains, from the amino terminus to the carboxy terminus, a nucleocapsid protein (C), envelope proteins (E1 and E2) and several non-structural proteins (NS1, 2, 3, 4a, 5a and 5b). NS3 is an approximately 68 kda protein, encoded by

approximately 1893 nucleotides of the HCV genome, and has two distinct domains: (a) a serine protease domain consisting of approximately 200 of the N-terminal amino acids; and (b) an RNA-dependent ATPase domain at the C-terminus of the protein. The NS3 protease is considered a member of the chymotrypsin family because of similarities in protein sequence, overall three-dimensional structure and mechanism of catalysis. 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.

[0007] 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).

[0008] 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 $\rightarrow$ 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).

[0009] 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), Ingallina 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<sub>H</sub>E2 (a “camelized” variable domain antibody fragment) (Martin et al., *Protein Eng*, 10(5):607-614 (1997)), and  $\alpha$ 1-antichymotrypsin (ACT) (Elzouki et al., *J Hepat*, 27(1):42-48 (1997)). A ribozyme designed to selectively destroy HCV RNA has recently been disclosed (see, *BioWorld Today*, 9(217):4 (Nov. 10, 1998)).

[0010] Reference is also made to the PCT Publications, No. WO 98/17679, published Apr. 30, 1998 (Vertex Pharmaceuticals Incorporated); WO 98/22496, published May 28, 1998 (F. Hoffmann-La Roche AG); and WO 99/07734, published Feb. 18, 1999 (Boehringer Ingelheim Canada Ltd.).

[0011] The following U.S. patents and pending U.S. patent applications disclose various types of peptides and/or other compounds as NS-3 serine protease inhibitors of HCV: U.S. Pat. No. 6,846,802, granted Jan. 25, 2005; U.S. Pat. No. 6,914,122, granted Jul. 5, 2005; U.S. Pat. No. 5,017,380, granted May 21, 1991; U.S. Pat. No. 4,812,561, granted Mar. 14, 1989; U.S. Pat. No. 4,933,443, granted Jun. 12, 1990; U.S. Pat. No. 4,634,697, granted Jan. 6, 1987; U.S. Pat. No. 6,838,475, granted Jan. 4, 2005; U.S. Pat. No. 6,800,434, granted Oct. 5, 2004; U.S. Ser. No. 09/909,012, filed Jul. 19, 2001 (corresponding to U.S. Publication No. 2002/0160962); U.S. Ser. No. 11/089,192, filed Mar. 24, 2005 (corresponding to U.S. Publication No. 2005/0176648); U.S. Pat. No. 6,911,428, granted Jun. 28, 2005; U.S. Ser. No. 09/909,164, filed Jul. 19, 2001 (corresponding to U.S. Publication No. 2002/0068702); U.S. Ser. No. 11/121,433, filed May 4, 2005 (corresponding to U.S. Publication No. 2005/0249702); and U.S. Pat. No. 7,012,066, granted Mar. 14, 2006.

[0012] HCV polymerase inhibitors are known. See, for example, (i) Ni, Zhi-Jie, Wagman, Allan S. *Current Opinion in Drug Discovery and Development* 2004 7 (4) 446; (ii) Tan, S-T; Pause, A.; Shi, Y.; Sonenberg, N. *Nature Reviews* 2002, 1, 867; and (iii) Beaulieu, P. L.; Tsantrizos, Y. S. *Current Opinion in Investigational Drugs* 2004, 5, 838.

[0013] There is a need for new treatments and therapies for HCV infection to treat, prevent or ameliorate one or more symptoms of HCV, 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.

[0014] Another aspect of the present invention is directed to inhibiting cathepsin activity. Cathepsins (Cats) belong to the papain superfamily of lysosomal cysteine proteases. Cathepsins are involved in the normal proteolysis and turnover of target proteins and tissues as well as in initiating proteolytic cascades by proenzyme activation and in participating in MHC class II molecule expression. Baldwin, *Proc Natl Acad Sci*, 90(14):6796-6800 (1993); Mizuochi, *Immunol Lett*, 43(3):189-193 (1994).

[0015] However, aberrant cathepsin expression has also been implicated in several serious human disease states. Cathepsins have been shown to be abundantly expressed in cancer cells, including breast, lung, prostate, glioblastoma and head/neck cancer cells, (Kos and Lah, *Oncol Rep*, 5(6):1349-1361 (1998); Yan et al., *Biol Chem*, 379(2):113-123 (1998); Mort and Buttle, *Int J Biochem Cell Biol*, 29(5): 715-720 (1997); Friedrich et al., *Eur J Cancer*, 35(1):138-144 (1999)) and are associated with poor treatment outcome of patients with breast cancer, lung cancer, brain tumor and head/neck cancer. Kos and Lah, supra. Additionally, aberrant expression of cathepsin is evident in several inflammatory disease states, including rheumatoid arthritis and osteoarthritis. Keyszer et al., *Arthritis Rheum*, 38(7):976-984 (1995).

[0016] The molecular mechanisms of cathepsin activity are not completely understood. Recently, it was shown that forced expression of cathepsin B rescued cells from serum deprivation-induced apoptotic death (Shibata et al., *Biochem Biophys Res Commun*, 251(1):199-203 (1998)) and that treatment of cells with antisense oligonucleotides of cathepsin B induced apoptosis. Isahara et al., *Neuroscience*,

91(1):233-249 (1999). These reports suggest an anti-apoptotic role for the cathepsins that is contrary to earlier reports that cathepsins are mediators of apoptosis. Roberts et al., *Gastroenterology*, 113(5):1714-1726 (1997); Jones et al., *Am J Physiol*, 275(4Pt1):G723-730 (1998).

[0017] Cathepsin K is a member of the family of enzymes which are part of the papain superfamily of cysteine proteases. Cathepsins B, H, L, N and S have been described in the literature. Recently, cathepsin K polypeptide and the cDNA encoding such polypeptide were disclosed in U.S. Pat. No. 5,501,969 (called cathepsin O therein). Cathepsin K has been recently expressed, purified, and characterized. Bossard et al., *J Biol Chem*, 271(21):12517-12524 (1996); Drake et al., *J Biol Chem*, 271(21):12511-12516 (1996); Bromme et al., *J. Biol. Chem.*, 271(4):2126-2132 (1996).

[0018] Cathepsin K has been variously denoted as cathepsin O, cathepsin X or cathepsin O2 in the literature. The designation cathepsin K is considered to be the more appropriate one (name assigned by Nomenclature Committee of the International Union of Biochemistry and Molecular Biology).

[0019] Cathepsins of the papain superfamily of cysteine proteases function in the normal physiological process of protein degradation in animals, including humans, e.g., in the degradation of connective tissue. However, elevated levels of these enzymes in the body can result in pathological conditions leading to disease. Thus, cathepsins have been implicated in various disease states, including but not limited to, infections by *pneumocystis carinii*, *trypanosoma cruzi*, *trypanosoma brucei brucei*, and *Crithidia fusciculata*; as well as in schistosomiasis malaria, tumor metastasis, metachromatic leukodystrophy, muscular dystrophy, amyotrophy, and the like. See International Publication Number WO 94/04172, published on Mar. 3, 1994, and references cited therein. See also European Patent Application EP 0 603 873 A1, and references cited therein. Two bacterial cysteine proteases from *P. gingivalis*, called gingipains, have been implicated in the pathogenesis of gingivitis. Potempa et al., *Perspectives in Drug Discovery and Design*, 2:445-458 (1994).

[0020] Cathepsin K is believed to play a causative role in diseases of excessive bone or cartilage loss. Bone is composed of a protein matrix in which spindle- or plate-shaped crystals of hydroxyapatite are incorporated. Type I Collagen represents the major structural protein of bone comprising approximately 90% of the structural protein. The remaining 10% of matrix is composed of a number of non-collagenous proteins, including osteocalcin, proteoglycans, osteopontin, osteonectin, thrombospondin, fibronectin, and bone sialoprotein. Skeletal bone undergoes remodeling at discrete foci throughout life. These foci, or remodeling units, undergo a cycle consisting of a bone resorption phase followed by a phase of bone replacement. Bone resorption is carried out by osteoclasts, which are multinuclear cells of hematopoietic lineage. In several disease states, such as osteoporosis and Paget's disease, the normal balance between bone resorption and formation is disrupted, and there is a net loss of bone at each cycle. Ultimately, this leads to weakening of the bone and may result in increased fracture risk with minimal trauma.

[0021] The abundant selective expression of cathepsin K in osteoclasts strongly suggests that this enzyme is essential

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

[0022] There are reports in the literature of the expression of Cathepsin B and L antigen and that activity is associated with early colorectal cancer progression. Troy et al., (2004) Eur J Cancer, 40(10):1610-6. The findings suggest that cysteine proteases play an important role in colorectal cancer progression.

[0023] Cathepsin L has been shown to be an important protein mediating the malignancy of gliomas and it has been suggested that its inhibition may diminish their invasion and lead to increased tumor cell apoptosis by reducing apoptotic threshold. Levicar et al., *Cancer Gene Ther*, 10(2):141-151 (2003).

[0024] Katunuma et al., *Arch Biochem Biophys*, 397(2):305-311 (2002) reports on antihypercalcemic and antimetastatic effects of CLIK-148 in vivo, which is a specific inhibitor of cathepsin L. This reference also reports that CLIK-148 treatment reduced distant bone metastasis to the femur and tibia of melanoma A375 tumors implanted into the left ventricle of the heart.

[0025] Rousselet et al., *Cancer Res*, 64(1):146-151 (2004) reports that anti-cathepsin L single chain variable fragment (ScFv) could be used to inhibit the tumorigenic and metastatic phenotype of human melanoma, depending on pro-cathepsin L secretion, and the possible use of anti-cathepsin L ScFv as a molecular tool in a therapeutic cellular approach.

[0026] Colella and Casey, *Biotech Histochem*, 78(2):101-108 (2003) reports that the cysteine proteinases cathepsin L and B participate in the invasive ability of the PC3 prostate cancer cell line, and the potential of using cystein protease inhibitors such as cystatins as anti-metastatic agents.

[0027] Krueger et al., *Cancer Gene Ther.* 8(7):522-528 (2001) reports that in human osteosarcoma cell line MNNG/HOS, cathepsin L influences cellular malignancy by promoting migration and basement membrane degradation.

[0028] Frohlich et al., *Arch Dermatol Res*, 295(10):411-421 (2004) reports that cathepsins B and L are involved in invasion of basal cell carcinoma (BCC) cells.

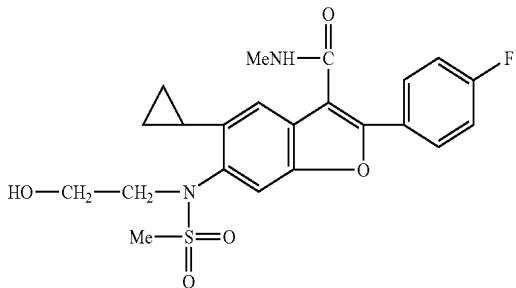
[0029] U.S. Provisional Patent Application Ser. No. 60/673,294, entitled "Compounds for Inhibiting Cathepsin Activity," filed Apr. 20, 2005, discloses various types of peptides and/or other compounds as inhibitors of cathepsin.

[0030] Cathepsins therefore are attractive targets for the discovery of novel chemotherapeutics and methods of treatment effective against a variety of diseases. There is a need

for compounds and combinations useful in the inhibition of cathepsin activity and in the treatment of these disorders.

## SUMMARY OF THE INVENTION

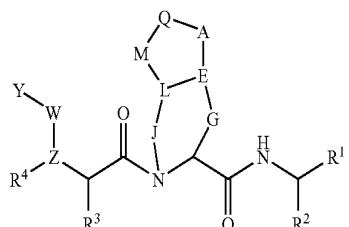
[0031] The present invention provides medicaments, pharmaceutical compositions, pharmaceutical kits, and methods based on combinations comprising, separately or together: (a) at least one HCV protease inhibitor selected from the group consisting of compounds of Formula I to XXVII detailed below or a pharmaceutically acceptable salt, solvate or ester thereof; and (b) at least one HCV polymerase inhibitor but not HCV-796, identified in the Investigational Drugs database and in the IMS Health database as having the structure shown below:



and also identified in the IMS Health database as 5-cyclopropyl-2-(4-fluorophenyl)-6-[(2-hydroxyethyl)(methylsulfonyl)amino]-N-methyl-3-benzofurancarboxamide as well as by the Chemical Abstracts Services (CAS) Number 691852-58-1 which corresponds to the Chemical Abstract index name 3-benzofurancarboxamide, 5-cyclopropyl-2-(4-fluorophenyl)-6-[(2-hydroxyethyl)(methylsulfonyl)amino]-N-methyl, and which is further described in WO 2004041201; 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.

[0032] In one embodiment, at least one HCV protease inhibitor is selected from the group consisting of compounds of Formula I to XXVI detailed below or a pharmaceutically acceptable salt, solvate or ester thereof.

[0033] 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:

[0034] 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-aryl-amino, aryl-amino, heteroaryl-amino, cycloalkylamino and heterocycloalkylamino, with the proviso that Y maybe optionally substituted with X<sup>11</sup> or X<sup>12</sup>;

[0035] X<sup>11</sup> is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocycl, heterocyclylalkyl, aryl, alkyl-aryl, arylalkyl, heteroaryl, alkylheteroaryl, or heteroarylalkyl, with the proviso that X<sup>11</sup> may be additionally optionally substituted with X<sup>12</sup>;

[0036] X<sup>12</sup> is hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxy carbonylamino, alkoxy carbonyloxy, 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<sup>12</sup>;

[0037] R<sup>1</sup> is COR<sup>5</sup>, wherein R<sup>5</sup> is COR<sup>7</sup> wherein R<sup>7</sup> is NHR<sup>9</sup>, wherein R<sup>9</sup> is selected from the group consisting of H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, cycloalkyl, arylalkyl, heteroarylalkyl, [CH(R<sup>1</sup>)<sub>p</sub>]COOR<sup>11</sup>, [CH(R<sup>1</sup>)<sub>p</sub>]CONR<sup>12</sup>R<sup>13</sup>, [CH(R<sup>1</sup>)<sub>p</sub>]SO<sub>2</sub>R<sup>11</sup>, [CH(R<sup>1</sup>)<sub>p</sub>]COR<sup>11</sup>, [CH(R<sup>1</sup>)<sub>p</sub>]CH(OH)R<sup>11</sup>, CH(R<sup>1</sup>)CONHCH(R<sup>2</sup>)COOR<sup>11</sup>, CH(R<sup>1</sup>)CONHCH(R<sup>2</sup>)CONR<sup>12</sup>R<sup>13</sup>, CH(R<sup>1</sup>)CONHCH(R<sup>2</sup>)CONHCH(R<sup>3</sup>)CONR<sup>12</sup>R<sup>13</sup>, CH(R<sup>1</sup>)CONHCH(R<sup>2</sup>)CONHCH(R<sup>3</sup>)CONHCH(R<sup>4</sup>)COOR<sup>11</sup>, CH(R<sup>1</sup>)CONHCH(R<sup>2</sup>)CONHCH(R<sup>3</sup>)CONHCH(R<sup>4</sup>)CONR<sup>12</sup>R<sup>13</sup>, CH(R<sup>1</sup>)CONHCH(R<sup>2</sup>)CONHCH(R<sup>3</sup>)CONHCH(R<sup>4</sup>)CONHCH(R<sup>5</sup>)COOR<sup>11</sup> and CH(R<sup>1</sup>)CONHCH(R<sup>2</sup>)CONHCH(R<sup>3</sup>)CONHCH(R<sup>4</sup>)CONHCH(R<sup>5</sup>)CONR<sup>12</sup>R<sup>13</sup>, wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>11</sup>, R<sup>12</sup>, R<sup>13</sup>, and R<sup>1</sup> are independently selected from the group consisting of H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, alkyl-aryl, alkyl-heteroaryl, aryl-alkyl and heteroaralkyl;

[0038] Z is selected from O, N, CH or CR;

[0039] W maybe present or absent, and if W is present, W is selected from C=O, C=S, C(=N—CN), or SO<sub>2</sub>;

[0040] Q maybe present or absent, and when Q is present, Q is CH, N, P, (CH<sub>2</sub>)<sub>p</sub>, (CHR)<sub>p</sub>, (CRR')<sub>p</sub>, O, NR, S, or SO<sub>2</sub>; and when Q is absent, M may be present or absent; when Q and M are absent, A is directly linked to L;

[0041] A is O, CH<sub>2</sub>, (CHR)<sub>p</sub>, (CHR—CHR')<sub>p</sub>, (CRR')<sub>p</sub>, NR, S, SO<sub>2</sub> or a bond;

[0042] E is CH, N, CR, or a double bond towards A, L or G;

[0043] G may be present or absent, and when G is present, G is (CH<sub>2</sub>)<sub>p</sub>, (CHR)<sub>p</sub>, or (CRR')<sub>p</sub>; 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;

[0044] J maybe present or absent, and when J is present, J is (CH<sub>2</sub>)<sub>p</sub>, (CHR)<sub>p</sub>, or (CRR')<sub>p</sub>, SO<sub>2</sub>, 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;

[0045] 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;

[0046] M may be present or absent, and when M is present, M is O, NR, S, SO<sub>2</sub>, (CH<sub>2</sub>)<sub>p</sub>, (CHR)<sub>p</sub>(CHR—CHR')<sub>p</sub>, or (CRR')<sub>p</sub>;

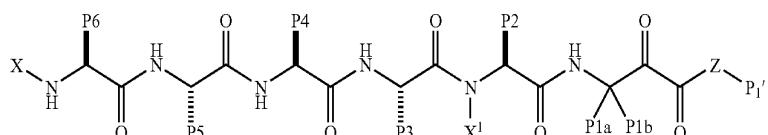
[0047] p is a number from 0 to 6; and

[0048] R, R', R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are independently selected from the group consisting of H; C<sub>1</sub>-C<sub>10</sub> alkyl; C<sub>2</sub>-C<sub>10</sub> alkenyl; C<sub>3</sub>-C<sub>8</sub> cycloalkyl; C<sub>3</sub>-C<sub>8</sub> 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;

[0049] 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;

[0050] 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.

[0051] 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:

[0052] Z is NH;

[0053] X is alkylsulfonyl, heterocyclsulfonyl, heterocyclalkylsulfonyl, arylsulfonyl, heteroarylalkylsulfonyl, alkylcarbonyl, heterocyclcarbonyl, heterocyclalkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxy carbonyl, heteroclyoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkyaminocarbonyl, heterocyclaminocarbonyl, arylaminocarbonyl, or heteroarylaminocarbonyl moiety, with the proviso that X may be additionally optionally substituted with R<sup>12</sup> or R<sup>13</sup>;

[0054] X<sup>1</sup> is H; C<sub>1</sub>-C<sub>4</sub> straight chain alkyl; C<sub>1</sub>-C<sub>4</sub> branched alkyl or; CH<sub>2</sub>-aryl (substituted or unsubstituted);

[0055] R<sup>12</sup> is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocycl, heterocyclalkyl, aryl, alkylaryl, arylalkyl, heteroaryl, alkylheteroaryl, or heteroarylalkyl moiety, with the proviso that R<sup>12</sup> may be additionally optionally substituted with R<sup>13</sup>.

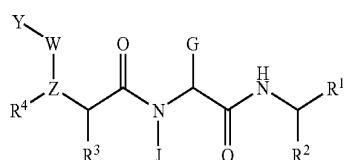
[0056] R<sup>13</sup> is hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxy carbonylamino, alkoxy carbonyloxy, alkylureido, arylureido, halogen, cyano, or nitro moiety, with the proviso that the alkyl, alkoxy, and aryl may be additionally optionally substituted with moieties independently selected from R<sup>13</sup>.

[0057] 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 (heterocycl)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;

[0058] wherein said alkyl, alkenyl, cycloalkyl, heterocycl; (cycloalkyl)alkyl and (heterocycl)alkyl moieties may be optionally substituted with R<sup>13</sup>, 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<sup>13</sup>; and

[0059] P1' is H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocycl, heterocyclalkyl, aryl, arylalkyl, heteroaryl, or heteroarylalkyl; with the proviso that said P1' may be additionally optionally substituted with R<sup>13</sup>.

[0060] 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:

[0061] G is carbonyl;

[0062] 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, heteroaryl amino, cycloalkylamino and heterocycloalkylamino, with the proviso that Y maybe additionally optionally substituted with X<sup>11</sup> or X<sup>12</sup>;

[0063] X<sup>11</sup> is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocycl, heterocyclalkyl, aryl, alkylaryl, arylalkyl, heteroaryl, alkyl-heteroaryl, or heteroarylalkyl moiety, with the proviso that X<sup>11</sup> may be additionally optionally substituted with X<sup>12</sup>;

[0064] X<sup>12</sup> is hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxy carbonylamino, alkoxy carbonyloxy, 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<sup>12</sup>,

[0065] R<sup>1</sup> is COR<sup>5</sup> or C(OR)<sub>2</sub>, wherein R<sup>5</sup> is selected from the group consisting of H, OH, OR<sup>8</sup>, NR<sup>9</sup>R<sup>10</sup>, CF<sub>3</sub>, C<sub>2</sub>F<sub>5</sub>, C<sub>3</sub>F<sub>7</sub>, CF<sub>2</sub>R<sup>6</sup>, R<sup>6</sup> and COR<sup>7</sup> wherein R<sup>7</sup> is selected from the group consisting of H, OH, OR<sup>8</sup>, CHR<sup>9</sup>R<sup>10</sup>, and NR<sup>9</sup>R<sup>10</sup>, wherein R<sup>6</sup>, R<sup>8</sup>, R<sup>9</sup> and R<sup>10</sup> 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<sup>1</sup>)COOR<sup>11</sup>, CH(R<sup>1</sup>)CONR<sup>12</sup>R<sup>13</sup>, CH(R<sup>1</sup>)CONHCH(R<sup>2</sup>)COOR<sup>11</sup>, CH(R<sup>1</sup>)CONHCH(R<sup>2</sup>)CONR<sup>12</sup>R<sup>13</sup>, CH(R<sup>1</sup>)CONHCH(R<sup>2</sup>)R<sup>1</sup>, CH(R<sup>1</sup>)CONHCH(R<sup>2</sup>)CONHCH(R<sup>3</sup>)COOR<sup>11</sup>, CH(R<sup>1</sup>)CONHCH(R<sup>2</sup>)CONHCH(R<sup>3</sup>)CONR<sup>12</sup>R<sup>13</sup>, CH(R<sup>1</sup>)CONHCH(R<sup>2</sup>)CONHCH(R<sup>3</sup>)CONHCH(R<sup>4</sup>)COOR<sup>11</sup>, CH(R<sup>1</sup>)CONHCH(R<sup>2</sup>)CONHCH(R<sup>3</sup>)CONHCH(R<sup>4</sup>)CONR<sup>12</sup>R<sup>13</sup>, CH(R<sup>1</sup>)CONHCH(R<sup>2</sup>)CONHCH(R<sup>3</sup>)CONHCH(R<sup>4</sup>)CONHCH(R<sup>5</sup>)COOR<sup>11</sup>, and CH(R<sup>1</sup>)CONHCH(R<sup>2</sup>)CONHCH(R<sup>3</sup>)CONHCH(R<sup>4</sup>)CONHCH(R<sup>5</sup>)CONR<sup>12</sup>R<sup>13</sup>, wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>11</sup>, R<sup>12</sup>, R<sup>13</sup>, and R<sup>1</sup> 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;

[0066] Z is selected from O, N, or CH;

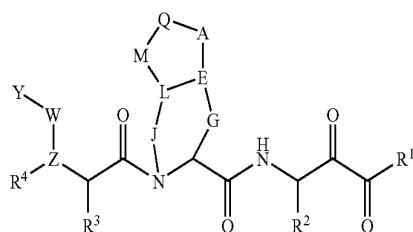
[0067] W maybe present or absent, and if W is present, W is selected from C=O, C=S, or SO<sub>2</sub>; and

[0068] R, R', R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> 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;

[0069] 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.

[0070] 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;

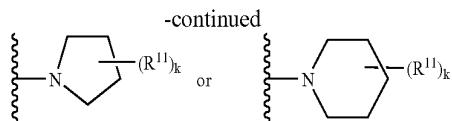
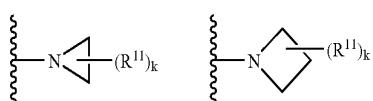
wherein in Formula IV:

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, heteroaryl-amino, cycloalkylamino and heterocycloalkylamino, with the proviso that Y maybe optionally substituted with X<sup>11</sup> or X<sup>12</sup>;

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

X<sup>12</sup> is hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxyl, carbalkoxy, carboxamido, alkoxy carbonyl amine, alkoxy carbonyloxy, 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<sup>12</sup>;

[0071] R<sup>1</sup> is selected from the following structures:



[0072] wherein k is a number from 0 to 5, which can be the same or different, R<sup>11</sup> 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, heteroaryl-amino, cycloalkylamino, heterocycloalkylamino, hydroxy, thio, alkylthio, arylthio, amino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxyl, carbalkoxy, carboxamido, alkoxy carbonyl amine, alkoxy carbonyloxy, alkylureido, arylureido, halogen, cyano, and nitro, with the proviso that R<sup>11</sup> (when R<sup>11</sup> ≠ H) maybe optionally substituted with X<sup>11</sup> or X<sup>12</sup>;

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<sub>2</sub>);

Q may be present or absent, and when Q is present, Q is CH, N, P, (CH<sub>2</sub>)<sub>p</sub>, (CHR)<sub>p</sub>, (CRR')<sub>p</sub>, O, N(R), S, or S(O<sub>2</sub>); 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<sub>2</sub>, (CHR)<sub>p</sub>, (CHR—CHR')<sub>p</sub>, (CRR')<sub>p</sub>, N(R), S, S(O<sub>2</sub>) 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<sub>2</sub>)<sub>p</sub>, (CHR)<sub>p</sub>, or (CRR')<sub>p</sub>; 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<sub>2</sub>)<sub>p</sub>, (CHR)<sub>p</sub>, or (CRR')<sub>p</sub>, S(O<sub>2</sub>), 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;

[0073] 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<sub>2</sub>), (CH<sub>2</sub>)<sub>p</sub>, (CHR)<sub>p</sub>(CHR—CHR')<sub>p</sub>, or (CRR')<sub>p</sub>;

p is a number from 0 to 6; and

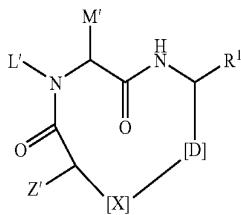
[0074] R, R', R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> can be the same or different, each being independently selected from the group consisting of H; C<sub>1</sub>-C<sub>10</sub> alkyl; C<sub>2</sub>-C<sub>10</sub> alkenyl; C<sub>3</sub>-C<sub>8</sub> cycloalkyl; C<sub>3</sub>-C<sub>8</sub> heterocycloalkyl, 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;

[0075] 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;

[0076] 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.

[0077] 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) R¹ is —C(O)R⁵ or —B(OR)₂;

(2) R⁵ is H, —OH, —OR⁸, —NR⁹R¹⁰, —C(O)OR⁸, —C(O)NR⁷R¹⁰, —CF₃, —C₂F₅, C₃F₇, —CF₂R⁶, —R⁶, —C(O)R or NR⁷SO₂R⁸;

(3) R⁷ is H, —OH, —OR⁸, or —CHR⁹R¹⁰;

(4) R⁶, R⁸, R⁹ and R¹⁰ are independently selected from the group consisting of H: alkyl, alkenyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, arylalkyl, heteroarylalkyl, R¹⁴, —CH(R¹)CH(R¹)C(O)OR¹¹, —[CH(R¹)]\_pC(O)OR¹¹, —[CH(R¹)]\_pC(O)NR¹²R¹³, —[CH(R¹)]\_pS(O₂)R¹¹, —[CH(R¹)]\_pC(O)R¹¹, —[CH(R¹)]\_pS(O₂)NR¹²R¹³, CH(R¹)C(O)N(H)CH(R²)(R), CH(R¹)CH(R¹)C(O)NR¹²R¹³, —CH(R¹)CH(R¹)S(O₂)R¹¹, —CH(R¹)CH(R¹)S(O₂)NR¹²R¹³, —CH(R¹)CH(R¹)C(O)R¹¹, —[CH(R¹)]\_pCH(OH)R¹¹, —CH(R¹)C(O)N(H)CH(R²)C(O)OR¹¹, C(O)N(H)CH(R²)C(O)OR¹¹, —C(O)N(H)CH(R²)C(O)R¹¹, CH(R¹)C(O)N(H)CH(R²)C(O)NR¹²R¹³, —CH(R¹)C(O)N(H)CH(R²)R¹¹, CH(R¹)C(O)N(H)CH(R²)C(O)N(H)CH(R³)C(O)OR¹¹, CH(R¹)C(O)N(H)CH(R²)C(O)CH(R³)NR¹²R¹³,

CH(R¹)C(O)N(H)CH(R²)C(O)NR¹²R¹³, CH(R¹)C(O)N(H)CH(R²)C(O)N(H)CH(R³)C(O)N(H)CH(R⁴)C(O)OR¹¹, H(R¹)C(O)N(H)CH(R²)C(O)N(H)CH(R³)C(O)N(H)CH(R⁴)C(O)NR¹²R¹³, CH(R¹)C(O)N(H)CH(R²)C(O)N(H)CH(R³)C(O)N(H)CH(R⁴)C(O)OR¹¹, and CH(R¹)C(O)N(H)CH(R²)C(O)N(H)CH(R³)C(O)NR¹²R¹³;

wherein R¹, R², R³, R⁴, R⁵, R¹¹, R¹² and R¹³ 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

R¹² and R¹³ are linked together wherein the combination is cycloalkyl, heterocycloalkyl, aryl or heteroaryl;

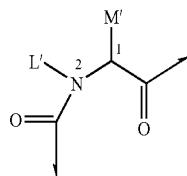
R¹⁴ is present or not and if present is selected from the group consisting of: H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, alkyl-aryl, allyl, alkyl-heteroaryl, alkoxy, aryl-alkyl, alkenyl, alkynyl and heteroaralkyl;

(5) R and R¹ are present or not and if present can be the same or different, each being independently selected from the group consisting of: H, OH, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₃-C₈ cycloalkyl, C₃-C₈ 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;

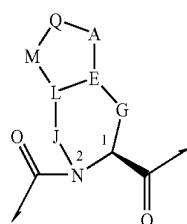
(6) L' is H, OH, alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, or heterocyclyl;

(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  $(\text{CH}_2)_p$ ,  $(\text{CHR}-\text{CHR}')_p$ ,  $(\text{CHR})_p$ ,  $(\text{CRR}')_p$ ,  $\text{S}(\text{O}_2)$ ,  $\text{N}(\text{H})$ ,  $\text{N}(\text{R})$  or  $\text{O}$ ; 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;

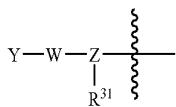
G is present or absent, and when G is present, G is  $(\text{CH}_2)_p$ ,  $(\text{CHR})_p$ ,  $(\text{CHR}-\text{CHR}')_p$  or  $(\text{CRR}')_p$ ; when G is absent, J is present and E is directly connected to the carbon atom marked position 1;

Q is present or absent, and when Q is present, Q is NR, PR,  $(\text{CR}=\text{CR})$ ,  $(\text{CH}_2)_p$ ,  $(\text{CHR})_p$ ,  $(\text{CRR}')_p$ ,  $(\text{CHR}-\text{CHR}')_p$ , O, NR, S, SO, or  $\text{SO}_2$ ; when Q is absent, M is (i) either directly linked to A or (ii) an independent substituent on L, said independent substituent being selected from —OR, — $\text{CH}(\text{R})(\text{R}')$ ,  $\text{S}(\text{O})_{0.2}\text{R}$  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 being selected from —OR, — $\text{CH}(\text{R})(\text{R}')$ ,  $\text{S}(\text{O})_{0.2}\text{R}$  or —NRR' or A is absent;

A is present or absent and if present A is O, O(R),  $(\text{CH}_2)_p$ ,  $(\text{CHR})_p$ ,  $(\text{CHR}-\text{CHR}')_p$ ,  $(\text{CRR}')_p$ , N(R), NRR', S,  $\text{S}(\text{O}_2)$ , —OR,  $\text{CH}(\text{R})(\text{R}')$  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,  $\text{S}(\text{O}_2)$ ,  $(\text{CH}_2)_p$ ,  $(\text{CHR})_p$ ,  $(\text{CHR}-\text{CHR}')_p$ , or  $(\text{CRR}')_p$ ; 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, alkylxylo, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocycloalkyloxy, heteroalkyl-heteroaryl, heteroalkyl-heterocycloalkyl, cycloalkyloxy, alkylamino, arylamino, alkyl-arylarnino, arylarnino, heteroarylarnino, cycloalkylarnino and heterocycloalkylarnino, and Y is unsubstituted or optionally substituted with one or two substituents which are the same or different and are independently selected from X<sup>11</sup> or X<sup>12</sup>;

X<sup>11</sup> is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocycl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, heteroaryl, alkylheteroaryl, or heteroarylalkyl, and X<sup>11</sup> is

unsubstituted or optionally substituted with one or more of X<sup>12</sup> moieties which are the same or different and are independently selected;

X<sup>12</sup> 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, alkoxy carbonylamino, alkoxy carbonyloxy, 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, heterocycl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, heteroaryl, alkylheteroaryl, or heteroarylalkyl;

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

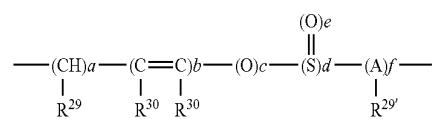
R<sup>31</sup> is H, hydroxyl, aryl, alkyl, alkyl-aryl, heteroalkyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkylxylo, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocycloalkyloxy, heteroalkyl-heteroaryl, cycloalkyloxy, alkylamino, arylamino, alkyl-arylarnino, arylarnino, heteroarylarnino, cycloalkylarnino or heterocycloalkylarnino, and R<sup>31</sup> is unsubstituted or optionally substituted with one or two substituents which are the same or different and are independently selected from X<sup>13</sup> or X<sup>14</sup>,

X<sup>13</sup> is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocycl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, heteroaryl, alkylheteroaryl, or heteroarylalkyl, and X<sup>13</sup> is unsubstituted or optionally substituted with one or more of X<sup>14</sup> moieties which are the same or different and are independently selected;

X<sup>14</sup> 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, heteroaryl sulfonamido, alkoxy carbonylamino, alkoxy carbonyloxy, 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, heterocycl, 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<sub>2</sub>);

(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;

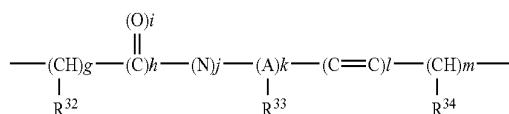
A is C, N, S or O;

R<sup>29</sup> and R<sup>29'</sup> 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)<sub>2</sub>, 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, heterocyclenyl, heterocyclyl, Y<sub>1</sub>Y<sub>2</sub>N-alkyl-, Y<sub>1</sub>Y<sub>2</sub>NC(O)— and Y<sub>1</sub>Y<sub>2</sub>NSO<sub>2</sub>—, wherein Y<sub>1</sub> and Y<sub>2</sub> can be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, and aralkyl; or

R<sup>29</sup> and R<sup>29'</sup> are linked together such that the combination is an aliphatic or heteroaliphatic chain of 0 to 6 carbons;

R<sup>30</sup> is present or absent and if present is one or two substituents independently selected from the group consisting of: H, alkyl, aryl, heteroaryl and cycloalkyl;

(10) D is represented by structural Formula 5:



wherein in Formula 5:

R<sup>32</sup>, R<sup>33</sup> and R<sup>34</sup> 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)<sub>2</sub>, 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, heterocyclenyl, Y<sub>1</sub>Y<sub>2</sub>N-alkyl-, Y<sub>1</sub>Y<sub>2</sub>NC(O)— and Y<sub>1</sub>Y<sub>2</sub>NSO<sub>2</sub>—, wherein Y<sub>1</sub> and Y<sub>2</sub> can be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, and aralkyl; or

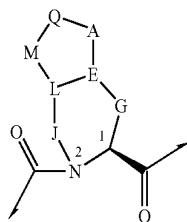
R<sup>32</sup> and R<sup>34</sup> are linked together such that the combination forms a portion of a cycloalkyl group;

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

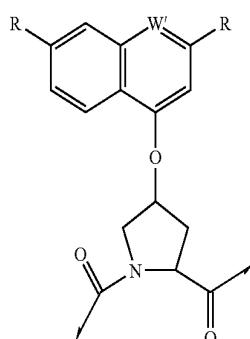
A is C, N, S or O,

(11) provided that when structural Formula 2:



Formula 2

is



[0078] and

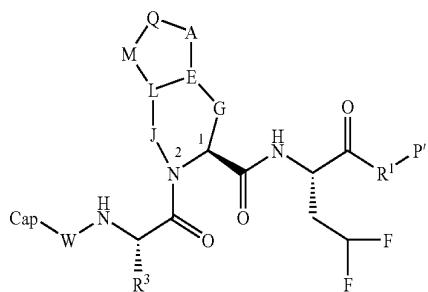
W is CH or N, both the following conditional exclusions (i) and (ii) apply:

conditional exclusion (i): Z' is not —NH—R<sup>36</sup>, wherein R<sup>36</sup> is H, C<sub>6</sub> or 10 aryl, heteroaryl, —C(O)—R<sup>37</sup>, —C(O)—OR<sup>37</sup> or —C(O)—NHR<sup>37</sup>, wherein R<sup>37</sup> is C<sub>1-6</sub> alkyl or C<sub>3-6</sub> cycloalkyl;

[0079] and

[0080] conditional exclusion (ii): R<sup>1</sup> is not —C(O)OH, a pharmaceutically acceptable salt of —C(O)OH, an ester of —C(O)OH or —C(O)NHR<sup>38</sup> wherein R<sup>38</sup> is selected from the group consisting of C<sub>1-8</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>6</sub> to 10 aryl or C<sub>7-16</sub> aralkyl.

[0081] 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:

[0082] Cap is H, alkyl, alkyl-aryl, heteroalkyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyloxy, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocyclyoxy, cycloalkyloxy, amino, alkylamino, arylamino, alkyl-arylamino, arylamino, heteroarylamino, cycloalkylamino, carboxyalkylamino, arylalkyloxy or heterocyclamino, wherein each of said alkyl, alkyl-aryl, heteroalkyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyloxy, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocyclyoxy, cycloalkyloxy, amino, alkylamino, arylamino, alkyl-arylamino, arylamino, heteroarylamino, cycloalkylamino, carboxyalkylamino, arylalkyloxy or heterocyclamino 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<sup>1</sup> and X<sup>2</sup>;

[0083] P' is —NHR;

[0084] X<sup>1</sup> is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocycl, heterocyclalkyl, aryl, alkylaryl, arylalkyl, arylheteroaryl, heteroaryl, heterocyclamino, alkylheteroaryl, or heteroarylalkyl, and X<sup>1</sup> can be unsubstituted or optionally independently substituted with one or more of X<sup>2</sup> moieties which can be the same or different and are independently selected;

[0085] X<sup>2</sup> is hydroxy, alkyl, aryl, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxy carbonylamino, alkoxy carbonyloxy, 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, heterocycl, heterocyclalkyl, aryl, alkylaryl, arylalkyl, arylheteroaryl, heteroaryl, heterocyclamino, alkylheteroaryl and heteroarylalkyl;

[0086] 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<sub>2</sub>);

[0087] Q maybe present or absent, and when Q is present, Q is N(R), P(R), CR=CR', (CH<sub>2</sub>)<sub>p</sub>, (CHR)<sub>p</sub>, (CRR')<sub>p</sub>, (CHR—CHR')<sub>p</sub>, O, S, S(O) or S(O<sub>2</sub>); 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')<sub>0-2</sub>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)<sub>0-2</sub>R or —NRR';

[0088] A is present or absent and if present A is —O—, —O(R)CH<sub>2</sub>—, —(CHR)<sub>p</sub>—, —(CHR—CHR')<sub>p</sub>—, (CRR')<sub>p</sub>, N(R), NRR', S, or S(O<sub>2</sub>), 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;

[0089] E is present or absent and if present E is CH, N, C(R);

[0090] G may be present or absent, and when G is present, G is (CH<sub>2</sub>)<sub>p</sub>, (CHR)<sub>p</sub>, or (CRR')<sub>p</sub>; when G is absent, J is present and E is directly connected to the carbon atom marked position 1;

[0091] J may be present or absent, and when J is present, J is (CH<sub>2</sub>)<sub>p</sub>, (CHR—CHR')<sub>p</sub>, (CHR)<sub>p</sub>, (CRR')<sub>p</sub>, S(O<sub>2</sub>), 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;

[0092] 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;

[0093] M may be present or absent, and when M is present, M is O, N(R), S, S(O<sub>2</sub>), (CH<sub>2</sub>)<sub>p</sub>, (CHR)<sub>p</sub>, (CHR—CHR')<sub>p</sub>, or (CRR')<sub>p</sub>;

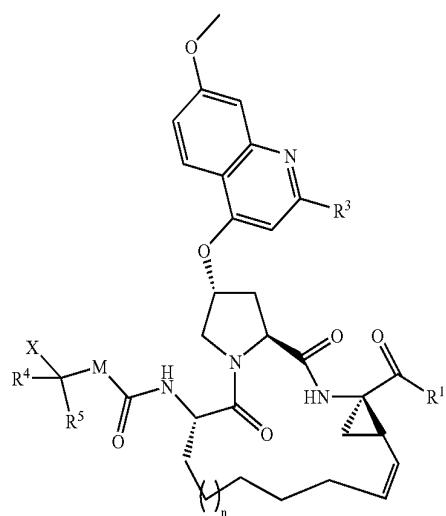
[0094] p is a number from 0 to 6;

[0095] R, R' and R<sup>3</sup> can be the same or different, each being independently selected from the group consisting of: H, C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>2</sub>-C<sub>10</sub> alkenyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>3</sub>-C<sub>8</sub> heterocycl, 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 (heterocycl)alkyl;

[0096] R and R' in (CRR') can be linked together such that the combination forms a cycloalkyl or heterocycl moiety; and

[0097] R<sup>1</sup> is carbonyl.

[0098] In another embodiment, at least one HCV protease inhibitor is a compound of structural Formula VII:



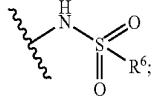
[0099] or a pharmaceutically acceptable salt, solvate or ester thereof;

[0100] wherein in Formula VII:

[0101] M is O, N(H), or CH<sub>2</sub>;

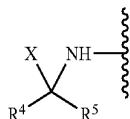
[0102] n is 0-4;

[0103] R<sup>1</sup> is —OR<sup>6</sup>, —NR<sup>6</sup>R<sup>7</sup> or

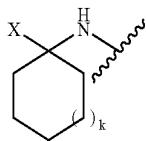


[0104] where R<sup>6</sup> and R<sup>7</sup> can be the same or different, each being independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylkyl, heterocycl, heterocyclalkyl, hydroxyl, amino, 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

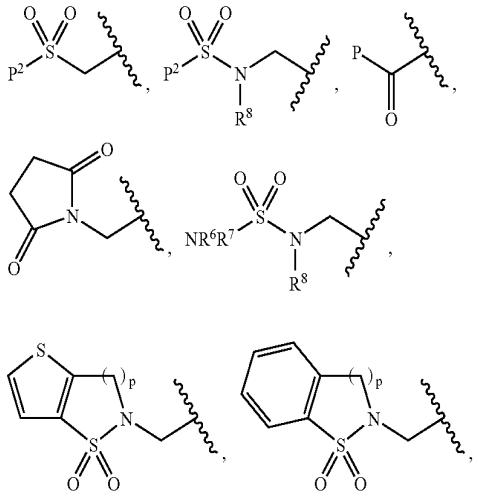


is represented by

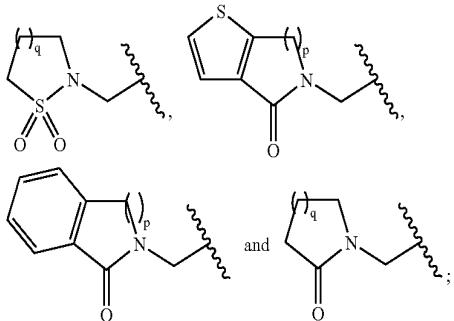


where k is 0 to 2;

X is selected from the group consisting of:



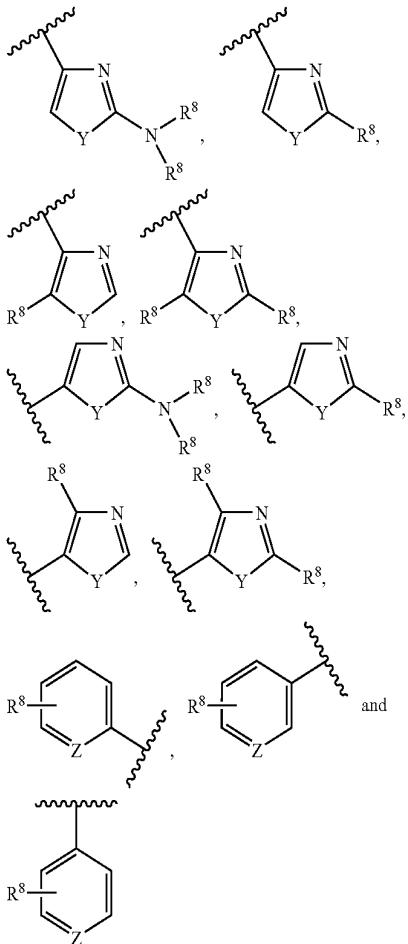
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[0105] where p is 1 to 2, q is 1-3 and  $P^2$  is alkyl, aryl, heteroaryl, heteroalkyl, cycloalkyl, dialkylamino, alkylamino, arylamino or cycloalkylamino;

and

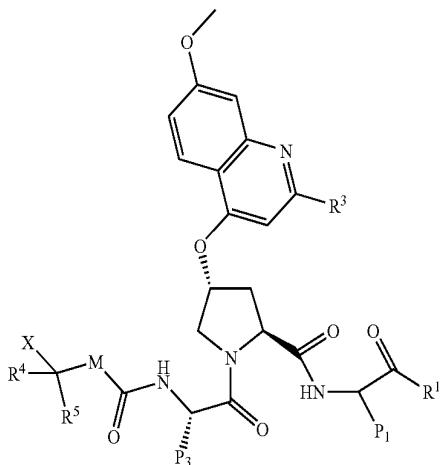
[0106] R<sup>3</sup> is selected from the group consisting of: aryl, heterocyclyl, heteroaryl,



where Y is O, S or NH, and Z is CH or N, and the R<sup>8</sup> moieties can be the same or different, each R<sup>8</sup> being independently selected from the group consisting of hydrogen, alkyl, heteroalkyl, cycloalkyl, aryl, heteroaryl, heterocycl,

hydroxyl, amino, arylamino, alkylamino, dialkylamino, halo, alkylthio, arylthio and alkyloxy.

[0107] 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:

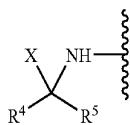
[0108] M is O, N(H), or CH<sub>2</sub>;

[0109] R<sup>1</sup> is —C(O)NHR<sup>6</sup>, where R<sup>6</sup> is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, hydroxyl, amino, arylamino or alkylamino;

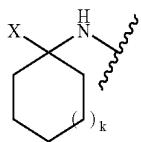
[0110] P<sub>1</sub> is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl haloalkyl;

[0111] P<sub>3</sub> is selected from the group consisting of alkyl, cycloalkyl, aryl and cycloalkyl fused with aryl;

[0112] R<sup>4</sup> and R<sup>5</sup> can be the same or different, each being independently selected from the group consisting of H, alkyl, aryl and cycloalkyl; or alternatively R<sup>4</sup> and R<sup>5</sup> together form part of a cyclic 5- to 7-membered ring such that the moiety

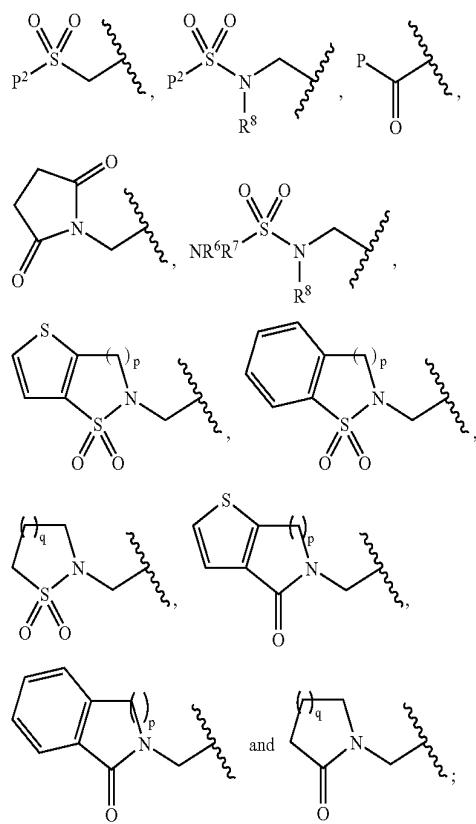


is represented by



where k is 0 to 2;

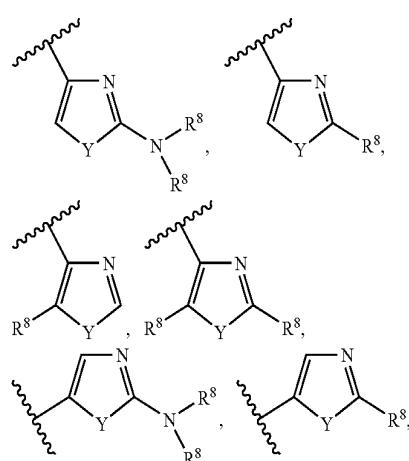
[0113] X is selected from the group consisting of:

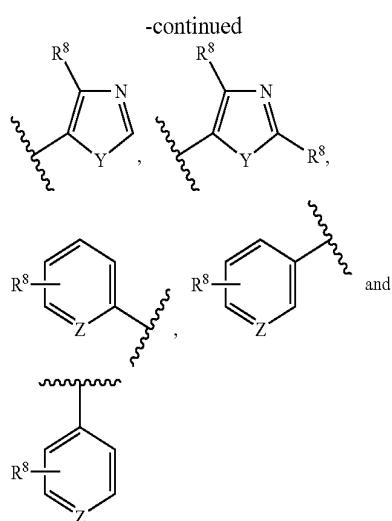


where p is 1 to 2, q is 1 to 3 and P<sup>2</sup> is alkyl, aryl, heteroaryl, heteroalkyl, cycloalkyl, dialkylamino, alkylamino, arylamino or cycloalkylamino;

and

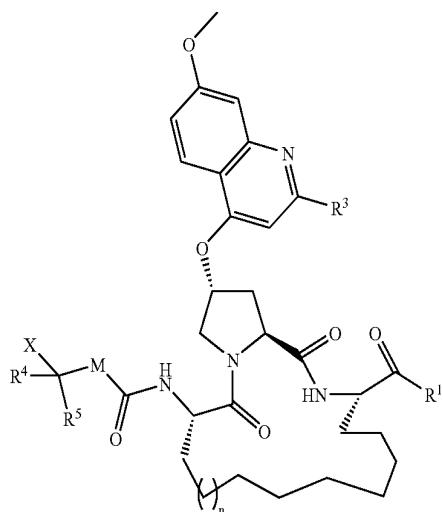
[0114] R<sup>3</sup> is selected from the group consisting of: aryl, heterocyclyl, heteroaryl,





where Y is O, S or NH, and Z is CH or N, and the R<sup>8</sup> moieties can be the same or different, each R<sup>8</sup> 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.

[0115] In another embodiment, at least one HCV protease inhibitor is a compound of structural Formula IX:



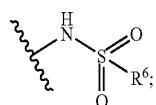
or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula IX:

[0116] M is O, N(H), or CH<sub>2</sub>;

[0117] n is 0-4;

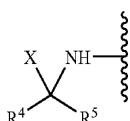
[0118] R<sup>1</sup> is —R<sup>6</sup>, —NR<sup>6</sup>R<sup>7</sup> or



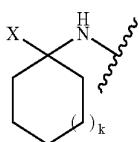
[0119] where R<sup>6</sup> and R<sup>7</sup> can be the same or different, each being independently selected from the group consisting of

hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, hydroxyl, amino, arylamino and alkylamino;

R<sup>4</sup> and R<sup>5</sup> can be the same or different, each being independently selected from the group consisting of H, alkyl, aryl and cycloalkyl; or alternatively R<sup>4</sup> and R<sup>5</sup> together form part of a cyclic 5- to 7-membered ring such that the moiety

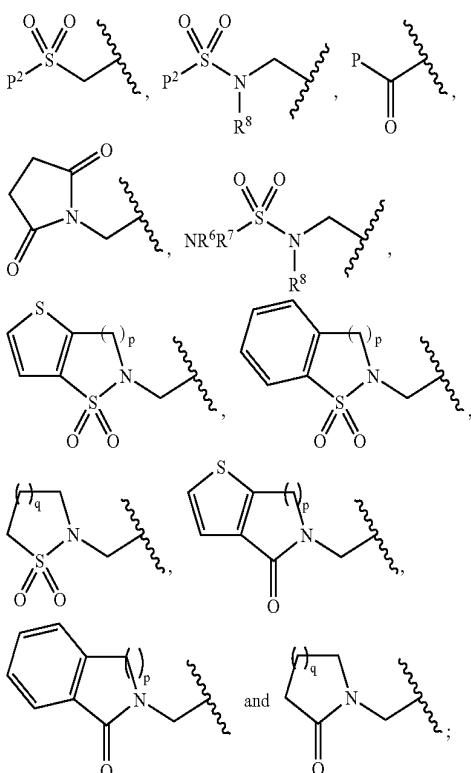


is represented by



where k is 0 to 2;

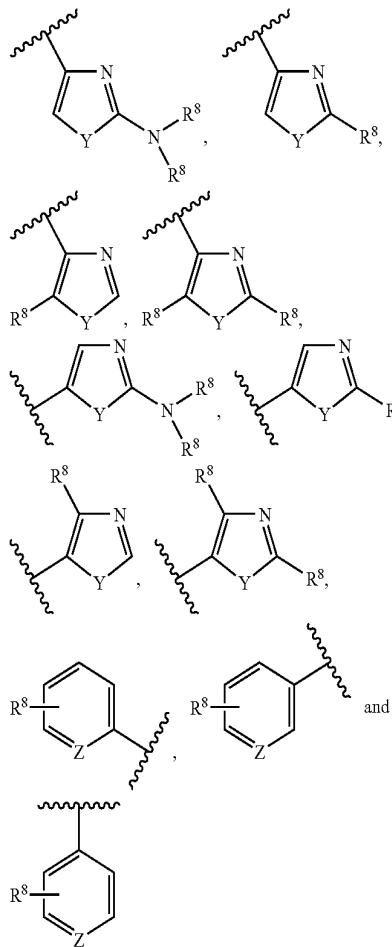
X is selected from the group consisting of:



[0120] where p is 1 to 2, q is 1 to 3 and P<sup>2</sup> is alkyl, aryl, heteroaryl, heteroalkyl, cycloalkyl, dialkylamino, alkylamino, arylamino or cycloalkylamino;

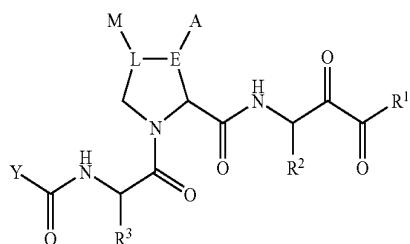
and

[0121]  $R^3$  is selected from the group consisting of: aryl, heterocyclyl, heteroaryl,



[0122] 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.

[0123] In another embodiment, at least one HCV protease inhibitor is a compound of structural Formula X:

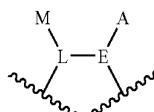


or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula X:

[0124]  $R^1$  is  $NHR^9$ , wherein  $R^9$  is H, alkyl-, alkenyl-, alkynyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, heterocyclyl-, arylalkyl-, or heteroarylalkyl;

[0125] A and M can be the same or different, each being independently selected from R, OR, NHR, NRR', SR, SO<sub>2</sub>R, and halo; or A and M are connected to each other such that the moiety:



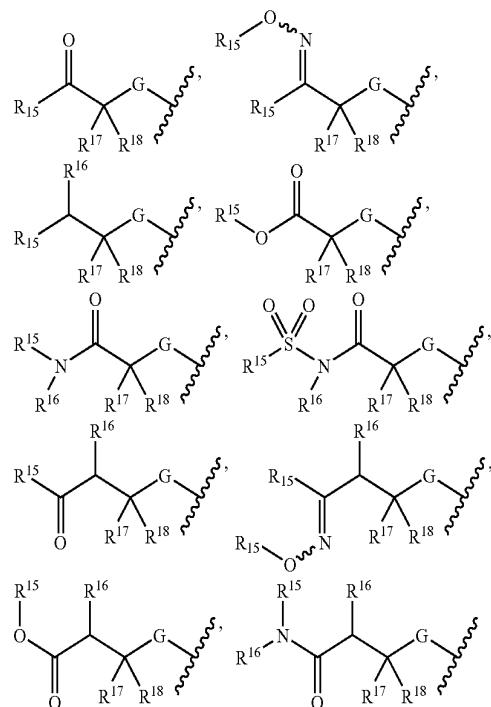
shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl;

[0126] E is C(H) or C(R);

[0127] L is C(H), C(R), CH<sub>2</sub>C(R), or C(R)CH<sub>2</sub>;

[0128] R, R', R<sup>2</sup>, and R<sup>3</sup> 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;

[0129] and Y is selected from the following moieties:

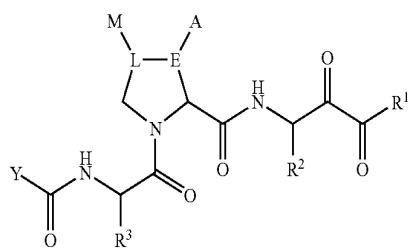


wherein G is NH or O; and R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup> and R<sup>18</sup> can be the same or different, each being independently selected from

the group consisting of H, alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, cycloalkyl, heterocyclcycl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, or alternately, R<sup>15</sup> and R<sup>16</sup> are connected to each other to form a four to eight-membered cycloalkyl, heteroaryl or heterocyclcycl structure, and likewise, independently R<sup>17</sup> and R<sup>18</sup> are connected to each other to form a three to eight-membered cycloalkyl or heterocyclcycl;

[0130] wherein each of said alkyl, aryl, heteroaryl, cycloalkyl or heterocyclcycl 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.

[0131] In one embodiment, at least one HCV protease inhibitor is a compound of structural Formula XI:

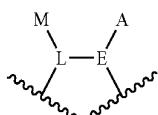


or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XI:

[0132] R<sup>1</sup> is NHR<sup>9</sup>, wherein R<sup>9</sup> is H, alkyl-, alkenyl-, alkynyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, heterocyclcycl-, arylalkyl-, or heteroarylalkyl;

[0133] A and M can be the same or different, each being independently selected from R, NR<sup>9</sup>R<sup>10</sup>, SR, SO<sub>2</sub>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, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclcycl, a six to ten-membered aryl, or a five to ten-membered heteroaryl;

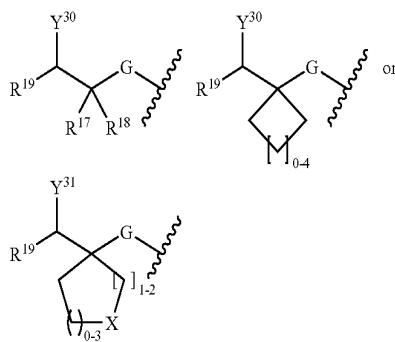
[0134] E is C(H) or C(R);

[0135] L is C(H), C(R), CH<sub>2</sub>C(R), or C(R)CH<sub>2</sub>;

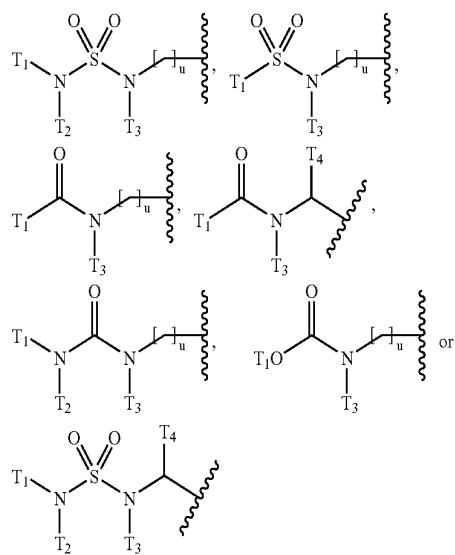
[0136] R, R', R<sup>2</sup>, and R<sup>3</sup> can be the same or different, each being independently selected from the group consisting of H, alkyl-, alkenyl-, alkynyl-, cycloalkyl-, heteroalkyl-, het-

erocyclcycl-, aryl-, heteroaryl-, (cycloalkyl)alkyl-, (heterocyclcycl)alkyl-, aryl-alkyl-, and heteroaryl-alkyl-; or alternately R and R' in NRR' are connected to each other such that NR R<sup>10</sup> forms a four to eight-membered heterocyclcycl;

[0137] Y is selected from the following moieties:



[0138] wherein Y<sup>30</sup> and Y<sup>31</sup> are selected from



[0139] where u is a number 0-6;

[0140] X is selected from O, NR<sup>15</sup>, NC(O)R<sup>16</sup>, S, S(O) and SO<sub>2</sub>;

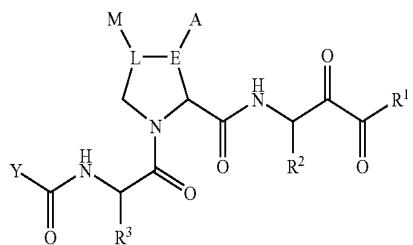
[0141] G is NH or O; and

[0142] R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup>, R<sup>18</sup>, R<sup>19</sup>, T<sub>1</sub>, T<sub>2</sub>, T<sub>3</sub> and T<sub>4</sub> can be the same or different, each being independently selected from the group consisting of H, alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, cycloalkyl, heterocyclcycl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, or alternately, R<sup>17</sup> and R<sup>18</sup> are connected to each other to form a three to eight-membered cycloalkyl or heterocyclcycl;

[0143] wherein each of said alkyl, aryl, heteroaryl, cycloalkyl or heterocyclcycl 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,

arylarnino, alkylsulfonyl, arylsulfonyl, sulfonamido, alkyl, aryl, heteroaryl, alkylsulfonamido, arylsulfonamido, keto, carboxy, carbalkoxy, carboxamido, alkoxy carbonylamino, alkoxy carbonyloxy, alkylureido, arylureido, halo, cyano, and nitro.

[0144] In another embodiment, at least one HCV protease inhibitor is a compound of structural Formula XII:

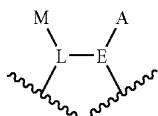


or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XII:

[0145]  $R^1$  is  $NHR^9$ , wherein  $R^9$  is H, alkyl-, alkenyl-, alkynyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, heterocycl-, arylalkyl-, or heteroarylalkyl;

[0146] 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:



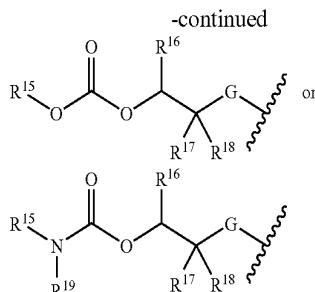
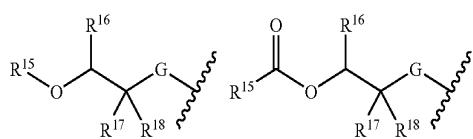
shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocycl, a six to ten-membered aryl, or a five to ten-membered heteroaryl;

[0147] E is C(H) or C(R);

[0148] L is C(H), C(R),  $CH_2C(R)$ , or  $C(R)CH_2$ ;

[0149] 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-, heterocycl-, aryl-, heteroaryl-, (cycloalkyl)alkyl-, (heterocycl-)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 heterocycl;

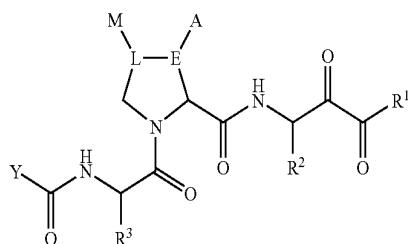
[0150] and Y is selected from the following moieties:



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, heterocycl-, 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 heterocycl;

[0151] wherein each of said alkyl, aryl, heteroaryl, cycloalkyl or heterocycl 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, alkoxy carbonylamino, alkoxy carbonyloxy, alkylureido, arylureido, halo, cyano, and nitro.

[0152] In another embodiment, at least one HCV protease inhibitor is a compound of structural Formula XIII:

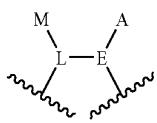


or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XIII:

[0153]  $R^1$  is  $NHR^9$ , wherein  $R^9$  is H, alkyl-, alkenyl-, alkynyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, heterocycl-, arylalkyl-, or heteroarylalkyl;

[0154] 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:



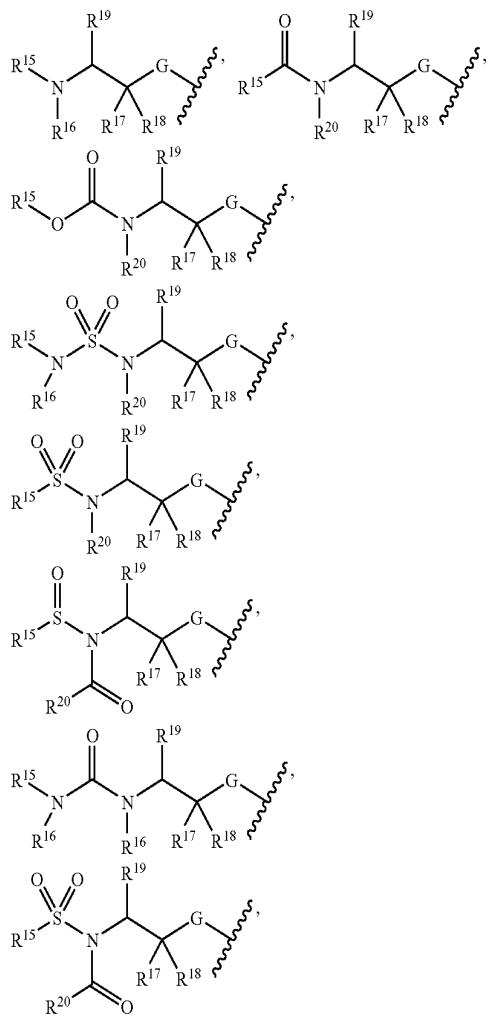
shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl;

[0155] E is C(H) or C(R);

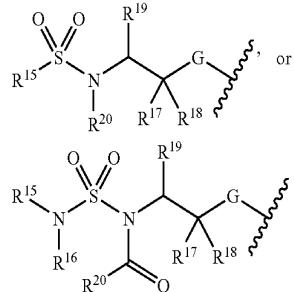
[0156] L is C(H), C(R), CH<sub>2</sub>C(R), or C(R)CH<sub>2</sub>;

[0157] R, R', R<sup>2</sup>, and R<sup>3</sup> can be the same or different, each being independently selected from the group consisting of H, alkyl-, alkenyl-, alkynyl-, cycloalkyl-, heteroalkyl-, heterocyclyl-, aryl-, heteroaryl-, (cycloalkyl)alkyl-, (heterocyclyl)alkyl-, aryl-alkyl-, and heteroaryl-alkyl-; or alternately R and R' in NRR' are connected to each other such that NRR' forms a four to eight-membered heterocyclyl;

and Y is selected from the following moieties:



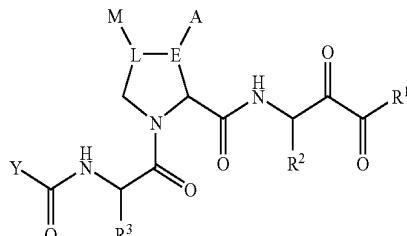
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wherein G is NH or O, and R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup>, R<sup>18</sup>, R<sup>19</sup> and R<sup>20</sup> can be the same or different, each being independently selected from the group consisting of H, C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>1</sub>-C<sub>10</sub> heteroalkyl, C<sub>2</sub>-C<sub>10</sub> alkenyl, C<sub>2</sub>-C<sub>10</sub> heteroalkenyl, C<sub>2</sub>-C<sub>10</sub> alkynyl, C<sub>2</sub>-C<sub>10</sub> heteroalkynyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>3</sub>-C<sub>8</sub> heterocyclyl, aryl, heteroaryl, or alternately: (i) either R<sup>15</sup> and R<sup>16</sup> can be connected to each other to form a four to eight-membered cycloalkyl or heterocyclyl, or R<sup>15</sup> and R<sup>19</sup> are connected to each other to form a five to eight-membered cycloalkyl or heterocyclyl, or R<sup>15</sup> and R<sup>20</sup> are connected to each other to form a five to eight-membered cycloalkyl or heterocyclyl, and (ii) likewise, independently, R<sup>17</sup> and R<sup>18</sup> are connected to each other to form a three to eight-membered cycloalkyl or heterocyclyl,

[0158] 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, alkoxy carbonyl amino, alkoxy carbonyloxy, alkylureido, arylureido, halo, cyano, and nitro.

[0159] In another embodiment, at least one HCV protease inhibitor is a compound of structural Formula XIV:



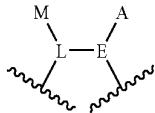
or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XIV:

[0160] R<sup>1</sup> is NHR<sup>9</sup>, wherein R<sup>9</sup> is H, alkyl-, alkenyl-, alkynyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, heterocyclyl-, arylalkyl-, or heteroarylalkyl;

[0161] A and M can be the same or different, each being independently selected from R, OR, NHR, NRR', SR, SO<sub>2</sub>R, and halo;

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



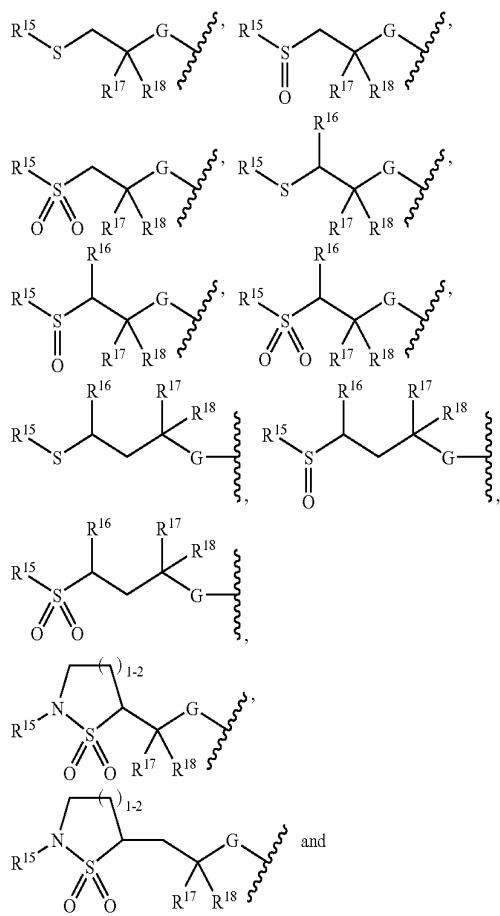
shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl;

[0162] E is C(H) or C=;

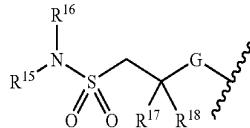
[0163] L is C(H), C=, CH<sub>2</sub>C=, or C=CH<sub>2</sub>;

[0164] R, R', R<sup>2</sup>, and R<sup>3</sup> 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;

[0165] and Y is selected from the following moieties:



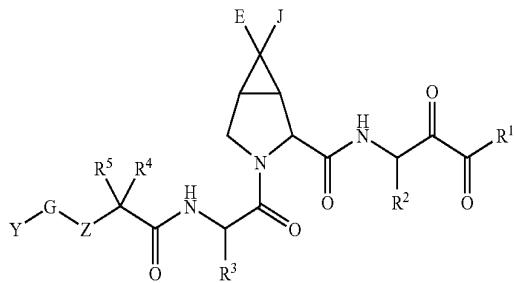
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[0166] wherein G is NH or O; and R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup> and R<sup>18</sup> can be the same or different, each being independently selected from the group consisting of H, alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, or alternately, (i) R<sup>15</sup> and R<sup>16</sup> are connected to each other to form a four to eight-membered cyclic structure, and (ii) likewise, independently R<sup>17</sup> and R<sup>18</sup> are connected to each other to form a three to eight-membered cycloalkyl or heterocyclyl;

[0167] 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, alkoxy carbonylamino, alkoxy carbonyloxy, alkylureido, arylureido, halo, cyano, and nitro.

[0168] 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:

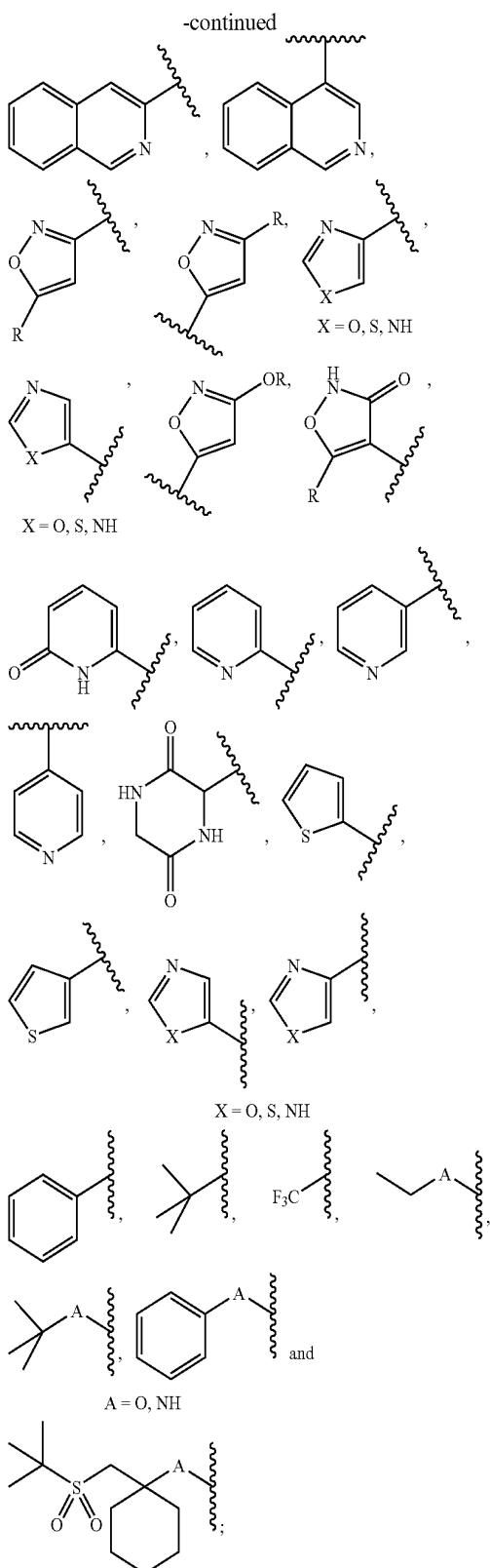
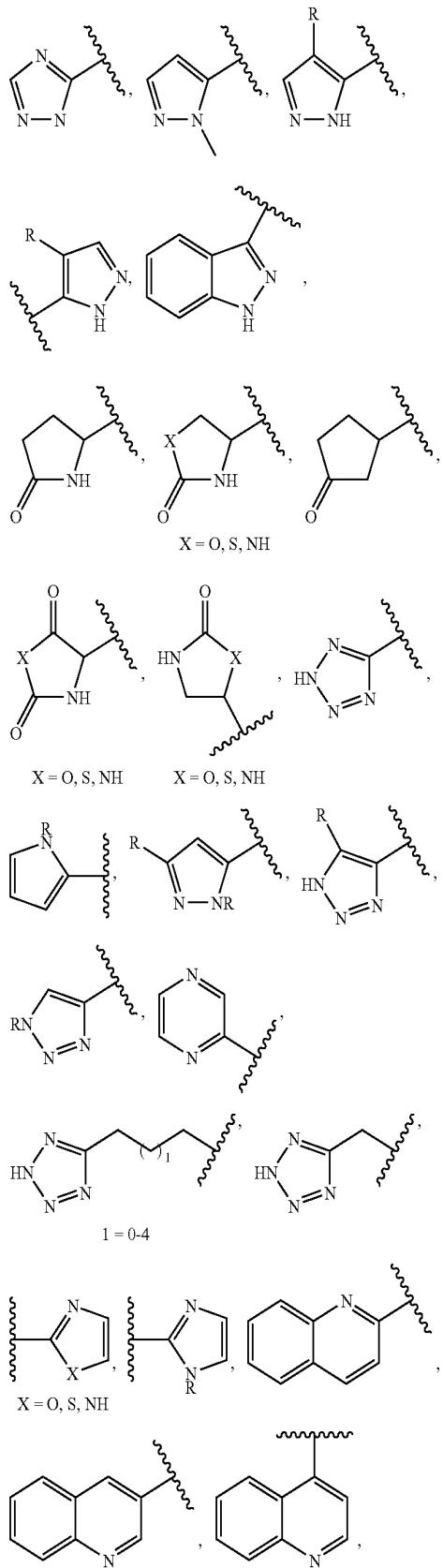
[0169] R<sup>1</sup> is NHR<sup>9</sup>, wherein R<sup>9</sup> is H, alkyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, cycloalkyl-, arylalkyl-, or heteroarylalkyl;

[0170] E and J can be the same or different, each being independently selected from the group consisting of R, OR, NHR, NRR<sup>7</sup>, SR, halo, and S(O<sub>2</sub>)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;

[0171] 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);

[0172] G maybe present or absent, and if G is present, G is C(=O) or S(O<sub>2</sub>), and when G is absent, Z is directly connected to Y;

[0173] Y is selected from the group consisting of:

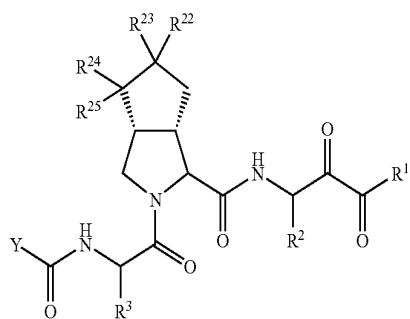


[0174] R,  $R^7$ ,  $R^2$ ,  $R^3$ ,  $R^4$  and  $R^5$  can be the same or different, each being independently selected from the group consisting of H, alkyl-, alkenyl-, alkynyl-, cycloalkyl-, heteroalkyl-, heterocycl-, aryl-, heteroaryl-, (cycloalkyl)a-

lkyl-, (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;

[0175] 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.

[0176] In another embodiment, at least one HCV protease inhibitor is a compound of structural Formula XVI:



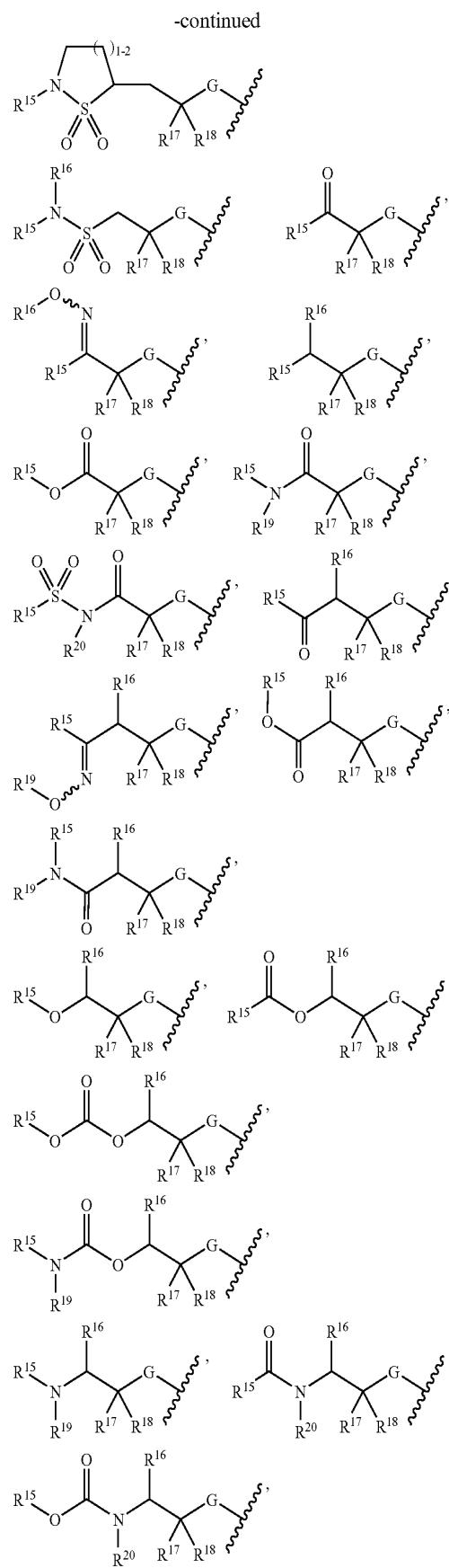
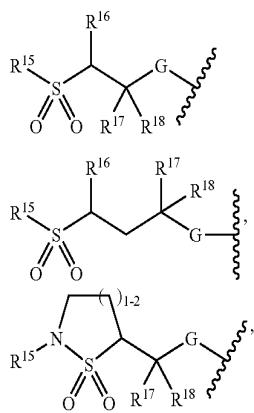
or a pharmaceutically acceptable salt, solvate or ester thereof;

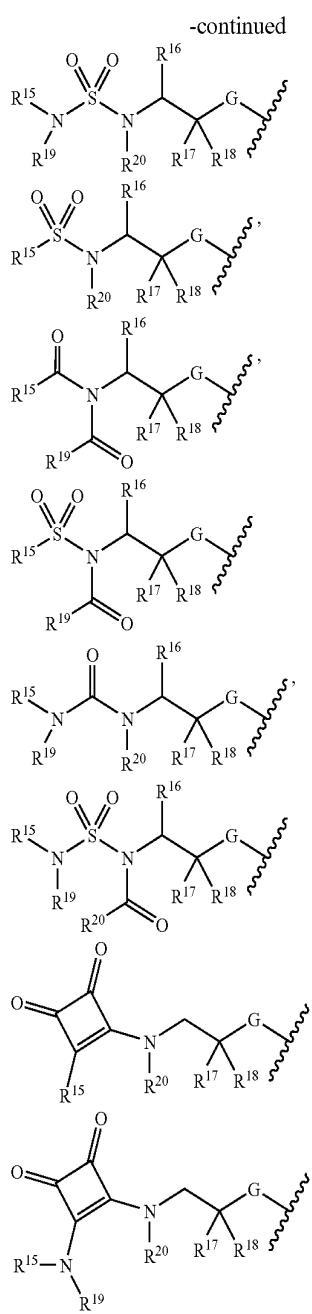
wherein in Formula XVI:

[0177] R<sup>1</sup> is NHR<sup>9</sup>, wherein R<sup>9</sup> is H, alkyl-, alkenyl-, alkynyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, heterocyclyl-, arylalkyl-, or heteroarylalkyl;

[0178] R<sup>2</sup> and R<sup>3</sup> 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;

[0179] Y is selected from the following moieties:



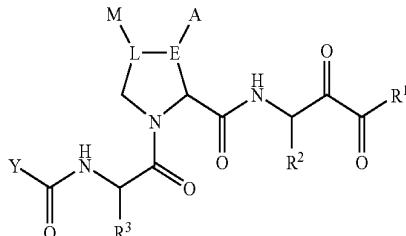


**[0180]** wherein G is NH or O; and R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup>, R<sup>18</sup>, R<sup>19</sup>, R<sup>20</sup>, R<sup>21</sup>, R<sup>22</sup>, R<sup>23</sup>, R<sup>24</sup> and R<sup>25</sup> can be the same or different, each being independently selected from the group consisting of H, alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteraryl, and heteroarylalkyl, or alternately (i) R<sup>17</sup> and R<sup>18</sup> are independently connected to each other to form a three to eight-membered cycloalkyl or heterocyclyl; (ii) likewise independently R<sup>15</sup> and R<sup>19</sup> are connected to each other to form a four to eight-membered heterocyclyl; (iii) likewise independently R<sup>15</sup> and R<sup>16</sup> are connected to each other to form a four to eight-membered heterocyclyl; (iv) likewise independently R<sup>15</sup> and R<sup>20</sup> are connected to each other to form a four to eight-membered heterocyclyl; (v) likewise independently R<sup>22</sup> and R<sup>23</sup> 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<sup>24</sup> and R<sup>25</sup> are connected to each other to form a three to eight-membered cycloalkyl or a four to eight-membered heterocyclyl;

**[0181]** 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, alkoxy carbonylamino, alkoxy carbonyloxy, alkylureido, arylureido, halo, cyano, and nitro.

**[0182]** In another embodiment, at least one HCV protease inhibitor is a compound of structural Formula XVII:

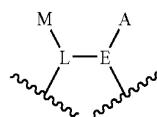


or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XVII:

**[0183]** R<sup>1</sup> is NHR<sup>9</sup>, wherein R<sup>9</sup> is H, alkyl-, alkenyl-, alkynyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, heterocyclyl-, arylalkyl-, or heteroarylalkyl;

**[0184]** A and M can be the same or different, each being independently selected from R, OR, NHR, NRR', SR, SO<sub>2</sub>R, 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;

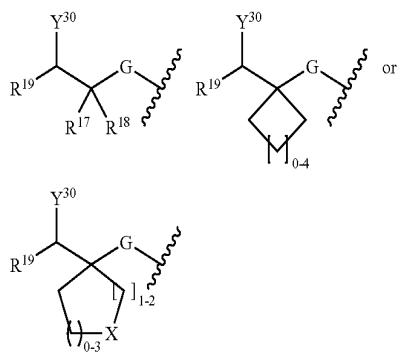
**[0185]** E is C(H) or C=;

**[0186]** L is C(H), C=, CH<sub>2</sub>C=, or C=CH<sub>2</sub>;

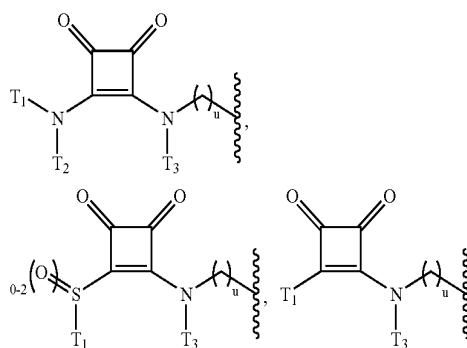
**[0187]** R, R', R<sup>2</sup>, and R<sup>3</sup> can be the same or different, each being independently selected from the group consisting of H, alkyl-, alkenyl-, alkynyl-, cycloalkyl-, heteroalkyl-, heterocyclyl-, aryl-, heteroaryl-, (cycloalkyl)alkyl-, (heterocyclyl)alkyl-, aryl-alkyl-, and heteroaryl-alkyl-; or alternately

R and R' in NRR' are connected to each other such that NRR' forms a four to eight-membered heterocyclyl;

[0188] Y is selected from the following moieties:



wherein Y<sup>30</sup> is selected from



[0189] where u is a number 0-1;

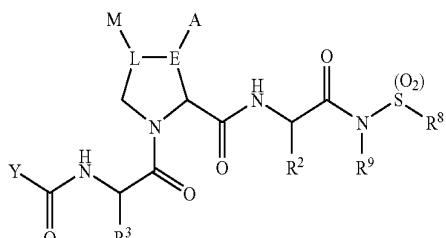
[0190] X is selected from O, NR<sup>15</sup>, NC(O)R<sup>16</sup>, S, S(O) and SO<sub>2</sub>;

[0191] G is NH or O; and

[0192] R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup>, R<sup>18</sup>, R<sup>19</sup>, T<sub>1</sub>, T<sub>2</sub>, and T<sub>3</sub> 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<sup>17</sup> and R<sup>18</sup> are connected to each other to form a three to eight-membered cycloalkyl or heterocyclyl;

[0193] 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, alkoxy carbonylamino, alkoxy carbonyloxy, alkylureido, arylureido, halo, cyano, and nitro.

[0194] In another embodiment, at least one HCV protease inhibitor is a compound of structural Formula XVIII:



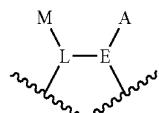
or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XVIII:

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

R<sup>9</sup> 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<sub>2</sub>)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:



[0195] 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;

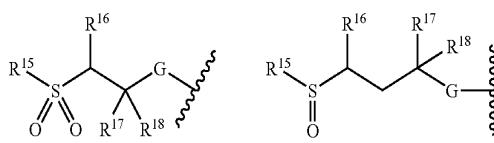
E is C(H) or C(R);

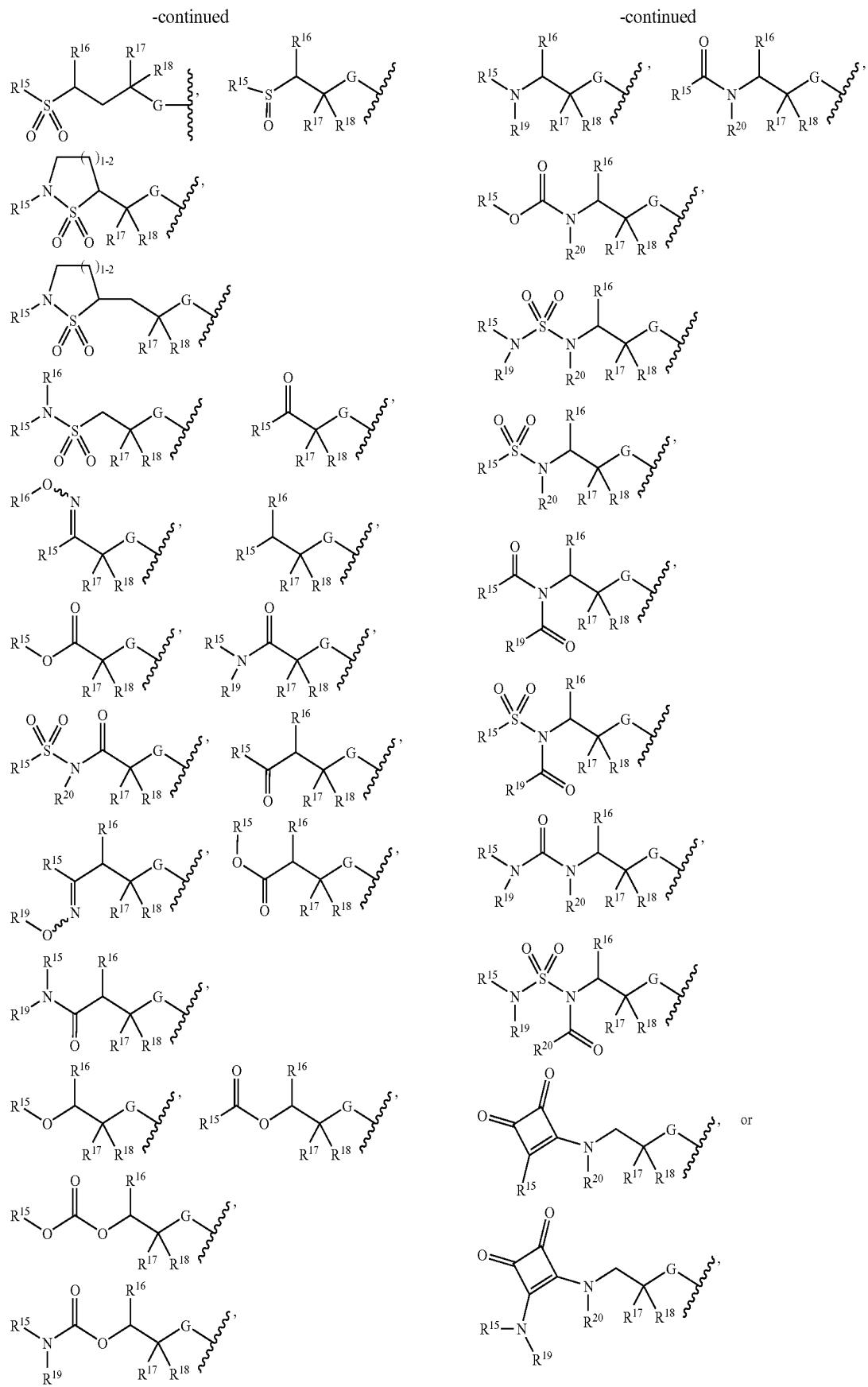
L is C(H), C(R), CH<sub>2</sub>C(R), or C(R)CH<sub>2</sub>;

[0196] 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;

[0197] R<sup>2</sup> and R<sup>3</sup> 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;

[0198] Y is selected from the following moieties:

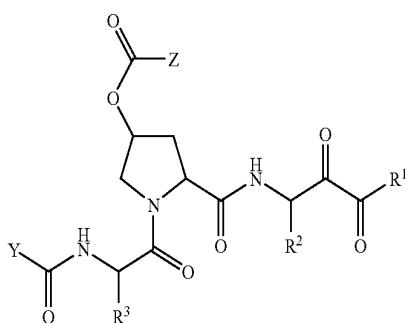




[0199] wherein G is NH or O; and R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup>, R<sup>18</sup>, R<sup>19</sup> and R<sup>20</sup> can be the same or different, each being independently selected from the group consisting of H, alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, or alternately (i) R<sup>17</sup> and R<sup>18</sup> are independently connected to each other to form a three to eight-membered cycloalkyl or heterocyclyl; (ii) likewise independently R<sup>15</sup> and R<sup>19</sup> are connected to each other to form a four to eight-membered heterocyclyl; (iii) likewise independently R<sup>15</sup> and R<sup>16</sup> are connected to each other to form a four to eight-membered heterocyclyl; and (iv) likewise independently R<sup>15</sup> and R<sup>20</sup> are connected to each other to form a four to eight-membered heterocyclyl;

[0200] 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, alkoxy carbonylamino, alkoxy carbonyloxy, alkylureido, arylureido, halo, cyano, and nitro.

[0201] 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;

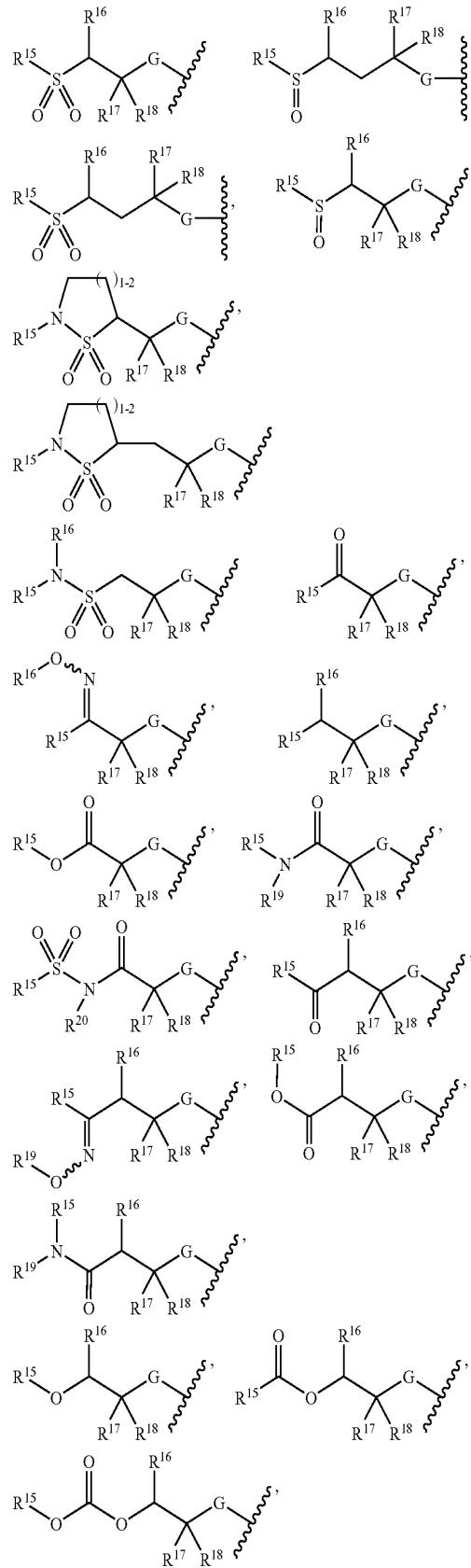
wherein in Formula XIX:

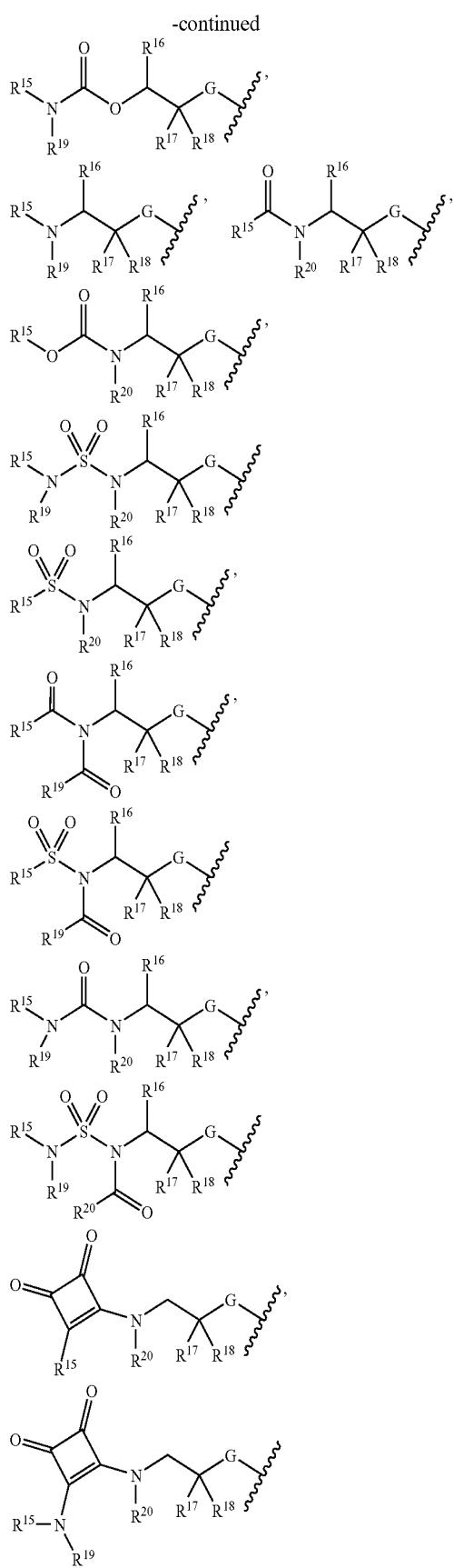
[0202] Z is selected from the group consisting of a heterocyclyl moiety, N(H)(alkyl), —N(alkyl)<sub>2</sub>, —N(H)(cycloalkyl), —N(cycloalkyl)<sub>2</sub>, —N(H)(aryl), —N(aryl)<sub>2</sub>, —N(H)(heterocyclyl), —N(heterocyclyl)<sub>2</sub>, —N(H)(heteroaryl), and —N(heteroaryl)<sub>2</sub>;

[0203] R<sup>1</sup> is NHR<sup>9</sup>, wherein R<sup>9</sup> is H, alkyl-, alkenyl-, alkynyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, heterocyclyl-, arylalkyl-, or heteroarylalkyl;

[0204] R<sup>2</sup> and R<sup>3</sup> 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;

[0205] Y is selected from the following moieties:

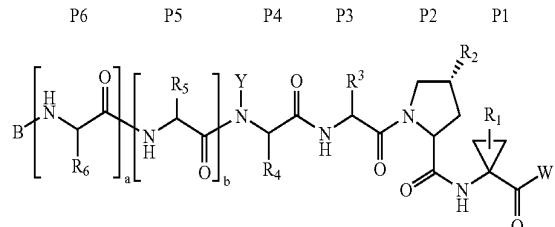




[0206] wherein G is NH or O; and R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup>, R<sup>18</sup>, R<sup>19</sup>, R<sup>20</sup> and R<sup>21</sup> can be the same or different, each being independently selected from the group consisting of H, alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, or alternately (i) R<sup>17</sup> and R<sup>18</sup> are independently connected to each other to form a three to eight-membered cycloalkyl or heterocyclyl; (ii) likewise independently R<sup>15</sup> and R<sup>19</sup> are connected to each other to form a four to eight-membered heterocyclyl; (iii) likewise independently R<sup>15</sup> and R<sup>16</sup> are connected to each other to form a four to eight-membered heterocyclyl; and (iv) likewise independently R<sup>15</sup> and R<sup>20</sup> are connected to each other to form a four to eight-membered heterocyclyl;

[0207] 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, alkoxy carbonylamino, alkoxy carbonyloxy, alkylureido, arylureido, halo, cyano, and nitro.

[0208] In another embodiment, at least one HCV protease inhibitor is a compound of structural 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<sub>1-6</sub>alkyl;

B is H, an acyl derivative of formula R<sub>7</sub>—C(O)— or a sulfonyl of formula R<sub>7</sub>—SO<sub>2</sub> wherein

R7 is

[0209] (i) C<sub>1-10</sub> alkyl optionally substituted with carboxyl, C<sub>1-6</sub> alkanoyloxy or C<sub>1-6</sub> alkoxy;

[0210] (ii) C<sub>3-7</sub> cycloalkyl optionally substituted with carboxyl, (C<sub>1-6</sub> alkoxy)carbonyl or phenylmethoxycarbonyl;

[0211] (iii) C<sub>6</sub> or C<sub>10</sub> aryl or C<sub>7-16</sub> aralkyl optionally substituted with C<sub>1-6</sub> alkyl, hydroxy, or amino optionally substituted with C<sub>1-6</sub> alkyl; or

[0212] (iv) Het optionally substituted with C<sub>1-6</sub> alkyl, hydroxy, amino optionally substituted with C<sub>1-6</sub> alkyl, or amido optionally substituted with C<sub>1-6</sub> 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  $C_{10}$  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  $CH_2-R_{20}$ ,  $NH-R_{20}$ ,  $O-R_{20}$  or  $S-R_{20}$ , wherein  $R_{20}$  is a saturated or unsaturated  $C_{3-7}$  cycloalkyl or  $C_{4-10}$  (alkylcycloalkyl) being optionally mono-, di- or tri-substituted with  $R_{21}$ , or  $R_{20}$  is a  $C_6$  or  $C_{10}$  aryl or  $C_{7-16}$  aralkyl optionally mono-, di- or tri-substituted with  $R_{21}$ ,

or  $R_{20}$  is Het or (lower alkyl)-Het optionally mono-, di- or tri-substituted with  $R_{21}$ , wherein each  $R_{21}$  is independently  $C_{1-6}$  alkyl;  $C_{1-6}$  alkoxy; amino optionally mono- or di-substituted with  $C_{1-6}$  alkyl; sulfonyl;  $NO_2$ ;  $OH$ ;  $SH$ ; halo; haloalkyl; amido optionally mono-substituted with  $C_{1-6}$  alkyl,  $C_6$  or  $C_{10}$  aryl,  $C_{7-16}$  aralkyl, Het or (lower alkyl)-Het; carboxyl; carboxy(lower alkyl);  $C_6$  or  $C_{10}$  aryl,  $C_{7-16}$  aralkyl or Het, said aryl, aralkyl or Het being optionally substituted with  $R_{22}$ ;

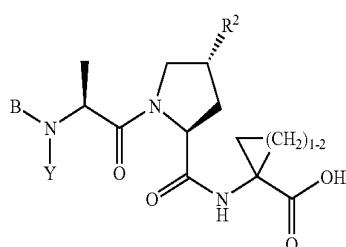
wherein  $R_{22}$  is  $C_{1-6}$  alkyl;  $C_{1-6}$  alkoxy; amino optionally mono- or di-substituted with  $C_{1-6}$  alkyl; sulfonyl;  $NO_2$ ;  $OH$ ;  $SH$ ; halo; haloalkyl; carboxyl; amide or (lower alkyl)amide;

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

$W$  is hydroxy or a N-substituted amino.

[0213] 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.

[0214] 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  $R_4-O-C(O)-$ ; 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  $R_4-SO_2$  wherein

[0215]  $R_4$  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;

[0216] (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;

[0217] (iii) amino optionally mono- or di-substituted with  $C_{1-6}$  alkyl; amido; or (lower alkyl)amide;

[0218] (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

[0219] (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;

[0220]  $R_2$  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  $R_{21}$ ,

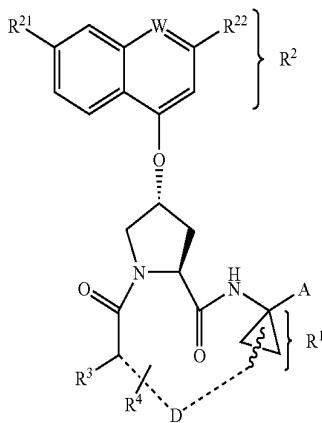
or  $R_{20}$  is Het or (lower alkyl)-Het, both optionally mono-, di- or tri-substituted with  $R_{21}$ ,

[0221] 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  $R_{22}$ ;

[0222] 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;

$R_1$  is  $H$ ;  $C_{1-6}$  alkyl,  $C_{3-7}$  cycloalkyl,  $C_{2-6}$  alkenyl, or  $C_{2-6}$  alkynyl, all optionally substituted with halogen.

[0223] 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;

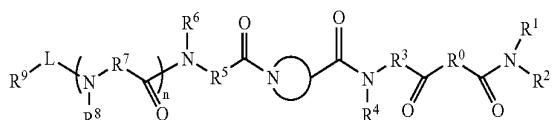
R<sup>22</sup> is H, halo, C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> thioalkyl, C<sub>1-6</sub> alkoxy, C<sub>3-6</sub> cycloalkoxy, C<sub>2-7</sub> alkoxy-alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>6</sub> or 10 aryl or Het, wherein Het is a five-, six-, 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  $NH-C(O)-OR$  wherein  $R^{26}$  is  $C_{1-6}$  alkyl or  $C_{3-6}$  cycloalkyl;

R<sup>3</sup> is hydroxy, NH<sub>2</sub>, or a group of formula —NH—R<sup>31</sup>, wherein R<sup>31</sup> is C<sub>6</sub> or <sub>10</sub> aryl, heteroaryl, —C(O)—R<sup>32</sup>, —C(O)<sub>32</sub>—NHR<sup>32</sup> or —C(O)—OR<sup>32</sup>, wherein R<sup>32</sup> is C<sub>1-6</sub> alkyl or C<sub>3-6</sub> 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<sup>41</sup>, wherein R<sup>41</sup> is H, C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl or —C(O)—R<sup>42</sup>, wherein R<sup>42</sup> is C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl or C<sub>6</sub> or 10 aryl; R<sup>4</sup> 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<sub>1-6</sub> alkyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkoxy, hydroxy, halo, amino, oxo, thio and C<sub>1-6</sub> thioalkyl, and A is an amide of formula —C(O)—NH—R<sup>5</sup>, wherein R<sup>5</sup> is selected from the group consisting of: C<sub>1-8</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>6</sub> or 10 aryl and C<sub>7-16</sub> aralkyl; or A is a carboxylic acid.

[0224] 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<sup>1</sup> 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:

[0225] optionally substituted (1,1- or 1,2-)cycloalkylene; or

[0226] optionally substituted (1,1- or 1,2-)heterocycloalkylene; or

[0227] 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, R6, R8 and R<sup>10</sup> are each independently hydrogen or optionally substituted aliphatic group;



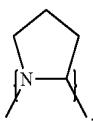
is substituted monocyclic azaheterocycl or optionally substituted multicyclic azaheterocycl, or optionally substituted multicyclic azaheterocyclenyl wherein the unsaturation is in the ring distal to the ring bearing the  $R^9\text{-}L\text{-}(N(R^8)\text{-}R^7\text{-}C(O)\text{-})_nN(R^6)\text{-}R^5\text{-}C(O)\text{-}N$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

provided

when

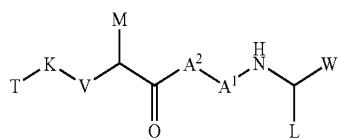


is substituted



then L is  $-\text{OC(O)}-$  and  $\text{R}^9$  is optionally substituted aliphatic; or at least one of  $\text{R}^3$ ,  $\text{R}^5$  and  $\text{R}^7$  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  $\text{R}^4$  is optionally substituted aliphatic.

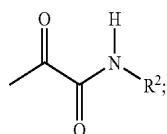
[0228] In another embodiment, at least one HCV protease inhibitor is a compound of structural Formula XXIV:



or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XXIV:

W is:



[0229] m is 0 or 1;

[0230]  $\text{R}^2$  is hydrogen, alkyl, alkenyl, aryl, aralkyl, aralkenyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, heterocyclalkyl, heterocyclalkyl, heterocyclalkenyl, heteroaryl, or heteroaralkyl; wherein any  $\text{R}^2$  carbon atom is optionally substituted with J;

[0231] J is alkyl, aryl, aralkyl, alkoxy, aryloxy, aralkoxy, cycloalkyl, cycloalkoxy, heterocycl, heterocyclalkyl, 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<sup>1</sup> groups;

[0232] J<sup>1</sup> is alkyl, aryl, aralkyl, alkoxy, aryloxy, heterocycl, heterocyclalkyl, keto, hydroxy, amino, alkylamino, aroylamino, carboxy, carboxyalkyl, carboxamidoalkyl, halo, cyano, nitro, formyl, sulfonyl, or sulfonamido;

[0233] 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 sulphydryl or hydroxy;

[0234] A<sup>1</sup> is a bond;

[0235]  $\text{R}^4$  is alkyl, cycloalkyl, aryl, aralkyl, heterocycl, heterocyclalkyl, heteroaryl, heteroaralkyl, carboxyalkyl, or carboxamidoalkyl, and is optionally substituted with 1-3 J groups;

[0236]  $\text{R}^5$  and  $\text{R}^6$  are independently hydrogen, alkyl, alkenyl, aryl, aralkyl, aralkenyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycl, heterocyclalkyl, heteroaryl, or heteroaralkyl, and is optionally substituted with 1-3 J groups;

[0237] X is a bond,  $-\text{C(H)(R}7\text{)}-$ ,  $-\text{O}-$ ,  $-\text{S}-$ , or  $-\text{N(R}8\text{)}-$ ;

[0238]  $\text{R}^7$  is hydrogen, alkyl, alkenyl, aryl, aralkyl, heterocycl, heterocyclalkyl, heteroaryl, or heteroaralkyl, and is optionally substituted with 1-3 J groups;

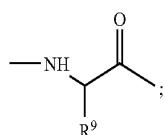
[0239]  $\text{R}^8$  is hydrogen alkyl, aryl, aralkyl, heterocycl, heterocyclalkyl, heteroaryl, heteroaralkyl, aralkanoyl, heterocyclanoyl, heteroaralkanoyl,  $-\text{C(O)R}^{14}$ ,  $-\text{SO}_2\text{R}^{14}$ , or carboxamido, and is optionally substituted with 1-3 J groups; or  $\text{R}^8$  and 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;

[0240]  $\text{R}^{14}$  is alkyl, aryl, aralkyl, heterocycl, heterocyclalkyl, heteroaryl, or heteroaralkyl;

[0241] Y is a bond,  $-\text{CH}_2-$ ,  $-\text{C(O)}-$ ,  $-\text{C(O)C(O)}-$ ,  $-\text{S(O)}-$ ,  $-\text{S(O)}_2-$ , or  $-\text{S(O)(NR}^7\text{)}-$ , wherein  $\text{R}^7$  is as defined above;

[0242] Z is alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocycl, heterocyclalkyl, heteroaryl, heteroaralkyl,  $-\text{OR}^2$ , or  $-\text{N(R}^2\text{)}_2$ , wherein any carbon atom is optionally substituted with J, wherein  $\text{R}^2$  is as defined above;

[0243] A<sup>2</sup> is a bond or



[0244]  $\text{R}^9$  is alkyl, cycloalkyl, aryl, aralkyl, heterocycl, heterocyclalkyl, heteroaryl, heteroaralkyl, carboxyalkyl, or carboxamidoalkyl, and is optionally substituted with 1-3 J groups;

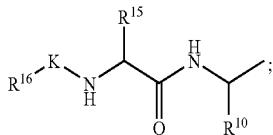
[0245] M is alkyl, cycloalkyl, aryl, aralkyl, heterocycl, heterocyclalkyl, heteroaryl, or heteroaralkyl, optionally substituted by 1-3 J groups, wherein any alkyl carbon atom may be replaced by a heteroatom;

[0246] V is a bond,  $-\text{CH}_2-$ ,  $-\text{C(H)(R}^{11}\text{)}-$ ,  $-\text{O}-$ ,  $-\text{S}-$ , or  $-\text{N(R}^{11}\text{)}-$ ;

[0247]  $\text{R}^{11}$  is hydrogen or C<sub>1-3</sub> alkyl;

[0248] K is a bond,  $-\text{O}-$ ,  $-\text{S}-$ ,  $-\text{C(O)}-$ ,  $-\text{S(O)}-$ ,  $-\text{S(O)}_2-$ , or  $-\text{S(O)(NR}^{11}\text{)}-$ , wherein  $\text{R}^{11}$  is as defined above;

[0249] T is  $-R^{12}$ , -alkyl- $R^{12}$ , -alkenyl- $R^{12}$ , -alkynyl- $R^{12}$ ,  $-\text{OR}^{12}$ ,  $-\text{N}(R^{12})_2$ ,  $-\text{C(O)R}^{12}$ ,  $-\text{C(=NOalkyl)R}^{12}$ , or



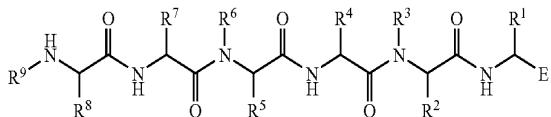
[0250]  $R^{12}$  is hydrogen, aryl, heteroaryl, cycloalkyl, heterocyclyl, cycloalkylidene, or heterocycloalkylidene, and is optionally substituted with 1-3 J groups, or a first  $R^{12}$  and a second  $R^{12}$ , together with the nitrogen to which they are bound, form a mono- or bicyclic ring system optionally substituted by 1-3 J groups;

[0251]  $R^{10}$  is alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, carboxyalkyl, or carboxamidoalkyl, and is optionally substituted with 1-3 hydrogens J groups;

[0252]  $R^{15}$  is alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, carboxyalkyl, or carboxamidoalkyl, and is optionally substituted with 1-3 J groups; and

[0253]  $R^{16}$  is hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, or heterocyclyl.

[0254] 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:

[0255] E represents CHO or  $\text{B(OH)}_2$ ;

[0256]  $R^1$  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;

[0257]  $R^2$  represents lower alkyl, hydroxy-lower alkyl, carboxylower alkyl, aryl-lower alkyl, aminocarbonyl-lower alkyl or lower cycloalkyl-lower alkyl; and

[0258]  $R^3$  represents hydrogen or lower alkyl;

[0259] or  $R^2$  and  $R^3$  together represent di- or trimethylene optionally substituted by hydroxy;

[0260]  $R^4$  represents lower alkyl, hydroxy-lower alkyl, lower cycloalkyl-lower alkyl, carboxy-lower alkyl, aryl-lower alkyl, lower alkylthio-lower alkyl, cyano-lower alkylthio-lower alkyl, aryl-lower alkylthio-lower alkyl, lower alkenyl, aryl or lower cycloalkyl;

[0261]  $R^5$  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;

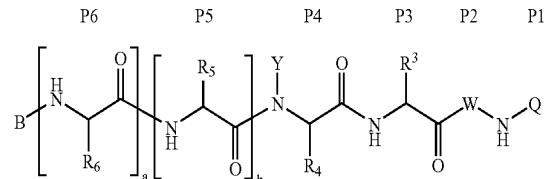
[0262]  $R^6$  represents hydrogen or lower alkyl;

[0263]  $R^7$  represent lower alkyl, hydroxydower alkyl, carboxylower alkyl, aryl-iower alkyl, lower cycloalkyl-lower alkyl or lower cycloalkyl;

[0264]  $R^8$  represents lower alkyl, hydroxy-lower alkyl, carboxylower alkyl or aryl-lower alkyl; and

[0265]  $R^9$  represents lower alkylcarbonyl, carboxy-lower alkylcarbonyl, arylcarbonyl, lower alkylsulphonyl, arylsulphonyl, lower alkoxy carbonyl or aryl-lower alkoxy carbonyl.

[0266] In another embodiment, at least one HCV protease inhibitor is a compound of structural Formula XXVI:



or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XXVI:

[0267] B is an acyl derivative of formula  $\text{R}_{11}-\text{C(O)}$ —wherein  $\text{R}_{11}$  is Cl-10 alkyl optionally substituted with carboxyl; or  $\text{R}_{11}$  is  $\text{C}_6$  or  $\text{C}_{10}$  aryl or  $\text{C}_{7-16}$  aralkyl optionally substituted with a  $\text{C}_{1-6}$  alkyl;

[0268] a is 0 or 1;

[0269]  $\text{R}_6$ , when present, is carboxy(lower)alkyl;

[0270] b is 0 or 1;

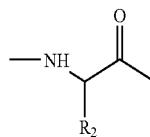
[0271]  $\text{R}_5$ , when present, is  $\text{C}_{1-6}$  alkyl, or carboxy(lower)alkyl;

[0272] Y is H or  $\text{C}_{1-6}$  alkyl;

[0273]  $\text{R}_4$  is  $\text{C}_{1-10}$  alkyl;  $\text{C}_{3-10}$  cycloalkyl;

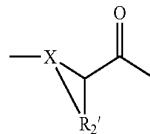
[0274]  $\text{R}_3$  is  $\text{C}_{1-10}$  alkyl;  $\text{C}_{3-10}$  cycloalkyl;

[0275] W is a group of formula:



[0276] wherein  $\text{R}_2$  is  $\text{C}_{1-10}$  alkyl or  $\text{C}_{3-7}$  cycloalkyl optionally substituted with carboxyl;  $\text{C}_6$  or  $\text{C}_{10}$  aryl; or  $\text{C}_{7-16}$  aralkyl; or

[0277] W is a group of formula:



[0278] wherein X is CH or N; and

[0279]  $\text{R}_2'$  is  $\text{C}_{3-4}$  alkylene that joins X to form a 5- or 6-membered ring, said ring optionally substituted with OH; SH; NH2; carboxyl;  $\text{R}_{12}$ ;  $\text{OR}_{12}$ ;  $\text{SR}_{12}$ ;  $\text{NHR}_{12}$  or  $\text{NR}_{12}\text{R}_{12}'$  wherein  $\text{R}_{12}$  and  $\text{R}_{12}'$  are independently:

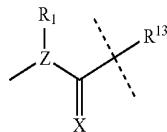
[0280] cyclic  $\text{C}_{3-16}$  alkyl or acyclic  $\text{C}_{1-16}$  alkyl or cyclic  $\text{C}_{3-16}$  alkenyl or acyclic  $\text{C}_{2-16}$  alkenyl, said alkyl or alkenyl optionally substituted with  $\text{NH}_2$ , OH, SH, halo, or carboxyl;

said alkyl or alkenyl optionally containing at least one heteroatom selected independently from the group consisting of: O, S, and N; or

[0281] R<sub>12</sub> and R<sub>12'</sub> are independently C<sub>6</sub> or C<sub>10</sub> aryl or C<sub>1-6</sub> aralkyl optionally substituted with C<sub>1-6</sub> alkyl, NH<sub>2</sub>, 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: O, S, and N;

[0282] 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<sub>2</sub>, OH, SH, halo, carboxyl or carboxy(lower)alkyl; C<sub>6</sub> or C<sub>10</sub> aryl, or heterocycle; said second ring optionally containing at least one heteroatom selected independently from the group consisting of: O, S, and N;

[0283] Q is a group of the formula:



[0284] wherein Z is CH;

[0285] X is O or S;

[0286] R<sub>1</sub> is H, C<sub>1-6</sub> alkyl or C<sub>1-6</sub> alkenyl both optionally substituted with thio or halo;

[0287] and

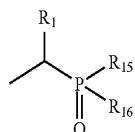
[0288] R<sub>13</sub> is CO—NH—R<sup>14</sup> wherein R<sub>14</sub> is hydrogen, cyclic C<sub>3-10</sub> alkyl or acyclic C<sub>3-10</sub> alkyl or cyclic C<sub>3-10</sub> alkenyl or acyclic C<sub>2-10</sub> alkenyl, said alkyl or alkenyl optionally substituted with NH<sub>2</sub>, OH, SH, halo or carboxyl; said alkyl or alkenyl optionally containing at least one heteroatom selected independently from the group consisting of: O, S, and N; or

[0289] R<sub>14</sub> is C<sub>6</sub> or C<sub>10</sub> aryl or C<sub>7-16</sub> aralkyl optionally substituted with C<sub>1-6</sub> alkyl, NH<sub>2</sub>, OH, SH, halo, carboxyl or carboxy(lower)alkyl or substituted with a further C<sub>3-7</sub> cycloalkyl, C<sub>6</sub> or C<sub>10</sub> aryl, or heterocycle; said aryl or aralkyl optionally containing at least one heteroatom selected independently from the group consisting of: O, S, and N;

[0290] 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<sub>2</sub>, OH, SH, halo, carboxyl or carboxy(lower)alkyl or substituted with a further C<sub>3-7</sub> cycloalkyl, C<sub>6</sub> or C<sub>10</sub> aryl, or heterocycle; said second ring optionally containing at least one heteroatom selected independently from the group consisting of: O, S, and N;

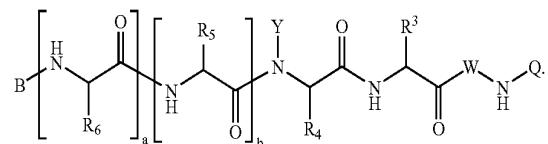
[0291] with the proviso that when Z is CH, then R<sub>13</sub> is not an α-amino acid or an ester thereof;

[0292] Q is a phosphonate group of the formula:

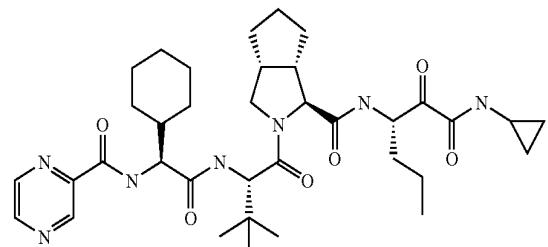


[0293] wherein R<sub>15</sub> and R<sub>16</sub> are independently C<sub>6-20</sub> aryloxy; and R<sub>1</sub> is as defined above.

[0294] 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:



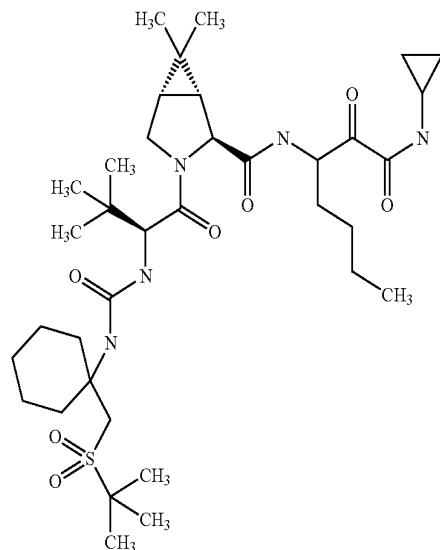
[0295] In another embodiment, at least one HCV protease inhibitor is a compound of structural Formula XXVII:



or a pharmaceutically acceptable salt, solvate or ester thereof.

[0296] The present invention also provides medicaments and methods using the same comprising, separately or together:

[0297] (a) at least one HCV protease inhibitor, wherein at least one HCV protease inhibitor is



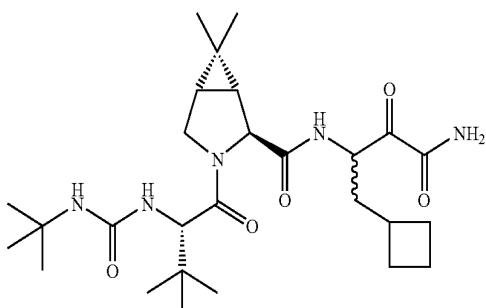
or a pharmaceutically acceptable salt, solvate or ester thereof, and

[0298] (b) at least one HCV polymerase inhibitor but not HCV-796;

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.

[0299] The present invention also provides medicaments and methods using the same comprising, separately or together:

[0300] (a) at least one HCV protease inhibitor, wherein at least one HCV protease inhibitor is

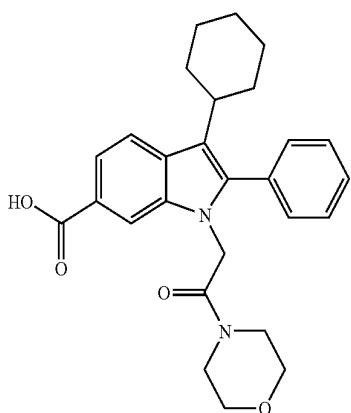


Formula Ia, or a pharmaceutically acceptable salt, solvate or ester thereof, and

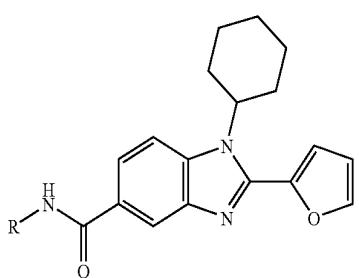
[0301] (b) at least one HCV polymerase inhibitor but not HCV-796;

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.

[0302] In one embodiment, at least one HCV polymerase inhibitor is selected from the group consisting of:



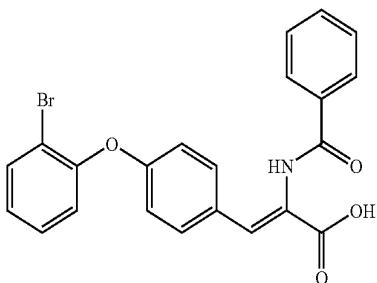
Formula XLI



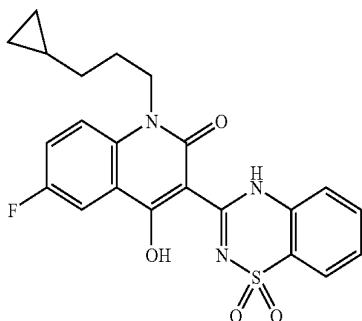
Formula XLII

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Formula XLIII



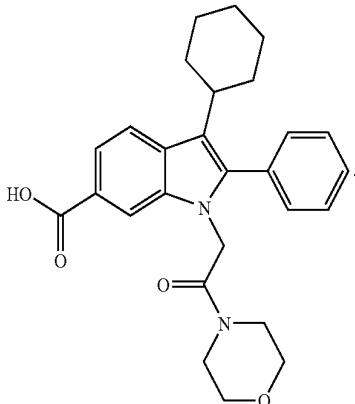
Formula XLIV



or a pharmaceutically acceptable salt, solvate or ester thereof.

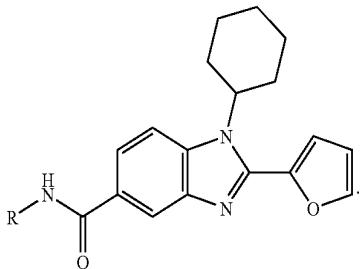
[0303] In one embodiment, at least one HCV polymerase inhibitor is:

Formula XLI

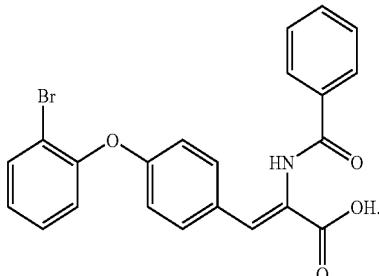


[0304] In one embodiment, at least one HCV polymerase inhibitor is:

Formula XLII

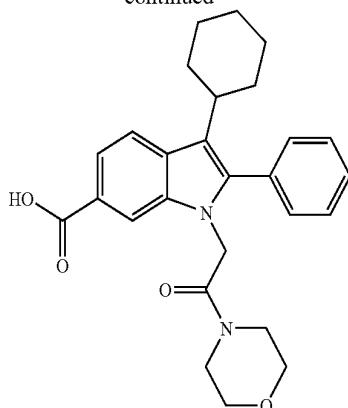


[0305] In one embodiment, at least one HCV polymerase inhibitor is:

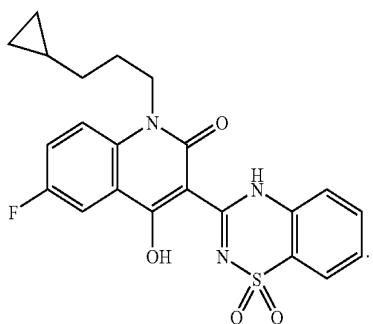


Formula XLIII

-continued



[0306] In one embodiment, at least one HCV polymerase inhibitor is:



Formula XLIV

2'methyl-adenosine, indole-N-acetamide, benzothiadiazine, or a pharmaceutically acceptable salt, solvate, or ester thereof.

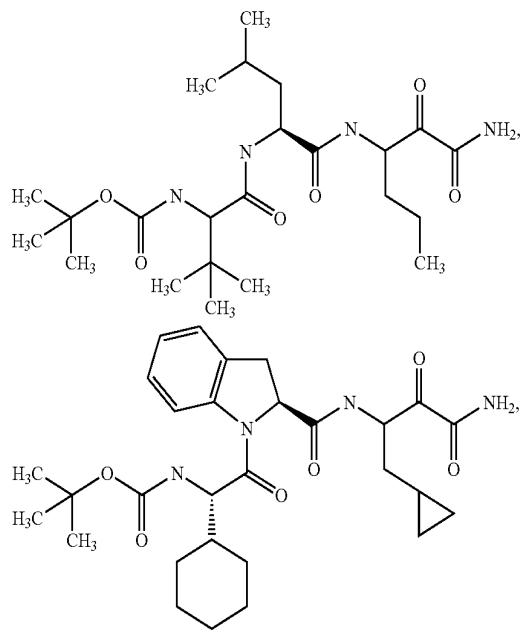
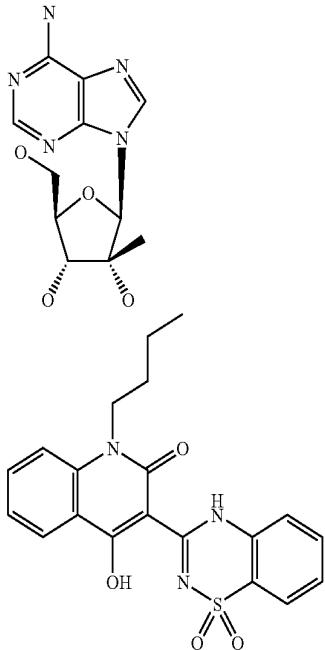
[0308] In one embodiment, at least one HCV polymerase inhibitor is 2'methyl-adenosine, or a pharmaceutically acceptable salt, solvate, or ester thereof.

[0309] In one embodiment, at least one HCV polymerase inhibitor is indole-N-acetamide, or a pharmaceutically acceptable salt, solvate, or ester thereof.

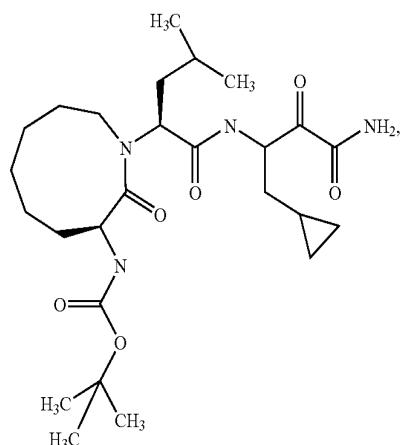
[0310] In one embodiment, at least one HCV polymerase inhibitor is benzothiadiazine, or a pharmaceutically acceptable salt, solvate, or ester thereof.

[0311] In one embodiment, at least one HCV protease inhibitor is administered in an amount ranging from about 100 to about 3600 mg per day.

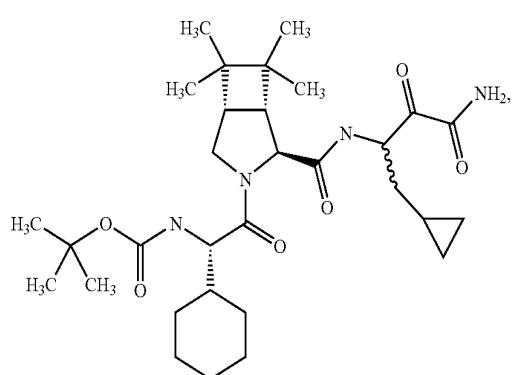
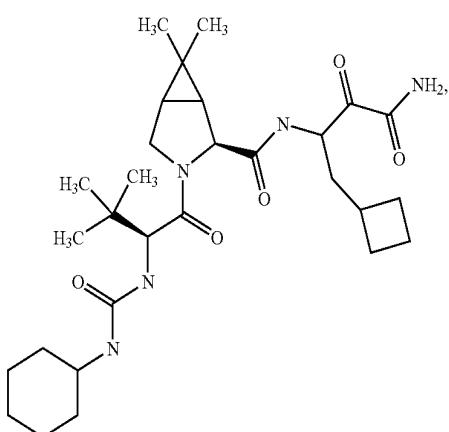
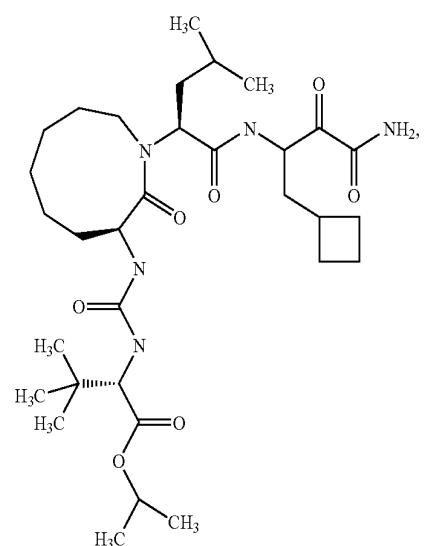
[0312] In one embodiment, at least one HCV protease inhibitor is selected from the group consisting of:



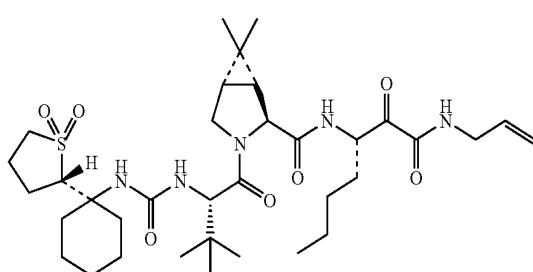
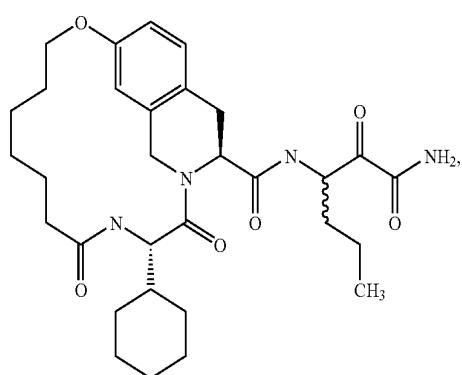
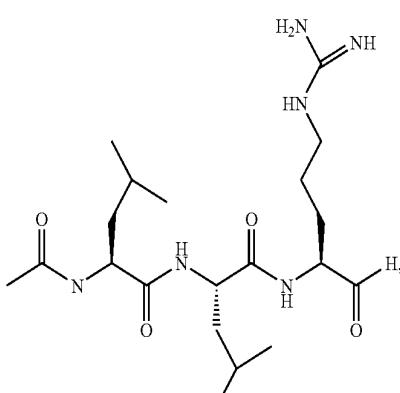
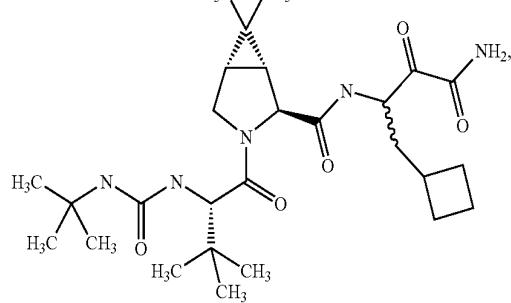
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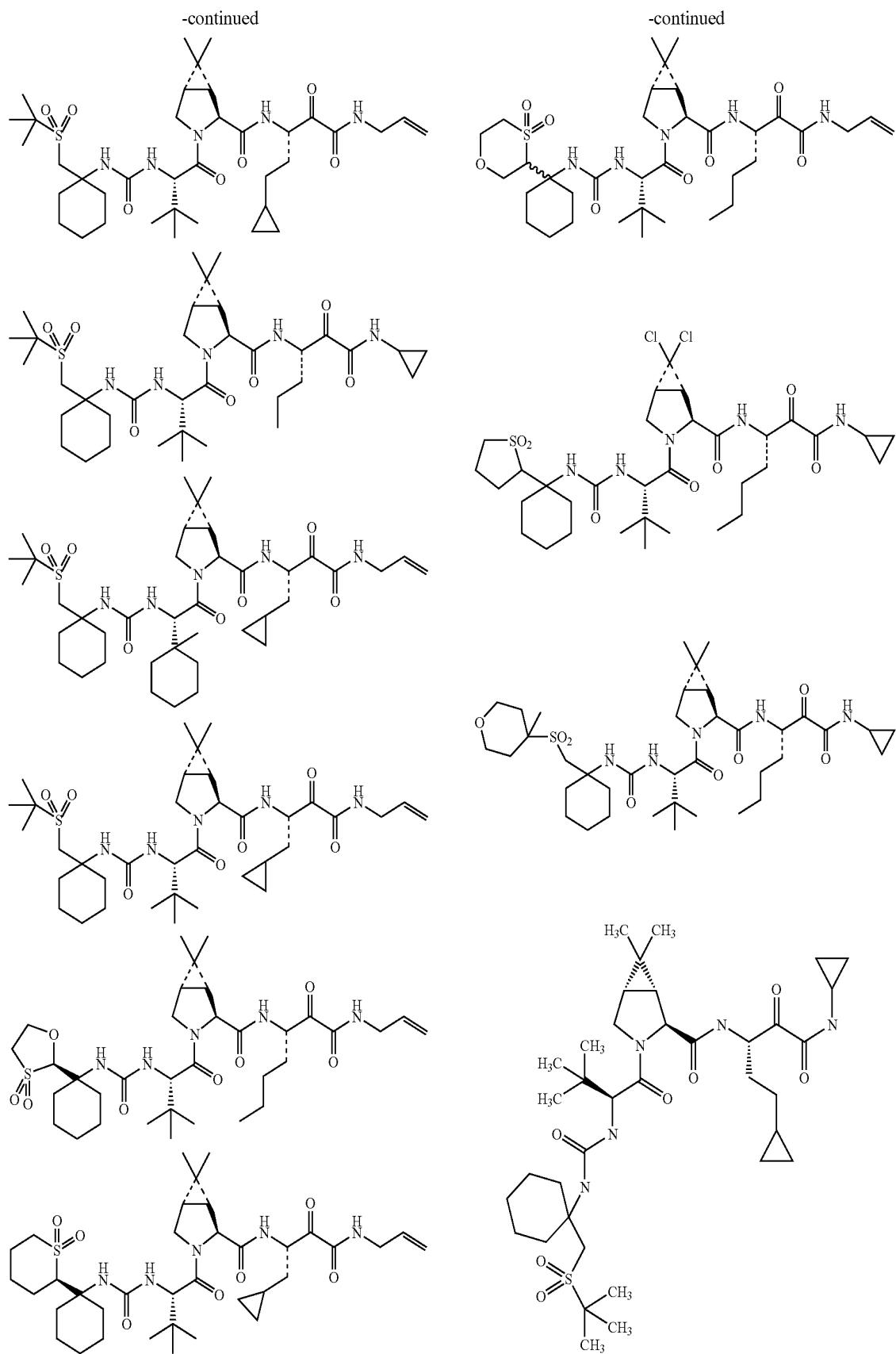


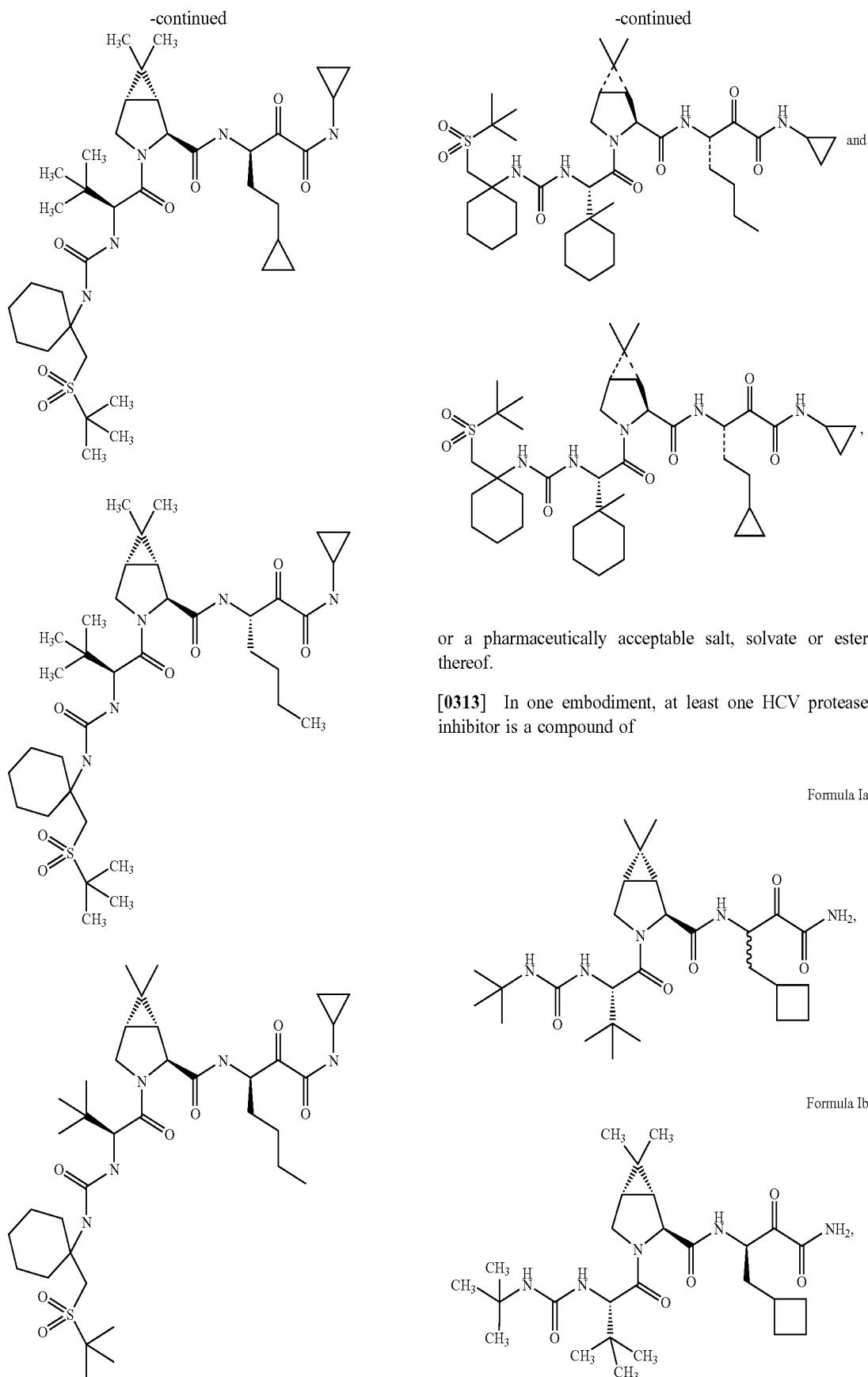
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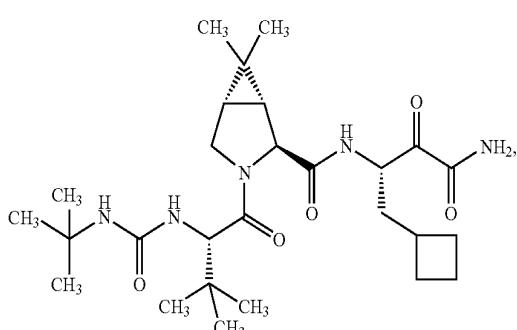






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Formula Ic



or a pharmaceutically acceptable salt, solvate or ester thereof.

[0314] In one embodiment, the medicament further comprises at least one other therapeutic agent. Preferably, at least one other therapeutic agent is ribavirin, levovirin, VP 50406, ISIS 14803, Heptazyme, VX 497, Thymosin, Maxamine, mycophenolate mofetil, interferon, an antibody specific to IL-10. In one embodiment, at least one other therapeutic agent is interferon, and in another embodiment further comprises ribavirin. In one embodiment, at least one other therapeutic agent is an antibody specific to IL-10, preferably, humanized 12G8.

[0315] 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 Roferon™, Pegasys™, Intron™, PEG-Intron™, Berofor Alpha™, and Infergen™. In one embodiment, the interferon is administered concurrently or consecutively with at least one HCV protease inhibitor and at least one HCV polymerase inhibitor.

[0316] In one embodiment, the medicament further comprises at least one aldo-keto reductase (AKR) competitor administered concurrently or consecutively with at least one HCV protease inhibitor and at least one HCV polymerase inhibitor in an amount sufficient to increase the bioavailability of at least one HCV protease inhibitor. In one embodiment, at least one AKR competitor is an AKR substrate, or an AKR inhibitor. In one embodiment, the AKR substrate is a fibrate, a 5α-dihydroxytestosterone, dolasetron, doxorubicin, 17β-estradiol, a non-steroidal anti-inflammatory drug (NSAID), ketotifen, naltrexone, Z-10-oxo nortriptyline, oestrone, a S-1360 HIV integrase inhibitor, progesterone, prostaglandin, sorbinil, testosterone, tibolone, tolrestat, naringenin, or a mixture of two or more thereof. Preferably, the fibrate is bezafibrate, bezafibrite, binifibrate, ciprofibrate, clinfibrate, clofibrate, fenofibrate, gemfibrozil, lifibrol, or a mixture of two or more thereof. In another embodiment, the AKR inhibitor is an AKR1C1 AKR inhibitor, an AKR1C2 AKR inhibitor, an AKR1C3 AKR inhibitor, an AKR1C4 AKR inhibitor, naringenin, or a mixture of two or more thereof. In one preferred embodiment, the AKR inhibitor is a benzodiazepine, a cyclooxygenase (COX) 2 inhibitor, a NSAID, testosterone, naringen-

nin, or a mixture of two or more thereof. Preferably, the benzodiazepine is cloxazolam, diazepam, estazolam, flunitrazepam, nitrazepam, medazepam, or a mixture of two or more thereof. Preferably, the COX 2 inhibitor is celecoxib. Preferably, the NSAID is ibuprofen, diclofenac, diflunisal, flufenamic acid, indomethacin, mefenamic acid, naproxen, or a mixture of two or more thereof. In one preferred embodiment, at least one AKR competitor is diflusinal. Preferably, diflunisal is administered in an amount sufficient to increase the bioavailability of at least one HCV protease inhibitor. In one embodiment, diflunisal is administered at a dosage range of about 1000 mg to about 1500 mg per day.

[0317] In one embodiment, the medicament further comprises at least one cytochrome P450 inhibitor (e.g., a cytochrome P450 isoenzyme 3A4 (CYP3A4) inhibitor). In one embodiment, the medicament further comprises at least one CYP3A4 inhibitor, administered concurrently or consecutively with at least one HCV protease inhibitor and at least one HCV polymerase inhibitor in an amount sufficient to increase the bioavailability of at least one HCV protease inhibitor. In one preferred embodiment, at least one CYP3A4 inhibitor is ritonavir, ketoconazole, or clarithromycin.

[0318] In one embodiment, the medicament further comprises both a CYP3A4 inhibitor and an AKR competitor. Preferably, the CYP3A4 inhibitor is ritonavir, ketoconazole, or clarithromycin; and the AKR competitor is diflunisal.

[0319] In yet another embodiment, the medicament further comprises a permeability-glycoprotein (Pgp) inhibitor, preferably, ritonavir.

[0320] The present invention also provides a pharmaceutical composition comprising a therapeutically effective amount of the medicament and a pharmaceutically acceptable carrier.

[0321] 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).

[0322] In one embodiment, the pharmaceutical kit further comprises at least one AKR competitor, preferably diflunisal. Preferably, the diflunisal is administered in an amount sufficient to increase the bioavailability of at least one HCV protease inhibitor.

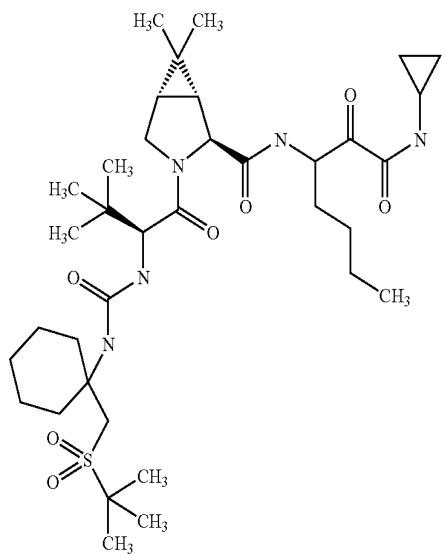
[0323] The present invention also provides methods for treating or ameliorating one or more symptoms of HCV, or disorders associated with HCV in a subject in need thereof, comprising the step of administering to the subject an effective amount of the medicament. In one preferred embodiment, administration of the medicament is oral, intravenous, intrathecal, or subcutaneous.

[0324] In one embodiment, the methods further comprise administering at least one AKR competitor in an amount sufficient to increase the bioavailability of at least one HCV protease inhibitor. In a preferred embodiment, the AKR competitor is diflunisal.

[0325] In one embodiment, the methods further comprise administering at least one CYP3A4 inhibitor in an amount sufficient to increase the bioavailability of at least one HCV

protease inhibitor. In a preferred embodiment, at least one CYP3A4 inhibitor is ritonavir, ketoconazole, or clarithromycin.

[0326] In one preferred embodiment, 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. In another preferred embodiment, at least one HCV protease inhibitor is selected from the group consisting of a compound of Formula I, Formula XIV, or a pharmaceutically acceptable salt, solvate, or ester thereof. In one embodiment, the method comprises administering at least one HCV protease inhibitor concurrently or consecutively with the AKR competitor. In one preferred embodiment, 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. In another preferred embodiment, at least one HCV protease inhibitor is



or a pharmaceutically acceptable salt, solvate, or ester thereof. In one preferred embodiment, the amount of diflunisal administered is sufficient to increase the blood level of a HCV protease inhibitor. In one embodiment, the subject is treatment naïve. In an alternative embodiment, the subject is treatment experienced.

#### BRIEF DESCRIPTION OF THE DRAWINGS

[0327] The foregoing summary, as well as the following detailed description, is better understood when read in conjunction with the appended drawings. In the drawings:

[0328] FIG. 1 depicts inhibitors of HIV protease as well as inhibitors of CYP3A4.

[0329] FIG. 2 is a graph of the relative inhibition of replicon RNA by Formula 1a in combination with 2'-methyl-adenosine (at a concentration of 0, 240, 600, or 1500 nM).

[0330] FIG. 3 is a graph of the relative inhibition of replicon RNA by Formula 1a in combination with indole-N-acetamide (at a concentration of 0, 2, 5, or 12.5 µM).

[0331] FIG. 4 is a graph of the relative inhibition of replicon RNA by Formula 1a in combination with benzothiadiazine (at a concentration of 0, 3.2, or 8 µM).

[0332] FIG. 5 is bar graph of the % resistant replicon colonies after treatment with either Formula 1a alone or Formula 1a in combination with 2'-methyl-adenosine or indole-N-acetamide.

[0333] FIG. 6 is a graph of the relative inhibition of replicon RNA by Formula 1 (i.e., SCH 446211 (SCH 6)) in combination with ribavirin (at a concentration of 0, 8, 31, or 500 µM).

#### DETAILED DESCRIPTION

[0334] The present invention provides medicaments, pharmaceutical compositions, pharmaceutical kits, and methods based on combinations comprising, separately or together: (a) at least one HCV protease inhibitor; and (b) at least one HCV polymerase inhibitor but not HCV-796; 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.

[0335] 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.

[0336] In one embodiment, the “HCV polymerase inhibitor” in (b) above refers to any known HCV polymerase inhibitor except for HCV-796. Non-limiting examples of suitable HCV polymerase inhibitors (excluding HCV-796) that can be used in the practice of the present invention are disclosed in the patents and publications listed in this application under the heading “HCV polymerase inhibitors.”

#### HCV Protease Inhibitors:

[0337] 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, US20020182227A1, US2003008828A1, US20020177725A1, US20050267018A1, US20010034019A1, US20050074465A1, US20040253577A1, US20040229840A1, US20040077551A1, EP1408031A1, WO9837180A2, U.S. Pat. No. 6,696,281B1, JP11137252A, WO0111089A1, U.S. Pat. No. 6,280,940B1, EP1106702A1, US20050118603A1, JP2000007645A, WO0053740A1, WO020400A1, WO2004013349A2, WO2005027871A2, WO2002100900A2, WO0155703A1, US20030125541A1, US20040039187A1, U.S. Pat. No. 6,608,027B1, US20030224977A1, WO2003010141A2, WO2003007945A1, WO2002052015A2, WO0248375A2, WO0066623A2, WO0009543A2, WO9907734A2, U.S. Pat. No. 6,767,991B1, US20030187018A1, US20030186895A1, WO2004087741A1, WO2004039833A1, WO2004030670A1, US20040224900A1, WO2004103996A1, WO2004064925A1, WO2004009121A1, WO2005034850A2, WO2004015131A2, WO2003099274A1, WO2002060926A2, WO0040745A1, U.S. Pat. No. 6,586,615B1, WO2002061048A2, WO0248157A2,

WO0248116A2, WO2005017125A2, WO0022160A1, US20060051745A1, WO2004021871 A2, WO2004011647A1, WO9816657A1, U.S. Pat. No. 5,371,017A, WO9849190A2, U.S. Pat. No. 5,807,829A, WO0005243A2, WO0208251A2, WO2005067437A2, WO9918856A1, WO0004914A1, WO0212543A2, WO9845040A1, WO0140262A1, WO0102424A2, WO196540A2, WO0164678A2, U.S. Pat. No. 5,512,391 A, WO0218369A2, WO9846597A1, WO2005010029A1, WO2004113365A2, WO2004093798A2, WO2004072243A2, WO9822496A2, WO2004046159A1, JP11199509A, WO2005012288A1, WO2004108687A2, WO9740168A1, US20060110755A1, WO2002093519A2, U.S. Pat. No. 6,187,905B1, WO2003077729A2, WO9524414A1, WO2005009418A2, WO2004003000A2, US20050037018A1, WO9963998A1, WO0063444A2, WO9938888A2, WO9964442A1, WO0031129A1, WO0168818A2, WO9812308A1, WO9522985A1, WO0132691 A1, WO9708304A2, WO2002079234A1, JP10298151A, JP09206076A, JP09009961A, JP2001103993A, JP11127861A, JP11124400A, JP11124398A, WO2003051910A2, WO2004021861A2, WO9800548A1, WO2004026896A2, WO0116379A1, U.S. Pat. No. 5,861,297A, WO2004007512A2, WO2004003138A2, WO2002057287A2, WO2004009020A2, WO2004000858A2, WO2003105770A2, WO0114517A1, WO9805333A1, U.S. Pat. No. 6,280,728B1, EP1443116A1, US20040063911A1, WO2003076466A1, WO2002087500A2, WO0190121A2, WO2004016222A2, WO9839030A1, WO9846630A1, WO0123331A1, WO9824766A1, U.S. Pat. No. 6,168,942B1, WO0188113A2, WO2005018330A1, WO2005003147A2, WO9115596A1, WO9719103A1, WO9708194A1, WO2002055693A2, WO2005030796A1, WO2005021584A2, WO2004113295A1, WO2004113294A1, WO2004113272A1, WO2003062228A1, WO0248172A2, WO0208198A2, WO0181325A2, WO0177113A2, WO0158929A1, WO9928482A2, WO9743310A1, WO9636702A2, WO9635806A1, WO9635717A2, U.S. Pat. No. 6,326,137B1, U.S. Pat. No. 6,251,583B1, U.S. Pat. No. 5,990,276A, U.S. Pat. No. 5,759,795A, U.S. Pat. No. 5,714,371A, U.S. Pat. No. 6,524,589B1, WO0208256A2, WO0208187A1, WO2003062265A2, U.S. Pat. No. 7,012,066B2, JP07184648A, JP06315377A, WO2002100851A2, WO2002100846A1, WO0039348A1, JP06319583A, JP1129840A, JP08205893A, WO0075338A2, WO0075337A1, WO2003059384A1, WO2002063035A2, WO2002070752A1, U.S. Pat. No. 6,190,920B1, 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, U.S. Pat. No. 5,837,464A, DE20201549U1, WO2003090674A2, WO9727334A1, WO0034308A2, U.S. Pat. No. 6,127,116A, US20030054000A1, JP2001019699A, U.S. Pat. No. 6,596,545B1, U.S. Pat. No. 6,329,209B1, IT1299179, CA2370400, KR2002007244, KR165708, KR2000074387, KR2000033010, KR2000033011, KR2001107178, KR2001107179, ES2143918, KR2002014283, KR149198, KR2001068676. Preferably, at least one HCV protease

inhibitor is a compound selected from the group of compounds of Formula I to XXVII (described above). In a particularly preferred embodiment, at least one HCV protease inhibitor is Formula I, disclosed in U.S. Pat. No. 7,012,066 as Example XXIV, on columns 448-451, which is incorporated herein by reference.

[0338] Preferably, 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.

[0339] 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.

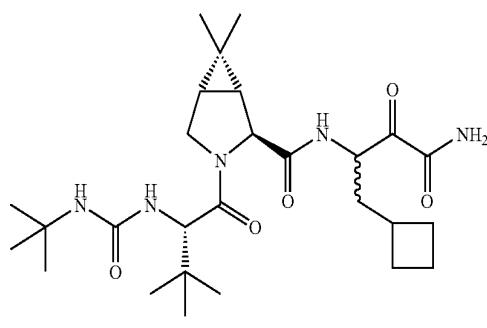
[0340] In another embodiment, where at least one HCV protease inhibitor is selected from the group consisting of Formula XXVII, or a pharmaceutically acceptable salt, solvate, or ester thereof, the preferred dosage range is about 1350 mg to about 2500 mg per day. In one preferred embodiment, where at least one HCV protease inhibitor is selected from the group consisting of Formula XXVII, or a pharmaceutically acceptable salt, solvate, or ester thereof, the dosage is about 1350 mg, about 2250 mg, or about 2500 mg per day administered as about 450 mg TID, about 750 BID, or about 1250 BID, respectively.

[0341] All HCV protease inhibitor compounds disclosed in these publications should be considered as being suitable in the practice of the present invention, although only a representative, non-limiting, sample of such compounds are illustrated below.

[0342] 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.

[0343] In one embodiment, at least one HCV protease inhibitor is selected from the group consisting of

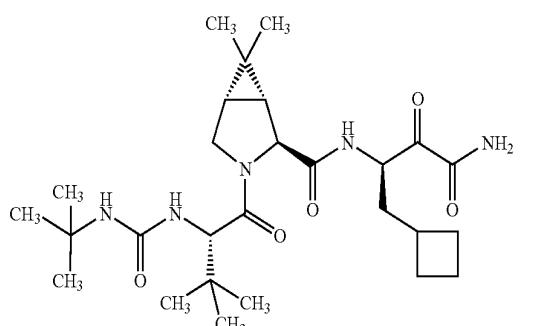
Formula Ia



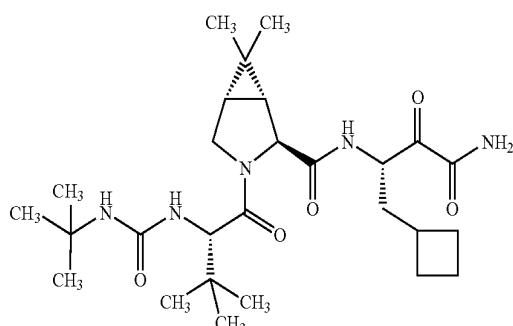
and pharmaceutically acceptable salts or solvates thereof, disclosed in U.S. Pat. No. 7,012,066 as Example XXIV, on columns 448-451, which is incorporated herein by reference.

[0344] The compound of formula Ia has been separated into its isomer/diastereomers of Formulas Ib and Ic, as disclosed in US2005/0249702 published Nov. 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



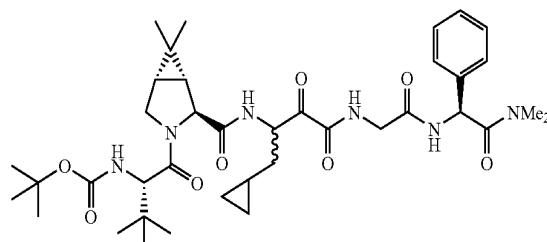
Formula Ic



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

[0345] 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.

[0346] Likewise, suitable compounds of Formula I include the structure of SCH 446211 (SCH 6) reproduced below:



24: Sch 6  
Ki\* = 3.8 nM  
IC<sub>90</sub> (replicon) = 100 nM

which is also described in Bogen et al., *J Med Chem*, 49:2750-2757 (2006).

[0347] Non-limiting examples of suitable compounds of Formula II and methods of making the same are disclosed in WO02/08256 and in U.S. Pat. No. 6,800,434, at col. 5 through col. 247, incorporated herein by reference.

[0348] 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.

[0349] Non-limiting examples of suitable compounds of Formula IV and methods of making the same are disclosed in U.S. Pat. No. 6,894,072, granted May 17, 2005, col. 5, lines 54 through col. 49, line 48, at incorporated herein by reference.

[0350] 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.

[0351] 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.

[0352] 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.

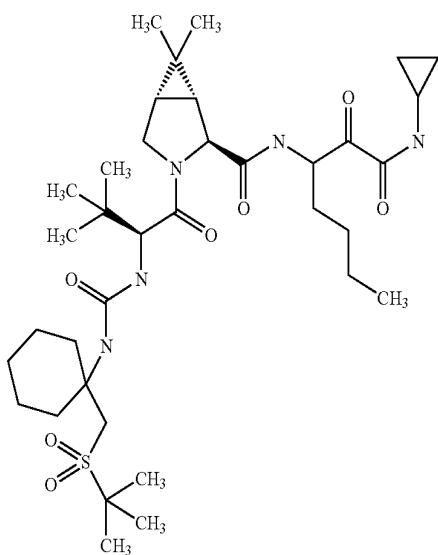
[0353] Non-limiting examples of suitable compounds of Formula X and methods of making the same are disclosed in International Patent Publication WO2005/085275 and in U.S. Patent Publication 2005/0267043 at page 4, paragraph [0026] through page 519, paragraph [0444], incorporated herein by reference.

[0354] 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.

[0355] 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.

[0356] 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.

[0357] 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.

[0358] 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.

[0359] 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.

[0360] 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.

[0361] 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 herein by reference.

[0362] 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.

[0363] 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.

[0364] 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.

[0365] 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. Pat. No. 6,608,027, at col. 65, line 65 through col. 141, line 20, each incorporated herein by reference.

[0366] 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.

[0367] 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. Pat. No. 6,265,380 at col. 3, line 35 through col. 121 and U.S. Pat. No. 6,617,309 at col. 3, line 40 through col. 121, each incorporated herein by reference.

[0368] 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.

[0369] 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.

[0370] Non-limiting examples of suitable compounds of Formula XXVII and methods of making the same are disclosed in U.S. Pat. No. 6,143,715 at col. 3, line 6 through col. 62, line 20, incorporated herein by reference.

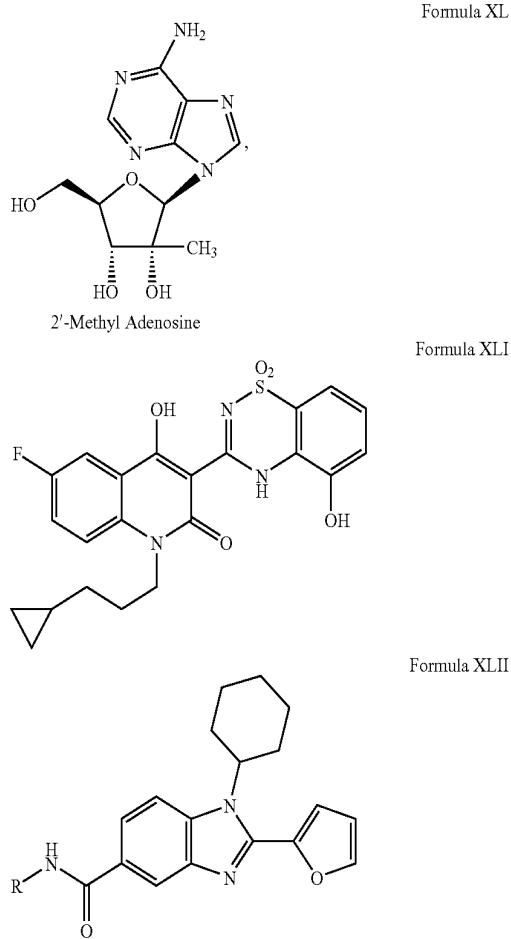
#### HCV Polymerase Inhibitors

[0371] HCV polymerase inhibitors suitable for use in the compositions and methods of the present invention include,

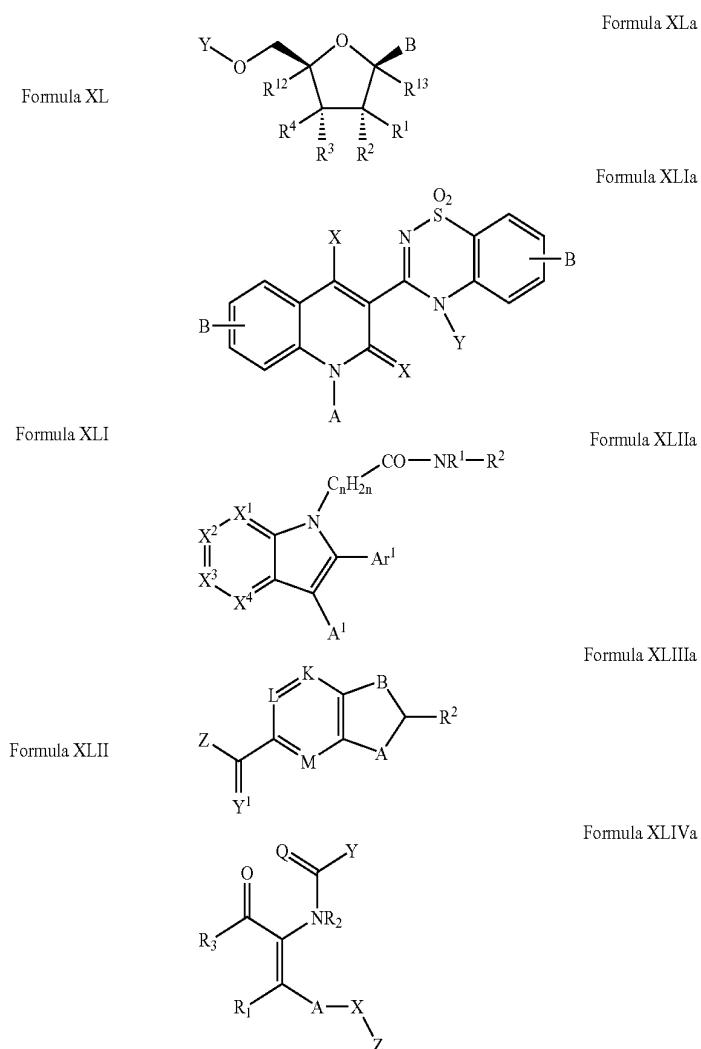
but are not limited to, compounds disclosed in the following patents and publications, the disclosures of which are incorporated herein by their entirety: US20040023921 A1, US20030224469A1, US20060183751 A1, US20060183111 A1, US20060074035A1, US20030037355A1, U.S. Pat. No. 6,322,966B1, US20010034019A1, US20050153877A1, US20050119318A1, US20050107364A1, US20050048472A1, US20050026923A1, US20040266708A1, US20040229936A1, US20040229840A1, US20040167123A1, US20040158054A1, US20040082075A1, WO2005019191A2, WO2004041818A1, WO2005095655A1, WO9949031A1, WO0040759A2, WO9949029A1, U.S. Pat. No. 6,280,940B1, US20050176701A1, EP1256628A2, EP 1106702A1, WO2006074346A2, US20020055162A1, WO9800547A1, U.S. Pat. No. 6,110,901A, WO9938985A2, U.S. Pat. No. 5,472,840A, WO2005017133A1, WO2006066079A2, WO2006076650A2, AT407256, WO2003084953A1, WO2006011719A1, WO2004108719A1, WO2004033450A1, WO2004108068A2, DE10225066A1, EP0655505A1, WO2003018832A1, WO0132153A2, WO2004106350A1, US20040014722A1, WO2006050161A2, WO2006002231A1, WO2002069903A2, US20050080053A1, US20040242599A1, US20040229839A1, WO2005021568A2, WO0155702A1, US20040039187A1, WO0053775A2, WO2005019449A2, WO2005053516A2, US20030224977A1, WO2005042530A1, WO2003014377A2, WO2003010141A2, WO2003007945A1, WO0204425A2, WO0183736A2, WO0009558A1, US20030187018A1, US20030186895A1, US20040229818A1, US20040224900A1, WO2006007693A1, WO2005080388A1, WO2005070955A1, WO2005028501A1, WO2004103996A1, WO2004065367A1, WO2004064925A1, WO2004099241A1, WO2005092855A1, WO2006020082A1, WO2005054430A2, WO2005051410A1, WO2005046712A1, WO2005034850A2, WO2004094452A2, WO2004014313A2, WO2003026587A2, WO2002061048A2, CA2370400, JP10165186A, WO0212477A2, WO9702352A1, CN1385540, CN1526826, CN1757725, WO2005040340A2, WO0157073A2, US20050095582A1, WO137654A2, WO2003002518A1, WO2002079187A1, WO0208292A2, WO0033635A2, WO9943792A1, U.S. Pat. No. 6,461,845B1, WO2004113365A2, WO2004093798A2, WO2004072243A2, WO2004113555A2, WO2006037102A2, WO2003042385A2, US20030092135A1, WO2004046159A1, WO2003099229A2, WO2004055216A2, WO2003082265A2, WO2005012288A1, US20060111311A1, WO2006076529A1, WO2004028481A2, WO2003093290A2, US20050090463A1, EP0454461A1, WO0006779A1, WO2005002626A2, WO2006045615A1, WO2006045613A1, WO2005092863A1, WO2005079799A1, WO2004096774A1, WO2004076415A1, WO2004060889A1, WO2004009543A2, WO2003037895A1, WO2003037894A1, WO2003037893A1, WO2003000713A1, WO9936572A1, WO2002093519A2, WO2003077729A2, WO9116902A1, WO0157266A1, WO2006037028A2, WO2003026589A2, WO2004003000A2, WO200600922A2, WO2004046331A2, WO9203539A1, US20050037018A1, WO0194644A1, WO2006016930A2, WO2005110455A2, WO2005067454A2, WO2005062949A2, WO2005037214A2, WO9967396A1, U.S. Pat. No. 5,576,302A, WO0006529A1, WO2006046030A2, WO2006021449A1, WO2005053670A1, WO2005034941A1, WO2005023819A1, WO2004110442A1, WO2004087714A1, WO0206246A1, WO9637619A1, WO2006038039A1, WO2006029912A1, WO2006008556A1, WO2003062211A1, WO2006027628A2, WO2006052013A1, WO2005080399A1, WO2005049622A1, WO2005014543A1, US20030050320A1, EP1065213A2, WO0063693A1, KR180274, KR2002070125, KR2003062773, KR2003070240, WO2006033409A1, WO9532200A1, WO2006042327A2, WO2004028471A2, WO2004096993A2, WO2004072090A1, WO2006065335A2, WO2005070957A1, U.S. Pat. No. 6,541,515B2, WO2004007512A2, WO2004003138A2, WO2003020222A2, WO2002057287A2, WO0127309A1, WO9962520A1, WO9962513A1, WO9421797A1, WO2006012078A2, U.S. Pat. No. 7,034,167B2, WO2005123087A2, WO2004009020A2, WO200400858A2, WO2003105770A2, WO2004011479A1, WO2006037227A1, WO2003028737A1, WO2002051425A1, WO0210396A1, U.S. Pat. No. 5,597,697A, WO2006071619A1, WO0190121A2, WO2005014806A2, WO2004011624A2, WO2006018725A1, WO2004074270A2, WO2004073599A2, WO2004044228A2, WO2003095441A1, WO2003082848A1, US20050154056A1, WO2004002977A1, WO2004002940A1, WO2005001417A2, WO2004013298A2, WO2005018330A1, WO2005003147A2, WO0204649A2, WO0053784A1, WO0050614A2, WO2002063039A2, WO2006019831A1, WO9933970A1, WO2004065398A2, WO2003062257A1, WO2003051899A1, WO2003051896A1, U.S. Pat. No. 6,906,190B2, WO0116312A2, WO0004141A2, U.S. Pat. No. 6,482,932B1, WO2005000308A2, US20060040927A1, US20060040890A1, U.S. Pat. No. 6,434,489B1, US20060094706A1, WO2006050035A1, WO2006050034A1, WO2005079837A1, WO0158929A1, U.S. Pat. No. 6,472,373B1, U.S. Pat. No. 6,967,075B2, US20040142322A1, DE102004063132A1, WO2003031645A1, WO0220497A1, WO0177371A1, WO2002100851A2, WO0160315A2, EP1321463A1, WO2002100846A1, WO2003100014A2, WO2003085084A2, WO2003059356A2, WO9929843A1, WO0014252A1, WO0056877A1, WO0189560A1, WO9802530A1, WO2002072776A2, U.S. Pat. No. 6,689,559B2, WO9830238A1, WO9610400A1, U.S. Pat. No. 5,882,852A, JP2002125683A, WO2003015798A1, WO0214362A2, WO0177091A2, EP1619246A1, WO2002095002A2, WO2003006477A1, WO2005037860A2, WO2006050250A2, WO2006039488A2, WO2005077969A2, WO2005043118A2, WO2005042570A1, WO2005042020A2, WO2005007681A2, WO2003035060A1,

WO2003006490A1, WO0174768A2, WO0107027A2, WO0024725A1, WO2003087092A2, WO2005028502A1, U.S. Pat. No. 5,837,464A, WO2004089983A2, US20060147997A1, U.S. Pat. No. 5,496,546A, U.S. Pat. No. 6,127,116A, WO2005044986A2, U.S. Pat. No. 6,218,142B1, WO2006065590A2, US20050277613A1, WO2004076621A2. An assay for HCV polymerase inhibitors is described in Harper et al., *J Med Chem*, 48:1314-1317 (2005).

[0372] In one embodiment, the preferred HCV polymerase inhibitor is selected from the following class of compounds: 2'-methyl-adenosine (e.g., Formula XL, disclosed in Migliaccio et al., *J Biol Chem*, 278:49164-49170 (2003) and WO 2002/057425 (e.g., page 21, line 5), which are incorporated herein by reference), benzothiadiazine (e.g., Formula XLI, disclosed in Dhanak et al., *J Biol Chem*, 277:38322-38327 (2002) and WO 2001/085172 (e.g., page 4, lines 6-24), which are incorporated herein by reference), and indole-N-acetamide (e.g., Formula XLII, disclosed in Harper et al., *J Med Chem*, 48:1314-1317 (2005) and WO 2003/010140 (e.g., page 2, line 25 to page 13, line 11), which are incorporated herein by reference).



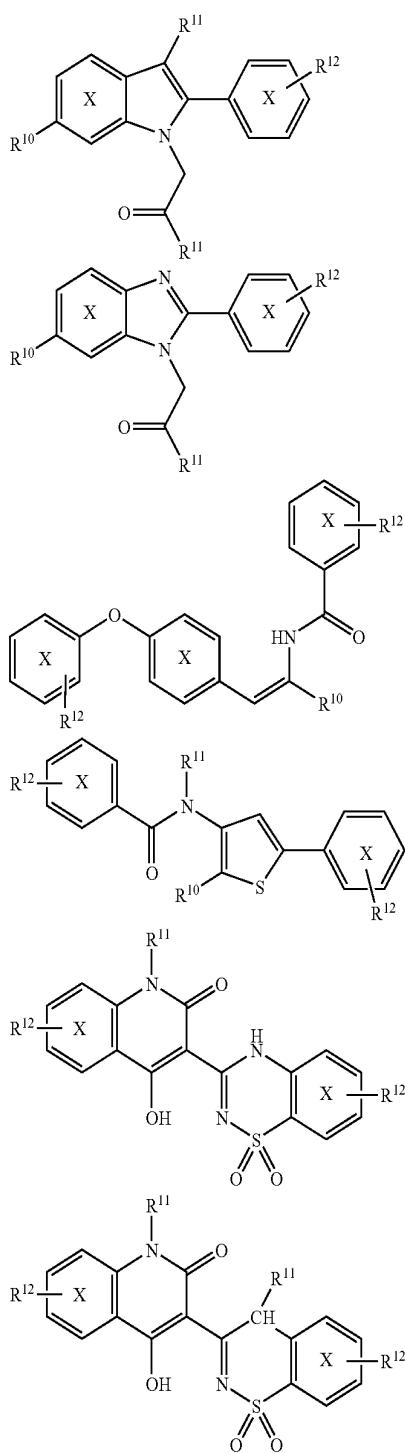
and Y are as defined in WO 02/057425, incorporated herein by reference; a benzothiadiazine compound of Formula XLIIa, wherein the groups A, B, X and Y are as defined in WO 01/85172, incorporated herein by reference; an indole of Formula XLIIa, wherein the groups R<sup>1</sup>, R<sup>2</sup>, Ar<sup>1</sup>, A<sup>1</sup>, X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, X<sup>4</sup> are as defined in WO 04/087714, incorporated herein by reference; a compound of Formula XLIIa, from Boehringer Ingelheim, Japan Tobacco and GeneLabs Technologies, Inc. (e.g., disclosed in Bealieu et al., "Discovery and characterization of novel indole-based non-nucleoside allosteric inhibitors of HCV NS5b polymerase," ACS, Seattle 2006, Roberts et al., "Potent allosteric inhibitors of the HCV NS5b RNA dependent RNA polymerase," 12th Symposium on Hepatitis C and Related Viruses, Montreal, Canada, Oct. 2-6, 2005, wherein the groups A, B, R<sup>2</sup>, L, K, M, Y<sup>1</sup> and Z are as defined in WO 2003/010140, incorporated herein by reference; a compound of Formula XLIIa from Pfizer, Inc., New York, N.Y., wherein the groups R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, Q, Y, A, X, and Z are as defined in WO 2004/002977, incorporated herein by reference;



[0373] Certain non-limiting specific examples of HCV polymerase inhibitors useful in the practice of the present invention are contemplated and include: an analog of Formula XLIII wherein the groups B, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>12</sup>, R<sup>13</sup>,

[0374] Additionally, HCV polymerase inhibitors useful in this invention include compounds represented by the following formulae, where rings marked with an X inside are

either aryl or heteroaryl ring, and R<sup>10</sup> can be a —CO<sub>2</sub>H, C(O)NH<sub>2</sub>, C(O)NHalkyl, —C(O)NHSO<sub>2</sub>alkyl, triazole, tetrazole; R<sup>11</sup> can be a alkyl, —(CH<sub>2</sub>)<sub>3</sub>-cyclopropyl, cycloalkyl or heterocycloalkyl ring; R<sup>12</sup> can be one or more substituents which can be the same or different, each being selected from the group consisting of OH, halogen, alkoxy, CN, aryloxy, aryl, heteroaryl, heterocyclyl, alkyl, and alkyl (substituted with aryl, heteroaryl, halogen, alkoxy and/or CN):

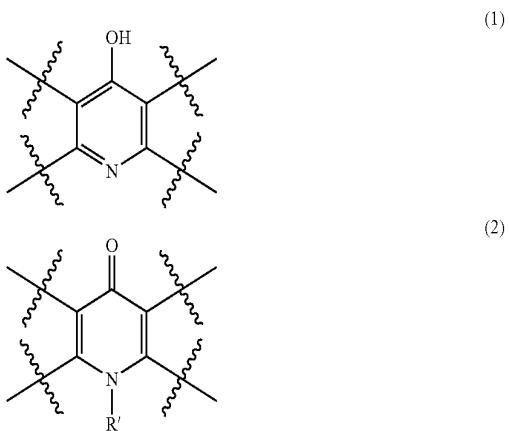


#### Medicaments, Compositions, and Methods

[0375] Isomers of the various compounds used in the medicaments, compositions, and methods of 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.

[0376] 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 <sup>13</sup>C- or <sup>14</sup>C-enriched carbon are also within the scope of this invention.

[0377] It will be apparent to one skilled in the art that certain compounds used in 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:



wherein R' is H or C<sub>1-6</sub> unsubstituted alkyl.

[0378] Prodrugs and solvates 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.

[0379] 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, alkoxy carbonyloxy methyl 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)aminoethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N- $(C_1-C_2)alkyl$ amino( $C_2-C_3)alkyl$  (such as  $\beta$ -dimethylaminoethyl), carbamoyl- $(C_1-C_2)alkyl$ , N,N-di( $C_1-C_2)alkyl$ carbamoyl- $(C_1-C_2)alkyl$  and piperidino-, pyrrolidino- or morpholino( $C_2-C_3)alkyl$ , and the like.

[0380] 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-(( $C_1-C_6)alkanoyloxy)ethyl$ , ( $C_1-C_6)alkoxycarbonyloxy methyl$ , N- $(C_1-C_6)alkoxycarbonyl$ aminomethyl, succinoyl,  $(C_1-C_6)alkanoyl$ ,  $\alpha$ -amino( $C_1-C_4)alkanyl$ , arylacyl and  $\alpha$ -aminoacyl, or  $\alpha$ -aminoacyl- $\alpha$ -aminoacyl, where each  $\alpha$ -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.

[0381] 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  $\alpha$ -aminoacyl or natural  $\alpha$ -aminoacyl,  $-C(OH)C(O)QY^1$  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- $(C_1-C_6)alkyl$ aminoalkyl,  $-C(Y^4)Y^5$  wherein  $Y^4$  is H or methyl and  $Y^5$  is mono-N- or di-N,N- $(C_1-C_6)alkyl$ amino morpholino, piperidin-1-yl or pyrrolidin-1-yl, and the like.

[0382] "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 ethano-

lates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is  $H_2O$ . Preparation of solvates is generally known. Thus, for example, Caira et al., *J Pharm 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 van Tonder et al., *AAPS PharmSciTech*, 5(1):E12 (2004); and A. L. Birmingham 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 a mixture 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).

[0383] "Effective amount" or "therapeutically effective amount" is meant to describe an amount effective against HCV to produce the desired therapeutic or ameliorative effect in a suitable human subject.

[0384] "Symptoms of HCV, or disorders associated with HCV" are described below. Symptoms of acute hepatitis C infection include decreased appetite, fatigue, abdominal pain, jaundice, itching, and flu-like symptoms. Chronic hepatitis C is defined as infection with the hepatitis C virus persisting for more than six months. The course of chronic hepatitis C varies considerably from one person to another. Virtually all people infected with HCV have evidence of inflammation on liver biopsy, however, the rate of progression of liver scarring (fibrosis) shows significant inter-individual variability. Symptoms specifically suggestive of liver disease are typically absent until substantial scarring of the liver has occurred. However, hepatitis C is a systemic disease and patients may experience a wide spectrum of clinical manifestations ranging from an absence of symptoms to debilitating illness prior to the development of advanced liver disease. Generalized signs and symptoms associated with chronic hepatitis C include fatigue, flu-like symptoms, muscle pain, joint pain, intermittent low-grade fevers, itching, sleep disturbances, abdominal pain (especially in the right upper quadrant), appetite changes, nausea, dyspepsia, cognitive changes, depression, headaches, and mood swings.

[0385] Once chronic hepatitis C has progressed to cirrhosis, signs and symptoms may appear that are generally caused by either decreased liver function or increased pressure in the liver circulation, a condition known as portal hypertension. Possible signs and symptoms of liver cirrhosis include ascites (accumulation of fluid in the abdomen), bruising and bleeding tendency, bone pain, varices (enlarged veins, especially in the stomach and esophagus), fatty stools (steatorrhea), jaundice, and a syndrome of cognitive impairment known as hepatic encephalopathy.

[0386] Some persons with chronic hepatitis C are diagnosed because of medical phenomena associated with the presence of HCV such as thyroiditis (inflammation of the thyroid), porphyria cutanea tarda, cryoglobulinemia (a form of vasculitis) and glomerulonephritis (inflammation of the kidney), specifically membranoproliferative glomerulonephritis (MPGN) [http://en.wikipedia.org/wiki/Hepatitis\\_C#note-johnson](http://en.wikipedia.org/wiki/Hepatitis_C#note-johnson). Hepatitis C is also associated with sicca syndrome, lichen planus, diabetes mellitus and with B-cell lymphoproliferative disorders.

[0387] The diagnosis of hepatitis C is rarely made during the acute phase of the disease because the majority of people infected experience no symptoms during this phase of the disease. Those who do experience acute phase symptoms are rarely ill enough to seek medical attention. The diagnosis of chronic phase hepatitis C is also challenging due to the absence or lack of specificity of symptoms until advanced liver disease develops, which may not occur until decades into the disease.

[0388] Chronic hepatitis C may be suspected on the basis of the medical history, unexplained symptoms, or abnormal liver enzymes or liver function tests found during routine blood testing. Occasionally, hepatitis C is diagnosed as a result of targeted screening such as blood donation (blood donors are screened for numerous blood-borne diseases including hepatitis C) or contact tracing.

[0389] Hepatitis C testing begins with serological blood tests used to detect antibodies to HCV. Anti-HCV antibodies can be detected in 80% of patients within 15 weeks after exposure, in >90% within 5 months after exposure, and in >97% by 6 months after exposure. Overall, HCV antibody tests have a strong positive predictive value for exposure to the hepatitis C virus, but may miss patients who have not yet developed antibodies (seroconversion), or have an insufficient level of antibodies to detect. While uncommon, it is important to note that a small minority of people infected with HCV never develop antibodies to the virus and therefore, never test positive using HCV antibody screening.

[0390] Anti-HCV antibodies indicate exposure to the virus, but cannot determine if ongoing infection is present. All persons with positive anti-HCV antibody tests must undergo additional testing for the presence of the hepatitis C virus itself to determine whether current infection is present. The presence of the virus is tested for using molecular nucleic acid testing methods such as polymerase chain reaction (PCR), transcription mediated amplification (TMA), or branched DNA (b-DNA). All HCV nucleic acid molecular tests have the capacity to detect not only whether the virus is present, but also to measure the amount of virus present in the blood (the HCV viral load). The HCV viral load is an important factor in determining the probability of response to interferon-base therapy, but does not indicate disease severity nor the likelihood of disease progression.

[0391] In people with confirmed HCV infection, genotype testing is generally recommended. There are six major genotypes of the hepatitis C virus, which are indicated numerically (e.g., genotype 1, genotype 2, etc.). HCV genotype testing is used to determine the required length and potential response to interferon-based therapy.

[0392] Reference to a compound 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.

[0393] 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.

[0394] 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, hydramines (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 quaternized 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.

[0395] 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.

[0396] 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, phenoxyethyl), aryl (for example, phenyl optionally substituted with, for example, halogen, C<sub>1-4</sub>alkyl, or C<sub>1-4</sub>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<sub>1-20</sub> alcohol or reactive derivative thereof, or by a 2,3-di(C<sub>6-24</sub>)acyl glycerol.

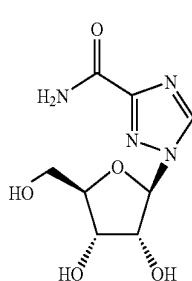
[0397] In such esters, unless otherwise specified, any alkyl moiety present preferably contains from 1 to 18 carbon atoms, particularly from 1 to 6 carbon atoms, more particularly from 1 to 4 carbon atoms. Any cycloalkyl moiety present in such esters preferably contains from 3 to 6 carbon atoms. Any aryl moiety present in such esters preferably comprises a phenyl group.

[0398] 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 and related disorders.

[0399] Another embodiment of the invention provides the use of the pharmaceutical compositions disclosed above for treatment of diseases such as, for example, HCV, inhibiting cathepsin activity and the like. 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.

[0400] In yet another embodiment, the compositions of the invention may be used for the treatment of HCV in humans in combination with at least one other therapeutic agent (e.g., antiviral and/or immunomodulatory agents). Examples of other therapeutic agents include Ribavirin (formula L, from Schering-Plough Corporation, Madison, N.J.) and Levovirin™ (from ICN Pharmaceuticals, Costa Mesa, Calif.), VP 50406™ (from Viropharma, Incorporated, Exton, Pa.), ISIS 14803™ (from ISIS Pharmaceuticals, Carlsbad, Calif.), Heptazyme™ (from Ribozyme Pharmaceuticals, Boulder, Colo.), VX 497™ (from Vertex Pharmaceuticals, Cambridge, Mass.), Thymosin™ (from SciClone Pharmaceuticals, San Mateo, Calif.), Maxamine™ (Maxim Pharmaceuticals, San Diego, Calif.), mycophenolate mofetil (from Hoffman-LaRoche, Nutley, N.J.), interferon (such as, for example, interferon-alpha, PEG-interferon alpha conjugates), antibodies specific to IL-10 (such as those disclosed in US2005/0101770, paragraphs [0086] to [0104] incorporated herein by reference, e.g., humanized 12G8, a humanized monoclonal antibody against human IL-10, plasmids containing the nucleic acids encoding the humanized 12G8 light and heavy chains were deposited with the American Type Culture Collection (ATCC) as deposit numbers PTA-5923 and PTA-5922, respectively), 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, N.J.) 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), interferon alpha fusion polypeptides, or consensus interferon as defined by determination of a consensus sequence of naturally occurring interferon alphas (Infergen™, from Amgen, Thousand Oaks, Calif.).



Formula L

[0401] The medicament comprising at least one HCV protease inhibitor and at least one HCV polymerase inhibitor can be administered in combination with interferon alpha, PEG-interferon alpha conjugates, interferon alpha fusion polypeptides, 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)/0.5 mL/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 interferon 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 180 mcg/1 mL or 180 mcg/0.5 mL 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 9 mcg/TIW is for 24 weeks for first time treatment and up to 15 mcg/TIW for 24 weeks for non-responsive or relapse treatment. Optionally, Ribavirin, a synthetic nucleoside analogue with activity against a broad spectrum of viruses including HCV, can be included in combination with the interferon and at least one 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).

[0402] The compositions and combinations of the present invention can be useful for treating human subjects of any hepatitis C virus (HCV) genotype. HCV types and subtypes may differ in their antigenicity, level of viremia, severity of disease produced, and response to interferon therapy. (Holland 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(2):192-195 (1998)). The nomenclature of Simmonds 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(Pt11):2391-2399 (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 et al., "Classification of hepatitis C variants in six major types based on analysis of the envelope 1 and nonstructural 5B genome regions and complete polyprotein sequences," *J Gen Virol*, 78(Pt1):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 et al., "Identification of genotypes of hepatitis C by sequence comparisons in the core, E1 and NS-5 regions," *J Gen Virol*, 75(Pt 5):1053-1061 (1994)).

[0403] In another embodiment, the medicaments and pharmaceutical compositions can be used to treat cellular proliferation diseases. Such cellular proliferation disease states which can be treated by the compounds, compositions and methods provided herein include, but are not limited to, cancer (further discussed below), hyperplasia, cardiac hypertrophy, autoimmune diseases, fungal disorders, arthritis, graft rejection, inflammatory bowel disease, immune disorders, inflammation, cellular proliferation induced after medical procedures, including, but not limited to, surgery, angioplasty, and the like. Treatment includes inhibiting cellular proliferation. It is appreciated that in some cases the cells may not be in a hyper- or hypoproliferation state (abnormal state) and still require treatment. For example, during wound healing, the cells may be proliferating "normally", but proliferation enhancement may be desired. Thus, in one embodiment, the invention herein includes application to cells or human subjects afflicted or subject to impending affliction with any one of these disorders or states.

[0404] The methods provided herein are particularly useful for the treatment of cancer including solid tumors such as skin, breast, brain, colon, gall bladder, thyroid, cervical carcinomas, testicular carcinomas, etc. More particularly, cancers that may be treated by the compounds, compositions and methods of the invention include, but are not limited to:

[0405] Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma;

[0406] Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma;

[0407] Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma);

[0408] Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor (nephroblastoma), lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma);

[0409] Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma;

[0410] Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors;

[0411] Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma);

[0412] Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma));

[0413] Hematologic: blood (myeloid leukemia (acute and chronic), acute lymphoblastic leukemia, acute and chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma (malignant lymphoma), B-cell lymphoma, T-cell lymphoma, hairy cell lymphoma, Burkett's lymphoma, promyelocytic leukemia;

[0414] Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis;

[0415] Adrenal glands: neuroblastoma; and

[0416] Other tumors: including xenoderoma pigmentosum, keratoanthoma and thyroid follicular cancer.

[0417] As used herein, treatment of cancer includes treatment of cancerous cells, including cells afflicted by any one of the above-identified conditions.

[0418] The medicaments and pharmaceutical compositions of the present invention may also be useful in the chemoprevention of cancer. Chemoprevention is defined as inhibiting the development of invasive cancer by either blocking the initiating mutagenic event or by blocking the progression of pre-malignant cells that have already suffered an insult or inhibiting tumor relapse.

[0419] The medicaments and pharmaceutical compositions of the present invention may also be useful in inhibiting tumor angiogenesis and metastasis.

[0420] The medicaments and pharmaceutical compositions of the present invention may also be useful as anti-fungal agents, by modulating the activity of the fungal members of the bimC kinesin subgroup, as is described in U.S. Pat. No. 6,284,480.

[0421] The present compounds are also useful in combination with one or more other known therapeutic agents and anti-cancer agents. Combinations of the present compounds with other anti-cancer or chemotherapeutic agents are within the scope of the invention. Examples of such agents can be found in *Cancer Principles and Practice of Oncology* by V. T. Devita and S. Hellman (editors), 6<sup>th</sup> edition (Feb. 15, 2001), Lippincott Williams & Wilkins Publishers. A person of ordinary skill in the art would be able to discern which combinations of agents would be useful based on the particular characteristics of the drugs and the cancer involved. Such anti-cancer agents include, but are not limited to, the following: estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic/cytostatic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors and other angiogenesis inhibitors, inhibitors of cell proliferation and survival signaling, apoptosis inducing agents and agents that interfere with cell cycle checkpoints. The present compounds are also useful when co-administered with radiation therapy.

[0422] The phrase "estrogen receptor modulators" refers to compounds that interfere with or inhibit the binding of estrogen to the receptor, regardless of mechanism. Examples of estrogen receptor modulators include, but are not limited to, tamoxifen, raloxifene, idoxifene, LY353381, LY117081, toremifene, fulvestrant, 4-[7-(2,2-dimethyl-1-oxopropoxy-4-methyl-2-[4-[2-(1-piperidinyl)ethoxy]phenyl]-2H-1-benzopyran-3-yl]-phenyl-2,2-dimethylpropanoate, 4,4'-dihydroxybenzophenone-2,4-dinitrophenyl-ydrazone, and SH646.

[0423] The phrase "androgen receptor modulators" refers to compounds which interfere or inhibit the binding of androgens to the receptor, regardless of mechanism. Examples of androgen receptor modulators include finasteride and other 5 $\alpha$ -reductase inhibitors, nilutamide, flutamide, bicalutamide, liarozole, and abiraterone acetate.

[0424] The phrase "retinoid receptor modulators" refers to compounds which interfere or inhibit the binding of retinoids to the receptor, regardless of mechanism. Examples of such retinoid receptor modulators include bexarotene, tretinoin, 13-cis-retinoic acid, 9-cis-retinoic acid, a difluoromethylornithine, ILX23-7553, trans-N-(4'-hydroxyphenyl)retinamide, and N-4-carboxyphenyl retinamide.

[0425] The phrase "cytotoxic/cytostatic agents" refer to compounds which cause cell death or inhibit cell prolifera-

tion primarily by interfering directly with the cell's functioning or inhibit or interfere with cell mycosis, including alkylating agents, tumor necrosis factors, intercalators, hypoxia activatable compounds, microtubule inhibitors/microtubule-stabilizing agents, inhibitors of mitotic kinesins, inhibitors of kinases involved in mitotic progression, antimetabolites; biological response modifiers; hormonal/anti-hormonal therapeutic agents, haematopoietic growth factors, monoclonal antibody targeted therapeutic agents, monoclonal antibody therapeutics, topoisomerase inhibitors, proteasome inhibitors and ubiquitin ligase inhibitors.

[0426] Examples of cytotoxic agents include, but are not limited to, sertenef, cachectin, ifosfamide, tasonermin, lonidamine, carboplatin, altretamine, prednimustine, dibromodulcitol, ranimustine, fotemustine, nedaplatin, oxaliplatin, temozolomide (TEMODART<sup>TM</sup> from Schering-Plough Corporation, Kenilworth, N.J.), cyclophosphamide, heptaplatin, estramustine, improsulfan tosilate, trofosfamide, nimustine, dibrosplidium chloride, pumitepa, lobaplatin, satraplatin, profiromycin, cisplatin, doxorubicin, irofulven, dexifosfamide, cis-aminodichloro(2-methyl-pyridine)platinum, benzylguanine, glufosfamide, GPX100, (trans,trans,trans)-bis-mu-(hexane-1,6-diamine)-mu-[diamine-platinum(II)]bis[diamine(chloro)platinum(II)]tetrachloride, diarizidinylspermine, arsenic trioxide, 1-(11-dodecylamino-10-hydroxyundecyl)-3,7-dimethylxanthine, zorubicin, idarubicin, daunorubicin, bisantrene, mitoxantrone, pirarubicin, pinafide, valrubicin, amrubicin, antineoplaston, 3'-deansino-3'-morpholino-13-deoxo-10-hydroxycaminoxyein, annamycin, galarubicin, elinafide, MEN10755, 4-demethoxy-3-deamino-3-aziridinyl-4-methylsulphonyl-daunomycin (see WO 00/50032), methotrexate, gemcitabine, and mixture thereof.

[0427] An example of a hypoxia activatable compound is tirapazamine.

[0428] Examples of proteasome inhibitors include, but are not limited to, lactacystin and bortezomib.

[0429] Examples of microtubule inhibitors/microtubule-stabilising agents include paclitaxel, vindesine sulfate, 3',4'-didehydro-4'-deoxy-8'-norvincaleukoblastine, docetaxel, rhizoxin, dolastatin, mivobulin isethionate, auristatin, cemadotin, RPR109881, BMS184476, vinflunine, cryptophycin, 2,3,4,5,6-pentafluoro-N-(3-fluoro-4-methoxyphenyl)benzene sulfonamide, anhydrovinblastine, N,N-dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-prolyl-L-proline-t-butylamide, TDX258, the epothilones (see for example U.S. Pat. Nos. 6,284,781 and 6,288,237) and BMS188797.

[0430] Some examples of topoisomerase inhibitors are topotecan, hycaptamine, irinotecan, rubitecan, 6-ethoxypropionyl-3',4'-O-exo-benzylidene-charteusin, 9-methoxy-N, N-dimethyl-5-nitropyrazolo[3,4,5-k]acridine-2-(6H) propanamine, 1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo[de]pyrano[3',4':b,7]-indolizino[1,2b]quinoline-10,13(9H,15H)dione, lurtocean, 7-[2-(N-isopropylamino)ethyl]-20S-camptothecin, BNP1350, BNPI1100, BN80915, BN80942, etoposide phosphate, teniposide, sobuzoxane, 2'-dimethylamino-2'-deoxy-etoposide, GL331, N-[2-(dimethylamino)ethyl]-9-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide, asulacrine, (5a,5aB,8aa,9b)-9-[2-[N-[2-(dimethylamino)ethyl]-N-methylamino]ethyl]-5-[4-hydroxy-3,5-dimethoxyphenyl]-5,5a,6,8,8a,9-

hexohydrofuro-(3',4':6,7)naphtho(2,3-d)-1,3-dioxol-6-one, 2,3-(methylenedioxy)-5-methyl-7-hydroxy-8-methoxybenzo[c]phenanthridinium, 6,9-bis[(2-aminoethyl)amino]benzo[g]isoquinoline-5,10-dione, 5-(3-aminopropylamino)-7,10-dihydroxy-2-(2-hydroxyethylaminomethyl)-6H-pyrazolo[4,5,1-de]acridin-6-one, N-[1-[2-(diethylamino)ethylamino]-7-methoxy-9-oxo-9H-thioxanthen-4-ylmethyl]formamide, N-(2-(dimethylamino)ethyl)acridine-4-carboxamide, 6-[2-(dimethylamino)ethyl]amino]-3-hydroxy-7H-indeno[2,1-c]quinolin-7-one, dimesna, and camptostar.

[0431] Other useful anti-cancer agents that can be used in combination with the present compounds include thymidilate synthase inhibitors, such as 5-fluorouracil.

[0432] In one embodiment, inhibitors of mitotic kinesins include, but are not limited to, inhibitors of KSP, inhibitors of MKLP1, inhibitors of CENP-E, inhibitors of MCAK, inhibitors of Kif14, inhibitors of Mphosph1 and inhibitors of Rab6-KIFL.

[0433] The phrase "inhibitors of kinases involved in mitotic progression" include, but are not limited to, inhibitors of aurora kinase, inhibitors of Polo-like kinases (PLK) (in particular inhibitors of PLK-1), inhibitors of bub-1 and inhibitors of bub-R1.

[0434] The phrase "antiproliferative agents" includes antisense RNA and DNA oligonucleotides such as G3139, ODN698, RVASKRAS, GEM231, and INX3001, and antimetabolites such as enocitabine, carmofur, tegafur, pentostatin, doxifluridine, trimetrexate, fludarabine, capecitabine, galocitabine, cytarabine ocfosfate, fosteabine sodium hydrate, raltitrexed, paltitrexid, emitefur, tiazofurin, decitabine, nolatrexed, pemetrexed, nelzarabine, 2'-deoxy-2'-methylidenecytidine, 2'-fluoromethylene-2'-deoxycytidine, N-[5-(2,3-dihydro-benzofuryl)sulfonyl]-N'-(3,4-dichlorophenyl)urea, N6-[4-deoxy-4-[N2-[2(E),4(E)-tetradecadienoyl]glycylamino]-L-glycero-B-L-manno-heptopyranosyl]adenine, aplidine, ecteinascidin, troxacitabine, 4-[2-amino-4-oxo-4,6,7,8-tetrahydro-3H-pyrimidino[5,4-b][1,4]thiazin-6-yl-(S)-ethyl]-2,5-thienoyl-L-glutamic acid, aminopterin, 5-fluorouracil, alanosine, 11-acetyl-8-(carbamoyloxymethyl)-4-formyl-6-methoxy-14-oxa-1,11-diazatetracyclo(7.4.1.0.0)-tetradeca-2,4,6-trien-9-yl acetic acid ester, swainsonine, lometrexol, dextrazoxane, methioninase, 2'-cyano-2'-deoxy-N4-palmitoyl-1-B-D-arabino furanosyl cytosine and 3-aminopyridine-2-carboxaldehyde thiosemicarbazone.

[0435] Examples of monoclonal antibody targeted therapeutic agents include those therapeutic agents which have cytotoxic agents or radioisotopes attached to a cancer cell specific or target cell specific monoclonal antibody. Examples include Bexxar.

[0436] Examples of monoclonal antibody therapeutics useful for treating cancer include Erbitux (Cetuximab).

[0437] The phrase "HMG-CoA reductase inhibitors" refers to inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase. Examples of HMG-CoA reductase inhibitors that may be used include but are not limited to lovastatin, simvastatin (ZOCOR®), pravastatin (PRAVACHOL®), fluvastatin and atorvastatin (LIPITOR®; see U.S. Pat. Nos. 5,273,995, 4,681,893, 5,489,691 and 5,342,952). The structural formulas of these and additional HMG-CoA reductase

inhibitors that may be used in the instant methods are described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs", *Chemistry & Industry*, pp. 85-89 (5 Feb. 1996) and U.S. Pat. Nos. 4,782,084 and 4,885,314. The term HMG-CoA reductase inhibitor as used herein includes all pharmaceutically acceptable lactone and open-acid forms (i.e., where the lactone ring is opened to form the free acid) as well as salt and ester forms of compounds which have HMG-CoA reductase inhibitory activity, and therefore the use of such salts, esters, open acid and lactone forms is included in the scope of this invention.

[0438] The phrase "prenyl-protein transferase inhibitor" refers to a compound which inhibits any one or any combination of the prenyl-protein transferase enzymes, including farnesyl-protein transferase (FPTase), geranylgeranyl-protein transferase type I (GGPTase-I), and geranylgeranyl-protein transferase type-II (GGPTase-II, also called Rab GGPTase).

[0439] Examples of prenyl-protein transferase inhibitors can be found in the following publications and patents: WO 96/30343, WO 97/18813, WO 97/21701, WO 97/23478, WO 97/38665, WO 98/28980, WO 98/29119, WO 95/32987, U.S. Pat. Nos. 5,420,245, 5,523,430, 5,532,359, 5,510,510, 5,589,485, 5,602,098, European Patent Publ. 0 618 221, European Patent Publ. 0 675 112, European Patent Publ. 0 604181, European Patent Publ. 0 696 593, WO 94/19357, WO 95/08542, WO 95/11917, WO 95/12612, WO 95/12572, WO 95/10514, U.S. Pat. No. 5,661,152, WO 95/10515, WO 95/10516, WO 95/24612, WO 95/34535, WO 95/25086, WO 96/05529, WO 96/06138, WO 96/06193, WO 96/16443, WO 96/21701, WO 96/21456, WO 96/22278, WO 96/24611, WO 96/24612, WO 96/05168, WO 96/05169, WO 96/00736, U.S. Pat. No. 5,571,792, WO 96/17861, WO 96/33159, WO 96/34850, WO 96/34851, WO 96/30017, WO 96/30018, WO 96/30362, WO 96/30363, WO 96/31111, WO 96/31477, WO 96/31478, WO 96/31501, WO 97/00252, WO 97/03047, WO 97/03050, WO 97/04785, WO 97/02920, WO 97/17070, WO 97/23478, WO 97/26246, WO 97/30053, WO 97/44350, WO 98/02436, and U.S. Pat. No. 5,532,359. For an example of the role of a prenyl-protein transferase inhibitor on angiogenesis see *European of Cancer*, Vol. 35, No. 9, pp. 1394-1401 (1999).

[0440] Examples of farnesyl protein transferase inhibitors include SARASARTM (4-[2-[4-[(11R)-3,10-dibromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl]-1-piperidinyl]-2-oxoethyl]-1-piperidinecarboxamide from Schering-Plough Corporation, Kenilworth, N.J.), tipifarnib (Zarnestra® or R115777 from Janssen Pharmaceuticals), L778,123 (a farnesyl protein transferase inhibitor from Merck & Company, Whitehouse Station, N.J.), BMS 214662 (a farnesyl protein transferase inhibitor from Bristol-Myers Squibb Pharmaceuticals, Princeton, N.J.).

[0441] The phrase "angiogenesis inhibitors" refers to compounds that inhibit the formation of new blood vessels, regardless of mechanism. Examples of angiogenesis inhibitors include, but are not limited to, tyrosine kinase inhibitors, such as inhibitors of the tyrosine kinase receptors Fit-1 (VEGFR1) and Flk-1/KDR (VEGFR2), inhibitors of epidermal-derived, fibroblast-derived, or platelet derived growth factors, MMP (matrix metalloprotease) inhibitors, integrin blockers, interferon- $\alpha$  (for example Intron and Peg-Intron),

interleukin-12, pentosan polysulfate, cyclooxygenase inhibitors, including nonsteroidal anti-inflammatories (NSAIDs) like aspirin and ibuprofen as well as selective cyclooxygenase-2 inhibitors like celecoxib and rofecoxib (Hla and Neilson, *Proc Natl Acad Sci USA*, 89(16):7384-7388 (1992); Ziche et al., *J Natl Cancer Inst*, 69(2):475-482 (1982); BenEzra et al., *Arch Ophthalmol*, 108(4):573-576 (1990); Diaz-Flores et al., *Anat Rec*, 238(1):68-76 (1994); Ben-Av et al., *FEBS Lett*, 372(1):83-87 (1995); Harada et al., *Clin Orthop Relat Res*, 313:76-80 (1995); Chakraborty et al., *J Mol Endocrinol*, 16(2):107-122 (1996); Majima et al., *Jpn J Pharmacol*, 75(2):105-114 (1997); Seed et al., *Cancer Res*, 57(9):1625-1629 (1997); Tsujii et al., *Cell*, 93(5):705-716 (1998); Chiarugi et al., *Intl J Mol Med*, 2(6):715-719 (1998); Xin et al., *J Biol Chem*, 274(13):9116-9121 (1999)), steroidal anti-inflammatories (such as corticosteroids, mineralocorticoids, dexamethasone, prednisone, prednisolone, methylpred, betamethasone), carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetylcarbonyl-fumagillo, thalidomide, angiostatin, troponin-1, angiotsensin II antagonists (see, Fernandez et al., *J Lab Clin Med*, 105(2):141-145 (1985)), and antibodies to VEGF (see, Brower, *Nature Biotechnol*, 17(10):963-968 (1999); Kim et al., *Nature*, 362(6423):841-844 (1993); WO 00/44777; and WO 00/61186).

[0442] Other therapeutic agents that modulate or inhibit angiogenesis and may also be used in combination with the compounds of the instant invention include agents that modulate or inhibit the coagulation and fibrinolysis systems (see review, Korte, *Clin Chem La Med*, 38(8):679-692 (2000)). Examples of such agents that modulate or inhibit the coagulation and fibrinolysis pathways include, but are not limited to, heparin (see Zacharski and Ornstein, *Thromb Haemost*, 80(1):10-23 (1998)), low molecular weight heparins and carboxypeptidase U inhibitors (also known as inhibitors of active thrombin activatable fibrinolysis inhibitor [TAFIa]) (see, Bouma et al., *Thromb Res*, 101(5):329-354 (2001)). Examples of TAFIa inhibitors have been described in PCT Publication WO 03/013,526.

[0443] The phrase "agents that interfere with cell cycle checkpoints" refers to compounds that inhibit protein kinases that transduce cell cycle checkpoint signals, thereby sensitizing the cancer cell to DNA damaging agents. Such agents include inhibitors of ATR, ATM, the Chk1 and Chk2 kinases and cdk and cdc kinase inhibitors and are specifically exemplified by 7-hydroxystauroporin, flavopiridol, CYC202 (Cyclacel) and BMS-387032.

[0444] The phrase "inhibitors of cell proliferation and survival signaling pathway" refers to agents that inhibit cell surface receptors and signal transduction cascades downstream of those surface receptors. Such agents include inhibitors of EGFR (for example gefitinib and erlotinib), antibodies to EGFR (for example C225), inhibitors of ERB-2 (for example trastuzumab), inhibitors of IGFR, inhibitors of cytokine receptors, inhibitors of MET, inhibitors of PI3K (for example LY294002), serine/threonine kinases (including but not limited to inhibitors of Akt such as described in WO 02/083064, WO 02/083139, WO 02/083140 and WO 02/083138), inhibitors of Raf kinase (for example BAY-43-9006), inhibitors of MEK (for example CI-1040 and PD-098059), inhibitors of mTOR (for example Wyeth CCI-779), and inhibitors of C-abl kinase (for

example GLEEVECTM, Novartis Pharmaceuticals). Such agents include small molecule inhibitor compounds and antibody antagonists.

[0445] The phrase "apoptosis inducing agents" includes activators of TNF receptor family members (including the TRAIL receptors).

[0446] The invention also encompasses combinations with NSAID's which are selective COX-2 inhibitors. For purposes of this specification NSAID's which are selective inhibitors of COX-2 are defined as those which possess a specificity for inhibiting COX-2 over COX-1 of at least 100 fold as measured by the ratio of IC50 for COX-2 over IC50 for COX-1 evaluated by cell or microsomal assays. Inhibitors of COX-2 that are particularly useful in the instant method of treatment are: 3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone; and 5-chloro-3-(4-methylsulfonyl)phenyl-2-(2-methyl-5 pyridinyl)pyridine; or a pharmaceutically acceptable salt thereof.

[0447] Compounds that have been described as specific inhibitors of COX-2 and are therefore useful in the present invention include, but are not limited to, parecoxib, CELEBREX® and BEXTRA® or a pharmaceutically acceptable salt thereof.

[0448] Other examples of angiogenesis inhibitors include, but are not limited to, endostatin, ukrain, ranpirnase, IM862, 5-methoxy-4-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]-1-oxaspiro[2.5]oct-6-yl(chloroacetyl)carbamate, acetyl-dinanaline, 5-amino-1-[[3,5-dichloro-4-(4-chlorobenzoyl)phenyl]methyl]-1H-1,2,3-triazole-4-carboxamide, CM101, squalamine, combretastatin, RPI4610, NX31838, sulfated mannosetaose phosphate, 7,7-(carbonyl-bis [imino-N-methyl-4,2-pyrrolocarbonylimino[N-methyl-4,2-pyrrole]-carbonylimino]-bis-(1,3-naphthalene disulfonate), and 3-[(2,4-dimethylpyrrol-5-yl)methylene]-2-indolinone (SU5416).

[0449] As used above, "integrin blockers" refers to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the  $\alpha_v\beta_3$  integrin, to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the  $\alpha_v\beta_5$  integrin, to compounds which antagonize, inhibit or counteract binding of a physiological ligand to both the  $\alpha_v\beta_3$  integrin and the  $\alpha_v\beta_5$  integrin, and to compounds which antagonize, inhibit or counteract the activity of the particular integrin(s) expressed on capillary endothelial cells. The term also refers to antagonists of the  $\alpha_v\beta_6$ ,  $\alpha_v\beta_8$ ,  $\alpha_1\beta_1$ ,  $\alpha_2\beta_1$ ,  $\alpha_5\beta_1$ ,  $\alpha_6\beta_1$  and  $\alpha_6\beta_4$  integrins. The term also refers to antagonists of any combination of  $\alpha_v\beta_3$ ,  $\alpha_v\beta_5$ ,  $\alpha_v\beta_6$ ,  $\alpha_v\beta_8$ ,  $\alpha_1\beta_1$ ,  $\alpha_2\beta_1$ ,  $\alpha_5\beta_1$ ,  $\alpha_6\beta_1$  and  $\alpha_6\beta_4$  integrins.

[0450] Some examples of tyrosine kinase inhibitors include N-(trifluoromethylphenyl)-5-methylisoxazol-4-carboxamide, 3-[(2,4-dimethylpyrrol-5-yl)methylidenyl]indolin-2-one, 17-(allylamino)-17-demethoxygeldanamycin, 4-(3-chloro-4-fluorophenylamino)-7-methoxy-6-[3-(4-morpholinyl)propoxyl]quinazoline, N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, BIBX1382, 2,3,9,10,11,12-hexahydro-10-(hydroxymethyl)-10-hydroxy-9-methyl-9,12-epoxy-1H-diindolo[1,2,3-fg:3',2',1-k]pyrrolo[3,4-i][1,6]benzodiazocin-1-one, SH268, genistein, STI571, CEP2563, 4-(3-chlorophenylamino)-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidinemethane sulfonate, 4-(3-bromo-4-hy-

droxyphenyl)amino-6,7-dimethoxyquinazoline, 4-(4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, SU6668, ST1571A, N-4-chlorophenyl-4-(4-pyridylmethyl)-1-phthalazinamine, and EMD121974.

[0451] Combinations with compounds other than anti-cancer compounds are also encompassed in the instant methods. For example, combinations of the present compounds with PPAR- $\gamma$  (i.e., PPAR-gamma) agonists and PPAR- $\delta$  (i.e., PPAR-delta) agonists are useful in the treatment of certain malingerances. PPAR- $\gamma$  and PPAR- $\delta$  are the nuclear peroxisome proliferator-activated receptors  $\gamma$  and  $\delta$ . The expression of PPAR- $\gamma$  on endothelial cells and its involvement in angiogenesis has been reported in the literature (see Gralinski et al., *J Cardiovasc Pharmacol*, 31(6):909-913 (1998); Xin et al., *J Biol Chem*, 274(13):9116-9121 (1999); Murata et al., *Invest Ophthalmol Vis Sci*, 41(8):2309-2317 (2000)). More recently, PPAR- $\gamma$  agonists have been shown to inhibit the angiogenic response to VEGF in vitro; both troglitazone and rosiglitazone maleate inhibit the development of retinal neovascularization in mice (Murata et al., *Arch Ophthalmol*, 119(5):709-717 (2001)). Examples of PPAR- $\gamma$  agonists and PPAR- $\gamma/\alpha$  agonists include, but are not limited to, thiazolidinediones (such as DRF2725, CS-011, troglitazone, rosiglitazone, and pioglitazone), fenofibrate, gemfibrozil, clofibrate, GW2570, SB219994, AR-H039242, JTT-501, MCC-555, GW2331, GW409544, NN2344, KRP297, NP0110, DRF4158, NN622, G1262570, PNU182716, DRF552926, 2-[5,7-dipropyl-3-trifluoromethyl-1,2-benzisoxazol-6-yl)oxy]-2-methylpropionic acid, and 2(R)-7-(3-(2-chloro-4-(4-fluorophenoxy)phenoxy)-2-ethylchromane-2-carboxylic acid.

[0452] In one embodiment, useful anti-cancer (also known as anti-neoplastic) agents that can be used in combination with the present compounds include, but are not limited to, Uracil mustard, Chlormethine, Ifosfamide, Melphalan, Chlorambucil, Pipobroman, Triethylenemelamine, Triethylenethiophosphoramide, Busulfan, Carmustine, Lomustine, Streptozocin, Dacarbazine, Flouxuridine, Cytarabine, 6-Mercaptopurine, 6-Thioguanine, Fludarabine phosphate, oxaliplatin, leucovirin, oxaliplatin (ELOXATIN™ from Sanofi-Synthelabo Pharmaceuticals, France), Pentostatine, Vinblastine, Vincristine, Vindesine, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Mithramycin, Deoxycoformycin, Mitomycin-C, L-Asparaginase, Teniposide 17 $\alpha$ -Ethinylestradiol, Diethylstilbestrol, Testosterone, Prednisone, Fluoxymesterone, Dromostanolone propionate, Testolactone, Megestrolacetate, Methyldprednisolone, Methyltestosterone, Prednisolone, Triamcinolone, Chlorotrianisene, Hydroxyprogesterone, Aminoglutethimide, Estramustine, Medroxyprogesterone acetate, Leuprolide, Flutamide, Toremifene, goserelin, Cisplatin, Carboplatin, Hydroxyurea, Amsacrine, Procarbazine, Mitotane, Mitoxantrone, Levamisole, Navelbene, Anastrozole, Letrazole, Capecitabine, Reloxafine, Droloxafine, Hexamethylmelamine, doxorubicin (adriamycin), cyclophosphamide (cytoxan), gemcitabine, interferons, pegylated interferons, Erbitux and mixtures of two or more thereof.

[0453] Another embodiment of the present invention is the use of the present compounds in combination with gene therapy for the treatment of cancer. For an overview of genetic strategies to treating cancer (see, Hall et al., *Am J Hum Genet*, 61(4):785-789 (1997) and Kufe et al., *Cancer*

*Medicine*, 5th Ed, pp 876-889, B C Decker, Hamilton (2000)). Gene therapy can be used to deliver any tumor suppressing gene. Examples of such genes include, but are not limited to, p53, which can be delivered via recombinant virus-mediated gene transfer (see U.S. Pat. No. 6,069,134, for example), a uPA/uPAR antagonist (Li et al., "Adenovirus-mediated delivery of a uPA/uPAR antagonist suppresses angiogenesis-dependent tumor growth and dissemination in mice," *Gene Ther*, 5(8):1105-1113 (1998), and interferon gamma (Fathallah-Shaykh et al., *J Immunol*, 164(1):217-222 (2000)).

[0454] The present compounds can also be administered in combination with one or more inhibitor of inherent multi-drug resistance (MDR), in particular MDR associated with high levels of expression of transporter proteins. Such MDR inhibitors include inhibitors of p-glycoprotein (P-gp), such as LY335979, XR9576, OC144-093, R101922, VX853 and PSC833 (valsopdar).

[0455] The present compounds can also be employed in conjunction with one or more anti-emetic agents to treat nausea or emesis, including acute, delayed, late-phase, and anticipatory emesis, which may result from the use of a compound of the present invention, alone or with radiation therapy. For the prevention or treatment of emesis, a compound of the present invention may be used in conjunction with one or more other anti-emetic agents, especially neurokinin-1 receptor antagonists, 5HT3 receptor, antagonists, such as ondansetron, granisetron, tropisetron, and zatisetron, GABAB receptor agonists, such as baclofen, a corticosteroid such as Decadron (dexamethasone), Kenalog, Aristocort, Nasalide, Preferid, Benecorten or those as described in U.S. Pat. Nos. 2,789,118, 2,990,401, 3,048,581, 3,126,375, 3,929,768, 3,996,359, 3,928,326 and 3,749,712, an anti-dopaminergic, such as the phenothiazines (for example prochlorperazine, fluphenazine, thioridazine and mesoridazine), metoclopramide or dronabinol. In one embodiment, an anti-emesis agent selected from a neurokinin-1 receptor antagonist, a 5HT3 receptor antagonist and a corticosteroid is administered as an adjuvant for the treatment or prevention of emesis that may result upon administration of the present compounds.

[0456] Examples of neurokinin-1 receptor antagonists that can be used in conjunction with the present compounds are described in U.S. Pat. Nos. 5,162,339, 5,232,929, 5,242,930, 5,373,003, 5,387,595, 5,459,270, 5,494,926, 5,496,833, 5,637,699, and 5,719,147, content of which are incorporated herein by reference. In an embodiment, the neurokinin-1 receptor antagonist for use in conjunction with the medicaments and pharmaceutical compositions of the present invention is selected from: 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine, or a pharmaceutically acceptable salt thereof, which is described in U.S. Pat. No. 5,719,147.

[0457] A compound of the present invention may also be administered with one or more immunologic-enhancing drug, such as for example, levamisole, isoprinosine and Zadaxin.

[0458] Thus, the present invention encompasses the use of the present compounds (for example, for treating or preventing cellular proliferative diseases) in combination with a second compound selected from: an estrogen receptor

modulator, an androgen receptor modulator, retinoid receptor modulator, a cytotoxic/cytostatic agent, an antiproliferative agent, a prenyl-protein transferase inhibitor, an HMG-CoA reductase inhibitor, an angiogenesis inhibitor, a PPAR- $\gamma$  agonist, a PPAR- $\delta$  agonist, an inhibitor of inherent multidrug resistance, an anti-emetic agent, an immunologic-enhancing drug, an inhibitor of cell proliferation and survival signaling, an agent that interferes with a cell cycle checkpoint, and an apoptosis inducing agent.

[0459] Methods for the treatment, prevention or amelioration of one or more symptoms of HCV, treating disorders associated with HCV, modulating activity of HCV, or inhibiting cathepsin activity or associated disorders in a human subject, comprising the step of administering to a human subject in need of such treatment an effective amount of the above compositions or therapeutic combinations, also are provided.

[0460] Examples of such cathepsin-associated disorders include proliferative diseases, such as cancer, autoimmune diseases, viral diseases, fungal diseases, neurological/neurodegenerative disorders, arthritis, inflammation, anti-proliferative (e.g., ocular retinopathy), neuronal, alopecia and cardiovascular disease. Many of these diseases and disorders are listed in U.S. Pat. No. 6,413,974, the disclosure of which is incorporated herein.

[0461] Other examples of diseases that can be treated include an inflammatory disease, such as organ transplant rejection, graft v. host disease, arthritis, rheumatoid arthritis, inflammatory bowel disease, atopic dermatitis, psoriasis, asthma, allergies, multiple sclerosis, fixed drug eruptions, cutaneous delayed-type hypersensitivity responses, tuberculous leprosy, type I diabetes, and viral meningitis.

[0462] Other examples of diseases that can be treated include Hepatitis B virus and related diseases, Hepatitis A virus and related diseases, HIV and related diseases (e.g., AIDS), and the like.

[0463] Another example of a disease that can be treated is a cardiovascular disease.

[0464] Other examples of diseases that can be treated include a central nervous system disease, such as depression, cognitive function disease, neurodegenerative disease such as Parkinson's disease, senile dementia such as Alzheimer's disease, and psychosis of organic origin.

[0465] Other examples of diseases that can be treated include diseases characterized by bone loss, such as osteoporosis; gingival diseases, such as gingivitis and periodontitis; and diseases characterized by excessive cartilage or matrix degradation, such as osteoarthritis and rheumatoid arthritis.

[0466] In one embodiment, the present invention encompasses the composition and use of the present compounds in combination with a second compound selected from: a cytostatic agent, a cytotoxic agent, taxanes, a topoisomerase II inhibitor, a topoisomerase I inhibitor, a tubulin interacting agent, hormonal agent, a thymidilate synthase inhibitors, anti-metabolites, an alkylating agent, a farnesyl protein transferase inhibitor, a signal transduction inhibitor, an EGFR kinase inhibitor, an antibody to EGFR, a C-abl kinase inhibitor, hormonal therapy combinations, and aromatase combinations.

[0467] The term "treatment naïve" with respect to a human subject refers to one that has never been treated with ribavirin or any interferon including, but not limited to an interferon-alpha. In contrast, the term "treatment experienced" with respect to a human subject refers to one that has been treated with ribavirin or any interferon including, but not limited to an interferon-alpha.

[0468] The term "treating cancer" or "treatment of cancer" refers to administration to a mammal afflicted with a cancerous condition and refers to an effect that alleviates the cancerous condition by killing the cancerous cells, but also to an effect that results in the inhibition of growth and/or metastasis of the cancer.

[0469] In one embodiment, the angiogenesis inhibitor to be used as the second compound is selected from a tyrosine kinase inhibitor, an inhibitor of epidermal-derived growth factor, an inhibitor of fibroblast-derived growth factor, an inhibitor of platelet derived growth factor, an MW (matrix metalloprotease) inhibitor, an integrin blocker, interferon- $\alpha$ , interleukin-12, pentosan polysulfate, a cyclooxygenase inhibitor, carboxyamidotriazole, combretastatin A-4, squalamine, 6-(O-chloroacetylcarbonyl)-fumagillo, thalidomide, angiostatin, troponin-1, or an antibody to VEGF. In an embodiment, the estrogen receptor modulator is tamoxifen or raloxifene.

[0470] Also included in the present invention is a method of treating cancer comprising administering a therapeutically effective amount of at least one compound of the present invention in combination with radiation therapy and at least one compound selected from: an estrogen receptor modulator, an androgen receptor modulator, retinoid receptor modulator, a cytotoxic/cytostatic agent, an antiproliferative agent, a prenyl-protein transferase inhibitor, an HMG-CoA reductase inhibitor, an angiogenesis inhibitor, a PPAR- $\gamma$  agonist, a PPAR- $\delta$  agonist, an inhibitor of inherent multidrug resistance, an anti-emetic agent, an immunologic-enhancing drug, an inhibitor of cell proliferation and survival signaling, an agent that interferes with a cell cycle checkpoint, and an apoptosis inducing agent.

[0471] Yet another embodiment of the invention is a method of treating cancer comprising administering a therapeutically effective amount of at least one compound of the present invention in combination with paclitaxel or trastuzumab.

[0472] The present invention also includes a pharmaceutical composition useful for treating or preventing the various disease states mentioned herein cellular proliferation diseases (such as cancer, hyperplasia, cardiac hypertrophy, autoimmune diseases, fungal disorders, arthritis, graft rejection, inflammatory bowel disease, immune disorders, inflammation, and cellular proliferation induced after medical procedures) that comprises a therapeutically effective amount of at least one compound of the present invention and at least one compound selected from: an estrogen receptor modulator, an androgen receptor modulator, a retinoid receptor modulator, a cytotoxic/cytostatic agent, an antiproliferative agent, a prenyl-protein transferase inhibitor, an HMG-CoA reductase inhibitor, an angiogenesis inhibitor, a PPAR- $\gamma$  agonist, a PPAR- $\delta$  agonist, an inhibitor of cell proliferation and survival signaling, an agent that interferes with a cell cycle checkpoint, and an apoptosis inducing agent.

[0473] When the disease being treated by the cathepsin inhibitor is inflammatory disease, an embodiment of the present invention comprises administering: (a) a therapeutically effective amount of at least one compound of the present cathepsin inhibitors (e.g., a compound according to Formula I-XXVII) or a pharmaceutically acceptable salt, solvate or ester thereof concurrently or sequentially with (b) at least one medicament selected from the group consisting of: disease modifying antirheumatic drugs; nonsteroidal anti-inflammatory drugs; COX-2 selective inhibitors; COX-1 inhibitors; immunosuppressives (non-limiting examples include methotrexate, cyclosporin, FK506); steroids; PDE IV inhibitors; anti-TNF- $\alpha$  compounds; TNF-alpha-convertase inhibitors; cytokine inhibitors; MMP inhibitors; glucocorticoids; chemokine inhibitors; CB2-selective inhibitors; p38 inhibitors; biological response modifiers; anti-inflammatory agents and therapeutics.

[0474] Another embodiment of the present invention is directed to a method of inhibiting or blocking T-cell mediated chemotaxis in a patient in need of such treatment the method comprising administering to the patient a therapeutically effective amount of at least one compound of the present cathepsin inhibitors (e.g., a compound according to Formula I-XXVII) or a pharmaceutically acceptable salt, solvate or ester thereof.

[0475] Another embodiment of this invention is directed to a method of treating inflammatory bowel disease in a patient in need of such treatment comprising administering to the patient a therapeutically effective amount of at least one compound according to the present cathepsin inhibitors or a pharmaceutically acceptable salt, solvate or ester thereof.

[0476] Another embodiment of this invention is directed to a method of treating or preventing graft rejection in a patient in need of such treatment comprising administering to the patient a therapeutically effective amount of at least one compound according to the present cathepsin inhibitors, or a pharmaceutically acceptable salt, solvate or ester thereof.

[0477] Another embodiment of this invention is directed to a method comprising administering to the patient a therapeutically effective amount of: (a) at least one compound according to the present cathepsin inhibitors, or a pharmaceutically acceptable salt, solvate or ester thereof concurrently or sequentially with (b) at least one compound selected from the group consisting of: cyclosporine A, FK-506, FTY720, beta-Interferon, rapamycin, mycophenolate, prednisolone, azathioprine, cyclophosphamide and an antilymphocyte globulin.

[0478] Another embodiment of this invention is directed to a method of treating multiple sclerosis in a patient in need of such treatment the method comprising administering to the patient a therapeutically effective amount of: (a) at least one aldo-keto reductase inhibitor and at least one cathepsin inhibitor compound according to the present invention, or a pharmaceutically acceptable salt, solvate or ester thereof concurrently or sequentially with (b) at least one compound selected from the group consisting of: beta-interferon, glatiramer acetate, glucocorticoids, methotrexate, azathioprine, mitoxantrone, VLA-4 inhibitors and/or CB2-selective inhibitors.

[0479] Another embodiment of this invention is directed to a method of treating multiple sclerosis in a patient in need

of such treatment the method comprising administering to the patient a therapeutically effective amount of the present combination concurrently or sequentially with at least one compound selected from the group consisting of: methotrexate, cyclosporin, leflunimide, sulfasalazine,  $\beta$ -methasone,  $\beta$ -interferon, glatiramer acetate, prednisone, etanercept, and infliximab.

[0480] Another embodiment of this invention is directed to a method of treating rheumatoid arthritis in a patient in need of such treatment the method comprising administering to the patient a therapeutically effective amount of the present combination concurrently or sequentially with at least one compound selected from the group consisting of: COX-2 inhibitors, COX inhibitors, immunosuppressives, steroids, PDE IV inhibitors, anti-TNF- $\alpha$  compounds, MMP inhibitors, glucocorticoids, chemokine inhibitors, CB2-selective inhibitors, caspase (ICE) inhibitors and other classes of compounds indicated for the treatment of rheumatoid arthritis.

[0481] Another embodiment of this invention is directed to a method of treating psoriasis in a patient in need of such treatment the method comprising administering to the patient a therapeutically effective amount of the present combination concurrently or sequentially with at least one compound selected from the group consisting of: immunosuppressives, steroids, and anti-TNF- $\alpha$  compounds.

[0482] Another embodiment of this invention is directed to a method of treating a disease selected from the group consisting of: inflammatory disease, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, graft rejection, psoriasis, fixed drug eruptions, cutaneous delayed-type hypersensitivity responses, tuberculoid leprosy, type I diabetes, viral meningitis and tumors in a patient in need of such treatment, such method comprising administering to the patient an effective amount of the present combination or a pharmaceutically acceptable salt, solvate or ester thereof.

[0483] Another embodiment of this invention is directed to a method of treating a disease selected from the group consisting of inflammatory disease, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, graft rejection, psoriasis, fixed drug eruptions, cutaneous delayed-type hypersensitivity responses, tuberculoid leprosy and cancer in a patient in need of such treatment, such method comprising administering to the patient an effective amount of the present combination or a pharmaceutically acceptable salt, solvate or ester thereof.

[0484] Another embodiment of this invention is directed to a method of treating a disease selected from the group consisting of inflammatory disease, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, graft rejection, psoriasis, fixed drug eruptions, cutaneous delayed-type hypersensitivity responses and tuberculoid leprosy, type I diabetes, viral meningitis and cancer in a patient in need of such treatment, such method comprising administering to the patient an effective amount of the present combination or a pharmaceutically acceptable salt, solvate or ester thereof concurrently or sequentially with at least one medicament selected from the group consisting of: disease modifying antirheumatic drugs; nonsteroidal anti-inflammatory drugs; COX-2 selective inhibitors; COX-1 inhibitors; immunosuppressives; steroids; PDE IV inhibitors, anti-TNF- $\alpha$  compounds, MMP inhibitors, glucocorticoids, chemokine inhibi-

tors, CB2-selective inhibitors, biological response modifiers; anti-inflammatory agents and therapeutics.

[0485] When the present invention involves a method of treating a cardiovascular disease, in addition to administering the amount of the present combination or a pharmaceutically acceptable salt, solvate or ester thereof, the method further comprises administering to the human subject in need one or more pharmacological or therapeutic agents or drugs such as cholesterol biosynthesis inhibitors and/or lipid-lowering agents discussed below.

[0486] Non-limiting examples of cholesterol biosynthesis inhibitors for use in the compositions, therapeutic combinations and methods of the present invention include competitive inhibitors of HMG CoA reductase, the rate-limiting step in cholesterol biosynthesis, squalene synthase inhibitors, squalene epoxidase inhibitors and mixtures of two or more thereof. Non-limiting examples of suitable HMG CoA reductase inhibitors include statins such as lovastatin (for example MEVACOR® which is available from Merck & Co.), pravastatin (for example PRAVACHOL® which is available from Bristol Meyers Squibb), fluvastatin, simvastatin (for example ZOCOR® which is available from Merck & Co.), atorvastatin, cerivastatin, rosuvastatin, rivastatin (sodium 7-(4-fluorophenyl)-2,6-diisopropyl-5-methoxymethylpyridin-3-yl)-3,5-dihydroxy-6-heptanoate, CI-981 and pitavastatin (such as NK-104 of Negma Kowa of Japan); HMG CoA synthetase inhibitors, for example L-659,699 ((E,E)-11-[3'R-(hydroxy-methyl)-4'-oxo-2'R-oxetanyl]-3,5,7'R-trimethyl-2,4-undecadienoic acid); squalene synthesis inhibitors, for example squalestatin 1; and squalene epoxidase inhibitors, for example, NB-598 ((E)-N-ethyl-N-(6,6-dimethyl-2-hepten-4-ynyl)-3-[(3,3'-bithiophen-5-yl)methoxy]benzene-methanamine hydrochloride) and other sterol biosynthesis inhibitors such as DMP-565. Preferred HMG CoA reductase inhibitors include lovastatin, pravastatin and simvastatin.

[0487] In another embodiment, the method of treatment comprises administering an amount of the present combination or a pharmaceutically acceptable salt, solvate or ester thereof in combination with one or more cardiovascular agents and one or more cholesterol biosynthesis inhibitors.

[0488] In another alternative embodiment, the method of treatment of the present invention can further comprise administering nicotinic acid (niacin) and/or derivatives thereof, optionally with the cardiovascular agent(s) and sterol absorption inhibitor(s) discussed above.

[0489] As used herein, "nicotinic acid derivative" means a compound comprising a pyridine-3-carboxylate structure or a pyrazine-2-carboxylate structure, including acid forms, salts, esters, zwitterions and tautomers, where available. Examples of nicotinic acid derivatives include nicoritrol, nicofurano and acipimox (5-methyl pyrazine-2-carboxylic acid 4-oxide). Nicotinic acid and its derivatives inhibit hepatic production of VLDL and its metabolite LDL and increases HDL and apo A-1 levels. An example of a suitable nicotinic acid product is NIASPAN® (niacin extended-release tablets) which are available from Kos.

[0490] In another alternative embodiment, the method of treatment of the present invention can further comprise administering one or more AcylCoA:Cholesterol O-acyltransferase ("ACAT") Inhibitors, which can reduce LDL and

VLDL levels, coadministered with or in combination with the cardiovascular agent(s) and sterol absorption inhibitor(s) discussed above. ACAT is an enzyme responsible for esterifying excess intracellular cholesterol and may reduce the synthesis of VLDL, which is a product of cholesterol esterification, and overproduction of apo B-100-containing lipoproteins.

[0491] Non-limiting examples of useful ACAT inhibitors include avasimibe ([2,4,6-tris(1-methylethyl)phenyl]acetyl)sulfamic acid, 2,6-bis(1-methylethyl)phenyl ester, formerly known as CI-1011), HL-004, lecimide (DuP-128) and CL-277082 (N-(2,4-difluorophenyl)-N-[[(4-(2,2-dimethylpropyl)phenyl)methyl]-N-heptylurea). See, Chong and Bachenheimer, "Current, new and future treatments in dyslipidaemia and atherosclerosis," *Drugs*, 60(1):55-93 (2000), which is incorporated by reference herein.

[0492] In another alternative embodiment, the method of treatment of the present invention can further comprise administering probucol or derivatives thereof (such as AGI-1067 and other derivatives disclosed in U.S. Pat. Nos. 6,121,319 and 6,147,250), which can reduce LDL levels, coadministered with or in combination with the cardiovascular agent(s) and sterol absorption inhibitor(s) discussed above.

[0493] In another alternative embodiment, the method of treatment of the present invention can further comprise administering fish oil, which contains Omega 3 fatty acids (3-PUFA), which can reduce VLDL and triglyceride levels, coadministered with or in combination with the cardiovascular agent(s) and sterol absorption inhibitor(s) discussed above. Generally, a total daily dosage of fish oil or Omega 3 fatty acids can range from about 1 to about 30 grams per day in single or 2-4 divided doses.

[0494] In another alternative embodiment, the method of treatment of the present invention can further comprise administering natural water soluble fibers, such as psyllium, guar, oat and pectin, which can reduce cholesterol levels, coadministered with or in combination with the cardiovascular agent(s) and sterol absorption inhibitor(s) discussed above. Generally, a total daily dosage of natural water soluble fibers can range from about 0.1 to about 10 grams per day in single or 2-4 divided doses.

[0495] In another alternative embodiment, the method of treatment of the present invention can further comprise administering plant sterols, plant stanols and/or fatty acid esters of plant stanols, such as sitostanol ester used in BENECOL® margarine, which can reduce cholesterol levels, coadministered with or in combination with the cardiovascular agent(s) and sterol absorption inhibitor(s) discussed above. Generally, a total daily dosage of plant sterols, plant stanols and/or fatty acid esters of plant stanols can range from about 0.5 to about 20 grams per day in single or 2-4 divided doses.

[0496] In another alternative embodiment, the method of treatment of the present invention can further comprise administering antioxidants, such as probucol, tocopherol, ascorbic acid,  $\beta$ -carotene and selenium, or vitamins such as vitamin B<sub>6</sub> or vitamin B<sub>12</sub>, coadministered with or in combination with the at least one aldo-keto reductase inhibitor and at least one cathepsin inhibitor compound according to the present invention. Generally, a total daily dosage of

antioxidants or vitamins can range from about 0.05 to about 10 grams per day in single or 2-4 divided doses.

[0497] In another alternative embodiment, the method of treatment of the present invention can further comprise administering one or more bile acid sequestrants (insoluble anion exchange resins), coadministered with or in combination with the at least one aldo-keto reductase inhibitor and at least one cathepsin inhibitor compound according to the present invention.

[0498] Bile acid sequestrants bind bile acids in the intestine, interrupting the enterohepatic circulation of bile acids and causing an increase in the faecal excretion of steroids. Use of bile acid sequestrants is desirable because of their non-systemic mode of action. Bile acid sequestrants can lower intrahepatic cholesterol and promote the synthesis of apo B/E (LDL) receptors which bind LDL from plasma to further reduce cholesterol levels in the blood.

[0499] Non-limiting examples of suitable bile acid sequestrants include cholestyramine (a styrene-divinylbenzene copolymer containing quaternary ammonium cationic groups capable of binding bile acids, such as QUESTRAN® or QUESTRAN LIGHT® cholestyramine which are available from Bristol-Myers Squibb), colestipol (a copolymer of diethylenetriamine and 1-chloro-2,3-epoxypropane, such as COLESTID® tablets which are available from Pharmacia), colesevelam hydrochloride (such as WelChol® Tablets (poly(allylamine hydrochloride) cross-linked with epichlorohydrin and alkylated with 1-bromodecane and (6-bromo-hexyl)-trimethylammonium bromide) which are available from Sankyo), water soluble derivatives such as 3,3-iodine, N-(cycloalkyl)alkylamines and poliglusam, insoluble quaternized polystyrenes, saponins and mixtures of two or more thereof. Other useful bile acid sequestrants are disclosed in PCT Patent Applications Nos. WO 97/11345 and WO 98/57652, and U.S. Pat. Nos. 3,692,895 and 5,703,188 which are incorporated herein by reference. Suitable inorganic cholesterol sequestrants include bismuth salicylate plus montmorillonite clay, aluminum hydroxide and calcium carbonate antacids.

[0500] Also useful with the present invention are methods of treatment that can further comprise administering at least one (one or more) activators for peroxisome proliferator-activated receptors (PPAR). These activators act as agonists for the peroxisome proliferator-activated receptors. Three subtypes of PPAR have been identified, and these are designated as peroxisome proliferator-activated receptor alpha (PPAR $\alpha$ ), peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) and peroxisome proliferator-activated receptor delta (PPAR $\delta$ ). It should be noted that PPAR $\delta$  is also referred to in the literature as PPAR $\beta$  and as NUC1, and each of these names refers to the same receptor.

[0501] PPAR $\alpha$  regulates the metabolism of lipids. PPAR $\alpha$  is activated by fibrates and a number of medium and long-chain fatty acids, and it is involved in stimulating  $\beta$ -oxidation of fatty acids. The PPAR $\gamma$  receptor subtypes are involved in activating the program of adipocyte differentiation and are not involved in stimulating peroxisome proliferation in the liver. PPAR $\delta$  has been identified as being useful in increasing high density lipoprotein (HDL) levels in humans. See, e.g., WO 97/28149.

[0502] PPAR $\alpha$  activator compounds are useful for, among other things, lowering triglycerides, moderately lowering

LDL levels and increasing HDL levels. Useful examples of PPAR $\alpha$  activators include the fibrates discussed above.

[0503] Other examples of PPAR $\alpha$  activators useful with the practice of the present invention include suitable fluorophenyl compounds as disclosed in U.S. Pat. No. 6,028,109 which is incorporated herein by reference; certain substituted phenylpropionic compounds as disclosed in WO 00/75103 which is incorporated herein by reference; and PPAR $\alpha$  activator compounds as disclosed in WO 98/43081 which is incorporated herein by reference.

[0504] Non-limiting examples of PPAR $\gamma$  activator include suitable derivatives of glitazones or thiazolidinediones, such as, troglitazone (such as REZULIN® troglitazone (-5-[4-[3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione) commercially available from Parke-Davis); rosiglitazone (such as AVANDIA® rosiglitazone maleate (-5-[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione, (Z)-2-butenedioate) (1:1) commercially available from SmithKline Beecham) and pioglitazone (such as ACTOSTM pioglitazone hydrochloride (5-[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-thiazolidinedione monohydrochloride) commercially available from Takeda Pharmaceuticals). Other useful thiazolidinediones include ciglitazone, englitazone, darglitazone and BRL 49653 as disclosed in WO 98/05331 which is incorporated herein by reference; PPAR $\gamma$  activator compounds disclosed in WO 00/76488 which is incorporated herein by reference; and PPAR $\gamma$  activator compounds disclosed in U.S. Pat. No. 5,994,554 which is incorporated herein by reference.

[0505] Other useful classes of PPAR $\gamma$  activator compounds include certain acetylphenols as disclosed in U.S. Pat. No. 5,859,051 which is incorporated herein by reference; certain quinoline phenyl compounds as disclosed in WO 99/20275 which is incorporated herein by reference; aryl compounds as disclosed by WO 99/38845 which is incorporated herein by reference; certain 1,4-disubstituted phenyl compounds as disclosed in WO 00/63161; certain aryl compounds as disclosed in WO 01/00579 which is incorporated herein by reference; benzoic acid compounds as disclosed in WO 01/12612 & WO 01/12187 which are incorporated herein by reference; and substituted 4-hydroxy-phenylalconic acid compounds as disclosed in WO 97/31907 which is incorporated herein by reference.

[0506] PPAR $\delta$  compounds are useful for, among other things, lowering triglyceride levels or raising HDL levels. Non-limiting examples of PPAR $\delta$  activators include suitable thiazole and oxazole derivates, such as C.A.S. Registry No. 317318-32-4, as disclosed in WO 01/00603 which is incorporated herein by reference); certain fluoro, chloro or thio phenoxy phenylacetic acids as disclosed in WO 97/28149 which is incorporated herein by reference; suitable non- $\beta$ -oxidizable fatty acid analogues as disclosed in U.S. Pat. No. 5,093,365 which is incorporated herein by reference; and PPAR $\delta$  compounds as disclosed in WO 99/04815 which is incorporated herein by reference.

[0507] Moreover, compounds that have multiple functionality for activating various combinations of PPAR $\alpha$ , PPAR $\gamma$  and PPAR $\delta$  are also useful with the practice of the present invention. Non-limiting examples include certain substituted aryl compounds as disclosed in U.S. Pat. No. 6,248,781; WO 00/23416; WO 00/23415; WO 00/23425; WO

00/23445; WO 00/23451; and WO 00/63153, all of which are incorporated herein by reference, are described as being useful PPAR $\alpha$  and/or PPAR $\gamma$  activator compounds. Other non-limiting examples of useful PPAR $\alpha$  and/or PPAR $\gamma$  activator compounds include activator compounds as disclosed in WO 97/25042 which is incorporated herein by reference; activator compounds as disclosed in WO 00/63190 which is incorporated herein by reference; activator compounds as disclosed in WO 01/21181 which is incorporated herein by reference; biaryl-oxa(thia)zole compounds as disclosed in WO 01/16120 which is incorporated herein by reference; compounds as disclosed in WO 00/63196 and WO 00/63209 which are incorporated herein by reference; substituted 5-aryl-2,4-thiazolidinediones compounds as disclosed in U.S. Pat. No. 6,008,237 which is incorporated herein by reference; arylthiazolidinedione and aryloxazolidinedione compounds as disclosed in WO 00/78312 and WO 00/78313G which are incorporated herein by reference; GW2331 or (2-(4-[difluorophenyl]-1-heptylureido)ethyl]phenoxy)-2-methylbutyric compounds as disclosed in WO 98/05331 which is incorporated herein by reference; aryl compounds as disclosed in U.S. Pat. No. 6,166,049 which is incorporated herein by reference; oxazole compounds as disclosed in WO 01/17994 which is incorporated herein by reference; and dithiolane compounds as disclosed in WO 01/25225 and WO 01/25226 which are incorporated herein by reference.

[0508] Other useful PPAR activator compounds include substituted benzylthiazolidine-2,4-dione compounds as disclosed in WO 01/14349, WO 01/14350 and WO/01/04351 which are incorporated herein by reference; mercaptocarboxylic compounds as disclosed in WO 00/50392 which is incorporated herein by reference; ascofuranone compounds as disclosed in WO 00/53563 which is incorporated herein by reference; carboxylic compounds as disclosed in WO 99/46232 which is incorporated herein by reference; compounds as disclosed in WO 99/12534 which is incorporated herein by reference; benzene compounds as disclosed in WO 99/15520 which is incorporated herein by reference; o-anisamide compounds as disclosed in WO 01/21578 which is incorporated herein by reference; and PPAR activator compounds as disclosed in WO 01/40192 which is incorporated herein by reference.

[0509] Also useful with the present invention are methods of treatment which further comprise administering hormone replacement agents and compositions. Useful hormone agents and compositions for hormone replacement therapy of the present invention include androgens, estrogens, progestins, their pharmaceutically acceptable salts and derivatives. Combinations of these agents and compositions are also useful.

[0510] The cathepsin inhibitors of the present invention are useful in the treatment of central nervous system diseases such as depression, cognitive function diseases and neurodegenerative diseases such as Parkinson's disease, senile dementia as in Alzheimer's disease, and psychoses of organic origin. In particular, the cathepsin inhibitors of the present invention can improve motor-impairment due to neurodegenerative diseases such as Parkinson's disease.

[0511] The other agents known to be useful in the treatment of Parkinson's disease which can be administered in combination with the cathepsin inhibitors of the present

invention include: L-DOPA; dopaminergic agonists such as quinpirole, ropinirole, pramipexole, pergolide and bromocriptine; MAO-B inhibitors such as deprenyl and selegiline; DOPA decarboxylase inhibitors such as carbidopa and benserazide; and COMT inhibitors such as tolcapone and entacapone.

[0512] 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.

[0513] The phrases "effective amount" and "therapeutically effective amount" mean that amount of a compound/composition of the present invention, and other pharmacological or therapeutic agents described herein, that will elicit a biological or medical response of a tissue, a system, or a human subject that is being sought by the administrator (such as a researcher or doctor) which includes alleviation of the symptoms of the condition or disease being treated and the prevention, slowing or halting of progression of one or more of the presently claimed diseases. The formulations or compositions, combinations and treatments of the present invention can be administered by any suitable means which produce contact of these compounds with the site of action in the body of, for example, a mammal or human.

[0514] 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.

[0515] As described above, this invention includes combinations comprising an amount of at least one HCV polymerase inhibitor and an amount of at least one HCV protease or cathepsin inhibitor compound or a pharmaceutically acceptable salt or ester thereof, and an amount of one or more additional therapeutic agents listed above (administered together or sequentially) wherein the amounts of the compounds/treatments result in desired therapeutic effect.

[0516] 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).

[0517] 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. Medicaments and pharmaceutical compositions 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.

[0518] The pharmacological properties of the compositions of this invention may be confirmed by a number of pharmacological assays for measuring HCV viral activity or cathepsin activity, such as are well known to those skilled in the art.

[0519] 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.

[0520] 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.

[0521] 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.

[0522] 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.

[0523] 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.

[0524] 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 or cathepsin inhibitory activity and the like. Suitable dosage forms for sustained release include layered tablets containing layers of varying disintegration rates or controlled release polymeric matrices impregnated with the active components and shaped in tablet form or capsules containing such impregnated or encapsulated porous polymeric matrices.

[0525] 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.

[0526] 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.

[0527] 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.

[0528] 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.

[0529] The medicaments and pharmaceutical compositions 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.

[0530] Preferably the compound is administered orally, intravenously, intrathecally or subcutaneously.

[0531] 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.

[0532] Some useful terms are described below:

[0533] 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.

[0534] 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.

[0535] Oral gel—refers to the active ingredients dispersed or solubilized in a hydrophilic semi-solid matrix.

[0536] Powder for constitution refers to powder blends containing the active ingredients and suitable diluents which can be suspended in water or juices.

[0537] 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%.

[0538] 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.

[0539] 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.

[0540] 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.

[0541] Glidient—material that prevents caking and improve the flow characteristics of granulations, so that flow is smooth and uniform. Suitable glidients include silicon dioxide and talc. The amount of glidient 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.

[0542] 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%.

[0543] 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.

[0544] 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.

[0545] 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*, 18<sup>th</sup> Edition, (1990), Mack Publishing Co., Easton, Pa.

[0546] 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. 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 human 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.

[0547] 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.

[0548] Preferably the composition is administered orally, intravenously or subcutaneously.

[0549] 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.

[0550] 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.

[0551] The amount and frequency of administration of the compositions of the present invention and/or the pharmaceutically acceptable salts or esters thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended daily dosage regimen for oral administration can range from about 1 mg/day to about 3600 mg/day, inclusive of each amount therebetween, preferably about 50 mg/day to about 800 mg/day, in two to four divided doses. In another embodiment, the daily dosage can range from about 50 to about 600 mg/day. In another embodiment, the daily dosage can range from about 50 to about 400 mg/day. In another embodiment, the daily dosage can range from about 50 to about 200 mg/day. Preferably, the dosage is 400 mg/TID.

[0552] The compositions 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 can be performed by a central or other 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).

[0553] It would also be desirable to modify the pharmacokinetic behavior of HCV treatments and cathepsin inhibitors to enhance the efficacy and duration of action thereof.

[0554] CYP3A4 Inhibitors

[0555] In one embodiment, at least one CYP3A4 inhibitor is selected from the group of CYP3A4 inhibitors referred to in the following documents (which are incorporated by reference herein): US20040052865A1, US20030150004A1, US20060099667A1, US20030096251A1, US20060073099A1, US20050272045A1, US20020061836A1, US20020016681A1, US20010041706A1, US20060009645A1, US20050222270A1, US20050031713A1, US20040254156A1, US20040214848A1, WO0173113A2, WO2005068611A1, US20050171037A1, WO2003089657A1, WO2003089656A1, WO2003042898A2, US20040243319A1, WO0045817A1, WO2006037993A2, WO2004021972A2, WO2006024414A2, WO2004060370A1, WO9948915A1, WO2006054755A1, WO2006037617A1, JP2006111597A, WO0111035A1, WO9844939A1, WO2003026573A2, WO2003047594A1, WO0245704A2, WO2005020962A1, WO2006021456A1, US20040047920A1, WO2003035074A1, WO2005007631A1, WO2005034963A1, WO2006061714A2, WO0158455A1, WO2003040121A1, WO2002094865A1, WO0044933A1, U.S. Pat. No. 6,673,778B1, WO2005098025A2, US20040106216A1, WO0017366A2, WO9905299A1, WO9719112A1, EP1158045A1, WO0034506A2, U.S. Pat. No. 5,886,157A, WO9841648A2, U.S. Pat. No. 6,200,754B1, U.S. Pat. No. 6,514,687B1, WO2005042020A2, WO9908676A1, WO9817667A1, WO0204660A2, WO2003046583A2, WO2003052123A1, WO2003046559A2, US20040101477A1, US20040084867A1, JP10204091A, WO9635415A2.

[0556] Non-limiting examples of suitable CYP3A4 inhibitors include ketoconazole (Nizoral<sup>TM</sup>, commercially available from Janssen Pharmaceutica), itraconazole (Sporanox<sup>R</sup>, commercially available from Janssen-Cilag), ritonavir (Norvir<sup>R</sup> commercially available from Abbott), nefazodone (Prozac<sup>R</sup> commercially available from Eli Lilly and Company, Zoloft<sup>R</sup> commercially available from Pfizer Pharmaceuticals, Anafranil<sup>R</sup> commercially available from Mallinckrodt Inc.), fluvoxamine (Luvox<sup>R</sup>), Zyflo (Zileuton<sup>R</sup> commercially available from Abbott Laboratories), clarithromycin (Biaxin<sup>R</sup>), troleandomycin (Tao<sup>R</sup>), saquinavir, nefazodone, fluconazole, grapefruit juice, fluoxetine (Prozac<sup>R</sup> commercially available from Eli Lilly and Company, Zoloft<sup>R</sup> commercially available from Pfizer Pharmaceuticals, Anafranil<sup>R</sup> commercially available from Mallinckrodt Inc.), fluvoxamine (Luvox<sup>R</sup>), Zyflo (Zileuton<sup>R</sup> commercially available from Abbott Laboratories), clotrimazole (Fungoid<sup>R</sup> Solution, Gyne-Lotrimin<sup>R</sup>, GyneLotrimin<sup>R</sup> 3, Gyne-Lotrimin<sup>R</sup> 3 Combination Pack, Gyne-Lotrimin<sup>R</sup>-3, Lotrim<sup>R</sup> AF Jock Itch Cream, Lotrimin<sup>R</sup>, Lotrimin<sup>R</sup> AF, Mycelex<sup>R</sup> Troche, Mycelex<sup>R</sup>-7), midazolam (available from Apotex Corp.), naringenin, and bergamottin. Preferably, the CYP3A4 inhibitor is ritonavir, ketoconazole (Nizoral<sup>TM</sup>) or clarithromycin (Biaxin<sup>R</sup>).

[0557] Preferably, the CYP3A4 inhibitor is administered in an amount sufficient to increase the bioavailability of at least one HCV protease inhibitor. Preferably, the clarithromycin is administered at a dosage range of about 5 mg to about 249 mg per day. Preferably, the clarithromycin is

administered at a unit dosage of 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 105 mg, 110 mg, 115 mg, 120 mg, 125 mg, 130 mg, 135 mg, 140 mg, 145 mg, 150 mg, 155 mg, 160 mg, 165 mg, 170 mg, 175 mg, 180 mg, 185 mg, 190 mg, 195 mg, 200 mg, 205 mg, 210 mg, 215 mg, 220 mg, 225 mg, 230 mg, 235 mg, 240 mg, 245 mg, or 249 mg.

[0558] In addition, non-limiting examples of suitable compounds that inhibit HIV protease which have also been identified as CYP3A4 inhibitors are disclosed in US 2005/0209301 (at page 3, paragraph [0025] to page 5, paragraph [0071] and page 10, paragraph [0170] to page 12, paragraph [0226]) as well as US 2005/0267074 (at page 3, paragraph [0025], paragraph [0028] to page 7, paragraph [0114], page 7, paragraph [0119] to paragraph [0124], and FIGS. 1-3), incorporated herein by reference. The following is a list of specific compounds depicted in US 2005/0209301: {1-Benzyl-3-[{3-(dimethylaminomethylene-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl)-isobutyl-amino]-2-hydroxy-propyl}-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; {1-Benzyl-3-[{3-(1-dimethylamino-ethylidene)-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl)-isobutyl-amino]-2-hydroxy-propyl}-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; {1-Benzyl-3-[{3-[{ethyl-methyl-amino)-methylene]-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl)-isobutyl-amino]-2-hydroxy-propyl}-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; {1-Benzyl-3-[{3-[{ethyl-methyl-amino)-ethylidene]-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl)-isobutyl-amino]-2-hydroxy-propyl}-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; {1-Benzyl-3-[{3-[{ethyl-methyl-amino)-ethylidene]-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl)-isobutyl-amino]-2-hydroxy-propyl}-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; {1-Benzyl-2-hydroxy-3-[{3-[{methyl-propyl-amino)-methylene]-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl)-amino)-propyl}-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; {1-Benzyl-2-hydroxy-3-[{3-[{1-(methyl-propyl-amino)-ethylidene]-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl)-amino)-propyl}-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; {1-Benzyl-2-hydroxy-3-[{3-[{1-(methyl-propyl-amino)-ethylidene]-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl)-amino)-propyl}-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; {1-Benzyl-3-[{3-diethylaminomethylene-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl)-isobutyl-amino]-2-hydroxy-propyl}-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; {1-Benzyl-3-[{3-dipropylaminomethylene-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl)-isobutyl-amino]-2-hydroxy-propyl}-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; {1-Benzyl-3-[{3-(1-diethylamino-ethylidene)-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl)-isobutyl-amino]-2-hydroxy-propyl}-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; {1-Benzyl-3-[{3-(1-diethylamino-ethylidene)-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl)-isobutyl-amino]-2-hydroxy-propyl}-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; {1-Benzyl-3-[{3-(1-dipropylamino-ethylidene)-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl)-isobutyl-amino]-2-hydroxy-propyl}-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; {1-Benzyl-3-[{3-(1-dipropylamino-ethylidene)-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl)-isobutyl-amino]-2-hydroxy-propyl}-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; {1-Benzyl-2-hydroxy-3-[{isobutyl-(2-oxo-3-piperidin-1-yl-methylene-2,-3-dihydro-1H-indole-5-sulfonyl)-amino)-propyl}-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; {1-Benzyl-2-hydroxy-3-[{isobutyl-(2-oxo-3-(1-piperidin-1-yl-ethylidene)-2,3-dihydro-1H-indole-5-sulfonyl)-amino)-propyl}-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; {1-Benzyl-2-hydroxy-3-[{isobutyl-(2-oxo-3-piperazin-1-ylmethylene-2,-3-dihydro-1H-indole-5-sulfonyl)-amino)-propyl}-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; {1-Benzyl-2-hydroxy-3-[{isobutyl-(3-morpholin-4-yl-methylene-2-oxo-2,-3-dihydro-1H-indole-5-sulfonyl)-amino)-propyl}-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; {3-[{3-Aminomethylene-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl)-isobutyl-amino]-1-benzyl-2-hydroxy-3-yl ester;

propyl}-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; {3-[3-(1-Amino-ethylidene)-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl]-1-isobutyl-amino}-1-benzyl-2-hydroxy-propyl}-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; {1-Benzyl-2-hydroxy-3-[isobutyl-(3-methylenaminomethylene-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl)-amino]-propyl}-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; (1-Benzyl-2-hydroxy-3-[isobutyl-[3-(1-methylenaminomethylene-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl)-amino]-propyl]-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; {1-Benzyl-3-[3-ethylaminomethylene-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl]-isobutyl-amino]-2-hydroxy-propyl}-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; (1-Benzyl-3-[3-(1-ethylaminomethylene-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl)-isobutyl-amino]-2-hydroxy-propyl)-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; [1-Benzyl-2-hydroxy-3-(isobutyl-[2-oxo-3-[2,2,2-trifluoro-ethylamino]-methylene]-2,3-dihydro-1H-indole-5-sulfonyl)-amino]-propyl]-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; [1-Benzyl-2-hydroxy-3-(isobutyl-[2-oxo-3-[1-(2,2,2-trifluoro-ethylamino)-ethylidene]-2,3-dihydro-1H-indole-5-sulfonyl)-amino)-propyl]-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; [1-Benzyl-2-hydroxy-3-[3-[2-hydroxy-ethylamino]-methylene]-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl]-isobutyl-amino)-propyl]-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; [1-Benzyl-2-hydroxy-3-[3-[1-(2-hydroxy-ethylamino)-ethylidene]-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl]-isobutyl-amino)-propyl]-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; [1-Benzyl-2-hydroxy-3-[3-[1-(2-methoxy-ethylamino)-methylene]-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl]-amino)-propyl]-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; [1-Benzyl-2-hydroxy-3-[3-[1-(2-methoxy-ethylamino)-ethylidene]-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl]-amino)-propyl]-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; [1-Benzyl-3-(3-[2-dimethylamino-ethylamino]-methylene)-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl]-isobutyl-amino)-2-hydroxy-propyl]-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; [1-Benzyl-3-(3-[1-(2-dimethylamino-ethylamino)-ethylidene]-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl)-amino)-propyl]-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; (1-Benzyl-2-hydroxy-3-[isobutyl-[3-(isopropylamino-methylene)-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl]-amino]-propyl)-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; (1-Benzyl-2-hydroxy-3-[isobutyl-[3-(1-isopropylamino-ethylidene)-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl]-amino]-propyl)-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; (1-Benzyl-2-hydroxy-3-[isobutyl-[2-oxo-3-propylaminomethylene-2,3-dihydro-1H-indole-5-sulfonyl]-amino]-propyl)-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; (1-Benzyl-2-hydroxy-3-[isobutyl-[2-oxo-3-propylaminomethylene-2,3-dihydro-1H-indole-5-sulfonyl]-amino]-propyl)-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; (1-Benzyl-2-hydroxy-3-[isobutyl-[2-oxo-3-pyrrolidin-2-ylidene]-2,3-dihydro-1H-indole-5-sulfonyl]-amino)-propyl]-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; (1-Benzyl-3-[3-butylaminomethylene-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl]-isobutyl-amino)-2-hydroxy-propyl]-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; (1-Benzyl-3-[3-(1-butylaminomethylene-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl)-isobutyl-amino]-2-hydroxy-propyl)-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; (1-Benzyl-3-[3-(1-butylaminomethylene-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl)-isobutyl-amino]-2-hydroxy-propyl)-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester.

isobutyl-amino}-2-hydroxy-propyl)-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; (1-Benzyl-2-hydroxy-3-{isobutyl-[3-(isobutylamino-methylene)-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl]-amino}-propyl)-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; (1-Benzyl-2-hydroxy-3-{isobutyl-[3-(1-isobutylamino-ethylidene)-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl]-amino}-propyl)-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; (1-Benzyl-3-{[3-(tert-butylamino-methylene)-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl]-isobutyl-amino}-2-hydroxy-propyl)-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; (1-Benzyl-3-{[3-(1-tert-butylamino-ethylidene)-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl]-isobutyl-amino}-2-hydroxy-propyl)-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; [1-Benzyl-3-{[(3-(2,2-dimethylpropylamino)-methylene)-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl]-isobutyl-amino}-2-hydroxy-propyl]-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; [1-Benzyl-3-{[(3-[1-(2,2-dimethyl-propylamino)-ethylidene]-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl]-isobutyl-amino}-2-hydroxy-propyl]-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; [1-Benzyl-3-{[(3-[1-(2,2-dimethyl-propylamino)-ethylidene]-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl]-isobutyl-amino}-2-hydroxy-propyl]-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; [1-Benzyl-2-hydroxy-3-{isobutyl-[3-(3-methyl-butylamino)-methylene]-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl]-amino}-propyl]-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; [1-Benzyl-2-hydroxy-3-{isobutyl-[3-(3-dimethyl-butylamino)-methylene]-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl]-isobutyl-amino}-2-hydroxy-propyl]-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; [1-Benzyl-2-hydroxy-3-{isobutyl-[3-(1-isopropyl-2-methyl-propylamino)-methylene]-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl]-amino}-propyl]-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; [1-Benzyl-2-hydroxy-3-{isobutyl-[2-oxo-2,3-dihydro-1H-indole-5-sulfonyl]-amino}-propyl]-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; {1-Benzyl-2-hydroxy-3-[isobutyl-(2-oxo-3-phenylaminomethylene)-2,3-dihydro-1H-indole-5-sulfonyl]-amino}-propyl]-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; (1-Benzyl-3-{[(3-(benzylamino-methylene)-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl]-isobutyl-amino}-2-hydroxy-propyl)-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; (1-Benzyl-3-{[3-(1-benzylamino-ethylidene)-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl]-isobutyl-amino}-2-hydroxy-propyl)-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; [1-Benzyl-3-{[(3-[cyclohexylmethyl-amino)-methylene]-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl]-isobutyl-amino}-2-hydroxy-propyl]-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; {1-Benzyl-2-hydroxy-3-[isobutyl-(2-oxo-3-{[pyridin-4-ylmethyl]-amino}-methylene)-2,3-dihydro-1H-indole-5-sulfonyl]-amino}-propyl]-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; (1-Benzyl-2-hydroxy-3-{isobutyl-[2-oxo-3-(phenethylamino-methylene)-2,3-dihydro-1H-indole-5-sulfonyl]-amino}-propyl)-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; [1-Benzyl-3-{[(2-cyclohex-1-enyl-ethylamino)-methylene]-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl]-isobutyl-amino}-2-hydroxy-propyl]-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; [1-Benzyl-3-{[(2-pyridin-2-yl-ethylamino)-methylene]-2-3-dihydro-1H-indole-5-sulfonyl]-amino}-propyl]-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; [1-Benzyl-2-hydroxy-3-{isobutyl-[2-oxo-3-(2-pyridin-2-yl-ethylamino)-methylene]-2,3-dihydro-1H-indole-5-sulfonyl]-amino}-propyl]-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; [1-Benzyl-2-hydroxy-3-{isobutyl-[2-oxo-3-(2-phenyl-propylamino)-methylene]-2,3-dihydro-1H-indole-5-sulfonyl]-amino}-propyl]-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester;

[1-Benzyl-2-hydroxy-3-(isobutyl-[2-oxo-3-[(4-phenyl-butylamino)-methylene]-2,3-dihydro-1H-indole-5-sulfonyl]-amino)-propyl]-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; {1-Benzyl-2-hydroxy-3-[isobutyl-(3-nonylaminomethylene)-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl]-amino}-propyl]-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; and (1-Benzyl-2-hydroxy-3-{[(3-(1-hydroxy-ethylidene)-2-oxo-2,3-dihydro-1H-indole-5-sulfonyl]-isobutyl-amino}-propyl]-carbamic acid hexahydro-furo[2,3-b]furan-3-yl ester; and the pharmaceutically acceptable salts thereof, as single stereoisomers or mixtures of stereoisomers. Likewise, see FIG. 1 for a list of specific compounds depicted in US 2005/0267074. Notably, US 2005/0267074 emphasizes that compounds having a benzofuran moiety are potent inhibitors of CYP3A4. HIV inhibitors useful as CYP3A4 inhibitors are also disclosed in U.S. Ser. No. 60/785,761, filed Mar. 23, 2006, incorporated herein by reference.

#### [0559] Pgp Inhibitors

[0560] In one embodiment, at least one Pgp inhibitor is selected from the group of Pgp inhibitors referred to in the following documents (which are incorporated by reference herein): US20030139352A1, US20060040908A1, US20020147197A1, US20050171202A1, US20040219609A1, US20040214848A1, US20040110244A1, WO9325705A1, WO0160387A1, WO0059931A1, WO2004019886A2, US20040030248A1, WO0205818A2, WO2002074048A2, WO0123565A1, WO0123540A2, WO0066173A2, WO2006041902A2, WO9600085A1, WO9746254A2, WO2005020962A1, WO0241884A2, U.S. Pat. No. 6,277,655B1, WO2006026592A2, WO2002071061A2, US20040197334A1, WO2006034219A2, WO174790A2, U.S. Pat. No. 6,376,514B1, WO9962537A1, U.S. Pat. No. 6,521,635B1, WO0125400A2, WO0221135A2, WO0046347A1.

[0561] Non-limiting examples of suitable Pgp inhibitors include WK-X-34, ketoconazole (Nizoral™, commercially available from Janssen Pharmaceutica) and ritonavir (Norvir® commercially available from Abbott). Preferably, the Pgp inhibitor is ketoconazole. An assay for Pgp inhibitors is described by Jekerle et al., *Int J Cancer*, 119(2):414-422 (2006).

#### [0562] AKR Competitors

[0563] In one embodiment, at least one AKR competitor is selected from the group of AKR competitors referred to in the following documents (which are incorporated by reference herein): US20060154366A1, US20060078631A1, US20020168765A1, US20030113728A1, WO9723630A2, WO2006022374A1, WO2003093826A2, WO2006061137A1, WO2006071794A2, WO2006071778A2, WO0179223A2, WO042211A1, WO9905283A2, FR2786201A1, FR2786189A1, WO2004083404A2, DE10300222A1, WO2003051182A2, WO2002053704A2, US20030148337A1, DE19910394A1, WO187973A1, U.S. Pat. No. 6,881,584B1, SU527686, WO0218438A1, WO2005113752A2, WO2006023821A2, WO9967269A1, U.S. Pat. No. 4,076,725A, WO2004072239A2, WO2006025060A2.

[0564] Non-limiting examples of suitable AKR competitors include AKR substrates, AKR inhibitors, or a mixture of

two or more thereof. Suitable AKR substrates include fibrates, 5 $\alpha$ -dihydroxytestosterone, dolasetron (such as ANZEMET dolasetron mesylate which is commercially available from Aventis Pharmaceuticals), doxorubicin (such as DOXIL, ADRIMYCIN OR ONCOJET doxorubicin hydrochloride), 17 $\beta$ -estradiol, non-steroidal anti-inflammatory drugs (NSAIDS), ketotifen (such as is commercially available from Apotex), naltrexone (such as ReVia naltrexone hydrochloride opioid antagonist), Z-10-oxo nortriptyline (such as AVENTYL or PAMELOR nortriptyline), oestrone, S-1360 HIV integrase inhibitor, progesterone, prostaglandin, sorbinil, testosterone, tibolone, tolrestat, naringenin (available from grapefruit juice or from R&S Pharmchem, Hangzhou City, China) and a mixture of two or more thereof.

[0565] Fibrates (fobic acid derivatives) are peroxisome proliferator-activated receptor (PPAR) alpha activators. Non-limiting examples of suitable fobic acid derivatives include clofibrate (such as ethyl 2-(p-chlorophenoxy)-2-methyl-propionate, for example ATROMID-S capsules which are commercially available from Wyeth-Ayerst); gemfibrozil (such as 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoic acid, for example LOPID® tablets which are commercially available from Parke Davis); ciprofibrate (C.A.S. Registry No. 52214-84-3, see U.S. Pat. No. 3,948,973 which is incorporated herein by reference); bezafibrate, bezafibrate (C.A.S. Registry No. 41859-67-0, see U.S. Pat. No. 3,781,328 which is incorporated herein by reference); clinofibrate (C.A.S. Registry No. 30299-08-2, see U.S. Pat. No. 3,716,583 which is incorporated herein by reference); binifibrate (C.A.S. Registry No. 69047-39-8, see BE 884722 which is incorporated herein by reference); lifibrol (C.A.S. Registry No. 96609-16-4); fenofibrate (such as TRICOR micronized fenofibrate (2-[4-(4-chlorobenzoyl)phenoxy]-2-methyl-propanoic acid, 1-methylethyl ester) which is commercially available from Abbott Laboratories or LIPANTHYL micronized fenofibrate which is commercially available from Laboratoire Fournier, France) and a mixture of two or more thereof. These compounds can be used in a variety of forms, including but not limited to acid form, salt form, racemates, enantiomers, zwitterions and tautomers.

[0566] Suitable NSAIDs include NSAIDS agents (e.g., cyclooxygenase-2 inhibitors such as Celecoxib (Celebrex®)), Diclofenac (Cataflam®, Voltaren®, Arthrotec®,) Diflunisal (Dolobid®, commercially available from Merck & Co), Etodolac (Lodine®), Fenoprofen (Nalfon®), Flurbiprofen (Ansaid®), Ibuprofen (Motrin®, ADVIL®, NUPRIN®, Tab-Profen®, Vicoprofen®, Combunox®), Indornethacin (Indocin®, Indo-Lemmon®, Indornethagan®), Ketoprofen (Oruvail®), Ketonolac (Toradol®), Mefenamic acid (Ponstel®, commercially available from First Horizon Pharmaceutical), flufenamic acid ([N-(3-trifluoromethylphenyl)anthranilic acid]), Meloxicam (Mobic®), Naburnetone (Relafen®), Naproxen (Naprosyn®, ALEVE®, Anaprox®, Naprelan®, Naprapac®), Oxaprozin (Daypro®), Piroxicam (Feldene®), Sulindac (Clinoril®) and Tolmetin (Tolectin®)) and a mixture of two or more thereof. Preferably, the AKR competitor is Flufenamic acid ([N-(3-trifluoromethylphenyl)anthranilic acid]), Mefenamic acid (Ponstel®), Diclofenac (Cataflam®, Voltaren®, Arthrotec®,) Diflunisal (Dolobid®), or phenolphthalein. More preferably, the AKR competitor is Diflunisal (Dolobid®).

[0567] In one embodiment, at least one AKR competitor is an AKR1C1 AKR inhibitor, an AKR1C2 AKR inhibitor, an AKR1C3 AKR inhibitor, or an AKR1C4 AKR inhibitor.

[0568] Examples of suitable AKR inhibitors include benzodiazepines, cyclooxygenase (COX) 2 inhibitors, non-steroidal anti-inflammatory drugs (NSAIDS), testosterone, and a mixture of two or more thereof.

[0569] Examples of suitable benzodiazepines include cloxazolam, diazepam, estazolam, flunitrazepam, nitrazepam, medazepam, and a mixture of two or more thereof.

[0570] An example of a suitable cyclooxygenase (COX) 2 inhibitor is celecoxib.

[0571] Preferably, the AKR competitor is administered at a dosage range of about 5 to about 3200 mg per day (e.g., 5 mg, 10 mg, 50 mg, 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 per day). In one preferred embodiment, the AKR competitor is administered at a dosage range of about 5 mg to about 1500 mg per day. Note that the dosage of AKR competitor may be administered as a single dose or divided over 2-4 doses per day. Preferably, the AKR competitor is administered orally or transdermally; more preferably, orally.

[0572] In one embodiment, the AKR competitor is diflunisal, preferably administered at a dosage range of about 5 mg to about 3200 mg per day. In one embodiment, where the AKR competitor is diflunisal, the preferred dosage range is about 500 mg to about 2000 mg per day. In another embodiment, the preferred dosage range of diflunisal is about 1000 mg to about 1500 mg per day. In one preferred embodiment, diflunisal is administered 500 mg B.I.D. or 500 mg T.I.D.

[0573] Preferably, the amount of diflunisal administered is sufficient to increase the bioavailability of a drug metabolized by aldo-keto reductase AKR (e.g., a HCV protease inhibitor). An increase in bioavailability of a drug includes, but is not limited to, one or more of the following: an increase in half-life ( $t_{1/2}$ ) of the drug, an increase in the time to peak plasma concentration ( $C_{max}$ ) of the drug, an increase in the area under the plasma concentration-time curve (AUC) of the drug, an increase in blood level of the drug.

#### Assay for HCV Protease Inhibitory Activity

#### Spectrophotometric Assay

[0574] Spectrophotometric assay for HCV serine protease can be performed on the inventive medicaments by following the procedure described by Zhang et al., *Analytical Biochemistry*, 270:268-275 (1999), 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

**[0575]** Materials: Chemical reagents for assay related buffers are obtained from Sigma Chemical Company (St. Louis, Mo.). Reagents for peptide synthesis were from Aldrich Chemicals, Novabiochem (San Diego, Calif.), Applied Biosystems (Foster City, Calif.) and Perseptive Biosystems (Framingham, Mass.). 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, Conn.) and 96-well UV plates were obtained from Corning (Corning, N.Y.). The prewarming block can be from USA Scientific (Ocala, Fla.) and the 96-well plate vortexer is from Labline Instruments (Melrose Park, Ill.). A Spectramax Plus microtiter plate reader with monochromometer is obtained from Molecular Devices (Sunnyvale, Calif.).

#### Expression and Purification of Recombinant Mutant Proteases

**[0576]** The expression and purification protocol was described in Taremi et al., *Protein Sci.*, 7(10):2143-2149 (1998). Briefly, plasmid DNAs encoding mutant proteases were transformed into JM109 cells. Single colonies were used to initiate bacteria culture in 25 µg/ml Kanamycin at 37° C. When the cell density reached OD<sub>600</sub>~1.5, the culture was induced with 0.4 mM IPTG and grown at 23° C. for 4 hrs. The cell pellet was resuspended in buffer A (25 mM HEPES, pH 7.3, 300 mM NaCl, 0.1% β-octylglucoside, 10% glycerol, 2 mM β-mercaptoethanol or 0.2 mM DTT), and cells were lysed by passage through a microfluidizer (Microfluids Corp). The lysed supernatants were incubated with Ni-NTA beads (Qiagen) for 2 hrs at 4° C. and then loaded onto columns. The Ni-columns were washed with buffer A supplemented with 20 mM imidazole and 1M NaCl. The bound His-tagged protease was eluted with buffer A supplemented with 250 mM imidazole. The eluted fractions were pooled and dialyzed at 4° C. for 18 hr against 50 mM HEPES, 300 mM NaCl, 5 mM DTT, 0.1% β-octylglucoside and 10% glycerol. The purified proteases were analyzed on 4-12% Novex NuPAGE gel (Invitrogen) and aliquoted for storage at -80° C.

#### Substrate Synthesis and Purification

**[0577]** Substrates were obtained from AnaSpec (San Jose, Calif.).

**[0578]** The synthesis of the substrates may be done as reported by R. Zhang et al, (ibid.) and is initiated by anchoring Fmoc-Nva-OH to 2-chlorotriyl chloride resin using a standard protocol (Barlos et al., *Int J Pept Protein Res.*, 37(6):513-520 (1991)). 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<sub>2</sub>CO<sub>3</sub> solution) to remove the acid used in cleavage. The DCM phase is dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated.

**[0579]** 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

**[0580]** 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 Activity Assay

**[0581]** Recombinant proteases were tested using a chromogenic assay as described in Zhang et al., *Anal Biochem*, 270(2):268-275 (1999). The assays were performed at 30° C. in 96-well microtiter plate. 100 µl protease was added to 100 µl of assay buffer (25 mM MOPS, pH 6.5, 20% glycerol, 0.3M NaCl, 0.05% lauryl maltoside, 5 µM EDTA, 5 µM DTT) containing chromogenic substrate Ac-DTEDVVP-(Nva)-O-PAP based on the NS5A carboxyl terminus coupled to p-nitrophenol. The reactions were monitored at an interval of 30 s for 1 hr for change in absorbance at 370 nm using a Spectromax Plus microtiter plate reader (Molecular Devices). To determine enzyme concentration to be used in the assay, proteases were tested (1.6-100 nM) to achieve ~12% substrate depletion over the course of the assay. To evaluate kinetic parameters of recombinant proteases, a range of substrate concentrations (0.293-150 µM) was used. Initial velocities were determined using linear regression and kinetic constants were obtained by fitting the data to the Michaelis-Menton equation using MacCurveFit (Kevin Raner Software). Turnover rates were then calculated using the nominal enzyme concentration (2-9 nM). To assess the potency of protease inhibitors, the inhibition constants were determined at fixed concentrations of enzyme (2-9 nM) and substrate (40 µM). The data were fitted to the two step slow-binding inhibition model:  $P=v_s t+(v_0-v_s)(1-e^{-kt})/k$  of

Morrison and Walsh {Morrison, 1988 #82} using SAS (SAS Institute Inc.). The overall inhibition constant  $K_i^*(v_s = V_{max}S/(K_m(1+I/K_i^*)))$  was used to measure inhibitor potency.

#### Evaluation of Inhibitors and Inactivators

[0582] The inhibition constants ( $K_i$ ) for the competitive inhibitors Ac-D-(D-Gla)-L-I-(Cha)-C—OH (27), Ac-DT-EDVVA(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.

#### Polymerase Assay

[0583] As noted above, an assay for HCV polymerase inhibitors is described in Harper et al., *J Med Chem*, 48:1314-1317 (2005).

[0584] The following non-limiting Examples illustrate the present invention.

### EXAMPLES

#### Combination of HCV Protease Inhibitor+HCV Polymerase Inhibitor

[0585] The effect on HCV replicon RNA after treatment with HCV protease inhibitor Formula Ia alone or in combination with a HCV polymerase inhibitor was examined. Notably, different classes of HCV NS5B polymerase inhibitors were examined (i.e., 2'-methyl-adenosine, benzothiadiazine, and indole-N-acetamide). Likewise, the effect of HCV replicon RNA after treatment with HCV protease inhibitor Formula I, i.e., SCH 446211 (SCH 6), alone or in combination with HCV polymerase inhibitor ribavirin was examined.

#### Replicon RNA Response to Antiviral Agent(s)

[0586] Replicon RNA response to antiviral agent(s) was examined using the HCV protease inhibitor Formula Ia alone or in combination with HCV NS5B polymerase inhibitors 2'-methyl-adenosine, benzothiadiazine, indole-N-acetamide, or NM 107. Likewise, replicon RNA response to antiviral agent(s) was examined using the HCV protease inhibitor SCH 446211 (SCH 6) alone or in combination with HCV polymerase inhibitor ribavirin.

[0587] In brief, replicon cells were seeded at 4000 cells/well in 96-well collagen 1-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 1× cell lysis buffer (Ambion cat #8721). The replicon RNA level was measured using real time PCR (Taqman assay). The amplicon was located in NS5B. The

PCR primers used were: 5B.2F, ATGGACAGGCGC-CCTGA (SEQ ID NO: 1); 5B.2R, TTGATGGCAGCTTG-GTTTC (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  $\Delta CT$  values ( $CT_{NS5B}-CT_{GAPDH}$ ) 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  $\Delta CT=1$  over the projected baseline.  $IC_{90}$  is the drug dose necessary to achieve  $\Delta CT=3.2$  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 50304, 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.

[0588] In particular, the relative inhibition of replicon RNA was examined using the following anti-viral agents:

[0589] Formula 1a (at a concentration of 2.5 µM) in combination with 2'-methyl-adenosine (at a concentration of 0, 240, 600, or 1500 nM).

[0590] Formula 1a (at a concentration of 2.5 µM) in combination with indole-N-acetamide (at a concentration of 0, 2, 5, or 12.5 µM)

[0591] Formula 1a (at a concentration of 2.5 µM) in combination with benzothiadiazine (at a concentration of 0, 3.2, or 8 µM)

[0592] Formula 1 (i.e., SCH 446211 (SCH 6), at a concentration of 2.5 µM) in combination with ribavirin (at a concentration of 0, 8, 31, or 500 µM).

#### Replicon Mutation Identification

[0593] To identify mutations which conferred resistance to Formula Ia and polymerase inhibitors, total cellular RNA was isolated from pooled colonies and amplified by RT-PCR for the NS3 protease and NS5B polymerase region. The RT-PCR reactions were carried out following manufacturer's instructions (Titan One Tube RT-PCR, Boehringer Mannheim). Briefly, 0.5-1 µg of RNA was reverse transcribed at 50° C. for 30 min, followed by 94° C. for 3 min, 35 cycles of 94° C. for 30 sec, 55° C. for 30 sec, 68° C. for 2 min, and a final extension at 68° C. for 7 min. The RT-PCR products were purified using QIAquick PCR purification kit (Qiagen) and sequenced using CEQ 2000 Cycle Sequencing kit (Beckman Coulter). Alternatively, the RT-PCR products were cloned into TOPO TA vector (Invitrogen) and plasmid DNA from bacterial colonies was sequenced. The sequences were aligned using Lasergene software (DNASTAR). See Tong et al., "Identification and Analysis of Fitness of Resistance Mutations against the HCV Protease Inhibitor SCH 50304," *Antiviral Res*, 70(2):28-38 (2006), incorporated herein by reference.

**[0594]** The combination of Formula Ia with a nucleoside analog (e.g., 2'-methyl-adenosine) or allosteric non-nucleoside polymerase inhibitor (e.g., benzothiadiazine, indole-N-acetamide) was more efficacious in inhibiting HCV RNA replication than either agent alone (FIGS. 2, 3 and 4). Furthermore, the combination of 2'-methyl-adenosine or indole-N-acetamide at a concentration of  $1\times IC_{90}$  (i.e., 0.5  $\mu M$  and 2.5  $\mu M$ , respectively) with Formula Ia (at a concentration of  $5\times IC_{90}$ , i.e., 2.5  $\mu M$ ) reduced the frequency of resistant replicon colonies emerging by 3- and 15-fold respectively (FIG. 5). Moreover, when this combination was employed using an increased dose of polymerase inhibitor (i.e.,  $5\times IC_{90}$ ), the emergence of resistant variants was suppressed below detectable levels.

TABLE 1

<u>Sensitivity of replicon cells selected by combination treatment</u>				
Cells selected by	Inhibitor $IC_{50}$ in replicon cells			
	Formula Ia	2'-methyl-adenosine	indole-N-acetamide	IFN
No treatment	0.3 $\mu M$	1.1 $\mu M$	0.3 $\mu M$	3.7 U/ml
Formula Ia + 2'-methyl-adenosine	3.5 $\mu M$	NA	0.8 $\mu M$	9 U/ml
Formula Ia + Indole-N-acetamide	2.4 $\mu M$	1.4 $\mu M$	3 $\mu M$	3.1 U/ml

The  $IC_{50}$  values of replicon cells presented in Table 1 reflect that although these cells are resistant to both Formula Ia and the corresponding polymerase inhibitors (i.e., 2'-methyl-adenosine or indole-N-acetamide), they remain sensitive to treatment with Formula Ia in combination with the other HCV polymerase inhibitor (i.e., indole-N-acetamide or 2'-methyl-adenosine, respectively). Likewise, the replicon cells remain sensitive to treatment with IFN.

**[0595]** Mutations have been identified in replicons resistant to HCV protease inhibitor Formula Ia at replicon loci

T54, V170, and A156. Likewise, mutations have been identified in replicons resistant to HCV polymerase inhibitors 2'-methyl-adenosine and indole-N-acetamide at replicon loci S282 and P495, respectively.

**[0596]** The inventors believe that double mutants (i.e., with mutations in both HCV protease and HCV polymerase regions) are responsible for the emergence of replicon colonies resistant to the HCV protease inhibitor Formula Ia in combination with the HCV polymerase inhibitor 2'-methyl-adenosine or indole-N-acetamide. Nonetheless, as demonstrated in Table 1, replicon colonies resistant to treatment with Formula Ia in combination with 2'-methyl-adenosine are still sensitive to treatment with Formula Ia in combination with indole-N-acetamide. Likewise, replicon colonies resistant to treatment with Formula Ia in combination with indole-N-acetamide are still sensitive to treatment with Formula Ia in combination with 2'-methyl-adenosine. Despite resistance to either treatment mentioned above, all replicon colonies are still sensitive to interferon.

**[0597]** Likewise, in a similar study the combination of HCV protease inhibitor of Formula I (i.e., SCH 446211 (SCH 6)) with HCV polymerase inhibitor ribavirin, a nucleoside analog, was found to be more efficacious in inhibiting HCV RNA replication in replicon cells than HCV protease inhibitor SCH 446211 (SCH 6) alone (FIG. 6).

**[0598]** 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.

**[0599]** Each granted patent, published patent application, and nonpatent publication such as journal articles referred to in this application is incorporated in its entirety by reference for all purposes.

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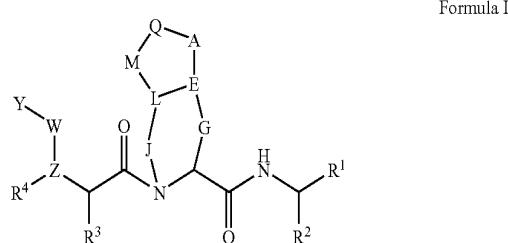
17

What is claimed is:

1. A medicament comprising, separately or together:

(a) at least one hepatitis C virus (HCV) protease inhibitor selected from the group consisting of a compound of Formula I to XXVI below:

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-amino, alkyl-aryl-amino, aryl-amino, heteroaryl-amino, cycloalkyl-amino and heterocycloalkyl-amino, with the proviso that Y maybe optionally substituted with X<sup>11</sup> or X<sup>12</sup>;

X<sup>11</sup> is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkyl-aryl, arylalkyl, heteroaryl, alkylheteroaryl, or heteroarylalkyl, with the proviso that X<sup>11</sup> may be additionally optionally substituted with X<sup>12</sup>;

X<sup>12</sup> is hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxy carbonylamino, alkoxy carbonyloxy, 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<sup>12</sup>;

R<sup>1</sup> is COR<sup>5</sup>, wherein R<sup>5</sup> is COR<sup>7</sup> wherein R<sup>7</sup> is NHR<sup>9</sup>, wherein R<sup>9</sup> is selected from the group consisting of H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, cycloalkyl, arylalkyl, heteroarylalkyl, [CH(R<sup>1'</sup>)<sub>p</sub>]COOR<sup>12</sup>R<sup>13</sup>, [CH(R<sup>1'</sup>)<sub>p</sub>]SO<sub>2</sub>R<sup>11</sup>, [CH(R<sup>1')</sup><sub>p</sub>]COR<sup>11</sup>, [CH(R<sup>1')</sup><sub>p</sub>]CH(OH)R<sup>11</sup>, CH(R<sup>1')</sup>CONHCH(R<sup>2')</sup>COOR<sup>11</sup>, CH(R<sup>1')</sup>CONHCH(R<sup>2')</sup>CONR<sup>12</sup>R<sup>13</sup>, CH(R<sup>1')</sup>CONHCH(R<sup>2')</sup>CONHCH(R<sup>3')</sup>CONHCH(R<sup>4')</sup>COOR<sup>11</sup>, CH(R<sup>1')</sup>CONHCH(R<sup>2')</sup>CONHCH(R<sup>3')</sup>CONHCH(R<sup>4')</sup>CONR<sup>12</sup>R<sup>13</sup>, CH(R<sup>1')</sup>CONHCH(R<sup>2')</sup>CONHCH(R<sup>3')</sup>CONHCH(R<sup>4')</sup>CONHCH(R<sup>5')</sup>COOR<sup>11</sup> and CH(R<sup>1')</sup>CONHCH(R<sup>2')</sup>CONHCH(R<sup>3')</sup>CONHCH(R<sup>4')</sup>CONHCH(R<sup>5')</sup>CONR<sup>12</sup>R<sup>13</sup>, wherein R<sup>1'</sup>, R<sup>2'</sup>, R<sup>3'</sup>, R<sup>4'</sup>, R<sup>5'</sup>, R<sup>11</sup>, R<sup>12</sup>, R<sup>13</sup>, 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<sub>2</sub>;Q maybe present or absent, and when Q is present, Q is CH, N, P, (CH<sub>2</sub>)<sub>p</sub>, (CHR)<sub>p</sub>, (CRR')<sub>p</sub>, O, NR, S, or SO<sub>2</sub>; 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<sub>2</sub>, (CHR)<sub>p</sub>, (CHR—CHR')<sub>p</sub>, (CRR')<sub>p</sub>, NR, S, SO<sub>2</sub> 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<sub>2</sub>)<sub>p</sub>, (CHR)<sub>p</sub>, or (CRR')<sub>p</sub>; 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<sub>2</sub>)<sub>p</sub>, (CHR)<sub>p</sub>, or (CRR')<sub>p</sub>, SO<sub>2</sub>, 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<sub>2</sub>, (CH<sub>2</sub>)<sub>p</sub>, (CHR)<sub>p</sub>(CHR—CHR')<sub>p</sub>, or (CRR')<sub>p</sub>;

p is a number from 0 to 6; and

R, R', R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are independently selected from the group consisting of H; C<sub>1</sub>-C<sub>10</sub> alkyl; C<sub>2</sub>-C<sub>10</sub> alkenyl; C<sub>3</sub>-C<sub>8</sub> cycloalkyl; C<sub>3</sub>-C<sub>8</sub> 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;

X<sup>1</sup> is H; C<sub>1</sub>-C<sub>4</sub> straight chain alkyl; C<sub>1</sub>-C<sub>4</sub> branched alkyl or; CH<sub>2</sub>-aryl (substituted or unsubstituted);

R<sup>12</sup> is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocycl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, heteroaryl, alkylheteroaryl, or heteroarylalkyl moiety, with the proviso that R<sup>12</sup> may be additionally optionally substituted with R<sup>13</sup>.

R<sup>13</sup> is hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxy carbonylamin, alkoxy carbonyloxy, alkylureido, alylureido, 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<sup>13</sup>.

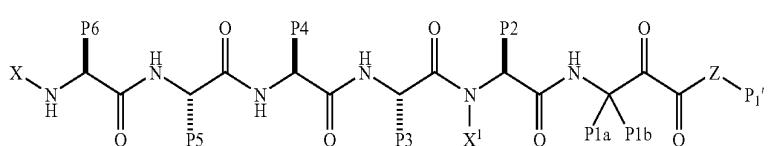
P1a, P1b, P2, P3, P4, P5, and P6 are independently: H; C<sub>1</sub>-C<sub>10</sub> straight or branched chain alkyl; C<sub>2</sub>-C<sub>10</sub> straight or branched chain alkenyl; C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>3</sub>-C<sub>8</sub> heterocyclic; (cycloalkyl)alkyl or (heterocycl)alkyl, 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, heterocycl; (cycloalkyl)alkyl and (heterocycl)alkyl moieties may be optionally substituted with R<sup>13</sup>, 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<sup>13</sup>; and

P1' is H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocycl, heterocycl-alkyl, aryl, aryl-

ii.



Formula II

or a pharmaceutically acceptable salt, solvate or ester thereof;

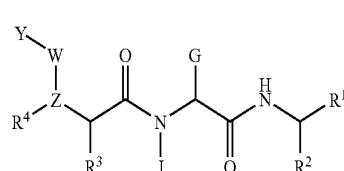
wherein in Formula II:

Z is NH;

X is alkylsulfonyl, heterocyclsulfonyl, heterocyclalkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylcarbonyl, heterocyclcarbonyl, heterocyclalkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxy carbonyl, heterocyclloxy carbonyl, aryloxy carbonyl, heteroaryl oxy carbonyl, alkyaminocarbonyl, heterocyclaminocarbonyl, arylaminocarbonyl, or heteroarylaminocarbonyl moiety, with the proviso that X may be additionally optionally substituted with R<sup>12</sup> or R<sup>13</sup>;

alkyl, heteroaryl, or heteroaryl-alkyl; with the proviso that said P1' may be additionally optionally substituted with R<sup>13</sup>;

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-aryl-amino, arylamino, heteroaryl-amino, cycloalkylamino and heterocycloalkylamino, with the proviso that Y maybe additionally optionally substituted with X<sup>11</sup> or X<sup>12</sup>;

X<sup>11</sup> 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<sup>11</sup> may be additionally optionally substituted with X<sup>12</sup>;

X<sup>12</sup> is hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxy carbonylamino, alkoxy carbonyloxy, 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<sup>12</sup>;

R<sup>1</sup> is COR<sup>5</sup> or B(OR)<sub>2</sub>, wherein R<sup>5</sup> is selected from the group consisting of H, OH, OR<sup>8</sup>, NR<sup>9</sup>R<sup>10</sup>, CF<sub>3</sub>, C<sub>2</sub>F<sub>5</sub>, C<sub>3</sub>F<sub>7</sub>, CF<sub>2</sub>R<sup>6</sup>, R<sup>6</sup> and COR<sup>7</sup> wherein R<sup>7</sup> is selected from the group consisting of H, OH, OR<sup>8</sup>, CHR<sup>9</sup>R<sup>10</sup>, and NR<sup>9</sup>R<sup>10</sup>, wherein R<sup>6</sup>, R<sup>8</sup>, R<sup>9</sup> and R<sup>10</sup> may be the same or different and are independently selected from the group consisting of H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, cycloalkyl, arylalkyl, heteroarylalkyl, heteroaryl, alkyl-heteroaryl, alkyl CONR<sup>11</sup>, CH(R<sup>1</sup>)COOR<sup>11</sup>, CH(R<sup>1</sup>)CONR<sup>12</sup>R<sup>13</sup>, CH(R<sup>1</sup>)CONHCH(R<sup>2</sup>)COOR<sup>11</sup>, CH(R<sup>1</sup>)CONHCH(R<sup>2</sup>)CONR<sup>12</sup>R<sup>13</sup>, CH(R<sup>1</sup>)CONHCH(R<sup>2</sup>)R<sup>1</sup>, CH(R<sup>1</sup>)CONHCH(R<sup>2</sup>)CONHCH(R<sup>3</sup>)COOR<sup>11</sup>, CH(R<sup>1</sup>)CONHCH(R<sup>2</sup>)CONHCH(R<sup>3</sup>)CONR<sup>12</sup>R<sup>13</sup>, CH(R<sup>1</sup>)CONHCH(R<sup>2</sup>)CONHCH(R<sup>3</sup>)CONHCH(R<sup>4</sup>)COOR<sup>11</sup>, CH(R<sup>1</sup>)CONHCH(R<sup>2</sup>)CONHCH(R<sup>3</sup>)CONHCH(R<sup>4</sup>)CONR<sup>12</sup>R<sup>13</sup>, CH(R<sup>1</sup>)CONHCH(R<sup>2</sup>)CONHCH(R<sup>3</sup>)CONHCH(R<sup>4</sup>)CONHCH(R<sup>5</sup>)COOR<sup>11</sup>, and CH(R<sup>1</sup>)CONHCH(R<sup>2</sup>)CONHCH(R<sup>3</sup>)CONHCH(R<sup>4</sup>)CONHCH(R<sup>5</sup>)CONR<sup>12</sup>R<sup>13</sup>, wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>11</sup>, R<sup>12</sup>, R<sup>13</sup>, and R<sup>1</sup> 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, arylalkyl 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<sub>2</sub>; and

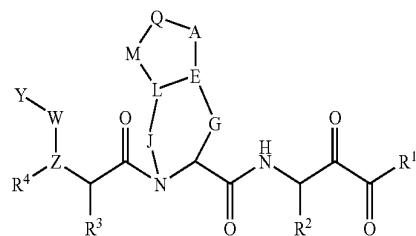
R, R', R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are independently selected from the group consisting of H; C1-C10 alkyl; C2-C10 alkenyl; C3-C8 cycloalkyl; C3-C8 heterocycloalkyl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, 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:

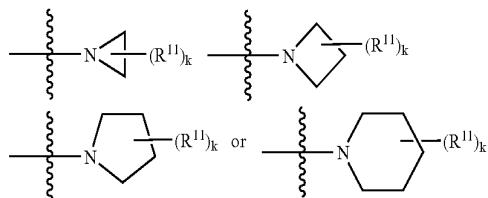
Y is selected from the group consisting of the following moieties: alkyl, alkyl-aryl, heteroalkyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyloxy, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocycloalkyloxy, cycloalkyloxy, alkylamino, arylamino, alkyl-aryl-amino, arylamino, heteroaryl-amino,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

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

X<sup>12</sup> 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<sup>12</sup>;

R<sup>1</sup> is selected from the following structures:



wherein k is a number from 0 to 5, which can be the same or different, R<sup>11</sup> 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, alkyl oxy, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocycloalkyloxy, cycloalkyloxy, alkylamino, arylamino, alkyl-aryl amino, arylamino, heteroaryl amino, cycloalkylamino, heterocycloalkylamino, hydroxy, thio, alkylthio, arylthio, amino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxyl, carbalkoxy, carboxamido, alkoxy carbonylamino, alkoxy carbonyloxy, alkylureido, arylureido, halogen, cyano, and nitro, with the proviso that R<sup>11</sup> (when R<sup>11</sup> ≠ H) maybe optionally substituted with X or X<sup>12</sup>;

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<sub>2</sub>);

Q may be present or absent, and when Q is present, Q is CH, N, P, (CH<sub>2</sub>)<sub>p</sub>, (CHR)<sub>p</sub>, (CRR')<sub>p</sub>, O, N(R), S, or S(O<sub>2</sub>); 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<sub>2</sub>, (CHR)<sub>p</sub>, (CHR—CHR')<sub>p</sub>(CRR')<sub>p</sub>, N(R), S, S(O<sub>2</sub>) 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<sub>2</sub>)<sub>p</sub>, (CHR)<sub>p</sub>, or (CRR')<sub>p</sub>; 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<sub>2</sub>)<sub>p</sub>, (CHR)<sub>p</sub>, or (CRR')<sub>p</sub>, S(O<sub>2</sub>), 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<sub>2</sub>), (CH<sub>2</sub>)<sub>p</sub>, (CHR)<sub>p</sub>(CHR—CHR')<sub>p</sub>, or (CRR')<sub>p</sub>;

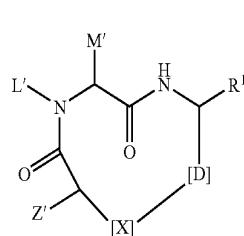
p is a number from 0 to 6; and

R, R', R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> can be the same or different, each being independently selected from the group consisting of H; C<sub>1</sub>-C<sub>10</sub> alkyl; C<sub>2</sub>-C<sub>10</sub> alkenyl; C<sub>3</sub>-C<sub>8</sub> cycloalkyl; C<sub>3</sub>-C<sub>8</sub> 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<sup>1</sup> is —C(O)R<sup>5</sup> or —B(OR)<sub>2</sub>;
- (2) R<sup>5</sup> is H, —OH, —OR<sup>8</sup>, —NR<sup>9</sup>R<sup>10</sup>, —C(O)OR<sup>3</sup>, —C(O)NR<sup>9</sup>R<sup>10</sup>, —CF<sub>3</sub>, —C<sub>2</sub>F<sub>5</sub>, C<sub>3</sub>F<sub>7</sub>, —CF<sub>2</sub>R<sup>6</sup>, —R<sup>6</sup>, —C(O)R<sup>7</sup> or NR<sup>7</sup>SO<sub>2</sub>R<sup>8</sup>;
- (3) R<sup>7</sup> is H, —OH, —OR<sup>8</sup>, or —CHR<sup>9</sup>R<sup>10</sup>;
- (4) R<sup>6</sup>, R<sup>8</sup>, R<sup>9</sup> and R<sup>10</sup> are independently selected from the group consisting of H: alkyl, alkenyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, arylalkyl, heteroarylalkyl, R<sup>14</sup>, —CH(R<sup>1</sup>)CH(R<sup>1</sup>)C(O)OR<sup>11</sup>, [CH(R<sup>1</sup>)<sub>p</sub>C(O)OR<sup>11</sup>], —[CH(R<sup>1</sup>)<sub>p</sub>C(O)NR<sup>12</sup>R<sup>13</sup>], —[CH(R<sup>1</sup>)<sub>p</sub>S(O<sub>2</sub>)R<sup>11</sup>],

$-\text{[CH(R}^1\text{)]}_p\text{C(O)R}^{11}$ ,  $-\text{[CH(R}^1\text{)]}_p\text{S(O}_2\text{)NR}^{12}\text{R}^{13}$ ,  
 $\text{CH(R}^1\text{)C(O)N(H)CH(R}^2\text{)(R}^1\text{)}$ ,  
 $\text{CH(R}^1\text{)CH(R}^1\text{)C(O)NR}^{12}\text{R}^{13}$ ,  
 $-\text{CH(R}^1\text{)CH(R}^1\text{)S(O}_2\text{)R}^{11}$ ,  
 $-\text{CH(R}^1\text{)CH(R}^1\text{)S(O}_2\text{)NR}^{12}\text{R}^{13}$ ,  
 $-\text{CH(R}^1\text{)CH(R}^1\text{)C(O)R}^{11}$ ,  $-\text{[CH(R}^1\text{)]}_p\text{CH(OH)R}^{11}$ ,  
 $-\text{CH(R}^1\text{)C(O)N(H)CH(R}^2\text{)C(O)OR}^{11}$ ,  
 $\text{C(O)N(H)CH(R}^2\text{)C(O)OR}^{11}$ ,  
 $-\text{C(O)N(H)CH(R}^2\text{)C(O)R}^{11}$ ,  
 $\text{CH(R}^1\text{)C(O)N(H)CH(R}^2\text{)C(O)NR}^{12}\text{R}^{13}$ ,  
 $-\text{CH(R}^1\text{)C(O)N(H)CH(R}^2\text{)R}^1$ ,  
 $\text{CH(R}^1\text{)C(O)N(H)CH(R}^2\text{)C(O)N(H)CH(R}^3\text{)C(O)$   
 $\text{OR}^{11}$ ,  $\text{CH(R}^1\text{)C(O)N(H)CH(R}^2\text{)C(O)CH(R}^3\text{)}$   
 $\text{NR}^{12}\text{R}^{13}$ ,  $\text{CH(R}^1\text{)C(O)N(H)CH(R}^2\text{)C(O)N(H)CH}$   
 $(\text{R}^3\text{)}\text{C(O)NR}^{12}\text{R}^{13}$ ,  $\text{CH(R}^1\text{)C(O)N(H)CH(R}^2\text{)C(O)CH(R}^3\text{)}$   
 $(\text{O})\text{N(H)CH(R}^3\text{)C(O)N(H)CH(R}^4\text{)C(O)OR}^{11}$ ,  
 $\text{H(R}^1\text{)C(O)N(H)CH(R}^2\text{)C(O)N(H)CH(R}^3\text{)C(O)N(H)$   
 $\text{CH(R}^4\text{)C(O)NR}^{12}\text{R}^{13}$ ,  $\text{CH(R}^1\text{)C(O)N(H)CH(R}^2\text{)}$   
 $\text{C(O)N(H)CH(R}^3\text{)C(O)N(H)CH(R}^4\text{)C(O)N(H)CH}$   
 $(\text{R}^5\text{)}\text{C(O)OR}^{11}$ , and  $\text{CH(R}^1\text{)C(O)N(H)CH(R}^2\text{)}$   
 $\text{C(O)N(H)CH(R}^3\text{)C(O)N(H)CH(R}^4\text{)C(O)N(H)CH}$   
 $(\text{R}^5\text{)}\text{C(O)NR}^{12}\text{R}^{13}$ ;

wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>11</sup>, R<sup>12</sup> and R<sup>13</sup> 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<sup>12</sup> and R<sup>13</sup> are linked together wherein the combination is cycloalkyl, heterocycloalkyl, ary or heteroaryl;

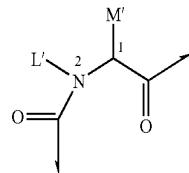
R<sup>14</sup> is present or not and if present is selected from the group consisting of: H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, alkyl-aryl, allyl, alkyl-heteroaryl, alkoxy, aryl-alkyl, alkenyl, alkynyl and heteroaralkyl;

(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<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>2</sub>-C<sub>10</sub> alkenyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>3</sub>-C<sub>8</sub> 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, alkyl-heteroaryl, 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;

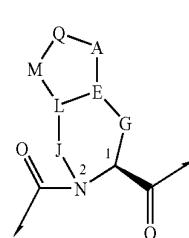
(6) L' is H, OH, alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, or heterocyclyl;

(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<sub>2</sub>)<sub>p</sub>, (CHR—CHR')<sub>p</sub>, (CHR)<sub>p</sub>, (CRR')<sub>p</sub>, S(O<sub>2</sub>), 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;

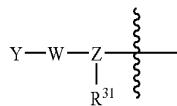
G is present or absent, and when G is present, G is (CH<sub>2</sub>)<sub>p</sub>, (CHR)<sub>p</sub>, (CHR—CHR')<sub>p</sub> or (CRR')<sub>p</sub>; when G is absent, J is present and E is directly connected to the carbon atom marked position 1;

Q is present or absent, and when Q is present, Q is NR, PR, (CR=CR), (CH<sub>2</sub>)<sub>p</sub>, (CHR)<sub>p</sub>, (CRR')<sub>p</sub>, (CHR—CHR')<sub>p</sub>, O, NR, S, SO, or SO<sub>2</sub>; when Q is absent, M is (i) either directly linked to A or (ii) an independent substituent on L, said independent substituent being selected from —OR, —CH(R)(R'), S(O)<sub>2</sub>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 being selected from —OR, —CH(R)(R'), S(O)<sub>2</sub>R or —NRR' or A is absent;

A is present or absent and if present A is O, O(R), (CH<sub>2</sub>)<sub>p</sub>, (CHR)<sub>p</sub>, (CHR—CHR')<sub>p</sub>, (CRR')<sub>p</sub>, N(R), NRR', S, S(O<sub>2</sub>), —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<sub>2</sub>), (CH<sub>2</sub>)<sub>p</sub>, (CHR)<sub>p</sub>(CHR—CHR')<sub>p</sub>, or (CRR')<sub>p</sub>; 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<sup>11</sup> or X<sup>12</sup>;

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

X<sup>12</sup> 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, sulfonyleurea, 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);

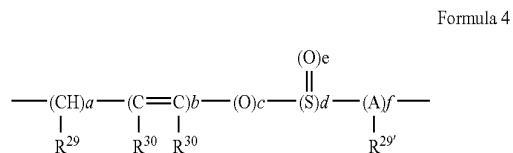
R<sup>31</sup> is H, hydroxyl, aryl, alkyl, alkyl-aryl, heteroalkyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyloxy, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocycloalkyloxy, heteroalkyl-heteroaryl, cycloalkyloxy, alkylamino, arylamino, alkyl-arylamino, arylamino, heteroarylamino,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

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

X<sup>14</sup> 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, heteroarylalkylsulfonamido, 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;

W may be present or absent, and if W is present, W is C(=O), C(=S), C(=N—CN), or S(O<sub>2</sub>);

(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;

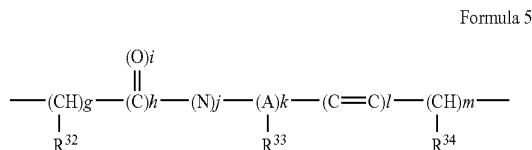
A is C, N, S or O;

R<sup>29</sup> and R<sup>29'</sup> 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)<sub>2</sub>, carboxyl, C(O)O-alkyl, heteroaryl, aralkyl, alkylaryl, aralkenyl, heteroaralkyl, alkylheteroaryl, heteroaralkenyl, hydroxyalkyl, aryloxy, aralkoxy, acyl, aroyl, nitro, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroaryl-sulfonyl, alkylsulfinyl, arylsulfinyl, heteroaryl-sulfinyl, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkenyl, heterocyclyl, heterocyclyl, Y<sub>1</sub>Y<sub>2</sub>N-alkyl-, Y<sub>1</sub>Y<sub>2</sub>NC(O)— and Y<sub>1</sub>Y<sub>2</sub>NSO<sub>2</sub>—, wherein Y<sub>1</sub> and Y<sub>2</sub> can be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, and aralkyl; or

R<sup>29</sup> and R<sup>29'</sup> are linked together such that the combination is an aliphatic or heteroaliphatic chain of 0 to 6 carbons;

R<sup>30</sup> is present or absent and if present is one or two substituents independently selected from the group consisting of: H, alkyl, aryl, heteroaryl and cycloalkyl;

(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, hydroxylalkyl, aryloxy, aralkoxy, acyl, aroyl, nitro, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, arylsulfinyl, heteroarylsulfinyl, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkenyl, heterocycl, heterocyclenyl,  $Y_1 Y_2 N$ -alkyl,  $Y_1 Y_2 NC(O)-$  and  $Y_1 Y_2 NSO_2-$ , 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

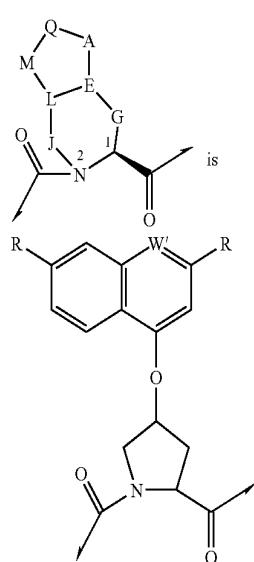
$R^{32}$  and  $R^{34}$  are linked together such that the combination forms a portion of a cycloalkyl group;

$g$  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:



and

$W'$  is CH or N, both the following conditional exclusions

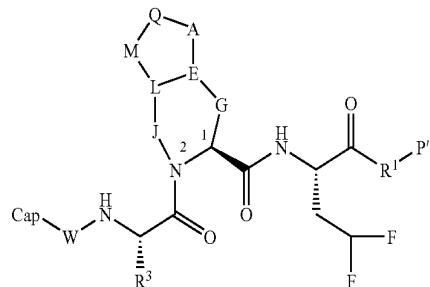
(i) and (ii) apply: conditional exclusion (i):  $Z'$  is not  $-NH-R^{36}$ , wherein  $R^{36}$  is H,  $C_{6-10}$  aryl, heteroaryl,  $-C(O)-R^{37}$ ,  $-C(O)-OR^{37}$  or  $-C(O)-NHR^{37}$ , wherein  $R^{37}$  is  $C_{1-6}$  alkyl or  $C_{3-6}$  cycloalkyl;

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,  $C_{6-10}$  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, heterocyclcloxy, cycloalkyloxy, amino, alkylamino, arylamino, alkyl-arylarnino, arylamino, heteroarylarnino, cycloalkylarnino, carboxyalkylarnino, arylalkyloxy or heterocyclarnino, wherein each of said alkyl, alkyl-aryl, heteroalkyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyloxy, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocyclcloxy, cycloalkyloxy, amino, alkylamino, arylamino, alkyl-arylarnino, arylamino, heteroarylarnino, cycloalkylarnino, carboxyalkylarnino, arylalkyloxy or heterocyclarnino 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, heterocycl, heterocyclalkyl, aryl, alkylaryl, arylalkyl, arylheteroaryl, heteroaryl, heterocyclamino, 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, alkyl-

sulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxy carbonylamino, alkoxy carbonyloxy, 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, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, arylheteroaryl, heteroaryl, heterocyclamino, 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<sub>2</sub>);

Q maybe present or absent, and when Q is present, Q is N(R), P(R), CR=CR', (CH<sub>2</sub>)<sub>p</sub>, (CHR)<sub>p</sub>, (CRR')<sub>p</sub>, (CHR—CHR')<sub>p</sub>, O, S, S(O) or S(O<sub>2</sub>); 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)<sub>0-2</sub>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)<sub>0-2</sub>R or —NRR';

A is present or absent and if present A is —O—, —O(R)CH<sub>2</sub>—, —(CHR)<sub>p</sub>—, —(CHR—CHR')<sub>p</sub>—, (CRR')<sub>p</sub>, N(R), NRR', S, or S(O<sub>2</sub>), 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<sub>2</sub>)<sub>p</sub>, (CHR)<sub>p</sub>, or (CRR')<sub>p</sub>; 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<sub>2</sub>)<sub>p</sub>, (CHR—CHR')<sub>p</sub>, (CHR)<sub>p</sub>, (CRR')<sub>p</sub>, S(O<sub>2</sub>), 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<sub>2</sub>), (CH<sub>2</sub>)<sub>p</sub>, (CHR)<sub>p</sub>, (CHR—CHR')<sub>p</sub>, or (CRR')<sub>p</sub>;

p is a number from 0 to 6;

R, R' and R<sup>3</sup> can be the same or different, each being independently selected from the group consisting of: H, C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>2</sub>-C<sub>10</sub> alkenyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>3</sub>-C<sub>8</sub> heterocyclyl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, arylthioamino, arylcarbonylamino, arylaminocarboxy, alkylaminocarboxy, heteroalkyl, heteroalkenyl, alkenyl, alkynyl, aryl-alkyl, heteroarylalkyl, ester, carboxylic acid, carbamate,

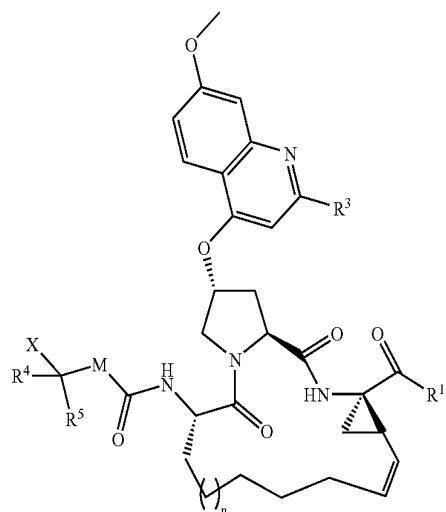
urea, ketone, aldehyde, cyano, nitro, halogen, (cycloalkyl)alkyl, aryl, heteroaryl, alkyl-aryl, alkyl-heteroaryl, alkyl-heteroaryl and (heterocyclyl)alkyl;

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

R<sup>1</sup> is carbonyl;

vii.

Formula VII



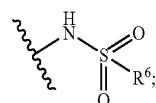
or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula VII:

M is O, N(H), or CH<sub>2</sub>;

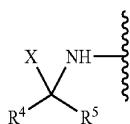
n is 0-4;

R<sup>1</sup> is —OR<sup>6</sup>, —NR<sup>6</sup>R<sup>7</sup> or

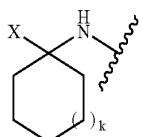


where R<sup>6</sup> and R<sup>7</sup> can be the same or different, each being independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, hydroxyl, amino,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

R<sup>4</sup> and R<sup>5</sup> can be the same or different, each being independently selected from the group consisting of H, alkyl, aryl and cycloalkyl; or alternatively R<sup>4</sup> and R<sup>5</sup> together form part of a cyclic 5- to 7-membered ring such that the moiety

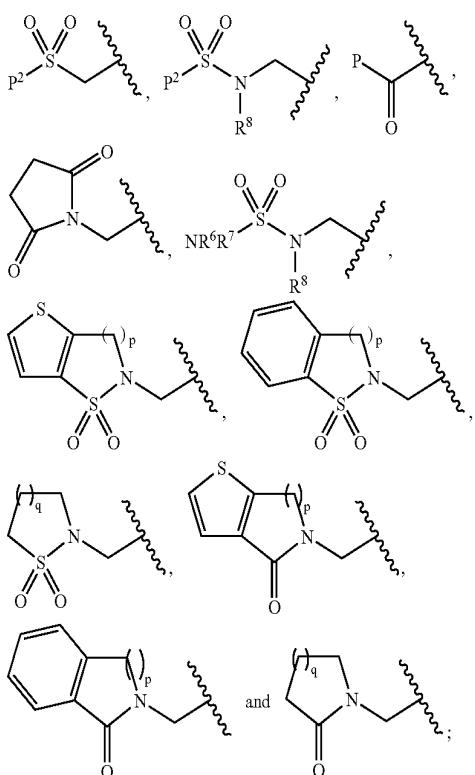


is represented by



where k is 0 to 2;

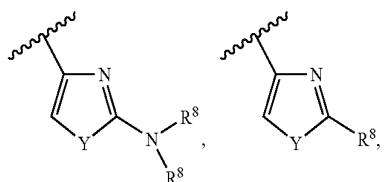
X is selected from the group consisting of:



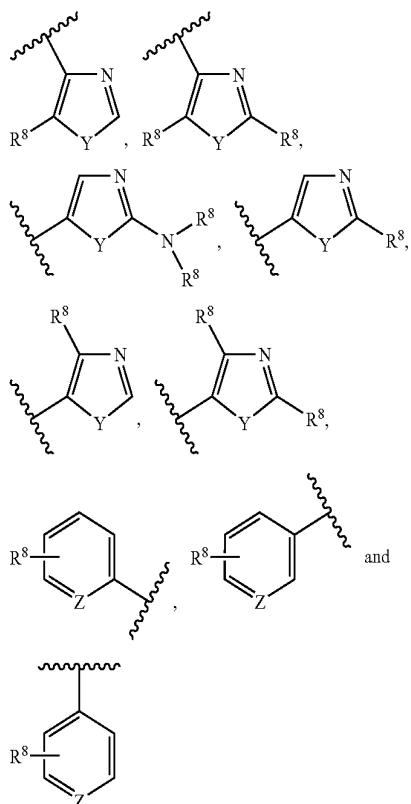
where p is 1 to 2, q is 1-3 and P<sup>2</sup> is alkyl, aryl, heteroaryl, heteroalkyl, cycloalkyl, dialkylamino, alkylamino, arylamino or cycloalkylamino;

and

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



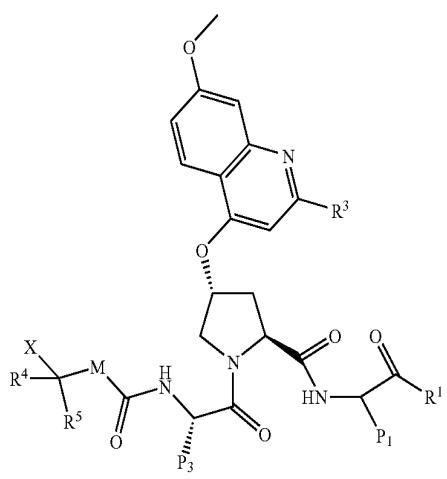
-continued



where Y is O, S or NH, and Z is CH or N, and the R<sup>8</sup> moieties can be the same or different, each R<sup>8</sup> 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:

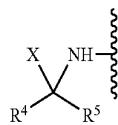
M is O, N(H), or CH<sub>2</sub>;

R<sup>1</sup> is —C(O)NHR<sup>6</sup>, where R<sup>6</sup> is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycl, heterocyclalkyl, hydroxyl, amino, arylamino or alkylamino;

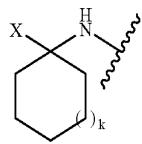
P<sub>1</sub> is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl haloalkyl;

P<sub>3</sub> is selected from the group consisting of alkyl, cycloalkyl, aryl and cycloalkyl fused with aryl;

R<sup>4</sup> and R<sup>5</sup> can be the same or different, each being independently selected from the group consisting of H, alkyl, aryl and cycloalkyl; or alternatively R<sup>4</sup> and R<sup>5</sup> together form part of a cyclic 5- to 7-membered ring such that the moiety

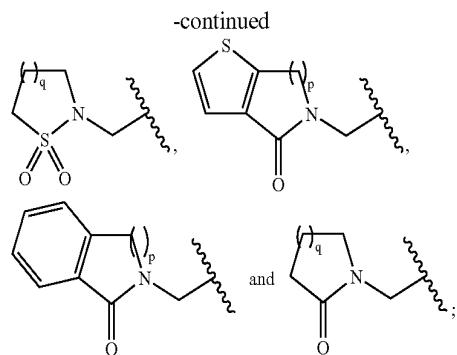
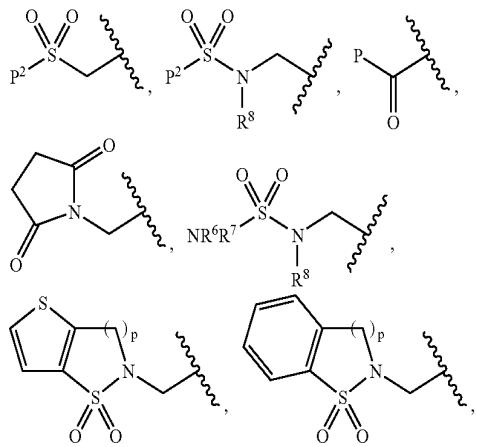


is represented by



where k is 0 to 2;

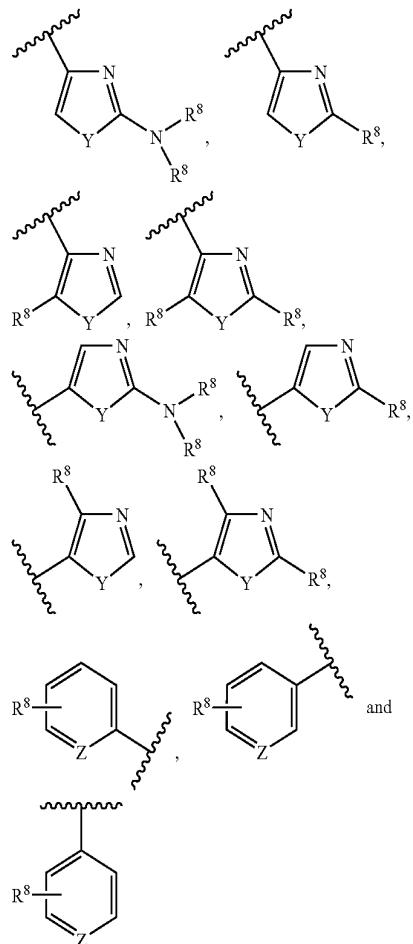
X is selected from the group consisting of:



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

and

R<sup>3</sup> is selected from the group consisting of: aryl, heterocycl, heteroaryl,

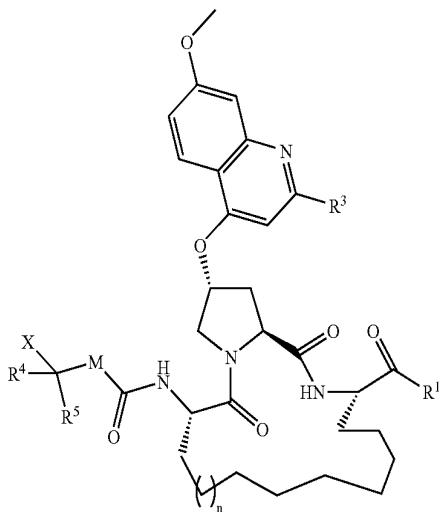


where Y is O, S or NH, and Z is CH or N, and the R<sup>8</sup> moieties can be the same or different, each R<sup>8</sup> being independently selected from the group consisting of hydrogen, alkyl, heteroalkyl, cycloalkyl, aryl, het-

eroaryl, heterocyclyl, hydroxyl, amino, arylamino, alkylamino, dialkylamino, halo, alkylthio, arylthio and alkyloxy;

ix.

### Formula IX



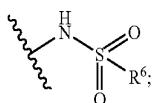
or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula IX:

M is O, N(H), or CH<sub>2</sub>;

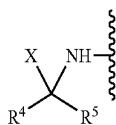
n is 0-4;

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

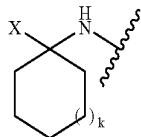


where R<sup>6</sup> and R<sup>7</sup> can be the same or different, each being independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycyl, heterocyclylalkyl, hydroxyl, amino, 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

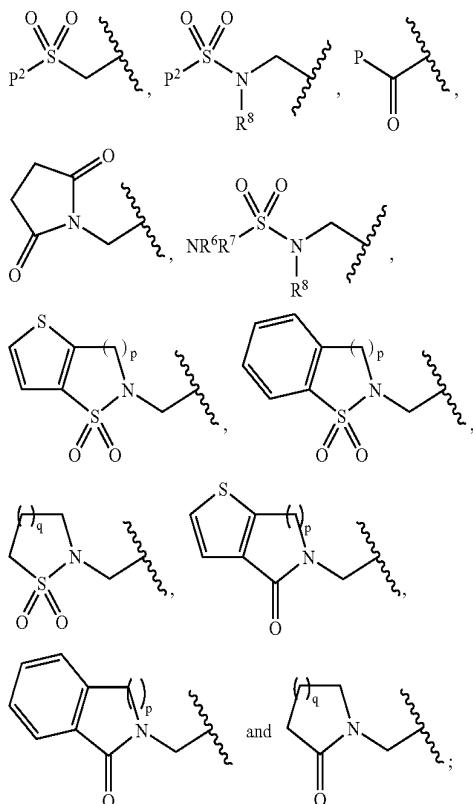


is represented by



where k is 0 to 2;

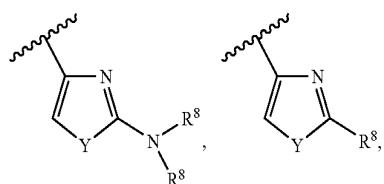
X is selected from the group consisting of:

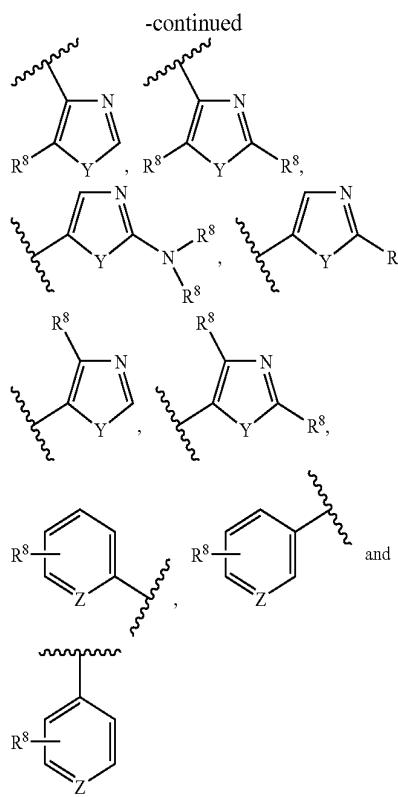


where p is 1 to 2, q is 1 to 3 and P<sup>2</sup> is alkyl, aryl, heteroaryl, heteroalkyl, cycloalkyl, dialkylamino, alkylamino, arylamino or cycloalkylamino;

and

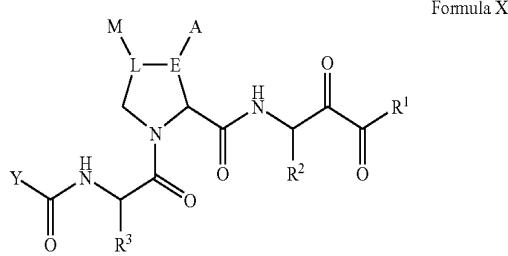
$R^3$  is selected from the group consisting of: aryl, heterocyclyl, heteroaryl,





where Y is O, S or NH, and Z is CH or N, and the R<sup>8</sup> moieties can be the same or different, each R<sup>8</sup> 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.

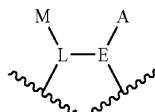


or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula X:

R<sup>1</sup> is NHR<sup>9</sup>, wherein R<sup>9</sup> 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<sub>2</sub>R, and halo; or A and M are connected to each other such that the moiety:



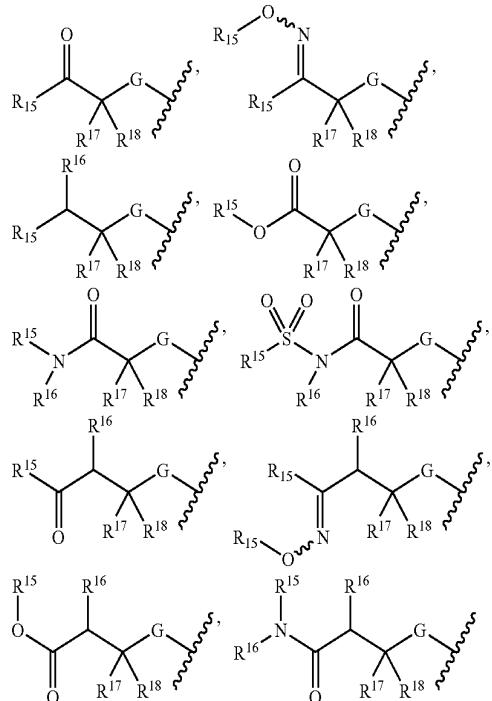
shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl;

E is C(H) or C=;

L is C(H), C=, CH<sub>2</sub>C=, or C=CH<sub>2</sub>;

R, R', R<sup>2</sup>, and R<sup>3</sup> 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:

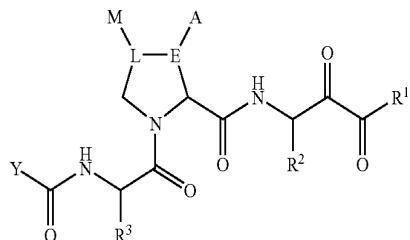


wherein G is NH or O; and R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup> and R<sup>18</sup> can be the same or different, each being independently selected from the group consisting of H, alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, or alternately, R<sup>15</sup> and R<sup>16</sup> are connected to each other to form a four to eight-membered cycloalkyl, heteroaryl or heterocyclyl structure, and likewise, independently R<sup>17</sup> and R<sup>18</sup> are connected to each other to form a three to eight-membered cycloalkyl or heterocyclyl;

wherein each of said alkyl, aryl, heteroaryl, cycloalkyl or heterocycl 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, alkoxy carbonylamino, alkoxy carbonyloxy, alkylureido, arylureido, halo, cyano, and nitro;

xi.

Formula XI

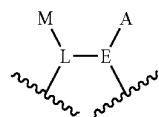


or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XI:

R<sup>1</sup> is NHR<sup>9</sup>, wherein R<sup>9</sup> is H, alkyl-, alkenyl-, alkynyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, heterocycl-, arylalkyl-, or heteroarylalkyl;

A and M can be the same or different, each being independently selected from R, NR<sup>9</sup>R<sup>10</sup>, SR, SO<sub>2</sub>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:



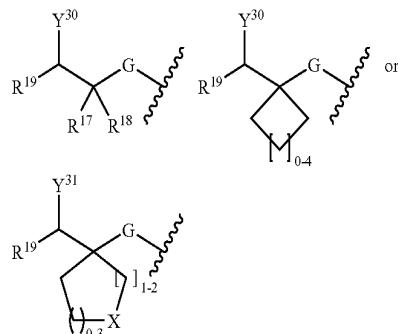
shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocycl, a six to ten-membered aryl, or a five to ten-membered heteroaryl;

E is C(H) or C=;

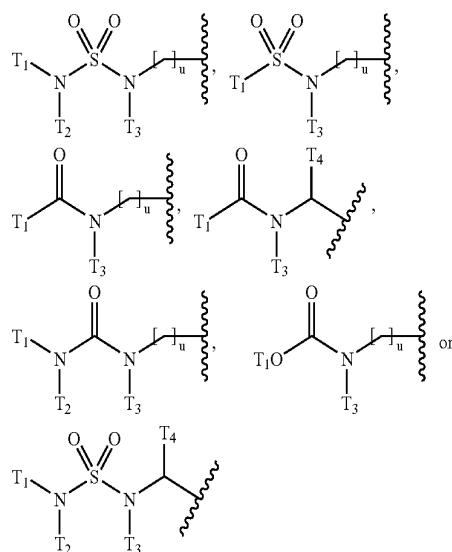
L is C(H), C=, CH<sub>2</sub>C=, or C=CH<sub>2</sub>;

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

Y is selected from the following moieties:



wherein Y<sup>30</sup> and Y<sup>31</sup> are selected from



where u is a number 0-6;

X is selected from O, NR<sup>15</sup>, NC(O)R<sup>16</sup>, S, S(O) and SO<sub>2</sub>;

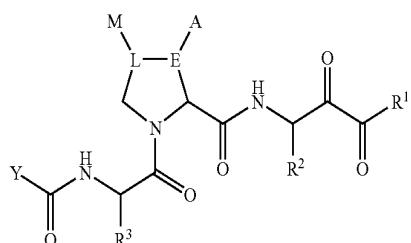
G is NH or O; and

R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup>, R<sup>18</sup>, R<sup>19</sup>, T<sub>1</sub>, T<sub>2</sub>, T<sub>3</sub> and T<sub>4</sub> can be the same or different, each being independently selected from the group consisting of H, alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, cycloalkyl, heterocycl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, or alternately, R<sup>17</sup> and R<sup>18</sup> are connected to each other to form a three to eight-membered cycloalkyl or heterocycl;

wherein each of said alkyl, aryl, heteroaryl, cycloalkyl or heterocycl 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, alkoxy carbonylamino, alkoxy carbonyloxy, alkylureido, arylureido, halo, cyano, and nitro;

xii.

Formula XII

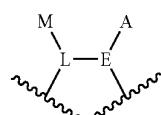


or a pharmaceutically acceptable salt, solvate or ester thereof;

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:



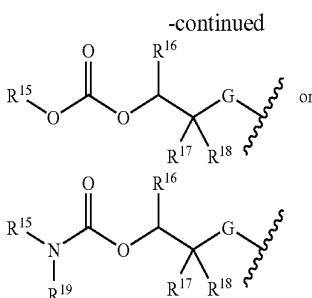
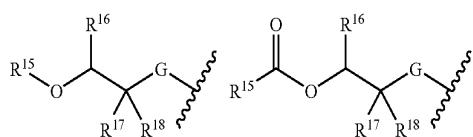
shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl;

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;

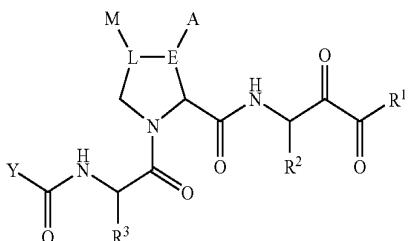
and Y is selected from the following moieties:



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: sulfonam, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, amido, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, sulfonamide, alkylsulfonamido, arylsulfonamido, alkyl, aryl, heteroaryl, keto, carboxy, carbalkoxy, carboxamido, alkoxy carbonylamino, alkoxy carbonyloxy, alkylureido, arylureido, halo, cyano, and nitro;

xiii.

Formula XIII

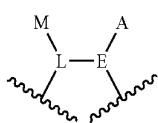


or a pharmaceutically acceptable salt, solvate or ester thereof;

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:



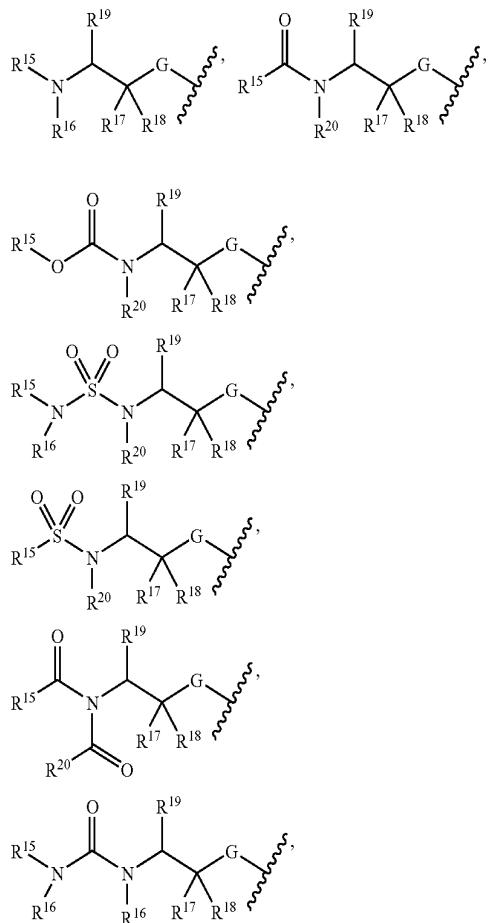
shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl;

E is C(H) or C=;

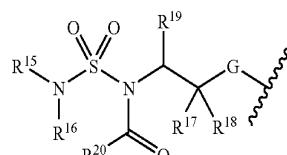
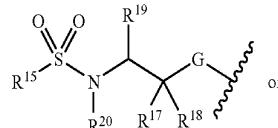
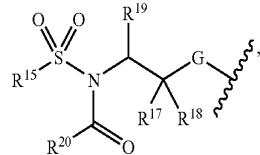
L is C(H), C=, CH<sub>2</sub>C=, or C=CH<sub>2</sub>;

R, R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> 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<sup>1</sup> in NRR<sup>1</sup> are connected to each other such that NRR<sup>1</sup> forms a four to eight-membered heterocyclyl;

and Y is selected from the following moieties:



-continued

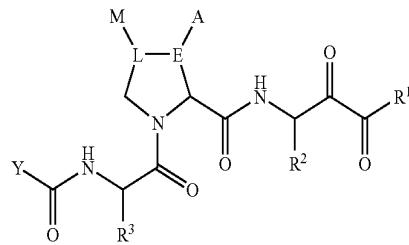


wherein G is NH or O, and R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup>, R<sup>18</sup>, R<sup>19</sup> and R<sup>20</sup> can be the same or different, each being independently selected from the group consisting of H, C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>1</sub>-C<sub>10</sub> heteroalkyl, C<sub>2</sub>-C<sub>10</sub> alkenyl, C<sub>2</sub>-C<sub>10</sub> heteroalkenyl, C<sub>2</sub>-C<sub>10</sub> alkynyl, C<sub>2</sub>-C<sub>10</sub> heteroalkynyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>3</sub>-C<sub>8</sub> heterocyclyl, aryl, heteroaryl, or alternately: (i) either R<sup>15</sup> and R<sup>16</sup> can be connected to each other to form a four to eight-membered cycloalkyl or heterocyclyl, or R<sup>15</sup> and R<sup>19</sup> are connected to each other to form a five to eight-membered cycloalkyl or heterocyclyl, or R<sup>15</sup> and R<sup>20</sup> are connected to each other to form a five to eight-membered cycloalkyl or heterocyclyl, and (ii) likewise, independently, R<sup>17</sup> and R<sup>18</sup> 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, alkoxy carbonylamino, alkoxy carbonyloxy, alkylureido, arylureido, halo, cyano, and nitro;

xiv.

Formula XIV



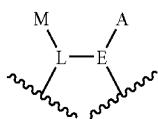
or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XIV:

$R^1$  is  $NHR^9$ , wherein  $R^9$  is H, alkyl-, alkenyl-, alkynyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, heterocycl-, 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:



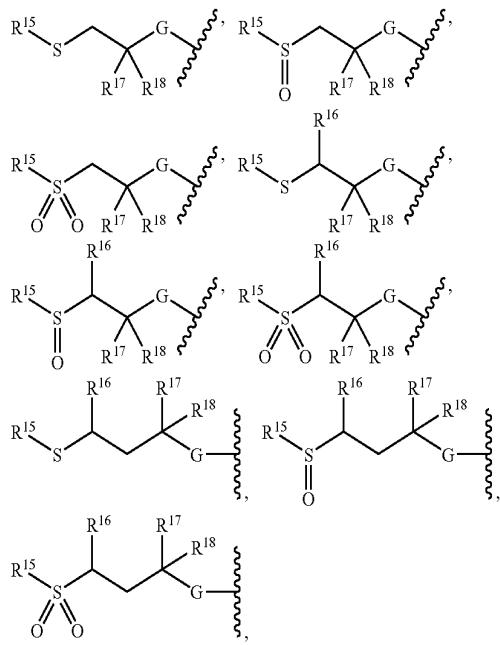
shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocycl, a six to ten-membered aryl, or a five to ten-membered heteroaryl;

E is C(H) or C=;

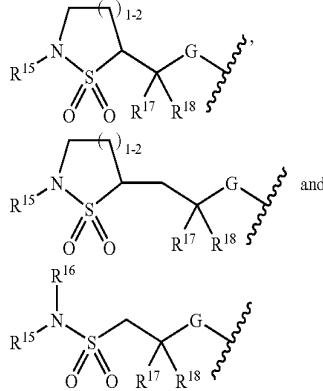
L is C(H), C=,  $CH_2C=$ , or  $C=CH_2$ ;

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

and Y is selected from the following moieties:



-continued

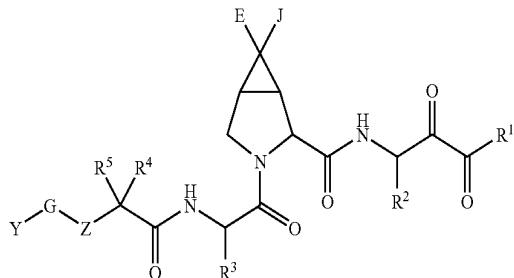


wherein G is NH or O; and  $R^{15}$ ,  $R^{16}$ ,  $R^{17}$  and  $R^{18}$  can be the same or different, each being independently selected from the group consisting of H, alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, cycloalkyl, heterocycl, aryl, and heteroaryl, or alternately,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

wherein each of said alkyl, aryl, heteroaryl, cycloalkyl or heterocycl 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, alkoxy carbonylamino, alkoxy carbonyloxy, alkylureido, arylureido, halo, cyano, and nitro;

xv.

Formula XV



or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XV:

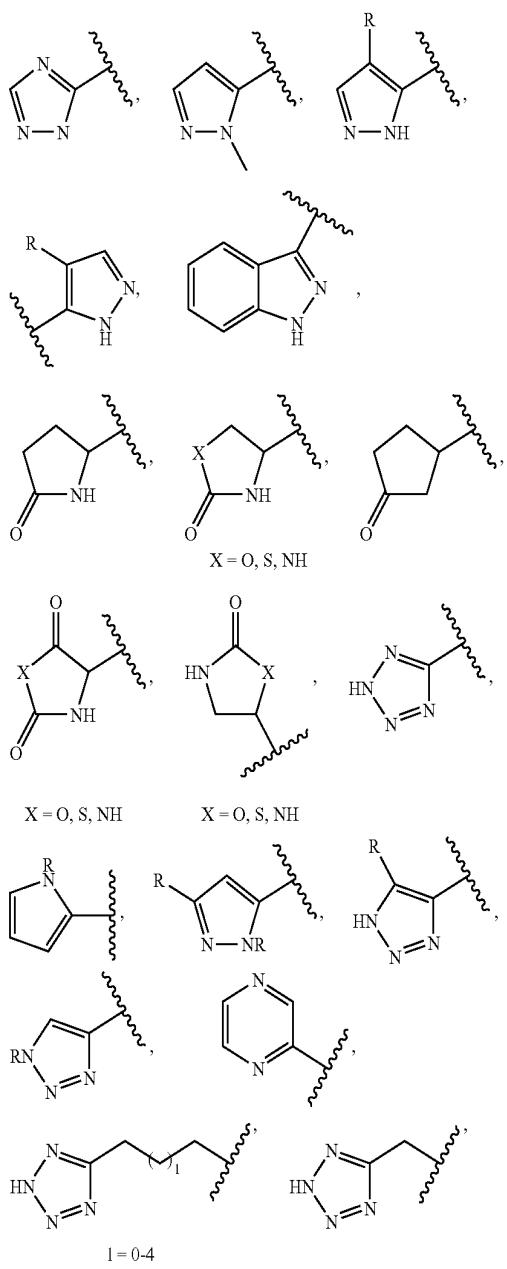
$R^1$  is  $NHR^9$ , wherein  $R^9$  is H, alkyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, cycloalkyl-, arylalkyl-, or heteroarylalkyl;

E and J can be the same or different, each being independently selected from the group consisting of R, OR, NHR, NRR<sup>7</sup>, SR, halo, and S(O<sub>2</sub>)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;

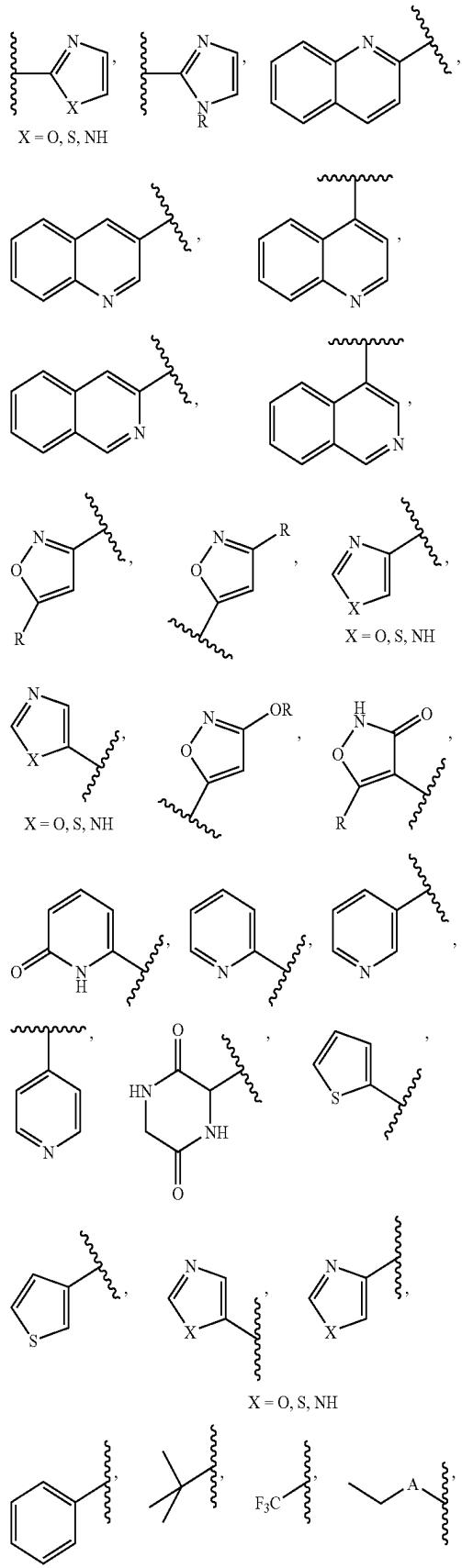
Z is N(H), N=, or O, with the proviso that when Z is O, G is present or absent and if G is present with Z being O, then G is C(=O);

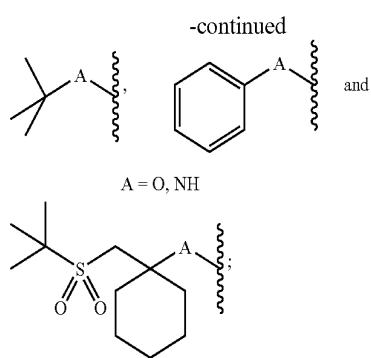
G maybe present or absent, and if G is present, G is C(=O) or S(O<sub>2</sub>), and when G is absent, Z is directly connected to Y;

Y is selected from the group consisting of:



-continued



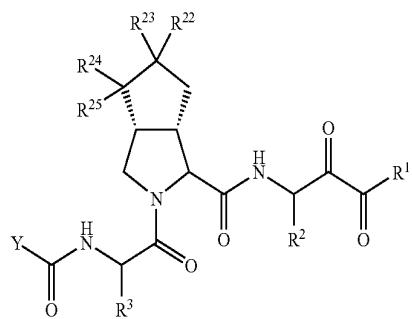


$R, R^7, R^2, R^3, R^4$  and  $R^5$  can be the same or different, each being independently selected from the group consisting of H, alkyl-, alkenyl-, alkynyl-, cycloalkyl-, heteroalkyl-, heterocyclyl-, aryl-, heteroaryl-, (cycloalkyl)alkyl-, (heterocyclyl)alkyl-, aryl-alkyl-, and heteroaryl-alkyl-, 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;

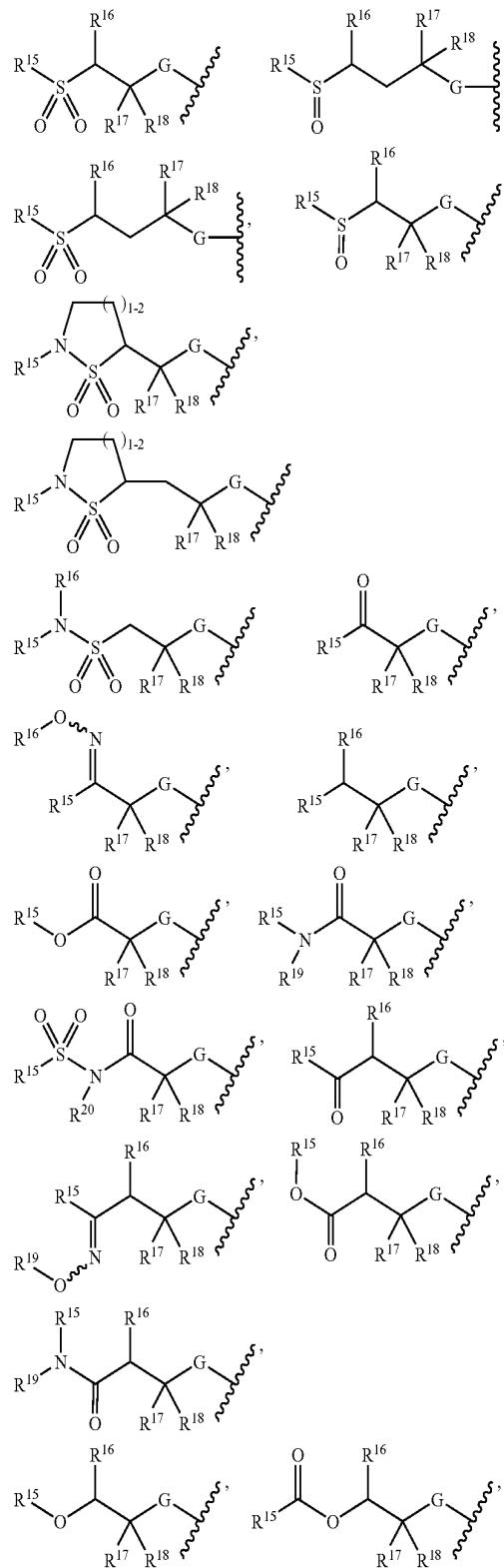
wherein in Formula XVI:

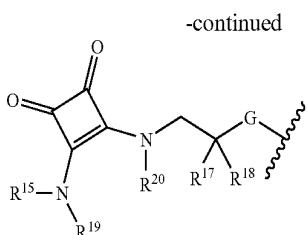
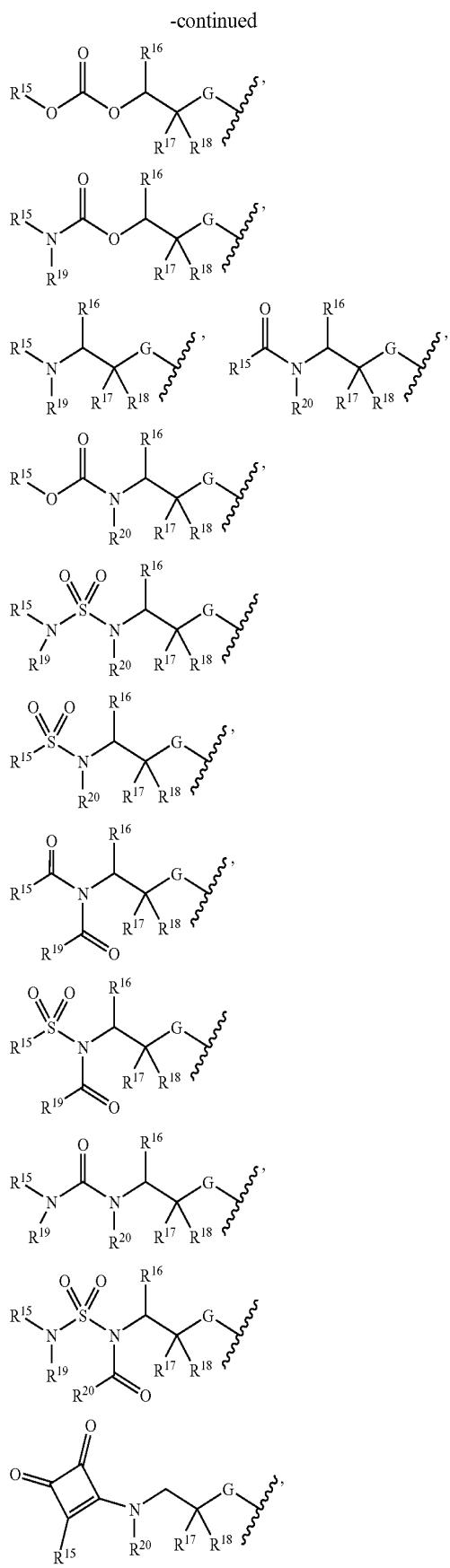
$R^1$  is  $NHR^9$ , wherein  $R^9$  is H, alkyl-, alkenyl-, alkynyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, heterocyclyl-, arylalkyl-, or heteroarylalkyl;

$R^2$  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:



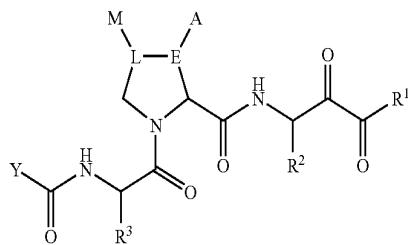


wherein G is NH or O; and R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup>, R<sup>18</sup>, R<sup>19</sup>, R<sup>20</sup>, R<sup>21</sup>, R<sup>22</sup>, R<sup>23</sup>, R<sup>24</sup> and R<sup>25</sup> can be the same or different, each being independently selected from the group consisting of H, alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, or alternately, (i) R<sup>17</sup> and R<sup>18</sup> are independently connected to each other to form a three to eight-membered cycloalkyl or heterocyclyl; (ii) likewise, independently, R<sup>15</sup> and R<sup>19</sup> are connected to each other to form a four to eight-membered heterocyclyl; (iii) likewise independently R<sup>15</sup> and R<sup>16</sup> are connected to each other to form a four to eight-membered heterocyclyl; (iv) likewise independently R<sup>15</sup> and R<sup>20</sup> are connected to each other to form a four to eight-membered heterocyclyl; (v) likewise independently R<sup>22</sup> and R<sup>23</sup> 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<sup>24</sup> and R<sup>25</sup> 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, alkyureido, arylureido, halo, cyano, and nitro;

xvii.

Formula XVII

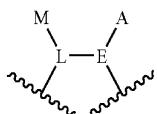


or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XVII:

$R^1$  is  $NHR^9$ , wherein  $R^9$  is H, alkyl-, alkenyl-, alkynyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, heterocycl-, 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:



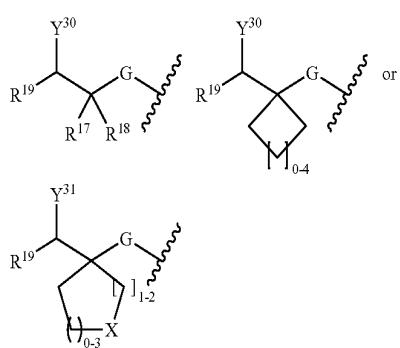
shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocycl, a six to ten-membered aryl, or a five to ten-membered heteroaryl;

E is C(H) or C=;

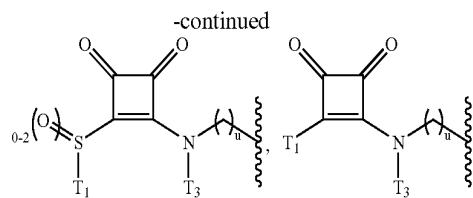
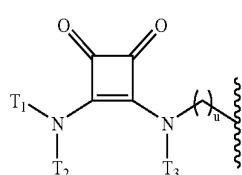
L is C(H), C=,  $CH_2C=$ , or  $C=CH_2$ ;

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-, heterocycl-, aryl-, heteroaryl-, (cycloalkyl)alkyl-, (heterocycl)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 heterocycl;

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  $SO_2$ ;

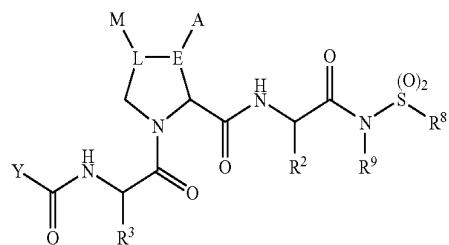
G is NH or O;

$R^{15}$ ,  $R^{16}$ ,  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $T_1$ ,  $T_2$ , 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, heterocycl, 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 heterocycl;

wherein each of said alkyl, aryl, heteroaryl, cycloalkyl or heterocycl 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, alkoxy carbonylamino, alkoxy carbonyloxy, alkylureido, arylureido, halo, cyano, and nitro;

xviii.

Formula XVIII



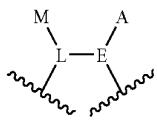
or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XVIII:

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

$R^9$  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;

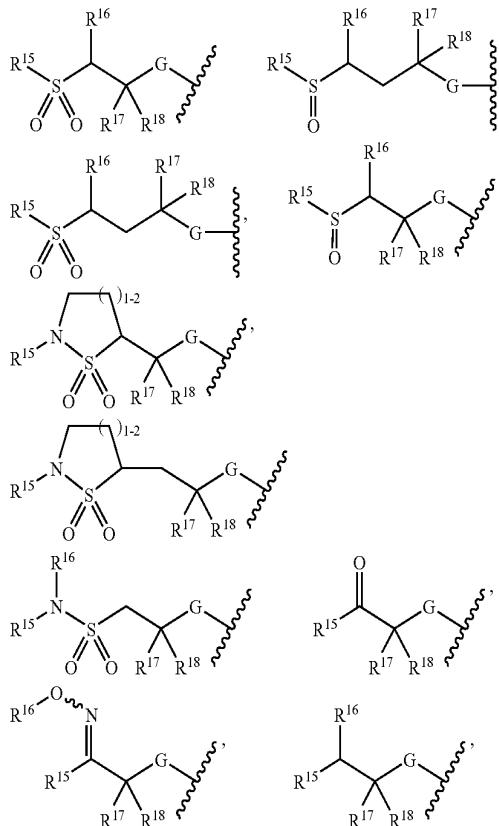
E is C(H) or C(R);

L is C(H), C(R), CH<sub>2</sub>C(R), or C(R)CH<sub>2</sub>;

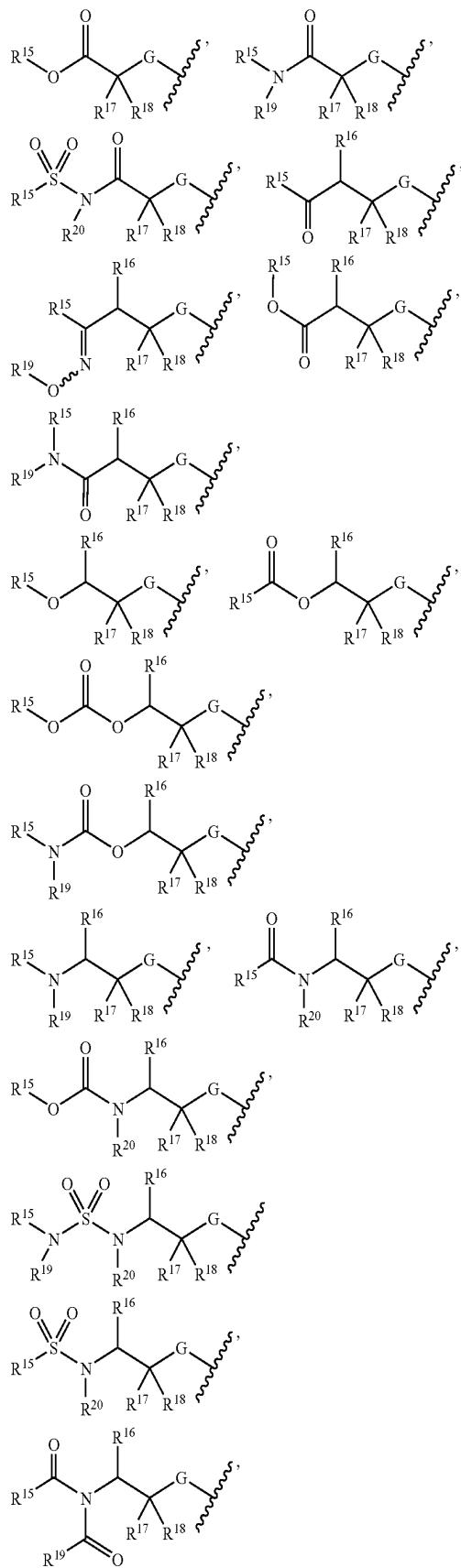
R and R' can be the same or different, each being independently selected from the group consisting of H, alkyl-, alkenyl-, alkynyl-, cycloalkyl-, heteroalkyl-, heterocyclyl-, aryl-, heteroaryl-, (cycloalkyl)alkyl-, (heterocyclyl)alkyl-, aryl-alkyl-, and heteroaryl-alkyl; or alternately R and R' in N(RR')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

R<sup>2</sup> and R<sup>3</sup> 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;

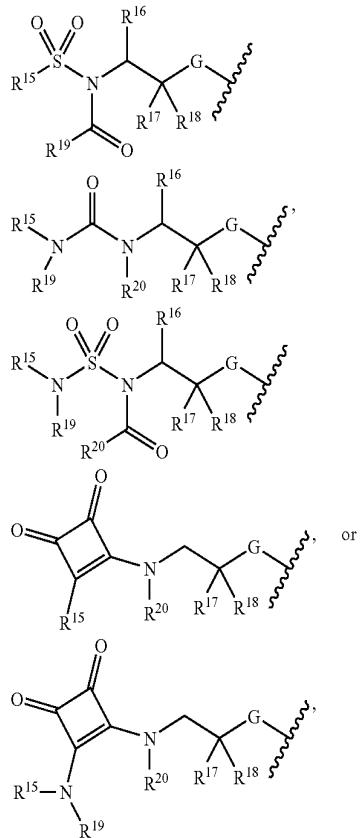
Y is selected from the following moieties:



-continued



-continued

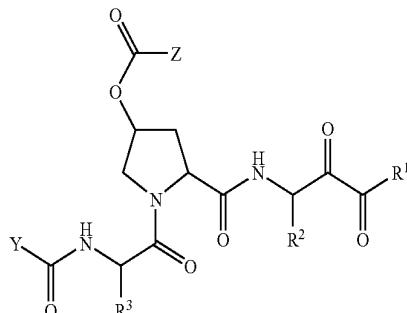


wherein G is NH or O; and R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup>, R<sup>18</sup>, R<sup>19</sup> and R<sup>20</sup> can be the same or different, each being independently selected from the group consisting of H, alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, cycloalkyl, heterocyclyl,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

xix.

Formula XIX



or a pharmaceutically acceptable salt, solvate or ester thereof;

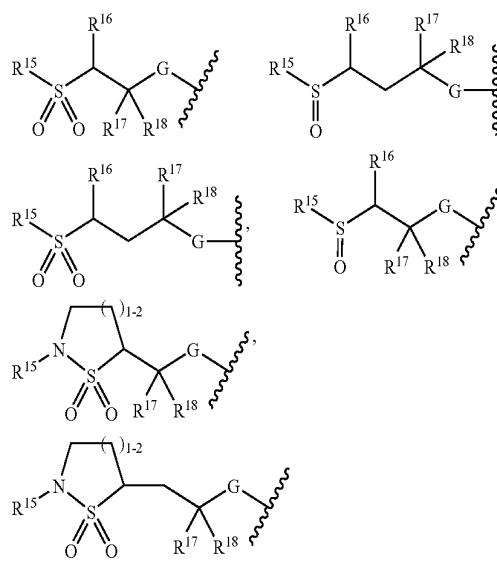
wherein in Formula XIX:

Z is selected from the group consisting of a heterocyclic moiety, N(H)(alkyl), —N(alkyl)<sub>2</sub>, —N(H)(cycloalkyl), —N(cycloalkyl)<sub>2</sub>, —N(H)(aryl), —N(aryl)<sub>2</sub>, —N(H)(heterocyclyl), —N(heterocyclyl)<sub>2</sub>, —N(H)(heteroaryl), and —N(heteroaryl)<sub>2</sub>;

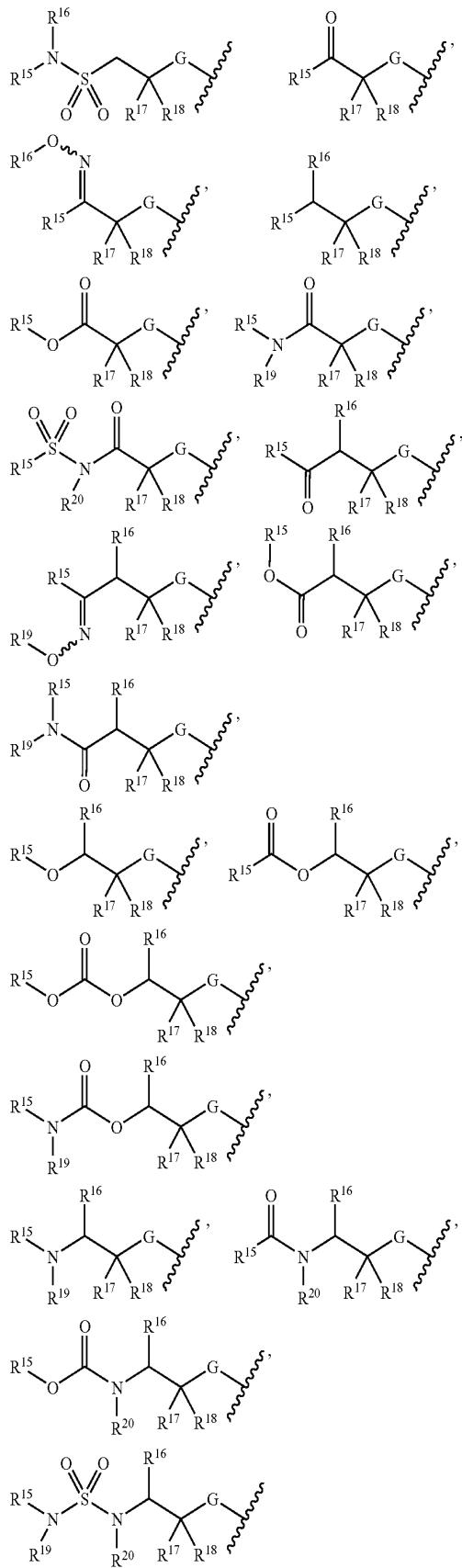
R<sup>1</sup> is NHR<sup>9</sup>, wherein R<sup>9</sup> is H, alkyl-, alkenyl-, alkynyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, heterocyclyl-, arylalkyl-, heteroaryl-, or heteroarylalkyl;

R<sup>2</sup> and R<sup>3</sup> 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;

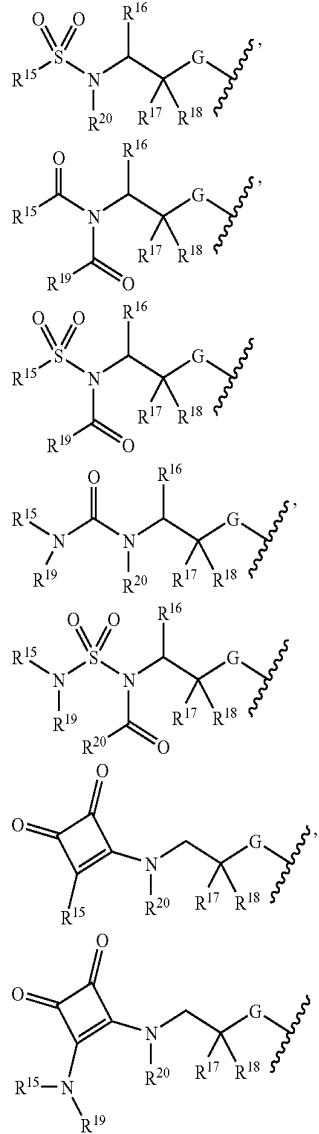
Y is selected from the following moieties:



-continued



-continued



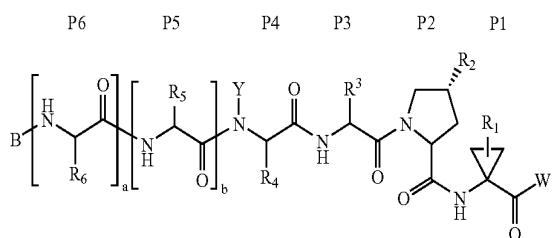
wherein G is NH or O; and R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup>, R<sup>18</sup>, R<sup>19</sup>, R<sup>20</sup> and R<sup>21</sup> can be the same or different, each being independently selected from the group consisting of H, alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, or alternately (i) R<sup>17</sup> and R<sup>18</sup> are independently connected to each other to form a three to eight-membered cycloalkyl or heterocyclyl; (ii) likewise independently R<sup>15</sup> and R<sup>19</sup> are connected to each other to form a four to eight-membered heterocyclyl; (iii) likewise independently R<sup>15</sup> and R<sup>16</sup> are connected to each other to form a four to eight-membered heterocyclyl; and (iv) likewise independently R<sup>15</sup> and R<sup>20</sup> 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, alkoxy carbonyl amino, alkoxy carbonyl oxy, 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<sub>1-6</sub>alkyl;

B is H, an acyl derivative of formula R<sub>7</sub>—C(O)— or a sulfonyl of formula R<sub>7</sub>—SO<sub>2</sub> wherein

R7 is

- (i) C<sub>1-10</sub> alkyl optionally substituted with carboxyl, C<sub>1-6</sub> alkanoyloxy or C<sub>1-6</sub> alkoxy;
- (ii) C<sub>3-7</sub> cycloalkyl optionally substituted with carboxyl, (C<sub>1-6</sub> alkoxy)carbonyl or phenylmethoxycarbonyl;
- (iii) C<sub>6</sub> or C<sub>10</sub> aryl or C<sub>7-16</sub> aralkyl optionally substituted with C<sub>1-6</sub> alkyl, hydroxy, or amino optionally substituted with C<sub>1-6</sub> alkyl; or
- (iv) Het optionally substituted with C<sub>1-6</sub> alkyl, hydroxy, amino optionally substituted with C<sub>1-6</sub> alkyl, or amido optionally substituted with C<sub>1-6</sub> alkyl;

R<sub>6</sub>, when present, is C<sub>1-6</sub> alkyl substituted with carboxyl;

R<sub>5</sub>, when present, is C<sub>1-6</sub> alkyl optionally substituted with carboxyl;

R<sub>4</sub> is C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl or C<sub>4-10</sub> (alkylcycloalkyl);

R<sub>3</sub> is C<sub>1-10</sub> alkyl, C<sub>3-7</sub> cycloalkyl or C<sub>4-10</sub> (alkylcycloalkyl);

R<sub>2</sub> is CH<sub>2</sub>—R<sub>20</sub>, NH—R<sub>20</sub>, O—R<sub>20</sub> or S—R<sub>20</sub>, wherein R<sub>20</sub> is a saturated or unsaturated C<sub>3-7</sub> cycloalkyl or C<sub>4-10</sub> (alkyl cycloalkyl) being optionally mono-, di- or tri-substituted with R<sub>21</sub>, or R<sub>20</sub> is a C<sub>6</sub> or C<sub>10</sub> aryl or C<sub>7-16</sub> aralkyl optionally mono-, di- or tri-substituted with R<sub>21</sub>,

or R<sub>20</sub> is Het or (lower alkyl)-Het optionally mono-, di- or tri-substituted with R<sub>21</sub>, wherein each R<sub>21</sub> is independently C<sub>1-6</sub> alkyl; C<sub>1-6</sub> alkoxy; amino optionally mono- or di-substituted with C<sub>1-6</sub> alkyl; sulfonyl; NO<sub>2</sub>; OH; SH; halo; haloalkyl; amido optionally mono-substituted with C<sub>1-6</sub> alkyl, C<sub>6</sub> or C<sub>10</sub> aryl, C<sub>7-16</sub> aralkyl, Het

or (lower alkyl)-Het; carboxyl; carboxy(lower alkyl); C or C<sub>10</sub> aryl, C<sub>7-16</sub> aralkyl or Het, said aryl, aralkyl or Het being optionally substituted with R<sub>22</sub>;

wherein R<sub>22</sub> is C<sub>1-6</sub>alkyl; C<sub>1-6</sub> alkoxy; amino optionally mono- or di-substituted with C<sub>1-6</sub> alkyl; sulfonyl; NO<sub>2</sub>; OH; SH; halo; haloalkyl; carboxyl; amide or (lower alkyl)amide;

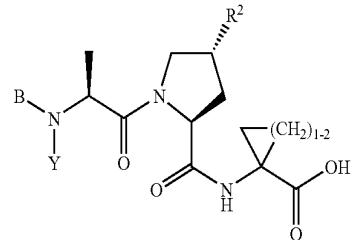
R<sub>1</sub> is C<sub>1-6</sub> alkyl or C<sub>2-6</sub> alkenyl optionally substituted with halogen; and

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<sub>6</sub> or C<sub>10</sub> aryl, C<sub>7-16</sub> aralkyl; Het or (lower alkyl)-Het, all of which optionally substituted with C<sub>1-6</sub> alkyl; C<sub>1-6</sub> alkoxy; C<sub>1-6</sub> alkanoyl; hydroxy; hydroxyalkyl; halo; haloalkyl; nitro; cyano; cyanoalkyl; amino optionally substituted with C<sub>1-6</sub> alkyl; amido; or (lower alkyl)amide;

or B is an acyl derivative of formula R<sub>4</sub>—C(O)—; a carboxyl of formula R<sub>4</sub>—O—C(O)—; an amide of formula R<sub>4</sub>—N(R<sub>5</sub>)—C(O)—; a thioamide of formula R<sub>4</sub>—N(R<sub>5</sub>)—C(S)—; or a sulfonyl of formula R<sub>4</sub>—SO<sub>2</sub> wherein

R<sub>4</sub> is

(i) C<sub>1-10</sub> alkyl optionally substituted with carboxyl, C<sub>1-6</sub> alkanoyl, hydroxy, C<sub>1-6</sub> alkoxy, amino optionally mono- or di-substituted with C<sub>1-6</sub> alkyl, amido, or (lower alkyl)amide;

(ii) C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkoxy, or C<sub>4-10</sub> alkylcycloalkyl, all optionally substituted with hydroxy, carboxyl, (C<sub>1-6</sub> alkoxy)carbonyl, amino optionally mono- or di-substituted with C<sub>1-6</sub> alkyl, amido, or (lower alkyl)amide;

(iii) amino optionally mono- or di-substituted with C<sub>1-6</sub> alkyl; amido; or (lower alkyl)amide;

(iv) C<sub>6</sub> or C<sub>10</sub> aryl or C<sub>7-16</sub> aralkyl, all optionally substituted with C<sub>1-6</sub> alkyl, hydroxy, amido, (lower alkyl)amide, or amino optionally mono- or di-substituted with C<sub>1-6</sub> alkyl; or

(v) Het or (lower alkyl)-Het, both optionally substituted with C<sub>1-6</sub> alkyl, hydroxy, amido, (lower alkyl)amide, or amino optionally mono- or di-substituted with C<sub>1-6</sub> alkyl;

R<sub>5</sub> is H or C<sub>1-6</sub> alkyl;

with the proviso that when R<sub>4</sub> is an amide or a thioamide, R<sub>4</sub> is not (ii) a cycloalkoxy;

Y is H or C<sub>1-6</sub> alkyl;

R<sub>3</sub> is C<sub>1-8</sub> alkyl, C<sub>3-7</sub> cycloalkyl, or C<sub>4-10</sub> alkylcycloalkyl, all optionally substituted with hydroxy, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> thioalkyl, amido, (lower alkyl)amido, C<sub>6</sub> or C<sub>10</sub> aryl, or C<sub>7-16</sub> aralkyl;

R<sub>2</sub> is CH<sub>2</sub>—R<sub>20</sub>, NH—R<sub>20</sub>, O—R<sub>20</sub> or S—R<sub>20</sub>, wherein R<sub>20</sub> is a saturated or unsaturated C<sub>3-7</sub> cycloalkyl or C<sub>4-10</sub> (alkylcycloalkyl), all of which being optionally mono-, di- or tri-substituted with R<sub>21</sub>, or R<sub>20</sub> is a C<sub>6</sub> or C<sub>10</sub> aryl or C<sub>7-14</sub> aralkyl, all optionally mono-, di- or tri-substituted with R<sub>21</sub>,

or R<sub>20</sub> is Het or (lower alkyl)-Het, both optionally mono-, di- or tri-substituted with R<sub>21</sub>,

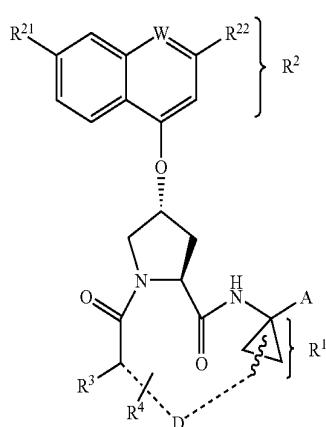
wherein each R<sub>21</sub> is independently C<sub>1-6</sub> alkyl; C<sub>1-6</sub> alkoxy; lower thioalkyl; sulfonyl; NO<sub>2</sub>; OH; SH; halo; haloalkyl; amino optionally mono- or di-substituted with C<sub>1-6</sub> alkyl, C<sub>6</sub> or C<sub>10</sub> aryl, C<sub>7-14</sub> aralkyl, Het or (lower alkyl)-Het; amido optionally mono-substituted with C<sub>1-6</sub> alkyl, C<sub>6</sub> or C<sub>10</sub> aryl, C<sub>7-14</sub> aralkyl, Het or (lower alkyl)-Het; carboxyl; carboxy-(lower alkyl); C<sub>6</sub> or C<sub>10</sub> aryl, C<sub>7-14</sub> aralkyl or Het, said aryl, aralkyl or Het being optionally substituted with R<sub>22</sub>;

wherein R<sub>22</sub> is C<sub>1-6</sub> alkyl; C<sub>3-7</sub> cycloalkyl; C<sub>1-6</sub> alkoxy; amino optionally mono- or di-substituted with C<sub>1-6</sub> alkyl; sulfonyl; (lower alkyl)sulfonyl; NO<sub>2</sub>; OH; SH; halo; haloalkyl; carboxyl; amide; (lower alkyl)amide; or Het optionally substituted with C<sub>1-6</sub> alkyl;

R1 is H; C<sub>1-6</sub> alkyl, C<sub>3-7</sub> cycloalkyl, C<sub>2-6</sub> alkenyl, or C<sub>2-6</sub> 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<sup>21</sup> is H, halo, C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkoxy, C<sub>3-6</sub> cycloalkoxy, hydroxy, or N(R<sup>23</sup>)<sub>2</sub>, wherein each R<sup>23</sup> is independently H, C<sub>1-6</sub> alkyl or C<sub>3-6</sub> cycloalkyl;

R<sup>22</sup> is H, halo, C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> thioalkyl, C<sub>1-6</sub> alkoxy, C<sub>3-6</sub> cycloalkoxy, C<sub>2-7</sub> alkoxyalkyl, C<sub>3-6</sub> cycloalkyl, C<sub>6</sub> 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<sup>24</sup>, wherein R<sup>24</sup> is H, halo, C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>1-6</sub> alkoxy, C<sub>3-6</sub> cycloalkoxy, NO<sub>2</sub>, N(R<sup>25</sup>)<sub>2</sub>, NH—C(O)—R<sup>25</sup> or NH—C(O)—NH—R<sup>25</sup>, wherein each R<sup>25</sup> is independently: H, C<sub>1-6</sub> alkyl or C<sub>3-6</sub> cycloalkyl;

or R<sup>24</sup> is NH—C(O)—OR<sup>26</sup> wherein R<sup>26</sup> is C<sub>1-6</sub> alkyl or C<sub>3-6</sub> cycloalkyl;

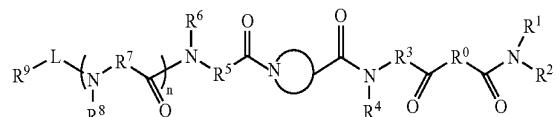
R<sup>3</sup> is hydroxy, NH<sub>2</sub>, or a group of formula —NH—R<sup>31</sup>, wherein R<sup>31</sup> is C<sub>6</sub> or 10 aryl, heteroaryl, —C(O)—R<sup>32</sup>, —C(O)—NHR<sup>32</sup> or —C(O)—OR<sup>32</sup>, wherein R<sup>32</sup> is C<sub>1-6</sub> alkyl or C<sub>3-6</sub> cycloalkyl;

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<sup>41</sup>, wherein R<sup>41</sup> is H, C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl or —C(O)—R<sup>42</sup>, wherein R<sup>42</sup> is C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl or C<sub>6</sub> or 10 aryl; R<sup>4</sup> 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<sub>1-6</sub> alkyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub> alkoxy, hydroxy, halo, amino, oxo, thio and C<sub>1-6</sub> thioalkyl, and A is an amide of formula —C(O)—NH—R<sup>5</sup>, wherein R<sup>5</sup> is selected from the group consisting of: C<sub>1-8</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>6</sub> or 10 aryl and C<sub>7-16</sub> aralkyl;

or A is a carboxylic acid;

xxiii.

Formula XXIII



or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XXIII:

R<sup>0</sup> is a bond or difluoromethylene;

R<sup>1</sup> is hydrogen;

R<sup>2</sup> and R<sup>9</sup> 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, R6, R8 and R<sup>10</sup> are each independently hydrogen or optionally substituted aliphatic group;



is substituted monocyclic azaheterocycl or optionally substituted multicyclic azaheterocycl, or optionally substituted multicyclic azaheterocyclenyl wherein the unsaturation is in the ring distal to the ring bearing the R<sup>9</sup>-L-(N(R<sup>8</sup>)-R<sup>7</sup>-C(O)-)<sub>n</sub>N(R<sup>6</sup>)-R<sup>5</sup>-C(O)-N moiety and to which the -C(O)-N(R)-R<sup>3</sup>-C(O)C(O)NR<sup>2</sup>R<sup>1</sup> moiety is attached;

L is —C(O)—, —OC(O)—, —NR<sup>10</sup>C(O)—, —S(O)<sub>2</sub>—, or —NR<sup>10</sup>S(O)<sub>2</sub>—; and

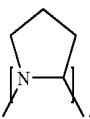
n is 0 or 1,

provided

when



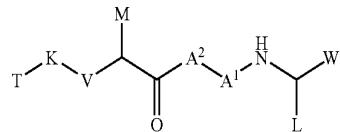
is substituted



then L is —OC(O)— and R<sup>9</sup> is optionally substituted aliphatic; or at least one of R<sup>3</sup>, R<sup>5</sup> and R<sup>7</sup> 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<sup>4</sup> is optionally substituted aliphatic;

xxiv.

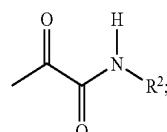
Formula XXIV



or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XXIV:

W is:



m is 0 or 1;

R<sup>2</sup> is independently hydrogen, alkyl, alkenyl, aryl, aralkyl, aralkenyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, heterocycl, heterocyclalkyl, heterocyclalkenyl, heteroaryl, or heteroaralkyl, wherein any R<sup>2</sup> carbon atom is optionally substituted with J;

J is alkyl, aryl, aralkyl, alkoxy, aryloxy, aralkoxy, cycloalkyl, cycloalkoxy, heterocycl, heterocyclalkyl, 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<sup>1</sup> groups;

J<sup>1</sup> is alkyl, aryl, aralkyl, alkoxy, aryloxy, heterocycl, heterocyclalkyl, keto, hydroxy, amino, alkanoylamino, aroylamino, carboxy, carboxyalkyl, carboxamidoalkyl, halo, cyano, nitro, formyl, sulfonyl, or sulfonamido;

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

A<sup>1</sup> is a bond;

R<sup>4</sup> is alkyl, cycloalkyl, aryl, aralkyl, heterocycl, heterocyclalkyl, heteroaryl, heteroaralkyl, carboxyalkyl, or carboxamidoalkyl, and is optionally substituted with 1-3 J groups;

R<sup>5</sup> and R<sup>6</sup> are independently hydrogen, alkyl, alkenyl, aryl, aralkyl, aralkenyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocycl, heterocyclalkyl, heteroaryl, or heteroaralkyl, and is optionally substituted with 1-3 J groups;

X is a bond, —C(H)(R7)-, —O—, —S—, or —N(R<sup>8</sup>)—;

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

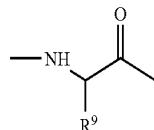
$R^8$  is hydrogen alkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl, heteroaralkyl, aralkanoyl, heterocyclanoyl, heteroaralkanoyl,  $-\text{C}(\text{O})\text{R}^{14}$ ,  $-\text{SO}_2\text{R}^{14}$ , or carboxamido, and is optionally substituted with 1-3 J groups; or  $R^8$  and Z, together 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, heterocyclalkyl, heteroaryl, or heteroaralkyl;

Y is a bond,  $-\text{CH}_2-$ ,  $-\text{C}(\text{O})-$ ,  $-\text{C}(\text{O})\text{C}(\text{O})-$ ,  $-\text{S}(\text{O})-$ ,  $-\text{S}(\text{O})_2-$ , or  $-\text{S}(\text{O})(\text{NR}^7)-$ , wherein R is as defined above;

Z is alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclalkyl, heteroaryl, heteroaralkyl,  $-\text{OR}^2$ , or  $-\text{N}(\text{R}^2)_2$ , 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, heterocyclalkyl, heteroaryl, heteroaralkyl, carboxyalkyl, or carboxamidoalkyl, and is optionally substituted with 1-3 J groups;

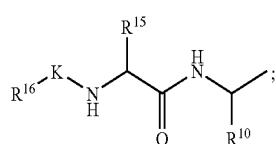
M is alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl, or heteroaralkyl, optionally substituted by 1-3 J groups, wherein any alkyl carbon atom may be replaced by a heteroatom;

V is a bond,  $-\text{CH}_2-$ ,  $-\text{C}(\text{H})(\text{R}^{11})-$ ,  $-\text{O}-$ ,  $-\text{S}-$ , or  $-\text{N}(\text{R}^{11})-$ ;

$R^{11}$  is hydrogen or  $\text{C}_{1-3}$  alkyl;

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

T is  $-\text{R}^{12}$ , -alkyl- $\text{R}^{12}$ , -alkenyl- $\text{R}^{12}$ , -alkynyl- $\text{R}^{12}$ ,  $-\text{OR}^{12}$ ,  $-\text{N}(\text{R}^{12})_2$ ,  $-\text{C}(\text{O})\text{R}^{12}$ ,  $-\text{C}(=\text{NOalkyl})\text{R}^{12}$ , or



$R^{12}$  is hydrogen, aryl, heteroaryl, cycloalkyl, heterocyclyl, cycloalkyldenyl, or heterocycloalkyldenyl,

and is optionally substituted with 1-3 J groups, or a first  $\text{R}^{12}$  and a second  $\text{R}^{12}$ , together with the nitrogen to which they are bound, form a mono- or bicyclic ring system optionally substituted by 1-3 J groups;

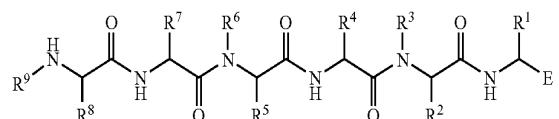
$\text{R}^{10}$  is alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl, heteroaralkyl, carboxyalkyl, or carboxamidoalkyl, and is optionally substituted with 1-3 hydrogens J groups;

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

$\text{R}^{16}$  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  $\text{B}(\text{OH})_2$ ;

$\text{R}^1$  represents lower alkyl, halo-lower alkyl, cyano-lower alkyl, lower alkylthio-lower alkyl, aryl-lower alkylthio-lower alkyl, aryl-lower alkyl, heteroaryl-lower alkyl, lower alkenyl or lower alkynyl;

$\text{R}^2$  represents lower alkyl, hydroxy-lower alkyl, carboxylower alkyl, aryl-lower alkyl, aminocarbonyl-lower alkyl or lower cycloalkyl-lower alkyl; and

$\text{R}^3$  represents hydrogen or lower alkyl;

or  $\text{R}^2$  and  $\text{R}^3$  together represent di- or trimethylene optionally substituted by hydroxy;

$\text{R}^4$  represents lower alkyl, hydroxy-lower alkyl, lower cycloalkyl-lower alkyl, carboxy-lower alkyl, aryl-lower alkyl, lower alkylthio-lower alkyl, cyano-lower alkylthio-lower alkyl, aryl-lower alkylthio-lower alkyl, lower alkenyl, aryl or lower cycloalkyl;

$\text{R}^5$  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;

$\text{R}^6$  represents hydrogen or lower alkyl;

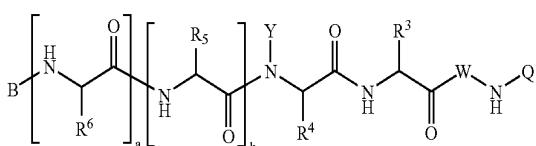
$\text{R}^7$  represent lower alkyl, hydroxydower alkyl, carboxylower alkyl, aryl-lower alkyl, lower cycloalkyl-lower alkyl or lower cycloalkyl;

$\text{R}^8$  represents lower alkyl, hydroxy-lower alkyl, carboxylower alkyl or aryl-lower alkyl; and

$\text{R}^9$  represents lower alkylcarbonyl, carboxy-lower alkylcarbonyl, arylcarbonyl, lower alkylsulphonyl, arylsulphonyl, lower alkoxy carbonyl or aryl-lower alkoxy carbonyl;

xxvi.

Formula XXVI



or a pharmaceutically acceptable salt, solvate or ester thereof;

wherein in Formula XXVI:

B is an acyl derivative of formula R<sub>11</sub>—C(O)— wherein R<sub>11</sub> is C<sub>1-10</sub> alkyl optionally substituted with carboxyl; or R<sub>11</sub> is C<sub>6</sub> or C<sub>10</sub> aryl or C<sub>7-16</sub> aralkyl optionally substituted with a C<sub>1-6</sub> alkyl;

a is 0 or 1;

R<sub>6</sub>, when present, is carboxy(lower)alkyl;

b is 0 or 1;

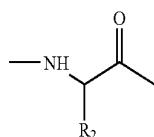
R<sub>5</sub>, when present, is C<sub>1-6</sub>alkyl, or carboxy(lower)alkyl;

Y is H or C<sub>1-6</sub> alkyl;

R<sub>4</sub> is C<sub>1-10</sub> alkyl; C<sub>3-10</sub> cycloalkyl;

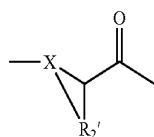
R<sub>3</sub> is C<sub>1-10</sub> alkyl; C<sub>3-10</sub> cycloalkyl;

W is a group of formula:



wherein R<sub>2</sub> is C<sub>1-10</sub> alkyl or C<sub>3-7</sub> cycloalkyl optionally substituted with carboxyl; C<sub>6</sub> or C<sub>10</sub> aryl; or C<sub>7-16</sub> aralkyl; or

W is a group of formula:



wherein X is CH or N; and

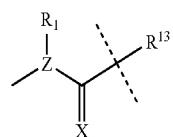
R<sub>2'</sub> is C<sub>3-4</sub> alkylene that joins X to form a 5- or 6-membered ring, said ring optionally substituted with OH; SH; NH<sub>2</sub>; carboxyl; R<sub>12</sub>; OR<sub>12</sub>; SR<sub>12</sub>; NHR<sub>12</sub> or NR<sub>12</sub>R<sub>12'</sub> wherein R<sub>12</sub> and R<sub>12'</sub> are independently:

cyclic C<sub>3-16</sub> alkyl or acyclic C<sub>1-16</sub> alkyl or cyclic C<sub>3-16</sub> alkenyl or acyclic C<sub>2-16</sub> alkenyl, said alkyl or alkenyl optionally substituted with NH<sub>2</sub>, OH, SH, halo, or carboxyl; said alkyl or alkenyl optionally containing at least one heteroatom selected independently from the group consisting of: O, S, and N; or

R<sub>12</sub> and R<sub>12'</sub> are independently C<sub>6</sub> or C<sub>10</sub> aryl or C<sub>7-16</sub> aralkyl optionally substituted with C<sub>1-6</sub> alkyl, NH<sub>2</sub>, 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: O, 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<sub>2</sub>, OH, SH, halo, carboxyl or carboxy(lower)alkyl; C<sub>6</sub> or C<sub>10</sub> aryl, or heterocycle; said second ring optionally containing at least one heteroatom selected independently from the group consisting of: O, S, and N;

Q is a group of the formula:



wherein Z is CH;

X is O or S;

R<sub>1</sub> is H, C<sub>1-6</sub> alkyl or C<sub>1-6</sub> alkenyl both optionally substituted with thio or halo; and

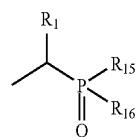
R<sub>13</sub> is CO—NH—R<sub>14</sub> wherein R<sub>14</sub> is hydrogen, cyclic C<sub>3-10</sub> alkyl or acyclic C<sub>1-10</sub> alkyl or cyclic C<sub>3-10</sub> alkenyl or acyclic C<sub>2-10</sub> alkenyl, said alkyl or alkenyl optionally substituted with NH<sub>2</sub>, OH, SH, halo or carboxyl; said alkyl or alkenyl optionally containing at least one heteroatom selected independently from the group consisting of: O, S, and N; or

R<sub>14</sub> is C<sub>6</sub> or C<sub>10</sub> aryl or C<sub>7-16</sub> aralkyl optionally substituted with C<sub>1-6</sub> alkyl, NH<sub>2</sub>, OH, SH, halo, carboxyl or carboxy(lower)alkyl or substituted with a further C<sub>3-7</sub> cycloalkyl, C<sub>6</sub> or C<sub>10</sub> aryl, or heterocycle; said aryl or aralkyl optionally containing at least one heteroatom selected independently from the group consisting of: O, 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<sub>2</sub>, OH, SH, halo, carboxyl or carboxy(lower)alkyl or substituted with a further C<sub>3-7</sub> cycloalkyl, C<sub>6</sub> or C<sub>10</sub> aryl, or heterocycle; said second ring optionally containing at least one heteroatom selected independently from the group consisting of: O, S, and N;

with the proviso that when Z is CH, then R<sub>13</sub> is not an α-amino acid or an ester thereof;

Q is a phosphonate group of the formula:



wherein R<sub>15</sub> and R<sub>16</sub> are independently C<sub>6-20</sub> aryloxy; and R<sub>1</sub> is as defined above; and

(b) at least one HCV polymerase inhibitor but not HCV-796;

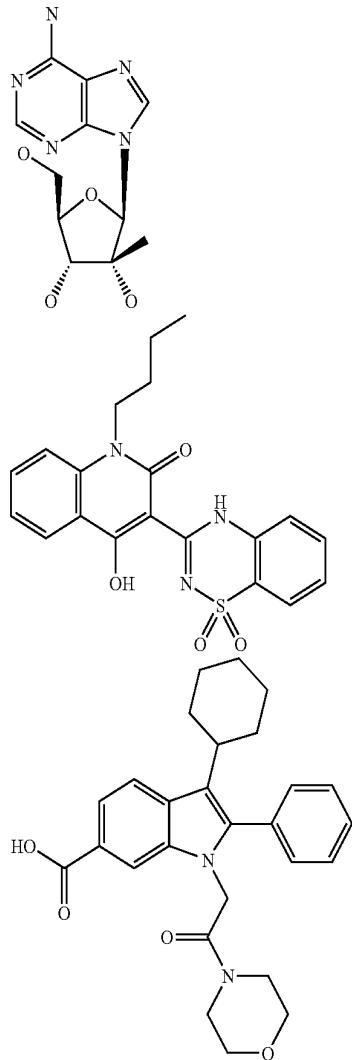
for concurrent or consecutive administration in treating or ameliorating one or more symptoms of HCV, or disorders associated with HCV in a subject in need thereof.

**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 interferon.

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

**5.** The medicament of claim 1, 2, 3, or 4, wherein at least one HCV polymerase inhibitor is selected from the group consisting of:



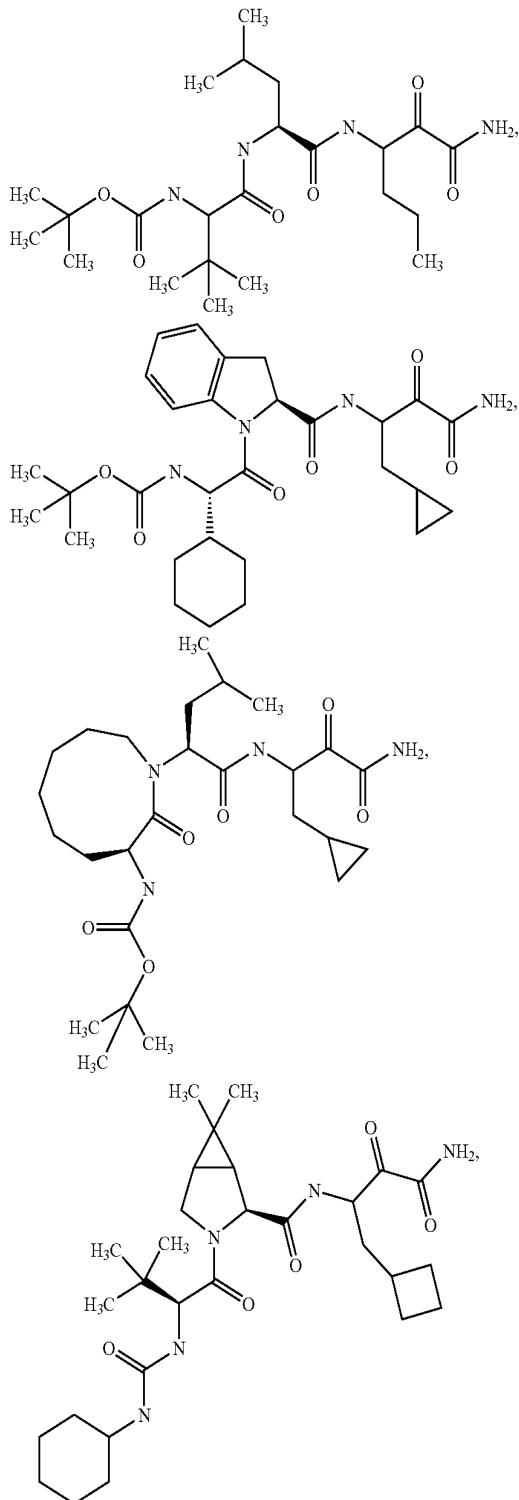
**6.** The medicament of claim 5, wherein at least one HCV polymerase inhibitor is 2'methyl-adenosine, or a pharmaceutically acceptable salt, solvate, or ester thereof.

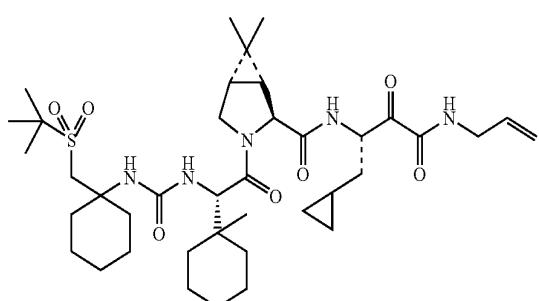
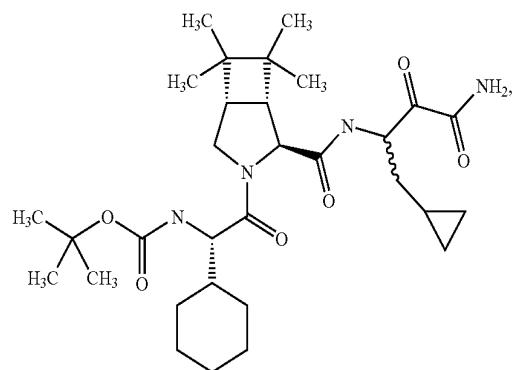
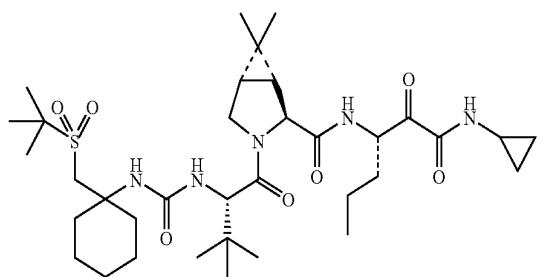
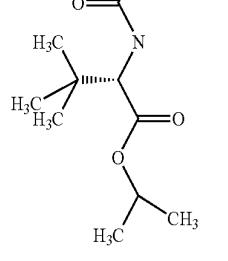
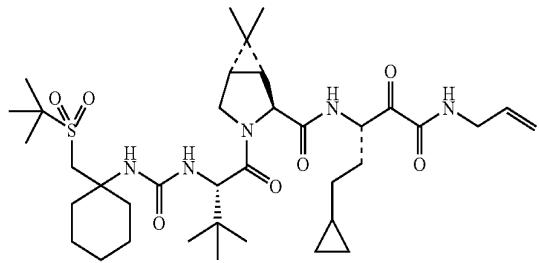
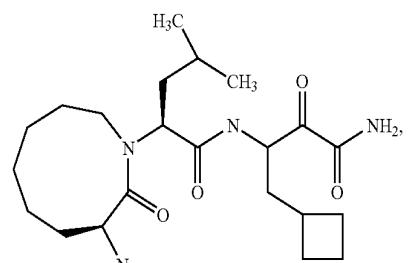
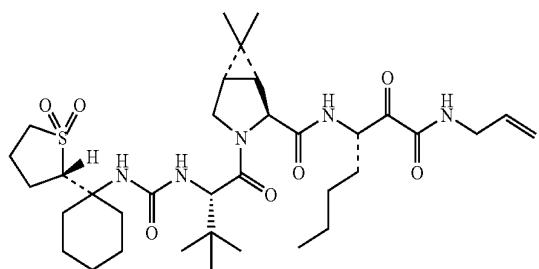
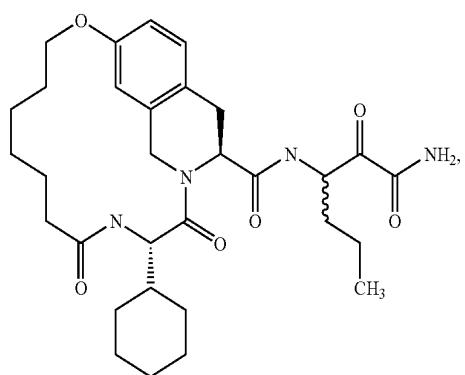
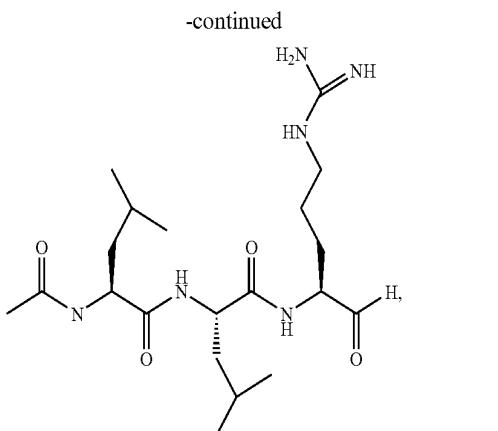
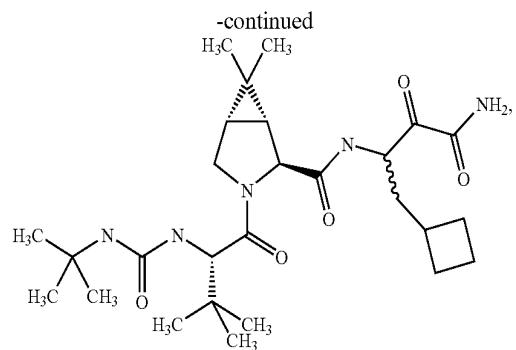
**7.** The medicament of claim 5, wherein at least one HCV polymerase inhibitor is indole-N-acetamide, or a pharmaceutically acceptable salt, solvate, or ester thereof.

**8.** The medicament of claim 5, wherein at least one HCV polymerase inhibitor is benzothiadiazine, or a pharmaceutically acceptable salt, solvate, or ester thereof.

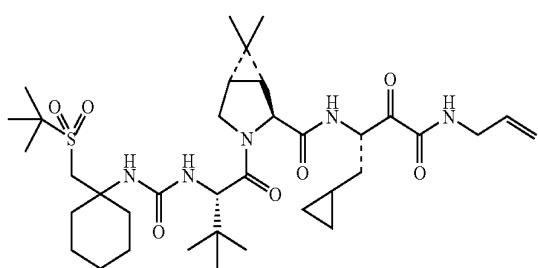
**9.** The medicament of claim 1, wherein at least one HCV protease inhibitor is administered in an amount ranging from about 100 to about 3600 mg per day.

**10.** The medicament of claim 1, 2, 3, or 4, wherein at least one HCV protease inhibitor is selected from the group consisting of:

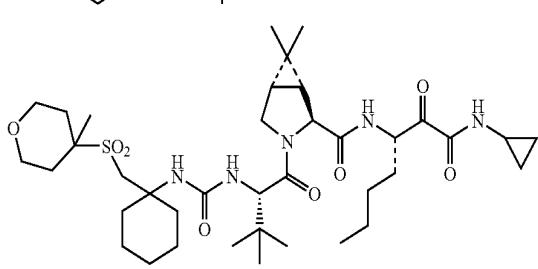
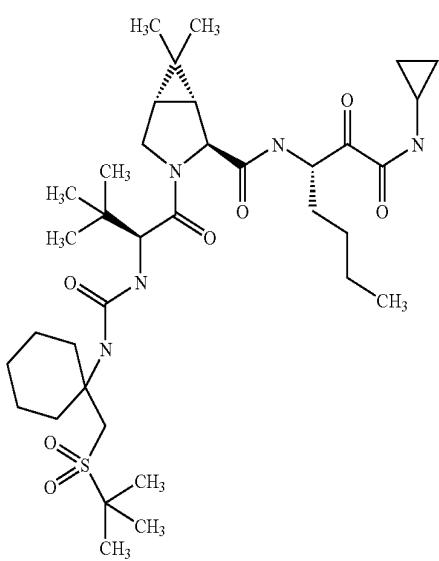
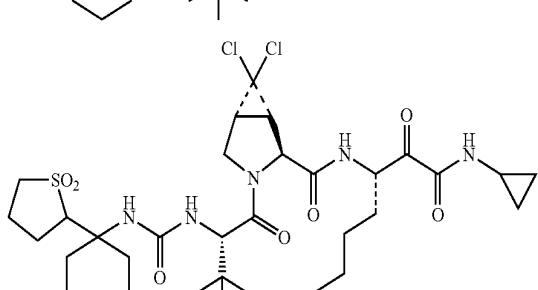
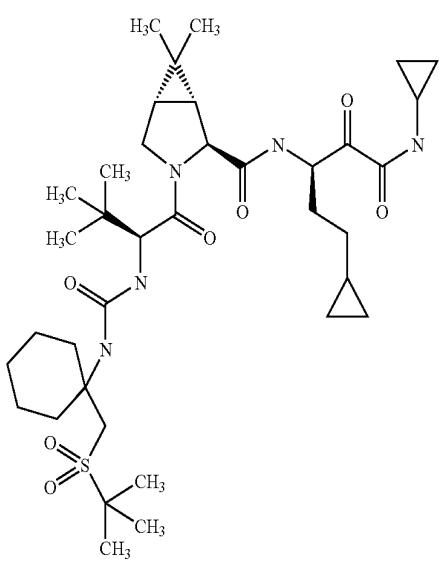
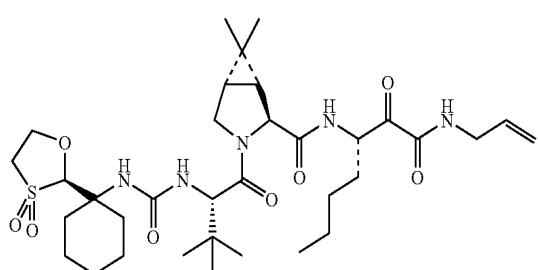
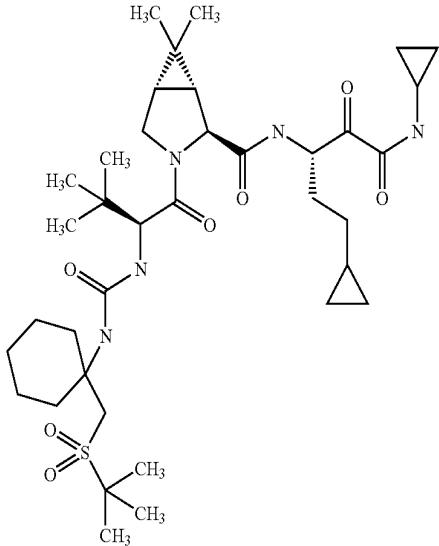


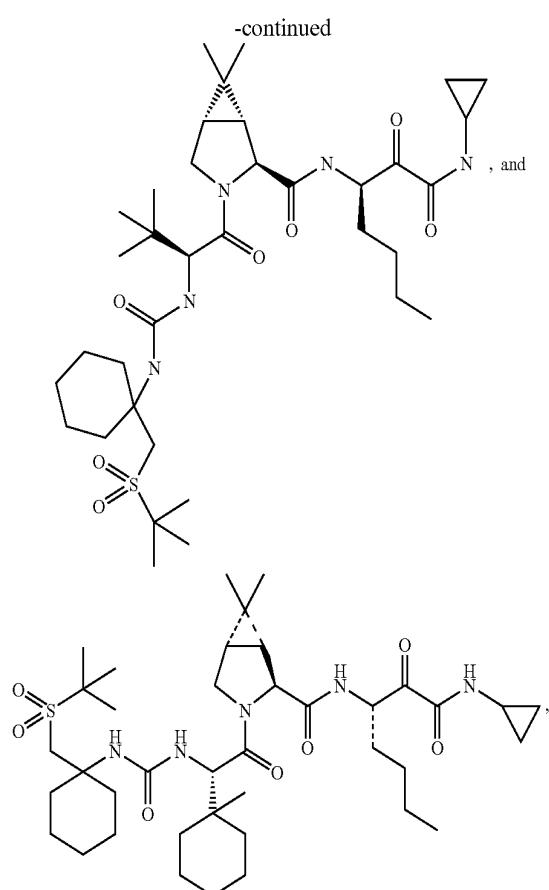


-continued



-continued





or a pharmaceutically acceptable salt, solvate or ester thereof.

**11.** 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.

**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 two or more thereof.

**14.** The medicament of any of claim 3, wherein said interferon is selected from the group consisting of Roferon™, Pegasys™, Intron™, PEG-Intron™, Berofer Alpha™, and Infergen™.

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

**16.** The medicament of claim 2, further comprising at least one aldo-keto reductase (AKR) competitor administered concurrently or consecutively with at least one HCV protease inhibitor and at least one HCV polymerase inhibitor in an amount sufficient to increase the bioavailability of at least one HCV protease inhibitor.

**17.** The medicament of claim 16, wherein at least one AKR competitor is flunisulim.

**18.** The medicament of claim 2, further comprising at least one cytochrome P450 isoenzyme 3A4 (CYP3A4) inhibitor administered concurrently or consecutively with at least one HCV protease inhibitor and at least one HCV

polymerase inhibitor in an amount sufficient to increase the bioavailability of at least one HCV protease inhibitor.

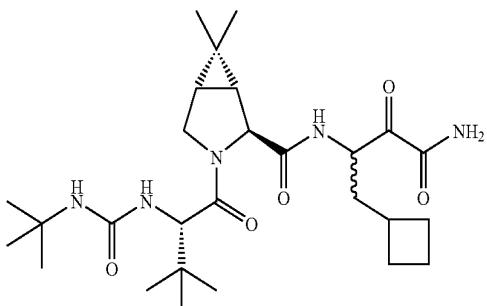
**19.** The medicament of claim 18, wherein at least one CYP3A4 inhibitor is ritonavir, ketoconazole, or clarithromycin.

**20.** A pharmaceutical composition comprising a therapeutically effective amount of the medicament of claim 1, and a pharmaceutically acceptable carrier.

**21.** 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).

**22.** A medicament comprising, separately or together:

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

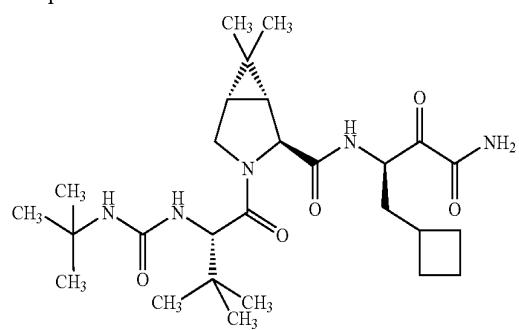


Formula Ia, or a pharmaceutically acceptable salt, solvate or ester thereof, and

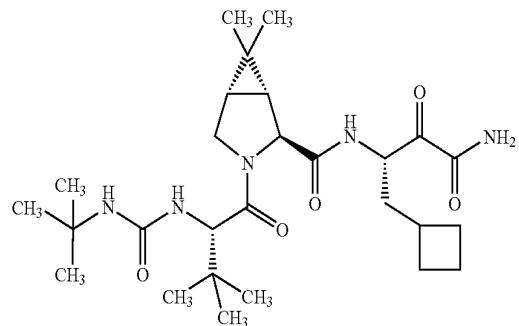
(b) at least one HCV polymerase inhibitor but not HCV-796;

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.

**23.** The medicament of claim 22, wherein at least one HCV protease inhibitor is



Formula Ib,



Formula Ic, or a pharmaceutically acceptable salt, solvate or ester thereof,

**24.** The medicament of claim 22, further comprising at least one other therapeutic agent.

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

**26.** The medicament of claim 25, further comprising ribavirin.

**27.** The medicament of claim 22, further comprising at least one aldo-keto reductase (AKR) competitor administered concurrently or consecutively with at least one HCV protease inhibitor and at least one HCV polymerase inhibitor in an amount sufficient to increase the bioavailability of at least one HCV protease inhibitor.

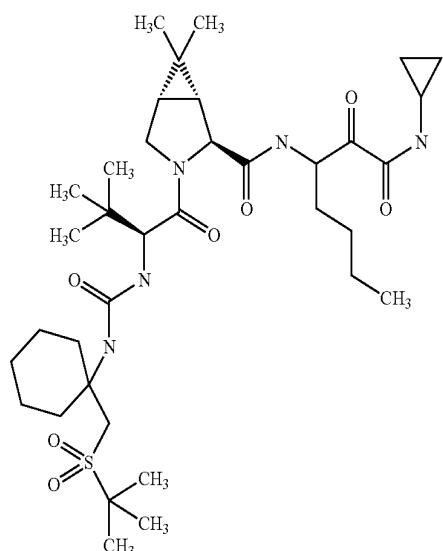
**28.** The medicament of claim 27, wherein at least one AKR competitor is diflunisal.

**29.** The medicament of claim 22, further comprising at least one cytochrome P450 isoenzyme 3A4 (CYP3A4) inhibitor administered concurrently or consecutively with at least one HCV protease inhibitor and at least one HCV polymerase inhibitor in an amount sufficient to increase the bioavailability of at least one HCV protease inhibitor.

**30.** The medicament of claim 29, wherein at least one CYP3A4 inhibitor is ritonavir, ketoconazole, clarithromycin.

**31.** A medicament comprising, separately or together:

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



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

(b) at least one HCV polymerase inhibitor but not HCV-796;

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.

**32.** The medicament of claim 31, further comprising at least one other therapeutic agent.

**33.** The medicament of claim 32, wherein at least one other therapeutic agent is interferon.

**34.** The medicament of claim 33, further comprising ribavirin.

**35.** The medicament of claim 31, further comprising at least one aldo-keto reductase (AKR) competitor administered concurrently or consecutively with at least one HCV protease inhibitor and at least one HCV polymerase inhibitor in an amount sufficient to increase the bioavailability of at least one HCV protease inhibitor.

**36.** The medicament of claim 35, wherein at least one AKR competitor is diflunisal.

**37.** The medicament of claim 31, further comprising at least one cytochrome P450 isoenzyme 3A4 (CYP3A4) inhibitor administered concurrently or consecutively with at least one HCV protease inhibitor and at least one HCV polymerase inhibitor in an amount sufficient to increase the bioavailability of at least one HCV protease inhibitor.

**38.** The medicament of claim 37, wherein at least one CYP3A4 inhibitor is ritonavir, ketoconazole, or clarithromycin.

**39.** 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.

**40.** The method of claim 39, further comprising the step of administering to the subject at least one AKR competitor in an amount sufficient to increase the bioavailability of at least one HCV protease inhibitor.

**41.** The method of claim 40, wherein at least one AKR competitor is diflunisal.

**42.** The method of claim 39, further comprising the step of administering to the subject at least one cytochrome P450 isoenzyme 3A4 (CYP3A4) inhibitor in an amount sufficient to increase the bioavailability of at least one HCV protease inhibitor.

**43.** The medicament of claim 42, wherein at least one CYP3A4 inhibitor is ritonavir, ketoconazole, or clarithromycin.

**44.** The method of claim 39, wherein said administration is oral, intravenous, intrathecal, or subcutaneous.

**45.** The method of claim 39, wherein the subject is treatment naïve.

**46.** The method of claim 39, wherein the subject is treatment experienced.

**47.** 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 22.

**48.** The method of claim 47, further comprising the step of administering to the subject at least one AKR competitor in an amount sufficient to increase the bioavailability of at least one HCV protease inhibitor.

**49.** The method of claim 48, wherein at least one AKR competitor is diflunisal.

**50.** The method of claim 47, further comprising the step of administering to the subject at least one cytochrome P450 isoenzyme 3A4 (CYP3A4) inhibitor in an amount sufficient to increase the bioavailability of at least one HCV protease inhibitor.

**51.** The medicament of claim 50, wherein at least one CYP3A4 inhibitor is ritonavir, ketoconazole, or clarithromycin.

**52.** The method of claim 47, wherein said administration is oral, intravenous, intrathecal, or subcutaneous.

**53.** The method of claim 47, wherein the subject is treatment naïve.

**54.** The method of claim 47, wherein the subject is treatment experienced.

**55.** 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 31.

**56.** The method of claim 55, further comprising the step of administering to the subject at least one AKR competitor in an amount sufficient to increase the bioavailability of at least one HCV protease inhibitor.

**57.** The method of claim 56, wherein at least one AKR competitor is diflunisal.

**58.** The method of claim 55, further comprising the step of administering to the subject at least one cytochrome P450 isoenzyme 3A4 (CYP3A4) inhibitor in an amount sufficient to increase the bioavailability of at least one HCV protease inhibitor.

**59.** The medicament of claim 58, wherein at least one CYP3A4 inhibitor is ritonavir, ketoconazole, or clarithromycin.

**60.** The method of claim 55, wherein said administration is oral, intravenous, intrathecal, or subcutaneous.

**61.** The method of claim 55, wherein the subject is treatment naïve.

**62.** The method of claim 55, wherein the subject is treatment experienced.

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