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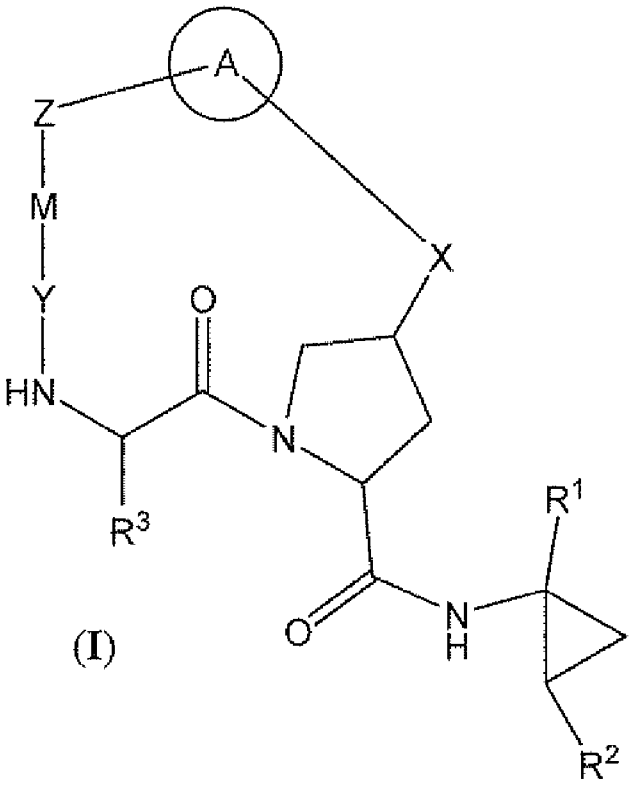
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(54) Title: HCV NS3 PROTEASE INHIBITORS



(I)

(57) Abstract: The present invention relates to macrocyclic compounds of formula I that are useful as inhibitors of the hepatitis C virus (HCV) NS3 protease, their synthesis, and their use for treating or preventing HCV infections.

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TITLE OF THE APPLICATION

HCV NS3 PROTEASE INHIBITORS

FIELD OF THE INVENTION

The present invention relates to macrocyclic compounds that are useful as inhibitors of the hepatitis C virus (HCV) NS3 protease, the synthesis of such compounds, and the use of such compounds for treating HCV infection and/or reducing the likelihood or severity of symptoms of HCV infection.

BACKGROUND OF THE INVENTION

Hepatitis C virus (HCV) infection is a major health problem that leads to chronic liver disease, such as cirrhosis and hepatocellular carcinoma, in a substantial number of infected individuals. Current treatments for HCV infection include immunotherapy with recombinant interferon-α alone or in combination with the nucleoside analog ribavirin.

Several virally-encoded enzymes are putative targets for therapeutic intervention, including a metalloprotease (NS2-3), a serine protease (NS3, amino acid residues 1-180), a helicase (NS3, full length), an NS3 protease cofactor (NS4A), a membrane protein (NS4B), a zinc metalloprotein (NS5A) and an RNA-dependent RNA polymerase (NS5B).

Potential treatments for HCV infection has been discussed in the different references including Balsano, *Mini Rev. Med. Chem. 8(4)*:307-318, 2008, Rönn *et al.*, *Current Topics in Medicinal Chemistry 8*:533-562, 2008, Sheldon *et al., Expert Opin. Investig. Drugs 16(8)*:1171-1181, 2007, and De Francesco *et al., Antiviral Research 58*:1-16, 2003.

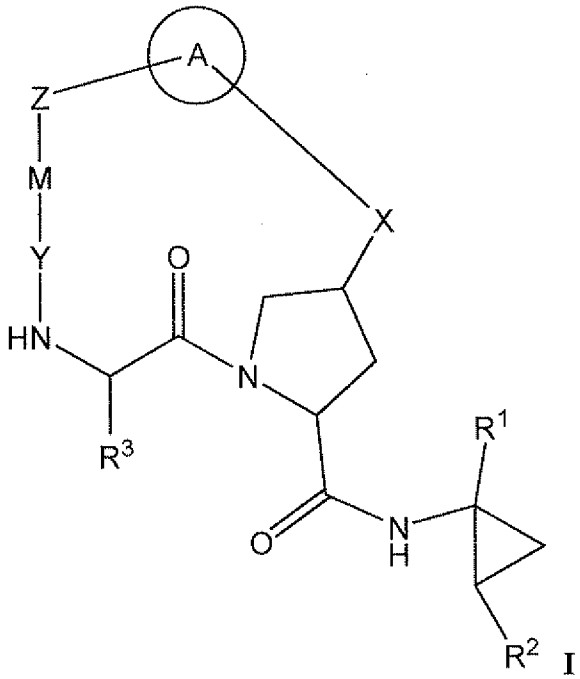
There is a clear and long-felt need to develop effective therapeutics for treatment of HCV infection. Specifically, there is a need to develop compounds that are useful for treating HCV-infected patients and compounds that selectively inhibit HCV viral replication. Thus, there is a need for compounds that are effective inhibitors of the NS3 protease.

SUMMARY OF THE INVENTION

The present invention relates to novel macrocyclic compounds of formula **I** and/or pharmaceutically acceptable salts or hydrates thereof. These compounds are useful in the inhibition of HCV (hepatitis C virus) NS3 (non-structural 3) protease, the prevention or treatment of one or more of the symptoms of HCV infection, either as compounds or their pharmaceutically acceptable salts or hydrates (when appropriate), or as pharmaceutical

composition ingredients. As pharmaceutical composition ingredients, these compounds, salts and hydrates may be the primary active therapeutic agent, and, when appropriate, may be combined with other therapeutic agents including but not limited to other HCV antivirals, anti-infectives, immunomodulators, antibiotics or vaccines.

More particularly, the present invention relates to a compound of formula **I** and/or a pharmaceutically acceptable salt or hydrate thereof:



I

wherein:

A is one or more rings selected from the group consisting of:

a) aryl rings,

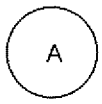
b) C_3-C_8 cycloalkyl rings, and

c) heterocyclic rings in which the heterocyclic ring system attaches to Z and X at points that are two independently selected ring atoms that are either two carbon ring atoms or one carbon ring atom and one nitrogen ring atom, and the heterocyclic ring system is selected from the group consisting of:

i) 5- or 6-membered saturated or unsaturated monocyclic rings with 1, 2, or 3 heteroatom ring atoms independently selected from the group consisting of N, O or S,

ii) 8-, 9- or 10-membered saturated or unsaturated bicyclic rings with 1, 2, or 3 heteroatom ring atoms independently selected from the group consisting of N, O or S, and

iii) 11- to 15-membered saturated or unsaturated tricyclic rings with 1, 2, 3, or 4 heteroatom ring atoms independently selected from the group consisting of N, O or S,

wherein  is substituted with 0 to 4 independently selected substituents R^4, R^5 or oxo; wherein for stable heterocyclic rings containing S or N, the heterocyclic ring is unsubstituted at the S or N atom or is substituted at the S by oxo; wherein the R^4 and R^5 substitutions are located on one or more ring atoms selected from C and N;

X is selected from the group consisting of -O-, $-CH_2O-$, -NHC(O)O-, $-CH_2NHC(O)O-$, $-C\equiv CCH_2O-$, -C(O)O-, $-(CH_2)_3O-$, -OC(O)NH-, $-(CH_2)_2C(O)NH-$, -C(O)NH- and a direct bond;

R^1 is selected from the group consisting of $-CO_2R^6$, $-CONR^6SO_2R^7$, $-CONR^6SO_2NR^8R^9$, tetrazolyl, $-CONHP(O)R^{10}R^{11}$, and $-P(O)R^{10}R^{11}$;

R^2 is selected from the group consisting of C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_3-C_8 cycloalkyl, wherein the R^2 are substituted with 0 to 3 independently selected halogen atoms;

R^3 is selected from the group consisting of H, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_8)alkyl, phenyl(C_1-C_8)alkyl, naphthyl(C_1-C_8)alkyl, and Het groups, wherein when R^3 is not H, the R^3 is substituted with 0 to 3 substituents independently selected from the group consisting of halogen atoms, $-OR^6$, $-SR^6$, $-N(R^6)_2$, -N(C_1-C_6 alkyl)O(C_1-C_6 alkyl), C_1-C_6 alkyl, C_1-C_6 haloalkyl, halo(C_1-C_6 alkoxy), $-NO_2$, -CN, $-CF_3$, $-SO_2$(C_1-C_6 alkyl), -S(O)(C_1-C_6 alkyl), $-NR^6SO_2R^7$, $SO_2N(R^7)_2$, $-NHCOOR^7$, $-NHCOR^7$, $-NHCONHR^7$, $-CO_2R^6$, $-C(O)R^6$, and $-CON(R^6)_2$;

Het is selected from the group consisting of substituted and unsubstituted 5- and 6-membered saturated heterocyclic rings having 1 or 2 heteroatoms independently selected from N, O and S;

Y is selected from the group consisting of -C(O)-, -SO_2-, -OC(O)-, -C(O)N(R^{12})L- and -LN(R^{12})C(O)-, where

R^{12} is selected from the group consisting of H, C_1-C_6 alkyl and C_1-C_6 alkenyl groups,

L is selected from the group consisting of a direct bond, -G-(C_1-C_6 alkylene)-, -(C_1-C_6 alkylene)-G-, -G-(C_1-C_6 alkenylene)-, and -(C_1-C_6 alkenylene)-G-, groups, where the G is selected from the group consisting of a direct bond, -O-, -N- and -S-, the alkylene and alkenylene groups are substituted with 0 to 4 substituents R^{13} independently selected from the group consisting of C_1-C_6 alkyl and C_1-C_6 alkenyl groups, and

the R^{12} and R^{13} may be taken together to form a 3- to 6-membered ring containing 0 to 3 heteroatoms selected from N, O and S;

M is selected from the group consisting of C_1-C_{12} alkylenes, C_2-C_{12} alkenylenes and C_2-C_{12} alkynylenes, wherein:

the M contains 0 or 1 -O- moiety in place of a methylene moiety, and

the M is substituted with from 0 to 4 substituents R^{14}, wherein:

each R^{14} is independently selected from the group consisting of C_1-C_8 alkyl, =CH_2, C_3-C_8 cycloalkyl(C_1-C_8 alkyl), and aryl(C_1-C_8 alkyl), and

any substituent R^{14} may be taken together with any adjacent substituent R^{14} or any adjacent substituent R^{12} or R^{13} to form a 3- to 6-membered ring containing 0 to 3 heteroatoms independently selected from the group consisting of N, O and S;

Z is selected from the group consisting of -C(O)- and a direct bond;

R^4 is selected from the group consisting of H, halogen atoms, -OH, C_1-C_6 alkoxy, C_1-C_6 alkyl, -CN, -CF_3, -OCF_3, -C(O)OH, -$C(O)CH_3$, -SR^6, -SO_2(C_1-C_6 alkyl), C_3-C_8 cycloalkyl, C_3-C_8 cycloalkoxy, C_1-C_6 haloalkyl, -N(R^{15})$_2$, phenyl, naphthyl, -O-phenyl, -O-naphthyl, heteroaryl and heterocyclyl groups; wherein:

the R^4 heteroaryl is selected from the group consisting of 5- and 6-membered aromatic rings having 1, 2 or 3 heteroatoms independently selected from N, O and S, and the R^4 heteroaryl is attached through a ring atom selected from C or N,

the R^4 heterocyclyl is selected from the group consisting of 5- to 7-membered saturated or unsaturated non-aromatic rings having 1, 2, 3 or 4 heteroatoms independently selected from N, O and S, and the R^4 heterocyclyl is attached through a ring atom selected from C or N, and

the R^4 heteroaryl, heterocyclyl, cycloalkyl, cycloalkoxy, alkyl and alkoxy groups are substituted with 0 to 4 substituents independently selected from the group consisting of halogen atoms, $-OR^6$, $-SR^6$, $-N(R^6)_2$, $-N(C_1\text{-}C_6$ alkyl$)O(C_1\text{-}C_6$ alkyl), $C_1\text{-}C_6$ alkyl, $C_1\text{-}C_6$ haloalkyl, halo($C_1\text{-}C_6$ alkoxy), $-NO_2$, $-CN$, $-CF_3$,$-SO_2(C_1\text{-}C_6$ alkyl), $-S(O)(C_1\text{-}C_6$ alkyl), $-NR^6SO_2R^7$, $SO_2N(R^7)_2$, $-NHCOOR^7$, $-NHCOR^7$, $-NHCONHR^7$, $-CO_2R^6$, $-C(O)R^6$, and $-CON(R^6)_2$, and 2 adjacent substituents of the R^4 heteroaryl, heterocyclyl, cycloalkyl, cycloalkoxy, alkyl and alkoxy groups may be taken together to form a 3- to 6-membered cyclic ring containing 0 to 3 heteroatoms independently selected from N, O and S;

each R^5 is independently selected from the group consisting of H, halogen atoms, $-OR^6$, $C_1\text{-}C_6$ alkyl, $-CN$, $-CF_3$, $-NO_2$, $-SR^6$, $-CO_2R^6$, $-CON(R^6)_2$, $-C(O)R^6$, $-N(R^6)C(O)R^6$, $-SO_2(C_1\text{-}C_6$ alkyl), $-S(O)(C_1\text{-}C_6$ alkyl), $C_3\text{-}C_8$ cycloalkyl, $C_3\text{-}C_8$ cycloalkoxy, $C_1\text{-}C_6$ haloalkyl, $-N(R^6)_2$, $-N(C_1\text{-}C_6$ alkyl$)O(C_1\text{-}C_6$ alkyl), halo($C_1\text{-}C_6$ alkoxy), $-NR^6SO_2R^6$, $-SO_2N(R^6)_2$, $-NHCOOR^6$, $-NHCONHR^6$, phenyl, naphthyl, heteroaryl and heterocyclyl groups, wherein

the R^5 heteroaryl is selected from the group consisting of 5- and 6-membered aromatic rings having 1, 2 or 3 heteroatoms independently selected from N, O and S, and the R^5 heteroaryl is attached through a ring atom selected from C or N,

the R^5 heterocyclyl is selected from the group consisting of 5- to 7-membered saturated or unsaturated non-aromatic rings having 1, 2, 3 or 4 heteroatoms independently selected from N, O and S, and the R^5 heterocyclyl is attached through a ring atom selected from C or N;

each R^6 is independently selected from the group consisting of H, $C_1\text{-}C_6$ alkyl and benzyl, wherein each R^6 is independently substituted with 0 to 4 substituents selected from the group consisting of halogen atoms, $C_1\text{-}C_6$ alkyl, $C_1\text{-}C_6$ haloalkyl, phenyl, naphthyl, $C_3\text{-}C_8$ cycloalkyl, heteroaryl, heterocyclyl, halo($C_1\text{-}C_6$ alkoxy), $-OH$, $-O(C_1\text{-}C_6$ alkyl), $-SH$, $-S(C_1\text{-}C_6$ alkyl), $-NH_2$, $-NH(C_1\text{-}C_6$ alkyl), $-N(C_1\text{-}C_6$ alkyl$)_2$, $-C(O)(C_1\text{-}C_6$ alkyl), NO_2, $-CN$, $-CF_3$, $-SO_2(C_1\text{-}C_6$ alkyl), $-S(O)(C_1\text{-}C_6$ alkyl), $-N(C_1\text{-}C_6$ alkyl$)SO_2(C_1\text{-}C_6$ alkyl), $-SO_2N(C_1\text{-}C_6$ alkyl$)_2$,

-NHCOO(C_1-C_6 alkyl), -NHCO(C_1-C_6 alkyl), -NHCONH(C_1-C_6 alkyl), -CO_2(C_1-C_6 alkyl), and -C(O)N(C_1-C_6 alkyl)$_2$;

R^7 is selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl(C_1-C_5)alkyl, phenyl, naphthyl, phenyl(C_1-C_4)alkyl, naphthyl(C_1-C_4)alkyl, heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl, and heterocyclyl(C_1-C_8 alkyl) groups, wherein

the R^7 are substituted with 0 to 2 independently selected R^5 substituents,

each R^7 heteroaryl is independently selected from the group consisting of 5- and 6-membered aromatic rings having 1, 2 or 3 heteroatoms independently selected from N, O and S, and the R^7 heteroaryl is attached through a ring atom selected from C or N, and

each R^7 heterocyclyl is independently selected from the group consisting of 5- to 7-membered saturated or unsaturated non-aromatic rings having 1, 2, 3 or 4 heteroatoms independently selected from N, O and S, and the R^7 heterocyclyl is attached through a ring atom selected from C or N;

R^8 is selected from the group consisting of H, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_8 alkyl), phenyl, naphthyl, phenyl(C_1-C_4)alkyl, naphthyl(C_1-C_4)alkyl, heteroaryl, heterocyclic, heteroaryl(C_1-C_4 alkyl), and heterocyclyl(C_1-C_8 alkyl) groups, wherein

the R^8 are substituted with 0 to 4 substituents selected from the group consisting of phenyl, naphthyl, C_3-C_8 cycloalkyl, heteroaryl, heterocyclyl, C_1-C_6 alkyl, halo(C_1-C_6 alkoxy), halogen atoms, -OR^6, -SR^6, -N(R^6)$_2$, -N(C_1-C_6 alkyl)O(C_1-C_6 alkyl), C_1-C_6 alkyl, -C(O)R^6, C_1-C_6 haloalkyl, -NO_2, -CN, -CF_3, -SO_2(C_1-C_6 alkyl), -S(O)(C_1-C_6 alkyl), -$NR^6SO_2R^7$, -SO_2N(R^7)$_2$, -NHCOOR^7, -NHCOR^7, -NHCONHR^7, -CO_2R^6, and -C(O)N(R^6)$_2$,

each R^8 heteroaryl is independently selected from the group consisting of 5- and 6-membered aromatic rings having 1, 2 or 3 heteroatoms independently selected from N, O and S, and the R^8 heteroaryl is attached through a ring atom selected from C or N,

each R^8 heterocyclyl is independently selected from the group consisting of 5- to 7-membered saturated or unsaturated non-aromatic rings having 1, 2, 3 or 4 heteroatoms independently selected from N, O and S, and the R^8 heterocyclyl is attached through a ring atom selected from C or N, and

2 adjacent substituents of the R^8 may be taken together to form a 3- to 6-membered ring containing 0 to 3 heteroatoms independently selected from the group consisting of N, O and S;

R^9 is selected from the group consisting of H, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_8 alkyl), C_1-C_8 alkoxy, C_3-C_8 cycloalkoxy, phenyl, naphthyl, phenyl(C_1-C_4)alkyl, naphthyl(C_1-C_4)alkyl, heteroaryl, heterocyclyl, heteroaryl(C_1-C_4 alkyl), or heterocyclyl(C_1-C_8 alkyl) groups, wherein

the R^9 are substituted with 0 to 4 substituents selected from the group consisting of phenyl, naphthyl, C_3-C_8 cycloalkyl, heteroaryl, heterocyclyl, C_1-C_6 alkyl, halo(C_1-C_6 alkoxy), halogen atoms, $-OR^6$, $-SR^6$, $-N(R^6)_2$, $-N(C_1$-C_6 alkyl)$O(C_1$-C_6 alkyl), C_1-C_6 alkyl, $-C(O)R^6$, C_1-C_6 haloalkyl, $-NO_2$, -CN, $-CF_3$,$-SO_2(C_1$-C_6 alkyl), $-S(O)(C_1$-C_6 alkyl), $-NR^6SO_2R^7$, $-SO_2N(R^7)_2$, $-NHCOOR^7$, $-NHCOR^7$, $-NHCONHR^7$, $-CO_2R^6$, and $-C(O)N(R^6)_2$,

each R^9 heteroaryl is independently selected from the group consisting of 5- and 6-membered aromatic rings having 1, 2 or 3 heteroatoms independently selected from N, O and S, and the R^9 heteroaryl is attached through a ring atom selected from C or N,

each R^9 heterocyclyl is independently selected from the group consisting of 5- to 7-membered saturated or unsaturated non-aromatic rings having 1, 2, 3 or 4 heteroatoms independently selected from N, O and S, and the R^9 heterocyclyl is attached through a ring atom selected from C or N, and

2 adjacent substituents of the R^9 may be taken together to form a 3- to 6-membered ring containing 0 to 3 heteroatoms independently selected from the group consisting of N, O and S, and

R^8 and R^9 may be taken together, with the N to which they are attached, to form a 4- to 8-membered monocyclic ring containing 0 to 2 additional heteroatoms independently selected from N, O and S;

each R^{10} is independently selected from the group consisting of H, C_1-C_6 alkyl, C_1-C_4 alkenyl, $-OR^{16}$, $-N(R^6)$-V-CO_2R^6, -O-V-CO_2R^6, -S-V-CO_2R^6, $-N(R^6)(R^{16})$, $-R^{17}$, and $-N(R^6)SO_2R^7$;

each R^{11} is independently selected from the group consisting of H, $-OR^{16}$, $-N(R^6)$-V-CO_2R^6, -O-V-CO_2R^6, -S-V-CO_2R^6, and $-N(R^6)(R^{16})$;

R^{10} and R^{11} may be taken together, with the phosphorus atom to which they are attached, to form a 5- to 7-membered monocyclic ring;

each V is independently selected from the group consisting of -CH(R^{18})- and -(C_1-C_4 alkylene)-CH(R^{18})-;

each R^{15} is independently selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl(C_1-C_5)alkyl, phenyl, naphthyl, phenyl(C_1-C_4)alkyl, naphthyl(C_1-C_4)alkyl, heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl, and heterocyclyl(C_1-C_8 alkyl) groups, wherein

when R^{15} is not H, the R^{15} are substituted with 0 to 2 R^5 substituents,

each R^{15} heteroaryl is independently selected from the group consisting of 5- and 6-membered aromatic rings having 1, 2 or 3 heteroatoms independently selected from N, O and S, and the R^{15} heteroaryl is attached through a ring atom selected from C or N, and

each R^{15} heterocyclyl is independently selected from the group consisting of 5- to 7-membered saturated or unsaturated non-aromatic rings having 1, 2, 3 or 4 heteroatoms independently selected from N, O and S, and the R^{15} heterocyclyl is attached through a ring atom selected from C or N, and

the R^{15} may be taken together with the atom to which it is attached and a second R^{15} substituent to form a 4- to 7-membered heterocyclic ring;

each R^{16} is independently selected from the group consisting of H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, aryl, heteroaryl, and heterocyclyl groups, wherein

when R^{16} is not H, the R^{16} is substituted with 0 to 2 substituents independnetly selected from the group consisting of phenyl, naphthyl, phenyl(C_1-C_4 alkyl), naphthyl(C_1-C_4 alkyl), C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl, heterocyclyl(C_1-C_4 alkyl), C_1-C_6 alkyl, halogen atoms, -OC(O)OR^7, -OC(O)R^7, -OR^6, -SR^6, -N(R^6)$_2$, -C(O)R^6, -NO_2, -CN, -CF_3, -SO_2(C_1-C_6 alkyl), -S(O)(C_1-C_6 alkyl), -N$R^6$$SO_2$$R^7$, -$SO_2$N($R^7$)$_2$, -NHCOO$R^7$, -NHCO$R^7$, -NHCONH$R^7$, -$CO_2$$R^6$, and -C(O)N($R^6$)$_2$,

each R^{16} heteroaryl is independently selected from the group consisting of 5- and 6-membered aromatic rings having 1, 2 or 3 heteroatoms independently selected from N, O and S, and the R^{16} heteroaryl is attached through a ring atom selected from C or N,

each R^{16} heterocyclyl is independently selected from the group consisting of 5- to 7-membered saturated or unsaturated non-aromatic rings having 1, 2, 3 or 4 heteroatoms independently selected from N, O and S, and the R^{16} heterocyclyl is attached through a ring atom selected from C or N, and

2 adjacent substituents of the R^{16} may be taken together to form a 3- to 6-membered ring containing 0 to 3 heteroatoms independently selected from the group consisting of N, O and S;

R^{17} is selected from the group consisting of H, C_1-C_6 alkyl, C_2-C_6 alkenyl, phenyl, naphthyl and heteroaryl, wherein

each R^{17} heteroaryl is independently selected from the group consisting of 5- and 6-membered aromatic rings having 1, 2 or 3 heteroatoms independently selected from N, O and S, and the R^{17} heteroaryl is attached through a ring atom selected from C or N, and

the R^{17} phenyl, naphthyl or heteroaryl may be substituted with 0 to 2 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen atoms, $-OC(O)OR^7$, $-OC(O)R^7$, $-OR^6$, $-SR^6$, $-N(R^6)_2$, $-C(O)R^6$, $-NO_2$, $-CN$, $-CF_3$, $-SO_2(C_1$-C_6 alkyl), $-S(O)(C_1$-C_6 alkyl), $-NR^6SO_2R^7$, $-SO_2N(R^7)_2$, $-NHCOOR^7$, $-NHCOR^7$, $-NHCONHR^7$, $-CO_2R^6$, and $-C(O)N(R^6)_2$; and

each R^{18} is independently selected from the group consisting of H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, phenyl, naphthyl, heteroaryl, and heterocyclyl groups, wherein

the R^{18} are substituted with 0 to 2 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen atoms, $-OC(O)OR^7$, $-OC(O)R^7$, $-OR^6$, $-SR^6$, $-N(R^6)_2$, $-C(O)R^6$, $-NO_2$, $-CN$, $-CF_3$, $-SO_2(C_1$-C_6 alkyl), $-S(O)(C_1$-C_6 alkyl), $-NR^6SO_2R^7$, $-SO_2N(R^7)_2$, $-NHCOOR^7$, $-NHCOR^7$, $-NHCONHR^7$, $-CO_2R^6$, and $-C(O)N(R^6)_2$,

each R^{18} heteroaryl is independently selected from the group consisting of 5- and 6-membered aromatic rings having 1, 2 or 3 heteroatoms independently selected from N, O and S, and the R^{18} heteroaryl is attached through a ring atom selected from C or N,

each R^{18} heterocyclyl is independently selected from the group consisting of 5- to 7-membered saturated or unsaturated non-aromatic rings having 1, 2, 3 or 4 heteroatoms independently selected from N, O and S, and the R^{18} heterocyclyl is attached through a ring atom selected from C or N, and

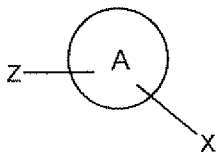
2 adjacent substituents of the R^{18} are optionally taken together to form a 3- to 6-membered ring containing 0 to 3 heteroatoms independently selected from the group consisting of N, O and S.

The present invention also includes pharmaceutical compositions containing a compound of the present invention and methods of preparing such pharmaceutical compositions. The present invention further includes methods of treating or preventing one or more symptoms of HCV infection.

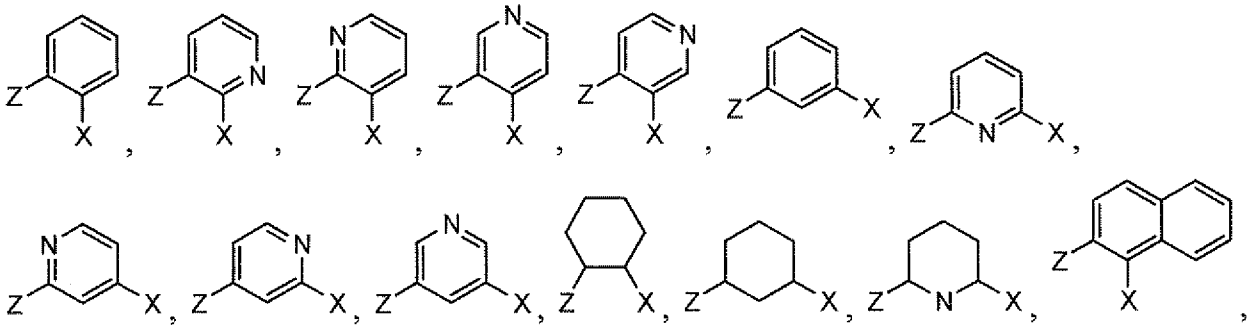
Other embodiments, aspects and features of the present invention are either further described in or will be apparent from the ensuing description, examples and appended claims.

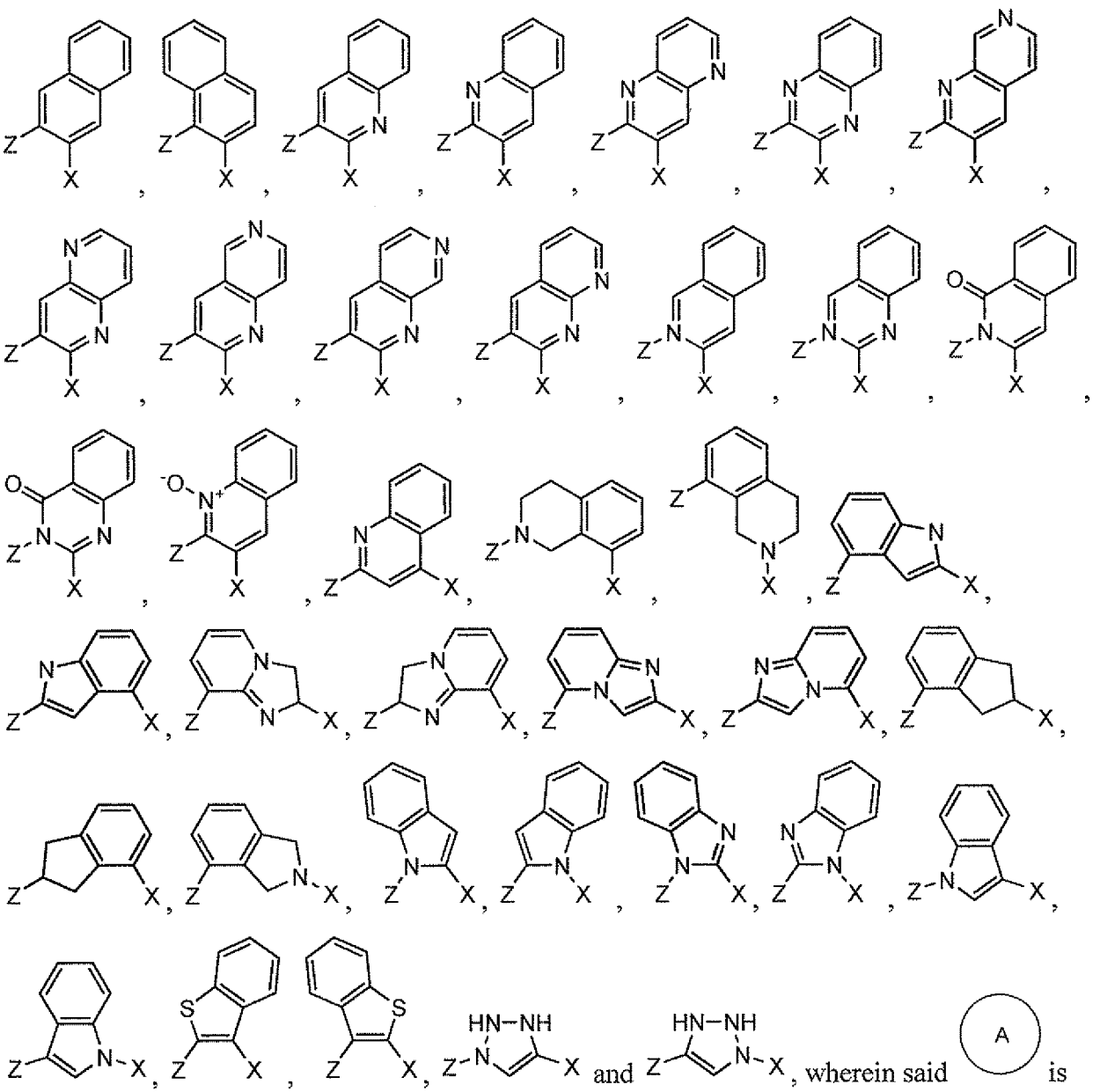
DETAILED DESCRIPTION OF THE INVENTION

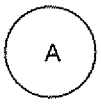
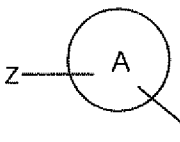
The present invention includes compounds of formula **I** above, and pharmaceutically acceptable salts and/or hydrates thereof. These compounds and their pharmaceutically acceptable salts and/or hydrates are HCV protease inhibitors (*e.g.*, HCV NS3 protease inhibitors).

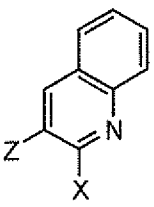
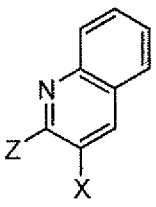
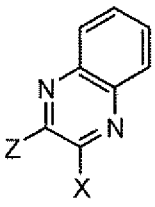
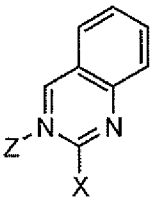
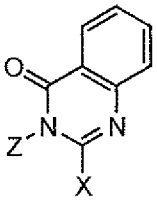
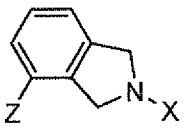
In a first embodiment of the invention, 

is selected from the group consisting of:

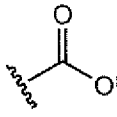
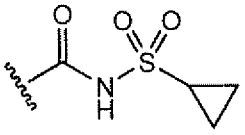
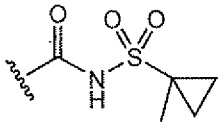
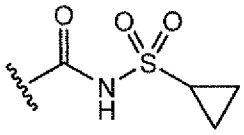
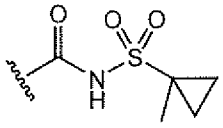




substituted with 0 to 4 independently selected substituents R^4, R^5 or oxo; wherein for stable heterocyclic rings containing S or N, the heterocyclic ring is unsubstituted at the S or N atom or is substituted at the S or N atom by oxo; wherein said R^4 and R^5 substitutions are located on one or more ring atoms selected from C and N. In aspects of the first embodiment,  is unsubstituted or mono-substituted with a moiety selected from the group consisting of -Br, -Cl, -CN, phenyl, -O-phenyl, $-OCF_3$, $-OCH_3$, -OH, C_1-C_6 alkoxy, C_1-C_6 alkyl, $-CF_3$, -C(O)OH, and $-C(O)CH_3$. In particular aspects of the first embodiment,  is selected from the

group consisting of  ,  ,  ,  ,  and  , and substituted with 0 to 2 independently selected substituents -Cl, -O-benzyl, $-OCH_3$, -OH, $-CH_3$. In all aspects of this embodiment, all other groups are as provided in the general formula above.

In a second embodiment of the invention, X is selected from the group consisting of -O- and -C(O)O-. In this embodiment, all other groups are as provided in the general formula above or in the first embodiment.

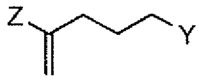
In a third embodiment of the invention, R^1 is selected from the group consisting of $-CO_2R^6$ and $-CONR^6SO_2R^7$. In aspects of this embodiment, R^1 is selected from the group consisting of  ,  and  . In particular aspects of this embodiment, R^1 is selected from the group consisting of  and  . In all aspects of this embodiment, all other groups are as provided in the general formula above or in either or both of the first or second embodiments.

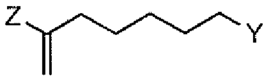
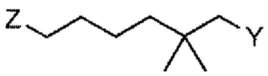
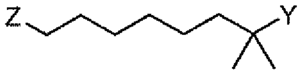
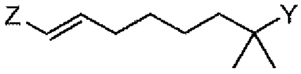
In a fourth embodiment of the invention, R^2 is selected from the group consisting of C_1-C_6 alkyl and C_2-C_6 alkenyl. In aspects of this embodiment, R^2 is selected from the group consisting of $-CH=CH_2$, $-CH_2CH_3$, and $-CH_2CH=CH_2$. In particular aspects of this embodiment, R^2 is selected from the group consisting of $-CH=CH_2$ and $-CH_2CH_3$. In all aspects of this embodiment, all other groups are as provided in the general formula above or in any or all of the first through third embodiments.

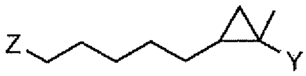
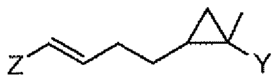
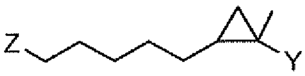
In a fifth embodiment of the invention, R^3 is selected from the group consisting of H, C_1-C_8 alkyl and C_3-C_8 cycloalkyl. In aspects of this embodiment, R^3 is selected from the group consisting of H, $-C(CH_3)_3$, $-(CH_2)_3CH_3$, cyclohexyl, and $-CH(CH_3)_2$. In particular aspects

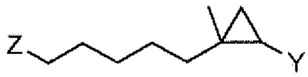
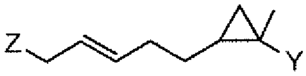
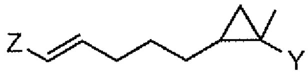
of this embodiment, R^3 is selected from the group consisting of $-C(CH_3)_3$ and cyclohexyl. In all aspects of this embodiment, all other groups are as provided in the general formula above or in any or all of the first through fourth embodiments.

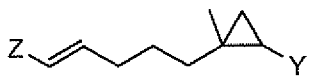
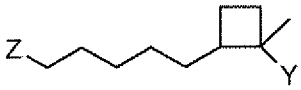
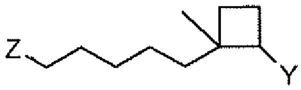
In a sixth embodiment of the invention, Y is selected from the group consisting of -OC(O)-, -C(O)N(R^{12})L- and -LN(R^{12})C(O)-. In aspects of this embodiment, Y is -OC(O)-. In this embodiment, all other groups are as provided in the general formula above or in any or all of the first through fifth embodiments.

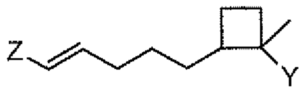
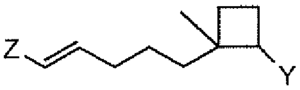
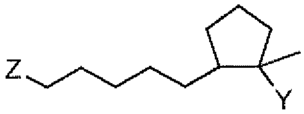
In a seventh embodiment of the invention, M is selected from the group consisting of C_1-C_{12} alkylene or C_2-C_{12} alkenylene, wherein M is substituted with 0 to 3 substituents R^{14} selected from the group consisting of C_1-C_8 alkyl, and $=CH_2$. In aspects of this embodiment, Z-M-Y is selected from the group consisting of  ,

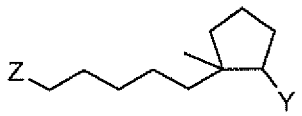
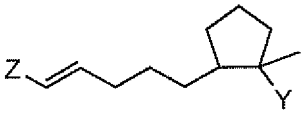
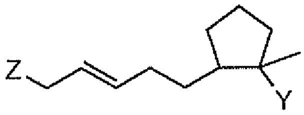
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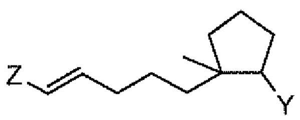
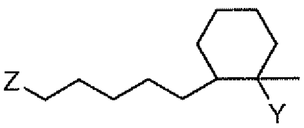
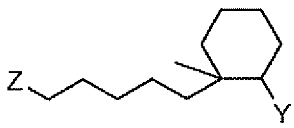
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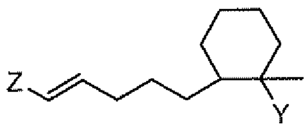
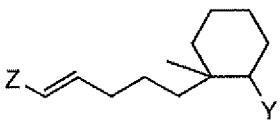
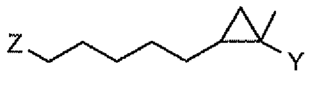
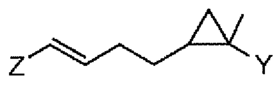
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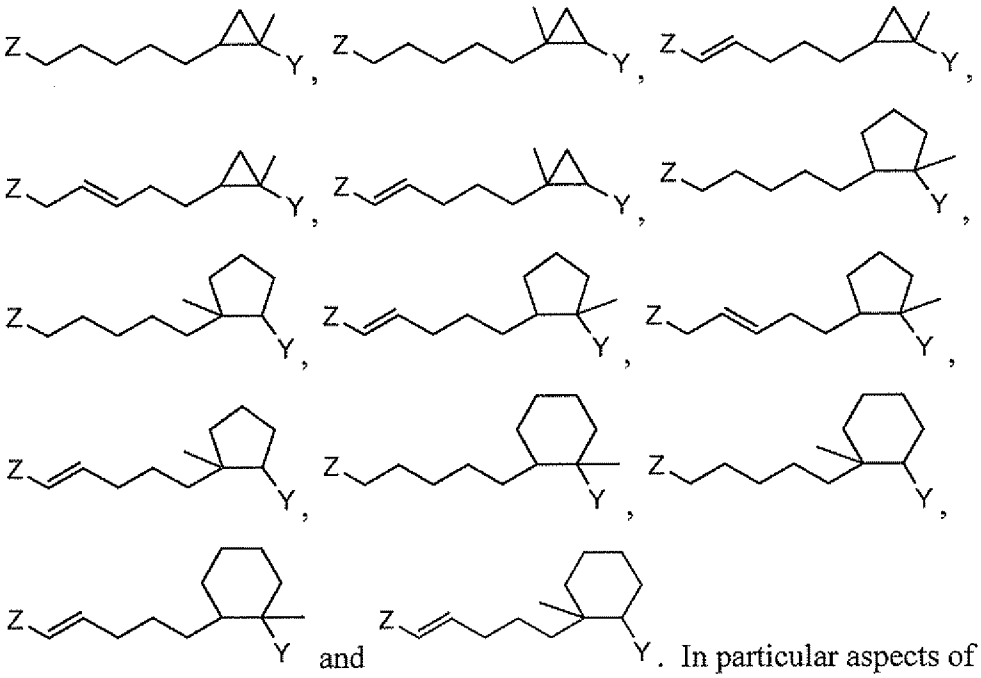
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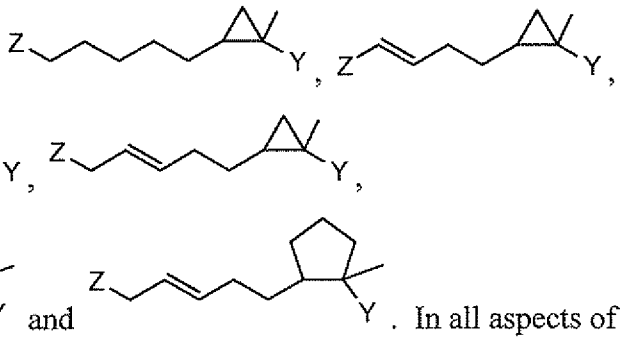
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 and  . In still further aspects of this embodiment, Z-M-Y is selected from the group consisting of  ,  ,

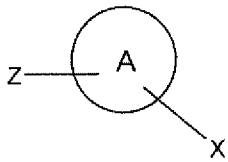
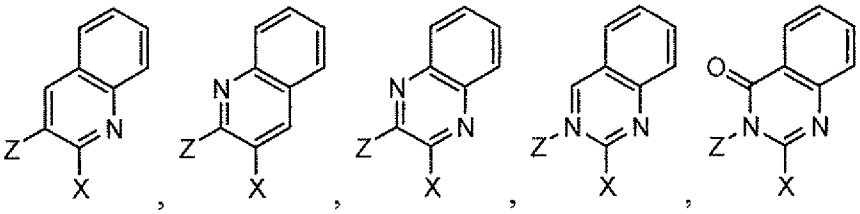
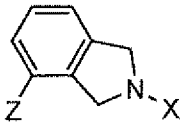
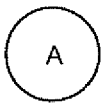
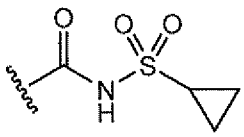
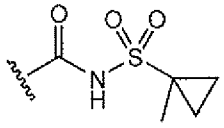
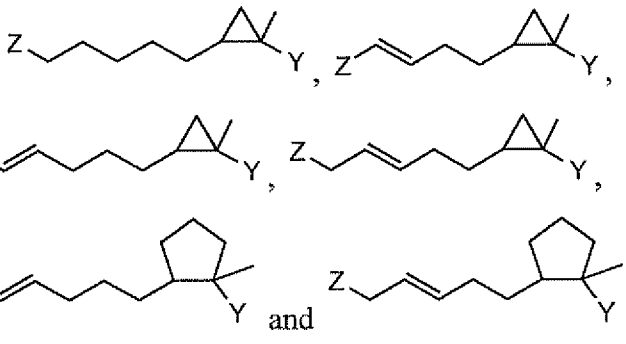


and . In particular aspects of this embodiment, Z-M-Y is selected from the group consisting of 

and . In all aspects of this embodiment, all other groups are as provided in the general formula above or in any or all of the first through sixth embodiments.

In an eighth embodiment of the invention, one or more substituents R^{14} are taken together and/or with one or more substituents chosen from substituents R^{12} and R^{13} to form a 3- to 6-membered ring containing 0 to 3 heteroatoms selected from the group consisting of N, O and S. In this embodiment, all other groups are as provided in the general formula above or in any or all of the first through seventh embodiments.

In a ninth embodiment of the invention, Z is a direct bond. In this embodiment, all other groups are as provided in the general formula above or in any or all of the first through eighth embodiments.

In a tenth embodiment of the invention,  is selected from the group consisting of:  and  , wherein said  is substituted with 0 to 2 independently selected substituents -Cl, -O-benzyl, $-OCH_3$, -OH, $-CH_3$; X is selected from the group consisting of -O- and -C(O)O-; R^1 is selected from the group consisting of  and  ; R^2 is selected from the group consisting of $-CH{=}CH_2$ and $-CH_2CH_3$; R^3 is selected from the group consisting of $-C(CH_3)_3$ and cyclohexyl; Y is -OC(O)-; Z-M-Y is selected from the group consisting of  and ; and Z is a direct bond.

In a tenth embodiment of the invention, the compound is selected from the compounds of Examples 1 through 32, *i.e.* compounds **I-1** through **I-32** and pharmaceutically acceptable salts thereof.

In another embodiment of the invention, the compound of the invention is selected from the exemplary species depicted in Examples 1 through 32 shown below.

Other embodiments of the present invention include the following:

(a) A pharmaceutical composition comprising an effective amount of a compound of formula **I** and a pharmaceutically acceptable carrier.

(b) The pharmaceutical composition of (a), further comprising a second therapeutic agent selected from the group consisting of HCV antiviral agents, immunomodulators, and anti-infective agents.

(c) The pharmaceutical composition of (b), wherein the HCV antiviral agent is an antiviral selected from the group consisting of HCV protease inhibitors and HCV NS5B polymerase inhibitors.

(d) A pharmaceutical combination which is (i) a compound of formula **I** and (ii) a second therapeutic agent selected from the group consisting of HCV antiviral agents, immunomodulators, and anti-infective agents; wherein the compound of formula **I** and the second therapeutic agent are each employed in an amount that renders the combination effective for inhibiting HCV NS3 protease, or for treating HCV infection and/or reducing the likelihood or severity of symptoms of HCV infection.

(e) The combination of (d), wherein the HCV antiviral agent is an antiviral selected from the group consisting of HCV protease inhibitors and HCV NS5B polymerase inhibitors.

(f) A method of inhibiting HCV NS3 protease in a subject in need thereof which comprises administering to the subject an effective amount of a compound of formula **I**.

(g) A method of treating HCV infection and/or reducing the likelihood or severity of symptoms of HCV infection in a subject in need thereof which comprises administering to the subject an effective amount of a compound of formula **I**.

(h) The method of (g), wherein the compound of formula **I** is administered in combination with an effective amount of at least one second therapeutic agent selected from the group consisting of HCV antiviral agents, immunomodulators, and anti-infective agents.

(i) The method of (h), wherein the HCV antiviral agent is an antiviral selected from the group consisting of HCV protease inhibitors and HCV NS5B polymerase inhibitors.

(j) A method of inhibiting HCV NS3 protease in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b), or (c) or the combination of (d) or (e).

(k) A method of treating HCV infection and/or reducing the likelihood or severity of symptoms of HCV infection in a subject in need thereof which comprises

administering to the subject the pharmaceutical composition of (a), (b), or (c) or the combination of (d) or (e).

The present invention also includes a compound of the present invention for use (i) in medicine, (ii) as a medicament for, or (iii) in the preparation of a medicament for: (a) inhibiting HCV NS3 protease, or (b) treating HCV infection and/or reducing the likelihood or severity of symptoms of HCV infection. In these uses, the compounds of the present invention can optionally be employed in combination with one or more second therapeutic agents selected from HCV antiviral agents, anti-infective agents, and immunomodulators.

Additional embodiments of the invention include the pharmaceutical compositions, combinations and methods set forth in (a)-(k) above and the uses set forth in the preceding paragraph, wherein the compound of the present invention employed therein is a compound of one of the embodiments, aspects, classes, sub-classes, or features of the compounds described above. In all of these embodiments, the compound may optionally be used in the form of a pharmaceutically acceptable salt or hydrate as appropriate.

In the embodiments of the compound provided above, it is to be understood that each embodiment may be combined with one or more other embodiments, to the extent that such a combination provides a stable compound and is consistent with the description of the embodiments. It is further to be understood that the embodiments of compositions and methods provided as (a) through (k) above are understood to include all embodiments of the compounds, including such embodiments as result from combinations of embodiments.

As used herein, all ranges are inclusive, and all sub-ranges are included within such ranges, although not necessarily explicitly set forth. In addition, the term "or," as used herein, denotes alternatives that may, where appropriate, be combined; that is, the term "or" includes each listed alternative separately as well as their combination.

As used herein, the term "alkyl" refers to any linear or branched chain alkyl group having a number of carbon atoms in the specified range. Thus, for example, "C_{1-6} alkyl" (or "C_1-C_6 alkyl") refers to all of the hexyl alkyl and pentyl alkyl isomers as well as n-, iso-, sec- and t-butyl, n- and isopropyl, ethyl and methyl. As another example, "C_{1-4} alkyl" refers to n-, iso-, sec- and t-butyl, n- and isopropyl, ethyl and methyl. The term "alkoxy" refers to an "alkyl-O-" group.

The term "halogenated" refers to a group or molecule in which a hydrogen atom has been replaced by a halogen. Similarly, the term "haloalkyl" refers to a halogenated alkyl

group. The term "halogen" (or "halo") refers to atoms of fluorine, chlorine, bromine and iodine (alternatively referred to as fluoro, chloro, bromo, and iodo).

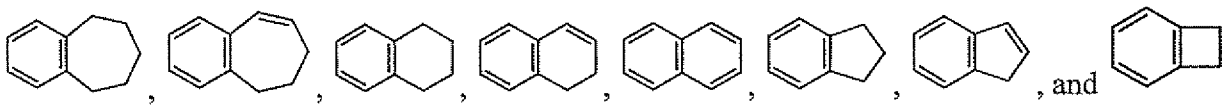
The term "alkylene" refers to any linear or branched chain alkylene group (or alternatively "alkanediyl") having a number of carbon atoms in the specified range. Thus, for example, "-C_{1-6} alkylene-" refers to any of the C_1 to C_6 linear or branched alkylenes. A class of alkylenes of particular interest with respect to the invention is -$(CH_2)_{1-6}$-, and sub-classes of particular interest include -$(CH_2)_{1-4}$-, -$(CH_2)_{1-3}$-, -$(CH_2)_{1-2}$-, and -CH_2-. Also of interest is the alkylene -$CH(CH_3)$-.

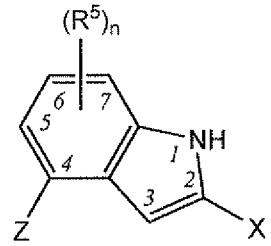
The terms "cycloalkyl" refers to any cyclic ring of an alkane or alkene having a number of carbon atoms in the specified range. Thus, for example, "C_{3-8} cycloalkyl" (or "C_3-C_8 cycloalkyl") refers to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. The term "cycloalkoxy" refers to a "-O-cycloalkyl" group.

The term "Het" refers to a 5- to 6-membered saturated cyclic ring having 1 or 2 heteroatoms selected from N, O and S, wherein said ring is optionally substituted with 1 to 3 substituents selected from halogen atoms, -OR^6, -SR^6, -$N(R^6)_2$, -$N(C_1$-C_6 alkyl)$O(C_1$-C_6 alkyl), C_1-C_6 alkyl, C_1-C_6 haloalkyl, halo(C_1-C_6 alkoxy), -NO_2, -CN, -CF_3, -$SO_2(C_1$-C_6 alkyl), -S(O)(C_1-C_6 alkyl), -$NR^6SO_2R^7$, $SO_2N(R^7)_2$, -NHCOOR^7, -NHCOR^7, -NHCONHR^7, -CO_2R^6, -C(O)R^6, and -$CON(R^6)_2$.

The term "carbocycle" (and variations thereof such as "carbocyclic" or "carbocyclyl") as used herein, unless otherwise indicated, refers to (i) a C_3 to C_8 monocyclic, saturated or unsaturated ring or (ii) a C_7 to C_{12} bicyclic saturated or unsaturated ring system. Each ring in (ii) is either independent of, or fused to, the other ring, and each ring is saturated or unsaturated. The carbocycle may be attached to the rest of the molecule at any carbon atom which results in a stable compound. The fused bicyclic carbocycles are a subset of the carbocycles; *i.e.*, the term "fused bicyclic carbocycle" generally refers to a C_7 to C_{10} bicyclic ring system in which each ring is saturated or unsaturated and two adjacent carbon atoms are shared by each of the rings in the ring system. A fused bicyclic carbocycle in which one ring is saturated and the other is saturated is a saturated bicyclic ring system. A fused bicyclic carbocycle in which one ring is benzene and the other is saturated is an unsaturated bicyclic ring system. A fused bicyclic carbocycle in which one ring is benzene and the other is unsaturated is an unsaturated ring system. Saturated carbocyclic rings are also referred to as cycloalkyl rings, *e.g.*, cyclopropyl, cyclobutyl, etc. Unless otherwise noted, carbocycle is unsubstituted or substituted with C_{1-6} alkyl, C_{1-6} alkenyl, C_{1-6} alkynyl, aryl, halogen, NH_2 or OH. A subset of the fused

bicyclic unsaturated carbocycles are those bicyclic carbocycles in which one ring is a benzene ring and the other ring is saturated or unsaturated, with attachment via any carbon atom that results in a stable compound. Representative examples of this subset include



Depicted ring systems include, where appropriate, an indication of the variable to which a particular ring atom is attached. For example, the indole structure 

shows ring atom 2 is directly attached to variable X and ring atom 4 is directly attached to variable Z. Variable R^5 is shown as a floating variable which can be attached to any ring atom, provided that such attachment results in formation of a stable ring.

The term "aryl" refers to aromatic mono- and poly-carbocyclic ring systems, also referred to as "arenes", wherein the individual carbocyclic rings in the polyring systems are fused or attached to each other via a single bond. Suitable aryl groups include phenyl, naphthyl, and biphenylenyl.

Unless indicated otherwise, the term "heterocycle" (and variations thereof such as "heterocyclic" or "heterocyclyl") broadly refers to (i) a stable 4- to 8-membered, saturated or unsaturated monocyclic ring, (ii) a stable 7- to 12-membered bicyclic ring system, or (iii) a stable 11- to 15-membered tricyclic ring stystem, wherein each ring in (ii) and (iii) is independent of, or fused to, the other ring or rings and each ring is saturated or unsaturated, and the monocyclic ring, bicyclic ring system or tricyclic ring system contains one or more heteroatoms (*e.g.*, from 1 to 6 heteroatoms, or from 1 to 4 heteroatoms) selected from N, O and S and a balance of carbon atoms (the monocyclic ring typically contains at least one carbon atom and the bicyclic and tricyclic ring systems typically contain at least two carbon atoms); and wherein any one or more of the nitrogen and sulfur heteroatoms is optionally oxidized, and any one or more of the nitrogen heteroatoms is optionally quaternized. Unless otherwise specified, the heterocyclic ring may be attached at any heteroatom or carbon atom, provided that attachment results in the creation of a stable structure. Unless otherwise specified, when the heterocyclic ring has substituents, it is understood that the substituents may be attached to any atom in the ring, whether a heteroatom or a carbon atom, provided that a stable chemical structure results.

Saturated heterocyclics form a subset of the heterocycles. Unless expressly stated to the contrary, the term "saturated heterocyclic" generally refers to a heterocycle as defined above in which the entire ring system (whether mono- or poly-cyclic) is saturated. The term "saturated heterocyclic ring" refers to a 4- to 8-membered saturated monocyclic ring, a stable 7- to 12-membered bicyclic ring system, or a stable 11- to 15-membered tricyclic ring system, which consists of carbon atoms and one or more heteroatoms selected from N, O and S. Representative examples include piperidinyl, piperazinyl, azepanyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, isothiazolidinyl, and tetrahydrofuryl (or tetrahydrofuranyl).

Unsaturated heterocyclics form another subset of the heterocycles. Unless expressly stated to the contrary, the term "unsaturated heterocyclic" generally refers to a heterocycle as defined above in which the entire ring system (whether mono- or poly-cyclic) is not saturated, i.e., such rings are either unsaturated or partially unsaturated. Unless expressly stated to the contrary, the term "heteroaromatic ring" refers to a 5- or 6-membered monocyclic aromatic ring, a 7- to 12-membered bicyclic ring system, or an 11- to 15-membered tricyclic ring system, which consists of carbon atoms and one or more heteroatoms selected from N, O and S. In the case of substituted heteraromatic rings containing at least one nitrogen atom (*e.g.*, pyridine), such substitutions can be those resulting in N-oxide formation. Representative examples of heteroaromatic rings include pyridyl, pyrrolyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl (or thiophenyl), thiazolyl, furanyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isooxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, and thiadiazolyl.

Representative examples of bicyclic heterocycles include benzotriazolyl, indolyl, isoindolyl, indazolyl, indolinyl, isoindolinyl, quinoxalinyl, quinazolinyl, cinnolinyl, chromanyl, isochromanyl, tetrahydroquinolinyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzo-1,4-dioxinyl, imidazo(2,1-b)(1,3)thiazole), and benzo-1,3-dioxolyl. In certain contexts herein, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzo-1,4-dioxinyl is alternatively referred to as phenyl having as a substituent methylenedioxy attached to 2 adjacent carbon atoms.

Unless otherwise specifically noted as only "unsubstituted" or only "substituted", alkyl, cycloalkyl, aryl and heterocycle groups are unsubstituted. As used herein, the terms "substituted alkyl", "substituted C_3-C_{10} cycloalkyl", "substituted aryl" and "substituted heterocycle" are intended to include the cyclic group containing from 1 to 3 substituents in addition to the point of attachment to the rest of the compound. Preferably, the substituents are

selected from the group which includes, but is not limited to, halo, C_1-C_{20} alkyl, -CF_3, -NH_2, -N(C_1-C_6 alkyl)$_2$, -NO_2, oxo, -CN, -N_3, -OH, -O(C_1-C_6 alkyl), C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, (C_0-C_6 alkyl)-S(O)$_{0\text{-}2}$-, aryl-S(O)$_{0\text{-}2}$-, (C_0-C_6 alkyl)S(O)$_{0\text{-}2}$(C_0-C_6 alkyl)-, (C_0-C_6 alkyl)C(O)NH-, H_2N-C(NH)-, -O(C_1-C_6 alkyl)CF_3, (C_0-C_6 alkyl)C(O)-, (C_0-C_6 alkyl)OC(O)-, (C_0-C_6alkyl)O(C_1-C_6 alkyl)-, (C_0-C_6 alkyl)C(O)$_{1\text{-}2}$(C_0-C_6 alkyl)-, (C_0-C_6 alkyl)OC(O)NH-, aryl, aralkyl, heteroaryl, heterocyclylalkyl, halo-aryl, halo-aralkyl, halo-heterocycle, halo-heterocyclylalkyl, cyano-aryl, cyano-aralkyl, cyano-heterocycle and cyano-heterocyclylalkyl. Unless specifically indicated, such substituents themselves are not substituted.

Unless expressly stated to the contrary, substitution by a named substituent is permitted on any atom in a ring (*e.g.*, aryl, a heteroaromatic ring, or a saturated heterocyclic ring) provided such ring substitution is chemically allowed and results in a stable compound. A "stable" compound is a compound which can be prepared and isolated and whose structure and properties remain or can be caused to remain essentially unchanged for a period of time sufficient to allow use of the compound for the purposes described herein (*e.g.*, therapeutic or prophylactic administration to a subject).

As a result of the selection of substituents and substituent patterns, certain of the compounds of the present invention can have asymmetric centers and can occur as mixtures of stereoisomers, or as individual diastereomers, or enantiomers. All isomeric forms of these compounds, whether isolated or in mixtures, are within the scope of the present invention.

As would be recognized by one of ordinary skill in the art, certain of the compounds of the present invention can exist as tautomers. For the purposes of the present invention a reference to a compound of formula **I** is a reference to the compound per se, or to any one of its tautomers *per se*, or to mixtures of two or more tautomers.

When any variable (*e.g.*, R^4, R^5 etc.) occurs more than one time in any constituent or in formula **I** or in any other formula depicting and describing compounds of the invention, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

Unless expressly stated to the contrary, all ranges cited herein are inclusive. For example, a heteroaryl ring described as containing from "1 to 3 heteroatoms" means the ring can contain 1, 2, or 3 heteroatoms. It is also to be understood that any range cited herein includes within its scope all of the sub-ranges within that range. The oxidized forms of the heteroatoms N and S are also included within the scope of the present invention.

The compounds of the present inventions are useful in the inhibition of HCV protease (*e.g.*, HCV NS3 protease) and the treatment of HCV infection and/or reduction of the likelihood or severity of symptoms of HCV infection. For example, the compounds of this invention are useful in treating infection by HCV after suspected past exposure to HCV by such means as blood transfusion, exchange of body fluids, bites, accidental needle stick, or exposure to patient blood during surgery.

The compounds of this invention are useful in the preparation and execution of screening assays for antiviral compounds. For example, the compounds of this invention are useful for isolating enzyme mutants, which are excellent screening tools for more powerful antiviral compounds. Furthermore, the compounds of this invention are useful in establishing or determining the binding site of other antivirals to HCV protease, *e.g.*, by competitive inhibition. Thus, the compounds of this invention are commercial products to be used for these purposes.

The compounds of the present invention may be administered in the form of pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt" refers to a salt which possesses the effectiveness of the parent compound and which is not biologically or otherwise undesirable (*e.g.*, is neither toxic nor otherwise deleterious to the recipient thereof). Suitable salts include acid addition salts which may, for example, be formed by mixing a solution of the compound of the present invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, acetic acid, trifluoroacetic acid, or benzoic acid. Many of the compounds of the invention carry an acidic moiety, in which case suitable pharmaceutically acceptable salts thereof can include alkali metal salts (*e.g.*, sodium or potassium salts), alkaline earth metal salts (*e.g.*, calcium or magnesium salts), and salts formed with suitable organic ligands such as quaternary ammonium salts. Also, in the case of an acid (-COOH) or alcohol group being present, pharmaceutically acceptable esters can be employed to modify the solubility or hydrolysis characteristics of the compound.

The term "administration" and variants thereof (*e.g.*, "administering" a compound) in reference to a compound of the invention mean providing the compound or a prodrug of the compound to the individual in need of treatment. When a compound of the invention or a prodrug thereof is provided in combination with one or more other active agents (*e.g.*, antiviral agents useful for treating HCV infection), "administration" and its variants are each understood to include concurrent and sequential provision of the compound or salt (or hydrate) and other agents.

As used herein, the term "prodrug" is intended to encompass a drug form or compound that is converted into an active drug form or compound by the action of enzymes, chemicals or metabolic processes in the body of an individual to whom it is administered.

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

By "pharmaceutically acceptable" is meant that the ingredients of the pharmaceutical composition must be compatible with each other and not deleterious to the recipient thereof.

The term "subject" (alternatively referred to herein as "patient") as used herein refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

The term "effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician. In one embodiment, the effective amount is a "therapeutically effective amount" for the alleviation of the symptoms of the disease or condition being treated. In another embodiment, the effective amount is a "prophylactically effective amount" for prophylaxis of the symptoms of the disease or condition whose likelihood of occurrence or severity is being reduced. The term also includes herein the amount of active compound sufficient to inhibit HCV NS3 protease and thereby elicit the response being sought (*i.e.*, an "inhibition effective amount"). When the active compound (*i.e.*, active ingredient) is administered as the salt, references to the amount of active ingredient are to the free acid or free base form of the compound.

For the purpose of inhibiting HCV NS3 protease and preventing or treating HCV infection, the compounds of the present invention, optionally in the form of a salt or a hydrate, can be administered by any means that produces contact of the active agent with the agent's site of action. They can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. They can be administered alone, but typically are administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice. The compounds of the invention can, for example, be administered orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion

techniques), by inhalation spray, or rectally, in the form of a unit dosage of a pharmaceutical composition containing an effective amount of the compound and conventional non-toxic pharmaceutically-acceptable carriers, adjuvants and vehicles. Liquid preparations suitable for oral administration (*e.g.*, suspensions, syrups, elixirs and the like) can be prepared according to techniques known in the art and can employ any of the usual media such as water, glycols, oils, alcohols and the like. Solid preparations suitable for oral administration (*e.g.*, powders, pills, capsules and tablets) can be prepared according to techniques known in the art and can employ such solid excipients as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like. Parenteral compositions can be prepared according to techniques known in the art and typically employ sterile water as a carrier and optionally other ingredients, such as a solubility aid. Injectable solutions can be prepared according to methods known in the art wherein the carrier comprises a saline solution, a glucose solution or a solution containing a mixture of saline and glucose. Further description of methods suitable for use in preparing pharmaceutical compositions of the present invention and of ingredients suitable for use in said compositions is provided in Remington's Pharmaceutical Sciences, 18th edition, edited by A. R. Gennaro, Mack Publishing Co., 1990.

The compounds of this invention can be administered orally in a dosage range of 0.001 to 1000 mg/kg of mammal (*e.g.*, human) body weight per day in a single dose or in divided doses. One preferred dosage range is 0.01 to 500 mg/kg body weight per day orally in a single dose or in divided doses. Another preferred dosage range is 0.1 to 100 mg/kg body weight per day orally in single or divided doses. For oral administration, the compositions can be provided in the form of tablets or capsules containing 1.0 to 500 milligrams of the active ingredient, particularly 1, 5, 10, 15, 20, 25, 50, 75, 100, 150, 200, 250, 300, 400, and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

As noted above, the present invention also relates to a method of inhibiting HCV NS3 protease, inhibiting HCV replication, or preventing or treating HCV infection with a compound of the present invention in combination with one or more therapeutic agents and a pharmaceutical composition comprising a compound of the present invention and one or more

therapeutic agents selected from the group consisting of a HCV antiviral agent, an immunomodulator, and an anti-infective agent. Such therapeutic agents active against HCV include, but are not limited to, ribavirin, levovirin, viramidine, thymosin alpha-1, RC025 (an enhanced interferon (Roche)), interferon-β, interferon-α, pegylated interferon-α (peginterferon-α), a combination of interferon-α and ribavirin, a combination of peginterferon-α and ribavirin, a combination of interferon-α and levovirin, and a combination of peginterferon-α and levovirin. Interferon-α includes, but is not limited to, recombinant interferon-α2a (such as ROFERON interferon available from Hoffmann-LaRoche, Nutley, NJ), pegylated interferon-α2a (PEGASYS), interferon-α2b (such as Intron-A interferon available from Schering Corp., Kenilworth, NJ), pegylated interferon-α2b (PEGINTRON), a recombinant consensus interferon (such as interferon alphacon-1), albuferon (interferon-α bound to human serum albumin (Human Genome Sciences)), and a purified interferon-α product. Amgen's recombinant consensus interferon has the brand name INFERGEN. Levovirin is the L-enantiomer of ribavirin which has shown immunomodulatory activity similar to ribavirin. Viramidine represents an analog of ribavirin disclosed in WO 01/60379 (assigned to ICN Pharmaceuticals). In accordance with the method of the present invention, the individual components of the combination can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms.

For the treatment of HCV infection, the compounds of the present invention may also be administered in combination with an agent that is an inhibitor of HCV NS3 serine protease. HCV NS3 serine protease is an essential viral enzyme and has been described to be an excellent target for inhibition of HCV replication. Both substrate and non-substrate based inhibitors of HCV NS3 protease inhibitors are disclosed in WO 98/22496, WO 98/46630, WO 99/07733, WO 99/07734, WO 99/38888, WO 99/50230, WO 99/64442, WO 00/09543, WO 00/59929, GB 2337262, WO 02/48116, WO 02/48172, and U.S. Patent No. 6,323,180.

Ribavirin, levovirin, and viramidine may exert their anti-HCV effects by modulating intracellular pools of guanine nucleotides via inhibition of the intracellular enzyme inosine monophosphate dehydrogenase (IMPDH). IMPDH is the rate-limiting enzyme on the biosynthetic route in *de novo* guanine nucleotide biosynthesis. Ribavirin is readily phosphorylated intracellularly and the monophosphate derivative is an inhibitor of IMPDH. Thus, inhibition of IMPDH represents another useful target for the discovery of inhibitors of HCV replication. Therefore, the compounds of the present invention may also be administered in combination with an inhibitor of IMPDH, such as VX-497, which is disclosed in

WO 97/41211 and WO 01/00622; another IMPDH inhibitor, such as that disclosed in WO 00/25780; or mycophenolate mofetil [*see* A.C. Allison and E.M. Eugui, Agents Action, 44 (Suppl.): 165 (1993)].

For the treatment of HCV infection, the compounds of the present invention may also be administered in combination with the antiviral agent amantadine (1-aminoadamantane) [for a comprehensive description of this agent, *see* J. Kirschbaum, Anal. Profiles Drug Subs. 12: 1-36 (1983)].

For the treatment of HCV infection, the compounds of the present invention may also be administered in combination with the antiviral agent polymerase inhibitor RC128 (Roche).

The compounds of the present invention may also be combined for the treatment of HCV infection with antiviral 2'-*C*-branched ribonucleosides disclosed in R. E. Harry-O'Kuru *et al.*, J. Org. Chem., 62: 1754-1759 (1997); M. S. Wolfe *et al.*, Tetrahedron Lett., 36: 7611-7614 (1995); U.S. Patent No. 3,480,613; International Publication Numbers WO 01/90121, WO 01/92282, WO 02/32920, WO 04/002999, WO 04/003000, and WO 04/002422; the contents of each of which are incorporated by reference in their entirety. Such 2'-*C*-branched ribonucleosides include, but are not limited to, 2'-*C*-methyl-cytidine, 2'-*C*-methyl-uridine, 2'-*C*-methyl-adenosine, 2'-*C*-methyl-guanosine, and 9-(2-*C*-methyl-β-D-ribofuranosyl)-2,6-diaminopurine, and the corresponding amino acid ester of the ribose C-2', C-3', and C-5' hydroxyls and the corresponding optionally substituted cyclic 1,3-propanediol esters of the 5'-phosphate derivatives.

The compounds of the present invention may also be combined for the treatment of HCV infection with other nucleosides having anti-HCV properties, such as those disclosed in WO 02/51425, WO 01/79246, WO 02/32920, WO 02/48165, and WO 2005003147 (including RL56, (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methylcytidine, shown as compounds 3-6 on page 77); WO 01/68663, WO 99/43691, WO 02/18404, US 2005/0038240, WO 2006021341 (including 4'-azido nucleosides such as RL26, 4'-azidocytidine), US 2002/0019363, WO 02/100415, WO 03/026589, WO 03/026675, WO 03/093290, US 2003/0236216, US 2004/0006007, WO 04/011478, WO 04/013300, US 2004/0063658, and WO 04/028481; the content of each is incorporated herein by reference in its entirety.

For the treatment of HCV infection, the compounds of the present invention may also be administered in combination with an agent that is an inhibitor of HCV NS5B polymerase. Such HCV NS5B polymerase inhibitors that may be used as combination therapy include, but

are not limited to, those disclosed in WO 02/057287, US 6,777,395, WO 02/057425, US 2004/0067901, WO 03/068244, WO 2004/000858, WO 04/003138 and WO 2004/007512; the content of each is incorporated herein by reference in its entirety. Other such HCV polymerase inhibitors include, but are not limited to, valopicitabine (NM-283; Idenix) and 2'-F-2'-beta-methylcytidine (*see also* WO 2005/003147).

In one embodiment, nucleoside HCV NS5B polymerase inhibitors that are used in combination with the present HCV NS3 protease inhibitors are selected from the following compounds: 4-amino-7-(2-C-methyl-β-D-arabinofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-methylamino-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-dimethylamino-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-cyclopropylamino-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(2-C-vinyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(2-C-hydroxymethyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(2-C-fluoromethyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-5-methyl-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carboxylic acid; 4-amino-5-bromo-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-5-chloro-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-5-fluoro-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 2,4-diamino-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 2-amino-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 2-amino-4-cyclopropylamino-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 2-amino-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-one; 4-amino-7-(2-C-ethyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(2-C,2-O-dimethyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-one; 2-amino-5-methyl-7-(2-C, 2-O-dimethyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-one; 4-amino-7-(3-deoxy-2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(3-deoxy-2-C-methyl-β-D-arabinofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-2-fluoro-7-(2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(3-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(3-C-methyl-β-D-xylofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(2,4-di-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2,3-d]pyrimidine; 4-amino-7-(3-deoxy-3-fluoro-2-C-methyl-β-D-ribofuranosyl)-7H-pyrrolo[2 ,3-d]pyrimidine; and the corresponding 5'-triphosphates; or a pharmaceutically acceptable salt thereof.

The compounds of the present invention may also be combined for the treatment of HCV infection with non-nucleoside inhibitors of HCV polymerase such as those disclosed in WO 01/77091, WO 01/47883, WO 02/04425, WO 02/06246, WO 02/20497, WO 2005/016927 (in particular, JTK003), and HCV-796 (ViroPharma Inc.); the content of each is incorporated herein by reference in its entirety.

In one embodiment, non-nucleoside HCV NS5B polymerase inhibitors that are used in combination with the present HCV NS3 protease inhibitors are selected from the following compounds: 14-cyclohexyl-6-[2-(dimethylamino)ethyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-(2-morpholin-4-ylethyl)-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-[2-(dimethylamino)ethyl]-3-methoxy-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-3-methoxy-6-methyl-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; methyl ({[(14-cyclohexyl-3-methoxy-6-methyl-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocin-11-yl)carbonyl]amino}sulfonyl)acetate; ({[(14-cyclohexyl-3-methoxy-6-methyl-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocin-11-yl)carbonyl]amino}sulfonyl)acetic acid; 14-cyclohexyl-N-[(dimethylamino)sulfonyl]-3-methoxy-6-methyl-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxamide; 3-chloro-14-cyclohexyl-6-[2-(dimethylamino)ethyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine 11-carboxylic acid; N'-(11-carboxy-14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocin-7-yl)-N,N-dimethylethane-1,2-diaminium bis(trifluoroacetate); 14-cyclohexyl-7,8-dihydro-6H-indolo[1,2-e][1,5]benzoxazocine-11-carboxylic acid; 14-cyclohexyl-6-methyl-7-oxo-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-3-methoxy-6-methyl-7-oxo-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-[2-(dimethylamino)ethyl]-3-methoxy-7-oxo-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-[3-(dimethylamino)propyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-7-oxo-6-(2-piperidin-1-ylethyl)-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-(2-morpholin-4-ylethyl)-7-oxo-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-[2-(diethylamino)ethyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-(1-methylpiperidin-4-yl)-7-oxo-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-N-[(dimethylamino)sulfonyl]-7-oxo-6-(2-piperidin-1-ylethyl)-5,6,7,8-

tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxamide; 14-cyclohexyl-6-[2-(dimethylamino)ethyl]-N-[(dimethylamino)sulfonyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxamide; 14-cyclopentyl-6-[2-(dimethylamino)ethyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 6-allyl-14-cyclohexyl-3-methoxy-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclopentyl-6-[2-(dimethylamino)ethyl]-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-[2-(dimethylamino)ethyl]-5,6,7,8-tetrahydroindolo[2,1-a][2,5]benzodiazocine-11-carboxylic acid; 13-cyclohexyl-5-methyl-4,5,6,7-tetrahydrofuro[3',2':6,7][1,4]diazocino[1,8-a]indole-10-carboxylic acid; 15-cyclohexyl-6-[2-(dimethylamino)ethyl]-7-oxo-6,7,8,9-tetrahydro-5H-indolo[2,1-a][2,6]benzodiazonine-12-carboxylic acid; 15-cyclohexyl-8-oxo-6,7,8,9-tetrahydro-5H-indolo[2,1-a][2,5]benzodiazonine-12-carboxylic acid; 13-cyclohexyl-6-oxo-6,7-dihydro-5H-indolo[1,2-d][1,4]benzodiazepine-10-carboxylic acid; and pharmaceutically acceptable salts thereof.

The HCV NS3 protease inhibitory activity of the present compounds may be tested using assays known in the art. One such assay is HCV NS3 protease time-resolved fluorescence (TRF) assay as described below and in International Patent Application Publication WO2006/102087. Other examples of such assays are described in *e.g.*, International Patent Application Publication WO2005/046712. HCV NS3 protease inhibitors, such as those described herein have a Ki less than 50 μM, such as less than 10 μM, and less than 100 nM. Ki is determined by an NS3 protease assay. The assay is performed in a final volume of 100 μl in assay buffer containing 50 mM HEPES, pH 7.5, 150 mM NaCl, 15 % glycerol, 0.15 % TRITON X-100, 10 mM DTT, and 0.1 % PEG 8000. NS3 protease is pre-incubated with various concentrations of inhibitors in DMSO for 30 minutes. The reaction is initiated by adding the TRF peptide substrate (final concentration 100 nM). NS3 mediated hydrolysis of the substrate is quenched after 1 hour at room temperature with 100 μl of 500 mM MES, pH 5.5. Product fluorescence is detected using either a VICTOR V2 or FUSION fluorophotometer (Perkin Elmer Life and Analytical Sciences) with excitation at 340 nm and emission at 615 nm with a 400 μs delay. Testing concentrations of different enzyme forms are selected to result in a signal to background ratio (S/B) of 10-30. IC_{50} values are derived using a standard four-parameter fit to the data. K_i values are derived from IC_{50} values using the following formula,

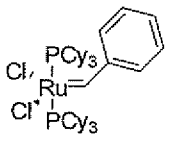
$$IC_{50} = K_i (1 + [S] / K_M), \qquad \text{Eqn (1)},$$

where [S] is the concentration of substrate peptide in the reaction and K_M is the Michaelis

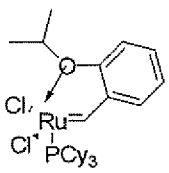
constant. *See* P. Gallinari *et al.*, 38 BIOCHEM. 5620-32(1999); P. Gallinari *et al.*, 72 J. VIROL. 6758-69 (1998); M. Taliani *et al.*, 240 ANAL. BIOCHEM. 60-67 (1996).

The present invention also includes processes for making compounds of formula (**I**). The compounds of the present invention can be readily prepared according to the following reaction schemes and examples, or modifications thereof, using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art, but are not mentioned in greater detail. Furthermore, other methods for preparing compounds of the invention will be readily apparent to the person of ordinary skill in the art in light of the following reaction schemes and examples. Unless otherwise indicated, all variables are as defined above. The following reaction schemes and examples serve only to illustrate the invention and its practice.

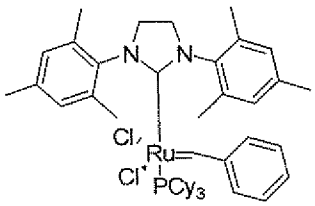
Olefin metathesis catalysts include the following Ruthenium-based species: Scott J. Miller *et al.*, *Application of Ring-Closing Metathesis to the Synthesis of Rigidified Amino Acids and Peptides*, 118 J. AM. CHEM. SOC.9606 (1996); Jason S. Kingsbury *et al.*, *A Recyclable Ru-Based Metathesis Catalyst*, 121 J. AM. CHEM. SOC. 791 (1999); Matthias Scholl *et al.*, *Synthesis and Activity of a New Generation of Ruthenium-Based Olefin Metathesis Catalysts Coordinated with 1,3-Dimesityl-4,5-dihydroimidazol-2-ylidene Ligands*, 1(6) ORGANIC LETTERS 953 (1999); US 2002/0107138; Alois Fürstner *et al.*, *Total Synthesis and Structural Refinement of the Cyclic Tripyrrole Pigment Nonylprodigiosin*, 64 J. ORG. CHEM. 8275 (1999). The utility of these catalysts in ring-closing metathesis is well known in the literature (*e.g.* Tina M. Trnka & Robert H. Grubbs, *The Development of L_2X_2Ru=CHR Olefin Metathesis Catalysts: An Organometallic Success Story*, 34 ACC. CHEM. RES. 18 (2001)).



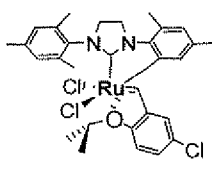
F



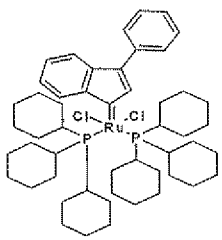
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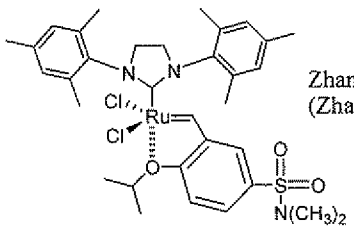
H



J



K



L

Zhan ruthenium metathesis catalyst RC-303
(Zhan catalyst 1B, RC-303, Zannan Pharma Ltd.)

The following examples serve only to illustrate the invention and its practice. The examples are not to be construed as limitations on the scope or spirit of the invention.

EXAMPLES

ABBREVIATIONS

BOC (also Boc)	t-Butyloxycarbonyl
$B(OMe)_3$	Trimethyl borate
BOP	Benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate
Brosyl chloride	4-Bromophenyl sulfonylchloride
tBuOH	t-Butanol
BuLi	Butyl lithium
CAN	Ceric ammonium nitrate
$CDCl_3$	Deuterio-trichloromethane
CDI	N,N'-Carbonyl diimidazole
CH_3CN	Acetonitrile
mCPBA	m-Chloroperbenzoic acid
Cs_2CO_3	Cesium carbonate
CuI	Copper iodide
$Cu(I)Br{\cdot}SMe_2$	Copper (I) bromide dimethyl sulfide complex
DABCO	1,4-diazabicyclo[2.2.2]octane
DBA (also dba)	Dibenzylidene acetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DCE	Dichloroethane
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DIAD	Diisopropyl azodicarboxylate
DIEA	Diethylamine
DIPA	Diethylpropylamine
DIPEA	Diisopropylethylamine
DMAP	4-Dimethylamino pyridine

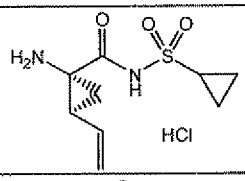
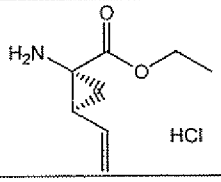
DMF	Dimethylformamide
DMSO	Dimethyl Sulfoxide
DPPF (also dppf)	1,1'-bid(Diphenylphosphino)ferrocene
EDC	*N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide
ESI	Electrospray ionization
Et_2O	Diethyl ether
EtOAc	Ethyl Acetate
EtOH	Ethanol
H_2	Hydrogen or hydrogen atomosphere
HATU	*O*-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
HBr	Hydrobromic acid
HCl	Hydrochloric acid
HMPA	Hexamethylphosphoramide
HOAc	Acetic acid
HOAt	1-Hydroxy-7-azabenzotriazole
HOBT	1-Hydroxy benzotriazole
H_2O	Water
H_2O_2	Hydrogen peroxide
HPLC	High performance liquid chromatography
I_2	Iodine
$KHSO_4$	Potassium bisulfate
K_2SO_4	Potassium sulfate
K_2CO_3	Potassium carbonate
KOH	Potassium hydroxide
LAH	Lithium aluminium hydride
LCMS	High performance liquid chromatography – mass spectrometry
LiOH	Lithium hydroxide
$LiOH \cdot H_2O$	Lithium hydroxide monohydrate
LRMS	Low resolution mass spectrometry
Me_3Al	Trimethylaluminium
MeLi	Methyllithium
MeOH	Methanol

$MgSO_4$	Magnesium Sulfate
MsCl	Mesyl chloride
N_2	Nitrogen or nitrogen atomosphere
NH_4Cl	Ammonium chloride
NH_4OH	Ammonium hydroxide
Nle	Norleucine
NMP	N-Methyl pyrrolidinone
NaH	Sodium hydride
$NaHCO_3$	Sodium hydrogen carbonate (sodium bicarbonate)
$NaHSO_3$	Sodium bisulfite
NaOH	Sodium hydroxide
NaOMe	Sodium methoxide
Na_2SO_3	Sodium sulfite
$Na_2S_2O_3$	Sodium thiosulfate
Na_2SO_4	Sodium sulfate (anhydrous)
PCy_3	Tricyclohexyl phosphine
POBr	Phosphoryl bromide
$POBr_3$	Phosphoryl tribromide
P_2O_5	phosphorus pentoxide (P_4O_{10})
Pd/C	Palladium on carbon
PhMe	Toluene
PPh_3	Triphenylphosphine
RT	Room temperature, approximately 25 C
Ru/C	Ruthenium on carbon
SiO_2	Silica or silica gel
TBAF	Tetrabutylammonium fluoride
TBTU	*O*-Benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydofuran
TIPSOTf	Triisopropylsilyl triflate
TMSCl	Chlorotrimethyl silane
TsCl	p-Toluenesulfonyl chloride

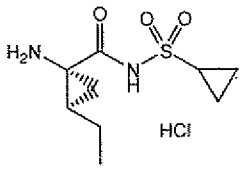
$Zn(CN)_2$ Zinc cyanide

Synthesis of Intermediates

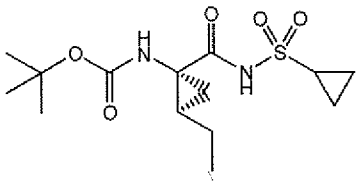
Intermediates A

Intermediate Number	Structure	Name	Literature Reference
A1		(1*R*,2*S*)-1-Amino-*N*-(cyclopropylsulfonyl)-2-vinylcyclopropanecarboxamide hydrochloride	US 6,995,174
A2		Ethyl (1*R*,2*S*)-1-amino-2-vinylcyclopropanecarboxylate hydrochloride	US 6,323,180

Intermediate A3: (1*R*,2*R*)-1-Amino-*N*-(cyclopropylsulfonyl)-2-ethylcyclopropanecarboxamide hydrochloride



*Step 1: t-Butyl((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl) carbamate*



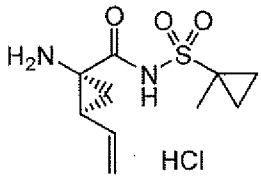
A hydrogenation vessel was charged with a MeOH (1000 mL) slurry of *t*-butyl ((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)carbamate (164 g, 0.50 mol) (US 6,995,174) and 5% Ru/C (dry, 7.5 wt%, 12.4 g) and stirred. The vessel was placed under N_2 (20 psi) and vented to atmospheric pressure (3x) to remove residual oxygen. The vessel was then placed under H_2 (50 psi). After 20 hours, the vessel was vented to atmospheric pressure. The reaction slurry was then transferred out of the reaction vessel and filtered through SOLKA FLOK (34 g, wetted with 100 mL MeOH) to yield a clear, light brown solution. The SOLKA FLOK was rinsed with MeOH (200 mL x 2). The combined MeOH solutions were concentrated under reduced pressure to yield crude product as a white solid (153 g). The crude product was slurried in EtOAc (800 mL), warmed to 40°C and aged

30 minutes. The solution was then seeded, aged 30 minutes, and heptane (500 mL) was added via addition funnel over 30 minutes. The partially crystallized solid was cooled to RT and aged overnight, after which additional heptane (500 mL) was added. After 1 hour, additional heptane (250 mL) was added *via* addition funnel, and the white slurry aged for 1 hour. The solution was filtered, and the solid was rinsed with heptane/EtOAc (500 mL, 4:1) and dried under reduced pressure to give *t*-butyl ((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino] carbonyl}-2-ethylcyclopropyl)carbamate (125.9 g).

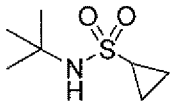
Step 2: (1R,2R)-1-Amino-N-(cyclopropylsulfonyl)-2-ethylcyclopropanecarboxamide hydrochloride (Intermediate A3)

A solution of the product from Step 1 (92 g, 0.28 mol) in DCM (1200 mL) was cooled to 0°C, and HCl was bubbled through the solution for 10 minutes. The cooling bath was then removed, and the reaction mixture stirred for 2 hours. N_2 was bubbled through the reaction mixture for 5 minutes, and the volatiles evaporated. The residue was azeotroped with DCM (3x) to give an off-white powder (75 g). LRMS $(M+H)^+$ calculated = 233; found 233.

Intermediate A4: (1*R*,2*S*)-1-amino-2-ethenyl-*N*-[(1-methylcyclopropyl)sulfonyl]cyclopropane-carboxamide hydrochloride

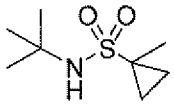


Step 1: N-tert-butylcyclopropanesulfonamide



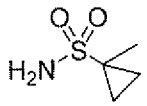
To solution of *t*-butylamine (17.3 mL, 164 mmol) in THF (100 mL) cooled to -20°C, cyclopropylsulfonyl chloride (11.55 g, 82 mmol) was added. The mixture was then warmed to RT and stirred for 20 hours. The resulting solid was removed by filtration, and the solvent was removed *in vacuo*. The residue was then dissolved in DCM and washed with 1 N HCl, dried over $MgSO_4$, and the solvent was removed *in vacuo*. The resulting material was crystallized from hexanes to yield the title compound as a white solid (14.5 g).

Step 2: N-tert-butyl-1-methylcyclopropanesulfonamide



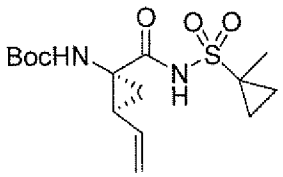
To a solution of the product from step 1 (8.6 g, 48.8 mmol) in THF (160 mL) cooled to -78°C, n-BuLi (42.9 mL, 2.5 M, 107 mmol) was added, while keeping the internal temperature less than -40°C. The mixture was then warmed to 6°C over 20 minutes, re-cooled to -78°C, and iodomethane (6.1 mL, 98 mmol) was added. After stirring for a further 2 hours, the reaction was quenched with aqueous NH_4Cl, extracted with EtOAc, dried over sodium sulfate, and the solvent was removed *in vacuo*. The resulting material was tritrated with hexanes to yield the title compound as an off-white powder (7.0 g).

Step 3: 1-methylcyclopropanesulfonamide (ref: WO 20080502;Commercially available from Asta Tech # 64790)



To the product from step 2 (7.0 g, 36.9 mmol) was added TFA (40 mL) and the resulting solution was stirred for 18 hours. The solvent was then removed *in vacuo*, and the resulting solid was crystallized from 1:4 EtOAc/hexanes to yield the title compound as a white solid (4.4 g).

Step 4: tert-butyl [(1R,2S)-2-ethenyl-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl} cyclopropyl]carbamate

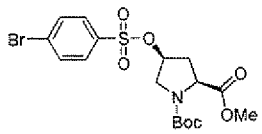


To a solution of (1*R*,2*S*)-1-[(*tert*-butoxycarbonyl)amino]-2-ethenylcyclopropanecarboxylic acid (4.35 g, 19.1 mmol) in THF (75 mL), carbonyldiimidazole (4.0 g, 24.88 mmol) was added, and the solution was then heated to reflux for 1 hour. The mixture was then cooled to RT, and the product from step 3 (4.35 g, 19.14 mmol) was then added followed by DBU (4.0 mL, 26.8 mmol). After stirring for 20 hours, 1 N HCl was added until acidic, and the mixture was extracted with EtOAc 2x. The combined organic layers were dried over Na_2SO_4, and the solvent was removed *in vacuo*. 1:1 EtOAc/hexanes (100 mL) was then added, and the resulting solid was filtered. The filtrate was concentrated and the 1:1 EtOAc/hexanes was added again to produce more solid. The combined solids were dried to yield the title compound as a solid (5 g). LCMS (ES+) m/z 289.3 $((M\text{-}t\text{-}Bu)+H)^+$.

Step 5: (1R,2S)-1-amino-2-ethenyl-N-[(1-methylcyclopropyl)sulfonyl]cyclopropanecarboxamide hydrochloride

To a solution of the product from step 4 (7.8 g, 22.7 mmol) in DCM (30 mL), TFA (30 mL) was added. After 1.5 hours, 4 N HCl in EtOAc was added, and the volitiles were removed *in vacuo*. The resulting material was dissolved in DCM/MeOH, and the solvent was removed *in vacuo*. This material was then tritrated with DCM to give the title compound as an off-white solid (5.7 g). LCMS (ES+) m/z 245.3 $(M+H)^+$.

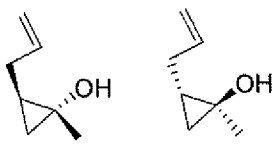
Intermediate A5: 1-tert-Butyl 2-methyl (2S,4S)-4-{[(4-bromophenyl)sulfonyl]oxy}pyrrolidine-1,2-dicarboxylate



A solution of brosyl chloride (3.14 g, 12.3 mmol) in PhMe (5 mL) was added to a solution of 1-*tert*-butyl 2-methyl (2*S*,4*S*)-4-hydroxypyrrolidine-1,2-dicarboxylate (2.15 g, 8.76 mmol) and DABCO (1.57 g, 14.0 mmol) in PhMe (10 mL) at RT. A white precipitate formed; the reaction mixture was stirred for 20 minutes and filtered. The filtrate was partitioned between EtOAc and saturated aqueous $NaHCO_3$. The layers were separated, and the organic layer was washed with 1 M HCl, water and brine, dried over Na_2SO_4, filtered and concentrated. The title compound (4.0 g, 98% yield) was then used without further purification. LRMS $(M+Na)^+$ calculated: 488; found 488.

Intermediates B

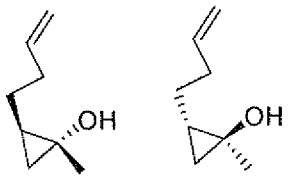
Intermediate B1: (1R, 2R)-2-allyl-1-methylcyclopropanol and (1S, 2S)-2-allyl-1-methylcyclopropanol



To a mixture of titanium(IV) isoproproxide (50.9 ml, 174 mmol) in THF (170 ml) at RT was added methylmagnesium bromide (260 ml, 260 mmol) over 5 minutes. The resulting solution was allowed to stir 5 minutes. The solution was cooled to -5°C and dry EtOAc (17.00 ml, 174 mmol) in THF (30 mL) was added. The reaction was stirred for 1 minute, and a solution of pentenylmagnesium bromide (0.76M in THF, 347 ml, 347 mmol) was added dropwise over 60

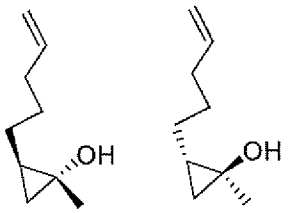
minutes from an addition funnel while maintaining the temperature at 0-5°C. The reaction was allowed to warm to RT and then aged for 1.5 hour. The reaction was cooled to -5°C and quenched by the dropwise addition of 10% aq. H_2SO_4 (600 mL) while the temperature was maintained at 0-10°C. The reaction was extracted with Et_2O (2x), then the organics were combined, washed with 10% aq. $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated to give a crude oil. The oil was purified on SiO_2 (gradient elution, 0-20% EtOAc/hexane) to afford the title compound as an oil (12 g, 61.6%).

Intermediate B2: (1*R*,2*R*)-2-(but-3-en-1-yl)-1-methylcyclopropanol and (1*S*,2*S*)-2-(but-3-en-1-yl)-1-methylcyclopropanol



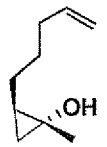
To a solution of EtOAc (12.9 mL, 132 mL) in THF (658 mL), 1,5-hexadiene (32.4 g, 395 mmol) and chlorotitanium triisopropoxide (132 mL, 1M, 132 mmol) were added. Cyclohexylmagnesium chloride (296 mL, 2M, 592 mmol) was then added over 2 hours via an addition funnel. The reaction was then stirred for an additional 1 hour. The mixture was then cooled in an ice bath and quenched with H_2O (27 mL), 15% NaOH (27 mL), and more H_2O (60 mL). Na_2SO_4 was then added; the mixture was filtered through CELITE, and the solvent was removed *in vacuo*. The crude product was purified by silica (gradient elution 10:1 to 4:1 hexanes/EtOAc) to yield the title compounds (11.5 g).

Intermediate B3: (1*R*,2*R*)-1-methyl-2-(pent-4-en-1-yl)cyclopropanol and (1*S*,2*S*)-1-methyl-2-(pent-4-en-1-yl)cyclopropanol



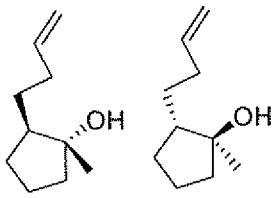
The title compounds were prepared according to the procedure for Intermediate B2 using 1,6-heptadiene in place of 1,5-hexadiene.

Intermediate B3-1: (1*R*,2*R*)-1-methyl-2-(pent-4-en-1-yl)cyclopropanol (single enantiomer of Intermediate B3)



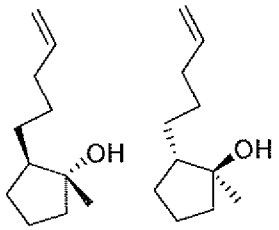
To a solution of 1,6-heptadiene (19.65 g, 204 mmol), in THF (341 ml) was added EtOAc (6.67 ml, 68.1 mmol), and chlorotitanium triisopropoxide (68.1 ml, 68.1 mmol). Cyclohexylmagnesium chloride (2M, 153 ml, 306 mmol) was then added slowly over 2 hours. After an additional 1 hour of stirring at RT, the reaction mixture was filtered through CELITE. The filtrate was then concentrated *in vacuo* and purified on SiO_2 (15% EtOAc/hexanes) to yield the title compound as a mixture of enantiomers. To a solution of the enantiomers (5.5 g, 39.2 mmol) in anhydrous DCM, at 0°C and under N_2, was added Et_3N (10.9 mL, 78 mmol) and 4-nitrobenzoyl chloride (8.7 g, 47.1 mmol). The reaction was stirred for 2 hours, diluted with H_2O (70 mL) and extracted with DCM (3 x 100 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified on SiO_2 (gradient elution, 0 to 50 % EtOAc in hexane) to yield (1*R*,2*R* and 1*S*,2*S*)-1-methyl-2-(pent-4-en-1-yl)cyclopropyl 4-nitrobenzoate. The benzoate enantiomers (12 g, 41.5 mmol) were separated by chiral chromatography on an AD-H column, eluting with 10 % CO_2 in MeOH. The desired peak fractions were concentrated to give (1*R*,2*R*)-1-methyl-2-(pent-4-en-1-yl)cyclopropyl 4-nitrobenzoate. To a solution of (1*R*,2*R*)-1-methyl-2-(pent-4-en-1-yl)cyclopropyl 4-nitrobenzoate (4.87 g, 16.83 mmol) in MeOH (67 mL) was added K_2CO_3 (4.65 g, 33.7 mmol). The mixture was stirred for 1 hour, filtered, and concentrated *in vacuo*. The material was purified on SiO_2 (gradient elution, 0-50% ether/hexanes) to give the title compound. ^1H NMR (500 MHz) ($CDCl_3$) δ 5.82 (m, 1H), 4.99 (m, 2H), 2.09 (m, 2H), 1.78 (s, 1H), 1.55 (m, 2H), 1.41 (s, 3H), 1.32 (m, 1H), 1.14 (m, 1H), 0.97 (m, 1H), 0.84 (m, 1H), 0.06 (m, 1H).

Intermediate B4: (1*R*,2*S*)-2-(but-3-en-1-yl)-1-methylcyclopentanol and (1*S*,2*R*)-2-(but-3-en-1-yl)-1-methylcyclopentanol



To a 0.5 M solution of 3-butenylmagnesium bromide (45.6 mL, 22.8 mmol), copper(I) chloride (113 mg, 1.14 mmol) was added at 0°C. A solution of methylcyclopentene oxide (1.12 g, 11.4 mmol) in diethyl ether (5 mL) was added to the resulting purple solution. The mixture was then warmed to RT overnight, and then cooled to 0°C and poured into a saturated solution of NH_4Cl also cooled to 0°C. The reaction mixture was then extracted with EtOAc, dried over $MgSO_4$, and the solvent was removed *in vacuo*. The crude material was purified on silica (gradient elution, 0-30% EtOAc/hexanes) to yield the title compounds (1.3 g).

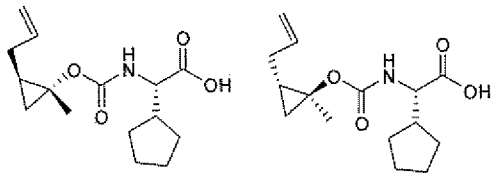
Intermediate B5: (1*R*,2*R*)-1-methyl-2-(pent-4-en-1-yl)cyclopentanol and (1S*R*,2S)-1-methyl-2-(pent-4-en-1-yl)cyclopentanol



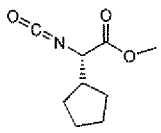
The title compounds were prepared according to the procedure for Intermediate B4 using 4-pentenylmagnesium bromide.

Intermediates C

Intermediate C1: (2S)-[({[(1R,2R)-2-allyl-1-methylcyclopropyl]oxy}carbonyl)amino](cyclopentyl)acetic acid and (2S)-[({[(1S,2S)-2-allyl-1-methylcyclopropyl]oxy}carbonyl)amino](cyclopentyl)acetic acid



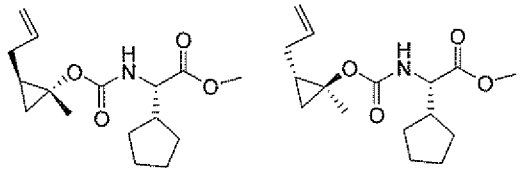
Step 1: methyl (2S)-cyclopentyl(isocyanato)acetate



To a mixture of methyl (2S)-amino(cyclopentyl)acetate hydrochloride (50 g, 258 mmol) in DCM (1229 ml), sodium bicarbonate (108 g, 1291 mmol) dissolved in water (1L) was added, and the mixture was stirred well with an overhead stirrer for 5 minutes. The reaction was cooled to 0°C, and triphosgene (25.3 g, 85 mmol) was added. The reaction was stirred

vigorously at 0°C for 1.5 hours. The reaction was poured into a separatory funnel, extracted aqueous with DCM, combined organics, washed with brine, dried over $MgSO_4$, filtered, concentrated *in vacuo* to yield the title compound as a colorless oil (43 g, 91%).

Step 2: Methyl (2S)-[({[(1R,2R)-2-allyl-1-methylcyclopropyl]oxy}carbonyl)amino](cyclopentyl) acetate and Methyl (2S)-[({[(1S,2S)-2-allyl-1-methylcyclopropyl]oxy}carbonyl)amino] (cyclopentyl) acetate

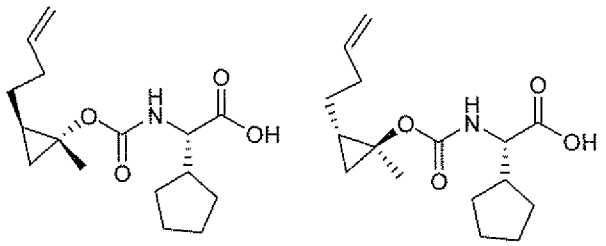


A mixture of intermediate B1 (12.0 g, 107 mmol), methyl (2S)-cyclopentyl(isocyanato)acetate (27.4 g, 150 mmol), DIPEA (74.7 ml, 428 mmol) and DMAP (13.07 g, 107 mmol) in toluene (350 ml) was heated to 85°C and stirred for 24 hours. The reaction was diluted with Et_2O (500 mL) and 1 M HCl (1500 mL), stirred well, and the organic layer was removed. The aqueous portion was extracted with ether, and the organics were combined, washed with brine, dried over Na_2SO_4, filtered through a pad of silica and washed with ether. The filtrate was concentrated to give crude oil, which was purified on SiO_2 (gradient elution, 0-30% EtOAc/hexane) to afford the title compound as an oil (25 g, 79%).

Step 3: (2S)-[({[(1R,2R)-2-allyl-1-methylcyclopropyl]oxy}carbonyl)amino](cyclopentyl)acetic acid and (2S)-[({[(1S,2S)-2-allyl-1-methylcyclopropyl]oxy}carbonyl)amino](cyclopentyl)acetic acid

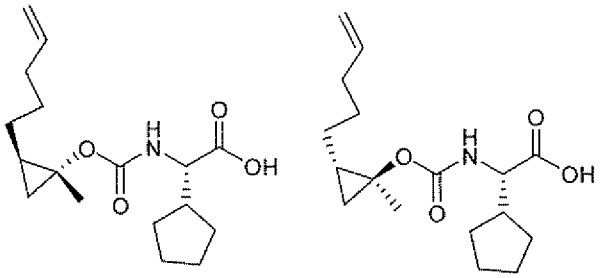
Intermediate from step 2 (42.5 g, 144 mmol) was dissolved in THF (750 ml) and treated with lithium hydroxide (17.23 g, 719 mmol) dissolved in H_2O (250 ml). The mixture was allowed to stir at RT for 3 hours. The reaction mixture was treated with 3N HCL (240mL), concentrated to remove THF, and diluted with aq. $KHSO_4$ (200 mL), and the product was extracted into DCM (3X 300 mL). The DCM layer was dried over magnesium sulfate, filtered, and concentrated to yield the title compound as a white solid (40.5g, 100%).

Intermediate C2: (2*S*)-[({[(1*R*,2*R*)-2-(but-3-en-1-yl)-1-methylcyclopropyl]oxy}carbonyl)amino](cyclopentyl)ethanoic acid and (2*S*)-[({[(1S,2*S*)-2-(but-3-en-1-yl)-1-methylcyclopropyl]oxy}carbonyl)amino](cyclopentyl)ethanoic acid



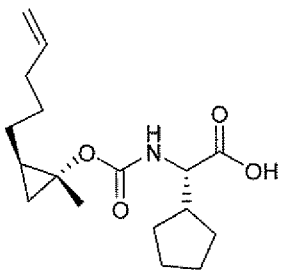
Using Intermediate B2, the title compounds were prepared according to the procedure used for Intermediate C1.

Intermediate C3: (2*S*)-cyclopentyl[({[(1*R*,2*R*)-1-methyl-2-(pent-4-en-1-yl)cyclopropyl]oxy}carbonyl)amino]ethanoic acid and (2*S*)-cyclopentyl[({[(1S,2S)-1-methyl-2-(pent-4-en-1-yl)cyclopropyl]oxy}carbonyl)amino]ethanoic acid



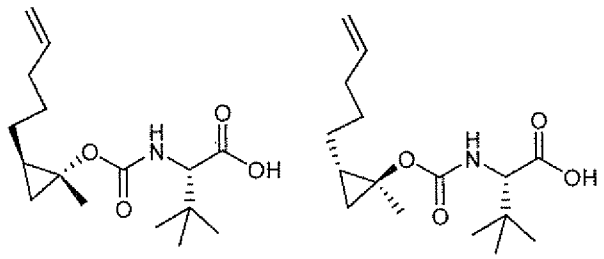
Using Intermediate B3, the title compounds were prepared according to the procedure used for Intermediate C1.

Intermediate C3-1: (2*S*)-cyclopentyl[({[(1*R*,2*R*)-1-methyl-2-(pent-4-en-1-yl)cyclopropyl]oxy}carbonyl)amino]ethanoic acid



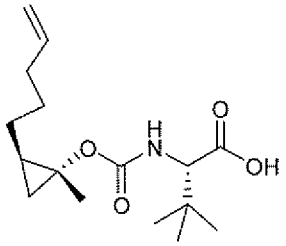
The title compound was prepared according to the procedure for Intermediate C1 using Intermediate B3-1.

Intermediate C4: 3-methyl-*N*-({[(1*R*,2*R*)-1-methyl-2-(pent-4-en-1-yl)cyclopropyl]oxy}carbonyl)-L-valine and 3-methyl-*N*-({[(1*S*,2*S*)-1-methyl-2-(pent-4-en-1-yl)cyclopropyl]oxy}carbonyl)-L-valine



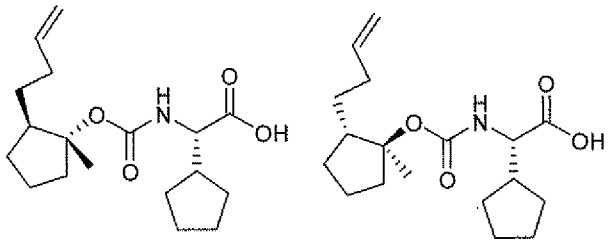
Using Intermediate B3 and methyl 3-methyl-L-valinate hydrochloride, the title compounds were prepared according to the procedure used for Intermediate C1.

Intermediate C4-1: 3-methyl-*N*-({[(1*R*,2*R*)-1-methyl-2-(pent-4-en-1-yl)cyclopropyl]oxy}carbonyl)-L-valine



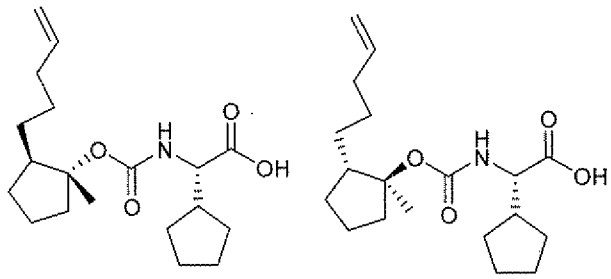
The title compound was prepared according to the procedure for Intermediate C4 using B3-1.

Intermediate C5: (2*S*)-[({[(1*R*,2*S*)-2-(but-3-en-1-yl)-1-methylcyclopentyl]oxy}carbonyl)amino](cyclopentyl)ethanoic acid and (2*S*)-[({[(1*S*,2*R*)-2-(but-3-en-1-yl)-1-methylcyclopentyl]oxy}carbonyl)amino](cyclopentyl)ethanoic acid



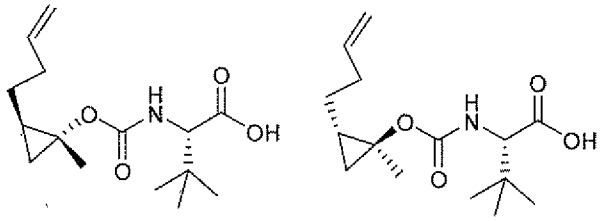
Using Intermediate B4, the title compounds were prepared according to the procedure used for Intermediate C1.

Intermediate C6: (2*S*)-cyclopentyl[({[(1*R*,2*R*)-1-methyl-2-(pent-4-en-1-yl)cyclopentyl]oxy}carbonyl)amino]ethanoic acid and (2*S*)-cyclopentyl[({[(1*R*,2*R*)-1-methyl-2-(pent-4-en-1-yl)cyclopentyl]oxy}carbonyl)amino]ethanoic acid



The title compounds were prepared according to procedure used for Intermediate C1 using Intermediate B5.

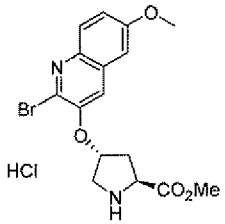
Intermediate C7: *N*-({[(1*R*,2*R*)-2-(but-3-en-1-yl)-1-methylcyclopropyl]oxy}carbonyl)-3-methyl-L-valine and *N*-({[(1S,2S)-2-(but-3-en-1-yl)-1-methylcyclopropyl]oxy}carbonyl)-3-methyl-L-valine



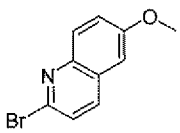
Using Intermediate B2 and methyl 3-methyl-L-valinate hydrochloride, the title compounds were prepared according to the procedure used for Intermediate C1.

Intermediates D

Intermediate D1: (2*S*,4*R*)-4-[(2-bromo-6-methoxyquinolin-3-yl)oxy]-2-(methoxycarbonyl) pyrrolidinium chloride

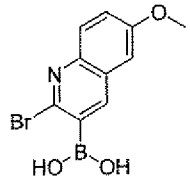


Step 1: 2-Bromo-6-methoxyquinoline



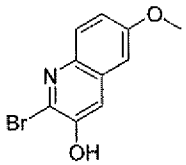
6-Methoxyquinolin-2(1*H*)-one (6.81 g, 38.9 mmol) was carefully added to $POBr_3$ (18.9 g, 66.1 mmol) at 60°C, and the resulting solution was stirred at 140°C for 2.5 hours. The reaction mixture was cooled and poured onto crushed ice, and the solid was collected by filtration. Purification of this material on SiO_2 (gradient elution, 5-12% EtOAc/petroleum ether) afforded the title compound (4.57 g, 49.3 %) as a solid. LCMS (ES+) m/z 238, 240 $(M+H)^+$.

Step 2: (2-Bromo-6-methoxyquinolin-3-yl)boronic acid



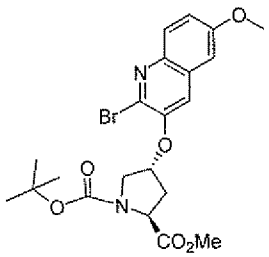
n-BuLi (1.6 N in hexanes, 14.4 mL, 23.0 mmol) was added at -78°C to a solution of 2,2,6,6-tetramethylpiperidine (3.11 g, 22.05 mmol) in anhydrous THF (59 mL), and the mixture was then warmed to 0°C for 30 minutes. The mixture was cooled back to -78°C and treated with a solution of 2-bromo-6-methoxyquinoline (4.57 g, 19.17 mmol) in THF (14 mL). After stirring for 1 hour, a solution of $B(OMe)_3$ (2.46 mL, 22.05 mmol) in THF (14 mL) was added, and the mixture was maintained at -78°C for a further 2 hours. A mixture of THF (14 mL) and H_2O (3.5 mL) was added, then the solution was warmed to -10°C and treated with H_2O (70 mL) and Et_2O (70 mL). $NaOH_{(aq.)}$ (1N, 75 mL) was added, and the aqueous layer was separated and acidified to pH 4 with $HCl_{(aq.)}$ (3N). The aqueous phase was extracted with Et_2O, and the combined extracts were washed with brine and dried over Na_2SO_4. Filtration and removal of the volatiles afforded the title compound (4.64 g, 86 % yield) as an oily solid that was used directly in the subsequent step. LCMS (ES+) m/z 282, 284 $(M+H)^+$.

Step 3: 2-Bromo-6-methoxyquinolin-3-ol



H_2O_2(aq.) (30%, 32.8 mL, 321 mmol) was added dropwise to a stirred solution of (2-bromo-6-methoxyquinolin-3-yl)boronic acid (4.64 g, 16.45 mmol) and NH_4Cl (3.29 g, 61.5 mmol) in Et_2O (82 mL) and H_2O (82 mL). After 13 hours, NH_4Cl (3.29 g, 61.5 mmol) and $H_2O_{2(aq.)}$ (30%, 32.8 mL, 321 mmol) were added, and the mixture was stirred for 48 hours. The precipitate was collected and washed with H_2O, then dried at 50°C to afford the title compound (4.18 g, 100 %) as a solid that was used directly in the subsequent step. LCMS (ES+) m/z 254, 256 $(M+H)^+$.

Step 4: 1-t-Butyl 2-methyl (2S,4R)-4-[(2-bromo-6-methoxyquinolin-3-yl)oxy]pyrrolidine-1,2-dicarboxylate

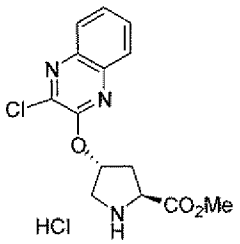


Cs_2CO_3 (10.7g, 32.9 mmol) was added to a stirred mixture of 1-*t*-butyl 2-methyl (2*S*,4*S*)-4-{[(4-bromophenyl)sulfonyl]oxy}pyrrolidine-1,2-dicarboxylate (Intemerdiate A5) (8.78 g, 18.9 mmol) and 2-bromo-6-methoxyquinolin-3-ol (4.18 g, 16.45 mmol) in NMP (46 mL). The resulting mixture was stirred at 50°C for 3 hours, then cooled and diluted with EtOAc. The organics were washed with saturated $NaHCO_{3(aq.)}$, H_2O and brine, then dried over Na_2SO_4. Filtration and removal of the volatiles gave a residue that was purified by column chromatography on SiO_2 (gradient elution, 1-100% EtOAc/petroleum ether) to give the title compound (5.56 g, 70.2 %). LCMS (ES+) m/z 481, 483 $(M+H)^+$.

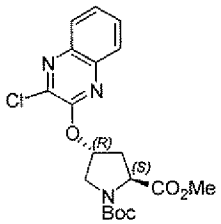
Step 5: (2S,4R)-4-[(2-bromo-6-methoxyquinolin-3-yl)oxy]-2-(methoxycarbonyl)pyrrolidinium chloride

A solution of 1-*t*-butyl 2-methyl (2*S*,4*R*)-4-[(2-bromo-6-methoxyquinolin-3-yl)oxy]pyrrolidine-1,2-dicarboxylate (5.01 g, 10.40 mmol) in HCl/dioxane (4 N , 31 ml) was prepared at 0°C, and the mixture was stirred at 20°C for 40 minutes. The volatiles were evaporated, and the residue was triturated with Et_2O to afford an approximately 1:1 mixture of the title compound and (2*S*,4*R*)-4-[(2-chloro-6-methoxyquinolin-3-yl)oxy]-2-(methoxycarbonyl) pyrrolidinium chloride (4.34 g) as a solid that was used directly in subsequent steps. LCMS (ES+) m/z 381, 383 $(M+H)^+$.

Intermediate D2: (2*S*,4*R*)-4-[(3-chloroquinoxalin-2-yl)oxy]-2-(methoxycarbonyl)pyrrolidinium chloride



Step 1: 1-t-Butyl 2-methyl (2S,4R)-4-[(3-chloroquinoxalin-2-yl)oxy]pyrrolidine-1,2-dicarboxylate

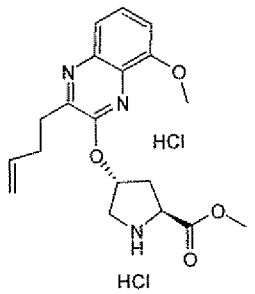


A solution of 3-chloroquinoxalin-2-ol (1.44 g, 7.97 mmol) and 1-*t*-butyl 2-methyl (2*S*,4*S*)-4-hydroxypyrrolidine-1,2-dicarboxylate (2.05 g, 8.37 mmol) in THF (190 ml) was cooled to 0°C, then treated with PPh_3 (2.51 g, 9.57 mmol). DIAD (1.86 ml, 9.57 mmol) was added dropwise, and the mixture was stirred at 20°C for 1 hour. After evaporation of the volatiles, the residue was purified on SiO_2 (gradient elution, 0-70% EtOAc/petroleum ether) to afford the title compound (2.5 g, 77%). LCMS (ES+) m/z 408 $(M+H)^+$.

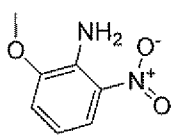
Step 2: (2S,4R)-4-[(3-chloroquinoxalin-2-yl)oxy]-2-(methoxycarbonyl)pyrrolidinium chloride

A solution of 1-*t*-butyl 2-methyl (2*S*,4*R*)-4-[(3-chloroquinoxalin-2-yl)oxy]pyrrolidine-1,2-dicarboxylate (1.05 g, 2.57 mmol) in HCl/dioxane (4 N, 5 mL) was prepared at 0°C, then stirred for 2 hours at 20°C. The reaction mixture was concentrated to afford a residue that was triturated with Et_2O to afford the title compound (0.88 g, 98%) as a white solid that was used directly in subsequent reactions. LCMS (ES+) m/z 308 $(M+H)^+$.

Intermediate D3: Methyl (4R)-4-[(3-but-3-en-1-yl-8-methoxyquinoxalin-2-yl)oxy]-L-prolinate dihydrochloride



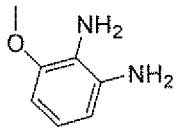
Step 1: 2-methoxy-6-nitroaniline



A mixture of 2-amino-3-nitrophenol (11.66 g, 76 mmol) and K_2CO_3 (12.55 g, 91 mmol) were stirred in DMF (100 ml) for 1 hour. Iodomethane (5.68 ml, 91 mmol) in DMF

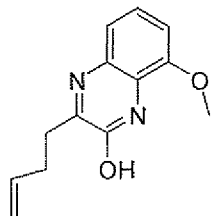
(10mL) was added dropwise, and the mixture was stirred 14 hours. The reaction was diluted with H_2O and extracted with EtOAc (2x). The organics were washed with brine, dried over Na_2SO_4, filtered, concentrated to a dark solid. The crude solid was purified by crystallization from hexane to give the title compound as an orange solid (11.6g, 91%). LCMS (ES+) m/z 169.0 $(M+H)^+$.

Step 2: 3-methoxybenzene-1,2-diamine



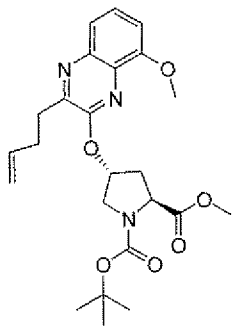
To a degassed solution of 2-methoxy-6-nitroaniline from step 1 (6.9 g, 41.0 mmol) in EtOH (200 ml) Pd/C (0.873 g, 0.821 mmol) was added, and the mixture was placed under a hydrogen atmosphere (balloon). After 6.5 hours, the reaction was filtered through a CELITE pad, and the filtrate was concentrated to yield the crude title compound as an orange oil (5.6g, 99%).

Step 3: 3-but-3-en-1-yl-8-methoxyquinoxalin-2-ol



To a solution of 3-methoxybenzene-1,2-diamine from step 2 (5.6 g, 40.5 mmol) in DCE (250 ml), ethyl 2-oxohex-5-enoate (9.50 g, 60.8 mmol) was added, and the mixture was stirred at 60°C for 14 hours. An additional charge of ethyl 2-oxohex-5-enoate (1.45 g, 9.28 mmol) was added, and the mixture was heated for 24 hours. The reaction mixture was concentrated and filtered from CH_2Cl_2 to remove a portion of the undesired regio-isomer as a tan solid. The filtrate was purified by column chromatography on SiO_2 (gradient elution, 1-9% acetone/CH_2Cl_2) to give the title compound as a tan solid (6.4 g, 68.6 %) after triturating with 10% Et_2O/hexane. LCMS (ES+) m/z 231.1 (M+H)+.

Step 4: 1-tert-butyl 2-methyl (2S,4R)-4-[(3-but-3-en-1-yl-8-methoxyquinoxalin-2-yl)oxy]pyrrolidine-1, 2-dicarboxylate

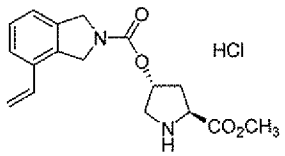


To a solution of 3-but-3-en-1-yl-8-methoxyquinoxalin-2-ol from step 3 (6.15 g, 26.7 mmol) in NMP (200 ml), 1-*t*-butyl 2-methyl (2S,4S)-4-{[(4-bromophenyl)sulfonyl]oxy} pyrrolidine-1,2-dicarboxylate (12.40 g, 26.7 mmol) and cesium carbonate (26.1 g, 80 mmol) were added. The resulting slurry was warmed to 50°C for 5 hours while under N_2. An additional amount of 1-*t*-butyl 2-methyl (2S,4S)-4-{[(4-bromophenyl)sulfonyl]oxy}pyrrolidine-1,2-dicarboxylate (3.7 g, 7.96 mmol) and cesium carbonate (2.5 g, 7.7 mmol) were added, and heating was continued for 14 hours. The reaction was diluted with EtOAc (200 mL) and filtered, the filtrate was quenched into 10% $KHSO_4$, and the product was extracted into EtOAc (2x). The organics were combined, washed with brine (2x), dried over sodium sulfate, filtered, and concentrated to a brown oil. Purification by column chromatography on SiO_2 (gradient elution, 20-45% EtOAc/hexane) gave the title compound as a colorless oil (9.4 g, 77 %). LCMS (ES+) m/z 458.0 (M+H)+.

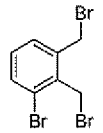
Step 5: Methyl (4R)-4-[(3-but-3-en-1-yl-8-methoxyquinoxalin-2-yl)oxy]-L-prolinate dihydrochloride

A solution of 1-tert-butyl 2-methyl (2S,4R)-4-[(3-but-3-en-1-yl-8-methoxyquinoxalin-2-yl)oxy]pyrrolidine-1, 2-dicarboxylate from step 4 (9.4 g, 20.55 mmol) in HCl/dioxane (4 N, 150 mL) was prepared at 0°C, then stirred for 2 hours at 20°C. The reaction mixture was concentrated to afford a residue that was triturated with Et_2O to afford the title compound (9.5 g, 100%) as a white solid that was used directly in subsequent reactions. LCMS (ES+) m/z 358.0 $(M+H)^+$.

Intermediate D4: (3*R*,5*S*)-5-(Methoxycarbonyl)pyrrolidin-3-yl 4-vinyl-1,3-dihydro-2*H*-isoindole-2-carboxylate Hydrochloride

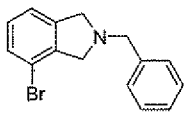


Step 1: 1-Bromo-2,3-bis(bromomethyl)benzene



A suspension of 3-bromo-o-xylene (196 g, 1.06 mol), *N*-bromosuccinimide (377 g, 2.15 mol) and benzoyl peroxide (0.26 g, 1.0 mmol) in carbon tetrachloride (1800 mL) was heated to reflux under N_2 for 15 hours. The contents of the reaction flask were cooled and filtered, and the filtrate was evaporated. The crude material was distilled under high vacuum; the major fractions were distilled between 88°C and 152°C. From these distillates, 108 g of pure material was recovered, and 182 g of slightly crude material, which could be used in the following reaction, was also recovered. ^{1}H NMR ($CDCl_3$) δ 7.56 (d, J = 8.0 Hz, 1 H), 7.31 (d, J = 8.0 Hz, 1 H), 7.26 (s, 1 H), 7.16 (t, J = 8.0 Hz, 1 H), 4.84 (s, 2 H), 4.64 (s, 2 H) ppm.

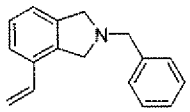
Step 2: 2-Benzyl-4-bromoisoindoline



$KHSO_4$ (204 g, 2.04 mol) was suspended in CH_3CN (12 L), and the mixture was heated to 80°C. Solutions of 1-bromo-2,3-bis(bromomethyl)benzene (280 g, 0.82 mol in 500 mL CH_3CN) and benzylamine (87.5 g, 0.82 mol in 500 mL CH_3CN) were added concurrently via addition funnels over 1 hour. The reaction mixture was stirred at 77°C for 16 hours. The contents of the reaction flask were cooled and filtered, and the solvent was removed by evaporation. The reaction was partitioned between 1M K_2CO_3 and EtOAc. The organics were washed with brine, dried with anhydrous Na_2SO_4, filtered and evaporated. Flash column chromatography (gradient elution: heptane to 10% EtOAc in heptane) gave, after evaporation, the title compound as a pale oil. ^{1}H NMR ($CDCl_3$) δ 7.41-7.39 (m, 2 H), 7.37-7.34 (m, 2 H), 7.32-7.27 (m, 2 H), 7.10-7.03 (m, 2 H), 4.02 (s, 2 H), 3.97 (s, 2 H), 3.91 (s, 2 H). LRMS (ESI) *m/z* 289 [$(M+H)^+$; calculated for $C_{15}H_{15}BrN$: 289].

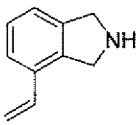
The product was converted to HCl salt in HCl/MeOH by the addition of MTBE and filtration of the solid to give 118 g of product as the HCl salt.

Step 3: 2-Benzyl-4-vinylisoindoline



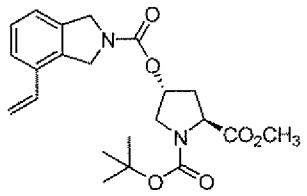
A solution of 2-benzyl-4-bromoisoindoline (16.7 g, 58.0 mmol) and tributyl(vinyl)tin (20.3 mL, 69.6 mmol) in PhMe (400 mL) was degassed by bubbling N_2 gas through the solution for 0.25 hour. Tetrakis(triphenylphosphine)palladium (0) (1.30 g, 1.16 mmol) was added, and the resulting solution heated in a 100°C oil bath under N_2 for 24 h. The contents of the reaction flask were cooled, evaporated and subjected to flash column chromatography eluting with hexane/EtOAc 95/5 to give after evaporation the title compound as a pale oil that turned pink on standing. LRMS (ESI) *m/z* 236 [$(M+H)^+$; calculated for $C_{17}H_{18}N$: 236].

Step 4: 4-Vinylisoindoline



A solution of 2-benzyl-4-vinylisoindoline (58 mmol) in 1,2-dichloroethane (150 mL) was placed in a 1L round-bottom flask under N_2. An addition funnel containing a solution of 1-chloroethyl chloroformate (7.51 mL, 69.6 mmol) in 1,2-dichloroethane was attached to the reaction flask. The reaction flask was cooled in an ice bath, and the contents of the addition funnel were added dropwise over 20 minutes, keeping the internal reaction temperature <5°C. After the addition was complete, the reaction flask was allowed to warm to RT, then heated to reflux for 45 minutes. The contents of the reaction flask were cooled to RT, then the solvent was removed by evaporation. MeOH (200 mL) was added, and the contents of the reaction flask were heated to reflux for 30 minutes. The reaction flask was cooled, and the solvent removed by evaporation. H_2O (200 mL) was added, and the resulting mixture washed with EtOAc (2 × 250 mL). The aqueous layer was made basic with 2N NaOH then extracted with methylene chloride (4 × 250 mL). The combined organic extracts were dried with anhydrous Na_2SO_4, filtered and the filtrate evaporated. The remaining residue was subjected to flash column chromatography eluting with methylene chloride/MeOH/NH_4OH 97/3/0.3 to 95/5/0.5. Evaporation of fractions gave the title compound as a brown oil, 6.00g (41.4 mmol, 71% yield for two steps). LRMS (ESI) *m/z* 146 [$(M+H)^+$; calculated for $C_{10}H_{12}N$: 146].

Step 5: 1-tert-*Butyl 2-methyl (2*S*,4*R*)-4-{[(4-vinyl-1,3-dihydro-2*H*-isoindol-2-yl)carbonyl]oxy}pyrrolidine-1,2-dicarboxylate*

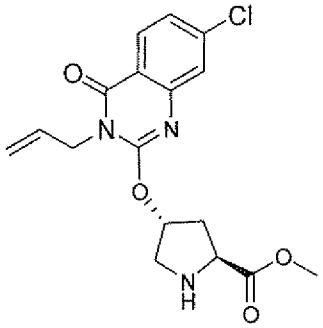


A solution of 1-*tert*-butyl 2-methyl (2*S*,4*R*)-4-hydroxypyrrolidine-1,2-dicarboxylate (10.1 g, 41.4 mmol) in DMF (90 mL) under N_2 was cooled to 0°C. Solid 1,1'-carbonyldiimidazole (6.70 g, 41.4 mmol) was added to the reaction. The contents of the reaction flask were warmed to RT, and, after 2 hours, a solution of 4-vinylisoindoline (6.00 g, 41.4 mmol) in DMF (10 mL) was added. The reaction was heated in a 60°C oil bath for 2 hours, then cooled and poured into H_2O and 5% $KHSO_4$. The resulting mixture was extracted with EtOAc (4 × 250 mL). The combined organics were washed with brine, dried with anhydrous Na_2SO_4, filtered and evaporated. Flash column chromatography eluting with hexane/EtOAc 70/30 gave the title compound as a white foam, 13.9 g (33.4 mmol, 81% yield). LRMS (ESI) *m/z* 417 $[(M+H)^+$; calculated for $C_{227}H_{29}N_2O_6$: 417].

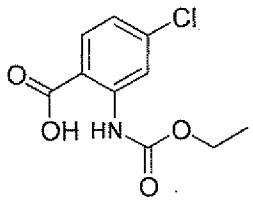
*Step 6: (3*R*,5*S*)-5-(Methoxycarbonyl)pyrrolidin-3-yl 4-vinyl-1,3-dihydro-2*H*-isoindole-2-carboxylate hydrochloride*

A solution of 1-*tert*-Butyl 2-methyl (2*S*,4*R*)-4-{[(4-vinyl-1,3-dihydro-2*H*-isoindol-2-yl)carbonyl]oxy}pyrrolidine-1,2-dicarboxylate (13.9 g, 33.4 mmol) in EtOAc (700 mL) was cooled in an ice bath the saturated with HCl gas. The reaction flask was sealed and allowed to warm to RT. After 3.5 hours, the solvent was removed by evaporation to give the title compound as a gray solid, 11.2 g, 95% yield). ^{1}H NMR (500 MHz, CD_3OD) δ 7.47-7.45 (m, 1 H), 7.32-7.31 (m, 1 H), 7.26-7.21 (m, 1 H), 6.79-6.73 (m, 1 H), 5.79 - 5.73 (m, 1 H), 5.46 (s, 1 H), 5.41 - 5.38 (m, 1 H), 4.80 - 4.72 (m, 4 H), 3.91 (s, 3 H), 3.74 - 3.63 (m, 2 H), 2.77 - 2.71(m, 1 H), 2.51 - 2.46 (m, 1 H). LRMS (ESI) *m/z* 317 $[(M+H)^+$; calculated for $C_{17}H_{21}N_2O_4$: 317].

Intermediate D5: methyl (4*R*)-4-{[7-chloro-4-oxo-3-(prop-2-en-1-yl)-3,4-dihydroquinazolin-2-yl]oxy}-L-prolinate

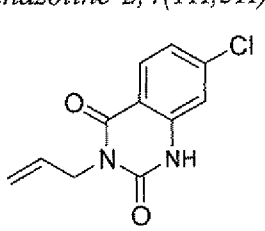


Step 1: 4-chloro-2-[(ethoxycarbonyl)amino]benzoic acid



To a solution of 2-amino-4-chlorobenzoic acid (30 g, 175 mmol) in THF (480 mL) at RT, ethyl chloroformate (50.4 mL, 525 mmol) was added. The mixture was heated to reflux overnight. The reaction was then concentrated *in vacuo* to an thick oil/foam that was flushed with PhMe, and the residue was slurried with ~500 mL 5% ether/hexane. The resulting solids were filtered and washed with 5% ether/hexanes to give upon air drying the title compound (39 g). LRMS (ESI) *m/z* 244 [$(M+H)^+$; calculated for $C_{10}H_{11}ClNO_4$: 244].

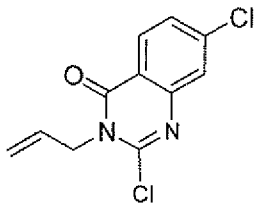
Step 2: 7-chloro-3-(prop-2-en-1-yl)quinazoline-2,4(1H,3H)-dione



To a solution of the product from step 1 (39.0 g, 160 mmol), N-methylmorpholine (35.2 mL, 320 mmol) and allylamine (14.97 mL, 200 mmol) in DMF (50 mL) at RT, BOP reagent (88 g, 200 mmol) was added. The mixture was stirred at RT over the weekend. DBU (121 mL, 800 mmol) was then added, and the mixture was heated to 60°C for 3 hours. The mixture was then poured into 0.5 N HCl (3000 mL), and the pH was adjusted to 2.0 with 3N HCl. Thick white solids observed, and the reaction was diluted to ~4000 mL and let stir 10 minutes. The solids were filtered, washed with 0.5 N HCl, and then slurry washed with water

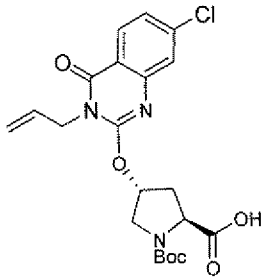
and sucked dry. The title compound was obtained after air drying overnight (36.3 g). LRMS (ESI) *m/z* 237 [$(M+H)^+$; calculated for $C_{11}H_{10}ClN_2O_2$: 237].

Step 3: 2,7-dichloro-3-(prop-2-en-1-yl)quinazolin-4(3H)-one



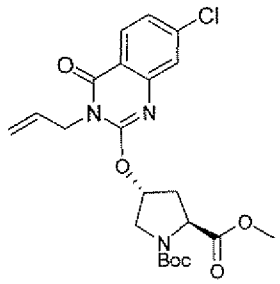
To the product from step 2 (10.25g, 43.3 mmol), phosphorous oxychloride (161 mL, 1732 mmol) and N,N-dimethylaniline (10.98 mL, 87 mmol) were added. The mixture was heated to reflux for 36 hours, concentrated *in vacuo*, and poured into ice water. The mixture was then extracted four times with EtOAc, and the combined organic portions were washed with water then brine, dried with anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude material was purified on silica (10% EtOAc/hexanes) to give a yellow solid that was triturated with 10% EtOAc/hexanes to give the title compound as a tan solid (7.5 g). LRMS (ESI) *m/z* 256 [$(M+H)^+$; calculated for $C_{11}H_9Cl_2N_2O$: 256].

Step 4: (4R)-1-(tert-butoxycarbonyl)-4-{[7-chloro-4-oxo-3-(prop-2-en-1-yl)-3,4-dihydroquinazolin-2-yl]oxy}-L-proline



To a solution of Boc-L-4-Hydroxyproline (5.44 g, 23.52 mmol) in DMF (100 mL) cooled reaction in an cold bath to -60°C was added NaHMDS (39.2 mL, 39.2 mmol) slowly. The mixture thickens and solids precipitate. The reaction was then warmed to 0°C for 15 minutes and then re-cooled to -60°C. The product from step 3 (4 g, 15.68 mmol), as a solid, was then added in one portion. The reaction was then warmed slowly to 0°C. After 30 minutes, the mixture was poured into 10% $KHSO_4$ (125 mL) cooled to 0°C. The mixture was then extracted with EtOAc and the combined organic portions were washed with water 3x then brine, dried with anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to give the title compound (7 g), which was used crude in the next step. LRMS (ESI) *m/z* 393 [$((M-t\text{-}Bu)+H)^+$; calculated for $C_{17}H_{17}ClN_3O_6$: 393].

Step 5: 1-tert-butyl 2-methyl (2S,4R)-4-{[7-chloro-4-oxo-3-(prop-2-en-1-yl)-3,4-dihydroquinazolin-2-yl]oxy}pyrrolidine-1,2-dicarboxylate

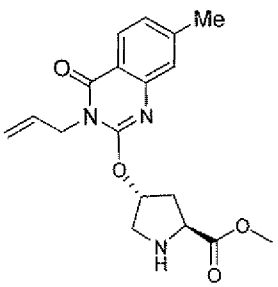


To a solution of the crude product from step 6 (14.1 g, 31.3 mmol) in DCM (157 mL) and MeOH (157 mL) cooled in an ice bath, TMS-diazomethane (47 mL, 94 mmol) was added slowly, keeping the internal temperature <10°C. The mixture was then quenched by dropwise addition of 5% potassium bisulfate. The reaction was then concentrated *in vacuo*, water was added, and the mixture was extracted with EtOAc 3x. The combined organics were washed with brine, dried over $MgSO_4$, and the solvent was removed *in vacuo*. The crude material was purified on silica (gradient elution, 0-50% EtOAc/hexanes) to yield the title compound (13.9 g). LRMS (ESI) *m/z* 408 [((M-*t*-Bu)+H)$^+$; calculated for $C_{18}H_{19}ClN_3O_6$: 408].

Step 6: methyl (4R)-4-{[7-chloro-4-oxo-3-(prop-2-en-1-yl)-3,4-dihydroquinazolin-2-yl]oxy}-L-prolinate

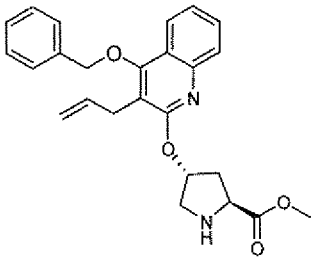
To a solution of the product from step 5 (5.2 g, 11.25 mmol) in DCM (37.5 mL), TFA (37.5) was added. After 30 minutes, the solvents were removed *in vacuo*, and the crude material was taken up in DCM, washed with $NaHCO_3$ and dried over $MgSO_4$, and the solvent was removed *in vacuo* to give the title compound (4.27 g). LRMS (ESI) *m/z* 364 [(M+H)$^+$; calculated for $C_{17}H_{19}ClN_3O_4$: 364].

Intermediate D6: methyl (4*R*)-4-{[7-methyl-4-oxo-3-(prop-2-en-1-yl)-3,4-dihydroquinazolin-2-yl]oxy}-L-prolinate

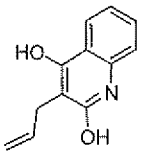


The title compound was prepared according to the procedure used for Intermediate D5 using 2-amino-4-methylbenzoic acid in step 1.

Intermediate D7: methyl (4*R*)-4-{[4-(benzyloxy)-3-(prop-2-en-1-yl)quinolin-2-yl]oxy}-L-prolinate

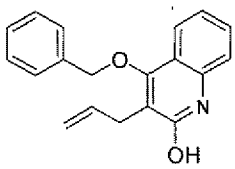


Step 1: 3-(prop-2-en-1-yl)quinoline-2,4-diol



To a degassed solution of 2,4-dihydroxyquinoline (10.0 g, 62.1 mmol) in DMF (100 mL), TEA (9.51 mL, 68.3 mmol) and $Pd(Ph_3P)_4$ (2.151 g, 1.862 mmol) were added, followed by allyl acetate (7.43 mL, 68.3 mmol), and the mixture was allowed to stir at 60°C under N_2 overnight. The reaction was cooled to RT and quenched into water (600 mL) and ~ 80 mL sat Na_2CO_3. The pH was adjusted to 12, and DCM was added (500 mL). The aqueous layer was washed with another portion of DCM (500mL). The aqueous layer was cooled in an ice bath, and pH adjusted to ~2.5 with 12N HCl slowly to give pink solids, which were filtered and washed with water to give the title compound (11.5 g). LRMS (ESI) *m/z* 202 $[(M+H)^+$; calculated for $C_{12}H_{12}NO_2$: 202].

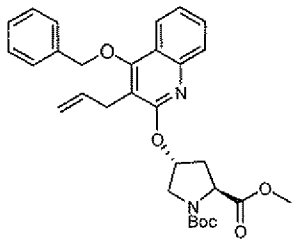
Step 2: 4-(benzyloxy)-3-(prop-2-en-1-yl)quinolin-2-ol



To a mixture of the product from step 1 (4.0 g, 19.88 mmol), triphenylphosphine (6.78 g, 25.8 mmol), and benzyl alcohol (2.274 mL, 21.87 mmol) in THF (240 mL) cooled to 0°C, a THF (12 mL) solution of diisopropylazodicarboxylate (5.02 mL, 25.8 mmol) was slowly added dropwise. Upon completion of addition, the mixture was allowed to stir at RT for 60 minutes, and then it was concentrated *in vacuo* to give a thick oil. The residue was dissolved in DCM (~20 mL), and solids then precipitated out of solution. The solids were filtered and washed with DCM (~10 mL) to yield the title compound (2 g). The mother liquors were then purified on silica (gradient elution, 1-8% acetone/DCM) to yield an oil, which was further

purified by trituration with Et_2O to yield more title compound as a white solid (1 g). LRMS (ESI) *m/z* 292 [$(M+H)^+$; calculated for $C_{19}H_{18}NO_2$: 292].

Step 3: 1-tert-butyl 2-methyl (2S,4R)-4-{[4-(benzyloxy)-3-(prop-2-en-1-yl)quinolin-2-yl]oxy}pyrrolidine-1,2-dicarboxylate

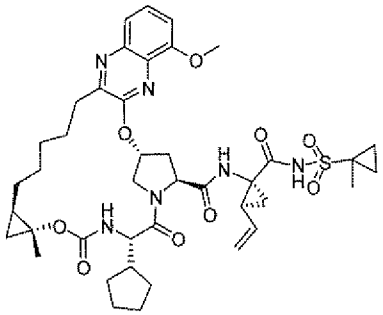


To a mixture 1-*t*-butyl 2-methyl (2*S*,4*S*)-4-{[(4-bromophenyl)sulfonyl]oxy}pyrrolidine-1,2-dicarboxylate (Intermediate A5) (5 g, 10.95 mmol) and the product from step 2 (2.9 g, 9.95 mmol) in N-Methyl-2-pyrrolidinone (25 mL), cesium carbonate (9.7 g, 29.9 mmol) was added, and the mixture was stirred at 60°C for 1 hour. Additional Intermediate A5 (1 g) and cesium carbonate (1 g) were then added, and heating was continued for 3 hours. Additional Intermediate A5 (1 g) and cesium carbonate added (1 g) were then added and heating was continued overnight. The reaction was then cooled and quenched into water (150 mL), and aq. $KHSO_4$ was added to pH=3.5. The mixtures was then extracted with EtOAc (150 mL), and the organic layer was washed with aq. $NaHCO_3$ and brine, dried over sodium sulfate, filtered concentrated *in vacuo*. The residue was purified on silica (gradient elution, 10-30% ethyl acetate/hexanes) to give impure title compound. Further purification was then carried out via reverse phase column chromatography (gradient elution, 10-100% acetonitrile/0.15% TFA-water) to yield pure title compound (3 g). LRMS (ESI) *m/z* 519 [$(M+H)^+$; calculated for $C_{30}H_{35}N_2O_6$: 519].

Step 4: methyl (4R)-4-{[4-(benzyloxy)-3-(prop-2-en-1-yl)quinolin-2-yl]oxy}-L-prolinate

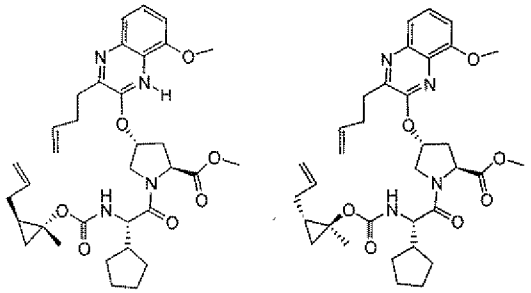
The title compound was prepared according to the procedure for Intermediate D5, step 6. LRMS (ESI) *m/z* 419 [$(M+H)^+$; calcd for $C_{25}H_{27}N_2O_4$: 419].

Example 1: (1*R*,18*R*,20*R*,24*S*,27*S*)-24-Cyclopentyl-6-methoxy-20-methyl-*N*-[(1*R*,2*S*)-1-({[(1-methylcyclopropyl)sulfonyl]amino}carbonyl)-2-vinylcyclopropyl]-22,25-dioxo-2,21-dioxa-4,11,23,26-tetraazapentacyclo[24.2.1.$0^{3,12}$.$0^{5,10}$.$0^{18,20}$]nonacosa-3,5,7,9,11-pentaene-27-carboxamide



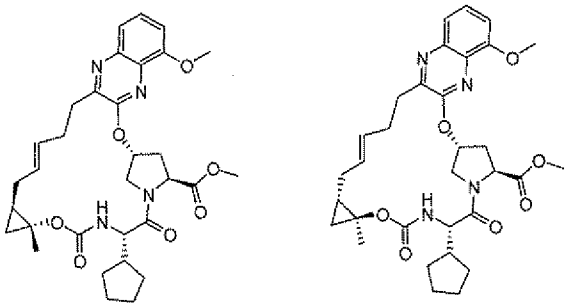
I-1

Step 1: Methyl (2S,4R)-1-{(2S)-2-[({[(1R,2R))-2-allyl-1-methylcyclopropyl]oxy}carbonyl)amino]-2-cyclopentylacetyl}-4-[(3-but-3-en-1-yl-8-methoxyquinoxalin-2-yl)oxy]pyrrolidine-2-carboxylate and Methyl (2S,4R)-1-{(2S)-2-[({[(1S,2S))-2-allyl-1-methylcyclopropyl]oxy}carbonyl)amino]-2-cyclopentylacetyl}-4-[(3-but-3-en-1-yl-8-methoxyquinoxalin-2-yl)oxy]pyrrolidine-2-carboxylate



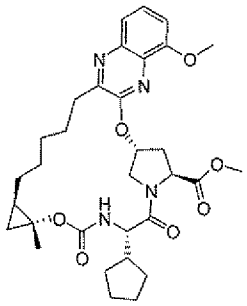
To a solution of intermediate D3 (9.5 g, 22.1 mmol) in DMF (145 ml), intermediate C1 (6.54 g, 23.2 mmol), HATU (8.83 g, 23.2 mmol), and DIEA (15.4 ml, 88.2 mmol) were added. After 1 hour, the reaction was diluted with EtOAc, and the organics were washed with 1N HCl (2x), brine, dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo* to yield an oil. The oil was purified by column chromatography on SiO_2 (gradient elution, 20-70% EtOAc/hexane) to give the title compound as a white foam from Et_2O (11.9 g). LRMS (ESI) *m/z* 621.2 $[(M+H)^+$; calculated for $C_{34}H_{45}N_4O_7$: 621.3].

Step 2: Methyl (1R, 15E, 18R, 20R, 24S, 27S))-24-cyclopentyl-6-methoxy-20-methyl-22,25-dioxo-2,21-dioxa-4,11,23,26-tetraazapentacyclo[24.2.1.03,12.05,10.018,20]nonacosa-3,5,7,9,11,15-hexaene-27-carboxylate and Methyl (1R, 15E, 18S, 20S, 24S, 27S))-24-cyclopentyl-6-methoxy-20-methyl-22,25-dioxo-2,21-dioxa-4,11,23,26-tetraazapentacyclo[24.2.1.03,12.05,10.018,20]nonacosa-3,5,7,9,11,15-hexaene-27-carboxylate



To a degassed solution of product from step 1 (10.7 g, 17.24 mmol) in DCE (2.5 L), p-benzoquinone (0.373 g, 3.45 mmol) and Zhan 1B catalyst (1.200 g, 1.551 mmol) were added. The solution was warmed to 75°C for 15 hours. The reaction was concentrated, and the residue was purified by column chromatography on SiO_2 (gradient elution, 20-60% EtOAc/hexane) to give the title compound as a brown foam from Et_2O (9.0 g). LRMS (ESI) *m/z* 593.2 $[(M+H)^+$; calculated for $C_{32}H_{41}N_4O_7$: 593.3].

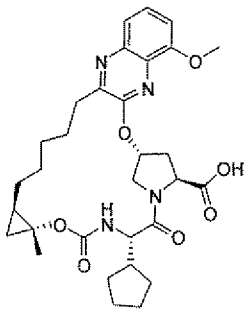
Step 3: methyl (1R, 18R, 20R, 24S, 27S))-24-cyclopentyl-6-methoxy-20-methyl-22,25-dioxo-2,21-dioxa-4,11,23,26-tetraazapentacyclo[24.2.1.03,12.05,10.018,20]nonacosa-3,5,7,9,11-pentaene-27-carboxylate



To a degassed solution of product from step 2 (37.3 g, 62.9 mmol) in EtOH (800 mL), palladium, 5 wt% on calcium carbonate (2.68 g, 1.259 mmol), was added. The resulting slurry was placed under a hydrogen atmosphere (balloon) and allowed to stir for 1 hour. The reaction mixture was filtered through a pad of CELITE, and the cake was washed with EtOH followed by DCM. The filtrate was concentrated, and the resulting residue was purified by column chromatography on SiO_2 (gradient elution, 20-70% EtOAc/hexane) to give a yellow solid, which was a mixture of diastereomers. Purified by column chromatography on SiO_2

(isocratic elution, 5% acetone/CH_2Cl_2) to give the title compound as a white solid (15.6 g). The second diastereomer was then eluted with 10% acetone/DCM with 1% MeOH to yield methyl (1a*S*,5*S*,8*S*,10*R*,22a*S*)-5-cyclopentyl-13-methoxy-1a-methyl-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8*H*-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-*b*]quinoxaline-8-carboxylate (14.9 g), which was used in Example 2. LRMS (ESI) *m/z* 595.1 $[(M+H)^+$; calculated for $C_{32}H_{43}N_4O_7$: 595.3].

Step 4: (1R, 18R, 20R, 24S, 27S))-24-cyclopentyl-6-methoxy-20-methyl-22,25-dioxo-2,21-dioxa-4,11,23,26-tetraazapentacyclo[24.2.1.03,12.05,10.018,20]nonacosa-3,5,7,9,11-pentaene-27-carboxylic acid



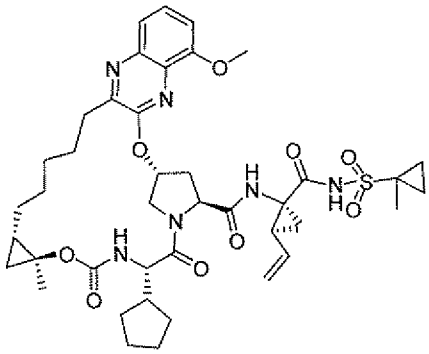
To a solution of the product from step 3 (15.6 g, 26.2 mmol) in THF (200 mL) / water (100 mL), lithium hydroxide monohydrate (2.187 ml, 79 mmol) was added, and the mixture was stirred for 3 hours. The reaction mixture was treated with 6N HCl (13.2 mL), and the solvents were removed *in vacuo*. The resulting residue was partitioned between CH_2Cl_2 and $KHSO_4$ (10%) and extracted with CH_2Cl_2 (3x). The combined organics were washed with brine, dried over Na_2SO_4, and concentrated to yield the title compound as a tan solid from Et_2O (15.0g). LRMS (ESI) *m/z* 581.1 $[(M+H)^+$; calculated for $C_{31}H_{41}N_4O_7$: 581.3].

Step 5: (1R, 18R, 20R, 24S, 27S))-24-cyclopentyl-6-methoxy-20-methyl-N-[(1R,2S)-1-({[(1-methylcyclopropyl)sulfonyl]amino}carbonyl)-2-vinylcyclopropyl]-22,25-dioxo-2,21-dioxa-4,11,23,26-tetraazapentacyclo[24.2.1.03,12.05,10.018,20]nonacosa-3,5,7,9,11-pentaene-27-carboxamide

To a solution of product from step 4 (5.8 g, 9.99 mmol) in DMF (60 mL), intermediate A4 (3.08 g, 10.99 mmol) and DIEA (6.98 ml, 40.0 mmol) were added, and then HATU (4.18 g, 10.99 mmol) was added while in an ice bath. The ice bath was removed, and the reaction was stirred for 1 hour. An additional amount of intermediate A4 (0.561 g, 2 mmol), DIEA (0.350 ml, 2 mmol), and HATU (0.760 g, 2 mmol) was added. After 1 hour, reaction was poured into water (270 mL) and stirred for 1 hour. The slurry was filtered, washed with water to yield a white solid. The solid was stirred in 30% EtOAc / hexane and warmed to 40°C for 2

hours. It was then cooled to RT and stirred for 14 hours. The mixture was filtered to yield the title compound as a white solid (6.94g). LRMS (ESI) *m/z* 807.2 $[(M+H)^+$; calculated for $C_{41}H_{55}N_6O_9S$: 807.3].

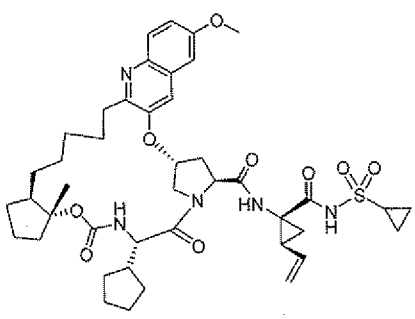
Example 2: (1a*S*,5*S*,8*S*,10*R*,22a*S*)-5-cyclopentyl-*N*-[(1*R*,2*S*)-2-ethenyl-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-13-methoxy-1a-methyl-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8*H*-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-*b*]quinoxaline-8-carboxamide



I-2

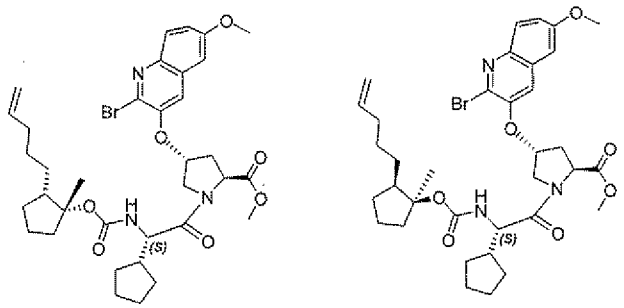
The title compound was prepared following the procedures for Steps 4 and 5 from Example 1 using diastereomer 2 (methyl (1a*S*,5*S*,8*S*,10*R*,22a*S*)-5-cyclopentyl-13-methoxy-1a-methyl-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8*H*-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-*b*]quinoxaline-8-carboxylate) isolated from Step 3, Example 1. LRMS (ESI) *m/z* 807.2 $[(M+H)^+$; calculated for $C_{41}H_{55}N_6O_9S$: 807.3].

Example 3: (1*R*,18*R*,22*R*,26*S*,29*S*)-26-Cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-7-methoxy-22-methyl-24,27-dioxo-2,23-dioxa-11,25,28-triazapentacyclo[26.2.1.$0^{3,12}$.$0^{5,10}$.$0^{18,22}$]hentriaconta-3(12),4,5,7,9,10-hexaene-29-carboxamide (WO 2008/057209, Example 116)



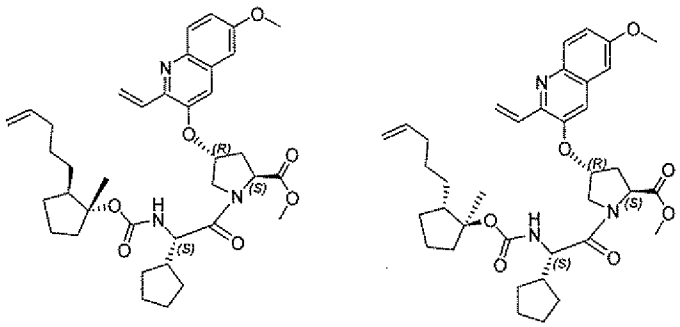
I-3

Step1: methyl (4R)-4-[(2-bromo-6-methoxyquinolin-3-yl)oxy]-1-{(2S)-2-cyclopentyl-2-[({[(1R,2S)-1-methyl-2-(pent-4-en-1-yl)cyclopentyl]oxy}carbonyl)amino]acetyl}-L-prolinate and methyl (4R)-4-[(2-bromo-6-methoxyquinolin-3-yl)oxy]-1-{(2S)-2-cyclopentyl-2-[({[(1S,2R)-1-methyl-2-(pent-4-en-1-yl)cyclopentyl]oxy}carbonyl)amino]acetyl}-L-prolinate



The title compound was prepared according to Example 1, Step 1 using Intermediates C6 and D1. LRMS (ESI) *m/z* 700/702 $[(M+H)^+$; calculated for $C_{35}H_{47}BrN_3O_7$: 700/702].

Step 2: methyl (4R)-1-{(2S)-2-cyclopentyl-2-[({[(1R,2R)-1-methyl-2-(pent-4-en-1-yl)cyclopentyl]oxy}carbonyl)amino]acetyl}-4-[(2-ethenyl-6-methoxyquinolin-3-yl)oxy]-L-prolinate and methyl (4R)-1-{(2S)-2-cyclopentyl-2-[({[(1S,2R)-1-methyl-2-(pent-4-en-1-yl)cyclopentyl]oxy}carbonyl)amino]acetyl}-4-[(2-ethenyl-6-methoxyquinolin-3-yl)oxy]-L-prolinate

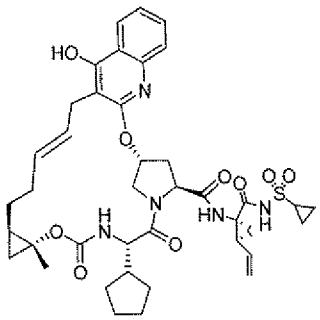


To a solution of the product from step 1 (735 mg, 1.0 mmol) in EtOH (70 mL), potassium vinyltrifluoroborate (211 mg, 1.5 mmol), triethylamine (0.22 mL, 1.5 mmol), and [1,1-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)-CH_2Cl_2 complex (25 mg, 0.03 mmol) were added. The reaction was heated to reflux for 1 hour, the solvent was removed *in vacuo*, and the residue was taken up in EtOAc and washed with water. The organic layer was dried over Na_2SO_4, and the solvent was removed *in vacuo*. The material was purified on silica (gradient elution, 10-40% EtOAc/hexanes) to yield the title compound (402 mg) as a yellow oil. LRMS (ESI) *m/z* 648 $[(M+H)^+$; calculated for $C_{37}H_{50}N_3O_7$: 648].

Step 3: (1R,18R,22R,26S,29S)-26-Cyclopentyl-N-((1R,2S)-1-{[(cyclopropylsulfonyl)amino] carbonyl}-2-vinylcyclopropyl)-7-methoxy-22-methyl-24,27-dioxo-2,23-dioxa-11,25,28-triazapentacyclo[26.2.1.$0^{3,12}$.$0^{5,10}$.$0^{18,22}$]hentriaconta-3(12),4,5,7,9,10-hexaene-29-carboxamide

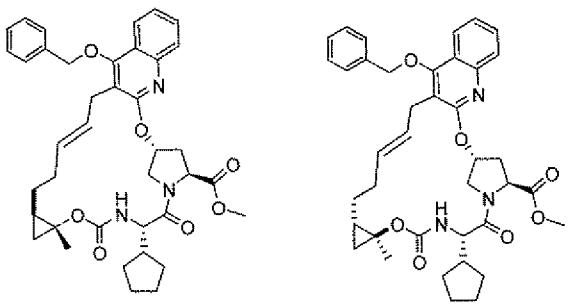
The title compound was prepared according to the procedures in Example 1, steps 2-5 using Intermediate A1 and with separation of the two diastereomers following step 5 via reverse phase chromatography. LRMS (ESI) *m/z* 820 [(M+H)$^+$; calculated for $C_{43}H_{58}N_5O_9S$: 820].

Example 4: (1*R*,14*E*,18*R*,20*R*,24*S*,27*S*)-24-Cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-11-hydroxy-20-methyl-22,25-dioxo-2,21-dioxa-4,23,26-triazapentacyclo[24.2.1.$0^{3,12}$.$0^{5,10}$.$0^{18,20}$]nonacosa-3,5,7,9,11,14-hexaene-27-carboxamide



I-4

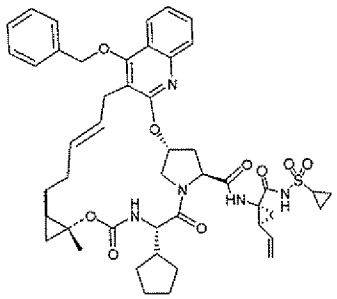
Step 1: methyl (1aR,5S,8S,10R,19E,22aR)-17-(benzyloxy)-5-cyclopentyl-1a-methyl-3,6-dioxo-1,1a,3,4,5,6,9,10,18,21,22,22a-dodecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6] dioxadiazacyclononadecino[11,12-b]quinoline-8-carboxylate and methyl (1aS,5S,8S,10R,19E, 22aS)-17-(benzyloxy)-5-cyclopentyl-1a-methyl-3,6-dioxo-1,1a,3,4,5,6,9,10,18,21,22,22a-dodecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoline-8-carboxylate



The title compounds were prepared according to Example 1, steps 1-2 using Intermediates C2 and D7. The crude products from step 2 were purified and separated on silica (gradient elution, 5-50% EtOAc/hexanes) to yield methyl (1a*R*,5*S*,8*S*,10*R*,19*E*,22a*R*)-17-

(benzyloxy)-5-cyclopentyl-1a-methyl-3,6-dioxo-1,1a,3,4,5,6,9,10,18,21,22,22a-dodecahydro-8*H*-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-*b*]quinoline-8-carboxylate as the first eluting isomer and methyl (1a*S*,5*S*,8*S*,10*R*,19*E*,22a*S*)-17-(benzyloxy)-5-cyclopentyl-1a-methyl-3,6-dioxo-1,1a,3,4,5,6,9,10,18,21,22,22a-dodecahydro-8*H*-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-*b*]quinoline-8-carboxylate as the second eluting isomer. LRMS (ESI) *m/z* 669 [(M+H)$^+$; calculated for $C_{39}H_{46}N_3O_7S$: 669].

Step 2: (1aR,5S,8S,10R,19E,22aR)-17-(benzyloxy)-5-cyclopentyl-N-{(1R,2S)-1-[(cyclopropylsulfonyl)carbamoyl]-2-ethenylcyclopropyl}-1a-methyl-3,6-dioxo-1,1a,3,4,5,6,9,10,18,21,22,22a-dodecahydro-8H-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-b]quinoline-8-carboxamide and



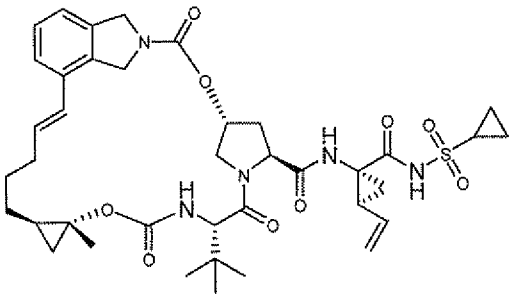
Using the first eluting isomer from step 1, the title compound was prepared according to example 1, steps 4-5 using Intermediate A1. LRMS (ESI) *m/z* 867 [(M+H)$^+$; caluclated for $C_{47}H_{56}N_5O_9S$: 867].

Step 3: (1R,14E,18R,20R,24S,27S)-24-Cyclopentyl-N-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-11-hydroxy-20-methyl-22,25-dioxo-2,21-dioxa-4,23,26-triazapentacyclo[24.2.1.$0^{3,12}$.$0^{5,10}$.$0^{18,20}$]nonacosa-3,5,7,9,11,14-hexaene-27-carboxamide

To the product from step 2 (51 mg, 0.059 mmol), TFA (681 µl, 8.83 mmol) was added, and the mixture was warmed to 55°C. After 45 minutes, the reaction was concentrated without heat, and the residue was dissolved in ACN and purified by reverse phase chromatography. Fractions were worked up with EtOAc and saturated aqueous $NaHCO_3$. The organic layer was dried over Na_2SO_4, and the solvent was removed *in vacuo* to yield the title compound (17 mg). LRMS (ESI) *m/z* 776 [(M+H)$^+$; calculated for $C_{40}H_{50}N_5O_9S$: 776].

Example 5: (1a*R*,5*S*,8*S*,10*R*,19*E*,23a*R*)-5-*tert*-butyl-*N*-{(1*R*,2*S*)-1-[(cyclopropylsulfonyl)carbamoyl]-2-ethenylcyclopropyl}-1a-methyl-3,6,12-trioxo-

1a,3,4,5,6,9,10,14,21,22,23,23a-dodecahydro-1*H*,8*H*-7,10:13,15-dimethanocyclopropa[*n*][4,13,2,8,11]benzodioxatriazacyclodocosine-8(12*H*)-carboxamide

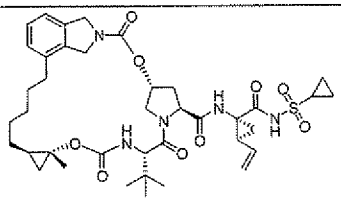


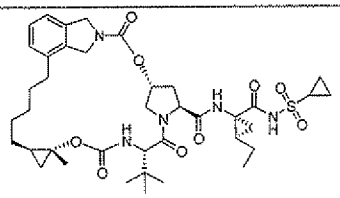
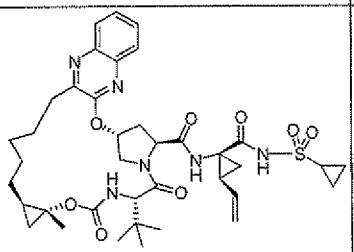
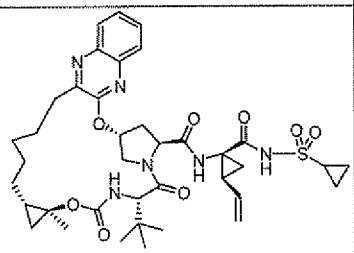
I-5

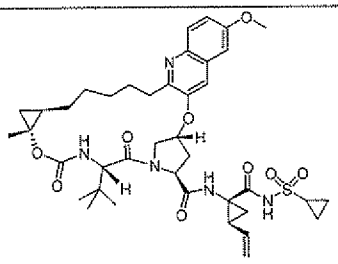
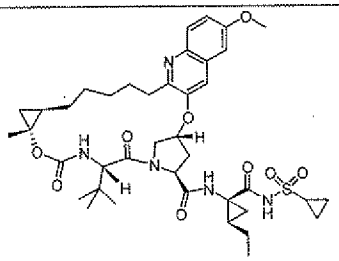
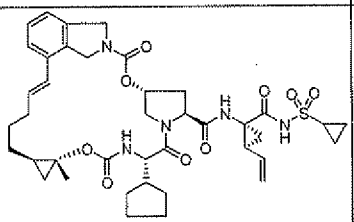
The title compound was prepared according to example 1, steps 1, 2, 4, and 5 using intermediates A1, C4-1, and D4. LRMS (ESI) *m/z* 766 $[(M+H)^+$; calculated for $C_{39}H_{52}N_5O_9S$: 766].

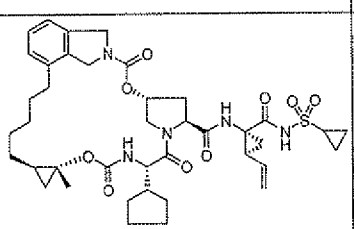
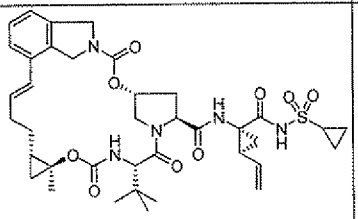
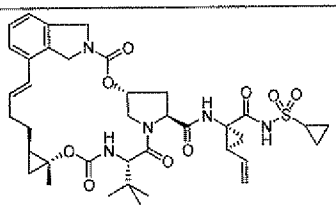
Examples 6-32

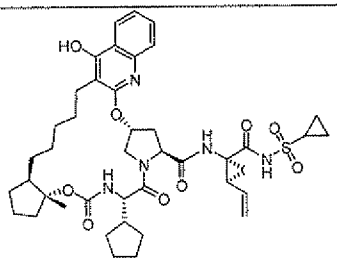
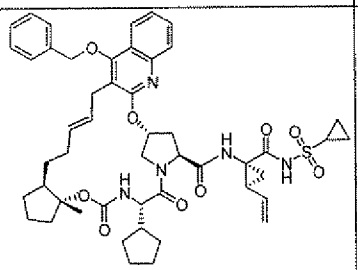
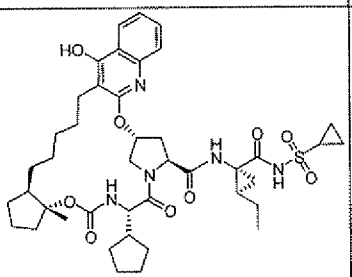
By using the appropriate procedures and the appropriate A, C, and D intermediates, the compounds of Examples 6-32 were prepared, as shown in Table 1 below. All compounds prepared from racemic intermediates C1, C2, C3, C4, C5, C6, and C7 were separated from resulting diastereomers using reverse or normal phase column chromatography following macrocycle formation or after the final step.

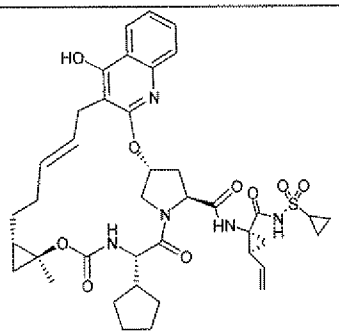
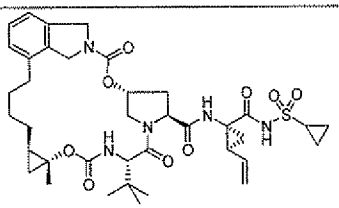
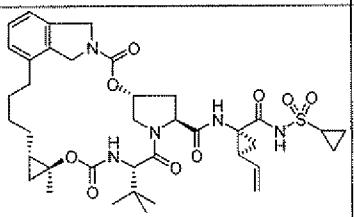
Ex.	Structure	Name	LRMS $(M+H)^+$	Intermediates	Procedure(s)
6	 **I-6**	(1a*R*,5*S*,8*S*,10*R*,23a*R*)-5-*tert*-butyl-*N*-{(1*R*,2*S*)-1-[(cyclopropylsulfonyl) carbamoyl]-2-ethenylcyclopropyl}-1a-methyl-3,6,12-trioxo-1a,3,4,5,6,9,10,14,19,20,21,22,23,23a-tetradecahydro-1*H*,8*H*-7,10:13,15-dimethano cyclopropa [*n*][4,13,2,8,11] benzodioxatriaza cyclodocosine-8(12*H*)-carboxamide	768	A1, C4-1, D4	Example 1

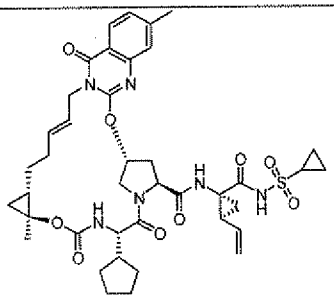
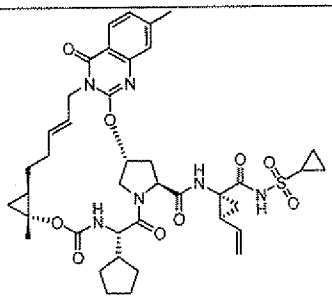
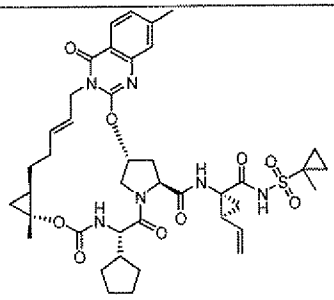
Ex.	Structure	Name	LRMS $(M+H)^+$	Intermediates	Procedure(s)
7	 **I-7**	(1a*R*,5*S*,8*S*,10*R*,23a*R*)-5-*tert*-butyl-*N*-{(1*R*,2*R*)-1-[(cyclopropylsulfonyl)carbamoyl]-2-ethylcyclopropyl}-1a-methyl-3,6,12-trioxo-1a,3,4,5,6,9,10,14,19,20,21,22,23,23a-tetradecahydro-1*H*,8*H*-7,10:13,15-dimethanocyclopropa[*n*][4,13,2,8,11]benzodioxatriazacyclodocosine-8(12*H*)-carboxamide	770	A3, C4-1, D4	Example 1
8	 **I-8**	(1a*R*,5*S*,8*S*,10*R*,22a*R*)-5-*tert*-butyl-*N*-{(1*R*,2*S*)-1-[(cyclopropylsulfonyl)carbamoyl]-2-ethenylcyclopropyl}-1a-methyl-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8*H*-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-*b*]quinoxaline-8-carboxamide	751	A1, C4, D2	Example 3
9	 **I-9**	(1a*S*,5*S*,8*S*,10*R*,22a*S*)-5-*tert*-butyl-*N*-{(1*R*,2*S*)-1-[(cyclopropylsulfonyl)carbamoyl]-2-ethenylcyclopropyl}-1a-methyl-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8*H*-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-*b*]quinoxaline-8-carboxamide	751	A1, C4, D2	Example 3

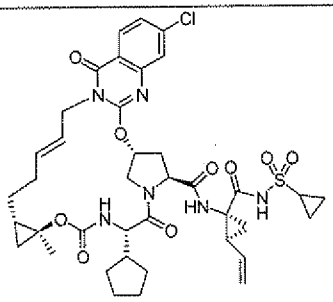
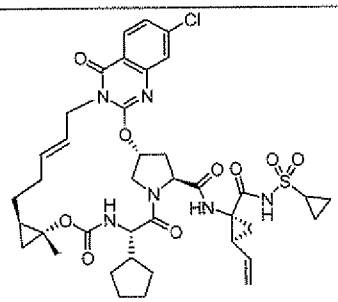
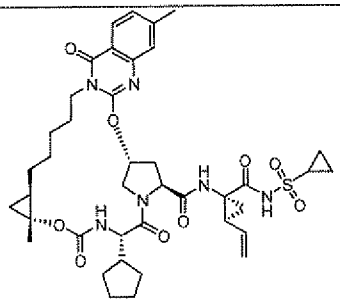
Ex.	Structure	Name	LRMS $(M+H)^+$	Intermediates	Procedure(s)
10	 **I-10**	(1a*R*,5*S*,8*S*,10*R*,22a*R*)-5-*tert*-butyl-*N*-{(1*R*,2*S*)-1-[(cyclopropylsulfonyl) carbamoyl]-2-ethenylcyclopropyl}-14-methoxy-1a-methyl-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8*H*-7,10-methanocyclo propa[18,19][1,10,3,6] dioxadiazacyclonona decino[12,11-*b*] quinoline-8-carboxamide	780	A3, C4, D1	Example 3
11	 **I-11**	(1a*R*,5*S*,8*S*,10*R*,22a*R*)-5-*tert*-butyl-*N*-{(1*R*,2*R*)-1-[(cyclopropylsulfonyl) carbamoyl]-2-ethylcyclopropyl}-14-methoxy-1a-methyl-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8*H*-7,10-methanocyclo propa[18,19][1,10,3,6] dioxadiazacyclonona decino[12,11-*b*] quinoline-8-carboxamide	782	A3, C4, D1	Example 3
12	 **I-12**	(1a*R*,5*S*,8*S*,10*R*,19*E*,23a*R*)-5-cyclopentyl-*N*-{(1*R*,2*S*)-1-[(cyclopropylsulfonyl) carbamoyl]-2-ethenylcyclopropyl}-1a-methyl-3,6,12-trioxo-1a,3,4,5,6,9,10,14,21,22,23,23a-dodecahydro-1*H*,8*H*-7,10:13,15-dimethano cyclopropa[*n*][4,13,2,8,11]benzodioxatriaza cyclodocosine-8(12*H*)-carboxamide	778	A1, C3-1, D4	Example 5

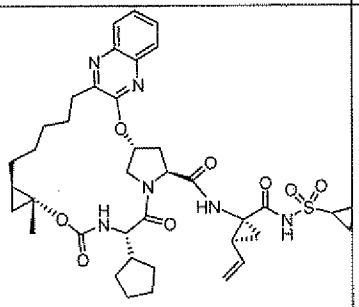
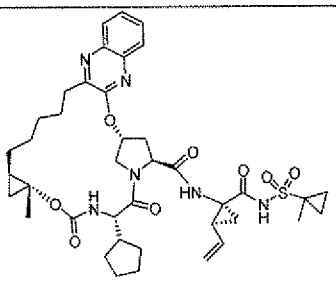
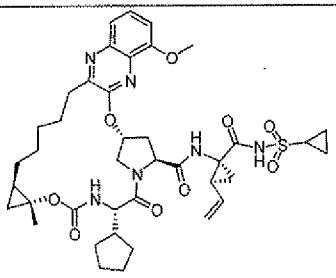
Ex.	Structure	Name	LRMS $(M+H)^+$	Intermediates	Procedure(s)
13	 **I-13**	(1a*R*,5*S*,8*S*,10*R*,23a*R*)-5-cyclopentyl-*N*-{(1*R*,2*S*)-1-[(cyclopropylsulfonyl) carbamoyl]-2-ethenylcyclopropyl}-1a-methyl-3,6,12-trioxo-1a,3,4,5,6,9,10,14,19,20,21,22,23,23a-tetradecahydro-1*H*,8*H*-7,10:13,15-dimethano cyclopropa[*n*][4,13,2,8,11]benzodioxatriaza cyclodocosine-8(12*H*)-carboxamide	780	A1, C3-1, D4	Example 1
14	 **I-14**	(1a*S*,5*S*,8*S*,10*R*,19*E*,22a*S*)-5-*tert*-butyl-*N*-{(1*R*,2*S*)-1-[(cyclopropylsulfonyl) carbamoyl]-2-ethenylcyclopropyl}-1a-methyl-3,6,12-trioxo-1,1a,3,4,5,6,9,10,14,21,22,22a-dodecahydro-8*H*-7,10:13,15-dimethano cyclopropa[*n*][4,13,2,8,11]benzodioxatriaza cyclohenicosine-8(12*H*)-carboxamide	752	A1, C7, D4	Example 5
15	 **I-15**	(1a*R*,5*S*,8*S*,10*R*,19*E*,22a*R*)-5-*tert*-butyl-*N*-{(1*R*,2*S*)-1-[(cyclopropylsulfonyl) carbamoyl]-2-ethenylcyclopropyl}-1a-methyl-3,6,12-trioxo-1,1a,3,4,5,6,9,10,14,21,22,22a-dodecahydro-8*H*-7,10:13,15-dimethanocyclo propa[*n*][4,13,2,8,11] benzodioxatriazacyclo henicosine-8(12*H*)-carboxamide	752	A1, C7, D4	Example 5

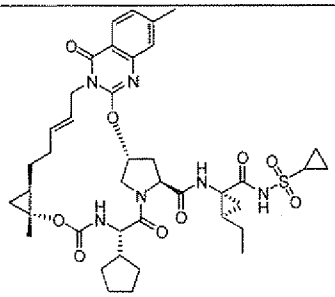
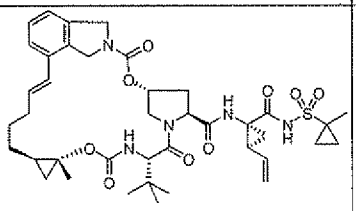
Ex.	Structure	Name	LRMS $(M+H)^+$	Intermediates	Procedure(s)
16	 **I-16**	(3a*R*,7*S*,10*S*,12*R*,24a*R*)-7-cyclopentyl-*N*-{(1*R*,2*S*)-1-[(cyclopropylsulfonyl)carbamoyl]-2-ethenylcyclopropyl}-19-hydroxy-3a-methyl-5,8-dioxo-1,2,3,3a,5,6,7,8,11,12,20,21,22,23,24,24a-hexadecahydro-10*H*-9,12-methanocyclopenta[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-*b*]quinoline-10-carboxamide	806	A1, C5, D7	Example 1
17	 **I-17**	(3a*R*,7*S*,10*S*,12*R*,21*E*,24a*S*)-19-(benzyloxy)-7-cyclopentyl-*N*-{(1*R*,2*S*)-1-[(cyclopropylsulfonyl)carbamoyl]-2-ethenylcyclopropyl}-3a-methyl-5,8-dioxo-1,2,3,3a,5,6,7,8,11,12,20,23,24,24a-tetradecahydro-10*H*-9,12-methanocyclopenta[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-*b*]quinoline-10-carboxamide	894	A1, C5, D7	Example 5
18	 **I-18**	(3a*R*,7*S*,10*S*,12*R*,24a*R*)-7-cyclopentyl-*N*-{(1*R*,2*R*)-1-[(cyclopropylsulfonyl)carbamoyl]-2-ethylcyclopropyl}-19-hydroxy-3a-methyl-5,8-dioxo-1,2,3,3a,5,6,7,8,11,12,20,21,22,23,24,24a-hexadecahydro-10*H*-9,12-methanocyclopenta[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-*b*]quinoline-10-carboxamide	808	A3, C5, D7	Example 1

Ex.	Structure	Name	LRMS $(M+H)^+$	Intermediates	Procedure(s)
19	 **I-19**	(1a*S*,5*S*,8*S*,10*R*,19*E*,22a*S*)-5-cyclopentyl-*N*-{(1*R*,2*S*)-1-[(cyclopropylsulfonyl)carbamoyl]-2-ethenylcyclopropyl}-17-hydroxy-1a-methyl-3,6-dioxo-1,1a,3,4,5,6,9,10,18,21,22,22a-dodecahydro-8*H*-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-*b*]quinoline-8-carboxamide	776	A1, C2, D7	Example 4
20	 **I-20**	(1a*R*,5*S*,8*S*,10*R*,22a*R*)-5-*tert*-butyl-*N*-{(1*R*,2*S*)-1-[(cyclopropylsulfonyl)carbamoyl]-2-ethenylcyclopropyl}-1a-methyl-3,6,12-trioxo-1,1a,3,4,5,6,9,10,14,19,20,21,22,22a-tetradecahydro-8*H*-7,10:13,15-dimethanocyclopropa[*n*][4,13,2,8,11]benzodioxatriazacyclohenicosine-8(12*H*)-carboxamide	754	A1, C7, D4	Example 1
21	 **I-21**	(1a*S*,5*S*,8*S*,10*R*,22a*S*)-5-*tert*-butyl-*N*-{(1*R*,2*S*)-1-[(cyclopropylsulfonyl)carbamoyl]-2-ethenylcyclopropyl}-1a-methyl-3,6,12-trioxo-1,1a,3,4,5,6,9,10,14,19,20,21,22,22a-tetradecahydro-8*H*-7,10:13,15-dimethanocyclopropa[*n*][4,13,2,8,11]benzodioxatriazacyclohenicosine-8(12*H*)-carboxamide	754	A1, C7, D4	Example 1

Ex.	Structure	Name	LRMS $(M+H)^+$	Intermediates	Procedure(s)
22	 I-22	(1a*S*,5*S*,8*S*,10*R*,20*E*,23a*S*)-5-cyclopentyl-*N*-{(1*R*,2*S*)-1-[(cyclopropylsulfonyl)carbamoyl]-2-ethenylcyclopropyl}-1a,14-dimethyl-3,6,17-trioxo-1,1a,3,4,5,6,9,10,19,22,23,23a-dodecahydro-8*H*,17*H*-7,10-methanocyclopropa[18,19][1,10,3,6,12]dioxatriazacyclononadecino[11,12-*b*]quinazoline-8-carboxamide	791	A1, C2, D6	Example 5
23	 I-23	(1a*R*,5*S*,8*S*,10*R*,20*E*,23a*R*)-5-cyclopentyl-*N*-{(1*R*,2*S*)-1-[(cyclopropylsulfonyl)carbamoyl]-2-ethenylcyclopropyl}-1a,14-dimethyl-3,6,17-trioxo-1,1a,3,4,5,6,9,10,19,22,23,23a-dodecahydro-8*H*,17*H*-7,10-methanocyclopropa[18,19][1,10,3,6,12]dioxatriazacyclononadecino[11,12-*b*]quinazoline-8-carboxamide	791	A1, C2, D6	Example 5
24	 I-24	(1a*R*,5*S*,8*S*,10*R*,20*E*,23a*R*)-5-cyclopentyl-*N*-[(1*R*,2*S*)-2-ethenyl-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-1a,14-dimethyl-3,6,17-trioxo-1,1a,3,4,5,6,9,10,19,22,23,23a-dodecahydro-8*H*,17*H*-7,10-methanocyclopropa[18,19][1,10,3,6,12]dioxatriazacyclononadecino[11,12-*b*]quinazoline-8-carboxamide	805	A4, C2, D6	Example 5

Ex.	Structure	Name	LRMS $(M+H)^+$	Intermediates	Procedure(s)
25	 **I-25**	(1a*S*,5*S*,8*S*,10*R*,20*E*,23a*S*)-14-chloro-5-cyclopentyl-*N*-{(1*R*,2*S*)-1-[(cyclopropylsulfonyl)carbamoyl]-2-ethenylcyclopropyl}-1a-methyl-3,6,17-trioxo-1,1a,3,4,5,6,9,10,19,22,23,23a-dodecahydro-8*H*,17*H*-7,10-methanocyclopropa[18,19][1,10,3,6,12]dioxatriazacyclononadecino[11,12-*b*]quinazoline-8-carboxamide	811	A1, C2, D5	Example 5
26	 **I-26**	(1a*R*,5*S*,8*S*,10*R*,20*E*,23a*R*)-14-chloro-5-cyclopentyl-*N*-{(1*R*,2*S*)-1-[(cyclopropylsulfonyl)carbamoyl]-2-ethenylcyclopropyl}-1a-methyl-3,6,17-trioxo-1,1a,3,4,5,6,9,10,19,22,23,23a-dodecahydro-8*H*,17*H*-7,10-methanocyclopropa[18,19][1,10,3,6,12]dioxatriazacyclononadecino[11,12-*b*]quinazoline-8-carboxamide	811	A1, C2, D5	Example 5
27	 **I-27**	(1a*R*,5*S*,8*S*,10*R*,23a*R*)-5-cyclopentyl-*N*-{(1*R*,2*S*)-1-[(cyclopropylsulfonyl)carbamoyl]-2-ethenylcyclopropyl}-1a,14-dimethyl-3,6,17-trioxo-1,1a,3,4,5,6,9,10,19,20,21,22,23,23a-tetradecahydro-8*H*,17*H*-7,10-methanocyclopropa[18,19][1,10,3,6,12]dioxatriazacyclononadecino[11,12-*b*]quinazoline-8-carboxamide	793	A1, C2, D6	Example 1

Ex.	Structure	Name	LRMS $(M+H)^+$	Intermediates	Procedure(s)
28	 **I-28**	(1a*R*,5*S*,8*S*,10*R*,22a*R*)-5-cyclopentyl-*N*-{(1*R*,2*S*)-1-[(cyclopropylsulfonyl) carbamoyl]-2-ethenylcyclopropyl}-1a-methyl-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8*H*-7,10-methanocyclo propa[18,19][1,10,3,6] dioxadiazacyclonona decino[11,12-*b*]quinoxaline-8-carboxamide	763	A1, C3-1, D2	Example 1
29	 **I-29**	(1a*R*,5*S*,8*S*,10*R*,22a*R*)-5-cyclopentyl-*N*-[(1*R*,2*S*)-2-ethenyl-1-{[(1-methylcyclo propyl)sulfonyl] carbamoyl}cyclopropyl]-1a-methyl-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8*H*-7,10-methanocyclo propa[18,19][1,10,3,6] dioxadiazacyclonona decino[11,12-*b*]quinoxaline-8-carboxamide	777	A4, C3-1, D2	Example 1
30	 **I-30**	(1a*R*,5*S*,8*S*,10*R*,22a*R*)-5-cyclopentyl-*N*-{(1*R*,2*S*)-1-[(cyclopropylsulfonyl) carbamoyl]-2-ethenylcyclopropyl}-13-methoxy-1a-methyl-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8*H*-7,10-methanocyclo propa[18,19][1,10,3,6] dioxadiazacyclonona decino[11,12-*b*]quinoxaline-8-carboxamide	793	A1, C1, D3	Example 1

Ex.	Structure	Name	LRMS $(M+H)^+$	Intermediates	Procedure(s)
31	 **I-31**	(1a*R*,5*S*,8*S*,10*R*,20*E*,23a*R*)-5-cyclopentyl-*N*-{(1*R*,2*R*)-1-[(cyclopropylsulfonyl)carbamoyl]-2-ethylcyclopropyl}-1a,14-dimethyl-3,6,17-trioxo-1,1a,3,4,5,6,9,10,19,22,23,23a-dodecahydro-8*H*,17*H*-7,10-methanocyclopropa[18,19][1,10,3,6,12]dioxatriazacyclononadecino[11,12-*b*]quinazoline-8-carboxamide	793	A3, C2, D6	Example 5
32	 **I-32**	(1a*R*,5*S*,8*S*,10*R*,19*E*,23a*R*)-5-*tert*-butyl-*N*-[(1*R*,2*S*)-2-ethenyl-1-{[(1-methylcyclopropyl)sulfonyl]carbamoyl}cyclopropyl]-1a-methyl-3,6,12-trioxo-1a,3,4,5,6,9,10,14,21,22,23,23a-dodecahydro-1*H*,8*H*-7,10:13,15-dimethanocyclopropa[*n*][4,13,2,8,11]benzodioxatriazacyclodocosine-8(12*H*)-carboxamide	780	A4, C4-1, D4	Example 5

Example 33

Comparison of Different Compounds

The compounds of Examples 1 through 32 were compared to the compound of Example 97 of International Patent Application Publication No. WO 2008/057209. The results are shown in Table 2 below. As illustrated in the table, the compounds of formula I, as illustrated by the compounds of Examples 1 through 32, appear to have several advantageous properties, such as improved activity against a one or more mutant compared to the compound of Example 97 of WO 2008/057209.

The activity table provided below illustrates the observed activity:

Table 2: NS3/4A Inhibitory Activity (Ki) & Compound Inhibitory Potency (Replicon (nM))

	Enzyme Activity (nM)			gt 1b Replicon EC50 (nM)	
Compound	**gt 1b Ki**	**gt 1b A156V Ki**	**gt 3a Ki**	**10% FBS**	**50% NHS**
WO 2008/057209, Example 97	0.02	8.2	2.7	3.3	20
I-1	0.04	1.0	1.6	2	7.6
I-2	--	--	--	--	--
I-3	0.03	3.3	0.5	6	23
I-4	0.04	0.9	0.7	7	17
I-5	0.02	1.3	1.0	3	22
I-6	0.02	0.3	2.9	3	54
I-7	0.02	2.2	8.7	4	27
I-8	0.02	11.5	0.5	2	6
I-9	0.06	--	12.5	--	--
I-10	0.02	4.2	0.2	4	10
I-11	0.03	--	0.5	4	7
I-12	0.02	1.4	12.0	5	19
I-13	0.02	0.4	32.9	4	16
I-14	0.08	6.3	112	--	--
I-15	0.09	8.9	93.5	--	--
I-16	0.02	2.4	1.4	9	27
I-17	0.07	9.6	27.9	--	--
I-18	0.07	42.5	9.2	30	35
I-19	0.5	30.0	21.8	--	--
I-20	0.02	27.2	58.3	--	--
I-21	1.4	8.1	300	--	--
I-22	0.3	134.9	82.2	--	--
I-23	0.02	1.2	1.0	2	6
I-24	0.02	0.9	0.7	2	8.5
I-25	0.2	142.3	41.0	--	--
I-26	0.02	1.6	0.8	3	13
I-27	0.04	4.1	2.8	2	6
I-28	0.04	2.7	3.2	2	10
I-29	0.04	1.7	3.1	3	9
I-30	0.02	1.9	2.2	1	5
I-31	0.1	13.3	5.3	4	10
I-32	0.03	1.0	1.8	1	11

Ki: Inhibition constant; gt: genotype; EC50: Effective concentration achieving 50% viral replicaiton suppression; FBS: Fetal Bovine Serum; NHS: Normal Human Serum.

Methods

Measuring NS3/4A Inhibitory Activity (Ki)

Compound described herein can be evaluated for different activities such as the ability to inhibit HCV NS3 activity, HCV replicon activity, and HCV replication activity using techniques well-known in the art. (*See*, for example, Steven S. Carroll *et al.*, *Inhibition of Hepatitis C Virus RNA Replication by 2'-Modified Nucleoside Analogs*, 278(14) J. BIOLOGICAL CHEMISTRY 11979 (2003))

One such assay is HCV NS3 protease time-resolved fluorescence (TRF) assay as described below and in Mao *et al., Anal. Biochem. 373*:1-8, 2008 and International Patent Application Publication WO 2006/102087. A NS3 protease assay can be performed, for example, in a final volume of 100 µl assay buffer containing 50 mM HEPES, pH 7.5, 150 mM NaCl, 15 % glycerol, 0.15 % TRITON X-100, 10 mM DTT, and 0.1 % PEG 8000. NS3 and NS4A protease is pre-incubated with various concentrations of inhibitors in DMSO for 30 minutes. The reaction is initiated by adding the TRF peptide substrate (final concentration 100 nM). NS3 mediated hydrolysis of the substrate is quenched after 1 hour at room temperature with 100 µl of 500 mM MES, pH 5.5. Product fluorescence is detected using either a VICTOR V2 or FUSION fluorophotometer (Perkin Elmer Life and Analytical Sciences) with excitation at 340 nm and emission at 615 nm with a 400 µs delay. Testing concentrations of different enzyme forms are selected to result in a signal to background ratio (S/B) of 10-30. IC_{50} values are derived using a standard four-parameter fit to the data. K_i values are derived from IC_{50} values using the following formula,

$$IC_{50} = K_i (1 + [S] / K_M), \qquad \text{Eqn (1)},$$

where [S] is the concentration of substrate peptide in the reaction and K_M is the Michaelis constant. *See* P. Gallinari *et al.*, 38 BIOCHEM. 5620-32(1999); P. Gallinari *et al.*, 72 J. VIROL. 6758-69 (1998); M. Taliani *et al.*, 240 ANAL. BIOCHEM. 60-67 (1996); Mao *et al., Analytical Biochemistry 373*: 1-8, 2008.

Measuring Compound Inhibitory Potency (Replicon EC50 (nM))

Measurement of inhibition by compounds was performed using the HCV replicon system. Several different replicons encoding different HCV genotypes or mutations were used. In addition, potency measurements were made using different formats of the replicon assay, including different ways of measurements and different plating formats. *See* Jan M. Vrolijk *et al., A replicons-based bioassay for the measurement of interferons in patients with chronic hepatitis C*, 110 J. VIROLOGICAL METHODS 201 (2003); Steven S. Carroll *et al.*, *Inhibition of*

Hepatitis C Virus RNA Replication by 2'-Modified Nucleoside Analogs, 278(14) J. BIOLOGICAL CHEMISTRY 11979 (2003). However, the underlying principles are common to all of these determinations, and are outlined below.

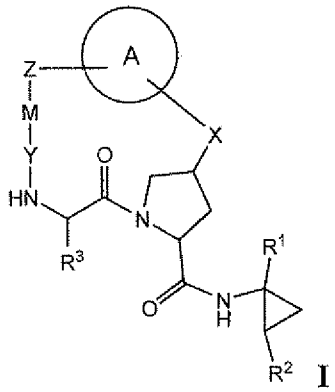
Stable neomycin phosphotransferase encoding replicon-harboring cell lines were used, so all cell lines were maintained under G418 selection prior to the assay. In some cases the cell lines encoded a luciferase:Neor fusion and could be assayed either directly by determination of RNA copy number, or indirectly through measurement of the luciferase activity.

To initiate an assay, replicon cells were plated in the presence of a dilution series of test compound in the absence of G418. Typically, the assays were performed in a 96-well plate format for manual operation, or a 384 well plate in an automated assay. Replicon cells and compound were incubated for 24-48 hours, depending on the assay. At the end of the assay, cells are washed free of media and compound and then lysed. For direct quantitation, RNA levels were measured by 32P-probe hybridization and protection, or in a TAQMAN based assay and normalized to cellular cyclophilin A RNA levels. In some cases, luciferase activity was measured using a conventional luciferase assay. In all cases EC50 determinations were calculated as a percent of a DMSO control by fitting the data to a four parameter fit function.

It will be appreciated that various of the above-discussed and other features and functions, or alternatives thereof, may be desirably combined into many other different systems or applications. Also that various presently unforeseen or unanticipated alternatives, modifications, variations or improvements therein may be subsequently made by those skilled in the art which are also intended to be encompassed by the following claims.

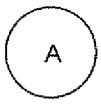
WHAT IS CLAIMED IS:

1. A compound of formula **I**:



I

or a pharmaceutically acceptable salt or hydrate thereof, wherein:



is one or more rings selected from the group consisting of:

a) aryl rings,

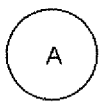
b) C_3-C_8 cycloalkyl rings, and

c) heterocyclic rings in which the heterocyclic ring system attaches to Z and X at points that are two independently selected ring atoms that are either two carbon ring atoms or one carbon ring atom and one nitrogen ring atom, and the heterocyclic ring system is selected from the group consisting of:

i) 5- or 6-membered saturated or unsaturated monocyclic rings with 1, 2, or 3 heteroatom ring atoms independently selected from the group consisting of N, O or S,

ii) 8-, 9- or 10-membered saturated or unsaturated bicyclic rings with 1, 2, or 3 heteroatom ring atoms independently selected from the group consisting of N, O or S, and

iii) 11- to 15-membered saturated or unsaturated tricyclic rings with 1, 2, 3, or 4 heteroatom ring atoms independently selected from the group consisting of N, O or S,

wherein 

is substituted with 0 to 4 independently selected substituents R^4, R^5 or oxo; wherein for stable heterocyclic rings containing S or N, the

heterocyclic ring is unsubstituted at the S or N atom or is substituted at the S by oxo; wherein the R^4 and R^5 substitutions are located on one or more ring atoms selected from C and N;

X is selected from the group consisting of -O-, -CH_2O-, -NHC(O)O-, -CH_2NHC(O)O-, -C≡CCH_2O-, -C(O)O-, -$(CH_2)_3$O-, -OC(O)NH-, -$(CH_2)_2$C(O)NH-, -C(O)NH- and a direct bond;

R^1 is selected from the group consisting of -CO_2R^6, -$CONR^6SO_2R^7$, -$CONR^6SO_2NR^8R^9$, tetrazolyl, -$CONHP(O)R^{10}R^{11}$, and -$P(O)R^{10}R^{11}$;

R^2 is selected from the group consisting of C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_3-C_8 cycloalkyl, wherein the R^2 are substituted with 0 to 3 independently selected halogen atoms;

R^3 is selected from the group consisting of H, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_8)alkyl, phenyl(C_1-C_8)alkyl, naphthyl(C_1-C_8)alkyl, and Het groups, wherein when R^3 is not H, the R^3 is substituted with 0 to 3 substituents independently selected from the group consisting of halogen atoms, -OR^6, -SR^6, -$N(R^6)_2$, -N(C_1-C_6 alkyl)O(C_1-C_6 alkyl), C_1-C_6 alkyl, C_1-C_6 haloalkyl, halo(C_1-C_6 alkoxy), -NO_2, -CN, -CF_3, -SO_2(C_1-C_6 alkyl), -S(O)(C_1-C_6 alkyl), -$NR^6SO_2R^7$, $SO_2N(R^7)_2$, -NHCOOR^7, -NHCOR^7, -NHCONHR^7, -CO_2R^6, -C(O)R^6, and -$CON(R^6)_2$;

Het is selected from the group consisting of substituted and unsubstituted 5- and 6-membered saturated heterocyclic rings having 1 or 2 heteroatoms independently selected from N, O and S;

Y is selected from the group consisting of -C(O)-, -SO_2-, -OC(O)-, -C(O)N(R^{12})L- and -LN(R^{12})C(O)-, where

R^{12} is selected from the group consisting of H, C_1-C_6 alkyl and C_1-C_6 alkenyl groups,

L is selected from the group consisting of a direct bond, -G-(C_1-C_6 alkylene)-, -(C_1-C_6 alkylene)-G-, -G-(C_1-C_6 alkenylene)-, and -(C_1-C_6 alkenylene)-G-, groups, where the G is selected from the group consisting of a direct bond, -O-, -N- and -S-, the alkylene

and alkenylene groups are substituted with 0 to 4 substituents R^{13} independently selected from the group consisting of C_1-C_6 alkyl and C_1-C_6 alkenyl groups, and

the R^{12} and R^{13} may be taken together to form a 3- to 6-membered ring containing 0 to 3 heteroatoms selected from N, O and S;

M is selected from the group consisting of C_1-C_{12} alkylenes, C_2-C_{12} alkenylenes and C_2-C_{12} alkynylenes, wherein:

the M contains 0 or 1 -O- moiety in place of a methylene moiety, and

the M is substituted with from 0 to 4 substituents R^{14}, wherein:

each R^{14} is independently selected from the group consisting of C_1-C_8 alkyl, $=CH_2$, C_3-C_8 cycloalkyl(C_1-C_8 alkyl), and aryl(C_1-C_8 alkyl), and

any substituent R^{14} may be taken together with any adjacent substituent R^{14} or any adjacent substituent R^{12} or R^{13} to form a 3- to 6-membered ring containing 0 to 3 heteroatoms independently selected from the group consisting of N, O and S;

Z is selected from the group consisting of -C(O)- and a direct bond;

R^4 is selected from the group consisting of H, halogen atoms, -OH, C_1-C_6 alkoxy, C_1-C_6 alkyl, -CN, $-CF_3$, $-OCF_3$, -C(O)OH, $-C(O)CH_3$, $-SR^6$, $-SO_2$(C_1-C_6 alkyl), C_3-C_8 cycloalkyl, C_3-C_8 cycloalkoxy, C_1-C_6 haloalkyl, $-N(R^{15})_2$, phenyl, naphthyl, -O-phenyl, -O-naphthyl, heteroaryl and heterocyclyl groups; wherein:

the R^4 heteroaryl is selected from the group consisting of 5- and 6-membered aromatic rings having 1, 2 or 3 heteroatoms independently selected from N, O and S, and the R^4 heteroaryl is attached through a ring atom selected from C or N,

the R^4 heterocyclyl is selected from the group consisting of 5- to 7-membered saturated or unsaturated non-aromatic rings having 1, 2, 3 or 4 heteroatoms independently selected from N, O and S, and the R^4 heterocyclyl is attached through a ring atom selected from C or N, and

the R^4 heteroaryl, heterocyclyl, cycloalkyl, cycloalkoxy, alkyl and alkoxy groups are substituted with 0 to 4 substituents independently selected from the group consisting of halogen atoms, $-OR^6$, $-SR^6$, $-N(R^6)_2$, -N(C_1-C_6 alkyl)O(C_1-C_6 alkyl), C_1-C_6 alkyl, C_1-C_6 haloalkyl, halo(C_1-C_6 alkoxy), $-NO_2$, -CN, $-CF_3$,$-SO_2$(C_1-C_6 alkyl), -S(O)(C_1-C_6 alkyl), $-NR^6SO_2R^7$, $SO_2N(R^7)_2$, $-NHCOOR^7$, $-NHCOR^7$, $-NHCONHR^7$, $-CO_2R^6$, $-C(O)R^6$, and

-$CON(R^6)_2$, and 2 adjacent substituents of the R^4 heteroaryl, heterocyclyl, cycloalkyl, cycloalkoxy, alkyl and alkoxy groups may be taken together to form a 3- to 6-membered cyclic ring containing 0 to 3 heteroatoms independently selected from N, O and S;

each R^5 is independently selected from the group consisting of H, halogen atoms, -OR^6, C_1-C_6 alkyl, -CN, -CF_3, -NO_2, -SR^6, -CO_2R^6, -$CON(R^6)_2$, -$C(O)R^6$, -$N(R^6)C(O)R^6$, -SO_2(C_1-C_6 alkyl), -S(O)(C_1-C_6 alkyl), C_3-C_8 cycloalkyl, C_3-C_8 cycloalkoxy, C_1-C_6 haloalkyl, -$N(R^6)_2$, -N(C_1-C_6 alkyl)O(C_1-C_6 alkyl), halo(C_1-C_6 alkoxy), -$NR^6SO_2R^6$, -$SO_2N(R^6)_2$, -$NHCOOR^6$, -$NHCONHR^6$, phenyl, naphthyl, heteroaryl and heterocyclyl groups, wherein

the R^5 heteroaryl is selected from the group consisting of 5- and 6-membered aromatic rings having 1, 2 or 3 heteroatoms independently selected from N, O and S, and the R^5 heteroaryl is attached through a ring atom selected from C or N,

the R^5 heterocyclyl is selected from the group consisting of 5- to 7-membered saturated or unsaturated non-aromatic rings having 1, 2, 3 or 4 heteroatoms independently selected from N, O and S, and the R^5 heterocyclyl is attached through a ring atom selected from C or N;

each R^6 is independently selected from the group consisting of H, C_1-C_6 alkyl and benzyl, wherein each R^6 is independently substituted with 0 to 4 substituents selected from the group consisting of halogen atoms, C_1-C_6 alkyl, C_1-C_6 haloalkyl, phenyl, naphthyl, C_3-C_8 cycloalkyl, heteroaryl, heterocyclyl, halo(C_1-C_6 alkoxy), -OH, -O(C_1-C_6 alkyl), -SH, -S(C_1-C_6 alkyl), -NH_2, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, -C(O)(C_1-C_6 alkyl), NO_2, -CN, -CF_3, -SO_2(C_1-C_6 alkyl), -S(O)(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)SO_2(C_1-C_6 alkyl), -SO_2N(C_1-C_6 alkyl)$_2$, -NHCOO(C_1-C_6 alkyl), -NHCO(C_1-C_6 alkyl), -NHCONH(C_1-C_6 alkyl), -CO_2(C_1-C_6 alkyl), and -C(O)N(C_1-C_6 alkyl)$_2$;

R^7 is selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl(C_1-C_5)alkyl, phenyl, naphthyl, phenyl(C_1-C_4)alkyl, naphthyl(C_1-C_4)alkyl, heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl, and heterocyclyl(C_1-C_8 alkyl) groups, wherein

the R^7 are substituted with 0 to 2 independently selected R^5 substituents,

each R^7 heteroaryl is independently selected from the group consisting of 5- and 6-membered aromatic rings having 1, 2 or 3 heteroatoms independently selected from N, O and S, and the R^7 heteroaryl is attached through a ring atom selected from C or N, and

each R^7 heterocyclyl is independently selected from the group consisting of 5- to 7-membered saturated or unsaturated non-aromatic rings having 1, 2, 3 or 4 heteroatoms independently selected from N, O and S, and the R^7 heterocyclyl is attached through a ring atom selected from C or N;

R^8 is selected from the group consisting of H, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_8 alkyl), phenyl, naphthyl, phenyl(C_1-C_4)alkyl, naphthyl(C_1-C_4)alkyl, heteroaryl, heterocyclic, heteroaryl(C_1-C_4 alkyl), and heterocyclyl(C_1-C_8 alkyl) groups, wherein

the R^8 are substituted with 0 to 4 substituents selected from the group consisting of phenyl, naphthyl, C_3-C_8 cycloalkyl, heteroaryl, heterocyclyl, C_1-C_6 alkyl, halo(C_1-C_6 alkoxy), halogen atoms, $-OR^6$, $-SR^6$, $-N(R^6)_2$, $-N(C_1$-C_6 alkyl)$O(C_1$-C_6 alkyl), C_1-C_6 alkyl, $-C(O)R^6$, C_1-C_6 haloalkyl, $-NO_2$, -CN, $-CF_3$, $-SO_2(C_1$-C_6 alkyl), $-S(O)(C_1$-C_6 alkyl), $-NR^6SO_2R^7$, $-SO_2N(R^7)_2$, $-NHCOOR^7$, $-NHCOR^7$, $-NHCONHR^7$, $-CO_2R^6$, and $-C(O)N(R^6)_2$,

each R^8 heteroaryl is independently selected from the group consisting of 5- and 6-membered aromatic rings having 1, 2 or 3 heteroatoms independently selected from N, O and S, and the R^8 heteroaryl is attached through a ring atom selected from C or N,

each R^8 heterocyclyl is independently selected from the group consisting of 5- to 7-membered saturated or unsaturated non-aromatic rings having 1, 2, 3 or 4 heteroatoms independently selected from N, O and S, and the R^8 heterocyclyl is attached through a ring atom selected from C or N, and

2 adjacent substituents of the R^8 may be taken together to form a 3- to 6-membered ring containing 0 to 3 heteroatoms independently selected from the group consisting of N, O and S;

R^9 is selected from the group consisting of H, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_8 alkyl), C_1-C_8 alkoxy, C_3-C_8 cycloalkoxy, phenyl, naphthyl, phenyl(C_1-C_4)alkyl, naphthyl(C_1-C_4)alkyl, heteroaryl, heterocyclyl, heteroaryl(C_1-C_4 alkyl), or heterocyclyl(C_1-C_8 alkyl) groups, wherein

the R^9 are substituted with 0 to 4 substituents selected from the group consisting of phenyl, naphthyl, C_3-C_8 cycloalkyl, heteroaryl, heterocyclyl, C_1-C_6 alkyl, halo(C_1-C_6 alkoxy), halogen atoms, $-OR^6$, $-SR^6$, $-N(R^6)_2$, $-N(C_1$-C_6 alkyl)$O(C_1$-C_6 alkyl), C_1-C_6 alkyl, $-C(O)R^6$, C_1-C_6 haloalkyl, $-NO_2$, -CN, $-CF_3$,$-SO_2(C_1$-C_6 alkyl), $-S(O)(C_1$-C_6 alkyl), $-NR^6SO_2R^7$, $-SO_2N(R^7)_2$, $-NHCOOR^7$, $-NHCOR^7$, $-NHCONHR^7$, $-CO_2R^6$, and $-C(O)N(R^6)_2$,

each R^9 heteroaryl is independently selected from the group consisting of 5- and 6-membered aromatic rings having 1, 2 or 3 heteroatoms independently selected from N, O and S, and the R^9 heteroaryl is attached through a ring atom selected from C or N,

each R^9 heterocyclyl is independently selected from the group consisting of 5- to 7-membered saturated or unsaturated non-aromatic rings having 1, 2, 3 or 4 heteroatoms independently selected from N, O and S, and the R^9 heterocyclyl is attached through a ring atom selected from C or N, and

2 adjacent substituents of the R^9 may be taken together to form a 3- to 6-membered ring containing 0 to 3 heteroatoms independently selected from the group consisting of N, O and S, and

R^8 and R^9 may be taken together, with the N to which they are attached, to form a 4- to 8-membered monocyclic ring containing 0 to 2 additional heteroatoms independently selected from N, O and S;

each R^{10} is independently selected from the group consisting of H, C_1-C_6 alkyl, C_1-C_4 alkenyl, $-OR^{16}$, $-N(R^6)$-V-CO_2R^6, -O-V-CO_2R^6, -S-V-CO_2R^6, $-N(R^6)(R^{16})$, $-R^{17}$, and $-N(R^6)SO_2R^7$;

each R^{11} is independently selected from the group consisting of H, $-OR^{16}$, $-N(R^6)$-V-CO_2R^6, -O-V-CO_2R^6, -S-V-CO_2R^6, and $-N(R^6)(R^{16})$;

R^{10} and R^{11} may be taken together, with the phosphorus atom to which they are attached, to form a 5- to 7-membered monocyclic ring;

each V is independently selected from the group consisting of $-CH(R^{18})$- and -(C_1-C_4 alkylene)-$CH(R^{18})$-;

each R^{15} is independently selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl(C_1-C_5)alkyl, phenyl, naphthyl, phenyl(C_1-C_4)alkyl, naphthyl(C_1-C_4)alkyl, heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl, and heterocyclyl(C_1-C_8 alkyl) groups, wherein

when R^{15} is not H, the R^{15} are substituted with 0 to 2 R^5 substituents,

each R^{15} heteroaryl is independently selected from the group consisting of 5- and 6-membered aromatic rings having 1, 2 or 3 heteroatoms independently selected from N, O and S, and the R^{15} heteroaryl is attached through a ring atom selected from C or N, and

each R^{15} heterocyclyl is independently selected from the group consisting of 5- to 7-membered saturated or unsaturated non-aromatic rings having 1, 2, 3 or 4 heteroatoms independently selected from N, O and S, and the R^{15} heterocyclyl is attached through a ring atom selected from C or N, and

the R^{15} may be taken together with the atom to which it is attached and a second R^{15} substituent to form a 4- to 7-membered heterocyclic ring;

each R^{16} is independently selected from the group consisting of H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, aryl, heteroaryl, and heterocyclyl groups, wherein

when R^{16} is not H, the R^{16} is substituted with 0 to 2 substituents independnetly selected from the group consisting of phenyl, naphthyl, phenyl(C_1-C_4 alkyl), naphthyl(C_1-C_4 alkyl), C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl, heterocyclyl(C_1-C_4 alkyl), C_1-C_6 alkyl, halogen atoms, $-OC(O)OR^7$, $-OC(O)R^7$, $-OR^6$, $-SR^6$, $-N(R^6)_2$, $-C(O)R^6$, $-NO_2$, $-CN$, $-CF_3$, $-SO_2(C_1$-C_6 alkyl), $-S(O)(C_1$-C_6 alkyl), $-NR^6SO_2R^7$, $-SO_2N(R^7)_2$, $-NHCOOR^7$, $-NHCOR^7$, $-NHCONHR^7$, $-CO_2R^6$, and $-C(O)N(R^6)_2$,

each R^{16} heteroaryl is independently selected from the group consisting of 5- and 6-membered aromatic rings having 1, 2 or 3 heteroatoms independently selected from N, O and S, and the R^{16} heteroaryl is attached through a ring atom selected from C or N,

each R^{16} heterocyclyl is independently selected from the group consisting of 5- to 7-membered saturated or unsaturated non-aromatic rings having 1, 2, 3 or 4 heteroatoms independently selected from N, O and S, and the R^{16} heterocyclyl is attached through a ring atom selected from C or N, and

2 adjacent substituents of the R^{16} may be taken together to form a 3- to 6-membered ring containing 0 to 3 heteroatoms independently selected from the group consisting of N, O and S;

R^{17} is selected from the group consisting of H, C_1-C_6 alkyl, C_2-C_6 alkenyl, phenyl, naphthyl and heteroaryl, wherein

each R^{17} heteroaryl is independently selected from the group consisting of 5- and 6-membered aromatic rings having 1, 2 or 3 heteroatoms independently selected from N, O and S, and the R^{17} heteroaryl is attached through a ring atom selected from C or N, and

the R^{17} phenyl, naphthyl or heteroaryl may be substituted with 0 to 2 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen atoms, -OC(O)OR^7, -OC(O)R^7, -OR^6, -SR^6, -$N(R^6)_2$, -C(O)R^6, -NO_2, -CN, -CF_3, -SO_2(C_1-C_6 alkyl), -S(O)(C_1-C_6 alkyl), -$NR^6SO_2R^7$, -$SO_2N(R^7)_2$, -NHCOOR^7, -NHCOR^7, -NHCONHR^7, -CO_2R^6, and -C(O)$N(R^6)_2$; and

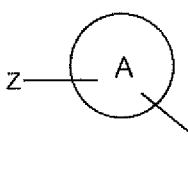
each R^{18} is independently selected from the group consisting of H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, phenyl, naphthyl, heteroaryl, and heterocyclyl groups, wherein

the R^{18} are substituted with 0 to 2 substituents independently selected from the group consisting of C_1-C_6 alkyl, halogen atoms, -OC(O)OR^7, -OC(O)R^7, -OR^6, -SR^6, -$N(R^6)_2$, -C(O)R^6, -NO_2, -CN, -CF_3, -SO_2(C_1-C_6 alkyl), -S(O)(C_1-C_6 alkyl), -$NR^6SO_2R^7$, -$SO_2N(R^7)_2$, -NHCOOR^7, -NHCOR^7, -NHCONHR^7, -CO_2R^6, and -C(O)$N(R^6)_2$,

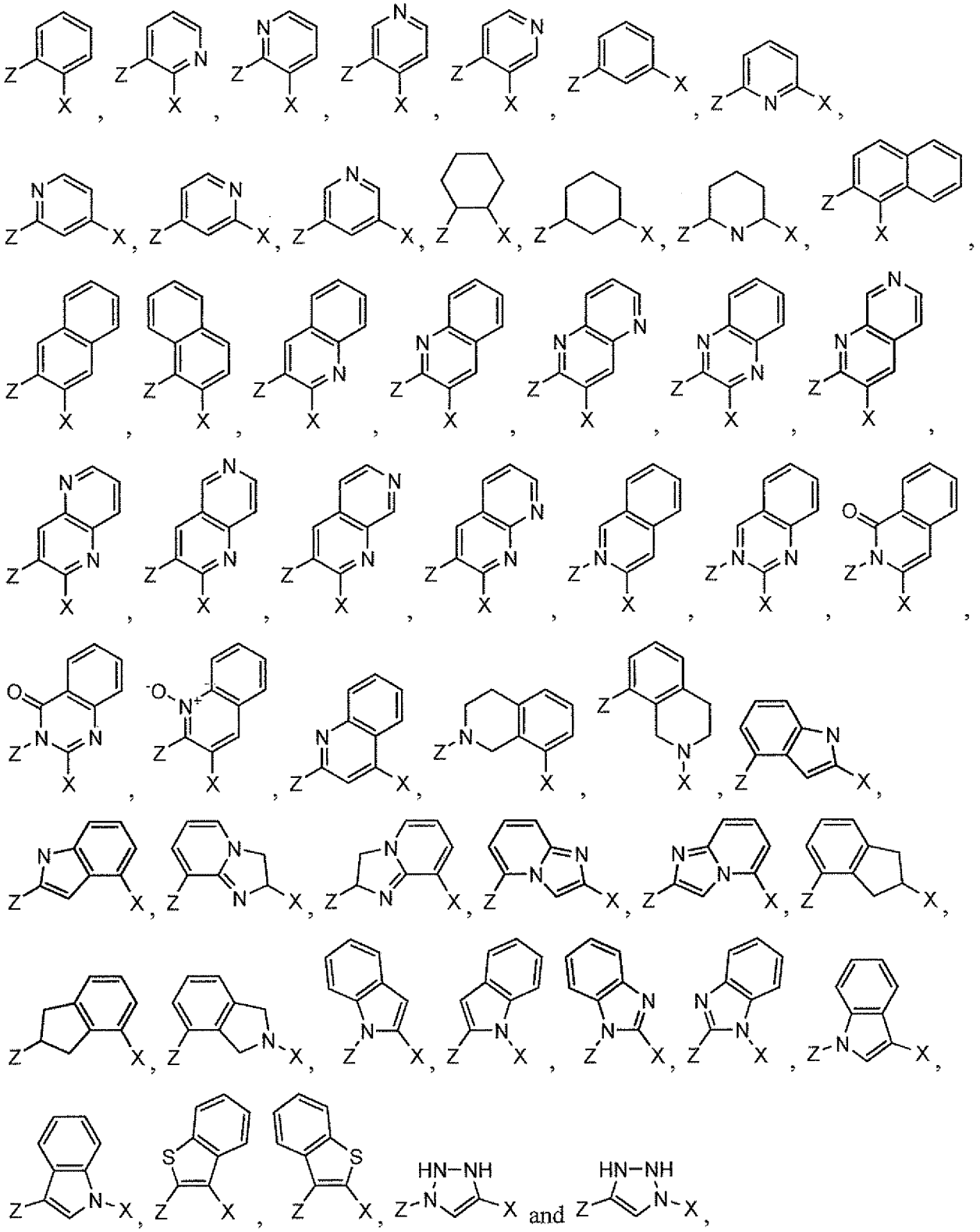
each R^{18} heteroaryl is independently selected from the group consisting of 5- and 6-membered aromatic rings having 1, 2 or 3 heteroatoms independently selected from N, O and S, and the R^{18} heteroaryl is attached through a ring atom selected from C or N,

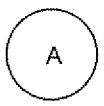
each R^{18} heterocyclyl is independently selected from the group consisting of 5- to 7-membered saturated or unsaturated non-aromatic rings having 1, 2, 3 or 4 heteroatoms independently selected from N, O and S, and the R^{18} heterocyclyl is attached through a ring atom selected from C or N, and

2 adjacent substituents of the R^{18} are optionally taken together to form a 3- to 6-membered ring containing 0 to 3 heteroatoms independently selected from the group consisting of N, O and S.

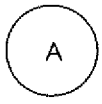
2. The compound according to claim 1, wherein 

is selected from the group consisting of:



wherein said  is substituted with 0 to 4 independently selected substituents R^4, R^5 or oxo; wherein for stable heterocyclic rings containing S or N, the heterocyclic ring is

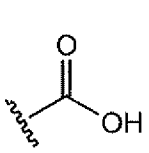
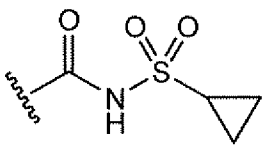
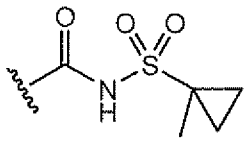
unsubstituted at the S or N atom or is substituted at the S by oxo; wherein said R^4 and R^5 substitutions are located on one or more ring atoms selected from C and N.

3. The compound according to claim 2, wherein 

is unsubstituted or mono-substituted with a moiety selected from the group consisting of -Br, -Cl, -CN, phenyl, -O-phenyl, -O-benzyl, $-OCF_3$, $-OCH_3$, -OH, C_1-C_6 alkoxy, C_1-C_6 alkyl, $-CF_3$, -C(O)OH, and $-C(O)CH_3$.

4. The compound according to any one of claims 1-3, wherein X is selected from the group consisting of -O- and -C(O)O-.

5. The compound according to any one of claims 1-4, wherein R^1 is selected from the group consisting of $-CO_2R^6$ and $-CONR^6SO_2R^7$.

6. The compound according to claim 5, wherein R^1 is selected from the group consisting of  ,  and  .

7. The compound according to any one of claims 1-6, wherein R^2 is selected from the group consisting of C_1-C_6 alkyl and C_2-C_6 alkenyl.

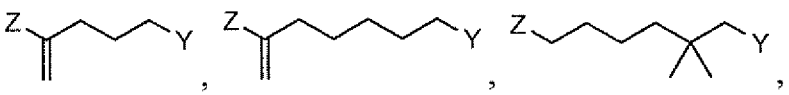
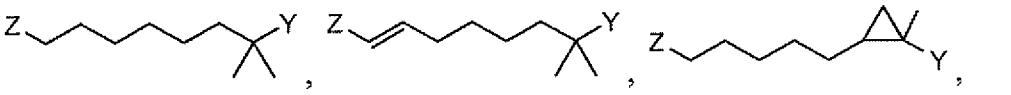
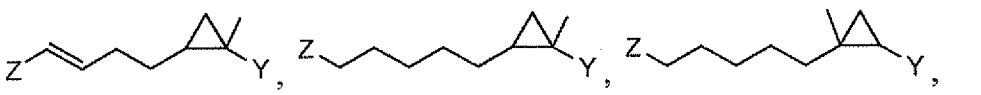
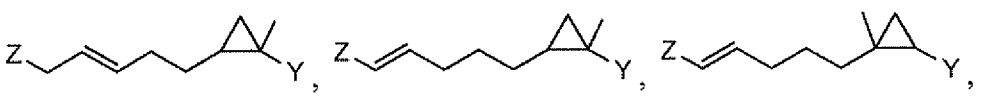
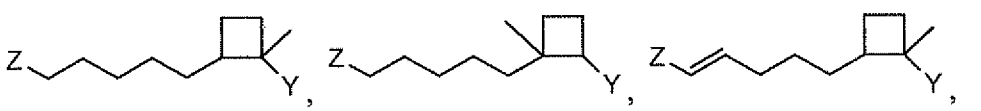
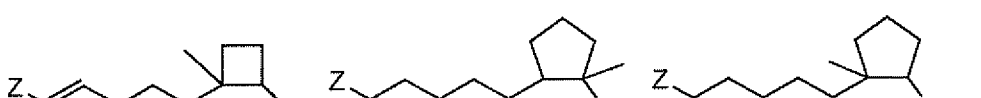
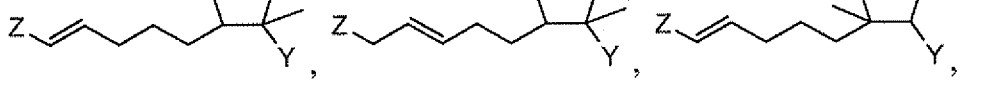
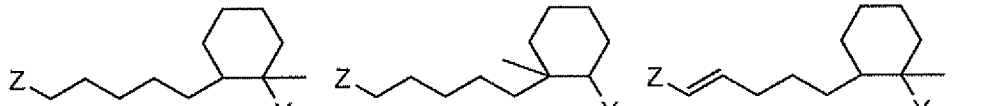
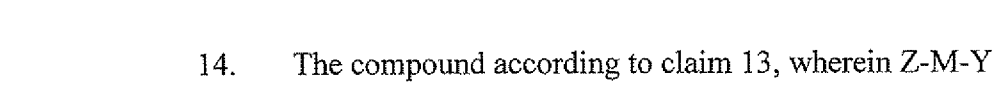
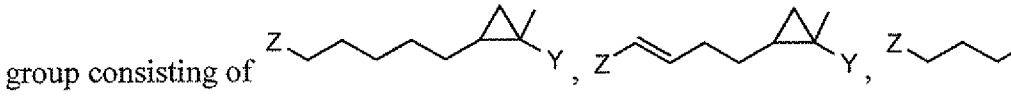
8. The compound according to claim 7, wherein R^2 is selected from the group consisting of $-CH=CH_2$, $-CH_2CH_3$, and $-CH_2CH=CH_2$.

9. The compound according to any one of claims 1-8, wherein R^3 is selected from the group consisting of H, C_1-C_8 alkyl and C_3-C_8 cycloalkyl.

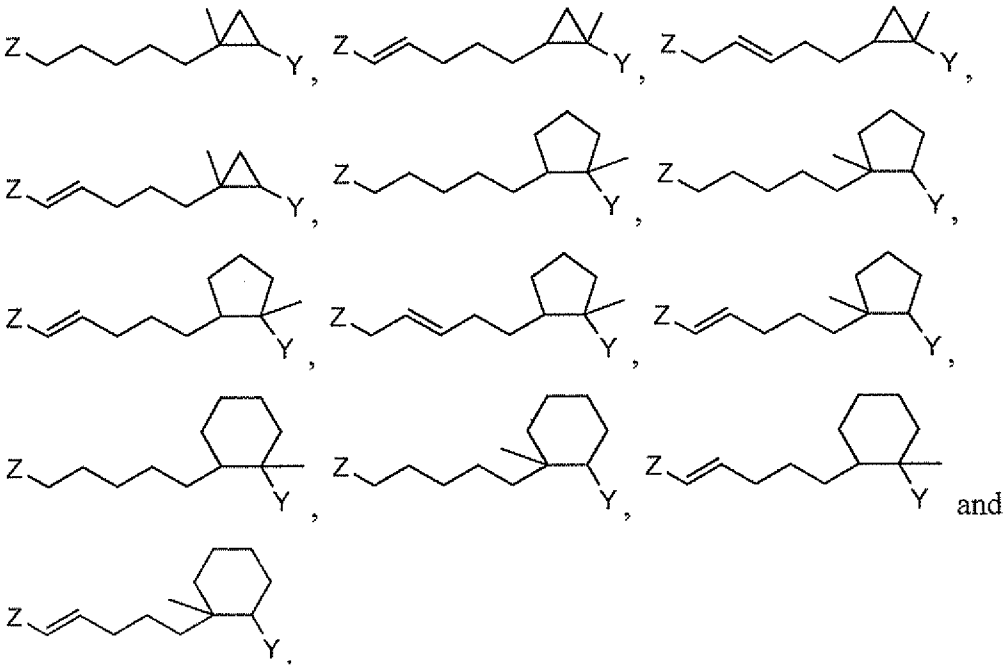
10. The compound according to claim 9, wherein R^3 is selected from the group consisting of $-C(CH_3)_3$, $-(CH_2)_3CH_3$, cyclohexyl, and $-CH(CH_3)_2$.

11. The compound according to any one of claims 1-10, wherein Y is selected from the group consisting of -OC(O)-, -C(O)N(D)L- and -LN(D)C(O)-.

12. The compound according to any one of claims 1-11, wherein M is selected from the group consisting of C_1-C_{12} alkylene or C_2-C_{12} alkenylene, wherein M is substituted with 0 to 3 substituents R^{14} selected from the group consisting of C_1-C_8 alkyl, and $=CH_2$.

13. The compound according to claim 12, wherein Z-M-Y is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  and .

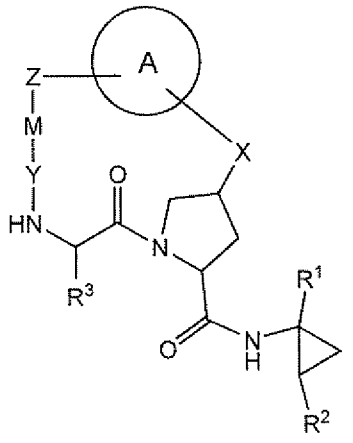
14. The compound according to claim 13, wherein Z-M-Y is selected from the group consisting of



and

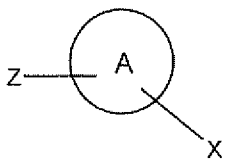
15. The compound according to any one of claims 1-14, wherein one or more substituents R^{14} are taken together and/or with one or more substituents chosen from substituents R^{12} and R^{13} to form a 3- to 6-membered ring containing 0 to 3 heteroatoms selected from the group consisting of N, O and S.

16. A compound of formula **I**:

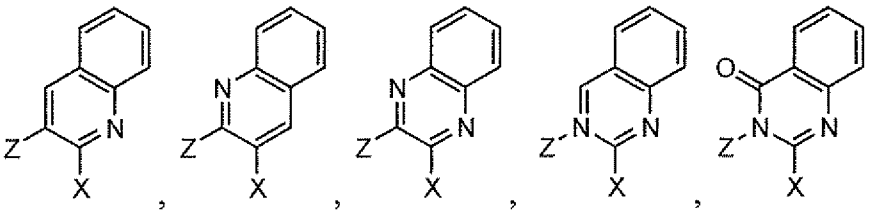


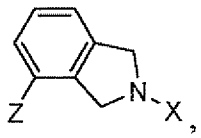
I

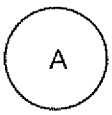
or a pharmaceutically acceptable salt or hydrate thereof, wherein:



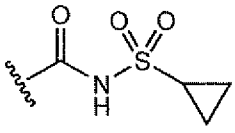
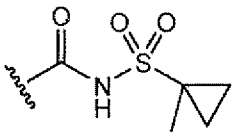
is selected from the group consisting of:


and



wherein said  is substituted with 0 to 2 independently selected substituents -Cl, -O-benzyl, $-OCH_3$, -OH, $-CH_3$;

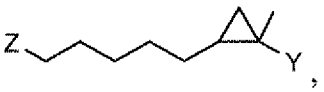
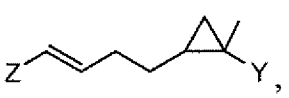
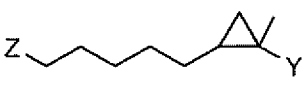
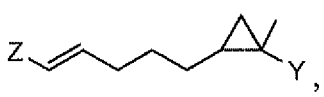
X is selected from the group consisting of -O- and -C(O)O-;

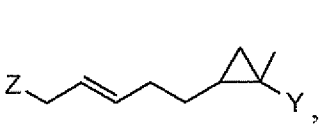
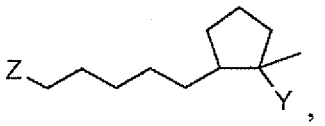
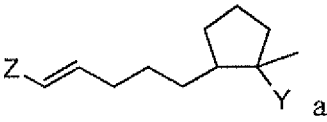
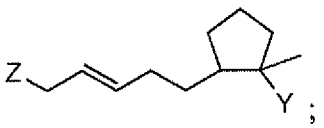
R^1 is selected from the group consisting of  and  ;

R^2 is selected from the group consisting of $-CH=CH_2$ and $-CH_2CH_3$;

R^3 is selected from the group consisting of $-C(CH_3)_3$ and cyclohexyl;

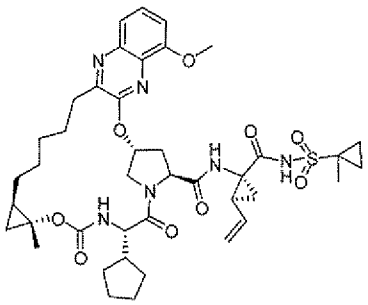
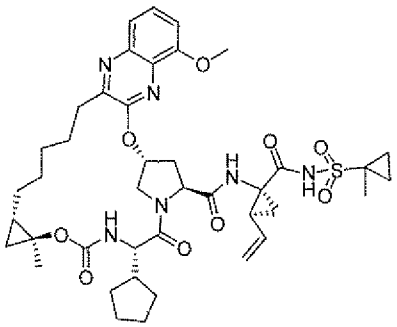
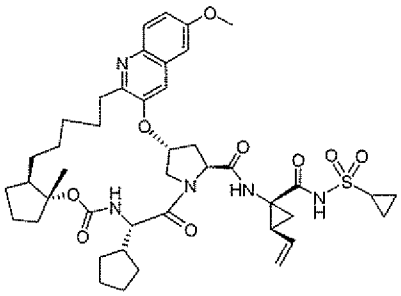
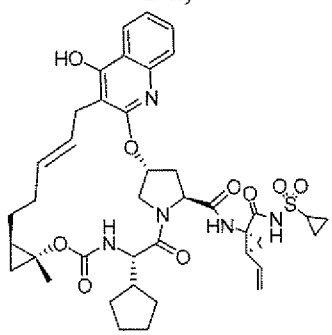
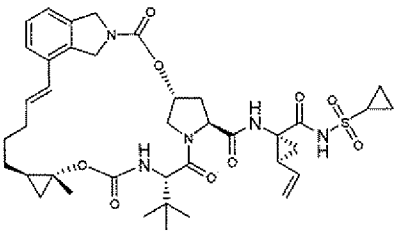
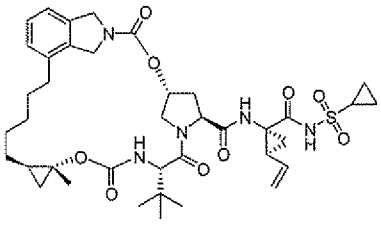
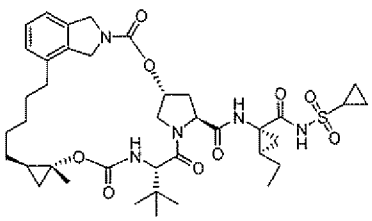
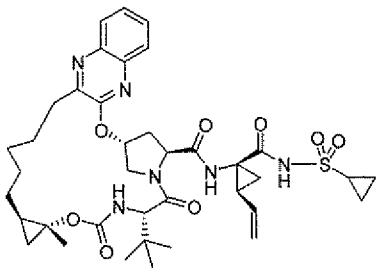
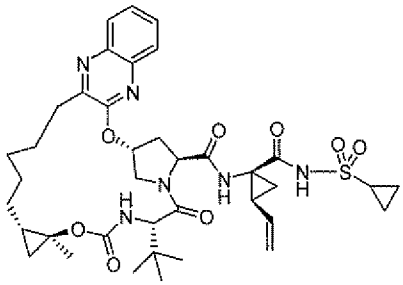
Y is -OC(O)-;

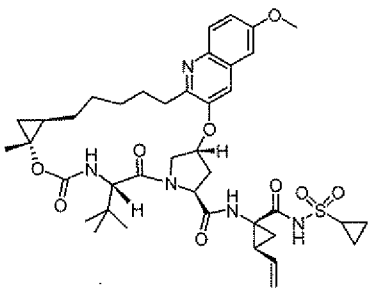
Z-M-Y is selected from the group consisting of  ,  ,  , 


,

,

and

; and

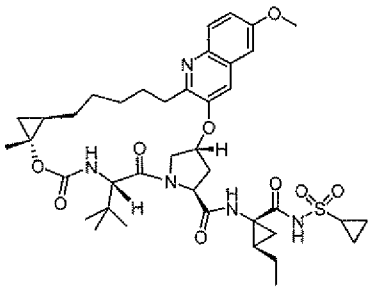
Z is a direct bond.

17. A compound selected from the group consisting of:

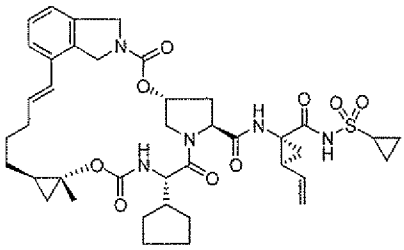

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I-2,

I-3,

I-4,

I-5,

I-6,

I-7,

I-8,

I-9,



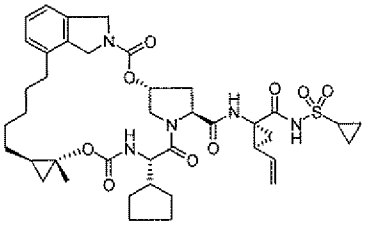
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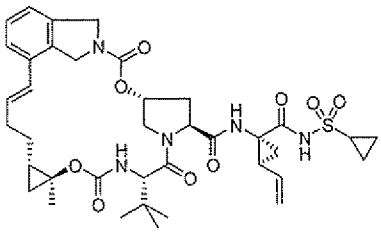
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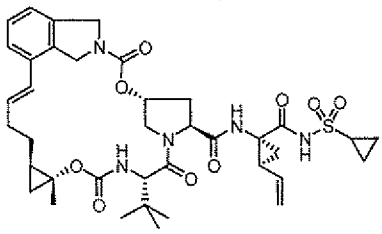
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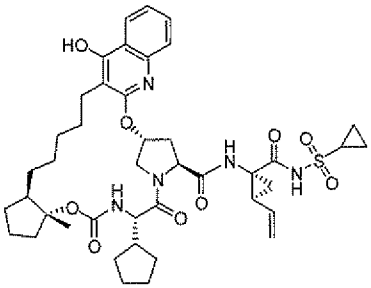
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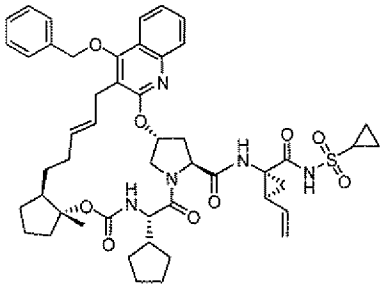
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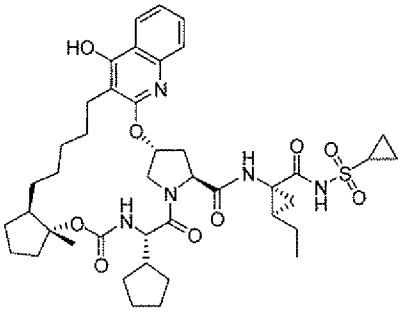
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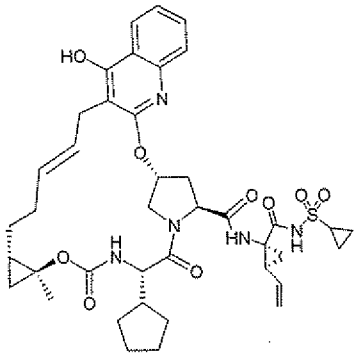
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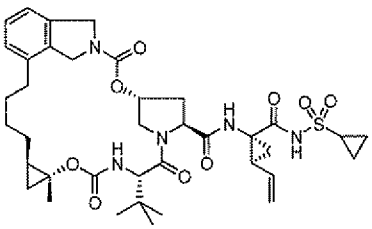
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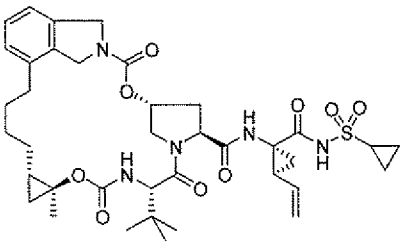
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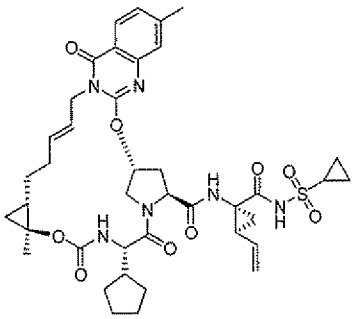
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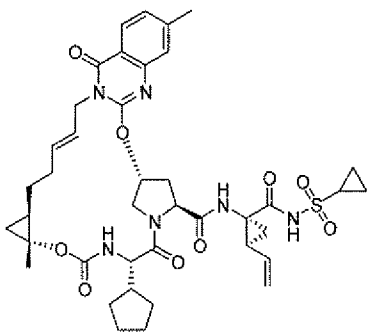
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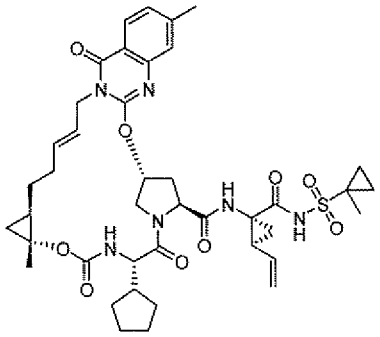
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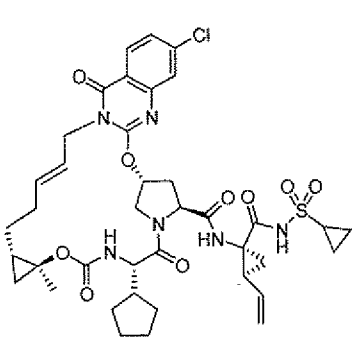
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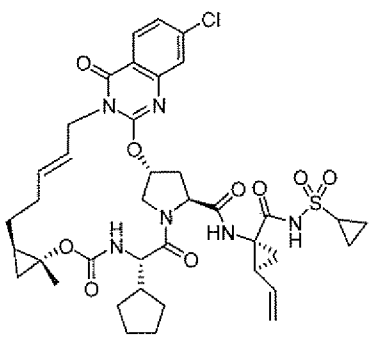
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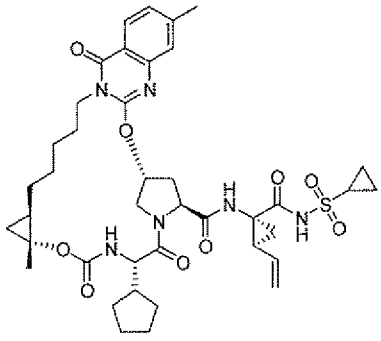
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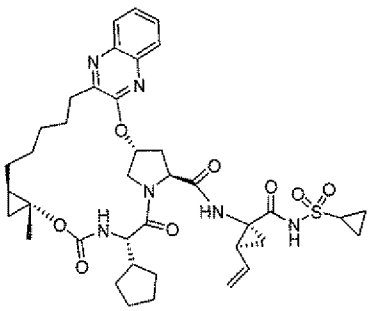
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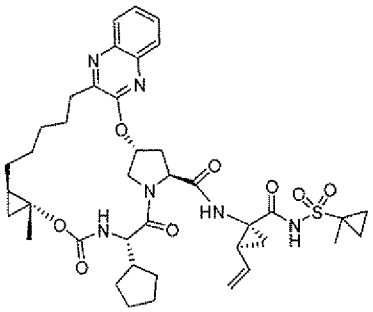
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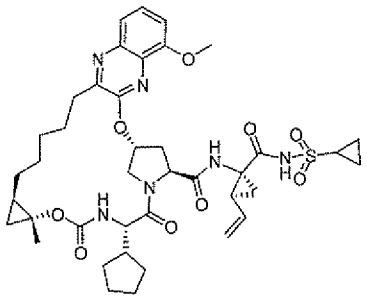
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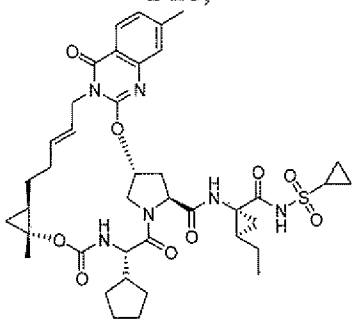
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I-29,

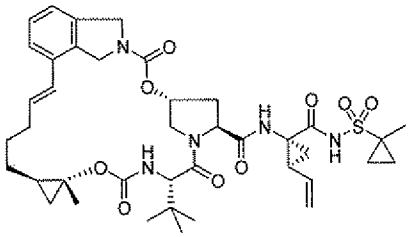


I-30,



I-31

and



I-32.

18. A pharmaceutical composition comprising an effective amount of the compound according to claim 1, and a pharmaceutically acceptable carrier.

19. The pharmaceutical composition according to claim 18, further comprising a second therapeutic agent selected from the group consisting of HCV antiviral agents, immunomodulators, and anti-infective agents.

20. The pharmaceutical composition according to claim 18, further comprising a second therapeutic agent selected from the group consisting of HCV protease inhibitors and HCV NS56 polymerase inhibitors.

21. A use of the compound according to claim 1 in the preparation of a medicament for inhibiting HCV NS3 protease activity in a subject in need thereof.

22. A use of the compound according to claim 1 in the preparation of a medicament for preventing or treating infection by HCV in a subject in need thereof.

23. A use of the compound according to claim 1 in the prevention or treatment of infection by HCV or in the reduction of likelihood or severity of symptoms of HCV infection of in a subject in need thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 11/51871

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/36; A61K 31/40 (2012.01)
USPC - 514/427
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC: 514/427

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/296, 309, 312, 314; 530/330; 540/460; 546/153 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (PGPB,USPT,EPAB,JPAB), Google Scholar
HCV, Hepatitis C, NS3 protease, inhibit$, modulat$, macrocycl$, prolin$, quinoline, quinoxaline

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/057209 A1 (LIVERTON et al.) 15 May 2008 (15.05.2008) pg 1, ln 5-8; pg 2, ln 17 to pg 10, ln 32; pg 14, ln 15-23; pg 15, ln 15-31	1-4, 16-23
X	US 2010/0099695 A1 (LIVERTON et al.) 22 April 2010 (22.04.2010) para [0005]-[0100], [0475], Table	1-4, 16-23

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 January 2012 (21.01.2012)	10 FEB 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 11/51871

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 5-15
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.