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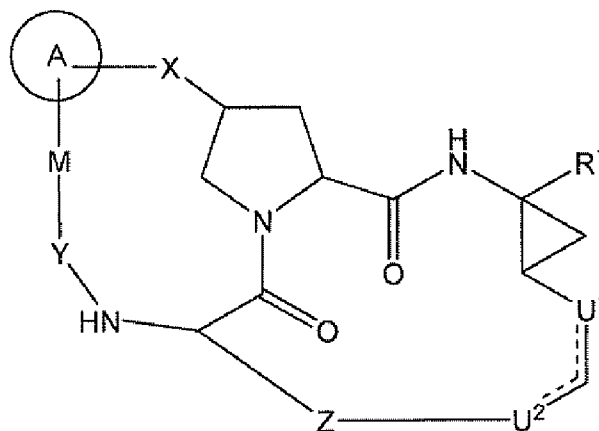
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(54) Title: HEPATITIS C VIRUS NS3 PROTEASE INHIBITORS



(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

HEPATITIS C VIRUS NS3 PROTEASE INHIBITORS

FIELD OF THE INVENTION

5 The present invention relates to macrocyclic compounds that are useful as inhibitors of the hepatitis C virus (HCV) NS3 (non-structural 3) protease, their synthesis, and their use for treating or preventing HCV infection.

BACKGROUND OF THE INVENTION

10 Hepatitis C viral 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.

15 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).

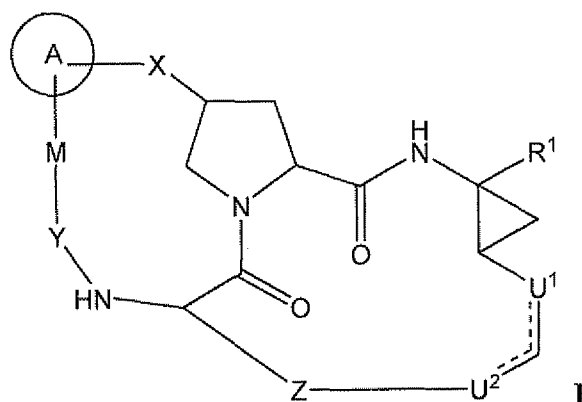
20 Potential treatments for HCV infection has been discussed in the different references including C. Blasano, *Recent Advances in Antiviral Agents: Established and Innovative Therapies for Viral Hepatitis*, 8(4) MINI-REV. MED. CHEM. 307 (2008); Robert Rönn & Anja Sandström, *New Developments in the Discovery of Agents to Treat Hepatitis C*, 8 CURRENT TOPICS MED. CHEM. 533 (2008); Julie Sheldon *et al.*, *Novel protease and polymerase inhibitors for the treatment of hepatitis C virus infection*, 16(8) EXPERT OPIN. INVESTIG. DRUGS 1171 (2007); and Raffaele De Francesco *et al.*, *Approaching a new era for hepatitis C virus*
25 *therapy: inhibitors of the NS3-4A serine protease and the NS5B RNA-dependent RNA polymerase*, 58 ANTIVIRAL RESEARCH 1 (2003).

30 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 NS3 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, whether or not in combination with 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, hydrate or prodrug thereof, wherein:



is selected from the group of rings consisting of:

- 1) an aryl,
- 2) a C₃-C₈ cycloalkyl; and
- 3) a heterocyclic ring system selected from the group consisting of:
 - a) a 5- or 6-membered saturated or unsaturated monocyclic ring with 1, 2, or 3 heteroatom ring atoms each independently selected from the group consisting of N, O or S,
 - b) a 8-, 9- or 10-membered saturated or unsaturated bicyclic ring with 1, 2, or 3 heteroatom ring atoms each independently selected from the group consisting of N, O or S, and
 - c) a 11- to 15-membered saturated or unsaturated tricyclic ring with 1, 2, 3, or 4 heteroatom ring atoms each independently selected from the group consisting of N, O or S,

wherein:

- i) the aryl or cycloalkyl ring has from 0 to 4 independently substituents R^2 ,
- ii) the heterocyclic ring has from 0 to 4 independently selected R^2 substitutions, and
- 5 iii) points of attachment to variables M and X are independently selected from a first pair of atoms comprising a first carbon ring atom and second carbon ring atom, and a second pair of atoms comprising a carbon ring atom and a nitrogen ring atom;

R^1 is selected from the group consisting of CO_2R^3 , $CONR^3SO_2R^4$,
 10 $CONR^3SO_2NR^5R^6$, tetrazolyl, $CONHP(O)R^7R^8$, and $P(O)R^7R^8$;

R^2 selected from the group consisting of H, halo, OR^3 , $C(O)R^3$, CO_2R^3 , C_1-C_6 alkyl, CN, CF_3 , SR^3 , $SO_2(C_1-C_6$ alkyl), C_3-C_8 cycloalkyl, C_3-C_8 cycloalkoxy, C_1-C_6 haloalkyl, $N(R^9)_2$, oxo, phenyl, naphthyl, Het A and Het B,

wherein the R^2 phenyl, naphthyl, Het A, Het B, cycloalkyl, cycloalkoxy,
 15 alkyl or alkoxy is substituted with from 0 to 4 substituents selected from the group consisting of halo, OR^3 , SR^3 , $N(R^9)_2$, $N(C_1-C_6$ alkyl)(C_1-C_6 alkoxy), C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkoxy, NO_2 , CN, CF_3 , $SO_2(C_1-C_6$ alkyl), $NR^3SO_2R^4$, $SO_2N(R^4)_2$, $S(O)(C_1-C_6$ alkyl), $NHC(O)OR^4$, $NHC(O)R^4$, $NHC(O)NHR^4$, CO_2R^3 , $C(O)R^3$, and $C(O)N(R^3)_2$,

20 wherein 2 adjacent substituents of the R^2 cycloalkyl, cycloalkoxy, phenyl, naphthyl, Het A or Het B are optionally taken together to form a 3- to 6-membered cyclic ring containing from 0 to 3 heteroatoms selected from N, O and S, and

wherein any R^2 oxo substituent, if present, is located on a carbon or sulfur ring atom;

25 Het A is a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen;

Het B is a 5- to 7-membered saturated or unsaturated non-aromatic ring having 1, 2, 3 or 4 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen;

each R^3 is independently selected from the group consisting of H, C_1-C_6 alkyl,
 30 phenyl and naphthyl;

each R^4 is independently selected from the group consisting of 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(C₁-C₄ alkyl), Het A, Het A(C₁-C₄ alkyl), Het B, and Het B(C₁-C₈ alkyl), wherein the R⁴ alkyl, cycloalkyl, phenyl, naphthyl, Het A and Het B is substituted with from 0 to 2 W substituents;

each R⁵ is independently selected from the group consisting of C₁-C₈ alkyl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl(C₁-C₈ alkyl), phenyl, naphthyl, phenyl(C₁-C₄ alkyl), naphthyl(C₁-C₄ alkyl), Het A, Het A(C₁-C₄ alkyl), Het B, and Het B(C₁-C₈ alkyl),

wherein the R⁵ alkyl, cycloalkyl, phenyl, naphthyl, phenyl(C₁-C₄ alkyl), naphthyl(C₁-C₄ alkyl), Het A, or Het B is substituted with from 0 to 4 substituents selected from the group consisting of phenyl, naphthyl, C₃-C₈ cycloalkyl, Het A, Het B, C₁-C₆ alkyl, C₁-C₆ haloalkoxy, halo, OR³, SR³, N(R³)₂, N(C₁-C₆ alkyl)(C₁-C₆ alkoxy), C₁-C₆ alkyl, C(O)R³, C₁-C₆ haloalkyl, NO₂, CN, CF₃, SO₂(C₁-C₆ alkyl), S(O)(C₁-C₆ alkyl), NR³SO₂R⁴, SO₂N(R⁴)₂, NHC(O)OR⁴, NHC(O)R⁴, NHC(O)NHR⁴, CO₂R³, and C(O)N(R³)₂, and

wherein 2 adjacent substituents of the R⁵ cycloalkyl, cycloalkoxy, aryl, heteroaryl or heterocyclyl are optionally taken together to form a 3- to 6-membered cyclic ring containing from 0 to 3 heteroatoms selected from N, O and S;

each R⁶ is independently selected from the group consisting of C₁-C₈ alkyl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl(C₁-C₈ alkyl), C₁-C₈ alkoxy, C₃-C₈ cycloalkoxy, phenyl, naphthyl, phenyl(C₁-C₄ alkyl), naphthyl(C₁-C₄ alkyl), Het A, Het A(C₁-C₄ alkyl), Het B, and Het B(C₁-C₈ alkyl),

wherein the R⁶ alkyl, cycloalkyl, alkoxy, cycloalkoxy, phenyl, naphthyl, Het A and Het B is substituted with from 0 to 4 substituents selected from the group consisting of phenyl, naphthyl, Het A, Het B, C₃-C₈ cycloalkyl, C₁-C₆ alkyl, C₁-C₆ haloalkoxy, halo, OR³, SR³, N(R³)₂, N(C₁-C₆ alkyl)(C₁-C₆ alkoxy), C₁-C₆ alkyl, C(O)R³, C₁-C₆ haloalkyl, NO₂, CN, CF₃, SO₂(C₁-C₆ alkyl), S(O)(C₁-C₆ alkyl), NR³SO₂R⁴, SO₂N(R⁴)₂, NHC(O)OR⁴, NHC(O)R⁴, NHC(O)NHR⁴, CO₂R³, and C(O)N(R³)₂; and

wherein 2 adjacent substituents of the R⁶ cycloalkyl, cycloalkoxy, aryl, heteroaryl or heterocyclyl are optionally taken together to form a 3- to 6-membered cyclic ring containing from 0 to 3 heteroatoms selected from N, O and S;

or R⁵ and R⁶ are optionally taken together, with the nitrogen atom to which they are attached, to form a 4- to 8-membered monocyclic ring containing from 0 to 2 additional heteroatoms selected from N, O and S;

each R^7 is independently selected from the group consisting of OR^{14} , $N(R^3)-V-CO_2R^3$, $O-V-CO_2R^3$, $S-V-CO_2R^3$, $N(R^3)(R^{10})$, R^{11} , and $N(R^3)SO_2R^4$;

each R^8 is independently selected from the group consisting of OR^{14} , $N(R^3)-V-CO_2R^3$, $O-V-CO_2R^3$, $S-V-CO_2R^3$, and $N(R^3)(R^{10})$;

5 or R^7 and R^8 are optionally taken together, with the phosphorus atom to which they are attached, to form a 5- to 7-membered monocyclic ring;

each R^9 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), Het A, Het A(C_1-C_4 alkyl), Het B, and Het B(C_1-C_8 alkyl), wherein the R^9
 10 alkyl, cycloalkyl, phenyl, naphthyl, Het A or Het B is substituted with from 0 to 2 W substituents;

each V is independently selected from the group consisting of $-CH(R^{12})-$ and $-C_1-C_4$ alkylene- $CH(R^{12})-$;

each R^{10} is independently selected from the group consisting of H, C_1-C_6 alkyl,
 15 C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, phenyl, naphthyl, Het A and Het B,

wherein the R^{10} alkyl, alkenyl, cycloalkyl, phenyl, naphthyl, Het A or Het B is substituted with from 0 to 2 substituents selected from the group consisting of phenyl, naphthyl, phenyl(C_1-C_4 alkyl), naphthyl(C_1-C_4 alkyl), Het A, Het A(C_1-C_4 alkyl), Het B, Het B(C_1-C_8 alkyl), C_1-C_6 alkyl, halo, $OC(O)OR^4$, $OC(O)R^4$, OR^3 , SR^3 , $N(R^3)_2$, $C(O)R^3$, NO_2 ,
 20 CN , CF_3 , $SO_2(C_1-C_6$ alkyl), $S(O)(C_1-C_6$ alkyl), $NR^3SO_2R^4$, $SO_2N(R^4)_2$, $NHC(O)OR^4$, $NHC(O)R^4$, $NHC(O)NHR^4$, CO_2R^3 , and $C(O)N(R^3)_2$; and

wherein 2 adjacent substituents of the R^{10} cycloalkyl, cycloalkoxy, phenyl, naphthyl, Het A or Het B are optionally taken together to form a 3- to 6-membered cyclic ring containing from 0 to 3 heteroatoms selected from N, O and S;

each R^{11} is independently selected from the group consisting of C_1-C_6 alkyl, C_2-C_6 alkenyl, phenyl, naphthyl, and Het A, wherein the R^{11} phenyl, naphthyl, or Het A is substituted with from 0 to 2 substituents selected from the group consisting of C_1-C_6 alkyl, halo, $OC(O)OR^4$, $OC(O)R^4$, OR^3 , SR^3 , $N(R^3)_2$, $C(O)R^3$, NO_2 , CN , CF_3 , $SO_2(C_1-C_6$ alkyl), $S(O)(C_1-C_6$ alkyl), $NR^3SO_2R^4$, $SO_2N(R^4)_2$, $NHC(O)OR^4$, $NHC(O)R^4$, $NHC(O)NHR^4$, CO_2R^3 , and
 30 $C(O)N(R^3)_2$;

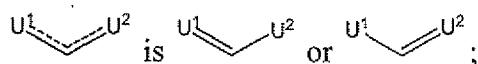
each R^{12} is independently selected from the group consisting of C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, phenyl, naphthyl, Het A and Het B,

wherein the R¹² alkyl, alkenyl, cycloalkyl, phenyl, naphthyl, Het A or Het B is substituted with from 0 to 2 substituents selected from the group consisting of C₁-C₆ alkyl, halo, OC(O)OR⁴, OC(O)R⁴, OR³, SR³, N(R³)₂, C(O)^{R3}, NO₂, CN, CF₃, SO₂(C₁-C₆ alkyl), S(O)(C₁-C₆ alkyl), NR³SO₂R⁴, SO₂N(R⁴)₂, NHC(O)OR⁴, NHC(O)R⁴, NHC(O)NHR⁴, CO₂R³,
 5 and C(O)N(R³)₂; and

wherein 2 adjacent substituents of the R¹² cycloalkyl, cycloalkoxy, phenyl, naphthyl, Het A or Het B are optionally taken together to form a 3- to 6-membered cyclic ring containing from 0 to 3 heteroatoms selected from N, O and S;

each W is independently selected from the group consisting of halo, OR³, C₁-C₆ alkyl, CN, CF₃, NO₂, SR³, CO₂R³, CON(R³)₂, C(O)R³, N(R³)C(O)R³, SO₂(C₁-C₆ alkyl), S(O)(C₁-C₆ alkyl), C₃-C₈ cycloalkyl, C₃-C₈ cycloalkoxy, C₁-C₆ haloalkyl, N(R³)₂, N(C₁-C₆ alkyl)O(C₁-C₆ alkyl), halo(C₁-C₆ alkoxy), NR³SO₂R³, SO₂N(R³)₂, NHCOOR³, NHCONHR³, phenyl, naphthyl, Het A and Het B;

Z is selected from the group consisting of C₃-C₉ alkylene having from 0 to 3 substituents independently selected from C₁-C₆ alkyl, where 2 such alkyl substituents are optionally taken together to form a spiro or fused ring containing the substituent atoms and shared atom or atoms;



X is selected from the group consisting of:

- 20
- 1) -C₀₋₅ alkylene-X¹-,
 - 2) -C₂₋₅ alkenylene-X¹-, and
 - 3) -C₂₋₅ alkynylene-X¹-,

wherein X¹ is selected from the group consisting of -O-, -NH-, -CH₂-, -C(O)O-, -C(O)NR¹³- or -NR¹³C(O)O-, and wherein alkylene, alkenylene and alkynylene is unsubstituted or substituted with from 0 to 3 C₁-C₆ alkyl, wherein:
 25

R¹³ is selected from the group consisting of H and C₁-C₆ alkyl;

Y is selected from the group consisting of -OC(O)-, -NR¹⁴C(O)-, -C(O)- and -NHSO₂-, wherein R¹⁴ is C₁₋₆ alkyl; and

M is selected from the group consisting of C₁-C₁₂ alkylenes, C₂-C₁₂ alkenylenes and C₂-C₁₂ alkynylenes, wherein:
 30

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

M is substituted with from 0 to 4 substituents R¹⁵, wherein:

each R¹⁵ is independently selected from the group consisting of C₁-C₈ alkyl, =CH₂, C₃-C₈ cycloalkyl(C₁-C₈ alkyl), phenyl(C₁-C₈ alkyl) and naphthyl(C₁-C₈ alkyl), and


5 any substituent R¹⁵ may be taken together with any adjacent substituent R¹⁵ or any adjacent substituent R¹⁴ 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
10 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
15 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
20 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:

- 1) an aryl,
- 25 2) a cyclohexyl, and
- 3) a heterocyclic ring system selected from the group consisting of:
 - a) a 5- or 6-membered saturated or unsaturated monocyclic ring containing 1, 2, or 3 nitrogen atoms, and
 - b) a 8-, 9- or 10-membered saturated or unsaturated bicyclic ring
30 containing 1 or 2 nitrogen atoms,

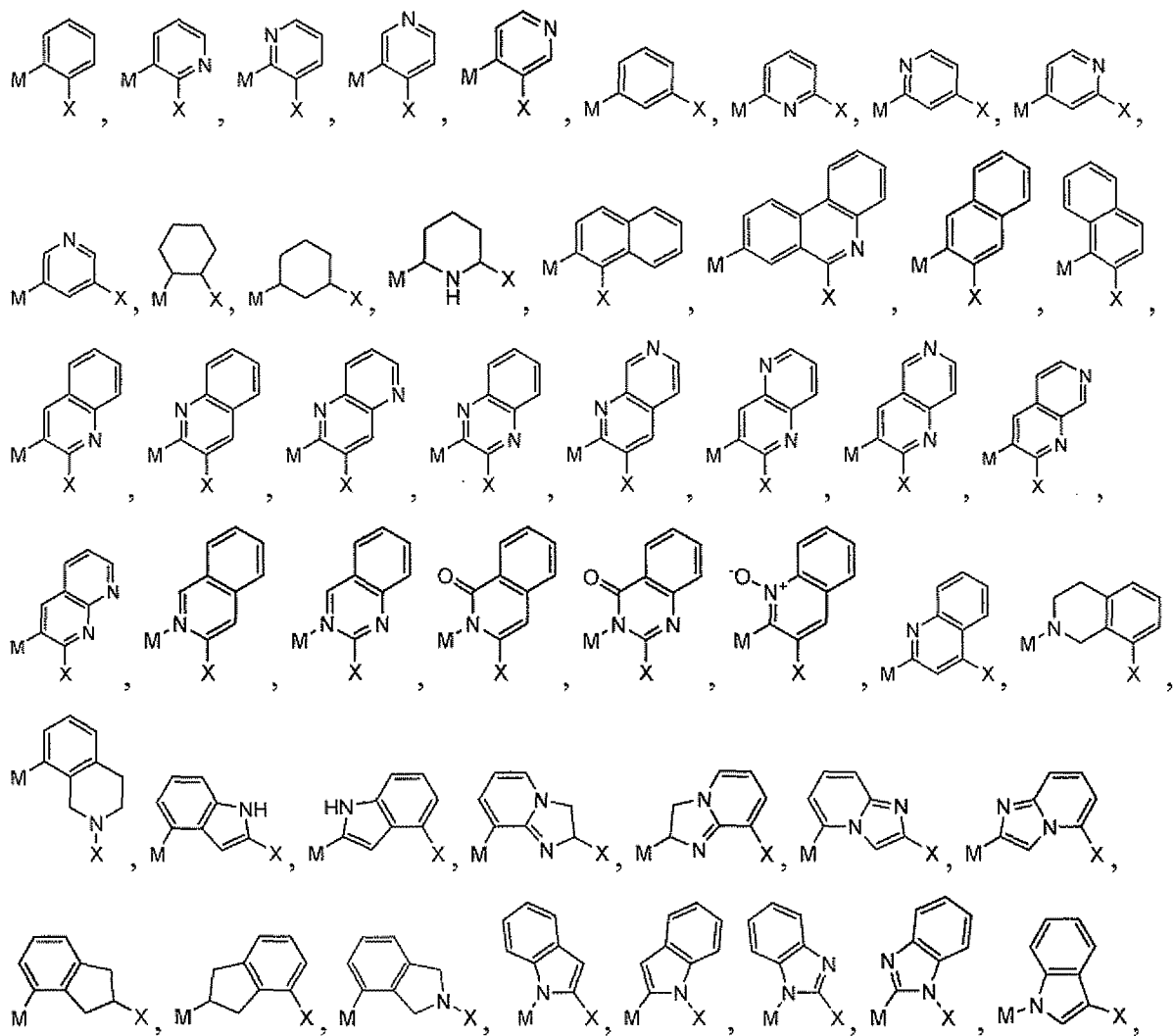
wherein:

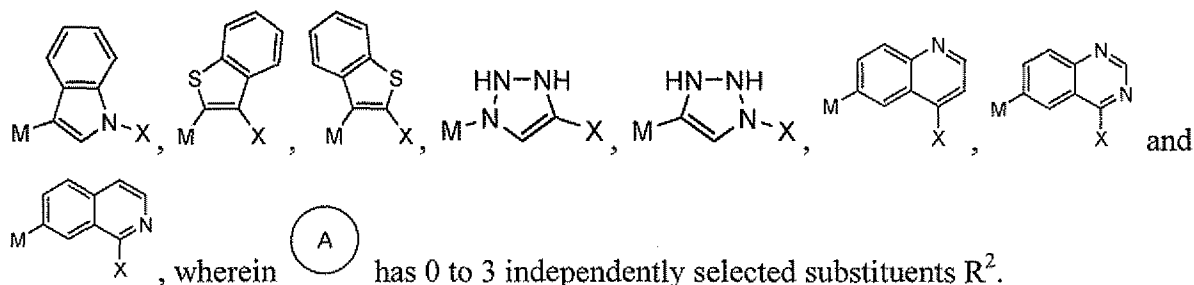
1) the aryl or cyclohexyl has from 0 to 4 independently selected substituents R^2 , and

2) the heterocyclic ring has from 0 to 4 independently selected R^2 substitutions. In this embodiment and all aspects of this embodiment described below, all other groups are as provided in the general formula above.

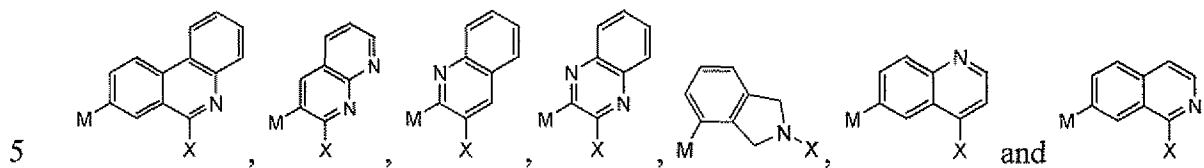
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In a first aspect of the first embodiment, A is selected from the group consisting of:



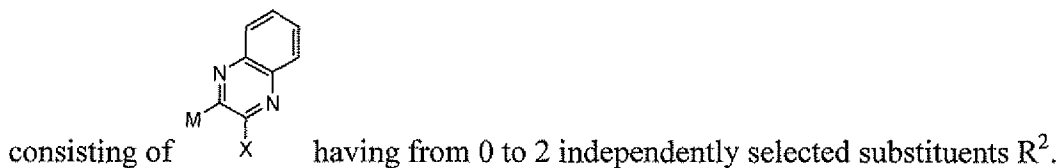


In a second aspect of the first embodiment, $\textcircled{\text{A}}$ is selected from the group consisting of:



wherein the $\textcircled{\text{A}}$ has 0 to 3 independently selected substituents R^2 .

In a third aspect of the first embodiment, $\textcircled{\text{A}}$ is selected from the group

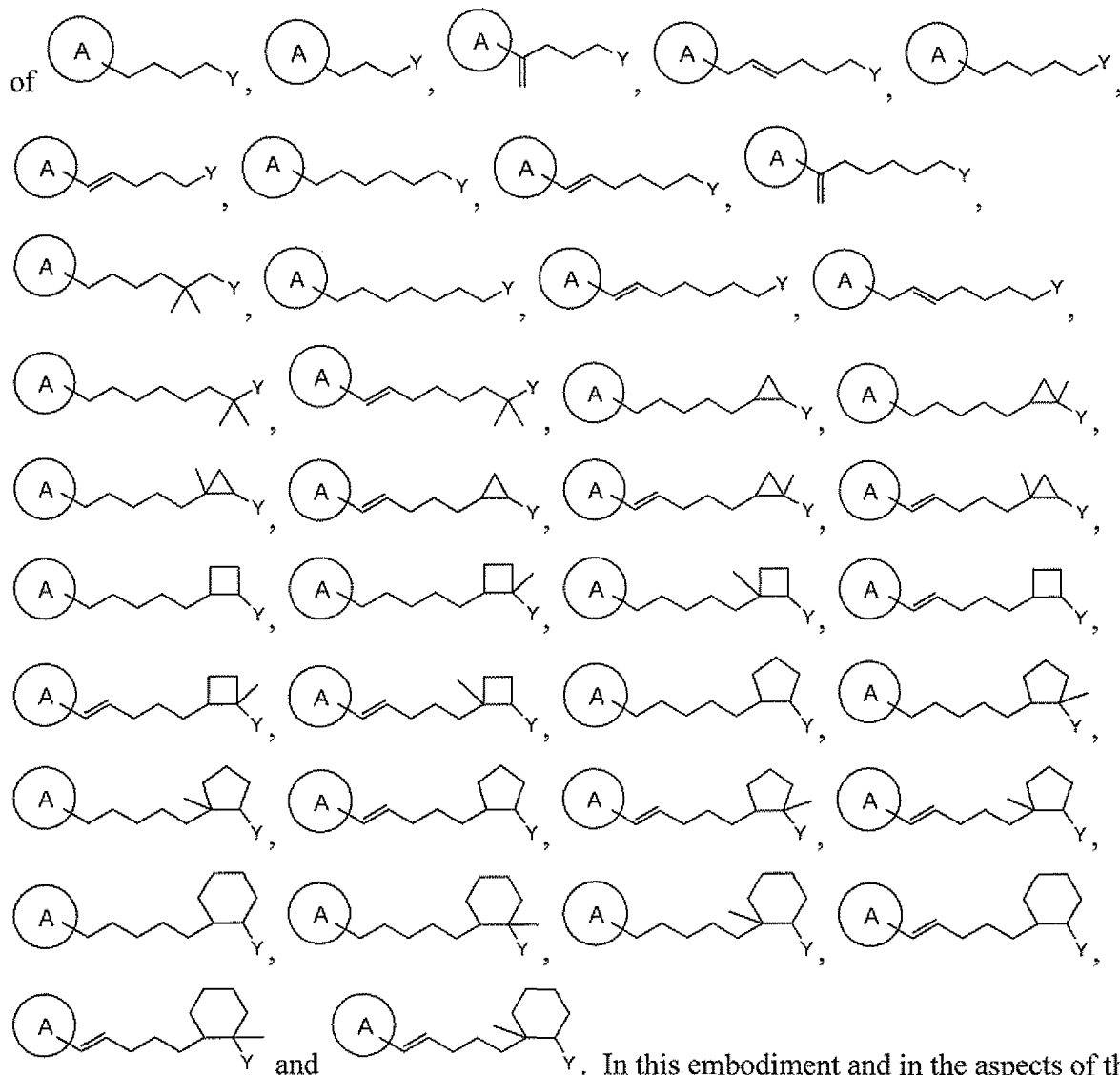


10 In further aspects of the first embodiment, $\textcircled{\text{A}}$ is substituted by from 0 to 1 R^2 , wherein R^2 is selected from the group consisting of -Br, -Cl, -CN, phenyl, -O-phenyl, -OCF₃, -OCH₃, -C(O)OH, -CH₃ and -C(O)CH₃.

15 In a second embodiment of the invention, X is selected from the group consisting of -C₀₋₅ alkylene-O- and -C₀₋₃ alkylene-C(O)O-. In particular aspects of the second embodiment, X is selected from the group consisting of -O- and -C(O)O-. In all aspects of this embodiment, all other groups are as provided in the general formula above and/or in the first embodiment.

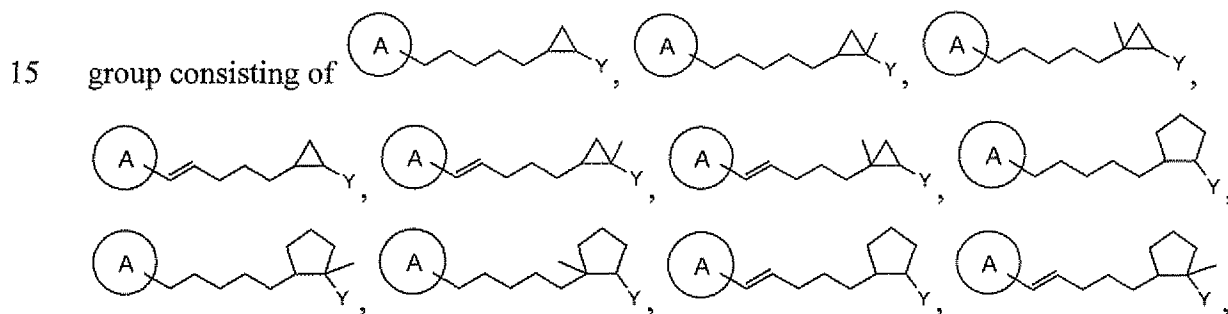
In a third embodiment of the invention, Y is selected from the group consisting of -OC(O)- and -C(O)-. In this embodiment, all other groups are as provided in the general formula above and/or in the first or second embodiments.

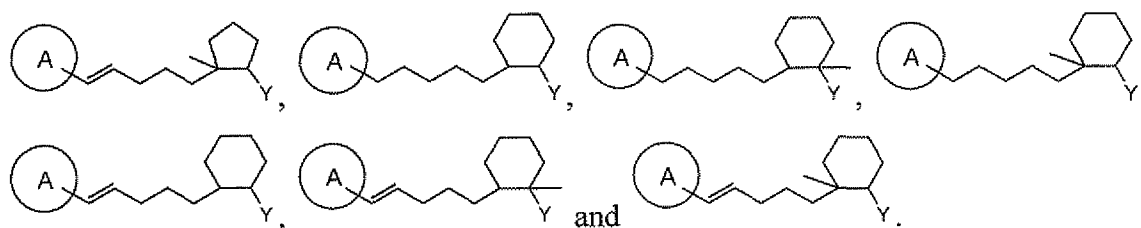
In a fourth embodiment of the invention, M is selected from the group consisting



embodiment described below, all other groups are as provided in the general formula above and/or in the first, second and third embodiments.

In a first aspect of the fourth embodiment of the invention, M is selected from the



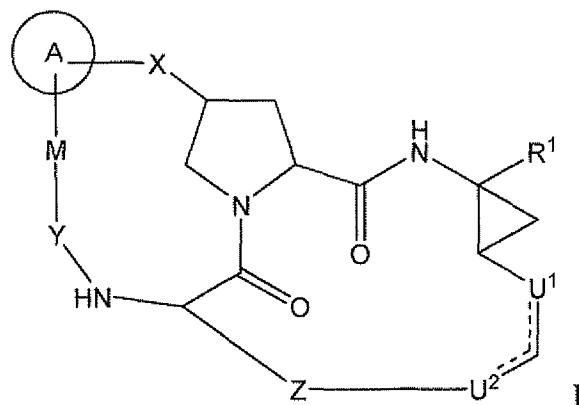


In a fifth embodiment of the invention, Z is $-(CH_2)_4-$. In this embodiment, all other groups are as provided in the general formula above and/or in the first, second, third and fourth embodiments.

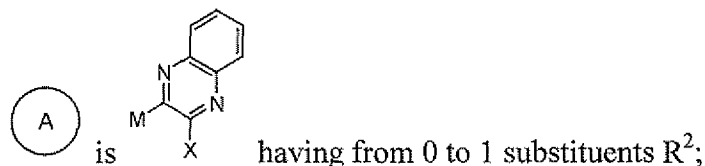
In a sixth embodiment of the invention, R^1 is selected from the group consisting of $-CO_2R^3$ and $-CONR^3SO_2R^6$. In particular aspects of this embodiment, R^1 is selected from the

group consisting of . In all aspects of this embodiment, all other groups are as provided in the general formula above and/or in the first, second, third, fourth and fifth embodiments.

A seventh embodiment of the invention is directed to compounds of Formula I:



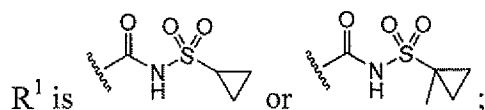
and/or pharmaceutically acceptable salts, hydrates or prodrugs thereof, wherein:



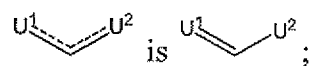
R^2 is $-OR^3$;

R^3 is methyl;

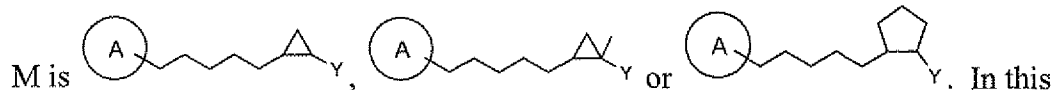
X is $-O-$;



15



Z is $-(CH_2)_4-$; and



embodiment, all other groups are as provided in the general formula above.

5 In a eighth embodiment of the invention, the compound of the invention is selected from the exemplary species depicted in Examples 1 through 11 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.
- 10 (b) The pharmaceutical composition of (a), further comprising at least one additional therapeutic agent independently selected from the group consisting of a HCV antiviral agent, an immunomodulator, and an anti-infective agent.
- (c) The pharmaceutical composition of (b), wherein the HCV antiviral agent is an antiviral selected from the group consisting of a HCV protease inhibitor and a HCV NS5B
- 15 polymerase inhibitor.
- (d) A pharmaceutical combination comprising (i) a compound of Formula I and (ii) at least one additional therapeutic agent independently selected from the group consisting of a HCV antiviral agent, an immunomodulator, and an anti-infective agent; wherein the compound of Formula I and the at least one additional therapeutic agent are each employed in an
- 20 amount that renders the combination effective for inhibiting HCV NS3 protease, or for treating or preventing infection by HCV.
- (e) The combination of (d), wherein the HCV antiviral agent is an antiviral selected from the group consisting of a HCV protease inhibitor and a HCV NS5B polymerase inhibitor.
- 25 (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 preventing or treating infection by HCV 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 additional therapeutic agent independently selected from the group consisting of a HCV antiviral agent, an immunomodulator, and an anti-infective agent.

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

(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
10 the combination of (d) or (e).

(k) A method of preventing or treating infection by HCV 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).

(l) The present invention also includes a compound of the present invention
15 (i) for use in, (ii) for use as a medicament for, or (iii) for use in the preparation of a medicament for: (a) inhibiting HCV NS3 protease or (b) preventing or treating infection by HCV. In these uses, the compounds of the present invention can optionally be employed in combination with at least one additional therapeutic agent independently selected from HCV antiviral agents, anti-infective agents, and immunomodulators.

20 Additional embodiments of the invention include the pharmaceutical compositions, combinations and methods set forth in (a)-(l) 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
25 in the form of a pharmaceutically acceptable salt or hydrate as appropriate.

In the embodiments provided above, it is to be understood that the compound of Formula I may be provided as a free base, a free acid or a pharmaceutically acceptable salt, hydrate or solvate of the compound of Formula I, to the extent that such a free base, a free acid or a pharmaceutically acceptable salt, hydrate or solvate provides a stable compound and is
30 consistent with the description of the embodiments. Thus, any reference to a "compound of Formula I" herein includes reference to the free base form or free acid form, as well as any pharmaceutically acceptable salts, hydrates or solvates, provided that these forms represent a

stable compound and are consistent with the description of the embodiments. It is also 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. A "stable" compound is a compound that can be prepared and isolated and
5 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).

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,
10 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, "C₁₋₆ alkyl" (or "C₁-C₆ alkyl") refers to all of the hexyl alkyl and pentyl alkyl isomers as well as *n*-, iso-, *sec*- and *tert*-butyl, *n*- and isopropyl, ethyl and methyl. As another example, "C₁₋₄ alkyl" refers to *n*-, iso-, *sec*- and *tert*-butyl, *n*- and isopropyl, ethyl and methyl.
15

The term "haloalkyl" refers to an alkyl group wherein a hydrogen atom has been replaced by a halogen atom. The term "alkoxy" refers to an "alkyl-O-" group.
20

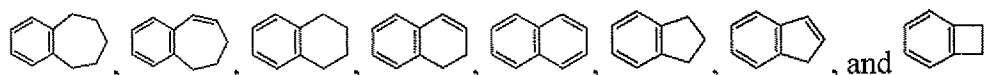
The term "alkylene" refers to any linear or branched chain alkylene group (or alternatively "alkanediyl") having a number of carbon atoms in the specified range. Thus, for example, "-C₁₋₆ alkylene-" refers to any of the C₁ to C₆ linear or branched alkylenes. A class of
25 alkylenes of particular interest with respect to the invention is -(CH₂)₁₋₆-, and sub-classes of particular interest include -(CH₂)₁₋₄-, -(CH₂)₁₋₃-, -(CH₂)₁₋₂-, and -CH₂-. Also of interest is the alkylene -CH(CH₃)-.

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, "C₃₋₈ cycloalkyl" (or "C₃-C₈
30 cycloalkyl") refers to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. The term "cycloalkoxy" refers to a "-O-cycloalkyl" group.

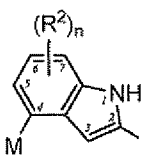
The terms "halogen", "halogen atom" and "halo" refer to fluorine, chlorine, bromine and iodine (alternatively referred to as fluoro, chloro, bromo, and iodo).

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 the ring is optionally substituted with 1 to 3 substituents selected from halo, OR³, SR³, N(R³)₂, N(C₁-C₆ alkyl)O(C₁-C₆ alkyl), C₁-C₆ alkyl, C₁-C₆ haloalkyl, halo(C₁-C₆ alkoxy), NO₂, CN, CF₃, SO₂(C₁-C₆ alkyl), S(O)(C₁-C₆ alkyl), NR³SO₂R⁴, SO₂N(R⁴)₂, NHCOOR⁴, NHCOR⁴, NHCONHR⁴, CO₂R³, C(O)R³, and CON(R³)₂. The oxidized forms of the heteroatoms N and S are included within the scope of the present invention.

The term "carbocycle" (and variations thereof such as "carbocyclic" or "carbocyclyl") as used herein, unless otherwise indicated, refers to (i) a C₃ to C₈ monocyclic, saturated or unsaturated ring or (ii) a C₇ to C₁₂ 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 that 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 C₇ to C₁₀ bicyclic ring system in which each ring is saturated (*i.e.*, containing only single bonds) or unsaturated (*i.e.*, containing at least one double and/or triple bonds) and two adjacent carbon atoms are shared by each of the rings in the ring system. A fused bicyclic carbocycle in which all rings are saturated is a saturated bicyclic ring system. A fused bicyclic carbocycle in which at least one ring is unsaturated is an unsaturated bicyclic 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 C₁₋₆ alkyl, C₁₋₆ alkenyl, C₁₋₆ alkynyl, aryl, halogen, NH₂ 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 M. Variable R² is shown as a floating variable that 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 and naphthyl.

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 system, 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 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, quinoxalyl, quinazolyl, cinnolyl, chromanyl, isochromanyl, tetrahydroquinolyl, quinolyl, tetrahydroisoquinolyl, isoquinolyl, 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, benzo-1,3-dioxolyl 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 or substituted. As used herein, the terms "substituted alkyl", "substituted C₃-C₁₀ 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 that includes, but is not limited to, halo, C₁-C₂₀ alkyl, -CF₃, -NH₂, -N(C₁-C₆ alkyl)₂, -NO₂, oxo, -CN, -N₃, -OH, -O(C₁-C₆ alkyl), C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, (C₀-C₆ alkyl)-S(O)₀₋₂-, aryl-S(O)₀₋₂-, (C₀-C₆ alkyl)S(O)₀₋₂(C₀-C₆ alkyl)-, (C₀-C₆ alkyl)C(O)NH-, H₂N-C(NH)-, -O(C₁-C₆ alkyl)CF₃, (C₀-C₆ alkyl)C(O)-, (C₀-C₆ alkyl)OC(O)-, (C₀-C₆alkyl)O(C₁-C₆ alkyl)-, (C₀-C₆ alkyl)C(O)₁₋₂(C₀-C₆ alkyl)-, (C₀-C₆ alkyl)OC(O)NH-, aryl, aralkyl, heteroaryl, heterocyclalkyl, halo-aryl, halo-aralkyl, halo-heterocycle, halo-heterocyclalkyl, cyano-aryl, cyano-aralkyl, cyano-heterocycle and cyano-heterocyclalkyl. Unless specifically indicated, such substituents themselves are not substituted.

When any variable (*e.g.*, R², R³ and R⁹) occurs more than one time in Formula I, any constituent of 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, 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.

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 the claimed 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.

The compounds of the present inventions are useful in the inhibition of HCV protease (*e.g.*, HCV NS3 protease) and the prevention or treatment of infection by HCV. 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 sold 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 that possesses the effectiveness of the parent compound and that is not biologically or otherwise undesirable (*e.g.*, is neither toxic nor otherwise deleterious to the recipient thereof). Suitable salts include acid addition salts that 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, salt, hydrate or solvate, and other agents.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients, as well as any product that 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 an 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
5 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
10 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
15 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
20 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
25 and glucose. Further description of methods suitable for use in preparing pharmaceutical compositions of the present invention and of ingredients suitable for use in such 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
30 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 patient 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- α 2a (such as ROFERON interferon available from Hoffmann-LaRoche, Nutley, NJ), pegylated interferon- α 2a (PEGASYS), interferon- α 2b (such as INTRON-A interferon available from Schering Corp., Kenilworth, NJ), pegylated interferon- α 2b (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 that has shown immunomodulatory activity similar to ribavirin. Viramidine represents an analog of ribavirin disclosed in WO 01/60379. 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,
5 WO 00/59929, GB 2337262, WO 02/48116, WO 02/48172, and US 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
10 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. The compounds of this 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 those disclosed in WO 00/25780; or
15 mycophenolate mofetil (*see* Anthony C. Allison & Elsie M. Eugui, *Immunosuppressive and other Anthi-Rheumatic Activities of Mycophenolate Mofetil*, 44 (Suppl.) AGENTS ACTION 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)
20 (*see* Joel Kirschbaum, *Amantadine* in 12 ANAL. PROFILES DRUG SUBS. 1 (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
25 of HCV infection with antiviral 2'-C-branched ribonucleosides disclosed in Rogers E. Harry-O'Kuru *et al.*, *A Short, Flexible Route toward 2'-C-Branched Ribonucleosides*, 62 J. ORG. CHEM. 1754 (1997); Michael S. Wolfe & Rogers E. Harry-O'Kuru, *A Concise Synthesis of 2'-C-Methylribonucleosides*, 36(42) TETRAHEDRON LETT. 7611 (1995); US 3,480,613; WO 01/90121; WO 01/92282; WO 02/32920; WO 2004/002999; WO 2004/003000; and WO 2004/002422; the
30 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
5 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; WO 2005/003147 (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 2006/021341 (including 4'-azido nucleosides such as RL26, 4'-azidocytidine); US 2002/0019363; WO 02/100415;
10 WO 2003/026589; WO 2003/026675; WO 2003/093290; US 2003/0236216; US 2004/0006007; WO 2004/011478; WO 2004/013300; US 2004/0063658; and WO 2004/028481; the contents 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.
15 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 2003/068244; WO 2004/000858; WO 2004/003138 and WO 2004/007512; the contents 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)
20 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-
25 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-
30 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; and pharmaceutically acceptable salts, solvates and hydrates thereof.

The claimed compounds 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 WO 2004/041201 (in particular HCV-796); the contents 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, solvates and hydrates thereof.

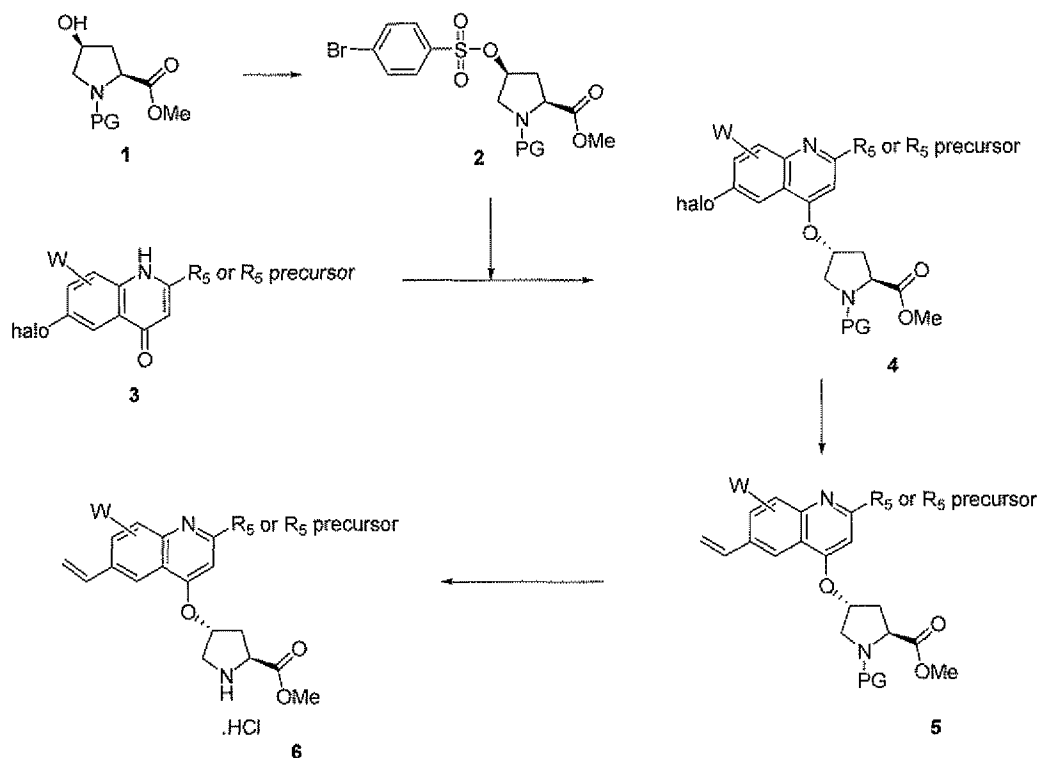
The HCV NS3 protease inhibitory activity of the present compounds may be tested using assays known in the art. One such assay is HCV NS3 protease time-resolved fluorescence (TRF) assay as described below and in WO 2006/102087. Other examples of such assays are described in, for example, WO 2005/046712. HCV NS3 protease inhibitors, such as those described herein have a K_i less than 50 μM , such as less than 10 μM , and less than 100 nM. K_i 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,

$$\text{IC}_{50} = K_i (1 + [S] / K_M), \quad \text{Eqn (1)},$$

where [S] is the concentration of substrate peptide in the reaction and K_M is the Michaelis constant. See Paola Gallinari *et al.*, *Modulation of Hepatitis C Virus NS3 Protease and Helicase Activities through the Interaction with NS4A*, 38 BIOCHEM. 5620 (1999); Paola Gallinari *et al.*, *Multiple Enzymatic Activities Associated with Recombinant NS3 Protein of Hepatitis C Virus*, 72(8) J. VIROLOGY 6758 (1998); Mariana Taliani *et al.*, *A Continuous Assay of Hepatitis C Virus Protease Based on Resonance Energy Transfer Depsipeptide Substrates*, 240 ANAL. BIOCHEM. 60 (1996).

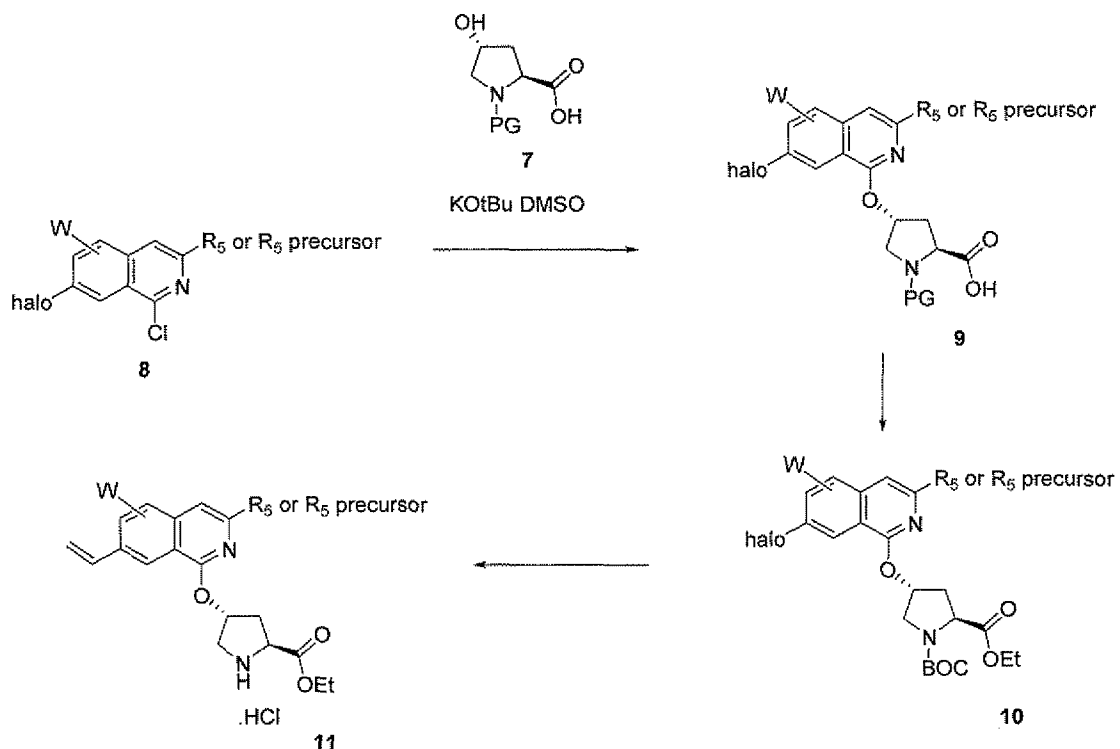
Intermediates C used in the preparation of compounds of the present invention can be prepared as outlined in Schemes 1-3.

In the following schemes, all variables are as defined above unless otherwise indicated. R is C_{1-6} alkyl unless otherwise indicated.

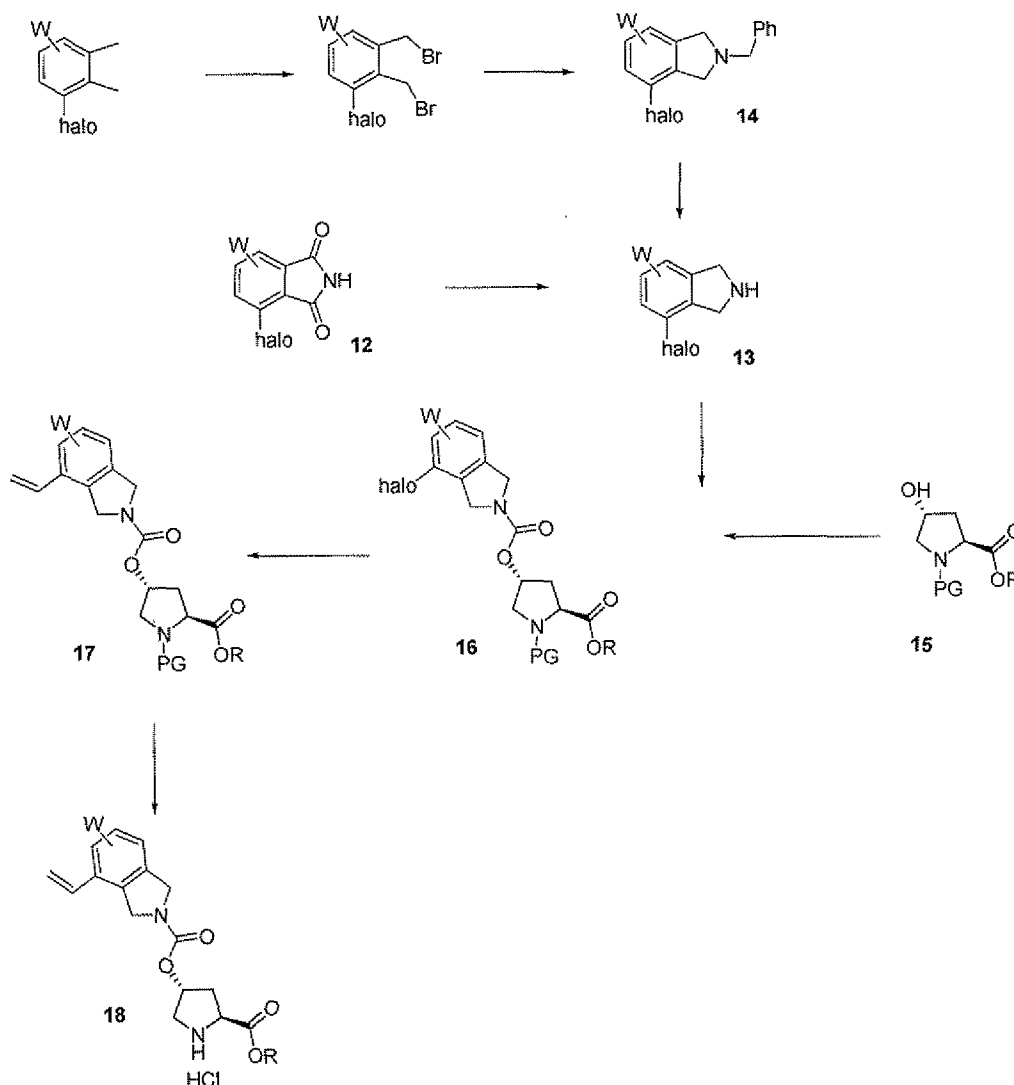
Scheme 1

Reaction of an appropriately substituted quinoline derivative 3 with the brosylate of a protected (PG) (e.g., Boc) cis-4-hydroxyproline methyl ester 2 affords the coupled product 4 (Scheme 1). The same intermediates can be prepared by direct reaction of an appropriately substituted quinoline derivative 1 with N-protected cis-4-hydroxyproline methyl ester, utilizing Mitsunobu coupling conditions (see Oyo Mitsunobu, *The Use of Diethyl Azodicarboxylate and Triphenylphosphine in Synthesis and Transformation of Natural Products*, SYNTHESIS 1 (January 1981)).

Vinylation of the halo quinoline 4 can then be carried out in a number of different ways including: reaction with vinyltributyltin and an appropriate palladium catalyst (e.g., Pd(PPh₃)₄) in a solvent such as toluene, DMF, DMSO, THF; reaction with potassium vinyltrifluoroborate and an appropriate palladium catalyst (e.g., dichloro[1,1'-bis(diphenylphosphino)ferrocene] palladium (II) dichloromethane adduct), in combination with an amine base such as triethylamine in ethanol or other suitable solvents; and a Heck reaction with ethylene and suitable palladium catalyst in an appropriate solvent. It will be apparent to a person skilled in the art that this vinylation step may also be carried out at alternative points in the synthetic sequences. In the case of a BOC protecting group, the BOC group of 5 can be removed by treatment with acid, such as HCl in a suitable solvent (e.g., dioxane or ethyl acetate) or trifluoroacetic acid either neat or diluted with a solvent such as dichloromethane to provide 6.

Scheme 2

Intermediates C possessing an isoquinolone moiety can be prepared as outlined in Scheme 2. Reaction of *N*-protected (e.g., BOC) trans 4-hydroxyproline (7) is accomplished by formation of the dianion with base (e.g., KOtBu) in appropriate solvent (DMSO, THF or mixtures thereof) and quenching with a suitably substituted 1-chloroisoquinoline (8). Where PG is BOC, the proline protecting group of the product 9 can be removed and the acid esterified in a single step by treatment with HCl in a suitable alcohol such as ethanol to give, after reformation of the BOC protected amine, 10. Vinylation and removal of the BOC protecting group can then be carried out as described for intermediates in Scheme 1 to provide 11.

Scheme 3

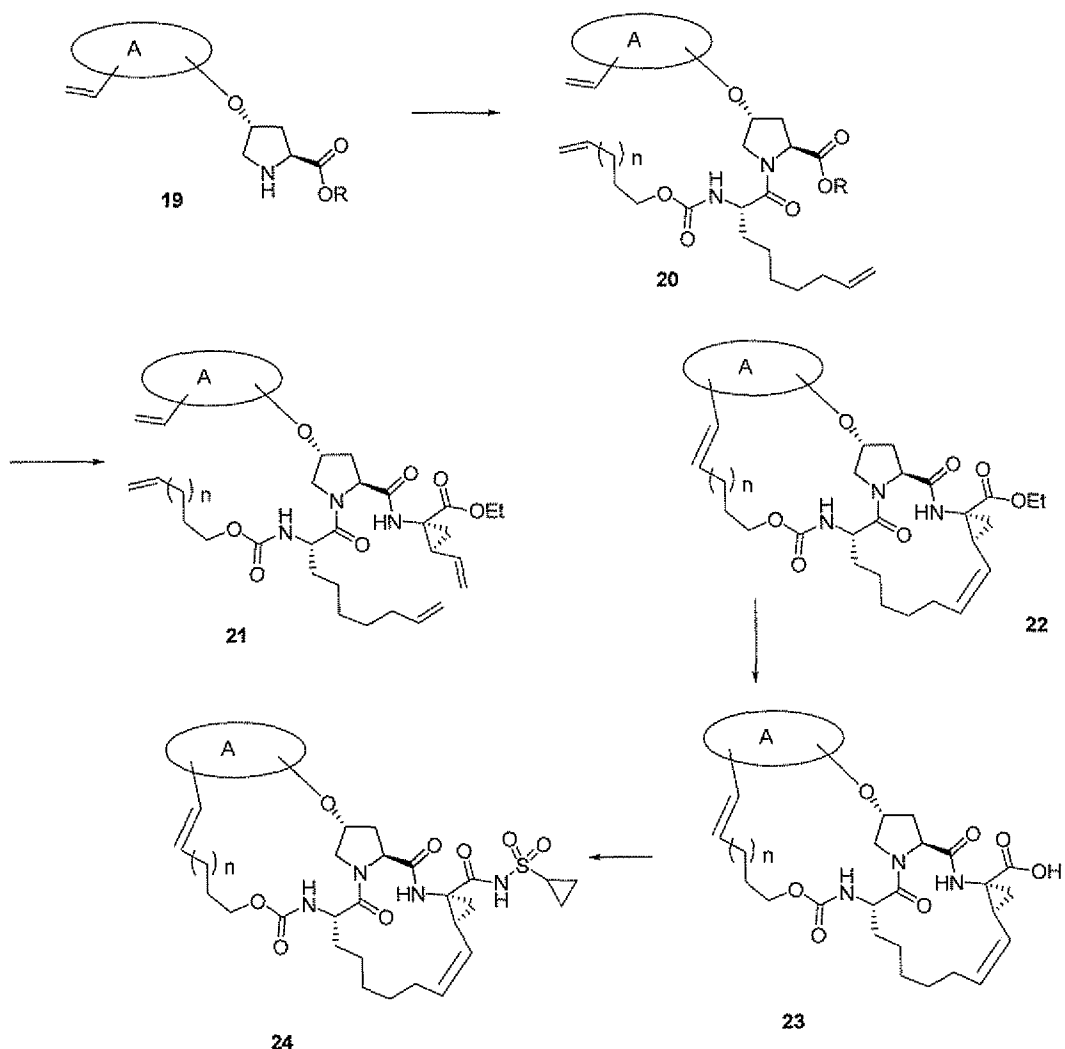
Intermediates C containing an isoindoline moiety can be prepared as outlined in Scheme 3. The appropriate haloisoindoline **13** may be formed either by reduction of an appropriate halo substituted phthalimide **12** with, for example, borane, or alternatively an

5 appropriate halo-xylene (*e.g.*, 3-bromo-*o*-xylene) may be doubly brominated utilizing N-bromosuccinimide and then ring closed by treatment with an amine such as benzylamine in the presence of an organic or inorganic base (*e.g.*, potassium bicarbonate) in a solvent (*e.g.*, acetonitrile). The benzyl group of the resultant isoindoline **14** can then be removed, for example

10 by treatment with α -chloroethylchloroformate (ACE-Cl), followed by treatment with an alcohol (*e.g.*, methanol). The haloisoindoline **13** can then be coupled with N-protected (*e.g.*, BOC) trans-4-hydroxyproline methyl (or ethyl) ester (**15**), by treatment of the latter with carbonyldiimidazole, phosgene or triphosgene, followed by addition of the haloisoindoline,

optionally in the presence of an amine base such as triethylamine. Vinylation of the resulting coupled product **16** to **17** and removal of the proline protecting group to afford **18**, can then be carried out as described for the compounds in Scheme 1.

Scheme 4



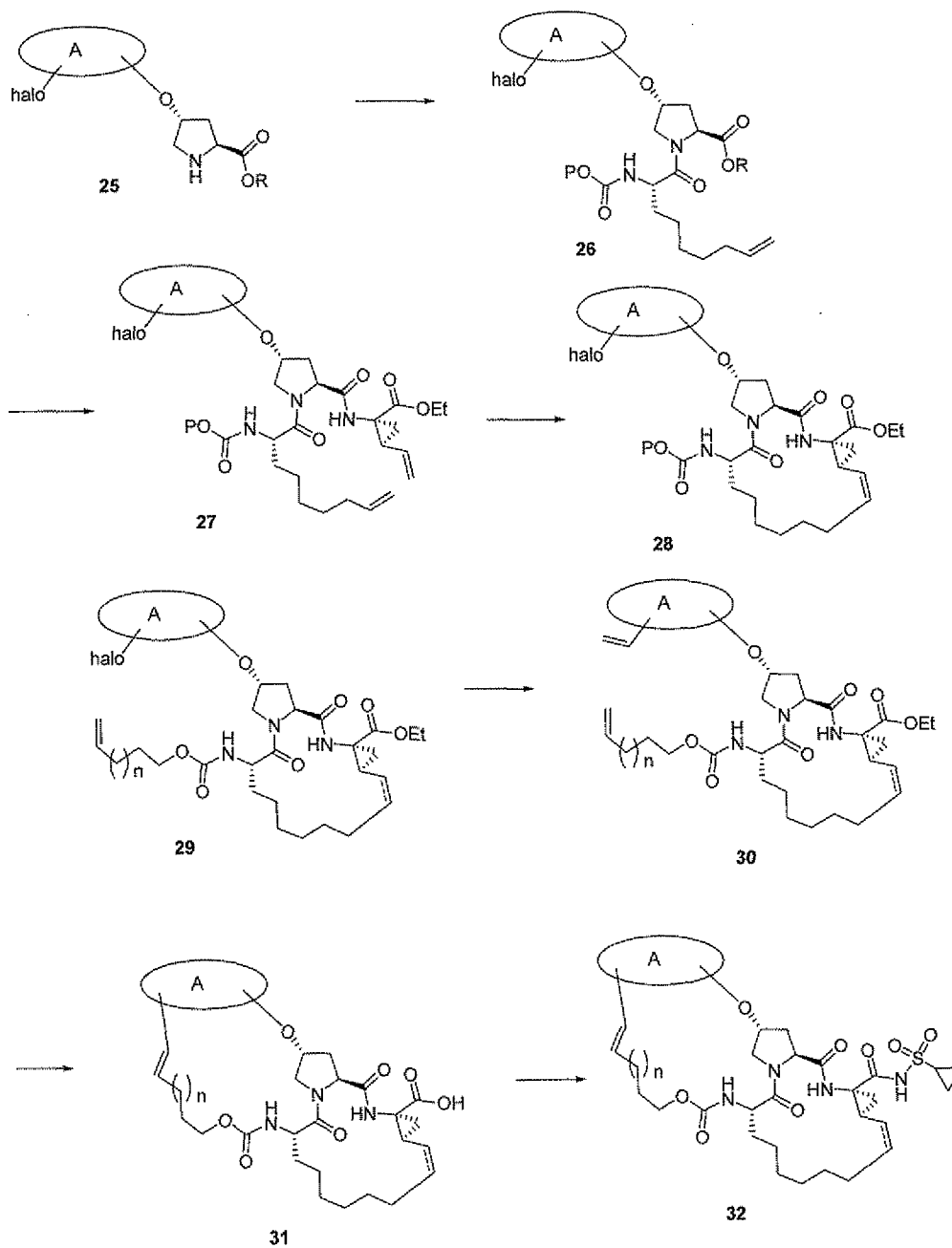
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Intermediates **C** can then be converted to compounds of the present invention by a number of alternative procedures. In the first of these (Scheme 4), an Intermediate **C** is coupled with an alkenyl carbamate derivative of 2(*S*)-*t*-butoxycarbonylamino-non-8-enoic acid (Acme Bioscience Inc.) is coupled with proline derivative **19**, using a standard peptide coupling reagent such as EDC, HATU or BOP to give intermediate **20**. Hydrolysis of the proline ester and coupling with (1*R*,2*S*)-1-amino-2-vinylcyclopropanecarboxylic acid (Pierre J. Beaulieu *et al.*, *Synthesis of (1*R*,2*S*)-1-Amino-2-vinylcyclopropanecarboxylic Acid Vinyl-ACCA) Derivatives: Key Intermediates for the Preparation of Inhibitors of the Hepatitis C Virus NS3 Protease*, 70 J.

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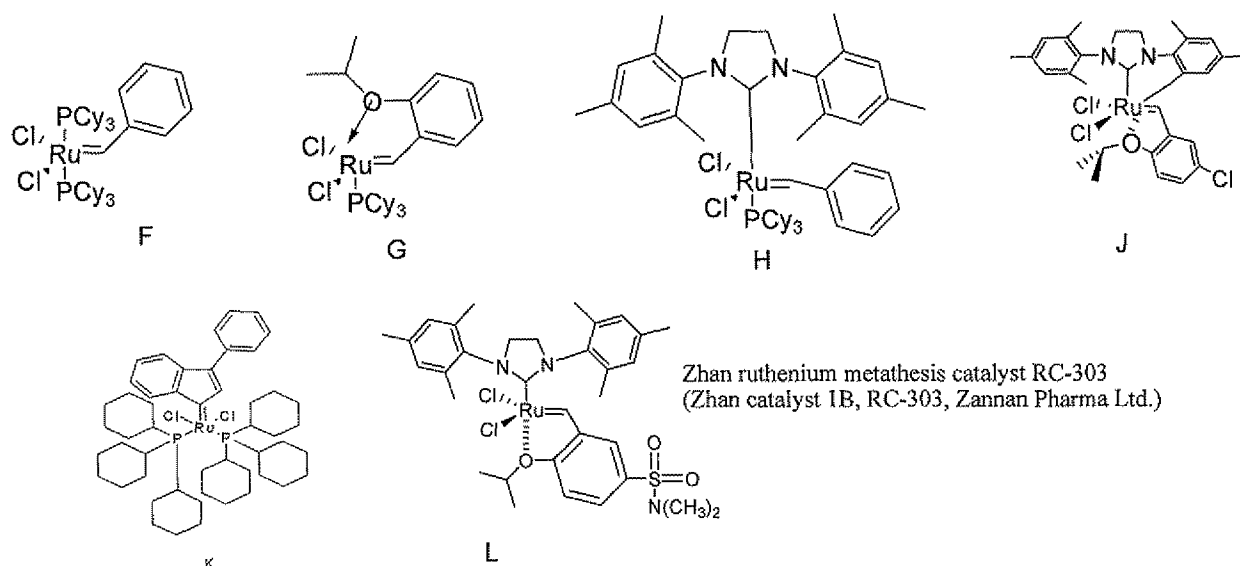
ORG. CHEM. 5869 (2005)) affords tetraolefin **21**, which can be subjected to a double ring-closing metathesis reaction to give **22**. Bismacrocycle **22**, can then be hydrolyzed to give carboxylic acid products **23**, which via activation of the carboxylic acid, for example by *N,N'*-carbonyldiimidazole and reaction with cyclopropylsulfonamide affords the corresponding acylsulfonamides **24**. In a variation on this method, the ester **20** can be hydrolyzed, coupled with (1*R*,2*S*)-1-amino-*N*-(cyclopropylsulfonyl)-2-vinylcyclopropanecarboxamide (WO 2003/099274) and macrocyclized to give directly the acylsulfonamides **24**.

Scheme 5



By using the halo-substituted proline-A intermediate **25** (Scheme 5), the macrocycles may be constructed in sequential fashion (Scheme 5). Thus, proline derivative **25** can be coupled with 2(*S*)-*tert*-butoxycarbonylamino-non-8-enoic acid (Acme Bioscience Inc.) to afford **26**, followed by hydrolysis of the proline ester and coupling with (1*R*,2*S*)-1-amino-2-
5 vinylcyclopropanecarboxylic acid (Pierre J. Beaulieu *et al.*, *Synthesis of (1R,2S)-1-Amino-2-vinylcyclopropanecarboxylic Acid Vinyl-ACCA) Derivatives: Key Intermediates for the Preparation of Inhibitors of the Hepatitis C Virus NS3 Protease*, 70 J. ORG. CHEM. 5869 (2005)) to afford bis-olefin **27**. Macrocyclization by ring-closing metathesis with an appropriate ruthenium or other metal catalyst affords macrocycle **28**. At this stage, a hydrogenation of the
10 macrocyclic olefin may optionally be carried out. Cleavage of the BOC group with acid and formation of an unsaturated carbamate by reaction with an appropriate unsaturated alcohol, which has been activated with *N,N'*-carbonyldiimidazole, phosgene or triphosgene yields **29**. Vinylation of **29** to give **30** can then be carried out in a number of different ways including: reaction with vinyltributyltin and an appropriate palladium catalyst (*e.g.*, Pd(PPh₃)₄) in a solvent
15 such as toluene, DMF, DMSO, THF; reaction with potassium vinyltrifluoroborate and an appropriate palladium catalyst (*e.g.*, dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct), in combination with an amine base such as triethylamine in ethanol or other suitable solvents; and a Heck reaction with ethylene and suitable palladium catalyst in an appropriate solvent. The second macrocycle may then be carried out with an appropriate
20 ruthenium or other metal catalyst to afford, after hydrolysis, bismacrocycle carboxylic acid **31**. This can then be converted to the corresponding acyl sulfonamide **32** as outlined above.

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
25 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
30 of these catalysts in ring-closing metathesis is well-known in the literature (*e.g.* Tina M. Trnka & Robert H. Grubbs, *The Development of L₂X₂Ru=CHR Olefin Metathesis Catalysts: An Organometallic Success Story*, 34 ACC. CHEM. RES. 18 (2001)).



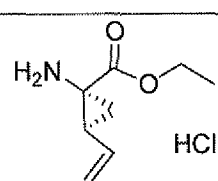
List of Abbreviations

BHT	Butylated hydroxytoluene
BOC ₂ O	Di- <i>tert</i> -butyl dicarbonate
BOP	Benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate
Brosyl	4-Bromobenzenesulfonyl
Brosyl chloride	4-Bromobenzenesulfonyl chloride
CDI	<i>N,N'</i> -Carbonyl diimidazole
CH ₃ CN	Acetonitrile
Cs ₂ CO ₃	Cesium carbonate
CsF	Cesium fluoride
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DCE	Dichloroethane
DCM	Dichloromethane
DIAD	Diisopropyl azodicarboxylate
DIPEA	Diisopropylethylamine
DMAP	4-Dimethylamino pyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide

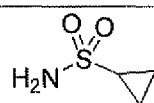
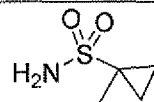
EDC	<i>N</i> -(3-Dimethylaminopropyl)- <i>N</i> '-ethylcarbodiimide
Et ₃ N	Triethylamine
Et ₂ O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol
HATU	<i>O</i> -(7-Azabenzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate
HBr	Hydrobromic acid
HCl	Hydrochloric acid
H ₂ O	Water
HOAc	Acetic acid
HOAt	1-Hydroxy-7-azabenzotriazole
KBH ₄	Potassium borohydride
K ₂ CO ₃	Potassium carbonate
KHSO ₄	Potassium bisulfate
LiOH	Lithium hydroxide
MeCN	Acetonitrile
MeOH	Methanol
MgSO ₄	Magnesium sulfate
MTBE	Methyl <i>tert</i> -butyl ether
N ₂	Nitrogen gas or atmosphere
Na ₂ SO ₄	Sodium sulfate
NaHCO ₃	Sodium bicarbonate
NaOH	Sodium hydroxide
NH ₄ Cl	Ammonium chloride
NH ₄ OH	Ammonium hydroxide
NMP	<i>N</i> -Methyl pyrrolidinone
Pd/C	Palladium on carbon
Pd(PPh ₃) ₄	Tetrakis(triphenylphosphine)palladium (0)
PhMe	Toluene
PPh ₃	Triphenylphosphine
PPTS	Pyridium <i>p</i> -toluenesulfonate

RT	Room temperature
SOCl ₂	Thionyl chloride
SiO ₂	Silica or silica gel
TBTU	<i>O</i> -Benzotriazol-1-yl- <i>N,N,N',N'</i> -tetramethyluronium tetrafluoroborate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran

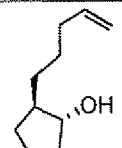
Synthesis of Intermediates**Intermediates A**

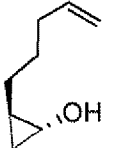
Intermediate #	Structure	Name	Literature Reference
A1		Ethyl (1 <i>R</i> ,2 <i>S</i>)-1-amino-2-vinylcyclopropanecarboxylate hydrochloride	US 6,323,180

5 Intermediates B

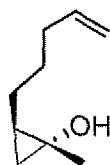
Intermediate #	Structure	Name	Literature Reference
B1		cyclopropanesulfonamide	WO 20080502 Commercially available from APAC Pharm # 816686
B2		1-methylcyclopropanesulfonamide	WO 20080502 Commercially available from Asta Tech # 64790

Intermediates C

Intermediate #	Structure	Name	Literature Reference
C1		(1 <i>R</i> ,2 <i>R</i>)-2-(pent-4-en-1-yl)cyclopentanol	WO 2008057209

C2		(1R,2R)-2-(pent-4-en-1-yl)cyclopropanol	WO 2008057209
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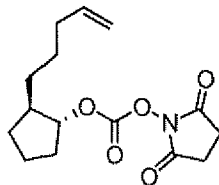
Intermediate C3: (1R,2R)-1-methyl-2-(pent-4-en-1-yl)cyclopropanol



To a solution of 1,6-heptadiene (19.65 g, 204 mmol), in THF (341 ml) was added
 5 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 SiO₂ (15% EtOAc/hexanes) to yield
 the title compound as a mixture of enantiomers. To a solution of the enantiomers (5.5 g,
 10 39.2 mmol) in anhydrous DCM, at 0°C and under N₂, was added Et₃N (10.9 mL, 78 mmol) and
 4-nitrobenzoyl chloride (8.7 g, 47.1 mmol). The reaction was stirred for 2 hours, diluted with
 H₂O (70 mL) and extracted with DCM (3 x 100 mL). The combined organic layer was dried
 over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified on SiO₂ (gradient
 elution, 0 to 50 % EtOAc in hexane) to yield (1R,2R and 1S,2S)-1-methyl-2-(pent-4-en-1-
 15 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 % CO₂ in MeOH. The desired peak
 fractions were concentrated to give (1R,2R)-1-methyl-2-(pent-4-en-1-yl)cyclopropyl 4-
 nitrobenzoate. To a solution of (1R,2R)-1-methyl-2-(pent-4-en-1-yl)cyclopropyl 4-nitrobenzoate
 (4.87 g, 16.83 mmol) in MeOH (67 mL) was added K₂CO₃ (4.65 g, 33.7 mmol). The mixture
 20 was stirred for 1 hour, filtered, and concentrated *in vacuo*. The material was purified on SiO₂
 (gradient elution, 0-50% ether/hexanes) to give the title compound. ¹H NMR (500 MHz)
 (CDCl₃) 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).

Intermediates D

Intermediate D1: 1-[(1*R*,2*R*)-2-(pent-4-en-1-yl)cyclopentyl]oxy}carbonyl)oxy]pyrrolidine-2,5-dione



- 5 To a solution of Intermediate **C1** (22 g, 143 mmol) in MeCN (285 ml) was added *N,N'*-disuccinimidyl carbonate (43.8 g, 171 mmol) followed by Et₃N (59.6 ml, 428 mmol). The mixture was then stirred for 20 hours at 40°C. After 45 minutes, an additional portion of *N'*-disuccinimidyl carbonate (10 g, 39 mmol) was added and stirring was continued for 5.5 hours. The mixture was concentrated *in vacuo* and purified on SiO₂ (gradient elution, 0% to 70%
- 10 EtOAc in hexanes) to yield the title compound. ¹H NMR (500 MHz) (CDCl₃) δ 5.80(m, 1H), 5.0 (m, 2H), 4.83 (m, 1H), 2.83 (s, 4H), 1.8-2.1 (m, 6H), 1.70 (m, 2H), 1.43 (m, 2H), 1.26 (m, 2H).

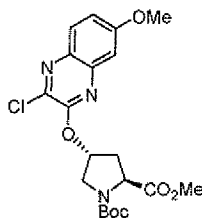
The following Intermediates (**D2**, **D3**) were prepared using the chemistry described for the preparation of Intermediate **D1**, by utilizing the appropriate alcohol.

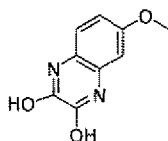
Intermediate #	Alcohol	Structure	Name
D2	C2		1-[(1 <i>R</i> ,2 <i>R</i>)-2-(pent-4-en-1-yl)cyclopropyl]oxy}carbonyl)oxy]pyrrolidine-2,5-dione
D3	C3		1-[(1 <i>R</i> ,2 <i>R</i>)-1-methyl-2-(pent-4-en-1-yl)cyclopropyl]oxy}carbonyl)oxy]pyrrolidine-2,5-dione

15

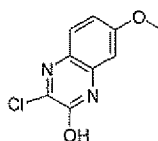
Intermediates E

Intermediate E1: 1-*tert*-butyl 2-methyl (2*S*,4*R*)-4-[(3-chloro-7-methoxyquinoxalin-2-yl)oxy]pyrrolidine-1,2-dicarboxylate



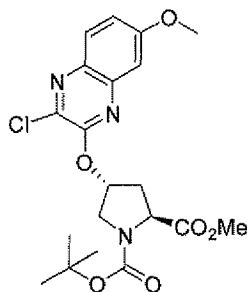
Step 1: 6-methoxyquinoxaline-2,3-diol

A suspension of 4-methoxybenzene-1,2-diamine dihydrochloride in diethyl oxalate (8 eq) was treated with Et₃N (2 eq) and then heated at 150°C for 2 hours. The mixture
 5 was cooled and filtered, and then the collected solid was washed with H₂O and EtOH. The residue was dried to give the title compound (69%). MS (ES⁺) *m/z* 193 (M+H)⁺

Step 2: 3-chloro-7-methoxyquinoxalin-2-ol

A solution (1.53M) of the product of step 1 in DMF was treated with SOCl₂ (1 eq)
 10 and heated at 110°C. After 1.5 hours, the reaction mixture was cooled and poured into aqueous HCl (1 N). The resulting precipitate was filtered and washed with H₂O and Et₂O. The dried solid contained predominantly the title compound as a mixture with 6-methoxyquinoxaline-2,3-diol and 2,3-dichloro-6-methoxyquinoxaline. This material was used directly in the subsequent step. MS (ES⁺) *m/z* 211 (M+H)⁺

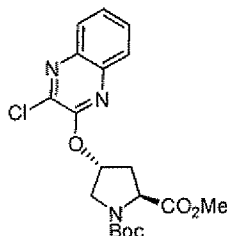
15 *Step 3: 1-tert-butyl 2-methyl (2S,4R)-4-[(3-chloro-7-methoxyquinoxalin-2-yl)oxy]pyrrolidine-1,2-dicarboxylate*



A solution (0.35M) of the product of step 2 in NMP was treated with Cs₂CO₃ (1.5 eq) and 1-*tert*-butyl 2-methyl (2*S*,4*S*)-4-[[4-(4-bromophenyl)sulfonyl]oxy] pyrrolidine-1,2-dicarboxylate (1.1 eq). The resulting mixture was stirred at 50°C for 18 hours, then a further
 20 portion (0.1 eq) of 1-*tert*-butyl 2-methyl (2*S*,4*S*)-4-[[4-(4-bromophenyl)sulfonyl]oxy]pyrrolidine-1,2-dicarboxylate was added. After stirring for 2 hours, the mixture was cooled and diluted with H₂O and EtOAc. The organic phases were washed with aqueous HCl (1 N), saturated aqueous

NaHCO₃ and brine. The dried organic phase was concentrated to a residue that was purified by flash-chromatography (0-60% EtOAc/petroleum ether) to give the title compound (35% for two steps) as a solid. MS (ES⁺) *m/z* 438 (M+H)⁺

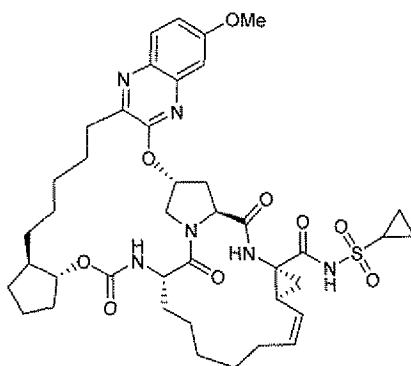
5 Intermediate E2: 1-tert-butyl 2-methyl (2S,4R)-4-[(3-chloroquinoxalin-2-yl)oxy]pyrrolidine-1,2-dicarboxylate



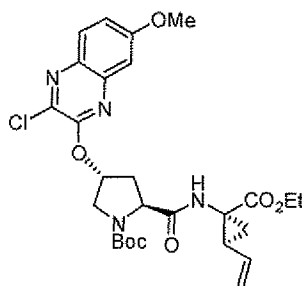
A solution of 3-chloroquinoxalin-2-ol (1.44 g, 7.97 mmol) (Yusuf Ahmad *et al.*, *Quinoxaline Derivatives. XI. The Reaction of Quinoxaline 1,4-Dioxide and Some of Its*
 10 *Derivatives with Acetyl Chloride*, 38(12) J. ORG. CHEM. 2176 (1973)) and 1-tert-butyl 2-methyl (2S,4S)-4-hydroxypyrrolidine-1,2-dicarboxylate (2.05 g, 8.37 mmol) in THF (190 ml) was cooled to 0°C, then treated with PPh₃ (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
 15 volatiles, the residue was purified on SiO₂ (gradient elution, 0-70% EtOAc/petroleum ether) to afford the title compound (2.5 g, 77%). LCMS (ES⁺) *m/z* 408 (M+H)⁺

EXAMPLE 1

(3R,20R,24R,28S,34Z,36S,38R,41S)-N-(Cyclopropylsulfonyl)-9-methoxy-26,40,42-trioxo-4,25-dioxa-1,6,13,27,39-pentaazaheptacyclo[26.13.1.1^{3,41}.0^{5,14}.0^{7,12}.0^{20,24}.0^{36,38}]tritetraconta-
 20 5,7,9,11,13,34-hexaene-38-carboxamide

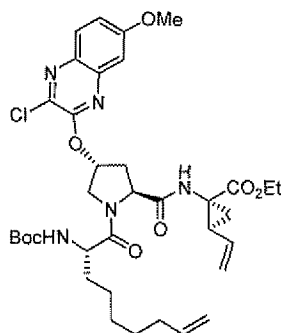


Step 1: *tert*-Butyl (2*S*,4*R*)-4-[(3-chloro-7-methoxyquinoxalin-2-yl)oxy]-2-[[*(1R,2S)*-2-ethenyl-1-(ethoxycarbonyl)cyclopropyl]carbamoyl]pyrrolidine-1-carboxylate



To a solution of Intermediate **E1** (12 g, 27.4 mmol) in THF (50 mL), MeOH
 5 (12.5 mL), and H₂O (25 mL) was added LiOH (3.28 g, 137 mmol). After 1 hour, the mixture
 was extracted with EtOAc and 1 N HCl. The organic layer was washed with brine, dried over
 Na₂SO₄, and concentrated *in vacuo* to yield (4*R*)-1-(*tert*-butoxycarbonyl)-4-[(3-chloro-7-
 methoxyquinoxalin-2-yl)oxy]-L-proline, which was dissolved in DMF (50 mL). To this solution
 was added Intermediate **A1** (6 g, 31.3 mmol), DIPEA (14.3 mL, 82 mmol), and HATU (11.5 g,
 10 30.1 mmol). After 1 hour, the mixture was extracted with Et₂O/EtOAc and 0.5 N HCl. The
 organic layer was washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The crude
 material was purified on SiO₂ (gradient elution, 5% to 100% EtOAc in hexanes) to yield the title
 compound. LRMS (ESI) *m/z* 561.5 [(M+H)⁺; calculated for C₂₇H₃₄ClN₄O₇ 561.2].

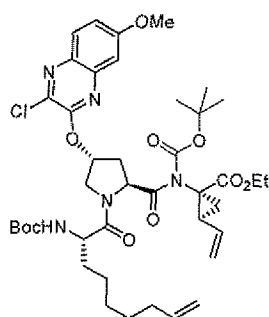
Step 2: Ethyl (1*R*,2*S*)-1-((4*R*)-1-((2*S*)-2-[(*tert*-butoxycarbonyl)amino]non-8-enoyl)-4-[(3-
 15 chloro-7-methoxyquinoxalin-2-yl)oxy]-L-prolyl)amino)-2-ethenylcyclopropanecarboxylate



To the product from step 1 (66.8 g, 119 mmol) was added HCl in dioxane (4M,
 595 mL, 2381 mmol). The mixture was stirred for 1 hour, diluted with Et₂O (500 mL), and
 filtered. The collected solid was washed with Et₂O and dried under vacuum to yield ethyl
 20 (1*R*,2*S*)-1-((4*R*)-4-[(3-chloro-7-methoxyquinoxalin-2-yl)oxy]-L-prolyl)amino)-2-
 ethenylcyclopropanecarboxylate hydrochloride, which was then added to DMF (226 mL). To
 this mixture was added (2*S*)-2-[(*tert*-butoxycarbonyl)amino]non-8-enoic acid (32.9 g, 121 mmol)

(commercially available from Synthetech as the dicyclohexylamine salt), DIPEA (59.3 mL, 340 mmol), and HATU (47.3 g, 125 mmol). After 1 hour, the mixture was extracted with EtOAc and 0.5N HCl. The organic layer was washed with brine, dried over MgSO₄, and concentrated *in vacuo*. The crude material was purified on silica (gradient elution, 0% to 100% EtOAc in
5 hexanes) to yield the title compound. LRMS (ESI) *m/z* 714.5; (M+H)⁺; calculated for C₃₆H₄₉ClN₅O₈ 714.3.

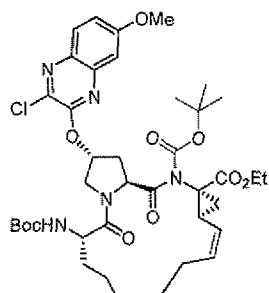
Step 3: Ethyl (1R,2S)-1-[(tert-butoxycarbonyl){(4R)-1-{(2S)-2-[(tert-butoxycarbonyl)amino]non-8-enoyl}-4-[(3-chloro-7-methoxyquinoxalin-2-yl)oxy]-L-prolyl}amino]-2-ethenylcyclopropanecarboxylate



10

To a solution of the product from step 2 (54.6 g, 76 mmol) and DMAP (2.80 g, 22.93 mmol) in EtOAc (648 ml) at 0°C was added BOC₂O (26.6 ml, 115 mmol) dropwise in 60 mL EtOAc. The mixture was warmed to RT, stirred for 18 hours, and extracted with EtOAc and H₂O. The organic layer was dried over MgSO₄, and concentrated *in vacuo*. The crude
15 material was then purified on SiO₂ (gradient elution, 0-70% EtOAc/hexanes) to yield the title compound. LRMS (ESI) *m/z* 814.6 [(M+H)⁺; calculated for C₄₁H₅₇ClN₅O₁₀ 814.4].

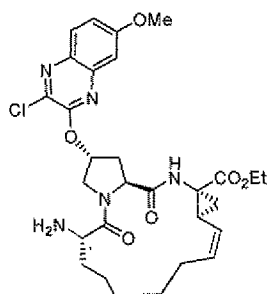
*Step 4: 15-tert-Butyl 14a-ethyl (2R,6S,12Z,13aS,14aR,16aS)-6-[(tert-butoxycarbonyl)amino]-2-[(3-chloro-7-methoxyquinoxalin-2-yl)oxy]-5,16-dioxo-2,3,6,7,8,9,10,11,13a,14,16,16a-dodecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a,15(1H,5H)-
20 dicarboxylate*



To a degassed solution of the product from step 3 (32.1 g, 39.4 mmol) in DCE (1.6 L) at 75°C was added Zhan 1b catalyst (435 mg, 0.59 mmol) and benzoquinone (129 mg, 1.18 mmol) in three portions over 1 hour. After 2 hours, the mixture was concentrated *in vacuo* and purified on SiO₂ (gradient elution, 0-70% EtOAc/hexanes) to yield the title compound.

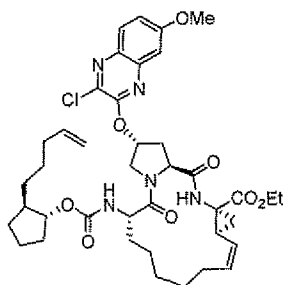
5 LRMS (ESI) m/z 786.5 [(M+H)⁺; calculated for C₃₉H₅₃ClN₅O₁₀ 786.4].

Step 5: Ethyl (2R,6S,12Z,13aS,14aR,16aS)-6-amino-2-[(3-chloro-7-methoxyquinoxalin-2-yl)oxy]-5,16-dioxo-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylate



10 To a solution of the product from step 4 (31 g, 39.4 mmol) in toluene (310 mL) was added benzenesulfonic acid (12.47 g, 79 mmol). The mixture was then heated to 75°C for 1 hour. The mixture was then cooled to RT and extracted with EtOAc/10% NaHCO₃. The organic layer was dried over MgSO₄, and concentrated *in vacuo*. The crude material was then used with no further purification in the next step. LRMS (ESI) m/z 586.4 [(M+H)⁺; calculated for C₂₉H₃₇ClN₅O₆ 586.3].

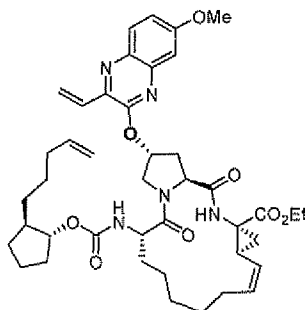
15 *Step 6: Ethyl (2R,6S,12Z,13aS,14aR,16aS)-2-[(3-chloro-7-methoxyquinoxalin-2-yl)oxy]-5,16-dioxo-6-[[[(1R,2R)-2-(pent-4-en-1-yl)cyclopentyl]oxy]carbonyl]amino]-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylate*



20 To a mixture of the product from step 5 (23.1 g, 39.4 mmol) in MeCN (250 mL) was added Et₃N (16.49 ml, 118 mmol) and Intermediate **D1** (13.4 g, 45.3 mmol) in MeCN (60 mL). The reaction mixture was stirred at 40°C for 30 minutes, and then extracted with

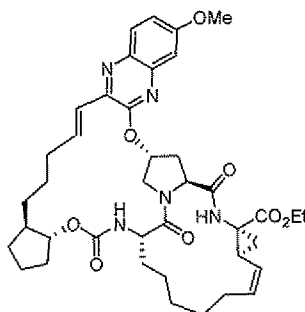
EtOAc and 5% KHSO₄. The aqueous layer was re-extracted aqueous with EtOAc. The combined organic layers were washed with brine, dried over MgSO₄, and concentrated *in vacuo*. The crude material was purified on SiO₂ (gradient elution, 0-70% EtOAc/hexanes) to give the title compound. LRMS (ESI) *m/z* 766.6 [(M+H)⁺; calculated for C₄₀H₅₃ClN₅O₈ 766.4].

- 5 *Step 7: Ethyl (2R,6S,12Z,13aS,14aR,16aS)-2-[(3-ethenyl-7-methoxyquinoxalin-2-yl)oxy]-5,16-dioxo-6-[[{[(1R,2R)-2-(pent-4-en-1-yl)cyclopentyl]oxy}carbonyl]amino]-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxylate*



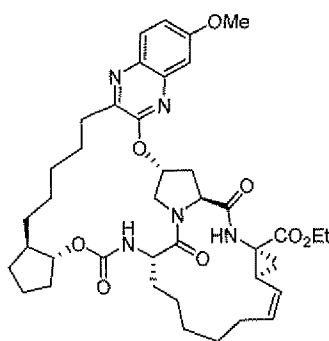
- 10 To a mixture of the product from step 6 (15 g, 19.57 mmol), CsF (6.5 g, 43.1 mmol), and BHT (0.216 g, 0.979 mmol) in dioxane (225 mL) under N₂ was added vinyltributyltin (8.6 ml, 29.4 mmol) and bis(tri-*t*-butylphosphine)palladium (0.5 g, 0.979 mmol). The mixture was heated to 70°C under N₂ for 1 hour, diluted with EtOAc, and filtered through CELITE. The filtrate was then concentrated *in vacuo* and purified on SiO₂ (gradient elution,
15 0-70% EtOAc/hexanes) to yield the title compound. LRMS (ESI) *m/z* 758.6 [(M+H)⁺; calculated for C₄₂H₅₆N₅O₈ 758.4].

- Step 8: Ethyl (3aR,7S,13Z,14aS,15aR,18S,21R,29E,33aR)-25-methoxy-5,17,35-trioxo-1,2,3,3a,5,6,7,8,9,10,11,12,14a,15,17,18,20,21,31,32,33,33a-docosahydro-7,19:18,21-dimethanocyclopenta[28,29]cyclopropa[12,13][1,20,3,14,17]dioxatriazacyclononacosino[21,22*
20 *-b]quinoxaline-15a(16H)-carboxylate*



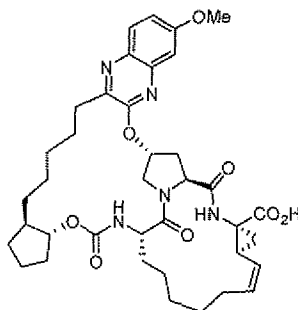
To a degassed solution of the product from step 7 (13.3 g, 17.55 mmol) in DCM (2.4 L) at reflux was added Zhan 1b catalyst (773 mg, 1.05 mmol) and benzoquinone (227 mg, 2.1 mmol) in three portions over 45 minutes. After 18 hours, the mixture was concentrated *in vacuo* and purified on SiO₂ (gradient elution, 0-75% EtOAc/hexanes) to yield the title compound. LRMS (ESI) *m/z* 730.6 [(M+H)⁺; calculated for C₄₀H₅₂N₅O₈ 730.4].

Step 9: Ethyl (3aR,7S,13Z,14aS,15aR,18S,21R,33aR)-25-methoxy-5,17,35-trioxo-1,2,3,3a,5,6,7,8,9,10,11,12,14a,15,17,18,20,21,29,30,31,32,33,33a-tetracosahydro-7,19:18,21-dimethanocyclopenta[28,29]cyclopropa[12,13][1,20,3,14,17]dioxatriazacyclononacosino[21,22-b]quinoxaline-15a(16H)-carboxylate



To a solution of the product from step 8 (16.8 g, 23.02 mmol) in EtOH (548 mL) was added bismuth(III)chloride (7.26 g, 23.02 mmol). The reaction was then cooled in an ice-salt bath to -17°C internal temperature. KBH₄ (12.4 g, 230 mmol) was then added in aliquots keeping the internal temperature < -10°C. The resulting black suspension was then slowly warmed to 0°C over 2 hours. The mixture was then diluted with EtOAc (500 mL), filtered through CELITE, and concentrated *in vacuo*. The residue was dissolved in EtOAc (300 mL), and H₂O (50 mL) was added. The pH was then adjusted with 0.5N HCl to pH <1. After separating the organic layer, the aqueous layer was washed with EtOAc. The combined organic layers were then extracted with NaHCO₃, washed with brine, dried over MgSO₄, and concentrated *in vacuo*. The crude material was then purified on SiO₂ (gradient elution, 0-60% EtOAc/hexanes) to yield the title compound. LRMS (ESI) *m/z* 732.6 [(M+H)⁺; calculated for C₄₀H₅₄N₅O₈ 732.4].

Step 10: (3aR,7S,13Z,14aS,15aR,18S,21R,33aR)-25-methoxy-5,17,35-trioxo-1,2,3,3a,5,6,7,8,9,10,11,12,14a,15,17,18,20,21,29,30,31,32,33,33a-tetracosahydro-7,19:18,21-dimethanocyclopenta[28,29]cyclopropa[12,13][1,20,3,14,17]dioxatriazacyclononacosino[21,22-b]quinoxaline-15a(16H)-carboxylic acid



5

To a solution of the product from step 9 (14.3 g, 19.54 mmol) in THF (200 mL), EtOH (50 mL), and H₂O (100 mL) was added LiOH (4.68 g, 195 mmol). The mixture was heated to 40°C for 4 hours, cooled to RT, and pH adjusted to 2 with 1N HCl. The resulting solid was collected by filtration, washed with H₂O, and combined with the material isolated from the extraction of the aqueous layer. The aqueous layer was then extracted with EtOAc two times. The combined organic layers were washed with brine, dried over MgSO₄, and concentrated *in vacuo*. The combined residues were then taken up in DCM and precipitated with Et₂O to give, after filtration, the title compound as a solid. LRMS (ESI) *m/z* 704.6 [(M+H)⁺; calculated for C₃₈H₅₀N₅O₈ 704.4].

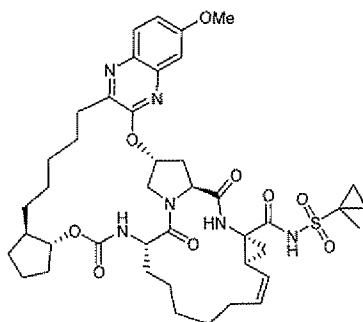
15 Step 11: (3R,20R,24R,28S,34Z,36S,38R,41S)-N-(Cyclopropylsulfonyl)-9-methoxy-26,40,42-trioxo-4,25-dioxa-1,6,13,27,39-pentaazaheptacyclo[26.13.1.1^{3,41}.0^{5,14}.0^{7,12}.0^{20,24}.0^{36,38}]tritetraconta-5,7,9,11,13,34-hexaene-38-carboxamide

To a mixture of the product from step 10 (460 mg, 0.654 mmol) in THF (22 mL) was added CDI (318 mg, 1.96 mol), and the resulting mixture was heated to 50°C for 2 hours. Intermediate **B1** (475 mg, 3.92 mmol) and DBU (0.59 mL, 3.92 mmol) were then added, and stirring was continued for 1 hours. The reaction was then cooled to RT and extracted with EtOAc and 0.5M HCl. The organic layer was washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The crude material was then purified on SiO₂ (gradient elution, 0-25% acetone/DCM), and then titrated with DCM. The mother liquors were then concentrated *in vacuo* to yield the title compound. LRMS (ESI) *m/z* 807.8 [(M+H)⁺; calculated for C₄₁H₅₅N₆O₉S 807.4].

25

EXAMPLE 2

(3R,20R,24R,28S,34Z,36S,38R,41S)-9-Methoxy-N-[(1-methylcyclopropyl)sulfonyl]-26,40,42-trioxo-4,25-dioxa-1,6,13,27,39-pentaazaheptacyclo[26.13.1.1^{3,41}.0^{5,14}.0^{7,12}.0^{20,24}.0^{36,38}]tritetraconta-5,7,9,11,13,34-hexaene-38-carboxamide



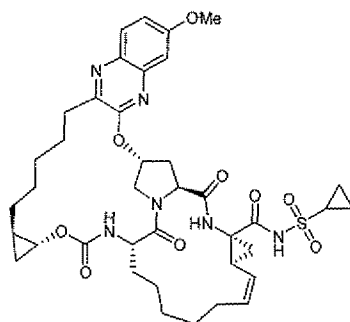
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To a mixture of the product from Example 1, step 10 (5.4 g, 7.67 mmol) in THF (96 mL) was added CDI (1.74 g, 10.74 mmol), and the resulting mixture was heated to 40°C for 30 minutes. Intermediate **B2** (1.56 g, 11.51 mmol) and DBU (2.3 mL, 15.34 mmol) were then added, and stirring was continued for 20 hours. The reaction was then cooled to RT and
 10 extracted with EtOAc and 5% KHSO₄. The organic layer was washed with NaHCO₃ and brine, dried over MgSO₄, and concentrated *in vacuo*. The crude material was then purified on SiO₂ (gradient elution, 0-30% acetone/DCM). The resulting material was then dissolved in 30% EtOAc/hexanes at 35 mL/g and stirred 18 hours. The resulting solid was collected and dried *in vacuo* to yield the title compound LRMS (ESI) *m/z* 821.6 [(M+H)⁺; calculated for C₄₂H₅₇N₆O₉S
 15 821.4].

EXAMPLE 3

(3R,20R,22R,26S,32Z,34S,36R,39S)-N-(Cyclopropylsulfonyl)-9-methoxy-24,38,40-trioxo-4,23-dioxa-1,6,13,25,37-pentaazaheptacyclo[24.13.1.1^{3,39}.0^{5,14}.0^{7,12}.0^{20,22}.0^{34,36}]hentetraconta-5,7,9,11,13,32-hexaene-36-carboxamide

20

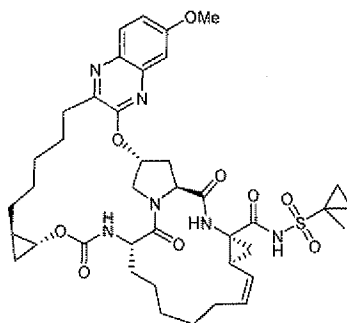


The title compound can be prepared according to the procedures in Example 1 using Intermediate **D2** in step 6. LRMS (ESI) m/z 779.4 [(M+H)⁺; calculated for C₃₉H₅₁N₆O₉S 779.4].

5

EXAMPLE 4

(3*R*,20*R*,22*R*,26*S*,32*Z*,34*S*,36*R*,39*S*)-9-Methoxy-*N*-[(1-methylcyclopropyl)sulfonyl]-24,38,40-trioxo-4,23-dioxa-1,6,13,25,37-pentaazaheptacyclo[24.13.1.1^{3,39}.0^{5,14}.0^{7,12}.0^{20,22}.0^{34,36}]hentetraconta-5,7,9,11,13,32-hexaene-36-carboxamide

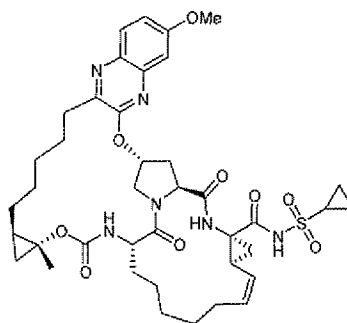


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The title compound can be prepared according to the procedures in Example 1 using Intermediates **D2** and **B2** in steps 6 and 11, respectively. LRMS (ESI) m/z 793.6 [(M+H)⁺; calculated for C₄₀H₅₃N₆O₉S 793.4].

EXAMPLE 5

15 (3*R*,20*R*,22*R*,26*S*,32*Z*,34*S*,36*R*,39*S*)-*N*-(Cyclopropylsulfonyl)-9-methoxy-22-methyl-24,38,40-trioxo-4,23-dioxa-1,6,13,25,37-pentaazaheptacyclo[24.13.1.1^{3,39}.0^{5,14}.0^{7,12}.0^{20,22}.0^{34,36}]hentetraconta-5,7,9,11,13,32-hexaene-36-carboxamide

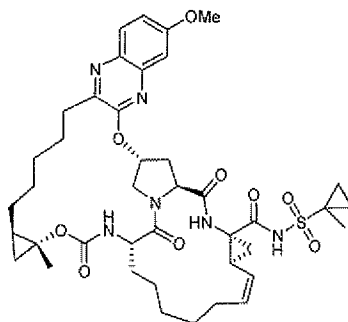


20

The title compound can be prepared according to the procedures in Example 1 using Intermediate **D3** in step 6. LRMS (ESI) m/z 793.6 [(M+H)⁺; calculated for C₄₀H₅₃N₆O₉S 793.4].

EXAMPLE 6

(3R,20R,22R,26S,32Z,34S,36R,39S)-9-Methoxy-22-methyl-N-[(1-methylcyclopropyl)sulfonyl]-24,38,40-trioxo-4,23-dioxo-1,6,13,25,37-pentaazaheptacyclo[24.13.1.1^{3,39}.0^{5,14}.0^{7,12}.0^{20,22}.0^{34,36}]
 5 hentetraconta-5,7,9,11,13,32-hexaene-36-carboxamide

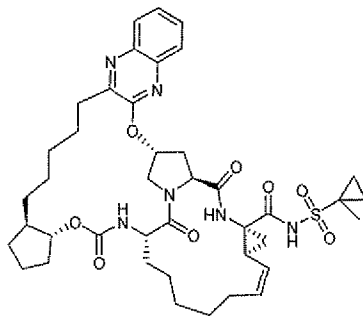


The title compound can be prepared according to the procedures in Example 1 using Intermediates **D3** and **B2** in steps 6 and 11, respectively. LRMS (ESI) m/z 807.6 [(M+H)⁺; calculated for C₄₁H₅₅N₆O₉S 807.4].

10

EXAMPLE 7

(3R,20R,24R,28S,34Z,36S,38R,41S)-N-[(1-Methylcyclopropyl)sulfonyl]-26,40,42-trioxo-4,25-dioxo-1,6,13,27,39-pentaazaheptacyclo[26.13.1.1^{3,41}.0^{5,14}.0^{7,12}.0^{20,24}.0^{36,38}]
 15 tritetraconta-5,7,9,11,13,34-hexaene-38-carboxamide

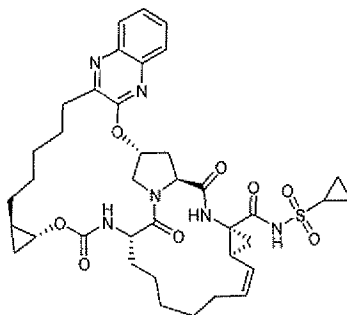


15

The title compound can be prepared according to the procedures in Example 1 using Intermediates **E2** and **B2** in steps 1 and 11, respectively. LRMS (ESI) m/z 791.5 [(M+H)⁺; calculated for C₄₁H₅₅N₆O₈S 791.4].

EXAMPLE 8

(3*R*,20*R*,22*R*,26*S*,32*Z*,34*S*,36*R*,39*S*)-*N*-(Cyclopropylsulfonyl)-24,38,40-trioxo-4,23-dioxo-1,6,13,25,37-pentaazaheptacyclo[24.13.1.1^{3,39}.0^{5,14}.0^{7,12}.0^{20,22}.0^{34,36}]hentetraconta-5,7,9,11,13,32-hexaene-36-carboxamide



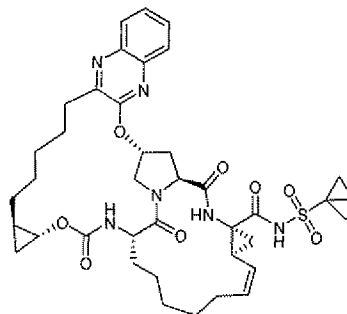
5

The title compound can be prepared according to the procedures in Example 1 using Intermediates **E2** and **D2** in steps 1 and 6, respectively. LRMS (ESI) m/z 749.5 [(M+H)⁺; calculated for C₃₈H₄₉N₆O₈S 749.4].

10

EXAMPLE 9

(3*R*,20*R*,22*R*,26*S*,32*Z*,34*S*,36*R*,39*S*)-*N*-[(1-Methylcyclopropyl)sulfonyl]-24,38,40-trioxo-4,23-dioxo-1,6,13,25,37-pentaazaheptacyclo[24.13.1.1^{3,39}.0^{5,14}.0^{7,12}.0^{20,22}.0^{34,36}]hentetraconta-5,7,9,11,13,32-hexaene-36-carboxamide

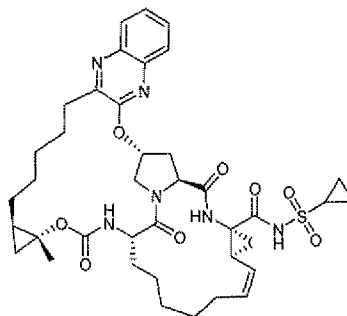


15

The title compound can be prepared according to the procedures in Example 1 using Intermediates **E2**, **D2**, and **B2** in steps 1, 6 and 11, respectively. LRMS (ESI) m/z 763.5 [(M+H)⁺; calculated for C₃₉H₅₁N₆O₈S 763.4].

EXAMPLE 10

(3R,20R,22R,26S,32Z,34S,36R,39S)-N-(Cyclopropylsulfonyl)-22-methyl-24,38,40-trioxo-4,23-dioxa-1,6,13,25,37-pentaazaheptacyclo[24.13.1.1^{3,39}.0^{5,14}.0^{7,12}.0^{20,22}.0^{34,36}]hentetraconta-5,7,9,11,13,32-hexaene-36-carboxamide



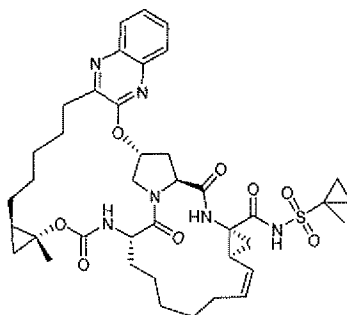
5

The title compound can be prepared according to the procedures in Example 1 using Intermediates **E2** and **D3** in steps 1 and 6, respectively. LRMS (ESI) m/z 763.5 [(M+H)⁺; calculated for C₃₉H₅₁N₆O₈S 763.4].

10

EXAMPLE 11

(3R,20R,22R,26S,32Z,34S,36R,39S)-22-Methyl-N-[(1-methylcyclopropyl)sulfonyl]-24,38,40-trioxo-4,23-dioxa-1,6,13,25,37-pentaazaheptacyclo[24.13.1.1^{3,39}.0^{5,14}.0^{7,12}.0^{20,22}.0^{34,36}]hentetraconta-5,7,9,11,13,32-hexaene-36-carboxamide



15

The title compound can be prepared according to the procedures in Example 1 using Intermediates **E2**, **D3**, and **B2** in steps 1, 6 and 11, respectively. LRMS (ESI) m/z 777.5 [(M+H)⁺; calculated for C₄₀H₅₃N₆O₈S 777.4].

EXAMPLE 1220 Comparison of Different Compounds

The compounds of Examples 1 through 11 were compared to the compound of Example 18 of WO 2008/057208. The results are shown in Tables 1 and 2 below. As illustrated

in the tables and the discussion of the results, compounds of Formula I, as illustrated by the compounds of Examples 1 through 11, appear to have several advantageous properties compared to the compound of Example 18 of WO 2008/057208.

The activity tables provided below illustrates the observed activity:

5 **Table 1: NS3/4A Inhibitory Activity (K_i)**

Compound	Enzyme Activity (nM)		
	gt 1b K _i	gt 1b A156V K _i	gt 3a K _i
WO 2008/057208 Example 18	0.85	8.7	1.88
Example 1	0.16	1.6	0.45
Example 2	0.05	1.1	0.48
Example 3	0.02	0.8	0.24
Example 4	0.04	0.6	0.27
Example 5	0.02	0.7	0.25
Example 6	0.03	0.6	0.32
Example 7	0.02	1.2	0.72
Example 8	0.02	0.9	0.49
Example 9	0.03	0.8	0.52
Example 10	0.02	0.6	0.35
Example 11	0.02	0.5	0.37

K_i: Inhibition constant; gt: Genotype.

Table 2: Compound Inhibitory Potency (Replicon (nM)) and In-Vivo Covalent Binding

Compound	gt 1b Replicon EC ₅₀ (nM)		Rat PK	
	10% FBS	50% NHS	5 mpk [liver] 4 h (nM)	5 mpk AUC (nMh)
WO 2008/057208 Example 18	4	22	Not Available	Not Available
Example 1	2	9	3600	0
Example 2	2	10	43000	0.55
Example 3	2	8	13000	0.19
Example 4	2	4	19000	0.1
Example 5	1	6	20000	0.18
Example 6	1	4	24000	0.16
Example 7	2	10	41000	1.35
Example 8	1	13	7000	0.06
Example 9	2	11	20000	0.26
Example 10	1	5	15000	0.6
Example 11	1	5	4000	0.07

EC₅₀: Effective concentration achieving 50% viral replication suppression; FBS: fetal bovine serum; NHS: normal human serum; AUC: Area under the plasma concentration/time curve.

Methods

Compounds described herein were analyzed 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).

Measuring NS3/4A Inhibitory Activity (K_i)

Compounds were analyzed using the HCV NS3 protease time-resolved fluorescence (TRF) assay as described below and in Shi-Shan Mao *et al.*, *A time-resolved, internally quenched fluorescence assay to characterize inhibition of hepatitis C virus nonstructural protein 3-4A protease at low enzyme concentrations*, 373 ANALYTICAL BIOCHEMISTRY 1 (2008), and WO 2006/102087. This NS3 protease assay was performed in a final volume of 100 μ l 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. NS3/4A protease was pre-incubated with various concentrations of inhibitors in DMSO for 30 minutes. The reaction was initiated by adding the TRF peptide substrate (final concentration 100 nM). NS3 mediated hydrolysis of the substrate was quenched after 1 hour at RT with 100 μ l of 500 mM MES, pH 5.5. Product fluorescence was 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 μ s delay. Testing concentrations of different enzyme forms were selected to result in a signal to background ratio (S/B) of 10-30. IC_{50} values were derived using a standard four-parameter fit to the data. K_i values are derived from IC_{50} values using the following formula,

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

where [S] is the concentration of substrate peptide in the reaction and K_M is the Michaelis constant. See Paola Gallinari *et al.*, *Modulation of Hepatitis C Virus NS3 Protease and Helicase Activities through the Interaction with NS4A*, 38 BIOCHEM. 5620 (1999); Paola Gallinari *et al.*, *Multiple Enzymatic Activities Associated with Recombinant NS3 Protein of Hepatitis C Virus*, 72(8) J. VIROLOGY 6758 (1998); Mariana Taliani *et al.*, *A Continuous Assay of Hepatitis C Virus Protease Based on Resonance Energy Transfer Depsipeptide Substrates*, 240 ANAL. BIOCHEM. 60 (1996); Shi-Shan Mao *et al.*, *A time-resolved, internally quenched fluorescence assay to*

characterize inhibition of hepatitis C virus nonstructural protein 3-4A protease at low enzyme concentrations, 373 ANALYTICAL BIOCHEMISTRY 1 (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 replicon-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:NEO 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 to 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.

Plasma and Liver Concentrations and Pharmacokinetics

Test compounds were dissolved in a suitable dosing vehicle for i.v. administration (*e.g.*, 20%:60%:20% DMSO:PEG400:H₂O) or per oral administration (*e.g.*, 10% POLYSORBATE80: 90% H₂O or 100% PEG400). Animals were administered (n = 2 or 3) using a crossover study design for non-rodents. Plasma samples were collected at time points between 2 minutes and 24 hours, and compound levels were determined by RP-LC/MS/MS. Liver samples were collected post-mortem in rat. Liver samples were weighed, homogenized, and

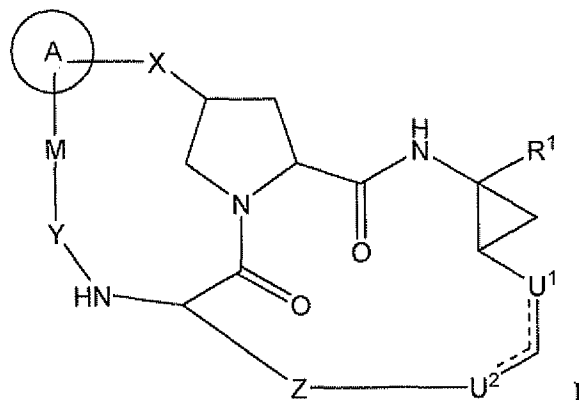
diluted using techniques known to those skilled in the art, and compound levels were determined by RP-LC/MS/MS.

Pharmacokinetic parameters were calculated based on non-compartmental analysis (*e.g.*, using WATSON, WINNOLIN). Predose concentrations that were below the limit of quantitation (BLQ) were assigned a value of 0. Standard pharmacokinetic parameters CL_p , V_{dss} , half-life (only for IV), % F, C_{max} , T_{max} , AUC_{0-last} , $AUC_{0-infinity}$ were calculated. AUC values were calculated using linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations.

10 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 various presently unforeseen or unanticipated alternatives, modifications, variations or improvements on the above-described and herein claimed subject matter may be subsequently made by those skilled in the art and are also intended to be encompassed by the
15 following claims.

WHAT IS CLAIMED IS:

1. A compound of Formula I:



- 5 or a pharmaceutically acceptable salt, solvate or hydrate thereof, wherein:



is selected from the group of rings consisting of:

- 1) an aryl,
- 2) a C₃-C₈ cycloalkyl; and
- 3) a heterocyclic ring system selected from the group consisting of:
 - 10 a) a 5- or 6-membered saturated or unsaturated monocyclic ring with 1, 2, or 3 heteroatom ring atoms each independently selected from the group consisting of N, O or S,
 - b) a 8-, 9- or 10-membered saturated or unsaturated bicyclic ring with 1, 2, or 3 heteroatom ring atoms each independently selected from the group consisting of N, O or S, and
 - 15 c) a 11- to 15-membered saturated or unsaturated tricyclic ring with 1, 2, 3, or 4 heteroatom ring atoms each independently selected from the group consisting of N, O or S,

wherein:

- 20 i) said aryl or cycloalkyl ring has from 0 to 4 independently substituted R²,
- ii) said heterocyclic ring has from 0 to 4 independently selected R² substitutions, and

iii) points of attachment to variables M and X are

independently selected from a first pair of atoms comprising a first carbon ring atom and second carbon ring atom, and a second pair of atoms comprising a carbon ring atom and a nitrogen ring atom;

5 R^1 is selected from the group consisting of CO_2R^3 , $CONR^3SO_2R^4$, $CONR^3SO_2NR^5R^6$, tetrazolyl, $CONHP(O)R^7R^8$, and $P(O)R^7R^8$;

R^2 selected from the group consisting of H, halo, OR^3 , $C(O)R^3$, CO_2R^3 , C_1-C_6 alkyl, CN, CF_3 , SR^3 , $SO_2(C_1-C_6$ alkyl), C_3-C_8 cycloalkyl, C_3-C_8 cycloalkoxy, C_1-C_6 haloalkyl, $N(R^9)_2$, oxo, phenyl, naphthyl, Het A and Het B,

10 wherein said R^2 phenyl, naphthyl, Het A, Het B, cycloalkyl, cycloalkoxy, alkyl or alkoxy is substituted with from 0 to 4 substituents selected from the group consisting of halo, OR^3 , SR^3 , $N(R^9)_2$, $N(C_1-C_6$ alkyl)(C_1-C_6 alkoxy), C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkoxy, NO_2 , CN, CF_3 , $SO_2(C_1-C_6$ alkyl), $NR^3SO_2R^4$, $SO_2N(R^4)_2$, $S(O)(C_1-C_6$ alkyl), $NHC(O)OR^4$, $NHC(O)R^4$, $NHC(O)NHR^4$, CO_2R^3 , $C(O)R^3$, and
15 $C(O)N(R^3)_2$,

wherein 2 adjacent substituents of said R^2 cycloalkyl, cycloalkoxy, phenyl, naphthyl, Het A or Het B are optionally taken together to form a 3- to 6-membered cyclic ring containing from 0 to 3 heteroatoms selected from N, O and S, and

20 wherein any R^2 oxo substituent, if present, is located on a carbon or sulfur ring atom;

Het A is a 5- or 6-membered aromatic ring having 1, 2 or 3 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen;

Het B is a 5- to 7-membered saturated or unsaturated non-aromatic ring having 1, 2, 3 or 4 heteroatoms selected from N, O and S, attached through a ring carbon or nitrogen;

25 each R^3 is independently selected from the group consisting of H, C_1-C_6 alkyl, phenyl and naphthyl;

each R^4 is independently selected from the group consisting of 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), Het A, Het A(C_1-C_4 alkyl), Het B, and Het B(C_1-C_8 alkyl), wherein said
30 R^4 alkyl, cycloalkyl, phenyl, naphthyl, Het A and Het B is substituted with from 0 to 2 W substituents;

each R^5 is independently selected from the group consisting of 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), Het A, Het A(C_1 - C_4 alkyl), Het B, and Het B(C_1 - C_8 alkyl),

wherein said R^5 alkyl, cycloalkyl, phenyl, naphthyl, phenyl(C_1 - C_4 alkyl), naphthyl(C_1 - C_4 alkyl), Het A, or Het B is substituted with from 0 to 4 substituents selected from the group consisting of phenyl, naphthyl, C_3 - C_8 cycloalkyl, Het A, Het B, C_1 - C_6 alkyl, C_1 - C_6 haloalkoxy, halo, OR^3 , SR^3 , $N(R^3)_2$, $N(C_1$ - C_6 alkyl)(C_1 - C_6 alkoxy), C_1 - C_6 alkyl, $C(O)R^3$, C_1 - C_6 haloalkyl, NO_2 , CN, CF_3 , $SO_2(C_1$ - C_6 alkyl), $S(O)(C_1$ - C_6 alkyl), $NR^3SO_2R^4$, $SO_2N(R^4)_2$, $NHC(O)OR^4$, $NHC(O)R^4$, $NHC(O)NHR^4$, CO_2R^3 , and $C(O)N(R^3)_2$, and

wherein 2 adjacent substituents of said R^5 cycloalkyl, cycloalkoxy, aryl, heteroaryl or heterocyclyl are optionally taken together to form a 3- to 6-membered cyclic ring containing from 0 to 3 heteroatoms selected from N, O and S;

each R^6 is independently selected from the group consisting of 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), Het A, Het A(C_1 - C_4 alkyl), Het B, and Het B(C_1 - C_8 alkyl),

wherein said R^6 alkyl, cycloalkyl, alkoxy, cycloalkoxy, phenyl, naphthyl, Het A and Het B is substituted with from 0 to 4 substituents selected from the group consisting of phenyl, naphthyl, Het A, Het B, C_3 - C_8 cycloalkyl, C_1 - C_6 alkyl, C_1 - C_6 haloalkoxy, halo, OR^3 , SR^3 , $N(R^3)_2$, $N(C_1$ - C_6 alkyl)(C_1 - C_6 alkoxy), C_1 - C_6 alkyl, $C(O)R^3$, C_1 - C_6 haloalkyl, NO_2 , CN, CF_3 , $SO_2(C_1$ - C_6 alkyl), $S(O)(C_1$ - C_6 alkyl), $NR^3SO_2R^4$, $SO_2N(R^4)_2$, $NHC(O)OR^4$, $NHC(O)R^4$, $NHC(O)NHR^4$, CO_2R^3 , and $C(O)N(R^3)_2$; and

wherein 2 adjacent substituents of said R^6 cycloalkyl, cycloalkoxy, aryl, heteroaryl or heterocyclyl are optionally taken together to form a 3- to 6-membered cyclic ring containing from 0 to 3 heteroatoms selected from N, O and S;

or R^5 and R^6 are optionally taken together, with the nitrogen atom to which they are attached, to form a 4- to 8-membered monocyclic ring containing from 0 to 2 additional heteroatoms selected from N, O and S;

each R^7 is independently selected from the group consisting of OR^{14} , $N(R^3)$ -V- CO_2R^3 , O-V- CO_2R^3 , S-V- CO_2R^3 , $N(R^3)(R^{10})$, R^{11} , and $N(R^3)SO_2R^4$;

each R^8 is independently selected from the group consisting of OR^{14} , $N(R^3)$ -V- CO_2R^3 , O-V- CO_2R^3 , S-V- CO_2R^3 , and $N(R^3)(R^{10})$;

or R⁷ and R⁸ are optionally taken together, with the phosphorus atom to which they are attached, to form a 5- to 7-membered monocyclic ring;

each R⁹ is independently selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₃-C₆ cycloalkyl(C₁-C₅alkyl), phenyl, naphthyl, phenyl(C₁-C₄ alkyl), naphthyl(C₁-C₄ alkyl), Het A, Het A(C₁-C₄ alkyl), Het B, and Het B(C₁-C₈ alkyl), wherein said R⁹ alkyl, cycloalkyl, phenyl, naphthyl, Het A or Het B is substituted with from 0 to 2 W substituents;

each V is independently selected from the group consisting of -CH(R¹²)- and -C₁-C₄ alkylene-CH(R¹²)-;

each R¹⁰ is independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₃-C₈ cycloalkyl, phenyl, naphthyl, Het A and Het B,

wherein said R¹⁰ alkyl, alkenyl, cycloalkyl, phenyl, naphthyl, Het A or Het B is substituted with from 0 to 2 substituents selected from the group consisting of phenyl, naphthyl, phenyl(C₁-C₄ alkyl), naphthyl(C₁-C₄ alkyl), Het A, Het A(C₁-C₄ alkyl), Het B, Het B(C₁-C₈ alkyl), C₁-C₆ alkyl, halo, OC(O)OR⁴, OC(O)R⁴, OR³, SR³, N(R³)₂, C(O)R³, NO₂, CN, CF₃, SO₂(C₁-C₆ alkyl), S(O)(C₁-C₆ alkyl), NR³SO₂R⁴, SO₂N(R⁴)₂, NHC(O)OR⁴, NHC(O)R⁴, NHC(O)NHR⁴, CO₂R³, and C(O)N(R³)₂; and

wherein 2 adjacent substituents of said R¹⁰ cycloalkyl, cycloalkoxy, phenyl, naphthyl, Het A or Het B are optionally taken together to form a 3- to 6-membered cyclic ring containing from 0 to 3 heteroatoms selected from N, O and S;

each R¹¹ is independently selected from the group consisting of C₁-C₆ alkyl, C₂-C₆ alkenyl, phenyl, naphthyl, and Het A, wherein said R¹¹ phenyl, naphthyl, or Het A is substituted with from 0 to 2 substituents selected from the group consisting of C₁-C₆ alkyl, halo, OC(O)OR⁴, OC(O)R⁴, OR³, SR³, N(R³)₂, C(O)R³, NO₂, CN, CF₃, SO₂(C₁-C₆ alkyl), S(O)(C₁-C₆ alkyl), NR³SO₂R⁴, SO₂N(R⁴)₂, NHC(O)OR⁴, NHC(O)R⁴, NHC(O)NHR⁴, CO₂R³, and C(O)N(R³)₂;

each R¹² is independently selected from the group consisting of C₁-C₆ alkyl, C₂-C₆ alkenyl, C₃-C₈ cycloalkyl, phenyl, naphthyl, Het A and Het B,

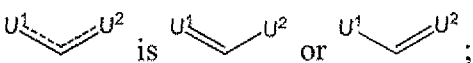
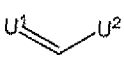
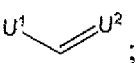
wherein said R¹² alkyl, alkenyl, cycloalkyl, phenyl, naphthyl, Het A or Het B is substituted with from 0 to 2 substituents selected from the group consisting of C₁-C₆ alkyl, halo, OC(O)OR⁴, OC(O)R⁴, OR³, SR³, N(R³)₂, C(O)R³, NO₂, CN, CF₃, SO₂(C₁-C₆ alkyl),

S(O)(C₁-C₆ alkyl), NR³SO₂R⁴, SO₂N(R⁴)₂, NHC(O)OR⁴, NHC(O)R⁴, NHC(O)NHR⁴, CO₂R³, and C(O)N(R³)₂; and

wherein 2 adjacent substituents of said R¹² cycloalkyl, cycloalkoxy, phenyl, naphthyl, Het A or Het B are optionally taken together to form a 3- to 6-membered cyclic ring containing from 0 to 3 heteroatoms selected from N, O and S;

each W is independently selected from the group consisting of halo, OR³, C₁-C₆ alkyl, CN, CF₃, NO₂, SR³, CO₂R³, CON(R³)₂, C(O)R³, N(R³)C(O)R³, SO₂(C₁-C₆ alkyl), S(O)(C₁-C₆ alkyl), C₃-C₈ cycloalkyl, C₃-C₈ cycloalkoxy, C₁-C₆ haloalkyl, N(R³)₂, N(C₁-C₆ alkyl)O(C₁-C₆ alkyl), halo(C₁-C₆ alkoxy), NR³SO₂R³, SO₂N(R³)₂, NHCOOR³, NHCONHR³, phenyl, naphthyl, Het A and Het B;

Z is selected from the group consisting of C₃-C₉ alkylene having from 0 to 3 substituents independently selected from C₁-C₆ alkyl, where 2 said alkyl substituents are optionally taken together to form a spiro or fused ring containing the substituent atoms and shared atom or atoms;

15  is  or  ;

X is selected from the group consisting of:

- 1) -C_{0,5} alkylene-X¹-,
- 2) -C_{2,5} alkenylene-X¹-, and
- 3) -C_{2,5} alkynylene-X¹-,

20 wherein X¹ is selected from the group consisting of -O-, -NH-, -CH₂-, -C(O)O-, -C(O)NR¹³- or -NR¹³C(O)O-, and wherein alkylene, alkenylene and alkynylene is unsubstituted or substituted with from 0 to 3 C₁-C₆ alkyl, wherein:

R¹³ is selected from the group consisting of H and C₁-C₆ alkyl;

25 Y is selected from the group consisting of -OC(O)-, -NR¹⁴C(O)-, -C(O)- and -NHSO₂-, wherein R¹⁴ is C_{1,6} alkyl; and


M is selected from the group consisting of C₁-C₁₂ alkylenes, C₂-C₁₂ alkenylenes and C₂-C₁₂ alkynylenes, wherein:

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

said M is substituted with from 0 to 4 substituents R¹⁵, wherein:

each R¹⁵ is independently selected from the group consisting of C₁-C₈ alkyl, =CH₂, C₃-C₈ cycloalkyl(C₁-C₈ alkyl), phenyl(C₁-C₈ alkyl) and naphthyl(C₁-C₈ alkyl), and


any substituent R¹⁵ may be taken together with any adjacent substituent R¹⁵ or any adjacent substituent R¹⁴ to form a 3- to 6-membered ring containing 0 to 3 heteroatoms independently selected from the group consisting of N, O and S.

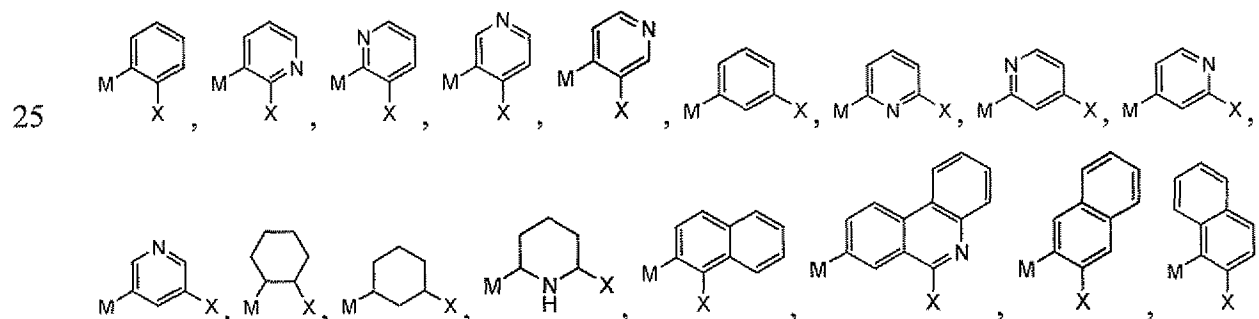
2. The compound according to claim 1, wherein  is selected from the group consisting of:

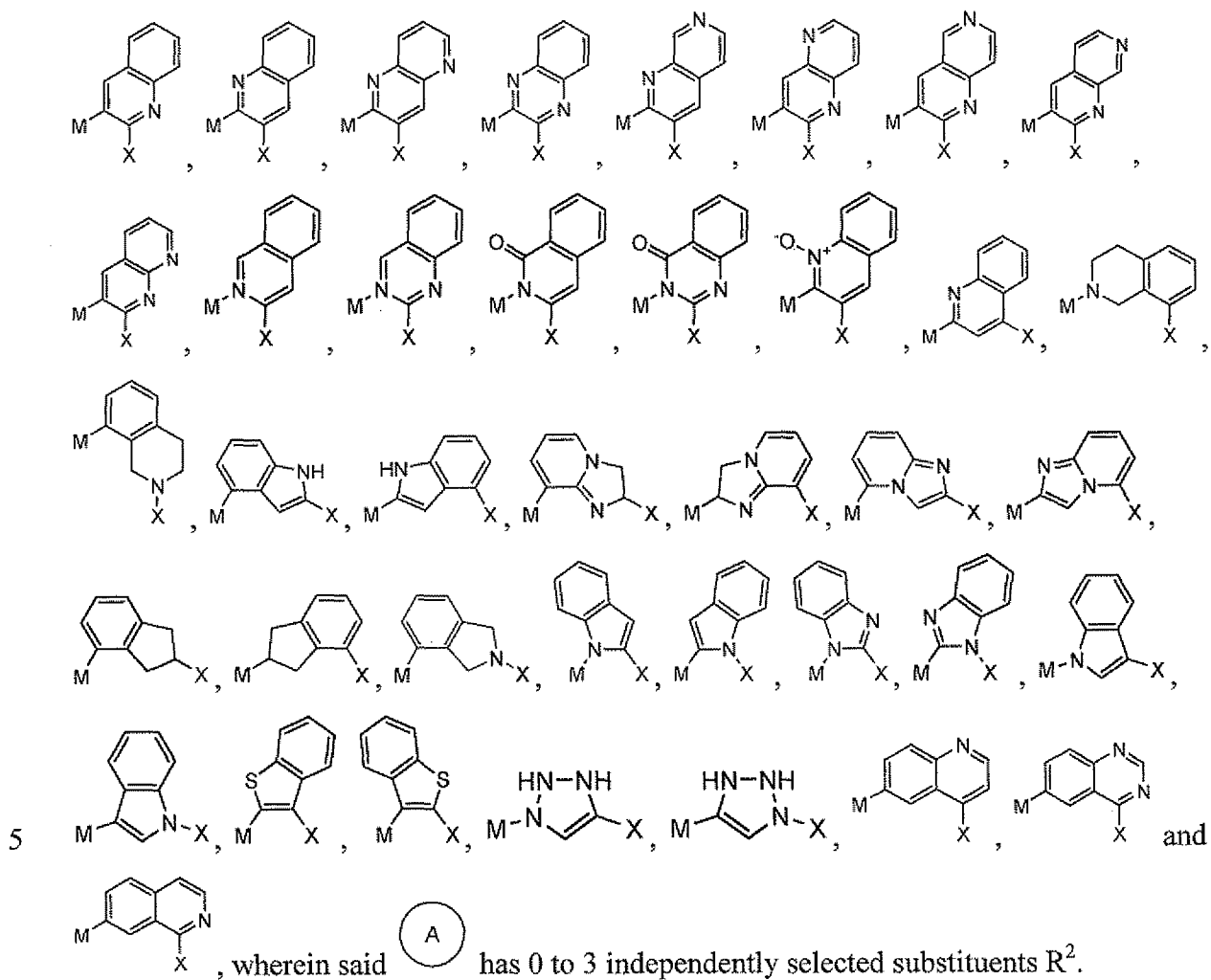
- 10 1) an aryl,
 2) a cyclohexyl, and
 3) a heterocyclic ring system selected from the group consisting of:
 a) a 5- or 6-membered saturated or unsaturated monocyclic ring containing 1, 2, or 3 nitrogen atoms, and
 b) a 8-, 9- or 10-membered saturated or unsaturated bicyclic ring containing 1 or 2 nitrogen atoms,

wherein:

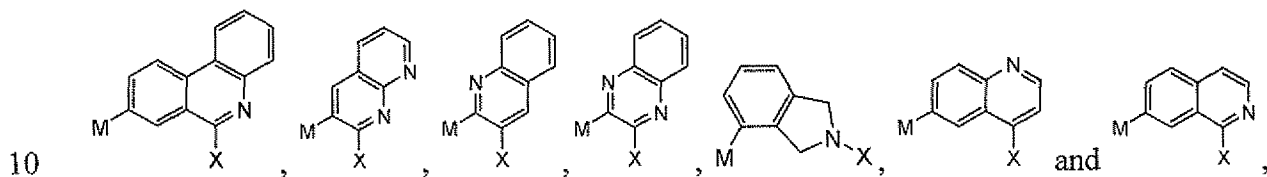
- 15 1) said aryl or cyclohexyl has from 0 to 4 independently selected substituents R², and
 2) said heterocyclic ring has from 0 to 4 independently selected R² substitutions.
- 20

3. The compound according to claim 1, wherein  is selected from the group consisting of:



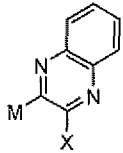


4. The compound according to claim 3, wherein said \textcircled{A} is selected from the group consisting of:



wherein said \textcircled{A} has 0 to 3 independently selected substituents R^2 .

5. The compound according to claim 4, wherein said $\text{\textcircled{A}}$ is selected from

the group consisting of  having from 0 to 2 independently selected substituents R^2 .

6. The compound according to any one of claims 1-5, wherein $\text{\textcircled{A}}$ is substituted by from 0 to 1 R^2 , wherein R^2 is selected from the group consisting of -Br, -Cl, -CN, phenyl, -O-phenyl, -OCF₃, -OCH₃, -C(O)OH, -CH₃ and -C(O)CH₃.

7. The compound according to any one of claims 1-6, wherein X is selected from the group consisting of -C₀₋₅ alkylene-O- and -C₀₋₃ alkylene-C(O)O-.

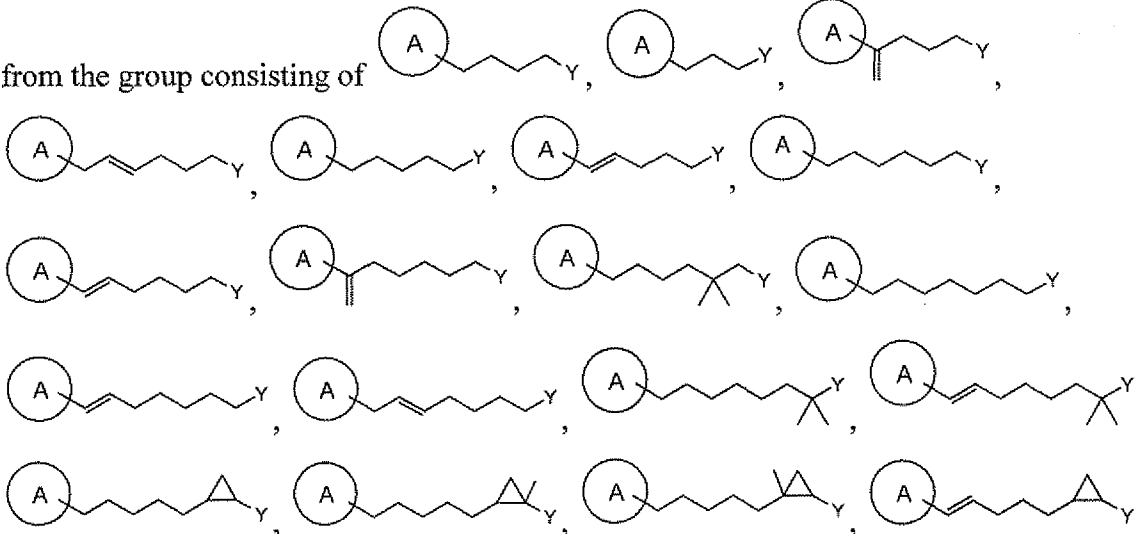
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8. The compound according to claim 7, wherein X is selected from the group consisting of -O- and -C(O)O-.

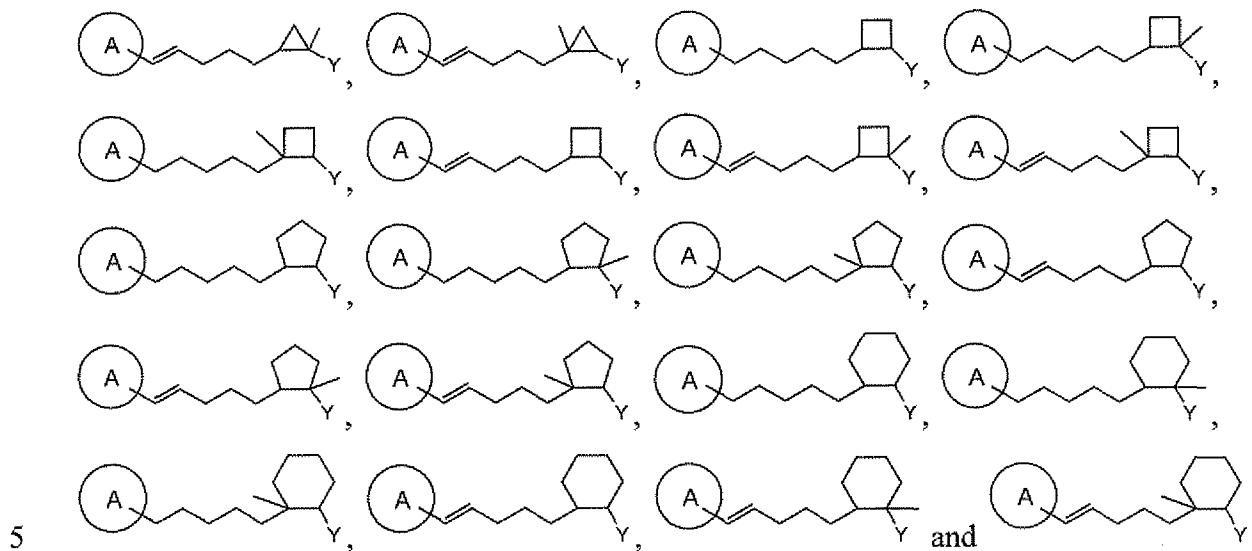
9. The compound according any one of claims 1-8, wherein Y is selected from the group consisting of -OC(O)- and -C(O)-.

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10. The compound according to any one of claims 1-9, wherein M is selected

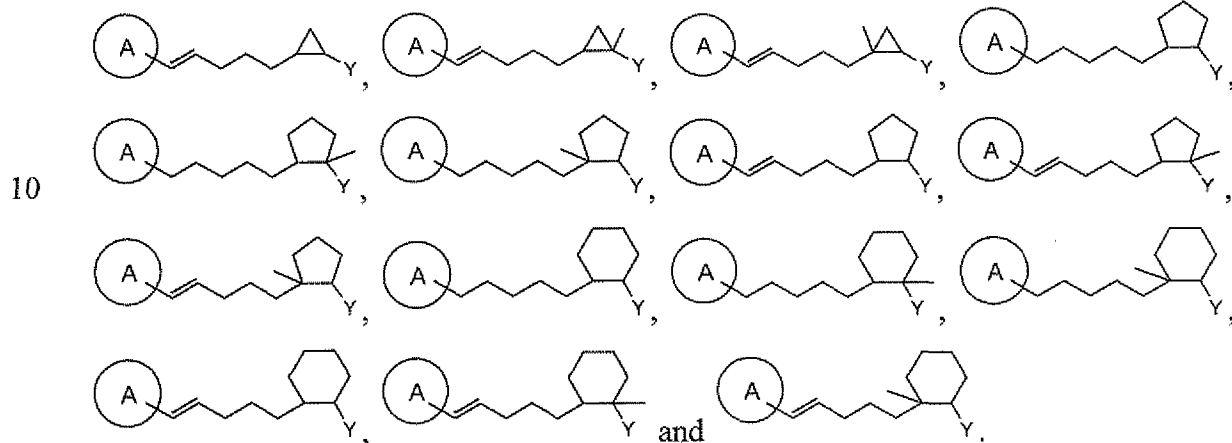
from the group consisting of 

20



11. The compound according to claim 10, wherein M is selected from the

group consisting of

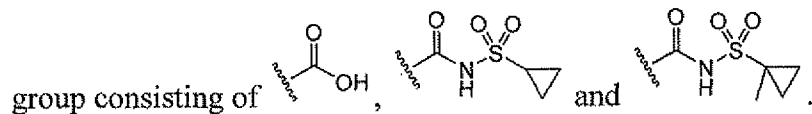


12. The compound according to any one of claims 1-11, wherein Z is $-(CH_2)_4-$

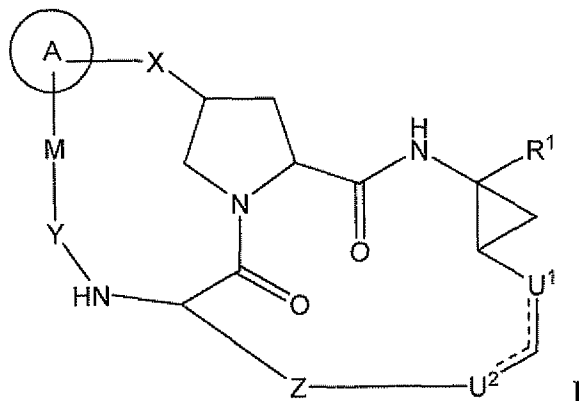
15 .

13. The compound according to any one of claims 1-12, wherein R^1 is selected from the group consisting of $-CO_2R^3$ and $-CONR^3SO_2R^6$.

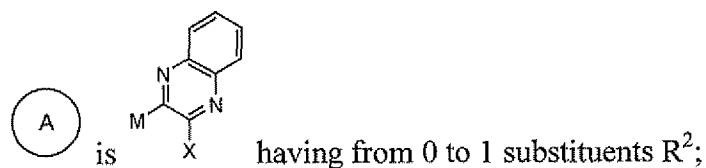
14. The compound according to claim 13, wherein R¹ is selected from the



15. The compound according to claim 1, wherein the compound is a
5 compound of Formula I:



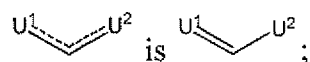
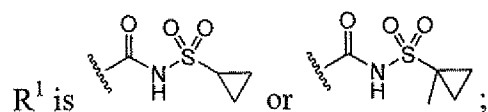
or a pharmaceutically acceptable salt, hydrate or prodrug thereof, wherein:



R² is -OR³;

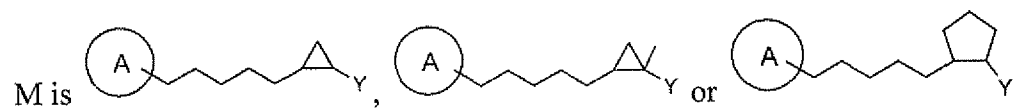
10 R³ is methyl;

X is -O-;

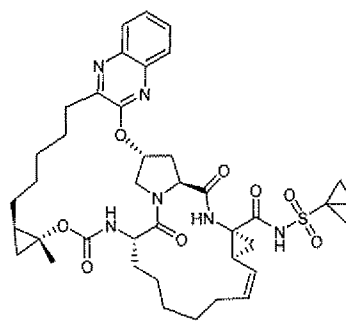
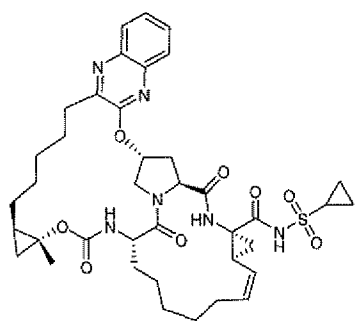
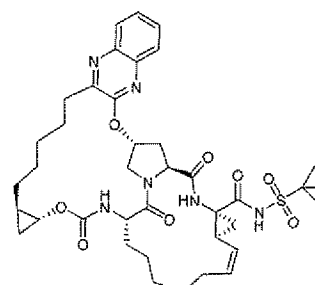
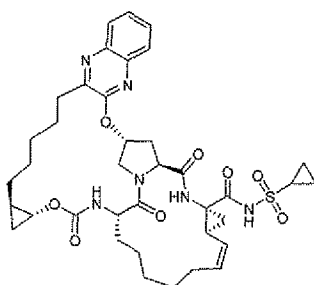
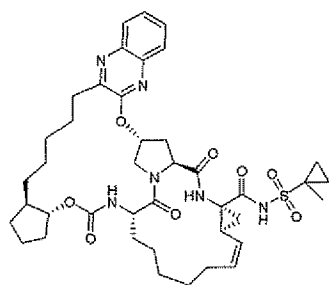
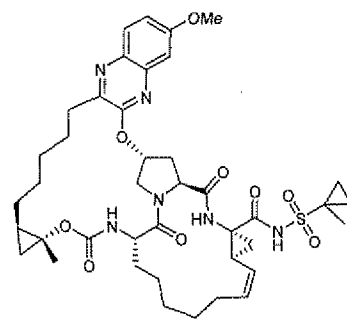
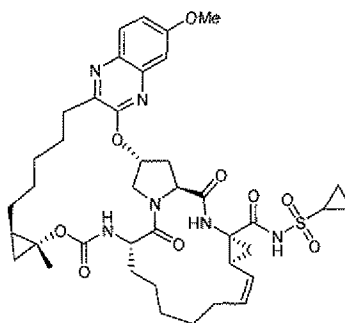
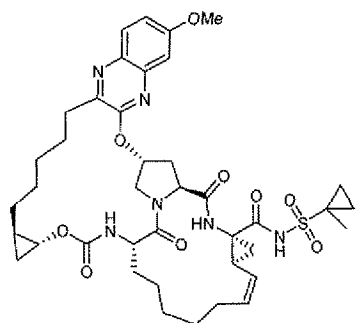
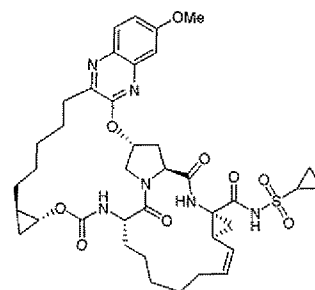
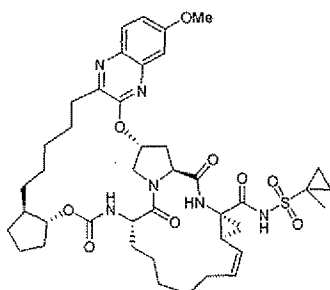
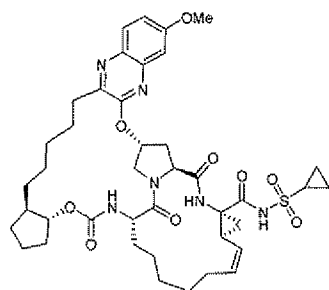


Z is -(CH₂)₄-; and

15

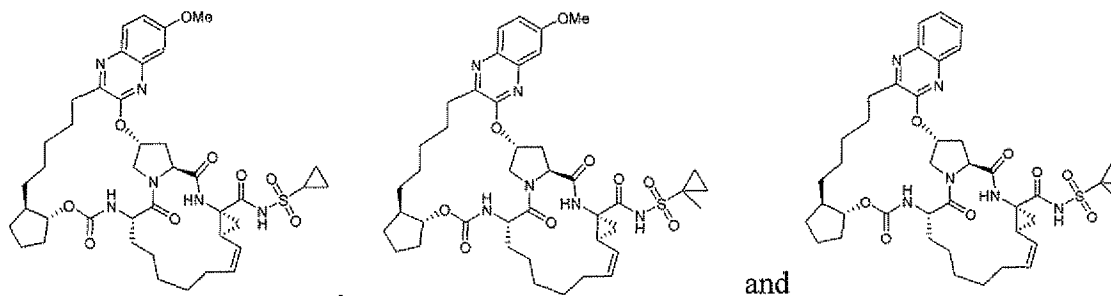


16. The compound according to claim 1 or claim 15, or a pharmaceutically acceptable salt, solvate or hydrate thereof, selected from the group consisting of:



and

17. The compound according to claim 16, or a pharmaceutically acceptable salt, solvate or hydrate thereof, selected from the group consisting of:



18. A pharmaceutical composition comprising an effective amount of a compound according any one of claims 1-17, and a pharmaceutically acceptable carrier.

19. The pharmaceutical composition according to claim 18, further comprising at least one additional therapeutic agent independently selected from the group consisting of a HCV antiviral agent, an immunomodulator, and an anti-infective agent.

20. The pharmaceutical composition according to claim 19, wherein the HCV antiviral agent is an antiviral selected from the group consisting of a HCV protease inhibitor and a HCV NS5B polymerase inhibitor.

21. A use of a compound according to any one of claims 1-17 in the preparation of a medicament for inhibiting HCV NS3 protease activity in a subject in need thereof.

22. A use of a compound according to any one of claims 1-17 in the preparation of a medicament for preventing or treating infection by HCV in a subject in need thereof.

23. The use according to claim 22, wherein said medicament further comprises at least one additional therapeutic agent independently selected from the group consisting of a HCV antiviral agent, an immunomodulator, and an anti-infective agent.

24. The use according to claim 23, wherein the HCV antiviral agent is an antiviral selected from the group consisting of a HCV protease inhibitor and a HCV NS5B polymerase inhibitor.

5 25. A method of treating infection by HCV in a subject in need thereof, said method comprising administering to the subject an effective amount of a compound according to any one of claims 1-17.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/043340

A. CLASSIFICATION OF SUBJECT MATTER
 INV. C07K5/08 A61K38/06 A61P31/14
 ADD.

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)
 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
 EPO-Internal, CHEM ABS Data, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/057208 A2 (MERCK & CO INC [US]; LIVERTON NIGEL J [US]; MCCAULEY JOHN A [US]; RUDD) 15 May 2008 (2008-05-15) cited in the application	1-15, 18-25
A	claims 1,11-17; tables A-C	16,17

Further documents are listed in the continuation of Box C.

See patent family annex.

- * 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 document 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 24 August 2010	Date of mailing of the international search report 31/08/2010
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Schleifenbaum, A
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2010/043340

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008057208	A2	15-05-2008	
		AU 2007318164 A1	15-05-2008
		CA 2667032 A1	15-05-2008
		CN 101568346 A	28-10-2009
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