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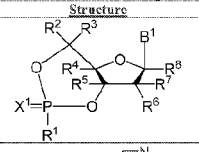
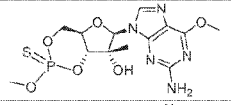
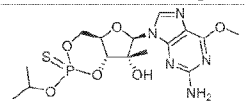
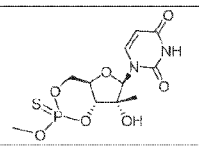
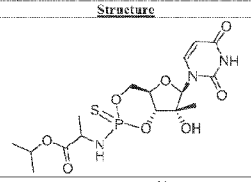
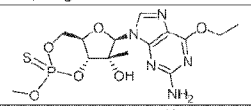
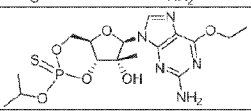
(54) **Title**: CYCLIC NUCLEOTIDE ANALOGS

Figure 8A: Compounds of Formula (I)

#	Structure
8000	
8001	
8002	
8003	

#	Structure
8004	
8005	
8006	

(57) **Abstract**: Disclosed herein are cyclic nucleotide analogs, methods of synthesizing cyclic nucleotide analogs and methods of treating diseases and/or conditions such as viral infections, cancer, and/or parasitic diseases with cyclic nucleotide analogs.

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CYCLIC NUCLEOTIDE ANALOGS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application Nos. 61/536,445, filed September 19, 2011; and 61/426,471, filed December 22, 2010; both of which are incorporated herein by reference in their entirety; including any drawings.

BACKGROUND

Field

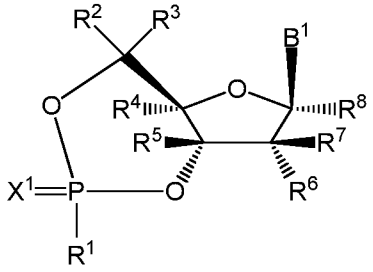
[0002] The present application relates to the fields of chemistry, biochemistry and medicine. More particularly, disclosed herein are cyclic nucleotide analogs, pharmaceutical compositions that include one or more cyclic nucleotide analogs and methods of synthesizing the same. Also disclosed herein are methods of treating diseases and/or conditions with cyclic nucleotide analogs alone or in combination therapy with other agents.

Description

[0003] Nucleoside analogs are a class of compounds that have been shown to exert antiviral and anticancer activity both in vitro and in vivo, and thus, have been the subject of widespread research for the treatment of viral infections and cancer. Nucleoside analogs are usually therapeutically inactive compounds that are converted by host or viral enzymes to their respective active anti-metabolites, which, in turn, may inhibit polymerases involved in viral or cell proliferation. The activation occurs by a variety of mechanisms, such as the addition of one or more phosphate groups and, or in combination with, other metabolic processes.

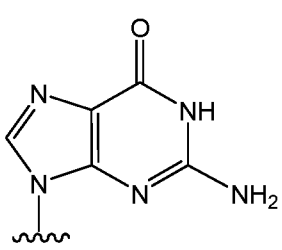
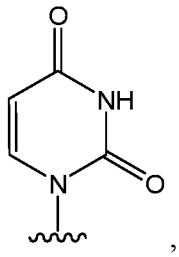
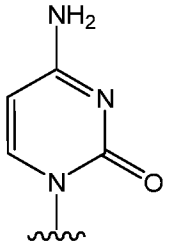
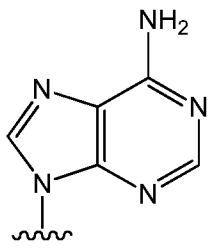
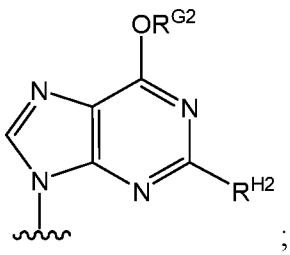
SUMMARY

[0003A] In one aspect, the present invention provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

B^1 is selected from the group consisting of  ,  ,  ,  and  ;

R^{G2} is an unsubstituted C_{1-6} alkyl;

R^{H2} is hydrogen or NH_2;

X^1 is S (sulfur);

R^1 is selected from the group consisting of $-Z^1-R^9$, an optionally substituted N-linked amino acid and an optionally substituted N-linked amino acid ester derivative;

Z^1 is selected from the group consisting of O (oxygen), S (sulfur) and $N(R^{10})$;

R^2 and R^3 are each hydrogen;

R^4 is selected from the group consisting of hydrogen and azido;

R^5 is hydrogen;

R^6 is selected from the group consisting of hydrogen, halogen, azido, $-OR^{11}$ and $-OC(=O)R^{12}$;

R^7 is selected from the group consisting of halogen and an optionally substituted C_{1-6} alkyl;

R^8 is hydrogen;

R^9 is selected from the group consisting of an unsubstituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl, an optionally substituted aryl(C_{1-6} alkyl), an optionally substituted heteroaryl(C_{1-6} alkyl) and an optionally substituted heterocyclyl(C_{1-6} alkyl);

R^{10} is hydrogen;

R^{11} is hydrogen or an optionally substituted C_{1-6} alkyl; and

R^{12} is an optionally substituted C_{1-6} alkyl or an optionally substituted C_{3-6} cycloalkyl.

[0003B] In another aspect, the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of the compound described above, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, excipient or combination thereof.

[0003C] In another aspect, the present invention provides the use of the compound described above, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition described above for preparing a medicament for ameliorating or treating a neoplastic disease.

[0003D] In another aspect, the present invention provides the use of the compound described above, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition described above for preparing a medicament for ameliorating or treating a viral infection.

[0003E] In another aspect, the present invention provides the use of the compound described above, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition described above for preparing a medicament for ameliorating or treating an HCV infection.

[0003F] In another aspect, the present invention provides the use of the compound described above, or a pharmaceutically acceptable salt thereof, for preparing a medicament for inhibiting NS5B polymerase activity of HCV.

[0003G] In another aspect, the present invention provides the use of the compound described above, or a pharmaceutically acceptable salt thereof, for preparing a medicament for inhibiting replication of HCV.

[0003H] In another aspect, the present invention provides a method of ameliorating or treating a neoplastic disease comprising administering an effective amount of the compound described above, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition described above to a subject suffering from the neoplastic disease.

[00031] In another aspect, the present invention provides a method of ameliorating or treating a viral infection comprising administering an effective amount of the compound described above, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition described above to a subject suffering from the viral infection.

[0003J] In another aspect, the present invention provides a method for ameliorating or treating an HCV infection comprising administering to a subject suffering from an HCV infection a therapeutically effective amount of the compound described above, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition described above.

[0003K] In another aspect, the present invention provides a method for inhibiting NSSB polymerase activity of HCV comprising contacting a cell infected with the virus with an effective amount of the compound described above, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition described above.

[0003L] In another aspect, the present invention provides a method for ameliorating or treating a HCV infection comprising contacting a cell infected with the virus with the compound described above, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition described above.

[0003M] In another aspect, the present invention provides a method for inhibiting replication of HCV comprising contacting a cell infected with the virus with the compound described above, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition described above.

[0004] Some embodiments disclosed herein relate to a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

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[0005] Some embodiments disclosed herein relate to methods of ameliorating and/or treating a neoplastic disease that can include administering to a subject suffering from the neoplastic disease a therapeutically effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof. Other embodiments described herein relate to using one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for ameliorating

and/or treating a neoplastic disease. Still other embodiments described herein relate to one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, that can be used for ameliorating and/or treating a neoplastic disease.

[0006] Some embodiments disclosed herein relate to methods of inhibiting the growth of a tumor that can include administering to a subject having a tumor a therapeutically effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof. Other embodiments described herein relate to using one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inhibiting the growth of a tumor. Still other embodiments described herein relate to one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, that can be used for inhibiting the growth of a tumor.

[0007] Some embodiments disclosed herein relate to methods of ameliorating and/or treating a viral infection that can include administering to a subject suffering from the viral infection a therapeutically effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof. Other embodiments described herein relate to using one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for ameliorating and/or treating a viral infection. Still other embodiments described herein relate to one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, that can be used for ameliorating and/or treating a viral infection.

[0008] Some embodiments disclosed herein relate to methods of ameliorating and/or treating a viral infection that can include contacting a cell infected with the virus with an effective amount of one or more compounds described herein, or a pharmaceutically acceptable salt of one or more compounds described herein, or a pharmaceutical composition that includes one or more compounds described herein, or a pharmaceutically acceptable salt thereof. Other embodiments described herein relate to using one or more compounds described herein, or a pharmaceutically acceptable salt of one or more compounds described herein, in the

manufacture of a medicament for ameliorating and/or treating a viral infection that can include contacting a cell infected with the virus with an effective amount of said compound(s). Still other embodiments described herein relate to one or more compounds described herein, or a pharmaceutically acceptable salt of one or more compounds described herein, or a pharmaceutical composition that includes one or more compounds described herein, or a pharmaceutically acceptable salt thereof, that can be used for ameliorating and/or treating a viral infection by contacting a cell infected with the virus with an effective amount of said compound(s).

[0009] Some embodiments disclosed herein relate to methods of inhibiting replication of a virus that can include contacting a cell infected with the virus with an effective amount of one or more compounds described herein, or a pharmaceutically acceptable salt of one or more compounds described herein, or a pharmaceutical composition that includes one or more compounds described herein, or a pharmaceutically acceptable salt thereof. Other embodiments described herein relate to using one or more compounds described herein, or a pharmaceutically acceptable salt of one or more compounds described herein, in the manufacture of a medicament for inhibiting replication of a virus that can include contacting a cell infected with the virus with an effective amount of said compound(s). Still other embodiments described herein relate to one or more compounds described herein, or a pharmaceutically acceptable salt of one or more compounds described herein, or a pharmaceutical composition that includes one or more compounds described herein, or a pharmaceutically acceptable salt thereof, that can be used for inhibiting replication of a virus by contacting a cell infected with the virus with an effective amount of said compound(s).

[0010] Some embodiments disclosed herein relate to methods of ameliorating and/or treating a parasitic disease that can include administering to a subject suffering from the parasitic disease a therapeutically effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof. Other embodiments described herein relate to using one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for ameliorating and/or treating a parasitic disease. Still other embodiments described herein relate to one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, that can be used for ameliorating and/or treating a parasitic disease.

[0011] Some embodiments disclosed herein relate to methods of ameliorating and/or treating a viral infection that can include administering to a subject suffering from the viral infection a therapeutically effective amount of a compound described herein or a pharmaceutically acceptable salt thereof (for example, one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof), or a pharmaceutical composition that includes a compound described herein, in combination with an agent selected from an interferon, ribavirin, a HCV protease inhibitor, a HCV polymerase inhibitor, a NS5A inhibitor, an other antiviral compound, a compound of Formula (AA), a mono-, di- and/or tri-phosphate thereof, a compound of Formula (CC), and a compound of Formula (DD), or a pharmaceutically acceptable salt or any of the foregoing. Some embodiments disclosed herein relate to methods of ameliorating and/or treating a viral infection that can include contacting a cell infected with the viral infection with a therapeutically effective amount of a compound described herein or a pharmaceutically acceptable salt thereof (for example, one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof), or a pharmaceutical composition that includes a compound described herein, in combination with an agent selected from an interferon, ribavirin, a HCV protease inhibitor, a HCV polymerase inhibitor, a NS5A inhibitor, an other antiviral compound, a compound of Formula (AA), a mono-, di- and/or tri-phosphate thereof, a compound of Formula (CC), and a compound of Formula (DD), or a pharmaceutically acceptable salt of any of the foregoing. Some embodiments disclosed herein relate to methods of inhibiting replication of a virus that can include administering to a subject a therapeutically effective amount of a compound described herein or a pharmaceutically acceptable salt thereof (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof), or a pharmaceutical composition that includes a compound described herein, or a pharmaceutically acceptable salt thereof, in combination with an agent selected from an interferon, ribavirin, a HCV protease inhibitor, a HCV polymerase inhibitor, a NS5A inhibitor, an other antiviral compound, a compound of Formula (AA), a mono-, di- and/or tri-phosphate thereof, a compound of Formula (CC), and a compound of Formula (DD), or a pharmaceutically acceptable salt of any of the foregoing. In some embodiments, the agent can be a compound, or a pharmaceutically acceptable salt thereof, selected from Compound 1001-1014, 2001-2010, 3001-3008, 4001-4005, 5001-5002, 6000-6078, 7000-7077 or 9000, or a pharmaceutical composition that includes one or more of the aforementioned compounds, or pharmaceutically acceptable salt thereof. In some embodiments, the method can include administering a second agent selected from an interferon, ribavirin, a HCV protease inhibitor, a HCV polymerase inhibitor, a NS5A inhibitor, an other antiviral compound, a compound of Formula (AA), a

mono-, di- and/or tri-phosphate thereof, a compound of Formula (CC), and a compound of Formula (DD), or a pharmaceutically acceptable salt of any of the foregoing. In some embodiments, the viral infection can be HCV.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] Figures 1A-1B show example HCV protease inhibitors.

[0013] Figure 2 shows example nucleoside HCV polymerase inhibitors.

[0014] Figure 3 shows example non-nucleoside HCV polymerase inhibitors.

[0015] Figure 4 shows example NS5A inhibitors.

[0016] Figure 5 shows example other antivirals.

[0017] Figures 6A-6M show example compounds of Formula (CC).

[0018] Figures 7A-7O show example compounds of Formula (AA), and triphosphates thereof.

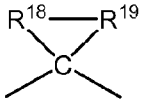
[0019] Figures 8A-8C show example compounds of Formula (I).

[0020] Figure 9 shows Formula (DD).

DETAILED DESCRIPTION

[0021] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. All patents, applications, published applications and other publications referenced herein are incorporated by reference in their entirety unless stated otherwise. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

[0022] As used herein, any "R" group(s) such as, without limitation, R, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{1A}, R^{2A}, R^{3A}, R^{3B}, R^{4A}, R^{5A}, R^{6A}, R^{7A} and R^{8A} represent substituents that can be attached to the indicated atom. An R group may be substituted or unsubstituted. If two "R" groups are described as being "taken together" the R groups and the atoms they are attached to can form a cycloalkyl, cycloalkenyl, aryl, heteroaryl or heterocycle. For example, without limitation, if R^{18} and R^{19} of an $-C(R^{18})(R^{19})-$ group are indicated to be "taken together," it means that they are covalently bonded to one another to form a ring:



[0023] Whenever a group is described as being "optionally substituted" that group may be unsubstituted or substituted with one or more of the indicated substituents. Likewise,

when a group is described as being "unsubstituted or substituted" if substituted, the substituent(s) may be selected from one or more the indicated substituents. If no substituents are indicated, it is meant that the indicated "optionally substituted" or "substituted" group may be substituted with one or more group(s) individually and independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicyclyl, aralkyl, heteroaralkyl, (heteroalicyclyl)alkyl, hydroxy, protected hydroxyl, alkoxy, aryloxy, acyl, mercapto, alkylthio, arylthio, cyano, halogen, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, protected C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, an amino, a mono-substituted amino and a di-substituted amino group, and protected derivatives thereof.

[0024] As used herein, "C_a to C_b" in which "a" and "b" are integers refer to the number of carbon atoms in an alkyl, alkenyl or alkynyl group, or the number of carbon atoms in the ring of a cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl or heteroalicyclyl group. That is, the alkyl, alkenyl, alkynyl, ring of the cycloalkyl, ring of the cycloalkenyl, ring of the cycloalkynyl, ring of the aryl, ring of the heteroaryl or ring of the heteroalicyclyl can contain from "a" to "b", inclusive, carbon atoms. Thus, for example, a "C_1 to C_4 alkyl" group refers to all alkyl groups having from 1 to 4 carbons, that is, CH_3-, CH_3CH_2-, $CH_3CH_2CH_2$-, $(CH_3)_2CH$-, $CH_3CH_2CH_2CH_2$-, $CH_3CH_2CH(CH_3)$- and $(CH_3)_3C$-. If no "a" and "b" are designated with regard to an alkyl, alkenyl, alkynyl, cycloalkyl cycloalkenyl, cycloalkynyl, aryl, heteroaryl or heteroalicyclyl group, the broadest range described in these definitions is to be assumed.

[0025] As used herein, "alkyl" refers to a straight or branched hydrocarbon chain that comprises a fully saturated (no double or triple bonds) hydrocarbon group. The alkyl group may have 1 to 20 carbon atoms (whenever it appears herein, a numerical range such as "1 to 20" refers to each integer in the given range; *e.g.*, "1 to 20 carbon atoms" means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 20 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated). The alkyl group may also be a medium size alkyl having 1 to 10 carbon atoms. The alkyl group could also be a lower alkyl having 1 to 6 carbon atoms. The alkyl group of the compounds may be designated as "C_1-C_4 alkyl" or similar designations. By way of example only, "C_1-C_4 alkyl" indicates that there are one to four carbon atoms in the alkyl chain, i.e., the alkyl chain is selected from methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, and t-butyl. Typical alkyl groups include, but are in no way limited

to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl and hexyl. The alkyl group may be substituted or unsubstituted.

[0026] As used herein, "alkenyl" refers to an alkyl group that contains in the straight or branched hydrocarbon chain one or more double bonds. An alkenyl group may be unsubstituted or substituted.

[0027] As used herein, "alkynyl" refers to an alkyl group that contains in the straight or branched hydrocarbon chain one or more triple bonds. An alkynyl group may be unsubstituted or substituted.

[0028] As used herein, "cycloalkyl" refers to a completely saturated (no double or triple bonds) mono- or multi-cyclic hydrocarbon ring system. When composed of two or more rings, the rings may be joined together in a fused fashion. Cycloalkyl groups can contain 3 to 10 atoms in the ring(s) or 3 to 8 atoms in the ring(s). A cycloalkyl group may be unsubstituted or substituted. Typical cycloalkyl groups include, but are in no way limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

[0029] As used herein, "cycloalkenyl" refers to a mono- or multi- cyclic hydrocarbon ring system that contains one or more double bonds in at least one ring; although, if there is more than one, the double bonds cannot form a fully delocalized pi-electron system throughout all the rings (otherwise the group would be "aryl," as defined herein). When composed of two or more rings, the rings may be connected together in a fused fashion. A cycloalkenyl group may be unsubstituted or substituted.

[0030] As used herein, "cycloalkynyl" refers to a mono- or multi- cyclic hydrocarbon ring system that contains one or more triple bonds in at least one ring. If there is more than one triple bond, the triple bonds cannot form a fully delocalized pi-electron system throughout all the rings. When composed of two or more rings, the rings may be joined together in a fused fashion. A cycloalkynyl group may be unsubstituted or substituted.

[0031] As used herein, "aryl" refers to a carbocyclic (all carbon) monocyclic or multicyclic aromatic ring system (including fused ring systems where two carbocyclic rings share a chemical bond) that has a fully delocalized pi-electron system throughout all the rings. The number of carbon atoms in an aryl group can vary. For example, the aryl group can be a C_6-C_{14} aryl group, a C_6-C_{10} aryl group, or a C_6 aryl group. Examples of aryl groups include, but are not limited to, benzene, naphthalene and azulene. An aryl group may be substituted or unsubstituted.

[0032] As used herein, "heteroaryl" refers to a monocyclic or multicyclic aromatic ring system (a ring system with fully delocalized pi-electron system) that contain(s) one or more

heteroatoms, that is, an element other than carbon, including but not limited to, nitrogen, oxygen and sulfur. The number of atoms in the ring(s) of a heteroaryl group can vary. For example, the heteroaryl group can contain 4 to 14 atoms in the ring(s), 5 to 10 atoms in the ring(s) or 5 to 6 atoms in the ring(s). Furthermore, the term "heteroaryl" includes fused ring systems where two rings, such as at least one aryl ring and at least one heteroaryl ring, or at least two heteroaryl rings, share at least one chemical bond. Examples of heteroaryl rings include, but are not limited to, furan, furazan, thiophene, benzothiophene, phthalazine, pyrrole, oxazole, benzoxazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, thiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, benzothiazole, imidazole, benzimidazole, indole, indazole, pyrazole, benzopyrazole, isoxazole, benzoisoxazole, isothiazole, triazole, benzotriazole, thiadiazole, tetrazole, pyridine, pyridazine, pyrimidine, pyrazine, purine, pteridine, quinoline, isoquinoline, quinazoline, quinoxaline, cinnoline, and triazine. A heteroaryl group may be substituted or unsubstituted.

[0033] As used herein, "heterocyclyl" or "heteroalicyclyl" refers to three-, four-, five-, six-, seven-, eight-, nine-, ten-, up to 18-membered monocyclic, bicyclic, and tricyclic ring system wherein carbon atoms together with from 1 to 5 heteroatoms constitute said ring system. A heterocycle may optionally contain one or more unsaturated bonds situated in such a way, however, that a fully delocalized pi-electron system does not occur throughout all the rings. The heteroatom(s) is an element other than carbon including, but not limited to, oxygen, sulfur, and nitrogen. A heterocycle may further contain one or more carbonyl or thiocarbonyl functionalities, so as to make the definition include oxo-systems and thio-systems such as lactams, lactones, cyclic imides, cyclic thioimides and cyclic carbamates. When composed of two or more rings, the rings may be joined together in a fused fashion. Additionally, any nitrogens in a heteroalicyclic may be quaternized. Heterocyclyl or heteroalicyclic groups may be unsubstituted or substituted. Examples of such "heterocyclyl" or "heteroalicyclyl" groups include but are not limited to, 1,3-dioxin, 1,3-dioxane, 1,4-dioxane, 1,2-dioxolane, 1,3-dioxolane, 1,4-dioxolane, 1,3-oxathiane, 1,4-oxathiin, 1,3-oxathiolane, 1,3-dithiole, 1,3-dithiolane, 1,4-oxathiane, tetrahydro-1,4-thiazine, 2H-1,2-oxazine, maleimide, succinimide, barbituric acid, thiobarbituric acid, dioxopiperazine, hydantoin, dihydrouracil, trioxane, hexahydro-1,3,5-triazine, imidazoline, imidazolidine, isoxazoline, isoxazolidine, oxazoline, oxazolidine, oxazolidinone, thiazoline, thiazolidine, morpholine, oxirane, piperidine *N*-Oxide, piperidine, piperazine, pyrrolidine, pyrrolidone, pyrrolidione, 4-piperidone, pyrazoline, pyrazolidine, 2-oxopyrrolidine, tetrahydropyran, 4H-pyran, tetrahydrothiopyran, thiamorpholine, thiamorpholine sulfoxide, thiamorpholine sulfone, and their benzo-fused analogs (e.g., benzimidazolidinone, tetrahydroquinoline, 3,4-methylenedioxyphenyl).

[0034] As used herein, "aralkyl" and "aryl(alkyl)" refer to an aryl group connected, as a substituent, via a lower alkylene group. The lower alkylene and aryl group of an aralkyl may be substituted or unsubstituted. Examples include but are not limited to benzyl, 2-phenylalkyl, 3-phenylalkyl, and naphthylalkyl.

[0035] As used herein, "heteroaralkyl" and "heteroaryl(alkyl)" refer to a heteroaryl group connected, as a substituent, via a lower alkylene group. The lower alkylene and heteroaryl group of heteroaralkyl may be substituted or unsubstituted. Examples include but are not limited to 2-thienylalkyl, 3-thienylalkyl, furylalkyl, thienylalkyl, pyrrolylalkyl, pyridylalkyl, isoxazolylalkyl, and imidazolylalkyl, and their benzo-fused analogs.

[0036] A "(heteroalicyclyl)alkyl" and "(heterocyclyl)alkyl" refer to a heterocyclic or a heteroalicyclylic group connected, as a substituent, via a lower alkylene group. The lower alkylene and heterocyclyl of a (heteroalicyclyl)alkyl may be substituted or unsubstituted. Examples include but are not limited tetrahydro-2H-pyran-4-yl)methyl, (piperidin-4-yl)ethyl, (piperidin-4-yl)propyl, (tetrahydro-2H-thiopyran-4-yl)methyl, and (1,3-thiazinan-4-yl)methyl.

[0037] "Lower alkylene groups" are straight-chained -CH_2- tethering groups, forming bonds to connect molecular fragments via their terminal carbon atoms. Examples include but are not limited to methylene (-CH_2-), ethylene (-CH_2CH_2-), propylene (-$CH_2CH_2CH_2$-), and butylene (-$CH_2CH_2CH_2CH_2$-). A lower alkylene group can be substituted by replacing one or more hydrogen of the lower alkylene group with a substituent(s) listed under the definition of "substituted."

[0038] As used herein, "alkoxy" refers to the formula –OR wherein R is an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl or a cycloalkynyl is defined as above. A non-limiting list of alkoxys are methoxy, ethoxy, n-propoxy, 1-methylethoxy (isopropoxy), n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, and the like. An alkoxy may be substituted or unsubstituted.

[0039] As used herein, "acyl" refers to a hydrogen, alkyl, alkenyl, alkynyl, or aryl connected, as substituents, via a carbonyl group. Examples include formyl, acetyl, propanoyl, benzoyl, and acryl. An acyl may be substituted or unsubstituted.

[0040] As used herein, "hydroxyalkyl" refers to an alkyl group in which one or more of the hydrogen atoms are replaced by a hydroxy group. Exemplary hydroxyalkyl groups include but are not limited to, 2-hydroxyethyl, 3-hydroxypropyl, 2-hydroxypropyl, and 2,2-dihydroxyethyl. A hydroxyalkyl may be substituted or unsubstituted.

[0041] As used herein, "haloalkyl" refers to an alkyl group in which one or more of the hydrogen atoms are replaced by a halogen (e.g., mono-haloalkyl, di-haloalkyl and tri-

haloalkyl). Such groups include but are not limited to, chloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1-chloro-2-fluoromethyl and 2-fluoroisobutyl. A haloalkyl may be substituted or unsubstituted.

[0042] As used herein, "haloalkoxy" refers to an alkoxy group in which one or more of the hydrogen atoms are replaced by a halogen (e.g., mono-haloalkoxy, di- haloalkoxy and tri-haloalkoxy). Such groups include but are not limited to, chloromethoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, 1-chloro-2-fluoromethoxy and 2-fluoroisobutoxy. A haloalkoxy may be substituted or unsubstituted.

[0043] As used herein, "aryloxy" and "arylthio" refers to RO- and RS-, in which R is an aryl, such as, but not limited to, phenyl. Both an aryloxy and arylthio may be substituted or unsubstituted.

[0044] A "sulfenyl" group refers to an "-SR" group in which R can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicyclyl, aralkyl, or (heteroalicyclyl)alkyl. A sulfenyl may be substituted or unsubstituted.

[0045] A "sulfinyl" group refers to an "-S(=O)-R" group in which R can be the same as defined with respect to sulfenyl. A sulfinyl may be substituted or unsubstituted.

[0046] A "sulfonyl" group refers to an "SO_2R" group in which R can be the same as defined with respect to sulfenyl. A sulfonyl may be substituted or unsubstituted.

[0047] An "O-carboxy" group refers to a "RC(=O)O-" group in which R can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicyclyl, aralkyl, or (heteroalicyclyl)alkyl, as defined herein. An O-carboxy may be substituted or unsubstituted.

[0048] The terms "ester" and "C-carboxy" refer to a "-C(=O)OR" group in which R can be the same as defined with respect to O-carboxy. An ester and C-carboxy may be substituted or unsubstituted.

[0049] A "thiocarbonyl" group refers to a "-C(=S)R" group in which R can be the same as defined with respect to O-carboxy. A thiocarbonyl may be substituted or unsubstituted.

[0050] A "trihalomethanesulfonyl" group refers to an "X_3CSO_2-" group wherein each X is a halogen.

[0051] A "trihalomethanesulfonamido" group refers to an "$X_3CS(O)_2N(R_A)$-" group wherein each X is a halogen, and R_A hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicyclyl, aralkyl, or (heteroalicyclyl)alkyl.

[0052] The term "amino" as used herein refers to a $-NH_2$ group.

[0053] As used herein, the term "hydroxy" refers to a –OH group.

[0054] A "cyano" group refers to a "-CN" group.

[0055] The term "azido" as used herein refers to a $-N_3$ group.

[0056] The term "allenyl" as used herein refers to a $R_2C=C=CR-$ group in which each R can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, or (heterocyclyl)alkyl.

[0057] An "isocyanato" group refers to a "-NCO" group.

[0058] A "thiocyanato" group refers to a "-CNS" group.

[0059] An "isothiocyanato" group refers to an " -NCS" group.

[0060] A "mercapto" group refers to an "-SH" group.

[0061] A "carbonyl" group refers to a C=O group.

[0062] An "S-sulfonamido" group refers to a "$-SO_2N(R_AR_B)$" group in which R_A and R_B can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicyclyl, aralkyl, or (heteroalicyclyl)alkyl. An S-sulfonamido may be substituted or unsubstituted.

[0063] An "N-sulfonamido" group refers to a "$RSO_2N(R_A)-$" group in which R and R_A can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicyclyl, aralkyl, or (heteroalicyclyl)alkyl. An N-sulfonamido may be substituted or unsubstituted.

[0064] An "O-carbamyl" group refers to a "$-OC(=O)N(R_AR_B)$" group in which R_A and R_B can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicyclyl, aralkyl, or (heteroalicyclyl)alkyl. An O-carbamyl may be substituted or unsubstituted.

[0065] An "N-carbamyl" group refers to an "$ROC(=O)N(R_A)$ -" group in which R and R_A can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicyclyl, aralkyl, or (heteroalicyclyl)alkyl. An N-carbamyl may be substituted or unsubstituted.

[0066] An "O-thiocarbamyl" group refers to a "$-OC(=S)-N(R_AR_B)$" group in which R_A and R_B can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicyclyl, aralkyl, or (heteroalicyclyl)alkyl. An O-thiocarbamyl may be substituted or unsubstituted.

[0067] An "N-thiocarbamyl" group refers to an "$ROC(=S)N(R_A)-$" group in which R and R_A can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicyclyl, aralkyl, or (heteroalicyclyl)alkyl. An N-thiocarbamyl may be substituted or unsubstituted.

[0068] A "C-amido" group refers to a "-C(=O)N(R_AR_B)" group in which R_A and R_B can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicyclyl, aralkyl, or (heteroalicyclyl)alkyl. A C-amido may be substituted or unsubstituted.

[0069] An "N-amido" group refers to a "RC(=O)N(R_A)-" group in which R and R_A can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicyclyl, aralkyl, or (heteroalicyclyl)alkyl. An N-amido may be substituted or unsubstituted.

[0070] The term "halogen atom" or "halogen" as used herein, means any one of the radio-stable atoms of column 7 of the Periodic Table of the Elements, such as, fluorine, chlorine, bromine and iodine.

[0071] Where the numbers of substituents is not specified (e.g., haloalkyl), there may be one or more substituents present. For example "haloalkyl" may include one or more of the same or different halogens. As another example, "C_1-C_3 alkoxyphenyl" may include one or more of the same or different alkoxy groups containing one, two or three atoms.

[0072] As used herein, the abbreviations for any protective groups, amino acids and other compounds, are, unless indicated otherwise, in accord with their common usage, recognized abbreviations, or the IUPAC-IUB Commission on Biochemical Nomenclature (See, Biochem. 11:942-944 (1972)).

[0073] The term "nucleoside" is used herein in its ordinary sense as understood by those skilled in the art, and refers to a compound composed of an optionally substituted pentose moiety or modified pentose moiety attached to a heterocyclic base or tautomer thereof via a N-glycosidic bond, such as attached via the 9-position of a purine-base or the 1-position of a pyrimidine-base. Examples include, but are not limited to, a ribonucleoside comprising a ribose moiety and a deoxyribonucleoside comprising a deoxyribose moiety. A modified pentose moiety is a pentose moiety in which an oxygen atom has been replaced with a carbon and/or a carbon has been replaced with a sulfur or an oxygen atom. A "nucleoside" is a monomer that can have a substituted base and/or sugar moiety. Additionally, a nucleoside can be incorporated into larger DNA and/or RNA polymers and oligomers. In some instances, the nucleoside can be a nucleoside analog drug.

[0074] As used herein, the term "heterocyclic base" refers to an optionally substituted nitrogen-containing heterocyclyl that can be attached to an optionally substituted pentose moiety or modified pentose moiety. In some embodiments, the heterocyclic base can be selected from an optionally substituted purine-base, an optionally substituted pyrimidine-base

and an optionally substituted triazole-base (for example, a 1,2,4-triazole). The term "purine-base" is used herein in its ordinary sense as understood by those skilled in the art, and includes its tautomers. Similarly, the term "pyrimidine-base" is used herein in its ordinary sense as understood by those skilled in the art, and includes its tautomers. A non-limiting list of optionally substituted purine-bases includes purine, adenine, guanine, hypoxanthine, xanthine, alloxanthine, 7-alkylguanine (e.g., 7-methylguanine), theobromine, caffeine, uric acid and isoguanine. Examples of pyrimidine-bases include, but are not limited to, cytosine, thymine, uracil, 5,6-dihydrouracil and 5-alkylcytosine (e.g., 5-methylcytosine). An example of an optionally substituted triazole-base is 1,2,4-triazole-3-carboxamide. Other non-limiting examples of heterocyclic bases include diaminopurine, 8-oxo-N^6-alkyladenine (e.g., 8-oxo-N^6-methyladenine), 7-deazaxanthine, 7-deazaguanine, 7-deazaadenine, N^4,N^4-ethanocytosin, N^6,N^6-ethano-2,6-diaminopurine, 5-halouracil (e.g., 5-fluorouracil and 5-bromouracil), pseudoisocytosine, isocytosine, isoguanine, and other heterocyclic bases described in U.S. Patent Nos. 5,432,272 and 7,125,855, which are incorporated herein by reference for the limited purpose of disclosing additional heterocyclic bases. In some embodiments, a heterocyclic base can be optionally substituted with an amine or an enol protecting group(s).

[0075] The term "–N–linked amino acid" refers to an amino acid that is attached to the indicated moiety via a main-chain amino or mono-substituted amino group. When the amino acid is attached in an –N–linked amino acid, one of the hydrogens that is part of the main-chain amino or mono-substituted amino group is not present and the amino acid is attached via the nitrogen. As used herein, the term "amino acid" refers to any amino acid (both standard and non-standard amino acids), including, but not limited to, α-amino acids, β-amino acids, γ-amino acids and δ-amino acids. Examples of suitable amino acids include, but are not limited to, alanine, asparagine, aspartate, cysteine, glutamate, glutamine, glycine, proline, serine, tyrosine, arginine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan and valine. Additional examples of suitable amino acids include, but are not limited to, ornithine, hypusine, 2-aminoisobutyric acid, dehydroalanine, gamma-aminobutyric acid, citrulline, beta-alanine, alpha-ethyl-glycine, alpha-propyl-glycine and norleucine. N-linked amino acids can be substituted or unsubstituted.

[0076] The term "–N–linked amino acid ester derivative" refers to an amino acid in which a main-chain carboxylic acid group has been converted to an ester group. In some embodiments, the ester group has a formula selected from alkyl-O-C(=O)-, cycloalkyl-O-C(=O)-, aryl-O-C(=O)- and aryl(alkyl)-O-C(=O)-. A non-limiting list of ester groups include substituted and unsubstituted versions of the following: methyl-O-C(=O)-, ethyl-O-C(=O)-, n-

propyl-O-C(=O)-, isopropyl-O-C(=O)-, n-butyl-O-C(=O)-, isobutyl-O-C(=O)-, tert-butyl-O-C(=O)-, neopentyl-O-C(=O)-, cyclopropyl-O-C(=O)-, cyclobutyl-O-C(=O)-, cyclopentyl-O-C(=O)-, cyclohexyl-O-C(=O)-, phenyl-O-C(=O)-, benzyl-O-C(=O)-, and naphthyl-O-C(=O)-. N-linked amino acid ester derivatives can be substituted or unsubstituted.

[0077] The terms "protecting group" and "protecting groups" as used herein refer to any atom or group of atoms that is added to a molecule in order to prevent existing groups in the molecule from undergoing unwanted chemical reactions. Examples of protecting group moieties are described in T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 3. Ed. John Wiley & Sons, 1999, and in J.F.W. McOmie, *Protective Groups in Organic Chemistry* Plenum Press, 1973, both of which are hereby incorporated by reference for the limited purpose of disclosing suitable protecting groups. The protecting group moiety may be chosen in such a way, that they are stable to certain reaction conditions and readily removed at a convenient stage using methodology known from the art. A non-limiting list of protecting groups include benzyl; substituted benzyl; alkylcarbonyls and alkoxycarbonyls (e.g., t-butoxycarbonyl (BOC), acetyl, or isobutyryl); arylalkylcarbonyls and arylalkoxycarbonyls (e.g., benzyloxycarbonyl); substituted methyl ether (e.g., methoxymethyl ether); substituted ethyl ether; a substituted benzyl ether; tetrahydropyranyl ether; silyls (e.g., trimethylsilyl, triethylsilyl, triisopropylsilyl, t-butyldimethylsilyl, tri-*iso*-propylsilyloxymethyl, [2-(trimethylsilyl)ethoxy]methyl or t-butyldiphenylsilyl); esters (e.g., benzoate ester); carbonates (e.g., methoxymethylcarbonate); sulfonates (e.g., tosylate or mesylate); acyclic ketal (e.g., dimethyl acetal); cyclic ketals (e.g., 1,3-dioxane, 1,3-dioxolanes, and those described herein); acyclic acetal; cyclic acetal (e.g., those described herein); acyclic hemiacetal; cyclic hemiacetal; cyclic dithioketals (e.g., 1,3-dithiane or 1,3-dithiolane); orthoesters (e.g., those described herein) and triarylmethyl groups (e.g., trityl; monomethoxytrityl (MMTr); 4,4'-dimethoxytrityl (DMTr); 4,4',4"-trimethoxytrityl (TMTr); and those described herein).

[0078] "Leaving group" as used herein refers to any atom or moiety that is capable of being displaced by another atom or moiety in a chemical reaction. More specifically, in some embodiments, "leaving group" refers to the atom or moiety that is displaced in a nucleophilic substitution reaction. In some embodiments, "leaving groups" are any atoms or moieties that are conjugate bases of strong acids. Examples of suitable leaving groups include, but are not limited to, tosylates and halogens. Non-limiting characteristics and examples of leaving groups can be found, for example in *Organic Chemistry*, 2d ed., Francis Carey (1992), pages 328-331; *Introduction to Organic Chemistry*, 2d ed., Andrew Streitwieser and Clayton Heathcock (1981), pages 169-171; and *Organic Chemistry*, 5th ed., John McMurry (2000), pages 398 and 408; all of

which are incorporated herein by reference for the limited purpose of disclosing characteristics and examples of leaving groups.

[0079] The term "pharmaceutically acceptable salt" refers to a salt of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. In some embodiments, the salt is an acid addition salt of the compound. Pharmaceutical salts can be obtained by reacting a compound with inorganic acids such as a hydrohalic acid (e.g., hydrochloric acid or hydrobromic acid), sulfuric acid, nitric acid and phosphoric acid. Pharmaceutical salts can also be obtained by reacting a compound with an organic acid such as aliphatic or aromatic carboxylic or sulfonic acids, for example formic, acetic, succinic, lactic, malic, tartaric, citric, ascorbic, nicotinic, methanesulfonic, ethanesulfonic, p-toluensulfonic, salicylic or naphthalenesulfonic acid. Pharmaceutical salts can also be obtained by reacting a compound with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, N-methyl-D-glucamine, tris(hydroxymethyl)methylamine, C_1-C_7 alkylamine, cyclohexylamine, triethanolamine, ethylenediamine, and salts with amino acids such as arginine and lysine.

[0080] Terms and phrases used in this application, and variations thereof, especially in the appended claims, unless otherwise expressly stated, should be construed as open ended as opposed to limiting. As examples of the foregoing, the term 'including' should be read to mean 'including, without limitation,' 'including but not limited to,' or the like; the term 'comprising' as used herein is synonymous with 'including,' 'containing,' or 'characterized by,' and is inclusive or open-ended and does not exclude additional, unrecited elements or method steps; the term 'having' should be interpreted as 'having at least;' the term 'includes' should be interpreted as 'includes but is not limited to;' the term 'example' is used to provide exemplary instances of the item in discussion, not an exhaustive or limiting list thereof; and use of terms like 'preferably,' 'preferred,' 'desired,' or 'desirable,' and words of similar meaning should not be understood as implying that certain features are critical, essential, or even important to the structure or function of the invention, but instead as merely intended to highlight alternative or additional features that may or may not be utilized in a particular embodiment. In addition, the term "comprising" is to be interpreted synonymously with the phrases "having at least" or "including at least". When used in the context of a process, the term "comprising" means that the process includes at least the recited steps, but may include additional steps. When used in the context of a compound, composition or device, the term "comprising" means that the compound,

composition or device includes at least the recited features or components, but may also include additional features or components. Likewise, a group of items linked with the conjunction 'and' should not be read as requiring that each and every one of those items be present in the grouping, but rather should be read as 'and/or' unless expressly stated otherwise. Similarly, a group of items linked with the conjunction 'or' should not be read as requiring mutual exclusivity among that group, but rather should be read as 'and/or' unless expressly stated otherwise.

[0081] With respect to the use of substantially any plural and/or singular terms herein, those having skill in the art can translate from the plural to the singular and/or from the singular to the plural as is appropriate to the context and/or application. The various singular/plural permutations may be expressly set forth herein for sake of clarity. The indefinite article "a" or "an" does not exclude a plurality. A single processor or other unit may fulfill the functions of several items recited in the claims. The mere fact that certain measures are recited in mutually different dependent claims does not indicate that a combination of these measures cannot be used to advantage. Any reference signs in the claims should not be construed as limiting the scope.

[0082] It is understood that, in any compound described herein having one or more chiral centers, if an absolute stereochemistry is not expressly indicated, then each center may independently be of R-configuration or S-configuration or a mixture thereof. Thus, the compounds provided herein may be enantiomerically pure, enantiomerically enriched, racemic mixture, diastereomerically pure, diastereomerically enriched, or a stereoisomeric mixture. In addition it is understood that, in any compound described herein having one or more double bond(s) generating geometrical isomers that can be defined as E or Z, each double bond may independently be E or Z a mixture thereof.

[0083] Likewise, it is understood that, in any compound described, all tautomeric forms are also intended to be included. For example all tautomers of phosphate groups are intended to be included. Furthermore, all tautomers of heterocyclic bases known in the art are intended to be included, including tautomers of natural and non-natural purine-bases and pyrimidine-bases.

[0084] It is to be understood that where compounds disclosed herein have unfilled valencies, then the valencies are to be filled with hydrogens or isotopes thereof, e.g., hydrogen-1 (protium) and hydrogen-2 (deuterium).

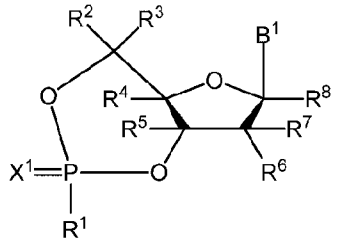
[0085] It is understood that the compounds described herein can be labeled isotopically. Substitution with isotopes such as deuterium may afford certain therapeutic

advantages resulting from greater metabolic stability, such as, for example, increased *in vivo* half-life or reduced dosage requirements. Each chemical element as represented in a compound structure may include any isotope of said element. For example, in a compound structure a hydrogen atom may be explicitly disclosed or understood to be present in the compound. At any position of the compound that a hydrogen atom may be present, the hydrogen atom can be any isotope of hydrogen, including but not limited to hydrogen-1 (protium) and hydrogen-2 (deuterium). Thus, reference herein to a compound encompasses all potential isotopic forms unless the context clearly dictates otherwise.

[0086] It is understood that the methods and combinations described herein include crystalline forms (also known as polymorphs, which include the different crystal packing arrangements of the same elemental composition of a compound), amorphous phases, salts, solvates, and hydrates. In some embodiments, the compounds described herein exist in solvated forms with pharmaceutically acceptable solvents such as water, ethanol, or the like. In other embodiments, the compounds described herein exist in unsolvated form. Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and may be formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol, or the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. In addition, the compounds provided herein can exist in unsolvated as well as solvated forms. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the compounds and methods provided herein.

[0087] Where a range of values is provided, it is understood that the upper and lower limit, and each intervening value between the upper and lower limit of the range is encompassed within the embodiments.

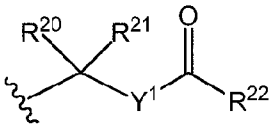
[0088] Some embodiments disclosed herein relate to a compound of Formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein: B^1 can be an optionally substituted heterocyclic base or an optionally substituted heterocyclic base with a protected amino group; X^1 can be O (oxygen) or S (sulfur); R^1 can be selected from $-Z^1-R^9$, an optionally substituted N-linked amino acid and an optionally substituted N-linked amino acid ester derivative; Z^1 can be selected from O (oxygen), S (sulfur)

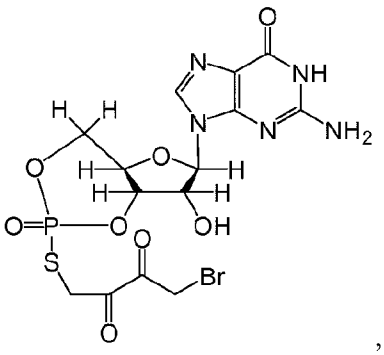
and N(R^{10}); R^2 and R^3 can be independently selected from hydrogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{2-6} alkynyl, an optionally substituted C_{1-6} haloalkyl and an optionally substituted aryl(C_{1-6} alkyl); or R^2 and R^3 can be taken together to form a group selected from an optionally substituted C_{3-6} cycloalkyl, an optionally substituted C_{3-6} cycloalkenyl, an optionally substituted C_{3-6} aryl and an optionally substituted C_{3-6} heteroaryl; R^4 can be selected from hydrogen, halogen, azido, cyano, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{2-6} alkynyl and an optionally substituted allenyl; R^5 can be hydrogen or an optionally substituted C_{1-6} alkyl; R^6 can be selected from hydrogen, halogen, azido, amino, cyano, an optionally substituted C_{1-6} alkyl, -OR^{11} and -OC(=O)R^{12}; R^7 can be selected from hydrogen, halogen, azido, cyano, an optionally substituted C_{1-6} alkyl, -OR^{13} and -OC(=O)R^{14}; R^8 can be selected from hydrogen, halogen, azido, cyano, an optionally substituted C_{1-6} alkyl, -OR^{15} and -OC(=O)R^{16}; R^9 can be selected from an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl, an optionally substituted aryl(C_{1-6} alkyl), an optionally substituted heteroaryl(C_{1-6} alkyl), an optionally substituted heterocyclyl(C_{1-6} alkyl), and Formula (II); R^{10} can be selected from hydrogen, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl, an optionally substituted aryl(C_{1-6} alkyl), an optionally substituted heteroaryl(C_{1-6} alkyl) and an optionally substituted heterocyclyl(C_{1-6} alkyl); R^{11}, R^{13} and R^{15} can be independently hydrogen or an optionally substituted C_{1-6} alkyl; R^{12}, R^{14} and R^{16} can be independently an optionally substituted C_{1-6} alkyl or an optionally substituted C_{3-6} cycloalkyl; and Formula (II) can be:



(II)

wherein: R^{20} and R^{21} can be independently selected from a hydrogen, an optionally substituted C_{1-24} alkyl and an optionally substituted aryl; R^{22} can be selected from a hydrogen, an optionally substituted C_{1-24} alkyl, an optionally substituted aryl, an optionally substituted –O–C_{1-24} alkyl and an optionally substituted –O–aryl; and Y^1 can be O (oxygen) or S (sulfur).

[0089] In some embodiments, a compound of Formula (I) cannot have a structure selected from: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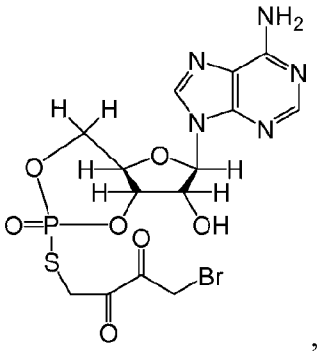
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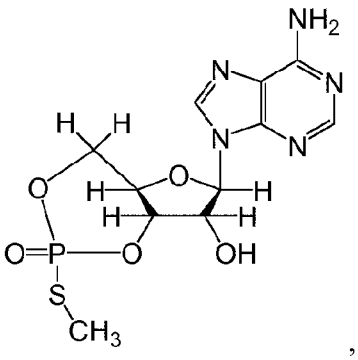
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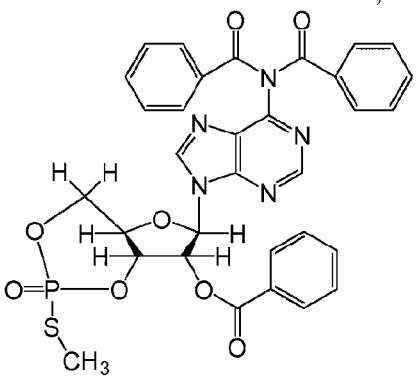
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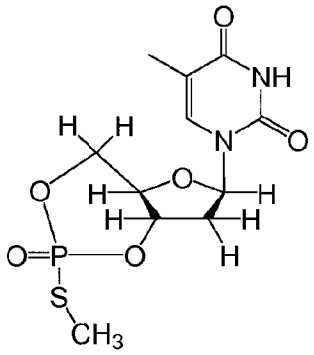
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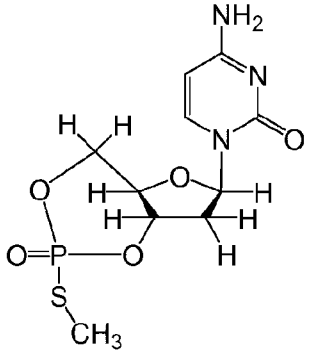
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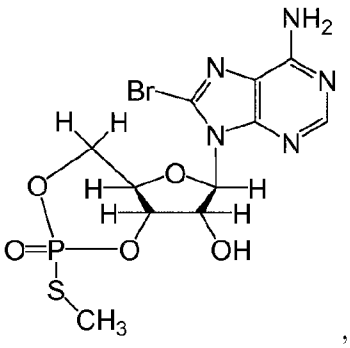
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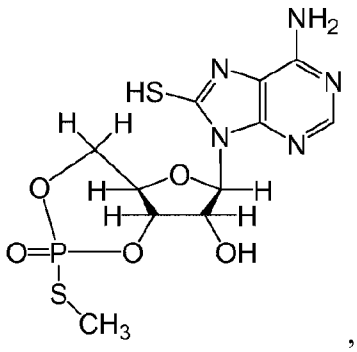
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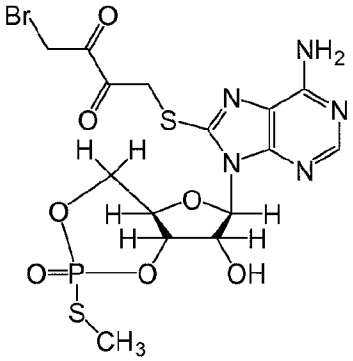
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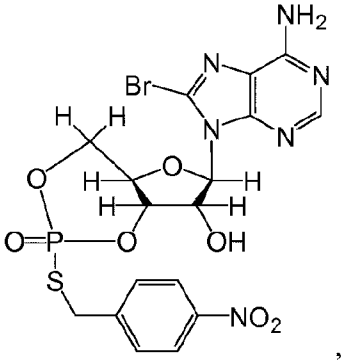
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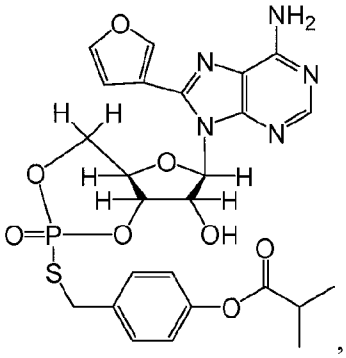
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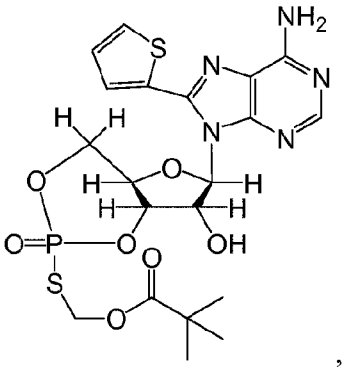
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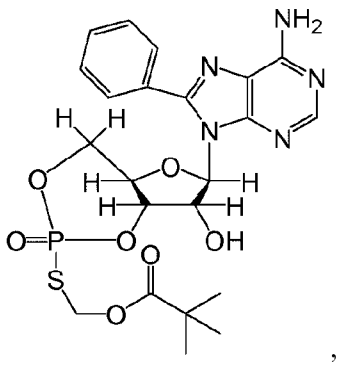
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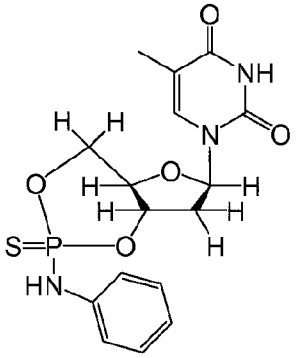
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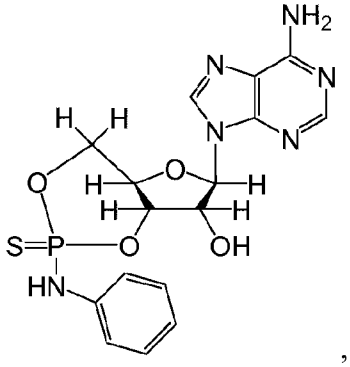
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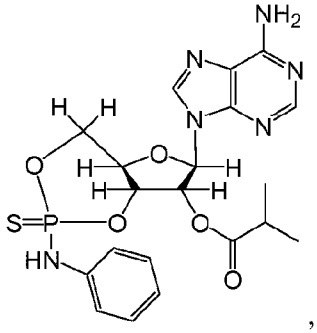
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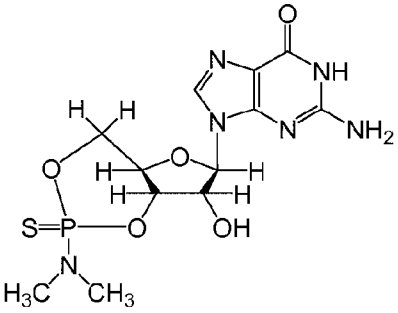
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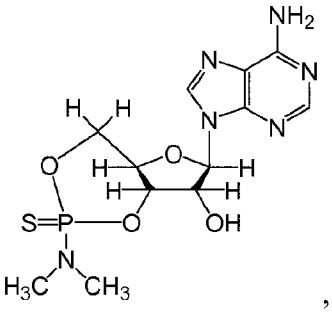
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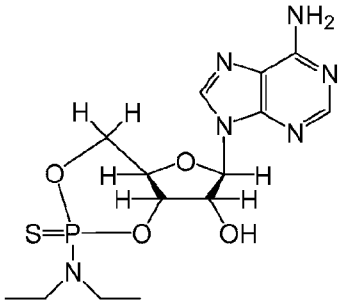
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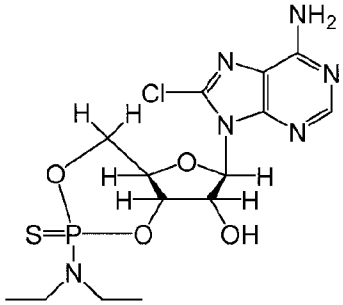
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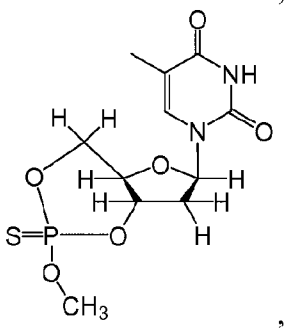
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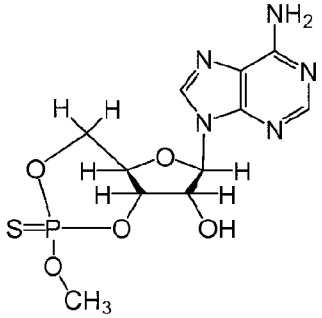
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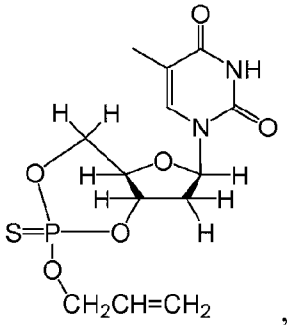
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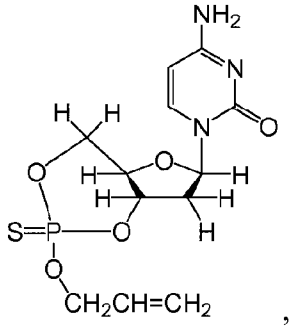
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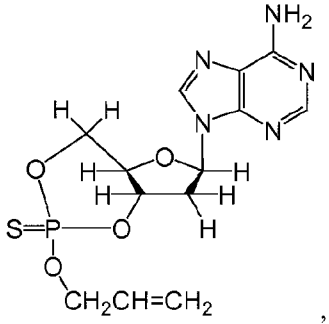
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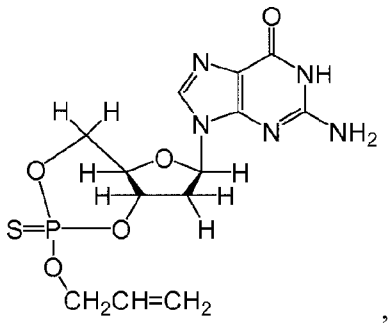
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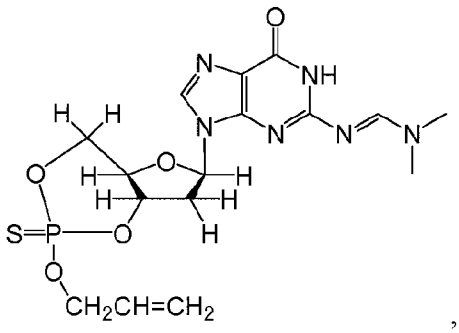

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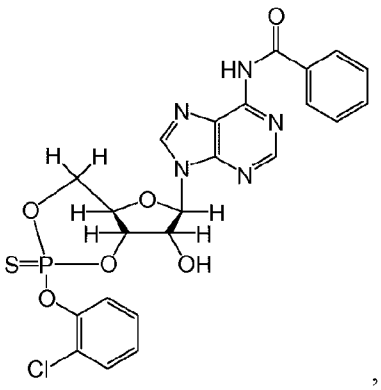

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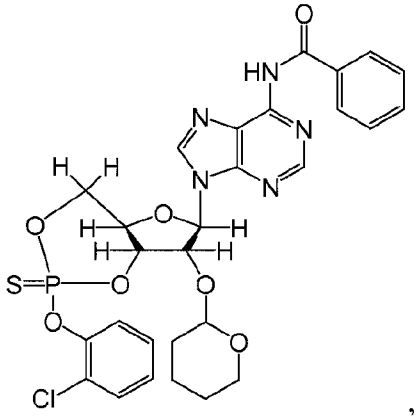

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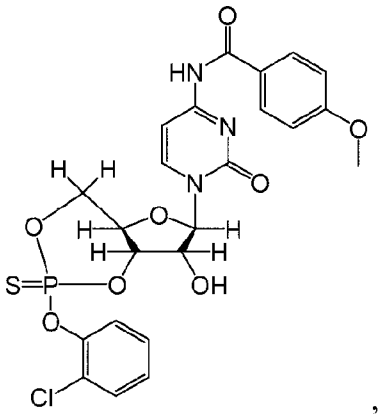

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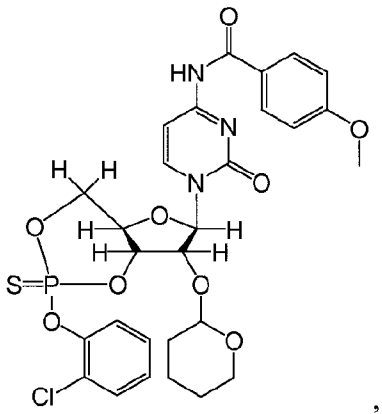

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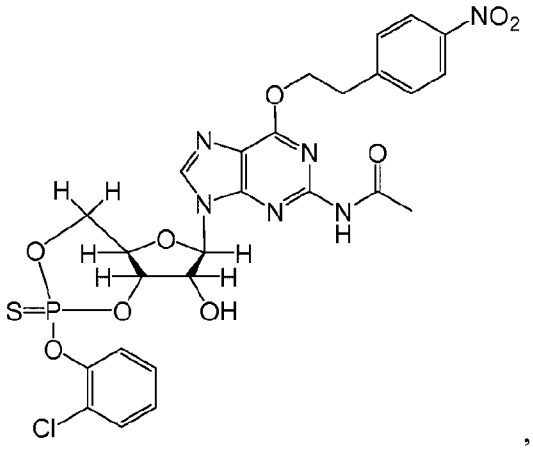

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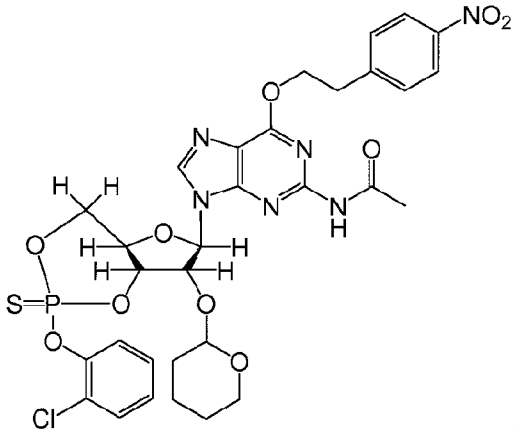

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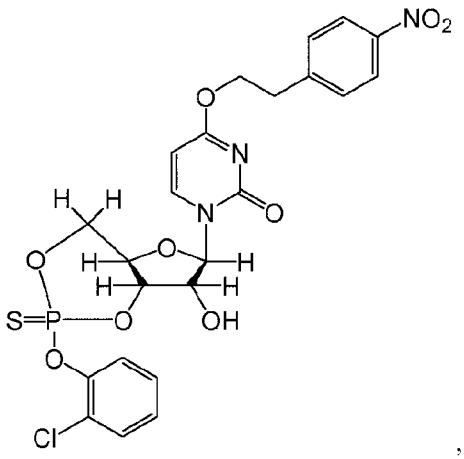
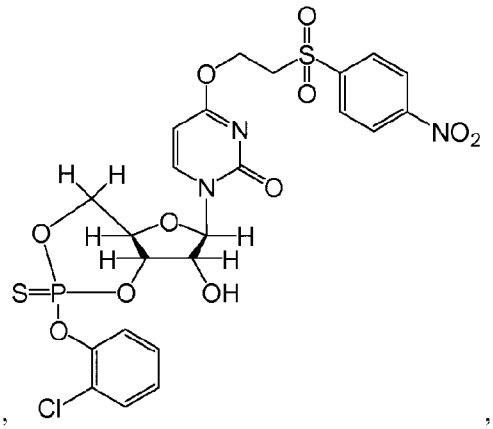
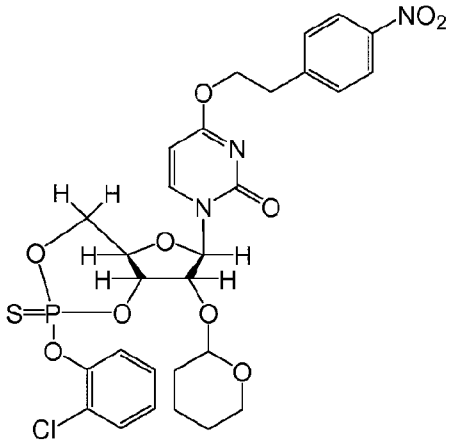
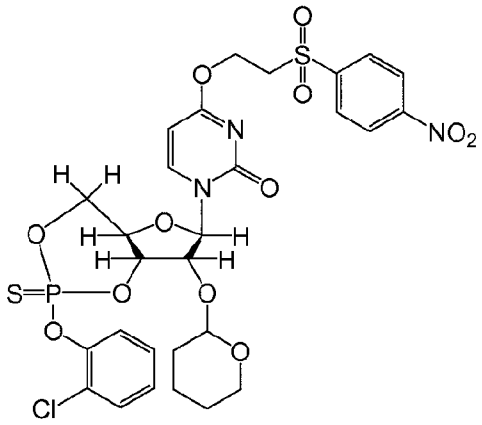
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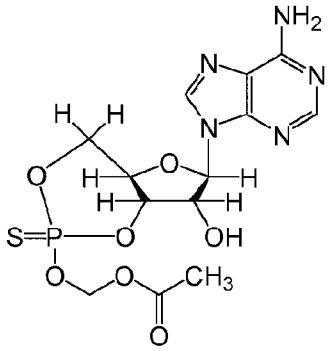


[0090] In some embodiments, when X^1 is S (sulfur), R^1 is $-Z^1-R^9$, Z^1 is $N(R^{10})$ and R^{10} is hydrogen, then R^9 cannot be an optionally substituted phenyl. In some embodiments, when X^1 is S (sulfur), Z^1 is $N(R^{10})$ and R^{10} is hydrogen, then R^9 cannot be an unsubstituted aryl, for example an unsubstituted phenyl. In other embodiments, when X^1 is S (sulfur), R^1 is $-Z^1-R^9$ and Z^1 is $N(R^{10})$, then R^9 and R^{10} cannot both be methyl or ethyl. In some embodiments, when X^1 is S (sulfur), R^1 is $-Z^1-R^9$ and Z^1 is $N(R^{10})$, then R^9 and R^{10} cannot both be an unsubstituted C_{1-4} alkyl. In some embodiments, when X^1 is S (sulfur), R^1 is $-Z^1-R^9$ and Z^1 is $N(R^{10})$, then R^9 and R^{10} cannot both be an optionally substituted C_{1-4} alkyl. In some embodiments, when X^1 is S (sulfur), R^1 is $-Z^1-R^9$ and Z^1 is $N(R^{10})$, then R^9 and R^{10} cannot both be an unsubstituted alkyl.

In some embodiments, when X^1 is S (sulfur), R^1 is $-Z^1-R^9$ and Z^1 is $N(R^{10})$, then R^9 and R^{10} cannot both be an optionally substituted alkyl.

[0091] In some embodiments, when X^1 is S (sulfur), R^1 is $-Z^1-R^9$ and Z^1 is O (oxygen), then R^9 cannot be methyl. In some embodiments, when X^1 is S (sulfur), R^1 is $-Z^1-R^9$ and Z^1 is O (oxygen), then R^9 cannot be an unsubstituted alkyl, for example an unsubstituted C_{1-4} alkyl. In some embodiments, when X^1 is S (sulfur), R^1 is $-Z^1-R^9$ and Z^1 is O (oxygen), then R^9 cannot be an optionally substituted alkyl, for example an optionally substituted C_{1-4} alkyl. In other embodiments, when X^1 is S (sulfur), R^1 is $-Z^1-R^9$ and Z^1 is O (oxygen), then R^9 cannot be $-CH_2-OC(=O)-(C_{1-4}$ alkyl), such as $-CH_2-OC(=O)CH_3$ or $-CH_2-OC(=O)C(CH_3)$. In some embodiments, when X^1 is S (sulfur), R^1 is $-Z^1-R^9$ and Z^1 is O (oxygen), then R^9 cannot be $-CH_2-OC(=O)-O-(C_{1-6}$ alkyl), such as $-CH_2-OC(=O)-O$-isopropyl. In still other embodiments, when X^1 is S (sulfur), R^1 is $-Z^1-R^9$ and Z^1 is O (oxygen), then R^9 cannot be $-CH_2CH=CH_2$. In some embodiments, when X^1 is S (sulfur), R^1 is $-Z^1-R^9$ and Z^1 is O (oxygen), then R^9 cannot be an unsubstituted C_{1-4} alkenyl. In some embodiments, when X^1 is S (sulfur), R^1 is $-Z^1-R^9$ and Z^1 is O (oxygen), then R^9 cannot be an unsubstituted alkenyl. In other embodiments, when X^1 is S (sulfur), R^1 is $-Z^1-R^9$ and Z^1 is O (oxygen), then R^9 cannot be 2-chlorophenyl. In some embodiments, when X^1 is S (sulfur), R^1 is $-Z^1-R^9$ and Z^1 is O (oxygen), then R^9 cannot be an optionally substituted aryl, such as an unsubstituted or substituted phenyl.

[0092] In some embodiments, when X^1 is O (oxygen), R^1 is $-Z^1-R^9$, Z^1 is $N(R^{10})$ and R^{10} is hydrogen, then R^9 cannot be an optionally substituted phenyl. In some embodiments, when X^1 is O (oxygen), R^1 is $-Z^1-R^9$, Z^1 is $N(R^{10})$ and R^{10} is hydrogen, then R^9 cannot be an optionally substituted aryl, such as an unsubstituted or substituted phenyl. In other embodiments, when X^1 is O (oxygen), R^1 is $-Z^1-R^9$, Z^1 is $N(R^{10})$ and R^{10} is hydrogen, then R^9 cannot be an optionally substituted benzyl. In some embodiments, when X^1 is O (oxygen), R^1 is $-Z^1-R^9$, Z^1 is $N(R^{10})$ and R^{10} is hydrogen, then R^9 cannot be an unsubstituted aryl(C_{1-6} alkyl). In still other embodiments, when X^1 is O (oxygen), R^1 is $-Z^1-R^9$, Z^1 is $N(R^{10})$ and R^{10} is hydrogen, then R^9 cannot be a substituted aryl(C_{1-6} alkyl). In yet still other embodiments, when X^1 is O (oxygen), R^1 is $-Z^1-R^9$ and Z^1 is $N(R^{10})$, then R^9 and R^{10} cannot be an unsubstituted C_{1-4} alkyl. Examples of C_{1-4} alkyls are described herein. In some embodiments, when X^1 is O (oxygen), R^1 is $-Z^1-R^9$ and Z^1 is $N(R^{10})$, then R^9 and R^{10} cannot both be an optionally substituted alkyl, such as an optionally substituted C_{1-4} alkyl.

[0093] In some embodiments, when X^1 is O (oxygen), R^1 is $-Z^1-R^9$ and Z^1 is O (oxygen), then R^9 cannot be methyl. In some embodiments, when X^1 is O (oxygen), R^1 is $-Z^1-R^9$ and Z^1 is O (oxygen), then R^9 cannot be an unsubstituted C_{1-4} alkyl. In some embodiments,

when X^1 is O (oxygen), R^1 is $-Z^1-R^9$ and Z^1 is O (oxygen), then R^9 cannot be an optionally substituted alkyl, such as an optionally substituted C_{1-4} alkyl. In other embodiments, when X^1 is O (oxygen), R^1 is $-Z^1-R^9$ and Z^1 is O (oxygen), then R^9 cannot be $-CH_2-OC(=O)-(C_{1-4}$ alkyl), such as $-CH_2-OC(=O)CH_3$, or $-CH_2-OC(=O)C(CH_3)$. In some embodiments, when X^1 is O (oxygen), R^1 is $-Z^1-R^9$ and Z^1 is O (oxygen), then R^9 cannot be $-CH_2-OC(=O)-O-(C_{1-6}$ alkyl), such as $-CH_2-OC(=O)-O$-isopropyl. In still other embodiments, when X^1 is O (oxygen), R^1 is $-Z^1-R^9$ and Z^1 is O (oxygen), then R^9 cannot be an optionally substituted phenyl. In some embodiments, when X^1 is O (oxygen), R^1 is $-Z^1-R^9$ and Z^1 is O (oxygen), then R^9 cannot be an unsubstituted aryl. In yet still other embodiments, when X^1 is O (oxygen), R^1 is $-Z^1-R^9$ and Z^1 is O (oxygen), then R^9 cannot be an optionally substituted aryl(C_{1-6} alkyl), for example, an optionally substituted benzyl.

[0094] In some embodiments, when X^1 is O (oxygen), R^1 is $-Z^1-R^9$ and Z^1 is S (sulfur), then R^9 cannot be methyl. In some embodiments, when X^1 is O (oxygen), R^1 is $-Z^1-R^9$ and Z^1 is S (sulfur), then R^9 cannot be an unsubstituted C_{1-4} alkyl. Examples of C_{1-4} alkyl groups are described herein. In some embodiments, when X^1 is O (oxygen), R^1 is $-Z^1-R^9$ and Z^1 is S (sulfur), then R^9 cannot be an optionally substituted alkyl. In other embodiments, when X^1 is O (oxygen), R^1 is $-Z^1-R^9$ and Z^1 is S (sulfur), then R^9 cannot be $-CH_2-C(=O)-C(=O)-CH_2$-halo, such as $-CH_2-C(=O)-C(=O)-CH_2Br$, $-CH_2-C(=O)-C(=O)-CH_2Cl$, $-CH_2-C(=O)-C(=O)-CH_2F$, or $-CH_2-C(=O)-C(=O)-CH_2I$. In other embodiments, when X^1 is O (oxygen), R^1 is $-Z^1-R^9$ and Z^1 is S (sulfur), then R^9 cannot be $-CH_2-OC(=O)-$t-butyl, $-CH_2-OC(=O)-$methyl, $-CH_2-OC(=O)(C_{1-6}$ alkyl), $-CH_2-OC(=O)-O$-isopropyl, or $-CH_2-OC(=O)-O-(C_{1-6}$ alkyl). In still other embodiments, when X^1 is O (oxygen), R^1 is $-Z^1-R^9$ and Z^1 is S (sulfur), then R^9 cannot be 4-nitro-benzyl or 4-isobutyryloxy-benzyl. In some embodiments, when X^1 is O (oxygen), R^1 is $-Z^1-R^9$ and Z^1 is S (sulfur), then R^9 cannot be an optionally substituted aryl(C_{1-6} alkyl).

[0095] The compound of Formula (I) can have various phosphorous containing groups. For example, the cyclic phosphorous containing group can be a cyclic phosphate, a cyclic phosphorothioate, a cyclic phosphoramidate or a cyclic thiophosphoramidate. In some embodiments, X^1 can be O (oxygen). In some embodiments, X^1 can be O (oxygen), and R^1 can be $-Z^1-R^9$. In some embodiments, X^1 can be O (oxygen), R^1 can be $-Z^1-R^9$, and Z^1 can be O (oxygen). In other embodiments, X^1 can be O (oxygen), R^1 can be $-Z^1-R^9$, and Z^1 can be S (sulfur). In other embodiments, X^1 can be O (oxygen), R^1 can be $-Z^1-R^9$, and Z^1 can be $N(R^{10})$.

[0096] In some embodiments, X^1 can be S (sulfur). In some embodiments, X^1 can be S (sulfur), and R^1 can be $-Z^1-R^9$. In some embodiments, X^1 can be S (sulfur), R^1 can be $-Z^1-$

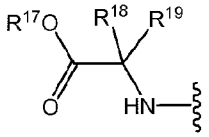
R^9, and Z^1 can be O (oxygen). In other embodiments, X^1 can be S (sulfur), R^1 can be $-Z^1-R^9$, and Z^1 can be S (sulfur). In other embodiments, X^1 can be S (sulfur), R^1 can be $-Z^1-R^9$, and Z^1 can be $N(R^{10})$.

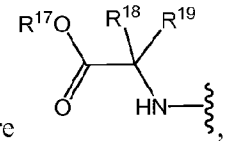
[0097] The substituents attached to the 5'-position of a compound of Formula (I) can vary. In some embodiments, R^2 and R^3 can be the same. In other embodiments, R^2 and R^3 can be different. In some embodiments, at least one of R^2 and R^3 can be hydrogen. In other embodiments, both R^2 and R^3 can be hydrogen. In some embodiments, at least one of R^2 and R^3 can be selected from of an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{2-6} alkynyl, an optionally substituted C_{1-6} haloalkyl and an optionally substituted aryl(C_{1-6} alkyl), or R^2 and R^3 can be taken together to form a group selected from an optionally substituted C_{3-6} cycloalkyl, an optionally substituted C_{3-6} cycloalkenyl, an optionally substituted C_{3-6} aryl and an optionally substituted C_{3-6} heteroaryl. In some embodiments, at least one of R^2 and R^3 cannot be hydrogen. In some embodiments, at least one of R^2 and R^3 can be an optionally substituted C_{1-6}-alkyl; and the other of R^2 and R^3 can be hydrogen. Examples of suitable optionally substituted C_{1-6} alkyls include optionally substituted variants of the following: methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, pentyl (branched and straight-chained), and hexyl (branched and straight-chained). In some embodiments, at least one of R^2 and R^3 can be methyl, and the other of R^2 and R^3 can be hydrogen. In other embodiments, at least one of R^2 and R^3 can be an optionally substituted C_{1-6}-haloalkyl, and the other of R^2 and R^3 can be hydrogen. One example of a suitable optionally substituted C_{1-6}-haloalkyl is CF_3. In some embodiments, when X^1 is O (oxygen), and R^1 is $-O-R^9$ or $-N(R^{10})-R^9$, then at least one of R^2 and R^3 can be selected from an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{2-6} alkynyl, an optionally substituted C_{1-6} haloalkyl and an optionally substituted aryl(C_{1-6} alkyl), or R^2 and R^3 can be taken together to form a group selected from an optionally substituted C_{3-6} cycloalkyl, an optionally substituted C_{3-6} cycloalkenyl, an optionally substituted C_{3-6} aryl and an optionally substituted C_{3-6} heteroaryl. In some embodiments, when X^1 is O (oxygen), and R^1 is $-O-R^9$ or $-N(R^{10})-R^9$, then at least one of R^2 and R^3 cannot be hydrogen. In some embodiments, R^3, R^4, R^5 and R^8 can each be hydrogen; and R^2 can be an optionally substituted C_{1-6} alkyl. Suitable C_{1-6} alkyl groups are described herein. When the substituents attached to the 5'-carbon make the 5'-carbon chiral, in some embodiments, the 5'-carbon can be a (R)-stereocenter. In other embodiments, the 5'-carbon can be an (S)-stereocenter.

[0098] Various amino acids derivatives can be used, including those described herein. In some embodiments, R^1 can be an optionally substituted N–linked α-amino acid.

Suitable amino acids include, but are not limited to, alanine, asparagine, aspartate, cysteine, glutamate, glutamine, glycine, proline, serine, tyrosine, arginine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan and valine. Additional suitable amino acids include, but are not limited to, alpha-ethyl-glycine, alpha-propyl-glycine and beta-alanine. In other embodiments, R^1 can be an optionally substituted N–linked α-amino acid ester derivative. Various amino acid ester derivatives can be used, including those described herein. For example, R^1 can be an ester derivative of any of the following amino acids: alanine, asparagine, aspartate, cysteine, glutamate, glutamine, glycine, proline, serine, tyrosine, arginine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan and valine. Additional examples of N-linked amino acid ester derivatives include, but are not limited to, an ester derivative of any of the following amino acids: alpha-ethyl-glycine, alpha-propyl-glycine and beta-alanine.

[0099] In some embodiments, R^1 can be an ester derivative of alanine. In some embodiments, R^1 can be selected from alanine methyl ester, alanine ethyl ester, alanine isopropyl ester, alanine cyclohexyl ester, alanine neopentyl ester, valine isopropyl ester and leucine isopropyl ester. In some embodiments, the optionally substituted N–linked amino acid or the optionally substituted N-linked amino acid ester derivative can be in the L-configuration. In other embodiments, the optionally substituted N–linked amino acid or the optionally substituted N-linked amino acid ester derivative can be in the D-configuration.

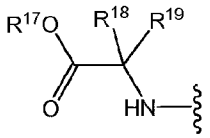
[0100] In some embodiments, R^1 can have the structure  wherein R^{17} can be selected from hydrogen, an optionally substituted C_{1-6}-alkyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted aryl, an optionally substituted aryl(C_{1-6} alkyl) and an optionally substituted C_{1-6} haloalkyl; R^{18} can be selected from hydrogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{1-6} haloalkyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted C_5 aryl, an optionally substituted C_{10} aryl and an optionally substituted aryl(C_{1-6} alkyl); and R^{19} can be hydrogen or an optionally substituted C_{1-4}-alkyl; or R^{18} and R^{19} can be taken together to form an optionally substituted C_{3-6} cycloalkyl.

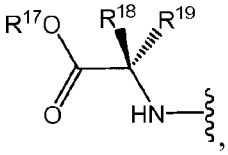
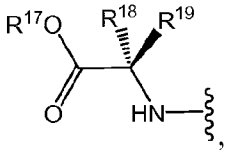
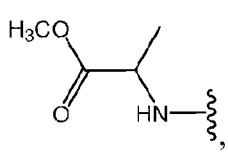
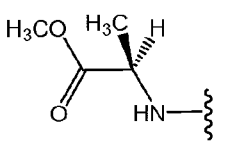
[0101] When R^1 has the structure  , R^{18} can be an optionally substituted C_{1-6}-alkyl. Examples of suitable optionally substituted C_{1-6}-alkyls include optionally substituted variants of the following: methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-

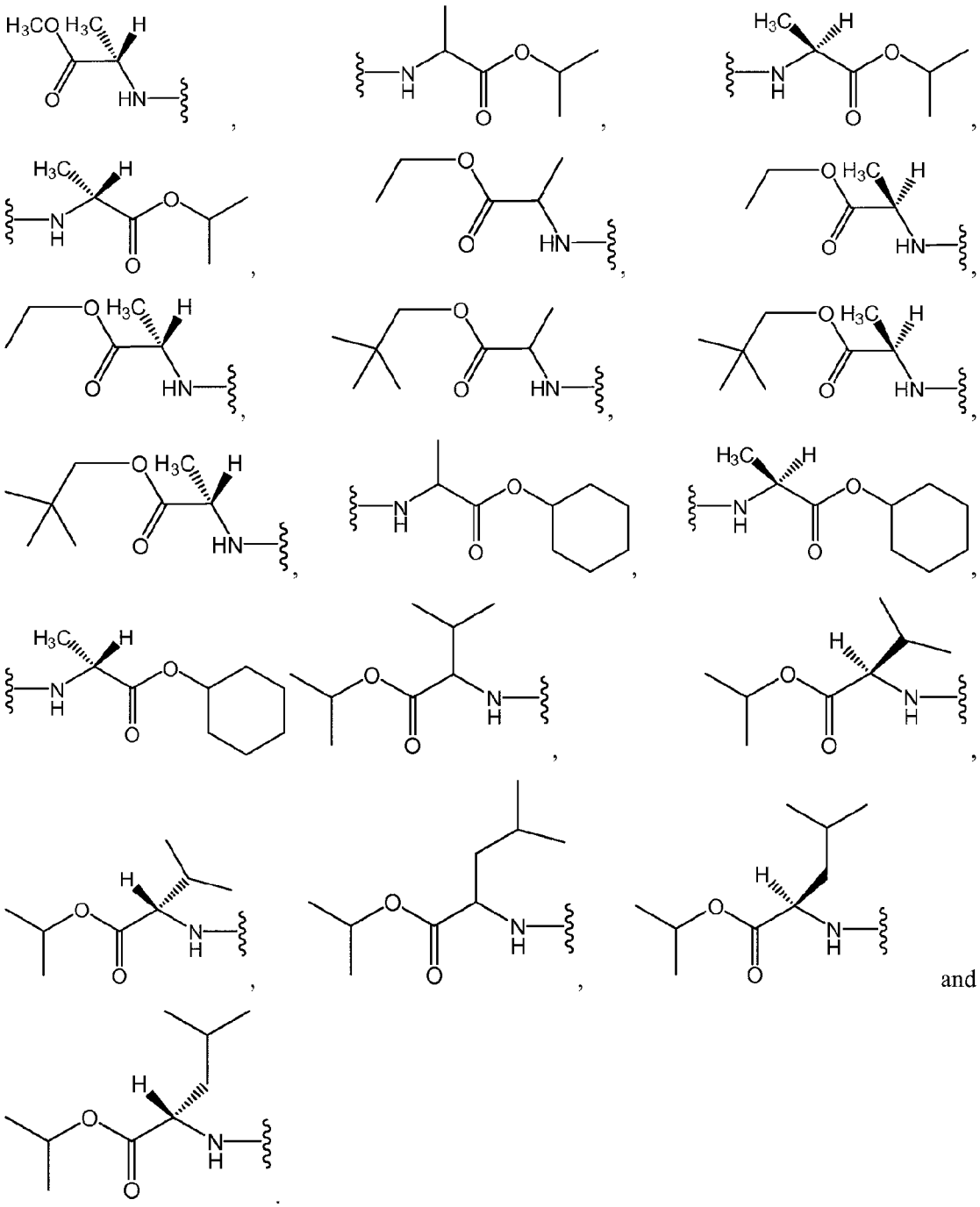
butyl, pentyl (branched and straight-chained), and hexyl (branched and straight-chained). When R^{18} is substituted, R^{18} can be substituted with one or more substituents selected from N-amido, mercapto, alkylthio, an optionally substituted aryl, hydroxy, an optionally substituted heteroaryl, O-carboxy, and amino. In some embodiments, R^{18} can be an unsubstituted C_{1-6}-alkyl, such as those described herein. In some embodiments, R^{18} can be methyl.

[0102] As to R^{17}, in some embodiments, R^{17} can be an optionally substituted C_{1-6} alkyl. Examples of optionally substituted C_{1-6}-alkyls include optionally substituted variants of the following: methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, pentyl (branched and straight-chained), and hexyl (branched and straight-chained). In some embodiments, R^{17} can be methyl or isopropyl. In some embodiments, R^{17} can be ethyl or neopentyl. In other embodiments, R^{17} can be an optionally substituted C_{3-6} cycloalkyl. Examples of optionally substituted C_{3-6} cycloalkyl include optionally substituted variants of the following: cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. In some embodiments, R^{17} can be an optionally substituted cyclohexyl. In still other embodiments, R^{17} can be an optionally substituted aryl, such as phenyl and naphthyl. In yet still other embodiments, R^{17} can be an optionally substituted aryl(C_{1-6} alkyl). In some embodiments, R^{17} can be an optionally substituted benzyl. In some embodiments, R^{17} can be an optionally substituted C_{1-6} haloalkyl, for example, CF_3.

[0103] In some embodiments, R^{19} can be hydrogen. In other embodiments, R^{19} can be an optionally substituted C_{1-4}-alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and tert-butyl. In some embodiments, R^{19} can be methyl. In some embodiments, R^{18} can be hydrogen. In some embodiments, R^{18} and R^{19} can be taken together to form an optionally substituted C_{3-6} cycloalkyl. Examples of optionally substituted C_{3-6} cycloalkyl include optionally substituted variants of the following: cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. Depending on the groups that are selected for R^{18} and R^{19}, the carbon to which R^{18} and R^{19} are attached may be a chiral center. In some embodiments, the carbon to which R^{18} and R^{19} are attached may be a (R)-chiral center. In other embodiments, the carbon to which R^{18} and R^{19} are attached may be a (S)-chiral center.

[0104] As example of a suitable  groups include the following:

 ,  ,  ,  ,



and

[0105] In some embodiments, R^4 can be halogen, azido, cyano, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{2-6} alkynyl or an optionally substituted allenyl. In some embodiments, R^4 can be hydrogen. In other embodiments, R^4 can be azido. In other embodiments, R^4 can be cyano. In still other embodiments, R^4 can be an optionally substituted allenyl. In yet still other embodiments, R^4 can be a halogen. In some embodiments, R^4 can be fluoro. In other embodiments, R^4 can be optionally substituted C_{1-6} alkyl, such as those described herein. In still other embodiments, R^4

can be optionally substituted C_{2-6} alkenyl. In yet still other embodiments, R^4 can be optionally substituted C_{2-6} alkynyl.

[0106] Various substituents can be attached to the 3'-carbon. In some embodiments, R^5 can be hydrogen. In other embodiments, R^5 can be an optionally substituted C_{1-6} alkyl. Examples of optionally substituted C_{1-6}-alkyls include optionally substituted variants of the following: methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, pentyl (branched and straight-chained), and hexyl (branched and straight-chained).

[0107] The substituents attached to the 2'-carbon can vary. In some embodiments, R^6 can be hydrogen. In some embodiments, R^6 can be halogen, azido, amino, cyano, an optionally substituted C_{1-6} alkyl, $-OR^{11}$ or $-OC(=O)R^{12}$. In some embodiments, R^6 can be halogen. In other embodiments, R^6 can be azido. In still other embodiments, R^6 can be amino. In yet still other embodiments, R^6 can be cyano. In some embodiments, R^6 can be an optionally substituted C_{1-6} alkyl. Examples of optionally substituted C_{1-6} alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and tert-butyl. In other embodiments, R^6 can be $-OR^{11}$. In some embodiments, when R^{11} is hydrogen, R^6 can be a hydroxy group. In other embodiments, when R^{11} is an optionally substituted C_{1-6} alkyl, R^6 can be an optionally substituted C_{1-6} alkoxy. Suitable optionally substituted C_{1-6} alkoxy groups are described herein. In some embodiments, R^6 can be $-OC(=O)R^{12}$, wherein R^{12} can be an optionally substituted C_{1-6} alkyl, such as optionally substituted variants of the following: methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, pentyl (branched and straight-chained), and hexyl (branched and straight-chained). In other embodiments, R^6 can be $-OC(=O)R^{12}$, wherein R^{12} can be an optionally substituted C_{3-6} cycloalkyl.

[0108] In some embodiments, R^7 can be hydrogen. In some embodiments, R^7 can be halogen, azido, cyano, an optionally substituted C_{1-6} alkyl, $-OR^{13}$ or $-OC(=O)R^{14}$. In some embodiments, R^7 can be halogen. In other embodiments, R^7 can be azido. In still other embodiments, R^7 can be cyano. In other embodiments, R^7 can be an optionally substituted C_{1-6} alkyl. Examples of optionally substituted C_{1-6} alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and tert-butyl. In still other embodiments, R^7 can be $-OR^{13}$. When R^{13} is hydrogen, R^7 can be hydroxy. Alternatively, when R^{13} is an optionally substituted C_{1-6} alkyl, R^7 can be an optionally substituted C_{1-6} alkoxy. Suitable alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, tert-butoxy, pentoxy (branched and straight-chained), and hexoxy (branched and straight-chained). In some embodiments, R^7 can be $-OC(=O)R^{14}$ in which R^{14} is an optionally substituted C_{1-6} alkyl

or an optionally substituted C_{3-6} cycloalkyl. Examples of suitable C_{1-6} alkyl groups are described herein.

[0109] In some embodiments, at least one of R^6 and R^7 can be a halogen. In some embodiments, R^6 and R^7 can both be a halogen. In other embodiments, R^6 can be a halogen and R^7 can be an optionally substituted C_{1-6} alkyl, such as those described herein. In still other embodiments, R^6 can be a hydroxy and R^7 can be an optionally substituted C_{1-6} alkyl, such as those described herein.

[0110] In some embodiments, R^8 can be hydrogen. In some embodiments, R^8 can be halogen, azido, cyano, an optionally substituted C_{1-6} alkyl, $-OR^{15}$ or $-OC(=O)R^{16}$. In some embodiments, R^8 can be halogen. In other embodiments, R^8 can be azido. In still other embodiments, R^8 can be cyano. In other embodiments, R^8 can be an optionally substituted C_{1-6} alkyl. Examples of optionally substituted C_{1-6} alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and tert-butyl. In still other embodiments, R^8 can be $-OR^{15}$. When R^{15} is hydrogen, R^8 can be hydroxy. Alternatively, when R^{15} is an optionally substituted C_{1-6} alkyl, R^8 can be an optionally substituted C_{1-6} alkoxy. Suitable alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, tert-butoxy, pentoxy (branched and straight-chained), and hexoxy (branched and straight-chained). In some embodiments, R^8 can be $-OC(=O)R^{16}$ in which R^{16} is an optionally substituted C_{1-6} alkyl or an optionally substituted C_{3-6} cycloalkyl. Examples of suitable C_{1-6} alkyl groups are described herein.

[0111] Those skilled in the art understand that when a hydrogen atom is removed or is absent from an oxygen atom, the oxygen atom can have a negative charge. For example, when R^6 is a hydroxy group and the hydrogen is removed or absent, the oxygen atom to which to hydrogen atom was associated with can be O^-. Likewise, when R^7 or R^8 is a hydroxy group and the hydrogen is removed or is absent, the oxygen atom to which to hydrogen atom was associated with can be O^-. In some embodiments, R^2, R^3, R^4, R^5 and R^8 can each be hydrogen.

[0112] When R^1 is Z^1-R^9, the R^9 group can vary. In some embodiments, R^9 can be selected from an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl, an optionally substituted aryl(C_{1-6} alkyl), an optionally substituted heteroaryl(C_{1-6} alkyl), an optionally substituted heterocyclyl(C_{1-6} alkyl) and Formula (II). In other embodiments, R^9 can be selected from an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted

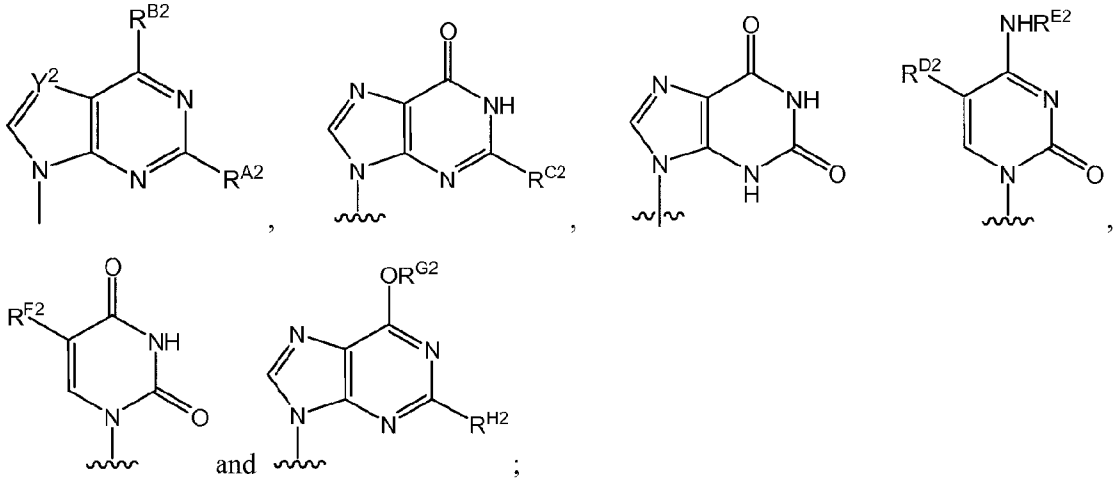
heteroaryl, an optionally substituted heterocyclyl, an optionally substituted heteroaryl(C_{1-6} alkyl) and an optionally substituted heterocyclyl(C_{1-6} alkyl). In some embodiments, R^9 can be an optionally substituted alkyl. In some embodiments, R^9 can be an optionally substituted C_{1-6} alkyl. Examples of optionally substituted C_{1-6} alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and tert-butyl. In some embodiments, R^9 can be an optionally substituted aryl. In some embodiments, R^9 can be an optionally substituted phenyl. In some embodiments, R^9 can be an optionally substituted aryl(C_{1-6} alkyl). In some embodiments, R^9 can be benzyl. In some embodiments, R^9 can be an optionally substituted cycloalkyl. In some embodiments, R^9 can be cyclobutyl, cyclopentyl, or cyclohexyl. In some embodiments, R^9 can be $-CH_2$-cyclopropyl. In some embodiments, R^{10} can be hydrogen or an optionally substituted alkyl (for example, an optionally substituted C_{1-6} alkyl).

[0113] In some embodiments, R^9 can be Formula (II). In some embodiments, R^{20} and R^{21} both can be hydrogen. In some embodiments, R^{20} and R^{21} can each be an optionally substituted C_{1-24} alkyl or an optionally substituted aryl. In some embodiments, at least one of R^{20} and R^{21} can an optionally substituted C_{1-24} alkyl or an optionally substituted aryl, and the other of R^{20} and R^{21} can be hydrogen. In some embodiments, R^{22} can be hydrogen. In some embodiments, R^{22} can be an optionally substituted C_{1-24} alkyl. In some embodiments, R^{22} can be an optionally substituted aryl. In some embodiments, R^{22} can be an optionally substituted $-O-C_{1-24}$ alkyl. In some embodiments, R^{22} can be an optionally substituted $-O-C_{1-6}$ alkyl. Examples of optionally substituted C_{1-6} alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, pentyl (branched and straight-chained), and hexyl (branched and straight-chained). In some embodiments, R^{22} can be an optionally substituted –O–aryl. In some embodiments, Y^1 can be O (oxygen). In some embodiments, Y^1 can be S (sulfur). In some embodiments, R^9 can be Formula (II), R^{20} and R^{21} both can be hydrogen, R^{22} can be an optionally substituted C_{1-24} alkyl, and Y^1 can be O (oxygen). In other embodiments, R^9 can be Formula (II), R^{20} and R^{21} both can be hydrogen, R^{22} can be an optionally substituted C_{1-24} alkyl, and Y^1 can be S (sulfur). In some embodiments, R^{20} and R^{21} both can be hydrogen, R^{22} can be tert-butyl, and Y^1 can be O (oxygen). In other embodiments, R^{20} and R^{21} both can be hydrogen, R^{22} can be tert-butyl, and Y^1 can be S (sulfur). In some embodiments, R^9 can be pivaloyloxymethyl. In some embodiments, R^9 can be isopropyloxycarbonyloxymethyl.

[0114] In some embodiments, R^5 and R^8 can each be hydrogen; and R^4 can be azido. In other embodiments, R^4, R^5, R^7 and R^8 can each be hydrogen; and R^6 can be -OH. In still other embodiments, R^4, R^5 and R^8 can each be hydrogen; and R^6 can be halogen. In yet still

other embodiments, R^4, R^5 and R^8 can each be hydrogen; and R^7 can be an optionally substituted C_{1-6} alkyl. In some embodiments, R^4, R^5 and R^8 can each be hydrogen; R^6 can be a halogen; and R^7 can be an optionally substituted C_{1-6} alkyl. In other embodiments, R^4, R^5 and R^8 can each be hydrogen; and R^7 can be methyl. In still other embodiments, R^4, R^5 and R^8 can each be hydrogen; and R^7 can be halogen. In some embodiments, R^4, R^5 and R^8 can each be hydrogen; R^6 can be a halogen; and R^7 can be a halogen. In yet still other embodiments, R^4, R^5 and R^8 can each be hydrogen; R^6 can be $-OR^{11}$; R^{11} can be hydrogen; and R^7 can be an optionally substituted C_{1-6} alkyl. In some embodiments, R^4, R^5 and R^8 can each be hydrogen; R^6 can be -OH; and R^7 can be methyl. In other embodiments, R^4, R^5 and R^8 can each be hydrogen; R^6 can be $-OR^{11}$; R^{11} can be hydrogen; and R^7 can be halogen. In some of the embodiments of this paragraph, R^2 and R^3 can both be hydrogen. In some of the embodiments of this paragraph, at least one of R^2 and R^3 can be an optionally substituted C_{1-6} alkyl; and the other of R^2 and R^3 can be hydrogen.

[0115] Various optionally substituted heterocyclic bases can be attached to the pentose ring. In some embodiments, one or more of the amine and/or amino groups may be protected with a suitable protecting group. For example, an amino group may be protected by transforming the amine and/or amino group to an amide or a carbamate. In some embodiments, B^1 can be an optionally substituted heterocyclic base or an optionally substituted heterocyclic base with one or more protected amino groups can have one of the following structures:

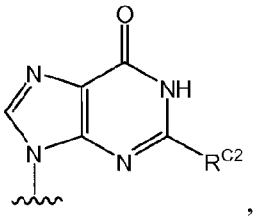


;

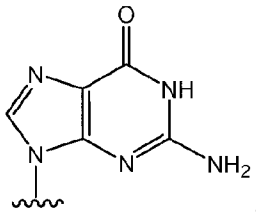
wherein: R^{A2} can be selected from hydrogen, halogen and NHR^{J2}, wherein R^{J2} can be selected from hydrogen, $-C(=O)R^{K2}$ and $-C(=O)OR^{L2}$; R^{B2} can be halogen or NHR^{W2}, wherein R^{W2} is selected from hydrogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{3-8} cycloalkyl, $-C(=O)R^{M2}$ and $-C(=O)OR^{N2}$; R^{C2} can be hydrogen or NHR^{O2}, wherein R^{O2} can be selected from hydrogen, $-C(=O)R^{P2}$ and $-C(=O)OR^{Q2}$; R^{D2} can be selected from hydrogen, halogen, an optionally substituted C_{1-6} alkyl, an optionally

substituted C_{2-6} alkenyl and an optionally substituted C_{2-6} alkynyl; R^{E2} can be selected from hydrogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{3-8} cycloalkyl, -$C(=O)R^{R2}$ and –$C(=O)OR^{S2}$; R^{F2} can be selected from hydrogen, halogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl and an optionally substituted C_{2-6} alkynyl; Y^2 can be N (nitrogen) or CR^{I2}, wherein R^{I2} can be selected from hydrogen, halogen, an optionally substituted C_{1-6}-alkyl, an optionally substituted C_{2-6}-alkenyl and an optionally substituted C_{2-6}-alkynyl; R^{G2} can be an optionally substituted C_{1-6} alkyl; R^{H2} can be hydrogen or NHR^{T2}, wherein R^{T2} can be independently selected from hydrogen, -$C(=O)R^{U2}$ and –$C(=O)OR^{V2}$, and R^{K2}, R^{L2}, R^{M2}, R^{N2}, R^{P2}, R^{Q2} R^{R2}, R^{S2}, R^{U2} and R^{V2} can be independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkenyl, C_{3-6} cycloalkynyl, C_{6-10} aryl, heteroaryl, heterocyclyl, aryl(C_{1-6} alkyl), heteroaryl(C_{1-6} alkyl) and heterocyclyl(C_{1-6} alkyl). In some embodiments, the structures shown above can be modified by replacing one or more hydrogens with substituents selected from the list of substituents provided for the definition of "substituted."

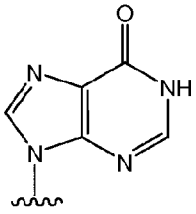
[0116] In some embodiments, B^1 can be selected from adenine, guanine, thymine, cytosine and uracil. In some embodiments, B^1 can be an optionally substituted



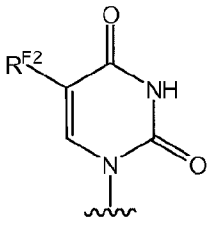
, such as



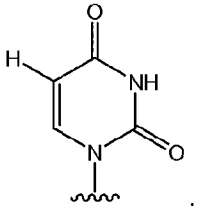
. In still other embodiments, B^1 can be



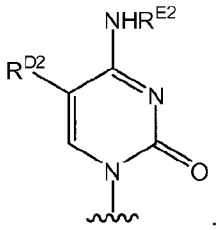
. In yet still other embodiments, B^1 can be an optionally substituted



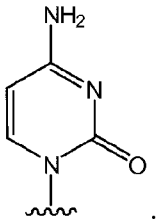
. In some embodiments R^{F2} can be hydrogen. In some embodiments, B^1 can



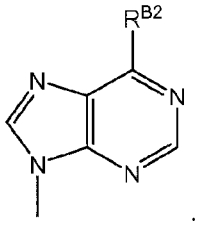
be . In some embodiments, B^1 can be an optionally substituted



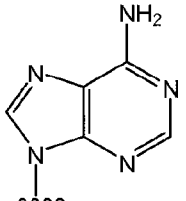
. In some embodiments R^{E2} is hydrogen. In some embodiments, B^1 can be



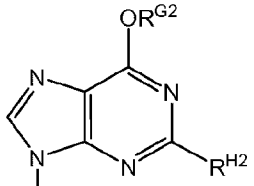
. In other embodiments, B^1 can be



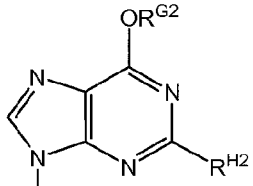
. In yet still other embodiments, B^1 can be



. In some embodiments, B^1 can be an optionally substituted



. For example, B^1 can be



, wherein R^{G2} can be an optionally substituted C_{1-4} alkyl; and R^{H2} can be NH_2. In some embodiments, R^{G2} can be methyl or ethyl.

[0117] In some embodiments, when X^1 is S (sulfur), R^1 is $-Z^1-R^9$ and Z^1 is $N(R^{10})$, then B^1 can be an optionally substituted cytosine or an optionally substituted uracil. In some embodiments, when X^1 is O (oxygen), R^1 is $-Z^1-R^9$ and Z^1 is S (sulfur), then B^1 can be an optionally substituted cytosine.

[0118] In some embodiments, if B^1 is an optionally substituted guanine, then R^1 can be an optionally substituted N-linked amino acid or an optionally substituted N-linked amino acid ester derivative. In other embodiments, if B^1 is an optionally substituted guanine and R^1 is $-Z^1-R^9$, then R^9 can be a substituted alkyl, such as a substituted C_{1-6} alkyl. In still other embodiments, if B^1 is an optionally substituted guanine and R^1 is $-Z^1-R^9$, then R^9 can be a substituted alkenyl. In yet still other embodiments, if B^1 is an optionally substituted guanine and R^1 is $-Z^1-R^9$, then R^9 can be an unsubstituted aryl. In some embodiments, if B^1 is an optionally substituted guanine and R^1 is $-Z^1-R^9$, then R^9 can be Formula (II). In some embodiments, if B^1 is an optionally substituted guanine and R^1 is $-Z^1-R^9$, then R^9 can be Formula (II), wherein R^{20}

and R^{21} both can be hydrogen, R^{22} can be an optionally substituted C_{1-24} alkyl, and Y^1 can be O (oxygen) or S (sulfur). In some embodiments, if B^1 is an optionally substituted guanine and R^1 is $-Z^1-R^9$, then R^9 can be pivaloyloxymethyl. In some embodiments, if B^1 is an optionally substituted guanine and R^1 is $-Z^1-R^9$, then R^9 can be isopropyloxycarbonyloxymethyl. In some of the embodiments of this paragraph, the optionally substituted guanine can be a protected guanine. In some of the embodiments of this paragraph, X^1 is S (sulfur). In some of the embodiments of this paragraph, X^1 is O (oxygen).

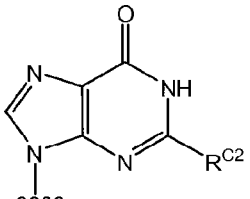
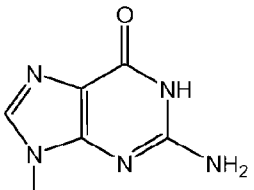
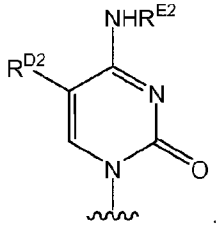
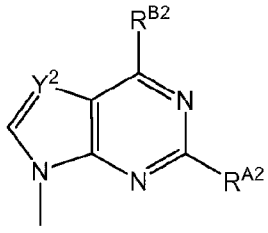
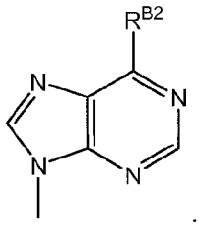
[0119] In some embodiments, if B^1 is an optionally substituted uracil, then R^1 can be an optionally substituted N-linked amino acid or an optionally substituted N-linked amino acid ester derivative. In other embodiments, if B^1 is an optionally substituted uracil and R^1 is $-Z^1-R^9$, then R^9 can be a substituted alkyl. In still embodiments, if B^1 is an optionally substituted uracil and R^1 is $-Z^1-R^9$, then R^9 can be an unsubstituted aryl. In some embodiments, if B^1 is an optionally substituted uracil and R^1 is $-Z^1-R^9$, then R^9 can be Formula (II). In some embodiments, if B^1 is an optionally substituted uracil and R^1 is $-Z^1-R^9$, then R^9 can be Formula (II), wherein R^{20} and R^{21} both can be hydrogen, R^{22} can be an optionally substituted C_{1-24} alkyl, and Y^1 can be O (oxygen) or S (sulfur). In some embodiments, if B^1 is an optionally substituted uracil and R^1 is $-Z^1-R^9$, then R^9 can be pivaloyloxymethyl. In some embodiments, if B^1 is an optionally substituted uracil and R^1 is $-Z^1-R^9$, then R^9 can be isopropyloxycarbonyloxymethyl. In some of the embodiments of this paragraph, the optionally substituted uracil can be a protected uracil. In some of the embodiments of this paragraph, X^1 is S (sulfur). In some of the embodiments of this paragraph, X^1 is O (oxygen).

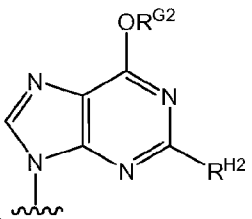
[0120] In some embodiments, if B^1 is an optionally substituted thymine, then R^1 can be an optionally substituted N-linked amino acid or an optionally substituted N-linked amino acid ester derivative. In other embodiments, if B^1 is an optionally substituted thymine and R^1 is $-Z^1-R^9$, then R^9 can be a substituted alkyl. In still other embodiments, if B^1 is an optionally substituted thymine and R^1 is $-Z^1-R^9$, then R^9 can be a substituted alkenyl. In yet still other embodiments, if B^1 is an optionally substituted thymine and R^1 is $-Z^1-R^9$, then R^9 can be a substituted aryl. In some embodiments, if B^1 is an optionally substituted thymine and R^1 is $-Z^1-R^9$, then R^9 can be Formula (II). In some embodiments, if B^1 is an optionally substituted thymine and R^1 is $-Z^1-R^9$, then R^9 can be Formula (II), wherein R^{20} and R^{21} both can be hydrogen, R^{22} can be an optionally substituted C_{1-24} alkyl, and Y^1 can be O (oxygen) or S (sulfur). In some embodiments, if B^1 is an optionally substituted thymine and R^1 is $-Z^1-R^9$, then R^9 can be pivaloyloxymethyl. In some embodiments, if B^1 is an optionally substituted thymine and R^1 is $-Z^1-R^9$, then R^9 can be isopropyloxycarbonyloxymethyl. In some of the embodiments

of this paragraph, the optionally substituted thymine can be a protected thymine. In some of the embodiments of this paragraph, X^1 is S (sulfur). In some of the embodiments of this paragraph, X^1 is O (oxygen).

[0121] In some embodiments, if B^1 is an optionally substituted adenine, then R^1 can be an optionally substituted N-linked amino acid or an optionally substituted N-linked amino acid ester derivative. In other embodiments, if B^1 is an optionally substituted adenine and R^1 is $-Z^1-R^9$, then R^9 can be a substituted alkyl. In still other embodiments, if B^1 is an optionally substituted adenine and R^1 is $-Z^1-R^9$, then R^9 can be a substituted alkenyl. In some embodiments, if B^1 is an optionally substituted adenine and R^1 is $-Z^1-R^9$, then R^9 can be Formula (II). In some embodiments, if B^1 is an optionally substituted adenine and R^1 is $-Z^1-R^9$, then R^9 can be Formula (II), wherein R^{20} and R^{21} both can be hydrogen, R^{22} can be an optionally substituted C_{1-24} alkyl, and Y^1 can be O (oxygen) or S (sulfur). In some embodiments, if B^1 is an optionally substituted adenine and R^1 is $-Z^1-R^9$, then R^9 can be pivaloyloxymethyl. In some embodiments, if B^1 is an optionally substituted adenine and R^1 is $-Z^1-R^9$, then R^9 can be isopropyloxycarbonyloxymethyl. In some of the embodiments of this paragraph, the optionally substituted adenine can be a protected adenine. In some of the embodiments of this paragraph, X^1 is S (sulfur). In some of the embodiments of this paragraph, X^1 is O (oxygen).

[0122] In some embodiments, if B^1 is an optionally substituted cytosine, then R^1 can be an optionally substituted N-linked amino acid or an optionally substituted N-linked amino acid ester derivative. In other embodiments, if B^1 is an optionally substituted cytosine and R^1 is $-Z^1-R^9$, then R^9 can be a substituted alkyl. In still other embodiments, if B^1 is an optionally substituted cytosine and R^1 is $-Z^1-R^9$, then R^9 can be a substituted alkenyl. In yet still other embodiments, if B^1 is an optionally substituted cytosine and R^1 is $-Z^1-R^9$, then R^9 can be a substituted aryl. In some embodiments, if B^1 is an optionally substituted cytosine and R^1 is $-Z^1-R^9$, then R^9 can be Formula (II). In some embodiments, if B^1 is an optionally substituted cytosine and R^1 is $-Z^1-R^9$, then R^9 can be Formula (II), wherein R^{20} and R^{21} both can be hydrogen, R^{22} can be an optionally substituted C_{1-24} alkyl, and Y^1 can be O (oxygen) or S (sulfur). In some embodiments, if B^1 is an optionally substituted cytosine and R^1 is $-Z^1-R^9$, then R^9 can be pivaloyloxymethyl. In some embodiments, if B^1 is an optionally substituted cytosine and R^1 is $-Z^1-R^9$, then R^9 can be isopropyloxycarbonyloxymethyl. In some of the embodiments of this paragraph, the optionally substituted cytosine can be a protected cytosine. In some of the embodiments of this paragraph, X^1 is S (sulfur). In some of the embodiments of this paragraph, X^1 is O (oxygen).

[0123] In some embodiments, R^4 cannot be hydrogen. In some embodiments, R^5 cannot be hydrogen. In some embodiments, R^6 cannot be hydrogen. In some embodiments, R^6 cannot be a hydroxy group. In other embodiments, when R^6 is $-OC(=O)R^{12}$, then R^{12} cannot be $-CH-(CH_3)_2$. In still other embodiments, when R^6 is $-OC(=O)R^{12}$, then R^{12} cannot be an optionally substituted alkyl, for example, a substituted C_{1-4} alkyl or an unsubstituted C_{1-4} alkyl. In some embodiments, R^7 cannot be hydrogen. In some embodiments, R^8 cannot be hydrogen. In some embodiments, R^9 cannot be an optionally substituted alkyl, such as a substituted or unsubstituted C_{1-4} alkyl. In other embodiments, R^9 cannot be an optionally substituted alkenyl, for example $-CH_2CH=CH_2$. In still other embodiments, R^9 cannot be an optionally substituted aryl, such as an optionally substituted phenyl. In yet still other embodiments, R^9 cannot be an optionally substituted aryl(C_{1-6} alkyl), such as an optionally substituted benzyl. In some embodiments, R^9 cannot be $-CH_2-OC(=O)CH_3$, $-CH_2-OC(=O)$–t-butyl, $-CH_2-OC(=O)(C_{1-6}$ alkyl), $-CH_2-OC(=O)$–O-isopropyl, or $-CH_2-OC(=O)-O-(C_{1-6}$ alkyl). In some embodiments, B^1 cannot be an optionally substituted  , such as  . In some embodiments, B^1 cannot be an optionally substituted  . In some embodiments, B^1 cannot be an optionally substituted  , such as  . In some embodiments, B^1 cannot be an optionally

substituted  . In some embodiments, B^1 cannot be a dimethylformamide protected guanine or a 2-(nitrophenyl)ethyl protected guanine. In other embodiments, B^1 cannot be an acyl protected guanine. In still other embodiments, B^1 cannot be a 2-(nitrophenyl)ethyl protected uracil. In some embodiments, B^1 cannot be a 2-(nitrophenyl)sulfonylethyl protected uracil. In yet still other embodiments, B^1 cannot be a benzoyl protected adenine. In some embodiments, B^1 cannot be an anisoyl protected cytosine. In some embodiments, if B^1 is an optionally substituted guanine and R^1 is $-Z^1-R^9$, then R^9 cannot be methyl, $-CH_2CH=CH_2$, 2-chlorophenyl or $-CH_2-C(=O)-C(=O)-CH_2$-halo, such as $-CH_2-C(=O)-C(=O)-CH_2Br$, $-CH_2-C(=O)-C(=O)-CH_2Cl$, $-CH_2-C(=O)-C(=O)-CH_2F$, or $-CH_2-C(=O)-C(=O)-CH_2I$. In some embodiments, if B^1 is an optionally substituted uracil and R^1 is $-Z^1-R^9$, then R^9 cannot be methyl or 2-chlorophenyl. In some embodiments, if B^1 is an optionally substituted thymine and R^1 is $-Z^1-R^9$, then R^9 cannot be methyl or $-CH_2CH=CH_2$. In other embodiments, if B^1 is an optionally substituted thymine and R^1 is $-Z^1-R^9$, then R^9 cannot be an optionally substituted phenyl. In yet still other embodiments, if B^1 is an optionally substituted adenine and R^1 is $-Z^1-R^9$, then R^9 cannot be methyl or ethyl. In some embodiments, if B^1 is an optionally substituted adenine and R^1 is $-Z^1-R^9$, then R^9 cannot be $-CH_2CH=CH_2$. In other embodiments, if B^1 is an optionally substituted adenine and R^1 is $-Z^1-R^9$, then R^9 cannot be phenyl. In some embodiments, if B^1 is an optionally substituted adenine and R^1 is $-Z^1-R^9$, then R^9 cannot be 2-chlorophenyl, 4-nitro-benzyl or 4-isobutyryloxy-benzyl. In other embodiments, if B^1 is an optionally substituted adenine and R^1 is $-Z^1-R^9$, then R^9 cannot be $-CH_2-C(=O)-C(=O)-CH_2$-halo, such as $-CH_2-C(=O)-C(=O)-CH_2Br$, $-CH_2-C(=O)-C(=O)-CH_2Cl$, $-CH_2-C(=O)-C(=O)-CH_2F$, or $-CH_2-C(=O)-C(=O)-CH_2I$. In other embodiments, if B^1 is an optionally substituted adenine and R^1 is $-Z^1-R^9$, then R^9 cannot be $-CH_2-OC(=O)CH_3$, $-CH_2-OC(=O)C(CH_3)_3$, $-CH_2-OC(=O)(C_{1-6}$ alkyl), $-CH_2-OC(=O)-O$-isopropyl, or $-CH_2-OC(=O)-O-(C_{1-6}$ alkyl).

[0124] Depending upon the substituents attached to the phosphorus atom, the phosphorus atom can be a chiral center. In some embodiments, the phosphorus can be a (R)-stereocenter. In other embodiments, the phosphorus can be a (S)-stereocenter.

[0125] In some embodiments, a compound of Formula (I) can be a single diastereomer. In other embodiments, a compound of Formula (I) can be a mixture of diastereomers. In some embodiments, a compound of Formula (I) can be a 1:1 mixture of two diastereomers. In some embodiments, a compound of Formula (I) can be diasteriometrically

enriched (for example, one diastereomer can be present at a concentration of > 55%, ≥ 75%, ≥ 80%, ≥ 90%, ≥ 95%, ≥ 98%, or ≥ 99% as compared to the total concentration of the other diastereomers).

[0126] Some embodiments of R^1 of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, are provided in Table 1. Tables 2-3 provide the structures of the variables aa01-aa11 and es01-es14, respectively. For example, the first entry in Table 1 is "aa01,es01," which corresponds to a compound of Formula (I), wherein R^1 is

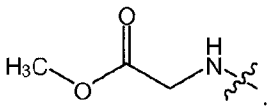
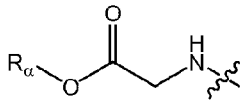
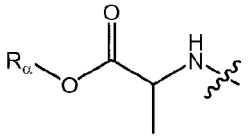
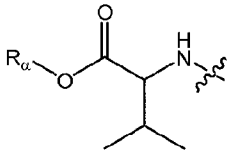


Table 1

R^1,R_α	R^1,R_α	R^1,R_α	R^1,R_α	R^1,R_α	R^1,R_α
aa01,es01	aa02,es01	aa03,es01	aa04,es01	aa05,es01	aa06,es09
aa01,es02	aa02,es02	aa03,es02	aa04,es02	aa05,es02	aa06,es10
aa01,es03	aa02,es03	aa03,es03	aa04,es03	aa05,es03	aa06,es11
aa01,cs04	aa02,cs04	aa03,cs04	aa04,cs04	aa05,cs04	aa06,cs12
aa01,es05	aa02,es05	aa03,es05	aa04,es05	aa05,es05	aa07,es09
aa01,es06	aa02,es06	aa03,es06	aa04,es06	aa05,es06	aa07,es10
aa01,es07	aa02,es07	aa03,es07	aa04,es07	aa05,es07	aa07,es11
aa01,es08	aa02,es08	aa03,es08	aa04,es08	aa05,es08	aa07,es12
aa01,cs09	aa02,cs09	aa03,cs09	aa04,cs09	aa05,cs09	aa08,es09
aa01,es10	aa02,es10	aa03,es10	aa04,es10	aa05,es10	aa08,es10
aa01,es11	aa02,es11	aa03,es11	aa04,es11	aa05,es11	aa08,es11
aa01,es12	aa02,es12	aa03,es12	aa04,es12	aa05,es12	aa08,es12
aa06,es01	aa07,es01	aa08,es01	aa09,es01	aa10,es01	aa09,es09
aa06,es02	aa07,es02	aa08,es02	aa09,es02	aa10,es02	aa09,es10
aa06,es03	aa07,es03	aa08,es03	aa09,es03	aa10,es03	aa09,es11
aa06,es04	aa07,es04	aa08,es04	aa09,es04	aa10,es04	aa09,es12
aa06,es05	aa07,es05	aa08,es05	aa09,es05	aa10,es05	aa10,es09
aa06,es06	aa07,es06	aa08,es06	aa09,es06	aa10,es06	aa10,es10
aa06,es07	aa07,es07	aa08,es07	aa09,es07	aa10,es07	aa10,es11
aa06,es08	aa07,es08	aa08,es08	aa09,es08	aa10,es08	aa10,es12

Table 2

aa01 	aa02 	aa03 

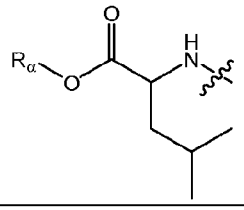
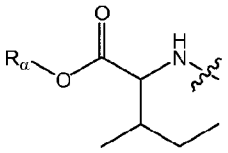
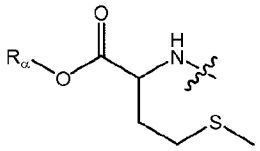
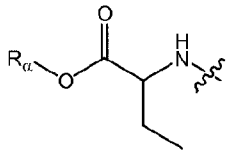
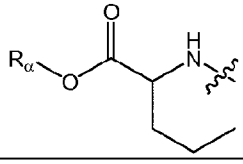
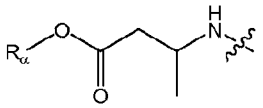
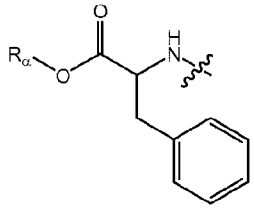
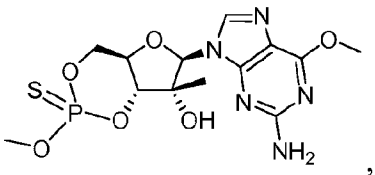
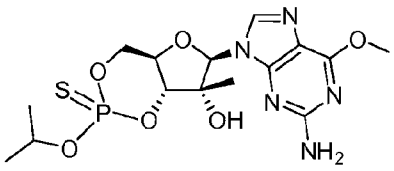
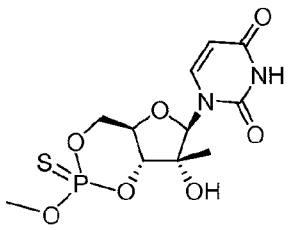
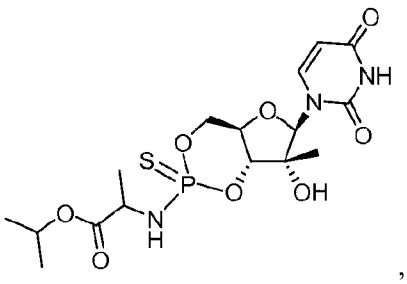
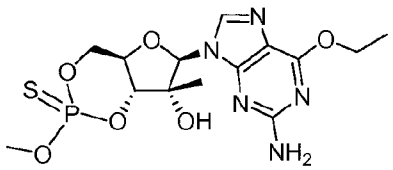
aa04 	aa05 	aa06 
aa07 	aa08 	aa09 
aa10 		

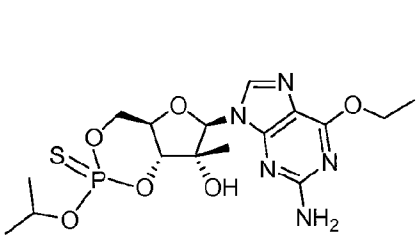
Table 3

es01	R_α = methyl	es02	R_α = ethyl	es03	R_α = isopropyl
es04	R_α = propyl	es05	R_α = cyclohexyl	es06	R_α = cyclopentyl
es07	R_α = cyclobutyl	es08	R_α = cyclopropyl	es09	R_α = benzyl
es11	R_α = neopentyl	es10	R_α = t-butyl	es12	R_α = hydrogen

[0127] Examples of compounds of Formula (I) include, but are not limited to the following:

 ,  ,  ,

 ,  ,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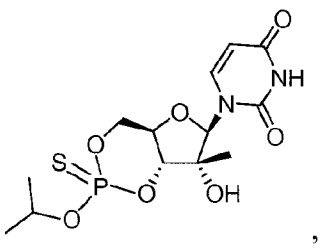
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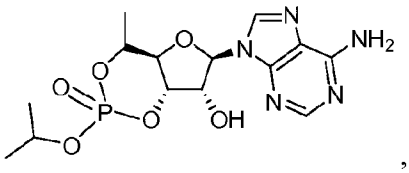
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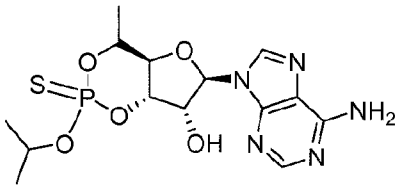
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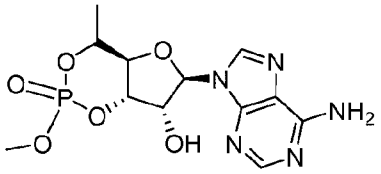
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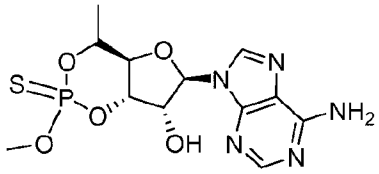
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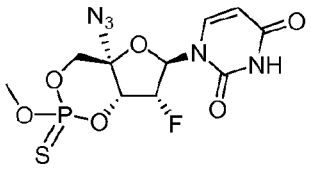
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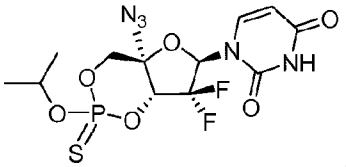
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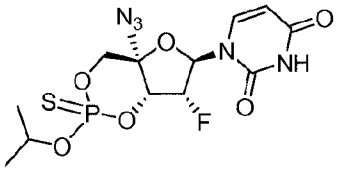
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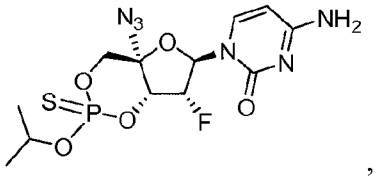
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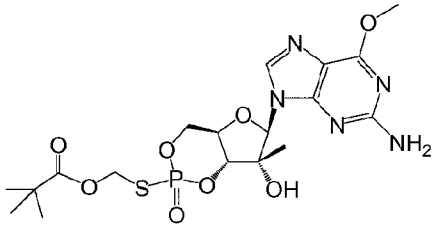
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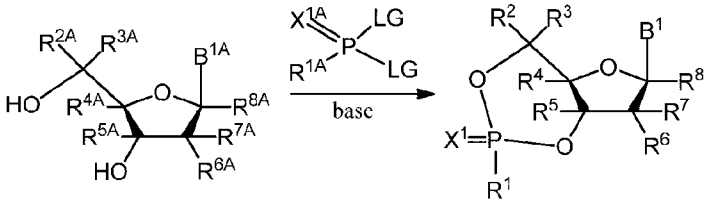
Synthesis

[0128] Compounds of Formula (I), and those described herein may be prepared in various ways. General synthetic routes to the compound of Formula (I), and some examples of starting materials used to synthesize the compounds of Formula (I) are shown in Schemes 1 and 2, and described herein. The routes shown and described herein are illustrative only and are not intended, nor are they to be construed, to limit the scope of the claims in any manner whatsoever. Those skilled in the art will be able to recognize modifications of the disclosed syntheses and to devise alternate routes based on the disclosures herein; all such modifications and alternate routes are within the scope of the claims.

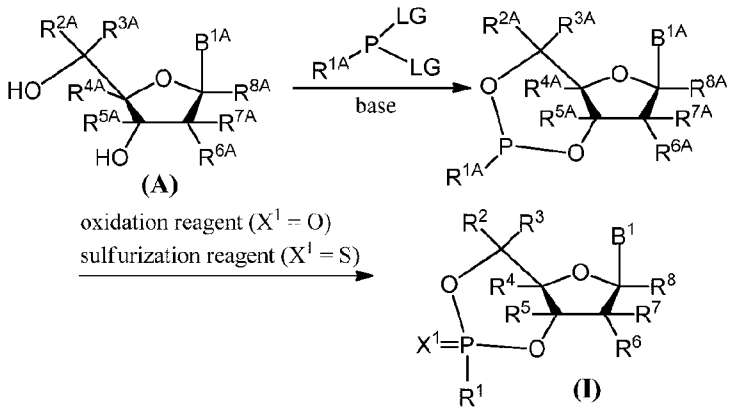
Scheme 1:



(A) (I)

[0129] One method for forming a compound of Formula (I) is shown in Scheme 1. In Scheme 1, R^{1A}, R^{2A}, R^{3A}, R^{4A}, R^{5A}, R^{6A}, R^{7A}, R^{8A}, X^{1A} and B^{1A} can be the same as R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X^1 and B^1 as described herein for Formula (I); and each LG can be a leaving group, such as a halogen or a sulfonate ester. As shown in Scheme 1, a nucleoside with a hydroxy group attached to the 3'-carbon and a hydroxy group attached to 5'-carbon can be reacted with a compound having the formula, $R^{1A}P(=X^{1A})(LG)_2$, in the presence of a base, to produce a compound of Formula (I). Suitable bases are known to those skilled in the art. For example, the base can be an amine base, such as an alkylamine (including mono-, di- and tri-alkylamines (e.g., triethylamine)), optionally substituted pyridines (e.g., collidine) and optionally substituted imidazoles (e.g., N-methylimidazole)).

Scheme 2:



[0130] Another method for forming a compound of Formula (I) is shown in Scheme 2. In Scheme 2, R^{1A}, R^{2A}, R^{3A}, R^{4A}, R^{5A}, R^{6A}, R^{7A}, R^{8A}, X^{1A} and B^{1A} can be the same as R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X^1 and B^1 as described herein for Formula (I); and each LG can be a leaving group, such as a halogen or a sulfonate ester. As illustrated in Scheme 2, a compound having a hydroxy group attached to the 3'-carbon and a hydroxy group attached to the 5'-carbon can be reacted with a compound having the formula, $R^{1A}P(LG)_2$, in the presence of a base, to produce a phosphite compound. Suitable bases are known to those skilled in the art and described herein. The phosphorus can then be oxidized to phosphorus(V) using a suitable

oxidizing agent, to produce a compound of Formula (I) where X^1 is O (oxygen). Alternatively, the phosphite compound can be reacted with a sulfurization reagent to produce a compound of Formula (I) where X^1 is S (sulfur). Suitable oxidizing and sulfurization agents are known to those skilled in the art. For example, the oxidation can be carried out using iodine as the oxidizing agent and water as the oxygen donor. Suitable sulfurization agents include, but are not limited to, elemental sulfur, Lawesson's reagent, cyclooctasulfur, 3H-1,2-Benzodithiole-3-one-1,1-dioxide (Beaucage's reagent), 3-((N,N-dimethylaminomethylidene)amino)-3H-1,2,4-dithiazole-5-thione (DDTT) and bis(3-triethoxysilyl)propyl-tetrasulfide (TEST).

[0131] Any –NH, NH_2 and/or keto groups present on B^{1A}, for example, when B^{1A} is an optionally substituted heterocyclic base, can be protected with one or more suitable protecting groups. Examples of suitable protecting groups include triarylmethyl groups, (2-nitrophenyl)ethyl groups, acyl groups, and dialkylformamidine groups. To reduce the formation of side products, one or more the groups attached to the pentose ring can be protected with one or more suitable protecting groups. As an example, if R^{4A}, R^{5A}, R^{6A}, R^{7A} and/or R^{8A} is/are hydroxy group(s), the hydroxy group(s) can be protected with suitable protecting groups, such as triarylmethyl and/or silyl groups. Examples of triarylmethyl groups include but are not limited to, trityl, monomethoxytrityl (MMTr), 4,4'-dimethoxytrityl (DMTr), 4,4',4"-trimethoxytrityl (TMTr), 4,4',4"-tris- (benzoyloxy) trityl (TBTr), 4,4',4"-tris (4,5-dichlorophthalimido) trityl (CPTr), 4,4',4"-tris (levulinyloxy) trityl (TLTr), p-anisyl-1-naphthylphenylmethyl, di-o-anisyl-1-naphthylmethyl, p-tolyldipheylmethyl, 3-(imidazolylmethyl)-4,4'-dimethoxytrityl, 9-phenylxanthen-9-yl (Pixyl), 9-(p-methoxyphenyl) xanthen-9-yl (Mox), 4-decyloxytrityl, 4- hexadecyloxytrityl, 4,4'-dioctadecyltrityl, 9-(4-octadecyloxyphenyl) xanthen-9-yl, 1,1'-bis-(4-methoxyphenyl)-1'-pyrenylmethyl, 4,4',4"-tris-(tert-butylphenyl) methyl (TTTr) and 4,4'-di-3, 5-hexadienoxytrityl. Examples of silyl groups include, but are not limited to, trimethylsilyl (TMS), *tert*-butyldimethylsilyl (TBDMS), triisopropylsilyl (TIPS), tert-butyldiphenylsilyl (TBDPS), tri-*iso*-propylsilyloxymethyl and [2-(trimethylsilyl)ethoxy]methyl. Alternatively, at least two of R^{4A}, R^{5A}, R^{6A}, R^{7A} and R^{8A} can be protected by a single achiral or chiral protecting group, for example, by forming an orthoester, a cyclic acetal or a cyclic ketal. Suitable orthoesters include methoxymethylene acetal, ethoxymethylene acetal, 2-oxacyclopentylidene orthoester, dimethoxymethylene orthoester, 1-methoxyethylidene orthoester, 1-ethoxyethylidene orthoester, methylidene orthoester, phthalide orthoester 1,2-dimethoxyethylidene orthoester, and alpha-methoxybenzylidene orthoester; suitable cyclic acetals include methylene acetal, ethylidene acetal, t-butylmethylidene acetal, 3-(benzyloxy)propyl acetal, benzylidene acetal, 3,4-dimethoxybenzylidene acetal and p-

acetoxybenzylidene acetal; and suitable cyclic ketals include 1-t-butylethylidene ketal, 1-phenylethylidene ketal, isopropylidene ketal, cyclopentylidene ketal, cyclohexylidene ketal, cycloheptylidene ketal and 1-(4-methoxyphenyl)ethylidene ketal.

[0132] The chirality of the 5'-carbon of compounds of Formulae (A) and/or (I) can be inverted using methods known to the skilled in the art. For example, the oxygen attached to the 5'-carbon can be oxidized, for example to an aldehyde for a compound of Formula (A) or ketone for a compound of Formula (I), using a suitable oxidizing agent. The aldehyde and/or ketone can then be reduced using a suitable reducing agent. Examples of suitable reducing agents include, but are not limited to, NaH, LiH, $NaBH_4$, $LiAlH_4$ and CaH_2. Suitable oxidizing and reducing agents are known to those skilled in the art. Examples of suitable oxidizing agents and conditions are described herein.

[0133] In some embodiments, R^6, R^7 and/or R^8 can be $-OC(=O)R^{11}$, $-OC(=O)R^{13}$, and $-OC(=O)R^{15}$, respectively. The $-OC(=O)R^{11}$, $-OC(=O)R^{13}$, and $-OC(=O)R^{15}$ groups can be formed at the 1' and 2'-positions using various methods known to those skilled in the art. As an example, a compound of Formula (I), wherein R^6 and R^8 are both hydroxy groups, can be treated with an alkyl anhydride (e.g., acetic anhydride and propionic anhydride) or an alkyl acid chloride (e.g., acetochloride). If desired, a catalyst can be used to facilitate the reaction. An example of suitable catalyst is 4-dimethylaminopyridine (DMAP). Alternatively, the $-OC(=O)R^{11}$ and $-OC(=O)R^{15}$ groups can be formed at the 1' and 2'-positions by reacting an alkyl acid (e.g., acetic acid and propionic acid) in the presences of a carbodiimide or a coupling reagent. Examples of carbodiimides include, but are not limited to, N,N'-dicyclohexylcarbodiimide (DCC), N,N'-diisopropylcarbodiimide (DIC) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC).

[0134] As described herein, B^{1A} can include a carbamate and/or an amide. Those skilled in the art know methods for forming a carbamate and/or an amide on B^{1A}. In some embodiments, the carbamate can be formed using 1,1'-carbonyldiimidazole and an alcohol.

[0135] During the synthesis of any of the compounds described herein, if desired, any hydroxy groups attached to the pentose ring, and any –NH, NH_2 and/or keto groups present on the B^{1A} can be protected with one or more suitable protecting groups. Suitable protecting groups are described herein. Those skilled in the art will appreciate that groups attached to the pentose ring and any –NH, NH_2 and/or keto groups present on the B^{1A} can be protected with various protecting groups, and any protecting groups present can be exchanged for other protecting groups. The selection and exchange of the protecting groups is within the skill of those of ordinary skill in the art. Any protecting group(s) can also be removed by methods

known in the art, for example, with an acid (e.g., a mineral or an organic acid), a base or a fluoride source.

[0136] In some embodiments, neutralizing the charge on the phosphate group may facilitate the penetration of the cell membrane by a compound of Formula (I), or a pharmaceutically acceptable salt thereof, by making the compound more lipophilic compared to a nucleotide having a comparable structure with one or more charges present on the phosphate. Once absorbed and taken inside the cell, the groups attached to the phosphate can be easily removed by esterases, proteases or other enzymes. In some embodiments, the groups attached to the phosphate can be removed by simple hydrolysis. Inside the cell, the monophosphate or mono-thiophosphate thus released may then be metabolized by cellular enzymes to the diphosphate or the active triphosphate, or the α-thiodiphosphate or the active α-thiotriphosphate, respectively. Furthermore, in some embodiments, varying the substituents on a cyclic nucleotide analog compound described herein, such as compound of Formula (I), can help maintain the efficacy of such compounds by reducing undesirable effects, such as isomerization.

[0137] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can act as a chain terminator of HCV replication. For example, incorporation of a compound of Formula (I) containing a moiety at the 2'-carbon position can terminate further elongation of the RNA chain of HCV. For example, a compound of Formula (I) can contain a 2'-carbon modification wherein R^7 is a non-hydrogen group selected from halogen or an optionally substituted C_{1-6} alkyl.

[0138] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can have increased metabolic and/or plasma stability. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be more resistant to hydrolysis and/or more resistant to enzymatic transformations. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can have improved properties. A non-limiting list of example properties include, but are not limited to, increased biological half life, increased bioavailability, increase potency, a sustained in vivo response, increased dosing intervals, decreased dosing amounts, decreased cytotoxicity, reduction in required amounts for treating disease conditions, reduction in viral load, reduction in time to seroconversion (i.e., the virus becomes undetectable in patient serum), increased sustained viral response, a reduction of morbidity or mortality in clinical outcomes, increased subject compliance, decreased liver conditions (such as liver fibrosis, liver cirrohis and/or liver cancer), and compatibility with other medications. In some embodiments, a compound of

Formula (I), or a pharmaceutically acceptable salt thereof, can have more potent antiviral activity (for example, a lower IC_{50} in an HCV replicon assay) as compared to the current standard of care.

[0139] Additionally, in some embodiments, the presence of a phosphorothioate, phosphoramidate or phosphorothioamidate in a compound of Formula (I) can increase the stability of the compound by inhibiting its degradation. Also, in some embodiments, the presence of a phosphorothioate, phosphoramidate or phosphorothioamidate can make the compound more resistant to cleavage *in vivo* and provide sustained, extended efficacy. In some embodiments, a phosphorothioate, phosphoramidate or phosphorothioamidate can facilitate the penetration of the cell membrane by a compound of Formula (I) by making the compound more lipophilic.

Pharmaceutical Compositions

[0140] Some embodiments described herein relates to a pharmaceutical composition, that can include a therapeutically effective amount of one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof) and a pharmaceutically acceptable carrier, diluent, excipient or combination thereof. In some embodiments, the pharmaceutical composition can include a single diastereomer of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, (for example, a single diastereomer is present in the pharmaceutical composition at a concentration of greater than 99% compared to the total concentration of the other diastereomers). In other embodiments, the pharmaceutical composition can include a mixture of diastereomers of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. For example, the pharmaceutical composition can include a concentration of one diastereomer of > 50%, ≥ 60%, ≥ 70%, ≥ 80%, ≥ 90%, ≥ 95%, or ≥ 98%, as compared to the total concentration of the other diastereomers. In some embodiments, the pharmaceutical composition includes a 1:1 mixture of two diastereomers of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0141] The term "pharmaceutical composition" refers to a mixture of one or more compounds disclosed herein with other chemical components, such as diluents or carriers. The pharmaceutical composition facilitates administration of the compound to an organism. Pharmaceutical compositions can also be obtained by reacting compounds with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, and salicylic acid.

Pharmaceutical compositions will generally be tailored to the specific intended route of administration.

[0142] The term "physiologically acceptable" defines a carrier, diluent or excipient that does not abrogate the biological activity and properties of the compound.

[0143] As used herein, a "carrier" refers to a compound that facilitates the incorporation of a compound into cells or tissues. For example, without limitation, dimethyl sulfoxide (DMSO) is a commonly utilized carrier that facilitates the uptake of many organic compounds into cells or tissues of a subject.

[0144] As used herein, a "diluent" refers to an ingredient in a pharmaceutical composition that lacks pharmacological activity but may be pharmaceutically necessary or desirable. For example, a diluent may be used to increase the bulk of a potent drug whose mass is too small for manufacture and/or administration. It may also be a liquid for the dissolution of a drug to be administered by injection, ingestion or inhalation. A common form of diluent in the art is a buffered aqueous solution such as, without limitation, phosphate buffered saline that mimics the composition of human blood.

[0145] As used herein, an "excipient" refers to an inert substance that is added to a pharmaceutical composition to provide, without limitation, bulk, consistency, stability, binding ability, lubrication, disintegrating ability etc., to the composition. A "diluent" is a type of excipient.

[0146] The pharmaceutical compositions described herein can be administered to a human patient *per se*, or in pharmaceutical compositions where they are mixed with other active ingredients, as in combination therapy, or carriers, diluents, excipients or combinations thereof. Proper formulation is dependent upon the route of administration chosen. Techniques for formulation and administration of the compounds described herein are known to those skilled in the art.

[0147] The pharmaceutical compositions disclosed herein may be manufactured in a manner that is itself known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or tableting processes. Additionally, the active ingredients are contained in an amount effective to achieve its intended purpose. Many of the compounds used in the pharmaceutical combinations disclosed herein may be provided as salts with pharmaceutically compatible counterions.

[0148] Multiple techniques of administering a compound exist in the art including, but not limited to, oral, rectal, topical, aerosol, injection and parenteral delivery, including

intramuscular, subcutaneous, intravenous, intramedullary injections, intrathecal, direct intraventricular, intraperitoneal, intranasal and intraocular injections.

[0149] One may also administer the compound in a local rather than systemic manner, for example, via injection of the compound directly into the infected area, often in a depot or sustained release formulation. Furthermore, one may administer the compound in a targeted drug delivery system, for example, in a liposome coated with a tissue-specific antibody. The liposomes will be targeted to and taken up selectively by the organ.

[0150] The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. The pack or dispenser may also be accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. Such notice, for example, may be the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. Compositions that can include a compound described herein formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

Methods of Use

[0151] Some embodiments disclosed herein relate to a method of treating and/or ameliorating a disease or condition that can include administering to a subject a therapeutically effective amount of one or more compounds described herein, such as a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes a compound described herein, or a pharmaceutically acceptable salt thereof.

[0152] Some embodiments disclosed herein relate to a method of ameliorating or treating a neoplastic disease that can include administering to a subject suffering from a neoplastic disease a therapeutically effective amount of one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof), or a pharmaceutical composition that includes a compound described herein, or a pharmaceutically acceptable salt thereof. In some embodiments, the neoplastic disease can be cancer. In some embodiments, the neoplastic disease can be a tumor such as a solid tumor. In some embodiments, the neoplastic disease can be leukemia. Exemplary leukemias include, but are not

limited to, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML) and juvenile myelomonocytic leukemia (JMML).

[0153] Some embodiments disclosed herein relate to a method of inhibiting the growth of a tumor that can include administering to a subject having a tumor a therapeutically effective amount of one or more compounds described herein (for example, a compound of Formula (I)), or a pharmaceutical composition that includes one or more compounds described herein, or a pharmaceutically acceptable salt thereof.

[0154] Other embodiments disclosed herein relates to a method of ameliorating or treating a viral infection that can include administering to a subject suffering from a viral infection a therapeutically effective amount of one or more compounds described herein (for example, a compound of Formula (I)), or a pharmaceutical composition that includes one or more compounds described herein, or a pharmaceutically acceptable salt thereof. In some embodiments, the viral infection can be caused by a virus selected from an adenovirus, an Alphaviridae, an Arbovirus, an Astrovirus, a Bunyaviridae, a Coronaviridae, a Filoviridae, a Flaviviridae, a Hepadnaviridae, a Herpesviridae, an Alphaherpesvirinae, a Betaherpesvirinae, a Gammaherpesvirinae, a Norwalk Virus, an Astroviridae, a Caliciviridae, an Orthomyxoviridae, a Paramyxoviridae, a Paramyxoviruses, a Rubulavirus, a Morbillivirus, a Papovaviridae, a Parvoviridae, a Picornaviridae, an Aphthoviridae, a Cardioviridae, an Enteroviridae, a Coxsackie virus, a Polio Virus, a Rhinoviridae, a Phycodnaviridae, a Poxviridae, a Reoviridae, a Rotavirus, a Retroviridae, an A-Type Retrovirus, an Immunodeficiency Virus, a Leukemia Viruses, an Avian Sarcoma Viruses, a Rhabdoviruses, a Rubiviridae, a Togaviridae an Arenaviridae and/or a Bornaviridae. In some embodiments, the viral infection can be a hepatitis C viral (HCV) infection. In other embodiments, the viral infection can be influenza. In still other embodiments, the viral infection can be HIV.

[0155] Some embodiments disclosed herein relate to methods of ameliorating and/or treating a viral infection that can include contacting a cell infected with the virus with an effective amount of one or more compounds described herein, or a pharmaceutically acceptable salt of a compound described herein, or a pharmaceutical composition that includes one or more compounds described herein, or a pharmaceutically acceptable salt thereof. Other embodiments described herein relate to using one or more compounds described herein, or a pharmaceutically acceptable salt of a compound described herein, in the manufacture of a medicament for ameliorating and/or treating a viral infection that can include contacting a cell infected with the virus with an effective amount of said compound(s). Still other embodiments described herein relate to one or more compounds described herein, or a pharmaceutically acceptable salt of a

compound described herein, that can be used for ameliorating and/or treating a viral infection by contacting a cell infected with the virus with an effective amount of said compound(s). In some embodiments, the compound can be a compound of Formula (I), or a pharmaceutical acceptable salt thereof. In other embodiments, the compound can be a mono-, di- and/or tri-phosphate of a compound of Formula (I), or a pharmaceutically acceptable salt of the foregoing. In some embodiments, the virus can be a HCV virus.

[0156] Some embodiments disclosed herein relate to methods of inhibiting replication of a virus that can include contacting a cell infected with the virus with an effective amount of one or more compounds described herein, or a pharmaceutically acceptable salt of a compound described herein, or a pharmaceutical composition that includes one or more compounds described herein, or a pharmaceutically acceptable salt thereof. Other embodiments described herein relate to using one or more compounds described herein, or a pharmaceutically acceptable salt of a compound described herein, in the manufacture of a medicament for inhibiting replication of a virus that can include contacting a cell infected with the virus with an effective amount of said compound(s). Still other embodiments described herein relate to a compound described herein, or a pharmaceutically acceptable salt of a compound described herein, that can be used for inhibiting replication of a virus by contacting a cell infected with the virus with an effective amount of said compound(s). In some embodiments, the compound can be a compound of Formula (I), or a pharmaceutical acceptable salt thereof. In other embodiments, the compound can be a mono-, di- and/or tri-phosphate of a compound of Formula (I), or a pharmaceutically acceptable salt of the foregoing. In some embodiments, the virus can be a HCV virus.

[0157] HCV is an enveloped positive strand RNA virus in the Flaviviridae family. There are various nonstructural proteins of HCV, such as NS2, NS3, NS4, NS4A, NS4B, NS5A, and NS5B. NS5B is believed to be an RNA-dependent RNA polymerase involved in the replication of HCV RNA.

[0158] Some embodiments described herein relate to a method of inhibiting NS5B polymerase activity that can include contacting a cell (for example, a cell infected with HCV) with an effective amount of a compound of Formula (I), or a pharmaceutical acceptable salt thereof. Some embodiments described herein relate to a method of inhibiting NS5B polymerase activity that can include administering a cell (for example, a cell infected with HCV) with an effective amount of a compound of Formula (I), or a pharmaceutical acceptable salt thereof. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can inhibit a RNA dependent RNA polymerase. In some embodiments, a compound of Formula

(I), or a pharmaceutically acceptable salt thereof, can inhibit a HCV polymerase (for example, NS5B polymerase).

[0159] Some embodiments described herein relate to a method of treating HCV infection in a subject suffering from a HCV infection that can include administering to the subject an effective amount of a compound of Formula (I), or a pharmaceutical acceptable salt thereof, or a pharmaceutical composition that includes an effective amount of a compound of Formula (I), or a pharmaceutical acceptable salt thereof. Some embodiments described herein relate to a method of treating a condition selected from liver fibrosis, liver cirrohis, and liver cancer in a subject suffering from one or more of the aforementioned liver conditions that can include administering to the subject an effective amount of a compound or a pharmaceutical composition described herein (for example, a compound of Formula (I), or a pharmaceutical acceptable salt thereof). One cause of liver fibrosis, liver cirrohis, and/or liver cancer can be a HCV infection. Some embodiments described herein relate to a method of increasing liver function in a subject having a HCV infection that can include administering to the subject an effective amount of a compound or a pharmaceutical composition described herein (for example, a compound of Formula (I), or a pharmaceutical acceptable salt thereof). Also contemplated is a method for reducing or eliminating further virus-caused liver damage in a subject having an HCV infection by administering to the subject an effective amount of a compound or a pharmaceutical composition described herein (for example, a compound of Formula (I), or a pharmaceutical acceptable salt thereof). In some embodiments, this method can include slowing or halting the progression of liver disease. In other embodiments, the course of the disease can be reversed, and stasis or improvement in liver function is contemplated.

[0160] There are a variety of genotypes of HCV, and a variety of subtypes within each genotype. For example, at present it is known that there are eleven (numbered 1 through 11) main genotypes of HCV, although others have classified the genotypes as 6 main genotypes. Each of these genotypes is further subdivided into subtypes (1a-1c; 2a-2c; 3a-3b; 4a-4e; 5a; 6a; 7a- 7b; 8a-8b; 9a; 10a; and 11a). In some embodiments, an effective amount of a compound of Formula (I), or a pharmaceutical acceptable salt thereof, or a pharmaceutical composition that includes an effective amount of a compound of Formula (I), or a pharmaceutical acceptable salt thereof, can be effective to treat at least one genotype of HCV. In some embodiments, a compound described herein (for example, a compound of Formula (I), or a pharmaceutical acceptable salt thereof) can be effective to treat all 11 genotypes of HCV. In some embodiments, a compound described herein (for example, a compound of Formula (I), or a pharmaceutical acceptable salt thereof) can be effective to treat 3 or more, 5 or more, 7 or more,

or 9 or more genotypes of HCV. In some embodiments, a compound of Formula (I), or a pharmaceutical acceptable salt thereof can be more effective against a larger number of HCV genotypes than the standard of care. In some embodiments, a compound of Formula (I), or a pharmaceutical acceptable salt thereof, can be more effective against a particular HCV genotype than the standard of care (such as genotype 1, 2, 3, 4, 5 and/or 6).

[0161] Various indicators for determining the effectiveness of a method for treating a HCV infection are known to those skilled in the art. Examples of suitable indicators include, but are not limited to, a reduction in viral load, a reduction in viral replication, a reduction in time to seroconversion (virus undetectable in patient serum), an increase in the rate of sustained viral response to therapy, a reduction of morbidity or mortality in clinical outcomes, a reduction in the rate of liver function decrease; stasis in liver function; improvement in liver function; reduction in one or more markers of liver dysfunction, including alanine transaminase, aspartate transaminase, total bilirubin, conjugated bilirubin, gamma glutamyl transpeptidase, and/or other indicator of disease response. Similarly, successful therapy with an effective amount of a compound or a pharmaceutical composition described herein (for example, a compound of Formula (I), or a pharmaceutical acceptable salt thereof) can reduce the incidence of liver cancer in HCV infected subjects.

[0162] In some embodiments, an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is an amount that is effective to reduce viral titers to undetectable levels, for example, to about 1000 to about 5000, to about 500 to about 1000, or to about 100 to about 500 genome copies/mL serum. In some embodiments, an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is an amount that is effective to reduce viral load compared to the viral load before administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. For example, wherein the viral load is measured before administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and again after completion of the treatment regime with the compound of Formula (I), or a pharmaceutically acceptable salt thereof (for example, 1 month after completion). In some embodiments, an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be an amount that is effective to reduce viral load to lower than about 100 genome copies/mL serum. In some embodiments, an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is an amount that is effective to achieve a reduction in viral titer in the serum of the subject in the range of about 1.5-log to about a 2.5-log reduction, about a 3-log to about a 4-log reduction, or a greater than about 5-log reduction compared to the viral load before administration of the compound of Formula

(I), or a pharmaceutically acceptable salt thereof. For example, the viral load can be measured before administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and again after completion of the treatment regime with the compound of Formula (I), or a pharmaceutically acceptable salt thereof (for example, 1 month after completion).

[0163] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can result in at least a 1, 2, 3, 4, 5, 10, 15, 20, 25, 50, 75, 100-fold or more reduction in the replication of HCV relative to pre-treatment levels in a subject, as determined after completion of the treatment regime (for example 1 month after completion). In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can result in a reduction of the replication of HCV relative to pre-treatment levels in the range of about 2 to about 5 fold, about 10 to about 20 fold, about 15 to about 40 fold, or about 50 to about 100 fold. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can result in a reduction of HCV replication in the range of 1 to 1.5 log, 1.5 log to 2 log, 2 log to 2.5 log, 2.5 to 3 log, 3 log to 3.5 log or 3.5 to 4 log more reduction of HCV replication compared to the reduction of HCV reduction achieved by pegylated interferon in combination with ribavirin, administered according to the standard of care, or may achieve the same reduction as that standard of care therapy in a shorter period of time, for example, in one month, two months, or three months, as compared to the reduction achieved after six months of standard of care therapy with ribavirin and pegylated interferon.

[0164] In some embodiments, an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is an amount that is effective to achieve a sustained viral response, for example, non-detectable or substantially non-detectable HCV RNA (e.g., less than about 500, less than about 400, less than about 200, or less than about 100 genome copies per milliliter serum) is found in the subject's serum for a period of at least about one month, at least about two months, at least about three months, at least about four months, at least about five months, or at least about six months following cessation of therapy.

[0165] In some embodiments, a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can reduce a level of a marker of liver fibrosis by at least about 10%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, or at least about 80%, or more, compared to the level of the marker in an untreated subject, or to a placebo-treated subject. Methods of measuring serum markers are known to those skilled in the art and include immunological-based methods, e.g., enzyme-linked immunosorbent assays (ELISA),

radioimmunoassays, and the like, using antibody specific for a given serum marker. A non-limiting list of example markers includes measuring the levels of serum alanine aminotransferase (ALT), asparatate aminotransferacse (AST), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT) and total bilirubin (TBIL) using known methods. In general, an ALT level of less than about 45 IU/L (international units/liter), an AST in the range of 10-34 IU/L, ALP in the range of 44-147 IU/L, GGT in the range of 0-51 IU/L, TBIL in the range of 0.3-1.9 mg/dL is considered normal. In some embodiments, an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be an amount effective to reduce ALT, AST, ALP, GGT and/or TBIL levels to with what is considered a normal level.

[0166] Subjects who are clinically diagnosed with HCV infection include "naïve" subjects (e.g., subjects not previously treated for HCV, particularly those who have not previously received IFN-alpha-based and/or ribavirin-based therapy) and individuals who have failed prior treatment for HCV ("treatment failure" subjects). Treatment failure subjects include "non-responders" (i.e., subjects in whom the HCV titer was not significantly or sufficiently reduced by a previous treatment for HCV ($\leq$ 0.5 log IU/mL), for example, a previous IFN-alpha monotherapy, a previous IFN-alpha and ribavirin combination therapy, or a previous pegylated IFN-alpha and ribavirin combination therapy); and "relapsers" (i.e., subjects who were previously treated for HCV, for example, who received a previous IFN-alpha monotherapy, a previous IFN-alpha and ribavirin combination therapy, or a previous pegylated IFN-alpha and ribavirin combination therapy, whose HCV titer decreased, and subsequently increased).

[0167] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be administered to a treatment failure subject suffering from HCV. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be administered to a non-responder subject suffering from HCV. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be administered to a relapsed subject suffering from HCV.

[0168] After a period of time, infectious agents can develop resistance to one or more therapeutic agents. The term "resistance" as used herein refers to a viral strain displaying a delayed, lessened and/or null response to a therapeutic agent(s). For example, after treatment with an antiviral agent, the viral load of a subject infected with a resistant virus may be reduced to a lesser degree compared to the amount in viral load reduction exhibited by a subject infected with a non-resistant strain. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be administered to a subject infected with an HCV

strain that is resistant to one or more different anti-HCV agents. In some embodiments, development of resistant HCV strains is delayed when a subject is treated with a compound of Formula (I), or a pharmaceutically acceptable salt thereof, compared to the development of HCV strains resistant to other HCV drugs.

[0169] In some embodiments, an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be administered to a subject for whom other anti-HCV medications are contraindicated. For example, administration of pegylated interferon alpha in combination with ribavirin is contraindicated in subjects with hemoglobinopathies (e.g., thalassemia major, sickle-cell anemia) and other subjects at risk from the hematologic side effects of current therapy. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be provided to a subject that is hypersensitive to interferon and/or ribavirin.

[0170] Some subjects being treated for HCV experience a viral load rebound. The term "viral load rebound" as used herein refers to a sustained ≥0.5 log IU/mL increase of viral load above nadir before the end of treatment, where nadir is a ≥0.5 log IU/mL decrease from baseline. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be administered to a subject experiencing viral load rebound, or can prevent such viral load rebound when used to treat the subject.

[0171] The standard of care for treating HCV has been associated with several side effects (adverse events). In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can decrease the number and/or severity of a side effect that can be observed in HCV patients being treated with ribavirin and pegylated interferon according to the standard of care. Examples of side effects include, but are not limited to fever, malaise, tachycardia, chills, headache, arthralgias, myalgias, fatigue, apathy, loss of apetite, nausea, vomiting, cognitive changes, asthenia, drowsiness, lack of initiative, irritability, confusion, depression, severe depression, suicidal ideation, anemia, low white blood cell counts, and thinning of hair. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be provided to a subject that discontinued a HCV therapy because of one or more adverse effects or side effects associated with one or more other HCV agents.

[0172] Table 4 provides some embodiments of the percentage improvement obtained using a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as compared to the standard of care. Examples include the following: in some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, results in a percentage of non-responders that is 10% less than the percentage of non-responders receiving the standard of care;

in some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, results in a number of side effects that is in the range of about 10% to about 30% less than compared to the number of side effects experienced by a subject receiving the standard of care; and in some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, results in a severity of a side effect (such as one of those described herein) that is 25% less than compared to the severity of the same side effect experienced by a subject receiving the standard of care. Methods of quantifying the severity of a side effect are known to those skilled in the art.

Table 4

Percentage of non-responders	Percentage of relapsers	Percentage of resistance	Percentage of viral load rebound	Number of side effects	Severity of side effects
10% less	10% less	10% less	10% less	10% less	10% less
25% less	25% less	25% less	25% less	25% less	25% less
40% less	40% less	40% less	40% less	40% less	40% less
50% less	50% less	50% less	50% less	50% less	50% less
60% less	60% less	60% less	60% less	60% less	60% less
70% less	70% less	70% less	70% less	70% less	70% less
80% less	80% less	80% less	80% less	80% less	80% less
90% less	90% less	90% less	90% less	90% less	90% less
about 10% to about 30% less	about 10% to about 30% less	about 10% to about 30% less	about 10% to about 30% less	about 10% to about 30% less	about 10% to about 30% less
about 20% to about 50% less	about 20% to about 50% less	about 20% to about 50% less	about 20% to about 50% less	about 20% to about 50% less	about 20% to about 50% less
about 30% to about 70% less	about 30% to about 70% less	about 30% to about 70% less	about 30% to about 70% less	about 30% to about 70% less	about 30% to about 70% less
about 20% to about 80% less	about 20% to about 80% less	about 20% to about 80% less	about 20% to about 80% less	about 20% to about 80% less	about 20% to about 80% less

[0173] Yet still other embodiments disclosed herein relate to a method of ameliorating or treating a parasitic disease that can include administering to a subject suffering from a parasitic disease a therapeutically effective amount of one or more compounds described herein (for example, a compound of Formula (I)), or a pharmaceutical composition that includes one or more compounds described herein. In some embodiments, the parasite disease can be Chagas' disease.

[0174] As used herein, a "subject" refers to an animal that is the object of treatment, observation or experiment. "Animal" includes cold- and warm-blooded vertebrates and

invertebrates such as fish, shellfish, reptiles and, in particular, mammals. "Mammal" includes, without limitation, mice, rats, rabbits, guinea pigs, dogs, cats, sheep, goats, cows, horses, primates, such as monkeys, chimpanzees, and apes, and, in particular, humans. In some embodiments, the subject is human.

[0175] As used herein, the terms "treating," "treatment," "therapeutic," or "therapy" do not necessarily mean total cure or abolition of the disease or condition. Any alleviation of any undesired signs or symptoms of a disease or condition, to any extent can be considered treatment and/or therapy. Furthermore, treatment may include acts that may worsen the patient's overall feeling of well-being or appearance.

[0176] The terms "therapeutically effective amount" and "effective amount" are used to indicate an amount of an active compound, or pharmaceutical agent, that elicits the biological or medicinal response indicated. For example, a therapeutically effective amount of compound can be the amount needed to prevent, alleviate or ameliorate symptoms of disease or prolong the survival of the subject being treated. This response may occur in a tissue, system, animal or human and includes alleviation of the signs or symptoms of the disease being treated. Determination of a therapeutically effective amount is well within the capability of those skilled in the art, in view of the disclosure provided herein. The therapeutically effective amount of the compounds disclosed herein required as a dose will depend on the route of administration, the type of animal, including human, being treated, and the physical characteristics of the specific animal under consideration. The dose can be tailored to achieve a desired effect, but will depend on such factors as weight, diet, concurrent medication and other factors which those skilled in the medical arts will recognize.

[0177] As will be readily apparent to one skilled in the art, the useful *in vivo* dosage to be administered and the particular mode of administration will vary depending upon the age, weight, the severity of the affliction, and mammalian species treated, the particular compounds employed, and the specific use for which these compounds are employed. The determination of effective dosage levels, that is the dosage levels necessary to achieve the desired result, can be accomplished by one skilled in the art using routine methods, for example, human clinical trials and *in vitro* studies.

[0178] The dosage may range broadly, depending upon the desired effects and the therapeutic indication. Alternatively dosages may be based and calculated upon the surface area of the patient, as understood by those of skill in the art. Although the exact dosage will be determined on a drug-by-drug basis, in most cases, some generalizations regarding the dosage can be made. The daily dosage regimen for an adult human patient may be, for example, an oral

dose of between 0.01 mg and 3000 mg of each active ingredient, preferably between 1 mg and 700 mg, e.g. 5 to 200 mg. The dosage may be a single one or a series of two or more given in the course of one or more days, as is needed by the subject. In some embodiments, the compounds will be administered for a period of continuous therapy, for example for a week or more, or for months or years. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be administered less frequently compared to the frequency of administration of an agent within the standard of care. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be administered one time per day. For example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be administered one time per day to a subject suffering from a HCV infection. In some embodiments, the total time of the treatment regime with a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can less compared to the total time of the treatment regime with the standard of care.

[0179] In instances where human dosages for compounds have been established for at least some condition, those same dosages may be used, or dosages that are between about 0.1% and 500%, more preferably between about 25% and 250% of the established human dosage. Where no human dosage is established, as will be the case for newly-discovered pharmaceutical compositions, a suitable human dosage can be inferred from ED_{50} or ID_{50} values, or other appropriate values derived from *in vitro* or *in vivo* studies, as qualified by toxicity studies and efficacy studies in animals.

[0180] In cases of administration of a pharmaceutically acceptable salt, dosages may be calculated as the free base. As will be understood by those of skill in the art, in certain situations it may be necessary to administer the compounds disclosed herein in amounts that exceed, or even far exceed, the above-stated, preferred dosage range in order to effectively and aggressively treat particularly aggressive diseases or infections.

[0181] Dosage amount and interval may be adjusted individually to provide plasma levels of the active moiety which are sufficient to maintain the modulating effects, or minimal effective concentration (MEC). The MEC will vary for each compound but can be estimated from in vitro data. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. However, HPLC assays or bioassays can be used to determine plasma concentrations. Dosage intervals can also be determined using MEC value. Compositions should be administered using a regimen which maintains plasma levels above the MEC for 10-90% of the time, preferably between 30-90% and most preferably between 50-90%.

In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration.

[0182] It should be noted that the attending physician would know how to and when to terminate, interrupt, or adjust administration due to toxicity or organ dysfunctions. Conversely, the attending physician would also know to adjust treatment to higher levels if the clinical response were not adequate (precluding toxicity). The magnitude of an administrated dose in the management of the disorder of interest will vary with the severity of the condition to be treated and to the route of administration. The severity of the condition may, for example, be evaluated, in part, by standard prognostic evaluation methods. Further, the dose and perhaps dose frequency, will also vary according to the age, body weight, and response of the individual patient. A program comparable to that discussed above may be used in veterinary medicine.

[0183] Compounds disclosed herein can be evaluated for efficacy and toxicity using known methods. For example, the toxicology of a particular compound, or of a subset of the compounds, sharing certain chemical moieties, may be established by determining *in vitro* toxicity towards a cell line, such as a mammalian, and preferably human, cell line. The results of such studies are often predictive of toxicity in animals, such as mammals, or more specifically, humans. Alternatively, the toxicity of particular compounds in an animal model, such as mice, rats, rabbits, or monkeys, may be determined using known methods. The efficacy of a particular compound may be established using several recognized methods, such as *in vitro* methods, animal models, or human clinical trials. When selecting a model to determine efficacy, the skilled artisan can be guided by the state of the art to choose an appropriate model, dose, route of administration and/or regime.

Combination Therapies

[0184] In some embodiments, the compounds disclosed herein, such as a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes a compound described herein, or a pharmaceutically acceptable salt thereof, can be used in combination with one or more additional agent(s). Examples of additional agents that can be used in combination with a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes a compound of Formula (I), or a pharmaceutically acceptable salt thereof, include, but are not limited to, agents currently used in a conventional standard of care for treating HCV, HCV protease inhibitors, HCV polymerase inhibitors, NS5A inhibitors, other antiviral compounds, compounds of Formula (AA) (including mono-, di, and/or tri-phosphates of Formula (AA), pharmaceutically acceptable salts and

pharmaceutical compositions that can include a compound of Formula (AA), mono-, di- and/or tri- phosphates thereof, or a pharmaceutically acceptable salt of the foregoing), compounds of Formula (CC) (including pharmaceutically acceptable salts and pharmaceutical compositions that can include a compound of Formula (CC), or a pharmaceutically acceptable salt thereof), compounds of Formula (DD) (including pharmaceutically acceptable salts and pharmaceutical compositions that can include a compound of Formula (DD), or a pharmaceutically acceptable salt thereof), and/or combinations thereof. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be used with one, two, three or more additional agents described herein. A non-limiting list of examples of combinations of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is provided in Tables A, B, C and D.

[0185] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be used in combination with an agent(s) currently used in a conventional standard of care therapy. For example, for the treatment of HCV, a compound disclosed herein can be used in combination with Pegylated interferon-alpha-2a (brand name PEGASYS®) and ribavirin, or Pegylated interferon-alpha-2b (brand name PEG-INTRON®) and ribavirin. As another example, a compound disclosed herein can be used in combination with oseltamivir (TAMIFLU®) or zanamivin (RELENZA®) for treating an influenza infection.

[0186] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be substituted for an agent currently used in a conventional standard of care therapy. For example, for the treatment of HCV, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be used in place of ribavirin.

[0187] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be used in combination with an interferon, such as a pegylated interferon. Examples of suitable interferons include, but are not limited to, Pegylated interferon-alpha-2a (brand name PEGASYS®), Pegylated interferon-alpha-2b (brand

name PEG-INTRON®), interferon alfacon-1 (brand name INFERGEN®), pegylated interferon lambda and/or a combination thereof.

[0188] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be used in combination with a HCV protease inhibitor. A non-limiting list of example HCV protease inhibitors include the following: VX-950 (TELAPREVIR®), MK-5172, ABT-450, BILN-2061, BI-201335, BMS-650032, SCH 503034 (BOCEPREVIR®), GS-9256, GS-9451, IDX-320, ACH-1625, ACH-2684, TMC-435, ITMN-191 (DANOPREVIR®) and/or a combination thereof. A non-limiting list of example HCV protease inhibitors includes the compounds numbered 1001-1014 in Figures 1A-1B.

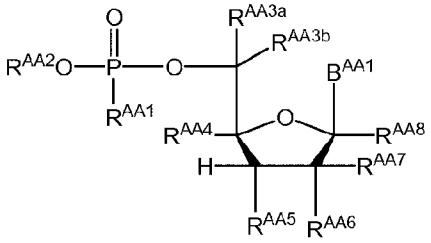
[0189] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be used in combination with a HCV polymerase inhibitor. In some embodiments, the HCV polymerase inhibitor can be a nucleoside inhibitor. In other embodiments, the HCV polymerase inhibitor can be a non-nucleoside inhibitor. Examples of suitable nucleoside inhibitors include, but are not limited to, RG7128, PSI-7851, PSI-7977, INX-189, PSI-352938, PSI-661, 4'-azidouridine (including known prodrugs of 4'-azidouridine), GS-6620, IDX-184 and TMC649128, and/or combinations thereof. A non-limiting list of example nucleoside inhibitors includes compounds numbered 2001-2010 in Figure 2. Examples of suitable non-nucleoside inhibitors include, but are not limited to, ABT-333, ANA-598, VX-222, HCV-796, BI-207127, GS-9190, PF-00868554 (FILIBUVIR®), VX-497 and/or combinations thereof. A non-limiting list of example non-nucleoside inhibitors includes the compounds numbered 3001-3008 in Figure 3.

[0190] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be used in combination with a NS5A inhibitor. A non-limiting list of example NS5A inhibitors include BMS-790052, PPI-461, ACH-2928, GS-5885, BMS-824393 and/or combinations thereof. A non-limiting list of example NS5A inhibitors includes the compounds numbered 4001-4005 in Figure 4.

[0191] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be used in combination with other antiviral compounds. Examples of other antiviral compounds include, but are not limited to, Debio-025,

MIR-122 and/or combinations thereof. A non-limiting list of example other antiviral compounds includes the compounds numbered 5001-5002 in Figure 5.

[0192] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be used in combination with a compound of Formula (AA), mono-, di- and/or tri-phosphate thereof, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition that includes a compound of Formula (AA), mono-, di- and/or tri-phosphate thereof, or a pharmaceutically acceptable salt of the foregoing (see, U.S. Application No. 13/236,450, filed September 19, 2011, and U.S. Provisional Application Nos. 61/385,425, filed September 22, 2010, and 61/426,467, filed December 22, 2010, the contents of which are incorporated by reference in their entireties):

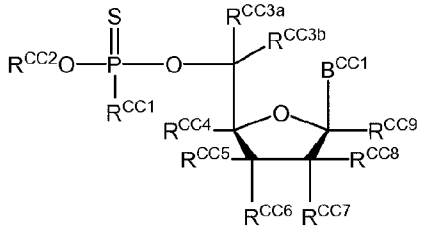


Formula (AA)

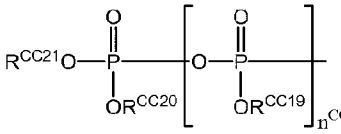
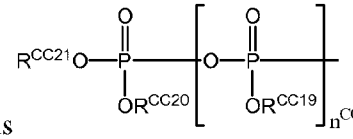
wherein B^{AA1} can be an optionally substituted heterocyclic base or an optionally substituted heterocyclic base with a protected amino group; R^{AA1} can be an optionally substituted N-linked amino acid or an optionally substituted N-linked amino acid ester derivative; R^{AA2} can be selected from an optionally substituted aryl, an optionally substituted heteroaryl and an optionally substituted heterocyclyl; R^{AA3a} and R^{AA3b} can be independently selected from hydrogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{2-6} alkynyl, an optionally substituted C_{1-6} haloalkyl and aryl(C_{1-6} alkyl), provided that at least one of R^{AA3a} and R^{AA3b} is not hydrogen; or R^{AA3a} and R^{AA3b} can be taken together to form a group selected from an optionally substituted C_{3-6} cycloalkyl, an optionally substituted C_{3-6} cycloalkenyl, an optionally substituted C_{3-6} aryl, and an optionally substituted C_{3-6} heteroaryl; R^{AA4} can be hydrogen; R^{AA5} can be selected from hydrogen, $-OR^{AA9}$ and $-OC(=O)R^{AA10}$; R^{AA6} can be selected from hydrogen, halogen, $-OR^{AA11}$ and $-OC(=O)R^{AA12}$; or R^{AA5} and R^{AA6} can be both oxygen atoms and linked together by a carbonyl group; R^{AA7} can be selected from hydrogen, halogen, an optionally substituted C_{1-6} alkyl, $-OR^{AA13}$ and $-OC(=O)R^{AA14}$; R^{AA8} can be hydrogen or an optionally substituted C_{1-6} alkyl; R^{AA9}, R^{AA11} and R^{AA13} can be independently selected from hydrogen and an optionally substituted C_{1-6} alkyl; and R^{AA10}, R^{AA12} and R^{AA14} can be independently selected from an optionally substituted C_{1-6} alkyl and an optionally substituted C_{3-6} cycloalkyl. A non-limiting list of examples of compounds of

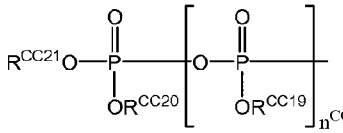
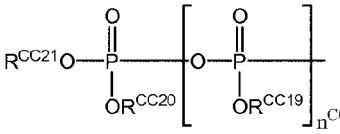
Formula (AA), and phosphates thereof, includes the compounds numbered 7000-7077 in Figures 7A-7O. In some embodiments, Formula (AA) cannot be compound 7044, 7045, 7046, 7047, 7048, 7049, 7050, 7072, 7073, 7074, 7075, 7076 or 7077.

[0193] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be used in combination with a compound of Formula (CC), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes a compound of Formula (CC), or a pharmaceutically acceptable salt thereof (see, U.S. Application No. 13/236,435, filed September 19, 2011, and U.S. Provisional Application Nos. 61/385,363, filed September 22, 2010, and 61/426,461, filed December 22, 2010, the contents of which are incorporated by reference in their entireties):

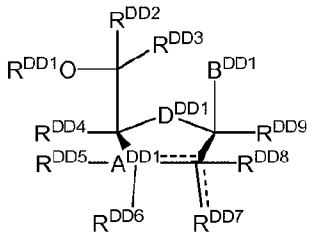


Formula (CC)

wherein B^{CC1} can be an optionally substituted heterocyclic base or an optionally substituted heterocyclic base with a protected amino group; R^{CC1} can be selected from O^-, OH, an optionally substituted N-linked amino acid and an optionally substituted N-linked amino acid ester derivative; R^{CC2} can be selected from an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl and  , wherein R^{CC19}, R^{CC20} and R^{CC21} can be independently absent or hydrogen, and n^{CC} can be 0 or 1; provided that when R^{CC1} is O^- or OH, then R^{CC2} is  ; R^{CC3a} and R^{CC3b} can be independently selected from hydrogen, deuterium, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{2-6} alkynyl, an optionally substituted C_{1-6} haloalkyl and aryl(C_{1-6} alkyl); or R^{CC3a} and R^{CC3b} can be taken together to form an optionally substituted C_{3-6} cycloalkyl; R^{CC4} can be selected from hydrogen, azido, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl and an optionally substituted C_{2-6} alkynyl; R^{CC5} can be selected from hydrogen, halogen, azido, cyano, an optionally substituted C_{1-6} alkyl, $-OR^{CC10}$ and $-OC(=O)R^{CC11}$; R^{CC6} can be selected from

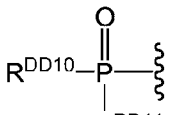
hydrogen, halogen, azido, cyano, an optionally substituted C_{1-6} alkyl, $-OR^{CC12}$ and $-OC(=O)R^{CC13}$; R^{CC7} can be selected from hydrogen, halogen, azido, cyano, an optionally substituted C_{1-6} alkyl, $-OR^{CC14}$ and $-OC(=O)R^{CC15}$; or R^{CC6} and R^{CC7} can be both oxygen atoms and linked together by a carbonyl group; R^{CC8} can be selected from hydrogen, halogen, azido, cyano, an optionally substituted C_{1-6} alkyl, $-OR^{CC16}$ and $-OC(=O)R^{CC17}$; R^{CC9} can be selected from hydrogen, azido, cyano, an optionally substituted C_{1-6} alkyl and $-OR^{CC18}$; R^{CC10}, R^{CC12}, R^{CC14}, R^{CC16} and R^{CC18} can be independently selected from hydrogen and an optionally substituted C_{1-6} alkyl; and R^{CC11}, R^{CC13}, R^{CC15} and R^{CC17} can be independently selected from an optionally substituted C_{1-6} alkyl and an optionally substituted C_{3-6} cycloalkyl. In some embodiments, when R^{CC3a}, R^{CC3b}, R^{CC4}, R^{CC5}, R^{CC7}, R^{CC8} and R^{CC9} are all hydrogen, then R^{CC6} is not azido. In some embodiments, R^{CC2} cannot be  when R^{CC3a} is hydrogen, R^{CC3b} is hydrogen, R^{CC4} is H, R^{CC5} is OH or H, R^{CC6} is hydrogen, OH, or $-OC(=O)CH_3$, R^{CC7} is hydrogen, OH, OCH_3 or $-OC(=O)CH_3$, R^{CC8} is hydrogen, OH or OCH_3, R^{CC9} is H and B^{CC1} is an optionally substituted adenine, an optionally substituted guanine, an optionally substituted uracil or an optionally substituted hypoxanthine. In some embodiments, R^{CC2} cannot be  . A non-limiting list of examples of compounds of Formula (CC) includes the compounds numbered 6000-6078 in Figures 6A-6M.

[0194] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be used in combination with a compound of Formula (DD), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes a compound of Formula (DD), or a pharmaceutically acceptable salt thereof (see, e.g., U.S. Publication No. 2010-0249068, filed March 19, 2010, the contents of which are incorporated by reference in its entirety):



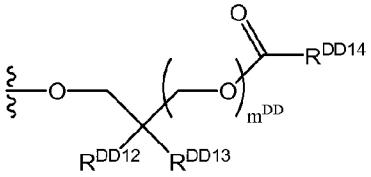
Formula (DD)

wherein each ====== can be independently a double or single bond; A^{DD1} can be selected from C (carbon), O (oxygen) and S (sulfur); B^{DD1} can be an optionally substituted heterocyclic base or a derivative thereof; D^{DD1} can be selected from $C{=}CH_2$, CH_2, O (oxygen), S (sulfur), CHF, and CF_2; R^{DD1} can be hydrogen, an optionally substituted alkyl, an optionally substituted cycloalkyl, an optionally substituted aralkyl, dialkylaminoalkylene, alkyl—C(=O)—, aryl—C(=O)—, alkoxyalkyl—C(=O)—, aryloxyalkyl—C(=O)—, alkylsulfonyl, arylsulfonyl, aralkylsulfonyl,

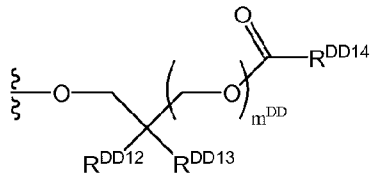


, an –O–linked amino acid, diphosphate, triphosphate or derivatives thereof; R^{DD2} and R^{DD3} can be each independently selected from hydrogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{2-6} alkynyl and an optionally substituted C_{1-6} haloalkyl, provided that at least one of R^{DD2} and R^{DD3} cannot be hydrogen; or R^{DD2} and R^{DD3} are taken together to form a group selected from among C_{3-6} cycloalkyl, C_{3-6} cycloalkenyl, C_{3-6} aryl, and a C_{3-6} heteroaryl; R^{DD4} and R^{DD9} can be independently selected from hydrogen, halogen, $-NH_2$, $-NHR^{DDa1}$, $NR^{DDa1}R^{DDb1}$, $-OR^{DDa1}$, $-SR^{DDa1}$, -CN, -NC, $-N_3$, $-NO_2$, $-N(R^{DDc1})-NR^{DDa1}R^{DDb1}$, $-N(R^{DDc1})-OR^{DDa1}$, $-S-SR^{DDa1}$, $-C(=O)R^{DDa1}$, $-C(=O)OR^{DDa1}$, $-C(=O)NR^{DDa1}R^{DDb1}$, $-O-(C=O)R^{DDa1}$, $-O-C(=O)OR^{DDa1}$, $-O-C(=O)NR^{DDa1}R^{DDb1}$, $-N(R^{DDc1})-C(=O)NR^{DDa1}R^{DDb1}$, $-S(=O)R^{DDa1}$, $S(=O)_2R^{DDa1}$, $-O-S(=O)_2NR^{DDa1}R^{DDb1}$, $-N(R^{DDc1})-S(=O)_2NR^{DDa1}R^{DDb1}$, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{2-6} alkynyl, an optionally substituted aralkyl and an –O–linked amino acid; R^{DD5}, R^{DD6} and R^{DD7} can be independently absent or selected from hydrogen, halogen, $-NH_2$, $-NHR^{DDa1}$, $NR^{DDa1}R^{DDb1}$, $-OR^{DDa1}$, $-SR^{DDa1}$, -CN, -NC, $-N_3$, $-NO_2$, $-N(R^{DDc1})-NR^{DDa1}R^{DDb1}$, $-N(R^{DDc1})-OR^{DDa1}$, $-S-SR^{DDa1}$, $-C(=O)R^{DDa1}$, $-C(=O)OR^{DDa1}$, $-C(=O)NR^{DDa1}R^{DDb1}$, $-O-(C=O)R^{DDa1}$, $-O-C(=O)OR^{DDa1}$, $-O-C(=O)NR^{DDa1}R^{DDb1}$, $-N(R^{DDc1})-C(=O)NR^{DDa1}R^{DDb1}$, $-S(=O)R^{DDa1}$, $S(=O)_2R^{DDa1}$, $-O-S(=O)_2NR^{DDa1}R^{DDb1}$, $-N(R^{DDc1})-S(=O)_2NR^{DDa1}R^{DDb1}$, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{2-6} alkynyl, an optionally substituted aralkyl and an –O–linked amino acid; or R^{DD6} and R^{DD7} taken together form —O—C(=O)—O—; R^{DD8} can be absent or selected from hydrogen, halogen, $-NH_2$, $-NHR^{DDa1}$, $NR^{DDa1}R^{DDb1}$, $-OR^{DDa1}$, $-SR^{DDa1}$, -CN, -NC, $-N_3$, $-NO_2$, $-N(R^{DDc1})-NR^{DDa1}R^{DDb1}$,

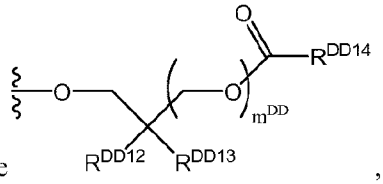
$-N(R^{DDc1})-OR^{DDa1}$, $-S-SR^{DDa1}$, $-C(=O)R^{DDa1}$, $-C(=O)OR^{DDa1}$, $-C(=O)NR^{DDa1}R^{DDb1}$, $-O-C(=O)OR^{DDa1}$, $-O-C(=O)NR^{DDa1}R^{DDb1}$, $-N(R^{DDc1})-C(=O)NR^{DDa1}R^{DDb1}$, $-S(=O)R^{DDa1}$, $S(=O)_2R^{DDa1}$, $-O-S(=O)_2NR^{DDa1}R^{DDb1}$, $-N(R^{DDc1})-S(=O)_2NR^{DDa1}R^{DDb1}$, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{2-6} alkynyl, an optionally substituted haloalkyl, an optionally substituted hydroxyalkyl and an –O–linked amino acid, or when the bond to R^{DD7} indicated by ------ is a double bond, then R^{DD7} is a C_{2-6} alkylidene and R^{DD8} is absent; R^{DDa1}, R^{DDb1} and R^{DDc1} can be each independently selected from hydrogen, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl and an optionally substituted heteroaryl(C_{1-6} alkyl); R^{DD10} can be selected from O^-, –OH, an optionally substituted aryloxy or aryl–O–,



, alkyl-C(=O)-O-CH_2–O–, alkyl-C(=O)-S-CH_2CH_2–O– and an –N–linked amino acid; R^{DD11} can be selected from O^-, –OH, an optionally substituted aryloxy or aryl–O–,



, alkyl-C(=O)-O-CH_2–O–, alkyl-C(=O)-S-CH_2CH_2–O– and an –N–linked amino acid; each R^{DD12} and each R^{DD13} can be independently -C≡N or an optionally substituted substituent selected from C_{1-8} organylcarbonyl, C_{1-8} alkoxycarbonyl and C_{1-8} organylaminocarbonyl; each R^{DD14} can be hydrogen or an optionally substituted C_{1-6}-alkyl; each m^{DD} can be independently 1 or 2, and if both R^{DD10} and R^{DD11} are



, each R^{DD12}, each R^{DD13}, each R^{DD14} and each m^{DD} can be the same or different. In some embodiments, R^{DD8} can be halogen, $-OR^{DDa1}$, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{2-6} alkynyl and an optionally substituted C_{1-6} haloalkyl.

[0195] Some embodiments described herein relate to a method of ameliorating or treating a viral infection that can include contacting a cell infected with the viral infection with a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable

salt thereof, in combination with one or more agents selected from an interferon, ribavirin, a HCV protease inhibitor, a HCV polymerase inhibitor, a NS5A inhibitor, an antiviral compound, a compound of Formula (AA), a mono-, di, and/or tri-phosphate thereof, a compound of Formula (CC) and a compound of Formula (DD), or a pharmaceutically acceptable salt of any of the aforementioned compounds.

[0196] Some embodiments described herein relate to a method of ameliorating or treating a viral infection that can include administering to a subject suffering from the viral infection a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with one or more agents selected from an interferon, ribavirin, a HCV protease inhibitor, a HCV polymerase inhibitor, a NS5A inhibitor, an antiviral compound, a compound of Formula (AA), a mono-, di, and/or tri-phosphate thereof, a compound of Formula (CC) and a compound of Formula (DD), or a pharmaceutically acceptable salt of any of the aforementioned compounds.

[0197] Some embodiments described herein relate to a method of inhibiting viral replication of a virus that can include contacting a cell infected with the virus an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with one or more agents selected from an interferon, ribavirin, a HCV protease inhibitor, a HCV polymerase inhibitor, a NS5A inhibitor, an antiviral compound, a compound of Formula (AA), a mono-, di, and/or tri-phosphate thereof, a compound of Formula (CC) and a compound of Formula (DD), or a pharmaceutically acceptable salt of any of the aforementioned compounds.

[0198] Some embodiments described herein relate to a method of ameliorating or treating a viral infection that can include contacting a cell infected with the viral infection with a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with one or more agents selected from an interferon, ribavirin, a HCV protease inhibitor, a HCV polymerase inhibitor, a NS5A inhibitor, an antiviral compound, a compound of Formula (AA), a compound of Formula (CC) and a compound of Formula (DD), or a pharmaceutically acceptable salt of any of the aforementioned compounds.

[0199] Some embodiments described herein relate to a method of ameliorating or treating a viral infection that can include administering to a subject suffering from the viral infection a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with one or more agents selected from an interferon, ribavirin, a HCV protease inhibitor, a HCV polymerase inhibitor, a NS5A inhibitor, an antiviral compound, a compound of Formula (AA), a compound of Formula (CC)

and a compound of Formula (DD), or a pharmaceutically acceptable salt of any of the aforementioned compounds.

[0200] Some embodiments described herein relate to a method of inhibiting viral replication of a virus that can include contacting a cell infected with the virus an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with one or more agents selected from an interferon, ribavirin, a HCV protease inhibitor, a HCV polymerase inhibitor, a NS5A inhibitor, an antiviral compound, a compound of Formula (AA), a compound of Formula (CC) and a compound of Formula (DD), or a pharmaceutically acceptable salt of any of the aforementioned compounds.

[0201] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be administered with one or more additional agent(s) together in a single pharmaceutical composition. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt the thereof, can be administered with one or more additional agent(s) as two or more separate pharmaceutical compositions. For example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be administered in one pharmaceutical composition, and at least one of the additional agents can be administered in a second pharmaceutical composition. If there are at least two additional agents, one or more of the additional agents can be in a first pharmaceutical composition that includes a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and at least one of the other additional agent(s) can be in a second pharmaceutical composition.

[0202] The dosing amount(s) and dosing schedule(s) when using a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and one or more additional agents are within the knowledge of those skilled in the art. For example, when performing a conventional standard of care therapy using art-recognized dosing amounts and dosing schedules, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be administered in addition to that therapy, or in place of one of the agents of a combination therapy, using effective amounts and dosing protocols as described herein.

[0203] The order of administration of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, with one or more additional agent(s) can vary. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be administered prior to all additional agents. In other embodiments, a compound of Formula (I),

or a pharmaceutically acceptable salt thereof, can be administered prior to at least one additional agent. In still other embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be administered concomitantly with one or more additional agent(s). In yet still other embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be administered subsequent to the administration of at least one additional agent. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be administered subsequent to the administration of all additional agents.

[0204] In some embodiments, the combination of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with one or more additional agent(s) in Figures 1-7 and 9 (including pharmaceutically acceptable salts and prodrugs thereof) can result in an additive effect. In some embodiments, the combination of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with one or more additional agent(s) in Figures 1-7 and 9 (including pharmaceutically acceptable salts and prodrugs thereof) can result in a synergistic effect. In some embodiments, the combination of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with one or more additional agent(s) in Figures 1-7 and 9 (including pharmaceutically acceptable salts and prodrugs thereof) can result in a strongly synergistic effect. In some embodiments, the combination of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with one or more additional agent(s) in Figures 1-7 and 9 (including pharmaceutically acceptable salts and prodrugs thereof) is not antagonistic.

[0205] As used herein, the term "antagonistic" means that the activity of the combination of compounds is less compared to the sum of the activities of the compounds in combination when the activity of each compound is determined individually (i.e. as a single compound). As used herein, the term "synergistic effect" means that the activity of the combination of compounds is greater than the sum of the individual activities of the compounds in the combination when the activity of each compound is determined individually. As used herein, the term "additive effect" means that the activity of the combination of compounds is about equal to the sum of the individual activities of the compound in the combination when the activity of each compound is determined individually.

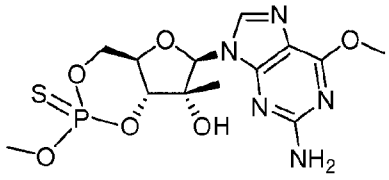
[0206] A potential advantage of utilizing a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with one or more additional agent(s) in Figures 1-7 and 9 (including pharmaceutically acceptable salts and prodrugs thereof) may be a reduction in the required amount(s) of one or more compounds of Figures 1-7 and 9 (including pharmaceutically acceptable salts and prodrugs thereof) that is effective in treating a disease

condition disclosed herein (for example, HCV), as compared to the amount required to achieve same therapeutic result when one or more compounds of Figures 1-7 and 9 (including pharmaceutically acceptable salts and prodrugs thereof) are administered without a compound of Formula (I), or a pharmaceutically acceptable salt thereof. For example, the amount of a compound in Figures 1-7 and 9 (including a pharmaceutically acceptable salt and prodrug thereof), can be less compared to the amount of the compound in Figures 1-7 and 9 (including a pharmaceutically acceptable salt and prodrug thereof), needed to achieve the same viral load reduction when administered as a monotherapy. Another potential advantage of utilizing a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with one or more additional agent(s) in Figures 1-7 and 9 (including pharmaceutically acceptable salts and prodrugs thereof) is that the use of two or more compounds having different mechanism of actions can create a higher barrier to the development of resistant viral strains compared to the barrier when a compound is administered as monotherapy.

[0207] Additional advantages of utilizing a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with one or more additional agent(s) in Figures 1-7 and 9 (including pharmaceutically acceptable salts and prodrugs thereof) may include little to no cross resistance between a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and one or more additional agent(s) in Figures 1-7 and 9 (including pharmaceutically acceptable salts and prodrugs thereof) thereof; different routes for elimination of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and one or more additional agent(s) in Figures 1-7 and 9 (including pharmaceutically acceptable salts and prodrugs thereof); little to no overlapping toxicities between a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and one or more additional agent(s) in Figures 1-7 and 9 (including pharmaceutically acceptable salts and prodrugs thereof); little to no significant effects on cytochrome P450; and/or little to no pharmacokinetic interactions between a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and one or more additional agent(s) in Figures 1-7 and 9 (including pharmaceutically acceptable salts and prodrugs thereof).

[0208] A non-limiting list of example combination of compounds of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes a compound described herein, with one or more additional agent(s) are provided in Tables A, B, C and D. Each numbered X and Y compound in Tables A, B, C and D has a corresponding name and/or structure provided in Figures 1 to 9. The numbered compounds in Tables A, B, C and D includes pharmaceutically acceptable salts of the compounds and pharmaceutical compositions

containing the compounds or a pharmaceutically acceptable salt thereof. For example, 1001 includes the compound corresponding to 1001, pharmaceutically acceptable salts thereof, and pharmaceutical compositions that include compound 1001 and/or a pharmaceutically acceptable salt thereof. The combinations exemplified in Tables A, B, C and D are designated by the formula X:Y, which represents a combination of a compound X with a compound Y. For example, the combination designated as 1001:8001 in Table A represents a combination of compound 1001 with compound 8001, including pharmaceutically acceptable salts of compound 1001 and/or 8001, and pharmaceutical compositions including compound 1001 and 8001 (including pharmaceutical compositions that include pharmaceutically acceptable salts of compound 1001 and/or compound 8001). Thus, the combination designated as 1001:8001 in Table A represents the combination of Telaprevir (compound 1001, as shown in Figure 1A) and



(compound 8001, as shown in Figure 8A), including pharmaceutically acceptable salts of compound 1001 and/or 8001, and pharmaceutical compositions including compound 1001 and 8001 (including pharmaceutical compositions that include pharmaceutically acceptable salts of compound 1001 and/or compound 8001). Each of the combinations provided in Tables A, B, C and D can be used with one, two, three or more additional agents described herein. In some embodimentsdescribed herein, the combination of agents can be used to treat, amerliorate and/or inhibit a virus and/or a viral infection, wherein the virus can be HCV and the viral infection can be an HCV viral infection.

Table A: Example combinations of a compound X with a compound Y.

X : Y	X : Y	X : Y	X : Y	X : Y	X : Y
1001 : 8000	1001 : 8001	1001 : 8002	1001 : 8003	1001 : 8004	1001 : 8005
1002 : 8000	1002 : 8001	1002 : 8002	1002 : 8003	1002 : 8004	1002 : 8005
1003 : 8000	1003 : 8001	1003 : 8002	1003 : 8003	1003 : 8004	1003 : 8005
1004 : 8000	1004 : 8001	1004 : 8002	1004 : 8003	1004 : 8004	1004 : 8005
1005 : 8000	1005 : 8001	1005 : 8002	1005 : 8003	1005 : 8004	1005 : 8005
1006 : 8000	1006 : 8001	1006 : 8002	1006 : 8003	1006 : 8004	1006 : 8005
1007 : 8000	1007 : 8001	1007 : 8002	1007 : 8003	1007 : 8004	1007 : 8005
1008 : 8000	1008 : 8001	1008 : 8002	1008 : 8003	1008 : 8004	1008 : 8005
1009 : 8000	1009 : 8001	1009 : 8002	1009 : 8003	1009 : 8004	1009 : 8005
1010 : 8000	1010 : 8001	1010 : 8002	1010 : 8003	1010 : 8004	1010 : 8005
1011 : 8000	1011 : 8001	1011 : 8002	1011 : 8003	1011 : 8004	1011 : 8005
1012 : 8000	1012 : 8001	1012 : 8002	1012 : 8003	1012 : 8004	1012 : 8005
1013 : 8000	1013 : 8001	1013 : 8002	1013 : 8003	1013 : 8004	1013 : 8005
1014 : 8000	1014 : 8001	1014 : 8002	1014 : 8003	1014 : 8004	1014 : 8005
2001 : 8000	2001 : 8001	2001 : 8002	2001 : 8003	2001 : 8004	2001 : 8005
2002 : 8000	2002 : 8001	2002 : 8002	2002 : 8003	2002 : 8004	2002 : 8005
2003 : 8000	2003 : 8001	2003 : 8002	2003 : 8003	2003 : 8004	2003 : 8005
2004 : 8000	2004 : 8001	2004 : 8002	2004 : 8003	2004 : 8004	2004 : 8005
2005 : 8000	2005 : 8001	2005 : 8002	2005 : 8003	2005 : 8004	2005 : 8005
2006 : 8000	2006 : 8001	2006 : 8002	2006 : 8003	2006 : 8004	2006 : 8005
2007 : 8000	2007 : 8001	2007 : 8002	2007 : 8003	2007 : 8004	2007 : 8005
2008 : 8000	2008 : 8001	2008 : 8002	2008 : 8003	2008 : 8004	2008 : 8005
2009 : 8000	2009 : 8001	2009 : 8002	2009 : 8003	2009 : 8004	2009 : 8005
2010 : 8000	2010 : 8001	2010 : 8002	2010 : 8003	2010 : 8004	2010 : 8005
3001 : 8000	3001 : 8001	3001 : 8002	3001 : 8003	3001 : 8004	3001 : 8005
3002 : 8000	3002 : 8001	3002 : 8002	3002 : 8003	3002 : 8004	3002 : 8005
3003 : 8000	3003 : 8001	3003 : 8002	3003 : 8003	3003 : 8004	3003 : 8005
3004 : 8000	3004 : 8001	3004 : 8002	3004 : 8003	3004 : 8004	3004 : 8005
3005 : 8000	3005 : 8001	3005 : 8002	3005 : 8003	3005 : 8004	3005 : 8005
3006 : 8000	3006 : 8001	3006 : 8002	3006 : 8003	3006 : 8004	3006 : 8005
3007 : 8000	3007 : 8001	3007 : 8002	3007 : 8003	3007 : 8004	3007 : 8005
3008 : 8000	3008 : 8001	3008 : 8002	3008 : 8003	3008 : 8004	3008 : 8005
4001 : 8000	4001 : 8001	4001 : 8002	4001 : 8003	4001 : 8004	4001 : 8005
4002 : 8000	4002 : 8001	4002 : 8002	4002 : 8003	4002 : 8004	4002 : 8005
4003 : 8000	4003 : 8001	4003 : 8002	4003 : 8003	4003 : 8004	4003 : 8005
4004 : 8000	4004 : 8001	4004 : 8002	4004 : 8003	4004 : 8004	4004 : 8005
4005 : 8000	4005 : 8001	4005 : 8002	4005 : 8003	4005 : 8004	4005 : 8005
5001 : 8000	5001 : 8001	5001 : 8002	5001 : 8003	5001 : 8004	5001 : 8005
5002 : 8000	5002 : 8001	5002 : 8002	5002 : 8003	5002 : 8004	5002 : 8005

X : Y	X : Y	X : Y	X : Y	X : Y	X : Y
1001 : 8006	1001 : 8007	1001 : 8008	1001 : 8009	1001 : 8010	1001 : 8011
1002 : 8006	1002 : 8007	1002 : 8008	1002 : 8009	1002 : 8010	1002 : 8011
1003 : 8006	1003 : 8007	1003 : 8008	1003 : 8009	1003 : 8010	1003 : 8011
1004 : 8006	1004 : 8007	1004 : 8008	1004 : 8009	1004 : 8010	1004 : 8011
1005 : 8006	1005 : 8007	1005 : 8008	1005 : 8009	1005 : 8010	1005 : 8011
1006 : 8006	1006 : 8007	1006 : 8008	1006 : 8009	1006 : 8010	1006 : 8011
1007 : 8006	1007 : 8007	1007 : 8008	1007 : 8009	1007 : 8010	1007 : 8011
1008 : 8006	1008 : 8007	1008 : 8008	1008 : 8009	1008 : 8010	1008 : 8011
1009 : 8006	1009 : 8007	1009 : 8008	1009 : 8009	1009 : 8010	1009 : 8011
1010 : 8006	1010 : 8007	1010 : 8008	1010 : 8009	1010 : 8010	1010 : 8011
1011 : 8006	1011 : 8007	1011 : 8008	1011 : 8009	1011 : 8010	1011 : 8011
1012 : 8006	1012 : 8007	1012 : 8008	1012 : 8009	1012 : 8010	1012 : 8011
1013 : 8006	1013 : 8007	1013 : 8008	1013 : 8009	1013 : 8010	1013 : 8011
1014 : 8006	1014 : 8007	1014 : 8008	1014 : 8009	1014 : 8010	1014 : 8011
2001 : 8006	2001 : 8007	2001 : 8008	2001 : 8009	2001 : 8010	2001 : 8011
2002 : 8006	2002 : 8007	2002 : 8008	2002 : 8009	2002 : 8010	2002 : 8011
2003 : 8006	2003 : 8007	2003 : 8008	2003 : 8009	2003 : 8010	2003 : 8011
2004 : 8006	2004 : 8007	2004 : 8008	2004 : 8009	2004 : 8010	2004 : 8011
2005 : 8006	2005 : 8007	2005 : 8008	2005 : 8009	2005 : 8010	2005 : 8011
2006 : 8006	2006 : 8007	2006 : 8008	2006 : 8009	2006 : 8010	2006 : 8011
2007 : 8006	2007 : 8007	2007 : 8008	2007 : 8009	2007 : 8010	2007 : 8011
2008 : 8006	2008 : 8007	2008 : 8008	2008 : 8009	2008 : 8010	2008 : 8011
2009 : 8006	2009 : 8007	2009 : 8008	2009 : 8009	2009 : 8010	2009 : 8011
2010 : 8006	2010 : 8007	2010 : 8008	2010 : 8009	2010 : 8010	2010 : 8011
3001 : 8006	3001 : 8007	3001 : 8008	3001 : 8009	3001 : 8010	3001 : 8011
3002 : 8006	3002 : 8007	3002 : 8008	3002 : 8009	3002 : 8010	3002 : 8011
3003 : 8006	3003 : 8007	3003 : 8008	3003 : 8009	3003 : 8010	3003 : 8011
3004 : 8006	3004 : 8007	3004 : 8008	3004 : 8009	3004 : 8010	3004 : 8011
3005 : 8006	3005 : 8007	3005 : 8008	3005 : 8009	3005 : 8010	3005 : 8011
3006 : 8006	3006 : 8007	3006 : 8008	3006 : 8009	3006 : 8010	3006 : 8011
3007 : 8006	3007 : 8007	3007 : 8008	3007 : 8009	3007 : 8010	3007 : 8011
3008 : 8006	3008 : 8007	3008 : 8008	3008 : 8009	3008 : 8010	3008 : 8011
4001 : 8006	4001 : 8007	4001 : 8008	4001 : 8009	4001 : 8010	4001 : 8011
4002 : 8006	4002 : 8007	4002 : 8008	4002 : 8009	4002 : 8010	4002 : 8011
4003 : 8006	4003 : 8007	4003 : 8008	4003 : 8009	4003 : 8010	4003 : 8011
4004 : 8006	4004 : 8007	4004 : 8008	4004 : 8009	4004 : 8010	4004 : 8011
4005 : 8006	4005 : 8007	4005 : 8008	4005 : 8009	4005 : 8010	4005 : 8011
5001 : 8006	5001 : 8007	5001 : 8008	5001 : 8009	5001 : 8010	5001 : 8011
5002 : 8006	5002 : 8007	5002 : 8008	5002 : 8009	5002 : 8010	5002 : 8011

X : Y	X : Y	X : Y	X : Y	X : Y	X : Y
1001 : 8012	1001 : 8013	1001 : 8014	1001 : 8015	1001 : 8016	
1002 : 8012	1002 : 8013	1002 : 8014	1002 : 8015	1002 : 8016	
1003 : 8012	1003 : 8013	1003 : 8014	1003 : 8015	1003 : 8016	
1004 : 8012	1004 : 8013	1004 : 8014	1004 : 8015	1004 : 8016	
1005 : 8012	1005 : 8013	1005 : 8014	1005 : 8015	1005 : 8016	
1006 : 8012	1006 : 8013	1006 : 8014	1006 : 8015	1006 : 8016	
1007 : 8012	1007 : 8013	1007 : 8014	1007 : 8015	1007 : 8016	
1008 : 8012	1008 : 8013	1008 : 8014	1008 : 8015	1008 : 8016	
1009 : 8012	1009 : 8013	1009 : 8014	1009 : 8015	1009 : 8016	
1010 : 8012	1010 : 8013	1010 : 8014	1010 : 8015	1010 : 8016	
1011 : 8012	1011 : 8013	1011 : 8014	1011 : 8015	1011 : 8016	
1012 : 8012	1012 : 8013	1012 : 8014	1012 : 8015	1012 : 8016	
1013 : 8012	1013 : 8013	1013 : 8014	1013 : 8015	1013 : 8016	
1014 : 8012	1014 : 8013	1014 : 8014	1014 : 8015	1014 : 8016	
2001 : 8012	2001 : 8013	2001 : 8014	2001 : 8015	2001 : 8016	
2002 : 8012	2002 : 8013	2002 : 8014	2002 : 8015	2002 : 8016	
2003 : 8012	2003 : 8013	2003 : 8014	2003 : 8015	2003 : 8016	
2004 : 8012	2004 : 8013	2004 : 8014	2004 : 8015	2004 : 8016	
2005 : 8012	2005 : 8013	2005 : 8014	2005 : 8015	2005 : 8016	
2006 : 8012	2006 : 8013	2006 : 8014	2006 : 8015	2006 : 8016	--
2007 : 8012	2007 : 8013	2007 : 8014	2007 : 8015	2007 : 8016	
2008 : 8012	2008 : 8013	2008 : 8014	2008 : 8015	2008 : 8016	
2009 : 8012	2009 : 8013	2009 : 8014	2009 : 8015	2009 : 8016	
2010 : 8012	2010 : 8013	2010 : 8014	2010 : 8015	2010 : 8016	
3001 : 8012	3001 : 8013	3001 : 8014	3001 : 8015	3001 : 8016	
3002 : 8012	3002 : 8013	3002 : 8014	3002 : 8015	3002 : 8016	
3003 : 8012	3003 : 8013	3003 : 8014	3003 : 8015	3003 : 8016	
3004 : 8012	3004 : 8013	3004 : 8014	3004 : 8015	3004 : 8016	
3005 : 8012	3005 : 8013	3005 : 8014	3005 : 8015	3005 : 8016	
3006 : 8012	3006 : 8013	3006 : 8014	3006 : 8015	3006 : 8016	
3007 : 8012	3007 : 8013	3007 : 8014	3007 : 8015	3007 : 8016	
3008 : 8012	3008 : 8013	3008 : 8014	3008 : 8015	3008 : 8016	
4001 : 8012	4001 : 8013	4001 : 8014	4001 : 8015	4001 : 8016	
4002 : 8012	4002 : 8013	4002 : 8014	4002 : 8015	4002 : 8016	
4003 : 8012	4003 : 8013	4003 : 8014	4003 : 8015	4003 : 8016	
4004 : 8012	4004 : 8013	4004 : 8014	4004 : 8015	4004 : 8016	
4005 : 8012	4005 : 8013	4005 : 8014	4005 : 8015	4005 : 8016	
5001 : 8012	5001 : 8013	5001 : 8014	5001 : 8015	5001 : 8016	
5002 : 8012	5002 : 8013	5002 : 8014	5002 : 8015	5002 : 8016	

Table B: Example combinations of a compound X with a compound Y.

X : Y	X : Y	X : Y	X : Y	X : Y	X : Y
8000 : 7000	8000 : 7041	8001 : 7000	8001 : 7041	8002 : 7000	8002 : 7041
8000 : 7001	8000 : 7042	8001 : 7001	8001 : 7042	8002 : 7001	8002 : 7042
8000 : 7002	8000 : 7043	8001 : 7002	8001 : 7043	8002 : 7002	8002 : 7043
8000 : 7003	8000 : 7044	8001 : 7003	8001 : 7044	8002 : 7003	8002 : 7044
8000 : 7004	8000 : 7045	8001 : 7004	8001 : 7045	8002 : 7004	8002 : 7045
8000 : 7005	8000 : 7046	8001 : 7005	8001 : 7046	8002 : 7005	8002 : 7046
8000 : 7006	8000 : 7047	8001 : 7006	8001 : 7047	8002 : 7006	8002 : 7047
8000 : 7007	8000 : 7048	8001 : 7007	8001 : 7048	8002 : 7007	8002 : 7048
8000 : 7008	8000 : 7049	8001 : 7008	8001 : 7049	8002 : 7008	8002 : 7049
8000 : 7009	8000 : 7050	8001 : 7009	8001 : 7050	8002 : 7009	8002 : 7050
8000 : 7010	8000 : 7051	8001 : 7010	8001 : 7051	8002 : 7010	8002 : 7051
8000 : 7011	8000 : 7052	8001 : 7011	8001 : 7052	8002 : 7011	8002 : 7052
8000 : 7012	8000 : 7053	8001 : 7012	8001 : 7053	8002 : 7012	8002 : 7053
8000 : 7013	8000 : 7054	8001 : 7013	8001 : 7054	8002 : 7013	8002 : 7054
8000 : 7014	8000 : 7055	8001 : 7014	8001 : 7055	8002 : 7014	8002 : 7055
8000 : 7015	8000 : 7056	8001 : 7015	8001 : 7056	8002 : 7015	8002 : 7056
8000 : 7016	8000 : 7057	8001 : 7016	8001 : 7057	8002 : 7016	8002 : 7057
8000 : 7017	8000 : 7058	8001 : 7017	8001 : 7058	8002 : 7017	8002 : 7058
8000 : 7018	8000 : 7059	8001 : 7018	8001 : 7059	8002 : 7018	8002 : 7059
8000 : 7019	8000 : 7060	8001 : 7019	8001 : 7060	8002 : 7019	8002 : 7060
8000 : 7020	8000 : 7061	8001 : 7020	8001 : 7061	8002 : 7020	8002 : 7061
8000 : 7021	8000 : 7062	8001 : 7021	8001 : 7062	8002 : 7021	8002 : 7062
8000 : 7022	8000 : 7063	8001 : 7022	8001 : 7063	8002 : 7022	8002 : 7063
8000 : 7023	8000 : 7064	8001 : 7023	8001 : 7064	8002 : 7023	8002 : 7064
8000 : 7024	8000 : 7065	8001 : 7024	8001 : 7065	8002 : 7024	8002 : 7065
8000 : 7025	8000 : 7066	8001 : 7025	8001 : 7066	8002 : 7025	8002 : 7066
8000 : 7026	8000 : 7067	8001 : 7026	8001 : 7067	8002 : 7026	8002 : 7067
8000 : 7027	8000 : 7068	8001 : 7027	8001 : 7068	8002 : 7027	8002 : 7068
8000 : 7028	8000 : 7069	8001 : 7028	8001 : 7069	8002 : 7028	8002 : 7069
8000 : 7029	8000 : 7070	8001 : 7029	8001 : 7070	8002 : 7029	8002 : 7070
8000 : 7030	8000 : 7071	8001 : 7030	8001 : 7071	8002 : 7030	8002 : 7071
8000 : 7031	8000 : 7072	8001 : 7031	8001 : 7072	8002 : 7031	8002 : 7072
8000 : 7032	8000 : 7073	8001 : 7032	8001 : 7073	8002 : 7032	8002 : 7073
8000 : 7033	8000 : 7074	8001 : 7033	8001 : 7074	8002 : 7033	8002 : 7074
8000 : 7034	8000 : 7075	8001 : 7034	8001 : 7075	8002 : 7034	8002 : 7075
8000 : 7035	8000 : 7076	8001 : 7035	8001 : 7076	8002 : 7035	8002 : 7076
8000 : 7036	8000 : 7077	8001 : 7036	8001 : 7077	8002 : 7036	8002 : 7077
8000 : 7037		8001 : 7037		8002 : 7037	
8000 : 7038		8001 : 7038		8002 : 7038	
8000 : 7039		8001 : 7039		8002 : 7039	
8000 : 7040		8001 : 7040		8002 : 7040	

X : Y	X : Y	X : Y	X : Y	X : Y	X : Y
8003 : 7000	8003 : 7042	8004 : 7000	8004 : 7042	8005 : 7000	8005 : 7042
8003 : 7001	8003 : 7043	8004 : 7001	8004 : 7043	8005 : 7001	8005 : 7043
8003 : 7002	8003 : 7044	8004 : 7002	8004 : 7044	8005 : 7002	8005 : 7044
8003 : 7003	8003 : 7045	8004 : 7003	8004 : 7045	8005 : 7003	8005 : 7045
8003 : 7004	8003 : 7046	8004 : 7004	8004 : 7046	8005 : 7004	8005 : 7046
8003 : 7005	8003 : 7047	8004 : 7005	8004 : 7047	8005 : 7005	8005 : 7047
8003 : 7006	8003 : 7048	8004 : 7006	8004 : 7048	8005 : 7006	8005 : 7048
8003 : 7007	8003 : 7049	8004 : 7007	8004 : 7049	8005 : 7007	8005 : 7049
8003 : 7008	8003 : 7050	8004 : 7008	8004 : 7050	8005 : 7008	8005 : 7050
8003 : 7009	8003 : 7051	8004 : 7009	8004 : 7051	8005 : 7009	8005 : 7051
8003 : 7010	8003 : 7052	8004 : 7010	8004 : 7052	8005 : 7010	8005 : 7052
8003 : 7011	8003 : 7053	8004 : 7011	8004 : 7053	8005 : 7011	8005 : 7053
8003 : 7012	8003 : 7054	8004 : 7012	8004 : 7054	8005 : 7012	8005 : 7054
8003 : 7013	8003 : 7055	8004 : 7013	8004 : 7055	8005 : 7013	8005 : 7055
8003 : 7014	8003 : 7056	8004 : 7014	8004 : 7056	8005 : 7014	8005 : 7056
8003 : 7015	8003 : 7057	8004 : 7015	8004 : 7057	8005 : 7015	8005 : 7057
8003 : 7016	8003 : 7058	8004 : 7016	8004 : 7058	8005 : 7016	8005 : 7058
8003 : 7017	8003 : 7059	8004 : 7017	8004 : 7059	8005 : 7017	8005 : 7059
8003 : 7018	8003 : 7060	8004 : 7018	8004 : 7060	8005 : 7018	8005 : 7060
8003 : 7019	8003 : 7061	8004 : 7019	8004 : 7061	8005 : 7019	8005 : 7061
8003 : 7020	8003 : 7062	8004 : 7020	8004 : 7062	8005 : 7020	8005 : 7062
8003 : 7021	8003 : 7063	8004 : 7021	8004 : 7063	8005 : 7021	8005 : 7063
8003 : 7022	8003 : 7064	8004 : 7022	8004 : 7064	8005 : 7022	8005 : 7064
8003 : 7023	8003 : 7065	8004 : 7023	8004 : 7065	8005 : 7023	8005 : 7065
8003 : 7024	8003 : 7066	8004 : 7024	8004 : 7066	8005 : 7024	8005 : 7066
8003 : 7025	8003 : 7067	8004 : 7025	8004 : 7067	8005 : 7025	8005 : 7067
8003 : 7026	8003 : 7068	8004 : 7026	8004 : 7068	8005 : 7026	8005 : 7068
8003 : 7027	8003 : 7069	8004 : 7027	8004 : 7069	8005 : 7027	8005 : 7069
8003 : 7028	8003 : 7070	8004 : 7028	8004 : 7070	8005 : 7028	8005 : 7070
8003 : 7029	8003 : 7071	8004 : 7029	8004 : 7071	8005 : 7029	8005 : 7071
8003 : 7030	8003 : 7072	8004 : 7030	8004 : 7072	8005 : 7030	8005 : 7072
8003 : 7031	8003 : 7073	8004 : 7031	8004 : 7073	8005 : 7031	8005 : 7073
8003 : 7032	8003 : 7074	8004 : 7032	8004 : 7074	8005 : 7032	8005 : 7074
8003 : 7033	8003 : 7075	8004 : 7033	8004 : 7075	8005 : 7033	8005 : 7075
8003 : 7034	8003 : 7076	8004 : 7034	8004 : 7076	8005 : 7034	8005 : 7076
8003 : 7035	8003 : 7077	8004 : 7035	8004 : 7077	8005 : 7035	8005 : 7077
8003 : 7036		8004 : 7036		8005 : 7036	
8003 : 7037		8004 : 7037		8005 : 7037	
8003 : 7038		8004 : 7038		8005 : 7038	
8003 : 7039		8004 : 7039		8005 : 7039	
8003 : 7040		8004 : 7040		8005 : 7040	
8003 : 7041		8004 : 7041		8005 : 7041	

X : Y	X : Y	X : Y	X : Y	X : Y	X : Y
8006 : 7000	8006 : 7042	8007 : 7000	8007 : 7042	8008 : 7000	8008 : 7042
8006 : 7001	8006 : 7043	8007 : 7001	8007 : 7043	8008 : 7001	8008 : 7043
8006 : 7002	8006 : 7044	8007 : 7002	8007 : 7044	8008 : 7002	8008 : 7044
8006 : 7003	8006 : 7045	8007 : 7003	8007 : 7045	8008 : 7003	8008 : 7045
8006 : 7004	8006 : 7046	8007 : 7004	8007 : 7046	8008 : 7004	8008 : 7046
8006 : 7005	8006 : 7047	8007 : 7005	8007 : 7047	8008 : 7005	8008 : 7047
8006 : 7006	8006 : 7048	8007 : 7006	8007 : 7048	8008 : 7006	8008 : 7048
8006 : 7007	8006 : 7049	8007 : 7007	8007 : 7049	8008 : 7007	8008 : 7049
8006 : 7008	8006 : 7050	8007 : 7008	8007 : 7050	8008 : 7008	8008 : 7050
8006 : 7009	8006 : 7051	8007 : 7009	8007 : 7051	8008 : 7009	8008 : 7051
8006 : 7010	8006 : 7052	8007 : 7010	8007 : 7052	8008 : 7010	8008 : 7052
8006 : 7011	8006 : 7053	8007 : 7011	8007 : 7053	8008 : 7011	8008 : 7053
8006 : 7012	8006 : 7054	8007 : 7012	8007 : 7054	8008 : 7012	8008 : 7054
8006 : 7013	8006 : 7055	8007 : 7013	8007 : 7055	8008 : 7013	8008 : 7055
8006 : 7014	8006 : 7056	8007 : 7014	8007 : 7056	8008 : 7014	8008 : 7056
8006 : 7015	8006 : 7057	8007 : 7015	8007 : 7057	8008 : 7015	8008 : 7057
8006 : 7016	8006 : 7058	8007 : 7016	8007 : 7058	8008 : 7016	8008 : 7058
8006 : 7017	8006 : 7059	8007 : 7017	8007 : 7059	8008 : 7017	8008 : 7059
8006 : 7018	8006 : 7060	8007 : 7018	8007 : 7060	8008 : 7018	8008 : 7060
8006 : 7019	8006 : 7061	8007 : 7019	8007 : 7061	8008 : 7019	8008 : 7061
8006 : 7020	8006 : 7062	8007 : 7020	8007 : 7062	8008 : 7020	8008 : 7062
8006 : 7021	8006 : 7063	8007 : 7021	8007 : 7063	8008 : 7021	8008 : 7063
8006 : 7022	8006 : 7064	8007 : 7022	8007 : 7064	8008 : 7022	8008 : 7064
8006 : 7023	8006 : 7065	8007 : 7023	8007 : 7065	8008 : 7023	8008 : 7065
8006 : 7024	8006 : 7066	8007 : 7024	8007 : 7066	8008 : 7024	8008 : 7066
8006 : 7025	8006 : 7067	8007 : 7025	8007 : 7067	8008 : 7025	8008 : 7067
8006 : 7026	8006 : 7068	8007 : 7026	8007 : 7068	8008 : 7026	8008 : 7068
8006 : 7027	8006 : 7069	8007 : 7027	8007 : 7069	8008 : 7027	8008 : 7069
8006 : 7028	8006 : 7070	8007 : 7028	8007 : 7070	8008 : 7028	8008 : 7070
8006 : 7029	8006 : 7071	8007 : 7029	8007 : 7071	8008 : 7029	8008 : 7071
8006 : 7030	8006 : 7072	8007 : 7030	8007 : 7072	8008 : 7030	8008 : 7072
8006 : 7031	8006 : 7073	8007 : 7031	8007 : 7073	8008 : 7031	8008 : 7073
8006 : 7032	8006 : 7074	8007 : 7032	8007 : 7074	8008 : 7032	8008 : 7074
8006 : 7033	8006 : 7075	8007 : 7033	8007 : 7075	8008 : 7033	8008 : 7075
8006 : 7034	8006 : 7076	8007 : 7034	8007 : 7076	8008 : 7034	8008 : 7076
8006 : 7035	8006 : 7077	8007 : 7035	8007 : 7077	8008 : 7035	8008 : 7077
8006 : 7036		8007 : 7036		8008 : 7036	
8006 : 7037		8007 : 7037		8008 : 7037	
8006 : 7038		8007 : 7038		8008 : 7038	
8006 : 7039		8007 : 7039		8008 : 7039	
8006 : 7040		8007 : 7040		8008 : 7040	
8006 : 7041		8007 : 7041		8008 : 7041	

X : Y	X : Y	X : Y	X : Y	X : Y	X : Y
8009 : 7000	8009 : 7042	8010 : 7000	8010 : 7042	8011 : 7000	8011 : 7042
8009 : 7001	8009 : 7043	8010 : 7001	8010 : 7043	8011 : 7001	8011 : 7043
8009 : 7002	8009 : 7044	8010 : 7002	8010 : 7044	8011 : 7002	8011 : 7044
8009 : 7003	8009 : 7045	8010 : 7003	8010 : 7045	8011 : 7003	8011 : 7045
8009 : 7004	8009 : 7046	8010 : 7004	8010 : 7046	8011 : 7004	8011 : 7046
8009 : 7005	8009 : 7047	8010 : 7005	8010 : 7047	8011 : 7005	8011 : 7047
8009 : 7006	8009 : 7048	8010 : 7006	8010 : 7048	8011 : 7006	8011 : 7048
8009 : 7007	8009 : 7049	8010 : 7007	8010 : 7049	8011 : 7007	8011 : 7049
8009 : 7008	8009 : 7050	8010 : 7008	8010 : 7050	8011 : 7008	8011 : 7050
8009 : 7009	8009 : 7051	8010 : 7009	8010 : 7051	8011 : 7009	8011 : 7051
8009 : 7010	8009 : 7052	8010 : 7010	8010 : 7052	8011 : 7010	8011 : 7052
8009 : 7011	8009 : 7053	8010 : 7011	8010 : 7053	8011 : 7011	8011 : 7053
8009 : 7012	8009 : 7054	8010 : 7012	8010 : 7054	8011 : 7012	8011 : 7054
8009 : 7013	8009 : 7055	8010 : 7013	8010 : 7055	8011 : 7013	8011 : 7055
8009 : 7014	8009 : 7056	8010 : 7014	8010 : 7056	8011 : 7014	8011 : 7056
8009 : 7015	8009 : 7057	8010 : 7015	8010 : 7057	8011 : 7015	8011 : 7057
8009 : 7016	8009 : 7058	8010 : 7016	8010 : 7058	8011 : 7016	8011 : 7058
8009 : 7017	8009 : 7059	8010 : 7017	8010 : 7059	8011 : 7017	8011 : 7059
8009 : 7018	8009 : 7060	8010 : 7018	8010 : 7060	8011 : 7018	8011 : 7060
8009 : 7019	8009 : 7061	8010 : 7019	8010 : 7061	8011 : 7019	8011 : 7061
8009 : 7020	8009 : 7062	8010 : 7020	8010 : 7062	8011 : 7020	8011 : 7062
8009 : 7021	8009 : 7063	8010 : 7021	8010 : 7063	8011 : 7021	8011 : 7063
8009 : 7022	8009 : 7064	8010 : 7022	8010 : 7064	8011 : 7022	8011 : 7064
8009 : 7023	8009 : 7065	8010 : 7023	8010 : 7065	8011 : 7023	8011 : 7065
8009 : 7024	8009 : 7066	8010 : 7024	8010 : 7066	8011 : 7024	8011 : 7066
8009 : 7025	8009 : 7067	8010 : 7025	8010 : 7067	8011 : 7025	8011 : 7067
8009 : 7026	8009 : 7068	8010 : 7026	8010 : 7068	8011 : 7026	8011 : 7068
8009 : 7027	8009 : 7069	8010 : 7027	8010 : 7069	8011 : 7027	8011 : 7069
8009 : 7028	8009 : 7070	8010 : 7028	8010 : 7070	8011 : 7028	8011 : 7070
8009 : 7029	8009 : 7071	8010 : 7029	8010 : 7071	8011 : 7029	8011 : 7071
8009 : 7030	8009 : 7072	8010 : 7030	8010 : 7072	8011 : 7030	8011 : 7072
8009 : 7031	8009 : 7073	8010 : 7031	8010 : 7073	8011 : 7031	8011 : 7073
8009 : 7032	8009 : 7074	8010 : 7032	8010 : 7074	8011 : 7032	8011 : 7074
8009 : 7033	8009 : 7075	8010 : 7033	8010 : 7075	8011 : 7033	8011 : 7075
8009 : 7034	8009 : 7076	8010 : 7034	8010 : 7076	8011 : 7034	8011 : 7076
8009 : 7035	8009 : 7077	8010 : 7035	8010 : 7077	8011 : 7035	8011 : 7077
8009 : 7036		8010 : 7036		8011 : 7036	
8009 : 7037		8010 : 7037		8011 : 7037	
8009 : 7038		8010 : 7038		8011 : 7038	
8009 : 7039		8010 : 7039		8011 : 7039	
8009 : 7040		8010 : 7040		8011 : 7040	
8009 : 7041		8010 : 7041		8011 : 7041	

X : Y	X : Y	X : Y	X : Y	X : Y	X : Y
8012 : 7000	8012 : 7042	8013 : 7000	8013 : 7042	8014 : 7000	8014 : 7042
8012 : 7001	8012 : 7043	8013 : 7001	8013 : 7043	8014 : 7001	8014 : 7043
8012 : 7002	8012 : 7044	8013 : 7002	8013 : 7044	8014 : 7002	8014 : 7044
8012 : 7003	8012 : 7045	8013 : 7003	8013 : 7045	8014 : 7003	8014 : 7045
8012 : 7004	8012 : 7046	8013 : 7004	8013 : 7046	8014 : 7004	8014 : 7046
8012 : 7005	8012 : 7047	8013 : 7005	8013 : 7047	8014 : 7005	8014 : 7047
8012 : 7006	8012 : 7048	8013 : 7006	8013 : 7048	8014 : 7006	8014 : 7048
8012 : 7007	8012 : 7049	8013 : 7007	8013 : 7049	8014 : 7007	8014 : 7049
8012 : 7008	8012 : 7050	8013 : 7008	8013 : 7050	8014 : 7008	8014 : 7050
8012 : 7009	8012 : 7051	8013 : 7009	8013 : 7051	8014 : 7009	8014 : 7051
8012 : 7010	8012 : 7052	8013 : 7010	8013 : 7052	8014 : 7010	8014 : 7052
8012 : 7011	8012 : 7053	8013 : 7011	8013 : 7053	8014 : 7011	8014 : 7053
8012 : 7012	8012 : 7054	8013 : 7012	8013 : 7054	8014 : 7012	8014 : 7054
8012 : 7013	8012 : 7055	8013 : 7013	8013 : 7055	8014 : 7013	8014 : 7055
8012 : 7014	8012 : 7056	8013 : 7014	8013 : 7056	8014 : 7014	8014 : 7056
8012 : 7015	8012 : 7057	8013 : 7015	8013 : 7057	8014 : 7015	8014 : 7057
8012 : 7016	8012 : 7058	8013 : 7016	8013 : 7058	8014 : 7016	8014 : 7058
8012 : 7017	8012 : 7059	8013 : 7017	8013 : 7059	8014 : 7017	8014 : 7059
8012 : 7018	8012 : 7060	8013 : 7018	8013 : 7060	8014 : 7018	8014 : 7060
8012 : 7019	8012 : 7061	8013 : 7019	8013 : 7061	8014 : 7019	8014 : 7061
8012 : 7020	8012 : 7062	8013 : 7020	8013 : 7062	8014 : 7020	8014 : 7062
8012 : 7021	8012 : 7063	8013 : 7021	8013 : 7063	8014 : 7021	8014 : 7063
8012 : 7022	8012 : 7064	8013 : 7022	8013 : 7064	8014 : 7022	8014 : 7064
8012 : 7023	8012 : 7065	8013 : 7023	8013 : 7065	8014 : 7023	8014 : 7065
8012 : 7024	8012 : 7066	8013 : 7024	8013 : 7066	8014 : 7024	8014 : 7066
8012 : 7025	8012 : 7067	8013 : 7025	8013 : 7067	8014 : 7025	8014 : 7067
8012 : 7026	8012 : 7068	8013 : 7026	8013 : 7068	8014 : 7026	8014 : 7068
8012 : 7027	8012 : 7069	8013 : 7027	8013 : 7069	8014 : 7027	8014 : 7069
8012 : 7028	8012 : 7070	8013 : 7028	8013 : 7070	8014 : 7028	8014 : 7070
8012 : 7029	8012 : 7071	8013 : 7029	8013 : 7071	8014 : 7029	8014 : 7071
8012 : 7030	8012 : 7072	8013 : 7030	8013 : 7072	8014 : 7030	8014 : 7072
8012 : 7031	8012 : 7073	8013 : 7031	8013 : 7073	8014 : 7031	8014 : 7073
8012 : 7032	8012 : 7074	8013 : 7032	8013 : 7074	8014 : 7032	8014 : 7074
8012 : 7033	8012 : 7075	8013 : 7033	8013 : 7075	8014 : 7033	8014 : 7075
8012 : 7034	8012 : 7076	8013 : 7034	8013 : 7076	8014 : 7034	8014 : 7076
8012 : 7035	8012 : 7077	8013 : 7035	8013 : 7077	8014 : 7035	8014 : 7077
8012 : 7036		8013 : 7036		8014 : 7036	
8012 : 7037		8013 : 7037		8014 : 7037	
8012 : 7038		8013 : 7038		8014 : 7038	
8012 : 7039		8013 : 7039		8014 : 7039	
8012 : 7040		8013 : 7040		8014 : 7040	
8012 : 7041		8013 : 7041		8014 : 7041	

X : Y	X : Y	X : Y	X : Y	X : Y	X : Y
8015 : 7000	8015 : 7042	8016 : 7000	8016 : 7042		
8015 : 7001	8015 : 7043	8016 : 7001	8016 : 7043		
8015 : 7002	8015 : 7044	8016 : 7002	8016 : 7044		
8015 : 7003	8015 : 7045	8016 : 7003	8016 : 7045		
8015 : 7004	8015 : 7046	8016 : 7004	8016 : 7046		
8015 : 7005	8015 : 7047	8016 : 7005	8016 : 7047		
8015 : 7006	8015 : 7048	8016 : 7006	8016 : 7048		
8015 : 7007	8015 : 7049	8016 : 7007	8016 : 7049		
8015 : 7008	8015 : 7050	8016 : 7008	8016 : 7050		
8015 : 7009	8015 : 7051	8016 : 7009	8016 : 7051		
8015 : 7010	8015 : 7052	8016 : 7010	8016 : 7052		
8015 : 7011	8015 : 7053	8016 : 7011	8016 : 7053		
8015 : 7012	8015 : 7054	8016 : 7012	8016 : 7054		
8015 : 7013	8015 : 7055	8016 : 7013	8016 : 7055		
8015 : 7014	8015 : 7056	8016 : 7014	8016 : 7056		
8015 : 7015	8015 : 7057	8016 : 7015	8016 : 7057		
8015 : 7016	8015 : 7058	8016 : 7016	8016 : 7058		
8015 : 7017	8015 : 7059	8016 : 7017	8016 : 7059		
8015 : 7018	8015 : 7060	8016 : 7018	8016 : 7060		
8015 : 7019	8015 : 7061	8016 : 7019	8016 : 7061		
8015 : 7020	8015 : 7062	8016 : 7020	8016 : 7062	--	--
8015 : 7021	8015 : 7063	8016 : 7021	8016 : 7063		
8015 : 7022	8015 : 7064	8016 : 7022	8016 : 7064		
8015 : 7023	8015 : 7065	8016 : 7023	8016 : 7065		
8015 : 7024	8015 : 7066	8016 : 7024	8016 : 7066		
8015 : 7025	8015 : 7067	8016 : 7025	8016 : 7067		
8015 : 7026	8015 : 7068	8016 : 7026	8016 : 7068		
8015 : 7027	8015 : 7069	8016 : 7027	8016 : 7069		
8015 : 7028	8015 : 7070	8016 : 7028	8016 : 7070		
8015 : 7029	8015 : 7071	8016 : 7029	8016 : 7071		
8015 : 7030	8015 : 7072	8016 : 7030	8016 : 7072		
8015 : 7031	8015 : 7073	8016 : 7031	8016 : 7073		
8015 : 7032	8015 : 7074	8016 : 7032	8016 : 7074		
8015 : 7033	8015 : 7075	8016 : 7033	8016 : 7075		
8015 : 7034	8015 : 7076	8016 : 7034	8016 : 7076		
8015 : 7035	8015 : 7077	8016 : 7035	8016 : 7077		
8015 : 7036		8016 : 7036			
8015 : 7037		8016 : 7037			
8015 : 7038		8016 : 7038			
8015 : 7039		8016 : 7039			
8015 : 7040		8016 : 7040			
8015 : 7041		8016 : 7041			

Table C: Example combinations of a compound X with a compound Y.

X : Y	X : Y	X : Y	X : Y	X : Y	X : Y
6000 : 8000	6043 : 8000	6000 : 8001	6043 : 8001	6000 : 8002	6043 : 8002
6001 : 8000	6044 : 8000	6001 : 8001	6044 : 8001	6001 : 8002	6044 : 8002
6002 : 8000	6045 : 8000	6002 : 8001	6045 : 8001	6002 : 8002	6045 : 8002
6003 : 8000	6046 : 8000	6003 : 8001	6046 : 8001	6003 : 8002	6046 : 8002
6004 : 8000	6047 : 8000	6004 : 8001	6047 : 8001	6004 : 8002	6047 : 8002
6005 : 8000	6048 : 8000	6005 : 8001	6048 : 8001	6005 : 8002	6048 : 8002
6006 : 8000	6049 : 8000	6006 : 8001	6049 : 8001	6006 : 8002	6049 : 8002
6007 : 8000	6050 : 8000	6007 : 8001	6050 : 8001	6007 : 8002	6050 : 8002
6008 : 8000	6051 : 8000	6008 : 8001	6051 : 8001	6008 : 8002	6051 : 8002
6009 : 8000	6052 : 8000	6009 : 8001	6052 : 8001	6009 : 8002	6052 : 8002
6010 : 8000	6053 : 8000	6010 : 8001	6053 : 8001	6010 : 8002	6053 : 8002
6011 : 8000	6054 : 8000	6011 : 8001	6054 : 8001	6011 : 8002	6054 : 8002
6012 : 8000	6055 : 8000	6012 : 8001	6055 : 8001	6012 : 8002	6055 : 8002
6013 : 8000	6056 : 8000	6013 : 8001	6056 : 8001	6013 : 8002	6056 : 8002
6014 : 8000	6057 : 8000	6014 : 8001	6057 : 8001	6014 : 8002	6057 : 8002
6015 : 8000	6058 : 8000	6015 : 8001	6058 : 8001	6015 : 8002	6058 : 8002
6016 : 8000	6059 : 8000	6016 : 8001	6059 : 8001	6016 : 8002	6059 : 8002
6017 : 8000	6060 : 8000	6017 : 8001	6060 : 8001	6017 : 8002	6060 : 8002
6018 : 8000	6061 : 8000	6018 : 8001	6061 : 8001	6018 : 8002	6061 : 8002
6019 : 8000	6062 : 8000	6019 : 8001	6062 : 8001	6019 : 8002	6062 : 8002
6020 : 8000	6063 : 8000	6020 : 8001	6063 : 8001	6020 : 8002	6063 : 8002
6021 : 8000	6064 : 8000	6021 : 8001	6064 : 8001	6021 : 8002	6064 : 8002
6022 : 8000	6065 : 8000	6022 : 8001	6065 : 8001	6022 : 8002	6065 : 8002
6023 : 8000	6066 : 8000	6023 : 8001	6066 : 8001	6023 : 8002	6066 : 8002
6024 : 8000	6067 : 8000	6024 : 8001	6067 : 8001	6024 : 8002	6067 : 8002
6025 : 8000	6068 : 8000	6025 : 8001	6068 : 8001	6025 : 8002	6068 : 8002
6026 : 8000	6069 : 8000	6026 : 8001	6069 : 8001	6026 : 8002	6069 : 8002
6027 : 8000	6070 : 8000	6027 : 8001	6070 : 8001	6027 : 8002	6070 : 8002
6028 : 8000	6071 : 8000	6028 : 8001	6071 : 8001	6028 : 8002	6071 : 8002
6029 : 8000	6072 : 8000	6029 : 8001	6072 : 8001	6029 : 8002	6072 : 8002
6030 : 8000	6073 : 8000	6030 : 8001	6073 : 8001	6030 : 8002	6073 : 8002
6031 : 8000	6074 : 8000	6031 : 8001	6074 : 8001	6031 : 8002	6074 : 8002
6032 : 8000	6075 : 8000	6032 : 8001	6075 : 8001	6032 : 8002	6075 : 8002
6033 : 8000	6076 : 8000	6033 : 8001	6076 : 8001	6033 : 8002	6076 : 8002
6034 : 8000	6077 : 8000	6034 : 8001	6077 : 8001	6034 : 8002	6077 : 8002
6035 : 8000	6078 : 8000	6035 : 8001	6078 : 8001	6035 : 8002	6078 : 8002
6036 : 8000		6036 : 8001		6036 : 8002	
6037 : 8000		6037 : 8001		6037 : 8002	
6038 : 8000		6038 : 8001		6038 : 8002	
6039 : 8000		6039 : 8001		6039 : 8002	
6040 : 8000		6040 : 8001		6040 : 8002	
6041 : 8000		6041 : 8001		6041 : 8002	
6042 : 8000		6042 : 8001		6042 : 8002	

X : Y	X : Y	X : Y	X : Y	X : Y	X : Y
6000 : 8003	6043 : 8003	6000 : 8004	6043 : 8004	6000 : 8005	6043 : 8005
6001 : 8003	6044 : 8003	6001 : 8004	6044 : 8004	6001 : 8005	6044 : 8005
6002 : 8003	6045 : 8003	6002 : 8004	6045 : 8004	6002 : 8005	6045 : 8005
6003 : 8003	6046 : 8003	6003 : 8004	6046 : 8004	6003 : 8005	6046 : 8005
6004 : 8003	6047 : 8003	6004 : 8004	6047 : 8004	6004 : 8005	6047 : 8005
6005 : 8003	6048 : 8003	6005 : 8004	6048 : 8004	6005 : 8005	6048 : 8005
6006 : 8003	6049 : 8003	6006 : 8004	6049 : 8004	6006 : 8005	6049 : 8005
6007 : 8003	6050 : 8003	6007 : 8004	6050 : 8004	6007 : 8005	6050 : 8005
6008 : 8003	6051 : 8003	6008 : 8004	6051 : 8004	6008 : 8005	6051 : 8005
6009 : 8003	6052 : 8003	6009 : 8004	6052 : 8004	6009 : 8005	6052 : 8005
6010 : 8003	6053 : 8003	6010 : 8004	6053 : 8004	6010 : 8005	6053 : 8005
6011 : 8003	6054 : 8003	6011 : 8004	6054 : 8004	6011 : 8005	6054 : 8005
6012 : 8003	6055 : 8003	6012 : 8004	6055 : 8004	6012 : 8005	6055 : 8005
6013 : 8003	6056 : 8003	6013 : 8004	6056 : 8004	6013 : 8005	6056 : 8005
6014 : 8003	6057 : 8003	6014 : 8004	6057 : 8004	6014 : 8005	6057 : 8005
6015 : 8003	6058 : 8003	6015 : 8004	6058 : 8004	6015 : 8005	6058 : 8005
6016 : 8003	6059 : 8003	6016 : 8004	6059 : 8004	6016 : 8005	6059 : 8005
6017 : 8003	6060 : 8003	6017 : 8004	6060 : 8004	6017 : 8005	6060 : 8005
6018 : 8003	6061 : 8003	6018 : 8004	6061 : 8004	6018 : 8005	6061 : 8005
6019 : 8003	6062 : 8003	6019 : 8004	6062 : 8004	6019 : 8005	6062 : 8005
6020 : 8003	6063 : 8003	6020 : 8004	6063 : 8004	6020 : 8005	6063 : 8005
6021 : 8003	6064 : 8003	6021 : 8004	6064 : 8004	6021 : 8005	6064 : 8005
6022 : 8003	6065 : 8003	6022 : 8004	6065 : 8004	6022 : 8005	6065 : 8005
6023 : 8003	6066 : 8003	6023 : 8004	6066 : 8004	6023 : 8005	6066 : 8005
6024 : 8003	6067 : 8003	6024 : 8004	6067 : 8004	6024 : 8005	6067 : 8005
6025 : 8003	6068 : 8003	6025 : 8004	6068 : 8004	6025 : 8005	6068 : 8005
6026 : 8003	6069 : 8003	6026 : 8004	6069 : 8004	6026 : 8005	6069 : 8005
6027 : 8003	6070 : 8003	6027 : 8004	6070 : 8004	6027 : 8005	6070 : 8005
6028 : 8003	6071 : 8003	6028 : 8004	6071 : 8004	6028 : 8005	6071 : 8005
6029 : 8003	6072 : 8003	6029 : 8004	6072 : 8004	6029 : 8005	6072 : 8005
6030 : 8003	6073 : 8003	6030 : 8004	6073 : 8004	6030 : 8005	6073 : 8005
6031 : 8003	6074 : 8003	6031 : 8004	6074 : 8004	6031 : 8005	6074 : 8005
6032 : 8003	6075 : 8003	6032 : 8004	6075 : 8004	6032 : 8005	6075 : 8005
6033 : 8003	6076 : 8003	6033 : 8004	6076 : 8004	6033 : 8005	6076 : 8005
6034 : 8003	6077 : 8003	6034 : 8004	6077 : 8004	6034 : 8005	6077 : 8005
6035 : 8003	6078 : 8003	6035 : 8004	6078 : 8004	6035 : 8005	6078 : 8005
6036 : 8003		6036 : 8004		6036 : 8005	
6037 : 8003		6037 : 8004		6037 : 8005	
6038 : 8003		6038 : 8004		6038 : 8005	
6039 : 8003		6039 : 8004		6039 : 8005	
6040 : 8003		6040 : 8004		6040 : 8005	
6041 : 8003		6041 : 8004		6041 : 8005	
6042 : 8003		6042 : 8004		6042 : 8005	

X : Y	X : Y	X : Y	X : Y	X : Y	X : Y
6000 : 8006	6043 : 8006	6000 : 8007	6043 : 8007	6000 : 8008	6043 : 8008
6001 : 8006	6044 : 8006	6001 : 8007	6044 : 8007	6001 : 8008	6044 : 8008
6002 : 8006	6045 : 8006	6002 : 8007	6045 : 8007	6002 : 8008	6045 : 8008
6003 : 8006	6046 : 8006	6003 : 8007	6046 : 8007	6003 : 8008	6046 : 8008
6004 : 8006	6047 : 8006	6004 : 8007	6047 : 8007	6004 : 8008	6047 : 8008
6005 : 8006	6048 : 8006	6005 : 8007	6048 : 8007	6005 : 8008	6048 : 8008
6006 : 8006	6049 : 8006	6006 : 8007	6049 : 8007	6006 : 8008	6049 : 8008
6007 : 8006	6050 : 8006	6007 : 8007	6050 : 8007	6007 : 8008	6050 : 8008
6008 : 8006	6051 : 8006	6008 : 8007	6051 : 8007	6008 : 8008	6051 : 8008
6009 : 8006	6052 : 8006	6009 : 8007	6052 : 8007	6009 : 8008	6052 : 8008
6010 : 8006	6053 : 8006	6010 : 8007	6053 : 8007	6010 : 8008	6053 : 8008
6011 : 8006	6054 : 8006	6011 : 8007	6054 : 8007	6011 : 8008	6054 : 8008
6012 : 8006	6055 : 8006	6012 : 8007	6055 : 8007	6012 : 8008	6055 : 8008
6013 : 8006	6056 : 8006	6013 : 8007	6056 : 8007	6013 : 8008	6056 : 8008
6014 : 8006	6057 : 8006	6014 : 8007	6057 : 8007	6014 : 8008	6057 : 8008
6015 : 8006	6058 : 8006	6015 : 8007	6058 : 8007	6015 : 8008	6058 : 8008
6016 : 8006	6059 : 8006	6016 : 8007	6059 : 8007	6016 : 8008	6059 : 8008
6017 : 8006	6060 : 8006	6017 : 8007	6060 : 8007	6017 : 8008	6060 : 8008
6018 : 8006	6061 : 8006	6018 : 8007	6061 : 8007	6018 : 8008	6061 : 8008
6019 : 8006	6062 : 8006	6019 : 8007	6062 : 8007	6019 : 8008	6062 : 8008
6020 : 8006	6063 : 8006	6020 : 8007	6063 : 8007	6020 : 8008	6063 : 8008
6021 : 8006	6064 : 8006	6021 : 8007	6064 : 8007	6021 : 8008	6064 : 8008
6022 : 8006	6065 : 8006	6022 : 8007	6065 : 8007	6022 : 8008	6065 : 8008
6023 : 8006	6066 : 8006	6023 : 8007	6066 : 8007	6023 : 8008	6066 : 8008
6024 : 8006	6067 : 8006	6024 : 8007	6067 : 8007	6024 : 8008	6067 : 8008
6025 : 8006	6068 : 8006	6025 : 8007	6068 : 8007	6025 : 8008	6068 : 8008
6026 : 8006	6069 : 8006	6026 : 8007	6069 : 8007	6026 : 8008	6069 : 8008
6027 : 8006	6070 : 8006	6027 : 8007	6070 : 8007	6027 : 8008	6070 : 8008
6028 : 8006	6071 : 8006	6028 : 8007	6071 : 8007	6028 : 8008	6071 : 8008
6029 : 8006	6072 : 8006	6029 : 8007	6072 : 8007	6029 : 8008	6072 : 8008
6030 : 8006	6073 : 8006	6030 : 8007	6073 : 8007	6030 : 8008	6073 : 8008
6031 : 8006	6074 : 8006	6031 : 8007	6074 : 8007	6031 : 8008	6074 : 8008
6032 : 8006	6075 : 8006	6032 : 8007	6075 : 8007	6032 : 8008	6075 : 8008
6033 : 8006	6076 : 8006	6033 : 8007	6076 : 8007	6033 : 8008	6076 : 8008
6034 : 8006	6077 : 8006	6034 : 8007	6077 : 8007	6034 : 8008	6077 : 8008
6035 : 8006	6078 : 8006	6035 : 8007	6078 : 8007	6035 : 8008	6078 : 8008
6036 : 8006		6036 : 8007		6036 : 8008	
6037 : 8006		6037 : 8007		6037 : 8008	
6038 : 8006		6038 : 8007		6038 : 8008	
6039 : 8006		6039 : 8007		6039 : 8008	
6040 : 8006		6040 : 8007		6040 : 8008	
6041 : 8006		6041 : 8007		6041 : 8008	
6042 : 8006		6042 : 8007		6042 : 8008	

Table D: Example combinations of a compound X with a compound Y.

X : Y	X : Y	X : Y	X : Y	X : Y	X : Y
6000 : 8009	6043 : 8009	6000 : 8010	6043 : 8010	6000 : 8011	6043 : 8011
6001 : 8009	6044 : 8009	6001 : 8010	6044 : 8010	6001 : 8011	6044 : 8011
6002 : 8009	6045 : 8009	6002 : 8010	6045 : 8010	6002 : 8011	6045 : 8011
6003 : 8009	6046 : 8009	6003 : 8010	6046 : 8010	6003 : 8011	6046 : 8011
6004 : 8009	6047 : 8009	6004 : 8010	6047 : 8010	6004 : 8011	6047 : 8011
6005 : 8009	6048 : 8009	6005 : 8010	6048 : 8010	6005 : 8011	6048 : 8011
6006 : 8009	6049 : 8009	6006 : 8010	6049 : 8010	6006 : 8011	6049 : 8011
6007 : 8009	6050 : 8009	6007 : 8010	6050 : 8010	6007 : 8011	6050 : 8011
6008 : 8009	6051 : 8009	6008 : 8010	6051 : 8010	6008 : 8011	6051 : 8011
6009 : 8009	6052 : 8009	6009 : 8010	6052 : 8010	6009 : 8011	6052 : 8011
6010 : 8009	6053 : 8009	6010 : 8010	6053 : 8010	6010 : 8011	6053 : 8011
6011 : 8009	6054 : 8009	6011 : 8010	6054 : 8010	6011 : 8011	6054 : 8011
6012 : 8009	6055 : 8009	6012 : 8010	6055 : 8010	6012 : 8011	6055 : 8011
6013 : 8009	6056 : 8009	6013 : 8010	6056 : 8010	6013 : 8011	6056 : 8011
6014 : 8009	6057 : 8009	6014 : 8010	6057 : 8010	6014 : 8011	6057 : 8011
6015 : 8009	6058 : 8009	6015 : 8010	6058 : 8010	6015 : 8011	6058 : 8011
6016 : 8009	6059 : 8009	6016 : 8010	6059 : 8010	6016 : 8011	6059 : 8011
6017 : 8009	6060 : 8009	6017 : 8010	6060 : 8010	6017 : 8011	6060 : 8011
6018 : 8009	6061 : 8009	6018 : 8010	6061 : 8010	6018 : 8011	6061 : 8011
6019 : 8009	6062 : 8009	6019 : 8010	6062 : 8010	6019 : 8011	6062 : 8011
6020 : 8009	6063 : 8009	6020 : 8010	6063 : 8010	6020 : 8011	6063 : 8011
6021 : 8009	6064 : 8009	6021 : 8010	6064 : 8010	6021 : 8011	6064 : 8011
6022 : 8009	6065 : 8009	6022 : 8010	6065 : 8010	6022 : 8011	6065 : 8011
6023 : 8009	6066 : 8009	6023 : 8010	6066 : 8010	6023 : 8011	6066 : 8011
6024 : 8009	6067 : 8009	6024 : 8010	6067 : 8010	6024 : 8011	6067 : 8011
6025 : 8009	6068 : 8009	6025 : 8010	6068 : 8010	6025 : 8011	6068 : 8011
6026 : 8009	6069 : 8009	6026 : 8010	6069 : 8010	6026 : 8011	6069 : 8011
6027 : 8009	6070 : 8009	6027 : 8010	6070 : 8010	6027 : 8011	6070 : 8011
6028 : 8009	6071 : 8009	6028 : 8010	6071 : 8010	6028 : 8011	6071 : 8011
6029 : 8009	6072 : 8009	6029 : 8010	6072 : 8010	6029 : 8011	6072 : 8011
6030 : 8009	6073 : 8009	6030 : 8010	6073 : 8010	6030 : 8011	6073 : 8011
6031 : 8009	6074 : 8009	6031 : 8010	6074 : 8010	6031 : 8011	6074 : 8011
6032 : 8009	6075 : 8009	6032 : 8010	6075 : 8010	6032 : 8011	6075 : 8011
6033 : 8009	6076 : 8009	6033 : 8010	6076 : 8010	6033 : 8011	6076 : 8011
6034 : 8009	6077 : 8009	6034 : 8010	6077 : 8010	6034 : 8011	6077 : 8011
6035 : 8009	6078 : 8009	6035 : 8010	6078 : 8010	6035 : 8011	6078 : 8011
6036 : 8009		6036 : 8010		6036 : 8011	
6037 : 8009		6037 : 8010		6037 : 8011	
6038 : 8009		6038 : 8010		6038 : 8011	
6039 : 8009		6039 : 8010		6039 : 8011	
6040 : 8009		6040 : 8010		6040 : 8011	
6041 : 8009		6041 : 8010		6041 : 8011	
6042 : 8009		6042 : 8010		6042 : 8011	

X : Y	X : Y	X : Y	X : Y	X : Y	X : Y
6000 : 8012	6043 : 8012	6000 : 8013	6043 : 8013	6000 : 8014	6043 : 8014
6001 : 8012	6044 : 8012	6001 : 8013	6044 : 8013	6001 : 8014	6044 : 8014
6002 : 8012	6045 : 8012	6002 : 8013	6045 : 8013	6002 : 8014	6045 : 8014
6003 : 8012	6046 : 8012	6003 : 8013	6046 : 8013	6003 : 8014	6046 : 8014
6004 : 8012	6047 : 8012	6004 : 8013	6047 : 8013	6004 : 8014	6047 : 8014
6005 : 8012	6048 : 8012	6005 : 8013	6048 : 8013	6005 : 8014	6048 : 8014
6006 : 8012	6049 : 8012	6006 : 8013	6049 : 8013	6006 : 8014	6049 : 8014
6007 : 8012	6050 : 8012	6007 : 8013	6050 : 8013	6007 : 8014	6050 : 8014
6008 : 8012	6051 : 8012	6008 : 8013	6051 : 8013	6008 : 8014	6051 : 8014
6009 : 8012	6052 : 8012	6009 : 8013	6052 : 8013	6009 : 8014	6052 : 8014
6010 : 8012	6053 : 8012	6010 : 8013	6053 : 8013	6010 : 8014	6053 : 8014
6011 : 8012	6054 : 8012	6011 : 8013	6054 : 8013	6011 : 8014	6054 : 8014
6012 : 8012	6055 : 8012	6012 : 8013	6055 : 8013	6012 : 8014	6055 : 8014
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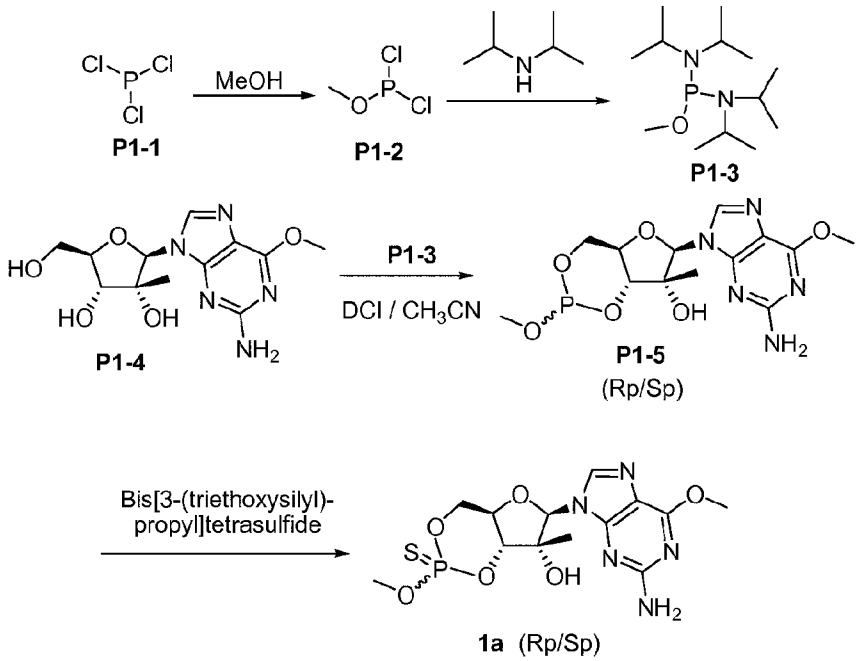
6042 : 8015		6042 : 8016			

EXAMPLES

[0209] Additional embodiments are disclosed in further detail in the following examples, which are not in any way intended to limit the scope of the claims.

Example 1

(*Rp/Sp*) 2'-*C*-methyl-6-*O*-methyl-guanosine-3',5'-cyclic-*O*-methyl phosphorothioate (1a)



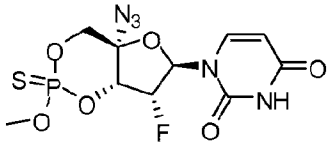
[0210] Step 1: Compound of **P1-2** – To a flask containing **P1-1** (20.0 g, 147.3 mmol) was added absolute MeOH (3.78 g, 118 mmol) dropwise over 2 hours at -40°C. The mixture was warmed to room temperature gradually and stirred for another hour. The reaction mixture was distilled to give **P1-2** (9.5 g, 61%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.90 (d, J = 10.4 Hz, 3H). ^{31}P NMR ($CDCl_3$, 162 MHz) δ180.81.

[0211] Step 2: Compound of **P1-3** – To a solution of **P1-2** (9.5 g, 72.0 mmol) in anhydrous ether (200 mL) was added diisopropylamine (43.5 g, 430.8 mmol) dropwise at 0°C. The mixture was stirred at room temperature overnight. The precipitate was filtered and the filtrate was concentrated to give a residue, which was distilled to give **P1-3** (6.5 g, 34%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.42-3.48 (m, 4H), 3.31 (d, J= 14.0 Hz, 3H), 1.02-1.11 (m, 27H). ^{31}P NMR ($CDCl_3$, 162 MHz) δ 130.99.

[0212] Step 3: Compound **1a** – A 1.0 M solution of 4,5-dicyanoimidazole (DCI) in CH_3CN (0.38 mL, 0.38 mmol) was added dropwise into a solution of 2'-*C*-methyl-6-*O*-methyl-guanosine **(P1-4)** (0.2 g, 0.64 mmol) in CH_3CN (10 mL) in N_2 atmosphere, and stirred at room temperature. After 40 minutes, the reaction mixture was cooled to 0-5 °C using an ice/water bath. A freshly prepared solution of methyl *N,N,N',N'*- tetraisopropylphosphorodiamidite in dichloromethane (DCM) (221 µl in 0.7 mL DCM, 0.77 mmol) was added. The reaction mixture was allowed to warm to room temperature and was stirred for 2 hours. Additional DCI (50 mg, 0.42 mmol) was added, and the reaction was stirred for 1 h to give a phosphite intermediate.

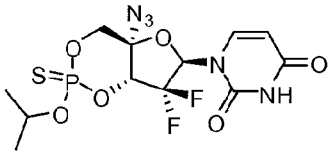
Bis[3-(triethoxysilyl)propyl]tetrasulfide (0.415 mL, 0.77 mmol) was added dropwise to the reaction mixture and the resultant light yellow suspension was stirred for 2 h at room temperature. The reaction mixture was cooled using an ice/water bath, and then diluted with ethyl acetate (EA) (150 mL), washed with saturated $NaHCO_3$ followed by brine, then dried over anhydrous Na_2SO_4 and concentrated *in-vacuo* to give a crude product residue which was purified by silica gel (DCM/MeOH; 95:5) to give 37.1 mg as white solid. Further purification by silica gel (DCM/isopropyl alcohol; 94:6) gave 16.9 mg of impure product, which was purified by RP-HPLC (H_2O/ CH_3CN; 0 to 50 %, 30 min) to afford compound **1a** (8.6 mg) as a white foam after lyophilization. ^1H NMR (400 MHz, $(CD_3)_2CO$, two isomers): δ 1.13 (s, 3H), 3.86 (2s, 3H), 3.71, 3.76 (2d, J = 13.6 Hz, 3H), 4.36-4.5 (m, 1H), 4.63-4.71 (m, 3H), 5.09, 5.18 (2s, 1H), 5.85-5.87 (br s, 2H), 6.00 (s, 1H), 7.91, 7.95 (2s, 1H); ^{31}P NMR ($(CD_3)_2CO$, two isomers): δ 65.07 (s), 68.4 (s); MS *m/z* 404.3 $(M+H)^+$.

EXAMPLE 2
Preparation of 4'-azido-2'-deoxy-2'-fluorouridine 3',5'-cyclic thiophosphoric acid methyl ester (2a)



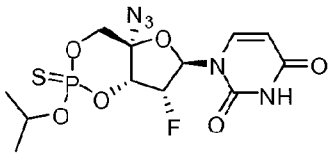
[0213] To an ice-cold suspension of 4'-azido-2'-deoxy-2'-fluorouridine (150 mg, 0.52 mmol) in dry pyridine (4 mL) was added tetrazole (0.37 M in MeCN, 4 mL, 1.48 mmol), followed by addition of methyl *N,N,N',N'*-tetraisopropylphosphordiamidite (204 mg, 0.78 mmol) dropwise over 5 min. The resultant mixture was stirred at the ambient temperature for 16 hours before bis(3-triethoxysilyl)propyl-tetrasulfide (TEST) (0.42 mL, 0.8 mmol) was added. The resulting light yellow suspension was stirred for 3 hours at room temperature. The reaction mixture was cooled down (ice/water bath), and was diluted with EA (100 mL), washed with saturated $NaHCO_3$ and followed by brine, dried over anhydrous Na_2SO_4 and concentrated *in-vacuo* to give a crude product residue. The crude product was purified by flash chromatography on silica gel and then further purified on HPLC to give compound **2a** (21.2 mg, 11%) as a white solid. ^1H NMR (CD_3OD, 400 MHz) δ 7.69 (d, J = 8.0 Hz, 1H), 6.06 (d, J = 22.0 Hz, 1H), 5.71 (d, J = 8.0 Hz, 1H), 5.67-5.52 (dd, J = 55.6 Hz, 5.6 Hz, 1H), 5.35-5.26 (dt, J = 25.6 Hz, 4.0 Hz, 1H), 4.66 (m, 2H), 3.85 (d, J = 13.6 Hz, 3H). ^{31}P NMR (CD_3OD, 162 MHz) δ 62.66. ESI-LCMS: m/z=402 $[M+Na]^+$.

EXAMPLE 3
Preparation of 4'-azido-2'-deoxy-2'-fluorouridine 3',5'-cyclic thiophosphoric acid isopropyl ester (3a)



[0214] Compound **3a** (white solid, 15.5 mg, 7.4%) was prepared using the procedure for preparing compound **2a** using 4'-azido-2'-deoxy-2',2'-difluorouridine (150 mg, 0.49 mmol) in place of 4'-azido-2'-deoxy-2'-fluorouridine, and isopropyl *N,N,N',N'*-tetraisopropylphosphordiamidite (213 mg, 0.74 mmol). ^{1}H NMR (CD_3OD, 400 MHz) δ 7.73 (d, J = 6.8 Hz, 1H), 6.35 (br, 1H), 5.77 (d, J = 8.0 Hz, 1H), 5.35 (br, 1H), 4.92 (m, 1H), 4.78 (m, 2H), 1.40 (t, 6H). ^{31}P NMR (CD_3OD, 162 MHz) δ 58.53. ESI-LCMS: m/z 426 $[M+H]^+$.

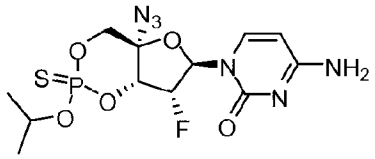
EXAMPLE 4
Preparation of 4'-azido-2'-deoxy-2'-fluorouridine 3',5'-cyclic thiophosphoric acid isopropyl ester (4a)



[0215] To an ice-cold suspension of 4'-azido-2'-deoxy-2'-fluorouridine (100 mg, 0.35 mmol) in dry pyridine (3 mL) was added tetrazole (0.37 M in MeCN, 3 mL, 1.11 mmol), followed by addition of isopropyl *N,N,N',N'*-tetraisopropylphosphordiamidite (151 mg, 0.52 mmol) dropwise after 5 min. The resultant mixture was stirred at the ambient temperature for 16 hours before TEST (0.42 mL, 0.8 mmol) was added. The resulting light yellow suspension was stirred for 3 hours at room temperature. The reaction mixture was cooled down (ice/water bath), diluted with EA (100 mL), washed with saturated aqueous $NaHCO_3$ and followed by brine, dried over anhydrous Na_2SO_4 and concentrated *in-vacuo* to give a crude product residue. The crude product was purified on silica gel (DCM/MeOH; 95:5) and then further purified on HPLC to give compound **4a** (30.5 mg, 21.6%) as a white solid. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.70 (d, J = 8.0 Hz, 1H), 6.15 (d, J = 22.4 Hz, 1H), 5.71 (d, J = 8.0 Hz, 1H), 5.62 (dd, J_1 = 5.2 Hz, J_2

= 55.6 Hz, 1H), 5.38-5.47 (m, 1H), 4.80-4.85 (m, 1H), 4.59-4.71 (m, 2H), 1.39-1.41 (m, 6H); ^{31}P NMR (CD_3OD, 162 MHz) δ 59.36; ESI-LCMS: m/z=430 $[M+Na]^+$.

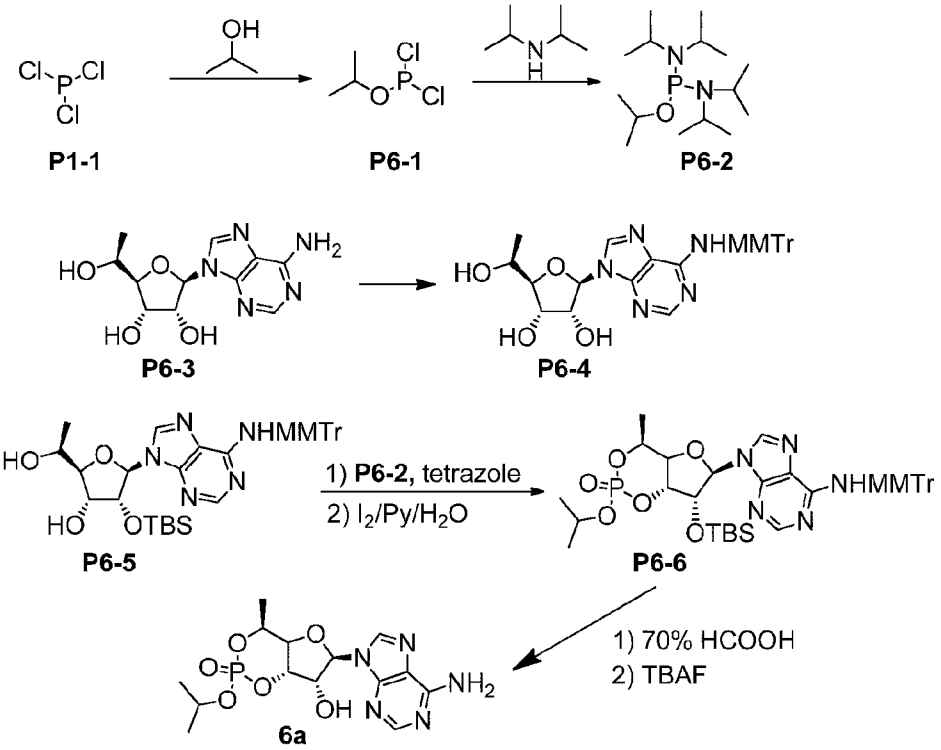
EXAMPLE 5
Preparation of 4'-azido-2'-deoxy-2'-fluorocytidine 3',5'-cyclic thiophosphoric acid isopropyl ester (5a)



[0216] Compound **5a** (white solid, 7.2 mg, 8.5%) was prepared using the procedure for preparing compound **4a** using 4'-azido-2'-deoxy-2'-fluorocytidine (60 mg, 0.21 mmol) in place of 4'-azido-2'-deoxy-2'-fluorouridine, and isopropyl *N,N,N',N'*-tetraisopropylphosphordiamidite (92 mg, 0.32 mmol). ^{1}H NMR (CD_3OD, 400 MHz) δ 7.69 (d, J = 7.6 Hz, 1H), 5.87-5.93 (m, 2H), 5.58-5.67 (m, 1H), 5.50-5.54 (m, 1H), 4.81-4.84 (m, 1H), 4.62-4.69 (m, 2H), 1.41 (t, J = 6.0 Hz, 6H); ^{31}P NMR (CD_3OD, 162 MHz) δ 59.58; ESI-LCMS: m/z 407 $[M+H]^+$.

EXAMPLE 6

Preparation of 6-(6-Amino-purin-9-yl)-2-isopropoxy-4-methyl-2-oxo-tetrahydro-2l5-furo[3,2-d][1,3,2]dioxaphosphinin-7-ol (6a)



[0217] Step 1: Compound **P6-1** – To a flask containing **P1-1** (20.0 g, 147.3 mmol) was added anhydrous i-PrOH (7.1 g, 118 mmol) dropwise over 2 hours at -40°C. The mixture was warmed to room temperature gradually and stirred for another 1 hour. The reaction mixture was distilled under reduced pressure to give pure **P6-1** (11.5 g, 61%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ4.98-5.11 (m, 1H), 1.42 (d, J= 3.2 Hz, 6H). ^{31}P NMR ($CDCl_3$, 162 MHz) δ174.48.

[0218] Step 2: Compound **P6-2** – To a solution of **P6-1** (11.5 g, 71.8 mmol) in anhydrous ether (200 mL) was added diisopropylamine (43.5 g, 430.8 mmol) dropwise at 0°C. The mixture was stirred at room temperature overnight. The precipitate was filtered and the filtrate was concentrated to give a residue which was distilled to give **P6-2** (8.8 g, 42%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.75-3.79 (m, 1H), 3.44-3.58 (m, 4H), 1.14-1.20 (m, 30H).1.42 (d, J= 3.2 Hz, 6H). ^{31}P NMR ($CDCl_3$, 162 MHz) δ 114.84.

[0219] Step 3: 2-(1-Hydroxy-ethyl)-5-(6-{[(4-methoxy-phenyl)-diphenyl-methyl]-amino}-purin-9-yl)-tetrahydro-furan-3,4-diol (**P6-4**) – To a solution of **P6-3** (4.5 g, 16 mmol) in dry pyridine (100 mL) was added TMSCl (12.2 g, 113 mmol) at 0 °C. The mixture was stirred at room temperature overnight, and then MMTrCl (10.0 g, 32.5 mmol) was added. The mixture was stirred at 40~50°C overnight. NH_4OH (300 mL) was added, and the mixture was stirred at

30~40°C overnight. The mixture was extracted with ethyl acetate and the organic layer was washed with H_2O and brine, dried by anhydrous Na_2SO_4 and filtered. The filtrate was evaporated, and the residue was purified by silica gel column chromatography (DCM: MeOH = 100:1 to 30:1) to give **P6-4** (5.8 g, 65%) as a brown solid.

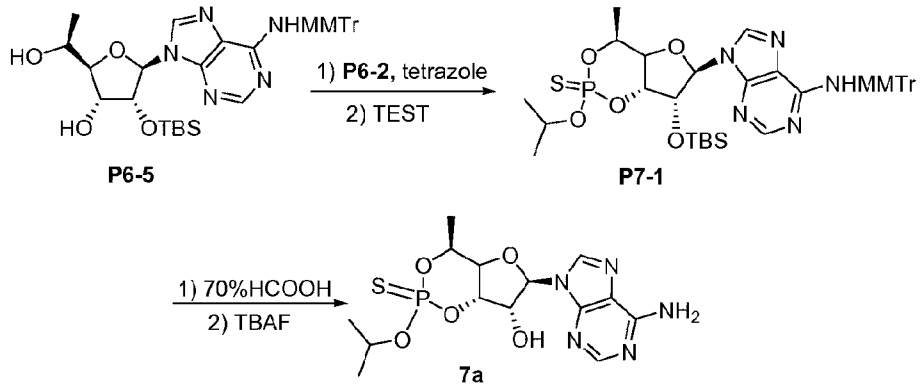
[0220] Step 4: 4-(tert-Butyl-dimethyl-silanyloxy)-2-(1-hydroxy-ethyl)-5-(6-{[(4-methoxy-phenyl)-diphenyl-methyl]-amino}-purin-9-yl)-tetrahydro-furan-3-ol (**P6-5**) – To a solution of **P6-4** (2.0 g, 3.62 mmol) in dry pyridine (40 mL) was added $AgNO_3$ (1.23 g, 7.24 mmol) and TBSCl (0.709 g, 4.71 mmol) at 0°C. The mixture was stirred at room temperature overnight and then was quenched with water. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (DCM: MeOH = 300:1 to 40:1) to give **P6-5** (0.5 g, 20.6%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ8.01 (s, 1H), 7.75 (s, 1H), 7.22-7.34 (m, 12H), 7.03 (s, 1H), 6.79 (d, J = 8.8 Hz, 1H), 6.25 (d, J = 12.0 Hz, 1H), 5.74 (d, J = 7.6 Hz, 1H), 5.29 (s, 1H), 5.05 (dd, J_1 = 7.2 Hz, J_2 = 4.8 Hz, 1H), 5.25 (d, J = 4.8 Hz, 1H), 4.18 (s, 1H), 3.89 (dd, J_1 = 11.6 Hz, J_2 = 6.4 Hz, 1H), 3.78 (s, 3H), 2.82 (bs, 1H), 1.23 (d, J = 6.4 Hz, 3H), 0.91 (s, 1H), 0.79 (s, 9H), 0.08 (s, 2H), -0.19 (s, 3H), -0.42 (s, 3H).

[0221] Step 5: {9-[7-(tert-Butyl-dimethyl-silanyloxy)-2-isopropoxy-4-methyl-2-oxo-tetrahydro-2l5-furo[3,2-d][1,3,2]dioxaphosphinin-6-yl]-9H-purin-6-yl}-[(4-methoxy-phenyl)-diphenyl-methyl]-amine (**P6-6**) – To a solution of **P6-5** (310 mg, 0.464 mmol) in dry pyridine (4 mL) was added a solution of tetrazole in MeCN (0.45 M, 4 mL) and **P6-2** (197 mg, 0.679 mmol) at 0°C. After stirring at room temperature overnight, a solution of I_2 (200 mg, 0.788 mmol) in pyridine (0.6 mL) and H_2O (0.2 mL) was added at 0°C. The mixture was stirred at room temperature for 30 min. The reaction was quenched with saturated aqueous $Na_2S_2O_3$. The solvent was removed, and the residue was purified via silica gel column chromatography (DCM: MeOH = 500:1 to 50:1) to give compound **P6-6** (190 mg, 53%).

[0222] Step 6: Compound **6a** – **P6-6** (90 mg, 0.116 mmol) was dissolved in 70% formic acid (5 mL) and stirred at room temperature overnight. Tetrabutylammonium fluoride (TBAF) (200 mg, 0.766 mmol) was added, and the mixture was stirred at room temperature for another 30 min. The solvent was removed, and the residue was purified by HPLC (0.1% HCOOH in water and MeCN) to afford compound **6a** (9.23 mg, 20.1%) as a white solid. ^{1}H NMR (MeOD, 400 MHz) δ8.21 (s, 1H), 8.18 (s, 1H), 6.01 (s, 1H), 5.80-5.84 (m, 1H), 5.00-5.09 (m, 1H), 4.83-4.85 (m, 1H), 4.79-4.71 (m, 1H), 4.50-4.54 (m, 1H), 1.42-1.50 (m, 9H). ^{31}P NMR (MeOD, 162 MHz) δ-6.07. LCMS m/z 385.8 (MH^+).

EXAMPLE 7

Preparation of 2-Isopropoxy-6-(6-{[(4-methoxy-phenyl)-diphenyl-methyl]-amino}-purin-9-yl)-4-methyl-2-thioxo-tetrahydro-2l5-furo[3,2-d][1,3,2]dioxaphosphinin-7-ol (7a)

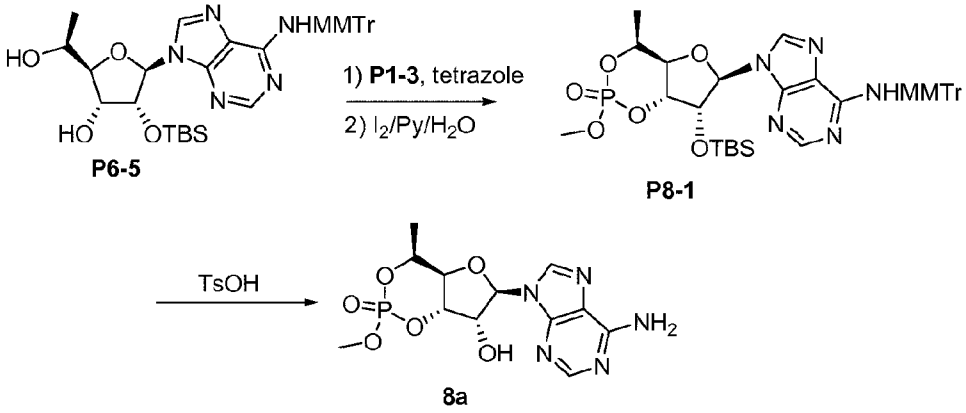


[0223] Step 1: {9-[7-(tert-Butyl-dimethyl-silanyloxy)-2-isopropoxy-4-methyl-2-thioxo-tetrahydro-2l5-furo[3,2-d][1,3,2]dioxaphosphinin-6-yl]-9H-purin-6-yl}-[(4-methoxy-phenyl)-diphenyl-methyl]-amine (**P7-1**) – To a solution of **P6-5** (584 mg, 0.876 mmol) in dry pyridine (7.5 mL) was added a solution of 0.45M tetrazole in MeCN (7.5 mL) and **P1-3** (381 mg, 1.312 mmol) at 0°C. The mixture was stirred at room temperature overnight and then Bis[3-(triethoxysilyl)propyl]tetrasulfide (TEST) (0.707 mL, 1.312 mmol) at 0°C. The mixture was stirred for another hour. The reaction mixture was concentrated and diluted with ethyl acetate, washed with saturated $NaHCO_3$ and brine, and dried over anhydrous Na_2SO_4. The organic layer was concentrated, and the residue was purified via silica gel column chromatography (DCM: MeOH = 500:1 to 50:1) to give compound **P7-1** (105 mg, 15%).

[0224] Step 2: Compound **7a** – Compound **P7-1** (80 mg, 0.102 mmol) was dissolved in 70% formic acid (10 mL) and stirred overnight. The solvent was evaporated, and the residue was dissolved in THF (2 mL). TBAF (162 mg, 0.62 mmol) was added, and the mixture was stirred for 30 min. The solvent was removed, and the residue was purified by preparative HPLC (0.1% HCOOH in water and MeCN) to afford compound **7a** (15.81 mg, 36.6%) as a white solid. ^{1}H NMR (MeOD, 400 MHz) δ 8.25 (s, 1H), 8.22 (s, 1H), 6.00 (s, 1H), 5.54-5.57 (m, 1H), 5.01-5.06 (m ,1H), 4.69-4.85 (m, 3H), 1.36-1.45 (m, 9H). ^{31}P NMR (MeOD, 162 MHz) δ 62.28, 62.03. LCMS *m/z* 402.0 (MH^+).

EXAMPLE 8

Preparation of 2-Methoxy-6-(6-{[(4-methoxy-phenyl)-diphenyl-methyl]-amino}-purin-9-yl)-4-methyl-2-oxo-tetrahydro-2l5-furo[3,2-d][1,3,2]dioxaphosphinin-7-ol (8a)



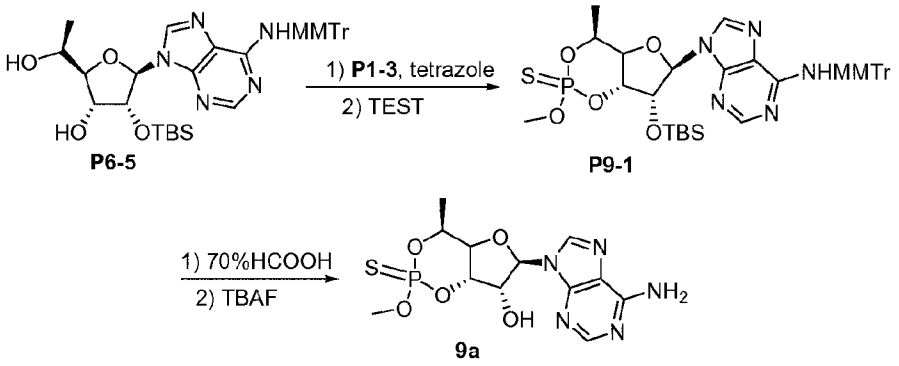
P6-5 P8-1 8a

[0225] Step 1: {9-[7-(tert-Butyl-dimethyl-silanyloxy)-2-methoxy-4-methyl-2-oxo-tetrahydro-2l5-furo[3,2-d][1,3,2]dioxaphosphinin-6-yl]-9H-purin-6-yl}-[(4-methoxy-phenyl)-diphenyl-methyl]-amine (**P8-1**) – To a solution of **P6-5** (500 mg, 0.750 mmol) in dry pyridine (7 mL) was added a solution of 0.45M tetrazole in MeCN (7 mL) and **P1-3** (324 mg, 1.236 mmol) at 0°C. After stirring at room temperature overnight, a solution of I_2 (300 mg, 1.182 mmol) in pyridine (0.9 mL) and H_2O (0.3 mL) was added at 0°C. The mixture was stirred at room temperature for 30 min and quenched with saturated aqueous $Na_2S_2O_3$. The solvent was removed, and the residue was purified via silica gel column chromatography (DCM: MeOH = 500:1 to 50:1) to give **P8-1** (216 mg, 38.8%).

[0226] Step 2: Compound **8a** – To a solution of **P8-1** (216 mg, 0.291 mmol) in DCM (3.2 mL) was added $TsOH \cdot H_2O$ (307 mg, 1.615 mmol). The mixture was warmed to room temperature and stirred overnight. The reaction was quenched with saturated aqueous Na_2CO_3. The organic layer was evaporated, and the residue was purified by preparative HPLC (0.1% HCOOH in water and MeCN) to afford compound **8a** (10.33 mg, 9.6%) as a white solid. ^1H NMR (MeOD, 400 MHz) δ 8.24 (s, 1H), 8.23 (s, 1H), 6.04 (s, 1H), 5.66-5.73 (m, 1H), 5.04-5.12 (m, 1H), 4.81-4.84 (m, 1H), 4.52-4.67 (m, 1H), 3.88 (2d, J = 11.6 Hz, 3H), 1.43-1.47 (m, 3H). ^{31}P NMR (MeOD, 162 MHz) δ 3.59-3.91. LCMS m/z 357.9 (MH^+).

EXAMPLE 9

Preparation of 2-Methoxy-6-(6-{[(4-methoxy-phenyl)-diphenyl-methyl]-amino}-purin-9-yl)-4-methyl-2-thioxo-tetrahydro-2l5-furo[3,2-d][1,3,2]dioxaphosphinin-7-ol (9a)

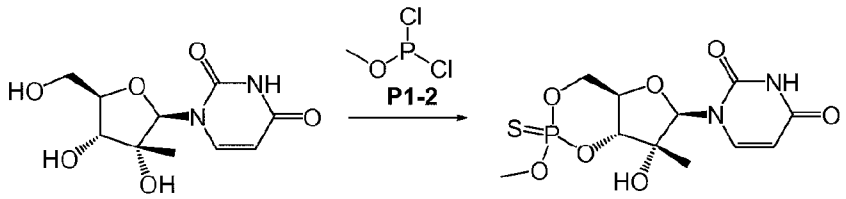


P6-5 P9-1 9a

[0227] Step 1: {9-[7-(tert-Butyl-dimethyl-silanyloxy)-2-methoxy-4-methyl-2-thioxo-tetrahydro-2l5-furo[3,2-d][1,3,2]dioxaphosphinin-6-yl]-9H-purin-6-yl}-[(4-methoxy-phenyl)-diphenyl-methyl]-amine (**P9-1**) – To a solution of **P6-5** (190 mg, 0.285 mmol) in dry pyridine (2.5 mL) was added a solution of 0.45M tetrazole in MeCN (2.5 mL) and **P1-3** (118 mg, 0.450 mmol) at 0°C. After stirring at room temperature overnight, Bis[3-(triethoxysilyl)propyl]tetrasulfide (TEST) was added (0.194 mL, 0.36 mmol) at 0°C. The mixture was stirred for 1 hour, and the reaction mixture was concentrated, diluted with ethyl acetate, washed with saturated $NaHCO_3$ and brine, and dried over anhydrous Na_2SO_4. The organic layer was concentrated, and the residue was purified via a silica gel column chromatography (DCM: MeOH=500:1 to 50:1) to give **P9-1** (375 mg, crude).

[0228] Step 2: Compound **9a** – Compound **P9-1** (375 mg, crude) was dissolved in 70% formic acid (10 mL) and stirred overnight. The solvent was evaporated, and the residue was dissolved in THF (10 mL). TBAF (191 mg, 0.73 mmol) was added, and the mixture was stirred for 30 min. The solvent was removed, and the residue was purified by preparative HPLC (0.1% HCOOH in water and MeCN) to afford compound **9a** (10.2 mg, 5.5% total yield over steps 1 and 2) as a white solid. ^{1}H NMR (MeOD, 400 MHz) δ 8.25 (s, 1H), 8.22 (s, 1H), 6.01 (s, 1H), 5.54-5.65 (m, 1H), 5.03-5.08 (m, 1H), 4.51-4.81 (m, 2H), 3.83 (2d, J = 14.0 Hz, 3H), 1.40-1.48 (m, 3H). ^{31}P NMR (MeOD, 162 MHz) δ 65.09. LCMS m/z 374.0 (MH^+).

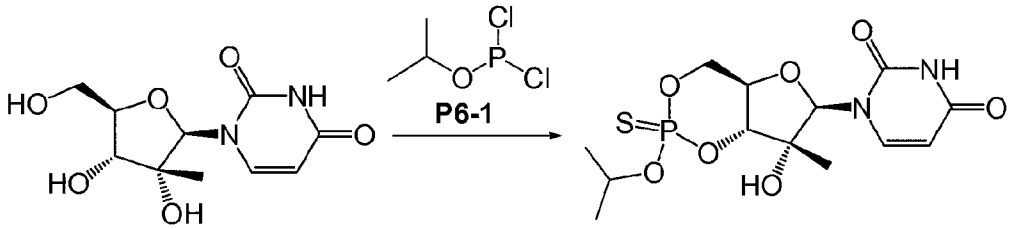
EXAMPLE 10
Preparation of 1-(7-Hydroxy-2-methoxy-7-methyl-2-thioxo-tetrahydro-2l5-furo[3,2-d][1,3,2]dioxaphosphinin-6-yl)-1H-pyrimidine-2,4-dione (10a)



P10-1 10a

[0229] To a solution of **P10-1** (320 mg, 1.24 mmol) in dry pyridine (9.0 mL) was added a solution of 0.45 M tetrazole in MeCN (9 mL) and **P1-2** (390 mg, 1.49 mmol) at 0°C. The reaction mixture was stirred at room temperature overnight, and bis[3-(triethoxysilyl)propyl]tetrasulfide (803 mg, 1.49 mmol) was then added at 0°C. The mixture was stirred for another hour. The reaction mixture was concentrated and diluted with ethyl acetate, washed with saturated $NaHCO_3$ and brine, and dried over anhydrous Na_2SO_4. The organic layer was concentrated, and the residue was purified by HPLC (MeCN and 0.1% HCOOH in water) to give compound **10a** as a white solid (35 mg, 7.7%). ^1H NMR (MeOD, 400 MHz) δ 7.63-7.65 (d J = 8.0 Hz, 1H), 6.07 (s, 1H), 5.75-5.79 (m, 1H), 4.60-4.70 (m, 1H), 4.21-4.46 (m, 1H), 4.10-4.12 (m, 1H), 3.81-3.90 (m, 3H), 1.26 (m, 3H). ^{31}P NMR (MeOD, 162 MHz) δ 64.3, 67.1. ESI-LCMS m/z 350.9 $[M + H]^+$.

EXAMPLE 11
Preparation of 1-(7-Hydroxy-2-isopropoxy-7-methyl-2-thioxo-tetrahydro-2l5-furo[3,2-d][1,3,2]dioxaphosphinin-6-yl)-1H-pyrimidine-2,4-dione (11a)

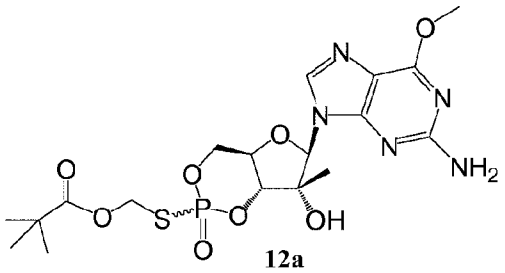


P10-1 11a

[0230] To a solution of **P10-1** (155 mg, 0.60 mmol) in dry pyridine (4.0 mL) was added a solution of 0.45 M tetrazole in MeCN (3.33 mL) and **P6-1** (190 mg, 0.72 mmol) at 0°C. The reaction mixture was stirred at room temperature overnight, and bis[3-(triethoxysilyl)propyl]tetrasulfide (388 mg, 0.72 mmol) was then added at 0°C. The mixture was stirred for another hour. The reaction mixture was concentrated and diluted with ethyl acetate, washed with saturated $NaHCO_3$ and brine, and dried over anhydrous Na_2SO_4. The organic layer was concentrated, and the residue was purified by HPLC (MeCN and 0.1%

HCOOH in water) to give compound **11a** as a white solid (21 mg, 9.1%). ^{1}H NMR (MeOD, 400 MHz) δ 7.61-7.66 (m, 1H), 6.08 (s, 1H), 5.78-5.80 (m, 1H), 4.82-4.97 (m, 1H), 4.61-4.66 (m, 1H), 4.29-4.43 (m ,1H), 4.09-4.23 (m, 1H), 1.37-1.42 (m, 6H), 1.25 (s, 3H). ^{31}P NMR (MeOD, 162 MHz) δ65.2, 61.3. ESI-LCMS *m/z* 379.0 $[M + H]^+$.

EXAMPLE 12
Preparation of 2′-*C*,*O*^{6}-Dimethylguanosine 3′,5′-cyclic *O*-pivaloyloxymethyl phosphorothioate (12a)



12a

[0231] Step 1: Iodomethyl pivalate – Chloromethyl pivalate (1.0 mL, 6.90 mmol) was added to a mixture of NaI (2.08 g, 13.80 mmol) and dry MeCN (10 mL). The reaction mixture was stirred at room temperature overnight in the dark. The mixture was evaporated to dryness. The resulting residue was dissolved in dichloromethane and washed with 5% aqueous $NaHSO_3$ and brine. The organic layer was dried over Na_2SO_4 and evaporated to dryness. The resulting iodomethyl pivalate was used without further purification in the next step.

[0232] Step 2: Compound **12a** – N^2-(4-Methoxytrityl)-2′-*C*,*O*^{6}-dimethylguanosine 3′,5′-cyclic phosphorothioate was dissolved in dry MeCN (3 mL) and iodomethyl pivalate (56 mg g, 0.23 mmol) was added. The reaction mixture was stirred for 2.5 hours at room temperature. Saturated aqueous $NaHCO_3$ was added, and the crude product was extracted with dichloromethane. The organic layer was dried over Na_2SO_4 and evaporated to dryness. The residue was dissolved in 80% aqueous acetic acid (2.0 mL), and the reaction mixture was stirred at room temperature for 20 hours. The reaction mixture was evaporated to dryness, and the resulting residue was coevaporated twice with water. The crude product was purified by silica gel chromatography eluting with dichlroromethane containing 10% MeOH. Compound **12a** was obtained as white solid in 14% yield (15.0 mg). ^{1}H NMR (500 MHz, CD_3OD) δ: 7.95 (s, 1H, H8); 5.93 (s, 1H, H1′), 5.58-5.54 (m, 2H, SCH_2), 4.80-4.69 (m, 3H, H3′, H4′, H5′′); 4.45 (m, 1H, H5′); 4.06 (s, 3H, OMe); 1.20 (s, 3H, $C(Me)_3$); 1.10 (s, 1H, 2′-Me). ^{13}C NMR (126 MHz, CD_3OD) δ: 177.48 (C=O), 161.50 (C6), 160.22 (C2), 152.66 (C4), 139.14 (C8), 129.34 (C5), 95.15 (C1′), 81.87 (C3′), 76.76 and 76.70 (C2′), 71.00, 70.93, 70.80 and 70.81 (C4′ and C5′), 60.23 and 60.20 (SCH_2), 52.87 (OMe), 38.52 (spiro C of Piv), 25.85 ($C(Me)_3$), 18.18 (2′-Me).

^{31}P NMR (202 MHz, CD_3OD) δ: 23.13. HR-ESI-MS: $[M+H]^+$ observed 504.1323, calculated 504.1312.

EXAMPLE 13
HCV Replicon Assay

Cells

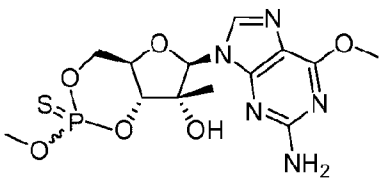
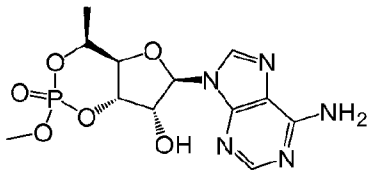
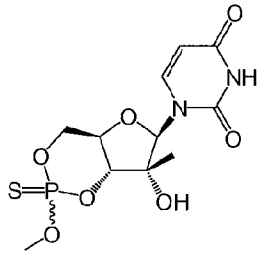
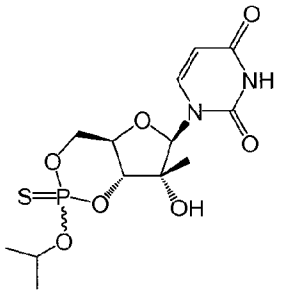
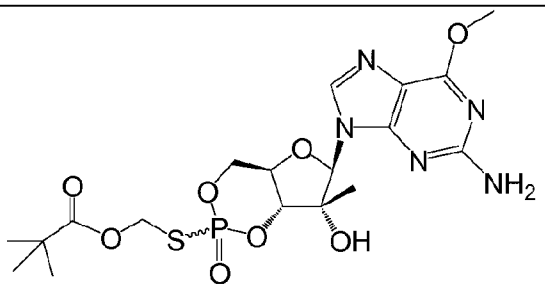
[0233] Huh-7 cells containing the self-replicating, subgenomic HCV replicon with a stable luciferase (LUC) reporter were cultured in Dulbecco's modified Eagle's medium (DMEM) containing 2mM L-glutamine and supplemented with 10% heat-inactivated fetal bovine serum (FBS), 1% penicillin-streptomyocin, 1% nonessential amino acids, and 0.5 mg/mL G418.

Determination of anti-HCV activity

[0234] Determination of 50% inhibitory concentration (EC_{50}) of compounds in HCV replicon cells were performed by the following procedure. On the first day, 5,000 HCV replicon cells were plated per well in a 96-well plate. On the following day, test compounds were solubilized in 100% DMSO to 100x the desired final testing concentration. Each compound was then serially diluted (1:3) up to 9 different concentrations. Compounds in 100% DMSO are reduced to 10% DMSO by diluting 1:10 in cell culture media. The compounds were diluted to 10% DMSO with cell culture media, which were used to dose the HCV replicon cells in 96-well format. The final DMSO concentration was 1%. The HCV replicon cells were incubated at 37°C for 72 hours. At 72 hours, cells were processed when the cells are still subconfluent. Compounds that reduce the LUC signal are determined by Bright-Glo Luciferase Assay (Promega, Madison, WI). % Inhibition was determined for each compound concentration in relation to the control cells (untreated HCV replicon) to calculate the EC_{50}.

[0235] Compounds of Formula (I) are active in the replicon assay. The antiviral activity of exemplary compounds is shown in Table 5, where 'A' indicates an $EC_{50} < 1$ μM, 'B' indicates an $EC_{50} \geq 1$ μM and < 10 μM, and 'C' indicates an $EC_{50} \geq 10$ μM and < 100 μM.

Table 5

No.	Compound	EC_{50}
1a		A
8a		C
10a		C
11a		B
12a		A

EXAMPLE 14
Combination of Compounds

Combination Testing

[0236] Two or more test compounds are tested in combination with each other using an HCV genotype 1b HCV replicon harbored in Huh7 cells with a stable luciferase (LUC) reporter. Cells are cultured under standard conditions in Dulbecco's modified Eagle's medium

(DMEM; Mediatech Inc, Herndon, VA) containing 10% heat-inactivated fetal bovine serum (FBS; Mediatech Inc, Herndon, VA) 2mM L-glutamine, and nonessential amino acids (JRH Biosciences). HCV replicon cells are plated in a 96-well plate at a density of 10^4 cells per well in DMEM with 10% FBS. On the following day, the culture medium is replaced with DMEM containing either no compound as a control, the test compounds serially diluted in the presence of 2% FBS and 0.5% DMSO, or a combination of one or more test compounds serially diluted in the presence of 2% FBS and 0.5% DMSO. The cells are incubated with no compound as a control, with the test compounds, or the combination of compounds for 72 h. The direct effects of the combination of the test compounds are examined using a luciferase (LUC) based reporter as determined by the Bright-Glo Luciferase Assay (Promega, Madison, WI). Dose-response curves are determined for individual compounds and fixed ratio combinations of two or more test compounds.

[0237] The effects of test compound combinations are evaluated by two separate methods. In the Loewe additivity model, the experimental replicon data is analyzed by using CalcuSyn (Biosoft, Ferguson, MO), a computer program based on the method of Chou and Talalay. The program uses the experimental data to calculate a combination index (CI) value for each experimental combination tested. A CI value of <1 indicates a synergistic effect, a CI value of 1 indicates an additive effect, and a CI value of >1 indicates an antagonistic effect.

[0238] The second method that is utilized for evaluating combination effects uses a program called MacSynergy II. MacSynergy II software was kindly provided by Dr. M. Prichard (University of Michigan). The Prichard Model allows for a three-dimensional examination of drug interactions and a calculation of the synergy volume (units: $\mu M^2\%$) generated from running the replicon assay using a checkerboard combination of two or more inhibitors. The volumes of synergy (positive volumes) or antagonism (negative volumes) represent the relative quantity of synergism or antagonism per change in the concentrations of the two drugs. Synergy and antagonism volumes are defined based on the Bliss independence model. In this model, synergy volumes of less than -25 indicate antagonistic interactions, volumes in the -25 – 25 range indicate additive behavior, volumes in the 25 – 100 range indicate synergistic behavior and volumes >100 indicate strong synergistic behavior. Determination of in vitro additive, synergistic and strongly synergistic behavior for combinations of compounds can be of utility in predicting therapeutic benefits for administering the combinations of compounds in vivo to infected patients.

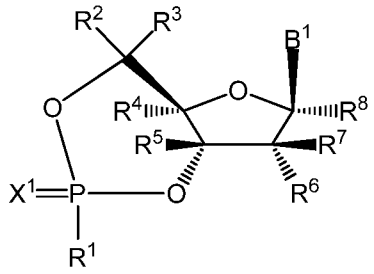
[0239] Furthermore, although the foregoing has been described in some detail by way of illustrations and examples for purposes of clarity and understanding, it will be

understood by those of skill in the art that numerous and various modifications can be made without departing from the spirit of the present disclosure. Therefore, it should be clearly understood that the forms disclosed herein are illustrative only and are not intended to limit the scope of the present disclosure, but rather to also cover all modification and alternatives coming with the true scope and spirit of the invention.

[0240] It is to be understood that, if any prior art publication is referred to herein, such reference does not constitute an admission that the publication forms a part of the common general knowledge in the art, in Australia or any other country.

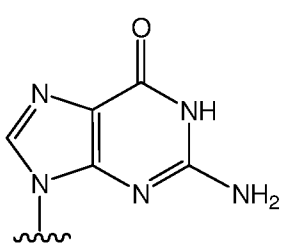
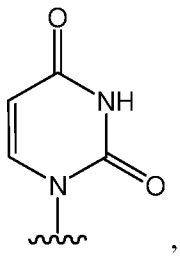
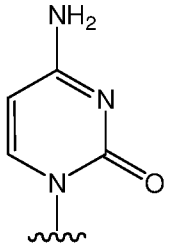
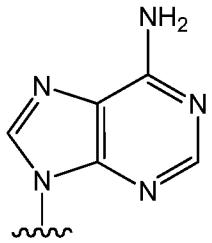
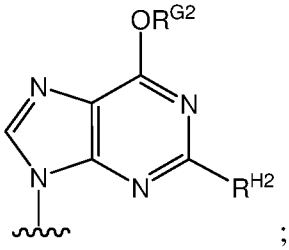
WHAT IS CLAIMED IS

1. A compound of Formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

B^1 is selected from the group consisting of  ,  ,  ,  and  ;

R^{G2} is an unsubstituted C_{1-6} alkyl;

R^{H2} is hydrogen or NH_2;

X^1 is S (sulfur);

R^1 is selected from the group consisting of $-Z^1-R^9$, an optionally substituted N-linked amino acid and an optionally substituted N-linked amino acid ester derivative;

Z^1 is selected from the group consisting of O (oxygen), S (sulfur) and $N(R^{10})$;

R^2 and R^3 are each hydrogen;

R^4 is selected from the group consisting of hydrogen and azido;

R^5 is hydrogen;

R^6 is selected from the group consisting of hydrogen, halogen, azido, $-OR^{11}$ and $-OC(=O)R^{12}$;

R^7 is selected from the group consisting of halogen and an optionally substituted C_{1-6} alkyl;

R^8 is hydrogen;

R^9 is selected from the group consisting of an unsubstituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl, an optionally substituted aryl(C_{1-6} alkyl), an optionally substituted heteroaryl(C_{1-6} alkyl) and an optionally substituted heterocyclyl(C_{1-6} alkyl);

R^{10} is hydrogen;

R^{11} is hydrogen or an optionally substituted C_{1-6} alkyl; and

R^{12} is an optionally substituted C_{1-6} alkyl or an optionally substituted C_{3-6} cycloalkyl.

2. The compound of Claim 1, wherein R^1 is $-Z^1-R^9$.

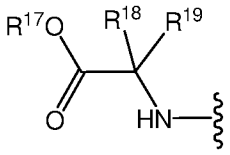
3. The compound of Claim 2, wherein Z^1 is O.

4. The compound of Claim 2, wherein Z^1 is S.

5. The compound of Claim 2, wherein Z^1 is $N(R^{10})$.

6. The compound of Claim 1, wherein R^1 is an optionally substituted N–linked α-amino acid or an optionally substituted N–linked α-amino acid ester derivative.

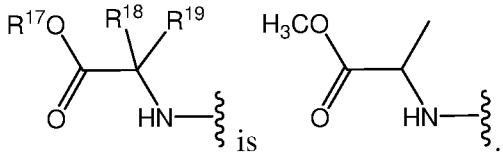
7. The compound of Claim 1 or 6, wherein R^1 is selected from the group consisting of alanine, asparagine, aspartate, cysteine, glutamate, glutamine, glycine, proline, serine, tyrosine, arginine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, valine and ester derivatives thereof.

8. The compound of Claim 1, wherein R^1 has the structure 

wherein R^{17} is selected from the group consisting of hydrogen, an optionally substituted C_{1-6}-alkyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted aryl, an optionally substituted aryl(C_{1-6} alkyl) and an optionally substituted C_{1-6} haloalkyl; R^{18} is selected from the group consisting of hydrogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{1-6} haloalkyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted C_6 aryl, an optionally substituted C_{10} aryl and an optionally substituted aryl(C_{1-6} alkyl); and R^{19} is hydrogen or an optionally substituted C_{1-4}-alkyl; or R^{18} and R^{19} are taken together to form an optionally substituted C_{3-6} cycloalkyl.

9. The compound of Claim 8, wherein R^{18} is an optionally substituted C_{1-6}-alkyl.

10. The compound of Claim 9, wherein the optionally substituted C_{1-6}-alkyl is substituted one or more substituents selected from the group consisting of N-amido, mercapto, alkylthio, an optionally substituted aryl, hydroxy, an optionally substituted heteroaryl, O-carboxy, and amino.

11. The compound Claim 8, wherein  is .

12. The compound of any one of Claims 1 to 11, wherein R^6 is hydrogen, halogen or an optionally substituted C_{1-6} alkyl.

13. The compound of any one of Claims 1 to 11, wherein R^6 is $-OR^{11}$.

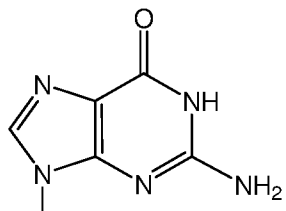
14. The compound of Claim 13, wherein R^{11} is hydrogen or an optionally substituted C_{1-6} alkyl.

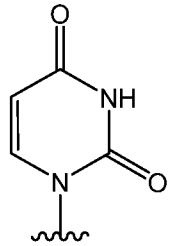
15. The compound of any one of Claims 1 to 11, wherein R^6 is $-OC(=O)R^{12}$.

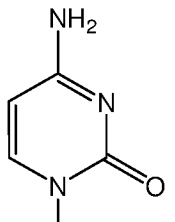
16. The compound of any one of Claims 1 to 15, wherein R^7 is halogen or an optionally substituted C_{1-6} alkyl.

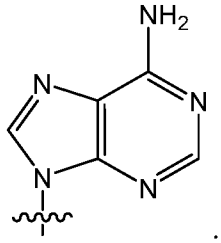
17. The compound of Claim 16, wherein R^7 is methyl.

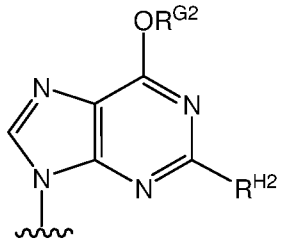
18. The compound of Claim 2, wherein R^1 is $-Z-R^9$; Z^1 is O, S or $N(R^{10})$; and R^9 is selected from the group consisting of an unsubstituted alkyl, an optionally substituted aryl and an optionally substituted aryl(C_{1-6} alkyl).

19. The compound of any one of Claims 1-18, wherein B^1 is  .

20. The compound of any one of Claims 1-18, wherein B^1 is  .

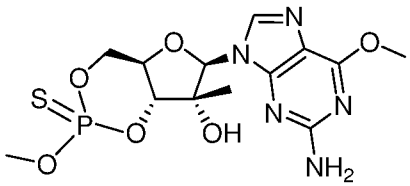
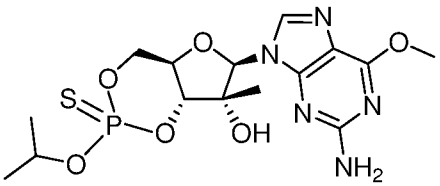
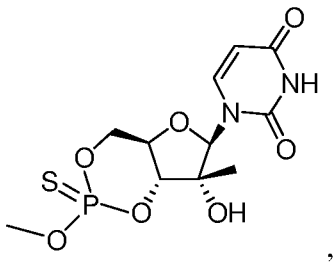
21. The compound of any one of Claims 1-18, wherein B^1 is  .

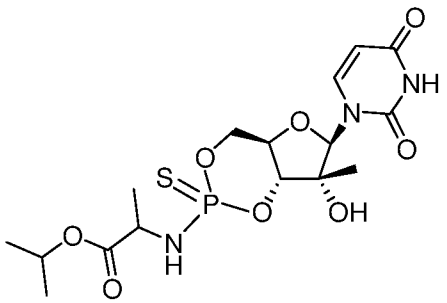
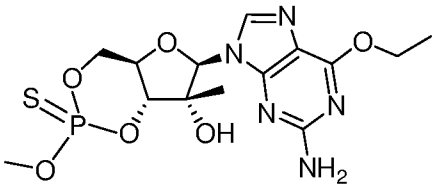
22. The compound of any one of Claims 1-18, wherein B^1 is  .

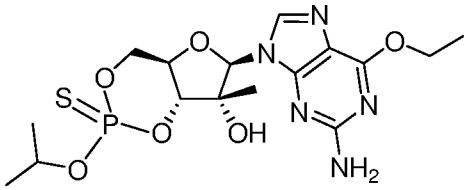
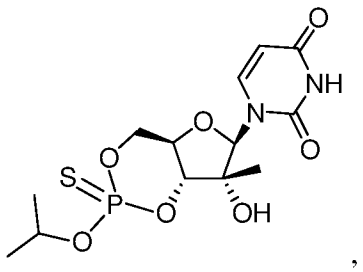
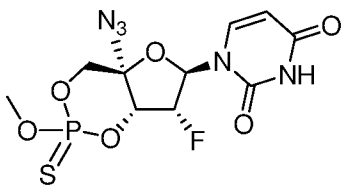
23. The compound of any one of Claims 1-18, wherein B^1 is  .

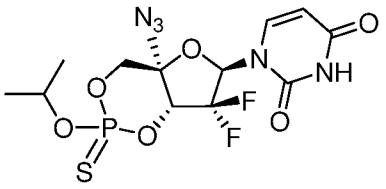
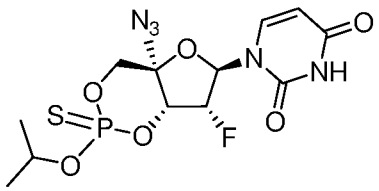
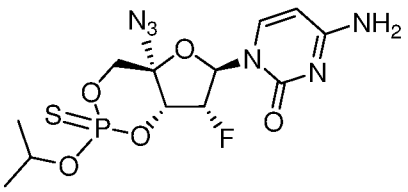
24. The compound of Claim 23, wherein R^{G2} is methyl or ethyl.

25. The compound of Claim 1, wherein the compound of Formula (I) is selected from the group consisting of:

 ,  ,  ,

 ,  ,

 ,  ,  .



and

, or a pharmaceutically acceptable salt of any of the foregoing.

26. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any one of Claims 1 to 25, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, excipient or combination thereof.

27. Use of a compound of any one of Claims 1 to 25, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Claim 26 for preparing a medicament for ameliorating or treating a neoplastic disease.

28. Use of a compound of any one of Claims 1 to 25, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Claim 26 for preparing a medicament for ameliorating or treating a viral infection.

29. The use of Claim 28, wherein the viral infection is caused by a virus selected from the group consisting of an adenovirus, an Alphaviridae, an Arbovirus, an Astrovirus, a Bunyaviridae, a Coronaviridae, a Filoviridae, a Flaviviridae, a Hepadnaviridae, a Herpesviridae, an Alphaherpesvirinae, a Betaherpesvirinae, a Gammaherpesvirinae, a Norwalk Virus, an Astroviridae, a Caliciviridae, an Orthomyxoviridae, a Paramyxoviridae, a Paramyxoviruses, a Rubulavirus, a Morbillivirus, a Papovaviridae, a Parvoviridae, a Picornaviridae, an Aphthoviridae, a Cardioviridae, an Enteroviridae, a Coxsackie virus, a Polio Virus, a Rhinoviridae, a Phycodnaviridae, a Poxviridae, a Reoviridae, a Rotavirus, a Retroviridae, an A-Type Retrovirus, an Immunodeficiency Virus, a Leukemia Viruses, an Avian Sarcoma Viruses, a Rhabdoviruses, a Rubiviridae and a Togaviridae.

30. Use of a compound of any one of Claims 1 to 25, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Claim 26 for preparing a medicament for ameliorating or treating an HCV infection.

31. Use of a compound of any one of Claims 1 to 25, or a pharmaceutically acceptable salt thereof, for preparing a medicament for inhibiting NS5B polymerase activity of HCV.

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32. Use of a compound of any one of Claims 1 to 25, or a pharmaceutically acceptable salt thereof, for preparing a medicament for inhibiting replication of HCV.

33. The use of any one of Claims 30 to 32, further comprising the use of one or more agents selected from the group consisting of an interferon, ribavirin, a HCV protease inhibitor, a HCV polymerase inhibitor, a NS5A inhibitor, an antiviral compound, a compound of Formula (AA), a mono-, di- or tri-phosphate thereof, a compound of Formula (CC) and a compound of Formula (DD), or a pharmaceutically acceptable salt any of the aforementioned compounds.

34. The use of Claim 33, wherein the one or more agents are selected from the group consisting of Compounds 1001-1014, 2001-2010, 3001-3008, 4001-4005, 5001-5002, 6000-6078, 7000-7077 or 9000, or a pharmaceutically acceptable salt of any of the aforementioned compounds.

35. A method of ameliorating or treating a neoplastic disease comprising administering an effective amount of a compound of any one of Claims 1 to 25, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Claim 26 to a subject suffering from the neoplastic disease.

36. A method of ameliorating or treating a viral infection comprising administering an effective amount of a compound of any one of Claims 1 to 25, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Claim 26 to a subject suffering from the viral infection.

37. The method of Claim 36, wherein the viral infection is caused by a virus selected from the group consisting of an adenovirus, an Alphaviridae, an Arbovirus, an Astrovirus, a Bunyaviridae, a Coronaviridae, a Filoviridae, a Flaviviridae, a Hepadnaviridae, a Herpesviridae, an Alphaherpesvirinae, a Betaherpesvirinae, a Gammaherpesvirinae, a Norwalk Virus, an Astroviridae, a Caliciviridae, an Orthomyxoviridae, a Paramyxoviridae, a Paramyxoviruses, a Rubulavirus, a Morbillivirus, a Papovaviridae, a Parvoviridae, a Picornaviridae, an Aphthoviridae, a Cardioviridae, an Enteroviridae, a Coxsackie virus, a Polio Virus, a Rhinoviridae, a Phycodnaviridae, a Poxviridae, a Reoviridae, a Rotavirus, a Retroviridae, an A-Type Retrovirus, an Immunodeficiency Virus, a Leukemia Viruses, an Avian Sarcoma Viruses, a Rhabdoviruses, a Rubiviridae and a Togaviridae.

38. A method for ameliorating or treating an HCV infection comprising administering to a subject suffering from an HCV infection a therapeutically effective amount of a compound of any one of Claims 1 to 25, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Claim 26.

39. A method for inhibiting NS5B polymerase activity of HCV comprising contacting a cell infected with the virus with an effective amount of a compound of any one of Claims 1 to 25, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Claim 26.

40. A method for ameliorating or treating a HCV infection comprising contacting a cell infected with the virus with a compound of any one of Claims 1 to 25, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Claim 26.

41. A method for inhibiting replication of HCV comprising contacting a cell infected with the virus with a compound of any one of Claims 1 to 25, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Claim 26.

42. The method of any one of Claims 38 to 40, further comprising the use of one or more agents selected from the group consisting of an interferon, ribavirin, a HCV protease inhibitor, a HCV polymerase inhibitor, a NS5A inhibitor, an antiviral compound, a compound of Formula (AA), a mono-, di- or tri-phosphate thereof, a compound of Formula (CC) and a compound of Formula (DD), or a pharmaceutically acceptable salt any of the aforementioned compounds.

43. The method of Claim 42, wherein the one or more agents are selected from the group consisting of Compounds 1001-1014, 2001-2010, 3001-3008, 4001-4005, 5001-5002, 6000-6078, 7000-7077 or 9000, or a pharmaceutically acceptable salt of any of the aforementioned compounds.

Figure 1A: HCV Protease Inhibitors

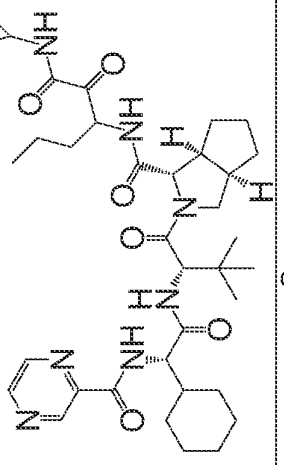
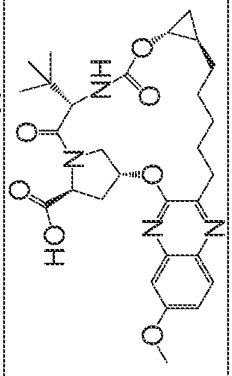
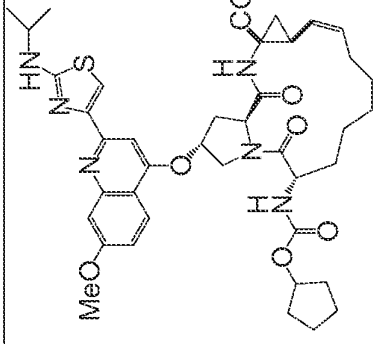
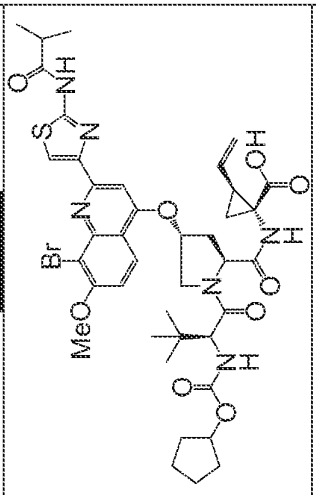
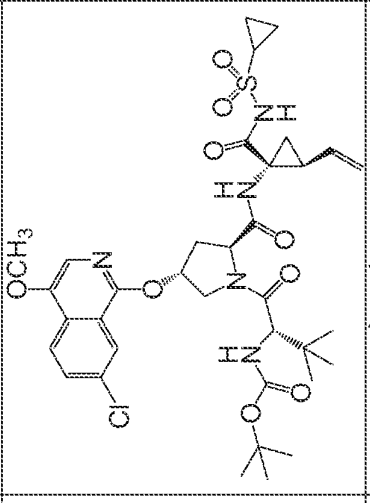
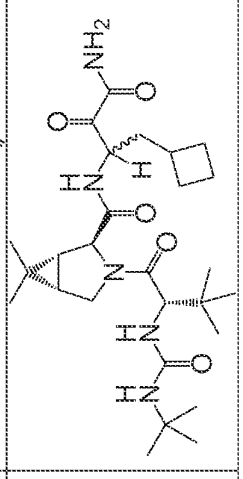
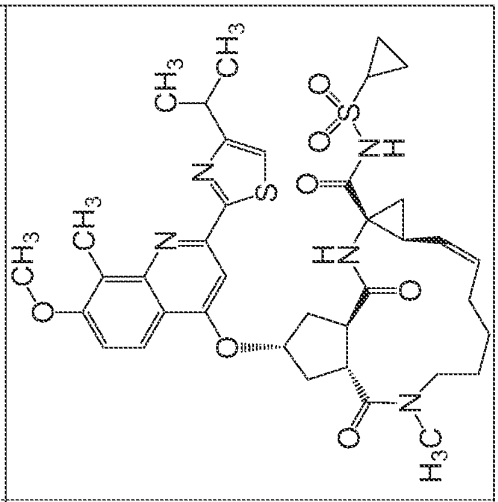
#	Name	Structure
1001	Telaprevir VX-950	
1002	MK-5172	
1003	ABT-450	
1004	BILN-2061	
1005	BI-201335	
1006	BMS-650032	
1007	Boceprevir SCH 503034	

Figure 1B: HCV Protease Inhibitors

#	Name	Structure
1008	GS-9256	
1009	GS-9451	
1010	IDX-320	
1011	ACH-1625	
1012	ACH-2684	
1013	TMC-435 TMC-435350	

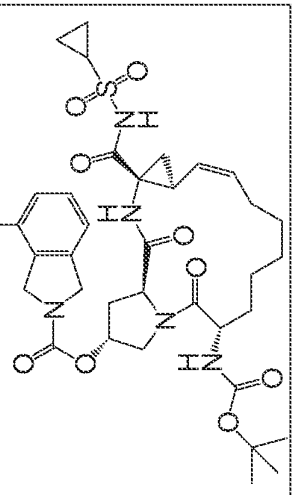
#	Name	Structure
1014	Danoprevir ITMN-191 RG7227 RO5190591	

Figure 2: HCV Polymerase Inhibitors – Nucleosides, Nucleotides and Analogs Thereof

#	Name	Structure
2001	RG7128	
2002	PSI-7851	
2003	PSI-7977	
2004	INX-189	
2005	PSI-352938	
2006	4'-azidouridine and its prodrugs	
2007	PSI-661	
2008	GS-6620	
2009	IDX-184	
2010	TMC649128	

Figure 3: HCV Polymerase Inhibitors – Non-Nucleosides

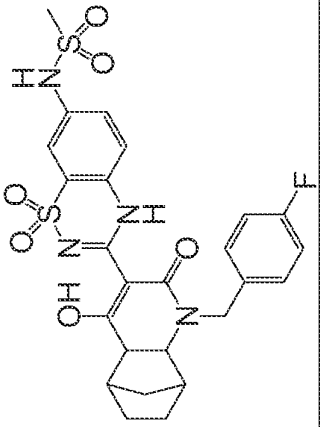
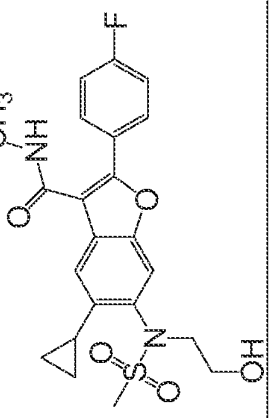
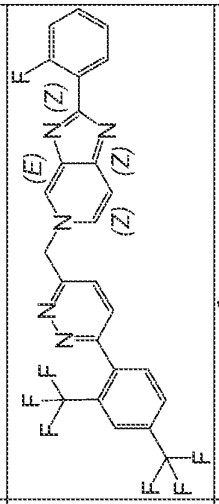
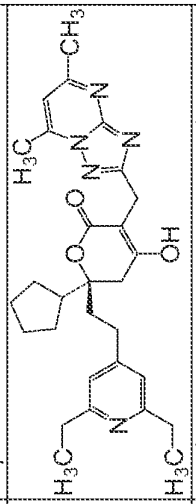
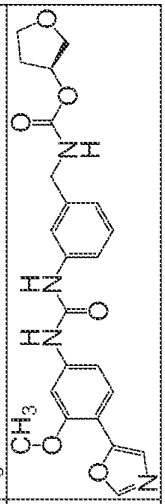
#	Name	Structure
3001	ABT-333	
3002	ANA-598	
3003	VX-222 S1480 VCH-222	
3004	HCV-796	
3005	BI-207127	
3006	GS-9190	
3007	Filibuvir PF- 00868554	
3008	VX-497	

Figure 4: NS5A Inhibitors

#	Name	Structure
4001	BMS-790052 S1482	
4002	PPI-461	
4003	ACH-2928	
4004	GS-5885	
4005	BMS-824393	

Figure 5: Other Antivirals

#	Name
5001	Debio-025
5002	MIR-122

Figure 6A: Compounds of Formula (CC)

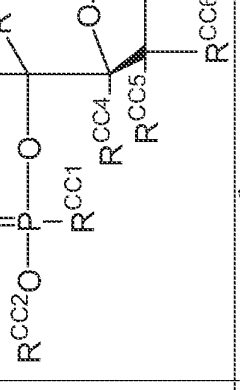
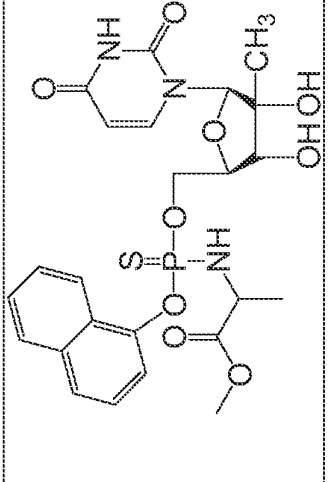
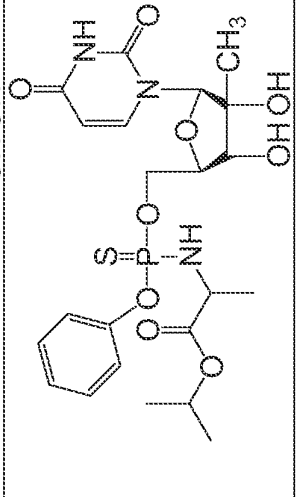
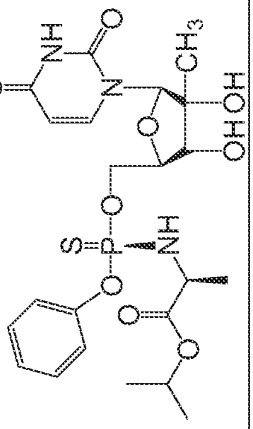
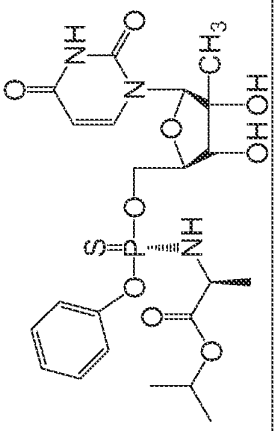
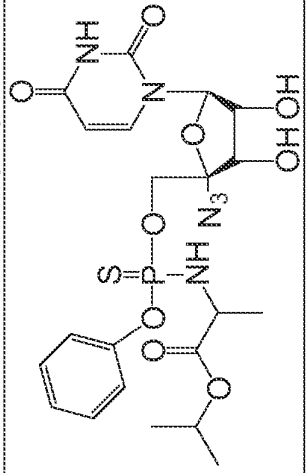
#	Structure
6000	
6001	
6002	
6003	
6004	
6005	

Figure 6B: Compounds of Formula (CC)

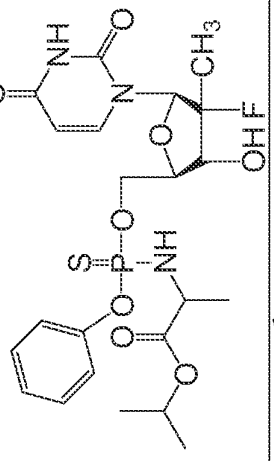
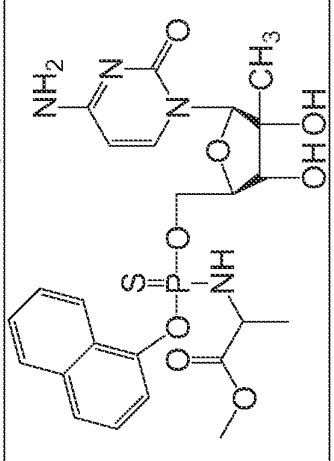
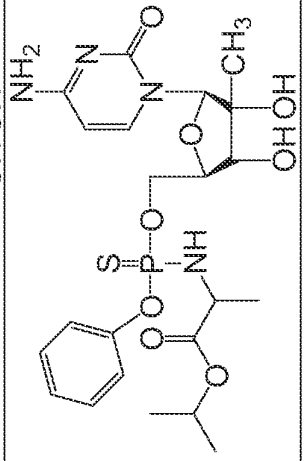
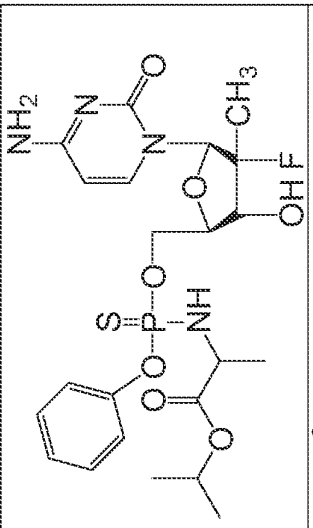
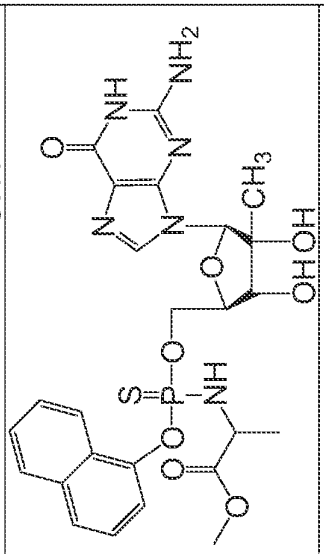
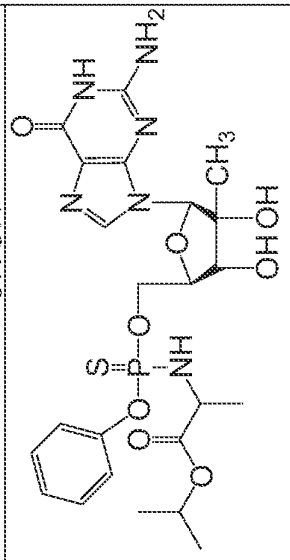
#	Structure
6006	
6007	
6008	
6009	
6010	
6011	

Figure 6C: Compounds of Formula (CC)

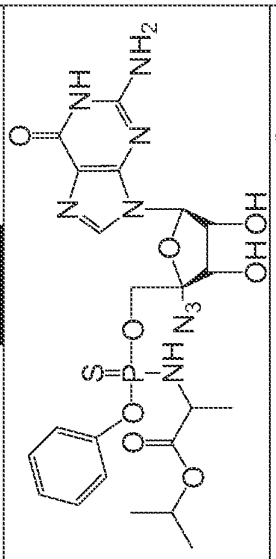
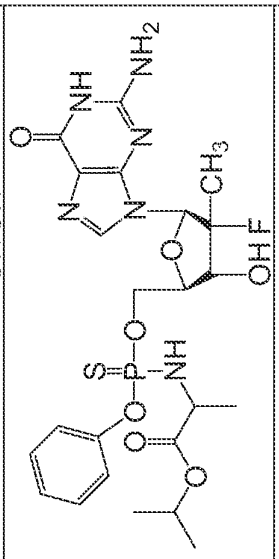
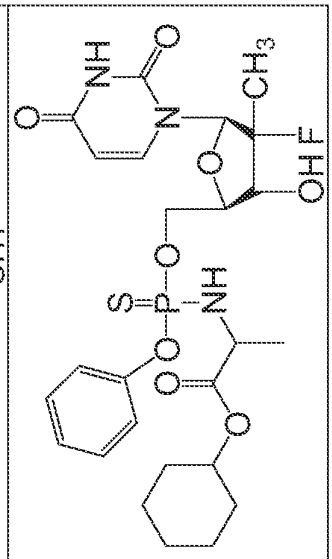
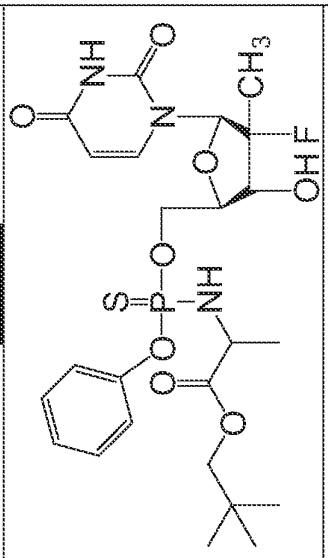
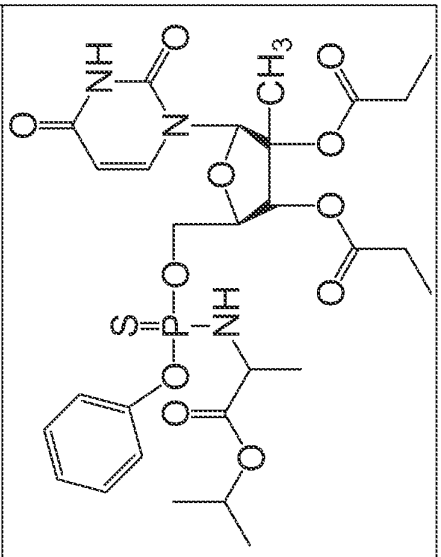
#	Structure
6012	
6013	
6014	
6015	
6016	

Figure 6D: Compounds of Formula (CC)

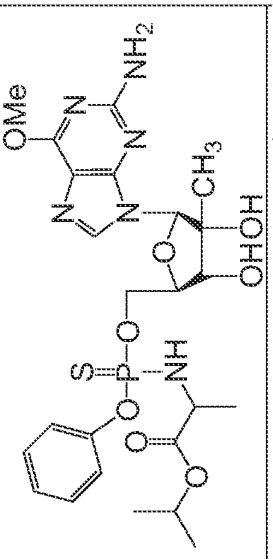
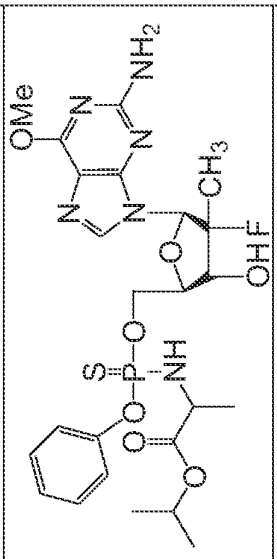
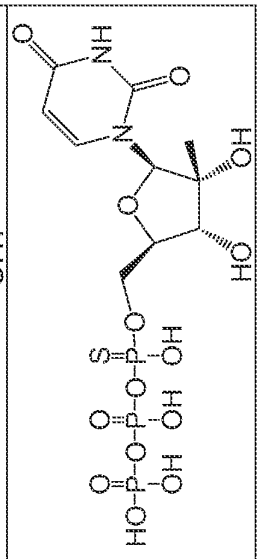
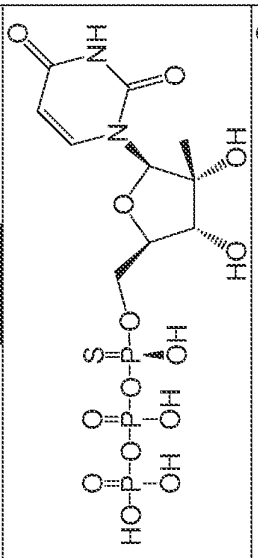
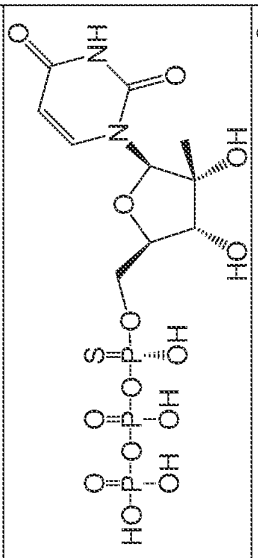
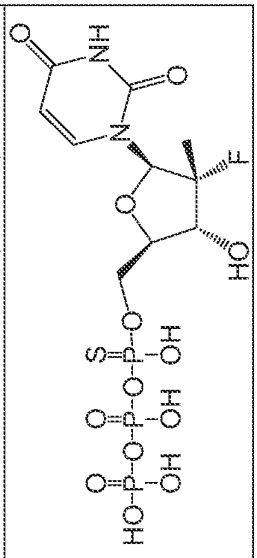
#	Structure
6017	
6018	
6019	
6020	
6021	
6022	

Figure 6E: Compounds of Formula (CC)

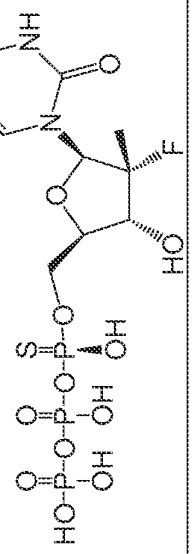
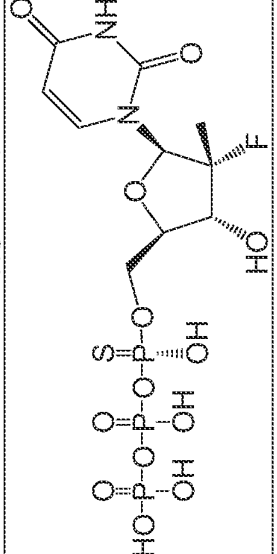
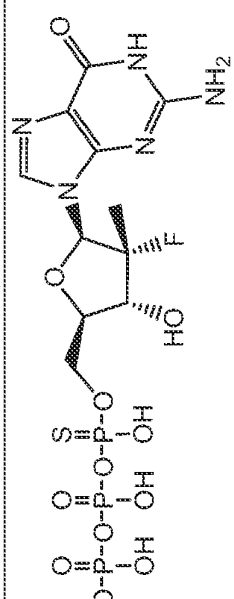
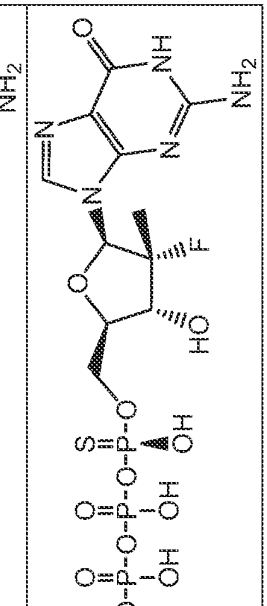
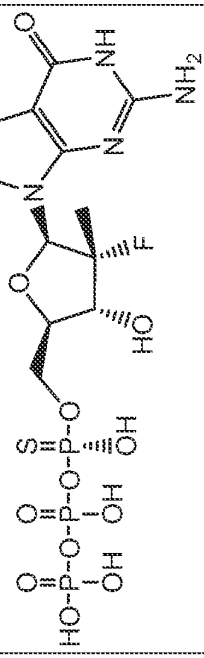
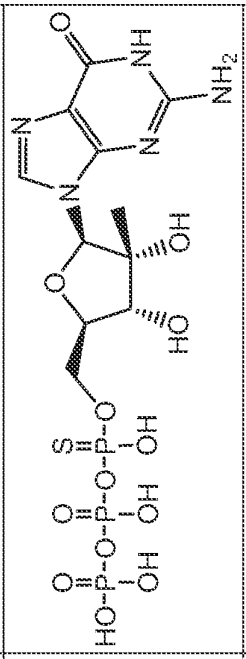
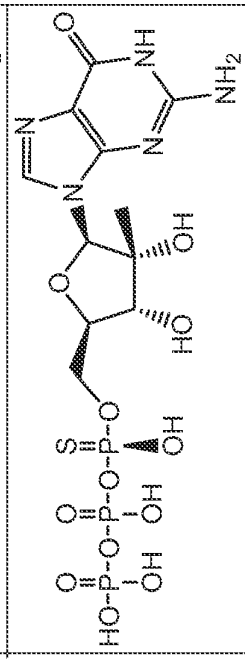
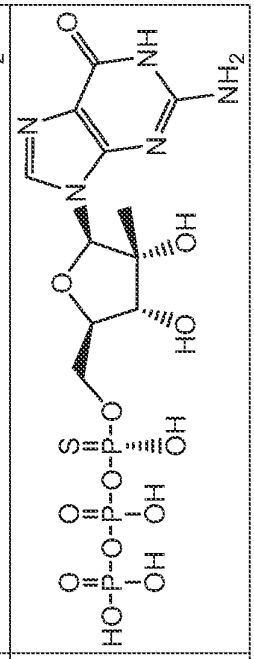
#	Structure
6023	
6024	
6025	
6026	
6027	
6028	
6029	
6030	

Figure 6F: Compounds of Formula (CC)

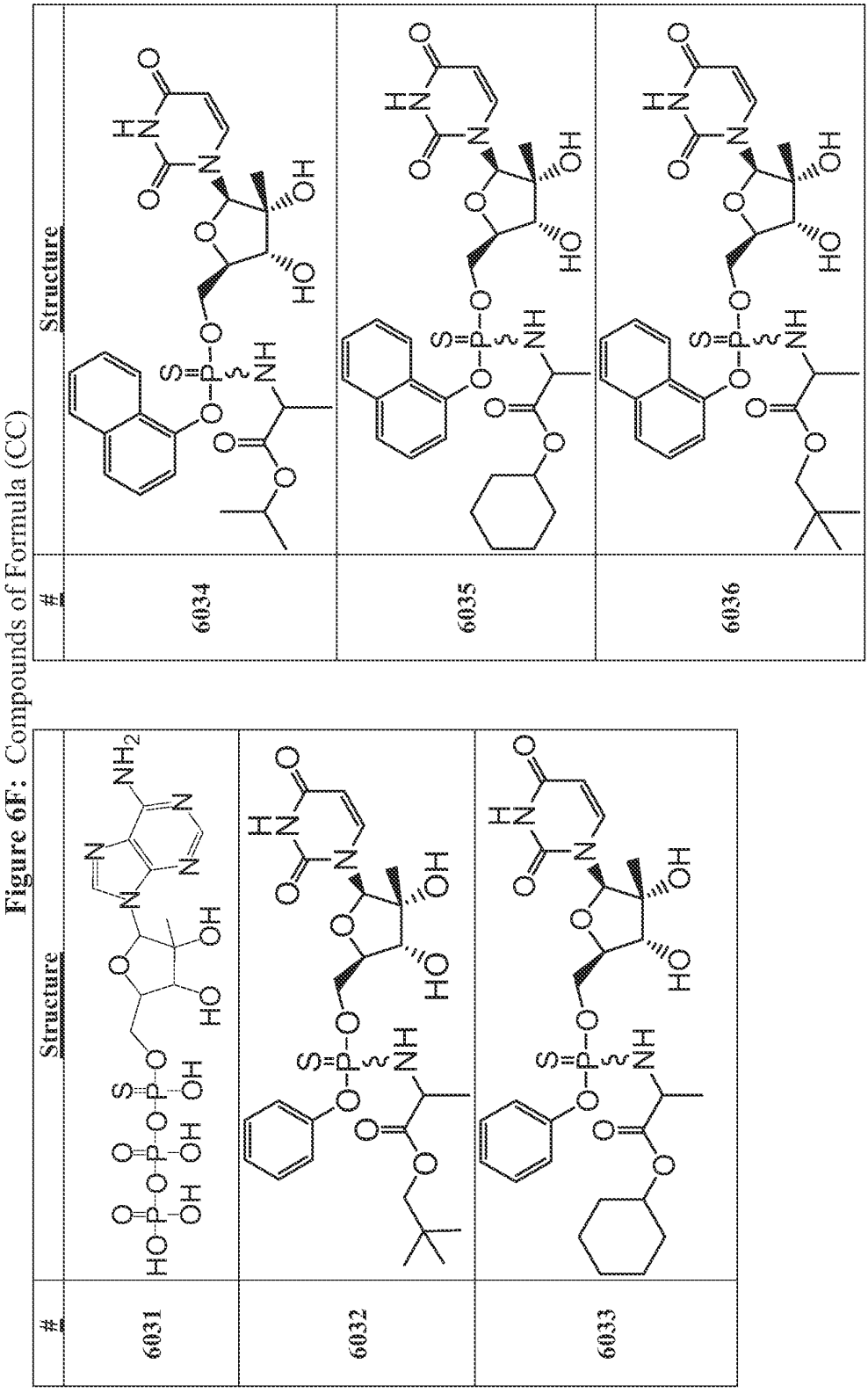


Figure 6G: Compounds of Formula (CC)

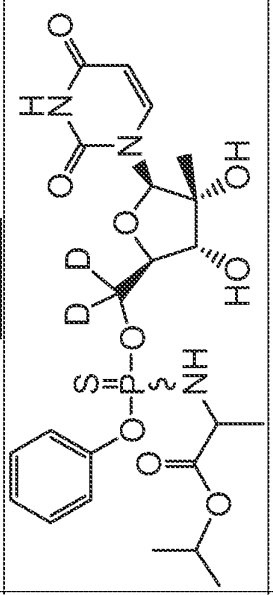
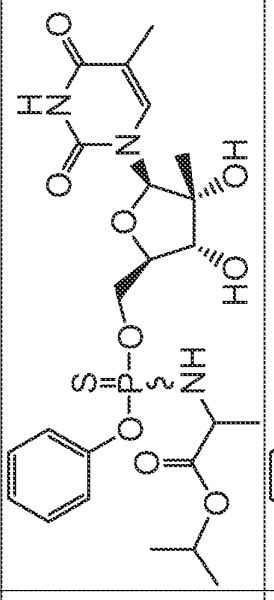
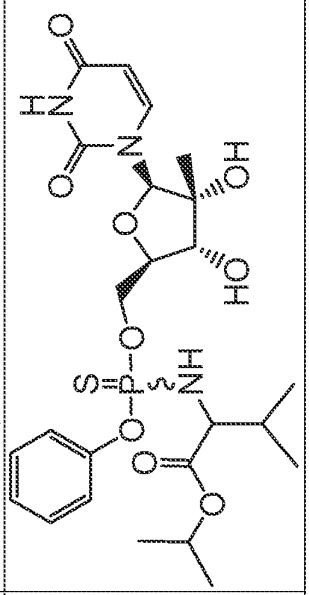
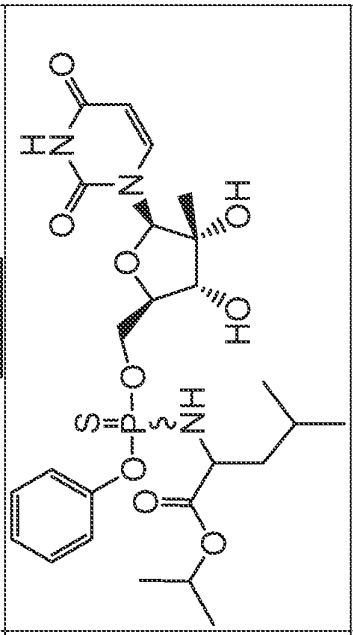
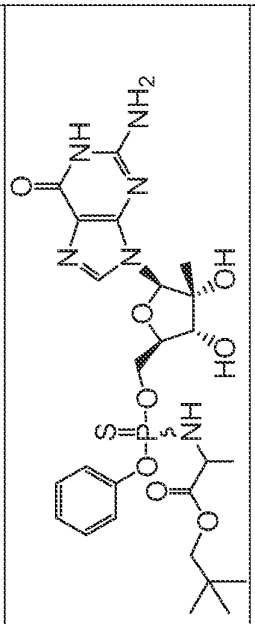
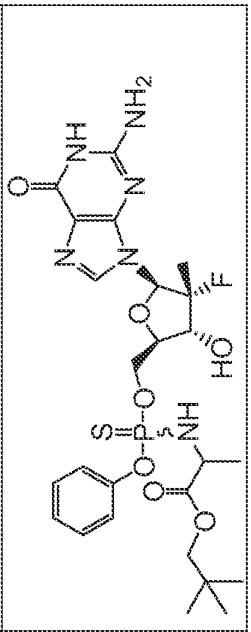
#	Structure
6037	
6038	
6039	
6040	
6041	
6042	

Figure 6H: Compounds of Formula (CC)

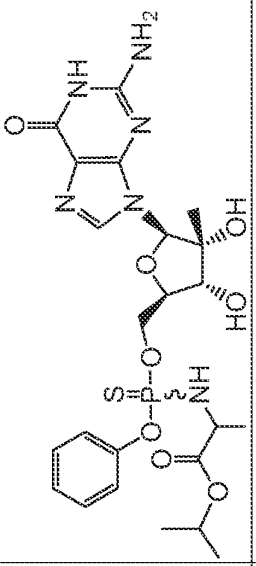
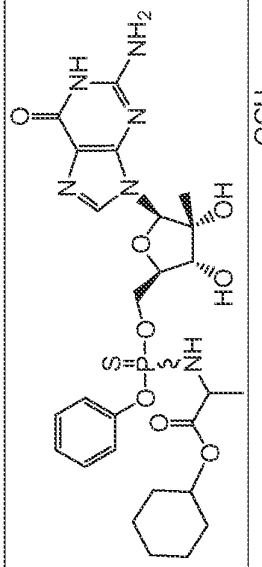
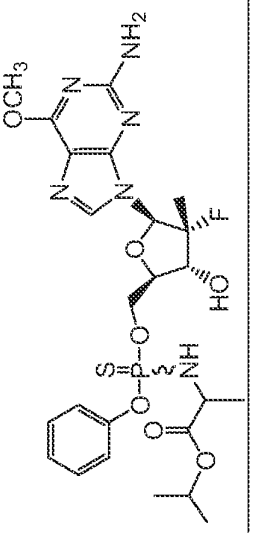
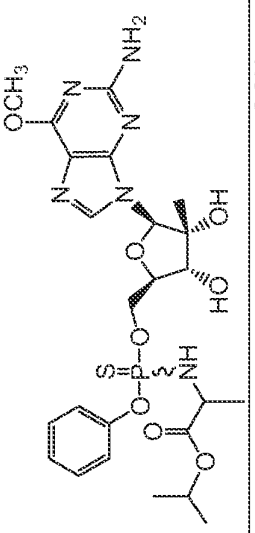
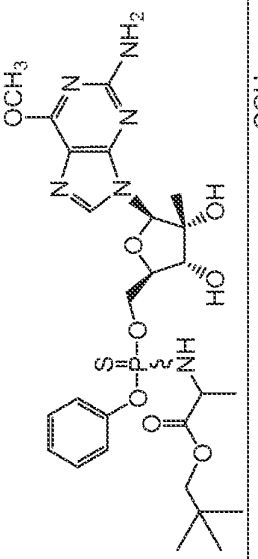
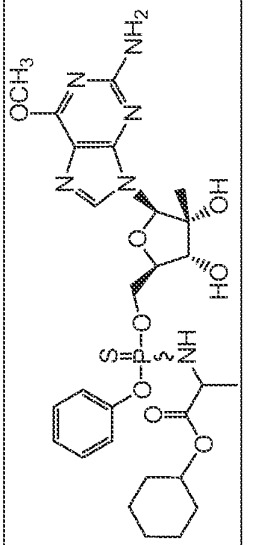
#	Structure
6043	
6044	
6045	
6046	
6047	
6048	

Figure 6I: Compounds of Formula (CC)

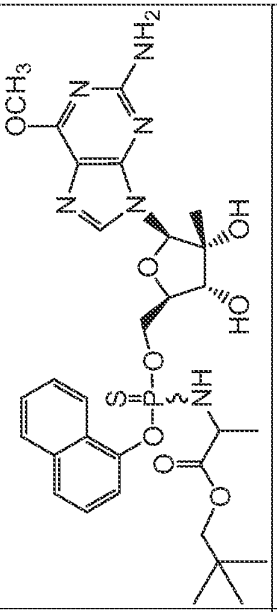
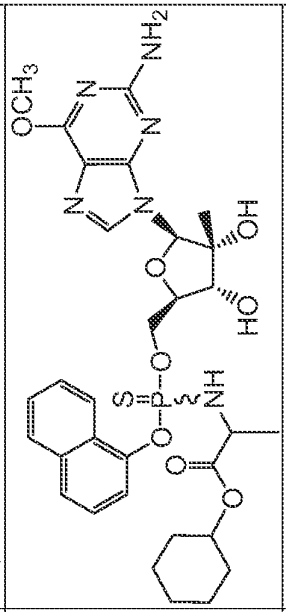
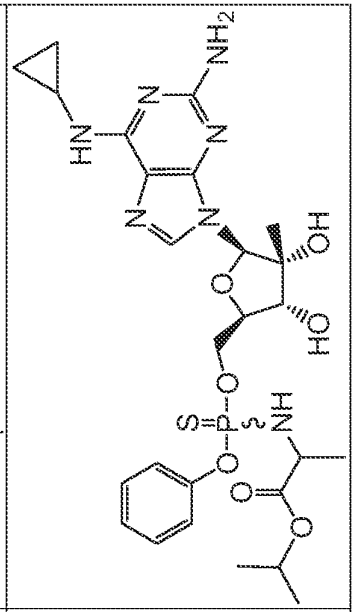
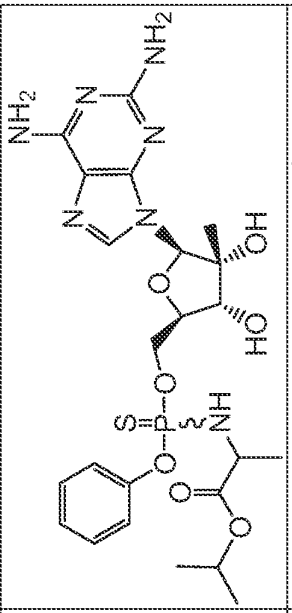
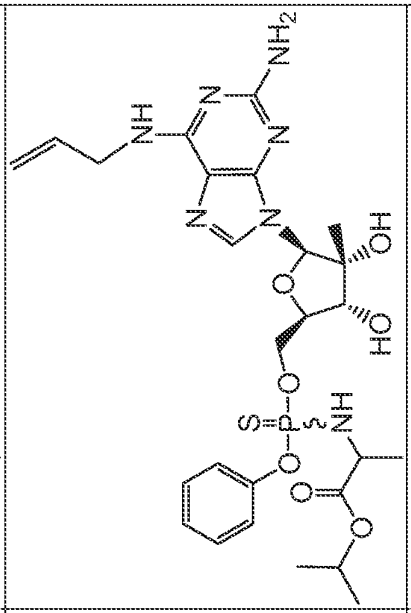
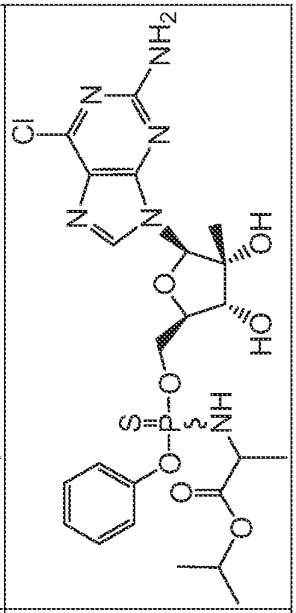
#	Structure
6049	
6050	
6051	
6052	
6053	
6054	

Figure 6J: Compounds of Formula (CC)

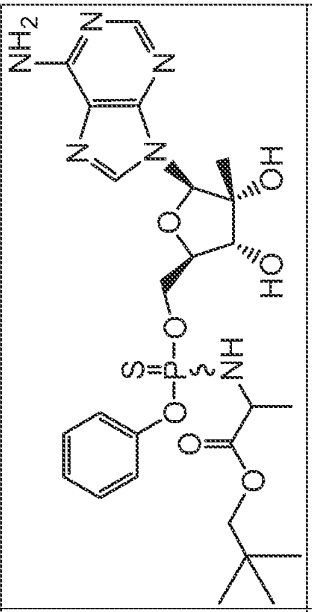
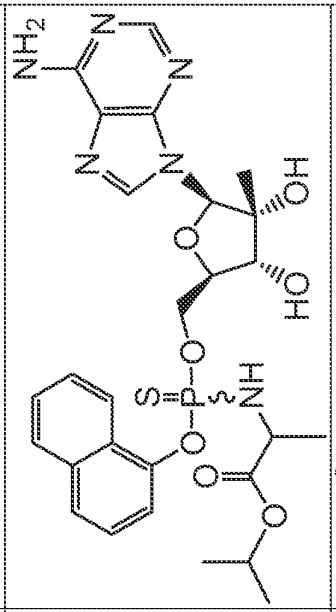
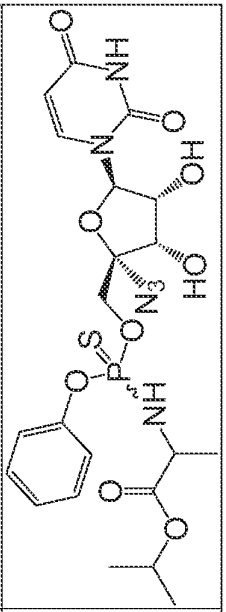
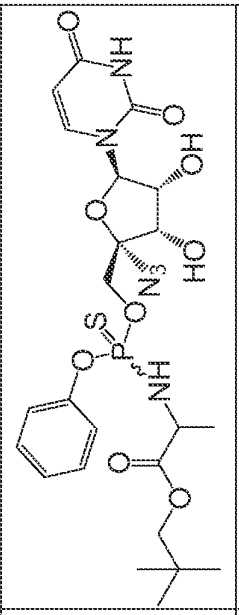
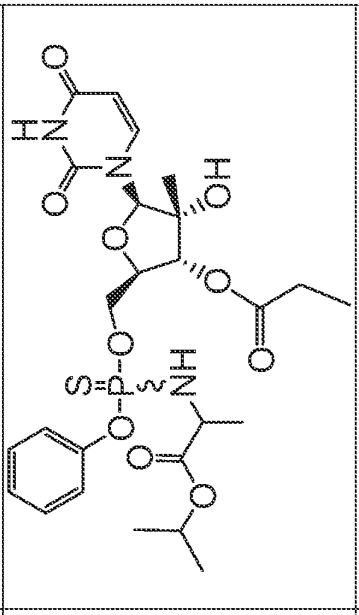
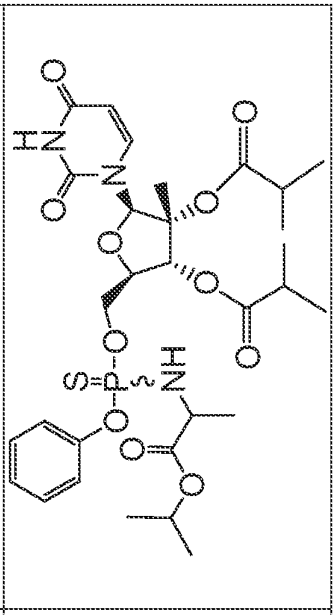
#	Structure
6055	
6056	
6057	
6058	
6059	
6060	

Figure 6K: Compounds of Formula (CC)

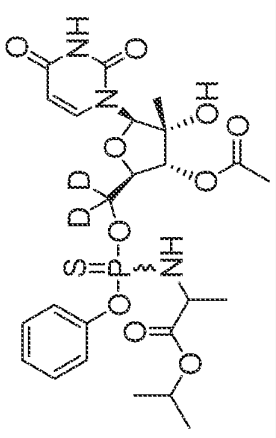
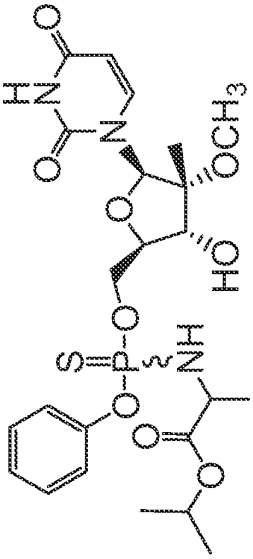
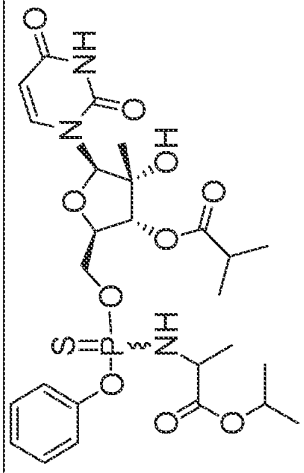
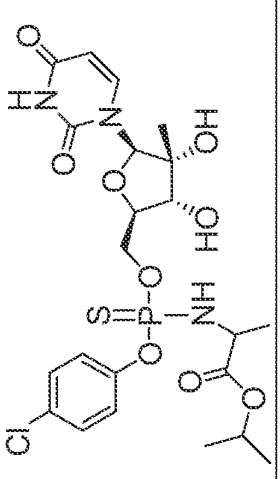
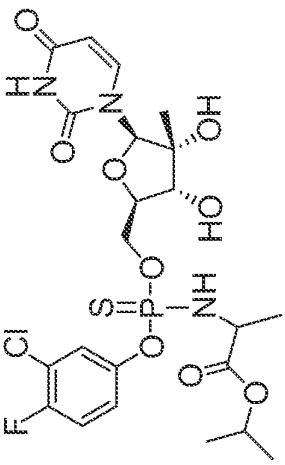
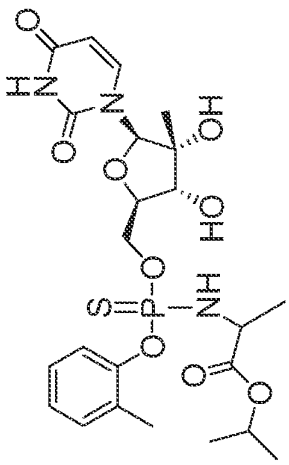
#	Structure
6061	
6062	
6063	
6064	
6065	
6066	

Figure 6L: Compounds of Formula (CC)

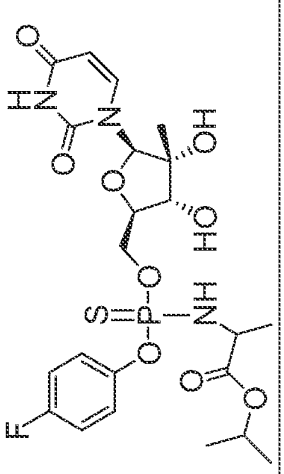
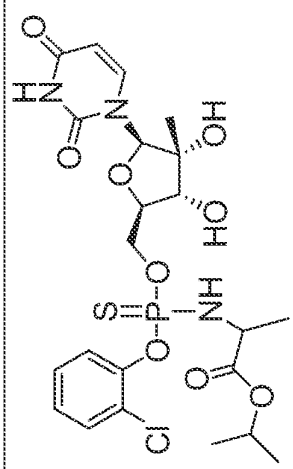
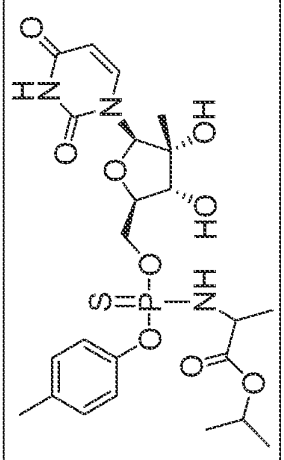
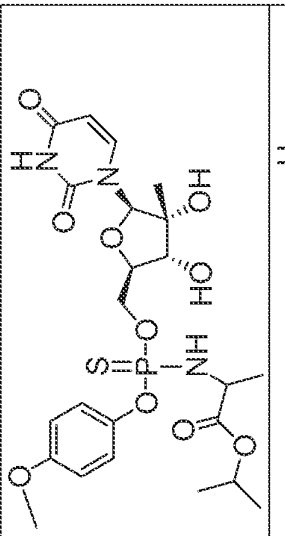
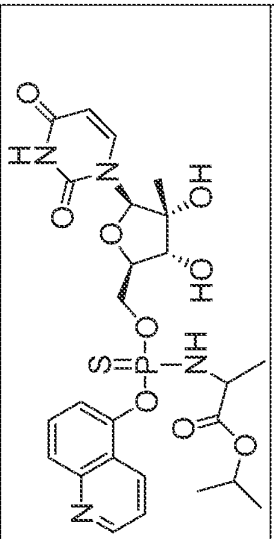
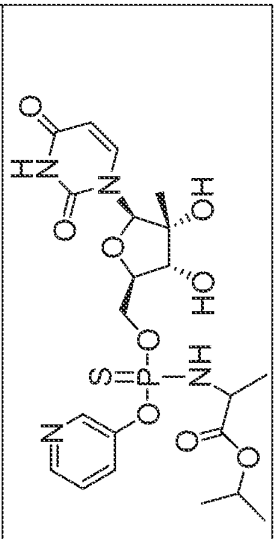
#	Structure
6067	
6068	
6069	
6070	
6071	
6072	

Figure 6M: Compounds of Formula (CC)

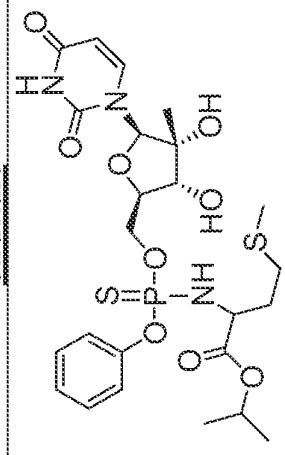
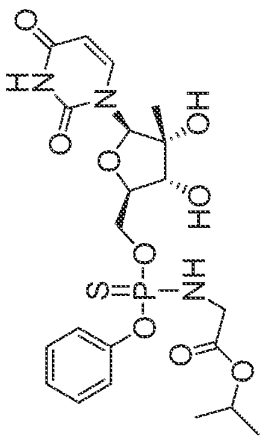
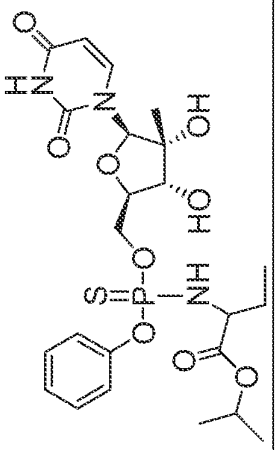
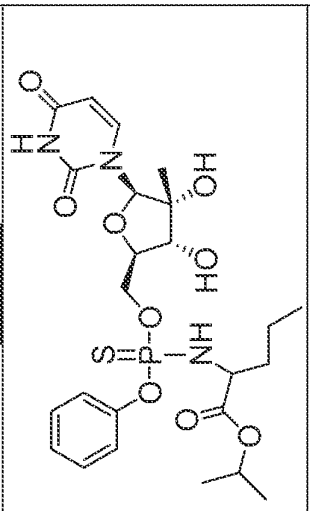
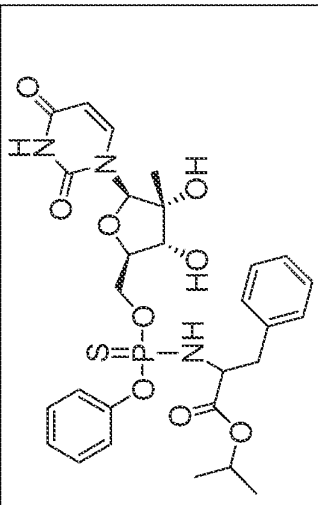
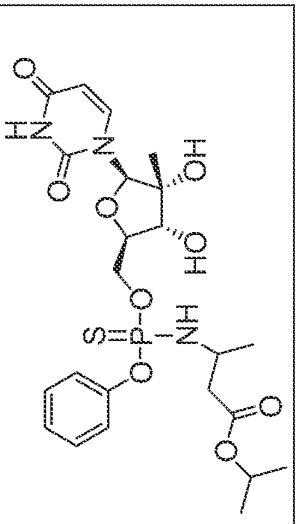
#	Structure
6073	
6074	
6075	
6076	
6077	
6078	

Figure 7A: Compounds of Formula (AA) and triphosphates thereof

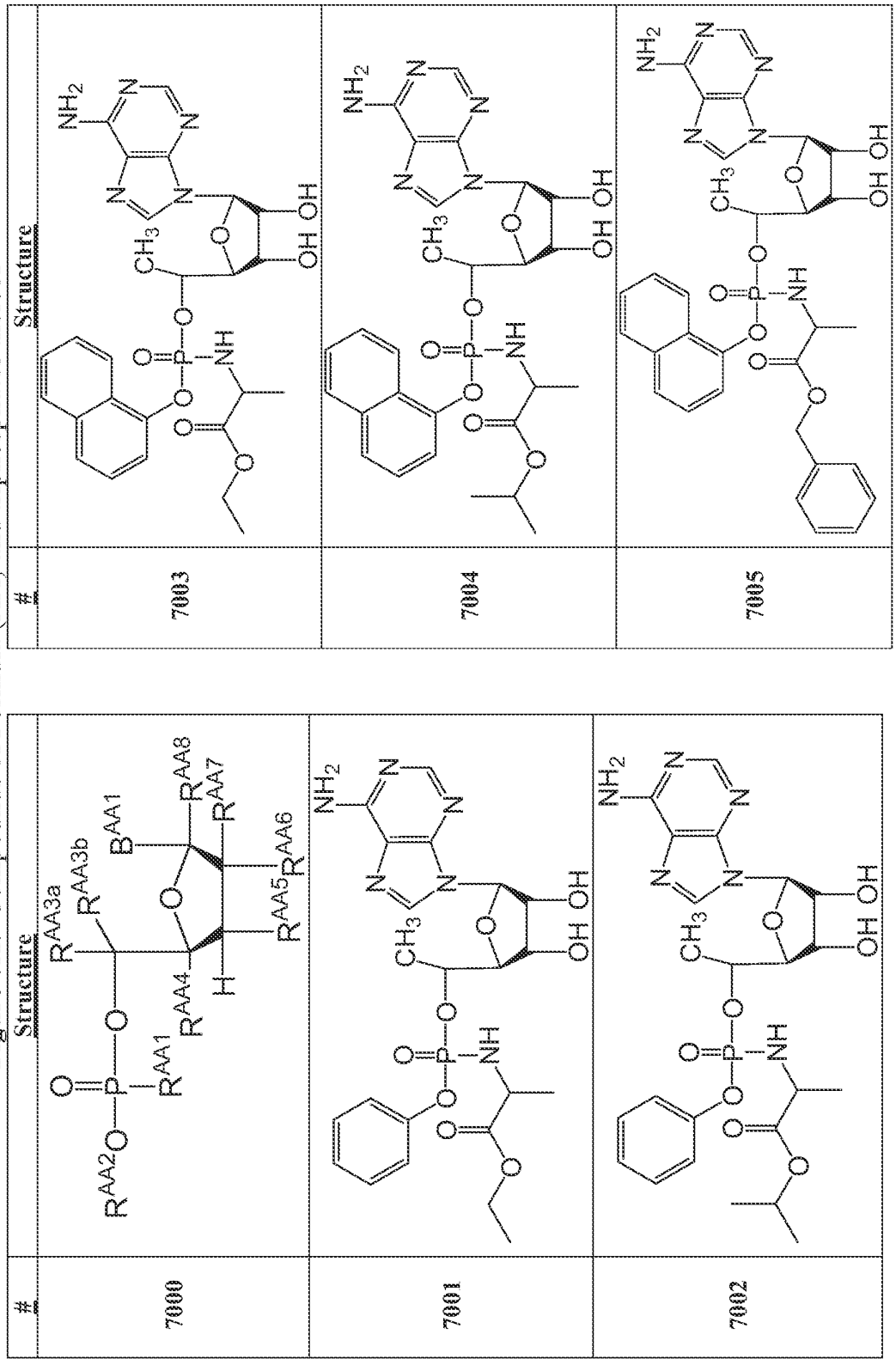


Figure 7B: Compounds of Formula (AA) and triphosphates thereof

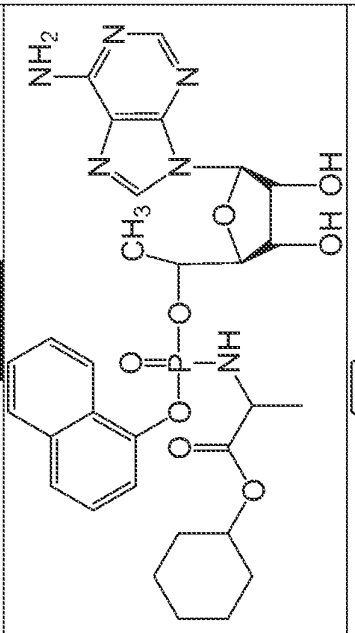
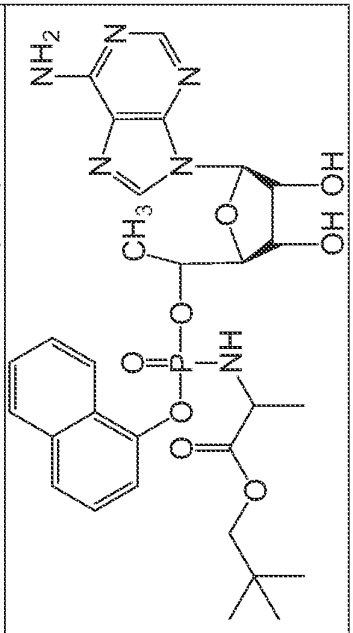
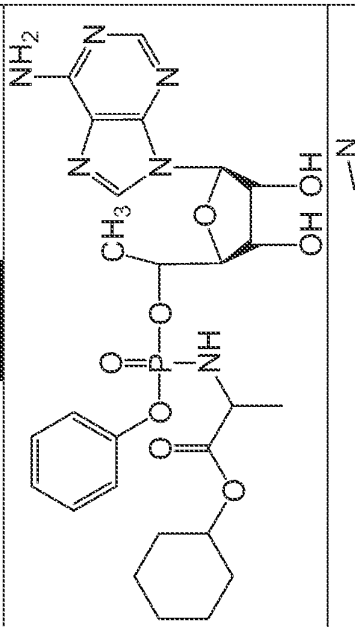
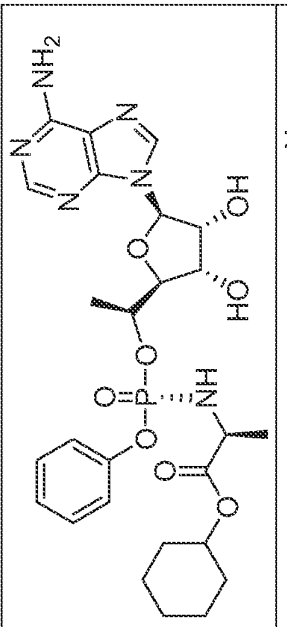
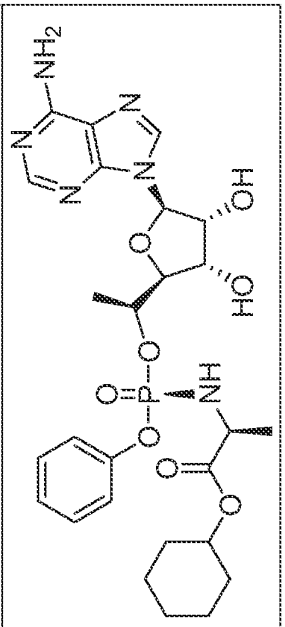
#	Structure
7006	
7007	
7008	
7009	
7010	

Figure 7C: Compounds of Formula (AA) and triphosphates thereof

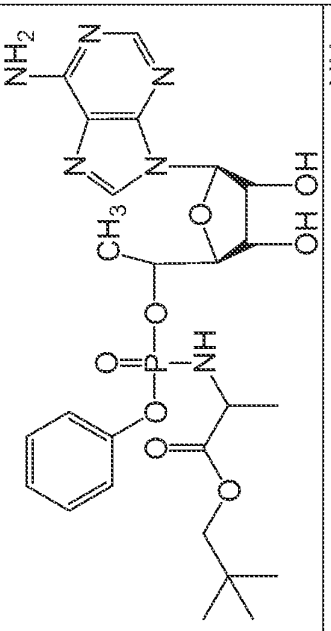
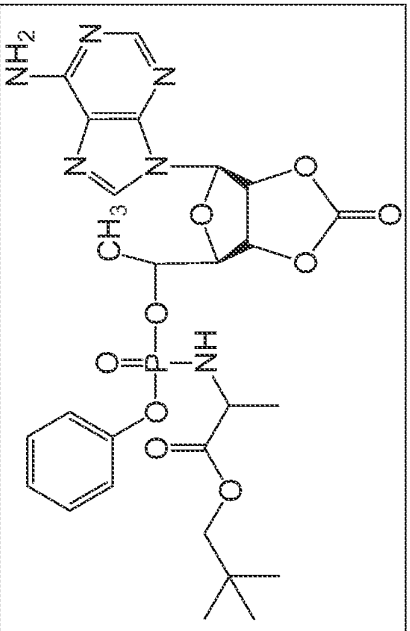
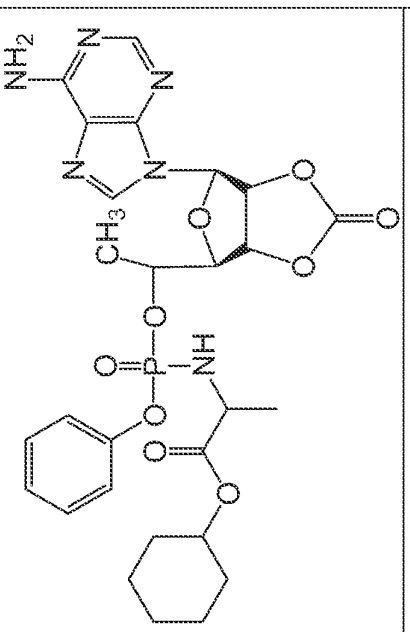
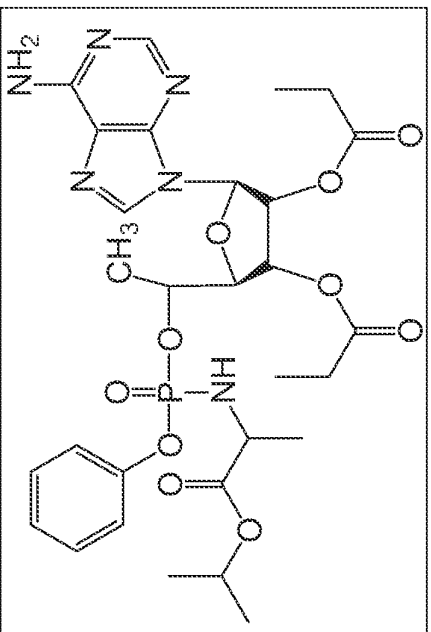
#	Structure
7011	
7012	
7013	
7014	

Figure 7D: Compounds of Formula (AA) and triphosphates thereof

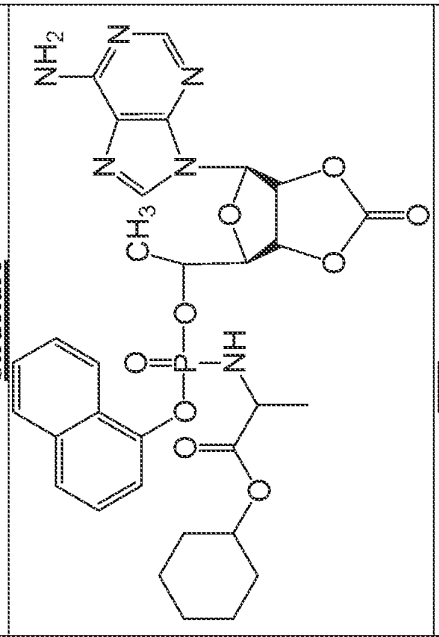
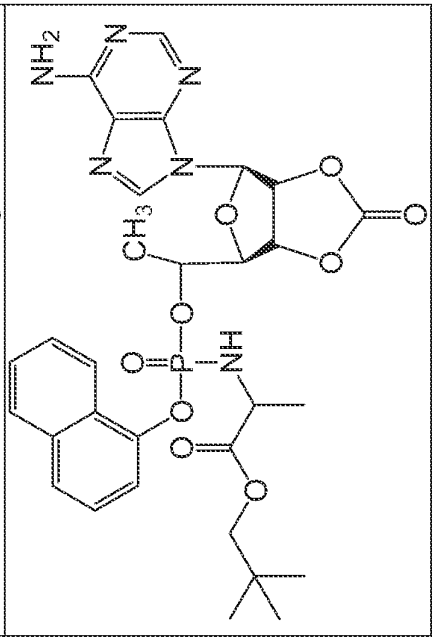
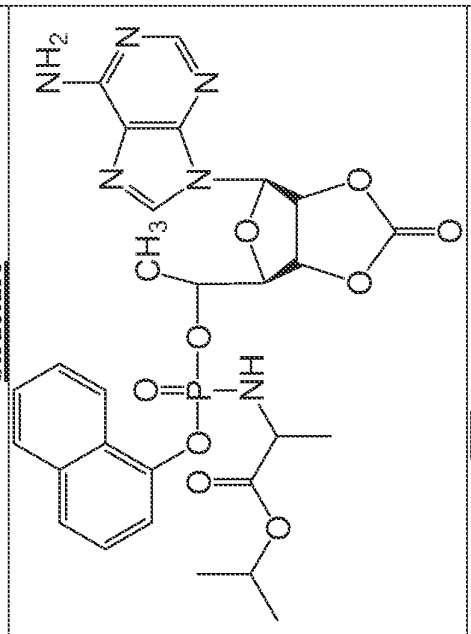
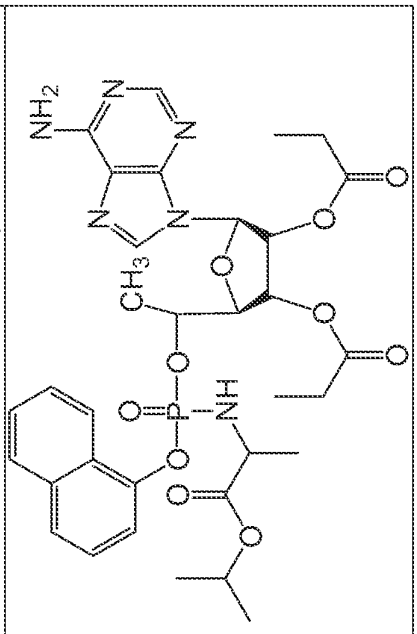
#	Structure
7015	
7016	
7017	
7018	

Figure 7E: Compounds of Formula (AA) and triphosphates thereof

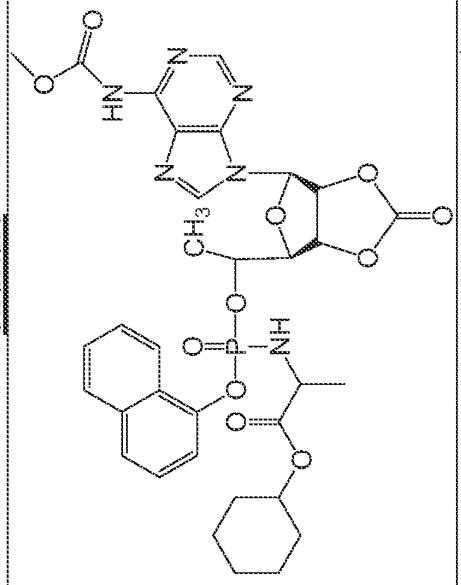
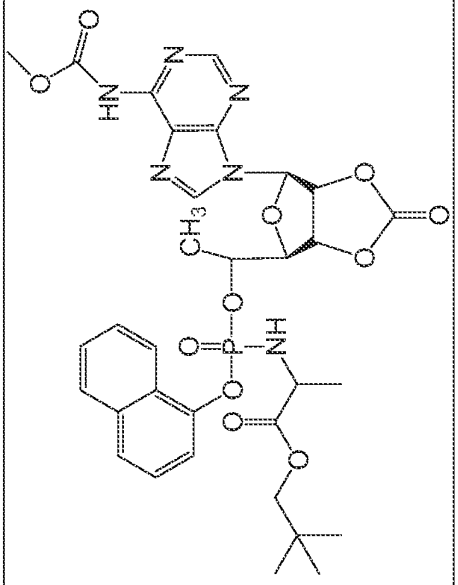
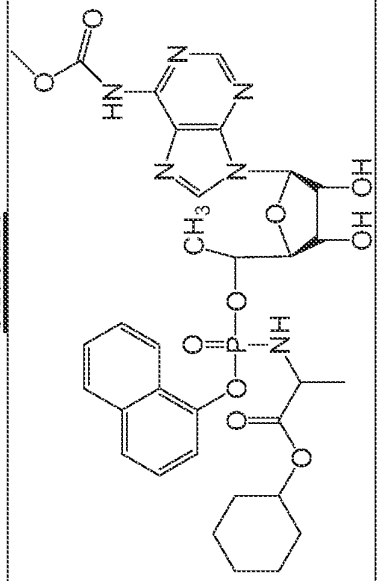
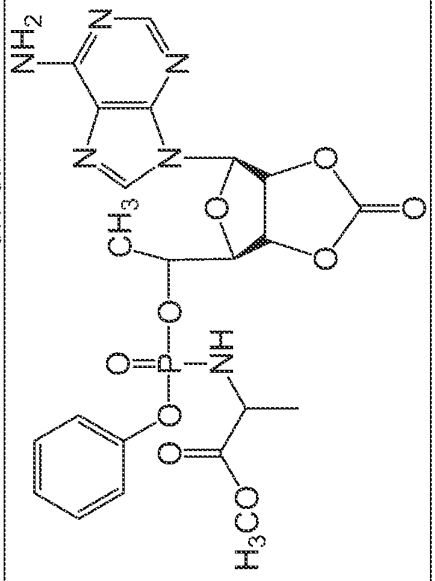
#	Structure
7019	
7020	
7021	
7022	

Figure 7F: Compounds of Formula (AA) and triphosphates thereof

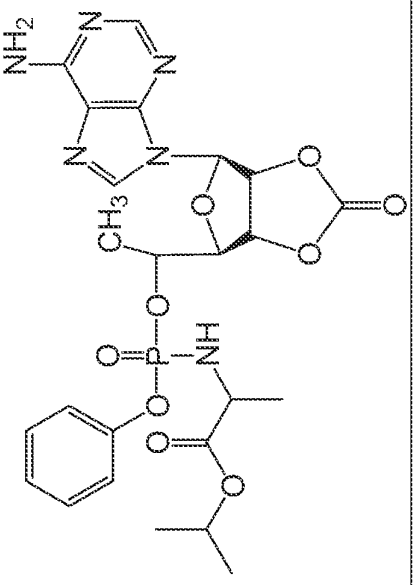
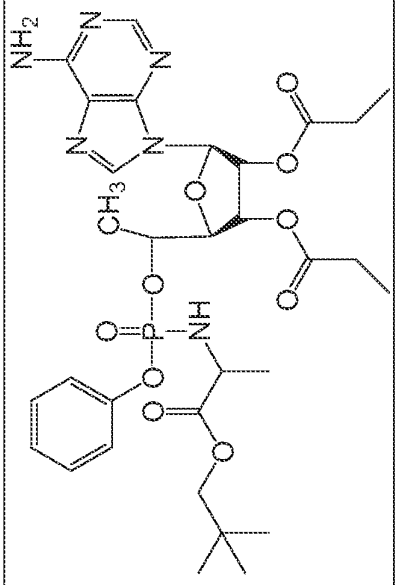
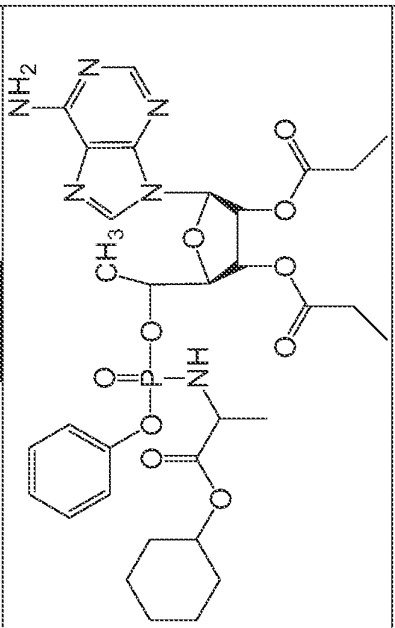
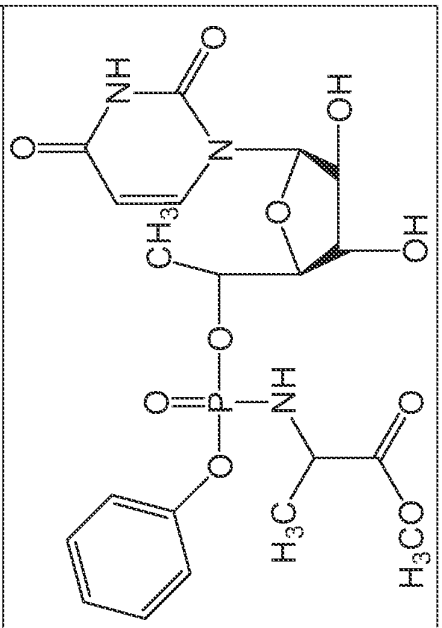
#	Structure
7023	
7024	
7025	
7026	

Figure 7G: Compounds of Formula (AA) and triphosphates thereof

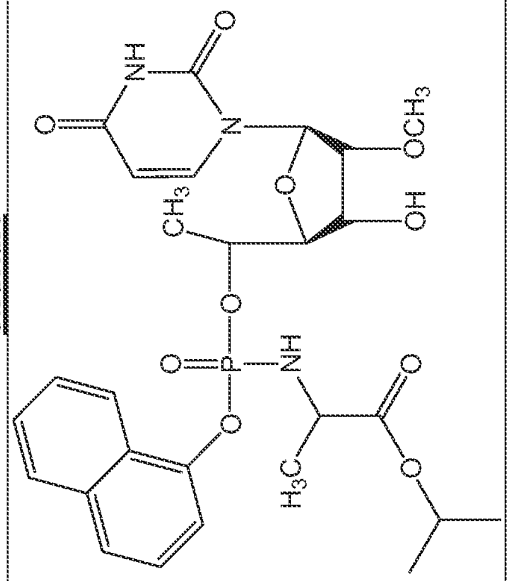
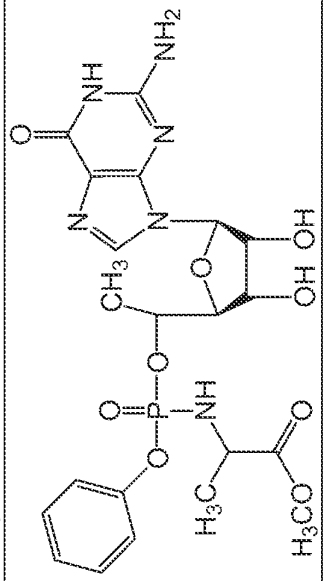
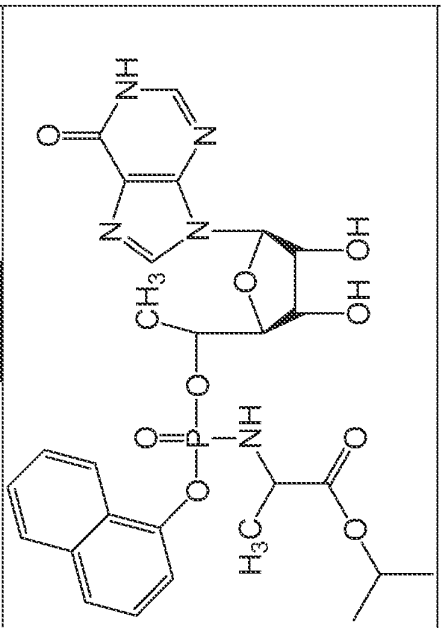
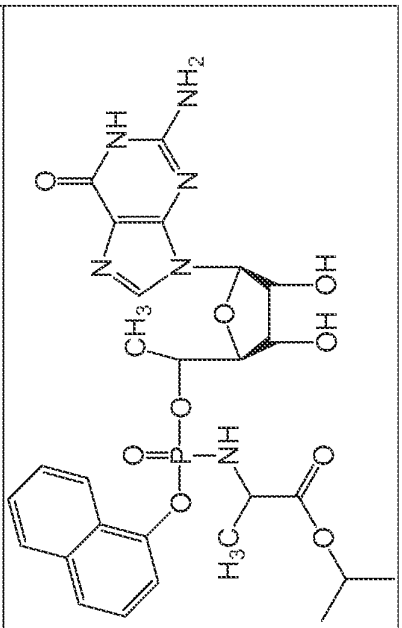
#	Structure
7027	
7028	
7029	
7030	

Figure 7H: Compounds of Formula (AA) and triphosphates thereof

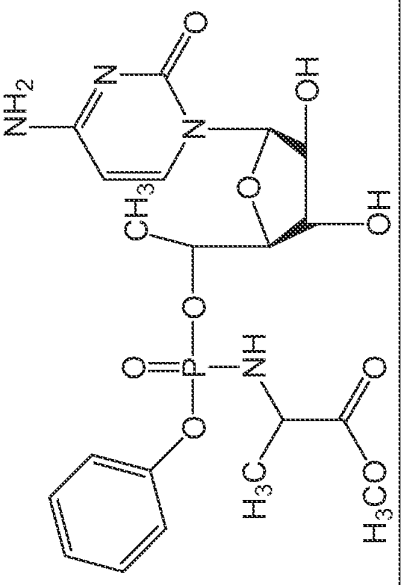
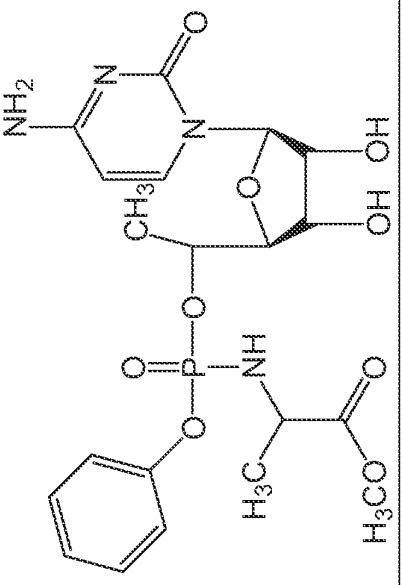
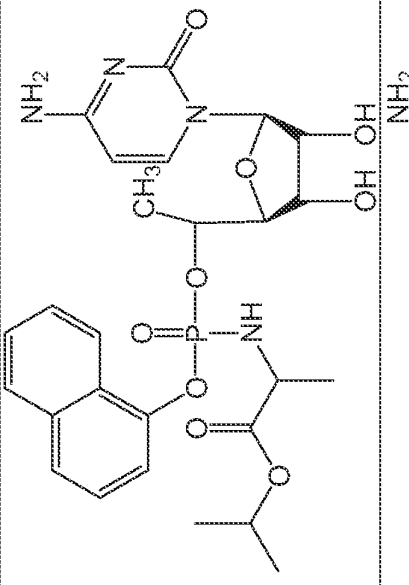
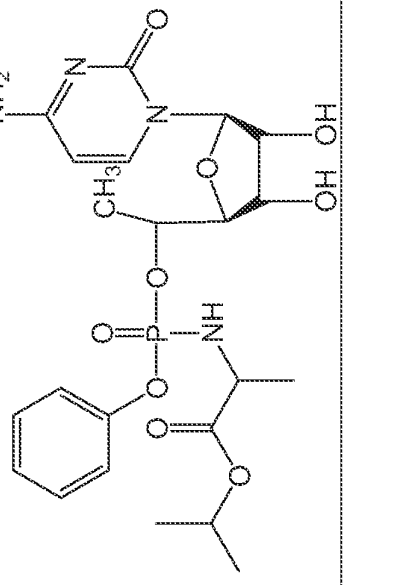
#	Structure
7031	
7032	
7033	
7034	

Figure 7I: Compounds of Formula (AA) and triphosphates thereof

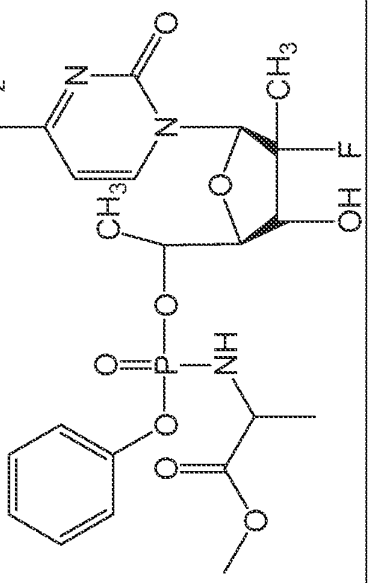
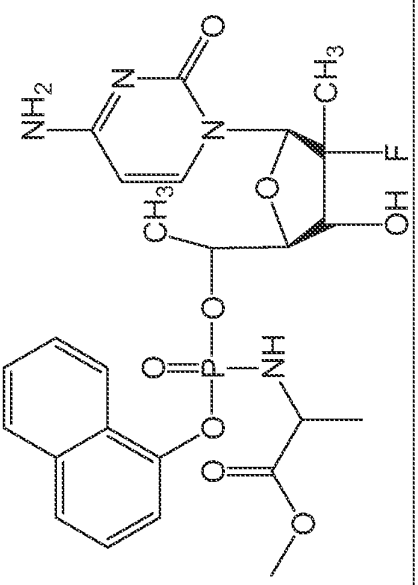
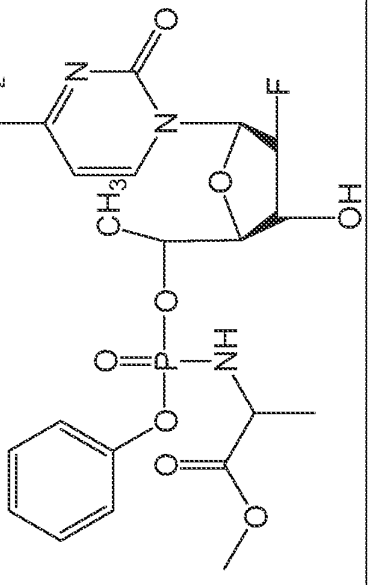
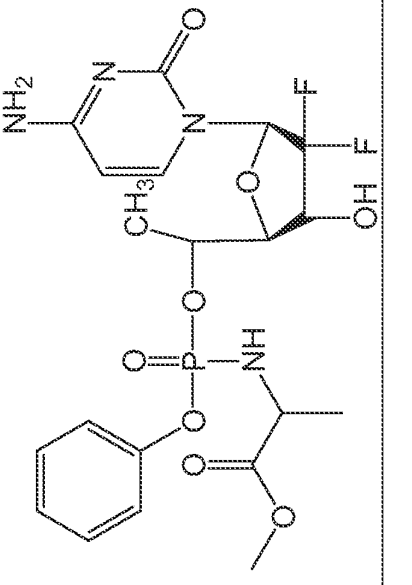
#	Structure
7035	
7036	
7037	
7038	

Figure 7J: Compounds of Formula (AA) and triphosphates thereof

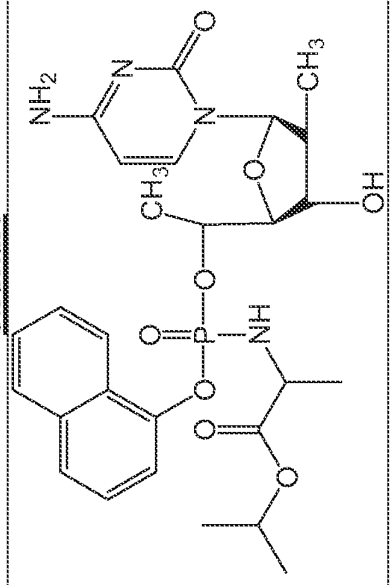
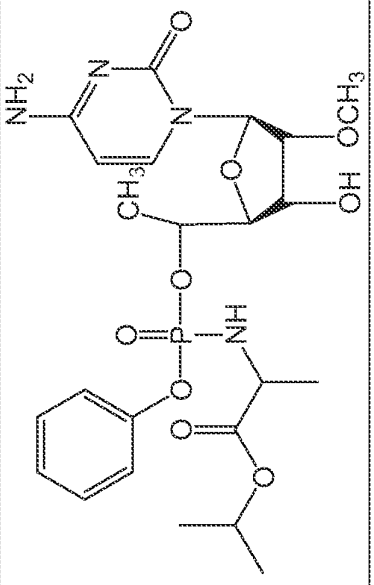
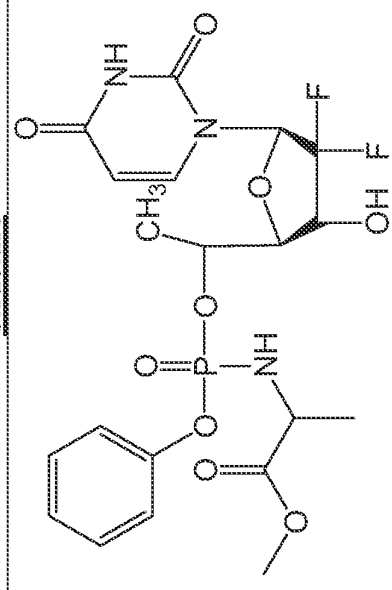
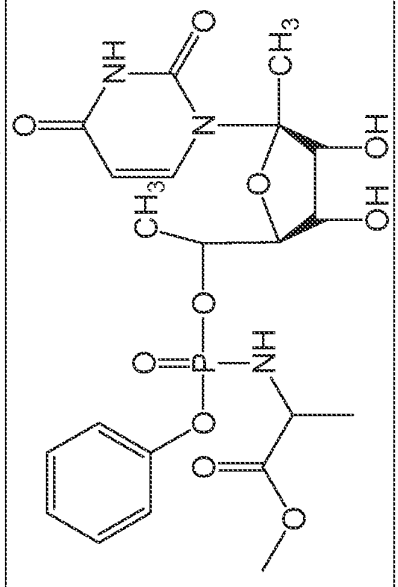
#	Structure
7039	
7040	
7041	
7042	

Figure 7K: Compounds of Formula (AA) and triphosphates thereof

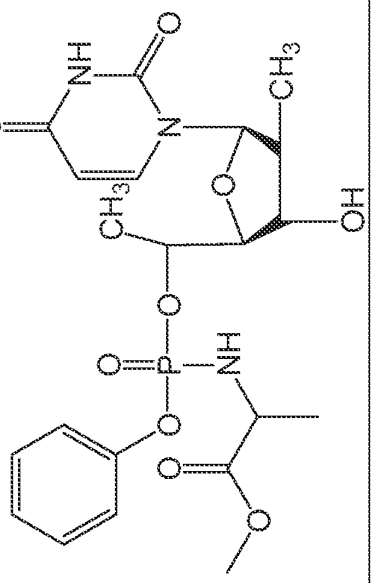
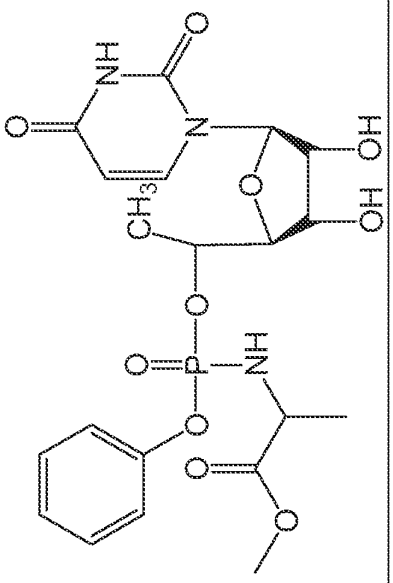
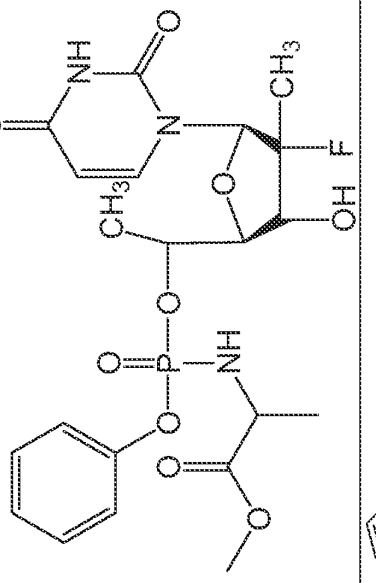
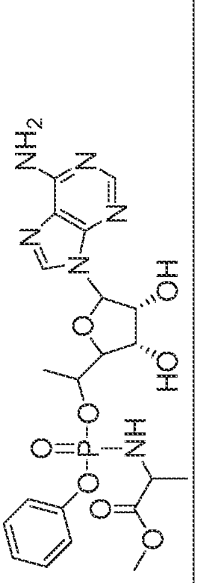
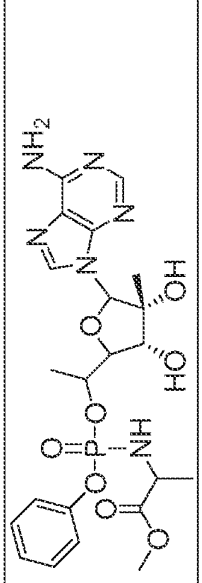
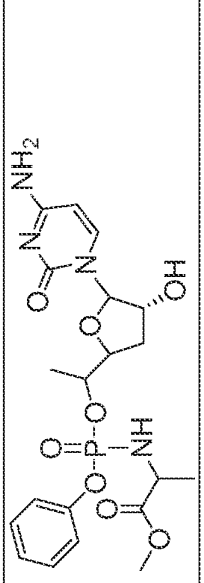
#	Structure
7043	
7044	
7045	
7046	
7047	
7048	

Figure 7L: Compounds of Formula (AA) and triphosphates thereof

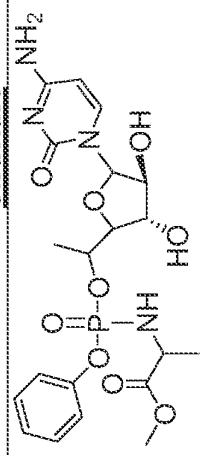
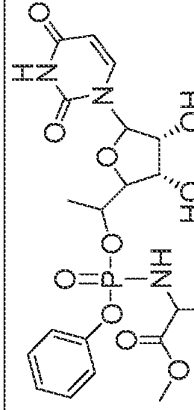
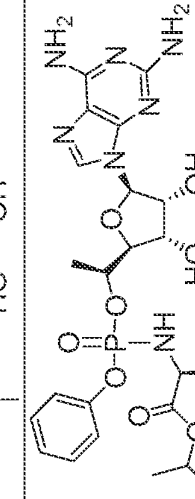
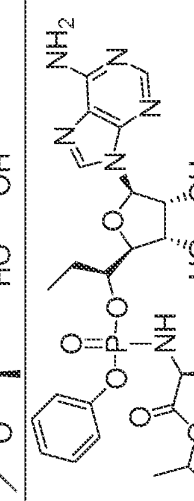
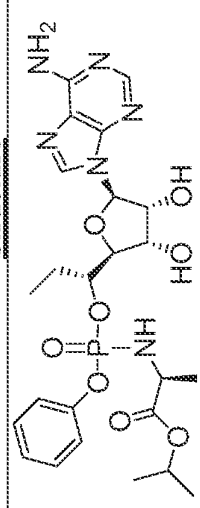
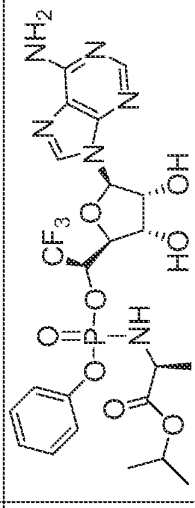
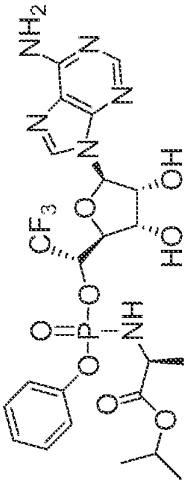
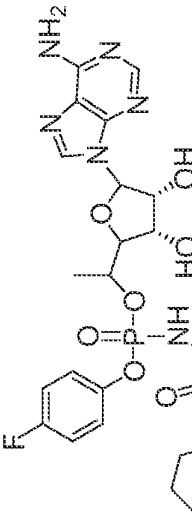
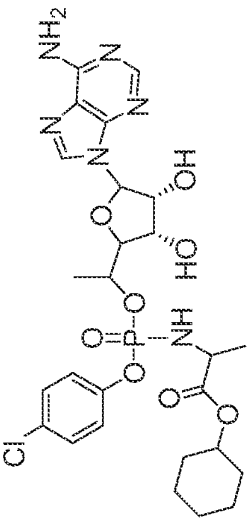
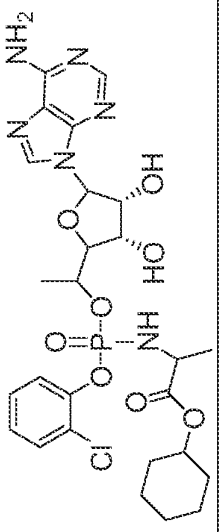
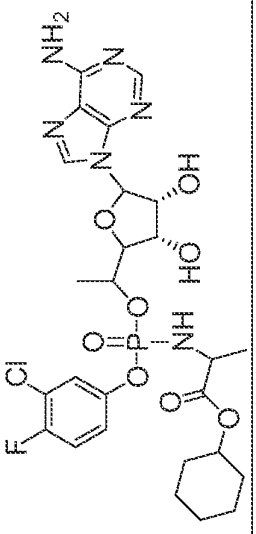
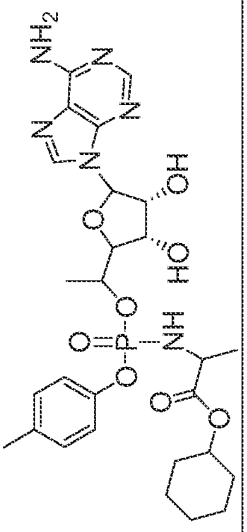
#	Structure
7049	
7050	
7051	
7052	
7053	
7054	
7055	
7056	

Figure 7M: Compounds of Formula (AA) and triphosphates thereof

#	Structure
7057	
7058	
7059	
7060	

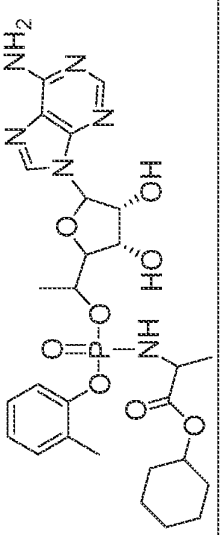
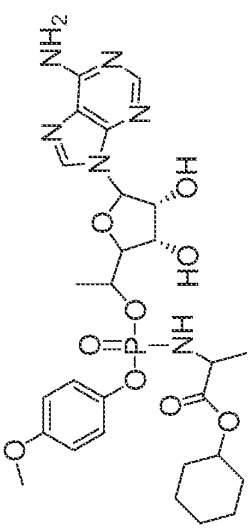
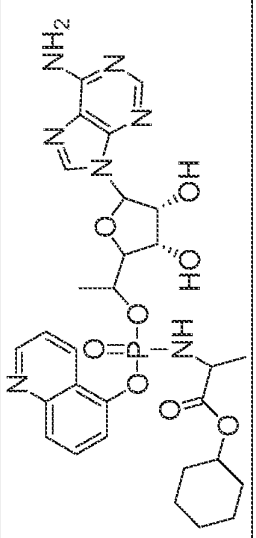
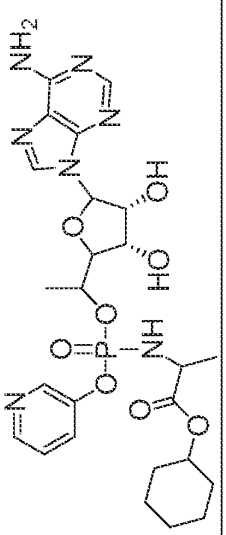
#	Structure
7061	
7062	
7063	
7064	

Figure 7N: Compounds of Formula (AA) and triphosphates thereof

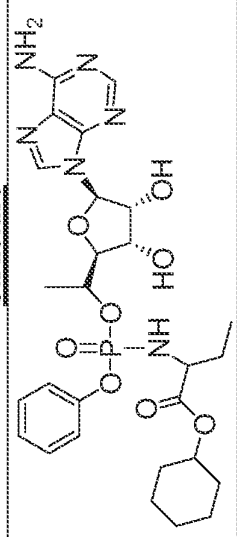
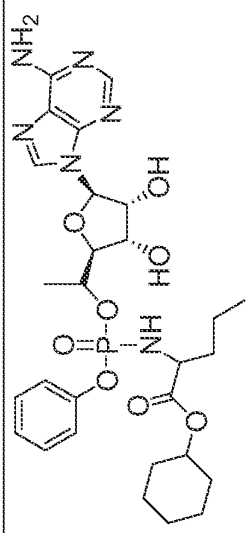
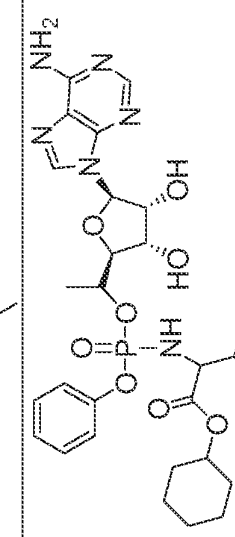
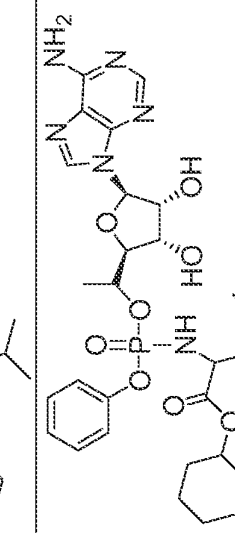
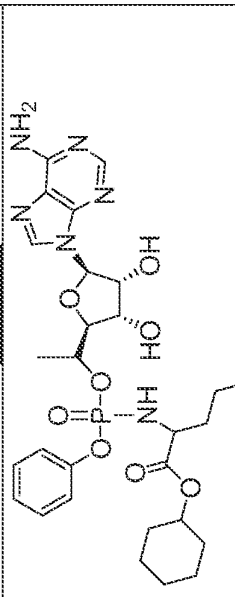
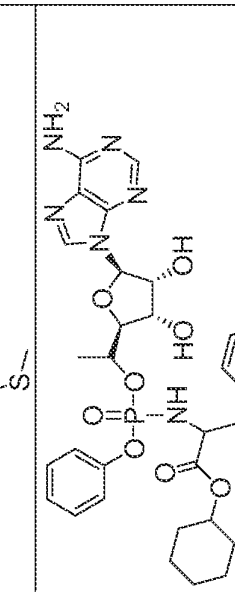
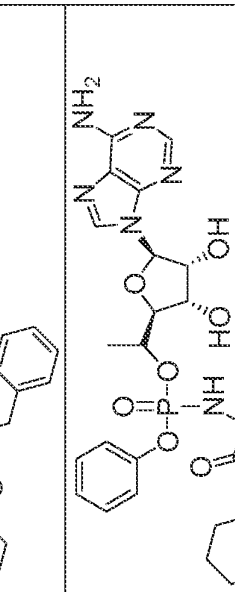
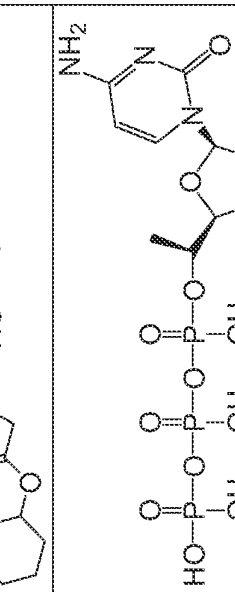
#	Structure
7065	
7066	
7067	
7068	
7069	
7070	
7071	
7072	

Figure 7O: Compounds of Formula (AA) and triphosphates thereof

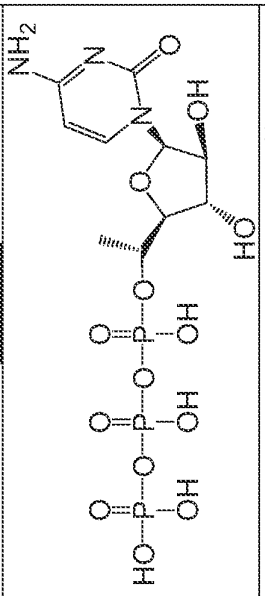
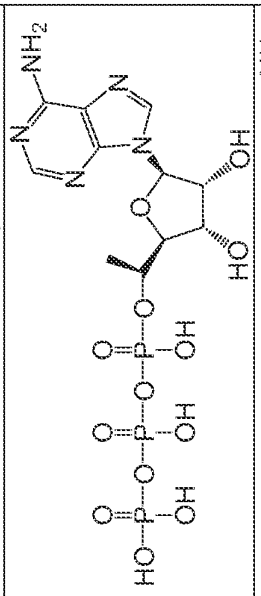
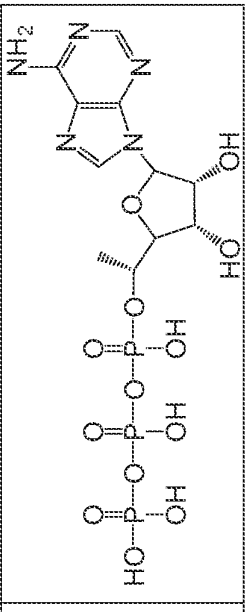
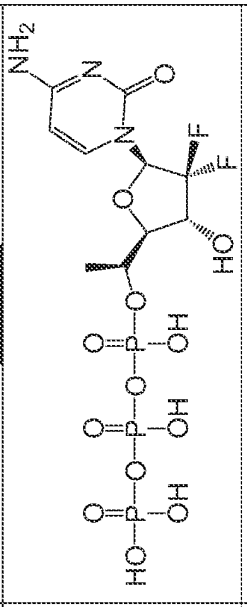
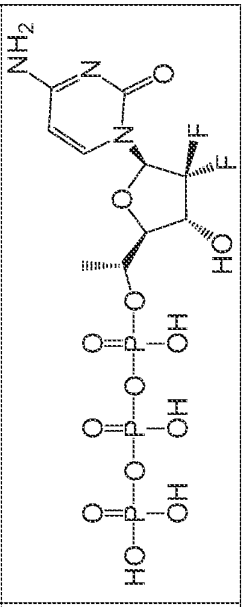
#	Structure
7073	
7074	
7075	
7076	
7077	

Figure 8A: Compounds of Formula (I)

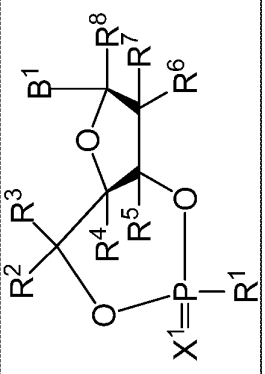
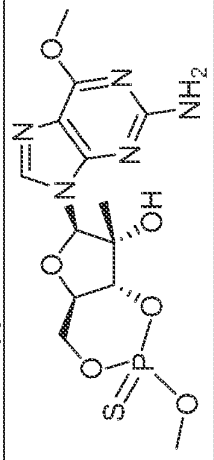
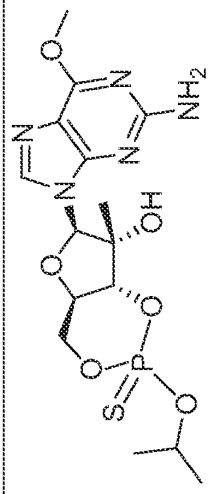
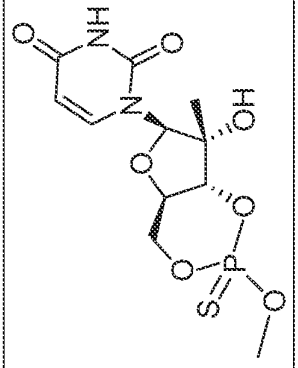
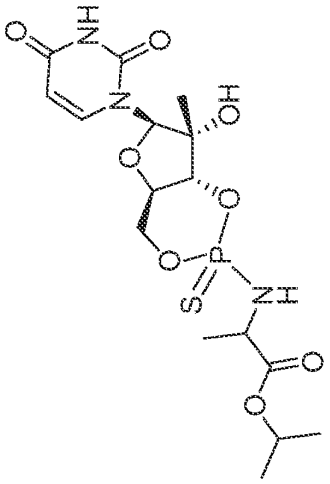
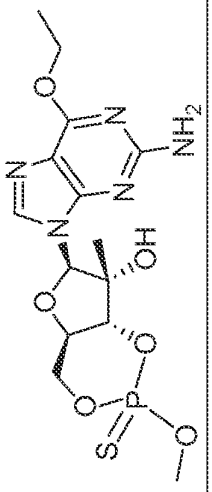
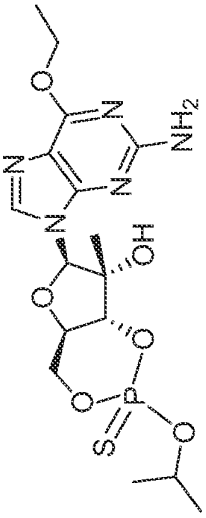
#	Structure
8000	
8001	
8002	
8003	
8004	
8005	
8006	

Figure 8B: Compounds of Formula (I)

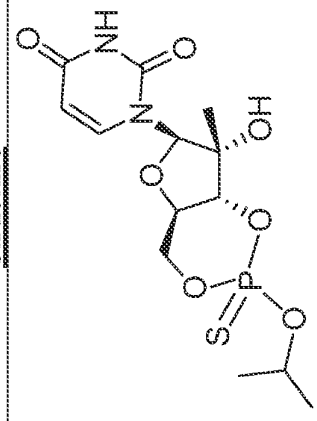
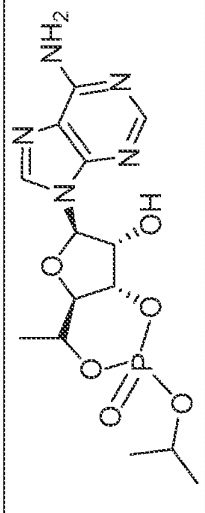
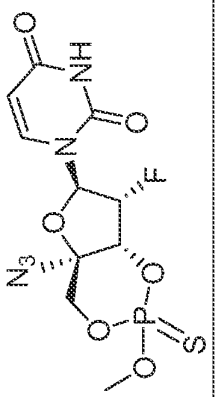
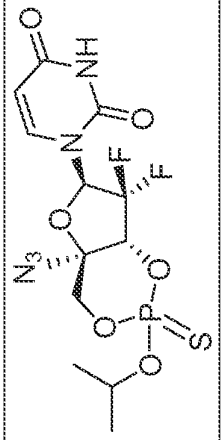
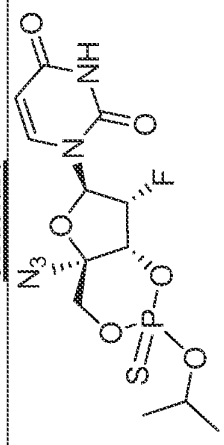
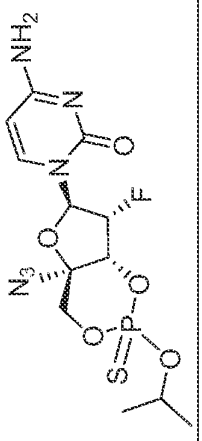
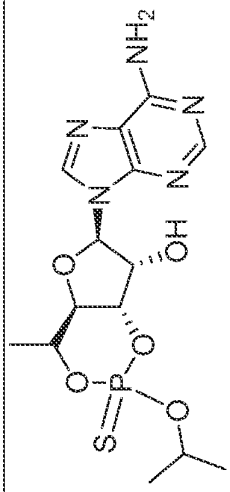
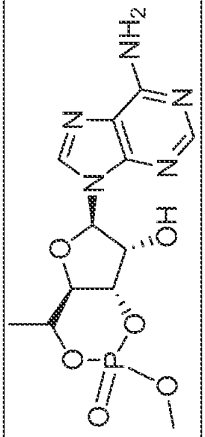
#	Structure
8007	
8008	
8009	
80010	
8011	
8012	
8013	
8014	

Figure 8C: Compounds of Formula (I)

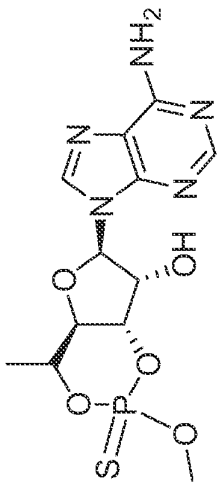
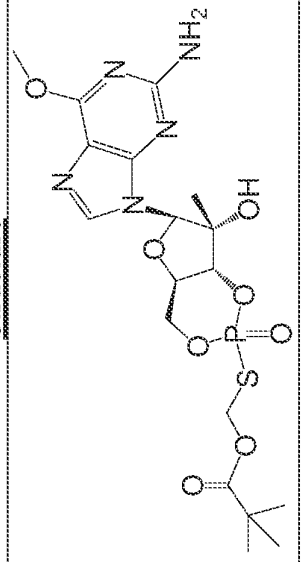
#	Structure
8015	
8016	

Figure 9: Formula (DD)

#	Structure
9000