(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 November 2016 (17.11.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/182934 A1

(51) International Patent Classification:
A61K 31/7115 (2006.01) *A61K 31/7125* (2006.01)
A61K 31/712 (2006.01)

(21) International Application Number:
PCT/US2016/031281

(22) International Filing Date:
6 May 2016 (06.05.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/158,949 8 May 2015 (08.05.2015) US

(71) Applicant: **ABBVIE INC.** [US/US]; 1 North Waukegan Road, North Chicago, Illinois 60064 (US).

(72) Inventors: **CHEN, Hui-Ju J.**; 4 Crow's Nest Court, Grayslake, Illinois 60030 (US). **CHEMBURKAR, Sanjay**; 509 Prescott Lane, Gurnee, Illinois 60031 (US). **DEGOEY, David A.**; 8649 226th Avenue, Salem, Wisconsin 53168 (US). **KALTHOD, Vikram**; 1401 Sheridan Road, North Chicago, Illinois 60064 (US). **KRUEGER, Allan C.**; 7260 Presidential Drive, Gurnee, Illinois 60031 (US). **RANDOLPH, John T.**; 304 Broadway Avenue, Libertyville, Illinois 60048 (US). **WAGNER, Rolf**; 42530 Sheridan Oaks, Antioch, Illinois 60002 (US).

(74) Agents: **ZHANG, Xu** et al.; AbbVie Inc. 1 North Waukegan Road, AP-23-2/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))*

WO 2016/182934 A1

(54) Title: ANTI-VIRAL COMPOUNDS

(57) Abstract: The present invention features compounds effective in inhibiting active against Hepatitis C virus ("HCV") polymerase. The invention also features processes of making such compounds, compositions comprising such compounds, and methods of using such compounds to treat HCV infection.

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.

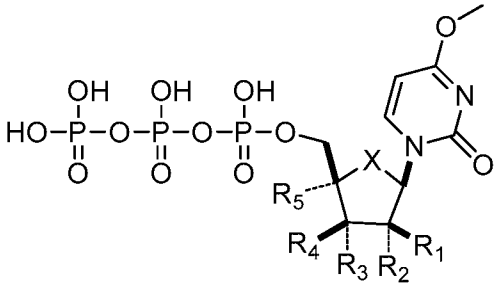
BACKGROUND OF THE INVENTION

[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_A, and pharmaceutically acceptable salts thereof,



I_A

and wherein for each compound of Formula I_A, X, R_1, R_2, R_3, R_4 and R_5 are as defined in Table 1:

Table 1.

Compound No.	X	R_1	R_2	R_3	R_4	R_5
1	O	Cl	F	OH	H	H
2	O	Cl	F	OH	H	F
3	O	F	F	OH	OH	H
4	O	F	F	OH	OH	F
5	O	F	F	OH	OH	D
6	C=CH_2	F	F	OH	OH	H
7	C=CH_2	F	F	OH	OH	F
8	C=CH_2	F	F	OH	OH	D
9	O	Cl	F	OH	OH	H
10	O	Cl	F	OH	OH	F
11	O	Cl	Cl	OH	H	H
12	O	Cl	Cl	OH	H	F
13	O	Cl	Cl	OH	OH	H
14	O	Cl	Cl	OH	OH	F
15	C=CH_2	Cl	F	OH	H	H
16	C=CH_2	Cl	F	OH	H	F
17	C=CH_2	Cl	F	OH	OH	H
18	C=CH_2	Cl	F	OH	OH	F
19	C=CH_2	Cl	Cl	OH	H	H
20	C=CH_2	Cl	Cl	OH	H	F
21	C=CH_2	Cl	Cl	OH	OH	H
22	C=CH_2	Cl	Cl	OH	OH	F
23	C=CH_2	CH_3	F	OH	H	H
24	C=CH_2	CH_3	F	OH	H	F
25	C=CH_2	CH_3	F	OH	OH	H
26	C=CH_2	CH_3	F	OH	OH	F
27	C=CH_2	CH_3	OH	OH	H	H
28	C=CH_2	CH_3	OH	OH	H	F
29	C=CH_2	CH_3	OH	OH	OH	H
30	C=CH_2	CH_3	OH	OH	OH	F
31	O	CH_2OH	F	OH	H	H
32	O	CH_2OH	F	OH	H	F
33	O	CH_2OH	F	OH	OH	H
34	O	CH_2OH	F	OH	OH	F
35	O	CH_2OH	CN	OH	H	H
36	O	CH_2OH	CN	OH	H	F
37	O	CH_2OH	CN	OH	OH	H

Compound No.	X	R_1	R_2	R_3	R_4	R_5
38	O	CH_2OH	CN	OH	OH	F
39	O	CH_2OH	H	OH	H	H
40	O	CH_2OH	H	OH	H	F
41	O	CH_2OH	H	OH	OH	H
42	O	CH_2OH	H	OH	OH	F
43	O	CH_2OH	OH	OH	H	H
44	O	CH_2OH	OH	OH	H	F
45	O	CH_2OH	OH	OH	OH	H
46	O	CH_2OH	OH	OH	OH	F
47	O	F	CH_2OH	OH	H	H
48	O	F	CH_2OH	OH	H	F
49	O	F	CH_2OH	OH	OH	H
50	O	F	CH_2OH	OH	OH	F
51	O	CN	CH_2OH	OH	H	H
52	O	CN	CH_2OH	OH	H	F
53	O	CN	CH_2OH	OH	OH	H
54	O	CN	CH_2OH	OH	OH	F
55	O	H	CH_2OH	OH	H	H
56	O	H	CH_2OH	OH	H	F
57	O	H	CH_2OH	OH	OH	H
58	O	H	CH_2OH	OH	OH	F
59	O	OH	CH_2OH	OH	H	H
60	O	OH	CH_2OH	OH	H	F
61	O	OH	CH_2OH	OH	OH	H
62	O	OH	CH_2OH	OH	OH	F
63	$C=CH_2$	CH_2OH	F	OH	H	H
64	$C=CH_2$	CH_2OH	F	OH	H	F
65	$C=CH_2$	CH_2OH	F	OH	OH	H
66	$C=CH_2$	CH_2OH	F	OH	OH	F
67	$C=CH_2$	CH_2OH	CN	OH	H	H
68	$C=CH_2$	CH_2OH	CN	OH	H	F
69	$C=CH_2$	CH_2OH	CN	OH	OH	H
70	$C=CH_2$	CH_2OH	CN	OH	OH	F
71	$C=CH_2$	CH_2OH	H	OH	H	H
72	$C=CH_2$	CH_2OH	H	OH	H	F
73	$C=CH_2$	CH_2OH	H	OH	OH	H
74	$C=CH_2$	CH_2OH	H	OH	OH	F
75	$C=CH_2$	CH_2OH	OH	OH	H	H

Compound No.	X	R_1	R_2	R_3	R_4	R_5
76	C=CH_2	CH_2OH	OH	OH	H	F
77	C=CH_2	CH_2OH	OH	OH	OH	H
78	C=CH_2	CH_2OH	OH	OH	OH	F
79	C=CH_2	F	CH_2OH	OH	H	H
80	C=CH_2	F	CH_2OH	OH	H	F
81	C=CH_2	F	CH_2OH	OH	OH	H
82	C=CH_2	F	CH_2OH	OH	OH	F
83	C=CH_2	CN	CH_2OH	OH	H	H
84	C=CH_2	CN	CH_2OH	OH	H	F
85	C=CH_2	CN	CH_2OH	OH	OH	H
86	C=CH_2	CN	CH_2OH	OH	OH	F
87	C=CH_2	H	CH_2OH	OH	H	H
88	C=CH_2	H	CH_2OH	OH	H	F
89	C=CH_2	H	CH_2OH	OH	OH	H
90	C=CH_2	H	CH_2OH	OH	OH	F
91	C=CH_2	OH	CH_2OH	OH	H	H
92	C=CH_2	OH	CH_2OH	OH	H	F
93	C=CH_2	OH	CH_2OH	OH	OH	H
94	C=CH_2	OH	CH_2OH	OH	OH	F
95	O	H	NHC(O)NH		H	H
96	O	H	NHC(O)NH		H	F
97	O	H	NHC(S)NH		H	H
98	O	H	NHC(S)NH		H	F
99	C=CH_2	H	NHC(O)NH		H	H
100	C=CH_2	H	NHC(O)NH		H	F
101	C=CH_2	H	NHC(S)NH		H	H
102	C=CH_2	H	NHC(S)NH		H	F
103	O	CH_3	NHC(O)NH		H	H
104	O	CH_3	NHC(O)NH		H	F
105	O	CH_3	NHC(S)NH		H	H
106	O	CH_3	NHC(S)NH		H	F
107	C=CH_2	CH_3	NHC(O)NH		H	H
108	C=CH_2	CH_3	NHC(O)NH		H	F
109	C=CH_2	CH_3	NHC(S)NH		H	H
110	C=CH_2	CH_3	NHC(S)NH		H	F

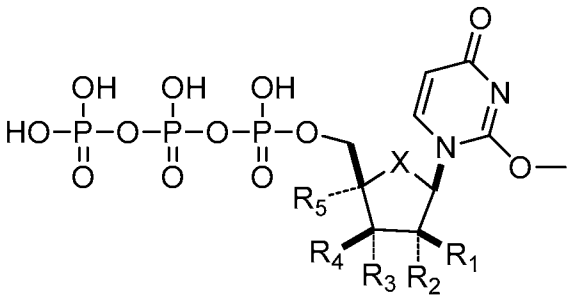
Compound No.	X	R_1	R_2	R_3	R_4	R_5
111	O	CH_2OH	NHC(O)NH		H	H
112	O	CH_2OH	NHC(O)NH		H	F
113	O	CH_2OH	NHC(S)NH		H	H
114	O	CH_2OH	NHC(S)NH		H	F
115	$C=CH_2$	CH_2OH	NHC(O)NH		H	H
116	$C=CH_2$	CH_2OH	NHC(O)NH		H	F
117	$C=CH_2$	CH_2OH	NHC(S)NH		H	H
118	$C=CH_2$	CH_2OH	NHC(S)NH		H	F
119	O	F	Cl	OH	H	H
120	O	F	Cl	OH	H	F
121	O	F	Cl	OH	OH	H
122	O	F	Cl	OH	OH	F
123	$C=CH_2$	F	Cl	OH	H	H
124	$C=CH_2$	F	Cl	OH	H	F
125	$C=CH_2$	F	Cl	OH	OH	H
126	$C=CH_2$	F	Cl	OH	OH	F
127	O	Cl	F	OH	H	D
128	O	Cl	F	OH	H	D
129	O	Cl	F	OH	OH	D
130	O	Cl	F	OH	OH	D
131	O	Cl	Cl	OH	H	D
132	O	Cl	Cl	OH	H	D
133	O	Cl	Cl	OH	OH	D
134	O	Cl	Cl	OH	OH	D
135	$C=CH_2$	Cl	F	OH	H	D
136	$C=CH_2$	Cl	F	OH	H	D
137	$C=CH_2$	Cl	F	OH	OH	D
138	$C=CH_2$	Cl	F	OH	OH	D
139	$C=CH_2$	Cl	Cl	OH	H	D
140	$C=CH_2$	Cl	Cl	OH	H	D
141	$C=CH_2$	Cl	Cl	OH	OH	D
142	$C=CH_2$	Cl	Cl	OH	OH	D
143	$C=CH_2$	CH_3	F	OH	H	D
144	$C=CH_2$	CH_3	F	OH	H	D
145	$C=CH_2$	CH_3	F	OH	OH	D
146	$C=CH_2$	CH_3	F	OH	OH	D
147	$C=CH_2$	CH_3	OH	OH	H	D

Compound No.	X	R_1	R_2	R_3	R_4	R_5
148	$C=CH_2$	CH_3	OH	OH	H	D
149	$C=CH_2$	CH_3	OH	OH	OH	D
150	$C=CH_2$	CH_3	OH	OH	OH	D
151	O	CH_2OH	F	OH	H	D
152	O	CH_2OH	F	OH	H	D
153	O	CH_2OH	F	OH	OH	D
154	O	CH_2OH	F	OH	OH	D
155	O	CH_2OH	CN	OH	H	D
156	O	CH_2OH	CN	OH	H	D
157	O	CH_2OH	CN	OH	OH	D
158	O	CH_2OH	CN	OH	OH	D
159	O	CH_2OH	H	OH	H	D
160	O	CH_2OH	H	OH	H	D
161	O	CH_2OH	H	OH	OH	D
162	O	CH_2OH	H	OH	OH	D
163	O	CH_2OH	OH	OH	H	D
164	O	CH_2OH	OH	OH	H	D
165	O	CH_2OH	OH	OH	OH	D
166	O	CH_2OH	OH	OH	OH	D
167	O	F	CH_2OH	OH	H	D
168	O	F	CH_2OH	OH	H	D
169	O	F	CH_2OH	OH	OH	D
170	O	F	CH_2OH	OH	OH	D
171	O	CN	CH_2OH	OH	H	D
172	O	CN	CH_2OH	OH	H	D
173	O	CN	CH_2OH	OH	OH	D
174	O	CN	CH_2OH	OH	OH	D
175	O	H	CH_2OH	OH	H	D
176	O	H	CH_2OH	OH	H	D
177	O	H	CH_2OH	OH	OH	D
178	O	H	CH_2OH	OH	OH	D
179	O	OH	CH_2OH	OH	H	D
180	O	OH	CH_2OH	OH	H	D
181	O	OH	CH_2OH	OH	OH	D
182	O	OH	CH_2OH	OH	OH	D
183	$C=CH_2$	CH_2OH	F	OH	H	D
184	$C=CH_2$	CH_2OH	F	OH	H	D
185	$C=CH_2$	CH_2OH	F	OH	OH	D
186	$C=CH_2$	CH_2OH	F	OH	OH	D

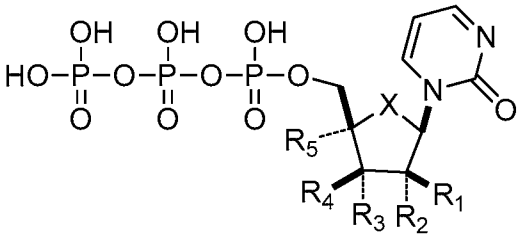
Compound No.	X	R_1	R_2	R_3	R_4	R_5
187	C=CH_2	CH_2OH	CN	OH	H	D
188	C=CH_2	CH_2OH	CN	OH	H	D
189	C=CH_2	CH_2OH	CN	OH	OH	D
190	C=CH_2	CH_2OH	CN	OH	OH	D
191	C=CH_2	CH_2OH	H	OH	H	D
192	C=CH_2	CH_2OH	H	OH	H	D
193	C=CH_2	CH_2OH	H	OH	OH	D
194	C=CH_2	CH_2OH	H	OH	OH	D
195	C=CH_2	CH_2OH	OH	OH	H	D
196	C=CH_2	CH_2OH	OH	OH	H	D
197	C=CH_2	CH_2OH	OH	OH	OH	D
198	C=CH_2	CH_2OH	OH	OH	OH	D
199	C=CH_2	F	CH_2OH	OH	H	D
200	C=CH_2	F	CH_2OH	OH	H	D
201	C=CH_2	F	CH_2OH	OH	OH	D
202	C=CH_2	F	CH_2OH	OH	OH	D
203	C=CH_2	CN	CH_2OH	OH	H	D
204	C=CH_2	CN	CH_2OH	OH	H	D
205	C=CH_2	CN	CH_2OH	OH	OH	D
206	C=CH_2	CN	CH_2OH	OH	OH	D
207	C=CH_2	H	CH_2OH	OH	H	D
208	C=CH_2	H	CH_2OH	OH	H	D
209	C=CH_2	H	CH_2OH	OH	OH	D
210	C=CH_2	H	CH_2OH	OH	OH	D
211	C=CH_2	OH	CH_2OH	OH	H	D
212	C=CH_2	OH	CH_2OH	OH	H	D
213	C=CH_2	OH	CH_2OH	OH	OH	D
214	C=CH_2	OH	CH_2OH	OH	OH	D
215	O	CH_3	OH	OH	H	H

[0005] For Compound Nos. 95-118, R_2 and R_3, taken together with the atoms to which they are attached, form a ring, as indicated in Table 1. As shown below, each compound number in Table 1 can represent compounds of different formulas but with the same X, R_1, R_2, R_3, R_4 and R_5 moieties.

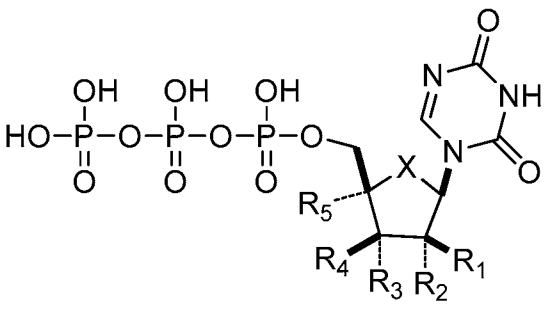
[0006] In another aspect, the present invention features compounds having Formula I_B, I_C, I_D, I_E, I_F or I_G, and pharmaceutically acceptable salts thereof, as well as prodrugs thereof, wherein for each compound of Formula I_B, X, R_1, R_2, R_3, R_4 and R_5 are as defined in Table 1; and likewise, for each compound of Formula I_C, I_D, I_E, I_F or I_G, X, R_1, R_2, R_3, R_4 and R_5 are as defined in Table 1.



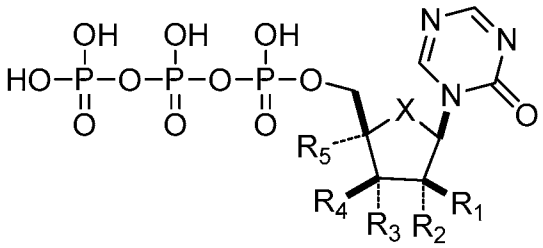
Formula I_B



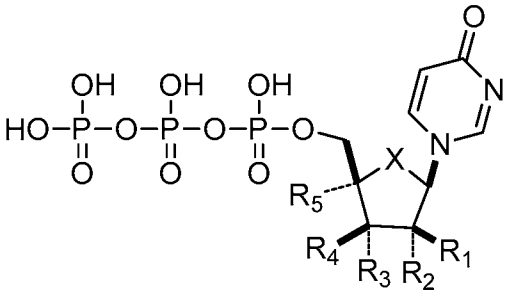
Formula I_C



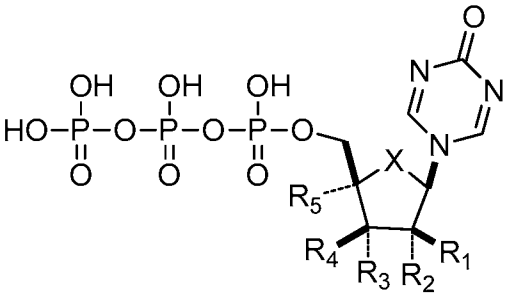
Formula I_D



Formula I_E



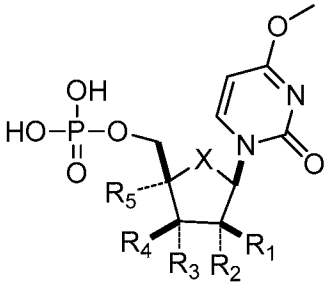
Formula I_F



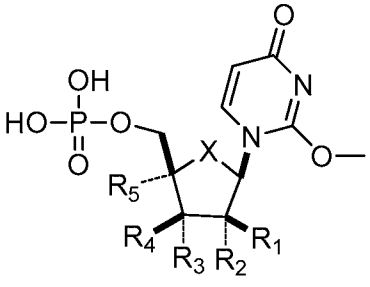
Formula I_G

[0007] As used herein, a compound of Formula I refers to a compound having Formula I_A, I_B, I_C, I_D, I_E, I_F or I_G as defined herein.

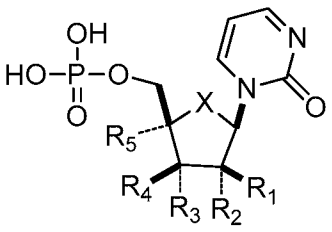
[0008] In another aspect, the present invention features compounds having Formula II_A, II_B, II_C, II_D, II_E, II_F or II_G, and pharmaceutically acceptable salts thereof, as well as prodrugs thereof,



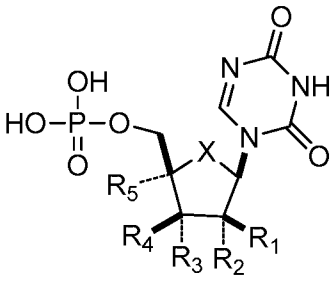
Formula II_A



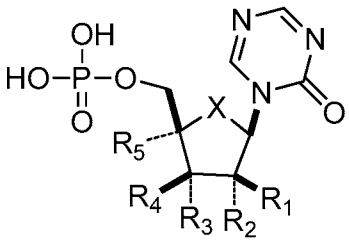
Formula II_B



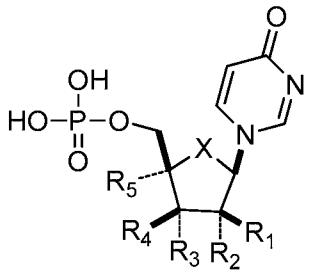
Formula II_C



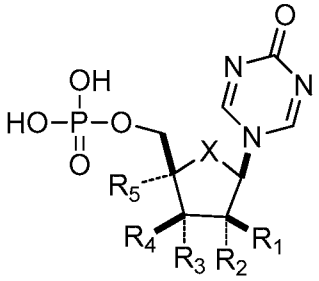
Formula II_D



Formula II_E



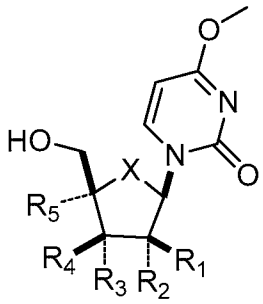
Formula II_F



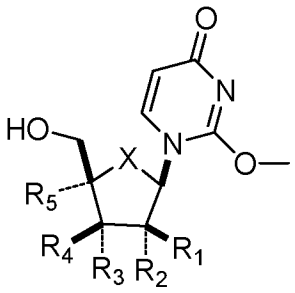
Formula II_G

wherein for each compound of Formula II_A, II_B, II_C, II_D, II_E, II_F or II_G, X, R_1, R_2, R_3, R_4 and R_5 are as defined in Table 1. As used herein, a compound of Formula II refers to a compound having Formula II_A, II_B, II_C, II_D, II_E, II_F or II_G as defined herein.

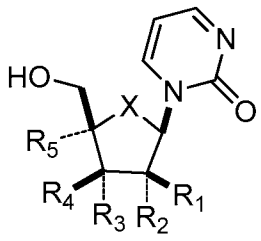
[0009] In still another aspect, the present invention features compounds having Formula III_A, III_B, III_C, III_D, III_E, III_F or III_G, and pharmaceutically acceptable salts thereof, as well as prodrugs thereof,



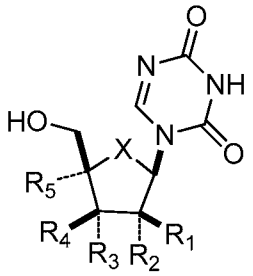
Formula III_A



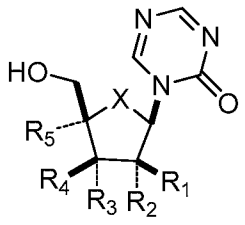
Formula III_B



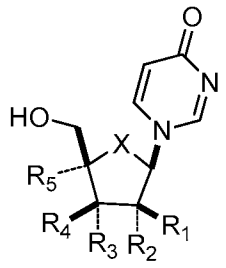
Formula III_C



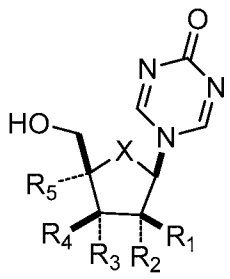
Formula III_D



Formula III_E



Formula III_F

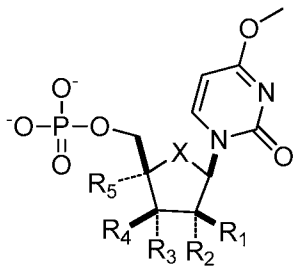


Formula III_G

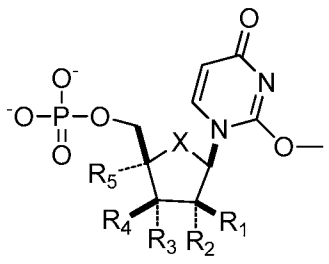
wherein for each compound of Formula III_A, III_B, III_C, III_D, III_E, III_F or III_G, X, R_1, R_2, R_3, R_4 and R_5 are as defined in Table 1. As used herein, a compound of Formula III refers to a compound having Formula III_A, III_B, III_C, III_D, III_E, III_F or III_G as defined herein.

[0010] In still another aspect, the present invention features phosphoramidate prodrugs of compounds having Formula III_A, III_B, III_C, III_D, III_E, III_F or III_G as described immediately hereinabove, wherein for each compound of Formula III_A, III_B, III_C, III_D, III_E, III_F or III_G, X, R_1, R_2, R_3, R_4 and R_5 are as defined in Table 1. As used herein, a compound of Formula III' refers to a phosphoramidate prodrug of a compound having III_A, III_B, III_C, III_D, III_E, III_F or III_G as defined herein.

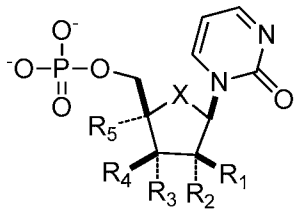
[0011] In yet another aspect, the present invention features compounds having Formula IV_A, IV_B, IV_C, IV_D, IV_E, IV_F or IV_G,



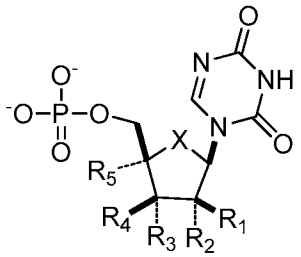
Formula IV_A



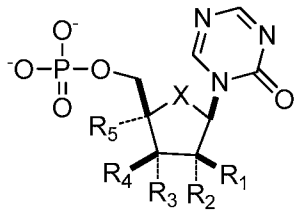
Formula IV_B



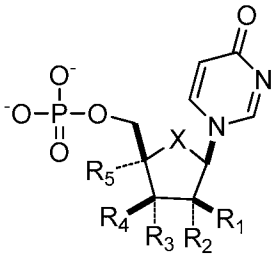
Formula IV_C



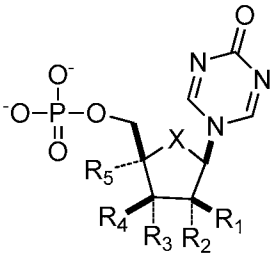
Formula IV_D



Formula IV_E



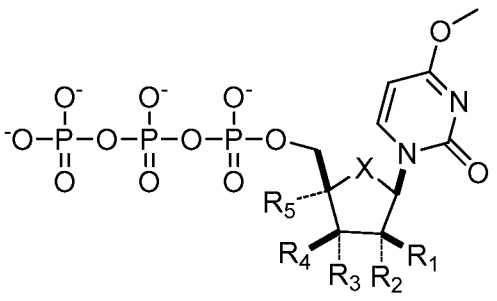
Formula IV_F



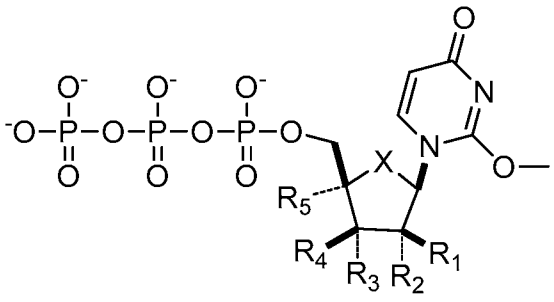
Formula IV_G

wherein for each compound of Formula IV_A, IV_B, IV_C, IV_D, IV_E, IV_F or IV_G, X, R_1, R_2, R_3, R_4 and R_5 are as defined in Table 1. As used herein, a compound of Formula IV refers to a compound having Formula IV_A, IV_B, IV_C, IV_D, IV_E, IV_F or IV_G as defined herein.

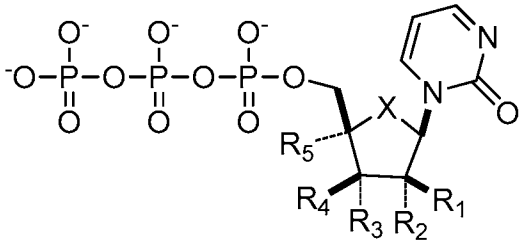
[0012] In yet another aspect, the present invention features compounds having Formula V_A, V_B, V_C, V_D, V_E, V_F or V_G,



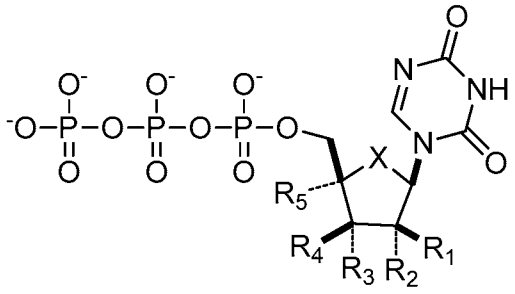
Formula V_A



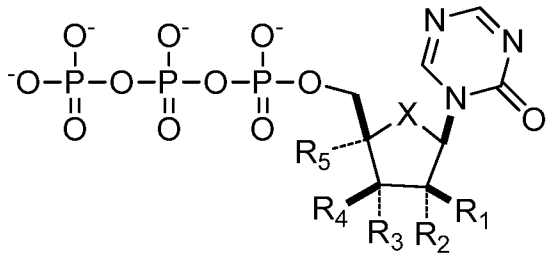
Formula V_B



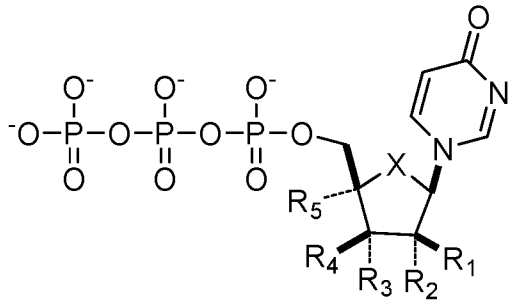
Formula V_C



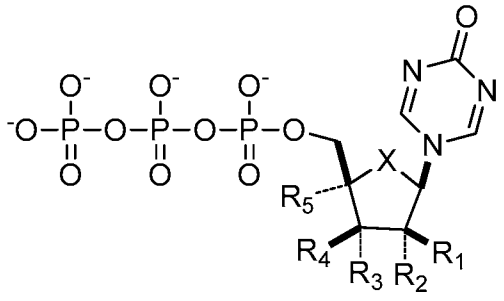
Formula V_D



Formula V_E



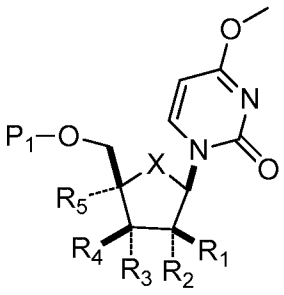
Formula V_F



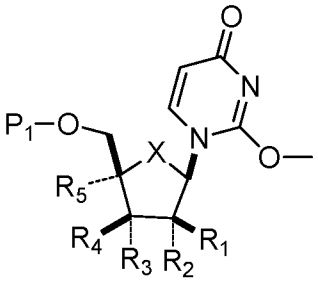
Formula V_G

wherein for each compound of Formula V_A, V_B, V_C, V_D, V_E, V_F or V_G, X, R_1, R_2, R_3, R_4 and R_5 are as defined in Table 1. As used herein, a compound of Formula V refers to a compound having Formula V_A, V_B, V_C, V_D, V_E, V_F or V_G as defined herein.

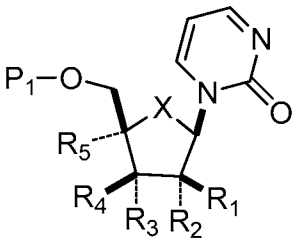
[0013] In yet another aspect, the present invention features compounds having Formula VI_A, VI_B, VI_C, VI_D, VI_E, VI_F or VI_G, and pharmaceutically acceptable salts thereof,



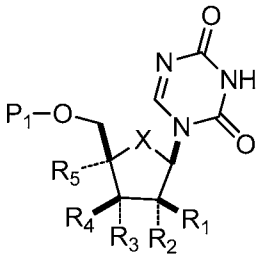
Formula VI_A



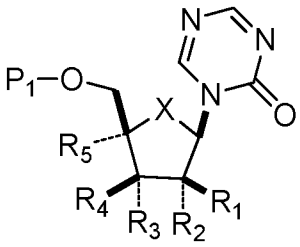
Formula VI_B



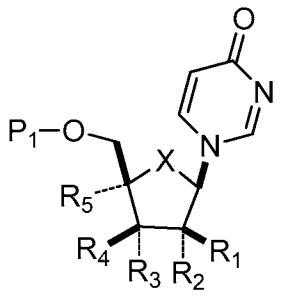
Formula VI_C



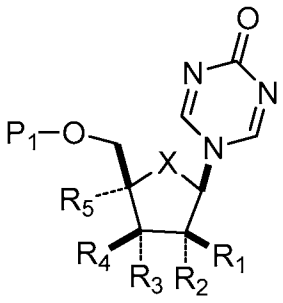
Formula VI_D



Formula VI_E



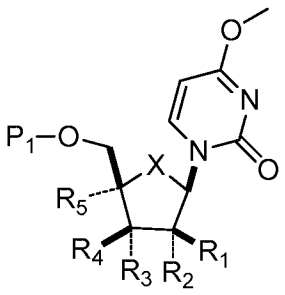
Formula VI_F



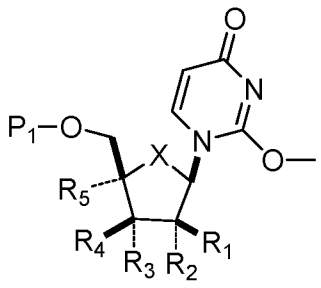
Formula VI_G

wherein for each compound of Formula VI_A, VI_B, VI_C, VI_D, VI_E, VI_F or VI_G, X, R_1, R_2, R_3, R_4 and R_5 are as defined in Table 1, and wherein P_1 is $(HO)_2P(O)$-O-P(O)(OH)-. As used herein, a compound of Formula VI refers to a compound Formula VI_A, VI_B, VI_C, VI_D, VI_E, VI_F or VI_G having as defined herein.

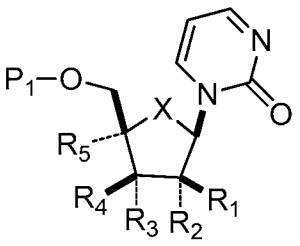
[0014] In yet another aspect, the present invention features compounds having Formula VI'_A, VI'_B, VI'_C, VI'_D, VI'_E, VI'_F or VI'_G, and pharmaceutically acceptable salts thereof,



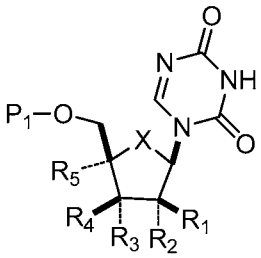
Formula VI'_A



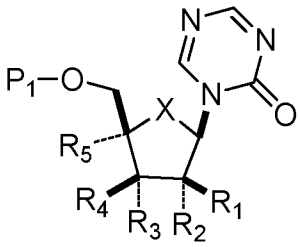
Formula VI'_B



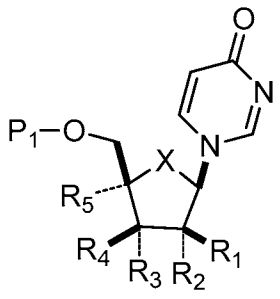
Formula VI'$_C$



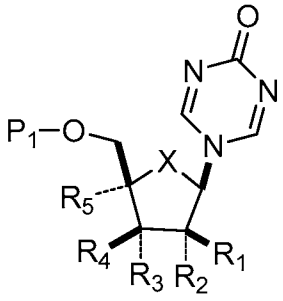
Formula VI'$_D$



Formula VI'$_E$



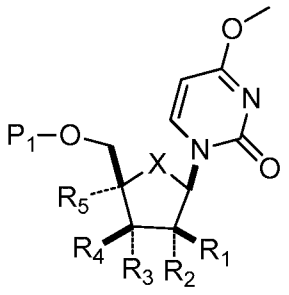
Formula VI'$_F$



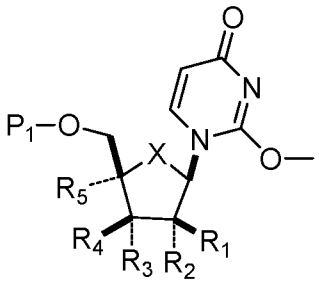
Formula VI'$_G$

wherein for each compound of Formula VI'$_A$, VI'$_B$, VI'$_C$, VI'$_D$, VI'$_E$, VI'$_F$ or VI'$_G$, X, R_1, R_2, R_3, R_4 and R_5 are as defined in Table 1, and wherein P_1 is $(O^-)_2P(O)$-O-P(O)(O^-)-. As used herein, a compound of Formula VI' refers to a compound Formula VI'$_A$, VI'$_B$, VI'$_C$, VI'$_D$, VI'$_E$, VI'$_F$ or VI'$_G$ having as defined herein.

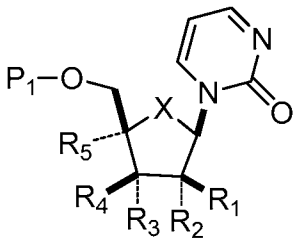
[0015] In yet another aspect, the present invention features compounds having Formula VI''$_A$, VI''$_B$, VI''$_C$, VI''$_D$, VI''$_E$, VI''$_F$ or VI''$_G$, and pharmaceutically acceptable salts thereof,



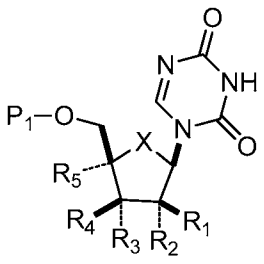
Formula VI''$_A$



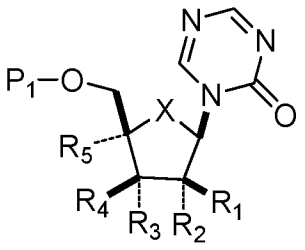
Formula VI''$_B$



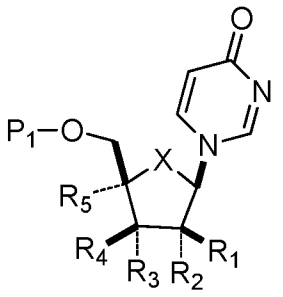
Formula VI''$_C$



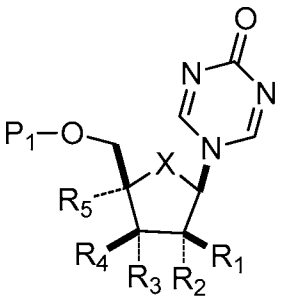
Formula VI''$_D$



Formula VI''$_E$



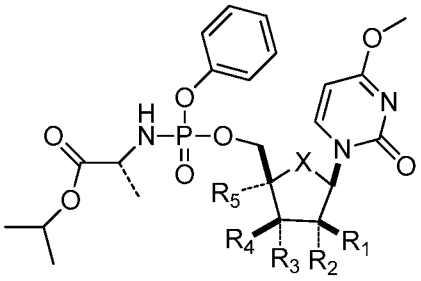
Formula VI''$_F$



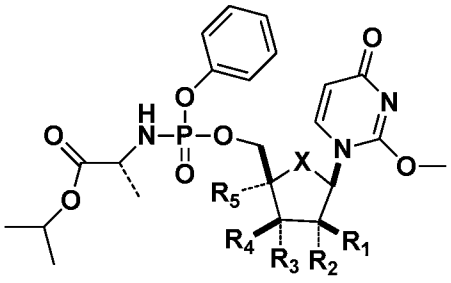
Formula VI''$_G$

wherein for each compound of Formula VI''$_A$, VI''$_B$, VI''$_C$, VI''$_D$, VI''$_E$, VI''$_F$ or VI''$_G$, X, R_1, R_2, R_3, R_4 and R_5 are as defined in Table 1, and wherein P_1 is a protected monophosphate prodrug substitution. As used herein, a compound of Formula VI'' refers to a compound Formula VI''$_A$, VI''$_B$, VI''$_C$, VI''$_D$, VI''$_E$, VI''$_F$ or VI''$_G$ having as defined herein.

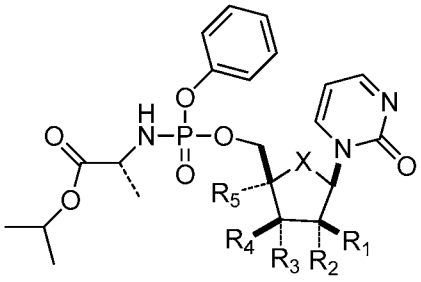
[0016] In a further aspect, the present invention features compounds having Formula VII_A, VII_B, VII_C, VII_D, VII_E, VII_F or VII_G,, and pharmaceutically acceptable salts thereof,



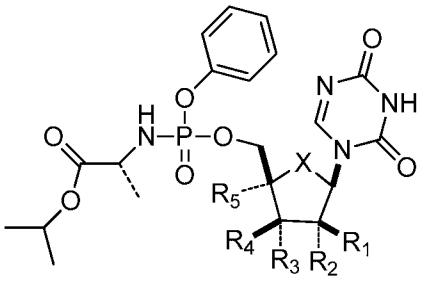
Formula VII_A



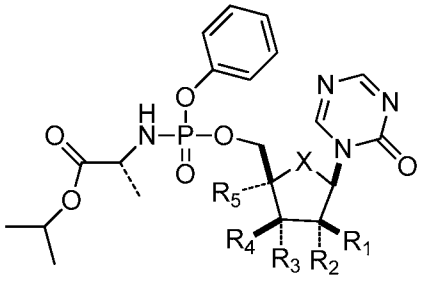
Formula VII_B



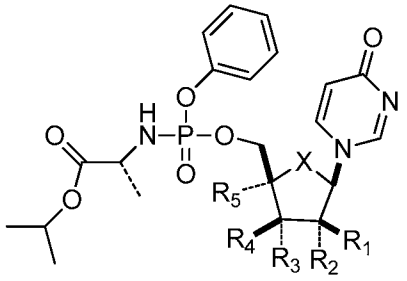
Formula VII_C



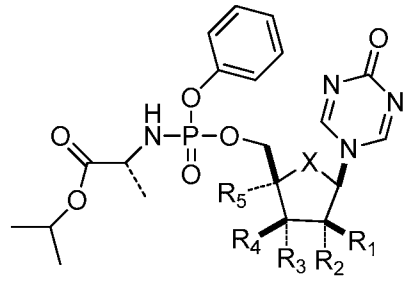
Formula VII_D



Formula VII_E



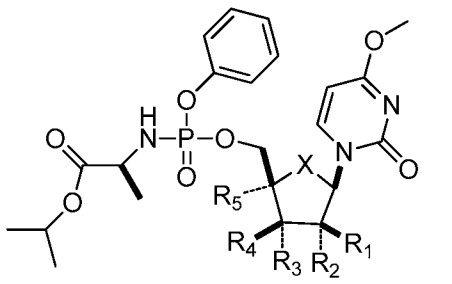
Formula VII_F



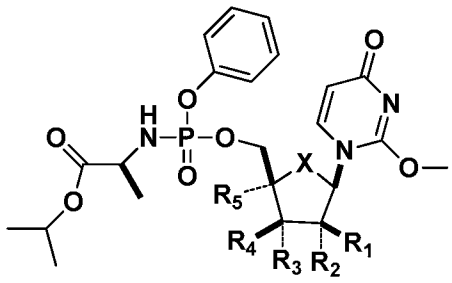
Formula VII_G

wherein for each compound of Formula VII_A, VII_B, VII_C, VII_D, VII_E, VII_F or VII_G, X, R_1, R_2, R_3, R_4 and R_5 are as defined in Table 1. As used herein, a compound of Formula VII refers to a compound having Formula VII_A, VII_B, VII_C, VII_D, VII_E, VII_F or VII_G as defined herein.

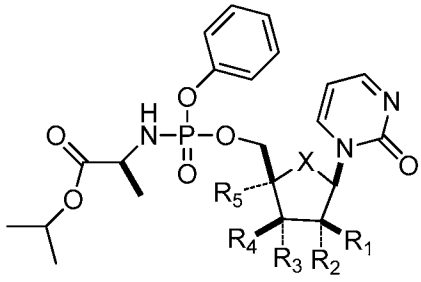
[0017] In a further aspect, the present invention features compounds having Formula $VIII_A$, $VIII_B$, $VIII_C$, $VIII_D$, $VIII_E$, $VIII_F$ or $VIII_G$, and pharmaceutically acceptable salts thereof,



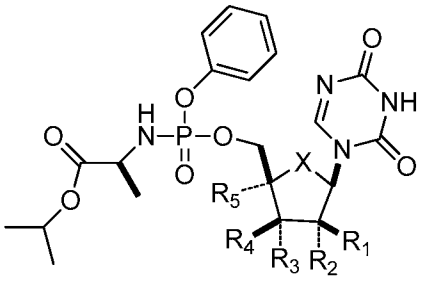
Formula $VIII_A$



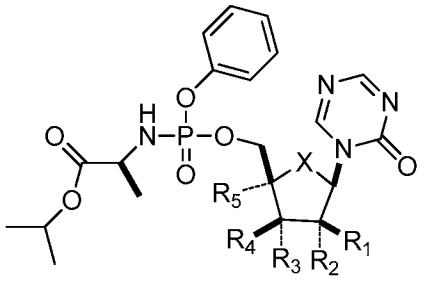
Formula $VIII_B$



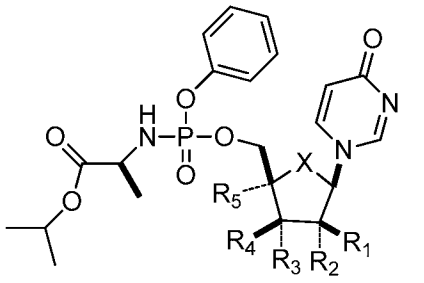
Formula $VIII_C$



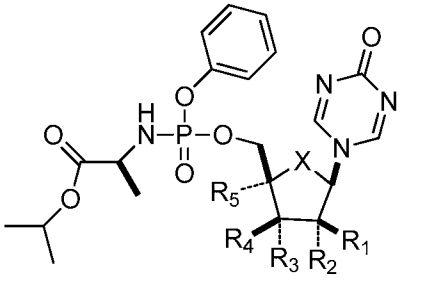
Formula $VIII_D$



Formula $VIII_E$



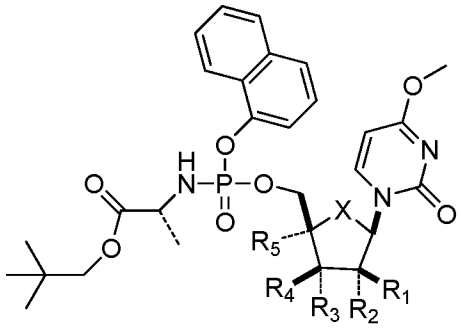
Formula $VIII_F$



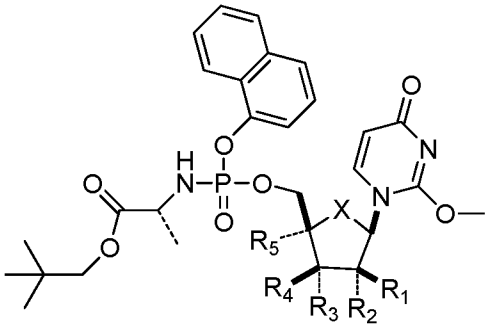
Formula $VIII_G$

wherein for each compound of Formula $VIII_A$, $VIII_B$, $VIII_C$, $VIII_D$, $VIII_E$, $VIII_F$ or $VIII_G$, X, R_1, R_2, R_3, R_4 and R_5 are as defined in Table 1. As used herein, a compound of Formula VIII refers to a compound having Formula $VIII_A$, $VIII_B$, $VIII_C$, $VIII_D$, $VIII_E$, $VIII_F$ or $VIII_G$ as defined herein.

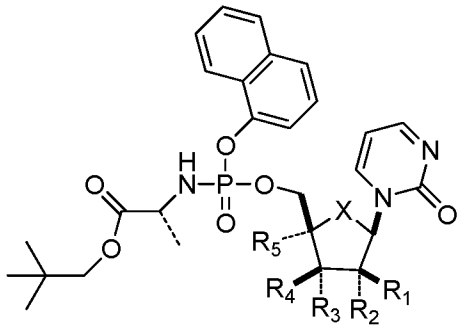
[0018] In a further aspect, the present invention features compounds having Formula IX_A, IX_B, IX_C, IX_D, IX_E, IX_F or IX_G, and pharmaceutically acceptable salts thereof,



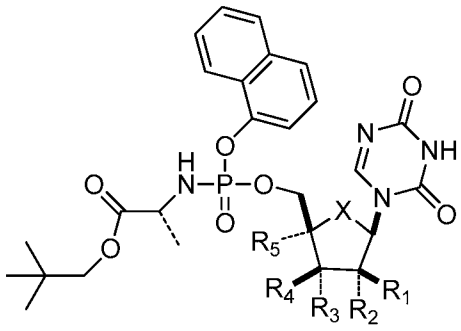
Formula IX_A



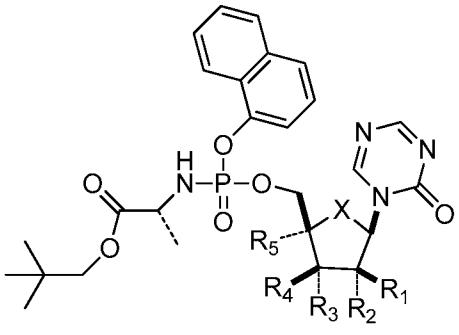
Formula IX_B



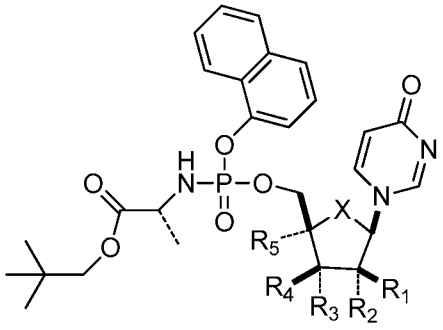
Formula IX_C



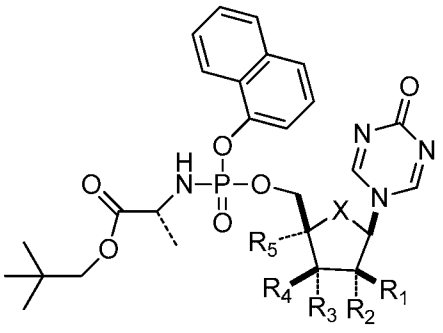
Formula IX_D



Formula IX_E



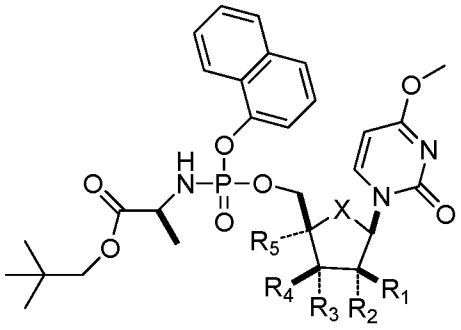
Formula IX_F



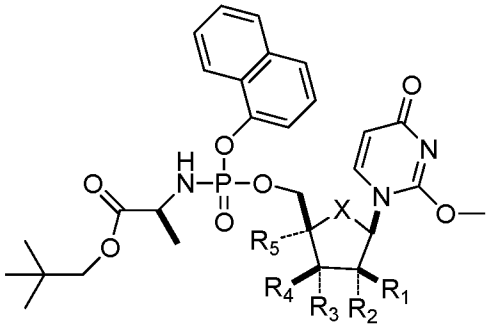
Formula IX_G

wherein for each compound of Formula IX_A, IX_B, IX_C, IX_D, IX_E, IX_F or IX_G, X, R_1, R_2, R_3, R_4 and R_5 are as defined in Table 1. As used herein, a compound of Formula IX refers to a compound having Formula IX_A, IX_B, IX_C, IX_D, IX_E, IX_F or IX_G as defined herein.

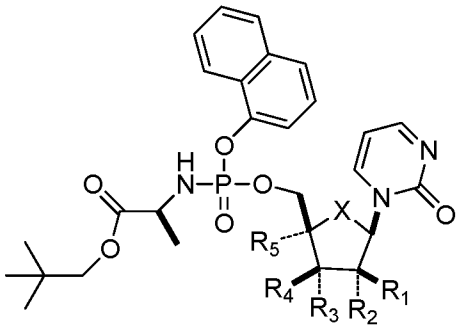
[0019] In a further aspect, the present invention features compounds having Formula A_1, A_2, A_3, A_4, A_5, A_6 or A_7, and pharmaceutically acceptable salts thereof,



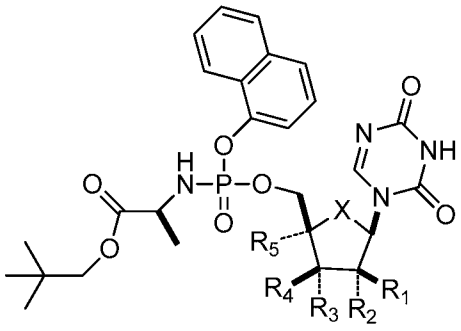
Formula A_1



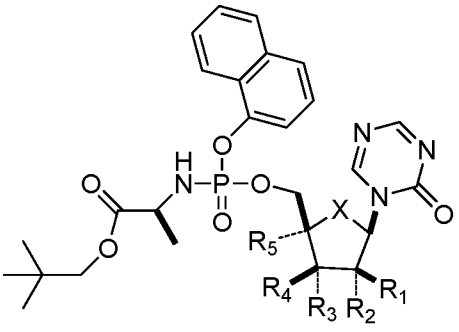
Formula A_2



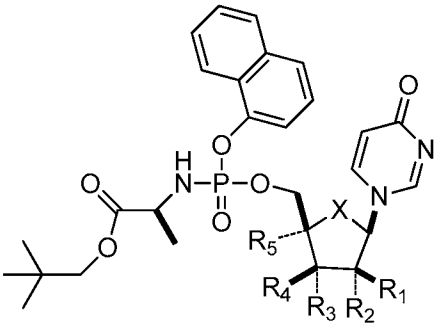
Formula A_3



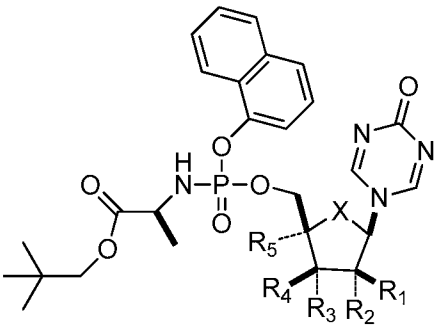
Formula A_4



Formula A_5



Formula A_6



Formula A_7

wherein for each compound of Formula A_1, A_2, A_3, A_4, A_5, A_6 or A_7, X, R_1, R_2, R_3, R_4 and R_5 are as defined in Table 1. As used herein, a compound of Formula A refers to a compound having Formula A_1, A_2, A_3, A_4, A_5, A_6 or A_7 as defined herein.

[0020] In another aspect, the present invention features Compound No. 3 according to Table 1, wherein the compound has Formula I.

[0021] In another aspect, the present invention features Compound No. 3 according to Table 1, wherein the compound has Formula II.

[0022] In another aspect, the present invention features Compound No. 3 according to Table 1, wherein the compound has Formula III.

[0023] In another aspect, the present invention features Compound No. 3 according to Table 1, wherein the compound has Formula III'.

[0024] In another aspect, the present invention features Compound No. 3 according to Table 1, wherein the compound has Formula IV.

[0025] In another aspect, the present invention features Compound No. 3 according to Table 1, wherein the compound has Formula IV'.

[0026] In another aspect, the present invention features Compound No. 3 according to Table 1, wherein the compound has Formula IV''.

[0027] In another aspect, the present invention features Compound No. 3 according to Table 1, wherein the compound has Formula V.

[0028] In another aspect, the present invention features Compound No. 3 according to Table 1, wherein the compound has Formula VI.

[0029] In another aspect, the present invention features Compound No. 3 according to Table 1, wherein the compound has Formula VII.

[0030] In another aspect, the present invention features Compound No. 3 according to Table 1, wherein the compound has Formula VIII.

[0031] In another aspect, the present invention features Compound No. 3 according to Table 1, wherein the compound has Formula IX.

[0032] In another aspect, the present invention features Compound No. 3 according to Table 1, wherein the compound has Formula A.

[0033] In another aspect, the present invention features Compound No. 31 according to Table 1, wherein the compound has Formula I.

[0034] In another aspect, the present invention features Compound No. 31 according to Table 1, wherein the compound has Formula II.

[0035] In another aspect, the present invention features Compound No. 31 according to Table 1, wherein the compound has Formula III.

[0036] In another aspect, the present invention features Compound No. 31 according to Table 1, wherein the compound has Formula III'.

[0037] In another aspect, the present invention features Compound No. 31 according to Table 1, wherein the compound has Formula IV.

[0038] In another aspect, the present invention features Compound No. 31 according to Table 1, wherein the compound has Formula IV'.

[0039] In another aspect, the present invention features Compound No. 31 according to Table 1, wherein the compound has Formula IV''.

[0040] In another aspect, the present invention features Compound No. 31 according to Table 1, wherein the compound has Formula V.

[0041] In another aspect, the present invention features Compound No. 31 according to Table 1, wherein the compound has Formula VI.

[0042] In another aspect, the present invention features Compound No. 31 according to Table 1, wherein the compound has Formula VII.

[0043] In another aspect, the present invention features Compound No. 31 according to Table 1, wherein the compound has Formula VIII.

[0044] In another aspect, the present invention features Compound No. 31 according to Table 1, wherein the compound has Formula IX.

[0045] In another aspect, the present invention features Compound No. 31 according to Table 1, wherein the compound has Formula A.

[0046] In another aspect, the present invention features Compound No. 35 according to Table 1, wherein the compound has Formula I.

[0047] In another aspect, the present invention features Compound No. 35 according to Table 1, wherein the compound has Formula II.

[0048] In another aspect, the present invention features Compound No. 35 according to Table 1, wherein the compound has Formula III.

[0049] In another aspect, the present invention features Compound No. 35 according to Table 1, wherein the compound has Formula III'.

[0050] In another aspect, the present invention features Compound No. 35 according to Table 1, wherein the compound has Formula IV.

[0051] In another aspect, the present invention features Compound No. 35 according to Table 1, wherein the compound has Formula IV'.

[0052] In another aspect, the present invention features Compound No. 35 according to Table 1, wherein the compound has Formula IV''.

[0053] In another aspect, the present invention features Compound No. 35 according to Table 1, wherein the compound has Formula V.

[0054] In another aspect, the present invention features Compound No. 35 according to Table 1, wherein the compound has Formula VI.

[0055] In another aspect, the present invention features Compound No. 35 according to Table 1, wherein the compound has Formula VII.

[0056] In another aspect, the present invention features Compound No. 35 according to Table 1, wherein the compound has Formula VIII.

[0057] In another aspect, the present invention features Compound No. 35 according to Table 1, wherein the compound has Formula IX.

[0058] In another aspect, the present invention features Compound No. 35 according to Table 1, wherein the compound has Formula A.

[0059] In another aspect, the present invention features Compound No. 43 according to Table 1, wherein the compound has Formula I.

[0060] In another aspect, the present invention features Compound No. 43 according to Table 1, wherein the compound has Formula II.

[0061] In another aspect, the present invention features Compound No. 43 according to Table 1, wherein the compound has Formula III.

[0062] In another aspect, the present invention features Compound No. 43 according to Table 1, wherein the compound has Formula III'.

[0063] In another aspect, the present invention features Compound No. 43 according to Table 1, wherein the compound has Formula IV.

[0064] In another aspect, the present invention features Compound No. 43 according to Table 1, wherein the compound has Formula IV'.

[0065] In another aspect, the present invention features Compound No. 43 according to Table 1, wherein the compound has Formula IV''.

[0066] In another aspect, the present invention features Compound No. 43 according to Table 1, wherein the compound has Formula V.

[0067] In another aspect, the present invention features Compound No. 43 according to Table 1, wherein the compound has Formula VI.

[0068] In another aspect, the present invention features Compound No. 43 according to Table 1, wherein the compound has Formula VII.

[0069] In another aspect, the present invention features Compound No. 43 according to Table 1, wherein the compound has Formula VIII.

[0070] In another aspect, the present invention features Compound No. 43 according to Table 1, wherein the compound has Formula IX.

[0071] In another aspect, the present invention features Compound No. 43 according to Table 1, wherein the compound has Formula A.

[0072] In another aspect, the present invention features Compound No. 47 according to Table 1, wherein the compound has Formula I.

[0073] In another aspect, the present invention features Compound No. 47 according to Table 1, wherein the compound has Formula II.

[0074] In another aspect, the present invention features Compound No. 47 according to Table 1, wherein the compound has Formula III.

[0075] In another aspect, the present invention features Compound No. 47 according to Table 1, wherein the compound has Formula III'.

[0076] In another aspect, the present invention features Compound No. 47 according to Table 1, wherein the compound has Formula IV.

[0077] In another aspect, the present invention features Compound No. 47 according to Table 1, wherein the compound has Formula IV'.

[0078] In another aspect, the present invention features Compound No. 47 according to Table 1, wherein the compound has Formula IV''.

[0079] In another aspect, the present invention features Compound No. 47 according to Table 1, wherein the compound has Formula V.

[0080] In another aspect, the present invention features Compound No. 47 according to Table 1, wherein the compound has Formula VI.

[0081] In another aspect, the present invention features Compound No. 47 according to Table 1, wherein the compound has Formula VII.

[0082] In another aspect, the present invention features Compound No. 47 according to Table 1, wherein the compound has Formula VIII.

[0083] In another aspect, the present invention features Compound No. 47 according to Table 1, wherein the compound has Formula IX.

[0084] In another aspect, the present invention features Compound No. 47 according to Table 1, wherein the compound has Formula A.

[0085] In another aspect, the present invention features Compound No. 59 according to Table 1, wherein the compound has Formula I.

[0086] In another aspect, the present invention features Compound No. 59 according to Table 1, wherein the compound has Formula II.

[0087] In another aspect, the present invention features Compound No. 59 according to Table 1, wherein the compound has Formula III.

[0088] In another aspect, the present invention features Compound No. 59 according to Table 1, wherein the compound has Formula III'.

[0089] In another aspect, the present invention features Compound No. 59 according to Table 1, wherein the compound has Formula IV.

[0090] In another aspect, the present invention features Compound No. 59 according to Table 1, wherein the compound has Formula IV'.

[0091] In another aspect, the present invention features Compound No. 59 according to Table 1, wherein the compound has Formula IV''.

[0092] In another aspect, the present invention features Compound No. 59 according to Table 1, wherein the compound has Formula V.

[0093] In another aspect, the present invention features Compound No. 59 according to Table 1, wherein the compound has Formula VI.

[0094] In another aspect, the present invention features Compound No. 59 according to Table 1, wherein the compound has Formula VII.

[0095] In another aspect, the present invention features Compound No. 59 according to Table 1, wherein the compound has Formula VIII.

[0096] In another aspect, the present invention features Compound No. 59 according to Table 1, wherein the compound has Formula IX.

[0097] In another aspect, the present invention features Compound No. 59 according to Table 1, wherein the compound has Formula A.

[0098] Likewise, in another aspect, the present invention features Compound No. 1 according to Table 1, wherein the compound has Formula I, II, III, III', IV, IV', IV'', V, VI,. VII, VIII, IX, or A.

[0099] Likewise, in another aspect, the present invention features Compound No. 2 according to Table 1, wherein the compound has Formula I, II, III, III', IV, IV', IV'', V, VI,. VII, VIII, IX, or A.

[00100] Likewise, in another aspect, the present invention features Compound No. 9 according to Table 1, wherein the compound has Formula I, II, III, III', IV, IV', IV'', V, VI,. VII, VIII, IX, or A.

[00101] Likewise, in another aspect, the present invention features Compound No. 10 according to Table 1, wherein the compound has Formula I, II, III, III', IV, IV', IV'', V, VI,. VII, VIII, IX, or A.

[0100] Likewise, in another aspect, the present invention features Compound No. 127 according to Table 1, wherein the compound has Formula I, II, III, III', IV, IV', IV'', V, VI,. VII, VIII, IX, or A.

[0101] Likewise, in another aspect, the present invention features Compound No. 128 according to Table 1, wherein the compound has Formula I, II, III, III', IV, IV', IV'', V, VI,. VII, VIII, IX, or A.

[0102] Likewise, in another aspect, the present invention features Compound No. 129 according to Table 1, wherein the compound has Formula I, II, III, III', IV, IV', IV'', V, VI,. VII, VIII, IX, or A.

[0103] Likewise, in another aspect, the present invention features Compound No. 130 according to Table 1, wherein the compound has Formula I, II, III, III', IV, IV', IV'', V, VI,. VII, VIII, IX, or A.

[0104] Likewise, in another aspect, the present invention features Compound No. 11 according to Table 1, wherein the compound has Formula I, II, III, III', IV, IV', IV'', V, VI,. VII, VIII, IX, or A.

[0105] Likewise, in another aspect, the present invention features Compound No. 12 according to Table 1, wherein the compound has Formula I, II, III, III', IV, IV', IV'', V, VI,. VII, VIII, IX, or A.

[0106] Likewise, in another aspect, the present invention features Compound No. 13 according to Table 1, wherein the compound has Formula I, II, III, III', IV, IV', IV'', V, VI,. VII, VIII, IX, or A.

[0107] Likewise, in another aspect, the present invention features Compound No. 14 according to Table 1, wherein the compound has Formula I, II, III, III', IV, IV', IV'', V, VI,. VII, VIII, IX, or A.

[0108] Likewise, in another aspect, the present invention features Compound No. 131 according to Table 1, wherein the compound has Formula I, II, III, III', IV, IV', IV'', V, VI,. VII, VIII, IX, or A.

[0109] Likewise, in another aspect, the present invention features Compound No. 132 according to Table 1, wherein the compound has Formula I, II, III, III', IV, IV', IV'', V, VI,. VII, VIII, IX, or A.

[0110] Likewise, in another aspect, the present invention features Compound No. 133 according to Table 1, wherein the compound has Formula I, II, III, III', IV, IV', IV'', V, VI,. VII, VIII, IX, or A.

[0111] Likewise, in another aspect, the present invention features Compound No. 134 according to Table 1, wherein the compound has Formula I, II, III, III', IV, IV', IV'', V, VI,. VII, VIII, IX, or A.

[0112] 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.

[0113] 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.

[0114] 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.

[0115] 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.

[0116] 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.

[0117] 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.

[0118] 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).

[0119] 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.

[0120] 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 naive, 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.

[0121] 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.

[0122] 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.

[0123] 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.

[0124] 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.

[0125] 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.

[0126] 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.

[0127] 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.

[0128] 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.

[0129] 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.

[0130] 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.

[0131] 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.

[0132] 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.

[0133] 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.

[0134] 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.

[0135] 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.

[0136] 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.

[0137] 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.

[0138] 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.

[0139] 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.

[0140] 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.

[0141] 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.

[0142] 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.

[0143] 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 therefore. 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.

[0144] 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.

[0145] Non-limiting examples of suitable cyclophilin inhibitors include alisporovir (Novartis & Debiopharm), NM-811 (Novartis), SCY-635 (Scynexis), or a combination thereof.

[0146] Non-limiting examples of suitable HCV entry inhibitors include ITX-4520 (iTherx), ITX-5061 (iTherx), or a combination thereof.

[0147] 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.

[0148] 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.

[0149] 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.

[0150] 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.

[0151] 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.

[0152] 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.

[0153] 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.

[0154] 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.

[0155] 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.

[0156] 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.

[0157] In any method described herein, the patient being treated can be a treatment-naïve patient.

[0158] In any method described herein, the patient being treated can be an interferon non-responder.

[0159] In any method described herein, the patient being treated can be an interferon null-responder.

[0160] In any method described herein, the patient being treated can be without cirrhosis.

[0161] In any method described herein, the patient being treated can be a cirrhotic patient.

[0162] In any method described herein, the patient being treated can be a patient with compensated cirrhosis.

[0163] 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/US 16/31281

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/7115; A61K 31/712; A61K 31/7125 (2016.01)
CPC - A61K 31/7115; A61K 31/712; A61K 31/7125
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)
IPC(8) - A61K 31/7115; A61K 31/712; A61K 31/7125 (2016.01)
CPC - A61K 31/7115; A61K 31/712; A61K 31/7125

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)
Pathase, Google Patent, Google Web
Search terms used - treat hcv infection inhibiting replication phosphate prodrugs nucleoside methylated uracil pyrimidine
Pubchem substructure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2004/0110718 A1 (Devos et al.) 10 June 2004 (10.06.2004); para [0358]	1-2
Y	US 2014/0128339 A1 (Girijavallabhan et al.) 08 May 2014 (08.05.2014); para [0008], [0029]	1-2
A	US 2012/0251487 A1 (Surleraux) 04 October 2012 (04.10.2012); entire document	1-2
A	US 7,250,416 B2 (Phiasivongsa et al.) 31 July 2007 (31.07.2007); entire document	1-2
A	US 2005/0009737 A1 (Clark) 13 January 2005 (13.01.2005); entire document	1-2

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

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

Date of the actual completion of the international search	Date of mailing of the international search report
29 June 2016	11 AUG 2016
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774