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(71) Applicant: **MERCK SHARP & DOHME CORP.** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065 (US).

(72) Inventors; and

(71) Applicants *(for US only)*: **YU, Wensheng** [CN/US]; 4 Maureen Court, Edison, New Jersey 08820 (US). **KOZLOWSKI, Joseph A.** [US/US]; 1066 Stuart Road, Princeton, New Jersey 08540 (US). **HU, Bin** [CN/CN]; Room 300B, Building No. 3, 288 Fute Zhong Road, Waigaoqiao Free Trade Zone, Shanghai 200131 (CN). **ZHONG, Bin** [CN/CN]; Room 300B, Building No. 3, 288 Fute Zhong Road, Waigaoqiao Free Trade Zone, Shanghai 200131 (CN). **HAO, Jinglai** [CN/CN]; Room 300B, Building No. 3, 288 Fute Zhong Road, Waigaoqiao Free Trade Zone, Shanghai 200131 (CN). **WANG, Dahai** [CN/CN]; Room 300B, Building No. 3, 288 Fute Zhong Road, Waigaoqiao Free Trade Zone, Shanghai 200131 (CN). **LEI, Zhixin** [CN/CN]; Room 300B, Building No. 3, 288 Fute Zhong Road, Waigaoqiao Free Trade Zone, Shanghai 200131 (CN).

(74) Agent: **WU, FENG & ZHANG CO.**; Room 305, Tower B, Beijing Aerospace Cpmiec Building, Beijing 100080 (CN).

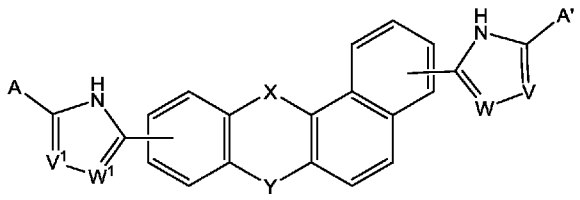
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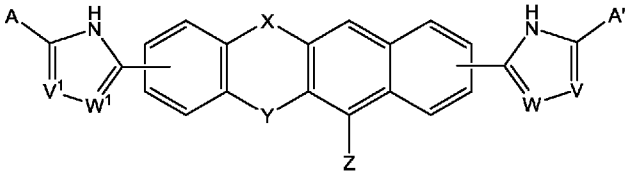
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(54) Title: HEPATITIS C VIRUS INHIBITORS



(I)



(II)

(57) Abstract: A compound of Formula (I) or (II), for treating or preventing an HCV infection in a subject.

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HEPATITIS C VIRUS INHIBITORS

FIELD OF THE INVENTION

Provided herein are hepatitis C virus inhibitor compounds, pharmaceutical compositions comprising the compounds, and preparation thereof. Also provided are methods of their use for treating an HCV infection.

BACKGROUND OF THE INVENTION

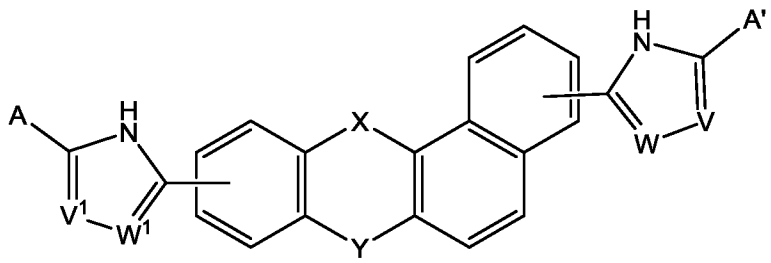
Hepatitis C virus (HCV) is known to cause at least 80% of post transfusion hepatitis and a substantial proportion of sporadic acute hepatitis (Kuo *et al.*, *Science* **1989**, *244*, 362-364; Thomas, *Curr. Top. Microbiol. Immunol.* **2000**, 25-41). Preliminary evidence also implicates HCV in many cases of "idiopathic" chronic hepatitis, "cryptogenic" cirrhosis, and probably hepatocellular carcinoma unrelated to other hepatitis viruses, such as hepatitis B virus (Di Besceglie *et al.*, *Scientific American* **1999**, *October*, 80-85; Boyer *et al.*, *J. Hepatol.* **2000**, *32*, 98-112).

HCV is an enveloped virus containing a positive-sense single-stranded RNA genome of approximately 9.4 kb (Kato *et al.*, *Proc. Natl. Acad. Sci. USA* **1990**, *87*, 9524-9528; Kato, *Acta Medica Okayama* **2001**, *55*, 133-159). The viral genome consists of a 5' untranslated region (UTR), a long open reading frame encoding a polyprotein precursor of approximately 3011 amino acids, and a short 3' UTR. The 5' UTR is the most highly conserved part of the HCV genome and is important for the initiation and control of polyprotein translation. Translation of the HCV genome is initiated by a cap-independent mechanism known as an internal ribosome entry. This mechanism involves the binding of ribosomes to an RNA sequence known as the internal ribosome entry site (IRES). An RNA pseudoknot structure has recently been determined to be an essential structural element of the HCV IRES. Viral structural proteins include a nucleocapsid core protein (C) and two envelope glycoproteins, E1 and E2. HCV also encodes two proteinases, a zinc-dependent metalloproteinase encoded by the NS2-NS3 region and a serine proteinase encoded in the NS3 region. These proteinases are required for cleavage of specific regions of the precursor polyprotein into mature peptides. The carboxyl half of nonstructural protein 5, NS5B, contains the RNA-dependent RNA polymerase. The function of the remaining nonstructural proteins, NS4A and NS4B, and that of NS5A (the amino-terminal half of nonstructural protein 5) remain unknown.

Presently, the most effective HCV therapy employs a combination of alpha-interferon and ribavirin, leading to sustained efficacy in about 40% of patients (Poynard *et al.*, *Lancet* **1998**, *352*, 1426-1432). Recent clinical results demonstrate that pegylated alpha-interferon is superior to unmodified alpha-interferon as monotherapy. However, even with experimental therapeutic regimens involving combinations of pegylated alpha-interferon and ribavirin, a substantial fraction of patients do not have a sustained reduction in viral load (Manns *et al.*, *Lancet* **2001**, *358*, 958-965; Fried *et al.*, *N. Engl. J. Med.* **2002**, *347*, 975-982; Hadziyannis *et al.*, *Ann. Intern. Med.* **2004**, *140*, 346-355). Thus, there is a clear and unmet need to develop effective therapeutics for the treatment of HCV infections.

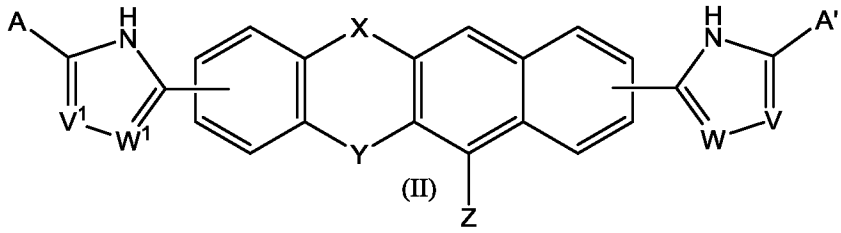
SUMMARY OF THE INVENTION

A compound of Formula (I) or (II),



(I)

or



(II)

or a pharmaceutically acceptable salt thereof, where

X is -O-, -C(O)-, $-C(R^AR^B)-$, NR^A, or SO_2;

Y is -O-, -C(O)-, $-C(R^AR^B)-$, NR^A, or SO_2;

V is CH or N;

W is CH or N;

V^1 is CH or N;

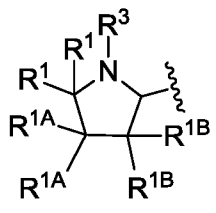
W^1 is CH or N;

Z is H or halo;

R^A is H, halo, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl, 4 to 6-membered monocyclic heterocycloalkyl, 5 or 6-membered monocyclic heteroaryl, 6 to 10-membered bicyclic heterocycloalkyl, C_6-C_{10} aryl, or -O-(C_1-C_6 alkyl), wherein said C_3-C_7 cycloalkyl group, said 4 to 6-membered monocyclic heterocycloalkyl group, said 5 or 6-membered monocyclic heteroaryl group, said 6 to 10-membered bicyclic heterocycloalkyl, or said C_6-C_{10} aryl group, can be optionally substituted with up to 3 groups, which can be the same or different, and are selected from halo, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -O-C_1-C_6 alkyl, –(C_1-C_6 alkylene)-O-C_1-C_6 alkyl and -O-(C_1-C_6 haloalkyl);

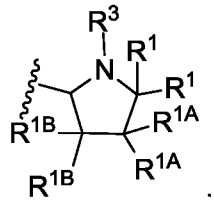
R^B is H, halo, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl, 4 to 6-membered monocyclic heterocycloalkyl, 5 or 6-membered monocyclic heteroaryl, 6 to 10-membered bicyclic heterocycloalkyl, C_6-C_{10} aryl, or -O-(C_1-C_6 alkyl), wherein said C_3-C_7 cycloalkyl group, said 4 to 6-membered monocyclic heterocycloalkyl group, said 5 or 6-membered monocyclic heteroaryl group, said 6 to 10-membered bicyclic heterocycloalkyl, or said C_6-C_{10} aryl group, can be optionally substituted with up to 3 groups, which can be the same or different, and are selected from halo, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -O-C_1-C_6 alkyl, –(C_1-C_6 alkylene)-O-C_1-C_6 alkyl and -O-(C_1-C_6 haloalkyl);

A is:



;

A' is:



;

each occurrence of R^1 is independently selected from H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl, and halo;

each occurrence of R^{1A} is independently selected from H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl, and halo, or one R^{1A} group and an R^1 group that are attached to same ring, together with the ring carbon atoms to which they are attached, can combine to form a fused C_3-C_7 cycloalkyl group, or two R^{1A} groups that are attached to the same carbon atom, and the common carbon atom to which they are attached, can combine to form a spirocyclic C_3-C_7 cycloalkyl group;

each occurrence of R^{1B} is independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl, or halo, or an R^{1B} group and an R^{1A} group that are attached to the same ring, together with the carbon atoms to which they are attached, can combine to form a fused C_3-C_7 cycloalkyl group, or an R^{1B} group and an R^1 group that are attached to the same ring, can combine to form a bridging group having the formula $–CH_2-$ or $–CH_2CH_2-$;

each occurrence of R^3 is independently H, $–C(O)-C(R^4)_2NHC(O)O-R^5$, $–C(O)O-R^5$, $C(O)NHR^5$ or $–C(O)-C(R^4)_2NR^7R^8$.

each occurrence of R^4 is independently selected from H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_6-C_{10} aryl, 4 to 8-membered monocyclic heterocycloalkyl, 6 to 10-membered bicyclic heterocycloalkyl and C_3-C_7 cycloalkyl, wherein said 4 to 8-membered monocyclic heterocycloalkyl group, said 6 to 10-membered bicyclic heterocycloalkyl group, said C_6-C_{10} aryl group and said C_3-C_7 cycloalkyl group can be optionally substituted with up to 5 groups, each independently selected from halo, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl, -O-C_1-C_6 alkyl, $–N(R^6)_2$ and -O-(C_1-C_6 haloalkyl), and wherein said C_3-C_7 cycloalkyl group can be optionally fused to a 4 to 6-membered monocyclic heterocycloalkyl group, and wherein said 4 to 8-membered monocyclic heterocycloalkyl group and said C_3-C_7 cycloalkyl group can be substituted on a ring carbon atom with a spirocyclic C_3-C_6 cycloalkyl group; and wherein said C_3-C_7 cycloalkyl group can be substituted on a ring carbon atom with a spirocyclic 3 to 6-membered monocyclic heterocycloalkyl group, and wherein two R^4 groups, that are attached to a common carbon atom,

together with the common carbon atom to which they are attached, can join to form a C_3-C_7 cycloalkyl group;

each occurrence of R^5 is independently selected from C_1-C_6 alkyl, C_3-C_7 cycloalkyl and C_6-C_{10} aryl;

each occurrence of R^6 is independently selected from H, C_1-C_6 alkyl and C_3-C_7 cycloalkyl;

each occurrence of R^7 is independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl, or phenyl, or R^7 and R^8, together with the nitrogen atom to which they are attached, form a 3 to 6-membered monocyclic heterocycloalkyl group; and

each occurrence of R^8 is independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl, or phenyl, or R^7 and R^8, together with the nitrogen atom to which they are attached, form a 3 to 6-membered monocyclic heterocycloalkyl group,

provided that at least one of V, V^1, W and W^1 is N.

Further provided herein are pharmaceutical compositions comprising a compound of Formula I or II, including a single enantiomer, a racemic mixture, a diastereomer, a mixture of diastereomers, or an isotopic variant thereof, or a pharmaceutically acceptable salt or solvate thereof, and optionally one or more pharmaceutically acceptable excipients or carriers.

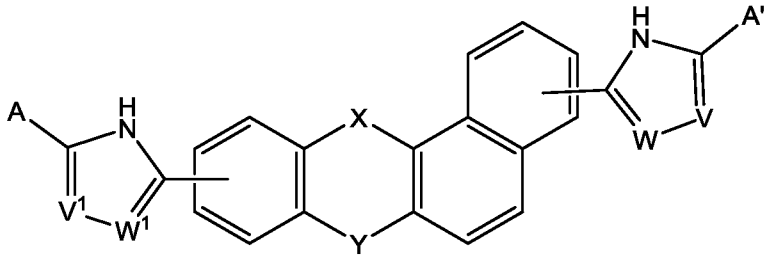
Provided herein is a method for treating or preventing an HCV infection in a subject, which comprises administering to the subject a compound of Formula I or II, including a single enantiomer, a racemic mixture, a diastereomer, a mixture of diastereomers, or an isotopic variant thereof, or a pharmaceutically acceptable salt or solvate thereof.

Provided herein is a method for treating, preventing, or ameliorating one or more symptoms of a liver disease or disorder associated with an HCV infection in a subject, comprising administering to the subject a compound of Formula I or II, including a single enantiomer, a racemic mixture, a diastereomer, a mixture of diastereomers, or an isotopic variant thereof, or a pharmaceutically acceptable salt or solvate thereof.

Provided herein is a method for inhibiting replication of a virus in a host, comprising contacting the host with a compound of Formula I or II, including a single enantiomer, a racemic mixture, a diastereomer, a mixture of diastereomers, or an isotopic variant thereof, or a pharmaceutically acceptable salt or solvate thereof.

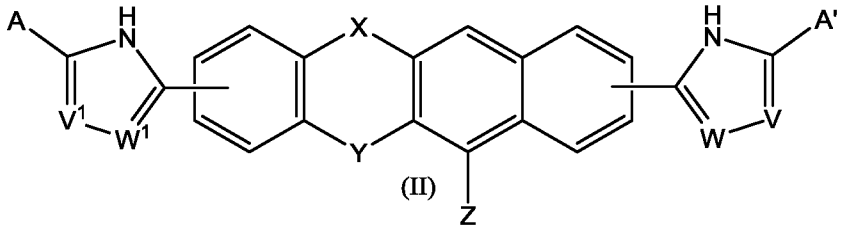
DETAILED DESCRIPTION

One embodiment of the invention is the compound of Formula (I)



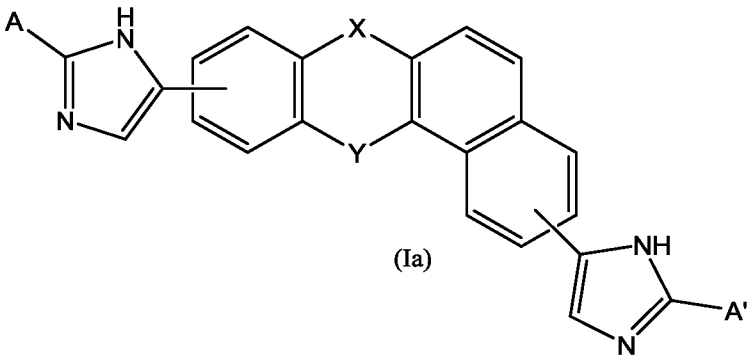
(I)

Another embodiment of the invention is the compound of Formula (II)



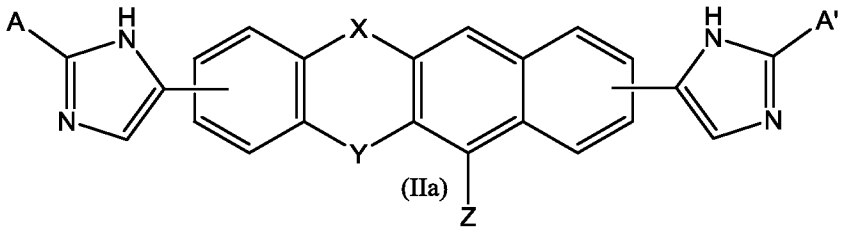
(II)

Another embodiment of the invention is the compound of Formula (Ia)



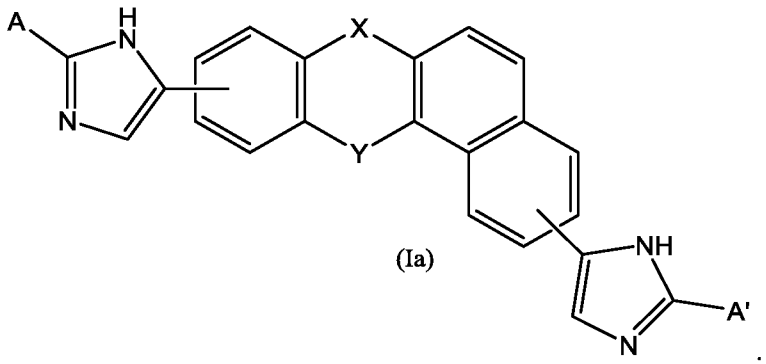
(Ia)

and the compound of Formula (IIa)



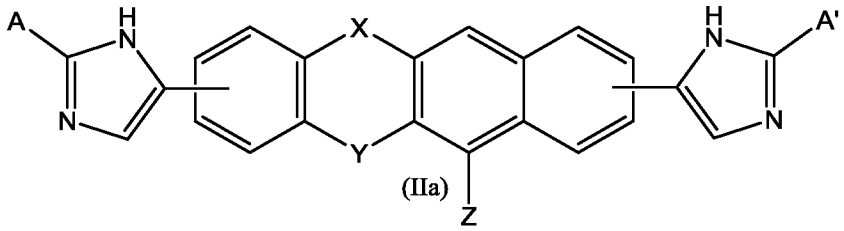
(IIa)

Another embodiment of the invention is the compound of Formula (Ia)



(Ia)

Another embodiment of the invention is the compound of Formula (IIa)



(IIa)

In another embodiment of the invention, R^1 is H

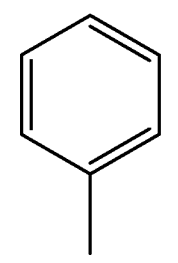
In another embodiment of the invention, R^A and R^B are independently H, halo, or -C_1-C_6 alkyl.

In another embodiment of the invention, R^A and R^B are independently H, fluoro, -CH_3 or -CH_2CH_3.

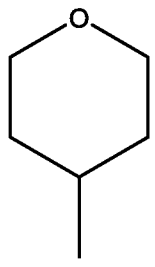
In another embodiment of the invention, R^{1A} is H or fluoro

In another embodiment of the invention, R^{1B} is H

In another embodiment of the invention, each R^3 is independently H, -C(O)CH(CH(CH_3)$_2$)(NHC(O)OCH_3), -C(O)O$C(CH_3)_3$, C(O)NH$C(CH_3)_3$,

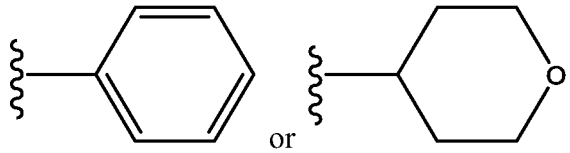


-C(O)CHN(CH_2CH_3)$_2$, or



-C(O)CHNHC(O)OCH_3.

In another embodiment of the invention, each R^4 is independently H, -$CH(CH_3)_3$,

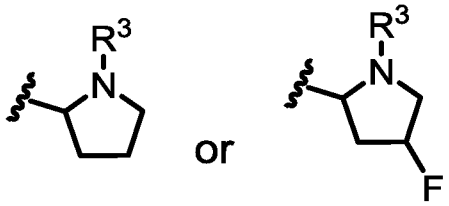


In another embodiment of the invention, each R^5 is independently CH_3 or $C(CH_3)_3$.

In another embodiment of the invention, R^7 and R^8 are independently -C_1-C_6 alkyl.

In another embodiment of the invention, R^7 and R^8 are independently H or -CH_2CH_3.

In another embodiment of the invention, A and A' are each independently



In another embodiment of the invention, the compound is one of the following:

Compound	Name
1	methyl [(1R)-1-({(2R)-2-[5-(9-{2-[(2R)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-7-oxo-7H-benzo[c]xanthen-3-yl)-1H-imidazol-2-yl]pyrrolidin-1-yl}carbonyl)-2-methylpropyl]carbamate
2	methyl [(1S)-1-({(2S)-2-[5-(3-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-12-methyl-12H-benzo[a]xanthen-9-yl)-1H-imidazol-2-yl]pyrrolidin-1-yl}carbonyl)-2-methylpropyl]carbamate
3	methyl [(1S)-1-({(2S)-2-[5-(3-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-12-methyl-12H-benzo[a]xanthen-9-yl)-1H-imidazol-2-yl]pyrrolidin-1-yl}carbonyl)-2-methylpropyl]carbamate
4	methyl [(1S)-1-({(2S)-2-[5-(3-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-

	imidazol-5-yl}-7-methyl-7H-benzo[c]xanthen-9-yl)-1H-imidazol-2-yl]pyrrolidin-1-yl}carbonyl)-2-methylpropyl]carbamate
5	methyl [(1S)-1-({(2S)-2-[5-(12-ethyl-3-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-12H-benzo[a]xanthen-9-yl)-1H-imidazol-2-yl]pyrrolidin-1-yl}carbonyl)-2-methylpropyl]carbamate
6	methyl [(1S)-1-({(2S)-2-[5-(12-ethyl-3-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-12H-benzo[a]xanthen-9-yl)-1H-imidazol-2-yl]pyrrolidin-1-yl}carbonyl)-2-methylpropyl]carbamate
7	methyl [(1S)-1-({(2S)-2-[5-(3-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-12,12-dimethyl-12H-benzo[a]xanthen-9-yl)-1H-imidazol-2-yl]pyrrolidin-1-yl}carbonyl)-2-methylpropyl]carbamate
8	methyl [(1R)-1-({(2S)-2-[5-(12,12-diethyl-3-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-12H-benzo[a]xanthen-9-yl)-1H-imidazol-2-yl]pyrrolidin-1-yl}carbonyl)-2-methylpropyl]carbamate
9	methyl [(1R)-1-({(2S)-2-[5-(12,12-diethyl-9-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-12H-benzo[b]xanthen-3-yl)-1H-imidazol-2-yl]pyrrolidin-1-yl}carbonyl)-2-methylpropyl]carbamate
10	blank
11	dimethyl [(12-methyl-12H-benzo[a]xanthene-3,9-diyl)bis{1H-imidazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethane-2,1-diyl]}]biscarbamate
12	dimethyl [(12-methyl-12H-benzo[a]xanthene-3,9-diyl)bis{1H-imidazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethane-2,1-diyl]}]biscarbamate
13	dimethyl [(12,12-dimethyl-12H-benzo[a]xanthene-3,9-diyl)bis{1H-imidazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethane-2,1-diyl]}]biscarbamate
14	dimethyl [(12-ethyl-12H-benzo[a]xanthene-3,9-diyl)bis{1H-imidazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethane-2,1-diyl]}]biscarbamate
15	dimethyl [(12-ethyl-12H-benzo[a]xanthene-3,9-diyl)bis{1H-imidazole-

	5,2-diyl(2S)pyrrolidine-2,1-diyl[(1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethane-2,1-diyl]}]biscarbamate
16	methyl [(1R)-2-[(2R)-2-{5-[12,12-diethyl-9-(2-{(2R)-1-[(2S)-2-[(methoxycarbonyl)amino]-2-(tetrahydro-2H-pyran-4-yl)acetyl]pyrrolidin-2-yl}-1H-imidazol-5-yl)-12H-benzo[a]xanthen-3-yl]-1H-imidazol-2-yl}pyrrolidin-1-yl]-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl]carbamate
17	methyl [(1R)-2-[(2S)-2-{5-[12,12-diethyl-9-(2-{(2S)-1-[(2S)-2-[(methoxycarbonyl)amino]-2-(tetrahydro-2H-pyran-4-yl)acetyl]pyrrolidin-2-yl}-1H-imidazol-5-yl)-12H-benzo[b]xanthen-3-yl]-1H-imidazol-2-yl}pyrrolidin-1-yl]-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl]carbamate
18	3-{2-[(2S,4R)-4-fluoropyrrolidin-2-yl]-1H-imidazol-5-yl}-9-{2-[(2S,4S)-4-fluoropyrrolidin-2-yl]-1H-imidazol-5-yl}-12H-benzo[a]xanthen-12-one
19	6-fluoro-2,9-bis{2-[(2S,4S)-4-fluoropyrrolidin-2-yl]-1H-imidazol-5-yl}-12H-benzo[b]xanthen-12-one
20	di-tert-butyl (2S,2'S)-2,2'-[(12-oxo-12H-benzo[a]xanthene-3,9-diyl)bis(1H-imidazole-5,2-diyl)]dipyrrolidine-1-carboxylate
21	(2S,4R,2'S,4'S)-2,2'-[(12-oxo-12H-benzo[a]xanthene-3,9-diyl)bis(1H-imidazole-5,2-diyl)]bis(N-tert-butyl-4-fluoropyrrolidine-1-carboxamide)
22	di-tert-butyl (2S,4R,2'S,4'S)-2,2'-[(12-oxo-12H-benzo[a]xanthene-3,9-diyl)bis(1H-imidazole-5,2-diyl)]bis(4-fluoropyrrolidine-1-carboxylate)
23	(2S,4S,2'S,4'S)-2,2'-[(6-fluoro-12-oxo-12H-benzo[b]xanthene-2,9-diyl)bis(1H-imidazole-5,2-diyl)]bis(N-tert-butyl-4-fluoropyrrolidine-1-carboxamide)
24	di-tert-butyl (2S,4S,2'S,4'S)-2,2'-[(6-fluoro-12-oxo-12H-benzo[b]xanthene-2,9-diyl)bis(1H-imidazole-5,2-diyl)]bis(4-fluoropyrrolidine-1-carboxylate)
25	methyl [(1S)-1-({(2S)-2-[5-(10-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-12-oxo-12H-benzo[a]xanthen-3-yl)-1H-imidazol-2-yl]pyrrolidin-1-yl}carbonyl)-2-methylpropyl]carbamate
26	methyl [(1S)-1-({(2S)-2-[5-(6-fluoro-9-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-12-oxo-12H-benzo[b]xanthen-2-yl)-1H-imidazol-2-

	yl]pyrrolidin-1-yl}carbonyl)-2-methylpropyl]carbamate
27	methyl [(1S)-1-({(2S,4R)-4-fluoro-2-[5-(10-{2-[(2S,4R)-4-fluoro-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-12-oxo-12H-benzo[a]xanthen-3-yl)-1H-imidazol-2-yl]pyrrolidin-1-yl}carbonyl)-2-methylpropyl]carbamate
28	methyl [(1S)-1-({(2S,4R)-4-fluoro-2-[5-(9-{2-[(2S,4R)-4-fluoro-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-12-oxo-12H-benzo[a]xanthen-3-yl)-1H-imidazol-2-yl]pyrrolidin-1-yl}carbonyl)-2-methylpropyl]carbamate
29	methyl [(1S)-1-({(2S,4R)-4-fluoro-2-[5-(6-fluoro-9-{2-[(2S,4R)-4-fluoro-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-12-oxo-12H-benzo[b]xanthen-2-yl)-1H-imidazol-2-yl]pyrrolidin-1-yl}carbonyl)-2-methylpropyl]carbamate
30	dimethyl [(12-oxo-12H-benzo[a]xanthene-3,9-diyl)bis{1H-imidazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethane-2,1-diyl]}]biscarbamate
31	3,9-bis(2-{(2S,4R)-1-[(2R)-2-(diethylamino)-2-phenylacetyl]-4-fluoropyrrolidin-2-yl}-1H-imidazol-5-yl)-12H-benzo[a]xanthen-12-one
32	dimethyl [(12-oxo-12H-benzo[a]xanthene-3,9-diyl)bis{1H-imidazole-5,2-diyl[(2S,4R)-4-fluoropyrrolidine-2,1-diyl][(1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethane-2,1-diyl]}]biscarbamate
33	methyl [(1S)-1-({(2S)-2-[5-(9-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-12-oxo-12H-benzo[a]xanthen-3-yl)-1H-imidazol-2-yl]pyrrolidin-1-yl}carbonyl)-2-methylpropyl]carbamate

To facilitate understanding of the disclosure set forth herein, a number of terms are defined below.

Generally, the nomenclature used herein and the laboratory procedures in organic chemistry, medicinal chemistry, and pharmacology described herein are those well known and commonly employed in the art. Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs.

The term “subject” refers to an animal, including, but not limited to, a primate (*e.g.*, human), cow, pig, sheep, goat, horse, dog, cat, rabbit, rat, or mouse. The terms “subject”

and "patient" are used interchangeably herein in reference, for example, to a mammalian subject, such as a human subject, in one embodiment, a human.

The term "host" refers to a unicellular or multicellular organism in which a virus can replicate, including, but not limited to, a cell, cell line, and animal, such as a human.

The terms "treat," "treating," and "treatment" are meant to include alleviating or abrogating a disorder, disease, or condition, or one or more of the symptoms associated with the disorder, disease, or condition; or alleviating or eradicating the cause(s) of the disorder, disease, or condition itself.

The terms "prevent," "preventing," and "prevention" are meant to include a method of delaying and/or precluding the onset of a disorder, disease, or condition, and/or its attendant symptoms; barring a subject from acquiring a disorder, disease, or condition; or reducing a subject's risk of acquiring a disorder, disease, or condition.

The term "therapeutically effective amount" are meant to include the amount of a compound that, when administered, is sufficient to prevent development of, or alleviate to some extent, one or more of the symptoms of the disorder, disease, or condition being treated. The term "therapeutically effective amount" also refers to the amount of a compound that is sufficient to elicit the biological or medical response of a biological molecule (*e.g.*, a protein, enzyme, RNA, or DNA), cell, tissue, system, animal, or human, which is being sought by a researcher, veterinarian, medical doctor, or clinician.

The term "IC_{50}" or "EC_{50}" refers to an amount, concentration, or dosage of a compound that is required for 50% inhibition of a maximal response in an assay that measures such a response.

The term "CC_{50}" refers to an amount, concentration, or dosage of a compound that results in 50% reduction of the viability of a host. In certain embodiments, the CC_{50} of a compound is the amount, concentration, or dosage of the compound that is required to reduce the viability of cells treated with the compound by 50%, in comparison with cells untreated with the compound.

The term "pharmaceutically acceptable carrier," "pharmaceutically acceptable excipient," "physiologically acceptable carrier," or "physiologically acceptable excipient" refers to a pharmaceutically-acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, solvent, or encapsulating material. In one embodiment, each component is "pharmaceutically acceptable" in the sense of being compatible with the other ingredients of a pharmaceutical formulation, and suitable for use in contact with the tissue or organ of humans

and animals without excessive toxicity, irritation, allergic response, immunogenicity, or other problems or complications, commensurate with a reasonable benefit/risk ratio. *See, Remington: The Science and Practice of Pharmacy*, 21st ed.; Lippincott Williams & Wilkins: Philadelphia, PA, 2005; *Handbook of Pharmaceutical Excipients*, 6th ed.; Rowe *et al.*, Eds.; The Pharmaceutical Press and the American Pharmaceutical Association: 2009; *Handbook of Pharmaceutical Additives*, 3rd ed.; Ash and Ash Eds.; Gower Publishing Company: 2007; *Pharmaceutical Preformulation and Formulation*, 2nd ed.; Gibson Ed.; CRC Press LLC: Boca Raton, FL, 2009.

The term "about" or "approximately" means an acceptable error for a particular value as determined by one of ordinary skill in the art, which depends in part on how the value is measured or determined. In certain embodiments, the term "about" or "approximately" means within 1, 2, 3, or 4 standard deviations. In certain embodiments, the term "about" or "approximately" means within 50%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, or 0.05% of a given value or range.

The terms "active ingredient" and "active substance" refer to a compound, which is administered, alone or in combination with one or more pharmaceutically acceptable excipients, to a subject for treating, preventing, or ameliorating one or more symptoms of a condition, disorder, or disease. As used herein, "active ingredient" and "active substance" may be an optically active isomer or an isotopic variant of a compound described herein.

The terms "drug," "therapeutic agent," and "chemotherapeutic agent" refer to a compound, or a pharmaceutical composition thereof, which is administered to a subject for treating, preventing, or ameliorating one or more symptoms of a condition, disorder, or disease.

The term "hepatitis C virus" or "HCV" refers to a viral species or a variant thereof, a pathogenic strain of which causes hepatitis C. Examples of HCV include, but are not limited to, HCV genotypes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and subtype 1a, 1b, 1c, 2a, 2b, 2c, 3a, 3b, 4a, 4b, 4c, 4d, 4e, 5a, 6a, 7a, 7b, 8a, 8b, 9a, 10a, and 11a. In certain embodiments, an HCV variant is an HCV species that contains a protein substantially homologous to a native HCV protein, *i.e.*, a protein having one or more naturally or non-naturally occurring amino acid deletions, insertions or substitutions (*e.g.*, derivatives, homologs, and fragments), as compared to the amino acid sequence of the native protein. The amino acid sequence of a protein of an HCV variant is at least about 80% identical, at least about 90% identical, or at least about 95% identical to a native HCV protein. In certain embodiments, the HCV variant contains an NS5A protein variant.

The term "NS5A" refers to nonstructural protein 5A of an HCV, or a variant thereof. NS5A variants include proteins substantially homologous to a native NS5A , *i.e.*, proteins having one or more naturally or non-naturally occurring amino acid deletions, insertions or substitutions (*e.g.*, NS5A derivatives, homologs, and fragments), as compared to the amino acid sequence of a native NS5A. The amino acid sequence of an NS5A variant is at least about 80% identical, at least about 90% identical, or at least about 95% identical to a native NS5A.

The term "alkyl" refers to a linear or branched saturated monovalent hydrocarbon radical, wherein the alkyl may optionally be substituted with one or more substituents Q as described herein. For example, C_{1-4} alkyl refers to a linear saturated monovalent hydrocarbon radical of 1 to 4 carbon atoms or a branched saturated monovalent hydrocarbon radical of 3 to 6 carbon atoms. In certain embodiments, the alkyl is a linear saturated monovalent hydrocarbon radical that has 1 to 20 (C_{1-20}), 1 to 15 (C_{1-15}), 1 to 10 (C_{1-10}), or 1 to 6 (C_{1-6}) carbon atoms, or branched saturated monovalent hydrocarbon radical of 3 to 20 (C_{3-20}), 3 to 15 (C_{3-15}), 3 to 10 (C_{3-10}), or 3 to 6 (C_{3-6}) carbon atoms. As used herein, linear C_{1-4} and branched C_{3-6} alkyl groups are also referred as "lower alkyl." Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl (including all isomeric forms), *n*-propyl, isopropyl, butyl (including all isomeric forms), *n*-butyl, isobutyl, *sec*-butyl, *t*-butyl, pentyl (including all isomeric forms), and hexyl (including all isomeric forms).

The term "halo" refers to fluoro, chloro, bromo, or iodo groups.

The term "haloalkyl" refers to alkyl radicals substituted with one or more, e.g., 1, 2, 3, or 4, etc., halo groups.

The term "cycloalkyl" refers to a non-aromatic mono- or multicyclic ring system comprising about 3 to about 7 carbon atoms, preferably about 3 to about 6 carbon atoms. Non-limiting examples of suitable monocyclic cycloalkyls include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Non-limiting examples of suitable multicyclic cycloalkyls include 1-decalin, norbornyl, adamantyl and the like.

The terms "heterocycloalkyl" and "heterocyclyl"refer to a non-aromatic saturated monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclyls contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is

present as a ring atom. The nitrogen or sulfur atom of the heterocyclyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic heterocyclyl rings include azetidinyl, piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,3-dioxolanyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like. The heterocycloalkyl rings of this invention can be "bridged heterocycloalkyl rings. The term "bridged heterocycloalkyl"" (or "bridged heterocyclyl") means a heterocycloalkyl group as defined above having an alkylene chain (generally a 1 or 2 carbon alkylene chain, not counting the atoms in the ring to which the alkylene chain is bound) bridging two carbon atoms in the ring.

The term "heteroaryl" refers to heteroaromatic rings and heteroaromatic fused ring systems which are aromatic and which contain at least one N, S or O atom, e.g. six-membered aromatic rings containing one to four nitrogen atoms; benzofused six-membered aromatic rings containing one to three nitrogen atoms; five-membered aromatic rings containing one oxygen, one nitrogen or one sulfur atom; benzofused five-membered aromatic rings containing one oxygen, one nitrogen or one sulfur atom; five-membered aromatic rings containing two heteroatoms independently selected from oxygen, nitrogen and sulfur and benzofused derivatives of such rings; five-membered aromatic rings containing three nitrogen atoms and benzofused derivatives thereof; a tetrazolyl ring; a thiazinyl ring; or coumarinyl. Examples of such ring systems are furanyl, thienyl, pyrrolyl, pyridinyl, pyrimidinyl, indolyl, quinolinyl, isoquinolinyl, imidazolyl, triazinyl, thiazolyl, isothiazolyl, pyridazinyl, pyrazolyl, oxazolyl, isoxazolyl, benzothienyl, quinazolinyl and quinoxalinyl.

The term "aryl" refers to an aromatic monocyclic or multicyclic ring system comprising about 6 to about 14 carbon atoms, preferably about 6 to about 10 carbon atoms. Non-limiting examples of suitable aryl groups include phenyl and naphthyl.

The term "alkylene" refers a chain comprising at least one -(CH_2)- group. Examples of alkylene chains include, but are not limited to: -(CH_2)$_{1-6}$-, -(CH_2)$_{1-4}$-, -(CH_2)$_{1-2}$- and -(CH_2)-.

The term "optionally substituted" is intended to mean that a group or substituent, such as an alkyl, may be substituted with one or more, in one embodiment, one, two, three, or four, substituents Q, each of which is independently selected from, *e.g.*, (a) oxo (=O), cyano (–CN), halo, or nitro (–NO_2); (b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl, each of which is further optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q^a; and (c) –C(O)R^a,

$-C(O)OR^a$, $-C(O)NR^bR^c$, $-C(NR^a)NR^bR^c$, $-OR^a$, $-OC(O)R^a$, $-OC(O)OR^a$, $-OC(O)NR^bR^c$, $-OC(=NR^a)NR^bR^c$, $-OP(O)(OR^e)_2$, $-OS(O)R^a$, $-OS(O)_2R^a$, $-OS(O)NR^bR^c$, $-OS(O)_2NR^bR^c$, $-NR^bR^c$, $-NR^aC(O)R^d$, $-NR^aC(O)OR^d$, $-NR^aC(O)NR^bR^c$, $-NR^aC(=NR^d)NR^bR^c$, $-NR^aS(O)R^d$, $-NR^aS(O)_2R^d$, $-NR^aS(O)NR^bR^c$, $-NR^aS(O)_2NR^bR^c$, $-P(O)(OR^a)R^d$, $-CH_2P(O)(OR^a)R^d$, $-CH_2OP(O)(OR^e)_2$, $-CH_2OC(O)C(R^a)_2NR^bR^c$, $-SR^a$, $-S(O)R^a$, $-S(O)_2R^a$, $-S(O)NR^bR^c$, or $-S(O)_2NR^bR^c$, wherein each R^a, R^b, R^c, and R^d is independently (i) hydrogen; (ii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl, each of which is optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q^a; or (iii) R^b and R^c together with the N atom to which they are attached form heterocyclyl, optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q^a; and each R^e is independently (i) hydrogen; (ii) a monovaluent cation, in one embodiment, Na^+ or K^+; (iii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl, each of which is optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q^a; or (iv) two R^e together are a divalent cation, in one embodiment, Mg^{2+} or Ca^{2+}. As used herein, all groups that can be substituted are "optionally substituted," unless otherwise specified.

In one embodiment, each Q^a is independently selected from of (a) oxo, cyano, halo, or nitro; (b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; and (c) $-C(O)R^f$, $-C(O)OR^f$, $-C(O)NR^gR^h$, $-C(NR^f)NR^gR^h$, $-OR^f$, $-OC(O)R^f$, $-OC(O)OR^f$, $-OC(O)NR^gR^h$, $-OC(=NR^f)NR^gR^h$, $-OP(O)(OR^n)_2$, $-OS(O)R^f$, $-OS(O)_2R^f$, $-OS(O)NR^gR^h$, $-OS(O)_2NR^gR^h$, $-NR^gR^h$, $-NR^fC(O)R^k$, $-NR^fC(O)OR^k$, $-NR^fC(O)NR^gR^h$, $-NR^fC(=NR^k)NR^gR^h$, $-NR^fS(O)R^k$, $-NR^fS(O)_2R^k$, $-NR^fS(O)NR^gR^h$, $-NR^fS(O)_2NR^gR^h$,$-P(O)(OR^f)R^k$, $-CH_2P(O)(OR^f)R^k$, $-SR^f$, $-S(O)R^f$, $-S(O)_2R^f$, $-S(O)NR^gR^h$, or $-S(O)_2NR^gR^h$; wherein each R^f, R^g, R^h, and R^k is independently (i) hydrogen; (ii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (iii) R^g and R^h together with the N atom to which they are attached form heterocyclyl; and each R^n is independently (i) hydrogen; (ii) a monovaluent cation, in one embodiment, Na^+ or K^+; (iii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl; or (iv) two R^n together are a divalent cation, in one embodiment, Mg^{2+} or Ca^{2+}.

The terms "optically active" and "enantiomerically active" refer to a collection of molecules, which has an enantiomeric excess of no less than about 50%, no less than about 70%, no less than about 80%, no less than about 90%, no less than about 91%, no less than about 92%,

no less than about 93%, no less than about 94%, no less than about 95%, no less than about 96%, no less than about 97%, no less than about 98%, no less than about 99%, no less than about 99.5%, or no less than about 99.8%. In certain embodiments, the compound comprises about 95% or more of one enantiomer and about 5% or less of the other enantiomer based on the total weight of the racemate in question.

In describing an optically active compound, the prefixes R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The (+) and (-) are used to denote the optical rotation of the compound, that is, the direction in which a plane of polarized light is rotated by the optically active compound. The (-) prefix indicates that the compound is levorotatory, that is, the compound rotates the plane of polarized light to the left or counterclockwise. The (+) prefix indicates that the compound is dextrorotatory, that is, the compound rotates the plane of polarized light to the right or clockwise. However, the sign of optical rotation, (+) and (-), is not related to the absolute configuration of the molecule, R and S.

The term "isotopic variant" refers to a compound that contains an unnatural proportion of an isotope at one or more of the atoms that constitute such a compound. In certain embodiments, an "isotopic variant" of a compound contains unnatural proportions of one or more isotopes, including, but not limited to, hydrogen (^{1}H), deuterium (^{2}H), tritium (^{3}H), carbon-11 (^{11}C), carbon-12 (^{12}C), carbon-13 (^{13}C), carbon-14 (^{14}C), nitrogen-13 (^{13}N), nitrogen-14 (^{14}N), nitrogen-15 (^{15}N), oxygen-14 (^{14}O), oxygen-15 (^{15}O), oxygen-16 (^{16}O), oxygen-17 (^{17}O), oxygen-18 (^{18}O), fluorine-17 (^{17}F), fluorine-18 (^{18}F), phosphorus-31 (^{31}P), phosphorus-32 (^{32}P), phosphorus-33 (^{33}P), sulfur-32 (^{32}S), sulfur-33 (^{33}S), sulfur-34 (^{34}S), sulfur-35 (^{35}S), sulfur-36 (^{36}S), chlorine-35 (^{35}Cl), chlorine-36 (^{36}Cl), chlorine-37 (^{37}Cl), bromine-79 (^{79}Br), bromine-81 (^{81}Br), iodine-123 (^{123}I), iodine-125 (^{125}I), iodine-127 (^{127}I), iodine-129 (^{129}I), and iodine-131 (^{131}I). In certain embodiments, an "isotopic variant" of a compound is in a stable form, that is, non-radioactive. In certain embodiments, an "isotopic variant" of a compound contains unnatural proportions of one or more isotopes, including, but not limited to, hydrogen (^{1}H), deuterium (^{2}H), carbon-12 (^{12}C), carbon-13 (^{13}C), nitrogen-14 (^{14}N), nitrogen-15 (^{15}N), oxygen-16 (^{16}O), oxygen-17 (^{17}O), oxygen-18 (^{18}O), fluorine-17 (^{17}F), phosphorus-31 (^{31}P), sulfur-32 (^{32}S), sulfur-33 (^{33}S), sulfur-34 (^{34}S), sulfur-36 (^{36}S), chlorine-35 (^{35}Cl), chlorine-37 (^{37}Cl), bromine-79 (^{79}Br), bromine-81 (^{81}Br), and iodine-127 (^{127}I). In certain embodiments, an "isotopic variant" of a compound is in an unstable form, that is, radioactive. In certain embodiments, an "isotopic variant" of a compound contains unnatural proportions of one or more isotopes, including, but not limited to, tritium (^{3}H), carbon-11 (^{11}C), carbon-14 (^{14}C),

nitrogen-13 (^{13}N), oxygen-14 (^{14}O), oxygen-15 (^{15}O), fluorine-18 (^{18}F), phosphorus-32 (^{32}P), phosphorus-33 (^{33}P), sulfur-35 (^{35}S), chlorine-36 (^{36}Cl), iodine-123 (^{123}I), iodine-125 (^{125}I), iodine-129 (^{129}I), and iodine-131 (^{131}I). It will be understood that, in a compound as provided herein, any hydrogen can be ^{2}H, for example, or any carbon can be ^{13}C, as example, or any nitrogen can be ^{15}N, as example, and any oxygen can be ^{18}O, where feasible according to the judgment of one of skill. In certain embodiments, an "isotopic variant" of a compound contains unnatural proportions of deuterium.

The term "solvate" refers to a complex or aggregate formed by one or more molecules of a solute, *e.g.*, a compound provided herein, and one or more molecules of a solvent, which present in stoichiometric or non-stoichiometric amount. Suitable solvents include, but are not limited to, water, methanol, ethanol, *n*-propanol, isopropanol, and acetic acid. In certain embodiments, the solvent is pharmaceutically acceptable. In one embodiment, the complex or aggregate is in a crystalline form. In another embodiment, the complex or aggregate is in a noncrystalline form. Where the solvent is water, the solvate is a hydrate. Examples of hydrates include, but are not limited to, a hemihydrate, monohydrate, dihydrate, trihydrate, tetrahydrate, and pentahydrate.

The phrase "a single enantiomer, a racemic mixture, a diastereomer, a mixture of diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt or solvate thereof" has the same meaning as the phrase "a single enantiomer, a racemic mixture, a diastereomer, a mixture of diastereomers, or an isotopic variant of the compound referenced therein; or a pharmaceutically acceptable salt or solvate of the compound referenced therein, or a single enantiomer, a racemic mixture, a diastereomer, a mixture of diastereomers, or an isotopic variant of the compound referenced therein."

HCV has a single positive-stranded RNA genome having about 9.6 kb in length that encodes a large polyprotein having about 3010 amino acids. This precursor polyprotein is then processed into a range of structural proteins, including core protein, C, and envelope glycoproteins, E1 and E2; and non-structural proteins, including NS2, NS3, NS4A, NS4B, NS5A, and NS5B, by host signal peptidases and two viral proteases, NS2-3 and NS3. The nonstructural protein 5A (NS5A) is a multifunctional protein essential for HCV replication. Because of its vital role in viral replication, HCV NS5A protein has been actively pursued as a drug target for developing anti-HCV therapy.

Provided herein are pharmaceutical compositions comprising a compound provided herein, *e.g.*, a compound of Formula I or II, as an active ingredient, including a single

enantiomer, a racemic mixture, a diastereomer, a mixture of diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt or solvate thereof; in combination with a pharmaceutically acceptable vehicle, carrier, diluent, or excipient, or a mixture thereof.

Suitable excipients are well known to those skilled in the art, and non-limiting examples of suitable excipients are provided herein. Whether a particular excipient is suitable for incorporation into a pharmaceutical composition or dosage form depends on a variety of factors well known in the art, including, but not limited to, the method of administration. For example, oral dosage forms such as tablets may contain excipients not suited for use in parenteral dosage forms. The suitability of a particular excipient may also depend on the specific active ingredients in the dosage form. For example, the decomposition of some active ingredients may be accelerated by some excipients such as lactose, or when exposed to water. Active ingredients that comprise primary or secondary amines are particularly susceptible to such accelerated decomposition. Consequently, provided herein are pharmaceutical compositions and dosage forms that contain little, if any, lactose, or other mono- or di-saccharides. As used herein, the term "lactose-free" means that the amount of lactose present, if any, is insufficient to substantially increase the degradation rate of an active ingredient. In one embodiment, lactose-free compositions comprise an active ingredient provided herein, a binder/filler, and a lubricant. In another embodiment, lactose-free dosage forms comprise an active ingredient, microcrystalline cellulose, pre-gelatinized starch, and magnesium stearate.

The compound provided herein may be administered alone, or in combination with one or more other compounds provided herein. The pharmaceutical compositions that comprise a compound a compound of Formula I or II, including a single enantiomer, a racemic mixture, a diastereomer, a mixture of diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt or solvate thereof, can be formulated in various dosage forms for oral, parenteral, and topical administration. The pharmaceutical compositions can also be formulated as modified release dosage forms, including delayed-, extended-, prolonged-, sustained-, pulsatile-, controlled-, accelerated-, fast-, targeted-, programmed-release, and gastric retention dosage forms. These dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art (*see, Remington: The Science and Practice of Pharmacy*, supra; *Modified-Release Drug Delivery Technology*, 2nd ed.; Rathbone *et al.*, Eds.; Marcel Dekker, Inc.: New York, NY, 2008).

The pharmaceutical compositions provided herein can be provided in a unit-dosage form or multiple-dosage form. A unit-dosage form, as used herein, refers to physically

discrete a unit suitable for administration to a human and animal subject, and packaged individually as is known in the art. Each unit-dose contains a predetermined quantity of an active ingredient(s) sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carriers or excipients. Examples of a unit-dosage form include an ampoule, syringe, and individually packaged tablet and capsule. For example, a 100 mg unit dose contains about 100 mg of an active ingredient in a packaged tablet or capsule. A unit-dosage form may be administered in fractions or multiples thereof. A multiple-dosage form is a plurality of identical unit-dosage forms packaged in a single container to be administered in segregated unit-dosage form. Examples of a multiple-dosage form include a vial, bottle of tablets or capsules, or bottle of pints or gallons.

The pharmaceutical compositions provided herein can be administered at once, or multiple times at intervals of time. It is understood that the precise dosage and duration of treatment may vary with the age, weight, and condition of the patient being treated, and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test or diagnostic data. It is further understood that for any particular individual, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the formulations.

The pharmaceutical compositions provided herein for oral administration can be provided in solid, semisolid, or liquid dosage forms for oral administration. As used herein, oral administration also includes buccal, lingual, and sublingual administration. Suitable oral dosage forms include, but are not limited to, tablets, fastmelts, chewable tablets, capsules, pills, strips, troches, lozenges, pastilles, cachets, pellets, medicated chewing gum, bulk powders, effervescent or non-effervescent powders or granules, oral mists, solutions, emulsions, suspensions, wafers, sprinkles, elixirs, and syrups. In addition to the active ingredient(s), the pharmaceutical compositions can contain one or more pharmaceutically acceptable carriers or excipients, including, but not limited to, binders, fillers, diluents, disintegrants, wetting agents, lubricants, glidants, coloring agents, dye-migration inhibitors, sweetening agents, flavoring agents, emulsifying agents, suspending and dispersing agents, preservatives, solvents, non-aqueous liquids, organic acids, and sources of carbon dioxide.

The pharmaceutical compositions provided herein can be administered parenterally by injection, infusion, or implantation, for local or systemic administration. Parenteral administration, as used herein, include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular, intrasynovial,

intravesical, and subcutaneous administration. The pharmaceutical compositions provided herein for parenteral administration can be formulated in any dosage forms that are suitable for parenteral administration, including solutions, suspensions, emulsions, micelles, liposomes, microspheres, nanosystems, and solid forms suitable for solutions or suspensions in liquid prior to injection. Such dosage forms can be prepared according to conventional methods known to those skilled in the art of pharmaceutical science (*see, Remington: The Science and Practice of Pharmacy*, supra).

The pharmaceutical compositions provided herein can be administered topically to the skin, orifices, or mucosa. The topical administration, as used herein, includes (intra)dermal, conjunctival, intracorneal, intraocular, ophthalmic, auricular, transdermal, nasal, vaginal, urethral, respiratory, and rectal administration. The pharmaceutical compositions provided herein can be formulated in any dosage forms that are suitable for topical administration for local or systemic effect, including emulsions, solutions, suspensions, creams, gels, hydrogels, ointments, dusting powders, dressings, elixirs, lotions, suspensions, tinctures, pastes, foams, films, aerosols, irrigations, sprays, suppositories, bandages, and dermal patches. The topical formulation of the pharmaceutical compositions provided herein can also comprise liposomes, micelles, microspheres, nanosystems, and mixtures thereof.

The pharmaceutical compositions provided herein can be formulated as a modified release dosage form. As used herein, the term "modified release" refers to a dosage form in which the rate or place of release of the active ingredient(s) is different from that of an immediate dosage form when administered by the same route. Modified release dosage forms include, but are not limited to, delayed-, extended-, prolonged-, sustained-, pulsatile-, controlled-, accelerated- and fast-, targeted-, programmed-release, and gastric retention dosage forms. The pharmaceutical compositions in modified release dosage forms can be prepared using a variety of modified release devices and methods known to those skilled in the art, including, but not limited to, matrix controlled release devices, osmotic controlled release devices, multiparticulate controlled release devices, ion-exchange resins, enteric coatings, multilayered coatings, microspheres, liposomes, and combinations thereof. The release rate of the active ingredient(s) can also be modified by varying the particle sizes and polymorphorism of the active ingredient(s).

Provided herein are methods for treating or preventing a hepatitis C viral infection in a subject, which comprises administering to the subject a therapeutically effective amount of a compound of Formula I or II, including a single enantiomer, a racemic mixture, a diastereomer, a mixture of diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt or

solvate thereof.

In another embodiment, provided herein are methods for treating, preventing, or ameliorating one or more symptoms of a liver disease or disorder associated with an HCV infection, comprising administering to a subject a therapeutically effective amount of a compound of Formula I or II, including a single enantiomer, a racemic mixture, a diastereomer, a mixture of diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt or solvate thereof. Non-limiting examples of diseases associated with HCV infection include chronic hepatitis, cirrhosis, hepatocarcinoma, or extra hepatic manifestation.

In yet another embodiment, provided herein are methods for treating or preventing a drug-resistant hepatitis C viral infection in a subject, which comprises administering to the subject a therapeutically effective amount of a compound a compound of Formula I or II, including a single enantiomer, a racemic mixture, a diastereomer, a mixture of diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt or solvate thereof.

In yet another embodiment, provided herein are methods for treating, preventing, or ameliorating one or more symptoms of a liver disease or disorder associated with a drug-resistant HCV infection, comprising administering to a subject a therapeutically effective amount of a compound of Formula I or II, including a single enantiomer, a racemic mixture, a diastereomer, a mixture of diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt or solvate thereof. Non-limiting examples of diseases associated with drug-resistant HCV infection include chronic hepatitis, cirrhosis, hepatocarcinoma, or extra hepatic manifestation.

In certain embodiments, the HCV infection is caused by a hepatitis C virus or variant thereof as described herein.

In certain embodiments, the drug-resistant HCV is resistant to an anti-HCV agent. In certain embodiments, the anti-HCV agent is an interferon. In certain embodiments, the anti-HCV agent is ribaririn. In certain embodiments, the anti-HCV agent is amantadine. In certain embodiments, the anti-HCV agent is an interleukin. In certain embodiments, the anti-HCV agent is a phenanthrenequinone. In certain embodiments, the anti-HCV agent is a thiazolidine. In certain embodiments, the anti-HCV agent is a benzanilide. In certain embodiments, the anti-HCV agent is a helicase inhibitor. In certain embodiments, the anti-HCV agent is a nucleotide analogue. In certain embodiments, the anti-HCV agent is a gliotoxin. In certain embodiments, the anti-HCV agent is a cerulenin. In certain embodiments, the anti-HCV agent is an antisense phopshorothioate ologodexoynucleotide. In certain embodiments, the anti-HCV agent is an

inhibitor of IRES-dependent translation. In certain embodiments, the anti-HCV agent is a ribozyme. In certain embodiments, the anti-HCV agent is a cyclophilin inhibitor. In certain embodiments, the anti-HCV agent is SYC-635.

In certain embodiments, the anti-HCV agent is a protease inhibitor. In certain embodiments, the anti-HCV agent is a cysteine protease inhibitor. In certain embodiments, the anti-HCV agent is a caspase inhibitor. In certain embodiments, the anti-HCV agent is GS 9450. In certain embodiments, the anti-HCV agent is a serine protease inhibitor. In certain embodiments, the anti-HCV agent is an NS3/4A serine protease inhibitor. In certain embodiments, the anti-HCV agent is a serine protease inhibitor selected from ABT-450, faldaprevir (BI-201335), asunaprevir (BMS-650032), boceprevir (SCH 503034), danoprevir (ITMN-191/R7227), GS-9256, GS-9451, IDX136, IDX316, IDX320, MK-5172, SCH900518, telaprevir (VX-950), TMC 435, vaniprevir (MK-7009), VX-985, and mixtures thereof.

In certain embodiments, the anti-HCV agent is a polymerase inhibitor. In certain embodiments, the anti-HCV agent is an NS5B polymerase inhibitor. In certain embodiments, the anti-HCV agent is a polymerase inhibitor selected from ABT-072, ABT-333, AG-02154, ANA598, ANA773, deleobuvir (BI 207127), GS-9190, GS-9669, HCV-796, IDX184, IDX375, JTK-109, MK-0608, MK-3281, NM283, PF-868554, PSI-879, PSI-938, PSI-6130, PSI-7851, sofosbuvir (PSI-7977), R1626, R7128, RG7128, VCH-759, VCH-916, VX-222 (VCH-222), and mixtures thereof. In certain embodiments, the NS5B polymerase inhibitor is a nucleotide inhibitor. In certain embodiments, the NS5B polymerase inhibitor is a 2'-*C*-methylnucleoside. In certain embodiments, the NS5B polymerase inhibitor is a 2'-F-2'-*C*-methylnucleoside. In certain embodiments, the NS5B polymerase inhibitor is a non-nucleoside inhibitor. In certain embodiments, the NS5B polymerase inhibitor is a benzofuran, benzothiadiazine, or thiophene.

In certain embodiments, the anti-HCV agent is an NS5A inhibitor. In certain embodiments, the anti-HCV agent is an NS5A inhibitor selected from daclatasvir (BMS-790052), BMS-824393, ledipasvir (GS-5885), GSK2336805, PPI-668, and mixtures thereof.

In certain embodiments, the drug-resistance of the HCV infection is caused by an HCV variant. In certain embodiments, the HCV variant contains an NS3 protein variant. In certain embodiments, the NS3 protein variant contains a mutation or deletion. In certain embodiments, the NS3 protein variant contains one or more mutations and/or deletions at the amino acid positions of 9, 16, 18, 23, 36, 39, 40, 41, 43, 54, 55, 65, 67, 70, 71, 80, 89, 109, 138, 155, 156, 162, 168, 170, 174, 176, 179, 260, and 489. In certain embodiments, the NS3 protein variant contains one or more mutations and/or deletions at the amino acid positions of 16, 23, 36,

39, 41, 43, 54, 55, 80, 89, 109, 138, 155, 156, 168, 170, 174, 176, 260, and 489. In certain embodiments, the NS3 protein variant contains one or more mutations and/or deletions at the amino acid positions of 36, 54, 155, 156, 168, and 170. In certain embodiments, the NS3 protein variant contains one, two, or more mutations and/or deletions, each independently selected from C16S, V23A, V36A, V36G, V36L, V36M, A39V, Q41R, F43C, F43I, F43S, F43V, T54A, T54S, V55A, Q80K, Q80G, Q80H, Q80L, Q80R, P89R, R109K, S138T, R155G, R155I, R155K, R155L, R155M, R155Q, R155S, R155T, E56G, E56I, E56S, E56T, E56V, D168A, D168E, D168G, D168H, D168I, D168N, D168T, D168V, D168Y, V170A, V170T, S174K, S174N, E176K, T260A, and S489L, provided that there is only one mutation or deletion at a given amino acid position in the NS3 protein variant. In certain embodiments, the NS3 protein variant contains one, two, or more mutations and/or deletions, each independently selected from R155K, E56S, E56T, D168V, and T260A, provided that there is only one mutation or deletion at a given amino acid position in the NS3 protein variant.

In certain embodiments, the HCV variant contains an NS4A protein variant. In certain embodiments, the NS4A protein variant contains a mutation or deletion. In certain embodiments, the NS4A protein variant contains a mutation at the amino acid position of 23. In certain embodiments, the NS4A protein variant contains the V23A mutation.

In certain embodiments, the HCV variant contains an NS4B protein variant. In certain embodiments, the NS4B protein variant contains a mutation or deletion. In certain embodiments, the NS4B protein variant contains a mutation at the amino acid position of 15. In certain embodiments, the NS4B protein variant contains the E15G mutation.

In certain embodiments, the HCV variant contains an NS5A protein variant. In certain embodiments, the NS5A protein variant contains a mutation or deletion. In certain embodiments, the NS5A protein variant contains one or more mutations and/or deletions at the amino acid positions of 23, 28, 30, 31, 32, 37, 54, 58, 63, and 93. In certain embodiments, the NS5A protein variant contains one or more mutations and/or deletions at the amino acid positions of 23, 24, 28, 30, 31, 32, 37, 54, 58, 63, 93, 295, 318, 320, 356, 404, and 442. In certain embodiments, the NS5A protein variant contains one or more mutations and/or deletions at the amino acid positions of 24, 28, 30, 31, 32, 54, 93, 295, and 318. In certain embodiments, the NS5A protein variant contains one, two, or more mutations and/or deletions, each independently selected from L23F, L28M, L28T, M28T, ΔQ30, Q30E, Q30H, Q30K, Q30R, ΔR30, R30E, R30Q, L31F, L31M, L31V, P32L, F37L, H54Y, Q54H, P58H, P58S, I63V, Y93C, Y93H, Y93N, and Y93S, provided that there is only one mutation or deletion at a given amino

acid position in the NS5A protein variant. In certain embodiments, the NS5A protein variant contains one, two, or more mutations and/or deletions, each independently selected from L23F, K24E, L28M, L28T, M28T, ΔQ30, Q30E, Q30H, Q30K, Q30R, ΔR30, R30E, R30Q, L31F, L31M, L31V, P32L, F37L, H54Y, Q54H, P58H, P58S, I63V, Y93C, Y93H, Y93N, Y93S, E295G, R318W, D320E, R356Q, G404S, and E442G, provided that there is only one mutation or deletion at a given amino acid position in the NS5A protein variant. In certain embodiments, the NS5A protein variant contains one, two, or more mutations and/or deletions, each independently selected from L23F, K24E, L28M, L28T, ΔQ30, Q30E, Q30H, Q30K, Q30R, L31F, L31M, L31V, P32L, F37L, H54Y, Q54H, P58H, P58S, I63V, Y93C, Y93H, Y93N, Y93S, E295G, R318W, D320E, R356Q, G404S, and E442G, provided that there is only one mutation or deletion at a given amino acid position in the NS5A protein variant. In certain embodiments, the NS5A protein variant contains one, two, or more mutations and/or deletions, each independently selected from L23F, K24E, M28T, ΔR30, R30E, R30Q, L31F, L31M, L31V, P32L, F37L, H54Y, Q54H, P58H, P58S, I63V, Y93C, Y93H, Y93N, Y93S, E295G, R318W, D320E, R356Q, G404S, and E442G, provided that there is only one mutation or deletion at a given amino acid position in the NS5A protein variant. In certain embodiments, the NS5A protein variant contains one, two, or more mutations and/or deletions, each independently selected from K24E, M28T, Q30E, Q30H, Q30K, Q30R, L31F, L31M, L31V, P32L, Y93C, Y93H, Y93N, E295G, and R318W, provided that there is only one mutation or deletion at a given amino acid position in the NS5A protein variant.

In certain embodiments, the HCV variant contains an NS5B protein variant. In certain embodiments, the NS5B protein variant contains a mutation or deletion. In certain embodiments, the NS5B protein variant contains one or more mutations and/or deletions at the amino acid positions of 15, 95, 96, 142, 152, 156, 222, 223, 244, 282, 309, 310, 316, 320, 321, 326, 329, 333, 365, 411, 414, 415, 423, 445, 448, 451, 452, 495, 554, 558, and 559. In certain embodiments, the NS5B protein variant contains one or more mutations and/or deletions at the amino acid positions of 316, 414, and 423. In certain embodiments, the NS5B protein variant contains one, two, or more mutations and/or deletions, each independently selected from S15G, H95Q, H95R, S96T, N142T, G152E, P156L, R222Q, C223H, C223Y, D244N, S282T, Q309R, D310N, C316N, C316S, C316Y, L320I, V321I, S326G, T329I, A333E, S365A, S365T, N411S, M414I, M414L, M414T, F415Y, M423I, M423T, M423V, C445F, Y448H, C451R, Y452H, P495A, P495I, G554D, G554S, G558R, D559G, D559N, and D559S, provided that there is only one mutation or deletion at a given amino acid position in the NS5B protein variant. In certain

embodiments, the NS5B protein variant contains one, two, or more mutations and/or deletions, each independently selected from C316Y, M414T, and M423T, provided that there is only one mutation or deletion at a given amino acid position in the NS5B protein variant.

In one embodiment, provided herein is a method for treating or preventing infection caused by or associated with a hepatitis C virus variant, comprising administering to a subject a therapeutically effective amount of a compound of Formula I or II, including a single enantiomer, a racemic mixture, a diastereomer, a mixture of diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt or solvate thereof.

In another embodiment, provided herein is a method for treating, preventing, or ameliorating one or more symptoms of a liver disease or disorder caused by or associated with a hepatitis C virus variant, comprising administering to a subject a therapeutically effective amount of a compound of Formula I or II, including a single enantiomer, a racemic mixture, a diastereomer, a mixture of diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt or solvate thereof.

In certain embodiments, the HCV variant contains an NS5A protein variant as described herein.

In one embodiment, provided herein is a method for treating or preventing infection caused by or associated with a hepatitis C virus containing an NS5A protein variant as described herein, comprising administering to a subject a therapeutically effective amount of a compound of Formula I or II, including a single enantiomer, a racemic mixture, a diastereomer, a mixture of diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt or solvate thereof.

In another embodiment, provided herein is a method for treating, preventing, or ameliorating one or more symptoms of a liver disease or disorder caused by or associated with hepatitis C virus containing an NS5A protein variant as described herein, comprising administering to a subject a therapeutically effective amount of a compound of Formula I or II, including a single enantiomer, a racemic mixture, a diastereomer, a mixture of diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt or solvate thereof.

In one embodiment, the subject is a mammal. In another embodiment, the subject is a human.

In one embodiment, provided herein is a method for inhibiting replication of a virus in a host, which comprises contacting the host with a therapeutically effective amount of a compound a compound of Formula I or II, including a single enantiomer, a racemic mixture, a

diastereomer, a mixture of diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt or solvate thereof.

In certain embodiments, the virus is a hepatitis C virus. In certain embodiments, the virus is a drug-resistant hepatitis C virus. In certain embodiments, the virus is a hepatitis C virus variant.

In one embodiment, the hepatitis C virus is HCV genotype 1. In certain embodiments, the hepatitis C virus is HCV subtype 1a. In certain embodiments, the hepatitis C virus is HCV subtype 1b. In certain embodiments, the hepatitis C virus is HCV subtype 1c.

In another embodiment, the hepatitis C virus is HCV genotype 2. In certain embodiments, the hepatitis C virus is HCV subtype 2a. In certain embodiments, the hepatitis C virus is HCV subtype 2b. In certain embodiments, the hepatitis C virus is HCV subtype 2c.

In yet another embodiment, the hepatitis C virus is HCV genotype 3. In certain embodiments, the hepatitis C virus is HCV subtype 3a. In certain embodiments, the hepatitis C virus is HCV subtype 3b.

In yet another embodiment, the hepatitis C virus is HCV genotype 4. In certain embodiments, the hepatitis C virus is HCV subtype 4a. In certain embodiments, the hepatitis C virus is HCV subtype 4b. In certain embodiments, the hepatitis C virus is HCV subtype 4c. In certain embodiments, the hepatitis C virus is HCV subtype 4d. In certain embodiments, the hepatitis C virus is HCV subtype 4e.

In yet another embodiment, the hepatitis C virus is HCV genotype 5. In yet another embodiment, the hepatitis C virus is HCV subtype 5a.

In yet another embodiment, the hepatitis C virus is HCV genotype 6. In yet another embodiment, the hepatitis C virus is HCV subtype 6a.

In yet another embodiment, the hepatitis C virus is HCV genotype 7. In yet another embodiment, the hepatitis C virus is HCV subtype 7a.

In yet another embodiment, the hepatitis C virus is HCV genotype 8. In yet another embodiment, the hepatitis C virus is HCV subtype 8a. In yet another embodiment, the hepatitis C virus is HCV subtype 8b.

In yet another embodiment, the hepatitis C virus is HCV genotype 9. In yet another embodiment, the hepatitis C virus is HCV subtype 9a.

In yet another embodiment, the hepatitis C virus is HCV genotype 10. In yet another embodiment, the hepatitis C virus is HCV subtype 10a.

In still another embodiment, the hepatitis C virus is HCV genotype 11. In yet

another embodiment, the hepatitis C virus is HCV subtype 11a.

In one embodiment, the HCV variant is a variant of HCV genotype 1. In certain embodiments, the HCV variant is a variant of HCV subtype 1a. In certain embodiments, the HCV variant is a variant of HCV subtype 1b. In certain embodiments, the HCV variant is a variant of HCV subtype 1c.

In certain embodiments, the HCV variant is a variant of HCV subtype 1a, which contains an NS5A protein variant. In certain embodiments, the NS5A protein variant contains a mutation or deletion. In certain embodiments, the NS5A protein variant contains one or more mutations and/or deletions at the amino acid positions of 28, 30, 31, 32, 54, and 93. In certain embodiments, the NS5A protein variant contains one or more mutations and/or deletions at the amino acid positions of 23, 24, 28, 30, 31, 32, 37, 54, 58, 63, 93, 295, 318, 320, 356, 404, and 442. In certain embodiments, the NS5A protein variant contains one or more mutations and/or deletions at the amino acid positions of 24, 28, 30, 31, 32, 54, 93, 295, and 318. In certain embodiments, the NS5A protein variant contains one, two, or more mutations and/or deletions, each independently selected from M28T, ΔQ30, Q30E, Q30H, Q30K, Q30R, L31F, L31M, L31V, P32L, H54Y, Y93C, Y93H, and Y93N, provided that there is only one mutation or deletion at a given amino acid position in the NS5A protein variant. In certain embodiments, the NS5A protein variant contains one, two, or more mutations and/or deletions, each independently selected from L23F, K24E, L28M, L28T, M28T, ΔQ30, Q30E, Q30H, Q30K, Q30R, ΔR30, R30E, R30Q, L31F, L31M, L31V, P32L, F37L, H54Y, Q54H, P58H, P58S, I63V, Y93C, Y93H, Y93N, Y93S, E295G, R318W, D320E, R356Q, G404S, and E442G, provided that there is only one mutation or deletion at a given amino acid position in the NS5A protein variant. In certain embodiments, the NS5A protein variant contains one, two, or more mutations and/or deletions, each independently selected from L23F, K24E, L28M, L28T, ΔQ30, Q30E, Q30H, Q30K, Q30R, L31F, L31M, L31V, P32L, F37L, H54Y, Q54H, P58H, P58S, I63V, Y93C, Y93H, Y93N, Y93S, E295G, R318W, D320E, R356Q, G404S, and E442G, provided that there is only one mutation or deletion at a given amino acid position in the NS5A protein variant. In certain embodiments, the NS5A protein variant contains one, two, or more mutations and/or deletions, each independently selected from L23F, K24E, M28T, ΔR30, R30E, R30Q, L31F, L31M, L31V, P32L, F37L, H54Y, Q54H, P58H, P58S, I63V, Y93C, Y93H, Y93N, Y93S, E295G, R318W, D320E, R356Q, G404S, and E442G, provided that there is only one mutation or deletion at a given amino acid position in the NS5A protein variant. In certain embodiments, the NS5A protein variant contains one, two, or more mutations and/or deletions, each independently

selected from K24E, M28T, Q30E, Q30H, Q30K, Q30R, L31F, L31M, L31V, P32L, Y93C, Y93H, Y93N, E295G, and R318W, provided that there is only one mutation or deletion at a given amino acid position in the NS5A protein variant. In certain embodiments, the NS5A protein variant contains one or more mutations at the amino acid positions of 28, 30, 31, 32, and 93. In certain embodiments, the NS5A protein variant contains one, two, or more mutations, each independently selected from M28T, Q30E, Q30H, Q30K, Q30R, L31F, L31M, L31V, P32L, Y93C, Y93H, and Y93N, provided that there is only one mutation at a given amino acid position in the NS5A protein variant. In certain embodiments, the NS5A protein variant contains one or more mutations at the amino acid positions of 24, 28, 30, 31, 32, 93, 295, and 318. In certain embodiments, the NS5A protein variant contains one, two, or more mutations, each independently selected from K24E, M28T, Q30E, Q30H, Q30K, Q30R, L31F, L31M, L31V, P32L, Y93C, Y93H, Y93N, E295G, and R318W, provided that there is only one mutation at a given amino acid position in the NS5A protein variant.

In certain embodiments, the HCV variant is a variant of HCV subtype 1b, which contains an NS5A protein variant. In certain embodiments, the NS5A protein variant contains a mutation or deletion. In certain embodiments, the NS5A protein variant contains one or more mutations and/or deletions at the amino acid positions of 23, 28, 30, 31, 32, 37, 54, 58, 63, and 93. In certain embodiments, the NS5A protein variant contains one or more mutations and/or deletions at the amino acid positions of 23, 24, 28, 30, 31, 32, 37, 54, 58, 63, 93, 295, 318, 320, 356, 404, and 442. In certain embodiments, the NS5A protein variant contains one or more mutations and/or deletions at the amino acid positions of 24, 28, 30, 31, 32, 54, 93, 295, and 318. In certain embodiments, the NS5A protein variant contains one, two, or more mutations and/or deletions, each independently selected from L23F, L28M, L28T, ΔR30, R30E, R30Q, L31F, L31M, L31V, P32L, F37L, Q54H, P58H, P58S, I63V, Y93C, Y93H, Y93N, and Y93S, provided that there is only one mutation or deletion at a given amino acid position in the NS5A protein variant. In certain embodiments, the NS5A protein variant contains one, two, or more mutations and/or deletions, each independently selected from L23F, K24E, L28M, L28T, M28T, ΔQ30, Q30E, Q30H, Q30K, Q30R, ΔR30, R30E, R30Q, L31F, L31M, L31V, P32L, F37L, H54Y, Q54H, P58H, P58S, I63V, Y93C, Y93H, Y93N, Y93S, E295G, R318W, D320E, R356Q, G404S, and E442G, provided that there is only one mutation or deletion at a given amino acid position in the NS5A protein variant. In certain embodiments, the NS5A protein variant contains one, two, or more mutations and/or deletions, each independently selected from L23F, K24E, L28M, L28T, ΔQ30, Q30E, Q30H, Q30K, Q30R, L31F, L31M, L31V, P32L, F37L, H54Y, Q54H, P58H,

P58S, I63V, Y93C, Y93H, Y93N, Y93S, E295G, R318W, D320E, R356Q, G404S, and E442G, provided that there is only one mutation or deletion at a given amino acid position in the NS5A protein variant. In certain embodiments, the NS5A protein variant contains one, two, or more mutations and/or deletions, each independently selected from L23F, K24E, M28T, ΔR30, R30E, R30Q, L31F, L31M, L31V, P32L, F37L, H54Y, Q54H, P58H, P58S, I63V, Y93C, Y93H, Y93N, Y93S, E295G, R318W, D320E, R356Q, G404S, and E442G, provided that there is only one mutation or deletion at a given amino acid position in the NS5A protein variant. In certain embodiments, the NS5A protein variant contains one, two, or more mutations and/or deletions, each independently selected from K24E, M28T, Q30E, Q30H, Q30K, Q30R, L31F, L31M, L31V, P32L, Y93C, Y93H, Y93N, E295G, and R318W, provided that there is only one mutation or deletion at a given amino acid position in the NS5A protein variant. In certain embodiments, the NS5A protein variant contains one or more mutations at the amino acid positions of 28, 30, 31, 32, and 93. In certain embodiments, the NS5A protein variant contains one, two, or more mutations, each independently selected from L28T, R30E, L31F, L31M, L31V, P32L, Y93C, Y93H, and Y93N, provided that there is only one mutation at a given amino acid position in the NS5A protein variant. In certain embodiments, the NS5A protein variant contains one or more mutations at the amino acid positions of 24, 28, 30, 31, 32, 93, 295, and 318. In certain embodiments, the NS5A protein variant contains one, two, or more mutations, each independently selected from K24E, M28T, Q30E, Q30H, Q30K, Q30R, L31F, L31M, L31V, P32L, Y93C, Y93H, Y93N, E295G, and R318W, provided that there is only one mutation at a given amino acid position in the NS5A protein variant.

In another embodiment, the HCV variant is a variant of HCV genotype 2. In certain embodiments, the HCV variant is a variant of HCV subtype 2a. In certain embodiments, the HCV variant is a variant of HCV subtype 2b. In certain embodiments, the HCV variant is a variant of HCV subtype 2c.

In yet another embodiment, the HCV variant is a variant of HCV genotype 3. In certain embodiments, the HCV variant is a variant of HCV subtype 3a. In certain embodiments, the HCV variant is a variant of HCV subtype 3b.

In yet another embodiment, the HCV variant is a variant of HCV genotype 4. In certain embodiments, the HCV variant is a variant of HCV subtype 4a. In certain embodiments, the HCV variant is a variant of HCV subtype 4b. In certain embodiments, the HCV variant is a variant of HCV subtype 4c. In certain embodiments, the HCV variant is a variant of HCV subtype 4d. In certain embodiments, the HCV variant is a variant of HCV subtype 4e.

In yet another embodiment, the HCV variant is a variant of HCV genotype 5. In yet another embodiment, the HCV variant is a variant of HCV subtype 5a.

In yet another embodiment, the HCV variant is a variant of HCV genotype 6. In yet another embodiment, the HCV variant is a variant of HCV subtype 6a.

In yet another embodiment, the HCV variant is a variant of HCV genotype 7. In yet another embodiment, the HCV variant is a variant of HCV subtype 7a.

In yet another embodiment, the HCV variant is a variant of HCV genotype 8. In yet another embodiment, the HCV variant is a variant of HCV subtype 8a. In yet another embodiment, the HCV variant is a variant of HCV subtype 8b.

In yet another embodiment, the HCV variant is a variant of HCV genotype 9. In yet another embodiment, the HCV variant is a variant of HCV subtype 9a.

In yet another embodiment, the HCV variant is a variant of HCV genotype 10. In yet another embodiment, the HCV variant is a variant of HCV subtype 10a.

In still another embodiment, the HCV variant is a variant of HCV genotype 11. In yet another embodiment, the HCV variant is a variant of HCV subtype 11a.

In certain embodiments, provided herein is a method for inhibiting replication of hepatitis C virus containing an NS5A protein variant in a host, which comprises administering to the host a therapeutically effective amount of a compound of Formula I or II, including a single enantiomer, a racemic mixture, a diastereomer, a mixture of diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt or solvate thereof.

In one embodiment, the host is a cell. In another embodiment, the host is a human cell. In yet another embodiment, the host is a mammal. In still another embodiment, the host is human.

In certain embodiments, administration of a therapeutically effective amount of a compound of Formula I or II, including a single enantiomer, a racemic mixture, a diastereomer, a mixture of diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt or solvate thereof) results in a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 99% or more reduction in the replication of the virus relative to a subject without administration of the compound, as determined at 1 day, 2 days, 3 days, 4 days, 5 days, 10 days, 15 days, or 30 days after the administration by a method known in the art, *e.g.*, determination of viral titer.

In certain embodiments, administration of a therapeutically effective amount of a compound of Formula I or II, including a single enantiomer, a racemic mixture, a diastereomer, a mixture of diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt or

solvate thereof) results in a 1, 2, 3, 4, 5, 10, 15, 20, 25, 50, 75, 100-fold or more reduction in the replication of the virus relative to a subject without administration of the compound, as determined at 1 day, 2 days, 3 days, 4 days, 5 days, 10 days, 15 days, or 30 days after the administration by a method known in the art.

In certain embodiments, administration of a therapeutically effective amount of a compound of Formula I or II, including a single enantiomer, a racemic mixture, a diastereomer, a mixture of diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt or solvate thereof) results in a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 99% or more reduction in the viral titer relative to a subject without administration of the compound, as determined at 1 day, 2 days, 3 days, 4 days, 5 days, 10 days, 15 days, or 30 days after the administration by a method known in the art.

In certain embodiments, administration of a therapeutically effective amount of a compound of Formula I or II, including a single enantiomer, a racemic mixture, a diastereomer, a mixture of diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt or solvate thereof) results in a 1, 2, 3, 4, 5, 10, 15, 20, 25, 50, 75, 100 or more fold reduction in the viral titer relative to a subject without administration of the compound, as determined at 1 day, 2 days, 3 days, 4 days, 5 days, 10 days, 15 days, or 30 days after the administration by a method known in the art.

In certain embodiments, provided herein is a method for inhibiting the replication of an HCV virus, which comprises contacting the virus with a therapeutically effective amount of a compound a compound of Formula I or II, including a single enantiomer, a racemic mixture, a diastereomer, a mixture of diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt or solvate thereof.

In certain embodiments, the contacting of the virus with a therapeutically effective amount of a compound of Formula I or II, including a single enantiomer, a racemic mixture, a diastereomer, a mixture of diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt or solvate thereof) results in a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 99% or more reduction in the virus titer relative to the virus without such contact, as determined at 1 day, 2 days, 3 days, 4 days, 5 days, 10 days, 15 days, or 30 days after the initial contact, by a method known in the art.

In certain embodiments, the contacting of the virus with a therapeutically effective amount of a compound of Formula I or II, including a single enantiomer, a racemic mixture, a diastereomer, a mixture of diastereomers, or an isotopic variant thereof; or a

pharmaceutically acceptable salt or solvate) results in a 1, 2, 3, 4, 5, 10, 15, 20, 25, 50, 75, 100 or more fold reduction in the viral titer relative to the virus without such contact, as determined at 1 day, 2 days, 3 days, 4 days, 5 days, 10 days, 15 days, or 30 days after the initial contact, by a method known in the art.

In still another embodiment, provided herein is a method for treating, preventing, or ameliorating one or more symptoms of a liver disease or disorder associated with an HCV infection, comprising administering to a subject a therapeutically effective amount of the compound a compound of Formula I or II, including a single enantiomer, a racemic mixture, a diastereomer, a mixture of diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt or solvate thereof. Non-limiting examples of diseases associated with HCV infection include chronic hepatitis, cirrhosis, hepatocarcinoma, or extra hepatic manifestation.

Depending on the condition, disorder, or disease, to be treated and the subject's condition, a compound provided herein may be administered by oral, parenteral (*e.g.*, intramuscular, intraperitoneal, intravenous, intracerebroventricular (ICV), intracistemal injection or infusion, subcutaneous injection, or implant), inhalation, nasal, vaginal, rectal, sublingual, or topical (*e.g.*, transdermal or local) routes of administration, and may be formulated, alone or together, in suitable dosage unit with pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration.

The dose may be in the form of one, two, three, four, five, six, or more sub-doses that are administered at appropriate intervals per day. The dose or sub-doses can be administered in the form of dosage units containing from about 0.1 to about 1,000 milligram, from about 0.1 to about 500 milligrams, or from 0.5 about to about 100 milligram active ingredient(s) per dosage unit, and if the condition of the patient requires, the dose can, by way of alternative, be administered as a continuous infusion.

In certain embodiments, an appropriate dosage level is about 0.01 to about 100 mg per kg patient body weight per day (mg/kg per day), about 0.01 to about 50 mg/kg per day, about 0.01 to about 25 mg/kg per day, or about 0.05 to about 10 mg/kg per day, which may be administered in single or multiple doses. A suitable dosage level may be about 0.01 to about 100 mg/kg per day, about 0.05 to about 50 mg/kg per day, or about 0.1 to about 10 mg/kg per day. Within this range the dosage may be about 0.01 to about 0.1, about 0.1 to about 1.0, about 1.0 to about 10, or about 10 to about 50 mg/kg per day.

The compounds provided herein may also be combined or used in combination with other therapeutic agents useful in the treatment and/or prevention of an HCV infection.

As used herein, the term "in combination" includes the use of more than one therapy (*e.g.*, one or more prophylactic and/or therapeutic agents). However, the use of the term "in combination" does not restrict the order in which therapies (*e.g.*, prophylactic and/or therapeutic agents) are administered to a subject with a disease or disorder. A first therapy (*e.g.*, a prophylactic or therapeutic agent such as a compound provided herein) can be administered prior to (*e.g.*, 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks before), concomitantly with, or subsequent to (*e.g.*, 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks after) the administration of a second therapy (*e.g.*, a prophylactic or therapeutic agent) to the subject. Triple therapy is also contemplated herein.

As used herein, the term "synergistic" includes a combination of a compound provided herein and another therapy (*e.g.*, a prophylactic or therapeutic agent) which has been or is currently being used to prevent, treat, or manage a condition, disorder, or disease, which is more effective than the additive effects of the therapies. A synergistic effect of a combination of therapies (*e.g.*, a combination of prophylactic or therapeutic agents) permits the use of lower dosages of one or more of the therapies and/or less frequent administration of said therapies to a subject with a condition, disorder, or disease. The ability to utilize lower dosages of a therapy (*e.g.*, a prophylactic or therapeutic agent) and/or to administer said therapy less frequently reduces the toxicity associated with the administration of said therapy to a subject without reducing the efficacy of said therapy in the prevention, treatment, or management of a condition, disorder, or disease). In addition, a synergistic effect can result in improved efficacy of agents in the prevention, treatment, or management of a condition, disorder, or disease. Finally, a synergistic effect of a combination of therapies (*e.g.*, a combination of prophylactic or therapeutic agents) may avoid or reduce adverse or unwanted side effects associated with the use of either therapy alone.

The compound provided herein can be administered in combination or alternation with another therapeutic agent, such as an anti-HCV agent. In combination therapy, effective dosages of two or more agents are administered together; whereas in alternation or sequential-step therapy, an effective dosage of each agent is administered serially or sequentially. The dosages given will depend on absorption, inactivation, and excretion rates of the drug as well as other factors known to those of skill in the art. It is to be noted that dosage values will also vary

with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens and schedules should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions.

It has been recognized that drug-resistant variants of HCV can emerge after prolonged treatment with an antiviral agent. Drug resistance most typically occurs due to the mutation of a gene that encodes for an enzyme used in viral replication. The efficacy of a drug against the viral infection can be prolonged, augmented, or restored by administering the compound in combination or alternation with a second, and perhaps third, antiviral compound that induces a different mutation from that caused by the principle drug. Alternatively, the pharmacokinetics, biodistribution, or other parameters of the drug can be altered by such combination or alternation therapy. In general, combination therapy is typically preferred over alternation therapy because it induces multiple simultaneous stresses on the virus.

In certain embodiments, the pharmaceutical compositions provided herein further comprise a second antiviral agent as described herein. In certain embodiments, the compound provided herein is combined with one or more agents selected from an interferon, ribavirin, amantadine, an interleukin, an NS3 protease inhibitor, a cysteine protease inhibitor, a phenanthrenequinone, a thiazolidine, a benzanilide, a helicase inhibitor, a polymerase inhibitor, a nucleotide analogue, a gliotoxin, a cerulenin, an antisense phosphorothioate oligodeoxynucleotide, an inhibitor of IRES-dependent translation, or a ribozyme. In one embodiment, the second antiviral agent is an interferon. In another embodiment, the interferon is selected from pegylated interferon alpha 2a, interferon alfacon-1, natural interferon, ALBUFERON®, interferon beta-1a, omega interferon, interferon alpha, interferon gamma, interferon tau, interferon delta, or interferon gamma-1b.

In certain embodiments, the compound provided herein is combined with an HCV protease inhibitor, including, but not limited to, BI 201335 (Boehringer Ingelheim); TMC 435 or TMC 435350 (Medivir/Tibotec); ITMN 191/R7227 (InterMune); MK 7009 (Merck); SCH 5034/SCH 503034/Boceprevir and SCH 900518/narlaprevir (Schering); VX950/telaprevir (Vertex); substrate-based NS3 protease inhibitors as disclosed in DE 19914474, WO 98/17679, WO 98/22496, WO 99/07734, and Attwood *et al.*, *Antiviral Chemistry and Chemotherapy* **1999**, *10*, 259-273; non-substrate-based NS3 protease inhibitors, including 2,4,6-trihydroxy-3-nitro-benzamide derivatives (Sudo *et al.*, *Biochem. Biophys. Res. Commun.* **1997**, *238*, 643-647), a phenanthrenequinone (Chu *et al.*, *Tetrahedron Letters* **1996**, *37*, 7229-7232), RD3-4082, RD3-

4078, SCH 68631, and SCH 351633 (Chu *et al.*, *Bioorganic and Medicinal Chemistry Letters* **1999**, *9*, 1949-1952); and Eglin C, a potent serine protease inhibitor (Qasim *et al.*, *Biochemistry* **1997**, *36*, 1598-1607).

Other suitable protease inhibitors for the treatment of HCV include those disclosed in, for example, U.S. Pat. No. 6,004,933, which discloses a class of cysteine protease inhibitors of HCV endopeptidase 2.

Additional hepatitis C virus NS3 protease inhibitors include those disclosed in, for example, Llinàs-Brunet *et al.*, *Bioorg. Med. Chem. Lett.* **1998**, *8,* 1713-1718; Steinkühler *et al.*, *Biochemistry* **1998**, *37*, 8899-8905; U.S. Pat. Nos.: 5,538,865; 5,990,276; 6,143,715; 6,265,380; 6,323,180; 6,329,379; 6,410,531; 6,420,380; 6,534,523; 6,608,027; 6,642,204; 6,653,295; 6,727,366; 6,838,475; 6,846,802; 6,867,185; 6,869,964; 6,872,805; 6,878,722; 6,908,901; 6,911,428; 6,995,174; 7,012,066; 7,041,698; 7,091,184; 7,169,760; 7,176,208; 7,208,600; and 7,491,794; U.S. Pat. Appl. Publ. Nos.: 2002/0016294, 2002/0016442; 2002/0032175; 2002/0037998; 2004/0229777; 2005/0090450; 2005/0153877; 2005/176648; 2006/0046956; 2007/0021330; 2007/0021351; 2007/0049536; 2007/0054842; 2007/0060510; 2007/0060565; 2007/0072809; 2007/0078081; 2007/0078122; 2007/0093414; 2007/0093430; 2007/0099825; 2007/0099929; 2007/0105781, 2008/0152622, 2009/0035271, 2009/0035272, 2009/0047244, 2009/0111969, 2009/0111982, 2009/0123425, 2009/0130059, 2009/0148407, 2009/0156800, 2009/0169510, 2009/0175822, 2009/0180981, and 2009/0202480; U.S. Pat. Appl. No. 12/365,127; and International Pat. Appl. Publ. Nos.: WO 98/17679; WO 98/22496; WO 99/07734; WO 00/09543; WO 00/59929; WO 02/08187; WO 02/08251; WO 02/08256; WO 02/08198; WO 02/48116; WO 02/48157; WO 02/48172; WO 02/60926; WO 03/53349; WO 03/64416; WO 03/64455; WO 03/64456; WO 03/66103; WO 03/99274; WO 03/99316; WO 2004/032827; WO 2004/043339; WO 2005/037214; WO 2005/037860; WO 2006/000085; WO 2006/119061; WO 2006/122188; WO 2007/001406; WO 2007/014925; WO 2007/014926; WO 2007/015824, WO 2007/056120, WO 2008/019289, WO 2008/021960, WO 2008/022006, WO 2008/086161, WO 2009/053828, WO 2009/058856, WO 2009/073713, WO 2009/073780, WO 2009/080542, WO 2009/082701, WO 2009/082697, and WO 2009/085978; the disclosure of each of which is incorporated herein by reference in its entirety.

Other protease inhibitors include thiazolidine derivatives, such as RD1-6250, RD4 6205, and RD4 6193, which show relevant inhibition in a reverse-phase HPLC assay with an NS3/4A fusion protein and NS5A/5B substrate (Sudo *et al.*, *Antiviral Research* **1996**, *32*, 9-18); and thiazolidines and benzanilides identified in Kakiuchi *et al.*, *FEBS Lett.* **1998**, *421*, 217-

220; and Takeshita *et al.*, *Analytical Biochemistry* **1997**, *247*, 242-246.

Suitable helicase inhibitors include, but are not limited to, those disclosed in U.S. Pat. No. 5,633,358; and International Pat. Appl. Publ. No. WO 97/36554.

Suitable nucleotide polymerase inhibitors include, but are not limited to, gliotoxin (Ferrari *et al.*, *Journal of Virology* **1999**, *73*, 1649-1654) and cerulenin (Lohmann *et al.*, *Virology* **1998**, *249*, 108-118).

Suitable interfering RNA (iRNA) based antivirals include, but are not limited to, short interfering RNA (siRNA) based antivirals, such as Sirna-034 and those described in International Pat. Appl. Publ. Nos.WO/03/070750 and WO 2005/012525, and U.S. Pat. Appl. Publ. No. 2004/0209831.

Suitable antisense phosphorothioate oligodeoxynucleotides (S-ODN) complementary to sequence stretches in the 5' non-coding region (NCR) of HCV virus include, but are not limited to those described in Alt *et al.*, *Hepatology* **1995**, *22*, 707-717, and nucleotides 326-348 comprising the 3' end of the NCR and nucleotides 371-388 located in the core coding region of HCV RNA (Alt *et al.*, *Archives of Virology* **1997**, *142*, 589-599; and Galderisi *et al.*, *Journal of Cellular Physiology* **1999**, *181*, 251-257);

Suitable inhibitors of IRES-dependent translation include, but are not limited to, those described in Japanese Pat. Appl. Publ. Nos.: JP 08268890 and JP 10101591.

Suitable ribozymes include those disclosed in, for example, U.S. Pat. Nos. 6,043,077; 5,869,253; and 5,610,054.

Suitable nucleoside analogs include, but are not limited to, the compounds described in U.S. Pat. Nos.: 6,660,721; 6,777,395; 6,784,166; 6,846,810; 6,927,291; 7,094,770; 7,105,499; 7,125,855; and 7,202,224; U.S. Pat. Appl. Publ. Nos. 2004/0121980; 2005/0009737; 2005/0038240; and 2006/0040890; and International Pat. Appl. Publ. Nos: WO 99/43691; WO 01/32153; WO 01/60315; WO 01/79246; WO 01/90121, WO 01/92282, WO 02/18404; WO 02/32920, WO 02/48165, WO 02/057425; WO 02/057287; WO 2004/002422, WO 2004/002999, and WO 2004/003000.

Other miscellaneous compounds that can be used as second agents include, for example, 1-amino-alkylcyclohexanes (U.S. Pat. No. 6,034,134), alkyl lipids (U.S. Pat. No. 5,922,757), vitamin E and other antioxidants (U.S. Pat. No. 5,922,757), squalene, amantadine, bile acids (U.S. Pat. No. 5,846,964), N-(phosphonacetyl)-L-aspartic acid (U.S. Pat. No. 5,830,905), benzenedicarboxamides (U.S. Pat. No. 5,633,388), polyadenylic acid derivatives (U.S. Pat. No. 5,496,546), 2',3'-dideoxyinosine (U.S. Pat. No. 5,026,687), benzimidazoles (U.S.

Pat. No. 5,891,874), plant extracts (U.S. Pat. Nos. 5,725,859; 5,837,257; and 6,056,961), and piperidines (U.S. Pat. No. 5,830,905).

In certain embodiments, one or more compounds provided herein are administered in combination or alternation with an anti-hepatitis C virus interferon, including, but not limited to, INTRON® A (interferon alfa-2b), PEGASYS® (Peginterferon alfa-2a) ROFERON® A (recombinant interferon alfa-2a), INFERGEN® (interferon alfacon-1), and PEG-INTRON® (pegylated interferon alfa-2b). In one embodiment, the anti-hepatitis C virus interferon is INFERGEN®, IL-29 (PEG-Interferon lambda), R7025 (Maxy-alpha), BELEROFON®, oral interferon alpha, BLX-883 (LOCTERON®), omega interferon, MULTIFERON®, medusa interferon, ALBUFERON®, or REBIF®.

In certain embodiments, one or more compounds provided herein are administered in combination or alternation with an anti-hepatitis C virus polymerase inhibitor, such as ribavirin, viramidine, NM 283 (valopicitabine), PSI-6130, R1626, HCV-796, R7128, and those as disclosed in U.S. Pat. Appl. Publ. Nos. 2009/0081158 and 2009/0238790, the disclosure of each of which is incorporated herein by reference in its entirety.

In certain embodiments, the one or more compounds provided herein are administered in combination with ribavirin and an anti-hepatitis C virus interferon, such as INTRON® A (interferon alfa-2b), PEGASYS® (Peginterferon alfa-2a), ROFERON® A (recombinant interferon alfa-2a), INFERGEN® (interferon alfacon-1), and PEG-INTRON® (pegylated interferon alfa-2b),

In certain embodiments, one or more compounds provided herein are administered in combination or alternation with an anti-hepatitis C virus protease inhibitor, such as GS-9451, ITMN-191, SCH 503034, VX950 (telaprevir), and TMC 435.

In certain embodiments, one or more compounds provided herein are administered in combination or alternation with an anti-hepatitis C virus vaccine, including, but not limited to, TG4040, PEVIPRO™, CGI-5005, HCV/MF59, GV1001, IC41, and INNO0101 (E1).

In certain embodiments, one or more compounds provided herein are administered in combination or alternation with an anti-hepatitis C virus monoclonal antibody, such as AB68 and XTL-6865 (formerly HepX-C); or an anti-hepatitis C virus polyclonal antibody, such as cicavir.

In certain embodiments, one or more compounds provided herein are administered in combination or alternation with an anti-hepatitis C virus immunomodulator, such

as ZADAXIN® (thymalfasin), NOV-205, and oglufanide.

In certain embodiments, one or more compounds provided herein are administered in combination or alternation with NEXAVAR®, doxorubicin, PI-88, amantadine, JBK-122, VGX-410C, MX-3253 (celgosivir), SUVUS® (BIVN-401 or virostat), PF-03491390 (formerly IDN-6556), G126270, UT-231B, DEBIO-025, EMZ702, ACH-0137171, MitoQ, ANA975, AVI-4065, bavituximab (tarvacin), ALINIA® (nitrazoxanide), GS-9620, and PYN17.

The compounds provided herein can also be administered in combination with other classes of compounds, including, but not limited to, (1) alpha-adrenergic agents; (2) antiarrhythmic agents; (3) anti-atherosclerotic agents, such as ACAT inhibitors; (4) antibiotics, such as anthracyclines, bleomycins, mitomycin, dactinomycin, and plicamycin; (5) anticancer agents and cytotoxic agents, *e.g.*, alkylating agents, such as nitrogen mustards, alkyl sulfonates, nitrosoureas, ethylenimines, and triazenes; (6) anticoagulants, such as acenocoumarol, argatroban, bivalirudin, lepirudin, fondaparinux, heparin, phenindione, warfarin, and ximelagatran; (7) anti-diabetic agents, such as biguanides (*e.g.*, metformin), glucosidase inhibitors (*e.g.*, acarbose), insulins, meglitinides (*e.g.*, repaglinide), sulfonylureas (*e.g.*, glimepiride, glyburide, and glipizide), thiozolidinediones (*e.g.*, troglitazone, rosiglitazone, and pioglitazone), PPAR-gamma agonists, DPP-IV inhibitors (e.g., sitagliptin), and SGLT2 inhibitors (e.g., ertugliflozin and ipragliflozin); (8) antifungal agents, such as amorolfine, amphotericin B, anidulafungin, bifonazole, butenafine, butoconazole, caspofungin, ciclopirox, clotrimazole, econazole, fenticonazole, filipin, fluconazole, isoconazole, itraconazole, ketoconazole, micafungin, miconazole, naftifine, natamycin, nystatin, oxyconazole, ravuconazole, posaconazole, rimocidin, sertaconazole, sulconazole, terbinafine, terconazole, tioconazole, and voriconazole; (9) antiinflammatories, *e.g.*, non-steroidal anti-inflammatory agents, such as aceclofenac, acemetacin, amoxiprin, aspirin, azapropazone, benorilate, bromfenac, carprofen, celecoxib, choline magnesium salicylate, diclofenac, diflunisal, etodolac, etoricoxib, faislamine, fenbufen, fenoprofen, flurbiprofen, ibuprofen, indometacin, ketoprofen, ketorolac, lornoxicam, loxoprofen, lumiracoxib, meclofenamic acid, mefenamic acid, meloxicam, metamizole, methyl salicylate, magnesium salicylate, nabumetone, naproxen, nimesulide, oxyphenbutazone, parecoxib, phenylbutazone, piroxicam, salicyl salicylate, sulindac, sulfinpyrazone, suprofen, tenoxicam, tiaprofenic acid, and tolmetin; (10) antimetabolites, such as folate antagonists, purine analogues, and pyrimidine analogues; (11) anti-platelet agents, such as GPIIb/IIIa blockers (*e.g.*, abciximab, eptifibatide, and tirofiban), P2Y(AC) antagonists (*e.g.*, clopidogrel, ticlopidine and CS-747), cilostazol, dipyridamole, and aspirin; (12)

antiproliferatives, such as methotrexate, FK506 (tacrolimus), and mycophenolate mofetil; (13) anti-TNF antibodies or soluble TNF receptor, such as etanercept, rapamycin, and leflunimide; (14) aP2 inhibitors; (15) beta-adrenergic agents, such as carvedilol and metoprolol; (16) bile acid sequestrants, such as questran; (17) calcium channel blockers, such as amlodipine besylate; (18) chemotherapeutic agents; (19) cyclooxygenase-2 (COX-2) inhibitors, such as celecoxib and rofecoxib; (20) cyclosporins; (21) cytotoxic drugs, such as azathioprine and cyclophosphamide; (22) diuretics, such as chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide, polythiazide, benzothiazide, ethacrynic acid, ticrynafen, chlorthalidone, furosenide, muzolimine, bumetanide, triamterene, amiloride, and spironolactone; (23) endothelin converting enzyme (ECE) inhibitors, such as phosphoramidon; (24) enzymes, such as L-asparaginase; (25) Factor VIIa Inhibitors and Factor Xa Inhibitors; (26) farnesyl-protein transferase inhibitors; (27) fibrates; (28) growth factor inhibitors, such as modulators of PDGF activity; (29) growth hormone secretagogues; (30) HMG CoA reductase inhibitors, such as pravastatin, lovastatin, atorvastatin, simvastatin, NK-104 (a.k.a. itavastatin, nisvastatin, or nisbastatin), and ZD-4522 (also known as rosuvastatin, atavastatin, or visastatin); neutral endopeptidase (NEP) inhibitors; (31) hormonal agents, such as glucocorticoids (*e.g.*, cortisone), estrogens/antiestrogens, androgens/antiandrogens, progestins, and luteinizing hormone-releasing hormone antagonists, and octreotide acetate; (32) immunosuppressants; (33) mineralocorticoid receptor antagonists, such as spironolactone and eplerenone; (34) microtubule-disruptor agents, such as ecteinascidins; (35) microtubule-stabilizing agents, such as pacitaxel, docetaxel, and epothilones A-F; (36) MTP Inhibitors; (37) niacin; (38) phosphodiesterase inhibitors, such as PDE III inhibitors (*e.g.*, cilostazol) and PDE V inhibitors (*e.g.*, sildenafil, tadalafil, and vardenafil); (39) plant-derived products, such as vinca alkaloids, epipodophyllotoxins, and taxanes; (40) platelet activating factor (PAF) antagonists; (41) platinum coordination complexes, such as cisplatin, satraplatin, and carboplatin; (42) potassium channel openers; (43) prenyl-protein transferase inhibitors; (44) protein tyrosine kinase inhibitors; (45) renin inhibitors; (46) squalene synthetase inhibitors; (47) steroids, such as aldosterone, beclometasone, betamethasone, deoxycorticosterone acetate, fludrocortisone, hydrocortisone (cortisol), prednisolone, prednisone, methylprednisolone, dexamethasone, and triamcinolone; (48) TNF-alpha inhibitors, such as tenidap; (49) thrombin inhibitors, such as hirudin; (50) thrombolytic agents, such as anistreplase, reteplase, tenecteplase, tissue plasminogen activator (tPA), recombinant tPA, streptokinase, urokinase, prourokinase, and anisoylated plasminogen streptokinase activator complex (APSAC); (51) thromboxane receptor

antagonists, such as ifetroban; (52) topoisomerase inhibitors; (53) vasopeptidase inhibitors (dual NEP-ACE inhibitors), such as omapatrilat and gemopatrilat; and (54) other miscellaneous agents, such as, hydroxyurea, procarbazine, mitotane, hexamethylmelamine, and gold compounds.

The compounds provided herein can also be provided as an article of manufacture using packaging materials well known to those of skill in the art. *See*, *e.g.*, U.S. Pat. Nos. 5,323,907; 5,052,558; and 5,033,252. Examples of pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, tubes, inhalers, pumps, bags, vials, containers, syringes, and any packaging material suitable for a selected formulation and intended mode of administration and treatment.

Provided herein also are kits which, when used by the medical practitioner, can simplify the administration of appropriate amounts of active ingredients to a subject. In certain embodiments, the kit provided herein includes a container and a dosage form of a compound a compound of Formula I or II, including a single enantiomer, a racemic mixture, a diastereomer, a mixture of diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt or solvate thereof.

In certain embodiments, the kit includes a container comprising a dosage form of the compound a compound of Formula I or II, including a single enantiomer, a racemic mixture, a diastereomer, a mixture of diastereomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt or solvate thereof, in a container comprising one or more other therapeutic agent(s) described herein.

Kits provided herein can further include devices that are used to administer the active ingredients. Examples of such devices include, but are not limited to, syringes, needle-less injectors drip bags, patches, and inhalers. The kits provided herein can also include condoms for administration of the active ingredients.

Kits provided herein can further include pharmaceutically acceptable vehicles that can be used to administer one or more active ingredients. For example, if an active ingredient is provided in a solid form that must be reconstituted for parenteral administration, the kit can comprise a sealed container of a suitable vehicle in which the active ingredient can be dissolved to form a particulate-free sterile solution that is suitable for parenteral administration. Examples of pharmaceutically acceptable vehicles include, but are not limited to: aqueous vehicles, including, but not limited to, Water for Injection USP, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles, including, but not limited to, ethyl alcohol, polyethylene

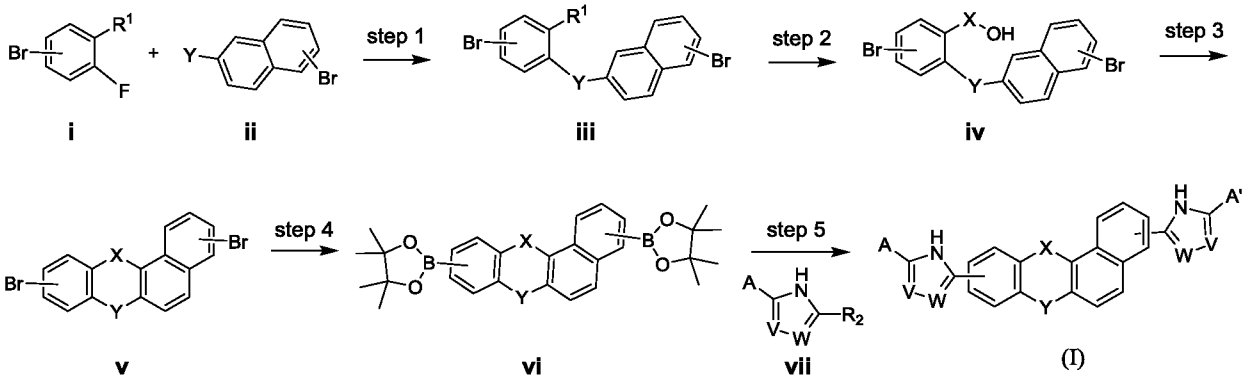
glycol, and polypropylene glycol; and non-aqueous vehicles, including, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

The disclosure will be further understood by the following non-limiting examples. As used herein, the symbols and conventions used in these processes, schemes and examples, regardless of whether a particular abbreviation is specifically defined, are consistent with those used in the contemporary scientific literature, for example, the Journal of the American Chemical Society or the Journal of Biological Chemistry. Specifically, but without limitation, the following abbreviations may be used in the examples and throughout the specification: g (grams); mg (milligrams); mL (milliliters); μL (microliters); L (liter); mM (millimolar); μM (micromolar); Hz (Hertz); MHz (megahertz); mmol (millimoles); eq. (equivalent); hr or hrs (hours); min (minutes); MS (mass spectrometry); NMR (nuclear magnetic resonance); ESI (electrospray ionization); HPLC (high-performance liquid chromatography or high pressure liquid chromatography); DCM (dichloromethane); DMF (*N*,*N*-dimethylformamide); EtOAc (ethyl acetate); THF (tetrahydrofuran); DIPEA (*N*,*N*-diisopropylethylamine); TEA (triethylamine); TFA (trifluoroacetic acid); HATU (2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate); Me (methyl); Et (ethyl); and Pd(dppf)Cl_2 ((1,1'-bis(diphenylphosphino)ferrocene) dichloropalladium(II); TLC (thin-layer chromatography); TFAA (trifluoroacetic acid); EA (ethyl acetate); BOC (t-butyloxycarbonyl); DMSO (dimethyl sulfoxide); RT (room temperature); TNE (tris(hydroxymethyl)aminomethane/ ethylenediaminetetraacetic acid/sodium chloride buffer); FBS (fetal bovine serum); PBS (phosphate-buffered saline); and DMEM (Dulbecco's Modified Eagle's medium).

Methods for Making the Compounds of Formula (I) or (II):

The Compounds of Formula (I) or (II) may be prepared from known or readily prepared starting materials, following methods known to one skilled in the art of organic synthesis. Methods useful for making the Compounds of Formula (I) or (II) are set forth in the Examples below and generalized in Scheme 1 below. Alternative synthetic pathways and analogous structures will be apparent to those skilled in the art of organic synthesis.

Scheme 1



Compound i is commercially available or prepared according to well known procedures. Examples of R^1 include CN, methyl ester, and other moieties having similar functionality. Examples of Y include hydroxyl, thiol, and amines. Substitution of the fluorine of compound **i** by the Y group of compound **ii** under basic condition leads to the formation of compound **iii**. R^1 is converted to X-OH, which may be anacid, substituted alcohol, or other moiety having similar functionality. Compound **iv** undergoes ring closure in the presence of TFAA, $AlCl_3$, or other similar reagents to give compound **v**. When X is a carbonyl group (-CO-), it can be further functionalized to other groups, such as $-CH(CH_3)-$, by using known chemistry. Compound **v** is converted to di-boronic ester **vi** under Pd catalyzed conditions or other similar conditions. Compound I is obtained by Pd catalyzed reaction between compound **vi** and **vii**. The preparation of **vii** is well described in the literature.

Compounds of Formula (II) can prepared by similar chemistry as outlined in Scheme 1 starting with correspondingly different staring materials.

Compounds of Formula (I) or (II) may be further elaborated using methods that would be well-known to those skilled in the art of organic synthesis or, for example, the methods described in the Examples below, to make the full scope of the Compounds of Formula (I) or (II).

One skilled in the art of organic synthesis will recognize that the synthesis of compounds with multiple reactive functional groups, such as –OH and NH_2, may require protection of certain functional group for the purpose of chemical compatibility with a particular reaction condition. Suitable protecting groups for the various functional groups of these compounds and methods for their installation and removal are well known in the art of organic chemistry. A summary of many of these methods can be found in Greene *et al.*, *supra*.

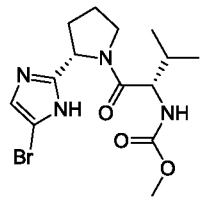
One skilled in the art of organic synthesis will also recognize that one route for the synthesis of the Compounds of Formula (I) or (II) may be more desirable depending on the

choice of appendage substituents. Additionally, one skilled in the relevant art will recognize that in some cases the order of reactions may differ from that presented herein to avoid functional group incompatibilities and thus adjust the synthetic route accordingly.

The starting materials used and the intermediates prepared using the methods set forth in Scheme 1 may be isolated and purified if desired using conventional techniques, including but not limited to filtration, distillation, crystallization, chromatography and the like. Such materials can be characterized using conventional means, including physical constants and spectral data.

Preparation of intermediate compounds

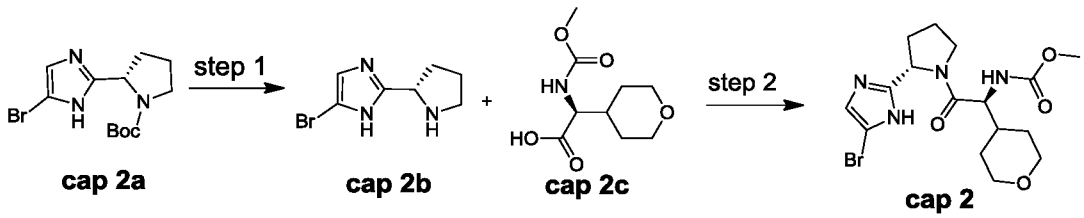
Intermediate compound **cap1**



cap 1

Compound **cap1** was prepared in Example **7** of WO2012041014.

Intermediate compound **cap2**



cap 2a **cap 2b** **cap 2c** **cap 2**

Step 1

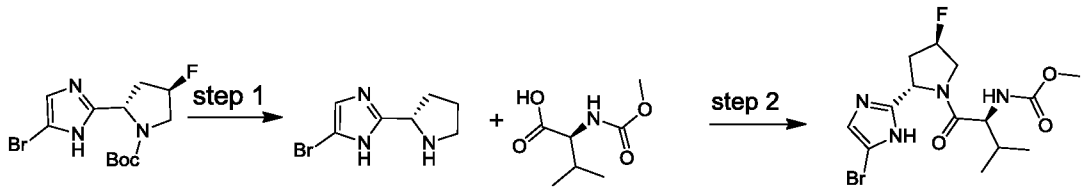
Compound **cap 2a** was prepared in Example **7** of WO 2012/040923 A1. Compound **cap 2a** (50 g, 0.16 mmol) was added into TFA/DCM (1:1, 10mL). The mixture was stirred at 25°C for 2 hours; then concentrated and dried under high vacuum to give to desired product **cap 2b** (34.4 g, 100% yield). LC/MS: Anal. Calcd. For $[M+H]^+$ $C_7H_{10}BrN_3$: 216.01; found 216.1.

Step 2

Compound **cap 2c** was prepared in Example **4** of WO 2012/040923 A1.

To a mixture of **cap 2b** (1.9 g, 9 mmol), **cap 2c** (1.9 g, 9 mmol) and DIPEA (4 mL) in CH_2Cl_2 (5 mL) was added HATU reagent (3.5 g, 9 mmol). The resulting mixture was stirred at 25°C for 2 hours. The reaction mixture was concentrated, then purified by SiO_2 chromatography (eluent: petroleum ether/ethyl acetate = 5:1 to 1:2) to give the compound **cap 2**. LC/MS: Anal. Calcd. For $[M+H]^+$ $C_{16}H_{23}BrN_4O_4$: 415.09, 417.09; found 415.1,417.1.

Intermediate compound **cap3**



Step 1

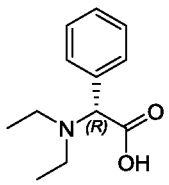
Compound **cap 3a** was prepared in Example **10** of WO2012041014 A1. Compound **cap 3a** (50 g, 0.16 mmol) was added into TFA/DCM (1:1, 10mL). The mixture was stirred at 25°C for 2 hours; then concentrated and dried under high vacuum to give to desired product **cap 3b** (34.4 g, 100% yield). LC/MS: Anal. Calcd. For $[M+H]^+$ $C_7H_{10}BrN_3$: 216.01; found 216.1.

Step 2

Compound **cap 3c** was prepared in Example **4** of WO 2012/040923 A1.

To a mixture of **cap 3b** (1.9 g, 9 mmol), **cap 3c** (1.9 g, 9 mmol) and DIPEA (4 mL) in CH_2Cl_2 (5 mL) was added HATU reagent (3.5 g, 9 mmol). The resulting mixture was stirred at 25°C for 2 hours. The reaction mixture was concentrated, then purified by SiO_2 chromatography (eluent: petroleum ether/ethyl acetate = 5:1 to 1:2) to give the compound **cap 3**. LC/MS: Anal. Calcd. For $[M+H]^+$ $C_{16}H_{23}BrN_4O_4$: 415.09, 417.09; found 415.1,417.1.

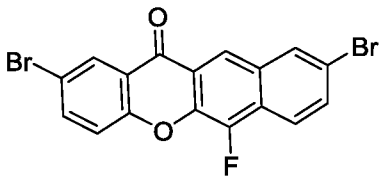
Intermediate compound **cap4**



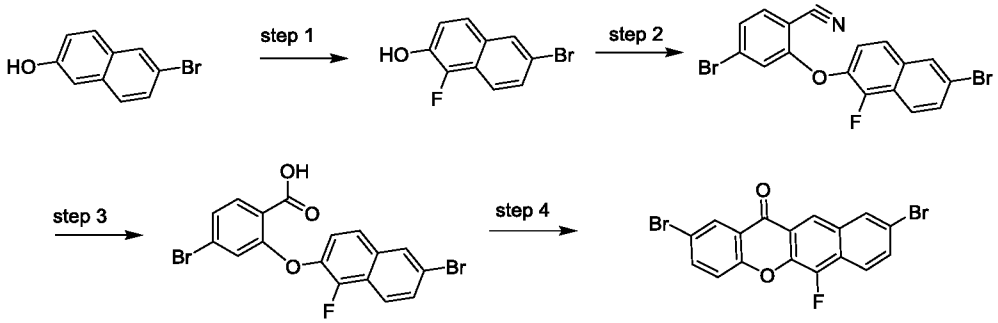
Step 1

Compound **cap 4** was prepared in Example **cap-2** of WO 2008144380A1.

Intermediate compound 2,9-dibromo-6-fluoro-12H-benzo[b]xanthen-12-one



2,9-dibromo-6-fluoro-12H-benzo[b]xanthen-12-one



Step 1

6-bromonaphthalen-2-ol (5 g, 22.41 mmol) was dissolved in DMF (50 mL) in a 250 mL flask. N-fluorobenzenesulfonimide (21.20 g, 67.2 mmol) was added, and the solution was stirred at 25°C for 2 days. The solution was concentrated. The residue was purified by column chromatography on silica gel (120 g), eluting with Hexane and EtOAc (0% to 50%) to give 6-bromo-1-fluoronaphthalen-2-ol.

Step 2

5-bromo-2-fluorobenzonitrile (2.293 g, 11.46 mmol), 6-bromo-1-fluoronaphthalen-2-ol (3.14 g, 11.46 mmol), and Cs_2CO_3 (7.47 g, 22.93 mmol) were added into a 500 ML flask. DMF (115 ml) was added. The solution was stirred at 80°C for 24 hours. EtOAc (150 mL) and water (100 mL) were added. The organic layer was separated and washed with water (100 mL x 2) , brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The product was purified by SiO_2 chromatography (120 g, Hexane/EtOAc 0% to 50%) to give 4-bromo-2-((6-bromo-1-fluoronaphthalen-2-yl)oxy)benzonitrile (4.25 g, 88%). LCMS: 424.0 $[M+H]^+$

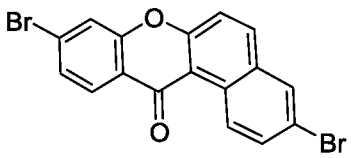
Step 3

4-bromo-2-((6-bromo-1-fluoronaphthalen-2-yl)oxy)benzonitrile (2 g, 4.75 mmol) was dissolved in Ethanol (23.75 ml). NaOH (19.00 ml, 47.5 mmol) was added. The solution was stirred at 85°C for 20 hours. After cooling down, TLC indicated staring material disappeared. The solution was poured into 100 mL 6N HCl with good stirring. The solid was collected by filtration, washed with water and dried at 50°C under vacuum for overnight to give crude 4-bromo-2-((6-bromo-1-fluoronaphthalen-2-yl)oxy)benzoic acid. To this crude material was added CH_2Cl_2 (15 mL) and the suspension was stirred at RT for 20 minutes. The solid was collected by filtration and washed with CH_2Cl_2, dried under vacuum for overnight to 4-bromo-2-((6-bromo-1-fluoronaphthalen-2-yl)oxy)benzoic acid batch 1 (435 mg). The filtrate was concentrated and stirred with 7 mL CH_2Cl_2. The solid was collected by filtration to give 4-bromo-2-((6-bromo-1-fluoronaphthalen-2-yl)oxy)benzoic acid batch 2 (150 mg). LCMS: 460.9,462.9 $[M+Na]^+$

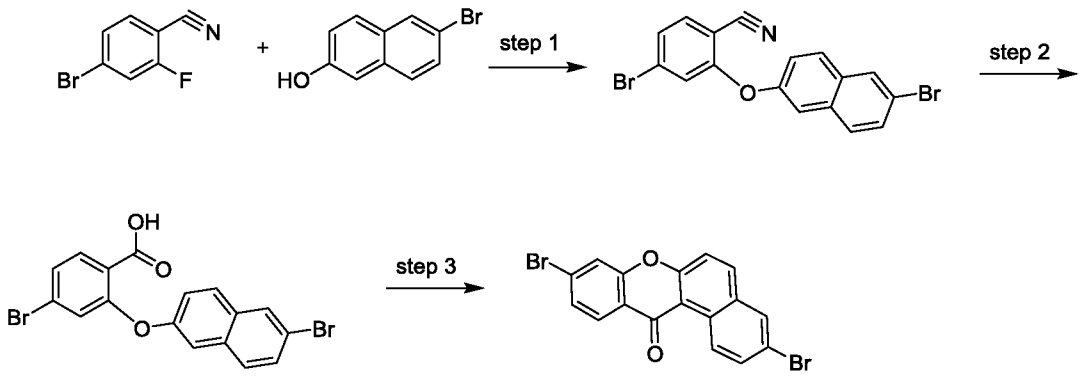
Step 4

4-bromo-2-((6-bromo-1-fluoronaphthalen-2-yl)oxy)benzoic acid (172 mg, 0.391 mmol) and CH_2Cl_2 (1954 µl) were added into a 40 mL flask and cooled to 0°C. TFAA (66.2 µl, 0.469 mmol) was added via syringe and the solution was stirred at 0°C for 30 min. Then $BF_3.OEt_2$ (9.91 µl, 0.078 mmol) was added via syringe and the solution was stirred at 0°C for 30 min, then at 25°C for 16 hours. A suspension was formed. The solid was collected by filtration to give 2,9-dibromo-6-fluoro-12H-benzo[b]xanthen-12-one. LCMS: 442.9 $[M+Na]^+$

Intermediate compound 3,9-dibromo-12H-benzo[a]xanthen-12-one



3,9-dibromo-12H-benzo[a]xanthen-12-one



Step 1

4-bromo-2-fluorobenzonitrile (5 g, 25.00 mmol), 6-bromonaphthalen-2-ol (5.58 g, 25.00 mmol), and cesium carbonate (16.29 g, 50.0 mmol) were added into a 500 ML flask. DMF (250 ml) was added. The solution was stirred at 80°C for 24 hours. EtOAc (350 mL) and water (200 mL) were added. The organic layer was separated and washed with water (150 mL x 2), brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The product was dried under vacuum for 2 hours and was used without further purification.

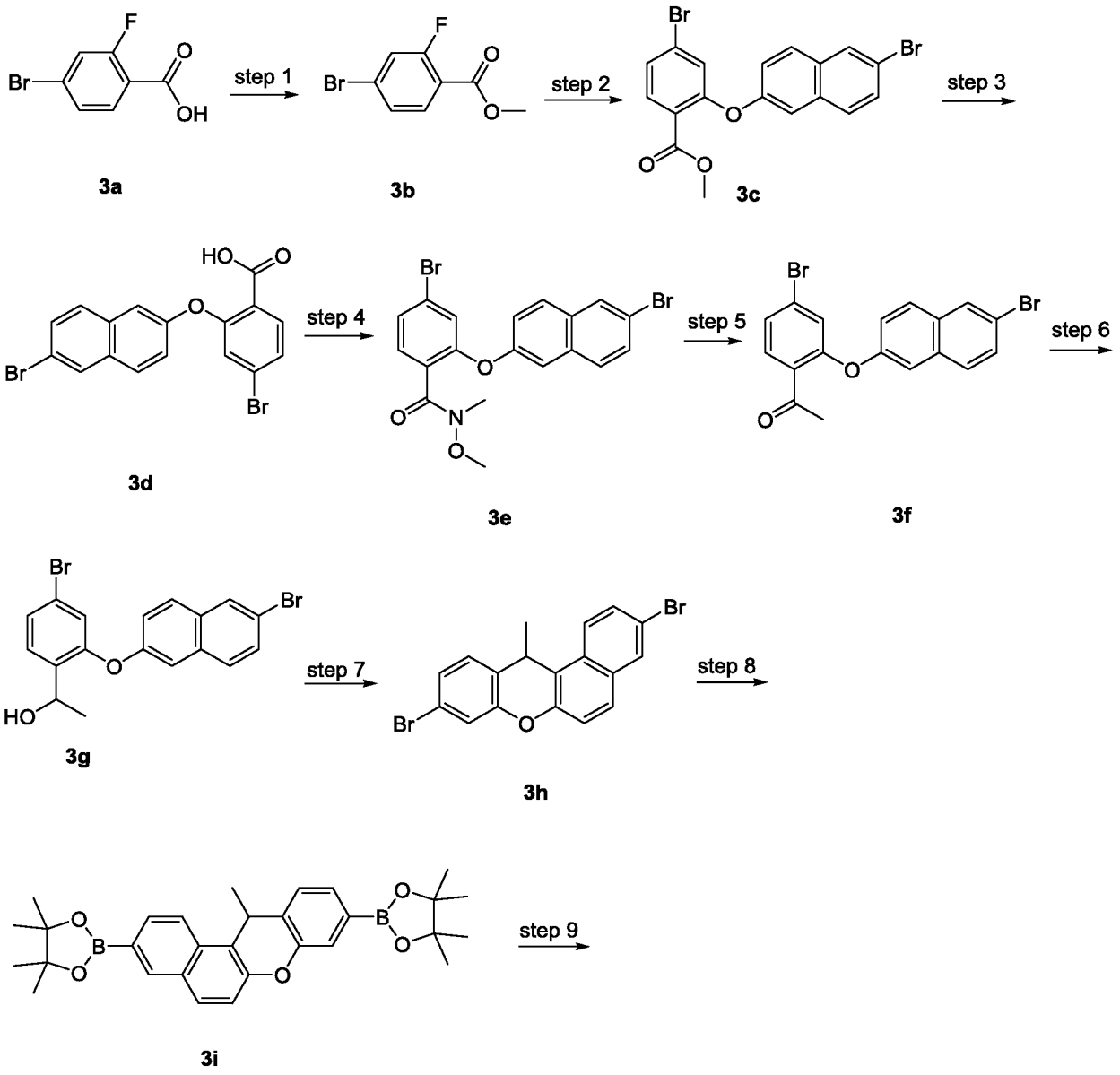
Step 2

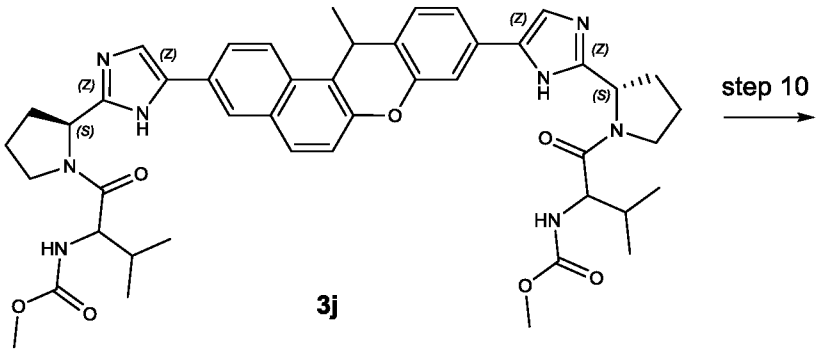
4-bromo-2-((6-bromonaphthalen-2-yl)oxy)benzonitrile (8.5 g, 21.09 mmol) was dissolved in Ethanol (105 ml). NaOH (84 ml, 211 mmol) was added. The solution was stirred at 85°C for 20 hours. After cooling down, TLC indicated starting material disappeared. The solution was poured into 200 mL 6N HCl with good stirring. The solid was collected by filtration, washed with water and dried at 50°C under vacuum for overnight to give 4-bromo-2-((6-bromonaphthalen-2-yl)oxy)benzoic acid (8.6 g, 97%). LCMS: 422.9 $[M+H]^+$

Step 3

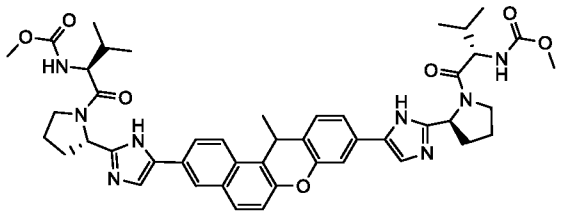
4-bromo-2-((6-bromonaphthalen-2-yl)oxy)benzoic acid (500 mg, 1.185 mmol) and CH_2Cl_2 (5923 µl) were added into a 40 mL flask and cooled to 0°C. TFAA (201 µl, 1.422 mmol) was added via syringe and the solution was stirred at 0°C for 30 min. Then $BF_3.OEt_2$ (15.01 µl, 0.118 mmol) was added via syringe and the solution was stirred at 0°C for 30 min, then at 25 °C for 2 hours. A suspension was formed. NaOH (1N, 10 mL) was added and stirred at RT for 10 min. The solid was collected by filtration, washed with water twice, and dried under vacuum at 50 °C for overnight to give 3,9-dibromo-12H-benzo[a]xanthen-12-one. LCMS: 405.0 $[M+H]^+$

Preparation of Compound 3


F
Br
O
OH
step 1
F
Br
O
O
step 2
Br
Br
O
O
O
step 3
3a
3b
3c
HO
O
O
Br
Br
step 4
Br
Br
O
O
N
O
step 5
Br
Br
O
O
step 6
3d
3e
3f
Br
Br
O
HO
step 7
Br
Br
O
step 8
3g
3h
O
B
O
O
B
O
step 9
O
3i



3j



3

Step 1

To a solution of compound **3a** (50 g, 210 mmol) in DCM (300 mL) was added oxalyl dichloride (40.38 g, 300 mmol) dropwise at room temperature. The reaction mixture was stirred at room temperature for 1h. Then MeOH (50 ml) was added dropwise, the solution was stirred at room temperature for another 1h. The solvent was removed to afford compound **3b**.

Step 2

To a solution of **3b** (52g, 227 mmol) in DMF (1500 mL) was added Cs_2CO_3 (148 g, 454 mmol) and 6-bromonaphthalen-2-ol (45.8 g, 204 mmol). The reaction mixture was stirred at 100°C for 12 h under N_2, before it was poured into water and extracted with EA. The combined organic phases were dried over Na_2SO_4. After filtration and concentration, the residue was purified by SiO_2 chromatography, eluting with petroleum ether: ethyl acetate (100/1~10/1) to afford compound **3c**.

Step 3

To a solution of compound **3c** (15 g, 34.5 mmol) in MeOH (20 mL) and H_2O (20 mL) was added NaOH (6.9 g, 172.8 mmol). The mixture was stirred at 80°C for 2h. After evaporation, the residue was re-dissolved into water and adjusted pH=6~7 with 3N HCl, then extracted with EA. The combined organic layers were washed with brine, dried over Na_2SO_4

and concentrated to afford compound **3d**.

Step 4

To a solution of compound **3d** (8 g, 19 mmol), N,O-dimethylhydroxylammonium chloride (2.43 g, 24.76 mmol)and Et_3N (5.76 g, 57 mmol) in DMF (40 mL) was added HATU (7.22 g, 19 mmol) at 0°C. The mixture was stirred under N_2 at room temperature for 12h before it was poured into water and extracted with DCM. The organic layer was washed with brine, dried over Na_2SO_4. After filtration and concentration, the residue was purified by SiO_2 chromatography, eluting with petroleum ether: ethyl acetate (10/1~1/1) to give compound **3e**.

Step 5

To a solution of compound **3e** (2.9 g, 6.26 mmol) in THF (30 mL) was added MeMgBr (3M solution in ether, 2.5 mL, 7.52 mmol) dropwise at 0°C. The mixture was stirred at 0°C for 3 h before ice-water (50 mL) was added to quench the reaction, extracted with EA. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated to give **3f**.

Step 6

To a solution of compound **3f** (2.3 g, 5.45 mmol) in MeOH (30 mL) was added $NaBH_4$ (0.41 g, 10.9 mmol) at 0°C. The mixture was stirred under N_2 at 0°C for 20 min, and then warmed to room temperature for 20 min. After filtration and concentration, the residue was portioned between water and EA. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated to give **3g**.

Step 7

To a solution of compound **3g** (530 mg, 1.25 mmol) in DCM (20 mL) was added $AlCl_3$ (333 mg, 2.5 mmol). The mixture was stirred under N_2 at room temperature for 30 min, before it was poured into water and extracted with DCM. The organic layer was washed with brine, dried over Na_2SO_4. After filtration and concentration, the residue was purified by SiO_2 chromatography, eluting with petroleum ether to give compound **3h**.

Step 8

The mixture of **3h** (300 mg, 0.74 mmol), bis(pinacolato)diboron (415 mg, 1.63 mmol), KOAc (363 mg, 3.7 mmol) and $Pd(dppf)Cl_2$ (108 mg, 0.15 mmol) in dioxane (10 mL)

was stirred at 100°C for 2 hours under N_2 protection. The reaction mixture was cooled and concentrated in vacuum, and the residue was purified by SiO_2 chromatography, eluting with petroleum ether: ethyl acetate (20/1~5/1) to give **3i**.

Step 9

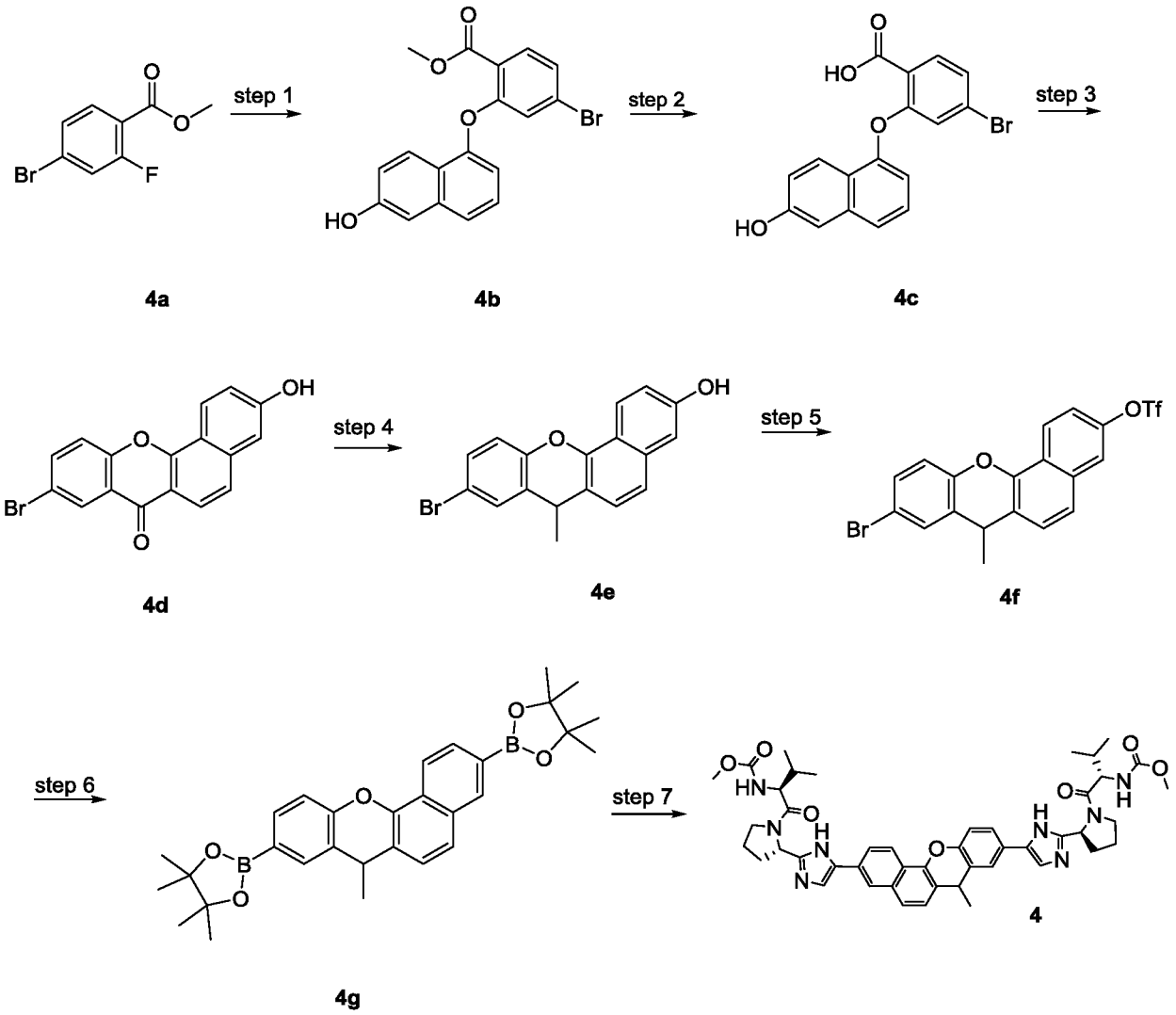
The mixture of **3i** (300 mg, 0.6 mmol), **Cap1** (493 mg, 1.325 mmol), Na_2CO_3 (318 mg, 3 mmol) and Pd(dppf)Cl_2 (66 mg, 0.09 mmol) in THF/H_2O/DMF (v/v=5/2/1, 16 mL) was stirred at 80°C overnight under N_2 protection. After that, the mixture was washed with water and extracted with ethyl acetate, washed with brine and dried over anhydrous sodium sulfate. After filtrated, the filtrate was concentrated in vacuum, the residue was dissolved in DMF and purified by Pre-HPLC to give **3j**.

Step 10

Compound **3** was obtained from compound **3j** (300 mg) by SFC separation by using the following conditions: Injection Volume: 5; Co-Solvent: IPA (0.05%DEA); Column: AS-H; Total Flow: 2.5; Wavelength : 340.

1H NMR (MeOD) δ 8.27-8.25 (d, J=8Hz, 1 H), 8.22 (s, 1 H), 7.97-7.89 (m, 2 H), 7.87-7.85 (d, J=8Hz, 2 H=), 7.58-7.56 (d, *J*=8Hz, 1 H), 7.21-7.23 (m, 2 H), 7.39-7.37 (m, 1 H), 5.28-5.22 (m, 2 H), 4.25-4.22 (m, 2 H), 4.10-4.09 (m, 2 H), 3.93-3.87 (m, 2 H), 3.65 (s, 6 H), 2.57-2.54 (m, 2 H), 2.29-2.23 (m, 2 H), 2.17-2.13 (m, 4 H), 2.10-2.05 (m, 2 H), 1.51-1.49 (m, 3 H), 0.99-0.86 (m, 13 H). LC/MS: Anal. Calcd. For $[M+H]^+$ $C_{46}H_{54}N_8O_7$: 830.99; found 831.6.

Preparation of Compound 4



Step 1

To a solution of **4a** (28 g, 113 mmol) in DMF (500 mL) was added naphthalene-1,6-diol (22 g, 136 mmol) and Cs_2CO_3 (74 g, 226 mmol). The resulting solution was stirred at 100°C for 12 h, before it was poured into water and extracted with EA. The combined organic phases were dried over Na_2SO_4. After filtration and concentration, the residue was purified by SiO_2 chromatography, eluting with petroleum ether: ethyl acetate (100/1~10/1) to give compound **4b**.

Step 2

To a solution of compound **4b** (17.1 g, 45.8 mmol) in MeOH (60 mL) and H_2O (20 mL) was added NaOH (9 g, 229 mmol). The mixture was stirred at 80°C for 2h before evaporated to remove the solvent. The residue was re-dissolved into water and adjusted pH=6~7

with 3N HCl, and then extracted with EA (30 ml). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated to afford compound **4c**.

Step 3

To a solution of compound **4c** (5.91 g, 16.4 mmol) in DCM (60 mL) was added TFAA (4.13 g, 19.7 mmol) and $BF_3.OEt_2$ (233 mg, 1.64 mmol). The mixture was stirred under N_2 at room temperature for 12h, before it was poured into water and extracted with DCM. The organic layer was washed with brine, dried over sodium sulfate. After filtration and concentration, the residue was purified by SiO_2 chromatography, eluting with petroleum ether to give compound **4d**.

Step 4

To a solution of compound **4d** (100 mg, 0.29 mmol) in THF (10 mL) was added MeMgBr (3M solution in ether, 2.5 mL, 7.52 mmol) dropwise at 0℃. The mixture was stirred at 0°C for 2 h before ice-water (10 mL) was added to quench the reaction, extracted with EA. The organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was dissolved in 10 ml of DCM, and then to the mixture was added $HSiEt_3$ (490 mg, 4.22 mmol) and TFA (319 mg, 2.8 mmol) at 0°C. The mixture was stirred at 0°C for 12 h before ice-water (20 mL) was added to quench the reaction, extracted with EA. The organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated to give **4e**.

Step 5

To a solution of compound **4e** (70 mg, 0.21 mmol) and pyridine (34 mg, 0.42 mmol) in DCM (20 mL) was added Tf_2O (87 mg, 0.31 mmol) at 0°C. The mixture was stirred under N_2 at room temperature for 30 min before it was poured into water and extracted with DCM. The organic layer was washed with brine, dried over sodium sulfate. After filtration and concentration, the residue was purified by SiO_2 chromatography, eluting with petroleum ether to give compound **4f**.

Step 6

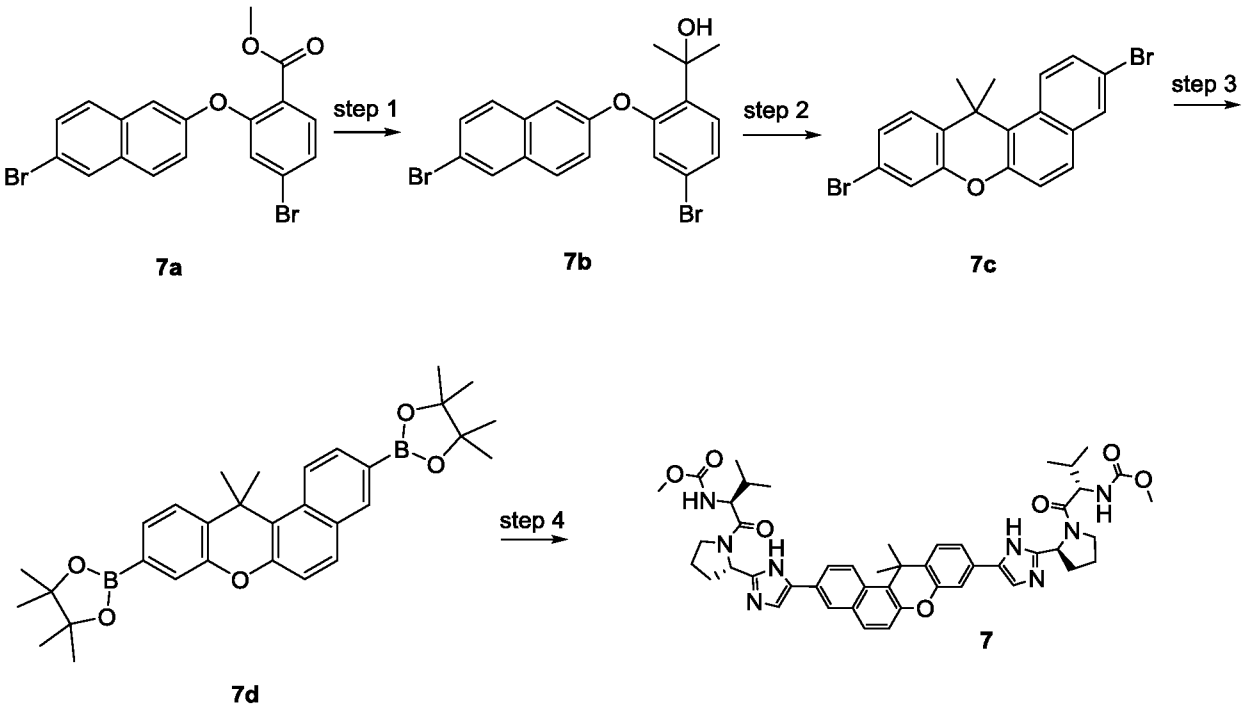
The mixture of **4f** (50 mg, 0.134 mmol), bis(pinacolato)diboron (75 mg, 0.294 mmol), KOAc (66 mg, 0.67 mmol) and $Pd(dppf)Cl_2$ (20 mg, 0.027 mmol) in dioxane (10 mL) was stirred at 100°C for 2 hours under N_2 protection. The reaction mixture was cooled and

concentrated in vacuum, and the residue was purified by SiO_2 chromatography, eluting with petroleum ether: ethyl acetate (20/1~5/1) to give **4g**.

Step 7

The mixture of **4g** (50 mg, 0.1 mmol), **Cap1** (82 mg, 0.22 mmol), Na_2CO_3 (53 mg, 0.5 mmol) and Pd(dppf)Cl_2 (11mg, 0.015 mmol) in THF/H_2O/DMF (v/v=5/2/1, 3 mL) was stirred at 80°C overnight under N_2 protection. After that, the mixture was washed with water and extracted with ethyl acetate, washed with brine and dried over anhydrous sodium sulfate. After filtrated, the filtrate was concentrated in vacuum, the residue was dissolved in DMF and purified by Pre-HPLC to give **4**. ^{1}H NMR (MeOD) δ: 8.43 (s, 1 H), 8.20 (s, 1 H), 7.93 (s, 1 H), 7.84-7.71 (m, 3 H), 7.58-7.52 (m, 2 H), 7.50-7.44 (m, 1 H), 7.37 (s, 1 H), 5.24-5.22 (m, 2 H), 4.31 (s, 1 H), 4.22-4.08 (m, 2 H), 3.88 (s, 2 H), 3.63-3.57 (m, 2 H), 3.42 (s, 6 H), 3.28 (s, 5 H), 2.57-2.51 (m, 2 H), 2.27-1.99 (m, 4 H), 1.56 (s, 2 H), 0.92-0.87 (m, 12 H). LC/MS: Anal. Calcd. For $[M+H]^+$ $C_{46}H_{54}N_8O_7$: 830.99; found 831.2.

Preparation of Compound 7



Step 1

Preparation of compound **7a** was described in the preparation of Compound 3. To a solution of compound **7a** (500 mg, 1.15 mmol) in THF (20 mL) was added MeMgBr (3M solution in ether, 1 mL, 2.88 mmol) dropwise at 0°C. The mixture was stirred at 0°C for 3 h before ice-water (50 mL) was added to quench the reaction, extracted with EA. The organic layer was washed with brine, dried over Na_2SO_4. After filtration and concentration, the residue was purified by SiO_2 chromatography, eluting with petroleum ether: ethyl acetate (20/1~4/1) to give compound **7b**.

Step 2

To a solution of compound **7b** (400 mg, 0.92 mmol) in DCM (20 mL) was added $AlCl_3$ (247 mg, 1.84 mmol). The mixture was stirred under N_2 at room temperature for 30 min, before it was poured into water and extracted with DCM. The organic layer was washed with brine, dried over Na_2SO_4. After filtration and concentration, the residue was purified by SiO_2 chromatography, eluting with petroleum ether to give compound **7c**.

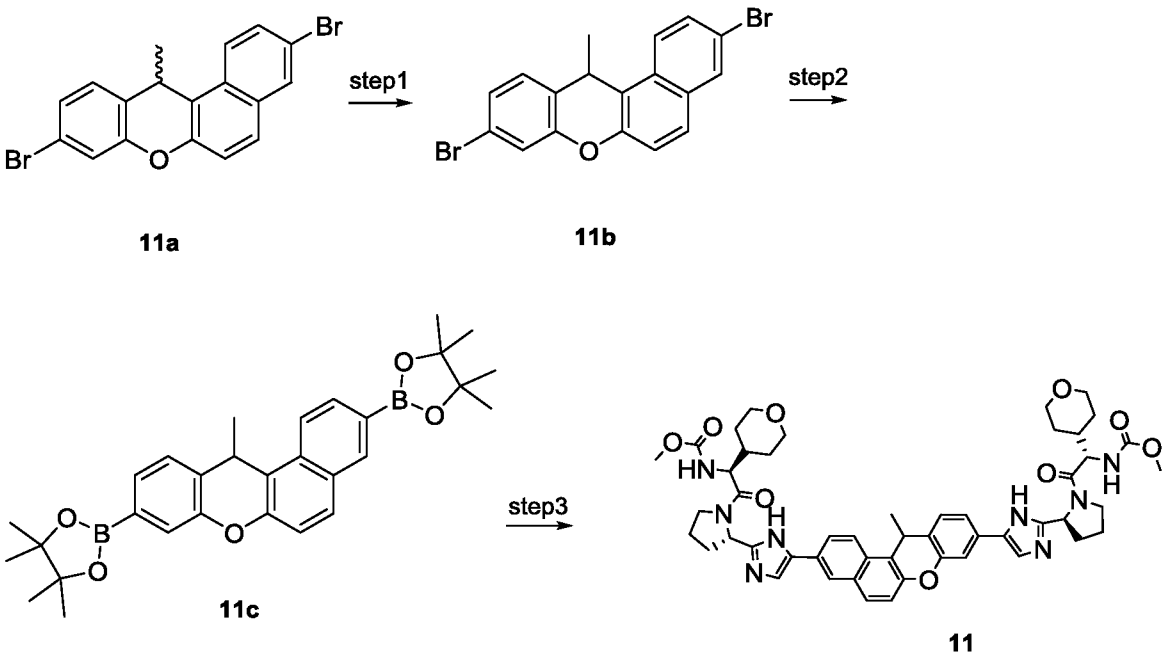
Step 3

The mixture of **7c** (416 mg, 1 mmol), (559 mg, 2.2 mmol), KOAc (490 mg, 5 mmol) and Pd(dppf)Cl_2 (146 mg, 0.2 mmol) in dioxane (15 mL) was stirred at 100°C for 2 hours under N_2 protection. The reaction mixture was cooled and concentrated in vacuum, and the residue was purified by SiO_2 chromatography, eluting with petroleum ether: ethyl acetate (20/1~5/1) to give **7d**.

Step 4

The mixture of **7d** (225 mg, 0.44 mmol), **Cap1** (358 mg, 0.96 mmol), Na_2CO_3 (233 mg, 2.2 mmol) and Pd(dppf)Cl_2 (50 mg, 0.066 mmol) in THF/H_2O/DMF (v/v=5/2/1, 16 mL) was stirred at 80°C overnight under N_2 protection. After that, the mixture was washed with water and extracted with ethyl acetate, washed with brine and dried over anhydrous sodium sulfate. After filtrated, the filtrate was concentrated in vacuum, the residue was dissolved in DMF and purified by Pre-HPLC to give **7**. ^{1}H NMR (MeOD) δ: 8.52-8.50 (d, *J*=8Hz, 1 H), 8.13 (s, 1 H), 7.87-7.83 (m, 1 H), 7.76-7.74 (m, 1 H), 7.64-7.62 (d, *J*=8Hz, 2 H), 7.44-7.42 (d, *J*=8Hz, 2 H), 7.24 (s, 1 H), 7.18-7.16 (d, *J*=8Hz, 1 H), 5.30-5.23 (m, 2 H), 4.28-4.10 (m, 4 H), 3.96-3.92 (m, 2 H), 3.65 (s, 6 H), 2.57-2.55 (m, 3 H), 2.29-2.22 (m, 3 H), 2.19-2.09 (m, 5 H), 2.03 (s, 6 H), 0.98-0.89 (m, 12 H). LC/MS: Anal. Calcd. For $[M+H]^+$ $C_{47}H_{56}N_8O_7$: 845.02; found 845.6.

Preparation of Compound 11



Step 1

Preparation of compound **11a** was described in the preparation of Compound 3. Compound **11b** (400 mg) was obtained from compound **11a** (1 g) by SFC separation by using the following conditions: Injection Volume: 3; Co-Solvent: IPA (0.05%DEA); Column: OJ-3; Total Flow: 2.5; Wavelength : 220.

Step 2

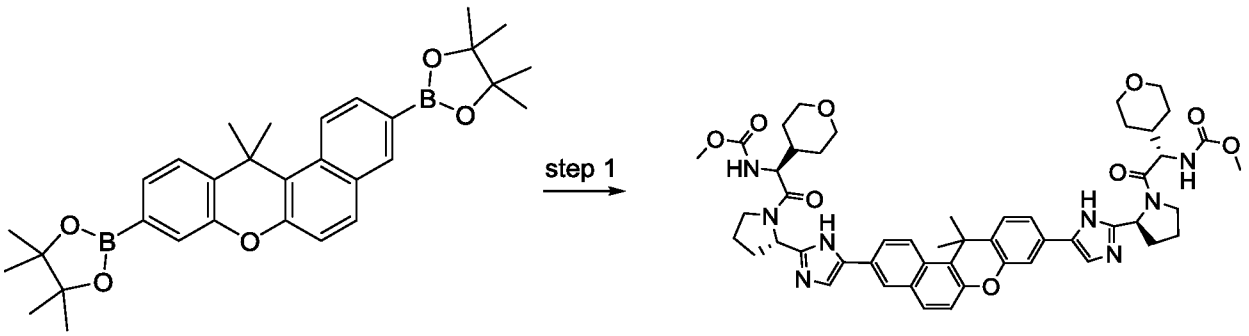
The mixture of compound **11b** (404 mg, 1 mmol), bis(pinacolato)diboron (559 mg, 2.2 mmol), KOAc (490 mg, 5 mmol) and $Pd(dppf)Cl_2$ (146 mg, 0.2 mmol) in dioxane (15 mL) was stirred at 100°C for 2 hours under N_2 protection. The reaction mixture was cooled and concentrated in vacuum, and the residue was purified by SiO_2 chromatography, eluting with petroleum ether: ethyl acetate (20/1~5/1) to give compound **11c**.

Step 3

A suspension of **11c** (297 mg, 0.6 mmol), **Cap2** (50 mg, 0.12 mmol), Na_2CO_3 (318 mg, 3mmol) and $Pd(dppf)Cl_2$ (66 mg, 0.09 mmol) in $THF/H_2O/DMF$ (v/v=5/2/1, 16 mL)

was stirred at 80°C overnight under N_2 protection. After that, the mixture was washed with water and extracted with ethyl acetate, washed with brine and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated in vacuum, the residue was dissolved in DMF and purified by Pre-HPLC to give **11**. ^{1}H NMR (MeOD) δ: 8.15 (s, 1 H), 7.91-7.87 (m, 2 H), 7.67-7.64 (m, 1 H), 7.56-7.49 (m, 3 H), 7.20-7.17 (m, 1 H), 7.10 (s, 1 H), 5.29-5.22 (m, 2 H), 4.57 (s, 1 H), 4.39-4.33 (m, 2 H), 4.17-4.13 (m, 4 H), 4.03-3.90 (m, 5 H), 3.68 (s, 6 H), 3.45-3.30 (m, 5 H), 2.57-2.56 (m, 2 H), 2.32-2.29 (m, 4 H), 1.62-1.33 (m, 12 H). LC/MS: Anal. Calcd. For $[M+H]^+$ $C_{50}H_{58}N_8O_9$: 915.06; found 915.6.

Preparation of Compound 13

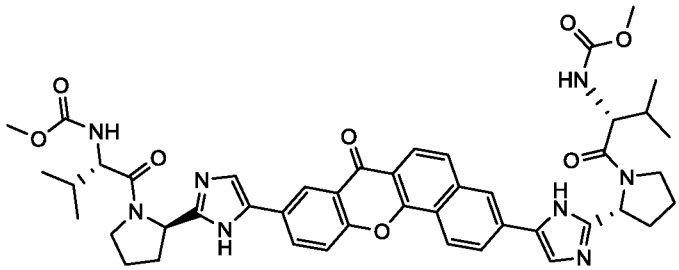
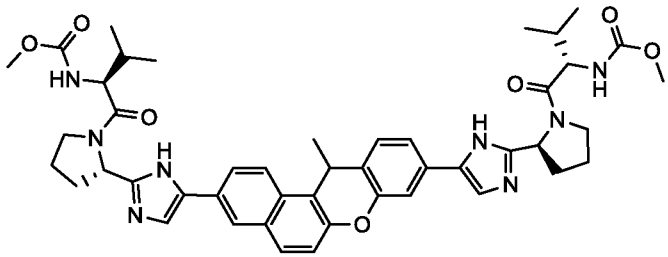
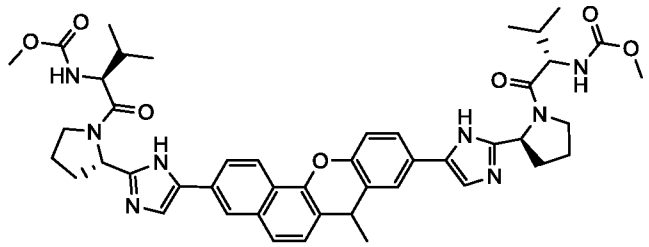
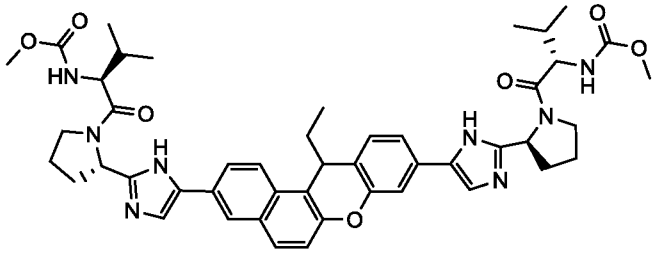
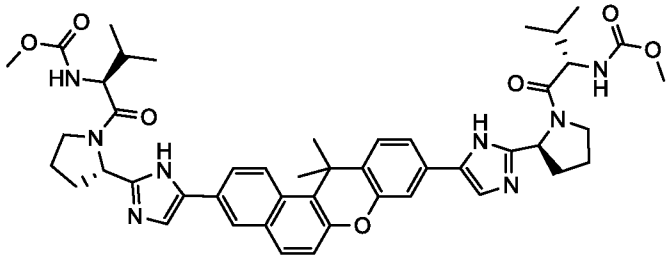
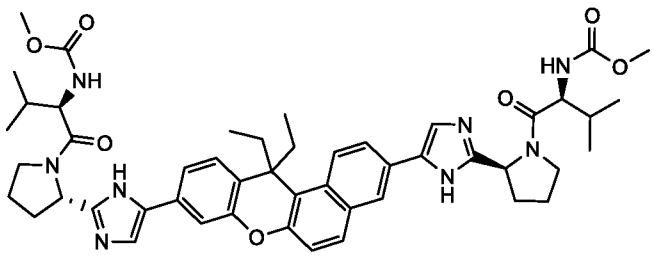


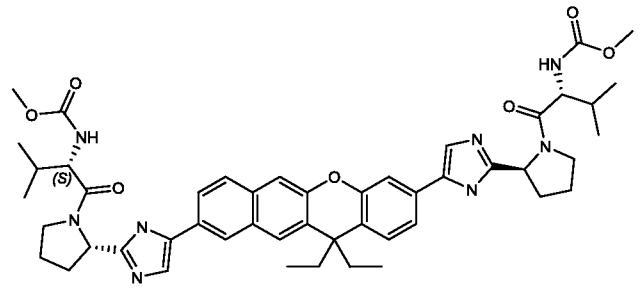
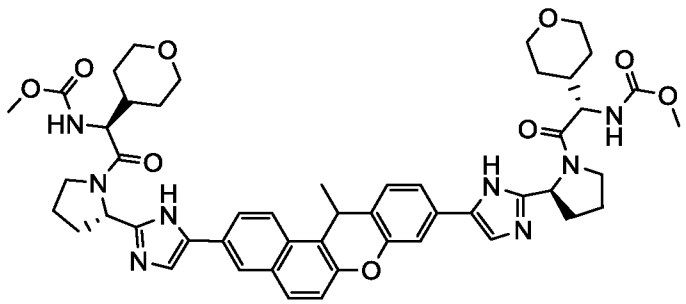
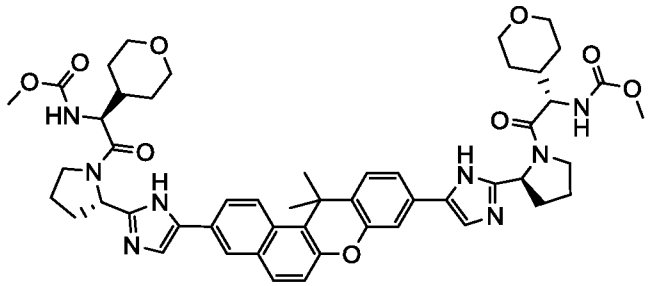
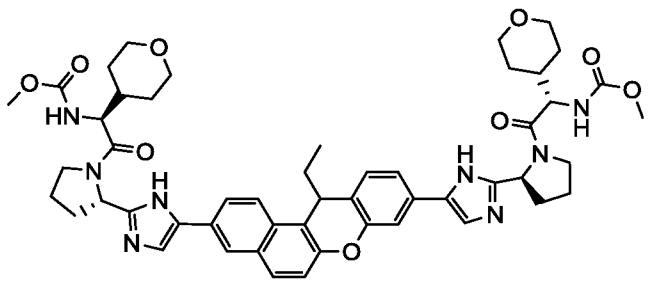
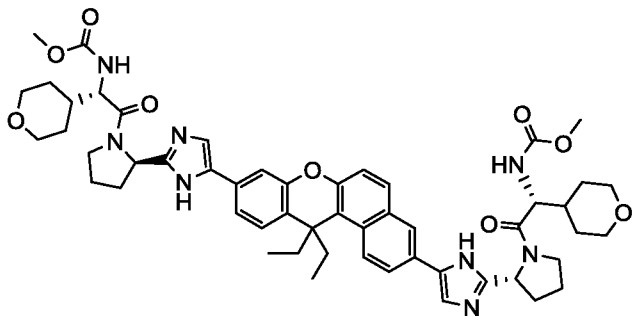
13a **13**

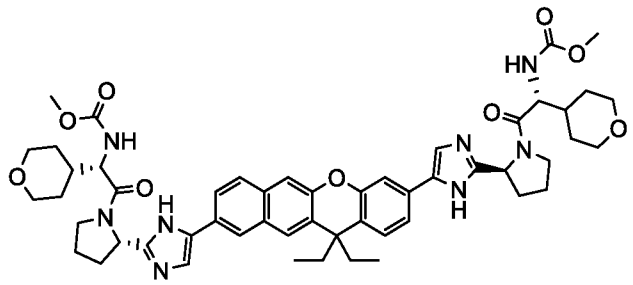
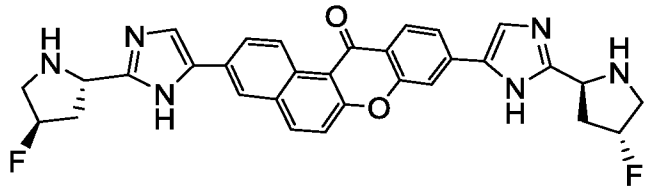
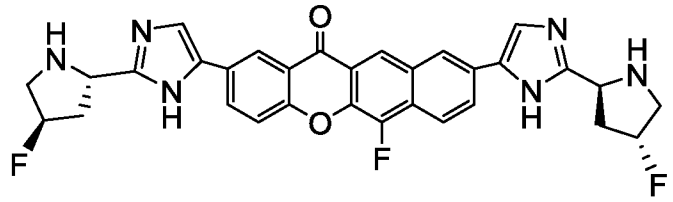
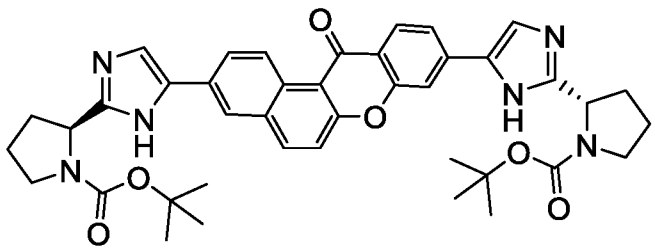
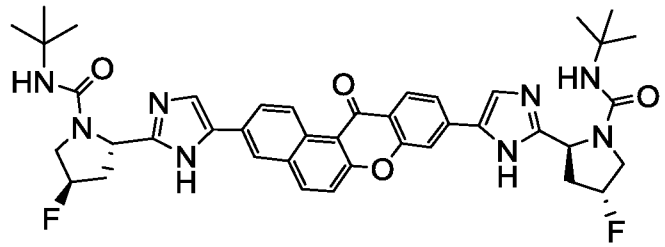
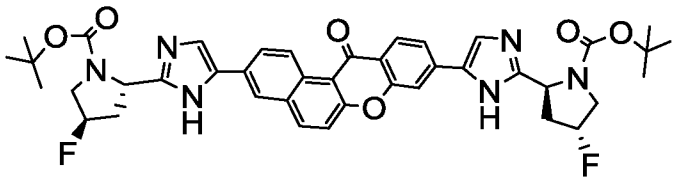
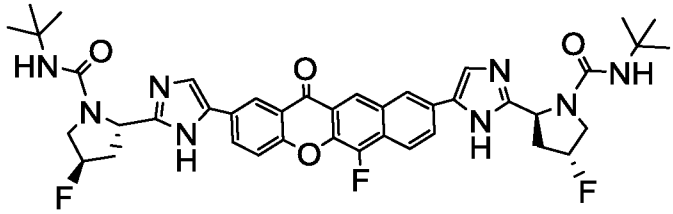
Step 1

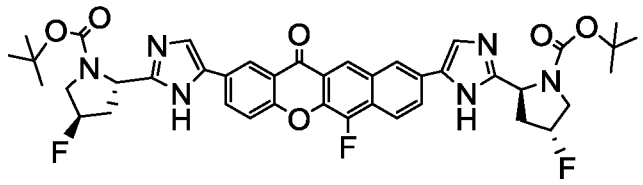
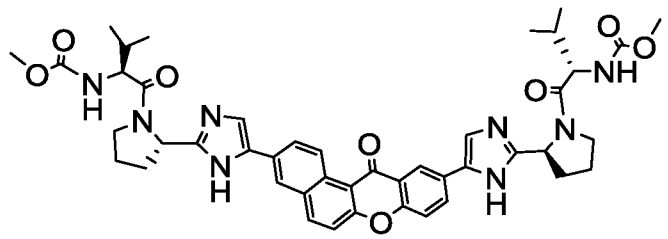
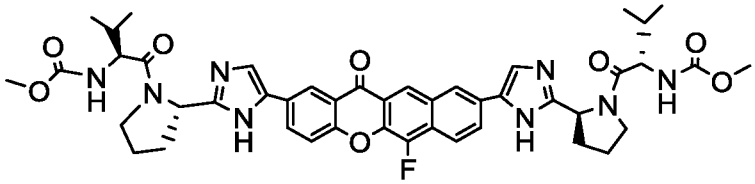
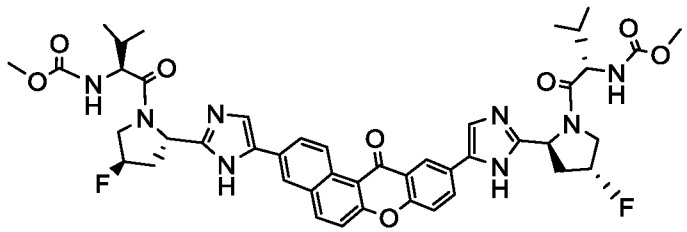
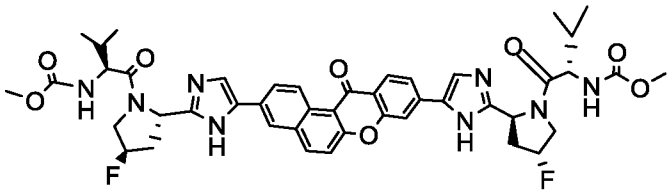
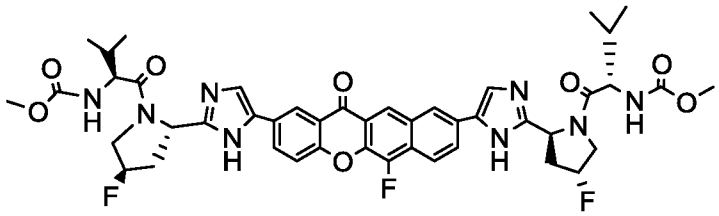
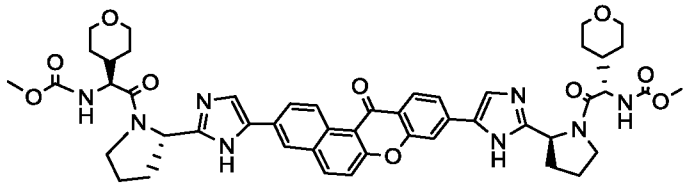
Preparation of compound **13a** was described in the preparation of Compound 7. The mixture of **13a** (225 mg, 0.44 mmol), **Cap2** (401 mg, 0.96 mmol), Na_2CO_3 (233 mg, 2.2 mmol) and $Pd(dppf)Cl_2$ (50 mg, 0.066 mmol) in THF/H_2O/DMF (v/v=5/2/1, 16 mL) was stirred at 80°C overnight under N_2 protection. After that, the mixture was washed with water and extracted with ethyl acetate, washed with brine and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated in vacuum, the residue was dissolved in DMF and purified by Pre-HPLC to give **13**. ^{1}H NMR (MeOD) δ: 8.54-8.52 (d, 1 H, J=8Hz), 8.16 (s, 1 H), 7.88-7.82 (m, 2 H), 7.78-7.76 (m, 2 H), 7.65-7.63 (d, *J*=8Hz, 1 H), 7.44-7.42 (d, *J*=8Hz, 1 H), 7.20-7.18 (m, 2 H), 5.29-5.23 (m, 2 H), 3.46-3.29 (m, 5 H), 3.98-3.89 (m, 5 H), 3.65 (s, 6 H), 3.46-3.29 (m, 5 H), 2.56-2.54 (m, 2 H), 2.28-2.05 (m, 10 H), 1.99-1.39 (m, 10 H). LC/MS: Anal. Calcd. For $[M+H]^+$ $C_{51}H_{60}N_8O_9$: 929.09; found 929.6.

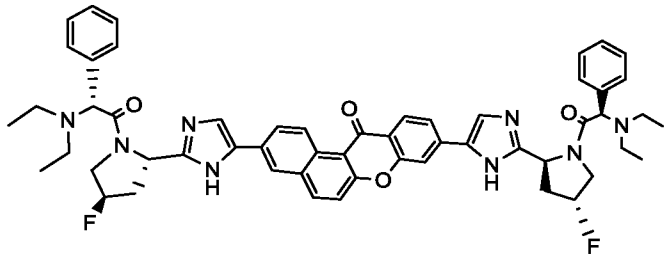
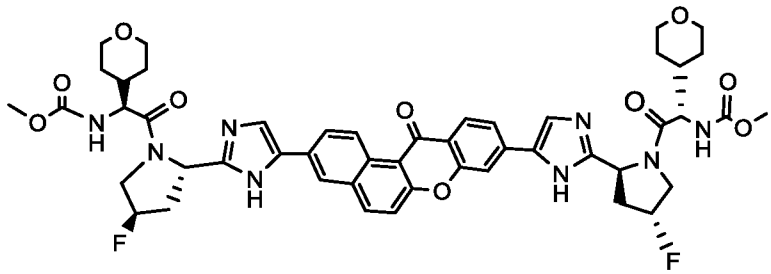
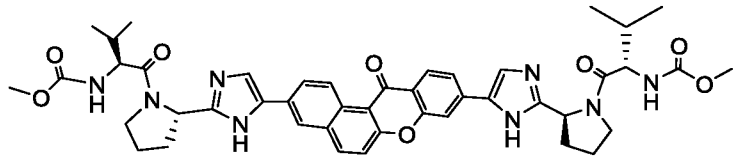
Using the appropriate intermediates and procedures outlined above, the following compounds were prepared.

Compound	structure	Isomer	MWt	Observed [M+1]+
1			830.949	831.4
2		Isomer 2	830.993	831.4
3		Isomer 1	830.993	831.6
4			830.993	831.2
5		Isomer 1	845.02	845.6
6		Isomer 2	845.02	845.2
7			845.02	845.6
8			873.074	873.4

Compound	structure	Isomer	MWt	Observed [M+1]+
9			873.074	873.4
10	blank			
11		Isomer 1	915.068	915.6
12		Isomer 2	915.068	915.4
13			929.095	929.6
14		Isomer 1	929.095	929.4
15		Isomer 2	929.095	929.6
16			957.149	957.4

Compound	structure	Isomer	MWt	Observed [M+1]+
17			957.149	957.4
18			552.589	553.2
19			570.579	571.3
20			716.844	717.4
21			750.856	751.4
22			752.825	753.4
23			768.846	769.4

Compound	structure	Isomer	MWt	Observed [M+1]+
24			770.816	771.3
25			830.949	831.5
26			848.939	849.4
27			866.93	867.5
28			866.93	867.3
29			884.92	885.4
30			915.024	915.4

Compound	structure	Isomer	MWt	Observed [M+1]+
31			931.108	931.4
32			951.005	951.4
33			830.949	831.5

Assays

HCV Replicon Assay

General procedure: Huh-7 cells containing HCV Con1 subgenomic replicon (GS4.1 cells) were grown in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum (FBS), 2 mM L-glutamine, 110 mg/L sodium pyruvate, 1X non-essential amino acids, 100 U/mL penicillin- streptomycin, and 0.5 mg/mL G418 (Invitrogen). For dose-response testing, the cells were seeded in 96-well plates at 7.5 x 10^3 cells/well in a volume of 50 µL, and incubated at 37 °C/5% CO_2. Three hours after plating, 50 µL of ten 2-fold serial dilutions of compounds (highest concentration, 75 µM) were added, and cell cultures were incubated at 37 °C/5% CO_2 in the presence of 0.5% DMSO. Alternatively, compounds were tested at a single concentration of 15 µM. In all cases, Huh-7 cells lacking the HCV replicon served as negative control. The cells were incubated in the presence of compounds for 72 hrs after which they were monitored for expression of the NS5A protein by enzyme-linked immunosorbent assay (ELISA). For this, the plates were then fixed for 1 min with acetone/methanol (1:1, v/v), washed twice with phosphate-buffered saline (PBS), 0.1% Tween

20, blocked for 1 hr at room temperature with TNE buffer containing 10% FBS and then incubated for 2 hr at 37 °C with the anti-NS5A mouse monoclonal antibody A-236 (ViroGen) diluted in the same buffer. After washing three times with PBS, 0.1% Tween 20, the cells were incubated 1 hr at 37 °C with anti-mouse immunoglobulin G- peroxidase conjugate in TNE, 10% FBS. After washing as described above, the reaction was developed with O-phenylenediamine (Zymed). The reaction was stopped after 30 min with 2 N H_2SO_4, and absorbance was read at 492 nm using Sunrise Tecan spectrophotometer. EC_{50} values were determined from the % inhibition *versus* concentration data using a sigmoidal non-linear regression analysis based on four parameters with Tecan Magellan software. When screening at a single concentration, the results were expressed as % inhibition at 15 μM.

For cytotoxicity evaluation, GS4.1 cells were treated with compounds as described above and cellular viability was monitored using the Cell Titer 96 AQ_{ueous} One Solution Cell Proliferation Assay (Promega). CC_{50} values were determined from the % cytotoxicity versus concentration data with Tecan Magellan software as described above.

Generation of HCV NS5A-intergenotypic stable cell lines
for genotypes 1a, 2a, 3a, and 4a

The nucleotide sequences of the NS5A region of genotype 2a (GenBank Accession # AB047639), genotype 3a (GenBank Accession # D17763), and genotype 4a (GenBank Accession# DQ418788) were synthesized by an outside vendor. The NS5A region of each of these genotypes included the first 11 amino acids of the protease recognition sequence of genotype 1b, as well as the last 10 amino acids of genotype 1b. The NS5A gene cassettes were excised with site specific restriction endonucleases and ligated into a ZS11-luciferase genotype 1b backbone (backbone contains the genotype 1b NS3 protease, NS4a, NS4b, and NS5b coding regions) with similarly cut restriction enzyme sites. Thus, the newly constructed plasmid contains a genotype 2a-, 3a- or 4a-specific NS5A gene within the 1b-replicon.

To generate the 1a-H77 NS5a intergenotypic plasmid, dual cut sites were inserted into the ZS11-lucifrease genotype 1b backbone that would bracket the NS5a region almost in its entirety. Using PCR and 1a-H77 specific primers also containing the corresponding restriction enzyme sites, the NS5a gene was amplified from the 1a-H77 replicon. The ZS11-luciferase genotype 1b backbone and the genotype1a NS5A PCR products were restriction enzyme digested and then ligated using standard molecular cloning techniques. The newly constructed plasmid contains the genotype 1a-specific NS5a gene where as the backbone remains 1b as

described herein.

These new intergenotypic plasmids were used to establish stable cell lines. RNA was generated from the NS5A intergenotypic plasmids and used in conjunction with a lipofectin reagent to transfect a cured Huh7 cell line. Transfected cells were selected for with G418. After selection has occurred the stable cell lines were propagated, tested for luciferase activity, and RT-PCR with genotype specific primers (either 1a, 2a, 3a, or 4a). Stable cell lines containing the intergenotypic replicon were then fully sequenced and analyzed for proper expression of NS3, NS5A and NS5B proteins.

Drug titration analysis was performed using the luciferase replicon assay described herein.

Genotype 2a infectious virus assay

The genotype 2a infectious virus assay measures the ability of a test compound to inhibit HCV replication in cell culture after 5 days of treatment at the time of HCV genotype 2a virus infection of a permissive human hepatoma cell line (HPC cells). The inhibition of HCV replication was measured by quantification of HCV core protein expression by an enzyme-linked immunosorbent assay (ELISA). Briefly, HPC cells were grown in DMEM containing glucose, L-glutamine and sodium pyruvate, 10% FBS, 100 IU/mL penicillin, 100 μg/mL streptomycin, 2 mM GlutaMAX, and non-essential amino acids. GlutaMAX was obtained from Invitrogen, Corp.; all other media reagents were obtained from Mediatech, Inc. For dose-response testing, ninety-six-well plates were seeded with HPC cells at a density of 2.5 x 10^3 cells/well in a volume of 50 μL, and incubated at 37°C/5% CO_2. Three hours after plating, 50 μL of ten 5-fold serial dilutions of compound and 100 μL of genotype 2a virus were added, and cell cultures were incubated at 37°C/5% CO_2. In all cases, mock infected HPC cells served as negative control. At 16 hours post treatment and infection, the virus inoculum was removed by aspiration. The cultures were treated at the same final concentrations of drug diluted in media and incubated for 4 additional days at 37°C/5% CO_2. Subsequently, the core ELISA was performed as follows. The plates were fixed for 90 seconds with acetone/methanol (1:1, v/v), washed three times with KPL wash solution (KPL, Inc.), blocked for 1 hr at room temperature with TNE buffer containing 10% FBS and then incubated for 2 hr at 37°C with the anti-HCV core mouse monoclonal antibody (Thermo Scientific) diluted in the same buffer. After washing three times with KPL wash solution, the cells were incubated for 1 hr at 37°C with an anti-mouse immunoglobulin G-peroxidase conjugate in TNE/10% FBS. After washing as described above,

the reaction was developed with O-phenylenediamine (Invitrogen). The reaction was stopped after 30 min with 2 N H_2SO_4, and absorbance was read at 490 nm in a Victor^{3}V 1420 multilabel counter (Perkin Elmer) and EC_{50} concentrations were determined using Microsoft Excel and XLfit 4.1 software.

For cytotoxicity evaluation, HPC cells were treated with compounds as described above in the absence of the genotype 2a virus and cellular viability was monitored using the Cell Titer 96 AQueous One Solution Cell Proliferation Assay (Promega). Plates were then read at 490 nm in a Victor^{3}V 1420 multilabel counter (Perkin Elmer) and CC_{50} concentrations were determined using Microsoft Excel and XLfit 4.1 software.

Luciferase replicon assay

The HCV luciferase replicon assay measures the ability of a test compound to inhibit HCV replication in cell culture after 3 days of treatment in a human hepatoma cell line (Huh-7) bearing an HCV replicon containing a luciferase-neomycin phosphotransferase fusion gene. The inhibition of HCV replication was measured by quantification of luciferase protein expression. Briefly, Huh-7 cells containing either the HCV genotype 1a H77 strain or genotype 1b Con1 strain subgenomic luciferase replicon (H1a-luc or Zluc, respectively) were grown in DMEM containing glucose, L-glutamine and sodium pyruvate, 10% fetal bovine serum (FBS), 100 IU/mL penicillin, 100 μg/mL streptomycin, 2 mM GlutaMAX, non-essential amino acids and 0.25 (H1a-luc) or 0.5 (Zluc) mg/mL G418. GlutaMAX was obtained from Invitrogen, Corp.; all other media reagents were obtained from Mediatech, Inc. For dose-response testing, the cells were seeded in 96-well plates at 1 x 10^4 (H1a-luc) or 7.5 x 10^3 (Zluc) cells/well in a volume of 50 μL, and incubated at 37 °C/5% CO_2. Three hours after plating, 50 μL of ten 5-fold serial dilutions of compound were added, and cell cultures were incubated at 37°C/5% CO_2 for 72 hours. In all cases, Huh-7 cells lacking the HCV replicon served as negative control. To assess luciferase expression, the media/compound was removed from the plates and ONE-glo Luciferase assay reagent (Promega) was added to each well. The assay plates were shaken for 3 minutes at room temperature and luciferase activity for each well was measured with a 1 sec read time on the Victor^{3}V multilabel counter using a 700 nm cut-off filter (Perkin Elmer). EC_{50} values were calculated from dose response curves from the resulting best-fit equations determined by Microsoft Excel and XLfit 4.1 software.

For cytotoxicity evaluation, H1a-luc or Zluc cells were treated with compounds as described above and cellular viability was monitored using the Cell Titer 96 AQueous One

Solution Cell Proliferation Assay (Promega). Plates were then read at 490 nm in a Victor^{3}V 1420 multilabel counter (Perkin Elmer) and CC_{50} concentrations were determined using Microsoft Excel and XLfit 4.1 software.

Luciferase Replicon Transient Transfection Assay

General procedure: The luciferase replicon transient transfection assay measures the ability of a test compound to inhibit the replication of a transiently-transfected HCV luciferase-bearing wild-type or mutant replicon in cured human hepatoma cells (Huh7.5). The inhibition of HCV replication was measured by quantification of luciferase protein expression. This assay has been validated using a panel of genotype 1a and 1b replicons bearing mutations known to be associated with resistance to BMS-790052. Briefly, subconfluent Huh7.5 cells were electroporated with 10 μg of wild-type or mutant luciferase-bearing HCV replicon RNA. The cells were then seeded in 96-well opaque white plates at $3x10^4$ cells/well in 150 μL/well and incubated for 4 hrs at 37°C/5% CO_2. Ten 1:5 serial dilutions of each test compound were made in media (DMEM containing glucose, L-glutamine and sodium pyruvate, 10% fetal bovine serum, 100 IU/mL penicillin, 100 μg/mL streptomycin, 2 mM GlutaMAX, and 1X MEM non-essential amino acids (Mediatech, Inc. and Invitrogen Corp.)) at concentrations that were 4X higher than the final concentrations to be tested and 50 μL/well was added to the transfected cells. Untreated, mock-transfected cells served as a negative control of luciferase expression. The plates were incubated at 37°C/5% CO_2 for 4 days whereupon the media was removed and 50 μL of ONE-glo luciferase substrate (Promega) was added to each well. The plates were agitated on a rotating platform at room temperature for 3 min and read in a Victor^{3}V microplate reader (Perkin-Elmer) using a 700 nm cut-off filter with a 1 sec read time. EC_{50} values were calculated from dose response curves from the resulting best-fit equations determined by Microsoft Excel and XLfit 4.1 software.

To determine the replication capacity of each mutant relative to the wild-type parental replicon, transfected cells were plated on two plates and were not treated with compound. Luciferase activity was measured at time points of 4 hrs and 4 days after plating for each replicon. Replication capacity was calculated by dividing the day 4 relative luminescence units by the 4 hour relative luminescence units for each replicon and determining the percentage present for each mutant replicon relative to wild-type replicon values. The NS3, NS4B, and NS5B mutants were prepared and tested according to the methods described herein.

The compounds disclosed herein have IC_{50} as follows:

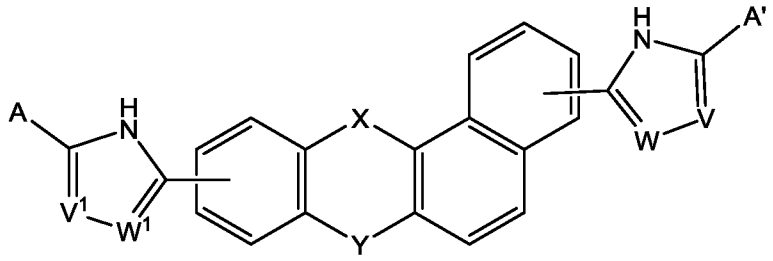
compound	1a IC_{50} (nM)	1aY93H IC_{50} (nM)	1b IC_{50} (nM)	2b IC_{50} (nM)	3a IC_{50} (nM)
1	0.0204	66.03			
2	0.0046	10.55	0.0036	37.11	1.383
3	0.0022	7.152	0.0016	1.953	0.721
4	0.0057	48.76			
5	0.0050	11.73		0.784	1.085
6	0.0027	15.01		12.81	1.718
7	0.0029	17.83		11.02	
8	0.0020	4.103		3.333	0.581
9	0.0020	3.28		4.533	1.112
10	0.0122	13.05		5.494	0.114
11	0.0037	0.391	0.0044	0.016	0.038
12	0.0045	0.548	0.0056	0.495	0.055
13	0.0023	0.682	0.0040	0.254	0.084
14	0.0042	0.221			0.034
15	0.0098	0.826	0.0036	0.292	0.218
16	0.0036	0.072	0.0044	0.032	0.015
17	0.0034	0.046	0.0305	0.028	0.055
18	208.1	146.6			
19	745	1390			
20					
21	63.13	96.21		505	

compound	1a IC_{50} (nM)	1aY93H IC_{50} (nM)	1b IC_{50} (nM)	2b IC_{50} (nM)	3a IC_{50} (nM)
22	291.1	717.3			
23	53.48	435.7		1000	
24	424.8	2465			
25	0.167	100	0.107	100	1
26	1	100	1	100	1
27	1	96.56	0.5907	100	1
28	0.0292	1.179	0.00445	89.83	1
29	1	100	1	100	1
30	0.0416	2.03		0.481	0.722
31	0.31	506		797	0.0262
32	0.0841	0.18		3.47	5.84
33	0.003	18.38	0.003326	14.08	1

The examples set forth above are provided to give those of ordinary skill in the art with a complete disclosure and description of how to make and use the claimed embodiments, and are not intended to limit the scope of what is disclosed herein. Modifications that are obvious to persons of skill in the art are intended to be within the scope of the following claims. All publications, patents, and patent applications cited in this specification are incorporated herein by reference as if each such publication, patent or patent application were specifically and individually indicated to be incorporated herein by reference.

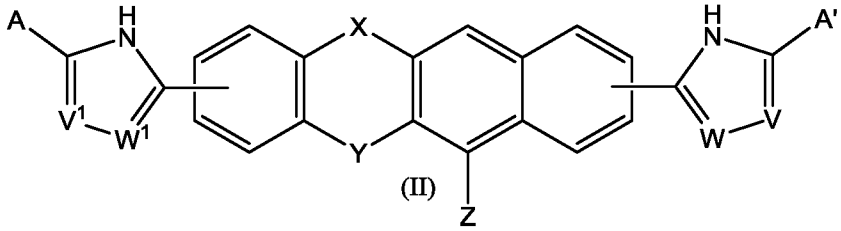
CLAIMS

1. A compound of Formula I or II,



(I)

or



(II)

or a pharmaceutically acceptable salt thereof, where

X is -O-, -C(O)-, $-C(R^AR^B)-$, NR^A, or SO_2;

Y is -O-, -C(O)-, $-C(R^AR^B)-$, NR^A, or SO_2;

V is CH or N;

W is CH or N;

V^1 is CH or N;

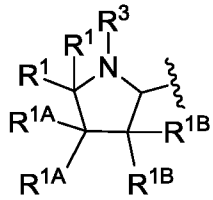
W^1 is CH or N;

Z is H or halo;

R^A is H, halo, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl, 4 to 6-membered monocyclic heterocycloalkyl, 5 or 6-membered monocyclic heteroaryl, 6 to 10-membered bicyclic heterocycloalkyl, C_6-C_{10} aryl, or -O-(C_1-C_6 alkyl), wherein said C_3-C_7 cycloalkyl group, said 4 to 6-membered monocyclic heterocycloalkyl group, said 5 or 6-membered monocyclic heteroaryl group, said 6 to 10-membered bicyclic heterocycloalkyl, or said C_6-C_{10} aryl group, can be optionally substituted with up to 3 groups, which can be the same or different, and are selected from halo, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -O-C_1-C_6 alkyl, –(C_1-C_6 alkylene)-O-C_1-C_6 alkyl and -O-(C_1-C_6 haloalkyl);

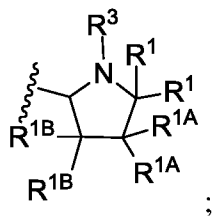
R^B is H, halo, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl, 4 to 6-membered monocyclic heterocycloalkyl, 5 or 6-membered monocyclic heteroaryl, 6 to 10-membered bicyclic heterocycloalkyl, C_6-C_{10} aryl, or -O-(C_1-C_6 alkyl), wherein said C_3-C_7 cycloalkyl group, said 4 to 6-membered monocyclic heterocycloalkyl group, said 5 or 6-membered monocyclic heteroaryl group, said 6 to 10-membered bicyclic heterocycloalkyl, or said C_6-C_{10} aryl group, can be optionally substituted with up to 3 groups, which can be the same or different, and are selected from halo, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -O-C_1-C_6 alkyl, –(C_1-C_6 alkylene)-O-C_1-C_6 alkyl and -O-(C_1-C_6 haloalkyl);

A is:



;

A' is:



;

each occurrence of R^1 is independently selected from H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl, and halo;

each occurrence of R^{1A} is independently selected from H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl, and halo, or one R^{1A} group and an R^1 group that are attached to same ring, together with the ring carbon atoms to which they are attached, can combine to form a fused C_3-C_7 cycloalkyl group, or two R^{1A} groups that are attached to the same carbon atom, and the common carbon atom to which they are attached, can combine to form a spirocyclic C_3-C_7 cycloalkyl group;

each occurrence of R^{1B} is independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl, or halo, or an R^{1B} group and an R^{1A} group that are attached to the same ring, together with the carbon atoms to which they are attached, can combine to form a fused C_3-C_7 cycloalkyl group, or an R^{1B} group and an R^1 group that are attached to the same ring, can combine to form a bridging group having the formula $–CH_2$- or $–CH_2CH_2$-;

each occurrence of R^3 is independently H, $–C(O)$-$C(R^4)_2NHC(O)O$-R^5, $–C(O)O$-R^5, $C(O)NHR^5$ or $–C(O)$-$C(R^4)_2NR^7R^8$;

each occurrence of R^4 is independently selected from H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_6-C_{10} aryl, 4 to 8-membered monocyclic heterocycloalkyl, 6 to 10-membered bicyclic heterocycloalkyl and C_3-C_7 cycloalkyl, wherein said 4 to 8-membered monocyclic heterocycloalkyl group, said 6 to 10-membered bicyclic heterocycloalkyl group, said C_6-C_{10} aryl group and said C_3-C_7 cycloalkyl group can be optionally substituted with up to 5 groups, each independently selected from halo, -CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl, -O-C_1-C_6 alkyl, $–N(R^6)_2$ and -O-(C_1-C_6 haloalkyl), and wherein said C_3-C_7 cycloalkyl group can be optionally fused to a 4 to 6-membered monocyclic heterocycloalkyl group, and wherein said 4 to 8-membered monocyclic heterocycloalkyl group and said C_3-C_7 cycloalkyl group can be substituted on a ring carbon atom with a spirocyclic C_3-C_6 cycloalkyl group; and wherein said C_3-C_7 cycloalkyl group can be substituted on a ring carbon atom with a spirocyclic 3 to 6-membered monocyclic heterocycloalkyl group, and wherein two R^4 groups, that are attached to a common carbon atom, together with the common carbon atom to which they are attached, can join to form a C_3-C_7 cycloalkyl group;

each occurrence of R^5 is independently selected from C_1-C_6 alkyl, C_3-C_7 cycloalkyl and C_6-C_{10} aryl;

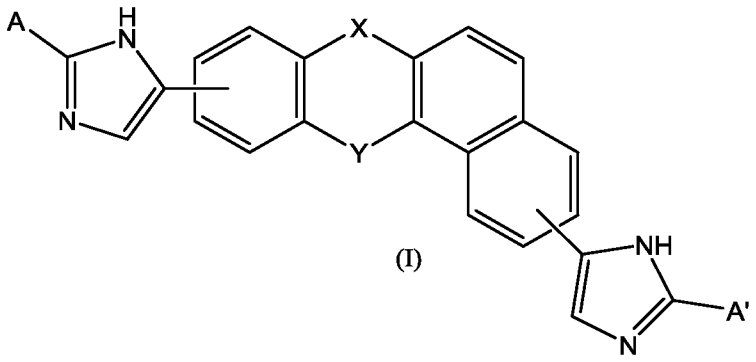
each occurrence of R^6 is independently selected from H, C_1-C_6 alkyl and C_3-C_7 cycloalkyl;

each occurrence of R^7 is independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl, or phenyl, or R^7 and R^8, together with the nitrogen atom to which they are attached, form a 3 to 6-membered monocyclic heterocycloalkyl group; and

each occurrence of R^8 is independently H, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl, or phenyl, or R^7 and R^8, together with the nitrogen atom to which they are attached, form a 3 to 6-membered monocyclic heterocycloalkyl group,

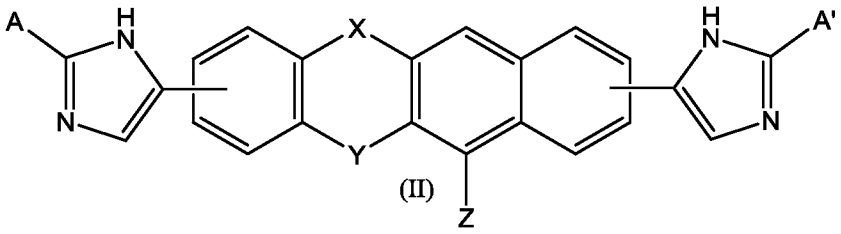
provided that at least one of V, V^1, W and W^1 is N.

2. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound of Formula (I) is



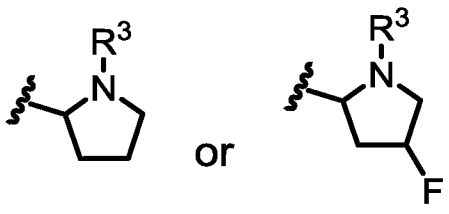
(I)

and the compound of Formula (II) is



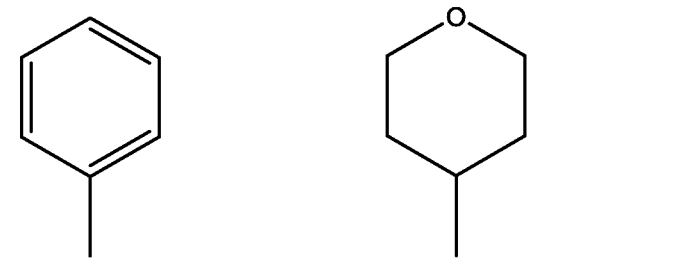
(II)

3. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein A and A' are each independently



4. The compound of Claim 3, or a pharmaceutically acceptable salt thereof, wherein each R^3 is independently

H, -C(O)CH(CH(CH$_3$)$_2$)(NHC(O)OCH$_3$), -C(O)OC(CH$_3$)$_3$, C(O)NHC(CH$_3$)$_3$,



-C(O)CHN(CH$_2$CH$_3$)$_2$, or -C(O)CHNHC(O)OCH$_3$.

5. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein each R^{1A} is independently H or fluoro.

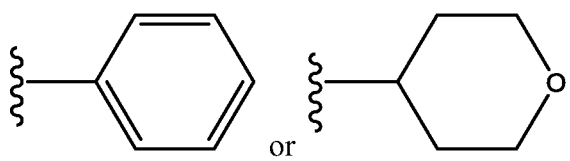
6. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein each R^{1B} is H.

7. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein each R^1 is H.

8. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein R^A and R^B are independently H, halo, or -C$_1$-C$_6$ alkyl.

9. The compound of Claim 8, or a pharmaceutically acceptable salt thereof, wherein R^A and R^B are independently H, fluoro, -CH$_3$ or -CH$_2$CH$_3$.

10. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein each R^4 is independently H, -CH(CH$_3$)$_3$,



or

11. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein each R^5 is independently CH_3 or $C(CH_3)_3$.

12. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein R^7 and R^8 are independently H or -C_1-C_6 alkyl.

13. The compound of Claim 12, or a pharmaceutically acceptable salt thereof, wherein R^7 and R^8 are independently H or -CH_2CH_3.

14. The compound of Claim 1 which is

methyl [(1R)-1-({(2R)-2-[5-(9-{2-[(2R)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-7-oxo-7H-benzo[c]xanthen-3-yl)-1H-imidazol-2-yl]pyrrolidin-1-yl}carbonyl)-2-methylpropyl]carbamate,

methyl [(1S)-1-({(2S)-2-[5-(3-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-12-methyl-12H-benzo[a]xanthen-9-yl)-1H-imidazol-2-yl]pyrrolidin-1-yl}carbonyl)-2-methylpropyl]carbamate,

methyl [(1S)-1-({(2S)-2-[5-(3-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-12-methyl-12H-benzo[a]xanthen-9-yl)-1H-imidazol-2-yl]pyrrolidin-1-yl}carbonyl)-2-methylpropyl]carbamate,

methyl [(1S)-1-({(2S)-2-[5-(3-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-7-methyl-7H-benzo[c]xanthen-9-yl)-1H-imidazol-2-yl]pyrrolidin-1-yl}carbonyl)-2-methylpropyl]carbamate,

methyl [(1S)-1-({(2S)-2-[5-(12-ethyl-3-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]
3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-12H-benzo[a]xanthen-9-yl)-1H-imidazol-2-yl]pyrrolidin-1-yl}carbonyl)-2-methylpropyl]carbamate,

methyl [(1S)-1-({(2S)-2-[5-(12-ethyl-3-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-12H-benzo[a]xanthen-9-yl)-1H-imidazol-2-yl]pyrrolidin-1-yl}carbonyl)-2-methylpropyl]carbamate,

methyl [(1S)-1-({(2S)-2-[5-(3-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-12,12-dimethyl-12H-benzo[a]xanthen-9-yl)-1H-imidazol-2-yl]pyrrolidin-1-yl}carbonyl)-2-methylpropyl]carbamate,

methyl [(1R)-1-({(2S)-2-[5-(12,12-diethyl-3-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-12H-benzo[a]xanthen-9-yl)-1H-imidazol-2-yl]pyrrolidin-1-yl}carbonyl)-2-methylpropyl]carbamate,

methyl [(1R)-1-({(2S)-2-[5-(12,12-diethyl-9-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-12H-benzo[b]xanthen-3-yl)-1H-imidazol-2-yl]pyrrolidin-1-yl}carbonyl)-2-methylpropyl]carbamate,

dimethyl [(12-methyl-12H-benzo[a]xanthene-3,9-diyl)bis{1H-imidazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethane-2,1-diyl]}]biscarbamate,

dimethyl [(12-methyl-12H-benzo[a]xanthene-3,9-diyl)bis{1H-imidazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethane-2,1-diyl]}]biscarbamate,

dimethyl [(12,12-dimethyl-12H-benzo[a]xanthene-3,9-diyl)bis{1H-imidazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethane-2,1-diyl]}]biscarbamate,

dimethyl [(12-ethyl-12H-benzo[a]xanthene-3,9-diyl)bis{1H-imidazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethane-2,1-diyl]}]biscarbamate,

dimethyl [(12-ethyl-12H-benzo[a]xanthene-3,9-diyl)bis{1H-imidazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethane-2,1-diyl]}]biscarbamate,

methyl [(1R)-2-[(2R)-2-{5-[12,12-diethyl-9-(2-{(2R)-1-[(2S)-2-[(methoxycarbonyl)amino]-2-(tetrahydro-2H-pyran-4-yl)acetyl]pyrrolidin-2-yl}-1H-

imidazol-5-yl)-12H-benzo[a]xanthen-3-yl]-1H-imidazol-2-yl}pyrrolidin-1-yl]-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl]carbamate,

methyl [(1R)-2-[(2S)-2-{5-[12,12-diethyl-9-(2-{(2S)-1-[(2S)-2-[(methoxycarbonyl)amino]-2-(tetrahydro-2H-pyran-4-yl)acetyl]pyrrolidin-2-yl}-1H-imidazol-5-yl)-12H-benzo[b]xanthen-3-yl]-1H-imidazol-2-yl}pyrrolidin-1-yl]-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl]carbamate,

3-{2-[(2S,4R)-4-fluoropyrrolidin-2-yl]-1H-imidazol-5-yl}-9-{2-[(2S,4S)-4-fluoropyrrolidin-2-yl]-1H-imidazol-5-yl}-12H-benzo[a]xanthen-12-one,

6-fluoro-2,9-bis{2-[(2S,4S)-4-fluoropyrrolidin-2-yl]-1H-imidazol-5-yl}-12H-benzo[b]xanthen-12-one,

di-tert-butyl (2S,2'S)-2,2'-[(12-oxo-12H-benzo[a]xanthene-3,9-diyl)bis(1H-imidazole-5,2-diyl)]dipyrrolidine-1-carboxylate,

(2S,4R,2'S,4'S)-2,2'-[(12-oxo-12H-benzo[a]xanthene-3,9-diyl)bis(1H-imidazole-5,2-diyl)]bis(N-tert-butyl-4-fluoropyrrolidine-1-carboxamide),

di-tert-butyl (2S,4R,2'S,4'S)-2,2'-[(12-oxo-12H-benzo[a]xanthene-3,9-diyl)bis(1H-imidazole-5,2-diyl)]bis(4-fluoropyrrolidine-1-carboxylate),

(2S,4S,2'S,4'S)-2,2'-[(6-fluoro-12-oxo-12H-benzo[b]xanthene-2,9-diyl)bis(1H-imidazole-5,2-diyl)]bis(N-tert-butyl-4-fluoropyrrolidine-1-carboxamide),

di-tert-butyl (2S,4S,2'S,4'S)-2,2'-[(6-fluoro-12-oxo-12H-benzo[b]xanthene-2,9-diyl)bis(1H-imidazole-5,2-diyl)]bis(4-fluoropyrrolidine-1-carboxylate),

methyl [(1S)-1-({(2S)-2-[5-(10-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-12-oxo-12H-benzo[a]xanthen-3-yl)-1H-imidazol-2-yl]pyrrolidin-1-yl}carbonyl)-2-methylpropyl]carbamate,

methyl [(1S)-1-({(2S)-2-[5-(6-fluoro-9-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-12-oxo-12H-benzo[b]xanthen-2-yl)-1H-imidazol-2-yl]pyrrolidin-1-yl}carbonyl)-2-methylpropyl]carbamate,

methyl [(1S)-1-({(2S,4R)-4-fluoro-2-[5-(10-{2-[(2S,4R)-4-fluoro-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-12-

oxo-12H-benzo[a]xanthen-3-yl)-1H-imidazol-2-yl]pyrrolidin-1-yl}carbonyl)-2-methylpropyl]carbamate,

methyl [(1S)-1-({(2S,4R)-4-fluoro-2-[5-(9-{2-[(2S,4R)-4-fluoro-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-12-oxo-12H-benzo[a]xanthen-3-yl)-1H-imidazol-2-yl]pyrrolidin-1-yl}carbonyl)-2-methylpropyl]carbamate,

methyl [(1S)-1-({(2S,4R)-4-fluoro-2-[5-(6-fluoro-9-{2-[(2S,4R)-4-fluoro-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-12-oxo-12H-benzo[b]xanthen-2-yl)-1H-imidazol-2-yl]pyrrolidin-1-yl}carbonyl)-2-methylpropyl]carbamate,

dimethyl [(12-oxo-12H-benzo[a]xanthene-3,9-diyl)bis{1H-imidazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethane-2,1-diyl]}]biscarbamate,

3,9-bis(2-{(2S,4R)-1-[(2R)-2-(diethylamino)-2-phenylacetyl]-4-fluoropyrrolidin-2-yl}-1H-imidazol-5-yl)-12H-benzo[a]xanthen-12-one,

dimethyl [(12-oxo-12H-benzo[a]xanthene-3,9-diyl)bis{1H-imidazole-5,2-diyl[(2S,4R)-4-fluoropyrrolidine-2,1-diyl][(1S)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethane-2,1-diyl]}]biscarbamate, or

methyl [(1S)-1-({(2S)-2-[5-(9-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-12-oxo-12H-benzo[a]xanthen-3-yl)-1H-imidazol-2-yl]pyrrolidin-1-yl}carbonyl)-2-methylpropyl]carbamate,

or a pharmaceutically acceptable salt thereof.

15. The pharmaceutical composition comprising the compound of claim 1, and one or more pharmaceutically acceptable carriers.

16. The pharmaceutical composition of claim 15, further comprising a second antiviral agent.

17. The pharmaceutical composition of claim 16, wherein the second antiviral

agent is selected from an interferon, ribavirin, an interleukin, an NS3 protease inhibitor, a cysteine protease inhibitor, a phenathrenequinone, a thiazolidine, a benzanilide, a helicase inhibitor, a polymerase inhibitor, a nucleotide analogue, a liotoxin, acerulenin, an antisense phosphorothioate oligodeoxynucleotide, an inhibitor of IRES-dependent translation, or a ribozyme.

18. The pharmaceutical composition of claim 17, wherein the second antiviral agent is an interferon.

19. The pharmaceutical composition of claim 18, wherein the interferon is selected from pegylated interferon alpha 2a, interferon alfahcon-1, natural interferon, albuferon, interferon beta-1a, omega interferon, interferon alpha, interferon gamma, interferon tau, interferon delta, or interferon gamma-1b.

20. The pharmaceutical composition of claim 15, wherein the composition is formulated for single dose administration.

21. The pharmaceutical composition of claim 15, wherein the composition is formulated as an oral, parenteral, or intravenous dosage form.

22. The pharmaceutical composition of claim 15, wherein the composition is formulated as an oral dosage form.

23. The pharmaceutical composition of claim 22, wherein the oral dosage form is a tablet or capsule.

24. The pharmaceutical composition of claim 15, wherein the compound is administered in a dose of about 0.5 milligram to about 1,000 milligram daily.

25. A method for treating or preventing an HCV infection in a subject, which comprises to the subject administering the compound of claim 1 or the pharmaceutical composition of claim 3.

26. A method of treating, preventing, or ameliorating one or more symptoms of a liver disease or disorder associated with an HCV infection in a subject, comprising administering

to the subject the compound of claim 1 or the pharmaceutical composition of claim 15.

27. The method of claim 24, wherein the method comprises administering to the subject a second antiviral agent, in combination or alternation.

28. The method of claim 27, wherein the second antiviral agent is selected from an interferon, ribavirin, amantadine, an interleukin, a NS3 protease inhibitor, a cysteine protease inhibitor, a phenathrenequinone, a thiazolidine, a benzanilide, a helicase inhibitor, a polymerase inhibitor, a nucleotide analogue, a liotoxin, acerulenin, an antisense phosphorothioate oligodeoxynucleotide, an inhibitor of IRES-dependent translation, or a ribozyme.

29. The method of claim 28, wherein the second antiviral agent is an interferon.

30. The method of claim 29, wherein the interferon is selected from pegylated interferon alpha 2a, interferon alfacon-1, natural interferon, albuferon, interferon beta-1a, omega interferon, interferon alpha, interferon gamma, interferon tau, interferon delta, or interferon gamma-1b.

31. The method of claim 25, wherein the subject is a human.

32. A method for inhibiting replication of a virus in a host, which comprises contacting the host with the compound of claim 1 or the pharmaceutical composition of claim 15.

33. The method of claim 32, wherein the host is a human.

34. The method of claim 32, wherein the host is a cell.

35. A method for inhibiting replication of a virus, which comprises contacting the virus with the compound of claim 1 or the pharmaceutical composition of claim 15.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2016/079871

A. CLASSIFICATION OF SUBJECT MATTER

C07D 407/14(2006.01)i; C07D 405/14(2006.01)i; A61K 31/4178(2006.01)i; A61K 31/352(2006.01)i; A61P 31/12(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D; A61K; A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, EPODOC, CNPAT(CN), CNKI(CN), Chinese Pharmaceutical Abstract (CN), CHEMICAL ABSTRACTS(US), EMBASE, STN: structrure search for compounds of claims 1-14, HCV, hepatitis c virus, inhibitor?, carbamate, pyrrolidin, imidazol

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2012050918 A2 (PRESIDIO PHARMACEUTICAL, INC.) 19 April 2012 (2012-04-19) the whole document	1-35

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

☑ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 January 2017	**26 January 2017**

Name and mailing address of the ISA/CN	Authorized officer
STATE INTELLECTUAL PROPERTY OFFICE OF THE P.R.CHINA **6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088** **China**	**XIU,Wen**
Facsimile No. **(86-10)62019451**	Telephone No. **(86-10)62089321**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2016/079871

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

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

1. ☑ Claims Nos.: **25-31**
because they relate to subject matter not required to be searched by this Authority, namely:

[1] Claims 25-31 relate to methods of treating or preventing an HCV infection or disorder associated with an HCV infection (PCT R39.1(iv)), but the search has been carried out and based on the reasonably anticipant subjects, i.e. the use of the compound of claim 1 in manufacture of medicaments for treating or preventing an HCV infection or disorder associated with an HCV infection.

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

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

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2016/079871

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)	Publication date (day/month/year)
WO 2012050918 A2	19 April 2012	WO 2012050918 A8	16 August 2012
		WO 2012050918 A3	21 June 2012
		US 8999967 B2	07 April 2015
		US 2013296304 A1	07 November 2013
		TW 201219385 A	16 May 2012