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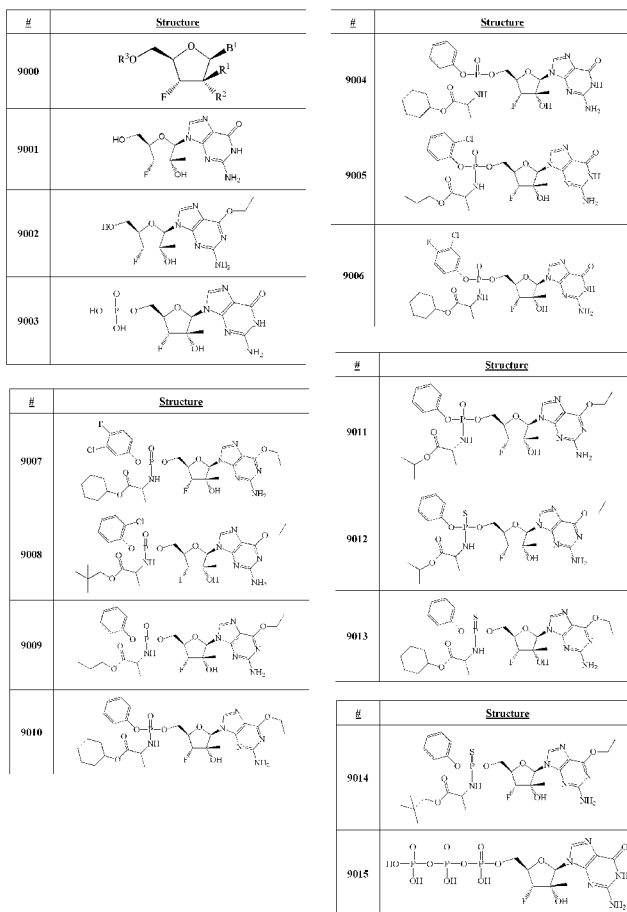
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[Continued on next page]

(54) Title: SUBSTITUTED NUCLEOSIDES, NUCLEOTIDES AND ANALOGS THEREOF

Figure 9: Compounds of Formula (I)



(57) Abstract: Disclosed herein are nucleotide analogs, methods of synthesizing nucleotide analogs and methods of treating diseases and/or conditions such as a HCV infection with one or more nucleotide analogs.



MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

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SUBSTITUTED NUCLEOSIDES, NUCLEOTIDES AND ANALOGS THEREOF**INCORPORATION BY REFERENCE TO ANY PRIORITY APPLICATIONS**

[0001] Any and all applications for which a foreign or domestic priority claim is identified in the Application Data Sheet as filed with the present application, are hereby incorporated by reference under 37 CFR 1.57.

REFERENCE TO SEQUENCE LISTING

[0002] The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled SEQLISTING_067.TXT, created December 19, 2013, which is 728 bytes in size. The information in the electronic format of the Sequence Listing is incorporated herein by reference in its entirety.

BACKGROUNDField

[0003] The present application relates to the fields of chemistry, biochemistry and medicine. More particularly, disclosed herein are 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 nucleotide analog, alone or in combination therapy with one or more other agents.

Description

[0004] 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. 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

[0005] Some embodiments disclosed herein relate to a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

[0006] Some embodiments disclosed herein relate to a method of ameliorating and/or treating a hepatitis C viral (HCV) infection that can include administering to a subject identified as suffering from the HCV 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 HCV infection. Still other embodiments described herein relate to one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, that can be used for ameliorating and/or treating a HCV infection.

[0007] Some embodiments disclosed herein relate to a method of ameliorating and/or treating a HCV infection that can include contacting a cell infected with the hepatitis C 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 HCV infection that can include contacting a cell infected with the hepatitis C virus with an effective amount of said compound(s). Still other embodiments described herein relate to one or more compounds described herein, or a pharmaceutically acceptable salt of one or more compounds described herein, or a pharmaceutical composition that includes one or more compounds described herein, or a pharmaceutically acceptable salt thereof, that can be used for ameliorating and/or treating a HCV infection by contacting a cell infected with the hepatitis C virus with an effective amount of said compound(s).

[0008] Some embodiments disclosed herein relate to a method of inhibiting replication of a hepatitis C virus that can include contacting a cell infected with the hepatitis C 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 hepatitis C virus that can include contacting a cell infected with the hepatitis C virus with an effective amount of said compound(s). Still other embodiments described herein relate to one or more compounds described herein, or a pharmaceutically acceptable salt of one or more compounds described herein, or a pharmaceutical composition that includes one or more compounds described herein, or a pharmaceutically acceptable salt thereof, that can be used for inhibiting replication of a hepatitis C virus by contacting a cell infected with the hepatitis C virus with an effective amount of said compound(s).

[0009] Some embodiments disclosed herein relate to a method of ameliorating and/or treating a HCV infection that can include administering to a subject identified as suffering from the HCV 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, 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 compound of Formula (BB) and a compound of Formula (CC), or a pharmaceutically acceptable salt of any of the foregoing. Some embodiments disclosed herein relate to a method of ameliorating and/or treating a HCV infection that can include contacting a cell infected with the HCV 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 compound of Formula (BB) and a compound of Formula (CC), or a pharmaceutically acceptable salt of any of the foregoing. Some embodiments disclosed herein relate to a method of inhibiting replication of a hepatitis C virus that can include administering to a subject identified as suffering from a HCV infection 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 compound of Formula

(BB) and a compound of Formula (CC), or a pharmaceutically acceptable salt of any of the foregoing. In some embodiments, the agent can be a compound, or a pharmaceutically acceptable salt thereof, selected from Compound 1001-1016, 2001-2012, 3001-3014, 4001-4012, 5001-5012, 6001-6078, 7000-7027 and 8000-8016, or a pharmaceutical composition that includes one or more of the aforementioned compounds, or a pharmaceutically acceptable salt of the foregoing. 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 compound of Formula (BB) and a compound of Formula (CC), or a pharmaceutically acceptable salt of any of the foregoing.

BRIEF DESCRIPTION OF THE DRAWINGS

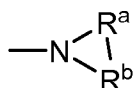
- [0010]** Figure 1 shows example HCV protease inhibitors.
- [0011]** Figure 2 shows example nucleoside HCV polymerase inhibitors.
- [0012]** Figure 3 shows example non-nucleoside HCV polymerase inhibitors.
- [0013]** Figure 4 shows example NS5A inhibitors.
- [0014]** Figure 5 shows example other antivirals.
- [0015]** Figure 6 shows example compounds of Formula (CC) and alpha-thiotriphosphates thereof, wherein Formula (CC) and alpha-thiotriphosphates thereof are described herein.
- [0016]** Figure 7 shows example compounds of Formula (AA), wherein Formula (AA) is described herein.
- [0017]** Figure 8 shows example compounds of Formula (BB) , wherein Formula (BB) is described herein.
- [0018]** Figure 9 shows example compounds of Formula (I) , wherein Formula (I) is described herein.
- [0019]** Figure 10 shows the gels from the assessment of incorporation of several compounds with a guanine base by the human mitochondrial RNA polymerase.
- [0020]** Figure 11 shows the results of the inhibition of mitochondrial protein synthesis assays.

DETAILED DESCRIPTION

Definitions

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

[0022] As used herein, any "R" group(s) such as, without limitation, R¹, R², R³, R^{4A}, R^{4B}, R⁵, R⁶, R⁷, R⁸, R^{9A}, R^{9B}, R^{9C}, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, R²², R^{A1}, R^{A2}, R^{A3} and R^{A4} represent substituents that can be attached to the indicated atom. An R group may be substituted or unsubstituted. If two "R" groups are described as being "taken together" the R groups and the atoms they are attached to can form a cycloalkyl, cycloalkenyl, aryl, heteroaryl or heterocycle. For example, without limitation, if R^a and R^b of an NR^aR^b group are indicated to be "taken together," it means that they are covalently bonded to one another to form a ring:



In addition, if two "R" groups are described as being "taken together" with the atom(s) to which they are attached to form a ring as an alternative, the R groups are not limited to the variables or substituents defined previously.

[0023] Whenever a group is described as being "optionally substituted" that group may be unsubstituted or substituted with one or more of the indicated substituents. Likewise, when a group is described as being "unsubstituted or substituted" if substituted, the substituent(s) may be selected from one or more the indicated substituents. If no substituents are indicated, it is meant that the indicated "optionally substituted" or "substituted" group may be substituted with one or more group(s) individually and independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heteroalicycyl, aralkyl, heteroaralkyl, (heteroalicycyl)alkyl, hydroxy, 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, 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.

[0024] As used herein, “C_a to C_b” in which “a” and “b” are integers refer to the number of carbon atoms in an alkyl, alkenyl or alkynyl group, or the number of carbon atoms in the ring of a cycloalkyl, cycloalkenyl, aryl, heteroaryl or heteroalicycyl group. That is, the alkyl, alkenyl, alkynyl, ring of the cycloalkyl, ring of the cycloalkenyl, 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, aryl, heteroaryl or heteroalicycyl group, the broadest range described in these definitions is to be assumed.

[0025] As used herein, “alkyl” refers to a straight or branched hydrocarbon chain that comprises a fully saturated (no double or triple bonds) hydrocarbon group. The alkyl group may have 1 to 20 carbon atoms (whenever it appears herein, a numerical range such as “1 to 20” refers to each integer in the given range; *e.g.*, “1 to 20 carbon atoms” means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 20 carbon atoms, although the present definition also covers the occurrence of the term “alkyl” where no numerical range is designated). The alkyl group may also be a medium size alkyl having 1 to 10 carbon atoms. The alkyl group could also be a lower alkyl having 1 to 6 carbon atoms. The alkyl group of the compounds may be designated as “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.

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

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

[0028] As used herein, “cycloalkyl” refers to a completely saturated (no double or triple bonds) mono- or multi- cyclic hydrocarbon ring system. When composed of two or more rings, the rings may be joined together in a fused fashion. Cycloalkyl groups can contain 3 to 10 atoms in the ring(s) or 3 to 8 atoms in the ring(s). A cycloalkyl group may be unsubstituted or

substituted. Typical cycloalkyl groups include, but are in no way limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

[0029] As used herein, “cycloalkenyl” refers to a mono- or multi- cyclic hydrocarbon ring system that contains one or more double bonds in at least one ring; although, if there is more than one, the double bonds cannot form a fully delocalized pi-electron system throughout all the rings (otherwise the group would be “aryl,” as defined herein). When composed of two or more rings, the rings may be connected together in a fused fashion. A cycloalkenyl can contain 3 to 10 atoms in the ring(s) or 3 to 8 atoms in the ring(s). A cycloalkenyl group may be unsubstituted or substituted.

[0030] As used herein, “aryl” refers to a carbocyclic (all carbon) monocyclic or polycyclic 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.

[0031] As used herein, “heteroaryl” refers to a monocyclic, bicyclic and tricyclic aromatic ring system (a ring system with fully delocalized pi-electron system) that contain(s) one or more heteroatoms (for example, 1 to 5 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.

[0032] 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 “heteroalicyclic” 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 and 3,4-methylenedioxyphenyl).

[0033] 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.

[0034] 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, imidazolylalkyl and their benzo-fused analogs.

[0035] A “(heteroalicyclyl)alkyl” and “(heterocyclyl)alkyl” refer to a heterocyclic or a heteroalicyclic group connected, as a substituent, via a lower alkylene group. The lower alkylene and heterocyclyl of a (heteroalicyclyl)alkyl may be substituted or unsubstituted. Examples include but are not limited tetrahydro-2H-pyran-4-yl)methyl, (piperidin-4-yl)ethyl, (piperidin-4-yl)propyl, (tetrahydro-2H-thiopyran-4-yl)methyl and (1,3-thiazinan-4-yl)methyl.

[0036] “Lower alkylene groups” are straight-chained $-CH_2-$ tethering groups, forming bonds to connect molecular fragments via their terminal carbon atoms. Examples include but are not limited to methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), propylene ($-CH_2CH_2CH_2-$) and butylene ($-CH_2CH_2CH_2CH_2-$). A lower alkylene group can be substituted by replacing one or more hydrogen of the lower alkylene group with a substituent(s) listed under the definition of “substituted.”

[0037] As used herein, “alkoxy” refers to the formula $-OR$ wherein R is an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heteroalicycyl, aralkyl, (heteroaryl)alkyl or (heteroalicycyl)alkyl is defined herein. A non-limiting list of alkoxy are methoxy, ethoxy, n-propoxy, 1-methylethoxy (isopropoxy), n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, phenoxy and benzoxy. An alkoxy may be substituted or unsubstituted.

[0038] 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.

[0039] 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.

[0040] As used herein, “haloalkyl” refers to an alkyl group in which one or more of the hydrogen atoms are replaced by a halogen (e.g., mono-haloalkyl, di-haloalkyl and tri-haloalkyl). Such groups include but are not limited to, chloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1-chloro-2-fluoromethyl and 2-fluoroisobutyl. A haloalkyl may be substituted or unsubstituted.

[0041] As used herein, “haloalkoxy” refers to an $-O$ -alkyl group in which one or more of the hydrogen atoms are replaced by a halogen (e.g., mono-haloalkoxy, di-haloalkoxy and tri-haloalkoxy). Such groups include but are not limited to, chloromethoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, 1-chloro-2-fluoromethoxy and 2-fluoroisobutoxy. A haloalkoxy may be substituted or unsubstituted.

[0042] As used herein, “arylthio” refers to $RS-$, in which R is an aryl, such as, but not limited to, phenyl. An arylthio may be substituted or unsubstituted.

[0043] A “sulfenyl” group refers to an “ $-SR$ ” group in which R can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heteroalicycyl, aralkyl, (heteroaryl)alkyl or (heteroalicycyl)alkyl. A sulfenyl may be substituted or unsubstituted.

[0044] 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.

[0045] 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.

[0046] An “O-carboxy” group refers to a “RC(=O)O-” group in which R can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heteroalicycyl, aralkyl, (heteroaryl)alkyl or (heteroalicycyl)alkyl, as defined herein. An O-carboxy may be substituted or unsubstituted.

[0047] 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.

[0048] 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.

[0049] A “trihalomethanesulfonyl” group refers to an “X₃CSO₂-” group wherein each X is a halogen.

[0050] A “trihalomethanesulfonamido” group refers to an “X₃CS(O)₂N(R_A)-” group wherein each X is a halogen, and R_A is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heteroalicycyl, aralkyl, (heteroaryl)alkyl or (heteroalicycyl)alkyl.

[0051] The term “amino” as used herein refers to a -NH₂ group.

[0052] As used herein, the term “hydroxy” refers to a -OH group.

[0053] A “cyano” group refers to a “-CN” group.

[0054] The term “azido” as used herein refers to a -N₃ group.

[0055] An “isocyanato” group refers to a “-NCO” group.

[0056] A “thiocyanato” group refers to a “-CNS” group.

[0057] An “isothiocyanato” group refers to an “-NCS” group.

[0058] A “mercapto” group refers to an “-SH” group.

[0059] A “carbonyl” group refers to a C=O group.

[0060] 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, aryl, heteroaryl, heteroalicycyl, aralkyl, (heteroaryl)alkyl or (heteroalicycyl)alkyl. An S-sulfonamido may be substituted or unsubstituted.

[0061] An “N-sulfonamido” group refers to a “RSO₂N(R_A)-” group in which R and R_A can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl,

heteroaryl, heteroalicycyl, aralkyl, (heteroaryl)alkyl or (heteroalicycyl)alkyl. An N-sulfonamido may be substituted or unsubstituted.

[0062] An “O-carbamyl” group refers to a “-OC(=O)N(R_AR_B)” group in which R_A and R_B can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heteroalicycyl, aralkyl, (heteroaryl)alkyl or (heteroalicycyl)alkyl. An O-carbamyl may be substituted or unsubstituted.

[0063] An “N-carbamyl” group refers to an “ROC(=O)N(R_A)-” group in which R and R_A can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heteroalicycyl, aralkyl, (heteroaryl)alkyl or (heteroalicycyl)alkyl. An N-carbamyl may be substituted or unsubstituted.

[0064] An “O-thiocarbamyl” group refers to a “-OC(=S)-N(R_AR_B)” group in which R_A and R_B can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heteroalicycyl, aralkyl, (heteroaryl)alkyl or (heteroalicycyl)alkyl. An O-thiocarbamyl may be substituted or unsubstituted.

[0065] An “N-thiocarbamyl” group refers to an “ROC(=S)N(R_A)-” group in which R and R_A can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heteroalicycyl, aralkyl, (heteroaryl)alkyl or (heteroalicycyl)alkyl. An N-thiocarbamyl may be substituted or unsubstituted.

[0066] A “C-amido” group refers to a “-C(=O)N(R_AR_B)” group in which R_A and R_B can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heteroalicycyl, aralkyl, (heteroaryl)alkyl or (heteroalicycyl)alkyl. A C-amido may be substituted or unsubstituted.

[0067] An “N-amido” group refers to a “RC(=O)N(R_A)-” group in which R and R_A can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heteroalicycyl, aralkyl, (heteroaryl)alkyl or (heteroalicycyl)alkyl. An N-amido may be substituted or unsubstituted.

[0068] 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.

[0069] 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.

[0070] 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)).

[0071] 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.

[0072] The term “nucleotide” is used herein in its ordinary sense as understood by those skilled in the art, and refers to a nucleoside having a phosphate ester bound to the pentose moiety, for example, at the 5'-position.

[0073] 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).

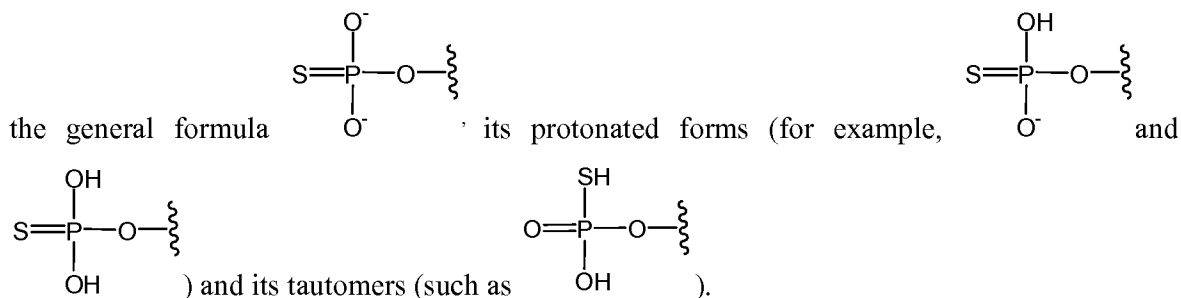
[0074] The term “–N–linked amino acid” refers to an amino acid that is attached to the indicated moiety via a main-chain amino or mono-substituted amino group. When the amino acid is attached in an –N–linked amino acid, one of the hydrogens that is part of the main-chain amino or mono-substituted amino group is not present and the amino acid is attached via the nitrogen. N-linked amino acids can be substituted or unsubstituted.

[0075] The term “–N–linked amino acid ester derivative” refers to an amino acid in which a main-chain carboxylic acid group has been converted to an ester group. In some embodiments, the ester group has a formula selected from alkyl-O-C(=O)-, cycloalkyl-O-C(=O)-, aryl-O-C(=O)- and aryl(alkyl)-O-C(=O)-. A non-limiting list of ester groups include substituted and unsubstituted versions of the following: methyl-O-C(=O)-, ethyl-O-C(=O)-, n-propyl-O-C(=O)-, isopropyl-O-C(=O)-, n-butyl-O-C(=O)-, isobutyl-O-C(=O)-, tert-butyl-O-C(=O)-, neopentyl-O-C(=O)-, cyclopropyl-O-C(=O)-, cyclobutyl-O-C(=O)-, cyclopentyl-O-C(=O)-, cyclohexyl-O-C(=O)-, phenyl-O-C(=O)-, benzyl-O-C(=O)- and naphthyl-O-C(=O)-. N-linked amino acid ester derivatives can be substituted or unsubstituted.

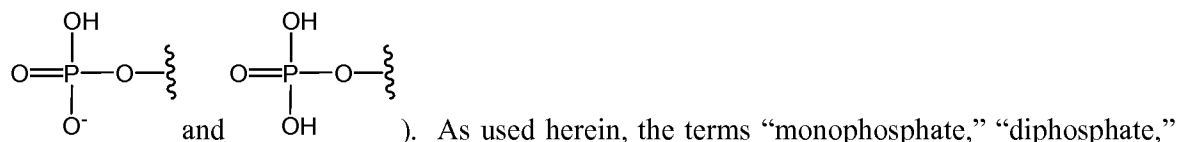
[0076] The term “–O–linked amino acid” refers to an amino acid that is attached to the indicated moiety via the hydroxy from its main-chain carboxylic acid group. When the amino acid is attached in an –O–linked amino acid, the hydrogen that is part of the hydroxy from its main-chain carboxylic acid group is not present and the amino acid is attached via the oxygen. O-linked amino acids can be substituted or unsubstituted.

[0077] 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.

[0078] The terms “phosphorothioate” and “phosphothioate” refer to a compound of



[0079] As used herein, the term “phosphate” is used in its ordinary sense as understood by those skilled in the art, and includes its protonated forms (for example,



and “triphosphate” are used in their ordinary sense as understood by those skilled in the art, and include protonated forms.

[0080] The terms “protecting group” and “protecting groups” as used herein refer to any atom or group of atoms that is added to a molecule in order to prevent existing groups in the molecule from undergoing unwanted chemical reactions. Examples of protecting group moieties are described in T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 3. Ed. John Wiley & Sons, 1999, and in J.F.W. McOmie, *Protective Groups in Organic Chemistry* Plenum Press, 1973, both of which are hereby incorporated by reference for the limited purpose of disclosing suitable protecting groups. The protecting group moiety may be chosen in such a way, that they are stable to certain reaction conditions and readily removed at a convenient stage using methodology known from the art. A non-limiting list of protecting groups include benzyl; substituted benzyl; alkylcarbonyls and alkoxycarbonyls (e.g., t-butoxycarbonyl (BOC), acetyl, or isobutyryl); arylalkylcarbonyls and arylalkoxycarbonyls (e.g., benzyloxycarbonyl); substituted methyl ether (e.g. methoxymethyl ether); substituted ethyl ether; a substituted benzyl ether; tetrahydropyranyl ether; silyls (e.g., trimethylsilyl, triethylsilyl, triisopropylsilyl, t-butyl dimethylsilyl, tri-*iso*-propylsilyloxymethyl, [2-(trimethylsilyl)ethoxy]methyl or t-butyl diphenylsilyl); 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).

[0081] 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.

[0082] 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, but instead as merely intended to highlight alternative or additional features that may or may not be utilized in a particular embodiment. In addition, the term “comprising” is to be interpreted synonymously with the phrases "having at least" or "including at least". When used in the context of a process, the term "comprising" means that the process includes at least the recited steps, but may include additional steps. When used in the context of a compound, composition or device, the term "comprising" means that the compound, composition or device includes at least the recited features or components, but may also include additional features or components. Likewise, a group of items linked with the conjunction ‘and’

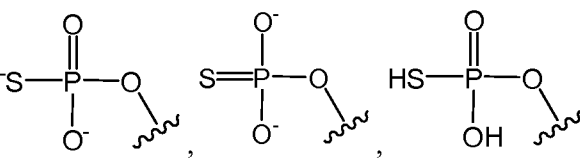
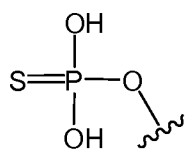
should not be read as requiring that each and every one of those items be present in the grouping, but rather should be read as ‘and/or’ unless expressly stated otherwise. Similarly, a group of items linked with the conjunction ‘or’ should not be read as requiring mutual exclusivity among that group, but rather should be read as ‘and/or’ unless expressly stated otherwise.

[0083] 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.

[0084] 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.

[0085] 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:

. 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.

[0086] 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).

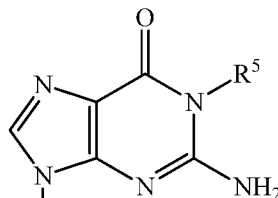
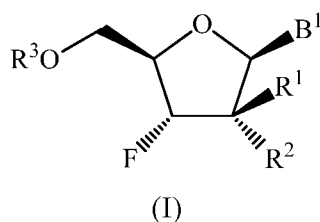
[0087] It is understood that the compounds described herein can be labeled isotopically. Substitution with isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, such as, for example, increased *in vivo* half-life or reduced dosage requirements. 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.

[0088] 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.

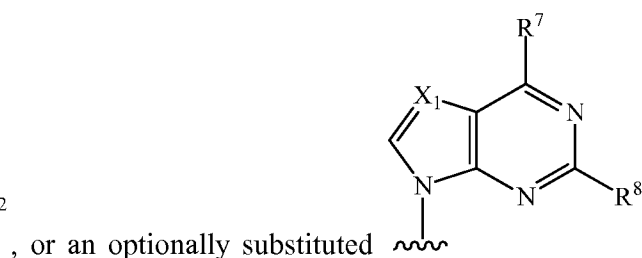
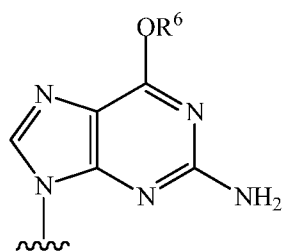
[0089] Where a range of values is provided, it is understood that the upper and lower limit, and each intervening value between the upper and lower limit of the range is encompassed within the embodiments.

Compounds

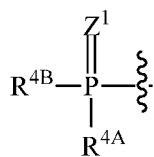
[0090] Some embodiments disclosed herein relate to a compound of Formula (I) or a pharmaceutically acceptable salt thereof:



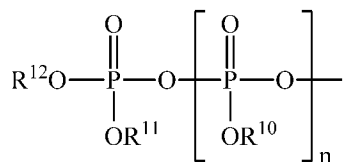
wherein: B¹ can be an optionally substituted , an optionally substituted



, or an optionally substituted ; R¹ can be selected from an unsubstituted C₁₋₆ alkyl, an unsubstituted C₂₋₆ alkenyl, an unsubstituted C₂₋₆ alkynyl, an unsubstituted C₃₋₆ cycloalkyl and an unsubstituted C₁₋₆ haloalkyl; R² can be halo, -OR^{9A} or -



N(R^{9B}R^{9C}); R³ can be hydrogen or ; R^{4A} can be selected from O-, OH, an optionally substituted N-linked amino acid and an optionally substituted N-linked amino acid ester derivative; R^{4B} can be selected from O-, OH, an -O-optionally substituted aryl, an -O-optionally substituted heteroaryl, an -O-optionally substituted heterocyclyl, an optionally substituted N-linked amino acid, an optionally substituted N-linked amino acid ester derivative



and ; R⁵ and R⁶ can be independently selected from hydrogen, an unsubstituted C₁₋₆ alkyl, an unsubstituted C₃₋₆ alkenyl, an unsubstituted C₃₋₆ alkynyl and an unsubstituted C₃₋₆ cycloalkyl; R⁷ can be NHR¹³; R⁸ can be NHR¹⁴; R^{9A} can be hydrogen or -C(=O)R¹⁵; R^{9B} and R^{9C} can be independently hydrogen or an optionally substituted C₁₋₆ alkyl; R¹⁰, R¹¹ and R¹² can be independently absent or hydrogen; R¹³ can be selected from hydrogen,

an optionally substituted C₁₋₆ alkyl, an optionally substituted C₃₋₆ alkenyl, an optionally substituted C₃₋₆ cycloalkyl, -C(=O)R^{A1} and -C(=O)OR^{A2}; R¹⁴ can be selected from hydrogen, an optionally substituted C₁₋₆ alkyl, an optionally substituted C₃₋₆ alkenyl, an optionally substituted C₃₋₆ cycloalkyl, -C(=O)R^{A3} and -C(=O)OR^{A4}; R¹⁵ can be an optionally substituted C₁₋₆ alkyl or an optionally substituted C₃₋₆ cycloalkyl; X¹ can be N or -CR¹⁶; R¹⁶ can be selected from hydrogen, halogen, an optionally substituted C₁₋₆ alkyl, an optionally substituted C₂₋₆ alkenyl and an optionally substituted C₂₋₆ alkynyl; R^{A1}, R^{A2}, R^{A3} and R^{A4} can be independently selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkenyl, C₆₋₁₀ aryl, heteroaryl, heteroalicycyl, aryl(C₁₋₆ alkyl), heteroaryl(C₁₋₆ alkyl) and heteroalicycyl(C₁₋₆ alkyl); n can be 0

or 1; Z¹ can be O or S; and provided that when R³ is $\begin{array}{c} Z^1 \\ || \\ R^{4B}-P-\zeta \\ | \\ R^{4A} \end{array}$; and R^{4A} is O⁻ or OH, then R^{4B}

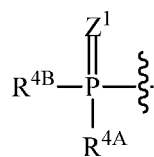
is O⁻, OH or $\begin{array}{c} O \\ || \\ R^{12}O-P-O-\left[\begin{array}{c} O \\ || \\ P-O \\ | \\ OR^{10} \end{array} \right]_n \\ | \\ OR^{11} \end{array}$.

[0091] The substituents attached to the 2'-carbon can vary. In some embodiments, R² can be halo. For example, R² can be fluoro or chloro. In other embodiments, R² can be -OH. In still other embodiments, R² can be OR^{9A}, wherein R^{9A} can be -C(=O)R¹⁵, and R¹⁵ can be an optionally substituted C₁₋₆ alkyl. Suitable alkyl groups include, but are not limited to 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 yet still other embodiments, R² can be OR^{9A}, wherein R^{9A} can be -C(=O)R¹⁵, and R¹⁵ can be an optionally substituted C₃₋₆ cycloalkyl. Suitable cycloalkyl groups include, but are not limited to optionally substituted variants of the following: cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. In some embodiment, R² can be -N(R^{9B}R^{9C}), wherein R^{9B} and R^{9C} can be independently hydrogen or an optionally substituted C₁₋₆ alkyl. In some embodiments, R^{9B} and R^{9C} can be both hydrogen. In other embodiments, at least one of R^{9B} and R^{9C} can be an optionally substituted C₁₋₆ alkyl. In some embodiments, R^{9B} and R^{9C} can be both an optionally substituted C₁₋₆ alkyl. In some embodiments, R^{9B} and R^{9C} can be the same. In other embodiments, R^{9B} and R^{9C} can be different.

[0092] In some embodiments, R¹ can be an unsubstituted C₁₋₆ alkyl. For example, R¹ can be unsubstituted methyl, unsubstituted ethyl, unsubstituted n-propyl, unsubstituted isopropyl, unsubstituted n-butyl, unsubstituted isobutyl, unsubstituted tert-butyl, unsubstituted pentyl (branched and straight-chained) or unsubstituted hexyl (branched and straight-chained).

In some embodiments, R^1 can be an unsubstituted C_{2-6} alkenyl. For example, R^1 can be ethenyl, n-propenyl, isopropenyl, n-butenyl, isobutenyl, tert-butenyl, pentenyl (branched and straight-chained), hexenyl (branched and straight-chained), vinyl or allenyl. In some embodiments, R^1 can be an unsubstituted alkynyl. Suitable alkynyl groups include, but are not limited to the following: ethynyl, propynyl, n-butyne, isobutyne, tert-butyne, pentynyl (branched and straight-chained) and hexynyl (branched and straight-chained). In still other embodiments, R^1 can be an unsubstituted C_{3-6} cycloalkyl such as those described herein. In yet other embodiments, R^1 can be an unsubstituted haloalkyl. Examples of suitable haloalkyl include, but are not limited to, chloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1-chloro-2-fluoromethyl and 2-fluoroisobutyl.

[0093] In some embodiments, R^3 can be hydrogen. In other embodiments, R^3 can be



. In some embodiments, the compound of Formula (I) can be a monophosphate. In other embodiments, the compound of Formula (I) can be a thiomonophosphate. In some embodiments, the compound of Formula (I) can be a diphosphate. In other embodiments, the compound of Formula (I) can be an alpha-thiodiphosphate. In some embodiments, the compound of Formula (I) can be a triphosphate. In other embodiments, the compound of Formula (I) can be an alpha-thiotriphosphate. In some embodiments, R^{4A} can be O^- or OH ; and R^{4B} can be O^- or OH . In other embodiments, R^{4A} can be O^- or OH ; and R^{4B} can be

$$R^{12}O-P(=O)(OR^{11})-O-\left[P(=O)(OR^{10})-O \right]_n$$

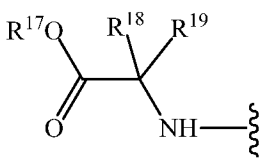
, wherein R^{10} , R^{11} and R^{12} can be independently absent or hydrogen; and n can be 0. In still other embodiments, R^{4A} can be O^- or OH ; and R^{4B} can be

$$R^{12}O-P(=O)(OR^{11})-O-\left[P(=O)(OR^{10})-O \right]_n$$

, wherein R^{10} , R^{11} and R^{12} can be independently absent or hydrogen; and n can be 1. The substituents attached to the phosphorus can vary. In some embodiments, a compound of Formula (I) can be a phosphoramidate. In other embodiments, a compound of Formula (I) can be a thiophosphoramidate. In still other embodiments, a compound of Formula (I) can be a phosphorbisamidate. In yet still other embodiments, a compound of Formula (I) can be a thiophosphorbisamidate.

[0094] In some embodiments, R^{4A} can be an optionally substituted N-linked amino acid. Various amino acids are suitable, including those described herein. 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. In other embodiments, R^{4A} can be an optionally substituted N-linked amino acid ester derivative. Examples of N-linked amino acid ester derivatives include, but are not limited to, 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. In some embodiments, the N-linked amino acid ester derivative can be a C_{1-6} alkyl ester derivative, for example, an isopropyl ester of alanine. In other embodiments, the N-linked amino acid ester derivative can be a C_{3-6} cycloalkyl ester derivative, such as a cyclohexyl ester of alanine.

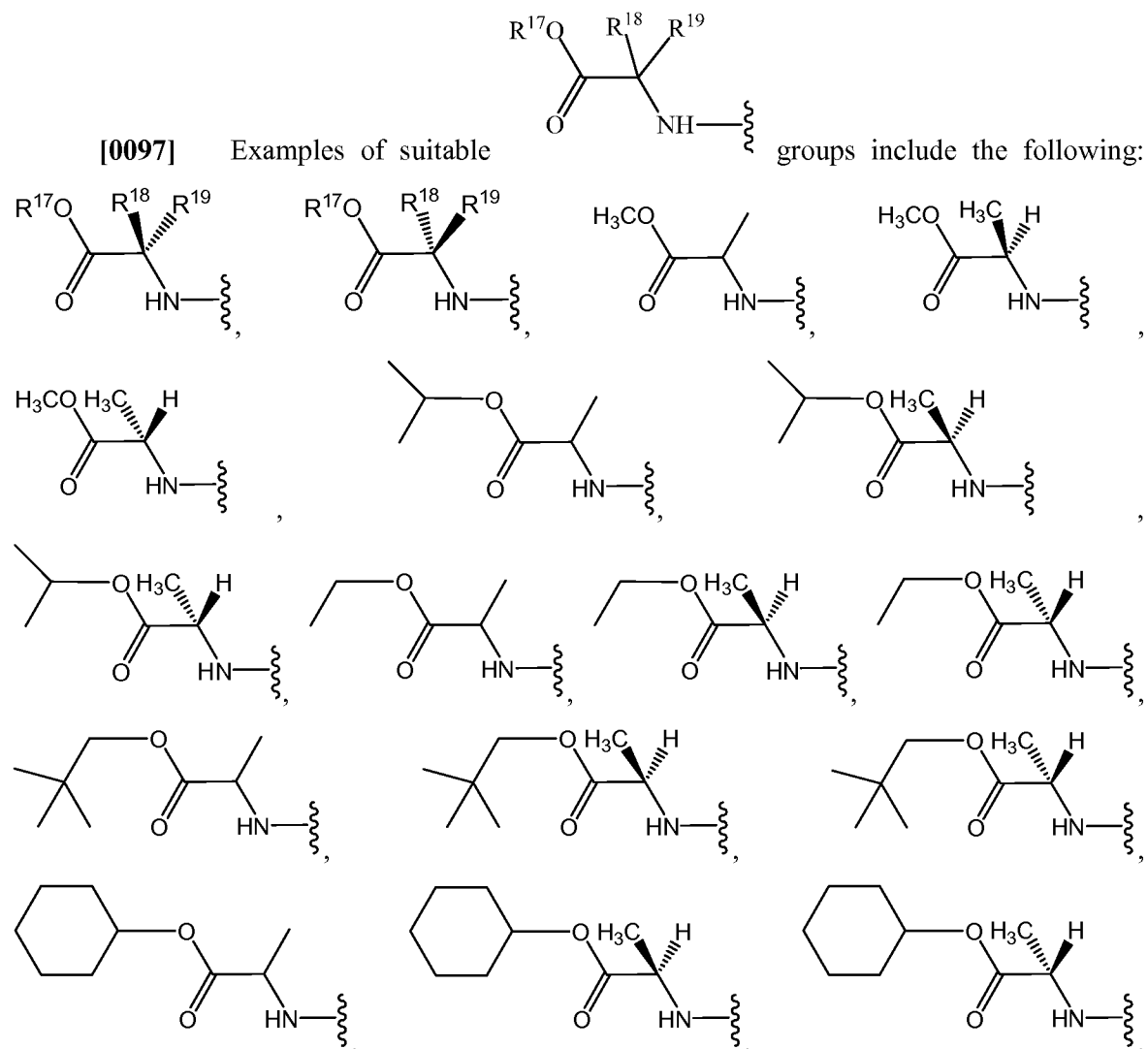
[0095] In some embodiments, R^{4A} can have the structure

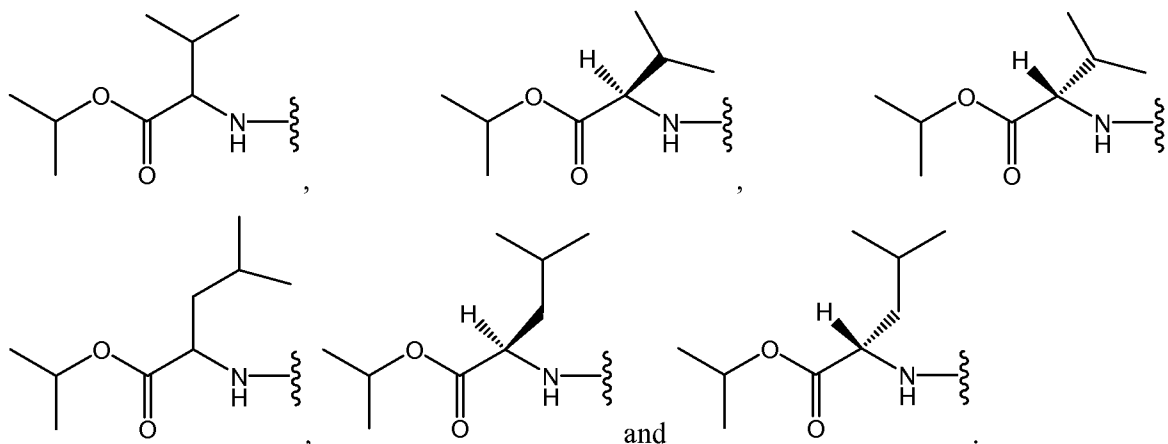


wherein R^{17} can be selected from hydrogen, an optionally substituted C_{1-6} -alkyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted aryl, an optionally substituted aryl(C_{1-6} alkyl) and an optionally substituted haloalkyl; R^{18} can be selected from hydrogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{1-6} haloalkyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted C_6 aryl, an optionally substituted C_{10} aryl and an optionally substituted aryl(C_{1-6} alkyl); and R^{19} can be hydrogen or an optionally substituted C_{1-4} -alkyl.

[0096] When R^{18} is substituted, R^{18} can be substituted with one or more substituents selected from N-amido, mercapto, alkylthio, an optionally substituted aryl, hydroxy, an optionally substituted heteroaryl, O-carboxy and amino. In some embodiments, R^{18} can be hydrogen. In some embodiments, R^{18} can be an unsubstituted C_{1-6} -alkyl, such as those described herein. In other embodiments, R^{18} can be methyl. In some embodiments, R^{17} can be an optionally substituted C_{1-6} alkyl. Examples of optionally substituted C_{1-6} -alkyls include optionally substituted variants of the following: methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, pentyl (branched and straight-chained) and hexyl (branched and straight-chained). In some embodiments, R^{17} can be methyl or isopropyl. In some embodiments, R^{17}

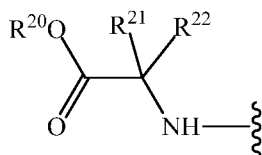
can be ethyl or neopentyl. In other embodiments, R^{17} can be an optionally substituted C_{3-6} cycloalkyl. Examples of optionally substituted C_{3-6} cycloalkyl include optionally substituted variants of the following: cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. In some embodiments, R^{17} can be an optionally substituted cyclohexyl. In still other embodiments, R^{17} can be an optionally substituted aryl, such as phenyl and naphthyl. In yet still other embodiments, R^{17} can be an optionally substituted aryl(C_{1-6} alkyl). In some embodiments, R^{17} can be an optionally substituted benzyl. In some embodiments, R^{17} can be an optionally substituted C_{1-6} haloalkyl, for example, CF_3 . In some embodiments, R^{19} can be hydrogen. In other embodiments, R^{19} can be an optionally substituted C_{1-4} -alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or tert-butyl. In some embodiments, R^{19} can be methyl. Depending on the groups that are selected for R^{18} and R^{19} , the carbon to which R^{18} and R^{19} are attached may be a chiral center. In some embodiment, the carbon to which R^{18} and R^{19} are attached may be a (R)-chiral center. In other embodiments, the carbon to which R^{18} and R^{19} are attached may be a (S)-chiral center.





[0098] In some embodiments, R^{4B} can be an $-O$ -optionally substituted aryl. For example, R^{4B} can be an $-O$ -optionally substituted phenyl. When the phenyl is substituted, the ring can be substituted 1, 2, 3 or more than 3 times. Suitable mono-substituted phenyl groups include, ortho-substituted phenyl, meta-substituted phenyl and para-substituted phenyl. In some embodiments, R^{4B} can be ortho-chlorophenyl. In some embodiments, R^{4B} can be 3-chloro-4-fluorophenyl. Alternatively, R^{4B} can be an $-O$ -optionally substituted naphthyl. In other embodiments, R^{4B} can be an $-O$ -optionally substituted heteroaryl. In still other embodiments, R^{4B} can be an $-O$ -optionally substituted heterocyclyl.

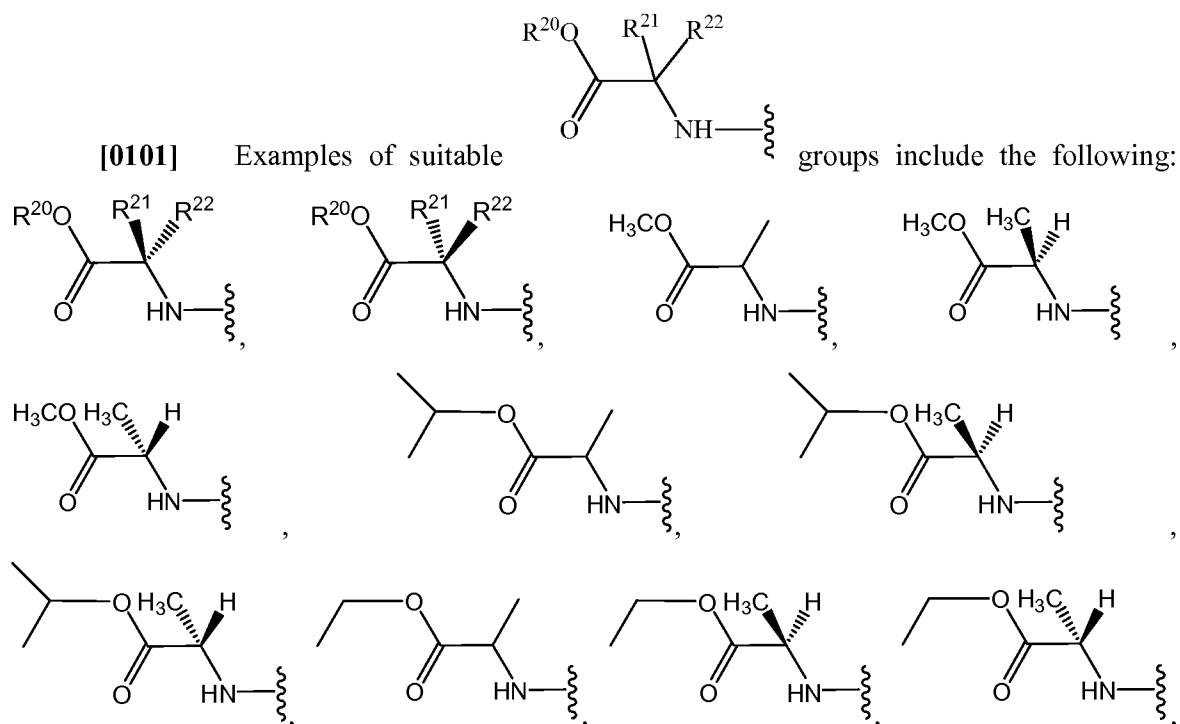
[0099] In some embodiments, R^{4B} can be an optionally substituted N-linked amino acid, such as those described for R^{4A} . In other embodiments, R^{4B} can be an optionally substituted N-linked amino acid ester derivative, for example, those described herein. In some

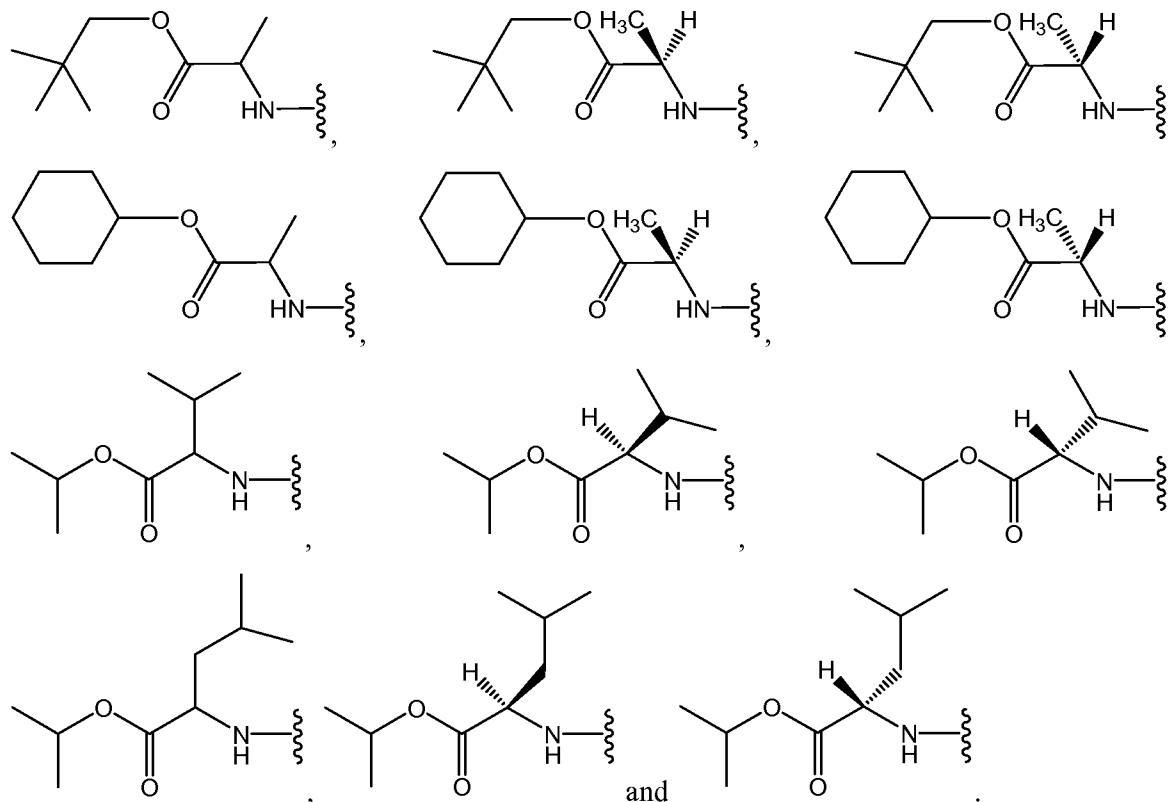


embodiments, R^{4B} can have the structure wherein R^{20} can be selected from hydrogen, an optionally substituted C_{1-6} -alkyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted aryl, an optionally substituted aryl(C_{1-6} alkyl) and an optionally substituted haloalkyl; R^{21} 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^{22} can be hydrogen or an optionally substituted C_{1-4} -alkyl.

[0100] When R^{21} is substituted, R^{21} can be substituted with one or more substituents selected from N-amido, mercapto, alkylthio, an optionally substituted aryl, hydroxy, an optionally substituted heteroaryl, O-carboxy and amino. In some embodiments, R^{21} can be an unsubstituted C_{1-6} -alkyl, such as those described herein. In some embodiments, R^{21} can be hydrogen. In other embodiments, R^{21} can be methyl. In some embodiments, R^{20} can be an

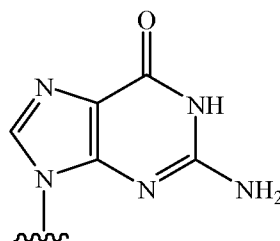
optionally substituted C_{1-6} alkyl. Examples of optionally substituted C_{1-6} alkyls include optionally substituted variants of the following: methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, pentyl (branched and straight-chained) and hexyl (branched and straight-chained). In some embodiments, R^{20} can be methyl or isopropyl. In some embodiments, R^{20} can be ethyl or neopentyl. In other embodiments, R^{20} 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^{20} can be an optionally substituted cyclohexyl. In still other embodiments, R^{20} can be an optionally substituted aryl, such as phenyl and naphthyl. In yet still other embodiments, R^{20} can be an optionally substituted aryl(C_{1-6} alkyl). In some embodiments, R^{20} can be an optionally substituted benzyl. In some embodiments, R^{20} can be an optionally substituted C_{1-6} haloalkyl, for example, CF_3 . In some embodiments, R^{22} can be hydrogen. In other embodiments, R^{22} can be an optionally substituted C_{1-4} -alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or tert-butyl. In an embodiment, R^{22} can be methyl. Depending on the groups that are selected for R^{21} and R^{22} , the carbon to which R^{21} and R^{22} are attached may be a chiral center. In some embodiment, the carbon to which R^{21} and R^{22} are attached may be a (R)-chiral center. In other embodiments, the carbon to which R^{21} and R^{22} are attached may be a (S)-chiral center.



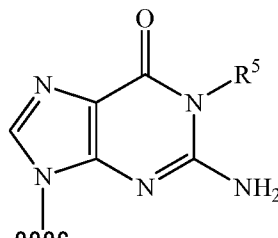


[0102] In some embodiments, R^{4A} can be an optionally substituted N-linked amino acid or an optionally substituted N-linked amino acid ester derivative and R^{4B} can be an $-O-$ optionally substituted aryl. In other embodiments, R^{4A} can be an optionally substituted N-linked amino acid or an optionally substituted N-linked amino acid ester derivative and R^{4B} can be an $-O-$ optionally substituted heteroaryl. In some embodiments, R^{4A} can be an optionally substituted N-linked amino acid or an optionally substituted N-linked amino acid ester derivative and R^{4B} can be an optionally substituted N-linked amino acid or an optionally substituted N-linked amino acid ester derivative. In some embodiments, R^{4A} and R^{4B} can be the same. In other embodiments, R^{4A} and R^{4B} can be different.

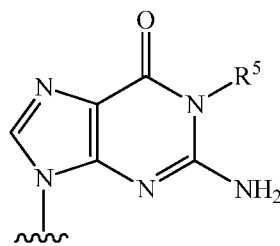
[0103] The nucleobase can vary. In some embodiments, B^1 can be guanine. In some



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

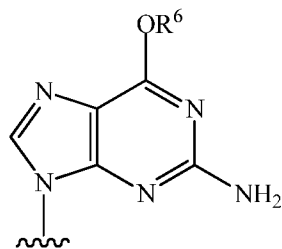


embodiments, B¹ can be an optionally substituted  wherein R⁵ can be selected from hydrogen, an unsubstituted C₁₋₆ alkyl, an unsubstituted C₃₋₆ alkenyl, an unsubstituted C₃₋₆ alkynyl and an unsubstituted C₃₋₆ cycloalkyl. In some embodiments, B¹ can

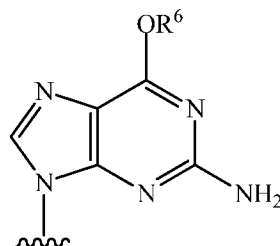


be unsubstituted  . In some embodiments, R⁵ can be an unsubstituted C₁₋₆ alkyl. For example, R⁵ can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, pentyl (branched and straight-chained) or hexyl (branched and straight-chained). In some embodiments, R⁵ can be an unsubstituted C₃₋₆ alkenyl. In other embodiments, R⁵ can be an unsubstituted C₃₋₆ alkynyl. In still other embodiments, R⁵ can be an unsubstituted C₃₋₆ cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

[0104] In some embodiments, B¹ can be an optionally substituted



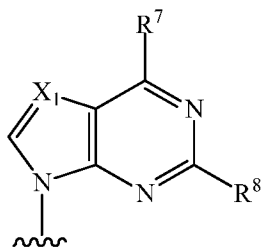
wherein R⁶ can be selected from hydrogen, an unsubstituted C₁₋₆ alkyl, an unsubstituted C₃₋₆ alkenyl, an unsubstituted C₃₋₆ alkynyl and an unsubstituted C₃₋₆ cycloalkyl.



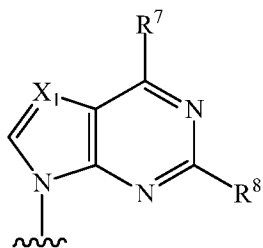
In some embodiments, B¹ can be unsubstituted  . In some embodiments, R⁶ can be hydrogen. In some embodiments, R⁶ can be an unsubstituted C₁₋₆ alkyl. For example, R⁶ can be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, pentyl (branched and straight-chained) or hexyl (branched and straight-chained). In some embodiments, R⁶ can be an ethyl. In some embodiments, R⁶ can be an unsubstituted C₃₋₆ alkenyl. In other embodiments, R⁶

can be an unsubstituted C₃₋₆ alkynyl. In other embodiments, R⁶ can be an unsubstituted C₃₋₆ cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

[0105] In some embodiments, B¹ can be an optionally substituted

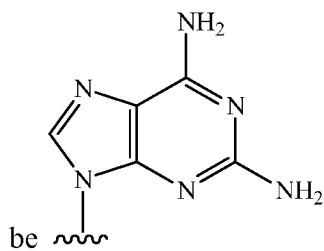


wherein X¹ can be N or -CR¹⁶; R¹⁶ can be selected from hydrogen, halogen, an optionally substituted C₁₋₆ alkyl, an optionally substituted C₂₋₆ alkenyl and an optionally substituted C₂₋₆ alkynyl; R⁷ can be NHR¹³; R⁸ can be NHR¹⁴; R¹³ can be selected from hydrogen, an optionally substituted C₁₋₆ alkyl, an optionally substituted C₃₋₆ alkenyl, an optionally substituted C₃₋₆ cycloalkyl, -C(=O)R^{A1} and -C(=O)OR^{A2}; R¹⁴ can be selected from hydrogen, an optionally substituted C₁₋₆ alkyl, an optionally substituted C₃₋₆ alkenyl, an optionally substituted C₃₋₆ cycloalkyl, -C(=O)R^{A3} and -C(=O)OR^{A4}; R^{A1}, R^{A2}, R^{A3} and R^{A4} can be independently selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkenyl, C₆₋₁₀ aryl, heteroaryl, heteroalicycyl, aryl(C₁₋₆ alkyl), heteroaryl(C₁₋₆ alkyl) and heteroalicycyl(C₁₋₆ alkyl). In other embodiments, B¹ can be an unsubstituted



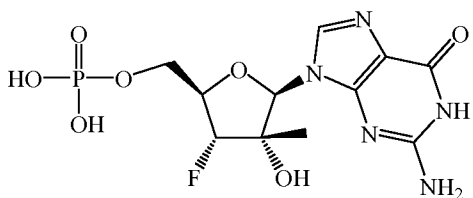
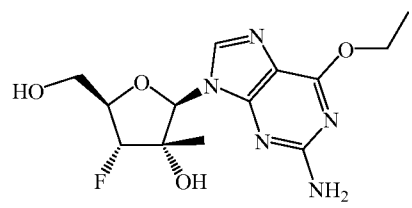
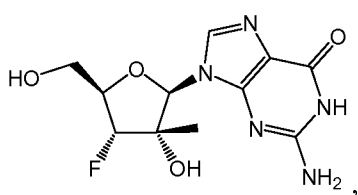
. In some embodiments, X¹ can be N (nitrogen). In other embodiments, X¹ can be -CR¹⁶, wherein R¹⁶ can be selected from hydrogen, halogen, an optionally substituted C₁₋₆ alkyl, an optionally substituted C₂₋₆ alkenyl and an optionally substituted C₂₋₆ alkynyl. In some embodiments, X¹ can be CH. In some embodiments, R⁷ and R⁸ can be both NH₂. In other embodiments, at least one of R⁷ and R⁸ can be NH₂. In some embodiments, R⁷ can be NHR¹³, wherein R¹³ can be an optionally substituted C₁₋₆ alkyl. In some embodiments, R⁸ can be NHR¹⁴, wherein R¹⁴ can be an optionally substituted C₁₋₆ alkyl. In other embodiments, R⁷ can be NHR¹³, wherein R¹³ can be selected from an optionally substituted C₃₋₆ alkenyl, an optionally substituted C₃₋₆ cycloalkyl, -C(=O)R^{A1} and -C(=O)OR^{A2}. In other embodiments, R⁸ can be NHR¹⁴, wherein R¹⁴ can be selected from an optionally substituted C₃₋₆ alkenyl, an optionally substituted C₃₋₆ cycloalkyl, -C(=O)R^{A3} and -C(=O)OR^{A4}. In some embodiments, R⁷ and R⁸ can

be the same. In other embodiments, R^7 and R^8 can be different. In some embodiments, B^1 can

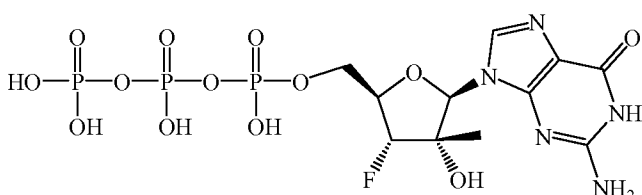


[0106] In some embodiments, Z^1 can be O (oxygen). In other embodiments, Z^1 can be S (sulfur).

[0107] Some examples of compounds of Formula (I) include, but are not limited to the following:

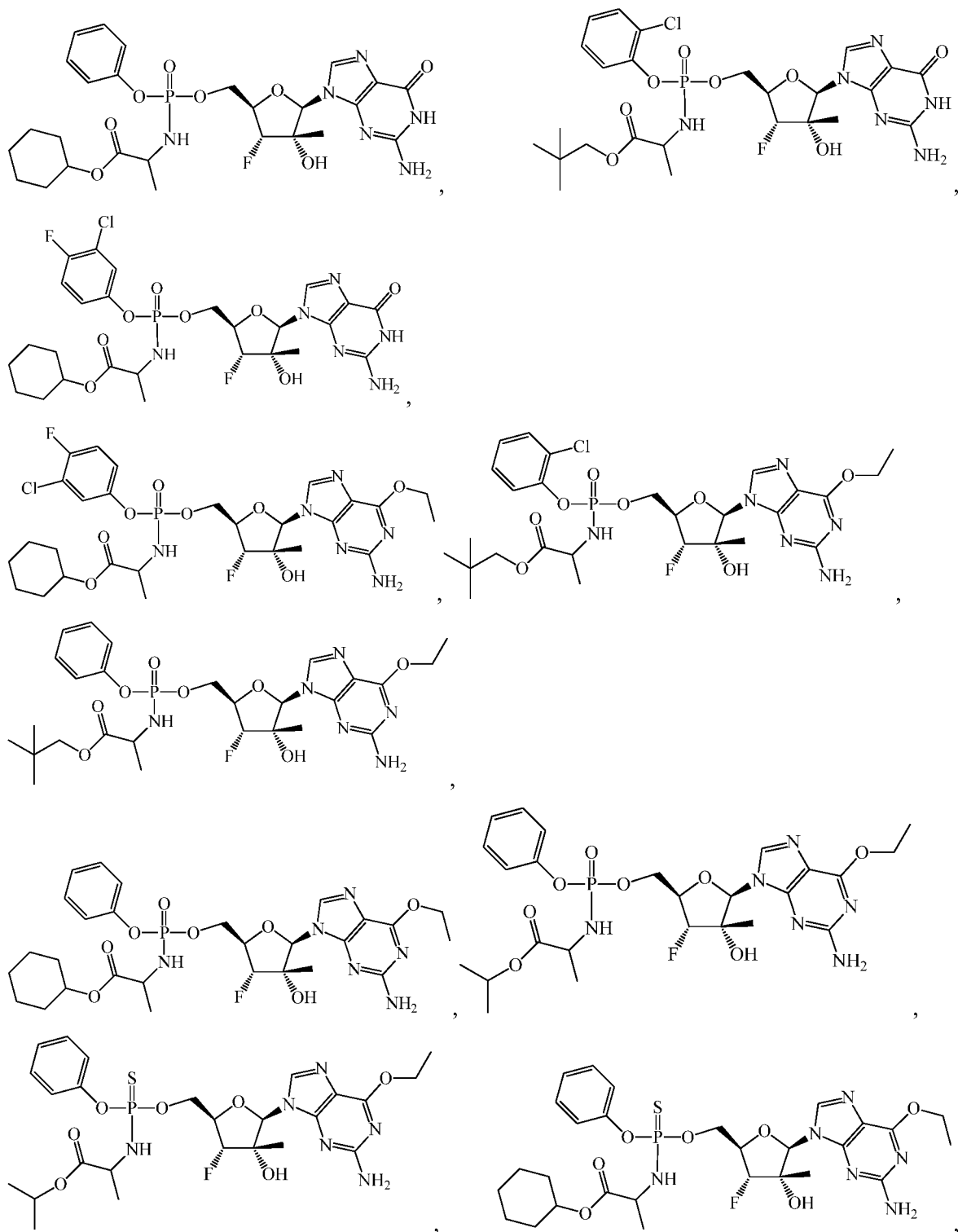


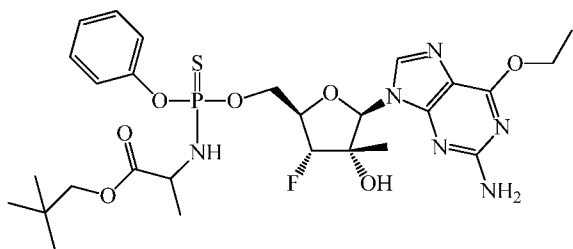
and



, or a pharmaceutically acceptable salt of the foregoing.

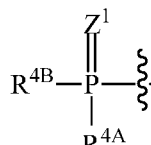
[0108] Further examples of compounds of Formula (I) include, but are not limited to the following:





, or a pharmaceutically acceptable salt of the foregoing.

[0109] As described herein, a compound of Formula (I), or a pharmaceutically



acceptable salt thereof, can have R^3 being R^{4B} ; R^{4A} being an optionally substituted N-linked amino acid or an optionally substituted N-linked amino acid ester derivative; and R^{4B} being an -O-optionally substituted aryl, an -O-optionally substituted heteroaryl, an -O-optionally substituted heterocyclyl, an optionally substituted N-linked amino acid or an optionally substituted N-linked amino acid ester derivative. By neutralizing the charge on the phosphate or thiophosphate, penetration of the cell membrane may be facilitated as a result of the increased lipophilicity of the compound. Once absorbed and taken inside the cell, the groups attached to the phosphorus can be easily removed by esterases, proteases and/or other enzymes. In some embodiments, the groups attached to the phosphorus can be removed by simple hydrolysis. Inside the cell, the phosphate thus released may then be metabolized by cellular enzymes to the diphosphate or the active triphosphate. Likewise, the thio-phosphate may be metabolized to the alpha-thiodiphosphate or the alpha-thiotriphosphate. Furthermore, in some embodiments, varying the substituents on a compound described herein, such as compound of Formula (I), can help maintain the efficacy of such the compound by reducing undesirable effects, such as isomerization.

[0110] 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) 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.

[0111] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can act as a chain terminator of HCV replication. For example, since compounds of Formula (I) do not contain a hydroxyl group at the 3'-position, once the compound is incorporated into an RNA chain no further chain elongation can occur.

[0112] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can have increased metabolic and/or plasma stability. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be more resistant to hydrolysis and/or more resistant to enzymatic transformations. 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 OH group in place of the fluoro at the 3'-position. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can have improved properties. A non-limiting list of example properties include, but are not limited to, increased biological half-life, increased bioavailability, increase potency, a sustained in vivo response, increased dosing intervals, decreased dosing amounts, decreased cytotoxicity, reduction in required amounts for treating disease conditions, reduction in viral load, reduction in time to seroconversion (i.e., the virus becomes undetectable in patient serum), increased sustained viral response, a reduction of morbidity or mortality in clinical outcomes, increased subject compliance, decreased liver conditions (such as liver fibrosis, liver 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 greater than a compound that is identical in structure but for having a OH group in place of the fluoro at the 3'-position. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can have more potent antiviral activity (for example, a lower EC₅₀ in an HCV replicon assay) as compared to the current standard of care. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, does not significantly inhibit mitochondrial function of the mitochondrial RNA polymerase. For example, a compound of Formula (I), or a

pharmaceutically acceptable salt thereof, is incorporated in the human mitochondrial RNA polymerase less than 10% compared to the natural 5'-triphosphate nucleotide with the same B¹.

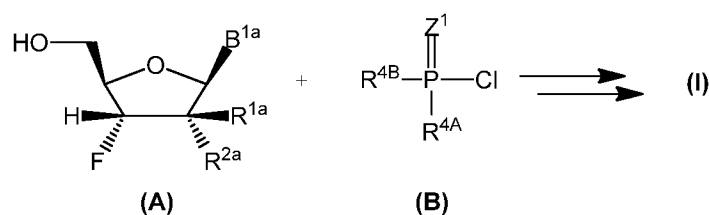
[0113] Additionally, in some embodiments, the presence of a thiophosphoramidate, phosphoramidate, thiophosphorbisamidate or phosphorbisamidate in a compound of Formula (I) can increase the stability of the compound by inhibiting its degradation. Also, in some embodiments, the presence of a thiophosphoramidate, phosphoramidate, thiophosphorbisamidate or phosphorbisamidate can make the compound more resistant to cleavage *in vivo* and provide sustained, extended efficacy. In some embodiments, a thiophosphoramidate, phosphoramidate, thiophosphorbisamidate or phosphorbisamidate can facilitate the penetration of the cell membrane by a compound of Formula (I) by making the compound more lipophilic. In some embodiments, a thiophosphoramidate, phosphoramidate, thiophosphorbisamidate or phosphorbisamidate can have improved oral bioavailability, improved aqueous stability and/or reduced risk of byproduct-related toxicity. In some embodiments, for comparison purposes, a compound of Formula (I) can be compared to a compound that is identical in structure but for having a OH group in place of the fluoro at the 3'-position.

Synthesis

[0114] Compounds of Formula (I) and those described herein may be prepared in various ways. General synthetic routes to the compound of Formula (I), and some examples of starting materials used to synthesize the compounds of Formula (I) are shown in Schemes 1 and 2, and described herein. The routes shown and described herein are illustrative only and are not intended, nor are they to be construed, to limit the scope of the claims in any manner whatsoever. Those skilled in the art will be able to recognize modifications of the disclosed syntheses and to devise alternate routes based on the disclosures herein; all such modifications and alternate routes are within the scope of the claims.

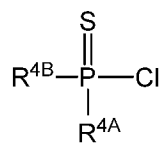
[0115] Compounds of Formula (I) can be prepared using various methods known to those skilled in the art. Examples of methods are shown in Schemes 1 and 2. Suitable phosphorus containing precursors can be commercially obtained or prepared by synthetic methods known to those skilled in the art. Examples of general structures of phosphorus containing precursors are shown in Schemes 1 and 2, and include phosphorochloridates and thiophosphorochloridates. Suitable phosphorochloridates and thiophosphorochloridates are commercially available and/or can be synthetically prepared.

Scheme 1



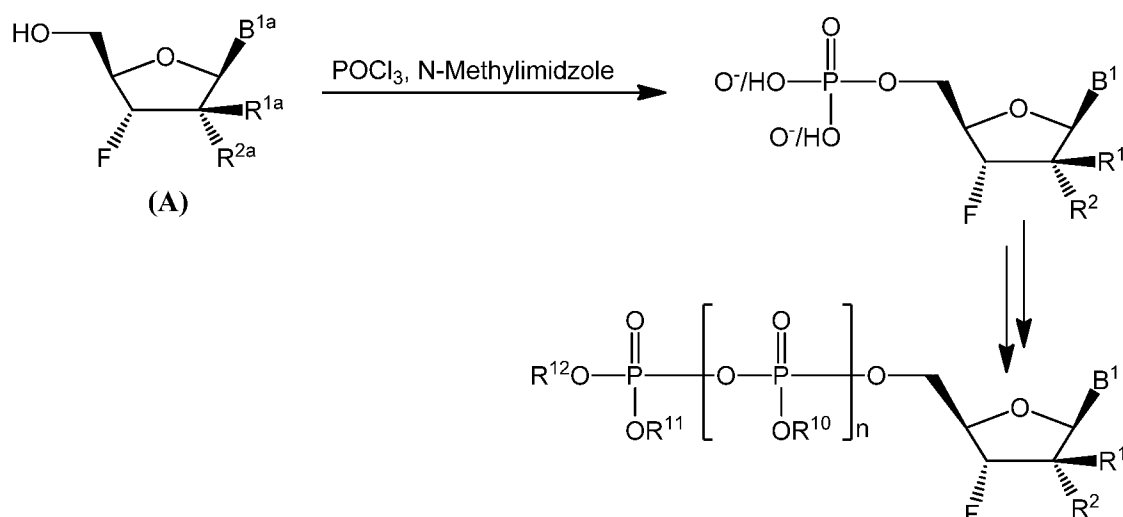
[0116] One method for forming a compound of Formula (I) is shown in Scheme 1. In Scheme 1, R^{1a} , R^{2a} and B^{1a} can be the same as R^1 , R^2 and B^1 as described herein for Formula (I). In some embodiments, a compound of Formula (I) can be generated from a compound of Formula (A) and a compound of Formula (B) using an organometallic reagent, such as a Grignard reagent. 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, an appropriate base can be used to form a compound of Formula (I). Examples of suitable 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 imidazoles (e.g., N-methylimidazole)).

[0117] When compounds of Formula (I) has Z^1 being sulfur, the sulfur can be added in various manners. In some embodiments, the sulfur can be part of the phosphorus containing



precursor, for example, $\text{R}^{4\text{B}}-\text{P}(\text{R}^{4\text{A}})=\text{S}-\text{Cl}$. Alternatively, one of the oxygens attached to the phosphorus can be exchanged with a sulfur using a sulfurization reagent. Suitable sulfurization agents are known to those skilled in the art, and include, but are not limited to, elemental sulfur, Lawesson's reagent, cyclooctasulfur, 3H-1,2-Benzodithiole-3-one-1,1-dioxide (Beaucage's reagent), 3-((N,N-dimethylaminomethylidene)amino)-3H-1,2,4-dithiazole-5-thione (DDTT) and bis(3-triethoxysilyl)propyl-tetrasulfide (TEST).

Scheme 2



[0118] A phosphorus containing precursor can be coupled to the nucleoside, for example, a compound of Formula (A). Following the coupling of the phosphorus containing precursor, any leaving groups can be cleaved under suitable conditions, such as hydrolysis. In Scheme 2, R^{1a}, R^{2a} and B^{1a} can be the same as R¹, R² and B¹ as described herein for Formula (I). Further phosphorus containing groups can be added using methods known to those skilled in the art, for example using a pyrophosphate. If desired, one or more bases can be used during the addition of each phosphorus-containing group. Examples of suitable bases are described herein.

[0119] As provided herein, R² can be -OC(=O)R¹⁵. The -OC(=O)R¹⁵ group can be formed at the 2'-position using various methods known to those skilled in the art. As an example, a compound of Formula (I), wherein R² is a hydroxy group, 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)R¹⁵ group can be formed at the 2'-position 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).

[0120] 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 R² is a hydroxy group, the hydroxy group can be protected with a suitable protecting group, such as triarylmethyl and/or silyl group. 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 (CPTTr), 4,4',4''-tris (levulinyloxy) trityl (TLTr), p-anisyl-1-naphthylphenylmethyl, di-o-anisyl-1-naphthylmethyl, p-tolyldipheylmethyl, 3-(imidazolylmethyl)-4,4'-dimethoxytrityl, 9-phenylxanthen-9-yl (Pixyl), 9-(p-methoxyphenyl)xanthen-9-yl (Mox), 4-decyloxytrityl, 4-hexadecyloxytrityl, 4,4'-dioctadecyltrityl, 9-(4-octadecyloxyphenyl)xanthen-9-yl, 1,1'-bis-(4-methoxyphenyl)-1'-pyrenylmethyl, 4,4',4''-tris-(tert-butylphenyl)methyl (TTTr) and 4,4'-di-3,5-hexadienoxytrityl. Examples of suitable silyl groups are described herein and include trimethylsilyl (TMS), *tert*-butyldimethylsilyl (TBDMS), triisopropylsilyl (TIPS), *tert*-butyldiphenylsilyl (TBDPS), tri-*iso*-propylsilyloxymethyl and [2-(trimethylsilyl)ethoxy]methyl.

Pharmaceutical Compositions

[0121] Some embodiments described herein relates to a pharmaceutical composition, that can include a therapeutically effective amount of one or more compounds described herein (e.g., a compound of Formula (I)), or a pharmaceutically acceptable salt thereof) and a pharmaceutically acceptable carrier, diluent, excipient or combination thereof. In some embodiments, the pharmaceutical composition can include a single diastereomer of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, (for example, a single diastereomer is present in the pharmaceutical composition at a concentration of greater than 99% compared to the total concentration of the other diastereomers). In other embodiments, the pharmaceutical composition can include a mixture of diastereomers of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. For example, the pharmaceutical composition can include a concentration of one diastereomer of $> 50\%$, $\geq 60\%$, $\geq 70\%$, $\geq 80\%$, $\geq 90\%$, $\geq 95\%$, 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.

[0122] 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.

[0123] The term “physiologically acceptable” defines a carrier, diluent or excipient that does not abrogate the biological activity and properties of the compound.

[0124] 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.

[0125] 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.

[0126] 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.

[0127] 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.

[0128] 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.

[0129] 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.

[0130] 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.

[0131] 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

[0132] Some embodiments disclosed herein relate to a method of treating and/or ameliorating a disease or condition that can include administering to a subject a therapeutically effective amount of one or more compounds described herein, such as a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes a compound described herein, or a pharmaceutically acceptable salt thereof. Other embodiments disclosed herein relate to a method of treating and/or ameliorating a disease or condition that can include administering to a subject identified as suffering from the disease or condition a therapeutically effective amount of one or more compounds described herein, such as a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes a compound described herein, or a pharmaceutically acceptable salt thereof.

[0133] Some embodiments disclosed herein relates to a method of ameliorating or treating a HCV infection that can include administering to a subject identified as suffering from a HCV infection a therapeutically effective amount of one or more compounds described herein (for example, a compound of Formula (I)), or a pharmaceutical composition that includes one or

more compounds described herein, or a pharmaceutically acceptable salt thereof. 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 HCV infection that can include administering to a subject identified as suffering from a HCV infection a therapeutically effective amount of one or more compounds described herein. 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 HCV infection by administering to a subject identified as suffering from a HCV infection a therapeutically effective amount of one or more compounds described herein.

[0134] Some embodiments disclosed herein relate to methods of ameliorating and/or treating a HCV infection that can include contacting a cell infected with the hepatitis C 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 HCV infection that can include contacting a cell infected with the hepatitis C 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 HCV infection by contacting a cell infected with the hepatitis C virus with an effective amount of said compound(s).

[0135] Some embodiments disclosed herein relate to methods of inhibiting replication of a hepatitis C virus that can include contacting a cell infected with the hepatitis C 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 hepatitis C virus that can include contacting a cell infected with the hepatitis C 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 hepatitis C virus by contacting a cell infected with the hepatitis C virus with an effective amount of said compound(s). In some embodiments, the compound of Formula (I), or a pharmaceutical acceptable salt thereof, that can be used to ameliorating and/or treating a viral infection (for example, a HCV infection) and/or inhibit replication of a virus (such as a HCV virus) can be any of the embodiments provided in any of the embodiments described in paragraphs [0090]-[0108].

[0136] In some embodiments, the compound can be a compound of Formula (I), or a pharmaceutical acceptable salt thereof, wherein R^3 is hydrogen. In other embodiments, the compound can be a compound of Formula (I), wherein compound of Formula (I) is a mono, di, or triphosphate, or a pharmaceutically acceptable salt of the foregoing. In still other embodiments, the compound can be a compound of Formula (I), wherein compound of Formula (I) is a thiomonophosphate, alpha-thiodiphosphate, or alpha-thiotriphosphate, or a pharmaceutically acceptable salt of the foregoing. In yet still other embodiments, the compound can be a compound of Formula (I), wherein compound of Formula (I) is phosphoramidate or phosphorbisamidate, or a pharmaceutically acceptable salt of the foregoing. In some embodiments, the compound can be a compound of Formula (I), wherein compound of Formula (I) is thiophosphoramidate or thiophosphorbisamidate, or a pharmaceutically acceptable salt of the foregoing.

[0137] 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.

[0138] Some embodiments described herein relate to a method of inhibiting NS5B polymerase activity that can include contacting a cell infected with hepatitis C virus with an effective amount of a compound of Formula (I), or a pharmaceutical acceptable salt thereof. Some embodiments described herein relate to a method of inhibiting NS5B polymerase activity that can include administering to a subject infected with hepatitis C virus an effective amount of a compound of Formula (I), or a pharmaceutical acceptable salt thereof. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can inhibit a RNA dependent RNA polymerase, and thus, inhibit the replication of HCV RNA. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can inhibit a HCV polymerase (for example, NS5B polymerase).

[0139] 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 Formula (I), or a pharmaceutical acceptable salt thereof), wherein the liver condition is caused by a HCV infection. Some embodiments described herein relate to a method of increasing liver function in a subject having a HCV infection that can include administering to the subject an effective amount of a compound or a pharmaceutical composition described herein (for example, a compound of Formula (I), or a pharmaceutical acceptable salt thereof). Also contemplated is a method for reducing or eliminating further virus-caused liver damage in a subject having an HCV infection by administering to the subject an effective amount of a compound or a pharmaceutical composition described herein (for example, a compound of Formula (I), or a pharmaceutical acceptable salt thereof). In some embodiments, this method can include slowing or halting the progression of liver disease. In other embodiments, the course of the disease can be reversed, and stasis or improvement in liver function is contemplated. In some embodiments, liver fibrosis, liver cirrhosis and/or liver cancer can be treated; liver function can be increased; virus-caused liver damage can be reduced or eliminated; progression of liver disease can be slowed or halted; the course of the liver disease can be reversed and/or liver function can be improved or maintained by contacting a cell infected with hepatitis C virus with an effective amount of a compound described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof.)

[0140] There are a variety of genotypes of HCV, and a variety of subtypes within each genotype. For example, at present it is known that there are eleven (numbered 1 through 11) main genotypes of HCV, although others have classified the genotypes as 6 main genotypes. Each of these genotypes is further subdivided into subtypes (1a-1c; 2a-2c; 3a-3b; 4a-4e; 5a; 6a; 7a- 7b; 8a-8b; 9a; 10a; and 11a). In some embodiments, an effective amount of a compound of Formula (I), or a pharmaceutical acceptable salt thereof, or a pharmaceutical composition that includes an effective amount of a compound of Formula (I), or a pharmaceutical acceptable salt thereof, can be effective to treat at least one genotype of HCV. In some embodiments, a compound described herein (for example, a compound of Formula (I), or a pharmaceutical acceptable salt thereof) can be effective to treat all 11 genotypes of HCV. In some embodiments, a compound described herein (for example, a compound of Formula (I), or a pharmaceutical acceptable salt thereof) can be effective to treat 3 or more, 5 or more, 7 or more, or 9 or more genotypes of HCV. In some embodiments, a compound of Formula (I), or a pharmaceutical acceptable salt thereof can be more effective against a larger number of HCV genotypes than the standard of care. In some embodiments, a compound of Formula (I), or a

pharmaceutical acceptable salt thereof, can be more effective against a particular HCV genotype than the standard of care (such as genotype 1, 2, 3, 4, 5 and/or 6).

[0141] Various indicators for determining the effectiveness of a method for treating a HCV infection are known to those skilled in the art. Examples of suitable indicators include, but are not limited to, a reduction in viral load, a reduction in viral replication, a reduction in time to seroconversion (virus undetectable in patient serum), an increase in the rate of sustained viral response to therapy, a reduction of morbidity or mortality in clinical outcomes, a reduction in the rate of liver function decrease; stasis in liver function; improvement in liver function; reduction in one or more markers of liver dysfunction, including alanine transaminase, aspartate transaminase, total bilirubin, conjugated bilirubin, gamma glutamyl transpeptidase and/or other indicator of disease response. Similarly, successful therapy with an effective amount of a compound or a pharmaceutical composition described herein (for example, a compound of Formula (I), or a pharmaceutical acceptable salt thereof) can reduce the incidence of liver cancer in HCV infected subjects.

[0142] In some embodiments, an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is an amount that is effective to reduce HCV viral titers to undetectable levels, for example, to about 100 to about 500, to about 50 to about 100, to about 10 to about 50, or to about 15 to about 25 international units/mL serum. In some embodiments, an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is an amount that is effective to reduce HCV viral load compared to the HCV viral load before administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. For example, wherein the HCV viral load is measured before administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and again after completion of the treatment regime with the compound of Formula (I), or a pharmaceutically acceptable salt thereof (for example, 1 month after completion). In some embodiments, an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be an amount that is effective to reduce HCV viral load to lower than about 25 international units/mL serum. In some embodiments, an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is an amount that is effective to achieve a reduction in HCV viral titer in the serum of the subject in the range of about 1.5-log to about a 2.5-log reduction, about a 3-log to about a 4-log reduction, or a greater than about 5-log reduction compared to the viral load before administration of the compound of Formula (I), or a pharmaceutically acceptable salt thereof. For example, the HCV viral load can be measured before administration of the compound of Formula (I), or a pharmaceutically

acceptable salt thereof, and again after completion of the treatment regime with the compound of Formula (I), or a pharmaceutically acceptable salt thereof (for example, 1 month after completion).

[0143] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can result in at least a 1, 2, 3, 4, 5, 10, 15, 20, 25, 50, 75, 100-fold or more reduction in the replication of the hepatitis C virus relative to pre-treatment levels in a subject, as determined after completion of the treatment regime (for example 1 month after completion). In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can result in a reduction of the replication of the hepatitis C virus relative to pre-treatment levels in the range of about 2 to about 5 fold, about 10 to about 20 fold, about 15 to about 40 fold, or about 50 to about 100 fold. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can result in a reduction of the hepatitis C virus 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 the hepatitis C virus replication compared to the reduction of the hepatitis C virus 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.

[0144] In some embodiments, an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, is an amount that is effective to achieve a sustained viral response, for example, non-detectable or substantially non-detectable HCV RNA (e.g., less than about 500, less than about 200, less than about 100, less than about 25, or less than about 15 international units 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.

[0145] In some embodiments, a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can reduce a level of a marker of liver fibrosis by at least about 10%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, or at least about 80%, or more, compared to the level of the marker in an untreated subject, or to a placebo-treated subject. Methods of measuring serum markers are known to those skilled in the art and include immunological-based methods, e.g., enzyme-linked immunosorbent assays (ELISA),

radioimmunoassays, and the like, using antibody specific for a given serum marker. A non-limiting list of examples of 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), or a pharmaceutically acceptable salt thereof, can be an amount effective to reduce ALT, AST, ALP, GGT and/or TBIL levels to with what is considered a normal level.

[0146] 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).

[0147] 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.

[0148] 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 (for example, an agent used in a conventional standard of care). In some embodiments, development of resistant HCV strains is delayed when a subject is treated with a compound of Formula (I), or a pharmaceutically acceptable salt thereof, compared to the development of HCV strains resistant to other HCV drugs (such as a drug used in a conventional standard of care).

[0149] In some embodiments, an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be administered to a subject for whom other anti-HCV medications are contraindicated. For example, administration of pegylated interferon alpha in combination with ribavirin is contraindicated in subjects with hemoglobinopathies (e.g., thalassemia major, sickle-cell anemia) and other subjects at risk from the hematologic side effects of current therapy. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be provided to a subject that is hypersensitive to interferon and/or ribavirin.

[0150] 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.

[0151] The standard of care for treating HCV has been associated with several side effects (adverse events). In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can decrease the number and/or severity of 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 (for example, an agent used in a conventional standard of care).

[0152] Table 1 provides some embodiments of the percentage improvement obtained using a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as compared to the standard of care. Examples include the following: in some embodiments, a compound of

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

Table 1

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

[0153] 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.

[0154] 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.

[0155] The terms “therapeutically effective amount” and “effective amount” are used to indicate an amount of an active compound, or pharmaceutical agent, that elicits the biological or medicinal response indicated. For example, a therapeutically effective amount of compound can be the amount needed to prevent, alleviate or ameliorate symptoms of disease or prolong the survival of the subject being treated. This response may occur in a tissue, system, animal or human and includes alleviation of the signs or symptoms of the disease being treated. Determination of a therapeutically effective amount is well within the capability of those skilled in the art, in view of the disclosure provided herein. The therapeutically effective amount of the compounds disclosed herein required as a dose will depend on the route of administration, the type of animal, including human, being treated, and the physical characteristics of the specific animal under consideration. The dose can be tailored to achieve a desired effect, but will depend on such factors as weight, diet, concurrent medication and other factors which those skilled in the medical arts will recognize.

[0156] 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.

[0157] The dosage may range broadly, depending upon the desired effects and the therapeutic indication. Alternatively dosages may be based and calculated upon the surface area of the patient, as understood by those of skill in the art. Although the exact dosage will be determined on a drug-by-drug basis, in most cases, some generalizations regarding the dosage can be made. The daily dosage regimen for an adult human patient may be, for example, an oral dose of between 0.01 mg and 3000 mg of each active ingredient, preferably between 1 mg and 700 mg, e.g. 5 to 200 mg. The dosage may be a single one or a series of two or more given in the course of one or more days, as is needed by the subject. In some embodiments, the compounds will be administered for a period of continuous therapy, for example for a week or

more, or for months or years. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be administered less frequently compared to the frequency of administration of an agent within the standard of care. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be administered one time per day. For example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be administered one time per day to a subject suffering from a HCV infection. In some embodiments, the total time of the treatment regime with a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be less compared to the total time of the treatment regime with the standard of care.

[0158] 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.

[0159] 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.

[0160] 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.

[0161] 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.

[0162] 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

[0163] In some embodiments, the compounds disclosed herein, such as a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes a compound described herein, or a pharmaceutically acceptable salt thereof, can be used in combination with one or more additional agent(s). Examples of additional agents that can be used in combination with a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes a compound of Formula (I), or a pharmaceutically acceptable salt thereof, include, but are not limited to, agents currently used in a conventional standard of care for treating HCV, HCV protease inhibitors, HCV polymerase inhibitors, NS5A inhibitors, other antiviral compounds, compounds of Formula (AA), (including pharmaceutically acceptable salts and pharmaceutical compositions that can include a compound of Formula (AA), or a pharmaceutically acceptable salt thereof), 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 (CC) (including pharmaceutically acceptable salts and pharmaceutical compositions that can include a compound of Formula (CC), 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, D and E.

[0164] 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.

[0165] 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.

[0166] 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.

[0167] 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. Additional HCV protease inhibitors suitable for use 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 VP-19744, PSI-879, VCH-759/VX-759, HCV-371, IDX-375, GL-60667, JTK-109, PSI-6130, R1479, R-1626, R-7182, MK-0608, INX-8014, INX-8018, A-848837, A-837093, BILB-1941, VCH-916, VCH-716, GSK-71185, GSK-625433, XTL-2125 and those disclosed in PCT Publication No. WO 2012/142085, which is hereby incorporated by reference for the limited purpose of its disclosure of HCV protease inhibitors, HCV polymerase inhibitors and NS5A inhibitors. A non-limiting list of example HCV protease inhibitors includes the compounds numbered 1001-1016 in Figure 1.

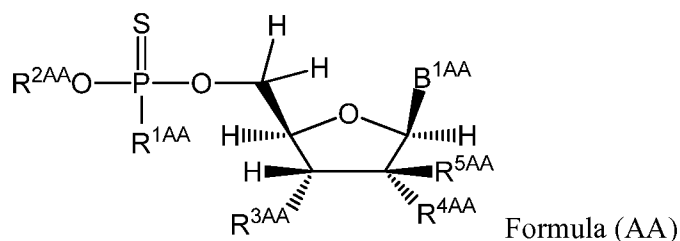
[0168] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be used in combination with a HCV polymerase inhibitor. In some embodiments, the HCV polymerase inhibitor can be a nucleoside inhibitor. In other embodiments, the HCV polymerase inhibitor can be a non-nucleoside inhibitor. Examples of suitable nucleoside inhibitors include, but are not limited to, RG7128, PSI-7851, PSI-7977, INX-189, PSI-352938, PSI-661, 4'-azidouridine (including known prodrugs of 4'-azidouridine), GS-6620, IDX-184, and TMC649128 and/or combinations thereof. A non-limiting list of example nucleoside inhibitors includes compounds numbered 2001-2012 in Figure 2. Examples of suitable non-nucleoside inhibitors include, but are not limited to, ABT-333, ANA-598, VX-222, HCV-796, BI-207127, GS-9190, PF-00868554 (FILIBUVIR®), VX-497 and/or combinations thereof. A non-limiting list of example non-nucleoside inhibitors includes the compounds numbered 3001-3014 in Figure 3. Further HCV polymerase inhibitors suitable for use 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 VX-500, VX-813, VBY-376, TMC-435350, EZ-058, EZ-063, GS-9132, ACH-1095, IDX-136, IDX-316, ITMN-8356, ITMN-8347, ITMN-8096, ITMN-7587, VX-985, and those disclosed in PCT Publication No. WO 2012/142085.

[0169] 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. Examples of NS5A inhibitors include BMS-790052, PPI-461, ACH-2928, GS-5885,

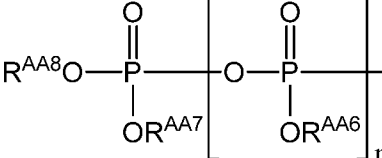
BMS-824393 and/or combinations thereof. A non-limiting list of example NS5A inhibitors includes the compounds numbered 4001-4012 in Figure 4. Additional NS5A inhibitors suitable for use in combination with a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes a compound of Formula (I), or a pharmaceutically acceptable salt thereof, include A-832, PPI-1301 and those disclosed in PCT Publication No. WO 2012/142085.

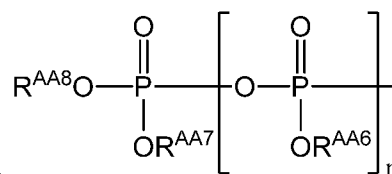
[0170] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be used in combination with other antiviral compounds. Examples of other antiviral compounds include, but are not limited to, Debio-025, MIR-122, cyclosporin A and/or combinations thereof. A non-limiting list of example other antiviral compounds includes the compounds numbered 5001-5012 in Figure 5.

[0171] 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), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes a compound of Formula (AA), or a pharmaceutically acceptable salt thereof (see, U.S. Publication No. 2013/0164261, filed June 27, 2013, the contents of which are incorporated by reference in its entirety):



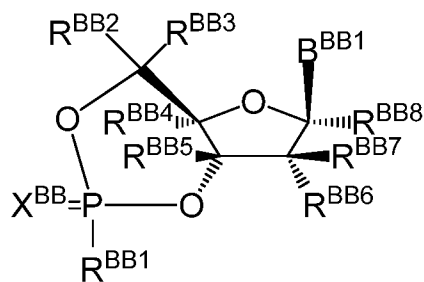
wherein: B^{AA1} can be an optionally substituted heterocyclic base or an optionally substituted heterocyclic base with a protected amino group; R^{AA1} can be selected from O⁻, OH, an optionally substituted N-linked amino acid and an optionally substituted N-linked amino acid ester derivative; R^{AA2} can be absent or selected from hydrogen, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl and

, wherein R^{AA6}, R^{AA7} and R^{AA8} can be independently absent or hydrogen, and n^{AA} can be 0 or 1; provided that when R^{AA1} is O⁻ or OH, then R^{AA2} is absent,



hydrogen or $\text{R}^{\text{AA}3}$ can be selected from hydrogen, halogen, $-\text{OR}^{\text{AA}9}$ and $-\text{OC}(=\text{O})\text{R}^{\text{AA}10}$; $\text{R}^{\text{AA}4}$ can be selected from halogen, $-\text{OR}^{\text{AA}11}$ and $-\text{OC}(=\text{O})\text{R}^{\text{AA}12}$; or $\text{R}^{\text{AA}3}$ and $\text{R}^{\text{AA}4}$ can be both an oxygen atom which are linked together by a carbonyl group; $\text{R}^{\text{AA}5}$ can be selected from an optionally substituted C_{2-6} alkyl, an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{2-6} alkynyl and an optionally substituted C_{3-6} cycloalkyl; or $\text{R}^{\text{AA}4}$ and $\text{R}^{\text{AA}5}$ together can form $-(\text{C}_{1-6} \text{ alkyl})-\text{O}-$ or $-\text{O}-(\text{C}_{1-6} \text{ alkyl})-$; $\text{R}^{\text{AA}9}$ and $\text{R}^{\text{AA}11}$ can be independently hydrogen or an optionally substituted C_{1-6} alkyl; and $\text{R}^{\text{AA}10}$ and $\text{R}^{\text{AA}12}$ can be independently an optionally substituted C_{1-6} alkyl or an optionally substituted C_{3-6} cycloalkyl. A non-limiting list of examples of compounds of Formula (AA) includes the compounds numbered 7000-7027 in Figure 7.

[0172] 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. Publication No. 2012/0165286, published June 28, 2012, the contents of which are incorporated by reference in their entireties):

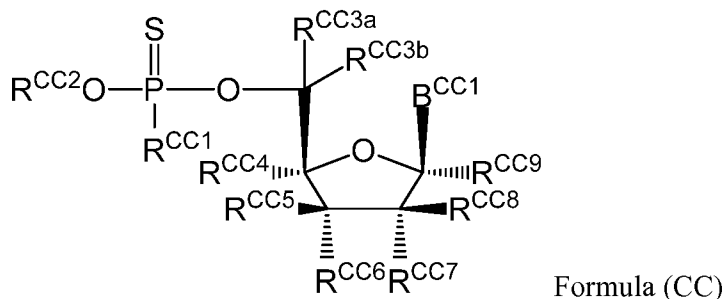


Formula (BB)

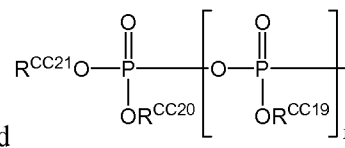
wherein $\text{B}^{\text{BB}1}$ can be an optionally substituted heterocyclic base or an optionally substituted heterocyclic base with a protected amino group; X^{BB} can be O (oxygen) or S (sulfur); $\text{R}^{\text{BB}1}$ can be selected from $-\text{Z}^{\text{BB}}-\text{R}^{\text{BB}9}$, an optionally 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 $\text{N}(\text{R}^{\text{BB}10})$; $\text{R}^{\text{BB}2}$ and $\text{R}^{\text{BB}3}$ can be independently selected from hydrogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{2-6} alkynyl, an optionally substituted C_{1-6} haloalkyl and an optionally substituted aryl(C_{1-6} alkyl); or $\text{R}^{\text{BB}2}$ and $\text{R}^{\text{BB}3}$ can be taken together to form a group selected from an optionally substituted C_{3-6} cycloalkyl, an optionally substituted C_{3-6} cycloalkenyl, an optionally substituted

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 8000-8016 in Figure 8.

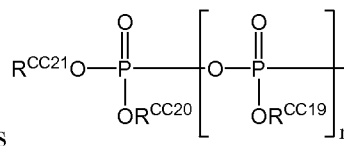
[0173] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be used in combination with a compound of Formula (CC), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition that includes a compound of Formula (CC), or a pharmaceutically acceptable salt thereof (see, U.S. Publication No. 2012/0071434, published March 22, 2012, the contents of which are incorporated by reference in its entirety):



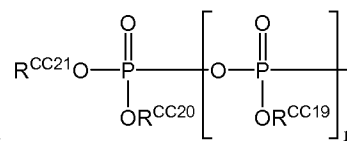
wherein B^{CC1} can be an optionally substituted heterocyclic base or an optionally substituted heterocyclic base with a protected amino group; R^{CC1} can be selected from O^- , OH, an optionally substituted N-linked amino acid and an optionally substituted N-linked amino acid ester derivative; R^{CC2} can be selected from an optionally substituted aryl, an optionally substituted



heteroaryl, an optionally substituted heterocyclyl and R^{CC19} , R^{CC20} and R^{CC21} can be independently absent or hydrogen, and n^{CC} can be 0 or 1;



provided that when R^{CC1} is O^- or OH, then R^{CC2} is R^{CC3a} and R^{CC3b} can be independently selected from hydrogen, deuterium, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{2-6} alkynyl, an optionally substituted C_{1-6} haloalkyl and aryl(C_{1-6} alkyl); or R^{CC3a} and R^{CC3b} can be taken together to form an optionally substituted C_{3-6} cycloalkyl; R^{CC4} can be selected from hydrogen, azido, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl and an optionally substituted C_{2-6} alkynyl; R^{CC5} can be selected from hydrogen, halogen, azido, cyano, an optionally substituted C_{1-6} alkyl, $-OR^{CC10}$ and $-OC(=O)R^{CC11}$; R^{CC6} can be selected from hydrogen, halogen, azido, cyano, an optionally substituted C_{1-6} alkyl, $-OR^{CC12}$ and $-OC(=O)R^{CC13}$; R^{CC7} can be selected from hydrogen, halogen, azido, cyano, an optionally substituted C_{1-6} alkyl, $-OR^{CC14}$ and $-OC(=O)R^{CC15}$; or R^{CC6} and R^{CC7} can be both oxygen atoms and linked together by a carbonyl group; R^{CC8} can be selected from hydrogen, halogen, azido, cyano, an optionally substituted C_{1-6} alkyl, $-OR^{CC16}$ and $-OC(=O)R^{CC17}$; R^{CC9} can be selected from hydrogen, azido, cyano, an optionally substituted C_{1-6} alkyl and $-OR^{CC18}$; R^{CC10} , R^{CC12} , R^{CC14} , R^{CC16} and R^{CC18} can be independently selected from hydrogen and an optionally substituted C_{1-6} alkyl; and R^{CC11} , R^{CC13} , R^{CC15} and R^{CC17} can be independently selected from an optionally substituted C_{1-6} alkyl and an optionally substituted C_{3-6} cycloalkyl. In some embodiments, when R^{CC3a} , R^{CC3b} , R^{CC4} , R^{CC5} , R^{CC7} , R^{CC8} and R^{CC9} are all hydrogen, then R^{CC6} is



not azido. In some embodiments, R^{CC2} cannot be hydrogen, R^{CC3b} is hydrogen, R^{CC4} is H, R^{CC5} is OH or H, R^{CC6} is hydrogen, OH, or $-OC(=O)CH_3$, R^{CC7} is hydrogen, OH, OCH_3 or $-OC(=O)CH_3$, R^{CC8} is hydrogen, OH or OCH_3 , R^{CC9} is H and B^{CC1} is an optionally substituted adenine, an optionally substituted guanine, an

optionally substituted uracil or an optionally substituted hypoxanthine. In some embodiments,

$$\text{R}^{\text{CC}2} \text{ cannot be } \text{R}^{\text{CC}21}\text{O}-\text{P}\left(\begin{array}{c} \text{O} \\ \parallel \\ \text{OR}^{\text{CC}20} \end{array}\right)-\left[\text{O}-\text{P}\left(\begin{array}{c} \text{O} \\ \parallel \\ \text{OR}^{\text{CC}19} \end{array}\right)\right]_{\text{n}^{\text{CC}}}$$
 A non-limiting list of examples of compounds of Formula (CC) includes the compounds numbered 6000-6078 in Figure 6.

[0174] Some embodiments described herein relate to a method of ameliorating or treating a HCV infection that can include contacting a cell infected with the HCV infection with a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with one or more agents selected from an interferon, ribavirin, a HCV protease inhibitor, a HCV polymerase inhibitor, a NS5A inhibitor, an antiviral compound, a compound of Formula (AA), a compound of Formula (BB) and a compound of Formula (CC), or a pharmaceutically acceptable salt of any of the aforementioned compounds.

[0175] Some embodiments described herein relate to a method of ameliorating or treating a HCV infection that can include administering to a subject suffering from the HCV infection a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with one or more agents selected from an interferon, ribavirin, a HCV protease inhibitor, a HCV polymerase inhibitor, a NS5A inhibitor, an antiviral compound, a compound of Formula (AA), a compound of Formula (BB) and a compound of Formula (CC), or a pharmaceutically acceptable salt of any of the aforementioned compounds.

[0176] Some embodiments described herein relate to a method of inhibiting the replication of a hepatitis C virus that can include contacting a cell infected with the hepatitis C virus with an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with one or more agents selected from an interferon, ribavirin, a HCV protease inhibitor, a HCV polymerase inhibitor, a NS5A inhibitor, an antiviral compound, a compound of Formula (AA), a compound of Formula (BB) and a compound of Formula (CC), or a pharmaceutically acceptable salt of any of the aforementioned compounds.

[0177] Some embodiments described herein relate to a method of inhibiting the replication of a hepatitis C virus that can include administering to a subject infected with the hepatitis C virus an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with one or more agents selected from an interferon, ribavirin, a HCV protease inhibitor, a HCV polymerase inhibitor, a NS5A inhibitor, an antiviral compound, a compound of Formula (AA), a compound of Formula (BB) and a compound of Formula (CC), or a pharmaceutically acceptable salt of any of the aforementioned compounds.

[0178] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be administered with one or more additional agent(s) together in a single pharmaceutical composition. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be administered with one or more additional agent(s) as two or more separate pharmaceutical compositions. For example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be administered in one pharmaceutical composition, and at least one of the additional agents can be administered in a second pharmaceutical composition. If there are at least two additional agents, one or more of the additional agents can be in a first pharmaceutical composition that includes a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and at least one of the other additional agent(s) can be in a second pharmaceutical composition.

[0179] 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.

[0180] The order of administration of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, with one or more additional agent(s) can vary. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be administered prior to all additional agents. In other embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be administered prior to at least one additional agent. In still other embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be administered concomitantly with one or more additional agent(s). In yet still other embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be administered subsequent to the administration of at least one additional agent. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can be administered subsequent to the administration of all additional agents.

[0181] In some embodiments, the combination of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with one or more additional agent(s) in

Figures 1-8 (including pharmaceutically acceptable salts and prodrugs thereof) can result in an additive effect. In some embodiments, the combination of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with one or more additional agent(s) in Figures 1-8 (including pharmaceutically acceptable salts and prodrugs thereof) can result in a synergistic effect. In some embodiments, the combination of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with one or more additional agent(s) in Figures 1-8 (including pharmaceutically acceptable salts and prodrugs thereof) can result in a strongly synergistic effect. In some embodiments, the combination of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with one or more additional agent(s) in Figures 1-8 (including pharmaceutically acceptable salts and prodrugs thereof) is not antagonistic.

[0182] 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.

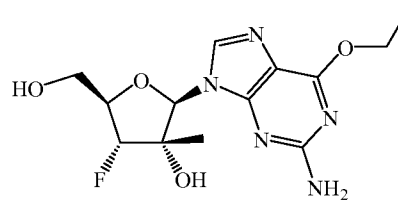
[0183] A potential advantage of utilizing a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with one or more additional agent(s) in Figures 1-8 (including pharmaceutically acceptable salts thereof) may be a reduction in the required amount(s) of one or more compounds of Figures 1-8 (including pharmaceutically acceptable salts thereof) that is effective in treating a disease condition disclosed herein (for example, HCV), as compared to the amount required to achieve same therapeutic result when one or more compounds of Figures 1-8 (including pharmaceutically acceptable salts thereof) are administered without a compound of Formula (I), or a pharmaceutically acceptable salt thereof. For example, the amount of a compound in Figures 1-8 (including a pharmaceutically acceptable salt thereof), can be less compared to the amount of the compound in Figures 1-8 (including a pharmaceutically acceptable salt thereof), needed to achieve the same viral load reduction when administered as a monotherapy. Another potential advantage of utilizing a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with one or more additional agent(s) in Figures 1-8 (including pharmaceutically acceptable salts 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.

[0184] Additional advantages of utilizing a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with one or more additional agent(s) in Figures 1-8 (including pharmaceutically acceptable salts thereof) may include little to no cross resistance between a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and one or more additional agent(s) in Figures 1-8 (including pharmaceutically acceptable salts thereof) thereof; different routes for elimination of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and one or more additional agent(s) in Figures 1-8 (including pharmaceutically acceptable salts thereof); little to no overlapping toxicities between a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and one or more additional agent(s) in Figures 1-8 (including pharmaceutically acceptable salts thereof); little to no significant effects on cytochrome P450; little to no pharmacokinetic interactions between a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and one or more additional agent(s) in Figures 1-8 (including pharmaceutically acceptable salts thereof); greater percentage of subjects achieving a sustained viral response compared to when a compound is administered as monotherapy and/or a decrease in treatment time to achieve a sustained viral response compared to when a compound is administered as monotherapy.

[0185] 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, D and E. Each numbered X and Y compound in Tables A, B, C, D and E has a corresponding name and/or structure provided in Figures 1-8. The numbered compounds in Tables A, B, C, D and E 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, D and E 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 1001:9002 in Table A represents a combination of compound 1001 with compound 9002, including pharmaceutically acceptable salts of compound 1001 and/or 9002, and pharmaceutical compositions including compound 1001 and 9002 (including pharmaceutical compositions that include

pharmaceutically acceptable salts of compound 1001 and/or compound 9002). Thus, the combination designated as 1001: 9002 in Table A represents the combination of Telaprevir



(compound 1001, as shown in Figure 1) and

(compound 9002

, as shown in Figure 9), including pharmaceutically acceptable salts of compound 1001 and/or 9002, and pharmaceutical compositions including compound 1001 and 9002 (including pharmaceutical compositions that include pharmaceutically acceptable salts of compound 1001 and/or compound 9002). Each of the combinations provided in Tables A, B, C, D and E can be used with one, two, three or more additional agents described herein. 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
1001 : 9000	1001 : 9001	1001 : 9002	1001 : 9003	1001 : 9004	1001 : 9005
1002 : 9000	1002 : 9001	1002 : 9002	1002 : 9003	1002 : 9004	1002 : 9005
1003 : 9000	1003 : 9001	1003 : 9002	1003 : 9003	1003 : 9004	1003 : 9005
1004 : 9000	1004 : 9001	1004 : 9002	1004 : 9003	1004 : 9004	1004 : 9005
1005 : 9000	1005 : 9001	1005 : 9002	1005 : 9003	1005 : 9004	1005 : 9005
1006 : 9000	1006 : 9001	1006 : 9002	1006 : 9003	1006 : 9004	1006 : 9005
1007 : 9000	1007 : 9001	1007 : 9002	1007 : 9003	1007 : 9004	1007 : 9005
1008 : 9000	1008 : 9001	1008 : 9002	1008 : 9003	1008 : 9004	1008 : 9005
1009 : 9000	1009 : 9001	1009 : 9002	1009 : 9003	1009 : 9004	1009 : 9005
1010 : 9000	1010 : 9001	1010 : 9002	1010 : 9003	1010 : 9004	1010 : 9005
1011 : 9000	1011 : 9001	1011 : 9002	1011 : 9003	1011 : 9004	1011 : 9005
1012 : 9000	1012 : 9001	1012 : 9002	1012 : 9003	1012 : 9004	1012 : 9005
1013 : 9000	1013 : 9001	1013 : 9002	1013 : 9003	1013 : 9004	1013 : 9005
1014 : 9000	1014 : 9001	1014 : 9002	1014 : 9003	1014 : 9004	1014 : 9005
1015 : 9000	1015 : 9001	1015 : 9002	1015 : 9003	1015 : 9004	1015 : 9005
1016 : 9000	1016 : 9001	1016 : 9002	1016 : 9003	1016 : 9004	1016 : 9005
2001 : 9000	2001 : 9001	2001 : 9002	2001 : 9003	2001 : 9004	2001 : 9005
2002 : 9000	2002 : 9001	2002 : 9002	2002 : 9003	2002 : 9004	2002 : 9005
2003 : 9000	2003 : 9001	2003 : 9002	2003 : 9003	2003 : 9004	2003 : 9005
2004 : 9000	2004 : 9001	2004 : 9002	2004 : 9003	2004 : 9004	2004 : 9005
2005 : 9000	2005 : 9001	2005 : 9002	2005 : 9003	2005 : 9004	2005 : 9005
2006 : 9000	2006 : 9001	2006 : 9002	2006 : 9003	2006 : 9004	2006 : 9005
2007 : 9000	2007 : 9001	2007 : 9002	2007 : 9003	2007 : 9004	2007 : 9005
2008 : 9000	2008 : 9001	2008 : 9002	2008 : 9003	2008 : 9004	2008 : 9005
2009 : 9000	2009 : 9001	2009 : 9002	2009 : 9003	2009 : 9004	2009 : 9005
2010 : 9000	2010 : 9001	2010 : 9002	2010 : 9003	2010 : 9004	2010 : 9005
2011 : 9000	2011 : 9001	2011 : 9002	2011 : 9003	2011 : 9004	2011 : 9005
2012 : 9000	2012 : 9001	2012 : 9002	2012 : 9003	2012 : 9004	2012 : 9005

X : Y	X : Y	X : Y	X : Y	X : Y	X : Y
1001 : 9006	1001 : 9007	1001 : 9008	1001 : 9009	1001 : 9010	1001 : 9011
1002 : 9006	1002 : 9007	1002 : 9008	1002 : 9009	1002 : 9010	1002 : 9011
1003 : 9006	1003 : 9007	1003 : 9008	1003 : 9009	1003 : 9010	1003 : 9011
1004 : 9006	1004 : 9007	1004 : 9008	1004 : 9009	1004 : 9010	1004 : 9011
1005 : 9006	1005 : 9007	1005 : 9008	1005 : 9009	1005 : 9010	1005 : 9011
1006 : 9006	1006 : 9007	1006 : 9008	1006 : 9009	1006 : 9010	1006 : 9011
1007 : 9006	1007 : 9007	1007 : 9008	1007 : 9009	1007 : 9010	1007 : 9011
1008 : 9006	1008 : 9007	1008 : 9008	1008 : 9009	1008 : 9010	1008 : 9011
1009 : 9006	1009 : 9007	1009 : 9008	1009 : 9009	1009 : 9010	1009 : 9011
1010 : 9006	1010 : 9007	1010 : 9008	1010 : 9009	1010 : 9010	1010 : 9011
1011 : 9006	1011 : 9007	1011 : 9008	1011 : 9009	1011 : 9010	1011 : 9011
1012 : 9006	1012 : 9007	1012 : 9008	1012 : 9009	1012 : 9010	1012 : 9011
1013 : 9006	1013 : 9007	1013 : 9008	1013 : 9009	1013 : 9010	1013 : 9011
1014 : 9006	1014 : 9007	1014 : 9008	1014 : 9009	1014 : 9010	1014 : 9011
1015 : 9006	1015 : 9007	1015 : 9008	1015 : 9009	1015 : 9010	1015 : 9011
1016 : 9006	1016 : 9007	1016 : 9008	1016 : 9009	1016 : 9010	1016 : 9011
2001 : 9006	2001 : 9007	2001 : 9008	2001 : 9009	2001 : 9010	2001 : 9011
2002 : 9006	2002 : 9007	2002 : 9008	2002 : 9009	2002 : 9010	2002 : 9011
2003 : 9006	2003 : 9007	2003 : 9008	2003 : 9009	2003 : 9010	2003 : 9011
2004 : 9006	2004 : 9007	2004 : 9008	2004 : 9009	2004 : 9010	2004 : 9011
2005 : 9006	2005 : 9007	2005 : 9008	2005 : 9009	2005 : 9010	2005 : 9011
2006 : 9006	2006 : 9007	2006 : 9008	2006 : 9009	2006 : 9010	2006 : 9011
2007 : 9006	2007 : 9007	2007 : 9008	2007 : 9009	2007 : 9010	2007 : 9011
2008 : 9006	2008 : 9007	2008 : 9008	2008 : 9009	2008 : 9010	2008 : 9011
2009 : 9006	2009 : 9007	2009 : 9008	2009 : 9009	2009 : 9010	2009 : 9011
2010 : 9006	2010 : 9007	2010 : 9008	2010 : 9009	2010 : 9010	2010 : 9011
2011 : 9006	2011 : 9007	2011 : 9008	2011 : 9009	2011 : 9010	2011 : 9011
2012 : 9006	2012 : 9007	2012 : 9008	2012 : 9009	2012 : 9010	2012 : 9011

X : Y	X : Y	X : Y	X : Y	X : Y	X : Y
1001 : 9012	1001 : 9013	1001 : 9014	1001 : 9015	--	--
1002 : 9012	1002 : 9013	1002 : 9014	1002 : 9015		
1003 : 9012	1003 : 9013	1003 : 9014	1003 : 9015		
1004 : 9012	1004 : 9013	1004 : 9014	1004 : 9015		
1005 : 9012	1005 : 9013	1005 : 9014	1005 : 9015		
1006 : 9012	1006 : 9013	1006 : 9014	1006 : 9015		
1007 : 9012	1007 : 9013	1007 : 9014	1007 : 9015		
1008 : 9012	1008 : 9013	1008 : 9014	1008 : 9015		
1009 : 9012	1009 : 9013	1009 : 9014	1009 : 9015		
1010 : 9012	1010 : 9013	1010 : 9014	1010 : 9015		
1011 : 9012	1011 : 9013	1011 : 9014	1011 : 9015		
1012 : 9012	1012 : 9013	1012 : 9014	1012 : 9015		
1013 : 9012	1013 : 9013	1013 : 9014	1013 : 9015		
1014 : 9012	1014 : 9013	1014 : 9014	1014 : 9015		
1015 : 9012	1015 : 9013	1015 : 9014	1015 : 9015		
1016 : 9012	1016 : 9013	1016 : 9014	1016 : 9015		
2001 : 9012	2001 : 9013	2001 : 9014	2001 : 9015		
2002 : 9012	2002 : 9013	2002 : 9014	2002 : 9015		
2003 : 9012	2003 : 9013	2003 : 9014	2003 : 9015		
2004 : 9012	2004 : 9013	2004 : 9014	2004 : 9015		
2005 : 9012	2005 : 9013	2005 : 9014	2005 : 9015		
2006 : 9012	2006 : 9013	2006 : 9014	2006 : 9015		
2007 : 9012	2007 : 9013	2007 : 9014	2007 : 9015		
2008 : 9012	2008 : 9013	2008 : 9014	2008 : 9015		
2009 : 9012	2009 : 9013	2009 : 9014	2009 : 9015		
2010 : 9012	2010 : 9013	2010 : 9014	2010 : 9015		
2011 : 9012	2011 : 9013	2011 : 9014	2011 : 9015		
2012 : 9012	2012 : 9013	2012 : 9014	2012 : 9015		

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

X : Y	X : Y	X : Y	X : Y	X : Y	X : Y
3001 : 9000	3001 : 9001	3001 : 9002	3001 : 9003	3001 : 9004	3001 : 9005
3002 : 9000	3002 : 9001	3002 : 9002	3002 : 9003	3002 : 9004	3002 : 9005
3003 : 9000	3003 : 9001	3003 : 9002	3003 : 9003	3003 : 9004	3003 : 9005
3004 : 9000	3004 : 9001	3004 : 9002	3004 : 9003	3004 : 9004	3004 : 9005
3005 : 9000	3005 : 9001	3005 : 9002	3005 : 9003	3005 : 9004	3005 : 9005
3006 : 9000	3006 : 9001	3006 : 9002	3006 : 9003	3006 : 9004	3006 : 9005
3007 : 9000	3007 : 9001	3007 : 9002	3007 : 9003	3007 : 9004	3007 : 9005
3008 : 9000	3008 : 9001	3008 : 9002	3008 : 9003	3008 : 9004	3008 : 9005
3009 : 9000	3009 : 9001	3009 : 9002	3009 : 9003	3009 : 9004	3009 : 9005
3010 : 9000	3010 : 9001	3010 : 9002	3010 : 9003	3010 : 9004	3010 : 9005
3011 : 9000	3011 : 9001	3011 : 9002	3011 : 9003	3011 : 9004	3011 : 9005
3012 : 9000	3012 : 9001	3012 : 9002	3012 : 9003	3012 : 9004	3012 : 9005
3013 : 9000	3013 : 9001	3013 : 9002	3013 : 9003	3013 : 9004	3013 : 9005
3014 : 9000	3014 : 9001	3014 : 9002	3014 : 9003	3014 : 9004	3014 : 9005
4001 : 9000	4001 : 9001	4001 : 9002	4001 : 9003	4001 : 9004	4001 : 9005
4002 : 9000	4002 : 9001	4002 : 9002	4002 : 9003	4002 : 9004	4002 : 9005
4003 : 9000	4003 : 9001	4003 : 9002	4003 : 9003	4003 : 9004	4003 : 9005
4004 : 9000	4004 : 9001	4004 : 9002	4004 : 9003	4004 : 9004	4004 : 9005
4005 : 9000	4005 : 9001	4005 : 9002	4005 : 9003	4005 : 9004	4005 : 9005
4006 : 9000	4006 : 9001	4006 : 9002	4006 : 9003	4006 : 9004	4006 : 9005
4007 : 9000	4007 : 9001	4007 : 9002	4007 : 9003	4007 : 9004	4007 : 9005
4008 : 9000	4008 : 9001	4008 : 9002	4008 : 9003	4008 : 9004	4008 : 9005
4009 : 9000	4009 : 9001	4009 : 9002	4009 : 9003	4009 : 9004	4009 : 9005
4010 : 9000	4010 : 9001	4010 : 9002	4010 : 9003	4010 : 9004	4010 : 9005
4011 : 9000	4011 : 9001	4011 : 9002	4011 : 9003	4011 : 9004	4011 : 9005
4012 : 9000	4012 : 9001	4012 : 9002	4012 : 9003	4012 : 9004	4012 : 9005
5001 : 9000	5001 : 9001	5001 : 9002	5001 : 9003	5001 : 9004	5001 : 9005
5002 : 9000	5002 : 9001	5002 : 9002	5002 : 9003	5002 : 9004	5002 : 9005
5003 : 9000	5003 : 9001	5003 : 9002	5003 : 9003	5003 : 9004	5003 : 9005
5004 : 9000	5004 : 9001	5004 : 9002	5004 : 9003	5004 : 9004	5004 : 9005
5005 : 9000	5005 : 9001	5005 : 9002	5005 : 9003	5005 : 9004	5005 : 9005
5006 : 9000	5006 : 9001	5006 : 9002	5006 : 9003	5006 : 9004	5006 : 9005
5007 : 9000	5007 : 9001	5007 : 9002	5007 : 9003	5007 : 9004	5007 : 9005
5008 : 9000	5008 : 9001	5008 : 9002	5008 : 9003	5008 : 9004	5008 : 9005
5009 : 9000	5009 : 9001	5009 : 9002	5009 : 9003	5009 : 9004	5009 : 9005
5010 : 9000	5010 : 9001	5010 : 9002	5010 : 9003	5010 : 9004	5010 : 9005
5011 : 9000	5011 : 9001	5011 : 9002	5011 : 9003	5011 : 9004	5011 : 9005
5012 : 9000	5012 : 9001	5012 : 9002	5012 : 9003	5012 : 9004	5012 : 9005

X : Y	X : Y	X : Y	X : Y	X : Y	X : Y
3001 : 9006	3001 : 9007	3001 : 9008	3001 : 9009	3001 : 9010	3001 : 9011
3002 : 9006	3002 : 9007	3002 : 9008	3002 : 9009	3002 : 9010	3002 : 9011
3003 : 9006	3003 : 9007	3003 : 9008	3003 : 9009	3003 : 9010	3003 : 9011
3004 : 9006	3004 : 9007	3004 : 9008	3004 : 9009	3004 : 9010	3004 : 9011
3005 : 9006	3005 : 9007	3005 : 9008	3005 : 9009	3005 : 9010	3005 : 9011
3006 : 9006	3006 : 9007	3006 : 9008	3006 : 9009	3006 : 9010	3006 : 9011
3007 : 9006	3007 : 9007	3007 : 9008	3007 : 9009	3007 : 9010	3007 : 9011
3008 : 9006	3008 : 9007	3008 : 9008	3008 : 9009	3008 : 9010	3008 : 9011
3009 : 9006	3009 : 9007	3009 : 9008	3009 : 9009	3009 : 9010	3009 : 9011
3010 : 9006	3010 : 9007	3010 : 9008	3010 : 9009	3010 : 9010	3010 : 9011
3011 : 9006	3011 : 9007	3011 : 9008	3011 : 9009	3011 : 9010	3011 : 9011
3012 : 9006	3012 : 9007	3012 : 9008	3012 : 9009	3012 : 9010	3012 : 9011
3013 : 9006	3013 : 9007	3013 : 9008	3013 : 9009	3013 : 9010	3013 : 9011
3014 : 9006	3014 : 9007	3014 : 9008	3014 : 9009	3014 : 9010	3014 : 9011
4001 : 9006	4001 : 9007	4001 : 9008	4001 : 9009	4001 : 9010	4001 : 9011
4002 : 9006	4002 : 9007	4002 : 9008	4002 : 9009	4002 : 9010	4002 : 9011
4003 : 9006	4003 : 9007	4003 : 9008	4003 : 9009	4003 : 9010	4003 : 9011
4004 : 9006	4004 : 9007	4004 : 9008	4004 : 9009	4004 : 9010	4004 : 9011
4005 : 9006	4005 : 9007	4005 : 9008	4005 : 9009	4005 : 9010	4005 : 9011
4006 : 9006	4006 : 9007	4006 : 9008	4006 : 9009	4006 : 9010	4006 : 9011
4007 : 9006	4007 : 9007	4007 : 9008	4007 : 9009	4007 : 9010	4007 : 9011
4008 : 9006	4008 : 9007	4008 : 9008	4008 : 9009	4008 : 9010	4008 : 9011
4009 : 9006	4009 : 9007	4009 : 9008	4009 : 9009	4009 : 9010	4009 : 9011
4010 : 9006	4010 : 9007	4010 : 9008	4010 : 9009	4010 : 9010	4010 : 9011
4011 : 9006	4011 : 9007	4011 : 9008	4011 : 9009	4011 : 9010	4011 : 9011
4012 : 9006	4012 : 9007	4012 : 9008	4012 : 9009	4012 : 9010	4012 : 9011
5001 : 9006	5001 : 9007	5001 : 9008	5001 : 9009	5001 : 9010	5001 : 9011
5002 : 9006	5002 : 9007	5002 : 9008	5002 : 9009	5002 : 9010	5002 : 9011
5003 : 9006	5003 : 9007	5003 : 9008	5003 : 9009	5003 : 9010	5003 : 9011
5004 : 9006	5004 : 9007	5004 : 9008	5004 : 9009	5004 : 9010	5004 : 9011
5005 : 9006	5005 : 9007	5005 : 9008	5005 : 9009	5005 : 9010	5005 : 9011
5006 : 9006	5006 : 9007	5006 : 9008	5006 : 9009	5006 : 9010	5006 : 9011
5007 : 9006	5007 : 9007	5007 : 9008	5007 : 9009	5007 : 9010	5007 : 9011
5008 : 9006	5008 : 9007	5008 : 9008	5008 : 9009	5008 : 9010	5008 : 9011
5009 : 9006	5009 : 9007	5009 : 9008	5009 : 9009	5009 : 9010	5009 : 9011
5010 : 9006	5010 : 9007	5010 : 9008	5010 : 9009	5010 : 9010	5010 : 9011
5011 : 9006	5011 : 9007	5011 : 9008	5011 : 9009	5011 : 9010	5011 : 9011
5012 : 9006	5012 : 9007	5012 : 9008	5012 : 9009	5012 : 9010	5012 : 9011

X : Y	X : Y	X : Y	X : Y	X : Y	X : Y
3001 : 9012	3001 : 9013	3001 : 9014	3001 : 9015		
3002 : 9012	3002 : 9013	3002 : 9014	3002 : 9015		
3003 : 9012	3003 : 9013	3003 : 9014	3003 : 9015		
3004 : 9012	3004 : 9013	3004 : 9014	3004 : 9015		
3005 : 9012	3005 : 9013	3005 : 9014	3005 : 9015		
3006 : 9012	3006 : 9013	3006 : 9014	3006 : 9015		
3007 : 9012	3007 : 9013	3007 : 9014	3007 : 9015		
3008 : 9012	3008 : 9013	3008 : 9014	3008 : 9015		
3009 : 9012	3009 : 9013	3009 : 9014	3009 : 9015		
3010 : 9012	3010 : 9013	3010 : 9014	3010 : 9015		
3011 : 9012	3011 : 9013	3011 : 9014	3011 : 9015		
3012 : 9012	3012 : 9013	3012 : 9014	3012 : 9015		
3013 : 9012	3013 : 9013	3013 : 9014	3013 : 9015		
3014 : 9012	3014 : 9013	3014 : 9014	3014 : 9015		
4001 : 9012	4001 : 9013	4001 : 9014	4001 : 9015		
4002 : 9012	4002 : 9013	4002 : 9014	4002 : 9015		
4003 : 9012	4003 : 9013	4003 : 9014	4003 : 9015		
4004 : 9012	4004 : 9013	4004 : 9014	4004 : 9015		
4005 : 9012	4005 : 9013	4005 : 9014	4005 : 9015		
4006 : 9012	4006 : 9013	4006 : 9014	4006 : 9015	--	--
4007 : 9012	4007 : 9013	4007 : 9014	4007 : 9015		
4008 : 9012	4008 : 9013	4008 : 9014	4008 : 9015		
4009 : 9012	4009 : 9013	4009 : 9014	4009 : 9015		
4010 : 9012	4010 : 9013	4010 : 9014	4010 : 9015		
4011 : 9012	4011 : 9013	4011 : 9014	4011 : 9015		
4012 : 9012	4012 : 9013	4012 : 9014	4012 : 9015		
5001 : 9012	5001 : 9013	5001 : 9014	5001 : 9015		
5002 : 9012	5002 : 9013	5002 : 9014	5002 : 9015		
5003 : 9012	5003 : 9013	5003 : 9014	5003 : 9015		
5004 : 9012	5004 : 9013	5004 : 9014	5004 : 9015		
5005 : 9012	5005 : 9013	5005 : 9014	5005 : 9015		
5006 : 9012	5006 : 9013	5006 : 9014	5006 : 9015		
5007 : 9012	5007 : 9013	5007 : 9014	5007 : 9015		
5008 : 9012	5008 : 9013	5008 : 9014	5008 : 9015		
5009 : 9012	5009 : 9013	5009 : 9014	5009 : 9015		
5010 : 9012	5010 : 9013	5010 : 9014	5010 : 9015		
5011 : 9012	5011 : 9013	5011 : 9014	5011 : 9015		
5012 : 9012	5012 : 9013	5012 : 9014	5012 : 9015		

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 : 9000	6043 : 9000	6000 : 9001	6043 : 9001	6000 : 9002	6043 : 9002
6001 : 9000	6044 : 9000	6001 : 9001	6044 : 9001	6001 : 9002	6044 : 9002
6002 : 9000	6045 : 9000	6002 : 9001	6045 : 9001	6002 : 9002	6045 : 9002
6003 : 9000	6046 : 9000	6003 : 9001	6046 : 9001	6003 : 9002	6046 : 9002
6004 : 9000	6047 : 9000	6004 : 9001	6047 : 9001	6004 : 9002	6047 : 9002
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X : Y	X : Y	X : Y	X : Y	X : Y	X : Y
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6042 : 9003		6042 : 9004		6042 : 9005	

X : Y	X : Y	X : Y	X : Y	X : Y	X : Y
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6001 : 9006	6044 : 9006	6001 : 9007	6044 : 9007	6001 : 9008	6044 : 9008
6002 : 9006	6045 : 9006	6002 : 9007	6045 : 9007	6002 : 9008	6045 : 9008
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6005 : 9006	6048 : 9006	6005 : 9007	6048 : 9007	6005 : 9008	6048 : 9008
6006 : 9006	6049 : 9006	6006 : 9007	6049 : 9007	6006 : 9008	6049 : 9008
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X : Y	X : Y	X : Y	X : Y	X : Y	X : Y
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6002 : 9009	6045 : 9009	6002 : 9010	6045 : 9010	6002 : 9011	6045 : 9011
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6006 : 9009	6049 : 9009	6006 : 9010	6049 : 9010	6006 : 9011	6049 : 9011
6007 : 9009	6050 : 9009	6007 : 9010	6050 : 9010	6007 : 9011	6050 : 9011
6008 : 9009	6051 : 9009	6008 : 9010	6051 : 9010	6008 : 9011	6051 : 9011
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6042 : 9009		6042 : 9010		6042 : 9011	

X : Y	X : Y	X : Y	X : Y	X : Y	X : Y
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6002 : 9012	6045 : 9012	6002 : 9013	6045 : 9013	6002 : 9014	6045 : 9014
6003 : 9012	6046 : 9012	6003 : 9013	6046 : 9013	6003 : 9014	6046 : 9014
6004 : 9012	6047 : 9012	6004 : 9013	6047 : 9013	6004 : 9014	6047 : 9014
6005 : 9012	6048 : 9012	6005 : 9013	6048 : 9013	6005 : 9014	6048 : 9014
6006 : 9012	6049 : 9012	6006 : 9013	6049 : 9013	6006 : 9014	6049 : 9014
6007 : 9012	6050 : 9012	6007 : 9013	6050 : 9013	6007 : 9014	6050 : 9014
6008 : 9012	6051 : 9012	6008 : 9013	6051 : 9013	6008 : 9014	6051 : 9014
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6040 : 9012		6040 : 9013		6040 : 9014	
6041 : 9012		6041 : 9013		6041 : 9014	
6042 : 9012		6042 : 9013		6042 : 9014	

X : Y	X : Y	X : Y	X : Y	X : Y	X : Y
6000 : 9015	6043 : 9015				
6001 : 9015	6044 : 9015				
6002 : 9015	6045 : 9015				
6003 : 9015	6046 : 9015				
6004 : 9015	6047 : 9015				
6005 : 9015	6048 : 9015				
6006 : 9015	6049 : 9015				
6007 : 9015	6050 : 9015				
6008 : 9015	6051 : 9015				
6009 : 9015	6052 : 9015				
6010 : 9015	6053 : 9015				
6011 : 9015	6054 : 9015				
6012 : 9015	6055 : 9015				
6013 : 9015	6056 : 9015				
6014 : 9015	6057 : 9015				
6015 : 9015	6058 : 9015				
6016 : 9015	6059 : 9015				
6017 : 9015	6060 : 9015				
6018 : 9015	6061 : 9015				
6019 : 9015	6062 : 9015				
6020 : 9015	6063 : 9015				
6021 : 9015	6064 : 9015	--	--	--	--
6022 : 9015	6065 : 9015				
6023 : 9015	6066 : 9015				
6024 : 9015	6067 : 9015				
6025 : 9015	6068 : 9015				
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6027 : 9015	6070 : 9015				
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6032 : 9015	6075 : 9015				
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6034 : 9015	6077 : 9015				
6035 : 9015	6078 : 9015				
6036 : 9015					
6037 : 9015					
6038 : 9015					
6039 : 9015					
6040 : 9015					
6041 : 9015					
6042 : 9015					

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

X : Y	X : Y	X : Y	X : Y	X : Y	X : Y
9000 : 7000	9001 : 7000	9002 : 7000	9003 : 7000	9004 : 7000	9005 : 7000
9000 : 7001	9001 : 7001	9002 : 7001	9003 : 7001	9004 : 7001	9005 : 7001
9000 : 7002	9001 : 7002	9002 : 7002	9003 : 7002	9004 : 7002	9005 : 7002
9000 : 7003	9001 : 7003	9002 : 7003	9003 : 7003	9004 : 7003	9005 : 7003
9000 : 7004	9001 : 7004	9002 : 7004	9003 : 7004	9004 : 7004	9005 : 7004
9000 : 7005	9001 : 7005	9002 : 7005	9003 : 7005	9004 : 7005	9005 : 7005
9000 : 7006	9001 : 7006	9002 : 7006	9003 : 7006	9004 : 7006	9005 : 7006
9000 : 7007	9001 : 7007	9002 : 7007	9003 : 7007	9004 : 7007	9005 : 7007
9000 : 7008	9001 : 7008	9002 : 7008	9003 : 7008	9004 : 7008	9005 : 7008
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9000 : 7011	9001 : 7011	9002 : 7011	9003 : 7011	9004 : 7011	9005 : 7011
9000 : 7012	9001 : 7012	9002 : 7012	9003 : 7012	9004 : 7012	9005 : 7012
9000 : 7013	9001 : 7013	9002 : 7013	9003 : 7013	9004 : 7013	9005 : 7013
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9000 : 7023	9001 : 7023	9002 : 7023	9003 : 7023	9004 : 7023	9005 : 7023
9000 : 7024	9001 : 7024	9002 : 7024	9003 : 7024	9004 : 7024	9005 : 7024
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9000 : 7027	9001 : 7027	9002 : 7027	9003 : 7027	9004 : 7027	9005 : 7027

X : Y	X : Y	X : Y	X : Y	X : Y	X : Y
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9006 : 7005	9007 : 7005	9008 : 7005	9009 : 7005	9010 : 7005	9011 : 7005
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X : Y	X : Y	X : Y	X : Y	X : Y	X : Y
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9012 : 7005	9013 : 7005	9014 : 7005	9015 : 7005		
9012 : 7006	9013 : 7006	9014 : 7006	9015 : 7006		
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9012 : 7012	9013 : 7012	9014 : 7012	9015 : 7012		
9012 : 7013	9013 : 7013	9014 : 7013	9015 : 7013		
9012 : 7014	9013 : 7014	9014 : 7014	9015 : 7014	--	--
9012 : 7015	9013 : 7015	9014 : 7015	9015 : 7015		
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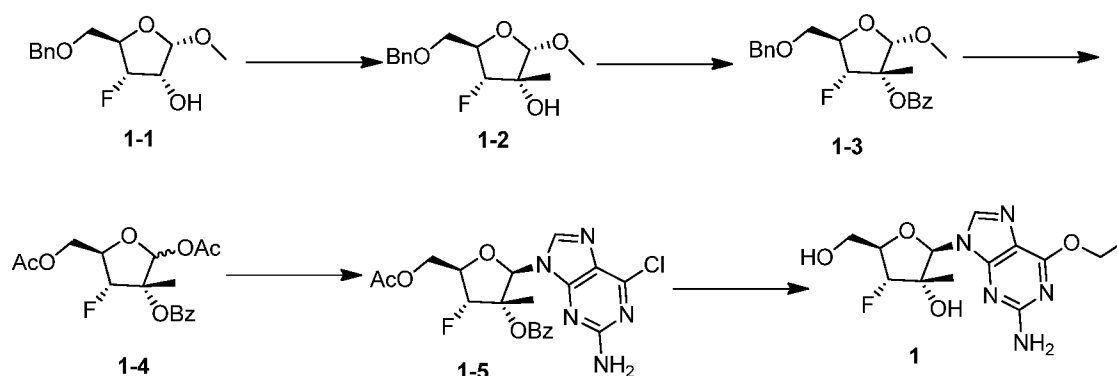
Table E: Example combinations of a compound X with a compound Y.

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8002 : 9000	8002 : 9001	8002 : 9002	8002 : 9003	8002 : 9004	8002 : 9005
8003 : 9000	8003 : 9001	8003 : 9002	8003 : 9003	8003 : 9004	8003 : 9005
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8005 : 9000	8005 : 9001	8005 : 9002	8005 : 9003	8005 : 9004	8005 : 9005
8006 : 9000	8006 : 9001	8006 : 9002	8006 : 9003	8006 : 9004	8006 : 9005
8007 : 9000	8007 : 9001	8007 : 9002	8007 : 9003	8007 : 9004	8007 : 9005
8008 : 9000	8008 : 9001	8008 : 9002	8008 : 9003	8008 : 9004	8008 : 9005
8009 : 9000	8009 : 9001	8009 : 9002	8009 : 9003	8009 : 9004	8009 : 9005
8010 : 9000	8010 : 9001	8010 : 9002	8010 : 9003	8010 : 9004	8010 : 9005
8011 : 9000	8011 : 9001	8011 : 9002	8011 : 9003	8011 : 9004	8011 : 9005
8012 : 9000	8012 : 9001	8012 : 9002	8012 : 9003	8012 : 9004	8012 : 9005
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8014 : 9000	8014 : 9001	8014 : 9002	8014 : 9003	8014 : 9004	8014 : 9005
8015 : 9000	8015 : 9001	8015 : 9002	8015 : 9003	8015 : 9004	8015 : 9005
8016 : 9000	8016 : 9001	8016 : 9002	8016 : 9003	8016 : 9004	8016 : 9005

X : Y	X : Y	X : Y	X : Y	X : Y	X : Y
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8002 : 9006	8002 : 9007	8002 : 9008	8002 : 9009	8002 : 9010	8002 : 9011
8003 : 9006	8003 : 9007	8003 : 9008	8003 : 9009	8003 : 9010	8003 : 9011
8004 : 9006	8004 : 9007	8004 : 9008	8004 : 9009	8004 : 9010	8004 : 9011
8005 : 9006	8005 : 9007	8005 : 9008	8005 : 9009	8005 : 9010	8005 : 9011
8006 : 9006	8006 : 9007	8006 : 9008	8006 : 9009	8006 : 9010	8006 : 9011
8007 : 9006	8007 : 9007	8007 : 9008	8007 : 9009	8007 : 9010	8007 : 9011
8008 : 9006	8008 : 9007	8008 : 9008	8008 : 9009	8008 : 9010	8008 : 9011
8009 : 9006	8009 : 9007	8009 : 9008	8009 : 9009	8009 : 9010	8009 : 9011
8010 : 9006	8010 : 9007	8010 : 9008	8010 : 9009	8010 : 9010	8010 : 9011
8011 : 9006	8011 : 9007	8011 : 9008	8011 : 9009	8011 : 9010	8011 : 9011
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8000 : 9012	8000 : 9013	8000 : 9014	8000 : 9015	--	--
8001 : 9012	8001 : 9013	8001 : 9014	8001 : 9015		
8002 : 9012	8002 : 9013	8002 : 9014	8002 : 9015		
8003 : 9012	8003 : 9013	8003 : 9014	8003 : 9015		
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8010 : 9012	8010 : 9013	8010 : 9014	8010 : 9015		
8011 : 9012	8011 : 9013	8011 : 9014	8011 : 9015		
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8013 : 9012	8013 : 9013	8013 : 9014	8013 : 9015		
8014 : 9012	8014 : 9013	8014 : 9014	8014 : 9015		
8015 : 9012	8015 : 9013	8015 : 9014	8015 : 9015		
8016 : 9012	8016 : 9013	8016 : 9014	8016 : 9015		

EXAMPLES

[0186] 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**(2R,3S,4R,5R)-2-(2-amino-6-ethoxy-9H-purin-9-yl)-4-fluoro-5-(hydroxymethyl)-3-methyltetrahydrofuran-3-ol (1)**

[0187] Preparation of (32-2): To a stirred solution of **1-1** (5.0 g, 19.53 mmol) in anhydrous MeCN was added IBX (7.66 g, 27.34 mmol), and the mixture was heated to 80 °C for 12 h. The mixture was cooled to room temperature (R.T.) and filtered. The filtrate was concentrated to dryness to give the ketone (4.87 g, 98%) as a colorless oil. To a solution of the ketone (4.87 g, 19.33 mmol) in anhydrous THF was added methyl magnesium bromide (19.53 mL, 58.59 mmol) dropwise at -78 °C under N₂. The mixture was warmed to R.T. for 12 h. The reaction was quenched with a saturated ammonium chloride solution, extracted with ethyl acetate (EA) and concentrated to give a residue, which was purified on a silica gel column (2-10% EA in PE) to give **1-2** (4.37 g, 83%) as colorless oil.

[0188] Preparation of (32-3): To a solution of **1-2** (4.37 g, 16.19 mmol) in anhydrous dichloromethane, DMAP (3.95 g, 32.38 mmol), TEA (4.91 g, 48.56 mmol) in ice water bath was added BzCl (6.80 g, 48.56 mmol). The mixture was stirred at R.T. for 12 h. The reaction was quenched with a saturated sodium hydrogen carbonate solution and extracted with EA. The organic phase was concentrated to dryness and purified on a silica gel column (2-20% EA in PE) to give **1-3** (5.3 g, 87%) as a colorless oil.

[0189] Preparation of (32-4): To a solution of **1-3** (2.0 g, 5.33 mmol) and Ac₂O (4.91 g, 48.13 mmol) in acetic acid (50 mL) was added concentrated H₂SO₄ (0.6 g, 6.01 mmol) at 0 °C. The mixture was stirred at R.T. for 12 h. The mixture was then poured into ice water and extracted with EA. The organic phase was concentrated to dryness, and the residue was purified on a silica gel column (2-30% EA in PE) to give **1-4** (1.5 g, 81%) as a colorless oil.

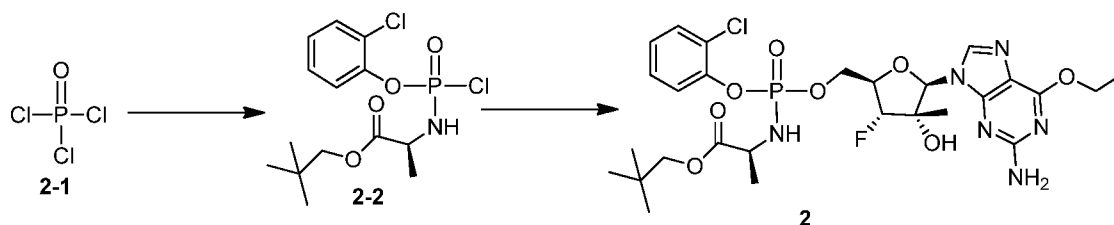
[0190] Preparation of (32-5): To a stirred solution of 6-chloroguanine (560 mg, 3.31 mmol) and **1-4** (1.11 g, 2.76 mmol) in anhydrous MeCN (5 mL) under N₂ was added 1,8-diazobicyclo[5.4.0]undec-7-ene (1.27 g, 8.28 mmol) at 0 °C. The mixture was stirred at R.T. for 0.5 h. TMSOTf (2.45 g, 11.04 mmol) was added at 0 °C. The mixture was heated to 60 °C for 4 h and then concentrated to dryness. The residue was partitioned between EA and saturated

sodium hydrogen carbonate. The organic phase was separated and concentrated to dryness. The residue was purified on a silica gel column (2-60% EA in PE) to give **1-5** (800 mg, 70%) as a white foam solid.

[0191] Preparation of (1): To a solution of **1-6** (500 mg, 0.68 mmol) in anhydrous ethanol was added sodium ethoxide (0.64 mL, 2.04 mmol) at R.T. The mixture was stirred at R.T. for 16 h. The reaction was quenched by acetic acid to pH = 7. The solvent was removed under reduce pressure. The residue was re-dissolved in EA, and washed with water and brine. The organic phase was dried and concentrated to dryness. The residue was purified on a silica gel column (1-3% DCM in MeOH) to give **1** (400 mg, 98%) as a white foam. ESI-MS: m/z 327.8 $[M+H]^+$.

EXAMPLE 2

(2S)-neopentyl 2-((((2R,3R,4S,5R)-5-(2-amino-6-ethoxy-1H-purin-9(6H)-yl)-3-fluoro-4-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(2-chlorophenoxy)phosphoryl)amino)propanoate (2)



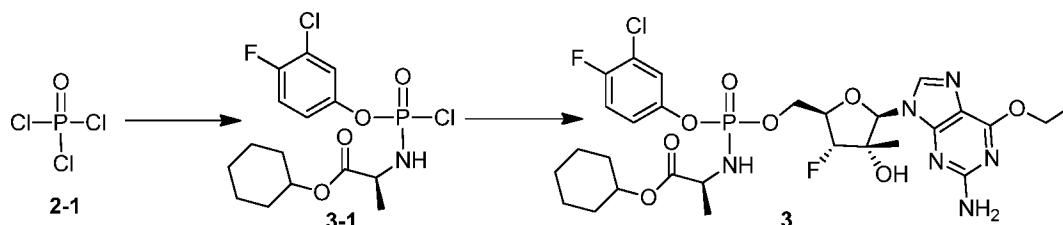
[0192] Preparation of (2-2): To a stirred solution of **2-1** (2.00 g, 13.16 mmol) and 2-chlorophenol (1.68 g, 13.16 mmol) in anhydrous DCM (100 mL) was added a solution of TEA (1.33 g, 13.16 mmol) in DCM (20 mL) dropwise at -78°C . After the addition, the mixture was gradually warmed to R.T. and stirred for 2 h. The solution was re-cooled to -78°C and neopentyl 2-aminopropanoate hydrogen chloride (3.51 g, 13.16 mmol) was added, followed by TEA (2.66 g, 26.32 mmol) dropwise at -78°C . The mixture was gradually warmed to R.T. and stirred at R.T. for 2 h. The solvent was removed, and the residue was dissolved in methyl-butyl ether. The precipitate was filtered off, and the filtrate was concentrated to dryness. The residue was purified on a silica gel column (pure anhydrous DCM) to give **2-2** (1.86 g, 32.18%) as a colorless oil.

[0193] Preparation of (2): To a stirred solution of **1** (100 mg, 0.31 mmol) in anhydrous THF (10 mL) was added *t*-BuMgCl (1.53 mL, 1M in THF) dropwise at -78°C . The mixture was stirred at R.T. for 30 mins and re-cooled to -78°C . To the above mixture was added **2-2** (561 mg, 1.53 mmol) dropwise. The mixture was stirred at R.T. for 2 h. The reaction was quenched with water and extracted with EA. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to dryness. The residue was purified on a silica gel column (1-8%

DCM in MeOH) to give the crude product, which was further purified by RP HPLC (water and MeCN system) to give **2** (19.83 mg, 10%) as a white solid. ESI-LCMS: m/z 659.3 $[M+H]^+$.

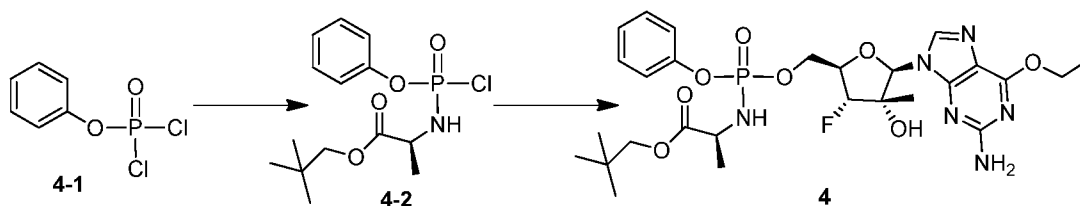
EXAMPLE 3

(2S)-cyclohexyl 2-((((((2R,3R,4S,5R)-5-(2-amino-6-ethoxy-1H-purin-9(6H)-yl)-3-fluoro-4-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(3-chloro-4-fluorophenoxy)phosphoryl)amino)propanoate (3)



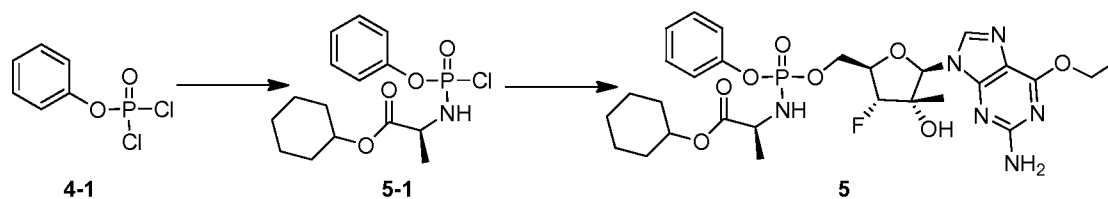
[0194] Preparation of (3-1): To a stirred solution of phosphoryl trichloride (2.00 g, 13.16 mmol) and phenol (1.92 g, 13.16 mmol) in anhydrous DCM (100 mL) was added a solution of TEA (1.33 g, 13.16 mmol) in DCM (20 mL) dropwise at -78 °C. After addition, the mixture was gradually warmed to R.T. and stirred for 2 h. The solution was re-cooled to -78 °C and the amine (2.72 g, 13.16 mmol) was added, followed by TEA (2.66 g, 26.32 mmol) dropwise at -78 °C. The mixture was gradually warmed to R.T. and stirred for 2 h. The solvent was removed, and the residue was dissolved in methyl-butyl ether. The precipitate was filtered off, and the filtrate was concentrated. The residue was purified on a silica gel column (pure anhydrous DCM) to give **3-1** (1.90 g, 36.39%) as a colorless oil.

[0195] Preparation of (3): To a stirred solution of **1** (181 mg, 0.55 mmol) in anhydrous THF (10 mL) was added *t*-BuMgCl (2.77 mL, 1M in THF) dropwise at -78 °C. The mixture was stirred at R.T. for 30 mins and re-cooled to -78 °C. To the mixture was added **3-1** (1.01 g, 2.77 mmol) dropwise. The mixture was stirred at R.T. for 12 h. The reaction was quenched with water and extracted with EA. The organic layer was dried over anhydrous Na₂SO₄ and concentrated to dryness. The residue was purified on a silica gel column (1-8% DCM in MeOH) to give the crude product, which was further purified by RP HPLC (water and MeCN system) to give **3** (76.81 mg, 20%) as a white solid. ESI-LCMS: m/z 689.3 $[M+H]^+$.

EXAMPLE 4**(2S)-neopentyl 2-((((2R,3R,4S,5R)-5-(2-amino-6-ethoxy-1H-purin-9(6H)-yl)-3-fluoro-4-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate**
(4)

[0196] Preparation of (4-2): To a stirred solution of **4-1** (3.20 g, 15.38 mmol) and amine (3.0 g, 15.38 mmol) in anhydrous DCM (100 mL) was added a solution of TEA (30.76 g, 30.76 mmol) in DCM (20 mL) dropwise at -78 °C. After addition, the mixture was gradually warmed to R.T. and stirred for 2 h. The solvent was removed, and the residue was dissolved in methyl-butyl ether. The precipitate was filtered off, and the filtrate was concentrated. The residue was purified on a silica gel column (pure anhydrous DCM) to give **4-2** (2.0 g, 39%) as a colorless oil.

[0197] Preparation of (4): To a stirred solution of **1** (83 mg, 0.25 mmol) in anhydrous THF (10 mL) was added a solution of *t*-BuMgCl (1.27 mL, 1M in THF) dropwise at -78 °C. The mixture was stirred at R.T. for 30 mins and then re-cooled to -78 °C. A solution of **4-2** (423 mg, 1.27 mmol) was added dropwise, and the mixture was stirred at R.T. for 12 h. The reaction was quenched with water and extracted with EA. The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified on a silica gel column to give the crude product, which was further purified by RP HPLC (water and MeCN system) to give **4** (80 mg, 51%) as a white solid. ESI-LCMS: *m/z* 625.1 [M+H]⁺.

EXAMPLE 5**(2S)-cyclohexyl 2-((((2R,3R,4S,5R)-5-(2-amino-6-ethoxy-1H-purin-9(6H)-yl)-3-fluoro-4-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate**
(5)

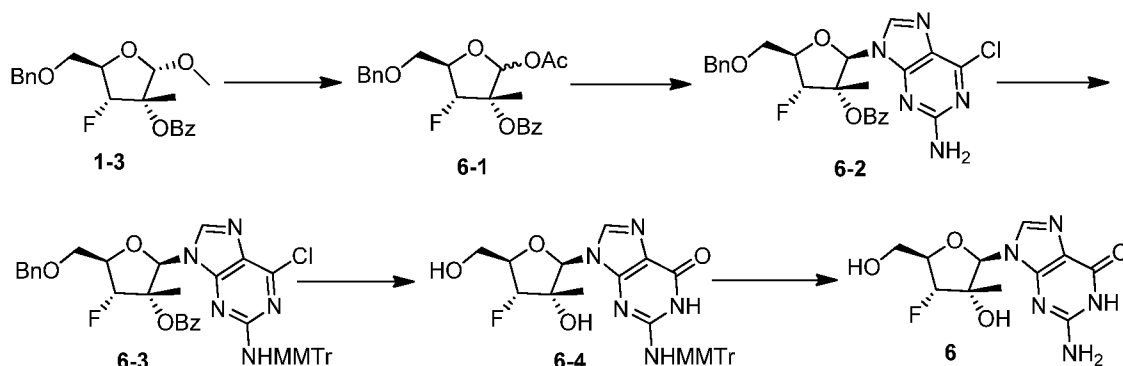
[0198] Preparation of (5-1): To a stirred solution of **4-1** (2.00 g, 9.57 mmol) and amine (1.98 g, 9.57 mmol) in anhydrous DCM (100 mL) was added a solution of TEA (1.93 g, 19.14 mmol) in DCM (20 mL) dropwise at -78 °C. After addition, the mixture was gradually warmed to R.T. and stirred for 2 h. The solvent was removed, and the residue was dissolved in

methyl-butyl ether. The precipitate was filtered off, and the filtrate was concentrated. The residue was purified on a silica gel column (pure anhydrous DCM) to give **5-1** (700 mg, 21%) as a colorless oil.

[0199] Preparation of (5): To a stirred solution of **1** (70 mg, 0.21 mmol) in anhydrous THF (1.5 mL) was added a solution of *t*-BuMgCl (1.07 mL, 1M in THF) dropwise at -78 °C. The mixture was stirred at R.T. for 30 mins and then re-cooled to -78 °C. A solution of **5-1** (369 mg, 1.07 mmol) was added dropwise. The mixture was stirred at R.T. for 2 h. The reaction was quenched with water and extracted with EA. The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified on a silica gel column to give the crude product, which was further purified by RP HPLC (water and MeCN system) to give **5** (50 mg, 38%) as a white solid. ESI-LCMS: *m/z* 637.01 [M+H]⁺.

EXAMPLE 6

2-amino-9-((2R,3S,4R,5R)-4-fluoro-3-hydroxy-5-(hydroxymethyl)-3-methyltetrahydrofuran-2-yl)-1H-purin-6(9H)-one (6)



[0200] Preparation of (6-1): To a solution of **1-3** (3.0 g, 8.02 mmol) and Ac₂O (4.91 g, 48.13 mmol) in acetic acid (30 mL) was added a solution of concentrated H₂SO₄ (2.41 g, 24.06 mmol) in acetic acid (10 mL) at 0 °C. The mixture was stirred at R.T. for 12 h. The mixture was poured into ice water and extracted with EA. The organic phase was dried and concentrated to give a residue, which was purified by silica gel column chromatography (10% EA in PE) to give **6-1** (2.3 g, 81%) as a colorless oil.

[0201] Preparation of (6-2): To a stirred mixture of 6-chloroguanine (560 mg, 3.31 mmol) and **6-1** (1.11 g, 2.76 mmol) in anhydrous MeCN (5 mL) under N₂ was added 1,8-diazobicyclo[5.4.0]undec-7-ene (1.27 g, 8.28 mmol) at 0 °C. The mixture was stirred at R.T. for 0.5 h. The mixture was re-cooled to 0 °C and TMSOTf (2.45 g, 11.04 mmol) was added. The resulting mixture was heated to 60 °C for 4 h and then concentrated to dryness. The residue was partitioned between EA and saturated sodium hydrogen carbonate. The organic phase was

separated and concentrated to give a residue, which was purified by silica gel column chromatography (2% MeOH in DCM) to give **6-2** (800 mg, 70%) as a white solid.

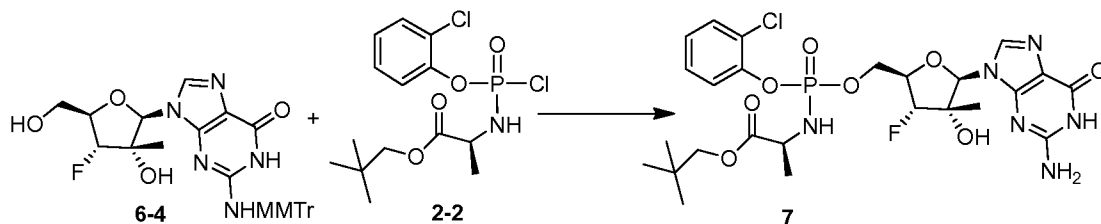
[0202] Preparation of (6-3): To a solution of **6-2** (839 mg, 1.64 mmol) in anhydrous dichloromethane (10 mL) were added MMTrCl (1.46 g, 4.75 mmol), AgNO₃ (697 mg, 4.1 mmol) and collidine (794 mg, 6.56 mmol). The mixture was stirred at R.T. for 12 h. The reaction was quenched with saturated sodium hydrogen carbonate solution. The mixture was filtered, and the filtrate was extracted with EA. The organic layer was washed with water and brine, dried and concentrated to give a residue, which was purified on silica gel column chromatography (20% EA in PE) to give **6-3** (1.3 g, 72.5%) as a white solid.

[0203] Preparation of (6-4): To a solution of 3-hydroxyl acrylic nitrile (413 g, 5.82 mmol) in anhydrous THF was added sodium hydrogen (464 mg, 11.6 mmol). The mixture was warmed to R.T. for 0.5 h, and then the mixture was re-cooled to 0 °C. To the mixture was added a solution of **6-3** (0.912 g, 1.16 mmol) in anhydrous THF (5 mL). The mixture was warmed to R.T. for 12 h. The reaction was quenched with water and extracted with EA. The organic phase was separated and concentrated to give a residue, which was purified by silica gel column chromatography (5% MeOH in DCM) to give **6-4** (600 mg, 85%) as a white solid.

[0204] Preparation of (6): To a solution of **6-4** (785 mg, 1.19 mmol) and ammonium formate (1.50 g, 23.75 mmol) in acetone (50 mL) was added dry Pd/C (785 mg). The mixture was heated to reflux for 12 h. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10% MeOH in DCM) to give **6** (400 mg, 59%) as a white solid. ESI-MS: *m/z* 299.77 [M+H]⁺.

EXAMPLE 7

(2S)-neopentyl 2-((((((2R,3R,4S,5R)-5-(2-amino-6-oxo-1H-purin-9(6H)-yl)-3-fluoro-4-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(2-chlorophenoxy)phosphoryl)amino)propanoate (7)

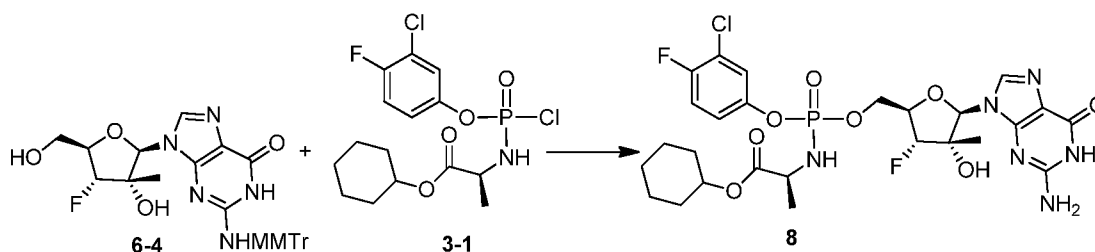


[0205] Preparation of (7): To a stirred solution of **6-4** (161 mg, 0.28 mmol) in anhydrous THF (1 mL) was added a solution of *t*-BuMgCl (1.41 mL, 1M in THF) dropwise at 0 °C. The mixture was stirred at R.T. for 0.5 h and then re-cooled to 0 °C. To the mixture was added a solution of **2-2** (517 mg, 1.41 mmol) dropwise. The mixture was stirred at R.T. for 2 h.

The reaction was quenched with water and extracted with EA. The organic layer was dried and concentrated. The residue was purified on a silica gel column to give a protected intermediate (100 mg). The protected intermediate was treated with a 60% acetic acid aqueous solution and stirred at R.T. for 12 h. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography and then RP HPLC separation (0.1% HCOOH in water and MeCN) to give **7** (12.13 mg, 10%) as a white solid. ESI-LCMS: m/z 631.1 $[M+H]^+$.

EXAMPLE 8

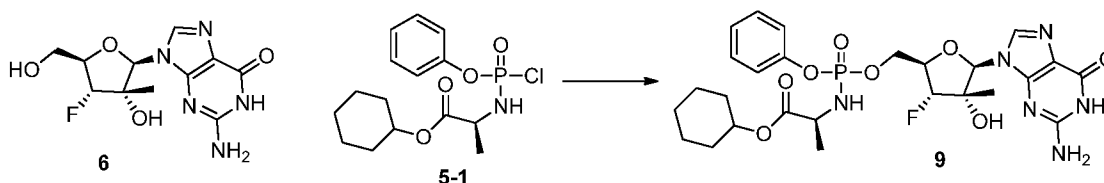
(2S)-cyclohexyl 2-((((2R,3R,4S,5R)-5-(2-amino-6-oxo-1H-purin-9(6H)-yl)-3-fluoro-4-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(3-chloro-4-fluorophenoxy)phosphoryl)amino)propanoate (8)



[0206] **Preparation of (8):** To a stirred solution of **6-4** (100 mg, 0.18 mmol) in anhydrous THF (1 mL) was added a solution of *t*-BuMgCl (0.9 mL, 0.9 mmol) dropwise at -78 °C. The mixture was stirred at R.T. for 0.5 h and then re-cooled to -78 °C. To the mixture was added a solution of **3-1** (357 mg, 0.9 mmol) dropwise. The mixture was stirred at R.T. for 12 h. The reaction was quenched with water and extracted with EA. The organic layer was dried and concentrated. The residue was purified on a silica gel column to give a protected intermediate (100 mg). The protected intermediate was treated with a 65% HCOOH aqueous solution and stirred at R.T. for 12 h. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography and then RP HPLC (0.1% HCOOH in water and MeCN) to give **8** (16.83 mg, 14%) as a white solid. ESI-LCMS: m/z 661.1 $[M+H]^+$.

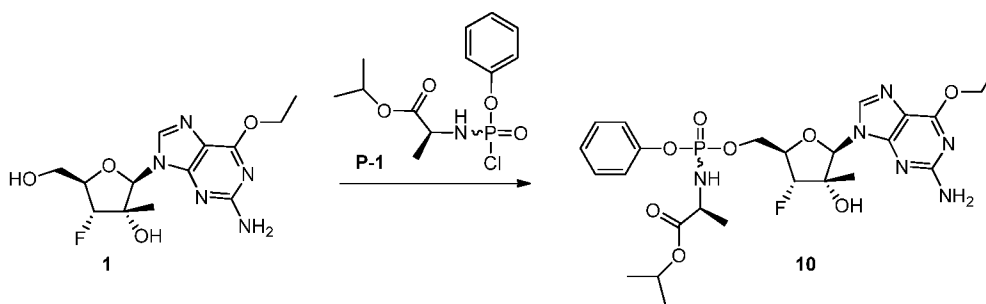
EXAMPLE 9

(2S)-cyclohexyl 2-((((2R,3R,4S,5R)-5-(2-amino-6-oxo-1H-purin-9(6H)-yl)-3-fluoro-4-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphoryl)amino)propanoate (9)



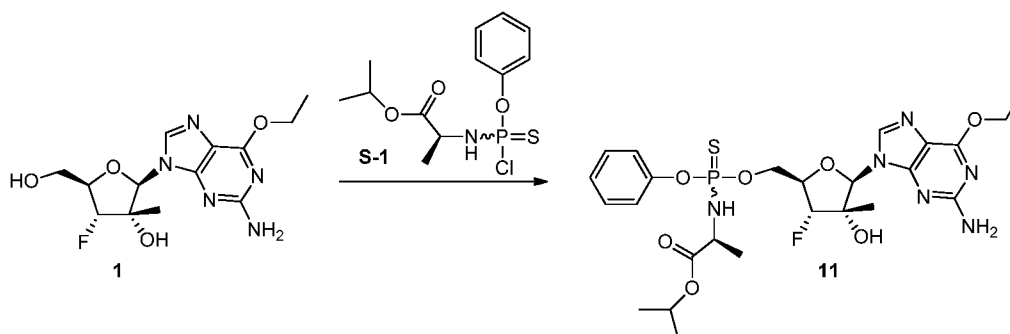
[0207] To a stirred solution of **6** (21 mg, 0.07 mmol) in NMI (0.25 mL) was added a solution of **5-1** (0.35 mL, 1M in THF) dropwise at 0°C. The mixture was stirred at R.T. for 5 h, then more **5-1** (0.21 mL) was added. The mixture was stirred for 3 days. Additionally, **5-1** (0.21 mL) was added, and the mixture was stirred at 35 °C for 1 day. After cooling to R.T., the mixture was diluted with EA, washed with NH₄Cl-AcOH (2 times), NH₄Cl (3 times), NaHCO₃. The organic layer was dried over sodium sulfate and concentrated. Chromatography on silica gel with 5-10% MeOH in DCM gave **9** (27 mg) as a slightly-yellow solid. Further chromatography on silica gel provided pure **9** (19 mg) as a white solid. ESI-LCMS: m/z 607.2 [M-H]⁻.

EXAMPLE 10
Compound (10)



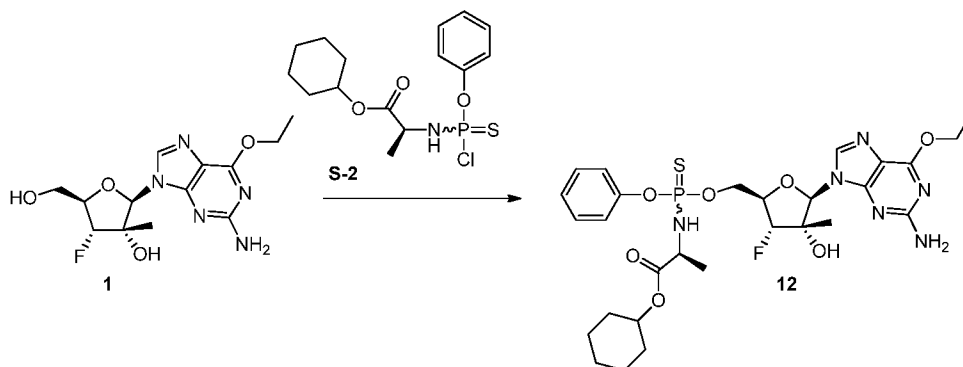
[0208] To an ice cold solution of **1** (53 mg; 0.16 mmol) in anhydrous THF (2 mL) was added isopropylmagnesium chloride (0.12 mL; 2 M in THF). The mixture stirred at 0 °C for 20 min. A solution of phosphorochloridate reagent **P-1** (0.15 g; 3 equiv.) in THF (0.3 mL) was added dropwise. The mixture stirred overnight at R.T. The reaction was quenched with saturated aq. NH₄Cl solution and stirred at R.T. for 10 min. The mixture was diluted with water and CH₂Cl₂. The resulting two layers were separated. The organic layer was washed with water, half saturated aq. NaHCO₃ and brine, and then dried with Na₂SO₄. The evaporated residue was purified on silica gel column with CH₂Cl₂-MeOH solvent system (2-10% gradient) to yield a Rp/Sp-mixture of **10** (48 mg; 50%). ³¹P-NMR (DMSO-d₆): δ 3.98, 3.81. MS: m/z = 595 [M-1]⁻.

EXAMPLE 11
Compound (11)



[0209] To an ice cold solution of **1** (95 mg; 0.29 mmol) in anhydrous THF (3 mL) was added isopropylmagnesium chloride (0.29 mL; 2 M in THF). The mixture stirred at 0 °C for 20 min. A solution of thiophosphorochloridate reagent **S-1** (0.28 g; 3 equiv.) in THF (0.3 mL) was added, and the mixture stirred 1 day at 40 °C. The reaction was quenched with saturated aq. NH₄Cl solution and stirred at R. T. for 10 min. The mixture was diluted with water and CH₂Cl₂, and the two layers were separated. The organic layer was washed with water, half saturated aq. NaHCO₃, and brine, and dried with Na₂SO₄. The evaporated residue was purified on silica gel column with CH₂Cl₂-MeOH solvent system (4-10% gradient) to yield Rp/Sp-mixture of **11** (42 mg; 24%). ³¹P-NMR (DMSO-d₆): δ 68.32, 68.19. MS: m/z = 611 [M-1].

EXAMPLE 12
Compound (12)

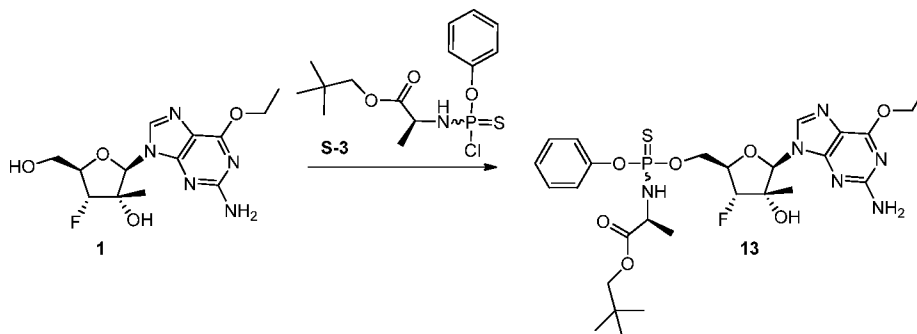


[0210] To a solution of **1** (91 mg; 0.28 mmol) in acetonitrile (2 mL) were added 1-methylimidazole (0.21 mL; 8 equiv.) and thiophosphorochloridate reagent **S-2** (0.3 g; 3 equiv). The mixture stirred 1 day at 40 °C. The reaction was quenched at R.T. with MeOH, and the mixture evaporated. The oily residue was dissolved in CH₂Cl₂ and washed with 1N citric acid, half saturated aq. NaHCO₃ and brine, and dried with Na₂SO₄. The evaporated residue was purified on silica gel column with CH₂Cl₂-MeOH solvent system (4-10% gradient) to yield

Rp/Sp-mixture of **12** (120 mg; 66%). ^{31}P -NMR (DMSO- d_6): δ 68.27, 68.24. MS: m/z = 651 [M-1].

EXAMPLE 13

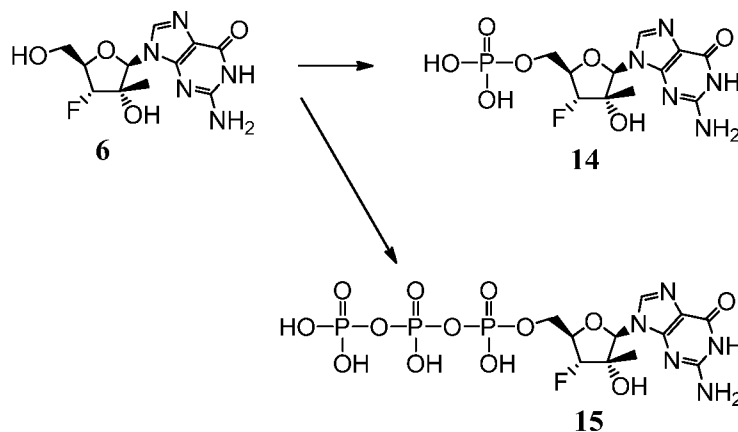
Compound (13)



[0211] Compound **13** was prepared in the same way as described for **12** from **1** (75 mg; 0.23 mmol) with 1-methylimidazole (0.15 mL) and thiophosphorochloridate reagent **S-3** (0.24 g) in acetonitrile (2 mL). 55 mg yield (37%). ^{31}P -NMR (DMSO- d_6): δ 68.40, 68.16. MS: m/z = 639 [M-1].

EXAMPLE 14

Compounds (14) and (15)



[0212] Dry **6** (18 mg, 0.05 mmol) was dissolved in the mixture of $\text{PO}(\text{OMe})_3$ (0.750 mL) and pyridine (0.5 mL). The mixture was evaporated in vacuum for 15 mins at bath temperature (42 $^{\circ}\text{C}$), and then cooled down to R.T. N-Methylimidazole (0.009 mL, 0.11 mmol) was added followed by POCl_3 (0.009 mL, 0.1 mmol). The mixture was kept at R.T. for 45 mins. Tributylamine (0.065 mL, 0.3 mmol) and N-tetrabutyl ammonium salt of pyrophosphate (100 mg) was added. Dry DMF (about 1 mL) was added to get a homogeneous solution. In 1 h, the reaction was quenched with 2M ammonium acetate buffer (1 mL, pH = 7.5), diluted to 10 mL with water and loaded on the column HiLoad 16/10 with Q Sepharose High Performance.

Separation was done in a linear gradient of NaCl from 0 to 1N in 50mM TRIS-buffer (pH = 7.5). The fractions eluted at 60% buffer B contained **14** and at 80% buffer B contained **15**. The corresponding fractions were concentrated, and the residue purified by RP HPLC on Synergy 4 micron Hydro-RP column (Phenomenex). A linear gradient of methanol from 0 to 30% in 50mM triethylammonium acetate buffer (pH 7.5) was used for elution. The corresponding fractions were combined, concentrated and lyophilized 3 times to remove excess of buffer. Compound **14**: P^{31} -NMR (D_2O): -3.76 (s); ^1H -NMR (D_2O): 8.00(s, 1H), 5.88(s, 1H), 5.10-4.95 (m, 2H), 4.05-3.98 (m, 2H), 1.00 (s, 3H); MS: 378.2 $[M-1]^-$. Compound **15**: P^{31} -NMR (D_2O): -10.24(P α), -11.46(P β), -23.18(P γ); ^1H -NMR (D_2O): (D_2O): 8.44(s, 1H), 8.17 (s, 1H), 5.05(s, 1H), 4.18 (m, 2H), 4.02 (m, 3H); MS 538.0 $[M-1]^-$.

EXAMPLE 15 **HCV Replicon Assay**

Cells

[0213] 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 0.5 mg/mL G418.

Determination of anti-HCV activity

[0214] 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 h. At 72 h, cells were processed when the cells are still subconfluent. Compounds that reduce the LUC signal are determined by Bright-Glo Luciferase Assay (Promega, Madison, WI). % Inhibition was determined for each compound concentration in relation to the control cells (untreated HCV replicon) to calculate the EC_{50} .

[0215] Compounds of Formula (I) are active in the replicon assay. The antiviral activity of exemplary compounds is shown in Table 2, where 'A' indicates an $EC_{50} < 1 \mu M$, 'B' indicates an $EC_{50} \geq 1 \mu M$ and $< 10 \mu M$, and 'C' indicates an $EC_{50} \geq 10 \mu M$ and $< 100 \mu M$.

Table 2

Compound #	EC_{50}	Compound #	EC_{50}	Compound #	EC_{50}
2	A	6	C	10	A
3	A	7	C	11	C
4	A	8	C	12	B
5	A	9	B	13	B

EXAMPLE 16
NS5B Inhibition Assay

[0216] 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 μCi tritiated NTP, 1 μM of competing cold NTP, 20 mM NaCl, 40 mM Tris-HCl (pH 8.0), 4 mM dithiothreitol, and 4 mM $MgCl_2$. Standard reactions were incubated for 2 h 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 3. 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 $IC_{50} \geq 1 \mu M$ and $< 10 \mu M$, and a value of 'C' indicates an IC_{50} value of $\geq 10 \mu M$ and $< 100 \mu M$.

Table 3

Compound #	IC_{50}
15	A

EXAMPLE 17**Assessment of inhibition of mitochondrial function**

[0217] Drug-associated dysfunction of mitochondria is believed to play a role in the etiology of the various adverse symptoms that occur in patients treated with antiviral nucleoside/nucleotides. For this reason, evaluation of compounds for their potential to inhibit mitochondrial function is useful. To assess the potential for nucleotide/nucleoside analogs to interfere with normal mitochondrial functions and exhibit mitochondrial toxicity, the following were measured: (1) the ability of nucleotides to be incorporated by human mitochondrial RNA polymerase in vitro and (2) the cellular inhibition of the synthesis of the mitochondrial DNA (mtDNA)-encoded protein, cytochrome c oxidase (COX-I), relative to the nuclear DNA (nDNA)-encoded mitochondrial protein succinate dehydrogenase subunit A (SDH-A) in HepG2 cells. Control compounds and compounds of Formula (I) were studied in these assays.

Biochemical assay

[0218] Arnold et al. "Sensitivity of Mitochondrial Transcription and Resistance of RNA Polymerase II Dependent Nuclear Transcription to Antiviral Ribonucleosides" PLoS Pathog (2012) 8(11): e1003030. doi:10.1371/journal.ppat.1003030, which is hereby incorporated by reference in its entirety.

Assessment of incorporation of nucleotides by human mitochondrial RNA polymerase (HMRP)**DdRp assay with human mitochondrial RNA polymerase**

[0219] The DdRp assay with human mitochondrial RNA polymerase was performed under single turnover conditions where enzyme concentration is in excess of the primer/template. The ³³P-RNA/DNA primer/template was used at a concentration of 100 nM, together with 320 nM enzyme. The standard 10-μL reactions were carried out at 30°C for 1 minute with 100 μM of each nucleotide 5'-triphosphate (NTP), 10 mM MgCl₂, 50 mM NaCl, 40 mM Tris, pH 7.5, and 1 mM DTT. The reaction was stopped by adding 20 μL of formamide loading dye containing 50 mM EDTA. RNA products were resolved by electrophoresis on 22.5% TBE Urea polyacrylamide sequencing gels that were scanned using a TYPHOON PhosphorImager.

[0220] The template strand shown in Figure 10 was designed to measure the incorporation of GTP analogs. Primer/Template: (SEQ ID NO: 1) UUUUGCCGCGCC and (SEQ ID NO: 2) GGGAATGCACGGCGCGGC. In the control water lanes, no incorporation was observed as indicated by the lack of product band. GTP and 3'-deoxy-GTP were found to be efficient substrates for incorporation as demonstrated by the significant product bands. The potential for misincorporation was assessed using the control nucleotide ATP. As shown by the

lack of product band in Figure 10, control ATP was a poor substrate for incorporation. Nucleotide analog 2'-Me-GTP (the nucleotide metabolite of monophosphate prodrug INX-0189/BMS-986094) was tested and found to be a good substrate for incorporation by HMRP as indicated by the product band. Nucleotide analog 2'-Me-2'-F-GTP (nucleotide metabolite of monophosphate prodrug GS-938) was tested and also found to be incorporated by HMRP. In contrast, compounds of Formula (I) were not efficient substrates for incorporation into the template strand by HMRP as indicated by the lack of product bands in Figure 10.

Assessment of inhibition of mitochondrial protein synthesis - Cell Based Assay

Assay Principle

[0221] MitoBiogenesis™ In Cell ELISA kits (Cat. #MS643) were obtained from Mitosciences, OR, USA. The MitoBiogenesis™ In Cell ELISA kit is a duplexing 96 well assay that ratios both an mtDNA and an nDNA encoded mitochondrial protein. Cells were seeded in 96 microplates and after exposure to compounds for several cell doublings, the levels of the two mitochondrial proteins were measured simultaneously in each well. The two proteins assayed were each subunits of different oxidative phosphorylation enzyme complexes, one protein being subunit I of Complex IV (cytochrome c oxidase; COX I) that is mtDNA encoded and the other being the 70 kDa subunit of Complex II (succinate dehydrogenase subunit A; SDH A) that is nDNA encoded. Complex IV includes several proteins that are encoded by the mtDNA while the proteins of Complex II are entirely encoded by nDNA. To control for the density of cells present at the end of the culture period, the number of cells were assessed by staining with Janus Green and the levels of COX I/SDH A normalized to the final cell density.

96 Well Plate Assay Format for HepG2 Cells

[0222] On the first day, 1000 HepG2 cells per well were plated in a 96 well plate. On the following day, compounds to be tested were solubilized in 100% DMSO to 100 x the desired final testing concentration. Each compound was serially diluted (1:3) up to 9 distinct concentrations. Compounds in 100% DMSO were reduced to 10% (v/v) DMSO by diluting 1:10 in cell culture media. A 10 µL aliquot of the compounds diluted to 10% (v/v) DMSO with cell culture media was used to dose the cells in duplicate. The final DMSO concentration was 1% (v/v). Untreated cells and wells containing no cells were included on the plate to serve as controls. Cells were then incubated with compounds and observed for 8 days at 37°C and 5% CO₂. Plates were processed as described below in the assay procedure.

Batch Assay Format for HepG2 Cells

[0223] An alternate cell culture procedure was employed to test the potential to mediate mitochondrial toxicity at higher concentrations than achievable in the 96 well plate format. HepG2 cells were grown either in media/DMSO alone or in a series of compound

concentrations in 15 cm² dishes or 6 well plates at an initial cell seeding density of 5×10^6 and 5×10^4 cells/mL, respectively. Cells were then incubated and observed for 8 days at 37°C and 5% CO₂. After 8 days, the cells were harvested by trypsinization, counted, and seeded in 96 well plates at a density of 25,000 cells/well in 16 replicate wells. Cells were allowed to adhere overnight and then the plates were processed as described below in the assay procedure.

Assay Procedure

[0224] The assay was performed according to the manufacturer's instructions. Briefly, after the end of the culture period the cell culture media was gently aspirated from the wells of the plate and replaced with 100 µL of 4% (v/v) paraformaldehyde solution in phosphate buffered saline (PBS, Electron Microscopy Sciences Cat. #15713). After a 20 mins incubation at R.T., the solution was removed and the wells washed 3 x with 300 µL of PBS. After the final wash, the PBS was removed and the wells overlayed with 100 µL PBS. The plates were then sealed and stored at 4°C until used. To perform the assay, the PBS overlay was removed by blotting on a paper towel and 100 µL of 0.5% (v/v) acetic acid added to each well to block endogenous alkaline phosphatase activity. After a 5 mins incubation at R.T., the acetic acid solution was removed and the cells washed once with 200 µL PBS. Then, 100 µL of permeabilization buffer (0.1% (v/v) Triton X 100) was added to each well. After 30 mins incubation at R.T., the permeabilization buffer was removed and each well was blocked with 200 µL of 2 x blocking solution for 2 h at R.T. The 2 x blocking solution was then removed and 100 µL of primary antibody solution containing anti COX I and anti SDH A antibodies in 1 x blocking solution was added to each well. Plates were then sealed and incubated overnight at 4°C. The primary antibody/blocking solution was removed and the plate washed 3 x with 250 µL 0.05% (v/v) Tween 20 in PBS. Then, 100 µL of secondary antibody solution containing alkaline phosphatase (AP) labeled anti SDH A antibody and horseradish peroxidase (HRP) labeled anti COX I antibody was added and incubated for 1 h at R.T. The plate was then washed 4 x with 250 µL 0.05% (v/v) Tween 20 in PBS. After blotting the plate dry 100 µL of AP detection reagent was added to each well, and the plate incubated in the dark for 30 mins at R.T. The optical density of each well was then measured at 405 nm. The AP detection reagent was then removed and replaced with 100 µL of HRP detection reagent, and the plate incubated in the dark for a further 30 mins at R.T. The optical density of each well was then measured at 600 nm. The HRP detection reagent was then removed and each well was then stained with 50 µL of 1 x Janus Green Stain for 5 mins at R.T. After removal of the dye, the plates were washed 5 x in ultrapure water to remove any remaining dye. The Janus Green stain was then solubilized

by the addition of 100 μ L of 0.5 M HCl and incubated for 10 mins. The optical density of each well was then measured at 595 nm.

Data Analysis

[0225] The average of all replicate background measurements from each experimental condition was calculated and subtracted from the experimental values of the same condition. The SDH A and COX I signals were then plotted as a ratio (COX I/SDH A) and normalized to the Janus Green staining intensity to correct for differences in cell density.

Results

[0226] Control compound d4T was tested and found not to inhibit mitochondrial protein synthesis at concentrations as shown in Figures 11A-B. Control compound ddC was tested and found to strongly inhibit mitochondrial protein synthesis. See Figures 11A-B. As demonstrated in Figure 11B, nucleoside monophosphate prodrug INX-08189/BMS-986094 (which delivers 2'-Me-GTP) was tested in the assay and found to strongly inhibit mitochondrial protein synthesis. In contrast, compounds of Formula (I) were tested and found to not inhibit mitochondrial protein synthesis as shown in Figure 11A.

EXAMPLE 18

Combination of Compounds

Combination Testing

[0227] Two or more test compounds are tested in combination with each other using an HCV genotype 1b HCV replicon harbored in Huh7 cells with a stable luciferase (LUC) reporter. Cells are cultured under standard conditions in Dulbecco's modified Eagle's medium (DMEM; Mediatech Inc, Herndon, VA) containing 10% heat-inactivated fetal bovine serum (FBS; Mediatech Inc, Herndon, VA) 2mM L-glutamine, and nonessential amino acids (JRH Biosciences). HCV replicon cells are plated in a 96-well plate at a density of 10^4 cells per well in DMEM with 10% FBS. On the following day, the culture medium is replaced with DMEM containing either no compound as a control, the test compounds serially diluted in the presence of 2% FBS and 0.5% DMSO, or a combination of a compound of Formula (I) with one or more test compounds serially diluted in the presence of 2% FBS and 0.5% DMSO. The cells are incubated with no compound as a control, with the test compounds, or the combination of compounds for 72 h. The direct effects of the combination of the test compounds are examined using a luciferase (LUC) based reporter as determined by the Bright-Glo Luciferase Assay (Promega, Madison, WI). Dose-response curves are determined for individual compounds and fixed ratio combinations of two or more test compounds.

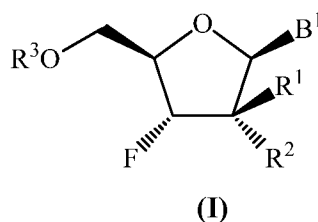
[0228] The method utilized for evaluating combination effects used a program called MacSynergy II. MacSynergy II software was kindly provided by Dr. M. Prichard (University of

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.

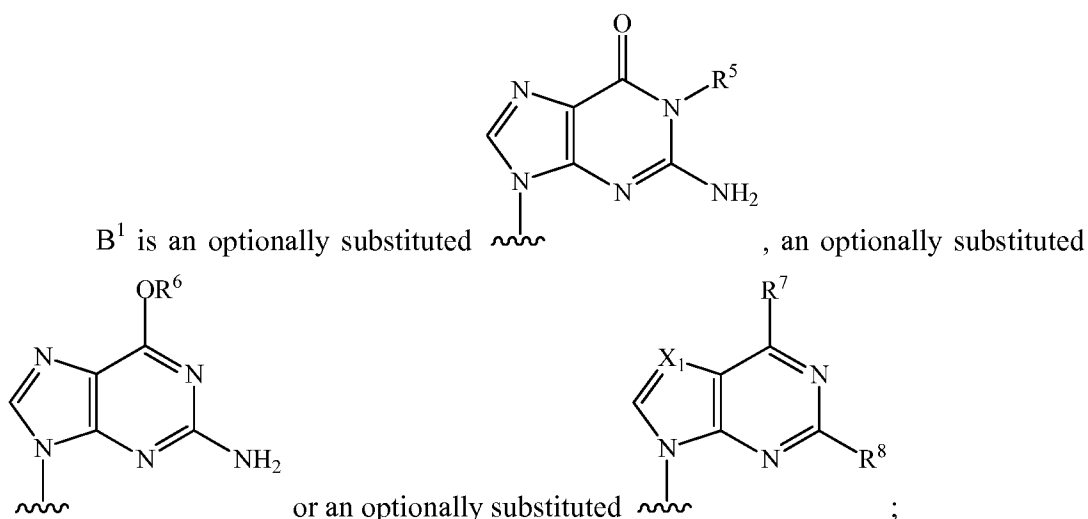
[0229] Although the foregoing has been described in some detail by way of illustrations and examples for purposes of clarity and understanding, it will be understood by those of skill in the art that numerous and various modifications can be made without departing from the spirit of the present disclosure. 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 within the true scope and spirit of the invention.

WHAT IS CLAIMED IS:

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

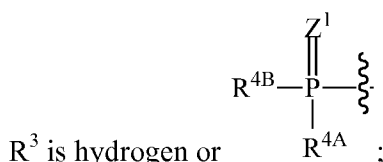


wherein:



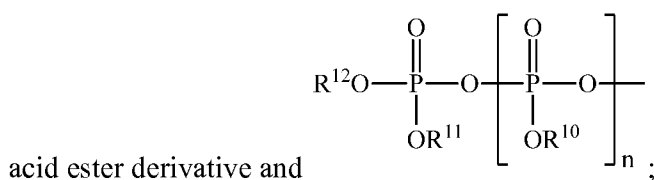
R^1 is selected from the group consisting of an unsubstituted C_{1-6} alkyl, an unsubstituted C_{2-6} alkenyl, an unsubstituted C_{2-6} alkynyl, an unsubstituted C_{3-6} cycloalkyl and an unsubstituted C_{1-6} haloalkyl;

R^2 is halo, $-OR^{9A}$ or $-N(R^{9B}R^{9C})$;



R^{4A} is selected from the group consisting of O^- , OH , an optionally substituted N-linked amino acid and an optionally substituted N-linked amino acid ester derivative;

R^{4B} is selected from the group consisting of O^- , OH , an $-O$ -optionally substituted aryl, an $-O$ -optionally substituted heteroaryl, an $-O$ -optionally substituted heterocyclyl, an optionally substituted N-linked amino acid, an optionally substituted N-linked amino



R^5 and R^6 are independently selected from the group consisting of hydrogen, an unsubstituted C_{1-6} alkyl, an unsubstituted C_{3-6} alkenyl, an unsubstituted C_{3-6} alkynyl and an unsubstituted C_{3-6} cycloalkyl;

R^7 is NHR^{13} ;

R^8 is NHR^{14} ;

R^{9A} is hydrogen or $-C(=O)R^{15}$;

R^{9B} and R^{9C} are independently hydrogen or an optionally substituted C_{1-6} alkyl;

R^{10} , R^{11} and R^{12} are independently absent or hydrogen;

R^{13} is selected from the group consisting of hydrogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{3-6} alkenyl, an optionally substituted C_{3-6} cycloalkyl, $-C(=O)R^{A1}$ and $-C(=O)OR^{A2}$;

R^{14} is selected from the group consisting of hydrogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{3-6} alkenyl, an optionally substituted C_{3-6} cycloalkyl, $-C(=O)R^{A3}$ and $-C(=O)OR^{A4}$;

R^{15} is an optionally substituted C_{1-6} alkyl or an optionally substituted C_{3-6} cycloalkyl;

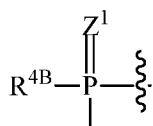
X^1 is N or $-CR^{16}$,

R^{16} 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;

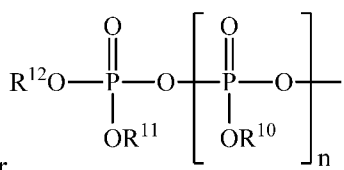
R^{A1} , R^{A2} , R^{A3} and R^{A4} are independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkenyl, C_{6-10} aryl, heteroaryl, heteroalicycyl, aryl(C_{1-6} alkyl), heteroaryl(C_{1-6} alkyl) and heteroalicycyl(C_{1-6} alkyl);

n is 0 or 1;

Z^1 is O or S; and



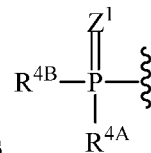
provided that when R^3 is



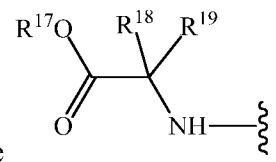
or

2. The compound of Claim 1, wherein R^2 is halo.
3. The compound of Claim 1, wherein R^2 is $-OR^{9A}$.

4. The compound of Claim 3, wherein R^{9A} is hydrogen.
5. The compound of Claim 3, wherein R^{9A} is -C(=O)R¹⁵.
6. The compound of Claim 1, wherein R² is -N(R^{9B}R^{9C}).
7. The compound of Claim 1, wherein R² is -NH₂.
8. The compound of Claim 6, wherein at least one of R^{9B} and R^{9C} is an optionally substituted C₁₋₆ alkyl.
9. The compound of Claim 6, wherein R^{9B} and R^{9C} are both an optionally substituted C₁₋₆ alkyl.
10. The compound of any one of Claims 1-9, wherein R¹ is an unsubstituted C₁₋₆ alkyl.
11. The compound of any one of Claims 1-9, wherein R¹ is an unsubstituted C₂₋₆ alkenyl.
12. The compound of any one of Claims 1-9, wherein R¹ is an unsubstituted C₂₋₆ alkynyl.
13. The compound of any one of Claims 1-9, wherein R¹ is an unsubstituted C₃₋₆ cycloalkyl.
14. The compound of any one of Claims 1-9, wherein R¹ is a C₁₋₆ haloalkyl.
15. The compound of any one of Claims 1-14, wherein R³ is hydrogen.



16. The compound of any one of Claims 1-14, wherein R⁴ is R^{4A}.
17. The compound of Claim 16, wherein R^{4A} is an optionally substituted N-linked amino acid.
18. The compound of Claim 16, wherein R^{4A} is an optionally substituted N-linked amino acid ester derivative.
19. The compound of Claim 16, wherein R^{4A} is selected from the group consisting of alanine, asparagine, aspartate, cysteine, glutamate, glutamine, glycine, proline, serine, tyrosine, arginine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, valine and ester derivatives thereof.
20. The compound of Claim 16, wherein R^{4A} is selected from the group consisting of alanine isopropyl ester, alanine cyclohexyl ester, alanine neopentyl ester, valine isopropyl ester, isoleucine isopropyl ester, methionine isopropyl ester and leucine isopropyl ester.



21. The compound of Claim 16, wherein R^{4A} has the structure wherein R^{17} is selected from the group consisting of hydrogen, an optionally substituted C_{1-6} -alkyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted aryl, an optionally substituted aryl(C_{1-6} alkyl) and an optionally substituted haloalkyl; R^{18} is selected from the group consisting of hydrogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{1-6} haloalkyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted C_6 aryl, an optionally substituted C_{10} aryl and an optionally substituted aryl(C_{1-6} alkyl); and R^{19} is hydrogen or an optionally substituted C_{1-6} -alkyl; or R^{18} and R^{19} is taken together to form an optionally substituted C_{3-6} cycloalkyl.

22. The compound of Claim 21, wherein R^{18} is hydrogen.

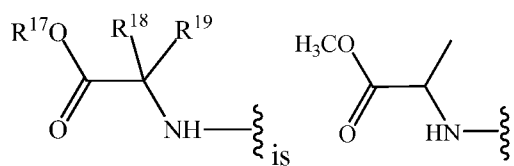
23. The compound of Claim 21, wherein R^{18} is an optionally substituted C_{1-6} alkyl.

24. The compound of any one of Claims 21-23, wherein R^{19} is hydrogen.

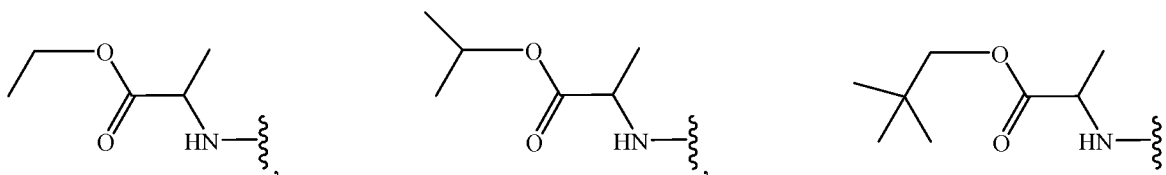
25. The compound of any one of Claims 21-23, wherein R^{19} is an optionally substituted C_{1-6} alkyl.

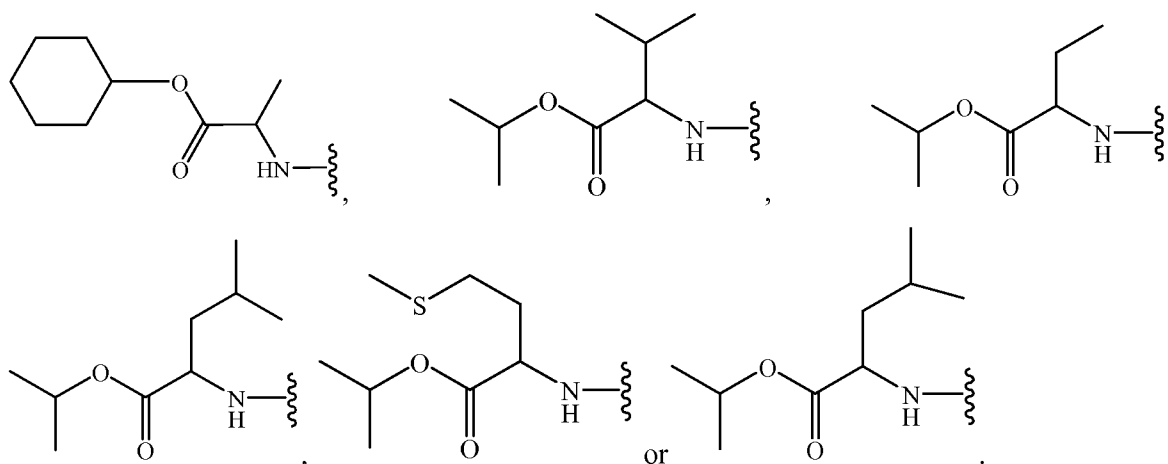
26. The compound of any one of Claims 21-25, wherein R^{17} is an optionally substituted C_{1-6} alkyl.

27. The compound of any one of Claims 21-25, wherein R^{17} is an optionally substituted C_{3-6} cycloalkyl.



28. The compound of Claim 21, wherein





29. The compound of any one of Claims 16-28, wherein R^{4B} is an $-O$ -optionally substituted aryl.

30. The compound of any one of Claims 16-28, wherein R^{4B} is an $-O$ -optionally substituted heteroaryl.

31. The compound of any one of Claims 16-28, wherein R^{4B} is an $-O$ -optionally substituted heterocyclyl.

32. The compound of any one of Claims 16-28, wherein R^{4B} is an optionally substituted N-linked amino acid.

33. The compound of any one of Claims 16-28, wherein R^{4B} is an optionally substituted N-linked amino acid ester derivative.

34. The compound of any one of Claims 16-28, wherein R^{4B} is selected from the group consisting of alanine, asparagine, aspartate, cysteine, glutamate, glutamine, glycine, proline, serine, tyrosine, arginine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, valine and ester derivatives thereof.

35. The compound of any one of Claims 16-28, wherein R^{4B} is selected from the group consisting of alanine isopropyl ester, alanine cyclohexyl ester, alanine neopentyl ester, valine isopropyl ester, isoleucine isopropyl ester, methionine isopropyl ester and leucine isopropyl ester.

36. The compound of any one of Claims 16-28, wherein R^{4B} has the structure

, wherein R^{20} 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^{21} is selected from the group consisting of hydrogen, an optionally substituted C_{1-6}

alkyl, an optionally substituted C₁₋₆ haloalkyl, an optionally substituted C₃₋₆ cycloalkyl, an optionally substituted C₆ aryl, an optionally substituted C₁₀ aryl and an optionally substituted aryl(C₁₋₆ alkyl); and R²² is hydrogen or an optionally substituted C₁₋₆-alkyl; or R²¹ and R²² is taken together to form an optionally substituted C₃₋₆ cycloalkyl.

37. The compound of Claim 36, wherein R²¹ is hydrogen.

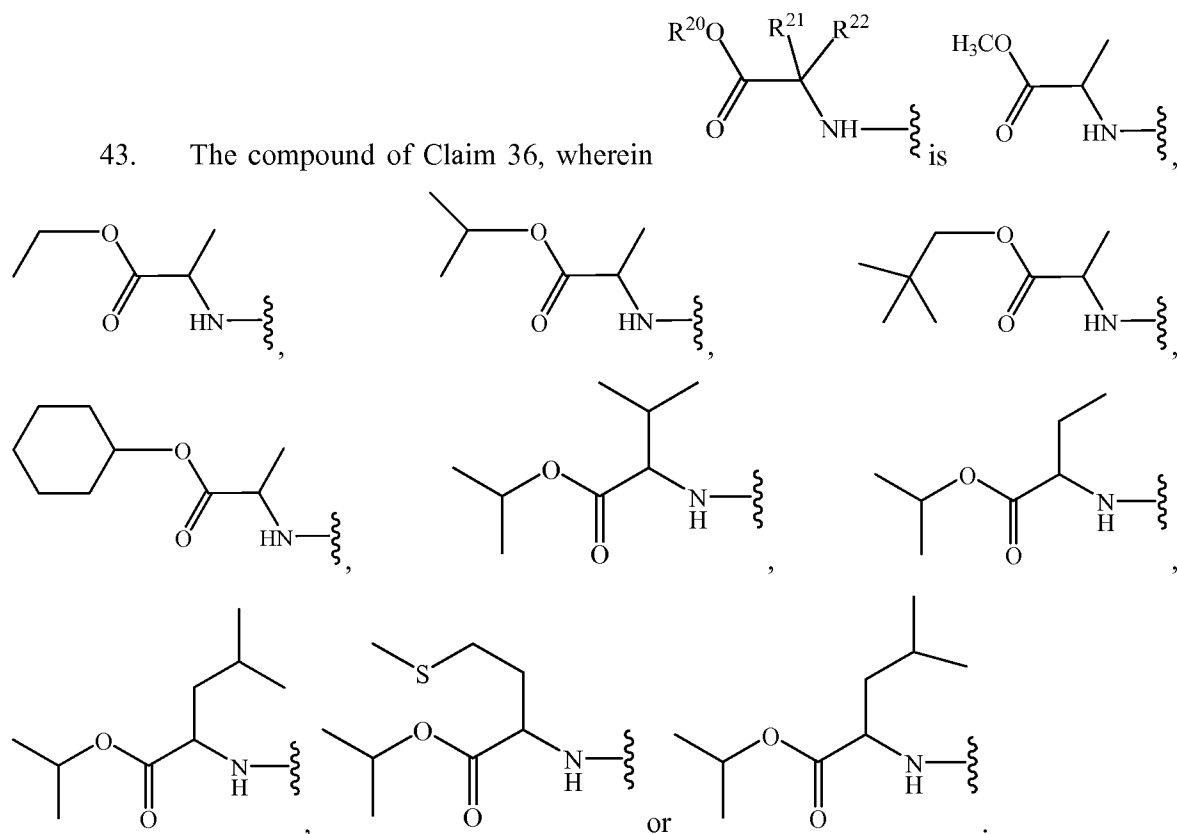
38. The compound of Claim 36, wherein R²¹ is an optionally substituted C₁₋₆ alkyl.

39. The compound of any one of Claims 36-38, wherein R²² is hydrogen.

40. The compound of any one of Claims 36-38, wherein R²² is an optionally substituted C₁₋₆ alkyl.

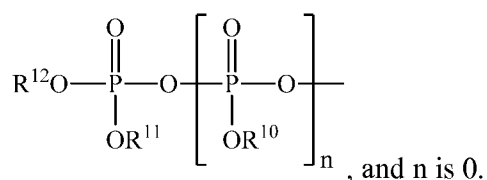
41. The compound of any one of Claims 36-40, wherein R²⁰ is an optionally substituted C₁₋₆ alkyl.

42. The compound of any one of Claims 36-40, wherein R²⁰ is an optionally substituted C₃₋₆ cycloalkyl.

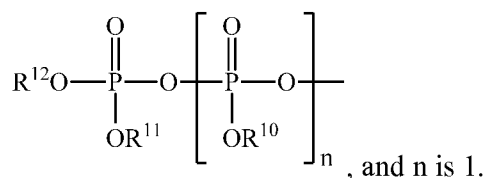


44. The compound of Claim 16, wherein R^{4A} is O⁻ or OH; and R^{4B} is O⁻ or OH.

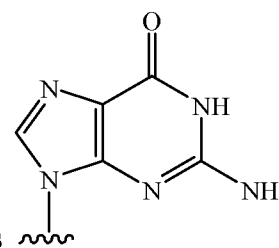
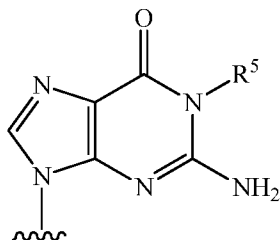
45. The compound of Claim 16, wherein R^{4A} is O⁻ or OH; and R^{4B} is



46. The compound of Claim 16, wherein R^{4A} is O^- or OH ; and R^{4B} is

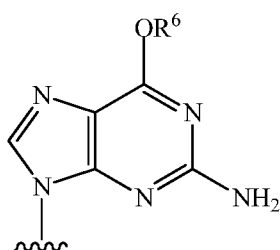


47. The compound of any one of Claims 1-46, wherein B^1 is an optionally substituted



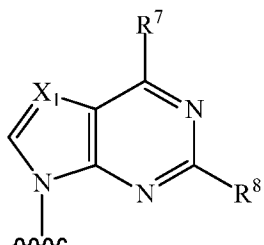
48. The compound of any one of Claims 1-46, wherein B^1 is

49. The compound of any one of Claims 1-46, wherein B^1 is an optionally substituted



50. The compound of Claim 49, wherein R^6 is an unsubstituted C_{1-6} alkyl or an unsubstituted C_{3-6} cycloalkyl.

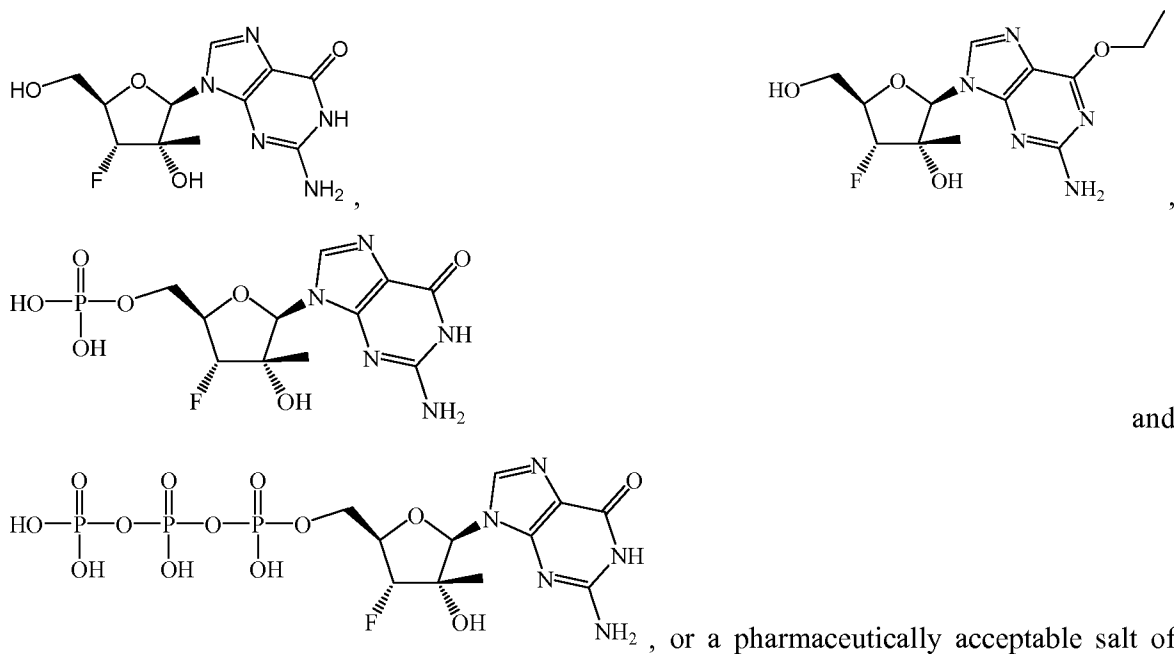
51. The compound of any one of Claims 1-46, wherein B^1 is an optionally substituted



52. The compound of any one of Claims 1-51, wherein Z^1 is O.

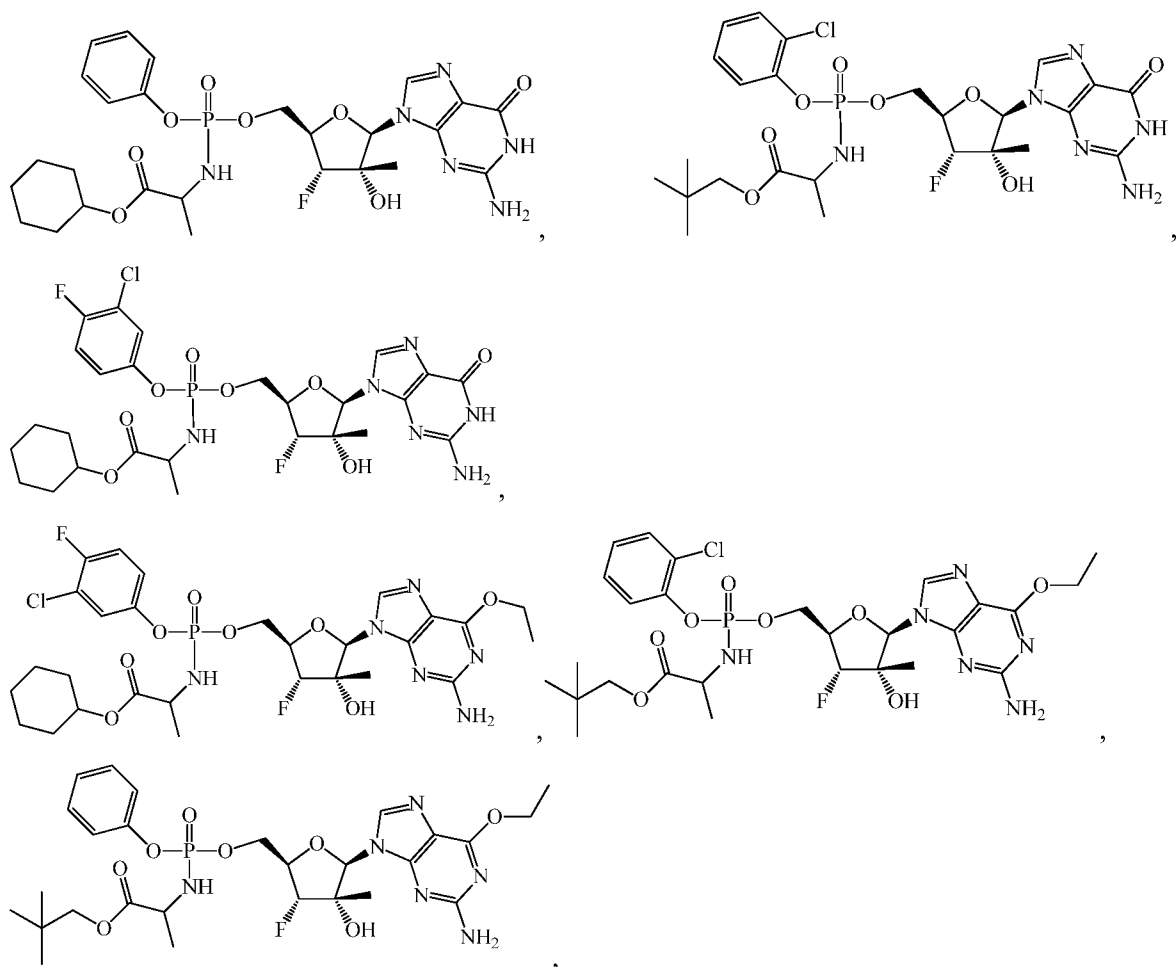
53. The compound of any one of Claims 1-51, wherein Z^1 is S.

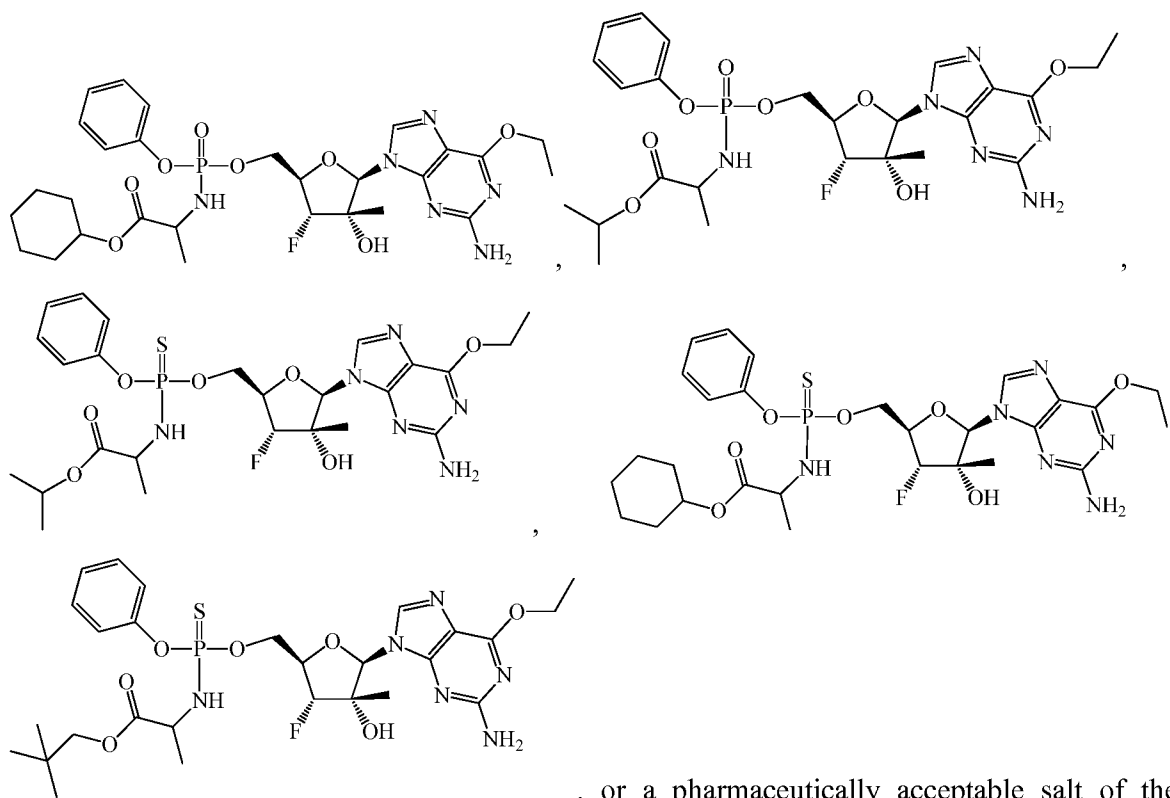
54. The compound of Claim 1 has a structure selected from the group consisting of:



the foregoing.

55. The compound of Claim 1 has a structure selected from the group consisting of:





56. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any one of Claims 1-55, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, excipient or combination thereof.

57. Use of a compound of any one of Claims 1-55, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Claim 56 for preparing a medicament for ameliorating or treating a HCV infection.

58. Use of a compound of any one of Claims 1-55, or a pharmaceutically acceptable salt thereof, for preparing a medicament for inhibiting NS5B polymerase activity of a hepatitis C virus.

59. Use of a compound of any one of Claims 1-55, or a pharmaceutically acceptable salt thereof, for preparing a medicament for inhibiting replication of a hepatitis C virus.

60. Use of a compound of any one of Claims 1-55, or a pharmaceutically acceptable salt thereof, for preparing a medicament for contacting a cell infected with a hepatitis C virus, whereby ameliorating or treating the HCV infection.

61. Use of a compound of any one of Claims 1-55 or a pharmaceutical composition of Claim 56 in the preparation of a medicament for ameliorating or treating a HCV 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 (AA), a compound of Formula (BB) and a compound of Formula (CC), or a pharmaceutically acceptable salt any of the aforementioned compounds.

62. Use of a compound of any one of Claims 1-55 in the preparation of a medicament for contacting a cell infected with a hepatitis C virus, 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 (AA), a compound of Formula (BB), a compound of Formula (BB) and a compound of Formula (CC), or a pharmaceutically acceptable salt any of the aforementioned compounds.

63. The use of any one of Claims 61-62, wherein the one or more agents are selected from the group consisting of Compounds 1001-1016, 2001-2012, 3001-3014, 4001-4012, 5001-5012, 6001-6078, 7000-7027 and 8000-8016, or a pharmaceutically acceptable salt of any of the aforementioned compounds.

64. A method of ameliorating or treating a HCV infection comprising administering to a subject suffering from the HCV infection a therapeutically effective amount of a compound of any one of Claims 1-55, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Claim 56.

65. A method for inhibiting NS5B polymerase activity of a hepatitis C virus comprising contacting a cell infected with the hepatitis C virus with an effective amount of a compound of any one of Claims 1-55, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Claim 56.

66. A method for inhibiting replication of a hepatitis C virus comprising contacting a cell infected with the hepatitis C virus with a compound of any one of Claims 1-55, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Claim 56.

67. A method for ameliorating or treating a HCV infection comprising contacting a cell infected with the hepatitis C virus with a compound of any one of Claims 1-55, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Claim 56.

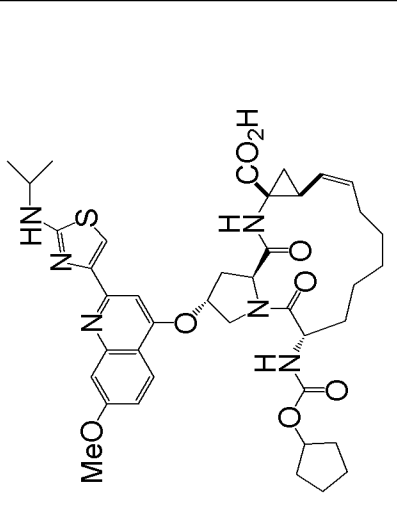
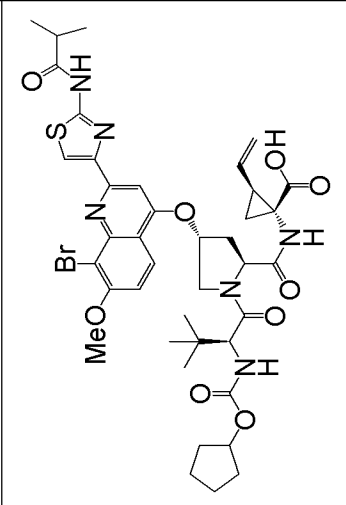
68. A method of ameliorating or treating a HCV infection comprising contacting a cell infected with the hepatitis C virus with a therapeutically effective amount of a compound of any one of Claims 1-55, in combination with one or more agents selected from the group consisting of an interferon, ribavirin, a HCV protease inhibitor, a HCV polymerase inhibitor, a NS5A inhibitor, an antiviral compound, a compound of Formula (AA), a compound of Formula

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

69. A method of ameliorating or treating a HCV infection comprising administering to a subject suffering from the HCV infection a therapeutically effective amount of a compound of any one of Claims 1-55, 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 (AA), a compound of Formula (BB) and a compound of Formula (CC), or a pharmaceutically acceptable salt any of the aforementioned compounds.

70. The method of any one of Claims 68-69, wherein the one or more agents are selected from the group consisting of Compounds 1001-1016, 2001-2012, 3001-3014, 4001-4012, 5001-5012, 6001-6078, 7000-7027 and 8000-8016, or a pharmaceutically acceptable salt of any of the aforementioned compounds.

Figure 1: HCV Protease Inhibitors

#	Name	Structure
1004	BILN-2061	
1005	BI-201335 BI335	

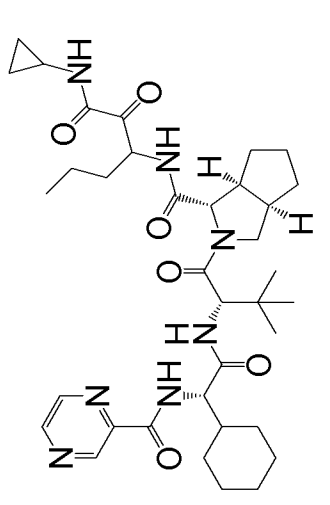
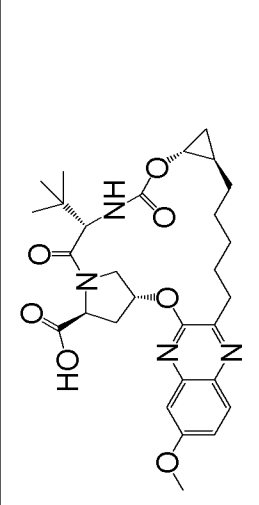
#	Name	Structure
1001	Telaprevir VX-950	
1002	MK-5172	
1003	ABT-450	

Figure 1 (cont.): HCV Protease Inhibitors

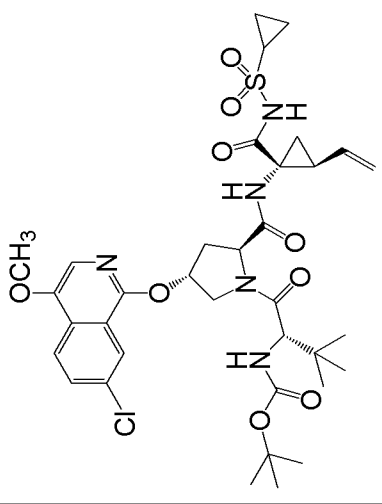
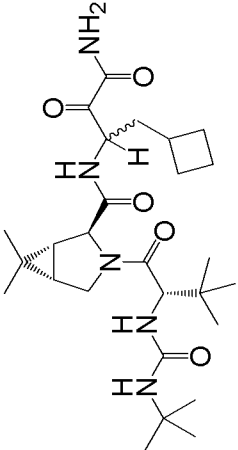
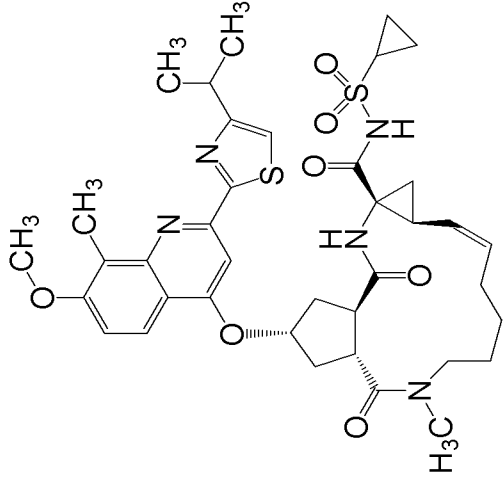
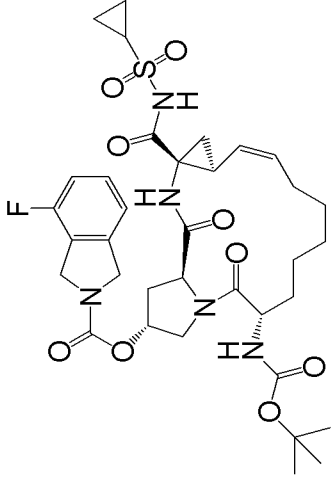
#	Name	Structure
1006	BMS-650032 BM032 Asunaprevir	
1007	Boceprevir SCH 503034	
1008	GS-9256	
1009	GS-9451	
1010	IDX-320	
1011	ACH-1625	
1012	ACH-2684	
1013	TMC-435 TMC-435350	
1014	Danoprevir ITMN-191 RG7227 RO5190591	

Figure 1 (cont.): HCV Protease Inhibitors

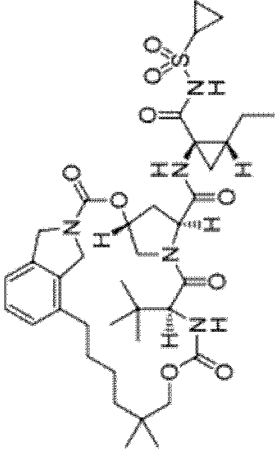
#	Name	Structure
1015	MK-7009 Vaniprevir	
1016	PHX1766	

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

#	Name	Structure
2004	PSI-352938 GS-938	
2005	4'-azidouridine and its prodrugs	
2006	PSI-661	
2007	GS-6620	
2008	TMC649128	

#	Name	Structure
2001	RG7128 Mericitabine	
2002	PSI-7851	
2003	PSI-7977 GS-7977, Sofosbuvir	

Figure 2 (cont.): HCV Polymerase Inhibitors – Nucleosides, Nucleotides and Analogs Thereof

#	Name	Structure
2009	NM283	
2010	BCX5191	
2011	IDX19368	
2012	IDX19370	

Figure 3: HCV Polymerase Inhibitors – Non-Nucleosides

#	Name	Structure
3004	HCV-796	
3005	BI-207127	
3006	GS-9190	
3007	Filibuvir PF-00868554	

#	Name	Structure
3001	ABT-333	
3002	ANA-598 Setrobuvir	
3003	VX-222 S1480 VCH-222	

Figure 3 (cont.): HCV Polymerase Inhibitors – Non-Nucleosides

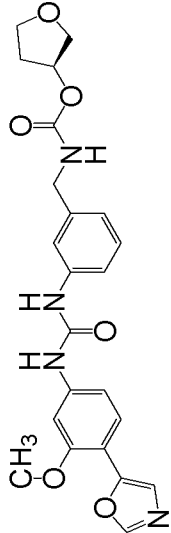
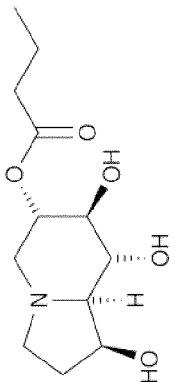
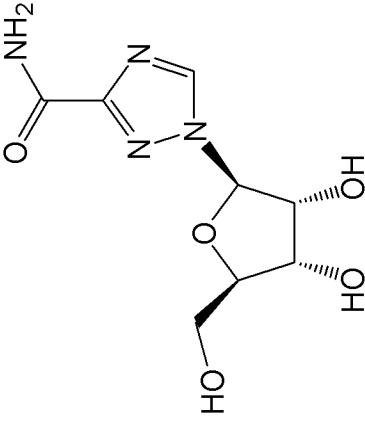
#	Name	Structure	#	Name	Structure
3008	VX-497		3011	TMC647055	
3009	ABT-072		3012	BMS-791325	
3010	MK-3281		3013	PPI-383	
			3014	GS9669	

Figure 5: Other Antivirals and Ribavirin

#	Name	Structure
5010	Celgosivir	
5011	GS9620	
5012	Ribavirin	

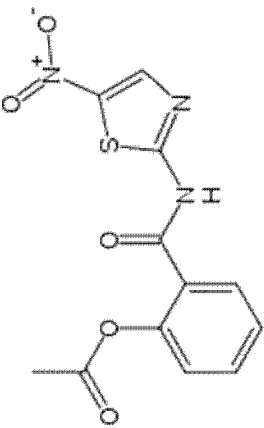
#	Name	Structure
5001	Debio-025 Alisporivir	
5002	MIR-122	
5003	clemizole	
5004	ITX 5061	
5005	BIT225	
5006	NIM811	
5007	SCY-635	
5008	Nitazoxanide	
5009	Miravirsen	

Figure 6: Compounds of Formula (CC) and alpha-thiotriphosphates thereof

#	Structure
6000	
6001	
6002	
6003	
6004	

Figure 6 (cont.): Compounds of Formula (CC) and alpha-thiotriphosphates thereof

#	Structure
6005	
6006	
6007	
6008	

Figure 6 (cont.): Compounds of Formula (CC) and alpha-thiotriphosphates thereof

#	Structure
6009	
6010	
6011	
6012	
6013	

Figure 6 (cont.): Compounds of Formula (CC) and alpha-thiotriphosphates thereof

#	Structure
6014	
6015	
6016	
6017	

Figure 6 (cont.): Compounds of Formula (CC) and alpha-thiotriphosphates thereof

#	Structure
6021	
6022	
6023	

#	Structure
6018	
6019	
6020	

Figure 6 (cont.): Compounds of Formula (CC) and alpha-thiotriphosphates thereof

#	Structure
6027	
6028	
6029	
6030	

#	Structure
6024	
6025	
6026	

Figure 6 (cont.): Compounds of Formula (CC) and alpha-thiotriphosphates thereof

#	Structure
6031	
6032	
6033	
6034	
6035	
6036	

Figure 6 (cont.): Compounds of Formula (CC) and alpha-thiotriphosphates thereof

#	Structure
6040	
6041	
6042	
6037	
6038	
6039	

Figure 6 (cont.): Compounds of Formula (CC) and alpha-thiotriphosphates thereof

#	Structure
6043	
6044	
6045	
6046	
6047	
6048	

Figure 6 (cont.): Compounds of Formula (CC) and alpha-thiotriphosphates thereof

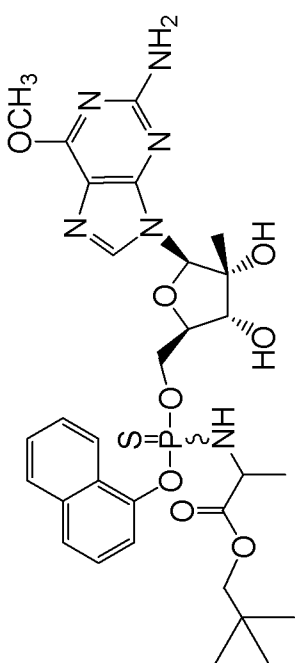
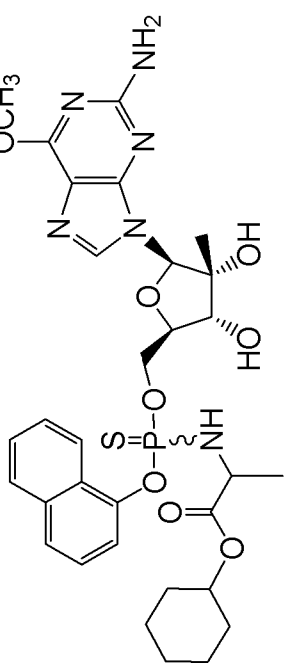
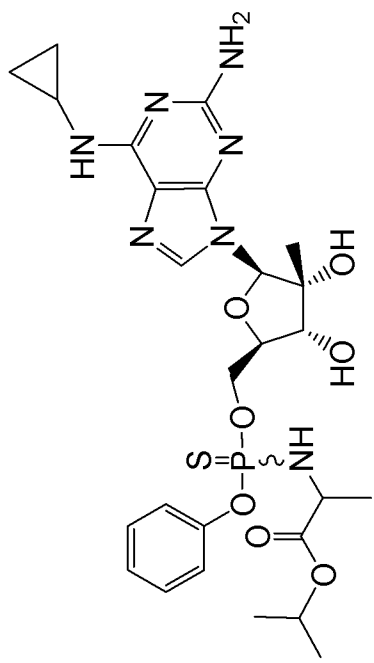
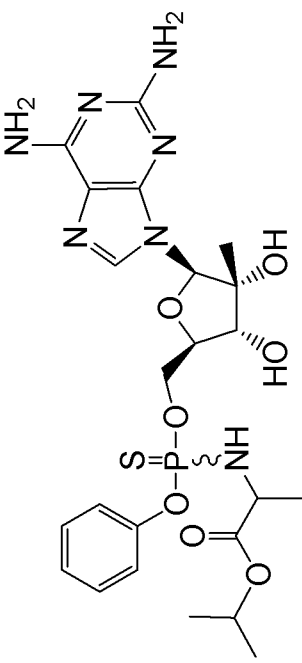
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6049	
6050	
6051	
6052	

Figure 6 (cont.): Compounds of Formula (CC) and alpha-thiotriphosphates thereof

#	Structure
6060	
6061	
6062	
6058	
6059	

Figure 6 (cont.): Compounds of Formula (CC) and alpha-thiotriphosphates thereof

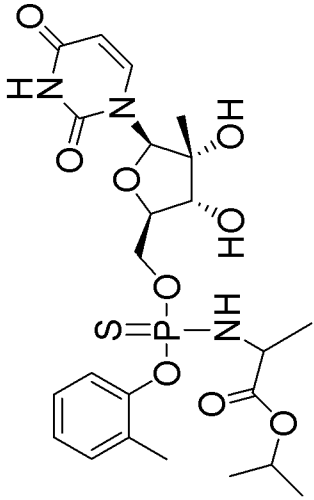
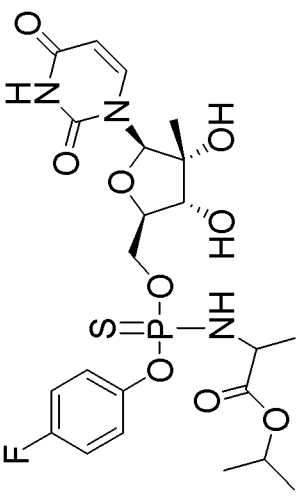
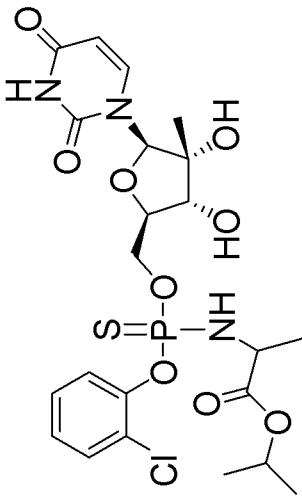
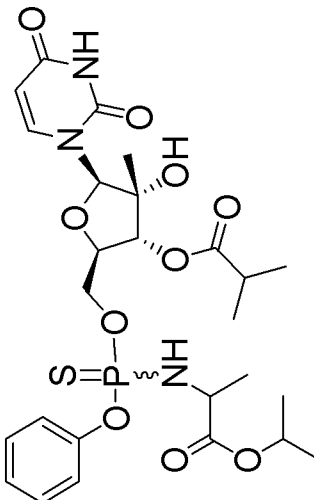
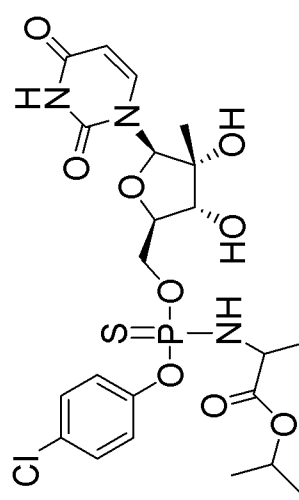
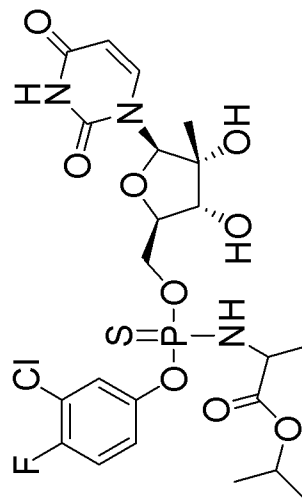
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6067	
6068	
6063	
6064	
6065	

Figure 6 (cont.): Compounds of Formula (CC) and alpha-thiotriphosphates thereof

#	Structure
6072	
6073	
6074	
6069	
6070	
6071	

Figure 6 (cont.): Compounds of Formula (CC) and alpha-thiotriphosphates thereof

#	Structure
6075	
6076	
6077	
6078	

Figure 7: Compounds of Formula (AA)

#	Structure
7000	
7001	
7002	
7003	

Figure 7 (cont.): Compounds of Formula (AA)

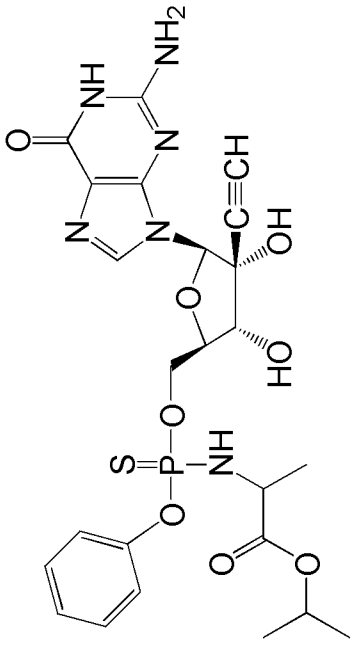
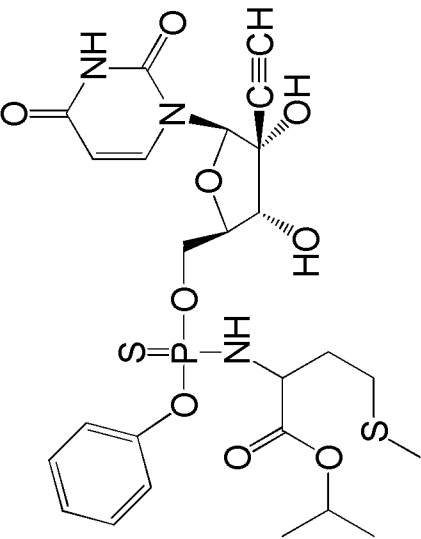
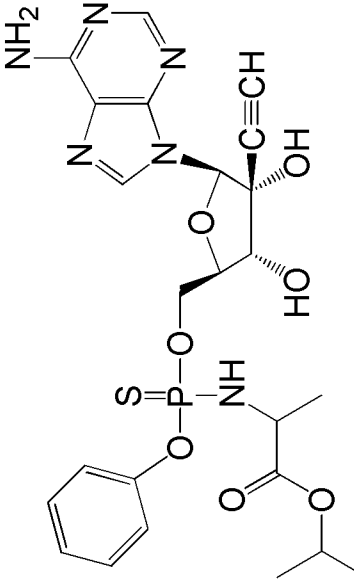
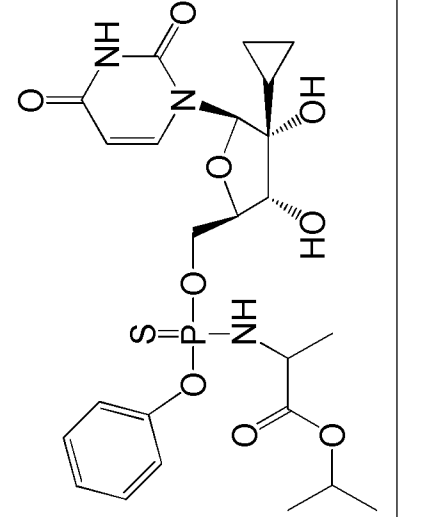
#	Structure
7006	
7007	
7004	
7005	

Figure 7 (cont.): Compounds of Formula (AA)

#	Structure
7010	
7011	

#	Structure
7008	
7009	

Figure 7 (cont.): Compounds of Formula (AA)

#	Structure
7014	
7015	

#	Structure
7012	
7013	

Figure 7 (cont.): Compounds of Formula (AA)

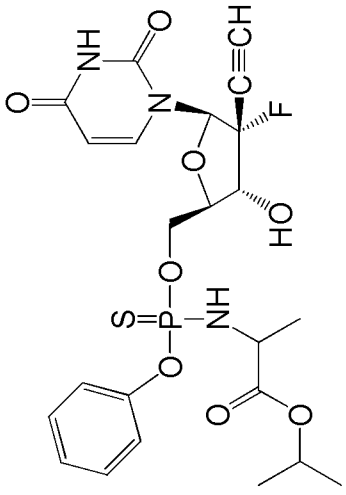
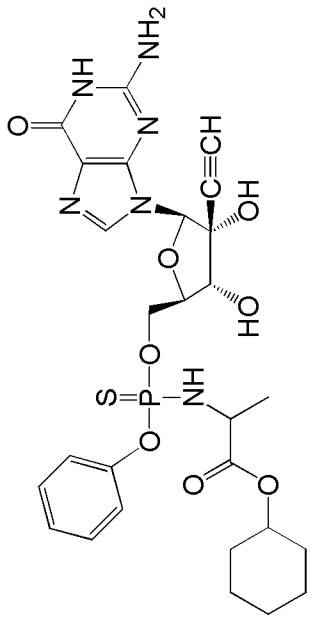
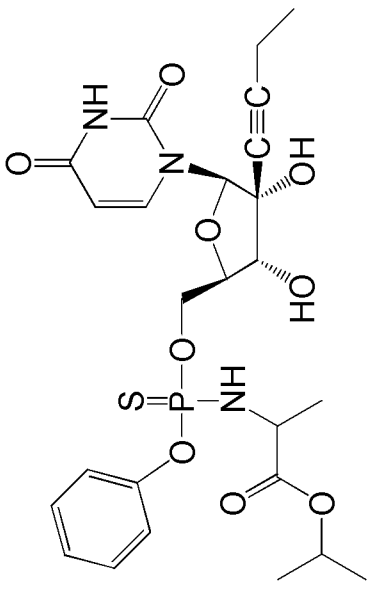
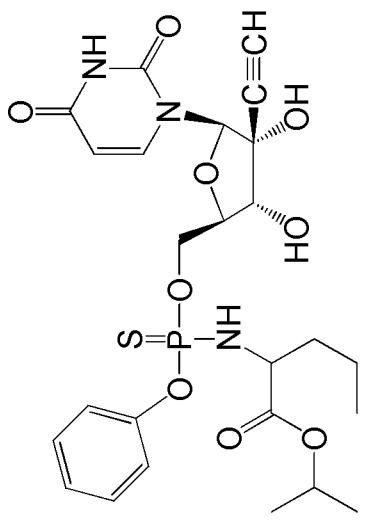
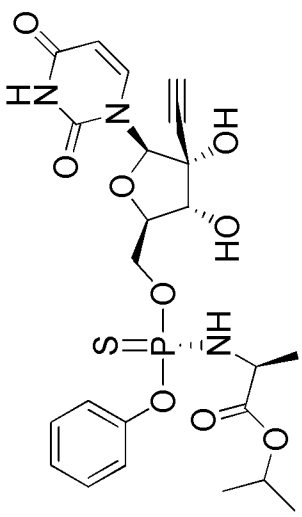
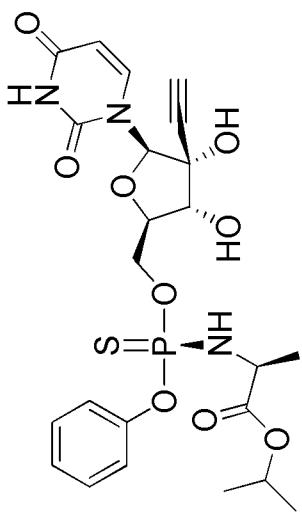
#	Structure
7016	
7017	
7018	
7019	

Figure 7 (cont.): Compounds of Formula (AA)

#	Structure
7020	
7021	
7022	
7023	

Figure 7 (cont.): Compounds of Formula (AA)

#	Structure
7026	
7027	

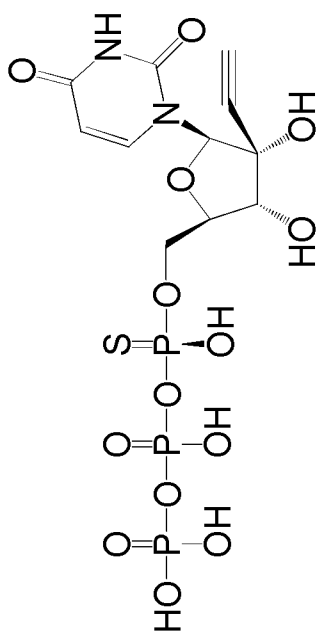
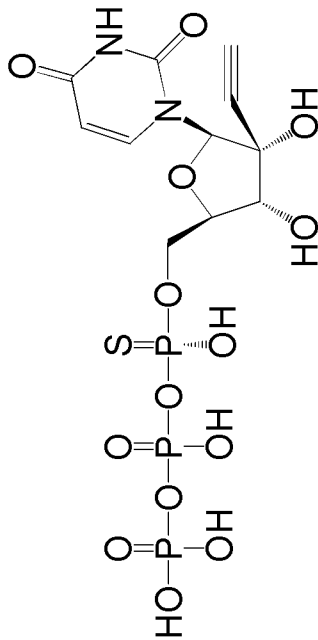
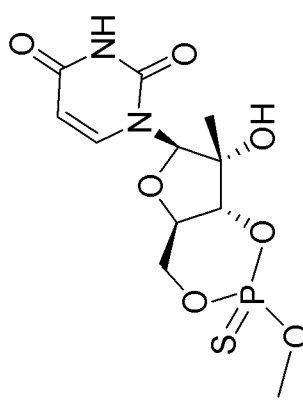
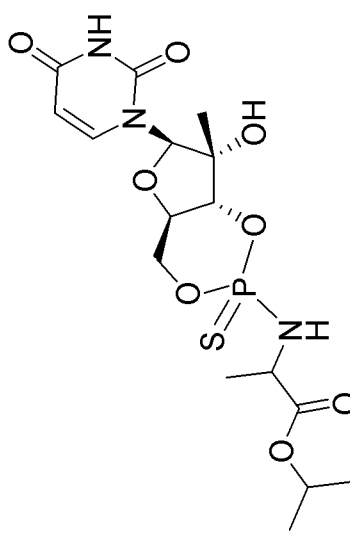
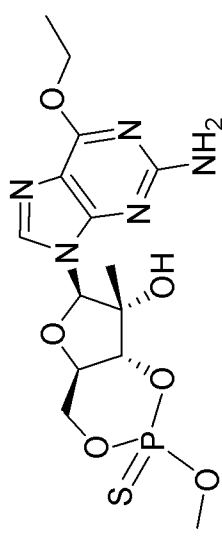
#	Structure
7024	
7025	

Figure 8: Compounds of Formula (BB)

#	Structure
8003	
8004	
8005	

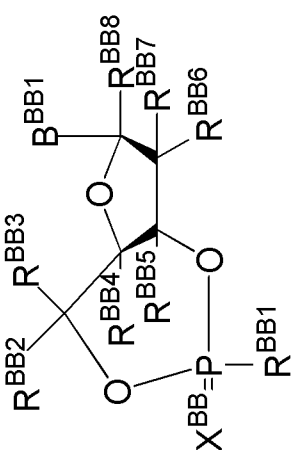
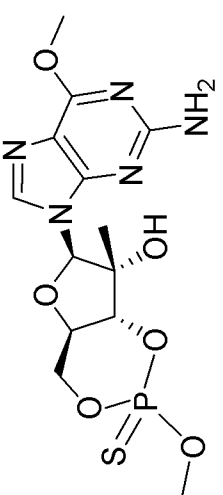
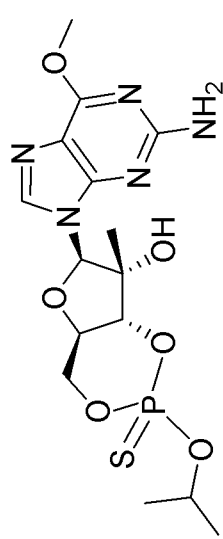
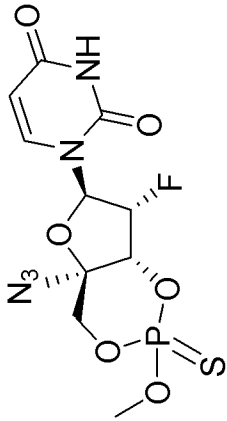
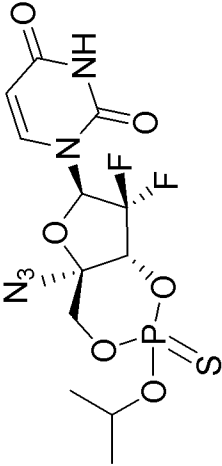
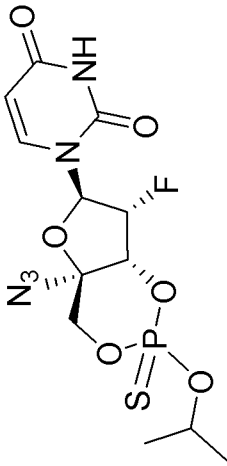
#	Structure
8000	
8001	
8002	

Figure 8 (cont.): Compounds of Formula (BB)

#	Structure
8009	
80010	
8011	

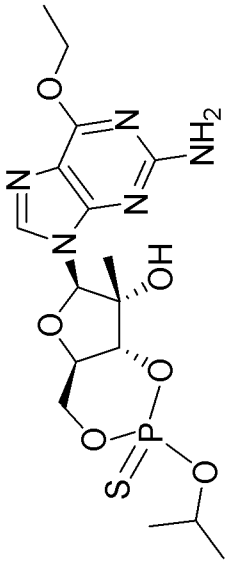
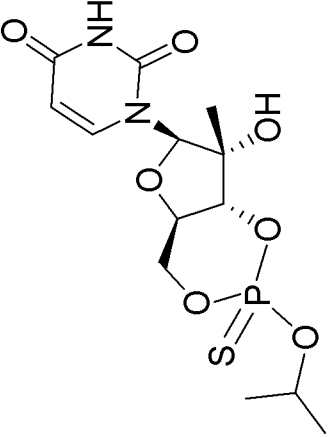
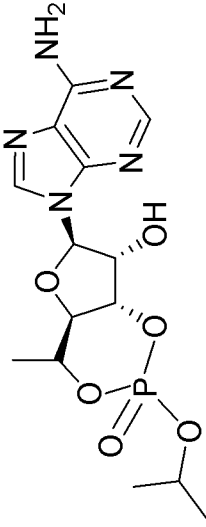
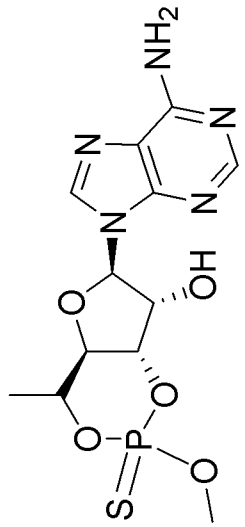
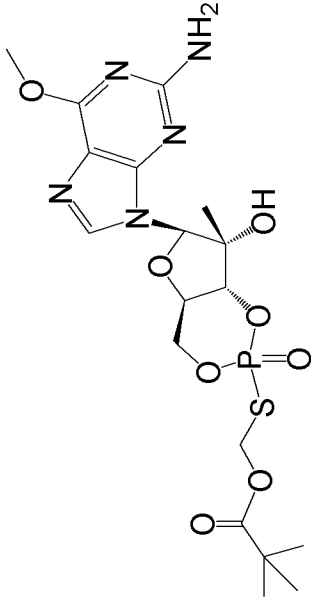
#	Structure
8006	
8007	
8008	

Figure 8 (cont.): Compounds of Formula (BB)

#	Structure
8015	
8016	

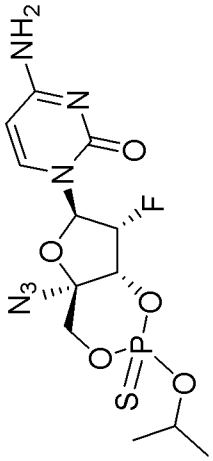
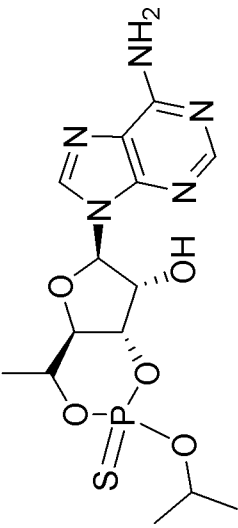
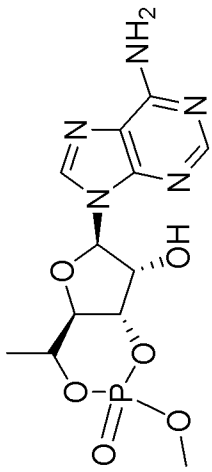
#	Structure
8012	
8013	
8014	

Figure 9: Compounds of Formula (I)

#	Structure
9004	
9005	
9006	

#	Structure
9000	
9001	
9002	
9003	

Figure 9 (cont.): Compounds of Formula (I)

#	Structure
9011	
9012	
9013	

#	Structure
9007	
9008	
9009	
9010	

Figure 9 (cont.): Compounds of Formula (I)

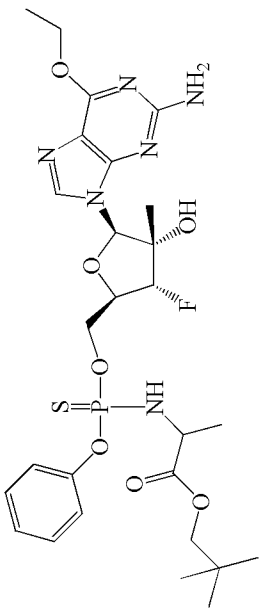
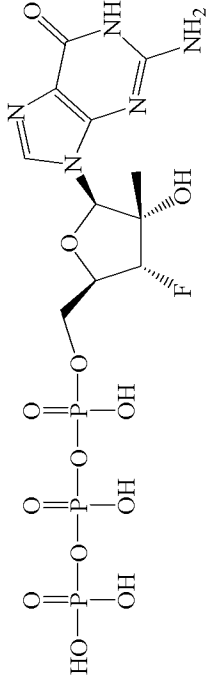
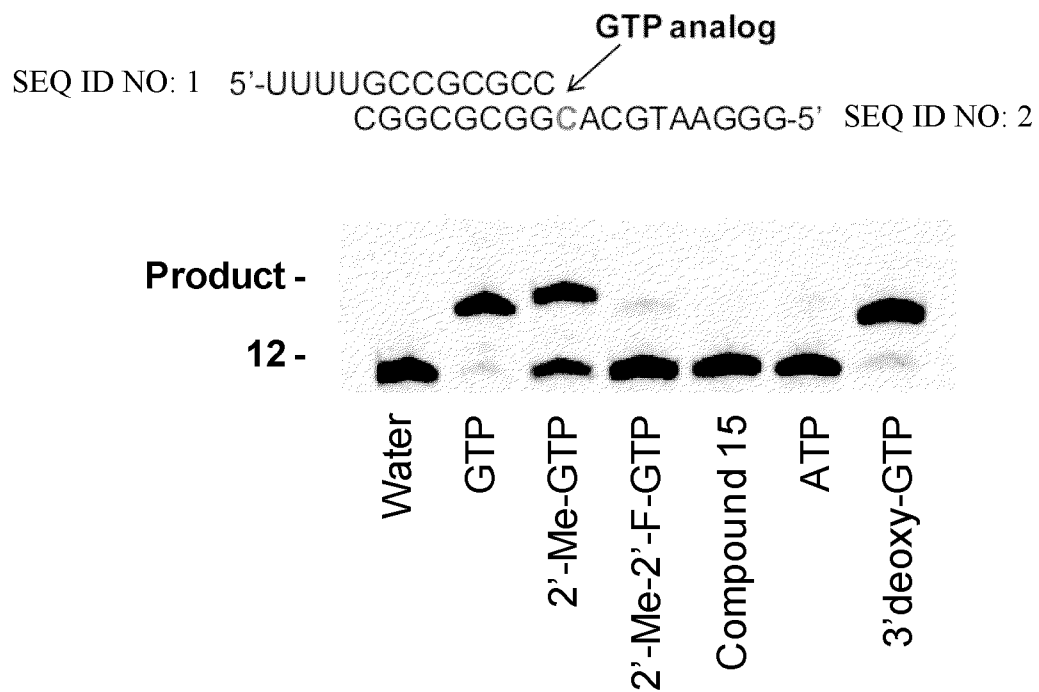
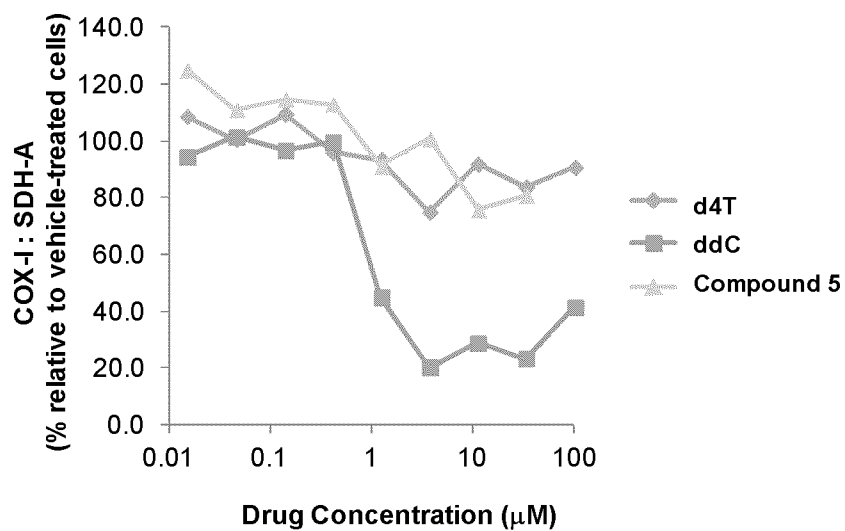
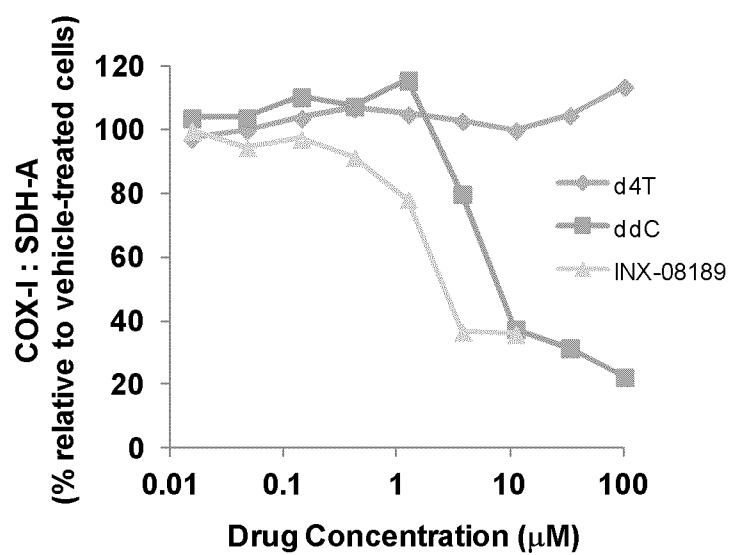
#	Structure
9014	
9015	

Figure 10

GTP = guanosine-5'-triphosphate

ATP = adenosine 5'-triphosphate

Figure 11**A****B**

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2013/076727

A. CLASSIFICATION OF SUBJECT MATTER

C07H 19/167 (2006.01) C07H 19/20 (2006.01) A61K 31/7052 (2006.01) A61P 31/14 (2006.01)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN Registry and CAPlus: Substructure search based on the compounds of Formula (I).

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

☒ Further documents are listed in the continuation of Box C
 ☒ See patent family annex

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

Date of the actual completion of the international search 28 February 2014	Date of mailing of the international search report 28 February 2014
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaustralia.gov.au Facsimile No.: +61 2 6283 7999	Authorised officer Bradley Man AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. +61 (02) 6283 2034

INTERNATIONAL SEARCH REPORT		International application No.
C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		PCT/US2013/076727
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ELDRUP, A. B. et al., "Structure-Activity Relationship of Purine Ribonucleosides for Inhibition of Hepatitis C Virus RNA-Dependent RNA Polymerase.", Journal of Medicinal Chemistry, 2004, Vol. 47, No. 9, pages 2283-2295. Whole document in particular compounds 4 and 8	1-70
A	WO 2002/057425 A2 (MERCK & CO., INC. et al.) 25 July 2002 See Examples 19, 24, 43 and 107	1-70
A	WO 2005/020885 A2 (ISIS PHARMACEUTICALS, INC.) 10 March 2005 See Table 1, pages 141-241	1-70
P,X	WO 2013/070887 A1 (INHIBITEX, INC. et al.) 16 May 2013 See Tables 1-4 (notably Table 1, Example 1-8, 12-31 and 34; Table 4, Example 1 and 2); page 8; page 96; page 127, Claim 1, Formula (I);	1, 3, 4, 10, 11, 15, 16, 18-30, 33-44, 46-52 and 54-70
Form PCT/ISA/210 (fifth sheet) (July 2009)		

INTERNATIONAL SEARCH REPORT		International application No.	
Information on patent family members		PCT/US2013/076727	
This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.			
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Publication Number	Publication Date	Publication Number	Publication Date
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		HR P20030565 B1	31 Dec 2011
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		IS 6860 A	25 Jun 2003
		IS 2449 B	15 Nov 2008
		JO 2318 B	12 Sep 2005
		JP 2004520367 A	08 Jul 2004
		JP 3914156 B2	16 May 2007
		JP 2007224045 A	06 Sep 2007
		JP 4931683 B2	16 May 2012
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		MX PA03006514 A	02 Dec 2004
		NO 20033289 A	19 Sep 2003
Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.			
Form PCT/ISA/210 (Family Annex)(July 2009)			

INTERNATIONAL SEARCH REPORT		International application No.	
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This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.			
Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
		NO 326431 B1	08 Dec 2008
		NZ 526703 A	24 Dec 2004
		PE 08232002 A1	11 Sep 2002
		PL 363216 A1	15 Nov 2004
		PL 207405 B1	31 Dec 2010
		YU P56903 A	03 Mar 2006
		RS 50236 B	15 Jul 2009
		TW I261056 B	01 Sep 2006
		US 2002147160 A1	10 Oct 2002
		US 6777395 B2	17 Aug 2004
		US 2004110717 A1	10 Jun 2004
		US 7105499 B2	12 Sep 2006
		US 2004067901 A1	08 Apr 2004
		US 7125855 B2	24 Oct 2006
		US 2006264390 A1	23 Nov 2006
		US 7202224 B2	10 Apr 2007
		US 2012165515 A1	28 Jun 2012
		US 8481712 B2	09 Jul 2013
		US 2004072788 A1	15 Apr 2004
		US 2005272676 A1	08 Dec 2005
		US 2006205686 A1	14 Sep 2006
		US 2007275912 A1	29 Nov 2007
		WO 02057287 A2	25 Jul 2002
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		ZA 200305078 A	21 May 2004
WO 2005/020885 A2	10 Mar 2005	None	
WO 2013/070887 A1	16 May 2013	None	
End of Annex			
Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001. Form PCT/ISA/210 (Family Annex)(July 2009)			