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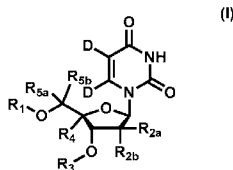
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(54) **Title:** 5, 6-D₂ URIDINE NUCLEOSIDE/TIDE DERIVATIVES



(57) **Abstract:** The invention provides nucleoside/nucleotide compounds and pharmaceutically acceptable salts, esters, stereoisomers, tautomers, solvates, and combinations thereof, pharmaceutical compositions comprising these compounds and the use of these compounds for treating a viral infection in a subject.

5, 6-D₂ URIDINE NUCLEOSIDE/TIDE DERIVATIVESRELATED APPLICATION

This application claims the benefit of U.S. Application No. 14/169,387, filed on January 31, 2014. The entire teachings of the above application are incorporated herein by reference.

TECHNICAL FIELD

The present invention relates generally to compounds and pharmaceutical compositions useful as antiviral and antiproliferative agents. Specifically, the present invention relates to 5, 6-d₂ uridine nucleoside/tide derivatives and methods for their preparation and use.

BACKGROUND OF THE INVENTION

Infection with HCV is a major cause of human liver disease throughout the world. In the US, an estimated 4.5 million Americans are chronically infected with HCV. Although only 30% of acute infections are symptomatic, greater than 85% of infected individuals develop chronic, persistent infection. Treatment costs for HCV infection have been estimated at \$5.46 billion for the US in 1997. Worldwide over 200 million people are estimated to be infected chronically. HCV infection is responsible for 40-60% of all chronic liver diseases and 30% of all liver transplants. Chronic HCV infection accounts for 30% of all cirrhosis, end-stage liver disease, and liver cancer in the U.S. The CDC estimates that the number of deaths due to HCV will minimally increase to 38,000/year by the year 2010.

Due to the high degree of variability in the viral surface antigens, existence of multiple viral genotypes, and demonstrated specificity of immunity, the development of a successful vaccine in the near future is unlikely. There are considerable barriers to the development of anti-HCV therapeutics, which include, but are not limited to, the persistence of the virus, the genetic diversity of the virus during replication in the host, the high incident rate of the virus developing drug-resistant mutants, and the lack of reproducible infectious culture systems and small-animal models for HCV replication and pathogenesis. In a majority of cases, given the mild course of the

infection and the complex biology of the liver, careful consideration must be given to antiviral drugs, which are likely to have significant side effects.

First identified by molecular cloning in 1989 (Choo, Q-L et al (1989) Science 244:359-362), HCV is now widely accepted as the most common causative agent of post-transfusion non-A, non-B hepatitis (NANBH) (Kuo, G et al (1989) Science 244:362-364). Due to its genome structure and sequence homology, this virus was assigned as a new genus in the *Flaviviridae* family. Like the other members of the *Flaviviridae*, such as flaviviruses (e.g. yellow fever virus and Dengue virus types 1-4) and pestiviruses (e.g. bovine viral diarrhea virus, border disease virus, and classic swine fever virus) (Choo, Q-L et al (1989) Science 244:359-362; Miller, R.H. and R.H. Purcell (1990) Proc. Natl. Acad. Sci. USA 87:2057-2061), HCV is an enveloped virus containing a single strand RNA molecule of positive polarity. The HCV genome is approximately 9.6 kilobases (kb) with a long, highly conserved, noncapped 5' nontranslated region (NTR) of approximately 340 bases which functions as an internal ribosome entry site (IRES) (Wang CY et al.) 'An RNA pseudoknot is an essential structural element of the internal ribosome entry site located within the hepatitis C virus 5' noncoding region' RNA – A Publication of the RNA Society. 1(5): 526-537, 1995 July). This element is followed by a region which encodes a single long open reading frame (ORF) encoding a polypeptide of ~3000 amino acids comprising both the structural and nonstructural viral proteins.

Upon entry into the cytoplasm of the cell, this RNA is directly translated into a polypeptide of ~3000 amino acids comprising both the structural and nonstructural viral proteins. This large polypeptide is subsequently processed into the individual structural and nonstructural proteins by a combination of host and virally-encoded proteinases (Rice, C.M. (1996) in B.N. Fields, D.M. Knipe and P.M. Howley (eds) Virology 2nd Edition, p931-960; Raven Press, N.Y.). There are three structural proteins, C, E1 and E2. The P7 protein is of unknown function and is comprised of a highly variable sequence. There are several non-structural proteins. NS2 is a zinc-dependent metalloproteinase that functions in conjunction with a portion of the NS3 protein. NS3 incorporates two catalytic functions (separate from its association with NS2): a serine protease at the N-terminal end, which requires NS4A as a cofactor, and an ATP-ase-dependent helicase function at the carboxyl terminus. NS4A is a tightly associated but non-covalent cofactor of the serine protease. NS5A is a membrane-anchored phosphoprotein that is observed in basally phosphorylated (56 kDa) and

hyperphosphorylated (58 kDa) forms. While its function has not fully been elucidated, NS5A is believed to be important in viral replication. The NS5B protein (591 amino acids, 65 kDa) of HCV (Behrens, S.E. *et al* (1996) *EMBO J.* 15:1-22), encodes an RNA-dependent RNA polymerase (RdRp) activity and contains canonical motifs
5 present in other RNA viral polymerases. The NS5B protein is fairly well conserved both intra-typically (~95-98% amino acid (aa) identity across 1b isolates) and inter-typically (~85% aa identity between genotype 1a and 1b isolates). The essentiality of the HCV NS5B RdRp activity for the generation of infectious progeny virions has been formally proven in chimpanzees (A. A. Kolykhalov *et al.*, (2000) *Journal of*
10 *Virology*, 74(4): 2046-2051). Thus, inhibition of NS5B RdRp activity (inhibition of RNA replication) is predicted to be useful to treat HCV infection.

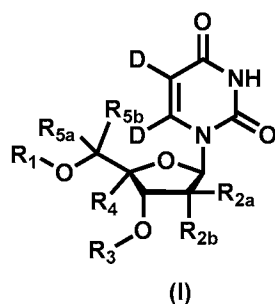
Current standard of care (SOC) therapy is the combination of peg-interferon- α and ribavirin. However, this therapy is limited in its clinical effectiveness and only ~50% of genotype 1a patients respond to the therapy. Recent approved NS3 protease
15 inhibitors, Boceprevir and Telaprevir, used in combination with SOC slightly improved effectiveness, but suffered significant side effects, such as rash. Therefore, there is still significant unmet medical need for more effective agents.

Inhibitors of HCV NS5B as potential therapies for HCV infection have been reviewed: S. Tan, A. Pause, Y. Shi, N. Sonenberg, Hepatitis C Therapeutics: Current
20 Status and Emerging Strategies, *Nature Rev. Drug Discov.* **1**, 867-881 (2002). The potential for the emergence of resistant HCV strains and the need to identify compounds with Pan-genotypic coverage supports the continuing efforts to identify novel and more effective nucleosides or nucleotides as HCV NS5B polymerase inhibitors.

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SUMMARY OF THE INVENTION

In one aspect, the invention provides compounds represented by Formula I, or pharmaceutically acceptable salts, esters, stereoisomer, tautomer, solvate, or combination thereof:

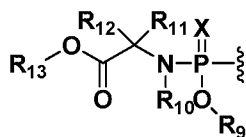


wherein:

D is deuterium;

R₁ is selected from the group consisting of:

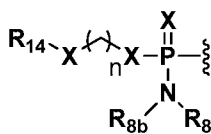
- 5 1) Hydrogen;
- 2) R₆; where R₆ is selected from the group consisting of: hydrogen, hydroxy protecting group, -C(O)R₇, -C(O)OR₇, and -C(O)NR_{8a}R_{8b}; wherein R₇ is selected from the group consisting of: substituted or unsubstituted -C₁-C₈ alkyl, substituted or unsubstituted -C₂-C₈ alkenyl, substituted or unsubstituted -C₂-C₈ alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, and substituted or unsubstituted heterocyclic; R_{8a} and R_{8b} are each independently selected from the group consisting of: hydrogen and R₇; or alternatively R_{8a} and R_{8b} taken together with the nitrogen atom to which they are attached form a heterocyclic ring;
- 10 3) -P(O)(OR_{7a})(OR_{7b}); wherein R_{7a} and R_{7b} are each independently selected from the group consisting of a) hydrogen; and b) unsubstituted or substituted -C₁-C₈ alkyl;
- 15 4) -P(O)(OR_{7a})-O-P(O)(OR_{7b})(OR_{7c}); wherein R_{7a} and R_{7b} are previously defined; R_{7c} is selected from the group consisting of a) hydrogen; and b) unsubstituted or substituted -C₁-C₈ alkyl;
- 20 5) -P(O)(OR_{7a})-O-P(O)(OR_{7b})-O-P(O)(OR_{7c})(OR_{7d}); wherein R_{7a}, R_{7b} and R_{7c} are previously defined; R_{7d} is selected from the group consisting of a) hydrogen; b) unsubstituted or substituted -C₁-C₈ alkyl;

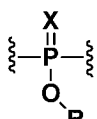


- 25 6) where X is O or S; R₉ is R₇ wherein R₇ is previously defined; R₁₀, R₁₁ and R₁₂ are each independently selected from the group

consisting of : a) hydrogen; b) unsubstituted or substituted $-C_1-C_8$ alkyl; c) R_{11} is hydrogen, R_{12} and R_{10} taken together with the nitrogen which R_{10} is attached to form a heterocyclic ring; d) R_{11} and R_{12} taken together with the carbon which they are attached form a ring; R_{13} is hydrogen or R_7 , wherein R_7 is previously defined; and

5

- 7)  7) $R_{14}-X-(CH_2)_n-X-P(=X)(R_{8b})-R_{8a}$, where X is O or S; n is 1-4; R_{8a} and R_{8b} are as previously defined; R_{14} is hydrogen or $-(CO)-R_7$, wherein R_7 is as previously defined;

- 8) Or, R_1 and R_3 are taken together to form , where X is O or S; and R_{15} is selected from the group consisting of a) hydrogen; b) unsubstituted or substituted $-C_1-C_8$ alkyl; c) substituted or unsubstituted $-C_2-C_8$ alkenyl; d) substituted or unsubstituted $-C_2-C_8$ alkynyl; e) substituted or unsubstituted aryl; f) substituted or unsubstituted heteroaryl.

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R_{2a} is selected from the group consisting of:

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- 1) hydrogen;
- 2) halogen;
- 3) Substituted or unsubstituted $-C_1-C_8$ alkyl;
- 4) Substituted or unsubstituted $-C_2-C_8$ alkenyl; and
- 5) Substituted or unsubstituted $-C_2-C_8$ alkynyl;

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R_{2b} and R_4 are independently selected from the group consisting of:

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- 1) hydrogen;
- 2) halogen;
- 3) $-CN$;
- 4) $-N_3$; and
- 5) OR_9 ;

R_9 at each occurrence is selected from the group consisting of: hydrogen, hydroxy protecting group, R_{10} , $-C(O)R_{10}$, $-C(O)OR_{10}$, and $-C(O)NR_{11a}R_{11b}$; wherein R_{10} at each occurrence is independently selected from the group consisting of: substituted or unsubstituted $-C_1-C_8$ alkyl, substituted or unsubstituted $-C_2-C_8$

alkenyl, substituted or unsubstituted $-C_2-C_8$ alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, and substituted or unsubstituted heterocyclic; R_{11a} and R_{11b} at each occurrence are each independently selected from the group consisting of: hydrogen and R_{10} ; or alternatively R_{11a} and R_{11b} taken together with the nitrogen atom to which they are attached form a heterocyclic ring;

R_3 is R_6 ; wherein R_6 is as previously defined;

R_{5a} and R_{5b} are independently selected from the group consisting of:

- 1) hydrogen;
 - 2) substituted or unsubstituted $-C_1-C_8$ alkyl;
 - 3) substituted or unsubstituted $-C_2-C_8$ alkenyl; and
 - 4) substituted or unsubstituted $-C_2-C_8$ alkynyl;
- or R_{5a} and R_{5b} are taken together with the carbon atom to which they are attached to form a group selected from $-C_3-C_8$ cycloalkyl, $-C_3-C_8$ cycloalkenyl, or $-C_3-C_8$ cycloalkynyl.

In certain embodiments of the compounds of Formula I, R_{2a} is C_1-C_6 -alkyl, preferably methyl; CF_3 , F or OH. In certain embodiments of the compounds of Formula I, R_{2b} is hydrogen, halogen, $-CN$, $-N_3$ or OH, preferably F or OH. In certain embodiments of the compounds of Formula I, R_4 is hydrogen, halogen or OH, preferably hydrogen. In certain embodiments of the compounds of Formula I, R_{5a} and R_{5b} are independently hydrogen or C_1-C_6 -alkyl or R_{5a} and R_{5b} , together with the carbon atom to which they are attached, form a C_3-C_6 -cycloalkyl group. Preferably one of R_{5a} and R_{5b} is methyl and the other is hydrogen; R_{5a} and R_{5b} are both hydrogen; or R_{5a} and R_{5b} , together with the carbon atom to which they are attached, form a cyclopropyl group. In certain embodiments of the compounds of Formula I, R_9 is aryl, substituted aryl or C_1-C_6 -alkyl, preferably phenyl, naphthyl, p-fluorophenyl or isopropyl. R_{11} is hydrogen, C_1-C_6 -alkyl or aryl- C_1-C_3 -alkyl, preferably hydrogen, methyl, isopropyl, isobutyl or benzyl. In certain embodiments of the compounds of Formula I, R_{12} is hydrogen. In certain embodiments of the compounds of Formula I, R_{13} is C_1-C_6 -alkyl or aryl- C_1-C_3 -alkyl, preferably hydrogen, methyl, isopropyl, isobutyl or benzyl. In certain embodiments of the compounds of Formula I, R_{2a} is methyl and R_{2b} is OH or F.

In certain embodiments of the compounds of Formula I, R_{2a} is C₁-C₆-alkyl, preferably methyl, CF₃, F or OH, and more preferably methyl; R_{2b} is hydrogen, halogen, -CN, -N₃ or OH, preferably F or OH; R₄ is hydrogen, halogen or OH, preferably hydrogen; R_{5a} and R_{5b} are independently hydrogen or C₁-C₆-alkyl or R_{5a} and R_{5b}, together with the carbon atom to which they are attached, form a C₃-C₆-cycloalkyl group; preferably one of R_{5a} and R_{5b} is methyl and the other is hydrogen; R_{5a} and R_{5b} are both hydrogen; or R_{5a} and R_{5b}, together with the carbon atom to which they are attached, form a cyclopropyl group; R₉ is aryl, substituted aryl or C₁-C₆-alkyl, preferably phenyl, naphthyl, p-fluorophenyl or isopropyl; R₁₁ is hydrogen, C₁-C₆-alkyl or aryl-C₁-C₃-alkyl, preferably hydrogen, methyl, isopropyl, isobutyl or benzyl; R₁₂ is hydrogen; and R₁₃ is C₁-C₆-alkyl or aryl-C₁-C₃-alkyl, preferably hydrogen, methyl, isopropyl, isobutyl or benzyl.

In another embodiment, the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound or combination of compounds of the present invention, or a pharmaceutically acceptable salt form, stereoisomer, tautomer, solvate, or combination thereof, in combination with a pharmaceutically acceptable carrier or excipient.

In yet another embodiment, the present invention provides a method of inhibiting the replication of an RNA or DNA containing virus comprising contacting said virus with a therapeutically effective amount of a compound or a combination of compounds of the present invention, or a pharmaceutically acceptable salt, stereoisomer, tautomer, solvate, or combination thereof. Particularly, this invention is directed to methods of inhibiting the replication of HCV, HBV and/or HIV.

In still another embodiment, the present invention provides a method of treating or preventing infection caused by an RNA or DNA-containing virus comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound or combination of compounds of the present invention, or a pharmaceutically acceptable salt form, stereoisomer, or tautomer, solvate, or combination thereof. Particularly, this invention is directed to methods of treating or preventing infection caused by HCV, HBV and/or HIV.

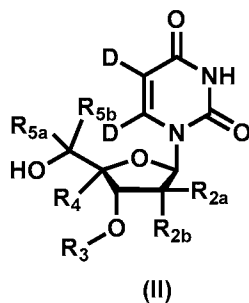
Yet another embodiment of the present invention provides the use of a compound or combination of compounds of the present invention, or a therapeutically acceptable salt form, stereoisomer or tautomer, solvate, or combination thereof, as defined hereinafter, in the preparation of a medicament for the treatment or prevention

of infection caused by RNA or DNA-containing virus, specifically HCV, HBV and/or HIV.

DETAILED DESCRIPTION OF THE INVENTION

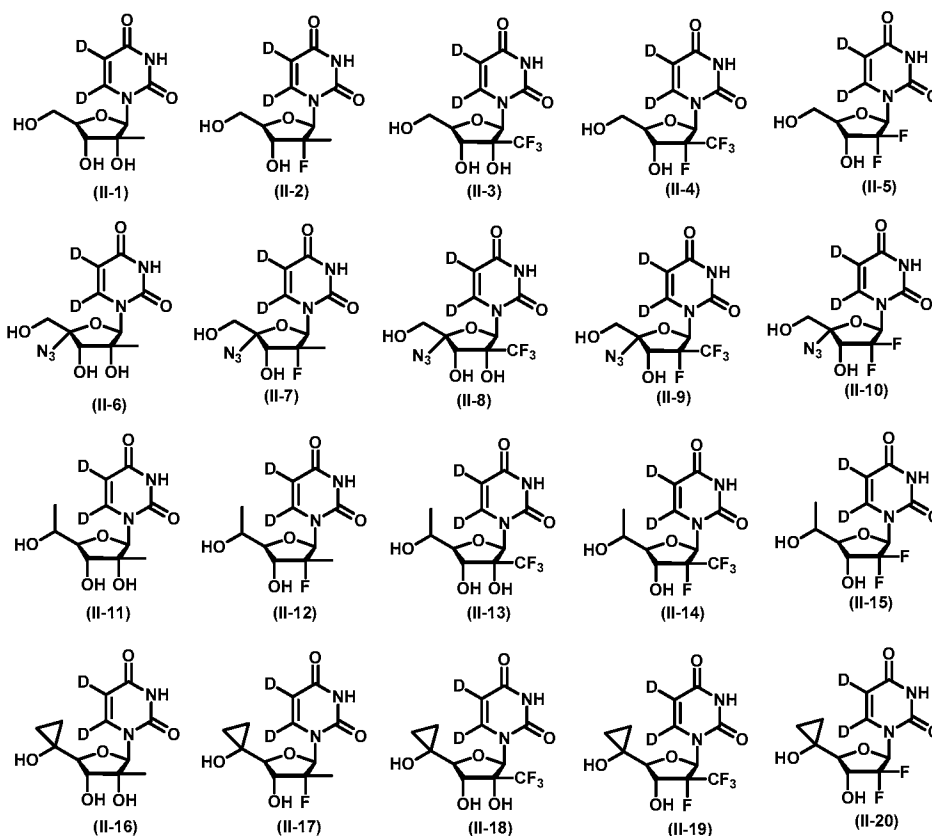
A first embodiment of the invention is a compound represented by Formula I
5 as described above, or a pharmaceutically acceptable salt, ester or prodrug thereof.

A second embodiment of the invention is a compound represented by Formula II or a pharmaceutically acceptable salt, ester or prodrug thereof.

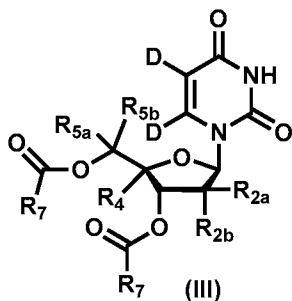


Wherein, R_{2a}, R_{2b}, R₃, R, R_{5a} and R_{5b} are as previously defined.

10 Illustrative structures of formula (II) can be represented, but not limited, by formula (II-1~II-20):



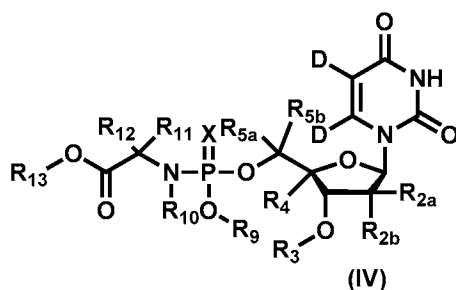
A third embodiment of the invention is a compound represented by Formula III or a pharmaceutically acceptable salt, ester or prodrug thereof.



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wherein, R_{2a} , R_{2b} , R_4 , R_{5a} , R_{5b} , and R_7 are as previously defined.

A fourth embodiment of the invention is a compound represented by Formula IV or a pharmaceutically acceptable salt, ester or prodrug thereof, alone or in
 10 combination with a pharmaceutically acceptable carrier or excipient.

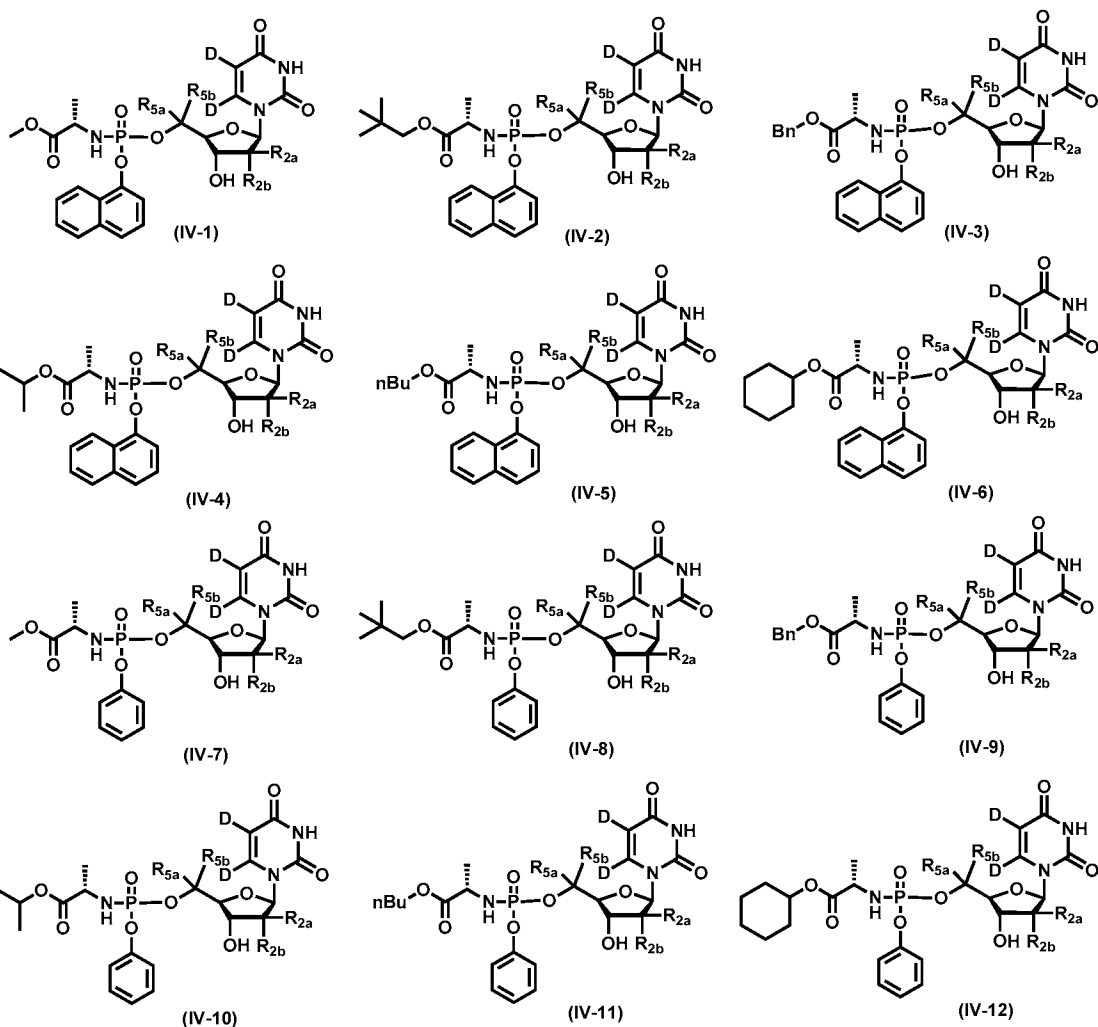


wherein, R_{2a} , R_{2b} , R_3 , R_4 , R_{5a} , R_{5b} , R_9 , R_{10} , R_{11} , R_{12} , and R_{13} are as previously defined.

X is O or S.

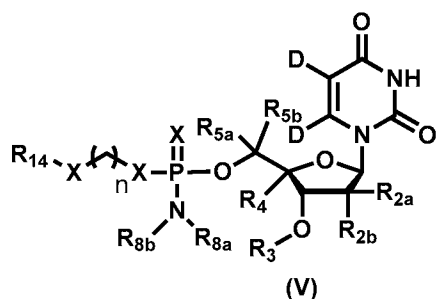
Illustrative structures of formula (IV) can be represented, but not limited, by formula

5 (IV-1~IV-12):



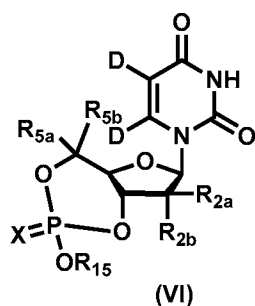
wherein, R_{2a} , R_{2b} , R_{5a} , and R_{5b} are as previously defined.

A fifth embodiment of the invention is a compound represented by Formula V
 10 or a pharmaceutically acceptable salt, ester or prodrug thereof.



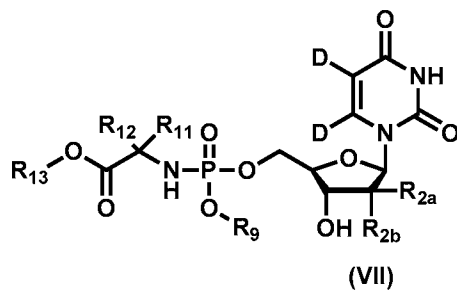
wherein, R_{2a} , R_{2b} , R_3 , R_4 , R_{5a} , R_{5b} , R_{8a} , R_{8b} , and R_{14} are as previously defined. X is O or S. n is 1~4.

A sixth embodiment of the invention is a compound represented by Formula
5 VI or a pharmaceutically acceptable salt, ester or prodrug thereof.



wherein, R_{2a} , R_{2b} , R_{5a} , R_{5b} , and R_{15} are as previously defined. X is O or S.

Compounds of the invention further include compounds of Formula (VII),



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and pharmaceutically acceptable salts, esters or prodrugs thereof, wherein R_{2a} , R_{2b} , R_9 , R_{11} , R_{12} and R_{13} are as previously defined. Representative compounds of the invention include, but are not limited to, the following compounds (example 1 to example 200 in Table 1) according to Formula VII, wherein, R_{2a} , R_{2b} , R_9 , R_{11} , R_{12} ,

15 and R_{13} are delineated for each example in Table 1.

Table 1

Example	R _{2a}	R _{2b}	R ₉	R ₁₁	R ₁₂	R ₁₃
1	Me	OH	Ph	Me	H	iPr
2	Me	OH	Ph	Me	H	Me
3	Me	OH	Ph	Me	H	Et
4	Me	OH	Ph	Me	H	Bn
5	Me	OH	Ph	Me	H	CH ₂ CH(CH ₃) ₂
6	Me	F	Ph	Me	H	iPr
7	Me	F	Ph	Me	H	Me
8	Me	F	Ph	Me	H	Et
9	Me	F	Ph	Me	H	Bn
10	Me	F	Ph	Me	H	CH ₂ CH(CH ₃) ₂
11	Me	OH	Ph	H	H	iPr
12	Me	OH	Ph	H	H	Me
13	Me	OH	Ph	H	H	Et
14	Me	OH	Ph	H	H	Bn
15	Me	OH	Ph	H	H	CH ₂ CH(CH ₃) ₂
16	Me	F	Ph	H	H	iPr
17	Me	F	Ph	H	H	Me
18	Me	F	Ph	H	H	Et
19	Me	F	Ph	H	H	Bn
20	Me	F	Ph	H	H	CH ₂ CH(CH ₃) ₂
21	Me	OH	Ph	iPr	H	iPr
22	Me	OH	Ph	iPr	H	Me
23	Me	OH	Ph	iPr	H	Et
24	Me	OH	Ph	iPr	H	Bn
25	Me	OH	Ph	iPr	H	CH ₂ CH(CH ₃) ₂
26	Me	F	Ph	iPr	H	iPr
27	Me	F	Ph	iPr	H	Me
28	Me	F	Ph	iPr	H	Et
29	Me	F	Ph	iPr	H	Bn
30	Me	F	Ph	iPr	H	CH ₂ CH(CH ₃) ₂
31	Me	OH	Ph	CH ₂ CH(CH ₃) ₂	H	iPr
32	Me	OH	Ph	CH ₂ CH(CH ₃) ₂	H	Me
33	Me	OH	Ph	CH ₂ CH(CH ₃) ₂	H	Et
34	Me	OH	Ph	CH ₂ CH(CH ₃) ₂	H	Bn
35	Me	OH	Ph	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
36	Me	F	Ph	CH ₂ CH(CH ₃) ₂	H	iPr
37	Me	F	Ph	CH ₂ CH(CH ₃) ₂	H	Me

38	Me	F	Ph	CH ₂ CH(CH ₃) ₂	H	Et
39	Me	F	Ph	CH ₂ CH(CH ₃) ₂	H	Bn
40	Me	F	Ph	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
41	Me	OH	Ph	CH ₂ Ph	H	iPr
42	Me	OH	Ph	CH ₂ Ph	H	Me
43	Me	OH	Ph	CH ₂ Ph	H	Et
44	Me	OH	Ph	CH ₂ Ph	H	Bn
45	Me	OH	Ph	CH ₂ Ph	H	CH ₂ CH(CH ₃) ₂
46	Me	F	Ph	CH ₂ Ph	H	iPr
47	Me	F	Ph	CH ₂ Ph	H	Me
48	Me	F	Ph	CH ₂ Ph	H	Et
49	Me	F	Ph	CH ₂ Ph	H	Bn
50	Me	F	Ph	CH ₂ Ph	H	CH ₂ CH(CH ₃) ₂
51	Me	OH	1-Naphthyl	Me	H	iPr
52	Me	OH	1-Naphthyl	Me	H	Me
53	Me	OH	1-Naphthyl	Me	H	Et
54	Me	OH	1-Naphthyl	Me	H	Bn
55	Me	OH	1-Naphthyl	Me	H	CH ₂ CH(CH ₃) ₂
56	Me	F	1-Naphthyl	Me	H	iPr
57	Me	F	1-Naphthyl	Me	H	Me
58	Me	F	1-Naphthyl	Me	H	Et
59	Me	F	1-Naphthyl	Me	H	Bn
60	Me	F	1-Naphthyl	Me	H	CH ₂ CH(CH ₃) ₂
61	Me	OH	1-Naphthyl	H	H	iPr
62	Me	OH	1-Naphthyl	H	H	Me
63	Me	OH	1-Naphthyl	H	H	Et
64	Me	OH	1-Naphthyl	H	H	Bn
65	Me	OH	1-Naphthyl	H	H	CH ₂ CH(CH ₃) ₂
66	Me	F	1-Naphthyl	H	H	iPr
67	Me	F	1-Naphthyl	H	H	Me
68	Me	F	1-Naphthyl	H	H	Et
69	Me	F	1-Naphthyl	H	H	Bn
70	Me	F	1-Naphthyl	H	H	CH ₂ CH(CH ₃) ₂
71	Me	OH	1-Naphthyl	iPr	H	iPr
72	Me	OH	1-Naphthyl	iPr	H	Me
73	Me	OH	1-Naphthyl	iPr	H	Et
74	Me	OH	1-Naphthyl	iPr	H	Bn
75	Me	OH	1-Naphthyl	iPr	H	CH ₂ CH(CH ₃) ₂
76	Me	F	1-Naphthyl	iPr	H	iPr

77	Me	F	1-Naphthyl	iPr	H	Me
78	Me	F	1-Naphthyl	iPr	H	Et
79	Me	F	1-Naphthyl	iPr	H	Bn
80	Me	F	1-Naphthyl	iPr	H	CH ₂ CH(CH ₃) ₂
81	Me	OH	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	iPr
82	Me	OH	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	Me
83	Me	OH	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	Et
84	Me	OH	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	Bn
85	Me	OH	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
86	Me	F	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	iPr
87	Me	F	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	Me
88	Me	F	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	Et
89	Me	F	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	Bn
90	Me	F	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
91	Me	OH	1-Naphthyl	CH ₂ Ph	H	iPr
92	Me	OH	1-Naphthyl	CH ₂ Ph	H	Me
93	Me	OH	1-Naphthyl	CH ₂ Ph	H	Et
94	Me	OH	1-Naphthyl	CH ₂ Ph	H	Bn
95	Me	OH	1-Naphthyl	CH ₂ Ph	H	CH ₂ CH(CH ₃) ₂
96	Me	F	1-Naphthyl	CH ₂ Ph	H	iPr
97	Me	F	1-Naphthyl	CH ₂ Ph	H	Me
98	Me	F	1-Naphthyl	CH ₂ Ph	H	Et
99	Me	F	1-Naphthyl	CH ₂ Ph	H	Bn
100	Me	F	1-Naphthyl	CH ₂ Ph	H	CH ₂ CH(CH ₃) ₂
101	Me	OH	p-F-Phenyl	Me	H	iPr
102	Me	OH	p-F-Phenyl	Me	H	Me
103	Me	OH	p-F-Phenyl	Me	H	Et
104	Me	OH	p-F-Phenyl	Me	H	Bn
105	Me	OH	p-F-Phenyl	Me	H	CH ₂ CH(CH ₃) ₂
106	Me	F	p-F-Phenyl	Me	H	iPr
107	Me	F	p-F-Phenyl	Me	H	Me
108	Me	F	p-F-Phenyl	Me	H	Et
109	Me	F	p-F-Phenyl	Me	H	Bn
110	Me	F	p-F-Phenyl	Me	H	CH ₂ CH(CH ₃) ₂
111	Me	OH	p-F-Phenyl	H	H	iPr
112	Me	OH	p-F-Phenyl	H	H	Me
113	Me	OH	p-F-Phenyl	H	H	Et
114	Me	OH	p-F-Phenyl	H	H	Bn
115	Me	OH	p-F-Phenyl	H	H	CH ₂ CH(CH ₃) ₂

116	Me	F	p-F-Phenyl	H	H	iPr
117	Me	F	p-F-Phenyl	H	H	Me
118	Me	F	p-F-Phenyl	H	H	Et
119	Me	F	p-F-Phenyl	H	H	Bn
120	Me	F	p-F-Phenyl	H	H	CH ₂ CH(CH ₃) ₂
121	Me	OH	p-F-Phenyl	iPr	H	iPr
122	Me	OH	p-F-Phenyl	iPr	H	Me
123	Me	OH	p-F-Phenyl	iPr	H	Et
124	Me	OH	p-F-Phenyl	iPr	H	Bn
125	Me	OH	p-F-Phenyl	iPr	H	CH ₂ CH(CH ₃) ₂
126	Me	F	p-F-Phenyl	iPr	H	iPr
127	Me	F	p-F-Phenyl	iPr	H	Me
128	Me	F	p-F-Phenyl	iPr	H	Et
129	Me	F	p-F-Phenyl	iPr	H	Bn
130	Me	F	p-F-Phenyl	iPr	H	CH ₂ CH(CH ₃) ₂
131	Me	OH	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	iPr
132	Me	OH	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	Me
133	Me	OH	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	Et
134	Me	OH	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	Bn
135	Me	OH	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
136	Me	F	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	iPr
137	Me	F	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	Me
138	Me	F	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	Et
139	Me	F	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	Bn
140	Me	F	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
141	Me	OH	p-F-Phenyl	CH ₂ Ph	H	iPr
142	Me	OH	p-F-Phenyl	CH ₂ Ph	H	Me
143	Me	OH	p-F-Phenyl	CH ₂ Ph	H	Et
144	Me	OH	p-F-Phenyl	CH ₂ Ph	H	Bn
145	Me	OH	p-F-Phenyl	CH ₂ Ph	H	CH ₂ CH(CH ₃) ₂
146	Me	F	p-F-Phenyl	CH ₂ Ph	H	iPr
147	Me	F	p-F-Phenyl	CH ₂ Ph	H	Me
148	Me	F	p-F-Phenyl	CH ₂ Ph	H	Et
149	Me	F	p-F-Phenyl	CH ₂ Ph	H	Bn
150	Me	F	p-F-Phenyl	CH ₂ Ph	H	CH ₂ CH(CH ₃) ₂
151	Me	OH	iPr	Me	H	iPr
152	Me	OH	iPr	Me	H	Me
153	Me	OH	iPr	Me	H	Et
154	Me	OH	iPr	Me	H	Bn

155	Me	OH	iPr	Me	H	CH ₂ CH(CH ₃) ₂
156	Me	F	iPr	Me	H	iPr
157	Me	F	iPr	Me	H	Me
158	Me	F	iPr	Me	H	Et
159	Me	F	iPr	Me	H	Bn
160	Me	F	iPr	Me	H	CH ₂ CH(CH ₃) ₂
161	Me	OH	iPr	H	H	iPr
162	Me	OH	iPr	H	H	Me
163	Me	OH	iPr	H	H	Et
164	Me	OH	iPr	H	H	Bn
165	Me	OH	iPr	H	H	CH ₂ CH(CH ₃) ₂
166	Me	F	iPr	H	H	iPr
167	Me	F	iPr	H	H	Me
168	Me	F	iPr	H	H	Et
169	Me	F	iPr	H	H	Bn
170	Me	F	iPr	H	H	CH ₂ CH(CH ₃) ₂
171	Me	OH	iPr	iPr	H	iPr
172	Me	OH	iPr	iPr	H	Me
173	Me	OH	iPr	iPr	H	Et
174	Me	OH	iPr	iPr	H	Bn
175	Me	OH	iPr	iPr	H	CH ₂ CH(CH ₃) ₂
176	Me	F	iPr	iPr	H	iPr
177	Me	F	iPr	iPr	H	Me
178	Me	F	iPr	iPr	H	Et
179	Me	F	iPr	iPr	H	Bn
180	Me	F	iPr	iPr	H	CH ₂ CH(CH ₃) ₂
181	Me	OH	iPr	CH ₂ CH(CH ₃) ₂	H	iPr
182	Me	OH	iPr	CH ₂ CH(CH ₃) ₂	H	Me
183	Me	OH	iPr	CH ₂ CH(CH ₃) ₂	H	Et
184	Me	OH	iPr	CH ₂ CH(CH ₃) ₂	H	Bn
185	Me	OH	iPr	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
186	Me	F	iPr	CH ₂ CH(CH ₃) ₂	H	iPr
187	Me	F	iPr	CH ₂ CH(CH ₃) ₂	H	Me
188	Me	F	iPr	CH ₂ CH(CH ₃) ₂	H	Et
189	Me	F	iPr	CH ₂ CH(CH ₃) ₂	H	Bn
190	Me	F	iPr	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
191	Me	OH	iPr	CH ₂ Ph	H	iPr
192	Me	OH	iPr	CH ₂ Ph	H	Me
193	Me	OH	iPr	CH ₂ Ph	H	Et

214	Me	OH	Ph	H	H	Bn
215	Me	OH	Ph	H	H	CH ₂ CH(CH ₃) ₂
216	Me	F	Ph	H	H	iPr
217	Me	F	Ph	H	H	Me
218	Me	F	Ph	H	H	Et
219	Me	F	Ph	H	H	Bn
220	Me	F	Ph	H	H	CH ₂ CH(CH ₃) ₂
221	Me	OH	Ph	iPr	H	iPr
222	Me	OH	Ph	iPr	H	Me
223	Me	OH	Ph	iPr	H	Et
224	Me	OH	Ph	iPr	H	Bn
225	Me	OH	Ph	iPr	H	CH ₂ CH(CH ₃) ₂
226	Me	F	Ph	iPr	H	iPr
227	Me	F	Ph	iPr	H	Me
228	Me	F	Ph	iPr	H	Et
229	Me	F	Ph	iPr	H	Bn
230	Me	F	Ph	iPr	H	CH ₂ CH(CH ₃) ₂
231	Me	OH	Ph	CH ₂ CH(CH ₃) ₂	H	iPr
232	Me	OH	Ph	CH ₂ CH(CH ₃) ₂	H	Me
233	Me	OH	Ph	CH ₂ CH(CH ₃) ₂	H	Et
234	Me	OH	Ph	CH ₂ CH(CH ₃) ₂	H	Bn
235	Me	OH	Ph	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
236	Me	F	Ph	CH ₂ CH(CH ₃) ₂	H	iPr
237	Me	F	Ph	CH ₂ CH(CH ₃) ₂	H	Me
238	Me	F	Ph	CH ₂ CH(CH ₃) ₂	H	Et
239	Me	F	Ph	CH ₂ CH(CH ₃) ₂	H	Bn
240	Me	F	Ph	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
241	Me	OH	Ph	CH ₂ Ph	H	iPr
242	Me	OH	Ph	CH ₂ Ph	H	Me
243	Me	OH	Ph	CH ₂ Ph	H	Et
244	Me	OH	Ph	CH ₂ Ph	H	Bn
245	Me	OH	Ph	CH ₂ Ph	H	CH ₂ CH(CH ₃) ₂
246	Me	F	Ph	CH ₂ Ph	H	iPr
247	Me	F	Ph	CH ₂ Ph	H	Me
248	Me	F	Ph	CH ₂ Ph	H	Et
249	Me	F	Ph	CH ₂ Ph	H	Bn
250	Me	F	Ph	CH ₂ Ph	H	CH ₂ CH(CH ₃) ₂
251	Me	OH	1-Naphthyl	Me	H	iPr
252	Me	OH	1-Naphthyl	Me	H	Me

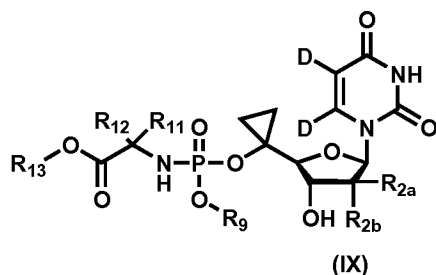
253	Me	OH	1-Naphthyl	Me	H	Et
254	Me	OH	1-Naphthyl	Me	H	Bn
255	Me	OH	1-Naphthyl	Me	H	CH ₂ CH(CH ₃) ₂
256	Me	F	1-Naphthyl	Me	H	iPr
257	Me	F	1-Naphthyl	Me	H	Me
258	Me	F	1-Naphthyl	Me	H	Et
259	Me	F	1-Naphthyl	Me	H	Bn
260	Me	F	1-Naphthyl	Me	H	CH ₂ CH(CH ₃) ₂
261	Me	OH	1-Naphthyl	H	H	iPr
262	Me	OH	1-Naphthyl	H	H	Me
263	Me	OH	1-Naphthyl	H	H	Et
264	Me	OH	1-Naphthyl	H	H	Bn
265	Me	OH	1-Naphthyl	H	H	CH ₂ CH(CH ₃) ₂
266	Me	F	1-Naphthyl	H	H	iPr
267	Me	F	1-Naphthyl	H	H	Me
268	Me	F	1-Naphthyl	H	H	Et
269	Me	F	1-Naphthyl	H	H	Bn
270	Me	F	1-Naphthyl	H	H	CH ₂ CH(CH ₃) ₂
271	Me	OH	1-Naphthyl	iPr	H	iPr
272	Me	OH	1-Naphthyl	iPr	H	Me
273	Me	OH	1-Naphthyl	iPr	H	Et
274	Me	OH	1-Naphthyl	iPr	H	Bn
275	Me	OH	1-Naphthyl	iPr	H	CH ₂ CH(CH ₃) ₂
276	Me	F	1-Naphthyl	iPr	H	iPr
277	Me	F	1-Naphthyl	iPr	H	Me
278	Me	F	1-Naphthyl	iPr	H	Et
279	Me	F	1-Naphthyl	iPr	H	Bn
280	Me	F	1-Naphthyl	iPr	H	CH ₂ CH(CH ₃) ₂
281	Me	OH	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	iPr
282	Me	OH	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	Me
283	Me	OH	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	Et
284	Me	OH	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	Bn
285	Me	OH	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
286	Me	F	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	iPr
287	Me	F	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	Me
288	Me	F	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	Et
289	Me	F	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	Bn
290	Me	F	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
291	Me	OH	1-Naphthyl	CH ₂ Ph	H	iPr

292	Me	OH	1-Naphthyl	CH ₂ Ph	H	Me
293	Me	OH	1-Naphthyl	CH ₂ Ph	H	Et
294	Me	OH	1-Naphthyl	CH ₂ Ph	H	Bn
295	Me	OH	1-Naphthyl	CH ₂ Ph	H	CH ₂ CH(CH ₃) ₂
296	Me	F	1-Naphthyl	CH ₂ Ph	H	iPr
297	Me	F	1-Naphthyl	CH ₂ Ph	H	Me
298	Me	F	1-Naphthyl	CH ₂ Ph	H	Et
299	Me	F	1-Naphthyl	CH ₂ Ph	H	Bn
300	Me	F	1-Naphthyl	CH ₂ Ph	H	CH ₂ CH(CH ₃) ₂
301	Me	OH	p-F-Phenyl	Me	H	iPr
302	Me	OH	p-F-Phenyl	Me	H	Me
303	Me	OH	p-F-Phenyl	Me	H	Et
304	Me	OH	p-F-Phenyl	Me	H	Bn
305	Me	OH	p-F-Phenyl	Me	H	CH ₂ CH(CH ₃) ₂
306	Me	F	p-F-Phenyl	Me	H	iPr
307	Me	F	p-F-Phenyl	Me	H	Me
308	Me	F	p-F-Phenyl	Me	H	Et
309	Me	F	p-F-Phenyl	Me	H	Bn
310	Me	F	p-F-Phenyl	Me	H	CH ₂ CH(CH ₃) ₂
311	Me	OH	p-F-Phenyl	H	H	iPr
312	Me	OH	p-F-Phenyl	H	H	Me
313	Me	OH	p-F-Phenyl	H	H	Et
314	Me	OH	p-F-Phenyl	H	H	Bn
315	Me	OH	p-F-Phenyl	H	H	CH ₂ CH(CH ₃) ₂
316	Me	F	p-F-Phenyl	H	H	iPr
317	Me	F	p-F-Phenyl	H	H	Me
318	Me	F	p-F-Phenyl	H	H	Et
319	Me	F	p-F-Phenyl	H	H	Bn
320	Me	F	p-F-Phenyl	H	H	CH ₂ CH(CH ₃) ₂
321	Me	OH	p-F-Phenyl	iPr	H	iPr
322	Me	OH	p-F-Phenyl	iPr	H	Me
323	Me	OH	p-F-Phenyl	iPr	H	Et
324	Me	OH	p-F-Phenyl	iPr	H	Bn
325	Me	OH	p-F-Phenyl	iPr	H	CH ₂ CH(CH ₃) ₂
326	Me	F	p-F-Phenyl	iPr	H	iPr
327	Me	F	p-F-Phenyl	iPr	H	Me
328	Me	F	p-F-Phenyl	iPr	H	Et
329	Me	F	p-F-Phenyl	iPr	H	Bn
330	Me	F	p-F-Phenyl	iPr	H	CH ₂ CH(CH ₃) ₂

331	Me	OH	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	iPr
332	Me	OH	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	Me
333	Me	OH	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	Et
334	Me	OH	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	Bn
335	Me	OH	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
336	Me	F	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	iPr
337	Me	F	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	Me
338	Me	F	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	Et
339	Me	F	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	Bn
340	Me	F	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
341	Me	OH	p-F-Phenyl	CH ₂ Ph	H	iPr
342	Me	OH	p-F-Phenyl	CH ₂ Ph	H	Me
343	Me	OH	p-F-Phenyl	CH ₂ Ph	H	Et
344	Me	OH	p-F-Phenyl	CH ₂ Ph	H	Bn
345	Me	OH	p-F-Phenyl	CH ₂ Ph	H	CH ₂ CH(CH ₃) ₂
346	Me	F	p-F-Phenyl	CH ₂ Ph	H	iPr
347	Me	F	p-F-Phenyl	CH ₂ Ph	H	Me
348	Me	F	p-F-Phenyl	CH ₂ Ph	H	Et
349	Me	F	p-F-Phenyl	CH ₂ Ph	H	Bn
350	Me	F	p-F-Phenyl	CH ₂ Ph	H	CH ₂ CH(CH ₃) ₂
351	Me	OH	iPr	Me	H	iPr
352	Me	OH	iPr	Me	H	Me
353	Me	OH	iPr	Me	H	Et
354	Me	OH	iPr	Me	H	Bn
355	Me	OH	iPr	Me	H	CH ₂ CH(CH ₃) ₂
356	Me	F	iPr	Me	H	iPr
357	Me	F	iPr	Me	H	Me
358	Me	F	iPr	Me	H	Et
359	Me	F	iPr	Me	H	Bn
360	Me	F	iPr	Me	H	CH ₂ CH(CH ₃) ₂
361	Me	OH	iPr	H	H	iPr
362	Me	OH	iPr	H	H	Me
363	Me	OH	iPr	H	H	Et
364	Me	OH	iPr	H	H	Bn
365	Me	OH	iPr	H	H	CH ₂ CH(CH ₃) ₂
366	Me	F	iPr	H	H	iPr
367	Me	F	iPr	H	H	Me
368	Me	F	iPr	H	H	Et
369	Me	F	iPr	H	H	Bn

370	Me	F	iPr	H	H	CH ₂ CH(CH ₃) ₂
371	Me	OH	iPr	iPr	H	iPr
372	Me	OH	iPr	iPr	H	Me
373	Me	OH	iPr	iPr	H	Et
374	Me	OH	iPr	iPr	H	Bn
375	Me	OH	iPr	iPr	H	CH ₂ CH(CH ₃) ₂
376	Me	F	iPr	iPr	H	iPr
377	Me	F	iPr	iPr	H	Me
378	Me	F	iPr	iPr	H	Et
379	Me	F	iPr	iPr	H	Bn
380	Me	F	iPr	iPr	H	CH ₂ CH(CH ₃) ₂
381	Me	OH	iPr	CH ₂ CH(CH ₃) ₂	H	iPr
382	Me	OH	iPr	CH ₂ CH(CH ₃) ₂	H	Me
383	Me	OH	iPr	CH ₂ CH(CH ₃) ₂	H	Et
384	Me	OH	iPr	CH ₂ CH(CH ₃) ₂	H	Bn
385	Me	OH	iPr	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
386	Me	F	iPr	CH ₂ CH(CH ₃) ₂	H	iPr
387	Me	F	iPr	CH ₂ CH(CH ₃) ₂	H	Me
388	Me	F	iPr	CH ₂ CH(CH ₃) ₂	H	Et
389	Me	F	iPr	CH ₂ CH(CH ₃) ₂	H	Bn
390	Me	F	iPr	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
391	Me	OH	iPr	CH ₂ Ph	H	iPr
392	Me	OH	iPr	CH ₂ Ph	H	Me
393	Me	OH	iPr	CH ₂ Ph	H	Et
194	Me	OH	iPr	CH ₂ Ph	H	Bn
395	Me	OH	iPr	CH ₂ Ph	H	CH ₂ CH(CH ₃) ₂
396	Me	F	iPr	CH ₂ Ph	H	iPr
397	Me	F	iPr	CH ₂ Ph	H	Me
398	Me	F	iPr	CH ₂ Ph	H	Et
399	Me	F	iPr	CH ₂ Ph	H	Bn
400	Me	F	iPr	CH ₂ Ph	H	CH ₂ CH(CH ₃) ₂

Compounds of the invention further include compounds of Formula (IX),



- and pharmaceutically acceptable salts, esters or prodrugs thereof, wherein R_{2a}, R_{2b}, R₉, R₁₁, R₁₂ and R₁₃ are as previously defined. Representative compounds of the invention include, but are not limited to, the following compounds (example 401 to example 600 in Table 3) according to Formula IX, wherein, R_{2a}, R_{2b}, R₉, R₁₁, R₁₂, and R₁₃ are delineated for each example in Table 3.

Table 3

Example	R _{2a}	R _{2b}	R ₉	R ₁₁	R ₁₂	R ₁₃
401	Me	OH	Ph	Me	H	iPr
402	Me	OH	Ph	Me	H	Me
403	Me	OH	Ph	Me	H	Et
404	Me	OH	Ph	Me	H	Bn
405	Me	OH	Ph	Me	H	CH ₂ CH(CH ₃) ₂
406	Me	F	Ph	Me	H	iPr
407	Me	F	Ph	Me	H	Me
408	Me	F	Ph	Me	H	Et
409	Me	F	Ph	Me	H	Bn
410	Me	F	Ph	Me	H	CH ₂ CH(CH ₃) ₂
411	Me	OH	Ph	H	H	iPr
412	Me	OH	Ph	H	H	Me
413	Me	OH	Ph	H	H	Et
414	Me	OH	Ph	H	H	Bn
415	Me	OH	Ph	H	H	CH ₂ CH(CH ₃) ₂
416	Me	F	Ph	H	H	iPr
417	Me	F	Ph	H	H	Me
418	Me	F	Ph	H	H	Et
419	Me	F	Ph	H	H	Bn
420	Me	F	Ph	H	H	CH ₂ CH(CH ₃) ₂
421	Me	OH	Ph	iPr	H	iPr
422	Me	OH	Ph	iPr	H	Me

423	Me	OH	Ph	iPr	H	Et
424	Me	OH	Ph	iPr	H	Bn
425	Me	OH	Ph	iPr	H	CH ₂ CH(CH ₃) ₂
426	Me	F	Ph	iPr	H	iPr
427	Me	F	Ph	iPr	H	Me
428	Me	F	Ph	iPr	H	Et
429	Me	F	Ph	iPr	H	Bn
430	Me	F	Ph	iPr	H	CH ₂ CH(CH ₃) ₂
431	Me	OH	Ph	CH ₂ CH(CH ₃) ₂	H	iPr
432	Me	OH	Ph	CH ₂ CH(CH ₃) ₂	H	Me
433	Me	OH	Ph	CH ₂ CH(CH ₃) ₂	H	Et
434	Me	OH	Ph	CH ₂ CH(CH ₃) ₂	H	Bn
435	Me	OH	Ph	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
436	Me	F	Ph	CH ₂ CH(CH ₃) ₂	H	iPr
437	Me	F	Ph	CH ₂ CH(CH ₃) ₂	H	Me
438	Me	F	Ph	CH ₂ CH(CH ₃) ₂	H	Et
439	Me	F	Ph	CH ₂ CH(CH ₃) ₂	H	Bn
440	Me	F	Ph	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
441	Me	OH	Ph	CH ₂ Ph	H	iPr
442	Me	OH	Ph	CH ₂ Ph	H	Me
443	Me	OH	Ph	CH ₂ Ph	H	Et
444	Me	OH	Ph	CH ₂ Ph	H	Bn
445	Me	OH	Ph	CH ₂ Ph	H	CH ₂ CH(CH ₃) ₂
446	Me	F	Ph	CH ₂ Ph	H	iPr
447	Me	F	Ph	CH ₂ Ph	H	Me
448	Me	F	Ph	CH ₂ Ph	H	Et
449	Me	F	Ph	CH ₂ Ph	H	Bn
450	Me	F	Ph	CH ₂ Ph	H	CH ₂ CH(CH ₃) ₂
451	Me	OH	1-Naphthyl	Me	H	iPr
452	Me	OH	1-Naphthyl	Me	H	Me
453	Me	OH	1-Naphthyl	Me	H	Et
454	Me	OH	1-Naphthyl	Me	H	Bn
455	Me	OH	1-Naphthyl	Me	H	CH ₂ CH(CH ₃) ₂
456	Me	F	1-Naphthyl	Me	H	iPr
457	Me	F	1-Naphthyl	Me	H	Me
458	Me	F	1-Naphthyl	Me	H	Et
459	Me	F	1-Naphthyl	Me	H	Bn
460	Me	F	1-Naphthyl	Me	H	CH ₂ CH(CH ₃) ₂
461	Me	OH	1-Naphthyl	H	H	iPr

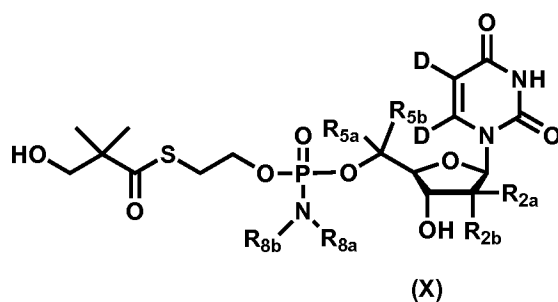
462	Me	OH	1-Naphthyl	H	H	Me
463	Me	OH	1-Naphthyl	H	H	Et
464	Me	OH	1-Naphthyl	H	H	Bn
465	Me	OH	1-Naphthyl	H	H	CH ₂ CH(CH ₃) ₂
466	Me	F	1-Naphthyl	H	H	iPr
467	Me	F	1-Naphthyl	H	H	Me
468	Me	F	1-Naphthyl	H	H	Et
469	Me	F	1-Naphthyl	H	H	Bn
470	Me	F	1-Naphthyl	H	H	CH ₂ CH(CH ₃) ₂
471	Me	OH	1-Naphthyl	iPr	H	iPr
472	Me	OH	1-Naphthyl	iPr	H	Me
473	Me	OH	1-Naphthyl	iPr	H	Et
474	Me	OH	1-Naphthyl	iPr	H	Bn
475	Me	OH	1-Naphthyl	iPr	H	CH ₂ CH(CH ₃) ₂
476	Me	F	1-Naphthyl	iPr	H	iPr
477	Me	F	1-Naphthyl	iPr	H	Me
478	Me	F	1-Naphthyl	iPr	H	Et
479	Me	F	1-Naphthyl	iPr	H	Bn
480	Me	F	1-Naphthyl	iPr	H	CH ₂ CH(CH ₃) ₂
481	Me	OH	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	iPr
482	Me	OH	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	Me
483	Me	OH	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	Et
484	Me	OH	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	Bn
485	Me	OH	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
486	Me	F	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	iPr
487	Me	F	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	Me
488	Me	F	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	Et
489	Me	F	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	Bn
490	Me	F	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
491	Me	OH	1-Naphthyl	CH ₂ Ph	H	iPr
492	Me	OH	1-Naphthyl	CH ₂ Ph	H	Me
493	Me	OH	1-Naphthyl	CH ₂ Ph	H	Et
494	Me	OH	1-Naphthyl	CH ₂ Ph	H	Bn
495	Me	OH	1-Naphthyl	CH ₂ Ph	H	CH ₂ CH(CH ₃) ₂
496	Me	F	1-Naphthyl	CH ₂ Ph	H	iPr
497	Me	F	1-Naphthyl	CH ₂ Ph	H	Me
498	Me	F	1-Naphthyl	CH ₂ Ph	H	Et
499	Me	F	1-Naphthyl	CH ₂ Ph	H	Bn
500	Me	F	1-Naphthyl	CH ₂ Ph	H	CH ₂ CH(CH ₃) ₂

501	Me	OH	p-F-Phenyl	Me	H	iPr
502	Me	OH	p-F-Phenyl	Me	H	Me
503	Me	OH	p-F-Phenyl	Me	H	Et
504	Me	OH	p-F-Phenyl	Me	H	Bn
505	Me	OH	p-F-Phenyl	Me	H	CH ₂ CH(CH ₃) ₂
506	Me	F	p-F-Phenyl	Me	H	iPr
507	Me	F	p-F-Phenyl	Me	H	Me
508	Me	F	p-F-Phenyl	Me	H	Et
509	Me	F	p-F-Phenyl	Me	H	Bn
510	Me	F	p-F-Phenyl	Me	H	CH ₂ CH(CH ₃) ₂
511	Me	OH	p-F-Phenyl	H	H	iPr
512	Me	OH	p-F-Phenyl	H	H	Me
513	Me	OH	p-F-Phenyl	H	H	Et
514	Me	OH	p-F-Phenyl	H	H	Bn
515	Me	OH	p-F-Phenyl	H	H	CH ₂ CH(CH ₃) ₂
516	Me	F	p-F-Phenyl	H	H	iPr
517	Me	F	p-F-Phenyl	H	H	Me
518	Me	F	p-F-Phenyl	H	H	Et
519	Me	F	p-F-Phenyl	H	H	Bn
520	Me	F	p-F-Phenyl	H	H	CH ₂ CH(CH ₃) ₂
521	Me	OH	p-F-Phenyl	iPr	H	iPr
522	Me	OH	p-F-Phenyl	iPr	H	Me
523	Me	OH	p-F-Phenyl	iPr	H	Et
524	Me	OH	p-F-Phenyl	iPr	H	Bn
525	Me	OH	p-F-Phenyl	iPr	H	CH ₂ CH(CH ₃) ₂
526	Me	F	p-F-Phenyl	iPr	H	iPr
527	Me	F	p-F-Phenyl	iPr	H	Me
528	Me	F	p-F-Phenyl	iPr	H	Et
529	Me	F	p-F-Phenyl	iPr	H	Bn
530	Me	F	p-F-Phenyl	iPr	H	CH ₂ CH(CH ₃) ₂
531	Me	OH	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	iPr
532	Me	OH	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	Me
533	Me	OH	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	Et
534	Me	OH	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	Bn
535	Me	OH	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
536	Me	F	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	iPr
537	Me	F	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	Me
538	Me	F	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	Et
539	Me	F	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	Bn

540	Me	F	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
541	Me	OH	p-F-Phenyl	CH ₂ Ph	H	iPr
542	Me	OH	p-F-Phenyl	CH ₂ Ph	H	Me
543	Me	OH	p-F-Phenyl	CH ₂ Ph	H	Et
544	Me	OH	p-F-Phenyl	CH ₂ Ph	H	Bn
545	Me	OH	p-F-Phenyl	CH ₂ Ph	H	CH ₂ CH(CH ₃) ₂
546	Me	F	p-F-Phenyl	CH ₂ Ph	H	iPr
547	Me	F	p-F-Phenyl	CH ₂ Ph	H	Me
548	Me	F	p-F-Phenyl	CH ₂ Ph	H	Et
549	Me	F	p-F-Phenyl	CH ₂ Ph	H	Bn
550	Me	F	p-F-Phenyl	CH ₂ Ph	H	CH ₂ CH(CH ₃) ₂
551	Me	OH	iPr	Me	H	iPr
552	Me	OH	iPr	Me	H	Me
553	Me	OH	iPr	Me	H	Et
554	Me	OH	iPr	Me	H	Bn
555	Me	OH	iPr	Me	H	CH ₂ CH(CH ₃) ₂
556	Me	F	iPr	Me	H	iPr
557	Me	F	iPr	Me	H	Me
558	Me	F	iPr	Me	H	Et
559	Me	F	iPr	Me	H	Bn
560	Me	F	iPr	Me	H	CH ₂ CH(CH ₃) ₂
561	Me	OH	iPr	H	H	iPr
562	Me	OH	iPr	H	H	Me
563	Me	OH	iPr	H	H	Et
564	Me	OH	iPr	H	H	Bn
565	Me	OH	iPr	H	H	CH ₂ CH(CH ₃) ₂
566	Me	F	iPr	H	H	iPr
567	Me	F	iPr	H	H	Me
568	Me	F	iPr	H	H	Et
569	Me	F	iPr	H	H	Bn
570	Me	F	iPr	H	H	CH ₂ CH(CH ₃) ₂
571	Me	OH	iPr	iPr	H	iPr
572	Me	OH	iPr	iPr	H	Me
573	Me	OH	iPr	iPr	H	Et
574	Me	OH	iPr	iPr	H	Bn
575	Me	OH	iPr	iPr	H	CH ₂ CH(CH ₃) ₂
576	Me	F	iPr	iPr	H	iPr
577	Me	F	iPr	iPr	H	Me
578	Me	F	iPr	iPr	H	Et

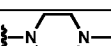
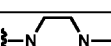
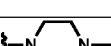
579	Me	F	iPr	iPr	H	Bn
580	Me	F	iPr	iPr	H	CH ₂ CH(CH ₃) ₂
581	Me	OH	iPr	CH ₂ CH(CH ₃) ₂	H	iPr
582	Me	OH	iPr	CH ₂ CH(CH ₃) ₂	H	Me
583	Me	OH	iPr	CH ₂ CH(CH ₃) ₂	H	Et
584	Me	OH	iPr	CH ₂ CH(CH ₃) ₂	H	Bn
585	Me	OH	iPr	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
586	Me	F	iPr	CH ₂ CH(CH ₃) ₂	H	iPr
587	Me	F	iPr	CH ₂ CH(CH ₃) ₂	H	Me
588	Me	F	iPr	CH ₂ CH(CH ₃) ₂	H	Et
589	Me	F	iPr	CH ₂ CH(CH ₃) ₂	H	Bn
590	Me	F	iPr	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
591	Me	OH	iPr	CH ₂ Ph	H	iPr
592	Me	OH	iPr	CH ₂ Ph	H	Me
593	Me	OH	iPr	CH ₂ Ph	H	Et
594	Me	OH	iPr	CH ₂ Ph	H	Bn
595	Me	OH	iPr	CH ₂ Ph	H	CH ₂ CH(CH ₃) ₂
596	Me	F	iPr	CH ₂ Ph	H	iPr
597	Me	F	iPr	CH ₂ Ph	H	Me
598	Me	F	iPr	CH ₂ Ph	H	Et
599	Me	F	iPr	CH ₂ Ph	H	Bn
600	Me	F	iPr	CH ₂ Ph	H	CH ₂ CH(CH ₃) ₂

Compounds of the invention further include compounds of Formula (X),



- and pharmaceutically acceptable salts, esters or prodrugs thereof, wherein R_{2a}, R_{2b},
5 R_{5a}, R_{5b}, R_{8a} and R_{8b} are as previously defined. Representative compounds of the invention include, but are not limited to, the following compounds (example 601 to example 660 in Table 4) according to Formula X, wherein, R_{2a}, R_{2b}, R_{5a}, R_{5b}, R_{8a}, and R_{8b} are delineated for each example in Table 4.

Table 4

Example	R _{2a}	R _{2b}		
601	Me	OH	PhCH ₂ NH	
602	Me	OH	PhCH ₂ NH	
603	Me	OH	PhCH ₂ NH	
604	Me	OH	ⁱ PrNH	
605	Me	OH	ⁱ PrNH	
606	Me	OH	ⁱ PrNH	
607	Me	OH	^t BuNH	
608	Me	OH	^t BuNH	
609	Me	OH	^t BuNH	
610	Me	OH		
611	Me	OH		
612	Me	OH		
613	Me	OH		
614	Me	OH		
615	Me	OH		
616	Me	OH		
617	Me	OH		
618	Me	OH		
619	Me	OH	NHCH ₂ CO ₂ Et	
620	Me	OH	NH CH ₂ CO ₂ Et	
621	Me	OH	NH CH ₂ CO ₂ Et	
622	Me	OH	NH CH ₂ CO ₂ ^t Bu	
623	Me	OH	NH CH ₂ CO ₂ ^t Bu	

624	Me	OH	NH CH ₂ CO ₂ ^t Bu	
625	Me	OH	NH CH ₂ CO ₂ H	
626	Me	OH	NH CH ₂ CO ₂ H	
627	Me	OH	NH CH ₂ CO ₂ H	
628	Me	OH	NH CH ₂ CH ₂ NMe ₂	
629	Me	OH	NH CH ₂ CH ₂ NMe ₂	
630	Me	OH	NH CH ₂ CH ₂ NMe ₂	
631	Me	F	PhCH ₂ NH	
632	Me	F	PhCH ₂ NH	
633	Me	F	PhCH ₂ NH	
634	Me	F	ⁱ PrNH	
635	Me	F	ⁱ PrNH	
636	Me	F	ⁱ PrNH	
637	Me	F	^t BuNH	
638	Me	F	^t BuNH	
639	Me	F	^t BuNH	
640	Me	F		
641	Me	F		
642	Me	F		
643	Me	F		
644	Me	F		
645	Me	F		
646	Me	F		
647	Me	F		
648	Me	F		
649	Me	F	NHCH ₂ CO ₂ Et	

650	Me	F	NH CH ₂ CO ₂ Et	
651	Me	F	NH CH ₂ CO ₂ Et	
652	Me	F	NH CH ₂ CO ₂ ^t Bu	
653	Me	F	NH CH ₂ CO ₂ ^t Bu	
654	Me	F	NH CH ₂ CO ₂ ^t Bu	
655	Me	F	NH CH ₂ CO ₂ H	
656	Me	F	NH CH ₂ CO ₂ H	
657	Me	F	NH CH ₂ CO ₂ H	
658	Me	F	NH CH ₂ CH ₂ NMe ₂	
659	Me	F	NH CH ₂ CH ₂ NMe ₂	
660	Me	F	NH CH ₂ CH ₂ NMe ₂	

The term “compound”, as used herein in reference to the compounds of Formulas I-X, refers to a collection of molecules of identical molecular structure, except for isotopic variation. Atoms within the compounds which are not designated as a specific isotope can be any stable isotope of the indicated element. Typically, the isotopic distribution of each such atom will correspond substantially to the natural isotopic abundance for that element. The designation of an atom as deuterium in the compounds of the invention indicates that this position is enriched with deuterium at a level which is significantly greater than the natural abundance of this isotope. For example, in preferred compounds of the invention, the designation of an atom as deuterium signifies that this position is deuterated in at least 5% of the molecules. Preferably, such a position is deuterated in at least 10, 20, 30, 40 or 50% of the molecules. In certain embodiments, such a position is deuterated in 60, 70, 80, 90 or 95% of the molecules. The compounds of the invention have two atoms designated as deuterium, and in preferred embodiments both positions are deuterated in at least 5%, 10%, 25%, 50%, 60%, 75% 80%, 90% or 95% of the molecules.

The present invention also features pharmaceutical compositions comprising a compound of the invention, or a pharmaceutically acceptable salt, ester or prodrug thereof. In one embodiment, the present invention features pharmaceutical compositions comprising a therapeutically effective amount of a compound of the

invention, or a pharmaceutically acceptable salt, ester or prodrug thereof, in combination with a pharmaceutically acceptable carrier or excipient. In another embodiment, the invention features methods of treating a hepatitis C infection in a subject in need of such treatment with said pharmaceutical composition.

5 In addition, the present invention features methods of using compounds of the present invention or pharmaceutically acceptable salts thereof to treat HCV infection. The methods comprise administering to an HCV patient in need thereof an effective amount of a compound of the invention or a pharmaceutically acceptable salt thereof.

10 It will be appreciated that the compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic, diastereoisomeric, and optically active forms. It should be understood that the compounds encompassed by the present invention are those that are suitably stable for use as pharmaceutical agent.

15 Yet a further embodiment of the present invention is a pharmaceutical composition comprising any single compound or a combination of two or more compounds delineated herein, or a pharmaceutically acceptable salt thereof, in combination with one or more agents known in the art, with a pharmaceutically acceptable carrier or excipient. In the methods described herein, a compound of the present invention or a pharmaceutically acceptable salt thereof can be administered
20 alone, or in combination with one or more other anti-HCV agents, such as HCV polymerase inhibitors, HCV protease inhibitors, HCV NS5A inhibitors, CD81 inhibitors, cyclophilin inhibitors, internal ribosome entry site (IRES) inhibitors or any combinations thereof. Interferon, ribavirin or both can also be included in the treatment. For example, the methods described herein can further comprise
25 administering to the patient peginterferon-alpha and ribavirin. Different agents can be administered simultaneously or sequentially. The dosing frequency of each agent in a treatment regimen can be the same or different. For instance, a compound of the invention can be dosed once daily and ribavirin can be dosed twice daily.

30 Compounds of the present invention can be administered as the sole active pharmaceutical agent, or used in combination with one or more agents to treat or prevent hepatitis C infections or the symptoms associated with HCV infection. Other agents to be administered in combination with a compound or combination of compounds of the invention include therapies for disease caused by HCV infection that suppresses HCV viral replication by direct or indirect mechanisms. These include

agents such as host immune modulators (for example, interferon-alpha, pegylated interferon-alpha, interferon-beta, interferon-gamma, CpG oligonucleotides and the like), cyclophilins (e.g., Debio 025), or antiviral compounds that inhibit host cellular functions such as inosine monophosphate dehydrogenase (for example, ribavirin and the like). Also included are cytokines that modulate immune function. Also included are vaccines comprising HCV antigens or antigen adjuvant combinations directed against HCV. Also included are agents that interact with host cellular components to block viral protein synthesis by inhibiting the internal ribosome entry site (IRES) initiated translation step of HCV viral replication or to block viral particle maturation and release with agents targeted toward the viroporin family of membrane proteins such as, for example, HCV P7 and the like. Other agents to be administered in combination with a compound of the present invention include any agent or combination of agents that inhibit the replication of HCV by targeting proteins of the viral genome involved in the viral replication. These agents include but are not limited to other inhibitors of HCV RNA dependent RNA polymerase such as, for example, nucleoside type polymerase inhibitors described in WO0190121(A2), or U.S. Pat. No. 6,348,587B1 or WO0160315 or WO0132153 or non-nucleoside inhibitors such as, for example, benzimidazole polymerase inhibitors described in EP 1162196A1 or WO0204425 or inhibitors of HCV protease such as, for example, peptidomimetic type inhibitors such as BILN2061 and the like or inhibitors of HCV helicase.

Other agents to be administered in combination with a compound of the present invention include any agent or combination of agents that inhibit the replication of other viruses for co-infected individuals. These agents include but are not limited to therapies for disease caused by hepatitis B (HBV) infection or therapies for disease caused by human immunodeficiency virus (HIV) infection.

Accordingly, one aspect of the invention is directed to a method for treating or preventing an infection caused by an RNA-containing virus comprising co-administering to a patient in need of such treatment one or more agents selected from the group consisting of a host immune modulator and a second antiviral agent, or a combination thereof, with a therapeutically effective amount of a compound or combination of compounds of the invention, or a pharmaceutically acceptable salt, stereoisomer, tautomer, prodrug, salt of a prodrug, or combination thereof. Examples of the host immune modulator are, but not limited to, interferon-alpha, pegylated-

interferon-alpha, interferon-beta, interferon-gamma, a cytokine, a vaccine, and a vaccine comprising an antigen and an adjuvant, and said second antiviral agent inhibits replication of HCV either by inhibiting host cellular functions associated with viral replication or by targeting proteins of the viral genome.

5 A further aspect of the invention is directed to a method of treating or preventing infection caused by an RNA-containing virus comprising co-administering to a patient in need of such treatment an agent or combination of agents that treat or alleviate symptoms of HCV infection including cirrhosis and inflammation of the liver, with a therapeutically effective amount of a compound or combination of
10 compounds of the invention, or a pharmaceutically acceptable salt, stereoisomer, tautomer, prodrug, salt of a prodrug, or combination thereof. Yet another aspect of the invention provides a method of treating or preventing infection caused by an RNA-containing virus comprising co-administering to a patient in need of such treatment one or more agents that treat patients for disease caused by hepatitis B (HBV)
15 infection, with a therapeutically effective amount of a compound or a combination of compounds of the invention, or a pharmaceutically acceptable salt, stereoisomer, tautomer, prodrug, salt of a prodrug, or combination thereof. An agent that treats patients for disease caused by hepatitis B (HBV) infection may be for example, but not limited thereto, L- deoxythymidine, adefovir, lamivudine or tenfovir, or any
20 combination thereof. Example of the RNA-containing virus includes, but not limited to, hepatitis C virus (HCV).

 Another aspect of the invention provides a method of treating or preventing infection caused by an RNA-containing virus comprising co-administering to a patient in need of such treatment one or more agents that treat patients for disease caused by
25 human immunodeficiency virus (HIV) infection, with a therapeutically effective amount of a compound or a combination of compounds of the invention, or a pharmaceutically acceptable salt, stereoisomer, tautomer, prodrug, salt of a prodrug, or combination thereof. An example of the RNA-containing virus includes, but not limited to, hepatitis C virus (HCV). In addition, the present invention provides the use
30 of a compound or a combination of compounds of the invention, or a therapeutically acceptable salt form, stereoisomer, or tautomer, prodrug, salt of a prodrug, or combination thereof, and one or more agents selected from the group consisting of a host immune modulator and a second antiviral agent, or a combination thereof, to prepare a medicament for the treatment of an infection caused by an RNA-containing

virus in a patient, particularly hepatitis C virus. Examples of the host immune modulator are, but not limited to, interferon-alpha, pegylated- interferon-alpha, interferon-beta, interferon-gamma, a cytokine, a vaccine, and a vaccine comprising an antigen and an adjuvant, and said second antiviral agent inhibits replication of HCV
5 either by inhibiting host cellular functions associated with viral replication or by targeting proteins of the viral genome.

When used in the above or other treatments, combination of compound or compounds of the invention, together with one or more agents as defined herein above, can be employed in pure form or, where such forms exist, in pharmaceutically
10 acceptable salt form, prodrug, salt of a prodrug, or combination thereof. Alternatively, such combination of therapeutic agents can be administered as a pharmaceutical composition containing a therapeutically effective amount of the compound or combination of compounds of interest, or their pharmaceutically acceptable salt form, prodrugs, or salts of the prodrug, in combination with one or more agents as defined
15 hereinabove, and a pharmaceutically acceptable carrier. Such pharmaceutical compositions can be used for inhibiting the replication of an RNA-containing virus, particularly Hepatitis C virus (HCV), by contacting said virus with said pharmaceutical composition. In addition, such compositions are useful for the treatment or prevention of an infection caused by an RNA-containing virus,
20 particularly Hepatitis C virus (HCV).

Hence, further aspect of the invention is directed to a method of treating or preventing infection caused by an RNA-containing virus, particularly a hepatitis C virus (HCV), comprising administering to a patient in need of such treatment a
25 pharmaceutical composition comprising a compound or combination of compounds of the invention or a pharmaceutically acceptable salt, stereoisomer, or tautomer, prodrug, salt of a prodrug, or combination thereof, one or more agents as defined hereinabove, and a pharmaceutically acceptable carrier.

When administered as a combination, the therapeutic agents can be formulated as separate compositions which are given at the same time or within a predetermined
30 period of time, or the therapeutic agents can be given as a single unit dosage form.

Antiviral agents contemplated for use in such combination therapy include agents (compounds or biologicals) that are effective to inhibit the formation and/or replication of a virus in a mammal, including but not limited to, agents that interfere with either host or viral mechanisms necessary for the formation and/or replication of

a virus in a mammal. Such agents can be selected from another anti-HCV agent; an HIV inhibitor; an HAV inhibitor; and an HBV inhibitor.

Other anti-HCV agents include those agents that are effective for diminishing or preventing the progression of hepatitis C related symptoms or disease. Such agents
5 include but are not limited to immunomodulatory agents, inhibitors of HCV NS3 protease, other inhibitors of HCV polymerase, inhibitors of another target in the HCV life cycle and other anti-HCV agents, including but not limited to, ribavirin, amantadine, levovirin and viramidine.

Immunomodulatory agents include those agents (compounds or biologicals)
10 that are effective to enhance or potentiate the immune system response in a mammal. Immunomodulatory agents include, but are not limited to, inosine monophosphate dehydrogenase inhibitors such as VX-497 (merimepodib, Vertex Pharmaceuticals), class I interferons, class II interferons, consensus interferons, asialo-interferons
15 pegylated interferons and conjugated interferons, including but not limited to, interferons conjugated with other proteins including but not limited to, human albumin. Class I interferons are a group of interferons that all bind to receptor type I, including both naturally and synthetically produced class I interferons, while class II interferons all bind to receptor type II. Examples of class I interferons include, but are
20 not limited to, [alpha]-, [beta]-, [delta]-, [omega]-, and [tau]-interferons, while examples of class II interferons include, but are not limited to, [gamma]-interferons.

Inhibitors of HCV NS3 protease include agents (compounds or biologicals) that are effective to inhibit the function of HCV NS3 protease in a mammal. Inhibitors of HCV NS3 protease include, but are not limited to, those compounds described in
25 WO 99/07733, WO 99/07734, WO 00/09558, WO 00/09543, WO 00/59929, WO 03/064416, WO 03/064455, WO 03/064456, WO 2004/030670, WO 2004/037855, WO 2004/039833, WO 2004/101602, WO 2004/101605, WO 2004/103996, WO 2005/028501, WO 2005/070955, WO 2006/000085, WO 2006/007700 and WO 2006/007708 (all by Boehringer Ingelheim), WO 02/060926, WO 03/053349, WO03/099274, WO 03/099316, WO 2004/032827, WO 2004/043339, WO
30 2004/094452, WO 2005/046712, WO 2005/051410, WO 2005/054430 (all by BMS), WO 2004/072243, WO 2004/093798, WO 2004/113365, WO 2005/010029 (all by Enanta), WO 2005/037214 (Intermune) and WO 2005/051980 (Schering), and the candidates identified as VX-950, ITMN-191 and SCH 503034.

Inhibitors of HCV polymerase include agents (compounds or biologicals) that are effective to inhibit the function of an HCV polymerase. Such inhibitors include, but are not limited to, non-nucleoside and nucleoside inhibitors of HCV NS5B polymerase. Examples of inhibitors of HCV polymerase include but are not limited to
5 those compounds described in: WO 02/04425, WO 03/007945, WO 03/010140, WO 03/010141, WO 2004/064925, WO 2004/065367, WO 2005/080388 and WO 2006/007693 (all by Boehringer Ingelheim), WO 2005/049622 (Japan Tobacco), WO 2005/014543 (Japan Tobacco), WO 2005/012288 (Genelabs), WO 2004/087714 (IRBM), WO 03/101993 (Neogenesis), WO 03/026587 (BMS), WO 03/000254
10 (Japan Tobacco), and WO 01/47883 (Japan Tobacco), and the clinical candidates XTL-2125, HCV 796, R-1626 and NM 283.

Inhibitors of another target in the HCV life cycle include agents (compounds or biologicals) that are effective to inhibit the formation and/or replication of HCV other than by inhibiting the function of the HCV NS3 protease. Such agents may
15 interfere with either host or HCV viral mechanisms necessary for the formation and/or replication of HCV. Inhibitors of another target in the HCV life cycle include, but are not limited to, entry inhibitors, agents that inhibit a target selected from a helicase, a NS2/3 protease and an internal ribosome entry site (IRES) and agents that interfere with the function of other viral targets including but not limited to, an NS5A protein
20 and an NS4B protein.

It can occur that a patient may be co-infected with hepatitis C virus and one or more other viruses, including but not limited to, human immunodeficiency virus (HIV), hepatitis A virus (HAV) and hepatitis B virus (HBV). Thus also contemplated is combination therapy to treat such co-infections by co-administering a compound
25 according to the present invention with at least one of an HIV inhibitor, an HAV inhibitor and an HBV inhibitor.

According to yet another embodiment, the pharmaceutical compositions of the present invention may further comprise inhibitor(s) of other targets in the HCV life cycle, including, but not limited to, helicase, polymerase, metalloprotease, and
30 internal ribosome entry site (IRES).

According to still another embodiment, the present invention includes methods of treating viral infection such as, but not limited to, hepatitis C infections in a subject in need of such treatment by administering to said subject an effective

amount of a compound of the present invention or a pharmaceutically acceptable salt, ester, or prodrug thereof.

According to a further embodiment, the present invention includes methods of treating hepatitis C infections in a subject in need of such treatment by administering
5 to said subject an anti-HCV virally effective amount or an inhibitory amount of a pharmaceutical composition of the present invention.

An additional embodiment of the present invention includes methods of treating biological samples by contacting the biological samples with the compounds of the present invention.

10 Yet a further aspect of the present invention is a process of making any of the compounds delineated herein employing any of the synthetic means delineated herein.

DEFINITIONS

Listed below are definitions of various terms used to describe this invention.

15 These definitions apply to the terms as they are used throughout this specification and claims, unless otherwise limited in specific instances, either individually or as part of a larger group.

The term "viral infection" refers to the introduction of a virus into cells or tissues, e.g., hepatitis C virus (HCV). In general, the introduction of a virus is also
20 associated with replication. Viral infection may be determined by measuring virus antibody titer in samples of a biological fluid, such as blood, using, e.g., enzyme immunoassay. Other suitable diagnostic methods include molecular based techniques, such as RT-PCR, direct hybrid capture assay, nucleic acid sequence based amplification, and the like. A virus may infect an organ, e.g., liver, and cause disease,
25 e.g., hepatitis, cirrhosis, chronic liver disease and hepatocellular carcinoma.

The term "immune modulator" refers to any substance meant to alter the working of the humoral or cellular immune system of a subject. Such immune modulators include inhibitors of mast cell-mediated inflammation, interferons, interleukins, prostaglandins, steroids, cortico-steroids, colony-stimulating factors,
30 chemotactic factors, etc.

The term "alkyl", as used herein, refers to a saturated, straight- or branched-chain hydrocarbongroup. Preferred alkyl radicals include C₁-C₆ alkyl and C₁-C₈ alkyl radicals. Examples of C₁-C₆ alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, *tert*-butyl, neopentyl, *n*-hexyl groups; and examples

of C₁-C₈ alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, *tert*-butyl, neopentyl, *n*-hexyl, heptyl, and octyl groups.

The term "alkenyl", as used herein, denote a monovalent group derived from a hydrocarbon moiety by the removal of a single hydrogen atom wherein the hydrocarbon moiety has at least one carbon-carbon double bond. Preferred alkenyl groups include C₂-C₆ alkenyl and C₂-C₈ alkenyl groups. Alkenyl groups include, but are not limited to, for example, ethenyl, propenyl, butenyl, 1-methyl-2-buten-1-yl, heptenyl, octenyl and the like.

The term "alkynyl", as used herein, denotes a monovalent group derived from a hydrocarbon moiety by the removal of a single hydrogen atom wherein the hydrocarbon moiety has at least one carbon-carbon triple bond. Preferred alkynyl groups include C₂-C₆ alkynyl and C₂-C₈ alkynyl groups. Representative alkynyl groups include, but are not limited to, for example, ethynyl, 1-propynyl, 1-butylnyl, heptynyl, octynyl and the like.

The term "carbocycle" refers to a saturated (e.g., "cycloalkyl"), partially saturated (e.g., "cycloalkenyl" or "cycloalkynyl") or completely unsaturated (e.g., "aryl") ring system containing zero heteroatom ring atom. "Ring atoms" or "ring members" are the atoms bound together to form the ring or rings. Where a carbocycle group is a divalent moiety linking two other elements in a depicted chemical structure (such as Z in Formula I_A), the carbocycle group can be attached to the two other elements through any two substitutable ring atoms. A C₄-C₆ carbocycle has 4-6 ring atoms.

The term "cycloalkyl", as used herein, denotes a monovalent group derived from a monocyclic or polycyclic saturated carbocyclic ring compound by the removal of a single hydrogen atom. Preferred cycloalkyl groups include C₃-C₈ cycloalkyl and C₃-C₁₂ cycloalkyl groups. Examples of C₃-C₈-cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentyl and cyclooctyl; and examples of C₃-C₁₂-cycloalkyl include, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo [2.2.1] heptyl, and bicyclo [2.2.2] octyl.

The term "cycloalkenyl" as used herein, denote a monovalent group derived from a monocyclic or polycyclic carbocyclic ring compound having at least one carbon-carbon double bond by the removal of a single hydrogen atom. Preferred cycloalkenyl groups include C₃-C₈ cycloalkenyl and C₃-C₁₂ cycloalkenyl groups. Examples of C₃-C₈-cycloalkenyl include, but are not limited to, cyclopropenyl,

cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, and the like; and examples of C₃-C₁₂-cycloalkenyl include, but not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, and the like.

The term "aryl," as used herein, refers to a mono- or bicyclic carbocyclic ring system having one or two aromatic rings including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, indenyl and the like.

The term "aryalkyl," as used herein, refers to a C₁-C₃ alkyl or C₁-C₆ alkyl residue attached to an aryl ring. Examples include, but are not limited to, benzyl, phenethyl and the like.

The term "heteroaryl," as used herein, refers to a mono-, bi-, or tri-cyclic aromatic radical or ring having from five to ten ring atoms of which at least one ring atom is selected from S, O and N; wherein any N or S contained within the ring may be optionally oxidized. Preferred heteroaryl groups are monocyclic or bicyclic. Heteroaryl groups include, but are not limited to, pyridinyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isooxazolyl, thiadiazolyl, oxadiazolyl, thiophenyl, furanyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzooxazolyl, quinoxalinyl, and the like.

The term "heteroarylalkyl," as used herein, refers to a C₁-C₃ alkyl or C₁-C₆ alkyl residue attached to a heteroaryl ring. Examples include, but are not limited to, pyridinylmethyl, pyrimidinylethyl and the like.

The term "substituted" as used herein, refers to independent replacement of one, two, or three or more of the hydrogen atoms thereon with substituents including, but not limited to, -F, -Cl, -Br, -I, -OH, protected hydroxy, -NO₂, -CN, -NH₂, N₃, protected amino, alkoxy, thioalkoxy, oxo, -halo- C₁-C₁₂-alkyl, -halo- C₂-C₁₂-alkenyl, -halo- C₂-C₁₂-alkynyl, -halo-C₃-C₁₂-cycloalkyl, -NH -C₁-C₁₂-alkyl, -NH -C₂-C₁₂-alkenyl, -NH -C₂-C₁₂-alkynyl, -NH -C₃-C₁₂-cycloalkyl, -NH -aryl, -NH -heteroaryl, -NH -heterocycloalkyl, -dialkylamino, -diarylamino, -diheteroarylamino, -O-C₁-C₁₂-alkyl, -O-C₂-C₁₂-alkenyl, -O-C₂-C₁₂-alkynyl, -O-C₃-C₁₂-cycloalkyl, -O-aryl, -O-heteroaryl, -O-heterocycloalkyl, -C(O)- C₁-C₁₂-alkyl, -C(O)- C₂-C₁₂-alkenyl, -C(O)-C₂-C₁₂-alkynyl, -C(O)-C₃-C₁₂-cycloalkyl, -C(O)-aryl, -C(O)-heteroaryl, -C(O)-heterocycloalkyl, -CONH₂, -CONH- C₁-C₁₂-alkyl, -CONH- C₂-C₁₂-alkenyl, -CONH-C₂-C₁₂-alkynyl, -CONH-C₃-C₁₂-cycloalkyl, -CONH-aryl, -CONH-heteroaryl, -CONH-heterocycloalkyl, -OCO₂- C₁-C₁₂-alkyl, -OCO₂- C₂-C₁₂-alkenyl, -OCO₂- C₂-

- C₁₂-alkynyl, -OCO₂-C₃-C₁₂-cycloalkyl, -OCO₂-aryl, -OCO₂-heteroaryl, -OCO₂-heterocycloalkyl, -OCONH₂, -OCONH- C₁-C₁₂-alkyl, -OCONH- C₂-C₁₂-alkenyl, -OCONH- C₂-C₁₂-alkynyl, -OCONH- C₃-C₁₂-cycloalkyl, -OCONH- aryl, -OCONH- heteroaryl, -OCONH- heterocycloalkyl, -NHC(O)- C₁-C₁₂-alkyl, -NHC(O)-C₂-C₁₂-alkenyl, -NHC(O)-C₂-C₁₂-alkynyl, -NHC(O)-C₃-C₁₂-cycloalkyl, -NHC(O)-aryl, -NHC(O)-heteroaryl, -NHC(O)-heterocycloalkyl, -NHCO₂- C₁-C₁₂-alkyl, -NHCO₂-C₂-C₁₂-alkenyl, -NHCO₂- C₂-C₁₂-alkynyl, -NHCO₂- C₃-C₁₂-cycloalkyl, -NHCO₂-aryl, -NHCO₂- heteroaryl, -NHCO₂- heterocycloalkyl, -NHC(O)NH₂, -NHC(O)NH- C₁-C₁₂-alkyl, -NHC(O)NH-C₂-C₁₂-alkenyl, -NHC(O)NH-C₂-C₁₂-alkynyl, -NHC(O)NH-C₃-C₁₂-cycloalkyl, -NHC(O)NH-aryl, -NHC(O)NH-heteroaryl, -NHC(O)NH-heterocycloalkyl, NHC(S)NH₂, -NHC(S)NH- C₁-C₁₂-alkyl, -NHC(S)NH-C₂-C₁₂-alkenyl, -NHC(S)NH-C₂-C₁₂-alkynyl, -NHC(S)NH-C₃-C₁₂-cycloalkyl, -NHC(S)NH-aryl, -NHC(S)NH-heteroaryl, -NHC(S)NH-heterocycloalkyl, -NHC(NH)NH₂, -NHC(NH)NH- C₁-C₁₂-alkyl, -NHC(NH)NH-C₂-C₁₂-alkenyl, -NHC(NH)NH-C₂-C₁₂-alkynyl, -NHC(NH)NH-C₃-C₁₂-cycloalkyl, -NHC(NH)NH-aryl, -NHC(NH)NH-heteroaryl, -NHC(NH)NH-heterocycloalkyl, -NHC(NH)-C₁-C₁₂-alkyl, -NHC(NH)-C₂-C₁₂-alkenyl, -NHC(NH)-C₂-C₁₂-alkynyl, -NHC(NH)-C₃-C₁₂-cycloalkyl, -NHC(NH)-aryl, -NHC(NH)-heteroaryl, -NHC(NH)-heterocycloalkyl, -C(NH)NH-C₁-C₁₂-alkyl, -C(NH)NH-C₂-C₁₂-alkenyl, -C(NH)NH-C₂-C₁₂-alkynyl, -C(NH)NH-C₃-C₁₂-cycloalkyl, -C(NH)NH-aryl, -C(NH)NH-heteroaryl, -C(NH)NH-heterocycloalkyl, -S(O)-C₁-C₁₂-alkyl, -S(O)-C₂-C₁₂-alkenyl, -S(O)-C₂-C₁₂-alkynyl, -S(O)-C₃-C₁₂-cycloalkyl, -S(O)-aryl, -S(O)-heteroaryl, -S(O)-heterocycloalkyl -SO₂NH₂, -SO₂NH- C₁-C₁₂-alkyl, -SO₂NH- C₂-C₁₂-alkenyl, -SO₂NH- C₂-C₁₂-alkynyl, -SO₂NH- C₃-C₁₂-cycloalkyl, -SO₂NH- aryl, -SO₂NH- heteroaryl, -SO₂NH- heterocycloalkyl, -NHSO₂-C₁-C₁₂-alkyl, -NHSO₂-C₂-C₁₂-alkenyl, -NHSO₂-C₂-C₁₂-alkynyl, -NHSO₂-C₃-C₁₂-cycloalkyl, -NHSO₂-aryl, -NHSO₂-heteroaryl, -NHSO₂-heterocycloalkyl, -CH₂NH₂, -CH₂SO₂CH₃, -aryl, -arylalkyl, -heteroaryl, -heteroarylalkyl, -heterocycloalkyl, -C₃-C₁₂-cycloalkyl, polyalkoxyalkyl, polyalkoxy, -methoxymethoxy, -methoxyethoxy, -SH, -S-C₁-C₁₂-alkyl, -S-C₂-C₁₂-alkenyl, -S-C₂-C₁₂-alkynyl, -S-C₃-C₁₂-cycloalkyl, -S-aryl, -S-heteroaryl, -S-heterocycloalkyl, methylthiomethyl, or -L'-R', wherein L' is C₁-C₆alkylene, C₂-C₆alkenylene or C₂-C₆alkynylene, and R' is aryl, heteroaryl, heterocyclic, C₃-C₁₂cycloalkyl or C₃-C₁₂cycloalkenyl. It is understood that the aryls, heteroaryls, alkyls, and the like can be further substituted. In some cases, each substituent in a substituted moiety is

additionally optionally substituted with one or more groups, each group being independently selected from -F, -Cl, -Br, -I, -OH, -NO₂, -CN, or -NH₂.

In accordance with the invention, any of the aryls, substituted aryls, heteroaryl and substituted heteroaryl described herein, can be any aromatic group.

5 Aromatic groups can be substituted or unsubstituted.

It is understood that any alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl moiety described herein can also be an aliphatic group, an alicyclic group or a heterocyclic group. An "aliphatic group" is non-aromatic moiety that may contain any combination of carbon atoms, hydrogen atoms, halogen atoms, oxygen, nitrogen
10 or other atoms, and optionally contain one or more units of unsaturation, e.g., double and/or triple bonds. An aliphatic group may be straight chained, branched or cyclic and preferably contains between about 1 and about 24 carbon atoms, more typically between about 1 and about 12 carbon atoms. In addition to aliphatic hydrocarbon groups, aliphatic groups include, for example, polyalkoxyalkyls, such as polyalkylene
15 glycols, polyamines, and polyimines, for example. Such aliphatic groups may be further substituted. It is understood that aliphatic groups may be used in place of the alkyl, alkenyl, alkynyl, alkylene, alkenylene, and alkynylene groups described herein.

The term "alicyclic," as used herein, denotes a monovalent group derived from a monocyclic or polycyclic saturated carbocyclic ring compound by the removal of a
20 single hydrogen atom. Examples include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo [2.2.1] heptyl, and bicyclo [2.2.2] octyl. Such alicyclic groups may be further substituted.

The term "heterocycloalkyl" and "heterocyclic" can be used interchangeably and refer to a non-aromatic 3-, 4-, 5-, 6- or 7-membered ring or a bi- or tri-cyclic
25 group fused system, where: (i) each ring contains between one and three heteroatoms independently selected from oxygen, sulfur and nitrogen, (ii) each 5-membered ring has 0 to 1 double bonds and each 6-membered ring has 0 to 2 double bonds, (iii) the nitrogen and sulfur heteroatoms may optionally be oxidized, (iv) the nitrogen heteroatom may optionally be quaternized, (v) any of the above rings may be fused to
30 a benzene ring, and (vi) the remaining ring atoms are carbon atoms which may be optionally oxo-substituted. Representative heterocycloalkyl groups include, but are not limited to, [1,3]dioxolane, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, oxazolidinyl, isoxazolidinyl, morpholinyl,

thiazolidinyl, isothiazolidinyl, quinoxaliny, pyridazinonyl, and tetrahydrofuryl. Such heterocyclic groups may be further substituted to give substituted heterocyclic.

It will be apparent that in various embodiments of the invention, the substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, arylalkyl, heteroarylalkyl, and heterocycloalkyl are intended to be monovalent or divalent. Thus, alkylene, alkenylene, and alkynylene, cycloalkylene, cycloalkenylene, cycloalkynylene, arylalkylene, heteroarylalkylene and heterocycloalkylene groups are to be included in the above definitions, and are applicable to provide the formulas herein with proper valency.

The term "hydroxy activating group", as used herein, refers to a labile chemical moiety which is known in the art to activate a hydroxy group so that it will depart during synthetic procedures such as in a substitution or elimination reactions. Examples of hydroxy activating group include, but not limited to, mesylate, tosylate, triflate, *p*-nitrobenzoate, phosphonate and the like.

The term "activated hydroxy", as used herein, refers to a hydroxy group activated with a hydroxy activating group, as defined above, including mesylate, tosylate, triflate, *p*-nitrobenzoate, phosphonate groups, for example.

The term "protected hydroxy," as used herein, refers to a hydroxy group protected with a hydroxy protecting group, as defined above, including benzoyl, acetyl, trimethylsilyl, triethylsilyl, methoxymethyl groups.

The terms "halo" and "halogen," as used herein, refer to an atom selected from fluorine, chlorine, bromine and iodine.

The compounds described herein contain one or more asymmetric centers and thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)-, or as (D)- or (L)- for amino acids. The present invention is meant to include all such possible isomers, as well as their racemic and optically pure forms. Optical isomers may be prepared from their respective optically active precursors by the procedures described above, or by resolving the racemic mixtures. The resolution can be carried out in the presence of a resolving agent, by chromatography or by repeated crystallization or by some combination of these techniques, which are known to those skilled in the art. Further details regarding resolutions can be found in Jacques, *et al.*, Enantiomers, Racemates, and Resolutions (John Wiley & Sons, 1981). When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless

specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included. The configuration of any carbon-carbon double bond appearing herein is selected for convenience only and is not intended to designate a particular configuration unless the text so states; thus a carbon-carbon double bond depicted arbitrarily herein as *trans* may be *cis*, *trans*, or a mixture of the two in any proportion.

The term "subject" as used herein refers to a mammal. A subject therefore refers to, for example, dogs, cats, horses, cows, pigs, guinea pigs, and the like. Preferably the subject is a human. When the subject is a human, the subject may be referred to herein as a patient.

As used herein, the term "pharmaceutically acceptable salt" refers to those salts of the compounds formed by the process of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art.

The term "hydroxy protecting group," as used herein, refers to a labile chemical moiety which is known in the art to protect a hydroxy group against undesired reactions during synthetic procedures. After said synthetic procedure(s) the hydroxy protecting group as described herein may be selectively removed. Hydroxy protecting groups as known in the art are described generally in T.H. Greene and P.G., S. M. Wuts, *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, New York (1999). Examples of hydroxy protecting groups include benzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, methoxycarbonyl, tert-butoxycarbonyl, isopropoxycarbonyl, diphenylmethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-(trimethylsilyl)ethoxycarbonyl, 2-furfuryloxycarbonyl, allyloxycarbonyl, acetyl, formyl, chloroacetyl, trifluoroacetyl, methoxyacetyl, phenoxyacetyl, benzoyl, methyl, t-butyl, 2,2,2-trichloroethyl, 2-trimethylsilyl ethyl, 1,1-dimethyl-2-propenyl, 3-methyl-3-butenyl, allyl, benzyl, para-methoxybenzyl, diphenylmethyl, triphenylmethyl (trityl), tetrahydrofuryl, methoxymethyl, methylthiomethyl, benzyloxymethyl, 2,2,2-trichloroethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, methanesulfonyl, para-toluenesulfonyl, trimethylsilyl, triethylsilyl, triisopropylsilyl, and the like. Preferred hydroxy protecting groups for the present invention are acetyl

(Ac or $-C(O)CH_3$), benzoyl (Bz or $-C(O)C_6H_5$), and trimethylsilyl (TMS or $-Si(CH_3)_3$). Berge, *et al.* describes pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 66: 1-19 (1977). The salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention, or separately by reacting the free

5 base function with a suitable organic acid. Examples of pharmaceutically acceptable salts include, but are not limited to, nontoxic acid addition salts e.g., salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using

10 other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include, but are not limited to, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate,

15 lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, *p*-toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or

20 alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, alkyl

25 having from 1 to 6 carbon atoms, sulfonate and aryl sulfonate.

The term "amino protecting group," as used herein, refers to a labile chemical moiety which is known in the art to protect an amino group against undesired reactions during synthetic procedures. After said synthetic procedure(s) the amino protecting group as described herein may be selectively removed. Amino protecting

30 groups as known in the art are described generally in T.H. Greene and P.G. M. Wuts, Protective Groups in Organic Synthesis, 3rd edition, John Wiley & Sons, New York (1999). Examples of amino protecting groups include, but are not limited to, *t*-butoxycarbonyl, 9-fluorenylmethoxycarbonyl, benzyloxycarbonyl, and the like.

As used herein, the term "pharmaceutically acceptable ester" refers to esters of the compounds formed by the process of the present invention which hydrolyze *in vivo* and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanolic, alkenolic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Examples of particular esters include, but are not limited to, formates, acetates, propionates, butyrates, acrylates and ethylsuccinates.

The term "pharmaceutically acceptable prodrugs" as used herein refers to those prodrugs of the compounds formed by the process of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals with undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the present invention. "Prodrug", as used herein means a compound, which is convertible *in vivo* by metabolic means (e.g. by hydrolysis) to afford any compound delineated by the formulae of the instant invention. Various forms of prodrugs are known in the art, for example, as discussed in Bundgaard, (ed.), *Design of Prodrugs*, Elsevier (1985); Widder, *et al.* (ed.), *Methods in Enzymology*, Vol. 4, Academic Press (1985); Krogsgaard-Larsen, *et al.*, (ed). "Design and Application of Prodrugs, *Textbook of Drug Design and Development*, Chapter 5, 113-191 (1991); Bundgaard, *et al.*, *Journal of Drug Deliver Reviews*, 8:1-38(1992); Bundgaard, J. of *Pharmaceutical Sciences*, 77:285 et seq. (1988); Higuchi and Stella (eds.) *Prodrugs as Novel Drug Delivery Systems*, *American Chemical Society* (1975); and Bernard Testa & Joachim Mayer, "Hydrolysis In Drug And Prodrug Metabolism: Chemistry, Biochemistry And Enzymology," John Wiley and Sons, Ltd. (2002).

The term "aprotic solvent," as used herein, refers to a solvent that is relatively inert to proton activity, i.e., not acting as a proton-donor. Examples include, but are not limited to, hydrocarbons, such as hexane and toluene, for example, halogenated hydrocarbons, such as, for example, methylene chloride, ethylene chloride, chloroform, and the like, heterocyclic compounds, such as, for example, tetrahydrofuran and N-methylpyrrolidinone, and ethers such as diethyl ether, bis-methoxymethyl ether. Such solvents are well known to those skilled in the art, and

individual solvents or mixtures thereof may be preferred for specific compounds and reaction conditions, depending upon such factors as the solubility of reagents, reactivity of reagents and preferred temperature ranges, for example. Further discussions of aprotic solvents may be found in organic chemistry textbooks or in
5 specialized monographs, for example: Organic Solvents Physical Properties and Methods of Purification, 4th ed., edited by John A. Riddick *et al.*, Vol. II, in the Techniques of Chemistry Series, John Wiley & Sons, NY, 1986.

The terms "protogenic organic solvent" or "protic solvent" as used herein, refer to a solvent that tends to provide protons, such as an alcohol, for example,
10 methanol, ethanol, propanol, isopropanol, butanol, t-butanol, and the like. Such solvents are well known to those skilled in the art, and individual solvents or mixtures thereof may be preferred for specific compounds and reaction conditions, depending upon such factors as the solubility of reagents, reactivity of reagents and preferred temperature ranges, for example. Further discussions of protogenic solvents may be
15 found in organic chemistry textbooks or in specialized monographs, for example: Organic Solvents Physical Properties and Methods of Purification, 4th ed., edited by John A. Riddick *et al.*, Vol. II, in the Techniques of Chemistry Series, John Wiley & Sons, NY, 1986.

Combinations of substituents and variables envisioned by this invention are
20 only those that result in the formation of stable compounds. The term "stable", as used herein, refers to compounds which possess stability sufficient to allow manufacture and which maintains the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (e.g., therapeutic or prophylactic administration to a subject).

25 The synthesized compounds can be separated from a reaction mixture and further purified by a method such as column chromatography, high pressure liquid chromatography, or recrystallization. Additionally, the various synthetic steps may be performed in an alternate sequence or order to give the desired compounds. In addition, the solvents, temperatures, reaction durations, etc. delineated herein are for
30 purposes of illustration only and variation of the reaction conditions can produce the desired bridged macrocyclic products of the present invention. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the compounds described herein include, for example, those described in R. Larock, Comprehensive Organic Transformations, VCH Publishers

(1989); T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 2d. Ed., John Wiley and Sons (1991); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995).

5 The compounds of this invention may be modified by appending various functionalities via synthetic means delineated herein to enhance selective biological properties. Such modifications include those which increase biological penetration into a given biological system (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter
10 metabolism and alter rate of excretion.

PHARMACEUTICAL COMPOSITIONS

 The pharmaceutical compositions of the present invention comprise a therapeutically effective amount of a compound of the present invention formulated
15 together with one or more pharmaceutically acceptable carriers. As used herein, the term "pharmaceutically acceptable carrier" means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as lactose, glucose and sucrose; starches such as corn starch and
20 potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such a propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering
25 agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants
30 can also be present in the composition, according to the judgment of the formulator. The pharmaceutical compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, or as an oral or nasal spray.

The pharmaceutical compositions of this invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir, preferably by oral administration or administration by injection. The pharmaceutical compositions of this invention may
5 contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. In some cases, the pH of the formulation may be adjusted with pharmaceutically acceptable acids, bases or buffers to enhance the stability of the formulated compound or its delivery form. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular,
10 intraarterial, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents
15 commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols
20 and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing
25 or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1, 3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils
30 are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form

of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution, which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or: a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid

polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

5 Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

10 The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical
15 formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such as magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage
20 forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

25 Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, eye ointments, powders and
30 solutions are also contemplated as being within the scope of this invention.

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

30 Powders and sprays can contain, in addition to the compounds of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons.

Transdermal patches have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled
5 by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

Antiviral Activity

An inhibitory amount or dose of the compounds of the present invention may
10 range from about 0.01 mg/Kg to about 500 mg/Kg, alternatively from about 1 to about 100 mg/Kg. Inhibitory amounts or doses will also vary depending on route of administration, as well as the possibility of co-usage with other agents.

According to the methods of treatment of the present invention, viral infections are treated or prevented in a subject such as a human or lower mammal by
15 administering to the subject an anti-hepatitis C virally effective amount or an inhibitory amount of a compound of the present invention, in such amounts and for such time as is necessary to achieve the desired result. An additional method of the present invention is the treatment of biological samples with an inhibitory amount of a compound of composition of the present invention in such amounts and for such time
20 as is necessary to achieve the desired result.

The term "anti-hepatitis C virally effective amount" of a compound of the invention, as used herein, mean a sufficient amount of the compound so as to decrease the viral load in a biological sample or in a subject (e.g., resulting in at least 10%, preferably at least 50%, more preferably at least 80%, and most preferably at least
25 90% or 95%, reduction in viral load). As well understood in the medical arts, an anti-hepatitis C virally effective amount of a compound of this invention will be at a reasonable benefit/risk ratio applicable to any medical treatment.

The term "inhibitory amount" of a compound of the present invention means a sufficient amount to decrease the hepatitis C viral load in a biological sample or a
30 subject (e.g., resulting in at least 10%, preferably at least 50%, more preferably at least 80%, and most preferably at least 90% or 95%, reduction in viral load). It is understood that when said inhibitory amount of a compound of the present invention is administered to a subject it will be at a reasonable benefit/risk ratio applicable to any medical treatment as determined by a physician. The term "biological

sample(s),” as used herein, means a substance of biological origin intended for administration to a subject. Examples of biological samples include, but are not limited to, blood and components thereof such as plasma, platelets, subpopulations of blood cells and the like; organs such as kidney, liver, heart, lung, and the like; sperm
5 and ova; bone marrow and components thereof; or stem cells. Thus, another embodiment of the present invention is a method of treating a biological sample by contacting said biological sample with an inhibitory amount of a compound or pharmaceutical composition of the present invention.

Upon improvement of a subject’s condition, a maintenance dose of a
10 compound, composition or combination of this invention may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained when the symptoms have been alleviated to the desired level, treatment should cease. The subject may, however, require intermittent treatment on a long-
15 term basis upon any recurrence of disease symptoms.

It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific inhibitory dose for any particular patient will depend upon a variety of factors including the disorder being
20 treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like
25 factors well known in the medical arts.

The total daily inhibitory dose of the compounds of this invention administered to a subject in single or in divided doses can be in amounts, for example, from 0.01 to 50 mg/kg body weight or more usually from 0.1 to 25 mg/kg body weight. Single dose compositions may contain such amounts or submultiples thereof
30 to make up the daily dose. In general, treatment regimens according to the present invention comprise administration to a patient in need of such treatment from about 10 mg to about 1000 mg of the compound(s) of this invention per day in single or multiple doses.

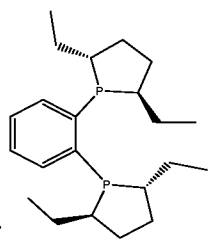
Unless otherwise defined, all technical and scientific terms used herein are accorded the meaning commonly known to one with ordinary skill in the art. All publications, patents, published patent applications, and other references mentioned herein are hereby incorporated by reference in their entirety.

5

Abbreviations

Abbreviations which have been used in the descriptions of the schemes and the examples that follow are:

- ACN for acetonitrile;
- 10 BME for 2-mercaptoethanol;
- BOP for benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate;
- BzCl for benzoyl chloride;
- CDI for carbonyldiimidazole;
- 15 COD for cyclooctadiene;
- DABCO for 1,4-diazabicyclo[2.2.2]octane;
- DAST for diethylaminosulfur trifluoride;
- DABCYL for 6-(N-4'-carboxy-4-(dimethylamino)azobenzene)- aminoethyl-1-O-(2-cyanoethyl)-(N,N-diisopropyl)-phosphoramidite;
- 20 DBU for 1, 8-Diazabicycloundec-7-ene;
- DCC for N, N'-dicyclohexylcarbodiimide;
- DCM for dichloromethane;
- DIAD for diisopropyl azodicarboxylate;
- DIBAL-H for diisobutylaluminum hydride;
- 25 DIPEA for diisopropyl ethylamine;
- DMAP for N,N-dimethylaminopyridine;
- DME for ethylene glycol dimethyl ether;
- DMEM for Dulbecco's Modified Eagles Media;
- DMF for N,N-dimethyl formamide;
- 30 DMSO for dimethylsulfoxide;
- DSC for N, N'-disuccinimidyl carbonate;



DUPHOS for ;

EDANS for 5-(2-Amino-ethylamino)-naphthalene-1-sulfonic acid;

EDCI or EDC for 1-(3-diethylaminopropyl)-3-ethylcarbodiimide
hydrochloride;

5 EtOAc for ethyl acetate;

EtOH for ethyl alcohol;

HATU for O (7-Azabenzotriazole-1-yl)-N,N,N',N'-tetramethyluronium
hexafluorophosphate;

HCl for hydrochloric acid;

10 Hoveyda's Cat. for Dichloro(*o*-isopropoxyphenylmethylene)
(tricyclohexylphosphine)ruthenium(II);

In for indium;

KHMDS is potassium bis(trimethylsilyl) amide;

Ms for mesyl;

15 NMM for N-4-methylmorpholine;

NMI for N-methylimidazole;

NMO for N-4-methylmorpholine-N-Oxide;

PyBrOP for Bromo-tri-pyrrolidino-phosphonium hexafluorophosphate;

Ph for phenyl;

20 RCM for ring-closing metathesis;

RT for reverse transcription;

RT-PCR for reverse transcription-polymerase chain reaction;

TBME for tert-butyl methyl ether;

TEA for triethyl amine;

25 Tf₂O for trifluoromethanesulfonic anhydride

TFA for trifluoroacetic acid;

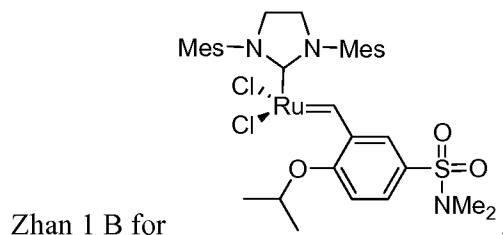
THF for tetrahydrofuran;

TLC for thin layer chromatography;

(TMS)₂NH for hexamethyldisilazane

30 TMSOTf for trimethylsilyl trifluoromethanesulfonate;

- TPAP tetrapropylammonium perruthenate;
 TPP or PPh₃ for triphenylphosphine;
 TrCl for trityl chloride;
 DMTrCl for 4,4'-dimethoxytrityl chloride;
 5 tBOC or Boc for tert-butyloxy carbonyl;
 Xantphos for 4,5-Bis-diphenylphosphanyl-9,9-dimethyl-9H-xanthene; and



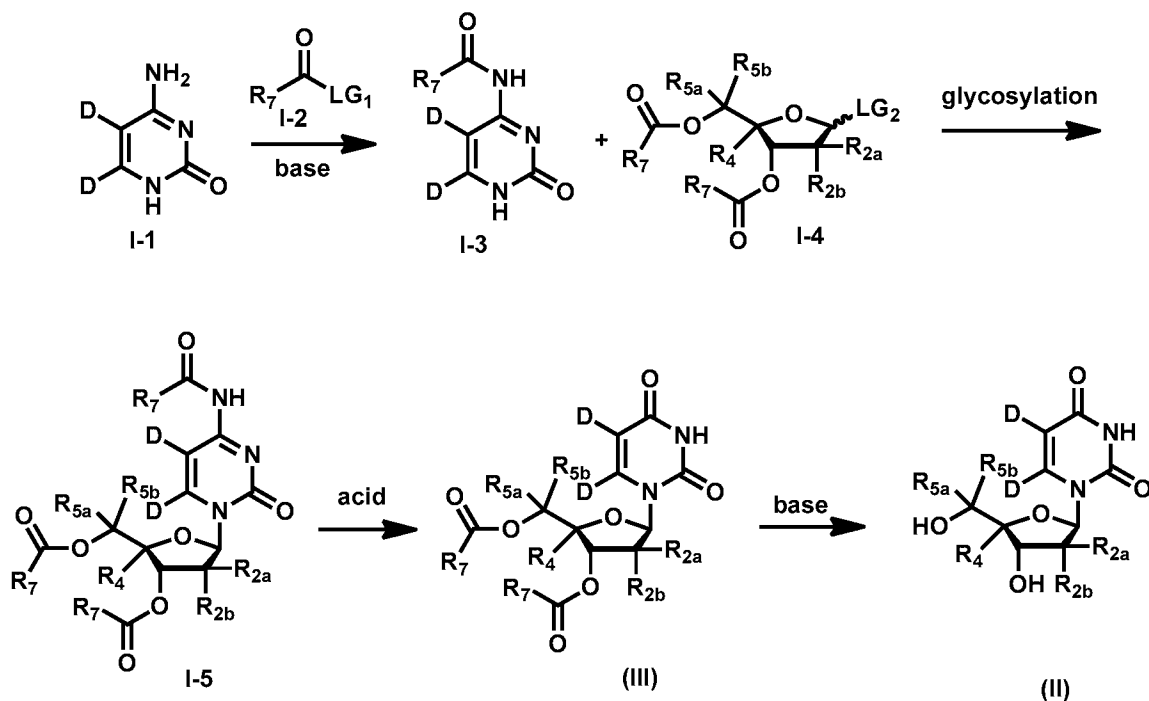
Synthetic Methods

- 10 The compounds and processes of the present invention will be better understood in connection with the following synthetic schemes that illustrate the methods by which the compounds of the invention may be prepared, which are intended as an illustration only and not to limit the scope of the invention. Various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art and such changes and modifications including, without limitation, those relating to the chemical structures, substituents, derivatives, and/or methods of the invention may be made without departing from the spirit of the invention and the scope of the appended claims.

- 20 One approach to the synthesis of deuterated compounds of Formula II is exemplified in Scheme 1, wherein R_{2a}, R_{2b}, R₄, R_{5a}, R_{5b} and R₇ is previously defined. The deuterated cytosine I-1 was treated with acylation reagent I-2 in the presence of base such as, but not limited to, DIEPA, TEA, DMAP, DBU to provide the acylated product I-3. LG₁ is defined as leaving group such as, but not limited to, -Cl, -Br, -I, -F, -OTs, -OCOCF₃, -OCOCH₃, -OSO₂CF₃, -NR₃⁺.

25

Scheme 1



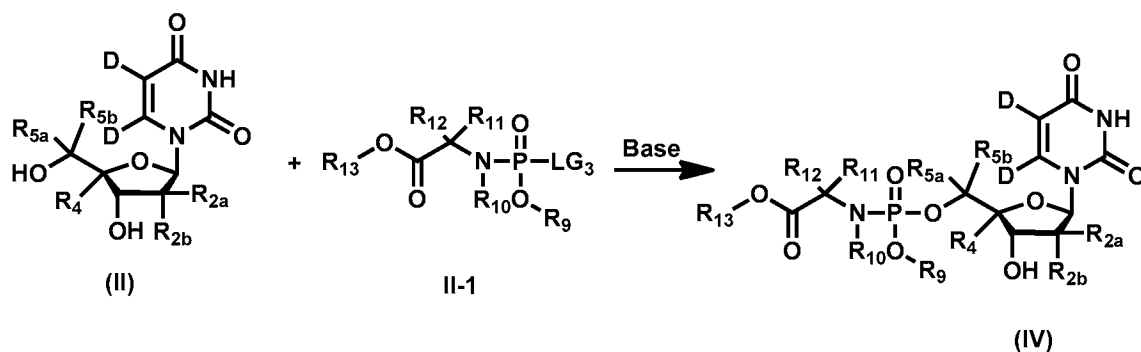
The compound I-5 could be synthesized from the glycosylation between
 5 compound I-4 and a deuterated base I-3 (or its derivatives such as, but not limited to the persilylated derivatives) employing a suitable catalyst such as, but not limited to TMSOTf or SnCl₄ with or without presence of a suitable base. Examples of suitable base includes, but not limited to, DIEPA, TEA, DMAP, DBU and DABCO. LG₂ is defined as leaving group such as, but not limited to, -Cl, -Br, -I, -F, -OTs, -OCOCF₃,
 10 -COCH₃, -OSO₂CF₃, -NR₃⁺.

The cytosine derivative I-5 could be converted into the uracil derivative of formula III via a deamination process employing a suitable acid such as, but not limited to acetic acid with or without water.

The compound of formula II could be synthesized from the deprotection of
 15 compound with formula III when treated with a suitable base such as, but not limited to NH₃ in the presence of alcohol such as, but not limited to methanol.

The compound of formula IV (R₃ = H, X = O) could be synthesized by coupling of nucleoside compound of formula II with phosphoramidate compound II-1 in the presence of organic/inorganic base such as, but not limited to, NMI, DIEPA,
 20 TEA, DMAP and iPrMgCl, as exemplified in Scheme 2. LG₃ is a leaving group such as, but not limited to, Cl or pentafluorophenoxy.

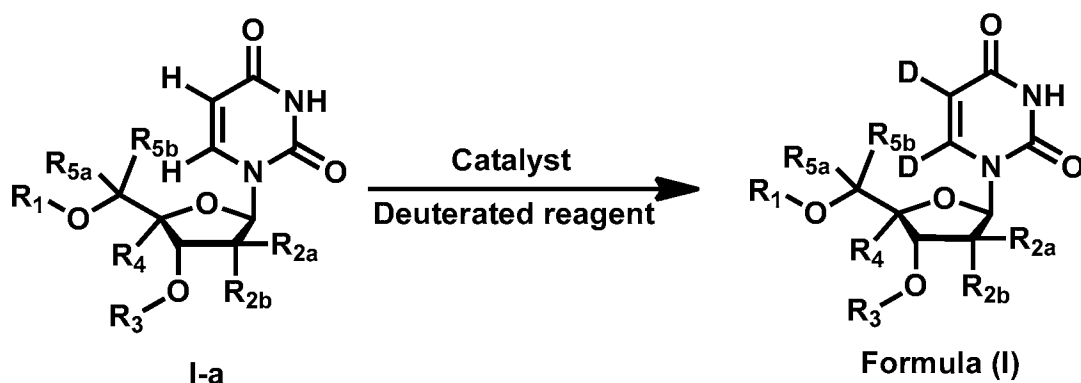
Scheme 2



5 Another approach to the synthesis of deuterated compound of Formula I is exemplified in Scheme 3. The deuterated compounds Formula (I) could be synthesized from selective deuteration of the base via H-D exchange process employing a suitable catalyst such as, but not limited to, Pd on Carbon, PtO₂, adam's catalyst with or without the presence of H₂, while D₂O or D₂ gas serving as the

10 deuterium source. (For further details on H-D exchanges see recent publications: Atzrodt et al., *Angew. Chem. Int. Ed.* **2007**, 46, 7744; Földesi et al., *Nucleos. Nucleot. Nucl.* **2000**, 19, 1615; Sajiki et al., *Synlett* **2005**, 9, 1385, Sajiki et al., *Synthesis* **2009**, 16, 2674; Maeda et al., *Tetrahedron Lett.* **1975**, 19, 1643).

Scheme 3

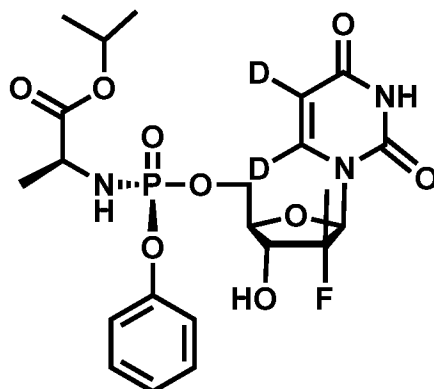


Examples

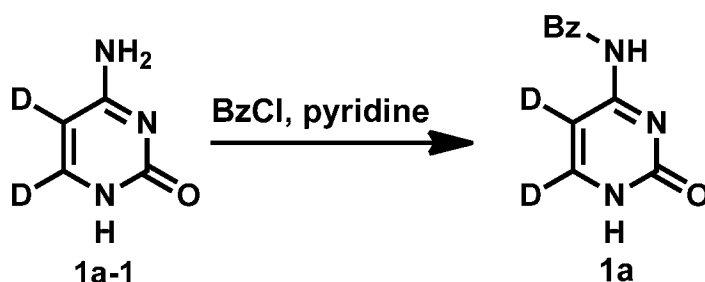
20 The compounds and processes of the present invention will be better understood in connection with the following examples, which are intended as an illustration only and not limiting of the scope of the invention. Various changes and

modifications to the disclosed embodiments will be apparent to those skilled in the art and such changes and modifications including, without limitation, those relating to the chemical structures, substituents, derivatives, formulations and/or methods of the invention may be made without departing from the spirit of the invention and the scope of the appended claims.

Example 1. Compound of Formula VII, wherein $R_{2a} = \text{Me}$, $R_{2b} = \text{F}$, $R_9 = \text{phenyl}$, $R_{11} = \text{H}$, $R_{12} = \text{Me}$, $R_{13} = \text{iPr}$,

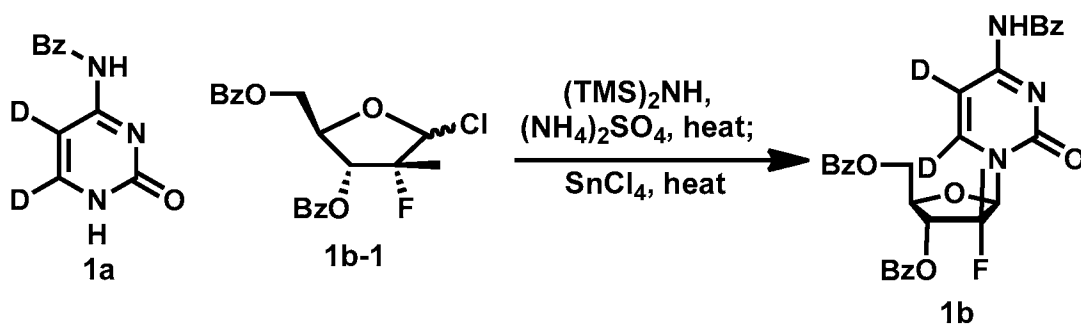


Step 1A



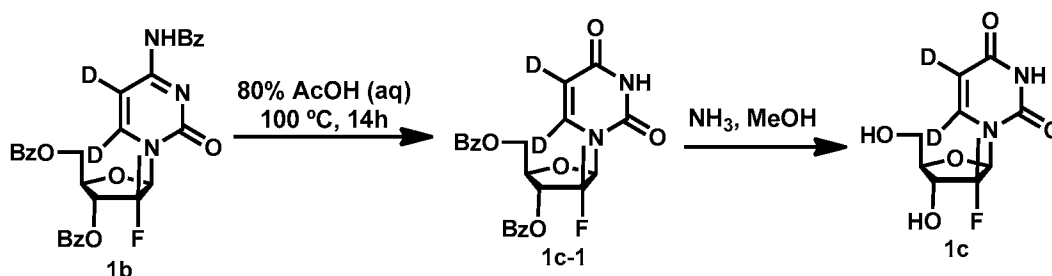
To a suspension of cytosine-5,6-d₂ **1a-1** (500 mg, 4.464 mmol) in pyridine (6 mL) at 0 °C was added BzCl (1.05 mL, 9.0 mmol) dropwise over 10 min. The resulted mixture was stirred at RT for 4 h, and quenched with MeOH (0.3 mL) and stirred for 10 min. The precipitate was collected by filtration and washed with EtOH and Et₂O. The residue was dried to give the product **1a** (642 mg, 67%). MS (ESI): *m/e* 218.11 (M+H). ¹H NMR (DMSO-D₆) δ 11.56 (s, 1H), 11.09 (s, 1H), 7.98 (d, *J* = 8.0 Hz, 2H), 7.6 (t, *J* = 8.0 Hz, 1H), 7.49 (t, *J* = 8.0 Hz, 2H).

Step 1B



- 5 To a suspension of compound (**1a**) (64 mg, 0.298 mmol) in chlorobenzene (1.5 mL) was added $(\text{NH}_4)_2\text{SO}_4$ (1.2 mg) and hexamethyldisilazane (0.8 mL). The resulted mixture was stirred at 140 °C for 1 h until the mixture became a clear solution, and the mixture was concentrated *in vacuo* without exposure to air. To this residue was added chlorobenzene (1.5 mL) and compound (**1b-1**) (~0.447 mmol) in chlorobenzene (1.5 mL) (synthesis of compound (**1b-1**) see: Steven et al. *PCT Int. Appl.* 2008045419.) and SnCl_4 (0.14 ml). The resulted mixture was heated up to 80 °C for 4 hrs and diluted with DCM. To the mixture was added NaHCO_3 (0.50 g) and celite (0.3 g) and water (84 uL). The resulted mixture was heated up to reflux for 20 min and then filtered. The filtrate was concentrated and first purified by CombiFlash (hexane to 80% EtOAc in hexane) followed by crystallization in DCM/PhCl to give the desired product **1b** (51 mg). MS (ESI): m/e 574.54 (M+H),

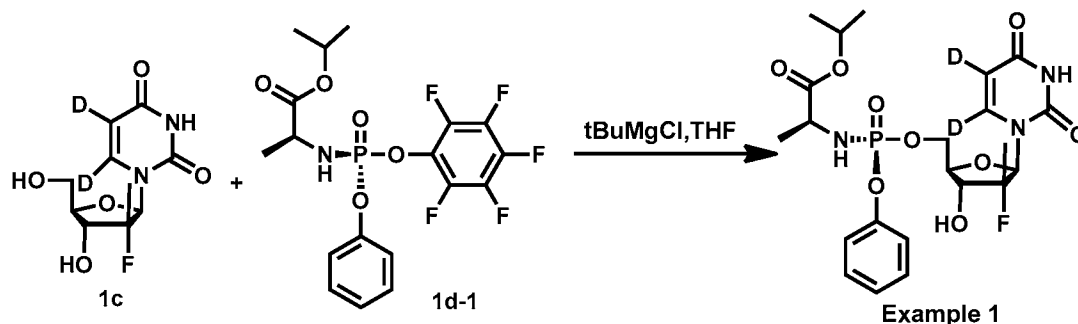
Step 1C



- 20 To compound **1b** (120 mg, 0.209 mmol) was added AcOH (2.4 mL) and water (0.6 mL), and the resulted mixture was heated up to 100 °C for 14h. The solvent was removed *in vacuo* and the residue was triturated with DCM and Et_2O to give compound **1c-1** as white powder (62 mg) after drying. To this powder was added NH_3 (3mL, 7 N in MeOH) and the suspension was stirred at RT for 14h until it became a

clear solution. The solvent was removed *in vacuo* and the residue was triturated with DCM and Et₂O to give the product **1c** (12 mg). ¹H NMR (CD₃OD) δ 6.13 (d, *J* = 18.5 Hz, 1H), 3.93-4.04 (m, 3H), 3.81 (d, *J* = 13.5 Hz, 1H), 1.36 (d, *J* = 22.5 Hz, 3H),

Step 1D



To compound **1c** (12 mg, 0.0454 mmol) in THF (1.5 mL) at 0 °C was added *t*BuMgCl (91 μL, 1.0 M in THF) dropwise and the resulted cloudy solution was stirred at RT for 20 min. To this mixture was added compound **1d-1** (37 mg, 0.817 mmol) in THF (1.0 mL) dropwise and the resulted mixture was stirred at RT for 14 h (for synthesis of compound **1d-1** see Ross et al. US 2011/0251152 A1). The resulted mixture was quenched with NaHCO₃ (aq) and the mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography (DCM to 8% MeOH in DCM) to afford the product **Example 1** (8 mg). MS (ESI): *m/e* 532.1 (M+H). ¹H NMR (CDCl₃) δ 8.73 (s, 1H), 7.35-7.40 (m, 2H), 7.17-7.26 (m, 3H), 6.19 (d, *J* = 18.0 Hz, 1H), 4.99-5.07 (m, 1H), 4.51-4.59 (m, 1H), 4.42-4.50 (m, 1H), 4.10-4.15 (m, 1H), 3.89-4.00 (m, 2H), 1.42 (d, *J* = 22.5 Hz, 6H), 1.34-1.38 (m, 3H), 1.25 (d, *J* = 7.0 Hz, 6H).

BIOLOGICAL ACTIVITY

1. HCV Replicon Cell Lines

HCV replicon cell lines (kindly provided by R. Bartenschlager) isolated from colonies as described by Lohman et al. (Lohman et al. (1999) Science 285: 110-113, expressly incorporated by reference in its entirety) and used for all experiments. One of the HCV replicon cell lines (strain Con1, genotype 1b) has the nucleic acid sequence set forth in EMBL Accession No.: AJ242651, the coding sequence of which is from nucleotides 1801 to 8406. Another replicon cell line (strain H77, genotype 1a) was constructed as described by Yi et. al. (Yi et. al. (2004) Journal of Virology 78(15):7904-15). The coding sequences of the published HCV replicons were

synthesized and subsequently assembled in plasmids using standard molecular biology techniques.

One replicon cell line ("SGR 11-7") stably expresses HCV replicon RNA, genotype 1b, which consists of (i) the HCV 5'UTR fused to the first 12 amino acids of the capsid protein, (ii) the neomycin phosphotransferase gene (neo), and (iii) the IRES from encephalomyocarditis virus (EMCV) and (iv) HCV NS2 to NS5B genes and the HCV 3'UTR. Another replicon cell line ("Huh-1a7") described by Yi et. al. (Yi et. al. (2004) Journal of Virology 78(15):7904-15, expressly incorporated by reference in its entirety) stably expresses HCV replicon RNA, genotype 1a, which consists of (i) the HCV 5'UTR fused to the first 12 amino acids of the capsid protein, (ii) the HIV tat protein, (iii) the neomycin phosphotransferase gene (neo), and (iv) the IRES from encephalomyocarditis virus (EMCV) and (vi) HCV NS3 to NS5B genes that harbor cell culture adaptive mutations (Q1067R, K1691R, S2204I) and the HCV 3'UTR.

These cell lines are maintained at 37°C, 5% CO₂, 100% relative humidity in DMEM (Cat# 11965-084, Invitrogen), with 10% fetal calf serum ("FCS", Invitrogen), 1% non-essential amino acids (Invitrogen), 1% of Glutamax (Invitrogen), 1% of 100X penicillin/streptomycin (Cat# 15140-122, Invitrogen) and Geneticin (Cat# 10131-027, Invitrogen) at 0.75 mg/ml or 0.25 mg/ml for 11-7 and Huh-1a7 cells, respectively.

2. HCV Replicon Assay – qRT-PCR.

EC₅₀ values of single agent compounds were determined by HCV RNA detection using quantitative RT-PCR, according to the manufacturer's instructions, with a TAQMAN® One-Step RT-PCR Master Mix Reagents Kit (Cat# AB 4309169, Applied Biosystems) on an ABI Model 7500 thermocycler. EC₅₀ values of combinations are similarly determined by HCV RNA detection using quantitative RT-PCR. The TAQMAN primers to use for detecting and quantifying HCV RNA obtained from Integrated DNA Technologies. HCV RNA is normalized to GAPDH RNA levels in drug-treated cells, which is detected and quantified using the Human GAPDH Endogenous Control Mix (Applied Biosystems, AB 4310884E). Total cellular RNA is purified from 96-well plates using the RNAqueous 96 kit (Ambion, Cat# AM1812). Chemical agent cytotoxicity is evaluated using an MTS assay according to the manufacturer's directions (Promega).

The compounds of the present invention can be effective against the HCV 1a and 1b genotypes. It should also be understood that the compounds of the present

invention can inhibit multiple genotypes of HCV. In one embodiment, compounds of the present invention are active against the 1a, 1b, 2a, 2b, 3a, 4a, and 5a genotypes.

Table 5 shows the EC₅₀ values of representative compounds of the present invention against the HCV 1a and 1b genotypes from the above described qRT-PCR. EC₅₀

5 ranges against HCV 1a are as follows: A >1 μ M; B 0.1-1 μ M; C < 0.1 μ M.

Table 5: Genotype-1a replicon EC₅₀

Example	1a EC ₅₀
1	B

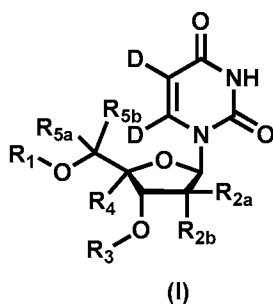
While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in

10 the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

CLAIMS

WHAT IS CLAIMED IS:

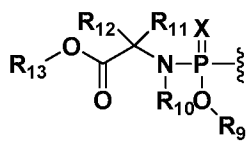
- 5 1. A compound represented by Formula I or a pharmaceutically acceptable salt, ester, stereoisomer, tautomer, solvate, or combination thereof:



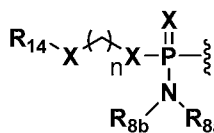
wherein:

- 10 R_1 is selected from the group consisting of:
- 1) Hydrogen;
 - 2) R_6 ; where R_6 is selected from the group consisting of: hydrogen, hydroxy protecting group, $-C(O)R_7$, $-C(O)OR_7$, and $-C(O)NR_{8a}R_{8b}$; wherein R_7 is selected from the group consisting of: substituted or unsubstituted $-C_1-C_8$ alkyl, substituted or unsubstituted $-C_2-C_8$ alkenyl, substituted or unsubstituted $-C_2-C_8$ alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, and substituted or unsubstituted heterocyclic; R_{8a} and R_{8b} are each independently selected from the group consisting of: hydrogen and R_7 ; or alternatively R_{8a} and R_{8b} taken together with the nitrogen atom to which they are attached form a heterocyclic ring;
 - 3) $-P(O)(OR_{7a})(OR_{7b})$; wherein R_{7a} and R_{7b} are each independently selected from the group consisting of a) hydrogen; b) unsubstituted or substituted $-C_1-C_8$ alkyl;
 - 4) $-P(O)(OR_{7a})-O-P(O)(OR_{7b})(OR_{7c})$; wherein R_{7a} and R_{7b} are previously defined; R_{7c} is selected from the group consisting of a) hydrogen; b) unsubstituted or substituted $-C_1-C_8$ alkyl;

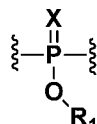
- 5) $-P(O)(OR_{7a})-O-P(O)(OR_{7b})-O-P(O)(OR_{7c})(OR_{7d})$; wherein R_{7a} , R_{7b} and R_{7c} are previously defined; R_{7d} is selected from the group consisting of a) hydrogen; b) unsubstituted or substituted $-C_1-C_8$ alkyl;



- 6) where X is O or S; R_9 is R_7 wherein R_7 is previously defined; R_{10} , R_{11} and R_{12} are each independently selected from the group consisting of : a) hydrogen; b) unsubstituted or substituted $-C_1-C_8$ alkyl; c) R_{11} is hydrogen, R_{12} and R_{10} taken together with the nitrogen which R_{10} is attached to form a heterocyclic ring; d) R_{11} and R_{12} taken together with the carbon which they are attached form a ring; R_{13} is hydrogen or R_7 , wherein R_7 is previously defined; and



- 7) where X is O or S; n is 1-4; R_{8a} and R_{8b} are as previously defined; R_{14} is hydrogen or $-(CO)-R_7$, wherein R_7 is as previously defined;



- 8) Or, R_1 and R_3 are taken together to form $-P(O)(OR_{15})-$, where X is O or S; and R_{15} is selected from the group consisting of a) hydrogen; b) unsubstituted or substituted $-C_1-C_8$ alkyl; c) substituted or unsubstituted $-C_2-C_8$ alkenyl; d) substituted or unsubstituted $-C_2-C_8$ alkynyl; e) substituted or unsubstituted aryl; f) substituted or unsubstituted heteroaryl;

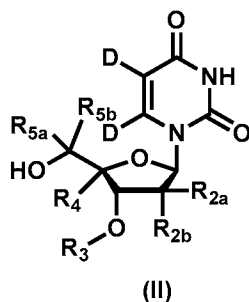
- R_{2a} at each occurrence is selected from the group consisting of:

- 1) hydrogen;
- 2) halogen;
- 3) Substituted or unsubstituted $-C_1-C_8$ alkyl;
- 4) Substituted or unsubstituted $-C_2-C_8$ alkenyl; and
- 5) Substituted or unsubstituted $-C_2-C_8$ alkynyl;

R_{2b} and R_4 are independently selected from the group consisting of:

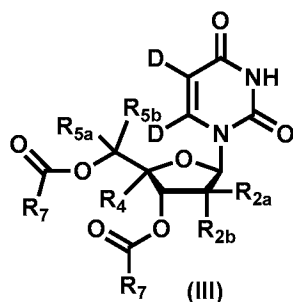
- 1) hydrogen;

- 2) halogen;
 3) $-\text{CN}$;
 4) $-\text{N}_3$; and
 5) OR_9 ;
- 5 R_9 at each occurrence is selected from the group consisting of: hydrogen, hydroxy protecting group, R_{10} , $-\text{C}(\text{O})\text{R}_{10}$, $-\text{C}(\text{O})\text{OR}_{10}$, and $-\text{C}(\text{O})\text{NR}_{11a}\text{R}_{11b}$; wherein R_{10} at each occurrence is independently selected from the group consisting of: substituted or unsubstituted $-\text{C}_1\text{-C}_8$ alkyl, substituted or unsubstituted $-\text{C}_2\text{-C}_8$ alkenyl, substituted or unsubstituted $-\text{C}_2\text{-C}_8$ alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, and substituted or unsubstituted heterocyclic; R_{11a} and R_{11b} at each occurrence are each independently selected from the group consisting of: hydrogen and R_{10} ; or alternatively R_{11a} and R_{11b} taken together with the nitrogen atom to which they are attached form a heterocyclic ring;
- 10 R_3 is R_6 ; wherein R_6 is as previously defined;
 R_{5a} and R_{5b} are independently selected from the group consisting of:
- 1) hydrogen;
 2) substituted or unsubstituted $-\text{C}_1\text{-C}_8$ alkyl;
 3) substituted or unsubstituted $-\text{C}_2\text{-C}_8$ alkenyl; and
 4) substituted or unsubstituted $-\text{C}_2\text{-C}_8$ alkynyl;
- 20 or R_{5a} and R_{5b} are taken together with the carbon atom to which they are attached to form a group selected from $-\text{C}_3\text{-C}_8$ cycloalkyl, $-\text{C}_3\text{-C}_8$ cycloalkenyl, or $-\text{C}_3\text{-C}_8$ cycloalkynyl.
- 25 2. A compound of claim 1 represented by Formula II or a pharmaceutically acceptable salt, ester, stereoisomer, tautomer, solvate, or combination thereof:



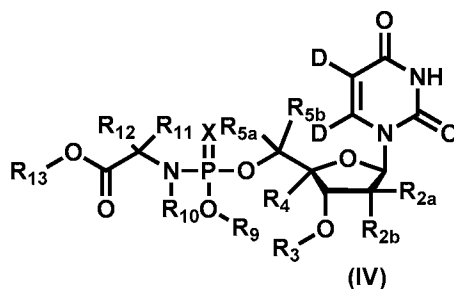
wherein, R_{2a} , R_{2b} , R_3 , R_4 , R_{5a} and R_{5b} are as previously defined.

3. A compound of claim 1 represented by Formula III or a pharmaceutically acceptable salt, ester, stereoisomer, tautomer, solvate, or combination thereof:



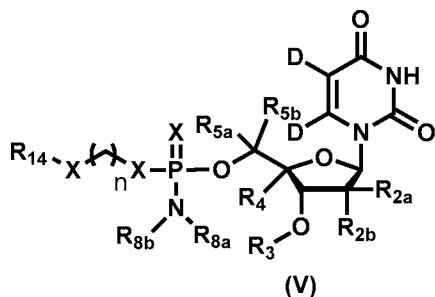
wherein, R_{2a} , R_{2b} , R_4 , R_{5a} , R_{5b} , and R_7 are as previously defined.

4. A compound of claim 1 represented by Formula IV or a pharmaceutically acceptable salt, ester, stereoisomer, tautomer, solvate, or combination thereof:



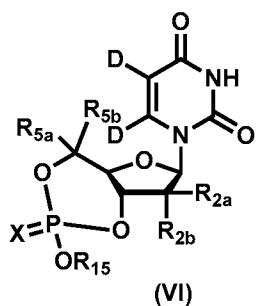
wherein, R_{2a} , R_{2b} , R_3 , R_4 , R_{5a} , R_{5b} , R_9 , R_{10} , R_{11} , R_{12} , and R_{13} are as previously defined.
X is O or S.

5. A compound of claim 1 represented by Formula V or a pharmaceutically acceptable salt, ester, stereoisomer, tautomer, solvate, or combination thereof:



wherein, R_{2a} , R_{2b} , R_3 , R_4 , R_{5a} , R_{5b} , R_{8a} , R_{8b} , and R_{14} are as previously defined, X is O or S, n is 1~4.

6. A compound of claim 1 represented by Formula VI or a pharmaceutically acceptable salt, ester, stereoisomer, tautomer, solvate, or combination thereof:



wherein, R_{2a} , R_{2b} , R_{5a} , R_{5b} , and R_{15} are as previously defined, X is O or S.

7. A compound according to claim 1 as set forth in any of Tables 1 ~ Table 4 which is selected from compounds of Formula VII ~ Formula X;

Compounds in Table 1 were illustrated according to Formula VII wherein, R_{2a} , R_{2b} , R_9 , R_{11} , R_{12} , and R_{13} are delineated for each example in Table 1;

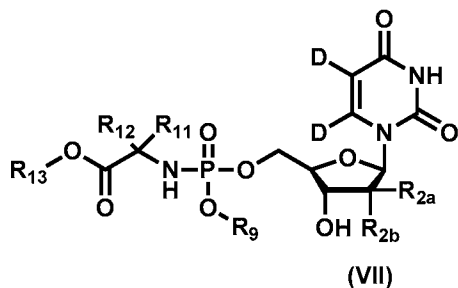


Table 1

Example	R_{2a}	R_{2b}	R_9	R_{11}	R_{12}	R_{13}
1	Me	OH	Ph	Me	H	iPr
2	Me	OH	Ph	Me	H	Me
3	Me	OH	Ph	Me	H	Et
4	Me	OH	Ph	Me	H	Bn
5	Me	OH	Ph	Me	H	$\text{CH}_2\text{CH}(\text{CH}_3)_2$
6	Me	F	Ph	Me	H	iPr
7	Me	F	Ph	Me	H	Me
8	Me	F	Ph	Me	H	Et

9	Me	F	Ph	Me	H	Bn
10	Me	F	Ph	Me	H	CH ₂ CH(CH ₃) ₂
11	Me	OH	Ph	H	H	iPr
12	Me	OH	Ph	H	H	Me
13	Me	OH	Ph	H	H	Et
14	Me	OH	Ph	H	H	Bn
15	Me	OH	Ph	H	H	CH ₂ CH(CH ₃) ₂
16	Me	F	Ph	H	H	iPr
17	Me	F	Ph	H	H	Me
18	Me	F	Ph	H	H	Et
19	Me	F	Ph	H	H	Bn
20	Me	F	Ph	H	H	CH ₂ CH(CH ₃) ₂
21	Me	OH	Ph	iPr	H	iPr
22	Me	OH	Ph	iPr	H	Me
23	Me	OH	Ph	iPr	H	Et
24	Me	OH	Ph	iPr	H	Bn
25	Me	OH	Ph	iPr	H	CH ₂ CH(CH ₃) ₂
26	Me	F	Ph	iPr	H	iPr
27	Me	F	Ph	iPr	H	Me
28	Me	F	Ph	iPr	H	Et
29	Me	F	Ph	iPr	H	Bn
30	Me	F	Ph	iPr	H	CH ₂ CH(CH ₃) ₂
31	Me	OH	Ph	CH ₂ CH(CH ₃) ₂	H	iPr
32	Me	OH	Ph	CH ₂ CH(CH ₃) ₂	H	Me
33	Me	OH	Ph	CH ₂ CH(CH ₃) ₂	H	Et
34	Me	OH	Ph	CH ₂ CH(CH ₃) ₂	H	Bn
35	Me	OH	Ph	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
36	Me	F	Ph	CH ₂ CH(CH ₃) ₂	H	iPr
37	Me	F	Ph	CH ₂ CH(CH ₃) ₂	H	Me
38	Me	F	Ph	CH ₂ CH(CH ₃) ₂	H	Et
39	Me	F	Ph	CH ₂ CH(CH ₃) ₂	H	Bn
40	Me	F	Ph	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
41	Me	OH	Ph	CH ₂ Ph	H	iPr
42	Me	OH	Ph	CH ₂ Ph	H	Me
43	Me	OH	Ph	CH ₂ Ph	H	Et
44	Me	OH	Ph	CH ₂ Ph	H	Bn
45	Me	OH	Ph	CH ₂ Ph	H	CH ₂ CH(CH ₃) ₂
46	Me	F	Ph	CH ₂ Ph	H	iPr
47	Me	F	Ph	CH ₂ Ph	H	Me

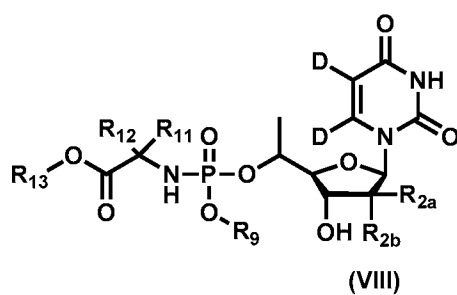
48	Me	F	Ph	CH ₂ Ph	H	Et
49	Me	F	Ph	CH ₂ Ph	H	Bn
50	Me	F	Ph	CH ₂ Ph	H	CH ₂ CH(CH ₃) ₂
51	Me	OH	1-Naphthyl	Me	H	iPr
52	Me	OH	1-Naphthyl	Me	H	Me
53	Me	OH	1-Naphthyl	Me	H	Et
54	Me	OH	1-Naphthyl	Me	H	Bn
55	Me	OH	1-Naphthyl	Me	H	CH ₂ CH(CH ₃) ₂
56	Me	F	1-Naphthyl	Me	H	iPr
57	Me	F	1-Naphthyl	Me	H	Me
58	Me	F	1-Naphthyl	Me	H	Et
59	Me	F	1-Naphthyl	Me	H	Bn
60	Me	F	1-Naphthyl	Me	H	CH ₂ CH(CH ₃) ₂
61	Me	OH	1-Naphthyl	H	H	iPr
62	Me	OH	1-Naphthyl	H	H	Me
63	Me	OH	1-Naphthyl	H	H	Et
64	Me	OH	1-Naphthyl	H	H	Bn
65	Me	OH	1-Naphthyl	H	H	CH ₂ CH(CH ₃) ₂
66	Me	F	1-Naphthyl	H	H	iPr
67	Me	F	1-Naphthyl	H	H	Me
68	Me	F	1-Naphthyl	H	H	Et
69	Me	F	1-Naphthyl	H	H	Bn
70	Me	F	1-Naphthyl	H	H	CH ₂ CH(CH ₃) ₂
71	Me	OH	1-Naphthyl	iPr	H	iPr
72	Me	OH	1-Naphthyl	iPr	H	Me
73	Me	OH	1-Naphthyl	iPr	H	Et
74	Me	OH	1-Naphthyl	iPr	H	Bn
75	Me	OH	1-Naphthyl	iPr	H	CH ₂ CH(CH ₃) ₂
76	Me	F	1-Naphthyl	iPr	H	iPr
77	Me	F	1-Naphthyl	iPr	H	Me
78	Me	F	1-Naphthyl	iPr	H	Et
79	Me	F	1-Naphthyl	iPr	H	Bn
80	Me	F	1-Naphthyl	iPr	H	CH ₂ CH(CH ₃) ₂
81	Me	OH	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	iPr
82	Me	OH	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	Me
83	Me	OH	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	Et
84	Me	OH	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	Bn
85	Me	OH	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
86	Me	F	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	iPr

87	Me	F	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	Me
88	Me	F	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	Et
89	Me	F	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	Bn
90	Me	F	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
91	Me	OH	1-Naphthyl	CH ₂ Ph	H	iPr
92	Me	OH	1-Naphthyl	CH ₂ Ph	H	Me
93	Me	OH	1-Naphthyl	CH ₂ Ph	H	Et
94	Me	OH	1-Naphthyl	CH ₂ Ph	H	Bn
95	Me	OH	1-Naphthyl	CH ₂ Ph	H	CH ₂ CH(CH ₃) ₂
96	Me	F	1-Naphthyl	CH ₂ Ph	H	iPr
97	Me	F	1-Naphthyl	CH ₂ Ph	H	Me
98	Me	F	1-Naphthyl	CH ₂ Ph	H	Et
99	Me	F	1-Naphthyl	CH ₂ Ph	H	Bn
100	Me	F	1-Naphthyl	CH ₂ Ph	H	CH ₂ CH(CH ₃) ₂
101	Me	OH	p-F-Phenyl	Me	H	iPr
102	Me	OH	p-F-Phenyl	Me	H	Me
103	Me	OH	p-F-Phenyl	Me	H	Et
104	Me	OH	p-F-Phenyl	Me	H	Bn
105	Me	OH	p-F-Phenyl	Me	H	CH ₂ CH(CH ₃) ₂
106	Me	F	p-F-Phenyl	Me	H	iPr
107	Me	F	p-F-Phenyl	Me	H	Me
108	Me	F	p-F-Phenyl	Me	H	Et
109	Me	F	p-F-Phenyl	Me	H	Bn
110	Me	F	p-F-Phenyl	Me	H	CH ₂ CH(CH ₃) ₂
111	Me	OH	p-F-Phenyl	H	H	iPr
112	Me	OH	p-F-Phenyl	H	H	Me
113	Me	OH	p-F-Phenyl	H	H	Et
114	Me	OH	p-F-Phenyl	H	H	Bn
115	Me	OH	p-F-Phenyl	H	H	CH ₂ CH(CH ₃) ₂
116	Me	F	p-F-Phenyl	H	H	iPr
117	Me	F	p-F-Phenyl	H	H	Me
118	Me	F	p-F-Phenyl	H	H	Et
119	Me	F	p-F-Phenyl	H	H	Bn
120	Me	F	p-F-Phenyl	H	H	CH ₂ CH(CH ₃) ₂
121	Me	OH	p-F-Phenyl	iPr	H	iPr
122	Me	OH	p-F-Phenyl	iPr	H	Me
123	Me	OH	p-F-Phenyl	iPr	H	Et
124	Me	OH	p-F-Phenyl	iPr	H	Bn
125	Me	OH	p-F-Phenyl	iPr	H	CH ₂ CH(CH ₃) ₂

126	Me	F	p-F-Phenyl	iPr	H	iPr
127	Me	F	p-F-Phenyl	iPr	H	Me
128	Me	F	p-F-Phenyl	iPr	H	Et
129	Me	F	p-F-Phenyl	iPr	H	Bn
130	Me	F	p-F-Phenyl	iPr	H	CH ₂ CH(CH ₃) ₂
131	Me	OH	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	iPr
132	Me	OH	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	Me
133	Me	OH	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	Et
134	Me	OH	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	Bn
135	Me	OH	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
136	Me	F	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	iPr
137	Me	F	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	Me
138	Me	F	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	Et
139	Me	F	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	Bn
140	Me	F	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
141	Me	OH	p-F-Phenyl	CH ₂ Ph	H	iPr
142	Me	OH	p-F-Phenyl	CH ₂ Ph	H	Me
143	Me	OH	p-F-Phenyl	CH ₂ Ph	H	Et
144	Me	OH	p-F-Phenyl	CH ₂ Ph	H	Bn
145	Me	OH	p-F-Phenyl	CH ₂ Ph	H	CH ₂ CH(CH ₃) ₂
146	Me	F	p-F-Phenyl	CH ₂ Ph	H	iPr
147	Me	F	p-F-Phenyl	CH ₂ Ph	H	Me
148	Me	F	p-F-Phenyl	CH ₂ Ph	H	Et
149	Me	F	p-F-Phenyl	CH ₂ Ph	H	Bn
150	Me	F	p-F-Phenyl	CH ₂ Ph	H	CH ₂ CH(CH ₃) ₂
151	Me	OH	iPr	Me	H	iPr
152	Me	OH	iPr	Me	H	Me
153	Me	OH	iPr	Me	H	Et
154	Me	OH	iPr	Me	H	Bn
155	Me	OH	iPr	Me	H	CH ₂ CH(CH ₃) ₂
156	Me	F	iPr	Me	H	iPr
157	Me	F	iPr	Me	H	Me
158	Me	F	iPr	Me	H	Et
159	Me	F	iPr	Me	H	Bn
160	Me	F	iPr	Me	H	CH ₂ CH(CH ₃) ₂
161	Me	OH	iPr	H	H	iPr
162	Me	OH	iPr	H	H	Me
163	Me	OH	iPr	H	H	Et
164	Me	OH	iPr	H	H	Bn

165	Me	OH	iPr	H	H	CH ₂ CH(CH ₃) ₂
166	Me	F	iPr	H	H	iPr
167	Me	F	iPr	H	H	Me
168	Me	F	iPr	H	H	Et
169	Me	F	iPr	H	H	Bn
170	Me	F	iPr	H	H	CH ₂ CH(CH ₃) ₂
171	Me	OH	iPr	iPr	H	iPr
172	Me	OH	iPr	iPr	H	Me
173	Me	OH	iPr	iPr	H	Et
174	Me	OH	iPr	iPr	H	Bn
175	Me	OH	iPr	iPr	H	CH ₂ CH(CH ₃) ₂
176	Me	F	iPr	iPr	H	iPr
177	Me	F	iPr	iPr	H	Me
178	Me	F	iPr	iPr	H	Et
179	Me	F	iPr	iPr	H	Bn
180	Me	F	iPr	iPr	H	CH ₂ CH(CH ₃) ₂
181	Me	OH	iPr	CH ₂ CH(CH ₃) ₂	H	iPr
182	Me	OH	iPr	CH ₂ CH(CH ₃) ₂	H	Me
183	Me	OH	iPr	CH ₂ CH(CH ₃) ₂	H	Et
184	Me	OH	iPr	CH ₂ CH(CH ₃) ₂	H	Bn
185	Me	OH	iPr	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
186	Me	F	iPr	CH ₂ CH(CH ₃) ₂	H	iPr
187	Me	F	iPr	CH ₂ CH(CH ₃) ₂	H	Me
188	Me	F	iPr	CH ₂ CH(CH ₃) ₂	H	Et
189	Me	F	iPr	CH ₂ CH(CH ₃) ₂	H	Bn
190	Me	F	iPr	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
191	Me	OH	iPr	CH ₂ Ph	H	iPr
192	Me	OH	iPr	CH ₂ Ph	H	Me
193	Me	OH	iPr	CH ₂ Ph	H	Et
194	Me	OH	iPr	CH ₂ Ph	H	Bn
195	Me	OH	iPr	CH ₂ Ph	H	CH ₂ CH(CH ₃) ₂
196	Me	F	iPr	CH ₂ Ph	H	iPr
197	Me	F	iPr	CH ₂ Ph	H	Me
198	Me	F	iPr	CH ₂ Ph	H	Et
199	Me	F	iPr	CH ₂ Ph	H	Bn
200	Me	F	iPr	CH ₂ Ph	H	CH ₂ CH(CH ₃) ₂

Compounds in Table 2 were illustrated according to Formula VIII, wherein, R_{2a}, R_{2b}, R₉, R₁₁, R₁₂, and R₁₃ are delineated for each example in Table 2;

**Table 2**

Example	R _{2a}	R _{2b}	R ₉	R ₁₁	R ₁₂	R ₁₃
201	Me	OH	Ph	Me	H	iPr
202	Me	OH	Ph	Me	H	Me
203	Me	OH	Ph	Me	H	Et
204	Me	OH	Ph	Me	H	Bn
205	Me	OH	Ph	Me	H	CH ₂ CH(CH ₃) ₂
206	Me	F	Ph	Me	H	iPr
207	Me	F	Ph	Me	H	Me
208	Me	F	Ph	Me	H	Et
209	Me	F	Ph	Me	H	Bn
210	Me	F	Ph	Me	H	CH ₂ CH(CH ₃) ₂
211	Me	OH	Ph	H	H	iPr
212	Me	OH	Ph	H	H	Me
213	Me	OH	Ph	H	H	Et
214	Me	OH	Ph	H	H	Bn
215	Me	OH	Ph	H	H	CH ₂ CH(CH ₃) ₂
216	Me	F	Ph	H	H	iPr
217	Me	F	Ph	H	H	Me
218	Me	F	Ph	H	H	Et
219	Me	F	Ph	H	H	Bn
220	Me	F	Ph	H	H	CH ₂ CH(CH ₃) ₂
221	Me	OH	Ph	iPr	H	iPr
222	Me	OH	Ph	iPr	H	Me
223	Me	OH	Ph	iPr	H	Et
224	Me	OH	Ph	iPr	H	Bn
225	Me	OH	Ph	iPr	H	CH ₂ CH(CH ₃) ₂
226	Me	F	Ph	iPr	H	iPr
227	Me	F	Ph	iPr	H	Me
228	Me	F	Ph	iPr	H	Et
229	Me	F	Ph	iPr	H	Bn

230	Me	F	Ph	iPr	H	CH ₂ CH(CH ₃) ₂
231	Me	OH	Ph	CH ₂ CH(CH ₃) ₂	H	iPr
232	Me	OH	Ph	CH ₂ CH(CH ₃) ₂	H	Me
233	Me	OH	Ph	CH ₂ CH(CH ₃) ₂	H	Et
234	Me	OH	Ph	CH ₂ CH(CH ₃) ₂	H	Bn
235	Me	OH	Ph	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
236	Me	F	Ph	CH ₂ CH(CH ₃) ₂	H	iPr
237	Me	F	Ph	CH ₂ CH(CH ₃) ₂	H	Me
238	Me	F	Ph	CH ₂ CH(CH ₃) ₂	H	Et
239	Me	F	Ph	CH ₂ CH(CH ₃) ₂	H	Bn
240	Me	F	Ph	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
241	Me	OH	Ph	CH ₂ Ph	H	iPr
242	Me	OH	Ph	CH ₂ Ph	H	Me
243	Me	OH	Ph	CH ₂ Ph	H	Et
244	Me	OH	Ph	CH ₂ Ph	H	Bn
245	Me	OH	Ph	CH ₂ Ph	H	CH ₂ CH(CH ₃) ₂
246	Me	F	Ph	CH ₂ Ph	H	iPr
247	Me	F	Ph	CH ₂ Ph	H	Me
248	Me	F	Ph	CH ₂ Ph	H	Et
249	Me	F	Ph	CH ₂ Ph	H	Bn
250	Me	F	Ph	CH ₂ Ph	H	CH ₂ CH(CH ₃) ₂
251	Me	OH	1-Naphthyl	Me	H	iPr
252	Me	OH	1-Naphthyl	Me	H	Me
253	Me	OH	1-Naphthyl	Me	H	Et
254	Me	OH	1-Naphthyl	Me	H	Bn
255	Me	OH	1-Naphthyl	Me	H	CH ₂ CH(CH ₃) ₂
256	Me	F	1-Naphthyl	Me	H	iPr
257	Me	F	1-Naphthyl	Me	H	Me
258	Me	F	1-Naphthyl	Me	H	Et
259	Me	F	1-Naphthyl	Me	H	Bn
260	Me	F	1-Naphthyl	Me	H	CH ₂ CH(CH ₃) ₂
261	Me	OH	1-Naphthyl	H	H	iPr
262	Me	OH	1-Naphthyl	H	H	Me
263	Me	OH	1-Naphthyl	H	H	Et
264	Me	OH	1-Naphthyl	H	H	Bn
265	Me	OH	1-Naphthyl	H	H	CH ₂ CH(CH ₃) ₂
266	Me	F	1-Naphthyl	H	H	iPr
267	Me	F	1-Naphthyl	H	H	Me
268	Me	F	1-Naphthyl	H	H	Et

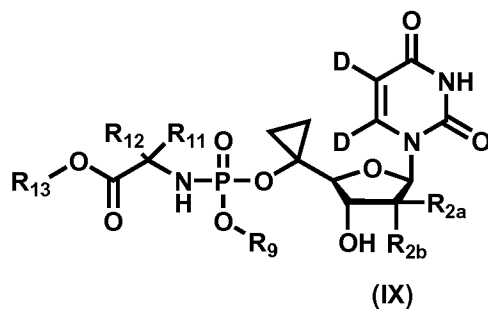
269	Me	F	1-Naphthyl	H	H	Bn
270	Me	F	1-Naphthyl	H	H	CH ₂ CH(CH ₃) ₂
271	Me	OH	1-Naphthyl	iPr	H	iPr
272	Me	OH	1-Naphthyl	iPr	H	Me
273	Me	OH	1-Naphthyl	iPr	H	Et
274	Me	OH	1-Naphthyl	iPr	H	Bn
275	Me	OH	1-Naphthyl	iPr	H	CH ₂ CH(CH ₃) ₂
276	Me	F	1-Naphthyl	iPr	H	iPr
277	Me	F	1-Naphthyl	iPr	H	Me
278	Me	F	1-Naphthyl	iPr	H	Et
279	Me	F	1-Naphthyl	iPr	H	Bn
280	Me	F	1-Naphthyl	iPr	H	CH ₂ CH(CH ₃) ₂
281	Me	OH	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	iPr
282	Me	OH	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	Me
283	Me	OH	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	Et
284	Me	OH	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	Bn
285	Me	OH	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
286	Me	F	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	iPr
287	Me	F	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	Me
288	Me	F	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	Et
289	Me	F	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	Bn
290	Me	F	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
291	Me	OH	1-Naphthyl	CH ₂ Ph	H	iPr
292	Me	OH	1-Naphthyl	CH ₂ Ph	H	Me
293	Me	OH	1-Naphthyl	CH ₂ Ph	H	Et
294	Me	OH	1-Naphthyl	CH ₂ Ph	H	Bn
295	Me	OH	1-Naphthyl	CH ₂ Ph	H	CH ₂ CH(CH ₃) ₂
296	Me	F	1-Naphthyl	CH ₂ Ph	H	iPr
297	Me	F	1-Naphthyl	CH ₂ Ph	H	Me
298	Me	F	1-Naphthyl	CH ₂ Ph	H	Et
299	Me	F	1-Naphthyl	CH ₂ Ph	H	Bn
300	Me	F	1-Naphthyl	CH ₂ Ph	H	CH ₂ CH(CH ₃) ₂
301	Me	OH	p-F-Phenyl	Me	H	iPr
302	Me	OH	p-F-Phenyl	Me	H	Me
303	Me	OH	p-F-Phenyl	Me	H	Et
304	Me	OH	p-F-Phenyl	Me	H	Bn
305	Me	OH	p-F-Phenyl	Me	H	CH ₂ CH(CH ₃) ₂
306	Me	F	p-F-Phenyl	Me	H	iPr
307	Me	F	p-F-Phenyl	Me	H	Me

308	Me	F	p-F-Phenyl	Me	H	Et
309	Me	F	p-F-Phenyl	Me	H	Bn
310	Me	F	p-F-Phenyl	Me	H	CH ₂ CH(CH ₃) ₂
311	Me	OH	p-F-Phenyl	H	H	iPr
312	Me	OH	p-F-Phenyl	H	H	Me
313	Me	OH	p-F-Phenyl	H	H	Et
314	Me	OH	p-F-Phenyl	H	H	Bn
315	Me	OH	p-F-Phenyl	H	H	CH ₂ CH(CH ₃) ₂
316	Me	F	p-F-Phenyl	H	H	iPr
317	Me	F	p-F-Phenyl	H	H	Me
318	Me	F	p-F-Phenyl	H	H	Et
319	Me	F	p-F-Phenyl	H	H	Bn
320	Me	F	p-F-Phenyl	H	H	CH ₂ CH(CH ₃) ₂
321	Me	OH	p-F-Phenyl	iPr	H	iPr
322	Me	OH	p-F-Phenyl	iPr	H	Me
323	Me	OH	p-F-Phenyl	iPr	H	Et
324	Me	OH	p-F-Phenyl	iPr	H	Bn
325	Me	OH	p-F-Phenyl	iPr	H	CH ₂ CH(CH ₃) ₂
326	Me	F	p-F-Phenyl	iPr	H	iPr
327	Me	F	p-F-Phenyl	iPr	H	Me
328	Me	F	p-F-Phenyl	iPr	H	Et
329	Me	F	p-F-Phenyl	iPr	H	Bn
330	Me	F	p-F-Phenyl	iPr	H	CH ₂ CH(CH ₃) ₂
331	Me	OH	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	iPr
332	Me	OH	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	Me
333	Me	OH	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	Et
334	Me	OH	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	Bn
335	Me	OH	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
336	Me	F	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	iPr
337	Me	F	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	Me
338	Me	F	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	Et
339	Me	F	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	Bn
340	Me	F	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
341	Me	OH	p-F-Phenyl	CH ₂ Ph	H	iPr
342	Me	OH	p-F-Phenyl	CH ₂ Ph	H	Me
343	Me	OH	p-F-Phenyl	CH ₂ Ph	H	Et
344	Me	OH	p-F-Phenyl	CH ₂ Ph	H	Bn
345	Me	OH	p-F-Phenyl	CH ₂ Ph	H	CH ₂ CH(CH ₃) ₂
346	Me	F	p-F-Phenyl	CH ₂ Ph	H	iPr

347	Me	F	p-F-Phenyl	CH ₂ Ph	H	Me
348	Me	F	p-F-Phenyl	CH ₂ Ph	H	Et
349	Me	F	p-F-Phenyl	CH ₂ Ph	H	Bn
350	Me	F	p-F-Phenyl	CH ₂ Ph	H	CH ₂ CH(CH ₃) ₂
351	Me	OH	iPr	Me	H	iPr
352	Me	OH	iPr	Me	H	Me
353	Me	OH	iPr	Me	H	Et
354	Me	OH	iPr	Me	H	Bn
355	Me	OH	iPr	Me	H	CH ₂ CH(CH ₃) ₂
356	Me	F	iPr	Me	H	iPr
357	Me	F	iPr	Me	H	Me
358	Me	F	iPr	Me	H	Et
359	Me	F	iPr	Me	H	Bn
360	Me	F	iPr	Me	H	CH ₂ CH(CH ₃) ₂
361	Me	OH	iPr	H	H	iPr
362	Me	OH	iPr	H	H	Me
363	Me	OH	iPr	H	H	Et
364	Me	OH	iPr	H	H	Bn
365	Me	OH	iPr	H	H	CH ₂ CH(CH ₃) ₂
366	Me	F	iPr	H	H	iPr
367	Me	F	iPr	H	H	Me
368	Me	F	iPr	H	H	Et
369	Me	F	iPr	H	H	Bn
370	Me	F	iPr	H	H	CH ₂ CH(CH ₃) ₂
371	Me	OH	iPr	iPr	H	iPr
372	Me	OH	iPr	iPr	H	Me
373	Me	OH	iPr	iPr	H	Et
374	Me	OH	iPr	iPr	H	Bn
375	Me	OH	iPr	iPr	H	CH ₂ CH(CH ₃) ₂
376	Me	F	iPr	iPr	H	iPr
377	Me	F	iPr	iPr	H	Me
378	Me	F	iPr	iPr	H	Et
379	Me	F	iPr	iPr	H	Bn
380	Me	F	iPr	iPr	H	CH ₂ CH(CH ₃) ₂
381	Me	OH	iPr	CH ₂ CH(CH ₃) ₂	H	iPr
382	Me	OH	iPr	CH ₂ CH(CH ₃) ₂	H	Me
383	Me	OH	iPr	CH ₂ CH(CH ₃) ₂	H	Et
384	Me	OH	iPr	CH ₂ CH(CH ₃) ₂	H	Bn
385	Me	OH	iPr	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂

386	Me	F	iPr	CH ₂ CH(CH ₃) ₂	H	iPr
387	Me	F	iPr	CH ₂ CH(CH ₃) ₂	H	Me
388	Me	F	iPr	CH ₂ CH(CH ₃) ₂	H	Et
389	Me	F	iPr	CH ₂ CH(CH ₃) ₂	H	Bn
390	Me	F	iPr	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
391	Me	OH	iPr	CH ₂ Ph	H	iPr
392	Me	OH	iPr	CH ₂ Ph	H	Me
393	Me	OH	iPr	CH ₂ Ph	H	Et
194	Me	OH	iPr	CH ₂ Ph	H	Bn
395	Me	OH	iPr	CH ₂ Ph	H	CH ₂ CH(CH ₃) ₂
396	Me	F	iPr	CH ₂ Ph	H	iPr
397	Me	F	iPr	CH ₂ Ph	H	Me
398	Me	F	iPr	CH ₂ Ph	H	Et
399	Me	F	iPr	CH ₂ Ph	H	Bn
400	Me	F	iPr	CH ₂ Ph	H	CH ₂ CH(CH ₃) ₂

Compounds in Table 3 were illustrated according to Formula IX, wherein, R_{2a}, R_{2b}, R₉, R₁₁, R₁₂, and R₁₃ are delineated for each example in Table 3;



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Table 3

Example	R _{2a}	R _{2b}	R ₉	R ₁₁	R ₁₂	R ₁₃
401	Me	OH	Ph	Me	H	iPr
402	Me	OH	Ph	Me	H	Me
403	Me	OH	Ph	Me	H	Et
404	Me	OH	Ph	Me	H	Bn
405	Me	OH	Ph	Me	H	CH ₂ CH(CH ₃) ₂
406	Me	F	Ph	Me	H	iPr
407	Me	F	Ph	Me	H	Me
408	Me	F	Ph	Me	H	Et
409	Me	F	Ph	Me	H	Bn
410	Me	F	Ph	Me	H	CH ₂ CH(CH ₃) ₂

411	Me	OH	Ph	H	H	iPr
412	Me	OH	Ph	H	H	Me
413	Me	OH	Ph	H	H	Et
414	Me	OH	Ph	H	H	Bn
415	Me	OH	Ph	H	H	CH ₂ CH(CH ₃) ₂
416	Me	F	Ph	H	H	iPr
417	Me	F	Ph	H	H	Me
418	Me	F	Ph	H	H	Et
419	Me	F	Ph	H	H	Bn
420	Me	F	Ph	H	H	CH ₂ CH(CH ₃) ₂
421	Me	OH	Ph	iPr	H	iPr
422	Me	OH	Ph	iPr	H	Me
423	Me	OH	Ph	iPr	H	Et
424	Me	OH	Ph	iPr	H	Bn
425	Me	OH	Ph	iPr	H	CH ₂ CH(CH ₃) ₂
426	Me	F	Ph	iPr	H	iPr
427	Me	F	Ph	iPr	H	Me
428	Me	F	Ph	iPr	H	Et
429	Me	F	Ph	iPr	H	Bn
430	Me	F	Ph	iPr	H	CH ₂ CH(CH ₃) ₂
431	Me	OH	Ph	CH ₂ CH(CH ₃) ₂	H	iPr
432	Me	OH	Ph	CH ₂ CH(CH ₃) ₂	H	Me
433	Me	OH	Ph	CH ₂ CH(CH ₃) ₂	H	Et
434	Me	OH	Ph	CH ₂ CH(CH ₃) ₂	H	Bn
435	Me	OH	Ph	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
436	Me	F	Ph	CH ₂ CH(CH ₃) ₂	H	iPr
437	Me	F	Ph	CH ₂ CH(CH ₃) ₂	H	Me
438	Me	F	Ph	CH ₂ CH(CH ₃) ₂	H	Et
439	Me	F	Ph	CH ₂ CH(CH ₃) ₂	H	Bn
440	Me	F	Ph	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
441	Me	OH	Ph	CH ₂ Ph	H	iPr
442	Me	OH	Ph	CH ₂ Ph	H	Me
443	Me	OH	Ph	CH ₂ Ph	H	Et
444	Me	OH	Ph	CH ₂ Ph	H	Bn
445	Me	OH	Ph	CH ₂ Ph	H	CH ₂ CH(CH ₃) ₂
446	Me	F	Ph	CH ₂ Ph	H	iPr
447	Me	F	Ph	CH ₂ Ph	H	Me
448	Me	F	Ph	CH ₂ Ph	H	Et
449	Me	F	Ph	CH ₂ Ph	H	Bn

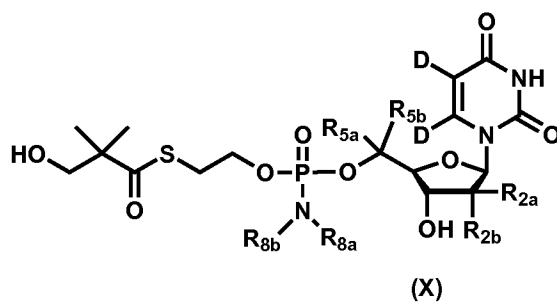
450	Me	F	Ph	CH ₂ Ph	H	CH ₂ CH(CH ₃) ₂
451	Me	OH	1-Naphthyl	Me	H	iPr
452	Me	OH	1-Naphthyl	Me	H	Me
453	Me	OH	1-Naphthyl	Me	H	Et
454	Me	OH	1-Naphthyl	Me	H	Bn
455	Me	OH	1-Naphthyl	Me	H	CH ₂ CH(CH ₃) ₂
456	Me	F	1-Naphthyl	Me	H	iPr
457	Me	F	1-Naphthyl	Me	H	Me
458	Me	F	1-Naphthyl	Me	H	Et
459	Me	F	1-Naphthyl	Me	H	Bn
460	Me	F	1-Naphthyl	Me	H	CH ₂ CH(CH ₃) ₂
461	Me	OH	1-Naphthyl	H	H	iPr
462	Me	OH	1-Naphthyl	H	H	Me
463	Me	OH	1-Naphthyl	H	H	Et
464	Me	OH	1-Naphthyl	H	H	Bn
465	Me	OH	1-Naphthyl	H	H	CH ₂ CH(CH ₃) ₂
466	Me	F	1-Naphthyl	H	H	iPr
467	Me	F	1-Naphthyl	H	H	Me
468	Me	F	1-Naphthyl	H	H	Et
469	Me	F	1-Naphthyl	H	H	Bn
470	Me	F	1-Naphthyl	H	H	CH ₂ CH(CH ₃) ₂
471	Me	OH	1-Naphthyl	iPr	H	iPr
472	Me	OH	1-Naphthyl	iPr	H	Me
473	Me	OH	1-Naphthyl	iPr	H	Et
474	Me	OH	1-Naphthyl	iPr	H	Bn
475	Me	OH	1-Naphthyl	iPr	H	CH ₂ CH(CH ₃) ₂
476	Me	F	1-Naphthyl	iPr	H	iPr
477	Me	F	1-Naphthyl	iPr	H	Me
478	Me	F	1-Naphthyl	iPr	H	Et
479	Me	F	1-Naphthyl	iPr	H	Bn
480	Me	F	1-Naphthyl	iPr	H	CH ₂ CH(CH ₃) ₂
481	Me	OH	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	iPr
482	Me	OH	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	Me
483	Me	OH	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	Et
484	Me	OH	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	Bn
485	Me	OH	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
486	Me	F	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	iPr
487	Me	F	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	Me
488	Me	F	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	Et

489	Me	F	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	Bn
490	Me	F	1-Naphthyl	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
491	Me	OH	1-Naphthyl	CH ₂ Ph	H	iPr
492	Me	OH	1-Naphthyl	CH ₂ Ph	H	Me
493	Me	OH	1-Naphthyl	CH ₂ Ph	H	Et
494	Me	OH	1-Naphthyl	CH ₂ Ph	H	Bn
495	Me	OH	1-Naphthyl	CH ₂ Ph	H	CH ₂ CH(CH ₃) ₂
496	Me	F	1-Naphthyl	CH ₂ Ph	H	iPr
497	Me	F	1-Naphthyl	CH ₂ Ph	H	Me
498	Me	F	1-Naphthyl	CH ₂ Ph	H	Et
499	Me	F	1-Naphthyl	CH ₂ Ph	H	Bn
500	Me	F	1-Naphthyl	CH ₂ Ph	H	CH ₂ CH(CH ₃) ₂
501	Me	OH	p-F-Phenyl	Me	H	iPr
502	Me	OH	p-F-Phenyl	Me	H	Me
503	Me	OH	p-F-Phenyl	Me	H	Et
504	Me	OH	p-F-Phenyl	Me	H	Bn
505	Me	OH	p-F-Phenyl	Me	H	CH ₂ CH(CH ₃) ₂
506	Me	F	p-F-Phenyl	Me	H	iPr
507	Me	F	p-F-Phenyl	Me	H	Me
508	Me	F	p-F-Phenyl	Me	H	Et
509	Me	F	p-F-Phenyl	Me	H	Bn
510	Me	F	p-F-Phenyl	Me	H	CH ₂ CH(CH ₃) ₂
511	Me	OH	p-F-Phenyl	H	H	iPr
512	Me	OH	p-F-Phenyl	H	H	Me
513	Me	OH	p-F-Phenyl	H	H	Et
514	Me	OH	p-F-Phenyl	H	H	Bn
515	Me	OH	p-F-Phenyl	H	H	CH ₂ CH(CH ₃) ₂
516	Me	F	p-F-Phenyl	H	H	iPr
517	Me	F	p-F-Phenyl	H	H	Me
518	Me	F	p-F-Phenyl	H	H	Et
519	Me	F	p-F-Phenyl	H	H	Bn
520	Me	F	p-F-Phenyl	H	H	CH ₂ CH(CH ₃) ₂
521	Me	OH	p-F-Phenyl	iPr	H	iPr
522	Me	OH	p-F-Phenyl	iPr	H	Me
523	Me	OH	p-F-Phenyl	iPr	H	Et
524	Me	OH	p-F-Phenyl	iPr	H	Bn
525	Me	OH	p-F-Phenyl	iPr	H	CH ₂ CH(CH ₃) ₂
526	Me	F	p-F-Phenyl	iPr	H	iPr
527	Me	F	p-F-Phenyl	iPr	H	Me

528	Me	F	p-F-Phenyl	iPr	H	Et
529	Me	F	p-F-Phenyl	iPr	H	Bn
530	Me	F	p-F-Phenyl	iPr	H	CH ₂ CH(CH ₃) ₂
531	Me	OH	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	iPr
532	Me	OH	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	Me
533	Me	OH	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	Et
534	Me	OH	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	Bn
535	Me	OH	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
536	Me	F	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	iPr
537	Me	F	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	Me
538	Me	F	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	Et
539	Me	F	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	Bn
540	Me	F	p-F-Phenyl	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
541	Me	OH	p-F-Phenyl	CH ₂ Ph	H	iPr
542	Me	OH	p-F-Phenyl	CH ₂ Ph	H	Me
543	Me	OH	p-F-Phenyl	CH ₂ Ph	H	Et
544	Me	OH	p-F-Phenyl	CH ₂ Ph	H	Bn
545	Me	OH	p-F-Phenyl	CH ₂ Ph	H	CH ₂ CH(CH ₃) ₂
546	Me	F	p-F-Phenyl	CH ₂ Ph	H	iPr
547	Me	F	p-F-Phenyl	CH ₂ Ph	H	Me
548	Me	F	p-F-Phenyl	CH ₂ Ph	H	Et
549	Me	F	p-F-Phenyl	CH ₂ Ph	H	Bn
550	Me	F	p-F-Phenyl	CH ₂ Ph	H	CH ₂ CH(CH ₃) ₂
551	Me	OH	iPr	Me	H	iPr
552	Me	OH	iPr	Me	H	Me
553	Me	OH	iPr	Me	H	Et
554	Me	OH	iPr	Me	H	Bn
555	Me	OH	iPr	Me	H	CH ₂ CH(CH ₃) ₂
556	Me	F	iPr	Me	H	iPr
557	Me	F	iPr	Me	H	Me
558	Me	F	iPr	Me	H	Et
559	Me	F	iPr	Me	H	Bn
560	Me	F	iPr	Me	H	CH ₂ CH(CH ₃) ₂
561	Me	OH	iPr	H	H	iPr
562	Me	OH	iPr	H	H	Me
563	Me	OH	iPr	H	H	Et
564	Me	OH	iPr	H	H	Bn
565	Me	OH	iPr	H	H	CH ₂ CH(CH ₃) ₂
566	Me	F	iPr	H	H	iPr

567	Me	F	iPr	H	H	Me
568	Me	F	iPr	H	H	Et
569	Me	F	iPr	H	H	Bn
570	Me	F	iPr	H	H	CH ₂ CH(CH ₃) ₂
571	Me	OH	iPr	iPr	H	iPr
572	Me	OH	iPr	iPr	H	Me
573	Me	OH	iPr	iPr	H	Et
574	Me	OH	iPr	iPr	H	Bn
575	Me	OH	iPr	iPr	H	CH ₂ CH(CH ₃) ₂
576	Me	F	iPr	iPr	H	iPr
577	Me	F	iPr	iPr	H	Me
578	Me	F	iPr	iPr	H	Et
579	Me	F	iPr	iPr	H	Bn
580	Me	F	iPr	iPr	H	CH ₂ CH(CH ₃) ₂
581	Me	OH	iPr	CH ₂ CH(CH ₃) ₂	H	iPr
582	Me	OH	iPr	CH ₂ CH(CH ₃) ₂	H	Me
583	Me	OH	iPr	CH ₂ CH(CH ₃) ₂	H	Et
584	Me	OH	iPr	CH ₂ CH(CH ₃) ₂	H	Bn
585	Me	OH	iPr	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
586	Me	F	iPr	CH ₂ CH(CH ₃) ₂	H	iPr
587	Me	F	iPr	CH ₂ CH(CH ₃) ₂	H	Me
588	Me	F	iPr	CH ₂ CH(CH ₃) ₂	H	Et
589	Me	F	iPr	CH ₂ CH(CH ₃) ₂	H	Bn
590	Me	F	iPr	CH ₂ CH(CH ₃) ₂	H	CH ₂ CH(CH ₃) ₂
591	Me	OH	iPr	CH ₂ Ph	H	iPr
592	Me	OH	iPr	CH ₂ Ph	H	Me
593	Me	OH	iPr	CH ₂ Ph	H	Et
594	Me	OH	iPr	CH ₂ Ph	H	Bn
595	Me	OH	iPr	CH ₂ Ph	H	CH ₂ CH(CH ₃) ₂
596	Me	F	iPr	CH ₂ Ph	H	iPr
597	Me	F	iPr	CH ₂ Ph	H	Me
598	Me	F	iPr	CH ₂ Ph	H	Et
599	Me	F	iPr	CH ₂ Ph	H	Bn
600	Me	F	iPr	CH ₂ Ph	H	CH ₂ CH(CH ₃) ₂

Compounds in Table 4 were illustrated according to Formula X, wherein, R_{2a}, R_{2b}, R_{5a}, R_{5b}, R_{8a}, and R_{8b} are delineated for each example in Table 4;

**Table 4**

Example	R _{2a}	R _{2b}		
601	Me	OH	PhCH ₂ NH	
602	Me	OH	PhCH ₂ NH	
603	Me	OH	PhCH ₂ NH	
604	Me	OH	^t PrNH	
605	Me	OH	^t PrNH	
606	Me	OH	^t PrNH	
607	Me	OH	^t BuNH	
608	Me	OH	^t BuNH	
609	Me	OH	^t BuNH	
610	Me	OH		
611	Me	OH		
612	Me	OH		
613	Me	OH		
614	Me	OH		
615	Me	OH		
616	Me	OH		
617	Me	OH		
618	Me	OH		
619	Me	OH	NHCH ₂ CO ₂ Et	

620	Me	OH	NH CH ₂ CO ₂ Et	
621	Me	OH	NH CH ₂ CO ₂ Et	
622	Me	OH	NH CH ₂ CO ₂ ^t Bu	
623	Me	OH	NH CH ₂ CO ₂ ^t Bu	
624	Me	OH	NH CH ₂ CO ₂ ^t Bu	
625	Me	OH	NH CH ₂ CO ₂ H	
626	Me	OH	NH CH ₂ CO ₂ H	
627	Me	OH	NH CH ₂ CO ₂ H	
628	Me	OH	NH CH ₂ CH ₂ NMe ₂	
629	Me	OH	NH CH ₂ CH ₂ NMe ₂	
630	Me	OH	NH CH ₂ CH ₂ NMe ₂	
631	Me	F	PhCH ₂ NH	
632	Me	F	PhCH ₂ NH	
633	Me	F	PhCH ₂ NH	
634	Me	F	ⁱ PrNH	
635	Me	F	ⁱ PrNH	
636	Me	F	ⁱ PrNH	
637	Me	F	^t BuNH	
638	Me	F	^t BuNH	
639	Me	F	^t BuNH	
640	Me	F		
641	Me	F		
642	Me	F		
643	Me	F		
644	Me	F		
645	Me	F		

646	Me	F		
647	Me	F		
648	Me	F		
649	Me	F	NHCH ₂ CO ₂ Et	
650	Me	F	NH CH ₂ CO ₂ Et	
651	Me	F	NH CH ₂ CO ₂ Et	
652	Me	F	NH CH ₂ CO ₂ ^t Bu	
653	Me	F	NH CH ₂ CO ₂ ^t Bu	
654	Me	F	NH CH ₂ CO ₂ ^t Bu	
655	Me	F	NH CH ₂ CO ₂ H	
656	Me	F	NH CH ₂ CO ₂ H	
657	Me	F	NH CH ₂ CO ₂ H	
658	Me	F	NH CH ₂ CH ₂ NMe ₂	
659	Me	F	NH CH ₂ CH ₂ NMe ₂	
660	Me	F	NH CH ₂ CH ₂ NMe ₂	

8. A pharmaceutical composition comprising an inhibitory amount of a compound according to claim 1 or a pharmaceutically acceptable salt, ester, or prodrug thereof, in combination with a pharmaceutically acceptable carrier or excipient.

9. A method of treating a viral infection in a subject, comprising administering to the subject an inhibitory amount of a pharmaceutical composition according to claim 8.

10

10. The method according to claim 9, wherein the viral infection is hepatitis C virus.

11. The method of claim 10, further comprising administering concurrently an additional anti-hepatitis C virus agent.

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12. The method of claim 11, wherein said additional anti-hepatitis C virus agent is selected from the group consisting of α -interferon, β -interferon, ribavirin, and adamantine.

5 13. The method of claim 11, wherein said additional anti-hepatitis C virus agent is an inhibitor of hepatitis C virus helicase, polymerase, metalloprotease, or IRES.

14. The pharmaceutical composition of claim 8, further comprising another anti-HCV agent.

10

15. The pharmaceutical composition of claim 8, further comprising an agent selected from interferon, ribavirin, amantadine, another HCV protease inhibitor, an HCV polymerase inhibitor, an HCV helicase inhibitor, or an internal ribosome entry site inhibitor.

15

16. The pharmaceutical composition of claim 8, further comprising pegylated interferon.

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/7072; C07H 17/02 (2014.01)

CPC - A61K 31/7072; C07H 17/02

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 31/7072; C07H 17/02 (2014.01)

CPC: A61K 31/7072; C07H 17/02 USPC: 424/85.6; 514/51; 536/28.53

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)

MicroPatent (US Granted, US Applications, EP-A, EP-B, WO, JP, DE-G, DE-A, DE-T, DE-U, GB-A, FR-A); ProQuest; Google Advanced Search; IP.com; KEYWORDS: method*, treat*, viral infect*, nucleosid*, HCV infect*, 5'2 phosphonat*, combinat* therap*, IRES*, HCV polymeras*, HCV helicase*, interferon*, pegylat* interferon*, D2 uridin*, glycosylat*, nucleotid*, phosphoramidat*, NS5B polymeras*

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2013/0078217 A1 (WANG, G et al.) 28 March 2013; paragraphs [0034]-[0056], [0058], [0072]-[0076], [0129], [0141], [0143], [0163]-[0164], [0182], [0186], [0194]; claims 10-11, 13-18	1-16
Y	PUBCHEM Uridine-5,6-d2, CID 46783218, pages 1-3, Create Date: 2010-07-26; page 1; [retrieved on 2014-08-25]. Retrieved from the Internet: <URL: https://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=46783218 >	1-16
Y	WO 2004/099241 A1 (COULOMBE, R et al.) 18 November 2004; page 2, lines 24-26, 31-34; page 3, lines 1-3; page 5, lines 31-35; page 6, lines 1-2, 26-34; page 20, lines 29-35; page 21, lines 1-35; page 22, lines 1-2; page 28, lines 23-35; page 29, lines 1-27; page 36, lines 7-10	1-16
Y	WO 2012/040127 A1 (SMITH, DB et al.) 29 March 2012; paragraphs [0007], [0011], [0116], [0154]	7
P,Y	US 2014/0219958 A1 (LULY, JR et al.) 07 August 2014; entire document	1-16

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

* Special categories of cited documents:

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"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

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"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

27 August 2014 (27.08.2014)

Date of mailing of the international search report

17 OCT 2014

Name and mailing address of the ISA/US

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