Abstract:

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Title: ORGANIC COMPOUNDS AND THEIR USES

Abstract: The present application describes organic compounds that are useful for the treatment, prevention and/or amelioration of human diseases.
ORGANIC COMPOUNDS AND THEIR USES

Background

Hepatitis C virus (HCV) is a (-f-) sense single-stranded RNA virus that has been implicated as the major causative agent in non-A, non-B hepatitis (NANBH), particularly in blood-associated NANBH (BB-NANBH). NANBH is to be distinguished from other types of viral-induced liver disease, such as hepatitis A virus (HAV), hepatitis B virus (HBV), delta hepatitis virus (HDV), cytomegalovirus (CMV) and Epstein-Barr virus (EBV), as well as from other forms of liver disease such as alcoholism and primary biliary cirrhosis.

Recently, an HCV protease necessary for polypeptide processing and viral replication has been identified, cloned and expressed. (See, e.g., U.S. Pat. No. 5,712,145). This approximately 3000 amino acid polypeptide contains, from the amino terminus to the carboxy terminus, a nucleocapsid protein (C), envelope proteins (E1 and E2) and several non-structural proteins (NS1, 2, 3, 4a, 5a and 5b). NS3 is an approximately 68 kda protein, encoded by approximately 1893 nucleotides of the HCV genome, and has two distinct domains: (a) a serine protease domain consisting of approximately 200 of the N-terminal amino acids; and (b) an RNA-dependent ATPase domain at the C-terminus of the protein. The NS3 protease is considered a member of the chymotrypsin family because of similarities in protein sequence, overall three-dimensional structure and mechanism of catalysis. The HCV NS3 serine protease is responsible for proteolysis of the polypeptide (polyprotein) at the NS3/NS4a, NS4a/NS4b, NS4b/NS5a and NS5a/NS5b junctions and is thus responsible for generating four viral proteins during viral replication. This has made the HCV NS3 serine protease an attractive target for antiviral chemotherapy.

It has been determined that the NS4a protein, an approximately 6 kda polypeptide, is a co-factor for the serine protease activity of NS3. Autocleavage of the NS3/NS4a junction by the NS3/NS4a serine protease occurs intramolecularly (i.e., cis) while the other cleavage sites are processed intermolecularly (i.e., trans).

HCV has been implicated in cirrhosis of the liver and in induction of hepatocellular carcinoma. The prognosis for patients suffering from HCV infection is currently poor. HCV infection is more difficult to treat than other forms of hepatitis due to the lack of immunity or remission associated with HCV infection. Current data indicates a less than 50% survival rate at four years post cirrhosis diagnosis. Patients diagnosed with localized resectable hepatocellular carcinoma have a five-year survival rate of 10-30%, whereas those with
embodiment, the interaction between the NS3 protease and NS4A cofactor is disrupted. In yet another embodiment, the compounds of the invention prevent or alter the severing of one or more of the NS4A-NS4B, NS4B-NS5A and NS5A-NS5B junctions of the HCV. In another embodiment, the invention provides a method of inhibiting the activity of a serine protease, comprising the step of contacting said serine protease with a compound of the invention. In another embodiment, the invention provides a method of treating, inhibiting or preventing the activity of HCV in a subject in need thereof, comprising administering to the subject a pharmaceutically acceptable amount of a compound of the invention, wherein the compound interacts with any target in the HCV life cycle. In one embodiment, the target of the HCV life cycle is selected from the group consisting of NS2 protease, NS3 protease, NS3 helicase, NS5a protein and NS5b polymerase.

In another embodiment, the invention provides a method of decreasing the HCV RNA load in a subject in need thereof comprising administering to the subject a pharmaceutically acceptable amount of a compound of the invention.

In another embodiment, the compounds of the invention exhibit HCV protease activity. In one embodiment, the compounds are an HCV NS3-4A protease inhibitor.

In another embodiment, the invention provides a method of treating an HCV-associated disorder in a subject, comprising administering to a subject in need thereof a pharmaceutically acceptable amount of a compound of the invention, and a pharmaceutically acceptable carrier, such that the HCV-associated disorder is treated.

In still another embodiment, the invention provides a method of treating an HCV-associated disorder comprising administering to a subject in need thereof a pharmaceutically effective amount of a compound of the invention, in combination with a pharmaceutically effective amount of an additional HCV-modulating compound, such as interferon or derivatized interferon, or a cytochrome P450 monooxygenase inhibitor, such that the HCV-associated disorder is treated. In one embodiment, the additional HCV-modulating compound is selected from the group consisting of Sch 503034 and VX-950.

In another embodiment, the invention provides a method of inhibiting hepatitis C virus replication in a cell, comprising contacting said cell with a compound of the invention.

In yet another embodiment, the invention provides a packaged HCV-associated disorder treatment, comprising an HCV-modulating compound of the invention, packaged with instructions for using an effective amount of the HCV-modulating compound to treat an HCV-associated disorder.
In certain embodiments, the HCV-associated disorder is selected from the group consisting of HCV infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma, cryoglobulinaemia, non-Hodgkin’s lymphoma, and a suppressed innate intracellular immune response.

In another embodiment, the invention provides a method of treating HCV infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma, cryoglobulinemia, non-Hodgkin's lymphoma, and/or a suppressed innate intracellular immune response in subject in need thereof comprising administering to the subject a pharmaceutically acceptable amount of a compound of the invention.

In one embodiment, the HGV to be treated is selected of any HCV genotype. In another embodiment, the HCV is selected from HCV genotype 1, 2 and/or 3.

*Detailed Description of the Invention*

This invention is directed to compounds, e.g., peptide compounds, and intermediates thereto, as well as pharmaceutical compositions containing the compounds for use in treatment of HCV infection. This invention is also directed to the compounds of the invention or compositions thereof as protease inhibitors, particularly as serine protease inhibitors, and more particularly as HCV NS3 protease inhibitors. The compounds are particularly useful in interfering with the life cycle of the hepatitis C virus and in treating or preventing an HCV infection or physiological conditions associated therewith. The present invention is also directed to methods of combination therapy for inhibiting HCV replication in cells, or for treating or preventing an HCV infection in patients using the compounds of the invention or pharmaceutical compositions, or kits thereof.

This application features novel functional substituents at the putative P2 position, P3 position, capping groups ("CG activity moiety") and the W position. The characteristics of these chemical embodiments include N-alkyl glycine amino-acids, beta-amino acids and heterocyclic capping groups. Pharmacokinetic properties can be improved by prolonging t1/2 as these substituents may be less likely to be recognized by degrading enzymes and other biological clearance mechanisms as compared to standard unsubstituted peptide-like amide linkages. In addition, the CG activity moieties of the invention may exploit advantageous interactions within the biological target emparting superior potency and/or replicon activity, as well as circumvent solubility and cyp interaction problems as compared to the current competitive templates.

In one aspect, the compounds of the invention are of the formula A:
and pharmaceutically acceptable salts and stereoisomers thereof; wherein

5  CG is selected from the group consisting of

wherein R^{18} is selected from the group consisting of hydrogen, a halogen atom, aryl, trihalomethyl, and Cl-4-alkyl;

10  P3 is a P3 activity moiety;

W is a W activity moiety;

y is O or 1;

x is 0 or 1; and

R^1, R^2, R^9, R^1', R^{12} and R^{13} are each, independently, selected from the group consisting of H, alkyl, alkyl-aryl, heteroalkyl, heterocyclyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyloxy, alkylaryloxy, arloxy, heteroaryloxy, heterocyclyloxy, cycloalkylloxy, amino, alkylamino, arylamino, alkyl-arylamino, arylamino, heteroarylamino, cycloalkylamino, carboxyalkylamino, arylalkylamino and heterocyclylamino; all of which may be further independently substituted one or more times with X^1 and X^2; wherein X^1 is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyi-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, arylheteroaryl, heteroaryl, heterocyclylamino, alkylheteroaryl, or heteroarylalkyl; wherein X^1 can be independently substituted with one or more of X^2 moieties which can be the same or different and are independently selected; wherein X^2 is hydroxy, alkyl, aryl, alkoxy, arloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxyaminocarboxyl, alkoxyaminocarbonyl, alkoxyureido, aminourido, halogen, cyano, keto, ester or nitro; wherein each of said alkyl, alkoxy, and aryl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different and
are independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, arylheteroaryl, heteroaryl, heterocyclylamino, alkylheteroaryl and heteroarylalkyl.

In another aspect, the compounds of the invention are of the formula B:

![Chemical Structure B](image)

and pharmaceutically acceptable salts and stereoisomers thereof.

wherein

- \( P_2 \) is represented by the formula Al:

![Chemical Structure Al](image)

wherein

- \( R_7, R_{16}, R_{15}, R_{17} \) and \( R_{22} \) are each, independently, selected from the group consisting of \( H, \) alkyl, alkyl-aryl, heteroalkyl, heterocyclyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyloxy, alkyl-aryloxy, arloxy, heteroaryloxy, heterocyclyloxy, cycloalkyloxy, amino, alkylamino, arylamino, alkyl-arylamino, arylamino, heteroarylamino, cycloalkylamino, carboxyalkylamino, arylalkyloxy and heterocyclylamino; all of which may be further independently substituted one or more times with \( X_1 \) and \( X_2; \) wherein \( X_1 \) is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, arylheteroaryl, heteroaryl, heterocyclylamino, alkylheteroaryl, or heteroarylalkyl; wherein \( X_1 \) can be independently substituted with one or more of \( X_2 \) moieties which can be the same or different and are independently selected; wherein \( X_2 \) is hydroxy, alkyl, aryl, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxy carbonylamino, alkoxy carbonyloxy, alkylureido, arylureido, halogen, cyano, keto, ester or nitro; wherein each of said alkyl, alkoxy, and aryl can be unsubstituted or optionally
localized unresectable hepatocellular carcinoma have a five-year survival rate of less than 1%.


Summary of the Invention

There remains a need for new treatments and therapies for HCV infection, as well as HCV-associated disorders. There is also a need for compounds useful in the treatment or prevention or amelioration of one or more symptoms of HCV as well as a need for methods of treatment or prevention or amelioration of one or more symptoms of HCV. Furthermore, there is a need for methods for modulating the activity of HCV-serine proteases, particularly the HCV NS3/NS4a serine protease, using the compounds provided herein.

In one aspect, the invention provides compounds of the formula A, B and C, each of which share the general formula:

\[
\begin{align*}
&\text{CG} \quad R^{12} \quad R^{11} \quad P^3 \quad N \quad R^8 \quad R^9 \quad P^2 \quad N \quad W \quad R^3 \\
&\quad R^1
\end{align*}
\]

and pharmaceutically acceptable salts and stereoisomers thereof.

In one embodiment, the invention provides a method of treating an HCV-associated disorder comprising administering to a subject in need thereof a pharmaceutically acceptable amount of a compound of the invention, such that the HCV-associated disorder is treated.

In another embodiment, the invention provides a method of treating an HIV infection comprising administering to a subject in need thereof a pharmaceutically acceptable amount of a compound of the invention.

In still another embodiment, the invention provides a method of treating, inhibiting or preventing the activity of HCV in a subject in need thereof, comprising administering to the subject a pharmaceutically acceptable amount of a compound of the invention. In one embodiment, the compounds of the invention inhibit the activity of the NS2 protease, the NS3 protease, the NS3 helicase, the NS5a protein, and/or the NS5b polymerase. In another
independently substituted with one or more moieties which can be the same or different and are independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, arylheteroaryl, heteroaryl, heterocyclylamino, alkylheteroaryl and heteroarylalkyl;

or \( R^{22} \) and \( R^{16} \) may together form a 3, 4, 5, 6 or 7-membered ring that is aromatic or non-aromatic and may contain one or more heteroatoms, wherein the ring may be further substituted one or more times;

or \( R^{7} \) and \( R^{15} \) may together form a 3, 4, 5, 6 or 7-membered ring that is aromatic or non-aromatic and may contain one or more heteroatoms, wherein the ring may be further substituted one or more times;

or \( R^{17} \) and \( R^{16} \) may together form a 4, 5, 6 or 7-membered ring of the formula III:

\[
\begin{align*}
& \text{HI} \\
\text{wherein} \\
& n \text{ and } g \text{ are each, independently, } 0, 1 \text{ or } 2, \text{ wherein } n \text{ and } g \text{ are not both } 2; \\
& m \text{ is } 0 \text{ or } 1; \\
& X \text{ is } O, N \text{ or } C; \\
& R^{4} \text{ and } R^{4a} \text{ are each, independently, selected from the group consisting of } H, C_{1-4}^{1-4} \text{-alkyl, O-} C_{1-4}^{1-4} \text{-alkyl, N(H)-} C_{1-4}^{1-4} \text{-alkyl, } (C_{2-3}^{2-3})^{6}-cycloalkyl, \text{aryl and heterocycle, all of which may be independently substituted one or more times with a halogen atom or } C_{1-4}^{1-4} \text{-alkyl; } \\
& R^{5} \text{ is selected from the group consisting of oxo, } -O-, H, C_{1-4}^{1-4} \text{-alkyl, } O-C_{1-4}^{1-4} \text{-alkyl, } N(H)-C_{1-4}^{1-4} \text{-alkyl, } (C_{2-3}^{2-3})^{6}-cycloalkyl, \text{aryl and heterocycle, and any combination thereof, all of which may be independently substituted one or more times with a halogen atom, aryl, trihalomethyl, or } C_{1-4}^{1-4} \text{-alkyl; } \\
& \text{or } R^{4} \text{ and } R^{5} \text{ may together form a } 4, 5, 6 \text{ or } 7 \text{-membered ring that is aromatic or non-aromatic and may contain one or more heteroatoms, wherein the ring may be further substituted one or more times; } \\
& \text{or } R^{15} \text{ and } R^{16} \text{ may together form a } 4, 5, 6 \text{ or } 7 \text{-membered ring that is aromatic or non-aromatic and may contain one or more heteroatoms, wherein the ring may be further substituted one or more times; wherein one of the rings that } R^{15} \text{ and } R^{16} \text{ may together form is}
a ring of the formula IV:

wherein:

- the dashed line represents a single or double bond, wherein formula IV may be further substituted one or more times;
- CG is a CG activity moiety;
- P3 is a P3 activity moiety;
- W is a W activity moiety;
- x is 0 or 1;
- y is 0 or 1;
- R₁, R₂, R₈, R⁹, R¹₁, R¹² and R¹³ are each, independently, selected from the group consisting of H, alkyl, alkyl-aryl, heteroalkyl, heterocyclyl, heteroaryl, aryl-heteroaryl, alkylheteroaryl, cycloalkyl, alkyloxy, alkyl-aryloxy, arloxy, heteroaryloxy, heterocyclyloxy, cycloalkyloxy, amino, alkylamino, arylamino, alkyl-arylamino, arylamine, heteroarylamine, cycloalkylamine, carboxyalkylamine, arylalkyloxy and heterocyclylamine; all of which may be further independently substituted one or more times with X¹ and X²; wherein X¹ is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, arylheteroaryl, heteroaryl, heterocyclylamine, alkylheteroaryl, or heteroarylalkyl; wherein X¹ can be independently substituted with one or more of X² moieties which can be the same or different and are independently selected; wherein X² is hydroxy, alkyl, aryl, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, aralkylamine, arylamine, alkylsulfonyl, alkylsulfonylamido, arylsulfonylamido, arylsulfonylamino, carboxy, carbalkoxy, carboxamido, alkoxy carbonylamino, alkoxy carbonyloxy, alkylureido, arylureido, halogen, cyano, keto, ester or nitro; wherein each of said alkyl, alkoxy, and aryl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different and are independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, arylheteroaryl, heteroaryl, heterocyclylamino, alkylheteroaryl and heteroarylalkyl.

In yet another aspect, the compounds of the invention are of the formula C:
and pharmaceutically acceptable salts and stereoisomers thereof, wherein

5  W is selected from the group consisting of

\[ \text{R}^{19} \]

wherein R\(^{19}\) is selected from the group consisting of hydrogen, a halogen atom, aryl, trihalomethyl, and C\(_{1-4}\)-alkyl.

CG is a CG activity moiety;

10  P2 is a P2 activity moiety;

P3 is a P3 activity moiety;

x is 0 or 1;

y is 0 or 1;

R\(^1\), R\(^2\), R\(^8\), R\(^9\), R\(^{11}\), R\(^{12}\) and R\(^{13}\) are each, independently, selected from the group consisting of H, alkyl, alkyl-aryl, heteroalkyl, heterocyclyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkylcyloxy, alkyl-aryloxy, arylcyloxy, heteroaryloxy, heterocyclyloxy, cycloalkyloxy, amino, alkylamino, arylamino, alkyl-arylamino, arylamino, heteroarylamino, cycloalkylamino, carboxyalkylamino, arylalkyloxy and heterocyclylamino; all of which may be further independently substituted one or more times with X\(^1\) and X\(^2\); wherein X\(^1\) is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heteroaryloxyalkyl, aryl, alkylaryl, arylalkyl, arylheteroaryl, heteroaryl, heterocyclylaminoalkyl, alkylheteroaryl, or heteroaryloxyalkyl; wherein X\(^1\) can be independently substituted with one or more of X\(^2\) moieties which can be the same or different and are independently selected; wherein X\(^2\) is hydroxy, alkyl, aryl, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carboalkoxy, carboxamido, alkoxy carbonylamino, alkoxy carbonyloxy, alkylureido, arylureido, halogen, cyano, keto, ester or nitro; wherein each of said alkyl, alkoxy, and aryl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different and
are independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkyaryl, arylalkyl, arylheteroaryl, heteroaryl, heterocyclylamino, alkylheteroaryl and heteroarylalkyl.

In one embodiment of formulas A, B and C, P3 is selected from the group consisting of H, C1-4-alkyl, and (CH2)3-4-C3-6-cycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocycle.

In one embodiment of formulas A and C, P2 is represented by the formula A1, A2, A3, A4, A5, A6, A7 or A8:

![Diagram](image)

wherein

R7, R16, R15 and R22 are each, independently, selected from the group consisting of H, alkyl, alkyl-aryl, heteroalkyl, heterocyclyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkylcyloxy, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocyclyloxy, cycloalkyloxy, amino, alkylamino, arylamino, alkyl-aiylamino, arylamino, heteroarylamino, cycloalkylamino, carboxyalkylamino, arylalkyloxy and heterocyclylamino; all of which may be further independently substituted one or more times with X1 and X2; wherein X1 is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, arylheteroaryl, heterocyclylamino, alkylheteroaryl or heteroarylalkyl; wherein X1 can be independently substituted with one or more of X2 moieties which can be the same or different and are independently selected; wherein X2 is hydroxy, alkyl, aryl, alkoxy, arylxy, thio, alkythio, arlythio, amino, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxyacylamino, alkoxyacarbonyloxy, alkyureido, arylureido, halogen, cyano, keto, ester or nitro; wherein each of said alkyl, alkoxy, and aryl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different and are independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, arylheteroaryl, heteroaryl, heterocyclylamino, alkylheteroaryl and heteroarylalkyl;

or R22 and R16 may together form a 3, 4, 5, 6 or 7-membered ring that is aromatic or non-aromatic and may contain one or more heteroatoms, wherein the ring may be further
substituted one or more times;

or $R^7$ and $R^{15}$ may together form a 3, 4, 5, 6 or 7-membered ring that is aromatic or non-aromatic and may contain one or more heteroatoms, wherein the ring may be further substituted one or more times;

or $R^{17}$ and $R^{16}$ may together form a 4, 5, 6 or 7-membered ring of the formula III:

wherein

- $n$ and $g$ are each, independently, 0, 1 or 2, wherein $i$ and $g$ are not both 2;
- $m$ is 0 or 1;
- X is O, N or C;
- $R^4$ and $R^{4a}$ are each, independently, selected from the group consisting of H, C$_{1-4}$-alkyl, O-C$_{1-4}$-alkyl, N(H)-C$_{1-4}$-alkyl, (CH$_2$)$_{0-4}$-C$_{3-6}$-cycloalkyl, aryl and heterocycle, all of which may be independently substituted one or more times with a halogen atom or C$_{1-4}$-alkyl;
- $R^8$ is selected from the group consisting of oxo, -O-, H, C$_{1-4}$-alkyl, Q-C$_{1-4}$-alkyl, N(H)-C$_{1-4}$-alkyl, (CH$_2$)$_{0-4}$-C$_{3-6}$-cycloalkyl, aryl and heterocycle, and any combination thereof, all of which may be independently substituted one or more times with a halogen atom, aryl, trihalomethyl, or C$_{1-4}$-alkyl;

or $R^4$ and $R^8$ may together form a 4, 5, 6 or 7-membered ring that is aromatic or non-aromatic and may contain one or more heteroatoms, wherein the ring may be further substituted one or more times;

or $R^{15}$ and $R^{16}$ may together form a 4, 5, 6 or 7-membered ring that is aromatic or non-aromatic and may contain one or more heteroatoms, wherein the ring may be further substituted one or more times; wherein one of the rings that $R^{15}$ and $R^{16}$ may together form is a ring of the formula IV:
wherein

the dashed line represents a single or double bond, wherein formula IV may be further substituted one or more times;

\[ \text{A2} \]

wherein

n is 0 or 1;

X is N or C;

R^4 is selected from the group consisting of H, C^-alkyl, C^-cycloalkyl, aryl, heterocycle and heteroaryl, all of which may be independently substituted one or more times with a halogen atom or C_i^-alkyl;

R^5 is selected from the group consisting of oxo, -O-, H, C_i^-alkyl, C^-cycloalkyl, aryl and heteroaryl, and any combination thereof, all of which may be independently substituted one or more times with a halogen atom, aryl, trihalomethyl, or C_i-4-alkyl;

or R^4 and R^5 may together form a dimethyl cyclopropyl ring, a cyclopentane ring, or a phenyl ring, wherein the phenyl ring and dimethyl cyclopropyl ring may be substituted with a halogen atom, aryl, trihalomethyl, or C^-alkyl, or such that a fused ring system is formed; and

R^6 and R^7 are each, independently, selected from the group consisting of H, C^-alkyl and (GH_2)o-4-C_3^-cycloalkyl;

\[ \text{A3} \]

wherein

R^4, R^5 and R^6 are each, independently, selected from the group consisting of H, alkyl,
alkyl-aryl, heteroalkyl, heterocyclyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl,
alkyloxy, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkyloxy, amino,
alanylino, arylamino, alkyl-arylamino, arylamino, heteroarylaminó, cycloalkylamino,
carboxyalkylamino, arylalkyloxy and heterocyclylamino; all of which may be further
independently substituted one or more times with X¹ and X²; wherein X¹ is alkyl, alkenyl,
alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl,
arylalkyl, arylheteroaryl, heteroaryl, heterocyclylamino, alkylheteroaryl, or heteroarylalkyl;
wherein X¹ can be independently substituted with one or more of X² moieties which can be
the same or different and are independently selected; wherein X² is hydroxy, alkyl, aryl,
alcoxy, arylloxy, thio, alkylthio, arylthio, amino, alkyloxy, arylamino, alkylsulfonyl,
arlylsulfonyl, alylsulfonamido, cyano, carboxy, carbalkoxy, carboxamido,
alkoxycarboxyloxy, alkoxycarbonyloxy, alkylureido, arylureido, halogen, cyano, keto,
ester or nitro; wherein each of said alkyl, alcoxy, and aryl can be unsubstituted or optionally
independently substituted with one or more moieties which can be the same or different and
are independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl,
heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, aryalkyl, arylheteroaryl, heteroaryl,
heterocyclylamino, alkylheteroaryl and heteroarylalkyl.

In still another embodiment of formula A and B, W is selected from the group
consisting of H, alkyl, alkyl-aryl, heteroalkyl, heterocyclyl, heteroaryl, aryl-heteroaryl, alkyl-
heteroaryl, cycloalkyl, alkylheteroaryl, cycloalkyl-alkyl, heterocyclyl, heteroaryl, heterocyclyloxy,
aminoc, alkylamino, arylamino, alkyl-arylamino, arylamino, heteroarylaminó, cycloalkylamino,
carboxyalkylamino, arylalkyloxy and heterocyclylamino; all of which may be further
independently substituted one or more times with X¹ and X²; wherein X¹ is alkyl, alkenyl,
alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl,
arylalkyl, arylheteroaryl, heteroaryl, heterocyclylamino, alkylheteroaryl, or heteroarylalkyl;
wherein X¹ can be independently substituted with one or more of X² moieties which can be
the same or different and are independently selected; wherein X² is hydroxy, alkyl, aryl,
alcoxy, arylloxy, thio, alkylthio, arylthio, amino, alkyloxy, arylamino, alkylsulfonyl,
arlylsulfonyl, alylsulfonamido, cyano, carboxy, carbalkoxy, carboxamido,
aloxycarboxyloxy, alkoxycarbonyloxy, alkylureido, arylureido, halogen, cyano, keto,
ester or nitro; wherein each of said alkyl, alcoxy, and aryl can be unsubstituted or optionally
independently substituted with one or more moieties which can be the same or different and
are independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl,
heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, aryalkyl, arylheteroaryl, heteroaryl,
heterocyclylamino, alkylheteroaryl and heteroaryalkyl.

In one embodiment of formulas B and C, CG is selected from the group consisting of

\[
\begin{align*}
\text{R}^{18} & \quad \text{N} \quad \text{R}^{18} \\
\text{R}^{18} & \quad \text{N} \quad \text{X} \quad \text{R}^{18} \\
\text{R}^{18} & \quad \text{N} \quad \text{X} \quad \text{R}^{18}
\end{align*}
\]

wherein \( \text{R}^{18} \) is selected from the group consisting of hydrogen, a halogen atom, aryl,

trihalomethyl, and \( \text{C}_{1,4}-\text{alkyl}. \)

In one embodiment of formulas A and B, W is selected from the group consisting of

\( H, \text{ alkyl, alkyl-aryl, heteroalkyl, heterocyclyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkylxoy, alkyl-aryloxy, arylxoy, heteroaryloxy, heterocyclyloxy, cycloalkyloxy, amino, alkylamino, arylamino, alkyl-arylamino, arylamino, heteroarylamino, \)

cycloalkylamino, carboxyalkylamino, arylalkyloxy and heterocyclylamino; all of which may
be further independently substituted one or more times with \( X^1 \) and \( X^2 \); wherein \( X^1 \) is alkyl,

alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl,

arylheteroaryl, heteroaryl, heterocyclylamino, alkylheteroaryl, or heteroaryalkyl; wherein \( X^1 \) can be independently substituted with one or more of \( X^2 \) moieties which can be
the same or different and are independently selected; wherein \( X^2 \) is hydroxy, alkyl, aryl,
alcohol, arylxoy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, alkylsulfonyl,

arylthio, alkylsulfonylamido, arylsulfonylamido, carboxy, carbalkoxy, carboxamido;
aikoxycarbonylamino, alkoxy carbonyloxy, alkylureido, arylureido, halogen, cyano, keto,
ester or nitro; wherein each of said alkyl, alkoxo, and aryl can be unsubstituted or optionally
independently substituted with one or more moieties which can be the same or different and
are independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl,
heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl. arylheteroaryl, heteroaryl,
heterocyclylamino, alkylheteroaryl and heteroaryalkyl;

The compound of any one of the above claims, wherein formula A2 is represented by
the formula A4:
wherein:

R²² and R⁷ are each, independently, selected from the group consisting of H, C₁-₄-alkyl, O-d⁻⁻alkyl, N(H)-Ci⁻⁻₄-alkyl, (CH₂)₀⁻⁻₄-C₃⁻⁻₆-cycloalkyl, aryl and heterocycle, all of which may be independently substituted one or more times with a halogen atom, Ci⁻⁻₄-alkyl, O-C₁⁻⁻₄-alkyl, N(H)-C⁻⁻₁⁻⁻₄-alkyl, Ci⁻⁻₄-alkyl substituted by one or more halogen atoms, or C₃⁻⁻₆-cycloalkyl;

n and g are each, independently, 0, 1 or 2, wherein n and g are not both 2;

η is O or 1;
X is O, N or C;
R⁴ and R⁴ᵃ are each, independently, selected from the group consisting of H, C₁⁻⁻₄-alkyl, O-C₁⁻⁻₄-alkyl, N(H)-Ci⁻⁻₄-alkyl, (CH₂)₀⁻⁻₄-C₃⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻⁻˓
wherein

R₇, R¹⁵, R²², R²⁵ and R²⁶ are each, independently, selected from the group consisting of H, alkyl, alkyl-aryl, heteroalkyl, heterocyclyl, heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyloxy, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocyclyloxy, cycloalkyloxy, amino, alkylamino, arylamino, alkyl-arylamino, arylamino, heteroarylaminó, cycloalkylaminó, carboxyalkylaminó, arylalkyloxy and heterocyclylamino; all of which may be further independently substituted one or more times with X¹ and X²; wherein X¹ is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclalkyl, aryl, alkylaryl, arylalkyl, arylheteroaryl, heteroaryl, heterocyclylamino, alkylheteroaryl, or heteroarylalkyl; wherein X² can be independently substituted with one or more of X² moieties which can be the same or different and are independently selected; wherein X² is hydroxy, alkyl, arkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamidó, alkoxy carbonylamino, alkoxy carbonyloxy, alkylureido, arylureido, halogen, cyano, keto, ester or nitro; wherein each of said alkyl, alkoxy, and aryl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different and are independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclalkyl, aryl, alkylaryl, arylalkyl, arylheteroaryl, heteroaryl, heterocyclylamino, alkylheteroaryl and heteroarylalkyl;

or R²² or R²⁶ may together form a 3-membered ring that may or may not be substituted;

wherein R⁷, R¹⁷, R²², R²⁷ and R²⁸ have the meanings for R²⁶ of A⁴ above;
wherein $R^7, R^{16}, R^{22}, R^{29}$ and $R^{30}$ have the meanings for $R^{26}$ of A4 above;

wherein $R^7, R^{15}, R^{30}$ and $R^{31}$ have the meanings for $R^{26}$ of A4 above;

wherein $R^7$ and $R^{15}$ have the meanings for $R^{26}$ of A4 above.

In one embodiment of formulas A, B and C, $R^1, R^2, R^8, R^9, R^{11}, R^{12}$ and $R^{13}$ are each, independently, selected from the group consisting of H, C$^\alpha$-alkyl, and (CH$_2$)$_n$-4-C$_3$-6-cycloalkyl.

In another embodiments of formulas A, B and C, W is selected from the group consisting of C(O)-C(O)H, C(=N-O-R$_{24}$)-C(O)-amine, C(O)-C(O)-amine, C(O)N(H)S(O)$_2$R$_{24}$ and C(0)-[C(0)]$_a$-heterocycle, wherein the heterocycle may be independently substituted one or more times with aryl, C$_1$-aryl, and alkyl substituted by one or more halogen atoms, and C$_3$-6-cycloalkyl, wherein $a$ is Oor 1, wherein each $R^{24}$ is independently selected from the group consisting of H, C$_1$-aryl, (CH$_2$)$_n$-4-C$_3$-6-cycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocycle, all of which may be independently substituted.
one or more times with a halogen atom or C^-alkyl.

In other embodiments of formulas A, B and C, W, R^1 and R^2 form a substituent of the following formulas:

\[ \text{Chemical structures and formulas here} \]

wherein R^3 is selected from the group consisting of H, phenyl, methyl, CF3, tBu, NO2, Cl, CN, NH2, OH, NHCH3, OCH3, NHPh, OPh, NHCOCH3, NHCOPh, 0CH2Ph, COCH3, CO2Et, CO2CH3, CONHPh and CONHCH3, or R^3 can be fused with the phenyl ring to form a naphthyl ring.

In other embodiments of formulas A, B and C, W, R^1 and R^2 form substituents selected from the group consisting of

\[ \text{Chemical structures and formulas here} \]
In other embodiments of formulas A, B and C, W is C(O)N(H)S(O)_2R^{24}, wherein R^{24} is selected from the group consisting of H, C_{1-4}-alkyl, (CH_2)_3-C_3-C_6-cycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocycle, all of which may be independently substituted one or more times with a halogen atom or C_{1-4}-alkyl.

In other embodiments of formulas A, B and C, R^1 and R^2 form a substituent of the following formula:

In other embodiments of formulas A, B and C, W, R^1 and R^2 form a substituent of the following formula:

In other embodiments of formulas A, B and C, W, R^1 and R^2 form a substituent of the following formula:

wherein each R^{24} is independently selected from the group consisting of H, substituted or unsubstituted-C_{1-4}-alkyl, substituted or unsubstituted-(CH_2)_3-C_3-C_6-cycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocycle.

In other embodiments of formulas A, B and C, W, R^1 and R^2 form a substituent selected from the group consisting of:

Preferred embodiments of the compounds of the invention (including pharmaceutically acceptable salts thereof, as well as enantiomers, stereoisomers, rotamers,
tautomers, diastereomers, or racemates thereof) are shown below in Table A, and are also considered to be "compounds of the invention."
### TABLE A

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</tr>
<tr>
<td><img src="image2" alt="Structure 2" /></td>
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<tr>
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<td><img src="image9.png" alt="Structure 9" /></td>
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</table>
TABLE C

[Chemical structures diagram]

-48-
Using the HCV NS3-4A protease and Luciferase-HCV replicon assays described in the exemplification section below, the compounds of the invention (including compounds of Table A depicted above) are found to show IC50 values for HCV inhibition in the range from 10 to more than 100 µM, or 0.5 to 30 µM, including, for example, the range from 0.5 to 0 µM or less.

In certain embodiments, a compound of the present invention is further characterized as a modulator of HCV, including a mammalian HCV, and especially including a human HCV. In a preferred embodiment, the compound of the invention is an HCV inhibitor.

In certain embodiments, the compound of the invention is not VX-950 or Sch 503034 (see, e.g., Curr. Med. Chem., 2005, 12, 2317-2342; and Antimicrob Agents Chemother. 2006, Mar;50(3):1013-20, both of which are incorporated herein by reference in their entirety).


The terms "HCV-associated state" or "HCV-associated disorder" include disorders and states (e.g., a disease state) that are associated with the activity of HCV, e.g., infection of HCV in a subject. HCV-associated states include HCV-infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma, cryoglobulinemia, non-Hodgkin's lymphoma, and a suppressed innate intracellular immune response.

HCV-associated states are often associated with the NS3 serine protease of HCV, which is responsible for several steps in the processing of the HCV polyprotein into smaller functional proteins. NS3 protease forms a heterodimeric complex with the NS4A protein, an essential cofactor that enhances enzymatic activity, and is believed to help anchor HCV to the endoplasmic reticulum. NS3 first autocatalyzes hydrolysis of the NS3-NS4A junction, and then cleaves the HCV polyprotein intermolecularly at the NS4A-NS4B, NS4B-NS5A and NS5A-NS5B intersections. This process is associated with replication of HCV in a subject. Inhibiting or modulating the activity of one or more of the NS3, NS4A, NS4B, NS5A and NS5B proteins will inhibit or modulate replication of HCV in a subject, thereby preventing or treating the HCV-associated state. In a particular embodiment, the HCV-associated state is associated with the activity of the NS3 protease. In another particular embodiment, the HCV-associated state is associated with the activity of NS3-NS4A heterodimeric complex.

In one embodiment, the compounds of the invention are NS3/NS4A protease inhibitors. In another embodiment, the compounds of the invention are NS2/NS3 protease inhibitors.
Without being bound by theory, it is believed that the disruption of the above protein-protein interactions by the compounds of the invention will interfere with viral polyprotein processing by the NS3 protease and thus viral replication.

HCV-associated disorders also include HCV-dependent diseases. HVC-dependent diseases include, e.g., any disease or disorder that depend on or related to activity or misregulation of at least one strain of HCV.

The present invention includes treatment of HCV-associated disorders as described above, but the invention is not intended to be limited to the manner by which the compound performs its intended function of treatment of a disease. The present invention includes treatment of diseases described herein in any manner that allows treatment to occur, e.g., HCV infection.

In a related embodiment, the compounds of the invention can be useful for treating diseases related to HIV, as well as HIV infection and AIDS (Acquired Immune Deficiency Syndrome).

In certain embodiments, the invention provides a pharmaceutical composition of any of the compounds of the present invention. In a related embodiment, the invention provides a pharmaceutical composition of any of the compounds of the present invention and a pharmaceutically acceptable carrier or excipient of any of these compounds. In certain embodiments, the invention includes the compounds as novel chemical entities.

In one embodiment, the invention includes a packaged HCV-associated disorder treatment. The packaged treatment includes a compound of the invention packaged with instructions for using an effective amount of the compound of the invention for an intended use.

The compounds of the present invention are suitable as active agents in pharmaceutical compositions that are efficacious particularly for treating HCV-associated disorders. The pharmaceutical composition in various embodiments has a pharmaceutically effective amount of the present active agent along with other pharmaceutically acceptable excipients, carriers, fillers, diluents and the like. The phrase, "pharmaceutically effective amount" as used herein indicates an amount necessary to administer to a host, or to a cell, issue, or organ of a host, to achieve a therapeutic result, especially an anti-HCV effect, e.g., inhibition of proliferation of the HCV virus, or of any other HCV-associated disease.

In one embodiment, the diseases to be treated by compounds of the invention include, for example, HCV infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma,
cryoglobulinemia, non-Hodgkin's lymphoma, and a suppressed innate intracellular immune response.

In other embodiments, the present invention provides a method for inhibiting the activity of HCV. The method includes contacting a cell with any of the compounds of the present invention. In a related embodiment, the method further provides that the compound is present in an amount effective to selectively inhibit the activity of one or more of the NS3, NS4A, NS4B, NS5A and NS5B proteins. In another related embodiment, the method provides that the compound is present in an amount effective to diminish the HCV RNA load in a subject.

In other embodiments, the present invention provides a use of any of the compounds of the invention for manufacture of a medicament to treat HCV infection in a subject.

In other embodiments, the invention provides a method of manufacture of a medicament, including formulating any of the compounds of the present invention for treatment of a subject.

Definitions

The term "CG activity moiety" includes moieties that allow the compound of the invention to perform its intended function by, e.g., enhancing the bioavailability, e.g., enhancing the solubility, of the compound of the invention such that the compound will properly interact with the HCV target. As used herein, the term "bioavailability" refers to the amount of the administered drug therapy (in this case the compound of the invention) that reaches and acts upon its target: The term is used for drugs whose efficacy is measured relative to the concentration in the blood even though the ultimate site of action of the drug might be outside the blood, e.g., intracellular (see van Berge-Henegouwen et al., Gastroenterology, 1977, 73, 300). In an embodiment, CG activity moieties include substituted and unsubstituted heterocycles.

The term "P3 activity moiety" includes moieties that allow the compound of the invention to perform its intended function by, e.g., improving the cellular potency of the compound of the invention, and/or reducing the hydrolytic instability of the compound of the invention, as well as increasing the bioavailability of the compound (see, e.g., Curr Med Chem. 2005;12(20):23 17-42). The P3 activity moiety may also conformationally restrain the template backbone of the compound of the invention, which optimizes the interaction with the HCV target, hi an embodiment, the P3 activity moiety is selected from the group consisting of H, alkyl, and \( \text{C}_{3-6}\)-cycloalkyl.
The term "W activity moiety" includes moieties that allow the compound of the invention to perform its intended function by, e.g., reversibly binding to the NS3/NS4A serine protease of the HCV target (see, e.g., Expert Opin. Invesig. Drugs (2005) 14(9): 1129-1144, which is incorporated herein by reference in its entirety). Non-limiting examples of W activity moieties include those substituents with a carbonyl functionality. In an embodiment, the W activity moiety contains an amide functional group.

The term "P2 activity moiety" includes moieties that allow the compound of the invention to perform its intended function by, e.g., situating the W activity moiety in the correct geometry such that the W-activity moiety can optimally interact with the HCV target. The P2 activity moiety can also play a role in inducing an effective stabilization of the catalytic His-Asp hydrogen bond of the NS3 protease of the HCV target, by shielding that region of the protease from the solvent (see, e.g., EMBO J. 2000 Mar 15;19(6):1195-206., incorporated herein by reference.) In an embodiment, the P2 activity moiety is a β-amino acid derivative, or an N-alkyl glycine derivative.


The term "treat," "treated," "treating" or "treatment" includes the diminishment or alleviation of at least one symptom associated or caused by the state, disorder or disease being treated. In certain embodiments, the treatment comprises the induction of an HCV-inhibited state, followed by the activation of the HCV-modulating compound, which would in turn diminish or alleviate at least one symptom associated or caused by the HCV-associated state, disorder or disease being treated. For example, treatment can be diminishment of one or several symptoms of a disorder or complete eradication of a disorder.

The term "subject" is intended to include organisms, e.g., prokaryotes and eukaryotes, which are capable of suffering from or afflicted with an HCV-associated disorder. Examples of subjects include mammals, e.g., humans, dogs, cows, horses, pigs, sheep, goats, cats, mice, rabbits, rats, and transgenic non-human animals. In certain embodiments, the subject is a human, e.g., a human suffering from, at risk of suffering from, or potentially capable of...
suffering from an HCV-associated disorder, and for diseases or conditions described herein, e.g., HCV infection. In another embodiment, the subject is a cell;

The language "HCV-modulating compound," "modulator of HCV" or "HCV inhibitor" refers to compounds that modulate, e.g., inhibit, or otherwise alter, the activity of HCV. Similarly, an "NS3/NS4A protease inhibitor," or an "NS2/NS3 protease inhibitor" refers to a compound that modulates, e.g., inhibits, or otherwise alters, the interaction of these proteases with one another. Examples of HCV-modulating compounds include compounds of the formula A, B and C, as well as Table A (including pharmaceutically acceptable salts thereof, as well as enantiomers, stereoisomers, rotamers, tautomers, diastereomers, or racemates thereof).

Additionally, the method includes administering to a subject an effective amount of an HCV-modulating compound of the invention, e.g., HCV-modulating compounds of the formula A, B and C, as well as Table A (including pharmaceutically acceptable salts thereof, as well as enantiomers, stereoisomers, rotamers, tautomers, diastereomers, or racemates thereof).

The term "alkyl" includes saturated aliphatic groups, including straight-chain alkyl groups (e.g., methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, etc.), branched-chain alkyl groups (isopropyl, tert-butyl, isobutyl, etc.), cycloalkyl (alicyclic) groups (cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl), alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. The term "alkyl" also includes alkenyl groups and alkynyl groups. Furthermore, the expression "C<sub>x</sub>-C<sub>y</sub>-alkyl", wherein x is 1-5 and y is 2-10 indicates a particular alkyl group (straight- or branched-chain) of a particular range of carbons. For example, the expression Ci-C<sub>y</sub>-alkyl includes, but is not limited to, methyl, ethyl, propyl, butyl, isopropyl, tert-butyl and isobutyl. Moreover, the term C<sub>3-6</sub>-cycloalkyl includes, but is not limited to, cyclopropyl, cyclopentyl, and cyclohexyl. As discussed below, these alkyl groups, as well as cycloalkyl groups, may be further substituted.

The term alkyl further includes alkyl groups which can further include oxygen, nitrogen, sulfur or phosphorous atoms replacing one or more carbons of the hydrocarbon backbone. In an embodiment, a straight chain or branched chain alkyl has 10 or fewer carbon atoms in its backbone (e.g., C<sub>1</sub>-Ci<sub>0</sub> for straight chain, C<sub>3</sub>-Ci<sub>0</sub> for branched chain), and more preferably 6 or fewer carbons. Likewise, preferred cycloalkyls have from 4-7 carbon atoms in their ring structure, and more preferably have 5 or 6 carbons in the ring structure.

Moreover, alkyl (e.g., methyl, ethyl, propyl, butyl, pentyl, hexyl, etc.) include both "unsubstituted alkyl" and "substituted alkyl", the latter of which refers to alkyl moieties
having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone, which allow the molecule to perform its intended function.

The term "substituted" is intended to describe moieties having substituents replacing a hydrogen on one or more atoms, e.g. C, O or N, of a molecule. Such substituents can include, for example, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxy carbonyloxy, aryloxy carbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonato, phosphinato, amino (including alkyl amino, dialkylamino, diarylamino, and alky larylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfoxyl, alkylthio, ary1thio, thiocarbonyl, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, morpholino, phenol, benzyl, phenyl, piperizine, cyclopentane, cyclohexane, pyridine, 5H-tetrazole, triazole, piperidine, or an aromatic or heteroaromatic moiety.

Further examples of substituents of the invention, which are not intended to be limiting, include moieties selected from straight or branched alkyl (preferably C1-C5), cycloalkyl (preferably C3-C8), alkoxy (preferably Ci-C6), thioalkyl (preferably Ci-C6), alkenyl (preferably C2-C6), alkynyl (preferably C2-C6), heterocyclic, carbocyclic, aryl (e.g., phenyl), aryloxy (e.g., phenoxy), aralkyl (e.g., benzyl), arylalkyl (e.g., phenyl alkylalkyl), arylacetamidoyl, alkylaryl, heteroarylalkyl, alkylcarbonyl and arylcarbonyl or other acyl group, heteroarylcarbonyl, or heteroaryl group, (CR'R")o-3NR'R" (e.g., -NH2, (CR'R")o-3CN (e.g., -CN), -NO2, halogen (e.g., -F, -Cl, -Br or I), (CR'R")o-3C(halogen)3 (e.g., -CF3), (CR'R")o-3CH(halogen)2, (CR'R")o-3CH2(halogen), (CR'R")Q-3CONR'R", (CR'R")O3S(NH)NRR", (CR'R")O3S(0), 2NR'R", (CR'R")O3CHO, (CR'R")o-30(CR'R")o-3S(0) 0-3R' (e.g., -SO3H, -OSO3H), (CR'R")o-30(CR'R")o-3H (e.g., -CH2OCH3 and -OCH2), (CR'R")o-3S(CR'R")o-3H (e.g., -SH and -SCH3), (CR'R")o-3OH (e.g., -OH), (CR'R")o-3COR (CR'R")O3(substituted or unsubstituted phenyl), (CR'R")o-3(C3-C8 cycloalkyl), (CR'R")o-3CO2R' (e.g., -CO2H), or (CR'R")o-30R' group, or the side chain of any naturally occurring amino acid; wherein R' and R" are each independently hydrogen, a Ci-Cs alkyl, C2-Cs alkenyl, C2-Cs alkynyl, or aryl group. Such substituents can include, for example, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxy carbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkoxy carbonyl, aminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino,
and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, oxime, sulphydrol, alkylthio, arylthio, thiocarboxylate, sulfates, sulfonate, sulfamoyl, amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonate, sulfamoyl, amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonate, sulfamoyl,

and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, oxime, sulphydrol, alkylthio, arylthio, thiocarboxylate, sulfates, sulfonate, sulfamoyl, amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonate, sulfamoyl, amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonate, sulfamoyl,

5 carbonyl moiety (C=O) may be further derivatized with an oxime moiety, e.g., an aldehyde moiety may be derivatized as its oxime (-C=N-OH) analog. It will be understood by those skilled in the art that the moieties substituted on the hydrocarbon chain can themselves be substituted, if appropriate. Cycloalkyls can be further substituted, e.g., with the substituents described above. An "aralkyl" moiety is an alkyl substituted with an aryl (e.g., phenylmethyl (i.e., benzyl)).

The term "alkenyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyds described above, but which contain at least one double bond.

For example, the term "alkenyl" includes straight-chain alkenyl groups (e.g., ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl, etc.), branched-chain alkenyl groups, cycloalkenyl (alicyclic) groups (cyclopropenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl), alkyl or aralkyl substituted cycloalkenyl groups, and cycloalkyl or cycloalkenyl substituted alkenyl groups. The term alkenyl further includes alkenyl groups that include oxygen, nitrogen, sulfur or phosphorous atoms replacing one or more carbons of the hydrocarbon backbone. In certain embodiments, a straight chain or branched chain alkenyl group has 6 or fewer carbon atoms in its backbone (e.g., C₂-C₆ for straight chain, C₃-C₆ for branched chain). Likewise, cycloalkenyl groups may have from 3-8 carbon atoms in their ring structure, and more preferably have 5 or 6 carbons in the ring structure. The term C₂-C₆ includes alkenyl groups containing 2 to 6 carbon atoms.

Moreover, the term alkenyl includes both "unsubstituted alkenyls" and "substituted alkenyls", the latter of which refers to alkenyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkyl groups, alkynyl groups, halogens, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxy carbonyloxy, aryloxy carbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonate, phosphinato, cyano, amino (including alkyl amino, dialkylamino, ary lamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulphydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonate, sulfamoyl,
sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

The term "alkynyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but which contain at least one triple bond. For example, the term "alkynyl" includes straight-chain alkynyl groups (e.g., ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl, etc.), branched-chain alkynyl groups, and cycloalkyl or cycloalkenyl substituted alkynyl groups. The term alkynyl further includes alkynyl groups that include oxygen, nitrogen, sulfur or phosphorous atoms replacing one or more carbons of the hydrocarbon backbone. In certain embodiments, a straight chain or branched chain alkynyl group has 6 or fewer carbon atoms in its backbone. (e.g., C₂-C₆ for straight chain, C₃-C₆ for branched chain). The term C₂-C₆ includes alkynyl groups containing 2 to 6 carbon atoms.

Moreover, the term alkynyl includes both "unsubstituted alkynyls" and "substituted alkynyls", the latter of which refers to alkynyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkyl groups, alkynyl groups, halogens, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxy carbonyloxy, aryloxy carbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyan, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

The term "amine" or "amino" should be understood as being broadly applied to both a molecule, or a moiety or functional group, as generally understood in the art, and may be primary, secondary, or tertiary. The term "amine" or "amino" includes compounds where a nitrogen atom is covalently bonded to at least one carbon, hydrogen or heteroatom. The terms include, for example, but are not limited to, "alkylamino," "arylamino," "diarylamino," "alkylarylamino," "alkylaminoaryl," "arylaminoalkyl," "alkaminoalkyl," "amido," "amido," and "aminocarbonyl." The term "alkyl amino" comprises groups and compounds wherein the nitrogen is bound to at least one additional alkyl group. The term "dialkyl amino" includes groups wherein the nitrogen atom is bound to at least two additional alkyl groups. The term "arylamino" and "diarylamino" include groups wherein the nitrogen is bound to at
least one or two aryl groups, respectively. The term "alkylarylamino," "alkylaminoaryl" or "arylaminoaalkyl" refers to an amino group which is bound to at least one alkyl group and at least one aryl group. The term "alkaminbalkyl" refers to an alkyl, alkenyl, or alkynyl group bound to a nitrogen atom which is also bound to an alkyl group.

The term "amide," "amido" or "aminocarboxyl" includes compounds or moieties which contain a nitrogen atom which is bound to the carbon of a carboxyl or a thipcarbonyl group. The terms include "alkaminocarboxyl" or "alkylaminocarboxyl" groups which include alkyl, alkenyl, aryl or alkynyl groups bound to an amino group bound to a carboxyl group. It includes alryaminocarboxyl and arylcarbonylamino groups which include aryl or heteroaryl moieties bound to an amino group which is bound to the carbon of a carboxyl or thiocarboxyl group. The terms "alkylaminocarboxyl," "alkenylaminocarboxyl," "alkynylaminocarboxyl," "arylaminocarboxyl," "alkylaminocarboxyl," "alkynylaminocarboxyl," and "arylaminocarboxyl" are included in term "amide." Amides also include urea groups (aminocarboxylamino) and carbamates (oxycarboxylamino).

The term "aryl" includes groups, including 5- and 6-membered single-ring aromatic groups that may include from zero to four heteroatoms, for example, phenyl, pyrrole, furan, thiophene, thiazole, isothiazole, imidazole, triazole, tetrazole, pyrazole, oxazole, isoxazole, pyridine, pyrazine, pyridazine, and pyrimidine, and the like. Furthermore, the term "aryl" includes multicyclic aryl groups, e.g., tricyclic, bicyclic, e.g., naphthalene, benzoxazole, benzodioxazole, benzothiazole, benzimidazole, benzothiophene, methylenedioxypHENYL, quinoline, isoquinoline, anthryl, phenanthryl, napthridine, indole, benzofuran, pyrrole, benzofuran, deazapurine, or indolizine. Those aryl groups having heteroatoms in the ring structure may also be referred to as "aryl heterocycles", "heterocycles," "heteroaryl" or "heteroaromatics." The aromatic ring can be substituted at one or more ring positions with such substituents as described above, as for example, alkyl, halogen, hydroxyl, alkoxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxy carbonyloxy, aryloxy carbonyloxy, carboxylate, alkylcarbonyl, alkylaminocarboxyl, aralkylaminocarboxyl, alklenylaminocarboxyl, alkylcarbonyl, aralkylcarbonyl, aralkylcarbonyl, alklenylcarbonyl, alkoxy carbonyl, amine
alkylaryl, or an aromatic or heteroaromatic moiety. Aryl groups can also be fused or bridged with alicyclic or heterocyclic rings which are not aromatic so as to form a polycycle (e.g., tetralin).

The term heteroaryl, as used herein, represents a stable monocyclic or bicyclic ring of up to 7 atoms in each ring, wherein at least one ring is aromatic and contains from 1 to 4 heteroatoms selected from the group consisting of O, N, and S. Heteroaryl groups within the scope of this definition include but are not limited to: acridinyl, carbazolyl, cinnolinyl, quinoxaliny, pyrazolyl, indolyl, benzotriazolyl, furanyl, thiienyl, benzothienyl, benzofuranyl, quinoliny, isquinolinyl, oxazolyl, isoxazolyl, indolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, tetrahydroquinoline. As with the definition of heterocycle below, "heteroaryl" is also understood to include the N-oxide derivative of any nitrogen-containing heteroaryl. In cases where the heteroaryl substituent is bicyclic and one ring is non-aromatic or contains no heteroatoms, it is understood that attachment is via the aromatic ring or via the heteroatom containing ring, respectively.

The term "heterocycle" or "heterocyclyl" as used herein is intended to mean a 5- to 10-membered aromatic or nonaromatic heterocycle containing from 1 to 4 heteroatoms selected from the group consisting of O, N, and S, and includes bicyclic groups. "Heterocyclyl" therefore includes the above mentioned heteroaryls, as well as dihydro and tetrahydro analogs thereof. Further examples of "heterocyclyl" include, but are not limited to the following: benzoimidazolyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indoliny, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolynyl, isothiazolyl, isoxazolyl, naphthopyridinyl, oxadiazoyl, oxazolyl, oxazole, isoxazoline, oxetanyl, pyrany, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl,
substituent can occur via a carbon atom or via a heteroatom.

The term "acyl" includes compounds and moieties which contain the acyl radical (CH$_3$CO-) or a carbonyl group. The term "substituted acyl" includes acyl groups where one or more of the hydrogen atoms are replaced by for example, alkyl groups, alkenyl groups, halogens, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxy carbonyloxy, aryl oxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkythiocarbonyl, alkoxy, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diaryl amino, and alkylaryl am ino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sul hydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sul fonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocycl yl, alkylaryl, or an aromatic or heteroaromatic moiety.

The term "acylamino" includes moieties wherein an acyl moiety is bonded to an amino group. For example, the term includes alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido groups.

The term "alkoxy" includes substituted and unsubstituted alkyl, alkenyl, and alkynyl groups covalently linked to an oxygen atom. Examples of alkoxy groups include methoxy, ethoxy, isopropylxy, propoxy, butoxy, and pentoxy groups and may include cyclic groups such as cyclopentoxy. Examples of substituted alkoxy groups include halogenated alkoxy groups. The alkoxy groups can be substituted with groups such as alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxy carbonyloxy, aryl oxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkythiocarbonyl, alkoxy, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diaryl amino, and alkylaryl am ino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sul hydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sul fonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocycl yl, alkylaryl, or an aromatic or heteroaromatic moiety. Examples of halogen substituted alkoxy groups include, but are not limited to, fluoro methylxy, difluoromethoxy, trifluoromethoxy, chlororriethoxy, dichloromethoxy, trichloromethoxy, etc.

The term "carbonyl" or "carboxy" includes compounds and moieties which contain a carbon connected with a double bond to an oxygen atom, and tautomeric forms thereof.
Examples of moieties that contain a carbonyl include aldehydes, ketones, carboxylic acids, amides, esters, anhydrides, etc. The term "carboxy moiety" or "carbonyl moiety" refers to groups such as "alkylcarbonyl" groups wherein an alkyl group is covalently bound to a carbonyl group, "alkenylcarbonyl" groups wherein an alkenyl group is covalently bound to a carbonyl group, "alkynylcarbonyl" groups wherein an alkynyl group is covalently bound to a carbonyl group, "arylcarbonyl" groups wherein an aryl group is covalently attached to the carbonyl group. Furthermore, the term also refers to groups wherein one or more heteroatoms are covalently bonded to the carbonyl moiety. For example, the term includes moieties such as, for example, aminocarbonyl moieties, (wherein a nitrogen atom is bound to the carbon of the carbonyl group, e.g., an amide), aminocarboxyloxy moieties, wherein an oxygen and a nitrogen atom are both bound to the carbon of the carbonyl group (e.g., also referred to as a "carbamate"). Furthermore, aminocarboxylamino groups (e.g., ureas) are also include as well as other combinations of carbonyl groups bound to heteroatoms (e.g., nitrogen, oxygen, sulfur, etc. as well as carbon atoms). Furthermore, the heteroatom can be further substituted with one or more alkyl, alkenyl, alkynyl, aryl, aralkyl, acyl, etc. moieties.

The term "thiocarbonyl" or "thiocarboxy" includes compounds and moieties which contain a carbon connected with a double bond to a sulfur atom. The term "thiocarbonyl moiety" includes moieties that are analogous to carbonyl moieties. For example, "thiocarbonyl" moieties include aminothiocarbonyl, wherein an amino group is bound to the carbon atom of the thiocarbonyl group, furthermore other thiocarbonyl moieties include, oxythiocarboxyls (oxygen bound to the carbon atom), aminothiocarboxylamino groups, etc.

The term "ether" includes compounds or moieties that contain an oxygen bonded to two different carbon atoms or heteroatoms. For example, the term includes "alkoxyalkyl" which refers to an alkyl, alkenyl, or alkynyl group covalently bonded to an oxygen atom that is covalently bonded to another alkyl group.

The term "ester" includes compounds and moieties that contain a carbon or a heteroatom bound to an oxygen atom that is bonded to the carbon of a carbonyl group. The term "ester" includes alkoxy carboxy groups such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, pentoxy carbonyl, etc. The alkyl, alkenyl, or alkynyl groups are as defined above.

The term "thioether" includes compounds and moieties which contain a sulfur atom bonded to two different carbon or heteroatoms. Examples of thioethers include, but are not limited to alkthioalkyls, alkthioalkenyls, and alkthioalkynyls. The term "alkthioalkyls" include compounds with an alkyl, alkenyl, or alkynyl group bonded to a sulfur atom that is
bonded to an alkyl group. Similarly, the term "alkthioalkenyls" and alkthioalkynyls" refer to compounds or moieties wherein an alkyl, alkenyl, or alkynyl group is bonded to a sulfur atom which is covalently bonded to an alkynyl group.

The term "hydroxy" or "hydroxyl" includes groups with an -OH or -O'.

The term "halogen" includes fluorine, bromine, chlorine, iodine, etc. The term "perhalogenated" generally refers to a moiety wherein all hydrogens are replaced by halogen atoms.

The terms "polycyclyl" or "polycycHc radical" include moieties with two or more rings (e.g., cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls) in which two or more carbons are common to two adjoining rings, e.g., the rings are "fused rings". Rings that are joined through non-adjoint atoms are termed "bridged" rings. Each of the rings of the polycycle can be substituted with such substituents as described above, as for example, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxy carbonyloxy, aryloxy carbonyloxy, carboxylate, alkylcarbonyl, alkoxy carbonyl, alkylamino acid, alkylaminocarbonyl, aralkylaminocarbonyl, alkenylaminocarbonyl, alkenyl carbonyl, aralkyl carbonyl, alkyl carbonyl, aralkyl carbonyl, alkenyl carbonyl, aminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylaryl amino), acylamino (including alky carbonylamino, arylcarbony lamino, carbamoyl and ureido), amidino, imino, sul lhydroxyl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfanyl, sul fonato, sulfamoyl, sul fonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkyl, alkylaryl, or an aromatic or heteroaromatic moiety.

The term "heteroatom" includes atoms of any element other than carbon or hydrogen. Preferred heteroatoms are nitrogen, oxygen, sulfur and phosphorus.

Additionally, the phrase "any combination thereof" implies that any number of the listed functional groups and molecules may be combined to create a larger molecular architecture. For example, the terms "phenyl," "carbonyl" (or "=O"), "-O-", "-OH," and Cl (i.e., -CH3 and -CH2CH2-) can be combined to form a 3-methoxy-4-propoxybenzoic acid substituent. It is to be understood that when combining functional groups and molecules to create a larger molecular architecture, hydrogens can be removed or added, as required to satisfy the valence of each atom.

It is to be understood that all of the compounds of the invention described above will further include bonds between adjacent atoms and/or hydrogens as required to satisfy the valence of each atom. That is, bonds and/or hydrogen atoms are added to provide the
following number of total bonds to each of the following types of atoms: carbon: four bonds; nitrogen: three bonds; oxygen: two bonds; and sulfur: two bonds.

It will be noted that the structures of some of the compounds of this invention include asymmetric carbon atoms. It is to be understood accordingly that the isomers arising from such asymmetry (e.g., all enantiomers, stereoisomers, rotamers, tautomers, diastereomers, or racemates) are included within the scope of this invention. Such isomers can be obtained in substantially pure form by classical separation techniques and by stereochemical controlled synthesis. Furthermore, the structures and other compounds and moieties discussed in this application also include all tautomers thereof. Compounds described herein may be obtained through art recognized synthesis strategies.

It will also be noted that the substituents of some of the compounds of this invention include isomeric cyclic structures. It is to be understood accordingly that constitutional isomers of particular substituents are included within the scope of this invention, unless indicated otherwise. For example, the term "tetrazole" includes tetrazole, 2Z-tetrazole, 3H-tetrazole, 4H-tetrazole and 5H-tetrazole.

Use in HCV-associated disorders

The compounds of the present invention have valuable pharmacological properties and are useful in the treatment of diseases. In certain embodiments, compounds of the invention are useful in the treatment of HCV-associated disorders, e.g., as drugs to treat HCV infection.

The term "use" includes any one or more of the following embodiments of the invention, respectively: the use in the treatment of HCV-associated disorders; the use for the manufacture of pharmaceutical compositions for use in the treatment of these diseases, e.g., in the manufacture of a medicament; methods of use of compounds of the invention in the treatment of these diseases; pharmaceutical preparations having compounds of the invention for the treatment of these diseases; and compounds of the invention for use in the treatment of these diseases; as appropriate and expedient, if not stated otherwise. In particular, diseases to be treated and are thus preferred for use of a compound of the present invention are selected from HCV-associated disorders, including those corresponding to HCV-infection, as well as those diseases that depend on the activity of one or more of the NS3, NS4A, NS4B, NS5A and NS5B proteins, or a NS3-NS4A, NS4A-NS4B, NS4B-NS5A or NS5A-NS5B complex. The term "use" further includes embodiments of compositions herein which bind to an HCV protein sufficiently to serve as tracers or labels, so that when coupled to a fluor or tag, or
made radioactive, can be used as a research reagent or as a diagnostic or an imaging agent.

In certain embodiments, a compound of the present invention is used for treating HCV-associated diseases, and use of the compound of the present invention as an inhibitor of any one or more HCVs. It is envisioned that a use can be a treatment of inhibiting one or more strains of HCV.

**Assays**

The inhibition of HCV activity may be measured as using a number of assays available in the art. An example of such an assay can be found in Anal Biochem. 1996 240(1): 60-7; which is incorporated by reference in its entirety. Assays for measurement of HCV activity are also described in the experimental section below.

**Pharmaceutical Compositions**

The language "effective amount" of the compound is that amount necessary or sufficient to treat or prevent an HCV-associated disorder, e.g. prevent the various morphological and somatic symptoms of an HCV-associated disorder, and/or a disease or condition described herein. In an example, an effective amount of the HCV-modulating compound is the amount sufficient to treat HCV infection in a subject. In another example, an effective amount of the HCV-modulating compound is the amount sufficient to treat HCV infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma, cryoglobulinemia, non-Hodgkin's lymphoma, and a suppressed innate intracellular immune response in a subject. The effective amount can vary depending on such factors as the size and weight of the subject, the type of illness, or the particular compound of the invention. For example, the choice of the compound of the invention can affect what constitutes an "effective amount.”

One of ordinary skill in the art would be able to study the factors contained herein and make the determination regarding the effective amount of the compounds of the invention without undue experimentation.

The regimen of administration can affect what constitutes an effective amount. The compound of the invention can be administered to the subject either prior to or after the onset of an HCV-associated state. Further, several divided dosages, as well as staggered dosages, can be administered daily or sequentially, or the dose can be continuously infused, or can be a bolus injection. Further, the dosages of the compound(s) of the invention can be proportionally increased or decreased as indicated by the exigencies of the therapeutic or prophylactic situation.
Compounds of the invention may be used in the treatment of states, disorders or diseases as described herein, or for the manufacture of pharmaceutical compositions for use in the treatment of these diseases. Methods of use of compounds of the present invention in the treatment of these diseases, or pharmaceutical preparations having compounds of the present invention for the treatment of these diseases.

The language "pharmaceutical composition" includes preparations suitable for administration to mammals, e.g., humans. When the compounds of the present invention are administered as pharmaceuticals to mammals, e.g., humans, they can be given per se or as a pharmaceutical composition containing, for example, 0.1 to 99.5% (more preferably, 0.5 to 90%) of active ingredient in combination with a pharmaceutically acceptable carrier.

The phrase "pharmaceutically acceptable carrier" is art recognized and includes a pharmaceutically acceptable material, composition or vehicle, suitable for administering compounds of the present invention to mammals. The carriers include liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting the subject agent from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically acceptable carriers include: sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients, such as cocoa butter and suppository waxes; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol; phosphate buffer solutions; and other non-toxic compatible substances employed in pharmaceutical formulations.

Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

Examples of pharmaceutically acceptable antioxidants include: water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; oil-soluble antioxidants, such as ascorbyl palmitate,
butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, α-tocopherol, and the like; and metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

Formulations of the present invention include those suitable for oral, nasal, topical, transdermal, buccal, sublingual, rectal, vaginal and/or parenteral administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient that can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound that produces a therapeutic effect. Generally, out of one hundred per cent, this amount will range from about 1 per cent to about ninety-nine percent of active ingredient, preferably from about 5 per cent to about 70 per cent, most preferably from about 10 per cent to about 30 per cent.

Methods of preparing these formulations or compositions include the step of bringing into association a compound of the present invention with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound of the present invention with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

Formulations of the invention suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound of the present invention as an active ingredient. A compound of the present invention may also be administered as a bolus, electuary or paste.

In solid dosage forms of the invention for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the active ingredient is mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; binders, such as, for example, carboxymethyl cellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; humectants, such as glycerol; disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; solution retarding agents, such as paraffin; absorption accelerators, such as quaternary ammonium compounds; wetting agents, such as,
for example, cetyl alcohol and glycerol monostearate; absorbents, such as kaolin and bentonite clay; lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and coloring agents. In the case of capsules, tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

The tablets, and other solid dosage forms of the pharmaceutical compositions of the present invention, such as dragees, capsules, pills and granules may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions that can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

Liquid dosage forms for oral administration of the compounds of the invention include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluent commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in
particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

Formulations of the pharmaceutical compositions of the invention for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing one or more compounds of the invention with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active compound.

Formulations of the present invention which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate.

Dosage forms for the topical or transdermal administration of a compound of this invention include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants that may be required.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols® silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to a compound of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.
Transdermal patches have the added advantage of providing controlled delivery of a compound of the present invention to the body. Such dosage forms can be made by dissolving or dispersing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the active compound in a polymer matrix or gel.

Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of this invention.

Pharmaceutical compositions of this invention suitable for parenteral administration comprise one or more compounds of the invention in combination with one or more pharmaceutically acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

Examples of suitable aqueous and nonaqueous carriers that may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents that delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively,
delayed absorption of a parenterally-administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsule matrices of the subject compounds in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions that are compatible with body tissue.

The preparations of the present invention may be given orally, parenterally, topically, or rectally. They are of course given by forms suitable for each administration route. For example, they are administered in tablets or capsule form, by injection, inhalation, eye lotion, ointment, suppository, etc., administration by injection, infusion or inhalation; topical by lotion or ointment; and rectal by suppositories. Oral administration is preferred.

The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intrarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion.

The phrases "systemic administration," "administered systemically," "peripheral administration" and "administered peripherally" as used herein mean the administration of a compound, drug or other material other than directly into the central nervous system, such that it enters the patient's system and, thus, is subject to metabolism and other like processes, for example, subcutaneous administration.

These compounds may be administered to humans and other animals for therapy by any suitable route of administration, including orally, nasally, as by, for example, a spray, rectally, intravaginally, parenterally, intracisternally and topically, as by powders, ointments or drops, including buccally and sublingually.

Regardless of the route of administration selected, the compounds of the present invention, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the present invention, are formulated into pharmaceutically acceptable dosage forms by conventional methods known to those of skill in the art.

Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient which is
effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

The selected dosage level will depend upon a variety of factors including the activity of the particular compound of the present invention employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the compounds of the invention employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

In general, a suitable daily dose of a compound of the invention will be that amount of the compound that is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above. Generally, intravenous and subcutaneous doses of the compounds of this invention for a patient, when used for the indicated analgesic effects, will range from about 0.0001 to about 100 mg per kilogram of body weight per day, more preferably from about 0.01 to about 50 mg per kg per day, and still more preferably from about 1.0 to about 100 mg per kg per day. An effective amount is that amount treats an HCV-associated disorder.

If desired, the effective daily dose of the active compound may be administered as two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms.

While it is possible for a compound of the present invention to be administered alone, it is preferable to administer the compound as a pharmaceutical composition.

**Synthetic Procedure**

Compounds of the present invention are prepared from commonly available compounds using procedures known to those skilled in the art, including any one or more of the following conditions without limitation:

Within the scope of this text, only a readily removable group that is not a constituent of the particular desired end product of the compounds of the present invention is designated

Salts of compounds of the present invention having at least one salt-forming group may be prepared in a manner known per se. For example, salts of compounds of the present invention having acid groups may be formed, for example, by treating the compounds with metal compounds, such as alkali metal salts of suitable organic carboxylic acids, e.g., the sodium salt of 2-ethylhexanoic acid, with organic alkali metal or alkaline earth metal compounds, such as the corresponding hydroxides, carbonates or hydrogen carbonates, such as sodium or potassium hydroxide, carbonate or hydrogen carbonate, with corresponding calcium compounds or with ammonia or a suitable organic amine, stoichiometric amounts or only a small excess of the salt-forming agent preferably being used. Acid addition salts of compounds of the present invention are obtained in customary manner, e.g., by treating the compounds with an acid or a suitable anion exchange reagent. Internal salts of compounds of the present invention containing acid and basic salt-forming groups, e.g., a free carboxy group and a free amino group, may be formed, e.g., by the neutralisation of salts, such as acid addition salts, to the isoelectric point, e.g., with weak bases, or by treatment with ion exchangers.
Salts can be converted in customary manner into the free compounds; metal and ammonium salts can be converted, for example, by treatment with suitable acids, and acid addition salts, for example, by treatment with a suitable basic agent.

Mixtures of isomers obtainable according to the invention can be separated in a manner known per se into the individual isomers; diastereoisomers can be separated, for example, by partitioning between polyphasic solvent mixtures, recrystallisation and/or chromatographic separation, for example over silica gel or by, e.g., medium pressure liquid chromatography over a reversed phase column, and racemates can be separated, for example, by the formation of salts with optically pure salt-forming reagents and separation of the mixture of diastereoisomers so obtainable, for example by means of fractional crystallisation, or by chromatography over optically active column materials.

Intermediates and final products can be worked up and/or purified according to standard methods, e.g., using chromatographic methods, distribution methods, (re-) crystallization, and the like.

**General process conditions**

The following applies in general to all processes mentioned throughout this disclosure.

The process steps to synthesize the compounds of the invention can be carried out under reaction conditions that are known per se, including those mentioned specifically, in the absence or, customarily, in the presence of solvents or diluents, including, for example, solvents or diluents that are inert towards the reagents used and dissolve them, in the absence or presence of catalysts, condensation or neutralizing agents, for example ion exchangers, such as cation exchangers, e.g., in the H⁺ form, depending on the nature of the reaction and/or of the reactants at reduced, normal or elevated temperature, for example in a temperature range of from about -100 °C to about 190 °C, including, for example, from approximately -80 °C to approximately 150 °C, for example at from -80 to -60 °C, at room temperature, at from -20 to 40 °C or at reflux temperature, under atmospheric pressure or in a closed vessel, where appropriate under pressure, and/or in an inert atmosphere, for example under an argon or nitrogen atmosphere.

At all stages of the reactions, mixtures of isomers that are formed can be separated into the individual isomers, for example diastereoisomers or enantiomers, or into any desired mixtures of isomers, for example racemates or mixtures of diastereoisomers, for example

The solvents from which those solvents that are suitable for any particular reaction may be selected include those mentioned specifically or, for example, water, esters, such as lower alkyl-lower alkanoates, for example ethyl acetate, ethers, such as aliphatic ethers, for example diethyl ether, or cyclic ethers, for example tetrahydrofurane or dioxane, liquid aromatic hydrocarbons, such as benzene or toluene, alcohols, such as methanol, ethanol or 1- or 2-propanol, nitriles, such as acetonitrile, halogenated hydrocarbons, such as methylene chloride or chloroform, acid amides, such as dimethylformamide or dimethyl acetamide, bases, such as heterocyclic nitrogen bases, for example pyridine or N-methylpyrrolidin-2-one, carboxylic acid anhydrides, such as lower alkanoic acid anhydrides, for example acetic anhydride, cyclic, linear or branched hydrocarbons, such as cyclohexane, hexane or isopentane, or mixtures of those solvents, for example aqueous solutions, unless otherwise indicated in the description of the processes. Such solvent mixtures may also be used in working up, for example by chromatography or partitioning.

The compounds, including their salts, may also be obtained in the form of hydrates, or their crystals may, for example, include the solvent used for crystallization. Different crystalline forms may be present.

The invention relates also to those forms of the process in which a compound obtainable as an intermediate at any stage of the process is used as starting material and the remaining process steps are carried out, or in which a starting material is formed under the reaction conditions or is used in the form of a derivative, for example in a protected form or in the form of a salt, or a compound obtainable by the process according to the invention is produced under the process conditions and processed further in situ.

Pro-drugs

The present invention also relates to pro-drugs of a compound of the present invention that are converted in vivo to the compounds of the present invention as described herein. Any reference to a compound of the present invention is therefore to be understood as referring also to the corresponding pro-drugs of the compound of the present invention, as appropriate and expedient.
Combinations

A compound of the present invention may also be used in combination with other agents, e.g., an additional HCV-modulating compound that is or is riot of the the formula A, B and C, for treatment of and HCV-associated disorder in a subject.

By the term "combination", is meant either a fixed combination in one dosage unit form, or a kit of parts for the combined administration where a compound of the present invention and a combination partner may be administered independently at the same time or separately within time intervals that especially allow that the combination partners show a cooperative, e.g., synergistic, effect, or any combination thereof.

For example, WO 2005/042020, incorporated herein by reference in its entirety, describes the combination of various HCV inhibitors with a cytochrome P450 ("CYP") inhibitor. Any CYP inhibitor that improves the pharmacokinetics of the relevant NS3/4A protease may be used in combination with the compounds of this invention. These CYP inhibitors include, but are not limited to, ritonavir (WO 94/14436, incorporated herein by reference in its entirety), ketoconazole, troleandomycin, 4-methyl pyrazole, cyclosporin, clomethiazole, cimetidine, itraconazole, fluconazole, miconazole, fluvoxamine, fluoxetine, nefazodone, sertraline, indinavir, nelfinavir, amparenavir, fosamprenavir, saquinavir, lopinavir, delavirdine, and erythromycin. Preferred CYP inhibitors include ritonavir, ketoconazole, troleandomycin, 4-methyl pyrazole, cyclosporin, and clomethiazole.

Methods for measuring the ability of a compound to inhibit CYP activity are known (see, e.g., US 6,037,157 and Yun, et al. Drug Metabolism & Disposition, vol. 21, pp. 403-407 (1993); incorporated herein by reference). For example, a compound to be evaluated may be incubated with 0.1, 0.5, and 1.0 mg protein/ml, or other appropriate concentration of human hepatic microsomes (e.g., commercially available, pooled characterized hepatic microsomes) for 0, 5, 10, 20, and 30 minutes, or other appropriate times, in the presence of an NADPH-generating system. Control incubations may be performed in the absence of hepatic microsomes for 0 and 30 minutes (triplicate). The samples may be analyzed for the presence of the compound. Incubation conditions that produce a linear rate of compound metabolism will be used a guide for further studies. Experiments known in the art can be used to determine the kinetics of the compound metabolism ($K_m$ and $V_{max}$). The rate of disappearance of compound may be determined and the data analyzed according to Michaelis-Menten kinetics by using Lineweaver-Burk, Eadie-Hofstee, or nonlinear regression analysis.
Inhibition of metabolism experiments may then be performed. For example, a compound (one concentration, \( \leq IC_{50} \)) may be incubated with pooled human hepatic microsomes in the absence or presence of a CYP inhibitor (such as ritonavir) under the conditions determined above. As would be recognized, control incubations should contain the same concentration of organic solvent as the incubations with the CYP inhibitor. The concentrations of the compound in the samples may be quantitated, and the rate of disappearance of parent compound may be determined, with rates being expressed as a percentage of control activity.

Methods for evaluating the influence of co-administration of a compound of the invention and a CYP inhibitor in a subject are also known (see, e.g., US2004/0028755; incorporated herein by reference). Any such methods could be used in connection with this invention to determine the pharmacokinetic impact of a combination. Subjects that would benefit from treatment according to this invention could then be selected.

Accordingly, one embodiment of this invention provides a method for administering an inhibitor of CYP3A4 and a compound of the invention. Another embodiment of this invention provides a method for administering an inhibitor of isozyme 3A4 ("CYP3A4"), isozyme 2C19 ("CYP2C19"), isozyme 2D6 ("CYP2D6"), isozyme 1A2 ("CYP1A2"), isozyme 2C9 ("CYP2C9"), or isozyme 2E1 ("CYP2E1"). As would be appreciated, CYP3A4 activity is broadly observed in humans. Accordingly, embodiments of this invention involving inhibition of isozyme 3A4 would be expected to be applicable to a broad range of patients.

Accordingly, this invention provides methods wherein the CYP inhibitor is administered together with the compound of the invention in the same dosage form or in separate dosage forms.

Methods of this invention may also involve administration of another component comprising an additional agent selected from an immunomodulatory agent; an antiviral agent; an inhibitor of HCV protease; an inhibitor of another target in the HCV life cycle; a CYP inhibitor; or combinations thereof.

Accordingly, in another embodiment, this invention provides a method comprising administering a compound of the invention and another anti-viral agent, preferably an anti-HCV agent. Such anti-viral agents include, but are not limited to, immunomodulatory agents, such as \( \alpha \), \( \beta \), and \( \delta \) interferons, pegylated derivatized interferon-a compounds, and thymosin;
other anti-viral agents, such as ribavirin, amantadine, and telbivudine; other inhibitors of hepatitis C proteases (NS2-NS3 inhibitors and NS3-NS4A inhibitors); inhibitors of other targets in the HCV life cycle, including helicase, polymerase, and metalloprotease inhibitors; inhibitors of internal ribosome entry; broad-spectrum viral inhibitors, such as IMPDH inhibitors (e.g., compounds of United States Patent 5,807, 876,6, 498,178, 6,344, 465,6, 054,472, WO 97/40028, WO 98/40381, WO 00/56331, and mycophenolic acid and derivatives thereof, or combinations of any of the above.

Examples of interferons for use in combination with the compounds of the invention, include, but are not limited to, interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, lymphoblastoid interferon, and interferon tau; and said compound having anti-hepatitis C virus activity is selected from the group consisting of interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, double stranded RNA, double stranded RNA complexed with tobramycin, Imiquimod, ribavirin, an inosine 5'-monophosphate dehydrogenase inhibitor, amantadine, and rimantadine.

Other agents (e.g., non-immunomodulatory or immunomodulatory compounds) that may be used in combination with a compound of this invention include, but are not limited to, those specified in WO 02/18369, which is incorporated herein by reference.

Still other agents for use in combination with the compounds of the invention include, but are not limited to, PEG-INTRON® (peginterferon alfa-2b, available from Schering Corporation, Kenilworth, NJ); INTRON-A®, (interferon alfa-2b available from Schering Corporation, Kenilworth, NJ); ribavirin (1-beta-D-ribofuranosyl-IH-1, 2,4-triazole-3-carboxamide, available from ICN Pharmaceuticals, Inc., Costa Mesa, CA; described in the Merck Index, entry 8365, Twelfth Edition); REBETROL® (Schering Corporation, Kenilworth, NJ), COPEGASUS® (Hoffmann-La Roche, Nutley, NJ); PEGASYS® (peginterferon alfa-2a available Hoffmann-La Roche, Nutley, NJ); ROFERONO® (recombinant interferon alfa-2a available from Hoffmann-La Roche, Nutley, NJ); BEREFOR® (interferon alfa 2 available from Böehringer Ingelheim Pharmaceutical, Inc., Ridgefield, CT); SUMIFERON® (a purified blend of natural alpha interferons such as Sumiferon available from Sumitomo, Japan); WELLFERON® (interferon alpha nl available from Glaxo Wellcome Ltd., Great Britain); ALFERON® (a mixture of natural alpha interferons made by Interferon Sciences, and available from Purdue Frederick Co., CT); a-interferon; natural alpha interferon 2a; natural alpha interferon 2b; pegylated alpha interferon

Each component of a combination according to this invention may be administered separately, together, or in any combination thereof. As recognized by skilled practitioners, dosages of interferon are typically measured in IU (e.g., about 4 million IU to about 12 million IU).

If an additional agent is selected from another CYP inhibitor, the method would, therefore, employ two or more CYP inhibitors. Each component may be administered in one or more dosage forms. Each dosage form may be administered to the patient in any order.

The compound of the invention and any additional agent may be formulated in separate dosage forms. Alternatively, to decrease the number of dosage forms administered to a patient, the compound of the invention and any additional agent may be formulated together in any combination. For example, the compound of the invention inhibitor may be formulated in one dosage form and the additional agent may be formulated together in
another dosage form. Any separate dosage forms may be administered at the same time or
different times.

Alternatively, a composition of this invention comprises an additional agent as
described herein. Each component may be present in individual compositions, combination
compositions, or in a single composition.
Exemplification of the Invention

The invention is further illustrated by the following examples, which should not be construed as further limiting. The assays used throughout the Examples are accepted. Demonstration of efficacy in these assays is predictive of efficacy in subjects.

GENERAL SYNTHESIS METHODS

All starting materials, building blocks, reagents, acids, bases, dehydrating agents, solvents, and catalysts utilized to synthesis the compounds of the present invention are either commercially available or can be produced by organic synthesis methods known to one of ordinary skill in the art (Houben-Weyl 4th Ed. 1952, Methods of Organic Synthesis, Thieme, Volume 21). Further, the compounds of the present invention can be produced by organic synthesis methods known to one of ordinary skill in the art as shown in the following examples.

Representative Synthesis I

[Chemical structure images]
(R)-l-(4-Chloro-benzyl)-piperazine-2-carboxylic acid methyl ester

R-4N-Boc-piperazine 2-carboxylic acid methyl ester (679.4mg, 2.78mmol) and 4-chlorobenzaldehyde (390.94mg, 2.78mmol) are mixed in dichloromethane (10ml) for 30 minutes. Sodium triacetoxyborohydride (800mg, 3.77mmol) is added. The mixture is stirred at room temperature for 16 hrf. Water is added. The aqueous layer is extracted with dichloromethane twice (30ml x 2). The dichloromethane solution is treated with trifluoracetic acid (30ml). After 4 hrs the solvent is evaporated and re-dissolved in water. The water solution is basified by adding K$_2$CO$_3$ (solid). The water solution is extracted with EtOAc three times. The organic layer is dried over Na$_2$SO$_4$. The product is colorless `oil (748mg, 100%) after removing solvent to dryness. Found m/z ES+=269.

(i?)-l-(4-Chloro-benzyl)-piperazine-2-carboxylic acid methyl ester

A dichloromethane (5ml) solution of (-S)-2-((S)-2-Cyclohexyl-2-[[pyrazine-2-carbonyO-aminol-acetylaminol-S^-dimethyl-butyryty-piperazine^-carboxylic acid methyl ester (268mg, 0.71mmol) is treated with 1,3-dicyclohexyl carbodiimide (160mg, 0.77mmol), and 7-aza-1-hydroxy (96.9mg, 0.71mmol). After stirring for 30 min., the reaction mixture is treated with a THF solution (5ml) of (i?)-l-(4-Chloro-benzyl)-piperazine-2-carboxylic acid methyl ester (174mg,
0.65mmol). The reaction mixture is stirred at room temperature for 16 hrs. The white solid is removed by filtration. The filtrates are concentrated in vacuo to give a residue that is purified by flash column chromatography 2%-100% EtOAc/Hexane. The product is obtained as a colorless oil (369mg). Found m/z ES+ = 627


To the solution of compound (Λ)-1-(4-Chloro-benzyl)-4-((S)-2-{((S)-2-cyclohexyl-2-[pyrazine-2-carbonyl]-amino]-acetylamino]-3,3-dimethyl-butyryl)-piperazine-2-carboxylic acid methyl ester(369mg, 0.589mmol) in THF/ H₂O (10ml/4ml) is added Lithium hydroxy (53mg, 1.26mmol). The mixture is stirred at room temperature for 16 hours. The solution is acidified by IN HCl; The aqueous layer is extracted by EtOAc. Dried over NaSO₄. The product is obtained as a white solid (390mg) after removing the solvent to dryness. Found m/z ES+ = 613

(±)-1-(4-Chloro-benzyl)-4-((S)-2-cyclohexyl-2-[(pyrazine-2-carbonyl)-amiηo]-acetylamino)-3,3-dimethyl-butyryl)-piperazine-2-carboxylic acid (62.72mg, 0.1mmol), 1-ethyl-3-(3′-(dimethylamino)propyl)carbodiimide hydrochloride (28.65, 0.15mmol), 1-hydroxybenzotriazole (20.26mg, 0.15mmol) are mixed in CH₂Cl₂/DMF (3mL/3mL). N-methyl morpholine (0.04ml, 0.36mmol) is added. The mixture is stirred for 16 hrs. Purified by Biotage 2%-100% EtOAc/Hexane, then 2%-10% MeOH/Hexane. The product is obtained as colorless oil 50mg. Found m/z ES+ = 766

Pyrazine-2-carboxylic acid ((S)-1-[(R)-3-(2-carbamoyl-1-cyclobutylmethyl-2-oxoethylcarbamoyl)-4-(4-chloro-benzyl)-piperazine-1-carbonyl]-2,2-dimethylpropylcarbamoyl]-cyclohexyl-methyl)-amide

To a dichloromethane solution (5mL) of Pyrazine-2-carboxylic acid ((S)-1-[(R)-3-(2-carbamoyl-1-cyclobutylmethyl-2-hydroxy-ethylcarbamoyl)-4-(4-chloro-benzyl)-piperazine-1-carbonyl]-2,2-dimethyl-propylcarbamoyl]-cyclohexyl-methyl)-amide (50mg, 0.065mmol) is added Dess-Martin periodinane (49.96mg, 0.12mmol). The reaction is stirred
at room temperature for 1 hr and quenched with 10% NaSO$_3$(1OmI) for 20 mins. The resulting mixture is extracted with EtOAc. The resulting residue is purified by Biotage 2%-100% EtOAc/Hexane, then 2%-20% MeOH/EtOAc. The product is obtained as a white solid (25.9mg). Found m/z ES$^+$=764.

Pyrazine-2-carboxylic acid (-(S)-(S))-1-(2-carbamoyl-1-cyclobutylmethyl-2-oxoethylcarbamoyl)-4-(4-chlorophenyl)-piperazine-1-carbonyl]-2,2-dimethylpropylcarbamoyl]-cyclohexyl-methyl)-amide

This compound is prepared similarly using (R)-1-(4-Chlorophenyl)-piperazine-2-carboxylic acid methyl ester as prepared below (after treatment with trifluoroacetic acid and basification with sodium carbonate) in place of (R)-1-(4-Chloro-benzyl)-piperazine-2-carboxylic acid methyl ester.

(R)-1-(4-Chlorophenyl)-piperazine-2-carboxylic acid methyl ester

R-4N-Boc-piperazine 2-carboxylic acid methyl ester (4.0gms, 16.4mmol) and 4-chlorophenylboronic acid (5.0gms, 32.8mmol) are mixed in dichloromethane (50ml) followed by addition of cupric acetate (3.0gms, 16.4mmol), 4A molecular sieves (1 gm) and pyridine (3.28ml, 32.8mmol). The mixture is stirred at room temperature for 50 hr. The reaction mixture is concentrated directly in vacuo, diluted with ethyl acetate, and filtered through Celite. The organic filtrate is concentrated and the remaining residue is purified over silica gel column chromatography eluting with hexane and ethyl acetate to give 860 mg as a
white solid.

Representative Synthesis II

To a solution of 1a (3.0 g, 7.84 mmol) in dichloromethane (20 mL) at room temperature is added trifluoroacetic acid (20 mL). The mixture is stirred for 3 hrs after which the solvent is concentrated in vacuo to give the desired product (4.5 g, quant.). Found m/z ES+ = 283 and ES- = 281.

Step B

A solution of 1c (2.18 g, 9.45 mmol) in anhydrous dichloromethane (57 mL) and
anhydrous DMF (57 mL) is stirred at 0°C and treated with HATU (1.4 eq, 5.0 g, 13.23 mmol), Ib (1.2 eq, 4.50 g, 11.34 mmol) is added in small portions. Then, N-
methylmorpholine (4.0 eq, 3.82 g, 4.16 mL, 37.8 mmol, d 0.92) is added dropwise. The reaction mixture is gradually warmed to room temperature and stirred for overnight. All the volatiles are removed under vacuum and the residue is dissolved in ethylacetate (300 mL). The organic layer is washed with water (60 mL), aqueous 1N HCl (60 mL), aqueous saturated sodium bicarbonate solution (60 mL), and brine (60 mL). The organic layer is dried over Na₂SO₄, filtered and concentrated in vacuo. The residue is chromatographed on silica gel (gradient: acetone/hexane; 2:8 to 1:1) to afford the desired product Id (3.11 g). Found m/z ES+ = 496.

Step C

To a solution of Id (3.1 g, 6.25 mmol) in dichloromethane (15 mL) at room temperature is added trifluoroacetic acid (15 mL). The mixture is stirred for 3 hrs after which the solvent is concentrated in vacuo to give the desired product (4.7 g, quant.). Found m/z ES+ = 396.

Step D
The reaction mixture is gradually warmed to room temperature and stirred overnight. All the volatiles are removed under vacuum and the residue is dissolved in ethylacetate (500 mL). The organic layer is washed with water (100 mL), aqueous IN HCl (100 mL), aqueous saturated sodium bicarbonate solution (100 mL), and brine (100 mL). The organic layer is dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue is chromatographed on silica gel (gradient: acetone/hexane; 2:8 to 1:1) to afford the desired product Ig (3.0 g). Found m/z ES⁺ = 635.

Step E

A solution of the allyl ester Ig (3.0 g, 4.72 mmol) in 45 mL of a 1:1:1 mixture of THF/MeOH/water is added lithium hydroxide monohydrate (2 eq, 394 mg). The mixture is stirred for overnight and checked by LC/MS and showed the completion of the reaction. All the volatiles are evaporated in a vacuo and to the residue is added dichloromethane (100 mL). The pH of the aqueous layer is adjusted to pH 5 with a dropwise addition of aqueous IN HCl and layers are separated. The aqueous layer is extracted with dichloromethane (3 x 50 mL). The combined organic layers are dried over sodium sulfate, filtered, and concentrated to afford the desired product Ih (1.87 g) as white solid. Found m/z ES⁺ = 595 and ES⁻ = 593.
A solution of the acid Ii (2.80 g, 4.7 mmol) in anhydrous dichloromethane (24 mL) and anhydrous DMF (24 mL) is stirred at 0°C and treated with HATU (1.4 eq, 2.5 g, 6.58 mmol). The hydroxy ketoamide amine Ij (1.2 eq, 1.05 g, 5.66 mmol) is added in small portions. Then, N-methylmorpholine (4.0 eq, 1.90 g, 2.06 mL, 18.80 mmol, d 0.92) is added dropwise. The reaction mixture is gradually warmed to room temperature and stirred for overnight. All the volatiles are removed under vacuum and the residue is dissolved in ethylacetate (200 mL). The organic layer is washed with water (50 mL), aqueous IN HCl (50 mL), aqueous saturated sodium bicarbonate solution (100 mL), and brine (50 mL). The organic layer is dried over Na2SO4, filtered and concentrated in vacuo. The residue is chromatographed on silica gel (gradient: acetone/hexane; 2:8 to 1:1) to afford the desired product Ik (3.0 g). Found m/z ES+ = 763 and ES- = 761.

To a solution of Ik (4.0 g, 5.24 mmol) in dichloromethane (26 mL) at room temperature is added trifluoroacetic acid (26 mL). The mixture is stirred for 3 hrs after which the solvent is concentrated in vacuo and the residue is added dichloromethane (100 mL). The pH is adjusted to pH 8 by dropwise addition of saturated sodium bicarbonate. The layers are separated and the organic layer with washed with brine, dried over Na2SO4, filtered and concentrated to give the desired product 11 (4.0 g). Found m/z ES+ = 663 and ES- =
Step H

To a solution of the amine (350 mg, 0.53 mmol) in dioxane (1.0 mL) at rt added 2-chlorobenzazazole (122 mg, 0.79 mmol) and sodium bicarbonate (89 mg, 1.1 mmol). The mixtures are stirred at 65 °C for 6 hs. The mixture is loaded directly to silical gel column and eluted with hexane/EtOH (from 95/5 to 85/15) to give the desired product (360 mg, 87 % yield). Found m/z ES+ = 780 and ES- = 778.

Step I

To a solution of the alcohol (253 mg, 0.32 mmol) in CH₂Cl₂ (1.6 mL) at 0 °C added DIPEA (1.3 mmol, 168 mg, 226µL) followed by a solution of pyridine sulfoxide (0.65 mmol, 103 mg) in DMSO (1.6 mL). The solution is stirred at 0 °C for 10 min. To the solution is added EtOAc and sat. aq. NH₄Cl solution. Phases are separated. The aqueous layer is extracted with EtOAc and the organic layers are combined, washed with brine, dried over Na₂SO₄ and concentrated. The residue is purified by silical gel column chromatography (hexane/Acetone, 1/1) to give the desired product (245 mg, 97 %). Found m/z in ES+ 778, m/z in ES- = 776.
Representative Synthesis III

To a solution of 2-pyrazinecarboxylic acid (1.44 g, 11.6 mmol) dissolved in THF (30 mL) at RT is added EDC (2.23 g, 11.6 mmol), HOBt (1.57 g, 11.6 mmol) and the solution stirred for 20 min. Cyclohexylglycine methyl ester (2.0 g, 9.6 mmol, Cat# 12003, Chemilempex), Diisopropylamine (2.5 g, 19.3 mmol) is added and the reaction stirred at overnight. The sample is then concentrated and then dissolved in EtOAc (100 mL) then washed with NH₄Cl (50 mL), NaHCO₃ (Sat'd, 50 mL), NaCl (Sat'd, 50 mL) then dried over...
MgSO₄ and concentrated to yield a yellow oil. The sample is then purified by FCC to furnish the white solid (2.6 g, 9.4 mmol): ES-MS: [M+H]⁺ = 278.2

Synthesis of Compound 4

![Diagram of Compound 4 synthesis](image)

The ester (416 mg, 1.5 mmol) in MeOH (12 mL) is added NaOH (2N, 1.9 mL, 3.75 mmol) and the solution allowed to stir overnight at RT. The reaction mixture is then acidified with resin (IR-120 H⁺). The solids are filtered off and the filtrate concentrated to afford a solid (395 mg, 1.50 mmol). The acid is used directly in the next step. ES-MS: [M+H]⁺ = 264.0.

Synthesis of Compound 6

![Diagram of Compound 6 synthesis](image)

To a solution acid (249 mg, 0.90 mmol) dissolved in THF (2.8 mL) at RT is added EDC (172 mg, 0.90 mmol), HOBt (121 mg, 0.90 mmol) and the solution stirred for 20 min. Amine (274 mg, 0.90 mmol) dissolved in DMF:THF (0.2 mL: 0.8 mL), Diisopropylamine (231 mg, 1.80 mmol) is added and the reaction stirred at RT overnight. The sample is then concentrated and then dissolved in EtOAc (50 mL) then washed with NH₄Cl (20 mL), NaHCO₃ (Sat'd, 20 mL), NaCl (Sat'd, 20 mL) then dried over MgSO₄ and concentrated to yield a yellow oil. The sample is then purified by FCC (EtOAc: Hexane 1:1) to furnish the product (406 g, 0.78 mmol). ES-MS: [M+H]⁺ = 516.1
Synthesis of Compound 7

To a solution of the ethyl ester (495 mg, 0.97 mmol) dissolved in THF: H2O (3:1, 3.9:1.3 mL) cooled at 0°C is added LiOH (1.3 mL, 1.3 mmol, 1.3 M solution) dropwise over a 10 min interval. The solution is allowed to warm to RT and stirred overnight. The reaction mixture is then acidified with resin (IR-120 H+) The solids are filtered off and the filtrate concentrated to afford a solid (472 mg, 0.97 mmol), ES-MS:[M+H]⁺ = 488.1.

Synthesis of Compound 9

The acid (474 mg, 0.98 mmol) is dissolved CH₂Cl₂:DMF (1:1 20 mL) and the solution cooled to 0°C and treated with HATU (525 mg, 1.38 mmol). The amine (218 mg, 1.17 mmol) is then added in small portions followed by dropwise addition of MMM (397 mg, 3.92 mmol). The reaction mixture is allowed to warm to RT and then stirred overnight. The sample is then concentrated and then dissolved in EtOAc (50 mL) then washed with Citric acid (20 mL, 10%), NaHCO₃ (Sat'd, 20 mL), NaCl (Sat'd, 20 mL) then dried over MgSO₄ and concentrated off with solid. The sample is then purified by FCC (Acetone: Heptane 1:1) to furnish the product (614 mg, 0.91 mmol), ES-MS:[M+H]⁺ = 656.4,
Synthesis of Compound 10

To a solution of the alcohol (740 mg, 1.13 mmol) in DCM (24 mL) is added DMP reagent and the mixture is stirred at RT for 1h. The mixture is then filtered through a pad of celite. The celite is washed with additional DCM (2x20 mL) and the combined filtrate washed with Na$_2$SO$_3$ (15 mL, 1M solution), NaHCO$_3$ (sat'd, 15 mL), NaCl (sat'd, 15 mL) then dried over MgSO$_4$ and evaporated to dryness. FCC (Acetone: Heptane 1:1) gave a white solid (309 mg, 0.47 mmol). ES-MS:[M+H$^+$] = 654.3.

**Representative Synthesis IV**

(S)-l-Quinolin-4-ylmethyl-pyrrolidine-3-carboxylic acid [(lR,2S)-l-(3-benzyloxy-benzenesulfonylaminocarbonyl)-2-vinyl-cyclopropyl]-amide

(S)-Pyrrolidine-3-carboxylic acid [(IR,2S)-l-(3-benzyloxy-benzenesulfonylaminocarbonyl)-2-vinyl-cyclopropyl]-amide (0.1 g) and quinoline-4-carboxaldehyde (0.033 g) in 2 mL OfCH$_2$Cl$_2$ are treated with sodiumtriacetoxyborohydride (0.071 g) and stirred overnight at RT. More sodiumtriacetoxyborohydride (0.071 g) in THF is added together with 2 drops of acetic acid. The reaction mixture is stirred at RT for 72 hours, taken up in CH$_2$Cl$_2$, extracted with aqueous NaHCO$_3$, and concentrated to an oil. The residue is chromatographed on SiO$_2$ gel (eluent CH$_2$Cl$_2$/MeOH 95:5 to 9:1) to give (S)-l-quinolin-4-ylmethyl-pyrrolidine-3-carboxylic acid [(IR,2S)-l-(3-benzyloxy-benzenesulfonylaminocarbonyl)-2-vinyl-cyclopropyl]-amide as a white powder. API-MS:
beiizenesulfonylaminocarbonyl^-vinyl-cyclopropyll-amide hydrochloride (0.08 g), 1-(chloromethyl)-naphthalene (0.033 g), and K$_2$CO$_3$ (0.066 g) in 1 mL of DMF is stirred at RT overnight. The reaction mixture is taken up in IN HCl, extracted with EtOAc, and concentrated. The residue is chromatographed by preparative reverse phase HPLC (CH$_3$CN, H$_2$O, TFA) to give (S)-I-naphthalen-1-ylmethyi-pyrrolidine-3-carboxylic acid [(lR,2S)-l-(3-benzyloxy-benzenesulfonylaminocarbonyl)-2-vinyl-cyclopropyl]-amide as a white powder. API-MS: M+1 = 610.

(S)-1-Naphthalen-1-ylmethyl-pyrrolidine-3-carboxylic acid [(lR,2S)-l-(3-benzyloxy-benzenesulfonylaminocarbonyl)-2-vinyl-cyclopropyl]-amide

A solution of (S)-pyrrolidine-3-carboxylic acid [(lR,2S)-l-(3-benzyloxy-beiizenesulfonylaminocarbonyl^-vinyl-cyclopropyll-amide hydrochloride (0.08 g), 1-(chloromethyl)-naphthalene (0.033 g), and K$_2$CO$_3$ (0.066 g) in 1 mL of DMF is stirred at RT overnight. The reaction mixture is taken up in IN HCl, extracted with EtOAc, and concentrated. The residue is chromatographed by preparative reverse phase HPLC (CH$_3$CN, H$_2$O, TFA) to give (S)-I-naphthalen-1-ylmethyi-pyrrolidine-3-carboxylic acid [(lR,2S)-l-(3-benzyloxy-benzenesulfonylaminocarbonyl)-2-vinyl-cyclopropyl]-amide as a white powder. API-MS: M+1 = 610.

(S)-Pyrrolidine-3-carboxylic acid [(lR,2S)-l-(3-benzyloxy-benzenesulfonylaminocarbonyl-2-vinyl-cyclopropyl]-amide is prepared as follows:

3-Bromophenol (19 g) and benzylbromide (15.7 mL) in acetone (200 mL) are treated with potassium carbonate (60.1 g) and the reaction mixture is stirred at RT for 72 hours. The reaction is filtered and the filter cake is washed with acetone. The filtrate is concentrated and purified via chromatography on SiO$_2$ gel (eluent hexanes/EtOAc 96:4) to give 1-benzyloxy-3-bromobenzene as a white solid.

{93-}
A solution of 1-benzyloxy-3-bromobenzene (28.3 g) in Et₂O (375 mL) is cooled to -70 °C and treated with TMEDA (19.2 mL) and t-BuLi in hexane (1.6 M, 79 mL). The solution is stirred at -70 °C for 1 h and transferred into a cooled solution (-70 °C) of SO₂ (54.4 g) in Et₂O (375 mL). The mixture is kept at -70 °C for 15 minutes, then allowed to warm to RT over 1 h. The solvent is evaporated and the residue is suspended in aqueous sodium phosphate (IM, 750 mL, pH 6). EtOAc (500 mL) is added and the solution is cooled to 0 °C. JV-Chlorosuccinimide (43.5 g) is slowly added and the pH is readjusted to pH 6 by addition of Na₂PO₄. The reaction mixture is stirred vigorously for 1 h. The phases are separated and the aqueous phase is extracted twice with EtOAc. The combined organic phases are washed with H₂O and brine, dried and concentrated to give a yellowish oil. The residue is taken up in dioxane (400 mL) and NH₃ in H₂O (28%, 200 mL) is added. The reaction mixture is stirred for 12 h and then concentrated to dryness. The residue is chromatographed on SiO₂ gel (eluent hexanes/EtOAc 4:1 to 3:7) to give 3-benzyloxybenzenesulfonamide as a white powder. API-MS: M-I = 262.

A solution of 0.7 g of (R,2S)-\-ter\-butoxycarbonylamino-2-vinylcyclopropanecarboxylic acid (prepared as described in Journal of Organic Chemistry, 2005, 5869-5879) in THF (10 mL) is treated with carbonyldiimidazole (0.789 g) and the reaction mixture is stirred at 65 °C for 30 min. The mixture is allowed to cool to RT and 3-benzyloxybenzenesulfonamide (1.05 g) and DBU (0.697 mL) are added. The solution is stirred at RT for
12 h. The reaction mixture is taken up in EtOAc, washed with 0.1N aqueous HCl, aqueous NaHCO₃ and brine, dried with Na₂SO₄ and concentrated. The residue is chromatographed on SiO₂ gel (eluent hexanes/EtOAc 7:3 to EtOAc, then EtOAc/MeOH 9:1) to give [(l/R,2S)-1-(3-benzylpopy-benzenesulfonylaminocarbonyl)-2-vinyl-cyclopropyl]-carbamic acid tert-butyl ester. API-MS: M+1 = 473.

A solution of [(lR,2S)-1-(3-benzylp oxy-benzenesulfonylaminocarbonyl)-2-vinyl-cyclopropyl]-carbamic acid tert-butyl ester (0.85 g) in dioxane (5 mL) is treated with HCl in dioxane (4N, 10 mL) and is stirred at RT for 4 h. The reaction mixture is evaporated to give N-((lR, 2S)-1-amino^-vinyl-cyclopropanecarbonyO-S-benzyloxy-benzenesulfonamide hydrochloride. API-MS: M+1 = 373.

A solution of (S)-pyrrolidine-1,3-dicarboxylic acid-1-tert-butylester (0.35 g), N-((lR, 2S)-1-aminio-2-vinyl-cyclopropanecarbonyl)-3-benzyloxy-benzenesulfonamide (0.665 g) and Hunig's base (0.852 mL) in 4 mL of DMF is treated with TBTU (0.627 g) and stirred at RT overnight. The reaction mixture is treated with 0.1 N HCl, extracted with EtOAc, washed with saturated aqueous NaHCO₃, brine, and concentrated in vacuo. The crude product is chromatographed by preparative reverse phase HPLC (CH₃CN, H₂O, TFA) to give (S)-[(lR,2S)-1-(3-Benzylp oxy-benzenesulfonylaminocarbonyl)-2-vinyl-cyclopropylcarbamoyl]-
pyrrolidine-1-carboxylic acid /erf-butyl ester. API-MS: M-I = 568.

A suspension of (S)-3-[(lR,2S)-l-(3-benzyloxy-benzenesulfonylamino)carbonyl]-2-vinyl-cyclopropylcarbamoyll-pyrrolidine-1-carboxylic acid tert-buty\ ester (0.669 g) and 4N HCl in dioxane (5 mL) in 20 mL of dioxane is stirred at RT for 3 hours. The reaction mixture is concentrated in vacuo, treated with MeOH, and concentrated again to give (S)-pyrrolidine-3-carboxylic acid [(lR,2S)-l-(3-benzyloxy-benzenesulfonylamino)carbonyl]-2-vinyl-cyclopropyl]-amide hydrochloride. API-MS: M+I = 470
BIOLOGICAL ACTIVITY

Example 1: HCV NS3-4A protease assay

The inhibitory activities of the compounds of the invention against HCV NS3-4A serine protease is determined in a homogenous assay using the full-length NS3-4A protein (genotype Ia, strain HCV-I) and a commercially available internally-quenched fluorogenic peptide substrate as described by Taliani, M., et al. 1996 Anal. Biochem. 240:60-67.

Example 2: Luciferase-based HCV repHcon assay

The antiviral activity and cytotoxicity of the compounds of the invention is determined using a subgenomic genotype Ib HCV replicon cell line (Huh-Luc/neo-ET) containing a luciferase reporter gene, the expression of which is under the control of HCV RNA replication and translation. Briefly, 5,000 replicon cells are seeded in each well of 96-well tissue culture plates and are allowed to attach in complete culture media without G418 overnight. On the next day, the culture media are replaced with media containing a serially diluted compound of the invention in the presence of 10% FBS and 0.5% DMSO. After a 48-h treatment with the compounds of the invention, the remaining luciferase activities in the cells are determined using BriteLite reagent (Perkin Elmer, Wellesley, Massachusetts) with a LMaxII plate reader (Molecular Probe, Invitrogen). Each data point represents the average of four replicates in cell culture! IC_{50} is the concentration of the compound of the invention at which the luciferase activity in the replicon cells is reduced by 50%. The cytotoxicity of the compound of the invention are evaluated using an MTS-based cell viability assay.
Equivalents

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments and methods described herein. Such equivalents are intended to be encompassed by the scope of the following claims.

Incorporation by Reference

The entire contents of all patents, published patent applications and other references cited herein are hereby expressly incorporated herein in their entireties by reference. The entire contents of copending provisional patent applications U.S.S.N. 60/791,611, U.S.S.N. 60/791,318, and U.S.S.N. 60/791,578, each of which was filed on April 11, 2006, and U.S.S.N. 60/866,874, filed on November 22, 2006 and non-provisional patent applications claiming the benefit therefrom are expressly incorporated herein, in their entirety, as applied to the compounds of the present invention.
CLAIMS

1. A compound of the formula A:

\[ \text{CG} \quad \text{P}_3 \quad \text{P}_2 \quad \text{W} \]

and pharmaceutically acceptable salts and stereoisomers thereof;

wherein

- CG is selected from the group consisting of

- wherein \( R^{18} \) is selected from the group consisting of hydrogen, a halogen atom, aryl, trihalomethyl, and \( \text{C}_{1-4}\)-alkyl;
  - \( P_3 \) is a \( P_3 \) activity moiety;
  - \( P_2 \) is a \( P_2 \) activity moiety;
  - \( W \) is a \( W \) activity moiety;
- \( y \) is 0 or 1;
- \( x \) is 0 or 1; and
- \( R^1, R^2, R^8, R^9, R^{11}, R^{12} \) and \( R^{13} \) are each, independently, selected from the group consisting of \( \text{H}, \text{alkyl}, \text{alkyl-aryl}, \text{heteroalkyl}, \text{heterocyclyl}, \text{heteroaryl}, \text{aryl-etheraryl}, \text{alkyl-heteroaryl}, \text{cycloalkyl}, \text{cycloalkyl-alkyl}, \text{heterocyclyl}, \text{heteroaryl-etheraryl}, \text{cycloalkyl}-\text{amino}, \text{alkylamino}, \text{arylamino}, \text{alkyl-aryl-aminino}, \text{arylamino}, \text{heteroaryl-aminino}, \text{cycloalkylamino}, \text{carboxyalkylamino}, \text{arylalkyloxoy} \) and heterocyclylamino; all of which may be further independently substituted one or more times with \( X^1 \) and \( X^2 \); wherein \( X^1 \) is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, alkyl, alkylaryl, arylalkyl, arylheteroaryl, heteroaryl, heterocyclylaminino, alkylheteroaryl, or heteroarylalkyl; wherein \( X^1 \) can be independently substituted with one or more of \( X^2 \) moieties which can be the same or different and are independently selected; wherein \( X^2 \) is hydroxy, alkyl, aryl, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, alkysulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carbamido,
alkoxycarbonylamino, alkoxycarbonyloxy, alkylureido, arylureido, halogen, cyan, keto,
esteric or nitro; wherein each of said alkyl, alkoxy, and aryl can be unsubstituted or optionally
independently substituted with one or more moieties which can be the same or different and
are independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl,
heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, arytheteroaryl, heteroaryl,
heterocyclylamino, alkylheteroaryl and heteroaryl alkyl.

2. The compound of claim 1, wherein P3 is selected from the group consisting of H, Ci-4-alkyl, and (CH₂)₀-₄-C₃₈₀-cycloalkyl, substituted or unsubstituted aryl, and substituted or
unsubstituted heterocycle.

3. The compound of claim 1, wherein P2 is represented by the formula A1, A2, A3, A4,
A5, A6, A7 or A8:

```
   O
  /  \  \
 N   A1
 /    \
R7   R22
\    /  \\
 R17 /  \  R16
    \   /
     R15
```

wherein
R₇, R₁₆, R₁₅, R₁₇ and R₂₂ are each, independently, selected from the group consisting
of H₃ alkyl, alkyl-aryl, heteroalkyl, heterocyclyl, heteroaryl. aryl-heteroaryl, alkyl-heteroaryl,
cycloalkyl, alkoxy, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocyclyloxy, cycloalkyl oxy,
amino, alkylamino, arylamino, alkyl-arylamino, arylamino, heteroarylaminio,
cycloalkylamino, carboxyalkylamino, arylalkyloxy and heterocyclylamino; all of which may
be further independently substituted one or more times with X¹ and X²; wherein X¹ is alkyl,
alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl,
arylalkyl, arylheteroaryl, heteroaryl, heterocyclylamino, alkylheteroaryl, or heteroarylalkyl;
wherein X¹ can be independently substituted with one or more of X² moieties which can be
the same or different and are independently selected; wherein X² is hydroxy, alkyl, aryl,
alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, alkylsulfonyl,
aryl sulfonyl, alkylsulfonamido, arylsulphonamido, carboxy, carboxyloxy, carboxamido,
alkoxycarbonylamino, alkoxycarbonyloxy, alkylureido, arylureido, halogen, cyano, keto,
ester or nitro; wherein each of said alkyl, alkoxy, and aryl can be unsubstituted or optionally
independently substituted with one or more moieties which can be the same or different and
are independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, arylheteroaryl, heteroaryl, heterocyclylamino, alkylheteroaryl and heteroarylalkyl;

or \( \mathbf{R}^2 \) and \( \mathbf{R}^6 \) may together form a 3, 4, 5, 6 or 7-membered ring that is aromatic or non-aromatic and may contain one or more heteroatoms, wherein the ring may be further substituted one or more times;

or \( \mathbf{R}^7 \) and \( \mathbf{R}^9 \) may together form a 3, 4, 5, 6 or 7-membered ring that is aromatic or non-aromatic and may contain one or more heteroatoms, wherein the ring may be further substituted one or more times;

or \( \mathbf{R}^{10} \) and \( \mathbf{R}^{14} \) may together form a 4, 5, 6 or 7-membered ring of the formula III:

![III](image)

wherein

\[
\begin{align*}
n & \text{and} \ g \text{ are each, independently, 0, 1 or 2, wherein } n \text{ and } g \text{ are not both 2;} \\
m & \text{is 0 or 1;} \\
X & \text{is O, N or C;} \\
\mathbf{R}^4 \text{ and } \mathbf{R}^{4a} & \text{are each, independently, selected from the group consisting of } H_3CM-alkyl, O-C_1-alkyl, N(H)-C_M-alkyl, (CH_2)_o-4-C_3^1-alkyl, \text{aryl and heterocycle, all of which may be independently substituted one or more times with a halogen atom or CM-alkyl;} \\
\mathbf{R}^5 & \text{is selected from the group consisting of oxo, -O-, H, Ci-alkyl, O-Ci-alkyl, N(H)-C M-alkyl, (CH_2)_o-4-C_3^1-alkyl, aryl and heterocycle, and any combination thereof, all of which may be independently substituted one or more times with a halogen atom, aryl, trihalomethyl, or CM-alkyl;} \\
\text{or } \mathbf{R}^4 \text{ and } \mathbf{R}^5 & \text{may together form a 4, 5, 6 or 7-membered ring that is aromatic or non-aromatic and may contain one or more heteroatoms, wherein the ring may be further substituted one or more times;} \\
\text{or } \mathbf{R}^{10} \text{ and } \mathbf{R}^{14} & \text{may together form a 4, 5, 6 or 7-membered ring that is aromatic or non-aromatic and may contain one or more heteroatoms, wherein the ring may be further substituted one or more times; wherein one of the rings that } \mathbf{R}^{10} \text{ and } \mathbf{R}^{14} \text{ may together form is a ring of the formula IV:}
\end{align*}
\]
wherein

the dashed line represents a single or double bond, wherein formula IV may be further

substituted one or more times;

wherein

n is 0 or 1;

X is N or C;

R^4 is selected from the group consisting of H, C_{1-4}-alkyl, C_{1-6}-cycloalkyl, aryl, heterocycle and heteroaryl, all of which may be independently substituted one or more times with a halogen atom or C_{1-4}-alkyl;

R^5 is selected from the group consisting of oxo, -O-, H, C_{1-4}-alkyl, C_{1-6}-cycloalkyl, aryl and heteroaryl, and any combination thereof, all of which may be independently substituted one or more times with a halogen atom, aryl, trihalomethyl, or C^-alkyl;

or R^4 and R^5 may together form a dimethyl cyclopropyl ring, a cyclopentane ring, or a phenyl ring, wherein the phenyl ring and dimethyl cyclopropyl ring may be substituted with a halogen atom, aryl, trihalomethyl, or C_{1-4}-alkyl, or such that a fused ring system is formed;

and

R^6 and R^7 are each, independently, selected from the group consisting of H, C_{1-4}-alkyl and (CH2)o-t-C_{3^-cycloalkyl};
wherein

R⁴, R⁵ and R⁶ are each, independently, selected from the group consisting of H, alkyl, alkyl-aryl, heteroalkyl, heterocyclyl, heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyloxy, alkyl-aryloxy, arylxy, heteroaryloxy, heterocyclyloxy, cycloalkyloxy, amino, alkylaminio, arylamino, alkyl-arylaminio, arylaminio, heteroarylaminio, cycloalkylaminio, carboxyalkylaminio, arylalkyloxy and heterocyclylaminio; all of which may be further independently substituted one or more times with X¹ and X²; wherein X¹ is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclalkyl, aryl, alkyaryl, arylalkyl, arylheteroaryl, heterocyclaminio, alkylheteroaryl, or heteroarylalkyl; wherein X¹ can be independently substituted with one or more of X² moieties which can be the same or different and are independently selected; wherein X² is hydroxy, alkyl, aryl, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylaminio, arylaminio, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxy carbonylamino, alkoxy carbonyloxy, alkylureido, arylureido, halogen, cyano, keto, ester or nitro; wherein each of said alkyl, alkoxy, and aryl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different and are independently selected from alkyl-, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocycl, heterocyclalkyl, aryl, alkyaryl, arylalkyl, arylheteroaryl, heteroaryl, heterocyclaminio, alkylheteroaryl and heteroarylalkyl;
amino, alkylamino, arylamino, alkyl-arylamino, arylamino, heteroarylamino, cycloalkylamino, carboxyalkylamino, arylalkyloxy and heterocyclamino; all of which may be further independently substituted one or more times with $X^1$ and $X^2$; wherein $X^1$ is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclalkyl, aryl, alkylaryl, arylalkyl, arylheteroaryl, heteroaryl, heterocyclamino, alkylheteroaryl, or heteroaryllalkyl; wherein $X^1$ can be independently substituted with one or more of $X^2$ moieties which can be the same or different and are independently selected; wherein $X^2$ is hydroxy, alkyl, aryl, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxy carbamylamino, alkoxy carbonyloxy, alkylureido, arylureido, halogen, cyano, keto, ester or nitro; wherein each of said alkyl, alkoxy, and aryl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different and are independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclalkyl, aryl, alkylaryl, arylalkyl, arylheteroaryl, heteroaryl, heterocyclamino, alkylheteroaryl and heteroaryllalkyl;

or $R^{22}$ or $R^{26}$ may together form a 3-membered ring that may or may not be substituted;

wherein $R^7$, $R^{17}$, $R^{22}$, $R^{27}$ and $R^{28}$ have the meanings for $R^{26}$ of A4 above;

wherein $R^7$, $R^{16}$, $R^{22}$, $R^{29}$ and $R^{30}$ have the meanings for $R^{26}$ of A4 above;
wherein $R_7$, $R_{15}$, $R_{30}$, and $R_{31}$ have the meanings for $R_{26}$ of A4 above;

wherein $R_7$ and $R_{15}$ have the meanings for $R_{26}$ of A4 above.

4. The compound of claim 1, wherein $W$ is selected from the group consisting of H, alkyl, alkyl-aryl, heteroalkyl, heterocyclyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkoxy, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocyclyloxy, cycloalkyloxy, amino, alkylamino, arylamino, alkyl-arylamino, arylmino, heteroarylamino, cycloalkylamino, carboxyalkylamino, arylalkyloxy and heterocyclylamino; all of which may be further independently substituted one or more times with $X_1$ and $X_2$; wherein $X_1$ is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, arylheteroaryl, heteroarylalkyl; wherein $X_1$ can be independently substituted with one or more of $X_2$ moieties which can be the same or different and are independently selected; wherein $X_2$ is hydroxy, alkyl, aryl, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxy carbonylamino, alkoxy carbonyloxy, alkylureido, arylureido, halogen, cyano, keto, ester or nitro; wherein each of said alkyl, alkoxy, and aryl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different and are independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, arylheteroaryl, heteroaryl,
heterocyclyl amino, alkylheteroaryl and heteroarylalkyl.

5. A compound of the formula B:

\[
\begin{array}{c}
\text{CG} \\
N \\
\text{P3} \\
\text{R1} \\
\text{R2} \\
\text{R3} \\
\text{W} \\
\text{B} \\
\end{array}
\]

and pharmaceutically acceptable salts and stereoisomers thereof, wherein

P2 is represented by the formula A1, A4, A6, A7 or A8:

\[
\begin{array}{c}
\text{A1} \\
\text{R13} \\
\text{R12} \\
\text{R11} \\
\text{R10} \\
\text{R9} \\
\text{R8} \\
\text{R7} \\
\text{R6} \\
\text{R5} \\
\text{R4} \\
\text{R3} \\
\text{R2} \\
\text{R1} \\
\end{array}
\]

wherein

\[R^7, R^{15}, R^{17}, R^{22}\] are each, independently, selected from the group consisting of H, alkyl, alkyl-aryl, heteroalkyl, heterocyclyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkoxy, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocycloxy, cycloalkyloxy, amino, alkylamino, arylamino, alkyl-arylamino, arylamino, heteroarylamino, cycloalkylamino, carboxyalkylamino, arylalkyloxy and heterocyclylamino; all of which may be further independently substituted one or more times with \(X^1\) and \(X^2\); wherein \(X^1\) is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-aryl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, arylheteroaryl, heteroaryl, heterocyclylamino, alkylheteroaryl, or heteroarylalkyl; wherein \(X^1\) can be independently substituted with one or more of \(X^2\) moieties which can be the same or different and are independently selected; wherein \(X^2\) is hydroxy, alkyl, aryl, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonylamido, arylsulfonylamido, carboxy, carbalkoxy, carboxyamido, alkoxyacylamino, alkoxyacyloxy, alkyureido, arlyureido, halogen, cyano, keto, ester or nitro; wherein each of said alkyl, alkoxy, and aryl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different and
are independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, arylheteroaryl, heteroaryl, heterocyclylamino, alkylheteroaryl and heteroarylalkyl; 

or R\textsuperscript{22} and R\textsuperscript{16} may together form a 3, 4, 5, 6 or 7-membered ring that is aromatic or non-aromatic and may contain one or more heteroatoms, wherein the ring may be further substituted one or more times; 

or R\textsuperscript{7} and R\textsuperscript{15} may together form a 3, 4, 5, 6 or 7-membered ring that is aromatic or non-aromatic and may contain one or more heteroatoms, wherein the ring may be further substituted one or more times; 

or R\textsuperscript{17} and R\textsuperscript{16} may together form a 4, 5, 6 or 7-membered ring of the formula III:

![](image)

wherein 

n and g are each, independently, 0, 1 or 2, wherein n and g are not both 2; 

m is 0 or 1; 

X is O, S or C; 

R\textsuperscript{4} and R\textsuperscript{4\textprime} are each, independently, selected from the group consisting of H, C\textsubscript{i}\textsuperscript{-alkyl, O-Ci\textsuperscript{-alkyl, N(H)-C}, \textsuperscript{4}alkyl, (CH\textsubscript{2})\textsuperscript{0-4}-C\textsubscript{3}\textsuperscript{6-cycloalkyl, aryl and heterocycle, all of which may be independently substituted one or more times with a halogen atom or Ci\textsuperscript{-alkyl;}} 

R\textsuperscript{5} is selected from the group consisting of oxo, -O-, H, d\textsuperscript{-alkyl, O-Ci\textsuperscript{-alkyl, N(H)-C}, \textsuperscript{4}alkyl, (CH\textsubscript{2})\textsuperscript{0-4}-C\textsubscript{3}\textsuperscript{6-cycloalkyl, aryl and heterocycle, and any combination thereof, all of which may be independently substituted one or more times with a halogen atom, aryl, trihalomethyl, or C\textsubscript{i}\textsuperscript{-alkyl;}} 

or R\textsuperscript{4} and R\textsuperscript{5} may together form a 4, 5, 6 or 7-membered ring that is aromatic or non-aromatic and may contain one or more heteroatoms, wherein the ring may be further substituted one or more times; 

or R\textsuperscript{15} and R\textsuperscript{16} may together form a 4, 5, 6 or 7-membered ring that is aromatic or non-aromatic and may contain one or more heteroatoms, wherein the ring may be further substituted one or more times; wherein one of the rings that R\textsuperscript{15} and R\textsuperscript{16} may together form is a ring of the formula IV:
wherein

the dashed line represents a single or double bond, wherein formula IV may be further

substituted one or more times;

CG is a CG activity moiety;

P3 is a P3 activity moiety;

W is a W activity moiety;

x is 0 or 1;

y is O or 1;

R1, R2, R5, R9, R11, R12 and R13 are each, independently, selected from the group
consisting of H, alkyl, alkyl-aryl, heteroalkyl, heterocyclyl, heteroaryl, aryl-heteroaryl, alkyl-
heteroaryl, cycloalkyl, alkyloxy, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocyclyloxy,
cycloalkyloxy, amino, alkylamino, arylamino, arylamino, arylamino, heteroarylamino,
cycloalkylamino, carboxyalkylamino, arylalkyloxy and heterocyclylamino; all of which may
be further independently substituted one or more times with X1 and X2; wherein X1 is alkyl,
alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl,
arylalkyl, arylheteroaryl, heteroaryl, heterocyclylamino, alkylheteroaryl, or heteroaryllalkyl;
wherein X1 can be independently substituted with one or more of X2 moieties which can be
the same or different and are independently selected; wherein X2 is hydroxy, alkyl, aryl,
alkoxy, aryloxy, thio, alkylthio, ariylthio, amino, alkylamino, arylamino, alkylsulfonyl,
aryl sulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carbarnido,
alkoxycarbonylamino, alkoxycarboxylxy, alkylureido, arylureido, halogen, cyano, ketp,
ester or nitro; wherein each of said alkyl, alkoxy, and aryl can be unsubstituted or optionally
independently substituted with one or more moieties which can be the same or different and
are independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl,
heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, arylheteroaryl, heteroaryl,
heterocyclylamino, alkylheteroaryl and heteroaryllalkyl;
wherein

\[ R^7, R^{18}, R^{22}, R^{25}, \text{ and } R^{26} \]

are each, independently, selected from the group consisting of \( H, \) alkyl, alkyl-aryl, heteroalkyl, heterocyclyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyloxy, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocyclyloxy, cycloalkyloxy, amino, alkylamino, arylamino, alkyl-arylamino, arylamino, heteroarylamin, cycloalkylamino, carboxyalkylamino, arylalkyloxy and heterocyclylamino; all of which may be further independently substituted one or more times with \( X^1 \) and \( X^2; \) wherein \( X^1 \) is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, arylheteroaryl, heteroaryl, heterocyclylamino, alkylheteroaryl, or heteroarylalkyl; wherein \( X^1 \) can be independently substituted with one or more of \( X^2 \) moieties which can be the same or different and are independently selected; wherein \( X^2 \) is hydroxy, alkyl, aryl, alkoxy, aryloxy, thio, alkylthio, arythio, amino, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxyamino, alkoxy carbonylamino, alkoxycarbonyloxy, alkylureido, arylureido, halogen, cyano, keto, ester or nitro; wherein each of said alkyl, alkoxy, and aryl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different and are independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, arylheteroaryl, heteroaryl, heterocyclylamino, alkylheteroaryl and heteroarylalkyl;

or \( R^{22} \) or \( R^{26} \) may together form a 3-membered ring that may or may not be substituted;
wherein $R_7$, $R_{17}$, $R_{22}$, $R_{27}$ and $R_{28}$ have the meanings for $R_{26}$ of A4 above;

![Chemical Structure](image1)

wherein $R_7$, $R_{16}$, $R_{22}$, $R_{29}$ and $R_{30}$ have the meanings for $R_{26}$ of A4 above;

![Chemical Structure](image2)

wherein $R_7$, $R_{15}$, $R_{30}$ and $R_{31}$ have the meanings for $R_{26}$ of A4 above;

![Chemical Structure](image3)

wherein $R_7$ and $R_{15}$ have the meanings for $R_{26}$ of A4 above.

6. The compound of claim 5, wherein P3 is selected from the group consisting of H, C1-alkyl, and (CH$_2$)$_n$-C$_3$-cycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocycle.

7. The compound of claim 5, wherein CG is selected from the group consisting of
wherein $R_{18}$ is selected from the group consisting of hydrogen, a halogen atom, aryl, trihalomethyl, and $\text{d}_{-4}$-alkyl.

8. The compound of claim 5, wherein $W$ is selected from the group consisting of H, alkyl, alkyl-aryl, heteroalkyl, heterocyclyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyloxy, alkyl-aryloxy, aryloxy, heteroarylxy, heterocyclyloxy, cycloalkyloxy, amino, alkylamino, arylamino, alkyl-arylmino, arylmino, heteroarylmino, cycloalkylamino, carboxyalkylamino, arylalkyloxy and heterocyclylamino; all of which may be further independently substituted one or more times with $X_1$ and $X_2$; wherein $X_1$ is alkyl, alkenyl, alkoxy, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryloxy, alkylaryl, arylalkyl, arylheteroaryl, heteroaryl, heterocyclylmino, alkylheteroaryl, or heteroarylalkyl; wherein $X_1$ can be independently substituted with one or more of $X_2$ moieties which can be the same or different and are independently selected; wherein $X_2$ is hydroxy, alkyl, aryl, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylysulfonamido, carboxy, carbalkoxy, carboxamido, alkoxy, alkoxycarboxy, alkoxycarbonyl, alkoxycarbonyloxy, alkylureido, arylureido, halogen, cyano, keto, ester or nitro; wherein each of said alkyl, alkoxy, and aryl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different and are independently selected from alkyl, alkenyl, alkoxy, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryloxy, alkylaryl, arylalkyl, arylheteroaryl, heteroaryl, heterocyclylmino, alkylheteroaryl and heteroarylalkyl.

9. A compound of the formula C:

and pharmaceutically acceptable salts and stereoisomers thereof,

wherein

$W$ is selected from the group consisting of
wherein $R^{19}$ is selected from the group consisting of hydrogen, a halogen atom, aryl, trihalomethyl, and C$_4$-alkyl.

CG is a CG activity moiety;

P2 is a P2 activity moiety;

P3 is a P3 activity moiety;

x is 0 or 1;

y is 0 or 1;


10. The compound of claim 9, wherein P3 is selected from the group consisting of H, C$_4$-4-alkyl, and (CH$_2$)$_n$-C$_3$-$C$-cycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heterocycle.

11. The compound of claim 9, wherein CG is selected from the group consisting of...
wherein \( R^{18} \) is selected from the group consisting of hydrogen, a halogen atom, aryl, trihalomethyl, and Ci-4-alkyl.

12. The compound of claim 9, wherein \( P_2 \) is represented by the formula \( A_1, A_2, \) or \( A_3: \)

wherein

\[
R^7, R^{16}, R^{15}, R^{17} \text{ and } R^{22} \text{ are each, independently, selected from the group consisting of H, alkyl, alkyl-aryl, heteroalkyl, heterocyclyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkoxy, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocyclyloxy, cycloalkyloxy. amino, alkylamino, aryloxyno, alkyl-arylamino, aminocycloalkyloxy, cycloalkylaminocycloalkyloxyl, arylamino, heteroarylaminocycloalkyl, alkylamino, and heteroarylaminocycloalkyl; all of which may be further independently substituted one or more times with } X^1 \text{ and } X^2; \text{ wherein } X^1 \text{ is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclylalkyl, aryl, alkylaryl, aryalkyl, aryldihydroxy, heteroaryl, heterocyclylaminocycloalkyl, alkylheteroaryl, or heteroarylalkyl; wherein } X^1 \text{ can be independently substituted with one or more of } X^2 \text{ moieties which can be the same or different and are independently selected; wherein } X^2 \text{ is hydroxy, alkyl, aryl, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylaminocycloalkyl, arylaminocycloalkyl, aromaticsulfonyl, alkylsulfonylamino, arylsulfonylamino, carboxy, carboxalkoxy, carbamido, alkoxybenzalyno, alkoxybenzoxyl, alkyldien, alkyldieno, alkyldieno, halogen, cyano, keto, ester or nitro; wherein each of said alkyl, alkoxy, and ary can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different and are independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, aryalkyl, aryldihydroxy, heteroaryl, heterocyclylaminocycloalkyl, alkylheteroaryl and heteroarylalkyl; or } R^{22} \text{ and } R^{16} \text{ may together form a 3, 4, 5, 6 or 7-membered ring that is aromatic or non-aromatic and may contain one or more heteroatoms, wherein the ring may be further} \]
substituted one or more times;

or $R^7$ and $R^{15}$ may together form a 3, 4, 5, 6 or 7-membered ring that is aromatic or non-aromatic and may contain one or more heteroatoms, wherein the ring may be further substituted one or more times;

or $R^{17}$ and $R^{16}$ may together form a 4, 5, 6 or 7-membered ring of the formula III:

![Diagram](image)

wherein

- $n$ and $g$ are each, independently, 0, 1 or 2, wherein $n$ and $g$ are not both 2;
- $m$ is 0 or 1;
- $X$ is O, N or C;
- $R^4$ and $R^{4a}$ are each, independently, selected from the group consisting of H, C$_{1-4}$-alkyl, O-C$_{1-4}$-alkyl, N(H)-C$_{1-4}$-alkyl, (CH$_2$)$_0$-C$_{3-6}$-cycloalkyl, aryl and heterocycle, all of which may be independently substituted one or more times with a halogen atom or C$_{1-4}$-alkyl;
- $R^5$ is selected from the group consisting of oxo, O-, H, C$_{1-4}$-alkyl, O-C$_{1-4}$-alkyl, N(H)-C$_{1-4}$-alkyl, (CH$_2$)$_0$-C$_{3-6}$-cycloalkyl, aryl and heterocycle, and any combination thereof, all of which may be independently substituted one or more times with a halogen atom, aryl, trihalomethyl, or C$_{1-4}$-alkyl;
- or $R^4$ and $R^5$ may together form a 4, 5, 6 or 7-membered ring that is aromatic or non-aromatic and may contain one or more heteroatoms, wherein the ring may be further substituted one or more times;
- or $R^{15}$ and $R^{16}$ may together form a 4, 5, 6 or 7-membered ring that is aromatic or non-aromatic and may contain one or more heteroatoms, wherein the ring may be further substituted one or more times; wherein one of the rings that $R^{15}$ and $R^{16}$ may together form is a ring of the formula IV:

![Diagram](image)
wherein the dashed line represents a single or double bond, wherein formula IV may be further substituted one or more times;

\[
\text{A2}
\]

wherein

- \( n \) is \( 0 \) or \( 1 \);
- \( X \) is \( N \) or \( C \);
- \( R^4 \) is selected from the group consisting of \( H \), \( \text{Ci}_4^-\text{-alkyl} \), \( \text{Ci}^\text{\textbullet}_4^-\text{-cycloalkyl} \), \( \text{aryl} \), \( \text{heterocycle} \) and \( \text{heteroaryl} \), all of which may be independently substituted one or more times with a halogen atom or \( \text{Cm}_m^-\text{-alkyl} \);
- \( R^5 \) is selected from the group consisting of \( \text{oxo}, -\text{O}, H, \text{Ci}_4^-\text{-alkyl}, \text{Ci}^\text{\textbullet}_4^-\text{-cycloalkyl} \), \( \text{aryl} \) and \( \text{heteroaryl} \), and any combination thereof, all of which may be independently substituted one or more times with a halogen atom, \( \text{aryl} \), \( \text{trihalomethyl} \), or \( \text{Ci}_4^-\text{-alkyl} \);
- or \( R^4 \) and \( R^5 \) may together form a \( \text{dimethyl cyclopropyl} \) ring, a \( \text{cyclopentane} \) ring, or a \( \text{phenyl} \) ring, wherein the \( \text{phenyl} \) ring and \( \text{dimethyl cyclopropyl} \) ring may be substituted with a halogen atom, \( \text{aryl} \), \( \text{trihalomethyl} \), or \( \text{Ci}_4^-\text{-alkyl} \), or such that a fused ring system is formed; and
- \( R^6 \) and \( R^7 \) are each, independently, selected from the group consisting of \( H \), \( \text{Ci}^\text{\textbullet}_4^-\text{-alkyl} \) and \( \text{(GH}_2\text{)}^\text{\textbullet}_4^-\text{-C}_3^-\text{C}_6^-\text{-cycloalkyl} \);

\[
\text{A3}
\]

wherein

- \( R^4 \), \( R^5 \) and \( R^6 \) are each, independently, selected from the group consisting of \( H \), alkyl,
alkyl-aryl, heteroalkyl, heterocyclyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkylcoxy, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocyclycoxy, cycloalkyloxy, amino, alkylamino, arylamino, alkyl-arylamino, arylamino, heteroarylamino, cycloalkylamino, carboxyalkylamino, arylalkyloxy and heterocyclylamino; all of which may be further independently substituted one or more times with X¹ and X²; wherein X¹ is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyloxy, alkylheterocyclyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, arylarylalkyl, or heteroarylalkyl; wherein X¹ can be independently substituted with one or more of X² moieties which can be the same or different and are independently selected; wherein X² is hydroxy, alkyl, aryl, alkoxy, aryloxy, thio, alkylthio, arythio, amino, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxy carbonylamino, alkoxy carbonyloxy, alkylureido, arylureido, halogen, cyano, keto, ester or nitro; wherein each of said alkyl, alkoxy, and aryl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different and are independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, arylheteroaryl, heteroaryl, heterocyclylamino, alkylheteroaryl and heteroarylalkyl.

13. The compound of claim 9, wherein W is selected from the group consisting of H, alkyl, alkyl-aryl, heteroalkyl, heterocyclyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkylcoxy, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocyclycoxy, cycloalkyloxy, amino, alkylamino, arylamino, alkyl-arylamino, arylamino, heteroarylamino, cycloalkylamino, carboxyalkylamino, arylalkyloxy and heterocyclylamino; all of which may be further independently substituted one or more times with X¹ and X²; wherein X¹ is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyloxy, alkylheterocyclyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, arylarylalkyl, or heteroarylalkyl; wherein X¹ can be independently substituted with one or more of X² moieties which can be the same or different and are independently selected; wherein X² is hydroxy, alkyl, aryl, alkoxy, aryloxy, thio, alkylthio, arythio, amino, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxy carbonylamino, alkoxy carbonyloxy, alkylureido, arylureido, halogen, cyano, keto, ester or nitro; wherein each of said alkyl, alkoxy, and aryl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different and are independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl,
heterocyclyl, heterocyclylalkyl, aryl, alkyaryl, axylalkyl, arylheteroaryl, heteroaryl,
heterocyclylamino, alkylheteroaryl and heteroarylalkyl.

14. The compound of any one of the above claims, wherein formula A2 is represented by
the formula A4:

\[
\text{A4}
\]

wherein:

- \( R^{22} \) and \( R^7 \) are each, independently, selected from the group consisting of \( H, C_{1-4} \)-alkyl, \( O-C_{M} \)-alkyl, \( N(H)-C_{M} \)-alkyl, \( (CH_{2})_{M}-C_{3-6} \)-cycloalkyl, aryl and heterocycle, all of which may be independently substituted one or more times with a halogen atom, \( C_{1-4} \)-alkyl, \( O-C_{i-4} \)-alkyl, \( N(H)-C_{i-4} \)-alkyl, \( C_{i-4} \)-alkyl substituted by one or more halogen atoms, or \( C_{3} \)-cycloalkyl;
- \( n \) and \( g \) are each, independently, 0 or 1, or 2, wherein \( n \) and \( g \) are not both 2;
- \( m \) is 0 or 1;
- \( X \) is \( O, N \) or \( C \);
- \( R^4 \) and \( R^{4a} \) are each, independently, selected from the group consisting of \( H, C_{1-4} \)-alkyl, \( O-C_{1-4} \)-alkyl, \( N(H)-C_{1-4} \)-alkyl, \( (CH_{2})_{o-4}-C_{3-6} \)-cycloalkyl, aryl and heterocycle, all of which may be independently substituted one or more times with a halogen atom or \( d-4 \)-alkyl;
- \( R^5 \) is selected from the group consisting of oxo, \( -O-, H, C^{\wedge} \)-alkyl, \( O-C_{1-4} \)-alkyl, \( N(H)-C_{1-4} \)-alkyl, \( (CH_{2})_{o-4}-C_{3-6} \)-cycloalkyl, aryl and heterocycle, and any combination thereof, all of which may be independently substituted one or more times with a halogen atom, aryl, trihalomethyl, or \( Cl-4 \)-alkyl;
- \( R^6 \) are each, independently, selected from the group consisting of \( H, C_{1-4} \)-alkyl, \( 0-C_{i-4} \)-alkyl, \( N(H)-C_{i-4} \)-alkyl, and \( (CH_{2})_{o}^{\wedge}-C_{3}^{\wedge} \)-cycloalkyl;
- or \( R^4 \) and \( R^5 \) may together form a 4, 5, 6 or 7-membered ring that is aromatic or non-aromatic and may contain one or more heteroatoms, wherein the ring may be further...
substituted one or more times.

15. The compound of any one of the above claims, wherein
R₁, R₂, R₈, R₉, R₁¹, R₁² and R₁₃ are each, independently, selected from the group consisting of H, Ci-₄-alkyl, and (CH₂)₀-₄-C₃⁻cycloalkyl.

16. The compound of any one of the above claims, wherein W is selected from the group consisting of C(OVC(O)H, C(=N-O-R²⁴)-C(O)-amine, C(O)-C(O)-amine, C(O)N(H)S(O)₂R²⁴ and C(O)-[C(O)]ₐ-heterocycle, wherein the heterocycle may be independently substituted one or more times with aryl, Ci-t-alkyl, Ci-₄-alkyl substituted by one or more halogen atoms, and C⁻cycloalkyl, wherein a is Oor 1, wherein each R²⁴ is independently selected from the group consisting of H, Ci-w-alkyl, (CH₂)ᵦ₆-s-cycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocycle, all of which may be independently substituted one or more times with a halogen atom or d-₄-alkyl.

17. The compounds of any one of the above claims, wherein W, R¹ and R² form a substituent of the following formulas:

wherein R³³ is selected from the group consisting of H, phenyl, methyl, CF₃, tBu, NO₂, Cl, CN, NH₂, OH, NHCH₃, OCH₃, NHPh, OPh, NHCOCH₃, NHCOPh, OCH₂Ph, COCH₃, CO₂Et, CO₂CH₃, CONHPH and CONHCH₃, or R³³ can be fused with the phenyl ring to form a naphthyl ring.

18. The compounds of any one of the above claims, wherein W, R¹ and R² form substituents selected from the group consisting of
19. The compound of any one of the above claims, wherein $W$ is $C(O)N(H)S(O)_2R^{24}$, wherein $R^{24}$ is selected from the group consisting of H, $C_{1-4}$-alkyl, $(CH_2)_{o-t-C^3^\wedge}$-cycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocycle, all of which may be independently substituted one or more times with a halogen atom or $C_{1-4}$-alkyl.

20. The compounds of any one of the above claims, wherein $R^1$ and $R^2$ form a substituent of the following formula:
21. The compounds of any one of the above claims, wherein W₅R¹ and R² form a substituent of the following formula:

\[
\begin{align*}
\text{amine} \\
\end{align*}
\]

22. The compounds of any one of the above claims, wherein W₅R¹ and R² form a substituent of the following formula:

\[
\begin{align*}
\text{N(R²⁴)}_2 \\
\end{align*}
\]

wherein each R²⁴ is independently selected from the group consisting of H, substituted or unsubstituted-C₄-alkyl, substituted or unsubstituted-(CH₂)₀-₄-C₃⁻cycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocycle.

23. The compound of any one of the above claims, wherein W₅R¹ and R² form a substituent selected from the group consisting of:

\[
\begin{align*}
\text{and} \\
\end{align*}
\]

24. A method of treating an HCV-associated disorder comprising administering to a subject in need thereof a pharmaceutically acceptable amount of a compound of formula A₅B or C, such that the HCV-associated disorder is treated.

25. The method of claim 24, wherein the HCV-associated disorder is selected from the group consisting of HCV infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma, cryoglobulinaemia, non-Hodgkin's lymphoma, and a suppressed innate intracellular immune response.

26. A method of treating an HIV infection comprising administering to a subject in need...
thereof a pharmaceutically acceptable amount of a compound of formula A, B or C.

27. A method of treating, inhibiting or preventing the activity of HCV in a subject in need thereof, comprising administering to the subject a pharmaceutically acceptable amount of a compound of formula A, B or C wherein the compound interacts with any target in the HCV life cycle.

28. The method of claim 27, wherein the target is selected from the group consisting of NS2 protease, NS3 protease, NS3 helicase, NS5a protein and NS5b polymerase.

29. A method of treating, inhibiting or preventing the activity of HCV in a subject in need thereof, comprising administering to the subject a pharmaceutically acceptable amount of a compound of formula A, B or C.

30. A method of inhibiting the activity of a serine protease, comprising the step of contacting said serine protease with a compound according to claim 29.

31. The method of claim 29, wherein the activity of the NS2 protease is inhibited.

32. The method of claim 29, wherein the activity of the NS3 protease is inhibited.

33. The method of claim 29, wherein the activity of the NS3 helicase is inhibited.

34. The method of claim 29, wherein the activity of the NS5a protein is inhibited.

35. The method of claim 29, wherein the activity of the NS5b polymerase is inhibited.

36. The method of claim 29, wherein the interaction between the NS3 protease and NS4A cofactor is disrupted.

37. The method of claim 29, wherein the severing one or more of the NS4A-NS4B, NS4B-NS5A and NS5A-NS5B junctions of the HCV is prevented or altered.

38. The method of any one of claims 29-37, wherein an HCV-associated disorder is
treated in a subject in need thereof.

39. The method of claim 38, wherein the HCV-associated disorder is selected from the group consisting of HCV infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma, cryoglobulinaemia, non-Hodgkin’s lymphoma, and a suppressed innate intracellular immune response.

40. A method of decreasing the HCV RNA load in a subject in need thereof comprising administering to the subject a pharmaceutically acceptable amount of a compound of formula A, B or C, such that the HCV RNA load in the subject is decreased.

41. A compound exhibiting HCV protease activity, wherein the compound is of the formula A; B or C.

42. The compound of claim 41, wherein the compound is a HCV NS3-4A protease inhibitor.

43. A method of treating an HCV-associated disorder in a subject, comprising administering to a subject in need thereof a pharmaceutically acceptable amount of a compound of the formula A, B or C, and a pharmaceutically acceptable carrier, such that the HCV-associated disorder is treated.

44. A method of treating an HCV-associated disorder comprising administering to a subject in need thereof a pharmaceutically effective amount of a compound of the formula A, B or C, in combination with a pharmaceutically effective amount of an additional HCV-modulating compound, such that the HCV-associated disorder is treated.

45. The method of claim 44, wherein the additional HCV-modulating compound is selected from the group consisting of Sch 503034 and VX-950.

46. The method of claim 44 wherein the additional HCV-modulating compound is interferon or derivatized interferon.

47. The method of claim 46, wherein the interferon is selected from the group consisting
of interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, lymphoblastoid interferon, and interferon tau; and said compound having anti-hepatitis C virus activity is selected from the group consisting of interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, double stranded RNA, double stranded RNA complexed with tobramycin, Imiquimod, ribavirin, an inosine 5’-monophosphate dehydrogenase inhibitor, amantadine, and rimantadine.

48. The method of claim 44 wherein the additional HCV-modulating compound is a cytochrome P450 monooxygenase inhibitor.

49. The method of claim 48, wherein the cytochrome P450 inhibitor is selected from the group consisting of ritonavir, ketoconazole, troleandomycin, 4-methyl pyrazole, cyclosporin, and clomethiazole.

50. The method of claims 43 or 44, wherein the HCV-associated disorder is selected from the group consisting of HCV infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma, cryoglobulinaemia, non-Hodgkin’s lymphoma, and a suppressed innate intracellular immune response.

51. A method of inhibiting hepatitis C virus replication in a cell, comprising contacting said cell with a compound of formula A, B or C.

52. A packaged HCV-associated disorder treatment, comprising an HCV-modulating compound of the formula A, B or C, packaged with instructions for using an effective amount of the HCV-modulating compound to treat an HCV-associated disorder.

53. The treatment of claim 50, wherein the HCV-associated disorder is selected from the group consisting of HCV infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma, cryoglobulinaemia, non-Hodgkin’s lymphoma, and a suppressed innate intracellular immune response.

54. A method of treating HCV infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma, cryoglobulinaemia, non-Hodgkin’s lymphoma, and or a suppressed innate intracellular immune response in subject in need thereof comprising administering to
the subject a pharmaceutically acceptable amount of a compound of formula A, B or C.

55. The method of claim 27, wherein the HCV is selected from all HCV genotypes

56. The method of claim 55, wherein the HCV is selected from HCV genotype 1, 2 and/or 3.

57. The compound, method or treatment of any of the above claims, wherein the compound is not VX-950.

58. The compound, method or treatment of any of the above claims, wherein the compound is not Sch 503034.