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

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

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, for example, in the Application Data Sheet or Request as filed with the present application, are hereby incorporated by reference under 37 CFR 1.57, and Rules 4.18 and 20.6.

BACKGROUND

Field

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

Description

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

SUMMARY

[0004] Some embodiments disclosed herein relate to a method of ameliorating and/or treating a Filoviridae virus infection that can include administering to a subject

identified as suffering from the Filoviridae virus infection an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt of 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 Filoviridae virus 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 Filoviridae virus infection.

[0005] Some embodiments disclosed herein relate to a method of ameliorating and/or treating a Filoviridae virus infection that can include contacting a cell infected with the Filoviridae virus with an effective amount of one or more compounds described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof), 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 (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) in the manufacture of a medicament for ameliorating and/or treating a Filoviridae virus infection that can include contacting a cell infected with the Filoviridae virus with an effective amount of said compound(s). Still other embodiments described herein relate to one or more compounds described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof), 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 Filoviridae virus infection by contacting a cell infected with the Filoviridae virus with an effective amount of said compound(s).

[0006] Some embodiments disclosed herein relate to a method of inhibiting replication of a Filoviridae virus that can include contacting a cell infected with the Filoviridae virus with an effective amount of one or more compounds described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt of the foregoing), 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 (for example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof) in the manufacture of a medicament for inhibiting replication of a Filoviridae virus that can include contacting a cell infected with the Filoviridae virus with an effective amount of said compound(s). Still other embodiments described herein relate to one or more compounds described herein (for example, a compound of Formula (I), or a pharmaceutically acceptable salt of the foregoing), 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 Filoviridae virus by contacting a cell infected with the Filoviridae with an effective amount of said compound(s). In some embodiments, the Filoviridae virus can be an Ebola virus and/or Marburg virus.

DETAILED DESCRIPTION

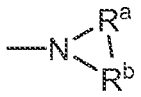
[0007] The viruses of the Filoviridae family are enveloped, negative sense, single-stranded, linear RNA viruses. Three genera within the Filoviridae family are Ebolavirus, Marburgvirus and "Cuevavirus" (tentative). The five recognized species of Ebolavirus are Ebola virus (EBOV), Reston ebolavirus (REBOV), Sudan ebolavirus (SEBOV), Taï Forest ebolavirus (TAFV) and Bundibugyo ebolavirus (BEBOV). The two recognized species of Marburgvirus are Marburg virus (MARV) and Ravn virus (RAVV). Ebolavirus and Marburgvirus are highly infectious and contagious. Both viruses are transmitted by direct contact with the blood, body fluids and/or tissues of infected persons. Ebolavirus and Marburgvirus can also be transmitted by handling sick or dead infected wild animals. Ebola hemorrhagic fever (EHF) is caused by an Ebolavirus infection. Marburg virus disease (MVD) is a human disease caused by a Marburgvirus, and causes Marburgvirus hemorrhagic fever (MHF).

Definitions

[0008] 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.

[0009] As used herein, any "R" group(s) such as, without limitation, R^1, R^2, R^3, R^4, R^{5A}, R^{5B}, R^{6A}, R^{6B}, R^{6C}, R^{6D}, R^{6E}, R^{6F}, R^{6G}, R^{6H}, R^{7A}, R^{7B}, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, 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 $NR^a R^b$ 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.

[0010] 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 of 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, heterocyclyl, aryl(alkyl), heteroaryl(alkyl), (heterocyclyl)alkyl, hydroxy, alkoxy, acyl, 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, azido, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, an amino, a mono-substituted amino group and a di-substituted amino group.

[0011] 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 heterocyclyl 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 heterocyclyl can contain from "a" to "b", inclusive, carbon atoms. Thus, for example, a "C_1 to C_4 alkyl" group refers to all alkyl groups having from 1 to 4 carbons, that is, CH_3-, CH_3CH_2-, $CH_3CH_2CH_2$-, $(CH_3)_2CH$-, $CH_3CH_2CH_2CH_2$-, $CH_3CH_2CH(CH_3)$- and $(CH_3)_3C$-. If no "a" and "b" are designated with regard to an alkyl, alkenyl, alkynyl, cycloalkyl cycloalkenyl, aryl, heteroaryl or heterocyclyl group, the broadest range described in these definitions is to be assumed.

[0012] As used herein, "alkyl" refers to a straight or branched hydrocarbon chain that comprises a fully saturated (no double or triple bonds) hydrocarbon group. The alkyl group may have 1 to 20 carbon atoms (whenever it appears herein, a numerical range such as "1 to 20" refers to each integer in the given range; *e.g.*, "1 to 20 carbon atoms" means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 20 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated). The alkyl group may also be a medium size alkyl having 1 to 10 carbon atoms. The alkyl group could also be a lower alkyl having 1 to 6 carbon atoms. The alkyl group of the compounds may be designated as "C_1-C_4 alkyl" or similar designations. By way of example only, "C_1-C_4 alkyl" indicates that there are one to four carbon atoms in the alkyl chain, i.e., the alkyl chain is selected from methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl and t-butyl. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl and hexyl. The alkyl group may be substituted or unsubstituted.

[0013] 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.

[0014] 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.

[0015] 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.

[0016] 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.

[0017] As used herein, "aryl" refers to a carbocyclic (all carbon) monocyclic or multicyclic aromatic ring system (including fused ring systems where two carbocyclic rings share a chemical bond) that has a fully delocalized pi-electron system throughout all the rings. The number of carbon atoms in an aryl group can vary. For example, the aryl group can be a C_6-C_{14} aryl group, a C_6-C_{10} aryl group, or a C_6 aryl group. Examples of aryl groups include, but are not limited to, benzene, naphthalene and azulene. An aryl group may be substituted or unsubstituted.

[0018] 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.

[0019] 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 heterocyclyl or a heteroalicyclyl may be quaternized. Heterocyclyl or heteroalicyclic groups may be unsubstituted or substituted. Examples of such "heterocyclyl" or "heteroalicyclyl" groups include but are not limited to, 1,3-dioxin, 1,3-dioxane, 1,4-dioxane, 1,2-dioxolane, 1,3-dioxolane, 1,4-dioxolane, 1,3-oxathiane, 1,4-oxathiin, 1,3-oxathiolane, 1,3-dithiole, 1,3-dithiolane, 1,4-oxathiane, tetrahydro-1,4-thiazine, 2H-1,2-oxazine, maleimide, succinimide, barbituric acid, thiobarbituric acid, dioxopiperazine, hydantoin, dihydrouracil, trioxane, hexahydro-1,3,5-triazine, imidazoline, imidazolidine, isoxazoline, isoxazolidine, oxazoline, oxazolidine, oxazolidinone, thiazoline, thiazolidine, morpholine, oxirane, piperidine *N*-Oxide, piperidine, piperazine, pyrrolidine, pyrrolidone, pyrrolidione, 4-piperidone, pyrazoline, pyrazolidine, 2-oxopyrrolidine, tetrahydropyran, 4H-pyran, tetrahydrothiopyran, thiamorpholine, thiamorpholine sulfoxide, thiamorpholine sulfone and their benzo-fused analogs (e.g., benzimidazolidinone, tetrahydroquinoline and 3,4-methylenedioxyphenyl).

[0020] 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 aryl(alkyl) may be substituted or unsubstituted. Examples include but are not limited to benzyl, 2-phenyl(alkyl), 3-phenyl(alkyl), and naphthyl(alkyl).

[0021] 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 heteroaryl(alkyl) may be substituted or unsubstituted. Examples include but are not limited to 2-thienyl(alkyl), 3-thienyl(alkyl), furyl(alkyl), thienyl(alkyl), pyrrolyl(alkyl), pyridyl(alkyl), isoxazolyl(alkyl), imidazolyl(alkyl), and their benzo-fused analogs.

[0022] A "(heteroalicyclyl)alkyl" and "(heterocyclyl)alkyl" refer to a heterocyclic or a heteroalicyclylic group connected, as a substituent, via a lower alkylene group. The lower alkylene and heterocyclyl of a (heteroalicyclyl)alkyl may be substituted or unsubstituted. Examples include but are not limited tetrahydro-2H-pyran-4-yl(methyl), piperidin-4-yl(ethyl), piperidin-4-yl(propyl), tetrahydro-2H-thiopyran-4-yl(methyl) and 1,3-thiazinan-4-yl(methyl).

[0023] "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."

[0024] As used herein, "alkoxy" refers to the formula –OR wherein R is an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, aralkyl, (heteroaryl)alkyl or (heterocyclyl)alkyl is defined herein. A non-limiting list of alkoxys 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.

[0025] As used herein, "acyl" refers to a hydrogen an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heteroalicyclyl, aralkyl, heteroaryl(alkyl) or heterocyclyl(alkyl) connected, as substituents, via a carbonyl group. Examples include formyl, acetyl, propanoyl, benzoyl, and acryl. An acyl may be substituted or unsubstituted.

[0026] 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.

[0027] 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.

[0028] 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.

[0029] A "sulfenyl" group refers to an "-SR" group in which R can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aralkyl, (heteroaryl)alkyl or (heterocyclyl)alkyl. A sulfenyl may be substituted or unsubstituted.

[0030] 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.

[0031] A "sulfonyl" group refers to an "SO_2R" group in which R can be the same as defined with respect to sulfenyl. A sulfonyl may be substituted or unsubstituted.

[0032] An "O-carboxy" group refers to a "RC(=O)O-" group in which R can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aralkyl, (heteroaryl)alkyl or (heterocyclyl)alkyl, as defined herein. An O-carboxy may be substituted or unsubstituted.

[0033] 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.

[0034] 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.

[0035] A "trihalomethanesulfonyl" group refers to an "X_3CSO_2-" group wherein each X is a halogen.

[0036] A "trihalomethanesulfonamido" group refers to an "$X_3CS(O)_2N(R_A)$-" group wherein each X is a halogen, and R_A is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aralkyl, (heteroaryl)alkyl or (heterocyclyl)alkyl.

[0037] The term "amino" as used herein refers to a $-NH_2$ group.

[0038] As used herein, the term "hydroxy" refers to a –OH group.

[0039] A "cyano" group refers to a "-CN" group.

[0040] The term "azido" as used herein refers to a $-N_3$ group.

[0041] An "isocyanato" group refers to a "-NCO" group.

[0042] A "thiocyanato" group refers to a "-CNS" group.

[0043] An "isothiocyanato" group refers to an " -NCS" group.

[0044] A "mercapto" group refers to an "-SH" group.

[0045] A "carbonyl" group refers to a C=O group.

[0046] An "S-sulfonamido" group refers to a "$-SO_2N(R_AR_B)$" group in which R_A and R_B can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aralkyl, (heteroaryl)alkyl or (heterocyclyl)alkyl. An S-sulfonamido may be substituted or unsubstituted.

[0047] An "N-sulfonamido" group refers to a "$RSO_2N(R_A)$-" group in which R and R_A can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aralkyl, (heteroaryl)alkyl or (heterocyclyl)alkyl. An N-sulfonamido may be substituted or unsubstituted.

[0048] 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, heterocyclyl, aralkyl, (heteroaryl)alkyl or (heterocyclyl)alkyl. An O-carbamyl may be substituted or unsubstituted.

[0049] 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, heterocyclyl, aralkyl, (heteroaryl)alkyl or (heterocyclyl)alkyl. An N-carbamyl may be substituted or unsubstituted.

[0050] 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, heterocyclyl, aralkyl, (heteroaryl)alkyl or (heterocyclyl)alkyl. An O-thiocarbamyl may be substituted or unsubstituted.

[0051] 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, heterocyclyl, aralkyl, (heteroaryl)alkyl or (heterocyclyl)alkyl. An N-thiocarbamyl may be substituted or unsubstituted.

[0052] 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, heterocyclyl, aralkyl, (heteroaryl)alkyl or (heterocyclyl)alkyl. A C-amido may be substituted or unsubstituted.

[0053] 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, heterocyclyl, aralkyl, (heteroaryl)alkyl or (heterocyclyl)alkyl. An N-amido may be substituted or unsubstituted.

[0054] 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.

[0055] Where the numbers of substituents is not specified (e.g. haloalkyl), there may be one or more substituents present. For example "haloalkyl" may include one or more of the same or different halogens. As another example, "C_1-C_3 alkoxyphenyl" may include one or more of the same or different alkoxy groups containing one, two or three atoms.

[0056] 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)).

[0057] 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, 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.

[0058] 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.

[0059] As used herein, the term "heterocyclic base" refers to an optionally substituted nitrogen-containing heterocyclyl that can be attached to an optionally substituted pentose moiety or modified pentose moiety. In some embodiments, the heterocyclic base can be selected from an optionally substituted purine-base, an optionally substituted pyrimidine-base and an optionally substituted triazole-base (for example, a 1,2,4-triazole). The term "purine-base" is used herein in its ordinary sense as understood by those skilled in the art, and includes its tautomers. Similarly, the term "pyrimidine-base" is used herein in its ordinary sense as understood by those skilled in the art, and includes its tautomers. A non-limiting list of optionally substituted purine-bases includes purine, adenine, guanine, hypoxanthine, xanthine, alloxanthine, 7-alkylguanine (e.g. 7-methylguanine), theobromine, caffeine, uric acid and isoguanine. Examples of pyrimidine-bases include, but are not limited to, cytosine, thymine, uracil, 5,6-dihydrouracil and 5-alkylcytosine (e.g., 5-methylcytosine). An example of an optionally substituted triazole-base is 1,2,4-triazole-3-carboxamide. Other non-limiting examples of heterocyclic bases include diaminopurine, 8-oxo-N^6-alkyladenine (e.g., 8-oxo-N^6-methyladenine), 7-deazaxanthine, 7-deazaguanine, 7-deazaadenine, N^4,N^4-ethanocytosin, N^6,N^6-ethano-2,6-diaminopurine, 5-halouracil (e.g., 5-fluorouracil and 5-bromouracil), pseudoisocytosine, isocytosine, isoguanine, and other heterocyclic bases described in U.S. Patent Nos. 5,432,272 and 7,125,855, which are incorporated herein by reference for the limited purpose of disclosing additional heterocyclic bases. In some embodiments, a heterocyclic base can be optionally substituted with an amine or an enol protecting group(s).

[0060] 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.

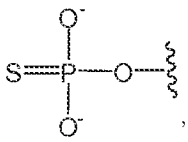
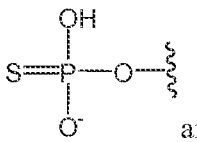
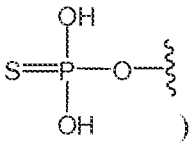
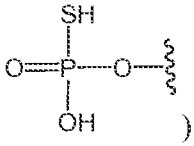
[0061] The term "–N–linked amino acid ester derivative" refers to an amino acid in which a main-chain carboxylic acid group has been converted to an ester group. In some embodiments, the ester group has a formula selected from alkyl-O-C(=O)-, cycloalkyl-O-C(=O)-, aryl-O-C(=O)- and aryl(alkyl)-O-C(=O)-. 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.

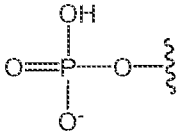
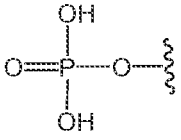
[0062] The term "–O–linked amino acid" refers to an amino acid that is attached to the indicated moiety via the hydroxy from its main-chain carboxylic acid group. When the amino acid is attached in an –O–linked amino acid, the hydrogen that is part of the hydroxy from its main-chain carboxylic acid group is not present and the amino acid is attached via the oxygen. O-linked amino acids can be substituted or unsubstituted.

[0063] 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.

[0064] The term "interferon" is used herein as is commonly understood by one of ordinary skill in the art. Several types of interferons are known to those skilled in the art, such as Type I interferons, Type 2 interferons and Type 3 interferons. A non-limiting list of examples include: alpha-interferons, beta-interferons, delta-interferons, gamma interferons, lambda interferons, omega-interferons, tau-interferons, x-interferons, consensus interferons

and asialo-interferons. Interferons can be pegylated. Examples of type 1 interferons include interferon alpha 1A, interferon alpha 1B, interferon alpha 2A, interferon alpha 2B, pegylated-interferon alpha 2a (PEGASYS, Roche), recombinant interferon alpha 2a (ROFERON, Roche), inhaled interferon alpha 2b (AERX, Aradigm), pegylated-interferon alpha 2b (ALBUFERON, Human Genome Sciences/Novartis, PEGINTRON, Schering), recombinant interferon alpha 2b (INTRON A, Schering), pegylated interferon alpha 2b (PEG-INTRON, Schering, VIRAFERONPEG, Schering), interferon beta-1a (REBIF, Serono, Inc. and Pfizer), consensus interferon alpha (INFERGEN, Valeant Pharmaceutical). Examples of type 2 interferons include interferon gamma 1, interferon gamma 2 and pegylated interferon gamma; and examples of type 3 interferons include interferon lambda 1, interferon lambda 2 and interferon lambda 3.

[0065] The terms "phosphorothioate" and "phosphothioate" refer to a compound of the general formula  its protonated forms (for example,  and ) and its tautomers (such as ).

[0066] 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 ). As used herein, the terms "monophosphate," "diphosphate," and "triphosphate" are used in their ordinary sense as understood by those skilled in the art, and include protonated forms.

[0067] The terms "protecting group" and "protecting groups" as used herein refer to any atom or group of atoms that is added to a molecule in order to prevent existing groups in the molecule from undergoing unwanted chemical reactions. Examples of protecting group moieties are described in T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 3. Ed. John Wiley & Sons, 1999, and in J.F.W. McOmie, *Protective Groups in Organic Chemistry* Plenum Press, 1973, both of which are hereby incorporated by reference

for the limited purpose of disclosing suitable protecting groups. The protecting group moiety may be chosen in such a way, that they are stable to certain reaction conditions and readily removed at a convenient stage using methodology known from the art. A non-limiting list of protecting groups include benzyl; substituted benzyl; alkylcarbonyls and alkoxycarbonyls (e.g., t-butoxycarbonyl (BOC), acetyl, or isobutyryl); arylalkylcarbonyls and arylalkoxycarbonyls (e.g., benzyloxycarbonyl); substituted methyl ether (e.g. methoxymethyl ether); substituted ethyl ether; a substituted benzyl ether; tetrahydropyranyl ether; silyls (e.g., trimethylsilyl, triethylsilyl, triisopropylsilyl, t-butyldimethylsilyl, tri-*iso*-propylsilyloxymethyl, [2-(trimethylsilyl)ethoxy]methyl or t-butyldiphenylsilyl); esters (e.g. benzoate ester); carbonates (e.g. methoxymethylcarbonate); sulfonates (e.g. tosylate or mesylate); acyclic ketal (e.g. dimethyl acetal); cyclic ketals (e.g., 1,3-dioxane, 1,3-dioxolanes and those described herein); acyclic acetal; cyclic acetal (e.g., those described herein); acyclic hemiacetal; cyclic hemiacetal; cyclic dithioketals (e.g., 1,3-dithiane or 1,3-dithiolane); orthoesters (e.g., those described herein) and triarylmethyl groups (e.g., trityl; monomethoxytrityl (MMTr); 4,4'-dimethoxytrityl (DMTr); 4,4',4"-trimethoxytrityl (TMTr); and those described herein).

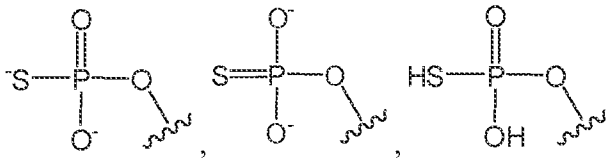
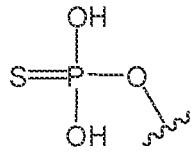
[0068] The term "pharmaceutically acceptable salt" refers to a salt of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. In some embodiments, the salt is an acid addition salt 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, C_1-C_7 alkylamine, cyclohexylamine, triethanolamine, ethylenediamine, and salts with amino acids such as arginine and lysine.

[0069] 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.

[0070] 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.

[0071] 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.

[0072] Likewise, it is understood that, in any compound described, all tautomeric forms are also intended to be included. For example all tautomers of a phosphate and a phosphorothioate groups are intended to be included. Examples of tautomers of a phosphorothioate include the following:  ,  and . Furthermore, all tautomers of heterocyclic bases known in the art are intended to be included, including tautomers of natural and non-natural purine-bases and pyrimidine-bases.

[0073] 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).

[0074] 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.

[0075] 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.

[0076] 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.

Methods of Use

[0077] Some embodiments disclosed herein relate to a method of treating and/or ameliorating an infection caused by a Filoviridae virus that can include administering to a subject an 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 (such as a compound of Formula (I), or a pharmaceutically acceptable salt thereof). Other embodiments disclosed herein relate to a method of treating and/or ameliorating an infection caused by a Filoviridae virus that can include administering to a subject identified as suffering from the viral infection an 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 (such as a compound of Formula (I), or a pharmaceutically acceptable salt thereof).

[0078] Some embodiments described herein relate to using one or more compounds described herein (such as a compound of Formula (I), or a pharmaceutically acceptable salt thereof), in the manufacture of a medicament for ameliorating and/or treating an infection caused by a Filoviridae virus that can include administering to a subject infected with the virus an effective amount of one or more compounds described herein (such as a compound of Formula (I), or a pharmaceutically acceptable salt thereof). Still other embodiments described herein relate to one or more compounds described herein (such as a compound of Formula (I), or a pharmaceutically acceptable salt thereof) that can be used for ameliorating and/or treating an infection caused by a Filoviridae virus by administering to a subject an effective amount of one or more compounds described herein.

[0079] Some embodiments disclosed herein relate to methods of ameliorating and/or treating an infection caused by a Filoviridae virus that can include contacting a cell infected with the virus with an 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 one or more compounds described herein (such as a compound of Formula (I), or a pharmaceutically acceptable salt thereof). Other embodiments described herein relate to using one or more compounds described herein (such as a compound of Formula (I), or a pharmaceutically acceptable salt thereof), in the manufacture of a medicament for ameliorating and/or treating an infection caused by a Filoviridae virus that can include contacting a cell infected with the virus with an effective amount of said compound(s). Still other embodiments described herein relate to one or more compounds described herein (such as a compound of Formula (I), or a pharmaceutically acceptable salt thereof), that can be used for ameliorating and/or treating an infection caused by a Filoviridae virus by contacting a cell infected with the virus with an effective amount of said compound(s).

[0080] Some embodiments disclosed herein relate to methods of inhibiting replication of a Filoviridae virus that can include contacting a cell infected with the virus with an 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 one or more compounds described herein (such as a compound of Formula (I), or a pharmaceutically acceptable salt thereof). Other embodiments described herein relate to using one or more compounds described herein (such as a compound of Formula (I), or a pharmaceutically acceptable salt thereof), in the manufacture of a medicament for inhibiting replication of a Filoviridae virus that can include contacting a cell infected with the virus with an effective amount of said compound(s). Still other embodiments described herein relate to a compound described herein (such as a compound of Formula (I), or a pharmaceutically acceptable salt thereof), that can be used for inhibiting replication of a Filoviridae virus by contacting a cell infected with the virus with an effective amount of said compound(s). In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can inhibit a RNA dependent RNA polymerase of a Filoviridae virus, and thus, inhibit the replication of RNA. In some embodiments, a polymerase of a Filoviridae virus can be inhibited by contacting a cell infected with the Filoviridae virus with a compound described herein (such as a compound of Formula (I), or a pharmaceutically acceptable salt thereof).

[0081] Ebolaviruses are members of the Filoviridae virus family. In some embodiments, a compound described herein (for example, a compound of Formula (I), or a pharmaceutical acceptable salt thereof) can ameliorate and/or treat an Ebolavirus infection. In other embodiments, one or more compounds described herein (such as a compound of Formula (I), or a pharmaceutically acceptable salt thereof), can be manufactured into a medicament for ameliorating and/or treating an infection caused by an Ebolavirus that can include contacting a cell infected with the virus with an effective amount of said compound(s). In still other embodiments, one or more compounds described herein (such as a compound of Formula (I), or a pharmaceutically acceptable salt thereof), can be used for ameliorating and/or treating an infection caused by an Ebolavirus that can include contacting a cell infected with the virus with an effective amount of said compound(s). As described herein, several Ebolaviruses are known (such as EBOV, REBOV, SEBOV, TAFV and BEBOV). In some embodiments, a compound described herein (for example, a compound of Formula (I), or a pharmaceutical acceptable salt thereof) can be effective against more than one species of Ebolaviruses, such as 2, 3, 4 and/or 5 species. In some embodiments, a compound of Formula (I), or a pharmaceutical acceptable salt thereof, can be effective

against an Ebolavirus, and thereby ameliorate one or more symptoms of an Ebolavirus infection. Examples of symptoms manifested by a subject infected with an Ebolavirus include severe hemorrhagic fever, malaise, fever, chills, arthralgia, myalgia, chest pain, nausea, weakness, abdominal pain, diarrhea, vomiting, weight loss, pharyngitis, sore throat, cough, dyspnea, hiccups, headaches, agitation, confusion, fatigue, depression, seizure, coma, maculopapular rash, petechiae, purpura, ecchymoses, hematomas, multiple organ dysfunction syndrome (MODS), hypotension, disseminated intravascular coagulation, focal tissue necroses, impaired kidney function, impaired liver function, low white blood cell count, low platelets, elevated liver enzymes and bleeding (internal and/or external including from the nose, mouth, rectum, eyes and/or ears).

[0082] Marburgviruses are also members of the Filoviridae virus family. In some embodiments, a compound described herein (for example, a compound of Formula (I), or a pharmaceutical acceptable salt thereof) can ameliorate and/or treat a Marburgvirus infection. In other embodiments, one or more compounds described herein (such as a compound of Formula (I), or a pharmaceutically acceptable salt thereof), can be manufactured into a medicament for ameliorating and/or treating an infection caused by a Marburgvirus that can include contacting a cell infected with the virus with an effective amount of said compound(s). In still other embodiments, one or more compounds described herein (such as a compound of Formula (I), or a pharmaceutically acceptable salt thereof), can be used for ameliorating and/or treating an infection caused by a Marburgvirus that can include contacting a cell infected with the virus with an effective amount of said compound(s). MARV and RAVV are two known Marburgviruses. In some embodiments, a compound described herein (for example, a compound of Formula (I), or a pharmaceutical acceptable salt thereof) can be effective against MARV and/or RAVV. In some embodiments, a compound of Formula (I), or a pharmaceutical acceptable salt thereof, can be effective against a Marburgvirus, and thereby ameliorate one or more symptoms of a Marburgvirus infection. Symptoms a Marburgvirus infection include severe hemorrhagic fever, fever, headaches, malaise, muscle aches, muscle pain, joint aches, joint pain, sore throat, weakness, red eyes, rash, diarrhea, abdominal pain, cramping, nausea, chest pain, cough, weight loss, vomiting, deep-set eyes, expressionless face, lethargy, rash, blood in the feces, vomiting

blood, bleeding from a venepuncture site, confusion, irritability, aggression, orchitis and bleeding (internal and/or external including from the nose, mouth, rectum, eyes and/or ears).

[0083] Ebola hemorrhagic fever (EHF) is a disease caused by an Ebolavirus infection; and marburgvirus hemorrhagic fever (MHF) is a disease caused by a Marburgvirus infection. Both Ebola and Marburgvirus hemorrhagic fever are severe and often fatal diseases. In some embodiments, a compound described herein (for example, a compound of Formula (I), or a pharmaceutical acceptable salt thereof) can ameliorate and/or treat EHF and/or MHF. In other embodiments, one or more compounds described herein (such as a compound of Formula (I), or a pharmaceutically acceptable salt thereof), can be manufactured into a medicament for ameliorating and/or treating EHF and/or MHF that can include contacting a cell infected with the virus with an effective amount of said compound(s). In still other embodiments, one or more compounds described herein (such as a compound of Formula (I), or a pharmaceutically acceptable salt thereof), can be used for ameliorating and/or treating EHF and/or MHF that can include contacting a cell infected with the virus with an effective amount of said compound(s).

[0084] Various indicators for determining the effectiveness of a method for treating and/or ameliorating a Filoviridae viral infection are known to those skilled in the art. Example of suitable indicators include, but are not limited to, a reduction in viral load, a reduction in viral replication, a reduction in time to seroconversion (virus undetectable in patient serum), a reduction of morbidity or mortality in clinical outcomes, and/or other indicator(s) of disease response. Further indicators include one or more overall quality of life health indicators, such as reduced illness duration, reduced illness severity, reduced time to return to normal health and normal activity, and reduced time to alleviation of one or more symptoms. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can result in the reduction, alleviation or positive indication of one or more of the aforementioned indicators compared to a subject who is untreated subject.

[0085] In some embodiments, an 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.

[0086] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can result in a reduction in the length and/or severity of one or more symptoms associated with a Filoviridae virus infection compared to a subject who is an untreated subject. Table 1 provides some embodiments of the percentage improvements obtained using a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as compared to an untreated subject. Examples include the following: in some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can result in a duration of illness that is in the range of about 10% to about 30% less than compared to the duration of illness experienced by a subject who is untreated for a Filoviridae virus infection (such as Marburg virus); and in some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, results in a severity of a symptom (such as one of those described herein) that is 25% less than compared to the severity of the same symptom experienced by a subject who is untreated for an Ebola virus infection. Methods of quantifying the severity of a side effect and/or symptom are known to those skilled in the art.

Table 1

Number of side effects	Severity of side effect(s)	Duration of illness	Severity of symptom(s)
10% less	10% less	10% less	10% less
25% less	25% less	25% less	25% less
40% less	40% less	40% less	40% less
50% less	50% less	50% less	50% less
60% less	60% less	60% less	60% less
70% less	70% less	70% less	70% less
80% less	80% less	80% less	80% 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 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 20% to about 80% less	about 20% to about 80% less	about 20% to about 80% less	about 20% to about 80% less

[0087] In some embodiments, the compound can be a compound of Formula (I), or a pharmaceutical acceptable salt thereof, wherein R^{1A} can be hydrogen. In other embodiments, the compound can be a compound of Formula (I), wherein compound of Formula (I) can be 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) can be a thiomonophosphate, alpha-thiodiphosphate, or alpha-thiotriphosphate, or a pharmaceutically acceptable salt of the foregoing. In some embodiments, the compound of Formula (I), or a pharmaceutical acceptable salt thereof, that can be used to ameliorate and/or treat a Filoviridae virus infection and/or inhibit replication of a Filoviridae virus can be any of the embodiments provided in any of the embodiments described in paragraphs [0111]-[0171].

[0088] 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.

[0089] 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.

[0090] 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, an 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 an effective amount is well within the capability of those skilled in the art, in view of the disclosure provided herein. The 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.

[0091] 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.

[0092] 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 another agent. In some embodiments, the total time of the treatment regime with a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can less compared to the total time of the treatment regime with another agent.

[0093] In instances where human dosages for compounds have been established for at least some condition, those same dosages may be used, or dosages that are between about 0.1% and 500%, more preferably between about 25% and 250% of the established human dosage. Where no human dosage is established, as will be the case for newly-discovered pharmaceutical compositions, a suitable human dosage can be inferred from ED_{50} or ID_{50} values, or other appropriate values derived from *in vitro* or *in vivo* studies, as qualified by toxicity studies and efficacy studies in animals.

[0094] 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.

[0095] 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.

[0096] It should be noted that the attending physician would know how to and when to terminate, interrupt, or adjust administration due to toxicity or organ dysfunctions. Conversely, the attending physician would also know to adjust treatment to higher levels if the clinical response were not adequate (precluding toxicity). The magnitude of an administrated dose in the management of the disorder of interest will vary with the severity of the condition to be treated and to the route of administration. The severity of the condition may, for example, be evaluated, in part, by standard prognostic evaluation methods. Further, the dose and perhaps dose frequency, will also vary according to the age, body weight, and response of the individual patient. A program comparable to that discussed above may be used in veterinary medicine.

[0097] 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.

[0098] As described herein, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can have a moiety(ies) that neutralize the charge of the phosphate or thiophosphate. 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 a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can help maintain the efficacy of such the compound by reducing undesirable effects, such as isomerization.

[0099] In some embodiments, the phosphorylation of a thio-monophosphate of a compound of Formula (I), or a 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%, ≥ 75%, ≥ 90%, ≥ 95% or ≥ 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 a 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 a pharmaceutically acceptable salt thereof, can result in formation of a compound that has the (*S*)-configuration at the 5'-O-phosphorous atom.

[0100] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can act as a chain terminator of RNA synthesis. For example, compounds of Formula (I) can contain a moiety at the 2'-carbon position such that once the compound is incorporated into an RNA chain, no further elongation is observed to occur. For example, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can contain a non-hydrogen 2'-carbon modification such as an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl or an optionally substituted C_{2-6} alkynyl.

[0101] 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 O^1 as OH, R^A, R^{2A}, R^{5A}, R^{a1} and R^{a2} are each hydrogen and R^{3A} and R^{4A} are each OH. 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 O^1 as OH, R^A, R^{2A}, R^{5A}, R^{a1} and R^{a2} are each hydrogen and R^{3A} and R^{4A} are each OH. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, can have more potent antiviral activity compared to a compound that is identical in structure but for having O^1 as OH, R^A, R^{2A}, R^{5A}, R^{a1} and R^{a2} are each hydrogen and R^{3A} and R^{4A} are each OH.

[0102] Additionally, in some embodiments, the presence of a moiety(ies) that neutralizes the charge of the phosphate or thiophosphate can increase the stability of the compound by inhibiting its degradation. Also, in some embodiments, the presence of a moiety(ies) that neutralizes the charge of the phosphate or thiophosphate can make the compound more resistant to cleavage *in vivo* and provide sustained, extended efficacy. In some embodiments, a moiety(ies) that neutralizes the charge of the phosphate or thiophosphate can facilitate the penetration of the cell membrane by a compound of Formula (I) by making the compound more lipophilic. In some embodiments, a moiety(ies) that neutralizes the charge of the phosphate or thiophosphate 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 O^1 as OH, R^A, R^{2A}, R^{5A}, R^{a1} and R^{a2} are each hydrogen and R^{3A} and R^{4A} are each OH.

Combination Therapies

[0103] 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) for treating, ameliorating and/or inhibiting a Filoviridae viral infection.

[0104] 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.

[0105] 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. 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.

[0106] 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) can result in an additive effect. In some embodiments, the combination of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, used in combination with one or more additional agent(s) can result in a synergistic effect. In some embodiments, the combination of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, used in combination with one or more additional agent(s) 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) is not antagonistic.

[0107] 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.

[0108] 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) may be a reduction in the required amount(s) of one or more additional agent(s) that is effective in treating a disease condition disclosed herein (for example, a Filoviridae virus infection), as compared to the amount required to achieve same therapeutic result when one

or more additional agent(s) are administered without a compound of Formula (I), or a pharmaceutically acceptable salt thereof. For example, for treating a Marburg viral infection, the amount of the additional agent (including a pharmaceutically acceptable salt thereof) used in combination can be less compared to the amount of the additional agent (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) 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.

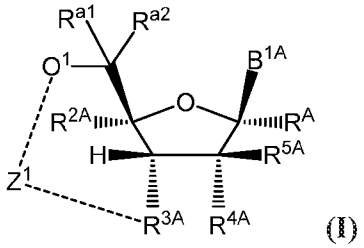
[0109] Additional advantages of utilizing a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with one or more additional agent(s) may include little to no cross resistance between a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and one or more additional agent(s) thereof; different routes for elimination of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and one or more additional agent(s); little to no overlapping toxicities between a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and one or more additional agent(s); 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); 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.

[0110] For treating of a Filoviridae virus infection, 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, are described herein. Compounds that can be used in combination for the treatment of a Filoviridae virus infection include an interferon (for example, those described herein such as interferon-alpha 2b and/or IFN-β treatment), ribavirin, (2S,3S,4R,5R)-2-(4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)-5-(hydroxymethyl)pyrrolidine-3,4-diol (BCX 4430, BioCryst), 5-Fluoro-2-oxo-1H-pyrazine-3-

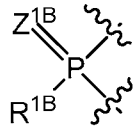
carboxamide (T-705, favipiravir), hexadecyloxypropyl-cidofovir (brincidofovir, CMX001), AVI-7537 (PMOplus oligomer that binds directly to the viral VP24 transcript RNA (GCC+ATG GT+T TT+T TC+T C+AG G), Sarepta Therapeutics), AVI-7288 (PMO*plus* oligomer that binds directly to viral RNA of the nucleoprotein (NP) transcript with a binding equilibrium constant of between 6.5 10-12M (CC+T GCC C+TT TGT+TCT+AGT+TG), Sarepta Therapeutics), ZMapp (a combination therapy of MB-003 (Pettitt, J., et al., *Sci Transl Med* (21 August 2013) 5(199):199ra113) and ZMab (Qiu, X., et al., *Sci Transl Med* (13 June 2012) 4(138):138ra81, Mapp Pharmaceuticals) and TKM-Ebola (an anti-Ebola virus RNAi therapeutic (Geisbert, T.W. et al., *The Lancet* (29 May 2010) 375(9729):1896-1905), Tekmira Pharmaceuticals).

Compounds

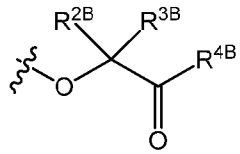
[0111] Some embodiments disclosed herein relate to a method and/or use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof:

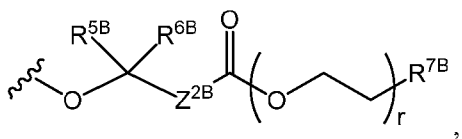
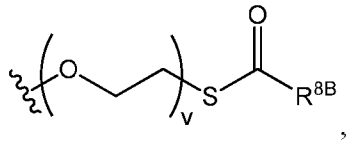
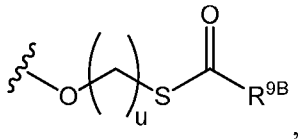
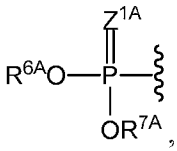
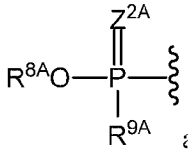
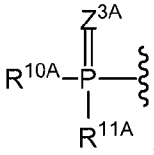
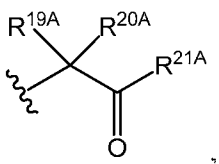
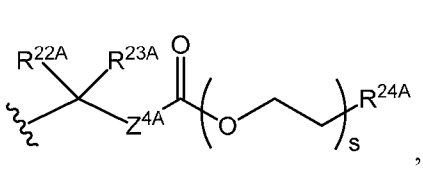
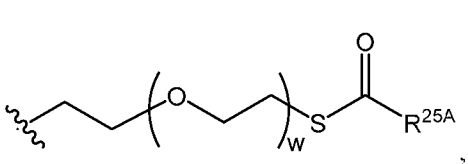


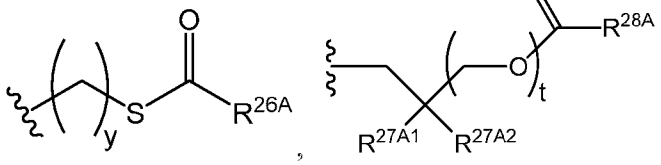
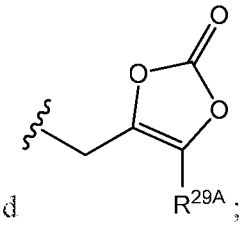
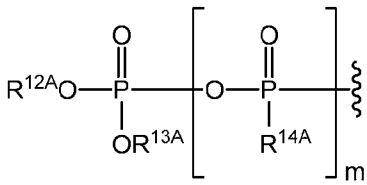
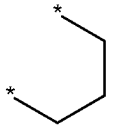
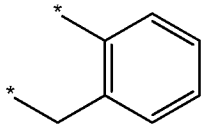
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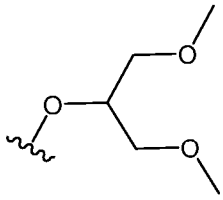
wherein: B^{1A} can be an optionally substituted heterocyclic base or an optionally substituted heterocyclic base with a protected amino group; -------- can be absent or a single bond, provided that both -------- are absent or both -------- are a single bond; when -------- are both absent, then Z^1 can be absent, O^1 can be OR^{1A}, R^{3A} can be selected from hydrogen, halogen, OH, –OC(=O)R"^{A} and an optionally substituted O-linked amino acid, R^{4A} can be selected from hydrogen, OH, halogen, N_3, –OC(=O)R"^{B}, an optionally substituted O-linked amino acid and NR"^{B1}R"^{B2}, or R^{3A} and R^{4A} can be both an oxygen atom connected via a carbonyl to form a 5-membered ring; when -------- are each a single bond, then Z^1 can be 

, O^1 can be O, R^{3A} can be O; R^{4A} can be selected from hydrogen, OH, halogen, N_3, –OC(=O)R"^{B}, an optionally substituted O-linked amino acid and NR"^{B1}R"^{B2}; and R^{1B} can be selected from



O^-, OH, an –O–optionally substituted C_{1-6} alkyl,  ,  ,  , an optionally substituted N-linked amino acid and an optionally substituted N-linked amino acid ester derivative; R^{a1} and R^{a2} can be independently hydrogen or deuterium; R^A can be hydrogen, deuterium, an unsubstituted C_{1-3} alkyl, an unsubstituted C_{2-4} alkenyl, an unsubstituted C_{2-3} alkynyl or cyano; R^{1A} can be selected from hydrogen, an optionally substituted acyl, an optionally substituted O-linked amino acid,  ,  and  ; R^{2A} can be hydrogen, azido (N_3), halogen, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{2-4} alkenyl, an unsubstituted C_{2-4} alkynyl, halogen(C_{1-6}alkyl), –$(CH_2)_{1-6}N_3$,–$(CH_2)_{1-6}NH_2$, –$(CH_2)_{1-6}$-ring A or –CN; R^{5A} can be selected from hydrogen, halogen, OH, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl and an optionally substituted C_{2-6} alkynyl; R^{6A}, R^{7A} and R^{8A} can be independently selected from absent, hydrogen, an optionally substituted C_{1-24} alkyl, an optionally substituted C_{2-24} alkenyl, an optionally substituted C_{2-24} alkynyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted C_{3-6} cycloalkenyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aryl(C_{1-6} alkyl), an optionally substituted *–$(CR^{15A}R^{16A})_p$–O–C_{1-24} alkyl, an optionally substituted *–$(CR^{17A}R^{18A})_q$–O–C_{1-24} alkenyl,  ,  ,  ,

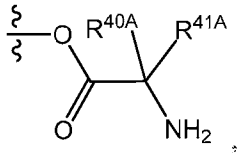
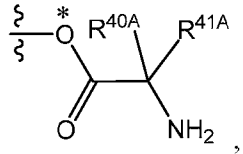

,
and 
; or R^{6A} can be 
and R^{7A} can be absent or hydrogen; or R^{6A} and R^{7A} can be taken together to form a moiety selected from an optionally substituted 
and an optionally substituted 
, wherein the oxygens connected to R^{6A} and R^{7A}, the phosphorus and the moiety form a six-membered to ten-membered ring system; R^{9A} can be independently selected from an optionally substituted C_{1-24} alkyl, an optionally substituted C_{2-24} alkenyl, an optionally substituted C_{2-24} alkynyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted C_{3-6} cycloalkenyl, $NR^{30A}R^{31A}$, an optionally substituted N-linked amino acid and an optionally substituted N-linked amino acid ester derivative; R^{10A} and R^{11A} can be independently an optionally substituted N-linked amino acid or an optionally substituted N-linked amino acid ester derivative; R^{12A} and R^{13A} can be independently absent or hydrogen; R^{14A} can be O^-, OH or methyl; each R^{15A}, each R^{16A}, each R^{17A} and each R^{18A} can be independently hydrogen, an optionally substituted C_{1-24} alkyl or an alkoxy; R^{19A}, R^{20A}, R^{22A}, R^{23A}, R^{2B}, R^{3B}, R^{5B} and R^{6B} can be independently selected from hydrogen, an optionally substituted C_{1-24} alkyl and an optionally substituted aryl; R^{21A} and R^{4B} can be independently selected from hydrogen, an optionally substituted C_{1-24} alkyl, an optionally substituted aryl, an optionally substituted –O–C_{1-24} alkyl, an optionally substituted –O–aryl, an optionally substituted –O–heteroaryl and an optionally substituted –O–monocyclic heterocyclyl; R^{24A} and R^{7B} can be independently selected from of hydrogen, an optionally substituted C_{1-24} alkyl, an optionally substituted aryl, an optionally substituted –O–C_{1-24} alkyl, an optionally substituted –O–aryl, an optionally substituted –O–heteroaryl, an

optionally substituted –O–monocyclic heterocyclyl and  ; R^{25A}, R^{26A}, R^{29A}, R^{8B} and R^{9B} can be independently selected from hydrogen, an optionally substituted C_{1-24} alkyl and an optionally substituted aryl; R^{27A1} and R^{27A2} can be independently selected from -C≡N, an optionally substituted C_{2-8} organylcarbonyl, an optionally substituted C_{2-8} alkoxycarbonyl and an optionally substituted C_{2-8} organylaminocarbonyl; R^{28A} can be selected from hydrogen, an optionally substituted C_{1-24} alkyl, an optionally substituted C_{2-24} alkenyl, an optionally substituted C_{2-24} alkynyl, an optionally substituted C_{3-6} cycloalkyl and an optionally substituted C_{3-6} cycloalkenyl; R^{30A} and R^{31A} can be independently selected from hydrogen, an optionally substituted C_{1-24} alkyl, an optionally substituted C_{2-24} alkenyl, an optionally substituted C_{2-24} alkynyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted C_{3-6} cycloalkenyl and an optionally substituted aryl(C_{1-4} alkyl); $R^{"A}$ and each $R^{"B}$ can be independently an optionally substituted C_{1-24} alkyl; each $R^{"B1}$ and each $R^{"B2}$ can be independently hydrogen or an optionally substituted C_{1-6} alkyl; ring A can be an optionally substituted mono-cyclic heteroaryl or an optionally substituted mono-cyclic heterocyclyl; m and w can be independently 0 or 1; p and q can be independently 1, 2 or 3; r and s can be independently 0, 1, 2 or 3; t and v can be independently 1 or 2; u and y can be independently 3, 4 or 5; and Z^{1A}, Z^{2A}, Z^{3A}, Z^{4A}, Z^{1B} and Z^{2B} can be independently oxygen (O) or sulfur (S).

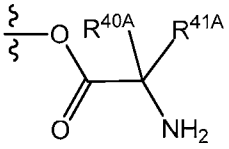
[0112] A compound of Formula (I) can be a nucleoside, a nucleotide (including a monophosphate, a diphosphate, a triphosphate, thiomonophosphate, alpha-thiodiphosphate and/or alpha-thiotriphosphate) or a nucleotide prodrug. In some embodiments, -------- can be both absent, Z^1 can be absent, O^1 can be OR^{1A}, R^{3A} can be selected from hydrogen, halogen, OH, –OC(=O)$R^{"A}$ and an optionally substituted O-linked amino acid, R^{4A} can be selected from OH, halogen, –OC(=O)$R^{"B}$ and an optionally substituted O-linked amino acid, or R^{3A} and R^{4A} can be both an oxygen atom connected via a carbonyl to form a 5-membered ring.

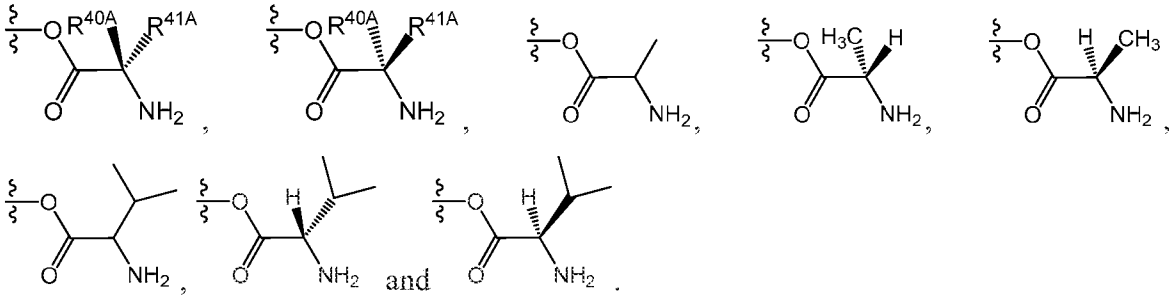
[0113] Various substituents can be attached to the 5'-position of Formula (I) when both ------- are absent. In some embodiments, R^{1A} can be hydrogen. In other embodiments, R^{1A} can be an optionally substituted acyl. For example, R^{1A} can be –C(=O)R^{39A}, wherein R^{39A} can be selected from an optionally substituted C_{1-12} alkyl, an

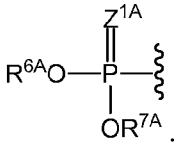
optionally substituted C_{2-12} alkenyl, an optionally substituted C_{2-12} alkynyl, an optionally substituted C_{3-8} cycloalkyl, an optionally substituted C_{5-8} cycloalkenyl, an optionally substituted C_{6-10} aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl, an optionally substituted aryl(C_{1-6} alkyl), an optionally substituted heteroaryl(C_{1-6} alkyl) and an optionally substituted heterocyclyl(C_{1-6} alkyl). In some embodiments, R^{39A} can be a substituted C_{1-12} alkyl. In other embodiments, R^{39A} can be an unsubstituted C_{1-12} alkyl. In some embodiments, R^{1A} can be –C(=O)-unsubstituted C_{1-4} alkyl. In some embodiments, both R^{a1} and R^{a2} can be hydrogen. In other embodiments, R^{a1} can be hydrogen and R^{a2} can be deuterium. In still other embodiments, both R^{a1} and R^{a2} can be deuterium.

[0114] In still other embodiments, R^{1A} can be an optionally substituted O-linked amino acid. Examples of suitable O-linked amino acids include 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. In some embodiments, the O-linked amino acid can have the structure  , wherein R^{40A} 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^{41A} can be hydrogen or an optionally substituted C_{1-4} alkyl; or R^{40A} and R^{41A} can be taken together to form an optionally substituted C_{3-6} cycloalkyl. Those skilled in the art understand that when R^{1A} is an optionally substituted O-linked amino acid, the oxygen of $R^{1A}O$- of Formula (I) is part of the optionally substituted O-linked amino acid. For example, when R^{1A} is  , the oxygen indicated with "*" is the oxygen of $R^{1A}O$- of Formula (I).

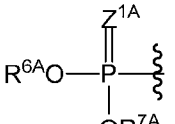
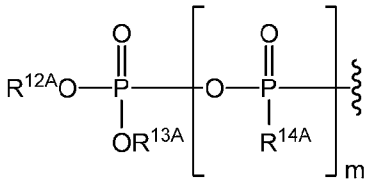
[0115] When R^{40A} is substituted, R^{40A} can be substituted with one or more substituents selected from N-amido, mercapto, alkylthio, an optionally substituted aryl, hydroxy, an optionally substituted heteroaryl, O-carboxy and amino. In some embodiments, R^{40A} can be an unsubstituted C_{1-6} alkyl, such as those described herein. In some embodiments, R^{40A} can be hydrogen. In other embodiments, R^{40A} can be methyl. In some embodiments, R^{41A} can be hydrogen. In other embodiments, R^{41A} can be an optionally substituted C_{1-4} alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and tert-butyl. In some embodiments, R^{41A} can be methyl. Depending on the groups that are selected for R^{40A} and R^{41A}, the carbon to which R^{40A} and R^{41A} are attached may be a chiral center. In some embodiment, the carbon to which R^{40A} and R^{41A} are attached may be a (*R*)-chiral center. In other embodiments, the carbon to which R^{40A} and R^{41A} are attached may be a (*S*)-chiral center.

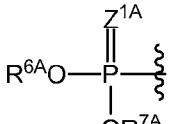
[0116] Examples of suitable  include the following:



[0117] In some embodiments, R^{1A} can be  . In some embodiments, R^{6A} and R^{7A} can be both hydrogen. In other embodiments, R^{6A} and R^{7A} can be both absent. In still other embodiments, at least one R^{6A} and R^{7A} can be absent. In yet still other embodiments, at least one R^{6A} and R^{7A} can be hydrogen. Those skilled in the art understand that when R^{6A} and/or R^{7A} are absent, the associated oxygen(s) will have a negative charge. For example, when R^{6A} is absent, the oxygen associated with R^{6A} will have a negative charge. In some embodiments, Z^{1A} can be O (oxygen). In other embodiments, Z^{1A} can be S

(sulfur). In some embodiments, R^{1A} can be a monophosphate. In other embodiments, R^{1A} can be a monothiophosphate.

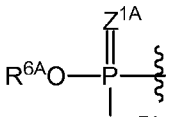
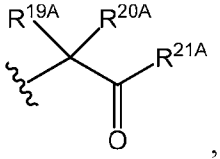
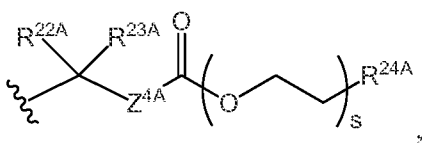
[0118] In some embodiments, R^{1A} can be  ; R^{6A} can be  ; R^{7A} can be absent or hydrogen; R^{12A} and R^{13A} can be independently absent or hydrogen; R^{14A} can be O^-, OH or methyl; and m can be 0 or 1. In some embodiments, m can be 0, and R^{7A}, R^{12A} and R^{13A} can be independently absent or hydrogen. In other embodiments, m can be 1, and R^{7A}, R^{12A} and R^{13A} can be independently absent or hydrogen; and R^{14A} can be O^-, OH or methyl. In some embodiments, m can be 1, and R^{7A}, R^{12A} and R^{13A} can be independently absent or hydrogen; and R^{14A} can be O^- or OH. In other embodiments, m can be 1, and R^{7A}, R^{12A} and R^{13A} can be independently absent or hydrogen; and R^{14A} can be methyl. Those skilled in the art understand that when m is 0, R^{6A} can be a diphosphate, when Z^{1A} is oxygen, or an alpha-thiodiphosphate, when Z^{1A} is sulfur. Likewise, those skilled in the art understand that when m is 1, R^{6A} can be a triphosphate, when Z^{1A} is oxygen, or an alpha-thiotriphosphate, when Z^{1A} is sulfur.

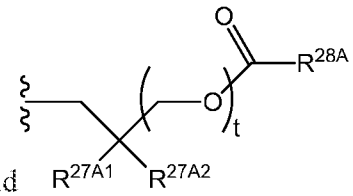
[0119] In some embodiments, when R^{1A} is  , one of R^{6A} and R^{7A} can be hydrogen, and the other of R^{6A} and R^{7A} can be selected from an optionally substituted C_{1-24} alkyl, an optionally substituted C_{2-24} alkenyl, an optionally substituted C_{2-24} alkynyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted C_{3-6} cycloalkenyl, an optionally substituted aryl, an optionally substituted heteroaryl and an optionally substituted aryl(C_{1-6} alkyl). In some embodiments, one of R^{6A} and R^{7A} can be hydrogen, and the other of R^{6A} and R^{7A} can be an optionally substituted C_{1-24} alkyl. In other embodiments, both R^{6A} and R^{7A} can be independently selected from an optionally substituted C_{1-24} alkyl, an optionally substituted C_{2-24} alkenyl, an optionally substituted C_{2-24} alkynyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted C_{3-6} cycloalkenyl, an optionally substituted aryl, an

optionally substituted heteroaryl and an optionally substituted aryl(C_{1-6} alkyl). In some embodiments, both R^{6A} and R^{7A} can be an optionally substituted C_{1-24} alkyl. In other embodiments, both R^{6A} and R^{7A} can be an optionally substituted C_{2-24} alkenyl. In some embodiments, R^{6A} and R^{7A} can be independently an optionally substituted group selected from the following: myristoleyl, myristyl, palmitoleyl, palmityl, sapienyl, oleyl, elaidyl, vaccenyl, linoleyl, α-linolenyl, arachidonyl, eicosapentaenyl, erucyl, docosahexaenyl, caprylyl, capryl, lauryl, stearyl, arachidyl, behenyl, lignoceryl and cerotyl.

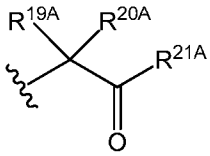
[0120] In some embodiments, at least one of R^{6A} and R^{7A} can be *–$(CR^{15A}R^{16A})_p$–O–C_{1-24} alkyl. In other embodiments, R^{6A} and R^{7A} can be both *–$(CR^{15A}R^{16A})_p$–O–C_{1-24} alkyl. In some embodiments, each R^{15A} and each R^{16A} can be hydrogen. In other embodiments, at least one of R^{15A} and R^{16A} can be an optionally substituted C_{1-24} alkyl. In other embodiments, at least one of R^{15A} and R^{16A} can be an alkoxy (for example, benzoxy). In some embodiments, p can be 1. In other embodiments, p can be 2. In still other embodiments, p can be 3.

[0121] In some embodiments, at least one of R^{6A} and R^{7A} can be *–$(CR^{17A}R^{18A})_q$–O–C_{2-24} alkenyl. In other embodiments, R^{6A} and R^{7A} can be both *–$(CR^{17A}R^{18A})_q$–O–C_{2-24} alkenyl. In some embodiments, each R^{17A} and each R^{18A} can be hydrogen. In other embodiments, at least one of R^{17A} and R^{18A} can be an optionally substituted C_{1-24} alkyl. In some embodiments, q can be 1. In other embodiments, q can be 2. In still other embodiments, q can be 3. When at least one of R^{6A} and R^{7A} is *–$(CR^{15A}R^{16A})_p$–O–C_{1-24} alkyl or *–$(CR^{17A}R^{18A})_q$–O–C_{2-24} alkenyl, the C_{1-24} alkyl can be selected from caprylyl, capryl, lauryl, myristyl, palmityl, stearyl, arachidyl, behenyl, lignoceryl, and cerotyl, and the C_{2-24} alkenyl can be selected from myristoleyl, palmitoleyl, sapienyl, oleyl, elaidyl, vaccenyl, linoleyl, α-linolenyl, arachidonyl, eicosapentaenyl, erucyl and docosahexaenyl.

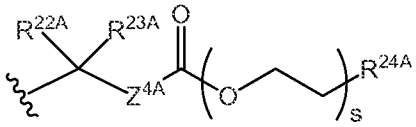
[0122] In some embodiments, when R^{1A} is  , at least one of R^{6A} and R^{7A} can be selected from  ,  ,



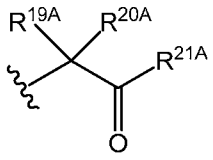
and ; and the other of R^{6A} and R^{7A} can be selected from absent, hydrogen, an optionally substituted C_{1-24} alkyl, an optionally substituted C_{2-24} alkenyl, an optionally substituted C_{2-24} alkynyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted C_{3-6} cycloalkenyl, an optionally substituted aryl, an optionally substituted heteroaryl and an optionally substituted aryl(C_{1-6} alkyl).



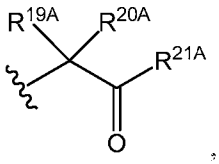
[0123] In some embodiments, at least one of R^{6A} and R^{7A} can be



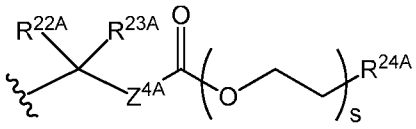
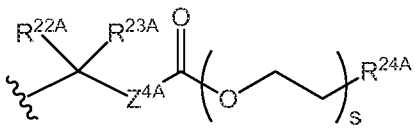
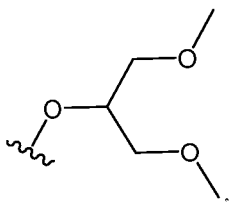
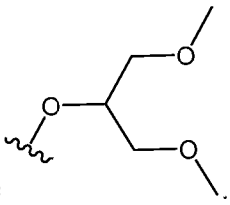
or . In some embodiments, both R^{6A} and R^{7A} can be



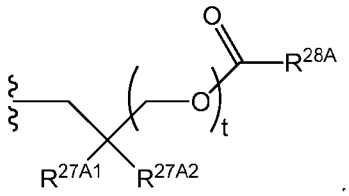
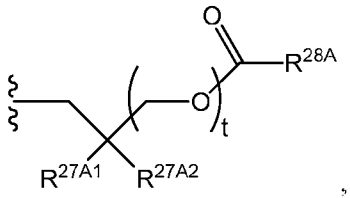
. When one or both of R^{6A} and R^{7A} are



, R^{19A} and R^{20A} can be independently selected from hydrogen, an optionally substituted C_{1-24} alkyl and an optionally substituted aryl; and R^{21A} can be selected from hydrogen, an optionally substituted C_{1-24} alkyl, an optionally substituted aryl, an optionally substituted –O–C_{1-24} alkyl, an optionally substituted –O–aryl, an optionally substituted –O–heteroaryl and an optionally substituted –O–monocyclic heterocyclyl. In some embodiments, R^{19A} and R^{20A} can be hydrogen. In other embodiments, at least one of R^{19A} and R^{20A} can be an optionally substituted C_{1-24} alkyl or an optionally substituted aryl. In some embodiments, R^{21A} can be an optionally substituted C_{1-24} alkyl. In some embodiments, R^{21A} can be an unsubstituted C_{1-4} alkyl. In other embodiments, R^{21A} can be an optionally substituted aryl. In still other embodiments, R^{21A} can be an optionally substituted –O–C_{1-24} alkyl, an optionally substituted –O–aryl, an optionally substituted –O–heteroaryl or an optionally substituted –O–monocyclic heterocyclyl. In some embodiments, R^{21A} can be an unsubstituted –O–C_{1-4} alkyl.

[0124] In some embodiments, both R^{6A} and R^{7A} can be  . When one or both of R^{6A} and R^{7A} are  , R^{22A} and R^{23A} can be independently selected from hydrogen, an optionally substituted C_{1-24} alkyl and an optionally substituted aryl; R^{24A} can be independently selected from hydrogen, an optionally substituted C_{1-24} alkyl, an optionally substituted aryl, an optionally substituted –O–C_{1-24} alkyl, an optionally substituted –O–aryl, an optionally substituted –O–heteroaryl and an optionally substituted –O–monocyclic heterocyclyl; s can be 0, 1, 2 or 3; and Z^{4A} can be independently O (oxygen) or S (sulfur). In some embodiments, R^{22A} and R^{23A} can be hydrogen. In other embodiments, at least one of R^{22A} and R^{23A} can be an optionally substituted C_{1-24} alkyl or an optionally substituted aryl. In some embodiments, R^{24A} can be an optionally substituted C_{1-24} alkyl. In some embodiments, R^{24A} can be an unsubstituted C_{1-4} alkyl. In other embodiments, R^{24A} can be an optionally substituted aryl. In still other embodiments, R^{24A} can be an optionally substituted –O–C_{1-24} alkyl, an optionally substituted –O–aryl, an optionally substituted –O–heteroaryl or an optionally substituted –O–monocyclic heterocyclyl. In yet still other embodiments, R^{24A} can be  . In some embodiments, R^{24A} can be an unsubstituted –O–C_{1-4} alkyl. In some embodiments, Z^{4A} can be O (oxygen). In other embodiments, Z^{4A} can be or S (sulfur). In some embodiments, s can be 0. In other embodiments, s can be 1. In still other embodiments, s can be 2. In yet still other embodiments, s can be 3. In some embodiments, s can be 0 and R^{24A} can be  . In some embodiments, one or both of R^{6A} and R^{7A} can be an optionally substituted isopropyloxycarbonyloxymethyl (POC). In some

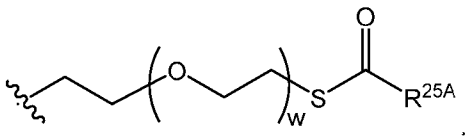
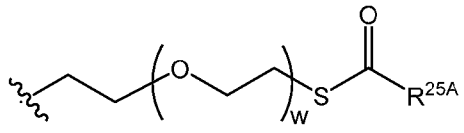
embodiments, R^{6A} and R^{7A} each can be an optionally substituted isopropyloxycarbonyloxymethyl (POC) group, and form an optionally substituted bis(isopropyloxycarbonyloxymethyl) (bis(POC)) prodrug. In other embodiments, one or both of R^{6A} and R^{7A} can be an optionally substituted pivaloyloxymethyl (POM). In some embodiments, R^{6A} and R^{7A} each can be an optionally substituted pivaloyloxymethyl (POM) group, and form an optionally substituted bis(pivaloyloxymethyl) (bis(POM)) prodrug.

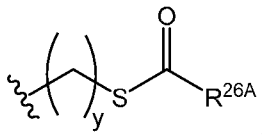
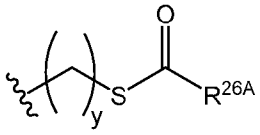
[0125] In some embodiments, both R^{6A} and R^{7A} can be  . When one or both of R^{6A} and R^{7A} are  , R^{27A1} and R^{27A2} can be independently -C≡N or an optionally substituted substituent selected from C_{2-8} organylcarbonyl, C_{2-8} alkoxycarbonyl and C_{2-8} organylaminocarbonyl; R^{28A} can be selected from hydrogen, an optionally substituted C_{1-24} alkyl, an optionally substituted C_{2-24} alkenyl, an optionally substituted C_{2-24} alkynyl, an optionally substituted C_{3-6} cycloalkyl and an optionally substituted C_{3-6} cycloalkenyl; and t can be 1 or 2. In some embodiments, R^{27A1} can be -C≡N and R^{27A2} can be an optionally substituted C_{2-8} alkoxycarbonyl, such as $-C(=O)OCH_3$. In other embodiments, R^{27A1} can be -C≡N and R^{27A2} can be an optionally substituted C_{2-8} organylaminocarbonyl, for example, $-C(=O)NHCH_2CH_3$ and $-C(=O)NHCH_2CH_2$phenyl. In some embodiments, both R^{27A1} and R^{27A2} can be an optionally substituted C_{2-8} organylcarbonyl, such as $-C(=O)CH_3$. In some embodiments, both R^{27A1} and R^{27A2} can be an optionally substituted C_{1-8} alkoxycarbonyl, for example, $-C(=O)OCH_2CH_3$ and $-C(=O)OCH_3$. In some embodiments, including those described in this paragraph, R^{28A} can be an optionally substituted C_{1-4} alkyl. In some embodiment, R^{28A} can be methyl or tert-butyl. In some embodiments, t can be 1. In other embodiments, t can be 2.

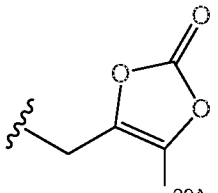
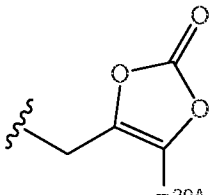
[0126] In some embodiments, R^{6A} and R^{7A} can be both an optionally substituted aryl. In some embodiments, at least one of R^{6A} and R^{7A} can be an optionally substituted aryl.

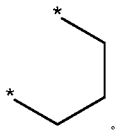
For example, both R^{6A} and R^{7A} can be an optionally substituted phenyl or an optionally substituted naphthyl. When substituted, the substituted aryl can be substituted with 1, 2, 3 or more than 3 substituents. When more the two substituents are present, the substituents can be the same or different. In some embodiments, when at least one of R^{6A} and R^{7A} is a substituted phenyl, the substituted phenyl can be a para-, ortho- or meta-substituted phenyl.

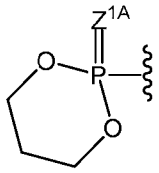
[0127] In some embodiments, R^{6A} and R^{7A} can be both an optionally substituted aryl(C_{1-6} alkyl). In some embodiments, at least one of R^{6A} and R^{7A} can be an optionally substituted aryl(C_{1-6} alkyl). For example, both R^{6A} and R^{7A} can be an optionally substituted benzyl. When substituted, the substituted benzyl group can be substituted with 1, 2, 3 or more than 3 substituents. When more the two substituents are present, the substituents can be the same or different. In some embodiments, the aryl group of the aryl(C_{1-6} alkyl) can be a para-, ortho- or meta-substituted phenyl.

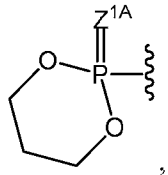
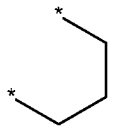
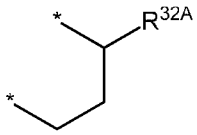
[0128] In some embodiments, R^{6A} and R^{7A} can be both  . In some embodiments, at least one of R^{6A} and R^{7A} can be  . In some embodiments, R^{25A} can be hydrogen. In other embodiments, R^{25A} can be an optionally substituted C_{1-24} alkyl. In still other embodiments, R^{25A} can be an optionally substituted aryl (for example, an optionally substituted phenyl). In some embodiments, R^{25A} can be a C_{1-6} alkyl, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, pentyl (branched and straight-chained), and hexyl (branched and straight-chained). In some embodiments, w can be 0. In other embodiments, w can be 1. In some embodiments, R^{6A} and R^{7A} can be both an optionally substituted S-acylthioethyl (SATE) group and form an optionally substituted SATE ester prodrug.

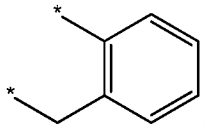
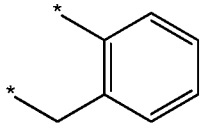
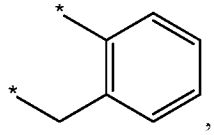
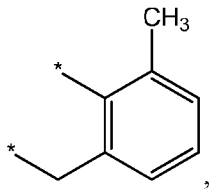
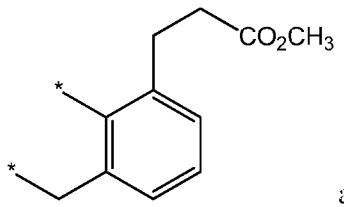
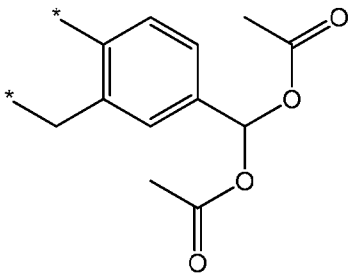
[0129] In some embodiments, R^{6A} and R^{7A} can be both  . In some embodiments, at least one of R^{6A} and R^{7A} can be  . In some embodiments, R^{26A} can be hydrogen. In other embodiments, R^{26A} can be an optionally substituted C_{1-24} alkyl. In still other embodiments, R^{26A} can be an optionally substituted aryl, for example, an optionally substituted phenyl. In some embodiments, R^{26A} can be an optionally substituted C_{1-6} alkyl. In some embodiments, R^{26A} can be an unsubstituted C_{1-6} alkyl. In some embodiments, y can be 3. In other embodiments, y can be 4. In still other embodiments, y can be 5.

[0130] In some embodiments, R^{6A} and R^{7A} can be both  . In some embodiments, at least one of R^{6A} and R^{7A} can be  . In some embodiments, R^{29A} can be hydrogen. In other embodiments, R^{29A} can be an optionally substituted C_{1-24} alkyl. In some embodiments, R^{29A} can be a C_{1-4} alkyl, such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl and t-butyl. In still other embodiments, R^{29A} can be an optionally substituted aryl, such as an optionally substituted phenyl or an optionally substituted naphthyl. In some embodiments, R^{6A} and R^{7A} can be both an optionally substituted dioxolenone group and form an optionally substituted dioxolenone prodrug.

[0131] In some embodiments, R^{6A} and R^{7A} can be taken together to form an optionally substituted  . For example, R^{1A} can be an optionally substituted

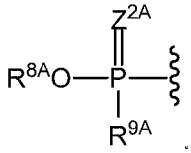


. When substituted, the ring can be substituted 1, 2, 3 or 3 or more times. When substituted with multiple substituents, the substituents can be the same or different. In some embodiments, when R^{1A} is  , the ring can be substituted with an optionally substituted aryl group and/or an optionally substituted heteroaryl. An example of a suitable heteroaryl is pyridinyl. In some embodiments, R^{6A} and R^{7A} can be taken together to form an optionally substituted  such as  , wherein R^{32A} can be an optionally substituted aryl, an optionally substituted heteroaryl or an optionally substituted heterocyclyl. In some embodiments, R^{6A} and R^{7A} can form an optionally substituted cyclic 1-aryl-1,3-propanyl ester (HepDirect) prodrug moiety.

[0132] In some embodiments, R^{6A} and R^{7A} can be taken together to form an optionally substituted  , wherein the oxygens connected to R^{6A} and R^{7A}, the phosphorus and the moiety form a six-membered to ten-membered ring system. Example of an optionally substituted  include  ,  ,  and  . In some embodiments, R^{6A} and R^{7A} can form an optionally substituted cyclosaligenyl (cycloSal) prodrug.

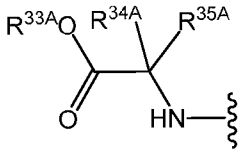
[0133] In some embodiments, R^{6A} and R^{7A} can be the same. In some embodiments, R^{6A} and R^{7A} can be different.

[0134] In some embodiments, Z^{1A} can be oxygen. In other embodiments, Z^{1A} can be sulfur.

[0135] In some embodiments, R^{1A} can be  . In some embodiments, R^{8A} can be selected from absent, hydrogen, an optionally substituted C_{1-24} alkyl, an optionally substituted C_{2-24} alkenyl, an optionally substituted C_{2-24} alkynyl, an optionally substituted C_{3-6} cycloalkyl and an optionally substituted C_{3-6} cycloalkenyl; and R^{9A} can be independently selected from an optionally substituted C_{1-24} alkyl, an optionally substituted C_{2-24} alkenyl, an optionally substituted C_{2-24} alkynyl, an optionally substituted C_{3-6} cycloalkyl and an optionally substituted C_{3-6} cycloalkenyl.

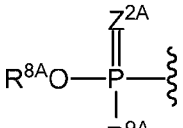
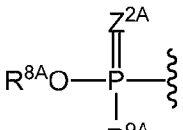
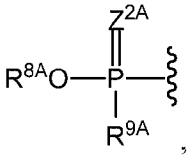
[0136] In some embodiments, R^{8A} can be hydrogen, and R^{9A} can be an optionally substituted C_{1-6} alkyl. Examples of suitable C_{1-6} alkyls include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, pentyl (branched and straight-chained), and hexyl (branched and straight-chained). In other embodiments, R^{8A} can be hydrogen, and R^{9A} can be $NR^{30A}R^{31A}$, wherein R^{30A} and R^{31A} can be independently selected from hydrogen, an optionally substituted C_{1-24} alkyl, an optionally substituted C_{2-24} alkenyl, an optionally substituted C_{2-24} alkynyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted C_{3-6} cycloalkenyl and an optionally substituted aryl(C_{1-4} alkyl). In some embodiments, one of R^{30A} and R^{31A} can be hydrogen and the other of R^{30A} and R^{31A} can be 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_{3-6} cycloalkyl, an optionally substituted C_{3-6} cycloalkenyl and an optionally substituted benzyl.

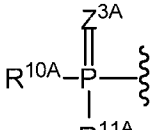
[0137] In some embodiments, R^{8A} can be absent or hydrogen; and R^{9A} can be an optionally substituted N-linked amino acid or an optionally substituted N-linked amino acid ester derivative. In other embodiments, R^{8A} can be an optionally substituted aryl; and R^{9A} can be an optionally substituted N-linked amino acid or an optionally substituted N-linked amino acid ester derivative. In still other embodiments, R^{8A} can be an optionally substituted

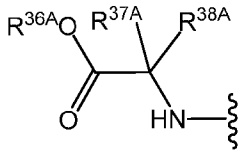
heteroaryl; and R^{9A} can be an optionally substituted N-linked amino acid or an optionally substituted N-linked amino acid ester derivative. In some embodiments, R^{9A} can be selected from alanine, asparagine, aspartate, cysteine, glutamate, glutamine, glycine, proline, serine, tyrosine, arginine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, valine and ester derivatives thereof. Examples of an optionally substituted N-linked amino acid ester derivatives include optionally substituted versions of the following: N-alanine isopropyl ester, N-alanine cyclohexyl ester, N-alanine neopentyl ester, N-valine isopropyl ester and N-leucine isopropyl ester. In some embodiments, R^{9A} can have the structure  wherein R^{33A} 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^{34A} 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^{35A} can be hydrogen or an optionally substituted C_{1-4} alkyl; or R^{34A} and R^{35A} can be taken together to form an optionally substituted C_{3-6} cycloalkyl.

[0138] When R^{34A} is substituted, R^{34A} 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^{34A} can be an unsubstituted C_{1-6} alkyl, such as those described herein. In some embodiments, R^{34A} can be hydrogen. In other embodiments, R^{34A} can be methyl. In some embodiments, R^{33A} 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^{33A} can be methyl or isopropyl. In some embodiments, R^{33A} can be ethyl or neopentyl. In other embodiments, R^{33A} 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^{33A} can be an optionally substituted

cyclohexyl. In still other embodiments, R^{33A} can be an optionally substituted aryl, such as phenyl and naphthyl. In yet still other embodiments, R^{33A} can be an optionally substituted aryl(C_{1-6} alkyl). In some embodiments, R^{33A} can be an optionally substituted benzyl. In some embodiments, R^{33A} can be an optionally substituted C_{1-6} haloalkyl, for example, CF_3. In some embodiments, R^{35A} can be hydrogen. In other embodiments, R^{35A} can be an optionally substituted C_{1-4} alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and tert-butyl. In some embodiments, R^{35A} can be methyl. In some embodiments, R^{34A} and R^{35A} can be taken together to form an optionally substituted C_{3-6} cycloalkyl. Examples of optionally substituted C_{3-6} cycloalkyl include optionally substituted variants of the following: cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. Depending on the groups that are selected for R^{34A} and R^{35A}, the carbon to which R^{34A} and R^{35A} are attached may be a chiral center. In some embodiment, the carbon to which R^{34A} and R^{35A} are attached may be a (*R*)-chiral center. In other embodiments, the carbon to which R^{34A} and R^{35A} are attached may be a (*S*)-chiral center.

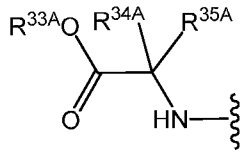
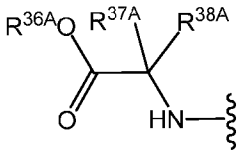
[0139] In some embodiments, when R^{1A} is  , Z^{2A} can be O (oxygen). In other embodiments, when R^{1A} is  , Z^{2A} can be S (sulfur). In some embodiments, when R^{1A} is  , a compound of Formula (I) can be an optionally substituted phosphoroamidate prodrug, such as an optionally substituted aryl phosphoroamidate prodrug.

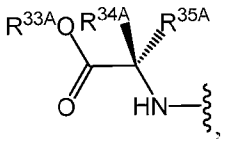
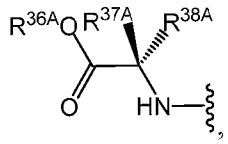
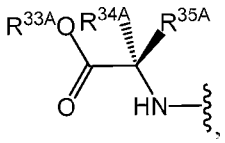
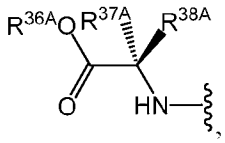
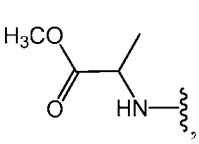
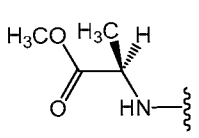
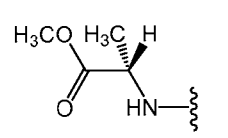
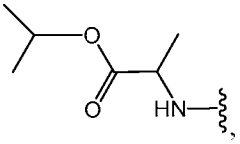
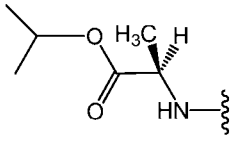
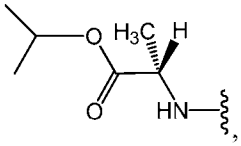
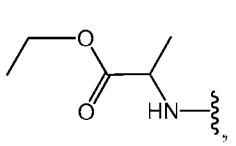
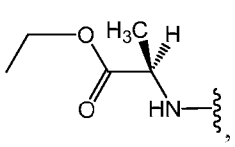
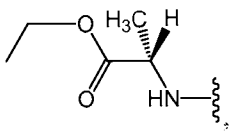
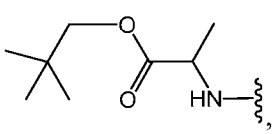
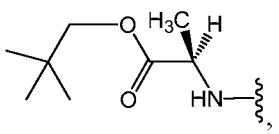
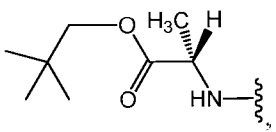
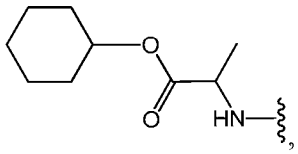
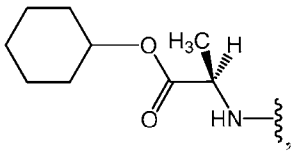
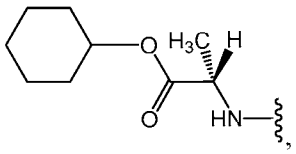
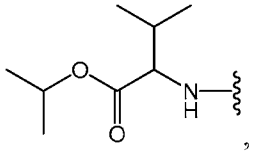
[0140] In some embodiments, R^{1A} can be  . In some embodiments, R^{10A} and R^{11A} can be both an optionally substituted N-linked amino acid or an optionally substituted N-linked amino acid ester derivative. In some embodiments, R^{10A} and R^{11A} can

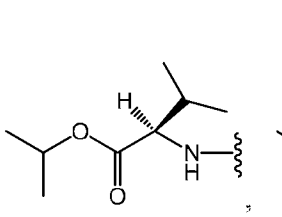
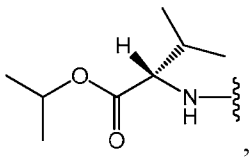
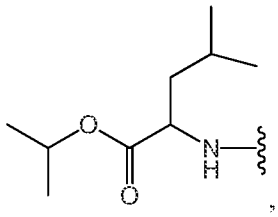
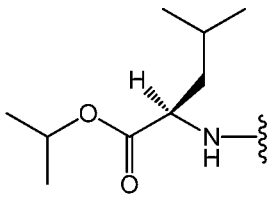
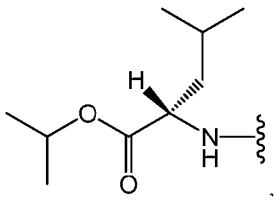
be independently selected from alanine, asparagine, aspartate, cysteine, glutamate, glutamine, glycine, proline, serine, tyrosine, arginine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, valine and ester derivatives thereof. In some embodiments, R^{10A} and R^{11A} can be an optionally substituted version of the following: N-alanine isopropyl ester, N-alanine cyclohexyl ester, N-alanine neopentyl ester, N-valine isopropyl ester and N-leucine isopropyl ester. In some embodiments, R^{10A} and R^{11A} can independently have the structure  wherein R^{36A} 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^{37A} 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^{38A} can be hydrogen or an optionally substituted C_{1-4} alkyl; or R^{37A} and R^{38A} can be taken together to form an optionally substituted C_{3-6} cycloalkyl.

[0141] When R^{37A} is substituted, R^{37A} 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^{37A} can be an unsubstituted C_{1-6} alkyl, such as those described herein. In some embodiments, R^{37A} can be hydrogen. In other embodiments, R^{37A} can be methyl. In some embodiments, R^{36A} 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^{36A} can be methyl or isopropyl. In some embodiments, R^{36A} can be ethyl or neopentyl. In other embodiments, R^{36A} 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^{36A} can be an optionally substituted cyclohexyl. In still other embodiments, R^{36A} can be an optionally substituted aryl, such as

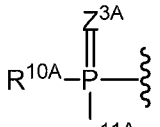
phenyl and naphthyl. In yet still other embodiments, R^{36A} can be an optionally substituted aryl(C_{1-6} alkyl). In some embodiments, R^{36A} can be an optionally substituted benzyl. In some embodiments, R^{36A} can be an optionally substituted C_{1-6} haloalkyl, for example, CF_3. In some embodiments, R^{38A} can be hydrogen. In other embodiments, R^{38A} can be an optionally substituted C_{1-4} alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and tert-butyl. In some embodiments, R^{38A} can be methyl. In some embodiments, R^{37A} and R^{38A} can be taken together to form an optionally substituted C_{3-6} cycloalkyl. Examples of optionally substituted C_{3-6} cycloalkyl include optionally substituted variants of the following: cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. Depending on the groups that are selected for R^{37A} and R^{38A}, the carbon to which R^{37A} and R^{38A} are attached may be a chiral center. In some embodiment, the carbon to which R^{37A} and R^{38A} are attached may be a (*R*)-chiral center. In other embodiments, the carbon to which R^{37A} and R^{38A} are attached may be a (*S*)-chiral center.

[0142] Examples of suitable  and  groups include the following:


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and

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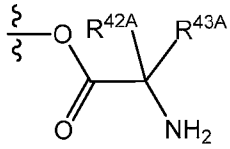
[0143] In some embodiments, R^{10A} and R^{11A} can be the same. In some embodiments, R^{10A} and R^{11A} can be different.

[0144] In some embodiments, Z^{3A} can be O (oxygen). In other embodiments, Z^{3A} can be S (sulfur). In some embodiments, when R^{1A} is  , a compound of Formula (I) can be an optionally substituted phosphonic diamide prodrug.

[0145] Various substituents can be present at the 4'-position of the pentose ring. In some embodiments, R^{2A} can be an unsubstituted C_{1-4} alkyl. Unsubstituted C_{1-4} alkyls include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl and tert-butyl. In other embodiments, R^{2A} can be an unsubstituted C_{2-4} alkenyl, such as ethenyl, propenyl and butenyl. In still other embodiments, R^{2A} can be an unsubstituted C_{2-4} alkynyl, for example, ethynyl, propynyl and butynyl. In yet still other embodiments, R^{2A} can be a halogen(C_{1-6}alkyl), such as $-(CH_2)_{0-5}(CR^{2A1}R^{2A2})$halogen, wherein R^{2A1} and R^{2A2} can be independently hydrogen or halogen provided that at least one of R^{2A1} and R^{2A2} is halogen. Examples of a halogen(C_{1-6}alkyl) are $-(CH_2)_{1-6}$halogen, $-(CH_2)_{0-5}(CH)(halogen)_2$ and $-(CH_2)_{0-5}$-$C(halogen)_3$. In some embodiments, the halogen(C_{1-6}alkyl) can be $-(CH_2)_{1-6}F$ or $-(CH_2)_{1-6}Cl$. In other embodiments, the haloalkyl can be $-(CH_2)_{0-5}CHF_2$ or $-(CH_2)_{0-5}CF_3$. In some embodiments, the halogen(C_{1-6}alkyl) can be fluoromethyl. In some embodiments, R^{2A} can be CHF_2. In still other embodiments, R^{2A} can be CF_3. In yet still other embodiments, R^{2A} can be a C_{1-6} azidoalkyl. For example, R^{2A} can be an azidomethyl, azidoethyl, azidopropyl, azidobutyl, azidopentyl or azidohexyl. In some embodiments, R^{2A} can be a C_{1-6} aminoalkyl.

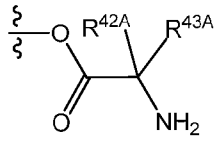
For example, R^{2A} can be an aminomethyl, aminoethyl, aminopropyl, aminobutyl, aminopentyl or aminohexyl. In other embodiments, R^{2A} can be halogen. For example, R^{2A} can be fluoro (F) or chloro (Cl). In still other embodiments, R^{2A} can be hydrogen. In yet still other embodiments, R^{2A} can be azido (N_3). In some embodiments, R^{2A} can be $-(CH_2)_{1-6}$ring A. As described herein, in some embodiments, ring A can be an optionally substituted mono-cyclic heteroaryl (for example, a 5- or 6-membered optionally substituted heteroaryl). In other embodiments, ring A can be an optionally substituted mono-cyclic heterocyclyl, such as, a 5- or 6-membered optionally substituted heterocyclyl. In still other embodiments, R^{2A} can be -CN.

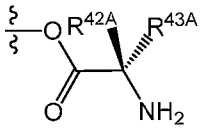
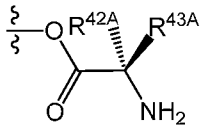
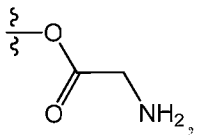
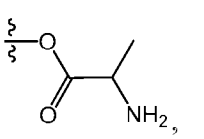
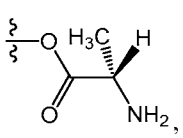
[0146] A variety of substituents can also be present at the 2'-position of the pentose ring. In some embodiments, R^{4A} can be OH. In other embodiments, R^{4A} can be $-OC(=O)R^{"B}$, wherein $R^{"B}$ can be an optionally substituted C_{1-24} alkyl. In some embodiments, R^{4A} can be $-OC(=O)R^{"B}$, wherein $R^{"B}$ can be an unsubstituted C_{1-4} alkyl. In still other embodiments, R^{4A} can be halogen. In some embodiments, R^{4A} can be F. In other embodiments, R^{4A} can be Cl. In some embodiments, R^{4A} can be N_3. In some embodiments, R^{4A} can be $NR^{"B1}R^{"B2}$. For example, R^{4A} can be NH_2. Other examples can be a mono-substituted C_{1-6} alkyl-amine or a di-substituted C_{1-6} alkyl-amine. In other embodiments, R^{4A} can be hydrogen (H).

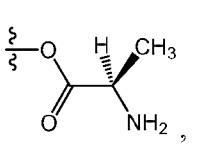
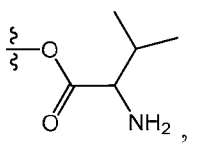
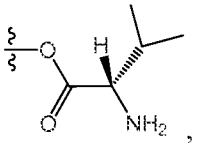
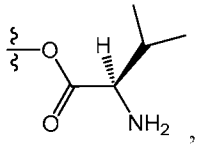
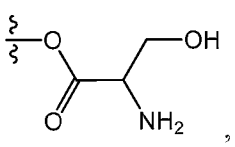
[0147] In still other embodiments, R^{4A} can be an optionally substituted O-linked amino acid, such as a O-linked alpha-amino acid. In some embodiments, the O-linked amino acid can have the structure  , wherein R^{42A} can be selected from hydrogen, an optionally substituted C_{1-6} alkyl, an optionally 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^{43A} can be hydrogen or an optionally substituted C_{1-4} alkyl; or R^{42A} and R^{43A} can be taken together to form an optionally substituted C_{3-6} cycloalkyl.

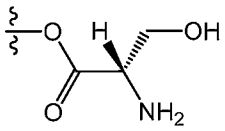
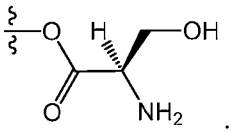
[0148] When R^{42A} is substituted, R^{42A} can be substituted with one or more substituents selected from N-amido, mercapto, alkylthio, an optionally substituted aryl, hydroxy, an optionally substituted heteroaryl, O-carboxy and amino. In some embodiments,

R^{42A} can be an unsubstituted C_{1-6} alkyl, such as those described herein. In some embodiments, R^{42A} can be hydrogen. In other embodiments, R^{42A} can be methyl. In some embodiments, R^{43A} can be hydrogen. In other embodiments, R^{43A} can be an optionally substituted C_{1-4} alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and tert-butyl. In some embodiments, R^{43A} can be methyl. Depending on the groups that are selected for R^{42A} and R^{43A}, the carbon to which R^{42A} and R^{43A} are attached may be a chiral center. In some embodiment, the carbon to which R^{42A} and R^{43A} are attached may be a (*R*)-chiral center. In other embodiments, the carbon to which R^{42A} and R^{43A} are attached may be a (*S*)-chiral center.

[0149] Examples of suitable  include the following:

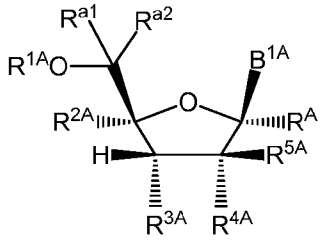
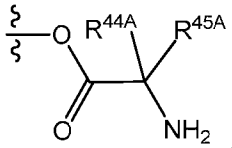
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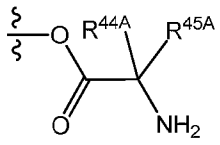
[0150] In some embodiments, R^{5A} can be hydrogen. In other embodiments, R^{5A} can be halogen, including F and Cl. In still other embodiments, R^{5A} can be an optionally substituted C_{1-6} alkyl. For example, R^{5A} can be a substituted or unsubstituted version of the following: methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, pentyl (branched or straight) and hexyl (branched or straight). In some embodiments, R^{5A} can be a halo-substituted C_{1-6} alkyl, such as $-CH_2F$. In yet still other embodiments, R^{5A} can be an optionally substituted C_{2-6} alkenyl. In some embodiments, R^{5A} can be an optionally substituted C_{2-6} alkynyl. For example, R^{5A} can be ethynyl. In some embodiments, R^{5A} can be hydroxy (OH).

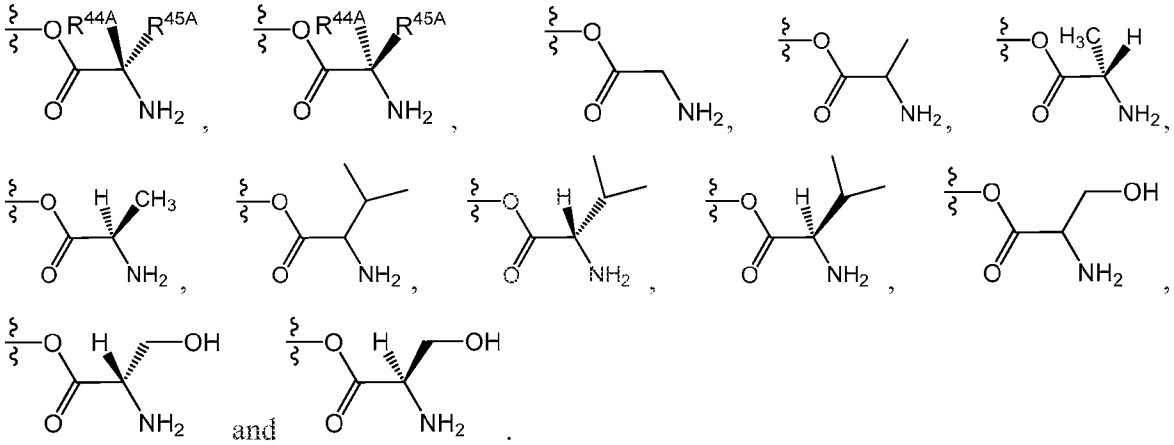
[0151] A variety of substituents can be present at the 1'-position of the pentose ring. In some embodiments, R^A can be hydrogen. In some embodiments, R^A can be deuterium. In still other embodiments, R^A can be an unsubstituted C_{1-3} alkyl (such as methyl, ethyl, n-propyl and iso-propyl). In yet still other embodiments, R^A can be an unsubstituted C_{2-4} alkenyl (for example, ethenyl, propenyl (branched or straight) and butenyl (branched or straight)). In some embodiments, R^A can be an unsubstituted C_{2-3} alkynyl (such as ethynyl and propynyl (branched or straight)). In other embodiments, R^A can be an unsubstituted cyano.

[0152] In some embodiments, -------- can be both absent such that a compound of Formula (I) has the structure:  . When -------- are both absent, the 3'-position can have various groups present. In some embodiments, R^{3A} can be hydrogen. In other embodiments, R^{3A} can be halogen. For example, R^{3A} can be fluoro (F) or chloro (Cl). In still other embodiments, R^{3A} can be OH. In some embodiments, R^{3A} can be $-OC(=O)R^{"A}$, wherein $R^{"A}$ can be an optionally substituted C_{1-24} alkyl. In some embodiments, R^{3A} can be $-OC(=O)R^{"A}$, wherein $R^{"A}$ can be an unsubstituted C_{1-4} alkyl. In other embodiments, R^{3A} can be an optionally substituted O-linked amino acid, such as an optionally substituted O-linked alpha-amino acid. The optionally substituted O-linked amino acid can have the structure:  , wherein R^{44A} 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^{45A} can be hydrogen or an optionally substituted C_{1-4} alkyl; or R^{44A} and R^{45A} can be taken together to form an optionally substituted C_{3-6} cycloalkyl.

[0153] When R^{44A} is substituted, R^{44A} 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^{44A} can be an unsubstituted C_{1-6} alkyl, such as those described herein. In some embodiments, R^{44A} can be hydrogen. In other embodiments, R^{44A} can be methyl. In some embodiments, R^{45A} can be hydrogen. In other embodiments, R^{45A} can be an optionally substituted C_{1-4} alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and tert-butyl. In some embodiments, R^{45A} can be methyl. Depending on the groups that are selected for R^{44A} and R^{45A}, the carbon to which R^{44A} and R^{45A} are attached may be a chiral center. In some embodiment, the carbon to which R^{44A} and R^{45A} are attached may be a (*R*)-chiral center. In other embodiments, the carbon to which R^{44A} and R^{45A} are attached may be a (*S*)-chiral center.

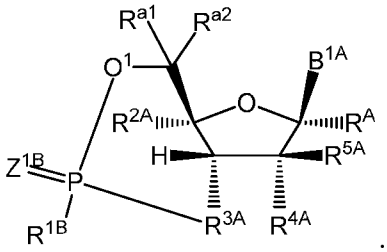
[0154] Examples of suitable  include the following:



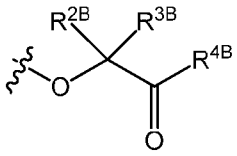
[0155] In some embodiments, R^{3A} and R^{4A} can be each an oxygen atom connected via a carbonyl to form a 5-membered ring.

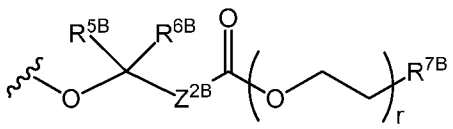
[0156] In some embodiments, R^{2A} can be fluoro and R^{3A} can be fluoro. In some embodiments, R^{2A} can be fluoro and R^{4A} can be fluoro. In some embodiments, R^{2A} can be fluoro, R^{3A} can be fluoro and R^{5A} can be an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl and an optionally substituted C_{2-6} alkynyl. In some embodiments, R^{2A} can be fluoro, R^{4A} can be fluoro and R^{5A} can be an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl and an optionally substituted C_{2-6} alkynyl. In some embodiments, R^{2A} can be fluoro, R^{3A} can be fluoro and R^{4A} can be OH or $-OC(=O)R^{"B}$. In

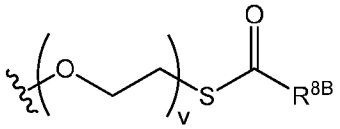
some embodiments, R^{2A} can be fluoro, R^{3A} can be OH or –OC(=O)$R^{"A}$ and R^{4A} can be fluoro. In some embodiments, R^{4A} and R^{5A} can be each F. In some embodiments, R^{2A} can be *-$(CH_2)_{1-6}$halogen (for example, -CH_2F), R^{3A} can be OH, -OC(=O)$R^{"A}$ or an optionally substituted O-linked amino acid and R^{4A} can be OH. In some embodiments, R^{2A} can be -$(CH_2)_{1-6}$halogen (for example, -CH_2F), R^{3A} can be OH, -OC(=O)$R^{"A}$ or an optionally substituted O-linked amino acid, R^{4A} can be OH, and R^{5A} can be an unsubstituted C_{1-6} alkyl. In some embodiments, R^{2A} can be -$(CH_2)_{1-6}N_3$ (such as, -CH_2N_3), R^{3A} can be OH and R^{4A} can be fluoro. In other embodiments, R^{2A} can be azido, R^{3A} can be OH and R^{4A} can be fluoro.

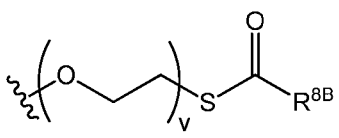
[0157] In some embodiments, -------- can be each a single bond such that a compound of Formula (I) has the structure: 

. When -------- are each a single bond, R^{3A} can be oxygen (O). In some embodiments, when -------- are each a single bond, R^{1B} can be O^- or OH. In other embodiments, when -------- are each a single bond, R^{1B} can be an –O–optionally substituted C_{1-6} alkyl. For example, R^{1B} can be an –O–unsubstituted C_{1-6} alkyl.

[0158] In some embodiments, when -------- are each a single bond, R^{1B} can be 

. In other embodiments, R^{1B} can be 

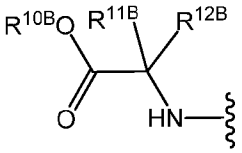
. For example, R^{1B} can be an optionally substituted isopropyloxycarbonyloxymethyloxy or an optionally substituted pivaloyloxymethyloxy group. In still some embodiments, R^{1B} can be 

. An optionally substituted S-acylthioethyl (SATE) group is an example of a 

group. In yet still other embodiments, R^{1B} can be an

optionally substituted N-linked amino acid or an optionally substituted N-linked amino acid ester derivative, such as an optionally substituted N-linked alpha-amino acid or an optionally substituted N-linked alpha-amino acid ester derivative.

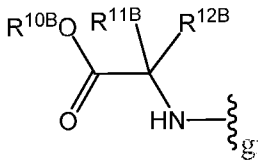
[0159] Examples of an optionally substituted N-linked amino acids and an optionally substituted N-linked amino acid ester derivatives are described herein. In some embodiments, R^{1B} can be selected from alanine, asparagine, aspartate, cysteine, glutamate, glutamine, glycine, proline, serine, tyrosine, arginine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, valine and ester derivatives thereof. In some embodiments, R^{1B} can be an optionally substituted version of the following: N-alanine isopropyl ester, N-alanine cyclohexyl ester, N-alanine neopentyl ester, N-valine isopropyl ester and N-leucine isopropyl ester. In some embodiments, R^{1B} can have the structure

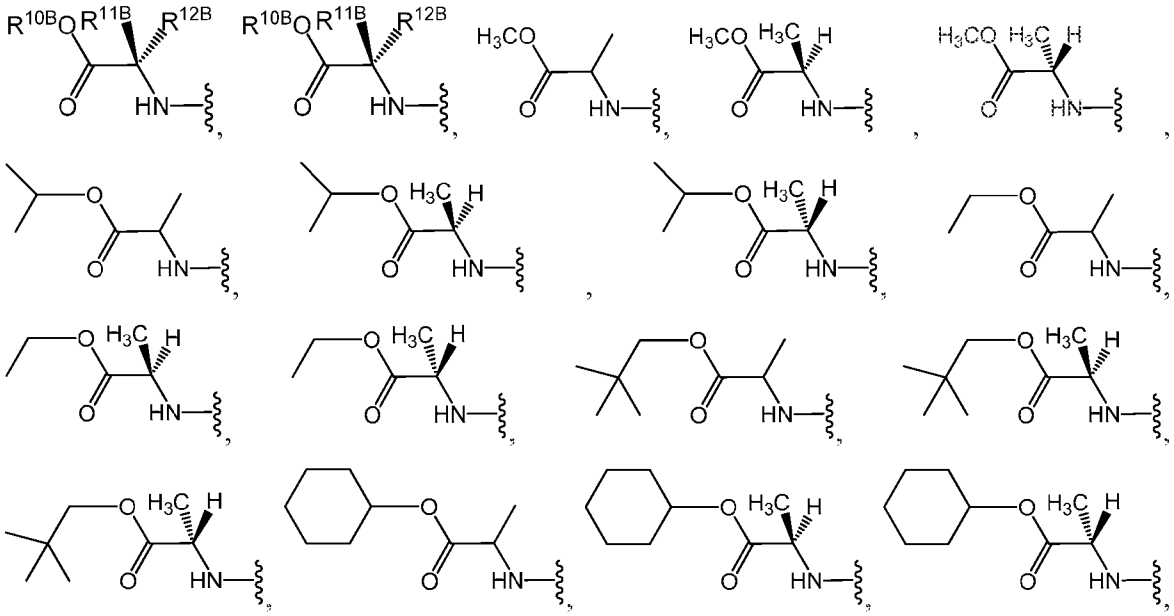


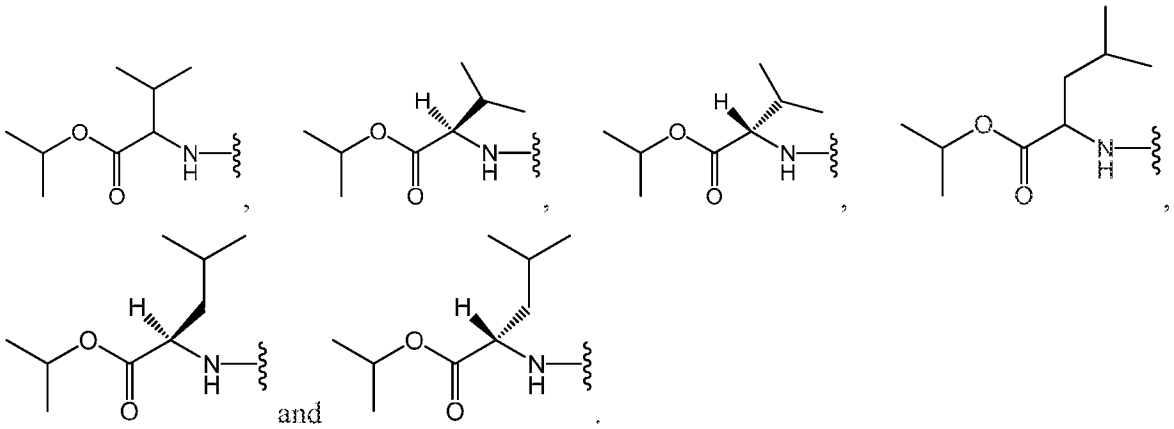
wherein R^{10B} can be selected from hydrogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted aryl, an optionally substituted aryl(C_{1-6} alkyl) and an optionally substituted haloalkyl; R^{11B} can be selected from hydrogen, an optionally 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^{12B} can be hydrogen or an optionally substituted C_{1-4} alkyl; or R^{11B} and R^{12B} can be taken together to form an optionally substituted C_{3-6} cycloalkyl.

[0160] As described herein, R^{11B} can be substituted. Examples of substituents include 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^{11B} can be an unsubstituted C_{1-6} alkyl, such as those described herein. In some embodiments, R^{11B} can be hydrogen. In other embodiments, R^{11B} can be methyl. In some embodiments, R^{10B} can be an optionally substituted C_{1-6} alkyl. In some embodiments, R^{10B} can be methyl, ethyl, isopropyl or neopentyl. In other embodiments, R^{10B} 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^{10B} can be an optionally substituted cyclohexyl. In

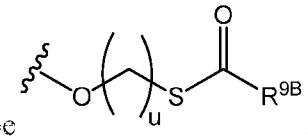
still other embodiments, R^{10B} can be an optionally substituted aryl, such as phenyl and naphthyl. In yet still other embodiments, R^{10B} can be an optionally substituted aryl(C_{1-6} alkyl), for example, an optionally substituted benzyl. In some embodiments, R^{10B} can be an optionally substituted C_{1-6} haloalkyl, for example, CF_3. In some embodiments, R^{12B} can be hydrogen. In other embodiments, R^{12B} can be an optionally substituted C_{1-4} alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and tert-butyl. In some embodiments, R^{12B} can be methyl. In some embodiments, R^{11B} and R^{12B} can be taken together to form an optionally substituted C_{3-6} cycloalkyl. Depending on the groups that are selected for R^{11B} and R^{12B}, the carbon to which R^{11B} and R^{12B} are attached may be a chiral center. In some embodiment, the carbon to which R^{11B} and R^{12B} are attached may be a (*R*)-chiral center. In other embodiments, the carbon to which R^{11B} and R^{12B} are attached may be a (*S*)-chiral center.

[0161] Examples of suitable  groups include the following:



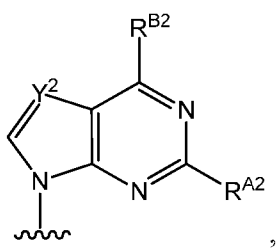
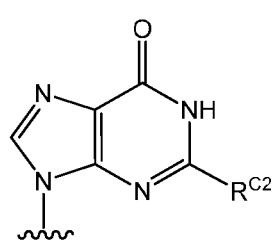
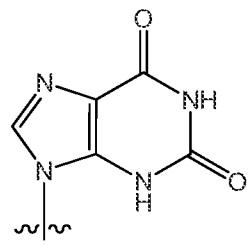
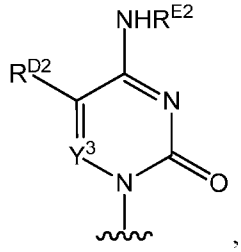
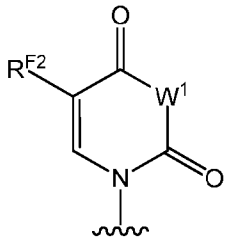
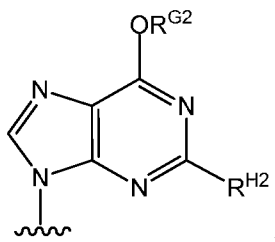


and

[0162] In some embodiments, R^{1B} can be  . In some embodiments, R^{9B} can be hydrogen. In other embodiments, R^{9B} can be an optionally substituted C_{1-24} alkyl. In still other embodiments, R^{9B} can be an optionally substituted aryl, for example, an optionally substituted phenyl. In some embodiments, R^{9B} can be an optionally substituted C_{1-6} alkyl. In some embodiments, R^{9B} can be an unsubstituted C_{1-6} alkyl. In some embodiments, u can be 3. In other embodiments, u can be 4. In still other embodiments, u can be 5.

[0163] In some embodiments, Z^{1B} can be oxygen (O). In other embodiments, Z^{1B} can be S (sulfur).

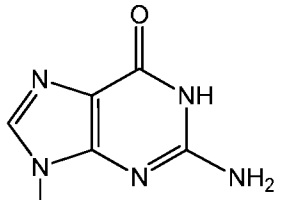
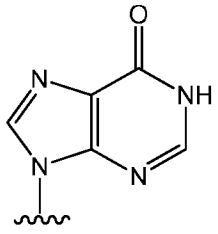
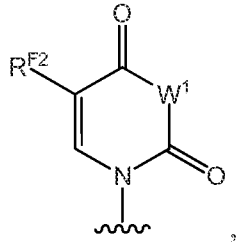
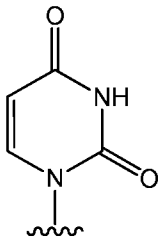
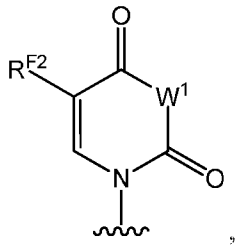
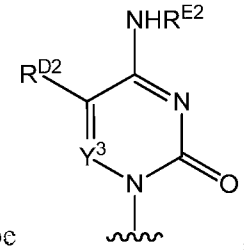
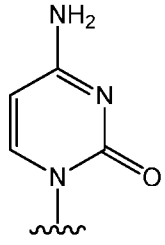
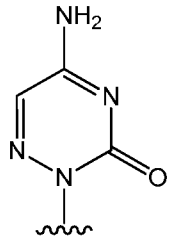
[0164] Various optionally substituted heterocyclic bases can be attached to the pentose ring. In some embodiments, one or more of the amine and/or amino groups of the optionally substituted heterocyclic base may be protected with a suitable protecting group. For example, an amino group may be protected by transforming the amine and/or amino group to an amide or a carbamate. In some embodiments, an optionally substituted heterocyclic base or an optionally substituted heterocyclic base can include a group that improves the solubility of the compound (for example, $-(CH_2)_{1-2}-O-P(=O)(OW^{1A})_2$). In some embodiments, an optionally substituted heterocyclic base or an optionally substituted heterocyclic base with one or more protected amino groups can have one of the following structures:

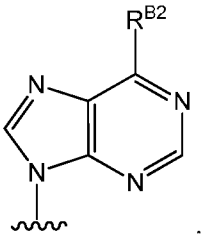







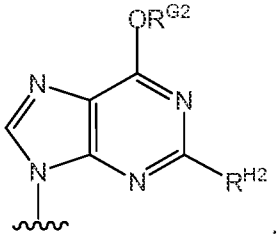
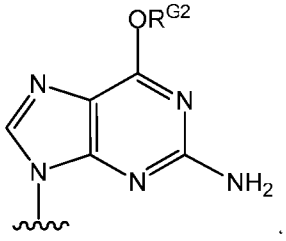
and ;

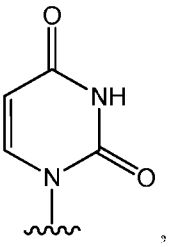
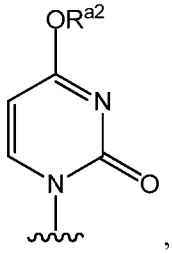
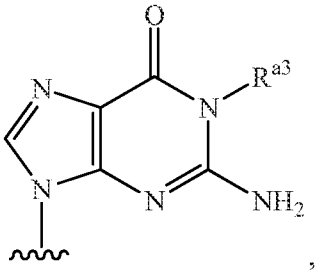
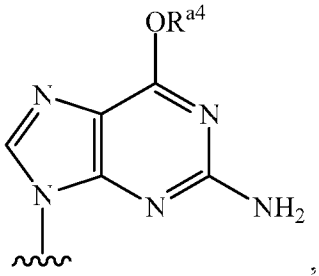
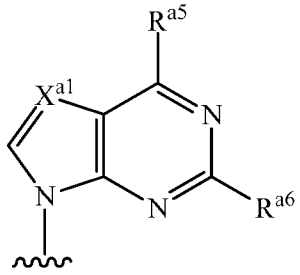
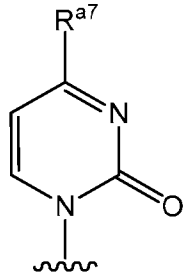
wherein: R^{A2} can be selected from hydrogen, halogen and NHR^{J2}, wherein R^{J2} can be selected from hydrogen, $-C(=O)R^{K2}$ and $-C(=O)OR^{L2}$; R^{B2} can be halogen or NHR^{W2}, wherein R^{W2} can be selected from hydrogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{3-8} cycloalkyl, $-C(=O)R^{M2}$ and $-C(=O)OR^{N2}$; R^{C2} can be hydrogen or NHR^{O2}, wherein R^{O2} can be selected from hydrogen, $-C(=O)R^{P2}$ and $-C(=O)OR^{Q2}$; R^{D2} can be selected from hydrogen, deuterium, halogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl and an optionally substituted C_{2-6} alkynyl; R^{E2} can be selected from hydrogen, hydroxy, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{3-8} cycloalkyl, $-C(=O)R^{R2}$ and $-C(=O)OR^{S2}$; R^{F2} can be selected from hydrogen, halogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl and an optionally substituted C_{2-6} alkynyl; Y^2 and Y^3 can be independently N (nitrogen) or CR^{I2}, wherein R^{I2} can be selected from hydrogen, halogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6}-alkenyl and an optionally substituted C_{2-6}-alkynyl; W^1 can be NH, $-NCH_2$-$OC(=O)CH(NH_2)$-$CH(CH_3)_2$ or $-(CH_2)_{1-2}$-O-$P(=O)(OW^{1A})_2$, wherein W^{1A} can be selected from absent, hydrogen and an optionally substituted C_{1-6} alkyl; R^{G2} can be an optionally substituted C_{1-6} alkyl; R^{H2} can be hydrogen or NHR^{T2}, wherein R^{T2} can be independently selected from hydrogen, $-C(=O)R^{U2}$ and $-C(=O)OR^{V2}$; and R^{K2}, R^{L2}, R^{M2}, R^{N2}, R^{P2}, R^{Q2}, R^{R2}, R^{S2}, R^{U2} and R^{V2} can be independently selected from hydrogen, 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, heterocyclyl, aryl(C_{1-6} alkyl), heteroaryl(C_{1-6} alkyl) and heterocyclyl(C_{1-6} alkyl). In some embodiments, the structures shown above can be modified

by replacing one or more hydrogens with substituents selected from the list of substituents provided for the definition of "substituted." In some embodiments of B^{1A}, a hydrogen can be replaced with a deuterium. Those skilled in the art understand that when W^{1A} is absent, the oxygen atom will have an associated negative charge. In some embodiments, the substituent on the base can result in the formation of a salt of a compound of Formula (I).

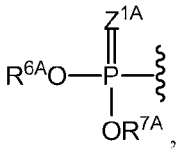
[0165] In some embodiments, B^{1A} can be an optionally substituted purine base. In other embodiments, B^{1A} can be an optionally substituted pyrimidine base. In some embodiments, B^{1A} can be  . In other embodiments, B^{1A} can be  . In still other embodiments, B^{1A} can be  , such as  . In yet still other embodiments, B^{1A} can be  , wherein W^1 can be $-NCH_2\text{-}OC(=O)CH(NH_2)\text{-}CH(CH_3)_2$ or $-(CH_2)_{1\text{-}2}\text{-}O\text{-}P(=O)(OW^{1A})_2$. In some embodiments, B^{1A} can be  , for example,  or  . In other embodiments, R^{D2} can be hydrogen. In still other embodiments, B^{1A} can be



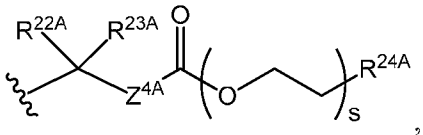
. In some embodiments, R^{B2} can be NH_2. In other embodiments, R^{B2} can be NHR^{W2}, wherein R^{W2} can be $-C(=O)R^{M2}$ or $-C(=O)OR^{N2}$. In still other embodiments, B^{1A} can be  . In some embodiments, B^{1A} can be  .

[0166] In some embodiments, when R^{2A} is halogen (such as fluoro); -------- are both absent; Z^1 is absent; O^1 is OR^{1A}; B^{1A} is selected from an optionally substituted  , an optionally substituted  , an optionally substituted  , an optionally substituted  , an optionally substituted  and an optionally substituted  , wherein R^{a2} is an optionally substituted C_{1-6} alkyl or an optionally substituted C_{3-6} cycloalkyl, R^{a3} and R^{a4} are independently selected from 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^{a5} is NHR^{a8}, and

R^{a6} is hydrogen, halogen or NHR^{a9}; R^{a7} is NHR^{a10}; R^{a8} is selected from hydrogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{3-6} alkenyl, an optionally substituted C_{3-6} cycloalkyl, $-C(=O)R^{a11}$ and $-C(=O)OR^{a12}$; R^{a9} is selected from hydrogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{3-6} alkenyl, an optionally substituted C_{3-6} cycloalkyl, $-C(=O)R^{a13}$ and $-C(=O)OR^{a14}$; R^{a10} is selected from hydrogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{3-6} alkenyl, an optionally substituted C_{3-6} cycloalkyl, $-C(=O)R^{a15}$ and $-C(=O)OR^{a16}$; X^{a1} is N or $-CR^{a17}$; R^{a17} is selected from hydrogen, halogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl and an optionally substituted C_{2-6} alkynyl; R^{a11}, R^{a12}, R^{a13}, R^{a14}, R^{a15} and R^{a16} are independently selected from 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, heterocyclyl, aryl(C_{1-6} alkyl), heteroaryl(C_{1-6} alkyl) and heterocyclyl(C_{1-6} alkyl); then R^{3A} is selected from hydrogen, halogen, and an optionally substituted O-linked amino acid; and R^{4A} is selected from OH, halogen, $-OC(=O)R^{"A}$ and an optionally substituted O-linked amino acid; or then R^{4A} is an optionally substituted O-linked amino acid; and R^{3A} is selected from hydrogen, halogen, OH, $-OC(=O)R^{"A}$ and an optionally substituted O-linked amino acid; or then R^{3A} and R^{4A} are both an oxygen atom connected via a carbonyl to form a 5-membered ring; or then R^{1A} is

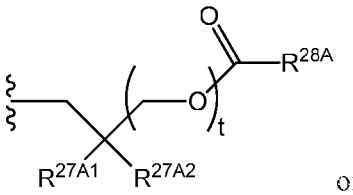


, wherein R^{6A} and R^{7A} are independently

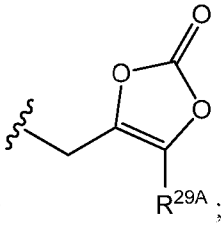


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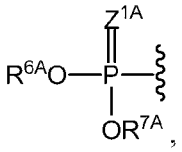
wherein s is 1, 2 or 3,



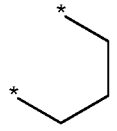
or



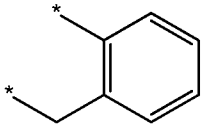
; or then R^{1A} is



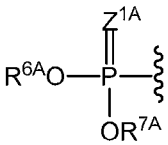
, wherein R^{6A} and R^{7A} are taken together to form a moiety selected from an optionally substituted

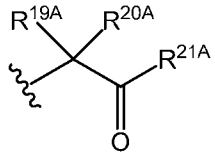


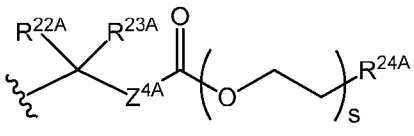
and an optionally substituted

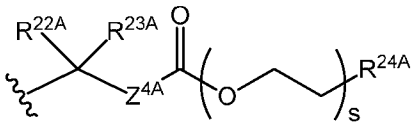


, wherein the

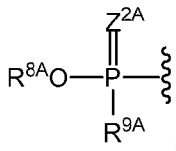
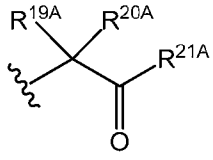
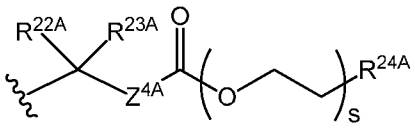
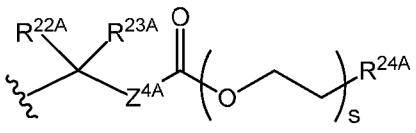
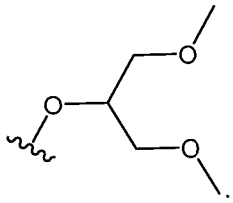
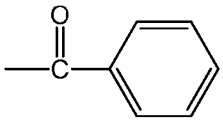
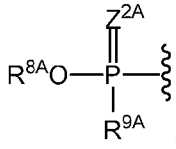
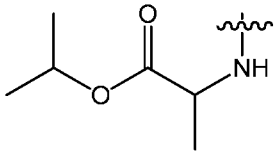
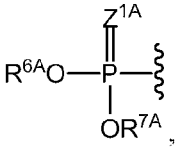
oxygens connected to R^{6A} and R^{7A}, the phosphorus and the moiety form a six-membered to ten-membered ring system. In some embodiments, when R^{2A} is halogen (such as fluoro); ---------- are each a single bond; then R^{4A} is $-OC(=O)R^{"B}$ or an optionally substituted O-linked amino acid. In some embodiments, when R^{2A} is an unsubstituted C_{1-4} alkyl, an unsubstituted C_{2-4} alkenyl, an unsubstituted C_{2-4} alkynyl, $-(CH_2)_{1-6}$ halogen or $-(CH_2)_{1-6}N_3$; -------- are both absent; Z^1 is absent; O^1 is OR^{1A}; R^{3A} is OH, $-OC(=O)R^{"A}$ or an optionally substituted O-linked amino acid; and R^{4A} is halogen; then R^{5A} is selected from an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl and an optionally substituted C_{2-6} alkynyl. In some embodiments, when R^{2A} is an unsubstituted C_{1-4} alkyl, an unsubstituted C_{2-4} alkenyl, an unsubstituted C_{2-4} alkynyl, $-(CH_2)_{1-6}$ halogen or $-(CH_2)_{1-6}N_3$; -------- are both absent; Z^1 is absent; O^1 is OR^{1A}; R^{4A} is halogen; and R^{5A} is hydrogen or halogen; then R^{3A} is hydrogen or halogen. In some embodiments, when R^{2A} is an unsubstituted C_{1-4} alkyl, an unsubstituted C_{2-4} alkenyl, an unsubstituted C_{2-4} alkynyl, $-(CH_2)_{1-6}$ halogen or $-(CH_2)_{1-6}N_3$; -------- are both absent; Z^1 is absent; O^1 is OR^{1A}; R^{3A} is OH, $-OC(=O)R^{"A}$ or an optionally substituted O-linked amino acid; R^{4A} is halogen; R^{5A} is hydrogen or halogen; and R^{1A} is 

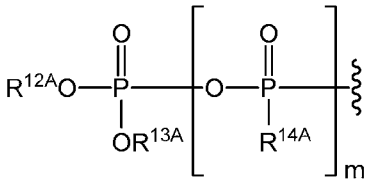
then at least one of R^{6A} and R^{7A} is 

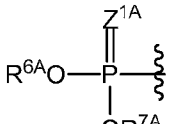
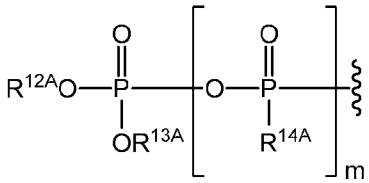
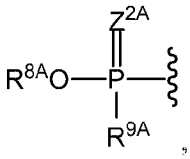
, wherein R^{21A} is independently selected from an optionally substituted –O–heteroaryl and an optionally substituted –O–monocyclic heterocyclyl; or then at least one of R^{6A} and R^{7A} is 

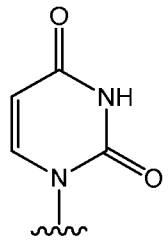
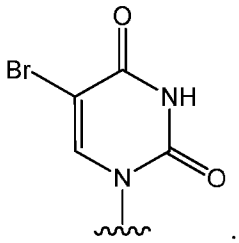
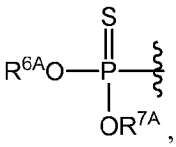
, wherein s is 1, 2 or 3; or then at least one of R^{6A} and R^{7A} is 

, wherein s is 0 and R^{24A} is an optionally substituted –O–heteroaryl or an optionally substituted –O–monocyclic heterocyclyl. In some embodiments, when R^{2A} is an unsubstituted C_{1-4} alkyl, an unsubstituted C_{2-4} alkenyl, an unsubstituted C_{2-4} alkynyl, $-(CH_2)_{1-6}$ halogen or $-(CH_2)_{1-6}N_3$; -------- are both absent; Z^1 is absent; O^1 is OR^{1A}; R^{3A} is OH, $-OC(=O)R^{"A}$ or an optionally

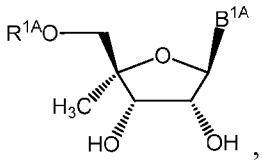
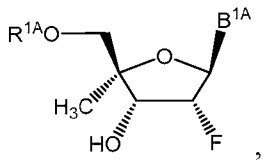
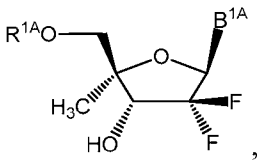
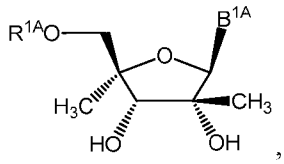
substituted O-linked amino acid; R^{4A} is halogen; R^{5A} is hydrogen or halogen; and R^{1A} is  ; then R^{8A} is  , wherein R^{21A} is independently selected from an optionally substituted –O–heteroaryl and an optionally substituted –O–monocyclic heterocyclyl; or then R^{8A} is  , wherein s is 1, 2 or 3; or then R^{8A} is  , wherein s is 0 and R^{24A} is an optionally substituted –O–heteroaryl, an optionally substituted –O–monocyclic heterocyclyl or  . In some embodiments, when -------- are both absent; Z^1 is absent; O^1 is OH; R^{2A} is methyl; R^{3A} is OH; then R^{4A} is halogen, $–OC(=O)R^{"B}$ or an optionally substituted O-linked amino acid. In some embodiments, when -------- are both absent; Z^1 is absent; O^1 is OR^{1A}; R^{2A} is halogen (for example, F); R^{3A} is OH or $–OC(=O)R^{"A}$; R^{4A} is halogen (for example, F); and R^{5A} is methyl, ethyl or ethenyl; then R^{1A} cannot be selected from hydrogen,  and  , wherein R^{8A} is an unsubstituted aryl; R^{9A} is  and Z^{2A} is oxygen. In some embodiments, R^{1A} is not hydrogen (H), for example, when R^{3A} is halo (such as fluoro) and R^{4A} is OH. In some embodiments, R^{1A} is not  , wherein Z^{1A}

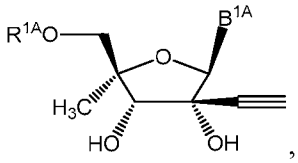
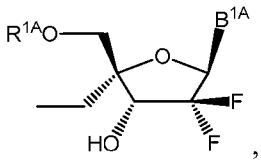
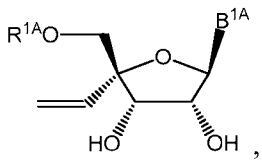
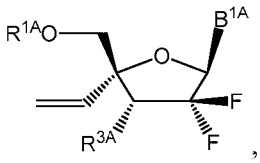


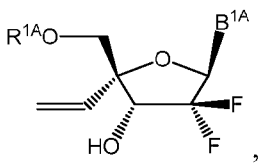
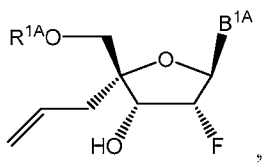
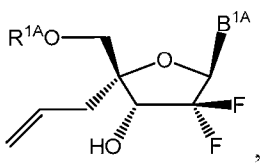
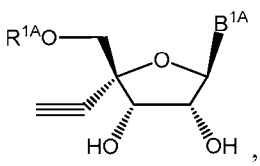
is O and R^{6A} is , for example, when R^{4A} is halo (such as fluoro) and R^{3A} is OH. In some embodiments, R^{2A} is not hydrogen (H). In some embodiments, R^{2A} is not halogen. In some embodiments, R^{2A} is not fluoro (F). In some embodiments, R^{2A} is not -CN. In some embodiments, R^{2A} is not $-CHF_2$. In some embodiments, R^{2A} is not $-CF_3$. In some embodiments, R^{5A} is not hydrogen or halo. In some embodiments, R^{5A} is not -OH. In some embodiments, R^{4A} is not hydrogen (H). In some embodiments, R^{4A} is not halo. In some embodiments, R^{4A} is not fluoro (F). In some embodiments, R^{4A} is not chloro (Cl). In some embodiments, R^{2A} is not an unsubstituted C_{1-4} alkyl. In some embodiments, R^{2A} is not an unsubstituted C_{2-4} alkenyl. In some embodiments, R^{2A} is not an unsubstituted C_{2-4} alkynyl. In some embodiments, R^{2A} is not $-(CH_2)_{1-6}$ halogen. In some embodiments, R^{2A} is not $-(CH_2)_{1-6}N_3$. In some embodiments, R^{4A} is not hydrogen, when R^{5A} is fluoro. In some embodiments, R^{6A} is not an optionally substituted aryl. In some embodiments, R^{6A} is not an unsubstituted aryl. In some embodiments, R^{9A} is not N-alanine isopropyl ester. In some embodiments, R^{5A} is not an optionally substituted C_{1-6} alkyl. For example, R^{5A} is not an unsubstituted C_{1-6} alkyl, such as methyl. In some embodiments, B^{1A} is not an optionally substituted uracil, for example, a halo-substituted uracil. In some embodiments, when R^{1A} is hydrogen, an optionally substituted acyl,  , wherein R^{6A} can be  , or  , wherein R^{8A} is an unsubstituted or substituted phenyl or an unsubstituted or substituted naphthyl and R^{9A} is an optionally substituted N-linked amino acid or an optionally substituted N-linked amino acid ester; R^{2A} is fluoro, R^{3A} is OH or -C(=O)-unsubstituted or substituted phenyl; R^{4A} is fluoro; and R^{5A} is a C_{1-4} alkyl (such as methyl); then B^{1A} cannot be an optionally substituted pyrimidine base,

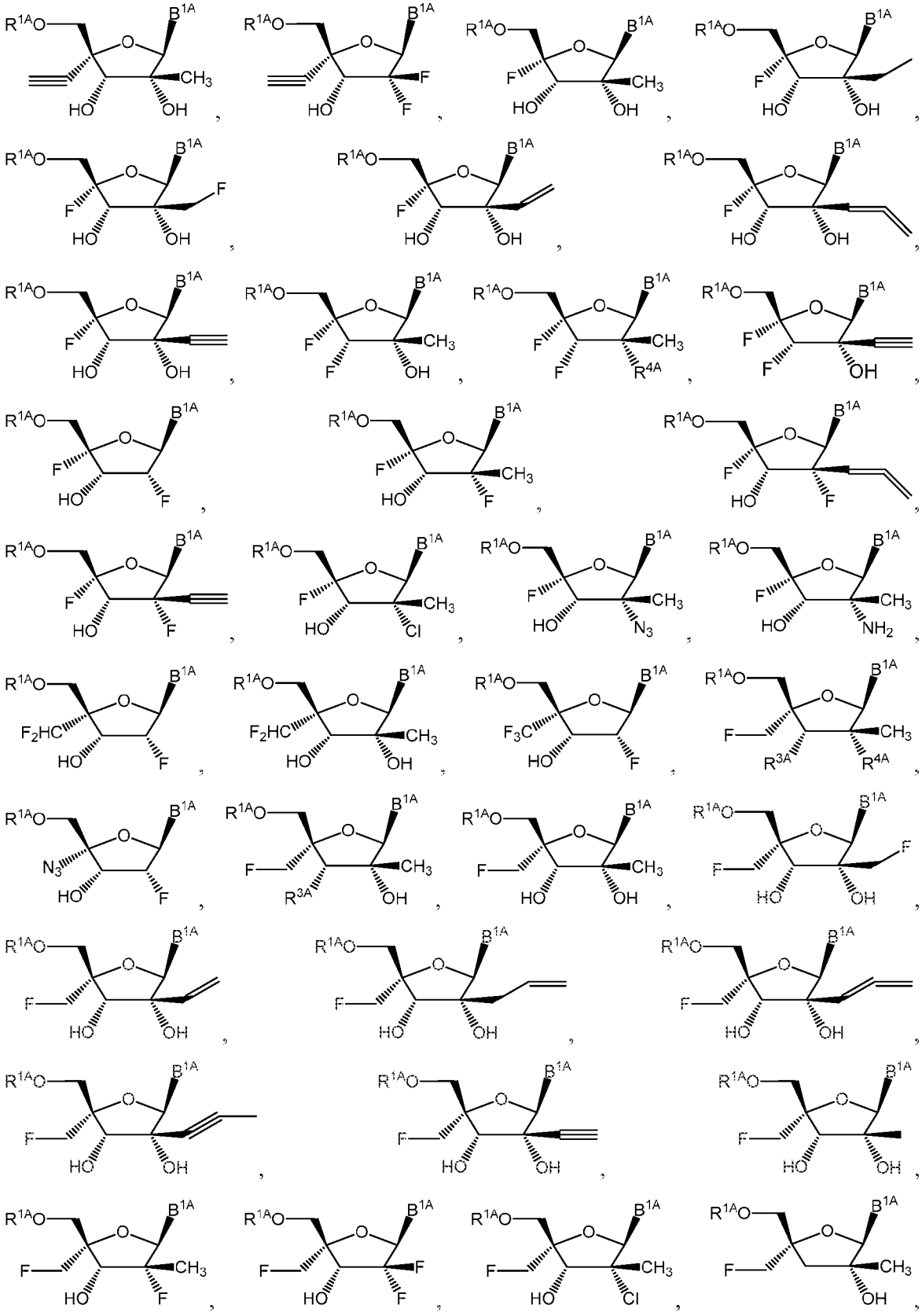
such as  or  . In some embodiments, when R^{1A} is  , R^{2A} is hydrogen, R^{3A} is OH and R^{4A} is OH or halogen (such as F), then R^{5A} is not an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl or an optionally substituted C_{2-6} alkynyl. In some embodiments, a compound of Formulae (I) and/or (II), or a pharmaceutically acceptable salt of the foregoing, is not a compound in WO 2013/092481 (filed December 17, 2012), U.S. 2014/0178338 (filed December 17, 2013), U.S. 2013/0164261 (filed December 20, 2012), WO 2014/100505 (filed December 19, 2013), WO 2013/096679 (filed December 20, 2012), WO 2013/142525 (filed March 19, 2013), WO 2014/209983 (filed June 24, 2014), WO 2014/209979 (filed June 24, 2014) and/or U.S. 2015/0105341 (filed October 9, 2014), or a pharmaceutically acceptable salt of the foregoing.

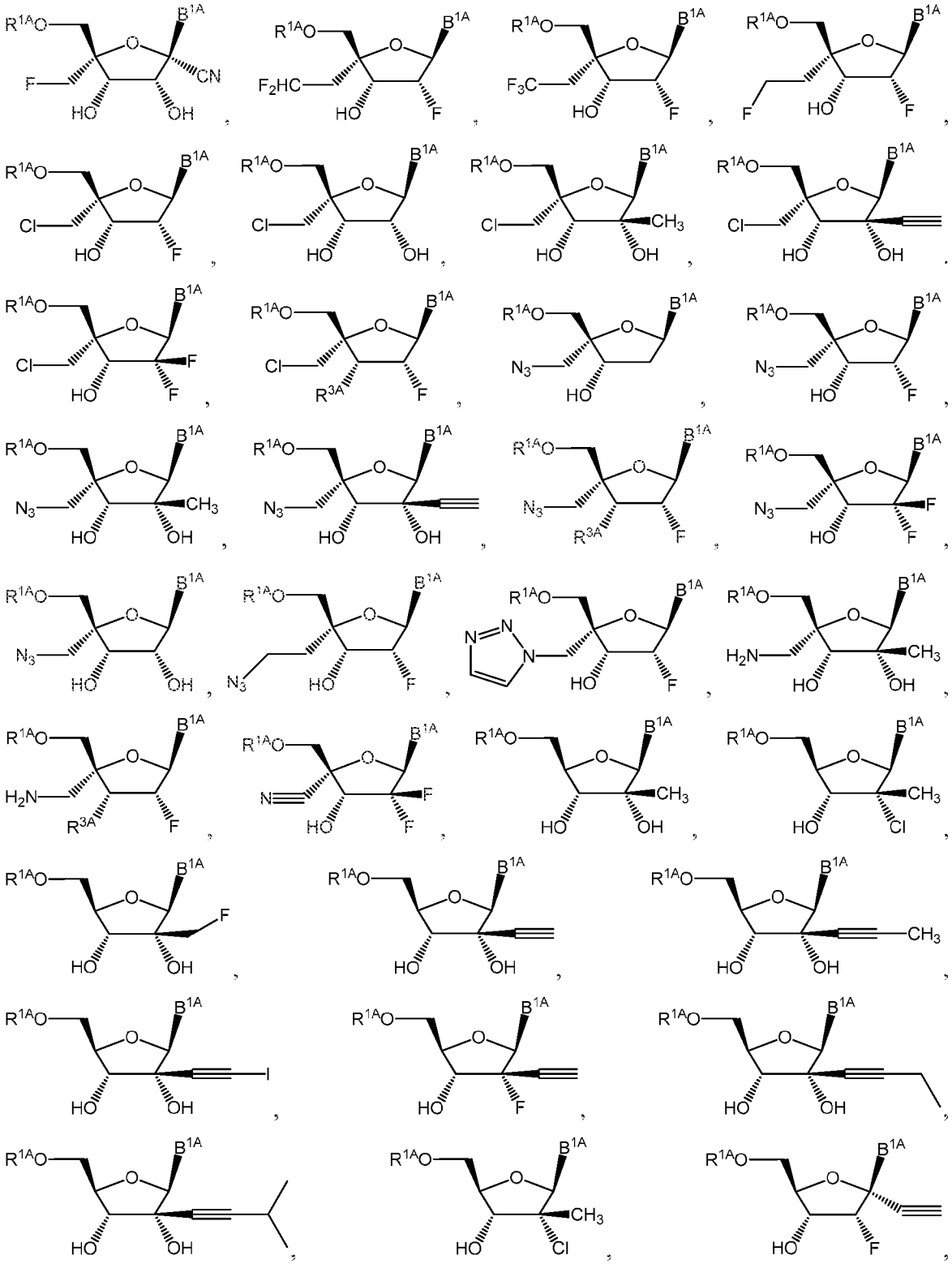
[0167] Examples of compounds of Formula (I), or a pharmaceutically acceptable salt thereof, include, but are not limited to:

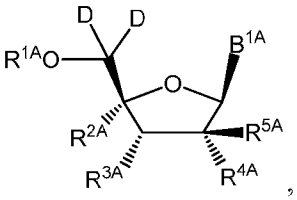
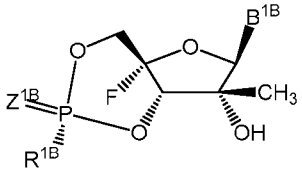
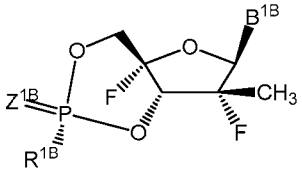
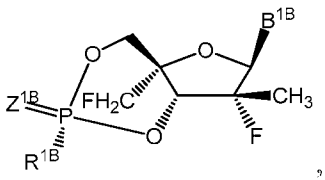
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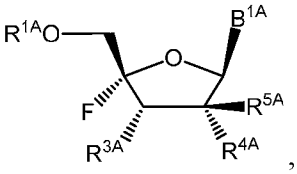
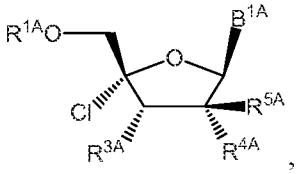
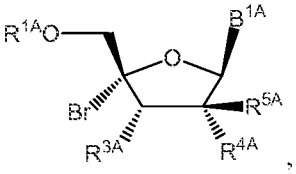
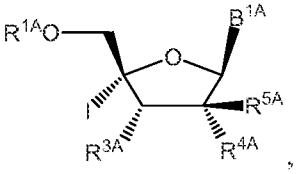
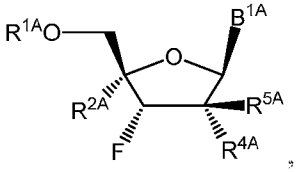
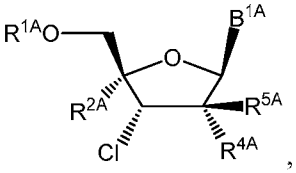
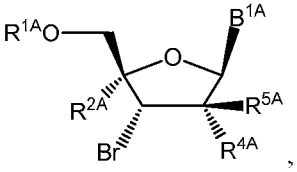
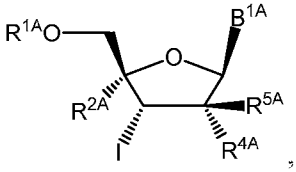
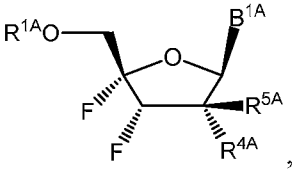
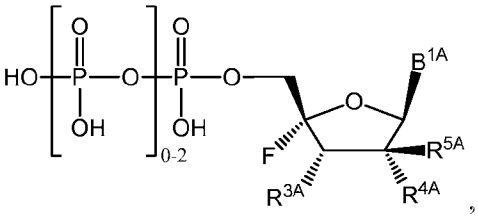
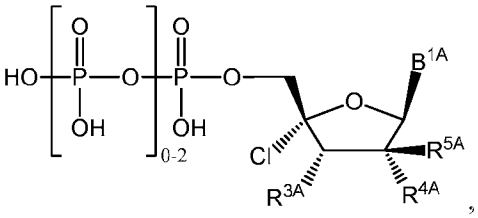
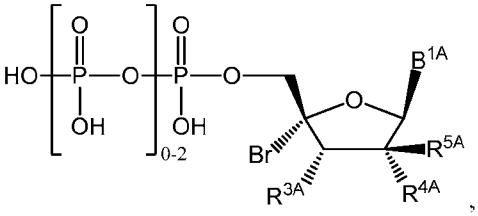
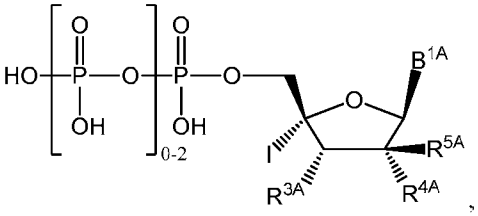
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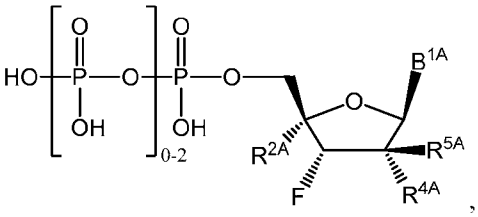
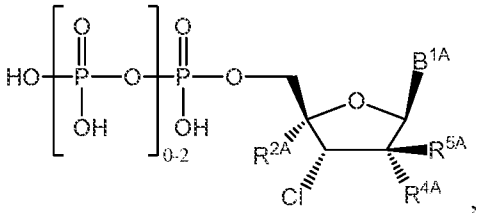
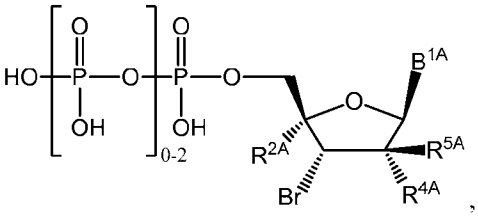
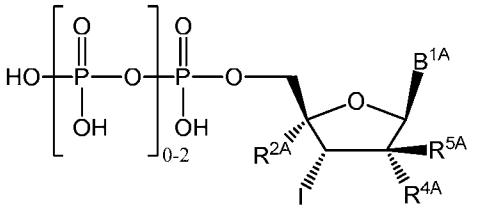
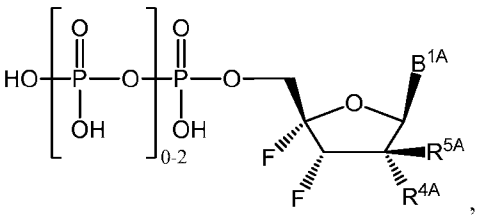




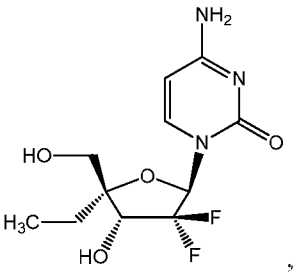
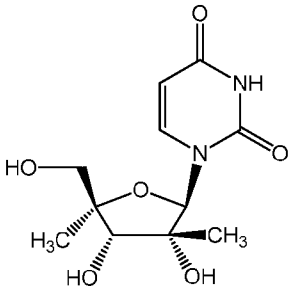
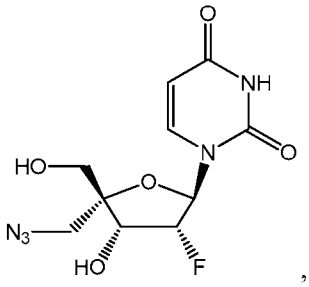
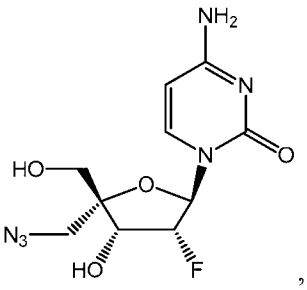
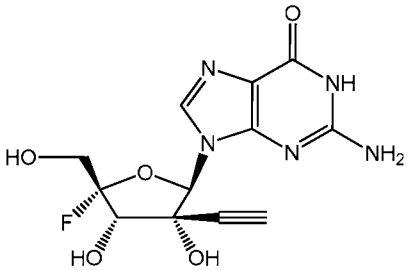
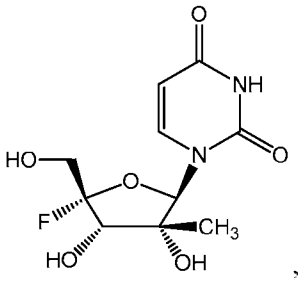

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and

, or a pharmaceutically acceptable salt of the foregoing.

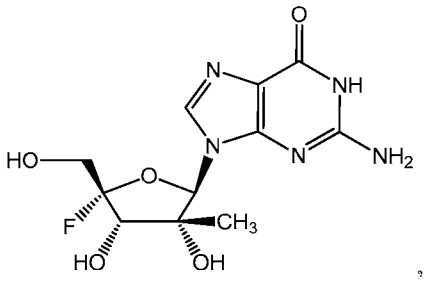
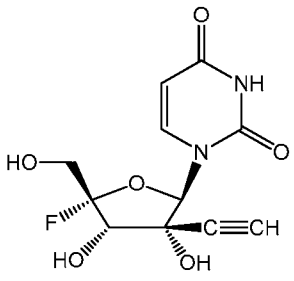
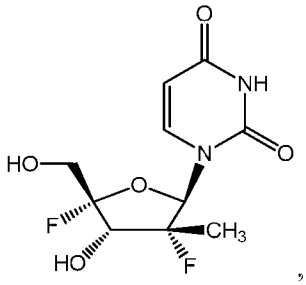
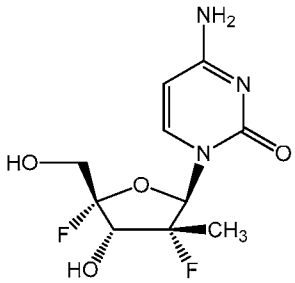
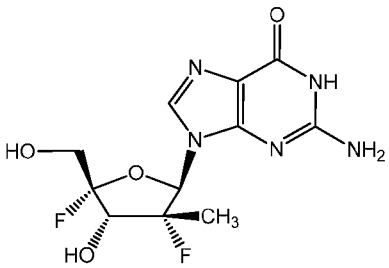
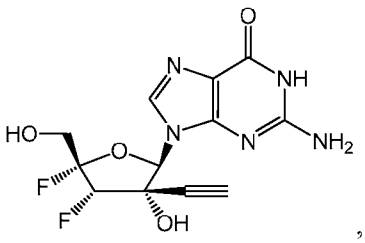
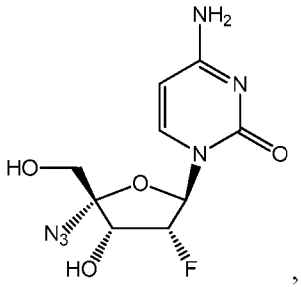
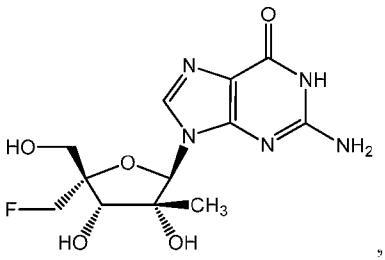
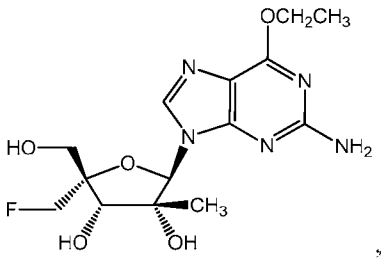
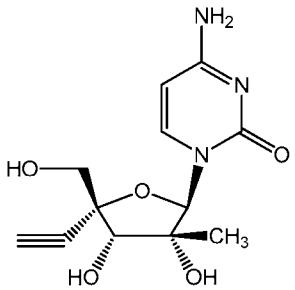
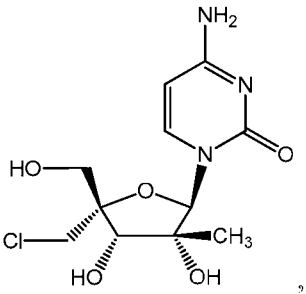
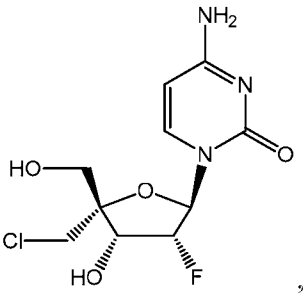
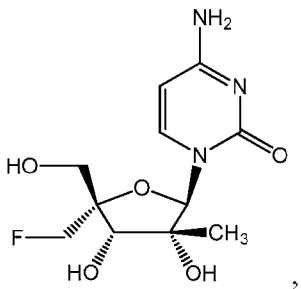
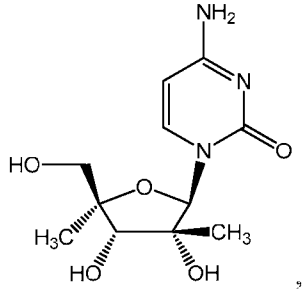
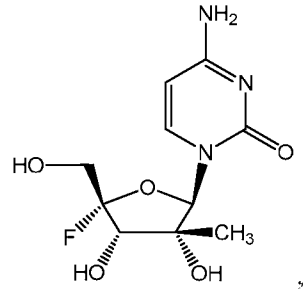
[0168] Additional examples of compounds of Formula (I), or a pharmaceutically acceptable salt thereof, include, but are not limited to:


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and

, or a pharmaceutically acceptable salt of the foregoing.

[0169] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, may be selected from:

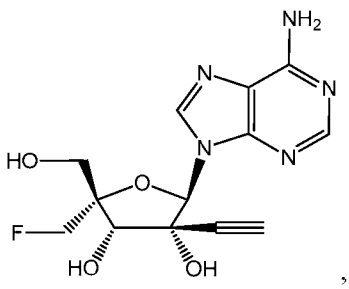
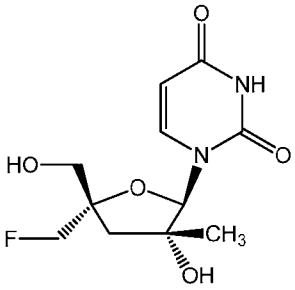
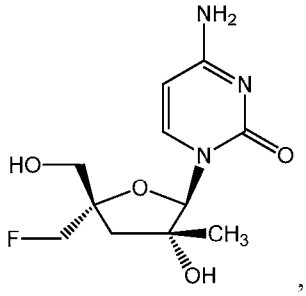
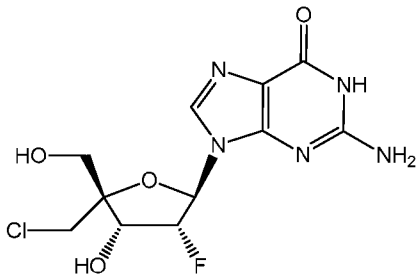
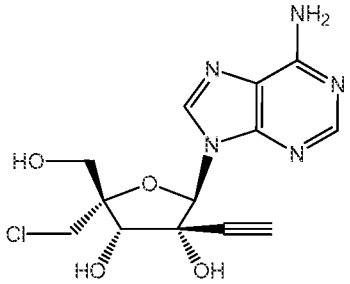
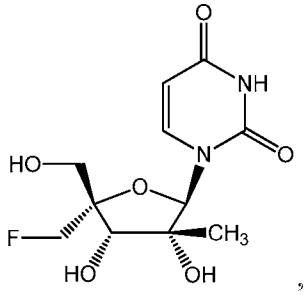
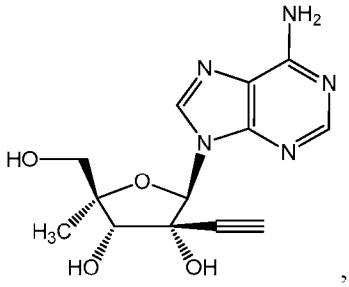
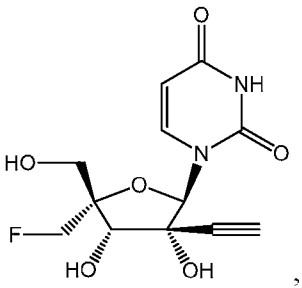
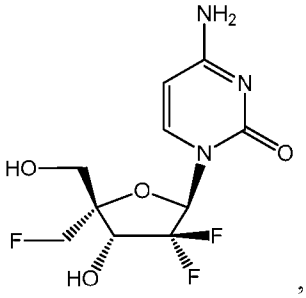
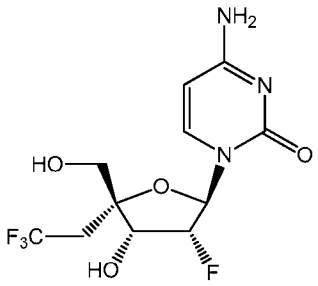
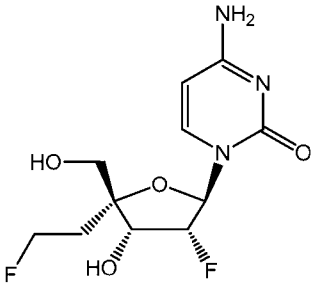
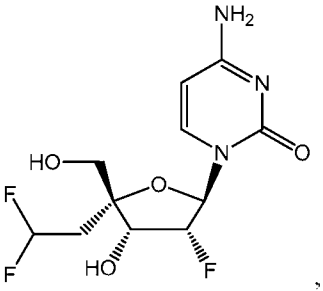
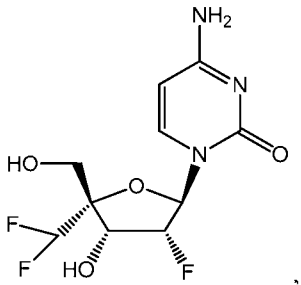
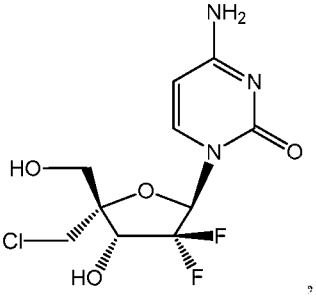
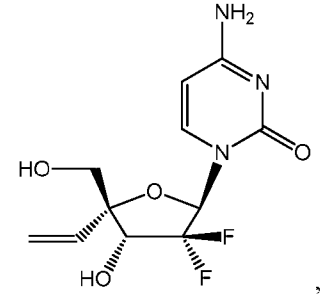

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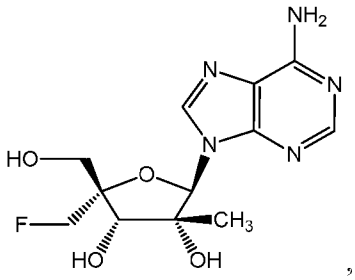
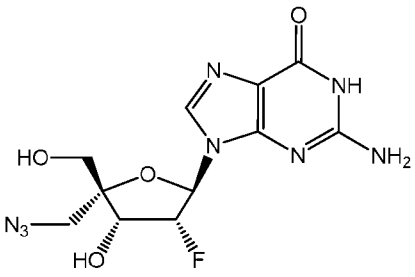
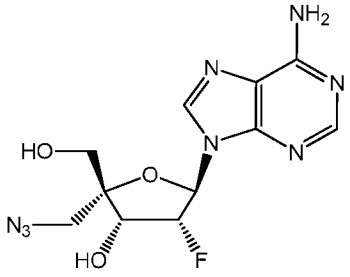
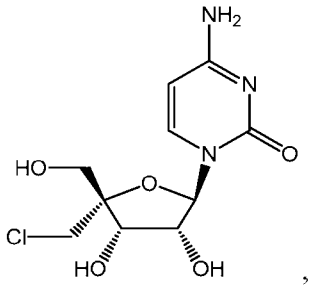
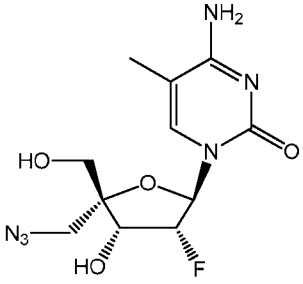
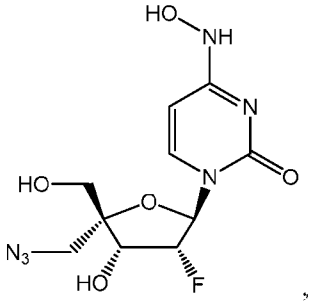
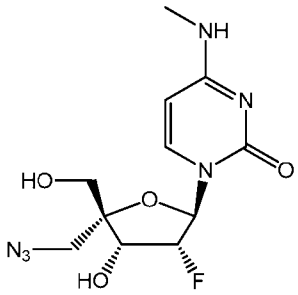
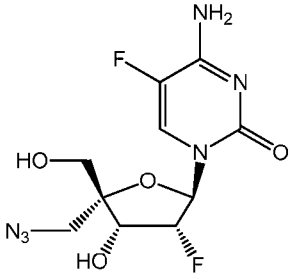
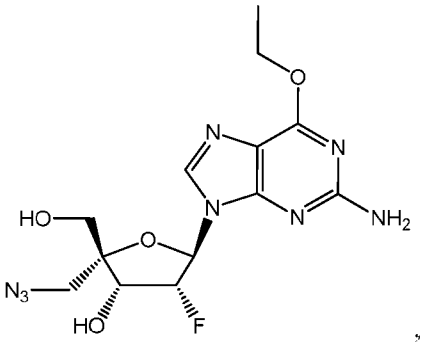
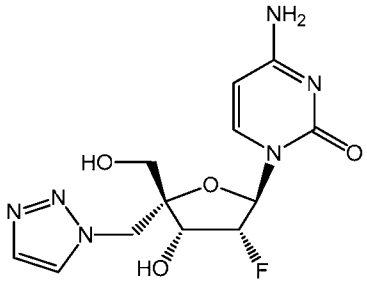
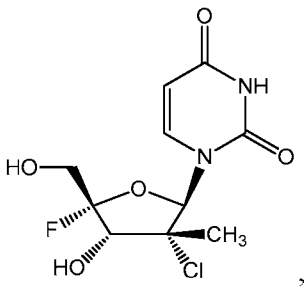
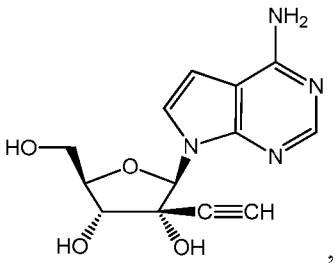
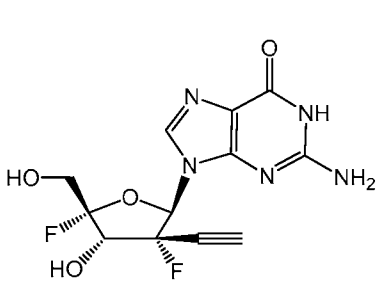
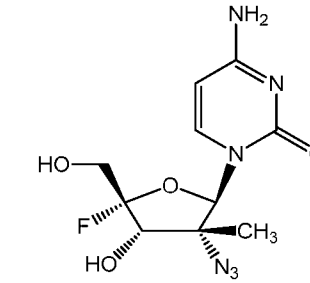
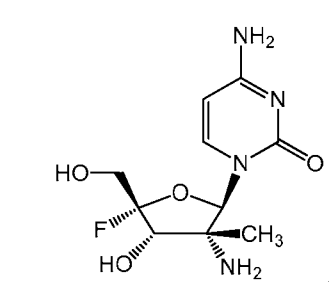
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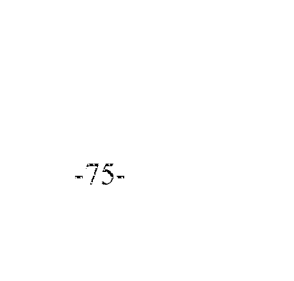

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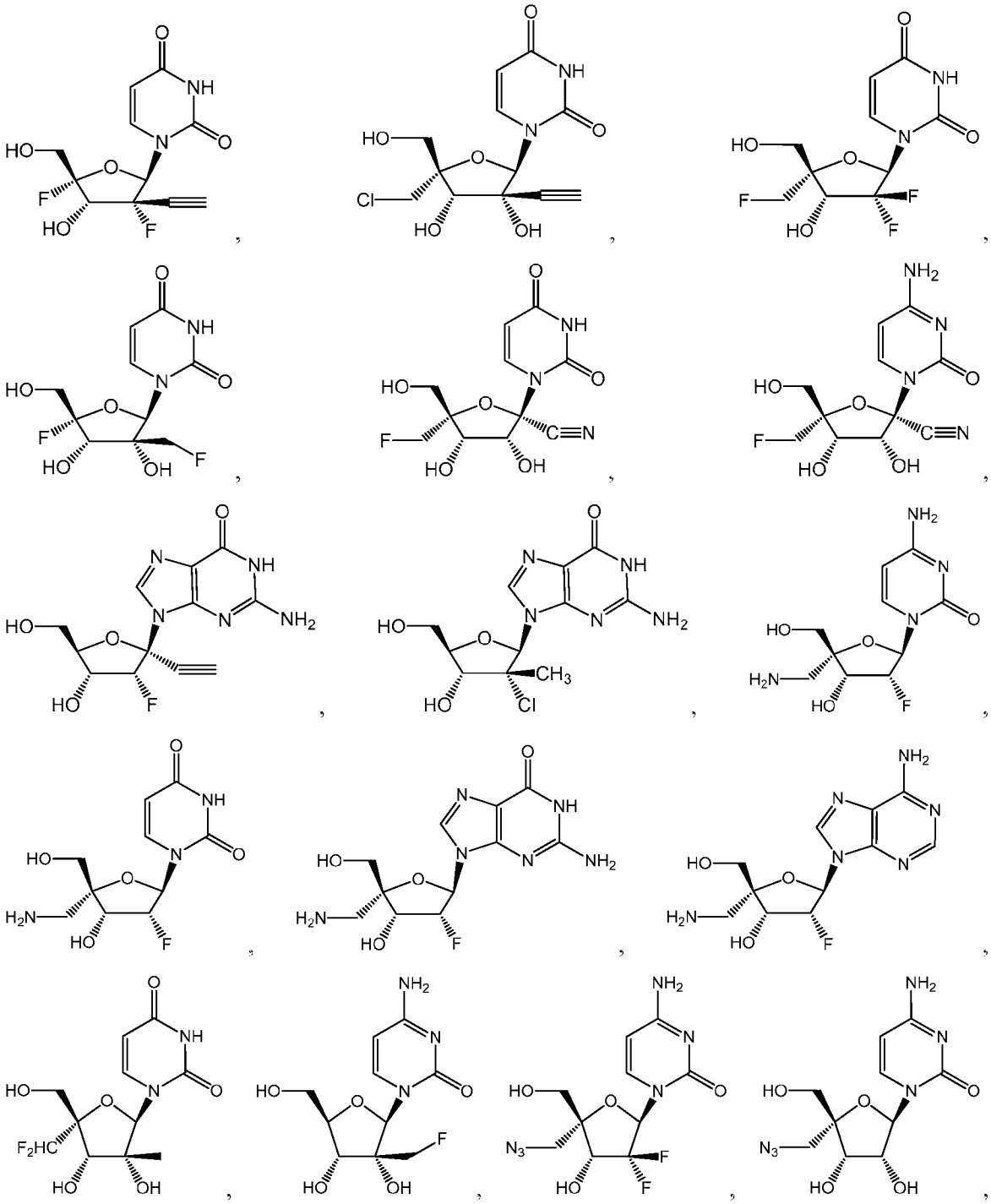
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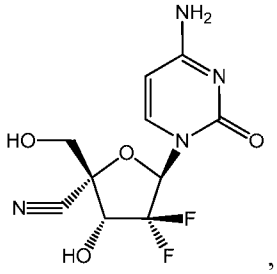
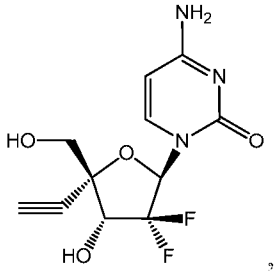
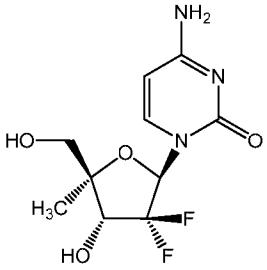
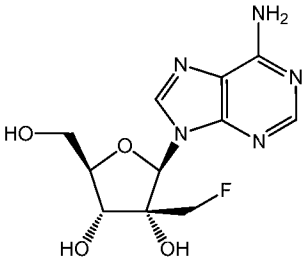
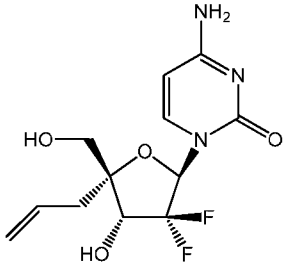
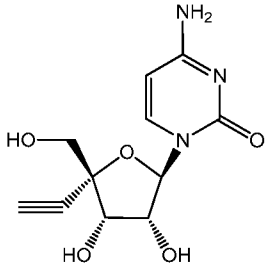
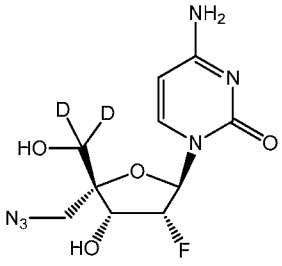
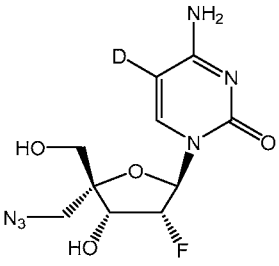
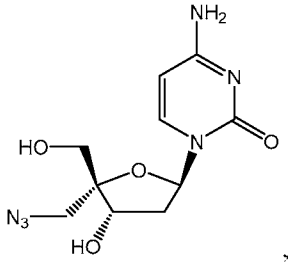
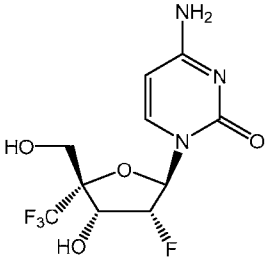
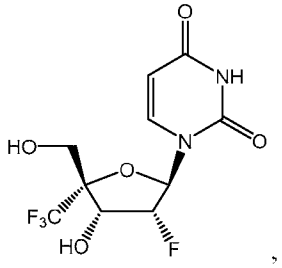
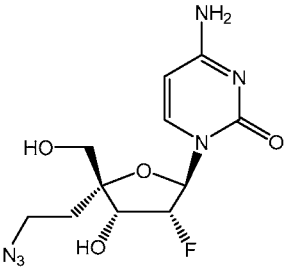
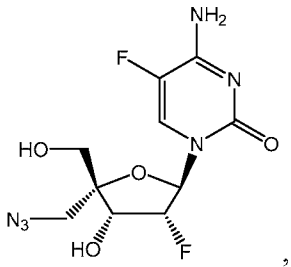
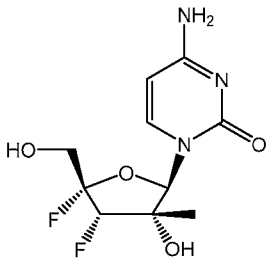
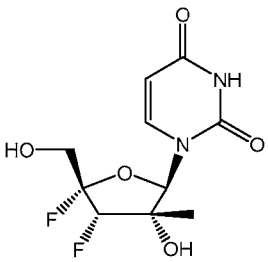
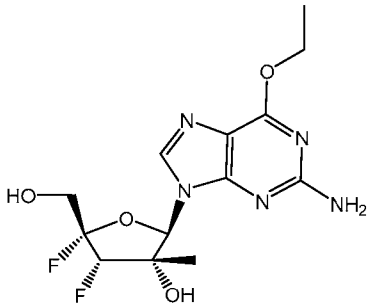
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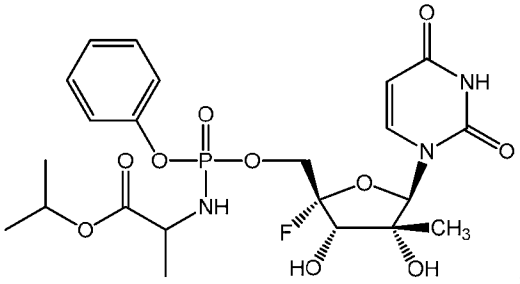
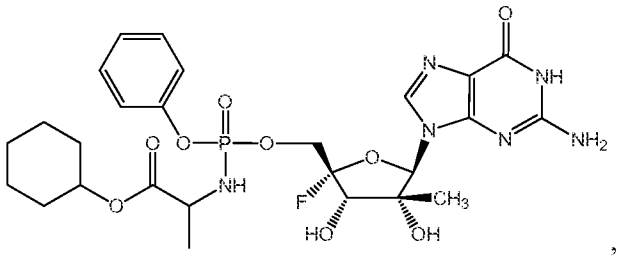
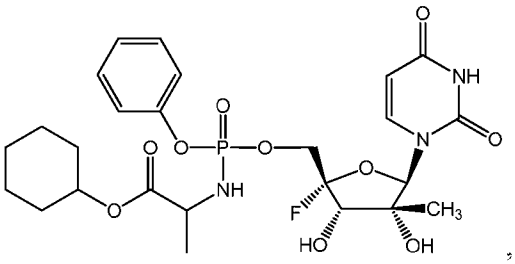
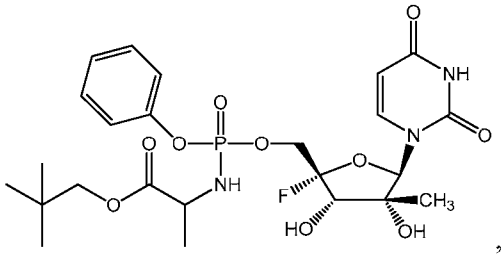
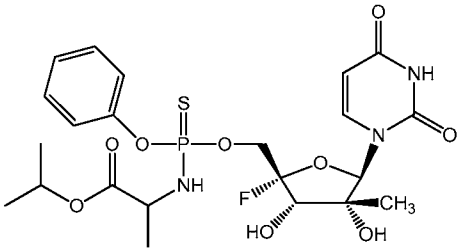
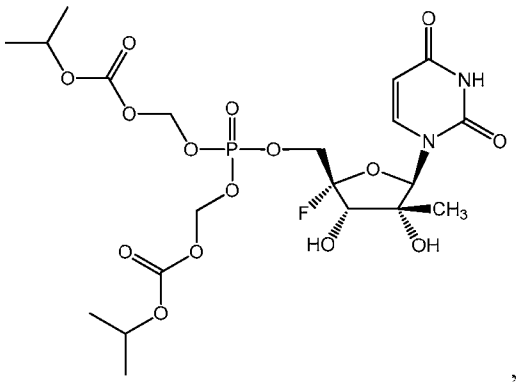
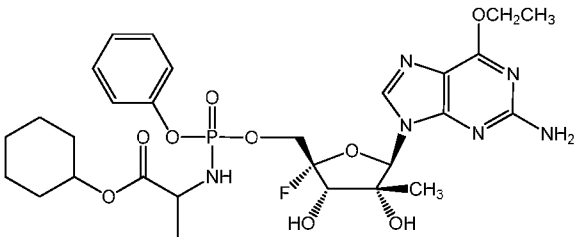
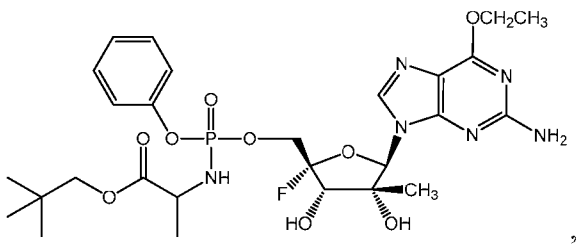
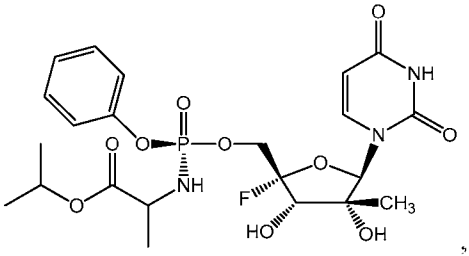
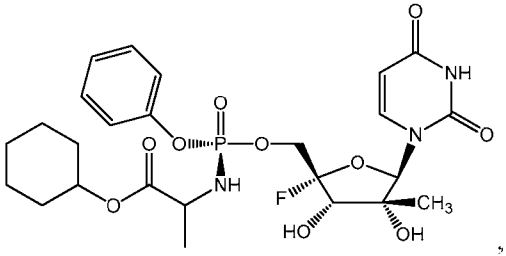
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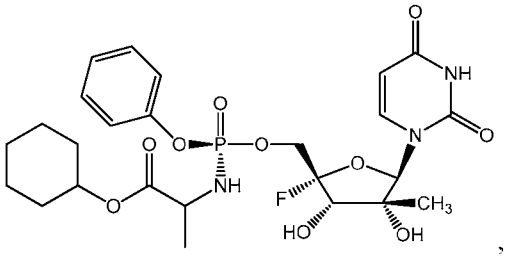
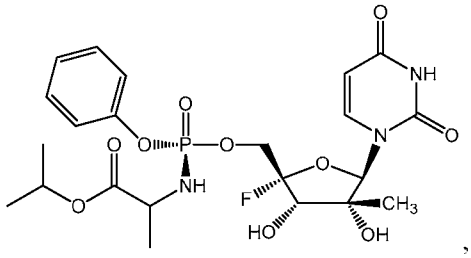
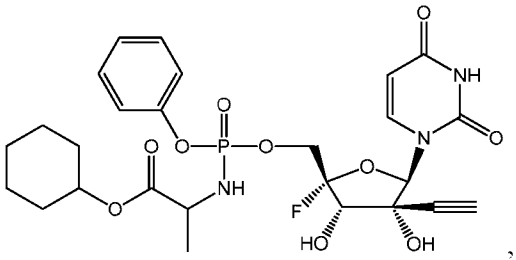
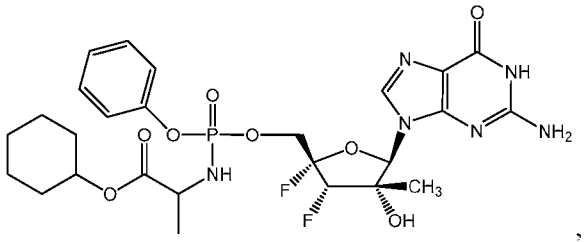
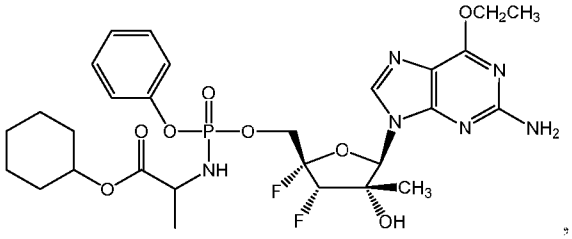
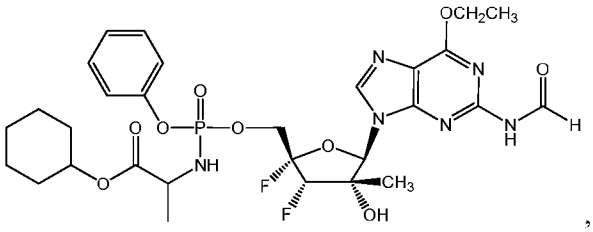
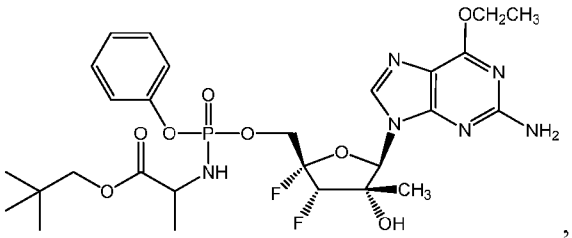
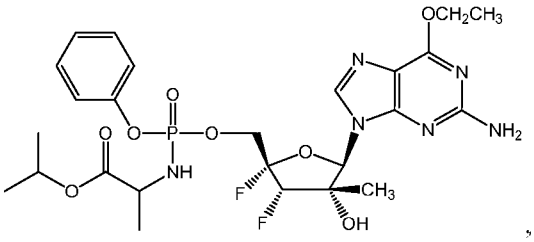
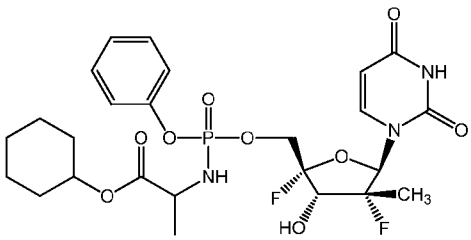
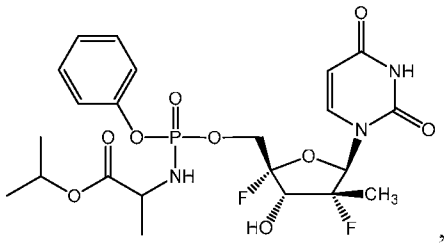
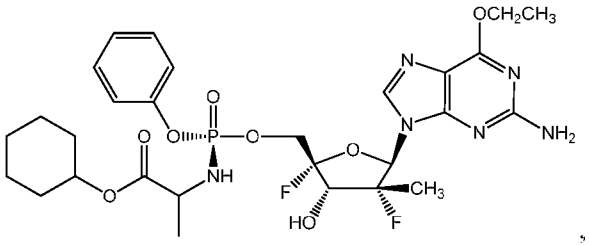
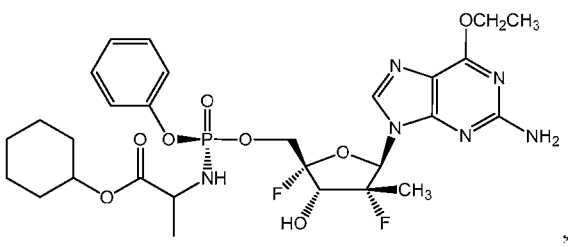
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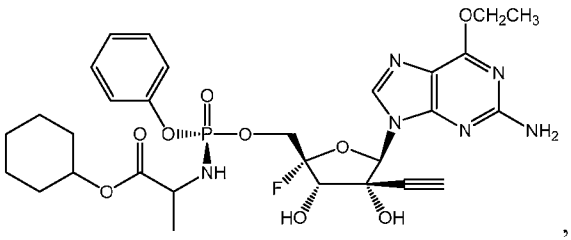


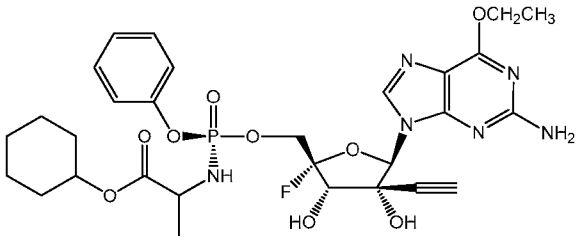

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, or a pharmaceutically acceptable salt of the foregoing.

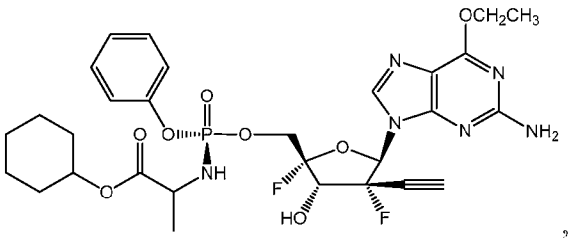
[0170] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, may be selected from:

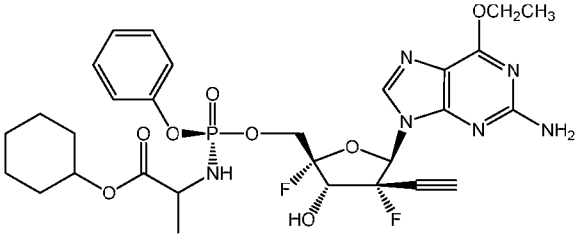

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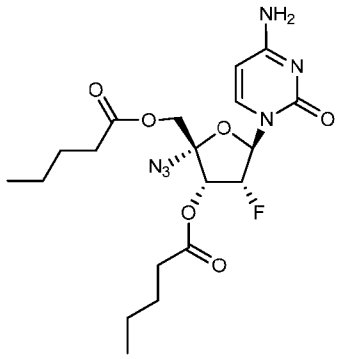

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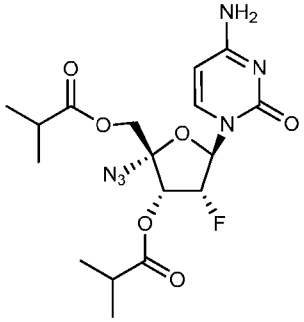

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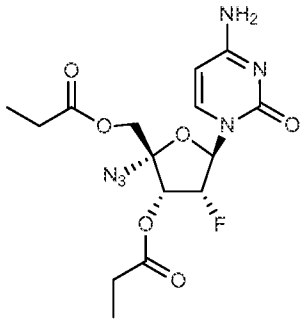

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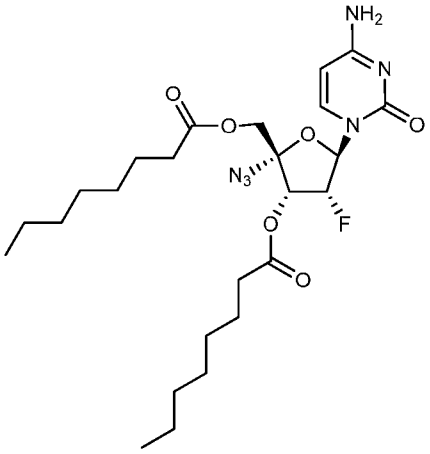

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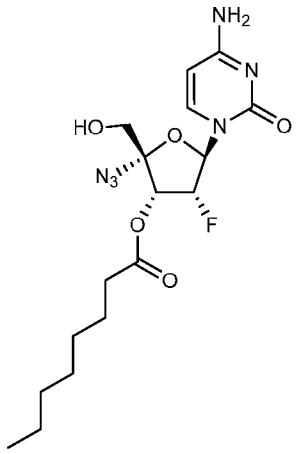

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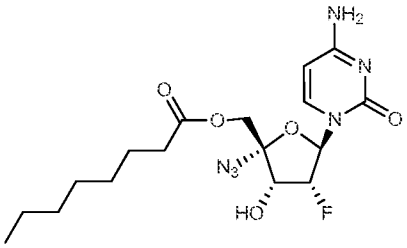
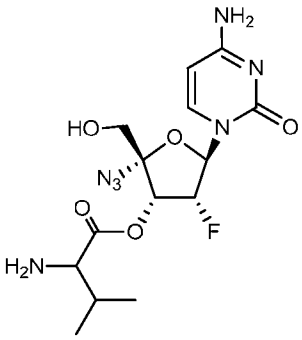
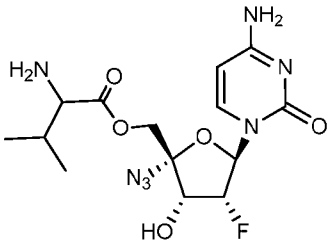
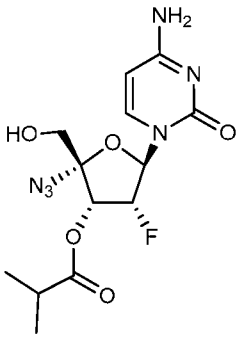
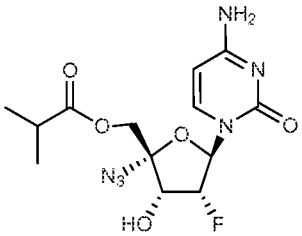
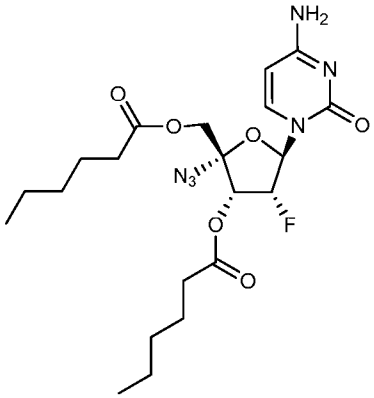
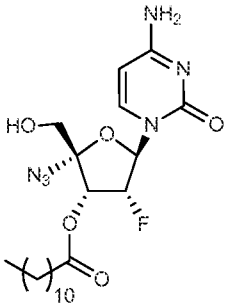
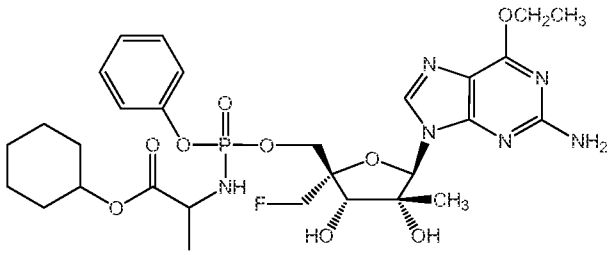
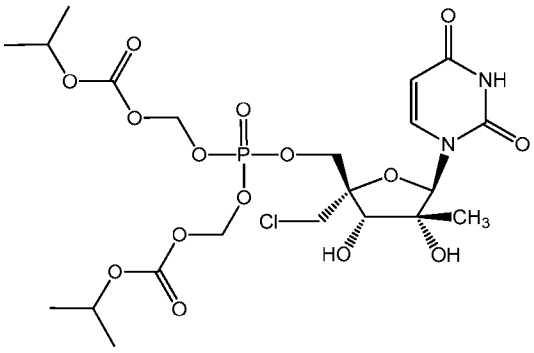
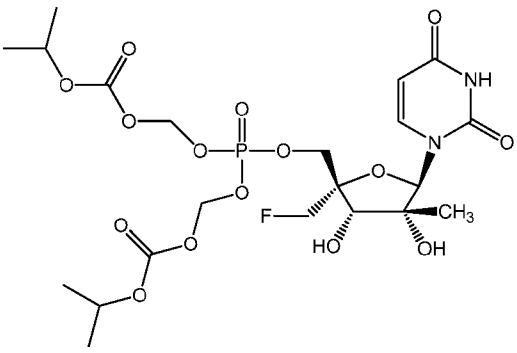

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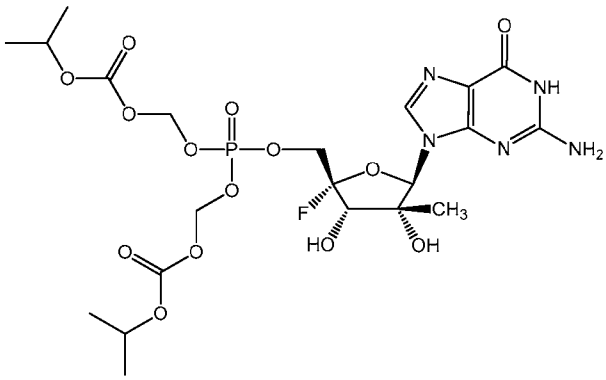

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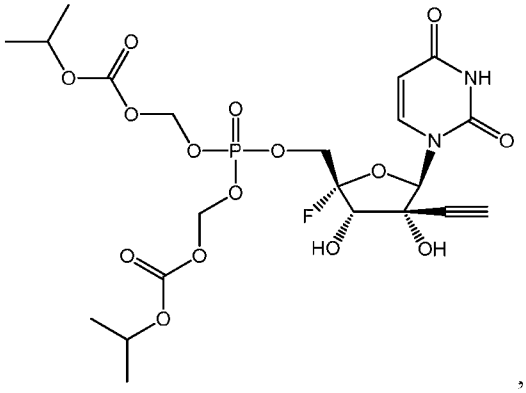

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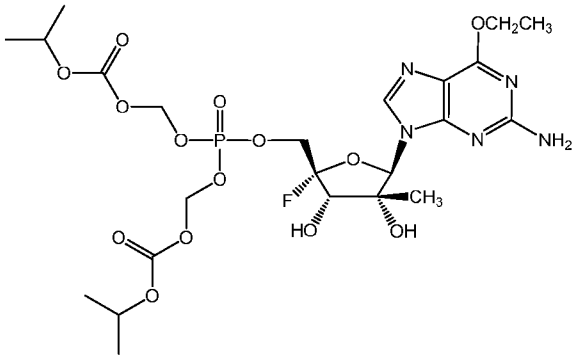

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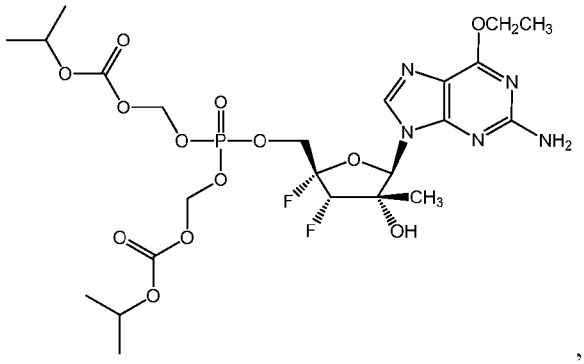
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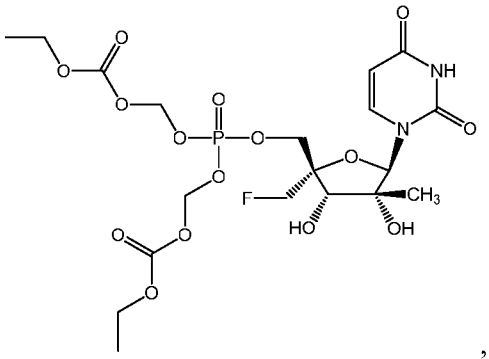
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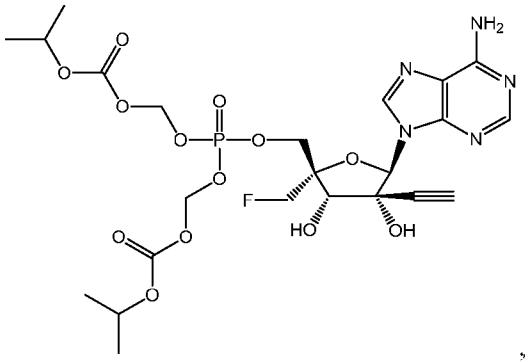
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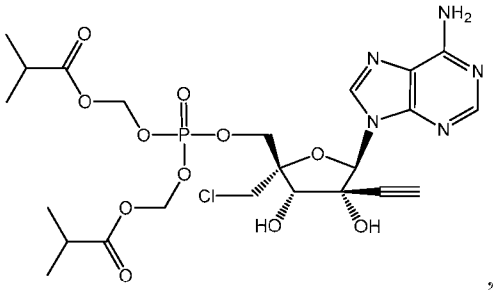
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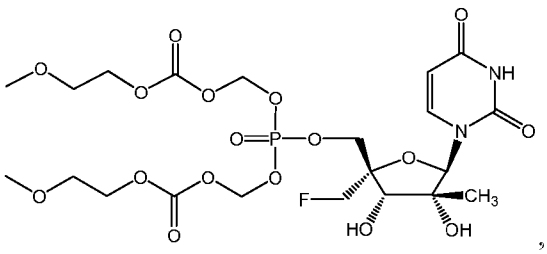
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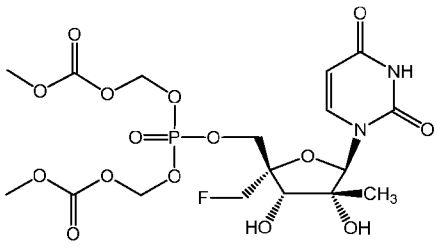
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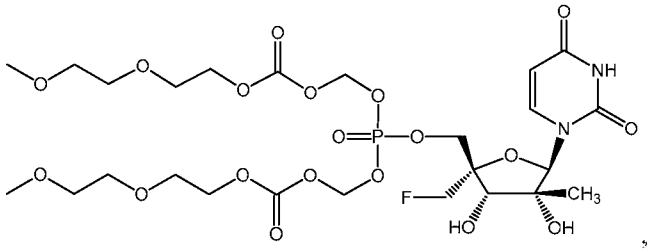
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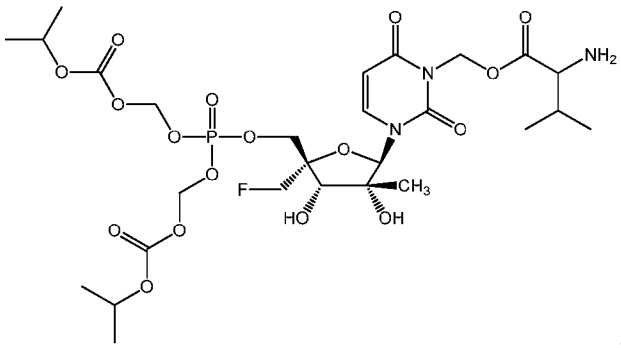
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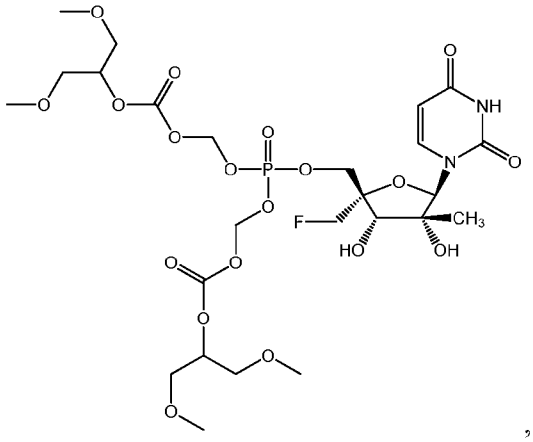
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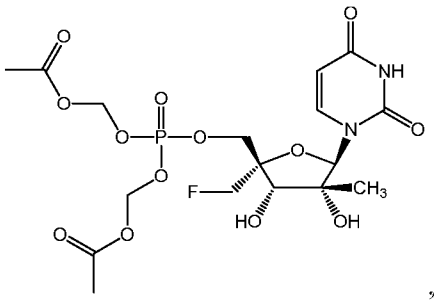
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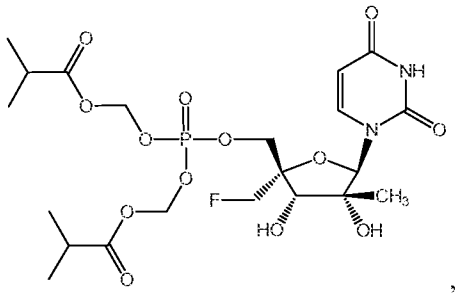
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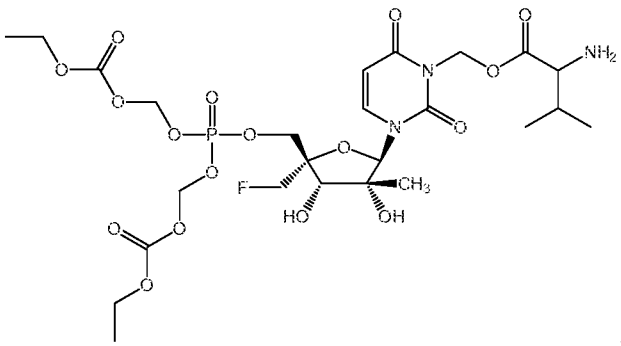
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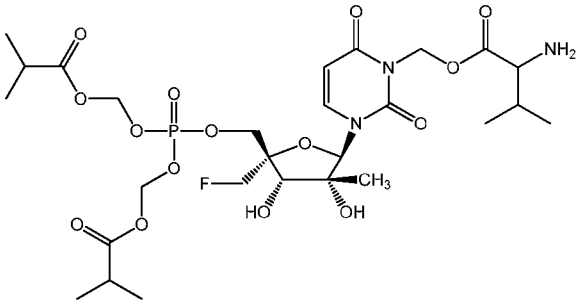
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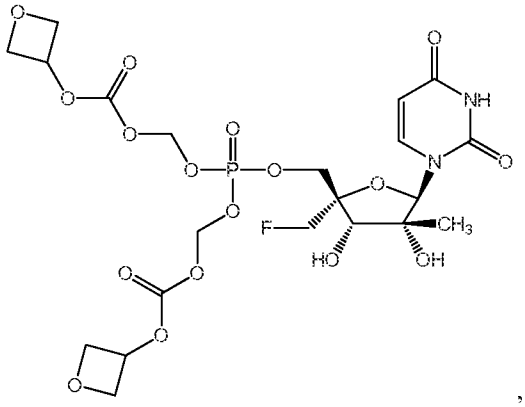
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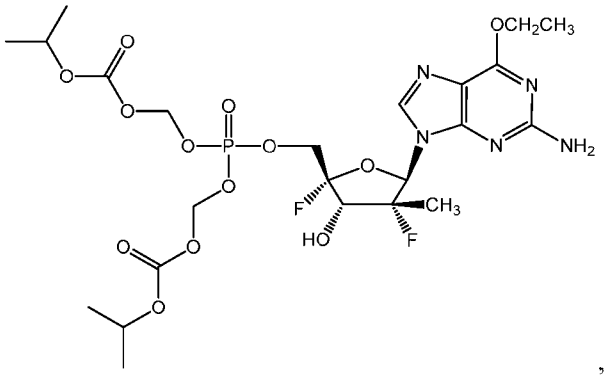
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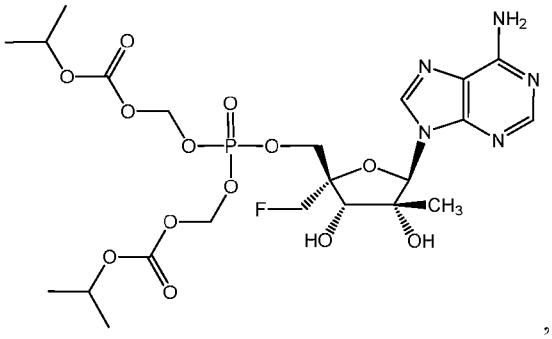
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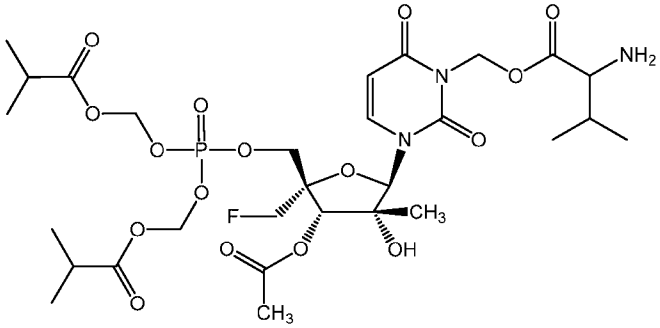
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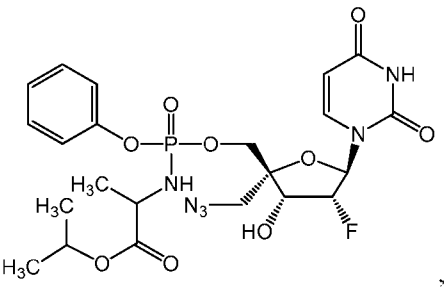
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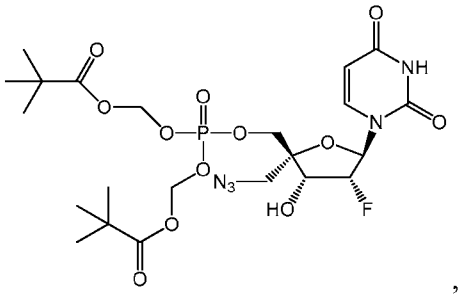
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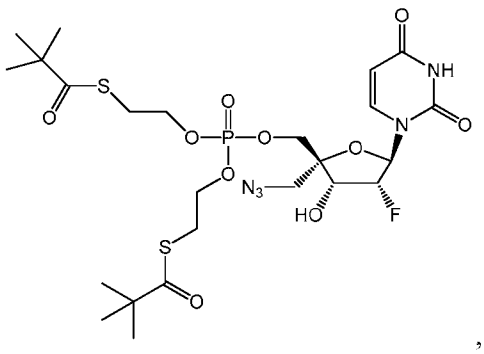
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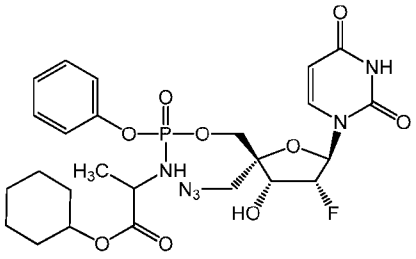
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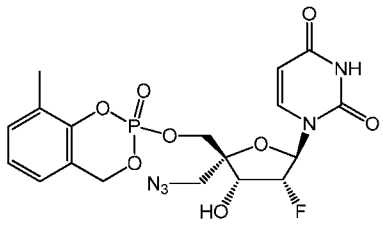
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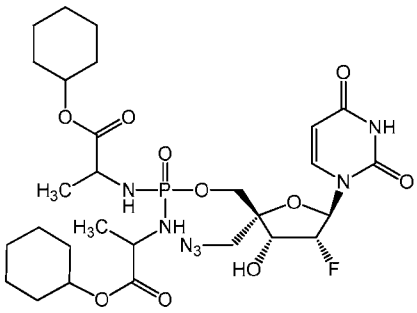
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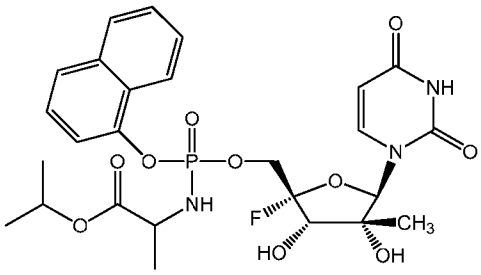
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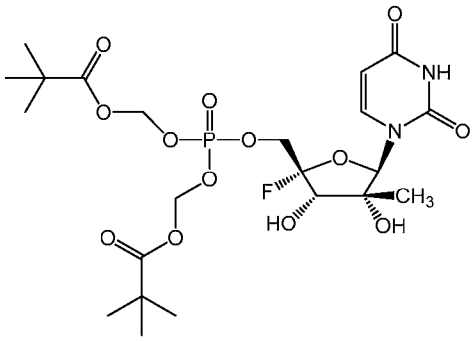
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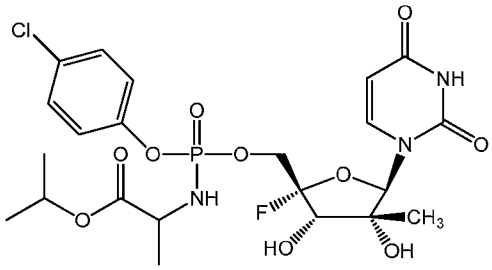
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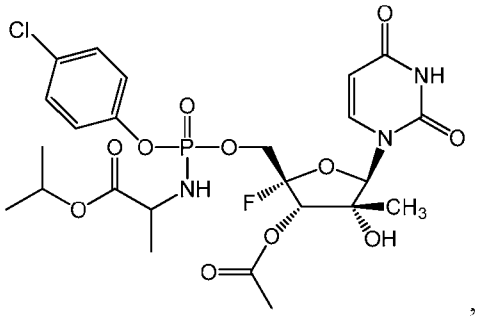
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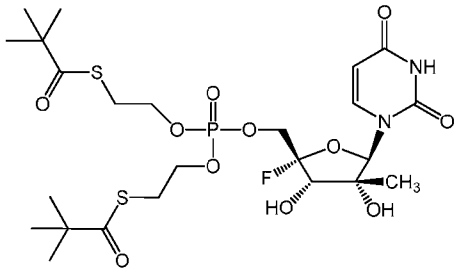
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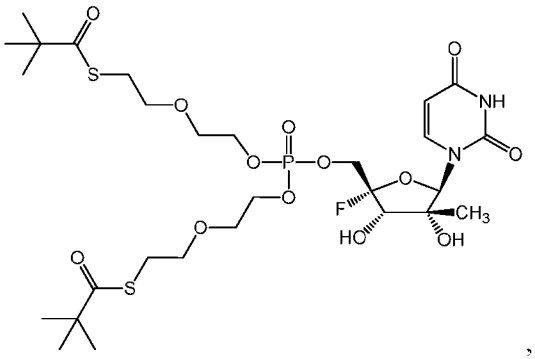
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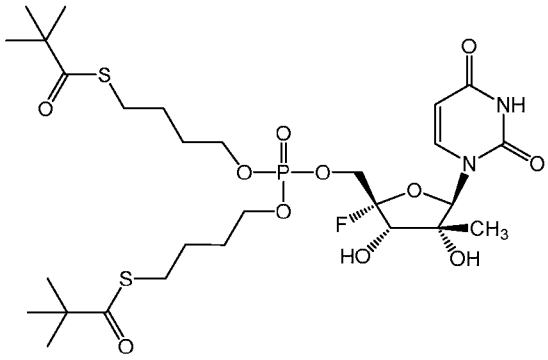
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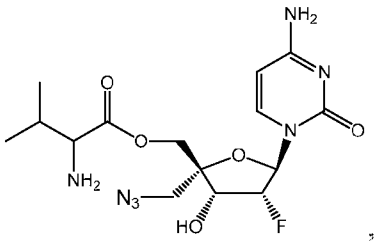
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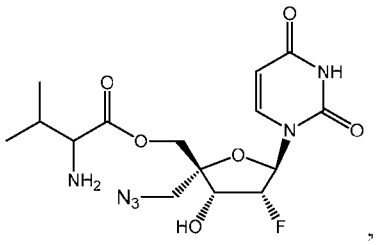


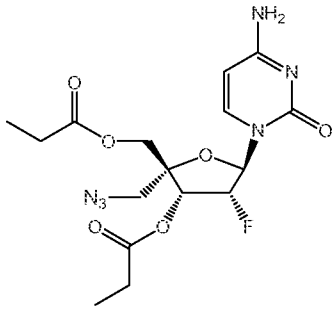
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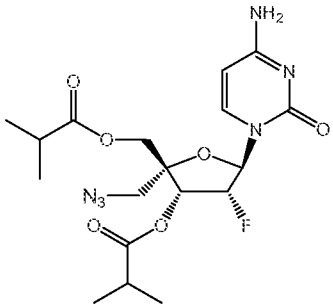


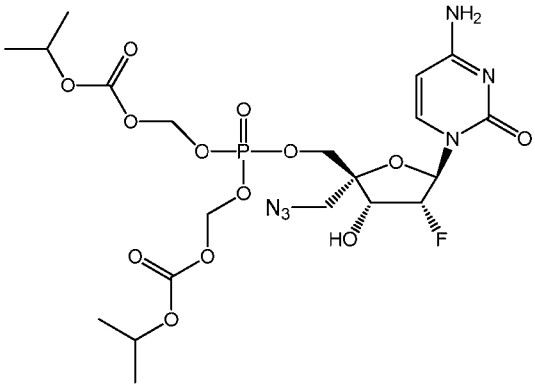
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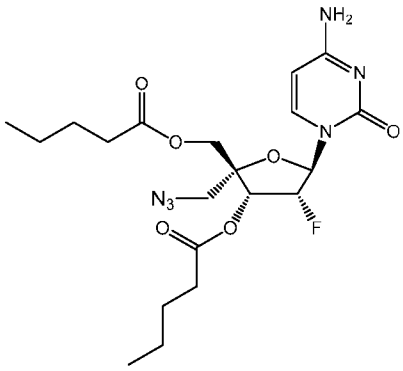


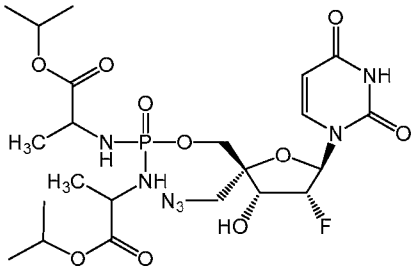


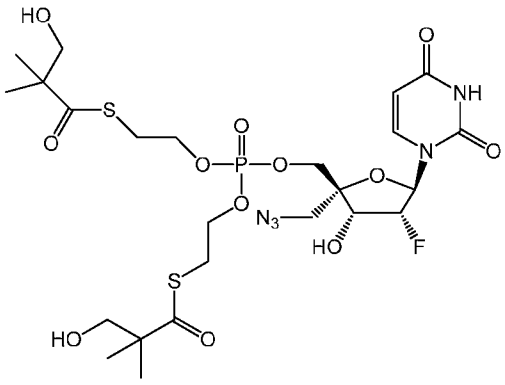


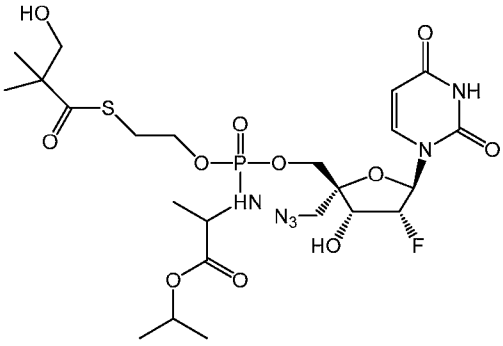


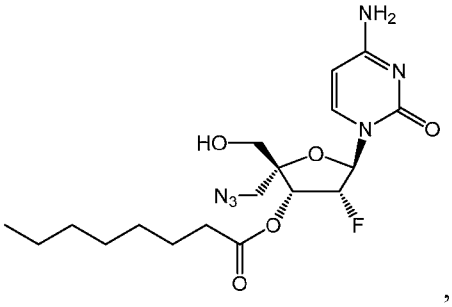




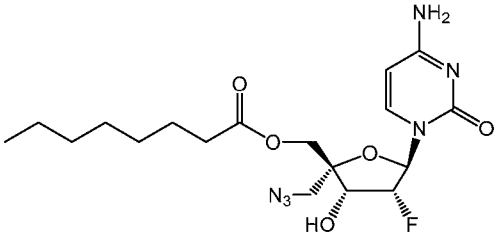




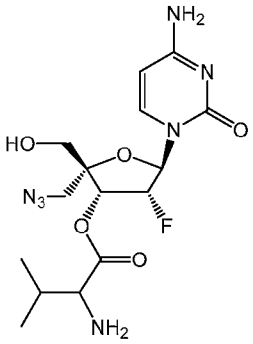




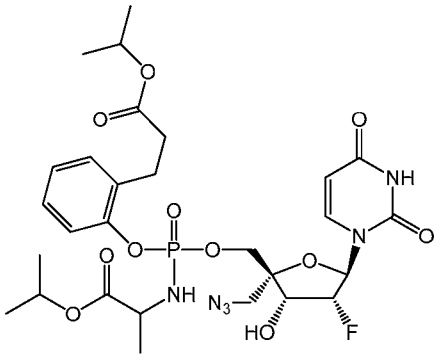
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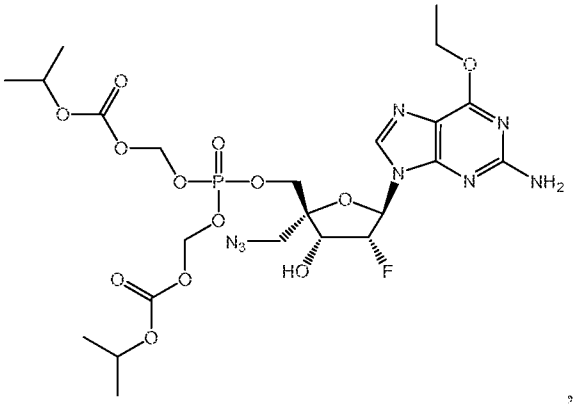
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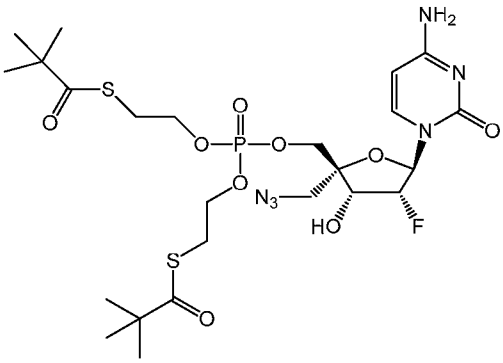
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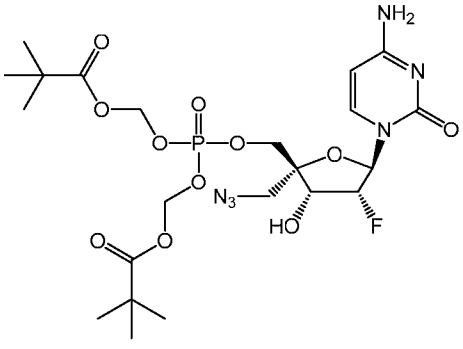
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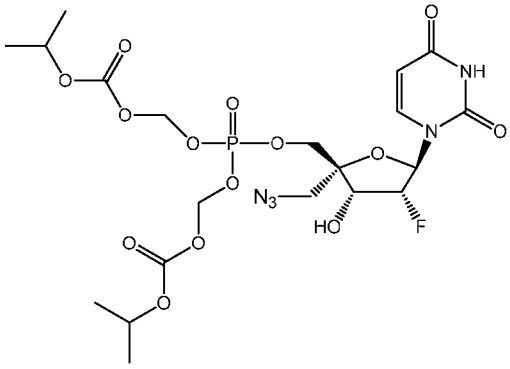
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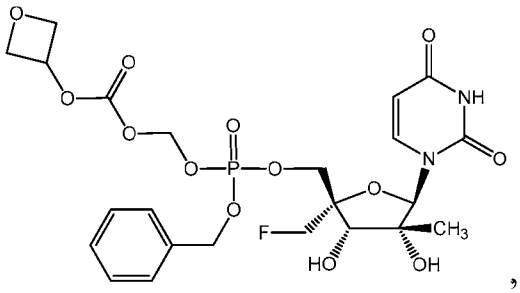
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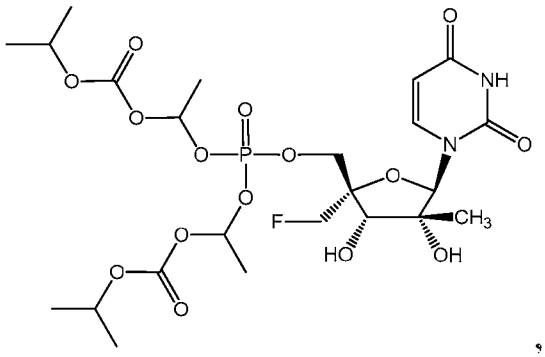
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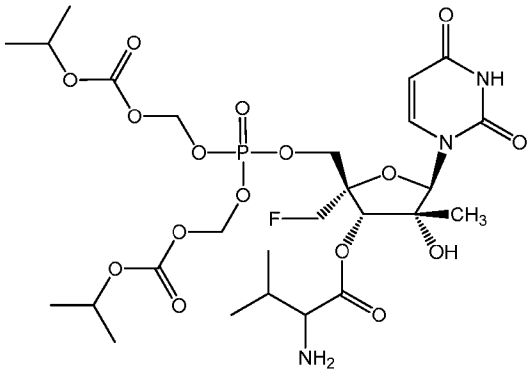
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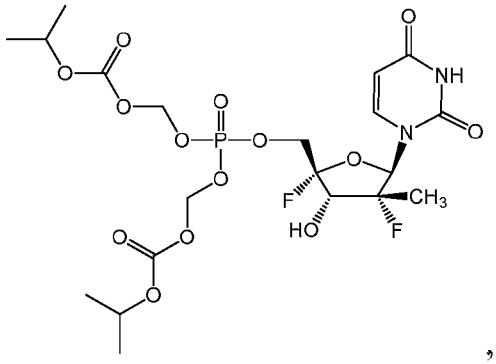
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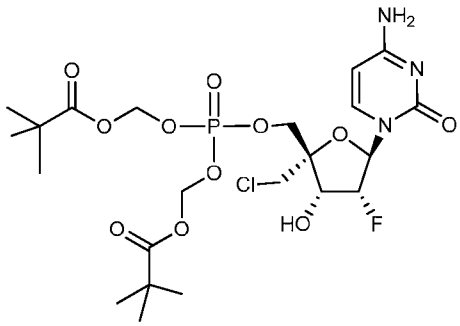
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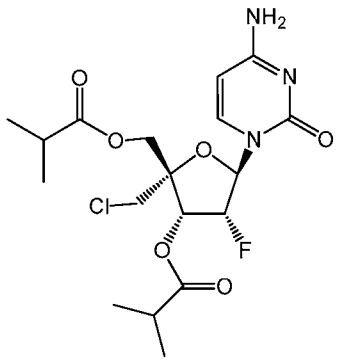
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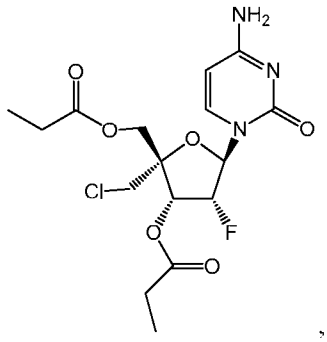
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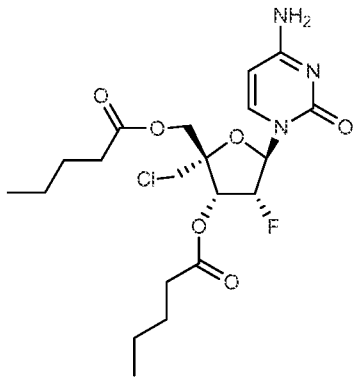
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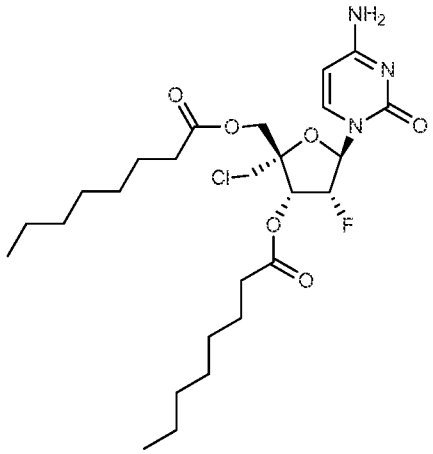
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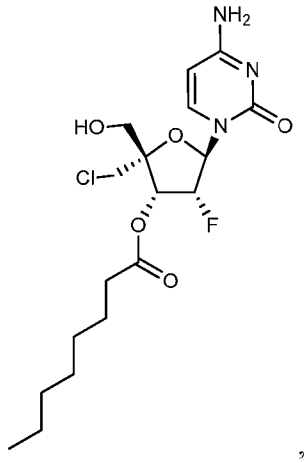
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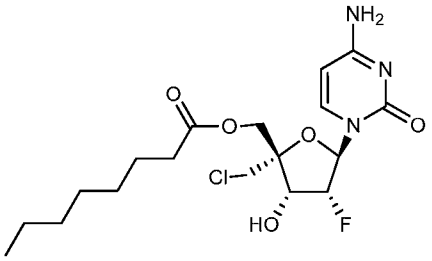
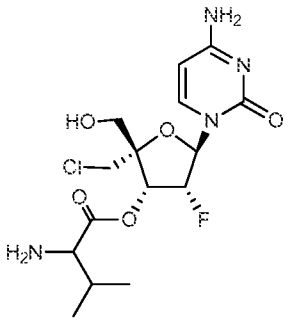
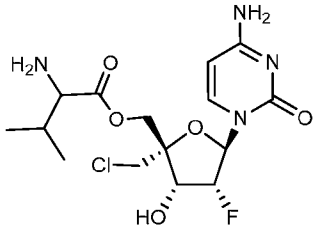
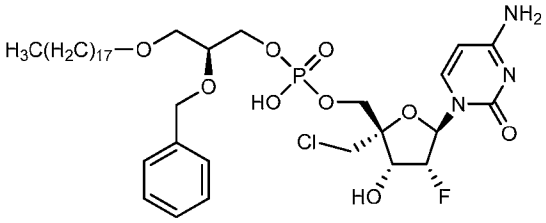
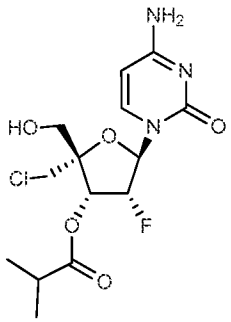
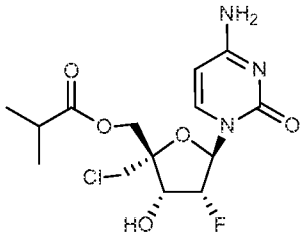
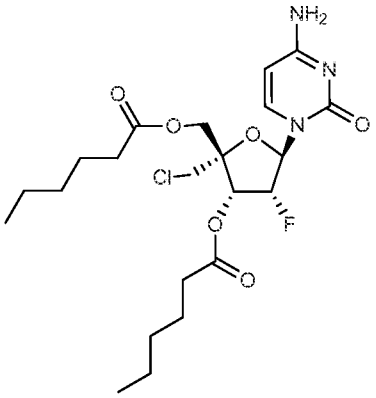
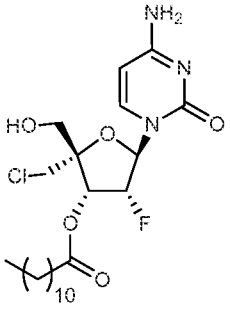
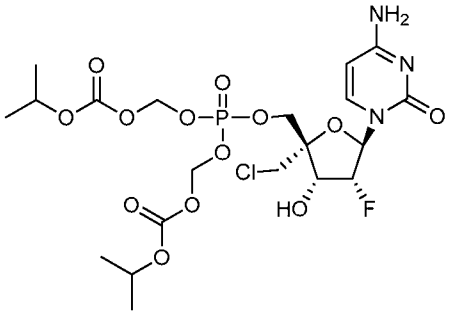
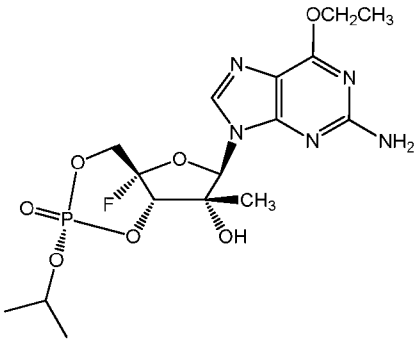
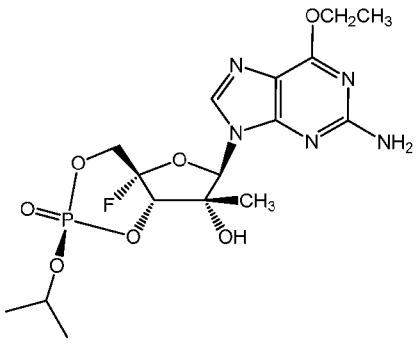
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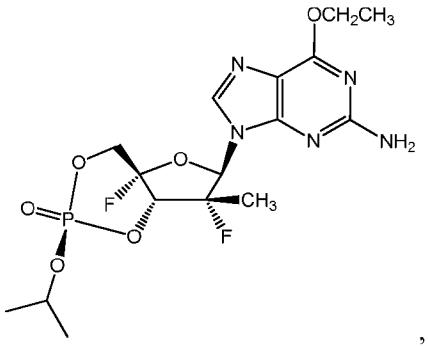


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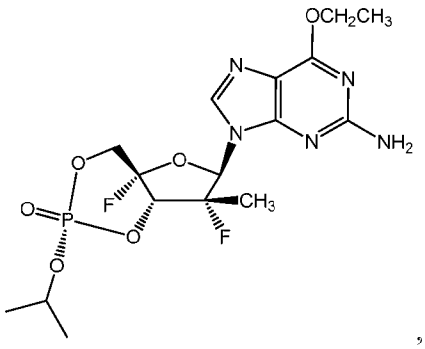


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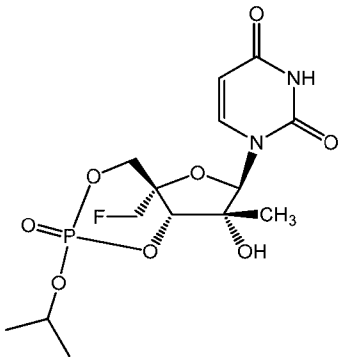

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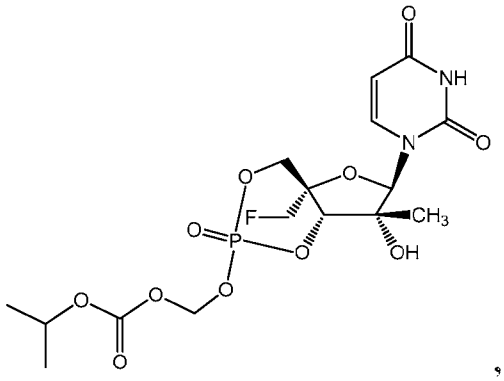
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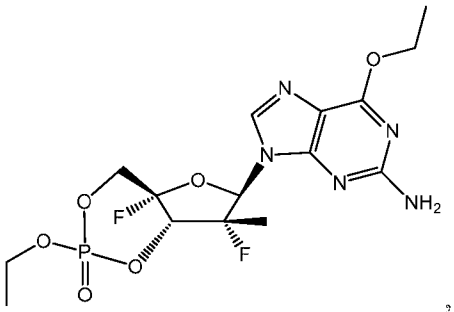
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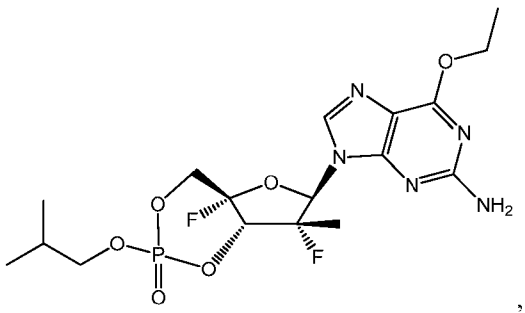
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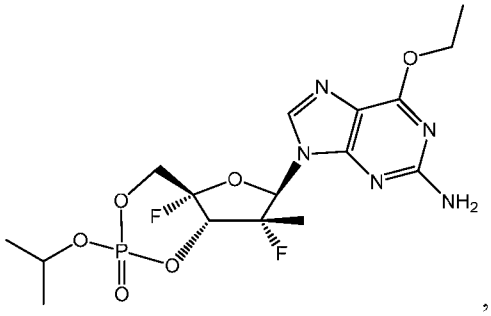
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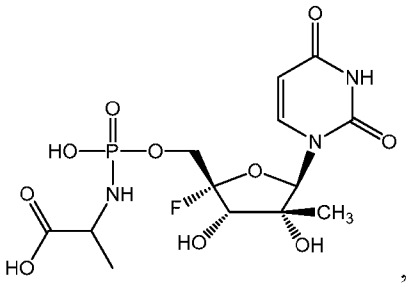
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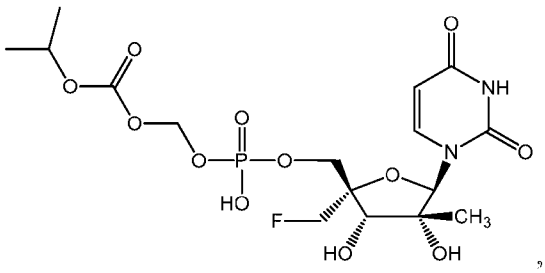
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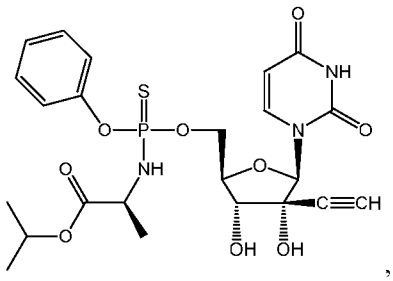


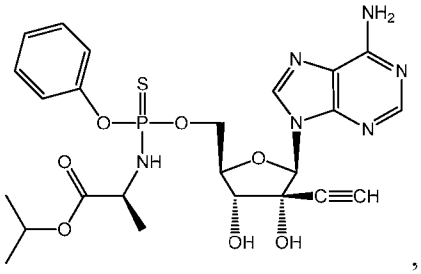
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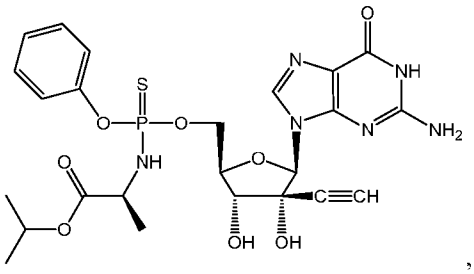


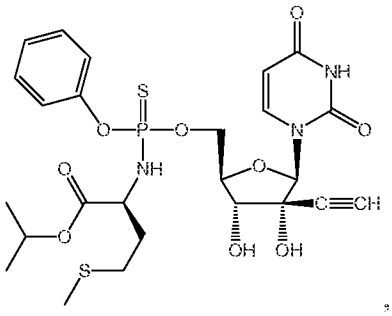
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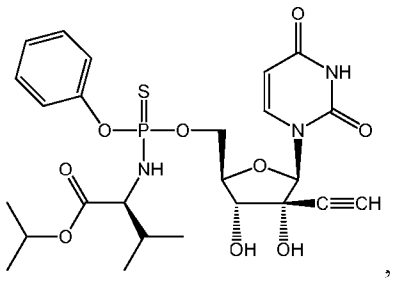


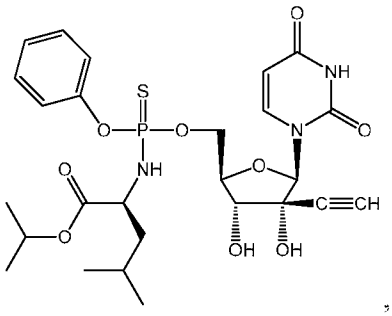


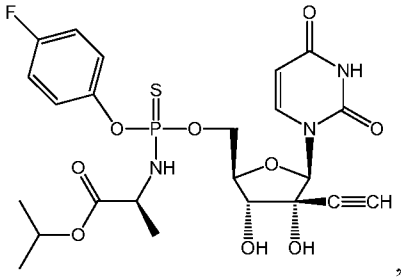


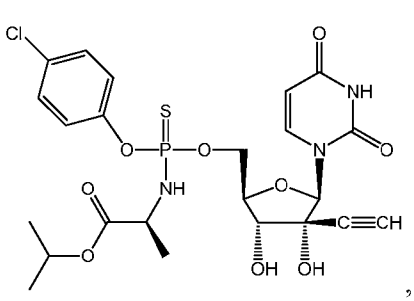


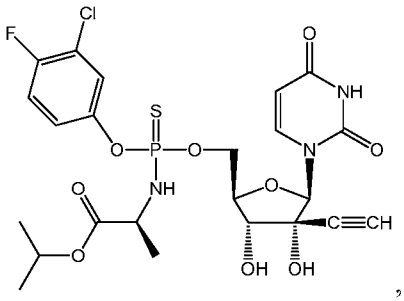


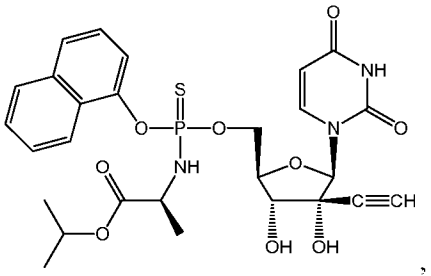




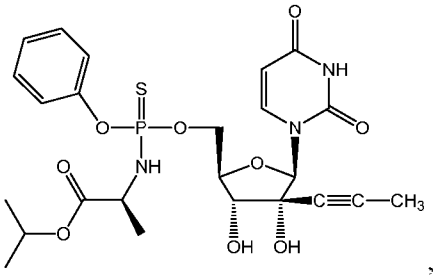




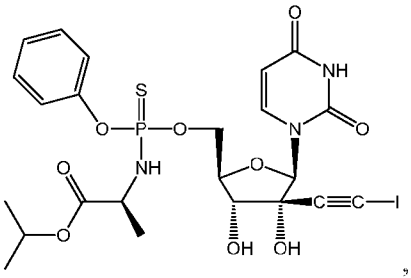




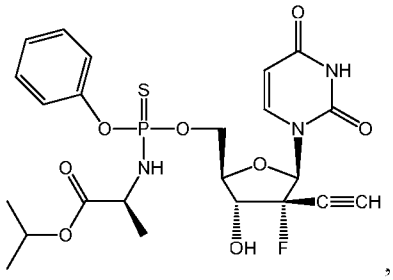
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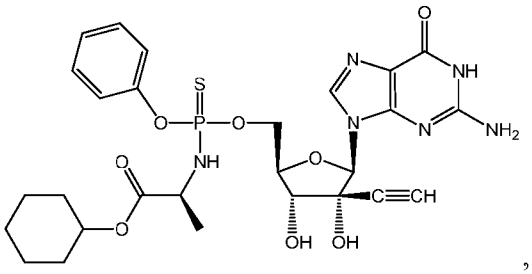
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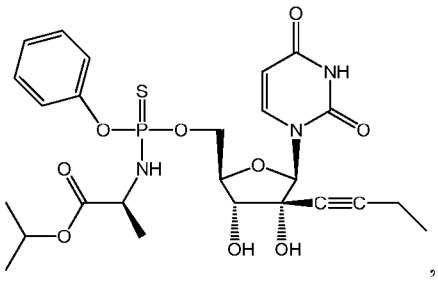
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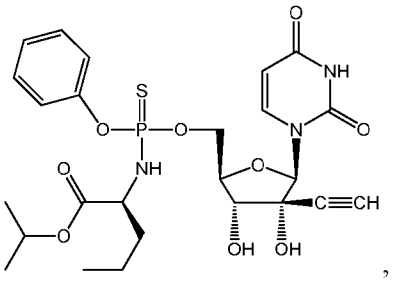
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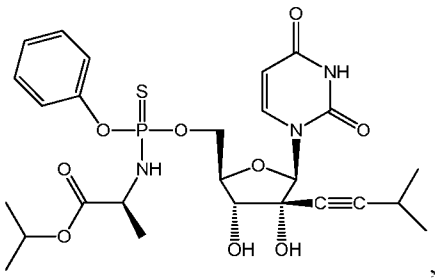
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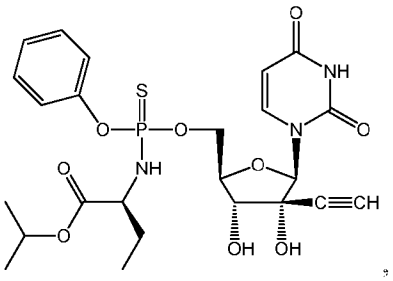
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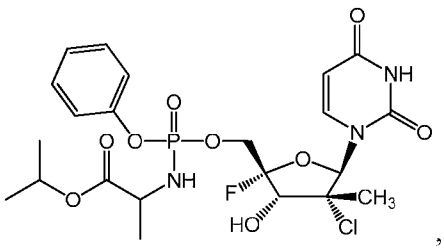
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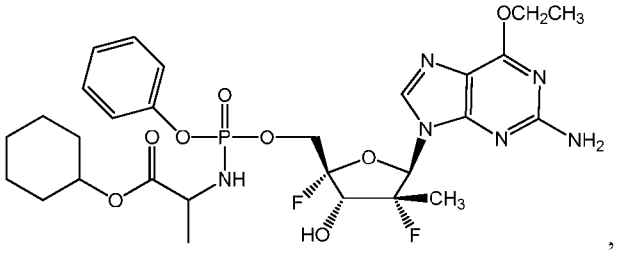
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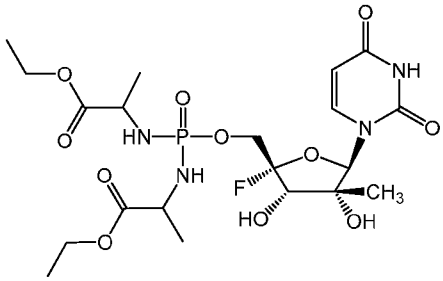
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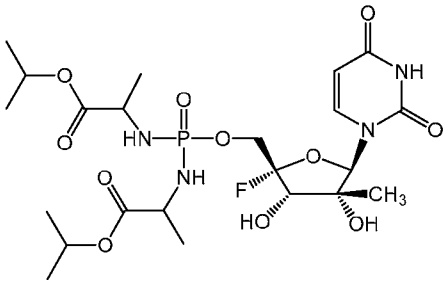
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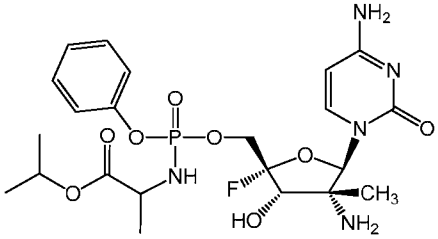
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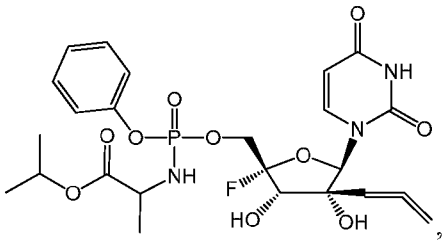
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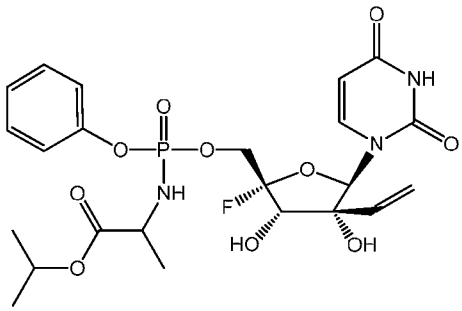
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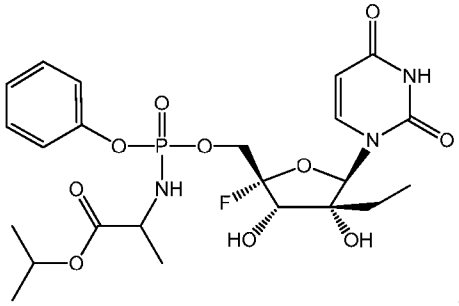
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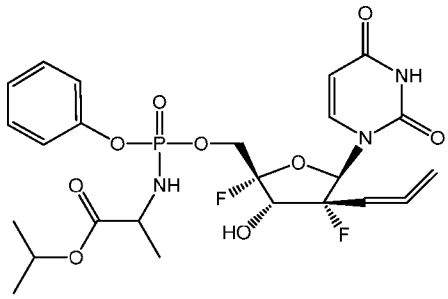
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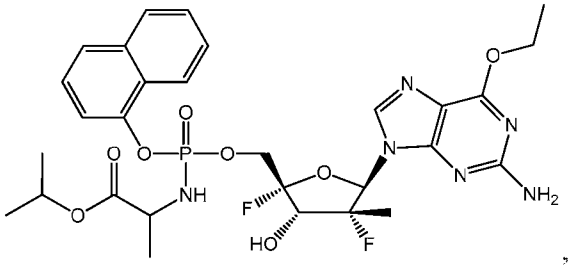
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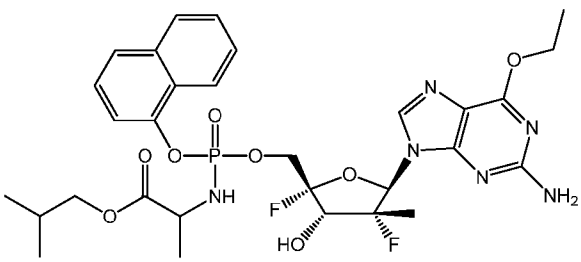
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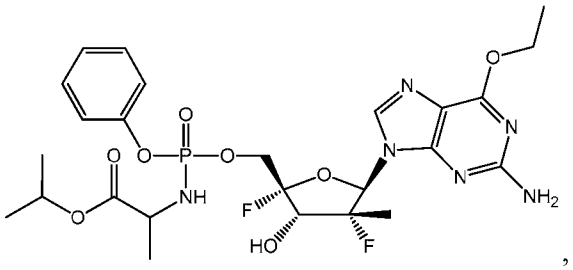
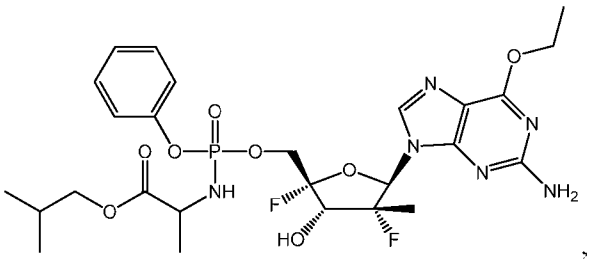
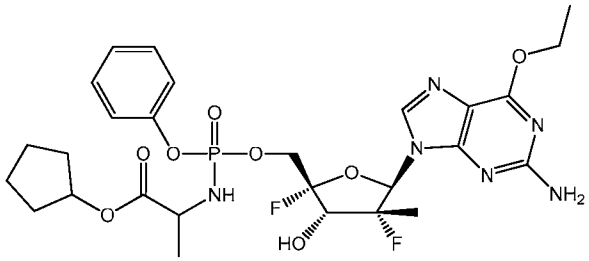
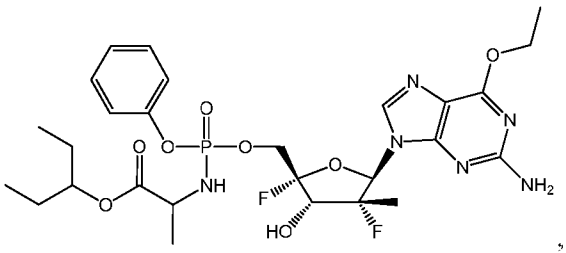
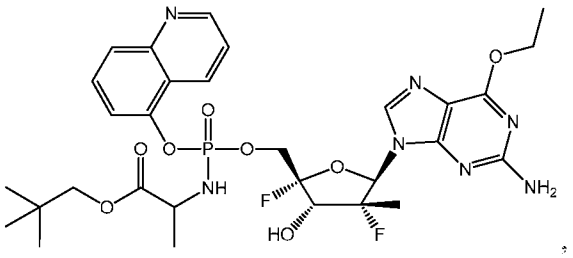
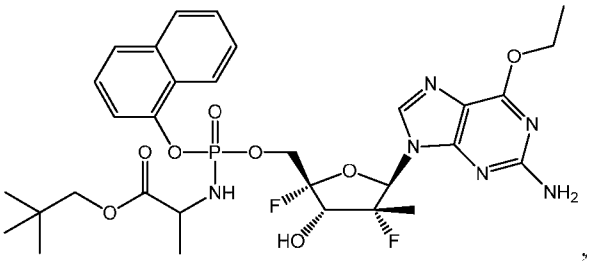
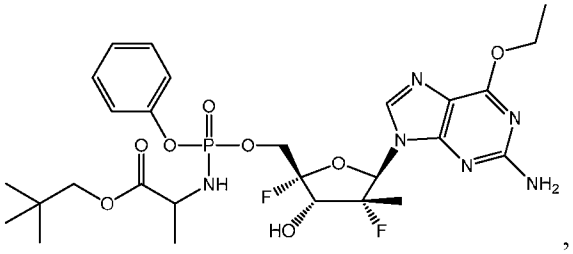
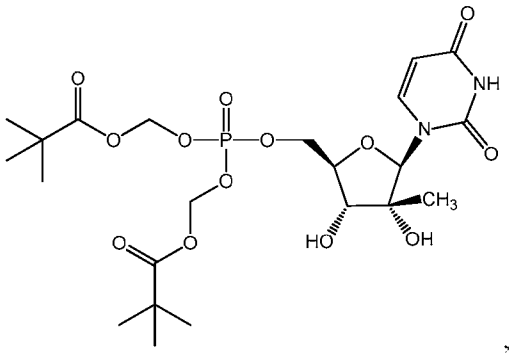
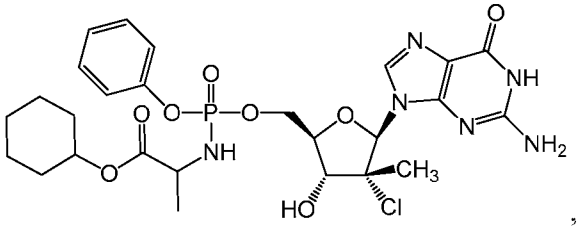
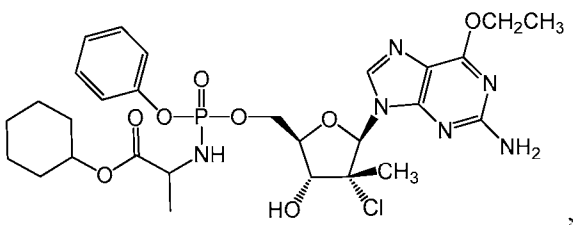
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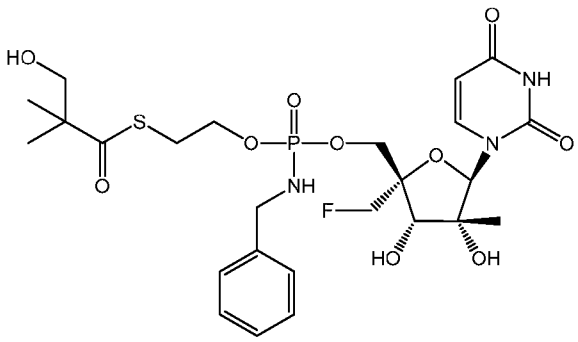
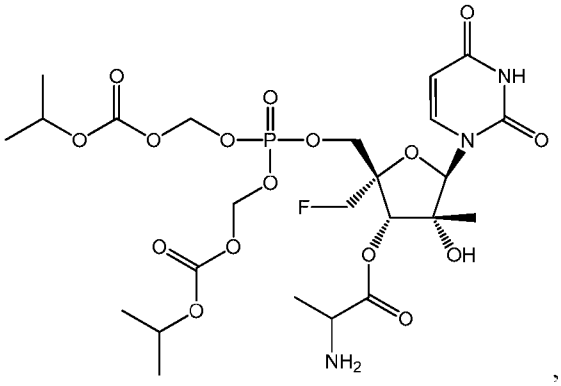
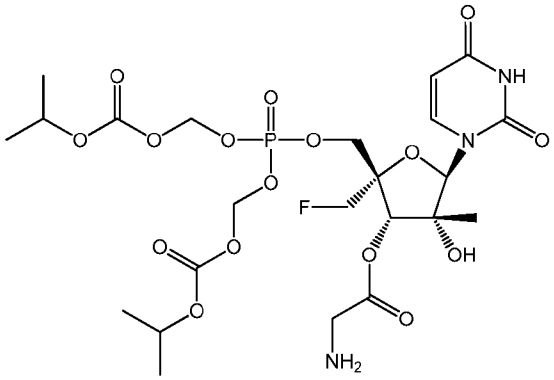
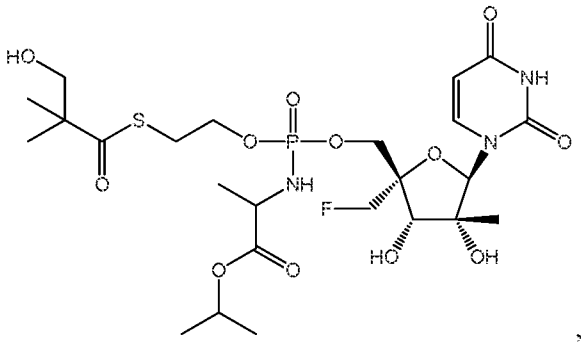
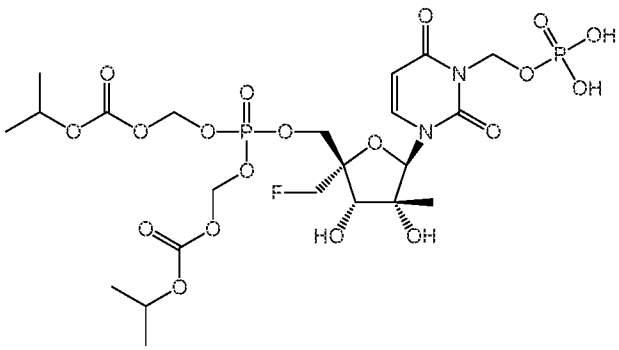
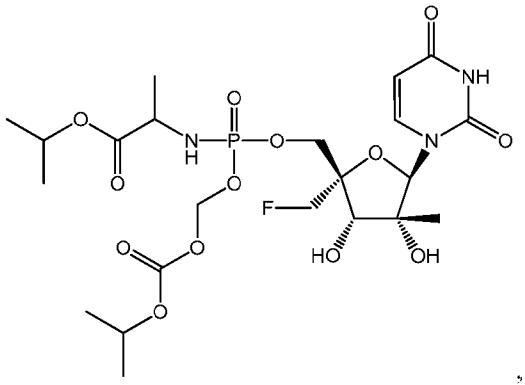
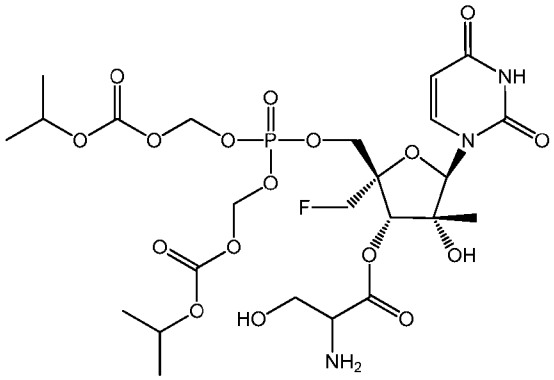
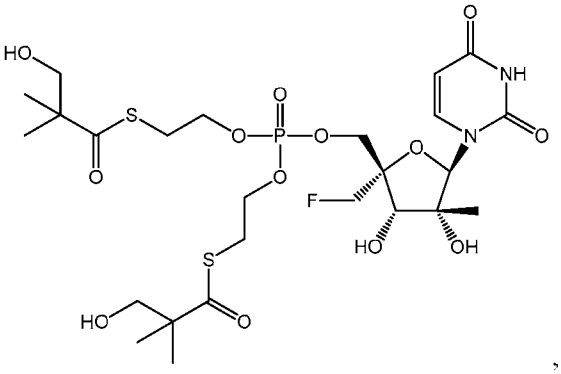


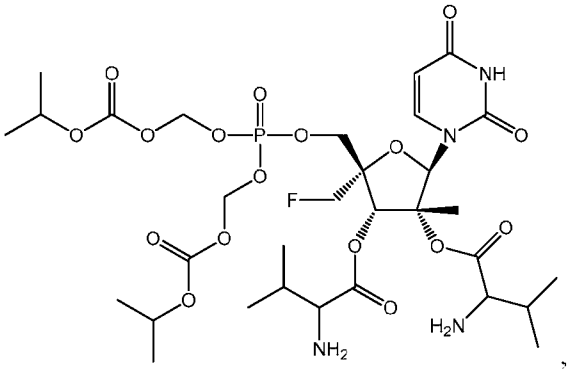
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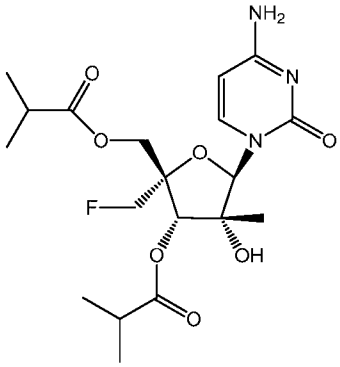
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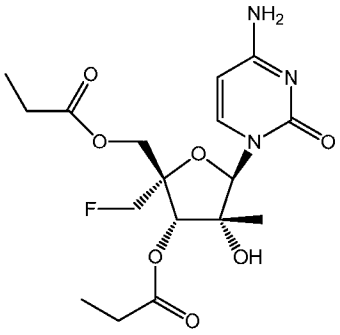

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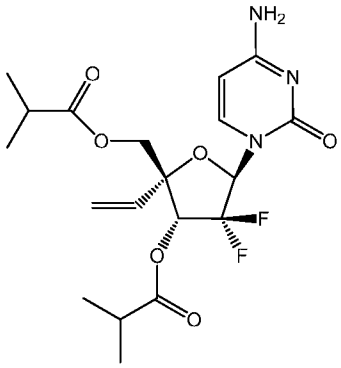
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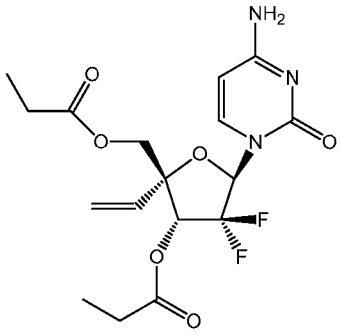
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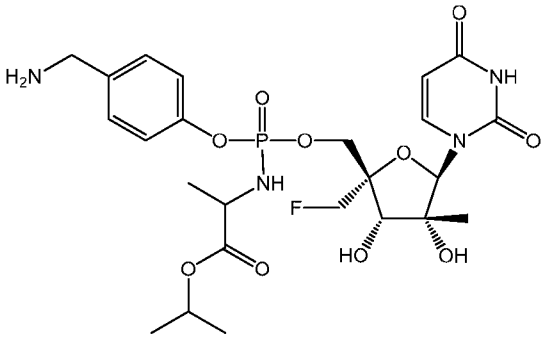
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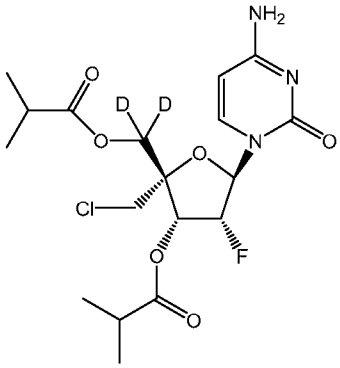
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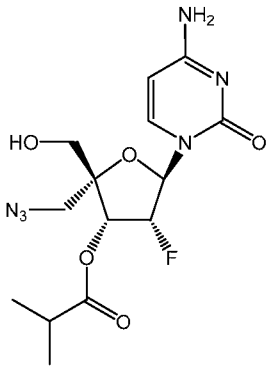
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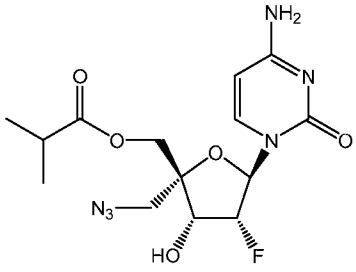
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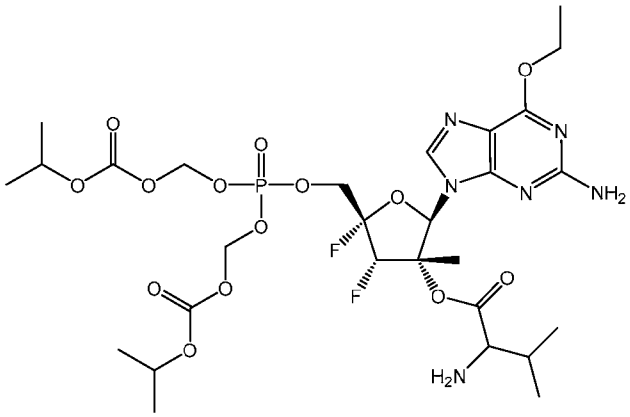
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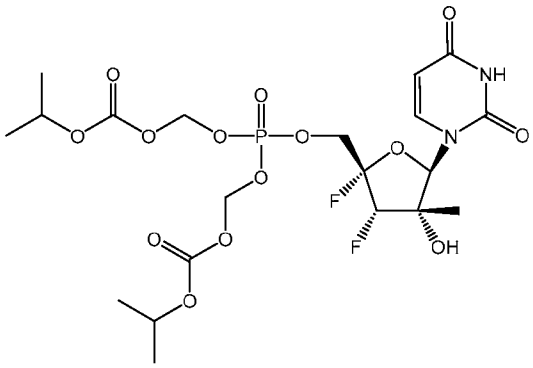
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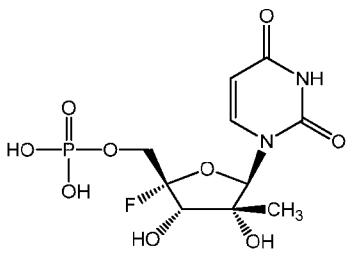


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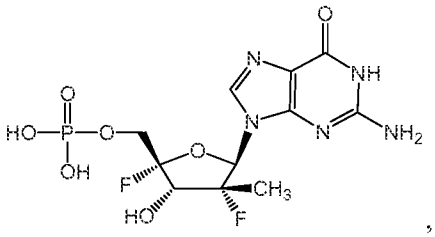


, or a pharmaceutically acceptable salt of the foregoing.

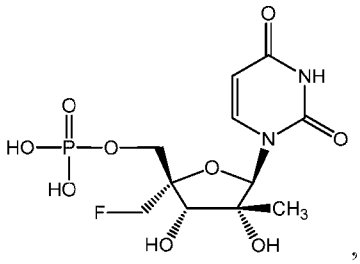
[0171] In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt thereof, may be selected from:



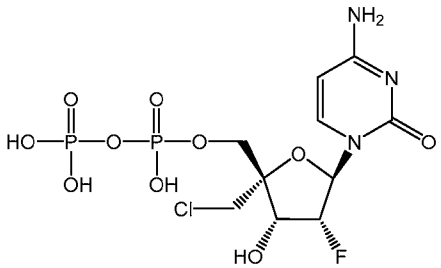
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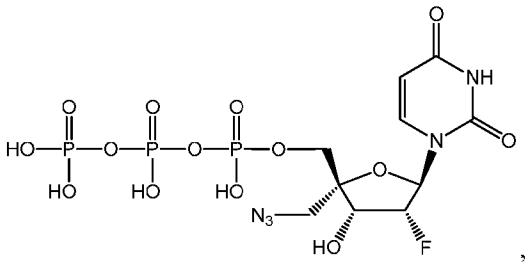
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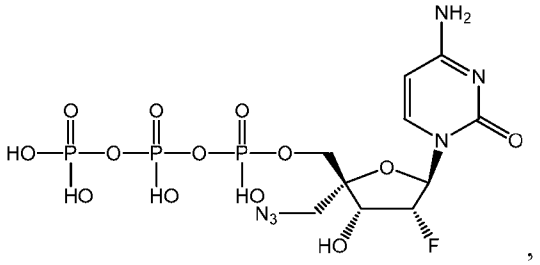
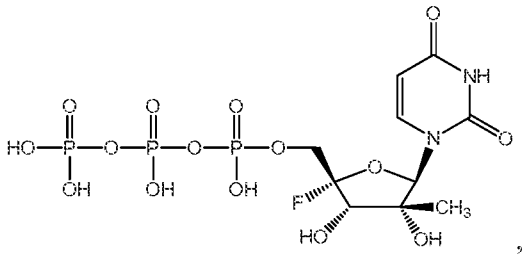
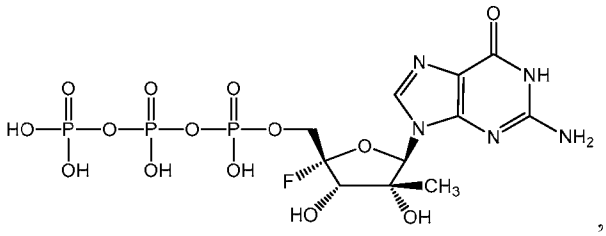
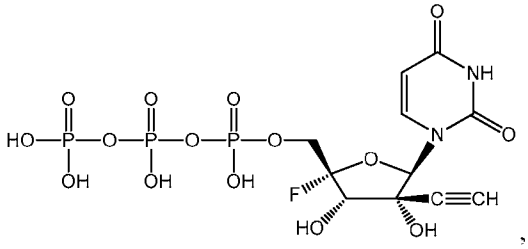
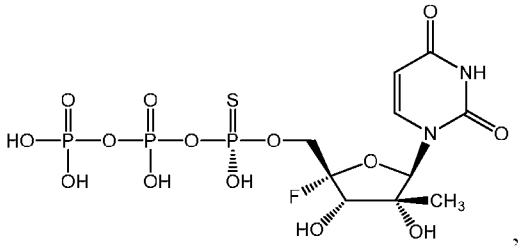
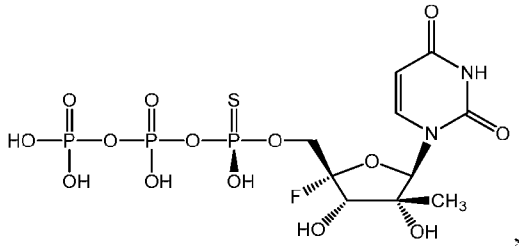
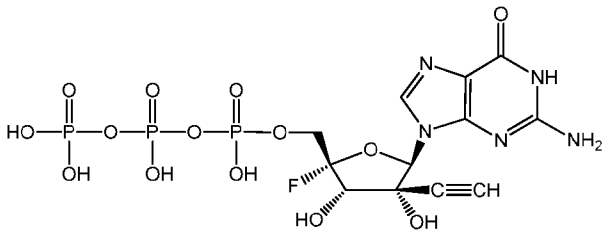
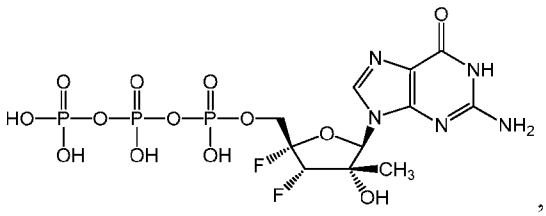
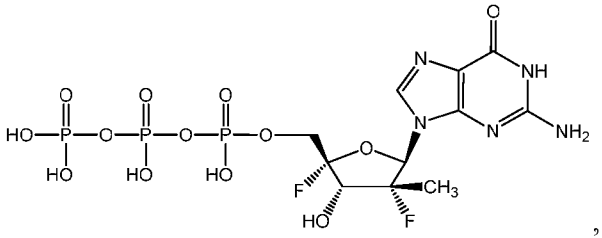
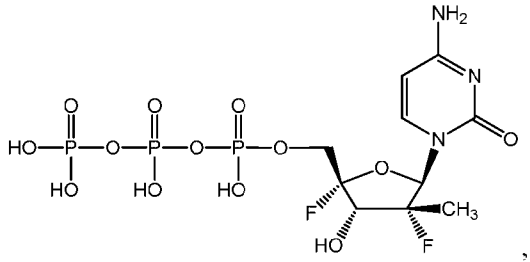
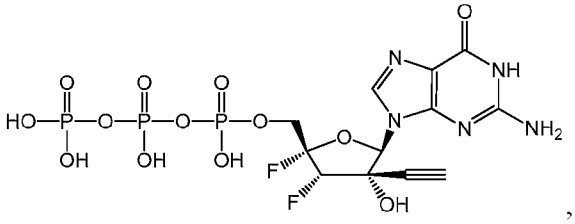
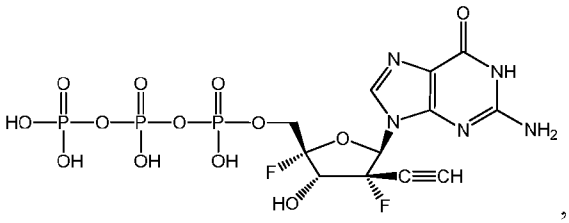
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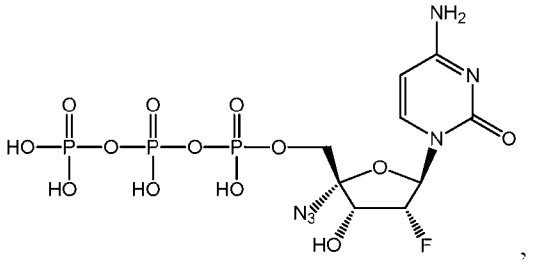
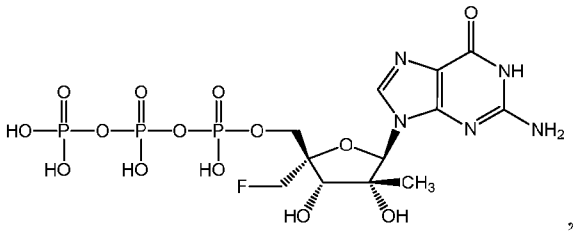
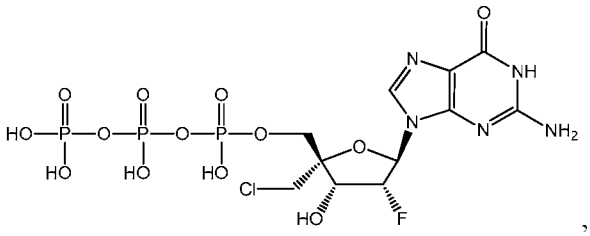


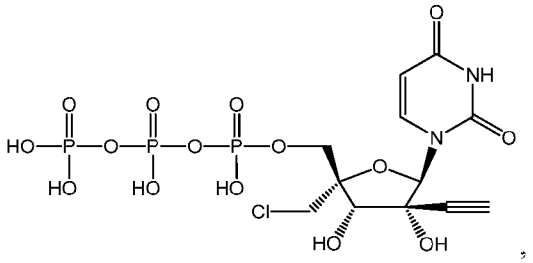
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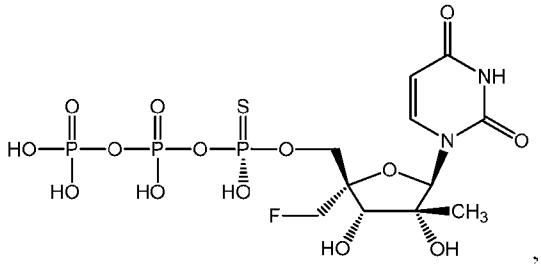


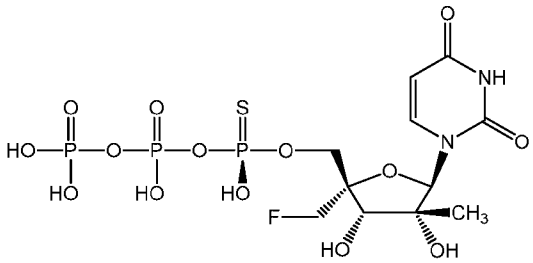
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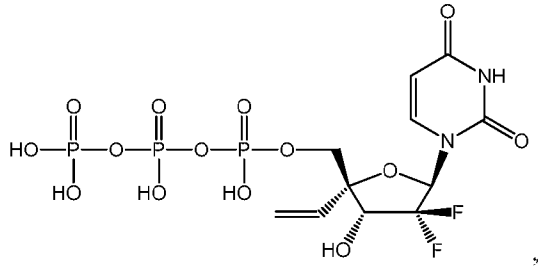

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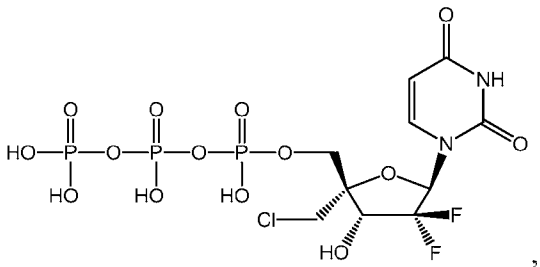

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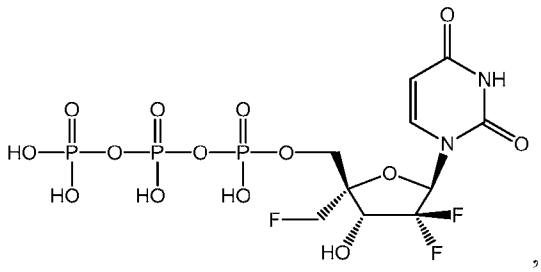


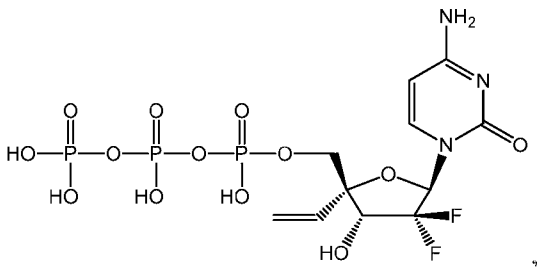


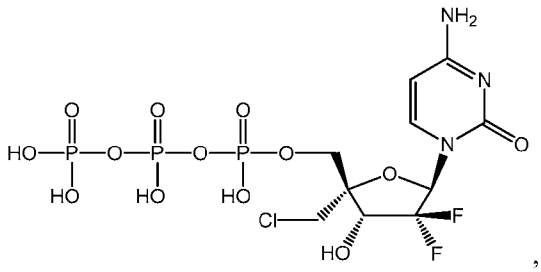


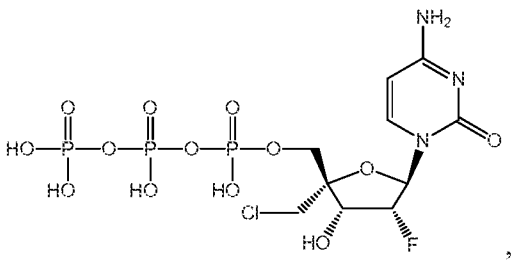


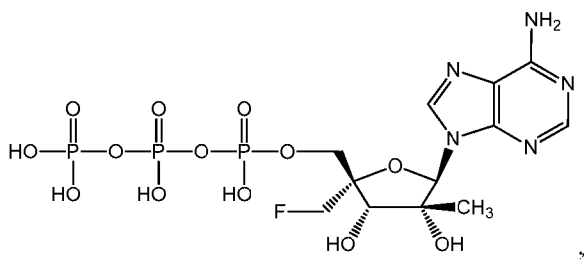


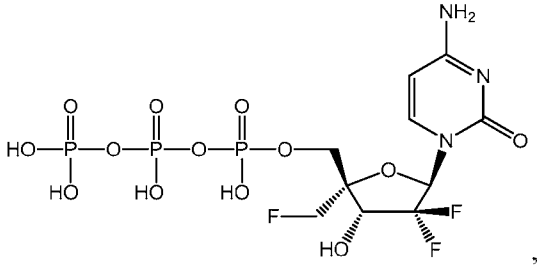


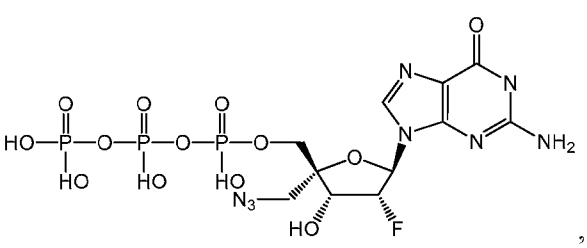


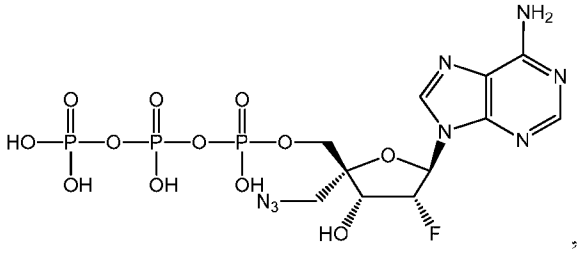


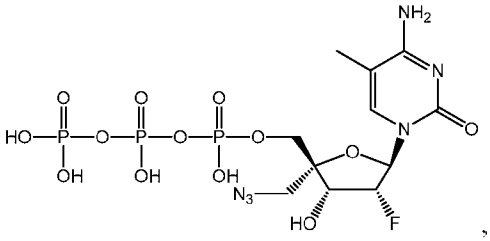


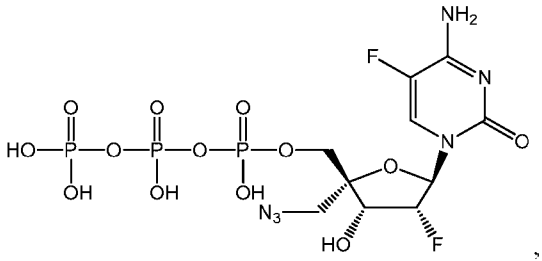


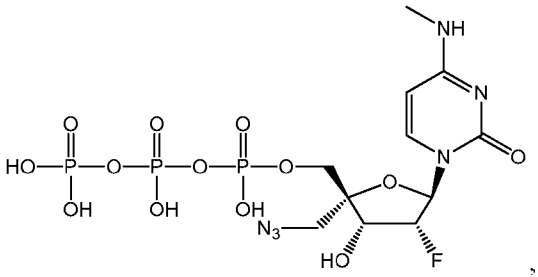


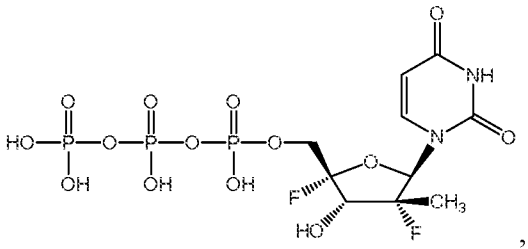


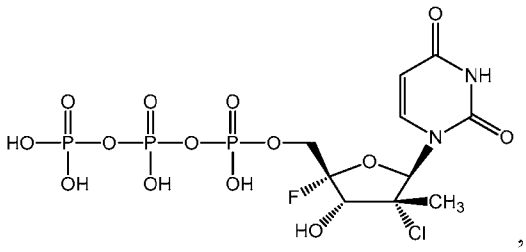

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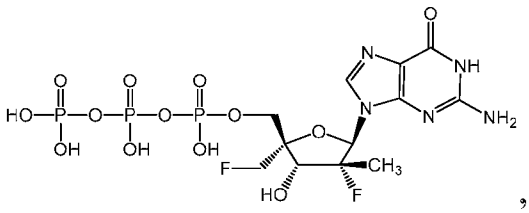

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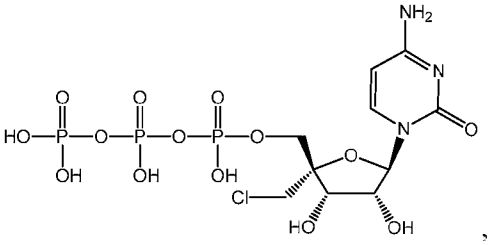

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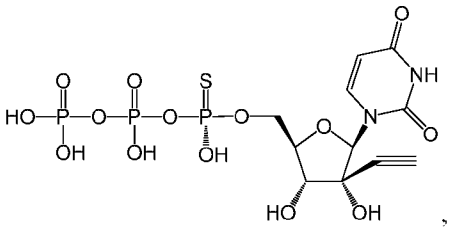

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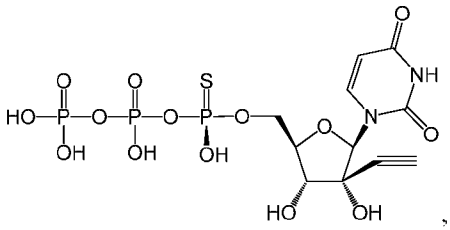

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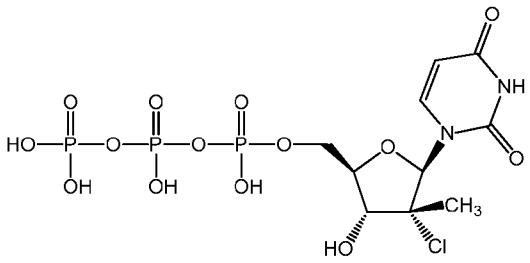

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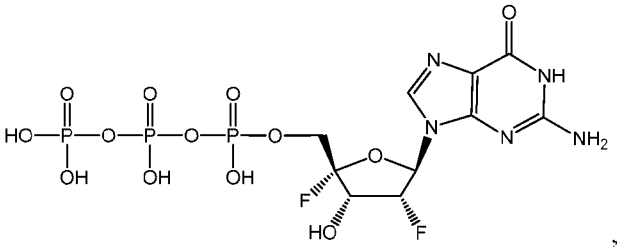

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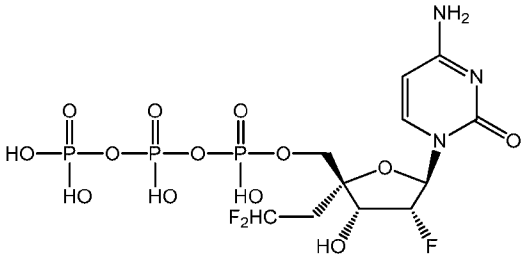
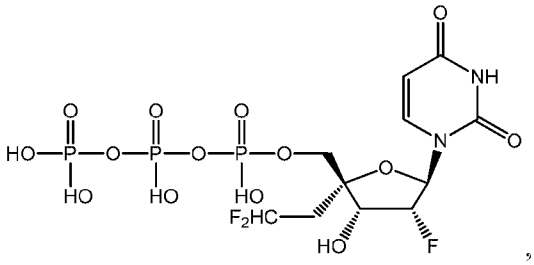
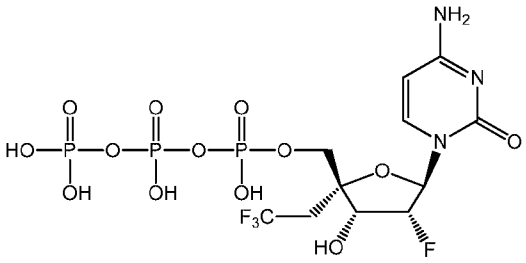
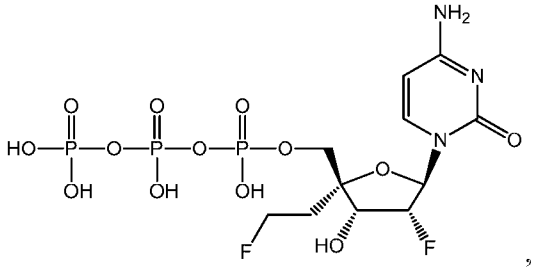
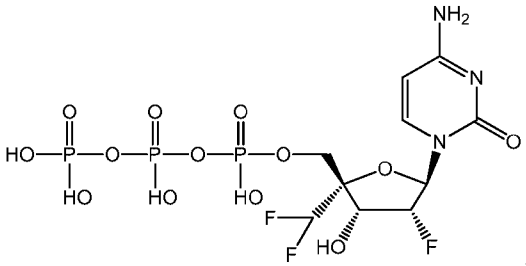
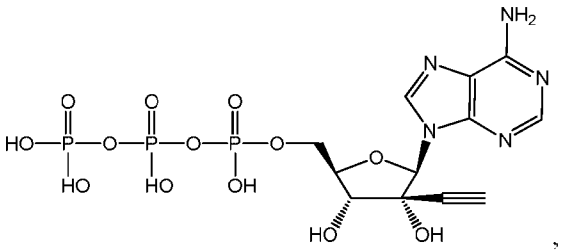
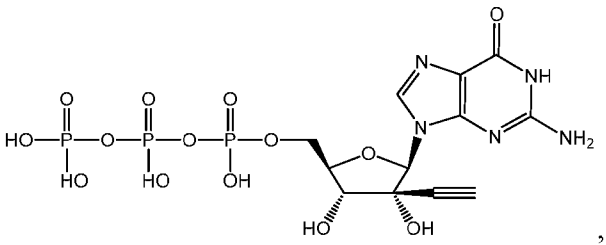
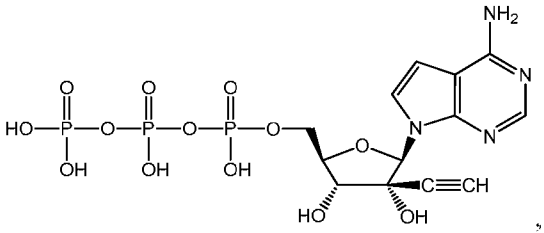
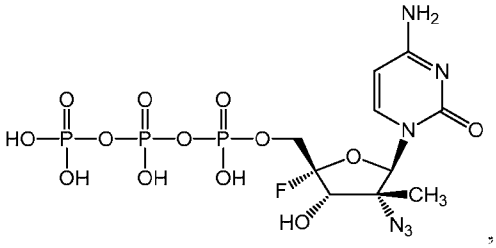
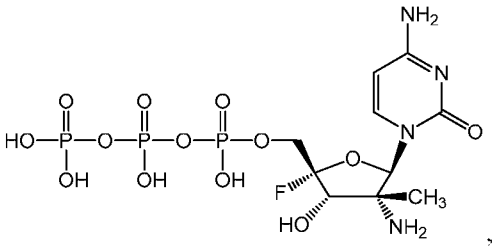
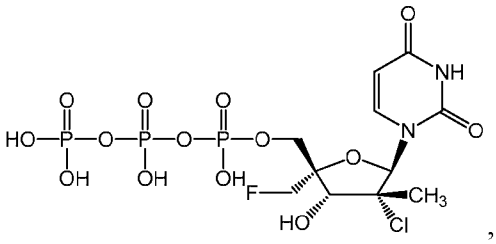
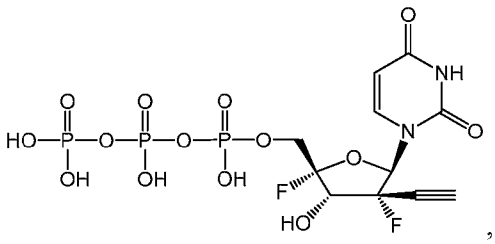

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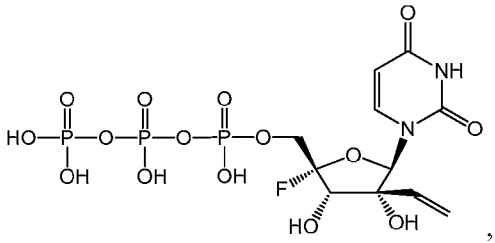
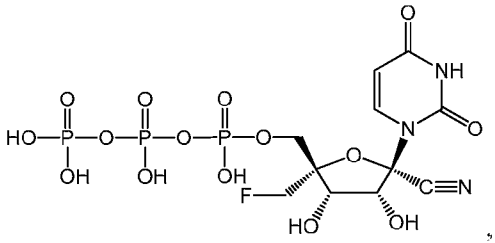
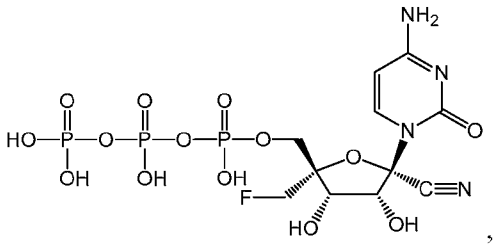
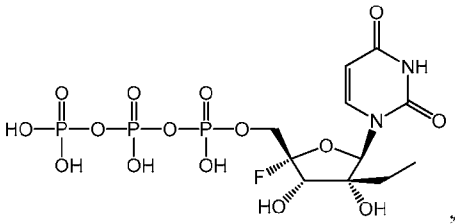
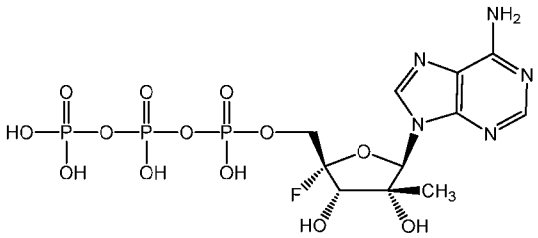
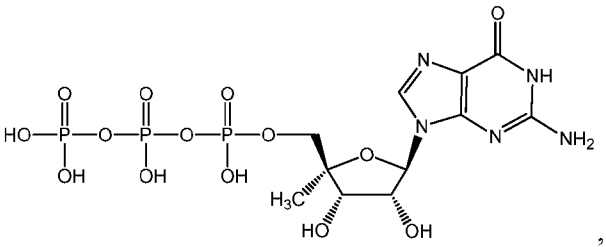
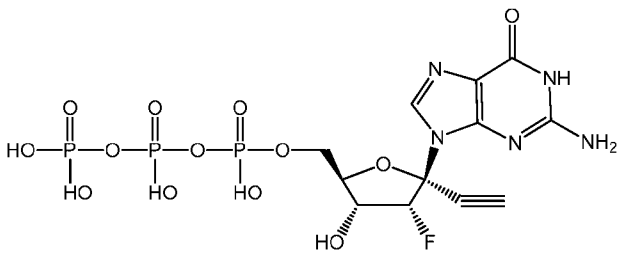
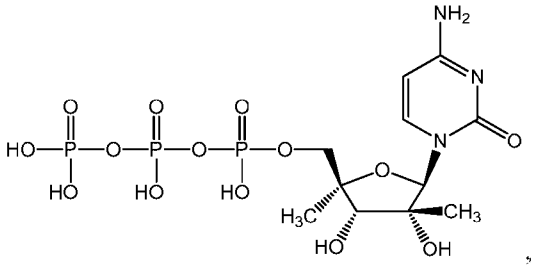
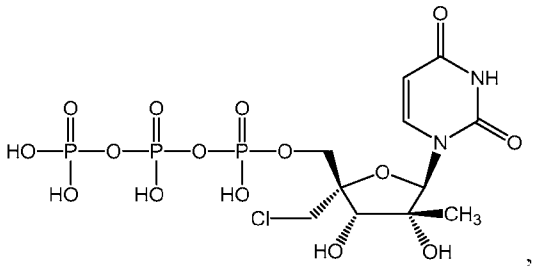
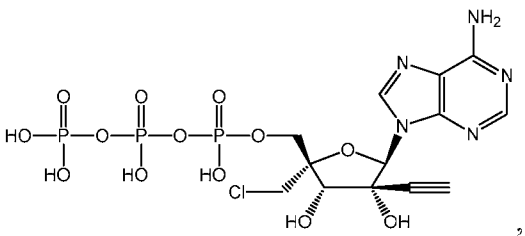
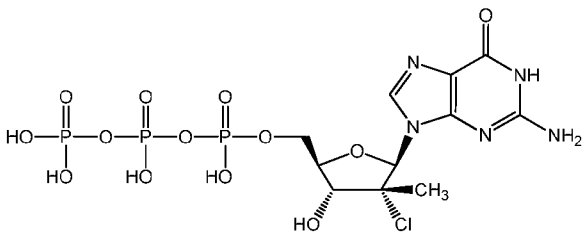
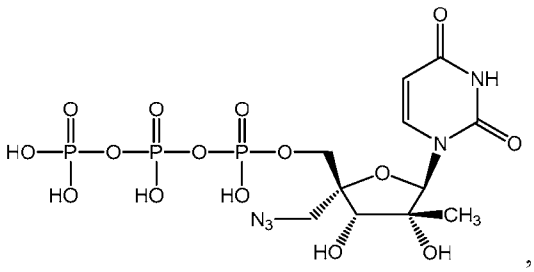

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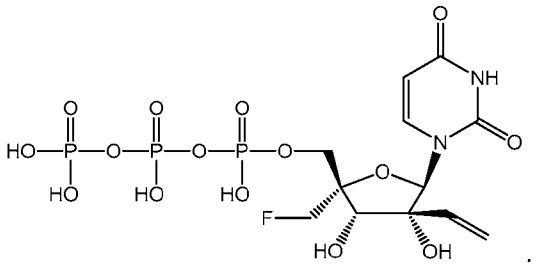

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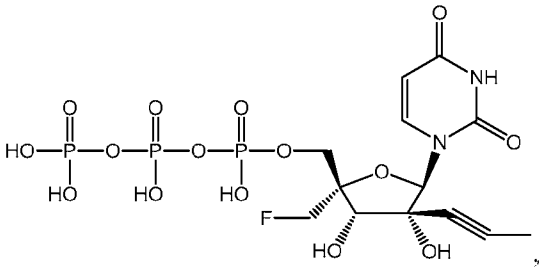

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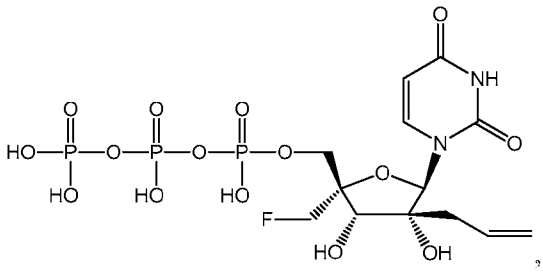
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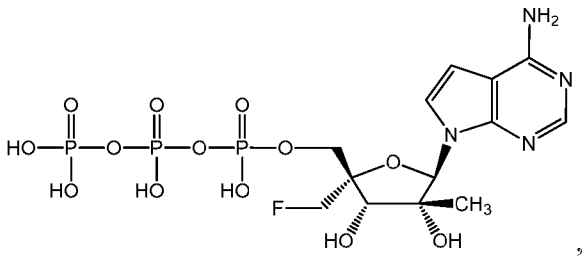
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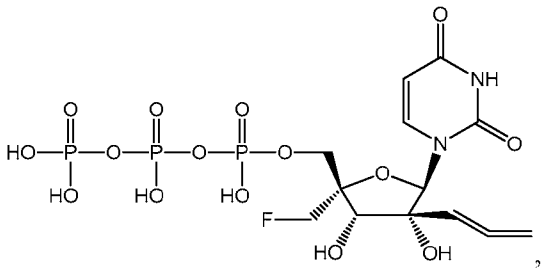

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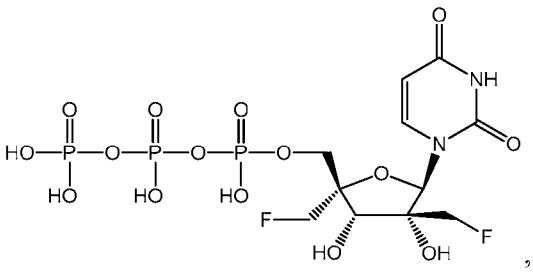


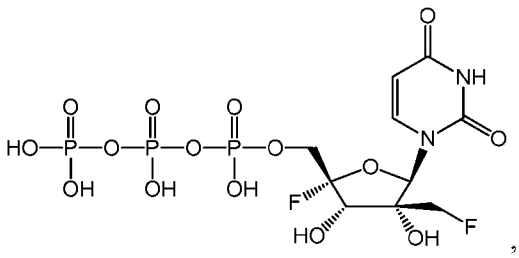


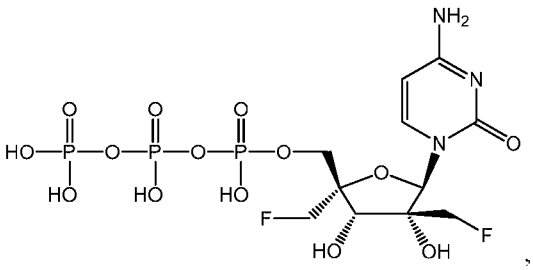


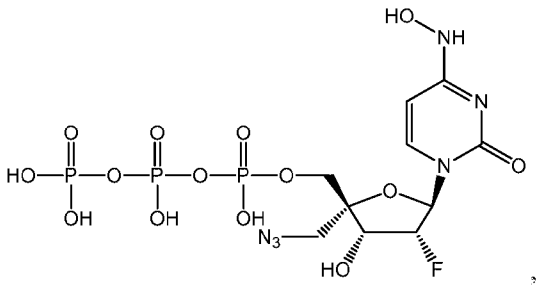


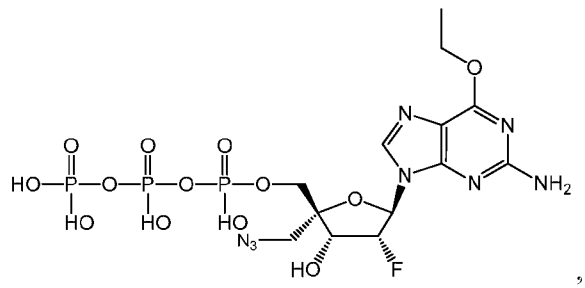


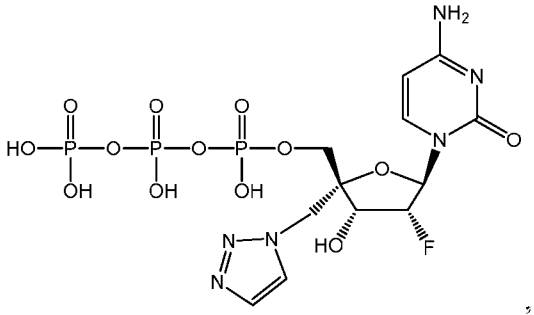




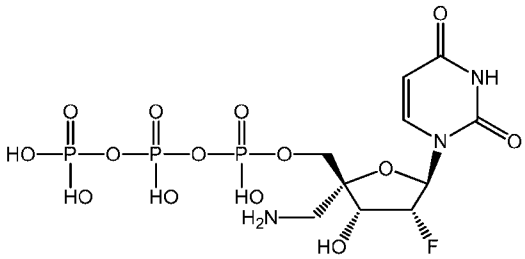




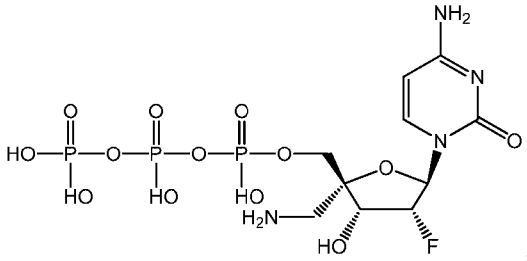




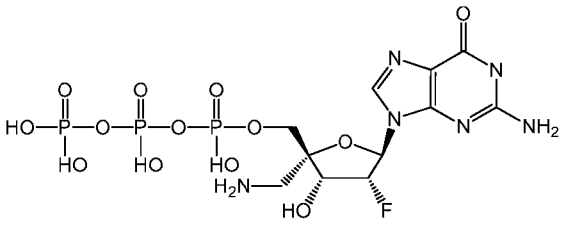
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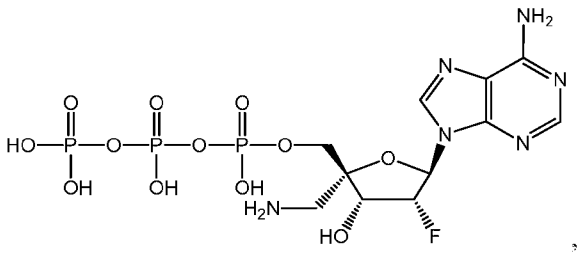
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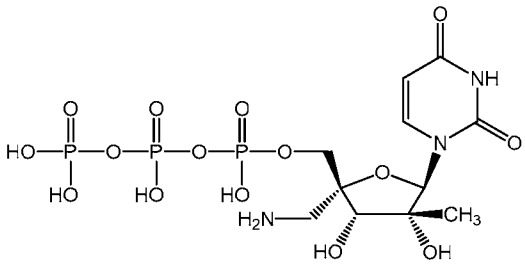
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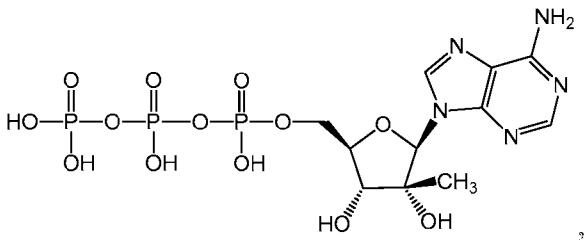
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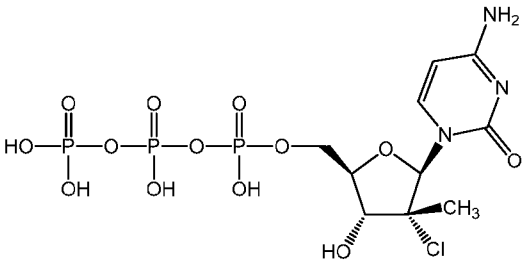
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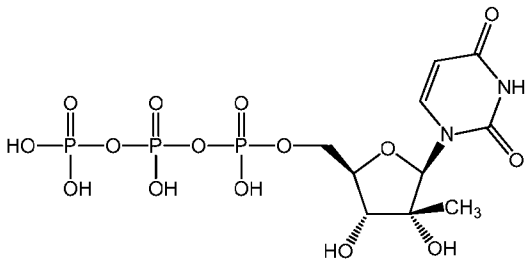
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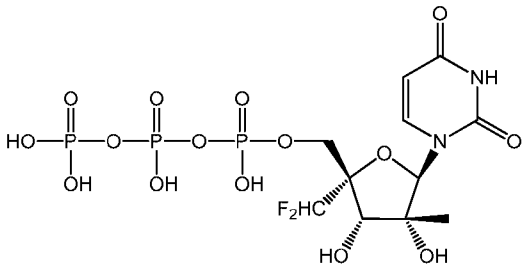
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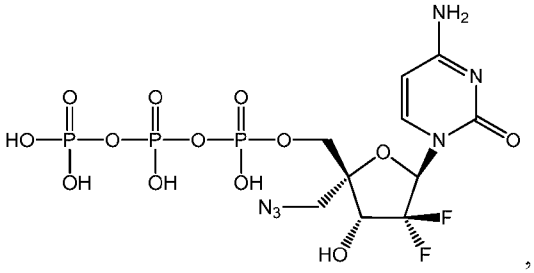
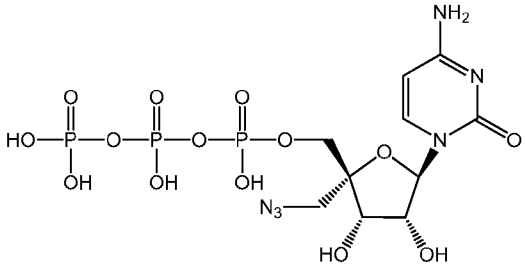
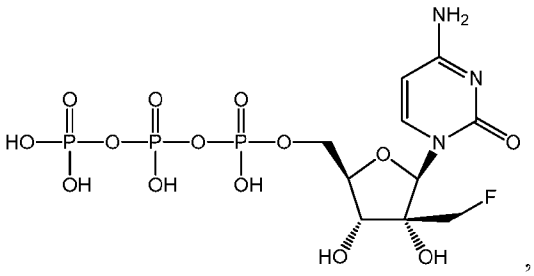
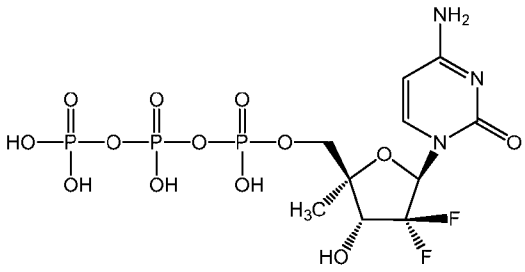
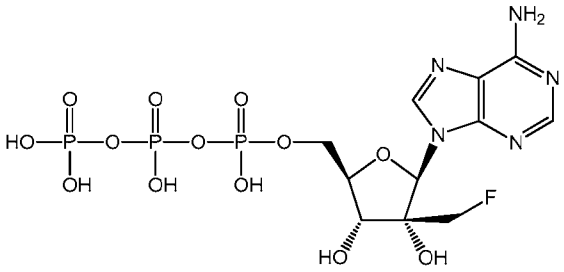
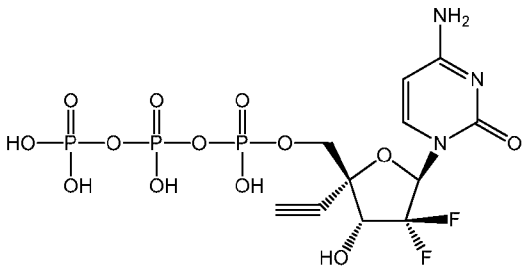
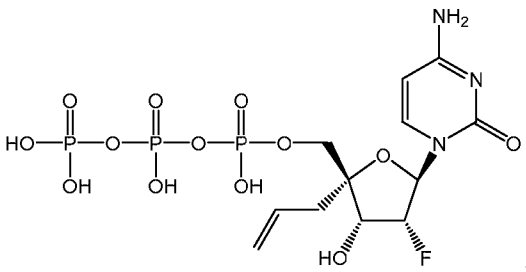
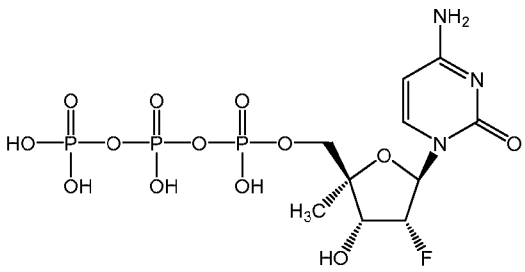
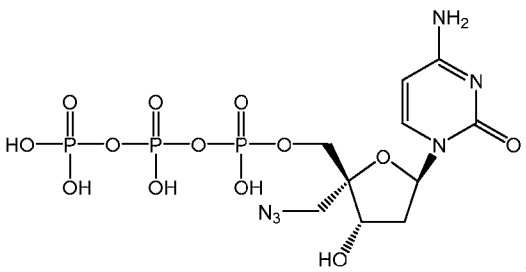
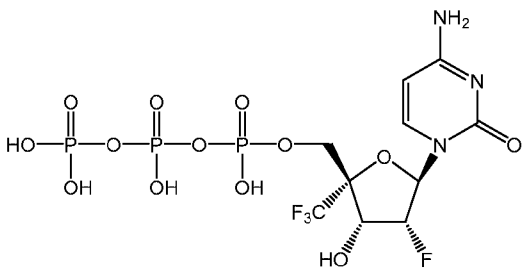
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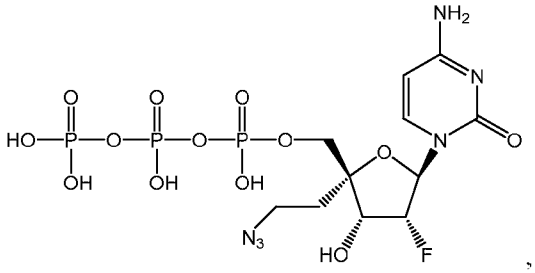
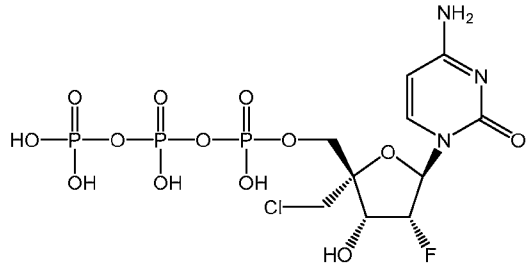
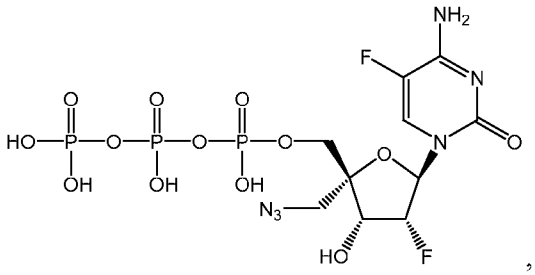
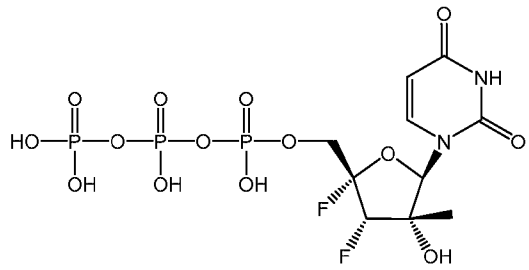
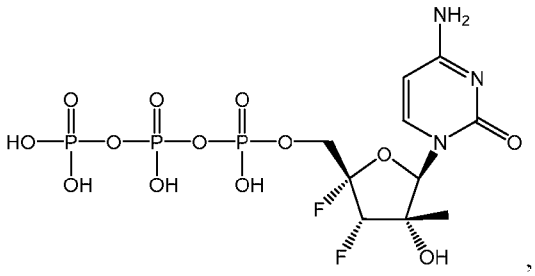
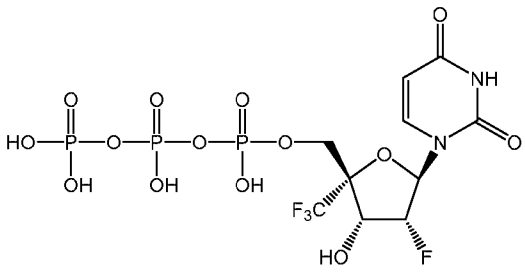
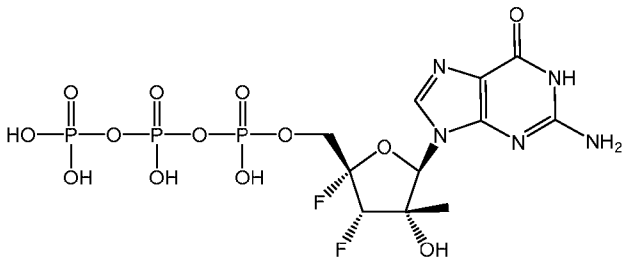


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, or a pharmaceutically acceptable salt of the foregoing.

Pharmaceutical Compositions

[0172] Some embodiments described herein relates to a pharmaceutical composition, that can include an effective amount of one or more compounds described herein (e.g., a compound of Formula (I), or a pharmaceutically acceptable salt thereof) and a pharmaceutically acceptable carrier, diluent, excipient or combination thereof. In some embodiments, the pharmaceutical composition can include a single diastereomer of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, (for example, a single diastereomer is present in the pharmaceutical composition at a concentration of greater than 99% compared to the total concentration of the other diastereomers). In other

embodiments, the pharmaceutical composition can include a mixture of diastereomers of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. For example, the pharmaceutical composition can include a concentration of one diastereomer of > 50%, ≥ 60%, ≥ 70%, ≥ 80%, ≥ 90%, ≥ 95%, or ≥ 98%, as compared to the total concentration of the other diastereomers. In some embodiments, the pharmaceutical composition includes a 1:1 mixture of two diastereomers of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0173] 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. A pharmaceutical composition is suitable for human and/or veterinary applications.

[0174] The term "physiologically acceptable" defines a carrier, diluent or excipient that does not abrogate the biological activity and properties of the compound.

[0175] 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.

[0176] 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.

[0177] 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.

[0178] 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.

[0179] 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.

[0180] 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.

[0181] 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.

[0182] 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

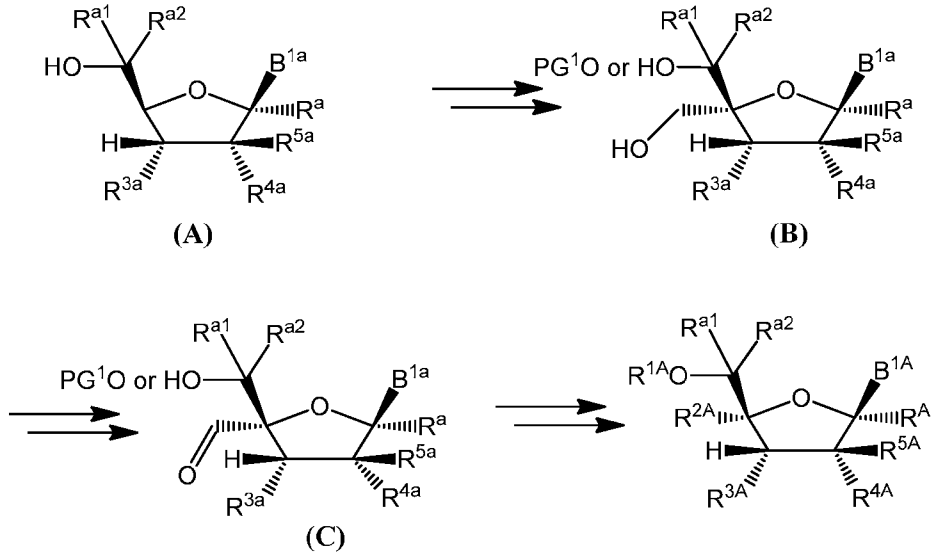
for human or veterinary administration. Such notice, for example, may be the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. Compositions that can include a compound described herein formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

Synthesis

[0183] 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 Scheme 1, 2, 3 and 4, 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.

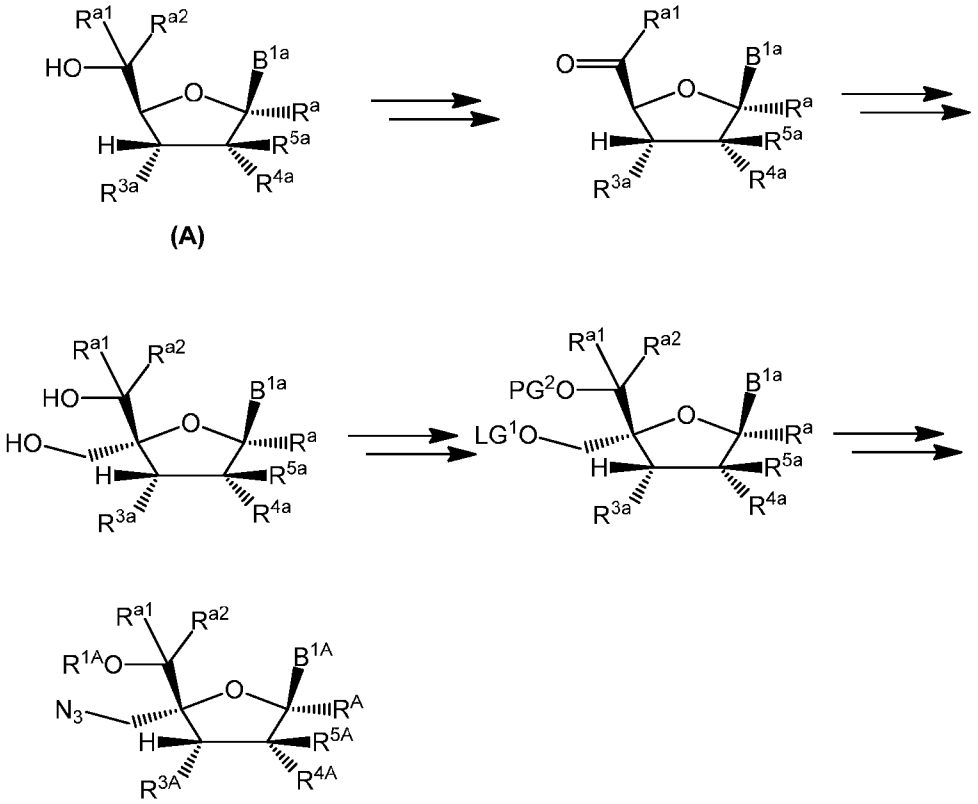
[0184] Compounds of Formula (I) can be prepared using various methods known to those skilled in the art. Examples of methods are shown in Schemes 1, 2, 3 and 4. Suitable phosphorus containing precursors can be commercially obtained or prepared by synthetic methods known to those skilled in the art. Examples of general structures of phosphorus containing precursors are shown in Schemes 1, 2, 3 and 4, and include phosphorochloridates and thiophosphorochloridates. Suitable phosphorochloridates and thiophosphorochloridates are commercially available and/or can be synthetically prepared.

Scheme 1



[0185] As shown in Scheme 1, compounds of Formula (I), wherein the 4'-position is a haloalkyl, can be prepared from a nucleoside, for example, a nucleoside of Formula (A). In Scheme 1, R^a, R^{3a}, R^{4a}, R^{5a}, and B^{1a} can be the same as R^A, R^{3A}, R^{4A}, R^{5A} and B^{1A} as described herein for Formula (I), and PG^1 is a suitable protecting group. A hydroxyalkyl group can be formed at the 4'-position of the pentose ring using suitable conditions known to those skilled in the art. Examples of suitable conditions for forming a hydroxyalkyl include the use of 2-iodoxybenzoic acid (IBX) aqueous formaldehyde and sodium borohydride. A compound of Formula (B) can be transformed to a haloalkyl using a suitable agent(s), for example, to an iodide using imidazole, triphenylphosphine and iodine; to a fluoro using diethylaminosulfur trifluoride (DAST); or to a chloro using triphenylphosphine and carbontetrachloride in dichloroethylene (DCE).

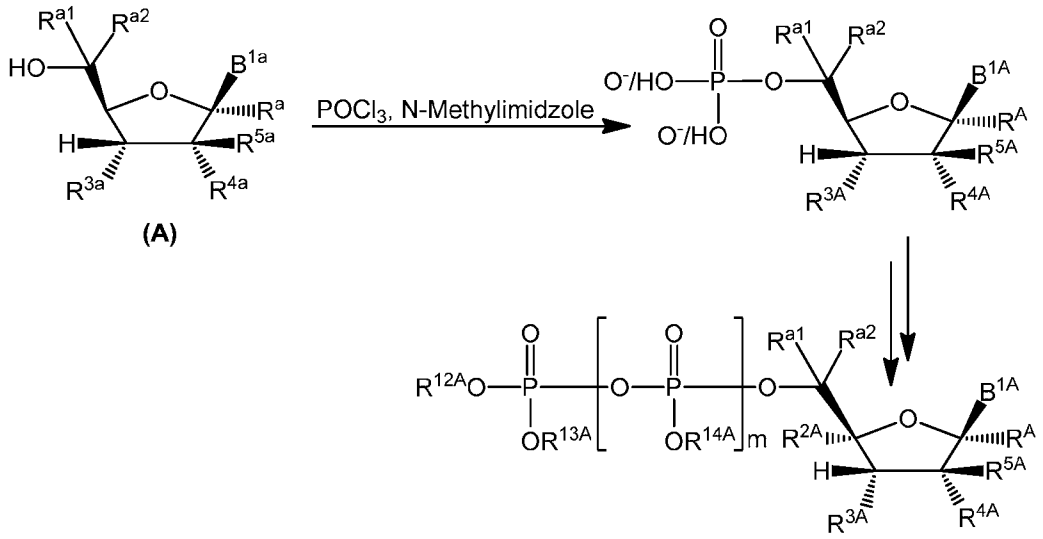
Scheme 2

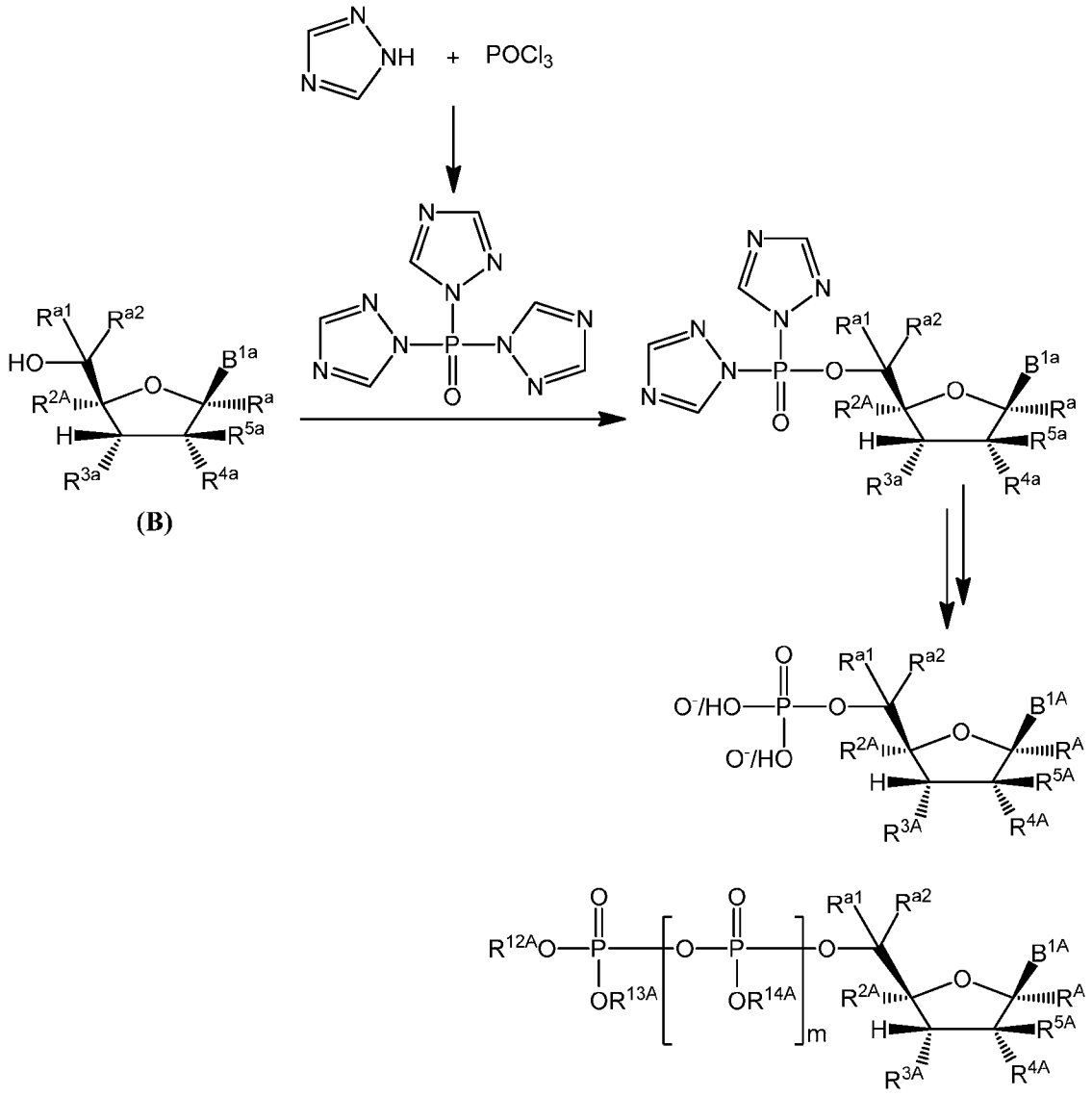


[0186] Compounds of Formula (I), where R^{2A} is a C_{1-6} azidoalkyl, can be prepared from a nucleoside, for example, a nucleoside of Formula (A). In Scheme 2, R^a, R^{3a}, R^{4a}, R^{5a} and B^{1a} can be the same as R^A, R^{3A}, R^{4A}, R^{5A} and B^{1A} as described herein for Formula (I), PG^2 can be a suitable protecting group and LG^2 can be a suitable leaving group. The 5'-position of the nucleoside can be oxidized to an aldehyde using methods known to those skilled in the art. Suitable oxidation conditions include, but are not limited to, Moffatt oxidation, Swern oxidation and Corey-Kim oxidation; and suitable oxidizing agents include, but are not limited to, Dess-Martin periodinane, IBX (2-iodoxybenzoic acid), TPAP/NMO (tetrapropylammonium perruthenate/N-methylmorpholine N-oxide), Swern oxidation reagent, PCC (pyridinium chlorochromate), PDC (pyridinium dichromate), sodium periodate, Collin's reagent, ceric ammonium nitrate CAN, $Na_2Cr_2O_7$ in water, Ag_2CO_3 on celite, hot HNO_3 in aqueous glyme, O_2-pyridine CuCl, $Pb(OAc)_4$-pyridine and benzoyl peroxide-$NiBr_2$. A hydroxymethyl group can be added to the 4'-position of the pentose ring along with the reduction of the aldehyde to an alcohol. The hydroxymethyl group can be added via a condensation reaction using formaldehyde and a base, such as sodium hydroxide. After

addition of the hydroxymethyl group, reduction of the intermediate compound with a 4'-hydroxymethyl group can be conducted using a reducing reagent. Examples of suitable reducing agents include, but are not limited to, $NaBH_4$ and $LiAlH_4$. A suitable leaving group, such as a triflate, can be formed by replacing the hydrogen of the hydroxymethyl group attached to the 4'-position, and the oxygen attached to the 5'-position can be protected with a suitable protecting group (for example, by cyclization with the base, B^{1a}, or with a separate protecting group). The leaving group can be replaced with an azido group using a metal azide reagent, for example, sodium azide. A C_{1-6} azidoalkyl at the 4'-position can be reduced to a C_{1-6} aminoalkyl. Various reduction agents/conditions known to those skilled in the art can be utilized. For example, the azido group can be reduced to an amino group via hydrogenation (for example, H_2-Pd/C or HCO_2NH_4-Pd/C), Staudinger Reaction, $NaBH_4/CoCl_2 \cdot 6\ H_2O$, Fe/NH_4Cl or Zn/NH_4Cl.

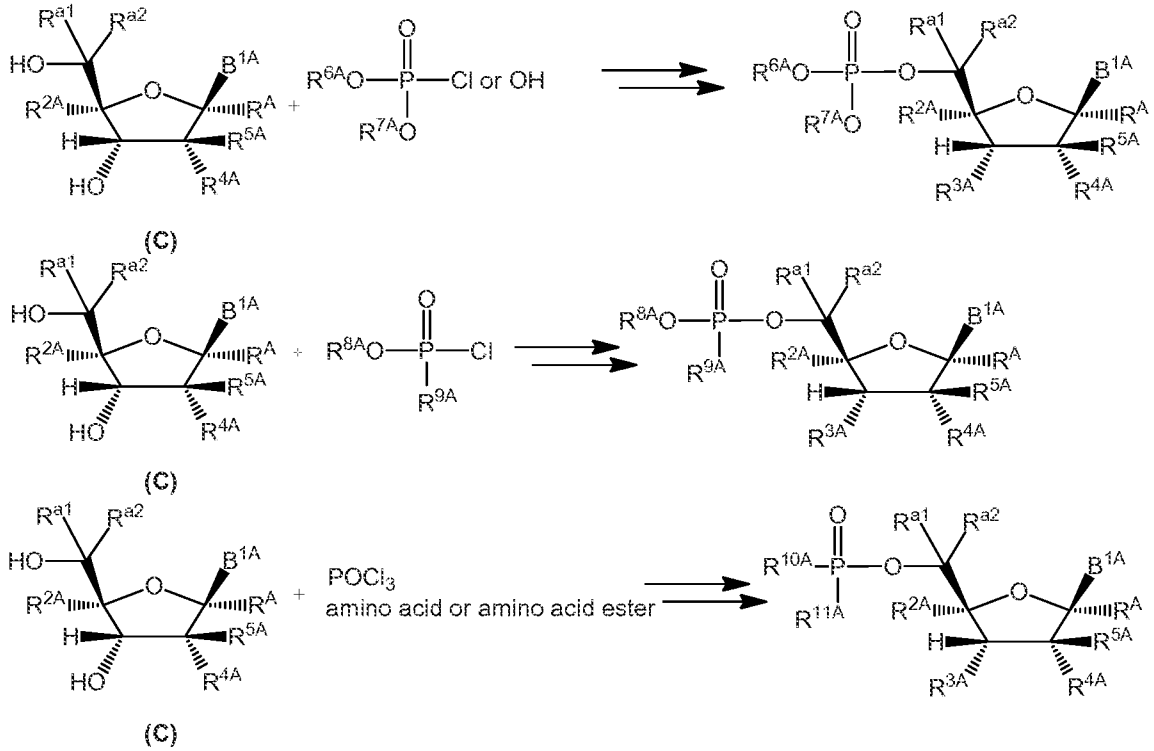
Scheme 3





(B)

Scheme 4

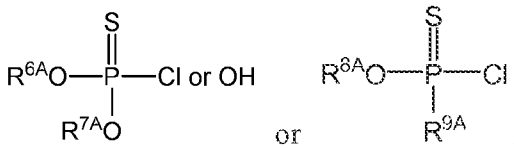


[0187] Compounds of Formula (I) having a phosphorus containing group attached to the 5'-position of the pentose ring can be prepared using various methods known to those skilled in the art. Examples of methods are shown in Schemes 3 and 4. In Schemes 3 and 4, R^a, R^{2a}, R^{3a}, R^{4a}, R^{5a} and B^{1a} can be the same as R^A, R^{2A}, R^{3A}, R^{4A}, R^{5A} and B^{1A} as described herein for Formulae (I). A phosphorus containing precursor can be coupled to the nucleoside, for example, a compound of Formula (B). Following the coupling of the phosphorus containing precursor, any leaving groups can be cleaved under suitable conditions, such as hydrolysis. 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.

[0188] In some embodiments, an alkoxide can be generated from a compound of Formula (C) using an organometallic reagent, such as a Grignard reagent. The alkoxide can be coupled to the phosphorus containing precursor. Suitable Grignard reagents are known to those skilled in the art and include, but are not limited to, alkylmagnesium chlorides and alkylmagnesium bromides. In some embodiments, an appropriate base can be used.

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)). Alternatively, a phosphorus containing precursor can be added to the nucleoside and form a phosphite. The phosphite can be oxidized to a phosphate using conditions known to those skilled in the art. Suitable conditions include, but are not limited to, meta-chloroperoxybenzoic acid (MCPBA) and iodine as the oxidizing agent and water as the oxygen donor.

[0189] When compounds of Formula (I) have Z^{1A}, Z^{2A} or Z^{3A} being sulfur, the sulfur can be added in various manners known to those skilled in the art. In some embodiments, the sulfur can be part of the phosphorus containing precursor, for example,



. Alternatively, the sulfur can be added 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).

[0190] As described herein, in some embodiments, R^{3A} and R^{4A} can be each an oxygen atom, wherein the oxygen atoms are linked together by a carbonyl groups. The -O-C(=O)-O- group can be formed using methods known to those skilled in the art. For example, a compound of Formula (I), wherein R^{3A} and R^{4A} are both hydroxy groups, can be treated with 1,1'-carbonyldiimidazole (CDI).

[0191] In some embodiments, the 2'-position and/or the 3'-position of the pentose ring can have an optionally substituted –O-acyl group attached, for example, $-OC(=O)R^{"A}$. The optionally substituted –O-acyl group can be formed at the 2'- and/or 3'-position using various methods known to those skilled in the art. As an example, a compound of Formulae (I), wherein the 2'-position and the 3'-position each have an hydroxy group attached, 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 optionally substituted –O-acyl group group(s) can be formed at the 2'- and 3'-positions by reacting an alkyl acid (e.g. acetic acid and propionic acid) in the presences of a carbodiimide or a coupling reagent. Examples of carbodiimides include, but are not limited to, N,N'-dicyclohexylcarbodiimide (DCC), N,N'-diisopropylcarbodiimide (DIC) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC).

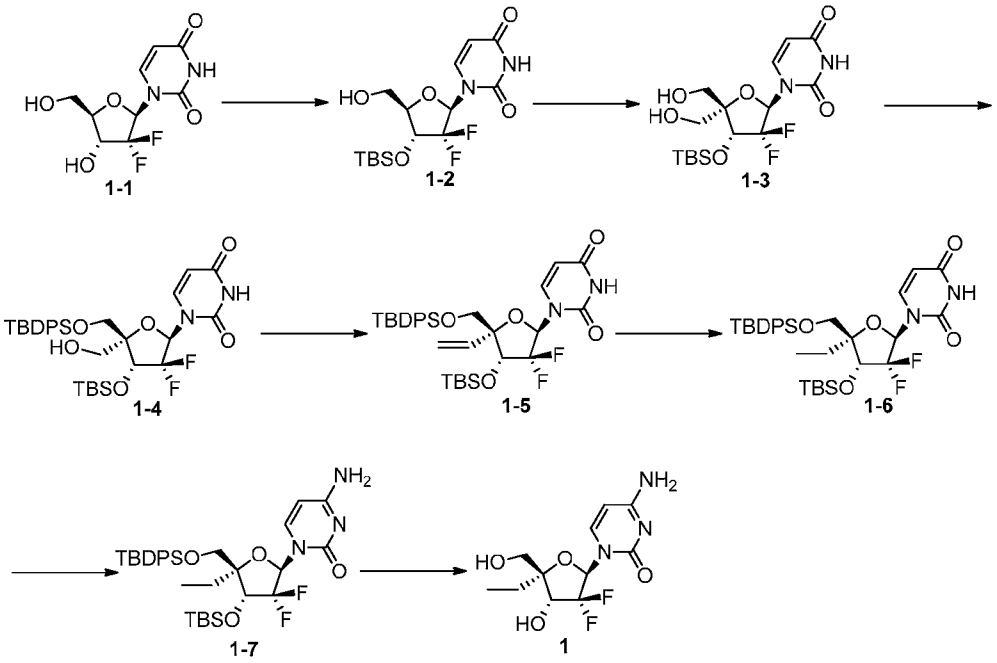
[0192] To reduce the formation of side products, one or more the groups attached to the pentose ring can be protected with one or more suitable protecting groups and/or any –NH and/or NH_2 groups present on the B^{1a}, can be protected with one or more suitable protecting groups. As an example, if 2'-position and/or the 3'-position is/are hydroxy group(s), the hydroxy group(s) can be protected with suitable protecting groups, such as triarylmethyl and/or silyl groups. Examples of triarylmethyl groups include but are not limited to, trityl, monomethoxytrityl (MMTr), 4,4'-dimethoxytrityl (DMTr), 4,4',4"-trimethoxytrityl (TMTr),. 4,4',4"-tris- (benzoyloxy) trityl (TBTr), 4,4',4"-tris (4,5-dichlorophthalimido) trityl (CPTr), 4,4',4"-tris (levulinyloxy) trityl (TLTr), p-anisyl-1-naphthylphenylmethyl, di-o-anisyl-1-naphthylmethyl, p-tolyldipheylmethyl, 3-(imidazolylmethyl)-4,4'-dimethoxytrityl, 9-phenylxanthen-9-yl (Pixyl), 9-(p-methoxyphenyl) xanthen-9-yl (Mox), 4-decyloxytrityl, 4- hexadecyloxytrityl, 4,4'-dioctadecyltrityl, 9-(4-octadecyloxyphenyl) xanthen-9-yl, 1,1'-bis-(4-methoxyphenyl)-1'-pyrenylmethyl, 4,4',4"-tris-(tert-butylphenyl) methyl (TTTr) and 4,4'-di-3,5-hexadienoxytrityl. Examples of 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. Alternatively, R^{3A} and/or R^{4A} can be protected by a single achiral or chiral protecting group, for example, by forming an orthoester, a cyclic acetal or a cyclic ketal. Suitable orthoesters include methoxymethylene acetal, ethoxymethylene acetal, 2-oxacyclopentylidene orthoester, dimethoxymethylene orthoester, 1-methoxyethylidene orthoester, 1-ethoxyethylidene orthoester, methylidene orthoester, phthalide orthoester 1,2-dimethoxyethylidene orthoester, and alpha-methoxybenzylidene orthoester; suitable cyclic acetals include methylene acetal, ethylidene acetal, t-butylmethylidene acetal, 3-(benzyloxy)propyl acetal, benzylidene acetal, 3,4-dimethoxybenzylidene acetal and p-acetoxybenzylidene acetal; and suitable cyclic ketals

include 1-t-butylethylidene ketal, 1-phenylethylidene ketal, isopropylidene ketal, cyclopentylidene ketal, cyclohexylidene ketal, cycloheptylidene ketal and 1-(4-methoxyphenyl)ethylidene ketal.

EXAMPLES

[0193] 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
COMPOUND 1



[0194] To a solution of **1-1** (100.0 g, 378.7 mmol) in pyridine (750 mL) was added DMTrCl (164.9 g, 487.8 mmol). The solution was stirred at RT for 15 h. MeOH (300 mL) was added, and the mixture was concentrated to dryness under reduced pressure. The residue was dissolved in EA and washed with water. The organic layer was dried over Na_2SO_4 and concentrated. The residue was dissolved in DCM (500 mL). To this solution were added imidazole (44.3 g, 650.4 mmol) and TBSCl (91.9 g, 609.8 mmol). The mixture was stirred at RT for 14 h. The solution was washed with $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, and concentrated to give the crude product as a light yellow solid. The crude (236.4 g, 347.6 mmol) was dissolved in 80% HOAc aqueous solution (500

mL). The mixture was stirred at RT for 15 h. The mixture was diluted with EA, and washed with $NaHCO_3$ solution and brine. The organic layer was dried over Na_2SO_4 and purified on a silica gel column chromatography (1-2% MeOH in DCM) to give **1-2** (131.2 g, 91.9%) as a light yellow solid. ESI-MS: m/z 802 $[M+H]^+$.

[0195] To a solution of **1-2** (131.2 g, 346.9 mmol) in anhydrous CH_3CN (1200 mL) was added IBX (121.2 g, 432.8 mmol) at RT. The mixture was refluxed for 3 h and then cooled to 0 °C. The precipitate was filtered, and the filtrate was concentrated to give the crude aldehyde (121.3 g) as a yellow solid. The aldehyde was dissolved in 1,4-dioxane (1000 mL). 37% CH_2O (81.1 mL, 1.35 mmol) and 2M NaOH aqueous solution (253.8 mL, 507.6 mmol) were added. The mixture was stirred at RT for 2 h., and then neutralized with AcOH to pH = 7. To the solution were added EtOH (400 mL) and $NaBH_4$ (51.2 g, 1.35 mol). The mixture was stirred at RT for 30 mins, the reaction was quenched with sat. aq. NH_4Cl. The mixture was extracted with EA. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (1-3% MeOH in DCM) to give **1-3** (51.4 g, 38.9%) as a white solid.

[0196] To a solution of **1-3** (51.4 g, 125.9 mmol) in anhydrous DCM (400 mL) were added pyridine (80 mL) and DMTrCl (49.1 g, 144.7 mmol) at 0 °C. The reaction was stirred at RT for 14 h, and then treated with MeOH (30 mL). The solvent was removed, and the residue was purified by silica gel column chromatography (1-3% MeOH in DCM) to give the mono-DMTr protected intermediate as a yellow foam (57.4 g, 62.9%). The intermediate (57.4 g, 82.8 mmol) was dissolved in CH_2Cl_2 (400 mL), and imidazole (8.4 g, 124.2 mmol), TBDPSCl (34.1 g, 124.2 mmol) were added. The mixture was stirred at RT for 14 h. The precipitate was filtered off, and the filtrate was washed with brine and dried with Na_2SO_4. The solvent was removed to give a residue (72.45 g) as a white solid. The residue was dissolved in 80% HOAc aqueous solution (400 mL). The mixture was stirred RT for 15 h. The mixture was diluted with EA and washed with $NaHCO_3$ solution and brine. The organic layer was dried over Na_2SO_4 and purified by silica gel column chromatography (1-2% MeOH in DCM) to give **1-4** (37.6 g, 84.2%) as a white solid.

[0197] A solution of **1-4** (700 mg, 1.09 mmol) in anhydrous dichloromethane was added Dess-Martin reagent (919 mg, 2.16 mmol) at 0 °C. The mixture was stirred at RT for 30 mins. The reaction was quenched with sat. sodium hydrogen carbonate and sodium

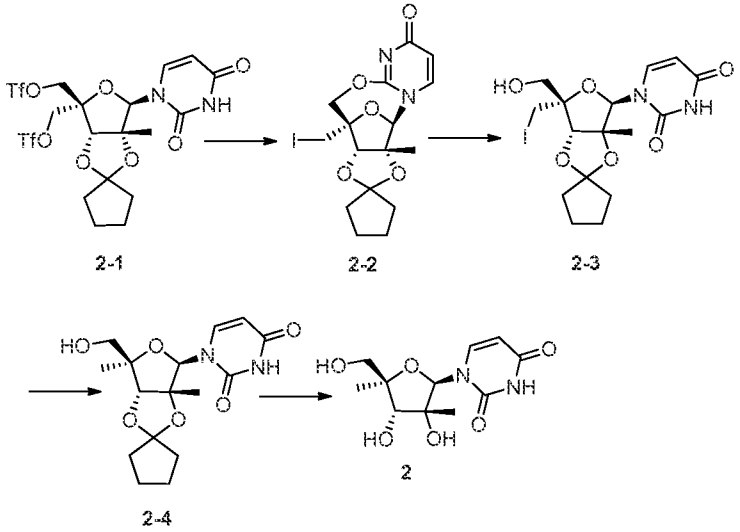
thiosulfate solution, and extracted with EA. The organic layers were concentrated to give the crude aldehyde, which was used for next step without purification. A solution of $MePPh_3Br$ (3.88 g, 10.87 mmol) in anhydrous THF was treated with a solution of t-BuOK (9.81 mL, 9.81 mmol) in THF at 0 °C. The mixture was warmed to RT for 1 h. After cooling to 0 °C for 1 h, a solution of the aldehyde (700 mg, 1.09 mmol) in THF was added. The mixture was stirred overnight at RT. The reaction was quenched with sat. ammonium chloride solution, and extracted with EA. The organic layers were purified by column chromatography to give **1-5** (167 mg, 30%).

[0198] To a solution of **1-5** (450 mg, 0.69 mmol) in MeOH (10 mL) was added Pd/C (200 mg) at RT. The reaction mixture was stirred at RT for 1 h under H_2 (balloon). Then the mixture was filtered and the filtrate was concentrated to give the crude **1-6** (440 mg, 97.1%) as a white solid.

[0199] A solution of **1-6** (317 mg, 0.49 mmol), TPSCl (373 mg, 1.23 mmol), DMAP (150 mg, 1.23 mmol) and TEA (124 mg, 1.23 mmol) in anhydrous MeCN was stirred at RT overnight. The reaction was quenched with $NH_3 \cdot H_2O$, and then stirred at RT for 3 h. The solvent was removed under reduced pressure. The residue was purified by column chromatography to give **1-7** (200 mg, 63%).

[0200] To a solution of **1-7** (280 mg, 0.44 mmol) in MeOH (10 mL) was added NH_4F (1.0 g, 27.0 mmol) at RT. The mixture was refluxed for 12 h. The mixture was filtered, and the filtrate was concentrated. The residue was purified on a silica gel column (10% MeOH in DCM) to give compound **1** (81 mg, 63.3%) as a white solid. ESI-MS: m/z 291.8 $[M+H]^+$.

EXAMPLE 2
COMPOUND 2



[0201] To a solution of **2-1** (2.5 g, 4.04 mmol) in DMF was added NaH (170 mg, 4.24 mmol, 60% purity) at 0 °C. The mixture was stirred for 3 h at RT. NaI (6.1 g, 40.4 mmol) was added at RT and stirred for 3 h. The reaction was diluted with water and extracted with EA. The organic layer was dried over anhydrous Na_2SO_4, and concentrated at low pressure to give **2-2** (1.7 g, 94%) as a yellow solid.

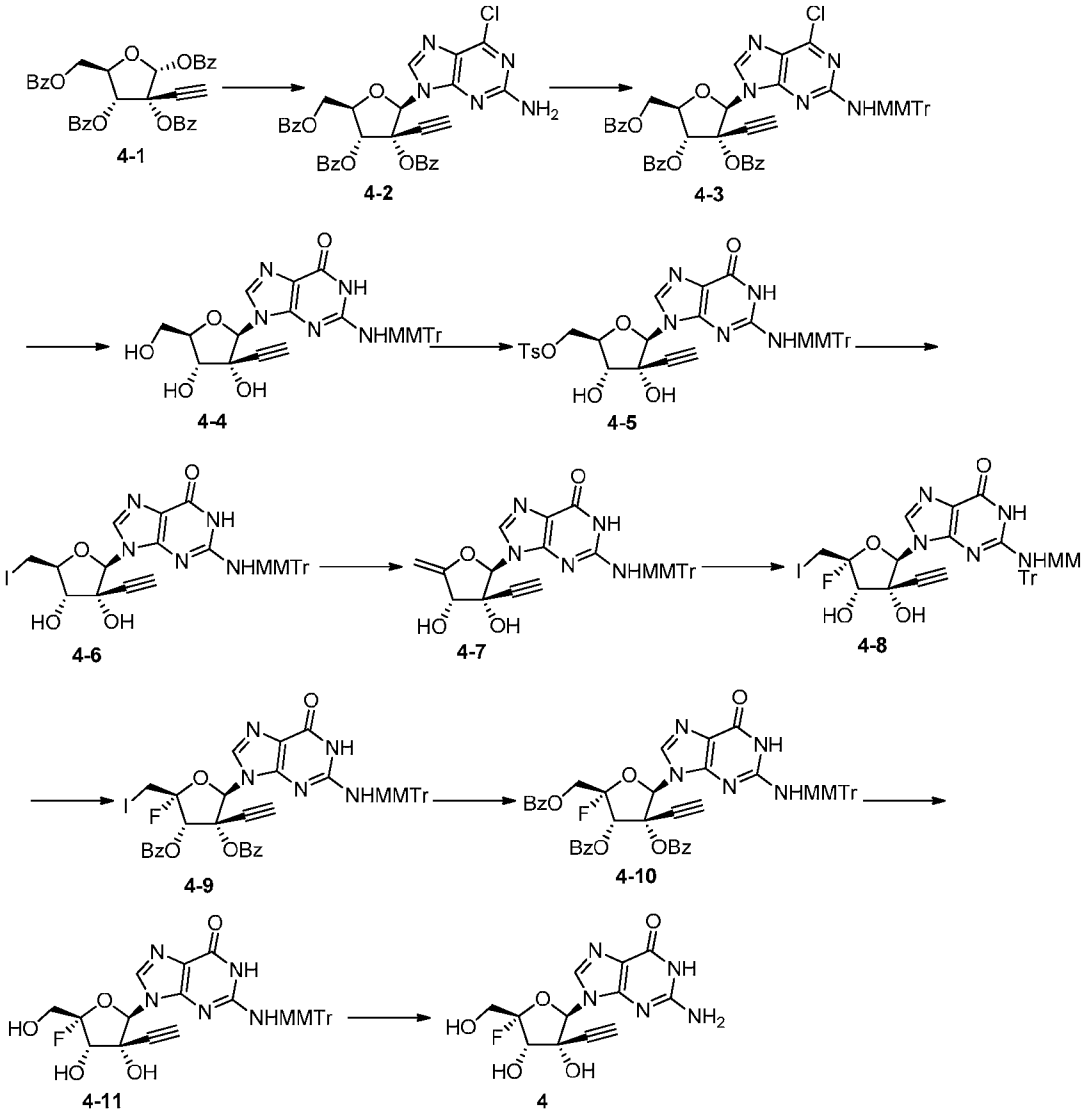
[0202] To a solution of **2-2** (1.7 g, 3.81 mmol) in THF (5 mL) was added 2 M NaOH solution (4.5 mL) at 0 °C. The solution was stirred for 2 h at RT. The mixture was adjusted to pH = 7, and concentrated under reduced pressure. The mixture was partitioned between DCM and water. The DCM layer was dried with high vacuum to give **2-3** (1.2 g, 68%) as a white solid, which was used without further purification.

[0203] To a solution of **2-3** (1.2 g, 2.58 mmol) in EtOH (20 mL) was added NH_4COOH(650 mg, 7.75 mmol) and Pd/C (120 mg). The mixture was stirred under H_2 (30 psi) for 1.5 h at RT. The suspension was filtered, and the filtrate was concentrated at a low pressure. The residue was purified on silica gel column (0.5% TEA and 1% MeOH in DCM) to give **2-4** (545 mg, 62%). ESI-MS: m/z 361.2 $[M + 23]^+$.

[0204] Compound **2-4** was dissolved in 80% aq. HCOOH (20 mL) and kept at 20 °C for 18 h. After cooling to RT, the solvent was removed in vacuo, and the residue co-evaporated with toluene (3 x 25 mL). The residue was dissolved in water (3 mL) and concentrated aqueous NH_4OH (1 mL) was added. After 2 h at 20 °C, the solvent was

removed in vacuo. The residue was purified by flash chromatography using a 5 to 50% gradient of methanol in DCM to give purified compound **2** (14 mg) as a white solid.

EXAMPLE 3
COMPOUND 4



[0205] Compound **4-1** (5.0 g, 8.5 mmol) and 2-amino-6-chloropurine (3.0 g, 17.7 mmol) were co-concentrated with anhydrous toluene for 3 times. To a stirred suspension of the mixture in anhydrous MeCN (50 mL) was added DBU (7.5 g, 49 mmol) at 0 °C. The mixture was stirred at 0 °C for 15 mins, and TMSOTf (15 g, 67.6 mmol) was added dropwise at 0 °C. The mixture was stirred at 0 °C for 15 mins and then heated to 70°C overnight. The mixture was cooled to RT, and diluted with EA (100 mL). The solution was washed with

sat. $NaHCO_3$ solution and brine. The organic layer was dried over Na_2SO_4 and then concentrated at low pressure. The residue was purified by column on silica gel (PE/EA: from 15/1 to 3/1) to give **4-2** (2.5 g, 46.3%) as a white foam.

[0206] To a solution of **4-2** (10 g, 15.7 mmol), $AgNO_3$ (8.0g, 47 mmol) and collidine (10 mL) in anhydrous DCM (20 mL) was added MMTrCl (14.5 g, 47 mmol) in small portions under N_2. The mixture was stirred at RT overnight. The mixture was filtered, and the filtrate was washed with sat. $NaHCO_3$ aqueous and brine. The organic layer was dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by silica gel column (PE/ME = 20/1 to 8/1) to give **4-3** (10 g, 70 %) as a yellow solid.

[0207] To a solution of 3-hydroxy-propionitrile (3.51 g, 49.4 mmol) in anhydrous THF (100 mL) was added NaH (2.8 g, 70 mmol) at 0°C, and the mixture was stirred at RT for 30 mins. To the mixture was added a solution of **4-3** (8.5 g, 9.35 mmol) in anhydrous THF (100 mL) at 0 °C, and the reaction mixture was stirred at RT overnight. The reaction was quenched by water, and extracted with EA (100 mL). The organic layer was dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by silica gel column (DCM/MeOH = 100/1 to 20/1) to give **4-4** (4.5 g, 83%) as a white solid.

[0208] Compound **4-4** (1.5g, 2.6 mmol) was co-concentrated with anhydrous pyridine 3 times. To an ice cooled solution of **4-4** in anhydrous pyridine (30 mL) was added TsCl (1.086 g, 5.7 mmol), and the reaction mixture was stirred at 0 °C for 1 h. The reaction was quenched with water, and extracted with EA (80 mL). The organic layer was dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by silica gel column (DCM/MeOH = 100/1 to 15/1) to give **4-5** (1.4 g, 73%) as a white solid.

[0209] To a solution of **4-5** (4.22 g, 5.7 mmol) in acetone (60 mL) was added NaI (3.45 g, 23 mmol), and the mixture was refluxed overnight. The reaction was quenched by sat. $Na_2S_2O_3$ aqueous, and then extracted with EA (100 mL). The organic layer was dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by silica gel column (DCM/MeOH = 100/1 to 15/1) to give **4-6** (4 g, 73%) as a white solid.

[0210] To a solution of **4-6** (4.0 g, 5.8 mmol) in anhydrous THF (60 mL) was added DBU (3.67 g, 24 mmol), and the mixture was stirred at 60 °C overnight. The mixture was diluted with EA (80 mL). The solution was washed with brine. The organic layer was

dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by silica gel column (DCM/MeOH = 100/1 to 20/1) to give **4-7** (2 g, 61%) as a white solid.

[0211] To an ice cooled solution of **4-7** (500 mg, 0.89 mmol) in anhydrous DCM (20 mL) was added AgF (618 mg, 4.9 mmol) and a solution of I_2 (500 mg, 1.97 mmol) in anhydrous DCM (20 mL). The mixture was stirred at RT for 3 h. The reaction was quenched with sat $Na_2S_2O_3$ and $NaHCO_3$ aqueous, and the mixture was extracted with DCM (50 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated to give crude **4-8** (250 mg, crude) as a yellow solid.

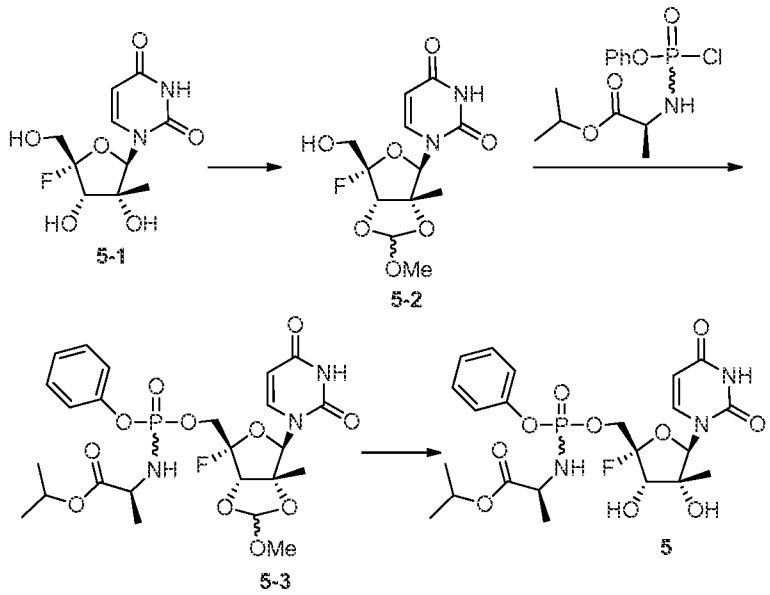
[0212] To a solution of crude **4-8** (900 mg, 1.28 mmol) in anhydrous DCM (50 mL) was added DMAP (1.0g, 8.2 mmol) and BzCl (795 mg, 5.66 mmol). The mixture was stirred at RT overnight. The mixture was washed with sat. $NaHCO_3$ aq. and brine. The organic layer was dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by prep-TLC (DCM/MeOH = 15:1) to give **4-9** (300 mg, 26%) as a white solid.

[0213] To a solution of crude **4-9** (750 mg, 0.82 mmol) in anhydrous HMPA (20 mL) was added NaOBz (1.2 g, 8.3 mmol) and 15-crown-5 (1.8 g, 8.3 mmol). The mixture was stirred at 60 °C for 2 d. The mixture was diluted with EA, and the solution was washed with brine. The organic layer was dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by prep-TLC (PE/EA = 1:1) to give crude **4-10** (550 mg, 73%) as a white solid.

[0214] Crude **4-10** (550 mg, 0.6 mmol) was dissolved in NH_3/MeOH (7N, 50 mL). The mixture was stirred at RT overnight. The mixture was concentrated, and the residue was purified by silica gel column (DCM/MeOH from 100/1 to 20/1) to give **4-11** (62 mg, 17%) as white solid. ESI-MS: m/z 598.0 $[M+H]^+$.

[0215] A solution of **4-11** (12 mg) in 80% formic acid (0.5 mL) stood at RT for 3.5 h and then was concentrated. The residue was co-evaporated with MeOH/toluene 4 times in a vial, then triturated with EtOAc at 40 °C. The EtOAc solution removed with pippet, and the trituration step was repeated several times. The remaining solid was dissolved in MeOH. The solution was concentrated and dried to give compound **4** (4.7 mg) as an off white solid. ESI-MS: m/z 326.6 $[M+H]^+$.

EXAMPLE 4
COMPOUND 5



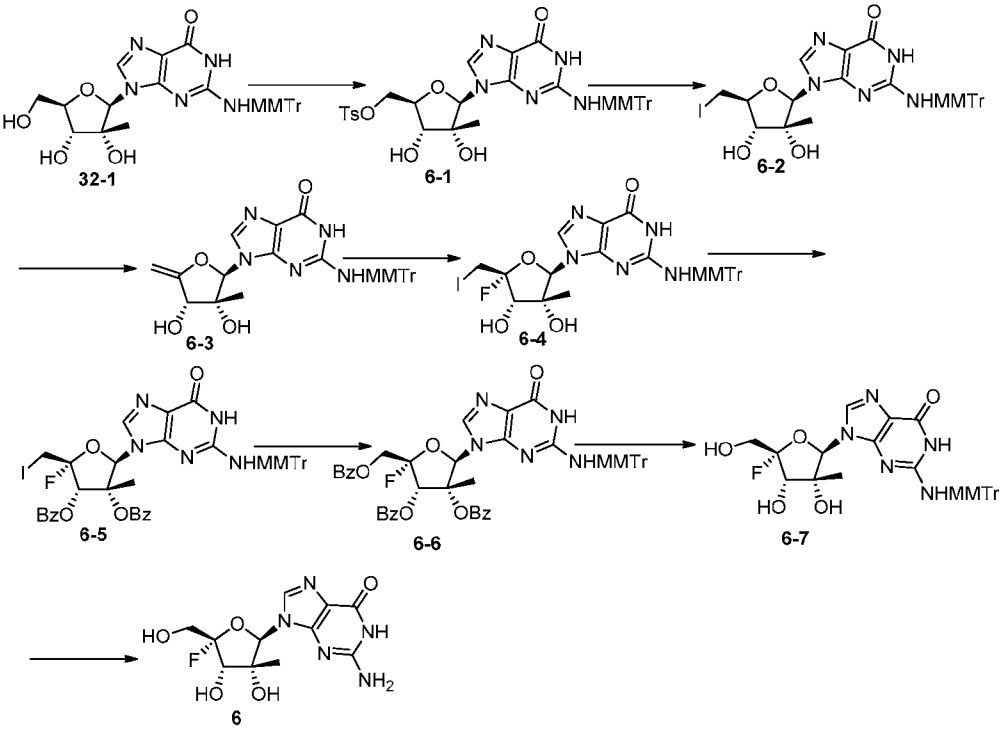
[0216] To a solution of **5-1** (1.2 g; 4.3 mmol) in dioxane (30 mL) were added p-toluenesulphonic acid monohydrate (820 mg; 1 eq.) and trimethyl orthoformate (14 mL; 30 eq.). The mixture was stirred overnight at RT. The mixture was then neutralized with methanolic ammonia and the solvent evaporated. Purification on silica gel column with CH_2Cl_2-MeOH solvent system (4-10% gradient) yielded **5-2** (1.18 g, 87%).

[0217] To an ice cooled solution of **5-2** (0.91 g; 2.9 mmol) in anhydrous THF (20 mL) was added iso-propylmagnesium chloride (2.1 mL; 2 M in THF). The mixture stirred at 0 °C for 20 mins. A solution of phosphorochloridate reagent (2.2 g; 2.5 eq.) in THF (2 mL) was added dropwise. The mixture stirred overnight at RT. The reaction was quenched with saturated aq. NH_4Cl solution and stirred at RT. for 10 mins. The mixture was then diluted with water and CH_2Cl_2, and the two layers were separated. The organic layer was washed with water, half saturated aq. $NaHCO_3$ and brine, and dried with Na_2SO_4. The evaporated residue was purified on silica gel column with CH_2Cl_2-iPrOH solvent system (4-10% gradient) to yield Rp/Sp-mixture of **5-3** (1.59 g; 93%).

[0218] A mixture of **5-3** (1.45 g; 2.45 mmol) and 80% aq. HCOOH (7 mL) was stirred at RT. for 1.5 h. The solvent was evaporated and coevaporated with toluene. The obtained residue was dissolved in MeOH, treated with Et_3N (3 drops) and the solvent was evaporated. Purification on silica gel column with CH_2Cl_2-MeOH solvent system (4-10%

gradient) yielded Rp/Sp-mixture of compound **5** (950 mg; 70%). ^{31}P-NMR (DMSO-d_6): δ 3.52, 3.37. MS: m/z = 544 [M-1].

EXAMPLE 5
COMPOUND 6



[0219] Compound **32-1** (5 g, 8.79 mmol) was co-evaporated with anhydrous pyridine. To an ice cooled solution of **32-1** in anhydrous pyridine (15 mL) was added TsCl (3.43 g, 17.58 mmol), and stirred for 1 h at 0 °C. The reaction was checked by LCMS and TLC. The reaction was quenched with H_2O, and extracted with EA. The organic phase was dried over anhydrous Na_2SO_4, and evaporated at low pressure. Compound **6-1** (6.35 g, 100%) was used for next step directly.

[0220] To a solution of **6-1** (31.77g, 43.94 mmol) in acetone (300 mL) was added NaI (65.86 g, 439.4 mmol), and heated to reflux overnight. The reaction was checked by LCMS. The reaction was quenched with sat. $Na_2S_2O_3$ solution, and extracted with EA. The organic layer was dried over anhydrous Na_2SO_4, and evaporated at low pressure. The residue was purified by silica gel column chromatography (MeOH in DCM from 1% to 6%) to give **6-2** (11.5g, 38%) as a white solid.

[0221] To a solution of **6-2** (11.5 g, 16.94 mmol) in dry THF (120 mL) was added DBU (12.87 g, 84.68 mmol), and heated to 60 °C. The reaction was stirred overnight and checked by LCMS. The reaction was quenched with sat. $NaHCO_3$ solution, and extracted with EA. The organic phase was dried over anhydrous Na_2SO_4, and evaporated at low pressure. The residue was purified by silica gel column chromatography (MeOH in DCM from 1% to 5%) to give **6-3** (5.5 g, 54%) as a white solid.

[0222] To an ice cooled solution of **6-3** (500 mg, 0.90 mmol) in dry DCM (20 mL) was added AgF (618 mg, 4.9 mmol) and a solution of I_2 (500 mg, 1.97 mmol) in dry DCM (20 mL). The reaction was stirred for 3 h., and checked by LCMS. The reaction was quenched with sat $Na_2S_2O_3$ solution and sat. $NaHCO_3$ solution, and the mixture was extracted with DCM. The organic layer was dried by anhydrous Na_2SO_4, and evaporated at low pressure to give crude **6-4** (420 mg, 66%).

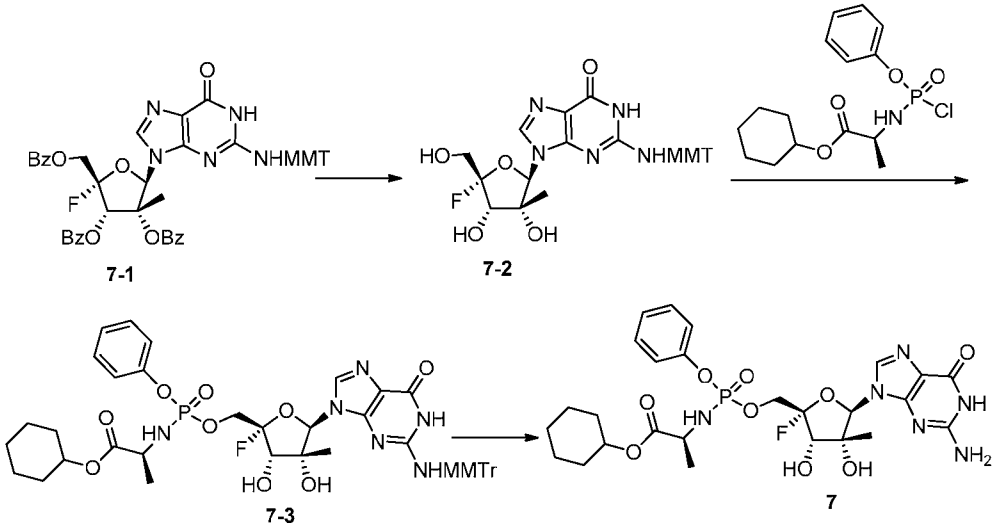
[0223] To a solution of crude **6-4** (250 mg, 0.36 mmol) in dry DCM (8 mL) was added DMAP (0.28 g, 2.33 mmol), TEA (145 mg, 1.44mmol) and BzCl (230 mg, 1.62 mmol) in a solution of DCM (2 mL). The reaction was stirred overnight, and checked by LCMS. The mixture was washed with sat. $NaHCO_3$ solution and brine. The organic layer was evaporated at low pressure. The residue was purified by prep-TLC to give crude **6-5** (150 mg, 46%).

[0224] To a solution of crude **6-5** (650 mg, 0.72 mmol) in dry HMPA (20 mL) was added NaOBz (1.03 g, 7.2 mmol) and 15-crown-5 (1.59 g, 7.2 mmol). The reaction was stirred for 2 d at 60 °C. The mixture was diluted with H_2O, and extracted with EA. The organic layer was evaporated at low pressure. The residue was purified by prep-TLC to give **6-6** (210 mg, 32.4%). ESI-MS: m/z: 900.4 $[M + H]^+$.

[0225] A mixture of **6-6** (25 mg) and $BuNH_2$ (0.8 mL) was stirred overnight at RT. The mixture was evaporated and purified on silica gel (10 g column) with CH_2Cl_2/MeOH (4-15% gradient) to yield **6-7** (15 mg, 91%).

[0226] A mixture of **6-7** (15 mg, 0.02 mmol) in ACN (0.25 mL) and 4 N HCL/dioxane (19 μL) was stirred at RT for 45 mins. The mixture was diluted with MeOH and evaporated. The crude residue was treated with MeCN, and the solid was filtered to yield compound **6** (7 mg). MS: m/z = 314 [M-1].

EXAMPLE 6
COMPOUND 7

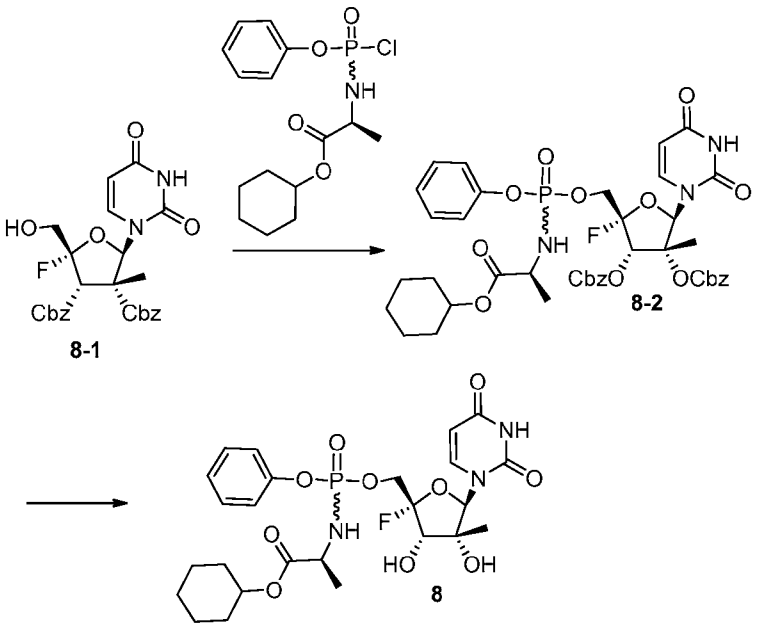


[0227] A mixture of **7-1** (170 mg, 0.19 mmol) and methanolic ammonia (7 N; 3 mL) was stirred at RT for 8 h, concentrated and purified on silica gel (10 g column) with CH_2Cl_2/MeOH (4-11% gradient) to give **7-2** (100 mg, 90%).

[0228] Compound **7-2** was rendered anhydrous by co-evaporating with pyridine, followed by toluene. To a solution of **7-2** (24 mg, 0.04 mmol), and N-methylimidazole (17 µL, 5 eq.) in acetonitrile (1 mL) was added the phosphorochloridate (50 mg, 3.5 eq.) in 2 portions in 6 h intervals. The mixture was stirred at RT for 1 d and evaporated. Purification on silica (10 g column) with CH_2Cl_2/MeOH (4-12% gradient) yielded **7-3** (10 mg, 28%).

[0229] A solution of **7-3** (9 mg, 0.01 mmol) in 80% formic acid was stirred 3 h at RT. The mixture was evaporated and purified on silica (10 g column) with CH_2Cl_2/MeOH (5-15% gradient) to give compound **7** (3 mg, 50%). MS: m/z = 624 [M-1].

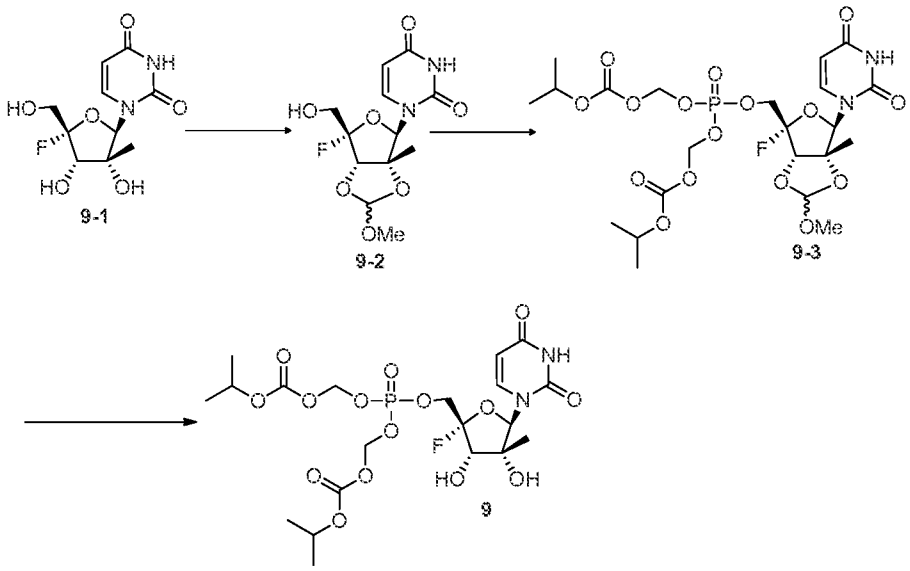
EXAMPLE 7
COMPOUND 8



[0230] To an ice cooled solution of **8-1** (80 mg; 015 mmol) in anhydrous THF (2 mL) was added isopropylmagnesium chloride (0.22 mL; 2 M in THF). The mixture stirred at 0 °C for 20 mins. A solution of the phosphorochloridate reagent (0.16 g; 0.45 mmol) in THF (0.5 mL) was added dropwise. The mixture stirred overnight at RT. The reaction was quenched with saturated aq. NH_4Cl solution and stirred at RT for 10 mins. The mixture was diluted with water and CH_2Cl_2, and the two layers were separated. The organic layer was washed with water, half saturated aq. $NaHCO_3$ and brine, and dried with Na_2SO_4. The evaporated residue was purified on silica gel column with CH_2Cl_2-MeOH solvent system (2-10% gradient) to yield Rp/Sp-mixture of **8-2** (102 mg; 80%).

[0231] A mixture of **8-2** (100 mg; 0.12 mmol) in EtOH (3 mL) and 10% Pd/C (10 mg) was stirred under the H_2 atmosphere for 1.5 h. The mixture was filtered through a Celite pad, evaporated and purified on silica gel column with CH_2Cl_2-MeOH solvent system (4-10% gradient) to yield Rp/Sp-mixture of compound **8** (52 mg, 74%). MS: m/z = 584 [M-1].

EXAMPLE 8
COMPOUND 9

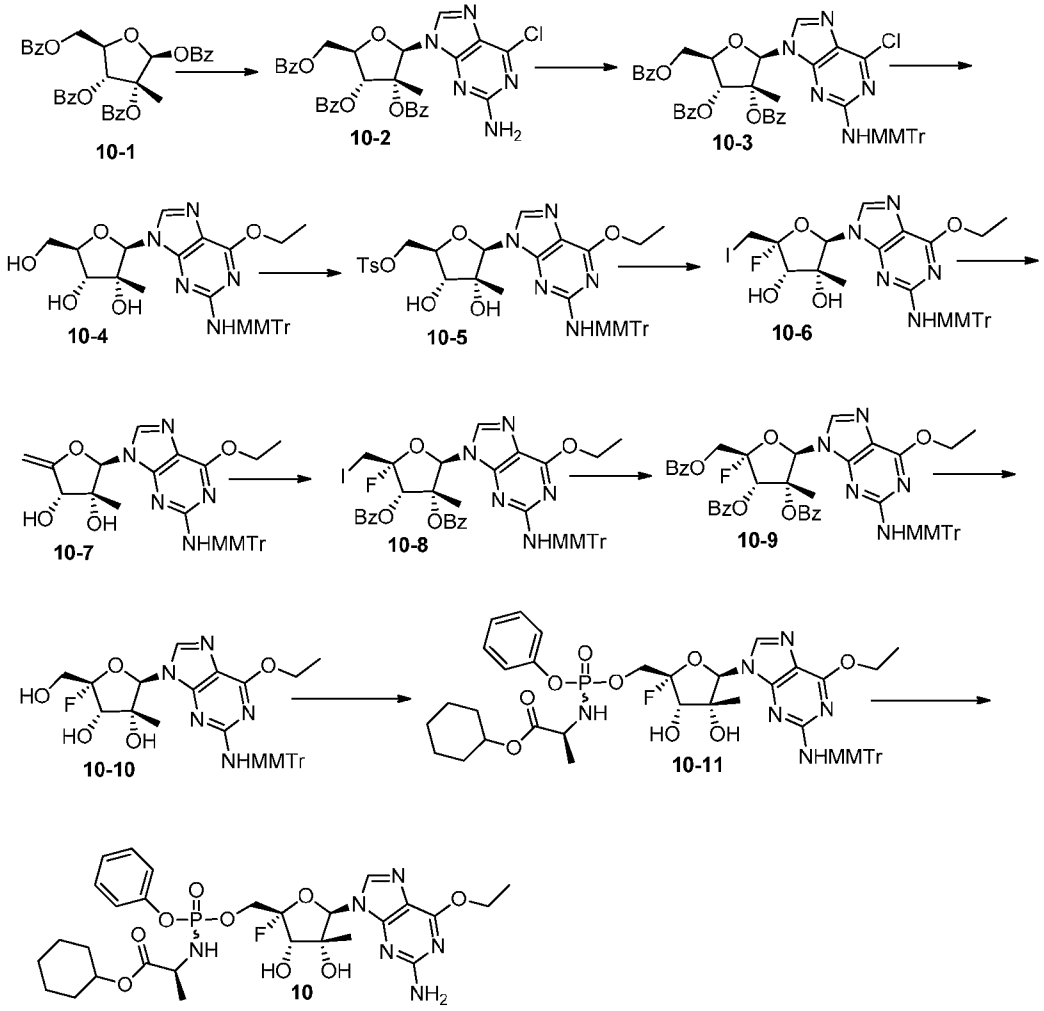


[0232] A mixture of **9-1** (1.2 g, 4.3 mmol), PTSA monohydrate (0.82 g, 1 eq.), and trimethyl orthoformate (14 mL, 30 eq.) in dioxane (30 mL) was stirred overnight at RT. The reaction was neutralized with 7 N NH_3/MeOH and a white solid removed by filtration. The residue was dissolved in THF (10 mL) and treated with 80% aq. AcOH (5 mL). The mixture was kept at RT for 45 mins and then evaporated. The residue was purified on silica gel (25 g column) with CH_2Cl_2/MeOH (4-10% gradient) to give **9-2** (1.18 g, 87%).

[0233] Compound **9-3** (137 mg, 75%) was prepared from **9-2** (93 mg, 0.29 mmol) and triethylammonium bis(isopropyloxycarbonyloxymethyl)phosphate (0.44 mmol) with DIPEA (0.2 mL), BopCl (147 mg), and 3-nitro-1,2,4-triazole (66 mg) in THF (3 mL). Purification was done with CH_2Cl_2 /i-PrOH solvent system (3-10% gradient).

[0234] A solution of **9-3** (137 mg) in 80% aq. HCOOH was stirred at RT for 2 h, and then concentrated. The residue was co-evaporated with toluene and then MeOH containing a small amount of a small amount of Et_3N (2 drops). Purification on silica (25 g column) with CH_2Cl_2/MeOH (4-10% gradient) gave compound **9** (100 mg, 77%). MS: m/z = 1175 (2M-1).

EXAMPLE 9
COMPOUND 10



[0235] Compound **10-1** (50 g, 86.0 mmol) and 6-Cl-guanine (16.1 g, 98.2 mmol) were co-evaporated with anhydrous toluene 3 times. To a solution of **10-1** in MeCN (200 mL) was added DBU (39.5 g, 258.0 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 mins, and then TMSOTf (95.5 g, 430.0 mmol) was added dropwise at 0 °C. The mixture was stirred at 0 °C for 30 mins. The mixture was heated to 70 °C, and stirred overnight. The solution was cooled to RT and diluted with EA (100 mL). The solution was washed with sat. $NaHCO_3$ solution and brine. The organic layer was dried over Na_2SO_4, and concentrated at low pressure. The residue was purified by column on silica gel (EA in PE from 10% to 40%) to give **10-2** (48.0 g, yield: 88.7%) as a yellow foam. ESI-MS: m/z 628 $[M+H]^+$.

[0236] To a solution of **10-2** (48.0 g, 76.4 mol), $AgNO_3$ (50.0 g, 294.1 mmol) and collidine (40 mL) in anhydrous DCM (200 mL) was added MMTrCl (46.0 g, 149.2 mmol) in small portions under N_2. The mixture was stirred at RT for 3 h under N_2. The reaction was monitored by TLC. The mixture was filtered, and the filter was washed with sat. $NaHCO_3$ solution and brine. The organic layer was dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by silica gel column (EA in PE from 5% to 50%) to the give crude **10-3** (68 g, 98%). ESI-MS: m/z 900.1 $[M+H]^+$.

[0237] Sodium (8.7 g, 378.0 mmol) was dissolved in dry EtOH (100 mL) at 0 °C, and slowly warmed to RT. Compound **10-3** (68.0 g, 75.6 mmol) was treated with freshly prepared NaOEt solution, and stirred overnight at RT. The reaction was monitored by TLC, and the mixture was concentrated at low pressure. The mixture was diluted with H_2O (100 mL), and extracted with EA (3 x 100 mL). The organic layer was dried over anhydrous Na_2SO_4, and evaporated at low pressure. The residue was purified by silica gel column chromatography (MeOH in DCM from 1% to 5%) to give **10-4** (34.0 g, 75.2%) as a yellow solid. ESI-MS: m/z 598 $[M+H]^+$.

[0238] Compound **10-4** (32.0 g, 53.5 mmol) was co-evaporated with anhydrous pyridine 3 times. To an ice cooled solution of **10-4** in anhydrous pyridine (100 mL) was added TsCl (11.2 g, 58.9 mmol) in pyridine (50 mL) dropwise at 0 °C. The mixture was stirred for 18 h. at 0 °C. The reaction was checked by LCMS (about 70% was the desired product). The reaction was quenched with H_2O, and the solution was concentrated at low pressure. The residue was dissolved in EA (100 mL), and washed with sat. $NaHCO_3$ solution. The organic layer was dried over anhydrous Na_2SO_4, and evaporated at low pressure. The residue was purified by silica gel column chromatography (MeOH in DCM from 1% to 5%) to give crude **10-5** (25.0 g, 62.2%) as a yellow solid. ESI-MS: m/z 752 $[M+H]^+$.

[0239] To a solution of **10-5** (23.0 g, 30.6 mmol) in acetone (150 mL) was added NaI (45.9 g, 306.0 mmol) and TBAI (2.0 g), and refluxed overnight. The reaction was monitored by LCMS. After the reaction was complete, the mixture was concentrated at low pressure. The residue was dissolved in EA (100 mL), washed with brine, and dried over anhydrous Na_2SO_4. The organic solution was evaporated at low pressure. The residue was purified by silica gel column chromatography (DCM: MeOH=100:1 to 20:1) to give the

crude product. To a solution of the crude product in dry THF (200 mL) was added DBU (14.0 g, 91.8 mmol), and heated to 60°C. The mixture was stirred overnight, and checked by LCMS. The reaction was quenched with sat. $NaHCO_3$, and the solution was extracted with EA (100 mL). The organic layer was dried over anhydrous Na_2SO_4, and evaporated at low pressure. The residue was purified by silica gel column chromatography (MeOH in DCM from 1% to 5%) to give **10-6** (12.0 g, 67.4%) as a yellow solid. ESI-MS: m/z 580 $[M+H]^+$.

[0240] To an ice cooled solution of **10-6** (8.0 g, 13.8 mmol) in dry MeCN (100 mL) was added NIS (3.9 g, 17.2 mmol) and TEA•3HF (3.3 g, 20.7 mmol) at 0 °C. The mixture was stirred at RT for 18 h and checked by LCMS. After the reaction was complete, the reaction was quenched with sat Na_2SO_3 and sat. $NaHCO_3$ solution. The solution was extracted with EA. The organic layer was dried over anhydrous Na_2SO_4, and evaporated at low pressure. The residue was purified by silica gel column chromatography (EA in PE from 10% to 50%) to give **10-7**(7.2 g, 72.0%) as a solid. ESI-MS: m/z 726 $[M+H]^+$.

[0241] To a solution of crude **10-7** (7.2 g, 9.9 mmol) in dry DCM (100 mL) was added DMAP (3.6 g, 29.8 mmol), and BzCl (2.8 g, 19.8 mmol) at 0 °C. The mixture was stirred overnight, and checked by LCMS. The mixture was washed with sat. $NaHCO_3$ solution. The organic layer was dried over anhydrous Na_2SO_4, and evaporated at low pressure. The residue was purified by silica gel column chromatography (EA in PE from 10% to 30%) to give **10-8** (8.0 g, 86.4%) as a solid. ESI-MS: m/z 934 $[M+H]^+$.

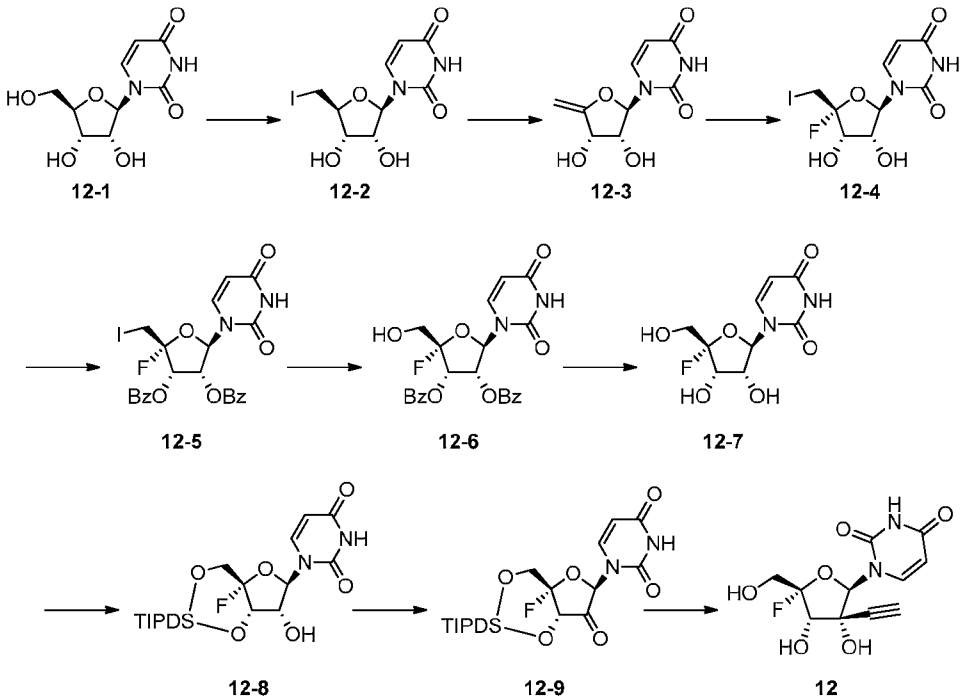
[0242] To a solution of **10-8** (7.5 g, 8.0 mmol) in dry DMF (100 mL) was added NaOBz (11.5 g, 80.0 mmol) and 15-crown-5 (15.6 mL). The mixture was stirred for 36 h. at 90 °C. The mixture was diluted with H_2O (100 mL), and extracted with EA (3x150 mL). The organic layer was dried over anhydrous Na_2SO_4, and evaporated at low pressure. The residue was purified by silica gel column chromatography (EA in PE from 10% to 30%) to give crude **10-9** (6.0 g, 80.0%) as a solid. ESI-MS: m/z 928 $[M+H]^+$.

[0243] Compound **10-9** (4.0 g, 4.3 mmol) was co-evaporated with anhydrous toluene 3 times, and treated with NH_3/MeOH (50 mL, 4N) at RT. The mixture was stirred for 18 h at RT. The reaction was monitored by LCMS, and the mixture was concentrated at low pressure. The residue was purified by silica gel column chromatography (EA in PE from 30% to 50%) to give **10-10** (1.9 g, 71.7%) as a solid. ESI-MS: m/z 616 $[M+H]^+$.

[0244] Compound **10-10** (300.0 mg, 0.49 mmol) was co-evaporated with anhydrous toluene 3 times, and was dissolved in MeCN (2 mL). The mixture was treated with NMI (120.5 mg, 1.47 mmol) and the phosphorochloridate reagent (338.1 mg, 0.98 mmol) in MeCN (1 mL) at 0°C. The mixture was stirred for 18 h at RT. The reaction was monitored by LCMS. The mixture was diluted with 10% $NaHCO_3$ solution, and extracted with EA. The residue was purified by silica gel column chromatography (EA in PE from 30% to 50%) to give **10-11** (240 mg, 53.3%) as a solid. ESI-MS: m/z 925 $[M+H]^+$.

[0245] Compound **10-11** (240.0 mg, 0.26 mmol) was treated with 80% AcOH (10 mL), and the mixture was stirred for 18 h at RT. The reaction was monitored by LCMS. The mixture was concentrated at low pressure. The residue was purified by silica gel column chromatography (MeOH in DCM from 1% to 3%) to give compound **10** (87.6 mg, 51.7%) as a solid. ESI-MS: m/z 653 $[M+H]^+$.

EXAMPLE 10
COMPOUND 12



[0246] To a stirred suspension of **12-1** (20.0 g, 81.3 mmol), imidazole (15.9 g, 234.0 mmol), PPh_3 (53.5 g, 203.3 mmol) and pyridine (90 mL) in anhydrous THF (100 mL) was added a solution of I_2 (41.3 g, 162.6 mmol) in THF (150 mL) dropwise at 0 °C. The mixture was slowly warmed to RT and stirred for 14 h. The reaction was quenched with sat.

aq. $Na_2S_2O_3$ (150 mL) and extracted with THF/EA (1/1) (100 mL x 3). The organic layer was dried over Na_2SO_4, and concentrated at a low pressure. The residue was recrystallized from EtOH to afford pure **12-2** (23 g, 79%) as a white solid.

[0247] To a stirred solution of **12-2** (23 g, 65 mmol) in anhydrous MeOH (200 mL) was added $NaOCH_3$ (10.5 g, 195 mmol) in MeOH (50 mL) at RT. The mixture was stirred at 60 °C for 3 h, and quenched with dry ice. A solid precipitated and removed by filtration. The filtrate was concentrated at a low pressure. The residue was purified on column silica gel column (MeOH in DCM from 1% to 10%) to provide **12-3** (13.1 g, 92.5%) as a white foam solid.

[0248] To a stirred solution of **12-3** (12.0 g, 53 mmol) in anhydrous CH_3CN was added TEA•3HF (8.5 g, 53 mmol) and NIS (10.2 g, 63.6 mmol) at 0 °C. The mixture was stirred for 30 mins, and slowly warmed to RT. The mixture was stirred for another 30 mins. The solid was removed by filtration, and washed with DCM to give **12-4** (14 g, 73%) as a yellow solid. ESI-MS: m/z 373.0 $[M+H]^+$.

[0249] To a stirred solution of **12-4** (12.0 g, 32 mmol) and DMAP (1.2 g, 9.6 mmol) in pyridine (100 mL) was added Bz_2O (21.7 g, 96 mmol) at RT. The mixture was stirred at 50 °C for 16 h. The resulting solution was quenched with water, and concentrated to dryness at low pressure. The crude was purified on silica gel column (50% EA in PE) to give **12-5** (15 g, 81%) as a white solid. ESI-TOF-MS: m/z 581.0 $[M+H]^+$.

[0250] Tetra-butylammonium hydroxide (288 mL as 54-56% aqueous solution, 576 mmol) was adjusted to pH~4 by adding TFA (48 mL). The resulting solution was treated with a solution of **12-5** (14 g, 24 mmol) in DCM (200 mL). *m*-Chloroperbenzoic acid (30 g, 60-70%, 120 mmol) was added portion wise with vigorous stirring, and the mixture was stirred overnight. The organic layer was separated and washed with brine. The resulting solution was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography to give **12-6** (7.5 g, 68%)

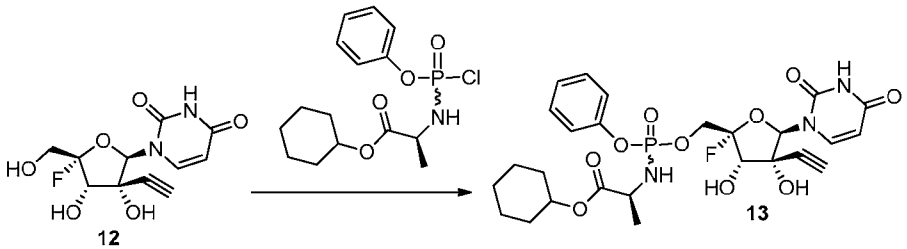
[0251] Compound **12-6** (5.0 g, 10.6 mmol) was treated with 7N NH_3•MeOH (100 mL), and the mixture was stirred for 5 h. The mixture was then concentrated to dryness at low pressure. The residue was washed with DCM, and the solid was filtered to give **12-7** (2.1 g, 75%) as a white foam. ESI-MS: m/z 263.0 $[M+H]^+$.

[0252] To a solution of **12-7** (2.1 g, 8.0 mmol) in pyridine was added TIDPSCl (2.5 g, 8.0 mmol) dropwise at 0 °C, and stirred for 12 h. at RT. The solution was quenched with water, and concentrated to dryness at low pressure. The crude was purified by column chromatography (EA in PE from 10% to 50%) to give pure **12-8** (1.6 g, 40%) as a white foam.

[0253] A solution of **12-8** (1.5 g, 3.0 mmol) and IBX (1.69 g, 6.0 mmol) in anhydrous CH_3CN (10 mL) was stirred at 80 °C for 3 h. The mixture was cooled down to RT and filtered. The filtrate was concentrated to dryness at low pressure. The residue was purified by column chromatography (EA in PE from 2% to 50%) to give pure **12-9** (1.2 g, 80%) as a white foam. ESI-MS: m/z 503.0 $[M+H]^+$

[0254] Compound **12-9** (500 mg, 1 mmol) was dissolved in dry THF (8 mL). Ethynyl magnesium bromide (8 mL of 0.5M solution in cyclohexane) was added at RT. After 30 mins, additional ethynyl magnesium bromide (8 mL) was added. The mixture was left for 30 mins, and then quenched with sat. solution of ammonium chloride. The product was extracted with EA. The organic extracts were washed with brine, dried, and concentrated. The residue was purified by flash chromatography on silica gel in EA to remove the dark color. The yellow compound was dissolved in THF (3 mL) and treated with TBAF (1mL, 2M solution in THF) for 30 mins. The solvent was evaporated, and the residue was subjected to silica gel chromatography on a Biotage cartridge (25g). EA saturated with water was used for isocratic elution. Each fractions were analyzed by TLC in DCM:MeOH (9:1 v:v). Fractions containing only the isomer with a high Rf were concentrated to give pure compound **12** (110 mg). MS: 285.1 [M-1].

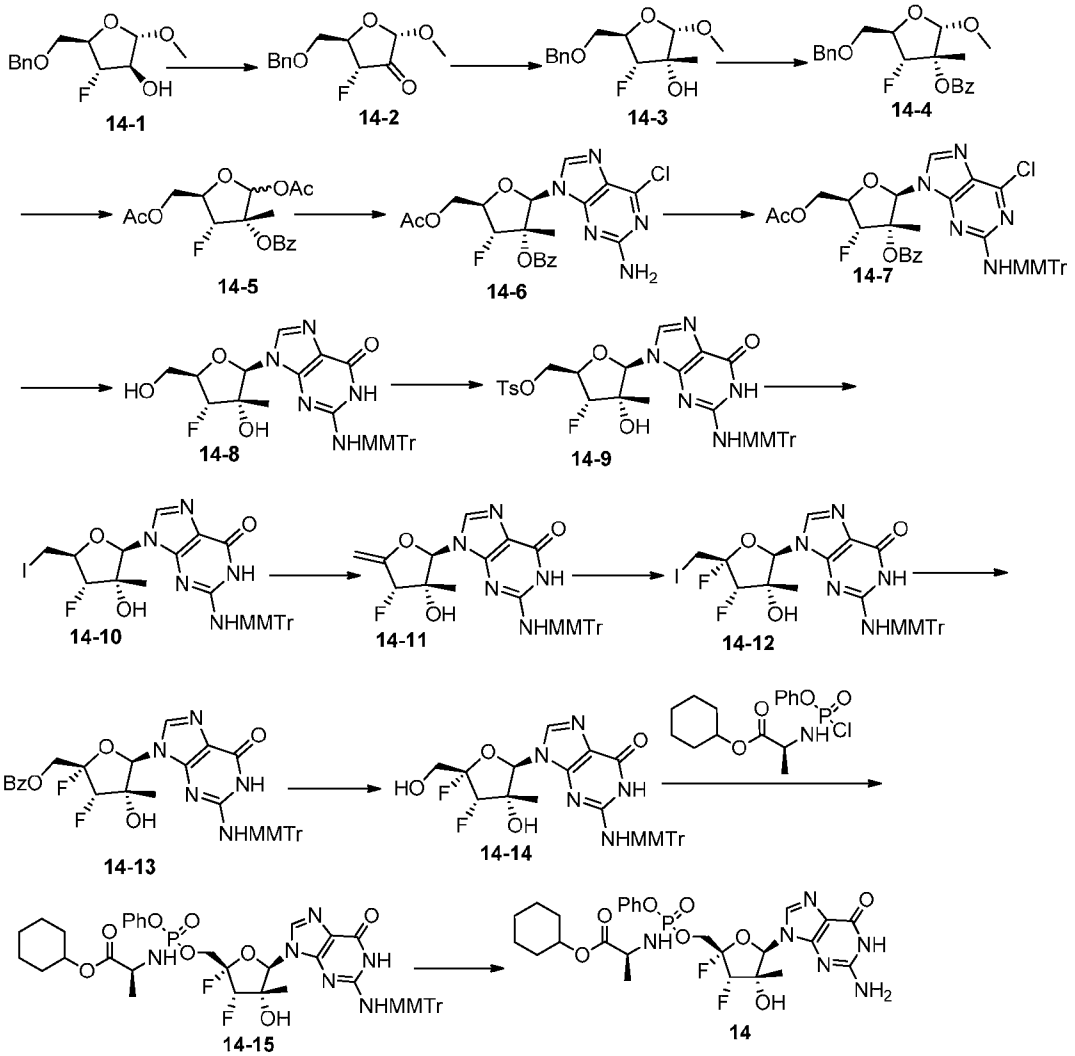
EXAMPLE 11
COMPOUND 13



[0255] Compound **12** (57 mg, 0.2 mmol) was dissolved in CH_3CN (2 mL), containing N-methylimidazole (40 uL). The phosphorochloridate reagent (207 mg, 0.6

mmol) was added, and the mixture was kept overnight at 40 ^{0}C. The mixture was distributed between water and EA. The organic layer was separated, washed with brine, dried and evaporated. The product was isolated by silica gel chromatography in gradient of methanol in DCM from 0% to 15%. Compound **13** was obtained (46 mg, 39%). MS: m/z 593.9 [M-1].

EXAMPLE 12
COMPOUND 14



[0256] To a stirred solution of **14-1** (5.0 g, 19.53 mmol) in anhydrous MeCN was added IBX (7.66 g, 27.34 mmol) at RT. The mixture was heated at 80 °C for 12 h, and then slowly cooled to RT. After filtration, the filtrate was concentrated to give crude **14-2** (4.87 g, 98%).

[0257] To a solution of **14-2** (4.96 g, 19.53 mmol) in anhydrous THF at -78 °C under N_2 was added methyl magnesium bromide (19.53 mL, 58.59 mmol) by dropwise. The mixture was slowly warmed to RT, and stirred for 12 h. The mixture was quenched with sat. NH_4Cl solution, and extracted with EA. The organic layer was dried over anhydrous Na_2SO_4, and evaporated at low pressure. The residue was purified by silica gel column chromatography to give **14-3** (4.37 g, 83%) as a white solid.

[0258] To a solution of **14-3** (4.37 g, 16.19 mmol) in anhydrous DCM (20 mL) was added DMAP (3.95 g, 32.38 mmol), TEA (4.91 g, 48.56 mmol), and BzCl (6.80 g, 48.56 mmol) at 0 °C. The mixture was stirred at RT overnight. The reaction was quenched with sat. $NaHCO_3$ solution (30 mL), and extracted with EA (3 x 50 mL). The organic layer was dried over anhydrous Na_2SO_4, and evaporated at low pressure. The residue was purified by silica gel column chromatography to give crude **14-4** (5.3 g, 87%) as a white solid.

[0259] To a solution of **14-4** (3.0 g, 8.02 mmol) and Ac_2O (4.91 g, 48.13 mmol) in acetic acid (10 mL) was added concentrated H_2SO_4 (98%, 2.41 g, 24.06 mmol) at 0 °C. The mixture was stirred at RT for 12 h. The solution was poured into ice water (30 mL), and extracted with EA (3 x 50 mL). The organic layer was dried over anhydrous Na_2SO_4, and evaporated at low pressure. The residue was purified by silica gel column chromatography to give **14-5** (2.3 g, 81%)) as a white solid.

[0260] To a stirred solution of 6-Cl-guanine (560 mg, 3.31 mmol) and**14-5** (1.11 g, 2.76 mmol) in anhydrous MeCN (5 mL) was added DBU (1.27 g, 8.28 mmol) under N_2 at 0 °C. The mixture was stirred at RT for 30 mins. The mixture was cooled to 0 °C, and TMSOTf (2.45 g, 11.04 mmol) was added slowly in 15 mins. The mixture was then warmed RT in 30 mins. The mixture was heated at 60 °C for 4 h. The mixture was then poured into ice water (30 mL), and extracted with EA (3 x 50 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated at low pressure. The residue was purified by silica gel column chromatography to give **14-6** (800 mg, 70%) as a white solid.

[0261] To a solution of **14-6** (839 mg, 1.64 mmol), MMTrCl (1.46 g, 4.75 mmol) and $AgNO_3$ (697 mg, 4.1 mmol) in DCM (10 mL) was added collidine (794 mg, 6.56 mmol). The mixture was stirred for 12 h at RT. The reaction was quenched with sat. $NaHCO_3$ solution (20 mL). After filtration, the filtrate was extracted with DCM (3 x 20 mL). The organic layer was dried over anhydrous Na_2SO_4, and evaporated at low pressure. The residue

was purified by silica gel column chromatography to give **14-7** (1.3 g, 72.5%) as a white solid.

[0262] 3-hydroxyl acrylic nitrile (4.13 g, 5.82 mmol) was dissolved in anhydrous THF (10 mL). The solution was treated with NaH (464 mg, 11.6 mmol) at 0°C, and slowly warmed to RT, and stirred for 30 mins. A solution of **14-7** (912 mg, 1.16 mmol) in anhydrous THF (5 mL) was added slowly. The mixture was stirred at RT overnight. The reaction was quenched with water (40 mL), and extracted with EA (3 x 50 mL). The organic layer was dried over anhydrous Na_2SO_4, and evaporated at low pressure. The residue was purified by silica gel column chromatography to give **14-8** (600 mg, 85%) as a white solid.

[0263] To a solution of **14-8** (6.20 g, 10.86 mmol) in anhydrous pyridine (10 mL) at 0 °C was added a solution of TsCl (4.54 g, 23.89 mmol) in anhydrous pyridine (10 mL) dropwise. The mixture was stirred at RT for 30 mins. The mixture was quenched with water (30 mL), and extracted with EA (3 x 50 mL). The organic layer was dried over anhydrous Na_2SO_4, and evaporated at low pressure. The residue was purified by silica gel column chromatography to give **14-9** (6.0 g, 76%) as a white solid.

[0264] To a solution of **14-9** (6.0 g, 8.28 mmol) in acetone (30 mL) was NaI (4.97 g, 33.12 mmol), and refluxed overnight. The mixture was evaporated under reduced pressure. The residue was dissolved in EA (50 mL), and washed with sat .$NaHCO_3$ solution (30 mL). The organic layer was dried over anhydrous Na_2SO_4, and evaporated at low pressure. The residue was purified by silica gel column chromatography to give **14-10** (5.43 g, 96.4%) as a white solid.

[0265] To a solution of **14-10** (5.0 g, 7.34 mmol) in anhydrous THF (20 mL) was added DBU (4.49 g, 29.37 mmol), and stirred at 60 °C overnight. The mixture was slowly cooled to RT. The mixture was quenched with water (30 mL), and extracted with EA (3 x 50 mL). The organic layer was dried over anhydrous Na_2SO_4, and evaporated at low pressure. The residue was purified by silica gel column chromatography to give **14-11** (3.5 g, 85%) as a white solid.

[0266] To a solution of **14-11** (3.5 g, 6.33 mmol) and AgF (4.42 g, 34.81 mmol) in anhydrous DCM (20 mL) was added a solution of iodine (3.54 g, 13.93 mmol) in anhydrous DCM (5 mL) dropwise at 0°C. The mixture was stirred for 3 h. The reaction mixture was washed with sat. $NaHCO_3$ solution (40 mL) and extracted with EA (3 x 50 mL).

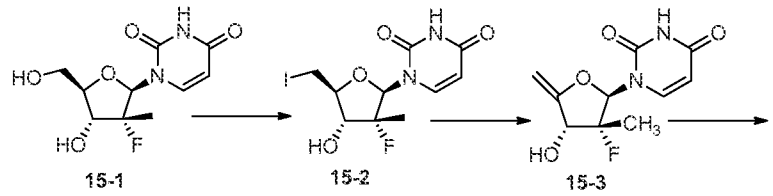
The organic layer was dried over anhydrous Na_2SO_4, and evaporated at low pressure. The residue was purified by silica gel column chromatography to give crude **14-12** (1.37g, 31%) as a white solid.

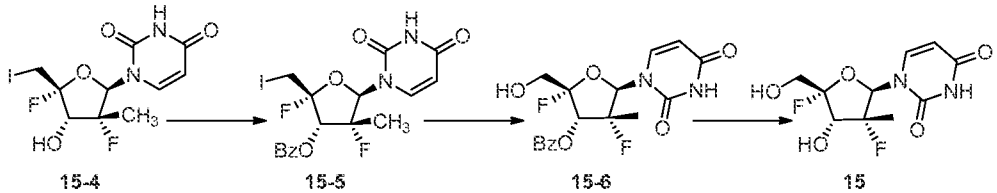
[0267] To a solution of **14-12** (1.37 g, 1.96 mmol) in anhydrous DMF (15 mL) was added sodium benzoate (2.82 g, 19.60 mmol) and 15-crown-5 (4.31 g, 19.60 mmol), and stirred at 90 °C for 3 d. The mixture was quenched with water (30 mL), and extracted with EA (3 x 50 mL). The organic layer was dried over anhydrous Na_2SO_4, and evaporated at low pressure. The residue was purified by HPLC separation to give **14-13** (250 mg, 20%). ESI-MS: m/z: 694 $[M+H]^+$

[0268] A mixture of **14-13** (250 mg, 0.36 mmol) in liquid ammonia was kept overnight at RT in high pressure glass vessel. Ammonia was then evaporated, and the residue purified on silica gel (10 g column) with CH_2Cl_2/MeOH (4-10% gradient) to give **14-14** (180 mg, 85%).

[0269] Compound **14** (85 mg, 56%) was prepared from **14-14** (99 mg) with i-PrMgCl (0.11 mL) and the phosphorochloridate reagent (94 mg) in THF (2 mL) followed by deprotection. MS: m/z = 627 [M+1].

EXAMPLE 13
COMPOUND 15





[0270] To a solution of **15-1** (260 mg, 1 mmol), PPh_3 (780 mg, 3 mmol) and pyridine (0.5 mL) in anhydrous THF (8 mL) were added I_2 (504 mg, 2 mmol) at RT, and the mixture was stirred at RT for 12 h. The mixture was diluted with EtOAc and washed with 1M HCl solution. The organic layer was dried over Na_2SO_4, filtered and concentrated at low

pressure. The residue was purified by silica gel column (5% MeOH in DCM) to give **15-2** (190 mg, 85%) as a white solid.

[0271] To a solution of **15-2** (190 mg, 0.52 mmol) in THF (4 mL) was added DBU (760 mg, 5 mmol) at RT, and the mixture was heated at 50 °C overnight. The mixture was diluted with EtOAc, and washed with water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by silica gel column (30% EA in PE) to give **15-3** (75 mg, 52%) as a white solid.

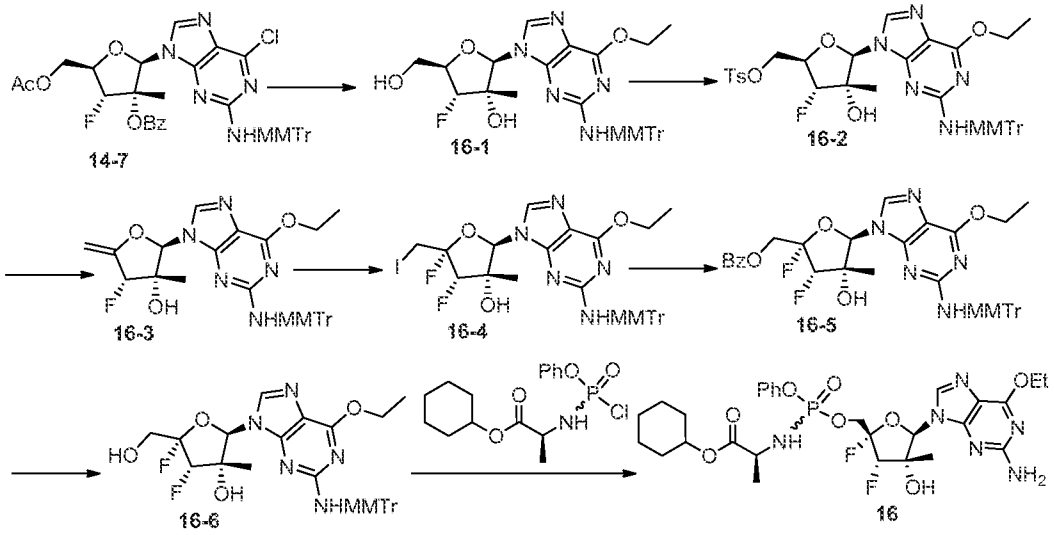
[0272] To a solution of **15-3** (200 mg, 0.82 mmol) in MeCN (anhydrous, 4 mL) was added NIS (337 mg, 1.5 mmol) and TEA•3HF (213 mg, 1.25 mmol) at RT, and the mixture was stirred at RT for 7 h. The reaction was quenched with sat. Na_2SO_3 solution and sat. aq. $NaHCO_3$ solution. The mixture was extracted with EA. The organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by silica gel column (20% EA in PE) to give **15-4** (300 mg, 62%) as a white solid.

[0273] To a solution of **15-4** (194 mg, 0.5 mmol) in pyridine(5 mL) was added BzCl (92 mg, 0.55 mmol) at 0 °C. The mixture was stirred at RT for 5 h, and the reaction was quenched with water. The mixture was concentrated at low pressure, and the residue was purified by silica gel column (20% EA in PE) to give **15-5** (397 mg, 81%) as a white solid.

[0274] To a solution of **15-5** (1.05 g, 2.13 mmol) in DCM (12 mL) was added a mixture of TFA (0.5 mL) and Bu_4NOH (1 mL), followed by addition of *m*-CPBA (1.3 g, 6 mmol) at RT. The mixture was stirred at RT for 5 h. The mixture was washed with sat. Na_2SO_3 solution and aq. $NaHCO_3$ solution. The organic layer was dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by silica gel column (30% EA in PE) to give **15-6** (450 mg, 63%) as a white solid.

[0275] Compound **15-6** (250 mg, 0.65 mmol) was dissolved in NH_3/MeOH (5 mL). The mixture was stirred at RT for 5 h, and then concentrated at low pressure. The residue was purified by silica gel column (5% MeOH in DCM) to give compound **15** (120 mg, 66%) as a white powder. ESI-MS: m/z 279.0 $[M+H]^+$.

EXAMPLE 14
COMPOUND 16



[0276] Sodium (6.0 g, 261.2 mmol) was dissolved in dry EtOH (400 mL) at 0 °C, and slowly warmed to RT. Compound **14-7** (32.0 g, 43.5 mmol) was treated with a freshly prepared NaOEt solution at 0 °C, and the mixture was stirred at RT overnight. The reaction was monitored by TLC and LCMS. After completion of the reaction, the mixture was concentrated at low pressure. The mixture was quenched with H_2O (40 mL), and extracted with EA (3 x 50 mL). The organic layer was dried over anhydrous Na_2SO_4, and evaporated at low pressure. The residue was purified by silica gel column chromatography (MeOH in DCM from 0.5% to 2%) to give **16-1** (20.0 g, 76.6%) as a white solid.

[0277] Compound **16-1** (20.0 g, 33.3 mmol) was co-evaporated with anhydrous pyridine 3 times. To an ice cooled solution of **16-1** in anhydrous pyridine (100 mL) was added TsCl (9.5 g, 49.9 mmol) at 0 °C. After addition, the reaction was stirred for 12 h at 20 °C, and monitored by LCMS. The reaction was quenched with H_2O, and concentrated at low pressure. The residue was dissolved in EA (50 mL). The solution was washed with sat. $NaHCO_3$ solution and brine. The organic layer was dried over anhydrous Na_2SO_4, and evaporated at low pressure. The residue was purified by silica gel column chromatography (MeOH in DCM from 0.5% to 2%) to give **16-2** (20.0 g, 80%) as a yellow solid.

[0278] To a solution of **16-2** (20.0 g, 26.5 mmol) in acetone (100 mL) was added NaI (31.8 g, 212 mmol), and heated to reflux overnight. The reaction was checked by LCMS. After the reaction was complete, the mixture was concentrated at low pressure. The

residue was dissolved in EA (50 mL). The solution was washed with brine. The organic layer was dried over anhydrous Na_2SO_4, and evaporated at low pressure. The residue was purified by silica gel column chromatography (MeOH in DCM from 0.5% to 2%) to give a crude product. To a solution of the crude product in dry THF (60 mL) was added DBU (16.2 g, 106 mmol), and heated to 60 °C. The mixture was stirred overnight and checked by LCMS. The reaction was quenched with sat. $NaHCO_3$ solution, and extracted with EA (3 x 50 mL). The organic phase was washed with brine, dried over anhydrous Na_2SO_4, and evaporated at low pressure. The residue was purified by silica gel column chromatography (MeOH in DCM from 0.5% to 2%) to give **16-3** (12.0 g, 77.9%) as a yellow solid.

[0279] To an ice-clod solution of **16-3** (11.0 g, 18.9 mmol) in dry MeCN (100 mL) was added NIS (5.4 g, 23.7 mmol) and NEt_3•3HF (3.0 g, 18.9 mmol) at 0 °C. The mixture was stirred at RT for 4 h., and checked by LCMS. After the reaction was complete, the reaction was quenched with sat. Na_2SO_3 solution and sat. $NaHCO_3$ solution. The solution was extracted with EA (3 x 100 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated at low pressure. The residue was purified by silica gel column chromatography (EA in PE from 12% to 50%) to give **16-4** (11.0 g, 79.9%).

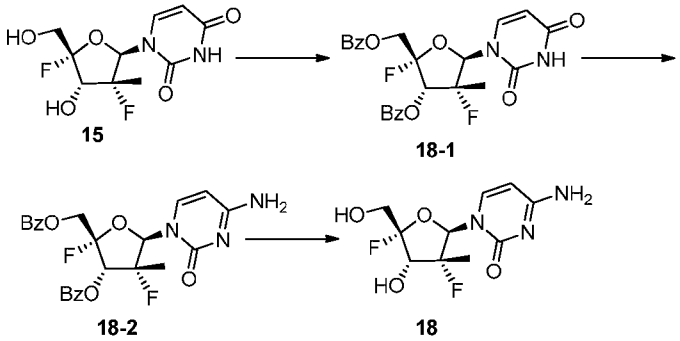
[0280] To a solution of **16-4** (10.0 g, 13.7 mmol) in dry DMF (100 mL) was added NaOBz (19.8 g, 137 mmol) and 15-crown-5 (30.2 g, 137 mmol). The reaction was stirred for 48 h at 90 °C, and diluted with EA. The solution was washed with water and brine, and dried over $MgSO_4$. The organic layer was evaporated at low pressure, and the residue was purified by silica gel column chromatography (EA in PE from 12% to 50%) to give **16-5** (8.0 g, 80.0%).

[0281] Compound **16-5** (6.0 g, 8.3 mmol) was co-evaporated with anhydrous toluene 3 times, and treated with NH_3 in MeOH (4N, 50 mL) at RT. The reaction was stirred for 18 h at RT. The reaction was monitored by LCMS. After the reaction was complete, the mixture was concentrated at low pressure. The residue was purified by silica gel column chromatography (EA in PE from 20% to 50%) to give **16-6** (4.5 g, 87.8%). ESI-MS: m/z 617.9 $[M+H]^+$.

[0282] To an ice cooled mixture of **16-6** (25 mg, 0.07 mmol) and NMI (46 μL, 8 eq.) in acetonitrile (0.7 mL) was added the phosphorochloridate reagent (73 mg, 3 eq.) and stirred overnight at RT. Additional amounts of NMI (46 uL) and the phosphorochloridate

reagent (73 mg) were added and stirring continued for 1 d. The reaction was quenched with sat. aq. NH_4Cl, diluted with EtOAc and water. The organic layer was separated and washed with aq. $NaHCO_3$, water, and brine, and then dried (Na_2SO_4). The residue was purified on silica gel (10 g column) with CH_2Cl_2/i-PrOH (4-10% gradient) to yield compound **16** (18 mg, 40%). MS: m/z = 655 [M+1].

EXAMPLE 15
COMPOUND 18

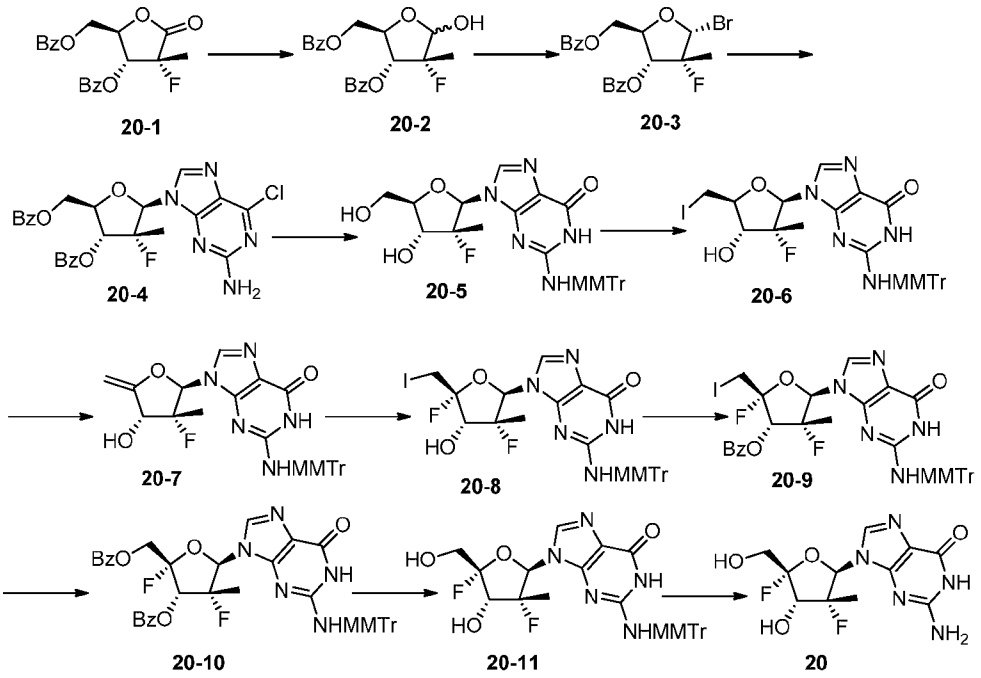


[0283] To a solution of compound **15** (139 mg, 0.5 mmol) in pyridine (5 mL) was added BzCl (92 mg, 0.55 mmol) at 0 °C. The mixture was stirred at RT for 5 h, diluted with EtOAc and washed with 1N HCl solution. The organic layer was dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by silica gel column (20% EA in PE) to give **18-1** (274 mg, 79%) as a white solid.

[0284] To a solution of **18-1** (490 mg, 1 mmol), DMAP (244 mg, 2 mmol) and TEA (205 mg, 2.1 mmol) in MeCN (10 mL) were added TPSCl (604 mg, 2 mmol) at 0 °C. The mixture was stirred at RT for 2 h., and then NH_4OH aq. was added at RT. The mixture was stirred for 0.5 h, diluted with EtOAc and washed with sat. aq. $NaHCO_3$ and brine. The organic layer was dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by silica gel column (30% EA in PE) to give **18-2** (250 mg, 41%) as a white solid.

[0285] Compound **18-2** (250 mg, 0.51 mmol) was dissolved in NH_3/MeOH (15 mL). The mixture was stirred at RT for 5 h. and then concentrated at low pressure. The residue was purified by silica gel column (5% DCM in DCM) to give compound **18** (95 mg, 66%) as a white powder. ESI-MS: m/z 278.1 $[M+H]^+$.

EXAMPLE 16
COMPOUND 20



[0286] To a solution of compound **20-1** (30 g, 0.08 mol) in anhydrous THF (300 mL) was added a solution of lithium tri-tert-butoxyaluminohydride (120 mL, 0.12 mol) dropwise at -78 °C under N_2. The mixture was stirred at -20 °C for 1 h. The reaction was quenched with sat. aq. NH_4Cl and then filtered. The filtrate was extracted with EA (3 x 300 mL). The organic layer was dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by silica gel column (10% EA in PE) to give **20-2** (26 g, 86%) as a colorless oil.

[0287] To a stirred solution of PPh_3 (37.7 g, 0.144 mol) in DCM (100 mL) was added compound **20-2** (27 g, 0.072 mol) at -20 °C under N_2. After the mixture was stirred at RT for 15 mins, CBr_4 (42 g, 0.129 mol) was added while maintaining the reaction temperature between -25 and -20°C under N_2. The mixture was then stirred below -17 °C for 20 mins. Silica gel was added into the solution, and then purified by flash silica gel column separation to give the crude oil product. The crude was purified by silica gel column (EA in PE from 2% to 20%) to give **20-3** (α-isomer, 17 g, 55%) as a colorless oil.

[0288] A mixture of 6-Cl-guanine (11.6 g, 68.8 mmol) and t-BuOK (8.2 g, 73 mmol) in t-BuOH (200 mL) and MeCN (150 mL) was stirred at 35 °C for 30 mins, and then

20-3 (10 g, 22.9 mmol) in MeCN 100 mL) was added at RT. The mixture was heated at 50 °C overnight. The reaction was quenched with a solution of NH_4Cl (5 g) in water (40 mL), and the mixture was filtered. The filtrate was evaporated at low pressure. The residue was purified by silica gel column (20% EA in PE) to give **20-4** (6 g, 42%) as a yellow solid.

[0289] To a solution of **20-4** (12.5 g, 23.8 mol) in DCM (50 mL) was added $AgNO_3$ (8.1 g, 47.6 mmol), collidine (5.77 g, 47.6 mmol) and MMTrCl (11 g, 35.7 mmol). The mixture was stirred at RT overnight. The reaction was quenched with MeOH (5 mL), filtered and concentrated at low pressure. The residue was purified by silica gel column (5% MeOH in DCM) to give the intermediate (16 g, 86%) as a yellow solid. To a solution of $HOCH_2CH_2CN$ (4.7 g, 66 mmol) in THF (200 mL) was added NaH (3.7 g, 92 mmol) at 0 °C. The mixture was stirred at RT for 30 mins. A solution of the intermediate (10.5 g, 13 mmol) in THF (50 mL) was added, and the reaction mixture was stirred at RT for 12 h. The reaction was quenched with MeOH (2 mL), diluted with EA (100 mL), and washed with brine. The organic layer was dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by silica gel column (5% MeOH in DCM) to give **20-5** (5.8 g, 77%) as a yellow solid.

[0290] To a solution of PPh_3 (7.0 g, 26.6 mmol) in anhydrous pyridine (100 mL) was added I_2 (6.3 g, 24.9 mmol), and stirred at RT for 30 mins. The mixture was treated with a solution of **20-5** (9.5 g, 16.6 mmol) in pyridine (40 mL). The mixture was stirred at RT overnight. The reaction was quenched with sat. $Na_2S_2O_3$ solution, and the mixture was extracted with EA. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by silica gel column (30% EA in PE) to give **20-6** (7 g, 66%) as a yellow solid.

[0291] To a solution of **20-6** (7.5 g, 11 mmol) in dry THF (50 mL) was added DBU (5.4 g, 33 mmol), and the mixture was heated to reflux for 4 h. The mixture was diluted with EA (3 x 100 mL), and washed with brine. The organic layer was dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by silica gel column (30% EA in PE) to give **20-7** (4.0 g, 67%) as a white solid.

[0292] To an ice-cooled solution of **20-7** (3.0 g, 5.4 mmol) in anhydrous MeCN (20 mL) was added TEA•3HF (0.65 g, 4.1 mmol) and NIS (1.53 g, 6.78 mmol) at RT, and the reaction mixture was stirred at RT for 2 h. The mixture was diluted with EA (50 mL),

and washed with sat. $Na_2S_2O_3$ solution and $NaHCO_3$ aq. The organic layer was dried over anhydrous Na_2SO_4, and concentrated to dryness at low pressure. The residue was purified by prep-HPLC (0.1% HCOOH in water and MeCN) to separate the two isomers (about 1:1). NOE showed the polar one was **20-8** (0.6 g, 16%) as a white solid.

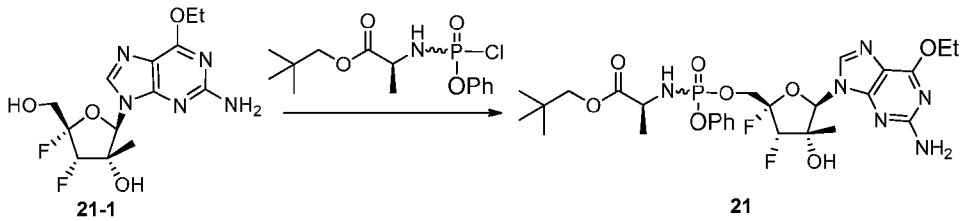
[0293] To a solution of **20-8** (0.7 g, 1 mmol) in dry pyridine (10 mL) was added BzCl (147 mg, 1.05 mmol) at 0 °C. The mixture was stirred at RT for 3 h. The mixture was then diluted with EA, and washed with sat. $NaHCO_3$ aq. and brine. The organic layer was dried over Na_2SO_4, and evaporated at low pressure. The residue was purified by silica gel column (20% EA in PE) to give **20-9** (0.65 g, 81%) as a white solid.

[0294] To a solution of **20-9** (0.65 g, 0.8 mmol) in dry DMF (40 mL) was added NaOBz (1.15 g, 8 mmol) and 15-crown-5 (1.77 g, 8 mmol). The mixture was stirred at 100 °C for 48 h. The solvent was evaporated at low pressure, and the residue was dissolved in EA (30 mL), and washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated at low pressure. The residue was purified by silica gel column (20% EA in PE) to give **20-10** (500 mg, 78%) as a white solid.

[0295] Compound **20-10** (400 mg, 0.5 mmol) in NH_3/MeOH (7N, 100 mL) was stirred at RT for 18 h. The mixture was concentrated at low pressure, and the residue was purified by silica gel column (5% MeOH in DCM) to give **20-11** (220 mg, 63%) as a white solid. ESI-MS: m/z 590.3 $[M+H]^+$.

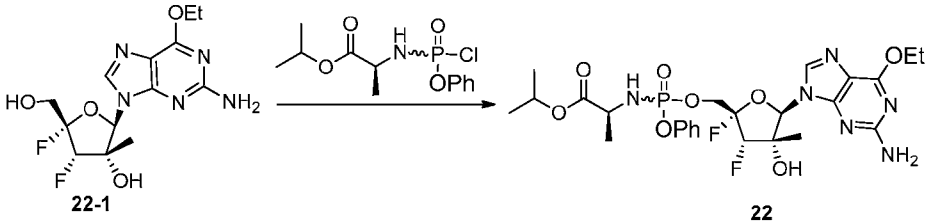
[0296] Compound **20-11** (59 mg, 0.1 mmol) was dissolved in 50% TFA in methanol (10 mL), and the mixture was kept at RT for 2 h. The solvent was evaporated and co-evaporated with a methanol/toluene mixture to remove traces of the acid. The residue was suspended in CH_3CN (1 mL) and centrifuged. The precipitate was washed with CH_3CN (1mL) and dried. Compound **20** was obtained as a colorless solid (21 mg, 65%. MS: m/z 316.2 [M-1].

EXAMPLE 17
COMPOUND 21



[0297] Compound **21** (15 mg, 16%) was prepared from **21-1** (50 mg) in acetonitrile (2 mL) with the phosphorochloridate reagent (0.14 g) and NMI (0.1 mL) in the same manner as compound 7. MS: m/z = 643 [M+1].

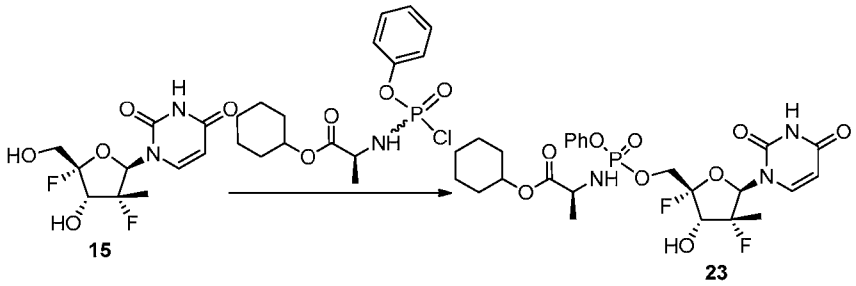
EXAMPLE 18
COMPOUND 22



22-1 **22**

[0298] Compound **22** (30 mg, 32%) was prepared from **22-1** (50 mg) in acetonitrile (2 mL) with the phosphorochloridate reagent (0.14 g) and NMI (0.1 mL) in the same manner as compound 7. MS: m/z = 615 [M+1].

EXAMPLE 19
COMPOUND 23

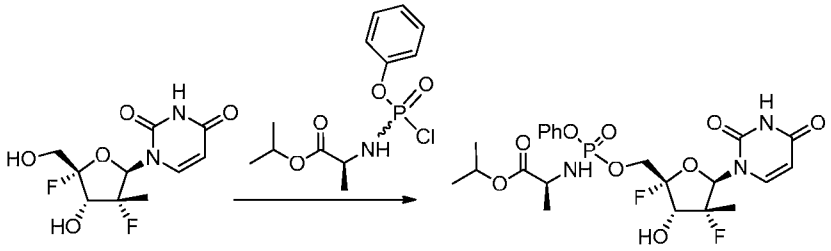


15 **23**

[0299] To a stirred solution of compound **15** (60 mg, 0.22 mmol) in anhydrous THF (2.0 mL) was added N-methylimidazole (0.142 mL, 1.73 mmol) at 0 ^{0}C (dry ice/acetone bath) followed by solution of phenyl (cyclohexanoxy-L-alaninyl) phosphorochloridate (235 mg, 0.68 mmol, dissolved in THF (2 mL). The resulting solution was stirred at 0 ^{0}C for 1 h, and the temperature was raised up-to 10 ^{0}C over the next 1 h. The reaction left at 10 ^{0}C for 3 h. The mixture was cooled to 0 to 5 ^{0}C, diluted with EA, and water (5 mL) was added. The solution was washed with H_2O and brine. The organic layer was separated, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated in vacuum to give a residue, which dissolved in 25% CH_3CN/H_2O. The compound was purified on a reverse-phase HPLC (C18) using acetonitrile and water, followed by lyophilization gave a white foam. The produce was re-dissolved in EtOAc, washed with 50 % aqueous citric acid solution,

dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated in vacuum, and lyophilized to give two isomers (*Rp/Sp*) of compound **23** (6.3 mg). MS *m/z* 586.05 (M-H).

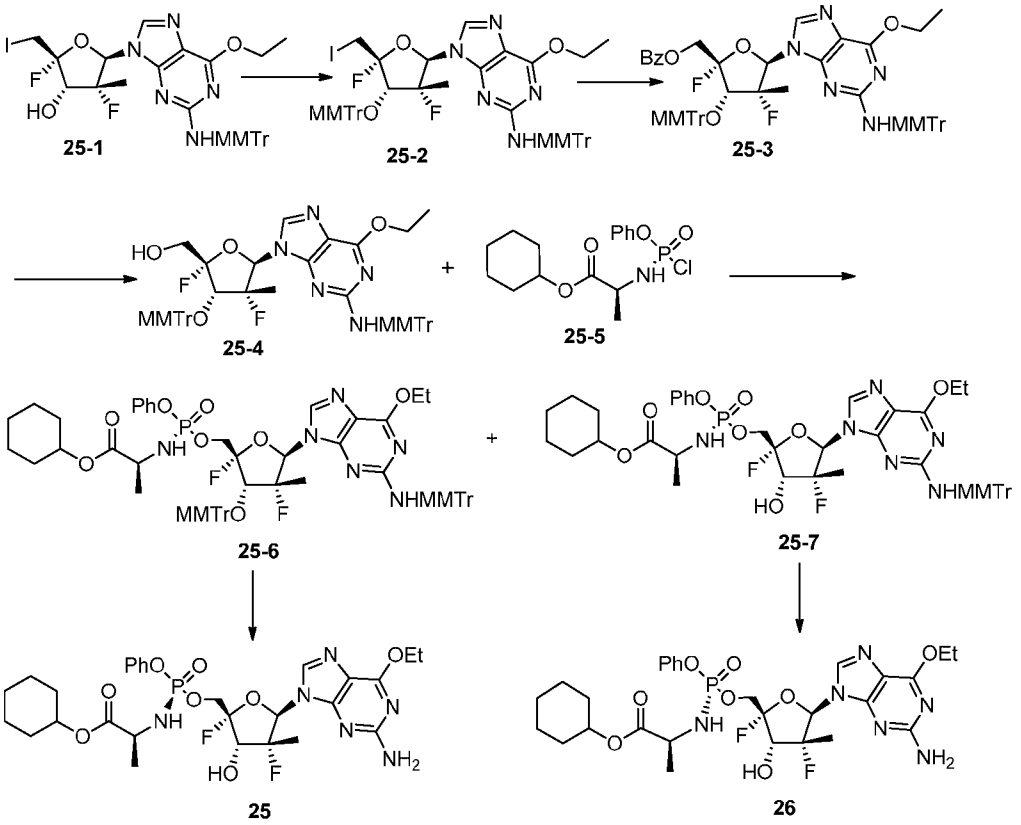
EXAMPLE 20
COMPOUND 24



15 **24**

[0300] To a stirred solution of compound **15** (100 mg, 0.36 mmol) in anhydrous THF (3.0 mL) was added N-methylimidazole (236 µL, 2.87 mmol) at 0 ^{0}C (dry ice/acetone bath) followed by a solution of the phosphorochloridate (329 mg, 1.08 mmol, dissolved in 2 mL of THF). The solution was stirred at 0 ^{0}C for 1 h, the reaction temperature was raised up-to 10 ^{0}C during the next 1 h, and the solution was left at 10 ^{0}C for the next 4 h. The mixture was cooled to 0 to 5 ^{0}C, diluted with EA, and water was added (15 mL). The solution was washed H_2O, 50 % aqueous citric acid solution and brine. The organic layer was separated, dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated in vacuum to give a residue, which dissolved in 25% CH_3CN/ H_2O. The residue was purified on a reverse-phase HPLC (C18) using acetonitrile and water, followed by lyophilization to give a mixture of two isomers of compound **24** (17.5 mg). MS *m/z* 546.05 (M-H).

EXAMPLE 21
COMPOUNDS 25 AND 26



[0301] To a solution of **25-1** (0.47 g, 0.65 mol) in DCM (3 mL) was added $AgNO_3$ (0.22 g, 1.29 mmol), collidine (0.15 g, 1.29 mmol) and MMTrCl (0.3 g, 0.974 mmol) at 0 °C. The mixture was stirred at RT overnight. The mixture was filtered, and the filter was washed with sat. aq. $NaHCO_3$ solution and brine. The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by silica gel column to give **25-2** (0.55, 85%) as a white solid.

[0302] To a solution of **25-2** (0.5 g, 0.5 mmol) in dry DMF (10 mL) was added NaOBz (0.72 g, 5 mmol) and 15-crown-5 (0.9 mL). The mixture was stirred at 95 °C for 72 h. The mixture was diluted with EA, and washed with water and brine. The organic phase was dried over $MgSO_4$ and concentrated at low pressure. The residue was purified by silica gel column (10% EA in PE) to give **25-3** (0.3 g, 60%) as a white solid.

[0303] Compound **25-3** (0.3 g, 0.3 mmol) in NH_3/MeOH (30 mL) was stirred at RT for 18 h. The mixture was concentrated at low pressure, and the residue was purified by

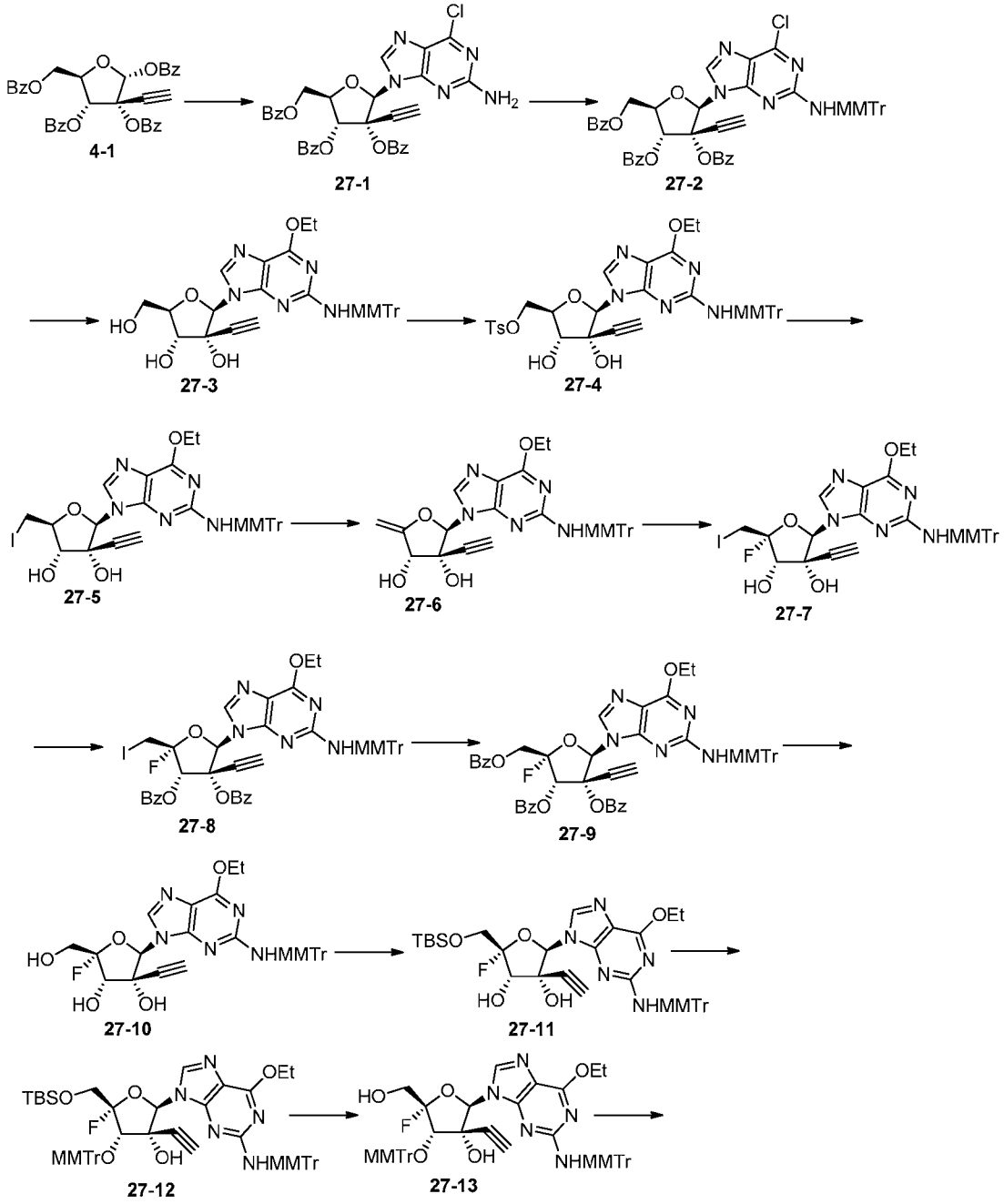
silica gel column (20% EA in PE) to give **25-4** (145 mg, 56%) as a white solid. ESI-LCMS: m/z 890.5 $[M+H]^+$.

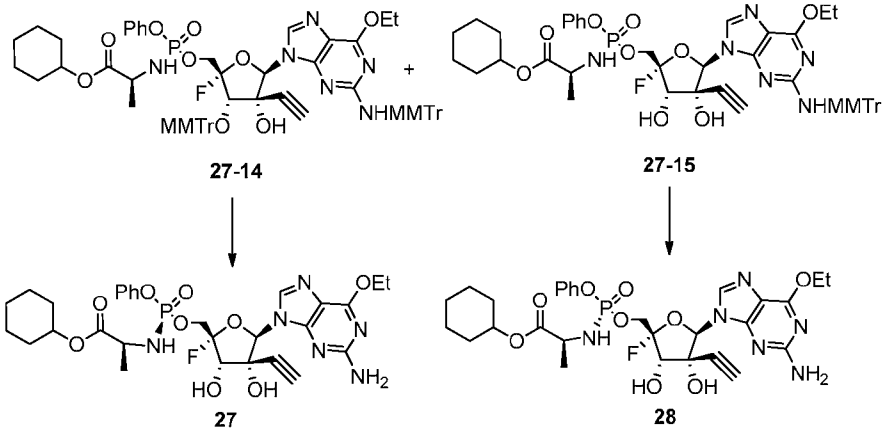
[0304] To a stirred solution of **25-4** (161 mg, 0.16 mmol) in anhydrous CH_3CN (2.0 mL) was added N-methylimidazole (118 μL, 2.87 mmol) at 0 to 5 ^{0}C (ice/water bath) followed by solution of **25-5** (186 mg, 0.54 mmol, dissolved in 2mL of CH_3CN). The solution was stirred at 0 to 5 °C for 4 h. The mixture was diluted with EA, and water was added (15 mL). The solution was washed H_2O, 50 % aqueous citric acid solution and brine. The organic layer was separated, dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated in vacuum to give a residue, which was purified on silica gel with 0 to 40% EA/hexanes to give as **25-6** (82.6 mg) as the faster eluting isomer and **25-7** (106 mg) as the slower eluting isomer.

[0305] Compound **25-6** (82.6 mg, 0.07 mmol) was dissolved in_anhydrous CH_3CN (0.5 mL), and 4N HCl in dioxane (35 μL) was added at 0 to 5 °C. The mixture was stirred at RT for 1 h, and anhydrous EtOH (100 μL) was added. The solvents were evaporated at RT and co-evaporated with toluene 3 times. The residue was dissolved in 50% CH_3CN/H_2O, and purified on a reverse-phase HPLC (C18) using acetonitrile and water, followed by lyophilization to give compound **25** (19.4 mg). ^{1}H NMR (CD_3OD-d_4, 400 MHz) δ 7.9 (s, 1H), 7.32-7.28 (t, J = 8.0 Hz, 2H), 7.2-7.12 (m, 3H), 6.43 (d, J = 17.6 Hz, 1H), 4.70-4.63 (m, 2H), 4.55-4.4 (m, 3H), 3.94-3.9 (m, 1H), 1.79-1.67 (m, 4H), 1.53-1.49 (m, 1H), 1.45-1.22 (m, 15H);^{31}P NMR (CD_3OD-d_4) δ 4.06 (s); ESI-LCMS: m/z = 655.2 $[M+H]^+$, 653.15 $[M-H]^-$.

[0306] Compound **25-7** (100 mg, 0.083 mmol) was dissolved in_anhydrous CH_3CN (0.5 mL), and 4N HCl in dioxane (50 μL) was added at 0 to 5 °C. Following the procedure for obtaining compound **25**, compound **26** (31.8 mg) was obtained. ^{1}H NMR (CD_3OD-d_4, 400 MHz) δ 7.93 (s, 1H), 7.33-7.29 (m, 2H), 7.24-7.14 (m, 3H), 6.41 (d, J = 17.6 Hz, 1H), 4.70-4.60 (m, 2H), 4.54-4.49 (m, 2H), 4.44-4.39 (m, 1H), 3.92-3.89 (m, 1H), 1.77-1.66 (m, 4H), 1.54-1.24 (m, 16H);^{31}P NMR (CD_3OD-d_4) δ 3.91 (s); ESI-LCMS: m/z = 655.2 $[M+H]^+$, 653.1 $[M-H]^-$.

EXAMPLE 22
COMPOUNDS 27 AND 28





27-14 **27-15**

27 **28**

[0307] To a stirred suspension of **4-1** (50 g, 84.8 mmol) and 2-amino-6-chloropurine (28.6 g, 169.2 mmol) in anhydrous MeCN (500 mL) was added DBU (77.8 g, 508 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 mins, and TMSOTf (150.5 g, 678 mmol) was added dropwise at 0 °C. The mixture was stirred at RT for 20 mins until a clear solution was formed. The mixture was stirred at 90-110°C overnight. The mixture was cooled to RT, and diluted with EA. The solution was washed with sat. $NaHCO_3$ solution and brine. The organic layer was dried over Na_2SO_4 and then concentrated at low pressure. The residue was purified by silica gel column (PE/EA = 2/1) to give **27-1** (30 g, 55.5%) as a white solid.

[0308] To a solution of **27-1** (30 g, 47.1 mmol) in anhydrous DCM (300 mL) was added collidine (30 mL), $AgNO_3$ (24 g, 141.4 mmol) and MMTrCl (43.6 g, 141.4 mmol). The mixture was stirred at RT overnight. The mixture was filtered, and the filtrate was washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by silica gel column (PE/EA= 4/1) to give **27-2** (35 g, 82%) as a white solid.

[0309] To a stirred solution of **27-2** (35 g, 38.5 mmol) in anhydrous EtOH (150 mL) was added a solution of EtONa in EtOH (2N, 150 mL). The mixture was stirred at RT overnight, and then concentrated at low pressure. The residue was dissolved in EA (200 mL) and the solution was washed with water and brine. The organic layer was dried over Na_2SO_4, and concentrated at low pressure. The residue was purified by silica gel column (DCM/MeOH = 100/2) to give **27-3** (19 g, 81%) as a white solid.

[0310] Compound **27-3** (19 g, 31.3 mmol) was co-concentrated with anhydrous pyridine for 3 times. To an ice cooled solution of **27-3** in anhydrous pyridine (120 mL) was added a solution of TsCl (6.6 g, 34.6 mmol) in pyridine (40 mL) dropwise at 0 °C. The mixture was stirred at 0 °C for 16 h. The mixture was quenched with water, and the reaction mixture was concentrated. The residue was re-dissolved in EA (200 mL). The solution was washed with sat. aq. $NaHCO_3$ and brine. The organic layer was dried over anhydrous Na_2SO_4 and filtered, and the filtrate was concentrated. The residue was purified by silica gel column (DCM/MeOH = 100/1) to give **27-4** (16 g, 67 %) as a yellow solid.

[0311] To a solution of **27-4** (15 g, 19.7 mmol) in acetone (100 mL) was added NaI (30 g, 197 mmol). The mixture was refluxed overnight, and then concentrated at low pressure. The residue was purified by silica gel column (DCM/MeOH = 100/1) to give **27-5** (9 g, 63.7%) as a white solid.

[0312] To a solution of **27-5** (8 g, 11.2 mmol) in anhydrous THF (60 mL) was added DBU (5.12 g, 33.5 mmol), and the mixture was heated at 60°C overnight. The mixture was diluted with EA, and washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and filtered, and the filtrate was concentrated. The residue was purified by silica gel column (PE/acetone = 4/1) to give **27-6** (5.7 g, 86%) as a white solid. ^{1}H-NMR (CD_3OH, 400MHz) δ = 8.18 (s, 1H), 7.17-7.33 (m, 12H), 6.80 (d, J = 8.8 Hz, 2H), 5.98 (s, 1H), 5.40 (d, J = 8.6 Hz, 1H), 3.87 (m, 5H), 3.75 (s, 3H), 2.69 (s, 1H), 1.05 (s, 3H).

[0313] To an ice cooled solution of **27-6** (4.44 g, 7.5 mmol) in anhydrous MeCN (45 mL) was added TEA•3HF (1.23 g, 7.6 mmol) and NIS (2.16 g, 9.5 mmol). The mixture was stirred at RT for 2-3 h. The reaction was quenched with sat. Na_2SO_3 and $NaHCO_3$ solution. The mixture was extracted with EA (3 x 100 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by silica gel column (DCM/acetone = 100/2) to give **27-7** (4.4 g, 79.8%) as a white solid.

[0314] To a solution of **27-7** (5.36 g, 7.3 mmol) in anhydrous DCM (50 mL) was added DMAP (3.6 g, 29.8 mmol) and BzCl (3.1 g, 22.1 mmol) at 0 °C. The mixture was stirred at RT overnight. The mixture was washed with sat. aq. $NaHCO_3$ and brine. The organic layer was concentrated, and the residue was purified by silica gel column (PE/EA= 5/1) to give**27-8** (5.6 g, 81.3%) as a white solid.

[0315] To a solution of **27-8** (5.0 g, 5.3 mmol) in anhydrous DMF (150 mL) was added NaOBz (7.64 g, 53 mmol) and 15-crown-5 (14 g, 68 mmol). The mixture was stirred at 90-100 °C for 48 h. The mixture was diluted with EA, and washed with water and brine. The organic layer was concentrated, and the residue was purified by silica gel column (PE/EA = 5/1) to give **27-9** (3.9 g, 78.5%) as a white solid.

[0316] Compound **27-9** in NH_3 in MeOH (7N, 60 mL) was stirred at RT for 18 h. The mixture was concentrated at low pressure. The residue was purified by silica gel column (DCM/acetone = 50/1) to give **27-10** (500 mg, 74.7%) as a white solid. ESI-MS: m/z 626.3 $[M+H]^+$.

[0317] To a solution of **27-10** (350 mg, 0.56 mmol) in anhydrous pyridine (4 mL) was added imidazole (50 mg, 0.72 mmol) and TBSCl (108 mg, 0.72 mmol) at 0 to 5 °C, and stirred at RT for 15 h. The reaction was quenched with absolute EtOH (0.5 mL). The solution was concentrated to dryness under reduced pressure. The residue was dissolved in EA (150 mL), and washed with water, sat. $NaHCO_3$ and brine. The combined organic layers were dried over Na_2SO_4, filtered and evaporated at low pressure. The residue was purified by silica gel column (10-30% EA in hexanes) to give **27-11** (338 mg, 81.8%) as a white solid.

[0318] To a solution of compound **27-11**(328 mg, 0.44 mmol), $AgNO_3$ (226 mg, 1.33 mmol) and collidine (0.59 mL, 4.84 mmol) in anhydrous DCM (4 mL) was added MMTrCl (410 mg, 1.33 mmol) under N_2. The mixture was stirred at RT overnight under N_2, and monitored by TLC to completion. The mixture was filtered through pre-packed Celite filter, and the filtrate was washed with water, 50% aqueous citric acid, and brine. The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and concentrated at low pressure. The residue was purified by silica gel column (EA in hexanes from 0% to 30%) to give **27-12** (337 mg).

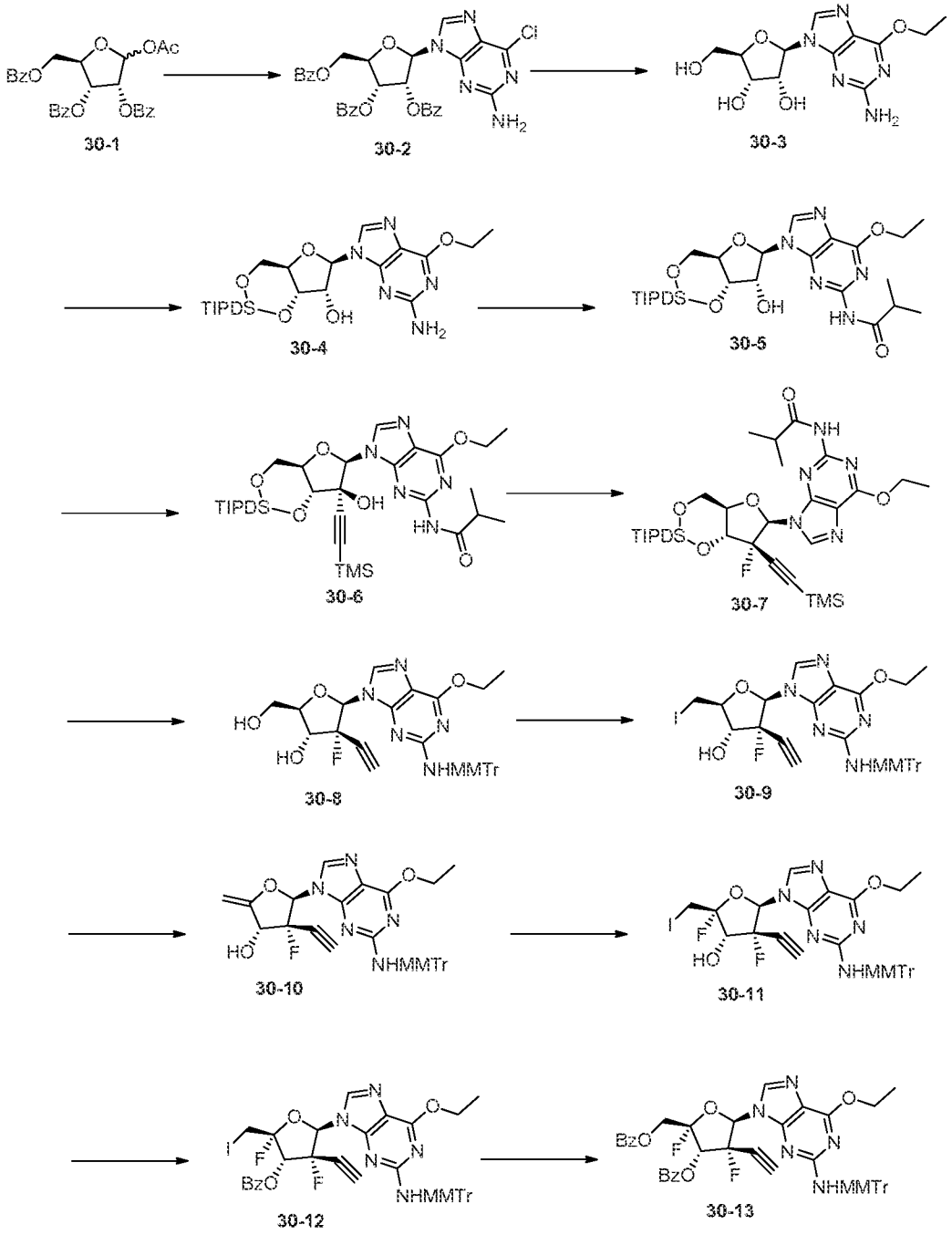
[0319] To a solution of **27-12** (337 mg, 0.33 mmol) in anhydrous THF (4 mL) was added 1.0 M solution of TBAF (0.66 ML, 0.66 mmol) at 0 to 5°C. The reaction was slowly warmed to RT, and stirred for 1 h. The mixture was quenched with silica gel, and filtered. The solvents were evaporated to give the crude product, which was purified by silica gel column (EA in hexanes from 0% to 50%) to give **27-13** (188 mg).

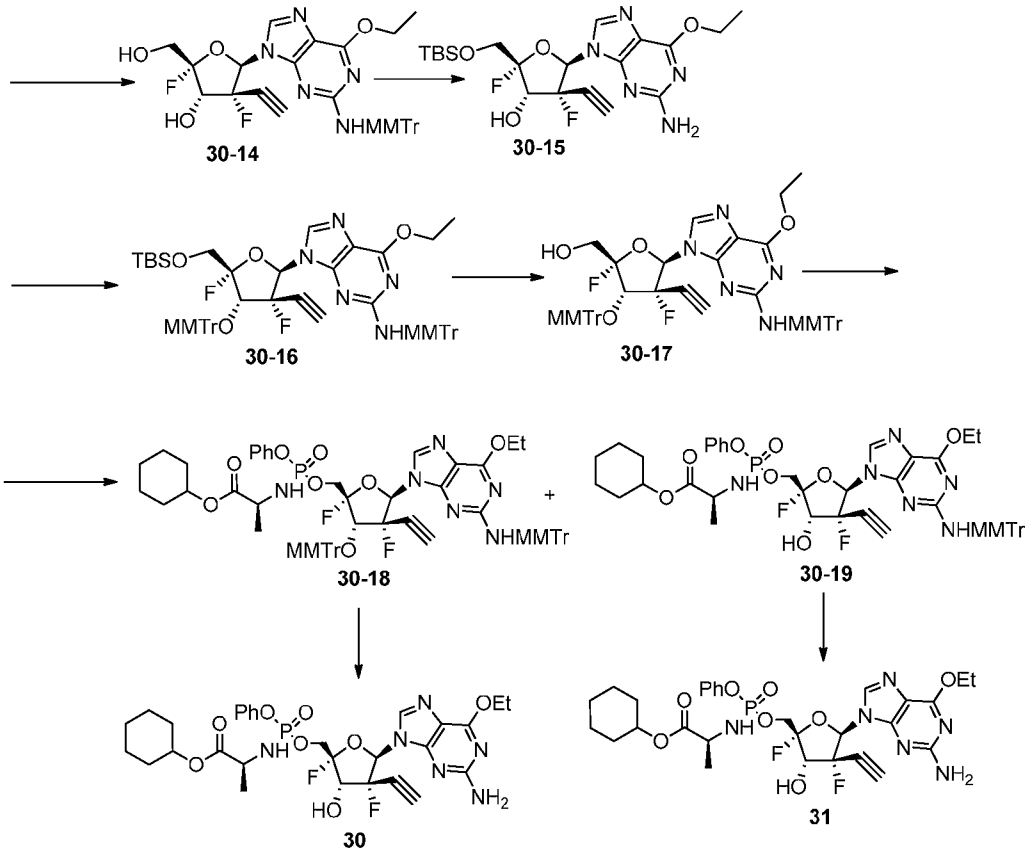
[0320] To a stirred solution of **27-13** (180 mg, 0.16 mmol) in anhydrous CH_3CN (2.5 mL) was added N-methylimidazole (132 µL, 1.6 mmol) at 0-5 ^{0}C (ice/water bath) followed by solution of phenyl (cyclohexanoxy-L-alaninyl) phosphorochloridate (207 mg, 0.6 mmol, dissolved in 2mL of CH_3CN). The solution was stirred at RT for 2.5 h, and the mixture was diluted with EA followed by addition of water (15 mL). The solution was washed H_2O, 50 % aqueous citric acid solution and brine. The organic layer was separated, dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated in vacuum to give a residue, which was purified on silica gel with 0 to 40% EA/hexanes to give **27-14** (75.8 mg) and **27-15** (108 mg) as a slower eluting isomer.

[0321] Compound **27-14** (76 mg, 0.063 mmol) was dissolved in_anhydrous CH_3CN (0.5 mL), and 4N HCl in dioxane (47 µL) was added at 0 to 5 ^{o}C (ice/ water bath). The mixture was stirred at RT for 40 mins, and anhydrous EtOH (200 µL) was added. The solvents were evaporated at RT and co-evaporated with toluene 3 times. The residue was dissolved in 50% CH_3CN/ H_2O, purified on a reverse-phase HPLC (C18) using acetonitrile and water, and lyophilized to give compound **27** (26.6 mg). ESI-LCMS: m/z = 663.3 $[M+H]^+$.

[0322] Compound **27-15** (108 mg, 0.089 mmol) was dissolved in_anhydrous CH_3CN (0.7 mL), and 4N HCl in dioxane (67 µL) was added at 0 to 5 ^{o}C (ice/ water bath). The mixture was stirred at RT for 60 mins, and anhydrous EtOH (200 µL) was added. The solvents were evaporated at RT and co-evaporated with toluene 3 times. The residue was dissolved in 50% CH_3CN/ H_2O, purified on a reverse-phase HPLC (C18) using acetonitrile and water, and lyophilized to give compound **28** (40.3 mg). ESI-LCMS: m/z = 663.2 $[M+H]^+$.

EXAMPLE 23
COMPOUNDS 30 AND 31





[0323] To a mixture of pre-silylated 6-Cl-guanine (using HMDS and $(NH_4)_2SO_4$) (25.2 g, 150 mmol) in DCE (300 mL) was added **30-1** (50 g, 100 mmol) and TMSOTf (33.3 g, 150 mmol) at 0 °C. The mixture was stirred at 70 °C for 16 h, and then concentrated at low pressure. The residue was re-dissolved in EA, and washed with sat. aq. $NaHCO_3$ and brine. The organic layer was dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified on silica gel column (PE/EA = 2/1) to give pure **30-2** (45 g, 73%) as a white solid.

[0324] To a solution of **30-2** (45 g, 73.4 mmol) in EtOH (73 mL) was added with EtONa (1N in EtOH, 360 mL). The mixture was stirred at RT for 16 h. The mixture was then concentrated to give a residue, which was purified by silica gel column (DCM/MeOH = 10/1) to give pure **30-3** (19 g, 83%) as a white solid.

[0325] To a solution of **30-3** (19 g, 61.1 mmol) in pyridine (120 mL) was added with $TIPDSCl_2$ (19.2 g, 61 mmol) dropwise at 0 °C. The mixture was stirred at RT for 16 h, and then concentrated at low pressure. The residue was re-dissolved in EA, and washed with sat. aq. $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4, and concentrated at

low pressure. The residue was purified by silica gel column (DCM/MeOH = 20/1) to give pure **30-4** (22 g, 65%) as a white solid.

[0326] To a solution of **30-4** (22 g, 39.8 mmol) in DMF/pyridine (5/1, 100 mL) was added TMSCl (12.9 g, 119 mmol) dropwise at 0 °C. The mixture was stirred at RT for 1 h and then treated with isobutyryl chloride (5.4 g, 50 mmol). The mixture was stirred at RT for 3 h and then quenched by NH_4OH. The mixture was concentrated at low pressure. The residue was dissolved in EA (200 mL). The solution was washed with sat. aq. $NaHCO_3$, and then the organic layer was dried and concentrated at low pressure. The residue was purified by silica gel column (DCM/MeOH = 50/1) to give pure **30-5** (15 g, 60%) as a white solid.

[0327] To a solution of **30-5** (15 g, 24.1 mmol) in DCM (100 mL) was added PDC (13.5 g, 26 mmol) and Ac_2O (9.8 g, 96 mmol) at 0 °C. The mixture was stirred at RT for 16 h. The reaction was quenched by sat. aq. $NaHCO_3$, and then extracted with EA. The organic layer was dried over anhydrous Na2SO4, and concentrated at low pressure. The residue was dissolved in anhydrous THF (100 mL). To a solution of TMSCCH (12 g, 112 mmol) in THF (200 mL) was added n-BuLi (2.5 N, 44 mL) at -78 °C. The mixture was stirred at -78 °C for 15 mins and 0 °C for 15 mins. The mixture was treated with a solution of crude ketone in THF at -78 °C and stirred at -30 °C for 2 h. The reaction was quenched by sat. aq. NH_4Cl, and then extracted by EA. The combined organic layer was dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by silica gel column (PE/EA= 10/1) to give pure **30-6** (3.1 g, 18%) as a white solid.

[0328] To a solution of **30-6** (7 g, 7.5 mmol) and pyridine (1.4 g, 17 mmol) in DCM (35 mL) was added with DAST (5.6 g, 35 mmol) at -78 °C. The mixture was stirred at -78 °C for 3 h. The reaction was quenched by sat. aq. $NaHCO_3$, and then extracted with EA. The combined organic layer was dried over anhydrous, and concentrated at low pressure. The residue was purified by silica gel column (PE/EA= 10/1) to give pure **30-7** (3.1 g, 18%) as a white solid.

[0329] Compound **30-7** (4.1 g, 5.7 mmol) in sat. NH_3/MeOH (100 mL) was stirred at RT for 16 h, and concentrated at low pressure. The residue was re-dissolved in anhydrous DCM (300 mL), and was treated with $AgNO_3$ (27.0 g, 160 mmol), collidine (22 mL) and MMTrCl (23.0 g, 75.9 mmol) in small portions under N_2. The mixture was stirred at RT for 16 h. The mixture was filtered, and the filtrate was washed with sat. $NaHCO_3$

solution and brine. The organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by silica gel column (PE/EA = 10/1) to give the pure intermediate. The intermediate was dissolved in a solution of TBAF/THF (1N, 20 mL). The mixture was stirred at RT for 2 h and then concentrated at low pressure. The residue was purified by silica gel column (DCM/MeOH = 50/1) to give pure **30-8** (3.0 g, 86%) as a white solid.

[0330] To a solution of **30-8** (3.0 g, 4.9 mmol) in THF (50 mL) was added imidazole (840 mg, 12 mmol), PPh_3 (3.2 g, 12 mmol), and I_2 (2.4 g, 9.2 mmol) at 0 °C. The mixture was stirred at RT for 16 h. The reaction was quenched by sat. aq. $Na_2S_2O_3$, and then extracted with EA. The combined organic layer was dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by silica gel column (PE/EA= 2/1) to give crude **30-9** (4.2 g, >100%, containing TPPO) as a white solid.

[0331] To a solution of crude **30-9** in anhydrous THF (30 mL) was added DBU (2.7 g, 18 mmol), and heated to 80 °C. The mixture was stirred for 1 h and checked by LCMS. The mixture was quenched by water, and extracted with EA. The organic layer was dried over anhydrous Na_2SO_4 and filtered, and the filtrate was concentrated at low pressure. The residue was purified by silica gel column (PE/EA= 2/1) to give **30-10** (2.0 g, 69%) as a white solid.

[0332] To an ice cooled solution of **30-10** (2.0 g, 3.38 mmol) in anhydrous MeCN (15 mL) was added NIS (777 mg, 3.5 mmol) and NEt_3•3HF (536 g, 3.3 mmol) at 0 °C. The mixture was stirred at RT for 16 h and checked by LCMS. After completion, the mixture was quenched by sat. Na_2SO_3 and sat. $NaHCO_3$ solution, and extracted with EA. The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by silica gel column chromatography (PE/EA=10/1 to 3/1) to give **30-11** (2.1 g, 84.0%) as a white solid.

[0333] To a solution of crude **30-11** (2.1 g, 2.85 mmol) in anhydrous DCM (100 mL) was added DMAP (490 mg, 4 mmol), and BzCl (580 mg, 4 mmol) at 0 °C. The mixture was stirred overnight and checked by LCMS. The reaction was washed with sat. $NaHCO_3$ solution. The organic layer was dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by silica gel column chromatography (PE/EA = 8/1 to 3/1) to give **30-12** (2.0 g, 83.4%) as a white solid.

[0334] To a solution of **30-12** (2.0 g, 2.4 mmol) in anhydrous DMF (60 mL) was added NaOBz (3.3 g, 23.0 mmol) and 15-crown-5 (5.11 g, 23 mmol). The mixture was stirred at 110 °C for 36 h. The reaction was quenched by water, and the mixture was extracted with EA. The organic layer was dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by silica gel column (PE/EA= 5/1 to 3/1) to give **30-13** (830 mg, 42.0%) as a white solid. ESI-MS: m/z 836.11 $[M+H]^+$.

[0335] A solution of **30-13** (831mg, 1.0 mmol) in anhydrous n-butylamine (4 mL) was stirred at RT for 3 h under N_2 atmosphere. The reaction was monitored by TLC. The solvent was evaporated in vacuo, and the residue was purified by silica gel column (MeOH in DCM from 0% to 10%) to give the crude product, which as re-purified using silica gel column to give **30-14** as a light pink solid (563 mg).

[0336] To a solution of **30-14** (560 mg, 0.89 mmol) in anhydrous pyridine (5 mL) was added imidazole (78.6 mg, 1.16 mmol) and TBSCl (202 mg, 1.34 mmol) at 0 to 5 °C. The mixture was stirred at RT for 15 h. The reaction was quenched by adding absolute EtOH (0.3 mL). The solution was concentrated to dryness under reduced pressure, and co-evaporated with toluene 3 times. The residue was dissolved in EA (150 mL), and washed with water, sat. $NaHCO_3$, and brine. The combined organic layer was dried over Na_2SO_4, filtered and evaporated at low pressure. The residue was purified by silica gel column (0-20% EA in hexanes) to give **30-15** (303 mg) as a white solid.

[0337] To a solution of **30-15** (303 mg, 0.41 mmol), $AgNO_3$ (208 mg, 1.23 mmol) and collidine (0.55 mL, 4.51 mmol) in anhydrous DCM (4 mL) was added MMTrCl (378 mg, 1.3 mmol) under N_2. The mixture was stirred at RT overnight under N_2, and monitored by TLC. The mixture was filtered through pre-packed celite filter, and the filtrate was washed with water and, 50% aqueous citric acid, and brine. The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and concentrated at low pressure. The residue was purified by silica gel column (EA in hexanes from 0% to 30%) to give **30-16** (374 mg, 90%).

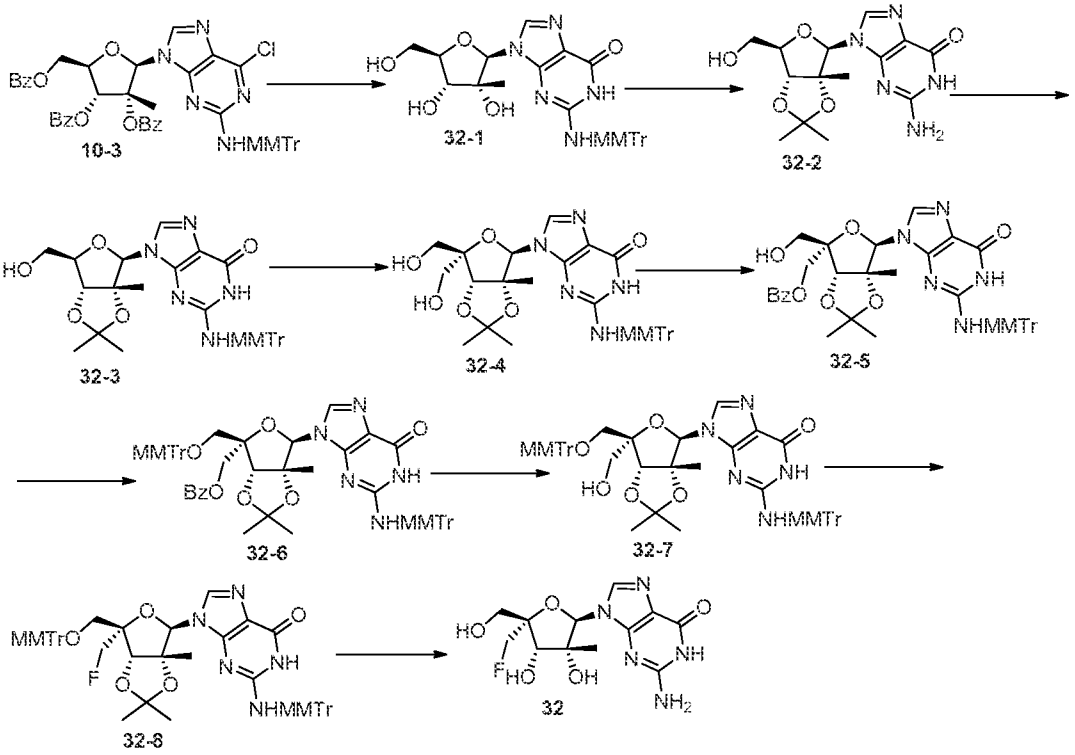
[0338] To a solution of **30-16** (374 mg, 0.37 mmol) in anhydrous THF (4 mL) was added 1.0 M solution of TBAF (0.74 mL, 0.74 mmol) at 0 to 5°C. The mixture was stirred at RT for 1 h. The mixture was quenched with silica gel, and filtered. The solvents were evaporated to give the crude product, which was purified by silica gel column (EA in hexanes from 0% to 50%) to give **30-17** (265 mg).

[0339] To a stirred solution of **30-17** (187.5 mg, 0.16 mmol) in anhydrous CH_3CN (2.5 mL) was added N-methylimidazole (136 μL, 1.66 mmol) at 0-5 ^{0}C (ice/water bath) followed by solution of phenyl (cyclohexanoxy-L-alaninyl) phosphorochloridate (214 mg, 0.62 mmol, dissolved in 0.5 mL of CH_3CN). The solution was stirred at RT for 3 h, and then diluted with EA followed by the addition of water (15 mL). The solution was washed with H_2O, 50 % aqueous citric acid solution and brine. The organic layer was separated, dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated in vacuum to give a residue, which was purified on silica gel with 0 to 40% EA/hexanes to give (single isomers) of **30-18** (108 mg) Elution of the latter fraction gave (single isomers) of **30-19** (120 mg) as glassy solid.

[0340] Compound **30-18** (108mg, 0.089 mmol) was dissolved in anhydrous CH_3CN (0.5 mL), and 4N HCl in dioxane (67 μL) was added at 0 to 5 ^{o}C (ice/ water bath). The mixture was stirred at RT for 40 mins, and anhydrous EtOH (200 μL) was added. The solvents were evaporated at RT and co-evaporated with toluene 3 times. The residue was dissolved in 50% CH_3CN/H_2O, was purified on a reverse-phase HPLC (C18) using acetonitrile and water, followed by lyophilization to give compound **30** (26.6 mg) as a white foam. ^{1}H NMR (CD_3OD-d_4, 400 MHz) δ 7.89 (s, 1H), 7.33-7.29 (m, 2H), 7.20-7.13 (m, 3H), 7.17 (m, 1H), 6.62 (d, J = 15.6 Hz, 1H), 5.39 (t, J = 25.2 Hz, 1H), 4.75-4.42 (m, 6H), 3.92 (t, J = 8.8 Hz, 1H), 3.24 (d, J = 5.6 Hz, 1H), 1.76-1.51 (m, 5H), 1.45-1.25 (m, 12H);^{31}P NMR (CD_3OD-d_4) δ4.04 (s); ESI-LCMS: m/z = 665.2 $[M+H]^+$.

[0341] Compound **31** (44.4 mg, single isomer) was obtained according to the procedure described for compound **30** using **30-19.** ^{1}H NMR (CD_3OD-d_4, 400 MHz) δ 7.93 (s, 1H),), 7.32 (t, J = 8.0 Hz, 1H), 7.24 (d, J = 7.6 Hz, 2H), 7.16 (t, J = 7.6 Hz, 1H), 6.61 (d, J = 16.0 Hz, 1H), 4.68-4.60 (m, 2H), 4.54-4.39 (m, 3H), 3.93-3.89 (m, 1H), 3.24 (d, J = 5.6 Hz, 1H), 1.75-1.5 (m, 5H), 1.48-1.23 (m, 12H); ^{19}F NMR (CD_3OD-d_4) δ-122.95 (s), -155.84-155.99 (m); ^{31}P NMR (CD_3OD-d_4) δ3.94 (s); ESI-LCMS: m/z = 665.15 $[M+H]^+$.

EXAMPLE 24
COMPOUND 32



[0342] To a solution of 3-hydroxypropanenitrile (27 g, 0.15 mol) in THF (150 mL) was added NaH (8.4 g, 0.21 mol) at 0 °C, and the mixture was stirred for 1 h. at RT. Compound **10-3** (27 g, 0.03 mol) in THF (100 mL) was treated with this mixture at 0 °C. The combined mixture was stirred for 6 h. at RT. The reaction was quenched with H_2O, and extracted with EA. The organic layer was dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by column chromatography to give **32-1** (9.38 g, 55%).

[0343] To a solution of **32-1** (1 g, 1.76 mmol) and TsOH (1 g, 5.28 mmol) in DMF (4 mL) and acetone (8 mL) was added 2,2-dimethoxypropane (1.8 g, 17.6 mmol) at RT. The mixture was heated to 50 °C for 3 h. The reaction was quenched with H_2O (50 mL), and extracted with EA (3 x 50 mL). The organic layer was dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by column chromatography to give **32-2** (520 mg, 87%).

[0344] To a stirred solution of **32-2** (10.0 g, 29.6 mmol) in pyridine (100 mL) was added TBSCl (53.4 g, 35.6 mmol) at RT, and the mixture was stirred for 5 h. The mixture

was concentrated at low pressure, and the residue was dissolved in EA (100 mL). The solution was washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4, and concentrated at low pressure. The crude product was co-evaporated with toluene 3 times. To a solution of anhydrous crude product (2.0 g, 4.43 mmol) in DCM (30 mL) was added DMTrCl (2.24 g, 6.65 mmol), 2,4,6-trimethylpyridine (1.07 g, 8.86 mmol) and $AgNO_3$ (1.5 g, 8.86 mmol). The mixture was stirred for 1.5 h. The mixture was filtered, and the filtrate was washed with 0.5 N HCl solution. The solution was washed with brine, dried over anhydrous Na_2SO_4, and concentrated at low pressure to give the crude yellow solid. The crude yellow solid (7.2 g, 10 mmol) was treated with a solution of NH_4F (7.2 g, 200 mmol) in MeOH (50 mL), and the mixture was heated to 50 °C for 8 h. The mixture was concentrated at low pressure. The residue was purified by silica gel column to give **32-3** (4.8 g, 80%).

[0345] To a solution of **32-3** (200 mg, 0.33 mmol) in DCM (5 mL) was added TFA•Py (40 mg, 0.328 mmol), DMSO (0.15 mL), and DCC (191 mg, 0.99 mmol) at RT. The mixture was stirred for 6 h, and concentrated at low pressure. The residue was purified by silica gel column to give the product. To a solution of the product (0.2 g, 0.328 mmol) and HCHO (0.2 mL) in 1,4-dioxane (2 mL) was added NaOH (0.4 mL, 2 M) at RT. The mixture was stirred for 5 h. The mixture was then treated with $NaBH_4$ (24 mg, 0.66 mmol), and stirred for 3 h. The mixture was diluted with EA (20 mL), and washed with brine. The organic phase was dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by silica gel column to give **32-4** (125 mg, 60%).

[0346] To a solution of **32-4** (4 g, 6.25 mmol) in DCM (40 mL) was added pyridine (10 mL) and BzCl (920 mg, 15.6 mmol) at -78 °C. The mixture was slowly warmed up to RT. The reaction was monitored by LCMS. The mixture was quenched with H_2O (40 mL), and extracted with DCM (3 x 50 mL). The organic layer was washed brine, dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by silica gel column to give **32-5** (3.25 g, 70%).

[0347] To a solution of **32-5** (5.75 g, 7.7 mmol) in DCM (20 mL) was added DMTrCl (3.58 g, 11.1 mmol), 2,4,6-trimethyl- pyridine (1.87 g,15.4 mmol) and $AgNO_3$ (2.63 g,15.4 mmol), and stirred for 3 h. The mixture was filtered, and the filtrate was washed with 0.5 N HCl solution. The organic phase was washed with brine, dried over anhydrous

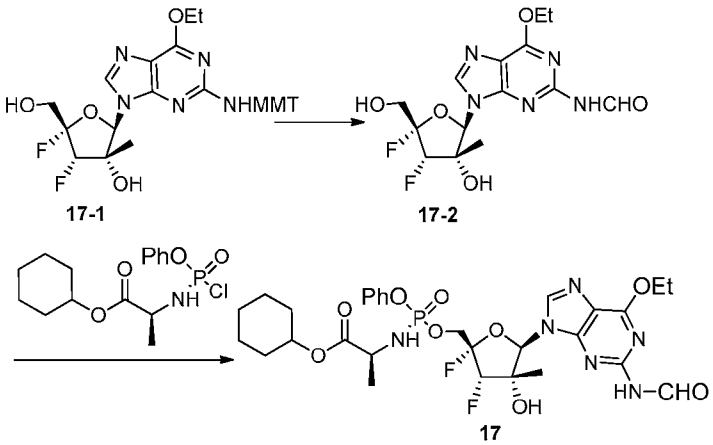
Na_2SO_4, and concentrated at low pressure. The residue was purified by silica gel column to give **32-6** (6.25 g, 80%).

[0348] To a solution of **32-6** (4.3 g, 4.23 mmol) in MeOH (40 mL) was added NaOMe (0.82 g, 12.6 mmol) at RT, and stirred for 3 h. The mixture was concentrated at low pressure. The residue was dissolved in EA (30 mL), and washed with brine. The organic layer was dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by silica gel column to give **32-7** (2.89 g, 75%).

[0349] To a solution of **32-7** (0.5 g, 0.54 mmol) and pyridine (0.478 g, 5.4 mmol) in DCM (4 mL) was slowly added a solution of Tf_2O (0.201 g, 0.713 mmol) in DCM (3 mL) at -35 ^oC. The mixture was warmed up to -5 ^0C slowly. The reaction was monitored by LCMS. The reaction was quenched with sat. $NaHCO_3$ solution, and extracted with DCM (3 x 20 mL). The organic phase was washed with brine, dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by silica gel column to give the product. To a solution of the product was added TBAF in THF (25 mL, 1N), and the mixture was stirred for 5 h at RT. The reaction was monitored by LCMS. The mixture was concentrated at low pressure, and the residue was purified by prep-HPLC to give **32-8** (221 mg, 45%). ESI-MS: m/z 914.4 $[M+H]^+$.

[0350] Compound **32-8** (2.14 g) was dissolved in 80% HCOOH (10 mL) and was at RT overnight. The solvent was evaporated to dryness, and the residue crystallized from methanol twice. The crystals were dissolved in a mixture of THF and 36% HCl 4:1 v:v and left overnight. The solvent was evaporated, and the nucleoside was isolated by RP HPLC on Synergy 4 micron Hydro-RP column (Phenominex). A linear gradient of methanol from 0 to 60% with 0.1 % HCOOH was used for elution. Compound **32** was obtained (370 mg, 48%). MS: m/z 316.2 [M-1].

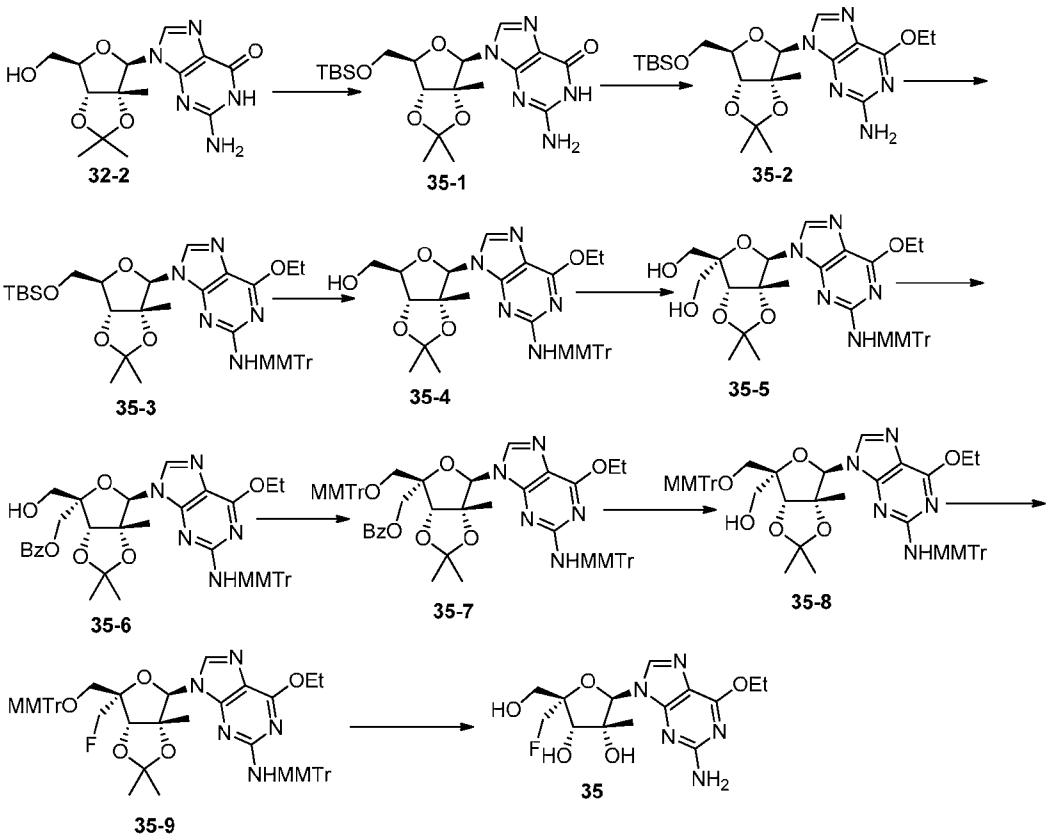
EXAMPLE 25
COMPOUND 17



[0351] A solution of **17-1** (25 mg, 0.04 mmol) in 80% aq. HCOOH was kept at RT for 3 h. The mixture was concentrated and coevaporated with toluene. The crude residue was purified on silica gel (10 g column) with CH_2Cl_2/MeOH (4-10% gradient) to yield **17-2** (8 mg, 54%).

[0352] A mixture of **17-2** (8 mg, 0.02 mmol) in acetonitrile (0.4 mL) was stirred with NMI (15 mL, 8 eq.) and the phosphorochloridate reagent overnight at RT. The reaction was quenched with sat. aq. NH_4Cl, diluted with EtOAc and water. The organic layer was separated, washed with aq. $NaHCO_3$, water and brine, and dried (Na_2SO_4). The residue was purified on silica gel (10 g column) with CH_2Cl_2/i-PrOH (4-10% gradient) to yield compound **17** (9 mg, 66%). MS: m/z = 683 [M+1].

EXAMPLE 26
COMPOUND 35



[0353] To a stirred solution of **32-2** (5.0 g, 14.83 mmol) in anhydrous pyridine (50 mL) was added TBSCl (3.33 g, 22.24 mmol) at RT under N_2. The mixture was stirred at RT for 12 h and concentrated at low pressure. The residue was purified by silica gel column chromatography to give **35-1** (5.69 g, 85.1%).

[0354] To a solution of PPh_3 (2.76 g, 10.6 mmol) and DIAD (2.15 g, 10.6 mmol) in dioxane (20 mL) was added EtOH (0.49 g, 10.6 mmol) at RT. After stirring for 30 mins, a solution of **35-1** (2.4 g, 5.3 mmol) in dioxane (10 mL) was added. The solution was stirred overnight at RT. After the reaction was complete, the reaction was quenched with sat. $NaHCO_3$ solution. The solution was extracted with EA (3 x 40 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by silica gel column (10% EA in PE) to give **35-2** (2 g, 78.4%) as a white solid.

[0355] To a solution of **35-2** (8 g, 16.9 mmol) in dichloromethane (60 mL) was added $AgNO_3$ (5.67 g, 33.4 mmol), collidine (4.03 g, 33.4 mmol) and MMTrCl (7.7 g, 25 mmol) in small portions under N_2 at 0 °C. The mixture was stirred at RT overnight. The reaction was monitored by TLC. After completion, the mixture was filtered. The filtrate was washed with sat. aq. $NaHCO_3$ and brine. The organic layer was dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by silica gel column to give **35-3** (10 g, 80%) as a white solid.

[0356] To a solution of **35-3** (10 g, 13.3 mmol) in methanol (100 mL) was added NH_4F (10 g, 270 mmol), and heated to reflux overnight. The mixture was concentrated at low pressure. The residue was purified by silica gel chromatography (50% PE in EA) to give **35-4** as a white solid (5 g, 59%).

[0357] To a solution of **35-4** (4 g, 6.27 mmol) and DCC (3.65 g, 18.8 mmol) in anhydrous DMSO (40 mL) was added TFA•Py (1.21 g, 6.27 mmol) at RT under N_2. The mixture was stirred at RT overnight. The reaction was quenched with water (100 mL), and diluted with EA (200 mL). After filtration, the filter was washed with sat. $NaHCO_3$ solution. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue (4 g, 6.27 mmol) was dissolved in dioxane (40 mL), and 37% formaldehyde (4 mL) followed by addition of 2N NaOH solution (8 mL) at RT. The mixture was stirred at 30 °C overnight. $NaBH_4$ (0.7 g, 18.9 mmol) was added in portions at 5 °C, and the mixture was stirred at RT for 30 mins. The reaction was quenched with water, and the mixture was extracted with EA (3 x 50 mL). The organic layer was dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified on a silica gel column (20% EA in PE) to give **35-5** (2.5 g, 60%) as a white solid.

[0358] To a solution of **35-5** (2.29 g, 3.43 mmol) in pyridine (5 mL) and DCM (20 mL) was added BzCl (0.53g, 3.77 mmol) at -78 °C, and stirred overnight at RT. The mixture was quenched with water, and extracted with DCM (3 x 40 mL). The organic layer was dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by silica gel column to give the **35-6** (1.62 mg, 62%).

[0359] To a solution of **35-6** (1.62 g, 2.1 mmol) in dichloromethane (20 mL) was added $AgNO_3$ (714 mg, 4.2 mmol), collidine (508 mg, 4.2 mmol) and MMTrCl (970 mg, 3.2 mmol) in small portions under N_2 at 0 °C. The mixture was stirred at RT overnight. The

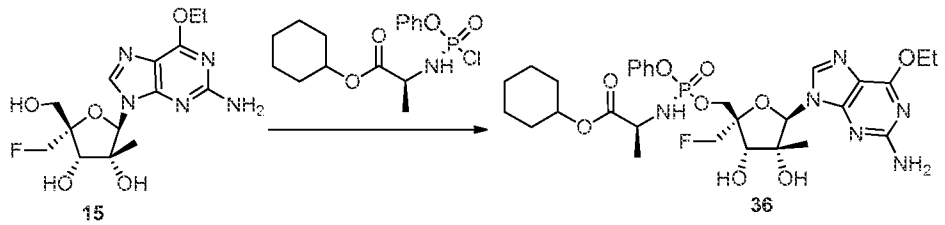
reaction was monitored by TLC. After filtration, the filter was washed with sat. aq. $NaHCO_3$ and brine. The combined organic layer was dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by silica gel column to give **35-7** (2 g, 91.3%) as a white solid.

[0360] To a solution of **35-7** (2.1 g, 2 mmol) in MeOH (30 mL) was added NaOMe (220 mg, 4 mmol) at RT and stirred for 1 h. After all starting material disappeared as indicated by TLC, the reaction was quenched with dry ice, and evaporated at low pressure. The residue was purified by silica gel column chromatography to give **35-8** (1.3 g, 69%) as a white solid.

[0361] To a solution of **35-8** (1.3 g, 1.38 mmol) in anhydrous DCM (15 mL) and pyridine (1 mL) was added dropwise Tf_2O (585 mg, 2.07 mmol) at -20 °C. The mixture was stirred at RT for 3 h, and diluted with DCM (150 mL). The solution was washed successively with water and brine. The organic solution was dried over Na_2SO_4 and concentrated at low pressure. The residue (1.48 g) was dissolved in anhydrous THF (15 mL), and treated with TBAF (3 mL, 1M in THF) at RT. The mixture was stirred overnight. The reaction was quenched with sat. aq. $NaHCO_3$, and extracted with EA (3 x 60 mL). The combined organic layer was dried over Na_2SO_4, and evaporated at low pressure. The residue was purified by silica gel column (30% EA in PE) to give **35-9** (1.25 g, 96%) as a white solid. ESI-LCMS: m/z 942.4 $[M+H]^+$.

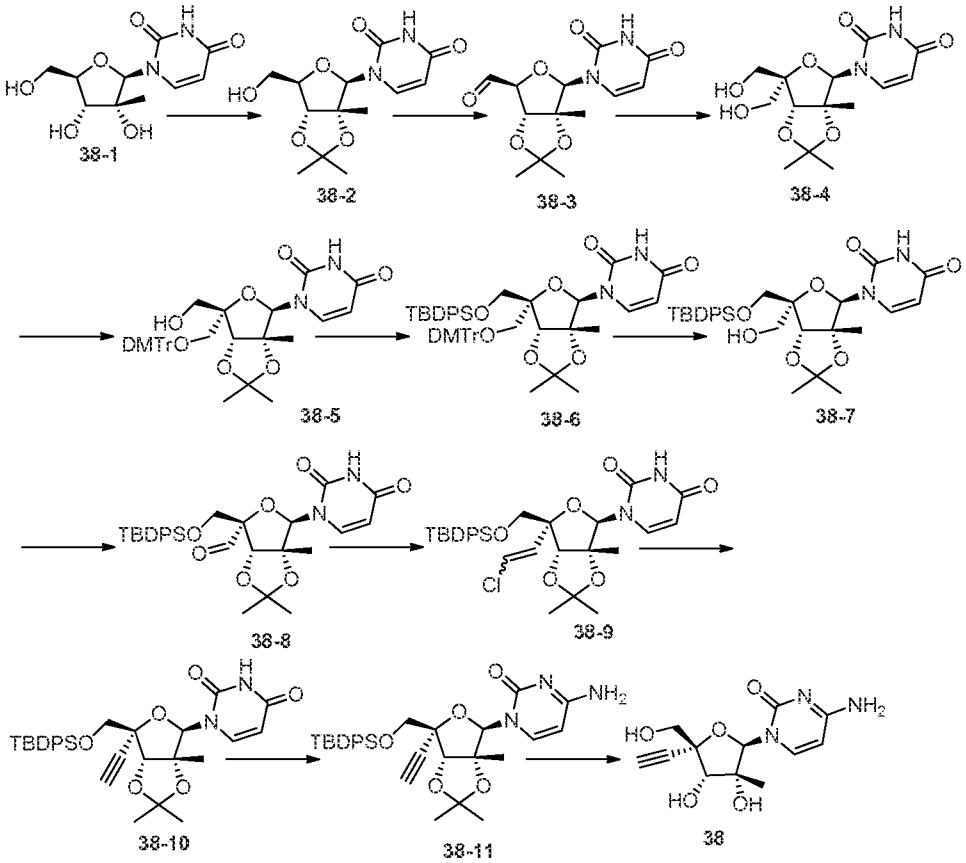
[0362] Compound **35-9** (0.55g, 0.58 mmol) was added into ice cooled 80% aq. TFA (5 mL) and kept overnight at 5 °C. The mixture was concentrated under reduced pressure at 5 °C. Thick oily residue was coevaporated several times with toluene and purified on silica gel (10 g column) with CH_2Cl_2/MeOH (4-15% gradient) to yield compound **35** (75 mg, 36%). MS: m/z = 358 [M+1].

EXAMPLE 27
COMPOUND 36



[0363] Compound **36** (8 mg, 10%) was prepared from compound **15** (48 mg) in acetonitrile (1.5 mL) with the phosphorochloridate reagent (0.14 g) and NMI (0.17 mL) in the same manner as compound 7. Purification was done by RP-HPLC (30-100% B, A: 50 mM TEAA in water, B: 50 mM TEAA in MeCN). MS: m/z = 665 [M-1].

EXAMPLE 28
COMPOUND 38



[0364] To a solution of **38-1** (17 g, 65.9 mmol) and 2,2-dimethoxypropane (34.27 g, 329.5 mmol, 5 eq.) in acetone (200 mL) was added *p*-toluenesulfonic acid monohydrate (11.89 g, 62.6 mmol, 0.95 eq.). The = mixture was allowed to stir overnight at RT. The reaction was quenched with sat. aq. $NaHCO_3$. The mixture was filtered, and dried over anhydrous Na_2SO_4. The filtrate was concentrated to give **38-2** (19 g, 97%).

[0365] To a solution of **38-2** (6 g, 20.1 mmol) in anhydrous CH_3CN (80 mL) was added IBX (7.05 g, 25.2 mmol, 1.25 eq.) at RT. The mixture was refluxed for 1 h., and cooled to 0 °C. The precipitate was filtered, and the filtrate was concentrated to give crude **38-3** (6 g 100%) as a yellow solid.

[0366] Compound **38-3** (6 g 20.1 mmol) was dissolved in 1,4-dioxane (60 mL). 37% HCHO (6 mL, 69 mol) and 2M NaOH aqueous solution (12 mL, 24 mmol, 1.2 eq.) were added at 10 °C. The mixture was stirred at RT overnight and neutralized with AcOH to pH = 7. The mixture was treated with $NaBH_4$ (1.53 g, 40.2 mmol, 2 eq.) at 10 °C. The mixture was stirred at RT for 30 mins, and then quenched with sat. aq. NH_4Cl. The mixture was extracted with EA. The organic layer was dried over anhydrous Na_2SO_4, and concentrated to dryness. The residue was purified on silica gel column (1-3% MeOH in DCM) to give **38-4** (3.5 g, 53 %) as a white solid.

[0367] To a solution of **38-4** (3.5 g, 10.7 mmol) in anhydrous pyridine (60 mL) was added DMTrCl (3.6 g, 10.7 mmol, 1 eq.) in anhydrous DCM (8 mL) dropwise at -30 °C. The mixture was stirred at RT overnight. The solution was treated with MeOH, and concentrated to dryness at low pressure. The residue was purified by column chromatography (0.5-2% MeOH in DCM) to give **38-5** (3 g, 45%) as a yellow solid.

[0368] To a solution of **38-5** (2.5 g, 4 mmol) in anhydrous CH_2Cl_2 (30 mL) was added $AgNO_3$ (0.816 g, 4.8 mmol, 1.2 eq.), imidazole (0.54 g, 8 mmol, 2 eq.) and TBDPSCl (1.18 g, 4.8 mmol, 1.2 eq.) under N_2 atmosphere. The mixture was stirred at RT for 14 h. The precipitate removed via filtration, and the filtrate was washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to give crude **38-6** (3.4 g, 100%) as a yellow solid.

[0369] Compound **38-6** (4 g, 4.6 mmol) was dissolved in 80% HOAc aqueous solution (50 mL). The mixture was stirred at RT for 3 h. The solution was treated with MeOH, and concentrated to dryness. The residue was purified by column chromatography (1-2% MeOH in DCM) to give **38-7** (1.2 g, 45%) as a white solid.

[0370] To a solution of **38-7** (1 g, 1.77 mmol) in anhydrous DCM (15 mL) was added Dess-Martin periodinane reagent (1.12 g, 2.65 mmol, 1.5 eq.) at 0 °C under nitrogen atmosphere. The reaction was stirred at RT for 2.5 h. The solution was quenched by addition of 4% $Na_2S_2O_3$ and washed with 4% sodium bicarbonate aqueous solution (50 mL). The mixture was stirred for another 15 mins. The organic layer was washed with brine, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (20% EtOAc in hexane) to give **38-8** (0.7 g, 70%) as a white solid.

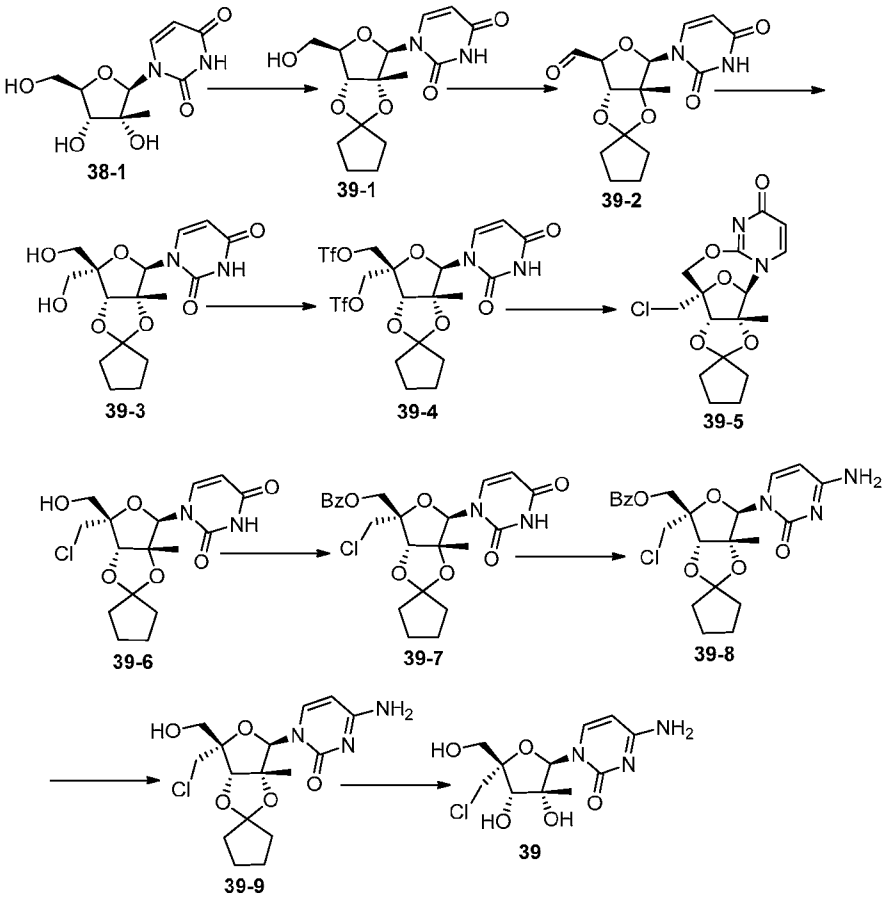
[0371] To a solution of methyltriphenylphosphonium chloride (2.95 g, 8.51 mmol, 4 eq.) in anhydrous THF (20 mL) was added n-BuLi (3.2 mL, 8.1 mmol, 3.8 eq.) dropwise at -70 °C under nitrogen atmosphere. The mixture was stirred at 0 °C for 1 h. A solution of **38-8** (1.2 g, 2.13 mmol) in anhydrous THF (3 mL) was added dropwise at 0 °C under nitrogen atmosphere. The solution was stirred 0 °C for 2 h. The reaction was quenched with NH_4Cl and extracted with EtOAc. The organic layer was washed with brine and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (20% EtOAc in hexane) to give **38-9** (0.9 g, 75%) as a white solid.

[0372] To a solution of **38-9** (0.85 g, 1.43 mmol) in anhydrous THF (50 mL) was added n-BuLi (5.7 mL, 14.3 mmol,10 eq.) at -70 °C under nitrogen atmosphere. The mixture was stirred at -70 °C for 2 h. The reaction was quenched with NH_4Cl and extracted with EtOAc. The organic layer was washed with brine and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (20% EtOAc in hexane) to give **38-10** (0.4 g, 50%) as a white solid.

[0373] To a solution of **38-10** (0.4 g, 0.714 mmol) in anhydrous CH_3CN (30 mL) were added TPSCl (0.433 g, 1.43 mmol, 2 eq.), DMAP (0.174 g, 1.43 mmol, 2 eq.) and TEA (1.5 mL) at RT. The mixture was stirred at RT for 3 h. NH_4OH (3 mL) was added, and the mixture was stirred for 1 h. The mixture was diluted with EA (150 mL), and washed with water, 0.1 M HCl and saturated aqueous $NaHCO_3$. The organic layer was washed with brine and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (2% MeOH in DCM) to give **38-11** (0.2 g, 50%) as a yellow solid.

[0374] Compound **38-11** (1.35 g, 1.5 mmol) was dissolved in 80% HOAc aqueous solution (40 mL). The mixture was stirred at 60 °C for 2 h and concentrated to dryness. The crude was purified on silica gel column (5% MeOH in DCM) to give compound **38** (180 mg, 35%) as a white solid. ESI-MS: m/z 282.1 $[M+H]^+$.

EXAMPLE 29
COMPOUND 39



[0375] To a solution of cyclopentanone (6.0 g, 71 mmol) in MeOH (60 mL) was added TsOH•H_2O (1.35 g, 7.1 mmol) and trimethoxymethane (8 mL) at RT. The solution was stirred at RT for 2 h. The reaction was quenched with NaOMe, and the mixture was extracted with hexane (30 mL). The organic layer was dried and concentrated to give crude 1,1-dimethoxycyclopentane (9.2 g), which was dissolved in 1,2-dichloroethane (50 mL). To the above solution was added **38-1** (5.0 g, 19.38 mmol) and TsOH•H_2O (0.36 g, 1.9 mmol) at RT. The mixture was stirred at 60 °C for 4 h. The reaction was quenched with TEA and concentrated at low pressure. The residue was purified on silica gel column (1% MeOH in DCM) to give **39-1** (4.77 g, 76%) as a white solid.

[0376] To a solution of **39-1** (4.77 g, 14.73 mmol) in anhydrous DCM (50 mL) was added DMP (6.56 g, 15.6 mmol) at 0 °C. The solution was stirred at RT for 10 h and concentrated to dryness. The residue was suspended in PE (30 mL) and DCM (5 mL), and

the solid was precipitated. After filtration, the filtrate was concentrated to give the crude **39-2** (4.78 g, 100%) as a foam.

[0377] Crude **39-2** (4.77 g, 14.73 mmol) was re-dissolved in anhydrous 1,4-dioxane (50 mL). To the solution was added CH_2O aq. (37%, 3.6 mL) and NaOH aq. (2M, 11.3 mL) at 0 °C. The mixture was stirred at RT for 16 h. The mixture was treated with $NaBH_4$ (1.48 g, 40 mmol) at 0 °C and stirred for 0.5 h. The reaction was quenched with water, and the mixture was extracted with EA. The organic layer was dried over anhydrous Na_2SO_4, and concentrated to dryness. The residue was purified on silica gel column (40% EA in PE) to give **39-3** (2.6 g, 49.9%) as a white solid.

[0378] To a stirred solution of **39-3** (5.0 g, 14.1 mmol) in pyridine (5.6 g, 71 mmol) and DCM (100 mL) was added Tf_2O (8.7 g, 31.2 mmol) dropwise at -35 °C. The mixture was allowed to warm to 0 °C slowly and stirred for 2 h. The mixture was quenched with 0.5M aq. HCl and the DCM layer was separated. The organic phase was dried over anhydrous Na_2SO_4, and concentrated to dryness. The crude was purified on silica gel column (20% EA in PE) to give **39-4** (4.5 g, 52%).

[0379] **39-4** (4.5 g, 7.28 mmol) was dissolved in anhydrous THF (50 mL) at 0 °C. The solution was treated with NaH (60% in mineral oil, 0.32 g, 8 mmol, 1.1 eq.) in portions, and the mixture was stirred at RT for 8 h. The reaction was quenched with water, and extracted with EA (3 x 60 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated at low pressure to give the crude product used directly for next step. To a solution of the crude product (2.0 g, 3.6 mmol) in MeCN (10 mL) was added LiCl (4.0 g, 13 mmol). The reaction was allowed to proceed overnight. Aqueous NaOH (1N, ~ 2 eq.) was added, and the mixture was stirred for 1 h. The mixture was partitioned between sat. NH_4Cl solution and EA. The organic layer was concentrated under reduced pressure, and the crude was purified on silica gel column (20% EA in PE) to give **39-6** (0.6 g, 46 %) as a white solid. ESI-MS: m/z 395.0 $[M+Na]^+$.

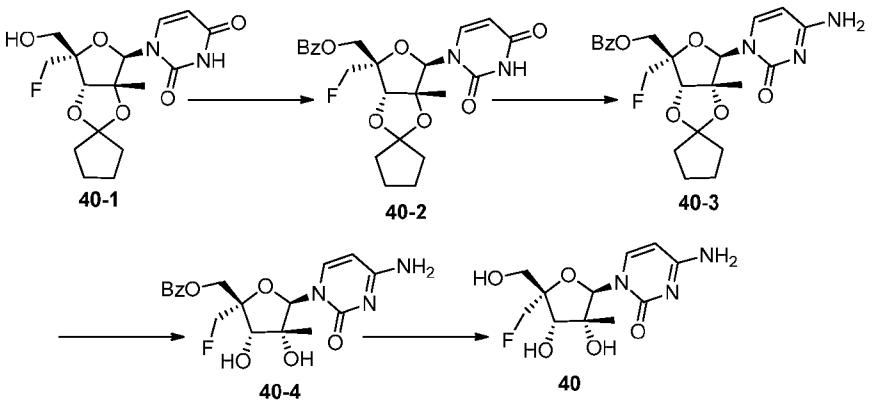
[0380] Compound **39-6** (3.0 g, 8.06 mmol) was co-evaporated with toluene (30 mL). To a solution of **39-6** (3.0 g, 8.06 mmol), DMAP (98 mg, 0.80 mmol) and TEA (2.3 mL, 2 eq.) in DCM (30 mL) was added Bz_2O (1.82 g, 8.06 mmol) at 0 °C and stirred for 3 h. The reaction was quenched with 1.0 M HCl and extracted with DCM. The DCM layer was dried over high vacuum pump to give crude **39-7** (3.3 g, 80.9%).

[0381] To a solution of **39-7** (400 mg, 0.84 mmol) in anhydrous CH_3CN (3 mL) was added TPSCl (507 mg, 1.68 mmol), TEA (169 mg, 1.68 mmol) and DMAP (207 mg, 1.68 mmol), and the mixture was stirred for 2 h. at RT. Completion of the reaction was determined by TLC. Ammonium solution (3.0 mL) was added at RT, and the solution was stirred for 2 h. The mixture was washed with 1.0 M HCl solution and extracted with DCM. The DCM layer was dried over Na_2SO_4 and concentrated to dryness. The crude was purified by column chromatography to provide **39-8** (250 mg, 63%).

[0382] Compound **39-8** (250 mg, 0.53 mmol) in 80% formic acid (3 mL) was stirred at RT for 3 h. Completion of the reaction was determined by TLC. The mixture was concentrated at a low pressure. The crude was purified by column chromatography to give **39-9** (130 mg, 66%).

[0383] Compound **39-9** (270 mg, 0.73 mmol) was dissolved in $MeOH/NH_3$ (10 mL), and the solution was stirred for 6 h. The mixture was concentrated at low pressure. The crude product was washed with DCM, and the solution was lyophilized to give compound **39** (118 mg, 52%). ESI-MS: m/z 328.3 $[M+H+Na]^+$.

EXAMPLE 30
COMPOUND 40



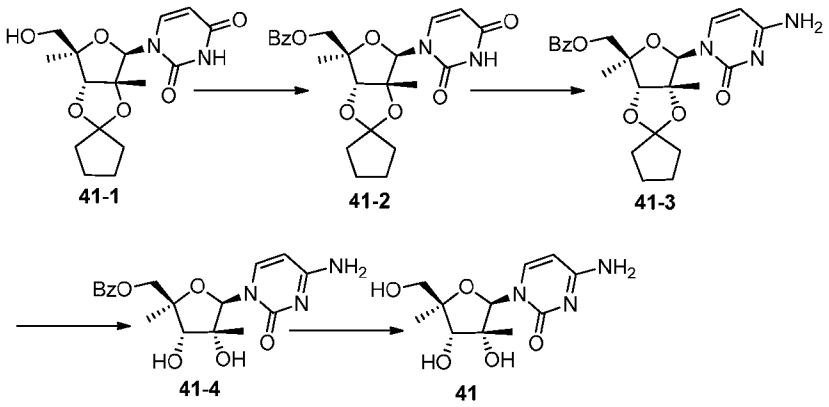
[0384] Compound **40-1** (3.0 g, 8.42 mmol) was co-evaporated with toluene (30 mL). To a solution of **40-1** (3.0 g, 8.42 mmol), DMAP (103 mg, 0.84 mmol) and TEA (2.5 mL, 2 eq.) in DCM (30 mL) was added Bz_2O (2.01 g, 8.42 mmol) at 0 °C and stirred for 3 h. The solution was quenched with 1.0 M HCl and extracted with DCM. The DCM layer was dried over high vacuum pump to give crude **40-2** (3.3 g, 85%).

[0385] To a solution of **40-2** (200 mg, 0.43 mmol) in anhydrous CH_3CN (2 mL) was added TPSCl (260 mg, 0.86 mmol), TEA (95 mg, 0.94 mmol) and DMAP (106.4 mg, 0.86 mmol), and the mixture was stirred for 2 h at RT. Completion of the reaction was determined by TLC. Ammonium solution (1.33 mL) was added at RT, and left to stir for 2 h. The mixture was washed with 1.0 M HCl solution, and extracted with DCM. The DCM layer was dried over anhydrous Na_2SO_4, and concentrated to dryness at low pressure. The residue was purified by column chromatography to provide **40-3** (150 mg, 75%).

[0386] Compound **40-3** (100 mg, 0.21 mmol) in 80% formic acid (2 mL) was stirred at RT for 3 h. Completion of the reaction was determined by TLC. The mixture was concentrated at low pressure, and the residue was purified by column chromatography to give **40-4** (50 mg, 58%).

[0387] Compound **40-4** (270 mg, 0.68 mmol) was dissolved in $MeOH/NH_3$ (10 mL), and the resulting solution was stirred for 6 h. The mixture was concentrated at low pressure. The crude product was washed with DCM, and the solution was lyophilized to give compound **40** (105 mg, 53.8%). ESI-MS: m/z 290.4 $[M+H]^+$.

EXAMPLE 31
COMPOUND 41



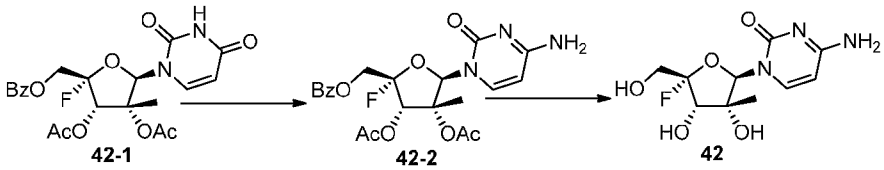
[0388] Compound **41-1** (3.0 g, 8.87 mmol) was co-evaporated with toluene (30 mL). To a solution of **41-1** (3.0 g, 8.87 mmol), DMAP (108mg, 0.88 mmol) and TEA (2.5 mL, 2 eq.) in DCM (30 mL) was added Bz_2O (2.01 g, 8.87 mmol) at 0 °C. The solution was stirred for 3 h. The reaction was quenched with 1.0 M HCl solution, and extracted with DCM. The DCM layer was dried over high vacuum pump to give crude **41-2** (3.5 g, 85%) as a solid.

[0389] To a solution of **41-2** (200 mg, 0.45 mmol) in anhydrous CH_3CN (2 mL) was added TPSCl (260 mg, 0.90 mmol), TEA (99 mg, 0.99 mmol) and DMAP (106.4 mg, 0.90 mmol). The mixture was stirred at RT for 2 h. Completion of the reaction was determined by TLC. An ammonium solution (1.33 mL) was added at RT, and the mixture was stirred for 2 h. The mixture was washed with 1.0 M HCl solution, and extracted with DCM. The DCM layer was dried over anhydrous Na_2SO_4, and concentrated to dryness at low pressure. The crude product was purified by column chromatography to provide **41-3** (150 mg, 75%).

[0390] Compound **41-3** (100 mg, 0.23 mmol) in 80% formic acid (2 mL) was stirred at RT for 3 h. Completion of the reaction was determined by TLC. The mixture was concentrated at a low pressure. The crude product was purified by column chromatography to give **41-4** (50 mg, 58%).

[0391] Compound **41-4** (270 mg, 0.72 mmol) was dissolved in $MeOH/NH_3$ (10 mL), and the solution was stirred for 6 h. The mixture was concentrated at low pressure. The crude product was washed with DCM, and the solution was lyophilized to give compound **41** (105 mg, 53.8%). ESI-MS: m/z 675.4 $[2M+H]^+$.

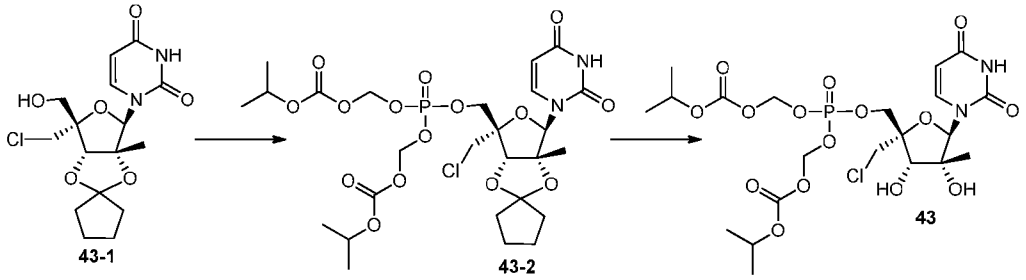
EXAMPLE 32
COMPOUND 42



[0392] To a solution of **42-1** (600 mg, 1.29 mmol) in anhydrous CH_3CN (4 mL) was added DMAP (315 mg, 2.59 mmol), TEA (391 mg, 3.87 mmol) and TPSCl (782 mg, 2.58 mmol). The mixture was stirred for 3 h. under N_2. A solution of NH_3 in THF (2 mL) was added, and stirred for 1 h. The reaction was quenched with sat. NH_4Cl solution, and extracted with EA. The organic layer was dried over anhydrous Na_2SO_4, and concentrated to dryness at low pressure. The residue was purified by column chromatography to provide **42-2** (370 mg, 62%) as a white foam solid.

[0393] Compound **42-2** (370 mg, 1.48 mmol) in methanolic ammonium was stirred at RT for 4 h. The solution was concentrated to dryness to give compound **42** (200 mg, 91%) as a white solid. ESI-MS: m/z 275.9 $[M+H]^+$.

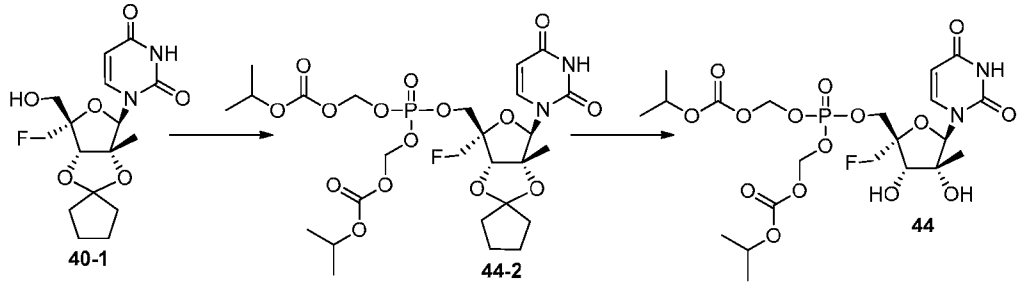
EXAMPLE 33
COMPOUND 43



[0394] To a solution of triethylammonium bis(isopropyloxycarbonyloxymethyl)phosphate (0.6 mmol, prepared from bis(POC)phosphate (0.2 g) and Et_3N (83 μL)) in THF was added **43-1** (74 mg, 0.2 mmol). The mixture evaporated and rendered anhydrous by co-evaporating with pyridine follow by toluene. The residue was dissolved in anhydrous THF (2 mL). Diisopropylethylamine (0.35 mL; 10 eq.) was added, followed by BOP-Cl (0.25 g; 5 eq.) and 3-nitro-1,2,4-triazole (0.11 g; 5 eq.). The mixture was stirred at RT for 90 mins, diluted with EtOAc, washed with sat. aq. $NaHCO_3$ and brine, and dried with Na_2SO_4. The residue was purified on silica (10 g column) with CH_2Cl_2/i-PrOH (4-10% gradient) to yield 50 mg (37%) of give **43-2**.

[0395] A solution of **43-2** (40 mg; 0.06 mmol) in 80% aq. HCOOH was heated at 45°C for 8 h. The mixture was evaporated, co-evaporated with toluene and purified on silica (10 g column) with CH_2Cl_2/MeOH (4-10% gradient) to yield compound **43**(35 mg ,91%). MS: m/z = 619 [M+1].

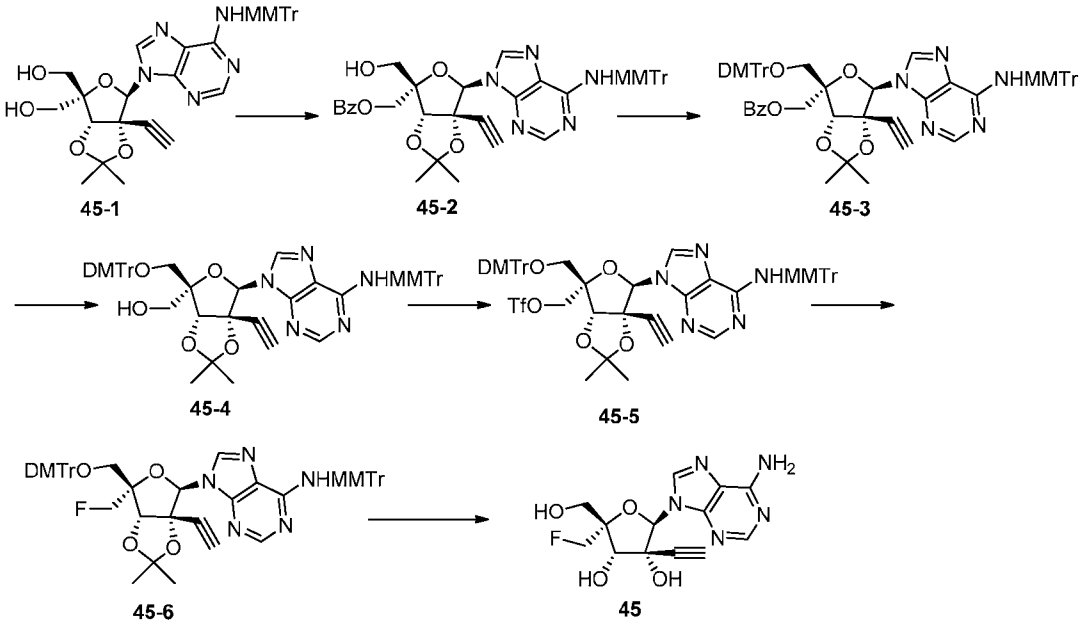
EXAMPLE 34
COMPOUND 44



[0396] Compound **44-2** was prepared from **40-1** following a similar procedure for the preparation of **43-2**. The residue was purified on silica (10 g column) with hexanes/EtOAc (35-100% gradient) to yield **44-2** (0.45 g, 75%).

[0397] A solution of **44-2** (0.40 g; 0.6 mmol) in 80% aq. HCOOH (15 mL) was heated at 45°C for 8 h. The mixture was evaporated, co-evaporated with toluene and purified on silica (10 g column) with CH_2Cl_2/MeOH (4-10% gradient) to yield compound **44** (0.27 g, 75%). MS: m/z = 603 [M+1].

EXAMPLE 35
COMPOUND 45



[0398] To a solution of **45-1** (3.0 g, 4.7 mmol) in CH_3CN/pyridine (15 mL/20 mL) was added BzCl (0.67g, 4.7 mmol) at 0 °C slowly. The mixture was stirred at 10 °C for 12 h. The reaction was quenched with sat. $NaHCO_3$ solution, and extracted with DCM. The solution was washed with brine, dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified on silica gel column (EA in PE from 2% to 50%) to afford **45-2** (2.6 g, 72%) as a solid.

[0399] To a solution of **45-2** (1.0 g, 1.35 mmol) in pyridine (8 mL) was added DMTrCl (0.64 g, 1.9 mmol). The mixture was stirred at 20-35°C overnight. The reaction was monitored by LCMS and TLC. The reaction was quenched with MeOH, and

concentrated at low pressure. The residue was purified by silica gel column to give **45-3** (1.5 g), which was used without further purification.

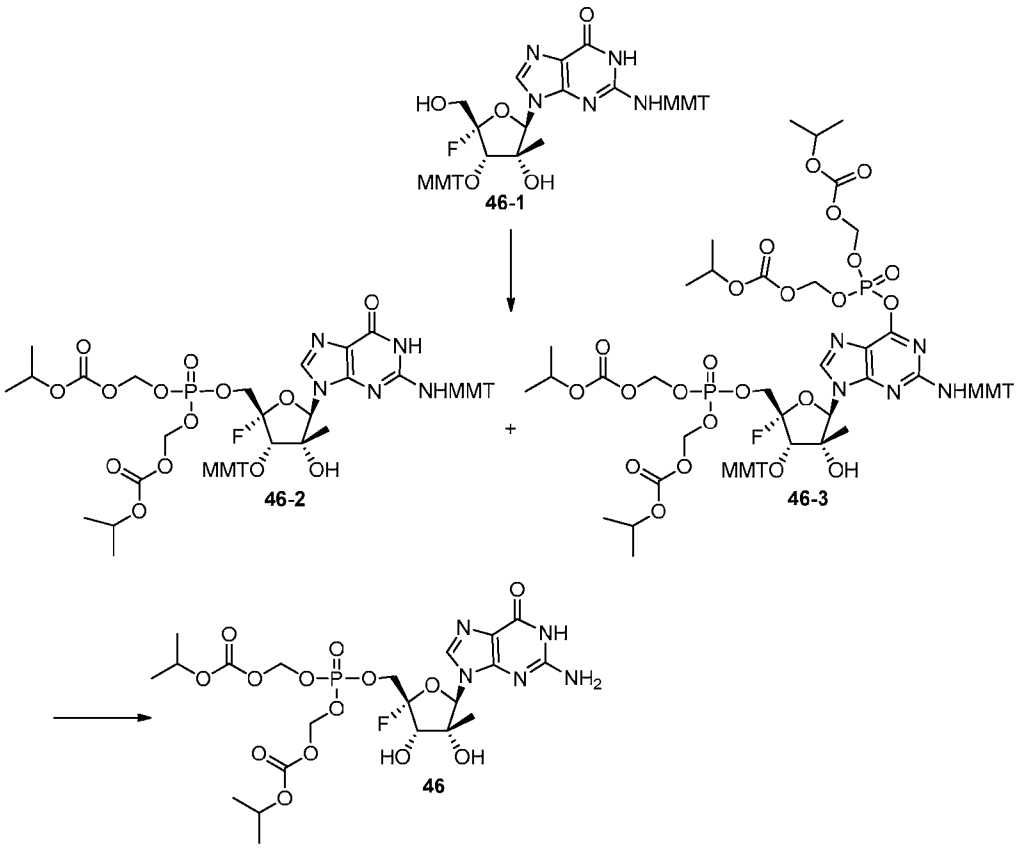
[0400] To a solution of **45-3** (1.5 g, 1.35 mmol) in MeOH/THF (1/1, 10 mL) was added NaOMe (0.11 g, 2.0 mmol), and stirred at 40 °C for 3 h. The reaction was monitored by TLC. The reaction was quenched with dry ice, and concentrated to dryness at low pressure. The residue was dissolved in DCM (100 mL). The solution was washed with brine, dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified on silica gel column (EA in PE from 2% to 50%) to provide **45-4** (1.0 g, 79%).

[0401] To a solution of **45-4** (950 mg, 1.02 mmol) in DCM (5 mL) was added pyridine (241 mg, 3.05 mmol) and Tf_2O (344 mg, 1.22 mmol) at 0 °C slowly. The mixture was stirred at RT for 12 h. Completion of the reaction was determined by TLC and LCMS. The reaction was quenched with sat. $NaHCO_3$ solution, and extracted with DCM (3 x 60 mL). The organic phase was dried over anhydrous Na_2SO_4, and concentrated at low pressure to give crude **45-5** (1.08 g, 1.02 mmol), which was used without further purification.

[0402] To a solution of **45-5** (1.08 g, 1.02 mmol) in THF (6 mL) was added TBAF (0.8 g, 3 mmol), and stirred at 30-40 °C for 12 h. The reaction was quenched with sat. $NaHCO_3$ solution, and extracted with EA (3 x 60 mL). The solution was dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by silica gel column (EA in PE from 2% to 50%) to afford **45-6** (0.62 g, 65%).

[0403] A mixture of **45-6** (0.55 g, 0.59 mmol) in TFA (90%, 5 mL) was stirred at 50-60 °C for 16 h. The mixture was treated with MeOH, and concentrated at low pressure. The residue was purified by prep-HPLC to afford compound **45** (60 mg, 31%). ESI-MS: m/z 324.0 $[M+H]^+$.

EXAMPLE 36
COMPOUND 46

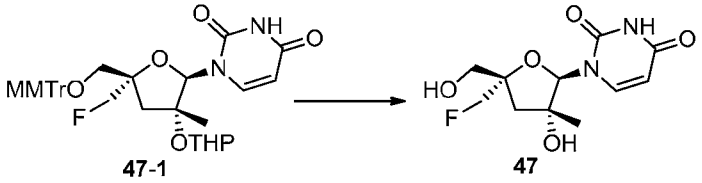


[0404] To a solution of triethylammonium bis(isopropyloxycarbonyloxymethyl)phosphate (0.33 mmol, prepared from 110 mg of bis(POC)phosphate and 46 μL of Et_3N) in THF was added **46-1** (91 mg, 0.11 mmol). The mixture evaporated and rendered anhydrous by co-evaporating with pyridine follow by toluene. The residue was dissolved in anhydrous THF (1.5 mL) and cooled in an ice-bath. Diisopropylethylamine (0.19 mL, 10 eq.) was added, followed by BOP-Cl (0.14 g, 5 eq.), and 3-nitro-1,2,4-triazole (63 mg, 5 eq.). The mixture was stirred 0 °C for 90 mins, diluted with EtOAc (30 mL), washed with sat. aq. $NaHCO_3$, brine, and dried (Na_2SO_4). The residue was purified on silica (10 g column) with CH_2Cl_2/i-PrOH solvent system (2-10% gradient) to obtain **46-2** (13 mg, 10%) and **46-3** (95 mg, 58%).

[0405] A solution of **46-2** and **46-3** (13 mg and 95 mg, respectively) in 80% aq. HCOOH (3 mL) was stirred at RT for 3 h, then evaporated and co-evaporated with toluene.

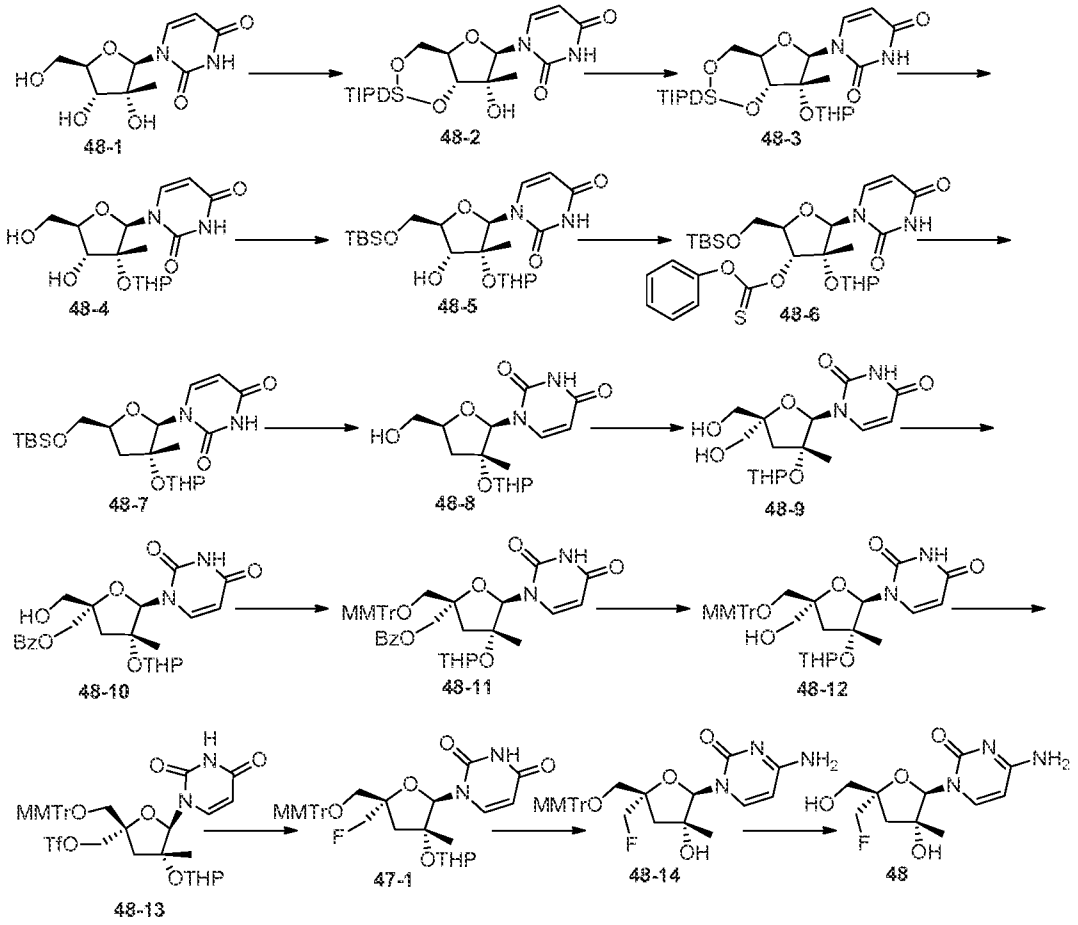
The residue was purified on silica (10 g column) with CH_2Cl_2/MeOH (4-10% gradient) to obtain compound **46** in (42 mg, 94%) yield. MS: m/z=628 [M+1].

EXAMPLE 37
COMPOUND 47



[0406] Compound **47-1** (320 mg, 0.51 mmol) was dissolved in a mixture of $CH_3COOH/THF/H_2O$ (4/2/1) (7 mL), and the mixture was stirred at 50 °C for 2 h. The solution was concentrated to dryness, and the residue was purified by prep-HPLC to give compound **47** (38mg, 31 %) as a white solid. ESI-MS: m/z 296.9 $[M+H+Na]^+$.

EXAMPLE 38
COMPOUND 48



[0407] To a stirred solution of **48-1** (30.0 g, 116 mmol) in anhydrous pyridine (240 mL) was added TIPDSCl (54.98 g, 174 mmol) in portions at 0 °C. The mixture was stirred at RT for 16 h. The reaction was quenched with water, and concentrated to dryness at low pressure. The residue was diluted with EA, and washed with water and brine. The organic phase was dried over sodium sulfate, and concentrated at low pressure. The residue was purified on a silica gel column (50% EA in PE) to give **48-2** (58 g, 99%).

[0408] To a stirred solution of **48-2** (20.0 g, 40 mmol) in anhydrous DCM (200 mL) at 0 °C was added DHP(33.6 g, 400 mmol) and TFA(6.84 g, 60 mmol) dropwise. The mixture was stirred at RT for 16 h. The solution was adjusted to pH = 8 by addition of 2 N NaOH solution. The mixture was washed with sat. aq. $NaHCO_3$, and extracted with DCM (100 mL). The organic phase was dried over anhydrous sodium sulfate, and concentrated to dryness at low pressure. The residue was purified on a silica gel column (20% EA in PE) to give **48-3** (16 g, 68%).

[0409] To a solution of **48-3** (41 g, 70 mmol) in anhydrous MeOH (400 mL) was added NH_4F (51.88 g, 140 mmol). The mixture was refluxed for 1 h, and then concentrated in vacuum. The residue was purified on a silica gel column (10% MeOH in DCM) to give **48-4** (23.1 g, 96%)

[0410] To a stirred solution of **48-4** (23.1 g, 67.54 mmol) in anhydrous pyridine (200 mL) was added imidazole (6.89g, 101.32 mmol) and TBSCl (10.92 g, 74.29 mmol) in portions at 0 °C. The mixture was stirred at RT for 16 h. The solution was quenched with water, and concentrated to dryness. The residue was diluted with EA, and washed with water and brine. The organic phase was dried over anhydrous sodium sulfate, and concentrated at low pressure. The residue was purified on a silica gel column to give **48-5** (23 g, 74%).

[0411] To a solution of **48-5** (27.56 g, 60.44 mmol) in anhydrous MeCN (560 mL) was added DMAP (18.43 g, 151.1 mol) and PhOCSCl (14.55 g, 84.61 mmol) at 0 °C under N_2. The mixture was stirred at RT overnight, and the reaction was quenched with water. The mixture was extracted with EA. The organic phase was dried with anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified on a silica gel column eluted with 30% EA in PE to provide **48-6** (23 g, 64%).

[0412] To a solution of **48-6** (14.5 g, 24.5 mmol) in anhydrous toluene (700 mL) was added AIBN (1.21 g, 7.3 mmol) and Bu_3SnH (10.73 g, 36.74 mmol) in toluene (10 mL).

N_2 was bubbled into the solution for 30 mins. The mixture was warmed to 135 °C for 2 h. Saturated aqueous CsF was added, and the mixture was stirred for 1 h. The mixture was diluted with EA (150 mL), and washed successively with water, sat. aq. $NaHCO_3$ and brine. The organic layer was removed at low pressure. The residue was purified on a silica gel column (30% EA in PE) to provide **48-7** (10.5 g, 97%).

[0413] To a solution of **48-7** (21 g, 47.73 mmol) in anhydrous MeOH (200 mL) was added NH_4F (35.32 g, 950 mmol). The mixture was refluxed for 1 h and concentrated in vacuum. The residue was purified on a silica gel column (20% MeOH in DCM) to give **48-8** (14 g, 90%).

[0414] TFA•Py (2.37g, 12.27mmol) was added to a mixture of **48-8** (4 g, 12.27 mmol) and DCC (7.58 g, 36.81 mmol) in anhydrous DMSO (40 mL) at RT under N_2 atmosphere. The mixture was stirred at RT for 2 h. 37% formaldehyde (10 mL, 115 mmol) was added at RT, and stirred for 15 mins, followed by treatment with 2N NaOH (20 mL, 40 mmol). The mixture was stirred at 30 °C overnight and neutralized with AcOH to pH = 7. $NaBH_4$ (1.87 g, 49.08 mmol) was added in portions at 5 °C, and the mixture was stirred at RT for 30 mins. The mixture was extracted with EtOAc (3 x 100 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified on a silica gel column (5% MeOH in DCM) to give **48-9** (2 g, 46%) as a white solid.

[0415] To a solution of **48-9** (2 g, 5.62 mmol) in anhydrous CH_3CN (8 mL) was added pyridine (10 mL) and BzCl (0.79 g, 5.62 mmol) in a solution of DCM (2 mL) at 0°C under N_2. The mixture was stirred at RT overnight. The reaction was quenched with water, and concentrated at low pressure. The residue was diluted with EA (50 mL), and washed successively with water and brine. The organic layer was dried over anhydrous Na_2SO_4, and concentrated at a low pressure. The residue was purified on a silica gel column (3% MeOH in DCM) to provide **48-10** (1.6 g, 62%)

[0416] To a solution of **48-10** (1.6 g, 3.48 mmol) in anhydrous pyridine (16 mL) was added MMTrCl (1.61 g, 5.22 mmol) at 0°C under N_2. The mixture was stirred at RT overnight. The reaction was quenched with water, and concentrated in vacuo. The residue was diluted with EA (50 mL) and washed successively with water and brine. The organic layer was dried over Na_2SO_4 and concentrated at a low pressure to give crude **48-11** (2.55 g, 100%), which used without further purification.

[0417] To a solution of **48-11** (2.55 g, 3.48 mmol) in anhydrous MeOH (50 mL) was added $NaOCH_3$ (0.28 g, 5.23 mmol). The mixture was stirred at 45 °C for 2 h, bubbled to pH = 7 by using dry ice and concentrated to dryness. The residue was purified on a silica gel column (2% MeOH in DCM) to give **48-12** (0.93 g, 42%).

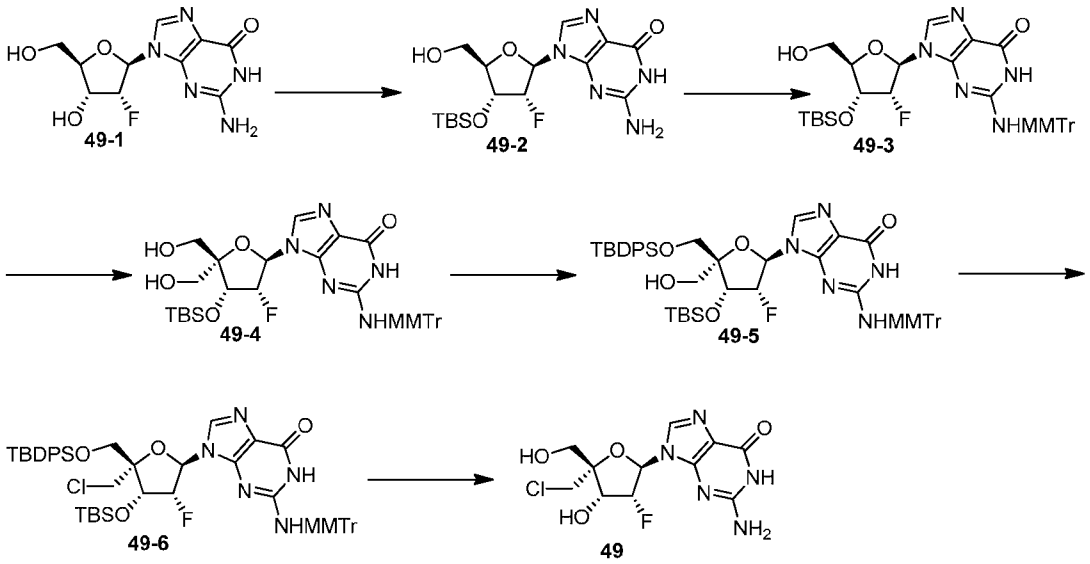
[0418] To a solution of **48-12** (0.93 g, 1.48 mmol) in anhydrous DCM (10 mL) was added pyridine (1.17 g, 14.8 mmol) at -30 °C. Tf_2O (0.63 g, 2.22 mmol) in DCM (3 mL) was added dropwise. The mixture was stirred at -30 °C-0 °C for 20 mins and at 0 °C for 10 mins. The reaction was quenched with water, and the mixture was extracted with DCM (3 x 100 mL). The organic layer was dried over anhydrous Na_2SO_4, and concentrated at low pressure to provide crude **48-13** (1.13 g, 100%), which was used without further purification.

[0419] To a solution of **48-13** (1.13 g, 1.48 mmol) in anhydrous THF (10 mL) was added TBAF (3.86 g, 14.8 mmol). The mixture was stirred at 30 °C for 2 h. The reaction was quenched with water, and the mixture was extracted with EtOAc (3 x 100 mL). The organic layer was dried over anhydrous Na_2SO_4, and concentrated to dryness at low pressure. The residue was purified on a silica gel column (3% MeOH in DCM) to give **47-1** (0.42 g, 45%).

[0420] To a solution of **47-1** (50 mg, 0.079 mmol) in anhydrous CH_3CN (1 mL) was added TPSCl (48.07 mg, 0.16 mmol), DMAP (19.36 mg, 0.16 mmol) and NEt_3 (0.2 mL) at RT. The mixture was stirred at RT for 3 h. 28% aqueous ammonia (0.4 mL) was added, and the mixture was stirred for 1 h. The mixture was diluted with EA (150 mL), and washed successively with water, sat. aq. $NaHCO_3$ and brine. The organic layer was dried over anhydrous Na_2SO_4, and concentrated at a low pressure. The residue was purified on a silica gel column (5% MeOH in DCM) to give **48-14** (40 mg, 80%).

[0421] Compound **48-14** (320 mg, 0.51 mmol) was dissolved in 80% HCOOH (6 mL), and the mixture was stirred at 10 °C for 1 h. The mixture was concentrated at low pressure, and the residue was purified by prep-HPLC to give compound **48** (43mg, 31 %)as a white solid. ESI-MS: m/z 273.9 $[M+H]^+$, 547.1 $[2M+H]^+$.

EXAMPLE 39
COMPOUND 49



[0422] To a solution of **49-1** (20.0 g, 70.2 mmol) in anhydrous pyridine (200 mL) was added imidazole (19.1 g, 280 mmol) and TBSCl (42.1 g, 281 mmol) at 25°C. The solution was stirred at 25°C for 15 h, and then concentrated to dryness under reduced pressure. The residue was dissolved in EtOAc and then filtered. The filtrate was concentrated to dryness to give the TBS protected derivative (36.4 g, 99%). The TBS protected derivative (36.5 g, 71.1 mmol) was dissolved in THF (150 mL). H_2O (100 mL), and then AcOH (300 mL) were added. The solution was stirred at 80°C for 13 h. The reaction was cooled to RT, and then concentrated to dryness under reduced pressure to give **49-2** (31.2 g, 61%) as a white solid.

[0423] To a solution of **49-2** (31.2 g, 78.2 mmol) in anhydrous pyridine (300 mL) was added Ac_2O (11.9 g, 117.3 mmol). The mixture was stirred at 25°C for 18 h. MMTrCl (72.3 g, 234.6 mmol) and $AgNO_3$ (39.9 g, 234.6 mmol) were added, and the solution was stirred at 25°C for 15 h. H_2O was added to quench the reaction and the solution was concentrated to dryness under reduced pressure. The residue was dissolved in EtOAc and washed with water. The organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated in vacuum to give a residue, which was purified by silica gel (DCM:MeOH = 200:1 to 50:1) to give the MMTr protected amine derivative (35.2 g, 63%). The MMTr protected amine derivative (35.2 g, 49.3 mmol) was dissolved in NH_3/MeOH (300 mL). The

mixture was stirred at 25°C for 20 h. The solution was evaporated to dryness, and purified by a silica gel column (DCM: MeOH = 100:1 to 50:1) to give **49-3** as a yellow solid (28.6 g, 87%).

[0424] To a solution of **49-3** (12.0 g, 17.9 mmol) in anhydrous DCM (200 mL) was added Dess-Martin periodinane (11.3 g, 26.8 mmol) at 0°C. The mixture was stirred at 0°C for 2 h, and then at RT for 2 h. The mixture was quenched with a saturated $NaHCO_3$ and $Na_2S_2O_3$ solution. The organic layer was washed with brine (2X) and dried over anhydrous Na_2SO_4. The solvent was evaporated to give the aldehyde (12.6 g), which was used directly in the next step. To a solution of the aldehyde (12.6 g, 18.0 mmol) in 1,4-dioxane (120 mL) was added 37% HCHO (11.6 g, 144 mmol) and 2N NaOH aqueous solution (13.5 mL, 27 mmol). The mixture was stirred at 25°C overnight. EtOH (60 mL) and $NaBH_4$ (10.9 g, 288 mmol) were added, and the reaction was stirred for 30 mins. The mixture was quenched with saturated aqueous NH_4Cl, and then extracted with EA. The organic layer was dried over Na_2SO_4, and purified by silica gel column chromatography (DCM: MeOH = 200:1 to 50:1) to give **49-4** (7.5g, 59%) as a yellow solid.

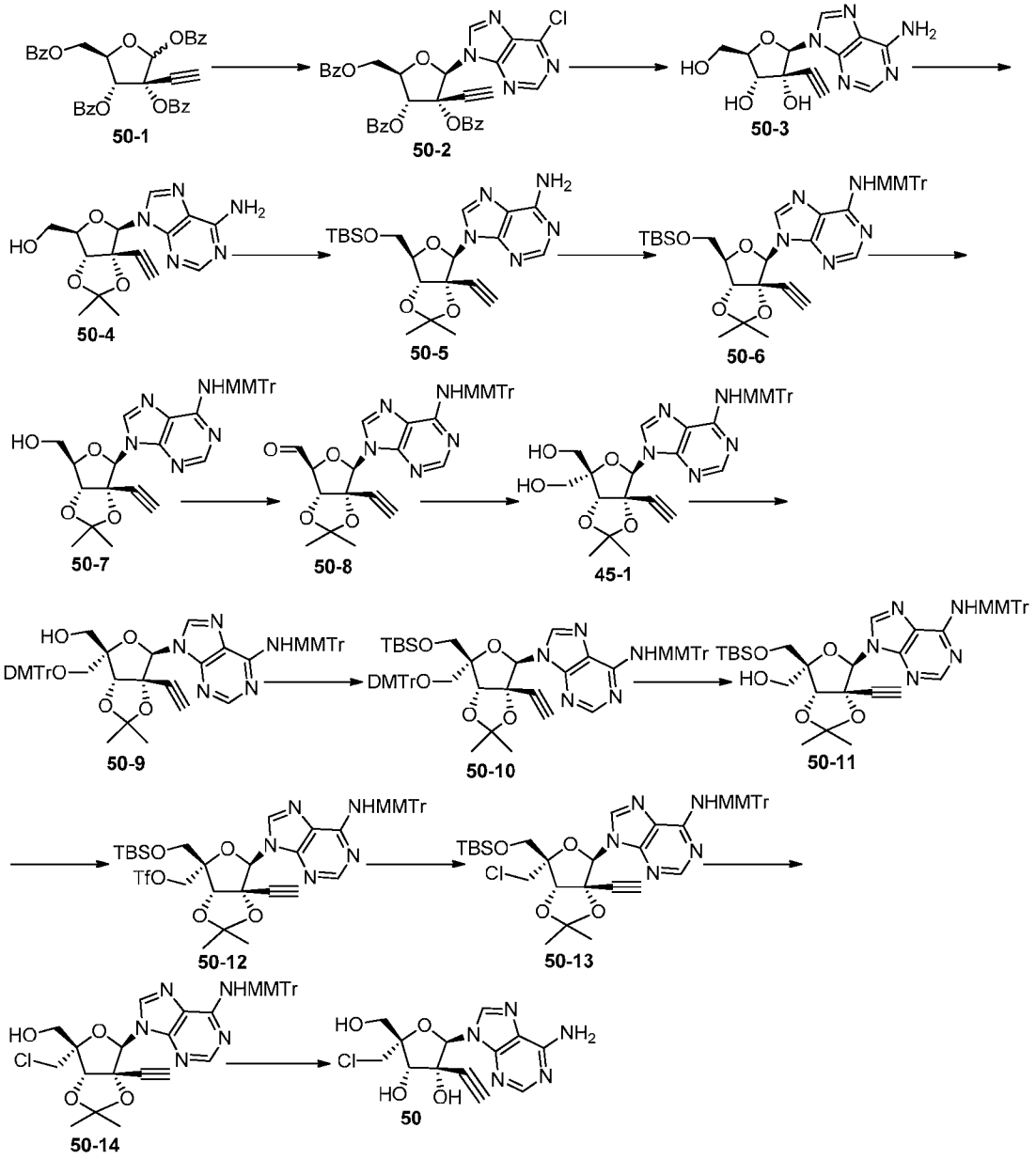
[0425] To a solution of **49-4** (3.8 g, 5.4 mmol) in DCM (40 mL) was added pyridine (10 mL) and DMTrCl (1.8 g, 5.4 mmol) at 0°C. The solution was stirred at 25°C for 1 h. MeOH (15 mL) was added, and the solution was concentrated. The residue was purified by silica gel column chromatography (DCM: MeOH = 200:1 to 50:1) to give the MMTr protected derivative (3.6 g, 66%) as a yellow solid. To a solution of the MMTr protected derivative (3.6 g, 3.6 mmol) in anhydrous pyridine (30 mL) was added TBDPSCl (2.96 g, 10.8 mmol) and $AgNO_3$ (1.84 g, 10.8 mmol). The mixture was stirred at 25°C for 15 h. The mixture was filtered and concentrated. The mixture was dissolved in EtOAc and washed with brine. The organic layer was dried over Na_2SO_4, and then purified by silica gel column chromatography (DCM: MeOH = 200:1 to 50:1) to give the TBDPS protected derivative (3.8 g, 85.1%) as a solid. To a solution of the TBDPS protected derivative (3.6 g, 2.9 mmol) in anhydrous DCM (50 mL) was added $Cl_2CHCOOH$ (1.8 mL) in anhydrous DCM (18 mL). The mixture was stirred at -78°C for 1 h. $Cl_2CHCOOH$ (3.6 mL) was added at -78°C. The mixture was stirred at -10°C for 30 mins. The mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with DCM. The organic layer was dried over

Na_2SO_4, and then purified by silica gel column chromatography (DCM: MeOH = 200:1 to 50:1) to give **49-5** (2.2 g, 80%).

[0426] To an ice cooled solution of **49-5** (800 mg, 0.85 mmol) in anhydrous DCM (20 mL) was added pyridine (336 mg, 4.25 mmol) and Tf_2O (360 mg, 1.28 mmol) dropwise. The reaction mixture was stirred at 0°C for 15 mins. The reaction was quenched by ice water and stirred for 30 mins. The mixture was extracted with EtOAc, washed with brine (50 mL) and dried over $MgSO_4$. The solvent was evaporated to give the crude bis(triflate) derivative. To the bis(triflate) derivative (790 mg, 0.73 mmol) in anhydrous DMF (35 mL) was added LiCl (302 mg, 7.19 mmol). The mixture was heated to 40°C and stirred overnight. Completion of the reaction was determined by LCMS. The solution was washed with brine and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, and the residue was purified on a silica gel column (DCM/MeOH = 100:1) to give **49-6** (430 mg, 61%).

[0427] To **49-6** (470 mg, 0.49 mmol) in MeOH (85 mL) was added NH_4F (8.1 g, 5.92 mmol), and the solution was heated to reflux overnight. The mixture was filtered, and the filtrate was concentrated to dryness. The residue was purified on a silica gel column (DCM/MeOH = 20:1) to give the diol (250 mg, 84%) as a white solid. The diol (130 mg, 0.21 mmol) in formic acid (5 mL) was stirred at 25°C overnight. The solution was concentration to dryness, and the residue in MeOH (30 mL) was stirred at 70°C overnight. Completion of the reaction was determined by LCMS and HPLC. The solvent was removed, and the crude product was washed with EtOAc to give compound **49** (58 mg, 81%) as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.73 (br, 1H), 7.98 (s, 1H), 6.58 (br, 2H), 6.08 (q, J = 4.8, 9.2 Hz, 2H), 5.64 (dt, J = 5.6, 52.8 Hz, 1H), 5.40 (m, 1H), 4.52 (m, 1H), 3.80-3.82 (m, 2H), 3.64 (q, 2H). ESI-MS: m/z 333.8 $[M+H]^+$, 666.6 $[2M+H]^+$.

EXAMPLE 40
COMPOUND 50



[0428] Compound **50-1** (5.0g, 8.5 mmol) and 6-chloropurine (3.0 g, 17.7mmol) were co-evaporated with anhydrous toluene 3 times. To a stirred suspension of **50-1** and 6-chloropurine in anhydrous MeCN (50 mL) was added DBU (7.5 g, 49 mmol) at 0 °C. The mixture was stirred at 0 °C for 15 mins, and TMSOTf (15 g, 67.6 mmol) was added dropwise at 0 °C. The mixture was stirred at 0 °C for 15 mins until a clear solution formed. The mixture was heated to 70 °C, and stirred overnight. The reaction was monitored by LCMS.

The mixture was cooled to RT, and diluted with EA (100 mL). The solution was washed with sat. $NaHCO_3$ solution and brine. The organic layer was dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified on silica gel column (EA in PE from 6% to 50%) to afford **50-2** (2.5 g, 46.3%) as a white foam.

[0429] Compound **50-2** (3.0 g, 4.8 mmol) was treated with NH_3 in MeOH (8 N, 20 mL) in autoclave at 40-60 °C for 12 h. The mixture was evaporated at low pressure, and the residue was purified on silica gel column (MeOH in EA from 0 to 10%) to give **50-3** (1.0 g, 71%) as a white foam.

[0430] To a solution of **50-3** (4.3 g, 14.8 mmol) in acetone/DMF (4/1, 40 mL) was added $TsOH•H_2O$ (8.4 g, 0.044 mol) and 2,2-dimethoxypropane (30 g, 0.296 mol), and the mixture stirred at 60-70 °C for 12 h. The mixture was concentrated at low pressure, and the residue was purified on silica gel column (EA in PE from 50% to 100%) to give **50-4** (5.0 g, 83%).

[0431] To a solution of **50-4** (10.5 g, 31.7 mmol) in pyridine (50 mL) was added TBSCl (5.3 g, 34.9 mmol), and the mixture stirred at RT for 12 h. The solvent was removed at low pressure, and the residue was dissolved in DCM (100 mL). The solution was washed with brine, dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by silica gel column to provide **50-5** (8.4 g, 60%), which used without further purification.

[0432] Compound **50-5** (8.4 g, 18.8 mmol) was co-evaporated with pyridine. To a stirred solution of **50-5** (8.4 g, 18.8 mmol) in pyridine (35 mL) was added MMTrCl (8.1 g, 26.4 mmol). The mixture was stirred at 30-40 °C for 12 h under N_2. The mixture was concentrated at a low pressure, and the residue was dissolved in DCM (150 mL). The solution was washed with saturated $NaHCO_3$ solution, dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified on silica gel column (EA in PE from 10% to 20%) to provide **50-6** (10.8 g, 80%) as a solid

[0433] To a solution of **50-6** (11.5 g, 0.016 mol) in THF (100 mL) was added TBAF (4.62 g, 0.018 mol) at RT, and the mixture stirred for 4 h. The solvent was evaporated at low pressure, and the mixture was dissolved in DCM (150 mL). The solution was washed with brine, dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was

purified on silica gel column (EA in PE from 50% to 100%) to afford **50-7** (8.8 g, 91%). ESI-MS: m/z 604.4 $[M+H]^+$.

[0434] To a solution of **50-7** (4.4 g, 7.3 mmol) in dioxane (50 mL) was added DCC (4.5 g, 21.9 mmol), DMSO (2.5 mL), TFA•Py (1.48 g, 7.65 mmol) at 0 °C. The mixture was slowly warm to RT and stirred for 4 h. Completion of the reaction was determined by LCMS. The mixture was concentrated at low pressure. The residue was purified on silica gel column to give **50-8** (4.4 g, 7.3 mmol), which was used without further purification.

[0435] To a solution of **50-8** in dioxane (40 mL) was added water (20 mL), HCHO (37 %, 7 mL) and NaOH (1N, 15 mL). The solution was stirred at RT overnight. The mixture was treated with $NaBH_4$ (1.1 g, 29.2 mmol) slowly, and stirred for 30 mins. The mixture was adjusted to pH = 7-8 by slow addition of HCl (1M) solution, and extracted with EA (150 mL). The solution was washed with brine, dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified on silica gel column to give **45-1** (3.0 g, 65%). ESI-MS: m/z 633.9 $[M+H]^+$.

[0436] To a solution of **45-1** (1.5 g, 2.37 mmol) in anhydrous pyridine (30 mL) was added DMTrCl (3.6 g, 10.7 mmol) at -30 °C. The mixture was stirred at RT overnight. The solution was quenched with MeOH, and concentrated at low pressure. The residue was purified by column chromatography to give **50-9** (3 g, 45%) as a yellow solid

[0437] To a solution of **50-9** (1.1 g, 1.18 mmol) in pyridine (10 mL) was added imidazole (0.24 g, 3.53 mmol) and TBSCl (0.35 g, 2.35 mmol). The mixture was stirred at RT for 12 h. The solvent was evaporated at low pressure, and the residue was dissolved in EA (50 mL). The solution was washed with brine, dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified on silica gel column (30% EA in PE) to afford **50-10** (0.83 g, 67%)

[0438] To a solution of **50-10** (1.1 g, 1.05 mmol) in DCM (12 mL) was added $Cl_2CHCOOH$ (0.5 mL) at -70 °C, and stirred for 1 h. The solution was treated with $Cl_2CHCOOH$ (1 mL) in DCM (10 mL) at -70 °C, and the mixture was stirred at -70~-10 °C for 20 mins. Completion of the reaction was determined by LCMS. The reaction was quenched with sat. $NaHCO_3$ solution, and extracted with DCM (3 x 40 mL). The organic

phase was dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified on silica gel column (EA in PE from 15% to 30%) to afford **50-11** (0.58 g, 74%).

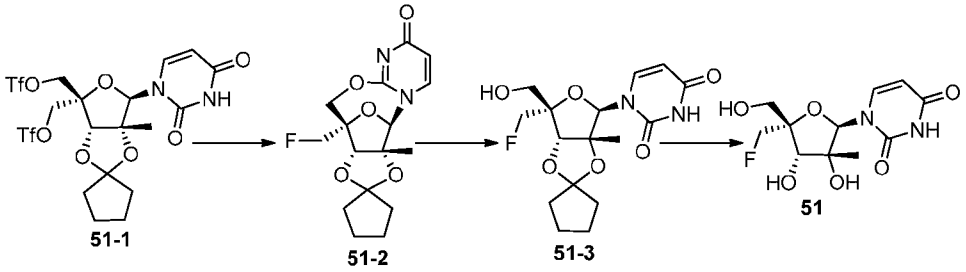
[0439] To a solution of **50-11** (200 mg, 0.268 mmol) and pyridine (53 mg, 0.67 mmol) in anhydrous DCM (5 mL) was added Tf_2O (90 mg, 0.32 mmol) at -30 °C. The mixture was stirred for 1 h, and slowly warmed to RT. Completion of the reaction was determined by TLC. The reaction was quenched with sat. $NaHCO_3$ solution, and extracted with DCM (3 x 30 mL). The organic phase was dried over anhydrous Na_2SO_4, and concentrated to dryness at low pressure. Crude **50-12** (200 mg, 0.27 mmol) was used without further purification.

[0440] To a solution of **50-12** (200 mg, 0.27 mmol) in DMF (5 mL) was added LiCl (45 mg, 1.07 mmol), and stirred at 30-40 °C for 12 h. The solvent was evaporated at low pressure, and the residue was dissolved in DCM (10 mL). The solution was washed with brine, dried over anhydrous Na_2SO_4, and concentrated at low pressure. Crude **50-13** was used without further purification.

[0441] A mixture of **50-13** (245 mg, 0.32 mmol) and TBAF (200 mg, 0.7 mmol) in THF was stirred at 30 °C for 1 h. The mixture was concentrated at a low pressure, and the residue was dissolved in DCM (15 mL). The solution was washed with brine, dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified on silica gel column (EA in PE from 2% to 50%) to provide **50-14** (150 mg, 72%). ESI-MS: m/z 652.3 $[M+H]^+$.

[0442] Compound **50-14** (0.2 mmol) was dissolved in 50% TFA (10 mL) in methanol, and the mixture was kept at RT overnight. The solvent was evaporated and co-evaporated with methanol/toluene mixture to remove traces of acid. The residue was dissolved in 20% triethylamine in methanol, kept for 15 mins and evaporated. The product was isolated by RP HPLC on Synergy 4 micron Hydro-RP column (Phenominex). A linear gradient of methanol from 0 to 60% in 50 mM triethylammonium acetate buffer (pH 7.5) was used for elution. The corresponding fractions were combined, concentrated and lyophilized 3 times to remove excess buffer. Compound **50** was obtained (45 mg, 67%). MS: m/z 338.0 [M-1].

EXAMPLE 41
COMPOUND 51

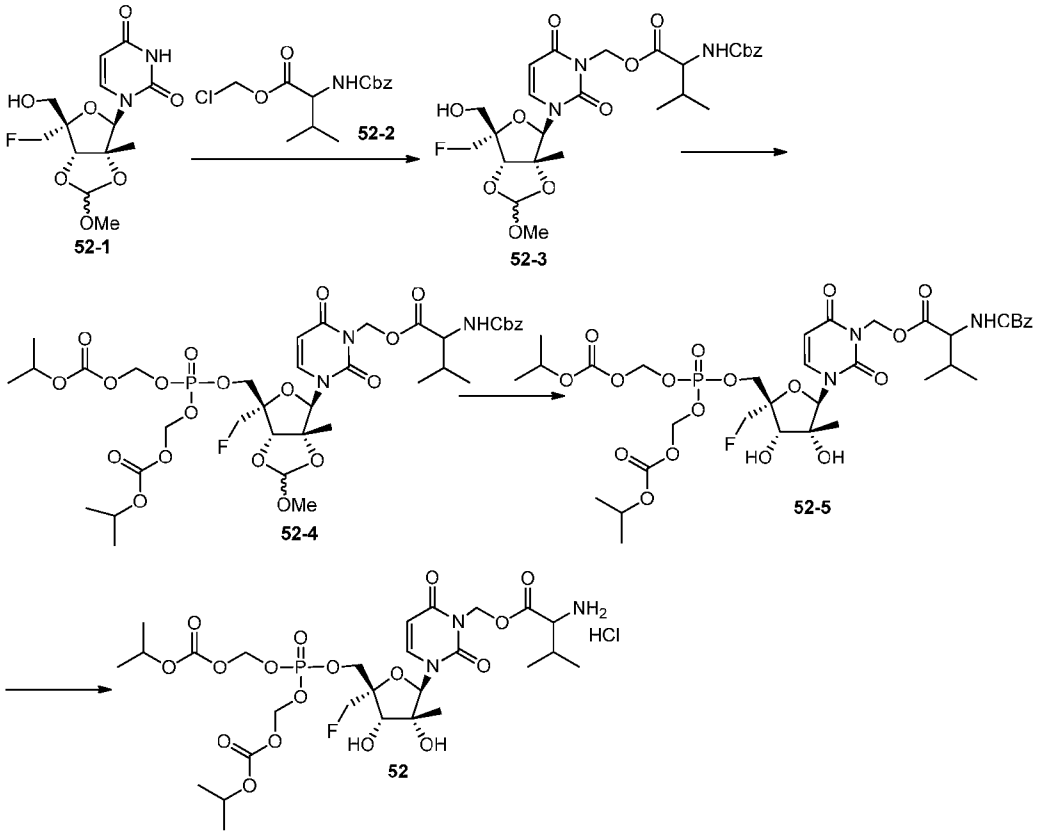


[0443] To a solution of **51-1** (12.3 g, 19.9 mmol) in DMF (50 mL) was added NaH (800 mg, 20 mmol) at 0 °C. The mixture was stirred at RT for 3 h. The mixture was treated with CsF (30.4 g, 200 mmol), and then stirred at RT for 3 h. The reaction was quenched with water, and extracted with EA. The organic layer was dried over anhydrous Na_2SO_4, and concentrated to dryness at low pressure. The residue was purified on silica gel column (20% EA in PE) to give **51-2** (4.1 g, 61%) as a white solid.

[0444] To a solution of **51-2** (4.1 g, 12.1 mmol) in THF (120 mL) was added NaOH solution (1N, 13 mL) at 0 °C. The mixture was stirred at RT for 3 h. The solution was neutralized with 0.5 M HCl aq. to pH ~7. The mixture was partitioned between EA and water. The organic layer was dried over anhydrous Na_2SO_4, and concentrated to dryness at low pressure. The residue was purified on silica gel column (30% EA in PE) to give **51-3** (3.1 g, 72%) as a white solid. ESI-MS:m/z 379.1 $[M+Na]^+$.

[0445] Compound **51-3** (0.2 mmol) was dissolved in 80% HCOOH (10 mL), and the mixture was heated at 45 °C for 24 h. The solvent was evaporated and co-evaporated with methanol/toluene mixture to remove traces of acid. The residue was dissolved in 20% triethylamine in methanol, kept for 15 mins and evaporated. Compound **51** (68%) was isolated by silica gel chromatography in gradient of methanol in DCM from 5% to 20%. MS: m/z 289.0 [M-1].

EXAMPLE 42
COMPOUND 52



[0446] A mixture of **52-2** (1.2 g; 4 mmol) and NaI (0.6 g; 4 mmol) in acetone (13 mL) was stirred at RT for 1 h. Compound **52-1** (1 g; 3 mmol) and K_2CO_3 (2.07 g; 45 mmol) were added. The mixture was stirred at RT for 24 h. The precipitate was filtered, and the filtrate was evaporated. Purification of the residue on silica (25 g column) with hexanes/EtOAc (30-100% gradient) yielded **52-3** as a colorless foam (1.14 g; 64%).

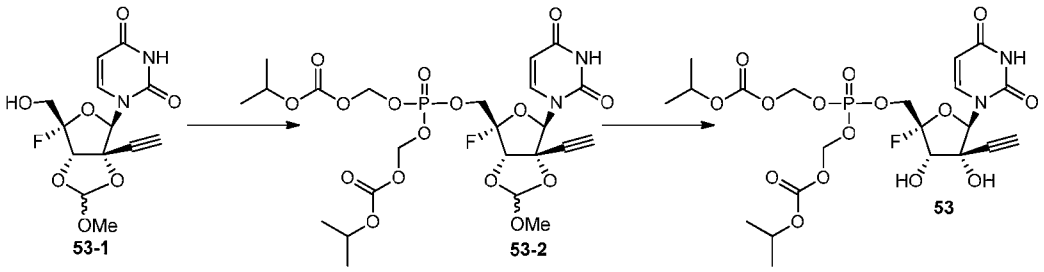
[0447] To a solution of triethylammonium bis(isopropyloxycarbonyloxymethyl)phosphate (2.3 mmol, prepared from of bis(POC)phosphate (0.75 g) and Et_3N (0.32 mL)) in THF was added **52-3** (1.14 g; 1.9 mmol). The mixture evaporated and rendered anhydrous by co-evaporating with pyridine follow by toluene. The residue was dissolved in anhydrous THF (20 mL) and cooled down in an ice-bath. Diisopropylethylamine (1.0 mL; 2 eq.) was added, followed by BOP-Cl (0.72 g; 1.5 eq.) and 3-nitro-1,2,4-triazole (0.32 g; 1.5 eq.). The n mixture was stirred at 0 °C for 90 mins, diluted with EtOAc, washed with sat. aq. $NaHCO_3$ and brine, and dried (Na_2SO_4). The

residue was purified on silica (25 g column) with CH_2Cl_2/i-PrOH (3-10% gradient) to yield (1.2 g, 70%) of **52-4**.

[0448] A solution of **52-4** (1.2 g; 1.3 mmol) in 80% aq. HCOOH was stirred at RT for 2 h, and then concentrated. The residue was co-evaporated with toluene and then with MeOH containing small amount of Et_3N (2 drops). Purification on silica (25 g column) with CH_2Cl_2/i-PrOH (4-10% gradient) yielded **52-5** (0.96 g, 85%).

[0449] To a solution of **52-5** (0.52 g; 0.57 mmol) in EtOH (25 mL) were added HCl (4 N/dioxane; 0.29 mL, 2 eq.) and 10% Pd/C (25 mg). The mixture was stirred under H_2 (normal pressure) for 1 h. The catalyst was removed by filtration through a Celite pad, and the filtrate was evaporated to yield compound **52** as its HCl salt (4.2 g; 96%). MS: m/z = 732 [M+1].

EXAMPLE 43
COMPOUND 53

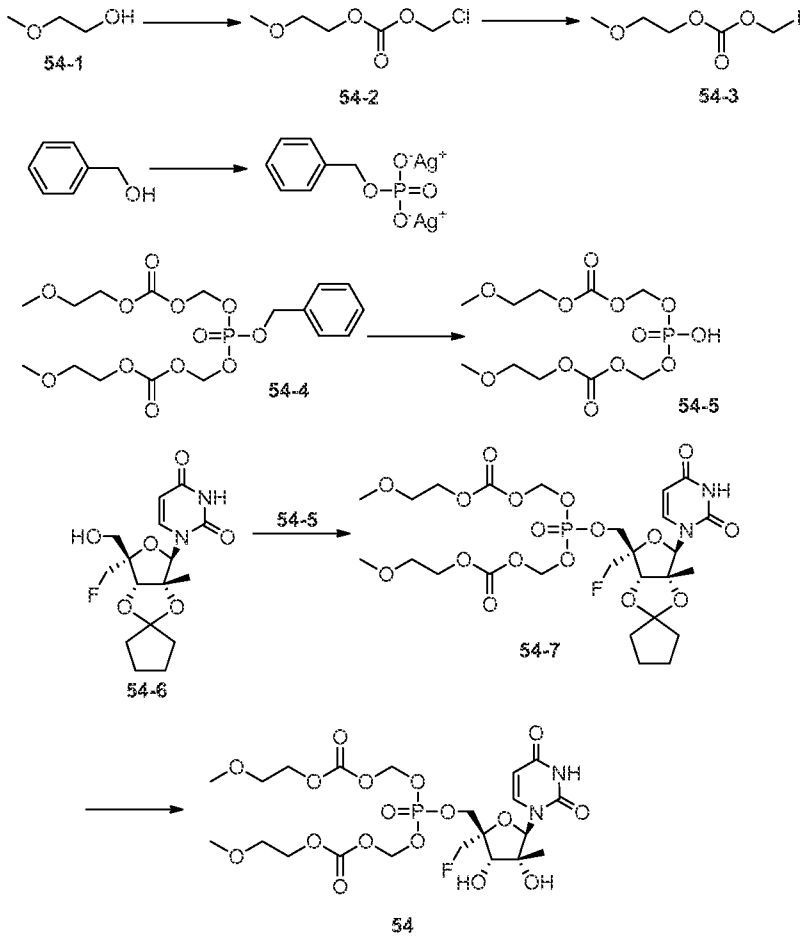


[0450] Compound **53-2** (0.20 g, 64%) was prepared in the same manner from **53-1** (0.16 g; 0.49 mmol) and triethylammonium bis(isopropyloxycarbonyloxymethyl)phosphate (0.74 mmol) with DIPEA (0.34 mL), BopCl (250 mg), and 3-nitro-1,2,4-triazole (112 mg) in THF (5 mL) following the procedure for the preparation of **52-4**.

[0451] A solution of **53-2** (0.20 g; 0.31 mmol) in 80% aq. HCOOH was stirred at RT for 2 h, and then concentrated. The residue was co-evaporated with toluene and then with MeOH containing small amount of Et_3N (2 drops). Purification on silica gel (10 g column) with CH_2Cl_2/MeOH (4-10% gradient) was followed by RP-HPLC purification in 5 runs on a Synergi Hydro RP column 250 x 30 mm (Phenomenex P/N 00G-4375-U0-AX) using H_2O and ACN both 50 mM TEAA. Gradient was 25-75% ACN in 20 mins at 24mL/mins, 254nM detection. The product eluted at 16.0 mins. Pure fractions were pooled and lyophilized. TEAA was removed by dissolving the product in DMSO (2 mL) and

injecting the product on the same column using only H_2O and ACN. Pure fractions were pooled and lyophilized to produce compound **53** (18 mg). MS: m/z = 1197 (2M+1).

EXAMPLE 44
COMPOUND 54



[0452] Chloromethyl chloroformate (112 mmol; 10.0 mL) was added to an ice cooled solution of 2-methoxyethanol (97 mmol; 7.7 mL) in dichloromethane (DMC) (100 mL) followed by pyridine (9.96 mL) at 0°C. After stirring overnight at RT, the mixture was washed twice with 0.5 M HCl, followed by water and aqueous sodium bicarbonate. The mixture was dried over magnesium sulfate, filtered, evaporated in vacuo and distillation in vacuo to afford **54-2** as a colorless oil (13.0 g).

[0453] Compound **54-2** (5.7 g) was added to a solution of sodium iodide (21.07 g) in acetone (45 mL). After 20 stirring at 40 °C for 2.5 h, the mixture was cooled in ice, filtered and evaporated in vacuo. The residue was taken up in dichloromethane, washed with aqueous sodium bicarbonate and sodium thiosulfate, dried over magnesium sulfate, filtered

and evaporated in vacuo to give **54-3** as a light yellow oil of **54-3** (8.5 g), which was used without further purification.

[0454] A mixture of phosphoric acid (crystal, 2.4 g) and triethylamine (6.6 mL) in benzyl alcohol (13 g; 12.5 mL) was stirred at RT until the phosphoric acid was completely dissolved. Trichloroacetonitrile (17 .2 g; 11.94 mL) was added, and the mixture was stirred at RT for 18 h. The solvent and excess trichloroacetonitrile were removed under reduced pressure. The residue was dissolved in water (about 200 mL), and the aqueous solution washed with ether (3 x 50 mL). Benzylphosphoric acid (triethylamine salt) was obtained after lyophilization as a yellowish semi-solid (7.15 g). A solution of benzylphosphoric acid (TEA salt, 1.6 g) in MeOH (90 mL) and water (30 mL) was treated with Dowex 50WX2-400 ("153 mL" settled resin) at RT for 18 h. The resin was removed by filtration, and silver carbonate powder (1.25 g) was added to the filtrate. After the suspension was heated at 80°C for 1 h, all solvent was removed under reduced pressure to dryness. The solid was used without further purification.

[0455] Dry acetonitrile (25 mL) was added to benzylphosphoric acid (silver salt) followed by addition of **54-3** (3.12 g; 12 mmol). The suspension was stirred at RT overnight. After the solid was removed by filtration, the product was purified by silica gel chromatography using hexane/ethyl acetate (3:1 v:v) as the eluent to give **54-4** as a colorless liquid (860 mg, 50%).

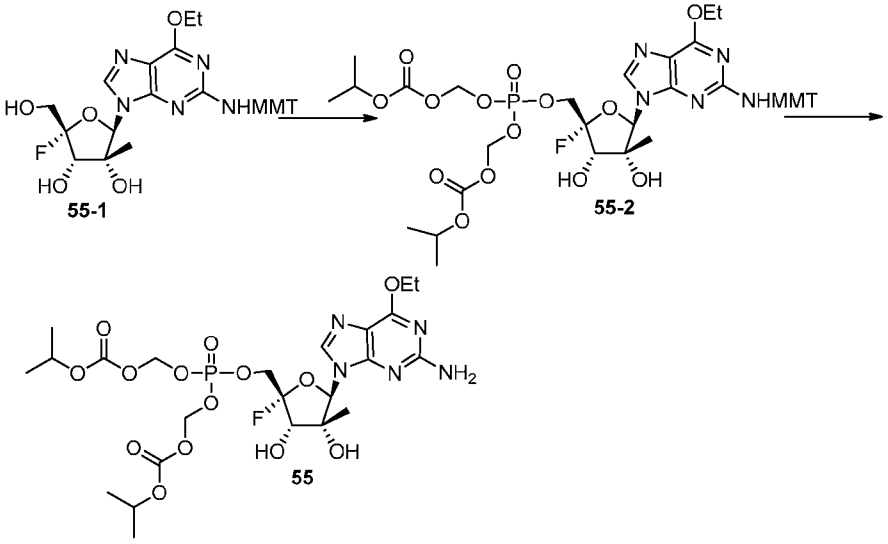
[0456] Compound **54-4** (750 mg; 1.65 mmol) was dissolved in methanol (10 mL). Pd-on-carbon (85 mg) and TEA (1 eq.) were added. The flask was charged with hydrogen gas for 1 h. The catalyst was filtered, and the solvent removed in vacuo to give **54-5** (triethylammonium salt) (510 mg) which was used immediately without further purification.

[0457] Compound **54-6** (320 mg; 0.9 mmol) and **54-5** (510 mg, 1.35 mmol; 1.5x) were co-evaporated twice with pyridine and twice with toluene. Compounds **54-5** and **54-6** were dissolved in THF (8 mL) at 0°C. Diisopropylethylamine (DIPEA) (0.62 mL; 4 eq.), bis(2-oxo-3-oxazolidinyl) phosphinic chloride (Bop-Cl) (0.45 g; 2 eq.), nitrotriazole (0.2 g, 2 eq.) were added. The mixture was kept at 0 °C for 2 h and then diluted with EA (50 mL). The mixture was then extracted with sat. sodium bicarbonate (2 x 50 mL) and dried over sodium sulfate. The solvents were removed in vacuo. The residue was purified by flash

chromatography using a 10 to 100% gradient of EA in hexane to give purified **54-7** (430 mg, 0.6 mmol).

[0458] Purified **54-7** was dissolved in 80% aq. HCOOH (20 mL) and kept at 45°C for 18 h. After cooling to RT, the solvent was removed in vacuo. The residue co-evaporated with toluene (3 x 25 mL). The residue was purified by flash chromatography using a 0 to 20% gradient of methanol in DCM to give purified compound **54** (200 mg , 0.3 mmol). ^{1}H-NMR ($CDCl_3$): δ 9.28 (s, 1H), 7.54 (d, 1H), 5.95 (s, 1H), 5.65-5.81 (m, 5H), (d, 2H), 4.76 (dd, 2H), 4.44-4.46 (m, 1H), 4.35-4.40 (m, 5H), 4.22 (2H), 4.04 (1H), 3.65 (t, 4H), 3.39 (6H), 1.8 (s, 1H), 1.24 (s, 3H). ^{31}P-NMR ($CDCl_3$): δ - 4.09 ppm.

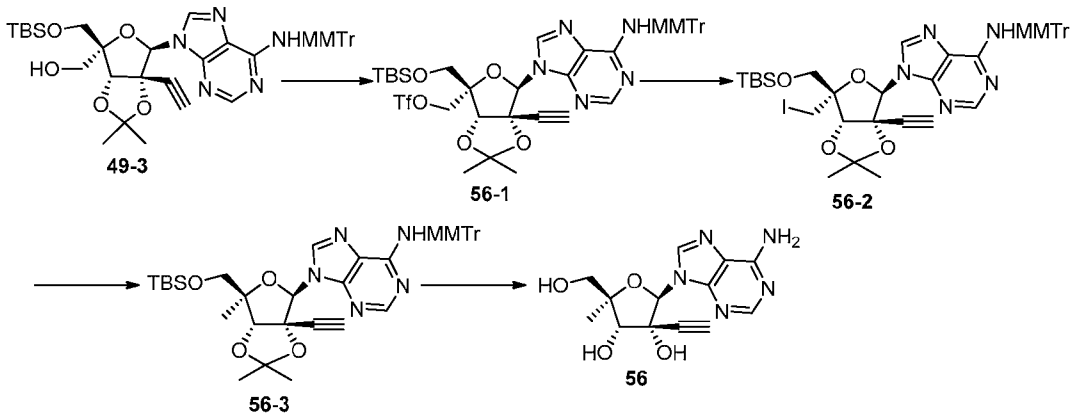
EXAMPLE 45
COMPOUND 55



[0459] Compound **55-2** (158 mg, 50%) was prepared from **55-1** (0.21 g; 0.35 mmol) and triethylammonium bis(isopropyloxycarbonyloxymethyl)phosphate (0.54 mmol) with DIPEA (0.18 mL), BopCl (178 mg), and 3-nitro-1,2,4-triazole (80 mg) in THF (4 mL).

[0460] A solution of **55-2** (158 mg) in acetonitrile (1 mL) and HCl (4 N/dioxane; 85 µL) was stirred at RT for 30 mins. The reaction was quenched with MeOH and concentrated. The residue was purified on silica gel (10 g column) with CH_2Cl_2/i-PrOH (3-10% gradient) to give compound **55** (85 mg, 76%). MS: m/z = 656 [M+1].

EXAMPLE 46
COMPOUND 56



[0461] To a solution of **49-3** (300 mg, 0.4 mmol) and pyridine (80 mg, 1.0 mmol) in DCM (5 mL) was added Tf_2O (136 mg, 0.48 mol) in a solution of DCM (1mL) dropwise at -30 °C. The mixture was stirred at -30 °C to 0 °C for 20 mins. The reaction was quenched with water, and extracted with DCM (20 mL). The organic phase was dried over anhydrous Na_2SO_4, and evaporated to give crude **56-1** (352.8 mg, 0.4 mmol), which was used without further purification.

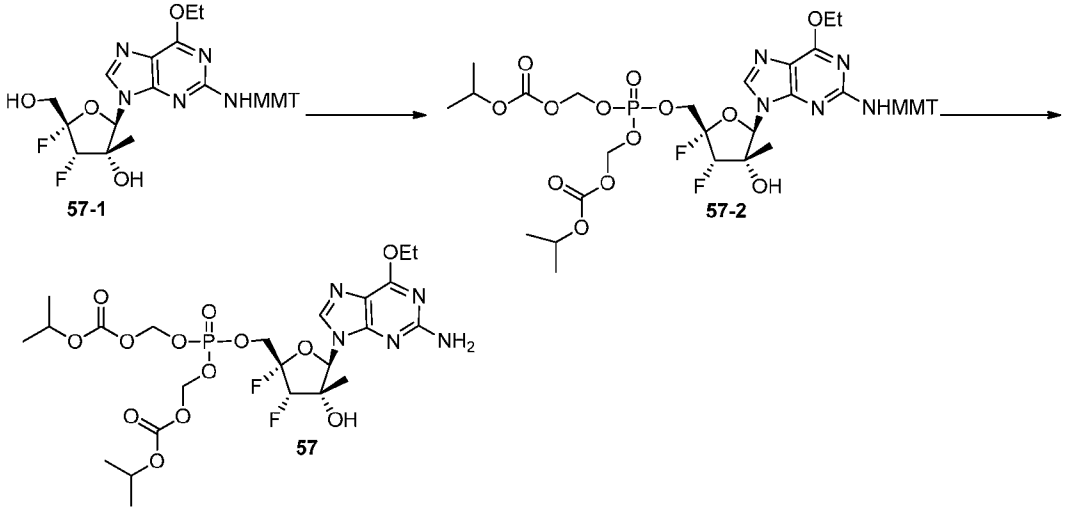
[0462] To a solution of **56-1** (352.8 mg, 0.4 mmol) in DMF (5 mL) was added NaI (480 mg, 3.2 mmol). The mixture was stirred at 30 °C for 10 h. The reaction was quenched with water, and extracted with DCM (20 mL). The organic phase was dried over anhydrous Na_2SO_4, and concentrated to dryness at low pressure. The residue was purified by prep-TLC (30% EA in PE) to give **56-2** (270 mg, 31%).

[0463] To a solution of **56-2** (600 mg, 0.7 mmol) in anhydrous toluene (30 mL) was added AIBN (34 mg, 0.21 mmol) and Bu_3SnH (307.7 mg, 1.05 mmol) in toluene (10 mL). The mixture was bubbled with N_2 for 30 mins, and heated to 135 °C for 2 h. The mixture was treated with sat. aq. CsF, and then stirred for 2 h. The mixture was diluted with EA (100 mL). The organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified on a silica gel column (10% EA in PE) to give **56-3** and a by-product (400 mg, 72%).

[0464] A mixture of **56-3** (400 mg, 0.55 mmol) in 90 % TFA (10 mL) was stirred at 50 °C for 4 h. The reaction was monitored by LCMS. The mixture was treated with

MeOH (5 mL), and concentrated under reducing pressure. The residue was purified by prep-HPLC to give compound **56** (46 mg, 27%). ESI-MS: m/z 306.1 $[M+H]^+$.

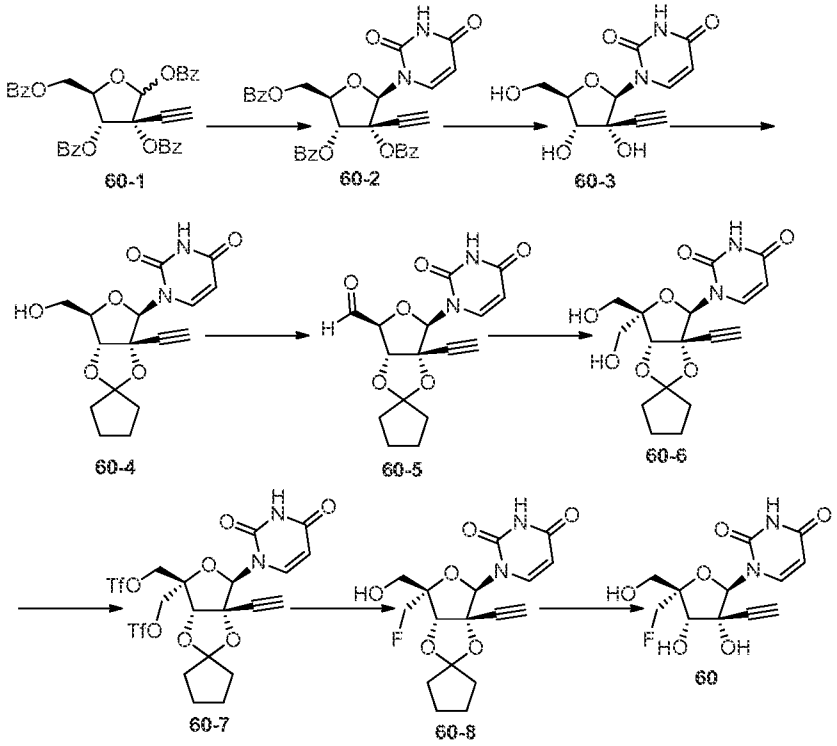
EXAMPLE 47
COMPOUND 57



[0465] Compound **57-2** (120 mg, 72%) was prepared in the same manner from **57-1** (0.11 g; 0.18 mmol) and triethylammonium bis(isopropyloxycarbonyloxymethyl)phosphate (0.35 mmol) with DIPEA (0.15 mL), BopCl (114 mg), and 3-nitro-1,2,4-triazole (51 mg) in THF (2.5 mL) using the method as described for **52-4** from **52-3**.

[0466] Compound **57** (14 mg, 77%) was prepared from **57-2** (25 mg) in acetonitrile (0.1 mL) and 4 N HCl/dioxane (8 μL) using the method as described for compound **55**. MS: m/z = 658 [M+1].

EXAMPLE 48
COMPOUND 60



[0467] To a stirred solution of uracil (21 g, 188 mmol) in anhydrous MeCN (200 mL) was added BSA (110 g, 541 mmol), and the mixture was refluxed for 2 h. The mixture was then cooled to RT and treated with **60-1**(55 g, 93.2 mmol) and TMSOTf (145 g, 653 mmol). The mixture was refluxed overnight. After the starting material disappeared, the reaction was quenched with sat. $NaHCO_3$ solution, and extracted with EA. The organic layer was dried over anhydrous Na_2SO_4, and concentrated to dryness at low pressure. The residue was purified on silica column gel (20% EA in PE) to give **60-2** (38 g, 70%) as a white sold.

[0468] Compound **60-2** (35 g, 0.06 mol) was treated with NH_3 in MeOH (7N, 200 mL) at RT. The mixture was stirred for 24 h at RT. Completion of the reaction was determined by LCMS. The mixture was concentrated at a low pressure, and the residue was washed with DCM to give **60-3** (13 g, 81%) as a white solid.

[0469] To a solution of cyclopentanone (6 g, 8.33 mmol), and trimethoxymethane (8 mL) in MeOH (60 mL) was added TsOH (1.35 g, 7.1 mmol) at RT, and the mixture was stirred 2 h. The resulting was quenched with NaOMe (0.385 g, 7.12 mmol), and extracted with n-hexane (30 mL). The organic layer was dried over anhydrous Na_2SO_4, and

concentrated at low pressure to give 1,1-dimethoxycyclopentane. To a solution of **60-3** (30 g, 0.11mol) and 1,1-dimethoxy cyclopentane (57 g, 0.44 mol) in 1,2-dichloroethane (200 mL) was added TsOH (2.1 g, 0.011 mol), and the mixture was heated to 60 °C overnight. The reaction was quenched with triethylamine, and concentrated to dryness at low pressure. The residue was washed with MeOH to give **60-4** (30 g, 82%).

[0470] To a solution of **60-4** (10 g, 30 mmol) in anhydrous CH_3CN (100 mL) was added IBX (8.4 g, 30 mmol, 1.05 eq.) at RT. The mixture was refluxed for 12 h., and then cooled to 0 °C. The precipitate was removed by filtration, and the filtrate was concentrated to give crude **60-5** (10 g, 100%) as a yellow solid.

[0471] Crude **60-5** (10 g, 30 mmol) was dissolved in 1,4-dioxane (100 mL). 37% HCHO (10 mL) and 2N NaOH aqueous solution (20 mL) were added at RT. The mixture was stirred at RT overnight, and adjusted to pH = 7. The mixture was treated with $NaBH_4$ (4.44 g, 120 mmol) at 0 °C. The reaction was stirred at RT for 30 mins and then quenched with sat. aq. NH_4Cl. The mixture was extracted with EA. The organic layer was dried over Na_2SO_4, and concentrated to dryness at low pressure. The residue was purified by silica gel column chromatography (1-3% MeOH in DCM) to give **60-6** (5.5 g, 50 %) as a white solid.

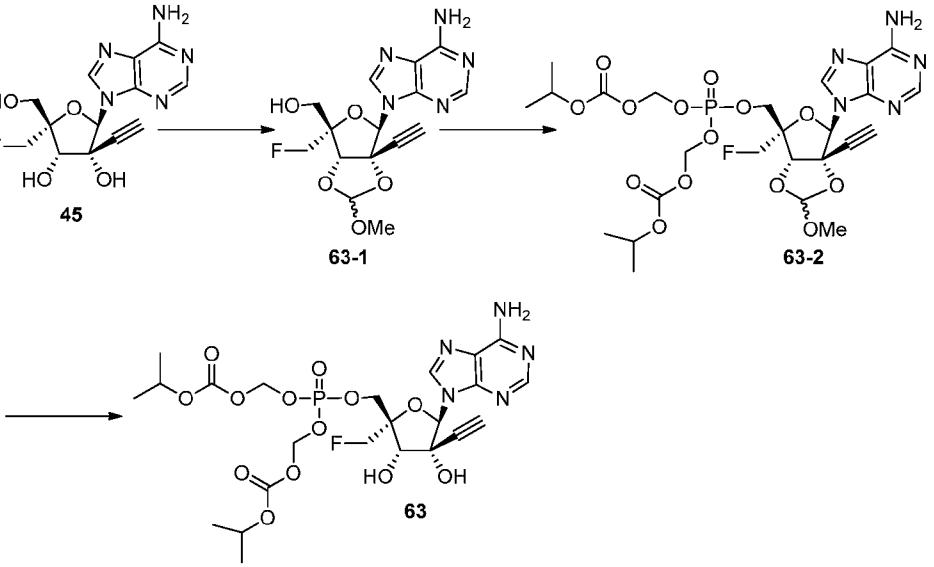
[0472] To a stirred solution of **60-6** (5.0 g, 13.8 mmol) and pyridine (5 mL) in DCM (20 mL) was added Tf_2O (8.5 g, 30.3 mmol) dropwise at -70 °C. The solution was warmed to 0 °C slowly, stirred at 0 °C for 0.5 h, and washed with HCl (0.5 M). The DCM layer was concentrated to dryness at low pressure, and the residue was purified on silica gel column to give **60-7** (4.5 g, 52 %) as a white solid.

[0473] To a solution of **60-7** (3.0 g, 4.8 mmol) in MeCN (10 mL) was added TBAF (5.0 g, 19.2 mmol). The reaction was allowed to proceed overnight. The reaction was monitored by HPLC and LCMS. Aqueous sodium hydroxide (1N ~2eq.) was added, and the solution was stirred for 1 h. The mixture was partitioned between sat. ammonium chloride solution and EA. The organic layer was separated, and concentrated under reduced pressure. The crude product was purified on silica gel column to give **60-8** (0.8 g, 46 %) as a white solid. ESI-MS: m/z 367.0 $[M+H]^+$, 389.0 $[M+Na]^+$.

[0474] Compound **60-8** (0.2 mmol) was dissolved in 80% HCOOH (10 mL), and the mixture was heated at 45°C for 24 h. The solvent was evaporated and co-evaporated with methanol/toluene mixture to remove traces of acid. The residue was dissolved in 20%

triethylamine in methanol, kept for 15 mins and evaporated. Compound **60** (65-68%) was isolated by silica gel chromatography in gradient of methanol in DCM from 5% to 20%. MS: m/z 321.0 [M-1].

EXAMPLE 49
COMPOUND 63

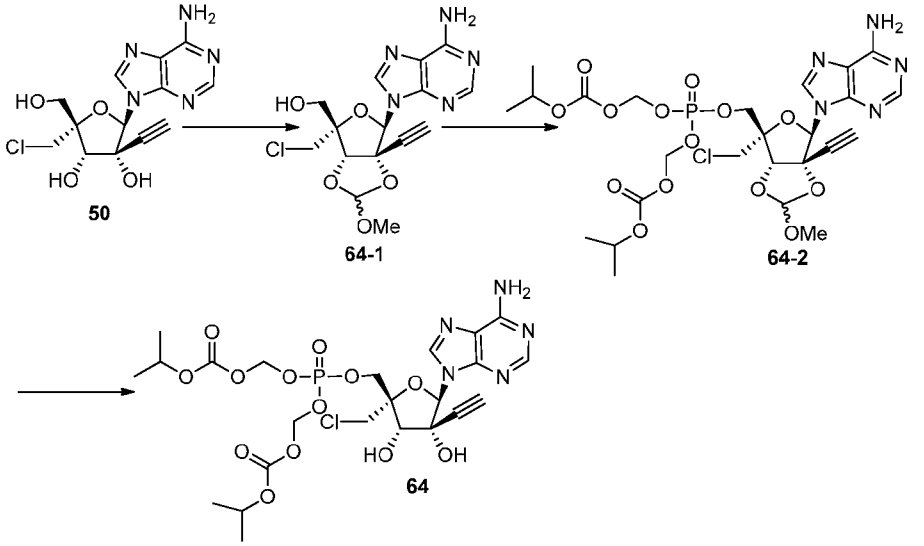


[0475] A mixture of compound **45** (30 mg, 0.09 mmol), PTSA monohydrate (18 mg, 1 eq.), and trimethyl orthoformate (0.3 mL; 30 eq.) in dioxane (1 mL) was stirred 1 d at RT. The reaction was neutralized with NH_3/MeOH and then filtered. The filtrate was dissolved in a mixture of THF (0.5 mL) and 80% aq. AcOH (0.25 mL). The solution kept for 1 h at RT, and then evaporated. The residue was purified on silica gel (10 g column) with CH_2Cl_2/MeOH (4-15% gradient) to yield **63-1** (30 mg, 91%).

[0476] Compound **63-2** (28 mg, 52%) was prepared in the same manner from **63-1** (30 mg, 0.08 mmol) and triethylammonium bis(isopropyloxycarbonyloxymethyl)phosphate (0.12 mmol) with DIPEA (56 µL), BopCl (40 mg), and 3-nitro-1,2,4-triazole (18 mg) in THF (1 mL) using the method for preparing **52-4** from **52-3**. Purification was done with CH_2Cl_2/MeOH (4-10% gradient).

[0477] Compound **63** (15 mg, 67%) was prepared from **63-2** (24 mg) using the method for preparing **52-5**. Purification was done with CH_2Cl_2/MeOH (4-10% gradient). MS: m/z = 636 [M+1].

EXAMPLE 50
COMPOUND 64

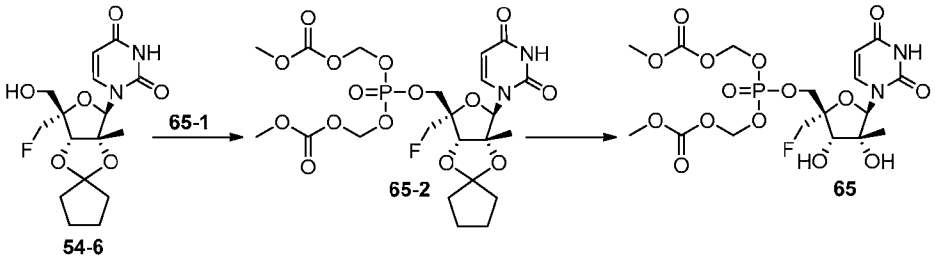


[0478] Compound **64-1** (8 mg, 40%) was prepared from compound **50** (17 mg) and trimethylorthoformate (0.15 mL) with PTSA monohydrate (9 mg) in dioxane (0.5 mL) in the same manner as **63-1.**

[0479] Compound **64-2** (10 mg, 72%) was prepared in the same manner from **64-1** (8 mg, 0.02 mmol) and triethylammonium bis(isopropyloxycarbonyloxymethyl)phosphate (0.036 mmol) with DIPEA (14 μL), BopCl (10 mg), and 3-nitro-1,2,4-triazole (5 mg) in THF (0.4 mL) in the same manner as **63-2**.

[0480] Compound **64** (15 mg, 67%) was prepared from **64-2** (24 mg) in the same manner as **63**. MS: m/z = 652 [M+1].

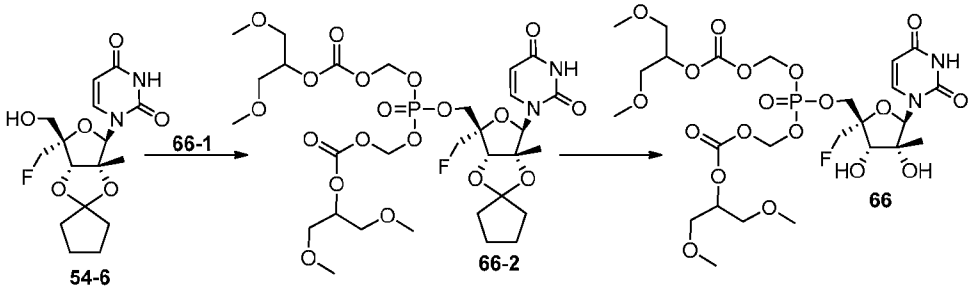
EXAMPLE 51
COMPOUND 65



[0481] Commercially available chloromethyl methyl carbonate (5.0 g) was treated with NaI to give **65a** (5.38 g). Benzylphosphate (silver salt) and **65a** were reacted to yield purified **65b** (1.5 g) as described for compound **54**. ^{1}H-NMR (CD_3CN): δ 7.39-7.42

(m, 5H), 5.60 (d, 4H), 5.11 (d, 2H), 3.8 (s, 6H). ^{31}P-NMR (CD_3CN): δ - 4.47 ppm. Compound **65b** (415 mg; 1.7 mmol) was deprotected to give **65-1** (triethylammonium salt) (510 mg), which was used immediately without further purification. Compound **54-6** (320 mg; 0.9 mmol) and **65-1** (510 mg) were reacted to purified **65-2** (400 mg). Compound **65-2** (230 mg) was deprotected to give purified compound **65** (250 mg). The aforementioned reactions were conducted using a method described in the preparation of compound **54**. ^{1}H-NMR ($CDCl_3$): δ 9.00 (s, 1H), 7.55 (d, 1H), 5.93 (s, 1H), 5.81 (d, 1H), 5.66-5.75 (m, 4H), 4.76 (dd, 2H), 4.37-4.46 (m, 2H), 4.15 (d, 2H), 3.86 (t, 6H), 3.70 (d, 6H), 1.65 (s, 6H), 1.25 (s, 3H). ^{31}P-NMR ($CDCl_3$): δ - 4.13 ppm.

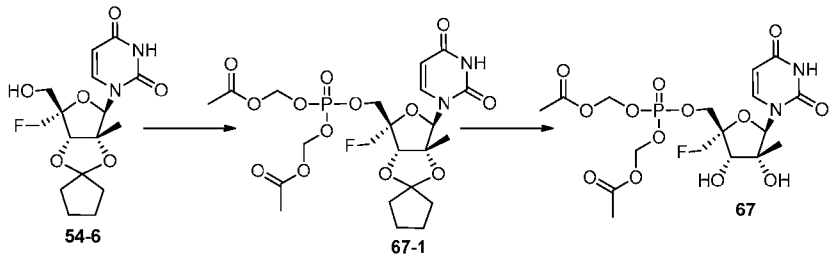
EXAMPLE 52
COMPOUND 66



[0482] Compound **66a** was prepared from 1,3-dimethoxypropan-2-ol. ^{1}H-NMR ($CDCl_3$) δ 5.73 (s,2H) , 5.03-5.06 (m,1H), 3.59 (d,4H), 3.38 (s,6H). Dry ACN (25 mL) was added to benzylphosphate (silver salt) (5 mmol) followed by addition of **66a** (3.12 g; 12 mmol). The suspension was heated at 60°C for 18 h. After the solid was removed by filtration, the product was purified by silica gel chromatography using hexane/EA (3: 1) as the eluent to provide **66b** as a colorless liquid (540 mg, 50%). ^{1}H-NMR (CD_3CN): δ 7.39-7.42 (m, 5H), 5.61 (d, 4H), 5.10 (d, 2H), 4.97-5.01 (m, 2H), 3.50-3.52 (m, 8H), 3.30 (s, 6H), 3.28 (s, 6H). ^{31}P-NMR (CD_3CN): δ - 4.42 ppm. Compound **66b** (540 mg; 1.0 mmol) was deprotected to give **66-1** (triethylammonium salt), which was used immediately without further purification. Compound **54-6** (285 mg; 0.8 mmol) and **66-1** were reacted to give purified **66-2** (300 mg). Compound **66-2** (300 mg) was deprotected to give purified compound **66** (290 mg). The aforementioned reactions were conducted using a method described in the preparation of compound **54**. ^{1}H-NMR ($CDCl_3$): δ 9.35 (s, 1H), 7.56 (d, 1H), 6.1 (s, 1H), 5.66-5.82 (m, 5H), 5.04 (s, 1H), 4.76 (dd, 2H), 4.60 (d, 1/2H), 4.37-4.48 (m,

2H), 4.22 (d, 2H), 4.06 (s, 1H), 3.58 (s, 8H), 3.57 (s, 12H), 1.93 (s, 1H), 1.23 (s, 3H). ^{31}P-NMR ($CDCl_3$): δ - 4.08 ppm.

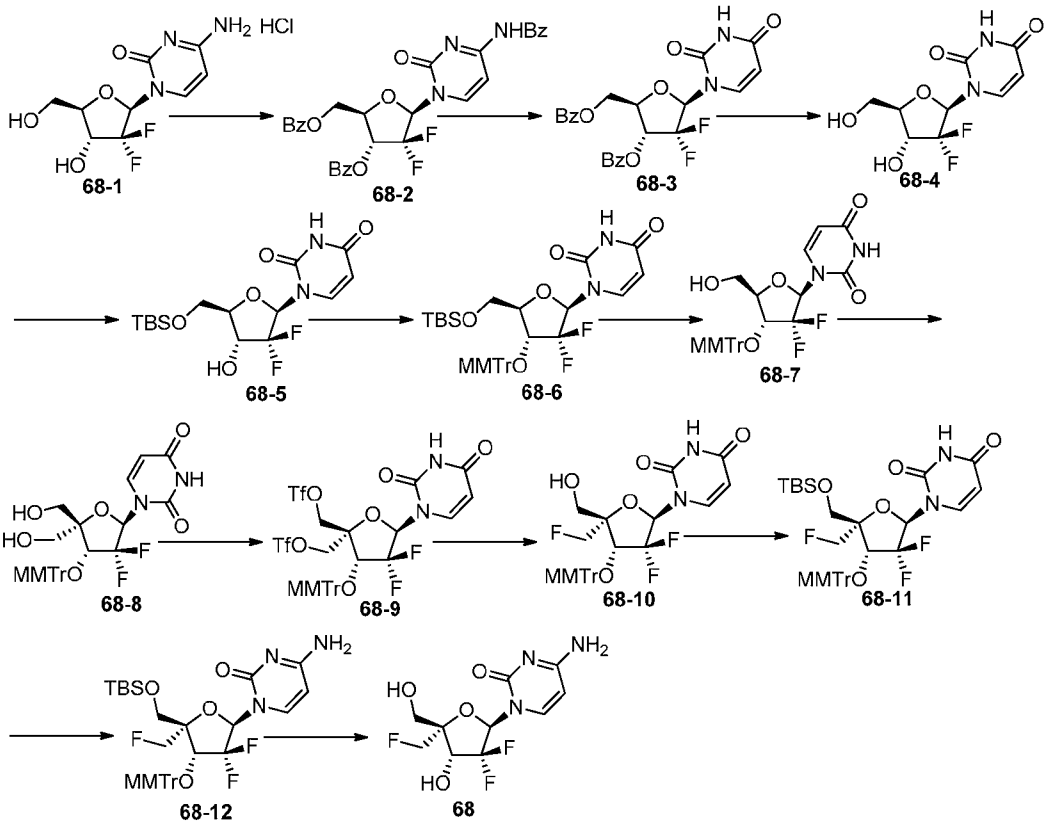
EXAMPLE 53
COMPOUND 67



[0483] Compound **67-1** (180 mg, 62%) was prepared in the same manner from **54-6** (0.18 g, 0.5 mmol) and triethylammonium bis(acetyloxymethyl)phosphate (1.0 mmol) with DIPEA (0.35 mL), BopCl (0.25 g), and 3-nitro-1,2,4-triazole (0.11 g) in THF (1 mL) using a method as described for compound **44**. Purification was done with CH_2Cl_2/i-PrOH (4-10% gradient).

[0484] Compound **67** (60 mg, 78%) was prepared from **67-1** (85 mg) using a method as described for compound **44**. MS: m/z = 1027 (2M-1).

EXAMPLE 54
COMPOUND 68



[0485] To a solution of **68-1** (15 g, 50.2 mmol) in anhydrous pyridine (180 mL) was added BzCl (23.3 g, 165.5 mmol) at 0 °C under nitrogen. The mixture was stirred overnight at RT. The mixture was diluted with EA and washed with $NaHCO_3$ aq. solution. The organic layer was dried with anhydrous Na_2SO_4, and concentrated to dryness. The organic layer was dried and concentrated to give a residue, which was purified by silica gel column chromatography (15 % EtOAc in PE) to give **68-2** (27 g, 93.5%) as a white solid.

[0486] Compound **68-2** (27g, 47 mmol) was dissolved in 90% HOAc (250 mL) and heated to 110 °C. The mixture was stirred overnight at 110 °C. The solvent was removed and diluted with EA. The mixture was washed with $NaHCO_3$ aq. solution and brine. The organic layer was dried and concentrated to give crude **68-3.**

[0487] Compound **68-3** was dissolved in NH_3/MeOH (600 mL) and stirred overnight. The solvent was concentrated to give the residue, which was purified by silica gel column chromatography (5% MeOH in DCM) to give **68-4** (12 g, 99%) as a white solid.

[0488] To a solution of **68-4** (15 g, 56.8 mmol) in anhydrous pyridine (200 mL) was added imidazole (7.7g, 113.6 mmol) and TBSCl (9.4 g, 62.5 mmol) at RT. The mixture was stirred overnight. And the solvent was removed and diluted with EA. The mixture was washed with $NaHCO_3$ aq. solution and brine. The organic layer was dried and concentrated to give crude **68-5.**

[0489] To a solution of **68-5** in anhydrous DCM (200 mL) was added collidine (6.8 g, 56.8 mmol), MMTrCl (17.8 g, 56.8 mmol) and $AgNO_3$ (9.6 g, 56.8 mmol) at RT. The mixture was stirred overnight. The mixture was filtered, and the filtrate was washed with $NaHCO_3$ aq. solution and brine. The organic layer was dried over Na_2SO_4, and concentrated at low pressure to give the residue, which was purified by silica gel column chromatography (5% EA in PE) to give **68-6** (32 g, 87%).

[0490] Compound **68-6** (32 g, 49.2 mmol) was dissolved in a solution of TBAF in THF (1M, 4 eq.) at RT. The mixture was stirred overnight, and the solvent was removed. The mixture was diluted with EA and washed with water. The organic layer was dried and concentrated to give the crude product, which was purified by silica gel column chromatography (33% EA in PE) to give **68-7** (21 g, 79%).

[0491] To a solution of **68-7** (21 g, 38.8 mmol) in DCM (200 mL) was added pyridine (9.2 mL, 116.4 mmol). The solution was cooled to 0 °C and Dess-Martin periodinane (49 g, 116.4 mmol) was added in a single portion. The mixture was stirred for 4 h at RT. The reaction was quenched with $Na_2S_2O_3$ solution and sodium bicarbonate aqueous solution. The mixture was stirred for 15 mins. The organic layer was separated, washed with diluted brine and concentrated under reduced pressure. The residue was dissolved in dioxane (200 mL), and the solution was treated with 37% aqueous formaldehyde (20 mL, 194 mmol) and 2 N aqueous sodium hydroxide (37.5 mL, 77.6 mmol). The mixture was stirred at RT overnight and $NaBH_4$ (8.8 g, 232.8 mmol) was added. After stirring for 0.5 h at RT, the excess of aqueous sodium hydroxide was removed with ice water. The mixture was diluted with EA. The organic phase was washed with brine, dried over magnesium sulfate and concentrated at low pressure. The residue was purified by column chromatography (4% MeOH in DCM) to give **68-8** (10 g, 50.5%) as a white foam.

[0492] Compound **68-8** (4.8 g, 8.5 mmol) was co-evaporated with toluene twice. The residue was dissolved in anhydrous DCM (45 mL) and pyridine (6.7 g, 85 mmol). The

solution was cooled to 0°C and triflic anhydride (4.8 g, 18.7 mmol) was added dropwise over 10 mins. At this temperature, the reaction was stirred for 40 mins. TLC (50% EA in PE) showed that the reaction was complete. The mixture was purified by column chromatography (EA in PE from 0 to 20%) to give **68-9** (6.1 g, 86.4%) as a brown foam.

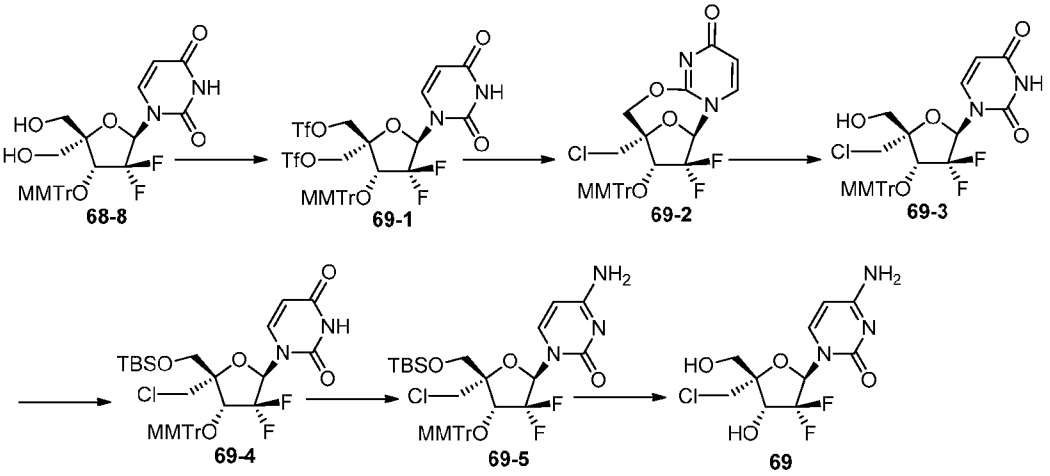
[0493] Compound **68-9** (6.1 g, 7.3 mmol) was dissolved in MeCN (25 mL). The mixture was treated with a solution of TBAF in THF (1M, 25 mL) at RT. The mixture was stirred overnight. TBAF in THF (1M, 15 mL) was added and stirred for 4 h. The mixture was treated with aqueous sodium hydroxide (1N, 14.6 mmol) and stirred for 1 h. The reaction was quenched with water (50 mL) at 0 °C and extracted with EA. The organic layer was dried and concentrated to give the crude product, which was purified by silica gel column chromatography (50% EA in PE) to give **68-10** (2.1 g, 50.6%).

[0494] To a solution of **68-10** (1.5 g, 2.6 mmol) in anhydrous pyridine (15 mL) was added imidazole (530 mg, 7.8 mmol) and TBSCl (585 mg, 3.9 mmol) at RT. The mixture was stirred for 2 h. The solvent was removed and diluted with EA. The mixture was washed with $NaHCO_3$ aq. solution and brine. The organic layer was dried and concentrated to give the residue, which was purified by silica gel column chromatography (10% EA in PE) to give **68-11**(1.5 g, 84.5%).

[0495] To a solution of **68-11** (1.5 g, 2.2 mmol) in anhydrous CH_3CN (11 mL) were added DMAP (671 mg, 5.5 mmol), TEA (555 mg, 5.5 mmol) and TPSCl (1.66 g, 5.5 mmol) at RT. The reaction was stirred overnight at RT. NH_4OH (10 mL) was added, and the mixture was stirred for 2 h. The mixture was diluted with EA and washed with $NaHCO_3$ solution. The organic layer was dried and concentrated at low pressure. The residue was purified by silica gel column chromatography (2% MeOH in DCM) to give crude **68-12,** which was purified by prep-TLC to give **68-12** (1.2 g, 80%) as a white solid.

[0496] A solution of **68-12** (1.2 g, 1.76 mmol) in 80% HCOOH (60 mL) was stirred for 4 h. The solvent was removed at low pressure. The crude product was dissolved in MeOH (40 mL) and stirred overnight. The solvent was concentrated to give the crude product, which was purified by column chromatography on silica gel (MeOH in DCM 10%) to give compound **68** (480 mg, 92%) as a white solid. ESI-MS: m/z 591 $[2M+H]^+$.

EXAMPLE 55
COMPOUND 69



[0497] A solution of **68-8** (2.63 g, 4.64 mmol) in anhydrous pyridine/DCM at 0 °C was added Tf_2O (3.27 g, 11.59 mmol). The mixture was stirred at RT for 40 mins. The solvent was removed at reduced pressure, and the residue was purified by column chromatography to give **69-1** (2.60 g, 67%).

[0498] A solution of **69-1** (2.65 g, 3.19 mmol) in anhydrous DMF was added sodium hydride (153 mg, 3.82 mmol) at 0 °C for 1 h. The solution was used for the next step without purification. The solution was treated with LiCl (402 mg, 9.57 mmol) at RT. The mixture was stirred at RT for 12 h. The reaction was quenched with saturated ammonium chloride solution, and extracted with EA. The organic layers were dried over Na_2SO_4, and concentrated at low pressure to give crude **69-2**.

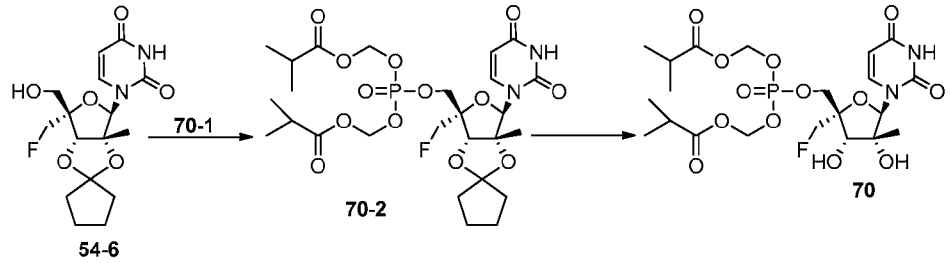
[0499] To a solution **69-2** (1.81 g, 3.19 mmol) in anhydrous THF (20 mL) was added 1 N NaOH (4 mL, 3.83 mmol) at RT. The mixture was stirred at RT for 2 h. The reaction was quenched with saturated sodium bicarbonate solution, and extracted with EA. The organic phase was dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by column chromatography to give **69-3**. (1.34 g, 72%).

[0500] A solution of **69-3** (925 mg, 1.58 mmol) in dichloromethane (10 mL) was added TBSCl (713 mg, 4.75 mmol) and imidazole (323 mg, 4.74 mmol), and stirred at RT overnight. The mixture was diluted with EA (20 mL), and washed with brine. T he organic phase was concentrated at low pressure to give the crude product. The residue was purified by column chromatography to give **69-4** (1.0 g, 90%).

[0501] A solution of **69-4** (1.24 g, 1.78 mmol) in anhydrous acetonitrile (10 mL) was added TPSCl(1.34 g, 4.45 mmol), DMAP (543 mg, 4.45 mmol) and TEA (450 mg, 4.45 mmol), and the mixture was stirred at RT for 3 h. The solvent was removed under reduced pressure, and the residue was dissolved in EA (30 mL). The solution was washed with brine, dried with anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified on silica gel to give **69-5** (1.0 g, 81%) as a white solid.

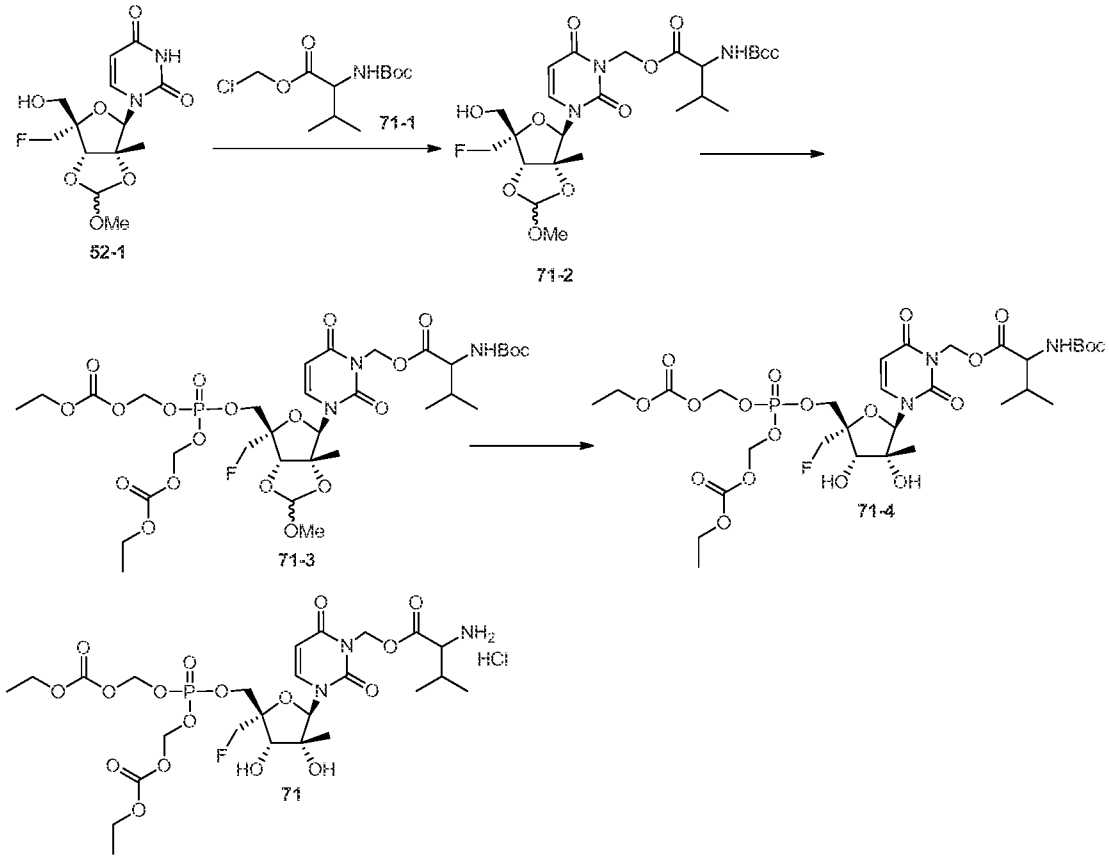
[0502] Compound **69-5** (1.0 g, 1.43 mmol) was treated with 80% HCOOH (10 mL), and stirred at RT overnight. The solvent was removed under reduced pressure, and the residue was purified on silica gel using 5% MeOH in CH_2Cl_2 to give compound **69** (264 mg, 60%). ESI-MS: m/z 311.9 $[M+H]^+$.

EXAMPLE 56
COMPOUND 70



[0503] Benzylphosphate (silver salt) and commercially available chloromethyl isobutylrate (5.0 g) yielded purified **70a** (3.84 g). ^{1}H-NMR (CD_3CN): δ 7.39-7.42 (m, 5H), 5.60 (d, 4H), 5.09 (d, 2H), 1.94-1.96 (m, 2H), 1.12-1.17 (m, 12H). ^{31}P-NMR (CD_3CN): δ -4.03 ppm. Compound **70a** (780 mg; 2.0 mmol) was deprotected to give **70-1** (triethylammonium salt), which was used immediately without further purification. Compound **54-6** (356 mg; 1.0 mmol) and **70-1** were reacted to give purified **70-2** (230 mg). Compound **70-2** (230 mg) was deprotected to yield purified compound **70** (80 mg, 0.14 mmol). The aforementioned reactions were conducted using a method described in the preparation of compounds **54** and **66**. ^{1}H-NMR ($CDCl_3$): δ 8.25 (s, 1H), 7.55 (d, 1H), 5.93 (s, 1H), 5.81 (d, 1H), 5.66-5.75 (m, 4H), 4.76 (dd, 2H), 4.37-4.46 (m, 2H), 4.15 (d, 2H), 3.86 (t, 6H), 3.70 (d, 6H), 1.65 (s, 6H), 1.25 (s, 3H). ^{31}P-NMR ($CDCl_3$): δ -4.41 ppm.

EXAMPLE 57
COMPOUND 71



[0504] Compound **71-2** (0.34 g, 60%) was prepared from **52-1** (0.33 g) and **71-1** (0.34 g) in acetone (6 mL) with NaI (0.19 g) and K_2CO_3 (0.69 g).

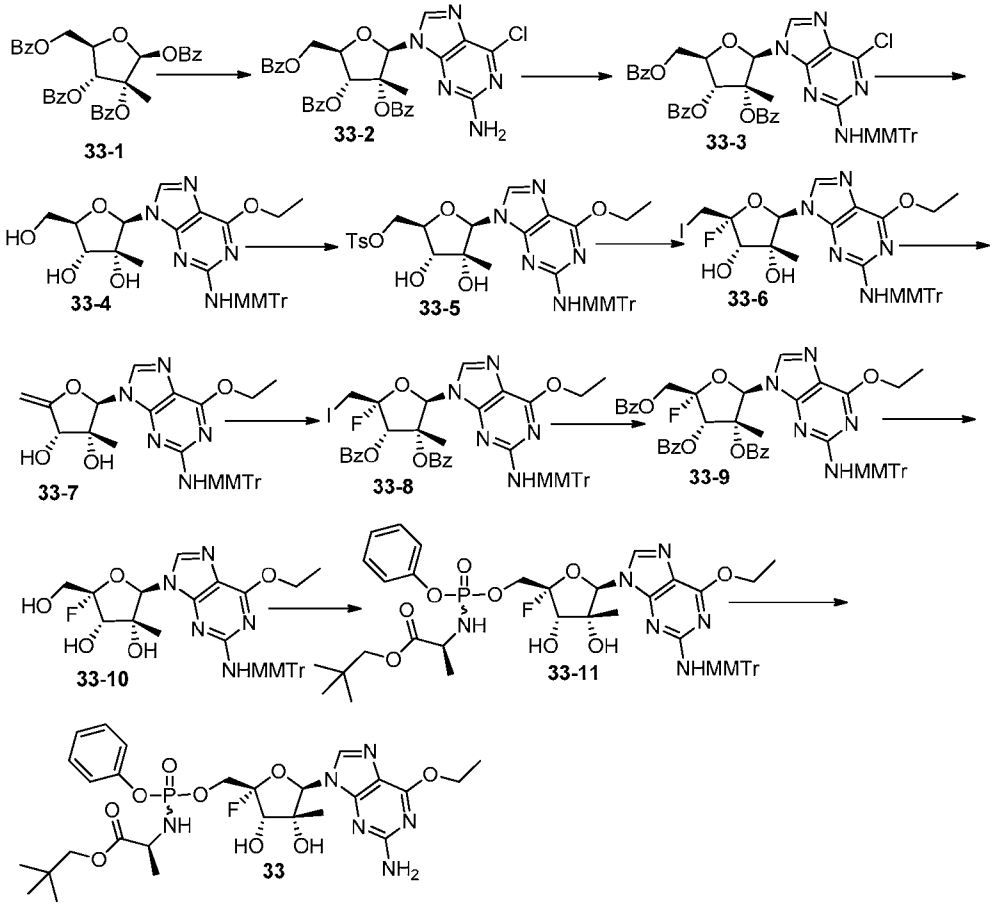
[0505] Compound **71-3** (0.28 g, 74%) was prepared in the same manner from **71-2** (0.25 g, 0.45 mmol) and triethylammonium bis(ethoxycarbonyloxymethyl)phosphate (0.9 mmol) with DIPEA (0.35 mL), BopCl (0.25 g), and 3-nitro-1,2,4-triazole (0.11 g) in THF (5 mL). Purification was done with hexanes/EtOAc (30-100% gradient).

[0506] A solution of **71-3** (0.28 g, 0.33 mmol) in 80% aq. AcOH was heated at 45 °C for 4 h and then concentrated. The residue was coevaporated with toluene and then with MeOH containing small amount of Et_3N (2 drops). Purification on silica gel (10 g column) with CH_2Cl_2/i-PrOH (4-10% gradient) yielded **71-4** (0.22 g, 84%).

[0507] To a solution of **71-4** (148 mg, 0.18 mmol) in EtOAc (0.6 mL) at 0 °C was added 4 N HCl/dioxane (0.5 mL), and the mixture kept at RT for 1 h. Ether was added and compound **71** precipitated. The mixture was filtered and washed with ether to give

compound **71** (100 mg, 75%). The aforementioned reactions were conducted using a method described in the preparation of compound **52**. MS: m/z=704 [M+1].

EXAMPLE 58
COMPOUND 33



[0508] Compound **33-1** (50 g, 86.0 mmol) and 6-Cl-guanine (16.1 g, 98.2 mmol) were co-evaporated with anhydrous toluene 3 times. To a solution of **33-1** (50 g, 86.0 mmol) and 6-Cl-guanine (16.1 g, 98.2 mmol) in MeCN (200 mL) was added DBU (39.5 g, 258.0 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 mins, and TMSOTf (95.5 g, 430.0 mmol) was added dropwise at 0 °C. The mixture was stirred at 0 °C for 30 mins until a clear solution was observed. The mixture was heated to 70 °C, and stirred overnight. The solution was cooled to RT, and diluted with EA (100 mL). The solution was washed with sat. $NaHCO_3$ solution and brine. The organic layer was dried over Na_2SO_4, and concentrated at low pressure. The residue was purified by column on silica gel (EA in PE from 10% to 40%) to give **33-2** (48.0 g, 88.7%) as a yellow foam. ESI-MS: m/z 628 $[M+H]^+$.

[0509] To a solution of **33-2** (48.0 g, 76.4 mol), $AgNO_3$ (50.0 g, 294.1 mmol) and collidine (40 mL) in anhydrous DCM (200 mL) was added MMTrCl (46.0 g, 149.2 mmol) in small portions under N_2. The mixture was stirred at RT for 3 h under N_2. Completion of the reaction was determined by TLC. After filtration, the filtrate was washed with sat. $NaHCO_3$ solution and brine. The organic layer was dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by silica gel column (EA in PE from 5% to 50%) to the give crude **33-3** (68 g, 98%). ESI-MS: m/z 900.1 $[M+H]^+$.

[0510] Sodium (8.7 g, 378.0 mmol) was dissolved in dry EtOH (100 mL) at 0 °C, and slowly warmed to RT. Compound **33-3** (68.0 g, 75.6 mmol) was treated with freshly prepared NaOEt solution, and stirred overnight at RT. Completion of the reaction was determined by TLC and LCMS. The mixture was concentrated at a low pressure, diluted with H_2O (100 mL), and extracted with EA (3 x 100 mL). The organic layer was dried over anhydrous Na_2SO_4, and evaporated at low pressure. The residue was purified by silica gel column chromatography (MeOH in DCM from 1% to 5%) to give **33-4** (34.0 g, 75.2%) as a yellow solid. ESI-MS: m/z 598 $[M+H]^+$.

[0511] Compound **33-4** (32.0 g, 53.5 mmol) was co-evaporated with anhydrous pyridine 3 times. To an ice cooled solution of **33-4** (32.0 g, 53.5 mmol) in anhydrous pyridine (100 mL) was added a solution of TsCl (11.2 g, 58.9 mmol) in pyridine (50 mL) dropwise at 0 °C. The mixture was stirred for 18 h. at 0 °C. The reaction was monitored by LCMS, and quenched with H_2O. The solution was concentrated at low pressure, and the residue was dissolved in EA (100 mL), and washed with sat. $NaHCO_3$ solution. The organic layer was dried over anhydrous Na_2SO_4, and evaporated at a low pressure. The residue was purified by silica gel column chromatography (MeOH in DCM from 1% to 5%) to give crude **33-5** (25.0 g, 62.2%) as a yellow solid. ESI-MS: m/z 752 $[M+H]^+$.

[0512] To a solution of **33-5** (23.0 g, 30.6 mmol) in acetone (150 mL) was added NaI (45.9 g, 306.0 mmol) and TBAI (2.0 g), and the mixture was refluxed overnight. Completion of the reaction was determined by LCMS. The mixture was concentrated at low pressure, and the residue was dissolved in EA (100 mL). The solution was washed with brine, and dried over anhydrous Na_2SO_4. The organic solution was evaporated at low pressure, and the residue was purified by silica gel column chromatography (DCM: MeOH=100:1 to 20:1) to give a crude product. To a solution of the crude product in dry

THF (200 mL) was added DBU (14.0 g, 91.8 mmol), and the mixture was heated to 60 °C and stirred overnight. The reaction was monitored by LCMS. The reaction was quenched with sat. $NaHCO_3$ solution, and the solution was extracted with EA (100 mL). The organic layer was dried over anhydrous Na_2SO_4, and evaporated at low pressure. The residue was purified by silica gel column chromatography (MeOH in DCM from 1% to 5%) to give **33-6** (12.0 g, 67.4%) as a yellow solid. ESI-MS: m/z 580 $[M+H]^+$.

[0513] To an ice cooled solution of **33-6** (8.0 g, 13.8 mmol) in anhydrous MeCN (100 mL) was added NIS (3.9 g, 17.2 mmol) and TEA•3HF (3.3 g, 20.7 mmol) at 0 °C. The mixture was stirred at RT for 18 h, and the reaction was checked by LCMS. After the reaction was completed, the reaction was quenched with sat. Na_2SO_3 solution and sat. $NaHCO_3$ solution. The solution was extracted with EA (3 x 100 mL). The organic layer was dried over anhydrous Na_2SO_4, and evaporated at low pressure. The residue was purified by silica gel column chromatography (EA in PE from 10% to 50%) to give **33-7** (7.2 g, 72.0%) as a solid. ESI-MS: m/z 726 $[M+H]^+$.

[0514] To a solution of **33-7** (7.2 g, 9.9 mmol) in dry DCM (100 mL) was added DMAP (3.6 g, 29.8 mmol), and BzCl (2.8 g, 19.8 mmol) at 0 °C. The mixture was stirred overnight, and checked by LCMS. The mixture was washed with sat. $NaHCO_3$ solution. The organic layer was dried over anhydrous Na_2SO_4, and evaporated at low pressure. The residue was purified by silica gel column chromatography (EA in PE from 10% to 30%) to give **33-8** (8.0 g, 86.4%) as a solid. ESI-MS: m/z 934 $[M+H]^+$.

[0515] To a solution of **33-8** (7.5 g, 8.0 mmol) in dry DMF (100 mL) was added NaOBz (11.5 g, 80.0 mmol) and 15-crown-5 (15.6 mL). The mixture was stirred for 36 h. at 90 °C. The mixture was diluted with H_2O (100 mL), and extracted with EA (3 x 150 mL). The organic layer was dried over anhydrous Na_2SO_4, and evaporated at low pressure. The residue was purified by silica gel column chromatography (EA in PE from 10% to 30%) to give crude **33-9** (6.0 g, 80.0%) as a solid. ESI-MS: m/z 928 $[M+H]^+$.

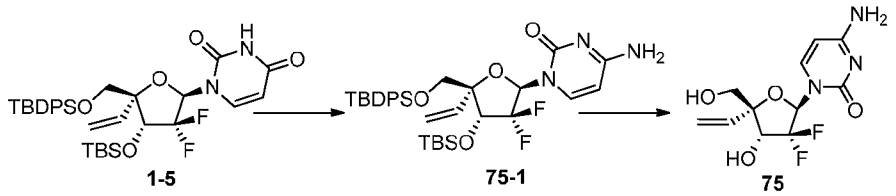
[0516] Compound **33-9** (4.0 g, 4.3 mmol) was co-evaporated with anhydrous toluene 3 times, and treated with NH_3/MeOH (50 mL, 4N) at RT. The mixture was stirred for 18 h. at RT. Completion of the reaction was determined by LCMS. The mixture was concentrated at low pressure, and the residue was purified by silica gel column

chromatography (EA in PE from 30% to 50%) to give product **33-10** (1.9 g, 71.7%) as a solid. ESI-MS: m/z 616 $[M+H]^+$.

[0517] Compound **33-10** (300.0 mg, 0.49 mmol) was co-evaporated with anhydrous toluene 3 times, and was dissolved in MeCN (2 mL). The mixture was treated with NMI (120.5 mg, 1.47 mmol) and the phosphorochloridate reagent (326.3 mg, 0.98 mmol) in MeCN (1 mL) at 0 °C. The mixture was stirred for 18 h at RT and monitored by LCMS. The mixture was diluted with 10% $NaHCO_3$ solution, and extracted with EA (3 x 30 mL). The residue was purified by silica gel column chromatography (EA in PE from 30% to 50%) to give **33-11** (210 mg, 47.5%) as a solid. ESI-MS: m/z 913.0 $[M+H]^+$.

[0518] Compound **33-11** (210 mg, 0.26 mmol) was treated with 80% of AcOH (15 mL), and the mixture was stirred for 18 h at RT. Completion of the reaction was determined by LCMS. The mixture was concentrated at low pressure, and the residue was purified by silica gel column chromatography (MeOH in DCM from 1% to 3%) to give compound **33** (71.8 mg, 48.7%) as a solid. ESI-MS: m/z 641.3 $[M+H]^+$.

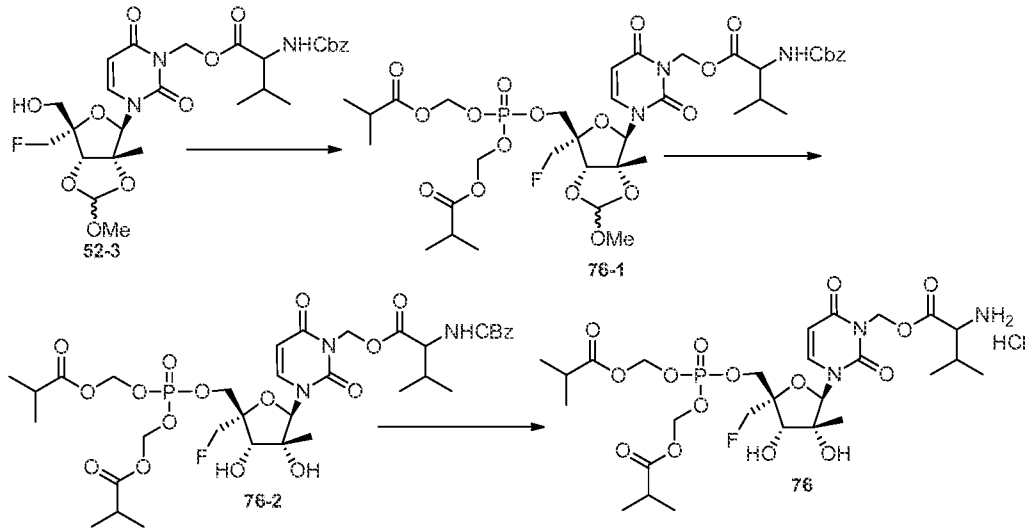
EXAMPLE 59
COMPOUND 75



[0519] A mixture solution of **1-5** (317 mg, 0.49 mmol), TPSCl (373 mg, 1.23 mmol), DMAP (150 mg, 1.23 mmol) and TEA (124 mg, 1.23 mmol) in anhydrous MeCN was stirred at RT overnight. The mixture was treated with ammonium solution, and then stirred at RT for 3 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography to give **75-1** (200 mg, 63%).

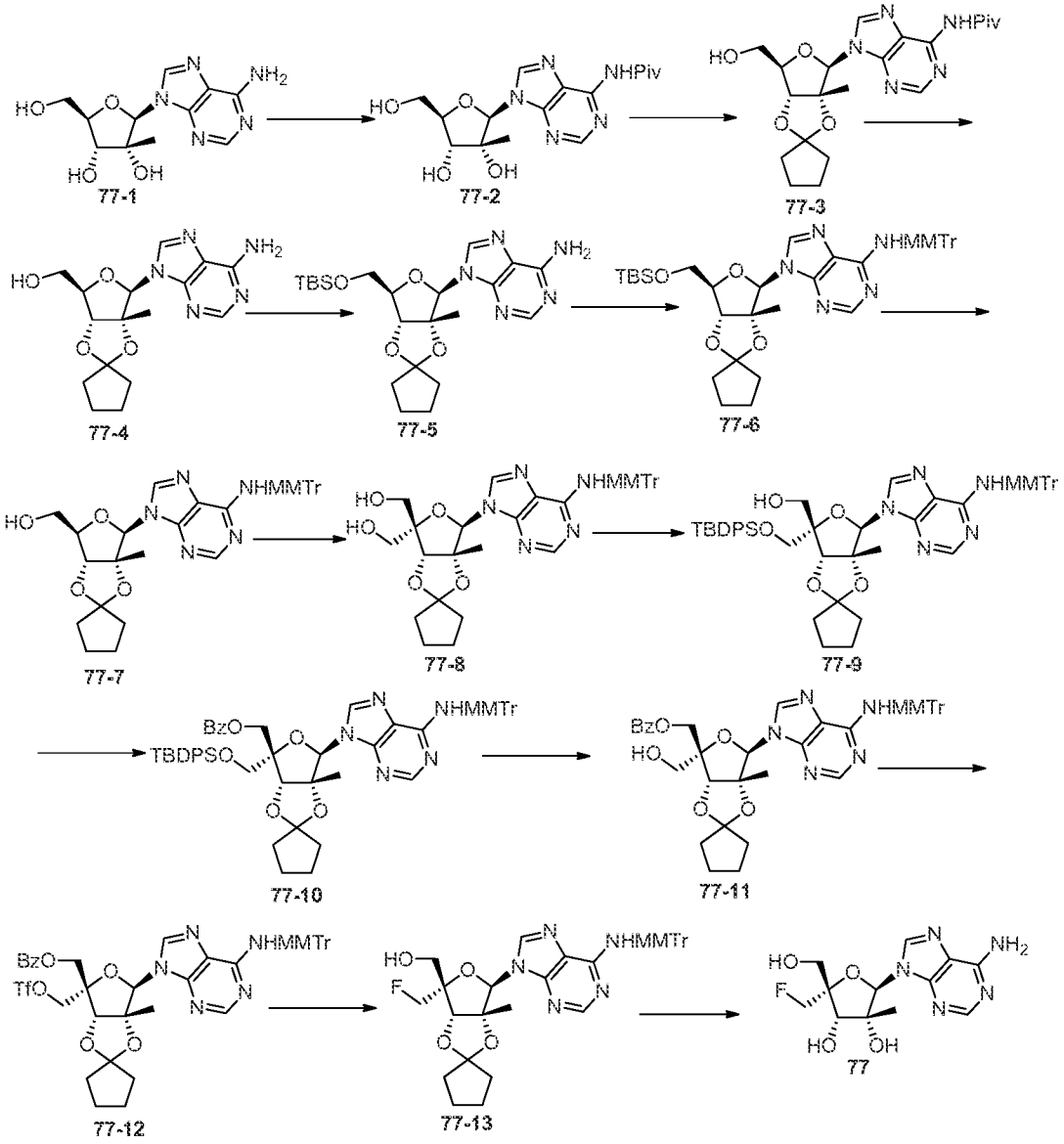
[0520] A solution of **75-1** (286 mg, 0.45 mmol) and ammonium fluoride (500 mg, 13.5 mmol) in methanol (10 mL) was refluxed overnight. The solvent was removed under reduced pressure and the residue was purified on silica gel to give compound **75** (75 mg, 57%). ESI-MS: m/z 289.9 $[M+H]^+$.

EXAMPLE 60
COMPOUND 76



[0521] Compound **76-1** (0.44 g, 34%) was prepared from **52-3** (0.88 g, 1.48 mmol) and triethylammonium bis(isobutyryloxymethyl)phosphate (3 mmol) with DIPEA (1.05 mL), BopCl (0.76 g), and 3-nitro-1,2,4-triazole (0.34 g) in THF (10 mL). Purification was done with hexanes/EtOAc (5-100 % gradient). Compound **76-2** (0.43 g, 85%) was prepared from **76-1** (0.44 g); and compound **76** (0.19 g, 98%) was prepared from **76-2** (0.22 g) in EtOH (10 mL) with 10% Pd/C (10 mg), 4 N HCl/dioxane (132 μL), and under the H_2 atmosphere. The aforementioned reactions were conducted using a method described in the preparation of compound **52**. MS: m/z = 700 [M+1].

EXAMPLE 61
COMPOUND 77



[0522] To a stirred solution of **77-1** (2.0 g, 7.12 mmol) in pyridine (20 mL) was added TMSCl (3.86 g, 35.58 mmol) at 0 °C under N_2. The mixture was slowly warmed to RT and stirred for 2 h. PivCl (1.71 g, 14.23 mmol) was added, and the mixture was stirred for 24 h. The solvent was evaporated at low pressure, and the residue was dissolved in EA (50 mL). The solution was washed with brine, dried over anhydrous Na_2SO_4, and concentrated at low pressure to give the crude product. The crude product was dissolved in MeOH (20 mL) and NH_4F (1.4 g, 37.86 mmol) was added. The mixture was refluxed for 2

h. The solvent was removed, and the residue was purified by column chromatography to give **77-2** (2.2 g, 85%).

[0523] To a solution of **77-2** (8.5 g, 23.28mmol) and 1,1-dimethoxycyclopentane (2 mL) in a mixture of DMF (15 mL) and cyclopentanone (6 mL) was added TsOH (6.63 g, 34.93mmol). The mixture was stirred at RT for 12 h. The reaction was quenched with triethylamine, and concentrated at low pressure. The residue was purified by column chromatography to give **77-3** (6.5 g, 65%).

[0524] To a stirred solution of **77-3** (6.0 g, 13.92 mmol) in anhydrous MeOH (60 mL) was added MeONa (2.25 g, 41.76 mmol) at RT. The mixture was stirred for 12 h and then neutralized with HOAc. The mixture was concentrated at low pressure, and the residue was purified by column chromatography to give **77-4** (4.4 g, 92%).

[0525] To a stirred solution of **77-4** (5.0 g, 14.40 mmol) in anhydrous pyridine (50 mL) was added TBSCl (3.24 g, 21.61 mmol) at RT under N_2, and the mixture was stirred overnight. The mixture was concentrated at low pressure, and the residue was purified by column chromatography to give **77-5** (5.44 g, 82%).

[0526] To a stirred solution of **77-5** (5.0 g, 10.84 mmol) in anhydrous DCM (50 mL) was added MMTrCl (5.01g, 16.26 mmol), collidine (5 mL), and $AgNO_3$ (2.76 g, 16.26 mmol) at RT under N_2, and the mixture was stirred for 2 h. The precipitate was removed by filtration, and the filtrate was concentrated at low pressure. The residue was purified by column chromatography to give **77-6** (7.1 g, 89%).

[0527] To a stirred solution of **77-6** (7.1 g, 9.68 mmol) in anhydrous THF (70 mL) was added TBAF (5.05 g, 19.37 mmol) at RT under N_2, and the mixture was stirred for 4 h. The mixture was concentrated at low pressure, and the residue was purified by column chromatography to give **77-7** (5.1 g, 87%).

[0528] To a stirred solution of **77-7** (3.2 g, 5.17 mmol) and pyridine (2.04 g, 25.85 mmol) in anhydrous DCM (30 mL) was added DMP (3.28 g, 7.75 mmol) at RT under N_2. The mixture was stirred at RT for 3 h. The reaction was quenched with sat. $Na_2S_2O_3$ solution, and washed with sat. $NaHCO_3$ solution and brine. The organic phase was dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by column chromatography to give the aldehyde (1.8 g). To a stirred solution of the aldehyde (1.8 g, 2.92 mmol) in dioxane (29.2 mL) was added 37% HCHO (2.36 g, 29.17 mmol) and 1N LiOH

(1.6 mL, 2.34 mmol) at RT. The mixture was stirred at RT for 1.5 h. The solution was neutralized with HOAc. The mixture was treated with EtOH (15 mL) and $NaBH_4$ (1.66 g, 43.8 mmol), and stirred at RT for 2 h. The mixture was quenched with water, and concentrated at low pressure. The residue was purified by column chromatography to give **77-8** (2.01 g, 61%).

[0529] To a stirred solution of **77-8** (200 mg, 0.31 mmol) in anhydrous DCM (2 mL) was added TBDPSCl (170 mg, 0.62 mmol) and imidazole (42 mg, 0.62 mmol) at RT under N_2. The mixture was stirred at RT for 2 h. The mixture was diluted with DCM (10 mL), and washed with brine. The organic phase was concentrated at low pressure, and the residue was purified by column chromatography to give **77-9** (175 mg, 64%).

[0530] To a stirred solution of **77-9** (270 mg, 0.304 mmol) in anhydrous DCM (2 mL) was added BzCl (63 mg, 0.61 mmol), DMAP (74 mg, 0.61 mmol) and TEA (61 mg, 0.61 mmol) at RT under N_2. The mixture was stirred at RT until the starting material disappeared. The = mixture was evaporated at low pressure, and the residue was purified by column chromatography to give **77-10** (250 mg, 83.3%).

[0531] Compound **77-10** (300 mg, 0.302 mmol) in THF (5 mL) was treated with a solution of TBAF (0.61 mL, 0.61 mmol, 1M in THF) and HOAc (0.2 mL) at RT. The mixture was stirred at RT for 12 h. The mixture was concentrated at low pressure, and the residue was purified by column chromatography to give **77-11** (170 mg, 75%).

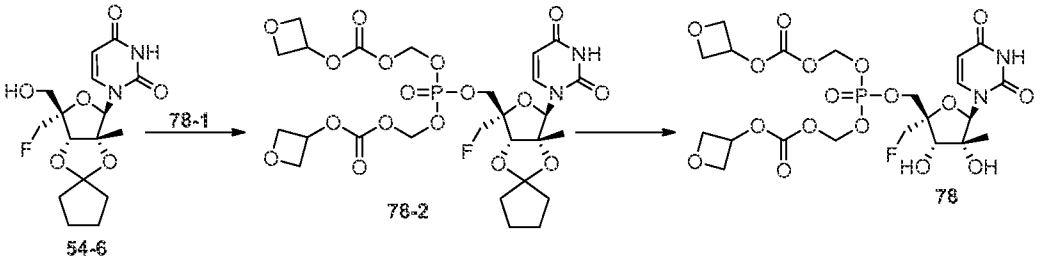
[0532] To a stirred solution of **77-11** (400 mg, 0.531 mmol) in anhydrous DCM (4 mL) was added Tf_2O (299 mg, 1.06 mmol) and pyridine (84 mg, 1.06 mmol) at RT under N_2. The mixture was stirred at RT until the starting material disappeared. The mixture was concentrated at low pressure, and the residue was purified by column chromatography to give **77-12** (401 mg, 85%).

[0533] Compound **77-12** (500 mg, 0.564 mmol) was treated with TBAF in THF (1.0 M, 2 mL) at RT under N_2. The mixture was diluted with water (20 mL), and extracted with DCM. The solution was washed with brine, dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by column chromatography to give **77-13** (150 mg, 40.8%) as a white solid. ESI-MS: m/z 652.1 $[M+H]^+$.

[0534] Compound **77-13** (50 mg) was dissolved in 80% HCOOH (10 mL), and the mixture was heated at 45^{0}C for 24 h. The solvent was evaporated and co-evaporated with

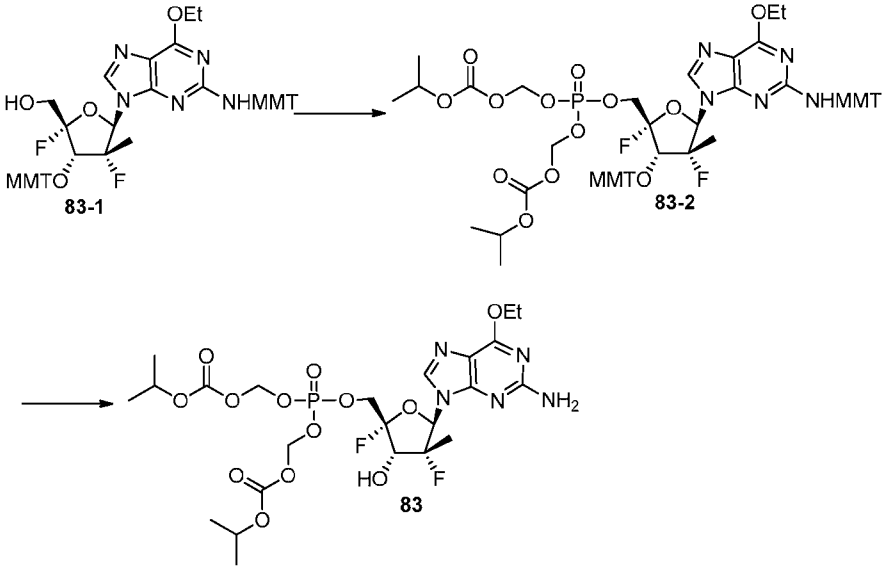
methanol/toluene to remove traces of acid. The residue was dissolved in 20% triethylamine in methanol, kept for 15 mins and then evaporated. Compound 77 (18 mg, 75%) was isolated by silica gel chromatography in a gradient of methanol in DCM from 0% to 15%. MS: m/z 312.5 [M-1].

EXAMPLE 62
COMPOUND 78



[0535] Compound **78a** was prepared from commercially available 3-hydroxyoxetane (5.0 g). ^{1}H-NMR ($CDCl_3$) δ 5.73 (s,2H) , 5.48-5.51 (m,1H), 4.90 (d,2H), 4.72 (d, 2H). Compound **78b** (8.0 g) was prepared from **78a**. ^{1}H-NMR ($CDCl_3$) δ 5.95 (s,2H) , 5.48-5.51 (m,1H), 4.90 (d,2H), 4.72 (d, 2H). Benzylphosphate (silver salt) and **78b** (8.0 g) were reacted to yield purified **78c** (1.92 g). ^{1}H-NMR (CD_3CN): δ 7.39-7.42 (m, 5H), 5.62 (d, 4H), 5.39-5.42 (m, 2H), 5.15 (d, 2H), 4.80-4.83 (m, 4H), 4.56-4.60 (m, 4H). ^{31}P-NMR (CD_3CN): δ - 4.55 ppm. Compound **78c** was deprotected to give **78-1** (triethylammonium salt), which was used immediately without further purification. Compound **54-6** (356 mg; 1.0 mmol) and **78-1** were reacted to give purified **78-2** (230 mg). Compound **78-2** (230 mg) was deprotected to yield purified compound **78** (12.5 mg, 0.02 mmol). The aforementioned reactions were conducted using a method described in the preparation of compound **54**. ^{1}H-NMR ($CDCl_3$): δ 8.25 (s, 1H), 7.54 (d, 1H), 5.90 (s, 1H), 5.81 (d, 1H), 5.66-5.75 (m, 4H), 5.44-5.49 (m, 2H), 4.88-4.92 (m, 5H), 4.61-4.78 (m, 5H), 4.37-4.46 (m, 2H), 4.21 (s, 1H), 3.49 (s, 1H), 1.25 (s, 3H). ^{31}P-NMR ($CDCl_3$): δ - 4.28 ppm.

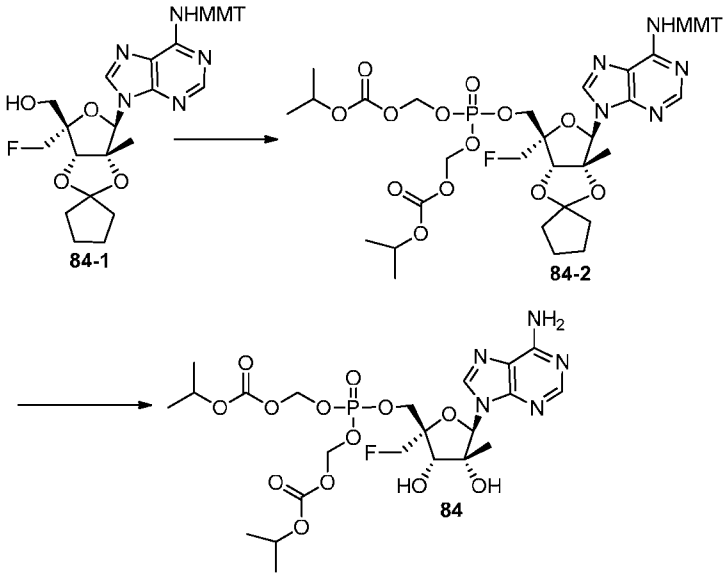
EXAMPLE 63
COMPOUND 83



[0536] Compound **83-2** (70 mg, 58%) was prepared in the same manner from compound **83-1** (90 mg; 0.1 mmol) and triethylammonium bis(isopropyloxycarbonyloxymethyl)phosphate (0.2 mmol) with DIPEA (87 μL), BopCl (44 mg), and 3-nitro-1,2,4-triazole (29 mg) in THF (2 mL) as described in the preparation of compound **44**. Purification was done with hexanes/EtOAc with a 20-80% gradient.

[0537] Compound **83** (25 mg, 64%) was prepared from **83-2** (70 mg) in acetonitrile (0.6 mL) and 4 N HCl/dioxane (50 μL) as described in the preparation of compound **55**. MS: m/z = 658 [M+1].

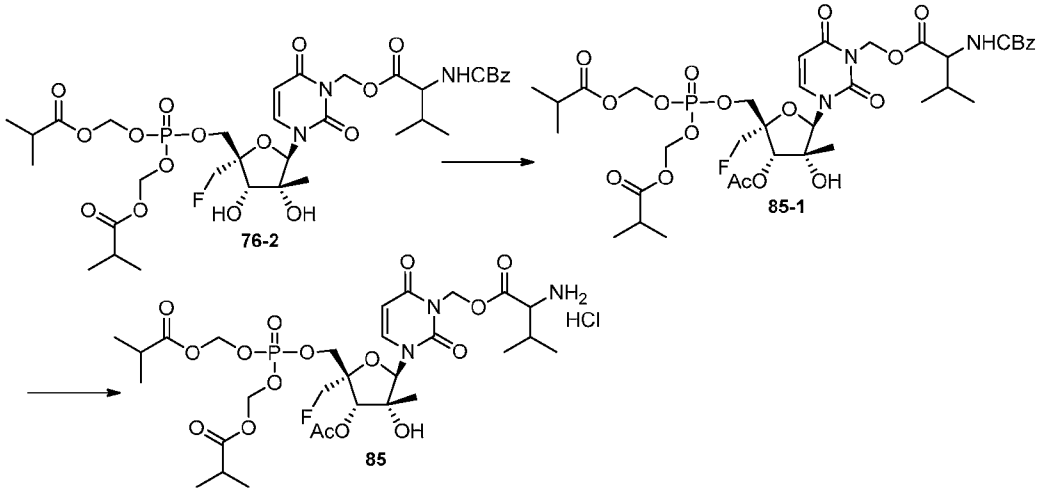
EXAMPLE 64
COMPOUND 84



[0538] Compound **84-2** (69 mg, 90%) was prepared from **84-1** (52 mg; 0.08mmol) and triethylammonium bis(isopropyloxycarbonyloxymethyl)phosphate (0.16 mmol) with DIPEA (74 μL), BopCl (51 mg), and 3-nitro-1,2,4-triazole (23 mg) in THF (1 mL) as described in the preparation of compound **44**. Purification was done with hexanes/EtOAc with a 20-100% gradient.

[0539] Compound **84** (27 mg, 62%) was prepared from **84-2** (65 mg) as described in the preparation of compound **44**. MS: m/z = 626 [M+1].

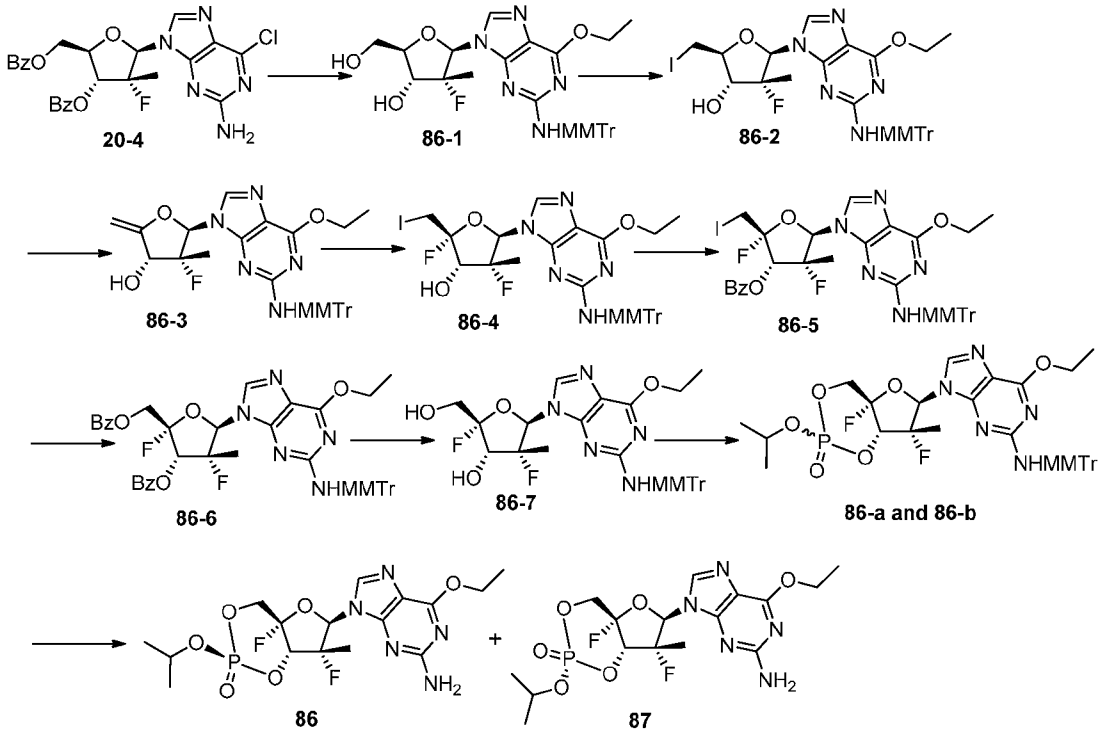
EXAMPLE 65
COMPOUND 85



[0540] A mixture of **76-2** and acetic anhydride in pyridine was stirred overnight at RT, then concentrated and purified on silica gel (10 g column) with CH_2Cl_2/i-PrOH (4-10% gradient) to yield **85-1** (12 mg, 69%).

[0541] Compound **85** (10 mg, 92%) was prepared from **85-1** (12 mg) in EtOH (0.5 mL) with 10% Pd/C (1 mg), 4 N HCl/dioxane (7 μL), and under the H_2 atmosphere in the same manner compound **52**. MS: m/z=742 [M+1].

EXAMPLE 66
COMPOUNDS 86 AND 87



[0542] A freshly prepared EtONa in dry EtOH (2N, 150 mL) was added to a solution of **20-4** (13.67 g, 17.15 mmol) in EtOH (50 mL) at 0 °C. The mixture was stirred at RT for 1 h, and then concentrated at low pressure. The residue was purified by silica gel column (5% MeOH in DCM) to give **86-1** (10 g, 98%) as a yellow solid.

[0543] To a solution of PPh_3 (2.73 g, 10.4 mol) in anhydrous pyridine (60 mL) was added I_2 (2.48 g, 9.76 mmol) at RT, and the reaction mixture was stirred RT for 30 mins. A solution of **86-1** (3.9 g, 6.51 mmol) in pyridine (10 mL) was added. The mixture was stirred at RT overnight. The reaction was quenched with sat. $Na_2S_2O_3$ solution and $NaHCO_3$ aq., and then extracted with EA (100 mL). The organic layer was dried over anhydrous

Na_2SO_4, and evaporated at low pressure. The residue was purified by silica gel column (2% MeOH in DCM) to give **86-2** (3.0 g, 75%) as a yellowed solid.

[0544] To a solution of **86-2** in dry THF (300 mL) was added DBU (14.0 g, 91.8 mmol), and the mixture was heated to reflux for 3 h. The mixture was concentrated at low pressure. The residue was dissolved in EA (100 mL), and washed with brine. The organic layer was dried over anhydrous Na_2SO_4, and evaporated at low pressure. The residue was purified by silica gel column (20% EA in PE) to give **86-3** (0.6 g, 37.5%) as a white solid.

[0545] To an ice-cooled solution of **86-3** (2.0 g, 3.44 mmol) in anhydrous MeCN (20 mL) was added NIS (0.975 g, 4.3 mmol) and TEA•3HF (0.82 g, 5.16 mmol) at 0 °C. The mixture was stirred at RT for 2 h. The reaction was quenched with sat. Na_2SO_3 and $NaHCO_3$ aqueous solution, and then concentrated at low pressure. The residue was dissolved in EA (50 mL), washed with brine, dried over anhydrous Na_2SO_4, and evaporated at low pressure. The residue was purified by silica gel column (20% EA in PE) to give **86-4** (1.5 g, 60%) as a white solid.

[0546] To a solution of **86-4** (1 g, 1.37 mmol) in dry pyridine (100 mL) was added BzCl (0.23 g, 1.65 mmol) at 0 °C. The reaction was stirred for 30 mins and checked by LCMS. The mixture was concentrated at low pressure, and the residue was dissolved in EA (50 mL). The solution was washed with brine. The organic layer was dried over $MgSO_4$, and evaporated at low pressure. The residue was purified by silica gel column chromatography (10% EA in PE) to give **86-5** (0.9 g, 78%) as a white solid.

[0547] To a solution of **86-5** (2 g, 2.4 mmol) in dry DMF (40 mL) was added NaOBz (3.46 g, 24 mmol) and 15-crown-5 (4.5 mL). The mixture was stirred at 95 °C for 72 h. The mixture was then diluted with EA (100 mL), and washed with water and brine. The organic phase was dried over $MgSO_4$, and concentrated at low pressure. The residue was purified by silica gel column (15% EA in PE) to give **86-6** (1.5 g, 75%) as a white solid.

[0548] Compound **86-6** (1.35 g, 1.64 mmol) in NH_3/MeOH (150 mL) was stirred at RT for 18 h. The mixture was concentrated at low pressure, and the residue was purified by silica gel column (5% MeOH in DCM) to give **86-7** (0.9 g, 90%) as a white solid. ESI-MS: m/z 618.3 $[M+H]^+$.

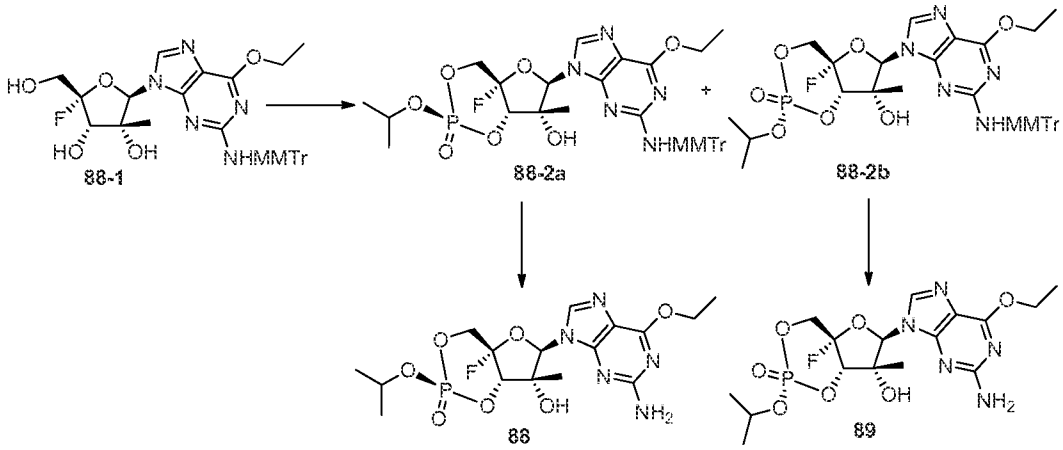
[0549] To a solution of **86-7** (99 mg, 0.16 mmol) in DCM (1.0 mL), triethylamine (92.7 μL, 0.64 mmol) was added at RT. The mixture was cooled to 0 to 5°C (ice/ water

bath), and freshly prepared and distilled isopropyl phosphorodichloridate (36.6 μL, 0.2 mmol, prepared according to a procedure , Reddy et al., *J. Org. Chem.* (2011) 76 (10):3782-3790) was added to the mixture. The mixture was stirred 0 to 5°C (ice/ water bath) for 15 mins, followed by addition of N-methylimidazole (26.3 μL, 0.32 mmol). The mixture was then stirred for 1 h at 0 to 5°C. TLC showed absence of **86-7.** EA (100 mL) was added, followed by water. The organic layer was washed H_2O, saturated aqueous NH_4Cl solution and brine. The organic layer was separated, dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated in vacuum to give a residue, which was purified on silica gel with 0 to 10% iPrOH/DCM to give a mixture of **86-a** and **86-b** (61.5 mg).

[0550] A mixture of **86-a** and **86-b** (61.5mg, 0.085 mmol) was dissolved in anhydrous CH_3CN (0.5 mL), and 4N HCl in dioxane (64 μL) was added at 0 to 5 °C (ice/ water bath). The mixture was stirred at RT for 40 mins, and anhydrous EtOH (200 μL) was added. The solvents were evaporated at RT and co-evaporated with toluene 3 times. The residue was dissolved in 50% CH_3CN/H_2O, was purified on a reverse-phase HPLC (C18) using acetonitrile and water, followed by lyophilization to give compound **86** (1.8 mg) and compound **87** (14.5 mg).

[0551] Compound **86:** ^{1}H NMR (CD_3OD-d_4, 400 MHz) δ 8.0 (s, 1H), 6.69 (d, J = 16.0 Hz, 1H),5.9-5.6 (br s, 1H), 4.94-4.85 (m, 1H), 4.68-4.52 (m, 3H), 1.49-1.3 (m, 12H); ^{19}F NMR (CD_3OD-d_4) δ -122.8 (s), -160.06 (s);; ^{31}P NMR (CD_3OD-d_4) δ -7.97 (s). ESI-LCMS: m/z = 450.1 $[M+H]^+$; Compound **87:** ^{1}H NMR (CD_3OD-d_4, 400 MHz) δ 7.96 (s, 1H), 6.68 (s, 1H), 6.69 (d, J = 16.8 Hz, 1H), 6.28-6.1 (br s, 1H), 4.81-4.5 (m, 4H), 1.45-1.39 (m, 12H); ^{31}P NMR (CD_3OD-d_4) δ -5.84 (s). ESI-LCMS: m/z = 450. $[M+H]^+$.

EXAMPLE 67
COMPOUNDS 88 AND 89



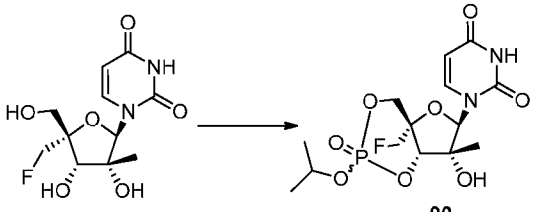
[0552] To a solution of **88-1** (150 mg, 0.24 mmol) in DCM (2.0 mL), triethylamine (141 µL, 2.0 mmol) was added at RT. The mixture was cooled to 0 to 5°C (ice/water bath), and freshly prepared and distilled isopropyl phosphorodichloridate (45 µL, 0.26 mmol, prepared according to a procedure , Reddy et al., *J. Org. Chem.* (2011) 76 (10):3782-3790) was added. The mixture was stirred at 0 to 5°C (ice/water bath) for 15 mins, followed by N-methylimidazole (40 µL, 0.49 mmol). The mixture was stirred for 1 h at 0 to 5°C. TLC showed the absence of starting material **88-1.** EA (100 mL) was added, followed by water. The organic layer was washed with H_2O, sat. aq. NH_4Cl solution and brine. The organic layer was separated, dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated in vacuum to give a residue, which was purified on silica gel with 0 to 10% iPrOH/ DCM to give **88-2a** (16.9 mg, faster eluting isomer) and **88-2b** (72.7 mg, slower eluting isomer).

[0553] Compounds **88-2a** and **88-2b** were deprotected using a procedure described herein. Compound **88** (7.3 mg, single isomers from **88-2a** (16.5 mg, 0.0235 mmol)) and compound **89** (29.0 mg, single isomers from **88-2b** (72.7 mg, 0.1 mmol)) were obtained.

[0554] Compound **88**: ^{1}H NMR (CD_3OD-d_4, 400 MHz) δ 7.94 (s, 1H), 6.32 (s, 1H), 6.00-5.9 (br s, 1H), 4.9-4.487 (m, 1H), 4.83-4.77 (m, 1H), 4.65-4.50 (m, 3H), 1.45-1.39 (s, 9H), 1.2 (s, 3H),; ^{19}F NMR (CD_3OD-d_4) δ -120.3 (s); ^{31}P NMR (CD_3OD-d_4) δ -5.19 (s); ESI-LCMS: m/z = 448.05 $[M+H]^+$. Compound **89**: ^{1}H NMR (CD_3OD-d_4, 400 MHz) δ 7.98

(s, 1H), 6.34 (s, 1H), 5.78-5.64 (br s, 1H), 4.95-4.48 (m, 2H), 4.62-4.52 (m, 3H), 1.48-1.42 (s, 9H), 1.1 (s, 3H),; ^{19}F NMR (CD_3OD-d_4) δ -121.3 (s); ^{31}P NMR (CD_3OD-d_4) δ -7.38 (s); ESI-LCMS: m/z = 448.05 $[M+H]^+$.

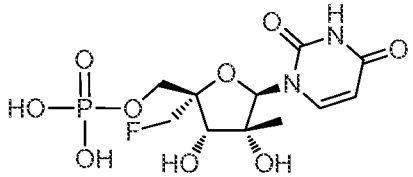
EXAMPLE 68
COMPOUND 90



90-1 **90**

[0555] To a stirred solution of **90-1** (532 mg, 1.84 mmol) in anhydrous CH_3CN (8.0 mL) was added N-methylimidazole (2.0 mL, 24.36 mmol) at 0 to 5 ^{0}C (ice/water bath) followed by a solution of freshly prepared and distilled isopropyl phosphorodichloridate (0.5 mL, 2.84 mmol). The solution was stirred at RT for 15 h. The mixture was diluted with EA, followed by water (15 mL). The solution was washed with H_2O, 50 % aqueous citric acid solution and brine. The organic layer was separated, dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated in vacuum to give a residue, which was purified on silica gel with 0 to 8% MeOH/ DCM to give the crude product (72 mg). The crude product was re-purified purified on a reverse-phase HPLC (C18) using acetonitrile and water, followed by lyophilization to give compound **90** (43.6 mg). MS: m/z = 395.05 $[M+H]^+$, 393.0 $[M-H]^-$, 787.05.0 $[2M-H]^-$.

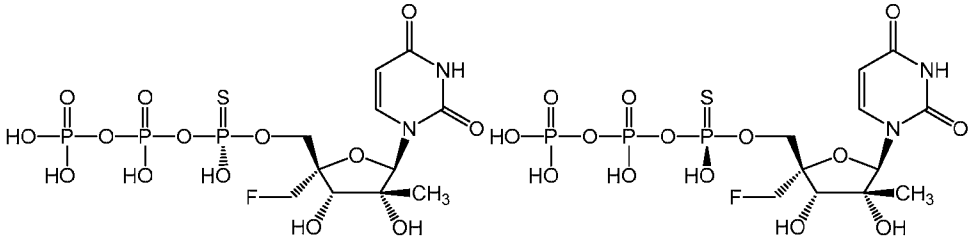
EXAMPLE 69
COMPOUND 96



[0556] Dry **51** (0.05 mmol) was dissolved in the mixture of $PO(OMe)_3$ (0.7 mL) and pyridine (0.3 mL). The mixture was evaporated in vacuum for 15 mins at bath temperature 42 ^{0}C, and then cooled to RT. N-Methylimidazole (0.009 mL, 0.11 mmol) was added followed by $POCl_3$ (9ul, 0.11 mmol), and the mixture was kept at RT for 20-40 mins. The reaction was controlled by LCMS and monitored by the appearance of **96**. Isolation was

performed by RP HPLC on Synergy 4 micron Hydro-RP column (Phenominex). A linear gradient of methanol from 0 to 30% in 50 mM 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 to yield compound **96**. MS: m/z 369.0 [M-1].

EXAMPLE 70
COMPOUNDS 97 AND 98

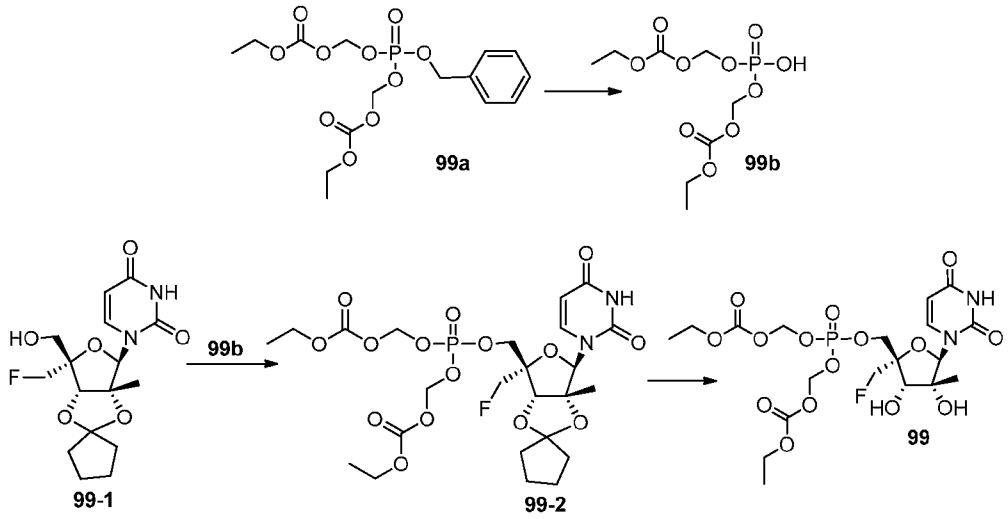


97 **98**

[0557] Dry **51** (0.05 mmol) was dissolved in the mixture of $PO(OMe)_3$ (0.7 mL) and pyridine (0.3 mL). The mixture was evaporated in vacuum for 15 mins at bath temperature 42 ^{0}C, than cooled to RT. N-Methylimidazole (0.009 mL, 0.11 mmol) was added followed by $PSCl_3$ (9 uL, 0.11 mmol), and the mixture was kept at RT for 20-40 mins. The reaction was controlled by LCMS and monitored by the appearance of the nucleoside 5'-thiophosphate. After completion of the reaction, tetrabutylammonium salt of pyrophosphate (150 mg) was added, followed by DMF (0.5 mL) to get a homogeneous solution. After 1.5 hours at ambient temperature, the reaction was quenched with water (10 mL). The 5'-triphosphate as mixture of diastereomers was isolated by IE chromatography on AKTA Explorer using column HiLoad 16/10 with Q Sepharose High Performance. Separation was done in linear gradient of NaCl from 0 to 1N in 50 mM TRIS-buffer (pH 7.5). Fractions containing thiotriphosphate were combined, concentrated and desalted by RP HPLC on Synergy 4 micron Hydro-RP column (Phenominex). Linear gradient of methanol from 0 to 30% in 50 mM triethylammonium buffer was used for elution over 20 mins, flow 10 mL/mins. Compounds **97** and **98** were collected. Analytical RP HPLC was done in 50 mM triethylammonium acetate buffer, pH 7.5 containing linear gradient of acetonitrile from 0% to 25% in 7 mins on Synergy 4 micron Hydro-RP column (Phenominex). Compound **97**: RT 5.50 mins. ^{31}P NMR: δ +42.45(1P, d), -6.80 (1P, d), -23.36 (1P, q). MS: m/z 544.9 [M-1].

Compound **98**: RT 6.01 mins. ^{31}P NMR: δ +41.80(1P, d), -6.57 (1P, d), -23.45 (1P, q). MS: m/z 544.9 [M-1].

EXAMPLE 71
COMPOUND 99



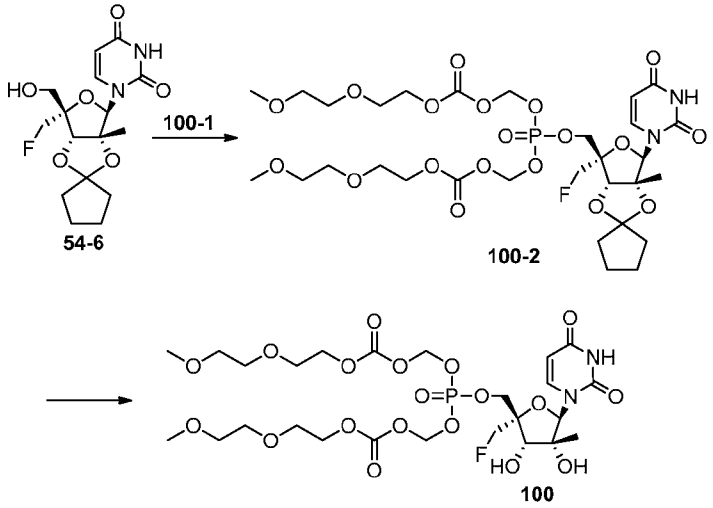
[0558] To a solution of **99a** (0.31 g, 0.8 mmol) in anhydrous methanol (2 mL), was added 10 % Pd/C (30 mg), and the mixture was stirred under H_2 atmosphere for 1 h. After completion, the mixture was filtered, and the catalyst cake was washed with methanol. The washing and filtrate were combined. The solvent was removed under vacuum to give **99b** as a semi-solid (252 mg), which was used without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.57 (d, J = 13.6 Hz, 4H), 4.23 (q, J = 7.2 Hz, 4H), 1.30 (t, J = 7.2 Hz, 6H), ^{31}P NMR ($CDCl_3$) δ 4.64 (s).

[0559] To a solution of triethylammonium bis (EOC) phosphate (0.7 mmol, prepared from 213 mg of **99b** and 0.2 mL of TEA) in THF (3 mL) was added **99-1** (160 mg, 0.45 mmol) followed by diisopropylethylamine (0.33 mL, 1.8 mmol), BOP-Cl (229 mg, 0.9 mmol), and 3-nitro-1,2,4-triazole (103 mg, 0.9 mmol). The mixture was stirred at RT for 90 mins. The mixture was diluted with EtOAc, and washed with water and brine. The organic layer was separated, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated in vacuum to a white solid, which was purified on silica gel column (CH_3OH:DCM; 9.5:0.5) to give **99-2** (189 mg, 66 %).

[0560] To a solution of **99-2** (180 mg, 0.28 mmol) in 80% HCOOH (7 mL), was heated for 6 h at 45 ^{0}C. The solvents were evaporated, and then co-evaporated with toluene

3 times. The residue was purified on silica gel column using 0 to 10% MeOH in DCM to obtain compound **99** (97.3 mg) as a white foam after lypholization. MS: m/z = 575.1 $[M+H]^+$.

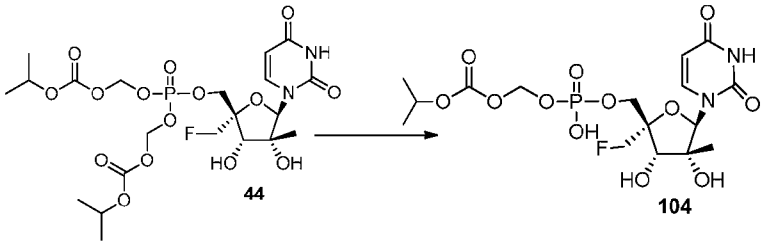
EXAMPLE 72
COMPOUND 100



[0561] Compound **100a** was prepared from commercially available 2-(2-methoxyethoxy)-ethanol (11.56 mL). Compound **100a** (13.5 g) was obtained as a clear colorless oil. ^{1}H-NMR ($CDCl_3$) δ 5.73 (s, 2H), 4.38-4.40 (m, 2H), 3.74-3.77 (m, 2H), 3.64-3.67 (m, 2H), 3.54-3.57 (m, 2H), 3.39 (s, 3H). Compound **100b** (9.6 g) was prepared from **100a**, and was obtained as a clear, slightly colored oil. ^{1}H-NMR ($CDCl_3$) δ 5.96 (s, 2H), 4.38-4.40 (m, 2H), 3.74-3.77 (m, 2H), 3.64-3.67 (m, 2H), 3.54-3.57 (m, 2H), 3.39 (s, 3H). Benzylphosphate (silver salt) and **100b** (2.4 g) were reacted and yielded purified **100c** (1.02 g). ^{1}H-NMR (CD_3CN): δ 7.39-7.42 (m, 5H), 5.60 (d, 4H), 5.11 (d, 2H), 4.27-4.29 (m, 4H), 3.65-3.67 (m, 4H), 3.56 (t, 4H), 3.46 (t, 4H), 3.30 (s, 6H). ^{31}P-NMR (CD_3CN): δ - 4.55 ppm. Compound **100c** (620 mg; 1.15 mmol) was deprotected to give **100-1** (triethylammonium salt), which was used immediately without further purification. Compound **54-6** (356 mg; 1.0 mmol) and **100-1** were reacted to give purified **100-2** (250 mg). Compound **100-2** (250 mg) was deprotected to yield purified compound **100** (110 mg , 0.14 mmol). The aforementioned reactions were conducted using a method described in the preparation of compound **54**. ^{1}H-NMR ($CDCl_3$): δ 8.62 (s, 1H), 7.54 (d, 1H), 5.96 (s, 1H), 5.64-5.79 (m,

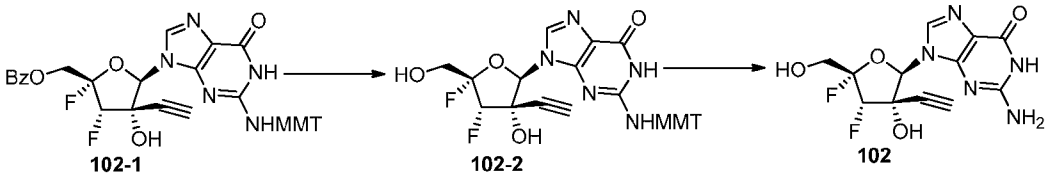
5H), 4.76 (dd, 2H), 4.37-4.46 (m, 6H), 4.25 (d, 2H), 3.86 (s, 1H), 3.75 (t, 4H), 3.70 (t, 4H), 3.58 (t, 4H), 3.38 (s, 6H), 1.65 (s, 6H), 1.25 (s, 3H). ^{31}P-NMR ($CDCl_3$): δ - 3.90 ppm.

EXAMPLE 73
COMPOUND 104



[0562] Compound **44** (0.010g, 0.016mmol) was added to normal saline solution (3 mL, pH 7.3), and stored in a heat block at 37°C for 6 days. The mixture was purified by preparative HPLC using a Synergi 4u Hydro-RP column (Phenomenex, 00G-4375-U0-AX), with H_2O (0.1% formic acid) and ACN (0.1% formic acid) solvents (0-65% gradient in 20 minutes). The compound eluted at 13.0 mins. Pure fractions were pooled and lyophilized to yield compound **104** (0.005g, 63%). MS: m/z = 487 [M+1].

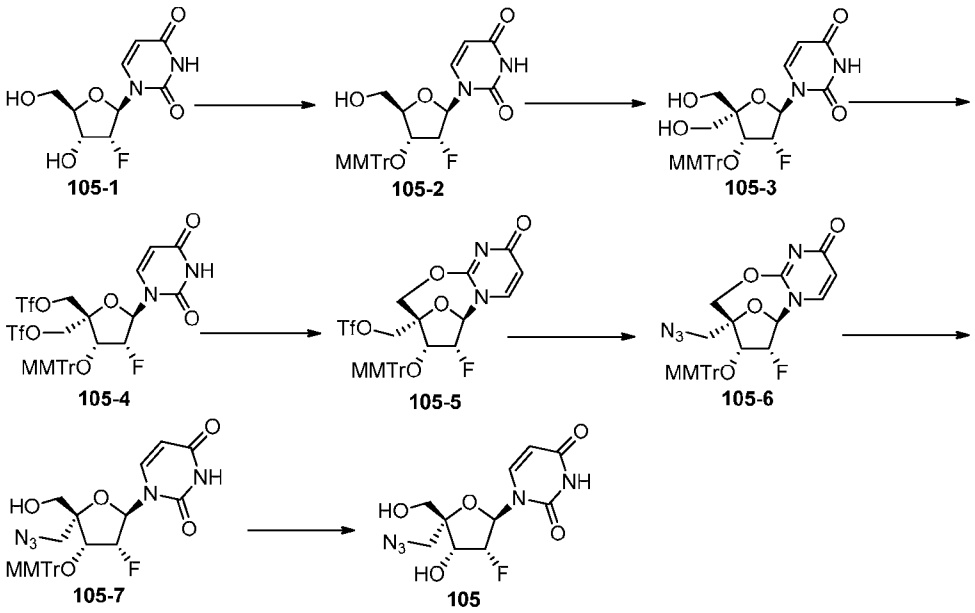
EXAMPLE 74
COMPOUND 102



[0563] A mixture of **102-1** (45 mg, 0.06 mmol) and butylamine (0.4 mL) was kept overnight at RT and then evaporated. The crude residue was purified on silica gel (10 g column) with CH_2Cl_2/MeOH (4-12% gradient) to yield **102-2** as a colorless glass (20 mg, 56%).

[0564] To a solution of **102-2** (20 mg, 0.03 mmol) in ACN (0.5 mL) was added 4N HCl in dioxane (35 µL). The mixture was stirred at RT for 4 h and then quenched with MeOH. The residue was treated with ACN to yield compound **102** as an off-white solid (9 mg, 80%). MS m/z = 328 [M+1].

EXAMPLE 75
COMPOUND 105



[0565] To a solution of **105-1** (50 g, 203 mmol) in anhydrous pyridine (200 mL) was added TBDPS-Cl (83.7 g, 304 mmol). The reaction was allowed to proceed overnight at RT. The solution was concentrated under low pressure to give a residue, which was partitioned between ethyl acetate and water. The organic layer was separated, washed with brine, dried over magnesium sulfate and concentrated under reduced pressure to give 5'-OTBDPS ether as a white foam (94 g).

[0566] To a solution of the 5'-OTBDPS ether (94.0 g, 194.2 mmol) in anhydrous DCM (300 mL) were added silver nitrate (66.03 g, 388.4 mmol) and collidine (235 mL, 1.94 mol). The mixture was stirred at RT. After 15 mins, the mixture was cooled to 0°C, and monomethoxytrityl chloride (239.3 g, 776.8 mmol) was added as a single portion. After being stirred overnight at RT., the mixture was filtered through Celite and the filtrate was diluted with TBME. The solution was washed successively with 1M citric acid, diluted brine and 5% sodium bicarbonate. The organic solution was dried over sodium sulfate and concentrated under vacuum to give the fully protected intermediate as a yellow foam.

[0567] This fully protected intermediate was dissolved in toluene (100 mL) and the solution was concentrated under reduced pressure. The residue was dissolved in anhydrous THF (250 mL) and treated with TBAF (60 g, 233 mmol). The mixture was stirred

for 2 h at RT., and the solvent was removed under reduced pressure. The residue was taken into ethyl acetate and the solution was washed first with saturated sodium bicarbonate and then with brine. After being dried over magnesium sulfate, the solvent was removed in vacuum and the residue was purified by column chromatography (50% EA in PE) to give **105-2** (91 g, 86.4%) as a white foam.

[0568] To a solution of **105-2** (13.5 g, 26 mmol) in DCM (100 mL) was added pyridine (6.17 mL, 78 mmol). The solution was cooled to 0°C, and Dess-Martin periodinane (33.8 g, 78 mmol) was added as a single portion. The reaction mixture was stirred for 4 h at RT., and quenched by the addition of $Na_2S_2O_3$ solution (4%) and sodium bicarbonate aqueous solution (4%) (the solution was adjusted to pH 6, ~150 mL). The mixture was stirred for 15 mins. The organic layer was separated, washed with diluted brine and concentrated under reduced pressure. The residue was dissolved in dioxane (100 mL) and the solution was treated with 37% aqueous formaldehyde (21.2 g, 10 eq.) and 2N aqueous sodium hydroxide (10 eq.). The reaction mixture was stirred at RT., overnight. After stirring for 0.5 h at RT., the excess of aqueous sodium hydroxide was removed with saturated NH_4Cl (~150 mL). The mixture was concentrated under reduced pressure, and the residue was partitioned between ethyl acetate and 5% sodium bicarbonate. The organic phase was separated, washed with brine, dried over magnesium sulfate and concentrated. The residue was purified by column chromatography (2% MeOH in DCM) to give **105-3** (9.2 g, 83.6%) as a white foam.

[0569] Compound **105-3** (23 g, 42.0 mmol) was co-evaporated with toluene twice. The residue was dissolved in anhydrous DCM (250 mL) and pyridine (20 mL). The solution was cooled to 0°C, and triflic anhydride (24.9 g, 88.1 mmol) was added dropwise over 10 mins. At this temperature, the reaction was stirred for 40 mins. The reaction was monitored by TLC (PE: EA= 2:1 and DCM: MeOH= 15:1). After completion, the reaction mixture was quenched with water (50 mL) at 0°C. The mixture was stirred for 30 mins, and extracted with EA. The organic phase was dried over Na_2SO_4 and filtered through a silica gel pad. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography (50% EA in PE) to give **105-4** (30.0 g, 88.3%) as a brown foam.

[0570] To a stirred solution of **105-4** (4.4 g, 5.42mmol) in anhydrous DMF (50 mL) was added NaH (260 mg, 6.5 mmol) at 0°C under nitrogen atmosphere. The solution

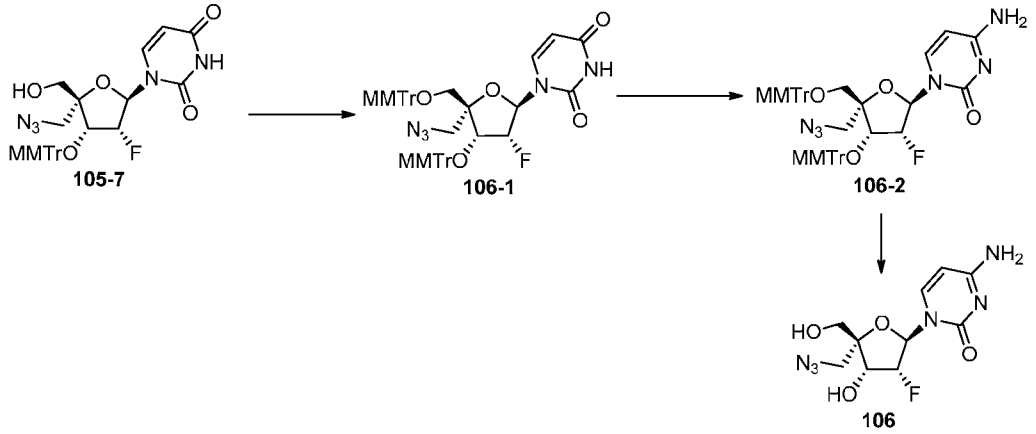
was stirred at RT., for 1.5 h. The solution was used for the next step without any further workup.

[0571] To the stirred solution was added NaN_3 (1.5 g, 21.68 mmol) at 0°C under nitrogen atmosphere, and the resulting solution was stirred at RT. for 1.5 h. The reaction was quenched with water, extracted with EA, washed with brine, and dried over $MgSO_4$. The concentrated organic phase was used for the next step without further purification.

[0572] To a solution of **105-6** (3.0 g, 5.4 mmol) in anhydrous 1,4-dioxane (18 mL) was added NaOH (5.4 mL, 2M in water) at RT. The reaction mixture was stirred at RT. for 3 h. The reaction was diluted with EA, washed with brine, and dried over $MgSO_4$. The concentrated organic phase was purified on a silica gel column (30% EA in PE) to give **105-7** (2.9 g, 93%) as a white foam.

[0573] Compound **105-7** (520 mg, 0.90 mmol) was dissolved in 80% of HCOOH (20 mL) at RT. The mixture was stirred for 3 h, and monitored by TLC. The solvent was removed and the residue was treated with MeOH and toluene for 3 times. NH_3/MeOH was added, and the reaction mixture was stirred at RT., for 5 mins. The solvent was concentrated to dryness and the residue was purified by column chromatography to give compound **105** (120 mg, 44.4%) as a white solid. ESI-LCMS: m/z 302.0 $[M+H]^+$, 324.0$[M+Na]^+$.

EXAMPLE 76
COMPOUND 106



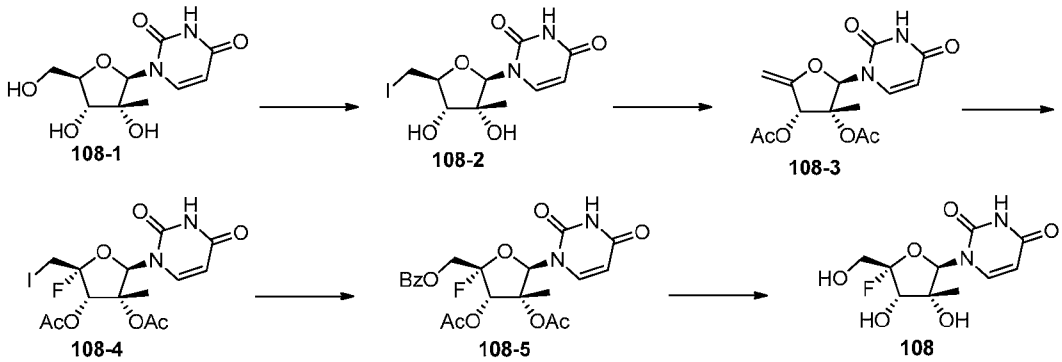
[0574] To a stirred solution of **105-7** (1.1 g, 2.88 mmol) in anhydrous DCM (10 mL) was added MMTrCl (1.77 g, 5.76 mmol), $AgNO_3$ (1.47 g, 8.64 mmol) and collidine (1.05 g, 8.64 mmol) at 25°C under a N_2 atmosphere. The reaction was refluxed for 12 h.

MeOH (20 mL) was added and the solvent was removed to dryness. The residue was purified on a silica gel column (20% EA in PE) to give **106-1** (1.6 g, 85.1%) as a white foam.

[0575] To a stirred solution of **106-1** (800 mg, 0.947 mmol) in anhydrous MeCN (10 mL) were added TPSCl (570 mg, 1.89 mmol), DMAP (230 mg, 1.89 mmol) and TEA (190 mg, 1.89 mmol) at RT. The mixture was stirred for 12 h. NH_4OH (25 mL) was added and the mixture was stirred for 2 h. The solvent was removed, and the residue was purified on a silica gel column as a yellow foam. Further purification by prep-TLC gave **106-2** (700 mg, 87.1%) as a white solid.

[0576] Compound **106-2** (300 mg, 0.355 mmol) was dissolved in 80% of HCOOH (5 mL) at RT. The mixture was stirred for 3 h, and monitored by TLC. The solvent was then removed and the residue was treated with MeOH and toluene (3 times). NH_3/MeOH was added and the mixture was stirred at RT, for 5 mins. The solvent was removed and the residue was purified by column chromatography to give compound **106** (124 mg, 82.6%) as a white solid. ESI-LCMS: m/z 301.0 $[M+H]^+$, 601.0$[2M+H]^+$.

EXAMPLE 77
COMPOUND 108



[0577] To a stirred suspension of **108-1** (20 g, 77.5 mmol), PPh_3 (30 g, 114.5 mmol), imidazole (10 g, 147 mmol) and pyridine (90 mL) in anhydrous THF (300 mL) was added a solution of I_2 (25 g, 98.4 mmol) in THF (100 mL) dropwise at 0 °C. The mixture was warmed to room temperature (RT) and stirred at RT for 10 h. The reaction was quenched by MeOH (100 mL). The solvent was removed, and the residue was re-dissolved in a mixture ethyl acetate (EA) and THF (2 L, 10:1). The organic phase was washed with saturated $Na_2S_2O_3$ aq., and the aqueous phase was extracted with a mixture of EA and THF (2 L, 10:1).

The organic layer was combined and concentrated to give a residue, which was purified on a silica gel column (0-10% MeOH in DCM) to give **108-2** (22.5 g, 78.9%) as a white solid. ^{1}H NMR: (DMSO-d_6, 400 MHz) δ 11.42 (s, 1H), 7.59 (d, J = 8.4 Hz, 1H), 5.82 (s, 1H), 5.63 (d, J = 8.0 Hz, 1H), 5.50 (s, 1H), 5.23 (s, 1H), 3.77-3.79 (m, 1H), 3.40-3.62 (m, 3H), 0.97 (s, 3H).

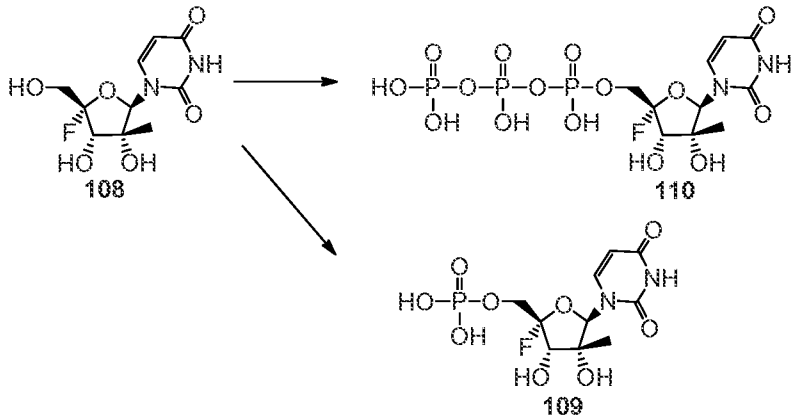
[0578] To a stirred solution of **108-2** (24.3 g, 66.03 mmol) in anhydrous MeOH (240 mL) was added NaOMe (10.69 g, 198.09 mmol) at RT under N_2. The mixture was refluxed for 3 h. The solvent was removed, and the residue was re-dissolved in anhydrous pyridine (200 mL). To the mixture was added Ac_2O (84.9 g, 833.3 mmol) at 0 °C. The mixture was warmed to 60 °C and stirred for 10 h. The solvent was removed, and the residue was diluted with DCM, washed with saturated $NaHCO_3$ and brine. The organic layer was concentrated and purified on a silica gel column (10-50% EA in PE) to give **108-3** (15 g, 70.1%) as a white solid. ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 8.82 (s, 1H), 7.23 (d, J = 2.0 Hz, 1H), 6.54 (s, 1H), 5.85 (s, 1H), 5.77 (dd, J = 8.0, 2.0 Hz, 1H), 4.69 (d, J = 2.4 Hz, 1H), 4.58 (d, J = 2.8Hz, 1H), 2.07 (d, J = 5.2Hz, 6H), 1.45 (s, 3H).

[0579] To an ice cooled solution of **108-3** (15 g, 46.29 mmol) in anhydrous DCM (300 mL) was added AgF (29.39 g, 231.4 mmol). I_2 (23.51 g, 92.58 mmol) in anhydrous DCM (1.0 L) was added dropwise to the solution. The reaction mixture was stirred at RT for 5 h. The reaction was quenched with saturated $Na_2S_2O_3$ and $NaHCO_3$, and extracted with DCM. The organic layer was separated, dried and evaporated to dryness. The residue was purified on a silica gel column (10-30% EA in PE) to give **108-4** (9.5 g, 43.6%) as a white solid. ^{1}H NMR: (Methanol-d_4, 400 MHz) δ 7.52 (d, J = 8.0 Hz, 1H), 6.21 (s, 1H), 5.80 (d, J = 17.2 Hz, 1H), 5.73 (d, J = 8.0 Hz, 1H), 3.58 (s, 1H), 3.54 (d, J = 6.8 Hz, 1H), 2.17 (s, 3H), 2.09 (s, 3H), 1.58 (s, 3H).

[0580] To a solution of **108-4** (7.0 g, 14.89 mmol) in anhydrous DMF (400 mL) were added NaOBz (21.44 g, 148.9 mmol) and 15-crown-5 (32.75 g, 148.9 mmol). The reaction mixture was stirred at 130 °C for 6 h. The solvent was removed, diluted with EA and washed with water and brine. The organic layer was evaporated and purified on a silica gel column (10-30% EA in PE) to give **108-5** (2.8 g, 40.5%). ESI-MS: m/z 444.9 [M - F + H]$^+$.

[0581] A mixture of **108-5** (4.0 g; 8.6 mmol) and liquid ammonia was kept overnight at RT in a high-pressure stainless-steel vessel. Ammonia was then evaporated, and the residue purified on silica (50g column) with a CH_2Cl_2/MeOH solvent mixture (4-12% gradient) to yield compound **108** as a colorless foam (2.0 g; 84% yield). ESI-MS: m/z 275.1 $[M-H]^-$.

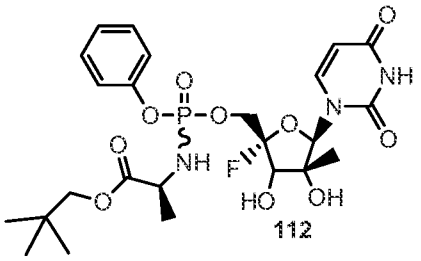
EXAMPLE 78
COMPOUNDS 109 AND 110



[0582] Dry compound **108** (14 mg, 0.05 mmol) was dissolved in the mixture of $PO(OMe)_3$ (0.750 mL) and pyridine (0.5 mL). The mixture was evaporated in vacuum for 15 mins at bath temperature 42 ^{0}C, and then cooled down to RT. 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 RT 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 water (10 mL) and loaded on a column HiLoad 16/10 with Q Sepharose High Performance. The separation was done in linear gradient of NaCl from 0 to 1N in 50 mM TRIS-buffer (pH7.5). The fractions eluted at 60% buffer B contained Compound **109** and at 80% buffer B contained Compound **110**. The corresponding fractions were concentrated, and the residue purified by RP HPLC on Synergy 4 micron Hydro-RP column (Phenominex). A linear gradient of methanol from 0 to 30% in 50 mM 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

109: P^{31}-NMR (D_20): -3.76 (s); MS: 378.2 [M-1]. Compound **110**: P^{31}-NMR (D_20): -9.28(d, 1H, Pα), -12.31(d, 1H, Pγ), -22.95(t, 1H, Pβ); MS 515.0 [M-1].

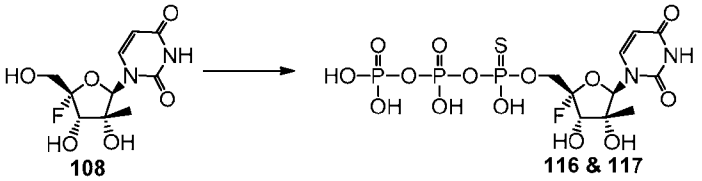
EXAMPLE 79
COMPOUND 112



112

[0583] Compound **112** (36 mg, 63%) was synthesized as described for compound **2** using a neopentyl ester phosphorochloridate reagent. MS: 572.6 [M-1].

EXAMPLE 80
COMPOUNDS 116 AND 117

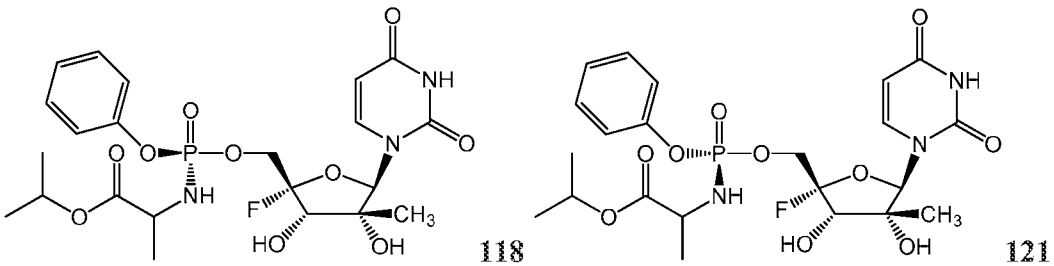


108 116 & 117

[0584] Dry compound **108** (14 mg, 0.05 mmol) was dissolved in the mixture of $PO(OMe)_3$ (0.750 mL) and pyridine (0.5 mL). The mixture was evaporated in vacuum for 15 mins at bath temperature 42 ^{0}C, and then cooled down to RT. N-Methylimidazole (0.009 mL, 0.11 mmol) was added followed by $PSCl_3$ (0.01 mL, 0.1 mmol). The mixture was kept at RT for 1 h. Tributylamine (0.065 mL, 0.3 mmol) and N-tetrabutyl ammonium salt of pyrophosphate (200 mg) was added. Dry DMF (about 1 mL) was added to get a homogeneous solution. In 2 h, the reaction was quenched with 2M ammonium acetate buffer (1 mL, pH = 7.5), diluted with water (10 mL) and loaded on a column HiLoad 16/10 with Q Sepharose High Performance. Separation was done in linear gradient of NaCl from 0 to 1N in 50 mM TRIS-buffer (pH7.5). The fractions eluted at 80% buffer B contained compounds **116** and **117.** The corresponding fractions were concentrated, and the residue purified by RP HPLC on Synergy 4 micron Hydro-RP column (Phenominex). A linear gradient of methanol from 0 to 20% in 50 mM triethylammonium acetate buffer (pH 7.5) was used for elution. Two peaks were collected. The corresponding fractions were combined, concentrated and lyophilized 3 times to remove excess of buffer. Peak 1 (more polar): ^{31}P-NMR (D_2O):

+42.68(d, 1H, Pα), -9.05(d, 1H, Pγ), -22.95(t, 1H, Pβ); MS 530.9.0 [M-1]. Peak 2 (less polar): ^{31}P-NMR (D_2O): +42.78(d, 1H, Pα), -10.12(bs, 1H, Pγ), -23.94(t, 1H, Pβ); and MS 530.9.0 [M-1].

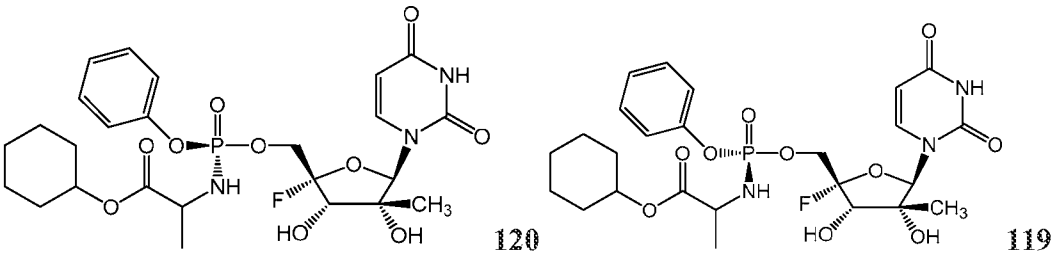
EXAMPLE 81
COMPOUNDS 118 AND 121



118 121

[0585] The diastereomers of compound **5** were separated by RP-HPLC. A gradient of 10-43%ACN in H_2O over 26 mins on a Synergi Hydro RP 30 x 250 m 4u particle column (Phenomenex PN 00G-4375-U0-AX) eluted compound **121** (29.5 mins) and compound **118** (30.1 mins). Pure fractions were lyophilized to produce a white powder. Compound **121**: ^{31}P-NMR (DMSO-d6) 3.448 ppm; MS: m/z: 544 M-1; Compound **118**: ^{31}P-NMR (DMSO-d6) 3.538 ppm; MS: m/z: 544 M-1.

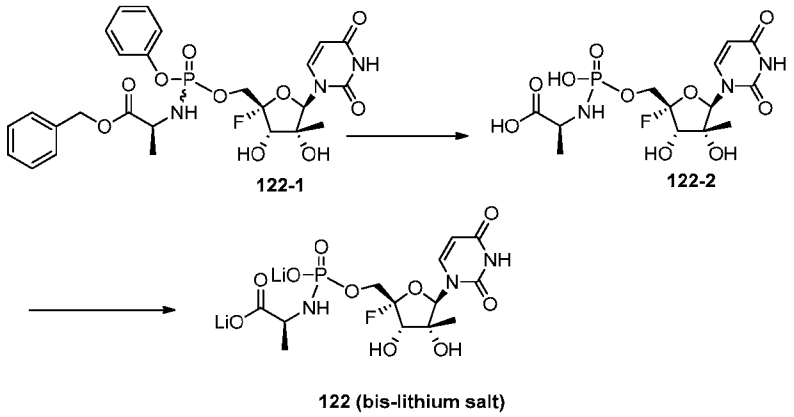
EXAMPLE 82
COMPOUNDS 120 AND 119



120 119

[0586] The diastereomers of compound **8** were separated by RP-HPLC. A gradient of 25-52%ACN in H_2O over 26 minutes on a Synergi Hydro RP 30x250 m 4u particle column (Phenomenex PN 00G-4375-U0-AX) eluted compound **119** (24.8 mins) and compound **120** (25.3 mins). Pure fractions were lyophilized to produce a white powder. Compound **119**: ^{31}P-NMR (DMSO-d6) 3.492 ppm; MS: m/z: 584 M-1. Compound **120**: ^{31}P-NMR (DMSO-d6) 3.528 ppm; MS: m/z: 584 M-1.

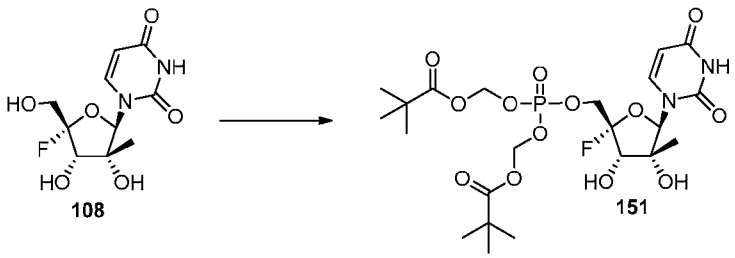
EXAMPLE 83
COMPOUND 122, Bis-lithium Salt



[0587] Compound **122-1** was synthesized using a procedure similar for preparing compound **2** using alanine benzyl ester hydrochloride. LCMS: m/z 592 $[M-1]^-$.

[0588] To a solution of **122-1** (1.1 g, 1.85 mmol) in dioxane (15 mL) and water (3 mL) was added aqueous triethylammonium acetate (2M, 2 mL, 4 mmol) followed by Pd-C (10%, 100 mg). The mixture was hydrogenated (balloon) for 2 h, and monitored by HPLC. The catalyst was filtered off, and the filtrate was concentrated to dryness. The residue was suspended in 3% solution of lithium perchlorate in acetone (25 mL). The solid was isolated by filtration, rinsed with acetone and dried under vacuum to give compound **122** (bis-lithium salt) (731 mg, 90%). LCMS: m/z 426 $[M-1]^-$.

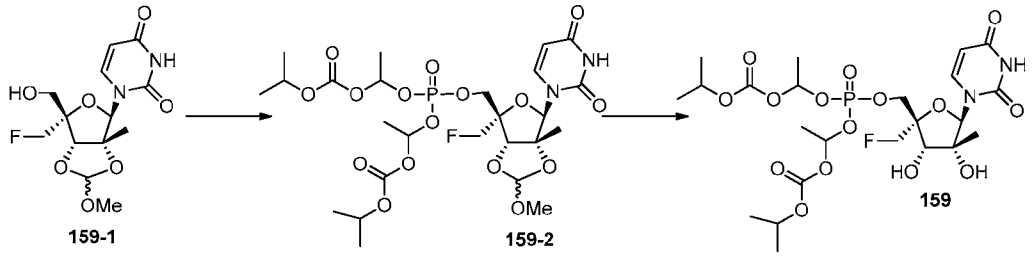
EXAMPLE 84
COMPOUND 151



[0589] Compound **108** (40 mg, 0.14 mmol) and triethylammonium bis(pivaloyloxymethyl)phosphate (0.21 mmol, prepared from 80 mg of bis(pivaloyloxymethyl)phosphate and 30 µL of Et_3N) were rendered anhydrous by coevaporating with pyridine, followed by toluene. The evaporated residue was dissolved in anhydrous THF (2 mL) and cooled in an ice-bath. Diisopropylethyl amine (73 µL, 3 eq.),

BopCl (71 mg, 2 eq.), and 3-nitro-1,2,4-triazole (32 mg, 2 eq.) were added. The mixture was stirred at 0 °C for 90 mins. The mixture was then diluted with EtOAc, washed with sat. aq. $NaHCO_3$ and brine, and dried (Na_2SO_4). Purification on silica gel column with CH_2Cl_2 /i-PrOH (4-10% gradient) followed by RP-HPLC purification (A: water, B: MeCN) yielded compound **151** (13 mg, 16%). MS: m/z = 1167 (2M-1).

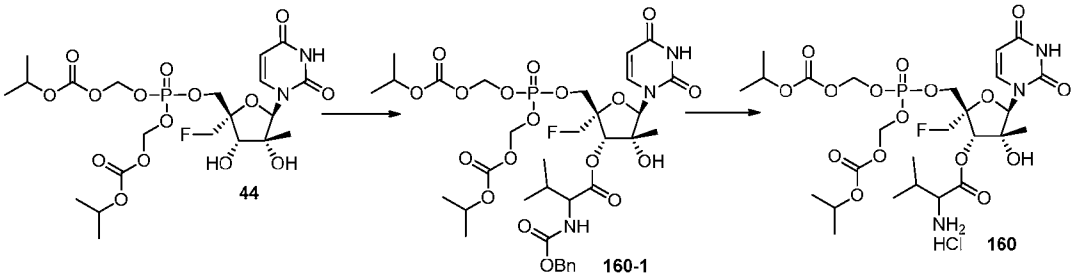
EXAMPLE 85
COMPOUND 159



[0590] To a solution of triethylammonium bis(isopropyloxycarbonyloxyethyl-1)phosphate (0.28 mmol, prepared from 100 mg of bis(isopropyloxycarbonyloxyethyl-1)phosphate and 40 µL of Et_3N) in THF was added **159-1** (60 mg, 0.18 mmol). The mixture was evaporated and rendered anhydrous by coevaporating with pyridine follow by toluene. The evaporated residue was dissolved in anhydrous THF (2.5 mL) and cooled in an ice-bath. Diisopropylethyl amine (94 µL, 3 eq.) was added, followed by BOP-Cl (92 mg, 2 eq.) and 3-nitro-1,2,4-triazole (41 mg, 2 eq.). The mixture was stirred at 0 °C for 90 mins., diluted with EtOAc and washed with sat. aq. $NaHCO_3$ and brine, and dried (Na_2SO_4). The residue was purified on a silica gel column with CH_2Cl_2/i-PrOH (3-10% gradient) to yield **159-2** (19 mg, 17%).

[0591] A solution of **159-2** (19 mg, 0.03 mmol) in 80% aq. HCOOH was stirred at RT for 90 mins., and then concentrated. The residue was coevaporated with toluene and then with MeOH containing small amount of Et_3N (1 drop). Purification on a silica gel column with CH_2Cl_2/MeOH (4-10% gradient) yielded compound **159** (5 mg, 26%). MS: m/z = 629 [M-1].

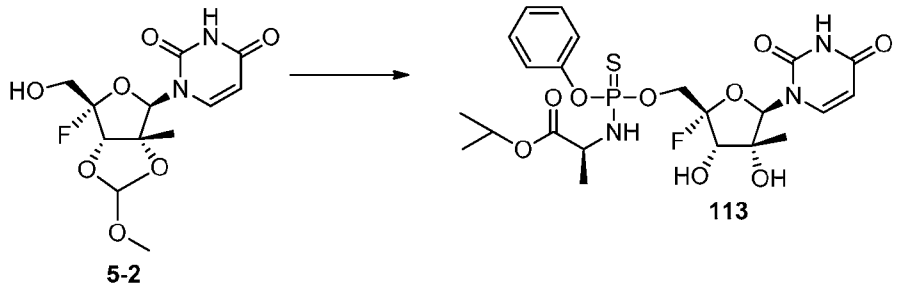
EXAMPLE 86
COMPOUND 160



[0592] A mixture of benzyloxycarbonyl-L-valine (55 mg, 0.22 mmol) in THF (1 mL) and CDI (36 mg, 0.22 mmol) was stirred at RT for 1.5 h and then at 40 °C for 20 mins. The solution was added to a mixture of compound **44** (122 mg, 0.2 mmol) and DMAP (3 mg, 0.03 mmol) in DMF (1.5 mL) and TEA (0.75 mL) at 80 °C. The mixture was stirred at 80 °C for 1 h. After cooling, the mixture was concentrated, and the residue partitioned between *tert*-butyl methyl ether and water. The organic layer was washed with 0.1 N citric acid, sat. aq. $NaHCO_3$ and brine, and dried (Na_2SO_4). The residue was purified on a silica gel column with CH_2Cl_2/i-PrOH (4-10% gradient) to yield **160-1** (83 mg, 50%) as a colorless foam.

[0593] To a solution of **160-1** (83 mg, 0.1 mmol) in EtOH were added HCl (4 N in dioxane; 50 µL, 2 eq.) and 10% Pd/C (5 mg). The mixture was stirred under H_2 atmosphere (normal pressure) for 1 h. The catalyst was removed by filtration through a Celite pad, and the filtrate evaporated to yield compound **160** (50 mg) as a white solid. MS: m/z = 702 [M+1].

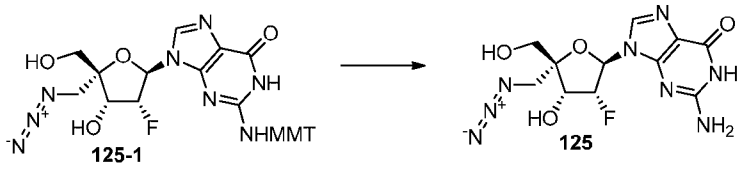
EXAMPLE 87
COMPOUND 113



[0594] Compound **5-2** (32 mg, 0.1 mmol) was dissolved in dry THF (3 mL) and 2M solution of isopropylmagnesium bromide in THF (0.1 mL) was added at 0 °C. The reaction was left for 1 h at RT, and phenyl(isopropyl-L-alaninyl) thiophosphorochloridate

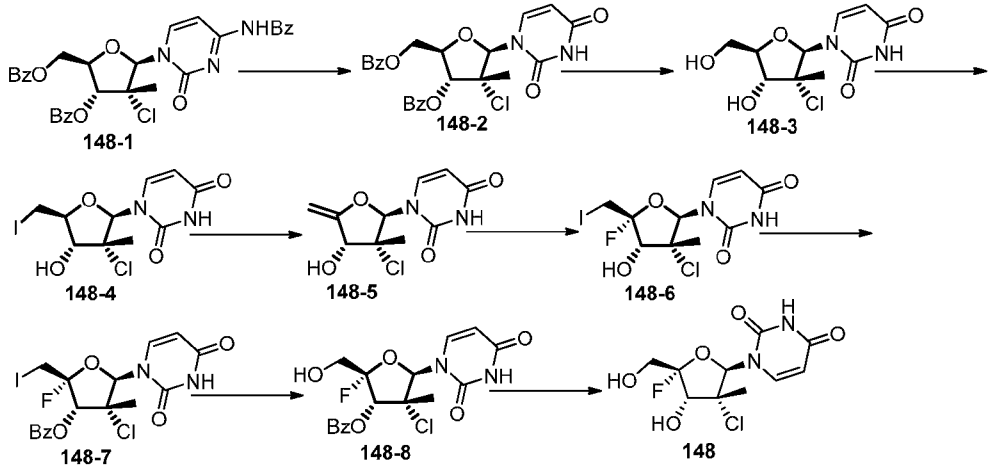
was added (0.3 mmol). The mixture was left overnight at RT. LSMS analysis showed about 20% of unreacted starting material. The same amount of Grignard reagent and thiophosphorochloridate were added, and the mixture was heated at 37 ^{0}C for 4 h. The reaction was quenched with NH_4Cl. The product was extracted with EA, washed with brine, dried over Na_2SO_4, and evaporated. The resulting oil was dissolved in 80% formic acid (4 mL) and in 1 h evaporated. Compound **113** was purified by RP HPLC in gradient of methanol in water from 30% to 95% on Synergy 4u Hydro-RP column (Phenominex) yielding a colorless solid. Compound **113** (7 mg, yield 12.5%). MS 560.0 (M-H).

EXAMPLE 88
COMPOUND 125



[0595] Compound **125-1** (109 mg) was dissolved in 80% HCOOH (15 mL) and kept for 3 h at RT, then evaporated. The residue was treated with NH_3/MeOH for 1 h at RT to remove formyl-containing side-products. After evaporation compound **125** was purified by crystallization using methanol to yield compound **125** (52 mg, 86%). MS: 339.6 [M-1], 679.7 (2M-1).

EXAMPLE 89
COMPOUND 148



[0596] Compound **148-1** (15.0 g, 25.55 mmol) was treated with 90% HOAc (150 mL) at RT. The mixture was stirred at 110 ^{o}C for 12 h, and then concentrated at a low

pressure. The residue was dissolved in DCM, and the solution was washed with brine. The organic phase was dried over anhydrous Na_2SO_4, and then concentrated at a low pressure. The residue was purified by column chromatography (5% MeOH in DCM) to give **148-2** (11.0 g, 88.9%) as a white solid.

[0597] Compound **148-2** (12.0 g, 24.79 mmol) was treated with NH_3 in MeOH (200 mL, 7 M) at RT. The solution was stirred at RT for 12 h, and then concentrated at a low pressure. The residue was purified by column chromatography (10% MeOH in DCM) to give **148-3** (6.5 g, 95.0%) as a white solid.

[0598] To a stirred suspension of **148-3** (4.3 g, 15.58 mmol), PPh_3 (8.16 g, 31.15 mmol), imidazole (2.11 g, 31.15 mmol) and pyridine (15 mL) in anhydrous THF (45 mL) was added a solution of I_2 (7.91 g, 31.15 mmol) in THF (100 mL) dropwise at 0 °C. The mixture was slowly warmed to RT and stirred overnight. The mixture was quenched with MeOH (100 mL). The solvent was removed at a low pressure, and the residue was re-dissolved in a mixture of EA and THF (0.2 L, 10:1). The organic phase was washed with sat. $Na_2S_2O_3$ aq. (2x). The aqueous phase was extracted with a mixture of EA and THF (0.2 L, 10:1, 2x). The concentrated organic phase was dried over anhydrous Na_2SO_4. The residue was purified on a silica gel column (0-10% MeOH in DCM) to afford **148-4** (5.1 g, 85.0%) as a white solid.

[0599] Compound **148-4** (800 mg, 2.07 mmol) was dissolved in a mixture of DBU (4 mL) and THF (4 mL) at RT under N_2. The solution was stirred at RT for 1 h. The mixture was neutralized with HOAc, and extracted with a mixture of EA and THF (10:1, 40 mL). The organic phase was washed with brine, and dried over anhydrous Na_2SO_4. The concentrated organic phase was purified by column chromatography (0-10% MeOH in DCM) to give **148-5** (240 mg, 44.9%) as a white solid.

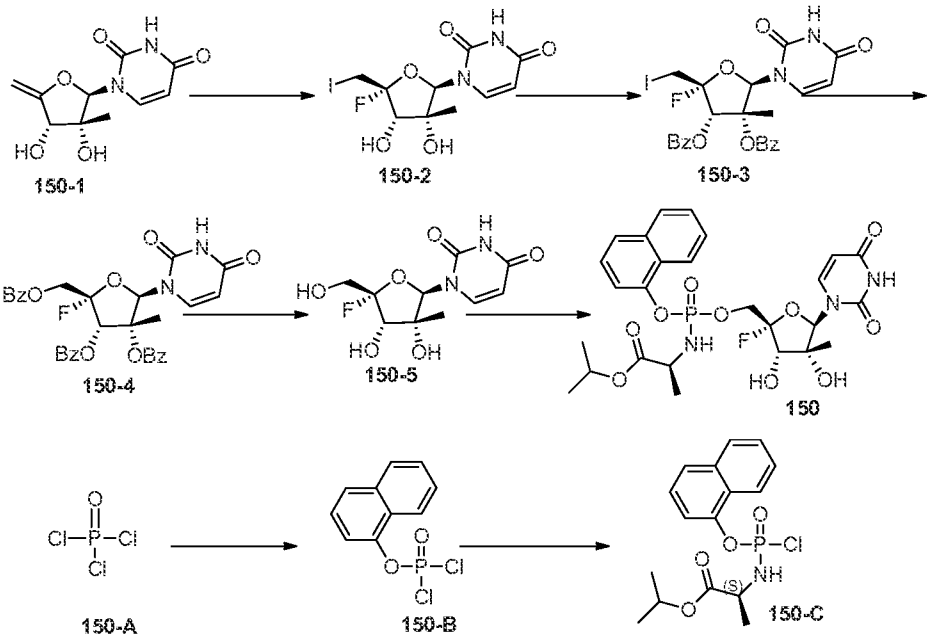
[0600] To an ice-cooled solution of **148-5** (1.20 g, 4.65 mmol) in anhydrous MeCN (12 mL) was added NIS (1.57 g, 6.97 mmol) and TEA•3HF (1.12 g, 6.97 mmol) under N_2. The mixture was stirred at RT for 5 h. The reaction was quenched with sat. $NaHCO_3$ solution, and extracted with EA (3 x 100 mL). The organic phase was dried over anhydrous Na_2SO_4, and evaporated to dryness at low pressure. The residue was purified on a silica gel column (0-5% MeOH in DCM) to give **148-6** (0.91 g, 48.6%) as a white solid.

[0601] To a stirred solution of **148-6** (1.2 g, 2.97 mmol) in anhydrous DCM (12 mL) was added BzCl (0.83 g, 5.94 mmol), TEA (0.6 g, 5.94 mmol) and DMAP (0.72 g, 5.94 mmol) successively at RT. The mixture was stirred at RT for 12 h. The reaction was quenched with water, and extracted with EA (3 x 60 mL). The organic phase was concentrated at low pressure. The residue was purified by column chromatography (0-5% MeOH in DCM) to give **148-7** (1.2 g, 66.2%) as a white solid.

[0602] Tetra-butyl ammonium hydroxide (25.78 mL, 51.78 mmol) was neutralized with TFA (4.3 mL) to pH=4, and the solution was added to a solution of **148-7** (1.09 g, 2.14 mmol) in DCM (30 mL). *m*-CPBA (1.85 g, 10.74 mmol) was added portion-wise under vigorous stirring, and the mixture was stirred for 12 h. The mixture was diluted with EA (100 mL), and washed with sat. sodium bicarbonate. The organic phase was concentrated at low pressure. The residue was purified by column chromatography (50% EA in PE) to give **148-8** (350 mg, 41.1%) as a white solid.

[0603] Compound **148-8** (280 mg, 0.704 mmol) was treated with NH_3 in MeOH (10 mL, 7 M) at RT. The mixture was stirred at RT for 2 h. The mixture was concentrated at a low pressure. The residue was purified by column chromatography (0-10% MeOH in DCM) to give compound **148** (110 mg, 53.1%) as a white solid. ESI-LCMS: m/z 295.1 $[M+H]^+$.

EXAMPLE 90
COMPOUND 150



[0604] To an ice-cooled solution of **150-1** (10 g, 42 mmol) in anhydrous MeCN (200 mL) was added TEA•3HF (10 g, 62.5 mmol) and NIS (28 g, 126 mmol). The mixture was stirred at RT for 1.5 h, and monitored by LCMS. After the reaction was completed, the mixture was concentrated at a low pressure. The residue was purified by silica gel column chromatography (15% MeCN in DCM) to give **150-2** (12 g, 74%) as a yellow solid.

[0605] To a solution of **150-2** (22 g, 57 mmol) in anhydrous DCM (200 mL) was added DMAP (21 g, 171 mmol) and BzCl (17.6 g, 125 mol). The mixture was stirred for 5 h at RT, and monitored by LCMS. The solution was washed with sat. $NaHCO_3$ solution and brine, and extracted with EA. The organic phase was dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated at low pressure. The residue was purified by silica gel column chromatography (20% EA in PE) to give **150-3** (30 g, 88%) as a white foam.

[0606] To a solution of **150-3** (6.5 g, 11 mmol) in anhydrous DMF (270 mL) was added NaOBz (15.8 g, 110 mmol) and 15-crown-5 (29 g, 132 mmol). The mixture was stirred at 95 °C for 48 h. The precipitate was removed by filtration, and the organic solvent was removed at low pressure. The residue was dissolved in EA (200 mL), and the solution was washed with sat. $NaHCO_3$ solution, and brine. The organic layer was dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated at low pressure. The residue

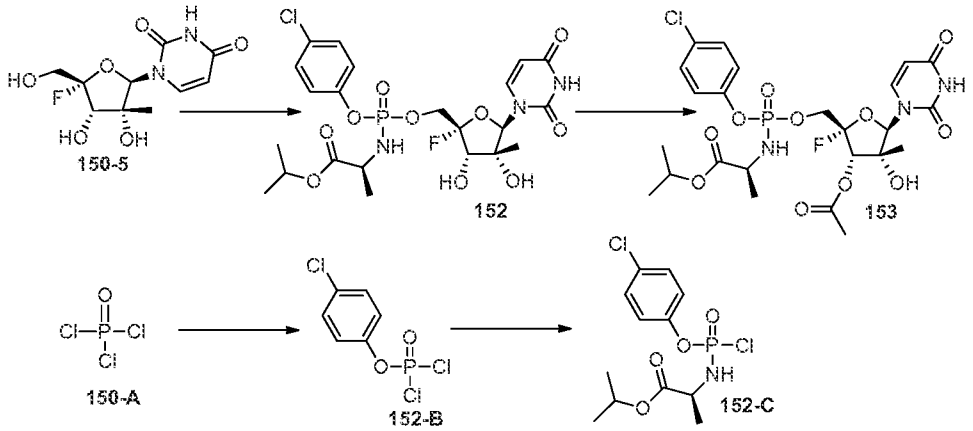
was purified by silica gel column chromatography (20% EA in PE) to give **150-4** (3 g crude, 46.1%) as an oil.

[0607] Compound **150-4** (3 g, crude) was treated with NH_3 in MeOH (120 mL, 7 M). The mixture was stirred for 3 h and monitored by TLC. The solution was concentrated at low pressure. The residue was purified by silica gel column chromatography (10% isopropanol in DCM) to give **150-5** (1.0 g, 67%) as a white solid. ^{1}H-NMR (CD_3OD, 400 mHz) δ = 1.19(s, 3H), 3.76-3.82 (m, 2H), 4.02 (d, J = 19.8 Hz, 1H), 5.70 (d, J = 8.07 Hz, 1H), 6.27 (s, 1H), 7.89 (d, J = 8.07 Hz, 1H).

[0608] Compound **150-5** (100 mg, 0.36 mmol) was co-evaporated with toluene 3 times. To a stirred solution of **150-5** (100 mg, 0.36 mmol) in a mixture of MeCN (1.0 mL) and NMI (295 mg, 3.6 mmol) was added a solution of **150-C** (255.6 mg, 0.72 mmol, preparation described below) in MeCN (0.5 mL) at 0 ^{0}C. The mixture was stirred at RT overnight. The reaction was quenched with water, and diluted with EA (20 mL). The organic layer was washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4. The organic phase was concentrated at low pressure. The residue was purified on a silica gel column (5% *i*-PrOH in DCM) to give the crude product. The product was purified by prep-HPLC (0.1% HCOOH in water and MeCN) to give compound **150** (46.7 mg, 23.3%) as a white solid. ESI-LCMS: m/z 618 $[M+Na]^+$.

[0609] To a stirred solution of **150-A** (2.0 g, 13.16 mmol) and naphthalen-1-ol (1.89 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 ^{o}C. After addition, the mixture was gradually warmed to RT, and stirred for 2 h. The solution was cooled to -78 ^{o}C, and (S)-isopropyl 2-aminopropanoate hydrochloride (2.20 g, 13.16 mmol) in DCM (20 mL) was added, followed by TEA (2.66 g, 26.29 mmol) in DCM (20 mL) dropwise. The mixture was gradually warmed to RT, and stirred for 2 h. The organic solvent was removed at low pressure. The residue was dissolved in methyl-butyl ether. The precipitate was filtered, and the filtrate was concentrated at low pressure. The residue was purified on a silica gel column (anhydrous DCM) to give **150-C** (1.0 g, 24.8%) as a colorless oil.

EXAMPLE 91
COMPOUNDS 152 AND 153

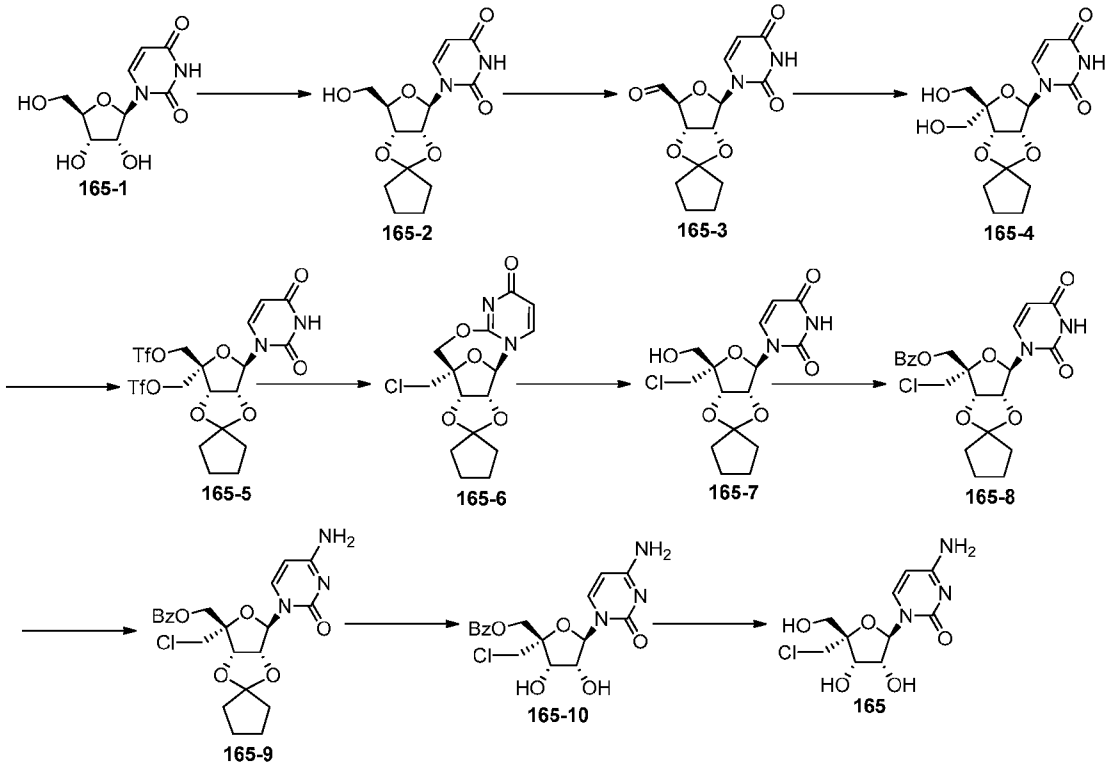


[0610] To a solution of **150-5** (300 mg, 1.08 mmol) and NMI (892 mg, 10 mmol) in anhydrous MeCN (4 mL) was added a solution of **152-C** (736 mg, 2 .17 mmol, preparation described below) in anhydrous MeCN (1 mL) dropwise at 0 °C. The mixture was stirred at RT overnight. The reaction was quenched with water, and diluted with EA (30 mL). The organic layer was washed with water and brine. The organic phase was dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by a silica gel column (iPrOH in DCM from 1% to 5%) to give crude compound **152** (276 mg, crude). Crude compound **152** (96 mg) was purified by prep-HPLC (0.1% HCOOH in water and MeCN) to give pure compound **152** (46 mg, 47.9%) as a white solid. ESI-LCMS: m/z 560 $[M - F]^+$.

[0611] To a solution of compound **152** (180 mg, 0.31 mmol) in anhydrous pyridine (6 mL) was added acetic anhydride (158 mg, 1.54 mmol) dropwise at 0 °C. The mixture was stirred at RT overnight. The solution was quenched with water and concentrated at a low pressure. The residue was dissolved in EA (10 mL), and washed with brine. The organic layer was dried over anhydrous Na_2SO_4. The organic phase was concentrated at low pressure. The residue was purified by silica gel column (*i*-PrOH in DCM from 1% to 3%) to give crude compound **153** (172 mg). Crude compound **153** was purified by prep-HPLC (0.1% HCOOH in water and MeCN) to give pure compound **153** (46 mg, 23.8%) as a white solid. ESI-LCMS: m/z 602.3 $[M - F]^+$.

[0612] Compound **152-C** (1.02 g, 23%, a colorless oil) was prepared using a procedure similar to the preparation of **150-C** using **150-A** (2.00 g, 13.16 mmol) and 4-chlorophenol (1.68 g, 13.16 mmol).

EXAMPLE 92
COMPOUND 165



[0613] To a solution of **165-1** (5 g, 0.02 mol), cyclopentanone (5.25 g, 0.06 mol, 4.5 eq.) and trimethoxymethane (6.52 g, 0.06 mol, 3 eq.) in MeCN (80 mL) was added TSOH•H_2O (1.95 g, 0.01 mol). The mixture was heated at 80 °C overnight. The mixture was concentrated at low pressure. The residue was purified by column chromatography (20% EA in PE) to give **165-2** (3.8 g, 60%) as a white oil.

[0614] To a solution of **165-2** (5 g, 0.16 mol) in MeCN (50 mL, anhydrous) was added IBX (5.33 g, 0.019 mol, 1.11 eq.) at RT. The mixture was heated at 80 °C for 5 h. The mixture was cooled to RT and filtered. The filtrate was concentrated to give **165-3** (4.5 g, purity: 90 %).

[0615] To a solution of **165-3** (5 g, 0.016 mol) and CH_2O (3.6 mL) in 1,4-dioxane (50 mL) was added NaOH solution (11.3 mL, 2 N) at RT. The mixture was stirred for 5 h at RT. $NaBH_4$ (1.48 g, 0.038 mol) was added at 0 °C, and stirred for 1 h. The reaction was quenched with H_2O (30 mL) and extracted with EA (3 x 30 mL). The organic layer was washed by brine, dried over anhydrous Na_2SO_4, and concentrated at low pressure. The

residue was purified by column chromatograph (50% EA in PE) to give **165-4** (2.1 g, 38%) as a white oil.

[0616] To a stirred solution of **165-4** (3 g, 0.0088 mol) and pyridine (3.51 mL, 5 eq.) in DCM (27 mL) was added Tf_2O (3.27 mL, 0.019 mol) at -35 °C. The mixture was slowly warmed to 0°C and stirred for 2 h at 0 °C. The mixture was washed with sat. $NaHCO_3$ solution and extracted with DCM (3 x 30 mL). The organic layer was separated and washed by brine, dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by column chromatography (5% EA in PE) to give **165-5** (2.65 g, 39%) as a white oil.

[0617] To a solution of **165-5** (12.3 g, 0.02 mol) in DMF (20 mL) was added NaH (0.977 g, 0.024 mol) at 0 °C. The mixture was stirred for 3 h at RT. The mixture was treated with LiCl (2.6 g, 0.062 mol), and then stirred for 2 h. The reaction was quenched with H_2O (20 mL) and extracted with EA (3 x 30 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by column chromatography (20% EA in PE) to give **165-6** (3.11 g, 45%) as a white oil.

[0618] To a solution of **165-6** (12 g, 0.035 mol) in THF (120 mL) was added NaOH solution (38.8 mL, 0.038 mol) at 0 °C, and stirred for 3 h. at RT. The mixture was adjusted to pH=7 with HCl (1.0 N) solution, and extracted with EA (3 x 80 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by column chromatography to give **165-7** (7.58 g, 60%) as a white solid.

[0619] **165-7** (3 g, 8.0 mmol) was co-evaporated with toluene (30 mL). To a solution of **165-7** (3 g), DMAP (100 mg) and TEA (2.5 mL, 2 eq.) in DCM (30 mL) was added Bz_2O (2.01 g, 1 eq.) at 0°C. The mixture was stirred for 3 h at RT. The reaction was quenched with H_2O, and extracted with DCM (3 x 30 mL). The DCM layer was dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by column chromatography (5% EA in PE) to give **165-8** (3.1 g, 80%) as a white solid.

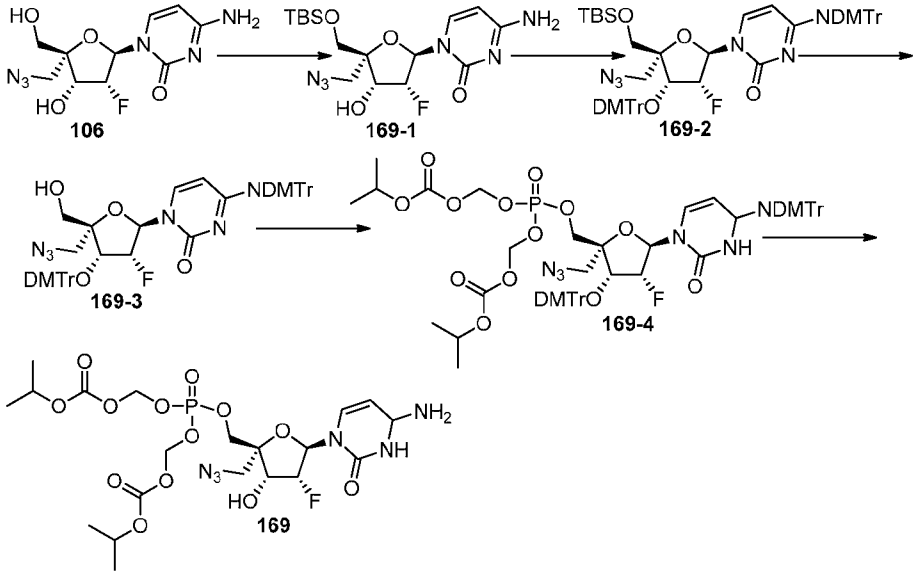
[0620] To a solution of **165-8** (200 mg, 0.43 mmol) in CH_3CN (2 mL, anhydrous) was added TPSCl (260 mg, 2 eq.), TEA (0.13 mL) and DMAP (106.4 mg, 2 eq.). The mixture was stirred for 2 h at RT.

[0621] The mixture was treated with $NH_3 \cdot H_2O$ (33%, 1.33 mL), and stirred for 2 h at RT. The reaction was quenched with 1 N HCl (30 mL), and extracted with DCM (3 x 30 mL). The DCM layer was dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by column chromatography to give **165-9** (85 mg, 50%) as a white solid.

[0622] **165-9** (100 mg, 0.216 mmol) was treated with HCOOH (7 mL, 80%), and stirred for 3 h at RT. The mixture was concentrated at low pressure. The residue was purified by column chromatography (90% EA in PE) to give **165-10** (51 mg, 60%) as a white solid.

[0623] **165-10** (270 mg, 0.68 mmol) was treated with NH_3 in MeOH (10 mL) at -60°C. The mixture was warmed to RT. The mixture was stirred for 6 h. at RT. The mixture was concentrated at low pressure. The residue was purified by reverse HPLC to give **165** (60 mg, 30%) as a white solid.

EXAMPLE 93
COMPOUND 169



[0624] To a solution of **106** (200 mg, 0.67 mmol) in anhydrous pyridine (5 mL) was added TBSCl (120 mg, 0.8 mmol) at RT. The mixture was stirred overnight, and the reaction mixture was diluted with EA. The mixture was washed with $NaHCO_3$ aq. solution and brine. The organic layer was dried, filtered and concentrated to give residue, which was

purified by silica gel column chromatography (5% MeOH in DCM to 25% MeOH in DCM to give **169-1** (153 mg, 55%) as a white solid.

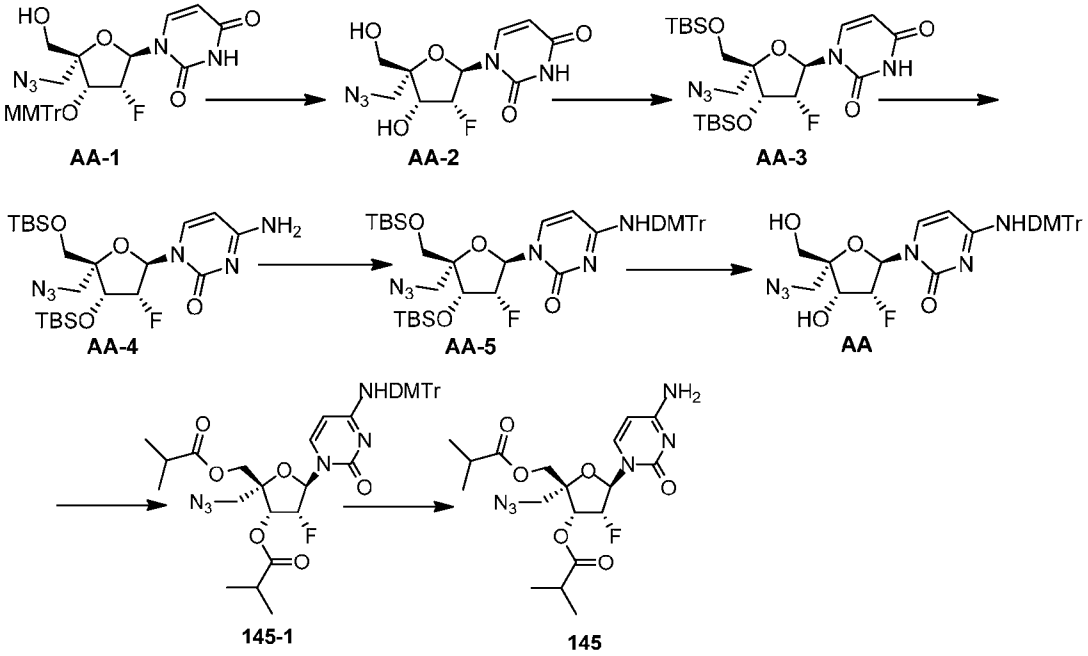
[0625] To a solution of **169-1** (54 mg, 0.13 mmol) in anhydrous DCM (2 mL) was added collidine (95 μL, 0.78 mmol), DMTrCl (262 mg, 0.78 mmol) and $AgNO_3$ (66 mg, 0.39 mmol) at RT. The mixture was stirred overnight, and then diluted with DCM (5 mL). The mixture was filtered through a pre-packed celite funnel, and the filtrate was washed with $NaHCO_3$ aq. solution, 1.0 M citric acid solution and then brine. The organic layer was dried over Na_2SO_4, and concentrated at low pressure to give a residue. The residue was purified by silica gel column chromatography (25% EA in PE to 100 %EA) to give **169-2** (83.5 mg, 63.6%).

[0626] To a solution of **169-2** (83 mg, 0.081 mmol) in THF (1 mL), was added a 1M solution of TBAF in THF (0.122 mL, 0.122 mmol) at ice bath temperature. The mixture was stirred for 1.5 h. The mixture was diluted with EA, and washed with water and brine. The organic layer was dried and concentrated to give the crude product, which was purified by silica gel column chromatography (DCM to 5% MeOH in DCM) to give **169-3** (66.6 mg, 91%) as a white foam.

[0627] **169-3** (66.6 mg, 0.074 mmol) was co-evaporated with toluene and THF (3x). Bis(POC)phosphate (33 mg, 0.96 mmol) was added, and then co-evaporated with toluene (3x). The mixture was dissolved in anhydrous THF (1.5 mL) and cooled in an ice bath (0 to 5 0C). 3-nitro-1,2,4-triazole (13 mg, 0.11 mmol), diisopropylethyl amine (54 μL, 0.3 mmol), and BOP-Cl (28 mg, 0.11 mmol) were added successively. The mixture was stirred 2 h at 0 to 5 ^{0}C, diluted with EtOAc, washed with 1.0M citric acid, sat. aq. $NaHCO_3$ and brine, and dried with Na_2SO_4. The residue was purified on silica (10 g column) with CH_2Cl_2:i-PrOH (4-10% gradient) to give **169-4** (68 mg, 76%) as a white solid.

[0628] **169-4** (68 mg, 0.07 mmol) was dissolved in 80% HCOOH. The mixture was stirred at RT for 2 h. The solvents were evaporated at RT and co-evaporated with toluene (3x). The residue was dissolved in 50% CH_3CN/H_2O, was purified on a reverse-phase HPLC (C18) using CH_3CN and H_2O. The product was lyophilization to give **169** (4.8 mg, 14%) as a white foam. ESI-LCMS: m/z = 613.1 $[M+H]^+$, 1225.2 $[2M+H]^+$.

EXAMPLE 94
COMPOUND 145



[0629] **AA-1** (2.20 g, 3.84 mmol) was dissolved in 80% HCOOH (40 mL) at RT (18 °C). The mixture was stirred at RT for 12 h. The solvent was removed at low pressure. The residue was purified by column chromatography using 50% EA in Hexane to give **AA-2** (1.05 g, 91.3%) as a white solid.

[0630] To a stirred solution of **AA-2** (1 g, 3.32 mmol) in anhydrous pyridine (20 mL) was added TBSCl (747 mg, 4.98 mmol) and imidazole (451 mg, 6.64 mmol) at RT (16 °C) under N_2 atmosphere. The mixture was stirred at RT for 4 h. The resulting solution was concentrated to dryness under reduced pressure, and the residue was dissolved in EA (100 mL). The solution was washed with sat. $NaHCO_3$ solution and brine, and dried over anhydrous $MgSO_4$. The solution was concentrated to dryness, and the residue was purified on a silica gel column using 20% EA in Hexane to give **AA-3** (1.4 g, 79.5%) as a white solid.

[0631] To a stirred solution of **AA-3** (1.50 g, 2.83 mmol, 1.00 eq.) in anhydrous CH_3CN (28 mL) was added TPSCl (1.71 g, 5.80 mmol, 2.05 eq.), DMAP (691.70 mg, 5.66 mmol, 2.00 eq.) and TEA (573.00 mg, 5.66 mmol, 2.00 eq.) at RT (15 °C). The mixture was stirred for 2 h. $NH_3.H_2O$ (20 mL) was added, and the mixture was stirred for 3 h. The mixture was extracted with EA (3 x 60 mL). The organic phase was washed with brine,

dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified on a silica gel column (30% EA in PE) to give **AA-4** (2.3 g, crude) as a yellow foam.

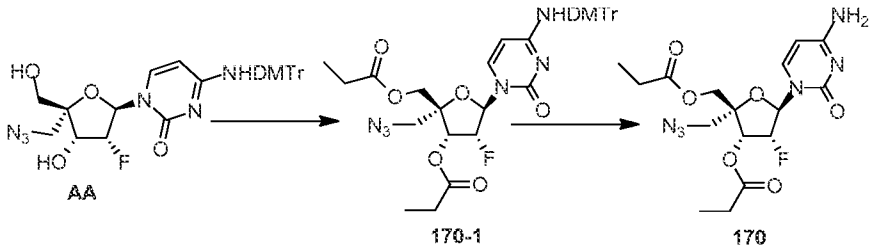
[0632] To a stirred solution of **AA-4** (1.90 g, 2.34 mmol) in anhydrous DCM (20 mL) was added DMTrCl (1.82 g, 3.49 mmol) and 2,4,6-trimethylpyridine (1.00 g, 8.25 mmol) at RT (15 °C) under N_2 atmosphere. The mixture was stirred at RT for 12 h. MeOH (20 mL) was added. The mixture was filtered, and the filtrate was concentrated to dryness. The residue was dissolved in EA (80 mL). The solution was washed with brine, dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified on a silica gel column (5% MeOH in DCM) to give **AA-5** (1.4 g, crude) as a white solid.

[0633] **AA-5** (2.40 g, 2.60 mmol) was dissolved in TBAF (10 mL, 1M in THF). The mixture was stirred at RT (15 °C) for 30 mins. The mixture was concentrated to dryness, and the residue was dissolved in EA (60 mL). The solution was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified on a silica gel column (5% MeOH in DCM) to give **AA** (1.50 g, 95.8%) as a white solid. ESI-MS: m/z 625.3 $[M+Na]^+$.

[0634] To a solution of **AA** (60.0 mg, 99.57 μmol, 1.00 eq.) in pyridine (1 mL) was added isobutyric anhydride (31.50 mg, 199.13 μmol, 2.00 eq.) in 1 portion at RT (15 °C) under N_2 atmosphere. The mixture was stirred at RT for 12 h. The mixture was concentrated, and the residue was partitioned between EA and water. The combined organic phases were washed with water and brine, and dried over anhydrous Na_2SO_4. The mixture was filtered, and the filtrate was concentrated to dryness. The residue was purified by silica gel chromatography (30% EA in PE) to afford **145-1** (59.00 mg, 79.77%) as a white solid.

[0635] **145-1** (57.00 mg, 76.74 μmol, 1.00 eq.) was dissolved in 80% CH_3COOH (8 mL). The solution was stirred at RT (15 °C) for 12 h. The mixture was concentrated to dryness. The residue was purified on a silica gel column (2.5% MeOH in DCM) to give **145** (23.00 mg, 68.05%) as a white foam. ESI-MS: m/z 441.2 $[M+H]^+$, 463.2$[M+Na]^+$.

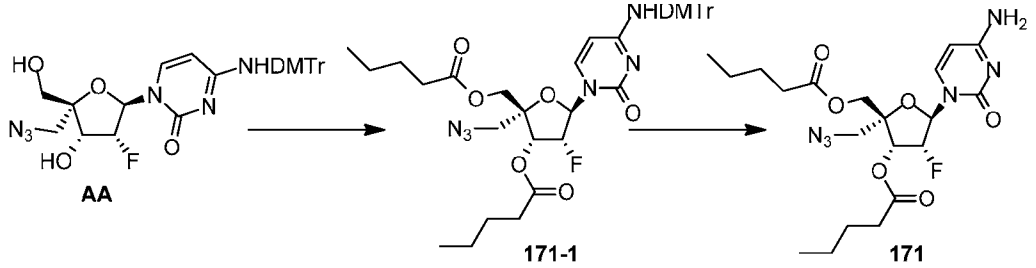
EXAMPLE 95
COMPOUND 170



[0636] **170-1** was prepared in similar manner as **145-1** using **AA** (60.00 mg, 99.57 μmol, 1.00 eq.) in pyridine (1 mL) and propionic anhydride (25.92 mg, 199.13 μmol, 2.00 eq.). **170-1** (white solid, 56.00 mg, 78.69%).

[0637] **170** was prepared in similar manner as **145** using **170-1** (54.00 mg, 75.55 μmol, 1.00 eq.) **170** (white foam, 18.00 mg, 57.78%). ESI-MS: m/z 413.1 $[M+H]^+$.

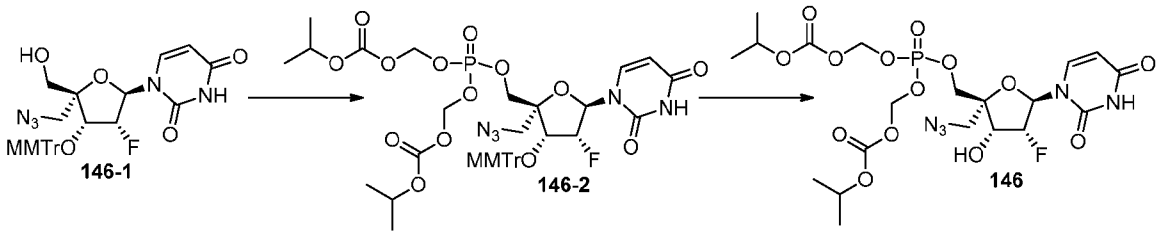
EXAMPLE 96
COMPOUND 171



[0638] **171-1** was prepared in similar manner as **145-1** using **AA** (62.00 mg, 102.89 μmol, 1.00 eq.) in pyridine (1 mL) and pentanoic anhydride (38.32 mg, 205.77 μmol, 2.00 eq.). **171-1** (white solid, 60.00 mg, 75.65%).

[0639] **171** was prepared in similar manner as **145** using **171-1** (75.00 mg, 97.30 μmol, 1.00 eq.) **171** (white foam, 28.00 mg, 61.43%). ESI-MS: m/z 469.2 $[M+H]^+$.

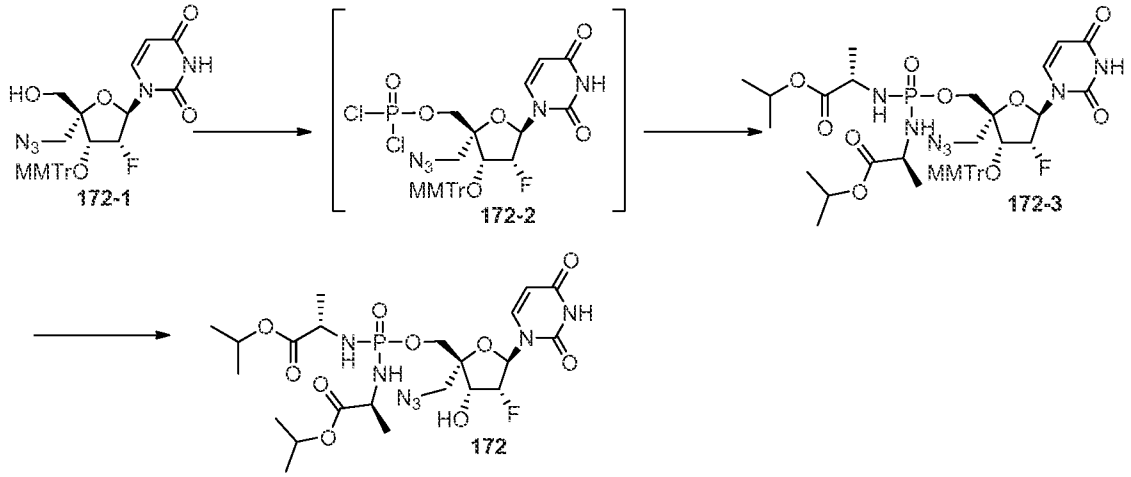
EXAMPLE 97
COMPOUND 146



[0640] **146-2** (40.7 mg, 53%) was prepared in the same manner from **146-1** (50 mg, 0.087 mmol) and bis(isopropyloxycarbonyloxymethyl)phosphate (58 mg,0.175 mmol) with DIPEA (75 μL, 0.52 mmol), BOP-Cl (66.2 mg, 0.26 mmol), and 3-nitro-1,2,4-triazole (30 mg, 0.26 mmol) in THF (0.4 mL) in a similar manner as **169-4**.

[0641] **146-2** (40 mg, 0.045 mmol) was dissolved in anhydrous CH_3CN (0.5 mL), and 4N HCl in dioxane (34 μL, 0.135 mmol) was added at 0 to 5 °C. The mixture was stirred at RT for 3 h. Anhydrous EtOH (200 μL) was added. The solvents were evaporated at RT and co-evaporated with toluene (3x). The residue was purified on silica (10 g column) with MeOH/CH_2Cl_2 (5-7% gradient) and lyophilized give **146** (15.4 mg, 76%) as a white foam. ESI-LCMS: m/z = 614.15 $[M+H]^+$, 1227.2 $[2M+H]^+$.

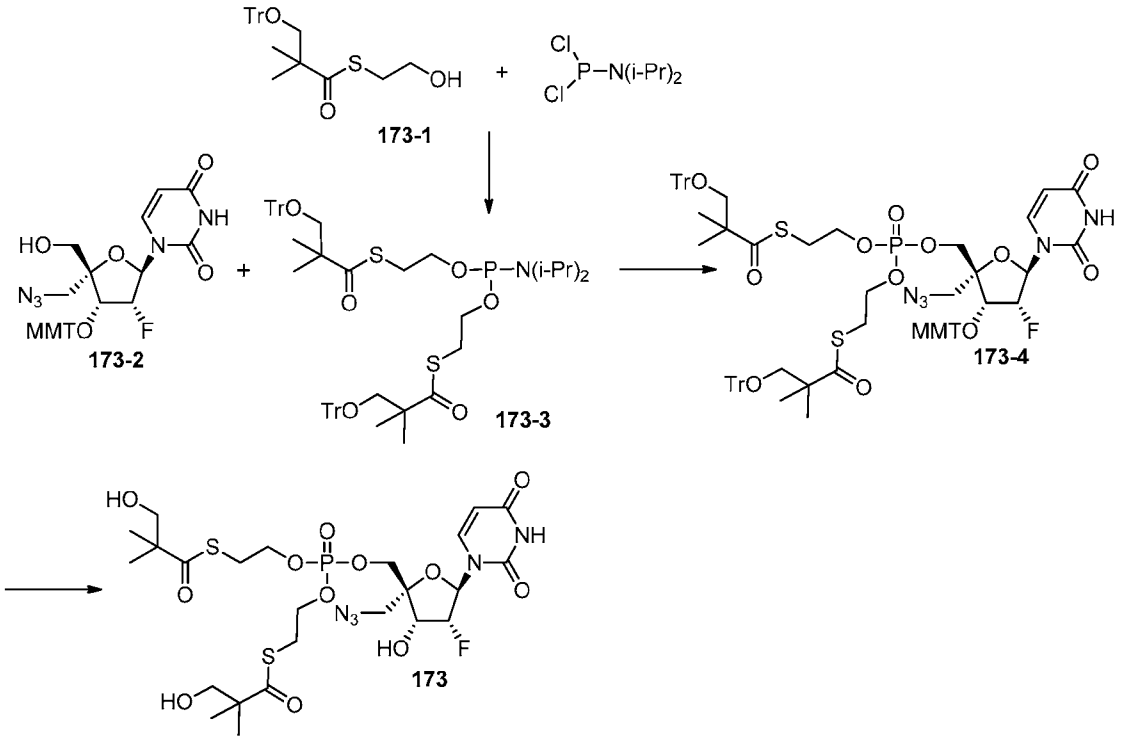
EXAMPLE 98
COMPOUND 172



[0642] **172-1** (100 mg, 0.174 mmol) was co-evaporated with anhydrous pyridine (3x), toluene (3x) and CH_3CN (3x), and dried under high vacuum overnight. **172-1** was dissolved in CH_3CN (2 mL). A proton sponge (112 mg, 0.52 mmol), $POCl_3$ (49 uL, 0.52 mmol) were added at 0 to 5 °C. The mixture was stirred for 3 h at 0 to 5 °C to give intermediate **172-2**. To this solution, L-alanine isopropyl ester hydrochloride (146 mg, 0.87 mmol), and TEA (114 uL, 1.74 mmol) were added. The mixture was stirred for 4 h at 0 to 5 °C. The mixture was stirred 2 h at 0 to 5 °C, then diluted with EtOAc. The mixture was washed with 1.0M citric acid, sat. aq. $NaHCO_3$ and brine, and dried with Na_2SO_4. The residue was purified on silica (10 g column) with CH_2Cl_2/MeOH (0-7% gradient) to give **172-3** (67 mg, 43.7%) as a white solid.

[0643] **172-3** (65 mg, 0.074 mmol) was dissolved in anhydrous CH_3CN (0.5 mL), and 4N HCl in dioxane (55 µL, 0.22 mmol) was added at 0 to 5 °C. The mixture was stirred at RT for 1.5 h. A second portion of 4N HCl in dioxane (15 µL) was added, and the mixture stirred at RT for 2 h. Anhydrous EtOH (300 µL) was added. The solvents were evaporated at RT and co-evaporated with toluene (3x). The residue was dissolved in 50% CH_3CN/H_2O, was purified on a reverse-phase HPLC (C18) with CH_3CN and water, and lyophilized to give **172** (9 mg, 20%) as a white foam. ESI-LCMS: m/z = 608.15 $[M+H]^+$, 1215.3 $[2M+H]^+$.

EXAMPLE 99
COMPOUND 173

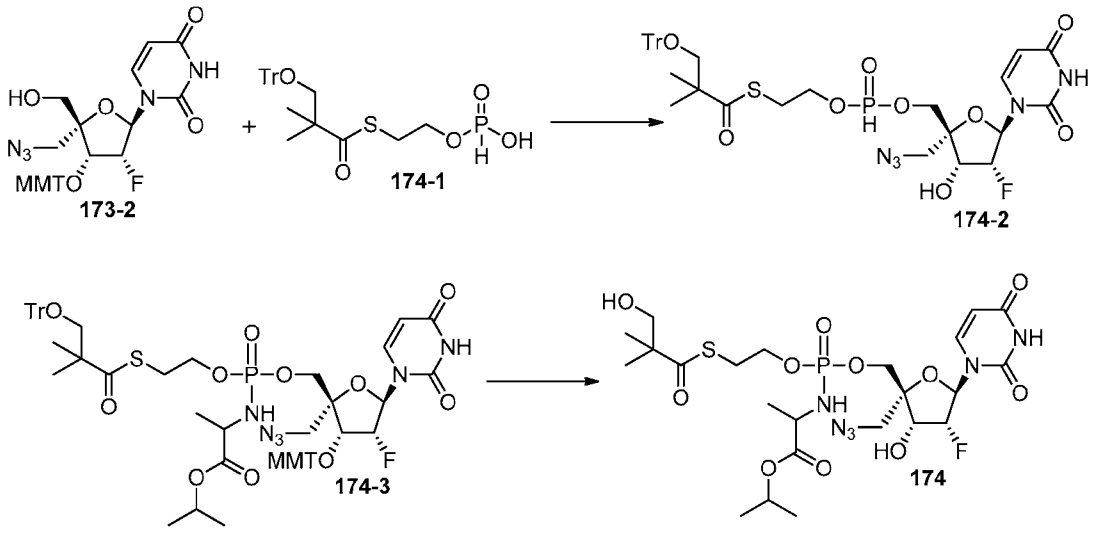


[0644] A solution of **173-1** (4.7 g, 11.2 mmol; prepared according to the procedure Villard et al., *Bioorg. Med. Chem.* (2008) 16:7321-7329) and Et_3N (3.4 mL, 24.2 mmol) in THF (25 mL) was added dropwise over 1 h to a stirred solution of *N,N*-diisopropylphosphorodichloridite (1.0 mL, 5.5 mmol) in THF (35 mL) at -75 °C. The mixture was stirred at RT for 4 h. The mixture was filtered, and the filtrate concentrated. The oily residue was purified on silica gel column with EtOAc/hexanes (2-20% gradient) to give **173-3** (1.4 g, 26%).

[0645] To a solution of **173-2** (50 mg, 0.08 mmol) and **173-3** (110 mg, 0.11 mmol) in CH_3CN (1.0 mL) was added 5-(ethylthio)tetrazole (0.75 mL, 0.16 mmol; 0.25 M in CH_3CN). The mixture was stirred at RT for 1 h. The mixture was cooled to -40 °C, and a solution of 3-chloroperoxybenzoic acid (37 mg, 0.16 mmol) in CH_2Cl_2 (0.3 mL) was added. The mixture was warmed to RT over 1 h. The reaction was quenched with 7% $Na_2S_2O_3$ solution in sat aq. $NaHCO_3$. The mixture was diluted with EtOAc, and the layers were separated. The organic layer was washed with brine and dried with Na_2SO_4. The solvent was evaporated, and the residue was purified on a silica gel column with EtOAc/hexanes (30-100% gradient) to give **173-4** (52 mg, 45%).

[0646] A solution of **173-4** (52 mg, 0.036 mmol) in MeCN (0.5 mL) and HCl (45 µL; 4 N in dioxane) was stirred 20 h at RT. The reaction was quenched with MeOH, and the solvents were evaporated. The residue was co-evaporated with toluene and purified on a silica gel column with MeOH/CH_2Cl_2 (4-10% gradient) to give **173** (14 mg, 51%). ESI-LCMS: m/z = 702 $[M+H]^+$.

EXAMPLE 100
COMPOUND 174



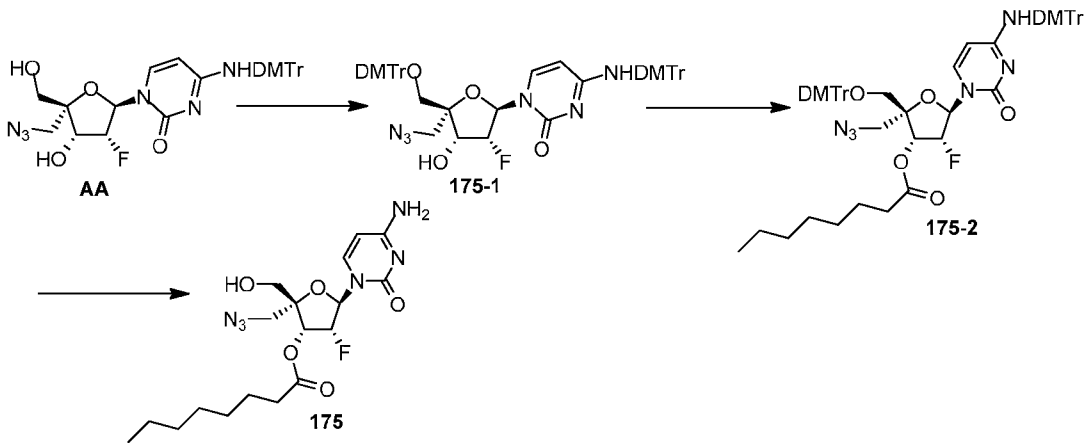
[0647] A mixture of **174-1** (0.14 g, 0.24 mmol; prepared according to the procedure described in WO 2008/082601, filed Dec. 28, 2007) and **173-2** (120 mg, 0.2 mmol) was rendered anhydrous by evaporating with pyridine and then dissolved in pyridine (3 mL). Pivaloyl chloride (48 µL) was added dropwise at -15 °C. The mixture was stirred at -15 °C for 2 h. The reaction was quenched with sat. aq. NH_4Cl solution and diluted with

CH_2Cl_2. The organic layer was washed with brine and dried with Na_2SO_4. The solvents were evaporated, and the residue was purified on a silica gel column with EtOAc/hexanes (30-100% gradient) to give **174-2** (50 mg, 24%).

[0648] A mixture of **174-2** (43 mg; 0.04 mmol) in CCl_4 (0.8 mL), L-valine isopropyl ester hydrochloride (20 mg, 0.12 mmol) and Et_3N (33 µl, 0.24 mmol) was stirred at RT for 2 h. The mixture was diluted with EtOAc. The mixture was washed with sat. aq. $NaHCO_3$ and brine, and dried with Na_2SO_4. The solvents were evaporated, and the residue was purified on a silica gel column with i-PrOH/CH_2Cl_2 (2-10% gradient) to **174-3** (35 mg, 75%).

[0649] A solution of **174-3** (35 mg, 0.03 mmol) in MeCN (0.4 mL) and HCl (40 µL; 4 N in dioxane) was stirred 4 h at RT. The reaction was quenched with the addition of MeOH, and the solvents were evaporated. The residue was co-evaporated with toluene and purified on a silica gel column with MeOH/CH_2Cl_2 (4-10% gradient) to give **174** (11 mg, 56%). ESI-LCMS: m/z = 655 $[M+H]^+$.

EXAMPLE 101
COMPOUND 175



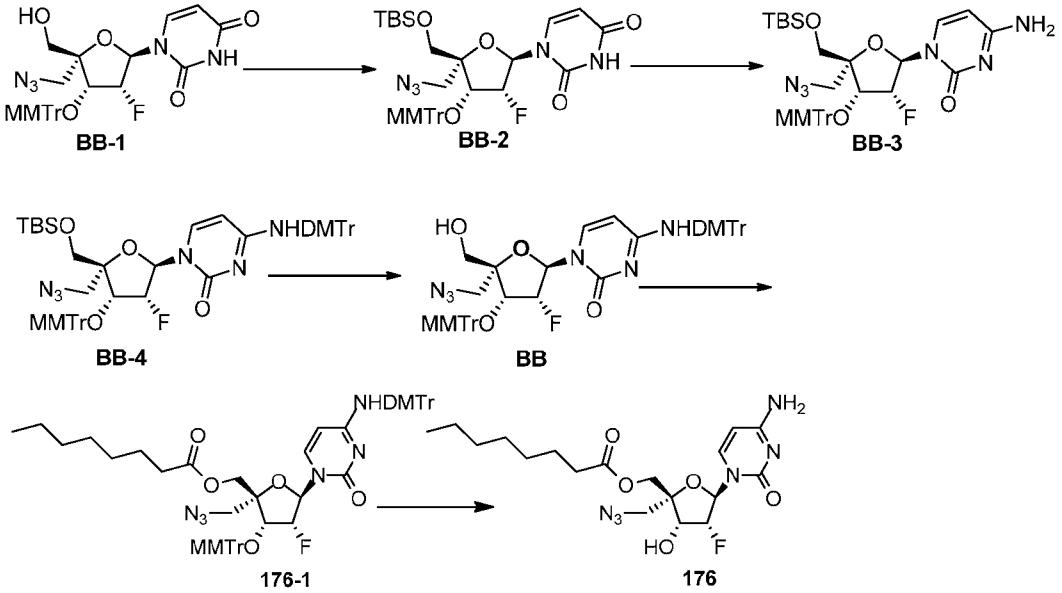
[0650] To a stirred solution of **AA** (300.0 mg, 497.83 µmol) in anhydrous pyridine (0.5 mL) was added DMTrCl (337.36 mg, 995.66 µmol) at RT (17 °C) under N_2 atmosphere. The solution was stirred at 50 °C~60 °C for 12 h. The mixture was concentrated to dryness under reduced pressure, and the residue was dissolved in EA (40 mL). The solution was washed with brine, dried over anhydrous $MgSO_4$, and concentrated to

dryness at low pressure. The residue was purified on a silica gel column using 20% EA in PE to give **175-1** (300 mg, 66.59%) as a white solid.

[0651] To a stirred solution of **175-1** (100.00 mg, 110.50 μmol) in anhydrous pyridine (0.5 mL) was added DMAP (6.75 mg, 55.25 μmol), DCC (22.80 mg, 110.50 μmol) and n-octanoic acid (31.87 mg, 221.00 μmol) at RT (18 °C) under N_2 atmosphere. The solution was stirred at RT for 12 h. The solution was concentrated to dryness under reduced pressure. The residue was purified on a silica gel column using 15% EA in PE to give **175-2** (98.00 mg, 86.0%) as a white foam.

[0652] **175-2** (90.00 mg, 87.28 μmol) was dissolved in 80% CH_3COOH (20 mL) at RT (16 °C). The mixture was stirred RT for 12 h. The reaction was quenched with MeOH, and the mixture was concentrated to dryness. The residue was purified on a silica gel column (5% MeOH in DCM) to give **175** (33.00 mg, 88.7%) as a white solid. ESI-MS: m/z 427.2 $[M+H]^+$.

EXAMPLE 102
COMPOUND 176



[0653] To a stirred solution of **BB-1** (500.00 mg, 0.87 mmol) in anhydrous pyridine (1 mL) was added TBSCl (236.5 mg, 1.57 mmol) at 20 °C under N_2. The solution was stirred at 50 °C~60 °C for 12 h. The solution was concentrated to dryness under reduced pressure. The residue was dissolved in EA (50 mL). The solution was washed with sat. $NaHCO_3$ solution and brine, and dried over anhydrous $MgSO_4$. The solution was filtered,

and the filtrate was concentrated to dryness. The residue was purified on a silica gel column to give **BB-2** (510.00 mg, 85.06%) as a white solid.

[0654] To a stirred solution of **BB-2** (430.00 mg, 625.15 mmol) in anhydrous MeCN (6 mL) was added TPSCl (368.65 mg, 1.25 mmol), DMAP (152.75 mg, 1.25 mmol) and TEA (126.52 mg, 1.25 mmol) at RT. The mixture was stirred for 2 h. NH_4OH (8 mL) was added, and the mixture stirred for 3 h. The mixture was extracted with EA (3 x 40 mL). The organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified on a silica gel column (25% EA in PE) to give **BB-3** (500 mg of crude) as a yellow foam.

[0655] To a stirred solution of **BB-3** (500 mg of crude, 0.72 mmol) in anhydrous DCM (7 mL) was added DMTrCl (365 mg, 1.0 mmol) and collidine (305 mg, 2.5 mmol) and $AgNO_3$ (184 mg, 1.08 mmol) at RT (15 °C) under N_2 atmosphere. The mixture was stirred at RT for 12 h. MeOH (5 mL) was added. The mixture was filtered, and the filtrate was concentrated to dryness. The residue was dissolved in EA (50 mL). The solution was washed with brine, dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified on a silica gel column (5% MeOH in DCM) to give **BB-4** (500 mg, 70.3%) as a white solid.

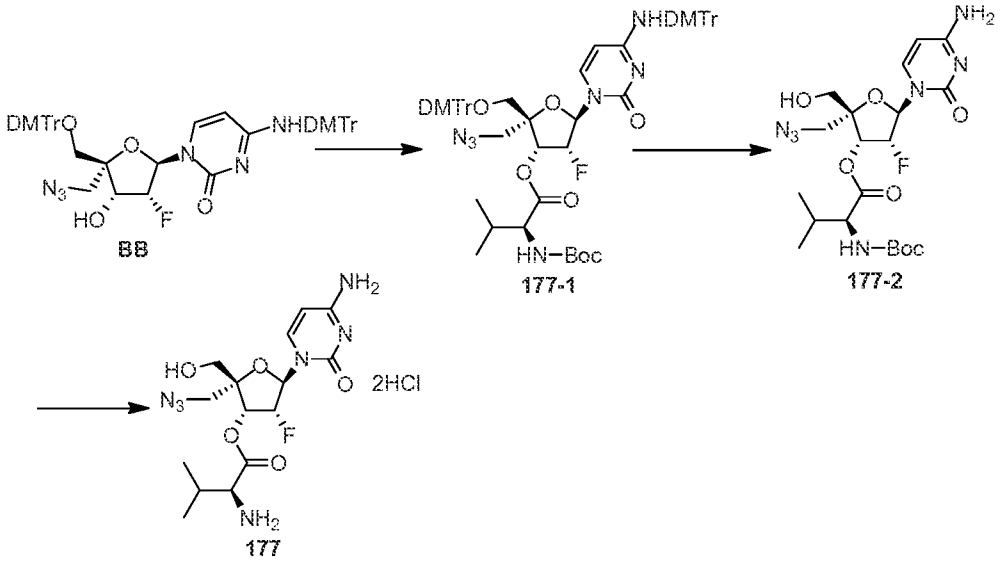
[0656] **BB-4** (1.00 g, 1.01 mmol) was dissolved in TBAF (5 mL, 1M in THF) and stirred at RT for 30 mins. The mixture was diluted with EA (100 mL). The mixture was washed with water and brine, and dried over anhydrous $MgSO_4$. The organic phase was concentrated to dryness. The residue was purified on the silica gel column (30% EA in PE) to give **BB** (0.80 g, 91.5%) as a white solid. ESI-MS: m/z 873.7 $[M+1]^+$.

[0657] To a solution of **BB** (100.00 mg, 114.29 μmol) in anhydrous pyridine (1.5 mL) was added DMAP (2.79 mg, 22.86 μmol), DCC (70.75 mg, 342.88 μmol) and n-octanoic acid (49.45 mg, 342.88 μmol) at RT (18 °C) under N_2 atmosphere. The solution was stirred at RT for 12 h. The solution was concentrated to dryness under reduced pressure. The residue was purified on a silica gel column using 15% EA in PE to give **176-1** (95.00 mg, 83.03%) as a white foam.

[0658] **176-1** (110.00 mg, 109.87 μmol) was dissolved in 80% CH_3COOH (25 mL) at RT (15°C). The mixture was stirred for 12 h. The reaction was quenched with

MeOH, and the solution was concentrated to dryness. The residue was purified on a silica gel column (5% MeOH in DCM) to give **176** (30.00 mg, 64.03%) as a white solid. ESI-MS: m/z 427.2 $[M+H]^+$.

EXAMPLE 103
COMPOUND 177

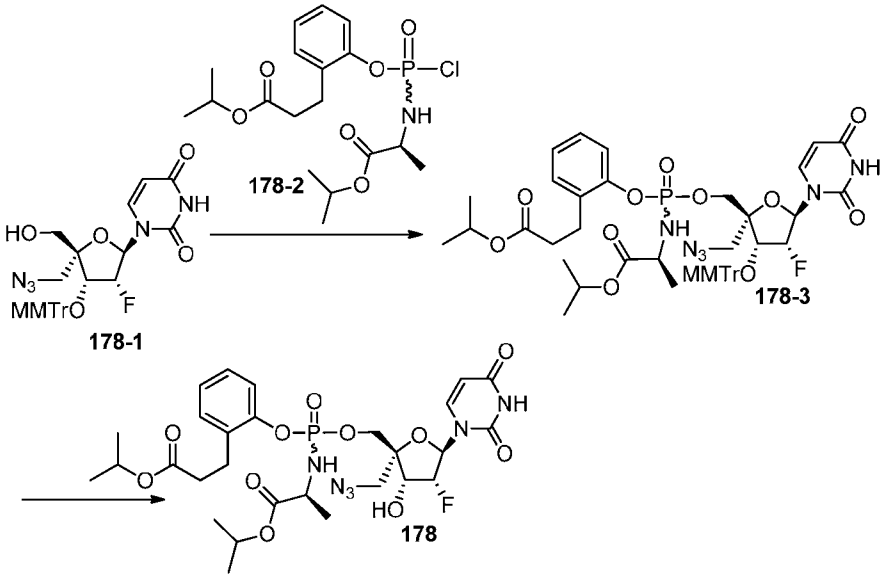


[0659] **177-1** was prepared in similar manner as **143-1** using **BB** (250.0 mg, 276.25 μmol), (2S)-2-(tert-butoxycarbonylamino)-3-methyl-butanoic acid (360.11 mg, 1.66 mmol) and TEA (83.86 mg, 828.75 μmol). **177-1** (white foam, 220.0 mg, 72.12%).

[0660] **177-2** was prepared in similar manner as **143-2** using **177-1** (230.00 mg, 208.29 μmol, 1.00 eq.). **177-2** (white foam, 80.00 mg, 77.66%).

[0661] **177** was prepared in similar manner as **143** using **177-2** (100.00 mg, 200.20 μmol, 1.00 eq.). **177** (white solid, 56 mg, 59.57 %). ESI-MS: m/z 400.0 $[M+H]^+$, 422.1$[M+Na]^+$; 799.1 $[2M+H]^+$, 821.2$[2M+Na]^+$.

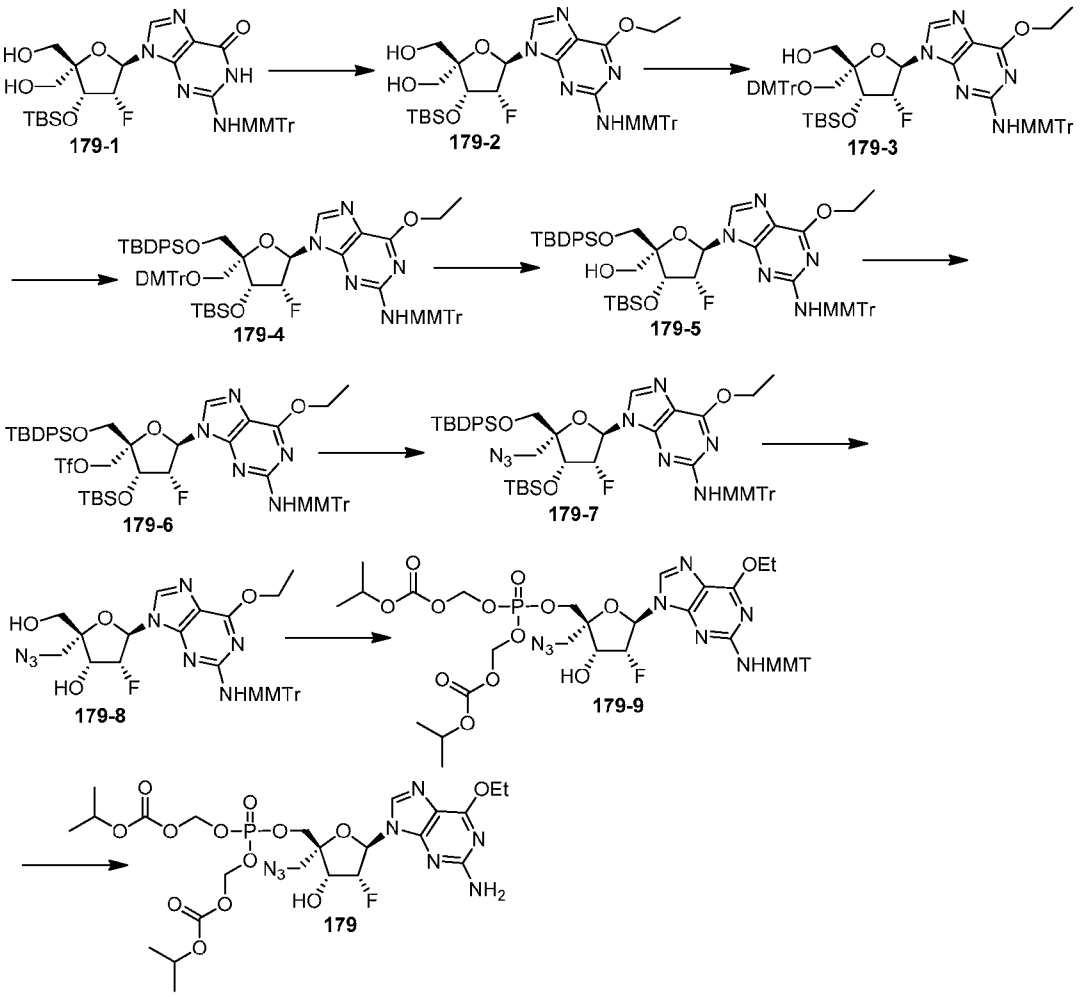
EXAMPLE 104
COMPOUND 178



[0662] To a stirred solution of **178-1** (100 mg, 0.175 mmol) in anhydrous CH_3CN (2.0 mL) was added N-methylimidazole (0.14 mL, 1.4 mmol) at 0 ^{0}C (ice/water bath). A solution of **178-2** (220 mg, 0.53 mmol, dissolved in 0.5 mL of CH_3CN), (prepared according to a general procedure described in Bondada, L. et al., *ACS Medicinal Chemistry Letters* (2013) 4(8):747-751) was added. The solution was stirred at 0 to 5 ^{o}C for 1 h and then stirred at RT for 16 h. The mixture was cooled to 0 to 5 ^{0}C, diluted with EA followed by addition of water (5 mL). The solution was washed with 1.0M citric acid, sat. aq. $NaHCO_3$ and brine, and dried with $MgSO_4$. The residue was purified on silica (10 g column) with EA/hexanes (25-100% gradient) to give **178-3** (56.4 mg, 33.7 %) as a white foam.

[0663] **178-3** (56mg, 0.0585 mmol) was dissolved in_anhydrous CH_3CN (0.7 mL), and 4N HCl in dioxane (44 µL, 0.176 mmol) was added at 0 to 5 ^{o}C. The mixture was stirred at RT for 2 h. 4N HCl in dioxane (20µL) was added. The mixture was stirred at RT for 2 h. Anhydrous EtOH (100 µL) was added. The solvents were evaporated at RT and co-evaporated with toluene (3x). The residue was purified on silica (10 g column) with MeOH/CH_2Cl_2 (1-7% gradient) and lyophilized to give **178** (27.6 mg, 69%) as a white foam. ESI-LCMS: m/z = 685.2$[M+H]^+$.

EXAMPLE 105
COMPOUND 179



[0664] To a stirred solution of **179-1** (1.92 g, 27.3 mmol), PPh_3 (1.43 g, 54.7 mmol), EtOH (0.25 g, 54.7 mmol) in anhydrous dioxane (20 mL) was added DIAD (1.11 g, 54.7 mmol) dropwise at 0 °C. The solution was stirred at 25 °C for 15 h. The reaction was quenched with water and extracted with EA. The mixture was washed with water and brine. The organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated in vacuum to dryness, and the residue was purified on a silica gel column (2% to 5% MeOH in DCM) to give **179-2** (1.43 g, 71%) as a white foam.

[0665] To a stirred solution of **179-2** (1.43 g, 19.6 mmol) in DMF (15 mL) was added TEA (0.59 g, 58.8 mmol) and DMTrCl (0.99 g, 29.4 mmol) at 0 °C. The solution was stirred at 25 °C for 12 h. The mixture was treated with MeOH (1 mL), and diluted with EA. The solution was washed with water and brine. The organic layer was dried over anhydrous

$NaSO_4$, and concentrated to dryness. The residue was purified on a silica gel column (2% MeOH in DCM) to give **179-3** (1.13 g, 56%) as a yellow solid.

[0666] To a stirred solution of **179-3** (1.13 g, 1.1mmol) in anhydrous pyridine (10 mL) was added TBDPSCl (0.91 g, 3.3 mmol) and $AgNO_3$ (0.61 g, 3.3 mmol). The mixture was stirred at 25 °C for 15 h. The solid was removed by filtration, and the filtrate was diluted with EA (50 mL). The solution was washed with brine. The organic layer was dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified on a silica gel column (2% MeOH in DCM) to give **179-4** (1.22 g, 88 %) as a white foam.

[0667] To a stirred solution of **179-4** (1.22 g, 1.0 mmol) in anhydrous DCM (15 mL) was added $Cl_2CHCOOH$ (0.6 mL) at -78 °C. The mixture was stirred at -20 °C for 1 h. The reaction was quenched with sat. aq. $NaHCO_3$ and extracted with DCM. The organic layer was dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by column chromatography (2% MeOH in DCM) to give **179-5** (0.52 g, 56%) as a white foam.

[0668] To a stirred solution of **179-5** (0.52 g, 0.5 mmol) in anhydrous DCM (15 mL) and pyridine (0.21 g, 2.5 mmol) was added Tf_2O (0.30 g, 1.0 mmol) in DCM (1 mL) dropwise at 0°C. The mixture was stirred at 0 °C for 15 mins. The reaction was quenched with ice water. The organic layer was separated and washed with water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated at low pressure to give **179-6** (442 mg crude) as a yellow foam.

[0669] To a stirred solution of **179-6** (442 mg, 0.4 mmol) in anhydrous DMF (5 mL) was added NaN_3 (131 mg, 2.0 mmol). The mixture was stirred at RT for 12 h. The reaction was quenched with water and extracted by EA (20 mL, 2x). The organic layer was washed with water and dried over Na_2SO_4. The organic phase was evaporated to dryness under reduced pressure. The residue was purified on a silica gel column (1%MeOH in DCM) to give **179-7** (352 mg, 88%) as a white foam.

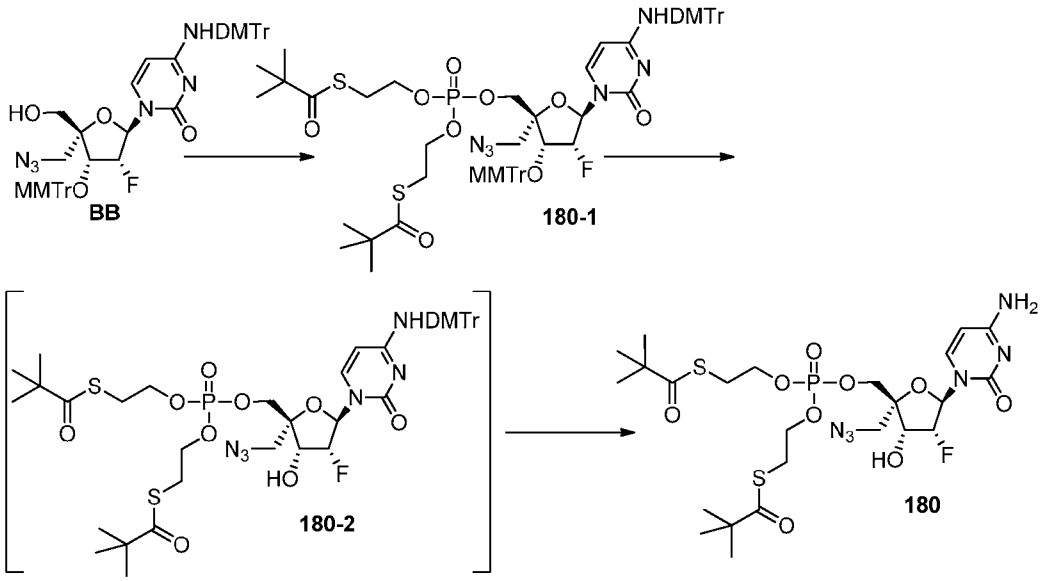
[0670] A mixture of **179-7** (352 mg, 0.35 mmol) and NH_4F (392 mg, 10.6 mmol) in MeOH (10 mL) was stirred at 80 °C for 12 h. The mixture was cooled to RT. The solid was removed by filtration. The solvent was concentrated under reduced pressure. The residue was purified on a silica gel column (2% to 5%MeOH in DCM) to give crude **179-8**

(151 mg). The crude product was purified by prep-HPLC (0.1% NH_4HCO_3 in water and CH_3CN) to give **179-8** (71.5 mg, 32%) as a white solid. MS: m/z 641$[M+H]^+$.

[0671] A mixture of **179-8** (64 mg, 0.1 mmol) and bis(pivaloyloxymethyl)phosphate, after rendered anhydrous by evaporating with toluene, was dissolved in CH_3CN (1 mL) and cooled to 0 °C. BopCl (40 mg, 0.15 mmol) and NMI (40 µL, 0.5 mmol) were added. The mixture was stirred at 0 °C for 2 h. EtOAc was added, and the mixture was washed with 0.5 N aq. citric acid, sat. aq. $NaHCO_3$ and brine, and then dried with Na_2SO_4. The solvents were removed, and the residue was purified on a silica gel column with 3% *i*-PrOH in CH_2Cl_2 to **179-9** (38 mg, 40%).

[0672] A solution of **179-9** (30 mg, 0.03 mmol) in CH_3CN (0.3 mL) and HCl (30 µL; 4 N dioxane) was stirred at RT for 100 mins. The reaction was quenched with EtOH, and the mixture was evaporated. The crude residue was purified on a silica gel column with *i*-PrOH/CH_2Cl_2 (3-10% gradient) to yield **179** (10 mg, 50%). ESI-LCMS: m/z = 681 $[M+H]^+$.

EXAMPLE 106
COMPOUND 180

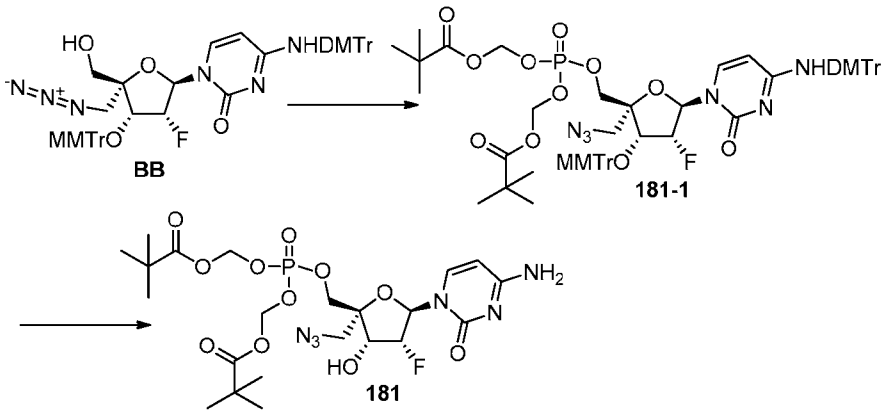


[0673] To a solution of **BB** (100 mg, 0.114 mmol) in anhydrous CH_3CN (2 mL) were added a solution of bis-SATE-phosphoroamidate (62.2 mg, 0.14 mmol) in CH_3CN (1 mL) followed by 5-ethylthio-1H-tetrazole in CH_3CN (0.25M; 0.56 mL, 0.14 mmol) at 0 to 5 °C dropwise. The mixture was stirred 2 h at 0 to 5 °C under Ar. A solution of 77% m-CPBA

(49 mg, 0.22 mmol) in DCM (1 mL) was added, and the mixture was stirred 2 h at 0 to 5 ^{0}C under Ar. The mixture was diluted with EtOAc (50 mL), washed with 1.0M citric acid, sat. $NaHCO_3$, and brine, and dried with $MgSO_4$. The mixture was filtered and the solvents were evaporated in vacuo. The residue was purified on silica (10 g column) with EA/hexanes (10-100% gradient) to give **180-1** (72 mg, 50.8 %) as a white solid.

[0674] **180-1** (72 mg, 0.056 mmol) was dissolved in anhydrous CH_3CN (1.0 mL), and 4N HCl in dioxane (87 µL, 0.35 mmol) was added at 0 to 5 °C. The mixture was stirred at RT for 2 h. Intermediate **180-2** was observed by LCMS. The solvents were evaporated at RT and co-evaporated with toluene (3x). The residue obtained was re-dissolved in 80% HCOOH (2 mL). The mixture was stirred at RT for 4.5 h. The solvents were evaporated at RT and co-evaporated with toluene (3x). Anhydrous EtOH (3 x 5 mL) was added. The residue was dissolved in 50% CH_3CN/H_2O, purified on a reverse-phase HPLC (C18) using CH_3CN and H_2O, and lyophilized to give **180** (19.2 mg) as a white foam. ESI-LCMS: m/z = 669.2 $[M+H]^+$, 1337.25 $[2M+H]^+$.

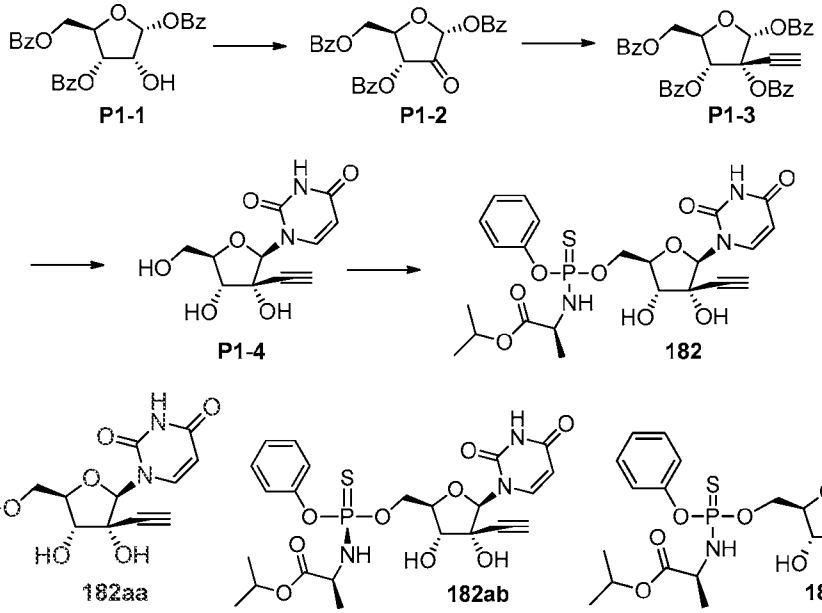
EXAMPLE 107
COMPOUND 181



[0675] **181-1** (98 mg, 72.6 %) was prepared in the same manner from **BB** (100 mg, 0.114 mmol) and bis(tert-butoxycarbonyloxymethyl)phosphate (83mg, 0.35 mmol) with DIPEA (126 µL, 0.69 mmol), BOP-Cl (87 mg, 0.34 mmol), and 3-nitro-1,2,4-triazole (39 mg, 0.34 mmol) in THF (1.5 mL) in the same manner as **169-4**.

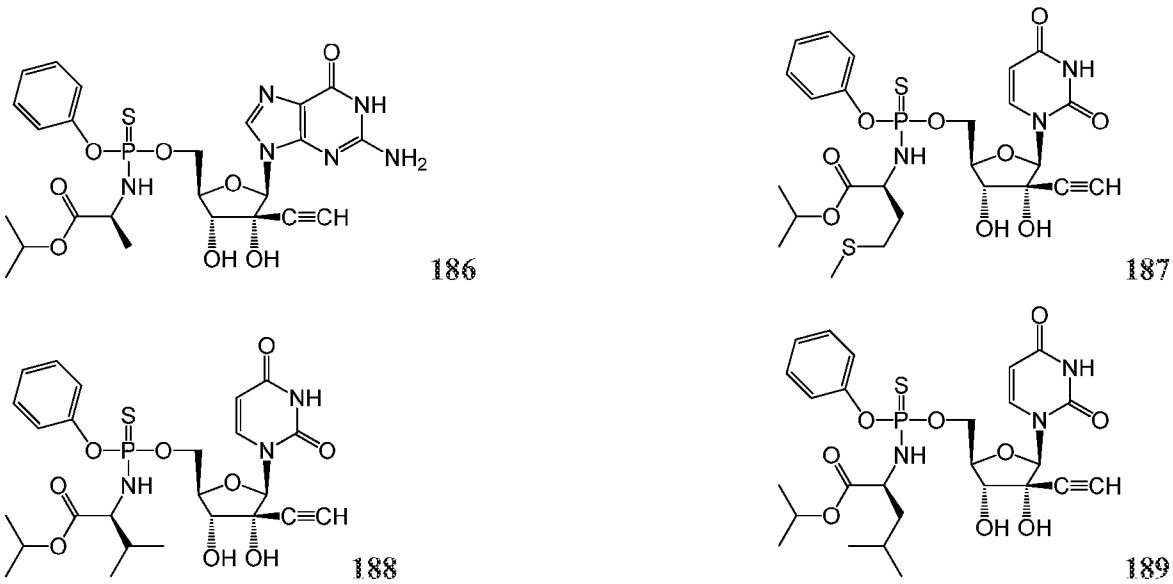
[0676] **181** (30.2 mg, 60%) was prepared from **181-1** (98 mg, 0.083 mmol) in the same manner as **146**. ESI-LCMS: m/z = 609.15 $[M+H]^+$, 1217.3 $[2M+H]^+$.

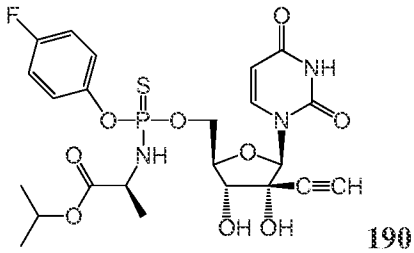
EXAMPLE 108
COMPOUNDS 182 and 183

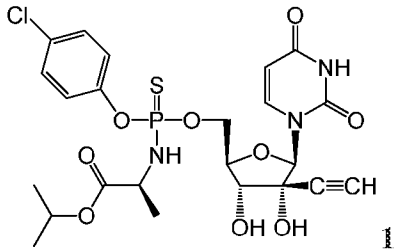


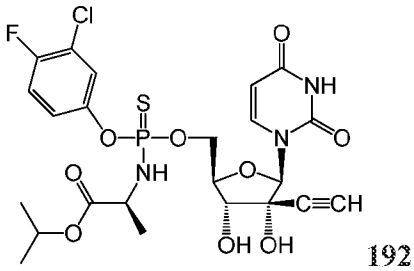
[0677] Compounds **182**, **182aa**, **182ab** and **183** were prepared as described in PCT Publication No. WO 2014/96680, published June 27, 2014. **182**: ESI-LCMS: m/z 554.0 $[M+H]^+$; **182aa** and **182ab**: Faster eluting diastereomer - ^{31}P NMR 67.1, LC/MS 552 $[M-1]^-$ Slower eluting diastereomer - ^{31}P NMR 67.9, LC/MS 552 [M–1]. **183**: ESI-MS: m/z 576.9 $[M+H]^+$.

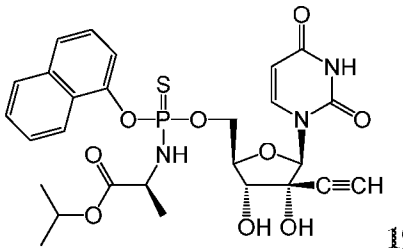
EXAMPLE 109
COMPOUNDS 186-201

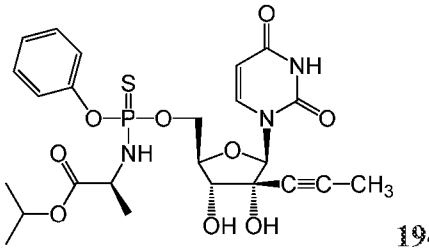


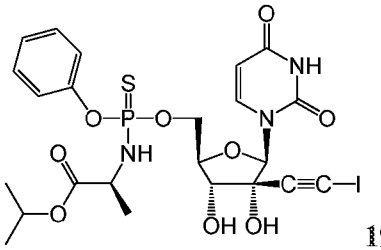

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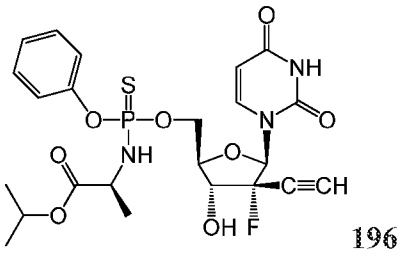

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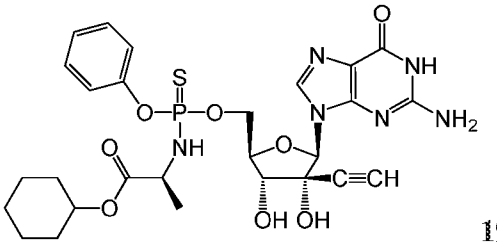

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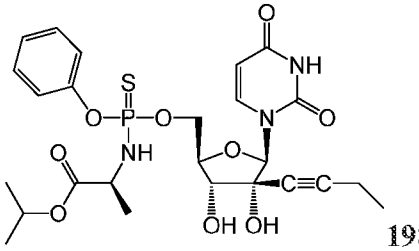

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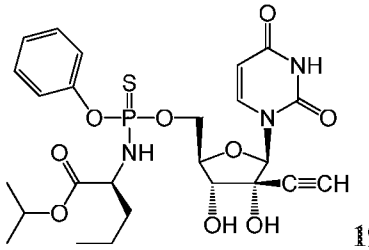

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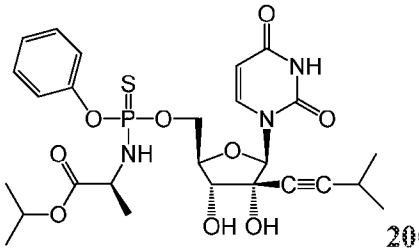

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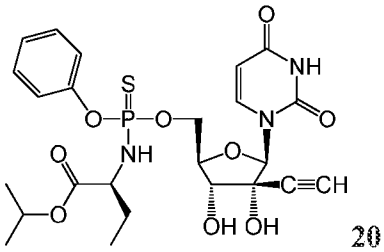

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197


198

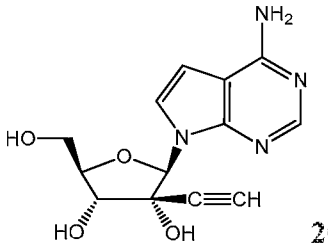

199


200


201

[0678] Compounds **186-201** were prepared as described in PCT Publication No. WO 2014/96680, published June 27, 2014. **186**: ESI-LCMS: m/z 593.0 $[M+H]^+$. **187:** ESI-LCMS: m/z 614.1 $[M+H]^+$. **188:** ESI-LCMS: m/z 582.1 $[M+H]^+$. **189:** ESI-LCMS: m/z 596.1 $[M+H]^+$. **190:** ESI-LCMS: m/z 672.0 $[M+H]^+$. **191:** ESI-LCMS: m/z 589.0 $[M+H]^+$. **192:** ESI-LCMS: m/z 606.0 $[M+H]^+$. **193:** ESI-LCMS: m/z 604.1 $[M+H]^+$. **194:** ESI-LCMS: m/z 568 $[M+H]^+$, 590 $[M+Na]^+$. **195:** ESI-LCMS: m/z 680 $[M+H]^+$. **196:** ESI-LCMS: m/z 578.0 $[M+Na]^+$. **197:** ESI-MS: m/z 633.1 $[M+H]^+$. **198:** ESI-LCMS: m/z 604 $[M+Na]^+$, 582 $[M+H]^+$. **199:** ESI-LCMS: m/z 582.0 $[M+H]^+$. **200:** ESI-LCMS: m/z 618 $[M+Na]^+$. **201:** ESI-LCMS: m/z 568.1 $[M+H]^+$.

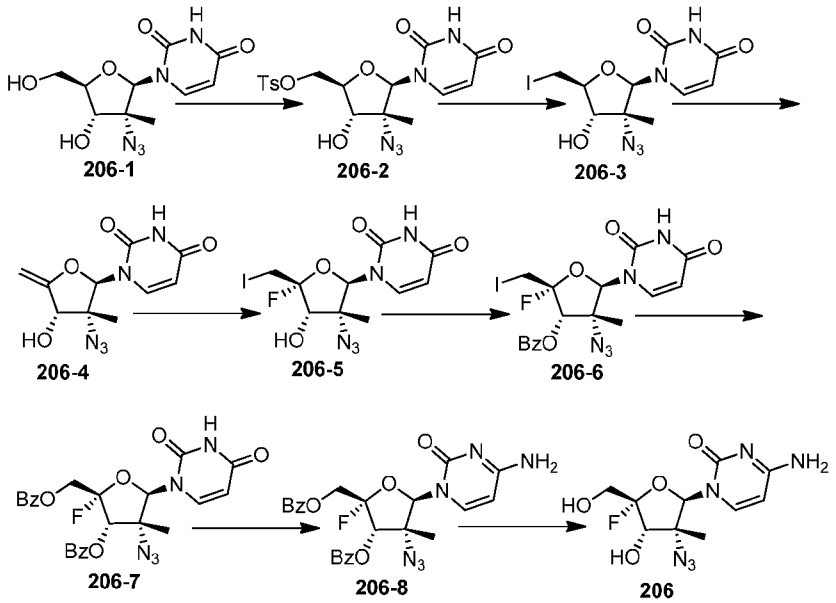
EXAMPLE 110
COMPOUND 204



204

[0679] A method for preparing compound **204** is provided in WO 2010/015643, filed August 4, 2009.

EXAMPLE 111
COMPOUND 206



[0680] **206-1** (1.0 g, 3.53 mmol) was coevaporated with anhydrous pyridine 3 times to remove H_2O. To an ice-cold solution of **206-1** in anhydrous pyridine (9 mL) was added TsCl (808 mg, 4.24 mmol) in pyridine (3 mL) drop-wise at 0°C, and the mixture was stirred for 18 h. at 0°C. The reaction was monitored by LCMS, and then quenched with H_2O. After concentration at low pressure, the residue was dissolved in EA (50 mL). The solution was washed with sat. $NaHCO_3$ solution and brine. The organic layer was dried over anhydrous Na_2SO_4 and filtered. The filtrate was evaporated at low pressure, and the residue was purified by silica gel column chromatography (1% MeOH in DCM) to give **206-2** (980 mg, 63 %) as a white solid.

[0681] To a solution of **206-2** (980 mg, 2.24 mmol) in acetone (10 mL) was added NaI (1.01 g, 6.73 mmol), and the mixture was heated to reflux overnight. The reaction was monitored by LCMS. After the reaction was completed, the mixture was concentrated at low pressure. The residue was dissolved in EA (50 mL). The solution was washed with brine, and dried over anhydrous Na_2SO_4. The solution was evaporated at low pressure, and the residue was purified by silica gel column chromatography (1% MeOH in DCM) to give **206-3** (700 mg, 79 %) as a solid.

[0682] To a solution of **206-3** (700 mg, 1.78 mmol) in dry THF (9 mL) was added DBU (817 mg, 5.34 mmol), and the mixture was heated to 60°C. The mixture was stirred overnight, and monitored by LCMS. The reaction was quenched with sat. $NaHCO_3$ and extracted with EA (3 x 50 mL). The organic phase was dried over anhydrous Na_2SO_4, and filtered. The filtrate was evaporated at low pressure, and the residue was purified by silica gel column chromatography (1% MeOH in DCM) to give **206-4** (250 mg, 53 %) as a white solid.

[0683] To an ice-clod solution of **206-4** (250 mg, 0.94 mmol) in dry MeCN (5mL) was added $NEt_3 \cdot 3HF$ (151 mg, 0.94 mmol) and NIS (255 mg, 1.13 mmol). The mixture was stirred at RT for 3 h., and checked by LCMS. The reaction was quenched with sat $Na_2S_2O_3$ and sat. $NaHCO_3$ solution, and extracted with EA (3 x 50 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, and evaporated at low pressure. The residue was purified by silica gel column chromatography (2% acetone in DCM) to give **206-5** (170 mg, 44 %).

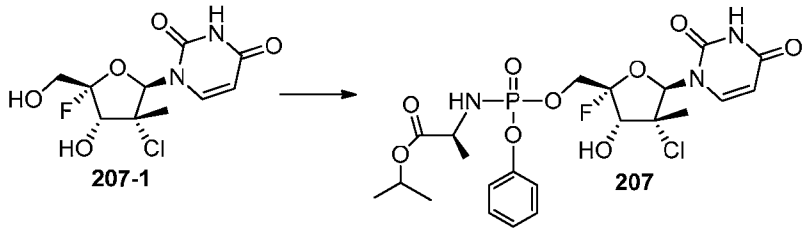
[0684] To a solution of **206-5** (270 mg, 0.65 mmol) in dry DCM (4 mL) was added DMAP (158.6 mg, 1.3 mmol), and BzCl (137 mg, 0.98 mmol). The mixture was stirred for 4-5 h. at RT and checked by LCMS. The mixture was diluted with CH_2Cl_2, and washed with sat. $NaHCO_3$ solution and brine. The organic layer was evaporated at low pressure, and the residue was purified by silica gel column chromatography (20% EA in PE) to give **206-6** (290 mg, 86 %) as a solid.

[0685] To a solution of **206-6** (900 mg, 1.74 mmol) in dry DMF (45 mL) was added NaOBz (2.5 g, 17.4 mmol) and 15-crown-5 (4.5 g, 20.9 mmol). The mixture was stirred for 48 h at 90-100°C. The mixture was diluted with EA (100 mL), and washed with brine. The organic layer was evaporated at low pressure, and the residue was purified by silica gel column chromatography (20% EA in PE) to give **206-7** (500 mg, 56 %) as a solid.

[0686] To a solution of **206-7** (500 mg, 0.98 mmol) in anhydrous CH_3CN (5 mL) was added TPSCl (741 mg, 2.45 mmol), DMAP (299.6 mg, 2.45 mmol) and NEt_3 (248 mg, 2.45 mmol) at RT, and the mixture was stirred overnight. The mixture was then treated with NH_3 in THF (5 mL) and then stirred for another 30 mins. The mixture was diluted with EA (100 mL). The solution was washed with 0.5% AcOH solution. The organic solvent was dried over anhydrous MgSO4, and concentrated at low pressure. The crude product was purified by silica gel column chromatography (2% Acetone in DCM) to give **206-8** (257 mg, 51.6 %) as a white solid. ESI-MS: m/z 509 $[M+H]^+$.

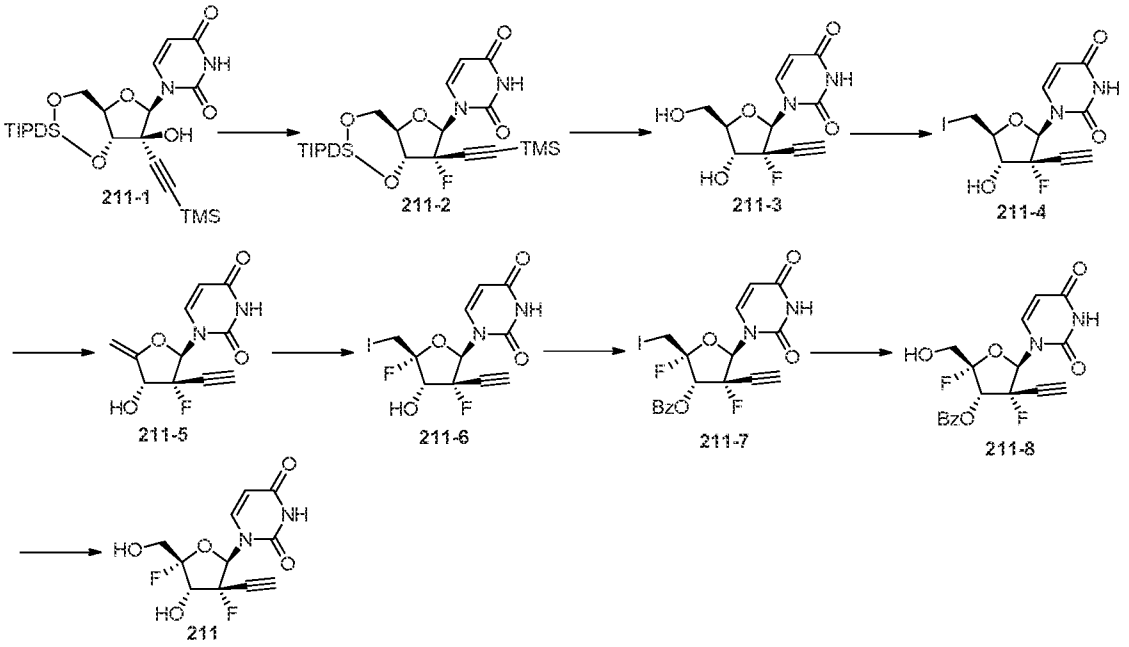
[0687] **206-8** (80 mg, 0.16 mmol) was dissolved in n-butylamine (3 mL). The mixture was kept overnight at RT and evaporated. The residue was crystallized from methanol to give **206** (30 mg). The mother liquor was purified by RP HPLC on Synergy 4 micron Hydro-RP column (Phenominex). A linear gradient of methanol from 0 to 30% in 50 mM 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 to yield additional **206** (13 mg). **206** (total yield 43 mg, 73%). MS: m/z 299.7 $[M-1]^-$.

EXAMPLE 112
COMPOUND 207



[0688] **207-1** (30 mg, 0.1 mmol) was dissolved in a mixture of CH_3CN (2 mL) and N-methylimidazole (200 uL). Phosphorochloridate (100 mg, 0.3 mmol) was added, and the mixture was kept for 5 d at RT. The mixture was distributed between water and EA. The organic layer was separated, washed with brine, dried and evaporated. The phosphoroamidate was isolated by silica gel chromatography in a gradient of methanol in DCM from 3% to 10%. The corresponding fractions were concentrated and re-purified by RP HPLC on Synergy 4 micron Hydro-RP column (Phenominex). A linear gradient of methanol in DCM from 3% to 95% containing 0.1% formic acid was used for elution. **207** was obtained as a mixture Rp and Rs isomers (9 mg, 16%). MS: m/z 562.1[M-1]$^-$.

EXAMPLE 113
COMPOUND 211



[0689] To a solution of **211-1** (23.0 g, 39.5 mmol) in anhydrous toluene (200 mL) was added DAST (31.9 g, 198 mmol) dropwise at -78°C, and the solution was stirred at -

78°C for 3 h. The mixture was quenched with sat. $NaHCO_3$, extracted with EA (2 x 200 mL) and dried over with anhydrous Na_2SO_4. The solution was concentrated to dryness under low pressure. The residue was purified on a silica gel column (50% EA in PE) to give **211-2** (16.5 g, 71%) as a yellow foam.

[0690] A mixture of **211-2** (16.0 g, 27.4 mmol) and NH_4F (3.0 g, 82.2 mmol) in methanol (100 mL) was stirred at 70°C for 12 h. The reaction was cooled, and the salt was removed by filtration. The filtrate was concentrated to dryness at low pressure. The residue was purified on a silica gel column (3% MeOH in DCM) to give **211-3** (5.1 g, 69.0%) as a white foam.

[0691] To a stirred suspension of **211-3** (4.1 g, 15.2 mmol), PPh_3 (8.0 g, 30.4 mmol), imidazole (2.1 g, 30.4 mmol) and pyridine (18.2 mL) in anhydrous THF (40 mL) was added dropwise a solution of I_2 (5.8 g, 22.8 mmol) in THF (20 mL) at 0°C. The mixture was stirred at RT for 12 h. The reaction was quenched with MeOH (100 mL), and the solvent was removed under reduced pressure. The residue was purified on a silica gel column (4% MeOH in DCM) to give pure **211-4** (4.4 g, 77%) as a white solid. ESI-MS: m/z 381.1 $[M+1]^+$.

[0692] To a stirred solution of **211-4** (2.5 g, 0.7 mmol) in anhydrous THF (3 mL) was added DBU (2.1 g, 14 mmol) at RT, and the mixture was stirred at RT for 1 h. The reaction was quenched with HOAc, and diluted with 2-Me-tetrahydrofuran. The solution was washed with brine, dried over with anhydrous Na_2SO_4 and concentrated to dryness at low pressure. The residue was purified on a silica gel column (MeOH 5% in DCM) to give **211-5** (1.1 g, 68.9%) as a white foam.

[0693] To a stirred solution of **211-5** (800 mg, 3.17 mmol) in anhydrous CH_3CN (10 mL) was added TEA•3HF (510 mg, 3.17 mmol) and NIS (785 mg, 3.49 mmol) at 0°C. The mixture was stirred for 30 mins, gradually warmed to RT and stirred for 1 h. The mixture was quenched with sat. $NaHCO_3$ solution and $Na_2S_2O_3$ solution, and extracted with EA (2 x 20 mL). The organic layer was dried over with anhydrous Na_2SO_4, and concentrated to dryness at low pressure. The residue was purified on a silica gel column to give pure **211-6** (695 mg, 57.9%) as a yellow solid.

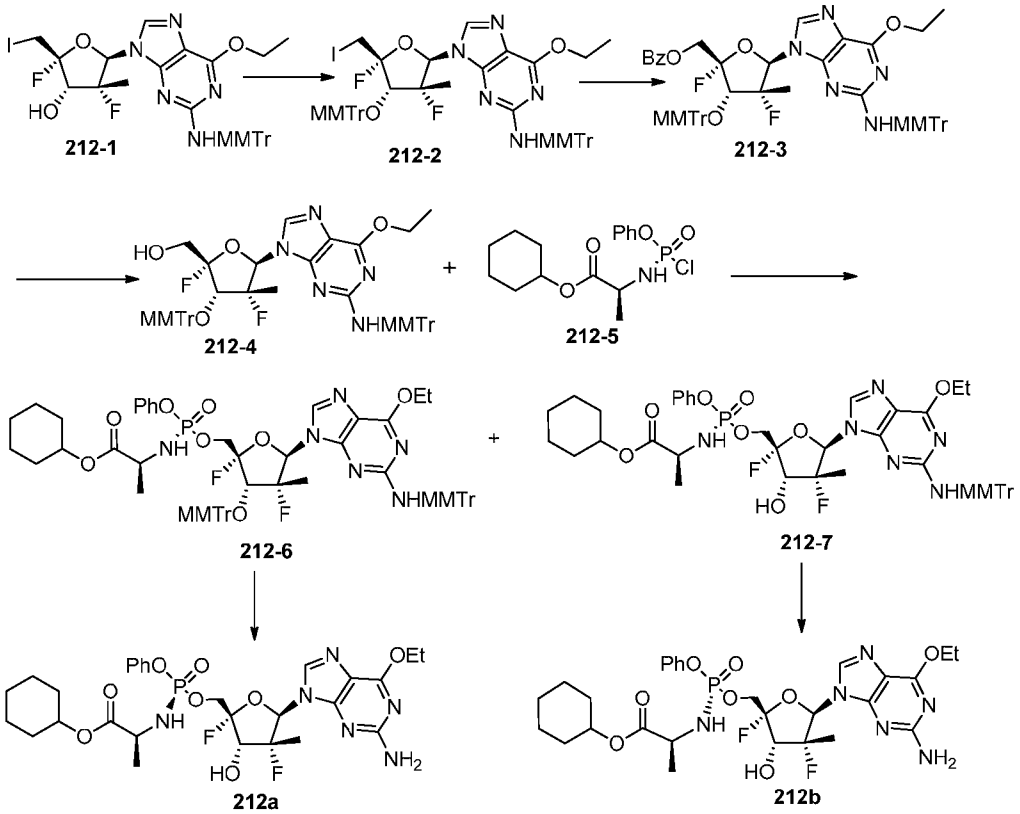
[0694] To a stirred solution of **211-6** (650 mg, 1.63 mmol) in pyridine (3 mL) was added BzCl (507 mg, 3.59 mmol) at 0°C, and stirred at RT for 12 h. The mixture was

quenched with water, and concentrated to dryness under reducing pressure. The residue was purified on a silica gel column (EA 50% in PE) to yield **211-7** (550 mg, 67%) as a white foam.

[0695] Tetra-butylammonium hydroxide (9 mL as 54-56% aqueous solution, 72 mmol) was neutralized with TFA to pH~4 (1.5 mL), and the mixture was added to a solution of **211-7** (375 mg, 0.75 mmol) in DCM (9 mL). *m*-Chloroperbenzoic acid (924 mg, 60-70%, 3.75 mmol) was added in portions with vigorous stirring, and the mixture was stirred overnight. The mixture was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (EA 50% in PE) to give **211-8** (230 mg, 78.8%) as a white foam. ESI-MS: m/z 393.1 $[M+1]^+$.

[0696] **211-8** (120 mg, 0.24 mmol) was treated with 7N NH_3•MeOH (20 mL), and stirred for 5 h. The mixture was concentrated to dryness at low pressure. The residue was purified on a silica gel column (propan-2-ol 15% in DCM) to yield **211** (53 mg, 60.2%) as a white solid. ESI-MS: m/z 288.8 $[M+1]^+$.

EXAMPLE 114
COMPOUNDS 212a AND 212b



[0697] To a solution of **212-1** (0.47 g, 0.65 mol) in DCM (3 mL) was added $AgNO_3$ (0.22 g, 1.29 mmol), collidine (0.15 g, 1.29 mmol) and MMTrCl (0.3 g, 0.974 mmol) at 0 °C. The mixture was stirred at RT overnight. The mixture was filtered, and the filter was washed with sat. aq. $NaHCO_3$ solution and brine. The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by silica gel column to give **212-2** (0.55, 85%) as a white solid.

[0698] To a solution of **212-2** (0.5 g, 0.5 mmol) in dry DMF (10 mL) was added NaOBz (0.72 g, 5 mmol) and 15-crown-5 (0.9 mL). The mixture was stirred at 95 °C for 72 h. The mixture was diluted with EA, and washed with water and brine. The organic phase was dried over $MgSO_4$ and concentrated at low pressure. The residue was purified by silica gel column (10% EA in PE) to give **212-3** (0.3 g, 60%) as a white solid.

[0699] **212-3** (0.3 g, 0.3 mmol) in NH_3/MeOH (30 mL) was stirred at RT for 18 h. The mixture was concentrated at low pressure, and the residue was purified by silica gel

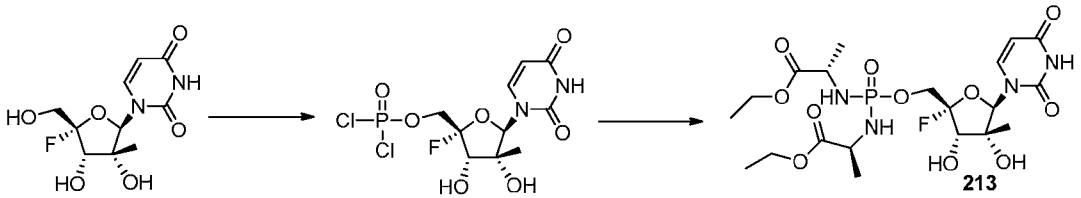
column (20% EA in PE) to give **212-4** (145 mg, 56%) as a white solid. ESI-LCMS: m/z 890.5 $[M+H]^+$.

[0700] To a stirred solution of **212-4** (161 mg, 0.16 mmol) in anhydrous CH_3CN (2.0 mL) was added N-methylimidazole (118 μL, 2.87 mmol) at 0 to 5 ^0C (ice/water bath) followed by solution of **212-5** (186 mg, 0.54 mmol, dissolved in 2mL of CH_3CN). The solution was stirred at 0 to 5 ^oC for 4 h. The mixture was diluted with EA, and water was added (15 mL). The solution was washed H_2O, 50 % aqueous citric acid solution and brine. The organic layer was separated, dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated in vacuum to give a residue, which was purified on silica gel with 0 to 40% EA/hexanes to give as **212-6** (82.6 mg) as the faster eluting isomer and **212-7** (106 mg) as the slower eluting isomer.

[0701] **212-6** (82.6 mg, 0.07 mmol) was dissolved in_anhydrous CH_3CN (0.5 mL), and 4N HCl in dioxane (35 μL) was added at 0 to 5 ^oC. The mixture was stirred at RT for 1 h, and anhydrous EtOH (100 μL) was added. The solvents were evaporated at RT and co-evaporated with toluene 3 times. The residue was dissolved in 50% CH_3CN/H_2O, and purified on a reverse-phase HPLC (C18) using acetonitrile and water, followed by lyophilization to give **212a** (19.4 mg). ESI-LCMS: m/z = 655.2 $[M+H]^+$, 653.15 $[M-H]^-$.

[0702] **212-7** (100 mg, 0.083 mmol) was dissolved in_anhydrous CH_3CN (0.5 mL), and 4N HCl in dioxane (50 μL) was added at 0 to 5 ^oC. Following the procedure for obtaining **212a**, **212b** (31.8 mg) was obtained. ESI-LCMS: m/z = 655.2 $[M+H]^+$, 653.1 $[M-H]^-$.

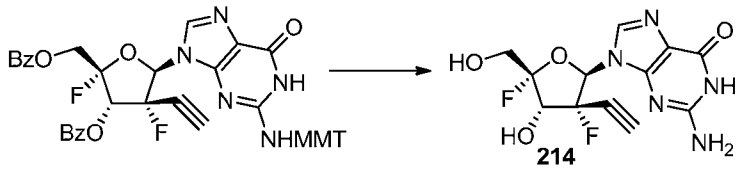
EXAMPLE 115
COMPOUND 213



[0703] To a solution of the nucleoside (300 mg, 1.09 mmol) and proton-sponge (467 mg, 2.18 mmol) in anhydrous CH_3CN (5 mL) at 0°C under N_2 was added dropwise a solution of phosphorus oxychloride (330 mg, 2.18 mmol) in anhydrous CH_3CN (1 mL). The mixture was stirred at 0°C for 30 mins, and the hydrogen chloride salt of (S)-ethyl 2-

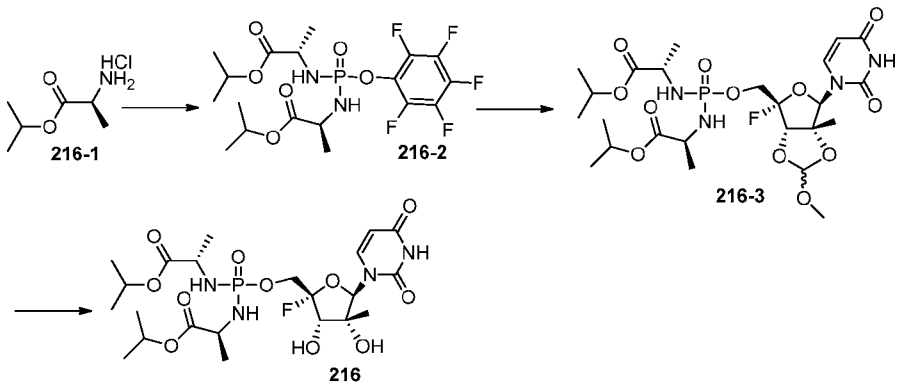
aminopropanoate (998 mg, 6.52 mmol) and triethylamine (1.5 mL, 10.87 mmol) at 0°C were added. The mixture was stirred overnight at 30°C. The reaction was quenched with water, and extracted with EA (3 x 20 mL). The organic layer was concentrated at low pressure, and the residue was purified by reverse phase HPLC to give **213** (20 mg, 3%) as a white solid. ESI-LCMS: m/z 535 $[M-F]^+$.

EXAMPLE 116
COMPOUND 214



[0704] The nucleoside (140 mg, 0.42 mmol) was dissolved in n-butylamine (0.5 mL). The mixture was kept for 2 h at RT, and the amine was then evaporated. The residue was dissolved in EtOAc, and the organic layer was washed twice with 10% citric acid, dried over Na_2SO_4, and evaporated. The residue purified by column chromatography on silica gel in linear gradient of methanol in DCM from 0% to 12% over 10 column volumes. The fractions containing the product were concentrated and treated with 80% HCOOH for 1 h at RT. The mixture was evaporated to dryness, and suspended in CH_3CN. The precipitate was separated, washed with CH_3CN (1 mL) and dried to yield **214** (27 mg, 50%). MS: m/z 326.5 $[M-1]^-$.

EXAMPLE 117
COMPOUND 216



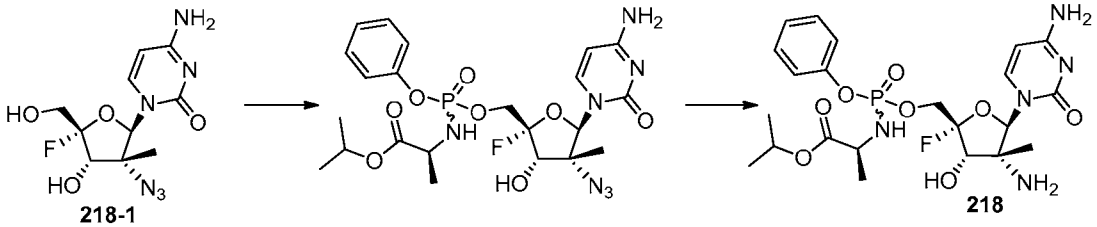
[0705] To a solution of **216-1** (3.0 g, 18.0 mmol) and $POCl_3$ (1.35 g, 9.0 mmol) in DCM (80 mL) was added TEA (3.6 g, 36.0 mmol) in DCM (20 mL) dropwise at 0°C. The

mixture was stirred at 0°C for 2 h. A solution of pentafluorophenol (1.65 g, 9.0 mmol) and TEA (0.9 g, 9.0 mmol) in DCM (20 mL) was added dropwise at 0°C, and the mixture was stirred at 0°C for 15 h. After the reaction was completed, the mixture was concentrated under reduced pressure. The residue was washed by TBME and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel chromatography (20% EA in PE) to give **216-2** (2.7 g, 62.7%) as a white solid. ESI-MS: m/z 491.1 $[M+1]^+$.

[0706] To a stirred solution of 1-((3aR,4R,6S,6aS)-6-fluoro-6-(hydroxymethyl)-2-methoxy-3a-methyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)pyrimidine-2,4(1H,3H)-dione (150 mg, 0.47 mmol) in anhydrous THF (2 mL) was added a solution of t-BuMgCl (0.46 mL, 1M in THF) dropwise at 0°C. The mixture was stirred at RT for 40 mins, and re-cooled to 0°C. A solution of **216-2** (462 mg, 0.94 mmol) was added, and the mixture was stirred at RT for 4 h. The mixture was quenched with H_2O, and extracted with EA. The organic layer was dried over Na_2SO_4 and concentrated under reducing pressure. The residue was purified on a silica gel column (50% EA in PE) to give **216-3** as a white foam (230 mg, 78%).

[0707] **216-3** (230 mg, 0.37 mmol) was dissolved in 80% HCOOH aqueous solution (20 mL), and the mixture was stirred at RT for 24 h. The solvent was removed at low pressure. The residue was purified on a silica gel column to give the crude product, which was purified by RP HPLC (HCOOH system) to give **216** as a mixture of two P-isomers (75 mg, 33%). ESI-TOF-MS: m/z 583.0 $[M+H]^+$.

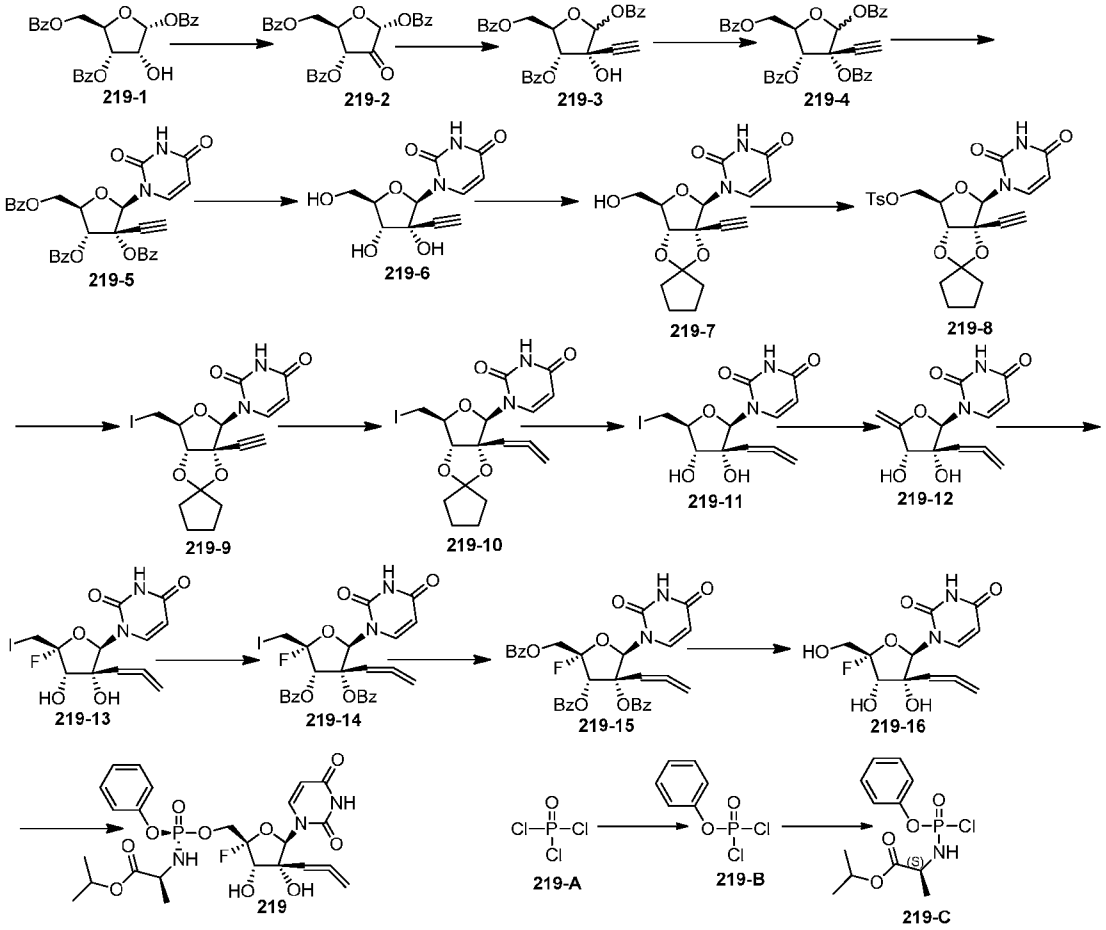
EXAMPLE 118
COMPOUND 218



[0708] **218-1** (30 mg, 0.1 mmol) was dissolved in a mixture of CH_3CN (2 mL) and N-methylimidazole (200 uL). Phosphorochloridate (100 mg, 0.3 mmol) was added, and the mixture was kept overnight at 40°C. The temperature was increased to 65°C and heated for 1 h. The mixture was distributed between water and EA. The organic layer was

separated, washed with brine, dried and evaporated. The azido-phosphoroamidate was purified by RP HPLC on Synergy 4 micron Hydro-RP column (Phenominex). A linear gradient of methanol from 30% to 100% in 50 mM triethylammonium acetate buffer (pH 7.5) was used for elution. The azido-phosphoroamidate (8 mg) was dissolved in pyridine/Et_3N (3 mL, 8:1 v:v) and cooled to 0^0C. H_2S gas was bubbled through the solution for 10 mins, and the reaction was kept for 1 h at RT. The solvents were evaporated, and the residue isolated by RP HPLC. The corresponding fractions were combined, concentrated and lyophilized 3 times to remove excess of buffer, to provide **218** (1.2 mg) as mixture Rp and Rs isomers. MS: m/z 544.1 $[M+1]^+$.

EXAMPLE 119
COMPOUND 219



[0709] To a solution of IBX (133.33 g, 476 mmol) in dry CH_3CN (2 L) was added **219-1** (100.0 g, 216 mol) at RT. The mixture was refluxed and stirred for 12 h. The

mixture was filtered, and the filtrate was concentrated at low pressure to give **219-2** as a yellow oil (90.0 g, 90.4%).

[0710] **219-2** (50.0 g, 108.70 mmol) was coevaporated with anhydrous toluene twice to remove H_2O. Ethynyl magnesium bromide, (800 mL, 400.0 mmol) was added dropwise into a solution of **73-2** in THF (500 mL) over 20 mins at -78°C. The mixture was stirred for about 10 mins at -78°C. When the starting material was consumed, the ice–acetone cooling bath was removed. The mixture was quenched with a sat. NH_4Cl solution with stirring, and then warmed to RT. The mixture was extracted with EA, filtered through Celite and washed with brine. The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated at low pressure to give crude **219-3** as a deep yellow oil (48.0g, yield: 90.8%).

[0711] **219-3** (200.0 g, 411.52 mmol) was dissolved in anhydrous CH_2Cl_2 (2000 mL) and then DMAP (100.41 g, 823.05 mmol) and Et_3N (124.94 g, 1.23 mol) were added at RT. The mixture was treated with benzoyl chloride (173.46 g, 1.23 mol) at 0°C. After stirring for 12 h at RT, the reaction was quenched with H_2O. The combined aq. phase was extracted with DCM. The combined organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated to dryness under reduced pressure to give a black oil. The oil was purified by column chromatography using 7%-20% EA in PE as the eluent to give a yellow oil. The residue triturated with CH_3OH and filtered. The filter cake was concentrated in vacuo to give **219-4** as a white solid (30.0 g, 36.4%).

[0712] Uracil (34.17 g, 305.08 mmol) were coevaporated with anhydrous toluene twice to remove H_2O. To a stirred suspension of uracil in anhydrous MeCN (150 mL) was added N,O-BSA (123.86 g, 610.17 mmol) at RT. The mixture was refluxed for 1.5 h and then cooled to RT. **219-4** (90 g, 152.54 mmol, which were coevaporated with anhydrous toluene twice to remove H_2O) was added. TMSOTf (237.05 g, 1.07 mol) was then added at RT. The mixture was heated to 70°C, and then stirred overnight and then monitored by LCMS. The mixture was cooled to RT and quenched with a sat. $NaHCO_3$ solution. The solution was extracted with EA. The organic layer was dried over Na_2SO_4, and then concentrated at low pressure. The residue was purified using a silica gel column eluted with 10%-50% EA in PE to give **219-5** as a white solid (45 g, 50.9%).

[0713] **219-5** (50 g, 86.21 mmol) was treated with NH_3 in MeOH (1 L) at RT, and then stirred for 48 h. The mixture was concentrated at low pressure, and the residue was purified by column chromatography (10% MeOH in DCM) to give **219-6** (12.6 g, 54.55%) as a white solid.

[0714] To a solution of cyclopentanone (100 g, 1.189 mmol) and trimethyl orthoformate (150 mL) in MeOH (600 mL) was added $TsOH \cdot H_2O$ (1.13 g, 5.9 mmol), and the mixture was stirred at RT for 30 mins. The reaction was quenched with NaOMe (0.32 g, 5.9 mmol) and H_2O, and the solution was extracted by n-hexane. The organic layer was dried over anhydrous Na_2SO_4, and then concentrated at low pressure. The cyclopentyl dimethoxy acetal and **219-6** (20 g, 74.63 mmol) was dissolved in DCE (200 mL), and then treated with $TsOH \cdot H_2O$ (0.71 g, 3.73 mmol). The mixture was stirred at 50°C for 12 h, and then concentrated at low pressure. The residue was purified by silica gel column chromatography (1-10% MeOH in DCM) to give **219-7** (15.4 g, 61.8%) as a white solid.

[0715] **219-7** (20.0 g, 0.06 mol) was coevaporated with anhydrous pyridine three times to remove H_2O. To an ice-cold solution of **219-7** in anhydrous pyridine (100 mL) was added TsCl (22.8 g, 0.12 mol) at 0°C, and the mixture was stirred overnight and monitored by LCMS and TLC. The reaction was quenched with H_2O and extracted with EA. The organic phase was dried over anhydrous $NaSO_4$ and evaporated at low pressure. The residue was purified by silica gel column chromatography (DCM: MeOH=100:1 to 15:1) to give **219-8** (20.0 g, 69.0%) as a white solid.

[0716] To a solution of **219-8** (20.0 g, 0.04 mol) in acetone (200 mL) was added NaI (31.0 g, 0.2 mol) and heated to reflux overnight and monitored by LCMS. The mixture was quenched with a sat. $Na_2S_2O_3$ solution, and extracted with EA. The organic phase was dried over anhydrous Na_2SO_4 and evaporated at low pressure. The residue was purified by silica gel column chromatography (DCM: MeOH=100:1 to 15:1) to give **219-9** (15.0 g, 83.3%) as a white solid.

[0717] To **219-9** (30.0 g, 0.068 mol) in dioxane (60 mL) in sealed tube was added CuBr (4.9 g, 0.034 mol), *i*-Pr_2NH(13.6 g, 0.135 mol) and $(CH_2O)_n$(5.1 g, 0.17 mol) under N_2. The mixture was heated at reflux for 16 h. The mixture was diluted with EtOAc, and washed with a sat. NH_4Cl solution and brine. The solution was dried over anhydrous $MgSO_4$, and

concentrated under reduced pressure. The residue was purified by column chromatography (DCM: MeOH=100:1 to 15:1) to give **219-10** (10.0 g, 32.3%) as a white solid.

[0718] **219-10** (10 g, 21.83 mmol) was treated with HCOOH (80%) in H_2O at RT. The solution was stirred at 60°C for 2 h, and then concentrated at a low pressure. The residue was purified by column chromatography (1%-10% MeOH in DCM) to give **219-11** (5.1 g, 58.55%) as a white solid.

[0719] **219-11** (5 g, 12.79 mmol) was dissolved in anhydrous MeOH (100 mL) and treated with NaOMe (4.83 g, 89.5 mmol) at RT.. The solution was stirred at 60°C for 36 h. The mixture was quenched with CO_2 and then concentrated at low pressure. The residue was purified by column chromatography (0-10% MeOH in DCM) to give **219-12** (2.3 g, 68.05%) as a yellow solid. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ = 7.29 (d, J = 8 Hz 1H), 6.10 (s, 1H), 5.71 (d, J = 8 .0 Hz 1H), 5.18 (t, J = 6.4 Hz, 1H), 4.79-4.84 (m, 1H), 4.61 (d, J = 8.0 Hz, 2H), 4.39 (s, 1H), 3.45 (s, 1H).

[0720] To an ice-cold solution of **219-12** (1.5 g, 5.68 mmol) in anhydrous MeCN (15 mL) was added NIS (1.66 g, 7.39 mmol) and TEA• 3HF (0.73 g, 4.55 mmol) under N_2. The mixture was stirred at RT for 1 h. The reaction was quenched with sat. $NaHCO_3$ and sat. Na_2SO_3 solution, and extracted with EA (3 x 100 mL). The organic phase was dried over anhydrous Na_2SO_4, and evaporated to dryness at low pressure. The residue was purified on a silica gel column (0-5% MeOH in DCM) to give **219-13** (1.08 g, 46.2%) as a yellow solid.

[0721] To a stirred solution of **219-13** (1 g, 2.44 mmol) in anhydrous DCM (10 mL) was added DMAP (0.60 g, 4.88 mmol) and Et_3N (0.74g, 7.32 mmol) at RT. The mixture was treated with benzoyl chloride (0.79 g, 5.61 mmol) at 0°C and then stirred at RT for 3 h. The reaction was quenched with water, and extracted with EA (3 x 60 mL). The organic phase was concentrated at low pressure, and the residue was purified by column chromatography (0-10% MeOH in DCM) to give **219-14** (0.9 g, 59.6%) as a white solid.

[0722] Bu_4NOH (55% in H_2O, 13.74 mL) was treated with TFA (to adjust pH=3-4). The mixture was cooled to RT. To a solution of **219-14** (0.9 g, 1.46 mmol) in DCM (9 mL) was added m-CPBA (80%, 1.57 g, 7.28 mmol) at RT. The mixture was stirred at 25°C for 48 h. The mixture was washed with sat. aq. $NaHCO_3$. The organic layer was passed through an anhydrous Al_2O_3 column, and the solution was concentrated at low pressure. The

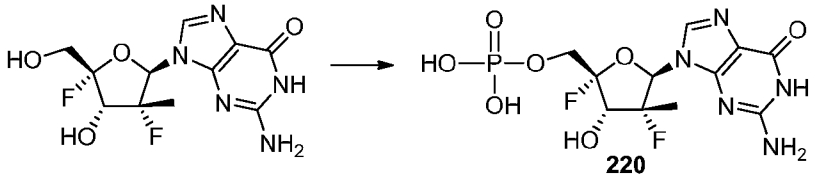
residue was purified by a silica gel column (30% EA in PE) to give **219-15** (0.26 g, 35.1%) as a yellow solid.

[0723] **219-15** (0.25 g, 0.49 mmol) was dissolved in NH_3/MeOH (5 mL, 7 M), and the mixture was stirred at RT for 24 h under N_2. The mixture was concentrated at low pressure at RT, and the residue was purified by a silica gel column (5% MeOH in DCM) to give **219-16** (100 g, 67.75%) as a white solid. ^{1}H-NMR (CD_3OD, 400 MHz) δ = 7.83 (d, J = 8 Hz 1H), 6.29 (s, 1H), 5.67 (d, J = 6 .0 Hz 1H), 5.12 (t, J = 6.8 Hz, 1H), 4.99-5.01 (m, 1H), 4.38 (d, J = 19.6 Hz 1H), 3.74-3.81 (m, 2H), 3.35 (s, 1H).

[0724] **219-16** (100 mg, 0.33 mmol) was co-evaporated with toluene three times to remove H_2O. To a stirred solution of **219-16** (100 mg, 0.33 mmol) in a mixture of MeCN (1.0 mL) and NMI (271 mg, 3.3 mmol) was added a solution of **219-C** (216.5 mg, 0.66 mmol) in MeCN (0.5 mL) at 0 ^{0}C. The mixture was stirred at RT overnight and then reaction was quenched with water. The mixture was diluted with EA (20 mL), and the organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4. The organic phase was concentrated at low pressure, and the residue was purified on a silica gel column (5% *i*-PrOH in DCM) to give the crude product. The crude product was purified by prep-HPLC (0.1% HCOOH in water and MeCN) to give **219** (35.6 mg, 19.0%) as a white solid. ESI-LCMS: m/z 592 $[M+Na]^+$.

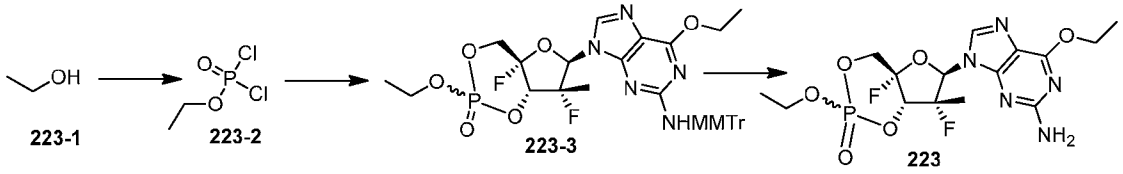
[0725] To a stirred solution of **219-A** (2.0 g, 13.16 mmol) and phenol (1.22 g, 13.16 mmol) in anhydrous DCM (100 mL) was added a solution of TEA (1.33 g, 13.16 mmol) in DCM (20 mL) dropwise at -78°C. The mixture was warmed gradually to RT, and then stirred for 2 h. The solution was re-cooled to -78°C, and (S)-isopropyl 2-aminopropanoate hydrochloride (2.20 g, 13.16 mmol) in DCM (20 mL) was added, followed by the dropwise addition of TEA (2.66 g, 26.29 mmol) in DCM (20 mL). The mixture was warmed gradually to RT, and then stirred for 2 h. The organic solvent was removed at low pressure, and the residue was dissolved in methyl-butyl ether. The precipitate was filtered, and the filtrate was concentrated at low pressure. The residue was purified on a silica gel column (anhydrous DCM) to give **219-C** (0.9 g, 22.3%) as a colorless oil.

EXAMPLE 120
COMPOUND 220



[0726] Dry nucleoside (0.05 mmol) was dissolved in a mixture of $PO(OMe)_3$ (0.7 mL) and pyridine (0.3 mL). The mixture was evaporated in vacuum for 15 mins. at 42^{0}C, then cooled to RT. N-Methylimidazole (0.009 mL, 0.11 mmol) was added followed by $POCl_3$ (0.009 mL, 0.11 mmol). The mixture was kept at RT for 20-40 mins and monitored for the formation of **220** by LCMS. The reaction was quenched with water and isolated by RP HPLC on Synergy 4 micron Hydro-RP column (Phenominex). A linear gradient of methanol from 0 to 30% in 50 mM 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. MS: m/z 396.5 $[M-1]^-$.

EXAMPLE 121
COMPOUND 223



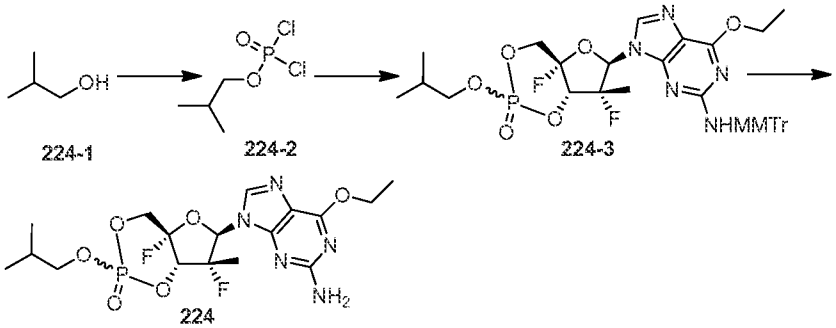
[0727] A solution of **223-1** (16.70 g, 0.363 mol) and TEA (36.66 g, 0.363 mol) in CH_2Cl_2 (150 mL) was added dropwise to a stirred solution of $POCl_3$ (55.65 g, 0.363 mol) in DCM (100 mL) over 25 mins at -78°C. After the mixture was stirred for 2 h. at RT, the triethylamine hydrochloride salt was filtered, and washed with CH_2Cl_2 (100 mL). The filtrate was concentrated at low pressure, and the residue was distilled under high vacuum (~10 mm Hg) with a cow-head fraction collector. **223-2** was collected between 45°C (distillation head temperature) as a colorless liquid (30.5 g, 50% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 4.44 (dq, *J*=10.85, 7.17 Hz, 2 H), 1.44 - 1.57 (m, 3 H); ^{31}P-NMR (162 MHz, $CDCl_3$) δ = 6.75 (br. s., 1 P).

[0728] To a stirred suspension of **227-A** (93 mg, 0.15 mmol) in CH_2Cl_2 (1 mL) was added TEA (61 mg, 0.15 mmol) at RT. The mixture was cooled to -20 °C, and then was

treated with a **223-2** (35 mg, 0.21 mmol) solution dropwise over a period of 10 mins. The mixture was stirred at this temperature for 15 mins., and then was treated with NMI (27 mg, 0.33 mmol). The mixture was stirred at -20°C, and then slowly warmed to RT. The mixture was stirred overnight. The mixture was suspended in EA (15 mL), washed with brine (10 mL) and dried over anhydrous sodium sulfate. The solution was concentrated at low pressure, and the residue was purified by chromatography (DCM: MeOH=100:1) to give **223-3** (60 mg, yield: 56%) as a solid.

[0729] A solution of **223-3** (60 mg, 0.085 mmol) in 80% AcOH aqueous (2 mL) was stirred at RT for 2 h. The mixture was concentrated under reduced pressure, and the residue was purified by a silica gel column eluting DCM/MeOH = 50/1and prep-HPLC to give **223** (23 mg, 62%) as a white solid. ESI-MS: m/z 436.3 $[M+H]^+$.

EXAMPLE 122
COMPOUND 224



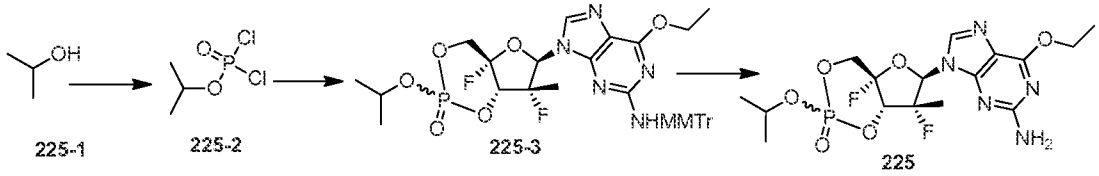
[0730] **224-2** was prepared using a similar procedure as for the preparation of **223-2** using a solution of iso-butanol (23.9 g, 322.98 mmol) and $POCl_3$ (49.5 g, 322.98 mmol). **224-2** (26 g, 42% yield) was obtained as a colorless liquid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 4.10 (dd, *J*=9.04, 6.39 Hz, 2 H), 2.09 (dq, *J*=13.24, 6.67, 6.67, 6.67, 6.67 Hz, 1 H), 1.01 (d, *J*=6.62 Hz, 6 H); ^{31}P-NMR (162 MHz, $CDCl_3$) δ = 7.06 (br. s., 1 P).

[0731] To a stirred suspension of **227-A** (310 mg, 0.5 mmol) in CH_2Cl_2 (3 mL) was added TEA (202 mg, 2 mmol) at RT. The mixture was cooled to -20 °C, and then was treated with **224-2** (134 mg, 0.7 mmol). The mixture was stirred at this temperature for 15 mins and then was treated with NMI (90 mg, 1.1 mmol). The mixture was stirred at -20°C for 1 h., and then slowly warmed to RT overnight. The mixture was suspended in EA (15 mL), washed with brine (10 mL), and dried over anhydrous sodium sulfate. The organic

phase was concentrated at low pressure, and the residue was purified by silica column gel (DCM: MeOH=100:1) to give **224-3** (310 mg, yield: 84%) as a solid.

[0732] A solution of **224-3** (310 mg, 0.43 mmol) in 80% AcOH aqueous (4 mL) was stirred at RT for 2 h. The mixture was concentrated at low pressure, and the residue was purified by a silica gel column eluting DCM/MeOH = 50/1 and prep-HPLC to give **224** (79 mg, 50%) as a white solid. ESI-MS: m/z 464.0 $[M+H]^+$.

EXAMPLE 123
COMPOUND 225

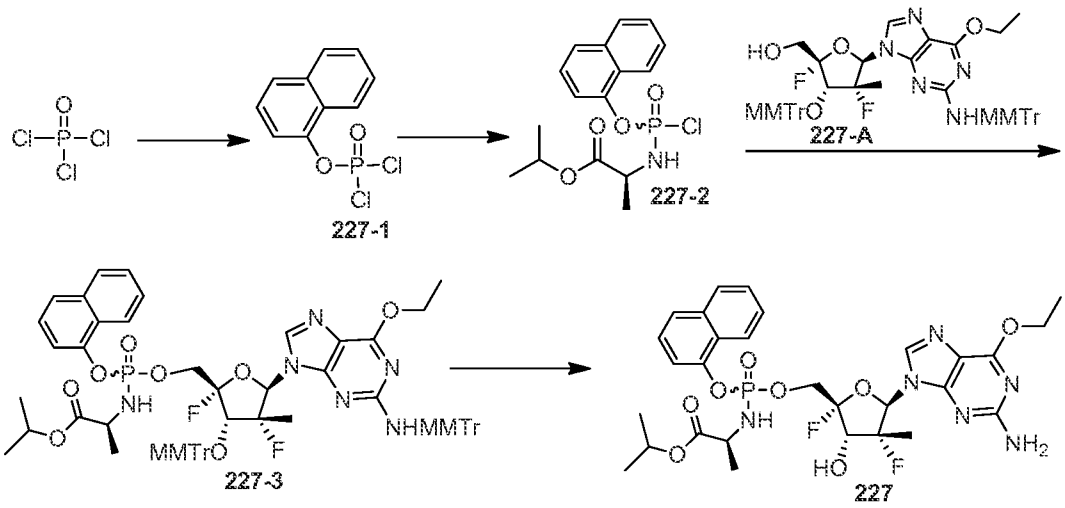


[0733] **225-2** was prepared using a similar procedure as for the preparation of **223-2** using a solution of isopropyl alcohol (21 g, 350 mmol) and $POCl_3$ (53.6 g, 350 mmol). **225-2** (40.5 g, 65% yield) was obtained as a colorless liquid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 4.94 - 5.10 (m, 1 H), 1.48 (d, *J*=6.17 Hz, 6 H); ^{31}P- NMR (162 MHz, $CDCl_3$) δ = 5.58 (br. s., 1 P).

[0734] **225-3** was prepared using a similar procedure as for the preparation of **224-3** using **225-2** (124 mg, 0.7 mmol) and **227-A** (310 mg, 0.5 mmol). **225-3** (300 mg, 83%) was obtained as a solid.

[0735] **225** was prepared using a similar procedure as for the preparation of **224** using **225-3** (300 mg, 0.41 mmol) in 80% AcOH aqueous (4 mL). **225** (80 mg, 43%) was obtained as a white solid. ESI-MS: m/z 450.0 $[M+H]^+$.

EXAMPLE 124
COMPOUND 227



[0736] To a stirred solution of $POCl_3$ (2.0 g, 13 mmol) in anhydrous DCM (10 mL) was added 1-naphthol (1.88 g, 13 mmol) at -70°C, and TEA (1.31 g, 13 mmol) in DCM (3 mL) dropwise at -70°C. The mixture was gradually warmed to RT and stirred for 1 h. Crude **227-1** was obtained.

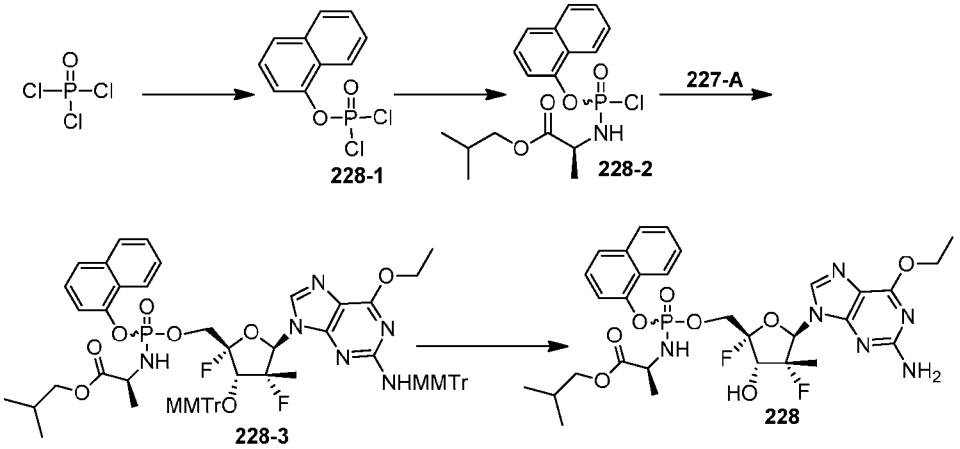
[0737] To a stirred solution of (S)-isopropyl 2-aminopropanoate hydrochloride (2.17 g, 13 mmol) in DCM (10 mL) was added crude **227-1** at -70°C. TEA (2.63 g, 26 mmol) was added to the stirred solution dropwise at -70°C. The mixture was gradually warmed to RT and stirred for 2 h. The reaction was monitored by LCMS and quenched with n-propylamine. The mixture was concentrated at low pressure, and the residue was purified by a silica gel column (PE:MTBE = 5:1~1:1) to give pure **227-2** (1.6 g, 35%).

[0738] To a solution of **227-A** (300 mg, 0.337 mmol) and NMI (276 mg, 3.37 mmol) in anhydrous CH_3CN (4 mL) was added **227-2** (240 mg, 0.674 mol, in DCM (5 mL)) at 0°C. The mixture was stirred at RT for 10 h. The reaction was monitored by LCMS. The reaction was quenched with water, and extracted with CH_2Cl_2 (3 x 20 mL). The organic phase was dried over anhydrous MgSO4, and concentrated at low pressure. The residue was purified by sil-gel (PE:EA = 5:1~2:1) to give **227-3** (380 mg, 93%).

[0739] **227-3** (380 mg, 0.314 mmol) was dissolved in CH_3COOH (80%, 8 mL), and stirred at 40-50°C for 2.5 h. The reaction was monitored by LCMS. The mixture was concentrated at low pressure, and the residue was purified by chromatography (PE:EA =

1:1~EA) to give crude **227**. The crude product was purified by prep-HPLC (neutral system, NH_4HCO_3) to give pure **227** (70 mg, 80%) as a white solid. ESI-MS: m/z 665.1 $[M+H]^+$.

EXAMPLE 125
COMPOUND 228



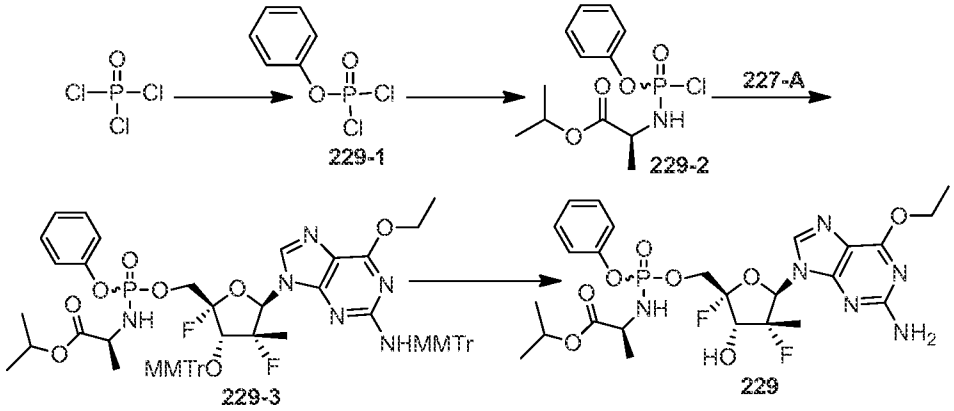
[0740] To a stirred solution of $POCl_3$ (2.0 g, 13 mmol) in anhydrous DCM (10 mL) was added 1-naphthol (1.88 g, 13 mmol) at -70°C and TEA (1.31 g, 13 mmol) in DCM (3 mL) dropwise at -70°C. The mixture was gradually warmed to RT, and stirred for 1 h. A crude solution of **228-1** was obtained.

[0741] To a stirred solution of (S)-isobutyl 2-aminopropanoate hydrochloride (2.35 g, 13 mmol) in DCM (20 mL) was added TEA (2.63 g, 26 mmol) and a crude solution of **228-1** at -70°C. The mixture was gradually warmed to RT, and stirred for 2 h. The reaction was monitored by LCMS and quenched with n-propylamine. The solvent was evaporated at low pressure, and the residue was purified by chromatography (PE:MTBE = 5:1~1:1) to give pure **228-2** (1.8 g, 37%).

[0742] To a solution of **227-A** (300 mg, 0.337 mmol) and NMI (276 mg, 3.37 mmol) in anhydrous CH_3CN (4 mL) was added **228-2** (249 mg, 0.674 mol, in DCM (5 mL)) at 0°C. The mixture was stirred at RT for 10 h. The reaction was monitored by LCMS, and then quenched with H_2O. The mixture was extracted with CH_2Cl_2 (3 x 20 mL). The organic phase was dried over anhydrous MgSO4, and concentrated at low pressure. The residue was purified by chromatography using PE:EA = 5:1~2:1 as the eluent to give **228-3** (360 mg, 87%).

[0743] **228-3** (360 mg, 0.294 mmol) was dissolved in CH_3COOH (80%, 8 mL), and stirred at 40-50°C for 2.5 h. The reaction was monitored by LCMS and then quenched with MeO. The mixture was concentrated at low pressure, and the residue was purified by chromatography using PE:EA = 1:1 as the eluent to generate crude **228**. The product purified by prep-HPLC (neutral system, NH_4HCO_3) to give **228** (70 mg, 75%) as a white solid. ESI-MS: m/z 679.2 $[M+H]^+$.

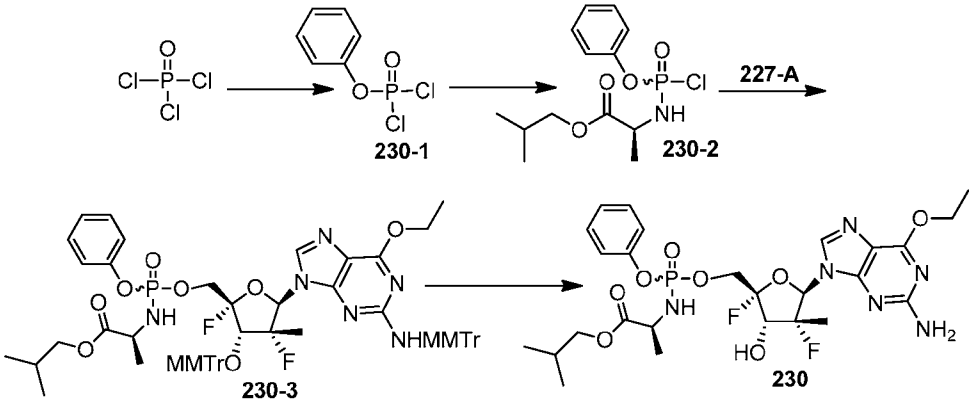
EXAMPLE 126
COMPOUND 229



[0744] To a stirred solution of $POCl_3$ (2.0 g, 13 mmol) in anhydrous DCM (10 mL) was added phenol (1.22 g, 13 mmol) at -70°C and TEA (1.31 g, 13 mmol) in DCM (3 mL) dropwise at -70°C. The mixture was gradually warmed to RT, and stirred for 1 h. A crude solution of **229-1** was obtained.

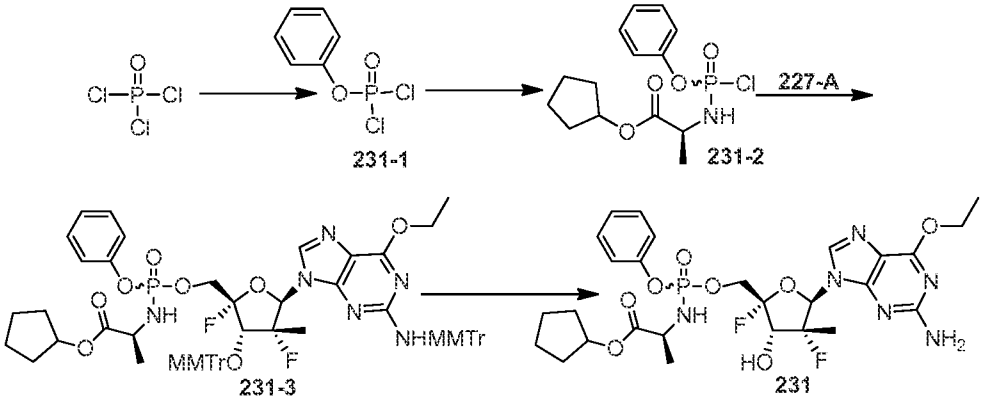
[0745] **229** was prepared using a similar procedure as for the preparation of **228** using **229-2** (205 mg, 0.674 mol, in DCM (5 mL) obtained from (S)-isopropyl 2-aminopropanoate hydrochloride and **229-1**) and **227-A** (300 mg, 0.337 mmol). **229** (50 mg, 74%) was obtained as a white solid. ESI-MS: m/z 615.2 $[M+H]^+$.

EXAMPLE 127
COMPOUND 230



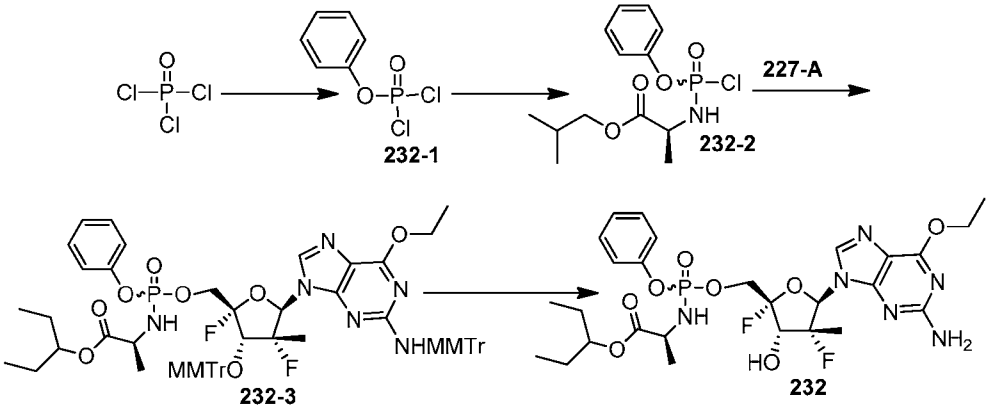
[0746] **230** was prepared using a similar procedure as for the preparation of **228** using **230-2** (214 mg, 0.674 mol, in DCM (5 mL) obtained from (S)-isobutyl 2-aminopropanoate hydrochloride and **230-1**) and **227-A** (300 mg, 0.337 mmol). **230** (70 mg, 87%) was obtained as a white solid. ESI-MS: m/z 629.2 $[M+H]^+$.

EXAMPLE 128
COMPOUND 231



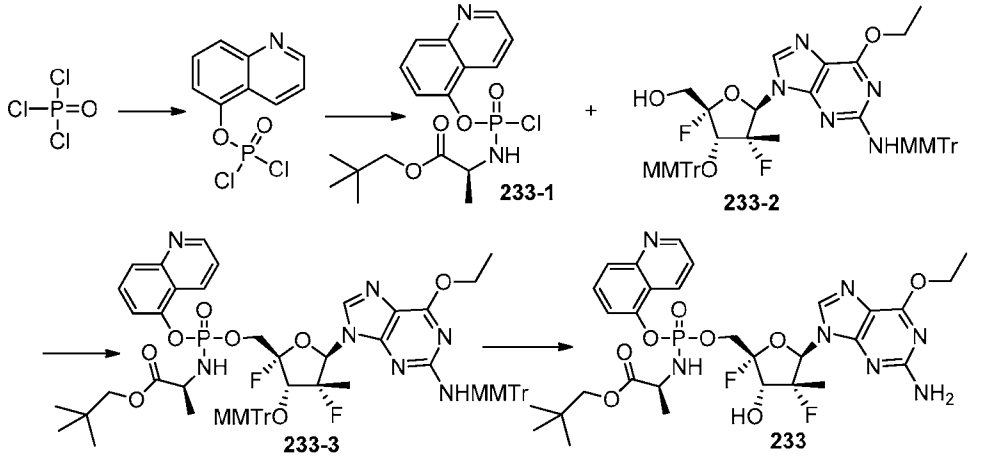
[0747] **231** was prepared using a similar procedure as for the preparation of **228** using **231-2** (223 mg, 0.674 mol, DCM (5 mL) obtained from (S)-cyclopentyl 2-aminopropanoate hydrochloride and **231-1**) and **227-A** (300 mg, 0.337 mmol). **231** (62 mg, 71%) was obtained as a white solid. ESI-MS: m/z 641.2 $[M+H]^+$.

EXAMPLE 129
COMPOUND 232



[0748] **232** was prepared using a similar procedure as for the preparation of **228** using **232-2** (223 mg, 0.674 mol, DCM (5 mL), obtained from (S)-3-pentyl 2-aminopropanoate hydrochloride and **232-1**) and **227-A** (300 mg, 0.337 mmol). **232** (42 mg, 60%) was obtained as a white solid. ESI-MS: m/z 643.2 $[M+H]^+$.

EXAMPLE 130
COMPOUND 233



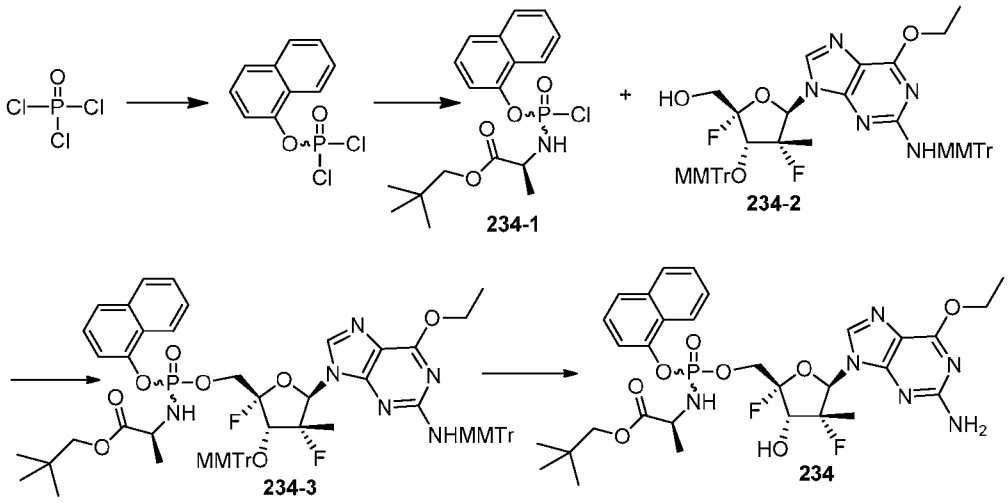
[0749] A stirred solution of phosphoryl trichloride (1.00 g, 6.58 mmol) and 5-quinoline (955 mg, 6.58 mmol) in anhydrous DCM (50 mL) was treated with a solution of TEA (665 mg, 6.58 mmol) in DCM (10 mL) at -78°C. The mixture was gradually warmed to RT, and stirred for 2 h. The solution was cooled to -78°C and then treated with (*S*)-neopentyl 2-aminopropanoate hydrochloride (1.28 g, 6.58 mmol). TEA (1.33 g, 13.16 mmol) was added dropwise at -78°C. The mixture was gradually warmed to RT, and stirred for 2 h. The mixture was concentrated at low pressure, and the residue was dissolved in methyl-butyl

ether. The precipitate was filtered off, and the filtrate was concentrated at low pressure. The residue was purified by a silica gel column (pure AcOEt) to give **233-1** as colorless oil (500 mg, 20%).

[0750] To a solution of **233-2** (300 mg, 0.337mmol) and NMI (276.6 mg, 3.37 mmol) in anhydrous CH_3CN (0.9 mL) was added **233-1** (388 mg, 1.011 mmol) in CH_3CN (0.3 mL) dropwise at 0°C. The mixture was stirred at RT overnight. The reaction was quenched with water, and extracted with AcOEt. The organic phase was washed with brine, dried over anhydrous sodium sulfate, and concentrated at low pressure. The residue was purified by silica gel column (33% EA in PE) to give **233-3** as a yellow powder (300 mg, 71.9%).

[0751] **233-3** (300 mg, 0.243 mmol) was dissolved in 80% CH_3COOH (3 mL), and the mixture was stirred at 60°C for 2.5 h. The mixture was partitioned between AcOEt and water. The organic layer phase was washed by brine, dried over sodium sulfate and concentrated at low pressure. The residue was purified by silica gel column (50% EA in PE) to give **233** as a yellow powder (81 mg, crude product). The crude product (81 mg) was purified by RP HPLC to give **233** as a white solid. (28.7 mg, 17.1%). ESI-LCMS: m/z 694.1 $[M+H]^+$.

EXAMPLE 131
COMPOUND 234



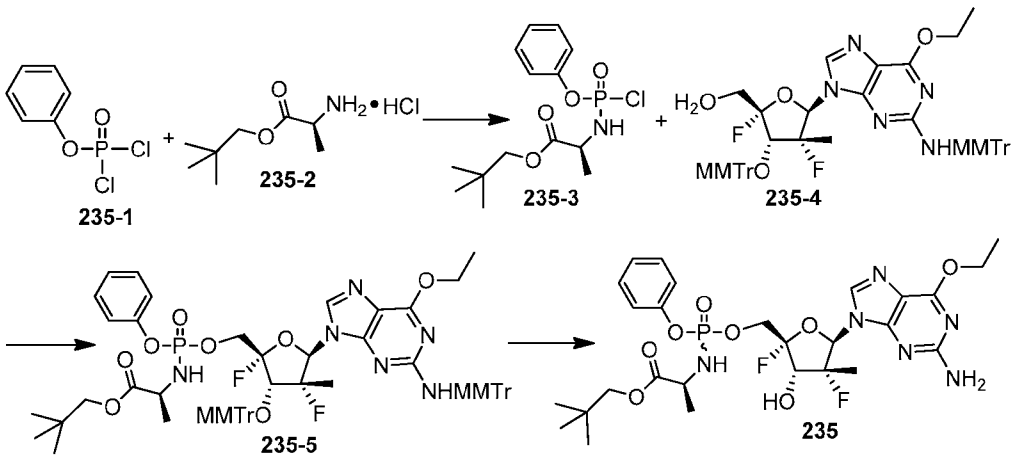
[0752] **234-1** was prepared using a similar procedure as for the preparation of **233-1** using phosphoryl trichloride (2.00 g, 13.16 mmol), 1-naphthol (1.882 g, 13.16 mmol)

and (*S*)-neopentyl 2-aminopropanoate hydrochloride (2.549 g, 13.16 mmol). **234-1** (600 mg, 12%) was obtained as a colorless oil.

[0753] A solution of **234-2** (230 mg 0.26 mmol) and NMI (212 mg 2.60 mmol) in anhydrous CH_3CN (1 mL) was treated with a solution of **234-1** (300 mg 0.78 mmol) in anhydrous CH_3CN (0.5 mL) at RT. The mixture was stirred at RT overnight. The reaction was quenched with water, and extracted with EA (3 x 20 mL). The organic layer was washed with brine, dried by anhydrous sodium sulfate, and concentrated at low pressure. The residue was purified by a silica gel column (CH_3OH in CH_2Cl_2 from 1% to 5%) to give **234-3** (300 mg, 93%) as a white solid.

[0754] **234-3** (300 mg, 0.24 mmol) was dissolved in CH_3COOH (80%, 5 mL). The mixture was stirred at 60°C for 2.5 h. The mixture was diluted with EA (30 mL) and washed with brine. The organic phase was dried over anhydrous sodium sulfate, and concentrated at low pressure. The residue was purified by a silica gel column (CH_3OH in CH_2Cl_2 from 1% to 5%) to give crude **234** (105 mg). The crude product was purified by HPLC (0.1% NH_4HCO_3 in water and CH_3CN) to give **234** (45 mg, 26%) as a white solid. ESI-LCMS: m/z 693.2 $[M+H]^+$.

EXAMPLE 132
COMPOUND 235



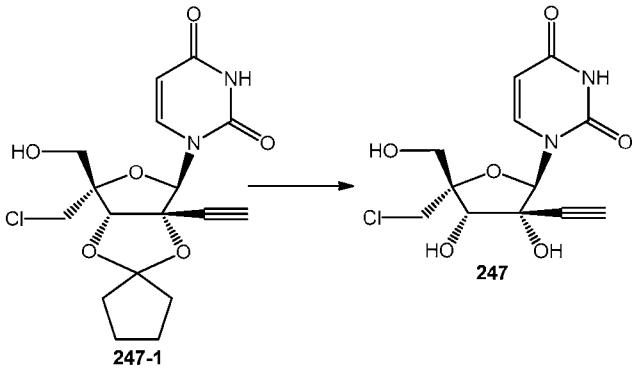
[0755] A stirred solution of **235-1** (2.00 g, 13.99 mmol) and **235-2** (2.00 g, 13.99 mmol) in anhydrous DCM (8 mL) was treated with a solution of TEA (3.11 g, 30.8 mmol) in DCM (20 mL) dropwise at -78°C. The mixture was stirred for 2 h. at -78 °C and then gradually warmed to RT. The organic solvent was removed at low pressure, and the residue

was dissolved in methyl-butyl ether. The precipitate was filtered off, and the filtrate was concentrated at low pressure. The residue was purified on a silica gel column (dry DCM) to give **235-3** as colorless oil (1 g, 20.96%).

[0756] **235-4** (260 mg, 0.29 mmol) was coevaporated with toluene 3 times to remove H_2O. Dried **235-4** was treated with MeCN (0.8 mL) and NMI (240 mg, 2.9 mmol) and then stirred for 10 mins. The mixture was treated with a solution of **235-3** (291 mg, 0.87 mmol) in MeCN (0.4 mL), and then concentrated at low pressure. The residue was purified on a silica gel column (75% EA in PE)) to give **235-5** (300 mg, 86%) as a white solid.

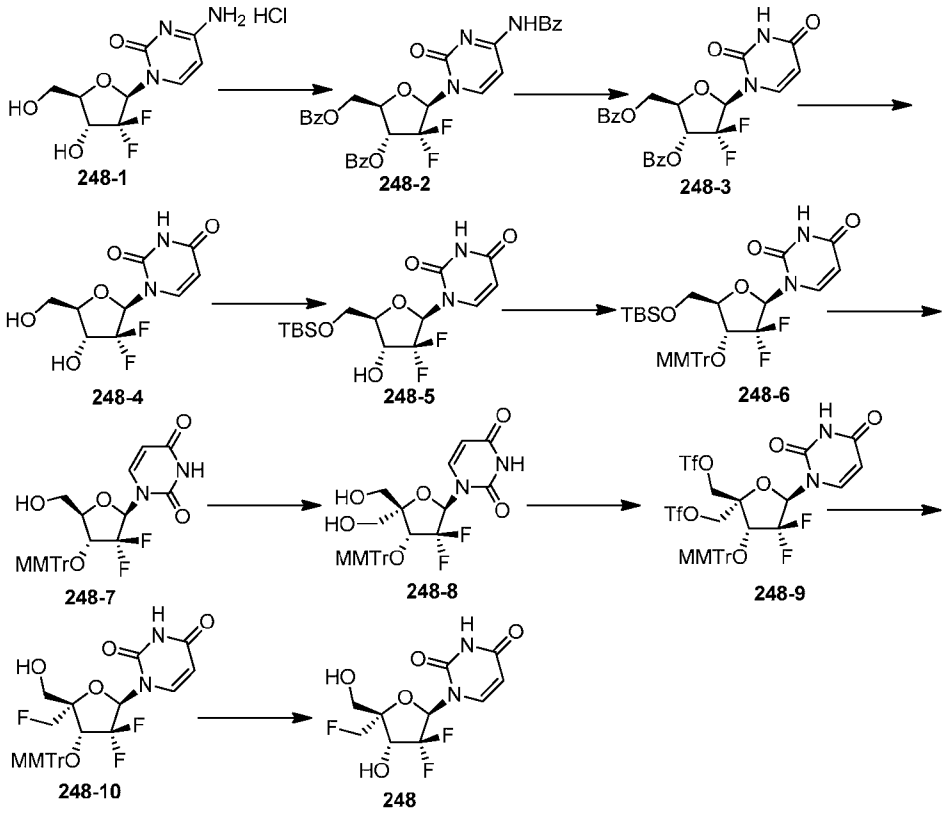
[0757] **235-5** (300 mg, 0.25 mmol) was treated with CH_3COOH (5 mL, 80%), and stirred at 50 °C for 3 h. The mixture was diluted with EA. The solution was washed with brine, dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by silica gel column chromatography (67% EA in PE) to give crude **235**, which was purified by HPLC. The product was dried by lyophilization to give **235** (30 mg, 18.5%) as a white solid. ESI-LCMS: m/z 643 $[M+H]^+$.

EXAMPLE 133
COMPOUND 247



[0758] **247-1** (50 mg, 0.13 mmol) was dissolved in 80% formic acid (3 mL) and heated at 50 °C overnight. The solvent was evaporated, co-evaporated with water to remove the acid. The residue was dissolved in a mixture of methanol and triethylamine (3 mL, 4:1 v:v). After 0.5 h, the solvent was evaporated. The nucleoside was lyophilized from water to yield **247** (40 mg, 97%). MS: m/z 315.5 [M-1].

EXAMPLE 134
COMPOUND 248



[0759] To a stirred solution of **248-1** (15.0 g, 50.2 mmol) in anhydrous pyridine (180 mL) was added BzCl (23.3 g, 165.5 mmol) at 0 °C under N_2 atmosphere. The mixture was stirred for 12 h at RT. The mixture was diluted with EA and washed with sat.$NaHCO_3$ aq. solution and brine. The organic layer was dried with anhydrous Na_2SO_4 and filtered. The organic phase was concentrated to dryness at low pressure. The residue was purified by column chromatography (15% EtOAc in PE) to give **248-2** (27 g, 93.5%) as a white solid.

[0760] **248-2** (27.0 g, 47 mmol) was dissolved in 90% HOAc (250 mL). The mixture was stirred at 110 °C for 12 h. The solvent was removed under reduced pressure. The residue was diluted with EA and washed with sat. $NaHCO_3$ aq. solution and brine. The organic layer was dried over anhydrous Na_2SO_4 and filtered. The organic phase was concentrated at low pressure to give crude **248-3** (21.7 g, crude) as a light yellow solid.

[0761] **248-3** (21.7 g, 45.9 mmol) was treated with NH_3/MeOH (600 mL) and stirred at RT for 12 h. The solvent was concentrated under reduced pressure to give the

crude product. The crude product was purified by column chromatography (5% MeOH in DCM) to give **248-4** (12 g, 99%) as a white solid.

[0762] To a stirred solution of **248-4** (15.0 g, 56.8 mmol) in anhydrous pyridine (200 mL) was added imidazole (7.7g, 113.6 mmol) and TBSCl (9.4 g, 62.5 mmol) at RT. The mixture was stirred at RT for 12 h. The solvent was removed under reduced pressure. The residue was diluted with EA and washed with sat. $NaHCO_3$ aq. solution and brine. The organic phase was dried over anhydrous Na_2SO_4 and filtered. The organic phase was concentrated at a low pressure to give crude **248-5** (21.3 g, crude) as a light yellow solid.

[0763] To a stirred solution of **248-5** (21.3 g, crude) in anhydrous DCM (200 mL) was added collidine (6.8 g, 56.8 mmol), MMTrCl (17.8 g, 56.8 mmol) and $AgNO_3$ (9.6 g, 56.8 mmol) at RT. The mixture was stirred at RT for 12 h. The solid was removed by filtration, and the filtrate was washed with sat.$NaHCO_3$ aq. solution and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by column chromatography (5% EA in PE) to give **248-6** (32 g, 87%) as a light yellow solid.

[0764] **248-6** (32 g, 49.2 mmol) was dissolved in a solution of TBAF in THF (1M, 4.0 eq.) at RT. The mixture was stirred at RT for 12 h. The solvent was removed under reduced pressure. The residue was diluted with EA and washed with brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated at low procedure. The residue was purified by column chromatography (33% EA in PE) to give **248-7** (21.0 g, 79%) as a white solid.

[0765] To a stirred solution of **248-7** (21.0 g, 38.8 mmol) in anhydrous DCM (200 mL) was added pyridine (9.2 mL, 116.4 mmol) and Dess-Martin periodinane (49 g, 116.4 mmol) at 0 °C. The mixture was stirred at RT for 4 h. The reaction was quenched with sat. $Na_2S_2O_3$ solution and sat. $NaHCO_3$ aq. solution. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude product (21.0 g).

[0766] The crude product (21.0 g, crude) was dissolved in dioxane (200 mL) and treated with 37% aqueous formaldehyde (20 mL, 194 mmol) and 2.0 N aqueous sodium hydroxide (37.5 mL, 77.6 mmol). The mixture was stirred at RT for 12 h. The solution was treated with $NaBH_4$ (8.8 g, 232.8 mmol). After stirring for 0.5 h at RT, the reaction was

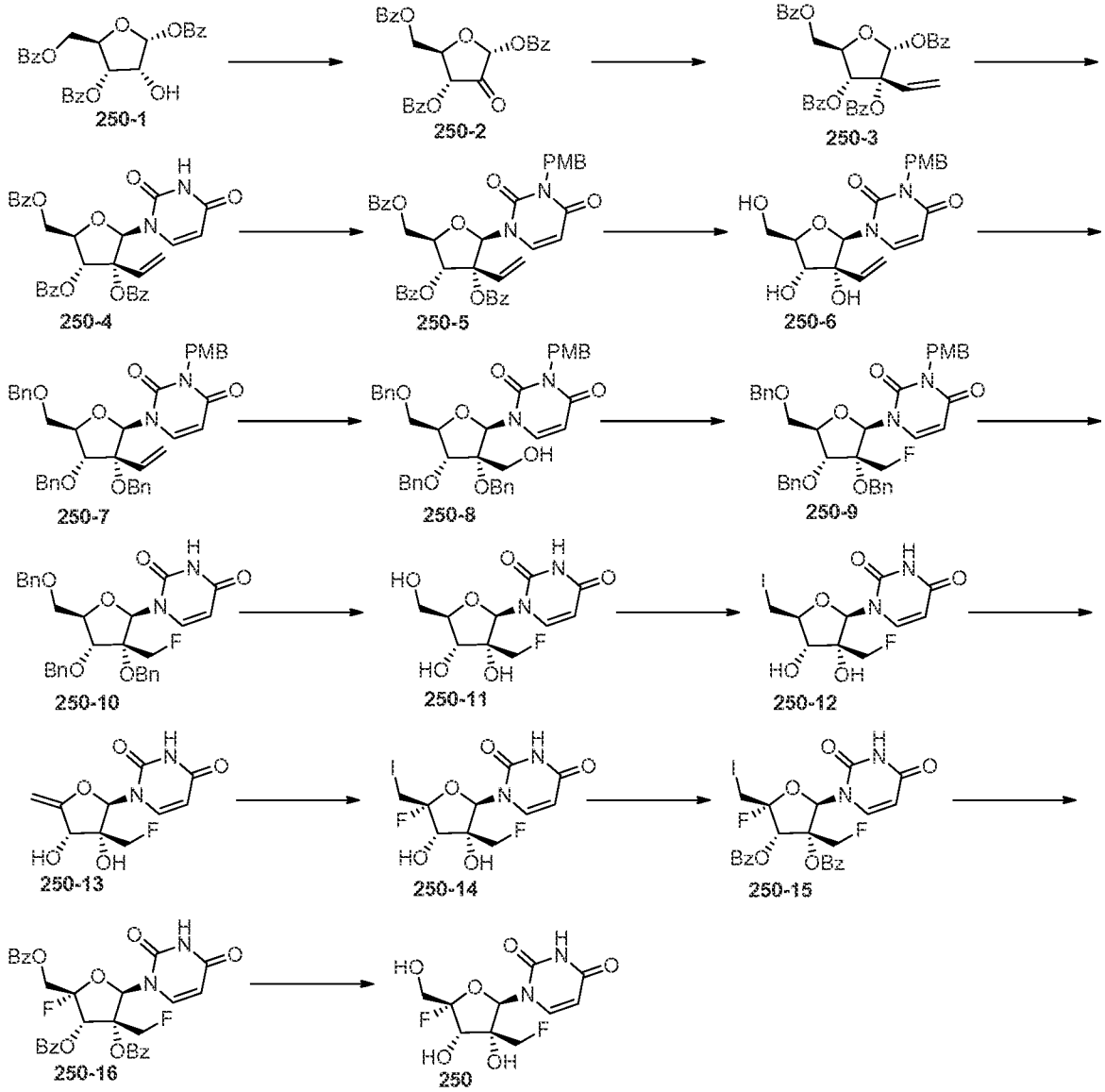
quenched with ice water. The mixture was diluted with EA and washed with brine. The organic phase was dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by column chromatography (4% MeOH in DCM) to give **248-8** (10.0 g, 50.5%) as a white foam.

[0767] **248-8** (4.8 g, 8.5 mmol) was co-evaporated with toluene (2x). The residue was dissolved in anhydrous DCM (45 mL) and pyridine (6.7 g, 85 mmol). The solution was cooled to 0 °C. Triflic anhydride (4.8 g, 18.7 mmol) was added dropwise over 10 mins. At 0 °C, the mixture was stirred over 40 mins and monitored by TLC (PE: EA= 1:1). The mixture was diluted with CH_2Cl_2 (50 mL). The solution was washed with sat. $NaHCO_3$ solution. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by column chromatography (PE: EA = 100:0-4:1) to give **248-9** (6.1 g, 86.4%) as a brown foam.

[0768] **248-9** (6.1 g, 7.3 mmol) was dissolved in MeCN (25 mL). A solution of TBAF in THF (1M, 25 mL) was added at RT. The mixture was stirred at RT for 12 h. A solution of TBAF in THF (1M, 15 mL) was added, and the mixture was stirred for 4 h. The mixture was treated with aq. NaOH (1N, 14.6 mmol) and the mixture was stirred for 1 h. The reaction was quenched with water and extracted with EA. The organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by column chromatography (50% EA in PE) to give **248-10** (2.1 g, 50.6%) as a white solid.

[0769] **248-10** (700 mg, 1.23 mmol) was dissolved in 80% HCOOH (40 mL) at RT. The mixture was stirred at RT for 2 h. The reaction was quenched with MeOH (40 mL) and stirred for 12 h. The solvent was concentrated at low pressure, and the residue was purified by column chromatography (5% MeOH in DCM) to give **248** (210 mg, 57.7%) as a white solid. ESI-MS: m/z 296.9 $[M+H]^+$.

EXAMPLE 135
COMPOUND 250



[0770] A mixture of **250-1** (120 g, 0.26 mol) and IBX (109 g, 0.39 mol) in CH_3CN (2.0 L) was heated to refluxed and stirred for 12 h. After cooling down to RT, the mixture was filtered. The filtrate was concentrated to dryness at low pressure.

[0771] **250-2** (130 g, crude, 0.26 mol) was co-evaporated with anhydrous toluene (3x). Vinyl magnesium bromide (700 mL, 0.78 mol, 1.0 N in THF) was added dropwise into a solution of **250-2** in THF (300 mL) over 30 mins at -78 °C, and the mixture was stirred for about 1 h at RT. When the starting material was consumed as determined by TLC, the

mixture was poured into a sat. NH_4Cl solution. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated at low pressure.

[0772] To a solution of the above residue (170 g, crude, 0.346 mol) in anhydrous CH_2Cl_2 was added TEA (105 g, 1.04 mol), DMAP (84 g, 0.69 mol), and benzoyl chloride (146 g, 1.04 mol), and stirred for 12 h at RT. The mixture was diluted with CH_2Cl_2 and washed with sat. aq. $NaHCO_3$. The combined aq. phase was extracted with DCM (100 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated to dryness under reduced pressure. The residue was purified by column chromatography using EA in PE (10% to 50%) to get **250-3** (107 g, 52%).

[0773] A mixture of uracil (co-evaporated with toluene (2x)) and NOBSA (81.4 g, 0.4 mol) and CH_3CN (150 mL) was stirred to reflux for 1.5 h. After cooling to RT, the mixture was treated with **250-3** (59 g, 0.1 mol) and TMSOTf (155 g, 0.7 mol). The mixture was heated to 60-70 °C, and stirred for 12 h. After cooling to RT, the mixture was poured into a sat. $NaHCO_3$ solution, and a solid precipitated. After filtration, pure **250-4** was obtained as a white solid (40 g, 69%) was obtained.

[0774] To a solution of **250-4** (50 g, 0.086 mol), K_2CO_3 (17.8 g, 0.13 mol) in DMF (50 mL) was added PMBCl (16 g, 0.1 mol) at 0 °C, and stirred at RT for 12 h. The reaction was quenched with water, and extracted with EA (3 x 100 mL). The organic phase was washed with brine, dried over anhydrous Na_2SO_4, and concentrated at low pressure to give **250-5** (65 g).

[0775] A mixture of **250-5** (65 g, 0.086 mol) and NaOMe (16.8 g, 0.3 mol) in MeOH:DCM (500 mL, v:v = 4:1) was stirred at RT for 2.5 h. The reaction was quenched with CO_2 (solid) and concentrated at low pressure. The residue was dissolved in EA (200 mL). The solution was washed with water, dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by column chromatography (4% MeOH in DCM) to give **250-6** as a yellow foam (25 g, 75%).

[0776] To a mixture of **250-6** (25.5 g, 0.065 mol) in DMF (60 mL) was added NaH (10.5 g, 0.26 mol, 60% in coal oil) BnBr (36.3 g, 0.21 mol) in an ice bath, and stirred at RT for 12 h. The reaction was quenched with NH_4Cl (aq.), and the mixture was diluted with EA (150 mL). The solution was washed with brine, dried over anhydride Na_2SO_4, and

concentrated at low pressure. The residue was purified by sil-gel (15% EA in PE) to give **250-7** (20 g, 46%).

[0777] To a solution of **250-7** (20 g, 0.03 mol) and NMMO (7 g, 0.06 mol) in THF:H_2O (100 mL, v:v = 5:1) was added OsO_4 (2.6 g, 0.01 mol) at RT, and stirred at RT for 24 h. The reaction was quenched with sat. $Na_2S_2O_3$ solution, and extracted with EA (3 x 80 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated at low pressure.

[0778] To a solution of diol-product (0.03 mol) in MeOH:H_2O:THF (v:v:v = 170 mL:30 mL:50 mL) was added $NaIO_4$ (9.6 g, 0.045 mol) at RT, and stirred at RT for 2 h. After filtration, the filter was used directly for the next step.

[0779] The previous solution was treated with $NaBH_4$ (1.8 g, 0.048 mol) at 0 °C, and stirred at RT for 30 mins. The reaction was quenched with HCl (1 N) solution. The mixture was extracted with EA (3 x 60 mL). The organic phase was washed with brine, dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by sil-gel (25 % EA in PE, TLC: PE:EA = 2:1, Rf = 0.6) to give **250-8** (12 g, 61% over 3 steps).

[0780] To a solution of **250-8** (14 g, 21 mmol) and DMAP (5.1 g, 42 mmol) in DCM (60 mL) was added MsCl (3.1 g, 27 mmol) at 0 °C, and stirred at RT for 40 mins. The reaction was quenched with sat. $NaHCO_3$ solution. The organic phase was washed with HCl (0.2 N) solution, dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by sil-gel (25% EA in PE) to give the Ms-product (14 g, 90%) as a white solid.

[0781] Ms-product (41 g, 55 mmol) was treated with TBAF (Alfa, 1 N in THF, 500 mL), and stirred at 70-80 °C for 3 days. The mixture was concentrated at low pressure. The residue was dissolved in EA (200 mL). The solution was washed with brine, dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by sil-gel column (25% EA in PE) to give **250-9** (9.9 g, 27%).

[0782] To a solution of **250-9** (6.3 g, 9.45 mmol) in CAN:H_2O (v:v = 3:1, 52 mL) was added CAN (15.5 g, 28.3 mmol), and stirred at RT overnight. The reaction was quenched with water, and extracted with EA (3 x 80 mL). The organic phase was washed with brine, dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was

purified by column chromatography (25% EA in PE) to give **250-10** (3.6 g, 71 %) as a yellow oil.

[0783] To a solution of **250-10** (2.4 g, 4.4 mmol) in anhydrous DCM (10 mL) was added BCl_3 (1 N, 30 mL) at -70 °C, and stirred for 2 h at -70 °C. The reaction was quenched with MeOH at -70 °C. The mixture was concentrated directly under 35 °C at low pressure. The residue was purified by column chromatography (50% EA in PE to 100% EA) to give **250-11** (1.2 g, 86%). ESI-MS: m/z 277.1 $[M+H]^+$.

[0784] To a solution of PPh_3 (3.37 g, 12.8 mmol) in pyridine (15 mL) was added I_2 (3.06 g, 12 mmol) at 0 °C, and stirred at RT for 30 mins until the orange color appeared. The mixture was cooled to 0 °C, and treated with **250-11** (2.2 g, 8 mmol) in pyridine (5 mL), and stirred at RT under N_2 for 12 h. The reaction was quenched with $Na_2S_2O_3$ (sat., 30 mL), and extracted with EA (3 x 60 mL). The organic phase was washed with brine, dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by column chromatography (1% to 2% MeOH in DCM) to give **250-12** (1.8 g, 58%) as a light yellow foam.

[0785] A mixture of **250-12** (1.35 g, 3.5 mmol) and DBU (1.06 g, 7 mmol) in THF:CH_3CN (v:v = 10 mL:5 mL) was stirred at 60-70 °C for 2 h. The mixture was diluted with EA (50 mL), and adjusted to pH=7-8 with HCl (0.2 N) solution. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by column chromatography to give **250-13** (0.5 g, 55%).

[0786] To a solution of **250-13** (670 mg, 2.6 mmol) in CH_3CN (6 mL) was added NIS (730 mg, 3.25 mmol) and 3HF·TEA (335 mg, 2.1 mmol) at 0 °C, and stirred at RT for 2 h. The reaction was quenched with $NaHCO_3$ (sat.) solution and $Na_2S_2O_3$ (sat.) solution, and extracted with EA (3 x 30 mL). The organic phase was washed with brine, dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by column chromatography (50% EA in PE and 2% MeOH in DCM) to give **250-14** (1.2 g, 80%) as a brown oil.

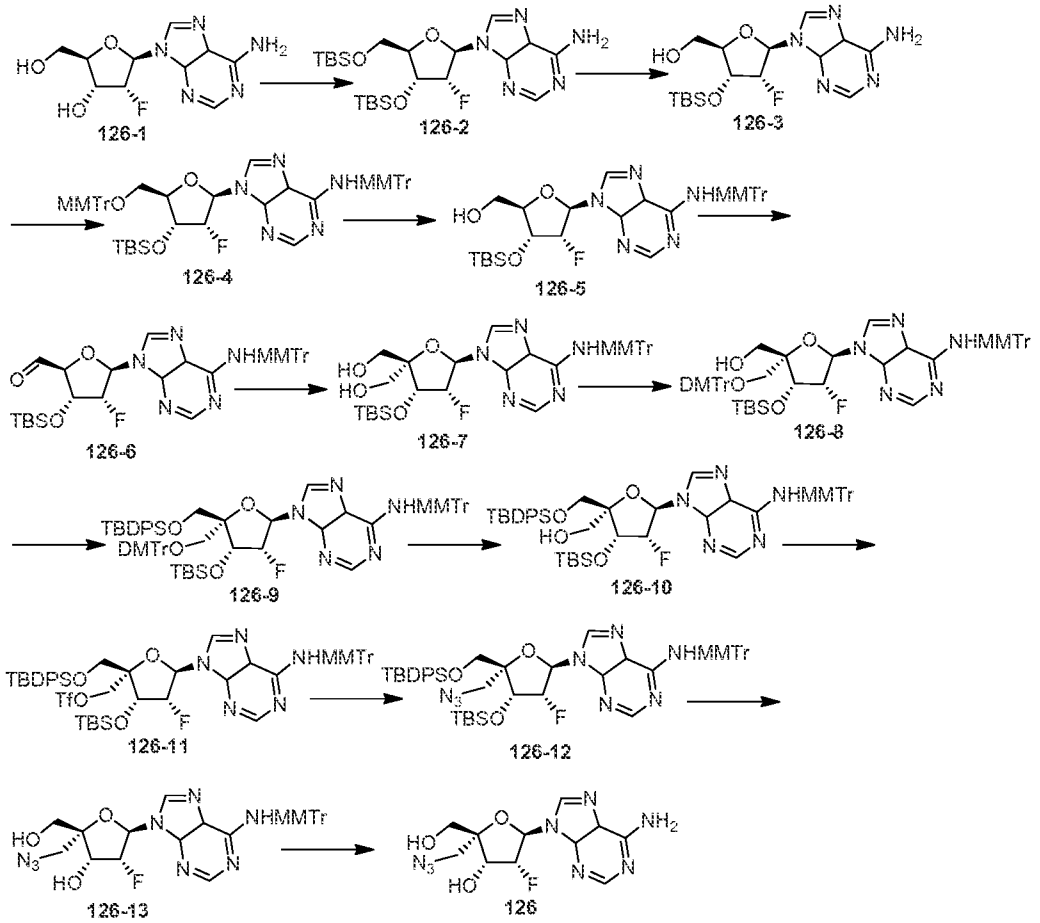
[0787] To a solution of **250-14** (1.0 g, 2.47 mmol), DMAP (0.75 g, 6.2 mmol) and TEA (0.75 g, 7.42 mmol) in DCM (10 mL) was added BzCl (1.15 g, 8.16 mmol) in DCM (1 mL) at 0 °C, and stirred at RT for 12 h. The reaction was quenched with $NaHCO_3$ (aq.) solution. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, and

concentrated at low pressure. The residue was purified by column chromatography (30% EA in PE) to give **250-15** (850 mg, 85%).

[0788] A mixture of **250-15** (600 mg, 1 mmol), BzONa (1.45 g, 10 mmol), and 15-crown-5 (2.2 g, 10 mmol) in DMF (25 mL) was stirred at 90-100 °C for 24 h. The mixture was diluted with EA (20 mL). The solution was washed with brine, dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by column chromatography (30% EA in PE) to give **250-16** (275 mg, 37%) as a light yellow foam.

[0789] A mixture of **250-16** (250 mg, 0.41 mmol) in NH_3·MeOH (7 N, 5 mL) was stirred at RT for 15 h. The mixture was concentrated at low pressure directly. The residue was purified by column chromatography (50% EA in PE) and re-purified by prep-HPLC to give **250** (33 mg, 25%) as a white solid. ESI-MS: m/z 295.1 $[M+H]^+$.

EXAMPLE 136
COMPOUND 126



[0790] To a solution of **126-1** (3.0 g, 11.15 mmol) in anhydrous pyridine (90 mL) was added imidazole (3.03 g, 44.59 mmol) and TBSCl (6.69 g, 44.59 mmol) at 25 °C under N_2 atmosphere. The solution was stirred at 25 °C for 15 h. The solution was concentrated to dryness under reduced pressure. The residue was dissolved in EA. The solution was washed with sat. $NaHCO_3$ and brine, and dried over anhydrous $MgSO_4$. The solvent was removed at low pressure to give crude **126-2** (4.49 g, 90 %) as a white solid.

[0791] To a stirred solution of **126-2** (3.5 g, 7.04 mmol) in a mixture of EA and EtOH (1:1, 55 mL) was added TsOH (10.7 g, 56.34 mmol) at 0 °C. The mixture was stirred at 30 °C for 8 h. Water (30 mL) was added, and the solution was removed to dryness. The residue was purified on a silica gel column (10% MeOH in DCM) to give **126-3** (1.75 g, 65%) as a white foam.

[0792] To a solution of **126-3** (3.4 g, 8.88 mmol) in anhydrous pyridine (17 mL) was added collidine (4.3 g, 35.51 mmol), $AgNO_3$ (5.50 g, 35.51 mmol) and MMTrCl (8.02 g, 26.63 mmol) at 25 °C under N_2. The mixture was stirred at 25 °C for 12 h. MeOH (20 mL) was added, and the solvent was removed to dryness at low pressure. The residue was purified on a silica gel column (10% EA in PE) to give **126-4** (5.76 g, 70%) as a white foam.

[0793] To a solution of **126-4** (2.0 g, 2.16 mmol) in anhydrous DCM (10 mL) was added $Cl_2CHCOOH$ (2.8 g, 21.57 mmol) dropwise at -78 °C. The mixture was warmed to -10 °C and stirred at this temperature for 20 mins. The reaction was quenched with sat.$NaHCO_3$ at -10 °C. The mixture was extracted with DCM, washed with brine, and dried over anhydrous $MgSO_4$. The solution was concentrated at low pressure. The residue was purified on silica gel column (10% EA in PE) to give **126-5** (0.99 g, 70%) as a white foam.

[0794] To a stirred solution of **126-5** (3.5 g, 5.34 mmol) in anhydrous DMSO (35 mL) was added DCC (3.30 g, 16.03 mmol) and Py·TFA (1.03 g, 5.34 mmol). The mixture was stirred at 30 °C for 1 h. The reaction was quenched with cold water at 0 °C, and extracted with EA (3 x 60 mL). The precipitate was filtered. The organic layers were washed with brine (3x) and dried over anhydrous $MgSO_4$. The organic phase was concentrated at low pressure to give crude **126-6** (3.5 g) as a yellow oil.

[0795] To a stirred solution of **126-6** (3.5 g, 5.34 mmol) in MeCN (35 mL) was added 37% HCHO (11.1 mL) and TEA (4.33 g, 42.7 mmol). The mixture was stirred at 25 °C for 12 h. The mixture was treated with EtOH (26 mL) and $NaBH_4$ (3.25 g, 85.5 mmol)

and then stirred for 30 mins. The reaction was quenched with sat. aq. NH_4Cl and extracted with EA (3 x 60 mL). The organic layer was dried over anhydrous $MgSO_4$, and concentrated at low pressure. The residue was purified by column chromatography (from 10% EA in PE to 50% DCM in PE) to give **126-7** (1.46 g, 40%) as a white solid.

[0796] To a stirred solution of **126-7** (1.85 g, 2.7 mmol) in pyridine (24 mL) and DCM (9.6 mL) was added DMTrCl (1.3 g, 3.9 mmol) at -35 °C under N_2 atmosphere. The solution was stirred at 25 °C for 16 h. The mixture was treated with MeOH (15 mL) and concentrated at low pressure. The residue was purified by column chromatography (EA in PE from 10% to 30%) to give **126-8** (1.60 g, 60 %) as a white solid.

[0797] To a solution of **126-8** (1.07 g, 1.08 mmol) in anhydrous pyridine (5 mL) was added $AgNO_3$ (0.65 g, 3.79 mmol) and TBDPSCl (1.04 g, 3.79 mmol). The mixture was stirred at 25 °C for 16 h. The solvent was removed under reduced pressure. The residue was dissolved in EA (50 mL). The resulting solution was washed with brine. The organic layer was dried over anhydrous $MgSO_4$, and concentrated at low pressure. The residue was purified on a silica gel column (10% EA in PE) to give **126-9** (0.93 g, 70%) as a white foam.

[0798] To a stirred solution of **126-9** (1 g, 0.82 mmol) in anhydrous DCM (13.43 mL) was added $Cl_2CHCOOH$ (2.69 mL) at -78 °C. The mixture was stirred at -10 °C for 20 mins. The reaction was quenched with sat. aq. $NaHCO_3$ and extracted with DCM. The organic layer was dried over anhydrous Na_2SO_4, and concentrated at low pressure. The organic phase was purified by column chromatography (MeOH in DCM form 0.5% to 2%) to give **126-10** (0.48 g, 65%) as a solid.

[0799] To an ice cold solution of **126-10** (0.4 g, 0.433 mmol) in anhydrous DCM (2.7 mL) was added pyridine (171 mg, 2.17 mmol) and Tf_2O (183 mg, 0.65 mmol) by dropwise at -35 °C. The mixture was stirred at -10 °C for 20 mins. The reaction was quenched with ice water and stirred for 30 mins. The mixture was extracted with DCM (3 x 20 mL). The organic phase was washed with brine (100 mL), dried over anhydrous Na_2SO_4, and concentrated at low pressure to give crude **126-11** (0.46 g), which was used for next step without further purification.

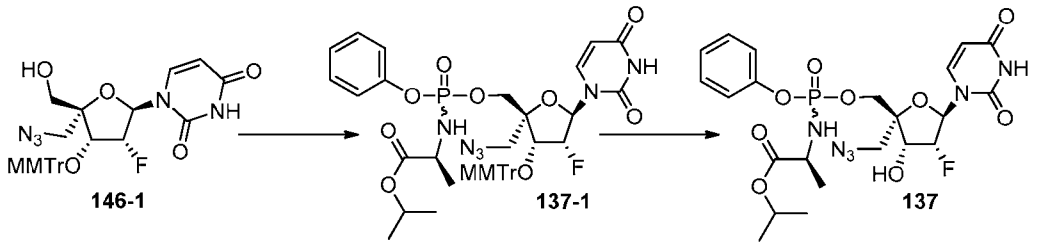
[0800] To a solution of **126-11** (0.46 g, 0.43 mmol) in anhydrous DMF (2.5 mL) was added NaN_3 (42 mg, 0.65 mmol). The mixture was stirred at 30 °C for 16 h. The solution was diluted with water and extracted with EA (3 x 30 mL). The combined organic

layers were dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified on a silica gel column (EA in PE from 5% to 15%) to give **126-12** (0.31 g, 70%) as a solid.

[0801] To a solution of **126-12** (0.31 g, 0.33 mmol) in MeOH (5 mL) was added NH_4F (0.36 g, 9.81 mmol) at 70 °C. The mixture was stirred at this temperature for 24 h. The mixture was evaporated to dryness. The residue was purified on silica gel column (MeOH in DCM from 0.5% to 2.5%) to give **126-13** (117 mg, 60%) as a white solid.

[0802] **126-13** (300 mg, 0.50 mmol) was dissolved in 80% of HOAc (20 mL). The mixture was stirred at 55 °C for 1 h. The reaction was quenched with MeOH and concentrated at low pressure. The residue was purified by prep-HPLC to give **126** (100 mg, 61.3 %) as a white solid. ESI-LCMS: m/z 325.1 $[M+H]^+$.

EXAMPLE 137
COMPOUND 137

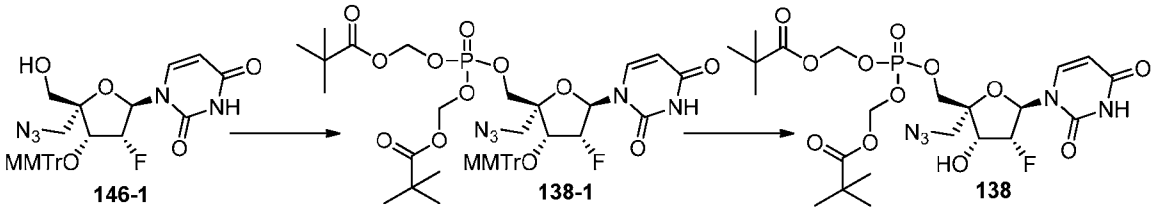


[0803] To a stirred solution of **146-1** (80 mg, 0.14 mmol) in anhydrous CH_3CN (2.0 mL) was added N-methylimidazole (0.092 mL, 1.12 mmol) at 0 °C (ice/water bath). A solution of phenyl (isopropoxy-L-alaninyl) phosphorochloridate (128 mg, 0.42 mmol, dissolved in CH_3CN (0.5 mL)) was then added (prepared according to a general procedure as described in McGuigan et al., *J. Med. Chem.* (2008) 51:5807-5812). The solution was stirred at 0 to 5 °C for h and then stirred at RT for 16 h. The mixture was cooled to 0 to 5 °C, diluted with EA followed by the addition of water (5 mL). The solution was washed with 1.0M citric acid, sat. aq. $NaHCO_3$ and brine, and dried with $MgSO_4$. The residue was purified on silica (10 g column) with EA/hexanes (25-100% gradient) to give **137-1** (57.3 mg, 49 %) as a foam.

[0804] **137-1** (57.3 mg, 0.07 mmol) was dissolved in anhydrous CH_3CN (0.5 mL), and 4N HCl in dioxane (68 µL, 0.27 mmol) was added at 0 to 5 °C. The mixture was stirred at RT for 2 h, and anhydrous EtOH (100 µL) was added. The solvents were

evaporated at RT and co-evaporated with toluene (3x). The residue was purified on silica (10 g column) with MeOH/CH_2Cl_2 (1-7% gradient) and lyophilized to give **137** (27.8 mg, 72%) as a white foam. ESI-LCMS: m/z = 571.1 $[M+H]^+$, 1141.2 $[2M+H]^+$.

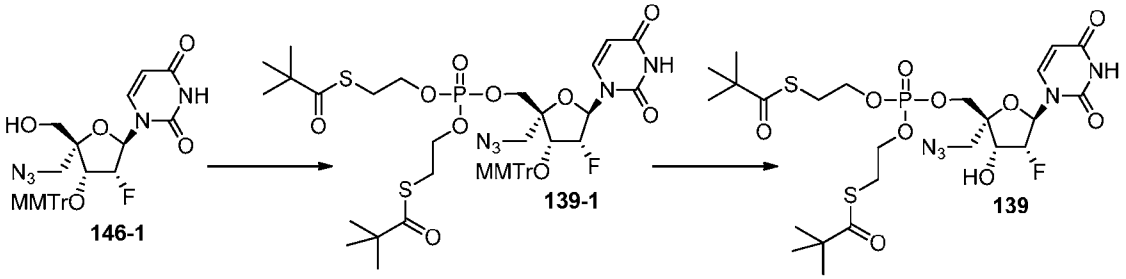
EXAMPLE 138
COMPOUND 138



[0805] **138-1** (68.4 mg, 44.7 %) was prepared from **146-1** (100 mg, 0.174 mmol) and bis(tert-butoxycarbonyloxymethyl)phosphate (126 mg, 0.35 mmol) with DIPEA (192 µL, 1.04 mmol), BOP-Cl (133 mg, 0.52 mmol), and 3-nitro-1,2,4-triazole (59 mg, 0.52 mmol) in THF (1.5 mL) in the same manner as **169-4**.

[0806] **138** (31.4 mg, 67%) was prepared from **138-1** (68 mg, 0.077 mmol) in the same manner as **146**. ESI-LCMS: m/z = 627.15 $[M+Na]^+$, 1219.25 $[2M+H]^+$.

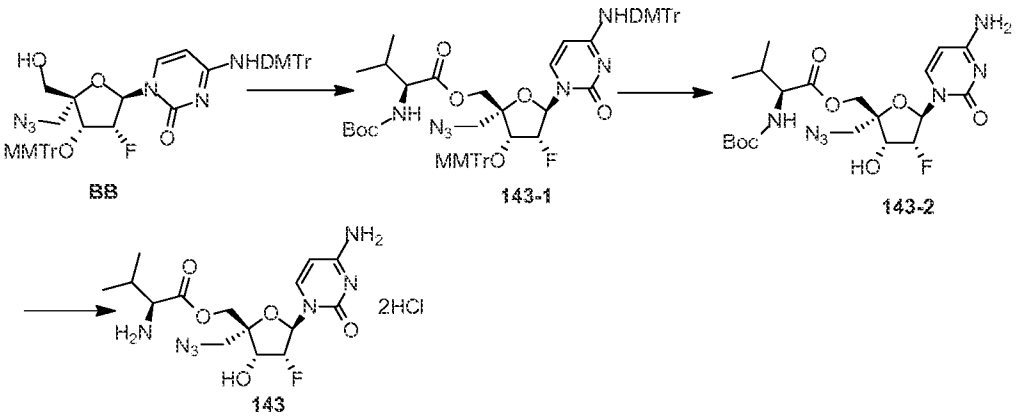
EXAMPLE 139
COMPOUND 139



[0807] To a solution of **146-1** (100 mg, 0.175 mmol) in anhydrous CH_3CN (2 mL) was added 5-ethylthio-1H-tetrazole in CH_3CN (0.25M; 0.84 mL, 0.21 mmol). Bis-SATE-phosphoroamidate (95 mg, 0.21 mmol) in CH_3CN (1 mL) was added at 0 to 5 ^{0}C dropwise. The mixture was stirred 2 h at 0 to 5 ^{0}C under Ar. A solution of 77% *m*-CPBA (78 mg, 0.35 mmol) in DCM (1 mL) was added, and the mixture stirred 2 h at 0 to 5 ^{0}C under Ar. The mixture was diluted with EtOAc (50 mL), washed with 1.0M citric acid, sat. $NaHCO_3$ and brine, and dried with $MgSO_4$. The mixture was filtered, and the solvents were evaporated in vacuo. The residue was purified on silica (10 g column) with EA/hexanes (20-100% gradient) to give **139-1** (105 mg, 63.6 %) as a white foam.

[0808] **139-1** (105 mg, 0.112 mmol) was dissolved in anhydrous CH_3CN (0.8 mL), and 4N HCl in dioxane (84 μL, 0.334 mmol) was added at 0 to 5 °C. The mixture was stirred at RT for 2 h. Anhydrous EtOH (100 μL) was added. The solvents were evaporated at RT, and co-evaporated with toluene (3x). The residue was purified on silica (10 g column) with MeOH/CH_2Cl_2 (1-7% gradient) and lypholized to give **139** (42.7 mg, 57%) as a white foam. ESI-LCMS: m/z = 692.15 $[M+Na]^+$, 1339.30 $[2M+H]^+$.

EXAMPLE 140
COMPOUND 143



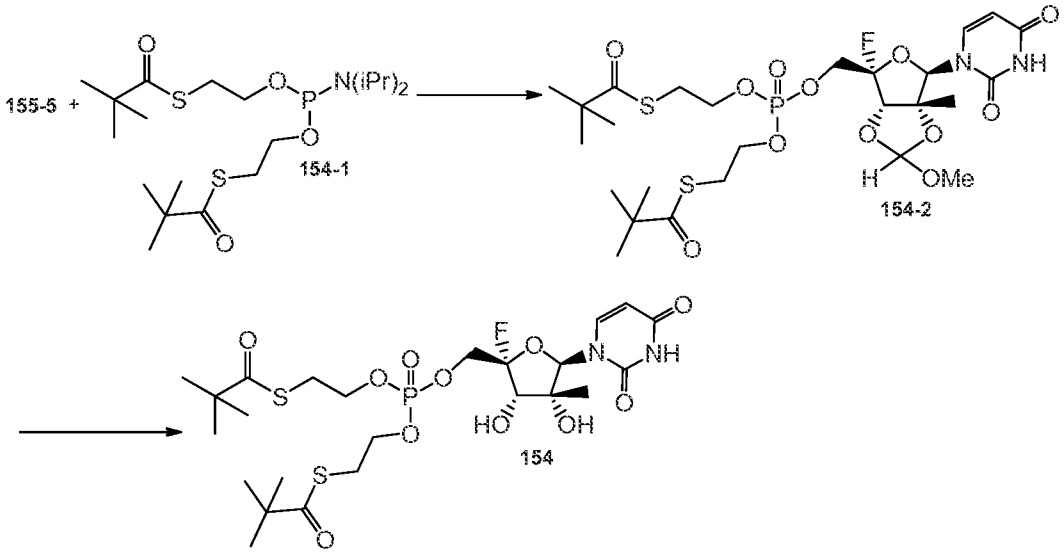
[0809] To a solution of N-Boc-L-Valine (620.78 mg, 2.86 mmol) and TEA (144.57 mg, 1.43 mmol) in anhydrous THF (2.5 mL) was added **BB** (250.00 mg, 285.73 μmol). The mixture was co-evaporated with pyridine and toluene to remove water. The residue was dissolved in THF (2.5 mL). DIPEA (369.28 mg, 2.86 mmol) was added, followed by addition of BOP-Cl (363.68 mg, 1.43 mmol) and 3-nitro-1H-1,2,4-triazole (162.95 mg, 1.43 mmol) at RT (18 °C). The mixture was stirred at RT for 12 h and then diluted with EA (40 mL). The solution was washed with brine, dried over anhydrous Na_2SO_4 and concentrated to dryness at low pressure. The residue was purified on a silica gel column (30% EA in PE) to give **143-1** (220 mg, crude) as a white foam.

[0810] **143-1** (250.0 mg, 232.73 μmol) was dissolved in 80% CH_3COOH (30 mL). The solution was heated to 50 °C and stirred for 12 h. The reaction was quenched with MeOH, and the solution was concentrated to dryness. The residue was purified on a silica gel column (5% MeOH in DCM) to give **143-2** (80.00 mg, 68.82%) as a white foam.

[0811] **143-2** (78.00 mg, 156.16 μmol) was dissolved in HCl/dioxane (1.5 mL) and EA (1.5 mL) at RT (19 °C). The mixture was stirred at RT for 30 mins. The solution

was concentrated to dryness at low pressure. The residue was purified by prep-HPLC to give **143** (23 mg, 31.25%) as a white solid. ESI-MS: m/z 400.20 $[M+H]^+$,799.36$[2M+H]^+$.

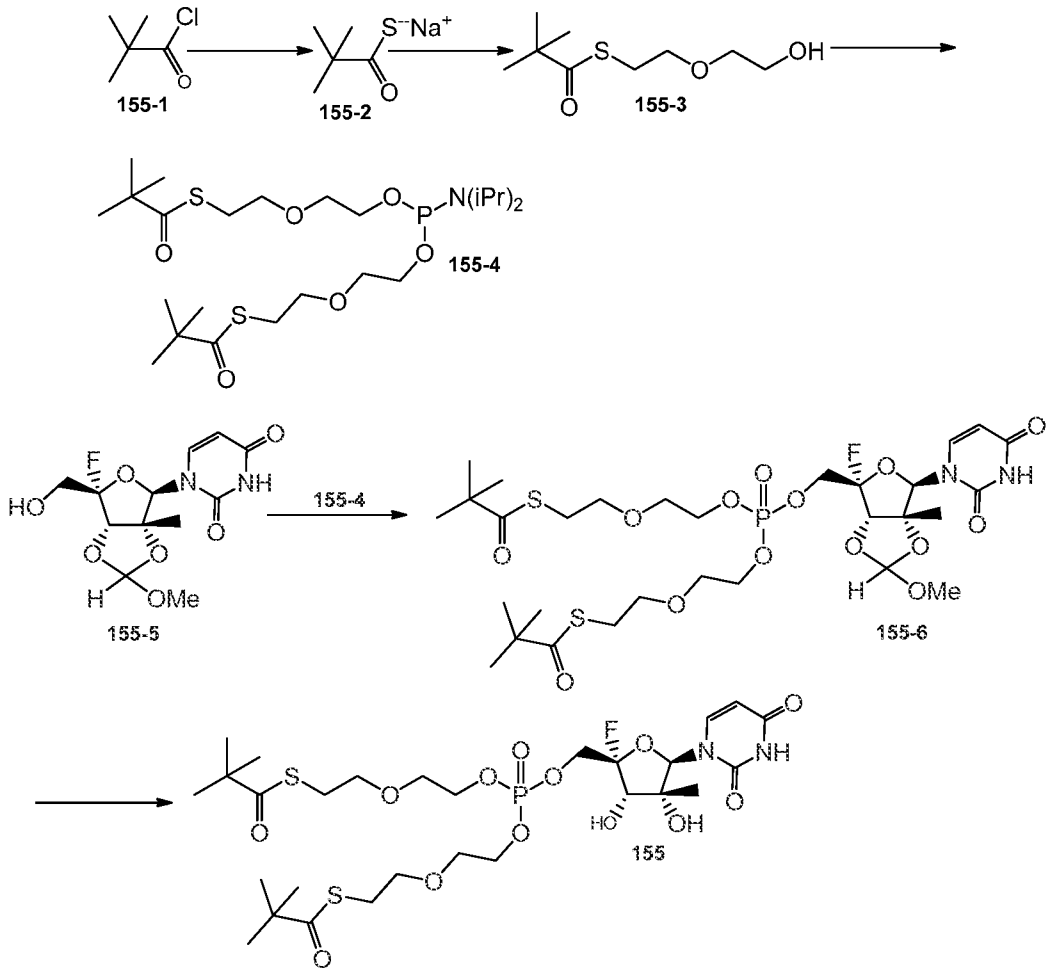
EXAMPLE 141
COMPOUND 154



[0812] **154-1** was prepared according to the procedure described in Lefebre et al., *J. Med. Chem.* (1995) 38:3941-3950, which is hereby incorporated by reference for the limited purpose of its description of the preparation of **154-1**.

[0813] **154-2** (0.33 g, 0.5 mmol) was prepared using a similar procedure to the one used to prepare **155-6** using **155-5** and **154-1**. **154-2** was obtained as a white solid. Using a similar procedure to the one used to prepare **155**, **154-2** was used to prepare **154** (130 mg). ^{1}H-NMR ($CDCl_3$): 7.40 (d, 1H), 6.1 (s, 1H), 5.83 (d, 1H), 4.3 (t, 2H), 4.1-4.2 (m, 6H), 3.2 (t, 4H), 1.69 (s, 4H), 1.3 (s, 3H), 1.23 (s, 18H); ^{31}P-NMR ($CDCl_3$): -2.4 ppm.

EXAMPLE 142
COMPOUND 155

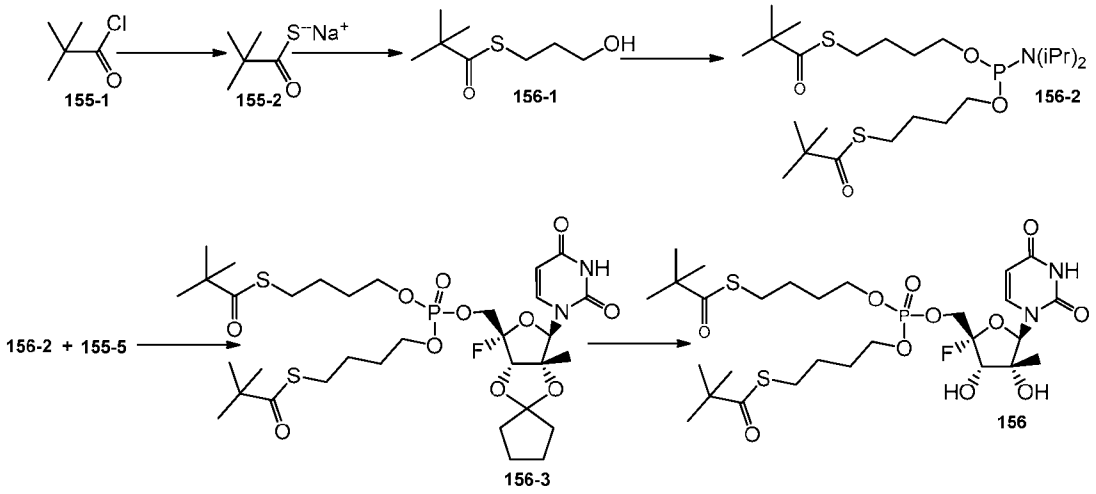


[0814] To a solution of sodium hydrosulfide (4.26 g, 76.0 mmol) in EtOH (100 mL) was added t-butyryl chloride (76.2 mmol; 9.35 mL) dropwise at 0 °C, and the mixture was stirred at RT for 1 h. A solution of 2-(2-chloroethoxy)ethanol (57 mmol; 6.0 mL) and TEA (21 mL, 120 mmol) was added, and the mixture was heated at reflux for 60 h. The mixture was filtered, and then concentrated to a small volume. The residue was dissolved in EA, and then washed with water, sat. aq. $NaHCO_3$ and brine. The organic phase was dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product (10.0 g) was isolated and 5 grams were purified by silica gel flash column chromatography using a gradient of 0 to 100% EA in hexane to give **155-3** (4.5 g, 22 mmol) as a clear, colorless oil. ^{1}H-NMR ($CDCl_3$): 3.70-3.74 (m, 2H), 3.5-3.65 (m, 4H), 3.1 (t, 2H), 1.25 (s, 9H).

[0815] A solution **155-3** (4.5 g; 21.8 mmol) and triethylamine (6.7 mL, 87.2 mmol) in tetrahydrofuran (50 mL) was added dropwise over 1 h to a stirred solution of N,N-diisopropylphosphorodichloridite (2.0 mL, 10.9 mmol) in THF (50 mL) under argon at -78°C. The mixture was stirred at RT for 2 h, and then diluted with EA (200 mL). The mixture was washed with sat. aq. NaCl and dried over Na_2SO_4. After filtration, the filtrate was evaporated under reduced pressure to give a pale yellow oil. Purification by flash column chromatography using a gradient of EA (0-5%) in hexane containing 5% triethylamine afforded **155-4** (2.5 g, 4.25 mmol) as a clear, colorless oil. ^{1}H-NMR ($CDCl_3$): 3.70-3.82 (m, 4H), 3.57-3.65 (m, 10H), 3.1 (t, 4H), 1.25 (s, 18H), 1.17 (t, 12H); ^{31}P-NMR ($CDCl_3$): 148.0 ppm.

[0816] **155-5** (285 mg, 0.9 mmol) and DCI (175 mg, 1.5 mmol) were coevaporated twice with ACN and then dissolved in ACN (5 mL). **155-4** (790 mg, 1.35 mmol) in ACN (4 mL) was added, and the reaction was monitored by TLC. After 15 mins, tert-butylhydroperoxide (0.5 mL of 5.5M solution in decane) was added, and the mixture was stirred for 10 mins. The mixture was diluted with EA (25 mL), washed with sat. aq. $NaHCO_3$ and sat. aq. NaCl solution, dried over Na_2SO_4, filtered and concentrated. Purification by flash column chromatography using a gradient of EA (0-100%) in hexane afforded **155-6** (0.17 g, 0.22 mmol) as a white solid. **155-6** was dissolved in 80% aq. HCOOH (5 mL). After 30 mins at RT, the solvent was removed and coevaporated twice with toluene. The residue was dissolved in methanol (10 mL) and TEA (0.2 mL) was added. After 2 mins at RT, the solvent was removed in vacuo. Purification by flash column chromatography using a gradient of methanol (0-15%) in DCM afforded **155** (90 mg). ^{1}H-NMR ($CDCl_3$): 7.40 (d, 1H), 6.1 (s, 1H), 5.83 (d, 1H), 4.3 (t, 2H), 4.1-4.2 (m, 6H), 3.70-3.82 (m, 4H), 3.57-3.65 (m, 4H), 3.1 (t, 4H) 1.61 (s, 8H), 1.3 (s, 3H), 1.23 (s, 18H). ^{31}P-NMR ($CDCl_3$): -1.55 ppm.

EXAMPLE 143
COMPOUND 156

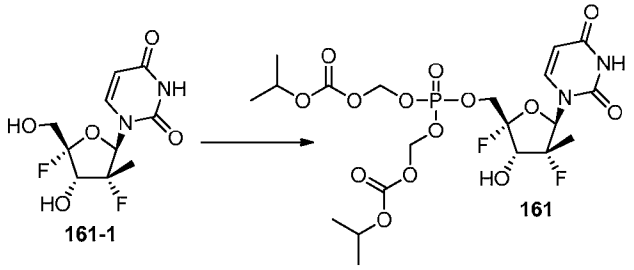


[0817] **156-1** (6.0 g, 31.6 mmol) was prepared using a similar procedure to the one used to prepare **155-3** using 4-chlorobutanol. **156-1** was obtained as a clear, colorless oil. ^{1}H-NMR ($CDCl_3$): 3.67 (s, 2H), 2.86 (m, 2H), 1.65 (m, 4H), 1.25 (s, 9H).

[0818] **156-2** (2.14 g, 4.0 mmol) was prepared using a similar procedure to the one used to prepare **155-4**. **156-2** was obtained as a clear, colorless oil. ^{1}H-NMR ($CDCl_3$): 3.67 (m, 6H), 2.86 (t, 4H), 1.65 (m, 8H), 1.25 (s, 18H), 1.17 (t, 12H). ^{31}P-NMR ($CDCl_3$): 143.7 ppm.

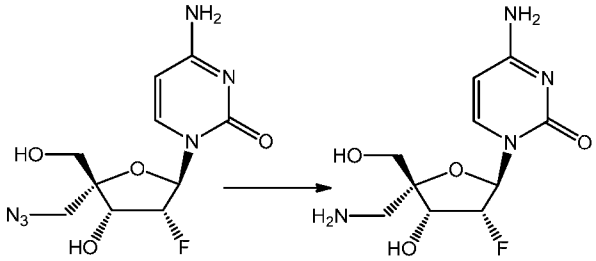
[0819] **156-3** (0.23 g, 0.22 mmol) was prepared using a similar procedure to the one used to prepare **155-6** using **155-5** and **156-2**. **156-3** was obtained as a white solid. Using a similar procedure to the one used to prepare **155**, **156-3** was used to prepare **156** (170 mg). ^{1}H-NMR ($CDCl_3$): 7.40 (d, 1H), 6.1 (s, 1H), 5.83 (d, 1H), 4.3 (t, 2H), 4.1-4.2 (m, 6H), 2.8 (t, 4H), 1.78 (m, 4H), 1.69 (s, 8H), 1.3 (s, 3H), 1.23 (s, 18H). ^{31}P-NMR ($CDCl_3$): -1.56 ppm.

EXAMPLE 144
COMPOUND 161



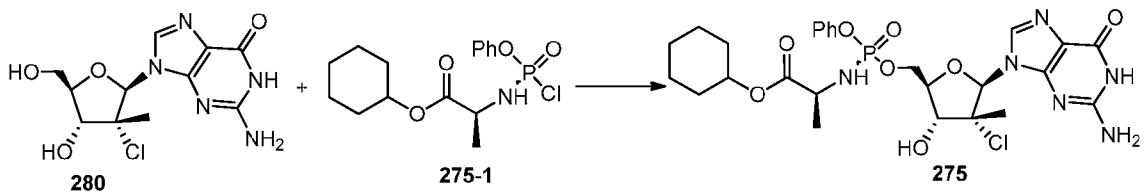
[0820] **161-1** (109 mg, 0.39 mmol) and triethylammonium bis(isopropyloxycarbonyloxymethyl)phosphate (0.6 mmol, prepared from 195 mg of bis(isopropyloxycarbonyloxymethyl)phosphate and 85 μL of Et_3N) were rendered anhydrous by coevaporating with pyridine, followed by toluene. The residue was dissolved in anhydrous THF (3 mL) and cooled in an ice-bath. Diisopropylethyl amine (0.2 mL, 3 eq.), BopCl (190 mg, 2 eq.), and 3-nitro-1,2,4-triazole (81 mg, 2 eq.) were added, and the mixture was stirred at 0°C for 90 mins. The mixture was diluted with EtOAc, washed with sat. aq. $NaHCO_3$ and brine, and dried (Na_2SO_4). Purification on silica gel column with CH_2Cl_2/i-PrOH (4-10% gradient) followed by RP-HPLC purification (A: 0.1% HCOOH in water, B: 0.1% HCOOH in MeCN) yielded **161** (28 mg, 12%). ^{1}H-NMR ($CDCl_3$): δ 7.24 (d, 1H), 6.6 (br, 1H), 5.84 (d, 1H), 5.65-5.73 (m, 4H), 4.94 (m, 2H), 4.38 (m, 2H), 4.1 (b, 1H), 2.88 (d, 1H), 1.47 (d, 3H), 1.33 (m, 12H).

EXAMPLE 145
COMPOUND 269



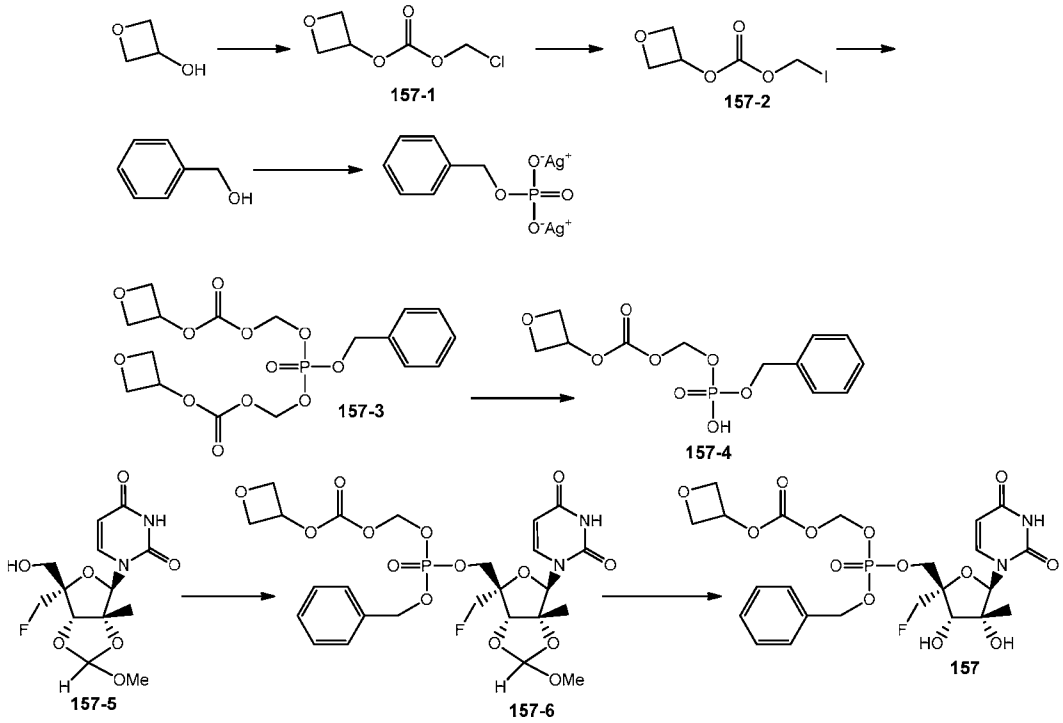
[0821] **106** (30 mg, 0.1 mmol) was hydrogenated in MeOH over 10% Pd/C at normal pressure. The catalyst was filtered off, and the filtrate was purified by RP HPLC on Synergy 4 micron Hydro-RP column (Phenominex). A linear gradient of MeOH from 0 to 20% in 50 mM triethylammonium acetate buffer (pH 7.5) was used for elution. The corresponding fractions were combined, concentrated and lyophilized (3x) to remove excess of buffer to yield **269** (17 mg, 63%). ESI-LCMS: m/z = 275.2 $[M+H]^+$, 297.1 $[M+Na]^+$.

EXAMPLE 146
COMPOUND 275



[0822] To an ice cold solution of **280** (50 mg, 0.16 mmol) and N-methylimidazole (50 µL, 0.64 mmol) in acetonitrile (1.5 mL) was added a solution of **275-1** (0.1 g, 0.28 mmol) in acetonitrile (0.15 mL). The mixture stirred at 5 °C for 1 h. The reaction was quenched with EtOH, and the mixture concentrated. The evaporated residue was partitioned between EtOAc and citric acid (0.5 N). The organic layer was washed with sat. aq. $NaHCO_3$ and brine, and then dried with Na_2SO_4. Purification by RP-HPLC (A: water, B: MeCN) yielded **275** (30 mg, 30%) as a white powder. MS: m/z 625 [M+1].

EXAMPLE 147
COMPOUND 157



[0823] Compound **157-1** was prepared from commercially available 3-hydroxyoxetane (5.0 g) using the procedure described for preparing **54-2** (5.6 g). ^{1}H-NMR ($CDCl_3$) δ 5.73 (s,2H) , 5.48-5.51 (m,1H), 4.90 (d,2H), 4.72 (d, 2H).

[0824] Compound **157-2** was prepared from **157-1** using the procedure described for preparing **54-3** (8.0 g). ^{1}H-NMR ($CDCl_3$) δ 5.95 (s,2H) , 5.48-5.51 (m,1H), 4.90 (d,2H), 4.72 (d, 2H).

[0825] Benzylphosphate (silver salt) and **157-2** (8.0 g) were reacted as described for preparing **54-4** to yield purified **157-3** (1.92 g). ^{1}H-NMR (CD_3CN): δ 7.39-7.42 (m, 5H),

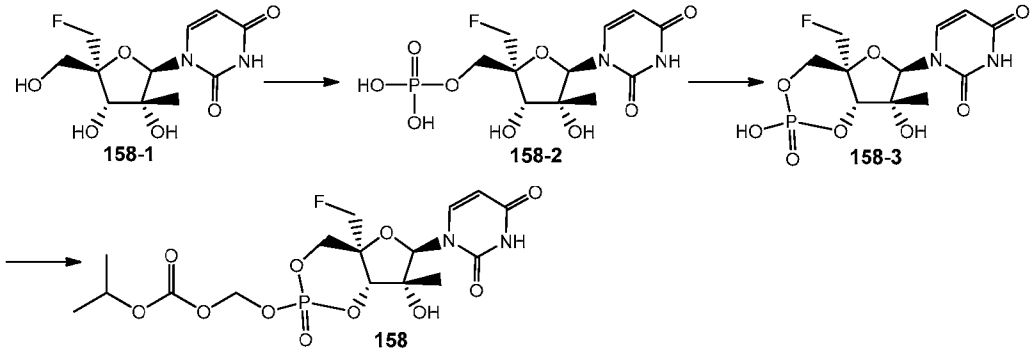
5.62 (d, 4H), 5.39-5.42 (m, 2H), 5.15 (d, 2H), 4.80-4.83 (m, 4H), 4.56-4.60 (m, 4H). ^{31}P-NMR (CD_3CN): δ - 4.55 ppm.

[0826] Compound **157-3** (970 mg, 2.16 mmol) was dissolved in methanol containing triethylamine (0.3 mL, 2.16 mmol). After 3 h at R.T, the solvents were removed in vacuo to give crude **157-4** that was used without further purification.

[0827] Compound **157-5** (400 mg; 1.2 mmol) and **157-4** (900 mg, 2.16 mmol; 1.5x) were coevaporated with pyridine (2x) and toluene (2x), and then dissolved in THF (8 mL) at 0°C. Diisopropylethylamine (DIPEA) (0.82 mL; 4 eq.), bis(2-oxo-3-oxazolidinyl) phosphinic chloride (Bop-Cl) (0.6 g; 2 eq.), nitrotriazole (0.266 g, 2 eq.) were added. The mixture kept at 0 °C for 2 h. The mixture was diluted with EA (50 mL) and extracted with saturated sodium bicarbonate (2 x 50 mL) and dried over sodium sulfate. The solvents were removed in vacuo. The residue was purified by flash chromatography using a 10 to 100% gradient of EA in hexane to give purified **157-6** (175 mg, 0.6 mmol).

[0828] Purified **157-6** was dissolved in 80% aq. HCOOH (20 mL) and kept at 20°C for 1 h. After cooling to RT, the solvent was removed in vacuo, and the residue coevaporated with toluene (3 x 25 mL). The residue was purified by flash chromatography using a 0 to 20% gradient of MeOH in DCM to give purified **157** (26 mg). ESI-LCMS: m/z 589.6 [M-H]$^-$.

EXAMPLE 148
COMPOUND 158



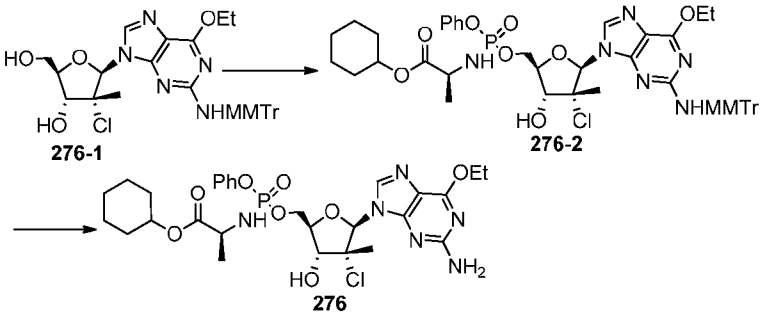
[0829] Nucleoside **158-1** (from Wuxi) (44 mg, 0.15 mmol) was dissolved in a mixture of trimethyl phosphate (2 mL) and dry pyridine (0.5 mL). The mixture was evaporated in vacuum for 15 mins at 42°C, than cooled to RT. N-Methylimidazole (0.027 mL, 0.33 mmol) was added followed by $POCl_3$ (0.027 mL, 0.3 mmol). The mixture was kept

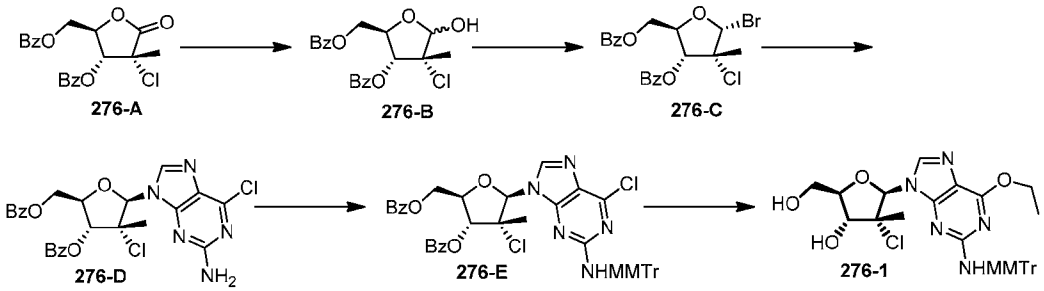
at RT. The reaction was monitored by LC/MS in 0-50% gradient. After 4 h, the reaction was complete. The reaction was quenched with 2M triethylammonium acetate buffer (2 mL), pH7.5 (TEAA). **158-2** was isolated on prep-HPLC (Phenomenex Synergi 4u Hydro-RP 250x21.2 mm) using a gradient of 0 – 30% ACN in 50 mM TEAA.

[0830] Compound **158-2** (triethylammonium salt; 45 mg, 0.1 mmol) was dried by repeated co-evaporation with dry pyridine (3x). **158-2** was dissolved in dry pyridine (1 mL) and the solution added dropwise into a boiling solution of diisopropylcarbodiimide (63 mg, 0.5 mmol) in pyridine (4 mL) over 2.5 h. The mixture was heated under reflux for 1 h. After being cooled to 25°C, the reaction was quenched with 2M TEAA buffer (2 mL) and kept at 25°C for 1 h. The solution was concentrated to dryness, and the residual pyridine removed by coevaporated with toluene (3 x 2 mL). **158-3** was isolated on prep-HPLC (Phenomenex Synergi 4u Hydro-RP 250x21.2 mm) using a gradient of 0 – 30% ACN in 50 mM TEAA.

[0831] Compound **158-3** (triethylammonium salt; 26 mg, 0.045 mmol) was dissolved in dry DMF (0.5 mL) at RT under argon. To the stirred solution was added N,N-diisopropylethylamine (40 uL, 0.22 mmol) followed by chloromethyl isopropyl carbonate (35 mg, 0.22 mmol). The mixture was stirred at 65 °C for 18 h. The mixture was evaporated to dryness, and the residue was purified by silica column using a 0-15% gradient of MeOH in CH_2Cl_2. The fractions having **158** were pooled, and the mixture was concentrated to dryness to give **158** (2.3 mg). ESI-LCMS: m/z 467.5 $[M-H]^-$.

EXAMPLE 149
COMPOUND 276





[0832] To a stirred solution of **276-1** (180 mg, 0.16 mmol) in anhydrous CH_3CN (2.0 mL) was added N-methylimidazole (53.4 µL, 0.65 mmol) at 0 ^{0}C (ice/water bath). A solution of phenyl (cyclohexyloxy-L-alaninyl) phosphorochloridate (101 mg, 0.29 mmol) dissolved in CH_3CN (0.5 mL), prepared according to a general procedure (McGuigan et al., *J. Med. Chem.* (2008) 51:5807-5812), was added. The solution was stirred at 0 to 5 ^{o}C for 3 h. N-methylimidazole (50 µL) at 0 ^{0}C (ice/water bath) followed by solution of phenyl (cyclohexyloxy-L-alaninyl) phosphorochloridate (52 mg, dissolved in 0.5 mL of CH_3CN) were added. The mixture was stirred at RT for 16 h. The mixture was cooled to 0 to 5 ^{0}C and diluted with EA. Water (5 mL) was added. The solution was washed with 1.0M citric acid, sat. aq. $NaHCO_3$ and brine, and dried with $MgSO_4$. The residue was purified on silica (10 g column) with DCM/MeOH (0-10% gradient) to give **276-2** (96.8 mg, 64 %) as foam.

[0833] Compound **276-2** (95 mg, 0.11 mmol) was dissolved in anhydrous CH_3CN (0.5 mL), and 4N HCl in dioxane (77 µL, 0.3 mmol) was added at 0 to 5 ^{o}C. The mixture was stirred at RT for 30 mins, and anhydrous EtOH (100 µL) was added. The solvents were evaporated at RT and co-evaporated with toluene (3x). The residue was purified on RP-HPLC with H_2O/CH_3CN (50-100% gradient) and lypholized to give **276** (37.7 mg, 52.5%) as a white foam. ESI-LCMS: m/z = 653.2 $[M+H]^+$, 1305.4 $[2M+H]^+$.

[0834] To a solution of **276-A** (56 g, 0.144 mol) in anhydrous THF (600 mL) was added a solution of lithium tri-tert-butoxyaluminohydride (216 mL, 1M, 0.216 mol) dropwise at -78 ^{o}C under N_2 for 30 mins. The solution was stirred between -78 ^{o}C to 0 ^{o}C for 1 h. The reaction was quenched with sat.NH_4Cl solution and extracted with EA (3 x 200 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtrated and concentrated to give **276-B** (52 g, 92%) as a colorless oil.

[0835] To a stirred solution of PPh_3 (45.7 g, 0.174 mol) in CH_2Cl_2 (200 mL) was added **276-B** (34 g, 0.087 mol) at -20 ^{o}C under N_2. The mixture was stirred for 15 mins.

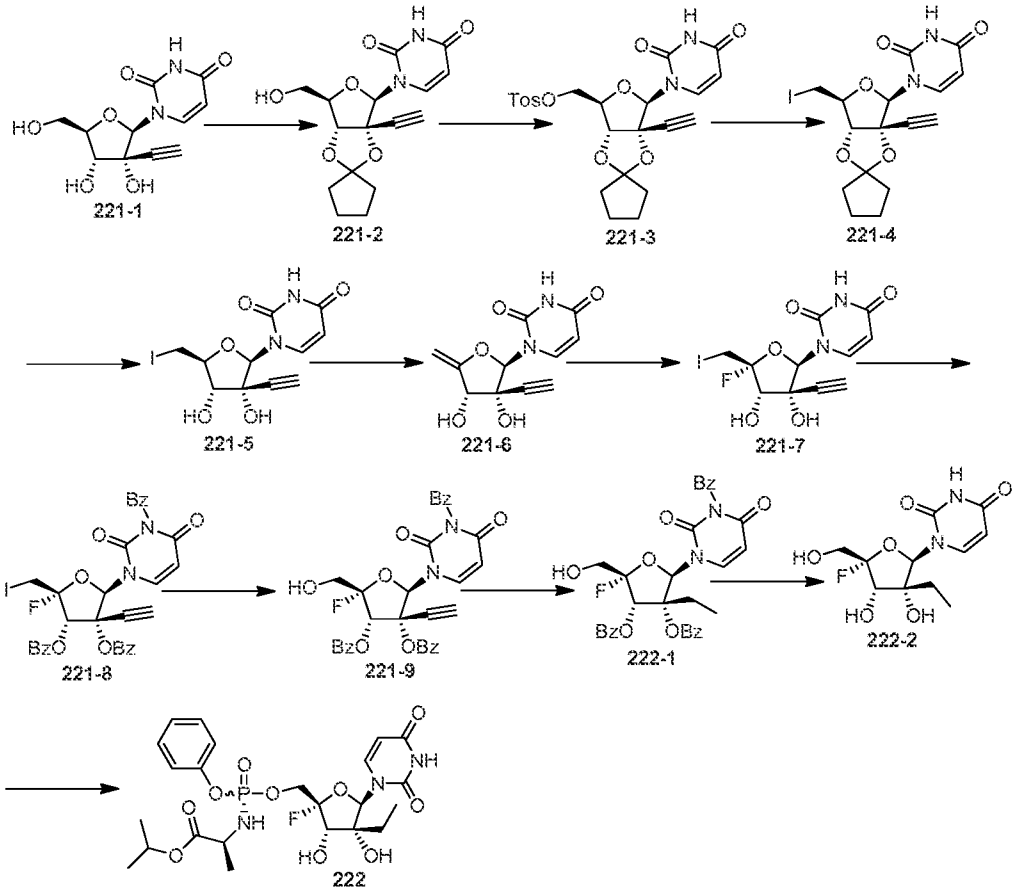
CBr_4 (58 g, 0.174 mol) was added dropwise while maintaining the temperature between -25 °C and -20 °C under N_2 flow. The mixture was then stirred below -17 °C for 20 mins. The mixture was treated with silica gel. The solution was filtered through cold silica column gel and washed with cold elute (PE:EA=50:1 to 4:1). The combined filtrates were concentrated under reduced pressure at RT to give the crude oil product. The residue was purified by silica column gel (PE:EA=50:1 to 4:1) to give **276-C** (α-isomer, 24 g, 61%) as a colorless oil. ^{1}H-NMR ($CDCl_3$, 400 MHz), δ = 8.16 (d, J = 6.8 Hz, 2H), 8.01 (d, J = 7.6 Hz, 2H), 7.42-7.62 (m, 6H), 6.43 (s, 1H), 5.37 (d, J = 4.4 Hz, 1H), 4.68-4.86 (m, 3H), 1.88 (s, 3H).

[0836] A mixture of 6-Cl-guanosine (80.8 g, 0.478 mol) and *t*-BuOK (57 g, 0.509 mol) in t-BuOH (1 L) was stirred at 30-35 °C for 30 mins. **276-C** (72 g, 0.159 mol, in MeCN 500 mL) was added at RT and the mixture was heated to 70 °C and stirred for 3 h. The reaction was quenched with sat. NH_4Cl solution, and extracted with EA (3 x 300 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated at low pressure. The residue was purified by silica gel column (PE:EA = 4:1 to 2:1) to give **276-D** (14 g, 16%).^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.93-8.04 (m, 4H), 7.90 (s, 1H), 7.30-7.50 (m, 6H), 6.53 (d, J = 8.8 Hz, 1H), 6.36 (s, 1H), 5.35 (s, 2H), 5.06-5.10 (m, 1H), 4.81-4.83 (m, 1H), 4.60-4.64 (m, 1H), 1.48 (s, 3H).

[0837] To a solution of **276-D** (14 g, 25.9 mmol) in DCM (15 mL) was added $AgNO_3$ (8.8 g, 51.8 mmol) and collidine (6.3 g, 51.8 mmol) and MMTrCl (12.1 g, 38.9 mmol). The mixture was stirred at RT for 1 h. The reaction was quenched with MeOH (5 mL). After filtration, the filter was washed with brine, dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by silica gel column (PE:EA = 10:1 to 3:1) to give **276-E** (16 g, 80%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ = 8.05-8.07 (m, 4H), 7.93 (s, 1H), 7.18-7.57 (m, 18H), 6.77 (d, J = 8.8 Hz, 2H), 6.71 (s, 1H), 5.86 (s, 1H), 5.6 (s, 1H), 4.77 (d, J =10.0 Hz, 1H), 4.67-4.76 (m, 1H), 4.55-4.59 (m, 1H), 3.75 (s, 1H), 1.06 (s, 3H).

[0838] Sodium (170 mg, 7.38 mmol) was dissolved in dry EtOH (5 mL) at 70 °C, and the solution was cooled to 0 °C. **276-E** (1 g, 1.23 mmol) was added in portions at 0 °C. The mixture was stirred for 8 h at RT. The mixture was neutralized with CO_2 to pH 7.0, and concentrated at low pressure. The residue was purified by prep-HPLC(10% CH_3CN/H_2O) to give **276-1** (0.4 g, 53%) as a yellow solid. ESI-MS: m/z 616 $[M+H]^+$.

EXAMPLE 150
COMPOUND 222



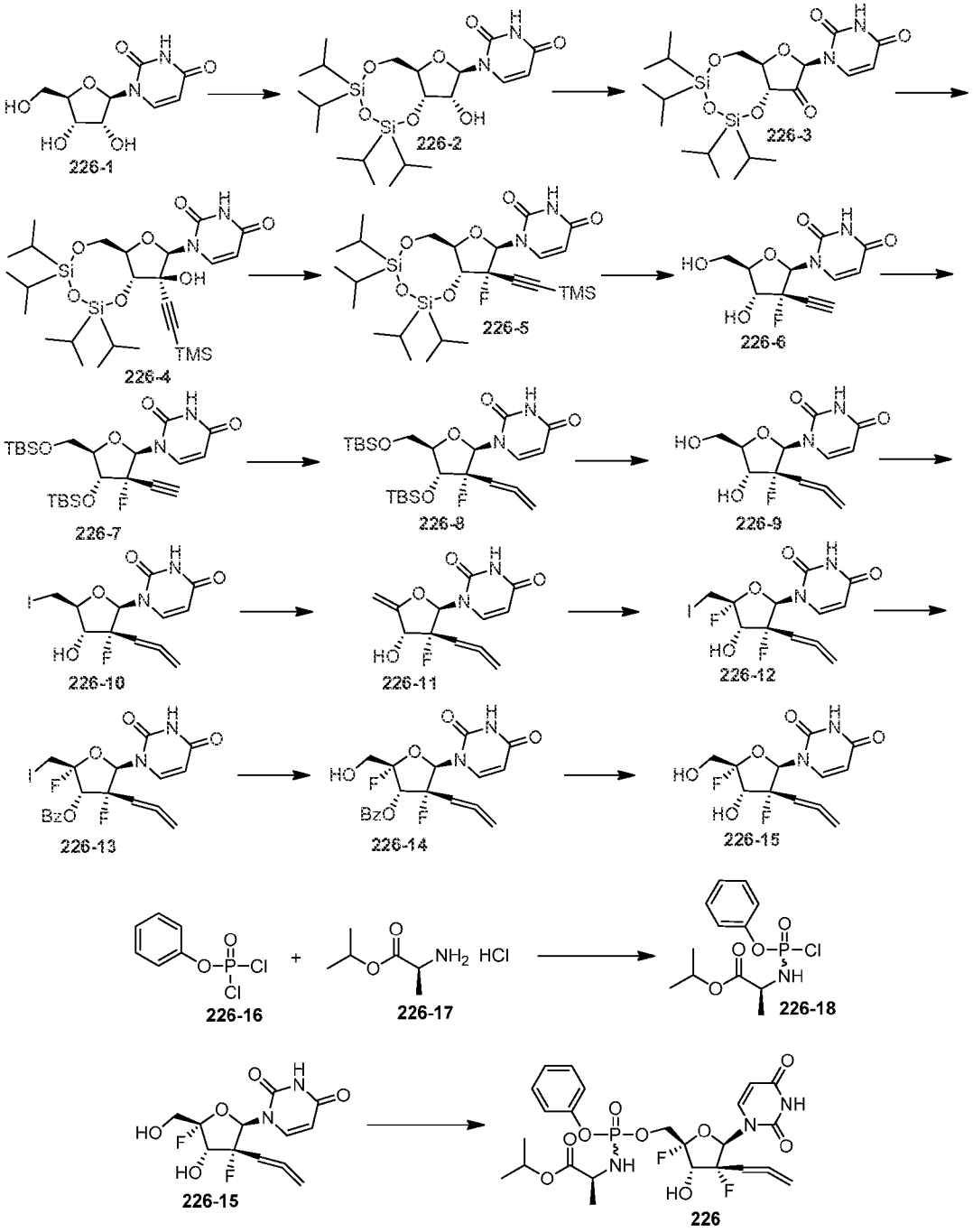
[0839] To a solution of **221-9** (300 mg, 0.50 mmol) in MeOH (30 mL) was added wet Pd/C (300 mg, 10%) under N_2. The mixture was stirred under H_2 (1 atm) at 25°C for 1.5 h. The suspension was filtered, and then concentrated at low pressure to give crude **222-1** (307 mg) as a white solid.

[0840] Compound **222-1** (307 mg, 0.48 mmol) was dissolved in NH_3/MeOH (30 mL, 7 M). The mixture was stirred at RT for 24 h under N_2 then concentrated at low pressure. The residue was purified by prep-HPLC (0.1% HCOOH in water and MeCN) to give **222-2** (30 mg, 21% over two steps) as a white solid.

[0841] Compound **222-2** (91 mg, 0.31 mmol) was co-evaporated with toluene 3 times to remove H_2O. To a stirred solution of **222-2** (91 mg, 0.31 mmol) in a mixture of MeCN (0.5 mL) and NMI (254 mg, 3.90 mmol) was added a solution **222-C** (203 mg, 0.66 mmol) in MeCN (0.5 mL) at 0°C. The mixture was stirred at RT overnight and then

concentrated at low pressure. The residue was purified on a silica gel column (5% MeOH in DCM) to the crude **222**, which purified by prep-HPLC (0.1% HCOOH in water and MeCN) to give **222** (30 mg, 17%) as a white solid. ESI-MS: m/z 540.1 $[M-F]^+$.

EXAMPLE 151
COMPOUND 226



[0842] To an ice cooled solution of **226-1** (50 g, 204.9 mmol) in dry pyridine (400 mL) was added TIPDSCl (70.78 g, 225.4 mmol) dropwise. The mixture was stirred at RT for 16 h, and then concentrated at low pressure. The residue was purified by chromatography using 20% EA in PE to generate **226-2** (111.5 g, 100%) as a white solid.

[0843] To a solution of **226-2** (50 g, 103 mmol) in anhydrous CH_3CN (400 mL) was added IBX (43 g, 153 mmol) at RT. The mixture was refluxed overnight and monitored by TLC (PE:EA=1:1). The precipitate was filtered off, and the filtrate was concentrated to give the crude **226-3** (50 g, 99%) as a white solid.

[0844] To a solution of trimethylsilylacetylene (20 g, 200 mmol) in anhydrous THF (400 mL) was added dropwise *n*-BuLi (80 mL, 200 mL) at -78°C. The mixture was stirred at -78°C for 30 mins, and then warmed to R.T for 10 mins. Compound **226-3** (30 g, 60 mmol) in THF (100 mL) was added to the mixture dropwise at -78°C. The mixture was stirred at -78°C for 1 h and then slowly warmed to RT. The mixture was stirred for 20 mins, and then the reaction was quenched with a sat. NH_4Cl solution at -78°C. The mixture was diluted with EA. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by silica gel column chromatography (15% EA in PE) to give **226-4** as a white solid (14 g, 50 %).

[0845] Compound **226-4** (14 g, 24 mmol) was dissolved in anhydrous toluene (100 mL) under N_2 and cooled to -78°C. DAST (19 g, 120 mmol) was added dropwise at -78°C and stirring was continued for 1.5 h. The mixture was diluted with EA and poured into a sat. $NaHCO_3$ solution. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by silica gel chromatography (20% EA in PE) to give **226-5** as a white solid (12 g, 81 %).

[0846] A mixture of **226-5** (12 g, 20 mmol) and NH_4F (11 g, 30 mmol) in MeOH (150 mL) was refluxed for 2 h. After cooling to R.T, the mixture was concentrated at low pressure, and the residue was purified by silica gel column chromatography (5% MeOH in DCM) to give **226-6** (3.1 g, 58%) as a white solid.

[0847] To a solution of **226-6** (3.1 g, 11.6 mmol) in dry Py (50 mL) was added imidazole (3.1 g, 46.4 mmol) and TBSCl (5.2 g, 34.8 mmol). The mixture was stirred at 50-60°C for 3 h. The mixture was concentrated at low pressure, and the residue was dissolved in EA (100 mL). The solution was washed with brine, dried over anhydrous Na_2SO_4, and

concentrated at low pressure. The residue was purified by silica gel chromatography (20% EA in PE) to give **226-7** as a white solid (5 g, 86%).

[0848] To a solution of **226-7** (4.5 g, 9 mmol) in 1,4-dioxane (45 mL) was added CuBr (643 mg, 4.5 mmol), dicyclohexylamine (3.3 g, 18 mmol) and paraformaldehyde (675 mg, 22.5 mmol). The mixture was refluxed for 24 h and then cooled to RT. The reaction was quenched with a sat. NH_4Cl solution. The mixture was extracted with EA (3 x 100 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by silica gel column chromatography (15% EA in PE) to give **226-8** as a white solid (2.0 g, 43%).

[0849] A mixture of **226-8** (2 g, 4 mmol) and NH_4F (2.2 g, 60 mmol) in MeOH (20 mL) was refluxed overnight. After cooling to RT, the mixture was concentrated at low pressure, and the residue was purified by silica gel column chromatography (5% MeOH in DCM) to give **226-9** (946 mg, 83%) as a white solid.

[0850] To a stirred suspension of **226-9** (946 mg, 3.33 mmol), PPh_3 (1.3 g, 5 mmol), imidazole (453 mg, 6.66 mmol) and pyridine (3 mL) in anhydrous THF (12 mL) was added a solution of I_2 (1 g, 4.33 mmol) in THF (4 mL) dropwise at 0°C. The mixture was warmed to RT and stirred for 16 h. The reaction was quenched with a sat. $Na_2S_2O_3$ aq. solution and extracted with EA (3 x 60 mL). The organic layer was dried over Na_2SO_4 and concentrated at low pressure. The residue was purified on a silica gel column (2% MeOH in DCM to 5% MeOH in DCM) to afford **226-10** (2.1 g, crude) as a white solid.

[0851] To a solution of **226-10** (2.1 g, 5.3 mmol) in THF (15 mL) was added DBU (15 g, 100 mmol) and the mixture stirred for 30 mins. The mixture was diluted with EA and neutralized with acetic acid. The solution was washed with brine, dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by silica gel column chromatography (1.5% MeOH in DCM) to give **226-11** as a white solid (800 mg, 90%).

[0852] To an ice-cooled solution of **226-11** (800 mg, 3 mmol) in dry MeCN (1.5 mL) was added $NEt_3 \cdot 3HF$ (484 mg, 3 mmol) and NIS (1.68 g, 7.5 mmol). The mixture was stirred at RT for 30 mins., and the reaction was monitored by LCMS. The reaction was quenched with sat. $Na_2S_2O_3$ and sat. $NaHCO_3$ solution, and extracted with EA (3 x 50 mL).

The organic layer was dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by a silica gel column (25% EA in PE) to afford **226-12** (850 mg, 68%) as a white solid.

[0853] To a solution of **226-12** (850 mg, 2 mmol) in dry DCM (10 mL) was added DMAP (488 mg, 4 mmol) and BzCl (422 mg, 3 mol). The mixture was stirred for 4-5 h at RT, and the reaction was monitored by LCMS. The mixture was diluted with CH_2Cl_2 (40 mL), and washed with a sat. $NaHCO_3$ solution. The organic layer was dried over anhydrous Na_2SO_4, and filtered. The filtrate was evaporated at low pressure, and the residue was purified by silica gel column chromatography (20% EA in PE) to give **226-13** (900 mg, 87%) as a white foam.

[0854] Tetra-butylammonium hydroxide (21 mL as 54-56% aqueous solution, ~ 42 mmol, 24 eq.) was adjusted with TFA to pH ~ 4 (~ 3.5 mL), and the solution was treated with a solution of **226-13** (900 mg, 1.7 mmol) in DCM (21 mL). *m*-Chloroperbenzoic acid (2.1 g, 60-70%, ~ 8.75 mmol, ~ 5 eq.) was added portionwise under vigorous stirring, and the mixture was stirred overnight. The mixture was diluted with CH_2Cl_2 (30 mL), and washed with a saturated $NaHCO_3$ solution. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography in (40-70% EA in PE) to give **226-14** as an oil. The residue was purified by TLC (50% EA in PE) to give pure **226-14** (350 mg 50%).

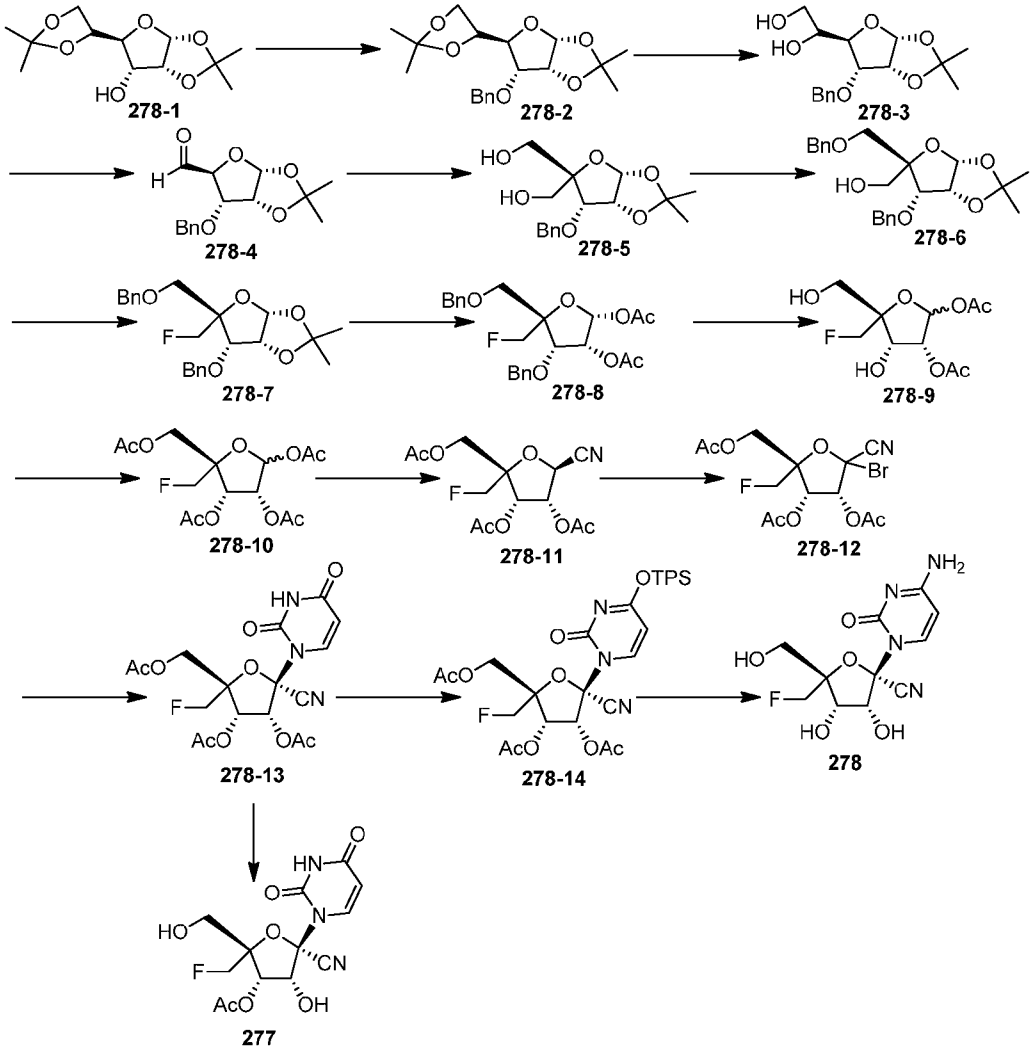
[0855] Compound **226-14** (350 mg, 0.86 mg) was treated with 7N NH_3 in MeOH (15 mL). The mixture was stirred for 2-3 h and monitored by TLC. The mixture was concentrated at low pressure, and the residue was purified by silica gel column chromatography (5% isopropanol in DCM) to give **226-15** (250 mg, 96%) as a white solid. ^{1}H NMR (CD_3OD, 400 M Hz) δ = 7.75 (d, J = 7.9 Hz, 1H), 6.60-6.35 (m, 1H), 5.72 (d, J = 8.2 Hz, 1H), 5.37-5.25 (m, 1H), 5.17-5.06 (m, 1H), 5.04-4.94 (m, 1H), 4.59-4.29 (m, 1H), 3.87-3.70 (m, 2H) .

[0856] To a stirred solution of **226-16** (3.79 g, 18 mmol) and **226-17** (3 g, 18 mmol) in anhydrous DCM (60 mL) was added with a solution of TEA (4 g, 39 mmol) in DCM (40 mL) dropwise at -78°C, and the mixture was stirred for 2 h. The mixture was concentrated at low pressure, and the residue was dissolved in methyl-butyl ether. The precipitate was removed by filtration, and the filtrate was concentrated to give the crude

product. The residue was purified by dry column chromatography (anhydrous DCM) to give pure **226-18** as a colorless oil (3 g, 54 %).

[0857] Compound **226-15** (200 mg, 0.66 mmol) was coevaporated with toluene 3 times to remove H_2O. Compound **226-15** was treated with MeCN (1.5 mL) and NMI (541 mg, 6.6 mmol). The mixture was stirred at RT, and then **226-18** (403 mg, 1.32 mmol) in MeCN (0.5 mL) was added. The residue was purified by a silica gel column (5% iPrOH in DCM) to give the crude product, which was purified by HPLC (0.1% HCOOH in water and MeCN) to give **226** (33 mg, 9%). ESI-LCMS: m/z 594 $[M+Na]^+$.

EXAMPLE 152
COMPOUNDS 277 and 278



[0858] Into a 2000-mL round-bottom flask, was placed a solution of **278-1** (100 g, 384.20 mmol, 1.00 eq.) in N,N-dimethylformamide (1000 mL) at RT. NaH (11.8 g, 491.67 mmol, 1.20 eq.) was added in several batches and the mixture was stirred at 0°C for 0.5 h. (bromomethyl)benzene (78.92 g, 461.44 mmol, 1.20 eq.) was added at 0°C and the solution was stirred overnight at RT. The reaction was quenched with water. The solution was diluted with EA (2000 mL), washed with aq. NaCl (3 x 500 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by a silica gel column with EA:PE (1:10) to yield **278-2** (105 g, 78%).

[0859] Into a 1000-mL round-bottom flask, was placed **278-2** (100 g, 285.38 mmol, 1.00 eq.), acetic acid (300 mL) and water (100 mL). The solution was stirred overnight at RT. The mixture was then diluted with EA (2000 mL), washed with aq. NaCl (2 x 500 mL) and aq. sodium bicarbonate (3 x 500 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Crude **278-3** (64 g) was obtained as light yellow oil. ESI MS m/z: 333 $[M+Na]^+$.

[0860] Into a 5000-mL round-bottom flask, was placed a solution of **278-3** (140 g, 451.11 mmol, 1.00 eq.) in MeOH (500 mL). A solution of sodium periodate (135.2 g, 632.10 mmol, 1.40 eq.) in water (1000 mL) was added. The solution was stirred at RT for 1 h, then diluted with EA (2000 mL), washed with sat. NaCl solution (3 x 500 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The solid was dried in an oven under reduced pressure to yield crude **278-4** (97 g) as yellow oil

[0861] Into a 3000-mL round-bottom flask, was placed a solution of **278-4** (100 g, 359.32 mmol, 1.00 eq.) in tetrahydrofuran (500 mL) at RT. Water (500 mL) was added. To the mixture was added a NaOH solution (600 mL, 2 N in water) at 0°C followed by aq. formaldehyde (240 mL, 37%). The solution was stirred overnight at RT. The mixture was diluted with EA (1500 mL), washed with sat. NaCl solution (3 x 500 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by a silica gel column with EA:PE (1:1) to give **278-5** (52.5 g, 47%) as a white solid. ESI MS m/z: 333 $[M+Na]^+$.

[0862] Into a 3000-mL round-bottom flask, was placed a solution of **278-5** (76 g, 244.89 mmol, 1.00 eq.) in acetonitrile (1500 mL) at RT. NaH (6.76 g, 281.67 mmol, 1.15 eq.) was added in several batches at 0 °C. The solution was stirred at 0 °C for 15 mins, then

(bromomethyl)benzene (48.2 g, 281.82 mmol, 1.15 eq.) was added. The solution was stirred overnight at RT. The reaction was quenched with water, diluted with EA (3000 mL), washed with aq. NH_4Cl (3 x 500 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by a silica gel column with EA:PE (1:5) to yield **278-6** (50 g, 51%) as a yellow oil. ESI MS m/z: 423 $[M+Na]^+$.

[0863] Into a 250-mL round-bottom flask, was placed a solution of diethylaminosulfur trifluoride (6.6 mL, 2.00 eq.) in toluene (10 mL) at RT. **278-6** (10 g, 24.97 mmol, 1.00 eq.) in toluene (120 mL) was added at 0°C. The solution was stirred for 3 h at 60 °C in an oil bath. The mixture was cooled to 0°C, diluted with EA (300 mL), washed with sat. NaCl solution (3 x 50 mL), dried over anhydrous sodium sulfate , filtered and concentrated under reduce pressure. The crude product was purified by a silica gel column with EA:PE (1:5) to give **278-7** (5000 mg, 50%) as a yellow oil. ESI MS m/z: 425 $[M+Na]^+$.

[0864] Into a 250-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of N_2, was placed **278-7** (10 g, 23.61 mmol, 1.00 eq., 95%) in acetic acid (80 mL). Acetic anhydride (6 mL) and sulfuric acid (0.05 mL) were added. The solution was stirred for 2 h at RT. The mixture was then diluted with EA (500 mL), washed with water (3 x 200 mL) and aq. sodium bicarbonate (3 x 200 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by a silica gel column with EA:PE (1:10~1:5) to yield **278-8** (6 g, 54%) as a yellow oil. ESI MS m/z: 469 $[M+Na]^+$.

[0865] Into a 50-mL round-bottom flask purged, was placed a solution of **278-8** (4 g, 8.96 mmol, 1.00 eq.), 10% Pd-C catalyst (4 g) in MeOH/DCM (25 mL/25 mL). To this mixture was introduced H_2 (gas) in, ~ 3 atmospheric pressure. The solution was stirred for 48 h at RT. The solids were collected by filtration, and the solution was concentrated under reduced pressure to give **278-9** (0.7 g, 29%) of as a colorless oil.

[0866] Into a 25-mL round-bottom flask, was placed **278-9** (2000 mg, 7.51 mmol, 1.00 eq.), Ac_2O (8 mL), 4-dimethylaminopyridine (183.2 mg, 0.20 eq.) in pyridine (8 mL). The solution was stirred for 3 h at RT. The reaction was a sat. sodium bicarbonate solution. The solution was diluted with EA (200 mL), washed with sat. NaCl solution (3 x 50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The

crude product was purified by a silica gel column with EA:PE (1:7) to yield (1500 mg, 57%) of **278-10** as a white solid. ESI MS m/z: 373 $[M+Na]^+$.

[0867] Into a 25-mL round-bottom flask, was placed a solution of **278-10** (300 mg, 0.86 mmol, 1.00 eq.) in dichloromethane (3 mL) at RT. Trimethylsilanecarbonitrile (169 mg, 1.70 mmol, 2.00 eq.) was added at RT, followed by tetrachlorostannane (223 mg, 0.86 mmol, 1.00 eq.) at 0 °C. The solution was stirred at 0 °C for 3 h. The reaction was quenched with sat. sodium bicarbonate solution. The solution was diluted with DCM (50 mL), washed with sat. NaCl solution (2 x 10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by a silica gel column with PE:EA (5:1) to give **278-11** (110 mg, 40%) as a yellow oil. ^{1}H-NMR (400MHz, $CDCl_3$): δ ppm 5.67~5.75(m, 2H), 4.25~4.78(m, 5H), 2.19(s, 3H), 2.14(s, 3H), 2.10(s, 3HI

[0868] Into a 25-mL round-bottom flask, was placed **278-11** (200 mg, 0.63 mmol, 1.00 eq.), NBS (223 mg, 1.25 mmol, 2.00 eq.) in tetrachloromethane (5 mL). The solution was heated under reflux for 3 h over a 250 W tungsten lamp, and then cooled to RT. The reaction was quenched sat. sodium bicarbonate solution. The solution was EA (100 mL), washed with sat. NaCl solution (3 x 20 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by a silica gel column with PE:EA (7:1) to give **278-12** (120 mg, 48%) as a yellow oil. ^{1}H-NMR (400MHz, $CDCl_3$): δ ppm 6.03(d, *J*=4.8Hz, 1H), 5.90(d, *J*=4.8Hz, 1H), 4.29-4.30(m, 4H), 2.25(s, 3H), 2.15(s, 3H), 2.25(s, 3H).

[0869] Into a 25-mL round-bottom flask purged and maintained with an inert atmosphere of argon, was placed a solution of N-(2-oxo-1,2-dihydropyrimidin-4-yl)benzamide (54.3 mg, 2.00 eq.) and $(NH_4)_2SO_4$ (5 mg) in HMDS (3 mL). The solution was stirred overnight at 120 °C in an oil bath. The solution was concentrated under vacuum, and the residue was dissolved DCE (1 mL) under Ar. A solution of **278-12** (50 mg, 0.13 mmol, 1.00 eq.) in MeCN (1 mL) was added followed by AgOTf (32.5 mg, 1.00 eq.). The solution was stirred for 3 h at 80 °C in a 10-mL sealed tube. After cooling to RT, the solution was diluted with EA (50 mL), washed with sat. sodium bicarbonate solution (3 x 10 mL) and sat. NaCl (2 x 10 mL) solution, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by a silica gel column with

DCM:MeOH (15:1) to yield **278-13** (30 mg, 45%) as a yellow oil. ESI MS m/z: 428 $[M+H]^+$.

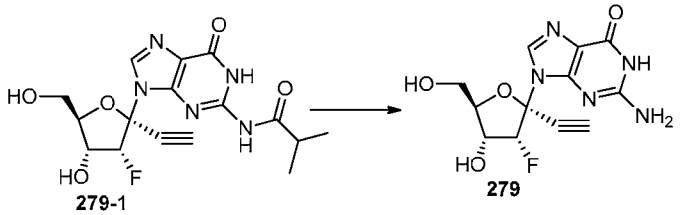
[0870] Into a 25-mL round-bottom flask, was placed a solution of **278-13** (100 mg, 0.23 mmol, 1.00 eq.) in ACN (3 mL). 4-dimethylaminopyridine (28.5 mg, 0.23 mmol, 1.00 eq.) and TEA (71 mg, 0.70 mmol, 3.00 eq.) was added followed by TPSCl (212.8 mg, 0.70 mmol, 3.00 eq.). The solution was stirred for 3 h at RT, and then concentrated under vacuum. Crude **278-14** (200 mg) was obtained as a yellow oil.

[0871] Into a 25-mL round-bottom flask, was placed a solution of **278-14** (140 mg, 0.10 mmol, 1.00 eq.) in ACN (3 mL) and ammonium oxidanide (3 mL). The solution was stirred for 4 h at 35 °C in an oil bath. The mixture was concentrated under vacuum. The crude product was purified by Prep-HPLC (Prep-HPLC-020): Column, XBridge Prep C18 OBD Column, 19*150 mm 5um 13nm; mobile phase, WATER WITH 0.05%TFA and ACN (35.0% ACN up to 48.0% in 8 mins); Detector, nm to yield **278** (21.3 mg, 25%) as a white solid. ESI MS m/z: 301.1 $[M+1]^+$.

[0872] Into a 25-mL round-bottom flask, was placed a solution of **278-13** (50 mg, 0.12 mmol, 1.00 eq.), sat. NH_4OH (2 mL) and 1,4-dioxane (2 mL). The solution was stirred for 2 h at RT. After concentrated under reduced pressure, the crude product was purified by Prep-HPLC [(Prep-HPLC-020): Column, XBridge Prep C18 OBD Column, 19*150 mm 5um 13nm; mobile phase, WATER WITH 0.05% TFA and ACN (35.0% ACN up to 48.0% in 8 mins); Detector, nm] to yield **277** (13.6 mg, 39%) as a white solid ESI MS m/z: 299.9 $[M-1]^-$

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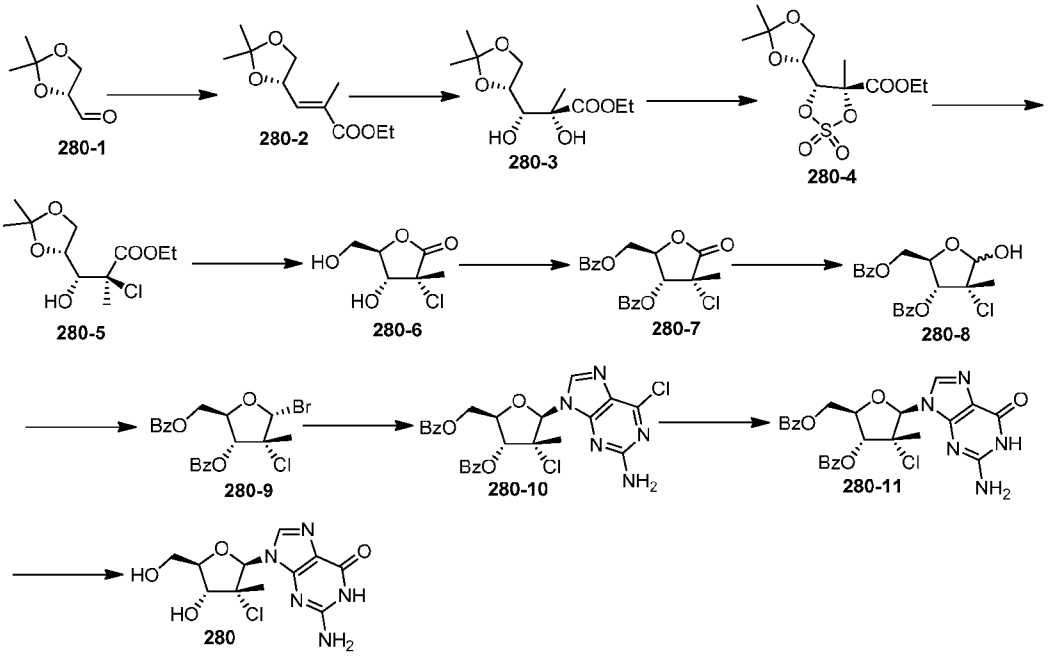
EXAMPLE 153
COMPOUND 279



[0873] Nucleoside **279-1** (100 mg, 0.26 mmol) was dissolved in n-butylamine (2 mL) and left for 2 h at RT. The solvent was evaporated, and the residue was purified by RP HPLC on Synergy 4 micron Hydro-RP column (Phenominex). A linear gradient of MeOH from 10 to 60% in 50 mM triethylammonium acetate buffer (pH 7.5) was used for elution.

The corresponding fractions were combined, concentrated and lyophilized (3x) to remove excess of buffer and yield **279** (20 mg, 25%). MS: m/z 308 [M-1].

EXAMPLE 154
COMPOUND 280



[0874] To a stirred solution of **280-1** (43.6 % in dichloromethane, 345.87 g, 1.16 mol) in anhydrous DCM (1.0 L) was added ethyl-2-(triphenylphosphoranylidene) propanoate (400 g, 1.100 mol) dropwise over a period of 30 mins at -40 °C. The mixture was allowed to warm to 25 °C and stirred for 12 h. The mixture was concentrated under reduced pressure. The residue was suspended in TMBE (2.0 L). The solid was removed by filtration. The filtrate was concentrated under reduced pressure. The residue was purified on silica gel column (1.2% EA in PE) to give **280-2** (191.3 g, 80.26%) as a white foam. ^{1}H-NMR (400 Hz, $CDCl_3$), δ = 6.66 (dd, J = 6.8, 8.0 Hz, 1H), 4.81-4.86 (m, 1H), 4.11-4.21 (m, 3H), 3.60 (t, J = 8.4 Hz, 1H), 1.87 (d, J = 1.2 Hz, 3H), 1.43 (s, 3H), 1.38 (s, 3H), 1.27 (t, J = 6.8 Hz, 3H).

[0875] To a stirred solution of **280-2** (100 g, 0.47 mol) in acetone (2.0 L) was added $KMnO_4$ (90 g, 0.57 mol) in portions at 0-5 °C. The mixture was stirred at 0-5 °C for 2 h. The reaction was quenched using sat. sodium sulfite solution (600 mL). After 2 h, a colorless suspension was formed. The solid was removed by filtration. The filter cake was washed with EA (300 mL). The filtrate was extracted with EA (3 x 300 mL). The organic

phase was dried over anhydrous Na_2SO_4. The organic phase was concentrated under reduced pressure to give crude **280-3** (50 g, 43.4%) as a solid.

[0876] To a stirred solution of **280-3** (50.0 g, 0.20 mol) and triethylamine (64.0 g, 0.63 mol) in anhydrous DCM (1.0 L) was added thionyl chloride (36.0 g, 0.31 mol) at 0 °C. After 30 mins, the mixture was diluted with dichloromethane (500 mL) and washed with cold water (1.0 L) and brine (600 mL). The organic phase was dried over anhydrous Na_2SO_4. The organic phase was concentrated under reduced pressure to give the crude as a brown oil. To crude in anhydrous acetonitrile were added TEMPO catalyst (500 mg) and $NaHCO_3$ (33.87 g, 0.40 mol) at 0 °C. A sodium hypochlorite solution (10-13%, 500 mL) was added dropwise at 0 °C for 20 mins. The solution was stirred at 25 °C for 1 h. The organic phase was concentrated, and the aqueous phase was extracted with dichloromethane (3x). The organic phase was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give **280-4** (53.0 g, 85.48 %) as a yellow oil.

[0877] To a stirred solution of **280-4** (62.0 g, 0.20 mol) in anhydrous dioxane (1.5 L) was added TBACl (155.4 g, 0.50 mol) at 25 °C. The solution was stirred at 100 °C for 10 h. The mixture was cooled to 25 °C, and treated with 2, 2-dimethoxypropane (700 mL), followed by conc. HCl (12 N, 42 mL). The mixture was stirred at 25 °C for 3 h and then concentrated under reduced pressure to give crude **280-5** as a brown oil (45.5 g, crude), which was used for next step without further purification.

[0878] Crude **280-5** (45.5 g, 171 mmol) was dissolved in a mixture of EtOH (500 mL) and conc. HCl (12 N, 3.0 mL). The mixture was stirred at 25 °C for 16 h. The solvent was removed under reduced pressure. The residue was co-evaporated with toluene (3x) to give crude **280-6** (24.6 g, crude) as a brown oil, which was used for the next step.

[0879] To a stirred solution of crude **280-6** (24.6 g, crude) and DMAP (4.8 g, 40.0 mmol) in anhydrous pyridine (800 mL) was added benzoyl chloride (84.0 g, 0.60 mol) dropwise over a period of 40 mins at 0 °C. The mixture was stirred at 25 °C for 12 h and then concentrated at low pressure. The residue was dissolved in EA (1.5 L). The solution was washed with 1.0 M HCl solution (400 mL) and brine (800 mL). The organic phase was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give a brown solid. The solid was suspended in MeOH (600 mL). After filtration, the filter cake was

washed with MeOH. The filter cake was dried under reduced pressure to give **280-7** (40.0 g, 75.0%) as a white solid.

[0880] To a stirred solution of **280-7** (7.0 g, 18.04 mmol) in anhydrous THF (70 mL) was added a solution of lithium tri-tert-butoxyaluminohydride (27 mL, 1.0 M, 27.06 mmol) dropwise over a period of 30 mins at -78 ^{0}C under N_2. The mixture was stirred at -20 ^{0}C for 1 h. The reaction was quenched with sat. NH_4Cl aq. and diluted with EA. After filtration, the filtrate was extracted with EA. The organic phase was dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by silica column gel (5% EA in PE) to give **280-8** (6.8 g, 96.7%) as a colorless oil.

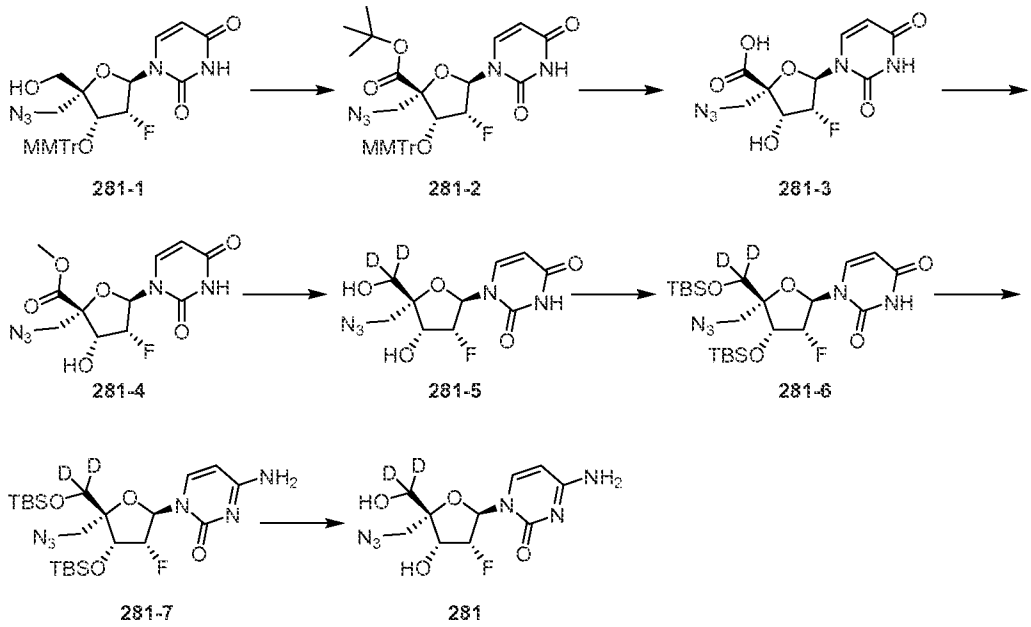
[0881] To a stirred solution of PPh_3 (1.34 g, 5.12 mmol) in CH_2Cl_2 (5 mL) was added **280-8** (1.0 g, 2.56 mmol) at -20 ^{0}C under N_2. After the mixture was stirred for 15 mins, CBr_4 (1.96 g, 5.89 mmol) was added in portions while maintaining the reaction temperature between -25 and -20 ^{0}C under N_2 flow. After completion of the addition, the mixture was stirred below -17 ^{0}C for 20 mins. The reaction was treated with silica gel. After filtration, the pad of silica gel was washed with CH_2Cl_2. The combined filtrates were purified by silica column gel (EA in PE from 2% to 25%) to give **280-9** (α-isomer, 0.5 g, 43.4%) as a colorless oil.

[0882] A 0.25 L three-neck round-bottomed flask was charged with 6-chloro-9H-purin-2-amine (5.5 g, 34.75 mmol) followed by anhydrous t-BuOH (45 mL) with stirring. To this solution was added potassium tert-butoxide (3.89 g, 32.58 mmol) in portions at RT under N_2 flow. After 30 mins, a solution of **280-9** (4.92 g, 10.86 mmol) in anhydrous acetonitrile (30 mL) was added over a period of 5 mins at 25 ^{0}C. The mixture was slowly heated to 50 ^{0}C and stirred for 12 h. The mixture was treated with solid NH_4Cl and water, and then filtered through a short pad of Celite. The pad was washed with EA, and the filtrates were neutralized with aqueous 1.0 M HCl. The combined organic layers were dried over anhydrous Na_2SO_4. The organic phase was concentrated under reduced pressure. The residue was purified by silica column gel (EA in PE from 2% to 20%) to give **280-10** (1.7 g, 28.9%) as a white foam. ^{1}H-NMR (400MHz, DMSO-d_6) δ = 8.37 (s, 1H), 8.07-8.01 (m, 2H), 7.93-7.87 (m, 2H), 7.75-7.69 (m, 1H), 7.65-7.53 (m, 3H), 7.41 (t, *J*=7.8 Hz, 2H), 7.13 (s, 2H), 6.37(d, *J*=19.3 Hz, 1H), 6.26-6.13 (m, 1H), 4.86-4.77 (m, 1H), 4.76-4.68 (m, 2H), 1.3 (d, *J*=20 Hz, 3 H).

[0883] Compound **280-10** (700 mg, 1.29 mmol) was dissolved in 4% HCl in MeOH (25 mL) at 25 ^{0}C. The mixture was stirred at 50 ^{0}C for 12 h. The solvent was removed under reduced pressure. The residue was purified by column chromatography to give **280-11** (401 mg, 59.2%) as a white solid.

[0884] Compound **280-11** (250 mg, 0.477 mmol) was treated with 7.0 M NH_3 in MeOH (25 mL) at 25 ^{0}C and stirred for 18 h. The solvent was removed at low pressure. The residue was purified by prep-HPLC (NH_4HCO_3 system) to give **280** (85 mg, 56.4%) as a white solid. MS: m/z 315.7 $[M+H]^+$, 630.5 $[2M+H]^+$.

EXAMPLE 155
COMPOUND 281



[0885] To a stirred solution of **281-1** (3.00 g, 5.23 mmol) in anhydrous DCM (36 mL) was added PDC (3.94 g, 10.46 mmol), Ac_2O (5.34 g, 52.30 mmol) and 2-methylpropan-2-ol (7.75 g, 104.60 mmol) at RT. The mixture was stirred at RT for 15 h. The mixture was loaded on a very short silica gel column and eluted with EA. The fractions containing the product were combined and concentrated under reduced pressure. The residue was purified by column chromatography (20% EA in PE) to give **281-2** (2.40 g, 71.3%) as a white foam.

[0886] To a stirred solution of **281-2** (2.00 g, 3.26 mmol) in DCM (30 mL) was added TFA (15 mL). The mixture was stirred at RT for 1.5 h. The mixture

was concentrated under reduced pressure to give **281-3** (1.00 g, crude), which was used in the next step without further purification.

[0887] Crude **281-3** (1.00 g, crude) was dissolved in a mixture of toluene (25 mL) and MeOH (20 mL). TMS-diazomethane (2 M, 3.17 mL) was added. After stirring for 2 h, the mixture was concentrated under reduced pressure at RT. The residue was diluted with EA (25 mL), washed with water (25 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (2% MeOH in DCM) to give **281-4** (451 mg, 43.2%) as a white solid. The aqueous phase was concentrated to give **281-3** (500 mg, 50.0%) as a white solid.

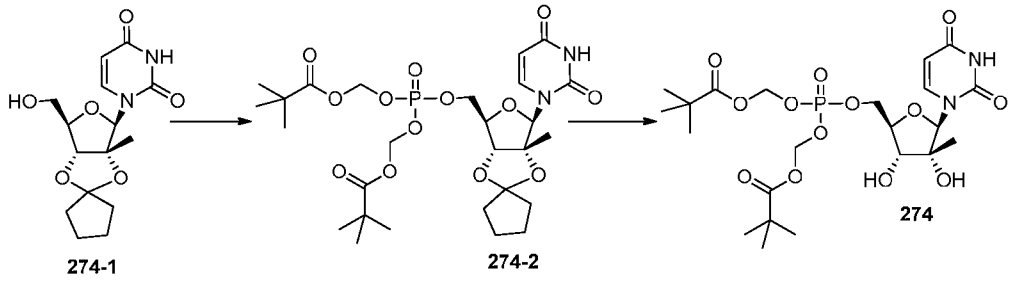
[0888] To a solution of **281-4** (451 mg, 1.37 mmol) in anhydrous CD_3OD (18 mL) was added $NaBD_4$ (344 mg, 8.22 mmol) at RT. The mixture was stirred at RT for 1 h. The reaction was quenched with CD_3OD (0.2 mL) and neutralized with AcOH (0.2 mL). The mixture was concentrated under reduced pressure. The residue was purified by column chromatography (4% MeOH in DCM) to give **281-5** (410 mg, 98.7%) as a white solid.

[0889] To a stirred solution of **281-5** (410 mg, 1.35 mmol) in pyridine (2.5 mL) was added imidazole (459 mg, 6.75 mmol) and TBSCl (610 mg, 4.05 mmol) at RT. The mixture was stirred at 60 °C for 10 h. The mixture was concentrated under reduced pressure. The residue was diluted with EA (20 mL) and washed with brine (20 mL). The organic layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (10% EA in PE) to give **281-6** (440 mg, 61.3%) as a white solid.

[0890] To a solution of **281-6** (440 mg, 827 μmol) in anhydrous MeCN (4 mL) were added DMAP (253 mg, 2.07 mmol), Et_3N (209.32 mg, 2.07 mmol) and 2,4,6-triisopropylbenzene-1-sulfonyl chloride (626.50 mg, 2.07 mmol) at RT. The mixture was stirred at RT for 16 h. $NH_3 \cdot H_2O$ (2 mL) was added, and the mixture was stirred for 1 h. The mixture was diluted with EA (20 mL) and washed with sat. aq. NH_4Cl (20 mL). The organic layer was dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (2% MeOH in DCM) to give the crude product. The crude product was purified by TLC (10% MeOH in DCM) to give **281-7** (420 mg, 95.63%) as a white solid.

[0891] To a solution of **281-7** (420 mg, 791 μmol) in MeOH (4 mL) was added NH_4F (586 mg, 15.83 mmol) at RT. The mixture was stirred at 90-100 °C for 10 h. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (10% MeOH in DCM) to give the crude product. The crude product was purified by prep-HPLC (neutral condition) to give **281** (201 mg, 61.8% yield, 100% deuterium) as a white solid. ESI-TOF-MS: m/z 303.1 $[M+H]^+$, 605.2 $[2M+H]^+$.

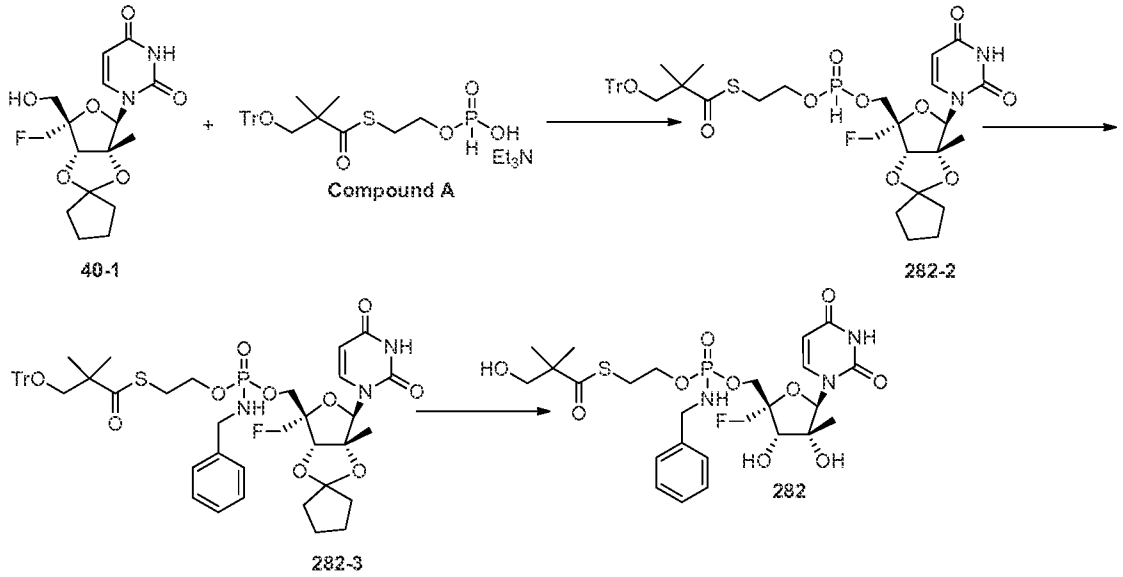
EXAMPLE 156
COMPOUND 274



[0892] To an ice-cold solution of triethylammonium bis(POM)phosphate (7 mmol, prepared from 2.3 g of bis(POM)phosphate and 1 mL of Et_3N) and **274-1** (1.36 g; 4.2 mmol) were added diisopropylethyl amine (3.6 mL; 21 mmol), BOP-Cl (2.68 g; 10.5 mmol) and 3-nitro-1,2,4-triazole (1.20 g; 10.5 mmol). The mixture was stirred at 0 °C for 2 h. The mixture was then diluted with EtOAc, washed with 1 M citric acid, sat. aq. $NaHCO_3$ and brine and dried with Na_2SO_4. The evaporated residue was purified on silica gel column with i-PrOH/CH_2Cl_2 solvent system (2-12% gradient) to yield **274-2** (2.13 g, 80%).

[0893] A solution of **274-2** (2.13 g) in 80% aq. HCOOH (10 mL) was stirred at 45 °C for 8 h. The mixture was cooled and concentrated to obtain a residue. The residue was coevaporated with toluene and MeOH containing few drops of Et_3N. The evaporated residue was purified on silica gel column with MeOH:CH_2Cl_2 (3-10% gradient) to yield **274** as a white foam (1.1 g, 56%). MS: m/z = 565 [M-1].

EXAMPLE 157
COMPOUND 282

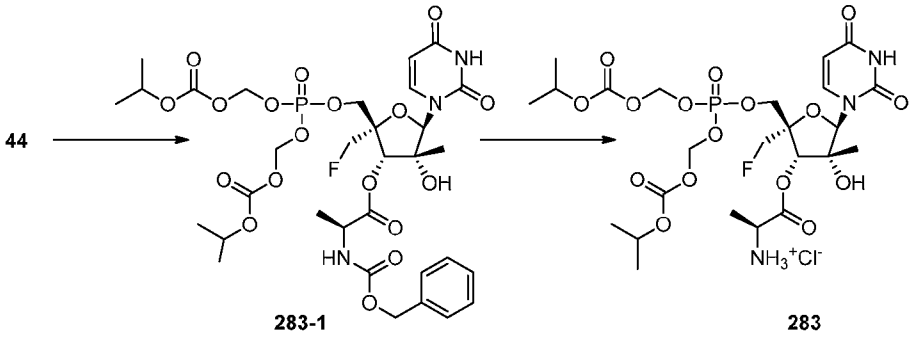


[0894] **40-1** (1.78 g, 5 mmol) and Compound **A** (3.22 g, 5.5 mmol; prepared according to the procedure provided in WO 2008/82601 A2) were coevaporated with pyridine and then dissolved in pyridine (70 mL). Pivaloyl chloride (1.22 mL; 10 mmol) was added dropwise at -15 °C, and the mixture stirred at -15 °C for 2 h. The mixture was diluted with CH_2Cl_2, washed with 0.5 M aq. NH_4Cl and brine, and dried with Na_2SO_4. The evaporated residue was purified on a silica column with CH_2Cl_2:i-PrOH (4-10% B gradient) to afford **282-2** (2.1 g, 50%).

[0895] To a solution of **282-2** (0.51 g, 0.62 mmol) in CCl_4 (6 mL) was added benzylamine (0.34 mL, 3.1 mmol) dropwise, and the mixture was stirred at RT for 1 h. The mixture was diluted with EtOAc, washed with 0.5 M aq. citric acid, sat. aq. $NaHCO_3$ and brine, and dried with Na_2SO_4. The evaporated residue was purified on a silica column with CH_2Cl_2:i-PrOH (4-10% B gradient) to afford **282-3** (0.46 g, 80%).

[0896] A mixture of **282-3** (130 mg, 0.14 mmol) and 80% aq. TFA (1.5 mL) was stirred at RT for 2 h. The mixture was evaporated and coevaporated with toluene. The residue was purified on a silica column with CH_2Cl_2:MeOH (4-12% B gradient) to afford **282** (32 mg (37%). MS: m/z = 620 $[M+1]^+$.

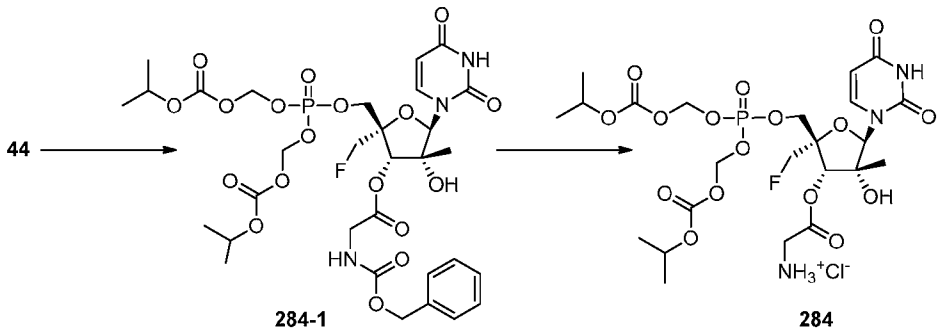
EXAMPLE 158
COMPOUND 283



[0897] A solution of Z-Ala-OH (111.6 mg, 0.5 mmol) in anhydrous THF (2 mL) was treated with carbonyldiimidazole (81 mg, 0.5 mmol). The mixture was stirred for 1 h at 40 ^{0}C under an Ar atmosphere. This solution was added to a solution of **44** (200 mg, 0.33 mmol), Et_3N (72 µL, 0.5 mmol) and DMAP (4 mg) in DMF (2 mL). The mixture was stirred at RT for 2.5 h. The reaction was quenched by the addition of 1M citric acid (2 mL) at 0 to 5 ^{0}C (ice/water bath) and diluted with EA. The organic layer was separated, washed with sodium bicarbonate and brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography in 40 to 90% EA-hexane to give **283-1** (202 mg, 76%) as a white foam.

[0898] To a solution of **283-1** (50 mg, 0.062 mmol) in anhydrous EtOH (2 mL), was added 10 % Pd/C (5 mg), followed by addition of 4N HCl (31 µL, 0.124 mmol), and the mixture was stirred under H_2 atmosphere for 1 h. After completion of the reaction, the mixture was filtered through celite. The catalyst cake was washed with anhydrous EtOH. The washings and the filtrate were combined, and the solvent was removed under vacuum to give **283** (33.3 mg, 79.7%) as an off white foam. MS:m/z = 674.1$[M+H]^+$, 1347.2$[2M+H]^+$.

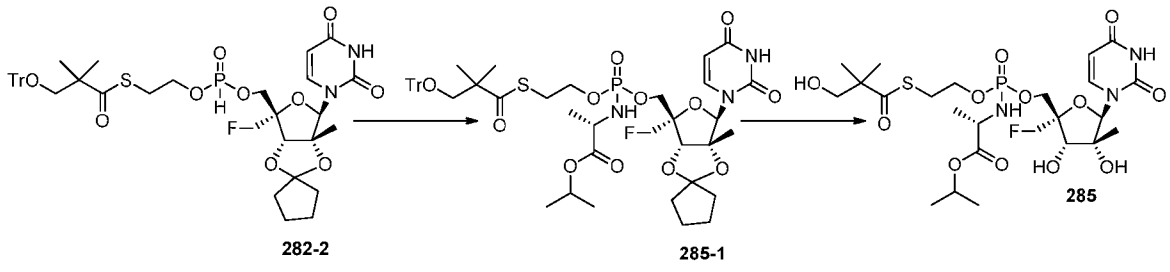
EXAMPLE 159
COMPOUND 284



[0899] A solution of Z-Gly-OH (105 mg, 0.5 mmol) in anhydrous THF (2 mL) was treated with carbonyldiimidazole (81 mg, 0.5 mmol). The mixture was stirred for 2 h at 40 °C, followed by 30 mins at 80 °C under an Ar atmosphere. This solution was added to a solution of **44** (200 mg, 0.33 mmol), Et_3N (72 μL, 0.5 mmol) and DMAP (4 mg) in DMF (2 mL). The mixture was stirred at RT for 3 h. The reaction was quenched by the addition of 1M citric acid (2 mL) at 0 to 5 ^{0}C (ice/water bath) and diluted with EA. The organic layer was separated, washed with sodium bicarbonate and brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography in 40 to 90% EA-hexane to give **284-1** (208.5 mg, 79.6%) as an off white foam.

[0900] To a solution of **284-1** (75 mg, 0.094 mmol) in anhydrous EtOH (3 mL), was added 10% Pd/C (10 mg), followed by the addition of 4N HCl (47 μL, 0.19 mmol). The mixture was stirred under H_2 atmosphere for 3 h. After completion of reaction, the mixture was filtered through celite. The catalyst cake was washed with anhydrous EtOH. The washings and the filtrate were combined, and the solvent was removed under vacuum to give **284** (44.3 mg, 71.5%) as an off white foam. MS:m/z = 658.05$[M+H]^+$, 1317.05$[M+H]^+$.

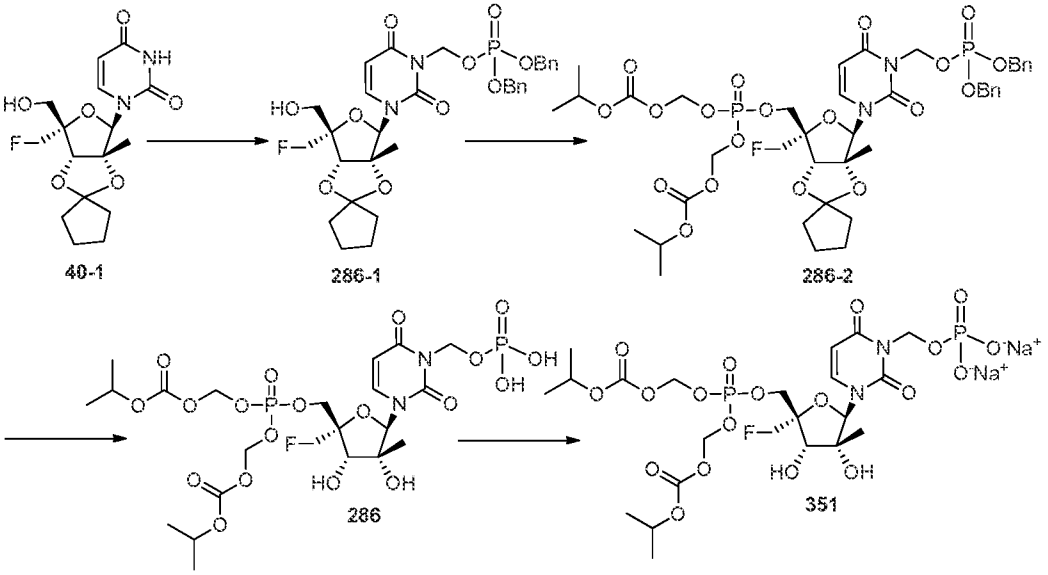
EXAMPLE 160
COMPOUND 285



[0901] To a solution of **282-2** (223 mg, 0.27 mmol) in CCl_4 (3 mL) were added L-alanine isopropyl ester hydrochloride (135 mg, 0.8 mmol) and dropwise Et_3N (0.22 mL, 1.6 mmol). The mixture was stirred at RT for 1 h. The mixture was then diluted with CH_2Cl_2, washed with sat aq. $NaHCO_3$ and brine, and dried with Na_2SO_4. The evaporated residue was purified on a silica column with CH_2Cl_2:i-PrOH (3-10% B gradient) to afford **285-1** (0.16 g, 62%).

[0902] A mixture of **285-1** (100 mg, 0.11 mmol) and 80% aq. TFA (3 mL) was stirred at RT for 2 h. The mixture was then evaporated and coevaporated with toluene. The residue was purified on a silica column with CH_2Cl_2:MeOH (4-10% B gradient) to afford **285** (31 mg, 46%). MS:m/z = 644 $[M+1]^+$.

EXAMPLE 161
COMPOUNDS 286 and 351



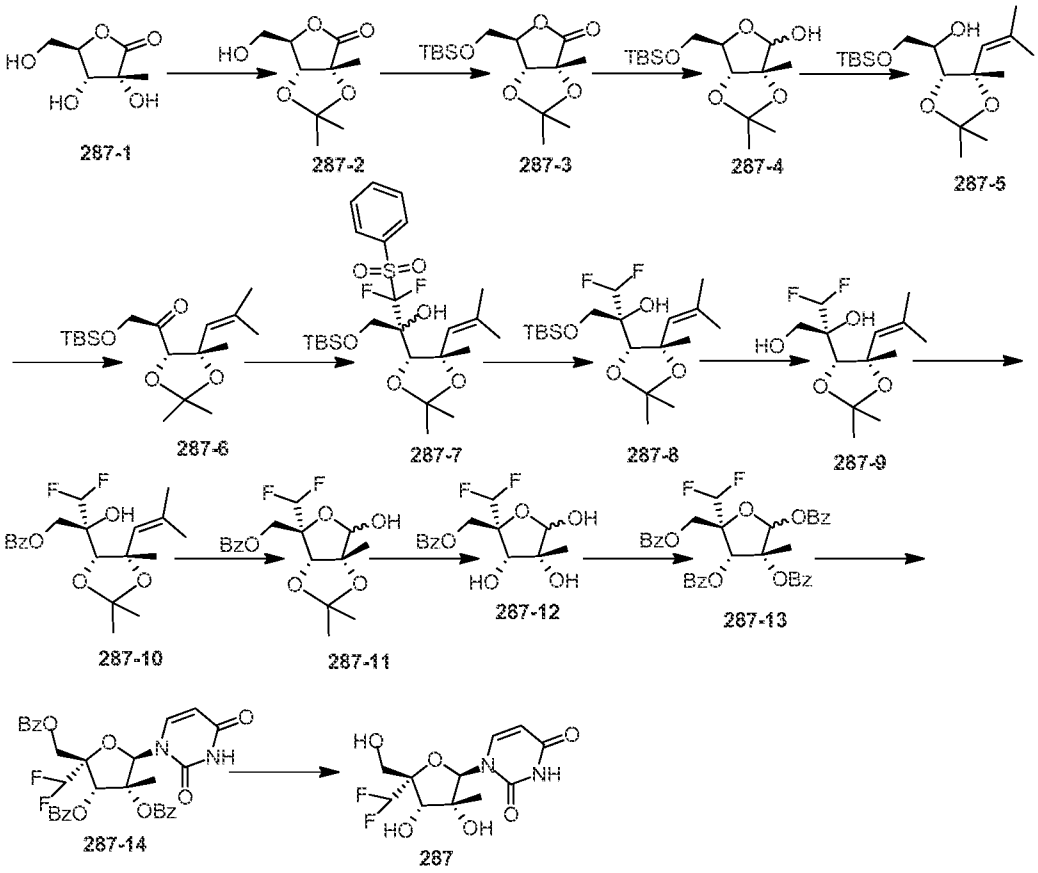
[0903] To a solution of **40-1** (1.08 g, 3.0 mmol) in *N,N*-dimethylacetamide (15 mL) was added $CsCO_3$ (1.22 g, 3.7 mmol), and the mixture was stirred at RT for 15 mins. Dibenzyl chloromethylphosphate (1g, 3.0 mmol) was added, and the mixture was stirred overnight at 40 °C. After cooling, the mixture was diluted with methyl tert-butylether and washed with water (3X) and brine, and dried with Na_2SO_4. The crude evaporated residue was purified on a silica column with CH_2Cl_2:i-PrOH (3-10% B gradient) to yield **286-1** (580 mg, 30%).

[0904] To a solution of triethylammonium bis(isopropyloxycarbonyloxymethyl)phosphate (1.8 mmol, prepared from 0.60 g of bis(isopropyloxycarbonyloxymethyl)phosphate and Et_3N) in THF was added **286-1** (0.58 g, 0.9 mmol). The mixture was evaporated and rendered anhydrous by coevaporating with pyridine follow by toluene. The evaporated residue was dissolved in anhydrous THF (9 mL) and cooled in an ice-bath. Diisopropylethyl amine (0.94 mL, 5.4 mmol) was added, followed by BOP-Cl (0.69 g, 2.7 mmol) and 3-nitro-1,2,4-triazole (0.31 g, 2.7 mmol). The mixture was stirred at 0-5 °C for 2 h, diluted with EtOAc, washed with sat. aq. $NaHCO_3$ and brine, and dried with Na_2SO_4. The evaporated residue was purified on a silica column with CH_2Cl_2:i-PrOH (3-10% B gradient) to yield **286-2** (0.77 g, 89%).

[0905] To a solution of **286-2** (50 mg; 0.05 mmol) in EtOH (2.5 mL) was added 10% Pd/C (8 mg), and the mixture was stirred under H_2 (atmospheric pressure) for 1 h. The mixture was filtered through a Celite pad, and the filtrate was evaporated. The residue was treated with 80% aq. HCOOH (2.5 mL) for 3 h, then evaporated and purified by RP-HPLC (A: 50 mM aq. TEAA, B: 50 mM TEAA in MeCN) to afford **286** (22 mg, 44%) as a white solid. MS:m/z = 713 $[M+1]^+$.

[0906] To a solution of **286** (14 mg, 0.02 mmol) in EtOH (0.3 mL) at 0 °C was added dropwise 0.1 M EtONa in EtOH (0.4 mL; 0.04 mmol). The mixture was allowed to warm to RT and the resulting white solid centrifuged. The supernatant was discarded. The solid was treated with EtOH (0.3 mL) and centrifuged to yield **351** (8 mg). MS:m/z = 713 $[M+1]^+$.

EXAMPLE 162
COMPOUND 287



[0907] To a stirred suspension of **287-1** (300 g, 1.86 mol) in acetone (4 L) was added conc.H_2SO_4 (56 mL) dropwise at RT. The mixture was stirred at RT for 3 h. The mixture was neutralized with solid $NaHCO_3$ and filtered. The filtrate was evaporated under reduced pressure to give **287-2** (381 g, crude) as a colorless oil, which was used for the next step without further purification.

[0908] To a stirred solution of **287-2** (380 g, crude, 1.88 mol) in anhydrous DCM (2 L) was added imidazole (191 g, 2.82 mol) and TBSCl (564 g, 3.76 mol) at 0 °C. The mixture was stirred at RT for 12 h, and then filtered. The filtrate was concentrated to dryness, and the residue was purified by silica gel column (2% EA in PE) to give **287-3** (569 g, 97% in 2 steps) as a white solid.

[0909] To a solution of **287-3** (150 g, 0.47 mol) in anhydrous THF (2 L) was added DIBAL-H (710 mL, 0.71 mol, 1.0 M in toluene) at -78 °C for 3 h. The reaction was quenched with sat. aq. NH_4Cl and then filtered. The filtrate was extracted with EA and

washed with brine. The organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated to dryness. The residue was purified by silica gel column (11% EA in PE) to give **287-4** (121 g, 80.5%) as a white solid.

[0910] Isopropyltriphenylphosphonium iodide (422.8 g, 0.98 mol) was suspended in anhydrous THF (1 L) and cooled to 0 °C. A BuLi solution (2.5M in THF, 391 mL, 0.98 mol) was added dropwise over 0.5 h. The deep red solution was maintained at 0 °C for 0.5 h and **287-4** (207.5 g, 0.65 mol) in THF (1 L) was added slowly over 2 h. The mixture was warmed to ambient temperature and stirred for 12 h. The reaction was quenched with sat. aq. $NaHCO_3$. The precipitated solid was removed by filtration. The filtrate was diluted with EA and washed with brine. The organic layer was dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated at low pressure, and the residue was purified by chromatography on silica gel (10% to 30% EA in PE) to give **287-5** (104.7 g, 47%) as a colorless oil.

[0911] To a stirred solution of **287-5** (4.9 g, 14.2 mmol) in anhydrous MeCN (70 mL) was added IBX (7.9 g, 28.4 mmol). The mixture was refluxed for 2 h. The mixture was filtered, and the filtrate was concentrated to dryness. The residue was purified by column chromatography (1% EA in PE) to give **287-6** (4.6 g, 94.8%) as a colorless oil.

[0912] To a stirred solution of **287-6** (2.0 g, 5.8 mmol) and difluoromethyl phenyl sulfone (2.24 g, 11.7 mmol) in anhydrous DMF (50 mL) was added LiHMDS (1.0 M in THF, 11.7 mL) dropwise at -78 °C. After stirring at -78 °C for 2 h, the reaction was quenched with sat. aq. NH_4Cl. The mixture was then stirred at 0 °C for 30 mins. The organic phase was separated, and the aqueous phase was extracted with EA. The combined organic phase was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated to dryness. The residue was purified on a silica gel chromatography (0.25% EA in PE) to give **287-7** (1.1 g, 32.1%) as a colorless oil. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ = 8.01-7.97 (m, 2H), 7.74-7.70 (m, 1H), 7.61-7.57 (m, 2H), 5.80 (d, J=1.6 Hz, 1H), 4.26 (d, J=11.2 Hz, 1H), 4.08 (s, 1H), 4.03 (d, J=11.2 Hz, 1H), 3.86 (s, 1H), 1.82 (s, 3H), 1.69 (s, 3H), 1.54 (s, 3H), 1.41 (d, J=12.4 Hz, 6H), 0.89 (s, 9H), 0.09 (d, J=9.6 Hz, 6H).

[0913] To a stirred solution of **287-7** (4.0 g, 7.5 mmol) in DMF (80 mL) and H_2O (16 mL) was added Mg (3.6 g, 149.8 mmol) followed by the addition of HOAc (13.5 g, 224.7 mmol). The mixture was stirred at RT for 6 h. The mixture was poured into ice water and

filtered. The filtrate was extracted with EA. The combined organic phase was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated to dryness, and the residue was purified on the silica gel chromatography (0.2% EA in PE) to give **287-8** (1.12 g, 38%) as a colorless oil. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ = 5.88-5.74 (m, 2H), 3.98-3.78 (m, 3H), 3.30 (s, 1H), 3.08 (s, 1H), 1.83 (s, 3H), 1.70 (s, 3H), 1.41(s, 3H), 1.35 (d, J=23.2 Hz, 6H), 0.90 (d, J=4.4 Hz, 9H), 0.08 (d, J=7.6 Hz, 6H).

[0914] To a solution of **287-8** (1.12 g, 2.84 mmol) was added a solution (6 mL, 1.0 M) of TBAF in THF, and the mixture was stirred at RT for 30 mins. The mixture was concentrated to dryness, and the residue was purified by silica gel column chromatography (3% EA in PE) to give **287-9** (332 mg, 41.7%) as a colorless oil.

[0915] To a solution of **287-9** (415 mg, 1.5 mmol) in anhydrous DCM (7.5 mL) was added Et_3N (224 mg, 2.2 mmol) and BzCl (248 mg, 1.7 mmol) at 0 °C. The mixture was stirred at RT for 4 h. After the reaction was completed, the reaction was quenched with sat. aq. $NaHCO_3$ and extracted with DCM. The organic layer was dried over Na_2SO_4 and filtered. The filtrate was evaporated, and the residue was purified by silica gel column chromatography (1% EA in PE) to give **287-10** (441 mg, 77.4%) as colorless oil.

[0916] To a stirred solution of **287-10** (440 mg, 1.2 mmol) in anhydrous DCM (10 mL) was bubbled O_3 at -78 °C until the solution turned blue. The reaction was then bubbled with O_2 until the solution turned to colorless. The organic layer was evaporated to give **287-11**(430 mg, crude), which was used for next step without further purification.

[0917] **287-11** (441 mg, 1.2 mmol) in 90% TFA (6 mL) was stirred at RT for 12 h. The mixture was concentrated under reduced pressure. The residue was purified via silica gel chromatography (50% EA in PE) to give **287-12** (404 mg, 97%) as a colorless oil.

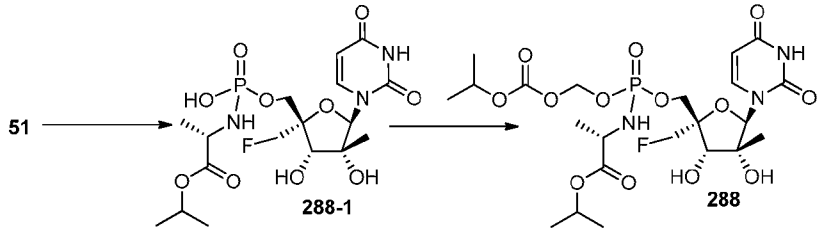
[0918] To a solution of **287-12** (404 mg, 1.3 mmol) in anhydrous DCM (6 mL) was added Et_3N (1.0 g, 10.2 mmol), DMAP (44 mg, 0.4 mmol) and BzCl (1.0 g, 7.6 mmol) at 0 °C. The mixture was stirred at RT for 4 h. The reaction was quenched with sat. aq. $NaHCO_3$ and extracted with DCM. The organic layer was dried over anhydrous Na_2SO_4 and filtered. The filtrate was evaporated, and the residue was purified by silica gel column chromatography (1% EA in PE) to give **287-13** (530 mg, 66.2%) as a light yellow foam.

[0919] To a stirred solution of uracil (190 mg, 1.7 mmol) in chlorobenzene (2.6 mL) was added N, O-bis (trimethylsilyl) acetamide (680 mg, 3.3 mmol). The solution was

stirred at 130 °C for 30 mins, and then cooled to ambient temperature. To a solution of **287-13** (536 mg, 0.8 mmol) in chlorobenzene was added $SnCl_4$ (770 mg, 3.5 mmol) slowly dropwise. The mixture was heated to reflux for 30 mins. The reaction was quenched by sat. aq. $NaHCO_3$ and extracted with EA. The organic layer was dried over anhydrous Na_2SO_4 and filtered. The filtrate was evaporated, and the residue was purified by silica gel column chromatography (20% EA in PE) to give **287-14** (336 mg, 64.6%) as a white solid.

[0920] **287-14** (80 mg, 0.1 mmol) was treated with 7.0 M NH_3 in MeOH. The mixture was stirred at RT for 12 h. The solvent was removed at low pressure. The residue was purified by silica gel column chromatography (5% MeOH in DCM) to give **287** (36 mg, 90.6%) as a white solid. ESI-LCMS:m/z 309.09 $[M+H]^+$; 331.07 $[M+Na]^+$.

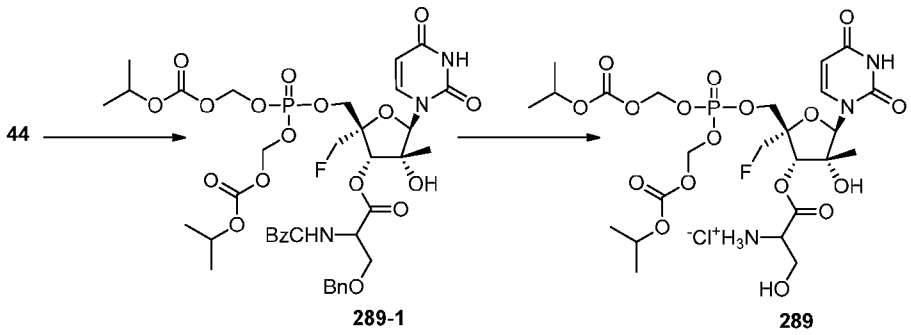
EXAMPLE 163
COMPOUND 288



[0921] To a mixture of **51** (240 mg, 0.8 mmol) in trimethyl phosphate (4 mL) at 0 °C was added $POCl_3$ (0.18 mL, 1.6 mmol), and the mixture was stirred at 0 °C for 90 mins. L-alanine isopropyl ester hydrochloride (0.24 g, 1.4 mmol) and Et_3N (0.6 mL, 4.3 mmol) were added. The mixture was warmed to RT and stirring was continued for 1.5 h. The reaction was quenched with 0.5 M aq. TEAA, and the mixture purified by RP-HPLC (A: 50 mM aq. TEAA, B: 50 mM TEAA in MeCN) to yield **288-1** (75 mg).

[0922] A mixture of **288-1** (52 mg, 0.1 mmol), DIPEA (0.11 mL, 0.6 mmol) and isopropyloxycarbonyloxymethyl iodide (77 mg, 0.3 mmol) in NMP (1.1 mL) was stirred at RT for 1 h. The mixture was diluted with tert-butyl methylether, washed with sat. aq. $NaHCO_3$ and brine, and dried with Na_2SO_4. The evaporated residue was purified on a silica column with CH_2Cl_2:MeOH (4-10% B gradient) to yield **288** (12 mg, 20%). MS:m/z = 600 $[M+1]^+$.

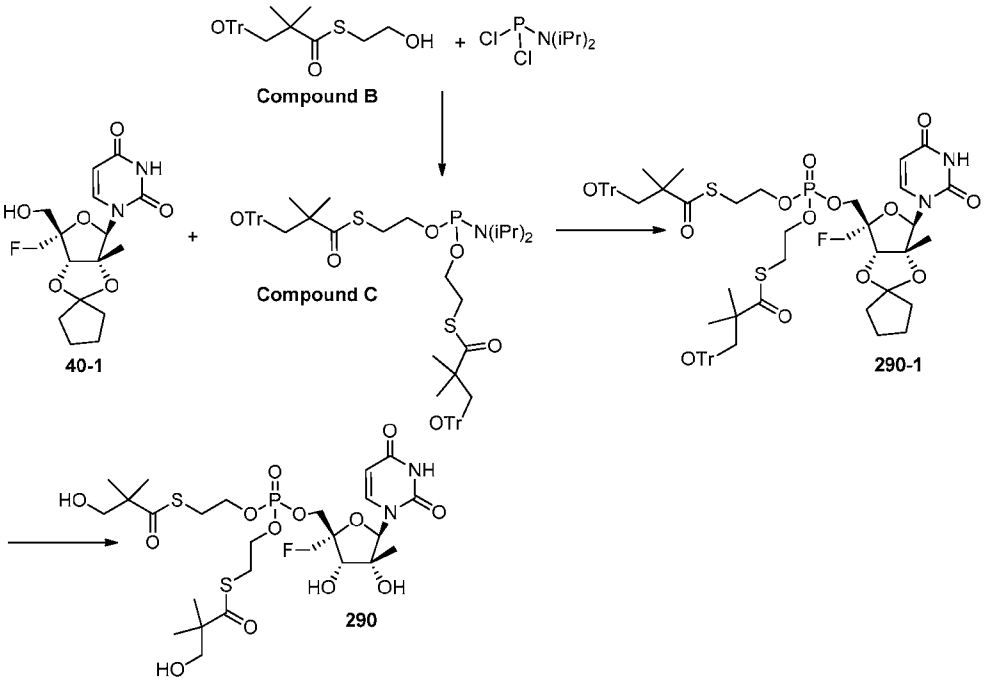
EXAMPLE 164
COMPOUND 289



[0923] To a solution of **44** (200 mg, 0.33 mmol) in anhydrous DCM (6 mL) was added DMAP (4 mg, 0.033 mmol), N-Cbz-O-benzyl-L-serine (164 mg, 0.5 mmol) and EDC (100 mg, 0.52 mmol) at 0 to 5 ^{0}C (ice/water bath). The mixture was stirred for 40 h at RT. The mixture was cooled using ice/water bath, diluted with DCM (10 mL), washed sat. NH_4Cl, dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography in 50 to 90% EA-hexane to give **289-1** (187 mg, 62%) as a white foam.

[0924] To a solution of **289-1** (68.7 mg, 0.075 mmol) in anhydrous EtOH (2.5 mL), was added 10 % Pd/C (11.4 mg), followed by the addition of 4N HCl (38 µL, 0.15 mmol), and the mixture was stirred under H_2 atmosphere for 3 h. After completion of reaction, the mixture was filtered through celite. The catalyst cake was washed with anhydrous EtOH. The washings and filtrate were combined, and the solvent was removed under vacuum to give **289** (40.1 mg, 77.6%) as an off white foam. MS:m/z = 690.1$[M+H]^+$.

EXAMPLE 165
COMPOUND 290

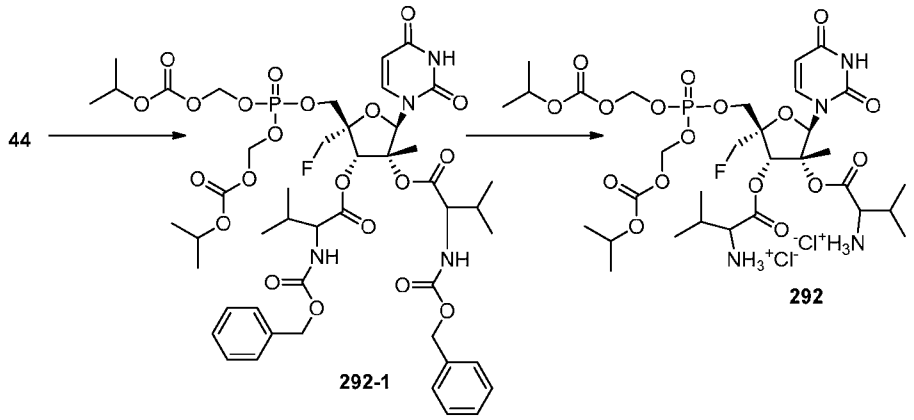


[0925] To a mixture of **Compound B** (0.84 g, 2 mmol; prepared according to Villard et al., *Bioorg. Med. Chem.* (2008) 16:7321-7329) and Et_3N (0.61 mL, 4.4 mmol) in THF (5 mL) at -78 °C was added dropwise a solution of *N,N*-diisopropyl dichlorophosphoroamidite (184 µL, 1 mmol) in THF (7 mL). The mixture was allowed to warm up and stirred at RT for 2 h. The solids were filtered off. The filtrate was concentrated and purified on a silica gel column with hexanes + 1% Et_3N:EtOAc (1-20% B gradient) to yield **Compound C** (0.38 g).

[0926] To a mixture of **40-1** (53 mg, 0.15 mmol) and **Compound C** (0.17 g, 0.17 mmol) in MeCN (1 mL) was added 5-ethylthio-1*H*-tetrazole (0.25 M in MeCN; 1.2 mL, 0.3 mmol). The mixture was stirred for 1 h at RT and then cooled to -40 °C. A solution of MCPBA (77%; 42 mg, 0.19 mmol) in CH_2Cl_2 (0.5 mL) was added. The mixture was allowed to warm up and stirred at RT for 30 mins. The reaction was quenched with 4% aq. $Na_2S_2O_3$ in 4% aq. $NaHCO_3$ (1 mL) and diluted with CH_2Cl_2. The organic layer was washed with sat. aq. $NaHCO_3$ and brine, and dried with Na_2SO_4. Purification of the evaporated residue on a silica gel column with hexanes:EtOAc (30-100% B gradient) yielded **290-1** (150 mg, 81%).

[0927] A solution of **290-1** (120 mg, 0.1 mmol) in 80% aq. TFA (5 mL) was kept at RT for 3 h. The mixture was concentrated, and the residue coevaported with toluene. The crude material was purified on a silica column with CH_2Cl_2:MeOH (4-10% B gradient) to give **290** (25 mg, 36%). MS:m/z = 691 $[M+1]^+$.

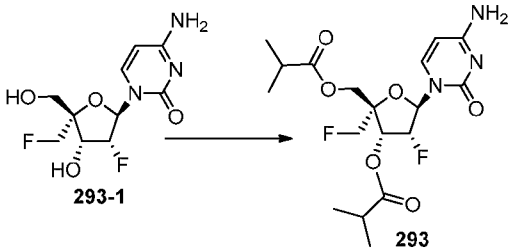
EXAMPLE 166
COMPOUND 292



[0928] To a mixture of DCC (412 mg, 1.98 mmol) in DMF (1 mL), DMAP (244 mg, 1.98 mmol) and Z-Val-OH (502 mg, 1.98 mmol) were added successively, followed by the addition of **44** (200 mg, 0.183 mmol). The mixture was stirred at RT for 1 h. The mixture was filtered, and the filtrate was concentrated with a rotary evaporator until ½ of its original volume. EA was added, and the mixture was washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a residue. The residue was purified by silica gel with 35-95% EA:hexanes to give **292-1** (107 mg, 31.2 %) as a white foam.

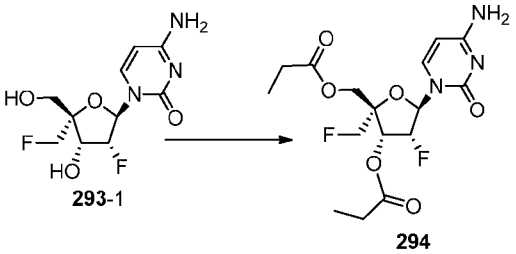
[0929] To a solution of **292-1** (68 mg, 0.064 mmol) in anhydrous EtOH (2.0 mL) was added 10 % Pd/C (12 mg), followed by the addition of 4N HCl (67 µl, 0.25 mmol). The mixture was stirred under H_2 atmosphere for 1.5 h. The mixture was filtered through celite, and the catalyst cake was washed with anhydrous EtOH. The washings and the filtrate were combined. The solvent was removed under vacuum to give **292** (41.6 mg, 82%) as a light yellow foam. MS:m/z = 801.25 $[M+H]^+$.

EXAMPLE 167
COMPOUND 293



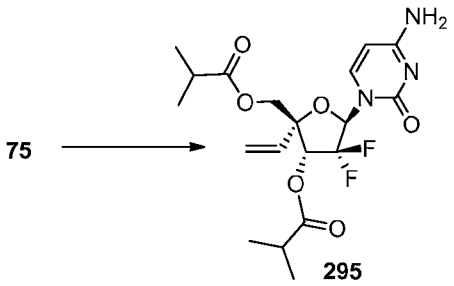
[0930] To a solution of **293-1** (40 mg, 0.144 mmol) in DMF (2 mL) were added DCC (65 mg, 0.32 mmol), isobutyric acid (28 μl, 0.32 mmol) and DMAP (18 mg, 0.144 mmol). The mixture was stirred at RT overnight. The mixture was filtered, and the filtrate was concentrated with a rotary evaporator to ½ of its original volume. The mixture was then diluted with 25% DMF/H_2O and purified on a reverse-phase HPLC (C18) using CH_3CN and water. Lyophilization gave **293** (17.5 mg, 29%) as a white powder. MS:m/z 416.1 $[M+H]^+$.

EXAMPLE 168
COMPOUND 294



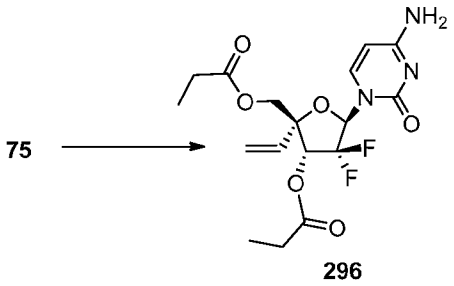
[0931] To a solution of **293-1** (50 mg, 0.18 mmol) in DMF (1.5 mL) were added DCC (93 mg, 0.45 mmol), propanoic acid (33.4 μl, 0.45 mmol) and DMAP (22 mg, 0.18 mmol). The mixture was stirred at RT overnight. The mixture was filtered, and then filtrate was concentrated with a rotary evaporator to ½ of its original volume. The mixture was then diluted with 25% DMF/H_2O , and purified on a reverse-phase HPLC (C18) using CH_3CN and water. Lyophilization gave **294** (30.2 mg, 43%) as a white powder. MS:m/z 390.1 $[M+H]^+$, 388.05 $[M-H]^-$.

EXAMPLE 169
COMPOUND 295



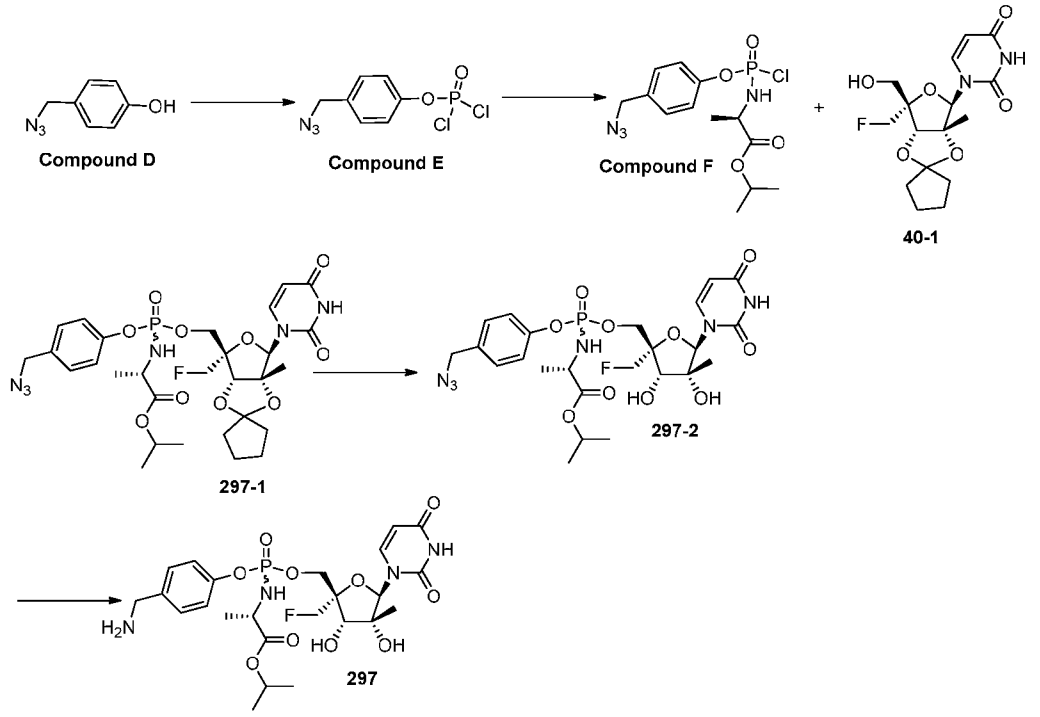
[0932] To a solution of **75** (20 mg, 0.073 mmol) in DMF (0.7 mL) were added DCC (37.6 mg, 0.183 mmol), isobutyric acid (16 µl, 0.183 mmol) and DMAP (9 mg, 0.073 mmol). The mixture was stirred at RT overnight. The mixture was filtered, and the filtrate was concentrated with a rotary evaporator to ½ of its original volume. The mixture was then diluted with 25% DMF/H_2O, and purified on a reverse-phase HPLC (C18) using 25-95% CH_3CN:water. Lyophilization gave **295** (12.1 mg, 38.7%) as a white powder. MS:m/z 430.15 $[M+H]^+$, 428.10 $[M-H]^-$.

EXAMPLE 170
COMPOUND 296



[0933] To a solution of **75** (20 mg, 0.073 mmol) in DMF (0.7 mL) were added DCC (37.6 mg, 0.183 mmol), propanoic acid (13.5 µl, 0.183 mmol) and DMAP (9 mg, 0.073 mmol). The mixture was stirred at RT overnight. The mixture was filtered, and then filtrate was concentrated with a rotary evaporator to ½ of its original volume. The mixture was then diluted with 25% DMF/H_2O, and purified on a reverse-phase HPLC (C18) using 25-95% CH_3CN:water Lyophilization gave **296** (14.1 mg, 48%) as a white powder. MS:m/z 402.1 $[M+H]^+$.

EXAMPLE 171
COMPOUND 297



[0934] To a mixture of **Compound D** (0.9 g, 6.0 mmol; prepared according to Qing et al., *Org. Lett.* (2008) 10:545-548) and $POCl_3$ (0.55 mL, 6.0 mmol) in diethyl ether (9 mL) at -78 °C was added Et_3N (0.84 mL, 6.0 mmol). The mixture was allowed to warm to RT in 2 h. The mixture was then filtered, and the solids were washed with Et_2O. The combined filtrates were evaporated, and the crude **Compound E** was used without purification.

[0935] To a solution of crude **Compound E** and L-alanine isopropyl ester hydrochloride (1.0 g, 6.0 mmol) in CH_2Cl_2 (15 mL) at -20 °C was added Et_3N (1.67 mL, 1.2 mmol). The mixture was allowed to warm up and stirring at RT for 2 h. The mixture was diluted with hexanes and filtered through a silica pad which was thoroughly washed with CH_2Cl_2:hexanes 1:1. The combined filtrates were concentrated and purified on a silica column with hexanes:EtOAc (5-50% B gradient) to yield **Compound F** (0.78 g, 38% for 2 steps).

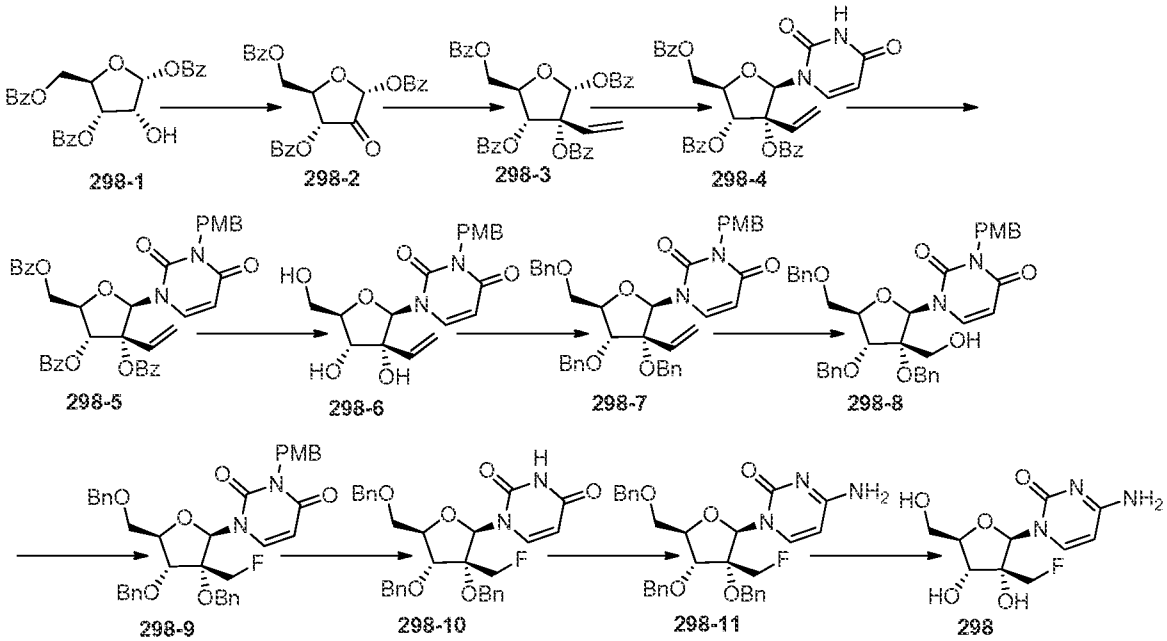
[0936] To a solution of **40-1** (0.36 g, 1.0 mmol) in THF (7.5 mL) at 0 °C was added isopropyl magnesium chloride (2 M in THF; 0.65 mL, 1.3 mmol), and the mixture was stirred at 0 °C for 30 mins. A solution of **Compound F** (0.78 g, 2.2 mmol) in THF (2 mL)

was added, and the mixture stirred at RT for 2 h. The reaction was quenched with sat. aq. NH_4Cl, and then diluted with EtOAc. The two layers were separated. The organic layer was washed with water and brine, and dried over Na_2SO_4. Purification of the evaporated residue on a silica gel column with CH_2Cl_2:i-PrOH (3-10% B gradient) yielded **297-1** (0.50 g, 74%).

[0937] A solution of **297-1** (0.28 g, 0.4 mmol) in 80 aq. TFA (4 mL) was stirred at RT for 4 h. The mixture was evaporated and coevaporated with toluene. The residue was purified on a silica column with CH_2Cl_2:MeOH (4-10% B gradient) to give **297-2** (0.17 g, 68%).

[0938] To a solution of **297-2** (85 mg, 0.14 mmol) in EtOH (3 mL) and HCl (4 N in dioxane; 35 μL, 0.14 mmol) was added 10% Pd/C (8 mg). The mixture was stirred under H_2 (atmospheric pressure) for 105 mins. The mixture was then filtered through a Celite pad. The evaporated residue was treated with Et_2O to yield **297** (55 mg, 63%) as a white solid. MS:m/z = 589 $[M+1]^+$.

EXAMPLE 172
COMPOUND 298



[0939] A mixture of **298-1** (120 g, 0.26 mol) and IBX (109 g, 0.39 mol) in CH_3CN (2.0 L) was heated to reflux and stirred for 12 h. After cooling to RT, the mixture was filtered. The filtrate was concentrated at low pressure and used directly for the next step.

[0940] **298-2** (130 g, crude, 0.26 mol) was co-evaporated with anhydrous toluene (3X) to remove H_2O. Vinyl magnesium bromide (700 mL, 0.78 mol, 1.0 N in THF) was added dropwise into a solution of **298-2** in THF (300 mL) over 30 mins at -78 °C. The mixture was stirred for about 1 h. at 25 °C and checked by LCMS trace. When the starting material was consumed, the mixture was poured into a sat. NH_4Cl solution, and extracted with EA (3 x 300 mL). The organic layer was washed with brine, dried with anhydrous Na_2SO_4, filtered and concentrated at low pressure to give the crude intermediate without further purification.

[0941] To a solution of this crude intermediate (170 g, 0.346 mol) in anhydrous CH_2Cl_2 was added TEA (105 g, 1.04 mol) and DMAP (84 g, 0.69 mol), and the mixture was stirred at RT. Benzoyl chloride (146 g, 1.04 mol) was added slowly at RT. After stirring for 12 h at RT, the mixture was diluted with CH_2Cl_2 and then washed with sat. aq. $NaHCO_3$. The combined aqueous phase was extracted with DCM (100 mL). The combined organic phase was dried with anhydrous Na_2SO_4, filtered and evaporated to dryness under reduced pressure. The residue was purified by column chromatography (PE:EA=10:1 to 5:1) to give **298-3** (107 g, 52%).

[0942] A mixture of uracil (treated by toluene twice) and NOBSA (81.4 g, 0.4 mol) in CH_3CN (200 mL) was stirred to reflux for 1.5 h. After the mixture was cooled to RT, **298-3** (59 g, 0.1 mol, treated by toluene) in CH_3CN (100 mL) was added. The mixture was treated with TMSOTf (155 g, 0.7 mol), and then warmed to 60-70 °C for 12 h. LCMS showed that no starting material remained. The mixture was poured into a $NaHCO_3$ (sat.) solution. The desired product precipitated. After filtration, pure **298-4** (40 g, 69%) was obtained as a white solid.

[0943] To a solution of **298-4** (50 g, 0.086 mol), K_2CO_3 (17.8 g, 0.13 mol) in DMF (500 mL) was added PMBCl (16 g, 0.1 mol) at 0 °C, and the mixture stirred at 25 °C for 12 h. The reaction was quenched with water, and the mixture was extracted with EtOAc (3 x 150 mL). The solution was washed with brine, dried over anhydrous Na_2SO_4 and concentrated at low pressure. Crude **298-5** (65 g) was obtained and used directly for the next step.

[0944] A mixture of **298-5** (65 g, 0.086 mol) and NaOMe (16.8 g, 0.3 mol) in MeOH:DCM (4:1, 200 mL) was stirred at RT for 2.5 h. LCMS showed that no starting

material remained. The reaction was quenched with dry ice. The solution was washed with brine, dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by column chromatography (DCM:MeOH=50:1 to 20:1) to give **298-6** as a yellow foam (25 g, 75%).

[0945] To a solution of **298-6** (25.5 g, 0.065 mol) in DMF was added NaH (10.5 g, 0.26 mol) slowly at ice bath, and the mixture was stirred for 30 mins. BnBr (36.3 g, 0.21 mol) was added, and the mixture was stirred at 25 °C for 12 h. TLC showed that the starting material disappeared. The reaction was quenched by sat. aq. NH_4Cl and extracted with EtOAc (3 x 100 mL). The organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by column chromatography (PE:EA=5:1 to 3:1 to 1:1) to give **298-7** (20 g, 46%).

[0946] To a solution of **298-7** (20 g, 0.03 mol), NMMO (7 g, 0.06 mol) in THF:H_2O (5:1, 100 mL) was added OsO_4 (2.6 g, 0.01 mol) at 25 °C, and the mixture was stirred at 25 °C for 24 h. The reaction was quenched with a sat. $Na_2S_2O_3$ solution, and extracted with EtOAc (3 x 100 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated at low pressure. The diol product residue was used directly for next step.

[0947] To a solution of diol product (0.03 mol) in MeOH:H_2O:THF (170 mL:30 mL:50 mL) was added $NaIO_4$ (9.6 g, 0.045 mol), and the mixture was stirred at 25 °C for 2 h. After the white solid was filtered, the filtrate was used directly for the next step.

[0948] The previous solution was treated with $NaBH_4$ (1.8 g, 0.048 mol) at 0 °C, and stirred at 25 °C for 30 mins. The reaction was quenched with HCl (1 N) solution and adjusted pH to 7-8. The solution was extracted by EtOAc (3 x 50 mL). The organic phase was washed with brine washed with brine, dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by column chromatography (PE:EA=6:1 to 4:1) to give **298-8** (12 g, 61% over 3 steps).

[0949] To a solution of **298-8** (14 g, 21 mmol), DMAP (5.1 g, 42 mmol) in DCM (50 mL) was added MsCl (3.1 g, 27 mmol) at 0 °C, and the mixture was stirred at 25 °C for 40 mins. LCMS shows that no starting material remained. The reaction was quenched by sat. aq. $NaHCO_3$ and extracted with DCM (3 x 100 mL). The solution was washed with HCl (0.2 N) solution, dried over anhydrous Na_2SO_4 and concentrated at low pressure. The

residue was purified by column chromatography (PE:EA=10:1 to 5:1) to give the OMs-product (14 g, 90%).

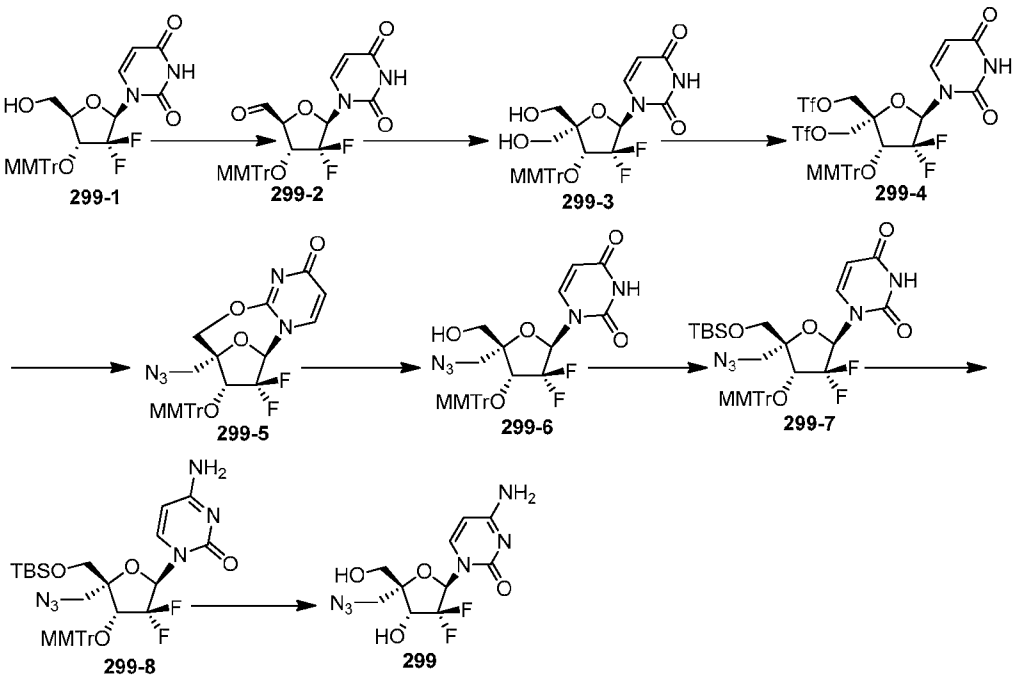
[0950] The OMs-product (6.1 g, 8.21 mmol) was dissolved in TBAF (Alfa, 1 N in THF, 120 mL), and the mixture was stirred at 70-80 °C over 3 days. LCMS shows that 50% of the starting material was converted to the desired product. The mixture was concentrated at low pressure. The residue was dissolved in EtOAc (100 mL). The solution was washed by brine, dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by column chromatography (PE:EA=10:1 to 5:1) to give **298-9** (1.3 g, 24%).

[0951] To a solution of **298-9** (6.3 g, 9.45 mmol) in CAN:H_2O (v:v = 3:1, 52 mL) was added CAN (15.5 g, 28.3 mmol), and the mixture was stirred at RT overnight. The reaction was quenched with water, and extracted with EA (3 x 80 mL). The organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by column chromatograph (25% EA in PE) to give **298-10** (3.6 g, 71 %) as a yellow oil.

[0952] To a solution of **298-10** (566 mg, 1.04 mmol), DMAP (253 mg, 2.07 mmol) and TEA (209 mg, 2.07 mmol) in anhydrous MeCN (6 mL) was added TPSCl (627 mg, 2.07 mmol) at 0°C. The mixture was stirred at RT for 2 h. The mixture was treated with $NH_3 \cdot H_2O$ (10 mL), and stirred at RT overnight. TLC showed that the reaction was completed. The solution was concentrated at low pressure. The residue was purified by silica gel column chromatography (DCM:MeOH=50:1 to 20:1) to give **298-11** (300 mg, 49%) as a white solid.

[0953] To a solution of **298-11** (200 mg, 0.37 mmol) in anhydrous DCM (0.5 mL) was added BCl_3 (2.5 mL, 1 N in DCM) at -70 °C, and the mixture was stirred for 2 h at -70 °C. TLC showed that no materials remained. The reaction was quenched with MeOH at -70 °C, and concentrated at low pressure directly under 40 °C. The residue was dissolved in H_2O, and washed with EtOAc over 3 times. The aqueous phase was lyophilized to give **298** (91 mg, 89%) as a white solid. ESI-LCMS:m/z 276.1 $[M+H]^+$.

EXAMPLE 173
COMPOUND 299



[0954] To a stirred solution of **299-1** (8.2 g, 15.3 mmol) in anhydrous CH_3CN (150 mL) was added IBX (4.7 g, 16.8 mmol) at 20 °C under N_2. The suspension was heated to 90 °C~100 °C and stirred at this temperature for 1 h. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue, **299-2**, (8.2 g, crude) was used in the next step without further purification.

[0955] To a solution of **299-2** (8.2 g, 15.4 mmol) in 1,4-dioxane (150 mL) was added aq. NaOH (15.4 mL, 2 M, 30.8 mmol) at 20 °C. The mixture was stirred at this temperature for 10 h. The solution was neutralized with AcOH to pH=7, followed by addition of EtOH (50 mL) and $NaBH_4$ (5.8 g, 154.3 mmol) at 0 °C. The mixture was stirred at this temperature for 1 h. The reaction was quenched with water (20 mL), extracted with EA (2 x 40 mL). The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$ and concentrated at low pressure. The residue was purified via silica gel chromatography (50% EA in PE) to give **299-3** (5.5 g, 62.92%) as a white solid.

[0956] **299-3** (480 mg, 0.8 mmol) was co-evaporated with toluene (2x). The residue was dissolved in anhydrous DCM (5 mL) and pyridine (671 mg, 85 mmol). Tf_2O (481 mg, 187 mmol) was added dropwise at 0 °C over 10 mins. The mixture was stirred at

this temperature for 40 mins. The mixture was purified by column chromatography (20% EA in PE) to give **299-4** (602 mg, 86.1%) as a brown foam.

[0957] To a solution of **299-4** (602.0 mg, 0.72 mmol) in anhydrous DMF (8 mL) was added NaH (34.8 mg, 0.87 mmol) at 0 °C under N_2 atmosphere. The reaction was stirred at 20 °C for 1 h, and then NaN_3 (1.59 g, 2.5 mmol) was added at 0 °C under N_2 atmosphere. The mixture was stirred at 20 °C for 2 h. The reaction was quenched with water at the same temperature, extracted with EA (2 x 20 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated to dryness under reduced pressure. The residue, **299-5**, (431 mg, crude) was used in next step without further purification.

[0958] To a solution of **299-5** (431 mg, crude) in 1,4-dioxane (14 mL) was added aq. NaOH (114.4 mg, 2 M, 2.9 mmol) at 18 °C. The mixture was stirred at the same temperature for 3 h. The mixture was diluted with EA (20 mL). The organic layer was washed with brine, dried over $MgSO_4$ and concentrated at low pressure. The residue was purified via silica gel chromatography (30% EA in PE) to give **299-6** (406.0 mg, 47.9%) as a white foam.

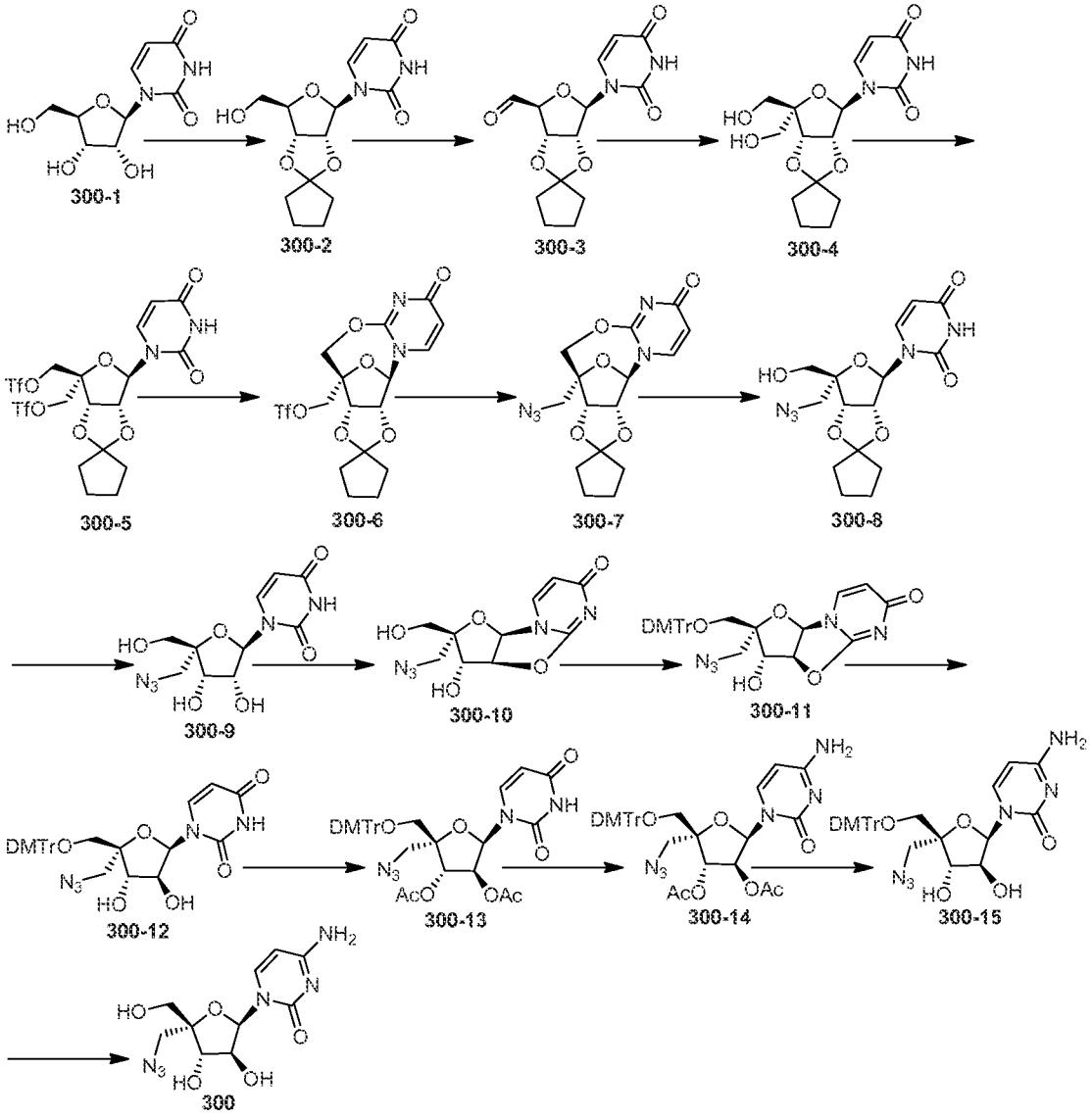
[0959] To a solution of **299-6** (406.0 mg, 0.68 mmol) in anhydrous DMF (8 mL) was added TBSCl (198.7 mg, 1.3 mmol) and imidazole (119.7 mg, 1.8 mmol) at 30 °C under N_2 atmosphere. The solution was stirred at this temperature for 3 h. The solution was diluted with EA (20 mL) and washed with water and brine. The organic phase was dried over $MgSO_4$ and concentrated at low pressure. The residue was purified via silica gel chromatography (50% EA in PE) to give **299-7** (405.0 mg, 65.28%) as a white solid.

[0960] To a solution of **299-7** (405.0 mg, 0.57 mmol) in anhydrous CH_3CN (6 mL) was added 2,4,6-triisopropylbenzene-1-sulfonyl chloride (343.3 mg, 1.13 mmol), DMAP (138.5 mg, 1.1 mmol) and TEA (114.7 mg, 1.1 mmol) at 30 °C. The mixture was stirred at this temperature for 9 h. $NH_3 \cdot H_2O$ (4 mL) was added, and the mixture was stirred for 3 h. The mixture was diluted with EA (20 mL) and washed with brine. The organic layer was dried over Na_2SO_4 and concentrated at low pressure. The residue was purified via silica gel chromatography (50% EA in PE) to give **299-8** (401.0 mg, crude) as a yellow foam.

[0961] **299-8** (380.0 mg, 0.54 mmol) was dissolved in 80%HCOOH (25 mL), and the mixture was stirred at 30°C for 12 h. The reaction was quenched with MeOH and

concentrated under reduced pressure. The residue was purified by silica gel chromatography (10% MeOH in DCM) to give **299** (144.0 mg, 83.93%) as a white foam. ESI-MS:m/z 319.1 $[M+H]^+$; 637.2 $[2M+H]^+$.

EXAMPLE 174
COMPOUND 300



[0962] To a solution of **300-1** (30 g, 122.85 mmol) and 1,1-dimethoxycyclopentane (86 g, 660.93 mmol) in DCE (200 mL) was added $TsOH \cdot H_2O$ (2.34 g, 12.29 mmol) in one portion at RT. The mixture was heated to 70 °C and stirred for 14 h. TLC showed that the reaction was completed. The mixture was cooled to RT and

concentrated under reduced pressure. The residue was purified by column chromatography (1-10% MeOH in DCM) to give **300-2** (25 g, 65.6%) as a white solid.

[0963] To a solution of **300-2** (20 g, 64.45 mmol) in anhydrous CH_3CN (200 mL) was added IBX (19.85 g, 70.9 mmol) at RT. The mixture was refluxed for 18 h. and then cooled to 0 °C. The precipitate was filtered-off, and the filtrate was concentrated to give crude **300-3** (20 g, 100%) as a yellow solid.

[0964] To a solution of **300-3** (20 g, 64.87 mmol) in 1,4-dioxane (200 mL) were added 37% HCHO (20 mL) and 2.0 M NaOH aq. solution (40 mL) at 0 °C. The mixture was stirred at RT overnight and then neutralized with AcOH to pH = 7. The solution was treated with $NaBH_4$ (4.91 g, 129.74 mmol) at 20 °C. The mixture was stirred at RT for 1.0 h, and the reaction was quenched with sat. aq. NH_4Cl. The mixture was extracted with EA (3 s 200 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by silica gel column chromatography (1-3% MeOH in DCM) to give **300-4** (9 g, 40.8 %) as a white solid.

[0965] To an ice cold solution of **300-4** (4.5 g, 13.22 mmol) in anhydrous DCM (50 mL) was added pyridine (10.46 g, 132.20 mmol) and Tf_2O (8.21 g, 29.08 mmol) dropwise at -30 °C. The mixture was stirred at the same temperature for 1 h. The reaction was quenched with ice water and extracted with EA (3 x 60 mL). The organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified on a silica gel column (PE:EA=5:1) to give **300-5** (5 g, 62.57%) as a white solid.

[0966] To a stirred solution of **300-5** (5 g, 8.27 mmol) in anhydrous DMF (25 mL) was added NaH (396.96 mg, 9.92 mmol) at 0 °C under N_2. The solution was stirred at RT for 2 h. TLC showed that the reaction was completed. The solution of **300-6** was used in next step without any further workup.

[0967] To a stirred solution of **300-6** (3.75 g, 8.25 mmol) was added NaN_3 (1.5g, 2.50 g, 38.46 mmol) at 0 °C under N2 atmosphere. The solution was stirred at RT for 2 h. The reaction was quenched with water and extracted with EA (3 x 60 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue, **300-7**, was used in the next step without further purification.

[0968] To a solution of **300-7** (2.87 g, 8.25 mmol) in anhydrous 1,4-dioxane (30 mL) was added NaOH (8.25 mL, 16.50 mmol, 2.0 M in water) at RT. The mixture was stirred at RT for 3 h. TLC showed that the reaction was completed. The mixture was diluted with EA. The solution was washed with brine, dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified on the silica gel column (PE:EA=10:1 to 2:1) to give **300-8** (2 g, 66.4%) as a white foam. ^{1}H-NMR (DMSO, 400 MHz), δ = 9.02 (s, 1H), 7.40 (d, J = 8.0 Hz, 1H), 5.75-5.77 (m, 1H), 5.57 (d, J = 3.6 Hz, 1H), 5.13-5.16 (m, 1H), 4.90 (d, J = 6.4 Hz, 1H), 3.79-3.85 (m, 2H), 5.51-5.56 (m, 2H), 3.06-3.09 (m, 1H), 2.05-2.09 (m, 2H), 1.65-1.75 (m, 6H).

[0969] **300-8** (2 g, 5.47 mmol) was dissolved in 80% HCOOH (20 mL) aq. solution, and the mixture was heated to 60 °C for 2 h. The mixture was evaporated at low pressure. The residue was dissolved in MeOH, and the pH was adjusted to 7~8 with NH_3•H_2O. The mixture was stirred for 10 mins, and then concentrated at low pressure. The residue was purified by silica gel chromatography (DCM:MeOH=20:1) to afford **300-9** (1.4 g, 85.5%) as a white solid.

[0970] To a solution of **300-9** (1.00 g, 3.34 mmol) in DMF (5 mL) was added diphenyl carbonate (157.49 mg, 735.20 μmol) and $NaHCO_3$ (28.06 mg, 0.334 mmol) at 120 °C. The mixture was stirred for 16 h. TLC showed that the reaction was completed. The mixture was cooled to RT and concentrated at low pressure. The residue was purified by silica gel chromatography (DCM:MeOH=15:1 to 10:1) to afford **300-10** (600. mg, 63.9%) as a yellow solid. ^{1}H-NMR (DMSO, 400 MHz), δ = 8.49 (s, 1H), 7.83 (d, J = 7.2 Hz, 4H), 6.46 (s, 1H), 6.31 (d, J = 4.8 Hz, 1H), 5.84 (d, J = 6.8 Hz, 1H), 5.27 (d, J = 5.6 Hz, 2H), 4.43 (s, 1H), 3.53 (d, J = 12.8 Hz, 1H), 3.43 (d, J = 13.2 Hz, 1H), 3.12 (d, J = 11.2 Hz, 1H).

[0971] To a solution of **300-10** (2 g, 7.11 mmol) and $AgNO_3$ (1.81 g, 10.67 mmol) in Py (20 mL) was added DMTrCl (3.61 g, 10.67 mmol) in one portion at RT. The mixture was stirred at RT for 12 h. TLC showed that the reaction was completed. The mixture was concentrated at low pressure, and the residue was purified by silica gel chromatography (DCM:MeOH = 50:1) to afford **300-11** (3 g, 72.3%) as a white solid.

[0972] To a solution of **300-11** (1.5 g, 2.57 mmol) in EtOH (5 mL) was added NaOH (5 mL, 2.0 N) in one portion at RT. The mixture was stirred at RT for 0.5 h. TLC showed that the reaction was completed. The aqueous phase was extracted with EA (3 x 60

mL). The organic phase was washed with brine, dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to afford **300-12** (1.50 g, 97%) as a yellow solid.

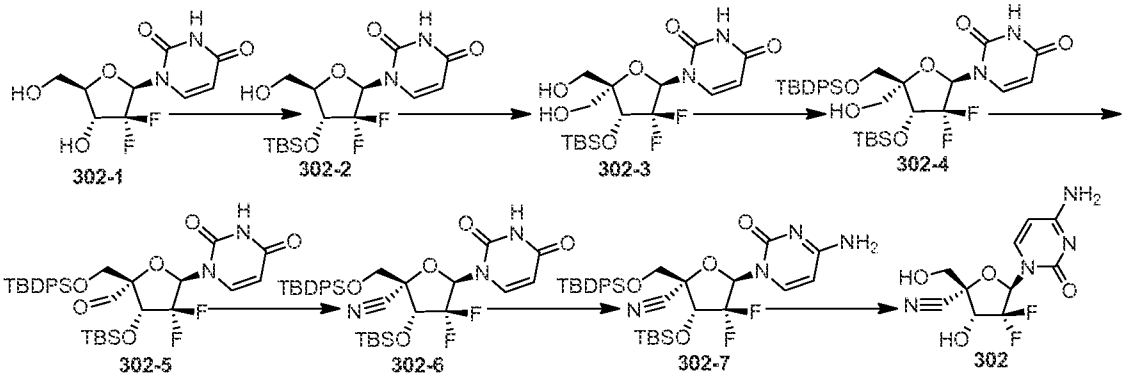
[0973] To a solution of **300-12** (1.50 g, 2.49 mmol) in Py (6 mL) was added AC_2O (3 mL) in one portion at RT. The mixture was stirred at RT for 12 h. TLC showed that the reaction was completed. The mixture was concentrated, and the residue was dissolved in water. The aqueous phase was extracted with EA (3 x 60 mL). The combined organic phase was washed with sat. brine, dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (PE:EA=1:1) to afford **300-13** (1.5 g, 87.8%) as a white solid. ^{1}H-NMR ($CDCl_3$, 400 MHz), δ = 8.10 (s, 1H), 7.29-7.34 (m, 10H), 6.77 (d, J = 8.0 Hz, 4H), 6.36 (d, J = 5.2 Hz, 1H), 5.36 (d, J = 3.6 Hz, 1H), 5.44 (t, J = 4.0 Hz, 1H), 5.32 (d, J = 8.0 Hz, 1H), 3.80 (s, 6H), 3.58 (d, J = 12.8 Hz, 1H), 3.44 (d, J = 12.8 Hz, 1H), 3.29 (s, 2H), 2.10 (s, 3H), 1.82 (s, 3H).

[0974] To a solution of **300-13** (500 mg, 729.2 μmol) in MeCN (10 mL) was added DMAP (178.17 mg, 1.46 mmol) and TPSCl (430.01 mg, 1.46 mmol) in one portion at RT. The mixture was stirred at RT for 3 h. NH_3/THF (20 mL, sat) was added, and the mixture was stirred for 1 h. The mixture was diluted with EA and washed with water. The combined organic phase was washed with sat. brine, dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (DCM:MeOH= 50:1) and then purified by pre-HPLC(CH_3CN/H_2O) to afford **300-14** (260 mg, 49.5%) as a yellow solid. ^{1}H-NMR (MeOD, 400 MHz), δ = 7.60 (d, J = 7.6 Hz, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.28-7.36 (m, 7H), 6.89 (d, J = 8.4 Hz, 4H), 6.44 (d, J = 4.8 Hz, 1H), 5.56-5.69 (m, 4H), 3.80 (s, 6H), 3.54 (d, J = 13.2 Hz, 1H), 3.39-3.46 (m, 4H), 2.17 (s, 3H), 1.83 (s, 3H).

[0975] To a solution of **300-14** (440 mg, 642.6 μmol) in NH_3:MeOH (5 mL, 7N) was stirred at RT for 16 h. TLC showed that the reaction was completed. The mixture was concentrated under reduced pressure at 40 °C. The residue was purified by silica gel chromatography (DCM:MeOH=100:1-20:1) to afford **300-15** (290 mg, 75.13%) as a white solid. ^{1}H-NMR (MeOD, 400 MHz), δ = 7.62 (d, J = 7.6 Hz, 1H), 7.43 (d, J = 7.6 Hz, 1H), 7.23-7.33 (m, 7H), 6.86 (d, J = 8.4 Hz, 4H), 6.31 (d, J = 4.8 Hz, 1H), 5.54 (d, J = 7.2 Hz, 1H), 4.34 (t, J = 4.4 Hz, 1H), 4.27 (d, J = 4.0 Hz, 1H), 3.78 (s, 6H), 3.69 (d, J = 12.8 Hz, 1H), 3.46 (d, J = 12.8 Hz, 1H), 3.41 (s, 2H).

[0976] A solution of **300-15** (150 mg, 249.74 μmol) in 80%CH_3COOH (5 mL) was stirred at 60 °C for 2 h. TLC showed that the reaction was completed. The mixture was treated with MeOH and concentrated under reduced pressure at 60 °C. The residue was purified by silica gel chromatography (1-10% MeOH in DCM) to afford **300** (65 mg, 78.5%) as a white solid. ESI-MS:m/z 299.1 $[M+H]^+$.

EXAMPLE 175
COMPOUND 302



[0977] To a solution of **302-1** (12 g, 45.42 mmol) in pyridine (100 mL) was added DMTrCl (16.16 g, 47.69 mmol) in portions at 0 °C over a period of 30 mins under N_2. The mixture was warmed to 25 °C and stirred for 16 h. LCMS and TLC (DCM:MeOH=20:1) showed that the starting material was consumed. The reaction was quenched with MeOH (10 mL) and then concentrated in vacuum. The residue was purified by silica gel chromatography (100-200 mesh silica gel, PE:EA=1:1) to give pure **DMTr-302-1** (20 g, 77.7%) as a white solid.

[0978] To a solution of **DMTr-302-1** (30.00 g, 52.95 mmol) and TBSCl (19.95 g, 132.38 mmol, 2.50 eq.) in DCM (200 mL) was added imidazole (9.00 g, 132.20 mmol, 2.50 eq.) in portions at 0 °C. The temperature was maintained below 5°C. The mixture was warmed to 25 °C, and stirred for 16 h. TLC (PE:EA=1:1) showed that the starting material was consumed. The reaction was quenched by ice and then extracted with DCM (2 x 50 mL). The combined organic phase was washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated at low pressure. The residue was purified by chromatography to give the pure product (30.00 g, 83.2%) as a white solid.

[0979] The product from the previous step (30.00 g, 44.07 mmol) was dissolved in 80% AcOH aqueous (300 mL), and the mixture was stirred at 25 °C for 16 h. TLC

(DCM:MeOH=10:1) showed that the reaction was completed. The reaction was quenched with sat. aq. $NaHCO_3$ (100 mL) and then extracted with EA (3 x 100 mL). The organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by a silica gel column (DCM:MeOH=50:1~20:1) to give **302-2** (15.5 g, 92.9%) as a white solid.

[0980] To a solution of **302-2** (8.00 g, 21.14 mmol) in MeCN (80 mL) was added IBX (6.51 g, 23.25 mmol, 1.10 eq.) at 25 °C under N_2. The mixture was heated to 81 °C for 1 h. LCMS showed that the starting material was consumed. The mixture was filtered, and the filtrates were concentrated in vacuum. The aldehyde residue (7.50 g, 19.92 mmol) was used in next step without further purification.

[0981] To a solution of the aldehyde from the previous step (7.5 g, 19.9 mmol) and aq. formaldehyde (7.85 mL) in dioxane (80 mL) was added 2.0 N aq. NaOH (19.5 mL) in one portion at 25 °C. The mixture was stirred at 25 °C for 16 h. TLC showed that the reaction was completed. The mixture was cooled to 0 °C and then neutralized with AcOH to pH = 7. The solution were treated with $NaBH_4$ (4.52 g, 119.52 mmol) at 0 °C. The mixture was stirred at 25 °C for 30 mins, and the reaction was quenched with sat. aq. NH_4Cl (100 mL). The mixture was extracted with EA (2 x 100 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (100-200 mesh silica gel, DCM:MeOH=20:1 to 10:1) to afford **302-3** (4.0 g, 49.2%) as a white solid.

[0982] To a solution of **302-3** (4.00 g, 9.79 mmol) in pyridine (20 mL) was added a solution of MMTrCl (3.48 g, 10.28 mmol) in DCM (20 mL) dropwise at 0 °C over a period of 15 mins. The temperature was maintained below 5°C. The mixture was warmed to 25 °C and stirred at 2 5°C for 16 h. TLC (DCM:MeOH=10:1) showed that the starting material was consumed. The reaction was quenched by MeOH (5 mL) and concentrated in vacuum. The residue was purified by column (DCM:MeOH=50:1) to give a pure intermediate (5.00 g, 71.85%) as a white solid.

[0983] To a solution of the above intermediate (5.00 g, 7.03 mmol) and $AgNO_3$ (2.39 g, 14.06 mmol, 2.00 eq.) in pyridine (40 mL) was added dropwise TBDPSCl (2.90 g, 10.55 mmol) at 0 °C over a period of 10 mins. The mixture was warmed to 25 °C and stirred for 16 h. TLC (PE:EA=1:1) showed that the starting material was consumed. The reaction

was quenched by ice and then extracted with EA (3 x 100 mL). The combined organic phase was washed with sat. brine (2 x 50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue (5.00 g, crude) was dissolved in 80% aq. AcOH (50 mL), and the mixture was stirred at 25 °C for 2 h. TLC (PE:EA=2:1) showed that the reaction was completed. The reaction was quenched by MeOH (5 mL) and then extracted with DCM (3 x 100 mL). The organic phase was washed with brine, dried over anhydrous $MgSO_4$ and concentrated at low pressure. The residue was purified by a silica gel column (PE:EA=5:1 to 2:1) to give **302-4** (2.50 g, 55%) as a yellow solid.

[0984] To a solution of **302-4** (400 mg, 618.36 μmol) in DCM (4 mL) was added DMP (393.4 mg, 927.54 μmol, 1.50 eq.) in one portion at 0 °C under N_2. The mixture was stirred at 25 °C for 2 h. TLC (PE:EA=2:1) showed that the reaction was completed. The mixture was cooled to 0 °C and quenched with sat. aq. Na_2SO_3 (5 mL) and aq. $NaHCO_3$ (5 mL). The aqueous layer was extracted with DCM (3 x 10 mL). The combined organic phase was washed with sat. brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (100-200 mesh silica gel, PE:EA =3:1) to afford **302-5** (300.00 mg, 75.24%) as a white solid.

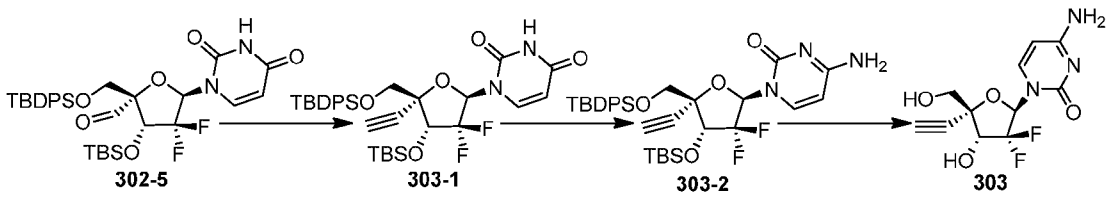
[0985] To a solution of **302-5** (500 mg, 775.37 μmol) in pyridine (5 mL) was added hydroxylamine hydrochloride (215.5 mg, 3.10 mmol, 4.00 eq.) in one portion at 0 °C under N_2. The mixture was stirred at 0 °C for 30 mins, and then warmed to 25°C and stirred for 4 h. LCMS showed that the reaction was completed. The mixture was concentrated in vacuum. The residue was purified by silica gel chromatography (100-200 mesh silica gel, PE:EA=2:1) to afford the oxime (450 mg, 87.95% yield) as a light yellow solid.

[0986] To a solution of this oxime (450.00 mg, 681.95 μmol) in DCM (5 mL) was added TEA (208.0 mg, 2.06 mmol) and MsCl (156.0 mg, 1.36 mmol) in one portion at 0 °C. The mixture was stirred at 25 °C for 4 h. TLC (PE:EA=2:1) showed that the reaction was completed. The reaction was quenched by sat. aq. $NaHCO_3$ (5 mL), and the aqueous phases were extracted with DCM (2 x 20 mL). The combined organic phase was washed with sat. brine (10 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by TLC (PE:EA=2:1) to afford **302-6** (400 mg, 91.4%) as a light yellow solid.

[0987] To a solution of **302-6** (450.0 mg, 701.10 μmol), DMAP (171.3 mg, 1.40 mmol) and TEA (212.8 mg, 2.10 mmol) in MeCN (5 mL) was added 2,4,6-triisopropylbenzene-1-sulfonyl chloride (424.7 mg, 1.40 mmol) in one portion at 0 °C. The mixture was stirred at 25 °C for 1 h. TLC (PE:EA=2:1) showed that the reaction was completed. The reaction was quenched by sat. aq. $NaHCO_3$ (5 mL) and extracted with EA (2 x 15 mL). The combined organic phase was washed with sat. brine (10 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue (580.00 mg, 638.59 μmol) was dissolved in MeCN (5 mL). The solution was treated with $NH_3 \cdot H_2O$ (10 mL) in one portion at 25 °C. The mixture was stirred at 25 °C 16 h. TLC (PE:EA=1:1) showed the reaction was completed. The mixture was extracted with EA (3 x 10 mL). The combined organic phase was washed with sat. brine (10 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (100-200 mesh silica gel, DCM:MeOH=40:1 to 25:1) to afford **302-7** (350.00 mg, 85.5%) as a light yellow solid.

[0988] To a solution of **302-7** (350.0 mg, 546.13 μmol) in MeOH (10 mL) was added NH_4F (405 mg, 10.9 mmol) in one portion at 25 °C. The mixture was heated to 65 °C and stirred for 2 h. TLC (EA:MeOH=8:1) showed that the reaction was completed. The mixture was cooled to 25 °C and concentrated under reduced pressure at 40 °C. The residue was purified by silica gel chromatography (100-200 mesh silica gel, EA:MeOH=20:1 to 10:1) to afford **302** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6), δ = 7.59 (d, *J*=7.28 Hz, 1 H), 7.49 (br. s., 2 H), 7.25 (br. s., 1 H), 6.29 (br. s., 1 H), 6.01 (br. s., 1 H), 5.82 (d, *J*=7.53 Hz, 1 H), 4.60 (br. s., 1 H), 3.88 (br. s., 2 H); ^{19}F NMR (376 MHz, DMSO-d_6) d ppm -116.61 (br. s., 1 F) -115.98 (br. s., 1 F).

EXAMPLE 176
COMPOUND 303



[0989] To a solution of K_2CO_3 (967.5 mg, 7.0 mmol) and TsN_3 (552.2 mg, 2.80 mmol) in MeCN (10 mL) was added 1-dimethoxyphosphorylpropan-2-one (465.1mg, 2.80

mmol) in one portion at 25 °C under N_2. The mixture was stirred at 25 °C for 2 H. A solution of **302-5** (900.0 mg, 1.40 mmol, 1.00 eq.) in MeOH (10 mL) was added in one portion at 25 °C under N_2. The mixture was stirred at 25 °C for 12 h. TLC (PE:EA=2:1) showed that the reaction was completed. The mixture was poured into water (10 mL) and extracted with EA (2 x 50 mL). The combined organic phase was washed with saturated brine (10 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (100-200 mesh silica gel, PE:EA=5:1 to 2:1) to afford **303-1** (800 mg, 98.2%) as an off-white solid.

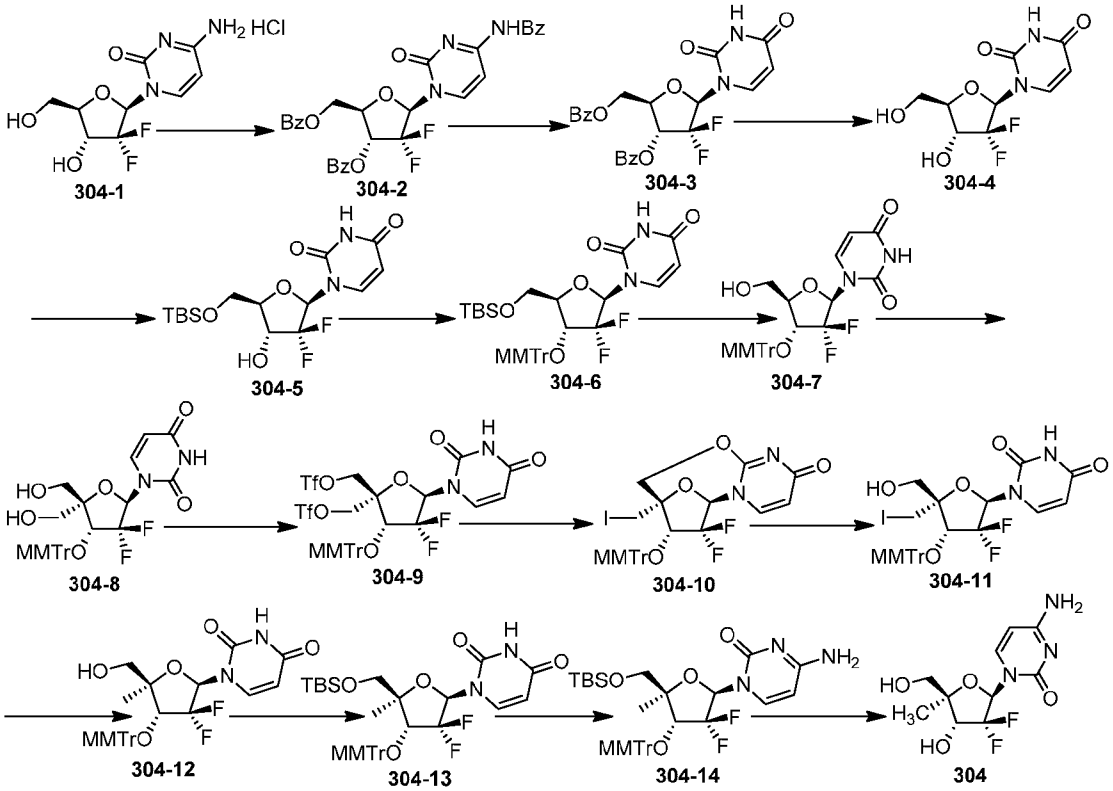
[0990] To a solution of **303-1** (500 mg, 780.20 μmol), DMAP (190.6 mg, 1.56 mmol) and TEA (236.9 mg, 2.34 mmol) in MeCN (5 mL), was added 2,4,6-triisopropylbenzene-1-sulfonyl chloride (472.8 mg, 1.56 mmol) in one portion at 0 °C under N_2. The mixture was stirred at 0 °C for 30 mins, then warmed to 25 °C and stirred for 2 h. TLC (PE:EA=2:1) showed that the reaction was completed. The reaction was quenched by water (5 mL) and extracted with EA (2 x 10 mL). The combined organic phase was washed with aq. HCl (1 mL, 0.5 M), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue (650.0 mg, 91.83%) was obtained as a light yellow gum, which was used in next step without further purification.

[0991] To a solution of the residue from the previous step (650 mg, 716.4 μmol) in MeCN (5 mL) was added $NH_3 \cdot H_2O$ (5 mL) in one portion at 25 °C, and the mixture was stirred at 25 °C for 16 h. TLC (DCM:MeOH=20:1) showed that the reaction was completed. The mixture was extracted with EA (2 x 20 mL). The combined organic phase was washed with brine (10 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (100-200 mesh silica gel, PE:EA=1:1) to afford **303-2** (350 mg, 76.35%) as an off-white solid.

[0992] A mixture of **303-2** (350.0 mg, 546.98 μmol) and NH_4F (405.0 mg, 10.93 mmol) in MeOH (5 mL) was heated to 65 °C and stirred for 2 h. LCMS and TLC (EA:MeOH=10:1) showed that the reaction was completed. The mixture was cooled to 25 °C and filtered, and the filtrate was concentrated in vacuum. The residue was purified by silica gel chromatography (300-400 mesh silica gel, EA:MeOH=20:1 to 10:1) to afford **303** (102 mg, 64.93%) as a white solid. ^{1}H-NMR (400 MHz, METHANOL-d_4), δ = 7.73 (d,

J=7.28 Hz, 1 H), 6.31 - 6.42 (m, 1 H), 5.95 (d, *J*=7.53 Hz, 1 H), 4.47 (t, *J*=13.55 Hz, 1 H), 3.92 (d, *J*=12.55 Hz, 1 H), 3.73 - 3.80 (m, 1 H) 3.25 (s, 1 H); ^{19}F NMR (376 MHz, METHANOL-d_4), δ = -115.52 - -112.60 (m, 1 F).

EXAMPLE 177
COMPOUND 304



[0993] To a solution of **304-1** (20 g, 66.8 mmol) in anhydrous pyridine (180 mL) was added BzCl (30.9 g, 220.3 mmol) at 0 °C under N_2. The mixture was stirred at 25 °C for 12 h. The mixture was diluted with EA and washed with sat. aq. $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4 and filtered, and the filtrate was concentrated to dryness. The residue was purified by silica gel column chromatography (30% EA in PE) to give **304-2** (34.6 g, 90%) as a white solid.

[0994] **304-2** (33 g, 57.3 mmol) was dissolved in 90% CH_3COOH (360 mL) and heated to 115 °C. The mixture was stirred at 115 °C for 12 h. The solvent was removed, and the residue was diluted with EA. The mixture was washed with sat. aq. $NaHCO_3$ and brine. The organic layer was dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated to give **304-3** (26 g, crude) as a white solid.

[0995] **304-3** (21 g, 44.5 mmol) was dissolved in a solution (400 mL, 10M) of NH_3 in MeOH. The mixture was stirred at 25 °C for 12 h. The mixture was concentrated to give a residue, which was purified by silica gel column chromatography (5% MeOH in DCM) to give **304-4** (9.4 g, 80.4%) as a white solid. ^{1}H-NMR (CD_3OD, 400MHz) δ = 7.90-7.80 (m, 1H), 6.18-6.09 (m, 1H), 5.71 (d, J=8.2 Hz, 1H), 4.26 (dt, J=8.2, 12.0 Hz, 1H), 3.98-3.84 (m, 2H), 3.76 (dd, J =2.8, 12.5 Hz, 1H), 3.33 (s, 1H).

[0996] To a solution of **304-4** (9 g, 34.1 mmol) in anhydrous pyridine (60 mL) was added TBSCl (7.7 g, 51.1 mmol) at 25 °C under N_2. The solution was stirred at 50 °C for 12 h. The mixture was concentrated to dryness under reduced pressure. The residue was dissolved in EA. The mixture was washed with sat. aq. $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$ and concentrated to dryness under reduced pressure. The residue was purified on a silica gel column (20% EA in PE) to give **304-5** (11 g, 85.5%) as a white solid.

[0997] To a solution of **304-5** (10.2 g, 27 mmol) in CH_2Cl_2 (100 mL) was added $AgNO_3$ (9.2 g, 53.9 mmol), collidine (13.1 g, 107.8 mmol) and MMTrCl (10 g, 32.3 mmol) at 25 °C under N_2. The solution was stirred at 25 °C for 12 h. The reaction was quenched with MeOH, and the mixture was filtrated on celite. The filtrate was diluted with CH_2Cl_2 and H_2O. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2. The combine organic layer was washed with brine, dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated to dryness under reduced pressure. The residue was purified by silica gel chromatography (25% EA in PE) to give **304-6** (15 g, 85.6%) as a white solid.

[0998] **304-6** (10.5 g, 16.1 mmol) was dissolved in a solution of TBAF in THF (1M, 60 mL) at 25 °C. The mixture was stirred at 25 °C for 4 h. The mixture was extracted with EA, and the combined layer was washed with water and brine. The organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated to give the crude product, which was purified by silica gel column chromatography (30% EA in PE) to give **304-7** (8.1 g, 93.6%) as a white foam.

[0999] To a solution of **304-7** (17.0 g, 31.7 mmol) in CH_3CN (150 mL) was added IBX (9.7 g, 34.9 mmol) at 25 °C. The mixture was heated to 100 °C, and the mixture was stirred at 100 °C for 1 h. The mixture was cooled to 25 °C. The mixture was filtered,

and the filter cake was washed with MeCN. The filtrate was concentrated under reduce pressure to give a residue (16 g, crude) as a yellow solid. The residue (16 g, crude) was dissolved in 1,4-dioxane (150 mL), and the solution was treated with 37% aq. formaldehyde (18.5 g, 227.5 mmol) and aq. NaOH (2 M, 30 mL) at 25 °C. The mixture was stirred at 25 °C for 12 h. EtOH (30 mL) and $NaBH_4$ (10 g, 265.7 mmol) were added at 0 °C. After stirring for 1 h at 25 °C, the reaction was quenched with sat. aq. NH_4Cl at 0 °C. The mixture was diluted with EA. The organic phase was separated, and the aqueous phase was extracted with EA. The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. The organic layer was concentrated in vacuum to give a residue, which was purified by silica gel chromatography (2% MeOH in DCM) to afford **304-8** (8.1 g, 53.1%) as a white solid. ^{1}H-NMR (400MHz, DMSO-d_6) δ =11.52 (s, 1H), 7.57 (d, *J* = 8.2 Hz, 1H), 7.46 - 7.22 (m, 13H), 6.90 (d, *J* =8.8 Hz, 2H), 6.30 (t, *J* =8.0 Hz, 1H), 5.61 (d, *J* =8.2 Hz, 1H), 5.06 (t, *J* =5.5 Hz, 1H), 4.92 - 4.86 (m, 1H), 4.61 - 4.51 (m, 1H), 3.83 (dd, *J* =5.1, 12.1 Hz, 1H), 3.74 (s, 3H).

[1000] To an ice cooled solution of **304-8** (2.5 g, 4.4 mmol) in anhydrous CH_2Cl_2 (35 mL) was added pyridine (3.5 g, 44.1 mmol) and Tf_2O (3.7 g, 13.2 mmol) dropwise. The mixture was stirred at 0 °C for 40 mins. The reaction was quenched with ice water and stirred for 10 mins. The mixture was extracted with CH_2Cl_2. The organic layer was washed with brine and dried over $MgSO_4$. The organic layer was concentrated to give a residue, which was purified on the silica gel column (15% EA in PE) to give **304-9** (2.6 g, 71%) as a yellow foam.

[1001] To a stirred solution of **304-9** (1.8 g, 2.2 mmol) in anhydrous DMF (25 mL) was added NaH (107 mg, 2.7 mmol) at 0 °C under N_2. The solution was stirred at 25 °C for 1 h. TLC (PE: EA=1:1) showed the reaction was complete. To the solution was added NaI (3.1 g, 20.6 mmol) at 25 °C. The mixture was stirred at 25 °C for 3 h. TLC (PE: EA=1:1) showed the reaction was complete. The mixture was diluted with water and extracted with EA. The organic layer was dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated at low pressure to give **304-10** (1.4 g, crude) as a yellow solid.

[1002] **304-10** (1.4 g, crude) was dissolved in 1,4-dioxane (25 mL), and the mixture was treated with aq. NaOH (2 M, 2.7 mL) at 0 °C. The solution was stirred for 4 h at 25 °C. The reaction was quenched with sat. aq. NH_4Cl and extracted with EA. The organic

layer was washed with brine. The organic layer was dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated to give the crude product, which was purified by silica gel column chromatography (40% EA in PE) to give **304-11** (1.4 g, 94.9%).

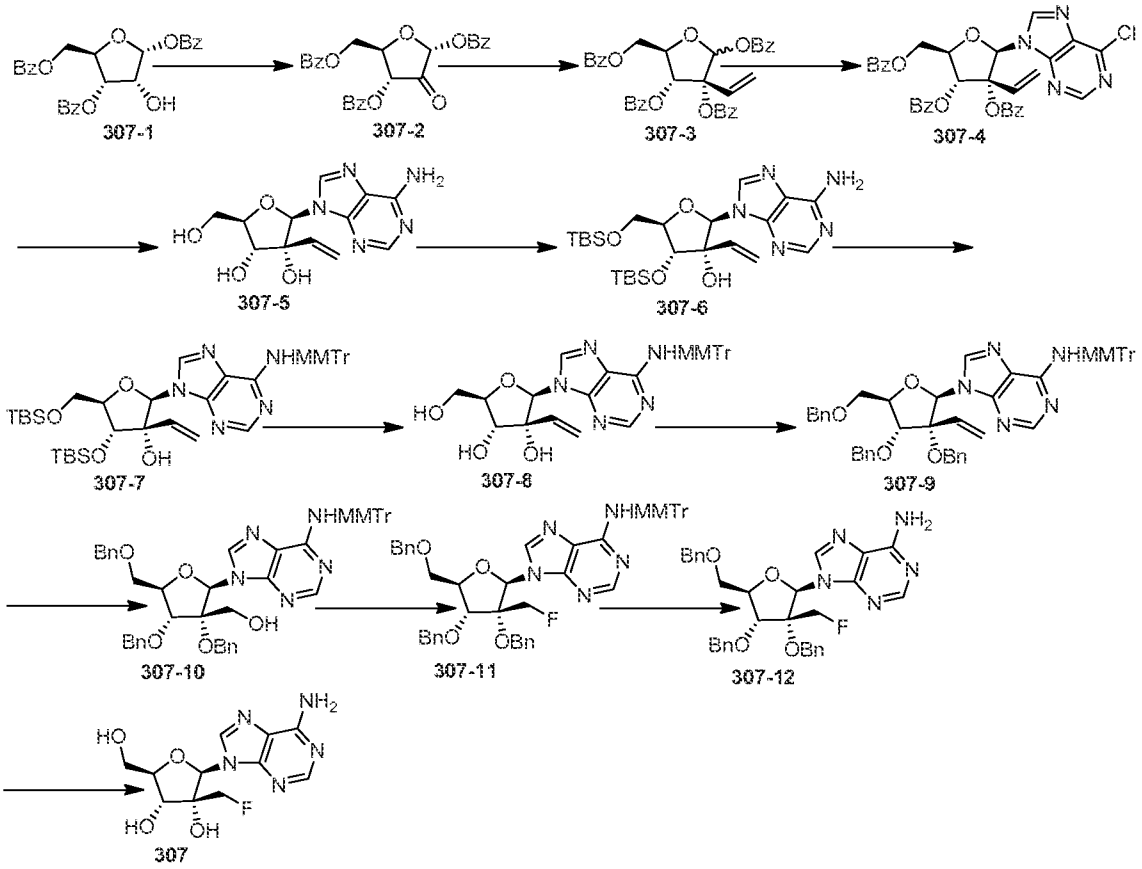
[1003] To a solution of **304-11**(1.45 g, 2.1 mmol) in EtOH (10 mL) was added Et_3N (434 mg, 4.3 mmol) and Pd/C (101 mg, 88.7 μmol). The mixture was stirred under H_2 (15 psi) for 12 h at 25 °C. The suspension was filtered, and the filtrate was concentrated at low pressure. The residue was purified on silica gel column (1% MeOH in DCM) to give **304-12** (1.2 g, 97.6%) as a yellow solid.

[1004] To a solution of **304-12** (930 mg, 1.7 mmol) in anhydrous DMF (10 mL) was added imidazole (287 mg, 4.2 mmol) and TBSCl (636 mg, 4.2 mmol) at 25 °C under N_2. The solution was stirred at 25 °C for 5 h. The mixture was concentrated to dryness under reduced pressure, and the residue was dissolved in EA. The mixture was washed with sat. aq. NH_4Cl and brine. The organic layer was dried over $MgSO_4$ and filtered. The filtrate was concentrated to dryness under reduced pressure. The residue was purified on silica gel column (15% EA in PE) to give **304-13** (968 mg, 86.2%) as a white solid.

[1005] To a stirred solution of **304-13** (568 mg, 854.4 μmol) in anhydrous CH_3CN (8 mL) was added DMAP (209 mg, 1.7 mmol), TPSCl (504 mg, 1.7 mmol) and TEA (173 mg, 1.7 mmol) at 25 °C. The mixture was stirred at 25 °C for 12 h. $NH_3•H_2O$ (10 mL) was added, and the mixture was stirred for 3 h. The mixture was extracted with EA and washed with sat. aq. NH_4Cl and brine. The organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated to give a residue, which was purified on a silica gel column (3% MeOH in DCM) to give **304-14** (480 mg, 84.6%) as a yellow foam. ^{1}H-NMR (400MHz, $CDCl_3$) δ = 7.65 - 7.40 (m, 13H), 6.97 (d, *J* =8.8 Hz, 2H), 6.44 (dd, *J* =6.4, 9.5 Hz, 1H), 5.71 (d, *J* =7.3 Hz, 1H), 4.76 (dd, *J* =9.0, 14.4 Hz, 1H), 4.29 (q, *J* =7.1 Hz, 1H), 3.92 - 3.92 (m, 1H), 3.95 (s, 3H), 3.60 (d, *J* =11.2 Hz, 1H), 3.44 (d, *J* =11.0 Hz, 1H), 1.66 - 1.55 (m, 3H), 0.95 (s, 9H), 0.08 (s, 3H), 0.00 (s, 3H).

[1006] **304-14** (501mg, 753.2 μmol) was dissolved in 80% HCOOH (20 mL), and the mixture was stirred at 25 °C for 4 h. The solvent was removed at low pressure, and the residue was purified on a silica gel column (6% MeOH in DCM) to give **304** (151mg, 71.8%) as a white solid. ESI-MS:m/z 278.11 $[M+H]^+$,555.18 $[2M+H]^+$.

EXAMPLE 178
COMPOUND 307



[1007] To a solution of **307-1** (120 g, 0.26 mol) in anhydrous MeCN (2 L) was added IBX (109 g, 0.39 mol). The mixture was heated to reflux and stirred for 18 h. The mixture was cooled to 0 °C and filtered. The filtrate was concentrated under vacuum to give **307-2** (142 g) as a brown oil, which was used without purification for the next step.

[1008] To a solution of **307-2** (142 g) in anhydrous THF (1.5 L) was added vinylmagnesium bromide (830 mL, 0.83 mol, 1 N) dropwise at -78 °C, and the mixture was stirred at -78 °C for 2 h. The reaction was quenched by sat. aq. NH_4Cl (2 L) at 0 °C. THF was removed under vacuum, and the residue was diluted with EtOAc. The solution was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give a light brown oil.

[1009] To the light brown oil in anhydrous DCM (2.5 L) was added DMAP (63.5 g, 0.52 mol), Et_3N (79 g, 0.78 mol) and BzCl (110 g, 0.78 mol) at 0 °C, and the mixture stirred overnight at RT. The mixture was diluted with DCM (2 L) and washed with sat. aq.

$NaHCO_3$ (3 L) and brine (1.5 L). The organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated to dryness under reduced pressure. The residue was purified by silica gel column (PE:EA=20:1~10:1) to give **307-3** (112.7 g, 72.3%) as a yellow oil.

[1010] A stirring mixture of uracil (36.25 g, 323.7 mmol) and N,O-bis(trimethylsilyl) acetamide (131.69 g, 647.4 mmol) in anhydrous MeCN (180 mL) was heated to reflux for 2 h, then cooled to RT. A solution of **307-3** (95.9 g, 161.85 mmol) in anhydrous MeCN (500 mL) was added, followed by treatment with $SnCl_4$ (168.66 g, 647.4 mmol) dropwise at 0 °C. The mixture was heated to reflux and stirred for 2 h. The reaction was quenched with sat. aq. $NaHCO_3$ (3 L), and extracted with EtOAc (3 x 1 L). The organic phase was washed with brine (500 mL), dried over anhydrous Na_2SO_4, filtered and evaporated to dryness under reduced pressure. The residue was purified by a silica gel column (PE:EA=20:1~10:1) to give **307-4** (33 g, 35%) as a light yellow oil.

[1011] **307-4** (33 g, 56.65 mmol) was dissolved in NH_3:MeOH (800 mL, 7 N), and the mixture was stirred at RT overnight. The solvent was removed under reduced pressure, and the residue was purified by a column (1% MeOH in DCM) to give **307-5** (12.6 g, 82.4%) as a light yellow foam.

[1012] To a solution of **307-5** (2.57 g, 8.76 mmol) in DMF (20 mL) was added $AgNO_3$ (8.93 g, 52.56 mmol) and imidazole (3.58 g, 52.56 mmol), then TBSCl (5.28 g, 35.04 mmol) was added in one portion at 0 °C under N_2. The mixture was stirred at 25°C for 12 h. TLC showed that the reaction was completed. The residue was poured into ice:water (w:w = 1:1) (30 mL). The aqueous phase was extracted with EA (3 x 100 mL). The combined organic phase was washed with sat. brine (3 x 20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, PE:EA=3:1 to 2:1) to afford **307-6** (3.68 g, 80.51%) as a yellow solid.

[1013] To a solution of **307-6** (3.48 g, 6.67 mmol) and $AgNO_3$ (3.40 g, 20.01 mmol) in pyridine (30 mL) was added (chloro(4-methoxyphenyl)methylene)dibenzene (4.12 g, 13.34 mmol) in one portion at 25 °C under N_2. The mixture was stirred at 25 °C for16 h. TLC showed that the reaction was completed. The mixture was diluted with EA and filtered. The filtrate was washed with brine and separated. The organic layer was concentrated to dryness. The residue was purified by silica gel chromatography (column height: 250 mm,

diameter: 100 mm, 100-200 mesh silica gel, PE:EA=10:1 to 5:1) to afford **307-7** (4.40 g, 83.07%) as a yellow foam.

[1014] To a solution of **307-7** (4.30 g, 5.41 mmol) in MeOH (100 mL) was added NH_4F (801.55 mg, 21.64 mmol) in one portion at 25 °C. The mixture was heated to 68 °C and stirred for 4 h. LCMS trace showed that the reaction was completed. The mixture was cooled to 25 °C and concentrated under reduced pressure. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, DCM:MeOH:$NH_3 \cdot H_2O$=30:1:0.05 to 10:1:0.05) to afford **307-8** (3.00 g, 98.04%) as a white solid.

[1015] To a solution of **307-8** (3.00 g, 5.30 mmol) in DMF (30 mL) was added NaH (848 mg, 21.20 mmol) in one portion at 0 °C under N_2. The mixture was stirred at 0 °C for 30 mins. BnBr (3.63 g, 21.20 mmol) was added at 0 °C, and the mixture was stirred for 16 h at 25 °C. TLC showed that the reaction was completed. The mixture was poured into ice-water (w:w = 1:1) (30 mL). The aqueous phase was extracted with EA (3 x 50 mL). The combined organic phase was washed with sat. brine (3 x 20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 200-300 mesh silica gel, PE:EA=20:1 to 10:1) to afford **307-9** (670 mg, 15.1%).

[1016] Ozone was bubbled into a solution of **307-9** (500 mg, 598.10 μmol) in DCM (8 mL) and MeOH (8mL) at -78 °C for 20 mins. After excess O_3 was purged by O_2, $NaBH_4$ (113.13 mg, 2.99 mmol) was added at 0 °C. The mixture was stirred at 25 °C for 20 mins. TLC showed that the starting material was consumed. The mixture was concentrated to give the crude product, which was purified by silica gel chromatography (PE:EA=5:1) to give **307-10** (167.00 mg, 33.24%) as a yellow solid.

[1017] To a solution of **307-10** (216.70 mg, 257.99 μmol) and DMAP (63.04 mg, 515.98 μmol) in DCM (2 mL) was added MsCl (44.33 mg, 386.98 μmol) in one portion at 0 °C under N_2. The mixture was stirred at 0 °C for 1 h and then warmed to 25 °C and stirred for 1 h. LCMS showed that the reaction was completed. The residue was poured into ice-water (w:w = 1:1) (10 mL), and extracted with EA (3 x 20 mL). The combined organic phase was washed with sat. brine (3 x 10 mL), dried with anhydrous Na_2SO_4, filtered and

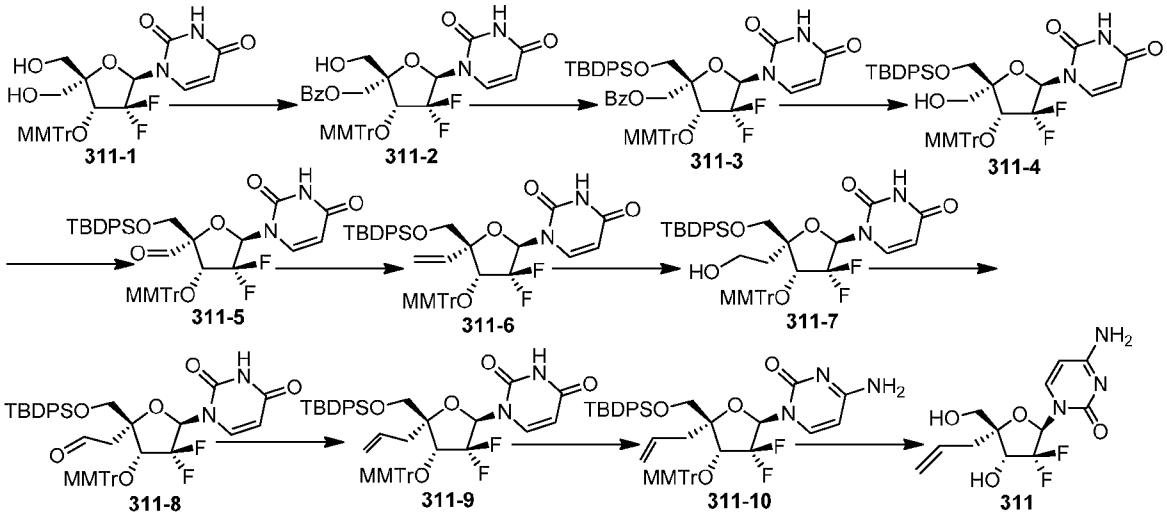
concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, PE:EA=10:1 to 5:1) to afford a mesylate intermediate (167.00 mg, 70.51%) as a yellow foam.

[1018] The mesylated intermediate (167 mg) was dissolved in TBAF:THF (10 mL, 1N) and the mixture was heated to reflux for 12 h. The mixture was slowly cooled to 25 °C, and quenched with sat. NH_4Cl solution. The solution was extracted with EA. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography (EA:PE=5:1-2:1) to give **307-11** (80 mg, 43.8%).

[1019] **307-11** (80.00 mg, 0.087 mmol) was dissolved in 80% AcOH (5 mL) solution, and stirred at 45°C for 1.0 h. The reaction was quenched with sat. Na_2HCO_3 solution and extracted with EA (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography to give **307-12** (38 mg, 60%) as a white foam solid. ESI-MS:m/z 570.4 $[M+H]^+$.

[1020] To a solution of **307-12** (113.8 mg, 0.2 mmol) in DCM (0.5 mL) was added BCl_3/DCM (1.0 N) (1 mL) at -78 °C, and the mixture was stirred at -78 °C for 30 mins. The reaction was quenched with MeOH and concentrated to dryness at low pressure. The residue was purified by prep-HPLC with $NH_3 \cdot H_2O$ buffer to give **307** (26 mg, 44%) as a white solid.

EXAMPLE 179
COMPOUND 311



[1021] To a mixture of **311-1** (2.00 g, 3.5 mmol) in pyridine (10 mL) and DCM (10 mL) was added BzCl (496 mg, 3.5 mmol) dropwise at 0 °C under N_2. The mixture was stirred at 0 °C for 30 mins, and then stirred at 25 °C for 6.5 h. The reaction was quenched with sat. aq. $NaHCO_3$ (80 mL). The mixture was extracted with EA (2 x 100 mL). The organic phase was washed with brine (80 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (30% EA in PE) to afford **311-2** (1.28 g, 54 %) as a white solid.

[1022] To a mixture of **311-2** (680 mg, 1.0 mmol) in DMF (5 mL) was added imidazole (412 mg, 6.1 mmol), $AgNO_3$ (514 mg, 3.0 mmol) and TBDPSCl (832 mg, 3.0 mmol) at 25 °C under N_2. The mixture was stirred at 25 °C for 12 h. The reaction was quenched with sat. aq. $NaHCO_3$ (30 mL), and then extracted with EA (2 x 30 mL). The combined organic phase was washed with brine (2 x 20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (25% EA in PE) to afford **311-3** (750 mg, 82 %) as a white solid.

[1023] **311-3** (660 mg, 0.7 mmol) was dissolved in NH_3:MeOH (15 mL). The mixture was stirred at 25 °C for 36 h in sealed tube, and then concentrated under reduced pressure. The residue was purified by silica gel chromatography (30% EA in PE) to afford **311-4** (430 mg, 73 %) as a white solid. ^{1}H-NMR ($CDCl_3$, 400MHz) δ = 9.05 (s, 1H), 7.81-

7.10 (m, 21H), 6.81 (d, J=9.2 Hz, 2H), 6.42 (m, 1H), 6.20 (m, 1H), 4.13-4.07 (m, 2H), 3.78-3.60 (m, 5H), 2.55 (s, 1H), 0.90-0.74 (m, 9H).

[1024] To a mixture of **311-4** (280 mg, 0.3 mmol) in DCM (3.5 mL) was added Dess-Martin (295 mg, 0.7 mmol) in one portion at 0 °C under N_2. The mixture was stirred at 25 °C for 3.5 h. The reaction was quenched with sat. aq. $NaHCO_3$ and sat. aq. $Na_2S_2O_3$. (v:v=1:1, 30 mL). The mixture was extracted with EA (2 x 20 mL). The combined organic phase was washed with brine (30 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated in vacuum to afford **311-5** (260 mg, crude) as a yellow solid, which was used in the next step without further purification.

[1025] To a stirred solution of Methyl-triphenyl-phosphonium bromide (359 mg, 1.0 mmol) in anhydrous THF (1 mL) was added KOBu-t (1 mL, 1.0 mmol, 1 M in THF) dropwise at 0 °C. The mixture was stirred at 25 °C for 1 h. A solution of **311-5** (260 mg, 0.3 mmol) in anhydrous THF (1 mL) was added at 0 °C. The mixture was stirred at 25 °C for 16 h. The reaction was quenched with sat. aq. NH_4Cl (20 mL) and extracted with EA (30 mL). The organic layer was washed with brine (20 mL), dried over $MgSO_4$, filtered and evaporated to give a light white solid, which was purified by column chromatography (10% EA in PE) to give **311-6** (131 mg, 50 %) as a yellow solid. ^{1}H-NMR ($CDCl_3$, 400MHz) δ = 8.40 (s, 1H), 7.55-7.21 (m, 21H), 7.10 (dd, *J*=1.8, 8.2 Hz, 1H), 6.84 (d, *J*=8.8 Hz, 2H), 6.37 (dd, *J*=11.0, 17.4 Hz, 1H), 6.09 (dd, *J*=7.2, 8.9 Hz, 1H), 5.59-5.43 (m, 2H), 5.10-4.92 (m, 2H), 3.85-3.78 (s, 3H), 3.78-3.73 (m, 1H), 3.56 (d, *J*=11.5 Hz, 1H), 0.99 - 0.77 (s, 9H).

[1026] To a solution of **311-6** (1.50 g, 1.9 mmol) in THF (5 mL) was added 9-BBN (0.5 M, 22.5 mL) at 27 °C under N_2. The mixture was heated to 70 °C by microwave and stirred for 0.5 h. Sat. aq. $NaHCO_3$ (15 mL) and H_2O_2 (7.5 mL) were added at 0 °C. The mixture was stirred vigorously at 27 °C for 1.5 h. The reaction was quenched with sat. aq. $Na_2S_2O_3$ (60 mL). The mixture was extracted with EA (2 x 50 mL). The organic layer was washed with brine (80 mL), dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by silica gel chromatography (30% EA in PE) to afford **311-7** (930 mg, 61 %) as a white solid.

[1027] To a solution of **311-7** (1.24 g, 1.5 mmol) in DCM (15 mL) was added Dess-Martin (1.28 g, 3.0 mmol) in one portion at 0 °C under N_2. The mixture was stirred at 27 °C for 2 h. The reaction was quenched with sat. aq. $NaHCO_3$ and sat. aq.

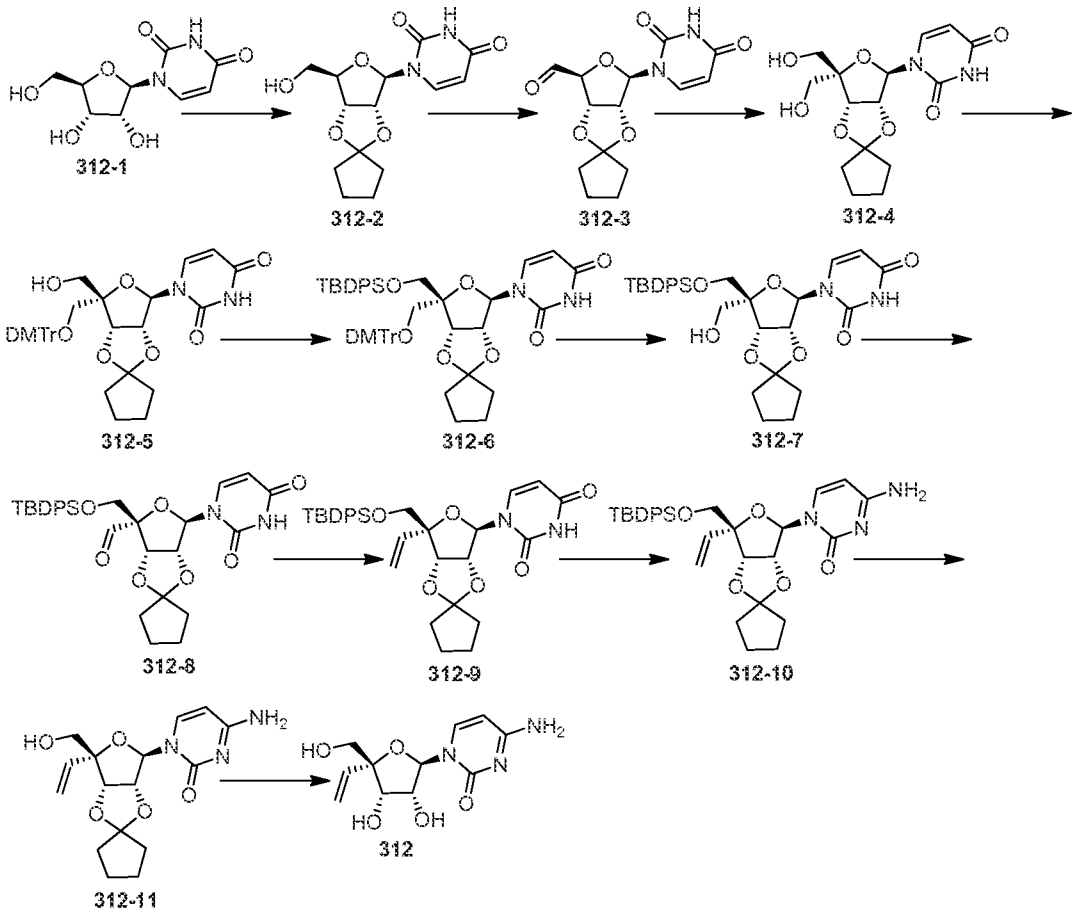
$Na_2S_2O_3$ (v:v=1:1, 60 mL). The mixture was extracted with EA (2 x 50 mL). The combined organic phase was washed with brine (80 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated in vacuum to afford **311-8** (1.21 g, crude) as a yellow solid.

[1028] To a stirred solution of Methyl-triphenyl-phosphonium bromide (1.64 g, 4.6 mmol) in anhydrous THF (5.5 mL) was added t-BuOK (1 M, 4.4 mL) at 0 °C dropwise. The mixture was stirred at 27 °C for 1 h. A solution of **311-8** (1.21 g crude, 1.5 mmol) in THF (5 mL) was added at 0 °C. The mixture was stirred at 27 °C for 12 h. The reaction was quenched with sat. aq. NH_4Cl (70 mL), extracted with EA (2 x 50 mL). The organic layer was washed with brine (80 mL), dried over $MgSO_4$, filtered and evaporated to dryness to give a light yellow solid, which was purified by column chromatography (15 EA in PE) to give **311-9** (970 mg, 80 %) as a white solid.

[1029] To a solution of **311-9** (970 mg, 1.2 mmol) in CH_3CN (10 mL) was added TPSCl (877 mg, 3.0 mmol), DMAP (363 mg, 3.0 mmol) and TEA (301 mg, 3.0 mmol) at 27 °C under N_2. The mixture was stirred at 27 °C for 1.5 h. $NH_3•H_2O$ (5 mL) was added, and the reaction mixture was stirred at 27 °C for 2 h. The reaction was quenched with sat. aq. NH_4Cl (60 mL), and then extracted with EA (2 x 40 mL). The combined organic phase was washed with brine (60 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (2% MeOH in DCM) to afford **311-10** (810 mg, 83 %) as a white solid.

[1030] To a solution of **311-10** (500 mg, 0.6 mmol) in MeOH (15 mL) was added NH_4F (455 mg, 12.3 mmol) at 27 °C under N_2. The mixture was stirred at 70 °C for 12 h. The mixture was then cooled to RT and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (5% MeOH in DCM) to afford crude **311** (120 mg, crude). The crude was purified by prep-HPLC (neutral condition) to give **311** (86 mg, 45 %) as a white solid. MS:m/z =304 $[M+H]^+$.

EXAMPLE 180
COMPOUND 312



[1031] To a mixture of **312-1** (30 g, 122.85 mmol) and 1,1-dimethoxycyclopentane (86 g, 660.93 mmol) in DCE (200 mL) was added $TsOH \cdot H_2O$ (2.34 g, 12.29 mmol) in one portion at RT. The mixture was heated to 70 °C and stirred for 14 h. The mixture was cooled to RT and concentrated under reduced pressure. The residue was purified by column chromatography (1-10% MeOH in DCM) to give **312-2** (25 g, 65.6%) as a white solid.

[1032] To a solution of **312-2** (20 g, 64.45 mmol) in anhydrous CH_3CN (200 mL) was added IBX (19.85 g, 70.9 mmol) at RT. The mixture was refluxed for 18 h. and then cooled to 0 °C. The precipitate was filtered-off, and the filtrate was concentrated to give crude **312-3** (20 g, 100%) as a yellow solid.

[1033] To a solution of **312-3** (20 g, 64.87 mmol) in 1,4-dioxane (200 mL) were added 37% HCHO (20 mL) and 2.0 M NaOH aq. solution (40 mL) at 0 °C. The mixture was

stirred at RT overnight and then neutralized with AcOH to pH = 7. The solution was treated with $NaBH_4$ (4.91 g, 129.74 mmol) at 20 °C. The mixture was stirred at RT for 1 h. The reaction was quenched with sat. aq. NH_4Cl. The mixture was extracted with EA (3 x 100 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by silica gel column chromatography (1-3% MeOH in DCM) to give **312-4** (9 g, 40.8 %) as a white solid.

[1034] To a solution of **312-4** (15.50 g, 45.54 mmol) in anhydrous pyridine (80.00 mL) was added DMTrCl (18.52 g, 54.65 mmol) in anhydrous DCM (20.00 mL) dropwise at -30 °C. The mixture was stirred at 25 °C overnight. The solution was treated with MeOH and concentrated at low pressure. The residue was purified by column chromatography (50% EA in PE) to give **312-5** (10.59 g, yield 32.56%) as a yellow solid.

[1035] To a solution of **312-5** (2.90 g, 4.51 mmol) in CH_2Cl_2 (20.00 mL) was added $AgNO_3$ (1.15 g, 6.77 mmol), imidazole (767.60 mg, 11.28 mmol) and TBDPSCl (1.86 g, 6.77 mmol). The mixture was stirred at 25 °C for 14 h. The precipitate was filtered off, and the filtrate was washed with water and dried over anhydrous Na_2SO_4. The solvent was removed at low pressure. The crude residue was purified by silica gel chromatography (PE:EA=5:1) to afford **312-6** (2.79 g, 63.19%) as a yellow solid.

[1036] **312-6** (2.79 g, 3.17 mmol) was dissolved in 80% HOAc aq. solution (50 mL). The mixture was stirred at 25 °C for 4 h. The solution was treated with MeOH and concentrated at low pressure. The residue was purified by silica gel column chromatography (PE:EA=4:1) to give **312-7** (0.9 g, 44%) as a yellow solid.

[1037] To a solution of **312-7** (1.50 g, 2.59 mmol) in anhydrous DCM (20 mL) was added Dess-Martin periodinane (1.32 g, 3.11 mmol) at 0 °C under N_2. The mixture was stirred at RT for 4 h. The reaction was quenched by the addition of $Na_2S_2O_3$/sodium bicarbonate saturated aqueous solution. The mixture was stirred for 15 mins. The organic layer was separated, washed with diluted brine and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (20% EtOAc in PE) to give **312-8** (1.12 g, yield 67.48%) as a white solid.

[1038] To a solution of PPh_3CH_3Br (1.49 g, 4.16 mmol) in anhydrous THF (15 mL) was added n-BuLi (0.41 mL, 3.47 mmol) at -70 °C under N_2. The mixture was stirred at 0 °C for 0.5 hour. A solution of **312-8** (800.00 mg, 1.39 mmol) in anhydrous THF (3 mL)

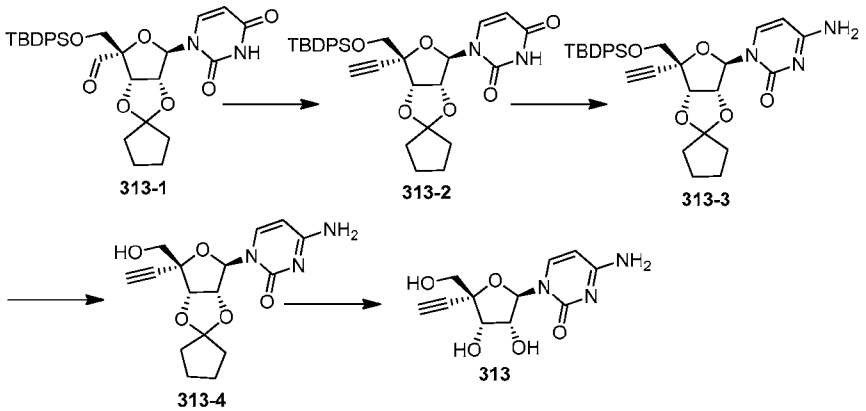
was added dropwise at 0 °C under N_2. The mixture was stirred 25 °C for 2 h. The reaction was quenched with sat. NH_4Cl solution and extracted with EtOAc (3 x 60 mL). The organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated at low pressure. The crude product was purified by silica gel column chromatography (20% EtOAc in PE) to give **312-9** (504 mg, 56.78%) as a white solid.

[1039] To a solution of **312-9** (500 mg, 869.96 μmol) in anhydrous CH_3CN (10.00 mL) was added 2,4,6-triisopropylbenzenesulfonyl chloride (526.95 mg, 1.74 mmol), DMAP (212.57 mg, 1.74 mmol) and Et_3N (1.83 g, 18.04 mmol) at RT. The mixture was stirred at 25 °C for 1 h. $NH_3•H_2O$ (5.00 mL) was added, and the mixture was stirred for 1 h. The mixture was extracted with EA and washed with brine, 0.1 M HCl and sat. aq. $NaHCO_3$. The organic phase was dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by silica gel chromatography (EtOAc) to give **312-10** (307 mg, 55.36%) as a yellow solid.

[1040] To a solution of **312-10** (307 mg, 535.08 μmol) in MeOH (4 mL) was added NH_4F (814 mg, 20 mmol) at 25 °C under N_2. The mixture was stirred at 65 °C for 16 h. The solution was filtered and evaporated to dryness. The residue was purified by silica gel column (EA:MeOH=50:1) to give **312-11** (130 mg, 65.2%) as a white solid.

[1041] **312-11** (108 mg, 322.05 μmol) was treated with HCl:MeOH (6mL, 1N) at 25 °C under N_2. The mixture was stirred at 25 °C for 1 h. The aqueous phase was extracted with EA (3 x 10 mL). The residual aqueous solution was lyophilized to afford **312** (80.00 mg yield 87.65%) as a yellow solid. ESI-MS:m/z 270 $[M+H]^+$.

EXAMPLE 181
COMPOUND 313



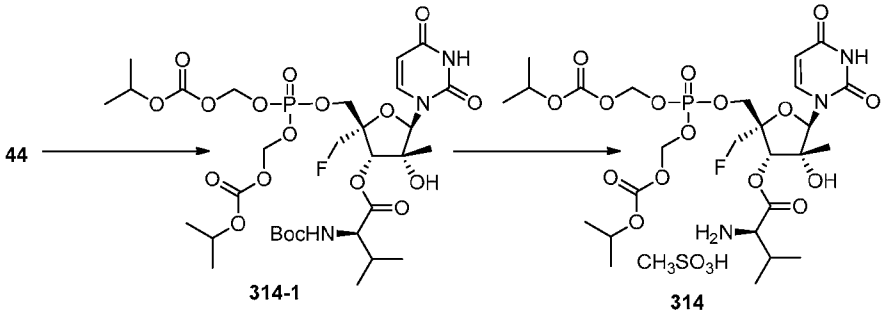
[1042] To a mixture of K_2CO_3 (2.40 g, 17.35 mmol) and TsN_3 (1.37 g, 6.94 mmol) in CH_3CN (20 mL) was added 1-dimethoxyphosphorylpropan-2-one (1.15 g, 6.94 mmol) in one portion at 25 °C under N_2. The mixture was stirred at 25 °C for 2 h. A solution of **313-1** (2.00 g, 3.47 mmol) in MeOH (20 mL) was added in one portion at 25 °C under N_2, and the mixture was stirred at 25 °C for 16 h. The mixture was poured into water and extracted with EtOAc (2 x 30 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (TFA buffer) to give **313-2** (1.50 g, 75%) as a white solid.

[1043] To a solution of **313-2** (600 mg, 1.05 mmol) in dry CH_3CN (60 mL) was added TEA (212 mg, 2.10 mmol), DMAP (256 mg, 2.10 mmol) and 2,4,6-triisopropylbenzenesulfonyl chloride (635 mg, 2.10 mmol) at 0°C. The mixture was stirred at 25°C for 1 h. $NH_3 \cdot H_2O$(10 mL) was added at 25 °C. The mixture was stirred at 25°C for 1 h. The reaction was quenched with sat. NH_4Cl solution, and extracted with EtOAc (2 x 10 mL). The organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by silica gel chromatography (PE:EA =3:1 to 0:1), and prep-TLC (DCM:MeOH = 10:1) to give **313-3** (380 mg, 63%) as a white solid.

[1044] A solution of **313-3** (300 mg, 0.52 mmol) and NH_4F (194 mg, 5.25 mmol) in dry MeOH (5 mL) was stirred at 65 °C for 12 h. The mixture was concentrated at low pressure. The residue was purified by silica gel column chromatography (DCM:MeOH = 50:1 to 10:1) to afford **313-4** (140 mg, 80%) as a white solid.

[1045] A solution of **313-4** (100 mg, 0.30 mmol) in 1 N HCl:MeOH (5 mL) was stirred at 25 °C for 2 h. The mixture was concentrated under 40 °C. The residue was washed with CH_3CN (5 x 2 mL) to give **313** (61 mg, 67%) as a white solid. ESI-LCMS:m/z 268.1 $[M+H]^+$.

EXAMPLE 182
COMPOUND 314



[1046] To a solution of *N*-(*tert*-Butoxycarbonyl)-L-valine (8.06 g, 37.1 mmol, 1.5 eq.) in anhydrous ACN (60 mL) was added carbonyldiimidazole (6.01 g, 37.1 mmol, 1.5 eq.). The reaction was stirred for 1 h at RT and then cooled to 0°C. A solution of **44** (14.9 g, 24.7 mmol, 1 eq.) in anhydrous ACN (50 mL) was added to the cooled solution of N-BOC-valine imidazolide, and the resulting solution was treated with Et_3N (6.4 mL, 49.4 mmol, 2 eq.). The reaction was allowed to proceed for 1 h at 0°C. The reaction was quenched 1M citric acid to pH 2-3 (150 mL), stirred for 15 mins and diluted with IPAC (200 mL). The organic layer was separated, washed sequentially with water and half sat. sodium bicarbonate and water (2x). The organic layer was concentrated under reduced pressure, and the residue was dissolved in MTBE (125 mL) under gentle heating (40 °C) to afford precipitation of the target compound. The solid was aged overnight at 0 °C and isolated by filtration to obtain **314-1** (18.0 g, 90.9%) as a white solid. MS:m/z = 802 $[M+1]^+$.

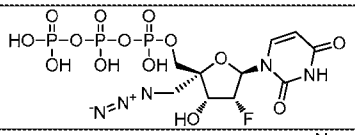
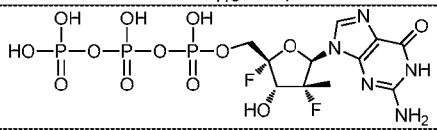
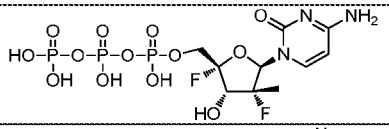
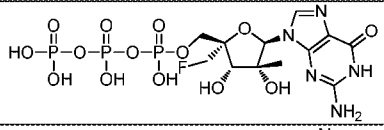
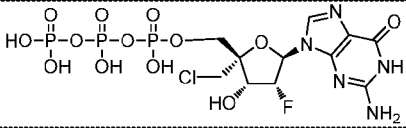
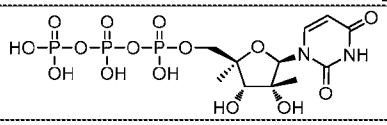
[1047] A stirred slurry of **314-1** (2.4 g, 3 mmol) in IPAC (45 mL) was treated with methanesulfonic acid (0.39 mL, 6 mmol, 2 eq.), and the mixture was stirred at 40 °C. After 1 h, methanesulfonic acid (2 x 0.2 mL, 6 mmol, 2 eq.) was added, and the temperature was increased to 50 °C. After 5 h, the mixture was cooled to RT. The solid was filtered off, washed with IPAC and dried under vacuum to yield **314** (2.0 g, 83%). MS:m/z = 702.2 $[M+1]^+$.

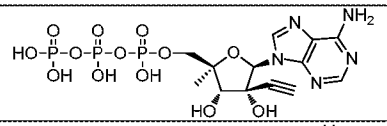
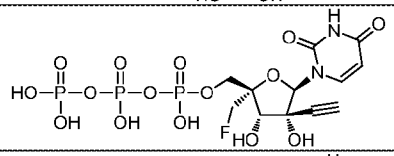
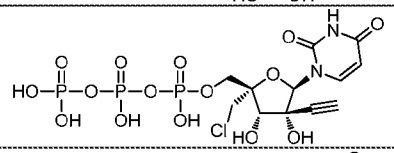
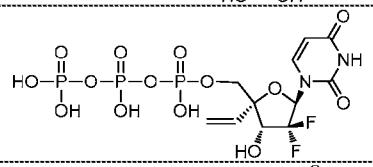
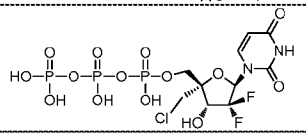
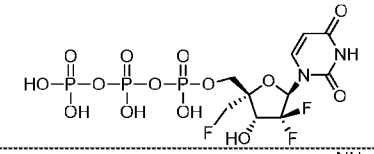
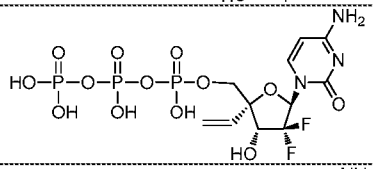
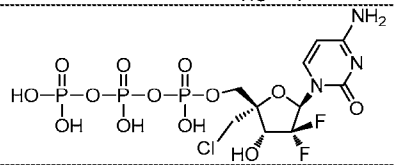
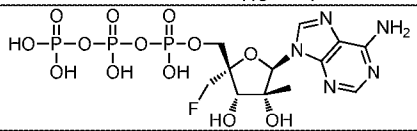
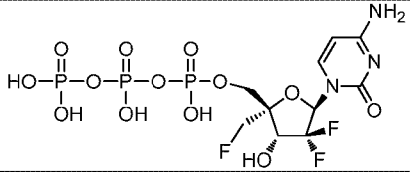
EXAMPLE 183
TRIPHOSPHATES

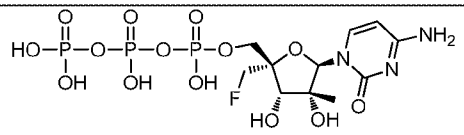
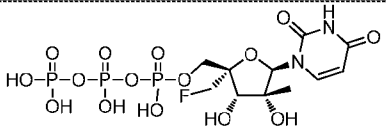
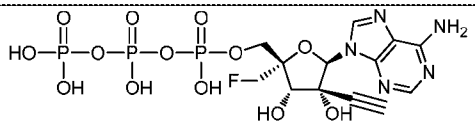
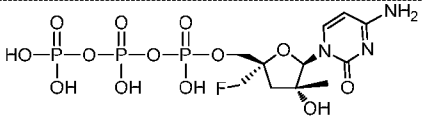
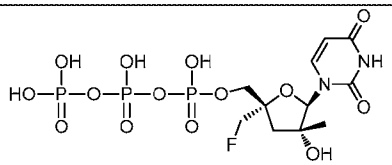
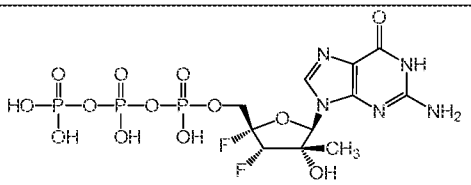
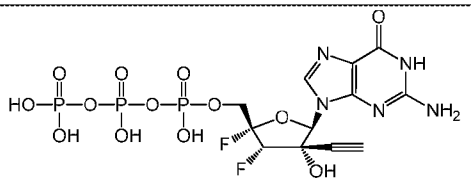
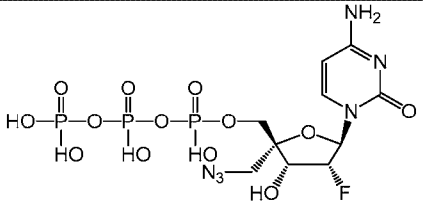
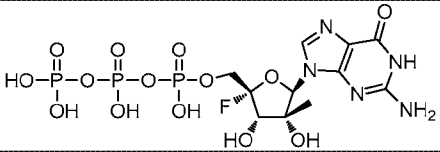
[1048] Dry nucleoside (0.05 mmol) was dissolved in the mixture of $PO(OMe)_3$ (0.7 mL) and pyridine (0.3 mL). The mixture was evaporated in vacuum for 15 mins at bath temperature (42^0C), than cooled down to RT. N-Methylimidazole (0.009 mL, 0.11 mmol)

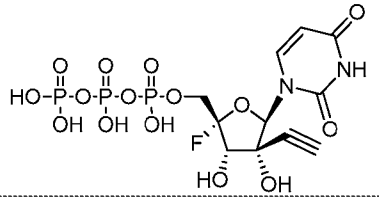
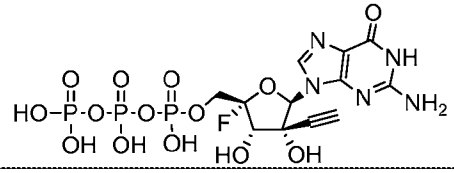
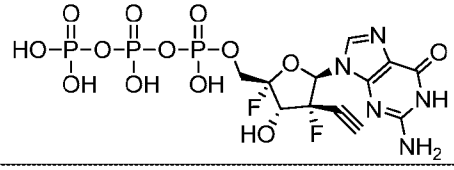
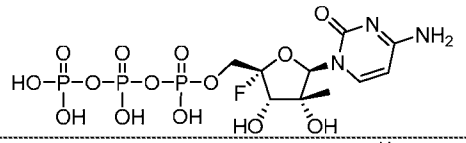
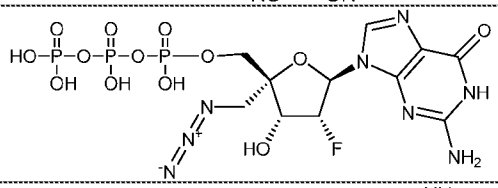
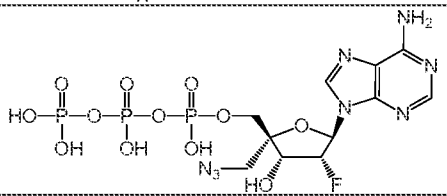
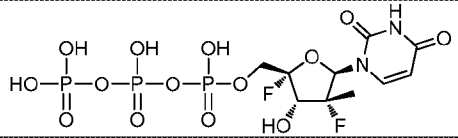
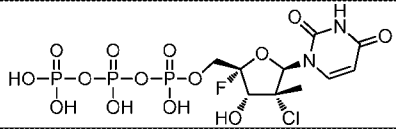
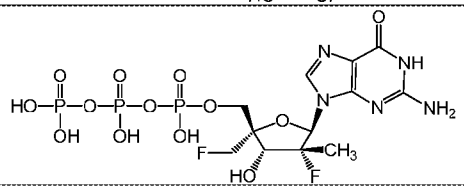
was added followed by $POCl_3$ (9 μL, 0.11 mmol), and the mixture was kept at RT for 20-40 mins. The reaction was controlled by LCMS and monitored by the appearance of corresponding nucleoside 5'-monophosphate. After completion, tetrabutylammonium salt of pyrophosphate (150 mg) was added, followed by DMF (0.5 mL) to get a homogeneous solution. After 1.5 h at ambient temperature, the reaction was diluted with water (10 mL) 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 50 mM TRIS-buffer (pH 7.5). Triphosphate was eluted at 75-80%B. Corresponding fractions were concentrated. Desalting was achieved by RP HPLC on Synergy 4 micron Hydro-RP column (Phenominex). A linear gradient of methanol from 0 to 30% in 50 mM 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. Examples of compound made according to this procedure are provided in Table 2.

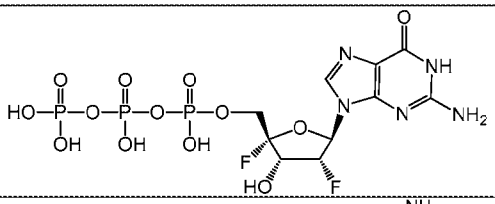
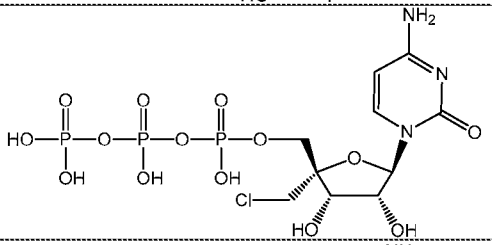
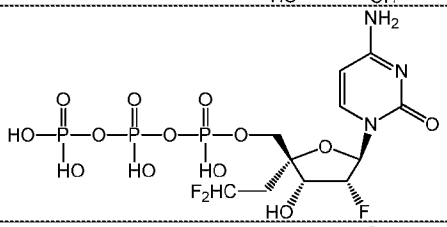
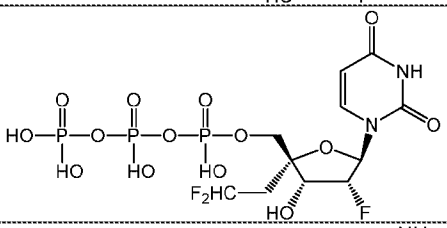
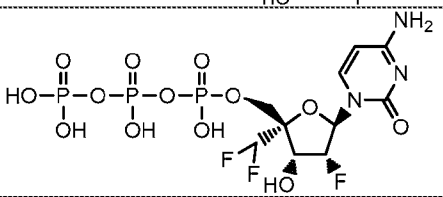
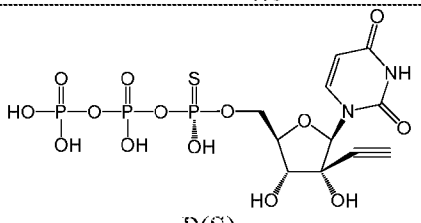
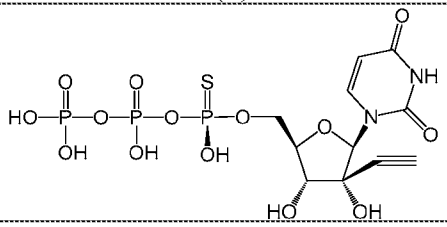
Table 2.

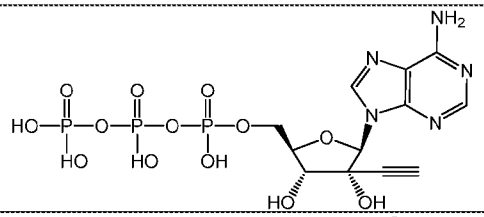
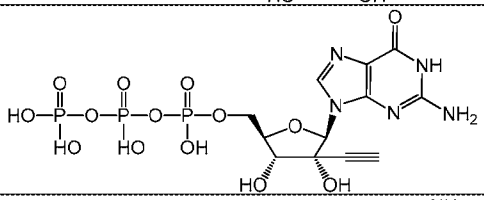
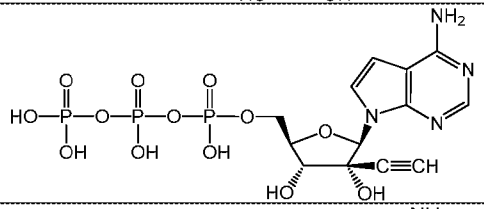
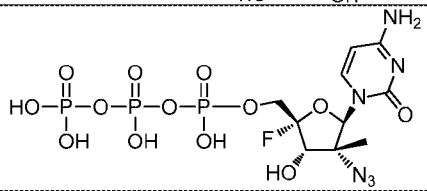
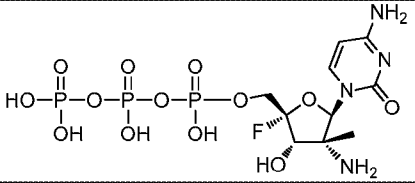
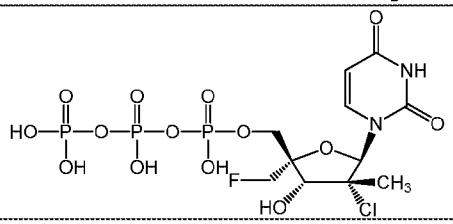
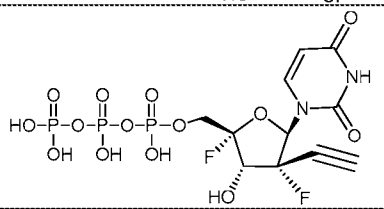
			31P NMR		
	Structure	**MS [M-1]**	**P(α)**	**P(β)**	**P(γ)**
3		540.4	-10.90 -11.03(d)	-23.38(t)	-11.91 -12.03(d)
19		556.2	-10.92 -11.03(d)	-23.18(t)	-11.86 -11.98(d)
29		516.1	-7.49 -7.61(d)	-22.42(t)	-12.17 -12.30(d)
34		568.2	-5.60 -5.72(d)	-21.13 (bs)	-10.93 -11.05(d)
37		539.3	-10.02 -10.36(d)	-20.72(t)	-11.27 -11.40(d)
58		510.8	-10.87 -10.99(d)	-23.35(t)	-11.76 -11.89(d)

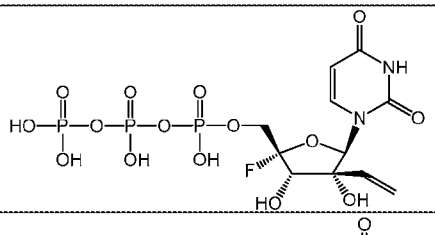
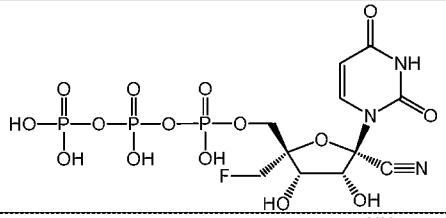
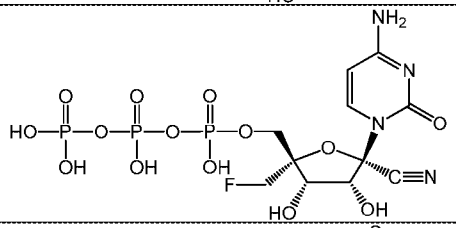
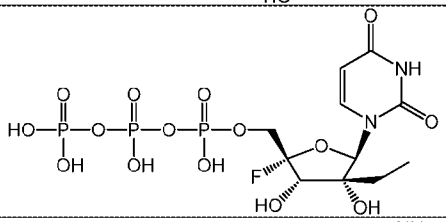
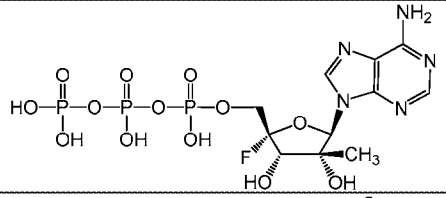
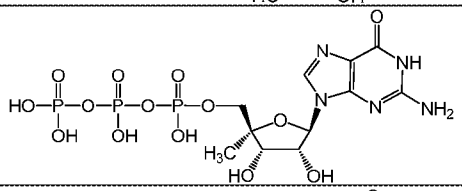
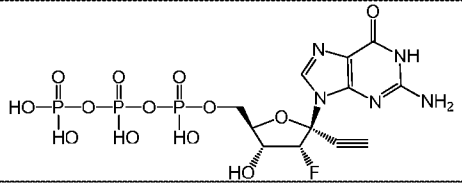
			31P NMR		
	Structure	MS [M-1]	P(α)	P(β)	P(γ)
59		543.8	-10.53 -10.66(d)	-23.23(t)	-11.63 -11.75(d)
61		538.9	-10.61 -10.73(d)	-23.20(t)	-11.74 -11.86(d)
62		538.9	-10.92 -11.04 (d)	-23.33(t)	-11.81 -11.93(d)
72		529.3	-5.25 -5.37 (d)	-20.53(t)	-11.42 -11.53(d)
73		551.4	-10.90 -11.02 (d)	-23.27(t)	-11.87 -11.99(d)
74		535.0	-5.41 -5.53 (d)	-23.27(t)	-11.39 -11.51(d)
79		529.2	-10.86 -10.98(d)	-23.23(t)	-11.85 -11.9(d)
80		535.0	-10.86 -10.98(d)	-23.21(t)	-11.81 -11.94(d)
81		529.2	-10.64 -10.73(d)	-20.78(t)	-11.42 -11.56(d)
82		534.3	-10.75 -10.89(d)	-23.19(t)	-11.46 -11.58(d)

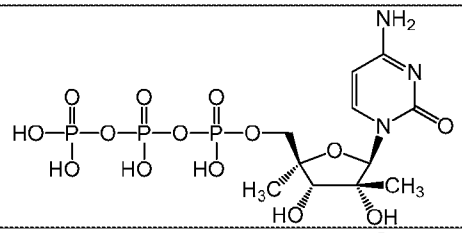
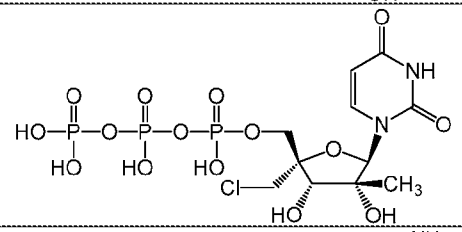
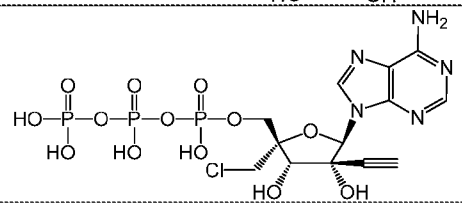
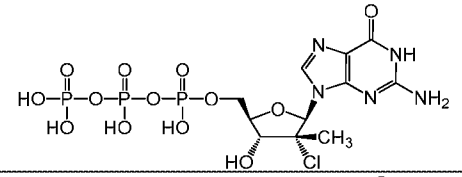
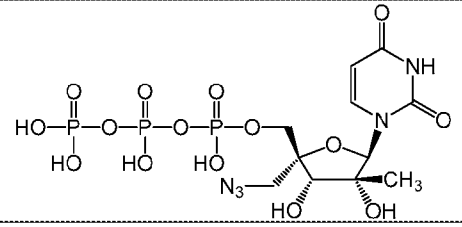
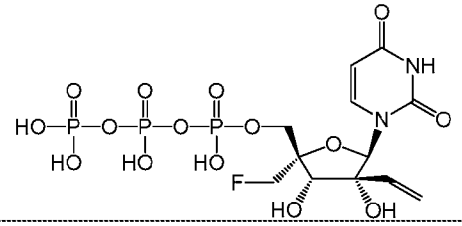
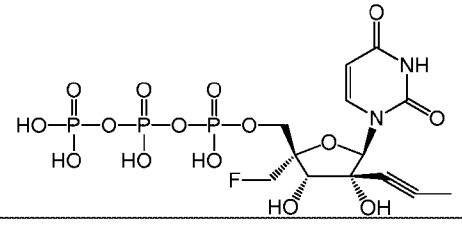
			31P NMR		
	Structure	MS [M-1]	P(α)	P(β)	P(γ)
91		528.0	-10.13 (bs)	-23.16(t)	-11.64 -11.81(d)
92		528.9	-11.05 -11.08(d)	-23.46(t)	-11.79 -11.91(d)
93		561.7	-10.73 -10.85(d)	-23.23(t)	-11.63 -11.75(d)
94		534.0	-10.92 -10.64(d)	-23.38(t)	-11.61 -11.73(d)
95		512.8	-10.98 -11.11(d)	-23.46(t)	-11.70 -11.8 (d)
101		556.2	-10.92 -10.07(d)	-23.34(t)	-11.70 -11.82(d)
103		566.0	-6.26 -6.39(d)	-22.45(t)	-11.66 -11.84 (d)
107		539.3	-5.36(d)	-20.72(t)	-11.40(d)
111		564.0	-10.94 -11.06(d)	-23.25(t)	-11.85 -11.97(d)

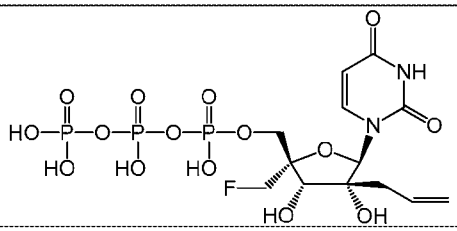
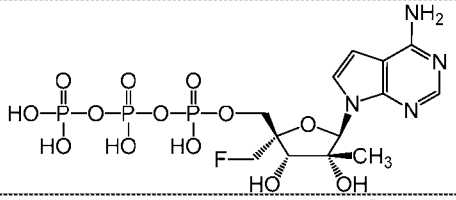
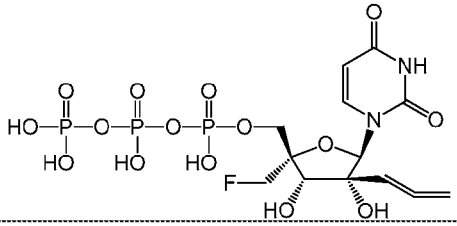
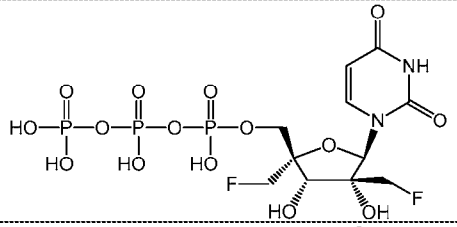
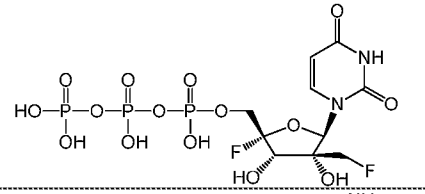
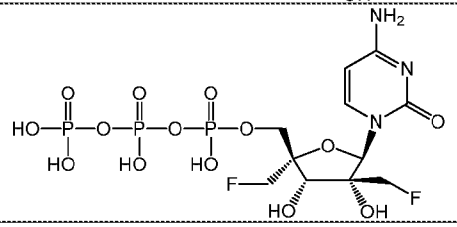
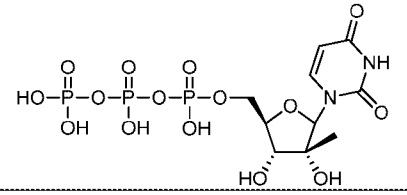
			31P NMR		
	Structure	MS [M-1]	P(α)	P(β)	P(γ)
114		546.9	-8.53(bs)	-22.61 (bs)	-12.17 -12.29(d)
115		564.4	-11.05(bs)	-23.25 (bs)	-11.96 -12.08(d)
123		566.0	-10.92 -11.04(d)	-23.18(t)	-11.93 -1(d)
124		513.8	-8.66(bs)	-22.80(t)	-12.17 -12.29(d)
132		579.4	-10.31 -10.44 (d)	-23.08(t)	-11.81 -11.92(d)
133		563.0	-10.79 -10.91(d)	-23.24(t)	-11.80 -11.92(d)
147		517.1	-13.60 -13.72(d)	-25.98(t)	-15.05 -15.17(d)
149		533.3	-10.89 -11.01(d)	-23.31(t)	-12.49 -1(d)
162		570.4	-9.25 -9.28(d)	-22.82(t)	-11.29 -11.42(d)

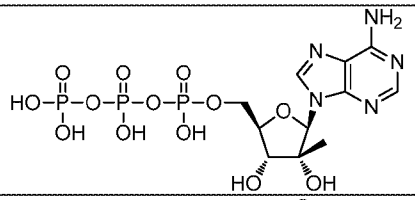
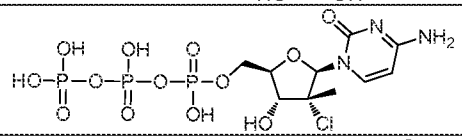
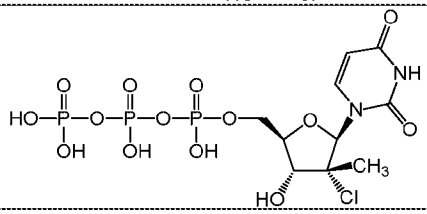
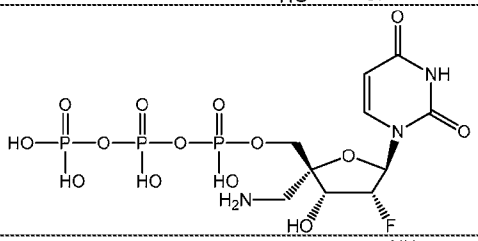
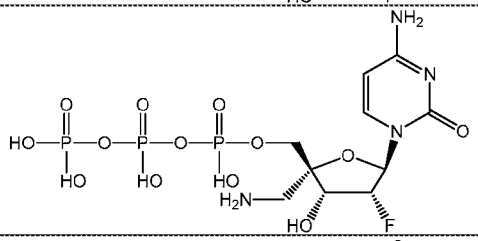
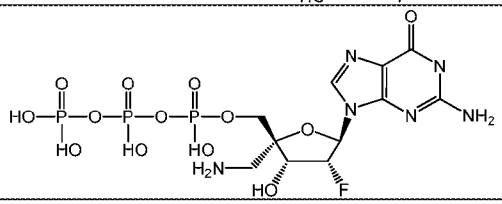
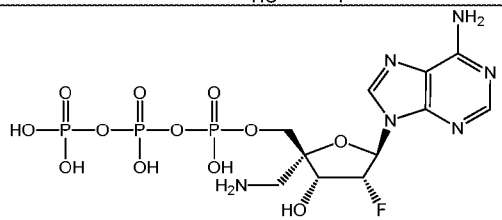
			31P NMR		
	Structure	MS [M-1]	P(α)	P(β)	P(γ)
163		542.2	-5.39 -5.40(d)	-20.71(t)	-11.52 -11.63(d)
164		529.8	-10.72 (bs)	-23.20(t)	-11.73 -11.84(d)
166		548.2	-10.93 -11.05(d)	-23.35(t)	-12.00 -12.13(d)
167		535.3	-12.86 -12.98(d)	-25.60(t)	-14.24 -14.36(d)
168		534.3	-7.78 (bs)	-22.30(t)	-11.70 (bs)
184	 P(S)	523.1	42.93	-23.28	-7.94
185		523.3	42.69	-22.93	-6.22

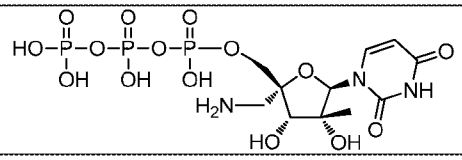
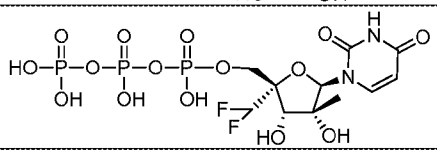
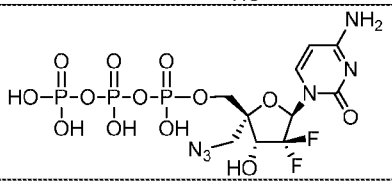
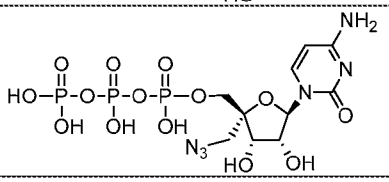
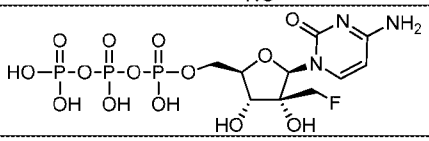
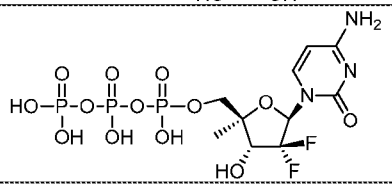
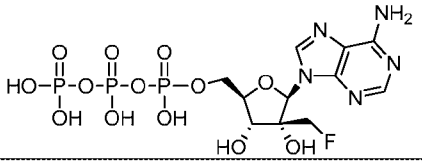
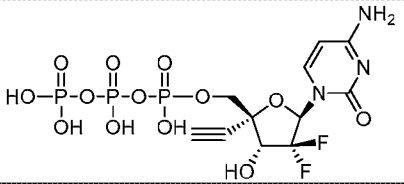
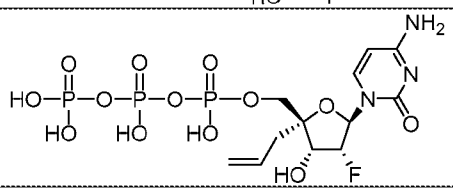
			31P NMR		
	Structure	MS [M-1]	P(α)	P(β)	P(γ)
	P(R)				
202		529.8	-6.53 (m)	-22.27 (m)	-11.27
203		545.9	-8.6 (br)	-22.80 (t)	-11.35 (d)
205		--	-4.97 (m)	-20.04 (m)	-10.72 (m)
208		539.5	-7.42 (bs)	-22.57(t)	-12.23 -12.34(d)
209		513.1	-6.36 -6.49(d)	-22.49(t)	-12.20 -12.33(d)
210		547.3	-10.95 -11.07(d)	-23.32(t)	-11.91 -12.03(d)
215		526.8	-10.96 -11.08(d)	-23.33(t)	-12.41 -12.53(d)

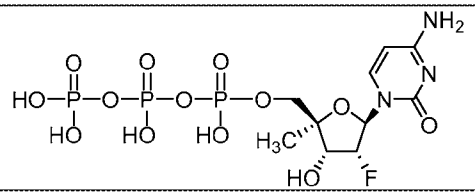
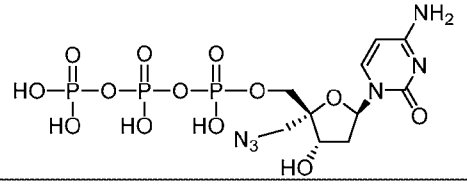
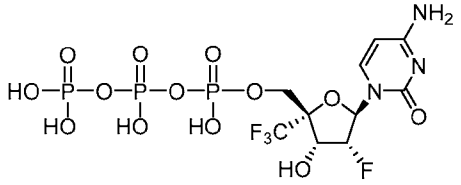
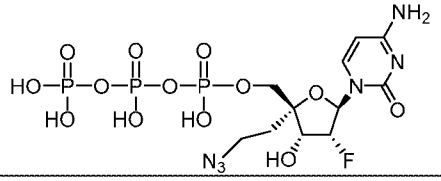
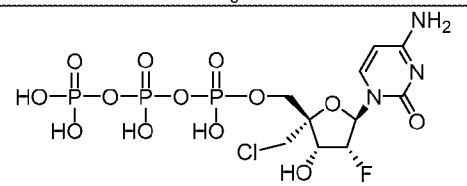
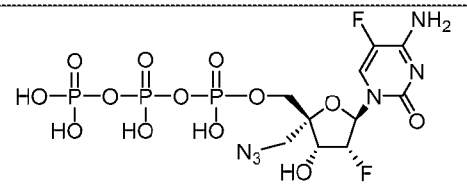
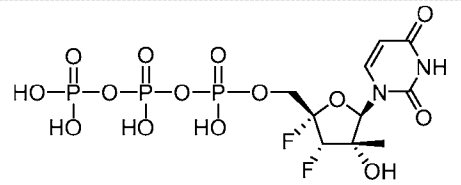
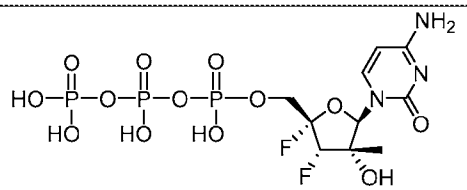
			31P NMR		
	Structure	MS [M-1]	P(α)	P(β)	P(γ)
236		527	-10.68 -10.80(d)	-23.35(t)	-12.30 -12.42(d)
237		540.5	-10.91 -11.03(d)	-23.38(t)	-12.24 -12.37(d)
238		539	-10.88 -10.99(d)	-23.41(t)	-12.15 -12.27(d)
239		529	-10.83 -10.95(d)	-23.27(t)	-12.25 -12.37(d)
240		538.4	-9.19 (bs)	-22.50(t)	-12.04 (bs)
241		536.0	-10.69 -10.81(d)	-23.27(t)	-11.72 -12.85(d)
242		548.2	-10.85 -10.97(d)	-23.27(t)	-11.62 -11.74(d)

			31P NMR		
	Structure	MS [M-1]	P(α)	P(β)	P(γ)
243		510.1	-10.55 -10.67(d)	-23.27(t)	-11.72 -12.85(d)
244		544.9	-10.97 -11.05(d)	-23.28(t)	-11.77 -12.89(d)
245		577.6	-10.42 -10.54(d)	-23.06(t)	-11.61 -12.73(d)
246		554.0	-10.85 -10.96(d)	-23.24(t)	-11.52 -11.64(d)
249		552.4	-6.17 (bs)	-21.02(t)	-10.09 (bs)
251		541.4	-10.87 -11.99(d)	-23.21(t)	-11.72 -11.84(d)
252		553.4	-10.91 -11.03(d)	-23.31(t)	-11.74 -11.87(d)

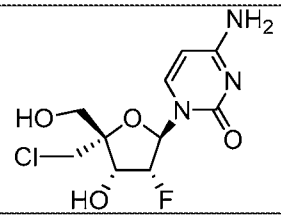
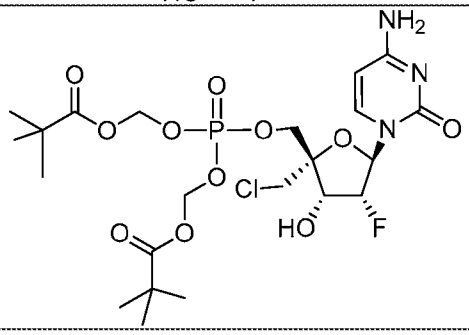
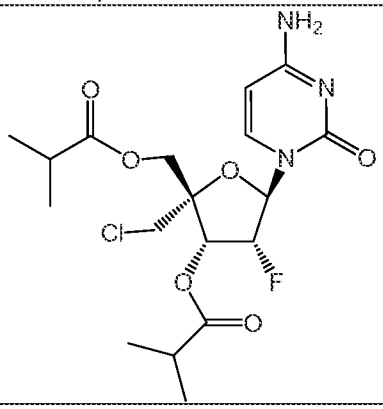
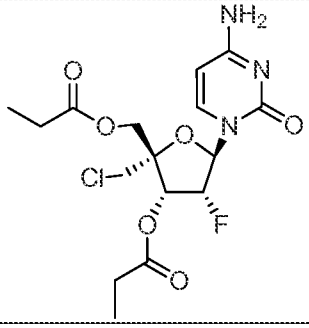
			31P NMR		
	Structure	MS [M-1]	P(α)	P(β)	P(γ)
253		555.6	-8.63 -8.76(d)	-24.61(t)	-13.90 -14.03(d)
254		551.4	-9.74 -9.86(d)	-22.89(t)	-11.46 -11.58(d)
255		553.4	-10.98 -11.10(d)	-23.38(t)	-11.86 -11.98(d)
256		547.2	-10.91 -11.03(d)	-23.33(t)	-11.79 -11.91(d)
257		533.4	-10.78 (br.s)	-23.22(t)	-12.24 -12.36(d)
258		546.3	-10.52(bs)	-23.05(t)	-11.64 -11.76(d)
261		496.9	-8.24 -8.36(d)	-21.66(t)	-11.14 -11.26(d)

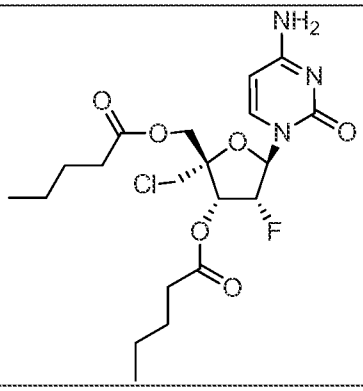
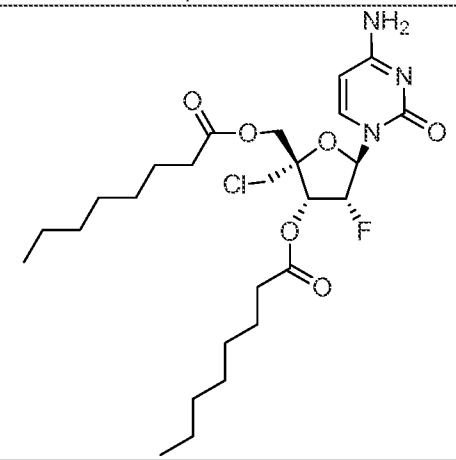
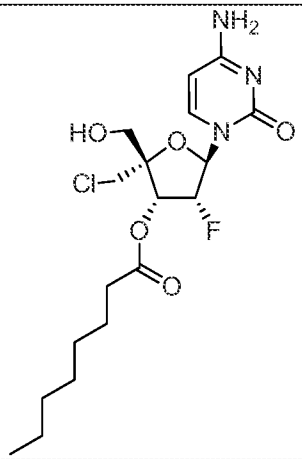
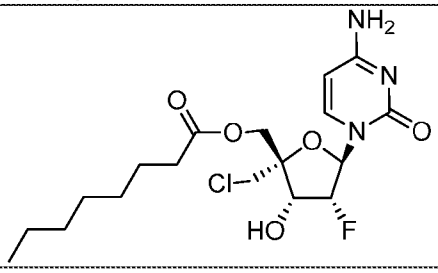
			31P NMR		
	Structure	MS [M-1]	P(α)	P(β)	P(γ)
262		520.4	-10.87 -10.97(d)	-23.34(t)	-11.86 -11.97(d)
263		513.8	-8.20 (bs)	-22.74(t)	-11.52 -11.64(d)
264		514.9	-9.95 -10.08(d)	-23.14(t)	-11.64 -11.76(d)
265		514.0	-6.68 -6.81(d)	-22.25(t)	-11.79 -11.92(d)
266		513	-5.95 -6.06(d)	-21.38(t)	-11.53 -11.65(d)
267		553	-9.94 -10.06(d)	-23.83(t)	-11.77 -11.89(d)
268		537.0	-6.48 -6.60(d)	-22.13(t)	-11.76 -11.88(d)

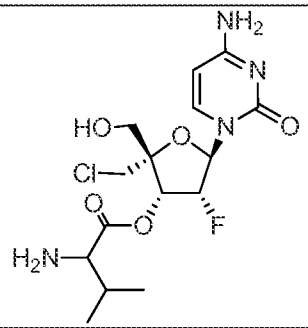
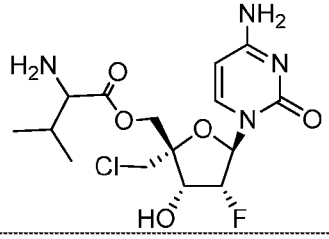
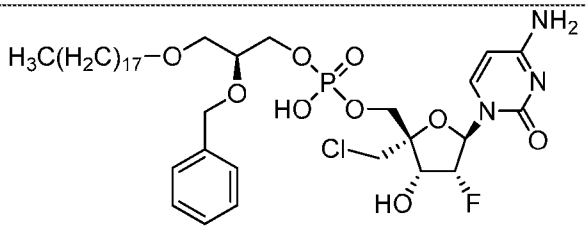
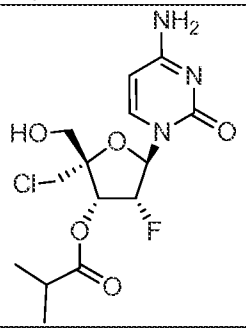
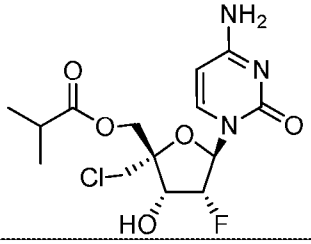
			31P NMR		
	Structure	MS [M-1]	P(α)	P(β)	P(γ)
270		526.2	-7.74 (bs)	-21.02(t)	-11.75 -11.87(d)
291		547.0	-10.78 -10.91(d)	-23.31(t)	-11.84 -11.96(d)
301		557.4	-10.96 -11.09(d)	-23.35(t)	-11.93 -12.05(d)
305		537.4	-10.90 -11.03(d)	-23.35(t)	-11.84 -11.96(d)
306		514.0	-10.27 -11.39(d)	-23.18(t)	-11.39 -11.51(d)
308		516.2	-9.52(br.s)	-22.74 (br.s)	-11.75 (br.s)
309		538.0	-10.15 (br.s)	-22.86(t)	-11.28 -11.40(d)
310		526.2	-9.97(br.s)	-22.81(t)	-12.12 -12.23(d)
367		524.6	-11.68(d)	-23.15(t)	-11.72(d)

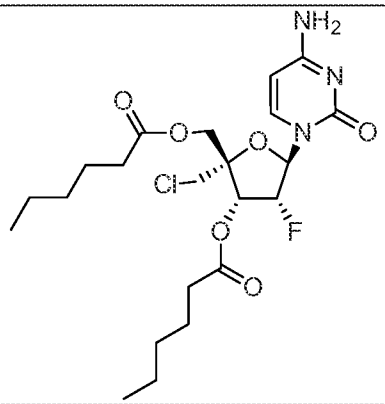
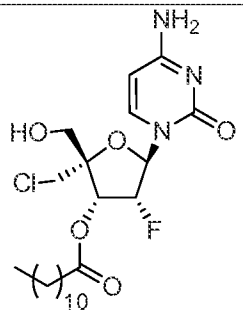
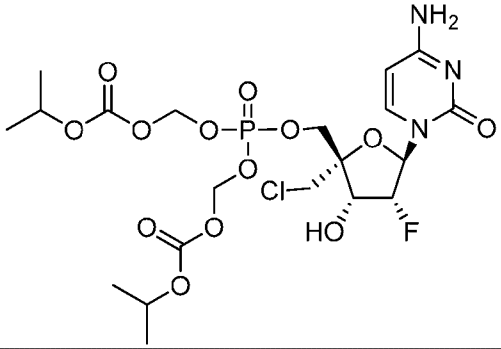
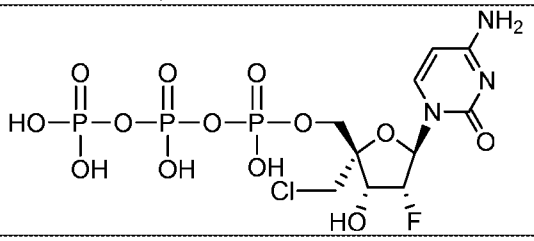
			31P NMR		
	Structure	MS [M-1]	P(α)	P(β)	P(γ)
368		498.2	-11.72(d)	-23.30(t)	-10.90(d)
369		521.3	-9.23 (d)	-22.57(t)	-8.06 (d)
370		552.3	-12.17(d)	-22.96(t)	-10.23(d)
371		553.0	-11.79(d)	-22.65(t)	-10.40(br.s)
372		553.0	-11.60(d)	-22.98(t)	-10.70(br.s)
373		557.3	-11.78(d)	-22.33(t)	-8.76(br.s)
374		517.2	-11.04(d)	-23.42(t)	-12.31(d)
375		516.6	-9.80(br.s)	-23.12(t)	-12.09(br.s)

EXAMPLE 184
COMPOUNDS 315-331

Compound No.	Structure	Analytical Data
315		294 $[M+H]^+$ 587 $[2M+H]^+$
316		646 [M+46-1].
317		434 [M+1]
318		404 [M-1]

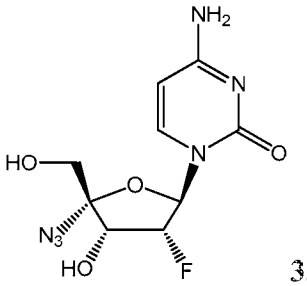
Compound No.	Structure	Analytical Data
319		462 [M+1]
320		544 [M-1]
321		418 [M-1]
322		418 [M-1]

Compound No.	Structure	Analytical Data
323		391 [M-1]
324		391 [M-1]
325		788.3 $[M-H]^+$
326		362.1 [M+1]
327		364 [M+1]

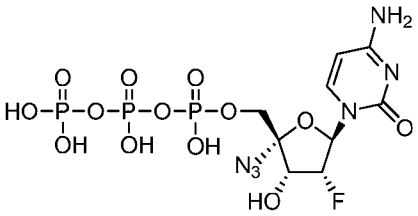
Compound No.	Structure	Analytical Data
328		488 [M-1]
329		474 [M-1]
330		606 [M+1]
331		532.1 [M-1]

[1049] Compounds **315-331** were prepared as described in U.S. Publication No. 2013/0165400, filed December 20, 2012, PCT Publication WO 2013/096679, filed December 20, 2012 and Publication No. WO 2013/142525, March 19, 2013, which are hereby incorporated by reference in their entireties.

EXAMPLE 185
COMPOUNDS 332 and 333



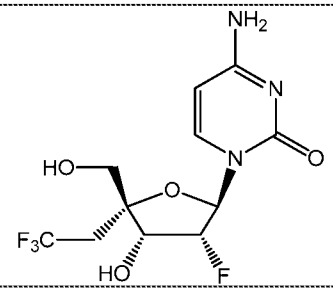
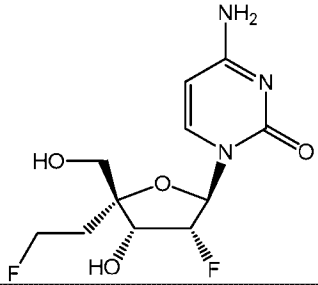
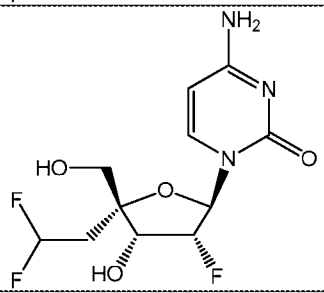
332

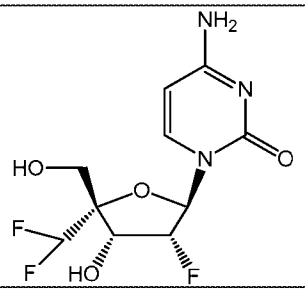
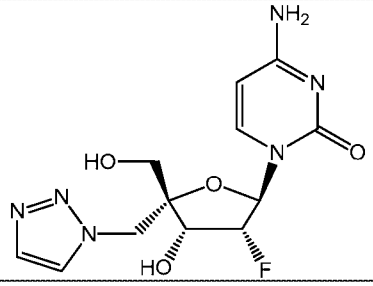


333

[1050] Compounds **332** and **333** were prepared as described in U.S. Publication No. 2012/0070415, filed September 19, 2011, which are hereby incorporated by reference in its entirety. **332**: 287 $[M+H]^+$, 573 $[2M+H]^+$; and **333**: 525.3 [M-1].

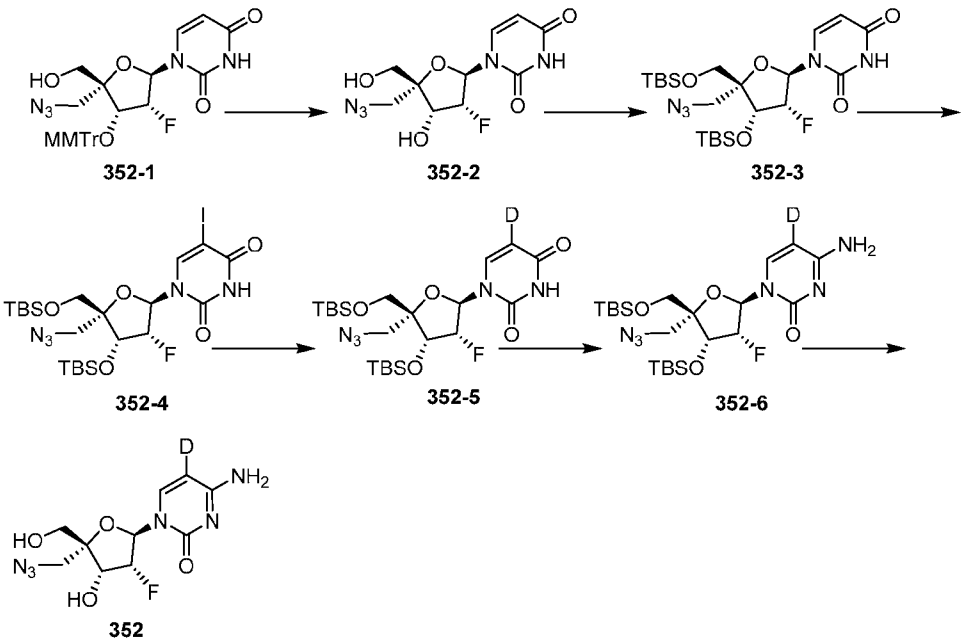
EXAMPLE 186
COMPOUNDS 346-350

Compound No.	Structure	Analytical Data
346		327.9 $[M+H]^+$
347		292 $[M+H]^+$
348		309.9 $[M+H]^+$

Compound No.	Structure	Analytical Data
349		294.5 $[M-H]^+$
350		326.8 $[M+H]^+$

[1051] Compounds **346-350** were prepared following one or more of the procedures described herein and using methods known to those skilled in the art.

EXAMPLE 187
COMPOUND 352



[1052] To a solution of **352-1** (1.2 g, 2.09 mmol) in DCE (40 mL) was added TFA (2 mL). The mixture was stirred at RT for 1 h. The mixture was concentrated under reduced

pressure, and the residue was purified by column chromatography (3% MeOH in DCM) to give **352-2** (600 mg, 95.3%) as a white solid.

[1053] To a solution of **352-2** (600 mg, 1.99 mmol) in pyridine (4 mL) was added imidazole (677 mg, 9.95 mmol) and TBSCl (900 mg, 5.97 mmol) at RT. The mixture was stirred at 60 °C for 16 h, and then concentrated under reduced pressure. The residue was diluted with EA (40 mL) and washed with brine (20 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography (10% EA in PE) to give **352-3** (700 mg, 65.7%) as a white solid.

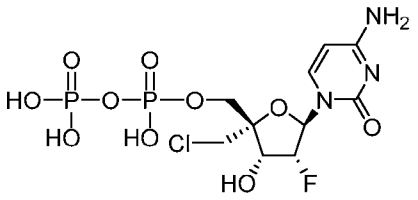
[1054] To a solution of **352-3** (700 mg, 1.32 mmol) in DCM (52 mL) was added NIS (356 mg, 1.58 mmol) and TFA (1.3 mL). The mixture was stirred at 60 °C for 3 h. After cooling to RT, the solution was extracted with DCM (30 mL), washed with sat. aq. $NaHCO_3$ and brine (20 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (10% EA in PE) to give **352-4** (400 mg, 46.2%) as a white solid.

[1055] A mixture of **352-4** (327 mg, 498 μmol), Bu_3SnH (174 mg, 598 μmol) and 2,2'-azobis(2,4-dimethylvaleronitrile) (25 mg, 100 μmol) in THF-d_8 (10 mL) was stirred at 90-100 °C for 3 h. The mixture was concentrated under reduced pressure. and the residue was purified by column chromatography (10% EA in PE) to give **352-5** (180 mg, 68.00%) as a white solid.

[1056] To a solution of **352-5** (210 mg, 395 μmol) in anhydrous MeCN (2 mL) were added DMAP (121 mg, 989 μmol), Et_3N (100 mg, 989 μmol) and 2,4,6-triisopropylbenzene-1-sulfonyl chloride (299 mg, 989 μmol) at RT. The mixture was stirred at RT for 16 h. $NH_3 \cdot H_2O$ (1 mL) was added, and the mixture was stirred for 1 h. The mixture was diluted with EA (15 mL) and washed with sat. aq. NH_4Cl (15 mL). The organic layer was dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography (2% MeOH in DCM) to give the crude product. The crude product was purified by prep-TLC (10% MeOH in DCM) to give **352-6** (200 mg, 95.42%) as a white solid.

[1057] To a solution of **352-6** (200 mg, 0.38 mmol) in MeOH (2 mL) was added NH_4F (210 mg, 5.66 mmol) at RT. The mixture was stirred at 90-100 °C for 16 h. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (10% MeOH in DCM) to give the crude product. The crude product was purified by prep-HPLC (neutral condition) to give **352** (70 mg, 61.8% yield, 78.4% deuterium) as a white solid. ESI-TOF-MS: m/z = 302.1 $[M+H]^+$, 603.2 $[2M+H]^+$.

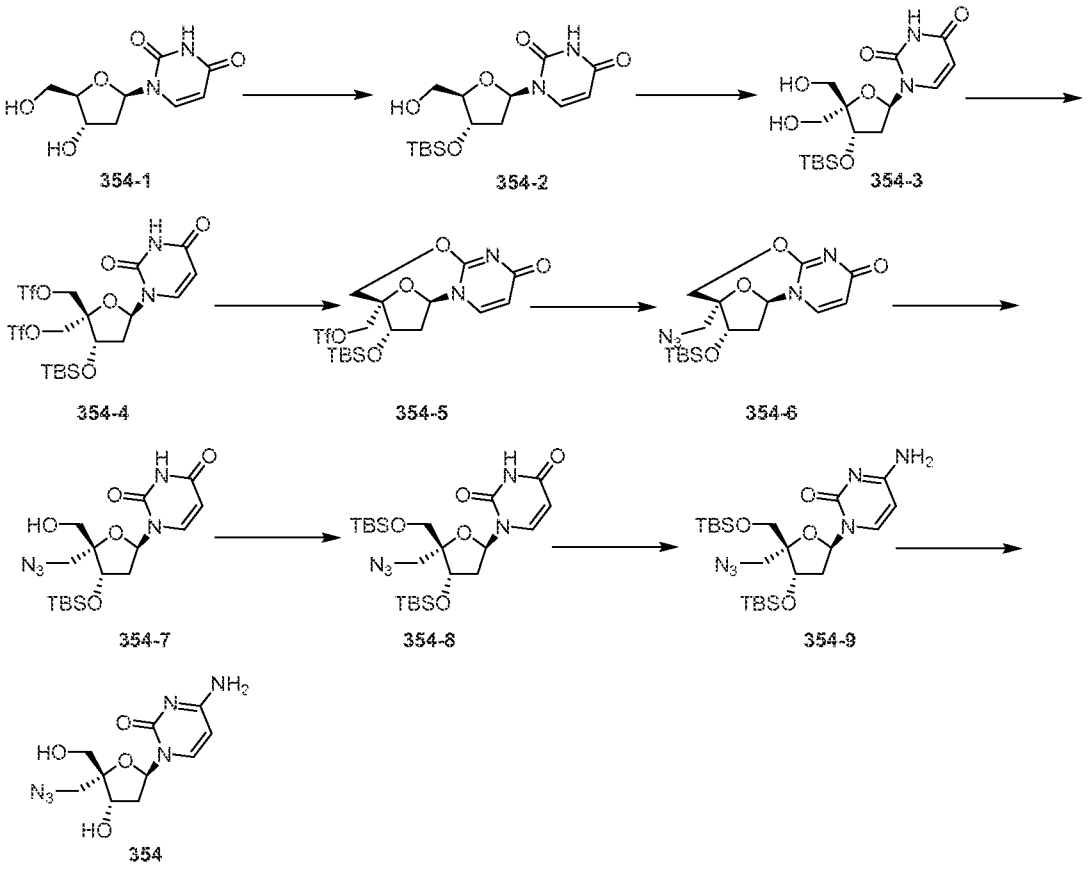
EXAMPLE 188
COMPOUND 353



353

[1058] The diphosphate, **353**, can be prepared using a similar procedure to preparing the triphosphate of Example 183 with the replacement of tetrabutylammonium salt of pyrophosphate with tetrabutylammonium phosphate (75 mg) and using 0.3 mL of DMF to get the homogeneous solution.

EXAMPLE 189
COMPOUND 354



[1059] To a solution of **354-1** (22.80 g, 99.91 mmol) in anhydrous pyridine (200 mL) was added DMTCl (37.24 g, 109.90 mmol), and the mixture stirred at 25 °C for 12 h. The reaction was quenched with a sat. NH_4Cl solution (200 mL), and extracted with EA (3 X 200 mL). The combined organic layers were washed with brine (2 X 100 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EA = 2:1 to 0:1) to give the desired product (43.00 g, 72.94 mmol) as a yellow foam.

[1060] To a solution of this product (20.00 g, 37.70 mmol), $AgNO_3$ (6.40 g, 37.70 mmol) and imidazole (5.13 g, 75.39 mmol) in DMF (200.00 mL) was added, followed by TBSCl (8.52 g, 56.54 mmol) at 0 °C. The mixture was stirred at 25 °C for 12 h, and then the mixture was concentrated under reduced pressure to remove the DMF. The residue was diluted with ice-water (300 mL) and extracted with EA (3 X 100 mL). The combined organic layers were washed with brine (3 X 50 mL), dried over anhydrous Na_2SO_4, filtered

and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EA = 3:1 to 1:1) to give 1-[(2R,4S,5R)-5-[[bis(4-methoxyphenyl)-phenyl-methoxy]methyl]-4-[tert-butyl(dimethyl)silyl]oxy-tetrahydrofuran-2-yl]pyrimidine-2,4-dione (15.70 g, 24.35 mmol) as a white solid.

[1061] A solution of 1-[(2R,4S,5R)-5-[[bis(4-methoxyphenyl)-phenyl-methoxy]methyl]-4-[tert-butyl(dimethyl)silyl]oxy-tetrahydrofuran-2-yl]pyrimidine-2,4-dione (20.00 g, 31.02 mmol) in AcOH (105 g, 1.40 mol) was stirred at 25 °C for 1 h. The reaction was quenched with MeOH (100 mL), and the mixture was concentrated under reduced pressure. The residue was diluted with water (100 mL). The solution was neutralized with solid $NaHCO_3$ to pH= 7, and extracted with EA (3 X 100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by column chromatography (PE:EA = 5:1 to 0:1) to give **354-2** (8.90 g, 20.79 mmol) as a white solid.

[1062] To a stirred solution of **354-2** (3.42 g, 9.99 mmol) in dioxane (15.00 mL) and DMSO (3.00 mL) was added DCC (6.18 g, 29.97 mmol) and Py • TFA (1.93 g, 9.99 mmol) at 0 °C. The mixture was stirred at 25 °C for 2 h. The solution was diluted with EA (50 mL), and the solid was removed by filtration. The filtrate was washed with brine (30 mL). The organic layer was dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was used in the next step without further purification.

[1063] To a solution of the residue from the previous step (3.4 g) and formaldehyde (aq., 3 mL) in dioxane (20 mL) was added 2.0 M NaOH (aq., 5 mL) in one portion at 25 °C. The mixture was stirred at 25 °C for 16 h. The mixture was cooled to 0°C and neutralized with AcOH to pH = 7. The solution was treated with $NaBH_4$ (452 mg, 11.952 mmol) at 0 °C. The mixture was stirred at 25 °C for 30 mins, and the reaction was then quenched with sat. aq. NH_4Cl (100 mL). The mixture was extracted with EA (2 X 100 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by column chromatography (DCM:MeOH =20:1 to 10:1) to afford **354-3** (1.43 g, 38.4%) as a white solid.

[1064] To a solution of **354-3** (1.43 g, 3.84 mmol) in DCM (10.00 mL) was added Tf_2O (2.38 g, 8.45 mmol) and pyridine (1.51 g, 19.2 mmol) at 0 °C, and the mixture stirred at 25 °C for 1 h. The reaction was quenched by ice-water (20 mL) at 0 °C, and then extracted

with DCM (2 X 30mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (DCM:MeOH =40:1) to give **354-4** (1.60 g, 2.14 mmol) as a yellow foam.

[1065] To a solution of **354-4** (1.60 g, 2.51 mmol) in DCM (10.00 mL) was added TEA (1.27 g, 12.57 mmol), and the mixture was stirred at 25 °C for 16 h. The reaction was quenched with 1.0 M HCl solution to pH= 7, and then extracted with DCM (30 mL). The organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by column chromatography (DCM:MeOH = 40:1 to 30:1) to give **354-5** (1.10 g, 81.07%) as a yellow solid.

[1066] To a solution **354-5** (1.10 g, 2.27 mmol) in DMF (10.00 mL) was added NaN_3 (441.84 mg, 6.80 mmol), and the mixture was stirred at 25 °C for 12 h. The reaction was quenched with H_2O (3 mL), and extracted with EA (3 X 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated at low pressure to give **354-6** (800.00 mg, 92.87%) as a yellow solid.

[1067] To a solution of **354-6** (800.00 mg, 2.11 mmol) in THF (20.00 mL) was added NaOH solution (1.05 mL, 2.11 mmol, 2.0 M), and the mixture was stirred at 25 °C for 12 h. The mixture was diluted with EA (20 mL), and washed with brine (15 mL). The solution was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give **354-7** (821.00 mg, 97.89%) as a yellow solid.

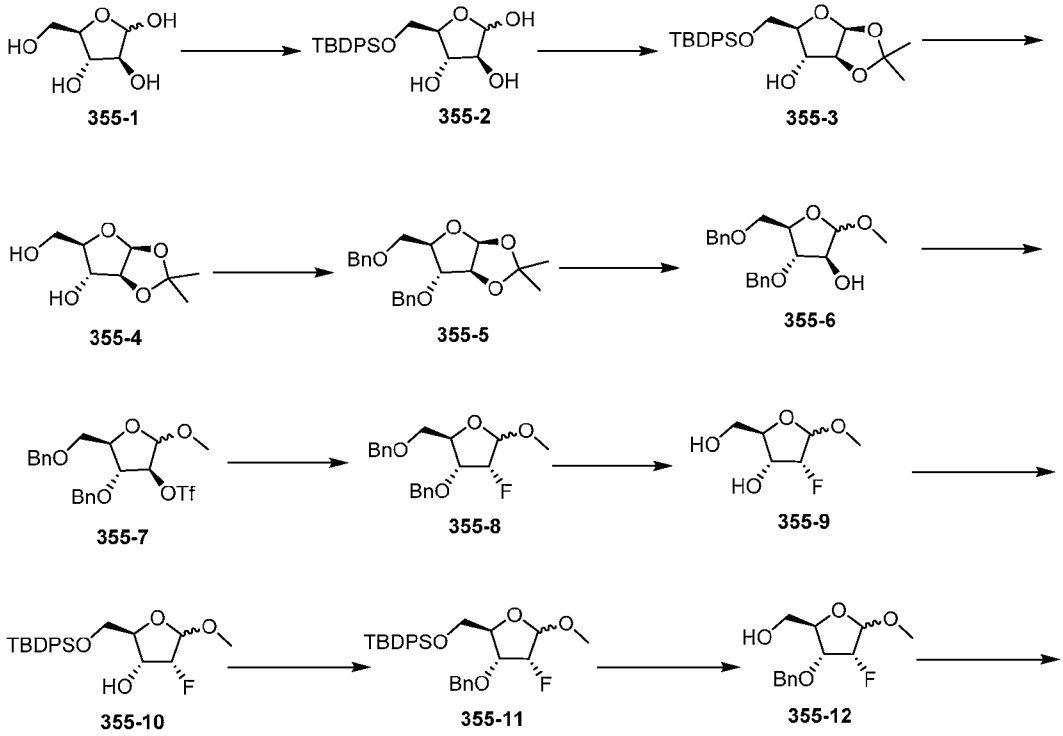
[1068] To a solution of **354-7** (596 mg, 1.50 mmol) in DCM (10 mL) was added TBSCl (452.16 mg, 3.00 mmol) and imidazole (306.36 mg, 4.50 mmol), and the mixture stirred at 25 °C for 5 h. The mixture was diluted with DCM (20 mL). The solution was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (DCM:MeOH = 40:1 to 30:1) to give **354-8** (750 mg, 87.93%) as a white solid.

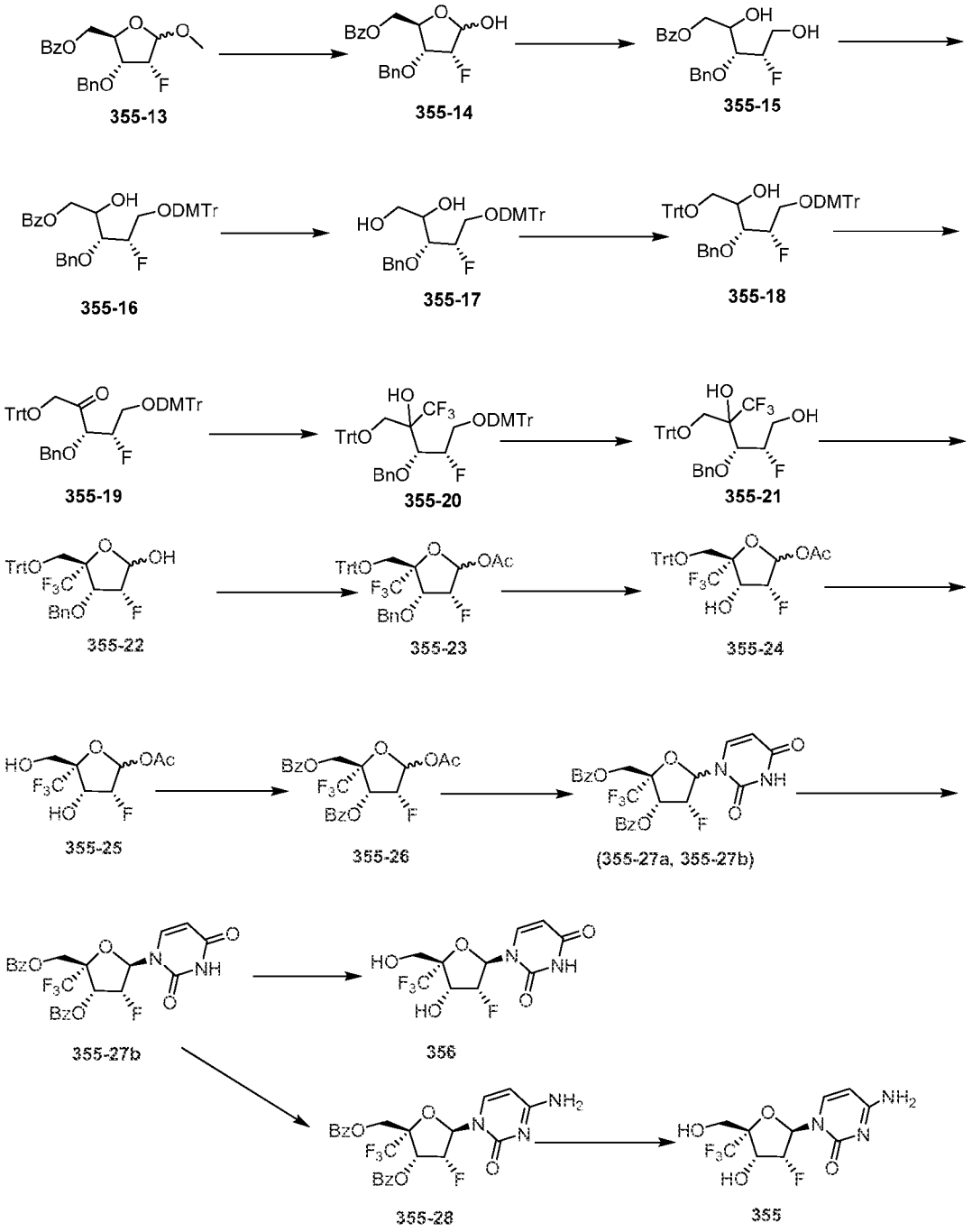
[1069] To a solution of **354-8** (600 mg, 1.17 mmol) and TEA (296 mg, 2.93 mmol) in CH_3CN (10 mL) was added TPSCl (862 mg, 2.93 mmol). The mixture was heated to 40 °C for 5 h. The reaction was quenched with 0.5 M HCl solution to pH = 6. The solution was extracted with EA (3 X 20 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was treated with NH_3/THF (20 mL, 10 M). The solution was stirred at 25 °C for 16 h, and then concentrated under reduced

pressure. The residue was purified by column chromatography (DCM:MeOH = 30:1 to 20:1) to give the crude product (500 mg). The crude product was purified by prep-TLC (DCM:MeOH = 10:1) to give **354-9** (310 mg, 52%) as a white solid.

[1070] To a solution of **354-9** (310 mg, 606.9 μmol) in THF (5 mL) was added TBAF in THF (2 mL, 1.0 M) at 25 °C. The solution was stirred at 25 °C for 0.5 h. The mixture was concentrated at low pressure. The residue was purified by prep-HPLC (HCl system) to give **354** (86 mg, 50.2%) as a white solid. ESI-TOF-MS: m/z = 283.1 $[M+H]^+$, 565.3 $[2M+H]^+$.

EXAMPLE 190
COMPOUNDS 355 and 356





[1071] To a solution of **355-1** (394 g, 2.62 mol) and imidazole (268 g, 3.93 mol) in DMF (3 L), was added TBDPSCl (756.14 g, 2.75 mol) in one portion at 25 °C. The mixture was heated to 50°C and stirred for 12 h. The mixture was poured into water/brine (v:v = 1:1) (6 L) and stirred for 20 mins. The mixture was extracted with EA (2 X 4 L). The

combined organic phase was washed with sat. brine (2 X 4 L), dried over anhydrous Na_2SO_4 and concentrated in vacuum to give **355-2** (800 g, crude) as a yellow solid.

[1072] To a solution of **355-2** (1000 g, 2.57 mol) and 2,2-dimethoxypropane (450 g, 4.32 mol) in DCM (6 L), was added $TsOH \cdot H_2O$ (490 g, 2.57 mol) in one portion at 25 °C. The mixture was stirred for 0.5 h. The reaction was quenched by water (1L). The organic layer was washed with water (2 X 4 L), dried over anhydrous Na_2SO_4 and concentrated in vacuum to give **355-3** (1.1 kg, crude), which was used directly for next step.

[1073] A mixture of **355-3** (1.0 kg, 2.33 mol) and NH_4F (198 g, 5.36 mol) in MeOH (3 L) was stirred to reflux for 4 h. After the solvent was evaporated, the crude product was purified by silica gel (PE:EA = 1:1) directly to give crude **355-4**, which was re-crystallized (PE:EA = 1:1) to give pure **355-4** (170 g, 38.4% yield) as a white solid. ^{1}H-NMR (400 MHz, CD3OD), δ = 5.90 (d, *J* = 4 Hz, 1 H), 4.52 (d, *J* = 4 Hz, 1 H), 4.15 (s, 1 H), 4.0-3.97 (m, 1 H), 3.75-3.65 (m, 2 H), 1.50 (s, 3 H), 1.31 (s, 3 H).

[1074] To a solution of **355-4** (300 g, 1.58 mol) in DMF (4 L) was added NaH (83.3 g, 3.47 mol) by portions at 0 °C, and the mixture was stirred at 25 °C for 1 h. BnBr (553 g, 3.23 mol) was added, and the mixture was stirred at 25 °C for 1 h. The reaction was quenched by NH_4Cl (sat., 1 L) and water (2 L). The solution was extracted with EA:PE (2 X 3 L, v:v=1:1). The combined organic layer was concentrated in vacuum. The residue was purified by silica gel chromatography (PE:EA = 50:1) to afford **355-5** (505 g, 79.4%) as a yellow oil.

[1075] To a solution of **355-5** (330 g, 891 mmol) in MeOH (1500 mL) was added H_2SO_4 (conc. 20 mL, 406 mmol) dropwise at 25 °C. The mixture was heated to 60 °C for 2 h. After the mixture was cooled to 25 °C, the mixture was adjusted to pH to 7-8 with HCl (2 N, ~160 mL). The solution was diluted with EA (1.5 L). The organic layer was washed with H_2O (2 X 1 L), dried over anhydrous Na_2SO_4 and concentrated in vacuum. The residue was purified by silica gel chromatography (PE:EA = 5:1) to afford pure **355-6** (280 g, 78.3%) as a yellow oil.

[1076] To a solution of **355-6** (150 g, 435.54 mmol) and DMAP (69.2 g, 566 mmol) in DCM (1.5 L) was added Tf_2O (135.2 g, 479 mmol) slowly at -10 °C under N_2. The mixture was warmed to 25 °C and stirred for 1.5 h. The reaction was quenched with water (600 mL), and adjusted pH to 4-5 with HCl (1 N). The organic layer was separated, and

washed with $NaHCO_3$ (sat., 1 L), brine (1 L), and dried over anhydrous Na_2SO_4. The solution was concentrated in vacuum to give **355-7** (207 g, crude) as a yellow oil.

[1077] A mixture of **355-7** (207 g, 435.50 mmol) and TBAF (1 M in THF, 870 mL) was stirred at 60-70 °C for 12 h. The solvent was evaporated at low pressure. The residue was dissolved in EA (800 mL). The solution was washed withy water (3 X 500 mL), brine (500 mL) and dried over anhydrous Na_2SO_4. The solution was concentrated at low pressure. The residue was purified by silica gel chromatography (PE:EA = 20:1) to afford **355-8** (40 g, 25.46%) as a light yellow oil. ^{1}H-NMR (400 MHz, CD_3OD) δ = 7.36-7.33 (m, 10H), 5.05 (d, *J* = 8 Hz, 1 H), 4.87 (m, 0.5 H), 4.80-4.70 (m, 1.5 H), 4.62-4.53 (m, 3 H), 4.36-4.30 (m, 1 H), 4.18-4.05 (m, 2 H), 3.70-3.53 (m, 2 H), 3.36 (s, 3 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ = -209.48.

[1078] To a solution of **355-8** (50 g, 144.35 mmol) in MeOH (50 mL) was added $Pd(OH)_2/C$ (13 g, 50% H_2O) under Ar. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (40 psi) at 40 °C for 8 h. After the catalyst was filtered off, the filtrate was concentrated in vacuum to give **355-9** (23 g, 91%) as a gray solid.

[1079] To a solution of **355-9** (55 g, 331 mmol) and imidazole (31.55 g, 463.4 mmol) in DCM (1 L) was added TBDPSCl (100 g, 364.13 mmol) slowly at 0 °C. The mixture was stirred at 25 °C for 12 h. The reaction was quenched with water (100 mL), and then the mixture was concentrated. The residue was dissolved in EA (500 mL). The solution was washed with water (2 X 500 mL), dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by silica gel chromatography (PE:EA = 5:1) to afford **355-10** (74 g, 55%) as a colorless oil.

[1080] To a solution of **355-10** (70 g, 173 mmol) in DMF (750 mL) was added NaH (7.61 g, 190 mmol) at 0 °C, and the mixture stirred at 25 °C for 1 hr. BnBr (32.55 g, 190.33 mmol) was added slowly at 0°C under N_2. The mixture was stirred at 25°C for 2 h, and the reaction was quenched with water (1000 mL). The solution was extracted by EA:PE (v:v = 2:1, 2 X 800 mL). The organic layer was separated and washed with brine:water (v:v = 1:1, 2 X 500 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated at low pressure to give **355-11** (80 g, crude) as a yellow oil.

[1081] A mixture of **355-11** (100 g, 202.1 mmol) and NH_4F (15 g, 404.3 mmol) in MeOH (2000 mL) was stirred at 65 °C for 12 h. The mixture was cooled to 25 °C and concentrated under reduced pressure. The residue was diluted with EA (500 mL) and washed with water (2 X 500 mL). The organic phase was washed with sat. brine (500 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (PE:EA = 8:1) to afford **355-12** (36 g, 69.5%) as a yellow oil.

[1082] To a solution of **355-12** (36 g, 148.4 mmol) and TEA (22.51 g, 222.4 mmol) in DCM (300 mL) was added BzCl (23 g, 163.1 mmol) dropwise at 25 °C under N_2, and the mixture was stirred at 25 °C for 12 h. The reaction was quenched with water (500 mL). The organic layer was separated, washed by water (400 mL) and dried over anhydrous Na_2SO_4. The organic layer was concentrated under reduced pressure to give **355-13** (55 g, crude) as a yellow oil.

[1083] A mixture of **355-13** (55 g, 152.62 mmol) in TFA:H_2O (500 mL, v:v = 9:1) was stirred at 25 °C for 30 h. The solution was evaporated in vacuum. The residue was diluted with EA (200 mL), and washed with $NaHCO_3$ (aq., 200 mL). The organic layer was dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by silica gel (PE:EA = 10:1) to afford **355-14** (45 g, 80.8% yield) as a yellow oil.

[1084] To a solution of **355-14** (45 g, 129.9 mmol) in EtOH (500 mL) was added $NaBH_4$ (5.41 g, 142.9 mmol) at 25 °C, and the mixture was stirred at 25 °C for 0.5 h. The reaction was quenched with aq. NH_4Cl (500 mL), and extracted with EA (2 X 300 mL). The organic layer was washed with brine (300 mL), and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EA = 2:1) to give **355-15** (42 g, 94 % yield) as a white solid. ^{1}H-NMR (400 MHz, MeOD), δ = 8.05 (d, *J* = 7.2 Hz, 2H), 7.65-7.20 (m, 9 H), 4.95 (m, 0.5 H), 4.80-4.65 (m, 2 H), 4.53-4.47 (m, 2 H), 4.15-4.07 (m, 1 H), 4.00-3.85 (m, 3 H). ^{19}F NMR (376 MHz, MeOD) δ = -196.75.

[1085] A mixture of **355-15** (90 g, 258.4 mmol) in pyridine (500 mL) was treated with DMTrCl (92 g, 271 mmol) at 25 °C for 16 h. The solvent was evaporated in vacuum. The residue was dissolved in EA (500 mL). The solution was washed with water (2 X 300 mL), dried over anhydrous Na_2SO_4 and concentrated at low pressure to give **355-16** (145 g, crude) as a yellow solid.

[1086] To a solution of **355-16** (145 g, 223 mmol) in MeOH:THF (2000 mL, v:v = 3:1) was added NaOMe (12 g, 53.8 mmol) in one portion. The mixture was stirred at 25 °C for 1 h, and the reaction was quenched with CO_2 (solid). The mixture was concentrated at low pressure. The residue was dissolved in EA (200 mL). The solution was washed with water (300 mL) and brine (300 mL), dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by silica gel chromatography (PE:EA = 5:1) to give **355-17** (85 g, 70%) as a yellow oil.

[1087] To a solution of **355-17** (35.0 g, 64 mmol) in pyridine (200 mL) was added TrtCl (21.42 g, 76.84 mmol) in one portion at 20 °C. The mixture was stirred at 20 °C for 15 h. The solution was evaporated in vacuum. The residue was dissolved in EA (300 mL). The solution was washed with water (2 X 200 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by silica gel chromatography (PE:EA = 20:1) to give **355-18** (31 g, 89.5%) as a yellow oil.

[1088] To a solution of **355-18** (31 g, 41.8 mmol) in CH_3CN (500 mL) was added IBX (11.7 g, 41.8 mmol) in one portion at 20 °C, and the mixture was stirred at 80 °C for 2 h. The mixture was cooled, and then filtered. The filtrate was concentrated at low pressure to give **355-19** (32 g, crude) as a yellow oil.

[1089] To a solution of **355-19** (32 g, 40.6 mmol) and CsF (18.53 g, 122 mmol) in THF (300 mL) was added $TMSCF_3$ (17.35 g, 122 mmol) at 15°C, and the mixture was stirred at 15 °C for 18 h. The reaction was quenched with MeOH (5 mL). The solution was extracted with EA (300 mL), and washed with water (2 X 200 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by column chromatography (PE:EA = 8:1) to give **355-20** (25 g, 71.7%) as a yellow oil. ^{19}F NMR (376 MHz, $CDCl_3$) δ = -74.93, -74.95, -186.74 , -186.83.

[1090] To a solution of **355-20** (50 g, 58.35 mmol) in THF (50 mL) was added AcOH (200 mL, 80%), and the mixture was stirred at 15 °C for 16 h. The mixture was then heated to 45°C and stirred for 2 h. The solvent was evaporated in vacuum (MeOH was added (5 X 5 mL) during evaporation). The residue was purified by column chromatography (PE:EA = 20:1) to give **355-21** (down spot, desired isomer) (7.4 g, 22.9%) as a yellow solid and the by-product (17.1 g, 52.84%) (up spot) as a yellow solid. Down spot: ^1H-NMR (400 MHz, $CDCl_3$), δ = 7.50-7.25 (m, 20 H), 4.85-4.65 (t, 2 H), 4.48-4.40 (m, 1 H), 4.35 (m, 0.5

H), 4.25 (m, 0.5 H), 3.75-3.65 (m, 3 H), 3.20 (d, J = 12 Hz, 1 H). ^{19}F-NMR (376 MHz, MeOD), δ = -75.55, -190.067. Up spot: ^{1}H-NMR (400 MHz, $CDCl_3$), δ = 7.50-7.25 (m, 20 H), 4.98-4.80 (m, 1 H), 4.67 (d, J = 12 Hz, 1 H), 4.42-4.39 (m, 1 H), 4.33-4.29 (m, 1 H), 3.85-3.71 (m, 2 H), 3.65-3.60 (m, 1 H), 3.54-5.52, (m, 2H). ^{19}F-NMR (376 MHz, MeOD), δ = -75.455 (s, 3 F), -189.53 (s, 1F).

[1091] To a solution of **355-21** (8.50 g, 15.3 mmol) in THF:DMSO (60 mL) was added IBX (4.29 g, 15.3 mmol), and the mixture was stirred at 35°C for 2 h. The solution was slowly warmed to 40°C, and the mixture was stirred for 2 h. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was diluted with EA (100 mL) and washed with water (100 mL). The organic phase was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (PE:EA = 25:1) to give **355-22** (8.0 g, 75%) as a yellow oil.

[1092] To a solution of **355-22** (4.50 g, 8.14 mmol) in pyridine (50 mL) was added Ac_2O (2.49 g, 24.4 mmol). The mixture was stirred at 15 °C for 3 h. The reaction was quenched with MeOH (1 mL), and the solvent was evaporated via vacuum. The residue was dissolved in EA (40 mL). The solution was washed with water (50 mL), dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by column chromatography (PE:EA = 20:1) to give **355-23** (4.30 g, 88.8%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$), δ = 7.50-7.20 (m, 20 H), 6.45 (d, J = 12 Hz, 1 H), 4.90 (m, 0.5 H), 4.77 (m, 0.5 H), 4.70-4.55 (m, 3 H), 3.40 (dd, J = 40 Hz, 2 H), 1.79 (s, 3 H). ^{19}F-NMR (376 MHz, MeOD), δ = -73.92 (d, J = 18 Hz, 3F), -204.95 (t, 1F).

[1093] To a solution of **355-23** (900 mg, 1.51 mmol) in MeOH (20 mL) was added $Pd(OH)_2/C$ (50%, 0.6 g) under N_2 atmosphere. The suspension was degassed and purged with H_2 (3x). The mixture was stirred under H_2 (40 psi) at 40 °C for 24 h, and then filtered. The filtrate was concentrated in vacuum. The residue was purified by column chromatography (PE:EA = 10:1) to give **355-24** (300 mg, 39.4%) as a yellow oil.

[1094] To a solution of **355-24** (200 mg, 396.5 μmol) in DCM (2 mL) was added TFA (153 mg, 1.34 mmol) and Et_3SiH (365 mg, 3.14 mmol). The mixture was stirred at 15 °C for 20 mins. The solvent was evaporated directly in vacuum. The residue was purified by column chromatography (PE:EA = 1:1) to give **355-25** (100 mg, 96%) as a white solid.

[1095] To a solution of **355-25** (100 mg, 381 μmol) in DCM (2 mL) was added DMAP (46.60 mg, 381 μmol) and TEA (115.8 mg, 1.14 mmol). BzCl (117.96 mg, 839.19 μmol) was added, and the mixture was stirred at 15 °C for 0.5 h. The reaction was quenched with HCl (0.3 N, 10 mL). The mixture was extracted with CH_2Cl_2 (3 X 10 mL), and washed with water (10 mL). The organic phase was dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by column chromatography (PE:EA = 20:1) to give **355-26** (144 mg, 81%) as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$), δ = 8.12 (d, J = 7.6 Hz, 1 H), 8.04 (d, J = 7.6 Hz, 1 H), 7.70-7.39 (m, 6 H), 6.57 (d, J = 11 Hz, 1 H), 6.02 (dd, J_1 = 22.8 Hz, J_2 = 4.8 Hz, 1 H), 5.28 (dd, J_1 = 52 Hz, J_2 = 4.4 Hz, 1 H), 4.74 (t, 2 H), 1.96 (s, 3 H). ^{19}F-NMR, (376 MHz, MeOD), δ = -74.18 (d, J = 18.8 Hz, 3 F), -204.08 (t, 1F).

[1096] A mixture of uracil (457.54 mg, 4.08 mmol) and HMDS (3.85 g, 23.86 mmol) was stirred at 120 °C for 1 h, and the solvent was evaporated at low pressure. **355-26** (480 mg, 1.02 mmol) was dissolved in CH_3CN (2 mL), and treated with the above mixture. The mixture was taken up into a microwave tube, and was treated with TMSOTf (1.60 g, 7.19 mmol). The mixture was heated at 140 °C for 4 h under microwave irradiation. The reaction was quenched with MeOH, and the mixture was concentrated directly at low pressure. The residue was purified by column chromatography (PE:EA = 5:1) to give the crude product (2.5 g), which was purified by prep-HPLC (TFA) to give two isomers (0.92 g). After the residue was purified by SFC (AD-H_6_30-65 6MIN, OJ (250mm*50mm, 10um), Base-MeOH), **355-27a** (α-isomer, 470 mg, 22%) and **355-27b** (β-isomer, 320 mg, 15%) were obtained as a white solid. **355-27a** (α-isomer): ^{1}H-NMR (400 MHz, $CDCl_3$), δ = 8.63 (s, 1H), 8.20-8.00 (m, 4 H), 7.75-6.95 (m, 6 H), 6.63 (d, J = 20.8 Hz, 1 H), 6.10 (dd, J_1 = 23.6 Hz, J_2 = 4 Hz, 1 H), 5.86 (d, J = 6.8 Hz, 1 H), 5.47 (d, J = 54 Hz, 1 H), 4.80 (s, 2H). ^{19}F-NMR (376 MHz, MeOD), δ = -73.65 (d, J = 16.4 Hz, 3 F), -212.54 (t, 1F). **355-27b** (β-isomer): ^{1}H-NMR (400 MHz, $CDCl_3$), δ = 8.48 (s, 1H), 8.15-8.00 (m, 4 H), 7.60-7.25 (m, 6 H), 6.22 (dd, J_1 = 16 Hz, J_2 = 6.4 Hz, 1 H), 5.95-5.20 (m, 3 H), 4.80 (s, 2H). ^{19}F-NMR (376 MHz, MeOD), δ = -73.31 (d, J = 11 Hz, 3 F), -192.56 (t, 1F).

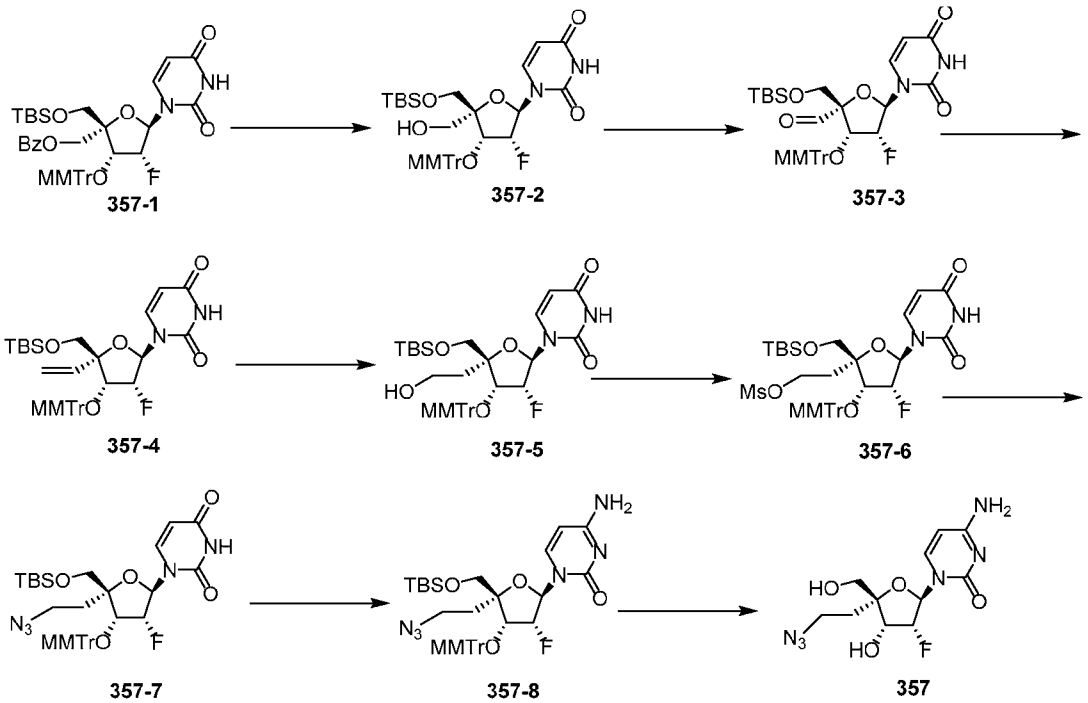
[1097] A mixture of **355-27b** (180 mg, 344 μmol, 1.0 eq.) in NH_3/MeOH (7 M, 5 mL) was stirred at 15 °C for 16 h. The solvent was concentrated directly in vacuum. The

residue was purified by prep-HPLC (neutral condition, NH_4HCO_3) to give **356** (86 mg, 79.4%) as a white solid. ESI-MS: m/z 315.1 $[M+H]^+$.

[1098] To a solution of **355-27b** (200 mg, 383 μmol) in CH_3CN (2 mL) was added DMAP (116 mg, 957 μmol), TEA (97 mg, 957 μmol), and 2,4,6-triisopropylbenzenesulfonyl chloride (290 mg, 957 μmol), and the mixture stirred at 15 °C for 20 mins. The mixture was treated with $NH_3 \cdot H_2O$ (2 mL), and the mixture was stirred at 15 °C for 10 mins. The mixture was extracted with EA (2 X 10 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by column chromatography (PE:EA = 2:1) and re-purified by prep-TLC (DCM:MeOH = 15:1) to give **355-28** (90 mg, 45%) as a white solid.

[1099] A mixture of **355-28** (90 mg, 172.61 μmol) in NH_3/MeOH (7 M, 3 mL) was stirred at 15 °C for 16 h. The solvent was concentrated directly in vacuum. The residue was purified by prep-HPLC (HCl condition) to give **355** (30 mg, 55%) as a white solid. ESI-MS: m/z 314.0 $[M+H]^+$.

EXAMPLE 191
COMPOUND 357



[1100] **357-1** (2.3 g, 3.0 mmol) was treated with NH_3 in MeOH (50 mL, 10 M) at 25 °C. The mixture was stirred at 25 °C for 24 h. The mixture was concentrated under

reduced pressure. The residue was purified by column chromatography (10%-30% EtOAc in PE) to afford **357-2** (1.5 g, 70.8%) as a white solid.

[1101] To a stirred solution of **357-2** (1.5 g, 2.26 mmol) in anhydrous DCM (15.00 mL) was added Dess-Martin (1.6 g, 3.84 mmol) in one portion at 0 °C under N_2. The mixture was stirred at 25 °C for 1.5 h. The reaction was quenched with sat.$Na_2S_2O_3$ and sat.$NaHCO_3$ (v:v = 1:1, 20 mL) at 0 °C. The aqueous phase was extracted with DCM (3 X 30 mL). The combined organic phase was washed with sat. brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to give **357-3** (1.6 g, crude), which was used in the next step without further purification.

[1102] To a solution of methyl (triphenyl)phosphonium;bromide (3.4 g, 9.4mmol) in anhydrous THF (12 mL) was added n-BuLi (2.5 M, 3.8 mL) dropwise at 0 °C under N_2. The mixture was stirred at 0 °C for 1 h. **357-3** (1.55 g, 2.35 mmol) in THF (8 mL) was added to the mixture dropwise at 0 °C. The solution was warmed and stirred at 25 °C for 12 h. The reaction was quenched with a sat.NH_4Cl solution. The mixture was extracted with EA (3 X 50 mL). The combined organic phase was washed with brine, dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by column chromatography (10%-20% EtOAc in PE) to give **357-4** (1.1 g, 71.05%) as a white solid.

[1103] **357-4** (501 mg, 758.9 μmol) was dissolved in 9-BBN (0.5 M, 15 mL) in one portion at 25 °C under N_2. The mixture was heated at 80 °C in microwave for 30 mins. Sat. aq. $NaHCO_3$ (5 mL) and H_2O_2 (30%, 2.5 mL) was added at 0 °C. The mixture was stirred at 25 °C for 2 h. The reaction was quenched with sat. $Na_2S_2O_3$ at 0°C. The mixture was diluted with EA and water. The aqueous phase was back-extracted with EA. The combined organic phase was washed with brine, dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by column chromatography (10%-25% EtOAc in PE) to give **357-5** (395 mg, 76.9%) as a white solid.

[1104] To a solution of **357-5** (360 mg, 531.8 μmol) in anhydrous DCM (4 mL) was added TEA (215 mg, 2.13 mmol) and MsCl (73 mg, 638.26 μmol) in DCM (1 mL) dropwise at 0 °C. The mixture was stirred at 25 °C for 2 h. The reaction was quenched with ice water and extracted with CH_2Cl_2. The organic layer was washed with brine and dried

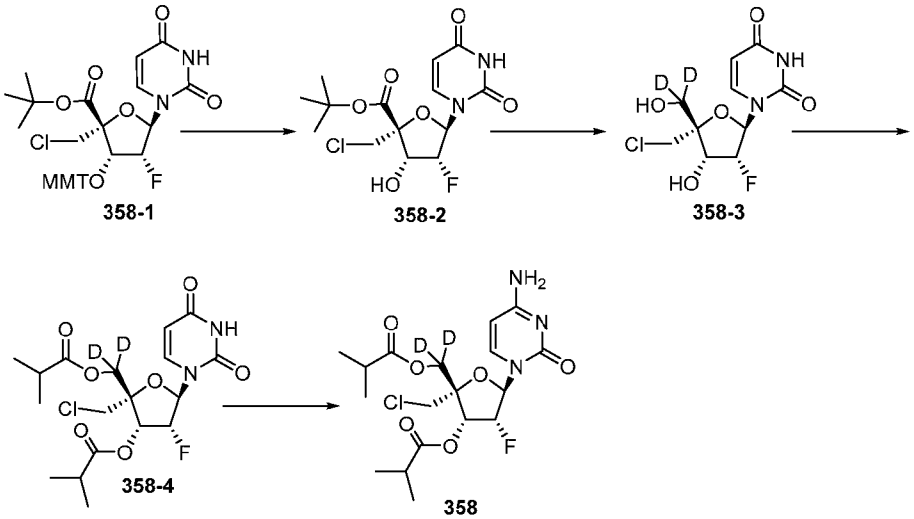
over anhydrous $MgSO_4$. The solution was filtered and concentrated to **357-6** (395 mg, crude) as a brown solid, which was used in the next step without further purification.

[1105] To a solution of **357-6** (380 mg, 504 μmol) in anhydrous DMF (4 mL) was added NaN_3 (98 mg, 1.51 mmol) at 25 °C. The mixture was stirred at 70 °C for 3 h. The reaction was quenched with water and extracted with EA. The organic layer was washed with brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated at low pressure. The residue was purified by column chromatography (10%-30% EtOAc in PE) to give **357-7** (295 mg, 83.5%) as a white solid.

[1106] To a stirred solution of **357-7** (295 mg, 420.3 μmol) in anhydrous CH_3CN (3 mL) was added DMAP (102.7 mg, 840.6 μmol), TEA (85.1 mg, 840.6 μmol) and TPSCl (247.9 mg, 840.6 μmol) at 25 °C. The mixture was stirred at 25 °C for 3 h. $NH_3 \cdot H_2O$ (10 mL, 28%) was added, and the mixture was stirred for 1 h. The mixture was diluted with EA, and washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by column chromatography (1%-2% MeOH in DCM) to give **357-8** (260 mg, 88.3%) as a white solid.

[1107] **357-8** (240 mg, 342.4 μmol) was treated with 80% HCOOH (10 mL) at 25 °C. The mixture was stirred at 70 °C for 2 h. The reaction was cooled to 25 °C and then concentrated under reduced pressure. The residue was purified on a silica gel column (2%-6% MeOH in DCM) to give **357** (85 mg, 79.1%) as a white solid. ESI-TOF-MS: m/z = 314.9 $[M+H]^+$, 629.1 $[2M+H]^+$.

EXAMPLE 192
COMPOUND 358



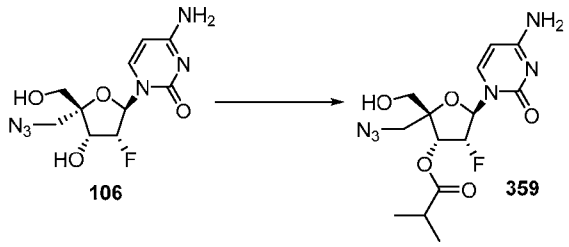
[1108] A solution of **358-1** (0.68 g, 1.07 mmol) in AcOH (10 mL) and TFA (0.25 mL) was stirred 1 h at RT. The mixture was evaporated, and the residue coevaporated with MeCN and toluene. Purification on silica column with MeOH:CH_2Cl_2 solvent system (2-12% gradient) afforded **358-1** (0.32 g, 82%).

[1109] A mixture of **358-1** (0.32 g, 0.9 mmol) in THF (9 mL) and $LiBH_4$ (94 mg, 3.6 mmol) was stirred 2 d at RT. The reaction was quenched with AcOH:EtOH, and the mixture evaporated. Purification on silica column with MeOH:CH_2Cl_2 solvent system (4-15% gradient) afforded **358-2** (80 mg, 30%).

[1110] A mixture of **358-2** (80 mg, 0.27 mmol) in pyridine (3 mL) and isobutyric anhydride (90 µL, 0.55 mmol) was stirred overnight at RT. The mixture was evaporated, and the residue coevaporated with toluene. Purification on silica column with EtOAc:hexanes solvent system (30-100% gradient) yielded **358-3** (72 mg, 61%) as a white solid.

[1111] To a solution of **358-3** (72 mg, 0.17 mmol) in MeCN (2 mL) were added triisopropylphenylsulfonyl chloride (102 mg, 0.34 mmol), DMAP (41 mg, 0.34 mmol) and Et_3N (47 µL, 0.34 mmol). The mixture was stirred at RT for 90 mins, and then ammonia was quickly bubbled (<1 min) through. The mixture was stirred for 10 mins. The mixture was diluted with CH_2Cl_2, washed with 0.1 N HCl, sat. aq. $NaHCO_3$, and brine, and dried with Na_2SO_4. Purification on silica column with MeOH:CH_2Cl_2 solvent system (4-12% gradient) afforded **358** (46 mg, 60%). MS: m/z = 434.00 [M-1].

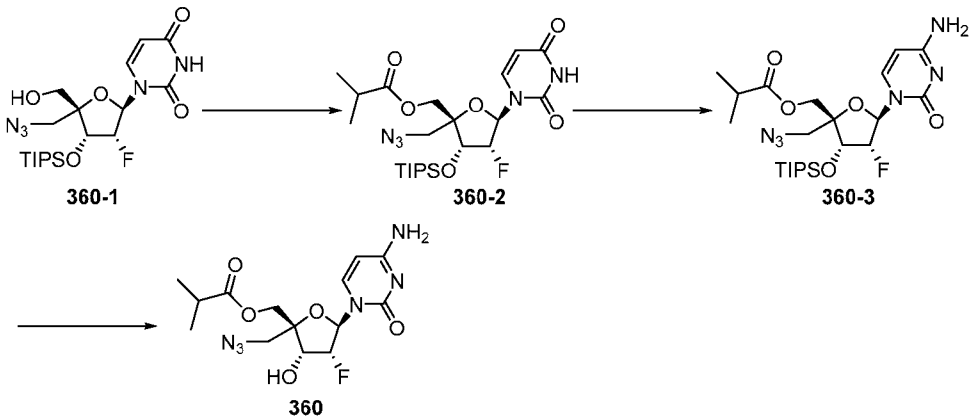
EXAMPLE 193
COMPOUND 359



106 359

[1112] To a solution of isobutiric acid (278 µL, 3 mmol) in THF (5 mL) was added CDI (486 mg, 3 mmol). After 1 h the solution of isobutiric acid imidazolide was added to a stirred solution of **106** (600 mg, 2 mmol), triethylamine (560 µL, 4 mmol) and DMAP (0.2 mmol) in DMF (5 mL). The solution was left overnight at RT. The reaction was partitioned between isopropyl acetate and sat. aq. ammonium chloride. The organic phase was washed with water and concentrated under reduced pressure. **359** (500 mg, 67%) was isolated by column chromatography (10 to 15% MeOH in DCM) followed by crystallization from isopropanol:hexane (1:2) as a white solid. MS: m/z 371 $[M+H]^+$.

EXAMPLE 194
COMPOUND 360



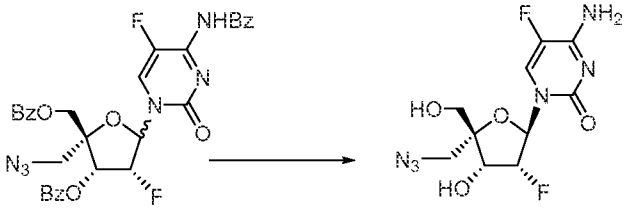
360-1 360-2 360-3 360

[1113] To a stirred solution of **360-1** (2.16 g, 4.73 mmol) in ACN (20 mL) were added triethylamine (1.9 mL, 15 mmol), DMAP (60 mg, 0.5 mmol) and isobutyric anhydride (1.08 mL, 6.5 mmol). The mixture was stirred at RT for 1 h, and then partitioned between isopropyl acetate and sat. aq. sodium bicarbonate solution. The organic phase was separated, washed with water and concentrated. **360-2** (2.1 g, 84%) was isolated by column chromatography using 25 to 50% EA in hexane as a white foam. MS: m/z 528 $[M+H]^+$.

[1114] **360-2** (2.1g, 3.98 mmol) was dissolved in ACN (15 mL,) and the solution was cooled to 0 °C. Triethylamine (1.1 mL, 8 mmol) and DMAP (537 mg, 4.4 mmol) were added to the solution followed by addition of triisopropylbenzenesulfonyl chloride (1.33 g, 4.4 mmol). The mixture was warmed to RT and then stirred for 1 h. The reaction was quenched with ammonium hydroxide (1 mL). The mixture was stirred for 2 h at RT, diluted with isopropyl acetate and filtered from ammonium salts. The filtrate was washed with water and aq. sodium bicarbonate and then concentrated under reduced pressure. **360-3** (2.1 g, ~100%) was isolated by column chromatography using 4-10% MeOH in CH_2Cl_2 as a yellowish foam. MS: m/z 527 $[M+H]^+$.

[1115] **360-3** (1.10 g, 2.09 mmol) was dissolved in THF (6 mL). The solution was cooled to 0 °C and treated with 1M TBAF solution in THF (2.1 mL, 2.1 mmol). The reaction was allowed to proceed for 1 h, and then quenched by the addition of a sat. aq. ammonium chloride solution. **360** (450 mg, 58%) was extracted with isopropyl acetate and isolated by column chromatography in 5-15% MeOH in CH_2Cl_2 as an off-white foam, MS: m/z 371 $[M+H]^+$.

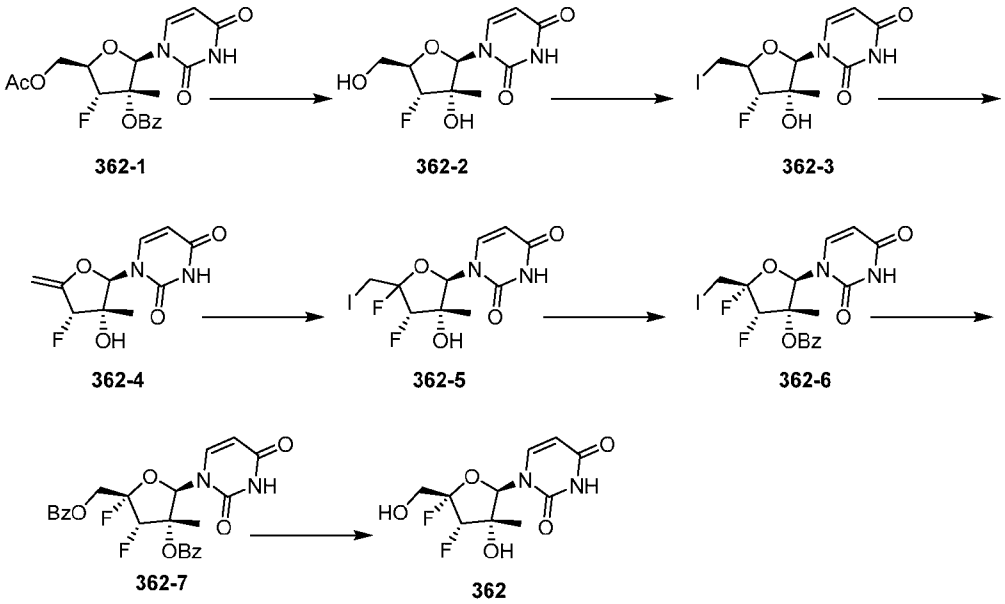
EXAMPLE 195
COMPOUND 361



361-1 361

[1116] **361-1** (400 mg) was dissolved in NH_3/methanol (10 mL), and the mixture was kept at ambient temperature over 2 d. The solvent was evaporated, and the residue purified by silica gel chromatography in gradient of MeOH in CH_2Cl_2 from 3% to 20%. The mixture of products was separated by RP HPLC on Synergy 4 micron Hydro-RP column (Phenominex). A linear gradient of MeOH from 0 to 50% in 50 mM triethylammonium acetate buffer (pH 7.5) was used for elution. The corresponding fractions were collected, concentrated and lyophilized (3x) to remove excess of buffer. The stereochemistry at the 1'-position of both isomers was proved by NOE NMR-experiments. The compound with shorter retention time was **361**. MS: m/z 319 $[M+1]^+$, 637$[2M+1]^+$.

EXAMPLE 196
COMPOUND 362



[1117] **362-1** (6.0 g, 14.77 mmol) was treated with NH_3 in MeOH (7.0 M, 150 mL) at RT. The mixture was stirred at 60 °C for 16 h. The mixture was concentrated under reduced pressure. The residue was purified by column chromatography (5% MeOH in DCM) to give **362-2** (3.4 g, 90%) as a white solid.

[1118] To a stirred suspension of **362-2** (3.4 g, 13.1 mmol) in anhydrous THF (60 mL) was added pyridine (15 mL), imidazole (1.8 g, 26.5 mol) and PPh_3 (5.1 g, 19.5 mol). A solution of I_2 (4.3 g, 16.9 mol) in THF (20 mL) was added dropwise at 0 °C. The mixture was warmed to RT and stirred for 16 h. The reaction was quenched with sat. aq. $Na_2S_2O_3$ solution and extracted with EA (3 X 100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (40% EA in PE) to afford **362-3** (4.6 g, crude) as a white solid.

[1119] To a solution of **362-3** (4.6 g, crude) in THF (35 mL) was added DBU (37.8 g, 247 mmol). The mixture was stirred at RT for 0.5 h. The mixture was neutralized with acetic acid to pH = 7 and extracted with EA (3 X 100 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (50% EA in PE) to give **362-4** (1.59 g, crude, 84% purity) as a white solid.

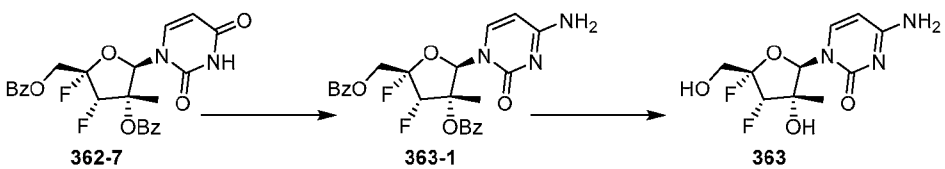
[1120] To an ice-cold solution of **362-4** (1.59 g, crude) in anhydrous MeCN (35 mL) was added NEt_3•3HF (1.06 g, 6.56 mmol l) and NIS (3.69 g, 16.40 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h. After the reaction was completed, the reaction was quenched with sat. aq. $Na_2S_2O_3$ solution and sat. aq. $NaHCO_3$ solution and extracted with EA (3 X 100 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated at low pressure. The residue was purified by column chromatography (50% EA in PE) to give **362-5** (2.0 g, two isomers) as a white solid.

[1121] To a solution of **362-5** (2.0 g, 5.15 mmol, two isomers) in anhydrous DCM (30 mL) was added DMAP (1.57 g, 12.88 mmol) and BzCl (1.27 g, 9.01 mmol), and the mixture was stirred at RT for 16 h. The reaction was quenched with sat. aq. NH4Cl solution and extracted with DCM (3 X 60 mL). The organic layer was dried over anhydrous Na2SO4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (25% EA in PE) to give the crude product. The crude was further purified by SFC separation (neutral conditions) to give **362-6** (1.60 g, 63.1%) as a white solid.

[1122] To a solution of **362-6** (573 mg, 1.16 mmol) in dry DMF (30 mL) was added NaOBz (1.68 g, 11.64 mmol) and 15-crown-5 (3.08 g, 13.97 mmol), and the mixture was stirred at 90-110 °C for 24 h. The mixture was filtered and extracted with EA (3 X 20 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated at low pressure. The residue was purified by column chromatography (30% EA in PE) to give **362-7** (492 mg, 87.20%) as a white solid.

[1123] **362-7** (293 mg, 0.6 mmol) was treated with NH_3 in MeOH (30 mL, 7.0 M). The mixture was stirred at 60 °C for 16 h, and then concentrated under reduced pressure. The residue was purified by column chromatography (3% isopropanol in DCM) to give the crude product. The crude product was purified by prep-HPLC (FA condition) to give **362** (108 mg, 53.41%) as a white solid. ESI-TOF-MS: m/z = 279.1 $[M+H]^+$.

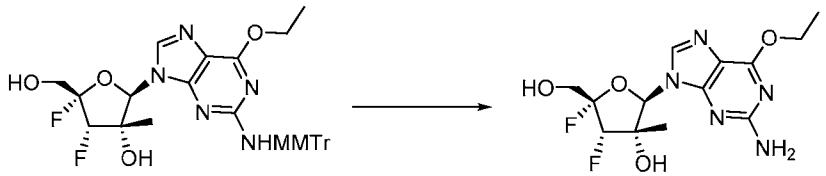
EXAMPLE 197
COMPOUND 363



[1124] To a solution of **362-7** (492 mg, 1.01 mmol) in anhydrous CH_3CN (8 mL) were added DMAP (308 mg, 2.53 mmol), Et_3N (255 mg, 2.53 mmol) and 2, 4, 6-triisopropylbenzene-1-sulfonyl chloride (765 mg, 2.53 mmol) at RT. The mixture was stirred at RT overnight. A solution of NH_3 in THF (4 mL, 7.0 M) was added, and the mixture was stirred for 30 mins. The solvent was removed under reduced pressure. The residue was diluted with EA. The solution was washed with 0.5% AcOH aq. solution and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (2% MeOH in DCM) and further purified by prep-TLC (10% MeOH in DCM) to give **363-1** (370 mg, 65.6%) as a white solid.

[1125] **363-1** (370 mg, 0.76 mmol) was treated with NH_3 in MeOH (40 mL, 7.0 M). The mixture was stirred at 60 °C for 16 h. The mixture was concentrated under reduced pressure. The residue was purified by column chromatography (8% isopropanol in DCM) to give the crude product. The crude product was purified by prep-HPLC (FA condition) to give **363** (65.6 mg, 30.2%) as a white solid. ESI-TOF-MS: m/z = 278.1 $[M+H]^+$, 555.2 $[2M+H]^+$.

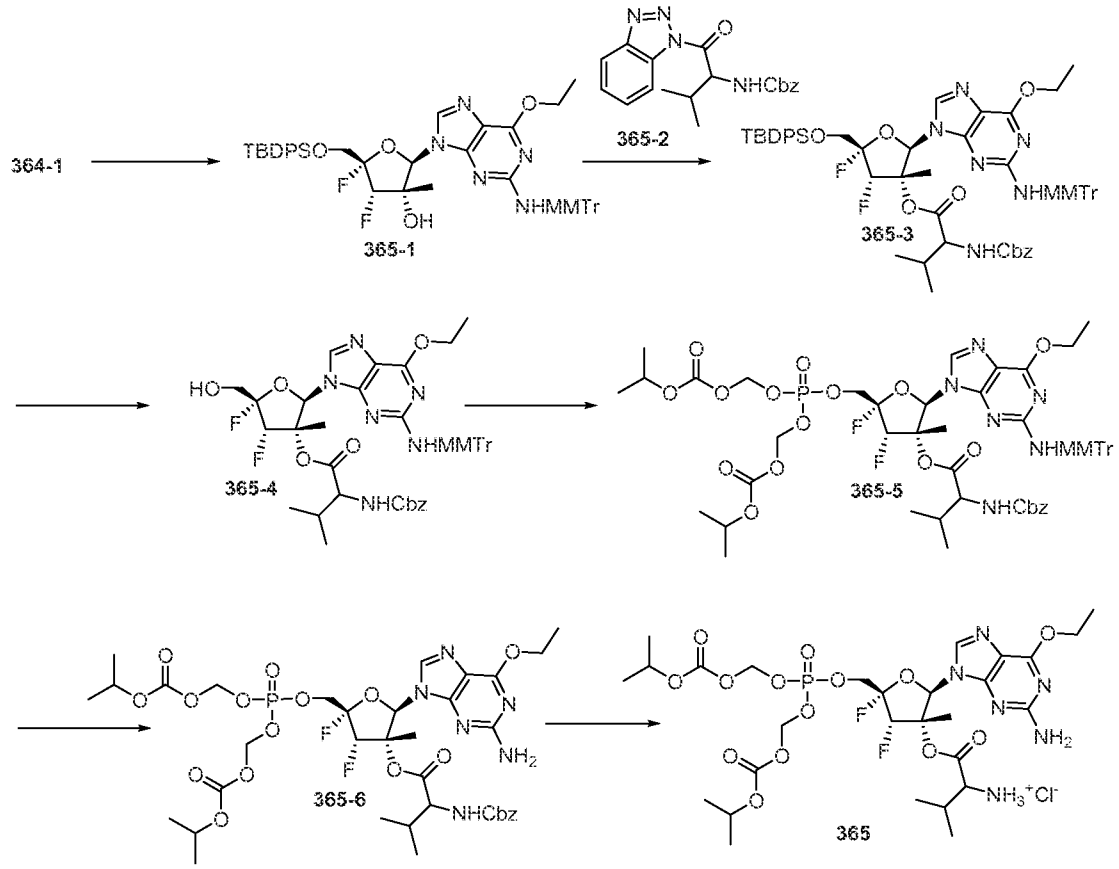
EXAMPLE 198
COMPOUND 364



364-1 **364**

[1126] **364-1** (50 mg, 0.081 mmol) was dissolved in anhydrous CH_3CN (1.0 mL), and 4N HCl in dioxane (81 µL, 0.32 mmol) was added at 0 to 5 °C. The mixture was stirred at RT for 1 h. The solvents were evaporated at RT and co-evaporated with toluene (3x). The residue was purified on silica gel column using 15- 30 % EA:DCM to give **364** (25.6 mg, 92 %) as a white solid after evaporation. ESI-LCMS: m/z = 346.05 $[M+H]^+$

EXAMPLE 199
COMPOUND 365



[1127] To a stirred solution of **364-1** (300 mg, 0.49 mmol) in anhydrous pyridine (3.0 mL) were added TBDPSCl (0.27 mL, 0.97 mmol) and DMAP (119 mg, 0.97 mmol) at 0 ^{0}C (ice/water bath). The solution was stirred at RT for 16 h. The mixture was cooled to 0 to 5 ^{0}C. The reaction was quenched with EtOH (0.3 mL), diluted with EA (100 mL). Water (50 mL) was added to the mixture. The solution was washed with sat. aq. $NaHCO_3$ and brine, and dried with $MgSO_4$. The residue was purified on silica with EA:hexanes (10-100% gradient) to give **365-1** (386 mg, 93 %) as an off white foam.

[1128] To a stirred solution of **365-1** (300 mg, 0.49 mmol) in anhydrous CH_3CN (4.0 mL) were added **365-2** (331.0 mg, 0.94 mmol, was prepared according to procedure described in Katritzky et al., *Synthesis* (2004) 2004(16):2645-2652), DIPEA (0.17 mL, 0.94 mmol) and DMAP (115 mg, 0.94 mmol). The solution was stirred at 70 $^{\circ}$C for 16 h. The mixture was cooled to 0 to 5 ^{0}C, diluted with EA (100 mL) and then water (50 mL) was added. The solution was washed with sat. aq. $NaHCO_3$ and brine, and dried with $MgSO_4$.

The residue was purified on silica with EA:hexanes (10-100% gradient) to give **365-3** (174 mg, 70 %) as a yellow foam.

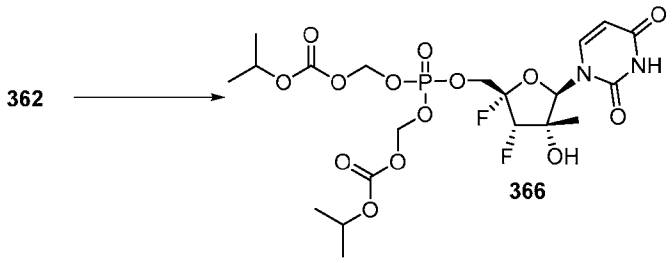
[1129] To a solution of **365-3** (166 mg, 0.153 mmol) in THF (2 mL), was added 3TEA•HF (98 µL, 0.61 mmol) and TEA (66 µl, 0.46 mmol) at ice bath temperature. The mixture was stirred for 18 h at RT. The mixture was diluted with EA and washed with water and brine. The organic layer was dried and concentrated to give the crude product, which was purified by silica gel column chromatography EA:hexanes (20-100% gradient) to give **365-4** (106 mg, 81.5%) as a white foam.

[1130] To a solution of triethylammonium bis (POC) phosphate (0.36 mmol, prepared from 118 mg of bis (POC) phosphate and 0.5 mL of TEA) in THF (3 mL) was added **365-4** (102 mg, 0.12 mmol) followed by 3-nitro-1,2,4-triazole (48 mg, 0.42 mmol), diisopropylethyl amine (0.11 mL, 0.6 mmol) and BOP-Cl (107 mg, 0.42 mmol) at 0 to 5 °C (ice water bath). The mixture was stirred at 2 h, diluted with EtOAc and washed with water and brine. The organic layer was separated, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated in vacuum to give a white solid, which was purified on silica gel column (EA:hexanes 5 to 60%) to give **365-5** as a light yellow foam (106 mg, 78 %).

[1131] **365-5** (102 mg, 0.088 mmol) was dissolved in_anhydrous CH_3CN (0.7 mL), and 4N HCl in dioxane (55 µL, 0.22 mmol) was added at 0 to 5 °C. The mixture was stirred at RT for 1 h, and then anhydrous EtOH (100 µL) was added. The solvents were evaporated at RT and co-evaporated with toluene (3x). The product was purified on silica gel column (EA:hexanes 15 to 100%) to give **365-6** as a white foam (60.3 mg, 77 %)

[1132] **365-6** (40 mg, 0.044 mmol) was dissolved in_anhydrous EtOH (1.3 mL), degassed (3x), flushed H_2, and then 10%Pd/C (6 mg) and 4N HCl in dioxane (22 µL, 0.089 mmol) were added. The mixture was stirred under H_2 atmosphere at RT for 2 h. The mixture was filtered through celite, and the celite was washed with anhydrous EtOH (1.5 mL). The solvents were evaporated, and triturated with anhydrous diethyl ether (3 X 1.5 mL). The ether layer was decanted, and the solid obtained was dried in high vacuum to give **365** (26.8 mg, 79.7%, hydrochloride salt) as a white solid. ESI-LCMS: m/z = 757.2 $[M+H]^+$.

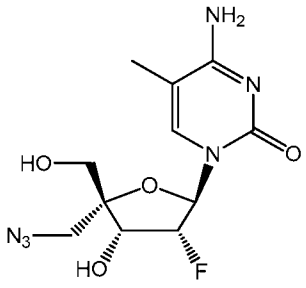
EXAMPLE 200
COMPOUND 366

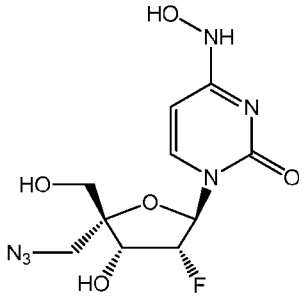


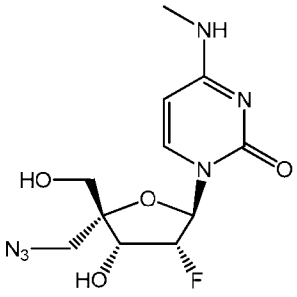
[1133] **366** was prepared according to the procedure described for **365-5** starting from **362** (36.5 mg, 0.13 mmol) and a solution of triethylammonium bis (POC) phosphate (0.26 mmol, prepared from bis (POC) phosphate (85 mg) and TEA (0.5 mL) in THF (1 mL)). ESI-LCMS: m/z = 589.0 $[M-H]^-$.

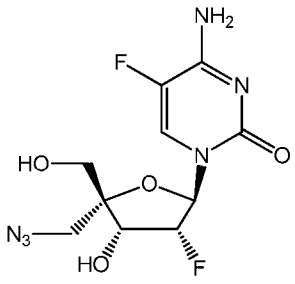
EXAMPLE 201
COMPOUNDS OF FORMULA (I)

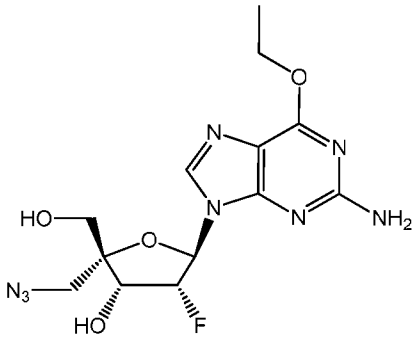
[1134] Some compounds of Formula (I) are commercially available. For some compounds, the foregoing syntheses are exemplary and can be used as a starting point to prepare additional compounds of Formula (I). Examples of additional compounds of Formula (I) are shown below. These compounds can be prepared in various ways, including those synthetic schemes shown and described herein. Those skilled in the art will be able to recognize modifications of the disclosed syntheses and to devise routes based on the disclosures herein; all such modifications and alternate routes are within the scope of the claims.

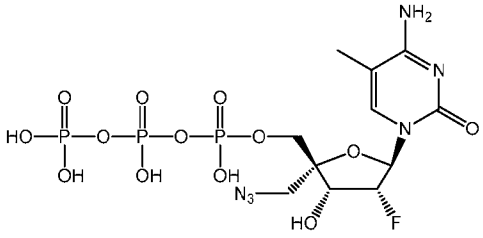

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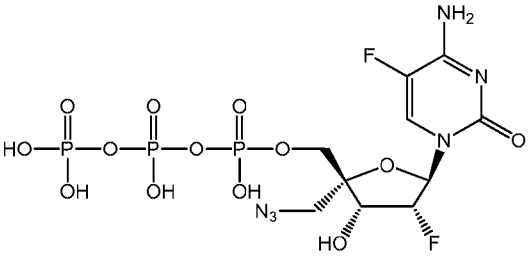

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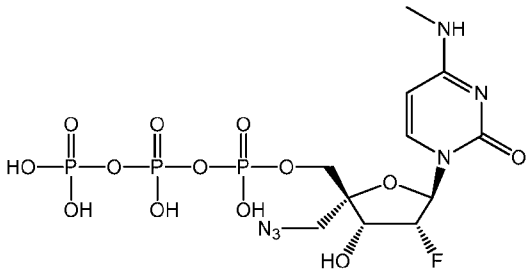

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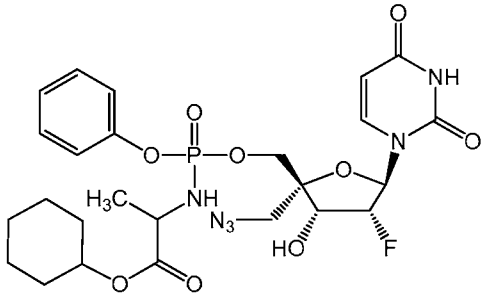

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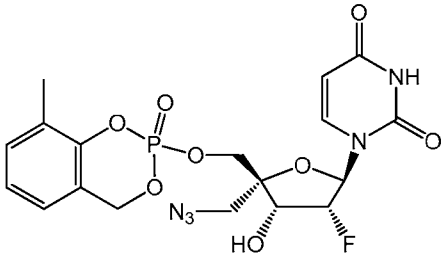

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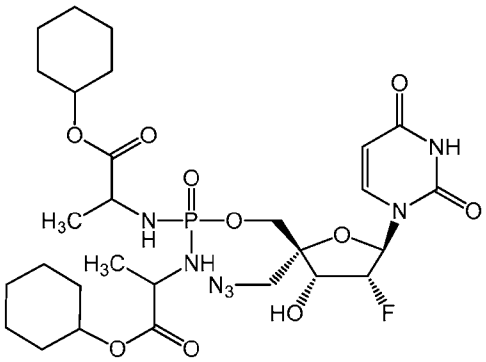

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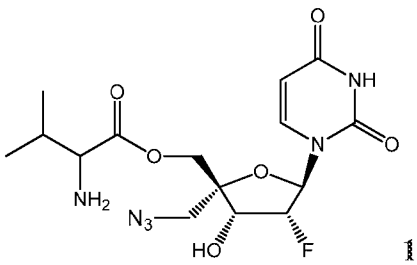

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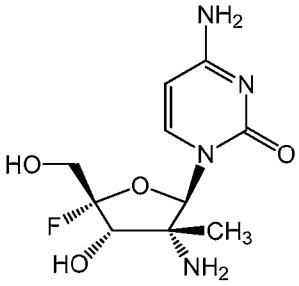

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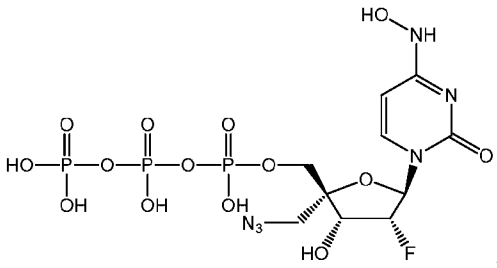

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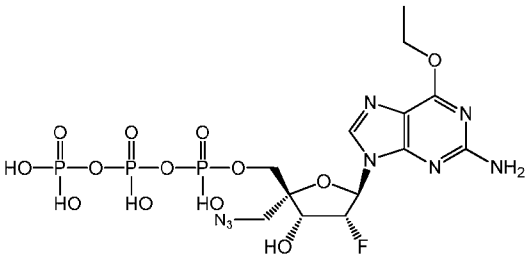

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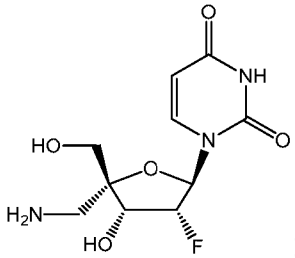

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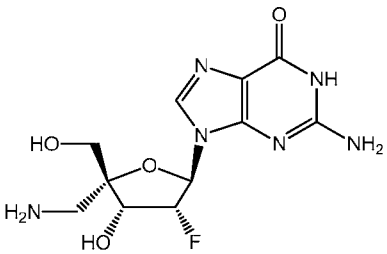

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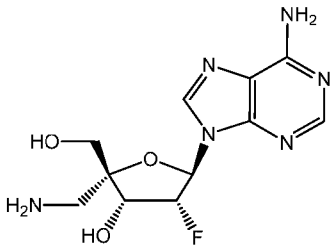

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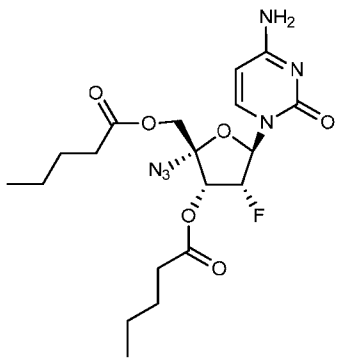

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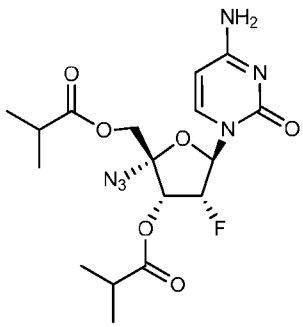

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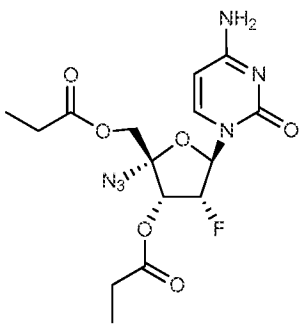

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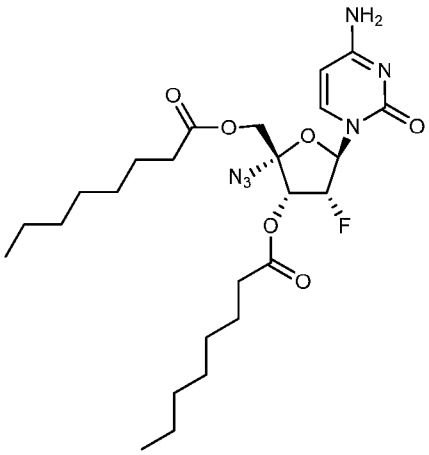

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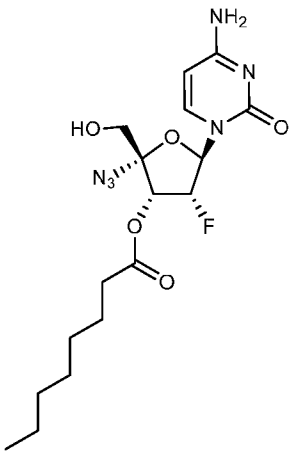

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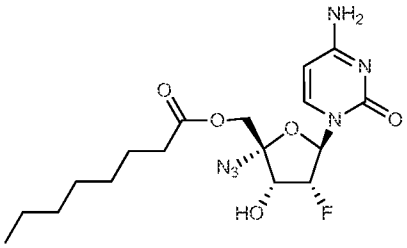

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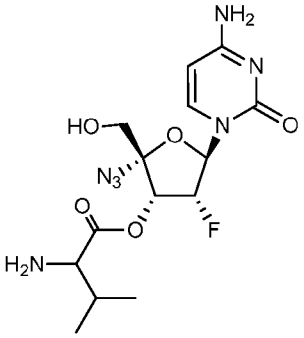
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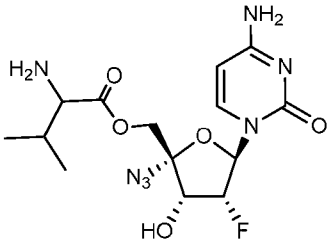
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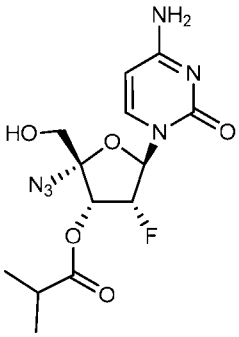
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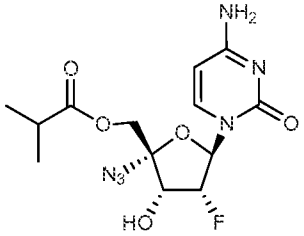
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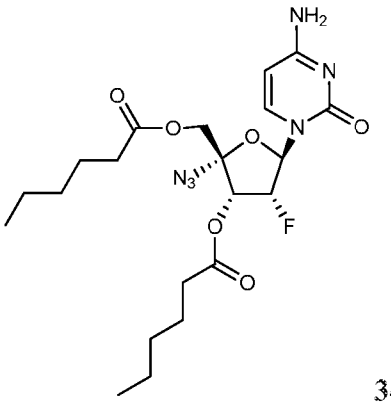
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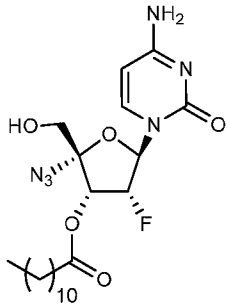
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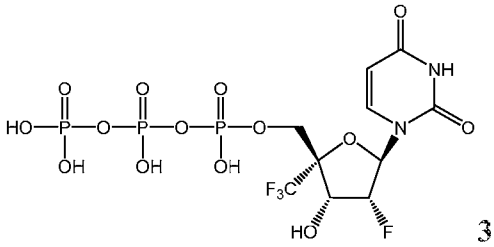
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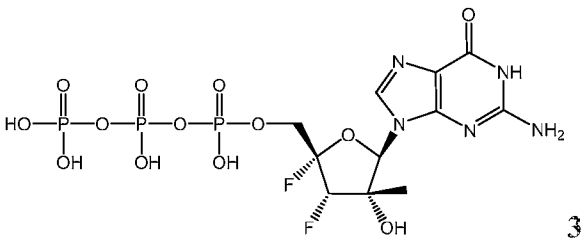
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EXAMPLE 202
FILOVIRUSES ASSAY

[1135] Compounds of Formula (I) were tested for activity against a filoviruses using methods described in Panchal et al., *J. Biomolecular Screening* (2010) 15(7):755-765. Several compounds of Formula (I) and described herein were active against a filovirus with an activity of EC_{50} < 25 μM. For example, compound 315 had an EC_{50} < 25 μM against Ebola, and compounds 106 and 332 both had an EC_{50} < 2 μM against Ebola in HeLa cells.

EXAMPLE 203
Combination Studies

[1136] Compounds were tested in combination using a recombinant Ebola virus (EBOV) Zaire engineered to express the enhanced green fluorescent protein (EBOV-eGFP) in a HeLa cell culture system. EBOV infection was performed at a multiplicity of infection (MOI) of 0.5. Compounds were tested in 10 point titrations starting at either 20 μM or 100 μM with 2-fold step dilutions. Consensus interferon (CIFN) was tested with each compound at 9 concentrations starting from a top concentration of 10 ng/mL with 3-fold step dilutions. HeLa cells were treated with CIFN 18-20 h prior to EBOV infection, and compounds were added to the cells 2 h before infection. The cells were then incubated with no compound as a control, with the test compounds, or the combination of compounds for a further 48 h. The direct effects of the combination of the test compounds were examined by fixing cells in

formalin, washing (3x) in phosphate-buffered saline and assessing the numbers of EBOV-eGFP infected cells by high content imaging. Dose-response curves were determined for individual compounds and fixed ratio combinations of the two test compounds.

[1137] MacSynergy II software was kindly provided by Dr. M. Prichard (University of Michigan). This program allows the three-dimensional examination of drug interactions of all data points generated from the checkerboard combination of two inhibitors with Bliss-Independence model. Confidence bounds are determined from replicate data. If the 95% confidence limits (CL) do not overlap the theoretic additive surface, then the interaction between the two drugs differs significantly from additive. The volumes of synergy or antagonism can be determined and graphically depicted in three dimensions and represent the relative quantity of synergism or antagonism per change in the two drug concentrations. Synergy and antagonism volumes are based on the Bliss independence model, which assumes that both compounds act independently on different targets. A set of predicted fractional responses *faAB* under the Bliss independence model is calculated as $faAB = faA + faB - faA \bullet faB$ with *faA* and *faB* representing the fraction of possible responses, e.g. % inhibition, of compounds *A* and *B* at amounts *dA* and *dB,* respectively, and describes the % inhibition of a combination of compounds *A* and *B* at amount *(dA+dB).* If $faAB > faA + faB - faA \bullet faB$ then we have Bliss synergy; if $faAB < faA + faB - faA \bullet faB$ then we have Bliss antagonism. The 95% synergy/antagonism volumes are the summation of the differences between the observed inhibition and the 95% confidence limit on the prediction of *faAB* under the Bliss independence model. MacSynergy II was used for data analysis.

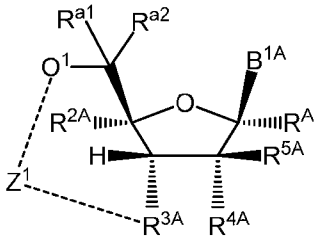
[1138] MacSynergy II Volume Descriptions: <25 $\mu M^2\%$ = Additive; 25-50 $\mu M^2\%$ = Minor synergism; 50-100 $\mu M^2\%$ = Significant synergism; and >100 $\mu M^2\%$ = Strong synergism. Combinations of Infergen® with compound 106, Infergen® with compound 315 and Infergen® with compound 332 with all showed strong synergy.

[1139] Although the foregoing has been described in some detail by way of illustrations and examples for purposes of clarity and understanding, it will be understood by those of skill in the art that numerous and various modifications can be made without departing from the spirit of the present disclosure. Therefore, it should be clearly understood that the forms disclosed herein are illustrative only and are not intended to limit the scope of

the present disclosure, but rather to also cover all modification and alternatives coming with the true scope and spirit of the invention.

WHAT IS CLAIMED IS:

1. Use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for ameliorating or treating a viral infection, wherein the compound of Formula (I) has the structure:



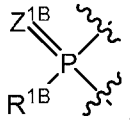
(I)

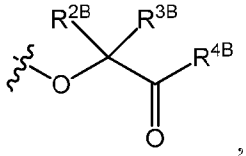
wherein:

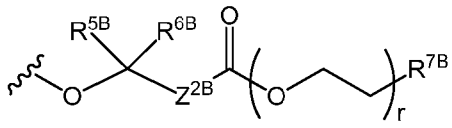
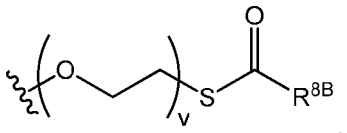
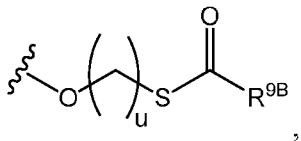
B^{1A} is an optionally substituted heterocyclic base or an optionally substituted heterocyclic base with a protected amino group;

-------- is absent or a single bond, provided that both -------- are absent or both -------- are a single bond;

when -------- are both absent, then Z^1 is absent, O^1 is OR^{1A}, R^{3A} is selected from the group consisting of hydrogen, halogen, OH, $-OC(=O)R^{"A}$ and an optionally substituted O-linked amino acid, R^{4A} is selected from the group consisting of hydrogen, OH, halogen, N_3, $-OC(=O)R^{"B}$, an optionally substituted O-linked amino acid and $NR^{"B1}R^{"B2}$, or R^{3A} and R^{4A} are both an oxygen atom connected via a carbonyl to form a 5-membered ring;

when -------- are each a single bond, then Z^1 is  , O^1 is O, R^{3A} is O; R^{4A} is selected from the group consisting of hydrogen, OH, halogen, N_3, $-OC(=O)R^{"B}$, an optionally substituted O-linked amino acid and $NR^{"B1}R^{"B2}$; and R^{1B} is selected from the group consisting of O^-, OH, an –O–optionally substituted C_{1-6} alkyl.

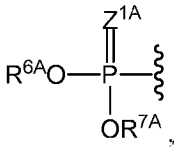
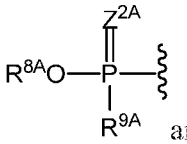
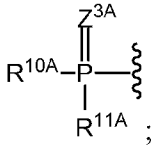


, an optionally substituted N-linked amino acid and an optionally substituted N-linked amino acid ester derivative;

R^{a1} and R^{a2} are independently hydrogen or deuterium;

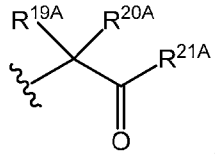
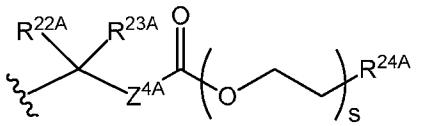
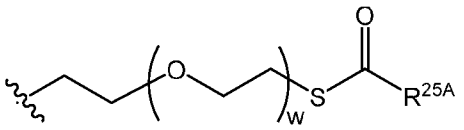
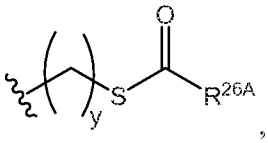
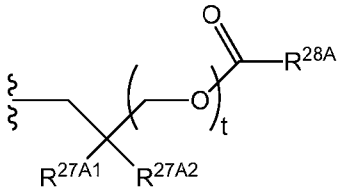
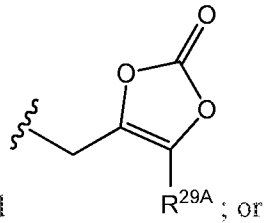
R^{A} is hydrogen, deuterium, an unsubstituted C_{1-3} alkyl, an unsubstituted C_{2-4} alkenyl, an unsubstituted C_{2-3} alkynyl or cyano;

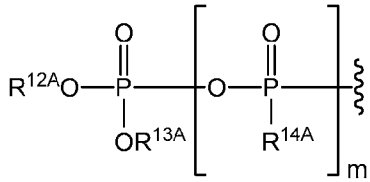
R^{1A} is selected from the group consisting of hydrogen, an optionally substituted acyl, an optionally substituted O-linked amino acid,  ,  and  ;

R^{2A} is hydrogen, azido, halogen, an unsubstituted C_{1-4} alkyl, an unsubstituted C_{2-4} alkenyl, an unsubstituted C_{2-4} alkynyl, halogen(C_{1-6}alkyl),–$(CH_2)_{1-6}N_3$,–$(CH_2)_{1-6}NH_2$, –$(CH_2)_{1-6}$ring A or –CN;

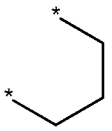
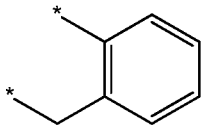
R^{5A} is selected from the group consisting of hydrogen, halogen, OH, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl and an optionally substituted C_{2-6} alkynyl;

R^{6A}, R^{7A} and R^{8A} are independently selected from the group consisting of absent, hydrogen, an optionally substituted C_{1-24} alkyl, an optionally substituted C_{2-24} alkenyl, an optionally substituted C_{2-24} alkynyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted C_{3-6} cycloalkenyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aryl(C_{1-6} alkyl), an optionally substituted *–$(CR^{15A}R^{16A})_p$–O–C_{1-24} alkyl, an optionally substituted *–

$(CR^{17A}R^{18A})_q$–O–C_{1-24} alkenyl,  ,  ,  ,  ,  and  ; or



R^{6A} is and R^{7A} is absent or hydrogen; or

R^{6A} and R^{7A} are taken together to form a moiety selected from the group consisting of an optionally substituted  and an optionally substituted  , wherein the oxygens connected to R^{6A} and R^{7A}, the phosphorus and the moiety form a six-membered to ten-membered ring system;.

R^{9A} is independently selected from the group consisting of an optionally substituted C_{1-24} alkyl, an optionally substituted C_{2-24} alkenyl, an optionally substituted C_{2-24} alkynyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted C_{3-6} cycloalkenyl, $NR^{30A}R^{31A}$, an optionally substituted N-linked amino acid and an optionally substituted N-linked amino acid ester derivative;

R^{10A} and R^{11A} are independently an optionally substituted N-linked amino acid or an optionally substituted N-linked amino acid ester derivative;

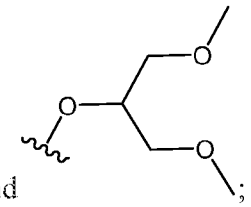
R^{12A} and R^{13A} are independently absent or hydrogen;

R^{14A} is O^-, OH or methyl;

each R^{15A}, each R^{16A}, each R^{17A} and each R^{18A} are independently hydrogen, an optionally substituted C_{1-24} alkyl or an alkoxy;

R^{19A}, R^{20A}, R^{22A}, R^{23A}, R^{2B}, R^{3B}, R^{5B} and R^{6B} are independently selected from the group consisting of hydrogen, an optionally substituted C_{1-24} alkyl and an optionally substituted aryl;

R^{21A} and R^{4B} are independently selected from the group consisting of hydrogen, an optionally substituted C_{1-24} alkyl, an optionally substituted aryl, an optionally substituted –O–C_{1-24} alkyl, an optionally substituted –O–aryl, an optionally substituted –O–heteroaryl and an optionally substituted –O–monocyclic heterocyclyl;

R^{24A} and R^{7B} are independently selected from the group consisting of hydrogen, an optionally substituted C_{1-24} alkyl, an optionally substituted aryl, an optionally substituted –O–C_{1-24} alkyl, an optionally substituted –O–aryl, an optionally substituted –O–heteroaryl, an optionally substituted –O–monocyclic heterocyclyl and  ;

R^{25A}, R^{26A}, R^{29A}, R^{8B} and R^{9B} are independently selected from the group consisting of hydrogen, an optionally substituted C_{1-24} alkyl and an optionally substituted aryl;

R^{27A1} and R^{27A2} are independently selected from the group consisting of -C≡N, an optionally substituted C_{2-8} organylcarbonyl, an optionally substituted C_{2-8} alkoxycarbonyl and an optionally substituted C_{2-8} organylaminocarbonyl;

R^{28A} is selected from the group consisting of hydrogen, an optionally substituted C_{1-24} alkyl, an optionally substituted C_{2-24} alkenyl, an optionally substituted C_{2-24} alkynyl, an optionally substituted C_{3-6} cycloalkyl and an optionally substituted C_{3-6} cycloalkenyl;

R^{30A} and R^{31A} are independently selected from the group consisting of hydrogen, an optionally substituted C_{1-24} alkyl, an optionally substituted C_{2-24} alkenyl, an optionally substituted C_{2-24} alkynyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted C_{3-6} cycloalkenyl and an optionally substituted aryl(C_{1-4} alkyl);

$R^{"A}$ and each $R^{"B}$ are independently an optionally substituted C_{1-24} alkyl;

each $R^{"B1}$ and each $R^{"B2}$ are independently hydrogen and an optionally substituted C_{1-6} alkyl;

ring A is an optionally substituted mono-cyclic heteroaryl or an optionally substituted mono-cyclic heterocyclyl;

m and w are independently 0 or 1;

p and q are independently 1, 2 or 3;

r and s are independently 0, 1, 2 or 3;

t and v are independently 1 or 2;

u and y can be independently 3, 4 or 5; and

Z^{1A}, Z^{2A}, Z^{3A}, Z^{4A}, Z^{1B} and Z^{2B} are independently O or S;

wherein the viral infection is caused by a Filoviridae virus.

2. The use of Claim 1, wherein the virus is a member of the Filoviridae family.

3. The use of Claim 2, wherein the Filoviridae virus is Ebolavirus.

4. The use of Claim 3, wherein the Ebolavirus is selected from the group consisting of Ebola virus (EBOV), Reston ebolavirus (REBOV), Sudan ebolavirus (SEBOV), Taï Forest ebolavirus (TAFV) and Bundibugyo ebolavirus (BEBOV).

5. The use of Claim 2, wherein the Filoviridae virus is Marburgvirus.

6. The use of Claim 5, wherein the Marburgvirus is selected from the group consisting of Marburg virus (MARV) and Ravn virus (RAVV).

7. The use of any one of Claims 1-6, wherein R^{2A} is halogen.

8. The use of Claim 7, wherein the halogen is fluoro.

9. The use of any one of Claims 1-6, wherein R^{2A} is an unsubstituted C_{1-4} alkyl.

10. The use of any one of Claims 1-6, wherein R^{2A} is an unsubstituted C_{2-4} alkenyl.

11. The use of any one of Claims 1-6, wherein R^{2A} is an unsubstituted C_{2-4} alkynyl.

12. The use of any one of Claims 1-6, wherein R^{2A} is halogen(C_{1-6}alkyl).

13. The use of any one of Claims 1-6, wherein R^{2A} is $-CHF_2$ or $-CF_3$.

14. The use of any one of Claims 1-6, wherein R^{2A} is $-(CH_2)_{1-6}F$.

15. The use of any one of Claims 1-6, wherein R^{2A} is $-(CH_2)_{1-6}Cl$.

16. The use of any one of Claims 1-6, wherein R^{2A} is azido.

17. The use of any one of Claims 1-6, wherein R^{2A} is $-(CH_2)_{1-6}N_3$.

18. The use of any one of Claims 1-6, wherein R^{2A} is hydrogen.

19. The use of any one of Claims 1-6, wherein R^{2A} is $-(CH_2)_{1-6}$ring A

20. The use of any one of Claims 1-6, wherein R^{2A} is –CN.

21. The use of any one of Claims 1-20, wherein R^{4A} is hydrogen.

22. The use of any one of Claims 1-20, wherein R^{4A} is OH.

23. The use of any one of Claims 1-20, wherein R^{4A} is halogen.

24. The use of Claim 23, wherein the halogen is F.

25. The use of Claim 23, wherein the halogen is Cl.

26. The use of any one of Claims 1-20, wherein R^{4A} is $-OC(=O)R^{"B}$ or an optionally substituted O-linked amino acid.

27. The use of any one of Claims 1-26, wherein R^{5A} is hydrogen.

28. The use of any one of Claims 1-26, wherein R^{5A} is halogen.

29. The use of any one of Claims 1-26, wherein R^{5A} is OH.

30. The use of any one of Claims 1-26, wherein R^{5A} is an optionally substituted C_{1-6} alkyl.

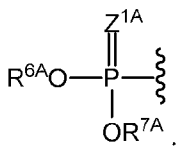
31. The use of any one of Claims 1-26, wherein R^{5A} is an optionally substituted C_{2-6} alkenyl.

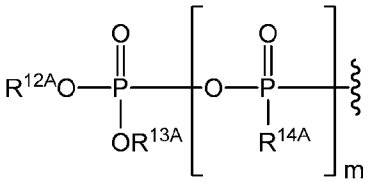
32. The use of any one of Claims 1-26, wherein R^{5A} is an optionally substituted C_{2-6} alkynyl.

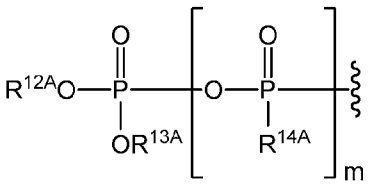
33. The use of any one of Claims 1-26, wherein -------- are both absent.

34. The use of Claim 33, wherein R^{1A} is hydrogen.

35. The use of Claim 33, wherein R^{1A} is an optionally substituted acyl or an optionally substituted O-linked amino acid.

36. The use of Claim 33, wherein R^{1A} is  .

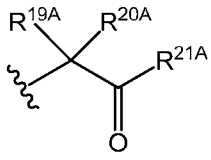
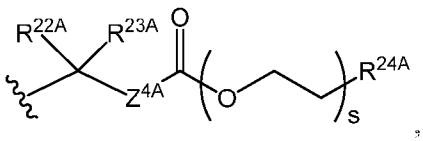
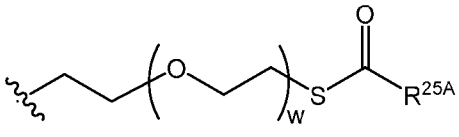
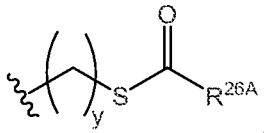
37. The use of Claim 36, wherein R^{6A} is  , R^{7A} is absent or hydrogen and m is 0.

38. The use of Claim 36, wherein R^{6A} is  , R^{7A} is absent or hydrogen and m is 1.

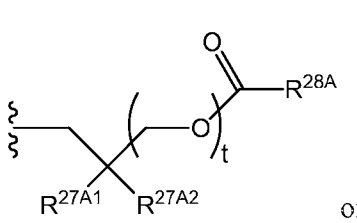
39. The use of Claim 36, wherein R^{6A} and R^{7A} are independently absent or hydrogen.

40. The use of Claim 36, wherein R^{6A} and R^{7A} are independently an optionally substituted C_{1-24} alkyl, an optionally substituted C_{2-24} alkenyl, an optionally substituted C_{2-24} alkynyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted C_{3-6} cycloalkenyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aryl(C_{1-6} alkyl).

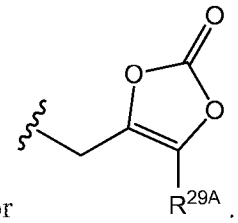
41. The use of Claim 36, wherein R^{6A} and R^{7A} are independently an optionally substituted *–$(CR^{15A}R^{16A})_p$–O–C_{1-24} alkyl or an optionally substituted *–$(CR^{17A}R^{18A})_q$–O–C_{1-24} alkenyl.

42. The use of Claim 36, wherein R^{6A} and R^{7A} are independently  ,  ,  or  .

43. The use of Claim 36, wherein R^{6A} and R^{7A} are independently

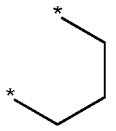


or

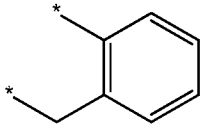


.

44. The use of Claim 36, wherein R^{6A} and R^{7A} are taken together to form a moiety selected from the group consisting of an optionally substituted



and an optionally substituted

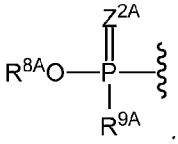


, wherein the oxygens connected to R^{6A} and R^{7A}, the phosphorus and the moiety form a six-membered to ten-membered ring system.

45. The use of any one of Claims 36-44, wherein Z^{1A} is O.

46. The use of any one of Claims 36-44, wherein Z^{1A} is S.

47. The use of Claim 33, wherein R^{1A} is



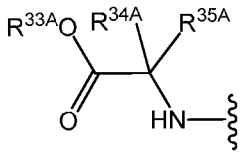
.

48. The use of Claim 47, wherein R^{8A} is an optionally substituted aryl.

49. The use of Claim 47, wherein R^{8A} is an optionally substituted heteroaryl.

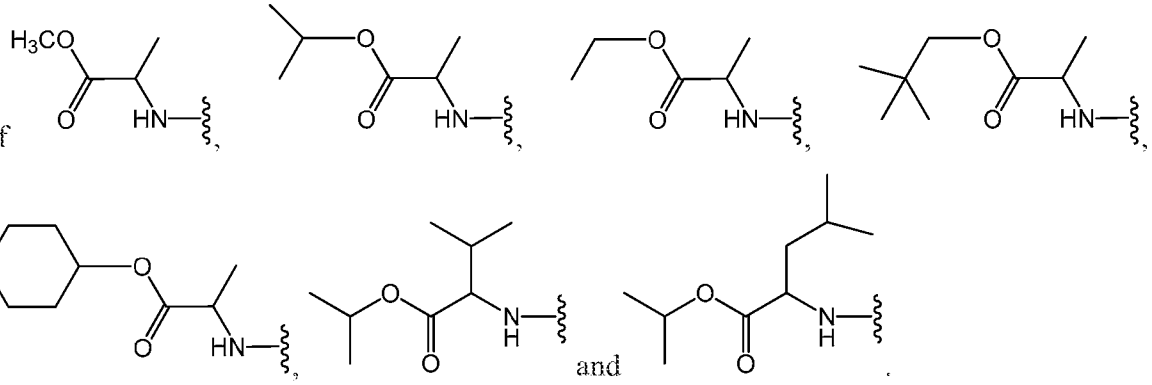
50. The use of any one of Claims 47-49, wherein R^{9A} is an optionally substituted N-linked amino acid or an optionally substituted N-linked amino acid ester derivative.

51. The use of Claim 50, wherein R^{9A} is



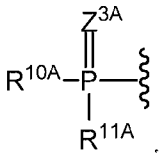
wherein R^{33A} is selected from the group consisting of hydrogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted aryl, an optionally substituted aryl(C_{1-6} alkyl) and an optionally substituted haloalkyl; R^{34A} is selected from the 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^{35A} is

hydrogen or an optionally substituted C_{1-4} alkyl; or R^{34A} and R^{35A} are taken together to form an optionally substituted C_{3-6} cycloalkyl.

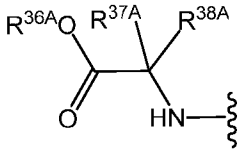
52. The use of Claim 51, wherein R^{9A} is selected from the group consisting of  , and .

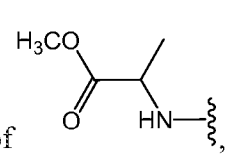
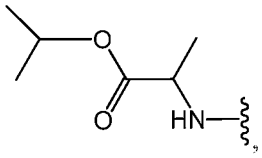
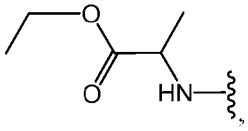
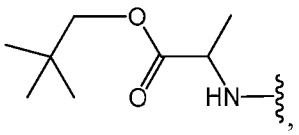
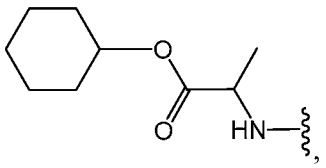
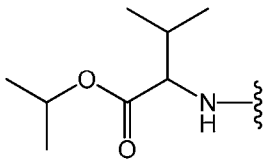
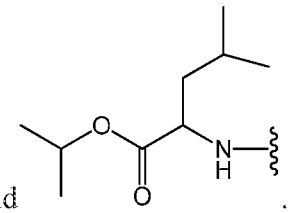
53. The use of any one of Claims 47-52, wherein Z^{2A} is O.

54. The use of any one of Claims 47-52, wherein Z^{2A} is S.

55. The use of Claim 33, wherein R^{1A} is  .

56. The use of Claim 55, wherein R^{10A} and R^{11A} are independently an optionally substituted N-linked amino acid or an optionally substituted N-linked amino acid ester derivative.

57. The compound of Claim 56, wherein R^{10A} and R^{11A} are independently  wherein R^{36A} 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^{37A} 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^{38A} is hydrogen or an optionally substituted C_{1-4} alkyl; or R^{37A} and R^{38A} are taken together to form an optionally substituted C_{3-6} cycloalkyl.

58. The use of Claim 57, wherein R^{10A} and R^{11A} are independently selected from the group consisting of       and  .

59. The use of any one of Claims 55-58, wherein Z^{3A} is O.

60. The use of any one of Claims 55-58, wherein Z^{3A} is S.

61. The use of any one of Claims 33-60, wherein R^{3A} is hydrogen.

62. The use of any one of Claims 33-60, wherein R^{3A} is halogen.

63. The use of Claim 62, wherein the halogen is fluoro.

64. The use of Claim 62, wherein the halogen is chloro.

65. The use of any one of Claims 33-60, wherein R^{3A} is OH.

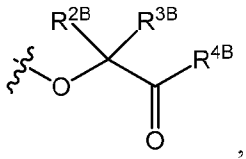
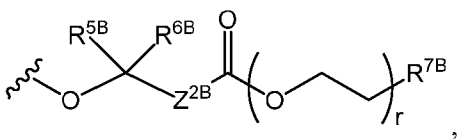
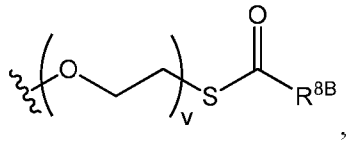
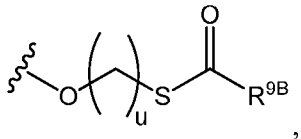
66. The use of any one of Claims 33-60, wherein R^{3A} is –OC(=O)$R^{"A}$ or an optionally substituted O-linked amino acid.

67. The use of any one of Claims 33-60, wherein R^{3A} and R^{4A} are both an oxygen atom connected via a carbonyl to form a 5-membered ring.

68. The use of any one of Claims 1-32, wherein --------- are each a single bond.

69. The use of Claim 68, wherein R^{1B} is O^- or OH.

70. The use of Claim 68, wherein R^{1B} is an –O–optionally substituted C_{1-6} alkyl.

71. The use of Claim 68, wherein R^{1B} is  ,  ,  ,  , an optionally substituted N-linked amino acid or an optionally substituted N-linked amino acid ester derivative.

72. The use of any one of Claims 1-71, wherein R^A is hydrogen.

73. The use of any one of Claims 1-71, wherein R^A is deuterium.

74. The use of any one of Claims 1-71, wherein R^A is an unsubstituted C_{1-3} alkyl.

75. The use of any one of Claims 1-71, wherein R^A is an unsubstituted C_{2-4} alkenyl.

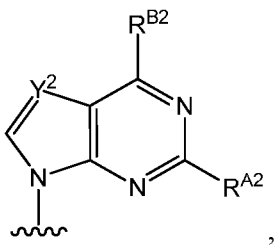
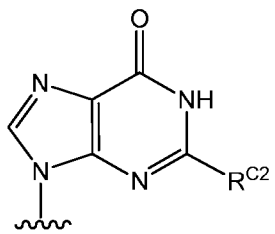
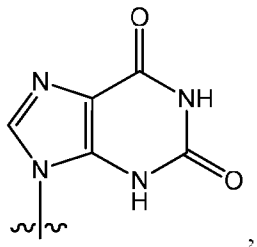
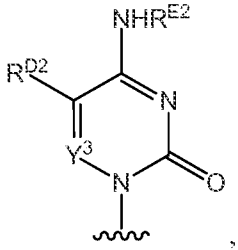
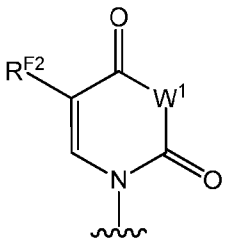
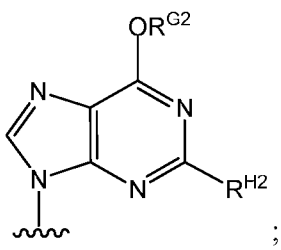
76. The use of any one of Claims 1-71, wherein R^A is an unsubstituted C_{2-3} alkynyl.

77. The use of any one of Claims 1-71, wherein R^A is cyano.

78. The use of any one of Claims 1-77, wherein R^{a1} and R^{a2} are both hydrogen.

79. The use of any one of Claims 1-77, wherein R^{a1} and R^{a2} are both deuterium.

80. The use of any one of Claims 1-79, wherein B^{1A} is selected from the group consisting of:

 ,  ,  ,  ,  and  ;

wherein:

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

R^{B2} is halogen or NHR^{W2}, wherein R^{W2} is selected from the group consisting of hydrogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{3-8} cycloalkyl, -C(=O)R^{M2} and –C(=O)OR^{N2};

R^{C2} is hydrogen or NHR^{O2}, wherein R^{O2} is selected from the group consisting of hydrogen, -C(=O)R^{P2} and –C(=O)OR^{Q2};

R^{D2} is selected from the group consisting of hydrogen, deuterium, halogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl and an optionally substituted C_{2-6} alkynyl;

R^{E2} is selected from the group consisting of hydrogen, hydroxy, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{3-8} cycloalkyl, -C(=O)R^{R2} and –C(=O)OR^{S2};

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

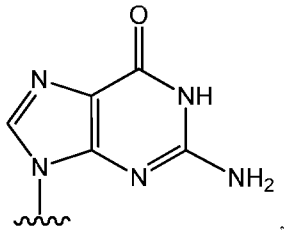
Y^2 and Y^3 are independently N or CR^{I2}, wherein R^{I2} is selected from the group consisting of hydrogen, halogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6}-alkenyl and an optionally substituted C_{2-6}-alkynyl;

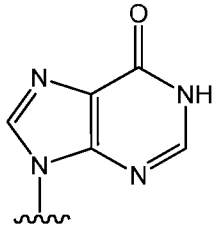
W^1 is NH, $–NCH_2$-OC(=O)CH(NH_2)-CH(CH_3)$_2$ or $–(CH_2)_{1-2}$–O-P(=O)(OW^{1A})$_2$, wherein W^{1A} is selected from the group consisting of absent, hydrogen and an optionally substituted C_{1-6} alkyl;

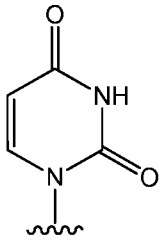
R^{G2} is an optionally substituted C_{1-6} alkyl;

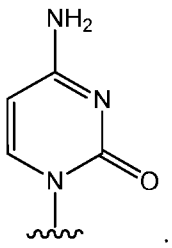
R^{H2} is hydrogen or NHR^{T2}, wherein R^{T2} is independently selected from the group consisting of hydrogen, -C(=O)R^{U2} and –C(=O)OR^{V2}; and

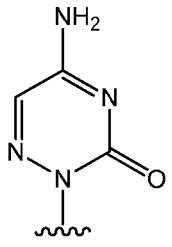
R^{K2}, R^{L2}, R^{M2}, R^{N2}, R^{P2}, R^{Q2} R^{R2}, R^{S2}, R^{U2} and R^{V2} are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkenyl, C_{6-10} aryl, heteroaryl, heterocyclyl, aryl(C_{1-6} alkyl), heteroaryl(C_{1-6}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

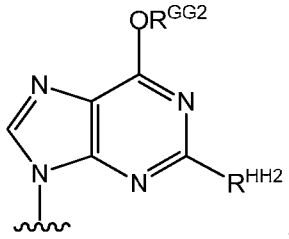
81. The use of Claim 80, wherein B^{1A} is  .

82. The use of Claim 80, wherein B^{1A} is  .

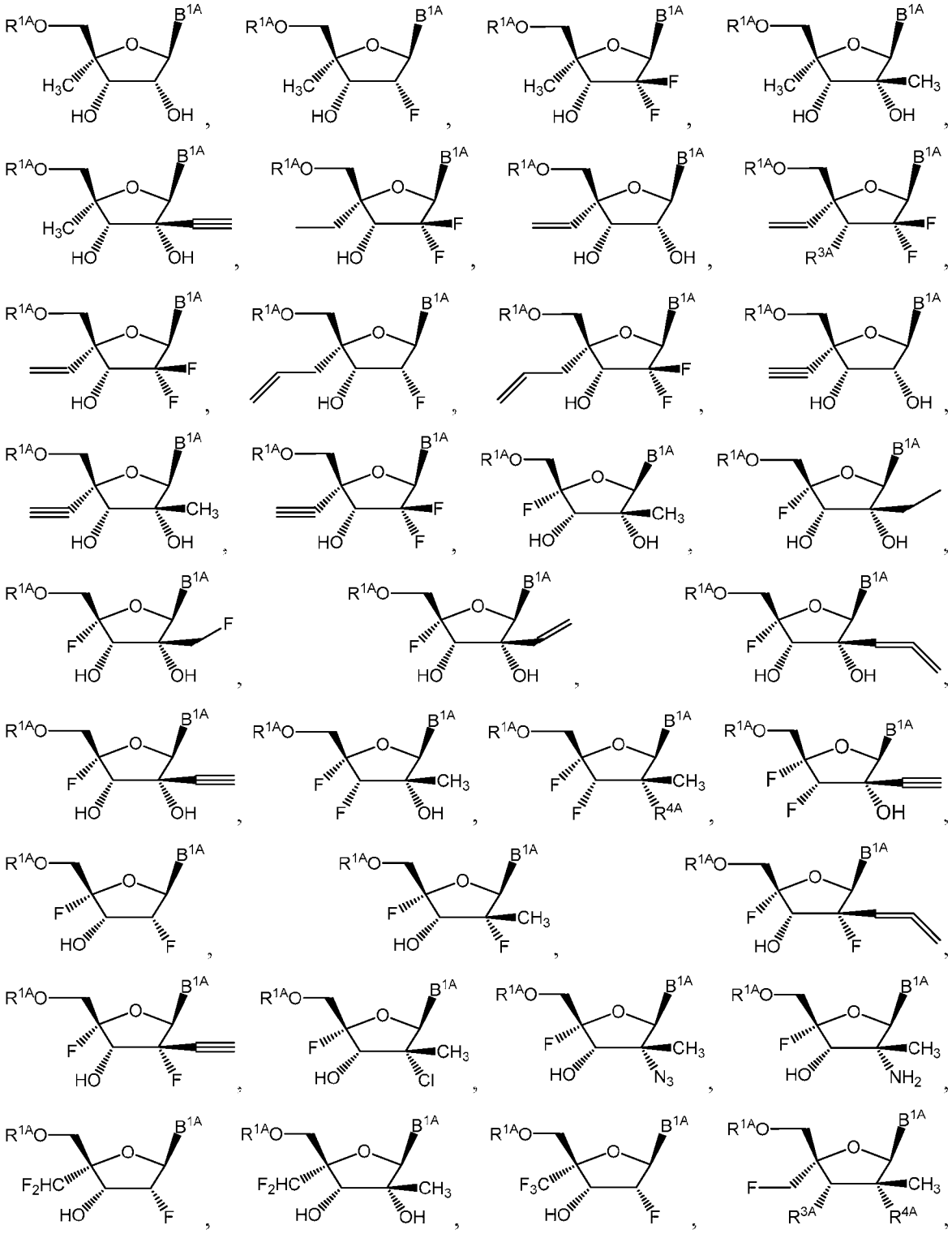
83. The use of Claim 80, wherein B^{1A} is  .

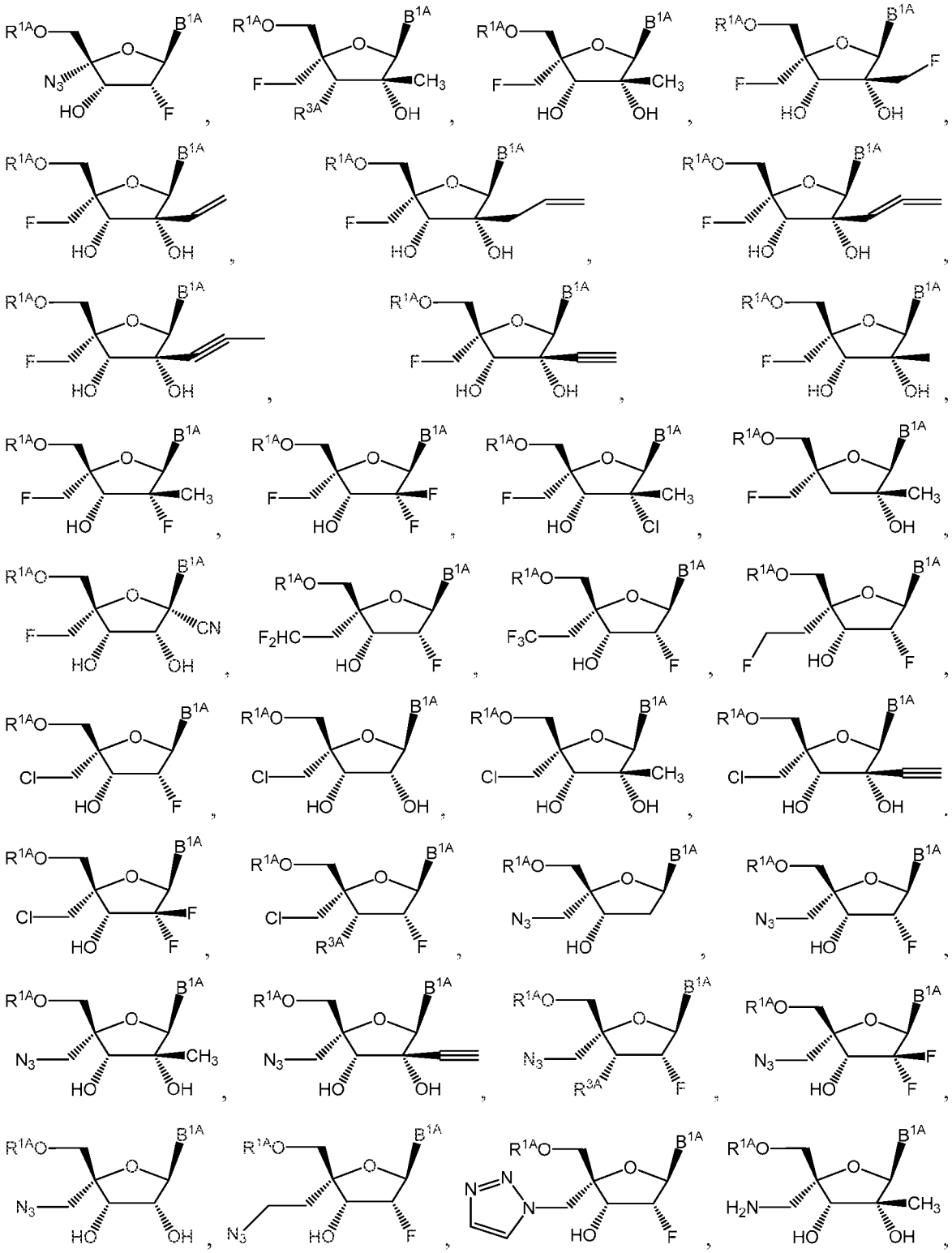
84. The use of Claim 80, wherein B^{1A} is  .

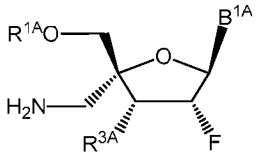
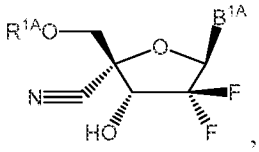
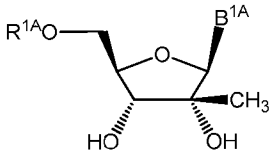
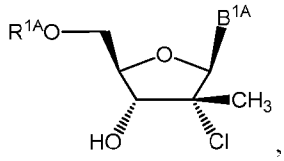
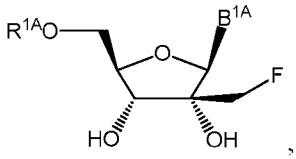
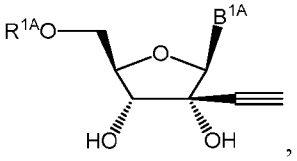
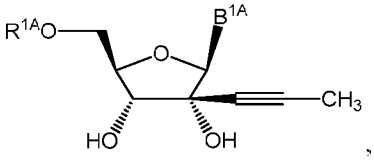
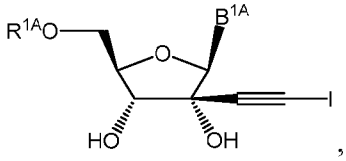
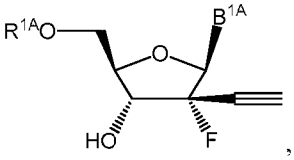
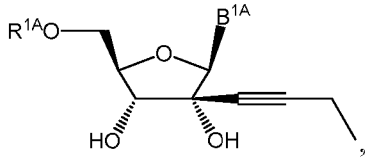
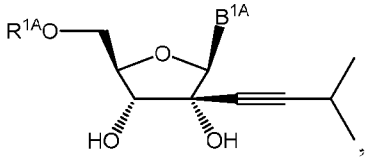
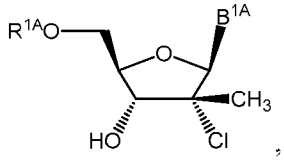
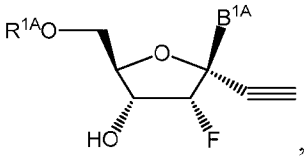
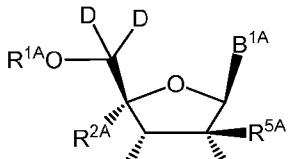
85. The use of Claim 80, wherein B^{1A} is  .

86. The use of Claim 80, wherein B^{1A} is  .

87. The use of any one of Claims 1-86, wherein the compound is selected from the group consisting of:






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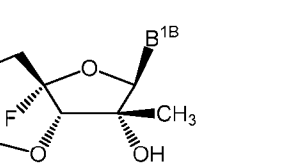
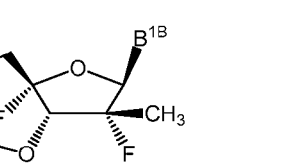
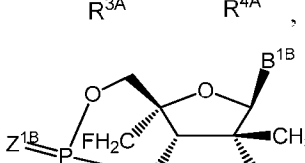
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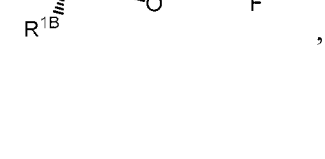
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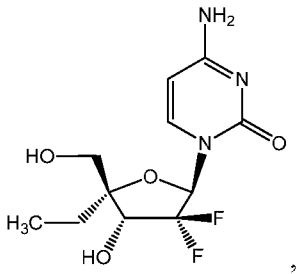
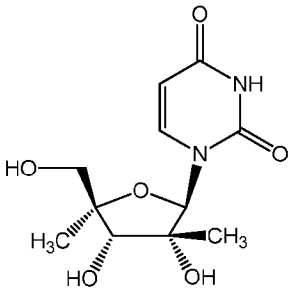
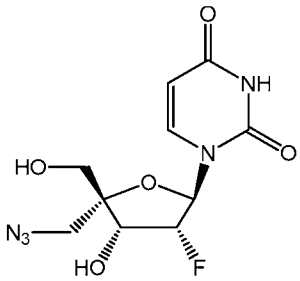
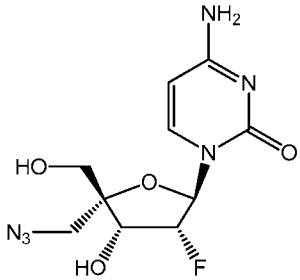
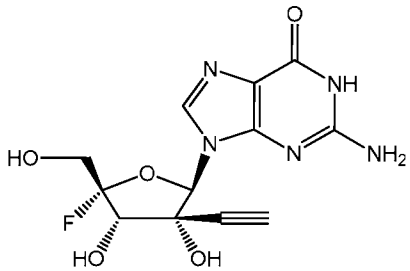
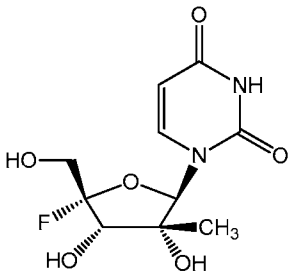
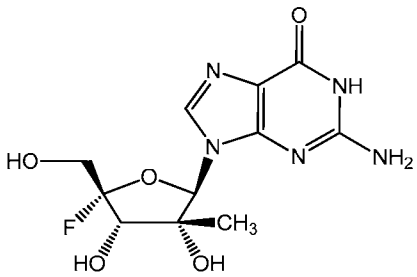
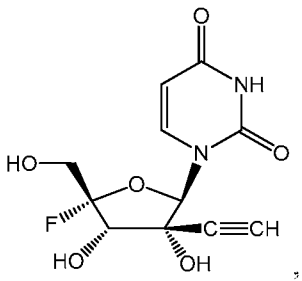
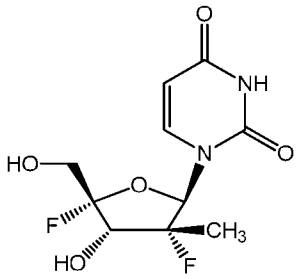
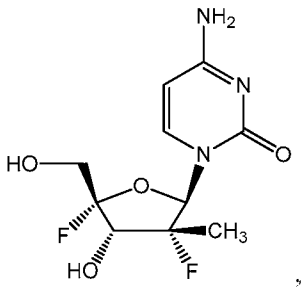
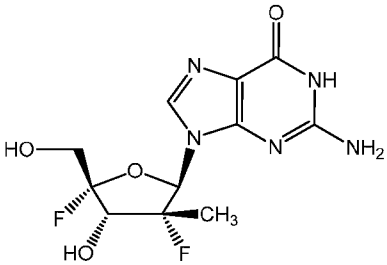
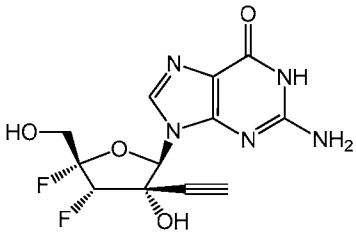
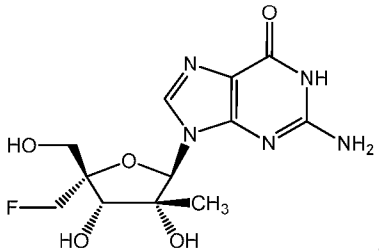
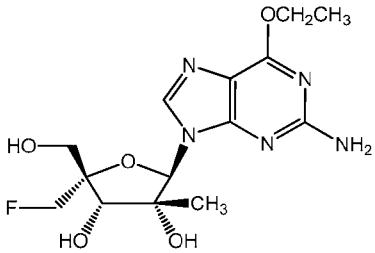
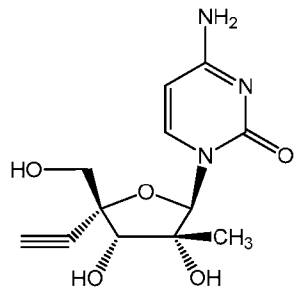
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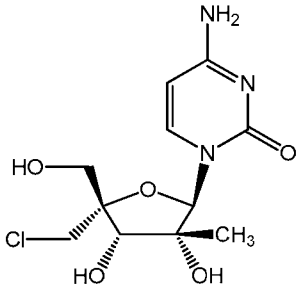
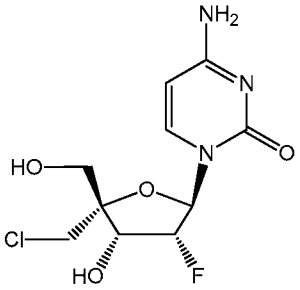
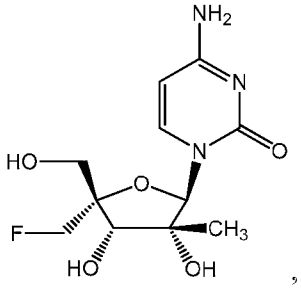
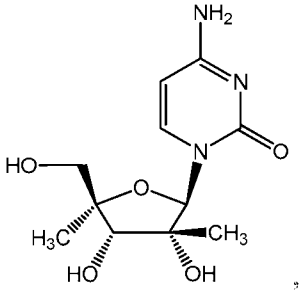
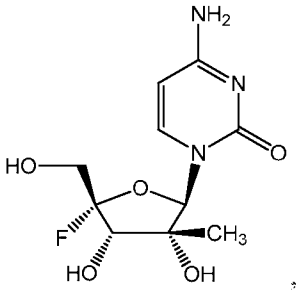
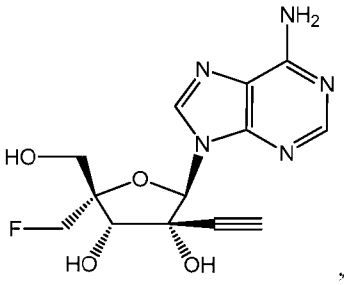
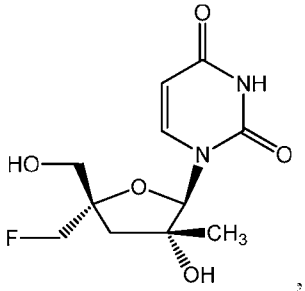
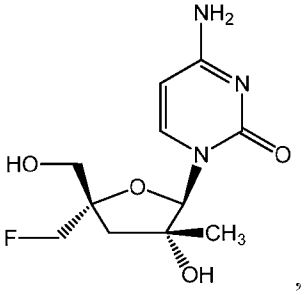
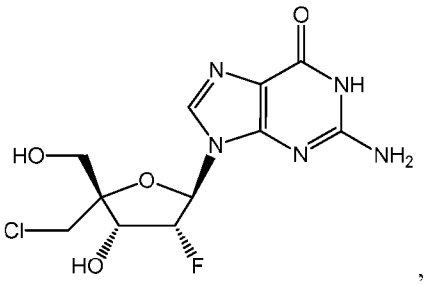
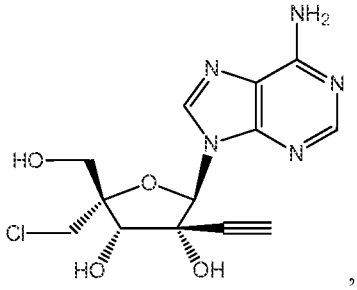
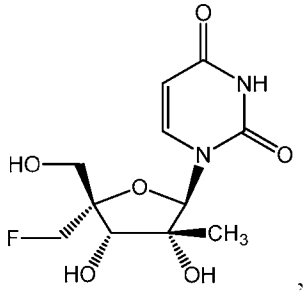
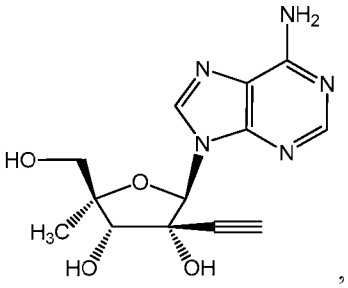
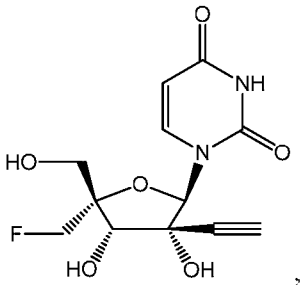
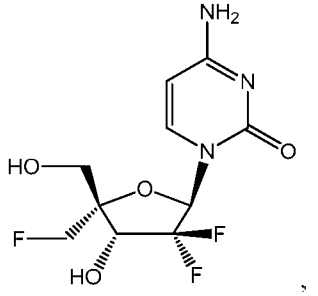
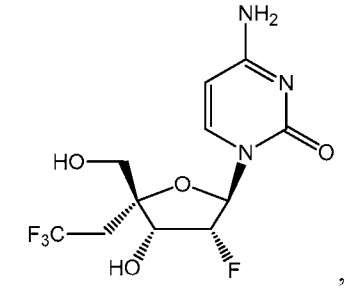
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and

, or a pharmaceutically acceptable salt of the foregoing.

88. The use of Claim 1, wherein the compound is selected from the group consisting of:

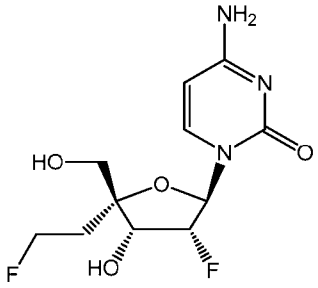
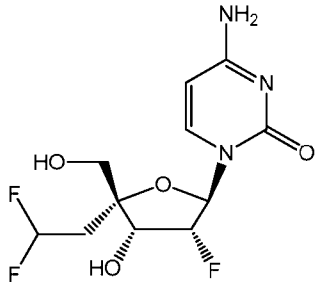
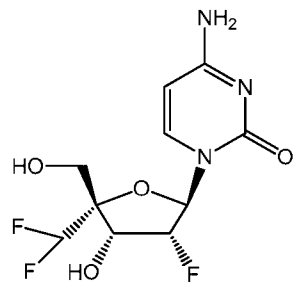
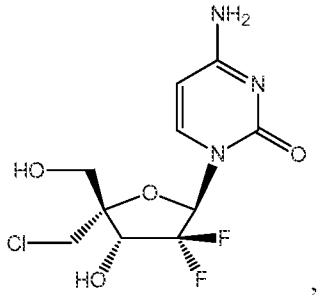
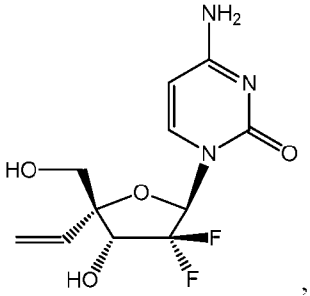
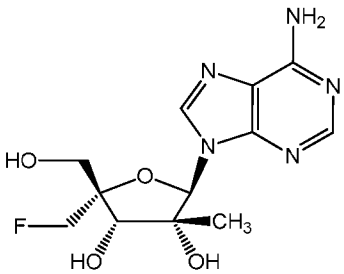
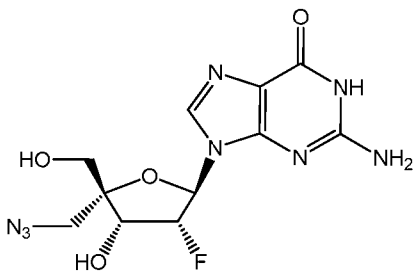
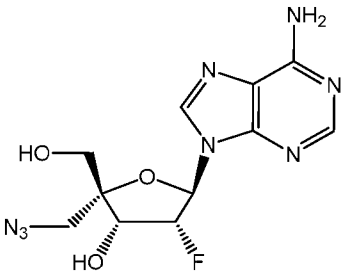
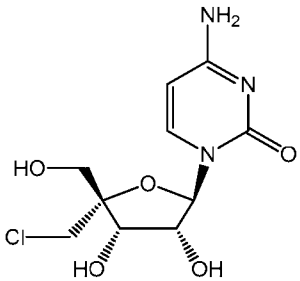
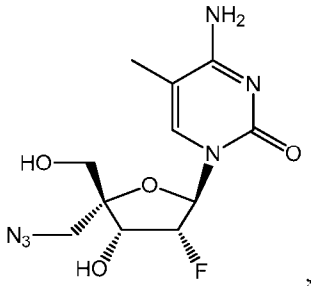
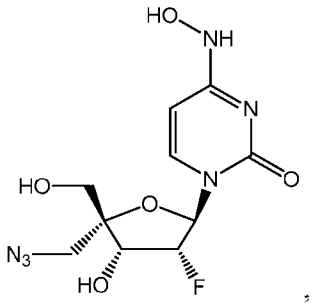
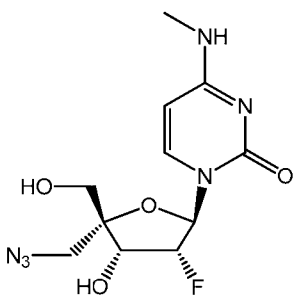
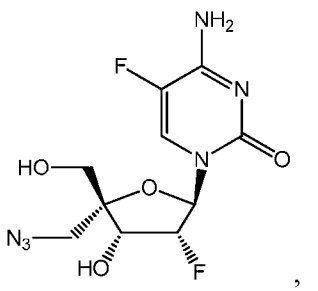
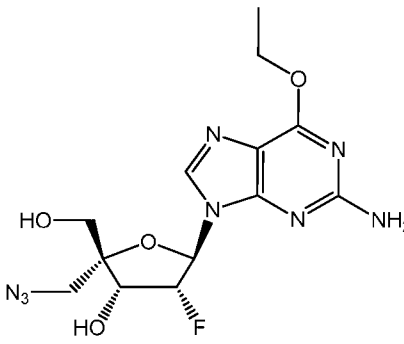
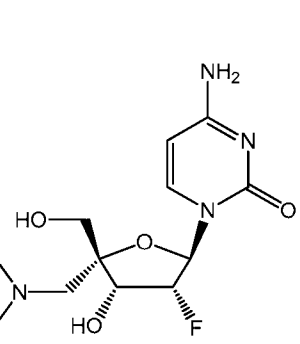

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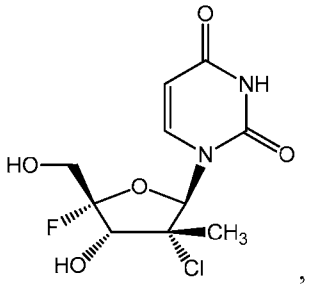
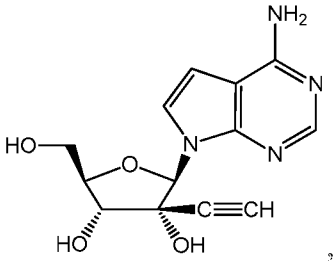
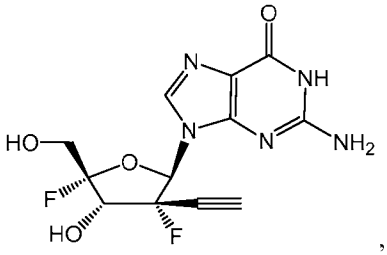
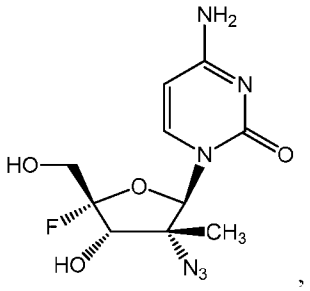
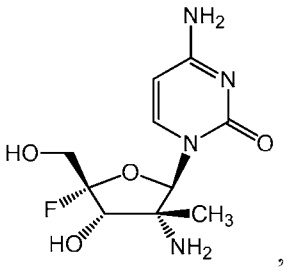
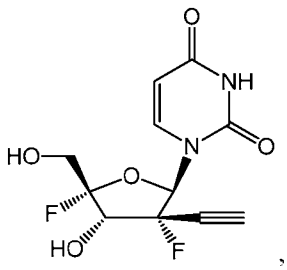
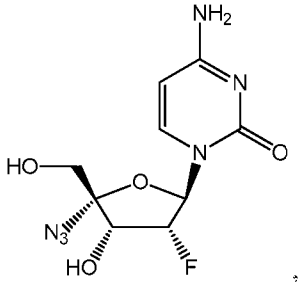
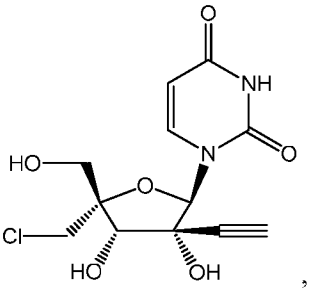
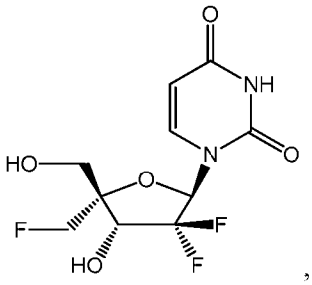
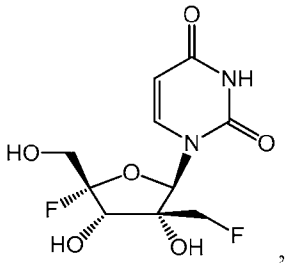
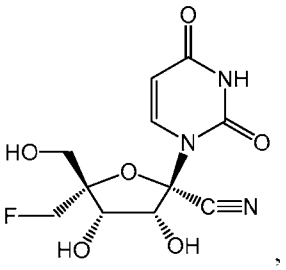
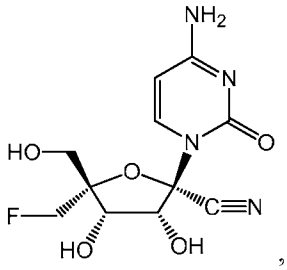
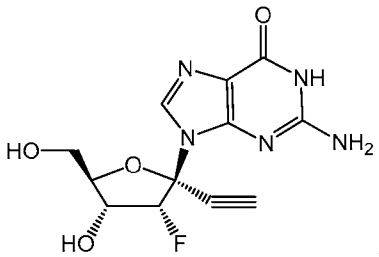
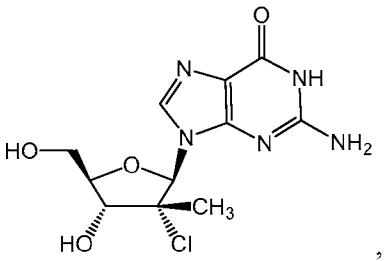
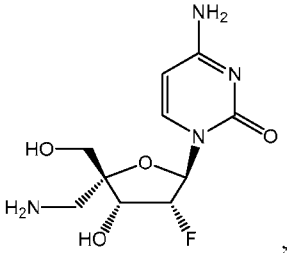
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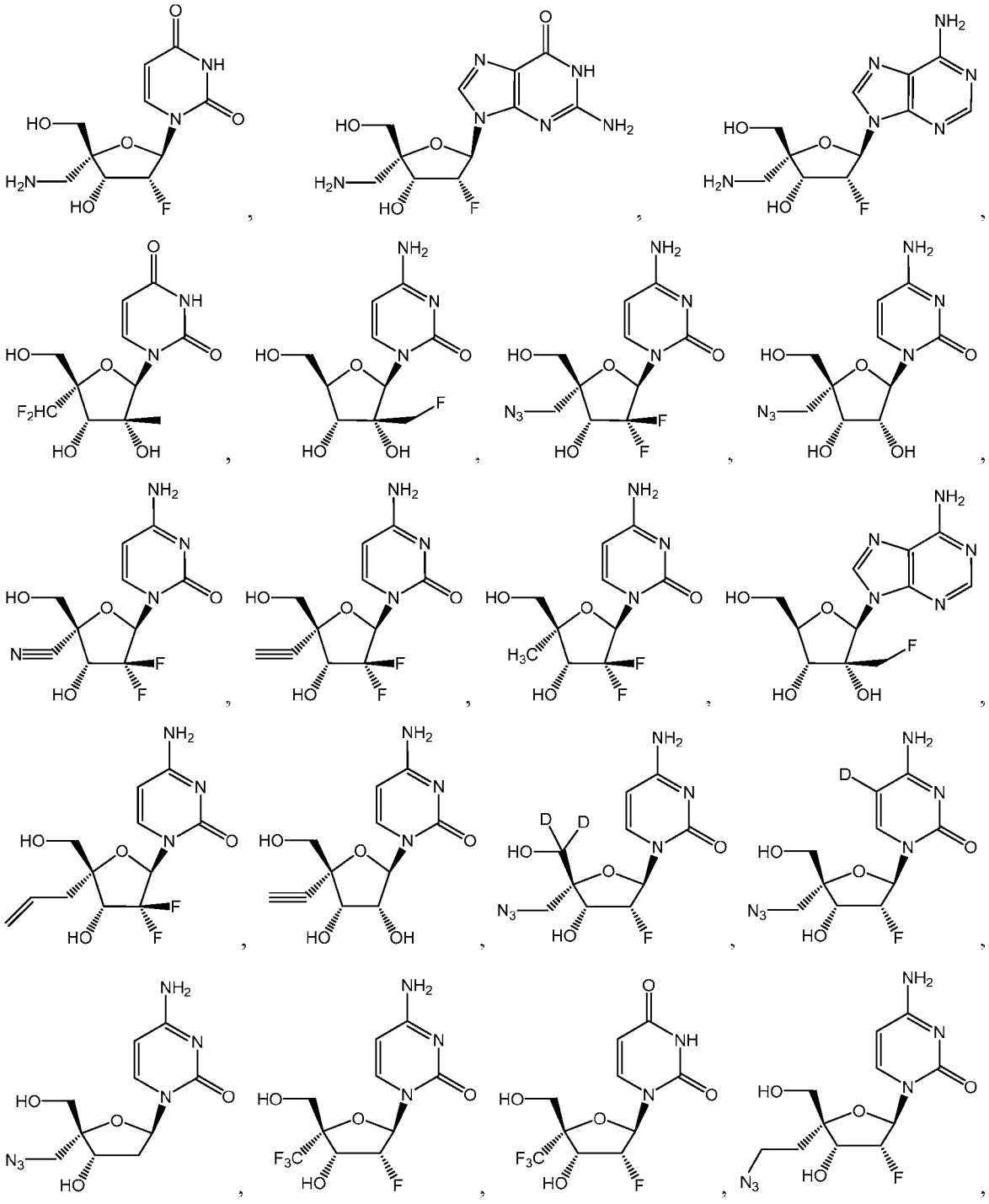
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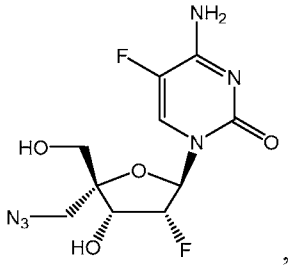
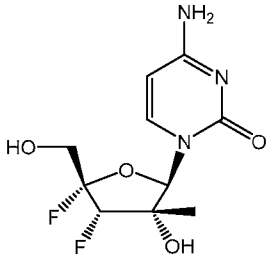
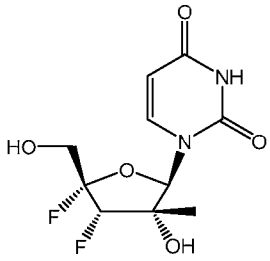
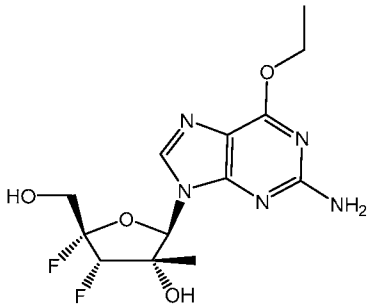
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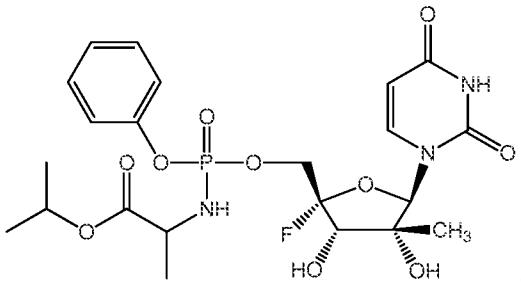
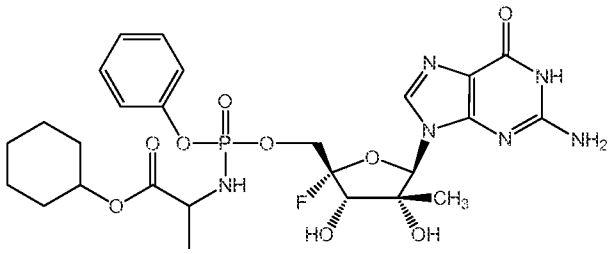
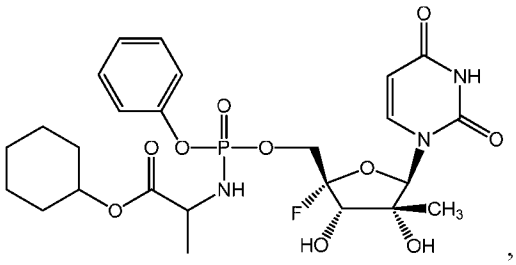
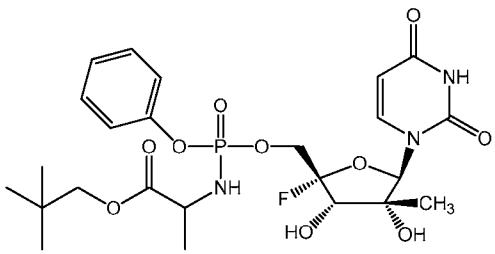
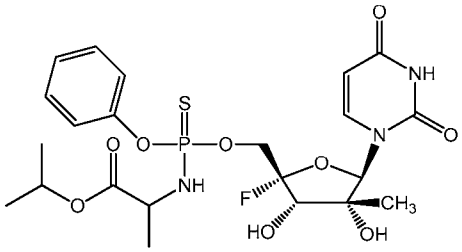
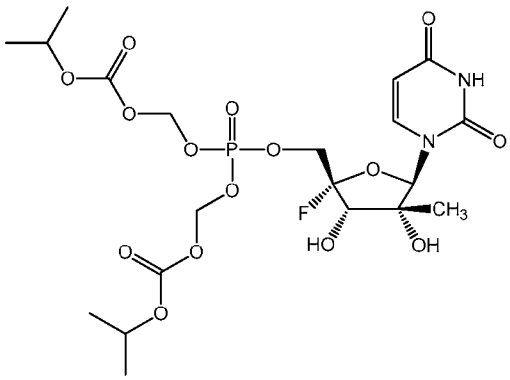
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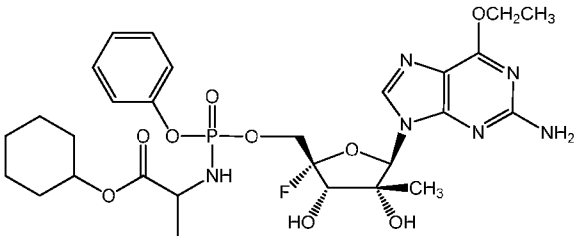
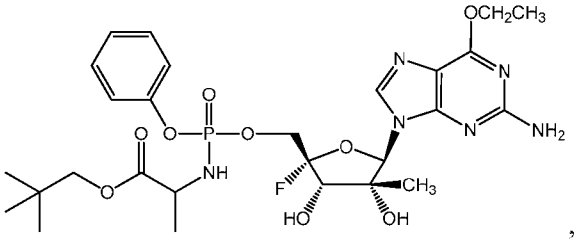
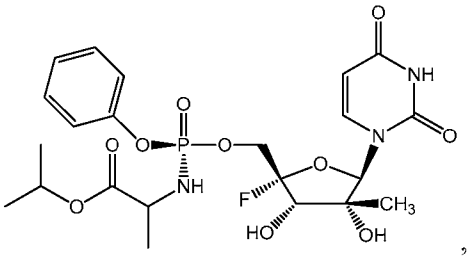
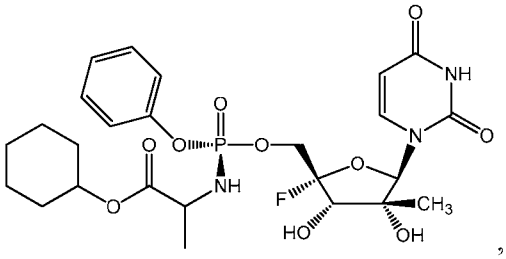
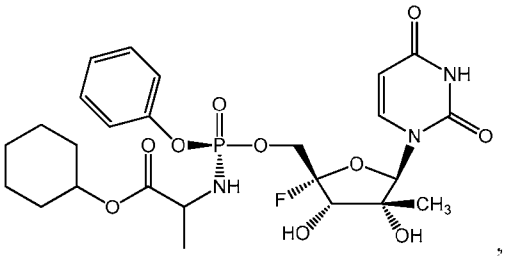
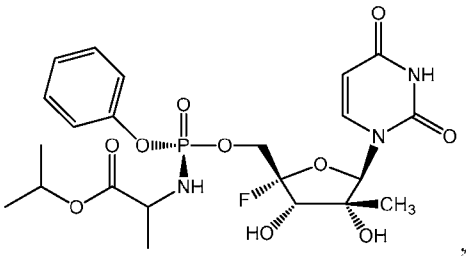
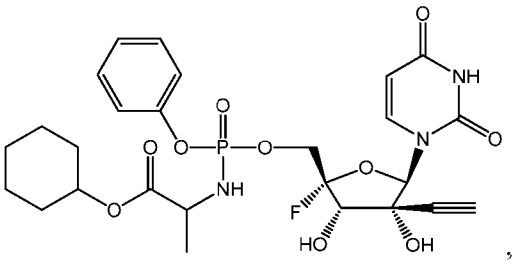
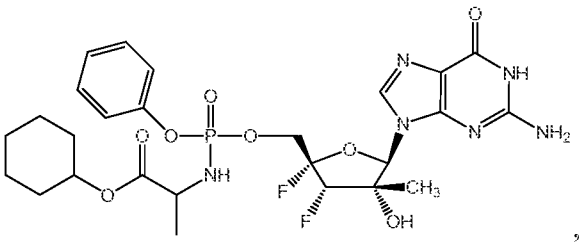
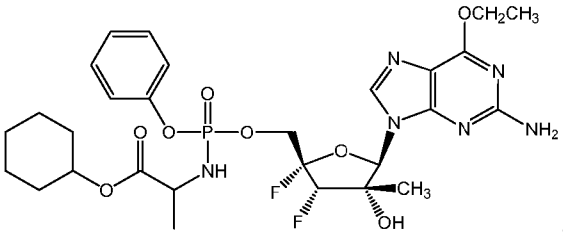
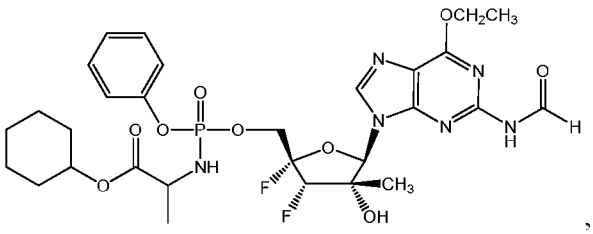
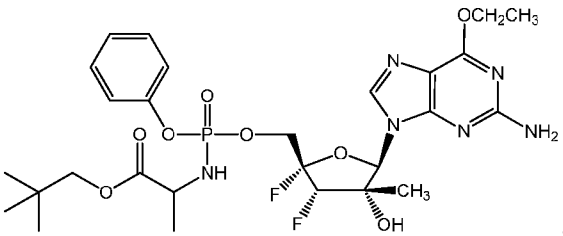

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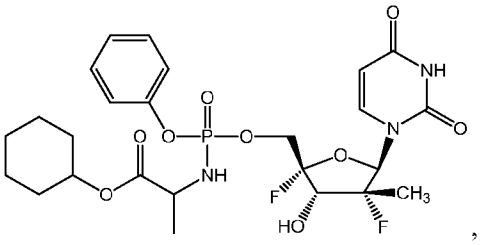
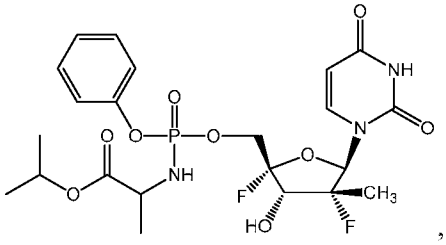
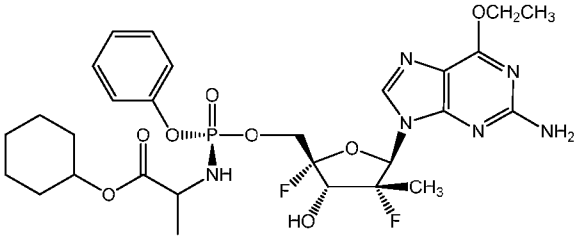
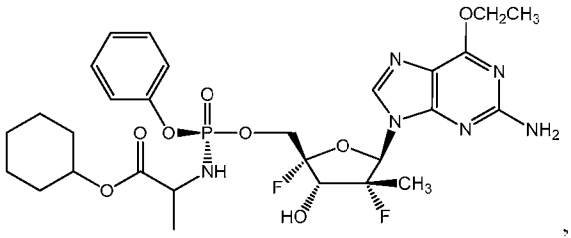
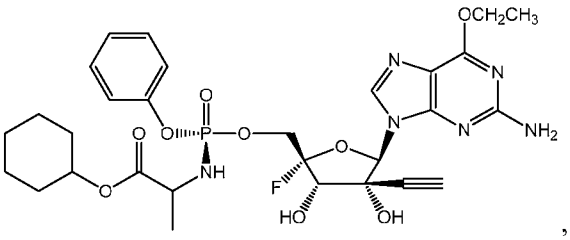
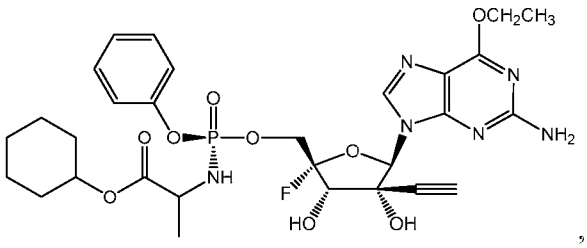
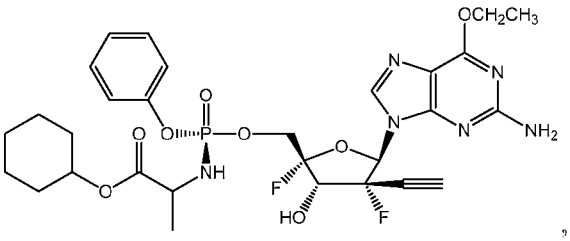
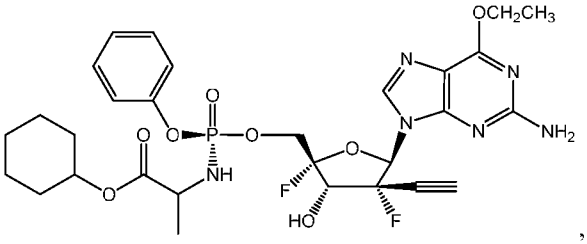
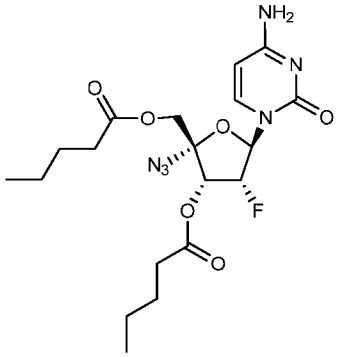
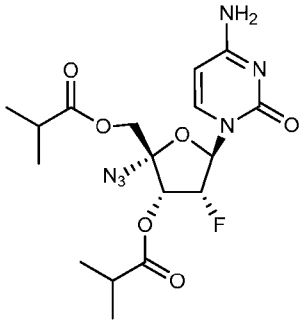
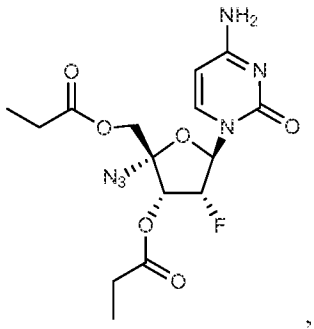


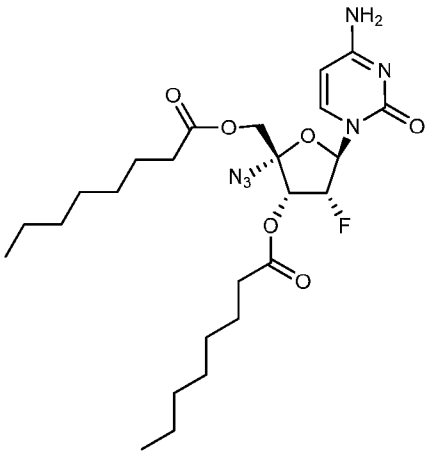

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, or a pharmaceutically acceptable salt of the foregoing.

89. The use of Claim 1, wherein the compound is selected from the group consisting of:

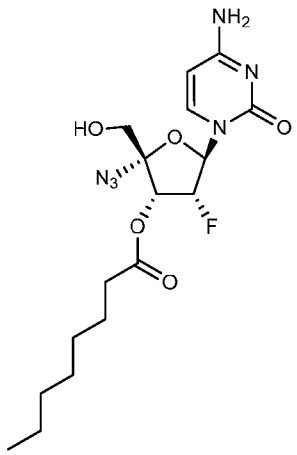

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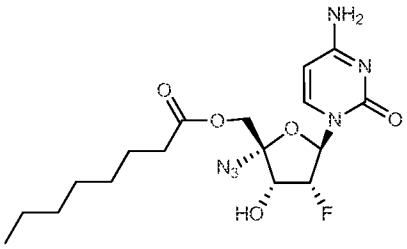

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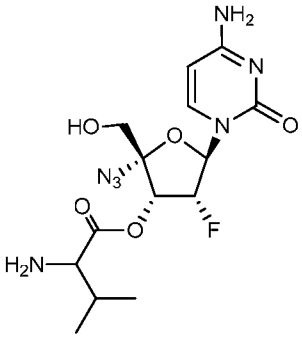
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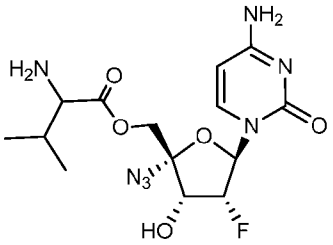
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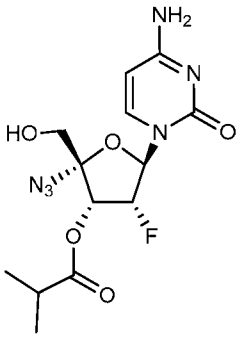
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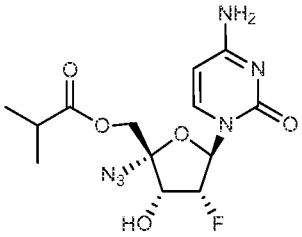
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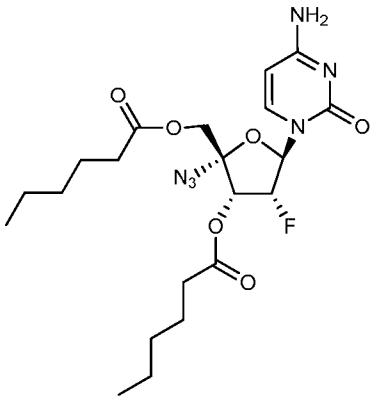
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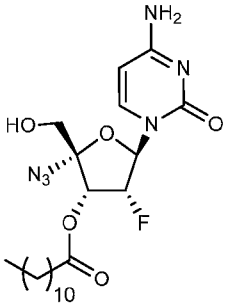
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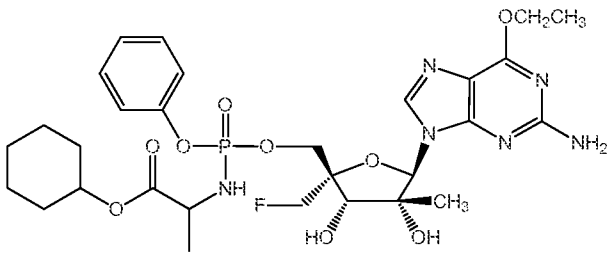
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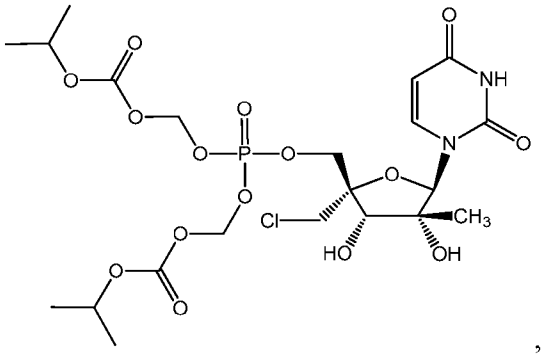
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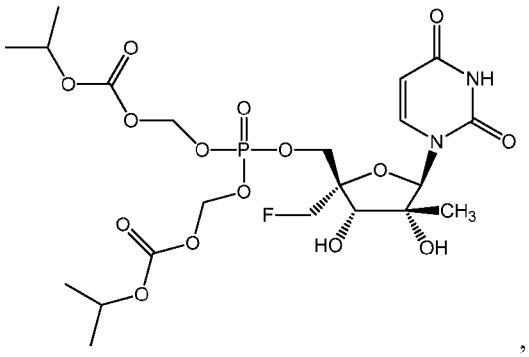


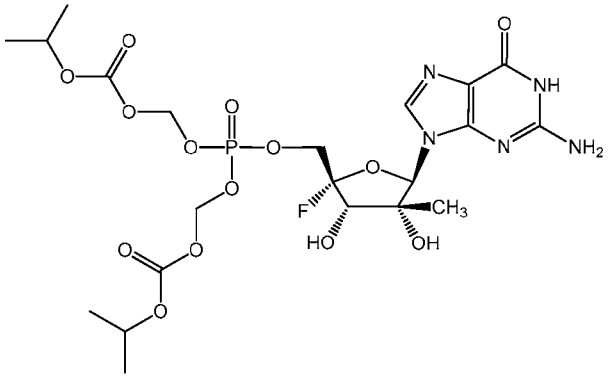
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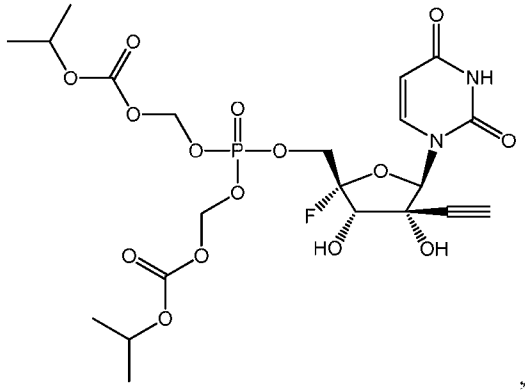


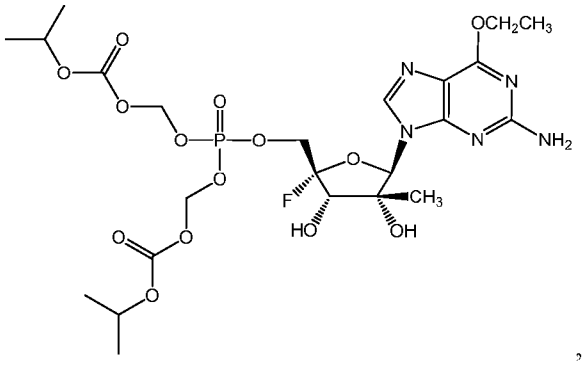
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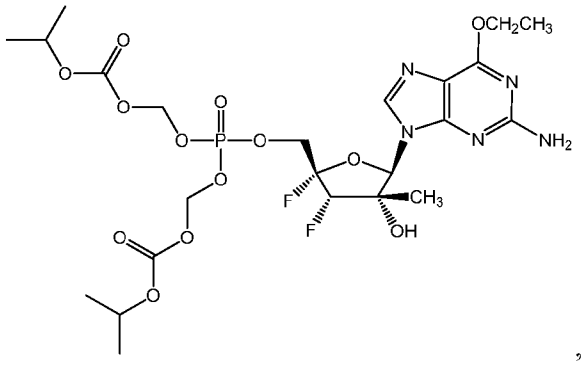


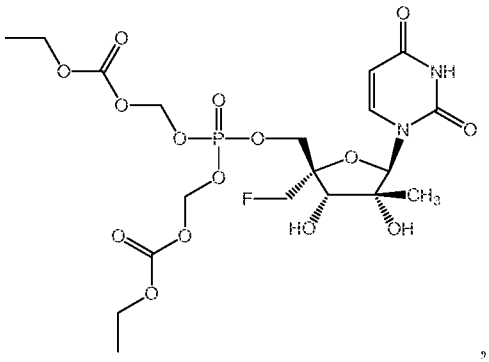


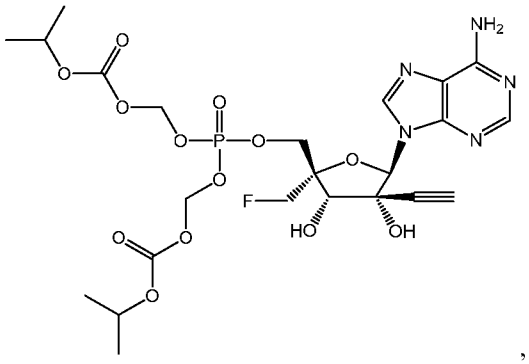


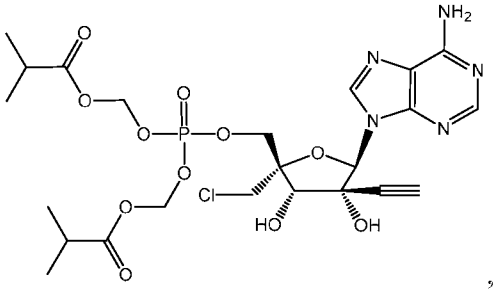




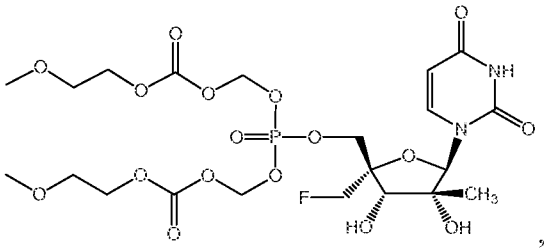




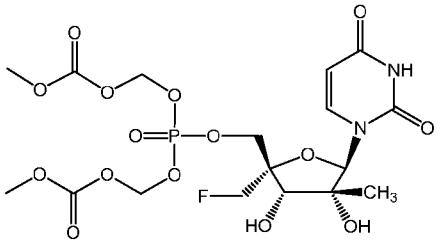




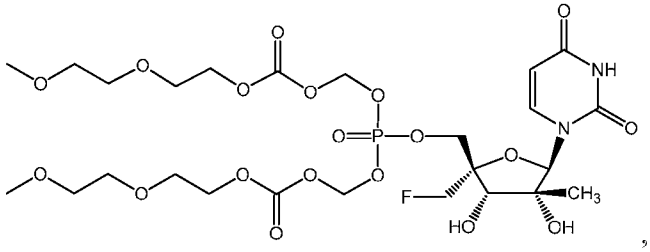
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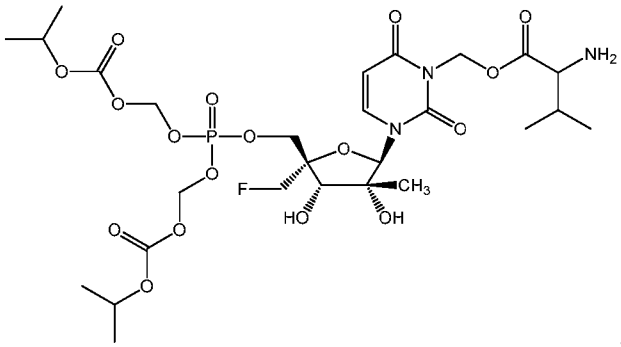
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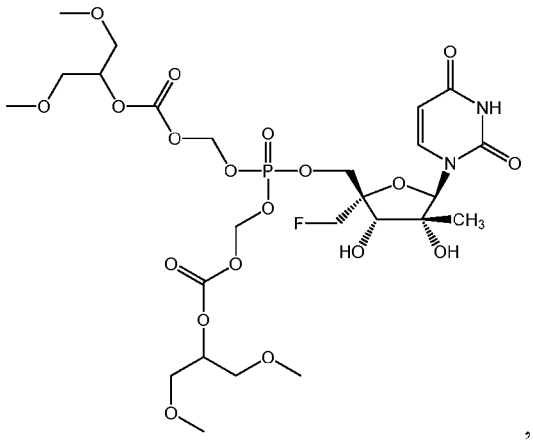
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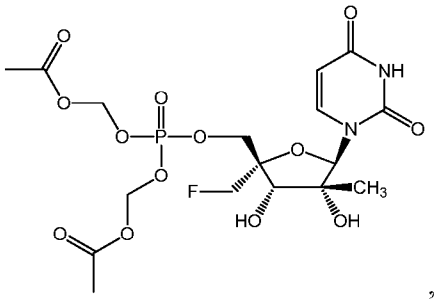
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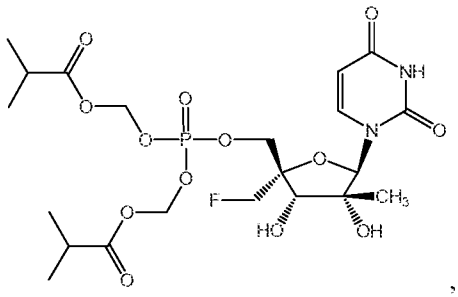
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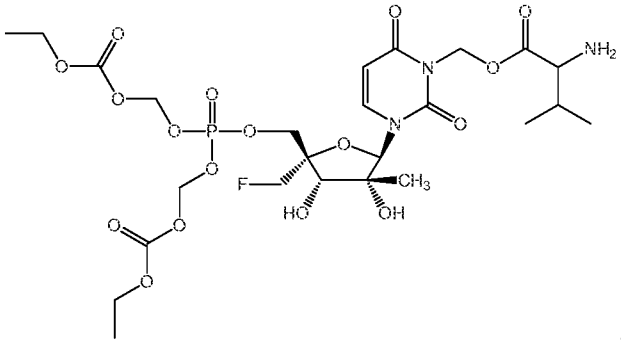
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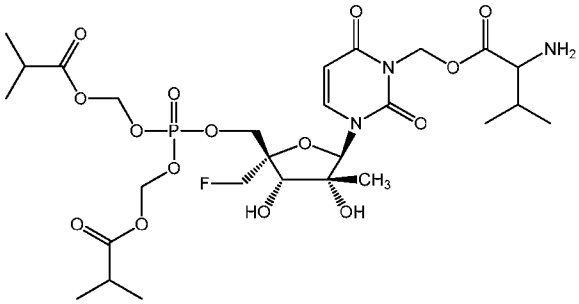
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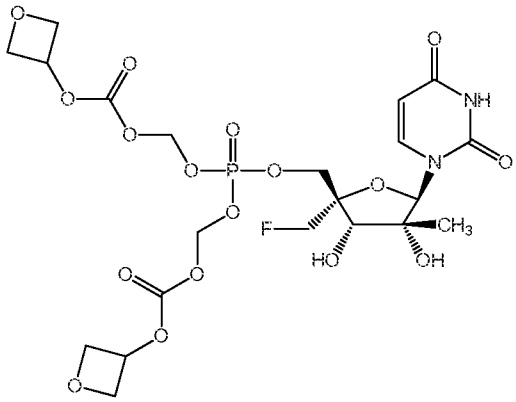
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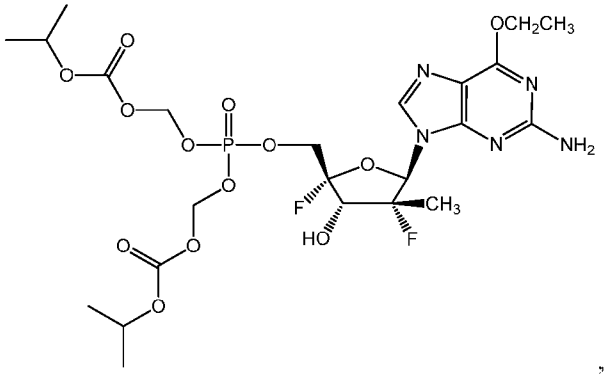
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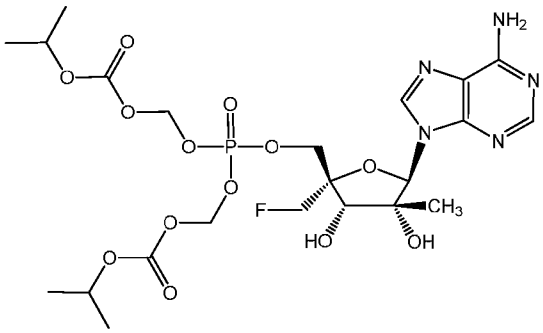
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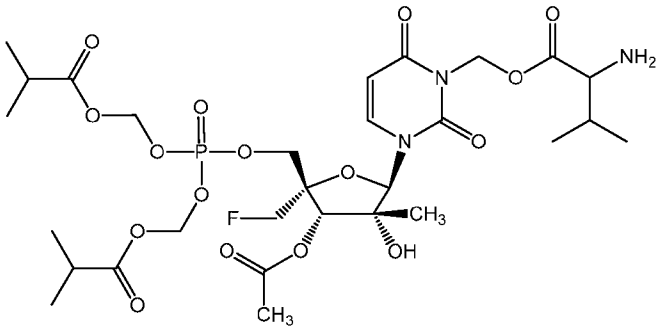
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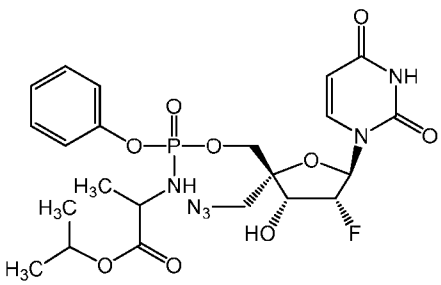
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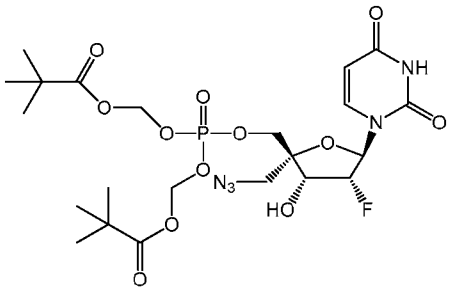
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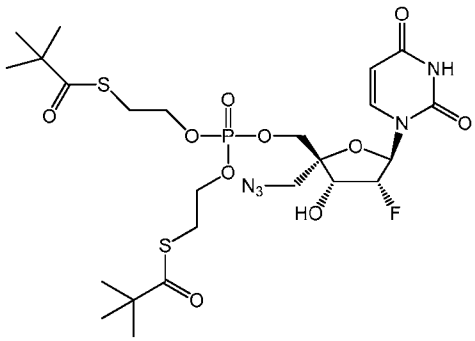


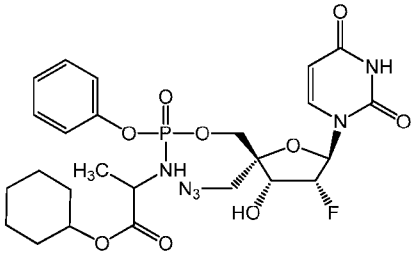
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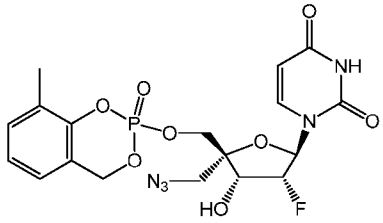


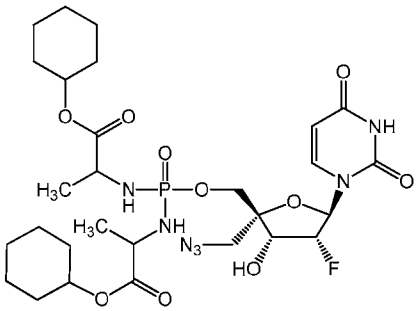
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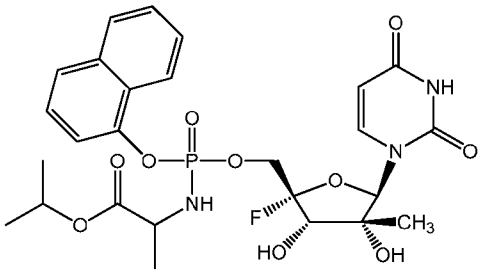


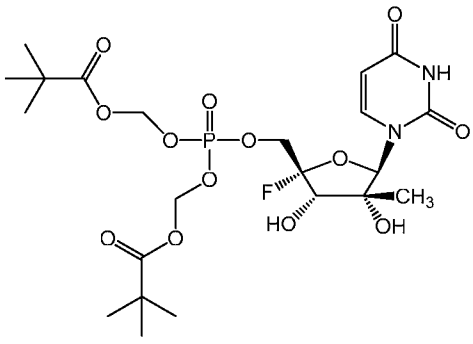


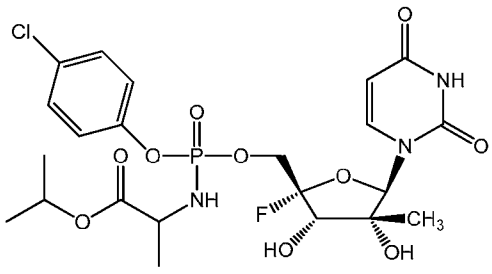


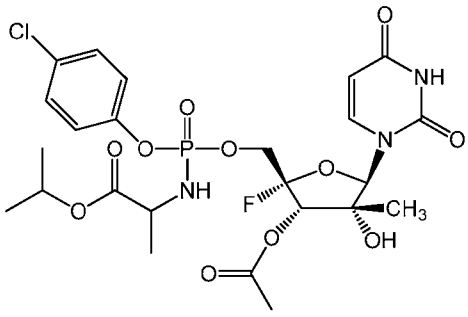


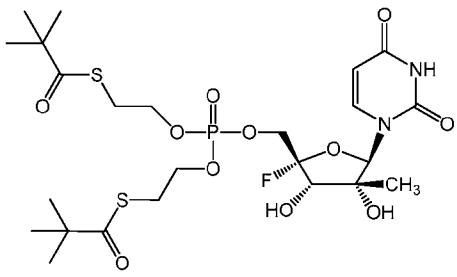


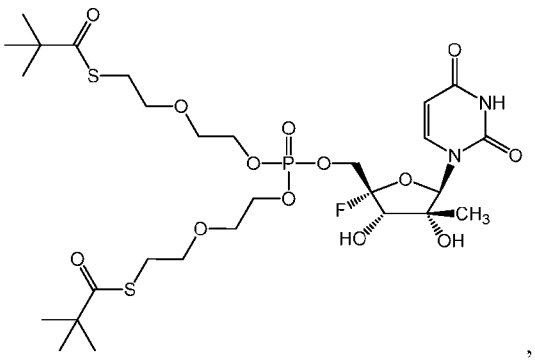


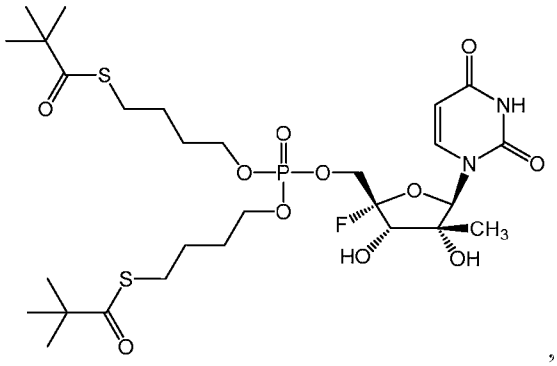


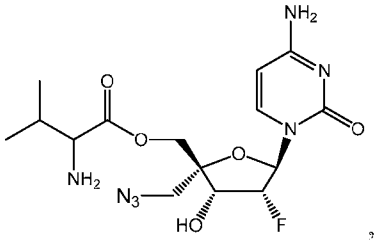


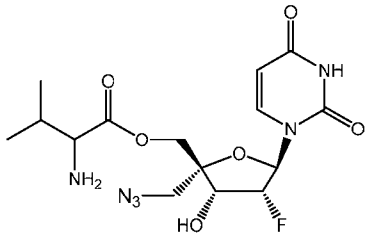


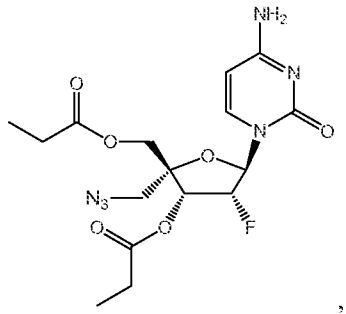


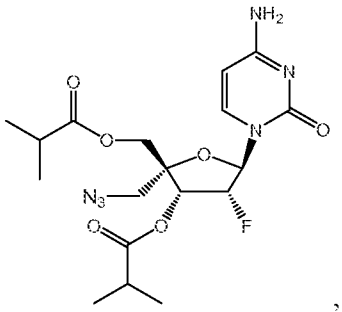


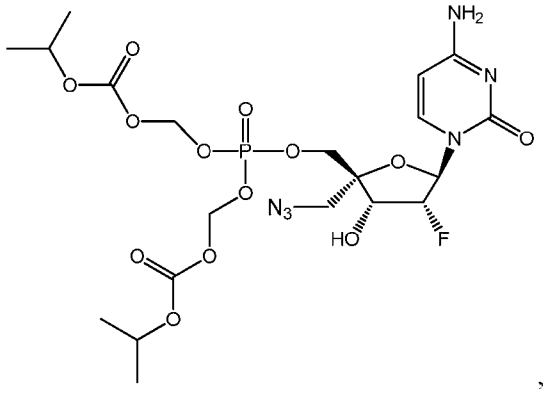


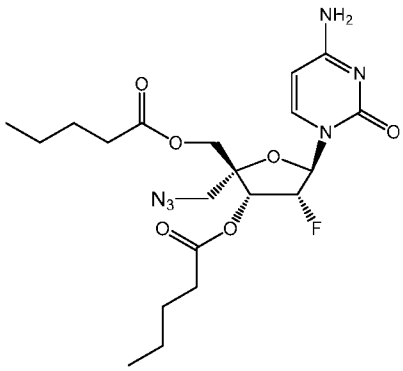


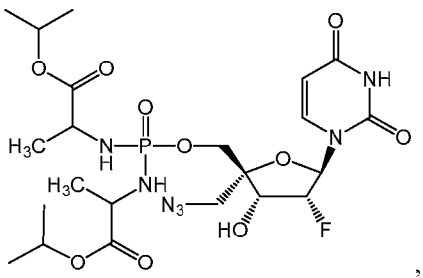


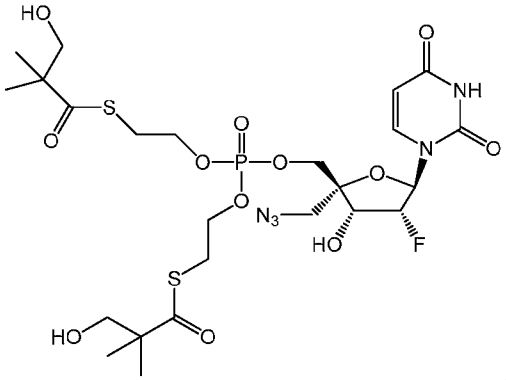




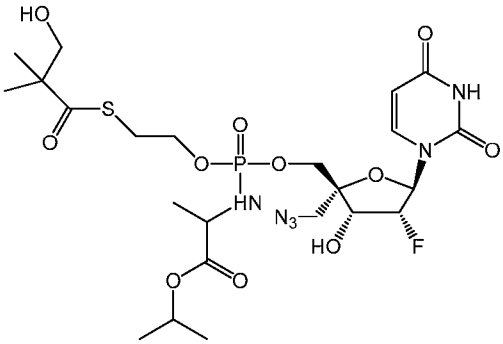




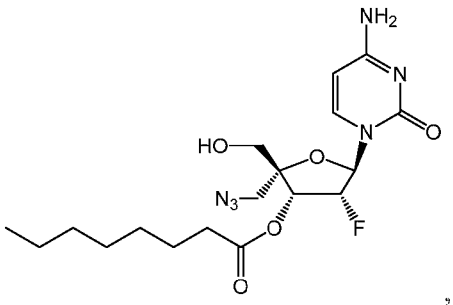




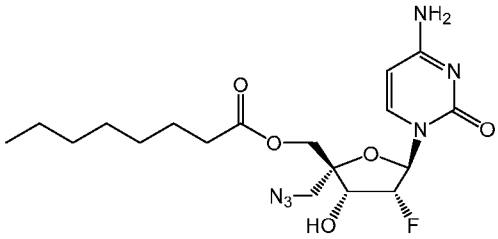
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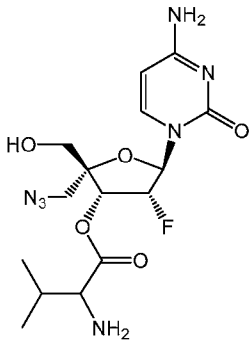
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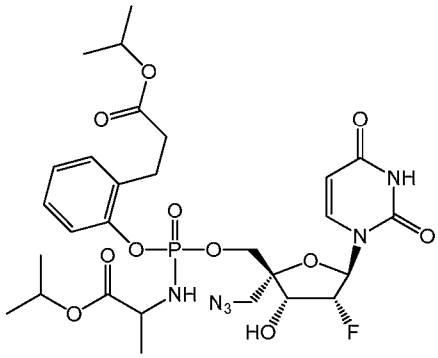
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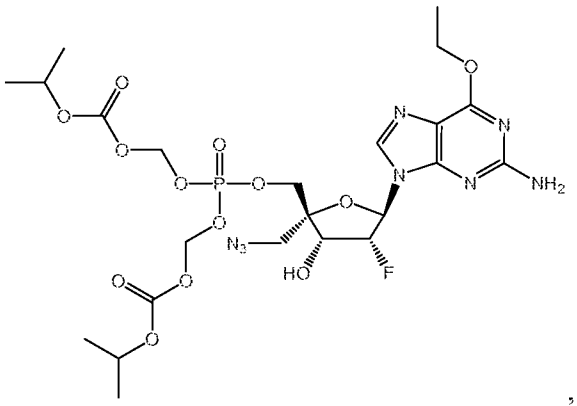
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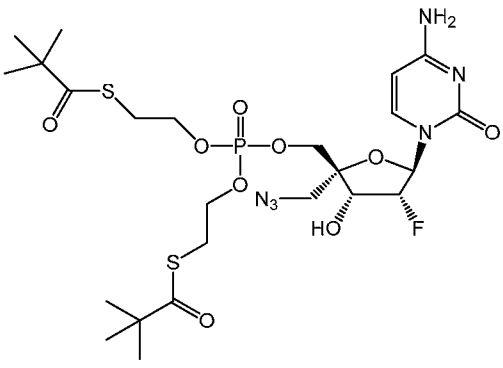
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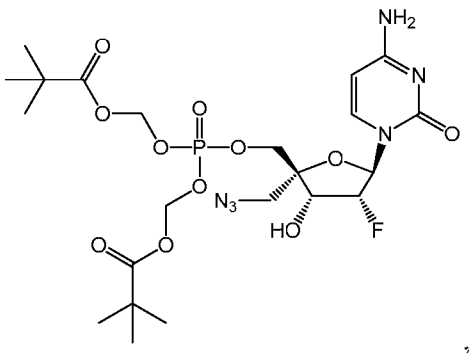
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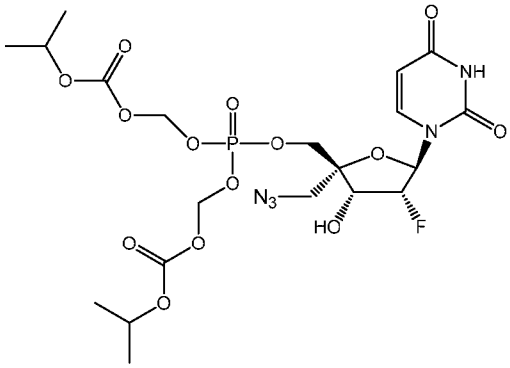
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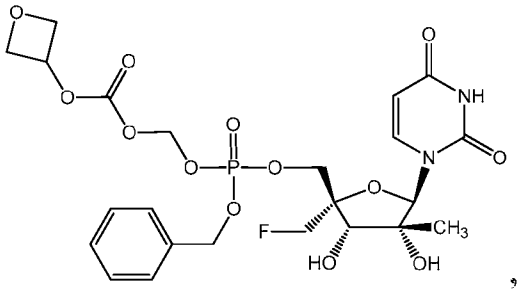
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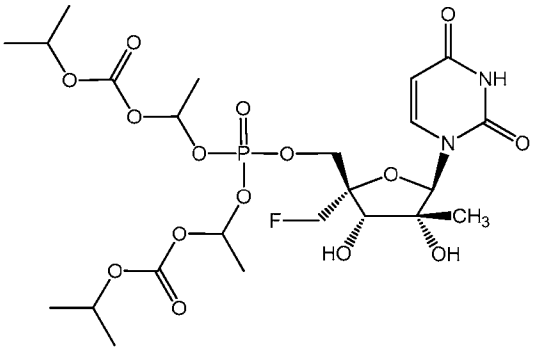
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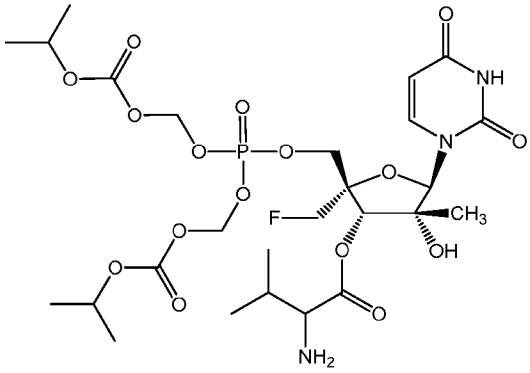
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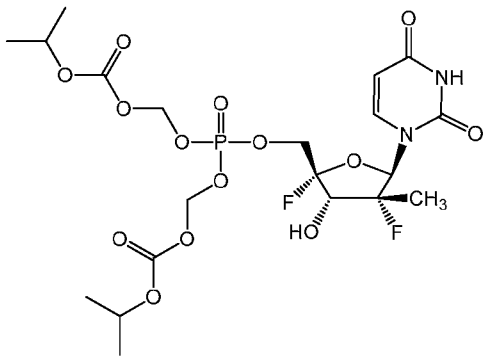
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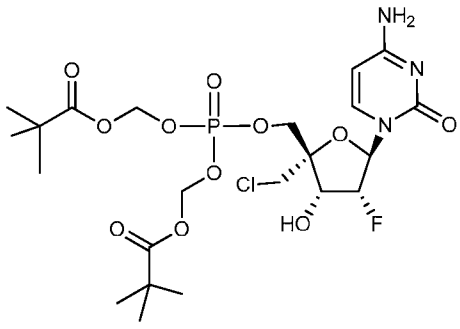
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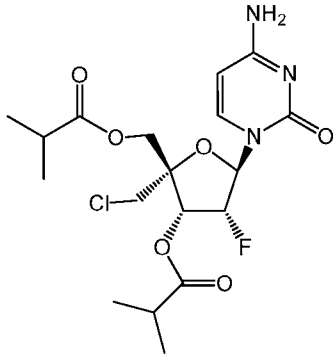
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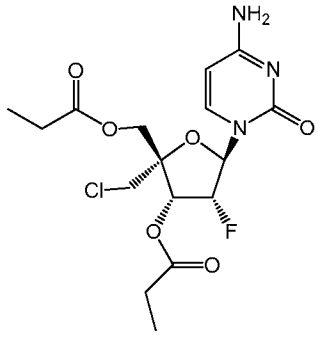
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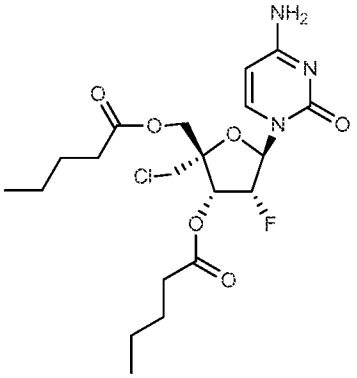
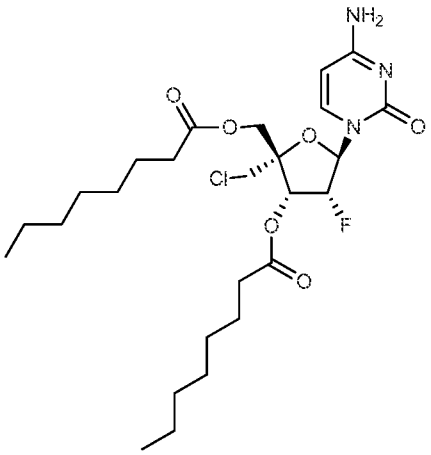
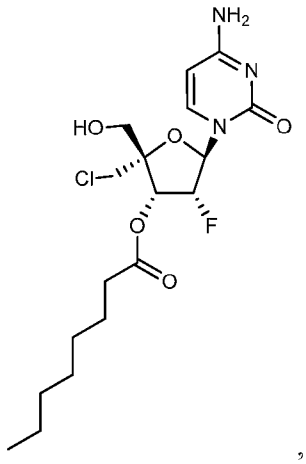
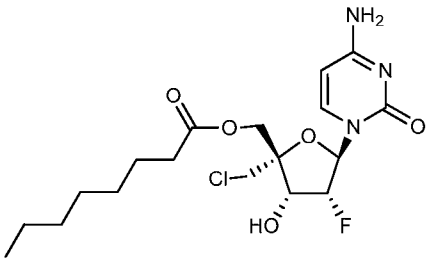
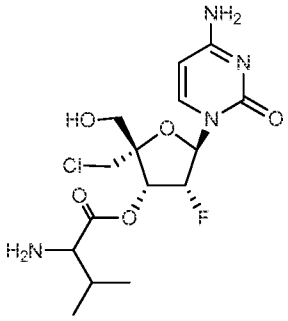
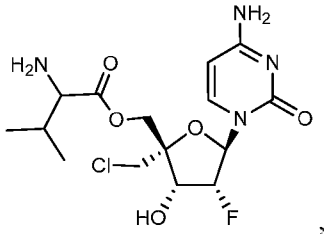
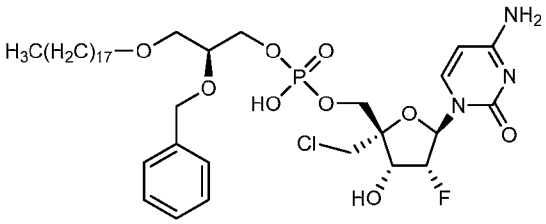
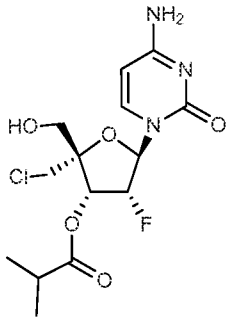
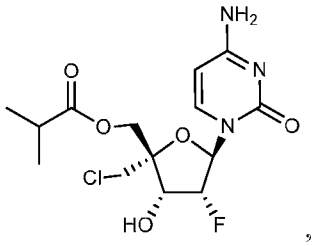
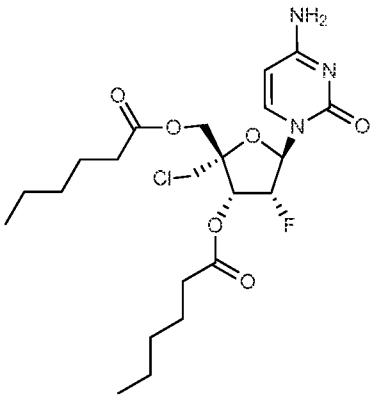
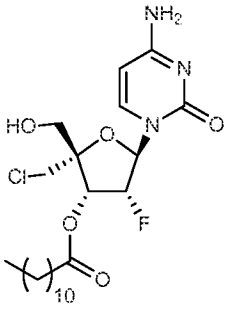
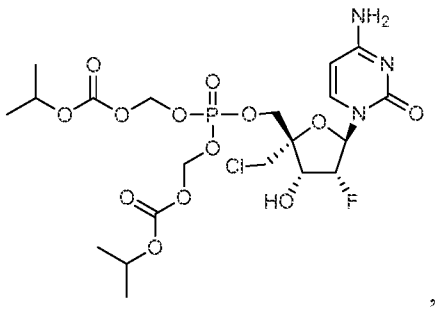
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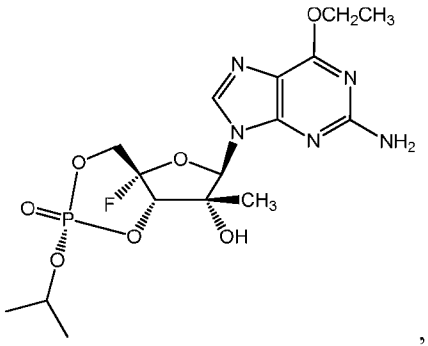


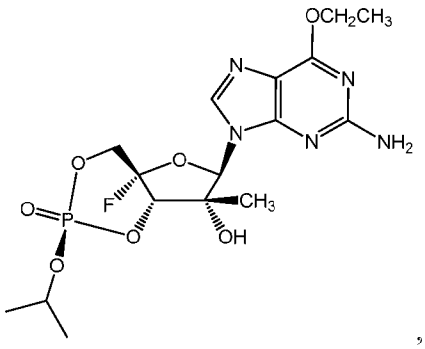
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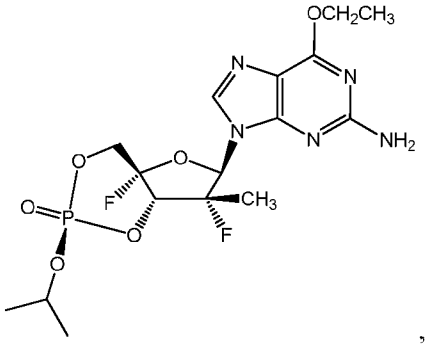


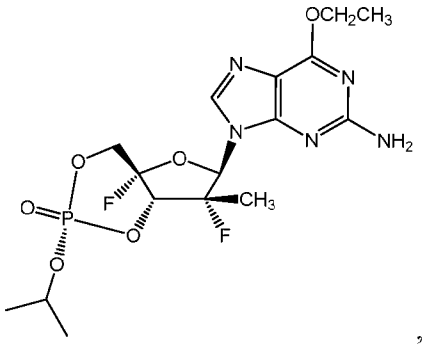
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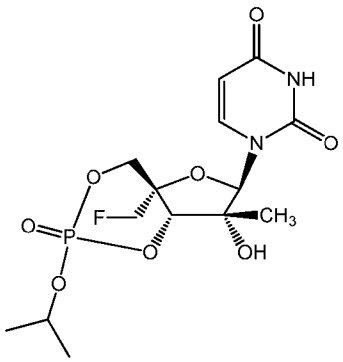

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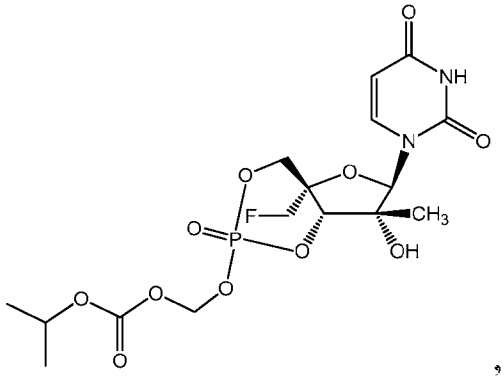


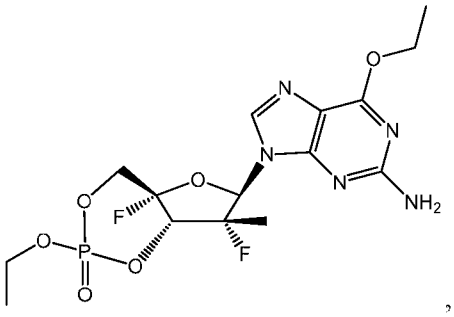


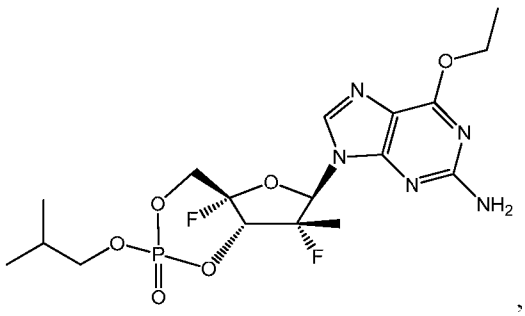


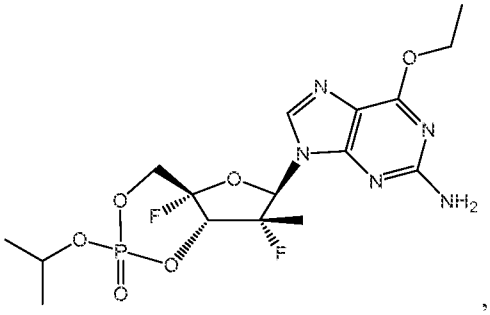


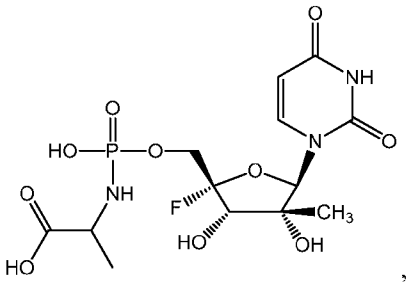


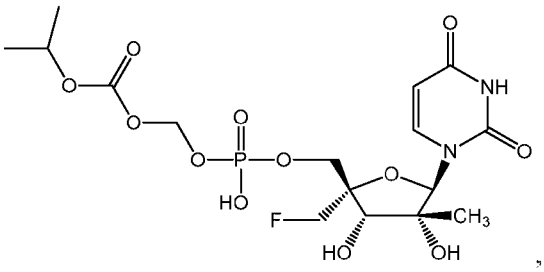


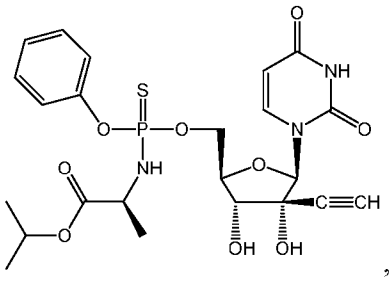


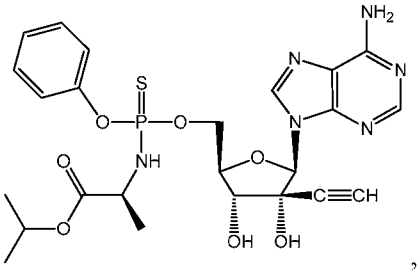


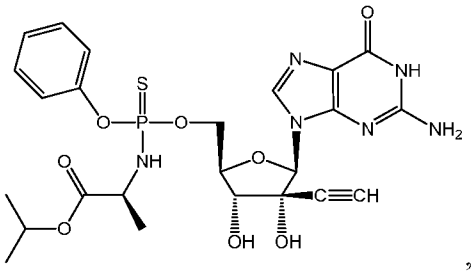


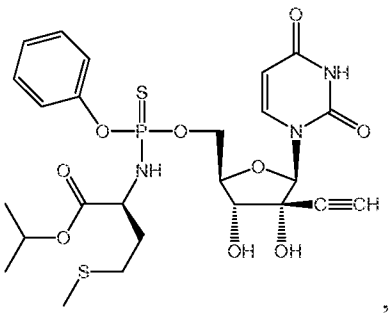


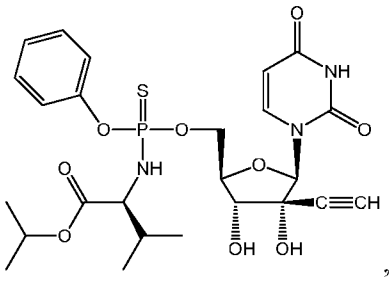


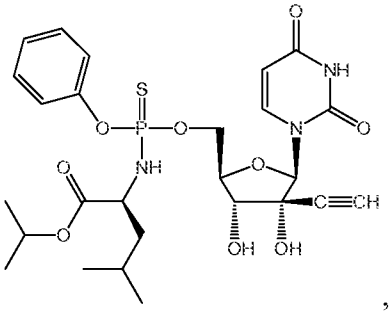


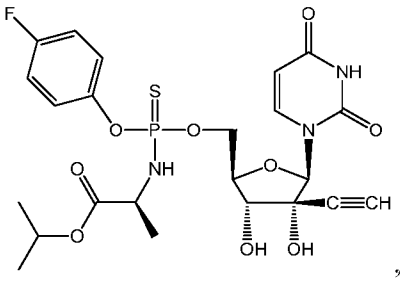


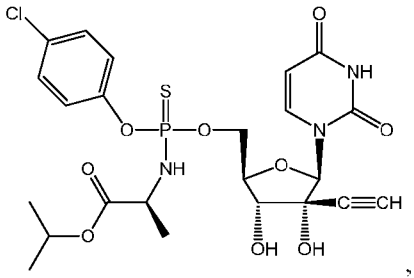




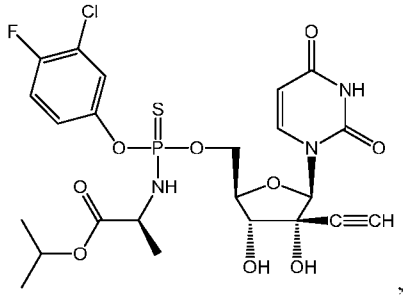




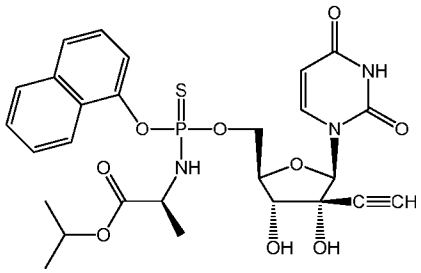




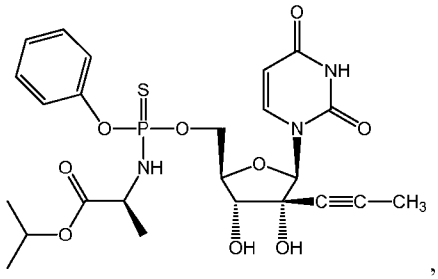
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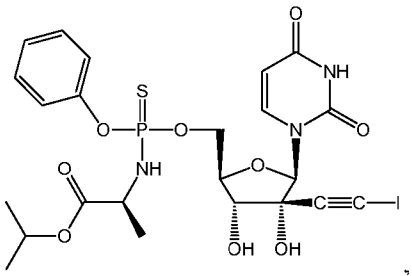
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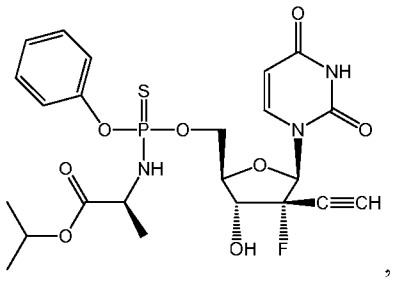
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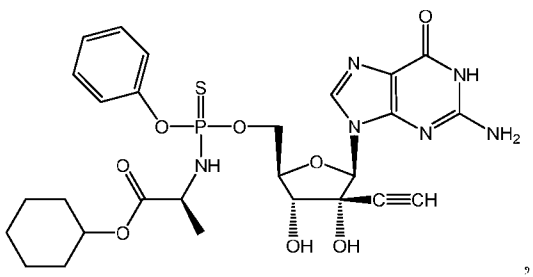
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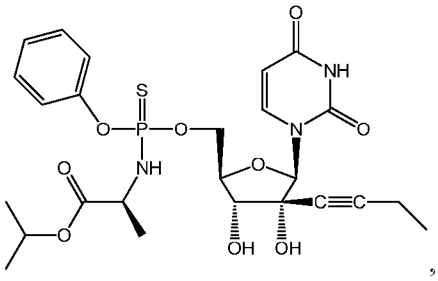
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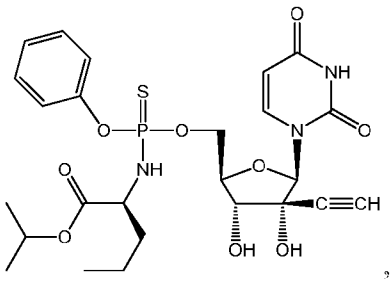
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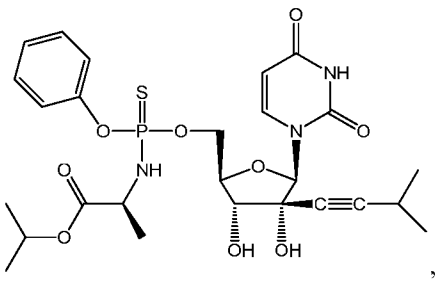
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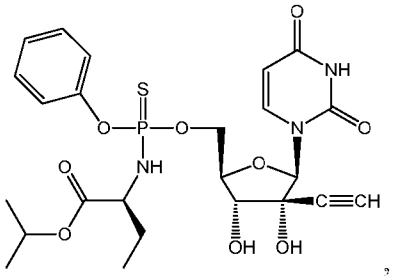
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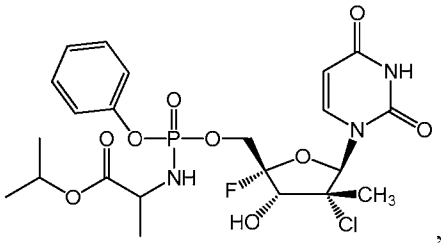
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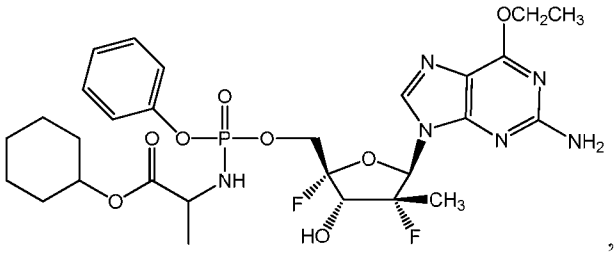
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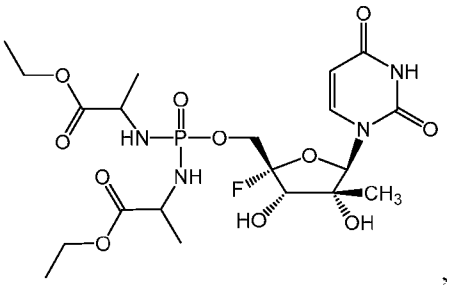
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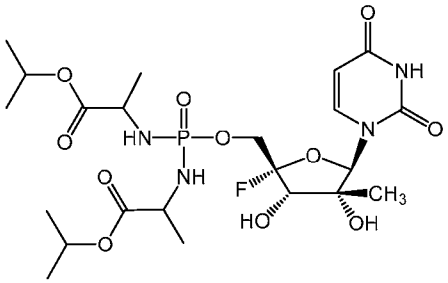
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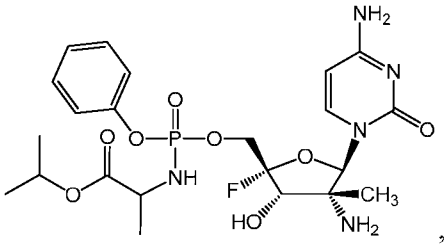
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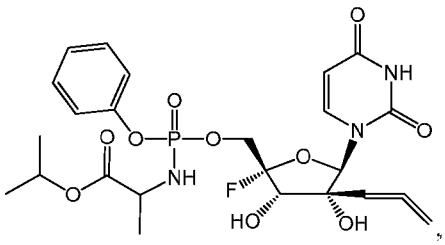
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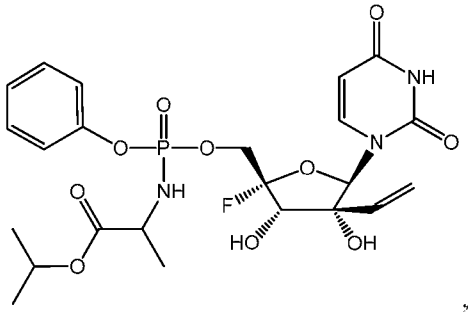
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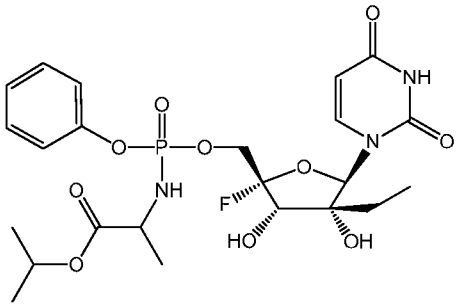
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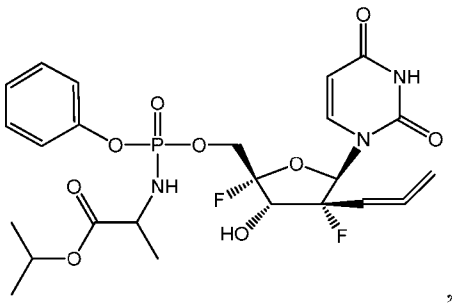
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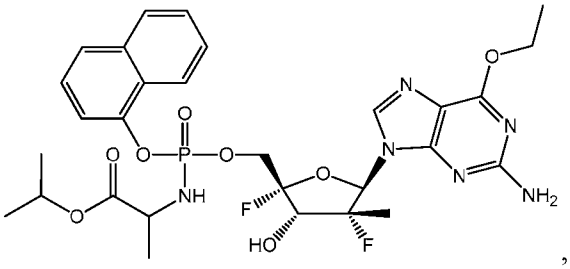
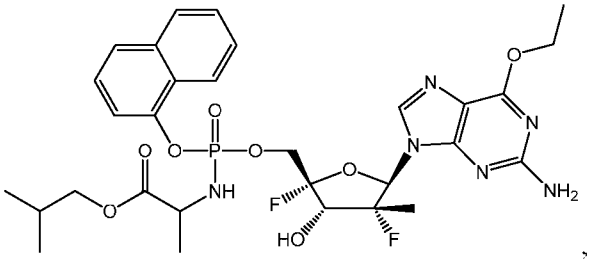
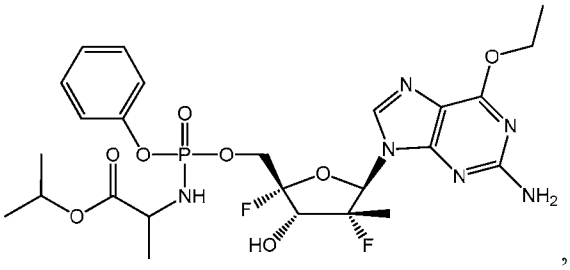
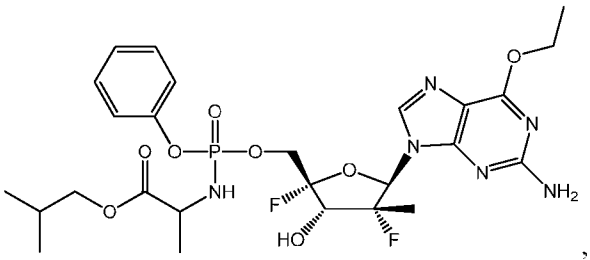
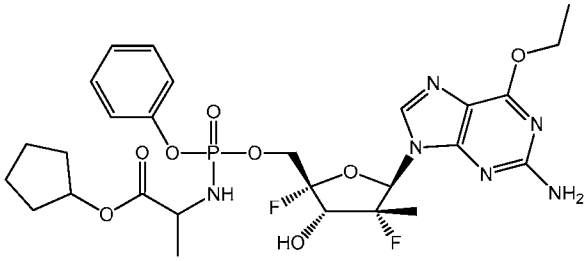
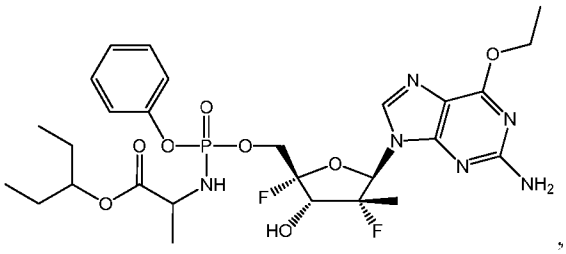
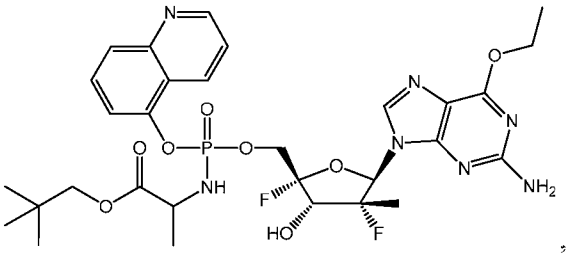
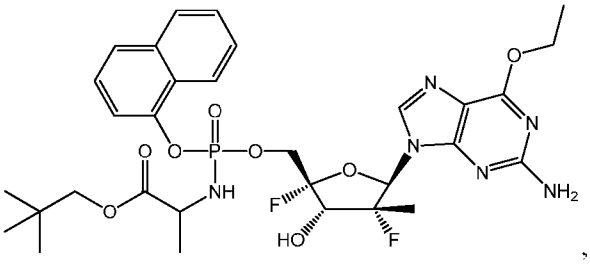
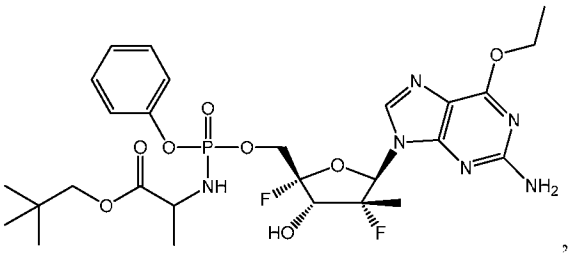
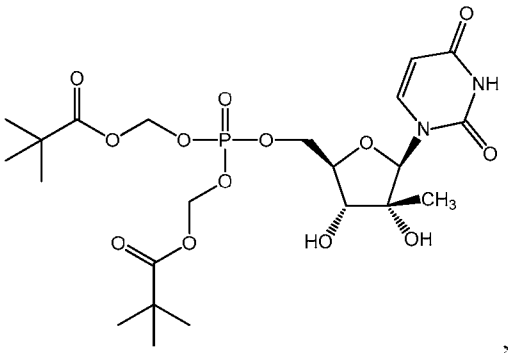
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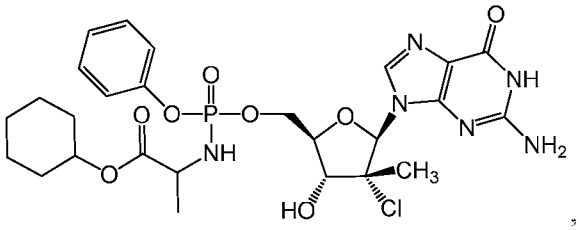


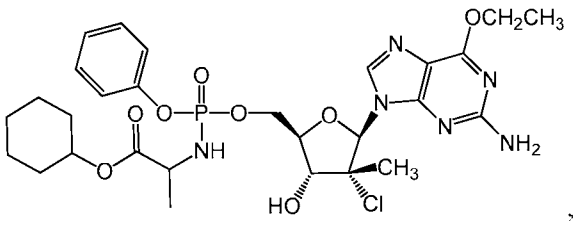
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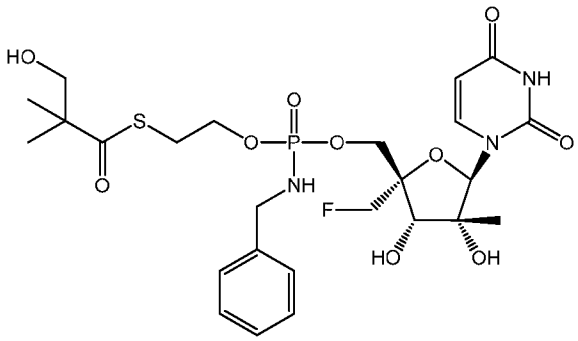
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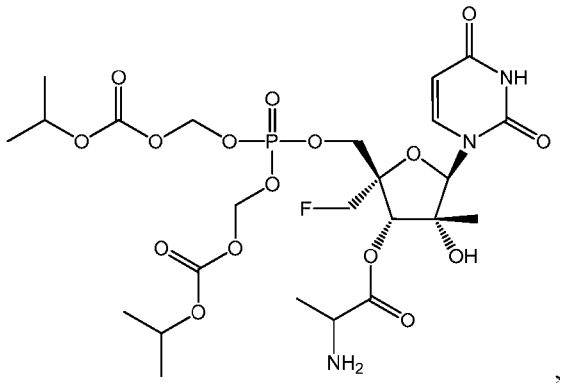
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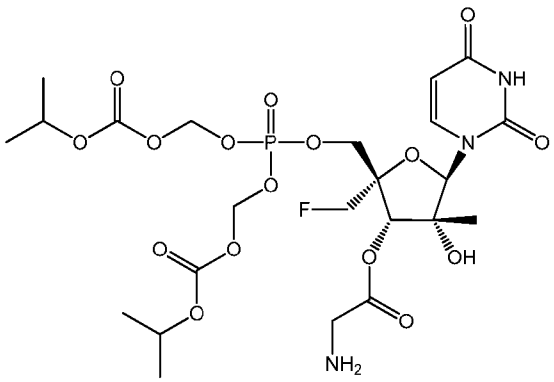

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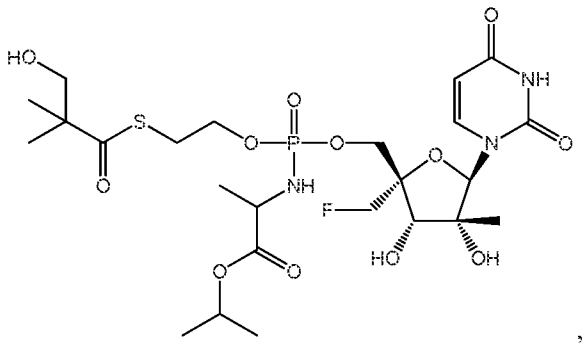


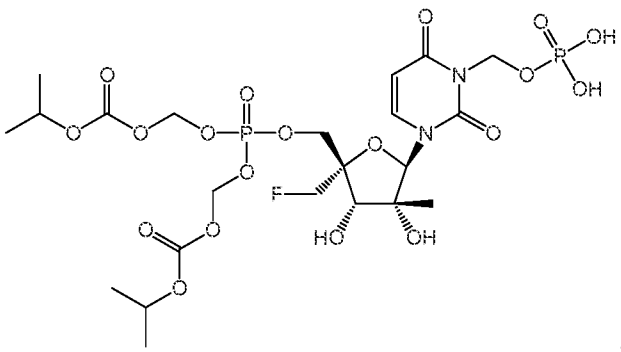


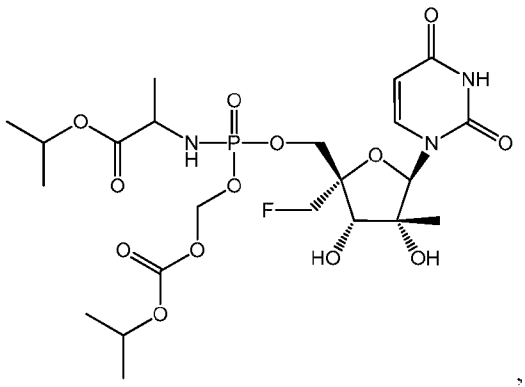


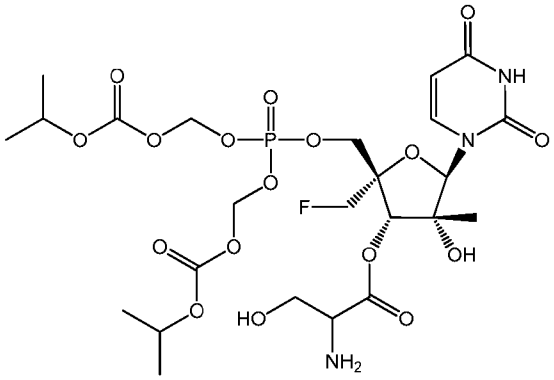


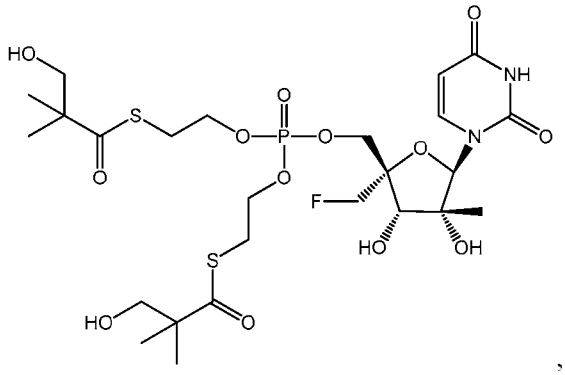


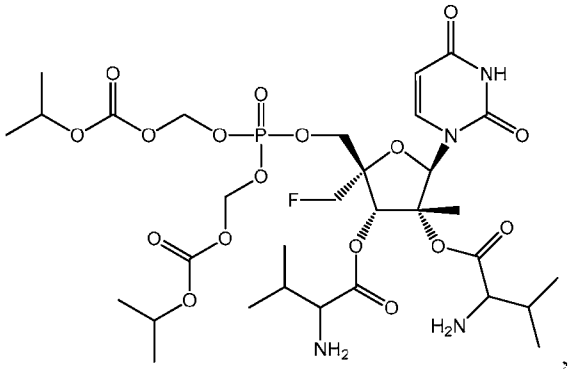


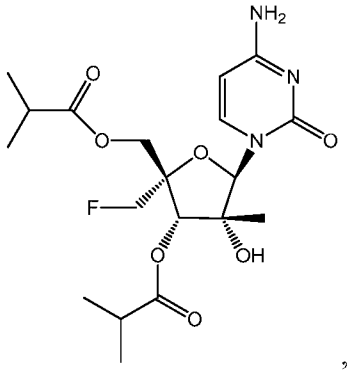


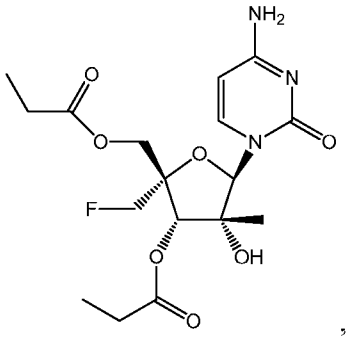


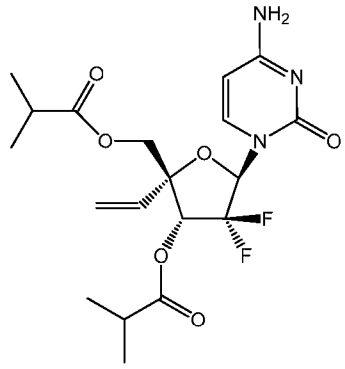


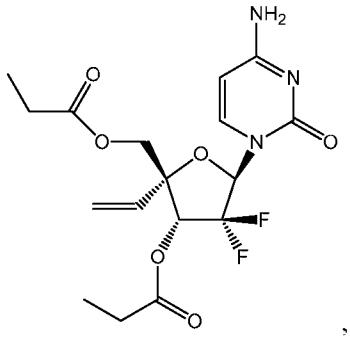


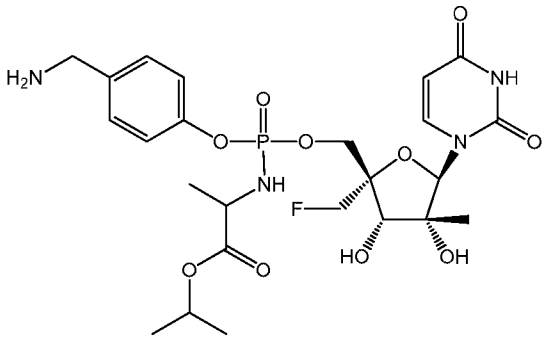


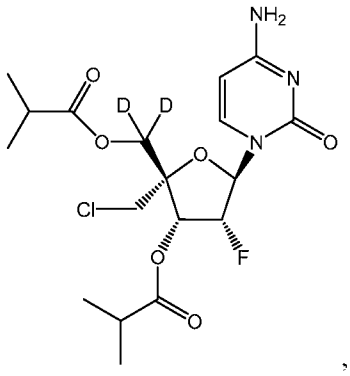


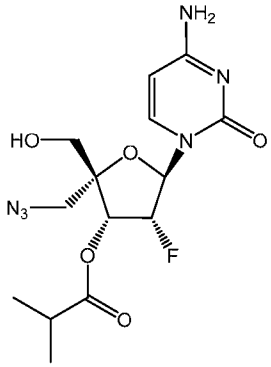




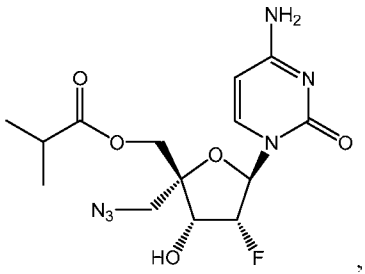




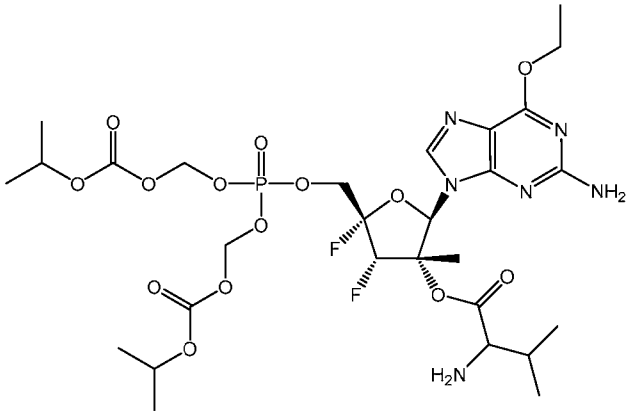




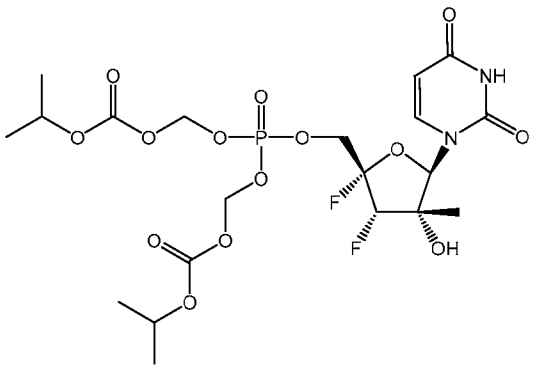
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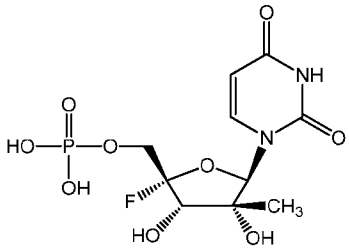
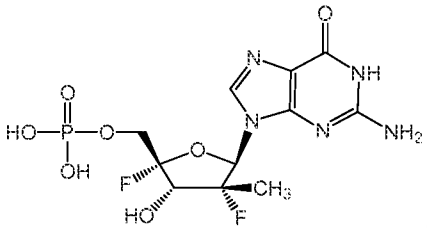
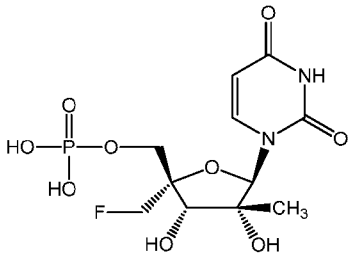
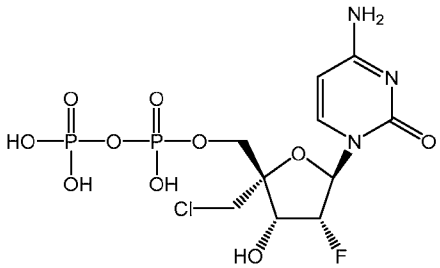
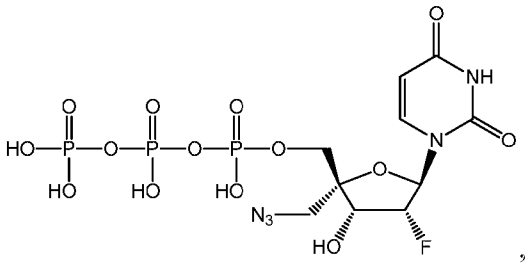
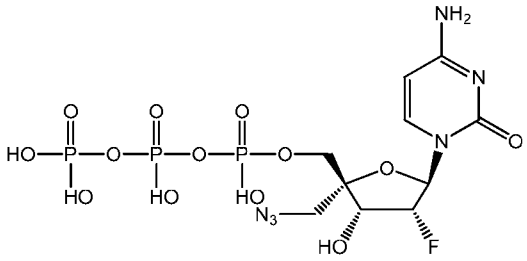
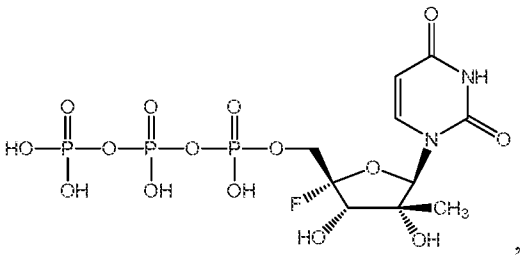
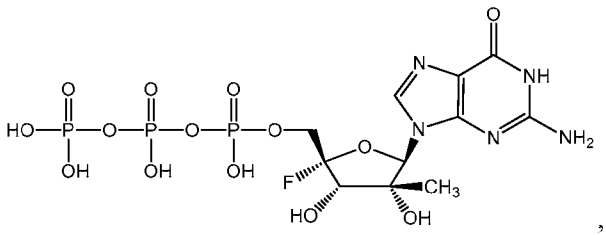
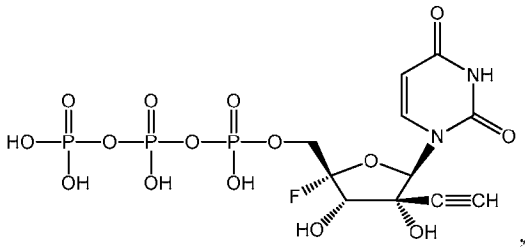
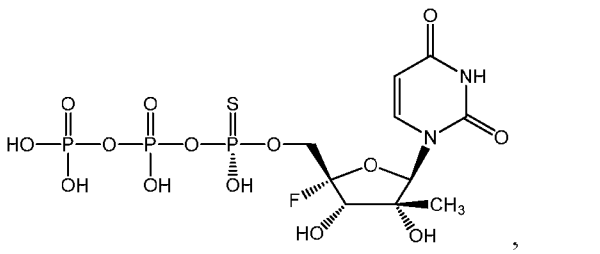
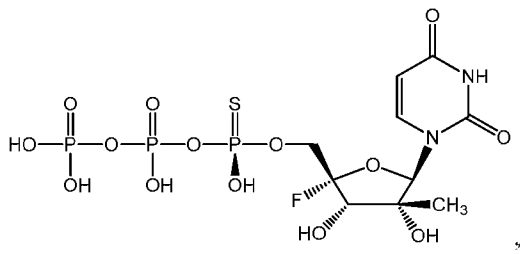


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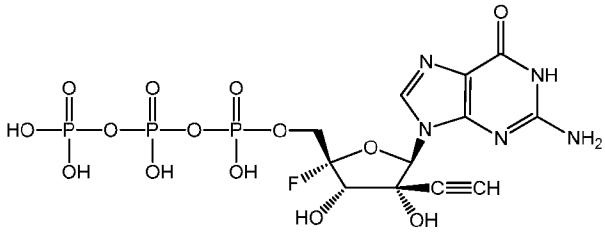
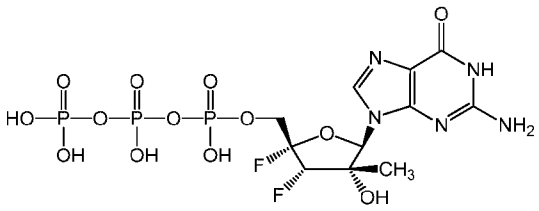
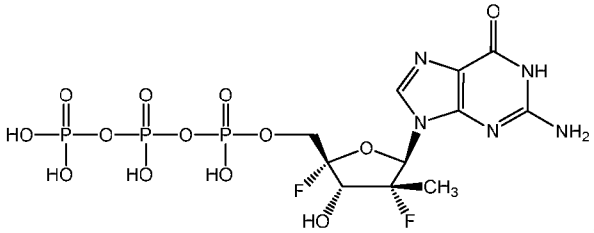
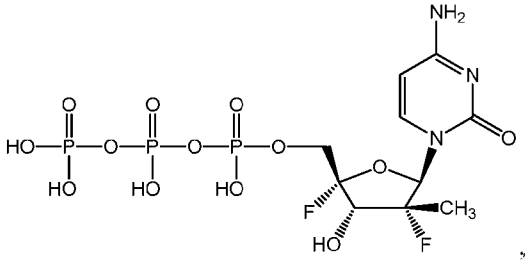
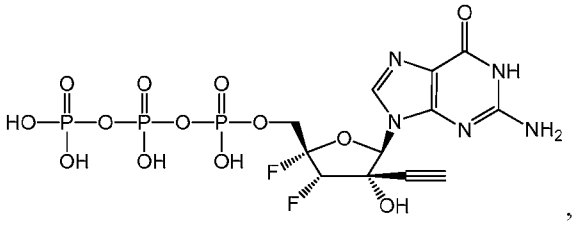
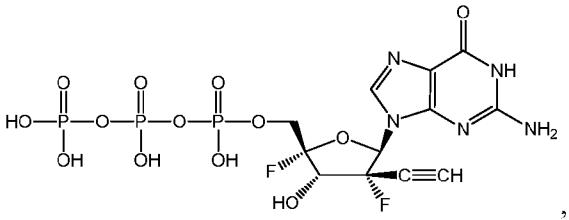
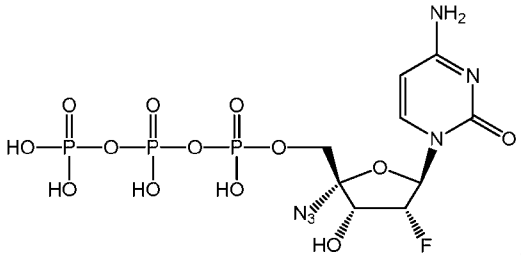
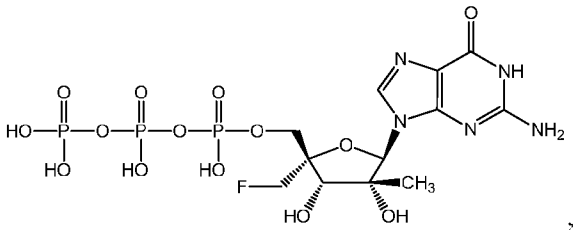
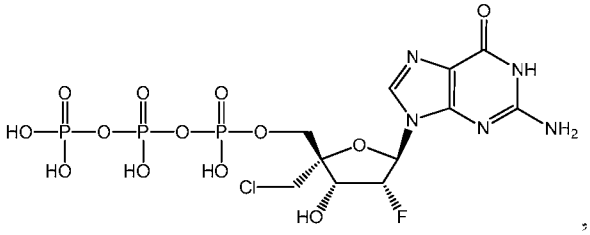
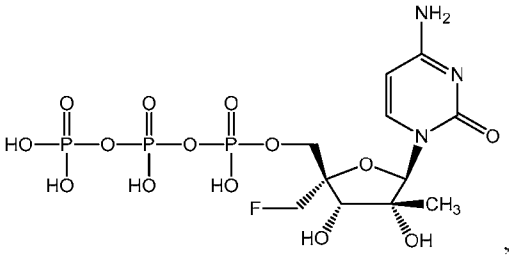
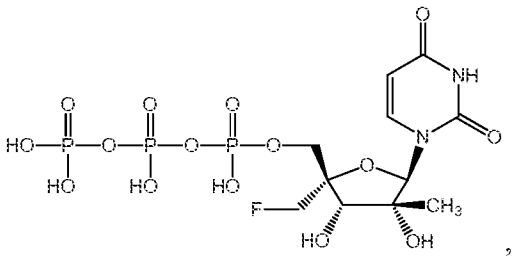
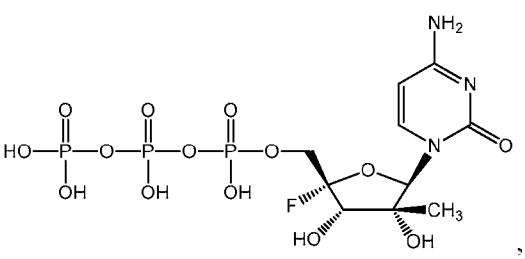
, or a pharmaceutically acceptable salt of the foregoing.

90. The use of Claim 1, wherein the compound is selected from the group consisting of:


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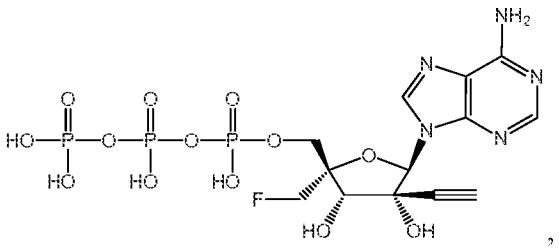
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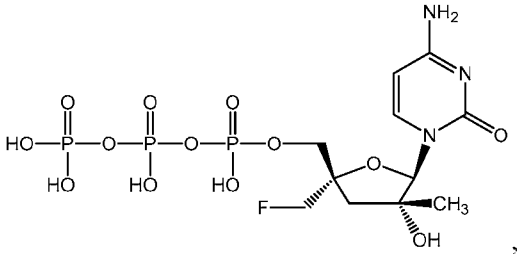
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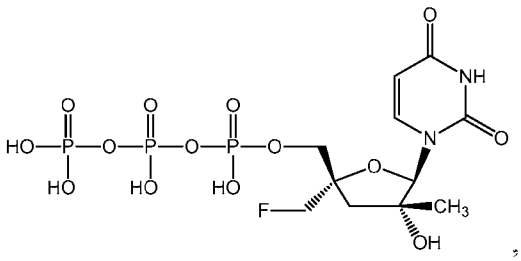

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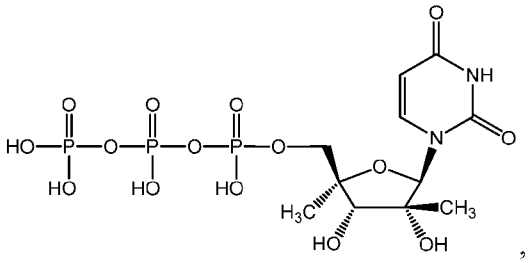
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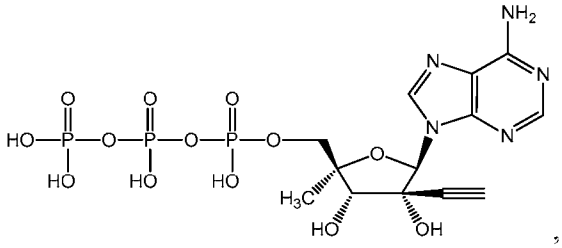
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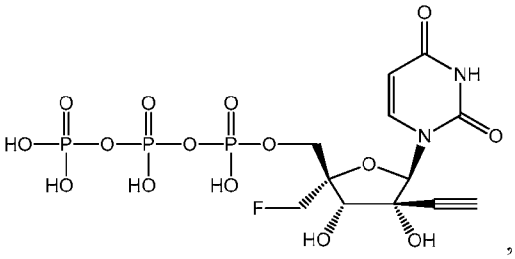


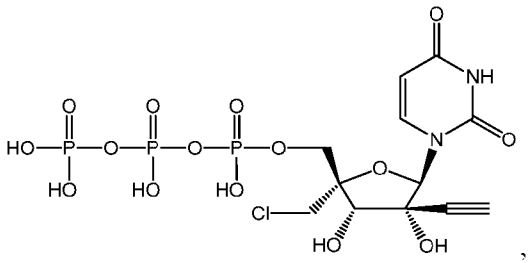


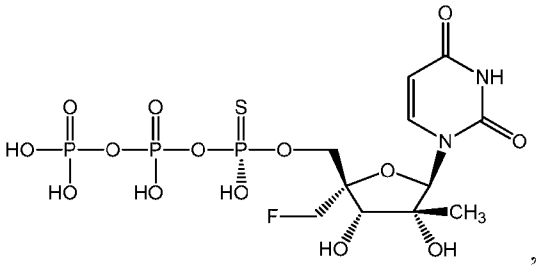


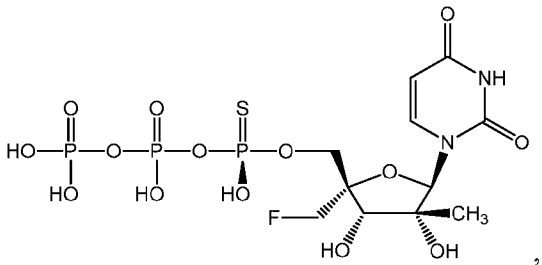


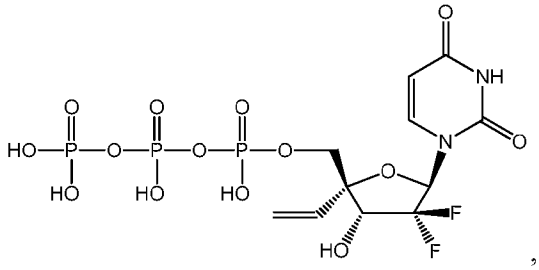


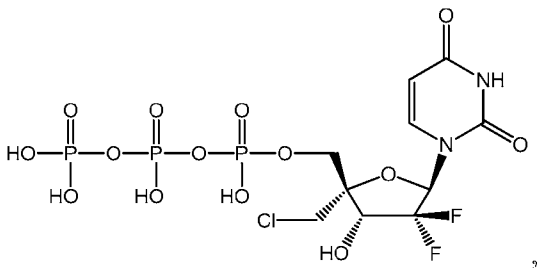


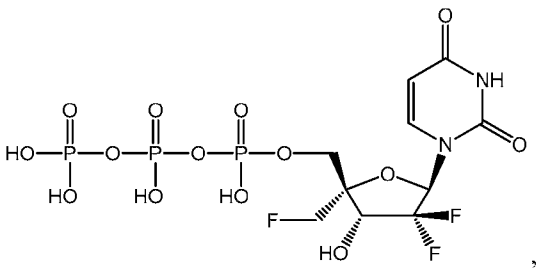


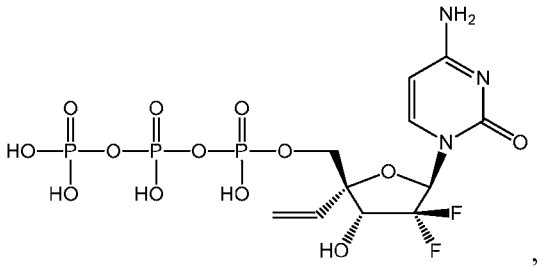
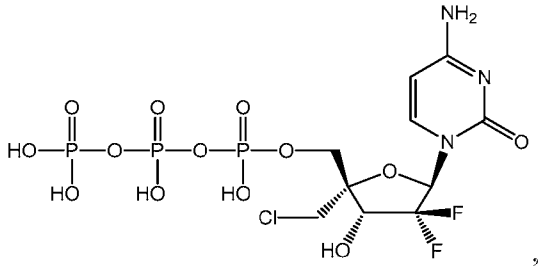
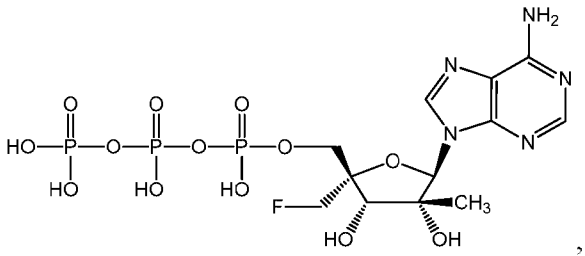
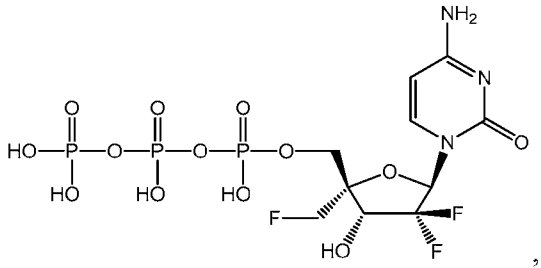
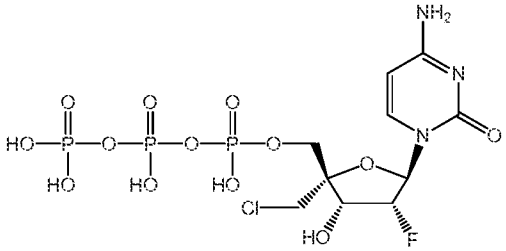
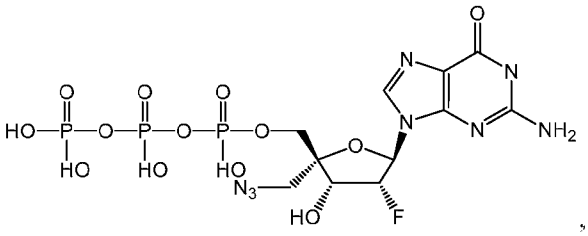
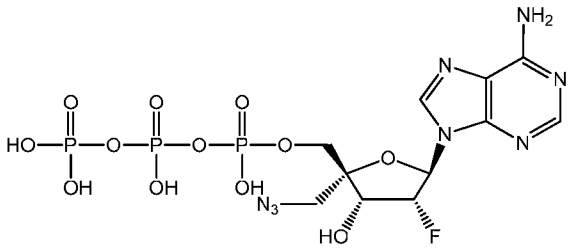
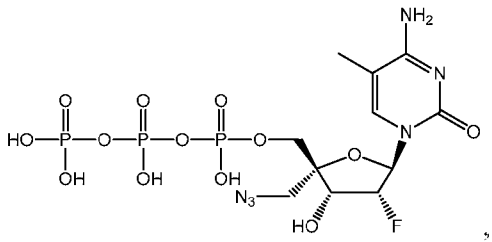
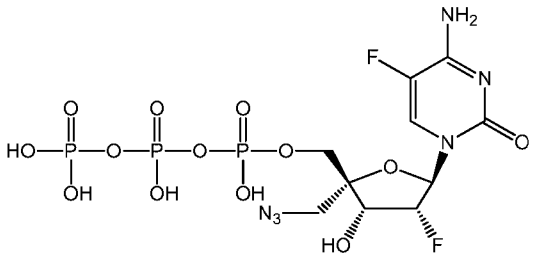
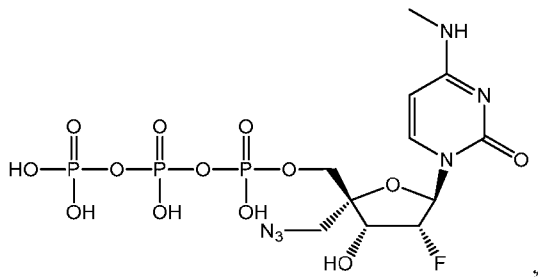
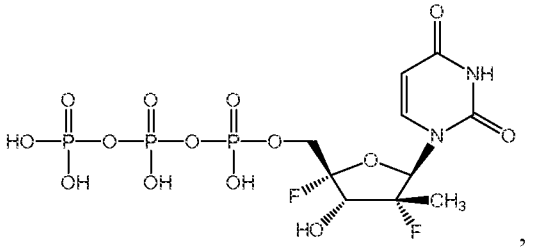




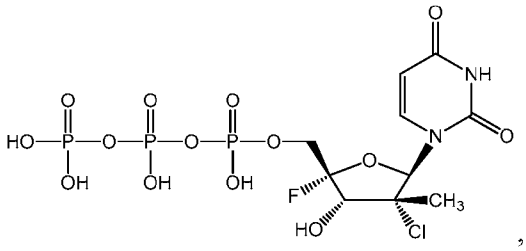






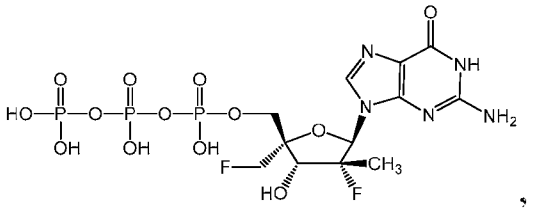
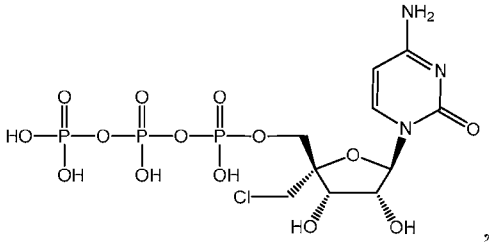
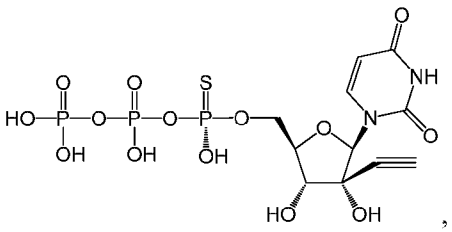
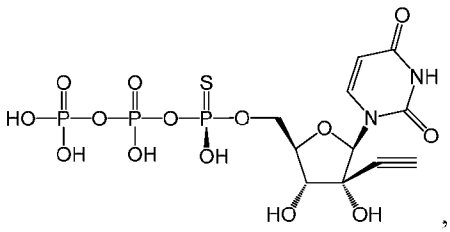
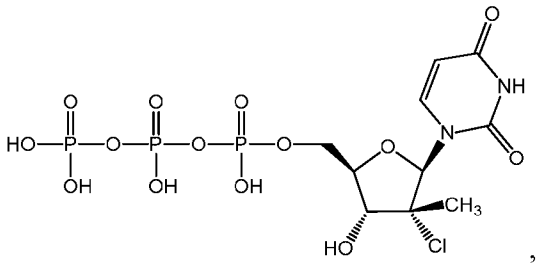
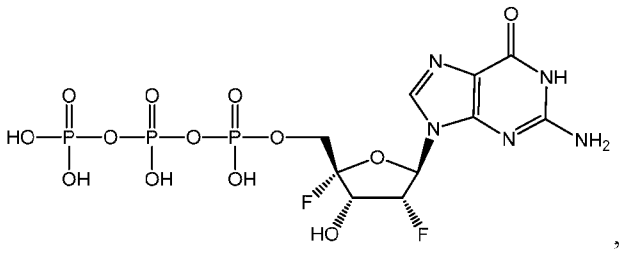
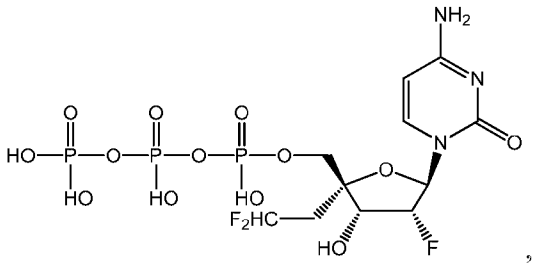
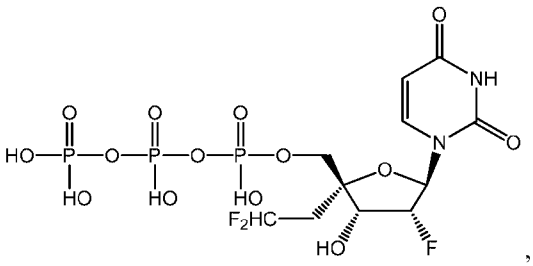
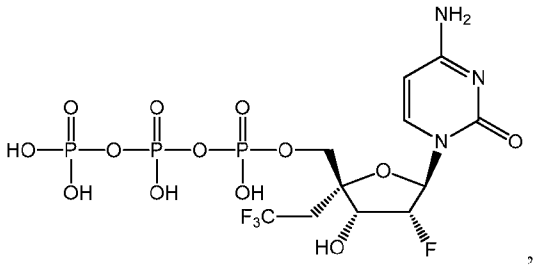
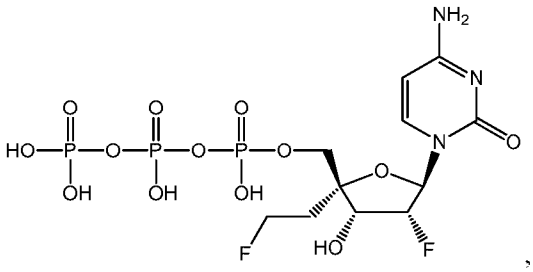
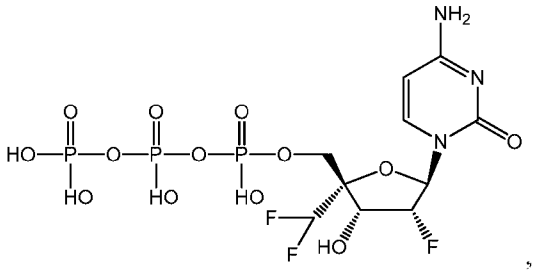
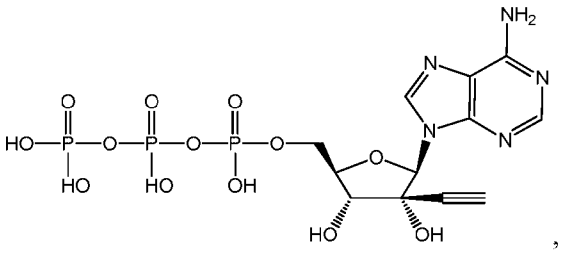

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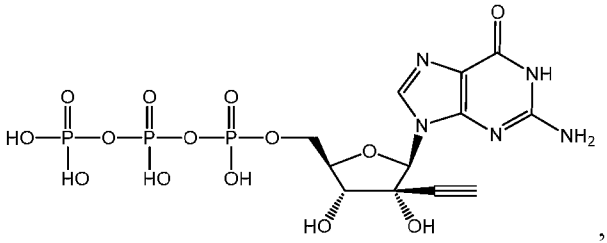
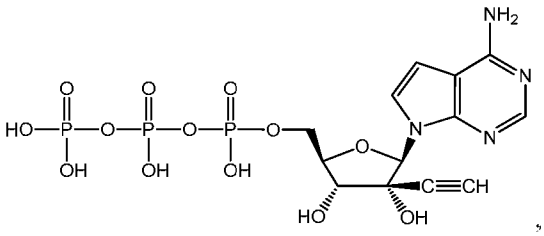
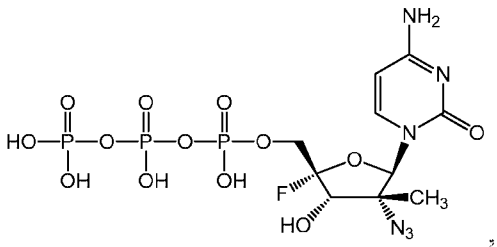
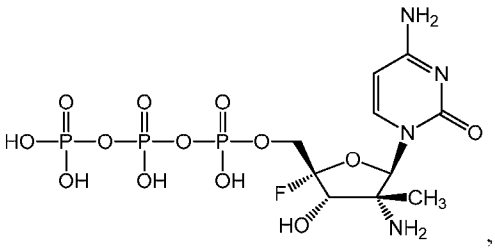
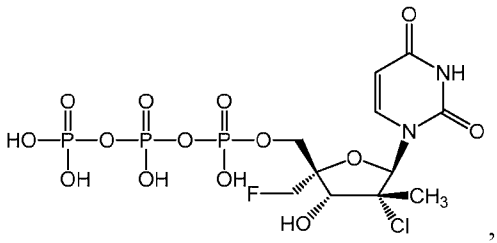
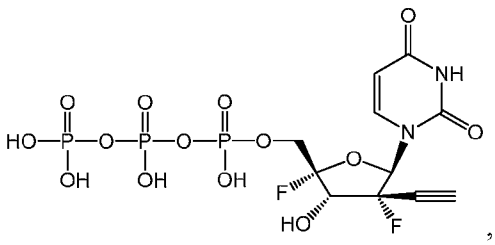
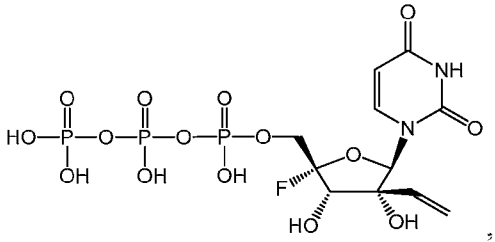
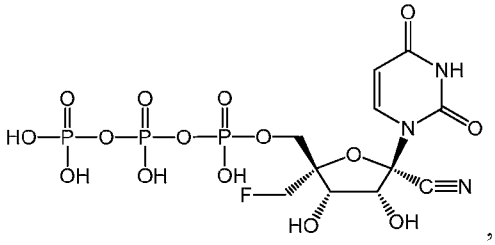
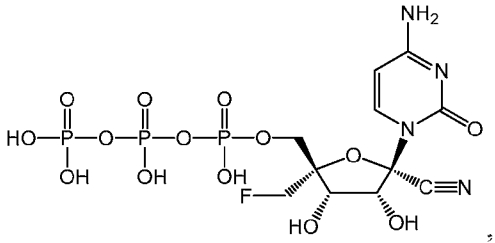
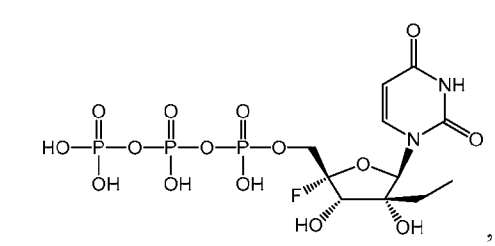
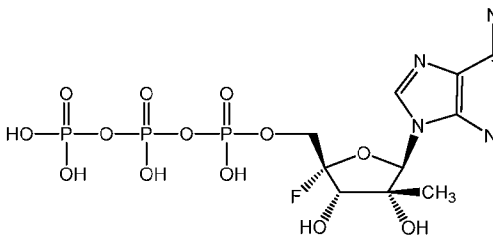
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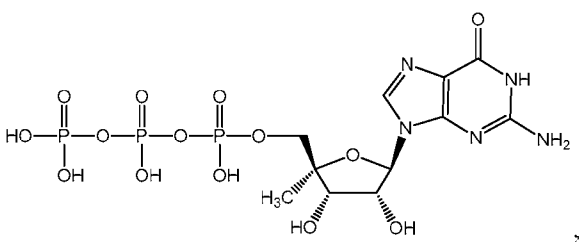
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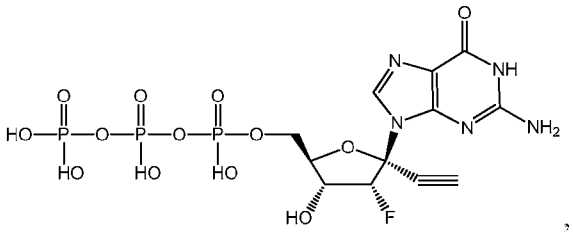
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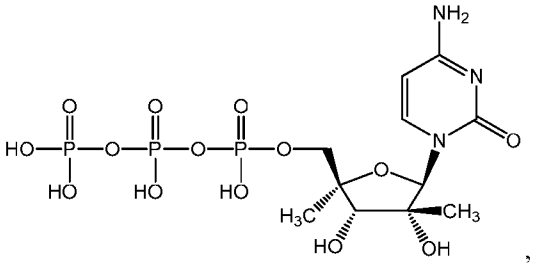

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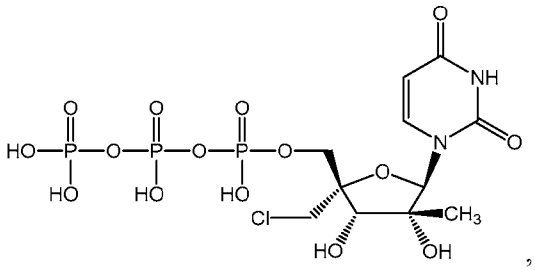

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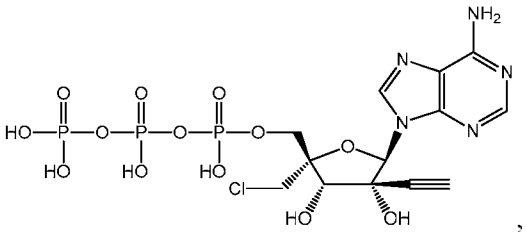
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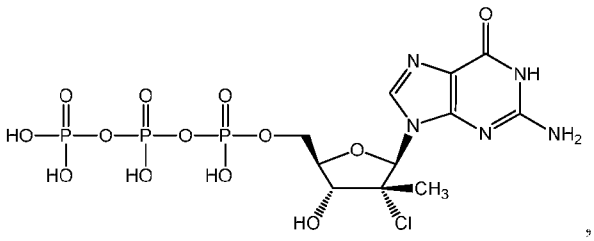
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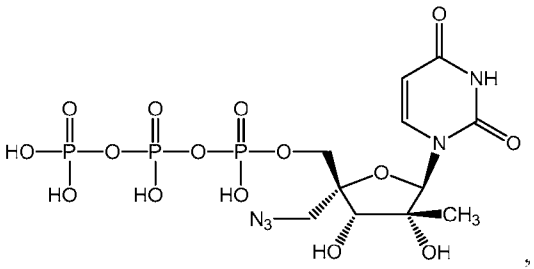


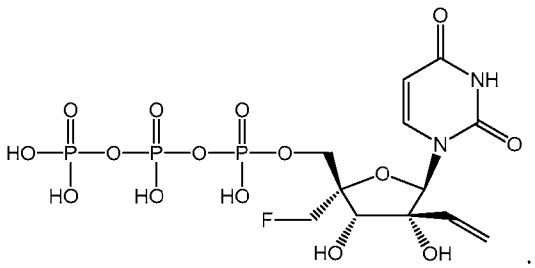


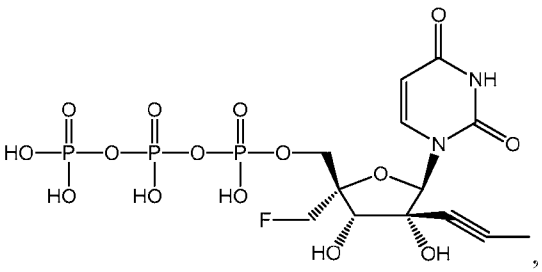


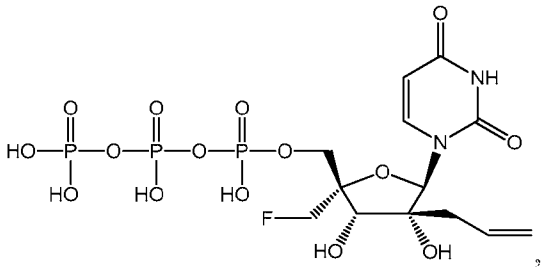


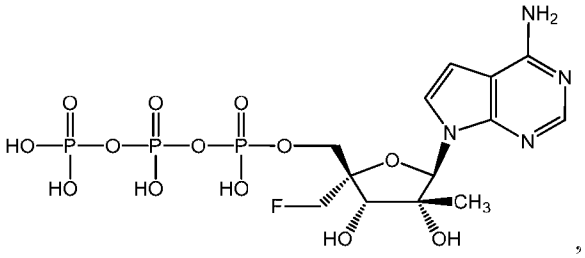


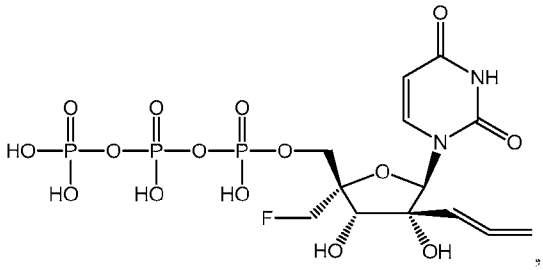


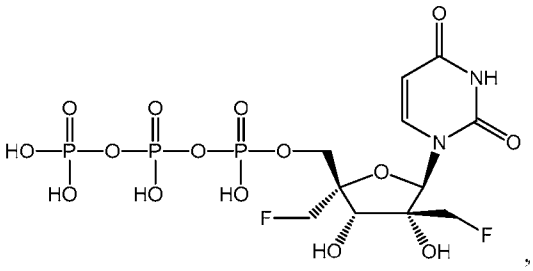


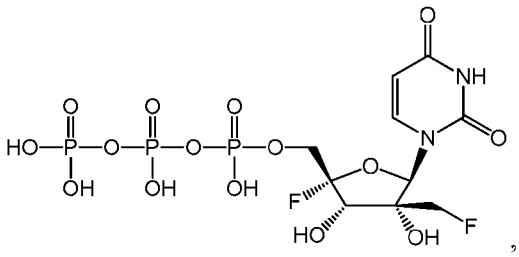


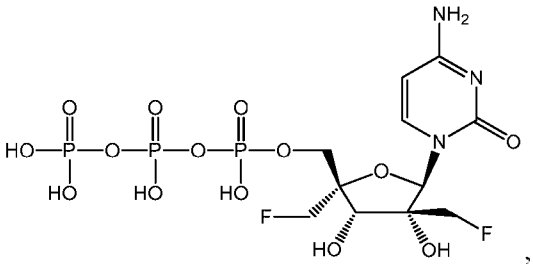


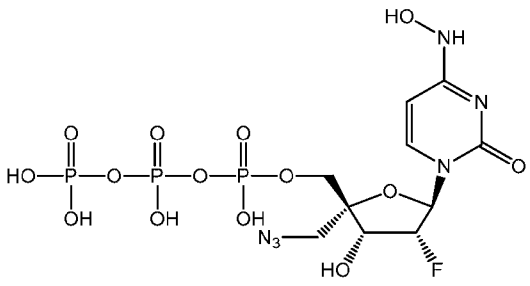


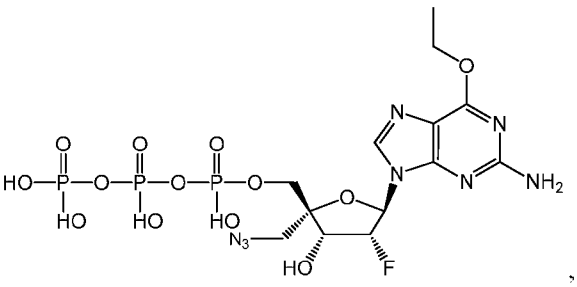


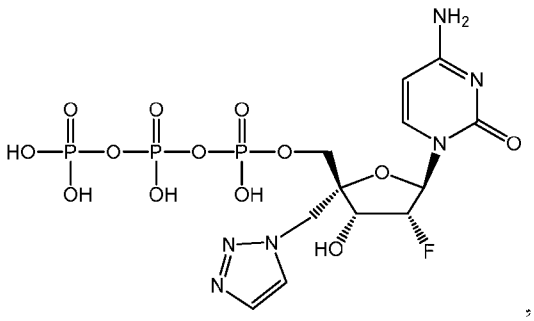


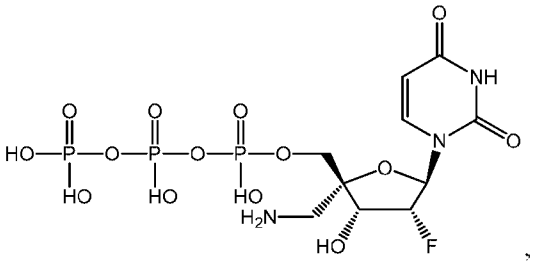


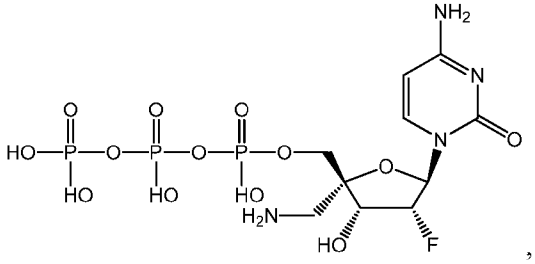


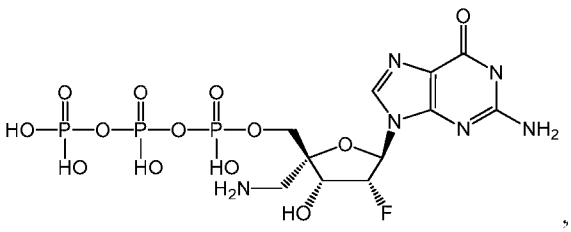


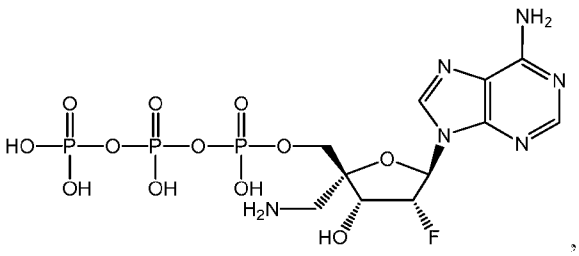


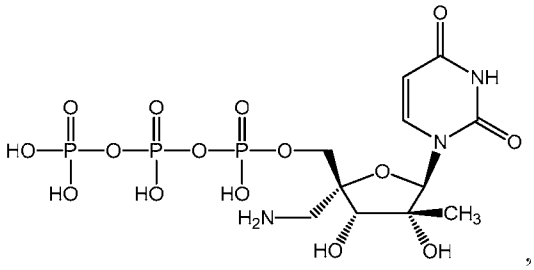


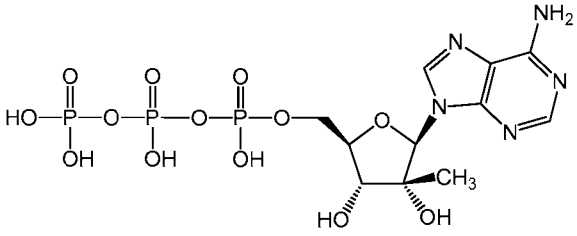


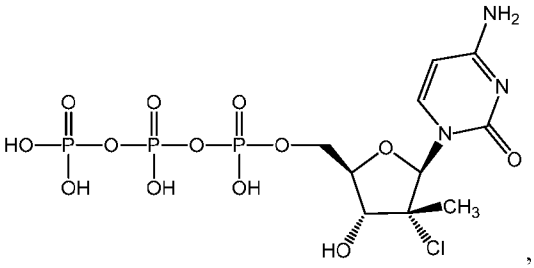


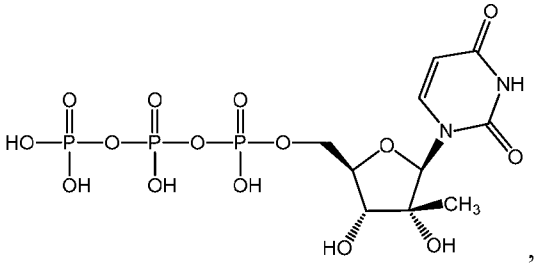


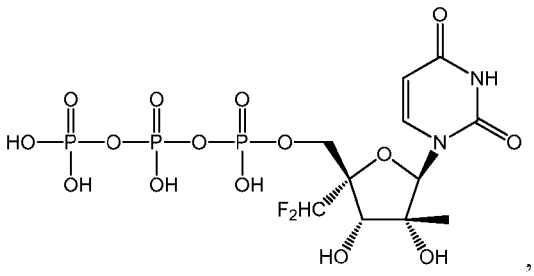


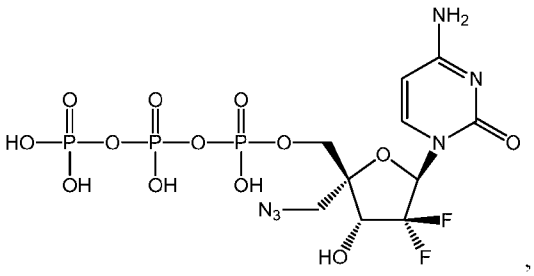


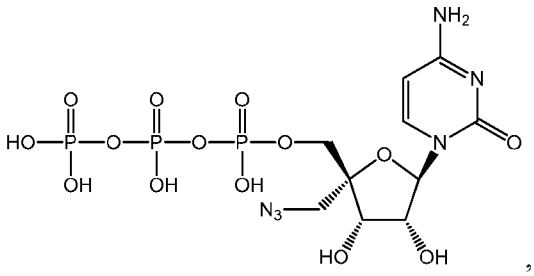


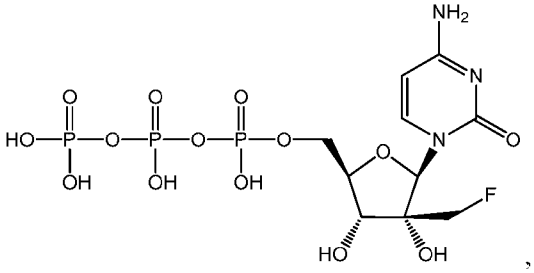


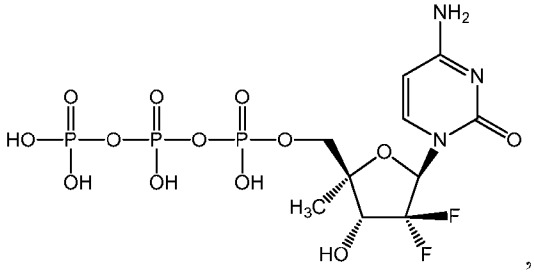


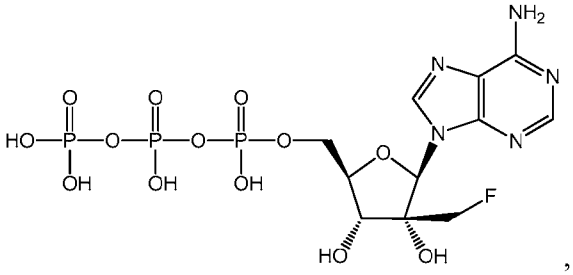


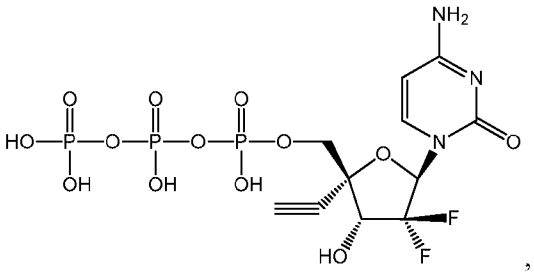


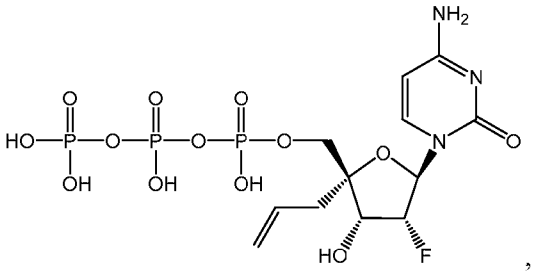


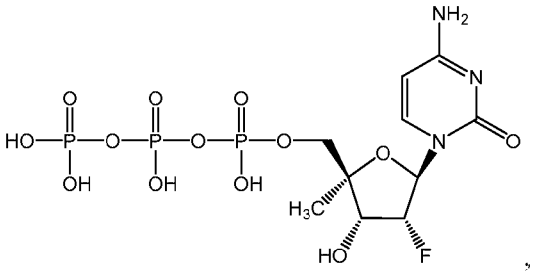


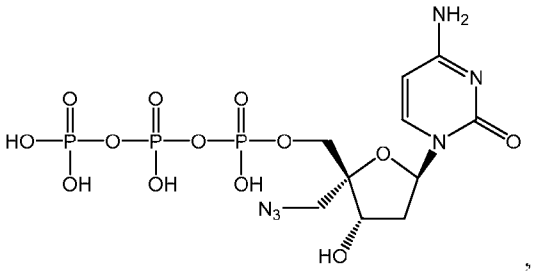


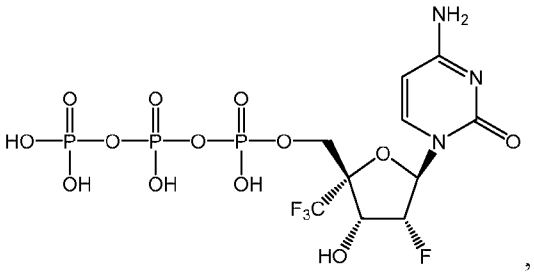


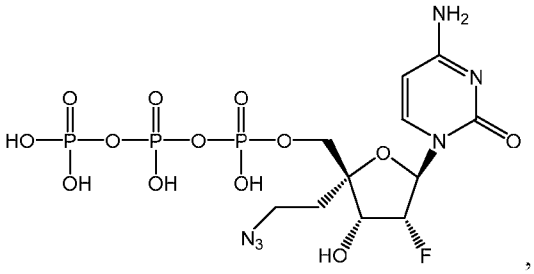


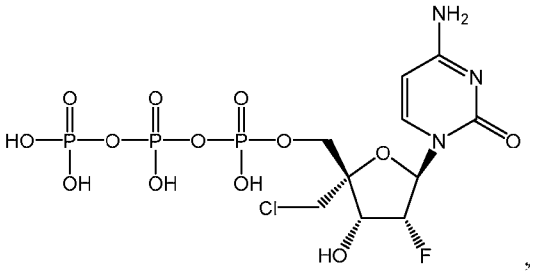


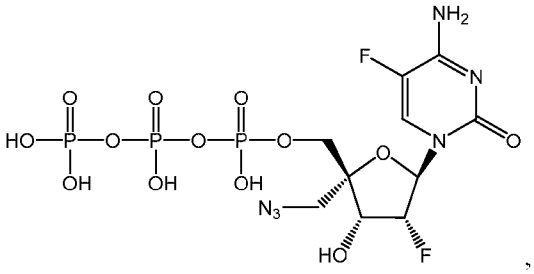


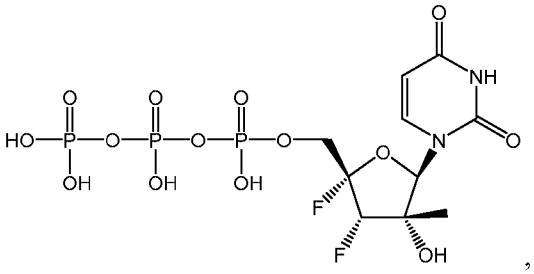


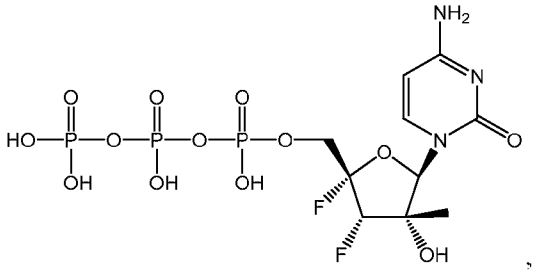
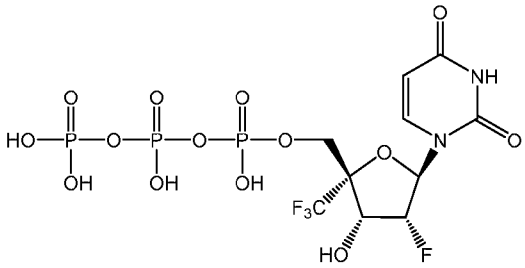
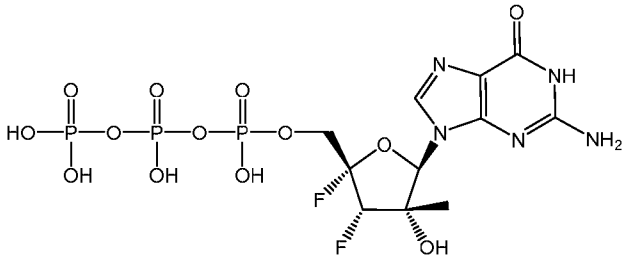












and

, or a pharmaceutically acceptable salt of the foregoing.

91. The use of any one of Claims 1-90, further comprising the use of an interferon.

92. The use of Claim 91, wherein the interferon is a pegylated interferon.

93. The use of any one of Claims 91-92, wherein the interferon is a Type 1 interferon.

94. The use of Claim 93, wherein the Type 1 interferon is an alpha-interferon (IFN-α).

95. The use of Claim 94, wherein the IFN-α is selected from the group consisting of Pegylated interferon-alpha-2a (PEGASYS®), Pegylated interferon-alpha-2b (PEG-INTRON®) and interferon alfacon-1 (INFERGEN®).

96. The use of Claim 93, wherein the interferon is a beta-interferon (IFN-β).

97. The use of any one of Claims 91-92, wherein the interferon is a Type 2 interferon.

98. The use of any one of Claims 91-92, wherein the interferon is a Type 3 interferon.

99. The use of Claim 98, wherein the Type 3 interferon is a lambda-interferon (IFN-λ).

100. The use of Claim 99, wherein the IFN-λ is pegylated interferon lambda.

101. The use of any one of Claims 1-100, further comprising the use of a compound selected from the group consisting of ribavirin, (2S,3S,4R,5R)-2-(4-amino-5H-pyrrolo[3,2-d]pyrimidin-7-yl)-5-(hydroxymethyl)pyrrolidine-3,4-diol, 5-Fluoro-2-oxo-1H-pyrazine-3-carboxamide, hexadecyloxypropyl-cidofovir, AVI-7537, AVI-7288, ZMapp and TKM-Ebola, or a pharmaceutically acceptable salt of the foregoing.