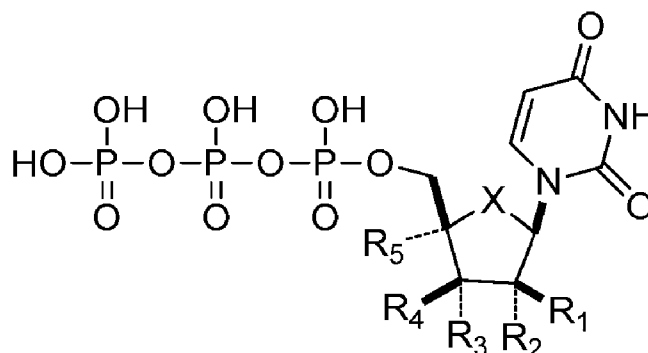




- (51) **International Patent Classification:**
C07D 403/04 (2006.01) **A61K 31/513** (2006.01)
C07F 9/06 (2006.01) **A61P 31/14** (2006.01)
- (21) **International Application Number:**
PCT/US2016/018317
- (22) **International Filing Date:**
17 February 2016 (17.02.2016)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**
62/117,697 18 February 2015 (18.02.2015) US
- (71) **Applicant:** ABBVIE INC. [US/US]; 1 North Waukegan Road, North Chicago, Illinois 60064 (US).
- (72) **Inventors:** CHEN, Hui-Ju; 4 Crow's Nest Court, Grayslake, Illinois 60030 (US). DEGOEY, David A.; 8649 226th Avenue, Salem, Wisconsin 53168 (US). KALTHOD, Vikram; 1401 Sheridan Road, North Chicago, Illinois 60064 (US). KRUEGER, Allan; 7260 Presidential Drive, Gurnee, Illinois 60031 (US). RANDOLPH, John T.; 304 Broadway Avenue, Libertyville, Illinois 60048 (US). WAGNER, Rolf; 42530 Sheridan Oaks Drive, Antioch, Illinois 60002 (US).
- (74) **Agents:** ZHANG, Xu et al.; AbbVie Inc. 1 North Waukegan Road AP34-2/V377, North Chicago, Illinois 60064 (US).
- (81) **Designated States** (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.
- (84) **Designated States** (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).
- Published:**
— with international search report (Art. 21(3))

(54) Title: ANTI-VIRAL COMPOUNDS



(I)

(57) **Abstract:** The present invention features compounds of e.g. formula (I) effective in inhibiting Hepatitis C virus ("HCV") polymerase. The invention also features compositions comprising such compounds and methods of using such compounds to treat HCV infection. X is -C(=CH₂)-; R₃ is OH; R₄ is H; R₅ is H, D or F; R₁ and R₂ together form -CRaRbNRC-, -NRCRbRb-, -CRaR-bCH₂NRC- or -NRCCH₂CRaRb-.

ANTI-VIRAL COMPOUNDS

FIELD OF THE INVENTION

[0001] The present invention relates to compounds effective in inhibiting replication of Hepatitis C virus ("HCV"). The present invention also relates to compositions comprising these compounds and methods of using these compounds to treat HCV infection.

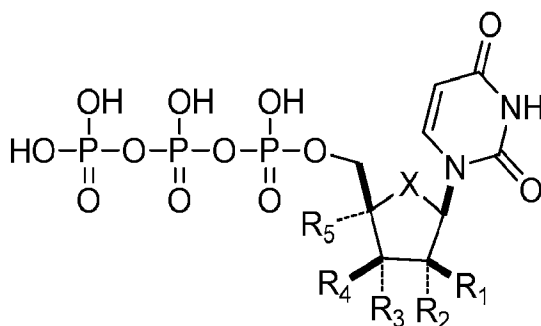
BACKGROUND OF THE INVENTION

[0002] The HCV is an RNA virus belonging to the Hepacivirus genus in the Flaviviridae family. The enveloped HCV virion contains a positive stranded RNA genome encoding all known virus-specific proteins in a single, uninterrupted, open reading frame. The open reading frame comprises approximately 9500 nucleotides and encodes a single large polyprotein of about 3000 amino acids. The polyprotein comprises a core protein, envelope proteins E1 and E2, a membrane bound protein p7, and the non-structural proteins NS2, NS3, NS4A, NS4B, NS5A and NS5B.

[0003] Chronic HCV infection is associated with progressive liver pathology, including cirrhosis and hepatocellular carcinoma. Chronic hepatitis C may be treated with peginterferon-alpha in combination with ribavirin. Substantial limitations to efficacy and tolerability remain as many users suffer from side effects, and viral elimination from the body is often incomplete. Therefore, there is a need for new therapies to treat HCV infection.

DETAILED DESCRIPTION

[0004] In one aspect, the present invention features compounds having Formula I, and pharmaceutically acceptable salts thereof,



I

wherein for each compound of Formula I, X, R₁, R₂, R₃, R₄ and R₅ are as defined in Table 1:

Table 1.

Compound No.	X	R ₁ -R ₂	R ₃	R ₄	R ₅	R _a	R _b	R _c
1	C=CH ₂	CRaRbNRc	OH	H	H	H	H	H
2	C=CH ₂	CRaRbNRc	OH	H	H	H	H	CH ₃
3	C=CH ₂	CRaRbNRc	OH	H	H	H	H	COCH ₃
4	C=CH ₂	CRaRbNRc	OH	H	H	H	CH ₃	H
5	C=CH ₂	CRaRbNRc	OH	H	H	H	CH ₃	CH ₃
6	C=CH ₂	CRaRbNRc	OH	H	H	H	CH ₃	COCH ₃
7	C=CH ₂	CRaRbNRc	OH	H	H	CH ₃	H	H
8	C=CH ₂	CRaRbNRc	OH	H	H	CH ₃	H	CH ₃
9	C=CH ₂	CRaRbNRc	OH	H	H	CH ₃	H	COCH ₃
10	C=CH ₂	CRaRbNRc	OH	H	H	CH ₃	CH ₃	H
11	C=CH ₂	CRaRbNRc	OH	H	H	CH ₃	CH ₃	CH ₃
12	C=CH ₂	CRaRbNRc	OH	H	H	CH ₃	CH ₃	COCH ₃
13	C=CH ₂	CRaRbNRc	OH	H	F	H	H	H
14	C=CH ₂	CRaRbNRc	OH	H	F	H	H	CH ₃
15	C=CH ₂	CRaRbNRc	OH	H	F	H	H	COCH ₃
16	C=CH ₂	CRaRbNRc	OH	H	F	H	CH ₃	H
17	C=CH ₂	CRaRbNRc	OH	H	F	H	CH ₃	CH ₃
18	C=CH ₂	CRaRbNRc	OH	H	F	H	CH ₃	COCH ₃
19	C=CH ₂	CRaRbNRc	OH	H	F	CH ₃	H	H
20	C=CH ₂	CRaRbNRc	OH	H	F	CH ₃	H	CH ₃
21	C=CH ₂	CRaRbNRc	OH	H	F	CH ₃	H	COCH ₃
22	C=CH ₂	CRaRbNRc	OH	H	F	CH ₃	CH ₃	H
23	C=CH ₂	CRaRbNRc	OH	H	F	CH ₃	CH ₃	CH ₃
24	C=CH ₂	CRaRbNRc	OH	H	F	CH ₃	CH ₃	COCH ₃
25	C=CH ₂	CRaRbNRc	OH	H	D	H	H	H
26	C=CH ₂	CRaRbNRc	OH	H	D	H	H	CH ₃
27	C=CH ₂	CRaRbNRc	OH	H	D	H	H	COCH ₃
28	C=CH ₂	CRaRbNRc	OH	H	D	H	CH ₃	H
29	C=CH ₂	CRaRbNRc	OH	H	D	H	CH ₃	CH ₃
30	C=CH ₂	CRaRbNRc	OH	H	D	H	CH ₃	COCH ₃
31	C=CH ₂	CRaRbNRc	OH	H	D	CH ₃	H	H
32	C=CH ₂	CRaRbNRc	OH	H	D	CH ₃	H	CH ₃
33	C=CH ₂	CRaRbNRc	OH	H	D	CH ₃	H	COCH ₃
34	C=CH ₂	CRaRbNRc	OH	H	D	CH ₃	CH ₃	H
35	C=CH ₂	CRaRbNRc	OH	H	D	CH ₃	CH ₃	CH ₃

Compound No.	X	R ₁ -R ₂	R ₃	R ₄	R ₅	R _a	R _b	R _c
36	C=CH ₂	CRaRbNRc	OH	H	D	CH ₃	CH ₃	COCH ₃
37	C=CH ₂	NRcCRaRb	OH	H	H	H	H	H
38	C=CH ₂	NRcCRaRb	OH	H	H	H	H	CH ₃
39	C=CH ₂	NRcCRaRb	OH	H	H	H	H	COCH ₃
40	C=CH ₂	NRcCRaRb	OH	H	H	H	CH ₃	H
41	C=CH ₂	NRcCRaRb	OH	H	H	H	CH ₃	CH ₃
42	C=CH ₂	NRcCRaRb	OH	H	H	H	CH ₃	COCH ₃
43	C=CH ₂	NRcCRaRb	OH	H	H	CH ₃	H	H
44	C=CH ₂	NRcCRaRb	OH	H	H	CH ₃	H	CH ₃
45	C=CH ₂	NRcCRaRb	OH	H	H	CH ₃	H	COCH ₃
46	C=CH ₂	NRcCRaRb	OH	H	H	CH ₃	CH ₃	H
47	C=CH ₂	NRcCRaRb	OH	H	H	CH ₃	CH ₃	CH ₃
48	C=CH ₂	NRcCRaRb	OH	H	H	CH ₃	CH ₃	COCH ₃
49	C=CH ₂	NRcCRaRb	OH	H	F	H	H	H
50	C=CH ₂	NRcCRaRb	OH	H	F	H	H	CH ₃
51	C=CH ₂	NRcCRaRb	OH	H	F	H	H	COCH ₃
52	C=CH ₂	NRcCRaRb	OH	H	F	H	CH ₃	H
53	C=CH ₂	NRcCRaRb	OH	H	F	H	CH ₃	CH ₃
54	C=CH ₂	NRcCRaRb	OH	H	F	H	CH ₃	COCH ₃
55	C=CH ₂	NRcCRaRb	OH	H	F	CH ₃	H	H
56	C=CH ₂	NRcCRaRb	OH	H	F	CH ₃	H	CH ₃
57	C=CH ₂	NRcCRaRb	OH	H	F	CH ₃	H	COCH ₃
58	C=CH ₂	NRcCRaRb	OH	H	F	CH ₃	CH ₃	H
59	C=CH ₂	NRcCRaRb	OH	H	F	CH ₃	CH ₃	CH ₃
60	C=CH ₂	NRcCRaRb	OH	H	F	CH ₃	CH ₃	COCH ₃
61	C=CH ₂	NRcCRaRb	OH	H	D	H	H	H
62	C=CH ₂	NRcCRaRb	OH	H	D	H	H	CH ₃
63	C=CH ₂	NRcCRaRb	OH	H	D	H	H	COCH ₃
64	C=CH ₂	NRcCRaRb	OH	H	D	H	CH ₃	H
65	C=CH ₂	NRcCRaRb	OH	H	D	H	CH ₃	CH ₃
66	C=CH ₂	NRcCRaRb	OH	H	D	H	CH ₃	COCH ₃
67	C=CH ₂	NRcCRaRb	OH	H	D	CH ₃	H	H
68	C=CH ₂	NRcCRaRb	OH	H	D	CH ₃	H	CH ₃
69	C=CH ₂	NRcCRaRb	OH	H	D	CH ₃	H	COCH ₃
70	C=CH ₂	NRcCRaRb	OH	H	D	CH ₃	CH ₃	H
71	C=CH ₂	NRcCRaRb	OH	H	D	CH ₃	CH ₃	CH ₃
72	C=CH ₂	NRcCRaRb	OH	H	D	CH ₃	CH ₃	COCH ₃
73	C=CH ₂	CRaRbCH ₂ NRc	OH	H	H	H	H	H

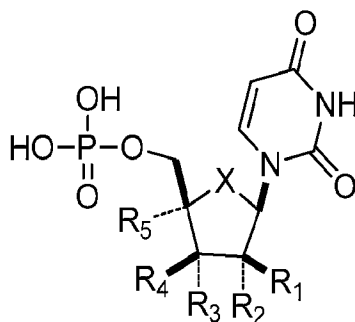
Compound No.	X	R ₁ -R ₂	R ₃	R ₄	R ₅	R _a	R _b	R _c
74	C=CH ₂	CRaRbCH ₂ NRc	OH	H	H	H	H	CH ₃
75	C=CH ₂	CRaRbCH ₂ NRc	OH	H	H	H	H	COCH ₃
76	C=CH ₂	CRaRbCH ₂ NRc	OH	H	H	H	CH ₃	H
77	C=CH ₂	CRaRbCH ₂ NRc	OH	H	H	H	CH ₃	CH ₃
78	C=CH ₂	CRaRbCH ₂ NRc	OH	H	H	H	CH ₃	COCH ₃
79	C=CH ₂	CRaRbCH ₂ NRc	OH	H	H	CH ₃	H	H
80	C=CH ₂	CRaRbCH ₂ NRc	OH	H	H	CH ₃	H	CH ₃
81	C=CH ₂	CRaRbCH ₂ NRc	OH	H	H	CH ₃	H	COCH ₃
82	C=CH ₂	CRaRbCH ₂ NRc	OH	H	H	CH ₃	CH ₃	H
83	C=CH ₂	CRaRbCH ₂ NRc	OH	H	H	CH ₃	CH ₃	CH ₃
84	C=CH ₂	CRaRbCH ₂ NRc	OH	H	H	CH ₃	CH ₃	COCH ₃
85	C=CH ₂	CRaRbCH ₂ NRc	OH	H	F	H	H	H
86	C=CH ₂	CRaRbCH ₂ NRc	OH	H	F	H	H	CH ₃
87	C=CH ₂	CRaRbCH ₂ NRc	OH	H	F	H	H	COCH ₃
88	C=CH ₂	CRaRbCH ₂ NRc	OH	H	F	H	CH ₃	H
89	C=CH ₂	CRaRbCH ₂ NRc	OH	H	F	H	CH ₃	CH ₃
90	C=CH ₂	CRaRbCH ₂ NRc	OH	H	F	H	CH ₃	COCH ₃
91	C=CH ₂	CRaRbCH ₂ NRc	OH	H	F	CH ₃	H	H
92	C=CH ₂	CRaRbCH ₂ NRc	OH	H	F	CH ₃	H	CH ₃
93	C=CH ₂	CRaRbCH ₂ NRc	OH	H	F	CH ₃	H	COCH ₃
94	C=CH ₂	CRaRbCH ₂ NRc	OH	H	F	CH ₃	CH ₃	H
95	C=CH ₂	CRaRbCH ₂ NRc	OH	H	F	CH ₃	CH ₃	CH ₃
96	C=CH ₂	CRaRbCH ₂ NRc	OH	H	F	CH ₃	CH ₃	COCH ₃
97	C=CH ₂	CRaRbCH ₂ NRc	OH	H	D	H	H	H
98	C=CH ₂	CRaRbCH ₂ NRc	OH	H	D	H	H	CH ₃
99	C=CH ₂	CRaRbCH ₂ NRc	OH	H	D	H	H	COCH ₃
100	C=CH ₂	CRaRbCH ₂ NRc	OH	H	D	H	CH ₃	H
101	C=CH ₂	CRaRbCH ₂ NRc	OH	H	D	H	CH ₃	CH ₃
102	C=CH ₂	CRaRbCH ₂ NRc	OH	H	D	H	CH ₃	COCH ₃
103	C=CH ₂	CRaRbCH ₂ NRc	OH	H	D	CH ₃	H	H
104	C=CH ₂	CRaRbCH ₂ NRc	OH	H	D	CH ₃	H	CH ₃
105	C=CH ₂	CRaRbCH ₂ NRc	OH	H	D	CH ₃	H	COCH ₃
106	C=CH ₂	CRaRbCH ₂ NRc	OH	H	D	CH ₃	CH ₃	H
107	C=CH ₂	CRaRbCH ₂ NRc	OH	H	D	CH ₃	CH ₃	CH ₃
108	C=CH ₂	CRaRbCH ₂ NRc	OH	H	D	CH ₃	CH ₃	COCH ₃
109	C=CH ₂	NRcCH ₂ CRaRb	OH	H	H	H	H	H
110	C=CH ₂	NRcCH ₂ CRaRb	OH	H	H	H	H	CH ₃
111	C=CH ₂	NRcCH ₂ CRaRb	OH	H	H	H	H	COCH ₃

Compound No.	X	R ₁ -R ₂	R ₃	R ₄	R ₅	R _a	R _b	R _c
112	C=CH ₂	NRcCH ₂ CRaRb	OH	H	H	H	CH ₃	H
113	C=CH ₂	NRcCH ₂ CRaRb	OH	H	H	H	CH ₃	CH ₃
114	C=CH ₂	NRcCH ₂ CRaRb	OH	H	H	H	CH ₃	COCH ₃
115	C=CH ₂	NRcCH ₂ CRaRb	OH	H	H	CH ₃	H	H
116	C=CH ₂	NRcCH ₂ CRaRb	OH	H	H	CH ₃	H	CH ₃
117	C=CH ₂	NRcCH ₂ CRaRb	OH	H	H	CH ₃	H	COCH ₃
118	C=CH ₂	NRcCH ₂ CRaRb	OH	H	H	CH ₃	CH ₃	H
119	C=CH ₂	NRcCH ₂ CRaRb	OH	H	H	CH ₃	CH ₃	CH ₃
120	C=CH ₂	NRcCH ₂ CRaRb	OH	H	H	CH ₃	CH ₃	COCH ₃
121	C=CH ₂	NRcCH ₂ CRaRb	OH	H	F	H	H	H
122	C=CH ₂	NRcCH ₂ CRaRb	OH	H	F	H	H	CH ₃
123	C=CH ₂	NRcCH ₂ CRaRb	OH	H	F	H	H	COCH ₃
124	C=CH ₂	NRcCH ₂ CRaRb	OH	H	F	H	CH ₃	H
125	C=CH ₂	NRcCH ₂ CRaRb	OH	H	F	H	CH ₃	CH ₃
126	C=CH ₂	NRcCH ₂ CRaRb	OH	H	F	H	CH ₃	COCH ₃
127	C=CH ₂	NRcCH ₂ CRaRb	OH	H	F	CH ₃	H	H
128	C=CH ₂	NRcCH ₂ CRaRb	OH	H	F	CH ₃	H	CH ₃
129	C=CH ₂	NRcCH ₂ CRaRb	OH	H	F	CH ₃	H	COCH ₃
130	C=CH ₂	NRcCH ₂ CRaRb	OH	H	F	CH ₃	CH ₃	H
131	C=CH ₂	NRcCH ₂ CRaRb	OH	H	F	CH ₃	CH ₃	CH ₃
132	C=CH ₂	NRcCH ₂ CRaRb	OH	H	F	CH ₃	CH ₃	COCH ₃
133	C=CH ₂	NRcCH ₂ CRaRb	OH	H	D	H	H	H
134	C=CH ₂	NRcCH ₂ CRaRb	OH	H	D	H	H	CH ₃
135	C=CH ₂	NRcCH ₂ CRaRb	OH	H	D	H	H	COCH ₃
136	C=CH ₂	NRcCH ₂ CRaRb	OH	H	D	H	CH ₃	H
137	C=CH ₂	NRcCH ₂ CRaRb	OH	H	D	H	CH ₃	CH ₃
138	C=CH ₂	NRcCH ₂ CRaRb	OH	H	D	H	CH ₃	COCH ₃
139	C=CH ₂	NRcCH ₂ CRaRb	OH	H	D	CH ₃	H	H
140	C=CH ₂	NRcCH ₂ CRaRb	OH	H	D	CH ₃	H	CH ₃
141	C=CH ₂	NRcCH ₂ CRaRb	OH	H	D	CH ₃	H	COCH ₃
142	C=CH ₂	NRcCH ₂ CRaRb	OH	H	D	CH ₃	CH ₃	H
143	C=CH ₂	NRcCH ₂ CRaRb	OH	H	D	CH ₃	CH ₃	CH ₃
144	C=CH ₂	NRcCH ₂ CRaRb	OH	H	D	CH ₃	CH ₃	COCH ₃

[0005] For each compound number in Table 1, R₁ and R₂, taken together with the atoms to which they are attached, form a ring, as indicated in column "R₁-R₂". As shown below, each compound number

in Table 1 can represent compounds of different formulas but with the same X, R₁-R₂, R₃, R₄, R₅, Ra, Rb and Rc moieties.

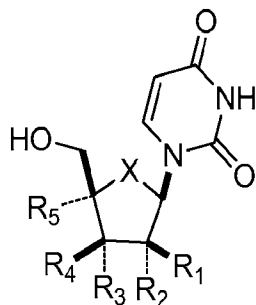
[0006] In another aspect, the present invention features compounds having Formula II, and pharmaceutically acceptable salts thereof, as well as prodrugs thereof,



II

wherein for each compound of Formula II, X, R₁, R₂, R₃, R₄ and R₅ are as defined in Table 1.

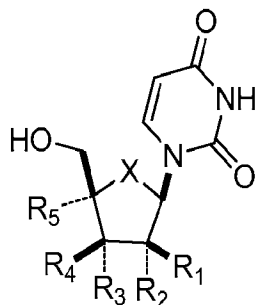
[0007] In still another aspect, the present invention features compounds having Formula III, and pharmaceutically acceptable salts thereof, as well as prodrugs thereof,



III

wherein for each compound of Formula III, X, R₁, R₂, R₃, R₄ and R₅ are as defined in Table 1.

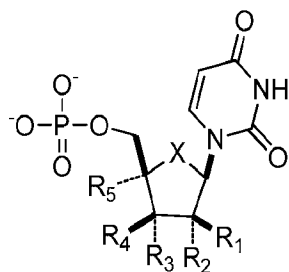
[0008] In still another aspect, the present invention features phosphoramidate prodrugs of compounds having Formula III',



III'

wherein for each compound of Formula III', X, R₁, R₂, R₃, R₄ and R₅ are as defined in Table 1.

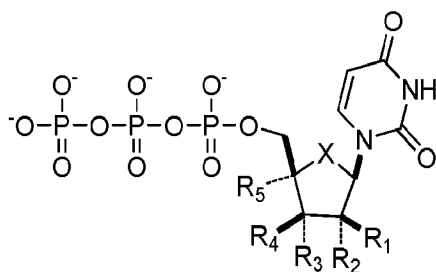
[0009] In yet another aspect, the present invention features compounds having Formula IV,



IV

wherein for each compound of Formula IV, X, R₁, R₂, R₃, R₄ and R₅ are as defined in Table 1.

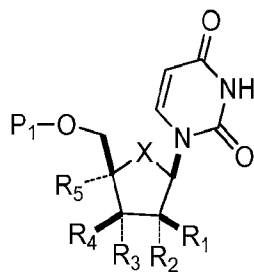
[0010] In yet another aspect, the present invention features compounds having Formula V,



V

wherein for each compound of Formula V, X, R₁, R₂, R₃, R₄ and R₅ are as defined in Table 1.

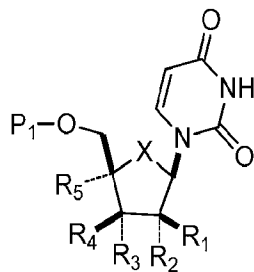
[0011] In yet another aspect, the present invention features compounds having Formula VI, and pharmaceutically acceptable salts thereof,



VI

wherein for each compound of Formula VI, X, R₁, R₂, R₃, R₄ and R₅ are as defined in Table 1, and wherein P₁ is (HO)₂P(O)-O-P(O)(OH)-.

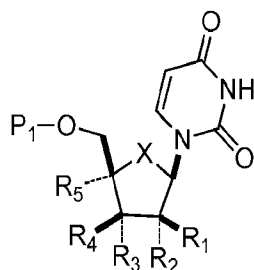
[0012] In yet another aspect, the present invention features compounds having Formula VI', and pharmaceutically acceptable salts thereof,



VI'

wherein for each compound of Formula VI', X, R₁, R₂, R₃, R₄ and R₅ are as defined in Table 1, and wherein P₁ is (O⁻)₂P(O)-O-P(O)(O⁻)₂.

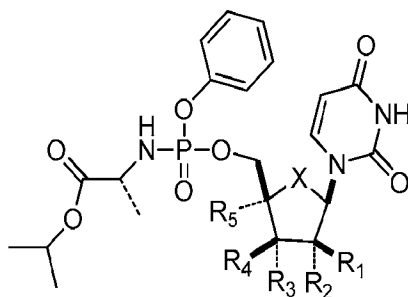
[0013] In yet another aspect, the present invention features compounds having Formula VI'', and pharmaceutically acceptable salts thereof,



VI''

wherein for each compound of Formula VI'', X, R₁, R₂, R₃, R₄ and R₅ are as defined in Table 1, and wherein P₁ is a protected monophosphate prodrug substitution.

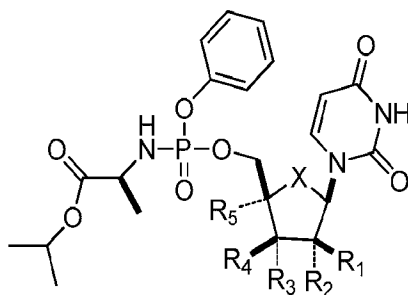
[0014] In a further aspect, the present invention features compounds having Formula VII, and pharmaceutically acceptable salts thereof,



VII

wherein for each compound of Formula VII, X, R₁, R₂, R₃, R₄ and R₅ are as defined in Table 1.

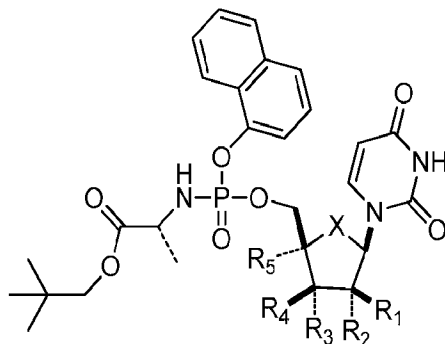
[0015] In a further aspect, the present invention features compounds having Formula VIII, and pharmaceutically acceptable salts thereof,



VIII

wherein for each compound of Formula VIII, X, R₁, R₂, R₃, R₄ and R₅ are as defined in Table 1.

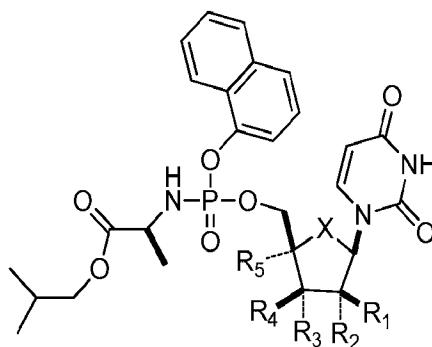
[0016] In a further aspect, the present invention features compounds having Formula IX, and pharmaceutically acceptable salts thereof,



IX

wherein for each compound of Formula IX, X, R₁, R₂, R₃, R₄ and R₅ are as defined in Table 1.

[0017] In a further aspect, the present invention features compounds having Formula A, and pharmaceutically acceptable salts thereof,



A

wherein for each compound of Formula A, X, R₁, R₂, R₃, R₄ and R₅ are as defined in Table 1.

[0018] Any compound according to any of the above-described aspects can be prepared and used in prodrug forms. A suitable prodrug has chemically or metabolically cleavable group(s) and becomes, by solvolysis or under physiological conditions, a compound that is pharmaceutically active *in vivo*. A prodrug can be formed in a conventional manner by reaction of a functional group of the compound (such as an amino, hydroxy or carboxy group). Prodrugs often offer advantages of better metabolism, potency, solubility, tissue compatibility, or delayed release in mammals. Prodrugs include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acidic compound with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a suitable amine. Examples of prodrugs include, but are not limited to, acetate, formate, benzoate or other acylated derivatives of alcohol or amine functional groups within the compounds of the invention. For example, prodrugs can be aliphatic or aromatic esters derived from acidic groups on a compound of the invention. For another example, prodrugs can be aliphatic or aromatic esters of hydroxyl or amino groups

on a compound of the invention. Phosphate prodrugs of hydroxyl groups are preferred prodrugs. Preferably, prodrugs used herein are phosphoramidate prodrugs.

[0019] In yet another aspect, any compound, salt or prodrug according to any aspect, embodiment, example and preference described herein can be isotopically substituted. Preferred isotopic substitutions include substitutions with stable or nonradioactive isotopes such as deuterium, ^{13}C , ^{15}N or ^{18}O . Incorporation of a heavy atom, such as substitution of deuterium for hydrogen, can give rise to an isotope effect that could alter the pharmacokinetics of the drug. In one example, at least 5 mol % (e.g., at least 10 mol %) of hydrogen in a compound of the present invention is substituted with deuterium. In another example, at least 25 mole % of hydrogen in a compound of the present invention is substituted with deuterium. In a further example, at least 50, 60, 70, 80 or 90 mole % of hydrogen in a compound of the present invention is substituted with deuterium. The natural abundance of deuterium is about 0.015%. Deuterium substitution or enrichment can be achieved, without limitation, by either exchanging protons with deuterium or by synthesizing the molecule with enriched or substituted starting materials. Other methods known in the art can also be used for isotopic substitutions.

[0020] In another aspect, the present invention features methods of using any compound/salt/prodrug according to any aspect, embodiment, example and preference described herein to treat HCV infection. Such a compound, salt or prodrug has inhibitory activity against HCV polymerase. The method comprises administering an effective amount of such a compound, salt or prodrug to an HCV patient in need thereof. In one embodiment, the patient is infected with HCV genotype 1. In another embodiment, the patient is infected with HCV genotype 2. In yet another embodiment, the patient is infected with HCV genotype 3. In yet another embodiment, the patient is infected with HCV genotype 4. In yet another embodiment, the patient is infected with HCV genotype 5. In yet another embodiment, the patient is infected with HCV genotype 6.

[0021] It is contemplated that different compounds of the invention may have different anti-viral activities and/or toxicity/safety profiles. Compounds with less antiviral activities can be dosed more frequently and/or with greater amounts. Compounds with higher antiviral activities can be dosed less frequently and/or with lesser amounts. Moreover, a compound that does not have a commercially desired toxicity/safety profile does not prevent its utility under patent law as an anti-viral agent, despite the fact that the US FDA might not approve it for human treatment due to the agency's benefit-cost analyses and/or other non-patent related concerns.

[0022] In yet another aspect, the present invention features methods for treating HCV infection in a subject in need of such treatment. The methods comprise administering at least two direct acting antiviral agents (DAAs) to the subject for a duration of no more than 12 weeks, or for another duration as set forth herein. Said at least two DAAs comprise (1) a compound/salt/prodrug according to any aspect,

embodiment, example and preference described herein, and (2) another DAA. The other DAA can be, for example, selected from an HCV protease inhibitor, an HCV polymerase inhibitor, an HCV NS5A inhibitor, or a cyclophilin inhibitor. Preferably, the other DAA is an HCV protease inhibitor, an HCV polymerase inhibitor, or an HCV NS5A inhibitor. More preferably, the other DAA is an HCV NS5A inhibitor, such as those described in US Patent Application Publication Nos. 2010/0317568 and 2012/0004196, both of which are incorporated herein by reference in their entireties. Highly preferably, the other DAA is the compound of Example 35 of US Patent Application Publication No. 2010/0317568. Also, highly preferably, the other DAA is the compound of Example 3.52 of US Patent Application Publication No. 2012/0004196. In one example, the duration of the treatment is 12 weeks. The duration of the treatment can also be, for example, no more than 8 weeks. Preferably, the two or more DAAs are administered in amounts effective to provide a sustained virological response (SVR) or achieve another desired measure of effectiveness in the subject. The subject is not administered ribavirin during the treatment regimen. The subject is also not administered interferon during the treatment regimen. Put another way, the methods exclude the administration of interferon or ribavirin to the subject, thereby avoiding the side effects associated with interferon and ribavirin.

[0023] In another aspect, the present invention features methods for treating a population of subjects having HCV infection. The methods comprise administering at least two DAAs to the subjects for a duration of no more than 12 weeks. Said at least two DAAs comprise (1) a compound/salt/prodrug according to any aspect, embodiment, example and preference described herein, and (2) another DAA. The other DAA can be, for example, selected from an HCV protease inhibitor, an HCV polymerase inhibitor, an HCV NS5A inhibitor, or a cyclophilin inhibitor. Preferably, the other DAA is an HCV protease inhibitor, an HCV polymerase inhibitor, or an HCV NS5A inhibitor. More preferably, the other DAA is an HCV NS5A inhibitor, such as those described in US Patent Application Publication Nos. 2010/0317568 and 2012/0004196, both of which are incorporated herein by reference in their entireties. Highly preferably, the other DAA is the compound of Example 35 of US Patent Application Publication No. 2010/0317568. Also, highly preferably, the other DAA is the compound of Example 3.52 of US Patent Application Publication No. 2012/0004196. Preferably, said at least two DAAs are administered to the subjects in amounts effective to result in SVR or another measure of effectiveness in at least about 70% of the population, preferably at least about 80% of the population, or more preferably at least about 90% of the population. The subjects are not administered ribavirin during the treatment regimen. The subjects are also not administered interferon during the treatment regimen. Put another way, the methods exclude the administration of interferon or ribavirin to the subject, thereby avoiding the side effects associated with interferon and ribavirin.

[0024] Non-limiting examples of the other DAAs include PSI-7977 (sofosbuvir), PSI-938, BMS-790052 (daclatasvir), BMS-650032 (asunaprevir), BMS-791325, GS-5885 (ledipasvir), GS-9451 (tegobuvir), GS-9190, GS-9256, BI-201335, BI-27127, telaprevir, VX-222, TMC-435 (simepravir), MK-5172, MK-7009 (vaniprevir), danoprevir, paritaprevir, ombitasvir, ABT-493, and R7128 (mericitabine).

[0025] In any method described herein, the DAAs can be administered in any effective dosing schemes and/or frequencies; for example, they can each be administered daily. Each DAA can be administered either separately or in combination, and each DAA can be administered once a day, twice a day, or three times a day. Preferably, the DAAs employed herein are administered once daily.

[0026] In yet another aspect, the present invention features a combination of a compound/salt/prodrug according to any aspect, embodiment, example and preference described herein, and another DAA, for use to treat HCV infection. The other DAA can be, for example, selected from an HCV protease inhibitor, an HCV polymerase inhibitor, an HCV NS5A inhibitor, or a cyclophilin inhibitor. Preferably, the other DAA is an HCV protease inhibitor, an HCV polymerase inhibitor, or an HCV NS5A inhibitor. More preferably, the other DAA is an HCV NS5A inhibitor, such as those described in US Patent Application Publication Nos. 2010/0317568 and 2012/0004196, both of which are incorporated herein by reference in their entireties. Highly preferably, the other DAA is the compound of Example 35 of US Patent Application Publication No. 2010/0317568. Also, highly preferably, the other DAA is the compound of Example 3.52 of US Patent Application Publication No. 2012/0004196. The treatment comprises administering the DAAs to a subject infected with HCV. The duration of the treatment regimen is no more than twelve weeks (e.g., the duration being 12 weeks; or the duration being 11, 10, 9, 8, 7, 6, 5, 4, or 3 weeks). Preferably, the duration of the treatment regimen is twelve weeks. The duration of the treatment can also last, for example, no more than eight weeks (e.g., the duration being 8 weeks; or the duration being 7, 6, 5, 4, or 3 weeks). The treatment does not include administering interferon or ribavirin. The DAAs can be administered concurrently or sequentially. Preferably, the DAAs are administered once daily. As a non-limiting example, the patient being treated is infected with HCV genotype 1, such as genotype 1a or 1b. As another non-limiting example, the patient is infected with HCV genotype 2. As another non-limiting example, the patient is infected with HCV genotype 3. As another non-limiting example, the patient is infected with HCV genotype 4. As another non-limiting example, the patient is infected with HCV genotype 5. As another non-limiting example, the patient is infected with HCV genotype 6. As yet another non-limiting example, the patient is a HCV-treatment naïve patient, a HCV-treatment experienced patient, an interferon non-responder (e.g., a null responder), or not a candidate for interferon treatment. As used in this application, the interferon non-responder patients include partial interferon responders and interferon rebound patients. *See* GUIDANCE FOR INDUSTRY – CHRONIC HEPATITIS C VIRUS INFECTION: DEVELOPING DIRECT-ACTING ANTIVIRAL

AGENTS FOR TREATMENT (FDA, September 2010, draft guidance) for the definitions of naïve, partial responder, responder relapser (i.e., rebound), and null responder patients. The interferon non-responder patients also include null responder patients. In one example of this aspect of the invention, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 7 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 6 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 5 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 4 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 3 weeks, and the subject being treated is a naïve patient infected with HCV genotype 1. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a naïve patient infected with HCV genotype. In another example, the treatment lasts for 11 weeks, and the subject being treated is a naïve patient infected with HCV selected from genotypes 2, 3, 4, 5 or 6. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a naïve patient infected with HCV selected from genotypes 2, 3, 4, 5 or 6. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a naïve patient infected with HCV selected from genotypes 2, 3, 4, 5 or 6. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a naïve patient infected with selected from genotypes 2, 3, 4, 5 or 6. In yet another example, the treatment lasts for 7 weeks, and the subject being treated is a naïve patient infected with selected from genotypes 2, 3, 4, 5 or 6. In yet another example, the treatment lasts for 6 weeks, and the subject being treated is a naïve patient infected with selected from genotypes 2, 3, 4, 5 or 6. In yet another example, the treatment lasts for 5 weeks, and the subject being treated is a naïve patient infected with selected from genotypes 2, 3, 4, 5 or 6. In yet another example, the treatment lasts for 4 weeks, and the subject being treated is a naïve patient infected with selected from genotypes 2, 3, 4, 5 or 6. In yet another example, the treatment lasts for 3 weeks, and the subject being treated is a naïve patient infected with selected from genotypes 2, 3, 4, 5 or 6. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In another example, the treatment lasts for 11 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In still another

example, the treatment lasts for 10 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 7 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 6 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 5 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 4 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 3 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV genotype 1. In yet another example, the treatment lasts for 12 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV selected from genotype 2, 3, 4, 5 or 6. In another example, the treatment lasts for 11 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV selected from genotype 2, 3, 4, 5 or 6. In still another example, the treatment lasts for 10 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV selected from genotype 2, 3, 4, 5 or 6. In yet another example, the treatment lasts for 9 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV selected from genotype 2, 3, 4, 5 or 6. In yet another example, the treatment lasts for 8 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV selected from genotype 2, 3, 4, 5 or 6. In yet another example, the treatment lasts for 7 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV selected from genotype 2, 3, 4, 5 or 6. In yet another example, the treatment lasts for 6 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV selected from genotype 2, 3, 4, 5 or 6. In yet another example, the treatment lasts for 5 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV selected from genotype 2, 3, 4, 5 or 6. In yet another example, the treatment lasts for 4 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV selected from genotype 2, 3, 4, 5 or 6. In yet another example, the treatment lasts for 3 weeks, and the subject being treated is a non-responder (e.g., a null responder) infected with HCV selected from genotype 2, 3, 4, 5 or 6.

[0027] A treatment regimen of the present invention generally constitutes a complete treatment regimen, i.e., no subsequent interferon-containing regimen is intended. Thus, a treatment or use described

herein generally does not include any subsequent interferon-containing treatment. Preferably, a treatment or use described herein does not include any subsequent ribavirin-containing treatment.

[0028] The methods of the present invention can provide effective treatment of HCV infection without the use of interferon or ribavirin and for a shorter period of time, for example and without limitation, a treatment duration of no more than twelve weeks, alternatively no more than eleven weeks, alternatively no more than ten weeks, alternatively no more than nine weeks, alternatively no more than eight weeks, alternatively no more than seven weeks, alternatively no more than six weeks, alternatively no more than five weeks, alternatively no more than four weeks, or alternatively, no more than three weeks.

[0029] In one aspect, the present invention features methods for treating HCV infection in a subject comprising administering at least two DAAs, in the absence of interferon and ribavirin, to the subject for a duration of no more than twelve weeks, alternatively no more than eight weeks. Put another way, the methods exclude interferon and ribavirin. Said at least two DAAs comprise a compound/salt/prodrug according to any aspect, embodiment, example and preference described herein, and another DAA, which can be co-administered, or administered separately or independently, with the same or different dosing frequencies. Preferably, said at least two DAAs are administered once a day. They can also be administered, for example, twice a day or three times a day. The other DAA can be, for example, selected from an HCV protease inhibitor, an HCV polymerase inhibitor, an HCV NS5A inhibitor, or a cyclophilin inhibitor. Preferably, the other DAA is an HCV protease inhibitor, an HCV polymerase inhibitor, or an HCV NS5A inhibitor. More preferably, the other DAA is an HCV NS5A inhibitor, such as those described in US Patent Application Publication Nos. 2010/0317568 and 2012/0004196. Highly preferably, the other DAA is the compound of Example 35 of US Patent Application Publication No. 2010/0317568. Also, highly preferably, the other DAA is the compound of Example 3.52 of US Patent Application Publication No. 2012/0004196.

[0030] Various measures may be used to express the effectiveness of a method of the present invention. One such measure is SVR, which, as used herein, means that the virus is undetectable at the end of therapy and for at least 8 weeks after the end of therapy (SVR8); preferably, the virus is undetectable at the end of therapy and for at least 12 weeks after the end of therapy (SVR12); more preferably, the virus is undetectable at the end of therapy and for at least 16 weeks after the end of therapy (SVR16); and highly preferably, the virus is undetectable at the end of therapy and for at least 24 weeks after the end of therapy (SVR24). SVR24 is often considered as a functional definition of cure; and a high rate of SVR at less than 24 week post-treatment (e.g., SVR8 or SVR12) can be predictive of a high rate of SVR24.

[0031] In some embodiments, a treatment regimen of the invention comprises treating a population of subjects having HCV infection (e.g. treatment naïve subjects), and the regimen comprises administering at least two DAAs to the subjects for a duration of no more than 12 weeks, or for another duration disclosed herein, wherein said at least two DAAs comprise a compound/salt/prodrug according to any aspect, embodiment, example and preference described herein, and another DAA, and are administered to the subjects in amounts effective to provide an SVR (e.g., SVR12 or SVR24) in at least about 70% of the population, alternatively at least about 75% of the population, alternatively at least about 80% of the population, alternatively at least about 85% of the population, alternatively at least about 90% of the population, alternatively at least about 95% of the population, alternatively about 100% of the population. The other DAA can be, for example, selected from an HCV protease inhibitor, an HCV polymerase inhibitor, an HCV NS5A inhibitor, or a cyclophilin inhibitor. Preferably, the other DAA is an HCV protease inhibitor, an HCV polymerase inhibitor, or an HCV NS5A inhibitor. More preferably, the other DAA is an HCV NS5A inhibitor, such as those described in US Patent Application Publication Nos. 2010/0317568 and 2012/0004196. Highly preferably, the other DAA is the compound of Example 35 of US Patent Application Publication No. 2010/0317568. Also, highly preferably, the other DAA is the compound of Example 3.52 of US Patent Application Publication No. 2012/0004196.

[0032] In some embodiments, a treatment regimen of the invention comprises treating a population of IFN experienced subjects (e.g., interferon non-responders) having HCV infection, and the method comprises administering at least two DAAs to the subjects for a duration of no more than 12 weeks, or for another duration disclosed herein, wherein said at least two DAAs comprise (1) a compound/salt/prodrug according to any aspect, embodiment, example and preference described herein (hereinafter “Compound 1”), and another DAA (hereinafter “Compound 2”), and are administered to the subjects in amounts effective to provide an SVR (e.g., SVR12 or SVR24) in at least about 50% of the population, alternatively at least about 55% of the population, alternatively at least about 60% of the population, alternatively at least about 65% of the population, alternatively at least about 70% of the population, alternatively at least about 75% of the population, alternatively at least about 80% of the population, alternatively at least about 85% of the population, alternatively at least about 90% of the population, alternatively at least about 95% of the population, or alternatively about 100% of the population.

[0033] In any aspect, embodiment, example and preference described herein, Compound 2 can be, for example, selected from an HCV protease inhibitor, an HCV polymerase inhibitor, an HCV NS5A inhibitor, or a cyclophilin inhibitor. Preferably, Compound 2 is an HCV protease inhibitor, an HCV polymerase inhibitor, or an HCV NS5A inhibitor. More preferably, Compound 2 is an HCV NS5A inhibitor, such as those described in US Patent Application Publication Nos. 2010/0317568 and 2012/0004196. Highly preferably, Compound 2 is the compound of Example 35 of US Patent

Application Publication No. 2010/0317568. Also, highly preferably, Compound 2 is the compound of Example 3.52 of US Patent Application Publication No. 2012/0004196.

[0034] In one aspect, the present invention features a method of treating HCV infection, comprising administering to a patient in need thereof an effective amount of a combination of at least two DAAs, wherein said at least two DAAs comprise Compound 1 and Compound 2. The treatment lasts 8 weeks and does not include administration of any interferon or ribavirin. The DAAs can be administered at the same or different dosing frequencies. The patient being treated can be a treatment naïve patient; a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, an interferon non-responder, or a null responder; or a patient unable to take interferon. The patient may be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3; or HCV genotype 4, 5 or 6. The treatment according to this aspect of the technology may also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times. In addition to Compound 1 and Compound 2, said at least two DAAs can also include one or more additional DAAs selected from, for example, HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. Non-limiting examples of such additional DAAs include PSI-7977, PSI-938, TMC-435, BMS-790052, BMS-650032, GS-5885, GS-9190, GS-9451, BI-201335, BI-207127, telaprevir, VX-222, mericitabine, and danoprevir.

[0035] In another aspect, the present invention features a method of treating HCV infection, comprising administering to a patient in need thereof an effective amount of a combination of at least two DAAs, wherein said at least two DAAs comprise Compound 1 and Compound 2. The treatment lasts 7 weeks and does not include administration of any interferon or ribavirin. The DAAs can be administered at the same or different dosing frequencies. The patient being treated can be a treatment naïve patient; a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, an interferon non-responder, or a null responder; or a patient unable to take interferon. The patient may be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3; or HCV genotype 4, 5 or 6. The treatment according to this aspect of the technology may also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times. In addition to Compound 1 and Compound 2, said at least two DAAs can also include one or more additional DAAs selected from, for example, HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. Non-limiting examples of such additional DAAs include PSI-7977, PSI-938, TMC-435, BMS-790052, BMS-650032, GS-5885, GS-9190, GS-9451, BI-201335, BI-207127, telaprevir, VX-222, mericitabine, and danoprevir.

[0036] In yet another aspect, the present invention features a method of treating HCV infection, comprising administering to a patient in need thereof an effective amount of a combination of at least two

DAAs, wherein said at least two DAAs comprise Compound 1 and Compound 2. The treatment lasts 6 weeks and does not include administration of any interferon or ribavirin. The DAAs can be administered at the same or different dosing frequencies. The patient being treated can be a treatment naïve patient; a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, an interferon non-responder, or a null responder; or a patient unable to take interferon. The patient may be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3; or HCV genotype 4, 5 or 6. The treatment according to this aspect of the technology may also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times. In addition to Compound 1 and Compound 2, said at least two DAAs can also include one or more additional DAAs selected from, for example, HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. Non-limiting examples of such additional DAAs include PSI-7977, PSI-938, TMC-435, BMS-790052, BMS-650032, GS-5885, GS-9190, GS-9451, BI-201335, BI-207127, telaprevir, VX-222, mericitabine, and danoprevir.

[0037] In yet another aspect, the present invention features a method of treating HCV infection, comprising administering to a patient in need thereof an effective amount of a combination of at least two DAAs, wherein said at least two DAAs comprise Compound 1 and Compound 2. The treatment lasts 5 weeks and does not include administration of any interferon or ribavirin. The DAAs can be administered at the same or different dosing frequencies. The patient being treated can be a treatment naïve patient; a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, an interferon non-responder, or a null responder; or a patient unable to take interferon. The patient may be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3; or HCV genotype 4, 5 or 6. The treatment according to this aspect of the technology may also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times. In addition to Compound 1 and Compound 2, said at least two DAAs can also include one or more additional DAAs selected from, for example, HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. Non-limiting examples of such additional DAAs include PSI-7977, PSI-938, TMC-435, BMS-790052, BMS-650032, GS-5885, GS-9190, GS-9451, BI-201335, BI-207127, telaprevir, VX-222, mericitabine, and danoprevir.

[0038] In yet another aspect, the present invention features a method of treating HCV infection, comprising administering to a patient in need thereof an effective amount of a combination of at least two DAAs, wherein said at least two DAAs comprise Compound 1 and Compound 2. The treatment lasts 4 weeks and does not include administration of any interferon or ribavirin. The DAAs can be administered at the same or different dosing frequencies. The patient being treated can be a treatment naïve patient; a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, an

interferon non-responder, or a null responder; or a patient unable to take interferon. The patient may be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3; or HCV genotype 4, 5 or 6. The treatment according to this aspect of the technology may also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times. In addition to Compound 1 and Compound 2, said at least two DAAs can also include one or more additional DAAs selected from, for example, HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. Non-limiting examples of such additional DAAs include PSI-7977, PSI-938, TMC-435, BMS-790052, BMS-650032, GS-5885, GS-9190, GS-9451, BI-201335, BI-207127, telaprevir, VX-222, mericitabine, and danoprevir.

[0039] In yet another aspect, the present invention features a method of treating HCV infection, comprising administering to a patient in need thereof an effective amount of a combination of at least two DAAs, wherein said at least two DAAs comprise Compound 1 and Compound 2. The treatment lasts 3 weeks and does not include administration of any interferon or ribavirin. The DAAs can be administered at the same or different dosing frequencies. The patient being treated can be a treatment naïve patient; a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, an interferon non-responder, or a null responder; or a patient unable to take interferon. The patient may be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3; or HCV genotype 4, 5 or 6. The treatment according to this aspect of the technology may also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times. In addition to Compound 1 and Compound 2, said at least two DAAs can also include one or more additional DAAs selected from, for example, HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. Non-limiting examples of such additional DAAs include PSI-7977, PSI-938, TMC-435, BMS-790052, BMS-650032, GS-5885, GS-9190, GS-9451, BI-201335, BI-207127, telaprevir, VX-222, mericitabine, and danoprevir.

[0040] In yet another aspect, the present invention features a method of treating HCV infection, comprising administering to a patient in need thereof an effective amount of a combination of at least two DAAs, wherein said at least two DAAs comprise Compound 1 and Compound 2. The treatment lasts 24 weeks and does not include administration of any interferon or ribavirin. The DAAs can be administered at the same or different dosing frequencies. The patient being treated can be a treatment naïve patient; a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, an interferon non-responder, or a null responder; or a patient unable to take interferon. The patient may be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3; or HCV genotype 4, 5 or 6. The treatment according to this aspect of the technology may also be effective against other HCV genotypes. The DAAs can be administered

around the same time or at different times. In addition to Compound 1 and Compound 2, said at least two DAAs can also include one or more additional DAAs selected from, for example, HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. Non-limiting examples of such additional DAAs include PSI-7977, PSI-938, TMC-435, BMS-790052, BMS-650032, GS-5885, GS-9190, GS-9451, BI-201335, BI-207127, telaprevir, VX-222, mericitabine, and danoprevir.

[0041] In yet another aspect, the present invention features a method of treating HCV infection, comprising administering to a patient in need thereof an effective amount of a combination of at least two DAAs, wherein said at least two DAAs comprise Compound 1 and Compound 2. The treatment lasts 13 to 23 weeks (e.g., the duration of the treatment is selected from 13, 14, 15, 16, 17, 18, 19, 20, 21, 22 or 23 weeks) and does not include administration of any interferon or ribavirin. The DAAs can be administered at the same or different dosing frequencies. The patient being treated can be a treatment naïve patient; a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, an interferon non-responder, or a null responder; or a patient unable to take interferon. The patient may be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3; or HCV genotype 4, 5 or 6. The treatment according to this aspect of the technology may also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times. In addition to Compound 1 and Compound 2, said at least two DAAs can also include one or more additional DAAs selected from, for example, HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. Non-limiting examples of such additional DAAs include PSI-7977, PSI-938, TMC-435, BMS-790052, BMS-650032, GS-5885, GS-9190, GS-9451, BI-201335, BI-207127, telaprevir, VX-222, mericitabine, and danoprevir.

[0042] In yet another aspect, the present invention features a method of treating HCV infection, comprising administering to a patient in need thereof an effective amount of a combination of at least two DAAs, wherein said at least two DAAs comprise Compound 1 and Compound 2. The treatment lasts 12 weeks and does not include administration of any interferon or ribavirin. The DAAs can be administered at the same or different dosing frequencies. The patient being treated can be a treatment naïve patient; a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, an interferon non-responder, or a null responder; or a patient unable to take interferon. The patient may be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3; or HCV genotype 4, 5 or 6. The treatment according to this aspect of the technology may also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times. In addition to Compound 1 and Compound 2, said at least two DAAs can also include one or more additional DAAs selected from, for example, HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. Non-limiting examples of such

additional DAAs include PSI-7977, PSI-938, TMC-435, BMS-790052, BMS-650032, GS-5885, GS-9190, GS-9451, BI-201335, BI-207127, telaprevir, VX-222, mericitabine, and danoprevir. As used in this application, a HCV polymerase inhibitor can be a nucleoside polymerase inhibitor, a nucleotide polymerase inhibitor, a non-nucleoside polymerase inhibitor, or a non-nucleotide polymerase inhibitor.

[0043] In yet another aspect, the present invention features a method of treating HCV infection, comprising administering to a patient in need thereof an effective amount of a combination of at least two DAAs, wherein said at least two DAAs comprise Compound 1 and Compound 2. The treatment lasts 11 weeks and does not include administration of any interferon or ribavirin. The DAAs can be administered at the same or different dosing frequencies. The patient being treated can be a treatment naïve patient; a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, an interferon non-responder, or a null responder; or a patient unable to take interferon. The patient may be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3; or HCV genotype 4, 5 or 6. The treatment according to this aspect of the technology may also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times. In addition to Compound 1 and Compound 2, said at least two DAAs can also include one or more additional DAAs selected from, for example, HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. Non-limiting examples of such additional DAAs include PSI-7977, PSI-938, TMC-435, BMS-790052, BMS-650032, GS-5885, GS-9190, GS-9451, BI-201335, BI-207127, telaprevir, VX-222, mericitabine, and danoprevir.

[0044] In yet another aspect, the present invention features a method of treating HCV infection, comprising administering to a patient in need thereof an effective amount of a combination of at least two DAAs, wherein said at least two DAAs comprise Compound 1 and Compound 2. The treatment lasts 10 weeks and does not include administration of any interferon or ribavirin. The DAAs can be administered at the same or different dosing frequencies. The patient being treated can be a treatment naïve patient; a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, an interferon non-responder, or a null responder; or a patient unable to take interferon. The patient may be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3; or HCV genotype 4, 5 or 6. The treatment according to this aspect of the technology may also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times. In addition to Compound 1 and Compound 2, said at least two DAAs can also include one or more additional DAAs selected from, for example, HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. Non-limiting examples of such additional DAAs include PSI-7977, PSI-938, TMC-435, BMS-790052, BMS-650032, GS-5885, GS-9190, GS-9451, BI-201335, BI-207127, telaprevir, VX-222, mericitabine, and danoprevir.

[0045] In yet another aspect, the present invention features a method of treating HCV infection, comprising administering to a patient in need thereof an effective amount of a combination of at least two DAAs, wherein said at least two DAAs comprise Compound 1 and Compound 2. The treatment lasts 9 weeks and does not include administration of any interferon or ribavirin. The DAAs can be administered at the same or different dosing frequencies. The patient being treated can be a treatment naïve patient; a treatment experienced patient, including, but not limited to, a relapser, an interferon partial responder, an interferon non-responder, or a null responder; or a patient unable to take interferon. The patient may be infected with, for example and without limitation, HCV genotype 1, such as HCV genotype 1a or HCV genotype 1b; or HCV genotype 2 or 3; or HCV genotype 4, 5 or 6. The treatment according to this aspect of the technology may also be effective against other HCV genotypes. The DAAs can be administered around the same time or at different times. In addition to Compound 1 and Compound 2, said at least two DAAs can also include one or more additional DAAs selected from, for example, HCV protease inhibitors, HCV polymerase inhibitors, or HCV NS5A inhibitors. Non-limiting examples of such additional DAAs include PSI-7977, PSI-938, TMC-435, BMS-790052, BMS-650032, GS-5885, GS-9190, GS-9451, BI-201335, BI-207127, telaprevir, VX-222, mericitabine, and danoprevir.

[0046] A method of the present invention can be used to treat a naïve patient or a treatment experienced patient. Treatment experienced patients include interferon non-responders (e.g., null responders), partial responders, and relapsers. A method of the present invention can also be used to treat patients who are not candidates for interferon treatment. Patients who are not candidates for interferon treatment include, but are not limited to, one or more of the following groups: patients intolerant to interferon, patients who refuse to take interferon treatment, patients with medical conditions which preclude them from taking interferon, and patients who have an increased risk of side effects or infection by taking interferon.

[0047] In any method described herein, one or more additional DAAs can be optionally used in the treatment regimen in addition to Compound 1 and Compound 2. These additional DAAs can be HCV protease inhibitors, HCV nucleoside or nucleotide polymerase inhibitors, HCV non-nucleoside polymerase inhibitors, HCV NS3B inhibitors, HCV NS4A inhibitors, HCV NS5A inhibitors, HCV NS5B inhibitors, HCV entry inhibitors, cyclophilin inhibitors, or combinations thereof.

[0048] Preferred HCV protease inhibitors for this purpose include, but are not limited to, telaprevir (Vertex), boceprevir (Merck), BI-201335 (Boehringer Ingelheim), GS-9451 (Gilead), and BMS-650032 (BMS). Other suitable protease inhibitors include, but are not limited to, ACH-1095 (Achillion), ACH-1625 (Achillion), ACH-2684 (Achillion), AVL-181 (Avila), AVL-192 (Avila), BMS-650032 (BMS), danoprevir (RG7227/ITMN-191, Roche), GS-9132 (Gilead), GS-9256 (Gilead), IDX-136 (Idenix), IDX-316 (Idenix), IDX-320 (Idenix), MK-5172 (Merck), narlaprevir (Schering-Plough Corp), PHX-1766

(Phenomix), TMC-435 (Tibotec), vaniprevir (MK-7009, Merck), VBY708 (Virobay), VX-500 (Vertex), VX-813 (Vertex), VX-985 (Vertex), or a combination thereof.

[0049] Preferred non-nucleoside HCV polymerase inhibitors for use in the present invention include, but are not limited to, GS-9190 (Gilead), BI-207127 (Boehringer Ingelheim), and VX-222 (VCH-222) (Vertex & ViraChem). Preferred nucleotide HCV polymerase inhibitors include, but are not limited to, PSI-7977 (Gilead), and PSI-938 (Gilead). Other suitable and non-limiting examples of suitable HCV polymerase inhibitors include ANA-598 (Anadys), BI-207127 (Boehringer Ingelheim), BILB-1941 (Boehringer Ingelheim), BMS-791325 (BMS), filibuvir, GL59728 (Glaxo), GL60667 (Glaxo), GS-9669 (Gilead), IDX-375 (Idenix), MK-3281 (Merck), tegobuvir, TMC-647055 (Tibotec), VCH-759 (Vertex & ViraChem), VCH-916 (ViraChem), VX-759 (Vertex), GS-6620 (Gilead), IDX-102 (Idenix), IDX-184 (Idenix), INX-189 (Inhibitex), MK-0608 (Merck), RG7128 (Roche), TMC64912 (Medivir), GSK625433 (GlaxoSmithKline), BCX-4678 (BioCryst), ALS-2200 (Alios BioPharma/Vertex), ALS-2158 (Alios BioPharma/Vertex), or a combination thereof. A polymerase inhibitor may be a nucleoside or nucleotide polymerase inhibitor, such as GS-6620 (Gilead), IDX-102 (Idenix), IDX-184 (Idenix), INX-189 (Inhibitex), MK-0608 (Merck), PSI-7977 (Gilead), PSI-938 (Gilead), RG7128 (Roche), TMC64912 (Medivir), ALS-2200 (Alios BioPharma/Vertex), ALS-2158 (Alios BioPharma/Vertex), or a combination thereof. A polymerase inhibitor may also be a non-nucleoside polymerase inhibitor, such as PF-00868554 (Pfizer), ANA-598 (Anadys), BI-207127 (Boehringer Ingelheim), BILB-1941 (Boehringer Ingelheim), BMS-791325 (BMS), filibuvir, GL59728 (Glaxo), GL60667 (Glaxo), GS-9669 (Gilead), IDX-375 (Idenix), MK-3281 (Merck), tegobuvir (Gilead), TMC-647055 (Tibotec), VCH-759 (Vertex & ViraChem), VCH-916 (ViraChem), VX-222 (VCH-222) (Vertex & ViraChem), VX-759 (Vertex), or a combination thereof.

[0050] Preferred NS5A inhibitors include, but are not limited to, BMS-790052 (BMS) and GS-5885 (Gilead). Non-limiting examples of suitable NS5A inhibitors include GSK62336805 (GlaxoSmithKline), ACH-2928 (Achillion), AZD2836 (Astra-Zeneca), AZD7295 (Astra-Zeneca), BMS-790052 (BMS), BMS-824393 (BMS), GS-5885 (Gilead), PPI-1301 (Presidio), PPI-461 (Presidio) A-831 (Arrow Therapeutics), A-689 (Arrow Therapeutics) or a combination thereof.

[0051] Non-limiting examples of suitable cyclophilin inhibitors include alisporovir (Novartis & Debiopharm), NM-811 (Novartis), SCY-635 (Scynexis), or a combination thereof.

[0052] Non-limiting examples of suitable HCV entry inhibitors include ITX-4520 (iTherx), ITX-5061 (iTherx), or a combination thereof.

[0053] Specific examples of other DAA agents that are suitable for inclusion in a method of the present invention include, but are not limited to, AP-H005, A-831 (Arrow Therapeutics) (NS5A inhibitor), A-689 (Arrow Therapeutics) (NS5A inhibitor), INX08189 (Inhibitex) (polymerase inhibitor), ITMN-191

(Intermune/Roche) (NS3/4A Protease inhibitor), VBY-376 (Protease Inhibitor) (Virobay), ACH-1625 (Achillion, Protease inhibitor), IDX136 (Idenix, Protease Inhibitor), IDX316 (Idenix, Protease inhibitor), VX-813 (Vertex), SCH 900518 (Schering-Plough), TMC-435 (Tibotec), ITMN-191 (Intermune, Roche), MK-7009 (Merck), IDX-PI (Novartis), R7128 (Roche), PF-868554 (Pfizer) (non-nucleoside polymerase inhibitor), PF-4878691 (Pfizer), IDX-184 (Idenix), IDX-375 (Idenix, NS5B polymerase inhibitor), PPI-461 (Presidio), BILB-1941 (Boehringer Ingelheim), GS-9190 (Gilead), BMS-790052 (BMS), CTS-1027 (Conatus), GS-9620 (Gilead), PF-4878691 (Pfizer), RO5303253 (Roche), ALS-2200 (Alios BioPharma/Vertex), ALS-2158 (Alios BioPharma/Vertex), GSK62336805 (GlaxoSmithKline), or any combinations thereof.

[0054] In some embodiments, the present invention features methods for treating patients infected with HCV genotype 1, such as 1a or 1b. The methods comprise administering to such a patient a combination of at least 2 DAAs for no more than 12 weeks (e.g., the duration being 12 weeks), such as no more than 8 weeks (e.g., the duration being 8 weeks), wherein the treatment does not include administration of either interferon or ribavirin, and said at least 2 DAAs comprise Compound 1 and Compound 2. Compound 1 and Compound 2 can be administered in therapeutically effective amounts to provide a SVR (for example, SVR12 or SVR24) after the completion of the treatment. The patients may be treatment naïve patients or treatment experienced patients. The treatment duration can be no more than 12 weeks, including but not limited to, no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, no more than 7 weeks, no more than 6 weeks, no more than 5 weeks, no more than 4 weeks, or no more than 3 weeks, e.g., the duration being 12 weeks, or the duration being 8 weeks.

[0055] In some embodiments, the present invention features methods for treating patients with HCV genotype 2 or 3 infection. The methods comprise administering to such a patient a combination of at least 2 DAAs for no more than 12 weeks (e.g., the duration being 12 weeks), such as no more than 8 weeks (e.g., the duration being 8 weeks), wherein the treatment does not include administration of either interferon or ribavirin, and said at least 2 DAAs comprise Compound 1 and Compound 2. Compound 1 and Compound 2 can be administered in therapeutically effective amounts to provide a SVR (for example, SVR12 or SVR24) after the completion of the treatment. The patients may be treatment naïve patients or treatment experienced patients. The treatment duration can be no more than 12 weeks, including but not limited to, no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, no more than 7 weeks, no more than 6 weeks, no more than 5 weeks, no more than 4 weeks, or no more than 3 weeks, e.g., the duration being 12 weeks, or the duration being 8 weeks.

[0056] In some embodiments, the present invention features methods for treating patients with HCV genotype 2 infection. The methods comprise administering to such a patient a combination of at least 2

DAAs for no more than 12 weeks (e.g., the duration being 12 weeks), such as no more than 8 weeks (e.g., the duration being 8 weeks), wherein the treatment does not include administration of either interferon or ribavirin, and said at least 2 DAAs comprise Compound 1 and Compound 2. Compound 1 and Compound 2 can be administered in therapeutically effective amounts to provide a SVR (for example, SVR12 or SVR24) after the completion of the treatment. The patients may be treatment naïve patients or treatment experienced patients. The treatment duration can be no more than 12 weeks, including but not limited to, no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, no more than 7 weeks, no more than 6 weeks, no more than 5 weeks, no more than 4 weeks, or no more than 3 weeks, e.g., the duration being 12 weeks, or the duration being 8 weeks.

[0057] In some embodiments, the present invention features methods for treating patients with HCV genotype 3 infection. The methods comprise administering to such a patient a combination of at least 2 DAAs for no more than 12 weeks (e.g., the duration being 12 weeks), such as no more than 8 weeks (e.g., the duration being 8 weeks), wherein the treatment does not include administration of either interferon or ribavirin, and said at least 2 DAAs comprise Compound 1 and Compound 2. Compound 1 and Compound 2 can be administered in therapeutically effective amounts to provide a SVR (for example, SVR12 or SVR24) after the completion of the treatment. The patients may be treatment naïve patients or treatment experienced patients. The treatment duration can be no more than 12 weeks, including but not limited to, no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, no more than 7 weeks, no more than 6 weeks, no more than 5 weeks, no more than 4 weeks, or no more than 3 weeks, e.g., the duration being 12 weeks, or the duration being 8 weeks.

[0058] In some embodiments, the present invention features methods for treating patients with HCV genotype 4 infection. The methods comprise administering to such a patient a combination of at least 2 DAAs for no more than 12 weeks (e.g., the duration being 12 weeks), such as no more than 8 weeks (e.g., the duration being 8 weeks), wherein the treatment does not include administration of either interferon or ribavirin, and said at least 2 DAAs comprise Compound 1 and Compound 2. Compound 1 and Compound 2 can be administered in therapeutically effective amounts to provide a SVR (for example, SVR12 or SVR24) after the completion of the treatment. The patients may be treatment naïve patients or treatment experienced patients. The treatment duration can be no more than 12 weeks, including but not limited to, no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, no more than 7 weeks, no more than 6 weeks, no more than 5 weeks, no more than 4 weeks, or no more than 3 weeks, e.g., the duration being 12 weeks, or the duration being 8 weeks.

[0059] In some embodiments, the present invention features methods for treating patients with HCV genotype 5 infection. The methods comprise administering to such a patient a combination of at least 2 DAAs for no more than 12 weeks (e.g., the duration being 12 weeks), such as no more than 8 weeks (e.g.,

the duration being 8 weeks), wherein the treatment does not include administration of either interferon or ribavirin, and said at least 2 DAAs comprise Compound 1 and Compound 2. Compound 1 and Compound 2 can be administered in therapeutically effective amounts to provide a SVR (for example, SVR12 or SVR24) after the completion of the treatment. The patients may be treatment naïve patients or treatment experienced patients. The treatment duration can be no more than 12 weeks, including but not limited to, no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, no more than 7 weeks, no more than 6 weeks, no more than 5 weeks, no more than 4 weeks, or no more than 3 weeks, e.g., the duration being 12 weeks, or the duration being 8 weeks.

[0060] In some embodiments, the present invention features methods for treating patients with HCV genotype 6 infection. The methods comprise administering to such a patient a combination of at least 2 DAAs for no more than 12 weeks (e.g., the duration being 12 weeks), such as no more than 8 weeks (e.g., the duration being 8 weeks), wherein the treatment does not include administration of either interferon or ribavirin, and said at least 2 DAAs comprise Compound 1 and Compound 2. Compound 1 and Compound 2 can be administered in therapeutically effective amounts to provide a SVR (for example, SVR12 or SVR24) after the completion of the treatment. The patients may be treatment naïve patients or treatment experienced patients. The treatment duration can be no more than 12 weeks, including but not limited to, no more than 11 weeks, no more than 10 weeks, no more than 9 weeks, but preferably no more than 8 weeks, no more than 7 weeks, no more than 6 weeks, no more than 5 weeks, no more than 4 weeks, or no more than 3 weeks, e.g., the duration being 12 weeks, or the duration being 8 weeks.

[0061] It will be understood that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination, and the severity of the disease undergoing therapy.

[0062] In any method described herein, Compound 1 and Compound 2 may be co-formulated in a single dosage form. Non-limiting examples of suitable dosage forms include liquid or solid dosage forms. Preferably, Compound 1 and Compound 2 are formulated in a single solid dosage form in which at least one of the DAAs is in an amorphous form, or highly preferably molecularly dispersed, in a matrix which comprises a pharmaceutically acceptable water-soluble polymer and a pharmaceutically acceptable surfactant. The other DAAs can also be in an amorphous form or molecularly dispersed in the matrix, or formulated in different form(s) (e.g., in a crystalline form). More preferably, each of the two DAAs is in an amorphous form, or highly preferably molecularly dispersed, in a matrix which comprises a pharmaceutically acceptable water-soluble polymer and a pharmaceutically acceptable surfactant.

[0063] In any method described herein, the patient being treated can be a treatment-naïve patient.

[0064] In any method described herein, the patient being treated can be an interferon non-responder.

[0065] In any method described herein, the patient being treated can be an interferon null-responder.

[0066] In any method described herein, the patient being treated can be without cirrhosis.

[0067] In any method described herein, the patient being treated can be a cirrhotic patient.

[0068] In any method described herein, the patient being treated can be a patient with compensated cirrhosis.

[0069] The foregoing description of the present invention provides illustration and description, but is not intended to be exhaustive or to limit the invention to the precise one disclosed. Modifications and variations are possible in light of the above teachings or may be acquired from practice of the invention. Thus, it is noted that the scope of the invention is defined by the claims and their equivalents.

WHAT IS CLAIMED IS:

1. A compound of any formula described hereinabove, or a pharmaceutically acceptable salt thereof or a prodrug thereof.
2. A method for treating HCV, comprising administering a compound, salt or prodrug of claim 1 to an HCV patient.

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2016/018317

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D403/04 C07F9/06 A61K31/513 A61P31/14
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D C07F

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)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2012/075140 A1 (PHARMASSET INC [US]; DU JINFA [US]) 7 June 2012 (2012-06-07) claims 1,2,40,43; examples 3,6,25,27; tables 1-5; compounds 36,48,115,117,136	1,2
A	CHANG HYUN OH ET AL: "Design and Synthesis of Novel Carbocyclic Versions of 2'-spirocyclopropyl Ribonucleosides as Potent Anti-HCV Agents", NUCLEOSIDES, NUCLEOTIDES AND NUCLEIC ACIDS., vol. 30, no. 6, 2011, pages 423-439, XP055265992, ISSN: 1525-7770, DOI: 10.1080/15257770.2011.587490 the whole document scheme 2; table 1; compound 19	1,2

☒ 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

19 April 2016

Date of mailing of the international search report

06/05/2016

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Ladenburger, Claude

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2016/018317

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DANG QUN ET AL: "Syntheses of nucleosides with 2'-spirolactam and 2'-spiropyrrolidine moieties as potential inhibitors of hepatitis C virus NS5B polymerase", TETRAHEDRON LETTERS, vol. 55, no. 28, 2014, pages 3813-3816, XP028855202, ISSN: 0040-4039, DOI: 10.1016/J.TETLET.2014.05.051 the whole document scheme 5; figure 3; compound 21 -----	1,2

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2016/018317

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2012075140 A1	07-06-2012	AR 084044 A1	17-04-2013
		AU 2011336632 A1	02-05-2013
		CA 2818853 A1	07-06-2012
		EP 2646453 A1	09-10-2013
		JP 2013544286 A	12-12-2013
		TW 201242974 A	01-11-2012
		US 2012142626 A1	07-06-2012
		US 2015018300 A1	15-01-2015
		WO 2012075140 A1	07-06-2012
