

SUBSTITUTED NUCLEOTIDE ANALOGS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application Nos. 61/385,363, filed September 22, 2010; and 61/426,461, 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 phosphorothioate nucleotide analogs, pharmaceutical compositions that include one or more nucleotide analogs and methods of synthesizing the same. Also disclosed herein are methods of treating diseases and/or conditions with a phosphorothioate nucleotide analog, 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

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

[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, 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, 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, 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, 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, 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, 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, or a pharmaceutically acceptable salt of the foregoing, a compound of Formula (BB), or a pharmaceutically acceptable salt thereof, and a compound of Formula (DD), or a pharmaceutically acceptable salt thereof. 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, or a pharmaceutically acceptable salt of the foregoing, a compound of Formula (BB), or a pharmaceutically acceptable salt thereof, and a compound of Formula (DD), or a pharmaceutically acceptable salt thereof. 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, or a pharmaceutically acceptable salt of the foregoing, a compound of Formula (BB), or a pharmaceutically acceptable salt thereof, and a compound of Formula (DD), or a pharmaceutically acceptable salt thereof. 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, 7000-7077, 8000-8012 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, or a pharmaceutically acceptable salt of the foregoing, a compound of Formula (BB), or a pharmaceutically acceptable salt thereof and a compound of Formula (DD), or a pharmaceutically acceptable salt thereof. In some embodiments, the viral infection is HCV.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] Figure 1 illustrates four chromatograms, labeled A, B, C and D, from the results of a hepatocyte activation assay.

[0013] Figure 2 shows example HCV protease inhibitors.

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

[0015] Figure 4 shows example non-nucleoside HCV polymerase inhibitors.

[0016] Figure 5 shows example NS5A inhibitors.

[0017] Figure 6 shows example other antivirals.

[0018] Figures 7A-7I show example compounds of Formula (I).

[0019] Figures 8A-8I show example compounds of Formula (AA), and triphosphates thereof.

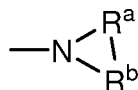
[0020] Figures 9A-9B show example compounds of Formula (BB).

[0021] Figure 10 shows Formula (DD).

DETAILED DESCRIPTION

[0022] 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.

[0023] As used herein, any "R" group(s) such as, without limitation, R, R¹, R², R^{3a}, R^{3b}, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, R^{1A}, R^{2A}, R^{3A}, R^{3B}, R^{4A}, R^{5A}, R^{6A}, R^{7A}, R^{8A}, R^{9A} and R" 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, aryl, heteroaryl or heterocycle. For example, without limitation, if R^{1a} and R^{1b} of an NR^{1a}R^{1b} group are indicated to be "taken together," it means that they are covalently bonded to one another to form a ring:



[0024] 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, heteroalicycyl, aralkyl, heteroaralkyl, (heteroalicycyl)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 group and a di-substituted amino group, and protected derivatives thereof.

[0025] 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 heteroalicycyl 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 heteroalicycyl can contain from “a” to “b”, inclusive, carbon atoms. Thus, for example, a “C₁ to C₄ alkyl” group refers to all alkyl groups having from 1 to 4 carbons, that is, CH₃-, CH₃CH₂-, CH₃CH₂CH₂-, (CH₃)₂CH-, CH₃CH₂CH₂CH₂-, CH₃CH₂CH(CH₃)- and (CH₃)₃C-. If no “a” and “b” are designated with regard to an alkyl, alkenyl, alkynyl, cycloalkyl cycloalkenyl, cycloalkynyl, aryl, heteroaryl or heteroalicycyl group, the broadest range described in these definitions is to be assumed.

[0026] 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 “C₁-C₄ alkyl” or similar designations. By way of example only, “C₁-C₄ 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.

[0027] 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.

[0028] 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.

[0029] 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.

[0030] 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.

[0031] 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.

[0032] 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 C₆-C₁₄ aryl group, a C₆-C₁₀ aryl group, or a C₆ aryl group. Examples of aryl groups include, but are not limited to, benzene, naphthalene and azulene. An aryl group may be substituted or unsubstituted.

[0033] 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.

[0034] 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).

[0035] 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.

[0036] 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.

[0037] A “(heteroalicycyl)alkyl” and “(heterocycyl)alkyl” refer to a heterocyclic or a heteroalicyclic group connected, as a substituent, via a lower alkylene group. The lower alkylene and heterocycyl of a (heteroalicycyl)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.

[0038] “Lower alkylene groups” are straight-chained -CH₂- tethering groups, forming bonds to connect molecular fragments via their terminal carbon atoms. Examples include but are not limited to methylene (-CH₂-), ethylene (-CH₂CH₂-), propylene (-CH₂CH₂CH₂-), and butylene (-CH₂CH₂CH₂CH₂-). 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.”

[0039] 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 and tert-butoxy. An alkoxy may be substituted or unsubstituted.

[0040] 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.

[0041] 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.

[0042] 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 and 1-chloro-2-fluoromethyl, 2-fluoroisobutyl. A haloalkyl may be substituted or unsubstituted.

[0043] 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 and 1-chloro-2-fluoromethoxy, 2-fluoroisobutoxy. A haloalkoxy may be substituted or unsubstituted.

[0044] 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.

[0045] A “sulfenyl” group refers to an “-SR” group in which R can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicycyl, aralkyl, or (heteroalicycyl)alkyl. A sulfenyl may be substituted or unsubstituted.

[0046] 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.

[0047] A “sulfonyl” group refers to an “SO₂R” group in which R can be the same as defined with respect to sulfenyl. A sulfonyl may be substituted or unsubstituted.

[0048] 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, heteroalicycyl, aralkyl, or (heteroalicycyl)alkyl, as defined herein. An O-carboxy may be substituted or unsubstituted.

[0049] 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.

[0050] 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.

[0051] A “trihalomethanesulfonyl” group refers to an “X₃CSO₂-” group wherein X is a halogen.

[0052] A “trihalomethanesulfonamido” group refers to an “X₃CS(O)₂N(R_A)-” group wherein X is a halogen and R_A hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicycyl, aralkyl, or (heteroalicycyl)alkyl.

[0053] The term “amino” as used herein refers to a -NH₂ group.

[0054] As used herein, the term “hydroxy” refers to a -OH group.

[0055] A “cyano” group refers to a “-CN” group.

[0056] The term “azido” as used herein refers to a -N₃ group.

[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 “-SO₂N(R_AR_B)” group in which R_A and R_B can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicycyl, aralkyl, or (heteroalicycyl)alkyl. An S-sulfonamido may be substituted or unsubstituted.

[0063] An “N-sulfonamido” group refers to a “ $\text{RSO}_2\text{N(R}_A\text{)-}$ ” group in which R and R_A can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicycyl, aralkyl, or (heteroalicycyl)alkyl. An N-sulfonamido may be substituted or unsubstituted.

[0064] An “O-carbamyl” group refers to a “ $\text{-OC(=O)N(R}_A\text{R}_B\text{)-}$ ” group in which R_A and R_B can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicycyl, aralkyl, or (heteroalicycyl)alkyl. An O-carbamyl may be substituted or unsubstituted.

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

[0066] An “O-thiocarbamyl” group refers to a “ $\text{-OC(=S)-N(R}_A\text{R}_B\text{)-}$ ” group in which R_A and R_B can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicycyl, aralkyl, or (heteroalicycyl)alkyl. An O-thiocarbamyl may be substituted or unsubstituted.

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

[0068] A “C-amido” group refers to a “ $\text{-C(=O)N(R}_A\text{R}_B\text{)-}$ ” group in which R_A and R_B can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicycyl, aralkyl, or (heteroalicycyl)alkyl. A C-amido may be substituted or unsubstituted.

[0069] An “N-amido” group refers to a “ $\text{RC(=O)N(R}_A\text{)-}$ ” group in which R and R_A can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicycyl, aralkyl, or (heteroalicycyl)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, “C₁-C₃ 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-N⁶-alkyladenine (e.g., 8-oxo-N⁶-methyladenine), 7-deazaxanthine, 7-deazaguanine, 7-dezaadenine, N⁴,N⁴-ethanocytosin, N⁶,N⁶-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, 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)-, and benzyl-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 alkoxy carbonyls (e.g., t-butoxycarbonyl (BOC), acetyl, or isobutyryl); arylalkylcarbonyls and arylalkoxy carbonyls (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 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-toluenesulfonic, 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, C₁-C₇ 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 of the invention. 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.

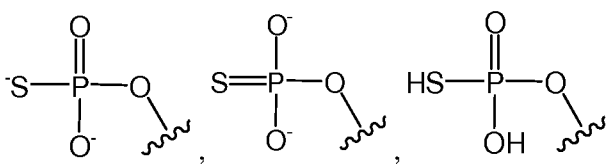
[0081] With respect to the use of substantially any plural and/or singular terms herein, those having skill in the art can translate from the plural to the singular and/or from the singular to the plural as is appropriate to the context and/or application. The various singular/plural permutations may 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.

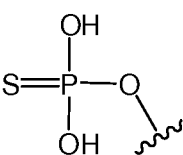
[0082] It is understood that, in any compound described herein having one or more chiral centers, if an absolute stereochemistry is not expressly indicated, then each center

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 a phosphate and a phosphorothioate groups are intended to be included. Examples of tautomers of a

phosphorothioate include the following:



and . 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.

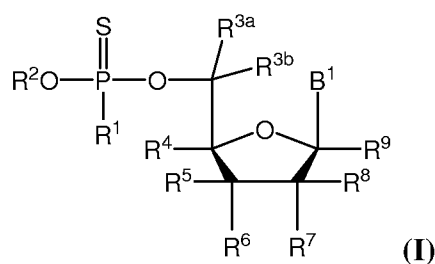
[0084] It is to be understood that where compounds disclosed herein have unfilled valencies, then the valencies are to be filled with hydrogens or isotopes thereof, e.g., hydrogen-1 (protium) and hydrogen-2 (deuterium).

[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.

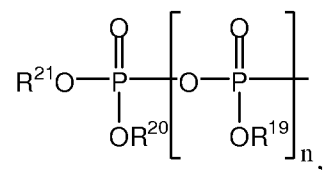
[0087] Where a range of values is provided, it is understood that the upper and lower limit, and each intervening value between the upper and lower limit of the range is encompassed within the embodiments.

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

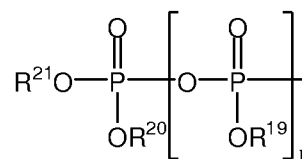


wherein: B¹ can be an optionally substituted heterocyclic base or an optionally substituted heterocyclic base with a protected amino group; R¹ can be selected from O⁻, OH, an optionally substituted N-linked amino acid and an optionally substituted N-linked amino acid ester derivative; R² can be selected from an optionally substituted aryl, an optionally

substituted heteroaryl, an optionally substituted heterocyclyl and

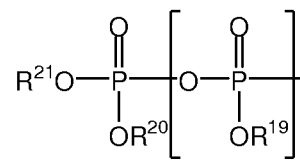


wherein R^{19} , R^{20} and R^{21} can be independently absent or hydrogen, and n can be 0 or 1;



provided that when R^1 is O^- or OH , then R^2 is 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^{3a} and R^{3b} can be taken together to form an optionally substituted C_{3-6} cycloalkyl; R^4 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^5 can be selected from hydrogen, halogen, azido, cyano, an optionally substituted C_{1-6} alkyl, $-OR^{10}$ and $-OC(=O)R^{11}$; R^6 can be selected from hydrogen, halogen, azido, cyano, an optionally substituted C_{1-6} alkyl, $-OR^{12}$ and $-OC(=O)R^{13}$; R^7 can be selected from hydrogen, halogen, azido, cyano, an optionally substituted C_{1-6} alkyl, $-OR^{14}$ and $-OC(=O)R^{15}$; or R^6 and R^7 can be both oxygen atoms and linked together by a carbonyl group; R^8 can be selected from hydrogen, halogen, azido, cyano, an optionally substituted C_{1-6} alkyl, $-OR^{16}$ and $-OC(=O)R^{17}$; R^9 can be selected from hydrogen, azido, cyano, an optionally substituted C_{1-6} alkyl and $-OR^{18}$; R^{10} , R^{12} , R^{14} , R^{16} and R^{18} can be independently selected from hydrogen and an optionally substituted C_{1-6} alkyl; and R^{11} , R^{13} , R^{15} and R^{17} can be independently selected from an optionally substituted C_{1-6} alkyl and an optionally substituted C_{3-6} cycloalkyl; with the proviso that when R^{3a} , R^{3b} , R^4 , R^5 , R^7 , R^8 and R^9 are all hydrogen, then R^6 cannot be azido.

[0089] With respect to R^2 , in some embodiments, R^2 can be an optionally substituted heteroaryl. In other embodiments, R^2 can be an optionally substituted heterocyclyl. In still other embodiments, R^2 can be an optionally substituted aryl. For example, R^2 can be an optionally substituted phenyl or an optionally substituted naphthyl. If R^2 is a substituted phenyl or a substituted naphthyl, the phenyl ring and the naphthyl ring(s) can be substituted one or more times. Suitable substituents that can be present on optionally substituted phenyl and an optionally substituted naphthyl include electron-donating groups and electron-withdrawing groups. In some embodiments, R^2 can be a para-substituted phenyl. In other embodiment, R^2 can be an unsubstituted phenyl or an unsubstituted



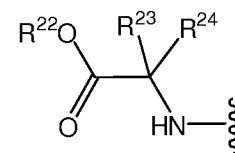
naphthyl. In yet still other embodiments, R^2 can be R^{19} , R^{20} and R^{21} can be independently absent or hydrogen, and n can be 0 or 1. In some embodiments, n can be 0. In other embodiments, n can be 1. Those skilled in the art understand when n is 0, R^2 can be an α -thiodiphosphate. Similarly, those skilled in the art understand when n is 1, R^2 can be an α -thiotriphosphate. In some embodiments, at least one of R^{19} , R^{20} and R^{21} can be absent. In other embodiments, at least one of R^{19} , R^{20} and R^{21} can be hydrogen. In some embodiments, R^{20} and R^{21} can be absent. In other embodiments, R^{20} and R^{21} can be hydrogen. In some embodiments, R^{19} , R^{20} and R^{21} can be absent. In some embodiments, R^{19} , R^{20} and R^{21} can be hydrogen. Those skilled in the art understand that when any of R^{19} , R^{20} and R^{21} are absent the oxygen atom to which R^{19} , R^{20} and R^{21} are associated with can have a negative charge. For example, when R^{20} is absent, the oxygen atom to which R^{20} is associated with can be O^- . Depending upon the substituents attached to each phosphorus atoms, one or more the phosphorus atoms can be a chiral center. For example, when n is 1, the alpha-phosphorus (the phosphorus nearest to the pentose ring) can be a chiral center. In some embodiments, the alpha-phosphorus can be a (R)-stereocenter. In other embodiments, the alpha-phosphorus can be a (S)-stereocenter.

[0090] In some embodiments, R^1 can be absent. In other embodiments, R^1 can be hydrogen. In still other embodiments, R^1 can be an optionally substituted N-linked α -amino acid. In yet still other embodiments, R^1 can be an optionally substituted N-linked α -amino acid ester derivative. Various amino acids and amino acid ester derivatives can be used, including those described herein. 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. Examples of an N-linked amino acid ester derivatives include, but are not limited to, an ester derivatives 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.

[0091] In an embodiment, R^1 can be an ester derivative of alanine. In an embodiment, 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.

[0092] In some embodiments, when R^1 is an optionally substituted N-linked α -amino acid or an optionally substituted N-linked α -amino acid ester derivative, then R^2 can be selected from optionally substituted aryl, an optionally substituted heteroaryl and an optionally substituted heterocyclyl. In some embodiments, when R^1 is an optionally substituted N-linked α -amino acid ester derivative, then R^2 can be an optionally substituted aryl. In other embodiments, when R^1 is an optionally substituted N-linked α -amino acid ester derivative, then R^2 can be an optionally substituted heteroaryl. In still other embodiments, when R^1 is an optionally substituted N-linked α -amino acid ester derivative, then R^2 can be an optionally substituted heterocyclyl.



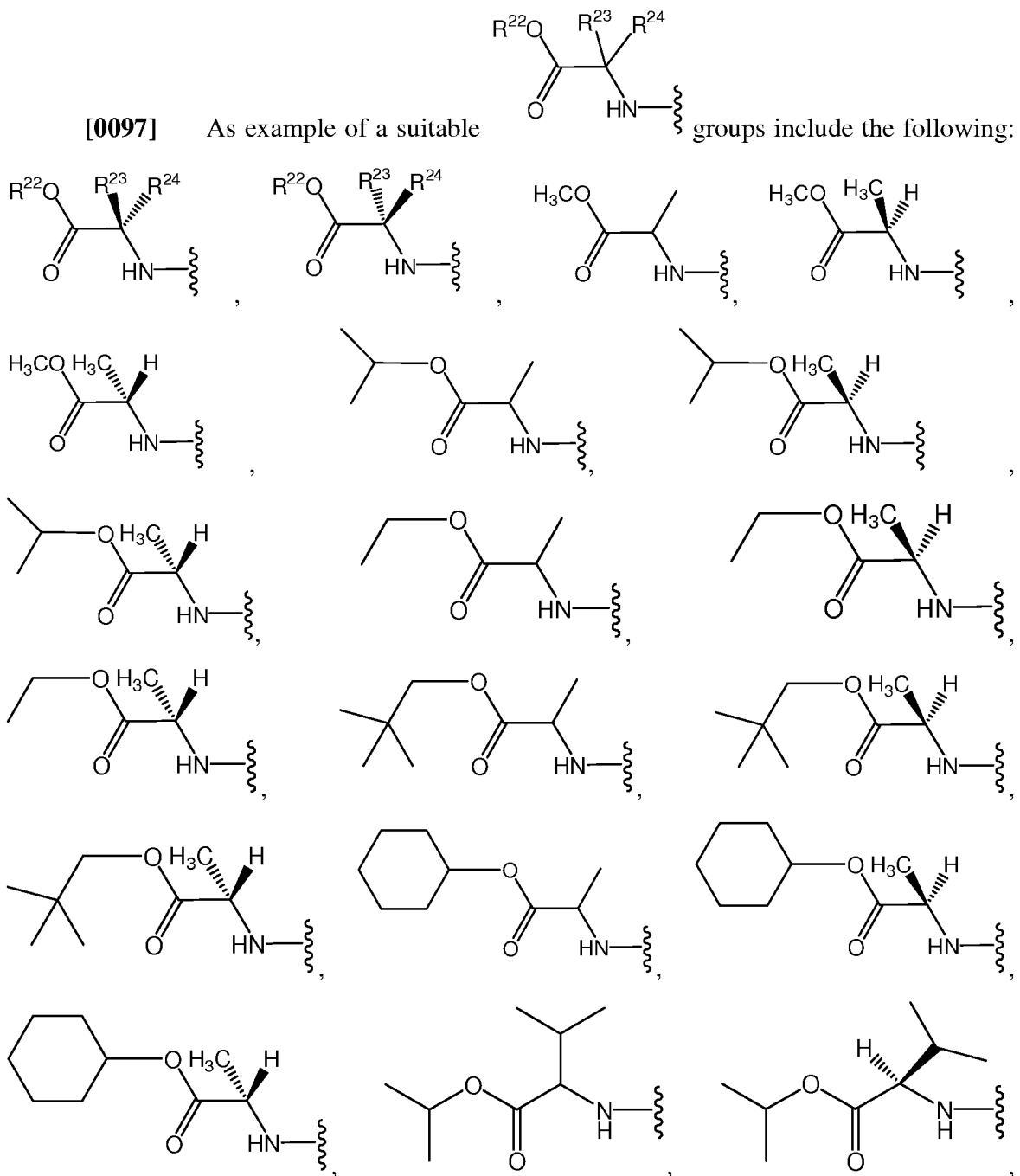
[0093] In some embodiments, R^1 can have the structure wherein R^{22} can be selected from hydrogen, an optionally substituted C_{1-6} -alkyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted aryl, an optionally substituted aryl(C_{1-6} alkyl) and an optionally substituted C_{1-6} haloalkyl; and R^{23} 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_6 aryl, an optionally substituted C_{10} aryl and an optionally substituted aryl(C_{1-6} alkyl); and R^{24} can be hydrogen or an optionally substituted C_{1-4} -alkyl; or R^{23} and R^{24} can be taken together to form an optionally substituted C_{3-6} cycloalkyl.

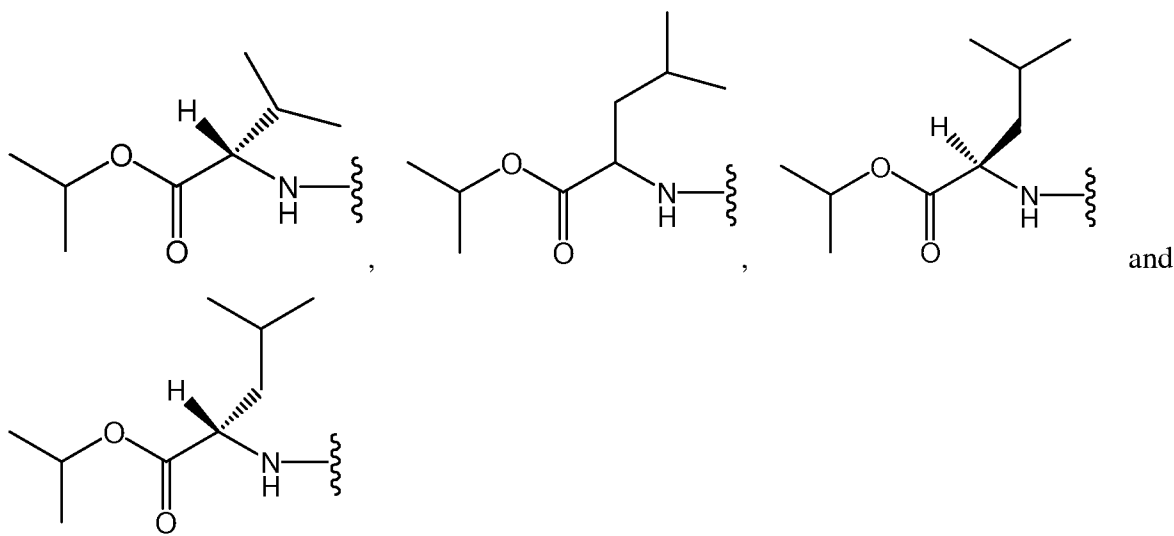
[0094] When R^1 has the structure shown above, R^{23} can be an optionally substituted C_{1-6} -alkyl. Examples of suitable optionally substituted C_{1-6} -alkyls include optionally substituted variants of the following: methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, pentyl (branched and straight-chained), and hexyl (branched and straight-chained). When R^{23} is substituted, R^{23} 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 embodiment, R^{23} can be an unsubstituted C_{1-6} -alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, pentyl (branched and straight-chained), and hexyl (branched and straight-chained). In an embodiment, R^{23} can be methyl.

[0095] As to R^{22} , in some embodiments, R^{22} 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^{22} can be methyl or isopropyl. In some embodiments, R^{22} can be ethyl or neopentyl. In other embodiments, R^{22} 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 an embodiment, R^{22} can be an optionally substituted cyclohexyl. In still other embodiments, R^{22} can be an optionally substituted aryl, such as phenyl and naphthyl. In yet still other embodiments, R^{22} can be an optionally substituted aryl(C_{1-6} alkyl). In some embodiments, R^{22} can be an optionally substituted benzyl. In some embodiments, R^{22} can be an optionally substituted C_{1-6} haloalkyl, for example, CF_3 .

[0096] In some embodiments, R^{24} can be hydrogen. In other embodiments, R^{24} can be an optionally substituted C_{1-4} -alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and tert-butyl. In an embodiment, R^{24} can be methyl. In some embodiments, R^{23} and R^{24} 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^{23} and R^{24} , the carbon to which R^{23} and R^{24} are attached may be a chiral center.

In some embodiment, the carbon to which R^{23} and R^{24} are attached may be a (R)-chiral center. In other embodiments, the carbon to which R^{23} and R^{24} are attached may be a (S)-chiral center.





[0098] The substituents attached to the 5'-position of a compound of Formula (I) can vary. In some embodiments, R^{3a} and R^{3b} can be the same. In other embodiments, R^{3a} and R^{3b} can be different. In some embodiments, R^{3a} and R^{3b} can be both hydrogen. In some embodiments, at least one of R^{3a} and R^{3b} can be an optionally substituted C_{1-6} -alkyl; and the other of R^{3a} and R^{3b} 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 an embodiment, at least one of R^{3a} and R^{3b} can be methyl, and the other of R^{3a} and R^{3b} can be hydrogen. In other embodiments, at least one of R^{3a} and R^{3b} can be an optionally substituted C_{1-6} -haloalkyl, and the other of R^{3a} and R^{3b} can be hydrogen. One example of a suitable optionally substituted C_{1-6} -haloalkyl is CF_3 . In other still embodiments, R^{3a} and R^{3b} can be taken together to form an optionally substituted C_{3-6} cycloalkyl. 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.

[0099] The substituents attached to the 4'-carbon can vary. In some embodiments, R^4 can be hydrogen. In other embodiments, R^4 can be azido. In still other embodiments, R^4 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 some

embodiments, R^4 can be an optionally substituted C_{2-6} alkenyl. In some embodiments, R^4 can be an optionally substituted C_{2-6} alkynyl.

[0100] The substituents attached to the 2'-carbon and the 3'-carbon can also vary. In some embodiments, R^5 can be hydrogen. In other embodiments, R^5 can be halogen. In still other embodiments, R^5 can be azido. In yet still other embodiments, R^5 can be cyano. In some embodiments, R^5 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^5 can be $-OR^{10}$, wherein R^{10} can be hydrogen. In still other embodiments, R^5 can be $-OR^{10}$, wherein R^{10} can be an optionally substituted C_{1-6} alkyl. In yet still other embodiments, R^5 can be $-OC(=O)R^{11}$, wherein R^{11} can be an optionally substituted C_{1-6} alkyl or an optionally substituted C_{3-6} cycloalkyl. Examples of suitable C_{1-6} alkyls and C_{3-6} cycloalkyls are described herein.

[0101] In some embodiments, R^6 can be hydrogen. In other embodiments, R^6 can be halogen. In still other embodiments, R^6 can be azido. In yet still other embodiments, R^6 can be cyano. In some embodiments, R^6 can be an optionally substituted C_{1-6} alkyl. In other embodiments, R^6 can be $-OR^{12}$, wherein R^{12} can be hydrogen. In still other embodiments, R^6 can be $-OR^{12}$, wherein R^{12} can be an optionally substituted C_{1-6} alkyl. A non-limiting list of examples of R^6 being $-OR^{12}$, wherein R^{12} can be an optionally substituted C_{1-6} alkyl are methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy and tert-butoxy, pentoxy (straight-chained or branched) and hexoxy (straight-chained or branched). In yet still other embodiments, R^6 can be $-OC(=O)R^{13}$, wherein R^{13} can be an optionally substituted C_{1-6} alkyl or an optionally substituted C_{3-6} cycloalkyl. 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). Examples of suitable optionally substituted C_{3-6} cycloalkyls include optionally substituted variants of the following: cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

[0102] In some embodiments, R^7 can be hydrogen. In other embodiments, R^7 can be halogen. In still other embodiments, R^7 can be azido. In yet still other embodiments, R^7

can be cyano. In some embodiments, R^7 can be an optionally substituted C_{1-6} alkyl. In other embodiments, R^7 can be $-OR^{14}$. In an embodiment, when R^{14} is hydrogen, R^7 can be a hydroxy group. In still other embodiments, when R^{14} is an optionally substituted C_{1-6} alkyl, R^7 can be an optionally substituted C_{1-6} alkoxy. Examples, of R^7 being $-OR^{14}$, wherein R^{14} can be an optionally substituted C_{1-6} alkyl include, but are not limited to, are methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, tert-butoxy, pentoxy (straight-chained or branched) and hexoxy (straight-chained or branched). In yet still other embodiments, R^7 can be $-OC(=O)R^{15}$, wherein R^{15} 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 some embodiments, R^7 can be $-OC(=O)R^{15}$, wherein R^{15} can be an optionally substituted C_{3-6} cycloalkyl

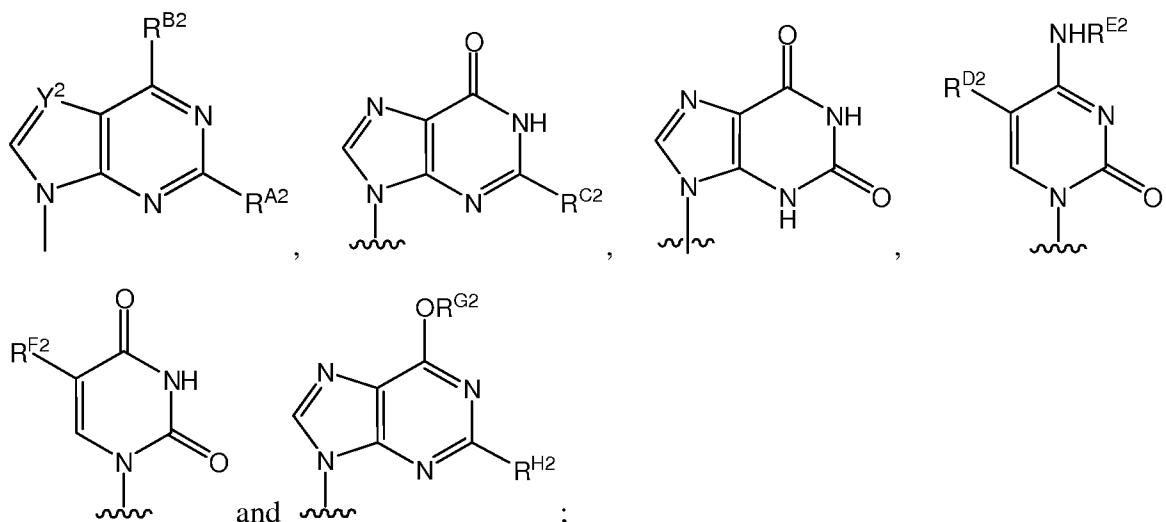
[0103] In some embodiments, R^8 can be hydrogen. In other embodiments, R^8 can be halogen. In still other embodiments, R^8 can be azido. In yet still other embodiments, R^8 can be cyano. In some embodiments, R^8 can be $-OR^{16}$. When R^{16} is hydrogen, R^8 can be hydroxy. Alternatively, when R^{16} is an optionally substituted C_{1-6} alkyl, R^8 can be an optionally substituted C_{1-6} alkoxy. Suitable alkoxy groups are described herein. In other embodiments, R^8 can be an optionally substituted C_{1-6} alkyl. In still other embodiments, R^8 can be $-OC(=O)R^{17}$ in which R^{17} is an optionally substituted C_{1-6} alkyl. In yet still other embodiments, R^8 can be $-OC(=O)R^{17}$ in which R^{17} is an optionally substituted C_{3-6} cycloalkyl. Examples of suitable C_{1-6} alkyl and C_{3-6} cycloalkyl groups are described herein.

[0104] In some embodiments, R^6 and R^7 can both be hydroxy. In still other embodiments, R^6 and R^7 can both be both oxygen atoms and linked together by a carbonyl group, for example, $-O-C(=O)-O-$. In some embodiments, at least one of R^7 and R^8 can be a halogen. In some embodiments, R^7 and R^8 can both be a halogen. In other embodiments, R^7 can be a halogen and R^8 can be an optionally substituted C_{1-6} alkyl, such as those described herein. In other embodiments, R^7 can be hydrogen and R^8 can be a halogen. In still other embodiments, at least one of R^6 and R^7 can be a hydroxy and R^8 can be an optionally substituted C_{1-6} alkyl. In yet still other embodiments, R^6 can be hydroxy, R^7 can be hydroxy, H or halogen, and R^8 can be an optionally substituted C_{1-6} alkyl. In some embodiments, R^{3a} ,

R^{3b} , R^4 , R^5 and R^9 can be hydrogen in any of the embodiments described in this paragraph. In some embodiments, B^1 can be an optionally substituted adenine, an optionally substituted guanine, and optionally substituted thymine, optionally substituted cytosine, or an optionally substituted uracil in any of the embodiments described in this paragraph.

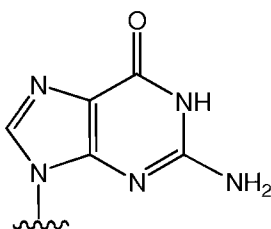
[0105] In some embodiments, R^9 can be hydrogen. In other embodiments, R^9 can be azido. In still other embodiments, R^9 can be cyano. In yet still other embodiments, R^9 can be an optionally substituted C_{1-6} alkyl, such as those described herein. In some embodiments, R^9 can be $-OR^{18}$. In some embodiments, when R^9 is $-OR^{18}$, R^9 can be a hydroxy group. In other embodiments, when R^9 is $-OR^{18}$, R^9 can be an optionally substituted C_{1-6} alkoxy. Examples of optionally substituted C_{1-6} alkoxy include the following: methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, tert-butoxy, pentoxy (branched and straight-chained), and hexoxy (branched and straight-chained).

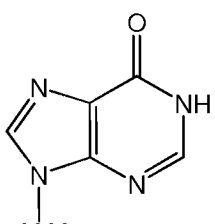
[0106] Various optionally substituted heterocyclic bases can be attached to the pentose ring. In some embodiments, one or more of the amine and/or amino groups may be protected with a suitable protecting group. For example, an amino group may be protected by transforming the amine and/or amino group to an amide or a carbamate. In some embodiments, 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:

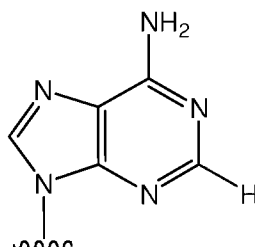
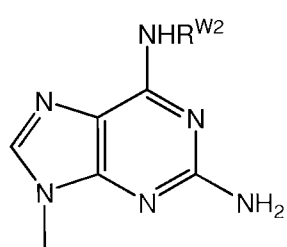


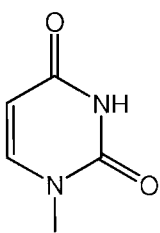
wherein: R^{A2} can be selected from hydrogen, halogen and NHR^{J2} , wherein R^{J2} can be selected from hydrogen, $-C(=O)R^{K2}$ and $-C(=O)OR^{L2}$; R^{B2} can be halogen or NHR^{W2} , wherein R^{W2} is selected from hydrogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} 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, heteroalicycyl, aryl(C_{1-6} alkyl), heteroaryl(C_{1-6} alkyl) and heteroalicycyl(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." Suitable optionally substituted C_{1-6} alkyl groups that can be present on an optionally substituted heterocyclic base or an optionally substituted heterocyclic base with one or more protected amino groups are described herein, and 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).

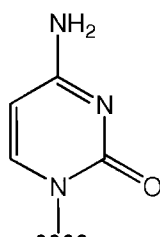
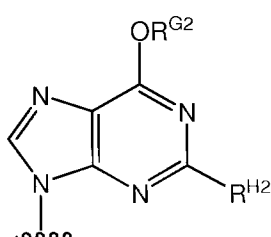
[0107] In some embodiments, B^1 can be selected from adenine, guanine, thymine, cytosine and uracil. In some embodiments, R^{B2} can be NH_2 . In other embodiments, R^{E2} can

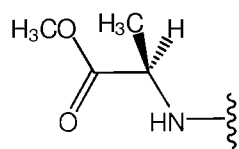
be hydrogen. In some embodiments, B¹ can be . In other

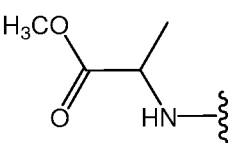
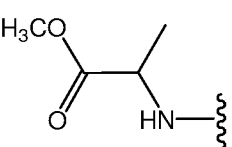
embodiments, B¹ can be . In some embodiments, B¹ can be

. In some embodiments, B¹ can be . In still other

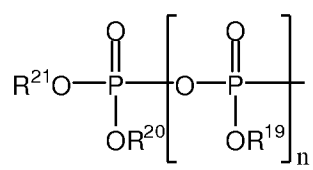
embodiments, B¹ can be . In yet still other embodiments, B¹ can be

. In some embodiments, B¹ can be . In some embodiments, when R² is a substituted or unsubstituted phenyl, then R¹ cannot be

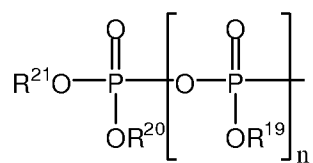
. In other embodiments, when R² is a substituted or unsubstituted

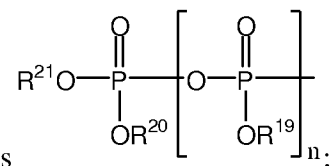
phenyl, then R^1 cannot be . In still other embodiments, when R^2 is a substituted or unsubstituted phenyl and R^1 is , then at least one of R^5 and R^6 cannot be hydroxy.

[0108] In some embodiments, when R^1 is O^- or OH, then R^2 cannot be

. In some embodiments, at least one of R^{3a} and R^{3b} cannot be hydrogen. In some embodiments, R^4 is not azido. In some embodiments, when R^4 is not azido, then R^7 and R^8 are not both halogen. In some embodiments, when R^4 is azido, then B^1 is not an optionally substituted uracil, optionally substituted uracil with one or more protected amino groups, an optionally substituted cytosine or optionally substituted cytosine with one or more protected amino groups. In some embodiments, R^6 cannot be azido. In some embodiments, when R^1 is a methyl ester of glycine, alanine, valine, or phenylalanine; R^2 is p-chlorophenyl or p-nitrophenyl; B^1 is thymine; and R^{3a} , R^{3b} , R^4 , R^5 , R^7 , R^8 , and R^9 are all hydrogen; then R^6 cannot be azido. In some embodiments, at least one of R^6 and R^7 cannot be hydroxy. For example, R^6 cannot be hydroxy, R^7 cannot be hydroxy, or both of R^6 and R^7 cannot be hydroxy.

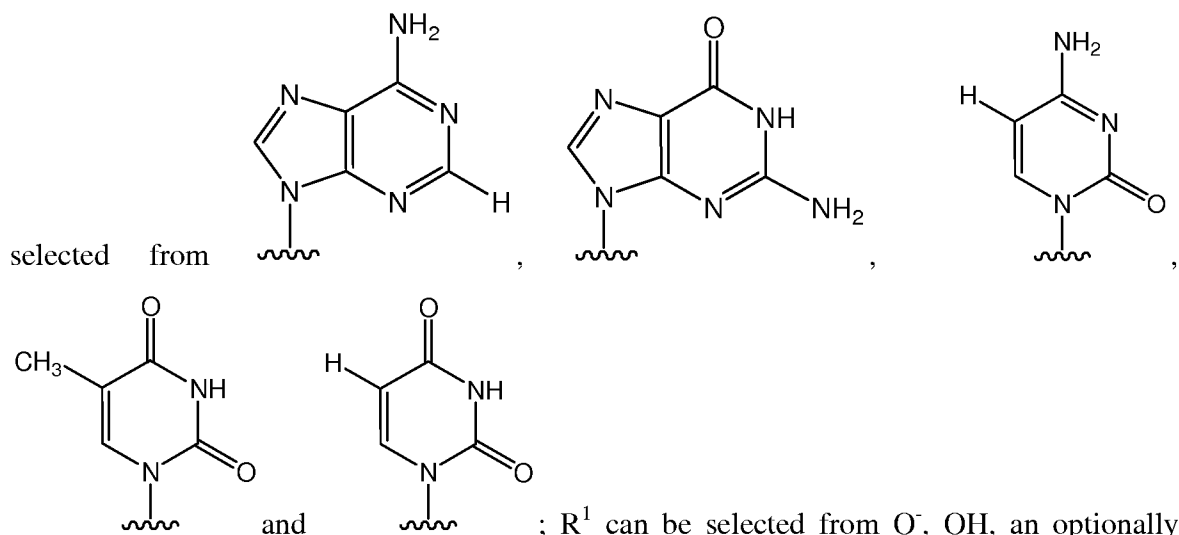
[0109] Some embodiments disclosed herein relate to a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein: B^1 can be an optionally substituted heterocyclic base as described in paragraph [0106]; R^1 can be selected from O^- , OH, an optionally substituted N-linked amino acid and an optionally substituted N-linked amino acid ester derivative; R^2 can be selected from an optionally substituted aryl and

, wherein R^{19} , R^{20} and R^{21} can be independently absent or hydrogen,

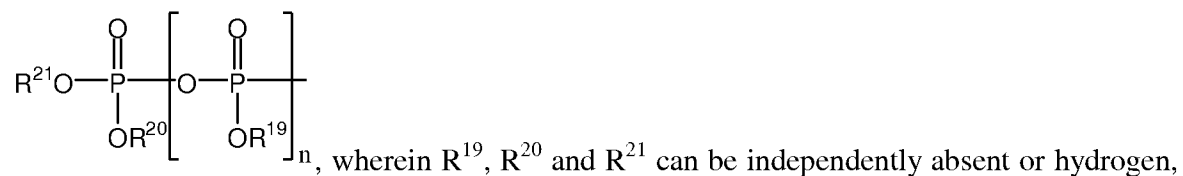


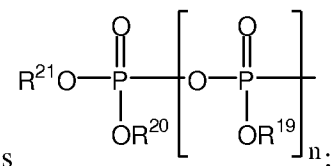
and n can be 0 or 1; provided that when R¹ is O⁻ or OH, then R² is R^{3a} and R^{3b} can be hydrogen; R⁴ can be hydrogen; R⁵ can be selected from hydrogen, halogen, an optionally substituted C₁₋₆ alkyl and -OR¹⁰; R⁶ can be selected from hydrogen, halogen, optionally substituted C₁₋₆ alkyl, -OR¹² and -OC(=O)R¹³; R⁷ can be selected from hydrogen, halogen, azido, cyano, an optionally substituted C₁₋₆ alkyl, -OR¹⁴ and -OC(=O)R¹⁵; or R⁶ and R⁷ can be both oxygen atoms and linked together by a carbonyl group; R⁸ can be selected from hydrogen, halogen, an optionally substituted C₁₋₆ alkyl and -OR¹⁶; R⁹ can be hydrogen; R¹⁰, R¹², R¹⁴ and R¹⁶ can be independently selected from hydrogen and an optionally substituted C₁₋₆ alkyl; and R¹³ and R¹⁵ can be independently selected from an optionally substituted C₁₋₆ alkyl and an optionally substituted C₃₋₆ cycloalkyl.

[0110] Some embodiments disclosed herein relate to a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein: B¹ can be an optionally substituted heterocyclic base or an optionally substituted heterocyclic base with a protected amino group



; R¹ can be selected from O⁻, OH, an optionally substituted N-linked amino acid and an optionally substituted N-linked amino acid ester derivative; R² can be selected from an optionally substituted aryl and

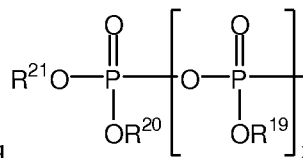




and n can be 0 or 1; provided that when R^1 is O^- or OH , then R^2 is

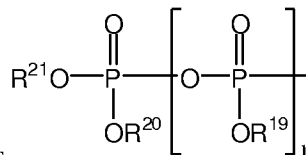
R^{3a} and R^{3b} can be hydrogen; R⁴ can be hydrogen; R⁵ can be selected from hydrogen, halogen, an optionally substituted C₁₋₆ alkyl and -OR¹⁰; R⁶ can be selected from hydrogen, halogen, optionally substituted C₁₋₆ alkyl, -OR¹² and -OC(=O)R¹³; R⁷ can be selected from hydrogen, halogen, azido, cyano, an optionally substituted C₁₋₆ alkyl, -OR¹⁴ and -OC(=O)R¹⁵; or R⁶ and R⁷ can be both oxygen atoms and linked together by a carbonyl group; R⁸ can be selected from hydrogen, halogen, an optionally substituted C₁₋₆ alkyl and -OR¹⁶; R⁹ can be hydrogen; R¹⁰, R¹², R¹⁴ and R¹⁶ can be independently selected from hydrogen and an optionally substituted C₁₋₆ alkyl; and R¹³ and R¹⁵ can be independently selected from an optionally substituted C₁₋₆ alkyl and an optionally substituted C₃₋₆ cycloalkyl.

[0111] In some embodiments, Formula (I) can be a compound of Formula (Ia), wherein: B¹ can be an optionally substituted heterocyclic base or an optionally substituted heterocyclic base with a protected amino group selected from cytosine, uridine, thymidine, guanine and adenine; R¹ can be selected from O⁻, OH, and an optionally substituted N-linked amino acid ester derivative of alanine, valine, or leucine; R² can be selected from an optionally substituted phenyl, an optionally substituted naphthyl, an optionally substituted



pyridyl, an optionally substituted quinolyl, and

and R^{21} independently can be hydrogen or absent, and n can be 0 or 1; provided that when R^1



is O^- or OH , then R^2 is

is O⁻ or OH, then R² is $\text{OR}^{2a} \left[\text{OR}^{2b} \right]_n$; R^{3a} and R^{3b} can be hydrogen; R⁴ can be hydrogen; R⁵ can be hydrogen; R⁶ can be -OR¹² or -OC(=O)R¹³; R⁷ can be selected from halogen, -OR¹⁴ and -OC(=O)R¹⁵; R⁸ can be an optionally substituted C₁₋₆ alkyl; R⁹ can be hydrogen; R¹² and R¹⁴ can be independently hydrogen or an optionally substituted C₁₋₆ alkyl; and R¹³ and R¹⁵ can be independently an optionally substituted C₁₋₆ alkyl.

[0112] Some embodiments relate to a compound of Formula (I) or a pharmaceutically acceptable salt thereof, wherein: B^1 can be an optionally substituted heterocyclic base or an optionally substituted heterocyclic base with a protected amino group; R^1 can be selected from O^- , OH, an optionally substituted N-linked amino acid and an optionally substituted N-linked amino acid ester derivative; R^2 can be selected from an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted

heterocyclyl and $R^{21}O-P(=O)(OR^{20})-O-P(=O)(OR^{19})_n$, wherein R^{19} , R^{20} and R^{21} can be independently absent or hydrogen, and n can be 0 or 1; provided that when R^1 is O^- or OH, then R^2 is

$R^{21}O-P(=O)(OR^{20})-O-P(=O)(OR^{19})_n$; R^{3a} and R^{3b} 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); or R^{3a} and R^{3b} can be taken together to form an optionally substituted C_{3-6} cycloalkyl; R^4 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^5 can be selected from hydrogen, halogen, azido, cyano, an optionally substituted C_{1-6} alkyl, $-OR^{10}$ and $-OC(=O)R^{11}$; R^6 can be selected from hydrogen, halogen, azido, cyano, an optionally substituted C_{1-6} alkyl, $-OR^{12}$ and $-OC(=O)R^{13}$; R^7 can be selected from hydrogen, halogen, azido, cyano, an optionally substituted C_{1-6} alkyl, $-OR^{14}$ and $-OC(=O)R^{15}$; or R^6 and R^7 can be both oxygen atoms and linked together by a carbonyl group; R^8 can be selected from hydrogen, halogen, azido, cyano, an optionally substituted C_{1-6} alkyl, $-OR^{16}$ and $-OC(=O)R^{17}$; R^9 can be selected from hydrogen, azido, cyano, an optionally substituted C_{1-6} alkyl and $-OR^{18}$; R^{10} , R^{12} , R^{14} , R^{16} and R^{18} can be independently selected from hydrogen and an optionally substituted C_{1-6} alkyl; and R^{11} , R^{13} , R^{15} and R^{17} can be independently an optionally substituted C_{1-6} alkyl and an optionally substituted C_{3-6} cycloalkyl.

[0113] 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 $> 55\%$, $\geq 75\%$, $\geq 80\%$, $\geq 90\%$, $\geq 95\%$, $\geq 98\%$, or $\geq 99\%$ as compared to the total concentration of the other diastereomers).

[0114] Some embodiments of R^1 and R^2 of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, are provided in Table 1. Tables 2-4 provide the structures of the variables bb01-bb12, aa01-aa11 and es01-es14, respectively. For example, the first entry in Table 1 is “bb01,aa01,es01,” corresponds to a compound of Formula (I),

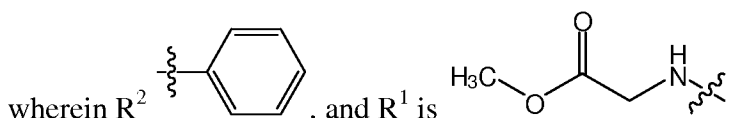


Table 1

R^2, R^1, R_α	R^2, R^1, R_α	R^2, R^1, R_α	R^2, R^1, R_α	R^2, R^1, R_α
bb01,aa01,es01	bb03,aa01,es01	bb05,aa01,es01	bb07,aa01,es01	bb09,aa01,es01
bb01,aa01,es02	bb03,aa01,es02	bb05,aa01,es02	bb07,aa01,es02	bb09,aa01,es02
bb01,aa01,es03	bb03,aa01,es03	bb05,aa01,es03	bb07,aa01,es03	bb09,aa01,es03
bb01,aa01,es04	bb03,aa01,es04	bb05,aa01,es04	bb07,aa01,es04	bb09,aa01,es04
bb01,aa01,es05	bb03,aa01,es05	bb05,aa01,es05	bb07,aa01,es05	bb09,aa01,es05
bb01,aa01,es06	bb03,aa01,es06	bb05,aa01,es06	bb07,aa01,es06	bb09,aa01,es06
bb01,aa01,es07	bb03,aa01,es07	bb05,aa01,es07	bb07,aa01,es07	bb09,aa01,es07
bb01,aa01,es08	bb03,aa01,es08	bb05,aa01,es08	bb07,aa01,es08	bb09,aa01,es08
bb01,aa01,es09	bb03,aa01,es09	bb05,aa01,es09	bb07,aa01,es09	bb09,aa01,es09
bb01,aa01,es10	bb03,aa01,es10	bb05,aa01,es10	bb07,aa01,es10	bb09,aa01,es10
bb01,aa01,es11	bb03,aa01,es11	bb05,aa01,es11	bb07,aa01,es11	bb09,aa01,es11
bb01,aa01,es12	bb03,aa01,es12	bb05,aa01,es12	bb07,aa01,es12	bb09,aa01,es12
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bb01,aa02,es03	bb03,aa02,es03	bb05,aa02,es03	bb07,aa02,es03	bb09,aa02,es03
bb01,aa02,es04	bb03,aa02,es04	bb05,aa02,es04	bb07,aa02,es04	bb09,aa02,es04
bb01,aa02,es05	bb03,aa02,es05	bb05,aa02,es05	bb07,aa02,es05	bb09,aa02,es05
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bb01,aa02,es07	bb03,aa02,es07	bb05,aa02,es07	bb07,aa02,es07	bb09,aa02,es07
bb01,aa02,es08	bb03,aa02,es08	bb05,aa02,es08	bb07,aa02,es08	bb09,aa02,es08
bb01,aa02,es09	bb03,aa02,es09	bb05,aa02,es09	bb07,aa02,es09	bb09,aa02,es09
bb01,aa02,es10	bb03,aa02,es10	bb05,aa02,es10	bb07,aa02,es10	bb09,aa02,es10
bb01,aa02,es11	bb03,aa02,es11	bb05,aa02,es11	bb07,aa02,es11	bb09,aa02,es11

R^2, R^1, R_α	R^2, R^1, R_α	R^2, R^1, R_α	R^2, R^1, R_α	R^2, R^1, R_α
bb01,aa02,es12	bb03,aa02,es12	bb05,aa02,es12	bb07,aa02,es12	bb09,aa02,es12
bb01,aa03,es01	bb03,aa03,es01	bb05,aa03,es01	bb07,aa03,es01	bb09,aa03,es01
bb01,aa03,es02	bb03,aa03,es02	bb05,aa03,es02	bb07,aa03,es02	bb09,aa03,es02
bb01,aa03,es03	bb03,aa03,es03	bb05,aa03,es03	bb07,aa03,es03	bb09,aa03,es03
bb01,aa03,es04	bb03,aa03,es04	bb05,aa03,es04	bb07,aa03,es04	bb09,aa03,es04
bb01,aa03,es05	bb03,aa03,es05	bb05,aa03,es05	bb07,aa03,es05	bb09,aa03,es05
bb01,aa03,es06	bb03,aa03,es06	bb05,aa03,es06	bb07,aa03,es06	bb09,aa03,es06
bb01,aa03,es07	bb03,aa03,es07	bb05,aa03,es07	bb07,aa03,es07	bb09,aa03,es07
bb01,aa03,es08	bb03,aa03,es08	bb05,aa03,es08	bb07,aa03,es08	bb09,aa03,es08
bb01,aa03,es09	bb03,aa03,es09	bb05,aa03,es09	bb07,aa03,es09	bb09,aa03,es09
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bb01,aa05,es11	bb03,aa05,es11	bb05,aa05,es11	bb07,aa05,es11	bb09,aa05,es11
bb01,aa05,es12	bb03,aa05,es12	bb05,aa05,es12	bb07,aa05,es12	bb09,aa05,es12
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bb01,aa06,es02	bb03,aa06,es02	bb05,aa06,es02	bb07,aa06,es02	bb09,aa06,es02
bb01,aa06,es03	bb03,aa06,es03	bb05,aa06,es03	bb07,aa06,es03	bb09,aa06,es03
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bb01,aa06,es05	bb03,aa06,es05	bb05,aa06,es05	bb07,aa06,es05	bb09,aa06,es05
bb01,aa06,es06	bb03,aa06,es06	bb05,aa06,es06	bb07,aa06,es06	bb09,aa06,es06

R^2, R^1, R_α	R^2, R^1, R_α	R^2, R^1, R_α	R^2, R^1, R_α	R^2, R^1, R_α
bb01,aa06,es07	bb03,aa06,es07	bb05,aa06,es07	bb07,aa06,es07	bb09,aa06,es07
bb01,aa06,es08	bb03,aa06,es08	bb05,aa06,es08	bb07,aa06,es08	bb09,aa06,es08
bb01,aa06,es09	bb03,aa06,es09	bb05,aa06,es09	bb07,aa06,es09	bb09,aa06,es09
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bb01,aa07,es03	bb03,aa07,es03	bb05,aa07,es03	bb07,aa07,es03	bb09,aa07,es03
bb01,aa07,es04	bb03,aa07,es04	bb05,aa07,es04	bb07,aa07,es04	bb09,aa07,es04
bb01,aa07,es05	bb03,aa07,es05	bb05,aa07,es05	bb07,aa07,es05	bb09,aa07,es05
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bb01,aa09,es10	bb03,aa09,es10	bb05,aa09,es10	bb07,aa09,es10	bb09,aa09,es10
bb01,aa09,es11	bb03,aa09,es11	bb05,aa09,es11	bb07,aa09,es11	bb09,aa09,es11
bb01,aa09,es12	bb03,aa09,es12	bb05,aa09,es12	bb07,aa09,es12	bb09,aa09,es12
bb01,aa10,es01	bb03,aa10,es01	bb05,aa10,es01	bb07,aa10,es01	bb09,aa10,es01

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R^2, R^1, R_α	R^2, R^1, R_α	R^2, R^1, R_α	R^2, R^1, R_α	R^2, R^1, R_α
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bb02,aa03,es10	bb04,aa03,es10	bb06,aa03,es10	bb08,aa03,es10	bb10,aa03,es10
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bb02,aa04,es02	bb04,aa04,es02	bb06,aa04,es02	bb08,aa04,es02	bb10,aa04,es02
bb02,aa04,es03	bb04,aa04,es03	bb06,aa04,es03	bb08,aa04,es03	bb10,aa04,es03
bb02,aa04,es04	bb04,aa04,es04	bb06,aa04,es04	bb08,aa04,es04	bb10,aa04,es04
bb02,aa04,es05	bb04,aa04,es05	bb06,aa04,es05	bb08,aa04,es05	bb10,aa04,es05
bb02,aa04,es06	bb04,aa04,es06	bb06,aa04,es06	bb08,aa04,es06	bb10,aa04,es06
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bb02,aa04,es08	bb04,aa04,es08	bb06,aa04,es08	bb08,aa04,es08	bb10,aa04,es08
bb02,aa04,es09	bb04,aa04,es09	bb06,aa04,es09	bb08,aa04,es09	bb10,aa04,es09
bb02,aa04,es10	bb04,aa04,es10	bb06,aa04,es10	bb08,aa04,es10	bb10,aa04,es10
bb02,aa04,es11	bb04,aa04,es11	bb06,aa04,es11	bb08,aa04,es11	bb10,aa04,es11
bb02,aa04,es12	bb04,aa04,es12	bb06,aa04,es12	bb08,aa04,es12	bb10,aa04,es12
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bb02,aa05,es02	bb04,aa05,es02	bb06,aa05,es02	bb08,aa05,es02	bb10,aa05,es02
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bb02,aa05,es10	bb04,aa05,es10	bb06,aa05,es10	bb08,aa05,es10	bb10,aa05,es10
bb02,aa05,es11	bb04,aa05,es11	bb06,aa05,es11	bb08,aa05,es11	bb10,aa05,es11
bb02,aa05,es12	bb04,aa05,es12	bb06,aa05,es12	bb08,aa05,es12	bb10,aa05,es12
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bb02,aa06,es02	bb04,aa06,es02	bb06,aa06,es02	bb08,aa06,es02	bb10,aa06,es02
bb02,aa06,es03	bb04,aa06,es03	bb06,aa06,es03	bb08,aa06,es03	bb10,aa06,es03
bb02,aa06,es04	bb04,aa06,es04	bb06,aa06,es04	bb08,aa06,es04	bb10,aa06,es04
bb02,aa06,es05	bb04,aa06,es05	bb06,aa06,es05	bb08,aa06,es05	bb10,aa06,es05
bb02,aa06,es06	bb04,aa06,es06	bb06,aa06,es06	bb08,aa06,es06	bb10,aa06,es06
bb02,aa06,es07	bb04,aa06,es07	bb06,aa06,es07	bb08,aa06,es07	bb10,aa06,es07
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bb02,aa06,es10	bb04,aa06,es10	bb06,aa06,es10	bb08,aa06,es10	bb10,aa06,es10
bb02,aa06,es11	bb04,aa06,es11	bb06,aa06,es11	bb08,aa06,es11	bb10,aa06,es11
bb02,aa06,es12	bb04,aa06,es12	bb06,aa06,es12	bb08,aa06,es12	bb10,aa06,es12
bb02,aa07,es01	bb04,aa07,es01	bb06,aa07,es01	bb08,aa07,es01	bb10,aa07,es01
bb02,aa07,es02	bb04,aa07,es02	bb06,aa07,es02	bb08,aa07,es02	bb10,aa07,es02
bb02,aa07,es03	bb04,aa07,es03	bb06,aa07,es03	bb08,aa07,es03	bb10,aa07,es03

[illegible]

R^2, R^1, R_α	R^2, R^1, R_α	R^2, R^1, R_α	R^2, R^1, R_α	R^2, R^1, R_α
bb02,aa10,es11	bb04,aa10,es11	bb06,aa10,es11	bb08,aa10,es11	bb10,aa10,es11
bb02,aa10,es12	bb04,aa10,es12	bb06,aa10,es12	bb08,aa10,es12	bb10,aa10,es12

Table 2

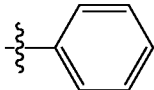
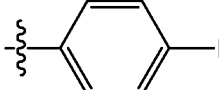
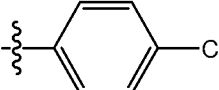
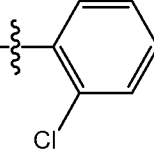
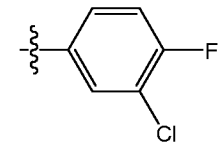
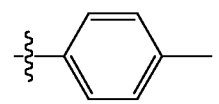
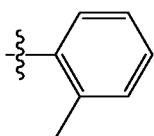
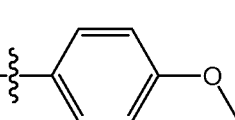
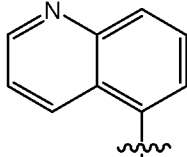
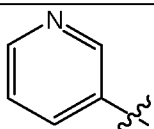
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bb10					

Table 3

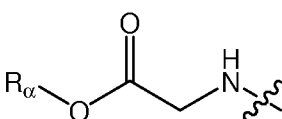
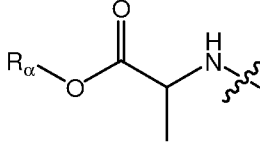
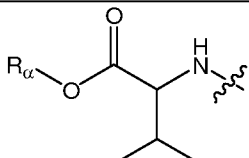
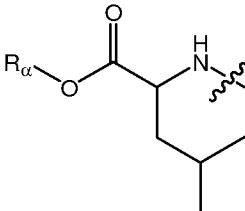
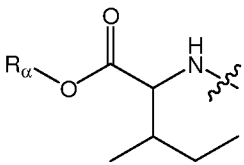
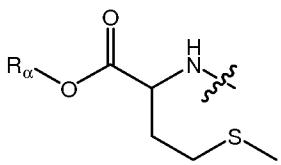
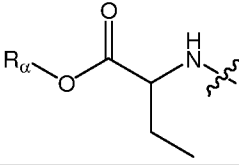
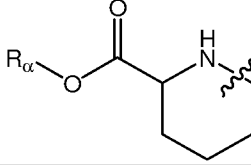
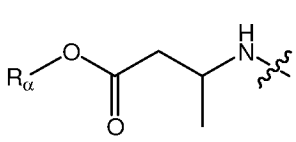
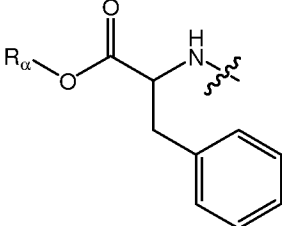
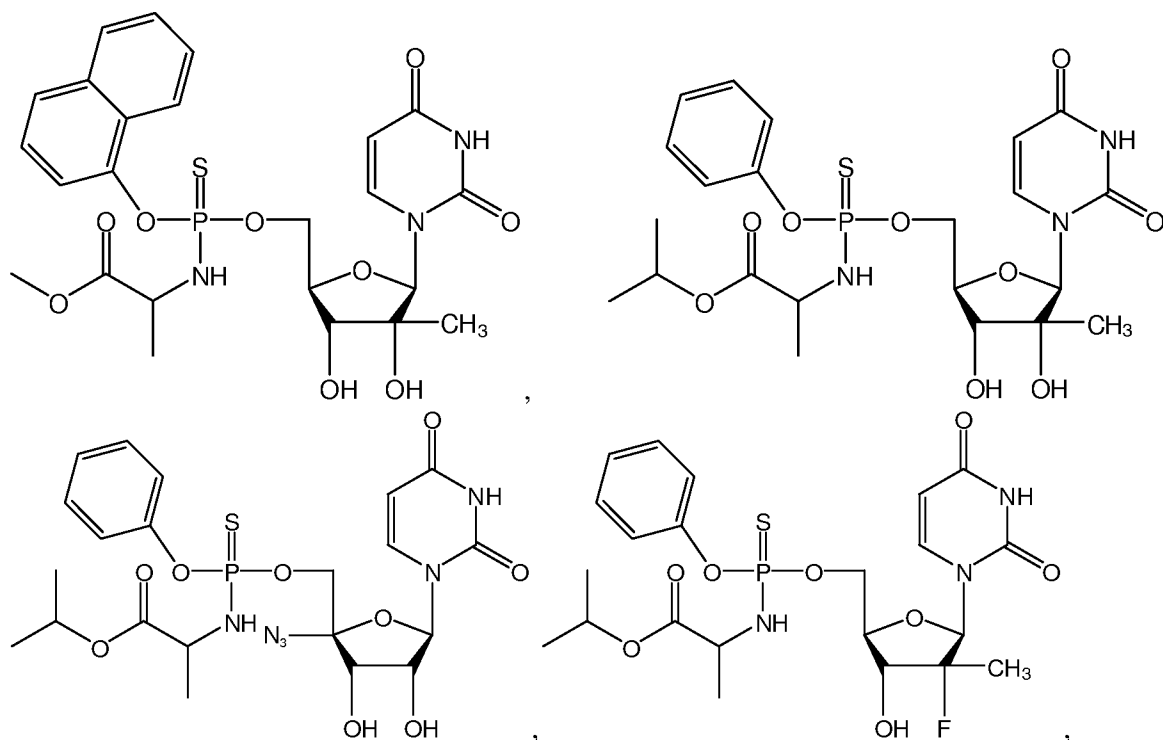
aa01		aa02		aa03	
aa04		aa05		aa06	
aa07		aa08		aa09	
aa10					

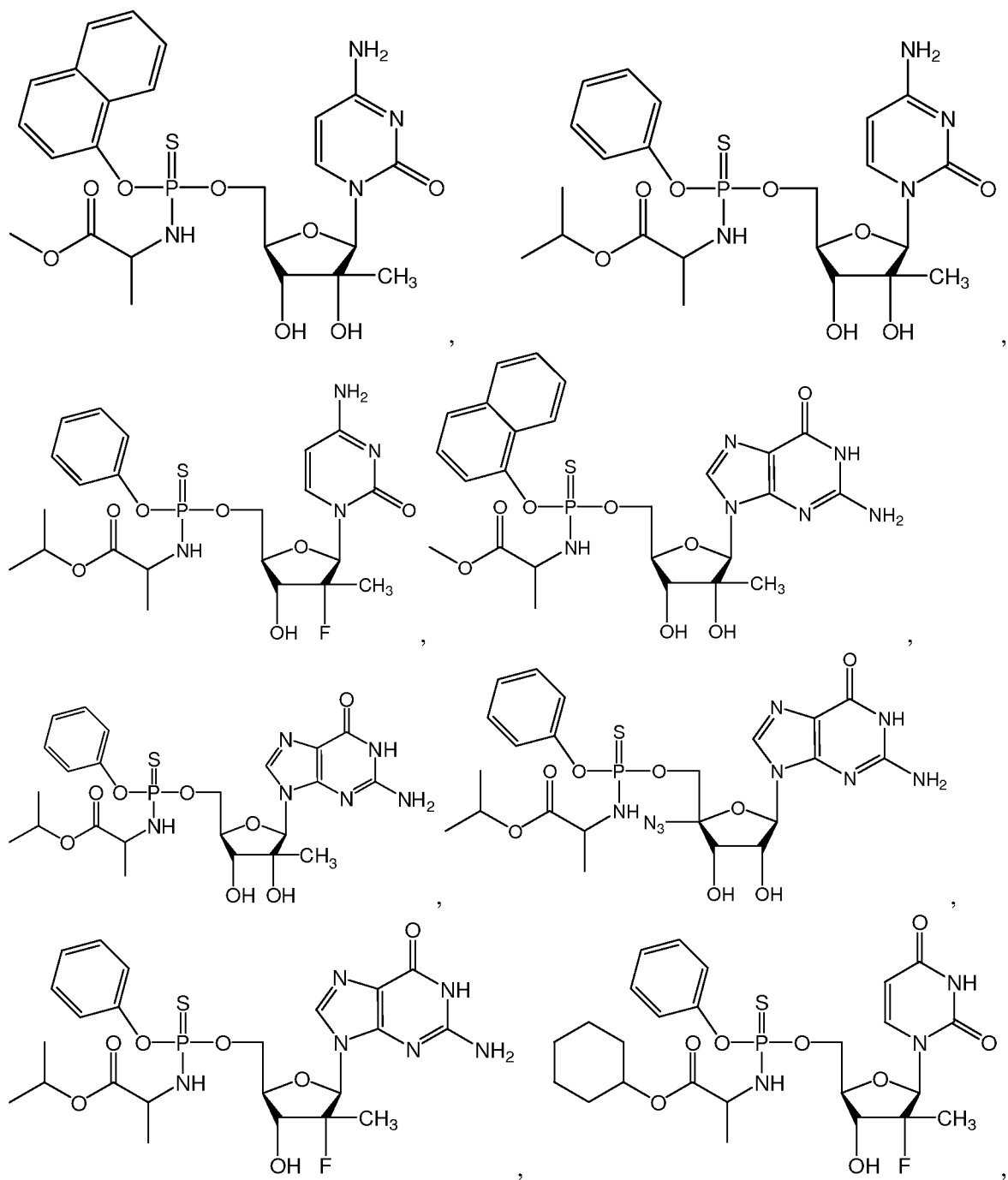
Table 4

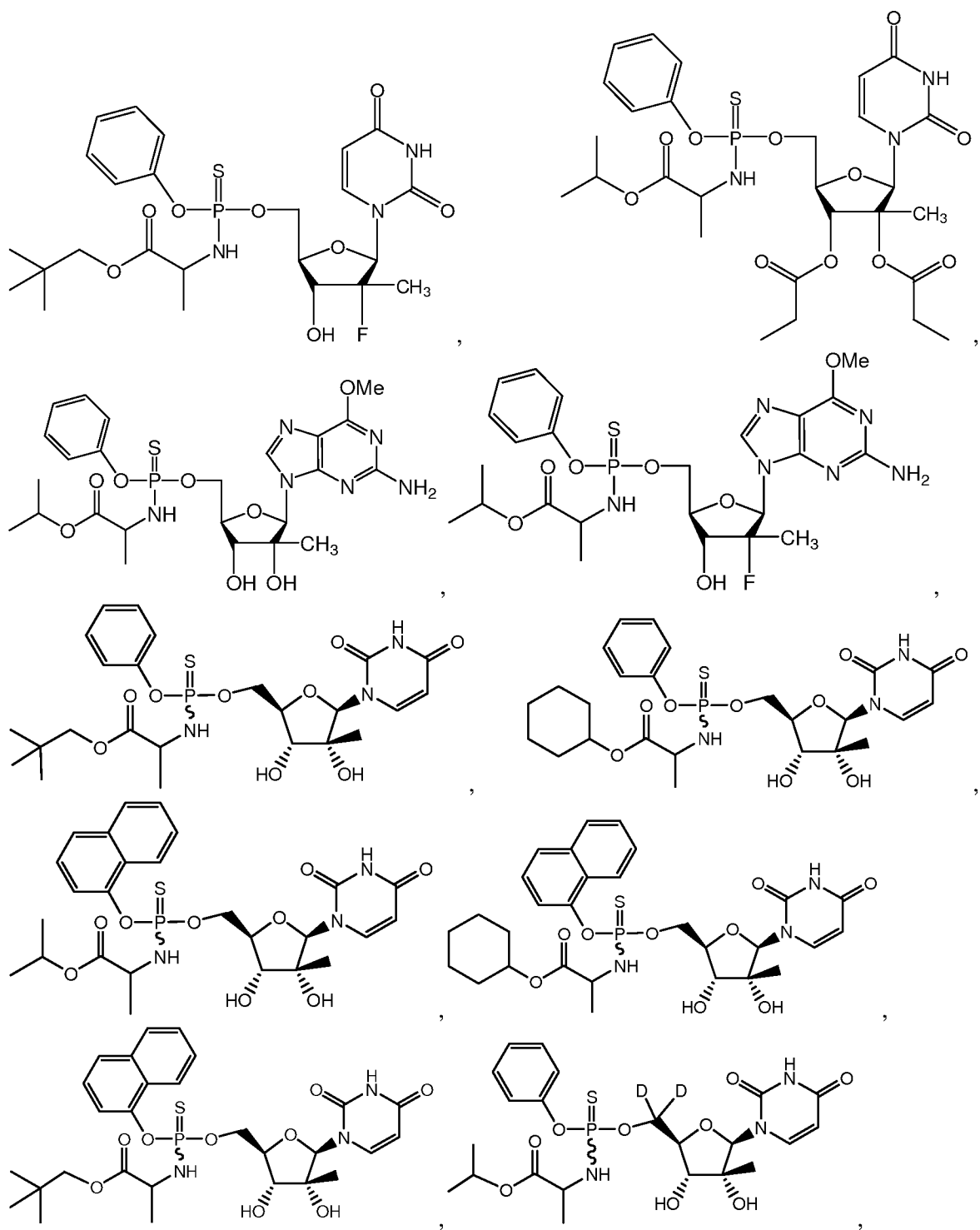
es01	R_{α} = methyl	es02	R_{α} = ethyl	es03	R_{α} = isopropyl
es04	R_{α} = propyl	es05	R_{α} = cyclohexyl	es06	R_{α} = cyclopentyl
es07	R_{α} = cyclobutyl	es08	R_{α} = cyclopropyl	es09	R_{α} = benzyl
es11	R_{α} = neopentyl	es10	R_{α} = t-butyl	es12	R_{α} = hydrogen

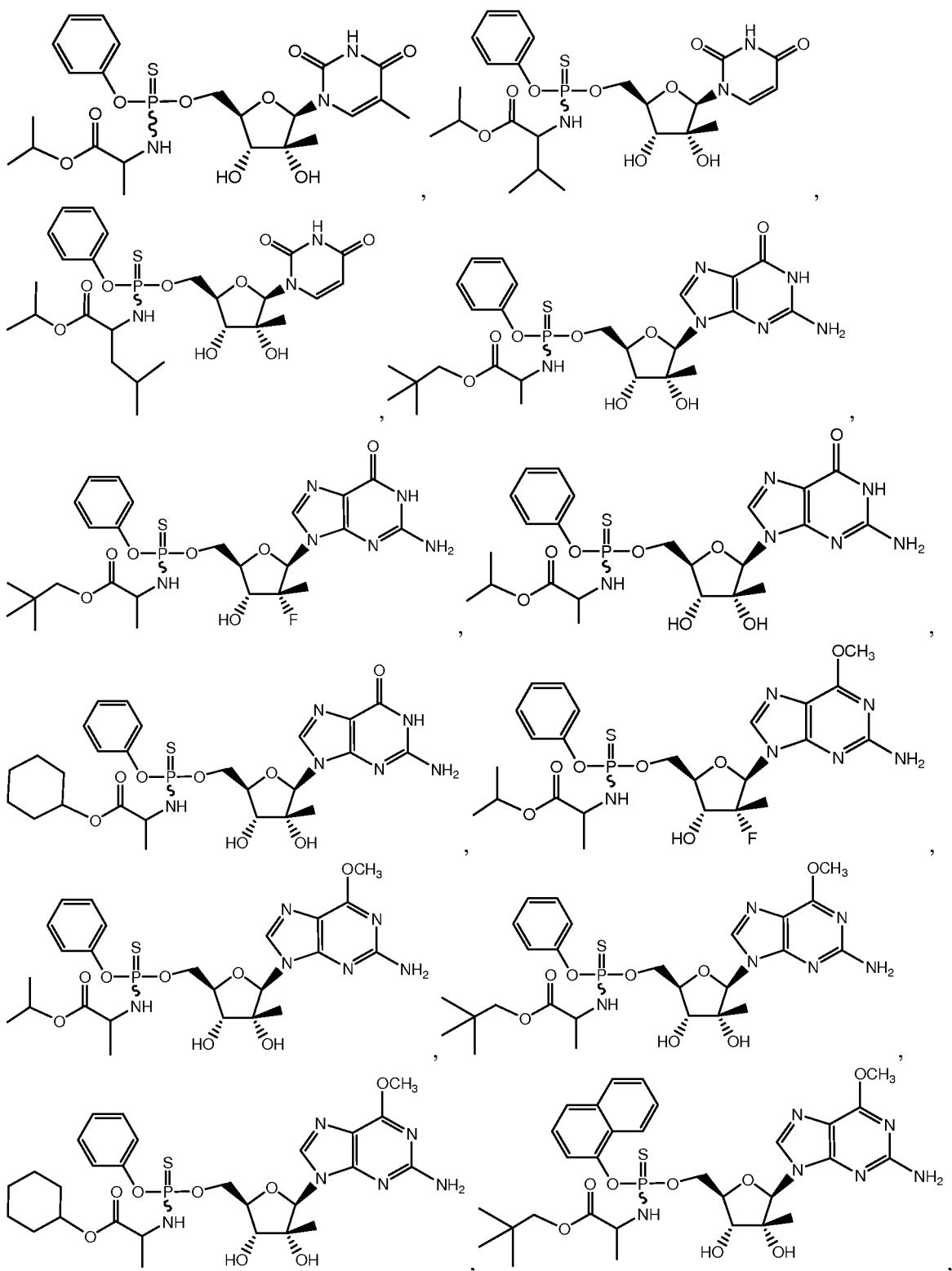
[0115] In some embodiments, R^{3a} , R^{3b} , R^4 , R^5 and R^9 can be all hydrogens in any of the embodiments described in Table 1. In some embodiments, at least one of R^6 and R^7 can be OH in any of the embodiments described in Table 1. In some embodiments, R^8 can be a C_{1-6} alkyl in any of the embodiments described in Table 1. In some embodiments, B^1 can be adenine, guanine, uracil, thymine or cystine in any of the embodiments described in Table 1. In some embodiments, R^{3a} , R^{3b} , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 and B^1 can be the groups provided with respect to Formula (Ia) in any of the embodiments described in Table 1.

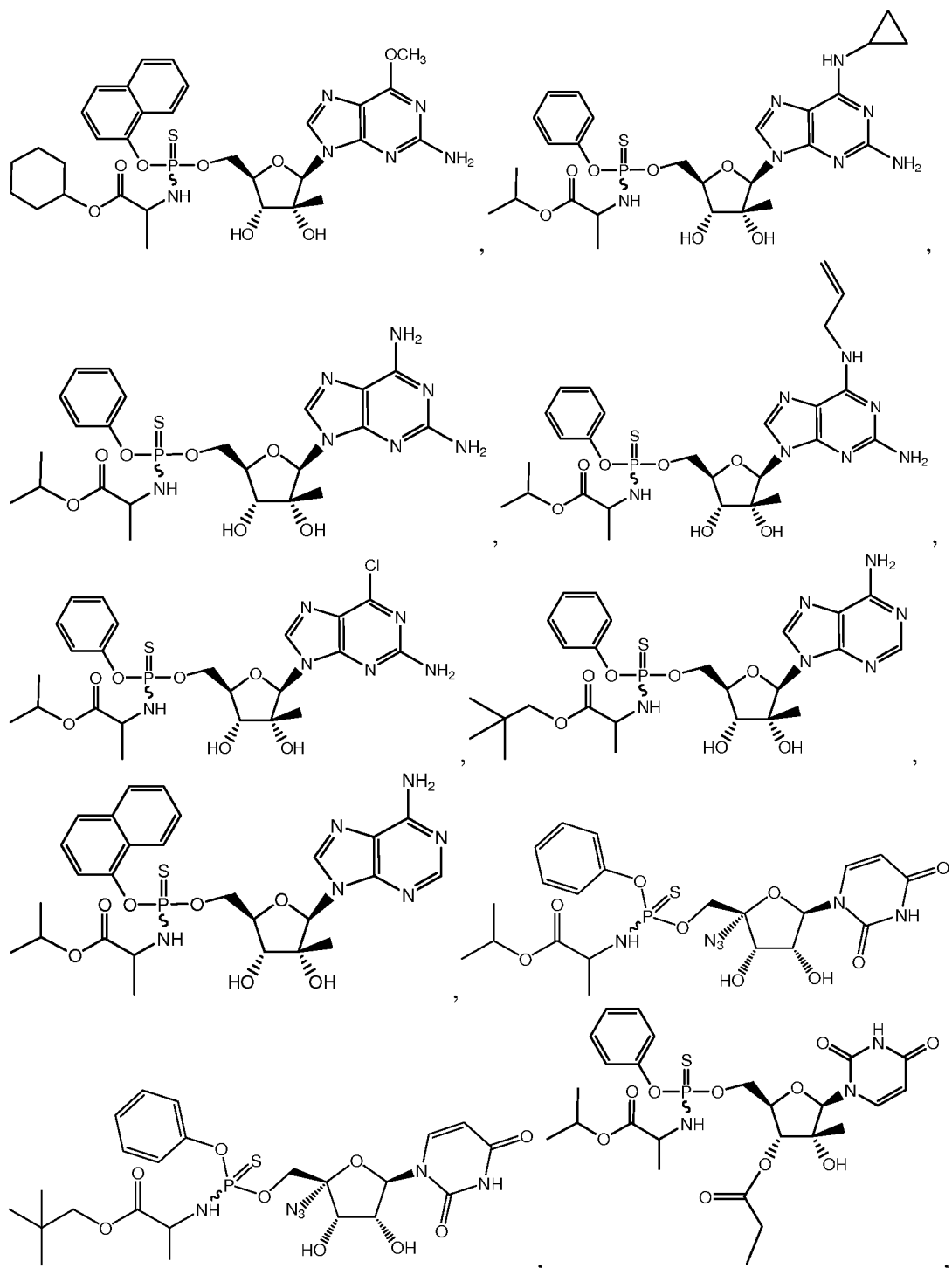
[0116] Examples of compounds of Formula (I) include, but are not limited to the following:

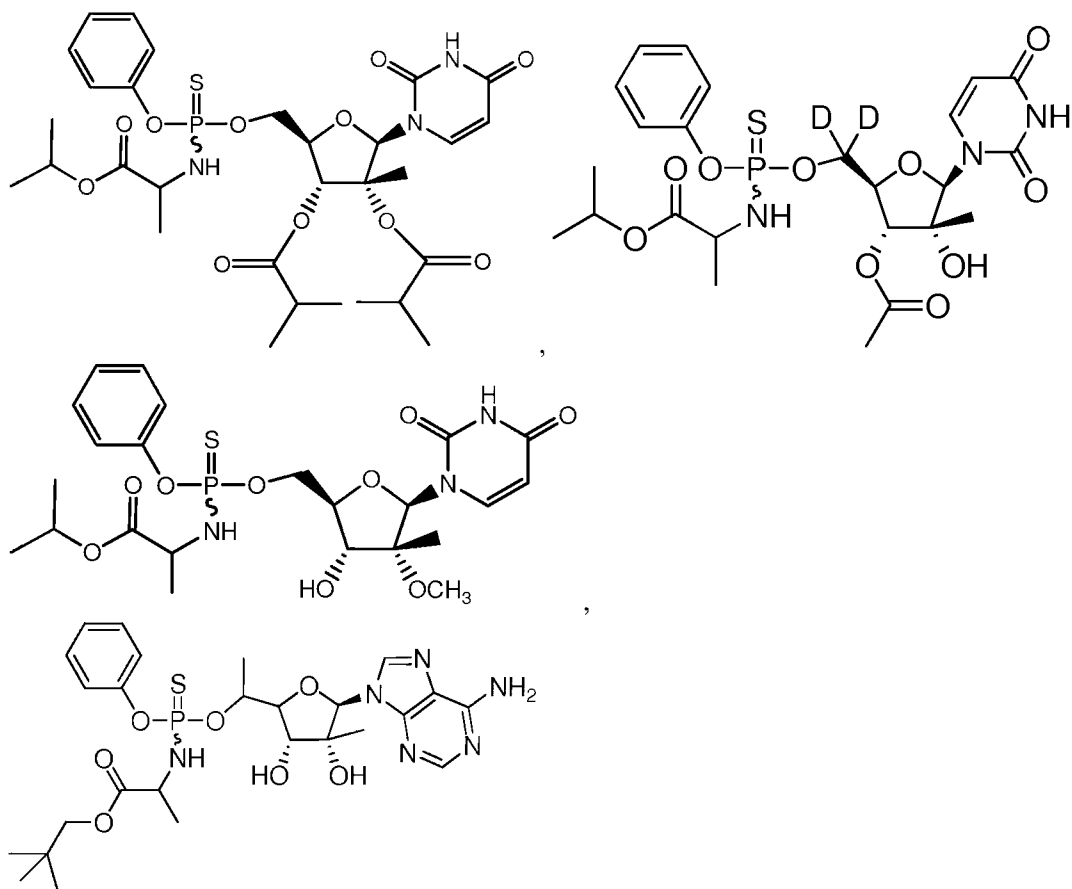




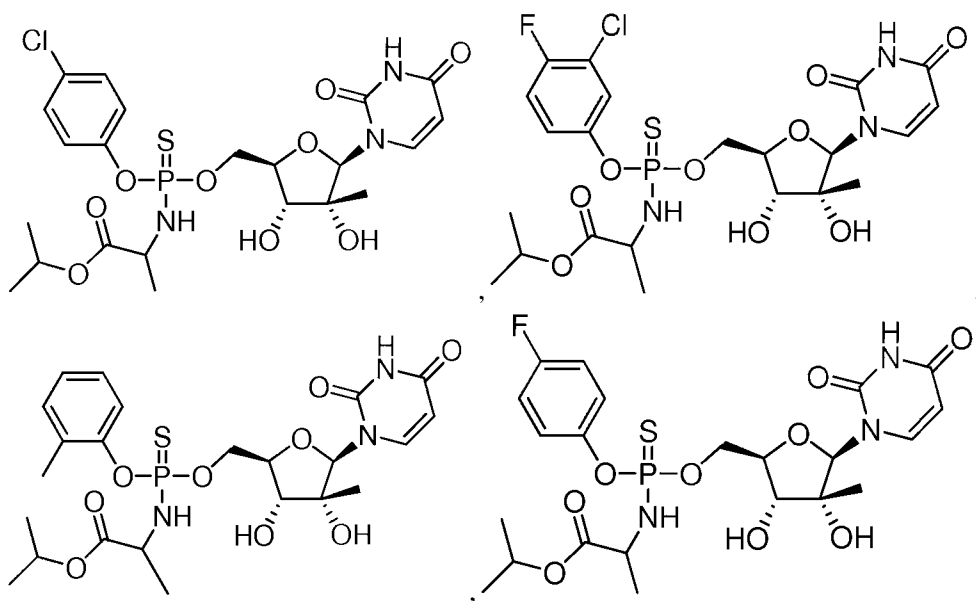


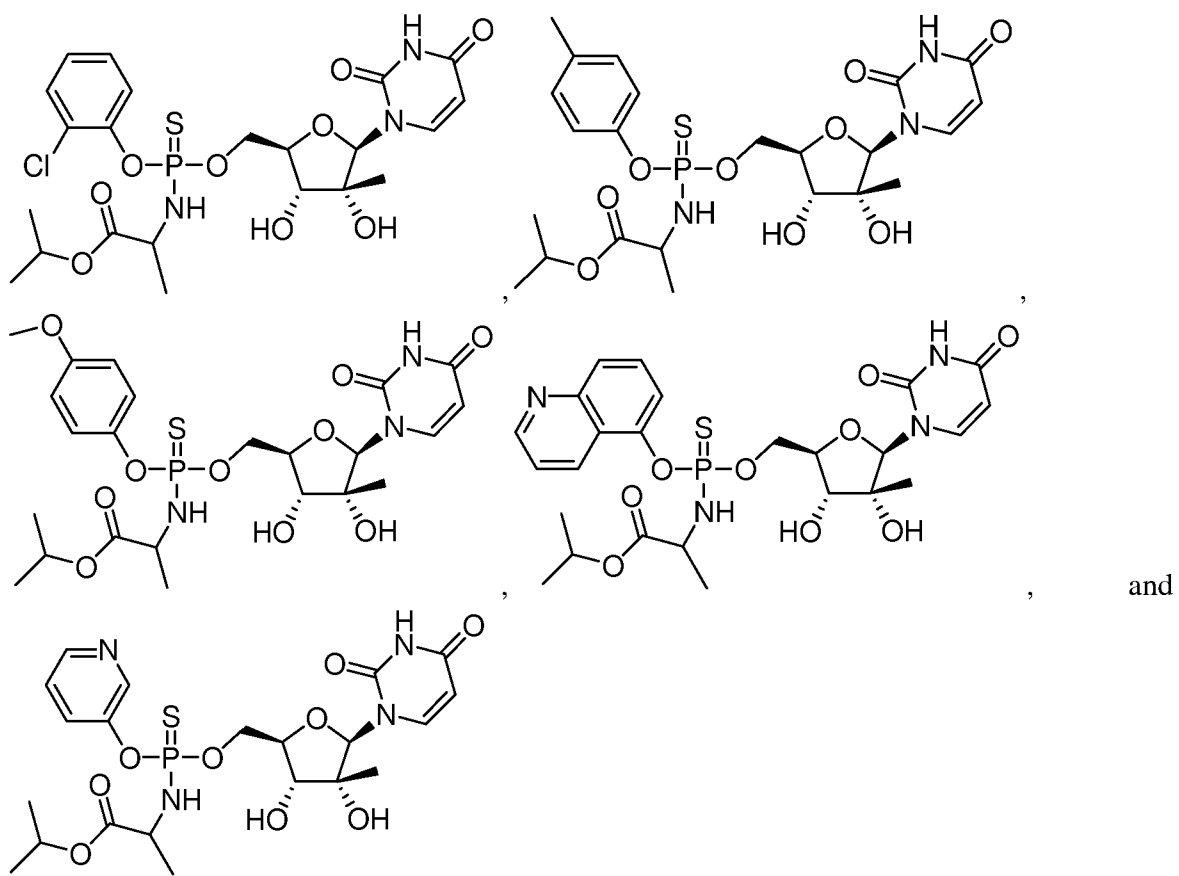




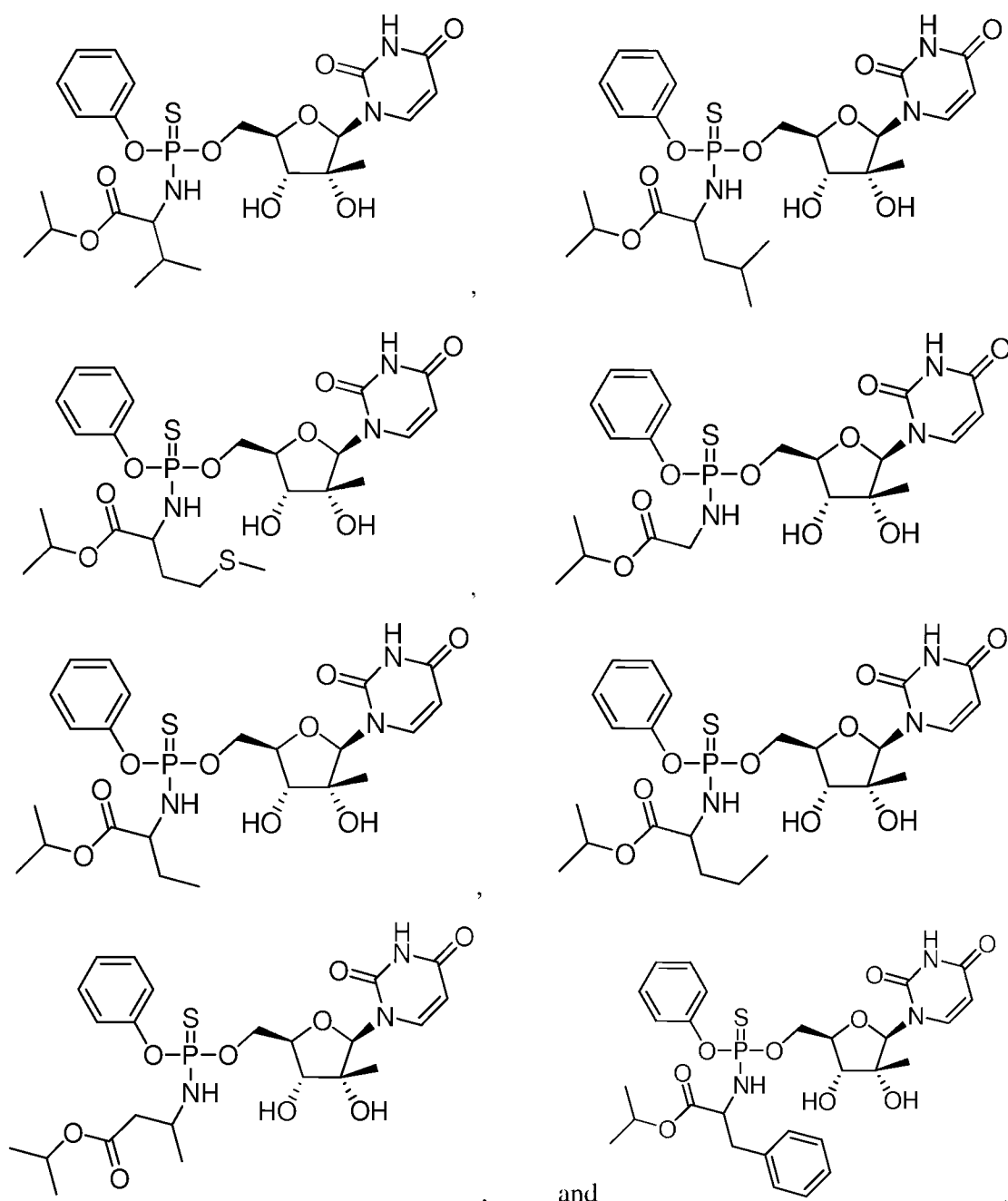


[0117] Additional examples of compounds of Formula (I) include, but are not limited to the following:

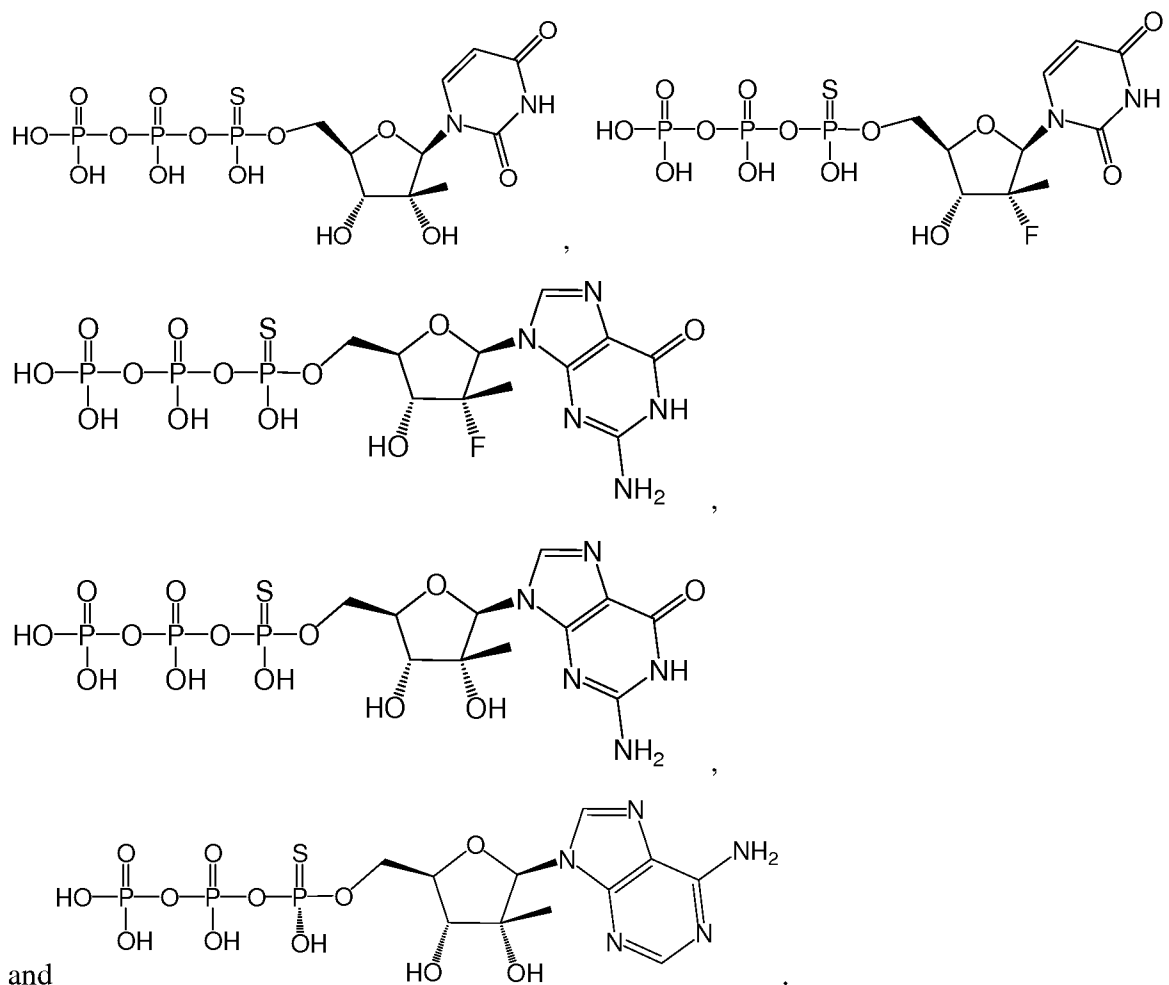




[0118] In some embodiments, the compound of Formula (I) can be the following:



[0119] Additional examples of compounds of Formula (I) include the following:



[0120] In some embodiments, neutralizing the charge on the thiophosphate group may facilitate the penetration of the cell membrane by a compound of Formula (I) (including a compound of Formula (Ia)) by making the compound more lipophilic compared to a thionucleotide 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 thiophosphate can be easily removed by esterases, proteases, or other enzymes. In some embodiments, the groups attached to the thiophosphate can be removed by simple hydrolysis. Inside the cell, the thio-monophosphate thus released may then be metabolized by cellular enzymes to the thio-diphosphate or the active thio-triphosphate. In some embodiments, the phosphorylation of a thio-monophosphate of a compound of Formula (I), or pharmaceutically acceptable salt thereof, can be stereoselective. For example, a thio-monophosphate of a compound of

Formula (I) (including a compound of Formula (I α)) can be phosphorylated to give an alpha-thiodiphosphate and/or an alpha-thiotriphosphate compound that can be enriched in the (*R*) or (*S*) diastereomer with respect to the 5'-O-phosphorous atom. For example, one of the (*R*) and (*S*) configuration with respect to the 5'-O-phosphorous atom of the alpha-thiodiphosphate and/or the alpha-thiotriphosphate compound can be present in an amount > 50%, $\geq 75\%$, $\geq 90\%$, $\geq 95\%$ or $\geq 99\%$ compared to the amount of the other of the (*R*) or (*S*) configuration with respect to the 5'-O-phosphorous atom. In some embodiments, phosphorylation of a compound of Formula (I), or pharmaceutically acceptable salt thereof, can result in the formation of a compound that has the (*R*)-configuration at the 5'-O-phosphorous atom. In some embodiments, phosphorylation of a compound of Formula (I), or pharmaceutically acceptable salt thereof, can result in formation of a compound that has the (*S*)-configuration at the 5'-O-phosphorous atom.

[0121] In some embodiments, a compound of Formula (I) (including a compound of Formula (I α)), 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 when R⁸ is a non-hydrogen group selected from halogen, azido, cyano, an optionally substituted C₁₋₆ alkyl, -OR¹⁶ and -OC(=O)R¹⁷.

[0122] In some embodiments, a compound of Formula (I) (including a compound of Formula (I α)), or a pharmaceutically acceptable salt thereof, can have increased metabolic and/or plasma stability. In some embodiments, a compound of Formula (I) (including a compound of Formula (I α)), or a pharmaceutically acceptable salt thereof, can be more resistant to hydrolysis and/or more resistant to enzymatic transformations. For example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can have increased metabolic stability, increased plasma stability, can be more resistant to hydrolysis and/or can be more resistant to enzymatic transformations compared to a compound that is identical in structure but for having a phosphate attached to the 5'-carbon of the ribose ring. In some embodiments, a compound of Formula (I) (including a compound of Formula (I α)), or a pharmaceutically acceptable salt thereof, can have improved properties. In previous studies,

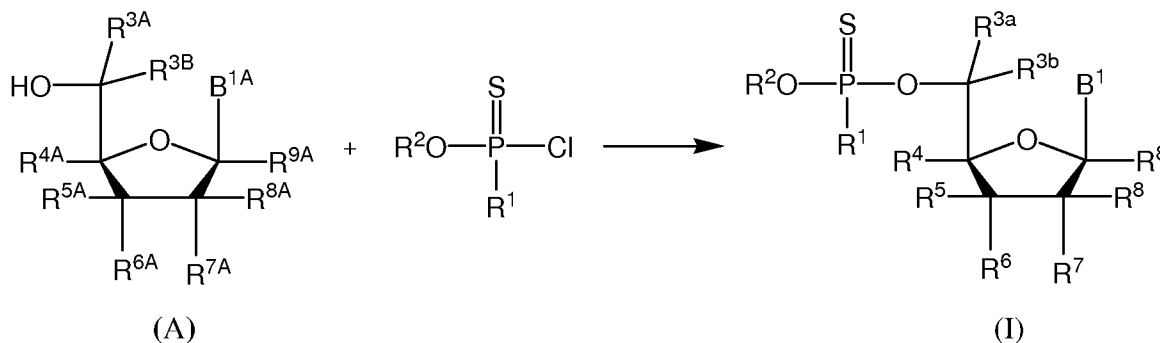
replacing a sulfur with an oxygen on the alpha-phosphate of a nucleotide phosphoramidate has resulted in more than a 1000-fold decrease in potency. See Venkatachalam et al. *European Journal of Medicinal Chemistry* (2004) 39:665–683. A non-limiting list of example properties include, but are not limited 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 cirrhosis 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 a biological half life of greater than 24 hours. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can have a biological half life in the range of about 40 hours to about 46 hours. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can have a biological half life greater than a compound that has a phosphate attached to the 5'-carbon of the ribose ring (for example, a compound that is identical in structure but for having a phosphate attached to the 5'-carbon of the ribose ring). In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can have more potent antiviral activity (for example, a lower IC₅₀ in an HCV replicon assay) as compared to the current standard of care.

Synthesis

[0123] Compounds of Formula (I) (including compounds of Formula (Ia)), 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 Scheme 1, 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



[0124] One method for forming a compound of Formula (I) is shown in Scheme 1. In Scheme 1, R^{3A}, R^{3B}, R^{4A}, R^{5A}, R^{6A}, R^{7A}, R^{8A}, R^{9A} and B^{1A} can be the same as R^{3a}, R^{3b}, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹ and B¹ as described herein for Formula (I); and R¹ and R² can be the same as described herein for Formula (I). As shown in Scheme 1, a compound of Formula (A) can be reacted with a compound having the formula R²O-P(=S)(R¹)-Cl to form a compound of Formula (I).

[0125] 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^{6A} and/or R^{7A} 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 (levulinoyloxy) trityl (TLTr), p-anisyl-1-naphthylphenylmethyl, di-o-anisyl-1-naphthylmethyl, p-tolyl-diphenylmethyl, 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 suitable silyl groups are described herein. Alternatively, R^{6A} and/or R^{7A} 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, methylenidene orthoester, phthalide orthoester 1,2-dimethoxyethylidene orthoester, and alpha-methoxybenzylidene orthoester; suitable cyclic acetals include methylene acetal, ethylidene acetal, t-butylmethylenidene 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.

[0126] If desired, any -NH and/or NH_2 groups present on the $\text{B}^{1\text{A}}$ can also be protected with one or more suitable protecting groups. Examples of suitable protecting groups include triarylmethyl groups and silyl groups. 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.

[0127] Suitable thiophosphorochloridates can be commercially obtained or prepared by a synthetic method described herein. An example of a general structure of a thiophosphorochloridate is shown in Scheme 1. In some embodiments, the thiophosphorochloridate can be coupled to a compound of Formula (A). In some embodiments, to facilitate the coupling, a Grignard reagent can be used. Suitable Grignard reagents are known to those skilled in the art and include, but are not limited to, alkylmagnesium chlorides and alkylmagnesium bromides. In other embodiments, the thiophosphorochloridate can be added to a compound of Formula (A) using a base. Suitable bases are known to those skilled in the art. Suitable bases are known to those skilled in the art. Examples of bases include, but are not limited to, 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 imidzoles (e.g., N-methylimidazole)).

[0128] When at least one of $\text{R}^{3\text{a}}$ and $\text{R}^{3\text{b}}$ is an optionally substituted C_{1-6} alkyl or an optionally substituted C_{1-6} haloalkyl, the optionally substituted C_{1-6} alkyl or the optionally substituted C_{1-6} haloalkyl can be added to the 5'-position using methods known to those

skilled in the art. In some embodiments, the hydroxy attached to the 5'-carbon can be oxidized to an aldehyde. Suitable oxidation conditions include, but are not limited to, DMSO in combination with an activating agent (usually an acylating agent or an acid) and an amine base, Moffatt oxidation, Swern oxidation and Corey-Kim oxidation, and suitable oxidizing agents include, but are not limited to, Dess-Martin periodinane, TPAP/NMO (tetrapropylammonium perruthenate/N-methylmorpholine N-oxide), Swern oxidation reagent, PCC (pyridinium chlorochromate), and/or PDC (pyridinium dichromate), sodium periodate, Collin's reagent, ceric ammonium nitrate CAN, $\text{Na}_2\text{Cr}_2\text{O}_7$ in water, Ag_2CO_3 on celite, hot HNO_3 in aqueous glyme, O_2 -pyridine CuCl , $\text{Pb}(\text{OAc})_4$ -pyridine and benzoyl peroxide- NiBr_2 . The resulting aldehyde compound can be reacted with a Grignard reagent, an organolithium reagent or trialkylaluminum (e.g., trimethylaluminum) to form a compound of Formula (A) where at least one of $\text{R}^{3\text{A}}$ and $\text{R}^{3\text{B}}$ is an optionally substituted C_{1-6} alkyl or an optionally substituted C_{1-6} haloalkyl. Optionally, the alkylating reagents can be in the presence of a Lewis acid. Suitable Lewis acids are known to those skilled in the art.

[0129] 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.

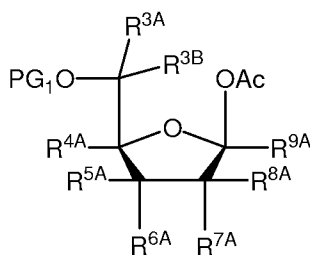
[0130] As described herein, in some embodiments, R^6 and R^7 can be both oxygen atoms linked together by a carbonyl groups. The $-\text{O}-\text{C}(=\text{O})-\text{O}-$ group can be formed using methods known to those skilled in the art. For example, a compound of Formula (I), wherein R^6 and R^7 are both hydroxy groups, can be treated with 1,1'-carbonyldiimidazole (CDI).

[0131] In some embodiments, R^6 and/or R^7 can be $-\text{OC}(=\text{O})\text{R}^{13}$ and $-\text{OC}(=\text{O})\text{R}^{15}$, respectively. The $-\text{OC}(=\text{O})\text{R}^{13}$ and $-\text{OC}(=\text{O})\text{R}^{15}$ groups can be formed at the 2'- and 3'-positions using various methods known to those skilled in the art. As an example, a compound of Formula (I), wherein R^6 and R^7 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., acetylchloride). 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^{13} and -OC(=O)R^{15} groups can be formed at the 2'- and 3'-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).

[0132] 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.

[0133] B^{1A} can be added to the pentose ring using various methods known to those skilled in the art. In some embodiments, a compound of Formula (B) can be reacted with a nitrogenous base. In some embodiments, R^{3A} , R^{3B} , R^{4A} , R^{5A} , R^{6A} , R^{7A} , R^{8A} , R^{9A} and B^{1A} of a compound of Formula (B) can be the same as disclosed herein, with respect to R^{3a} , R^{3b} , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 and B^1 ; and PG^1 can be an appropriate protecting group. In some embodiments, PG^1 can be p-nitrobenzyl group. In some embodiments, any hydroxy groups attached to the pentose ring can be protected with one or more suitable protecting groups. In some embodiments, any hydroxy groups attached to the pentose ring can be protected with benzoyl groups. Examples of nitrogenous bases include an optionally substituted heterocyclic bases described herein, wherein the nitrogen atom (-N) connected to the pentose ring is -NH. If desired, any -NH and/or NH_2 groups present on the nitrogenous base can be protected with one or more suitable protecting groups. Suitable protecting groups are described herein. In some embodiments, the nitrogenous base can be added via a coupling reaction in the presence of a Lewis acid or TMSOTf. Suitable Lewis acids are known to those skilled in the art.



(B)

[0134] Various methods can be used to make a compound of Formula (I), wherein

$$R^1 \text{ is } R^{21}O-P(=O)(OR^{20})-O-P(=O)(OR^{19})- \left[O-P(=O)(OR^{19})-O \right]_n$$

For example, a thiophosphorochloridate having the general formula of $P(=S)Cl_3$ can be transformed into a phosphorus reagent having the general formula, $P(=S)LG_3$, wherein each LG can be amine-based leaving group. In some embodiments, each LG can be a triazole. The phosphorus reagent having the general formula, $P(=S)LG_3$, can be reacted with a compound of Formula (I). Using a suitable pyrophosphorylation reagent, the β and γ phosphates can be added. An example of a suitable pyrophosphorylation reagent is tris(tetrabutylammonium) hydrogen pyrophosphate.

[0135] During the synthesis of any of the compounds described herein, if desired, any hydroxy groups attached to the pentose ring, and any $-NH$ and/or NH_2 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 $-NH$ and/or NH_2 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.

Pharmaceutical Compositions

[0136] 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 Formulae (I) or (I α)), 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%, $\geq$ 60%, $\geq$ 70%, $\geq$ 80%, $\geq$ 90%, $\geq$ 95%, or $\geq$ 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.

[0137] 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.

[0138] The term “physiologically acceptable” defines a carrier, diluent or excipient that does not abrogate the biological activity and properties of the compound.

[0139] 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.

[0140] 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.

[0141] 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.

[0142] 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.

[0143] 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.

[0144] 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.

[0145] 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.

[0146] 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

[0147] One embodiment disclosed herein relates 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) (including compounds of Formula (I α)), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes a compound described herein.

[0148] 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 Formulae (I) and/or (I α), or a pharmaceutically acceptable salt thereof), or a pharmaceutical composition that includes a compound described herein). In an embodiment, the neoplastic disease can be cancer. In some embodiments, the neoplastic disease can be a tumor such as a solid tumor. In an embodiment, 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).

[0149] 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 Formulae (I) and/or (I α)), or a pharmaceutical composition that includes one or more compounds described herein.

[0150] 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 Formulae (I) and/or (I α)), or a pharmaceutical composition that includes one or more compounds described herein. In an embodiment, 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 still other embodiments, the viral infection can be HIV.

[0151] 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 Formulae (I) and/or (Ia), or a pharmaceutical acceptable salt thereof. In other embodiments, the compound can be a mono-, di- and/or tri-phosphate of a compound of Formulae (I) and/or (Ia), or a pharmaceutically acceptable salt of the foregoing. In some embodiments, the virus can be a HCV virus.

[0152] 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 Formulae (I) and/or (Ia), or a pharmaceutical acceptable salt thereof. In other embodiments, the compound can be a mono-, di- and/or tri-phosphate of a compound of Formulae (I) and/or (Ia), or a pharmaceutically acceptable salt of the foregoing. In some embodiments, the virus can be a HCV virus.

[0153] 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.

[0154] Some embodiments described herein relate to a method of inhibiting NS5B polymerase activity can include contacting a cell (for example, a cell infected with HCV) with an effective amount of a compound of Formulae (I) and/or (I α), or a pharmaceutical acceptable salt thereof. Some embodiments described herein relate to a method of inhibiting NS5B polymerase activity can include administering a cell (for example, a cell infected with HCV) with an effective amount of a compound of Formulae (I) and/or (I α), or a pharmaceutical acceptable salt thereof. In some embodiments, a compound of Formula (I) (including a compound of Formula (I α)), or a pharmaceutically acceptable salt thereof, can inhibit a RNA dependent RNA polymerase. In some embodiments, a compound of Formula (I) (including a compound of Formula (I α)), or a pharmaceutically acceptable salt thereof, can inhibit a HCV polymerase (for example, NS5B polymerase).

[0155] 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 Formulae (I) and/or (I α), or a pharmaceutical acceptable salt thereof, or a pharmaceutical composition that includes an effective amount of a compound of Formulae (I) and/or (I α), or a pharmaceutical acceptable salt thereof. Some embodiments described herein relate to a method of treating a condition selected from liver fibrosis, liver cirrhosis, 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 Formulae (I) and/or (I α), or a pharmaceutical acceptable salt thereof). One cause of the liver fibrosis, liver cirrhosis, 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 Formulae (I) and/or (I α), 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 Formulae (I) and/or (I α), or a pharmaceutical acceptable salt thereof). In one embodiment, this method

comprises slowing or halting the progression of liver disease. In another embodiment, the course of the disease is reversed, and stasis or improvement in liver function is contemplated.

[0156] 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 Formulae (I) and/or (I α), or a pharmaceutical acceptable salt thereof, or a pharmaceutical composition that includes an effective amount of a compound of Formulae (I) and/or (I α), 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 Formulae (I) and/or (I α), 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 Formulae (I) and/or (I α), or a pharmaceutical acceptable salt thereof) can be effective to treat 3 or more, 5 or more, 7 or more of 9 more genotypes of HCV. In some embodiments, a compound of Formula (I) and/or (I α), or a pharmaceutical acceptable salt thereof is more effective against a larger number of HCV genotypes than the standard of care. In some embodiments, a compound of Formula (I) and/or (I α), or a pharmaceutical acceptable salt thereof, is more effective against a particular HCV genotype than the standard of care (such as genotype 1, 2, 3, 4, 5 and/or 6).

[0157] Various indicators for determining the effectiveness of a method for treating a HCV infection are known to those skilled in the art. Example 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 Formulae (I) and/or (I α), or a pharmaceutical acceptable salt thereof) can reduce the incidence of liver cancer in HCV patients.

[0158] In some embodiments, an effective amount of a compound of Formulae (I) and/or (I α), 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) and/or (I α), 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) and/or (I α), or a pharmaceutically acceptable salt thereof. For example, wherein the viral load is measured before administration of the compound of Formula (I) and/or (I α), or a pharmaceutically acceptable salt thereof, and again after completion of the treatment regime with the compound of Formula (I) and/or (I α), or a pharmaceutically acceptable salt thereof (for example, 1 month after completion). In some embodiments, an effective amount of a compound of Formula (I) and/or (I α), 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) and/or (I α), 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) and/or (I α), or a pharmaceutically acceptable salt thereof. For example, the viral load can be measured before administration of the compound of Formula (I) and/or (I α), or a pharmaceutically acceptable salt thereof, and again after completion of the treatment regime with the compound of Formula (I) and/or (I α), or a pharmaceutically acceptable salt thereof (for example, 1 month after completion).

[0159] In some embodiments, a compound of Formula (I) and/or (I α), 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) and/or (I α), 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) and/or (I α), 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.

[0160] In some embodiments, an effective amount of a compound of Formula (I) and/or (I α), 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.

[0161] In some embodiments, a therapeutically effective amount of a compound of Formula (I) and/or (I α), 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 examples of a markers includes

measuring the levels of serum alanine aminotransferase (ALT), aspartate aminotransferase (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) and/or (Ia) is an amount effective to reduce ALT, AST, ALP, GGT and/or TBIL levels to with what is considered a normal level.

[0162] 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 (≤ 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).

[0163] 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.

[0164] 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 patients are 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.

[0165] 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 or ribavirin.

[0166] 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.

[0167] The standard of care for treating HCV has been associated with several side effects (adverse events). In some embodiments, a compound of Formula (I) (including a compound of Formula (I α)), or a pharmaceutically acceptable salt thereof, can decrease the number and/or severity of side effects 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 appetite, 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.

[0168] Table 5 provides some embodiments of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, 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 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 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 5

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

[0169] Yet still other embodiments disclosed herein relates 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) and/or (I α)), or a pharmaceutical composition that includes one or more compounds described herein. In an embodiment, the parasite disease can be Chagas' disease.

[0170] 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.

[0171] 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.

[0172] The term “therapeutically effective amount” is 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.

[0173] 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.

[0174] 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) (including a compound of Formula (I α)), 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) (including a compound of Formula (I α)), 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) (including a compound of Formula (I α)), or a pharmaceutically acceptable salt thereof, can be less compared to the total time of the treatment regime with the standard of care.

[0175] 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 ED₅₀ or ID₅₀ values, or other appropriate values derived from *in vitro* or *in vivo* studies, as qualified by toxicity studies and efficacy studies in animals.

[0176] 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.

[0177] 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.

[0178] 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 administered 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.

[0179] 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

[0180] In some embodiments, the compounds disclosed herein, such as a compound of Formula (I) (including compounds of Formula (I α)), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes a compound described herein, 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 (BB) (including pharmaceutically acceptable salts and pharmaceutical compositions that can include a compound of Formula (BB), 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.

[0181] 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 zanamivir (RELENZA®) for treating an influenza infection.

[0182] 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.

[0183] 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.

[0184] 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 Figure 2.

[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 a

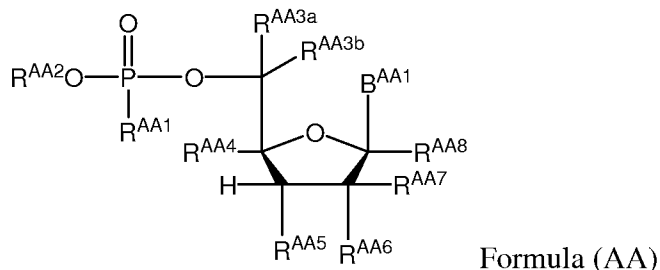
HCV polymerase inhibitor. In some embodiments, the HCV polymerase inhibitor can be a nucleoside inhibitor. In other embodiments, the HCV polymerase inhibitor can be a non-nucleoside inhibitor. Examples of suitable nucleoside inhibitors include, but are not limited to, RG7128, PSI-7851, PSI-7977, INX-184, 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 3. 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 4.

[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 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 5.

[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 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 6.

[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 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. Provisional Application Nos. 61/385,425, filed September 22,

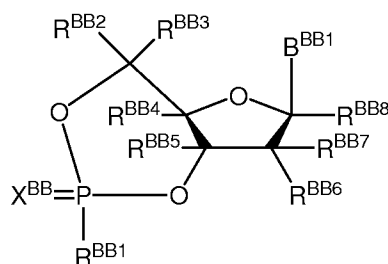
2010, and 61/426,467, filed December 22, 2010, the contents of which are incorporated by reference in its entirety):



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 C₁₋₆ alkyl, an optionally substituted C₂₋₆ alkenyl, an optionally substituted C₂₋₆ alkynyl, an optionally substituted C₁₋₆ haloalkyl and aryl(C₁₋₆ 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 C₃₋₆ cycloalkyl, an optionally substituted C₃₋₆ cycloalkenyl, an optionally substituted C₃₋₆ aryl, and an optionally substituted C₃₋₆ 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 C₁₋₆ alkyl, -OR^{AA13} and -OC(=O)R^{AA14}; R^{AA8} can be hydrogen or an optionally substituted C₁₋₆ alkyl; R^{AA9}, R^{AA11} and R^{AA13} can be independently selected from hydrogen and an optionally substituted C₁₋₆ alkyl; and R^{AA10}, R^{AA12} and R^{AA14} can be independently selected from an optionally substituted C₁₋₆ alkyl and an optionally substituted C₃₋₆ cycloalkyl. A non-limiting list of examples of compounds of Formula (AA), and phosphates thereof, includes the compounds numbered 7000-7077 in Figures 8A-8I. In some embodiments, Formula (AA) cannot be compound 7044, 7045, 7046, 7047, 7048, 7049, 7050, 7072, 7073, 7074, 7075, 7076 or 7077.

[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 compound of Formula (BB), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes a compound of Formula (BB), or a pharmaceutically acceptable salt thereof (see, U.S. Provisional Application No. 61/426,471, filed December 22, 2010, the contents of which are incorporated by reference in its entirety):

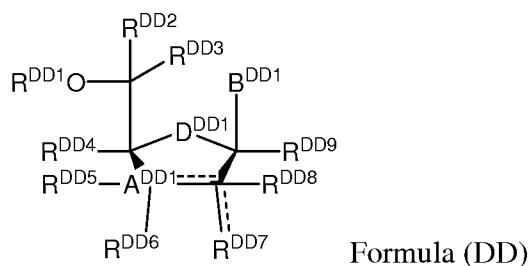


Formula (BB)

wherein B^{BB1} can be an optionally substituted heterocyclic base or an optionally substituted heterocyclic base with a protected amino group; X^{BB} can be O (oxygen) or S (sulfur); R^{BB1} can be selected from -Z^{BB}-R^{BB9}, an optionally substituted N-linked amino acid and an optionally substituted N-linked amino acid ester derivative; Z^{BB} can be selected from O (oxygen), S (sulfur) and N(R^{BB10}); R^{BB2} and R^{BB3} can be independently selected from hydrogen, an optionally substituted C₁₋₆ alkyl, an optionally substituted C₂₋₆ alkenyl, an optionally substituted C₂₋₆ alkynyl, an optionally substituted C₁₋₆ haloalkyl and an optionally substituted aryl(C₁₋₆ alkyl); or R^{BB2} and R^{BB3} can be taken together to form a group selected from an optionally substituted C₃₋₆ cycloalkyl, an optionally substituted C₃₋₆ cycloalkenyl, an optionally substituted C₃₋₆ aryl and an optionally substituted C₃₋₆ heteroaryl; R^{BB4} can be selected from hydrogen, halogen, azido, cyano, an optionally substituted C₁₋₆ alkyl, an optionally substituted C₂₋₆ alkenyl, an optionally substituted C₂₋₆ alkynyl and an optionally substituted allenyl; R^{BB5} can be hydrogen or an optionally substituted C₁₋₆ alkyl; R^{BB6} can be selected from hydrogen, halogen, azido, amino, cyano, an optionally substituted C₁₋₆ alkyl, -OR^{BB11} and -OC(=O)R^{BB12}; R^{BB7} can be selected from hydrogen, halogen, azido, cyano, an optionally substituted C₁₋₆ alkyl, -OR^{BB13} and -OC(=O)R^{BB14}; R^{BB8} can be selected from hydrogen, halogen, azido, cyano, an optionally substituted C₁₋₆ alkyl, -OR^{BB15} and -OC(=O)R^{BB16}; R^{BB9} can be selected from an optionally substituted alkyl, an optionally

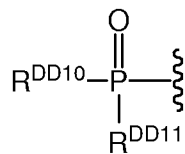
substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl, an optionally substituted aryl(C₁₋₆alkyl), an optionally substituted heteroaryl(C₁₋₆alkyl) and an optionally substituted heterocyclyl(C₁₋₆alkyl); R^{BB10} 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(C₁₋₆alkyl), an optionally substituted heteroaryl(C₁₋₆alkyl) and an optionally substituted heterocyclyl(C₁₋₆alkyl); R^{BB11}, R^{BB13} and R^{BB15} can be independently hydrogen or an optionally substituted C₁₋₆ alkyl; and R^{BB12}, R^{BB14} and R^{BB16} can be independently an optionally substituted C₁₋₆ alkyl or an optionally substituted C₃₋₆ cycloalkyl. In some embodiments, at least one of R^{BB2} and R^{BB3} is not hydrogen. A non-limiting list of example compounds of Formula (BB) includes the compound numbered 8000-8012 in Figures 9A-9B.

[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 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, U.S. Publication No. 2010-0249068, filed March 19, 2010, the contents of which are incorporated by reference in its entirety):



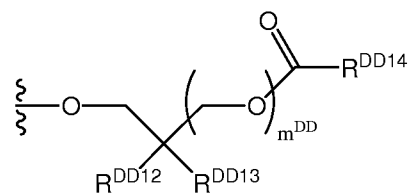
wherein each ===== can be independently a double or single bond; A^{DD1} can be selected from C (carbon), O (oxygen) and S (sulfur); B^{DD1} can be an optionally substituted heterocyclic base or a derivative thereof; D^{DD1} can be selected from C=CH₂, CH₂, O (oxygen), S (sulfur), CHF, and CF₂; R^{DD1} can be hydrogen, an optionally substituted alkyl, an

optionally substituted cycloalkyl, an optionally substituted aralkyl, dialkylaminoalkylene, alkyl-C(=O)-, aryl-C(=O)-, alkoxymethyl-C(=O)-, aryloxyalkyl-C(=O)-, alkylsulfonyl,

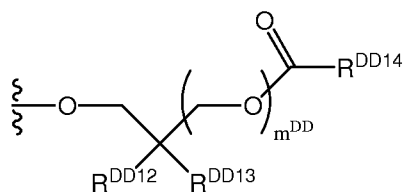


arylsulfonyl, aralkylsulfonyl, R^{DD11}, an -O-linked amino acid, diphosphate, triphosphate or derivatives thereof; R^{DD2} and R^{DD3} can be each independently selected from hydrogen, an optionally substituted C₁₋₆ alkyl, an optionally substituted C₂₋₆ alkenyl, an optionally substituted C₂₋₆ alkynyl and an optionally substituted C₁₋₆ 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 C₃₋₆ cycloalkyl, C₃₋₆ cycloalkenyl, C₃₋₆ aryl, and a C₃₋₆ heteroaryl; R^{DD4} and R^{DD9} can be independently selected from hydrogen, halogen, -NH₂, -NHR^{DDa1}, NR^{DDa1}R^{DDb1}, -OR^{DDa1}, -SR^{DDa1}, -CN, -NC, -N₃, -NO₂, -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 C₁₋₆ alkyl, an optionally substituted C₂₋₆ alkenyl, an optionally substituted C₂₋₆ 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, -NH₂, -NHR^{DDa1}, NR^{DDa1}R^{DDb1}, -OR^{DDa1}, -SR^{DDa1}, -CN, -NC, -N₃, -NO₂, -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 C₁₋₆ alkyl, an optionally substituted C₂₋₆ alkenyl, an optionally substituted C₂₋₆ 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 the group consisting of hydrogen, halogen, -NH₂, -NHR^{DDa1}, NR^{DDa1}R^{DDb1}, -OR^{DDa1}, -SR^{DDa1}, -CN, -NC, -N₃, -NO₂, -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 C₁₋₆ alkyl, an optionally substituted C₂₋₆

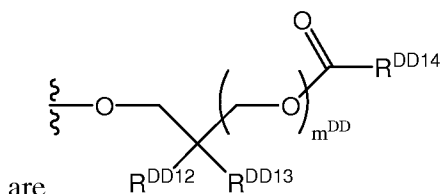
alkenyl, an optionally substituted C₂₋₆ alkynyl, an optionally substituted haloalkyl, an optionally substituted hydroxyalkyl and an -O-linked amino acid, or when the bond to R^{DD7} indicated by ===== is a double bond, then R^{DD7} is a C₂₋₆ alkylidene and R^{DD8} is absent; R^{DDa1}, R^{DDb1} and R^{DDc1} 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(C₁₋₆ alkyl); R^{DD10} can be selected from O⁻, -



OH, an optionally substituted aryloxy or aryl-O-, alkyl-C(=O)-O-CH₂-O-, alkyl-C(=O)-S-CH₂CH₂-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-CH₂-O-, alkyl-C(=O)-S-CH₂CH₂-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 C₁₋₈ organylcarbonyl, C₁₋₈ alkoxy carbonyl and C₁₋₈ organylaminocarbonyl; each R^{DD14} can be hydrogen or an optionally substituted C₁₋₆ 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 C₁₋₆ alkyl, an optionally substituted C₂₋₆ alkenyl, an optionally substituted C₂₋₆ alkynyl and an optionally substituted C₁₋₆ haloalkyl.

[0191] 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) (including a compound of Formula (I α)), 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 (BB), and a compound of Formula (DD), or a pharmaceutically acceptable salt of any of the aforementioned compounds.

[0192] 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) (including a compound of Formula (I α)), 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 (BB), and a compound of Formula (DD), or a pharmaceutically acceptable salt of any of the aforementioned compounds.

[0193] 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 with an effective amount of a compound of Formula (I) (including a compound of Formula (I α)), 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 (BB), and a compound of Formula (DD), or a pharmaceutically acceptable salt of any of the aforementioned compounds.

[0194] 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) (including a compound of Formula (I α)), 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 (BB), and a compound of Formula (DD), or a pharmaceutically acceptable salt of any of the aforementioned compounds.

[0195] 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) (including a compound of Formula (I α)), 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 (BB), 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 inhibiting viral replication of a virus that can include contacting a cell infected with the virus with an effective amount of a compound of Formula (I) (including a compound of Formula (I α)), 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 (BB), and a compound of Formula (DD), or a pharmaceutically acceptable salt of any of the aforementioned compounds.

[0197] In some embodiments, a compound of Formula (I) (including a compound of Formula (I α)), 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) (including a compound of Formula (I α)), or a pharmaceutically acceptable salt 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) (including a compound of Formula (I α)), 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) (including a compound

of Formula (I α)), or a pharmaceutically acceptable salt thereof, and at least one of the other additional agent(s) can be in a second pharmaceutical composition.

[0198] 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.

[0199] 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) (including a compound of Formula (I α)), or a pharmaceutically acceptable salt thereof, can be administered prior to all additional agents. In other embodiments, a compound of Formula (I) (including a compound of Formula (I α)), 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) (including a compound of Formula (I α)), 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) (including a compound of Formula (I α)), 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) (including a compound of Formula (I α)), or a pharmaceutically acceptable salt thereof, can be administered subsequent to the administration of all additional agents.

[0200] 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 2-6 and 8-10 (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 2-6 and 8-10 (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 2-6 and 8-10 (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 2-6 and 8-10 (including pharmaceutically acceptable salts and prodrugs thereof) is not antagonistic.

[0201] 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.

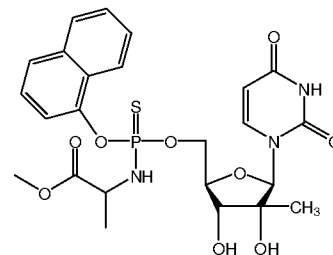
[0202] A potential advantage of utilizing a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with one or more additional agent(s) in Figures 2-6 and 8-10 (including pharmaceutically acceptable salts and prodrugs thereof) may be a reduction in the required amount(s) of one or more compounds of Figures 2-6 and 8-10 (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 2-6 and 8-10 (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 2-6 and 8-10 (including a pharmaceutically

acceptable salt and prodrug thereof), can be less compared to the amount of the compound in Figures 2-6 and 8-10 (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 2-6 and 8-10 (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.

[0203] 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 2-6 and 8-10 (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 2-6 and 8-10 (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 2-6 and 8-10 (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 2-6 and 8-10 (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 2-6 and 8-10 (including pharmaceutically acceptable salts and prodrugs thereof).

[0204] 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 2 to 10. 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 1001:6001 in Table A represents a combination of compound 1001 with compound 6001, including pharmaceutically acceptable salts of compound 1001 and/or 6001, and pharmaceutical compositions including compound 1001 and 6001 (including pharmaceutical compositions that include pharmaceutically acceptable salts of compound 1001 and/or compound 6001). Thus, the combination designated as 1001:6001 in Table A represents the combination of



Telaprevir (compound 1001, as shown in Figure 2) and (compound 6001, as shown in Figure 7A), including pharmaceutically acceptable salts of compound 1001 and/or 6001, and pharmaceutical compositions including compound 1001 and 6001 (including pharmaceutical compositions that include pharmaceutically acceptable salts of compound 1001 and/or compound 6001). 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 embodiments, in some embodiments described herein, the combination of agents can be used to treat, ameliorate 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	X : Y
1001 : 6000	1001 : 6001	1001 : 6002	1001 : 6003	1001 : 6004	1001 : 6005	1001 : 6006
1002 : 6000	1002 : 6001	1002 : 6002	1002 : 6003	1002 : 6004	1002 : 6005	1002 : 6006
1003 : 6000	1003 : 6001	1003 : 6002	1003 : 6003	1003 : 6004	1003 : 6005	1003 : 6006
1004 : 6000	1004 : 6001	1004 : 6002	1004 : 6003	1004 : 6004	1004 : 6005	1004 : 6006
1005 : 6000	1005 : 6001	1005 : 6002	1005 : 6003	1005 : 6004	1005 : 6005	1005 : 6006
1006 : 6000	1006 : 6001	1006 : 6002	1006 : 6003	1006 : 6004	1006 : 6005	1006 : 6006
1007 : 6000	1007 : 6001	1007 : 6002	1007 : 6003	1007 : 6004	1007 : 6005	1007 : 6006
1008 : 6000	1008 : 6001	1008 : 6002	1008 : 6003	1008 : 6004	1008 : 6005	1008 : 6006
1009 : 6000	1009 : 6001	1009 : 6002	1009 : 6003	1009 : 6004	1009 : 6005	1009 : 6006
1010 : 6000	1010 : 6001	1010 : 6002	1010 : 6003	1010 : 6004	1010 : 6005	1010 : 6006
1011 : 6000	1011 : 6001	1011 : 6002	1011 : 6003	1011 : 6004	1011 : 6005	1011 : 6006
1012 : 6000	1012 : 6001	1012 : 6002	1012 : 6003	1012 : 6004	1012 : 6005	1012 : 6006
1013 : 6000	1013 : 6001	1013 : 6002	1013 : 6003	1013 : 6004	1013 : 6005	1013 : 6006
1014 : 6000	1014 : 6001	1014 : 6002	1014 : 6003	1014 : 6004	1014 : 6005	1014 : 6006
2001 : 6000	2001 : 6001	2001 : 6002	2001 : 6003	2001 : 6004	2001 : 6005	2001 : 6006
2002 : 6000	2002 : 6001	2002 : 6002	2002 : 6003	2002 : 6004	2002 : 6005	2002 : 6006
2003 : 6000	2003 : 6001	2003 : 6002	2003 : 6003	2003 : 6004	2003 : 6005	2003 : 6006
2004 : 6000	2004 : 6001	2004 : 6002	2004 : 6003	2004 : 6004	2004 : 6005	2004 : 6006
2005 : 6000	2005 : 6001	2005 : 6002	2005 : 6003	2005 : 6004	2005 : 6005	2005 : 6006
2006 : 6000	2006 : 6001	2006 : 6002	2006 : 6003	2006 : 6004	2006 : 6005	2006 : 6006
2007 : 6000	2007 : 6001	2007 : 6002	2007 : 6003	2007 : 6004	2007 : 6005	2007 : 6006
2008 : 6000	2008 : 6001	2008 : 6002	2008 : 6003	2008 : 6004	2008 : 6005	2008 : 6006
2009 : 6000	2009 : 6001	2009 : 6002	2009 : 6003	2009 : 6004	2009 : 6005	2009 : 6006
2010 : 6000	2010 : 6001	2010 : 6002	2010 : 6003	2010 : 6004	2010 : 6005	2010 : 6006
3001 : 6000	3001 : 6001	3001 : 6002	3001 : 6003	3001 : 6004	3001 : 6005	3001 : 6006
3002 : 6000	3002 : 6001	3002 : 6002	3002 : 6003	3002 : 6004	3002 : 6005	3002 : 6006
3003 : 6000	3003 : 6001	3003 : 6002	3003 : 6003	3003 : 6004	3003 : 6005	3003 : 6006
3004 : 6000	3004 : 6001	3004 : 6002	3004 : 6003	3004 : 6004	3004 : 6005	3004 : 6006
3005 : 6000	3005 : 6001	3005 : 6002	3005 : 6003	3005 : 6004	3005 : 6005	3005 : 6006
3006 : 6000	3006 : 6001	3006 : 6002	3006 : 6003	3006 : 6004	3006 : 6005	3006 : 6006
3007 : 6000	3007 : 6001	3007 : 6002	3007 : 6003	3007 : 6004	3007 : 6005	3007 : 6006
3008 : 6000	3008 : 6001	3008 : 6002	3008 : 6003	3008 : 6004	3008 : 6005	3008 : 6006
4001 : 6000	4001 : 6001	4001 : 6002	4001 : 6003	4001 : 6004	4001 : 6005	4001 : 6006
4002 : 6000	4002 : 6001	4002 : 6002	4002 : 6003	4002 : 6004	4002 : 6005	4002 : 6006
4003 : 6000	4003 : 6001	4003 : 6002	4003 : 6003	4003 : 6004	4003 : 6005	4003 : 6006
4004 : 6000	4004 : 6001	4004 : 6002	4004 : 6003	4004 : 6004	4004 : 6005	4004 : 6006
4005 : 6000	4005 : 6001	4005 : 6002	4005 : 6003	4005 : 6004	4005 : 6005	4005 : 6006
5001 : 6000	5001 : 6001	5001 : 6002	5001 : 6003	5001 : 6004	5001 : 6005	5001 : 6006
5002 : 6000	5002 : 6001	5002 : 6002	5002 : 6003	5002 : 6004	5002 : 6005	5002 : 6006

[illegible]

X : Y	X : Y	X : Y	X : Y	X : Y	X : Y	X : Y
1001 : 6014	1001 : 6015	1001 : 6016	1001 : 6017	1001 : 6018	1001 : 6019	1001 : 6020
1002 : 6014	1002 : 6015	1002 : 6016	1002 : 6017	1002 : 6018	1002 : 6019	1002 : 6020
1003 : 6014	1003 : 6015	1003 : 6016	1003 : 6017	1003 : 6018	1003 : 6019	1003 : 6020
1004 : 6014	1004 : 6015	1004 : 6016	1004 : 6017	1004 : 6018	1004 : 6019	1004 : 6020
1005 : 6014	1005 : 6015	1005 : 6016	1005 : 6017	1005 : 6018	1005 : 6019	1005 : 6020
1006 : 6014	1006 : 6015	1006 : 6016	1006 : 6017	1006 : 6018	1006 : 6019	1006 : 6020
1007 : 6014	1007 : 6015	1007 : 6016	1007 : 6017	1007 : 6018	1007 : 6019	1007 : 6020
1008 : 6014	1008 : 6015	1008 : 6016	1008 : 6017	1008 : 6018	1008 : 6019	1008 : 6020
1009 : 6014	1009 : 6015	1009 : 6016	1009 : 6017	1009 : 6018	1009 : 6019	1009 : 6020
1010 : 6014	1010 : 6015	1010 : 6016	1010 : 6017	1010 : 6018	1010 : 6019	1010 : 6020
1011 : 6014	1011 : 6015	1011 : 6016	1011 : 6017	1011 : 6018	1011 : 6019	1011 : 6020
1012 : 6014	1012 : 6015	1012 : 6016	1012 : 6017	1012 : 6018	1012 : 6019	1012 : 6020
1013 : 6014	1013 : 6015	1013 : 6016	1013 : 6017	1013 : 6018	1013 : 6019	1013 : 6020
1014 : 6014	1014 : 6015	1014 : 6016	1014 : 6017	1014 : 6018	1014 : 6019	1014 : 6020
2001 : 6014	2001 : 6015	2001 : 6016	2001 : 6017	2001 : 6018	2001 : 6019	2001 : 6020
2002 : 6014	2002 : 6015	2002 : 6016	2002 : 6017	2002 : 6018	2002 : 6019	2002 : 6020
2003 : 6014	2003 : 6015	2003 : 6016	2003 : 6017	2003 : 6018	2003 : 6019	2003 : 6020
2004 : 6014	2004 : 6015	2004 : 6016	2004 : 6017	2004 : 6018	2004 : 6019	2004 : 6020
2005 : 6014	2005 : 6015	2005 : 6016	2005 : 6017	2005 : 6018	2005 : 6019	2005 : 6020
2006 : 6014	2006 : 6015	2006 : 6016	2006 : 6017	2006 : 6018	2006 : 6019	2006 : 6020
2007 : 6014	2007 : 6015	2007 : 6016	2007 : 6017	2007 : 6018	2007 : 6019	2007 : 6020
2008 : 6014	2008 : 6015	2008 : 6016	2008 : 6017	2008 : 6018	2008 : 6019	2008 : 6020
2009 : 6014	2009 : 6015	2009 : 6016	2009 : 6017	2009 : 6018	2009 : 6019	2009 : 6020
2010 : 6014	2010 : 6015	2010 : 6016	2010 : 6017	2010 : 6018	2010 : 6019	2010 : 6020
3001 : 6014	3001 : 6015	3001 : 6016	3001 : 6017	3001 : 6018	3001 : 6019	3001 : 6020
3002 : 6014	3002 : 6015	3002 : 6016	3002 : 6017	3002 : 6018	3002 : 6019	3002 : 6020
3003 : 6014	3003 : 6015	3003 : 6016	3003 : 6017	3003 : 6018	3003 : 6019	3003 : 6020
3004 : 6014	3004 : 6015	3004 : 6016	3004 : 6017	3004 : 6018	3004 : 6019	3004 : 6020
3005 : 6014	3005 : 6015	3005 : 6016	3005 : 6017	3005 : 6018	3005 : 6019	3005 : 6020
3006 : 6014	3006 : 6015	3006 : 6016	3006 : 6017	3006 : 6018	3006 : 6019	3006 : 6020
3007 : 6014	3007 : 6015	3007 : 6016	3007 : 6017	3007 : 6018	3007 : 6019	3007 : 6020
3008 : 6014	3008 : 6015	3008 : 6016	3008 : 6017	3008 : 6018	3008 : 6019	3008 : 6020
4001 : 6014	4001 : 6015	4001 : 6016	4001 : 6017	4001 : 6018	4001 : 6019	4001 : 6020
4002 : 6014	4002 : 6015	4002 : 6016	4002 : 6017	4002 : 6018	4002 : 6019	4002 : 6020
4003 : 6014	4003 : 6015	4003 : 6016	4003 : 6017	4003 : 6018	4003 : 6019	4003 : 6020
4004 : 6014	4004 : 6015	4004 : 6016	4004 : 6017	4004 : 6018	4004 : 6019	4004 : 6020
4005 : 6014	4005 : 6015	4005 : 6016	4005 : 6017	4005 : 6018	4005 : 6019	4005 : 6020
5001 : 6014	5001 : 6015	5001 : 6016	5001 : 6017	5001 : 6018	5001 : 6019	5001 : 6020
5002 : 6014	5002 : 6015	5002 : 6016	5002 : 6017	5002 : 6018	5002 : 6019	5002 : 6020

[illegible]

X : Y	X : Y	X : Y	X : Y	X : Y	X : Y	X : Y
1001 : 6028	1001 : 6029	1001 : 6030	1001 : 6031	1001 : 6032	1001 : 6033	1001 : 6034
1002 : 6028	1002 : 6029	1002 : 6030	1002 : 6031	1002 : 6032	1002 : 6033	1002 : 6034
1003 : 6028	1003 : 6029	1003 : 6030	1003 : 6031	1003 : 6032	1003 : 6033	1003 : 6034
1004 : 6028	1004 : 6029	1004 : 6030	1004 : 6031	1004 : 6032	1004 : 6033	1004 : 6034
1005 : 6028	1005 : 6029	1005 : 6030	1005 : 6031	1005 : 6032	1005 : 6033	1005 : 6034
1006 : 6028	1006 : 6029	1006 : 6030	1006 : 6031	1006 : 6032	1006 : 6033	1006 : 6034
1007 : 6028	1007 : 6029	1007 : 6030	1007 : 6031	1007 : 6032	1007 : 6033	1007 : 6034
1008 : 6028	1008 : 6029	1008 : 6030	1008 : 6031	1008 : 6032	1008 : 6033	1008 : 6034
1009 : 6028	1009 : 6029	1009 : 6030	1009 : 6031	1009 : 6032	1009 : 6033	1009 : 6034
1010 : 6028	1010 : 6029	1010 : 6030	1010 : 6031	1010 : 6032	1010 : 6033	1010 : 6034
1011 : 6028	1011 : 6029	1011 : 6030	1011 : 6031	1011 : 6032	1011 : 6033	1011 : 6034
1012 : 6028	1012 : 6029	1012 : 6030	1012 : 6031	1012 : 6032	1012 : 6033	1012 : 6034
1013 : 6028	1013 : 6029	1013 : 6030	1013 : 6031	1013 : 6032	1013 : 6033	1013 : 6034
1014 : 6028	1014 : 6029	1014 : 6030	1014 : 6031	1014 : 6032	1014 : 6033	1014 : 6034
2001 : 6028	2001 : 6029	2001 : 6030	2001 : 6031	2001 : 6032	2001 : 6033	2001 : 6034
2002 : 6028	2002 : 6029	2002 : 6030	2002 : 6031	2002 : 6032	2002 : 6033	2002 : 6034
2003 : 6028	2003 : 6029	2003 : 6030	2003 : 6031	2003 : 6032	2003 : 6033	2003 : 6034
2004 : 6028	2004 : 6029	2004 : 6030	2004 : 6031	2004 : 6032	2004 : 6033	2004 : 6034
2005 : 6028	2005 : 6029	2005 : 6030	2005 : 6031	2005 : 6032	2005 : 6033	2005 : 6034
2006 : 6028	2006 : 6029	2006 : 6030	2006 : 6031	2006 : 6032	2006 : 6033	2006 : 6034
2007 : 6028	2007 : 6029	2007 : 6030	2007 : 6031	2007 : 6032	2007 : 6033	2007 : 6034
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2010 : 6028	2010 : 6029	2010 : 6030	2010 : 6031	2010 : 6032	2010 : 6033	2010 : 6034
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3002 : 6028	3002 : 6029	3002 : 6030	3002 : 6031	3002 : 6032	3002 : 6033	3002 : 6034
3003 : 6028	3003 : 6029	3003 : 6030	3003 : 6031	3003 : 6032	3003 : 6033	3003 : 6034
3004 : 6028	3004 : 6029	3004 : 6030	3004 : 6031	3004 : 6032	3004 : 6033	3004 : 6034
3005 : 6028	3005 : 6029	3005 : 6030	3005 : 6031	3005 : 6032	3005 : 6033	3005 : 6034
3006 : 6028	3006 : 6029	3006 : 6030	3006 : 6031	3006 : 6032	3006 : 6033	3006 : 6034
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3008 : 6028	3008 : 6029	3008 : 6030	3008 : 6031	3008 : 6032	3008 : 6033	3008 : 6034
4001 : 6028	4001 : 6029	4001 : 6030	4001 : 6031	4001 : 6032	4001 : 6033	4001 : 6034
4002 : 6028	4002 : 6029	4002 : 6030	4002 : 6031	4002 : 6032	4002 : 6033	4002 : 6034
4003 : 6028	4003 : 6029	4003 : 6030	4003 : 6031	4003 : 6032	4003 : 6033	4003 : 6034
4004 : 6028	4004 : 6029	4004 : 6030	4004 : 6031	4004 : 6032	4004 : 6033	4004 : 6034
4005 : 6028	4005 : 6029	4005 : 6030	4005 : 6031	4005 : 6032	4005 : 6033	4005 : 6034
5001 : 6028	5001 : 6029	5001 : 6030	5001 : 6031	5001 : 6032	5001 : 6033	5001 : 6034
5002 : 6028	5002 : 6029	5002 : 6030	5002 : 6031	5002 : 6032	5002 : 6033	5002 : 6034

X : Y	X : Y	X : Y	X : Y	X : Y	X : Y	X : Y
1001 : 6042	1001 : 6043	1001 : 6044	1001 : 6045	1001 : 6046	1001 : 6047	1001 : 6048
1002 : 6042	1002 : 6043	1002 : 6044	1002 : 6045	1002 : 6046	1002 : 6047	1002 : 6048
1003 : 6042	1003 : 6043	1003 : 6044	1003 : 6045	1003 : 6046	1003 : 6047	1003 : 6048
1004 : 6042	1004 : 6043	1004 : 6044	1004 : 6045	1004 : 6046	1004 : 6047	1004 : 6048
1005 : 6042	1005 : 6043	1005 : 6044	1005 : 6045	1005 : 6046	1005 : 6047	1005 : 6048
1006 : 6042	1006 : 6043	1006 : 6044	1006 : 6045	1006 : 6046	1006 : 6047	1006 : 6048
1007 : 6042	1007 : 6043	1007 : 6044	1007 : 6045	1007 : 6046	1007 : 6047	1007 : 6048
1008 : 6042	1008 : 6043	1008 : 6044	1008 : 6045	1008 : 6046	1008 : 6047	1008 : 6048
1009 : 6042	1009 : 6043	1009 : 6044	1009 : 6045	1009 : 6046	1009 : 6047	1009 : 6048
1010 : 6042	1010 : 6043	1010 : 6044	1010 : 6045	1010 : 6046	1010 : 6047	1010 : 6048
1011 : 6042	1011 : 6043	1011 : 6044	1011 : 6045	1011 : 6046	1011 : 6047	1011 : 6048
1012 : 6042	1012 : 6043	1012 : 6044	1012 : 6045	1012 : 6046	1012 : 6047	1012 : 6048
1013 : 6042	1013 : 6043	1013 : 6044	1013 : 6045	1013 : 6046	1013 : 6047	1013 : 6048
1014 : 6042	1014 : 6043	1014 : 6044	1014 : 6045	1014 : 6046	1014 : 6047	1014 : 6048
2001 : 6042	2001 : 6043	2001 : 6044	2001 : 6045	2001 : 6046	2001 : 6047	2001 : 6048
2002 : 6042	2002 : 6043	2002 : 6044	2002 : 6045	2002 : 6046	2002 : 6047	2002 : 6048
2003 : 6042	2003 : 6043	2003 : 6044	2003 : 6045	2003 : 6046	2003 : 6047	2003 : 6048
2004 : 6042	2004 : 6043	2004 : 6044	2004 : 6045	2004 : 6046	2004 : 6047	2004 : 6048
2005 : 6042	2005 : 6043	2005 : 6044	2005 : 6045	2005 : 6046	2005 : 6047	2005 : 6048
2006 : 6042	2006 : 6043	2006 : 6044	2006 : 6045	2006 : 6046	2006 : 6047	2006 : 6048
2007 : 6042	2007 : 6043	2007 : 6044	2007 : 6045	2007 : 6046	2007 : 6047	2007 : 6048
2008 : 6042	2008 : 6043	2008 : 6044	2008 : 6045	2008 : 6046	2008 : 6047	2008 : 6048
2009 : 6042	2009 : 6043	2009 : 6044	2009 : 6045	2009 : 6046	2009 : 6047	2009 : 6048
2010 : 6042	2010 : 6043	2010 : 6044	2010 : 6045	2010 : 6046	2010 : 6047	2010 : 6048
3001 : 6042	3001 : 6043	3001 : 6044	3001 : 6045	3001 : 6046	3001 : 6047	3001 : 6048
3002 : 6042	3002 : 6043	3002 : 6044	3002 : 6045	3002 : 6046	3002 : 6047	3002 : 6048
3003 : 6042	3003 : 6043	3003 : 6044	3003 : 6045	3003 : 6046	3003 : 6047	3003 : 6048
3004 : 6042	3004 : 6043	3004 : 6044	3004 : 6045	3004 : 6046	3004 : 6047	3004 : 6048
3005 : 6042	3005 : 6043	3005 : 6044	3005 : 6045	3005 : 6046	3005 : 6047	3005 : 6048
3006 : 6042	3006 : 6043	3006 : 6044	3006 : 6045	3006 : 6046	3006 : 6047	3006 : 6048
3007 : 6042	3007 : 6043	3007 : 6044	3007 : 6045	3007 : 6046	3007 : 6047	3007 : 6048
3008 : 6042	3008 : 6043	3008 : 6044	3008 : 6045	3008 : 6046	3008 : 6047	3008 : 6048
4001 : 6042	4001 : 6043	4001 : 6044	4001 : 6045	4001 : 6046	4001 : 6047	4001 : 6048
4002 : 6042	4002 : 6043	4002 : 6044	4002 : 6045	4002 : 6046	4002 : 6047	4002 : 6048
4003 : 6042	4003 : 6043	4003 : 6044	4003 : 6045	4003 : 6046	4003 : 6047	4003 : 6048
4004 : 6042	4004 : 6043	4004 : 6044	4004 : 6045	4004 : 6046	4004 : 6047	4004 : 6048
4005 : 6042	4005 : 6043	4005 : 6044	4005 : 6045	4005 : 6046	4005 : 6047	4005 : 6048
5001 : 6042	5001 : 6043	5001 : 6044	5001 : 6045	5001 : 6046	5001 : 6047	5001 : 6048
5002 : 6042	5002 : 6043	5002 : 6044	5002 : 6045	5002 : 6046	5002 : 6047	5002 : 6048

X : Y	X : Y	X : Y	X : Y	X : Y	X : Y	X : Y
1001 : 6049	1001 : 6050	1001 : 6051	1001 : 6052	1001 : 6053	1001 : 6054	1001 : 6055
1002 : 6049	1002 : 6050	1002 : 6051	1002 : 6052	1002 : 6053	1002 : 6054	1002 : 6055
1003 : 6049	1003 : 6050	1003 : 6051	1003 : 6052	1003 : 6053	1003 : 6054	1003 : 6055
1004 : 6049	1004 : 6050	1004 : 6051	1004 : 6052	1004 : 6053	1004 : 6054	1004 : 6055
1005 : 6049	1005 : 6050	1005 : 6051	1005 : 6052	1005 : 6053	1005 : 6054	1005 : 6055
1006 : 6049	1006 : 6050	1006 : 6051	1006 : 6052	1006 : 6053	1006 : 6054	1006 : 6055
1007 : 6049	1007 : 6050	1007 : 6051	1007 : 6052	1007 : 6053	1007 : 6054	1007 : 6055
1008 : 6049	1008 : 6050	1008 : 6051	1008 : 6052	1008 : 6053	1008 : 6054	1008 : 6055
1009 : 6049	1009 : 6050	1009 : 6051	1009 : 6052	1009 : 6053	1009 : 6054	1009 : 6055
1010 : 6049	1010 : 6050	1010 : 6051	1010 : 6052	1010 : 6053	1010 : 6054	1010 : 6055
1011 : 6049	1011 : 6050	1011 : 6051	1011 : 6052	1011 : 6053	1011 : 6054	1011 : 6055
1012 : 6049	1012 : 6050	1012 : 6051	1012 : 6052	1012 : 6053	1012 : 6054	1012 : 6055
1013 : 6049	1013 : 6050	1013 : 6051	1013 : 6052	1013 : 6053	1013 : 6054	1013 : 6055
1014 : 6049	1014 : 6050	1014 : 6051	1014 : 6052	1014 : 6053	1014 : 6054	1014 : 6055
2001 : 6049	2001 : 6050	2001 : 6051	2001 : 6052	2001 : 6053	2001 : 6054	2001 : 6055
2002 : 6049	2002 : 6050	2002 : 6051	2002 : 6052	2002 : 6053	2002 : 6054	2002 : 6055
2003 : 6049	2003 : 6050	2003 : 6051	2003 : 6052	2003 : 6053	2003 : 6054	2003 : 6055
2004 : 6049	2004 : 6050	2004 : 6051	2004 : 6052	2004 : 6053	2004 : 6054	2004 : 6055
2005 : 6049	2005 : 6050	2005 : 6051	2005 : 6052	2005 : 6053	2005 : 6054	2005 : 6055
2006 : 6049	2006 : 6050	2006 : 6051	2006 : 6052	2006 : 6053	2006 : 6054	2006 : 6055
2007 : 6049	2007 : 6050	2007 : 6051	2007 : 6052	2007 : 6053	2007 : 6054	2007 : 6055
2008 : 6049	2008 : 6050	2008 : 6051	2008 : 6052	2008 : 6053	2008 : 6054	2008 : 6055
2009 : 6049	2009 : 6050	2009 : 6051	2009 : 6052	2009 : 6053	2009 : 6054	2009 : 6055
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[illegible]

[illegible]

[illegible]

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6033 : 7041	6033 : 7042	6033 : 7043	6033 : 7044	6033 : 7045	6033 : 7046	6033 : 7047
6034 : 7041	6034 : 7042	6034 : 7043	6034 : 7044	6034 : 7045	6034 : 7046	6034 : 7047
6035 : 7041	6035 : 7042	6035 : 7043	6035 : 7044	6035 : 7045	6035 : 7046	6035 : 7047

[illegible]

[illegible]

[illegible]

[illegible]

X : Y	X : Y	X : Y	X : Y	X : Y	X : Y	X : Y
6048 : 7026	6048 : 7027	6048 : 7028	6048 : 7029	6048 : 7030	6048 : 7031	6048 : 7032
6049 : 7026	6049 : 7027	6049 : 7028	6049 : 7029	6049 : 7030	6049 : 7031	6049 : 7032
6050 : 7026	6050 : 7027	6050 : 7028	6050 : 7029	6050 : 7030	6050 : 7031	6050 : 7032
6051 : 7026	6051 : 7027	6051 : 7028	6051 : 7029	6051 : 7030	6051 : 7031	6051 : 7032
6052 : 7026	6052 : 7027	6052 : 7028	6052 : 7029	6052 : 7030	6052 : 7031	6052 : 7032
6053 : 7026	6053 : 7027	6053 : 7028	6053 : 7029	6053 : 7030	6053 : 7031	6053 : 7032
6054 : 7026	6054 : 7027	6054 : 7028	6054 : 7029	6054 : 7030	6054 : 7031	6054 : 7032
6055 : 7026	6055 : 7027	6055 : 7028	6055 : 7029	6055 : 7030	6055 : 7031	6055 : 7032
6056 : 7026	6056 : 7027	6056 : 7028	6056 : 7029	6056 : 7030	6056 : 7031	6056 : 7032
6057 : 7026	6057 : 7027	6057 : 7028	6057 : 7029	6057 : 7030	6057 : 7031	6057 : 7032
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6059 : 7026	6059 : 7027	6059 : 7028	6059 : 7029	6059 : 7030	6059 : 7031	6059 : 7032
6060 : 7026	6060 : 7027	6060 : 7028	6060 : 7029	6060 : 7030	6060 : 7031	6060 : 7032
6041 : 7033	6041 : 7034	6041 : 7035	6041 : 7036	6041 : 7037	6041 : 7038	6041 : 7039
6042 : 7033	6042 : 7034	6042 : 7035	6042 : 7036	6042 : 7037	6042 : 7038	6042 : 7039
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6046 : 7033	6046 : 7034	6046 : 7035	6046 : 7036	6046 : 7037	6046 : 7038	6046 : 7039
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6051 : 7033	6051 : 7034	6051 : 7035	6051 : 7036	6051 : 7037	6051 : 7038	6051 : 7039
6052 : 7033	6052 : 7034	6052 : 7035	6052 : 7036	6052 : 7037	6052 : 7038	6052 : 7039
6053 : 7033	6053 : 7034	6053 : 7035	6053 : 7036	6053 : 7037	6053 : 7038	6053 : 7039
6054 : 7033	6054 : 7034	6054 : 7035	6054 : 7036	6054 : 7037	6054 : 7038	6054 : 7039
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6056 : 7033	6056 : 7034	6056 : 7035	6056 : 7036	6056 : 7037	6056 : 7038	6056 : 7039
6057 : 7033	6057 : 7034	6057 : 7035	6057 : 7036	6057 : 7037	6057 : 7038	6057 : 7039
6058 : 7033	6058 : 7034	6058 : 7035	6058 : 7036	6058 : 7037	6058 : 7038	6058 : 7039
6059 : 7033	6059 : 7034	6059 : 7035	6059 : 7036	6059 : 7037	6059 : 7038	6059 : 7039
6060 : 7033	6060 : 7034	6060 : 7035	6060 : 7036	6060 : 7037	6060 : 7038	6060 : 7039
6041 : 7040	6041 : 7041	6041 : 7042	6041 : 7043	6041 : 7044	6041 : 7045	6041 : 7046
6042 : 7040	6042 : 7041	6042 : 7042	6042 : 7043	6042 : 7044	6042 : 7045	6042 : 7046
6043 : 7040	6043 : 7041	6043 : 7042	6043 : 7043	6043 : 7044	6043 : 7045	6043 : 7046
6044 : 7040	6044 : 7041	6044 : 7042	6044 : 7043	6044 : 7044	6044 : 7045	6044 : 7046
6045 : 7040	6045 : 7041	6045 : 7042	6045 : 7043	6045 : 7044	6045 : 7045	6045 : 7046
6046 : 7040	6046 : 7041	6046 : 7042	6046 : 7043	6046 : 7044	6046 : 7045	6046 : 7046
6047 : 7040	6047 : 7041	6047 : 7042	6047 : 7043	6047 : 7044	6047 : 7045	6047 : 7046
6048 : 7040	6048 : 7041	6048 : 7042	6048 : 7043	6048 : 7044	6048 : 7045	6048 : 7046
6049 : 7040	6049 : 7041	6049 : 7042	6049 : 7043	6049 : 7044	6049 : 7045	6049 : 7046
6050 : 7040	6050 : 7041	6050 : 7042	6050 : 7043	6050 : 7044	6050 : 7045	6050 : 7046

[illegible]

X : Y	X : Y	X : Y	X : Y	X : Y	X : Y	X : Y
6054 : 7054	6054 : 7055	6054 : 7056	6054 : 7057	6054 : 7058	6054 : 7059	6054 : 7060
6055 : 7054	6055 : 7055	6055 : 7056	6055 : 7057	6055 : 7058	6055 : 7059	6055 : 7060
6056 : 7054	6056 : 7055	6056 : 7056	6056 : 7057	6056 : 7058	6056 : 7059	6056 : 7060
6057 : 7054	6057 : 7055	6057 : 7056	6057 : 7057	6057 : 7058	6057 : 7059	6057 : 7060
6058 : 7054	6058 : 7055	6058 : 7056	6058 : 7057	6058 : 7058	6058 : 7059	6058 : 7060
6059 : 7054	6059 : 7055	6059 : 7056	6059 : 7057	6059 : 7058	6059 : 7059	6059 : 7060
6060 : 7054	6060 : 7055	6060 : 7056	6060 : 7057	6060 : 7058	6060 : 7059	6060 : 7060
6041 : 7061	6041 : 7062	6041 : 7063	6041 : 7064	6041 : 7065	6041 : 7066	6041 : 7067
6042 : 7061	6042 : 7062	6042 : 7063	6042 : 7064	6042 : 7065	6042 : 7066	6042 : 7067
6043 : 7061	6043 : 7062	6043 : 7063	6043 : 7064	6043 : 7065	6043 : 7066	6043 : 7067
6044 : 7061	6044 : 7062	6044 : 7063	6044 : 7064	6044 : 7065	6044 : 7066	6044 : 7067
6045 : 7061	6045 : 7062	6045 : 7063	6045 : 7064	6045 : 7065	6045 : 7066	6045 : 7067
6046 : 7061	6046 : 7062	6046 : 7063	6046 : 7064	6046 : 7065	6046 : 7066	6046 : 7067
6047 : 7061	6047 : 7062	6047 : 7063	6047 : 7064	6047 : 7065	6047 : 7066	6047 : 7067
6048 : 7061	6048 : 7062	6048 : 7063	6048 : 7064	6048 : 7065	6048 : 7066	6048 : 7067
6049 : 7061	6049 : 7062	6049 : 7063	6049 : 7064	6049 : 7065	6049 : 7066	6049 : 7067
6050 : 7061	6050 : 7062	6050 : 7063	6050 : 7064	6050 : 7065	6050 : 7066	6050 : 7067
6051 : 7061	6051 : 7062	6051 : 7063	6051 : 7064	6051 : 7065	6051 : 7066	6051 : 7067
6052 : 7061	6052 : 7062	6052 : 7063	6052 : 7064	6052 : 7065	6052 : 7066	6052 : 7067
6053 : 7061	6053 : 7062	6053 : 7063	6053 : 7064	6053 : 7065	6053 : 7066	6053 : 7067
6054 : 7061	6054 : 7062	6054 : 7063	6054 : 7064	6054 : 7065	6054 : 7066	6054 : 7067
6055 : 7061	6055 : 7062	6055 : 7063	6055 : 7064	6055 : 7065	6055 : 7066	6055 : 7067
6056 : 7061	6056 : 7062	6056 : 7063	6056 : 7064	6056 : 7065	6056 : 7066	6056 : 7067
6057 : 7061	6057 : 7062	6057 : 7063	6057 : 7064	6057 : 7065	6057 : 7066	6057 : 7067
6058 : 7061	6058 : 7062	6058 : 7063	6058 : 7064	6058 : 7065	6058 : 7066	6058 : 7067
6059 : 7061	6059 : 7062	6059 : 7063	6059 : 7064	6059 : 7065	6059 : 7066	6059 : 7067
6060 : 7061	6060 : 7062	6060 : 7063	6060 : 7064	6060 : 7065	6060 : 7066	6060 : 7067
6041 : 7068	6041 : 7069	6041 : 7070	6041 : 7071	6041 : 7072	6041 : 7073	6041 : 7074
6042 : 7068	6042 : 7069	6042 : 7070	6042 : 7071	6042 : 7072	6042 : 7073	6042 : 7074
6043 : 7068	6043 : 7069	6043 : 7070	6043 : 7071	6043 : 7072	6043 : 7073	6043 : 7074
6044 : 7068	6044 : 7069	6044 : 7070	6044 : 7071	6044 : 7072	6044 : 7073	6044 : 7074
6045 : 7068	6045 : 7069	6045 : 7070	6045 : 7071	6045 : 7072	6045 : 7073	6045 : 7074
6046 : 7068	6046 : 7069	6046 : 7070	6046 : 7071	6046 : 7072	6046 : 7073	6046 : 7074
6047 : 7068	6047 : 7069	6047 : 7070	6047 : 7071	6047 : 7072	6047 : 7073	6047 : 7074
6048 : 7068	6048 : 7069	6048 : 7070	6048 : 7071	6048 : 7072	6048 : 7073	6048 : 7074
6049 : 7068	6049 : 7069	6049 : 7070	6049 : 7071	6049 : 7072	6049 : 7073	6049 : 7074
6050 : 7068	6050 : 7069	6050 : 7070	6050 : 7071	6050 : 7072	6050 : 7073	6050 : 7074
6051 : 7068	6051 : 7069	6051 : 7070	6051 : 7071	6051 : 7072	6051 : 7073	6051 : 7074
6052 : 7068	6052 : 7069	6052 : 7070	6052 : 7071	6052 : 7072	6052 : 7073	6052 : 7074
6053 : 7068	6053 : 7069	6053 : 7070	6053 : 7071	6053 : 7072	6053 : 7073	6053 : 7074
6054 : 7068	6054 : 7069	6054 : 7070	6054 : 7071	6054 : 7072	6054 : 7073	6054 : 7074
6055 : 7068	6055 : 7069	6055 : 7070	6055 : 7071	6055 : 7072	6055 : 7073	6055 : 7074
6056 : 7068	6056 : 7069	6056 : 7070	6056 : 7071	6056 : 7072	6056 : 7073	6056 : 7074

[illegible]

[illegible]

X : Y	X : Y	X : Y	X : Y	X : Y	X : Y	X : Y
6069 : 7025	6069 : 7026	6069 : 7027	6069 : 7028	6069 : 7029	6069 : 7030	6069 : 7031
6070 : 7025	6070 : 7026	6070 : 7027	6070 : 7028	6070 : 7029	6070 : 7030	6070 : 7031
6071 : 7025	6071 : 7026	6071 : 7027	6071 : 7028	6071 : 7029	6071 : 7030	6071 : 7031
6072 : 7025	6072 : 7026	6072 : 7027	6072 : 7028	6072 : 7029	6072 : 7030	6072 : 7031
6073 : 7025	6073 : 7026	6073 : 7027	6073 : 7028	6073 : 7029	6073 : 7030	6073 : 7031
6074 : 7025	6074 : 7026	6074 : 7027	6074 : 7028	6074 : 7029	6074 : 7030	6074 : 7031
6075 : 7025	6075 : 7026	6075 : 7027	6075 : 7028	6075 : 7029	6075 : 7030	6075 : 7031
6076 : 7025	6076 : 7026	6076 : 7027	6076 : 7028	6076 : 7029	6076 : 7030	6076 : 7031
6077 : 7025	6077 : 7026	6077 : 7027	6077 : 7028	6077 : 7029	6077 : 7030	6077 : 7031
6078 : 7025	6078 : 7026	6078 : 7027	6078 : 7028	6078 : 7029	6078 : 7030	6078 : 7031
6061 : 7032	6061 : 7033	6061 : 7034	6061 : 7035	6061 : 7036	6061 : 7037	6061 : 7038
6062 : 7032	6062 : 7033	6062 : 7034	6062 : 7035	6062 : 7036	6062 : 7037	6062 : 7038
6063 : 7032	6063 : 7033	6063 : 7034	6063 : 7035	6063 : 7036	6063 : 7037	6063 : 7038
6064 : 7032	6064 : 7033	6064 : 7034	6064 : 7035	6064 : 7036	6064 : 7037	6064 : 7038
6065 : 7032	6065 : 7033	6065 : 7034	6065 : 7035	6065 : 7036	6065 : 7037	6065 : 7038
6066 : 7032	6066 : 7033	6066 : 7034	6066 : 7035	6066 : 7036	6066 : 7037	6066 : 7038
6067 : 7032	6067 : 7033	6067 : 7034	6067 : 7035	6067 : 7036	6067 : 7037	6067 : 7038
6068 : 7032	6068 : 7033	6068 : 7034	6068 : 7035	6068 : 7036	6068 : 7037	6068 : 7038
6069 : 7032	6069 : 7033	6069 : 7034	6069 : 7035	6069 : 7036	6069 : 7037	6069 : 7038
6070 : 7032	6070 : 7033	6070 : 7034	6070 : 7035	6070 : 7036	6070 : 7037	6070 : 7038
6071 : 7032	6071 : 7033	6071 : 7034	6071 : 7035	6071 : 7036	6071 : 7037	6071 : 7038
6072 : 7032	6072 : 7033	6072 : 7034	6072 : 7035	6072 : 7036	6072 : 7037	6072 : 7038
6073 : 7032	6073 : 7033	6073 : 7034	6073 : 7035	6073 : 7036	6073 : 7037	6073 : 7038
6074 : 7032	6074 : 7033	6074 : 7034	6074 : 7035	6074 : 7036	6074 : 7037	6074 : 7038
6075 : 7032	6075 : 7033	6075 : 7034	6075 : 7035	6075 : 7036	6075 : 7037	6075 : 7038
6076 : 7032	6076 : 7033	6076 : 7034	6076 : 7035	6076 : 7036	6076 : 7037	6076 : 7038
6077 : 7032	6077 : 7033	6077 : 7034	6077 : 7035	6077 : 7036	6077 : 7037	6077 : 7038
6078 : 7032	6078 : 7033	6078 : 7034	6078 : 7035	6078 : 7036	6078 : 7037	6078 : 7038
6061 : 7039	6061 : 7040	6061 : 7041	6061 : 7042	6061 : 7043	6061 : 7044	6061 : 7045
6062 : 7039	6062 : 7040	6062 : 7041	6062 : 7042	6062 : 7043	6062 : 7044	6062 : 7045
6063 : 7039	6063 : 7040	6063 : 7041	6063 : 7042	6063 : 7043	6063 : 7044	6063 : 7045
6064 : 7039	6064 : 7040	6064 : 7041	6064 : 7042	6064 : 7043	6064 : 7044	6064 : 7045
6065 : 7039	6065 : 7040	6065 : 7041	6065 : 7042	6065 : 7043	6065 : 7044	6065 : 7045
6066 : 7039	6066 : 7040	6066 : 7041	6066 : 7042	6066 : 7043	6066 : 7044	6066 : 7045
6067 : 7039	6067 : 7040	6067 : 7041	6067 : 7042	6067 : 7043	6067 : 7044	6067 : 7045
6068 : 7039	6068 : 7040	6068 : 7041	6068 : 7042	6068 : 7043	6068 : 7044	6068 : 7045
6069 : 7039	6069 : 7040	6069 : 7041	6069 : 7042	6069 : 7043	6069 : 7044	6069 : 7045
6070 : 7039	6070 : 7040	6070 : 7041	6070 : 7042	6070 : 7043	6070 : 7044	6070 : 7045
6071 : 7039	6071 : 7040	6071 : 7041	6071 : 7042	6071 : 7043	6071 : 7044	6071 : 7045
6072 : 7039	6072 : 7040	6072 : 7041	6072 : 7042	6072 : 7043	6072 : 7044	6072 : 7045
6073 : 7039	6073 : 7040	6073 : 7041	6073 : 7042	6073 : 7043	6073 : 7044	6073 : 7045
6074 : 7039	6074 : 7040	6074 : 7041	6074 : 7042	6074 : 7043	6074 : 7044	6074 : 7045
6075 : 7039	6075 : 7040	6075 : 7041	6075 : 7042	6075 : 7043	6075 : 7044	6075 : 7045

[illegible]

X : Y	X : Y	X : Y	X : Y	X : Y	X : Y	X : Y
6065 : 7060	6065 : 7061	6065 : 7062	6065 : 7063	6065 : 7064	6065 : 7065	6065 : 7066
6066 : 7060	6066 : 7061	6066 : 7062	6066 : 7063	6066 : 7064	6066 : 7065	6066 : 7066
6067 : 7060	6067 : 7061	6067 : 7062	6067 : 7063	6067 : 7064	6067 : 7065	6067 : 7066
6068 : 7060	6068 : 7061	6068 : 7062	6068 : 7063	6068 : 7064	6068 : 7065	6068 : 7066
6069 : 7060	6069 : 7061	6069 : 7062	6069 : 7063	6069 : 7064	6069 : 7065	6069 : 7066
6070 : 7060	6070 : 7061	6070 : 7062	6070 : 7063	6070 : 7064	6070 : 7065	6070 : 7066
6071 : 7060	6071 : 7061	6071 : 7062	6071 : 7063	6071 : 7064	6071 : 7065	6071 : 7066
6072 : 7060	6072 : 7061	6072 : 7062	6072 : 7063	6072 : 7064	6072 : 7065	6072 : 7066
6073 : 7060	6073 : 7061	6073 : 7062	6073 : 7063	6073 : 7064	6073 : 7065	6073 : 7066
6074 : 7060	6074 : 7061	6074 : 7062	6074 : 7063	6074 : 7064	6074 : 7065	6074 : 7066
6075 : 7060	6075 : 7061	6075 : 7062	6075 : 7063	6075 : 7064	6075 : 7065	6075 : 7066
6076 : 7060	6076 : 7061	6076 : 7062	6076 : 7063	6076 : 7064	6076 : 7065	6076 : 7066
6077 : 7060	6077 : 7061	6077 : 7062	6077 : 7063	6077 : 7064	6077 : 7065	6077 : 7066
6078 : 7060	6078 : 7061	6078 : 7062	6078 : 7063	6078 : 7064	6078 : 7065	6078 : 7066
6061 : 7067	6061 : 7068	6061 : 7069	6061 : 7070	6061 : 7071	6061 : 7072	6061 : 7073
6062 : 7067	6062 : 7068	6062 : 7069	6062 : 7070	6062 : 7071	6062 : 7072	6062 : 7073
6063 : 7067	6063 : 7068	6063 : 7069	6063 : 7070	6063 : 7071	6063 : 7072	6063 : 7073
6064 : 7067	6064 : 7068	6064 : 7069	6064 : 7070	6064 : 7071	6064 : 7072	6064 : 7073
6065 : 7067	6065 : 7068	6065 : 7069	6065 : 7070	6065 : 7071	6065 : 7072	6065 : 7073
6066 : 7067	6066 : 7068	6066 : 7069	6066 : 7070	6066 : 7071	6066 : 7072	6066 : 7073
6067 : 7067	6067 : 7068	6067 : 7069	6067 : 7070	6067 : 7071	6067 : 7072	6067 : 7073
6068 : 7067	6068 : 7068	6068 : 7069	6068 : 7070	6068 : 7071	6068 : 7072	6068 : 7073
6069 : 7067	6069 : 7068	6069 : 7069	6069 : 7070	6069 : 7071	6069 : 7072	6069 : 7073
6070 : 7067	6070 : 7068	6070 : 7069	6070 : 7070	6070 : 7071	6070 : 7072	6070 : 7073
6071 : 7067	6071 : 7068	6071 : 7069	6071 : 7070	6071 : 7071	6071 : 7072	6071 : 7073
6072 : 7067	6072 : 7068	6072 : 7069	6072 : 7070	6072 : 7071	6072 : 7072	6072 : 7073
6073 : 7067	6073 : 7068	6073 : 7069	6073 : 7070	6073 : 7071	6073 : 7072	6073 : 7073
6074 : 7067	6074 : 7068	6074 : 7069	6074 : 7070	6074 : 7071	6074 : 7072	6074 : 7073
6075 : 7067	6075 : 7068	6075 : 7069	6075 : 7070	6075 : 7071	6075 : 7072	6075 : 7073
6076 : 7067	6076 : 7068	6076 : 7069	6076 : 7070	6076 : 7071	6076 : 7072	6076 : 7073
6077 : 7067	6077 : 7068	6077 : 7069	6077 : 7070	6077 : 7071	6077 : 7072	6077 : 7073
6078 : 7067	6078 : 7068	6078 : 7069	6078 : 7070	6078 : 7071	6078 : 7072	6078 : 7073
6061 : 7074	6061 : 7075	6061 : 7076	6061 : 7077	--	--	--
6062 : 7074	6062 : 7075	6062 : 7076	6062 : 7077			
6063 : 7074	6063 : 7075	6063 : 7076	6063 : 7077			
6064 : 7074	6064 : 7075	6064 : 7076	6064 : 7077			
6065 : 7074	6065 : 7075	6065 : 7076	6065 : 7077			
6066 : 7074	6066 : 7075	6066 : 7076	6066 : 7077			
6067 : 7074	6067 : 7075	6067 : 7076	6067 : 7077			
6068 : 7074	6068 : 7075	6068 : 7076	6068 : 7077			
6069 : 7074	6069 : 7075	6069 : 7076	6069 : 7077			
6070 : 7074	6070 : 7075	6070 : 7076	6070 : 7077			
6071 : 7074	6071 : 7075	6071 : 7076	6071 : 7077			

X : Y	X : Y	X : Y	X : Y	X : Y	X : Y	X : Y
6072 : 7074	6072 : 7075	6072 : 7076	6072 : 7077			
6073 : 7074	6073 : 7075	6073 : 7076	6073 : 7077			
6074 : 7074	6074 : 7075	6074 : 7076	6074 : 7077			
6075 : 7074	6075 : 7075	6075 : 7076	6075 : 7077			
6076 : 7074	6076 : 7075	6076 : 7076	6076 : 7077			
6077 : 7074	6077 : 7075	6077 : 7076	6077 : 7077			
6078 : 7074	6078 : 7075	6078 : 7076	6078 : 7077			

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	6000 : 8001	6000 : 8002	6000 : 8003	6000 : 8004	6000 : 8005
6001 : 8000	6001 : 8001	6001 : 8002	6001 : 8003	6001 : 8004	6001 : 8005
6002 : 8000	6002 : 8001	6002 : 8002	6002 : 8003	6002 : 8004	6002 : 8005
6003 : 8000	6003 : 8001	6003 : 8002	6003 : 8003	6003 : 8004	6003 : 8005
6004 : 8000	6004 : 8001	6004 : 8002	6004 : 8003	6004 : 8004	6004 : 8005
6005 : 8000	6005 : 8001	6005 : 8002	6005 : 8003	6005 : 8004	6005 : 8005
6006 : 8000	6006 : 8001	6006 : 8002	6006 : 8003	6006 : 8004	6006 : 8005
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6008 : 8000	6008 : 8001	6008 : 8002	6008 : 8003	6008 : 8004	6008 : 8005
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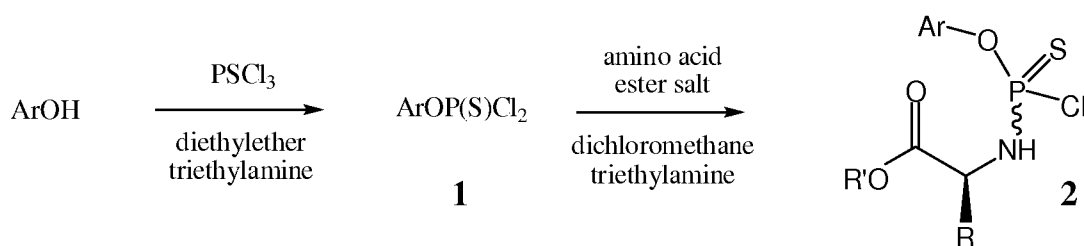
Table D: Example combinations of a compound X with a compound Y.

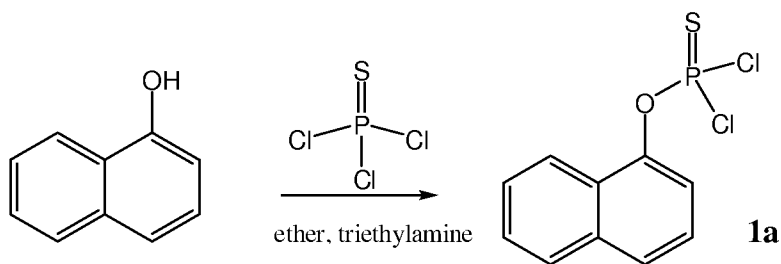
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EXAMPLES

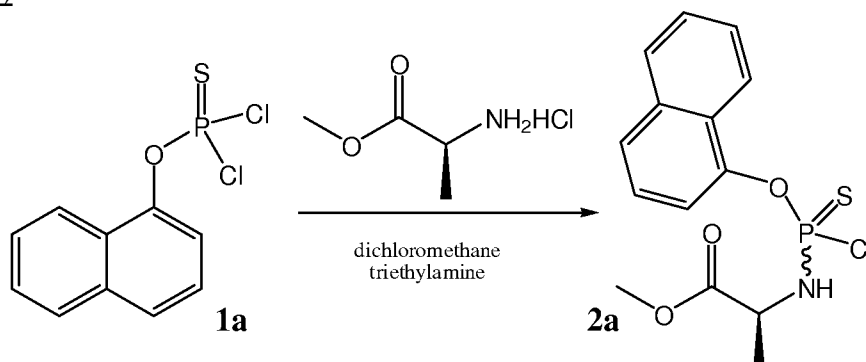
[0205] Additional embodiments are disclosed in further detail in the following examples, which are not in any way intended to limit the scope of the claims.

Example 1
General Synthesis of Reagents 1 and 2



Step 1: Synthesis of 1-naphthyloxydichlorophosphothioate reagent (1a)

[0206] A 500 mL round bottom flask containing a magnetic stir bar was charged with phosphorus trichloride (5.7 g, 33.65 mmol) and 1-naphthol (4.85 g, 33.64 mmol), and 40 mL of diethyl ether was added. Under an argon atmosphere, the solution was cooled in a dry ice/acetone bath. After 10 minutes of cooling, triethylamine (4.7 mL, 33.7 mmol) was added, and a precipitate formed. The mixture was allowed to warm to ambient temperature, and was then stirred for 2 days. The precipitated triethylammonium hydrochloride was filtered off, and was washed twice with ether. The solvents were removed under reduced pressure to leave 9.8 g of compound **1a** as a cloudy, light yellow oil. **1a** was used in the next step without further purification.

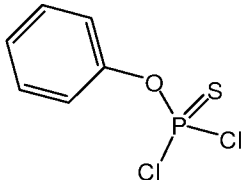
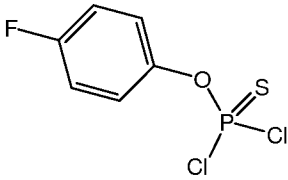
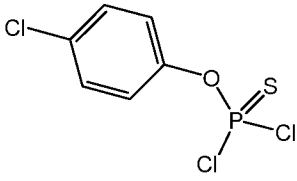
Step 2: Synthesis of the L-alanine methyl ester derived 1-naphthyloxy-chlorophosphothioate reagent (2a)

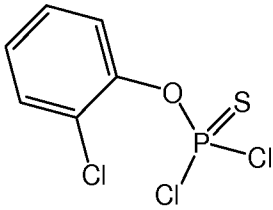
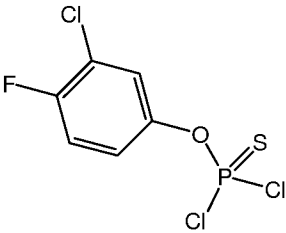
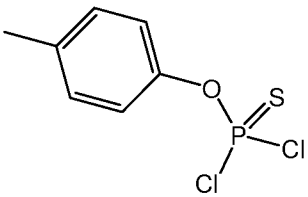
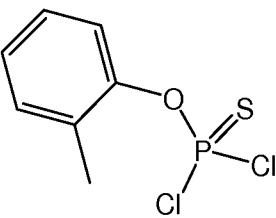
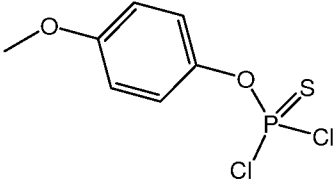
[0207] Into a 250 mL round bottom flask containing 1-naphthol-dichlorophosphothioate reagent **1a** (1.97 g, 7.1 mmol) and L-alanine methyl ester hydrochloride (0.99 g, 7.1 mmol) was added in 50 mL of dichloromethane. At water/ice temperature under an argon atmosphere, triethylamine (1 mL, 7.2 mmol) was added. The reaction was allowed to warm to ambient temperature and was then stirred overnight. The solvents were removed using a rotary evaporator. The residue was purified using chromatography on silica gel, and eluting with 20% ethyl acetate in hexanes. The product **2a**

(1.0 g) was obtained as a viscous oil. ^{31}P NMR (CDCl_3 , 64.78, 65.0) (approximately a 1:1 mixture of diastereomers).

[0208] The reagents shown in Tables 6 and 7 were prepared using the procedures described for compounds **1a** and **2a**, with the ArOH compounds listed in Table 6 in place of 1-naphthol, and with hydrochloride salts of the amino acids listed in Table 7 in place of L-alanine methyl ester hydrochloride.

Table 6

ArOH	Dichloridates	Reagent No.
Phenol		1b
p-fluoro-phenol		1c
p-chloro-phenol		1d

ArOH	Dichloridates	Reagent No.
o-chloro-phenol		1e
p-chloro-m-chloro-phenol		1f
p-methyl-phenol		1g
o-methyl-phenol		1h
p-methoxy-phenol		1i

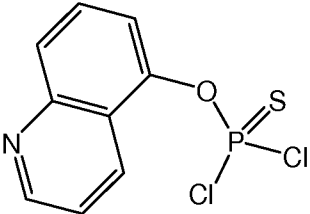
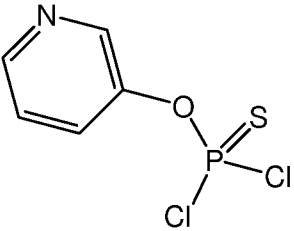
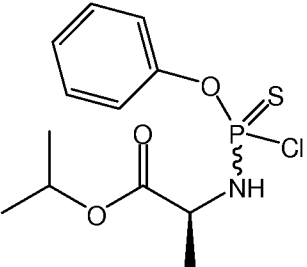
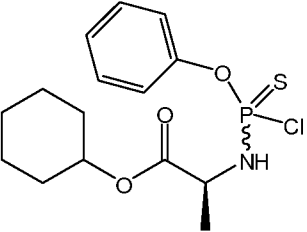
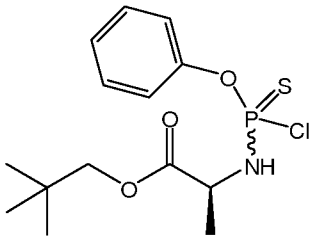
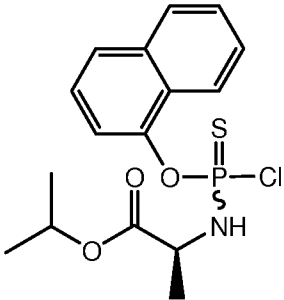
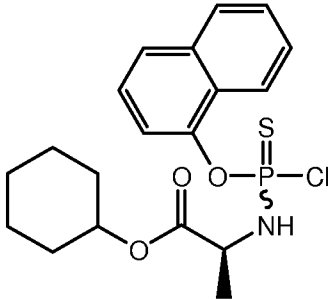
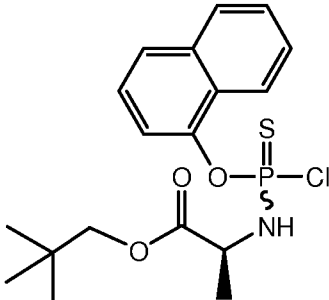
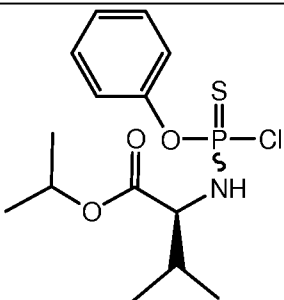
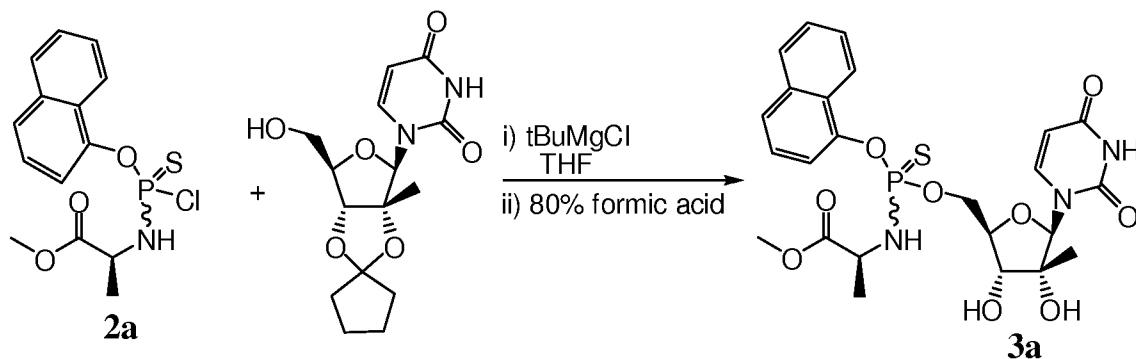
ArOH	Dichloridates	Reagent No.
quinolin-5-ol		1j
pyridine-3-ol		1k

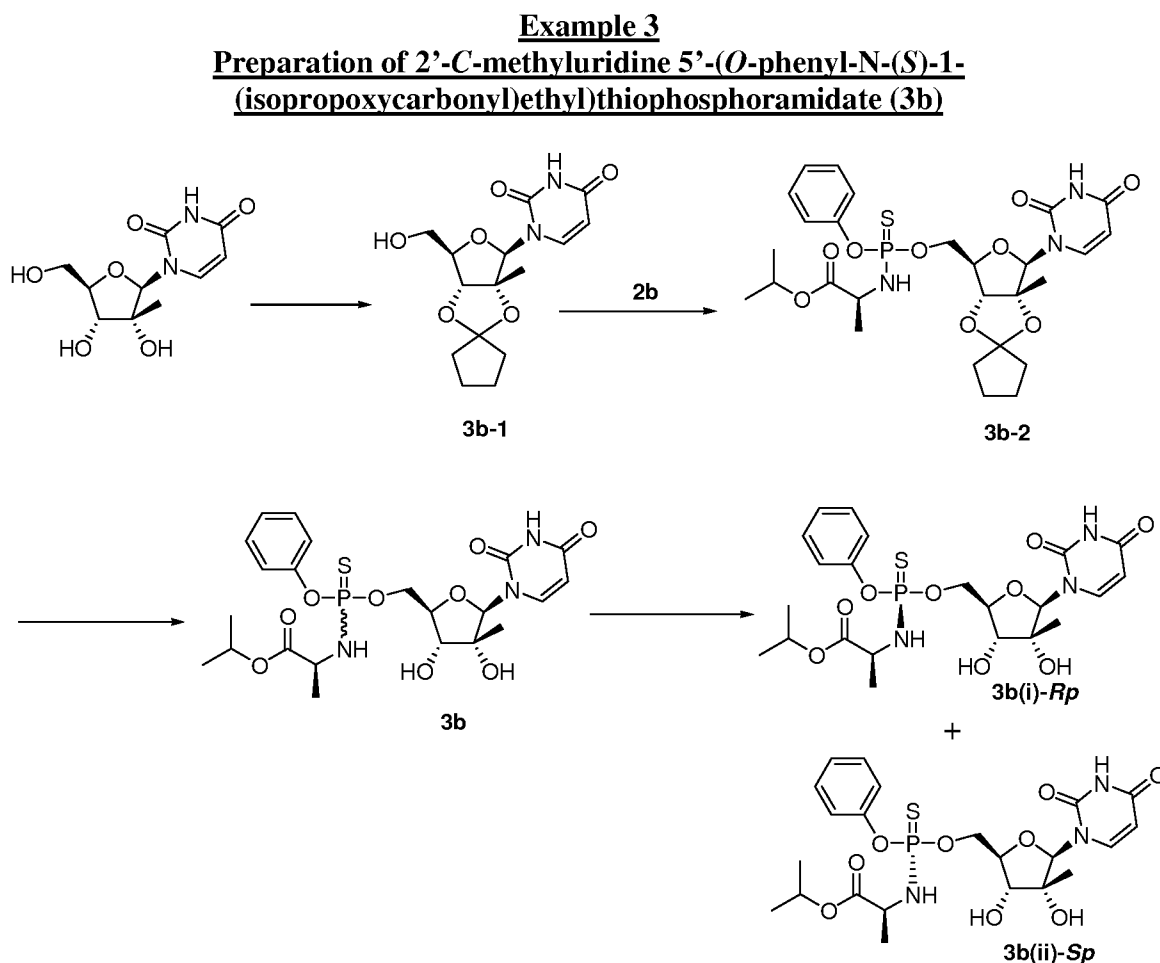
Table 7

Amino Acid	Aryloxy amino acid thiophosphochloridate	Reagent No.	³¹ P NMR (CDCl ₃)
L-alanine isopropyl ester		2b	64.75 (s) 64.65 (s)
L-alanine cyclohexyl ester		2c	64.80 (s) 64.69 (s)

Amino Acid	Aryloxy amino acid thiophosphochloridate	Reagent No.	³¹ P NMR (CDCl ₃)
L-alanine neopentyl ester		2d	64.59 (s) 64.31 (s)
L-alanine isopropyl ester		2e	64.51 (s) 64.23 (s)
L-alanine cyclohexyl ester		2f	64.55 (s) 64.25 (s)
L-alanine neopentyl ester		2g	64.51 (s) 64.27 (s)
L-valine isopropyl ester		2h	67.72 65.87

Example 2**Preparation of 2'-C-Methyluridine 5'-(*O*-(1-naphthyl)-*N*-(*S*)-1-(methoxycarbonyl)ethyl) thiophosphoramidate (3a)**

[0209] A solution of cyclopentylidene protected 2'-*C*-methyluridine (262 mg, 0.81 mmol) in 2 mL tetrahydrofuran was cooled in an ice/water bath under argon, and treated with 2.1 mL $t\text{BuMgCl}$ (1 M, 2.1 mmol). After 10 minutes, reagent **2a** (0.83 g, 2.4 mmol) was added as a solution in 2 mL of tetrahydrofuran (THF). The reaction was stirred at ambient temperature for 2 days. An additional 1 mL $t\text{BuMgCl}$ was then added (1 mmol). After an additional 2 days, the reaction was diluted with ethyl acetate and water. The organic layer was washed two times with brine, and dried over sodium sulfate. Chromatography on silica gel using a gradient of 1% methanol in dichloromethane to 10% methanol in dichloromethane afforded 0.2 g of a residue which was used without further purification. To the residue was added 4 mL of 80% aqueous formic acid. The mixture was heated to 50°C using a water bath. After 2 hours, the reaction was cooled, and the solvents were removed under reduced pressure. A solution of 1:1 methanol: toluene was added to the residue. The solvents were then removed under reduced pressure. The addition of a solution of 1:1 methanol: toluene and removal of solvents were repeated 2 more times. The product was isolated following chromatography using silica gel with a gradient from 4% to 8% methanol in dichloromethane. The solvent was removed, and the residue was taken up in chloroform and treated with excess hexanes. The supernatant was decanted off, and the remaining solid was subjected to high vacuum overnight. Product **3a** was isolated as a colorless solid (22.2 mg). ^{31}P NMR (CDCl_3 , 67.12, 67.86) and mass spectral data (M-H^+ , 564.5) were consistent with the desired product **3a** as a near 1:1 mixture of diastereomers at the phosphorus chiral center.



[0210] Step 1: Compound **3b-1** - To a suspension of 2'-methyluridine (20 g, 77.52 mmol) in dry CH₃CN (200 mL) were added cyclopentanone (20 mL) and trimethylorthoformate (20 mL) followed by p-toluenesulfonic acid monohydrate (7.4 g, 38.76 mmol). The reaction mixture was stirred at 40°C overnight. The solvent was evaporated. The residue was dissolved in ethyl acetate and washed with brine. The organic layer was dried and evaporated to give pure **3b-1** as a white solid (14.5 g, 57.7%). ¹H NMR (CDCl₃, 400 MHz) δ 8.86 (s, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 6.06 (s, 1H), 5.73 (d, *J* = 8.0 Hz, 1H), 4.50 (d, *J* = 4.8 Hz, 1H), 4.21 (m, 1H), 4.02-3.86 (m, 2H), 2.17 (m, 1H), 1.98, 1.83, 1.68 (m, 8H), 1.30 (s, 3H).

[0211] Step 2: Compound **3b-2** - To a suspension of **3b-1** (20 g, 61.7 mmol) in dry CH₃CN (100 mL) was added *N*-methylimidazole (50 mL) and **2b** (80 g, 249.2 mmol).

The reaction mixture was stirred at 70°C for 2h. Solvent was removed and the residue was dissolved in ethyl acetate (500 mL). The solution was washed with brine, dried and evaporated. The residue was purified on a silica gel column (20~50% ethylacetate (EA) in petroleum ether (PE)) to give **3b-2** as a white foam (two isomers, 12.5 g, 33%). ¹H NMR (CDCl₃, 400 MHz) δ 8.79-8.92 (m, 1H), 7.55 (m, 1H), 7.34 (m, 2H), 7.20 (m, 3H), 6.09 (d, J = 13.6 Hz, 1H), 5.70-5.61 (m, 1H), 5.06-5.01 (m, 1H), 4.38-4.09 (m, 6H), 2.08 (m, 1H), 1.96 (m, 1H), 1.73 (m, 2H), 1.66 (m, 5H), 1.39 (m, 3H), 1.23 (m, 9H); ³¹P NMR (CDCl₃, 162 MHz) δ 67.62, 67.31.

[0212] Step 3: Compound **3b** – Compound **3b-2** (10 g, 16.4 mmol) was suspended in 100 mL of 80% formic acid and the reaction mixture was stirred at 50°C for 1.5 hours. Solvent was evaporated and the residue was co-evaporated with toluene to remove traces of acid and water. The residue was purified by RP HPLC (0.5% HCOOH in MeCN and water as mobile phase) to give **3b** (a mixture of two *P*-diastereomers, 5.6 g, 63%). ¹H NMR (CD₃OD, 400 MHz) δ 7.79, 7.87 (2d, J = 8.0 Hz, 1H), 7.18-7.38 (m, 5H), 5.98, 6.01 (2s, 1H), 5.59, 5.63 (2d, J = 8.0 Hz, 1H), 4.95-5.05 (m, 1H), 4.51-4.56 (m, 1H), 4.30-4.44 (m, 1H), 4.05-4.17 (m, 2H), 3.82-3.87 (m, 1H), 1.34, 1.38 (2d, J = 7.2 Hz, 3H), 1.17, 1.25 (2d, J = 6.0 Hz, 6H), 1.24, 1.25 (2s, 3H); ³¹P NMR (CD₃OD, 162 MHz) δ 68.17, 68.40; ESI-LCMS: m/z 544.0 [M + H]⁺.

[0213] Step 4: Separation of **3b(i)-Rp** and **3b(ii)-Sp** - Compound **3b** was separated into its *Rp* and *Sp* diastereomers by two methods: (a) supercritical fluid chromatography (SFC) and (b) crystallization.

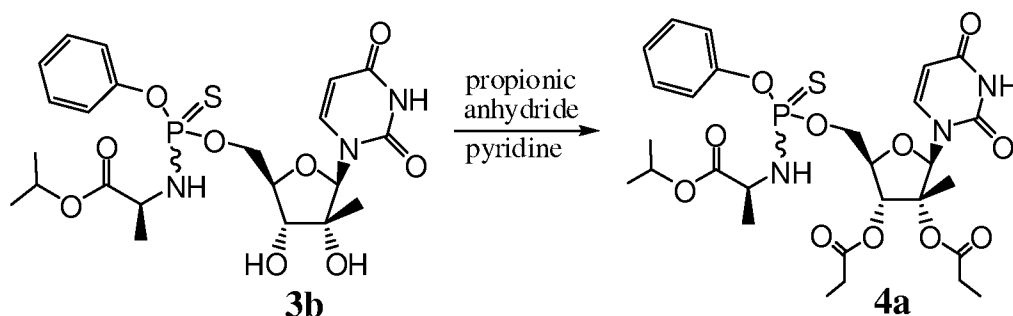
[0214] (a) Via SFC: Compound **3b** (440 mg, consisting of both **3b(i)-Rp** and **3b(ii)-Sp** in ~1:1 ratio) was subjected to separation by SFC (chiral PAK AD, 5 μ m, 250*30 mm using 25% MeOH and 75% CO₂ as mobile phase) to give **3b(i)-Rp** (123.8 mg) and **3b(ii)-Sp** (162.5 mg) as a white solid; **3b(i)-Rp**: ¹H NMR (CD₃OD, 400 MHz) δ 7.87 (d, J = 8.4 Hz, 1H), 7.36 (t, J = 8.0 Hz, 2H), 7.28 (d, J = 8.8 Hz, 2H), 7.19 (t, J = 7.6 Hz, 1H), 6.01 (s, 1H), 5.62 (d, J = 8.0 Hz, 1H), 5.03-4.97 (m, 1H), 4.56-4.92 (m, 1H), 4.44-4.39 (m, 1H), 4.16-4.13 (m, 1H), 4.10-4.05 (m, 1H), 3.86 (d, J = 9.2 Hz, 1H), 1.34 (d, J = 7.2 Hz, 3H), 1.25 (d, J = 6.4 Hz, 6H), 1.16 (s, 3H); ³¹P NMR (CD₃OD, 162 MHz) δ 68.18; ESI-LCMS: m/z = 544 [M + H]⁺. **3b(ii)-Sp**: ¹H NMR (CD₃OD, 400 MHz) δ 7.89 (d, J = 8.0 Hz, 1H), 7.36 (t, J

= 8.0 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 7.20 (t, J = 8.0 Hz, 1H), 5.99 (s, 1H), 5.60 (d, J = 8.4 Hz, 1H), 5.03-4.97 (m, 1H), 4.56-4.51 (m, 1H), 4.35-4.30 (m, 1H), 4.14-4.10 (m, 2H), 3.83 (d, J = 9.2 Hz, 1H), 1.39 (d, J = 7.2 Hz, 3H), 1.25 (d, J = 6.4 Hz, 6H), 1.17 (s, 3H); ^{31}P NMR (CD_3OD , 162 MHz) δ 68.42; ESI-LCMS: m/z = 566 $[\text{M} + \text{Na}]^+$.

[0215] (b) Via crystallization: Compound **3b** as a mixture of diastereomers (1:1, 10 g) was dissolved in 100 mL of dichloromethane (DCM) / ether (1:3). Hexane was added dropwise until the solution became cloudy. The solution was left at (room temperature) RT for 5 h and overnight at -20°C . Precipitated crystals were recrystallized from DCM/ether 1:3 v/v, and one more time from DCM/ether 1:2. Compound **3b(i)-Rp** (3 g) was obtained as a pure single diastereomer. The mother liquor after first crystallization was concentrated, and then dissolved in isopropanol. Hexane was added (30% by volume). The clear solution was left overnight at RT to produce a small amount of crystals, which were used as seeds. The mother liquor was evaporated and crystallized 2 times from hexane/isopropanol (4:1) to give 2.3 g of **3b(ii)-Sp**.

Example 4

Preparation of 2',3'-O-dipropionyl-2'-C-methyluridine 5'-(O-phenyl-N-(S)-1-(isopropoxycarbonyl)ethyl)thiophosphoramidate (4a)

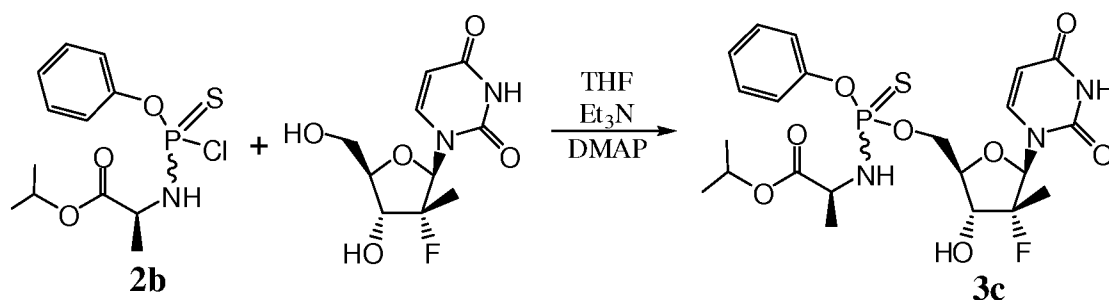


[0216] Compound **3b** (85 mg, 0.156 mmol) was dissolved in 3 mL of dry pyridine. Propionic anhydride (0.1 mL, 0.624 mmol) was added, and the mixture left for 18 hours at ambient temperature. Water (7 mL) and ethyl acetate (7 mL) were added. The organic phase was separated, and the aqueous phase was extracted with ethyl acetate (2 x 5 mL). The combined organic extracts were washed with water, brine, dried over Na_2SO_4 , and evaporated. The resulting oil was purified by flash chromatography using a gradient of methanol in dichloromethane from 0 to 4%. The fractions containing phosphorothioate were

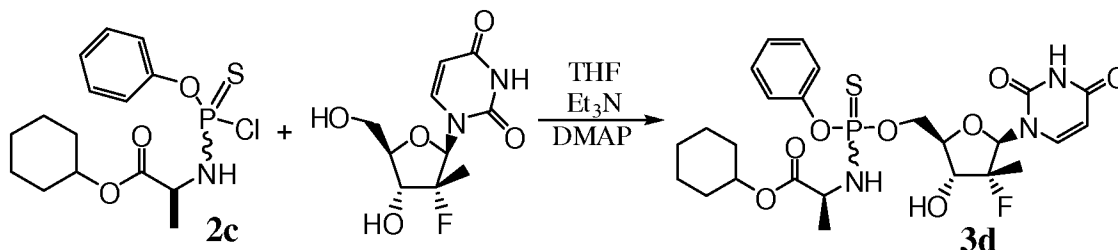
combined and concentrated in vacuum. Repurification by RP HPLC using a gradient of methanol in water from 50% to 100% yielded 44 mg of product **4a**. ^{31}P NMR (CDCl_3 , 67.71, 67.74) and mass spectral analysis (M^+ , 654.5) were consistent with the desired product **4a** as near 1:1 mixture of diastereomers at the phosphorus chiral center.

Example 5

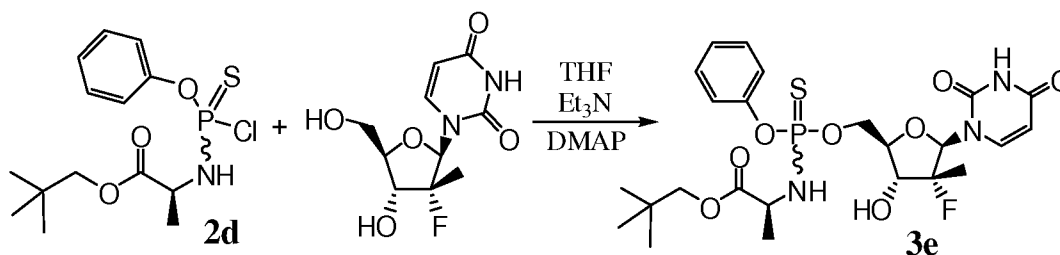
Preparation of 2'-deoxy-2'- α -fluoro-2'- β -C-methyluridine 5'-(*O*-phenyl-*N*-(*S*)-1-(isopropoxycarbonyl)ethyl)thiophosphoramidate (**3c**)



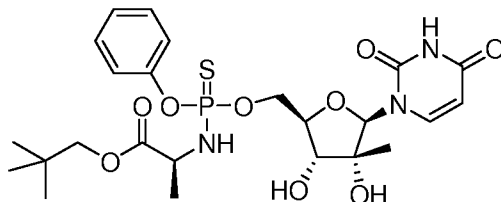
[0217] 2'-Deoxy-2'-fluoro-2'-methyluridine (200 mg, 0.62 mmol) was suspended in dry THF (20 mL) under N_2 . A solution of **2b** in dry THF (3 mL, 3 mmol), DMAP (4-dimethylaminopyridine) (100 mg, 0.9 mmol) and triethylamine (1 mL, 7 mmol) were added at RT. The reaction was stirred at 80°C for 18 hrs. The solvents were removed, and the residue was purified by column and RP HPLC (HCOOH system) to give **3c** as a white solid (3.5 mg). ^1H NMR (CDCl_3) δ 8.49, 8.31 (m, 1H), 7.49, 7.43 (2d, $J = 8.0$ Hz, 1H), 7.31, 7.26 (m, 2H), 7.19, 7.11 (m, 3H), 6.17, 6.11 (2d, $J = 7.2$ Hz, 1H), 5.62, 5.53 (2d, 1H), 4.99, 4.93 (m, 1H), 4.54, 4.27 (m, 2H), 4.08, 4.02 (m, 3H), 3.89, 3.83 (m, 1H), 1.36, 1.22 (m, 6H), 1.20, 1.12 (m, 6H). ^{31}P NMR (CDCl_3) δ 68.08, 67.05. LCMS m/z 545.8 (MH^+).

Example 6**Preparation of 2'-deoxy-2'- α -fluoro-2'- β -C-methyluridine 5'-(*O*-phenyl-*N*-(*S*)-1-(cyclohexoxycarbonyl)ethyl)thiophosphoramidate (3d)**

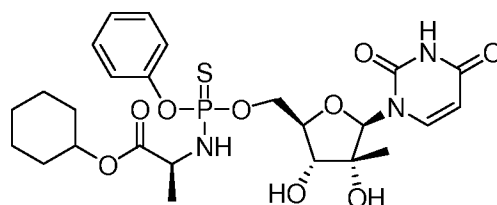
[0218] Compound **3d** was prepared using the procedure for preparing compound **3c**, with **2c** in place of **2b**. ^1H NMR (DMSO- d_6) δ 11.55 (s, 1H), 7.61 (d, J = 8.4 Hz, 0.43H), 7.57 (d, J = 7.6 Hz, 0.56H), 7.40 (m, 2H), 7.21 (overlap, 3H), 6.68 (m, 1H), 6.04 (m, 1H), 5.95 (d, J = 7.6 Hz, 0.40H), 5.88 (d, J = 6.8 Hz, 0.60H), 5.57 (s, 0.50H), 5.55 (s, 0.50H), 4.64 (s, 1H), 4.39 (m, 1H), 4.23 (m, 1H), 4.09-3.86 (m, 2H), 3.84 (m, 1H), 1.63 (s, 2H), 1.45 (s, 2H), 1.36 (brs, 1H), 1.34-1.29 (m, 11H). ^{31}P NMR (DMSO- d_6) δ 67.96, 67.89; MS m/z 586.2 (MH^+).

Example 7**Preparation of 2'-deoxy-2'- α -fluoro-2'- β -C-methyluridine 5'-(*O*-phenyl-*N*-(*S*)-1-(neopentoxycarbonyl)ethyl)thiophosphoramidate (3e)**

[0219] Compound **3e** was prepared using the procedure for preparing compound **3c**, with **2d** in place of **2b**. ^1H NMR (CD_3OD) δ 7.77-7.66 (q, J = 8.0, 8.4 Hz, 1H), 7.36-7.16 (m, 5H), 6.13 (m, 1H), 6.04 (m, 1H), 5.65-5.56 (q, J = 8.4, 8.0 Hz, 1H), 4.19-4.09 (m, 2H), 3.93-3.75 (m, 2H), 1.41-1.28 (m, 6H), 0.93 (s, 9H). ^{31}P NMR (CD_3OD) δ 66.9, 66.9. MS m/z 574.2 (MH^+).

Example 8**Preparation of 2'-C-methyluridine 5'-(O-phenyl-N-(S)-1-(neopentoxycarbonyl)ethyl)thiophosphoramidate (3f)**

[0220] 2'-C-methyluridine (77 mg, 0.3 mmol) was dissolved in 10 mL of anhydrous acetonitrile and 2 mL of *N*-methylimidazole. Compound **2d** was added (0.3 g, 0.9 mmol) and the mixture was heated at 70°C for 2 h. The solvent was removed under reduced pressure. The residue was dissolved in 30 mL of ethyl acetate, washed with 10% citric acid (2 x 10 mL), water, brine, dried over Na₂SO₄, and concentrated. The crude product was purified by flash chromatography on silica gel with methanol in dichloromethane (0 to 10%) to give **3f** (224 mg) as light-tan solid. An analytical sample was obtained as a colorless solid by RP HPLC purification in gradient of methanol in water from 10% to 95% on a Synergy 4u Hydro-RP column (Phenomenex). ¹H NMR (CDCl₃): δ 9.90 (bs, 1H), 7.62-7.58 (m, 1H), 7.32-7.28 (m, 2H), 7.20-7.16 (m, 2H), 5.97 & 5.94 (2s, 1H), 5.65 & 5.52 (2d, 1H), 4.54-4.46 (m, 1H), 4.39-4.24 (m, 1H), 4.20-4.04 (m, 3H), 3.85-3.79 (m, 1H), 3.73-3.65 (m, 2H), 1.39-1.32 (dd, 3H), 1.16-1.14 (d, 1H), 0.87-0.86 (m, 9H); ³¹P NMR: δ 67.85, 67.16 (1:1 mixture of diastereomers); ESI-LCMS: m/z 570.4 [M + H]⁺.

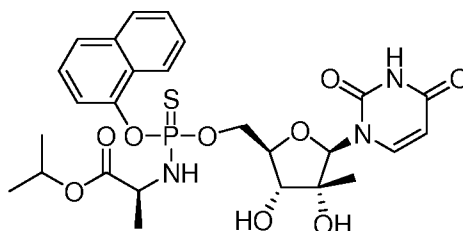
Example 9**Preparation of 2'-C-Methyluridine 5'-(O-phenyl-N-(S)-1-(cyclohexoxycarbonyl)ethyl)thiophosphoramidate (3g)**

[0221] Compound **3g** was prepared using the procedure for preparing compound **3f**, with **2c** in place of **2d**. ¹H NMR (CDCl₃): δ 9.40 (bs, 1H), 7.60-7.55 (m, 1H), 7.29-7.11(m, 5H), 5.95 & 5.92 (2s, 1H), 5.63 & 5.53 (2d, 1H), 4.75-4.68 (m, 1H), 4.50-4.23 (m,

2H), 4.10-4.00 (m, 3H), 3.74-3.72 (m, 1H), 1.80-1.05 (m, 17H); ^{31}P NMR: δ 67.80, 67.16 (3:4 mixture of diastereomers); ESI-LCMS: m/z 582.5 $[\text{M} + \text{H}]^+$.

Example 10

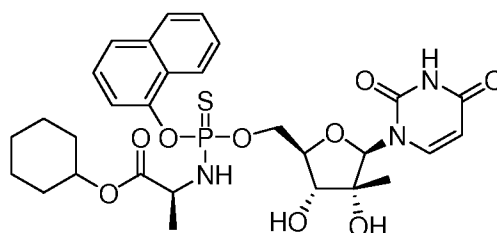
Preparation of 2'-C-Methyluridine 5'-(*O*-(1-naphthyl)-*N*-(*S*)-1-(isopropoxycarbonyl)ethyl) thiophosphoramidate (3h)



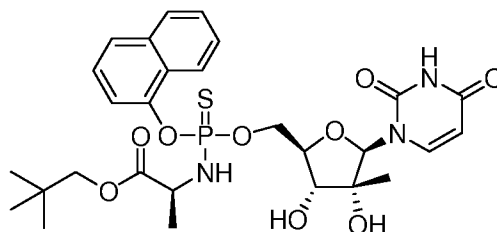
[0222] Compound **3h** was prepared using the procedure for preparing compound **3f**, with **2e** in place of **2d**. ^1H NMR (CDCl_3): δ 9.10 (bs, 1H), 8.05-7.20 (m, 9H), 5.95&5.92 (2s, 1H), 5.38 & 5.33 (2d, 1H), 4.99-4.91 (m, 1H), 4.59-4.28 (m, 2H), 4.20-4.03 (m, 3H), 3.72-3.69 (m, 1H), 1.36-1.27 (2d, 3H), 1.20-1.11 (m, 6H), 1.06-1.04 (2s, 3H); ^{31}P NMR: δ 67.92, 67.28 (2:3 mixture of diastereomers); ESI-LCMS: m/z 592.2 $[\text{M} + \text{H}]^+$.

Example 11

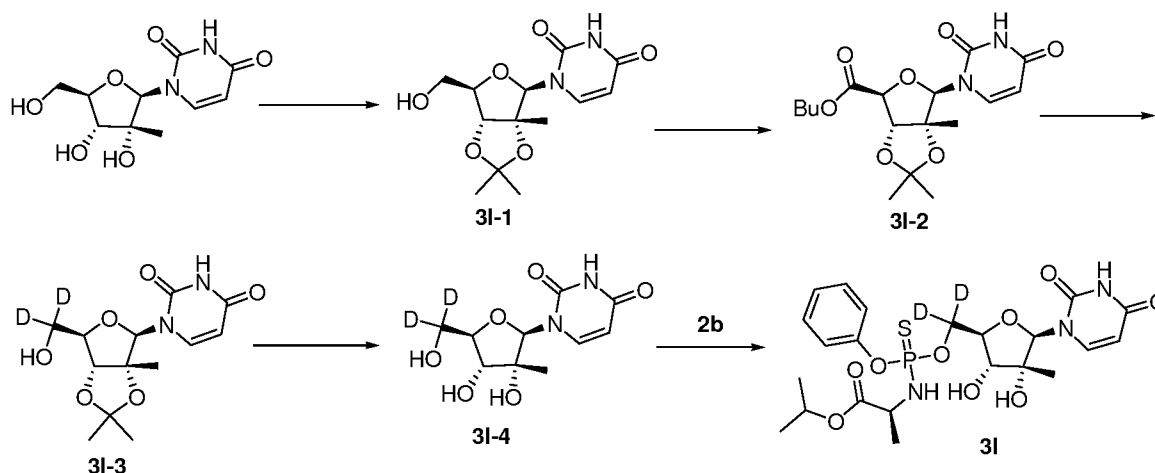
Preparation of 2'-C-Methyluridine 5'-(*O*-(1-naphthyl)-*N*-(*S*)-1-(cyclohexoxycarbonyl)ethyl) thiophosphoramidate (3i)



[0223] Compound **3i** was prepared using the procedure for preparing compound **3f**, with **2f** in place of **2d**. ^1H NMR (CDCl_3): δ 9.80 (bs, 1H), 8.05-7.30 (m, 9H), 5.92 & 5.91 (2s, 1H), 5.38-5.29 (2d, 1H), 4.79-4.69 (m, 1H), 4.59-4.32 (m, 1H), 4.50-4.46 (m, 1H), 4.38-4.03 (m, 4H), 3.70-3.66 (m, 1H), 1.80-1.00 (m, 17H); ^{31}P NMR: δ 67.74, 67.43 (1:1 mixture of diastereomers); ESI-LCMS: m/z 632.5 $[\text{M} + \text{H}]^+$.

Example 12**Preparation of 2'-C-Methyluridine 5'-(*O*-(1-naphthyl)-*N*-(*S*)-1-(neopentoxycarbonyl)ethyl)thiophosphoramidate (3j)**

[0224] Compound **3j** was prepared using the procedure for preparing compound **3f**, with **2g** in place of **2d**. ^1H NMR (CDCl_3): δ 9.80 (bs, 1H), 8.05-7.30 (m, 9H), 5.90 & 5.87 (2s, 1H), 5.38 & 5.30 (2d, 1H), 4.60-3.60 (m, 9H), 3.72-3.69 (m, 1H), 1.41 & 1.39 (2d, 3H), 1.08 & 1.06 (2s, 3H), 0.87 & 0.86 (2s, 9H); ^{31}P NMR: δ 68.01, 67.35 (1:1 mixture of diastereomers); ESI-LCMS: m/z 620.8 $[\text{M} + \text{H}]^+$.

Example 13**Preparation of 5'-dideuterated 2'-C-methyluridine 5'-(*O*-phenyl-*N*-(*S*)-1-(isopropoxycarbonyl)ethyl)thiophosphoramidate (3l)**

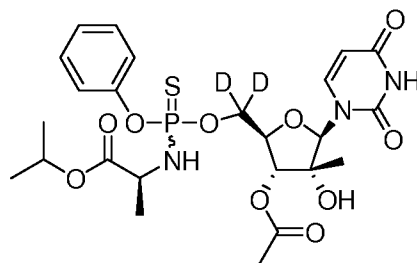
[0225] **Step 1. Compound 3l-1** - To a suspension of 2'-C-methyluridine (2.50 g, 7.6 mmol) in acetone (100 mL) were added *p*-Toluenesulfonic acid monohydrate (1.76 g, 9.2 mmol) and 2,2-dimethoxypropane (20 mL). The mixture was stirred at RT for 16 h. Then saturated NaHCO_3 was added to adjust the pH to between approximately 6-7. The suspension was concentrated and the residue was purified on a silica gel column (5-7% MeOH in DCM) to give **3l-1** as a white solid (2.30 g, 82%).

[0226] Step 2. Compound 3I-2 - To a solution of **3I-1** (2.30 g, 7.7 mmol) in anhydrous DCM (50 mL) was added pyridinium dichromate (PDC) (5.80 g, 15.4 mmol), followed by acetic anhydride (7.87 g, 77.18 mmol) and *tert*-butyl alcohol (11.40 g, 154.0 mmol). The resulting solution was stirred at RT for 3 h. The mixture was loaded on a very short silica gel column and eluted with EA. The fractions containing **3I-2** were combined and concentrated. Chromatography on silica gel with EA/hexanes (1:1 to 3:2) gave **3I-2** as a white foam (2.07 g, 73%).

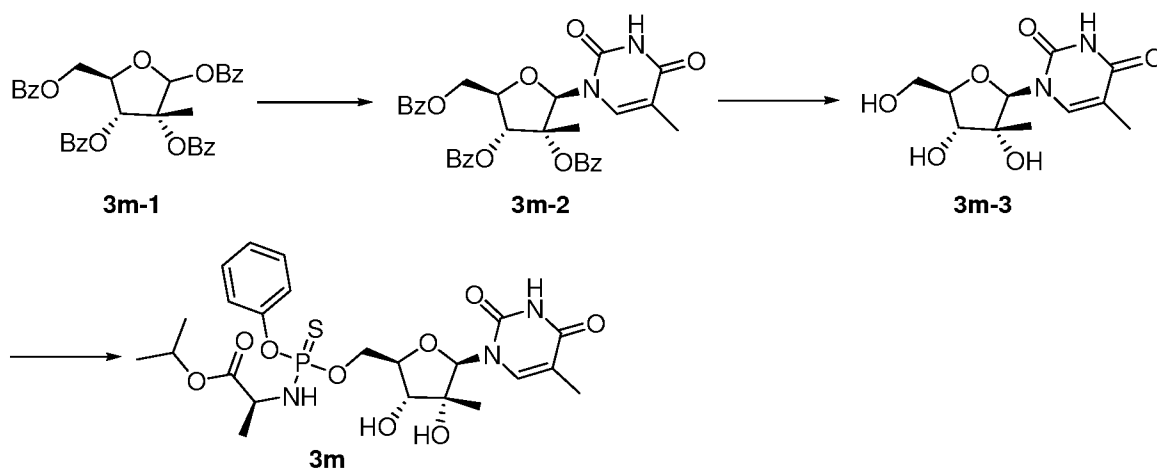
[0227] Step 3. Compound 3I-3 - NaBD₄ (1.10 g, 26.22 mmol) was added to a solution of **3I-2** (2.07 g, 6.9 mmol) at RT and the resulting mixture stirred at 80°C overnight. The reaction was quenched with acetic acid (AcOH) at 0°C. The mixture was diluted with EA and washed with brine. The organic phase was dried and concentrated. The residue was purified by chromatography on silica gel (2-5% MeOH in DCM) to give **3I-3** as a white foam (854 mg, 50.83%).

[0228] Step 4. Compound 3I-4 - Compound **3I-3** (850 mg, 2.8 mmol) was dissolved in 95% trifluoroacetic acid (TFA) / 5% water at 0°C and then stirred at RT for 30 minutes. The solvent was evaporated and the residue was purified by chromatography on silica gel (5-10% MeOH in DCM) to give **3I-4** (663 mg, 90%). ¹H NMR (CD₃OD, 400 MHz) δ 8.16 (d, 1H), 5.98 (s, 1H), 5.69 (d, 1H), 3.86-3.92 (m, 2H), 1.13 (s, 3H); ESI-MS: m/z 261.1 [M+H]⁺.

[0229] Step 5. Compound 3I - To a suspension of **3I-4** (150 mg, 0.57 mmol) in anhydrous acetonitrile (1.0 mL) was added *N*-methylimidazole (0.5 mL), followed by **2b** (1.7 mmol, 1 M in CH₃CN) at RT. The resulting solution was stirred at RT for 24h. The mixture was diluted with EA and concentrated. The residue was purified by RP HPLC (0.5 HCOOH in MeCN and water) to give **3I** as a white solid (two isomers, 122 mg, 39%). ¹H NMR (CD₃OD, 400 MHz) δ 7.79, 7.87 (2d, *J* = 8.0 Hz, 1H), 7.20-7.38 (m, 5H), 5.98, 6.01 (2s, 1H), 5.59, 5.62 (2d, *J* = 8.0 Hz, 1H), 4.99-5.01 (m, 1H), 4.10-4.12 (m, 2H), 3.82-3.84 (m, 1H), 1.34, 1.38 (2d, *J* = 7.2 Hz, 3H), 1.24, 1.25 (2s, 3H), 1.17, 1.26 (2d, *J* = 6.0 Hz, 6H); ³¹P NMR (CD₃OD, 162 MHz) δ 68.42, 68.21; ESI-LCMS: m/z 546.1 [M + H]⁺.

Example 14**Preparation of 3'-O-acetyl-5'-dideuterated 2'-C-methyluridine 5'-(O-phenyl-N-(S)-1-(isopropoxycarbonyl)ethyl)thiophosphoramidate (4d)**

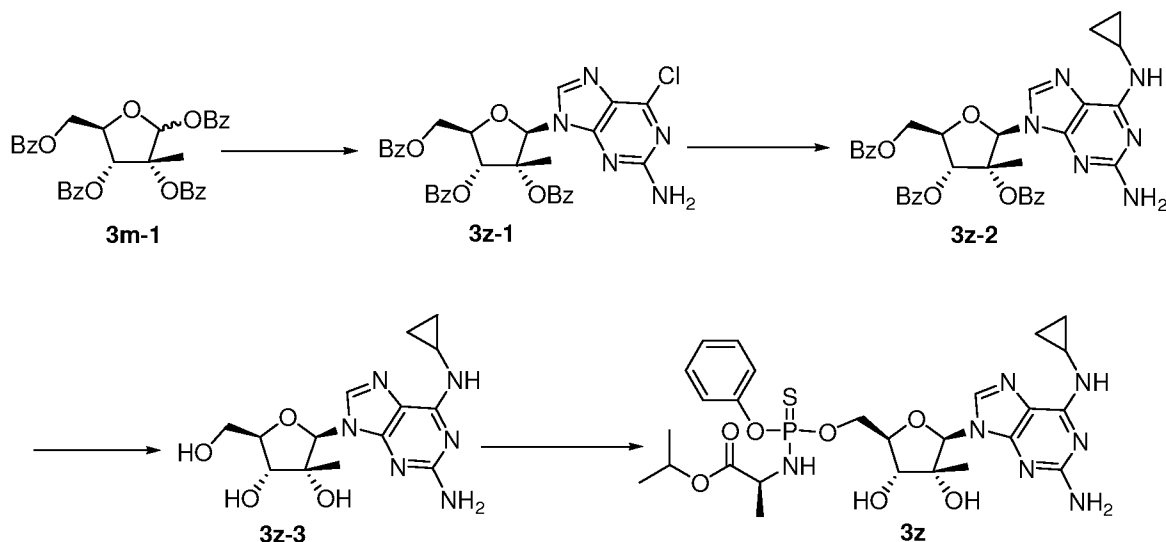
[0230] To a suspension of **3l** (750 mg, 1.38 mmol) in dry pyridine (50 mL) was added acetic anhydride (704 mg, 6.9 mmol). The reaction mixture was heated at 35°C for 16 h. The reaction was quenched with water and the solvent was removed. The residue was purified on a silica gel column (1~3% MeOH in DCM) to give **4d** as a white solid (710 mg, 88%). ¹H NMR (CD₃OD, 400 MHz) δ 7.78, 7.84 (2d, J = 8.0 Hz, 1H), 7.38-7.34 (m, 2H), 7.17-7.38 (m, 5H), 5.99, 6.02 (2s, 1H), 5.59, 5.61 (2d, J = 8.0 Hz, 1H), 5.13, 5.17 (2d, J = 9.2 Hz, 1H), 5.04-4.97 (m, 1H), 4.52-4.25 (m, 3H), 4.14-4.06 (m, 1H), 2.16 (s, 3H), 1.35, 1.38 (2d, J = 7.2 Hz, 1H), 1.18-1.24 (m, 9H); ³¹P NMR (CD₃OD, 162 MHz) δ 68.90, 68.23; ESI-LCMS: m/z = 585.9 [M+H]⁺.

Example 15**Preparation of 2'-C-methylthymidine 5'-(O-phenyl-N-(S)-1-(isopropoxycarbonyl)ethyl)thiophosphoramidate (3m)**

[0231] Step 1. Compound **3m-2** - To a suspension of thymine (0.869 g, 5.63 mmol) in acetonitrile (27 mL) was added *N,O*-bis(trimethylsilyl)acetamide (5 mL) and the mixture was refluxed for 2 hours. The resulting solution was cooled to ambient temperature and a solution of **3m-1** (2.0 g, 3.45 mmol) in acetonitrile (10 mL) was added. Then SnCl₄ (1.6 mL, 13.6 mmol) was slowly added and the reaction mixture was heated to 100°C for 5 h. The reaction mixture was cooled to 0°C and solid NaHCO₃ was added, and a minimal amount of ice was added into the mixture. The reaction mixture was partially concentrated, diluted with EA and treated with a cold saturated aqueous solution of NaHCO₃. The salts were filtered through celite and extracted with EA. The organic phase was washed successively with a saturated aqueous solution of NaHCO₃ and brine, dried by anhydrous Na₂SO₄, and concentrated to dryness. The residue was purified by silica gel column (0-20% EA in CH₂Cl₂) to give **3m-2** (1.6 g, 85%) as a white solid.

[0232] Step 2. Compound **3m-3** - Compound **3m-2** (1.6 g, 2.74 mmol) was dissolved in methanolic ammonia (120 mL, saturated at 0°C). The mixture was stirred at RT for 20 hours. The solution was evaporated to dryness and the residue was purified on a silica gel column (DCM:MeOH=100:1 to 50:1) to give **3m-3** as a light yellow foam (620 mg, 83.1 %). ¹H NMR (MeOD, 400 MHz) δ 8.05 (s, 1H), 5.93 (s, 1H), 4.01-3.97 (m, 1H), 3.91-3.86 (m, 2H), 3.80-3.76 (m, 1H), 1.85 (s, 3H), 1.13 (s, 3H).

[0233] Step 3. Compound **3m** - To a suspension of **3m-3** (150 mg, 0.55 mmol) in anhydrous CH₃CN (3 mL) was added *N*-methylimidazole (0.4 mL), followed by addition of **2b** (530 mg, 1.65 mmol) in anhydrous CH₃CN (1 mL). The resulting solution was stirred at RT for 12 h. The reaction was quenched with water and the solvent was removed. The residue was purified by RP HPLC (0.5 HCOOH in MeCN and water) to give compound **3m** as a white solid (two isomers, 43 mg, 14.0 %). ¹H NMR (MeOD, 400 MHz) δ 7.54, 7.64 (2s, 1H), 7.16-7.36 (m, 5H), 5.98, 6.01 (2s, 1H), 5.02-4.94 (m, 1H), 4.56-4.52 (m, 1H), 4.43-4.29 (m, 1H), 4.17-4.02 (m, 2H), 3.94-3.84 (m, 1H), 1.81, 1.84 (2s, 3H), 1.31, 1.36 (2d, J = 7.2 Hz, 3H), 1.25-1.23 (m, 6H), 1.15 (s, 3H); ³¹P NMR (MeOD, 162MHz) δ 69.17, 68.68; ESI-LCMS: m/z = 558.1 [M + H]⁺.

Example 16**Preparation of 1-(2-amino-6-cyclopropylaminopurin-9-yl)-2-C-methyl- β -D-ribofuranose 5-(*O*-phenyl-*N*-(*S*)-1-(isopropoxycarbonyl)ethyl)thiophosphoramidate (**3z**)**

[0234] **Step 1. Compound **3z-1**** - To a solution of compound **3m-1** (20.0 g, 34.47 mmol) and 6-chloro-2-aminopurine (5.90 g, 34.91 mmol) in anhydrous MeCN (300 mL) was added 1,8-diazabicycloundec-7-ene (DBU) (15.8 g, 103.9 mmol) at 0°C. The mixture was stirred at 0°C for 5 minutes and then trimethylsilyltrifluoromethane sulfonate (TMSOTf) (27.0 mL, 137.8 mmol) was added dropwise. Stirring was continued for another 30 minutes and then the mixture was heated to 70°C and stirred for 18 hour. The reaction was then cooled to RT and diluted with EA. The solution was washed with saturated NaHCO₃ and brine. The organic layer was dried over Na₂SO₄ and then concentrated. The residue was purified by a silica gel column (20~40% EA in PE) and then RP HPLC (0.5% HCOOH in MeCN and water) to give compound **23-2** as a white solid (5.4 g , 25.6 %). ¹H NMR (DMSO-d₆, 400 MHz) δ 8.38 (s, 1H), 7.97 -8.05 (m, 4H), 7.82-7.85 (m, 2H), 7.58-7.66 (m, 3H), 7.39-7.53 (m, 4H), 7.18-7.37 (m, 2H), 7.19 (brs, 2H), 6.61 (s, 1H), 5.94 (d, *J* = 4.8 Hz, 1H), 4.70-4.89 (m, 3H), 1.58 (s, 3H).

[0235] **Step 2. Preparation of compound **3z-2**** - Compound **3z-1** (100 mg, 0.16 mmol) and THF (10 mL) were placed into a dry flask and then cyclopropyl amine (1.61 g, 28.21 mmol) was added. After the addition, the mixture was heated to reflux overnight. Then

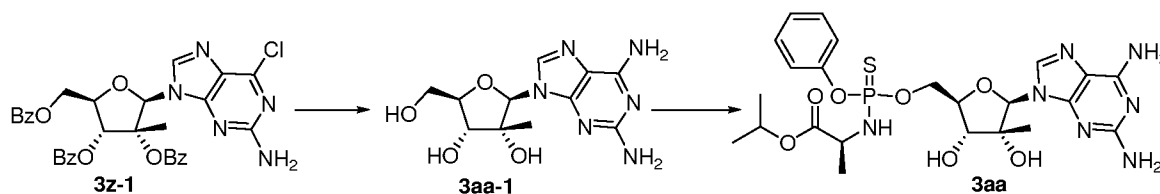
the solvent was removed and the residue was purified on a silica gel column (2~10% MeOH in DCM) to give **3z-2** as a white solid (82 mg, 77.6%).

[0236] Step 3. Compound **3z-3** - Compound **3z-2** (402 mg, 0.62 mmol) was dissolved in methanolic ammonia (20 mL, saturated at 0°C) and the mixture was stirred at RT for 12 hours. The solvent was removed and the residue was purified on a silica gel column (2~10% MeOH in DCM) to give **3z-3** as a white solid (149 mg, 72.4%). ¹H NMR (CD₃OD, 400 MHz) δ 8.14 (d, *J* = 11.2 Hz, 1H), 5.93 (s, 1H), 4.22 (d, *J* = 8.4 Hz, 1H), 4.03 (d, *J* = 10.8 Hz, 2H), 3.86 (d, *J*₁ = 12.8 Hz, *J*₂ = 3.2 Hz, 1H), 2.91 (s, 1H), 0.79-0.98 (m, 2H), 0.61-0.70 (m, 2H); ESI-LCMS: *m/z* 337.1 [M + H]⁺, 360.1 [M+Na]⁺.

[0237] Step 4. Compound **3z** - To a stirred suspension of **3z-3** (110 mg, 0.33 mmol) in anhydrous acetonitrile (1.0 mL) was added *N*-methylimidazole (0.5 mL) followed by slow addition of **2b** (1.05 g, 3.273 mmol, 1M in MeCN) at RT. The resulting solution was stirred at 50°C for 4 hours and then diluted with EA. The solution was washed with 10% AcOH/H₂O, brine, 5% NaHCO₃ aqueous solution, and dried over Na₂SO₄. The solvent was removed and the residue was purified by RP HPLC (0.5% HCOOH in MeCN and water) to give **3z** as a white solid (two isomers, 131 mg, 64 %). ¹H NMR (CD₃OD, 400 MHz) δ 7.96, 8.00 (2s, 1H), 7.28-7.36 (m, 5H), 7.14-7.20 (m, 1H), 5.96, 5.99 (2s, 1H), 4.92-4.98 (m, 1H), 4.37-4.57 (m, 2H), 4.04-4.23 (m, 3H), 2.91 (br, 1H), 1.36, 1.32 (2d, *J* = 7.2 Hz, 3H), 1.17-1.23 (m, 7H), 0.96, 0.99 (2s, 3H), 0.87-0.90 (m, 2H), 0.63-0.69 (m, 2H); ³¹P NMR (CD₃OD, 162 MHz) δ 68.53, 68.38; ESI-LCMS: *m/z* 622.2 [M + H]⁺, 644.2 [M+Na]⁺.

Example 17

Preparation of 1-(2,6-diaminopurin-9-yl)-2-*C*-methyl-β-*D*-ribofuranose 5-(*O*-phenyl-*N*-(*S*)-1-(isopropoxycarbonyl)ethyl)thiophosphoramidate (**3aa**)



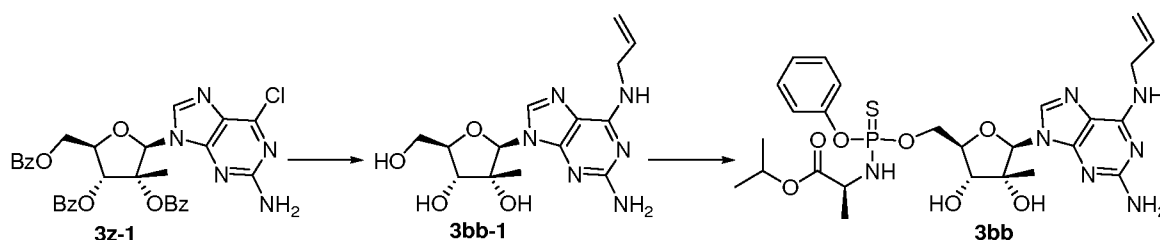
[0238] Step 1. Compound **3aa-1** - Compound **3z-1** (1.01 g, 1.56 mmol) was suspended in aqueous ammonia (28%, 40 mL) and dioxane (4 mL) in a sealed vessel. The mixture was heated at 100°C overnight. Then the solvent was removed and the residue was

purification on a silica gel column (2~10% MeOH in DCM) to give **3aa-1** as a white solid (418 mg, 88.9%). ^1H NMR (CD_3OD , 400 MHz) δ 8.17 (s, 1H), 5.93 (s, 1H), 4.24 (d, $J = 8.8$ Hz, 1H), 4.01-4.04 (m, 2H), 3.86 (dd, $J_1 = 12.8$ Hz, $J_2 = 3.2$ Hz, 1H), 0.96 (s, 3H); ESI-LCMS: m/z 297.1 $[\text{M}+\text{H}]^+$.

[0239] Step 2. Compound **3aa** - To a stirred suspension of **3aa-1** (62 mg, 0.20 mmol) in anhydrous acetonitrile (1.0 mL) was added *N*-methylimidazole (0.5 mL) followed by slow addition of **2b** (652 mg, 2.02 mmol, 1M in MeCN) at RT. The resulting solution was stirred at RT for 24 hours. The solution was diluted with EA and washed with 10% AcOH in H_2O , brine, 5% NaHCO_3 aqueous solution, and dried over Na_2SO_4 . The solvent was removed and the residue was purified by RP HPLC (0.5% HCOOH in MeCN and water) to give **3aa** as a white solid (31 mg, 25.6%). ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 7.81, 7.83 (2s, 1H), 7.33-7.38 (m, 2H), 7.17-7.25 (m, 3H), 6.58-6.78 (m, 3H), 5.81-5.83 (m, 3H), 5.32-5.43 (m, 1H), 5.19, 5.20 (2s, 1H), 4.78-4.85 (m, 1H), 4.21-4.42 (m, 2H), 3.87-4.15 (m, 3H), 1.24-1.26 (m, 3H), 1.08-1.15 (m, 6H), 0.83, 0.84 (2s, 3H); ^{31}P NMR ($\text{DMSO}-d_6$, 162 MHz) δ 68.19, 67.90; ESI-LCMS: m/z 589.1 $[\text{M} + \text{H}]^+$, 604.1 $[\text{M}+\text{Na}]^+$.

Example 18

Preparation of 1-(2-amino-6-allylaminopurin-9-yl)-2-C-methyl- β -D-ribofuranose 5-(*O*-phenyl-*N*-(*S*)-1-(isopropoxycarbonyl)ethyl)thiophosphoramidate (**3bb**)



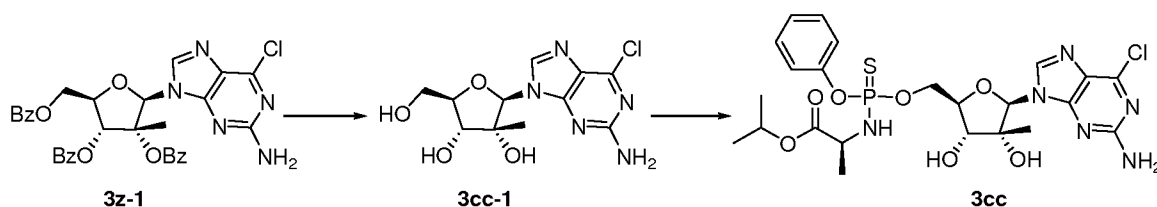
[0240] Step 1. Compound **3bb-1** - A mixture of **3z-1** (802 mg, 1.27 mmol) and allylamine (7.26 g, 127.3 mmol) in THF (30 mL) was refluxed overnight. The solvent was removed and the residue was purified on a silica gel column (2~10% MeOH in DCM) to give crude **3bb-1** (405 mg), which was dissolved in 20 mL methanolic ammonia (saturated at 0°C). The mixture was stirred at RT for 12 hours. The solvent was removed and the residue was purified on a silica gel column (2~10% MeOH in DCM) to give **3bb-1** as a white solid (153 mg, 35.9%). ^1H NMR (CD_3OD , 400 MHz) δ 8.10 (s, 1H), 5.92-6.03 (m, 2H), 5.27 (d, J

= 17.6 Hz, 1H), 5.14 (d, J = 10.4 Hz, 1H), 4.18-4.24 (m, 3H), 4.03 (d, J = 10.0 Hz, 2H), 3.86 (d, J = 10.4 Hz, 1H), 0.95 (s, 3H); ESI-LCMS: m/z 337.1 $[M+H]^+$.

[0241] **Step 2. Compound 3bb** - To a stirred suspension of **3bb-1** (200 mg, 0.59 mmol) in anhydrous acetonitrile (1.0 mL) was added *N*-methylimidazole (0.5 mL) followed by **2b** (573 mg, 1.79 mmol, 1M in MeCN) at RT. The resulting solution was stirred at RT for 24 hrs and then was diluted with EA. The solution was washed with 10% AcOH in H₂O, brine and 5% NaHCO₃ aqueous solution. The organic solution was dried and concentrated. The residue was purified by RP HPLC (0.5% HCOOH in MeCN and water) to give **3bb** as a white solid (two isomers, 155 mg, 40.8%). ¹H NMR (CD₃OD, 400 MHz) δ 7.94, 7.98 (2s, 1H), 7.29-7.34 (m, 4H), 7.18-7.28 (m, 1H), 5.96-6.09 (m, 2H), 5.27, 5.31 (2s, 1H), 5.15, 5.17 (2d, J = 1.2 Hz, 1H), 4.92-4.96 (m, 1H), 4.35-4.57 (m, 2H), 4.01-4.28 (m, 5H), 1.32, 1.36 (2d, J = 7.2 Hz, 3H), 1.16-1.25 (m, 6H), 0.97 (2s, 3H); ³¹P NMR (CD₃OD, 160 MHz) δ 68.51, 68.40; ESI-LCMS: m/z 622.1 $[M+H]^+$, 644.1 $[M+Na]^+$.

Example 19

Preparation of 1-(2-amino-6-chloropurin-9-yl)-2-*C*-methyl- β -*D*-ribofuranose 5-(*O*-phenyl-*N*-(*S*)-1-(isopropoxycarbonyl)ethyl)thiophosphoramidate (3cc)



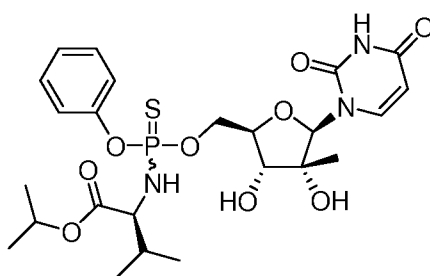
[0242] **Step 1. Compound 3cc-1** - Compound **3z-1** (506 mg, 0.79 mmol) was dissolved in 100 mL of methanolic ammonia and the mixture was stirred at RT for 12 h. The solvent was removed and the residue was purified on a silica gel column (2~10% MeOH in DCM) to give **3cc-1** as a white solid (204 mg, yield: 79.9%).

[0243] **Step 2. Compound 3cc** - To a stirred suspension of **3cc-1** (198 mg, 0.63 mmol) in anhydrous acetonitrile (1.0 mL) was added *N*-methylimidazole (0.5 mL) followed by **2b** (611 mg, 1.904 mmol, 1M in MeCN) at RT. The resulting solution was stirred at 30-40°C for 12 hours and then diluted with EA. The solution was washed with 10% AcOH in H₂O, brine, and 5% NaHCO₃. The organic phase was dried and concentrated. The residue was purified by RP HPLC (0.5% HCOOH in MeCN and water) to give **3cc** as a white solid

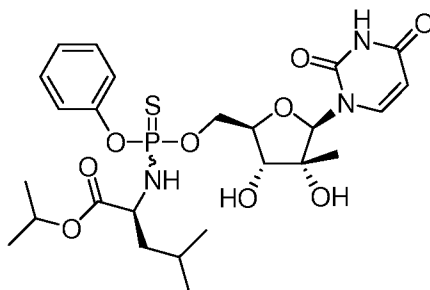
(118 mg, 31.6%). ^1H NMR (CD_3OD , 400 MHz) δ 8.25, 8.28 (2s, 1H), 7.27-7.35 (m, 4H), 7.15-7.18 (m, 1H), 6.02, 6.05 (2s, 1H), 4.93-4.98 (m, 1H), 4.40-4.54 (m, 2H), 4.20-4.27 (m, 2H), 4.05-4.13 (m, 1H), 1.15-1.35 (m, 9H), 0.99, 1.01 (2s, 3H); ^{31}P NMR (CD_3OD , 162 MHz) δ 68.66, 68.53; ESI-LCMS: m/z 601.1 $[\text{M}+\text{H}]^+$.

Example 20

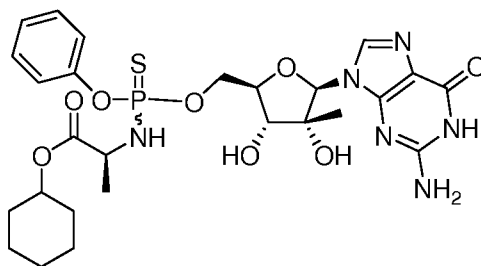
Preparation of 2'-C-methyluridine 5'-(O-phenyl-N-(S)-1-(isopropoxycarbonyl)isobutyl)thiophosphoramidate (3n)



[0244] To a solution of 2'-C-methyluridine (150 mg, 0.581 mmol) in MeCN (1 mL) and *N*-methylimidazole (0.7 mL) was added **2h** (651 mg, 1.86 mmol). The mixture was stirred at RT for 3 days. The solvent was removed and the residue was purified by RP HPLC (0.1% HCOOH in MeCN and water) to give **3n** as a white solid (two isomers, 22 mg, 6.6%). ^1H NMR (CD_3OD , 400 MHz) δ 7.76, 7.78 (2d, $J = 9.2$ Hz, 1H), 7.14-7.35 (m, 5H), 5.95, 5.97 (2s, 1H), 5.56, 5.63 (2d, $J = 8.4$ Hz, 1H), 4.95-5.03 (m, 1H), 4.44-4.56 (m, 1H), 4.30-4.41 (m, 1H), 4.08-4.11 (m, 1H), 3.75-3.90 (m, 2H), 2.00-2.07 (m, 1H), 1.12-1.25 (m, 6H), 1.11, 1.15 (2s, 3H), 0.87-0.97 (m, 6H); ^{31}P NMR (CD_3OD , 162 MHz) δ 70.38, 69.13; ESI-LCMS: m/z 572 $[\text{M}+\text{H}]^+$.

Example 21**Preparation of 2'-C-methyluridine 5'-(O-phenyl-N-(S)-1-(isopropoxycarbonyl)isopentyl)thiophosphoramidate (3o)**

[0245] Compound **3o** was prepared using the procedure for preparing compound **3n**, with **2i** in place of **2h**. ^1H NMR (CD_3OD , 400 M Hz) δ 7.77, 7.84 (2d, $J = 8.0$ Hz, 1H), 7.14-7.35 (m, 5H), 5.96 (2s, 1H), 5.57, 5.62 (2d, $J = 8.0$ Hz, 1H), 4.84-4.98 (m, 1H), 4.46-4.53 (m, 1H), 4.28-4.42 (m, 1H), 3.97-4.12 (m, 2H), 3.80 (2s, 1H), 1.58-1.81 (m, 1H), 1.48-1.56 (m, 2H), 1.20-1.23 (m, 6H), 1.13 (2s, 3H), 0.81-0.92 (m, 6H); ^{31}P NMR (CD_3OD , 400 M Hz) δ 68.56, 69.15; ESI-MS: m/z 586 $[\text{M} + \text{H}]^+$, m/z 608 $[\text{M} + \text{Na}]^+$.

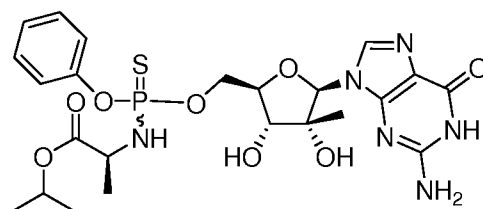
Example 22**Preparation of 2'-C-methylguanosine 5'-(O-phenyl-N-(S)-1-(cyclohexoxycarbonyl)ethyl)thiophosphoramidate (3s)**

[0246] To a stirred suspension of commercial 2'-C-methylguanosine (100 mg, 0.34 mmol) in anhydrous acetonitrile (1.5 mL) was added *N*-methylimidazole (0.56 mL, 6.8 mmol, 20 equivalent) followed by **2c** (303 mg, 0.84 mmol, 1M in MeCN) at RT. The resulting solution was stirred at 40°C for 3 hours and then diluted with EA. The solution was washed with 10% AcOH in H_2O , and brine. The organic layer was separated, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated in vacuum to give a residue which was purified on a silica gel column (3~7% MeOH in DCM). The collected fractions

were concentrated and re-purified on a silica gel column (2~5% MeOH in DCM) to give (127.8 mg, 61.2%) of **3s** as a white solid. ^1H NMR (DMSO- d_6 , 400 MHz) δ 10.6 (s, 1H), 7.76 (d, J = 5.6 Hz, 1H), 7.36-7.31 (m, 2H), 7.22-7.01 (m, 4H), 6.56-6.48 (m, 3H), 5.74 (d, J = 8.4 Hz, 1H), 5.42 & 5.35 (2d, each J = 6.4 Hz, 1H), 5.16 (d, J = 2.8 Hz, 1H), 4.62-3.93 (m, 6H), 1.67-1.58 (m, 5H), 1.33-1.16 (m, 12H), 0.79 (s, 3H); ^{31}P NMR (DMSO- d_6) δ 68.07, 67.71; ESI-LCMS: m/z = 623.1 $[\text{M} + \text{H}]^+$.

Example 23

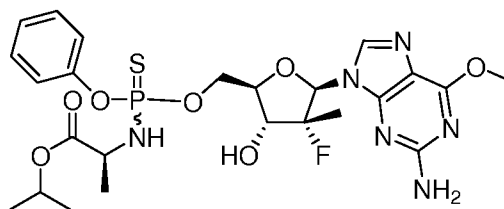
Preparation of 2'-C-Methylguanosine 5'-(*O*-phenyl-*N*-(*S*)-1-(isopropoxycarbonyl)ethyl)thiophosphoramidate (**3r**)



[0247] Compound **3r** was prepared using the procedure for preparing compound **3s**, with **2b** in place of **2c**. ^1H NMR (DMSO- d_6 , 400 MHz) δ 10.6 (s, 1H), 7.76 (d, J = 1.6 Hz, 1H), 7.34-7.31 (m, 2H), 7.22-7.14 (m, 4H), 6.62-6.48 (m, 3H), 5.74 (d, J = 7.2 Hz, 1H), 5.42 & 5.33 (2d, each J = 6.8 Hz, 1H), 5.16 (d, J = 2.4 Hz, 1H), 4.84-3.77 (m, 1H), 4.42-3.85 (m, 5H), 1.25-1.1 (m, 12H), 0.81 & 0.8 (2s, 3H); ^{31}P NMR (DMSO- d_6) δ 68.23, 67.64; ESI-LCMS: m/z = 583.4 $[\text{M} + \text{H}]^+$.

Example 24

Preparation of 2'-Deoxy-2'-fluoro-2'-C-methyl-6-methoxyguanosine 5'-(*O*-phenyl-*N*-(*S*)-1-(isopropoxycarbonyl)ethyl)-thiophosphoramidate (**3t**)

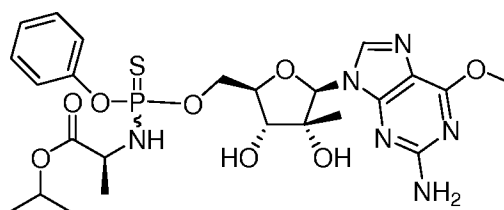


[0248] Compound **3t** was prepared using the procedure for preparing compound **3s**, with **2b** in place of **2c**, and with 2'-deoxy-2'-fluoro-2'-C-methyl-6-methoxyguanosine in place of 2'-C-methylguanosine. ^1H NMR (DMSO- d_6 , 400 MHz) δ 7.96 & 9.95 (2s, 1H),

7.36-7.29 (m, 2H), 7.21-7.14 (m, 3H), 6.57 (br s, 2H), 6.1 & 6.05 (2d, each $J = 8.8$ Hz, 1H), 5.75 (br s, 2H), 4.82-4.76 (m, 1H), 4.45-4.04 (m, 3H), 3.93 (s, 3H), 1.24-1.13 (m, 3H), 1.12-1.03 (m, 9H); ^{31}P NMR (DMSO- d_6) δ 68.21, 67.82; ESI-LCMS: $m/z = 599.4$ $[\text{M} + \text{H}]^+$.

Example 25

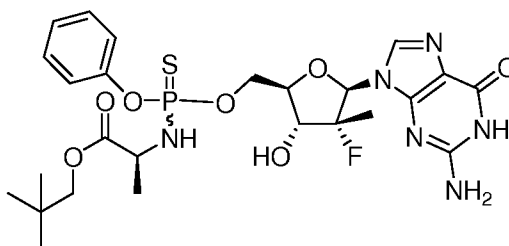
Preparation of 1-(2-Amino-6-methoxypurin-9-yl)-2-C-methyl- β -D-ribofuranose 5-(O-phenyl-N-(S)-1-(isopropoxycarbonyl)ethyl)-thiophosphoramidate (3u)



[0249] Compound **3u** was prepared using the procedure for preparing compound **3s**, with **2b** in place of **2c**, and with 1-(2-Amino-6-methoxypurin-9-yl)-2-C-methyl- β -D-ribofuranose in place of 2'-C-methylguanosine. ^1H NMR (DMSO- d_6 , 400 MHz) δ 7.93 (s, 1H), 7.35-7.30 (m, 2H), 7.22-7.14 (m, 3H), 6.61-6.52 (m, 1H), 6.48 (br s, 2H), 5.86 (d, each $J = 5.2$ Hz, 1H), 5.43, 5.32 (br s, 1H), 5.20 (br s, 1H), 4.84-4.76 (m, 1H), 4.36-4.04 (m, 4H), 3.93 (s, 3H), 1.24-1.15 (m, 3H), 1.19-1.06 (m, 6H), 0.8-0.78 (m, 3H); ^{31}P NMR (DMSO- d_6) δ 68.21, 67.65; ESI-LCMS: $m/z = 597.5$ $[\text{M} + \text{H}]^+$.

Example 26

Preparation of 2'-Deoxy-2'- α -fluoro-2'- β -C-methylguanosine 5'-(O-phenyl-N-(S)-1-(neopentoxycarbonyl)ethyl)thiophosphoramidate (3q)

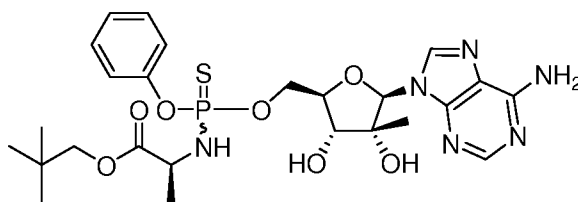


[0250] Compound **3q** was prepared using the procedure for preparing compound **3s**, with **2d** in place of **2c**, and with 2'-deoxy-2'- α -fluoro-2'- β -C-methylguanosine in place of 2'-C-methylguanosine. ^1H NMR (DMSO- d_6 , 400 MHz) δ 10.66 (br s, 1H), 7.79 (s, 1H), 7.36-7.30 (m, 2H), 7.22-7.15 (m, 3H), 6.61-6.52 (m, 1H), 6.48 (br s, 2H), 6.72-6.56 (m, 3H),

6.00, 5.95 (2d, $J = 8.0, 8.4$ Hz, 1H), 5.75-5.82 (m, 1H), 4.43-3.92 (m, 5H), 3.76-3.53 (m, 2H), 1.29-1.24 (m, 3H), 1.09-1.00 (m, 4H), 0.84, 0.81 (2s, 8H); ^{31}P NMR (DMSO- d_6) δ 68.09, 68.03; ESI-LCMS: $m/z = 613.7$ $[\text{M} + \text{H}]^+$.

Example 27

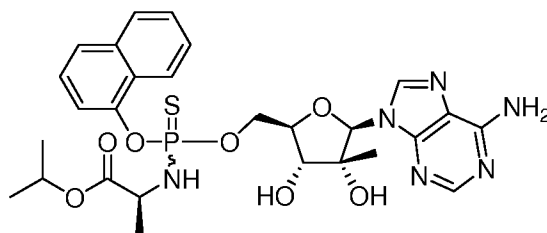
Preparation of 2'-C-Methyladenosine 5'-(O-phenyl-N-(S)-1-(neopentoxycarbonyl)ethyl)thiophosphoramidate (3dd)



[0251] Compound **3dd** was prepared using the procedure for preparing compound **3s**, with **2d** in place of **2c**, and with 2'-C-methyladenosine in place of 2'-C-methylguanosine. ^1H NMR (DMSO- d_6 , 400 MHz) δ 8.22, 8.2 (2s, 1H), 8.12 (s, 1H), 7.36-7.13 (m, 6H), 6.61-6.55 (m, 1H), 5.97, 5.94 (2s, 1H), 5.40, 5.34, 5.31 (3d, $J = 6.8, 6.8, 6.0$ Hz, 2H), 4.39-3.99 (m, 5H), 3.76-3.61 (m, 2H), 3.42 (d, $J = 10.4$ Hz, 1H), 1.27-1.23 (m, 3H), 0.83, 0.77 (2s, 4H), 0.77, 0.76 (2s, 8H); ^{31}P NMR (DMSO- d_6) δ 68.15, 67.74; ESI-LCMS: $m/z = 595.0$ $[\text{M} + \text{H}]^+$.

Example 28

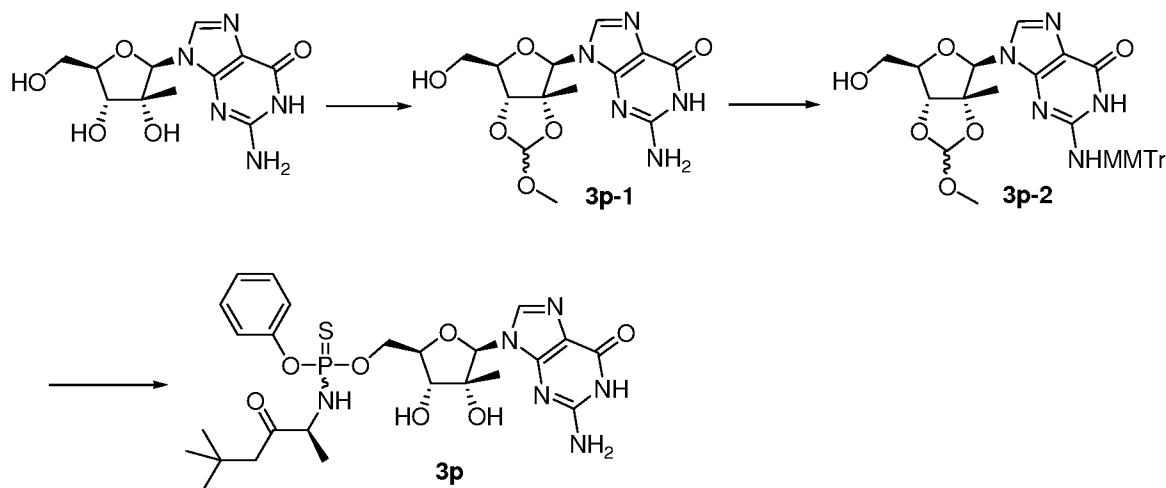
Preparation of 2'-C-Methyladenosine 5'-(O-(1-naphthyl)-N-(S)-1-(isopropoxycarbonyl)ethyl) thiophosphoramidate (3ee)



[0252] Compound **3dd** was prepared using the procedure for preparing compound **3s**, with **2e** in place of **2c**, and with 2'-C-methyladenosine in place of 2'-C-methylguanosine. ^1H NMR (DMSO- d_6 , 400 MHz) δ 8.28, 8.24 (2s, 1H), 8.12-8.06 (m, 2H), 7.93-7.91 (m, 1H), 7.29-7.68 (m, 1H), 7.54-7.37 (m, 4H), 7.26 (br s, 2H), 6.82-6.72 (m, 1H), 6.00, 5.98 (2s, 1H), 5.47, 5.39, 5.31 (3d, $J = 6.4, 6.8, 10.0$ Hz, 2H), 4.82-4.74 (m, 1H), 4.48-4.35 (m, 2H), 4.28-

4.15 (m, 2H), 4.03-3.96 (m, 1H), 1.27-1.24 (m, 3H), 1.1-1.00 (m, 6H), 0.8 (s, 3H); ESI-LCMS: $m/z = 617.1 [M + H]^+$.

Example 29
Preparation of 2'-C-methylguanosine 5'-(*O*-phenyl-*N*-(*S*)-1-(neopentoxycarbonyl)ethyl)thiophosphoramidate (3p**)**



[0253] Step 1. Compound **3p-1** - A mixture of 2'-C-methylguanosine (1.0 g, 3.36 mmol), trimethyl orthoformate (20 mL) and *p*-toluenesulfonic acid monohydrate (961 mg, 5.05 mmol) in 1,4-dioxane (30 mL) was stirred at RT for 24 h. Dowex MWA-1 basic resin we added and stirred until the solution was neutralized. The resin was filtered and washed thoroughly with MeOH and then with MeOH/DCM (1:1). The filtrate was concentrated and the residue was subjected to flash chromatography on a silica gel column eluting with 5-10% MeOH in DCM to give (0.94 g) of **3p-1** as a white solid.

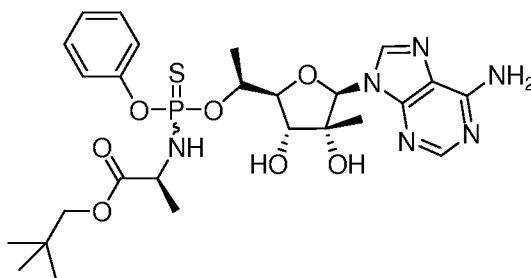
[0254] Step 2. Compound **3p-2** - A solution of **3p-1** (0.94 g, 2.77 mmol), dimethylaminopyridine (DMAP) (338 mg, 2.77 mmol) and *t*-butyldimethylsilyl chloride (TBSCl) (543 mg, 3.60 mmol) in pyridine (10 mL) was stirred at 25°C overnight. 4-Methoxytrityl chloride (1.56g, 5.0 mmol) was added and the resulting mixture stirred at RT 50°C for 3 h. The mixture was diluted with ethyl acetate, and washed with brine three times. The solvent was evaporated and the residue was chromatographed on silica gel with 3-5% MeOH in DCM to give 1.66 g of a protected intermediate as foam solid. A solution of the intermediate (1.66 g, 2.66 mmol) and 1.0 M tetrabutylammonium fluoride (TBAF) / THF (4

mL) in 10 mL of THF stood at RT for 20 h. The solution was concentrated. The residue was subjected to flash chromatography on silica gel with 5-6% MeOH in DCM to give 1.33 g of **3p-2** as a white foam. MS m/z 611.9 (MH^+).

[0255] Step 3. Compound **3p** – Compound **2d** (1.0 M in MeCN, 0.5 mL) was added dropwise to a solution of **3p-2** (61 mg, 0.1 mmol) and diisopropylethylamine (0.3 mL) in anhydrous acetonitrile (0.4 mL). The resulting solution was heated at 82°C for 20 h, diluted with ethyl acetate, washed with brine three times, dried over sodium sulfate, and concentrated. Chromatography on silica gel with 20-30% ethyl acetate in hexanes gave 82 mg of a protected intermediate as a white foam, which was dissolved in a mixture of 80% formic acid and 20% water (3 mL). The solution stood at RT overnight, was concentrated, and then co-evaporated with MeOH/toluene three times. Chromatography on silica gel with 6-10% MeOH in DCM gave 27 mg of **3p** as a white solid; 1H NMR (acetone- d_6) δ 7.83, 7.92 (2s, 1H), 7.10-7.34 (m, 5H), 5.88, 5.90 (2s, 1H), 4.33-3.53 (m, 2H), 4.11-4.24 (m, 3H), 3.61-3.79 (m, 2H), 1.39, 1.36 (2d, $J = 7.2$ Hz, 3H), 0.94, 0.95 (2s, 3H), 0.84, 0.87 (2s, 9H); ^{31}P NMR (acetone- d_6) δ 68.27, 67.85; ESI-LCMS: m/z 611.3 $[M+H]^+$.

Example 30

Preparation of 2',5'-(S)-C,C-Dimethyladenosine 5'-(O-phenyl-N-(S)-1-(neopentoxycarbonyl)ethyl)thiophosphoramidate (**3hh**)

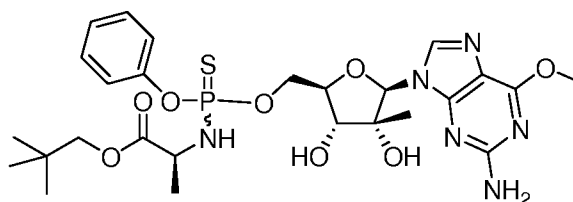


[0256] Compound **3hh** was prepared using the procedure for preparing compound **3p**, with 2',5'-C,C-dimethyladenosine in place of 2'-C-methylguanosine. 1H NMR (CD_3OD) δ 8.40, 8.36 (2s, 1H), 8.22, 8.20 (2s, 1H), 7.07-7.36 (m, 5H), 6.06, 6.05 (2d, $J = 5.2$ Hz, 1H), 5.88, 5.90 (2s, 1H), 4.59 (t, $J = 5.2$ Hz, 0.5 H), 4.50 (q, $J = 5.2$ Hz, 1H), 4.40 (q, $J = 3.6, 5.2$ Hz, 0.5H), 4.04 -4.19 (m, 2H), 3.81 (d, $J = 0.8$ Hz, 1H), 3.75 (d, $J = 10.4$ Hz, 1H), 3.65 (d, J

= 10.4 Hz, 1H), 1.52, 1.40 (2d, J = 6.4 Hz, 3H), 1.29, 1.30 (2s, 3H), 0.93, 0.87 (2s, 9H); ^{31}P NMR (acetone- d_6) δ 68.40, 67.43; ESI-LCMS: m/z 595.1 $[\text{M}+\text{H}]^+$.

Example 31

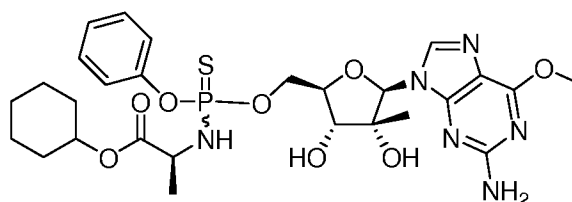
Preparation of 1-(2-Amino-6-methoxypurin-9-yl)-2-C-methyl- β -D-ribofuranose 5-(*O*-phenyl-*N*-(*S*)-1-(neopentoxycarbonyl)ethyl)-thiophosphoramidate (3v)



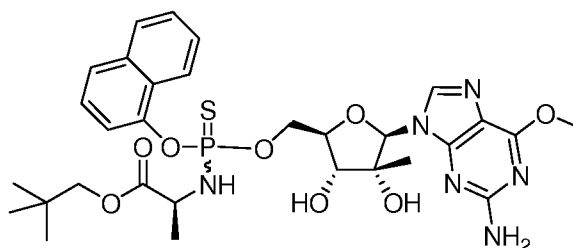
[0257] Compound **3v** was prepared using the procedure for preparing compound **3p**, with 1-(2-amino-6-methoxypurin-9-yl)-2-*C*-methyl- β -D-ribofuranose in place of 2'-*C*-methylguanosine. ^1H NMR (CD_3OD , 400 MHz) δ 7.97, 8.00 (2s, 1H), 7.10-7.33 (m, 5H), 5.99, 5.96 (2s, 1H), 4.33-4.55 (m, 2H), 4.031, 4.034 (2s, 3H), 3.56-3.72 (m, 2H), 1.31-1.36 (m, 3H), 0.94, 0.92 (2s, 3H), 0.89, 0.85 (2s, 9H); ^{31}P NMR ($\text{DMSO}-d_6$) δ 68.52, 68.27. ESI-LCMS: m/z 625.3 $[\text{M}+\text{H}]^+$.

Example 32

Preparation of 1-(2-Amino-6-methoxypurin-9-yl)-2-C-methyl- β -D-ribofuranose 5-(*O*-phenyl-*N*-(*S*)-1-(cyclohexoxycarbonyl)ethyl)-thiophosphoramidate (3w)



[0258] Compound **3w** was prepared using the procedure for preparing compound **3p**, with **2c** in place of **2d**, and with 1-(2-Amino-6-methoxypurin-9-yl)-2-*C*-methyl- β -D-ribofuranose in place of 2'-*C*-methylguanosine. ^1H NMR (CD_3OD , 400 MHz) δ 7.98, 8.01 (2s, 1H), 7.24-7.32 (m, 4H), 7.10-7.17 (m, 1H), 6.00, 5.96 (2s, 1H), 4.36-4.73 (m, 3H), 4.036, 4.034 (2s, 3H), 4.01-4.22 (m, 3H), 1.60-1.80 (m, 4H), 1.19-1.55 (m, 9H), 0.92, 0.94 (2s, 3H); ^{31}P NMR ($\text{DMSO}-d_6$) δ 68.43, 68.32. ESI-LCMS: m/z 637.6 $[\text{M}+\text{H}]^+$.

Example 33**Preparation of 1-(2-Amino-6-methoxypurin-9-yl)-2-C-methyl- β -D-ribofuranose 5-(O-(1-naphthyl)-N-(S)-1-(neopentoxycarbonyl)ethyl)-thiophosphoramidate (3x)**

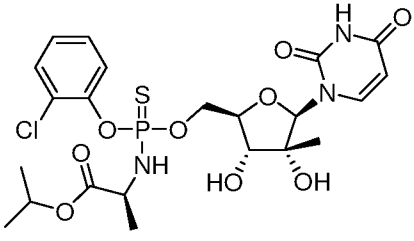
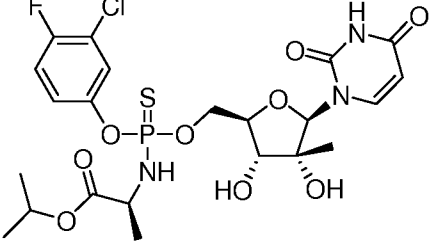
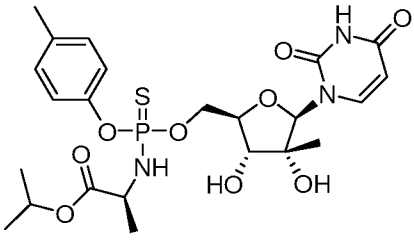
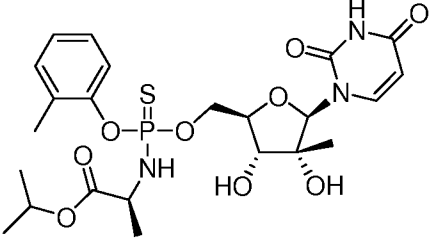
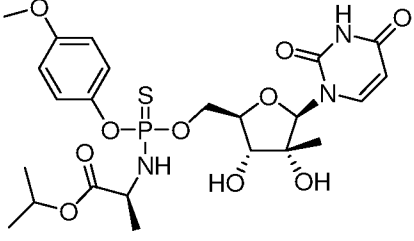
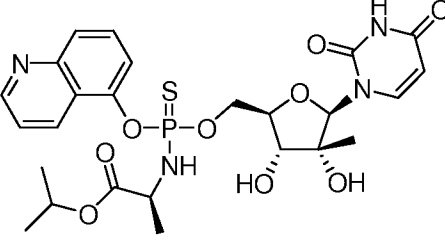
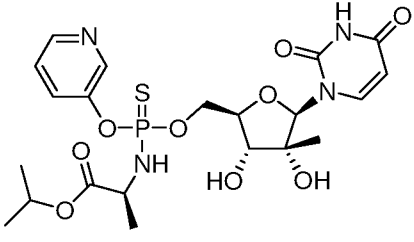
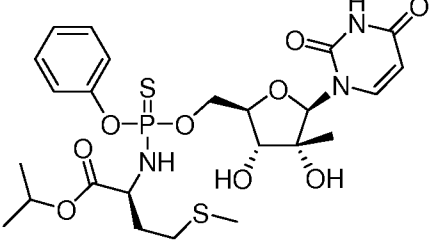
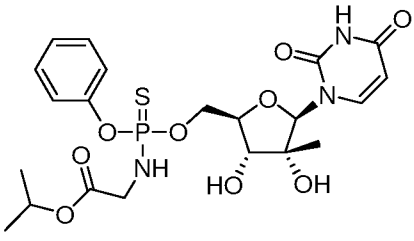
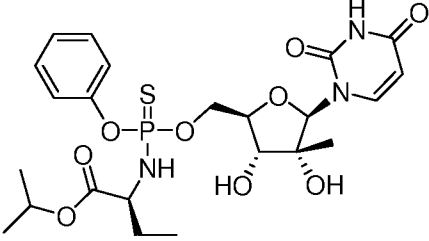
[0259] Compound **3x** was prepared using the procedure for preparing compound **3p**, with **2g** in place of **2d**, and with 1-(2-Amino-6-methoxypurin-9-yl)-2-C-methyl- β -D-ribofuranose in place of 2'-C-methylguanosine. ^1H NMR (CD_3OD , 400 MHz) δ 8.15-8.19 (m, 1H), 8.03, 7.97 (2s, 1H), 7.80-7.85 (m, 1H), 7.31-7.67 (m, 5H), 6.00, 5.98 (2s, 1H), 4.43-4.62 (m, 2H), 4.18-4.27 (m, 3H), 4.01 (s, 3H), 3.57-3.79 (m, 2H), 1.33-1.37 (m, 3H), 0.941, 0.946 (2s, 3H), 0.855, 0.848 (2s, 9H); ^{31}P NMR ($\text{DMSO}-d_6$) δ 68.55, 68.57. ESI-LCMS: m/z 675.3 $[\text{M}+\text{H}]^+$.

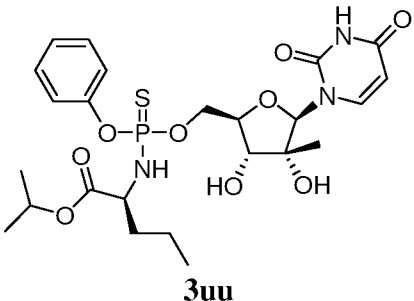
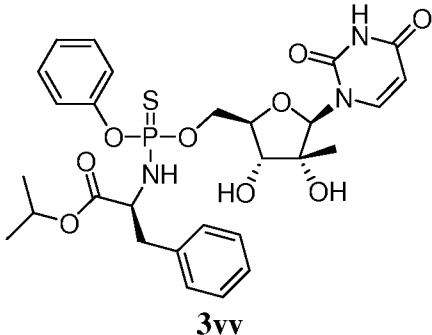
Example 34**Preparation of additional 2'-C-methyluridine 5'-thiophosphoramidates**

[0260] Compounds **3ii** – **3vv**, as shown in Table 8, were prepared using a similar procedure for preparing compound **3n**.

Table 8

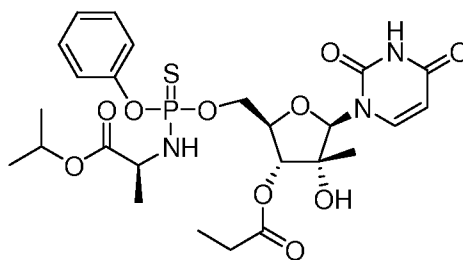
Compound	^{31}P NMR ppm	Compound	^{31}P NMR ppm
 3ii	69.30 69.09	 3jj	68.92 68.58

Compound	³¹ P NMR ppm	Compound	³¹ P NMR ppm
 3kk	68.45 68.16	 3ll	69.69 69.28
 3mm	68.60 68.42	 3nn	68.25 67.79
 3oo	69.25 69.12	 3pp	69.52 68.53
 3qq	70.03 69.56	 3rr	68.87 68.76
 3ss	70.83 69.38	 3tt	69.12 68.45

Compound	³¹ P NMR ppm	Compound	³¹ P NMR ppm
 3uu	69.14 68.46	 3vv	68.74 66.82

Example 35

Preparation of 2'-C-Methyl-3'-O-propionyluridine 5'-(O-phenyl-N-(S)-1-(isopropoxycarbonyl)ethyl)-thiophosphoramidate (4b)



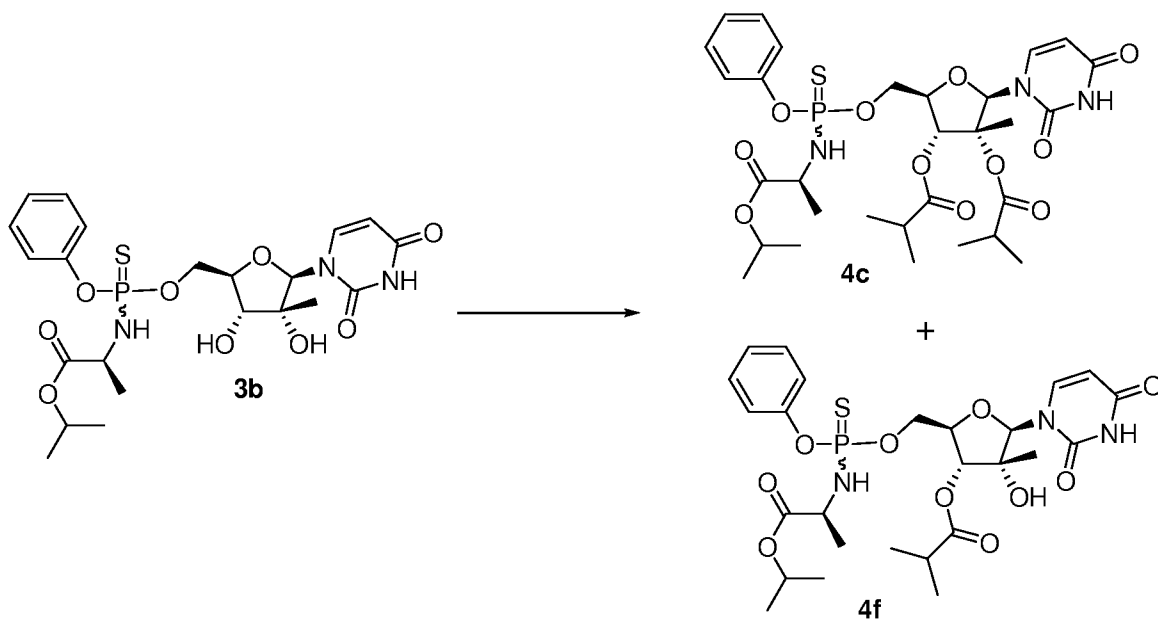
[0261] Compound **3b** (1g, 1.88 mmol) was dissolved in 10 mL of dry pyridine, propionic anhydride was added (385 mg, 2.81 mmol) and reaction mixture was left overnight at RT. TLC showed that reaction was not completed. More anhydride (385 mg, 2.81 mmol) was added and the mixture was heated at 40°C for 2 hours. Solvents were evaporated. The residue was distributed between ethyl acetate and water. The organic layer was washed with water, brine, dried over Na₂SO₄, and concentrated. Purification by column chromatography on silica gel in a gradient of methanol in DCM from 2% to 7% resulted in 725 mg of **4b** (64%). ¹H NMR (CDCl₃): δ 8.70 & 8.66 (2s, 1H), 7.59-7.48 (2d, 1H), 7.30-7.08 (m, 5H), 5.93 & 5.90 (2s, 1H), 5.60 & 5.49 (2d, 1H), 5.01-4.94 (m, 2H), 4.50-4.38 (m, 1H), 4.32-4.02 (m, 3H), 2.45-2.35 (m, 2H), 1.38-1.30 (m, 3H), 1.20-1.11 (m, 12H); ³¹P NMR: δ 67.72, 67.54 (1:1 mixture of diastereomers); ESI-LCMS: m/z 598.3 [M + H]⁺.

Example 36

Preparation of 2',3'-*O*-diisobutyryl-2'-*C*-methyluridine 5'-(*O*-phenyl-*N*-(*S*)-1-(isopropoxycarbonyl)ethyl)thiophosphoramidate (4c)

and

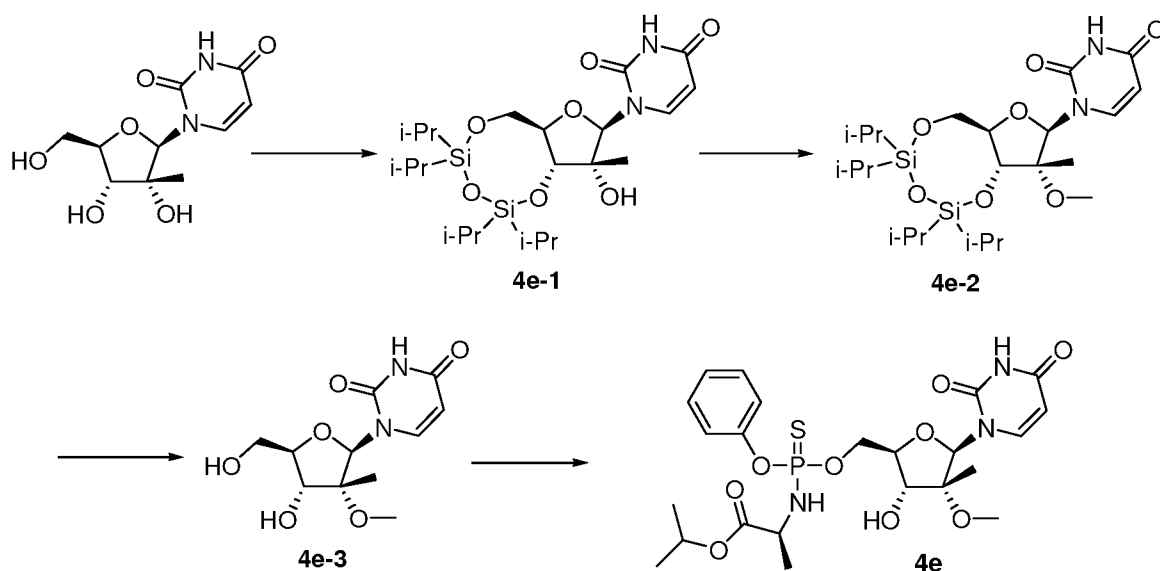
Preparation of 2'-*C*-methyl-3'-*O*-isobutyryluridine 5'-(*O*-phenyl-*N*-(*S*)-1-(isopropoxycarbonyl)ethyl)thiophosphoramidate (4f)



[0262] **Step 1. Compound 4c** - To a solution of **3b** (0.1 g, 0.18 mmol) in anhydrous pyridine (2 mL), was added DMAP (22 mg, 0.18 mmol) followed by isobutyric anhydride (0.1 mL, 0.63 mmol) under N₂ atmosphere. The reaction mixture was stirred at RT for 1h. The reaction was quenched by adding isopropanol (0.5 mL). The solvent was removed under vacuum and the residue was taken up into EA (100 mL). The solution was washed with saturated NaHCO₃ and brine. The organic layer was separated, dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated in vacuum to give a residue which was purified on a silica gel column (1~5% MeOH in DCM) to give the faster eluting product **4c** as a white solid (36.5 mg). ¹H NMR (DMSO-d₆, 400 MHz) δ 11.46 (s, 1H), 7.59 & 7.55 (2d, *J* = 8.4, 8.4 Hz, 1H), 7.37-7.32 (m, 2H), 7.21-7.15 (m, 3H), 6.67-6.66 (m, 1H), 6.14 & 6.11 (each s, 1H), 5.58 (d, *J* = 8.0 Hz, 1H), 5.2 (br s, 1H), 4.88-4.84 (m, 1H), 4.28-4.27 (m, 1H), 3.95-3.85 (m, 1H), 2.54-2.49 (m, 2H), 1.38 & 1.36 (2s, 3H), 1.26-1.21 (m, 2H), 1.56-1.12 (m, 6H), 1.09-1.05 (m, 12H); ³¹P NMR (DMSO-d₆) δ 68.44, 68.42; ESI-LCMS: *m/z* = 682.4 [*M*-H]⁻.

[0263] Step 2. Compound 4f - Further elution of the residue on the silica gel column using 5% MeOH in DCM gave the slower eluting product **4f** (54.5 mg) as white foam after evaporation of solvent *in-vacuo*. ^1H NMR (DMSO- d_6 , 400 MHz) δ 11.42 (s, 1H), 7.65 & 7.63 (2d, J = 8.0, 8.4 Hz, 1H), 7.37-7.32 (m, 2H), 7.21-7.15 (m, 3H), 6.68-6.61 (m, 1H), 5.84 & 5.81 (each s, 1H), 5.71 & 5.68 (each s, 1H), 5.56 & 5.47 (each d, each J = 8.0 Hz, 1H), 4.98-4.94 (m, 1H), 4.87-4.82 (m, 1H), 4.31-4.16 (m, 3H), 3.85-3.95 (m, 1H), 2.62-2.58 (m, 1H), 1.26 & 1.2 (each d, J = 7.2, 6.8 Hz, 3H), 1.16-1.08 (m, 12H), 1.01 (s, 3H); ^{31}P NMR (DMSO- d_6) δ 68.93, 67.96; ESI-LCMS: m/z = 612.4 $[\text{M}+\text{H}]^+$.

Example 37
Preparation of 2'-C-2'-O-dimethyluridine 5'-(O-phenyl-N-(S)-1-(isopropoxycarbonyl)ethyl)thiophosphoramidate (4e)



[0264] Step 1. Compound 4e-1 - To an ice-cold solution of 2'-C-methyluridine (2.0 g, 7.6 mmol) in anhydrous pyridine (20 mL) was added 1,3-dichloro-1,1,3,3-tetraisopropylidisiloxane (TIPDSCl₂) (2.40 g, 7.6 mmol) in small portions under N₂. The reaction mixture was stirred at RT overnight. The solvent was removed under vacuum and the residue was taken up into EA (100 mL). The solution was washed with saturated NaHCO₃ and brine. The organic layer was separated, dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated in vacuum to give a residue, which was purified on a silica gel column (DCM/MeOH = 100/1 to 50/1) to give **4e-1** (3.2 g, 85%) as a white foam.

[0265] Step 2. Compound 4e-2 - To a solution of **4e-1** (2.0 g, 4.0 mmol) in anhydrous THF (30 mL) was added NaH (384 mg, 16 mmol) at 0°C. The mixture was stirred at 0°C for 30 minutes before CH₃I (1.2 g, 8 mmol) was added. Stirring was continued for 4 h at 0°C. The mixture was diluted with EA (100 mL), washed with saturated NaHCO₃ and brine. The organic layer was dried with Na₂SO₄ and concentrated to a residue which was purified on a silica gel column (DCM/MeOH = 100/1 to 50/1) to give **4e-2** (556 mg, 26.93%) as a white foam.

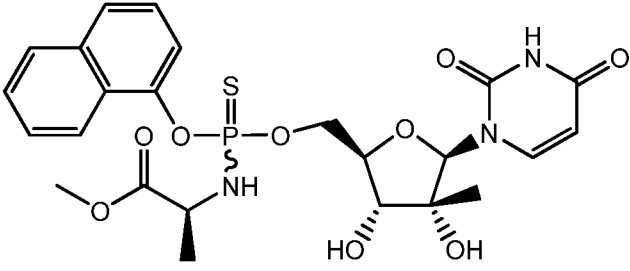
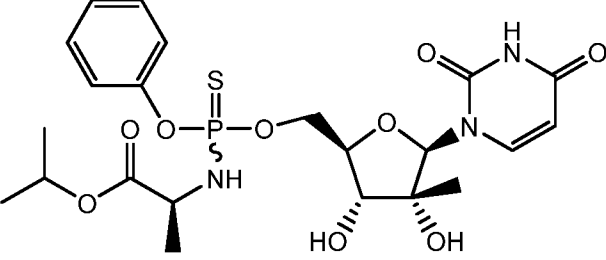
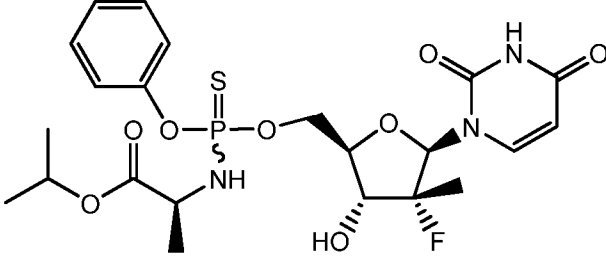
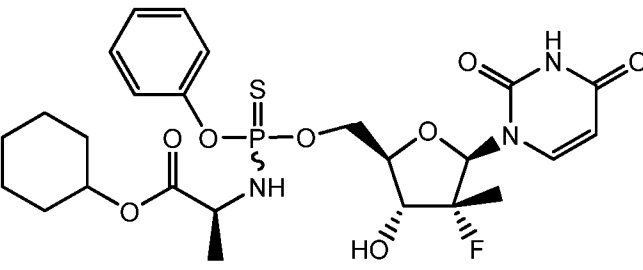
[0266] Step 3. Compound 4e-3 - To a stirred solution of **4e-2** (556 mg, 1.08 mmol) in MeOH (10 mL) was added NH₄F (232 mg, 6.46 mmol). The mixture was stirred at 80°C for 12 h. The solvent was removed and the residue was purified on a silica gel column (DCM/MeOH = 100/1 to 20/1) to give **4e-3** (220 mg, 74%) as a white solid. ¹H NMR (DMSO-d₆, 400 MHz) δ 11.39 (brs, 1H), 8.07 (d, *J* = 8.0 Hz, 1H), 5.91 (s, 1H), 5.63 (d, *J* = 8.0 Hz, 1H), 5.21 (t, *J* = 4.8 Hz, 1H), 5.05 (d, *J* = 8.0 Hz, 1H), 3.78-3.82 (m, 2H), 3.59-3.71 (m, 2H), 3.36 (3, 3H), 1.08 (s, 3H); ESI-LCMS: *m/z* = 273.1 [M + H]⁺.

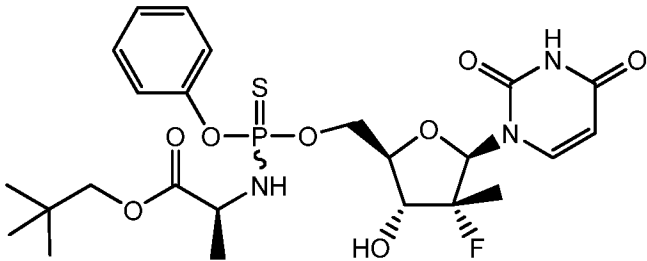
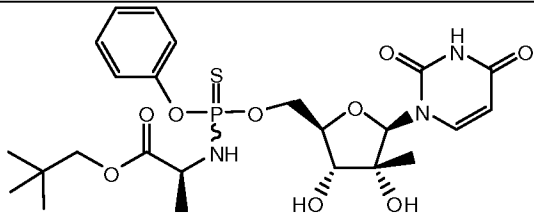
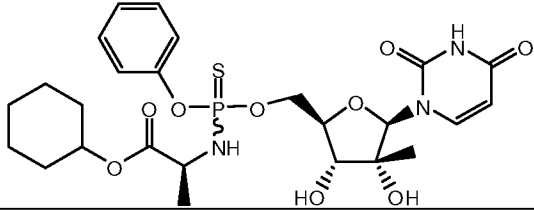
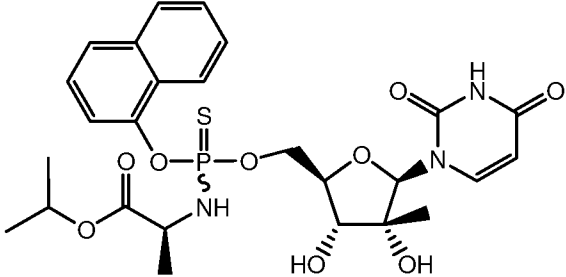
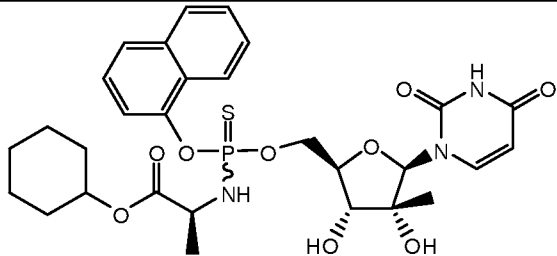
[0267] Step 4. Compound 4e - To a stirred suspension of **4e-3** (170 mg, 0.63 mmol) in anhydrous THF (2 mL) were added *N*-methylimidazole (0.5 mL) followed by **2b** (598 mg, 1.875 mmol). The reaction mixture was stirred at 70°C for 1 h. Solvents were evaporated and the residue was purified by RP HPLC (MeCN and 0.1% HCOOH in water) to give **4e** (two isomers, 108 mg, 30.2%) as a white solid. ¹H NMR (CD₃OD, 400 MHz) δ 7.77, 7.85 (2d, *J* = 8.0 Hz, 1H), 7.18-7.36 (m, 5H), 6.09, 6.12 (2s, 1H), 5.54, 5.63 (2d, *J* = 8.0 Hz, 1H), 4.94-5.01 (m, 1H), 4.49-4.53 (m, 1H), 4.26-4.39 (m, 1H), 4.03-4.13 (m, 2H), 3.77-3.81 (m, 1H), 3.47 (s, 3H), 1.32, 1.36 (2d, *J* = 7.2 Hz, 3H), 1.18-1.24 (m, 6H); ³¹P NMR (CD₃OD, 162 MHz) δ 68.2, 67.7; ESI-MS: *m/z* 558.2 [M+H]⁺.

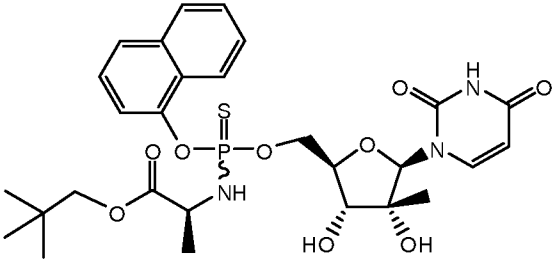
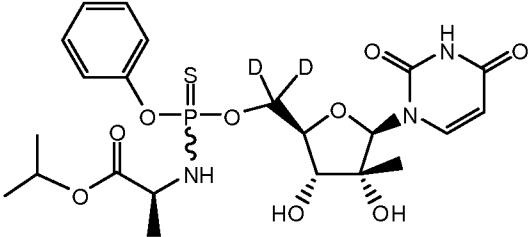
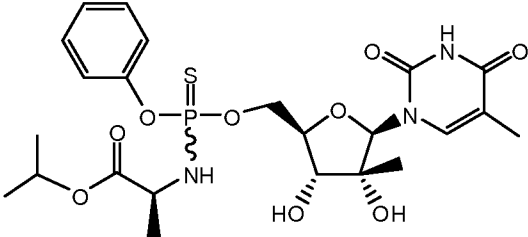
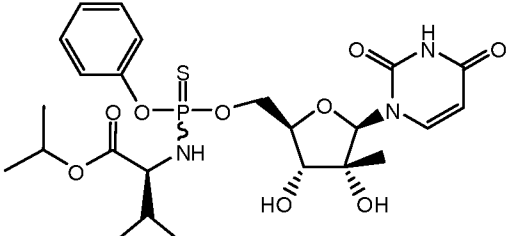
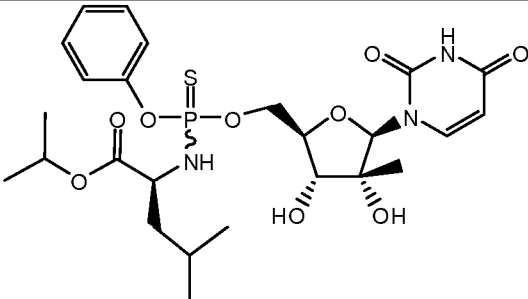
Example 38

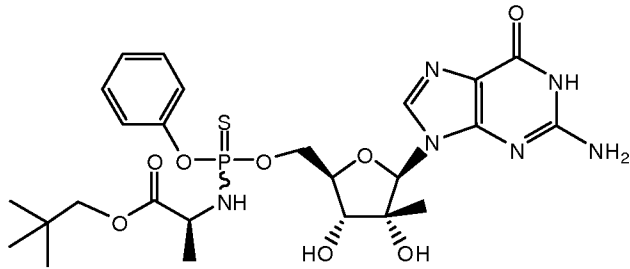
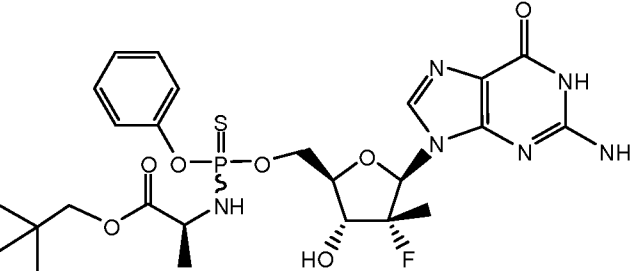
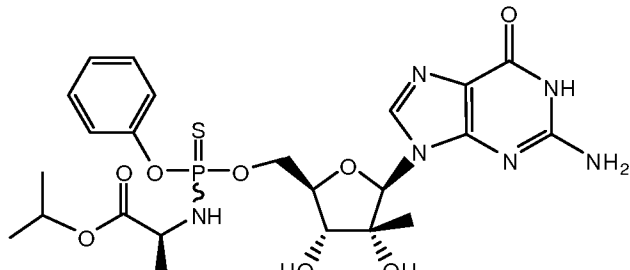
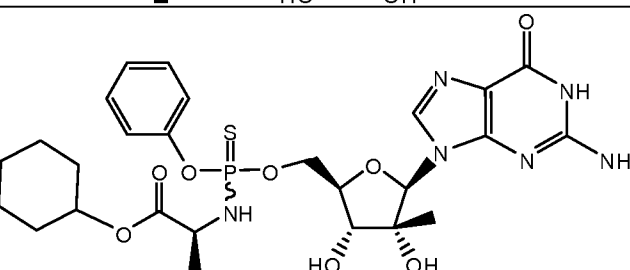
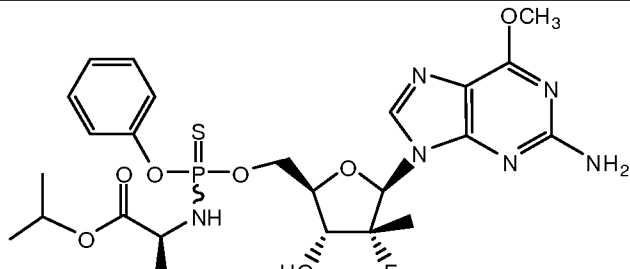
[0268] The structures of compounds **3a** through **3vv** and **4a** through **4f** are shown in Table 9.

Table 9.

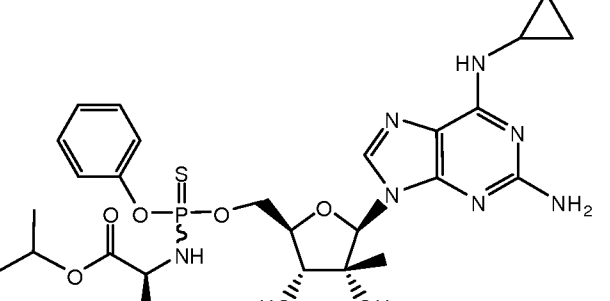
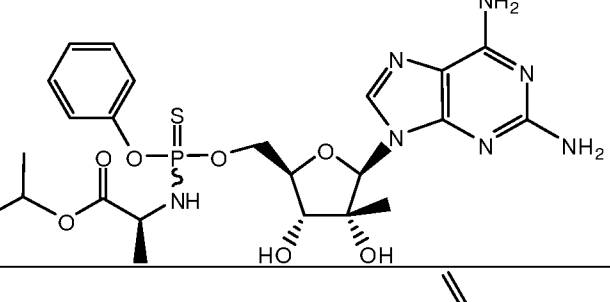
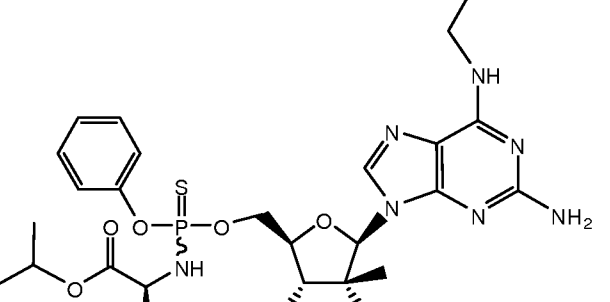
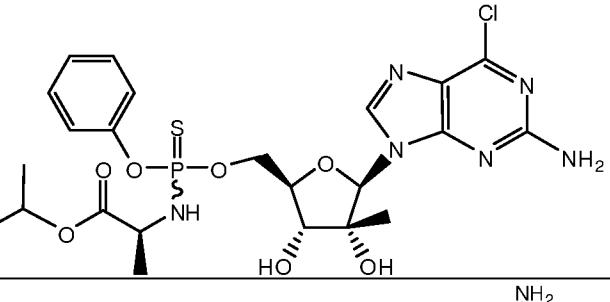
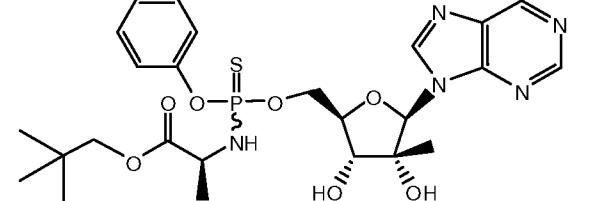
Compound	Product	³¹ P NMR (solvent)	MS
	3a	67.12 67.86 (CDCl ₃)	564.5 (M-H ⁺)
	3b	67.16 67.71 (CDCl ₃)	543.2 (M-H ⁺)
	3c	67.05 68.08 (CDCl ₃)	545.8 (MH ⁺)
	3d	67.89 67.96 (DMSO)	586.2 (MH ⁺)

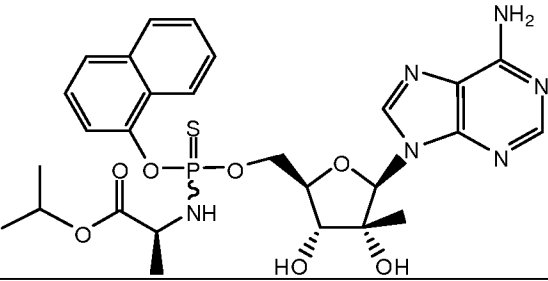
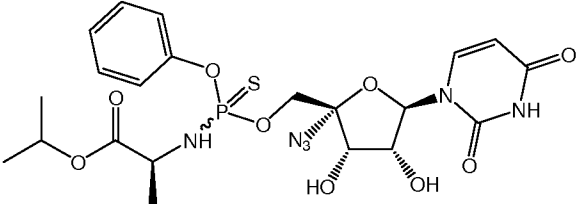
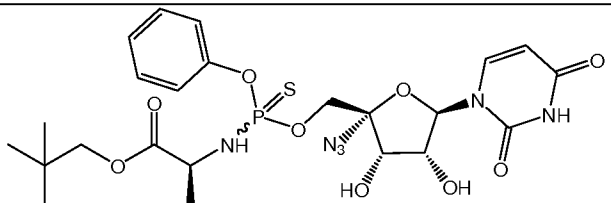
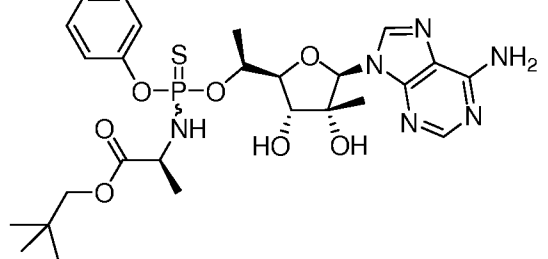
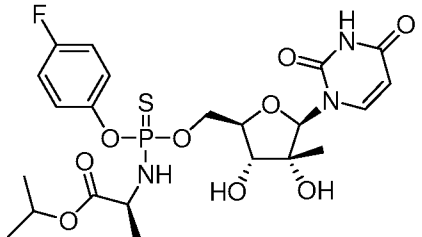
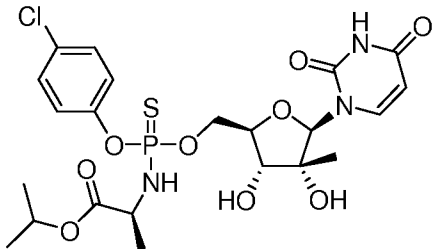
Compound	Product	³¹ P NMR (solvent)	MS
	3e	66.9 66.9 (CD ₃ OD)	574.2 (MH ⁺)
	3f	67.85 67.16	570.4 (MH ⁺)
	3g	67.80 67.16	582.5 (MH ⁺)
	3h	67.92 67.28	592.2 (MH ⁺)
	3i	67.74 67.43	632.5 (MH ⁺)

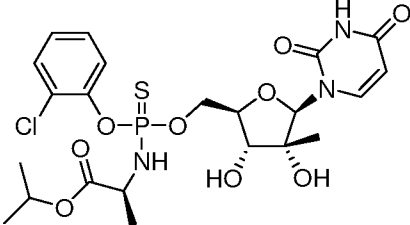
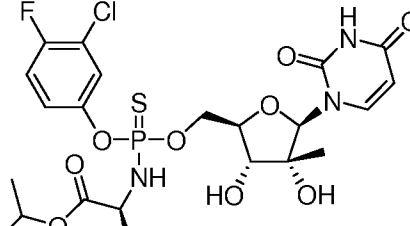
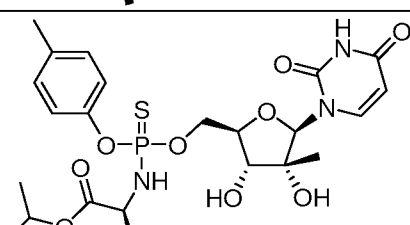
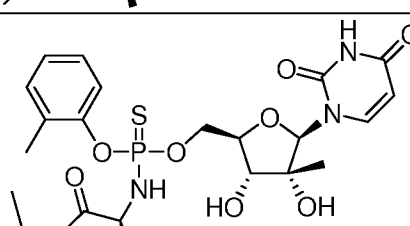
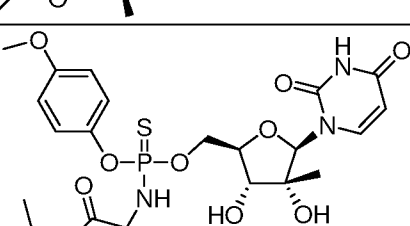
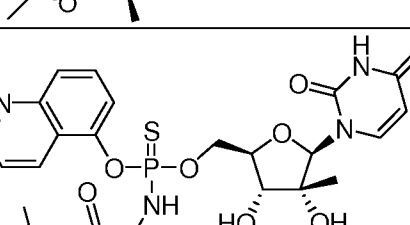
Compound	Product	³¹ P NMR (solvent)	MS
	3j	68.01 67.35	620.8 (MH ⁺)
	3l	68.42 68.21	546.1 (MH ⁺)
	3m	69.17 68.68	558.1 (MH ⁺)
	3n	70.38 69.13	572 (MH ⁺)
	3o	69.15 68.56	586 (MH ⁺)

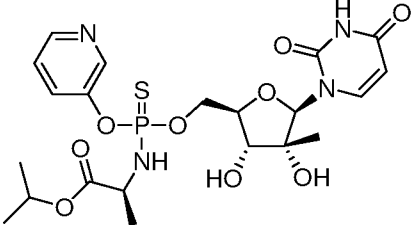
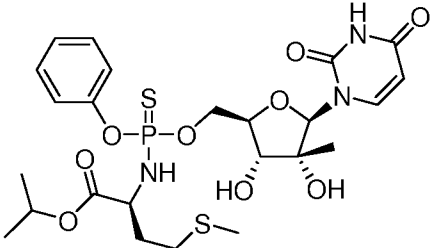
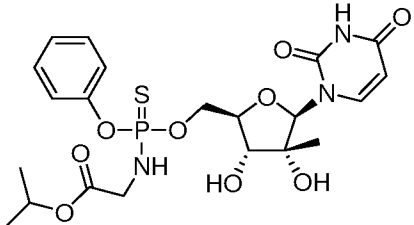
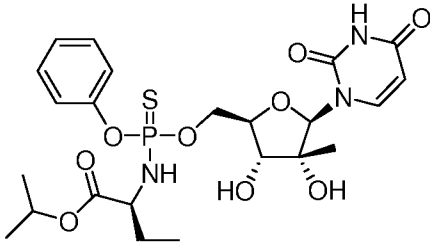
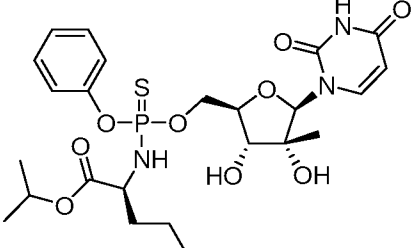
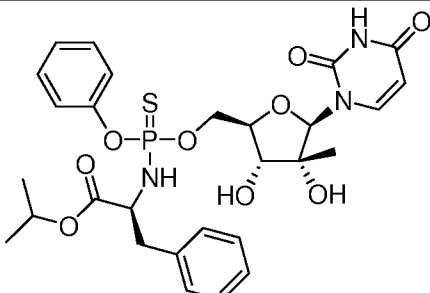
Compound	Product	³¹ P NMR (solvent)	MS
	3p	68.27 67.85	611.3 (MH ⁺)
	3q	68.09 68.03	613.7 (MH ⁺)
	3r	68.23 67.64	583.4 (MH ⁺)
	3s	68.07 67.71	623.1 (MH ⁺)
	3t	68.21 67.82	599.4 (MH ⁺)

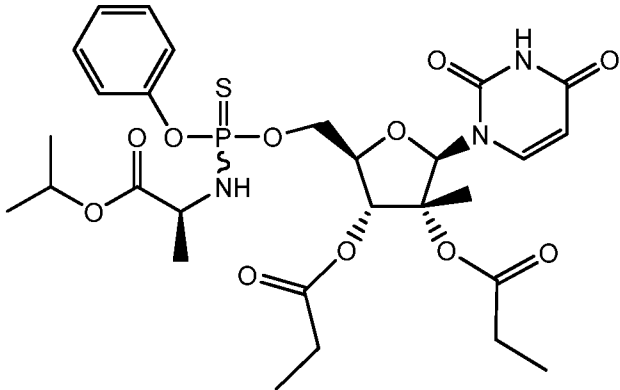
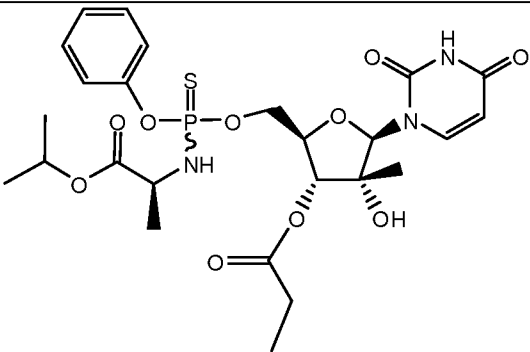
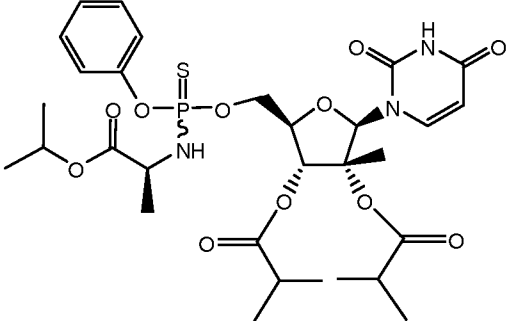
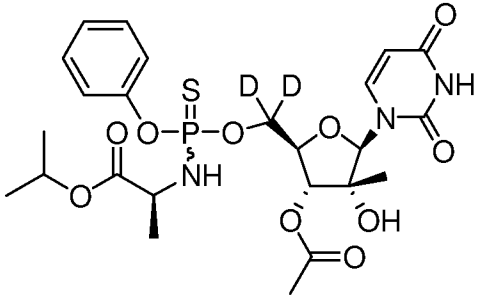
Compound	Product	³¹ P NMR (solvent)	MS
	3u	68.21 67.65	597.5 (MH ⁺)
	3v	68.52 68.27	625.3 (MH ⁺)
	3w	68.43 68.32	637.6 (MH ⁺)
	3x	68.55 68.57	675.3 (MH ⁺)
	3y	68.66 68.36	687.4 (MH ⁺)

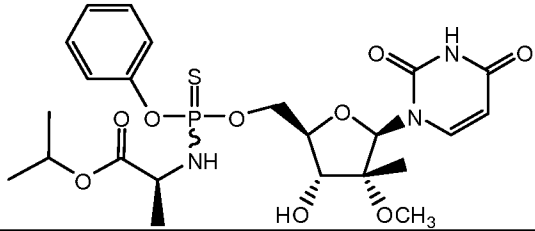
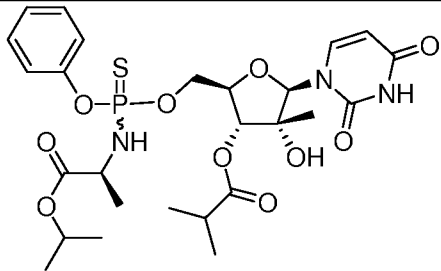
Compound	Product	³¹ P NMR (solvent)	MS
	3z	68.53 68.38	622.2 (MH ⁺)
	3aa	68.19 67.90	589.1 (MH ⁺)
	3bb	68.51 68.40	622.1 (MH ⁺)
	3cc	68.66 68.53	601.1 (MH ⁺)
	3dd	68.15 67.74	595.0 (MH ⁺)

Compound	Product	³¹ P NMR (solvent)	MS
	3ee	68.49 67.46	617.1 (MH ⁺)
	3ff	67.78 66.86	569.4 (M-1) ⁻
	3gg	68.11 67.06	597.5 (M-1) ⁻
	3hh	68.40 67.43	595.1 (MH ⁺)
	3ii	69.30 69.09	562.2 (MH ⁺)
	3jj	68.92 68.58	578.0 (MH ⁺)

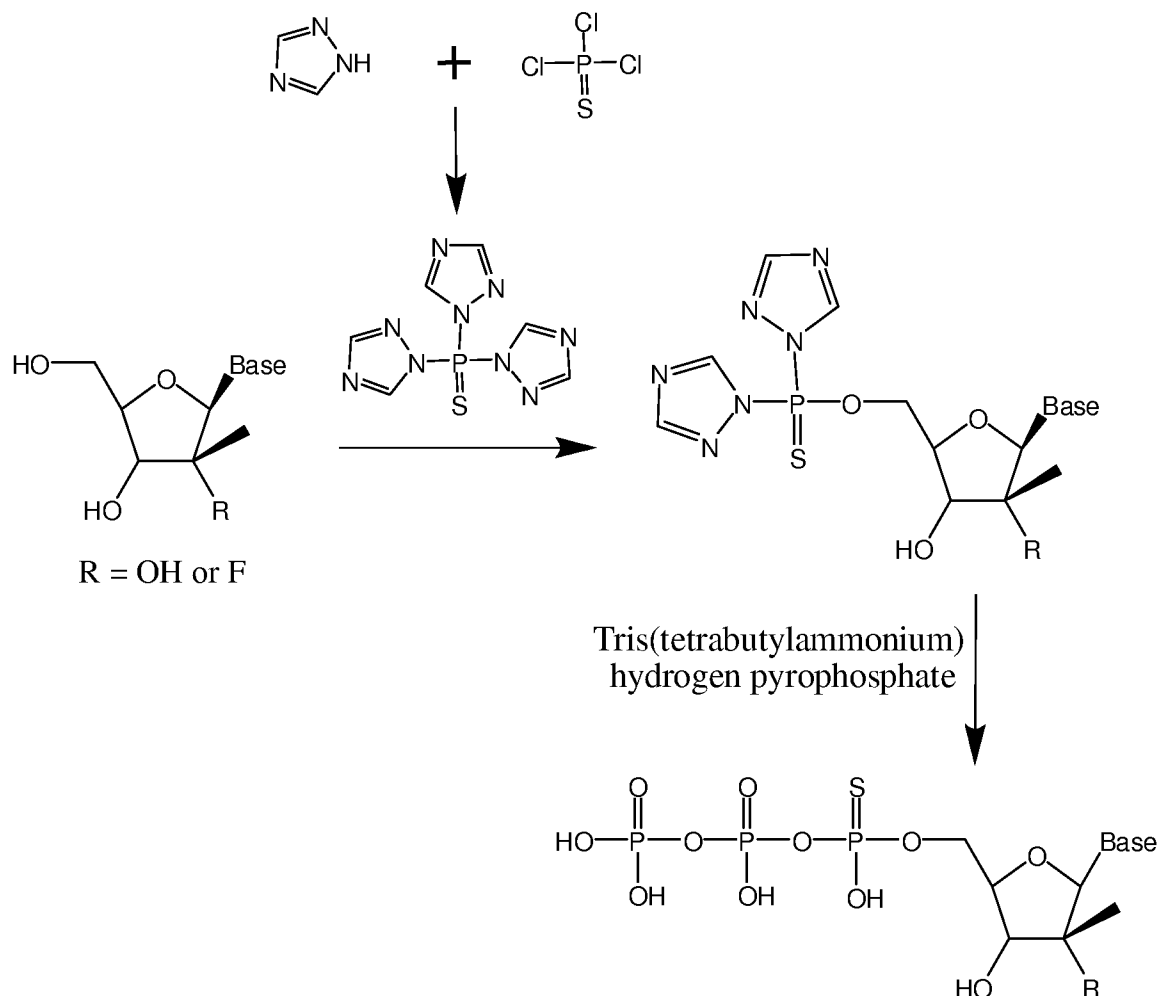
Compound	Product	³¹ P NMR (solvent)	MS
	3kk	68.45 68.16	578.1 (MH ⁺)
	3ll	69.69 69.28	618.0 (M+Na) ⁺
	3mm	68.60 68.42	558.0 (MH ⁺)
	3nn	68.25 67.79	558.2 (MH ⁺)
	3oo	69.25 69.12	574.0 (MH ⁺)
	3pp	69.52 68.53	595.0 (MH ⁺)

Compound	Product	³¹ P NMR (solvent)	MS
	3qq	70.03 69.56	545.1 (MH ⁺)
	3rr	68.87 68.76	626.2 (M+Na) ⁺
	3ss	70.83 69.38	530.0 (MH ⁺)
	3tt	69.12 68.45	558.0 (MH ⁺)
	3uu	69.14 68.46	572.0 (MH ⁺)
	3vv	68.74 66.82	620.0 (MH ⁺)

Compound	Product	³¹ P NMR (solvent)	MS
	4a	67.71 67.74 (CDCl ₃)	654.5 (M-H ⁺)
	4b	67.72 67.54	598.3 (MH ⁺)
	4c	68.44 68.42	682.4 (MH ⁺)
	4d	68.90 68.23	585.9 (MH ⁺)

Compound	Product	³¹ P NMR (solvent)	MS
	4e	68.2 67.7	558.2 (MH ⁺)
	4f	68.93 67.96	612.4 (MH ⁺)

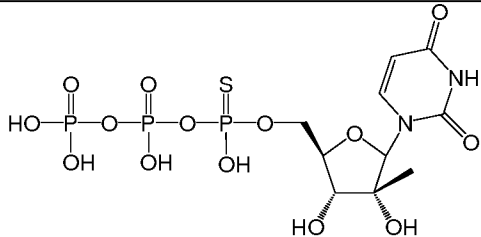
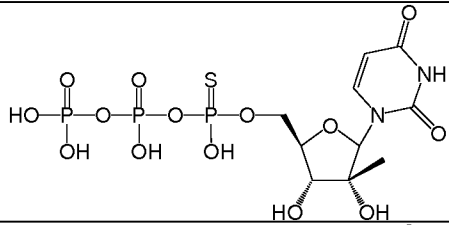
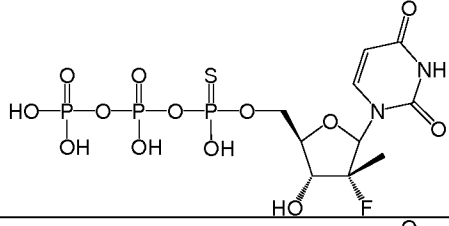
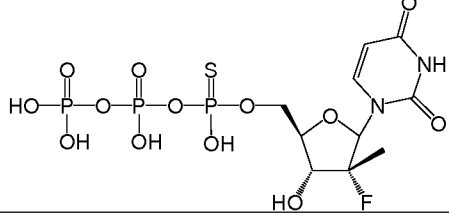
Example 39
General Synthesis of nucleoside 5'-O-(1-thiotriphosphates)

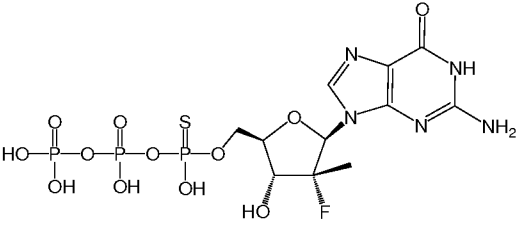
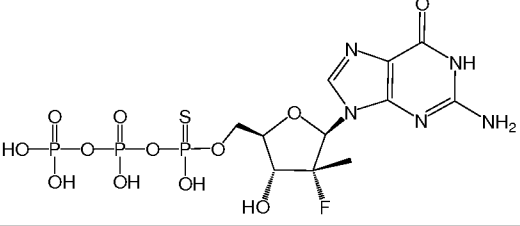
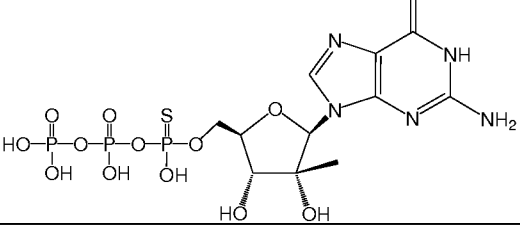
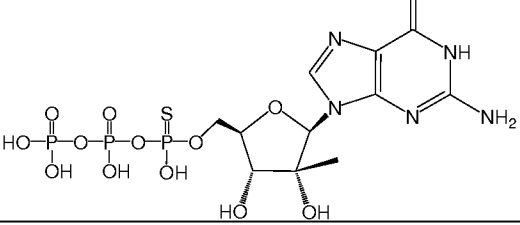


[0269] 1,2,4-Triazole (42 mg, 0.6 mmol) was suspended 1 mL of dry CH₃CN. Triethylamine was added (0.088 mL, 0.63 mmol), and the mixture was vortexed to obtain a clear solution. After addition of PSCl₃ (0.01 mL, 0.1 mmol), the mixture was vortexed and left for 20 minutes. The mixture was then centrifuged. The supernatant was added to the nucleoside (0.05 mmol), and the mixture was kept at ambient temperature for 1 hour. Tris(tetrabutylammonium) hydrogen pyrophosphate (180 mg, 0.2 mmol) was added. The mixture was then kept for 2 hours at RT. The reaction was cooled in an ice-water bath and quenched with water. The 5'-triphosphate, as mixture of diastereomers, was isolated by IE chromatography on an AKTA Explorer using column HiLoad 16/10 with Q Sepharose High Performance. The separation was done using a linear gradient of NaCl from 0 to 1N in

50mM TRIS-buffer (pH7.5). The fractions containing the nucleotide α -thiotriphosphate were combined, concentrated and desalted by RP HPLC on the same column as in Example 3. A linear gradient of methanol from 0 to 30% in 50mM triethylammonium buffer was used for elution over 20minutes, flow 10mL/min. Two separate compounds corresponding to individual diastereomers at the phosphorus chiral center were collected. Analytical RP HPLS was done in 50 mM triethylammonium acetate buffer, pH 7.5, containing linear gradient of acetonitrile from 0% to 25% in 7minutes on a Synergy 4 micron Hydro-RP column (Phenomenex). Retention time (R.T.) for the individual diastereomers is provided in Table 10.

Table 10. α -Thiotriphosphates

Structure		³¹ P NMR P α	³¹ P NMR P β	³¹ P NMR P γ	MS	R.T. min
	5b	43.17 d	-21.69 m	-5.32 d	513.0	4.17
	5a	42.89 d	-21.75 q	-5.28 d	513.0	4.50
	5c	43.14 d	-23.80 m	-10.20 bs	515.0	4.90
	5d	42.12 d	-23.48 q	-6.49 d	515.0	5.52

Structure		³¹ P NMR P α	³¹ P NMR P β	³¹ P NMR P γ	MS	R.T. min
	5e	43.42 d	-21.93 q	-5.47 d	554.3	5.39
	5f	43.07 d	-21.90 q	-5.40 d	554.2	5.79
	5g	43.41 d	-23.26 m	-10.10 bs	552.2	5.23
	5h	43.12 d	-24.20 m	-11.05 d	552.2	5.82

R.T. = retention time

[0270] In Table 10, **5a** and **5b** are diastereomers, and distinguishable by the chirality of the alpha-thiophosphate. Likewise, **5b** and **5c**; **5d** and **5e**; and **5f** and **5h**, respectively, are diastereomers and distinguishable by the chirality of the alpha-thiophosphate.

Example 40
HCV Replicon Assay

Cells

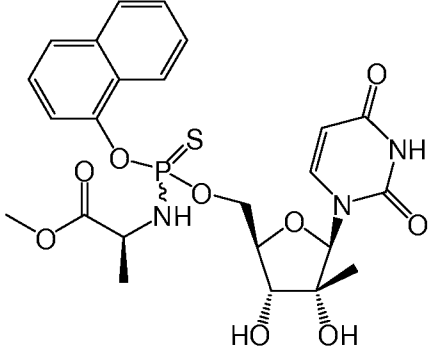
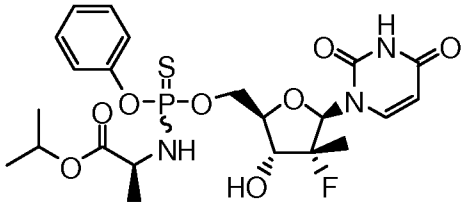
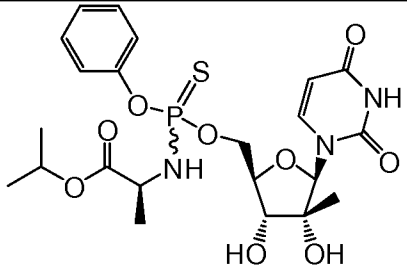
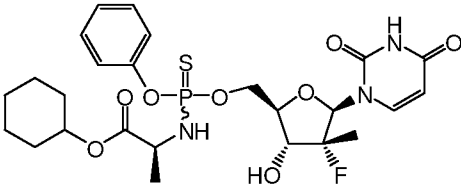
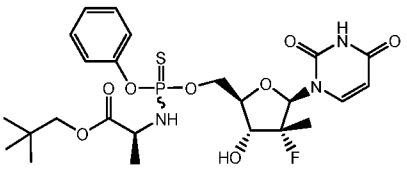
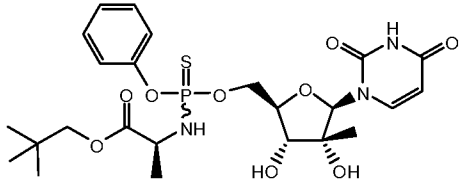
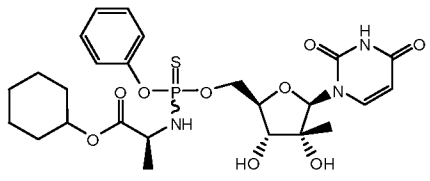
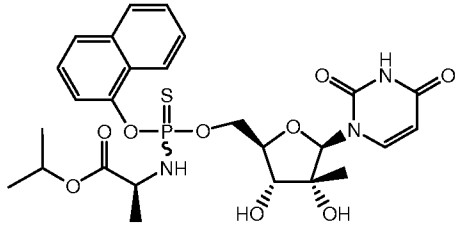
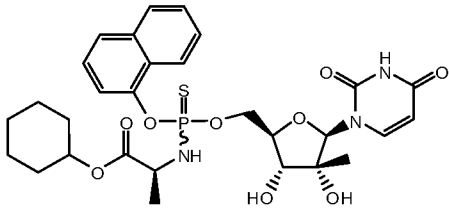
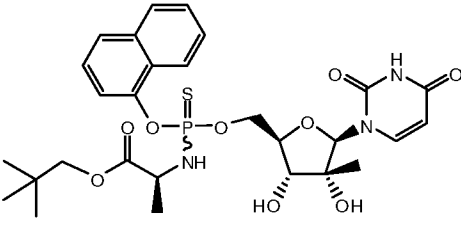
[0271] Huh-7 cells containing the self-replicating, subgenomic HCV replicon with a stable luciferase (LUC) reporter were cultured in Dulbecco's modified Eagle's medium (DMEM) containing 2mM L-glutamine and supplemented with 10% heat-inactivated fetal bovine serum (FBS), 1% penicillin-streptomycin, 1% nonessential amino acids, and 0.5mg/mL G418.

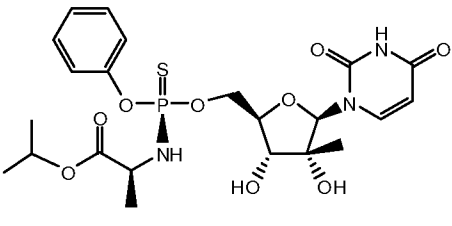
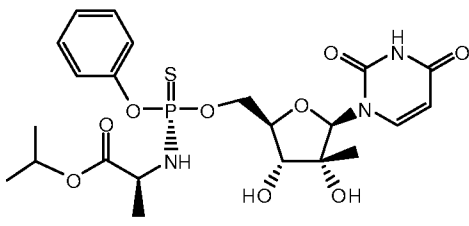
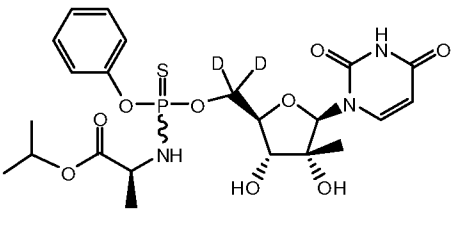
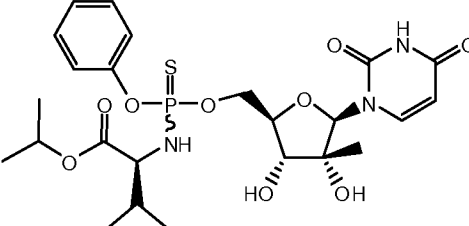
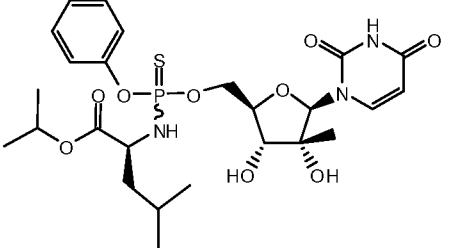
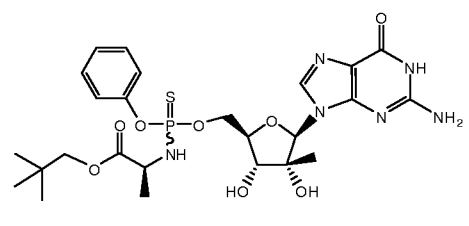
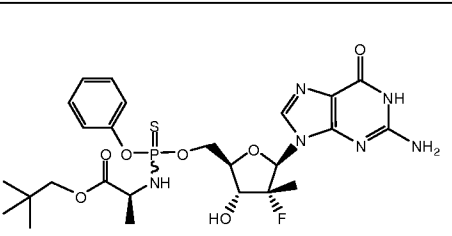
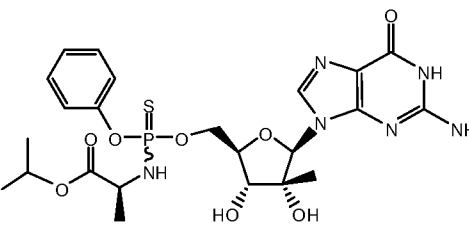
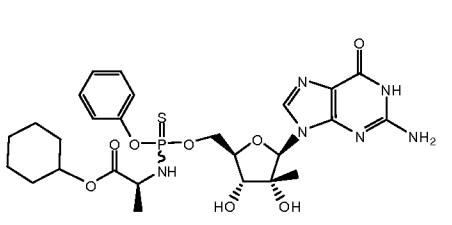
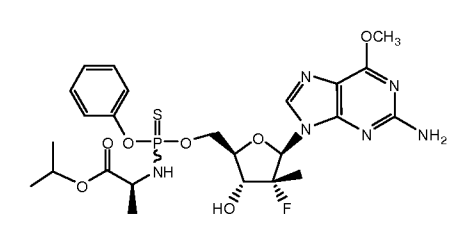
Determination of anti-HCV activity

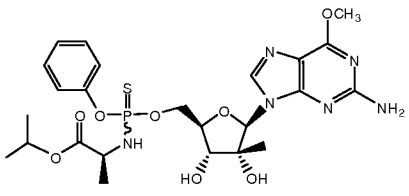
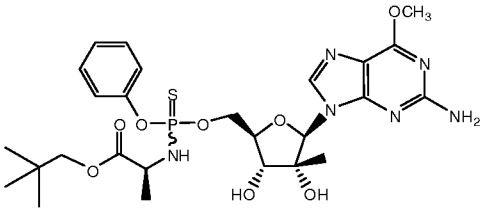
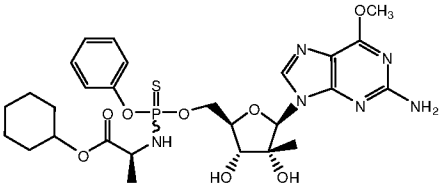
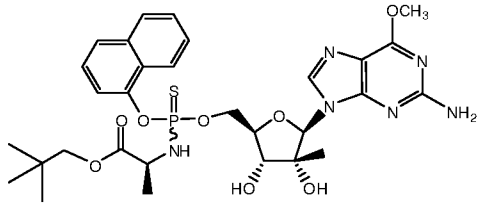
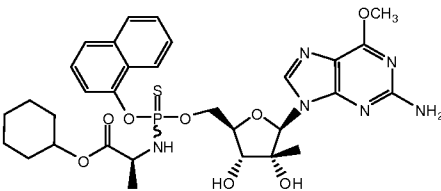
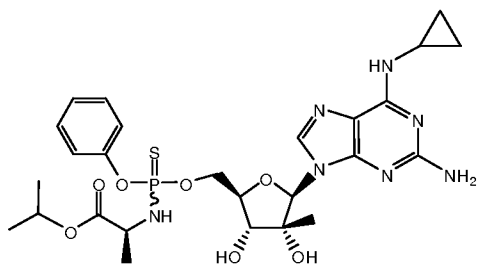
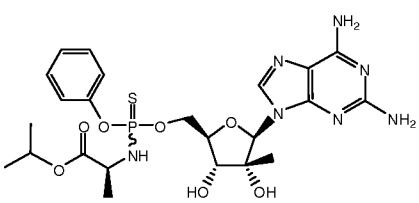
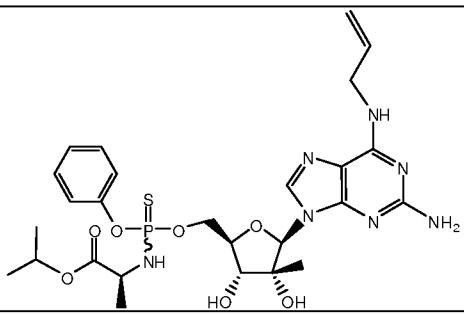
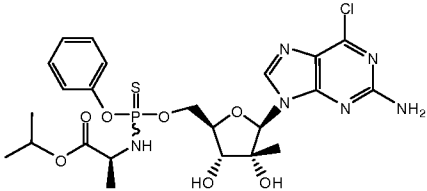
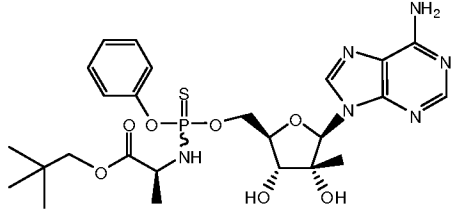
[0272] Determination of 50% inhibitory concentration (EC_{50}) of compounds in HCV replicon cells were performed by the following procedure. On the first day, 5,000 HCV replicon cells were plated per well in a 96-well plate. On the following day, test compounds were solubilized in 100% DMSO to 100x the 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). Percent Inhibition was determined for each compound concentration in relation to the control cells (untreated HCV replicon) to calculate the EC_{50} .

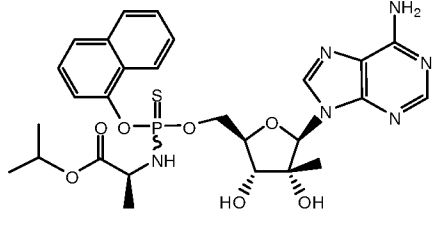
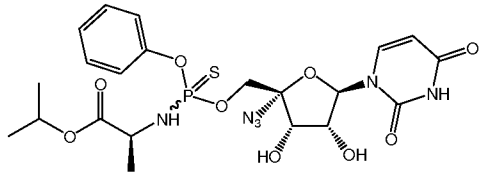
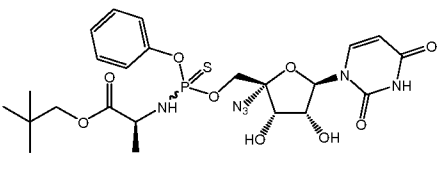
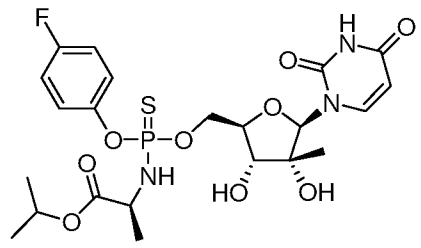
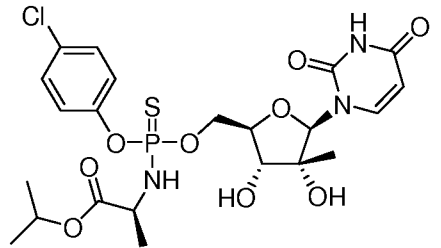
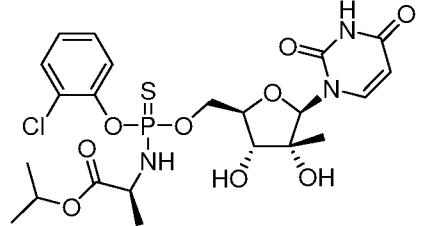
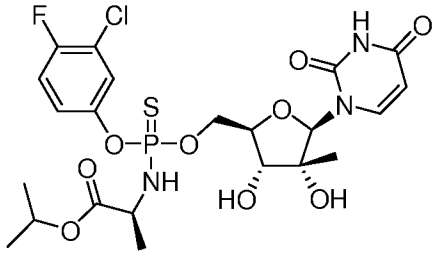
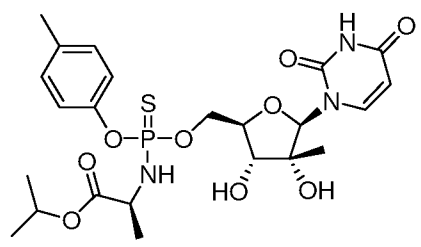
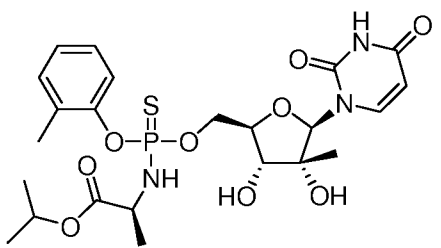
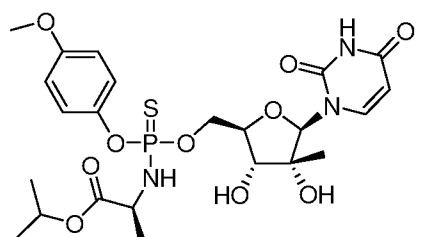
[0273] Compounds of Formula (I) are active in the replicon assay. The antiviral activity of exemplary compounds is shown in Table 11, where 'A' indicates an $EC_{50} < 1 \mu M$, 'B' indicates an $EC_{50} < 10 \mu M$, and 'C' indicates an $EC_{50} < 100 \mu M$.

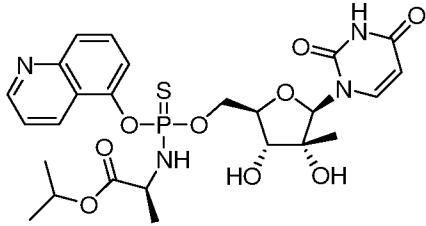
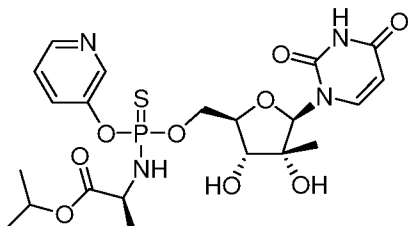
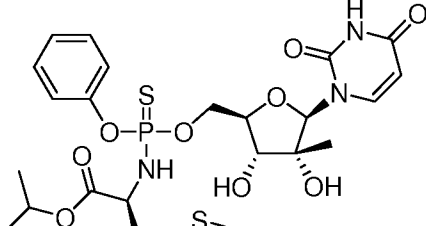
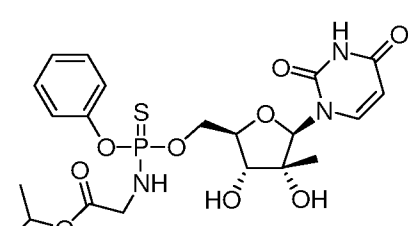
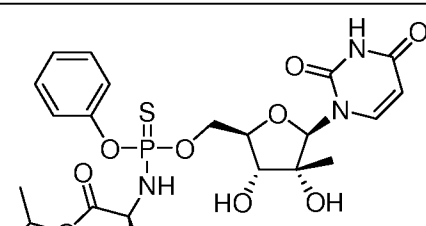
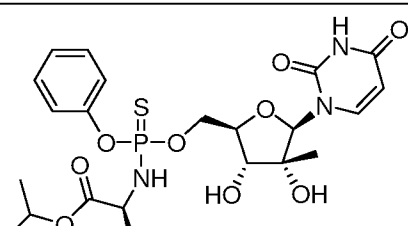
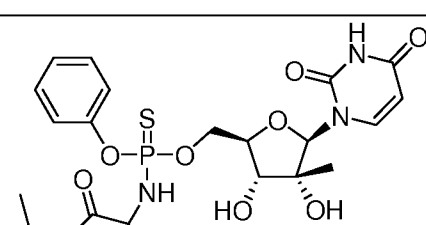
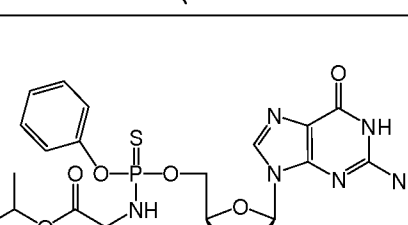
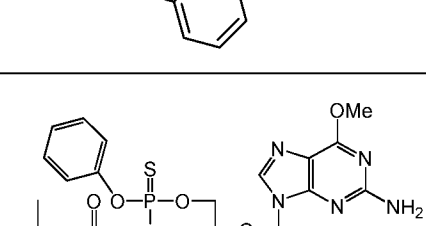
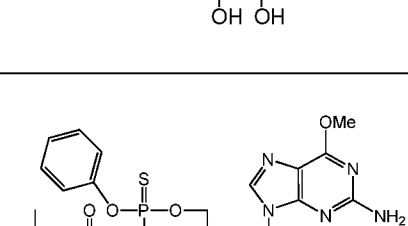
Table 11

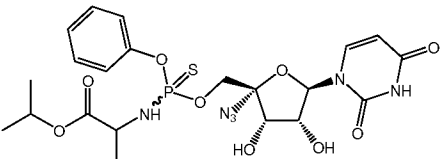
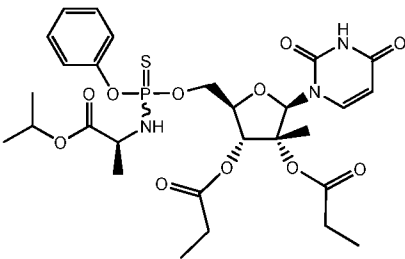
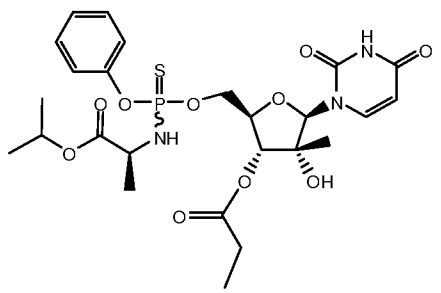
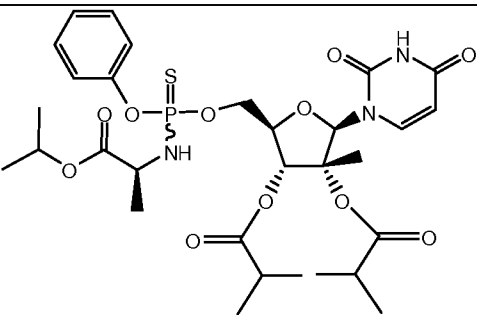
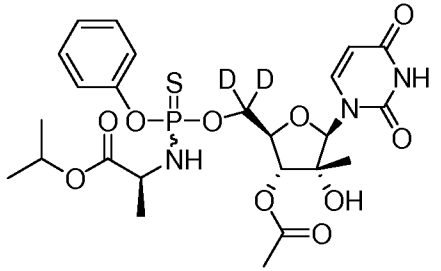
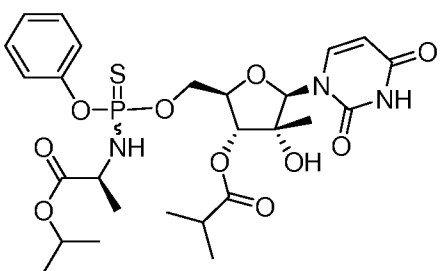
Compound	EC ₅₀	Compound	EC ₅₀
	A		B
	A		A
	A		A
	A		A
	A		A

Compound	EC ₅₀	Compound	EC ₅₀
	A		A
	A		C
	B		A
	A		A
	A		A

Compound	EC ₅₀	Compound	EC ₅₀
	A		A
	A		A
	A		A
	A		A
	A		A

Compound	EC ₅₀	Compound	EC ₅₀
	A		C
	C		A
	A		A
	A		A
	A		A

Compound	EC ₅₀	Compound	EC ₅₀
	A		A
	B		B
	A		A
	B		A
	A		A

Compound	EC ₅₀	Compound	EC ₅₀
	C		A
	A		A
	A		A

Example 41
NS5B Inhibition Assay

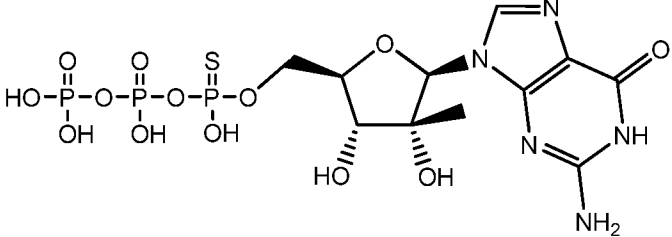
[0274] The enzyme activity of NS5B570-Con1 (Delta-21) was measured as an incorporation of tritiated NMP into acid-insoluble RNA products. The complementary IRES (cIRES) RNA sequence was used as a template, corresponding to 377 nucleotides from the 3'-end of HCV (–) strand RNA of the Con-1 strain, with a base content of 21% Ade, 23% Ura, 28% Cyt, and 28% Gua. The cIRES RNA was transcribed *in vitro* using a T7 transcription kit (Ambion, Inc.) and purified using the Qiagen RNeasy maxi kit. HCV polymerase reactions contained 50 nM NS5B570-Con1, 50 nM cIRES RNA, about 0.5 μ Ci tritiated NTP, 1 μ M of competing cold NTP, 20 mM NaCl, 40 mM Tris-HCl (pH 8.0), 4 mM dithiothreitol, and 4 mM MgCl₂. Standard reactions were incubated for 2 hours at 37°C, in the presence of increasing concentration of inhibitor. At the end of the reaction, RNA was

precipitated with 10% TCA, and acid-insoluble RNA products were filtered on a size exclusion 96-well plate. After washing of the plate, scintillation liquid was added and radio labeled RNA products were detected according to standard procedures with a Trilux Topcount scintillation counter. The compound concentration at which the enzyme-catalyzed rate was reduced by 50% (IC_{50}) was calculated by fitting the data to a non-linear regression (sigmoidal). The IC_{50} values were derived from the mean of several independent experiments and are shown in Table 12. Compounds of Formula (I) showed activity in this assay. A value of 'A' in the table below indicates an IC_{50} of $< 1 \mu M$, a value of 'B' indicates an $IC_{50} < 10 \mu M$, and a value of 'C' indicates an IC_{50} value of $< 100 \mu M$.

Table 12

	Structure	IC_{50} value
5a		C
5b		A

	Structure	IC ₅₀ value
5c		B
5d		C
5e		A
5f		A
5g		A

	Structure	IC ₅₀ value
5h		B

Example 42
Hepatocyte Activation Assay

[0275] Plated human hepatocytes were purchased from CellzDirect. 30 μ L of test article (compound **3a**) in DMSO at 5mM was dosed to the incubation medium (3 mL) of each well containing ~1.5 million human hepatocytes to reach a final concentration of 50 μ M. After 6 hours of incubation at 37°C, the medium was removed and the cells were washed twice with 500 μ L cold 0.9% NaCl in H₂O. An aliquot of 500 μ L cold methanol/H₂O (70/30) was added to the well to lyse the hepatocytes. The cells were scraped off the well, and the entire content was removed to an Eppendorf tube. After more than 3 hours of storing at -20°C, the lysate was warmed to RT, vortexed, and centrifuged. The supernatant was evaporated in a Speed-Vac, and the sample was reconstituted with 500 μ L 1 mM ammonium phosphate in H₂O. 20 μ L was injected into the LC/MS/MS system for the specific detection of the α -thiotriphosphate of the test article (see Figure 1, panel D). A Thermo HyPurity C18 column (50x2.1 mm, 3 μ particle size) was used to achieve HPLC separation. Mobile phase A consisted of 3 mM ammonium formate and 10 mM dimethyl-hexylamine in H₂O and mobile phase B consisted of 3 mM ammonium formate and 10 mM dimethyl-hexylamine in acetonitrile/H₂O (50/50). The HPLC elution was via a linear gradient on increased mobile phase B at a flow rate of 0.22 mL/min. Compounds **5a** and **5b** were detected by a Sciex API 3200 via a negative ion MRM mode.

[0276] In Figure 1, Panels A, B, C and D show the following. Panel **A**. HPLC chromatogram of a synthetic sample of the α -thiotriphosphate, **5a**, at 300 nM in 1 mM ammonium phosphate in H₂O. Panel **B**. HPLC chromatogram of a synthetic sample the α -thiotriphosphate, **5b**, at 300 nM in 1 mM ammonium phosphate in H₂O. Panel **C**. HPLC

chromatogram of a purposely prepared 1:1 mixture of a synthetic sample of the α -thiotriphosphate diastereomers **5a** and **5b**, each at 150 nM in 1 mM ammonium phosphate in H₂O. This shows that compounds **5a** and **5b** can be distinguished. Panel **D**. HPLC chromatogram of the α -thiotriphosphate diastereomer formed following incubation of compound **3a** in human hepatocytes. As illustrated by Panel D, only compound **5b** is formed.

Example 43

Combination of Compounds

Combination Testing

[0277] Two or more test compounds were tested in combination with each other using an HCV genotype 1b HCV replicon harbored in Huh7 cells with a stable luciferase (LUC) reporter. Cells were 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 were plated in a 96-well plate at a density of 10⁴ cells per well in DMEM with 10% FBS. On the following day, the culture medium was 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 compound 3b with one or more test compounds serially diluted in the presence of 2% FBS and 0.5% DMSO. The cells were 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 were examined using a luciferase (LUC) based reporter as determined by the Bright-Glo Luciferase Assay (Promega, Madison, WI). Dose-response curves were determined for individual compounds and fixed ratio combinations of two or more test compounds.

[0278] The effects of test compound combinations were evaluated by two separate methods. In the Loewe additivity model, the experimental replicon data was 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.

[0279] The second method utilized for evaluating combination effects used 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: $\mu\text{M}^2\%$) 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.

[0280] The CI and synergy volume results for the combinations are provided in Table 13.

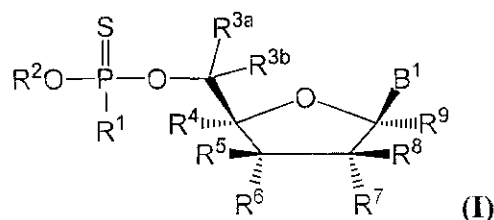
Table 13

Combination Compound	CI at EC ₅₀	Synergy Volume (μM ² %)
INX-189	0.42	65
PSI-938	0.73	27
PSI-6130	0.78	15
PSI-7851	1.1	0
GS-9190	0.92	79
Filibuvir	0.85	23
ANA-598	0.02	161
7008	0.01	127
VX-222	0.67	38
VX-950	0.06	76
ITMN-191	0.28	126
TMC-435	0.5	126
BMS-790052	0.64	26
Ribavirin	1	22
Pegylated Interferon	0.33	117
Consensus Interferon	1	31
Cyclosporin A	0.07	60
BILN-2061	0.7	31
HCV-796	0.42	31
IFN-Lambda 1	0.35	116
IFN-Lambda 2	0.49	34
IFN-Lambda 3	0.63	35

[0281] 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.

CLAIMS

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



wherein:

B^1 is an optionally substituted heterocyclic base or an optionally substituted heterocyclic base with a protected amino group;

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

R^2 is selected from an optionally substituted aryl or an optionally substituted heteroaryl;

R^{3a} and R^{3b} are independently selected from the group consisting of 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^{3a} and R^{3b} are taken together to form an optionally substituted C_{3-6} cycloalkyl;

R^4 is selected from the group consisting of hydrogen, azido, an optionally substituted C_{1-6} alkyl, and an optionally substituted C_{2-6} alkynyl;

R^5 is selected from the group consisting of hydrogen, halogen, azido, cyano, an optionally substituted C_{1-6} alkyl, $-OR^{10}$ and $-OC(=O)R^{11}$;

R^6 is selected from the group consisting of hydrogen, halogen, azido, cyano, an optionally substituted C_{1-6} alkyl, $-OR^{12}$ and $-OC(=O)R^{13}$;

R^7 is selected from the group consisting of hydrogen, halogen, azido, cyano, an optionally substituted C_{1-6} alkyl, $-OR^{14}$ and $-OC(=O)R^{15}$;

or R^6 and R^7 are both oxygen atoms and linked together by a carbonyl group;

R^8 is selected from the group consisting of hydrogen, halogen, azido, cyano, an optionally substituted C_{1-6} alkyl, $-OR^{16}$ and $-OC(=O)R^{17}$;

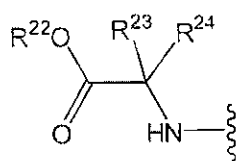
R^9 is selected from the group consisting of hydrogen, azido, cyano, an optionally substituted C_{1-6} alkyl and $-OR^{18}$;

R^{10} , R^{12} , R^{14} , R^{16} and R^{18} are independently selected from the group consisting of hydrogen and an optionally substituted C_{1-6} alkyl; and

R^{11} , R^{13} , R^{15} and R^{17} are independently an optionally substituted C_{1-6} alkyl or an optionally substituted C_{3-6} cycloalkyl;

with the proviso that when R^{3a} , R^{3b} , R^4 , R^5 , R^7 , R^8 and R^9 are all hydrogen, then R^6 is not azido.

2. The compound of Claim 1, wherein R^8 is hydrogen.
3. The compound of Claim 1 or 2, wherein R^2 is an optionally substituted aryl.
4. The compound of Claim 3, wherein the optionally substituted aryl is an optionally substituted phenyl.
5. The compound of Claim 3, wherein the optionally substituted aryl is an optionally substituted naphthyl.
6. The compound of Claim 1 or 2, wherein R^2 is an optionally substituted heteroaryl.
7. The compound of any one of Claims 1 to 6, wherein R^1 is an optionally substituted N-linked α -amino acid.
8. The compound of any one of Claims 1 to 6, wherein R^1 is an optionally substituted N-linked α -amino acid ester.
9. The compound of any one of Claims 1 to 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 esters thereof.
10. The compound of Claim 9, wherein R^1 is selected from the group consisting of alanine isopropyl ester, alanine cyclohexyl ester, alanine neopentyl ester, valine isopropyl ester, and leucine isopropyl ester.
11. The compound of Claim 10, wherein R^1 is alanine isopropyl ester.
12. The compound of any one of Claims 1 to 6, wherein R^1 has the structure

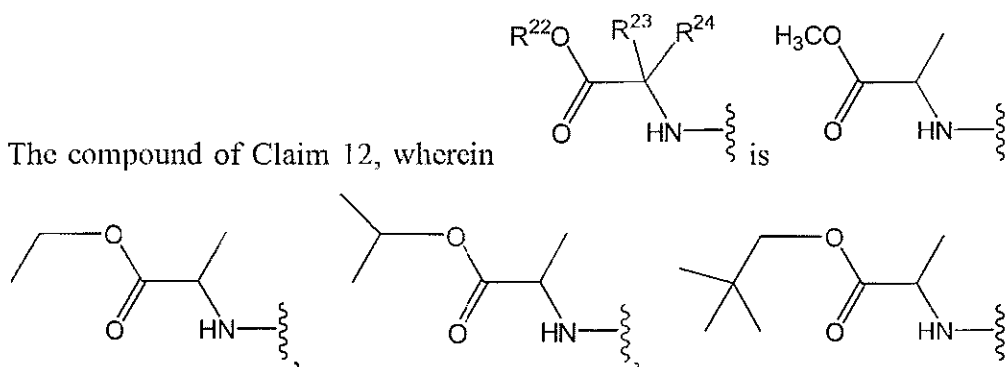


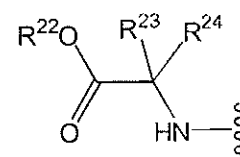
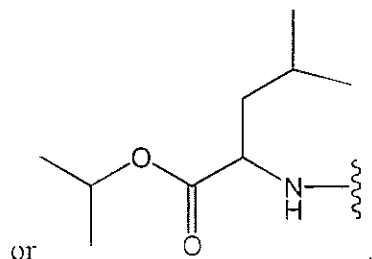
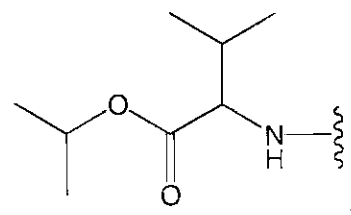
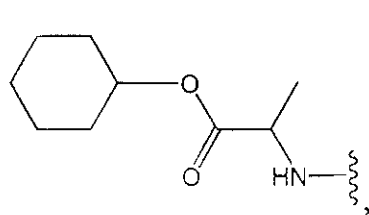
wherein R^{22} is selected from the group consisting of hydrogen, an optionally substituted C_{1-6} -alkyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted aryl, an optionally substituted aryl(C_{1-6}

alkyl) and an optionally substituted haloalkyl; R^{23} 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^{24} is hydrogen or an optionally substituted C_{1-4} -alkyl; or R^{23} and R^{24} are taken together to form an optionally substituted C_{3-6} cycloalkyl.

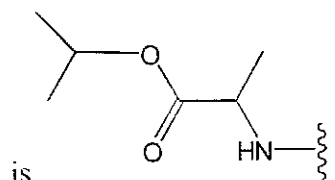
13. The compound of Claim 12, wherein R^{23} is an optionally substituted C_{1-6} -alkyl.
14. The compound of Claim 13, wherein the optionally substituted C_{1-6} -alkyl is methyl.
15. The compound of any one of Claims 12 to 14, wherein the optionally substituted C_{1-6} -alkyl is substituted with one or more substituents selected from the group consisting of N-amido, mercapto, alkylthio, an optionally substituted aryl, hydroxy, an optionally substituted heteroaryl, C-carboxy, and amino.
16. The compound of any one of Claims 12 to 15, wherein R^{24} is hydrogen.
17. The compound of any one of Claims 12 to 16, wherein R^{22} is an optionally substituted C_{1-6} alkyl.
18. The compound of any one of Claims 12 to 16, wherein R^{22} is an optionally substituted C_{3-6} cycloalkyl.

19. The compound of Claim 12, wherein

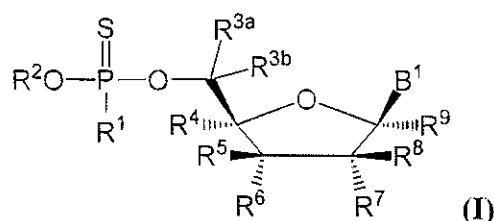




20. The compound of Claim 19, wherein



21. A compound of Formula (I), or a thio-monophosphate thereof, or a pharmaceutically acceptable salt of the foregoing:



wherein:

B^1 is an optionally substituted heterocyclic base or an optionally substituted heterocyclic base with a protected amino group;

R^1 is O^- or OH ;

R^2 is $R^{21}O-P(=O)(OR^{20})-O-P(=O)(OR^{19})_n$, wherein R^{19} , R^{20} and R^{21} are independently absent or hydrogen, and n is 0 or 1;

R^{3a} and R^{3b} are independently selected from the group consisting of 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 C₁₋₆ haloalkyl and aryl(C₁₋₆ alkyl); or R^{3a} and R^{3b} are taken together to form an optionally substituted C₃₋₆ cycloalkyl;

R⁴ is selected from the group consisting of hydrogen, azido, an optionally substituted C₁₋₆ alkyl, and an optionally substituted C₂₋₆ alkynyl;

R⁵ is selected from the group consisting of hydrogen, halogen, azido, cyano, an optionally substituted C₁₋₆ alkyl, -OR¹⁰ and -OC(=O)R¹¹;

R⁶ is selected from the group consisting of hydrogen, halogen, azido, cyano, an optionally substituted C₁₋₆ alkyl, -OR¹² and -OC(=O)R¹³;

R⁷ is selected from the group consisting of hydrogen, halogen, azido, cyano, an optionally substituted C₁₋₆ alkyl, -OR¹⁴ and -OC(=O)R¹⁵;

or R⁶ and R⁷ are both oxygen atoms and linked together by a carbonyl group;

R⁸ is selected from the group consisting of halogen, azido, cyano, an optionally substituted C₁₋₆ alkyl, and -OC(=O)R¹⁷;

R⁹ is selected from the group consisting of hydrogen, azido, cyano, an optionally substituted C₁₋₆ alkyl and -OR¹⁸;

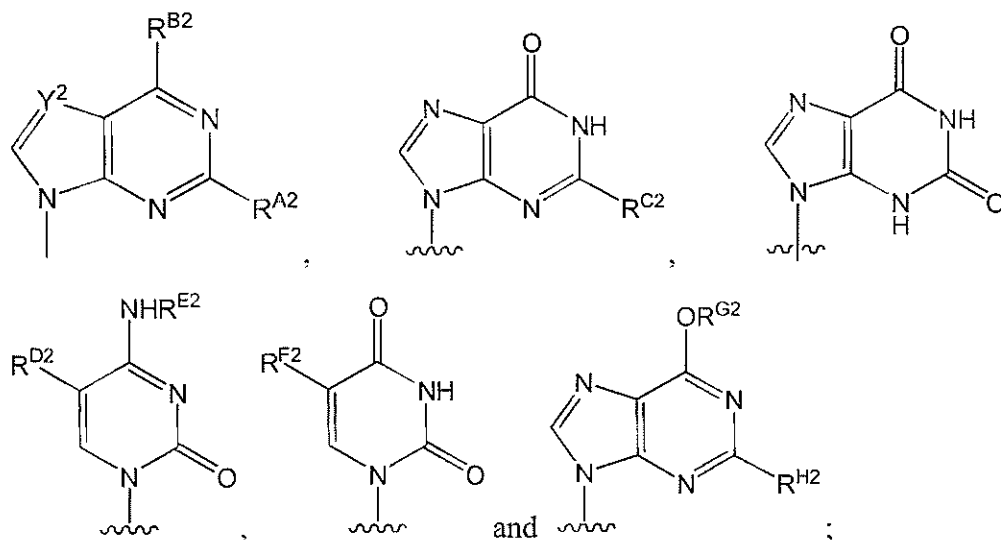
R¹⁰, R¹², R¹⁴, and R¹⁸ are independently selected from the group consisting of hydrogen and an optionally substituted C₁₋₆ alkyl; and

R¹¹, R¹³, R¹⁵ and R¹⁷ are independently an optionally substituted C₁₋₆ alkyl or an optionally substituted C₃₋₆ cycloalkyl;

with the proviso that when R^{3a}, R^{3b}, R⁴, R⁵, R⁷ and R⁹ are all hydrogen, then R⁶ is not azido.

22. The compound of Claim 21, wherein n is 1.
23. The compound of Claim 21, wherein n is 0.
24. The compound of any one of Claims 1 or 3 to 23, wherein R⁸ is an optionally substituted C₁₋₆ alkyl.
25. The compound of any one of Claims 1 or 3 to 23, wherein R⁸ is an unsubstituted C₁₋₆ alkyl.
26. The compound of Claim 25, wherein R⁸ is methyl.
27. The compound of any one of Claims 1 or 3 to 23, wherein R⁸ is halogen.
28. The compound of any one of Claims 1 to 27, wherein R^{3a} and R^{3b} are both hydrogen.

29. The compound of any one of Claims 1 to 27, wherein at least one of R^{3a} and R^{3b} is an optionally substituted C_{1-6} -alkyl; and the other of R^{3a} and R^{3b} is hydrogen.
30. The compound of any one of Claims 1 to 29, wherein R^4 is hydrogen.
31. The compound of any one of Claims 1 to 30, wherein R^5 is hydrogen.
32. The compound of any one of Claims 1 to 31, wherein R^6 is $-OR^{12}$.
33. The compound of Claim 32, wherein R^{12} is hydrogen.
34. The compound of Claim 32, wherein R^{12} is an optionally substituted C_{1-6} alkyl.
35. The compound of any one of Claims 1 to 31, wherein R^6 is $-OC(=O)R^{13}$.
36. The compound of any one of Claims 1 to 35, wherein R^7 is $-OR^{14}$.
37. The compound of Claim 36, wherein R^{14} is hydrogen.
38. The compound of Claim 36, wherein R^{14} is an optionally substituted C_{1-6} alkyl.
39. The compound of any one of Claims 1 to 35, wherein R^7 is $-OC(=O)R^{15}$.
40. The compound of any one of Claims 1 to 35, wherein R^7 is halogen.
41. The compound of any one of Claims 1 to 31, wherein R^6 and R^7 are both oxygen atoms and linked together by a carbonyl group.
42. The compound of any one of Claims 1 to 41, wherein R^9 is hydrogen.
43. The compound of any one of Claims 1 to 42, wherein B^1 is selected from the group consisting of:



wherein:

R^{A2} is selected from the group consisting of hydrogen, halogen and NHR^{J2} , wherein R^{J2} is selected from the group consisting of hydrogen, $-C(=O)R^{K2}$ and $-C(=O)OR^{L2}$;

R^{B2} is halogen or NHR^{W2} , wherein R^{W2} is selected from the group consisting of 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} is hydrogen or NHR^{O2} , wherein R^{O2} is selected from the group consisting of hydrogen, $-C(=O)R^{P2}$ and $-C(=O)OR^{Q2}$;

R^{D2} is selected from the group consisting of 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} is selected from the group consisting of hydrogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{3-8} cycloalkyl, $-C(=O)R^{R2}$ and $-C(=O)OR^{S2}$;

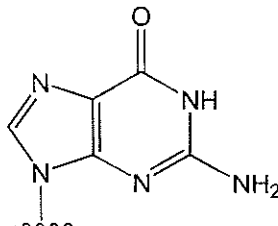
R^{F2} is selected from the group consisting of hydrogen, halogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl and an optionally substituted C_{2-6} alkynyl;

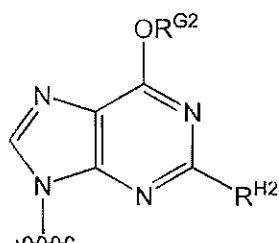
Y^2 is N or CR^{I2} , wherein R^{I2} is selected from the group consisting of hydrogen, halogen, an optionally substituted C_{1-6} -alkyl, an optionally substituted C_{2-6} -alkenyl and an optionally substituted C_{2-6} -alkynyl;

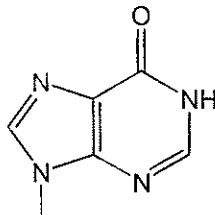
R^{G2} is an optionally substituted C_{1-6} alkyl;

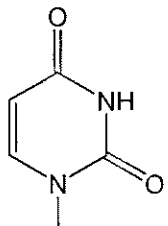
R^{H2} is hydrogen or NHR^{T2} , wherein R^{T2} is independently selected from the group consisting of hydrogen, $-C(=O)R^{U2}$ and $-C(=O)OR^{V2}$, and

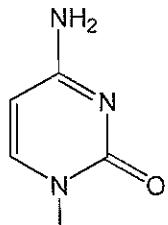
R^{K2} , R^{L2} , R^{M2} , R^{N2} , R^{P2} , R^{Q2} , R^{R2} , R^{S2} , R^{U2} and R^{V2} are independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkenyl, C_{3-6} cycloalkynyl, C_{6-10} aryl, heteroaryl, heteroalicycyl, aryl(C_{1-6} alkyl), heteroaryl(C_{1-6} alkyl) and heteroalicycyl(C_{1-6} alkyl).

44. The compound of Claim 43, wherein B¹ is  or

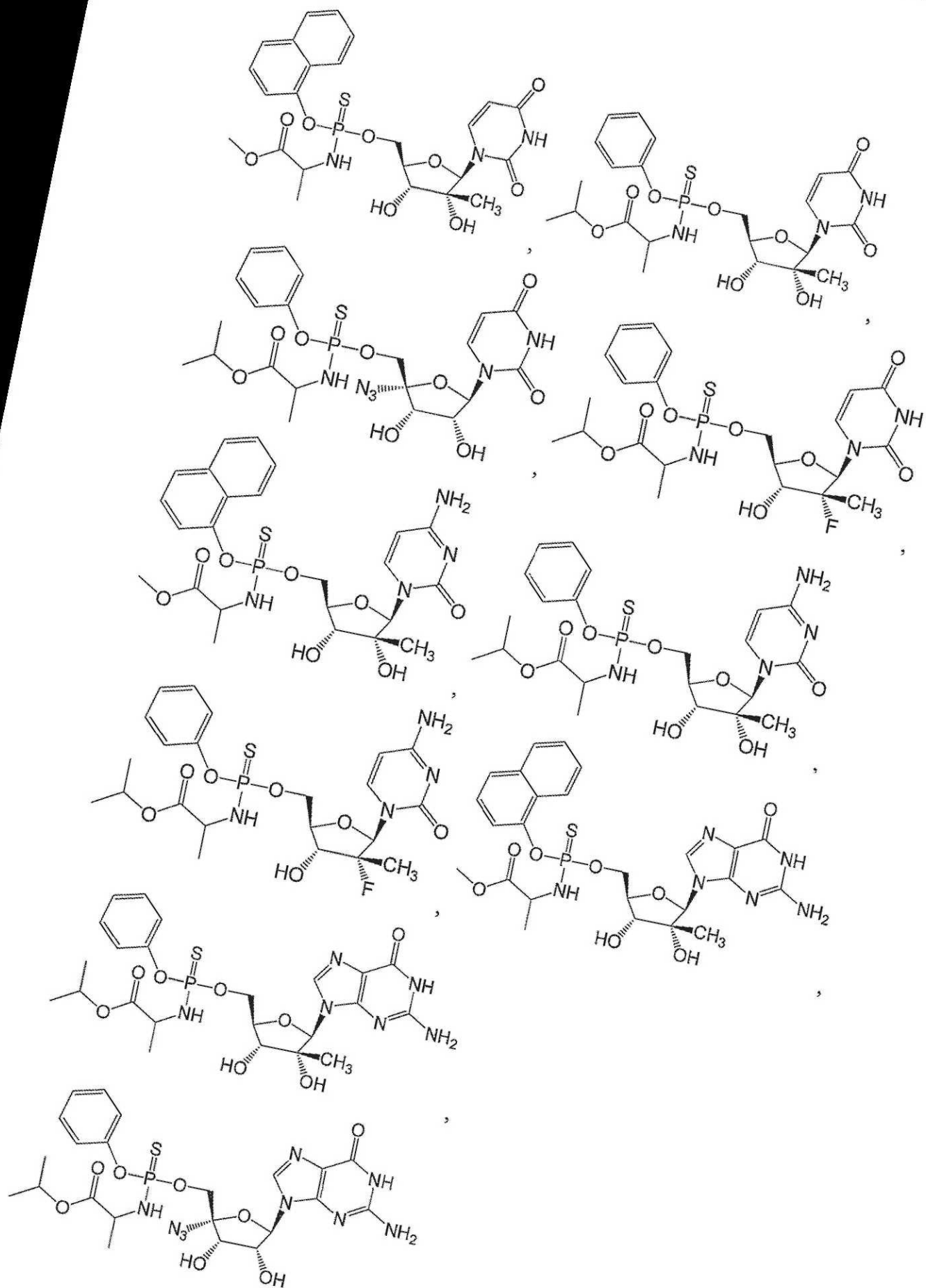


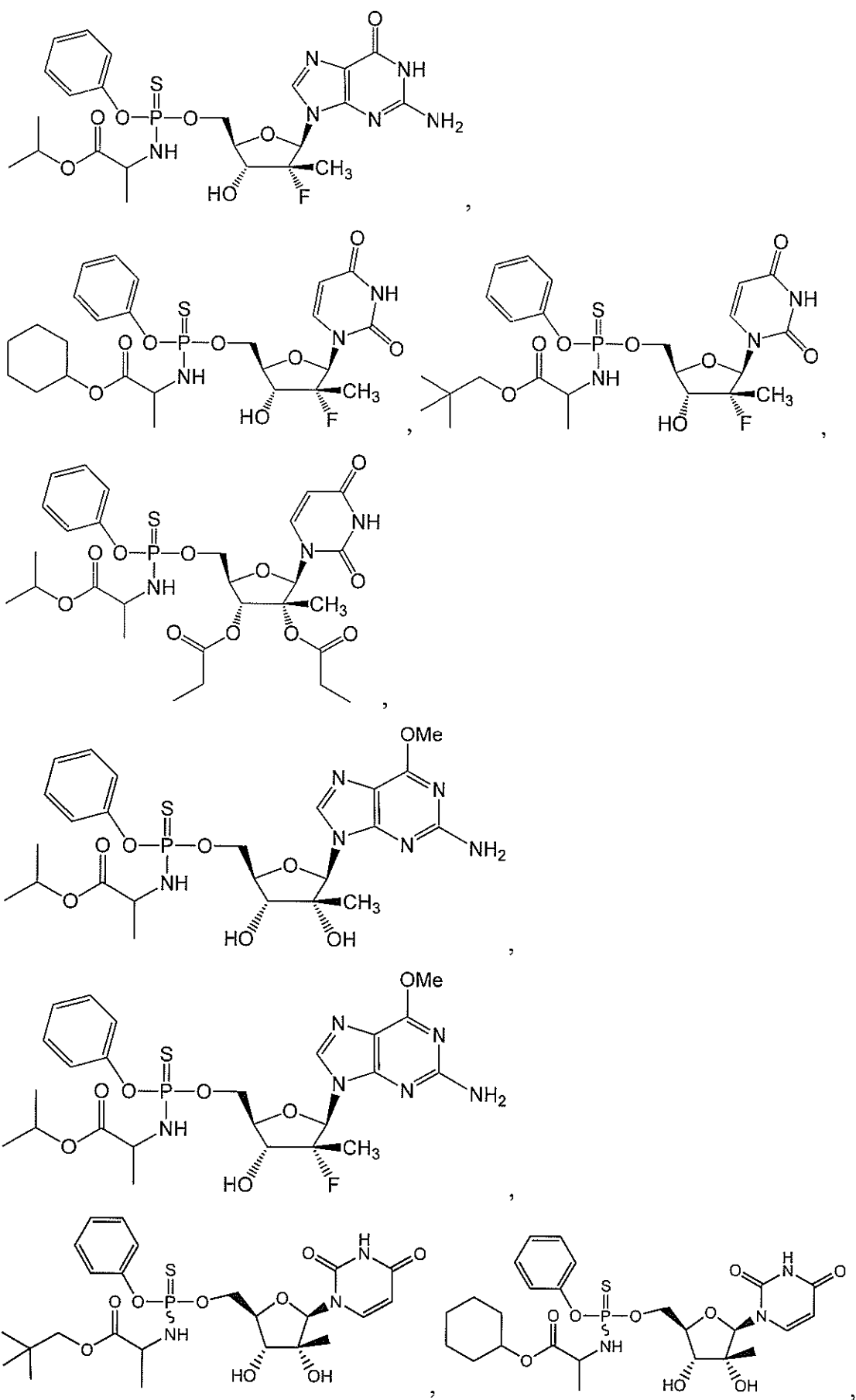
45. The compound of Claim 43, wherein B¹ is .

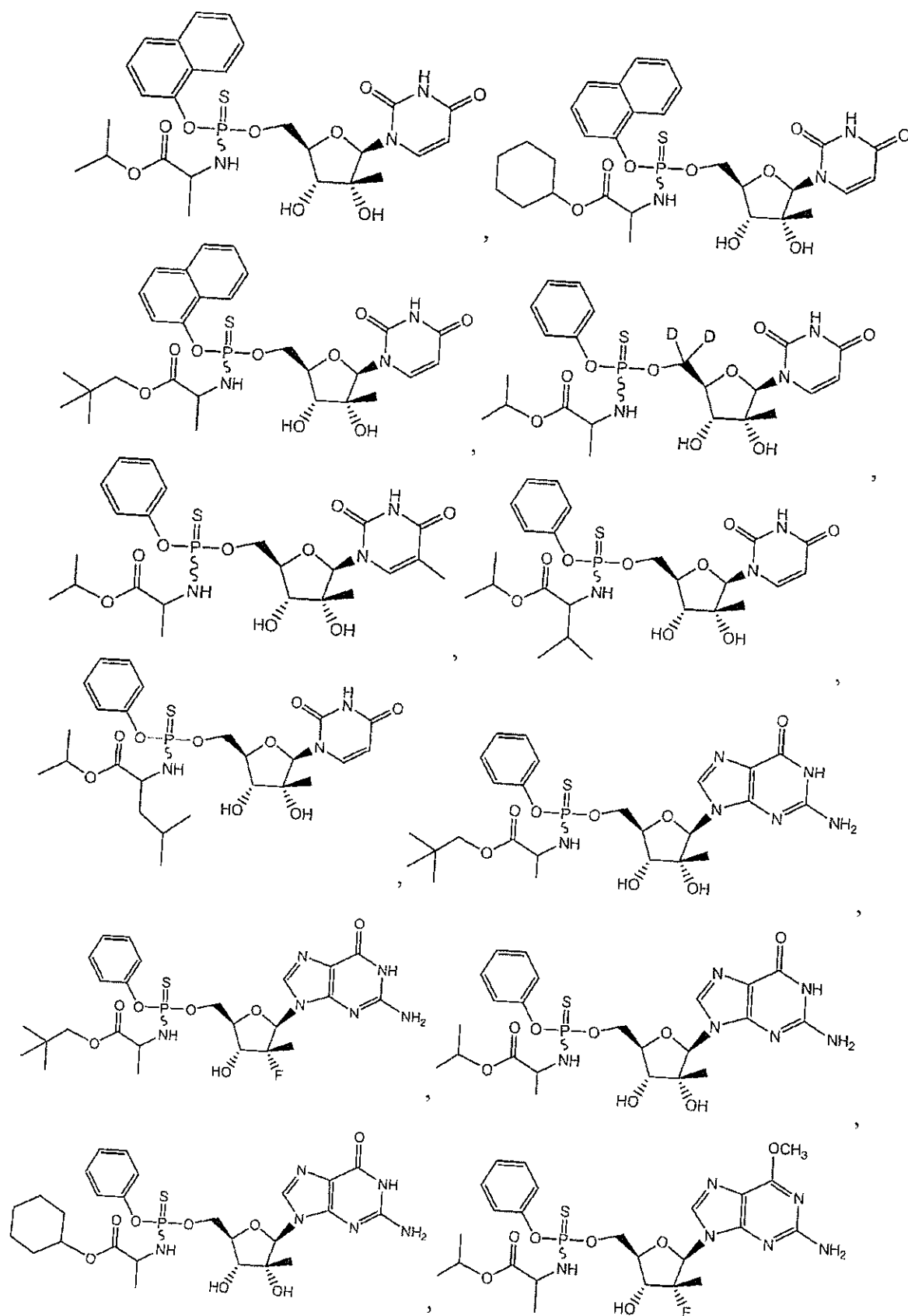
46. The compound of Claim 43, wherein B¹ is .

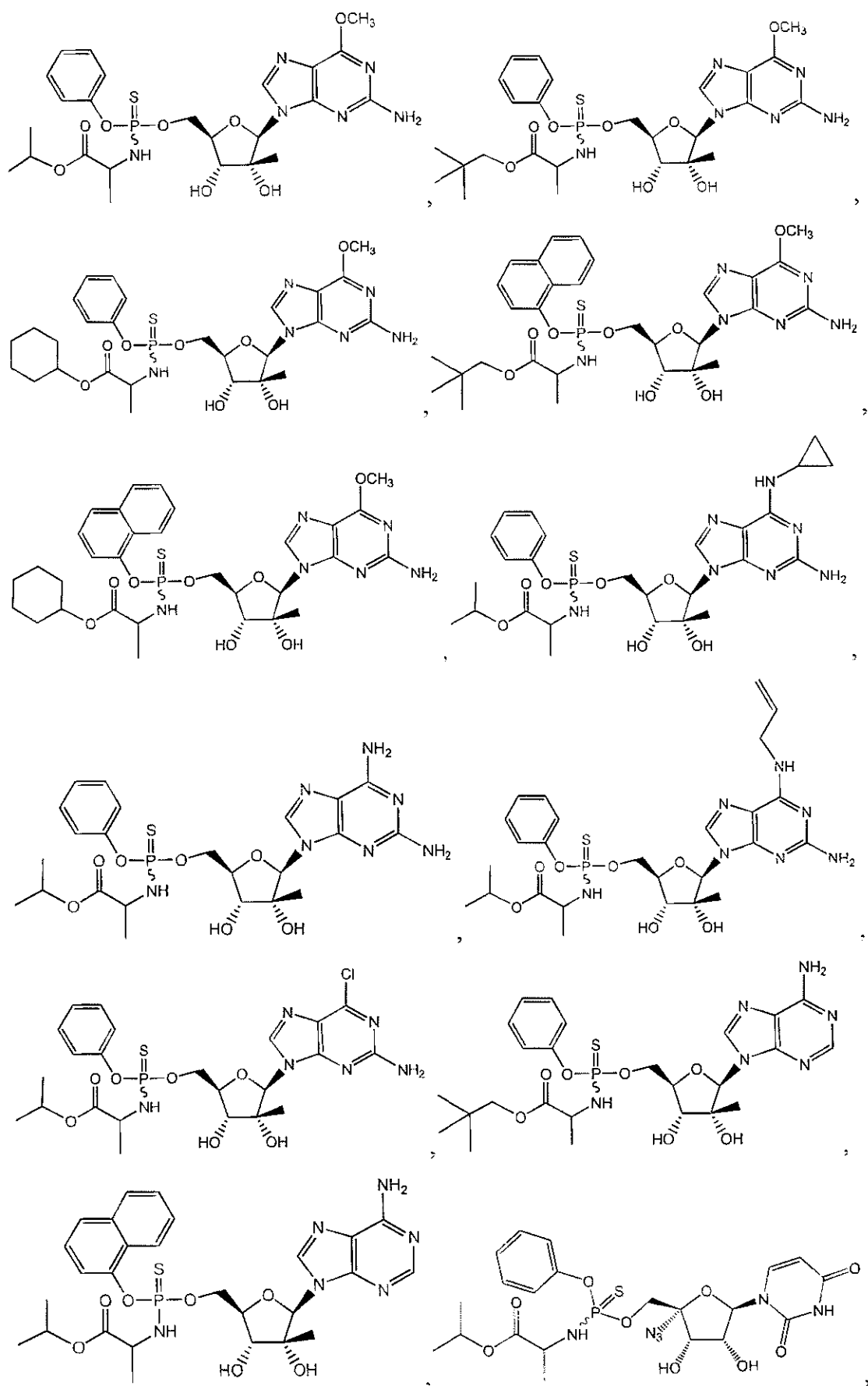
47. The compound of Claim 43, wherein B¹ is .

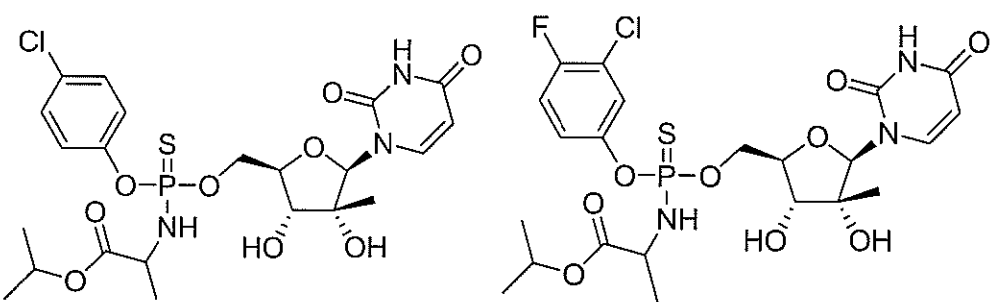
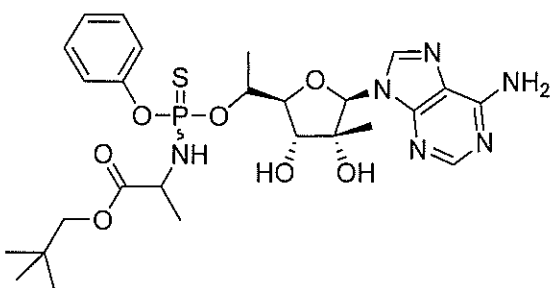
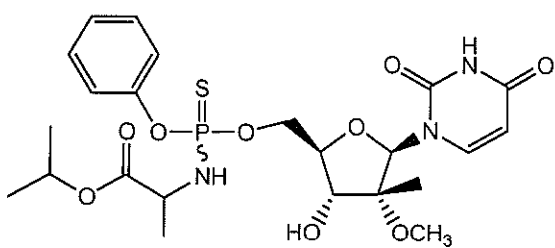
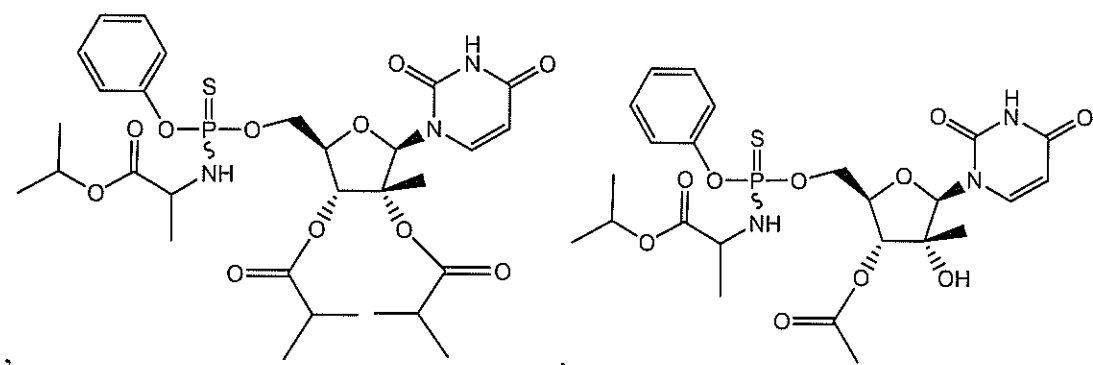
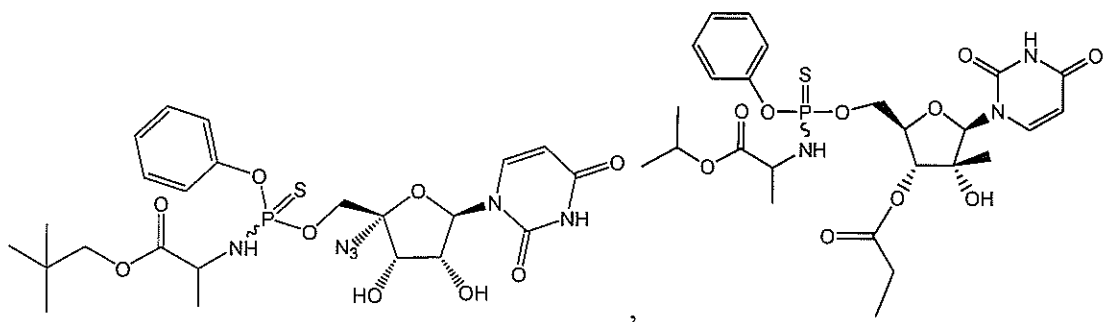
48. The compound of Claim 1, wherein the compound of Formula (I) is selected from the group consisting of:

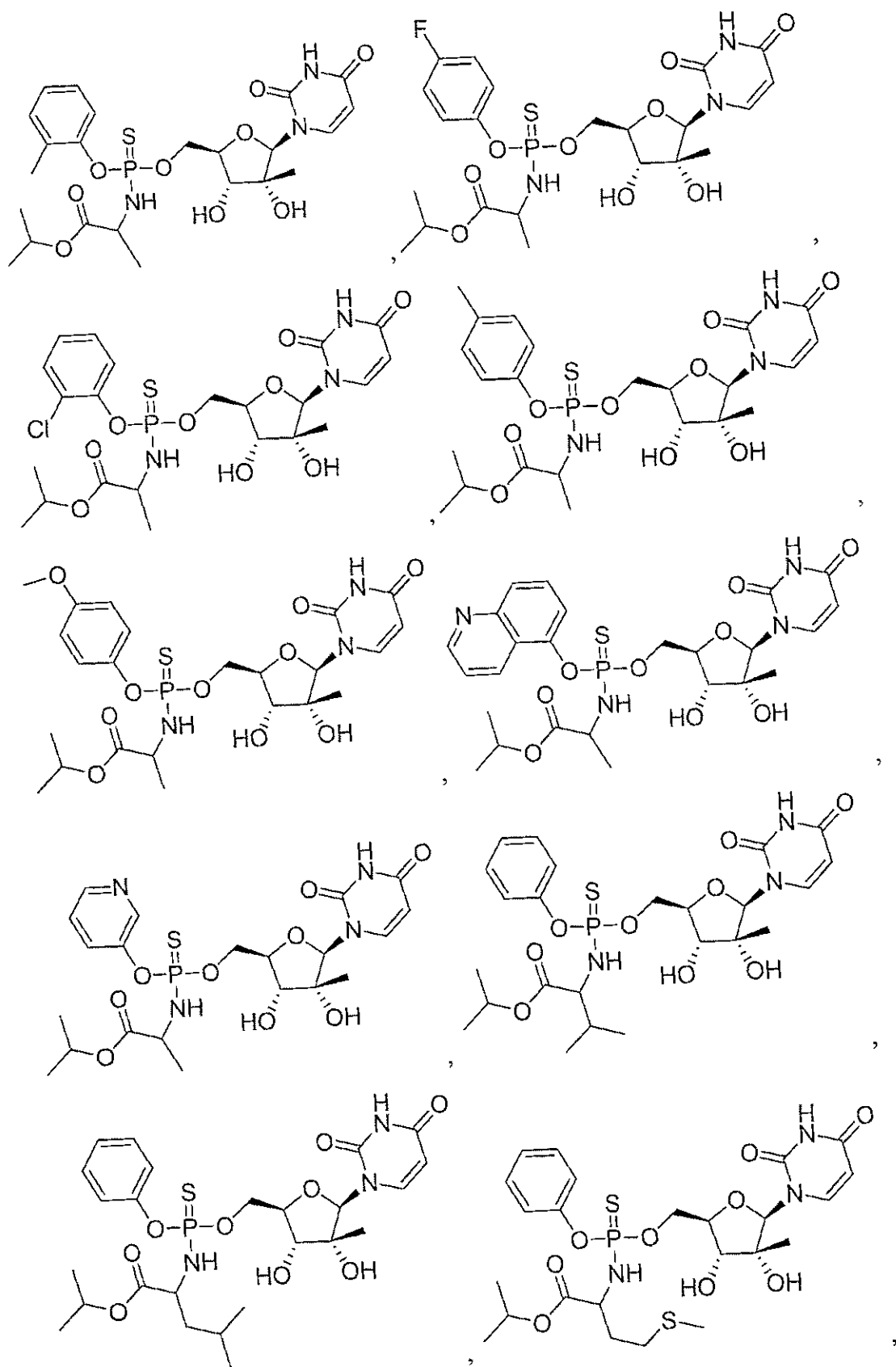


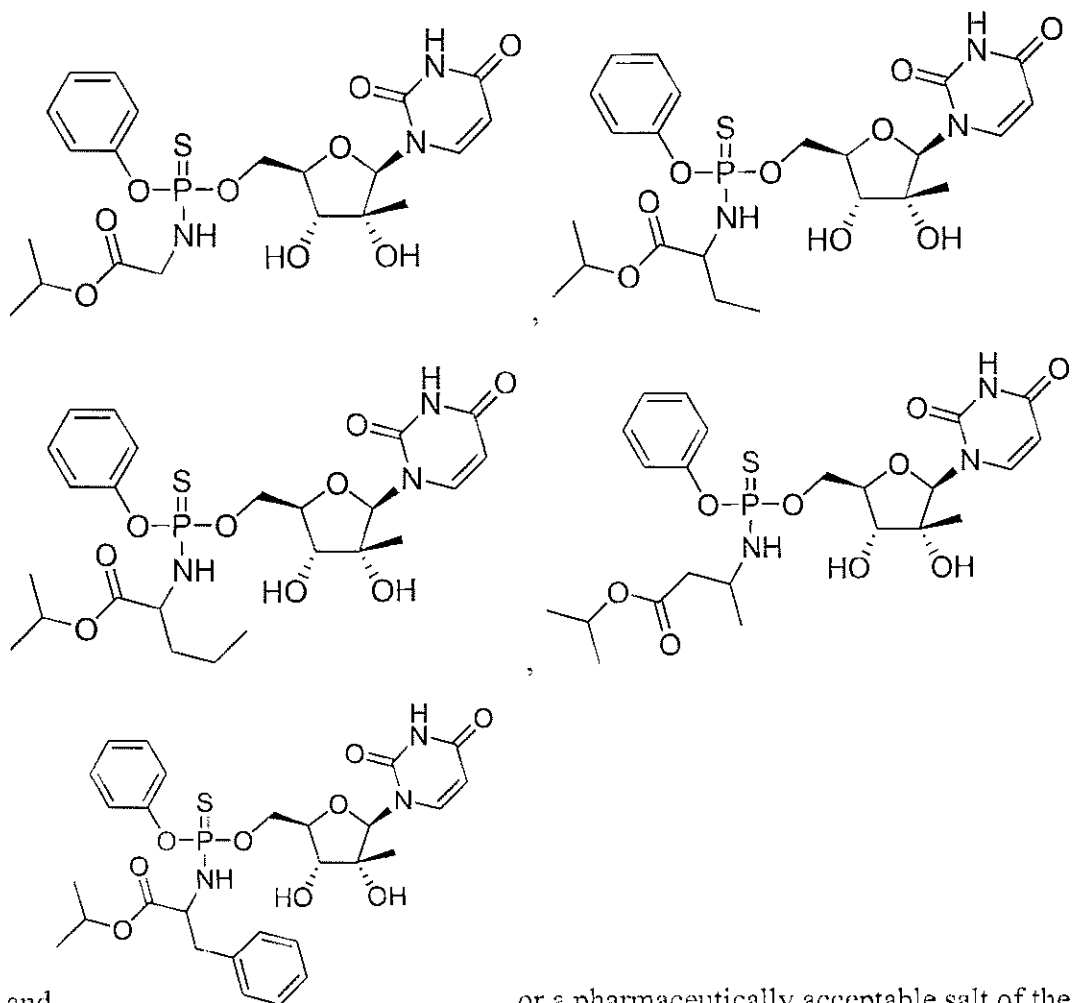






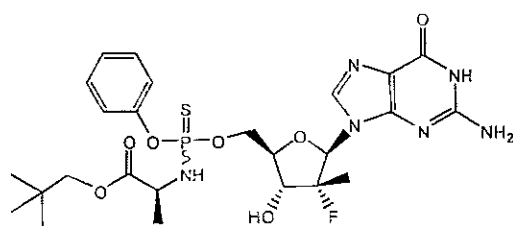






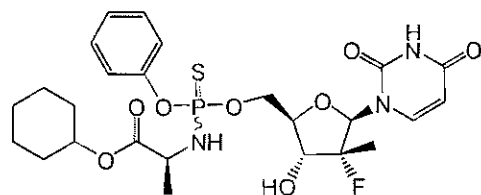
and , or a pharmaceutically acceptable salt of the foregoing.

49. The compound of Claim 1, wherein the compound of Formula (I) is



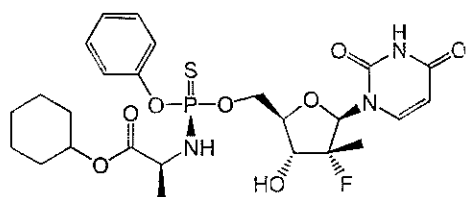
, or a pharmaceutically acceptable salt thereof.

50. The compound of Claim 1, wherein the compound of Formula (I) is



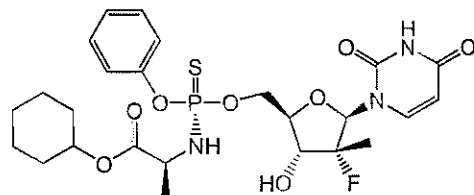
, or a pharmaceutically acceptable salt thereof.

51. The compound of Claim 50, wherein the compound of Formula (I) is



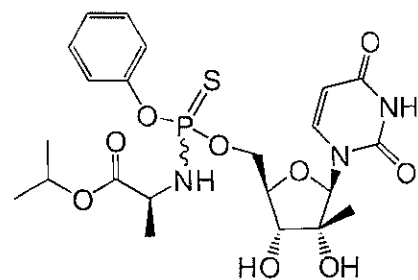
, or a pharmaceutically acceptable salt thereof.

52. The compound of Claim 50, wherein the compound of Formula (I) is



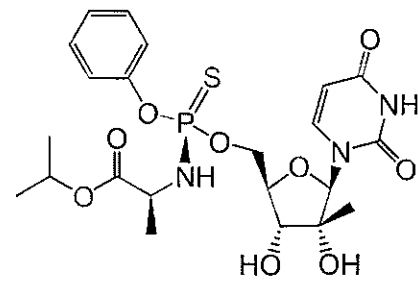
, or a pharmaceutically acceptable salt thereof.

53. The compound of Claim 1, wherein the compound of Formula (I) is



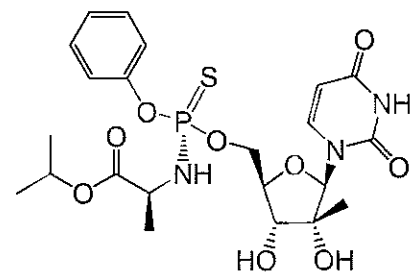
, or a pharmaceutically acceptable salt thereof.

54. The compound of Claim 53, wherein the compound of Formula (I) is



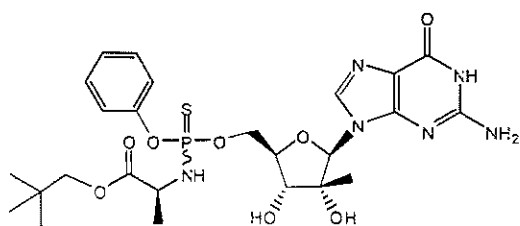
, or a pharmaceutically acceptable salt thereof.

55. The compound of Claim 53, wherein the compound of Formula (I) is



, or a pharmaceutically acceptable salt thereof.

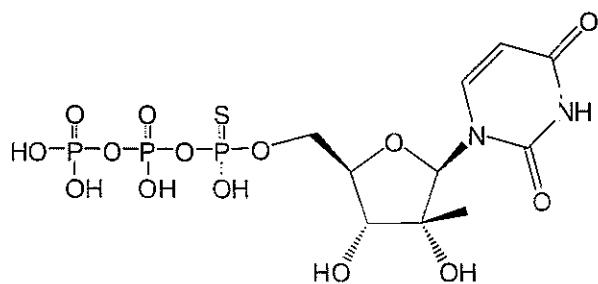
56. The compound of Claim 1, wherein the compound of Formula (I) is



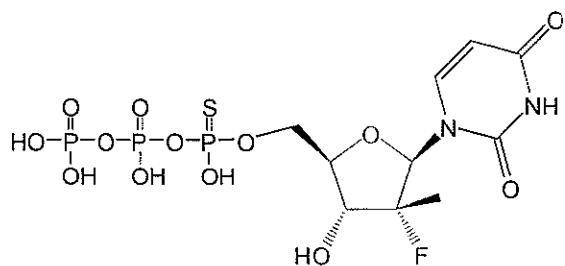
, or a pharmaceutically acceptable salt

thereof.

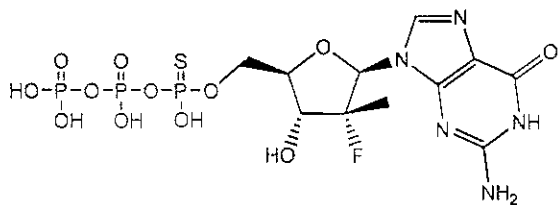
57. The compound of Claim 21, wherein the compound of Formula (I) is selected from the group consisting of:



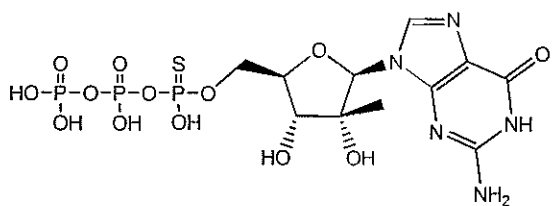
,



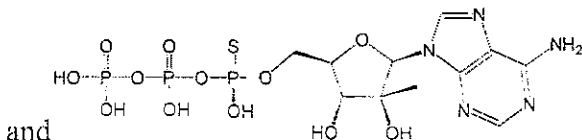
,



,



,

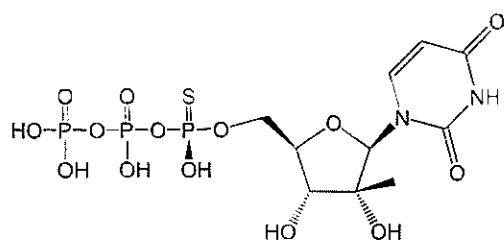


and

, or a pharmaceutically acceptable salt of

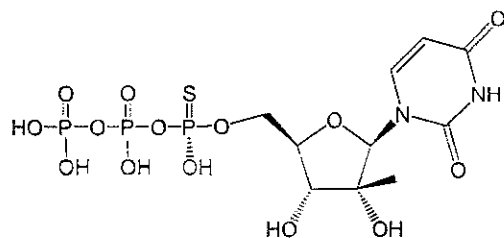
the foregoing.

58. The compound of Claim 57, wherein the compound of Formula (I) is:



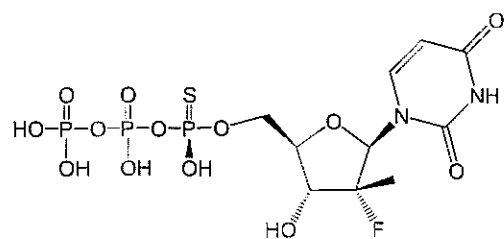
, or a pharmaceutically acceptable salt thereof.

59. The compound of Claim 57, wherein the compound of Formula (I) is:



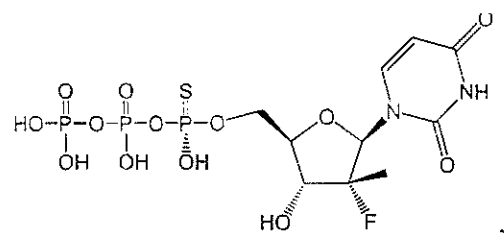
, or a pharmaceutically acceptable salt thereof.

60. The compound of Claim 57, wherein the compound of Formula (I) is:



, or a pharmaceutically acceptable salt thereof.

61. The compound of Claim 57, wherein the compound of Formula (I) is:



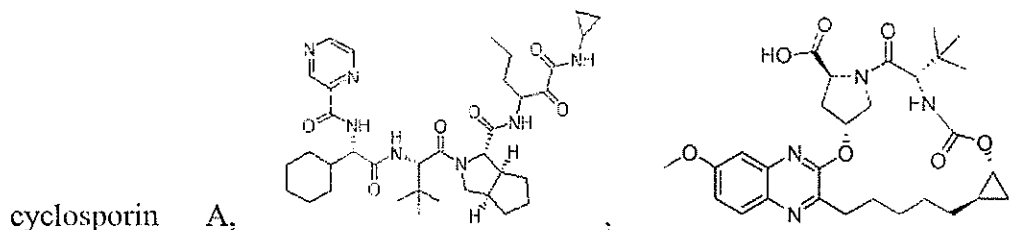
, or a pharmaceutically acceptable salt thereof.

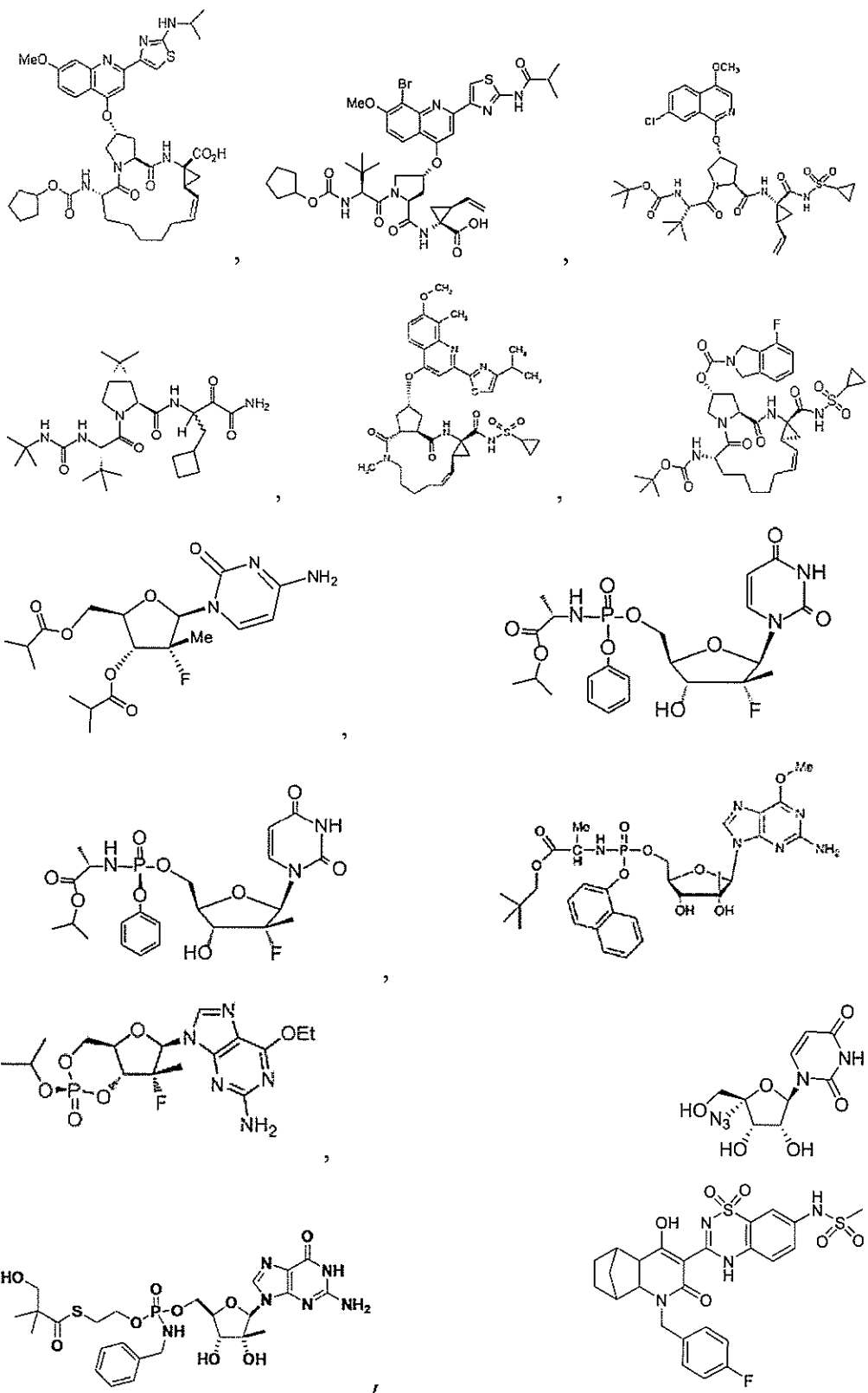
62. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any one of Claims 1 to 61, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, excipient or combination thereof.

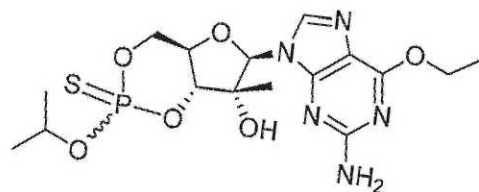
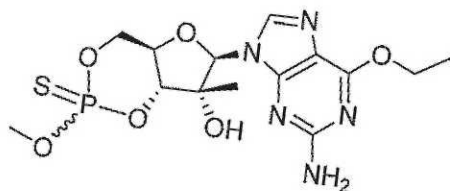
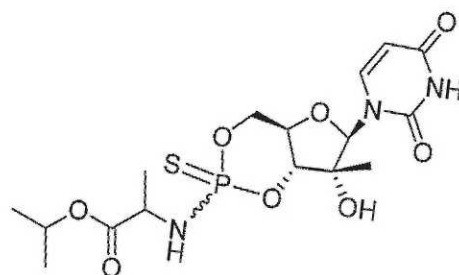
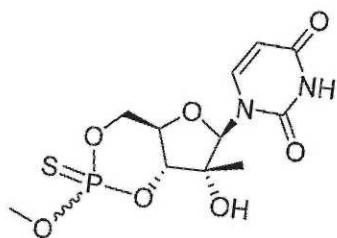
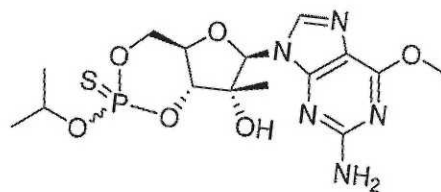
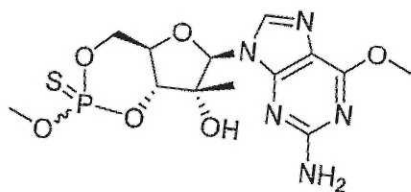
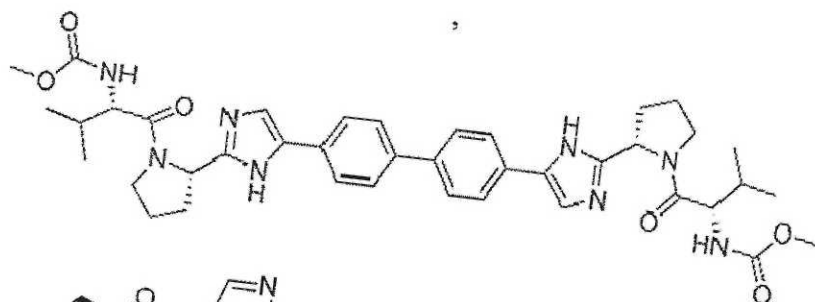
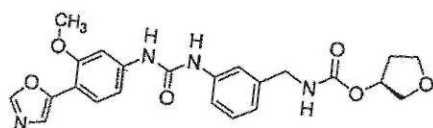
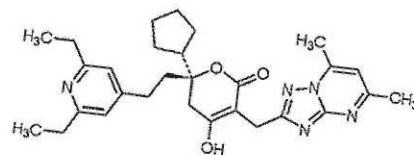
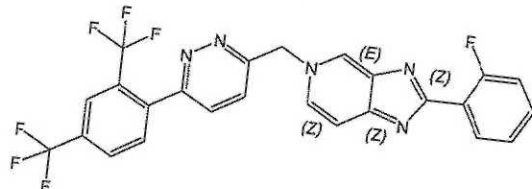
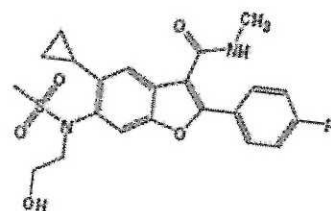
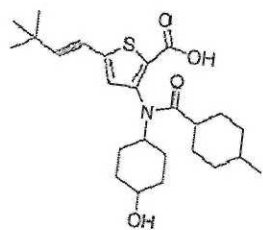
63. Use of a compound of any one of Claims 1 to 61, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Claim 62 for preparing a medicament for ameliorating or treating an HCV infection.

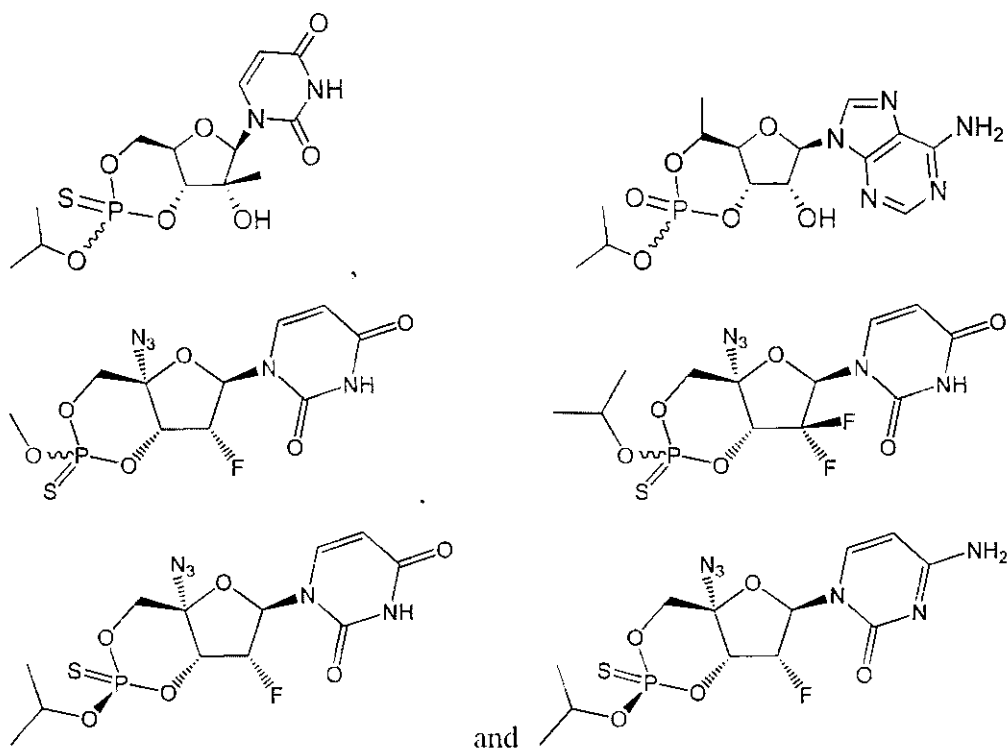
64. Use of a compound of any one of Claims 1 to 61, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Claim 62 for preparing a medicament for inhibiting NS5B polymerase activity of hepatitis C virus.

65. Use of a compound of any one of Claims 1 to 61, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Claim 62 for preparing a medicament for inhibiting replication of a hepatitis C virus.
66. Use of a compound of any one of Claims 1 to 61, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Claim 62 for preparing a medicament for contacting a cell infected with a hepatitis C virus, whereby ameliorating or treating the hepatitis C viral infection.
67. Use of a compound of any one of Claims 1 to 61, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Claim 62 in the preparation of a medicament for ameliorating or treating a viral infection, wherein the medicament is manufactured for use in combination with 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 (BB) and a compound of Formula (DD), or a pharmaceutically acceptable salt any of the aforementioned compounds.
68. Use of a compound of any one of Claims 1 to 61, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Claim 62 in the preparation of a medicament for contacting a cell infected with a viral infection, wherein the medicament is manufactured for use in combination with 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 (BB) and a compound of Formula (DD), or a pharmaceutically acceptable salt any of the aforementioned compounds.
69. The use of Claim 67 or 68, wherein the one or more agents are selected from the group consisting of pegylated interferon alpha, pegylated interferon-alpha-2a, pegylated interferon-alpha-2b, interferon alfacon-1, pegylated interferon lambda, interferon lambda 1, interferon lambda 2, consensus interferon,



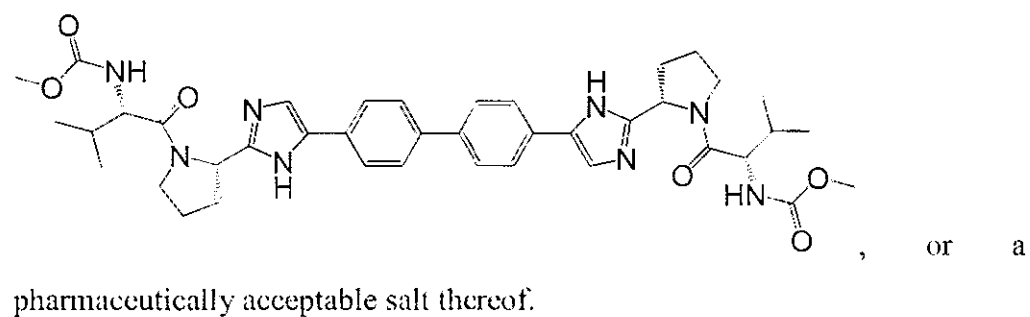
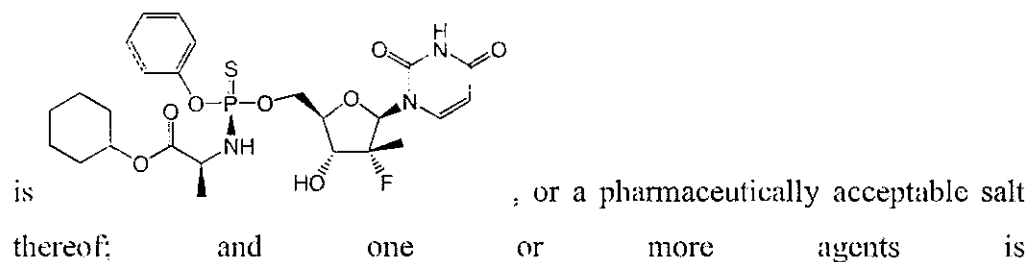




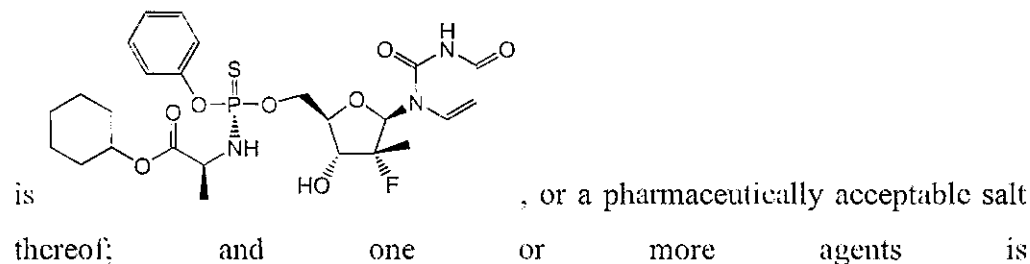


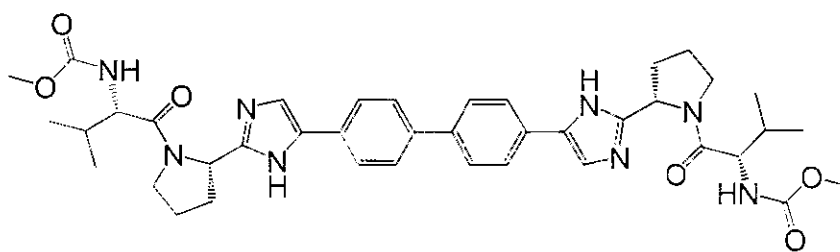
or a pharmaceutically acceptable salt of any of the aforementioned compounds.

70. The use of any one of Claims 67 to 68, wherein the compound of Formula (I)



71. The use of any one of Claims 67 to 68, wherein the compound of Formula (I)

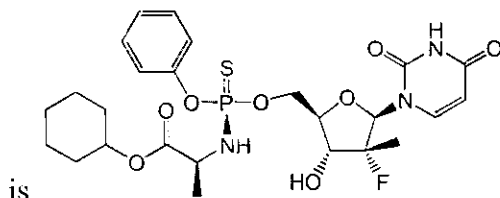




, or a

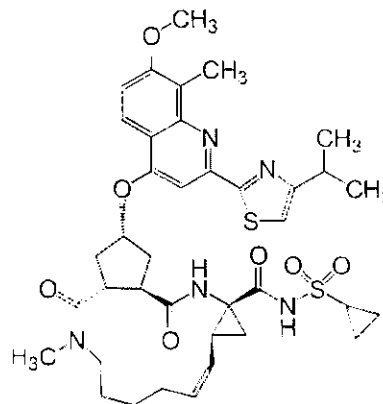
pharmaceutically acceptable salt thereof.

72. The use of any one of Claims 67 to 68, wherein the compound of Formula (I)



is

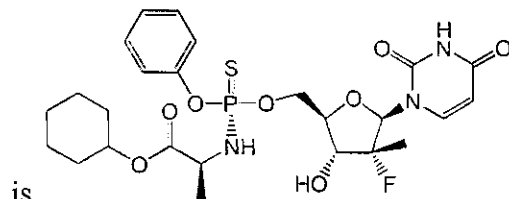
, or a pharmaceutically acceptable salt



thereof; and one or more agents is pharmaceutically acceptable salt thereof.

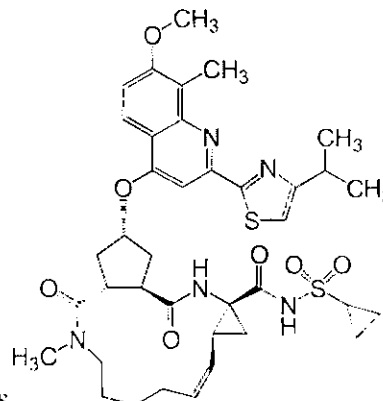
, or a

73. The use of any one of Claims 67 to 68, wherein the compound of Formula (I)



is

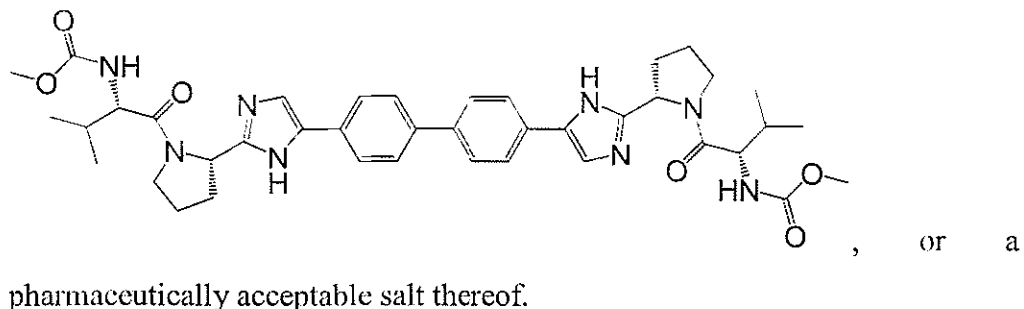
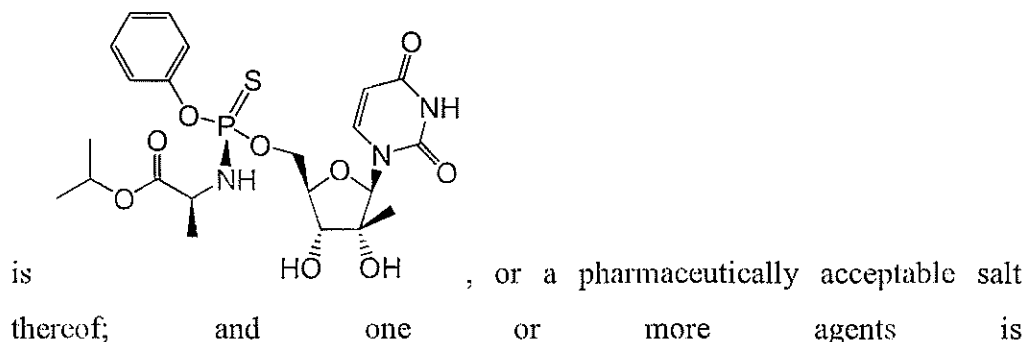
, or a pharmaceutically acceptable salt



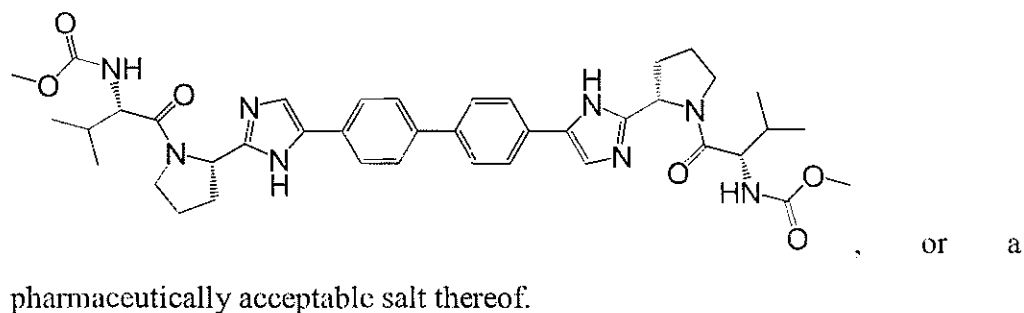
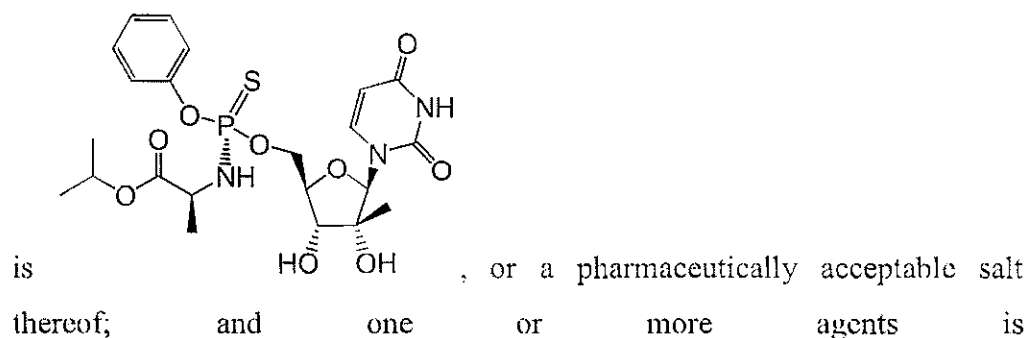
thereof; and one or more agents is pharmaceutically acceptable salt thereof.

, or a

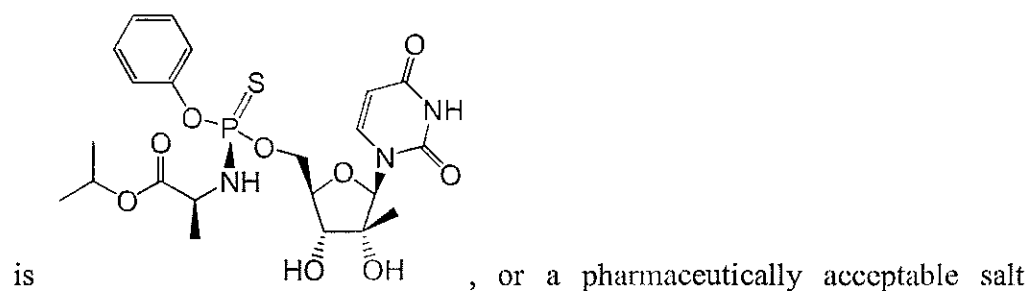
74. The use of any one of Claims 67 to 68, wherein the compound of Formula (I)

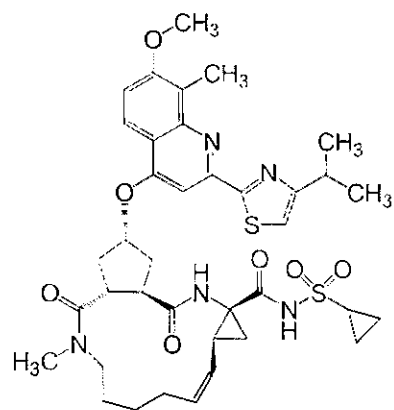


75. The use of any one of Claims 67 to 68, wherein the compound of Formula (I)



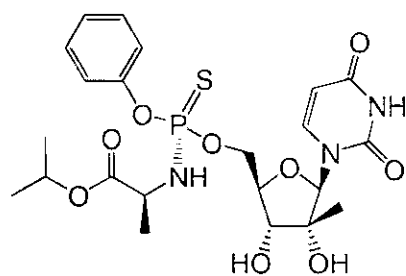
76. The use of any one of Claims 67 to 68, wherein the compound of Formula (I)



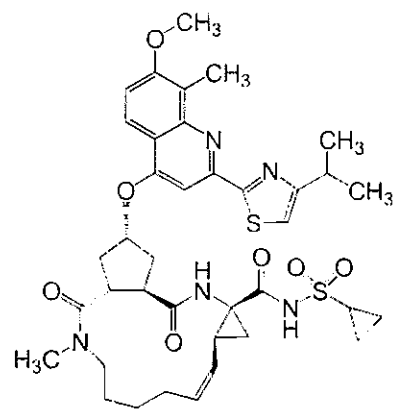


thereof; and one or more agents is , or a pharmaceutically acceptable salt thereof.

77. The use of any one of Claims 67 to 68, wherein the compound of Formula (I)



is , or a pharmaceutically acceptable salt



thereof; and one or more agents is , or a pharmaceutically acceptable salt thereof.