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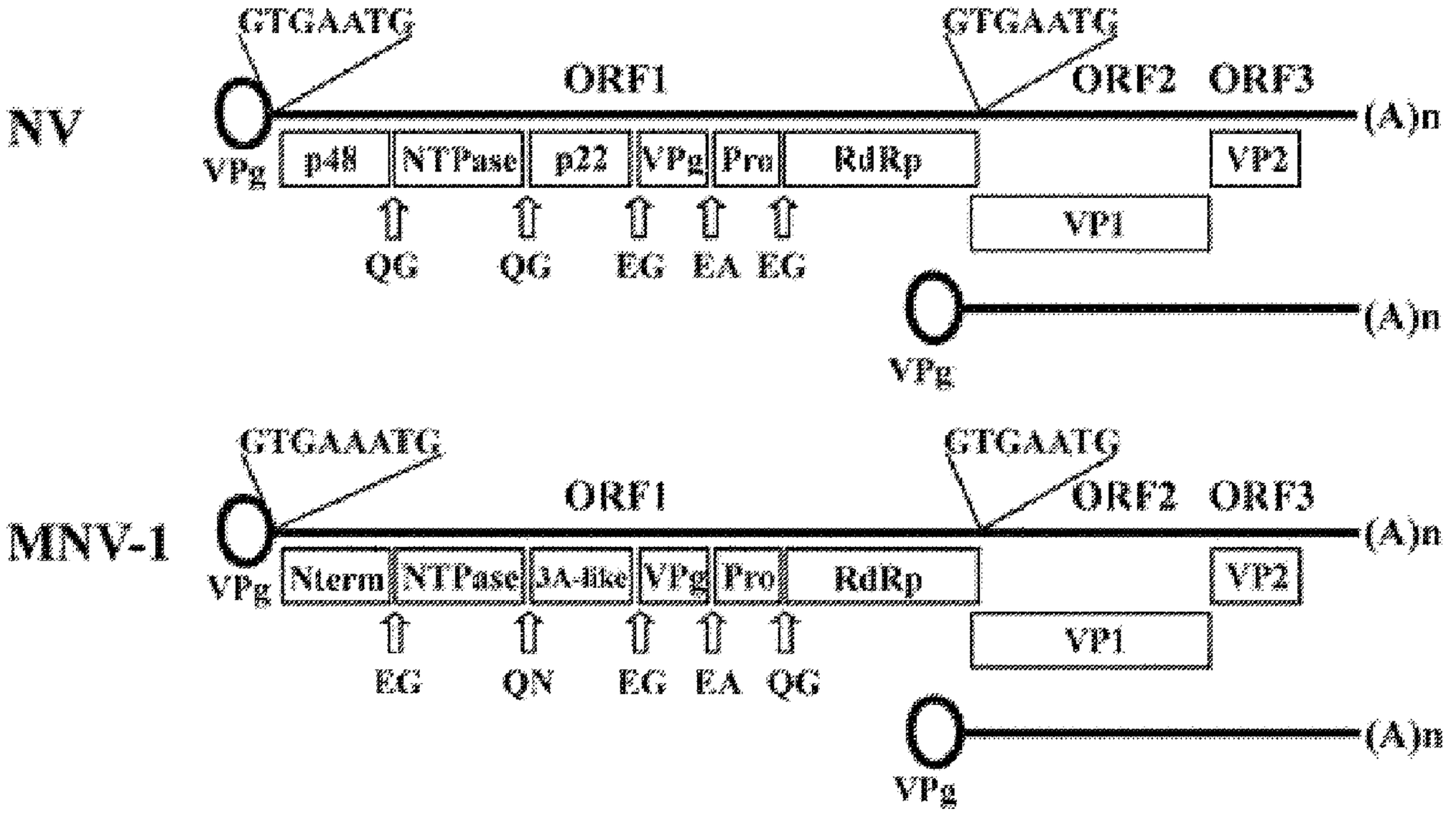
(71) **Demandeur/Applicant:**
ALIOS BIOPHARMA, INC., US

(72) **Inventeurs/Inventors:**
BEIGELMAN, LEONID, US;
DEVAL, JEROME, US;
JIN, ZHINAN, US

(74) **Agent:** SMART & BIGGAR

(54) **Titre : NUCLEOSIDES, NUCLEOTIDES SUBSTITUES ET LEURS ANALOGUES**
(54) **Title: SUBSTITUTED NUCLEOSIDES, NUCLEOTIDES AND ANALOGS THEREOF**

Figure 1



(57) **Abrégé/Abstract:**
Disclosed herein are nucleosides, nucleotides and analogs thereof, pharmaceutical compositions that include one or more of nucleosides, nucleotides and analogs thereof, and methods of synthesizing the same. Also disclosed herein are methods of

(21) **2 913 206**

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(57) **Abrégé(suite)/Abstract(continued):**
ameliorating and/or treating a disease and/or a condition, including an infection from a norovirus, with a nucleoside, a nucleotide and an analog thereof.

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(71) Applicant: **ALIOS BIOPHARMA, INC.** [US/US]; 260 E. Grand Ave, 2nd Floor, South San Francisco, CA 94080 (US).

(72) Inventors: **BEIGELMAN, Leonid**; 991 East Grant Place, San Mateo, CA 94402 (US). **DEVAL, Jerome**; 143 Carmel Ave., Pacific, CA 94044 (US). **JIN, Zhinan**; 2700 Del Medio Ct #120, Mountain Veiw, CA 94040 (US).

(74) Agent: **MILLER, Kimberly, J.**; Knobbe Martens Olson & Bear LLP, 2040 Main Street, 14th Floor, Irvine, CA 92614 (US).

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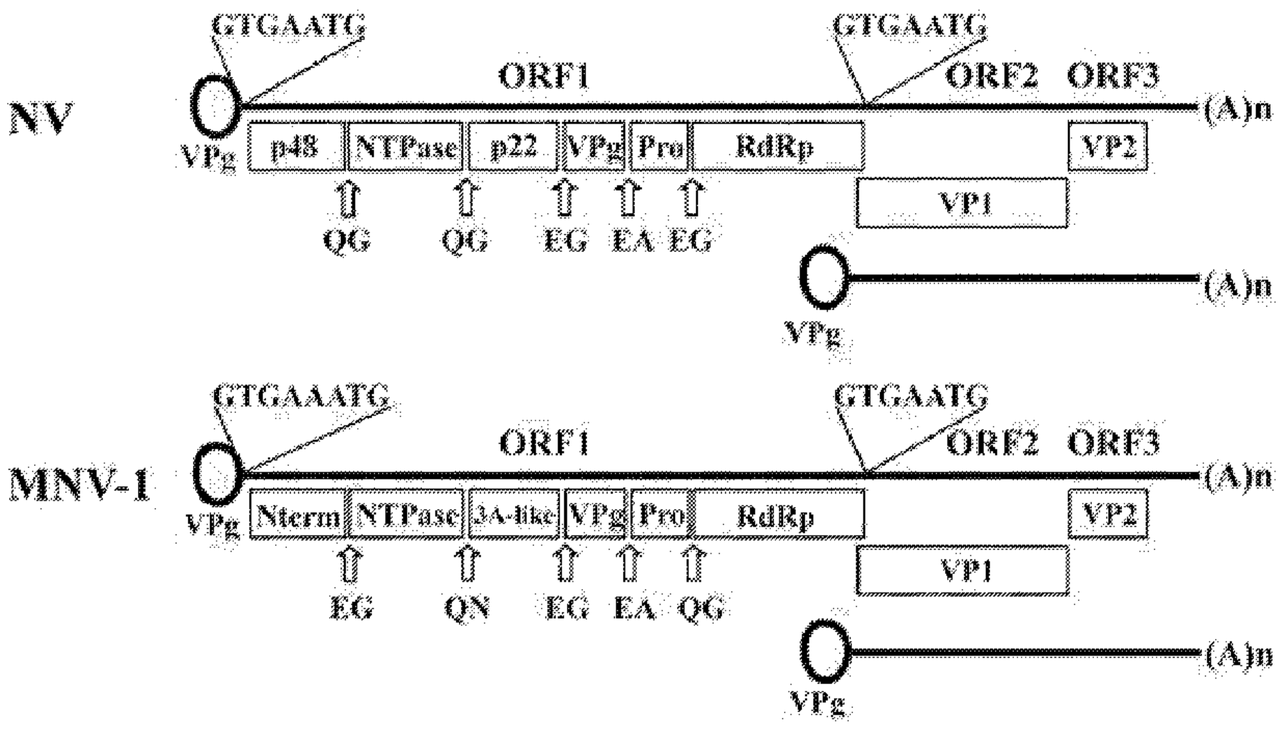
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(54) Title: SUBSTITUTED NUCLEOSIDES, NUCLEOTIDES AND ANALOGS THEREOF

Figure 1



(57) Abstract: Disclosed herein are nucleosides, nucleotides and analogs thereof, pharmaceutical compositions that include one or more of nucleosides, nucleotides and analogs thereof, and methods of synthesizing the same. Also disclosed herein are methods of ameliorating and/or treating a disease and/or a condition, including an infection from a norovirus, with a nucleoside, a nucleotide and an analog thereof.

WO 2014/209979 A1

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME	1	DE	2
CONTENANT LES PAGES	1	À	398

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JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME	1	OF	2
CONTAINING PAGES	1	TO	398

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SUBSTITUTED NUCLEOSIDES, NUCLEOTIDES AND ANALOGS THEREOF

INCORPORATION BY REFERENCE TO ANY PRIORITY APPLICATIONS

[0001] Any and all applications for which a foreign or domestic priority claim is identified, 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.

SEQUENCE LISTING

[0002] The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled ALIOS066.TXT, created June 23, 2014, which is 4 kb in size. The information in the electronic format of the Sequence Listing is incorporated herein by reference in its entirety.

BACKGROUND

Field

[0003] The present application relates to the fields of chemistry, biochemistry and medicine. More particularly, disclosed herein are nucleoside, nucleotides and analogs thereof, pharmaceutical compositions that include one or more nucleosides, nucleotides and analogs thereof, and methods of synthesizing the same. Also disclosed herein are methods of ameliorating and/or treating a norovirus infection with one or more nucleosides, nucleotides and analogs thereof.

Description

[0004] Nucleoside analogs are a class of compounds that have been shown to exert antiviral activity both *in vitro* and *in vivo*, and thus, have been the subject of widespread research for the treatment of viral infections. Nucleoside analogs are usually therapeutically inactive compounds that are converted by host or viral enzymes to their respective active anti-metabolites, which, in turn, may inhibit polymerases involved in viral or cell proliferation. The activation occurs by a variety of mechanisms, such as the addition of one or more phosphate groups and, or in combination with, other metabolic processes.

SUMMARY

[0005] Some embodiments disclosed herein relate to methods of ameliorating, treating and/or preventing a norovirus infection that can include administering to a subject an effective amount of one or more compounds of Formula (I), Formula (II) and/or Formula (III), or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition that includes one or more compounds of Formula (I), Formula (II) and/or Formula (III), or a pharmaceutically acceptable salt of the foregoing. Other embodiments described herein relate to using one or more compounds of Formula (I), Formula (II) and/or Formula (III), or a pharmaceutically acceptable salt of the foregoing, in the manufacture of a medicament for ameliorating, treating and/or preventing a norovirus infection. Still other embodiments described herein relate to compounds of Formula (I), Formula (II) and/or Formula (III), or a pharmaceutically acceptable salt of the foregoing, that can be used for ameliorating, treating and/or preventing a norovirus infection. Yet still other embodiments disclosed herein relate to methods of ameliorating, treating and/or preventing a norovirus infection that can include contacting a cell infected with the norovirus infection with an effective amount of one or more compounds of Formula (I), Formula (II) and/or Formula (III), or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition that includes one or more compounds of Formula (I), Formula (II) and/or Formula (III), or a pharmaceutically acceptable salt of the foregoing. Some embodiments disclosed herein relate to methods of inhibiting the replication of a norovirus that can include contacting a cell infection with the norovirus with an effective amount of one or more compounds of Formula (I), Formula (II) and/or Formula (III), or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition that includes one or more compounds of Formula (I), Formula (II) and/or Formula (III), or a pharmaceutically acceptable salt of the foregoing.

BRIEF DESCRIPTION OF THE DRAWINGS

[0006] Figure 1 is a schematic of the genetic organization of norovirus (NV) and first murine norovirus virus (MNV-1).

DETAILED DESCRIPTION

[0007] *Noroviruses* are a member of the *Caliciviridae* family, and positive single-stranded RNA, non-enveloped viruses that are approximately 27-35 nm in diameter. To date, noroviruses have been classified into 6 recognized genogroups, GI, GII, GIII, GIV, GV and GVI, with GI, GII and GIV affecting humans. Examples of the noroviruses include Norwalk virus, Desert Shield virus, Southampton virus, Hawaii virus, Snow Mountain virus, Mexico virus, Toronto virus, Bristol virus and Lordsdale virus. The RNA genomes of the noroviruses are organized into 3 major open reading frames (OFR1, OFR2, and OFR3) with a polyadenylated 3'-end. OFR1 enclosed a large polyprotein that is proteolytically processed into mature nonstructural proteins; OFR2 enclosed the major capside protein (VP1); and OFR3 enclosed a minor structural protein (VP2).

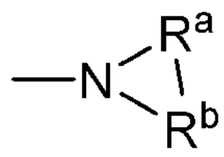
[0008] Noroviruses are highly contagious. According to the U.S. Center for Disease Control (CDC), a person with a norovirus infection can shed billions of norovirus particles, and it only takes as few as 18 viral particles to infect another person. http://www.cdc.gov/norovirus/hcp/clinical-overview.html (Nov. 2012). The virus is transmitted in various manners, including contacting a contaminated person, consuming contaminated food and/or water, and contacting contaminated surfaces, objects and/or substances. Outbreaks of norovirus infection can occur in closed or semi-closed spaces such as long-term facilities, overnight camps, hospitals, prisons, dorms, cruise ships and military settings. Norovirsuses have been attributed as being the leading cause of gastroenteritis. Symptoms of gastroenteritis include abdominal cramps, nausea, diarrhea and vomiting; and the diarrhea and vomiting associated with gastroenteritis can lead to dehydration. The duration of illness can vary from a couple of hours to several days.

[0009] According to the CDC, there is no specific therapy to treat or approved vaccine to prevent a norovirus infection. http://www.cdc.gov/norovirus/preventing-infection.html. Rather, a person can try to prevent a norovirus infection by practicing proper hygiene (including washing the hands with soap and water), washing fruits and vegetables, cooking seafood thoroughly, limiting exposure to others when infected, cleaning and disinfecting contaminated surfaces, washing laundry that may be contaminated and wearing gloves when handling soiled items.

Definitions

[0010] 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.

[0011] As used herein, any "R" group(s) such as, without limitation, R^{A}, R^{1A}, R^{2A}, R^{3A}, R^{4A}, R^{5A}, R^{6A}, R^{7A}, R^{8A}, R^{9A}, R^{10A}, R^{11A}, R^{12A}, R^{13A}, R^{14A}, R^{15A}, R^{16A}, R^{17A}, R^{18A}, R^{19A}, R^{20A}, R^{21A}, R^{22A}, R^{23A}, R^{24A}, R^{25A1}, R^{25A2}, R^{26A}, R^{27A}, R^{28A}, R^{29A}, R^{30A}, R^{31A}, R^{32A}, R^{33A}, R^{34A}, R^{35A}, R^{36A}, R^{37A}, R^{38A}, R^{1B}, R^{2B}, R^{3B}, R^{4B}, R^{5B}, R^{6B}, R^{7B}, R^{8B}, R^{9B}, R^{10B}, R^{11B1}, R^{11B2}, R^{12B}, R^{13B}, R^{14B}, R^{1C}, R^{2C}, R^{3C}, R^{4C}, R^{5C}, R^{6C}, R^{7C}, R^{8C}, R^{9C}, R^{10C}, R^{11C}, R^{12C}, R^{13C}, R^{14C}, R^{15C2}, R^{15C1}, R^{16C}, R^{17C}, R^{18C}, R^{19C}, R^{20C}, R^{21C}, R^{22C} and R^{23C} 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.

[0012] Whenever a group is described as being "optionally substituted" that group may be unsubstituted or substituted with one or more of the indicated substituents. Likewise, when a group is described as being "unsubstituted or substituted" if substituted, the substituent(s) may be selected from one or more the indicated substituents. If no substituents are indicated, it is meant that the indicated "optionally substituted" or "substituted" group may be substituted with one or more group(s) individually and independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl),

heteroaryl(alkyl), heterocyclyl(alkyl), hydroxy, alkoxy, aryloxy, acyl, mercapto, alkylthio, arylthio, cyano, halogen, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, protected C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, azido, nitro, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, an amino, a mono-substituted amino group and a di-substituted amino group, and protected derivatives thereof.

[0013] 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(s) of the cycloalkyl, ring(s) of the cycloalkenyl, ring(s) of the aryl, ring(s) of the heteroaryl or ring(s) 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.

[0014] 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.

[0015] As used herein, "alkenyl" refers to an alkyl group that contains in the straight or branched hydrocarbon chain one or more double bonds. Examples of alkenyl groups include allenyl, vinylmethyl and ethenyl. An alkenyl group may be unsubstituted or substituted.

[0016] As used herein, "alkynyl" refers to an alkyl group that contains in the straight or branched hydrocarbon chain one or more triple bonds. Examples of alkynyls include ethynyl and propynyl. An alkynyl group may be unsubstituted or substituted.

[0017] 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.

[0018] 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.

[0019] 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.

[0020] 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.

[0021] As used herein, "heterocyclyl" or "heteroalicyclyl" refers to three-, four-, five-, six-, seven-, eight-, nine-, ten-, up to 18-membered monocyclic, bicyclic, and tricyclic ring system wherein carbon atoms together with from 1 to 5 heteroatoms constitute said ring system. A heterocycle may optionally contain one or more unsaturated bonds situated in such a way, however, that a fully delocalized pi-electron system does not occur throughout all the rings. The heteroatom(s) is an element other than carbon including, but not limited to, oxygen, sulfur, and nitrogen. A heterocycle may further contain one or more carbonyl or thiocarbonyl functionalities, so as to make the definition include oxo-systems and thio-systems such as lactams, lactones, cyclic imides, cyclic thioimides and cyclic carbamates. When composed of two or more rings, the rings may be joined together in a fused fashion. Additionally, any nitrogens in a heteroalicyclic may be quaternized. Heterocyclyl or heteroalicyclic groups may be unsubstituted or substituted. Examples of such "heterocyclyl" or "heteroalicyclyl" groups include but are not limited to, 1,3-dioxin, 1,3-dioxane, 1,4-dioxane, 1,2-dioxolane, 1,3-dioxolane, 1,4-dioxolane, 1,3-oxathiane, 1,4-oxathiin, 1,3-oxathiolane, 1,3-dithiole, 1,3-dithiolane, 1,4-oxathiane, tetrahydro-1,4-thiazine, 2H-1,2-

oxazine, maleimide, succinimide, barbituric acid, thiobarbituric acid, dioxopiperazine, hydantoin, dihydrouracil, trioxane, hexahydro-1,3,5-triazine, imidazoline, imidazolidine, isoxazoline, isoxazolidine, oxazoline, oxazolidine, oxazolidinone, thiazoline, thiazolidine, morpholine, oxirane, piperidine *N*-Oxide, piperidine, piperazine, pyrrolidine, pyrrolidone, pyrrolidione, 4-piperidone, pyrazoline, pyrazolidine, 2-oxopyrrolidine, tetrahydropyran, 4H-pyran, tetrahydrothiopyran, thiamorpholine, thiamorpholine sulfoxide, thiamorpholine sulfone, and their benzo-fused analogs (e.g., benzimidazolidinone, tetrahydroquinoline, and 3,4-methylenedioxyphenyl).

[0022] 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).

[0023] 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.

[0024] 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 heterocyclyl(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)

[0025] "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."

[0026] As used herein, "alkoxy" refers to the formula –OR wherein R is an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heteroalicyclyl, 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.

[0027] 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.

[0028] 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.

[0029] 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.

[0030] As used herein, "haloalkoxy" refers to a 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.

[0031] A "sulfenyl" group refers to an "-SR" group in which R can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). A sulfenyl may be substituted or unsubstituted.

[0032] 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.

[0033] 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.

[0034] 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, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl), as defined herein. An O-carboxy may be substituted or unsubstituted.

[0035] 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.

[0036] 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.

[0037] A "trihalomethanesulfonyl" group refers to an "X_3CSO_2-" group wherein each X is a halogen.

[0038] A "trihalomethanesulfonamido" group refers to an "$X_3CS(O)_2N(R_A)$-" group wherein each X is a halogen, and R_A hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl).

[0039] The term "amino" as used herein refers to a $–NH_2$ group.

[0040] As used herein, the term "hydroxy" refers to a –OH group.

[0041] A "cyano" group refers to a "-CN" group.

[0042] The term "azido" as used herein refers to a $–N_3$ group.

[0043] An "isocyanato" group refers to a "-NCO" group.

[0044] A "thiocyanato" group refers to a "-CNS" group.

[0045] An "isothiocyanato" group refers to an " -NCS" group.

[0046] A "mercapto" group refers to an "-SH" group.

[0047] A "carbonyl" group refers to a C=O group.

[0048] 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, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An S-sulfonamido may be substituted or unsubstituted.

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

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

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

[0052] 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, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An O-thiocarbamyl may be substituted or unsubstituted.

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

[0054] 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, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). A C-amido may be substituted or unsubstituted.

[0055] 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, aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl). An N-amido may be substituted or unsubstituted.

[0056] 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.

[0057] 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.

[0058] 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)).

[0059] The term "nucleoside" is used herein in its ordinary sense as understood by those skilled in the art, and refers to a compound composed of an optionally substituted pentose moiety or modified pentose moiety attached to a heterocyclic base or tautomer thereof via a N-glycosidic bond, such as attached via the 9-position of a purine-base or the 1-position of a pyrimidine-base. Examples include, but are not limited to, a ribonucleoside comprising a ribose moiety and a deoxyribonucleoside comprising a deoxyribose moiety. A modified pentose moiety is a pentose moiety in which an oxygen atom has been replaced with a carbon and/or a carbon has been replaced with a sulfur or an oxygen atom. A "nucleoside" is a monomer that can have a substituted base and/or sugar moiety. Additionally, a nucleoside can be incorporated into larger DNA and/or RNA polymers and oligomers. In some instances, the nucleoside can be a nucleoside analog drug.

[0060] 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.

[0061] 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

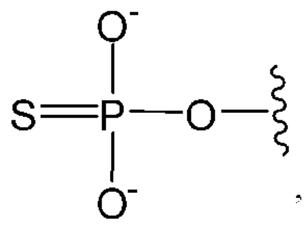
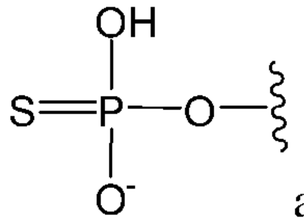
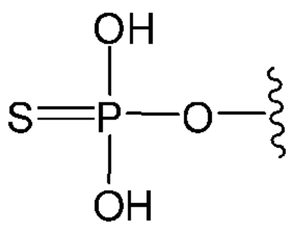
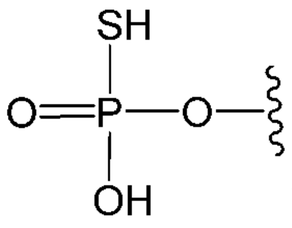
"purine-base" is used herein in its ordinary sense as understood by those skilled in the art, and includes its tautomers. Similarly, the term "pyrimidine-base" is used herein in its ordinary sense as understood by those skilled in the art, and includes its tautomers. A non-limiting list of optionally 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).

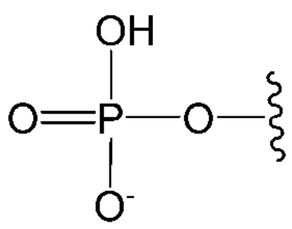
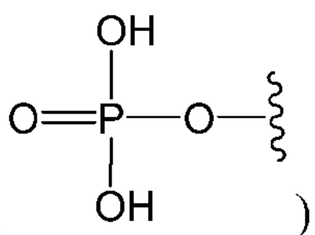
[0062] The term "–N–linked amino acid" refers to an amino acid that is attached to the indicated moiety via a main-chain amino or mono-substituted amino group. When the amino acid is attached in an –N–linked amino acid, one of the hydrogens that is part of the main-chain amino or mono-substituted amino group is not present and the amino acid is attached via the nitrogen. N-linked amino acids can be substituted or unsubstituted.

[0063] 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.

[0064] 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.

[0065] 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.

[0066] The terms "phosphorothioate" and "phosphothioate" refer to a compound of the general formula  its protonated forms (for example,  and ) and its tautomers (such as ).

[0067] 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.

[0068] 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).

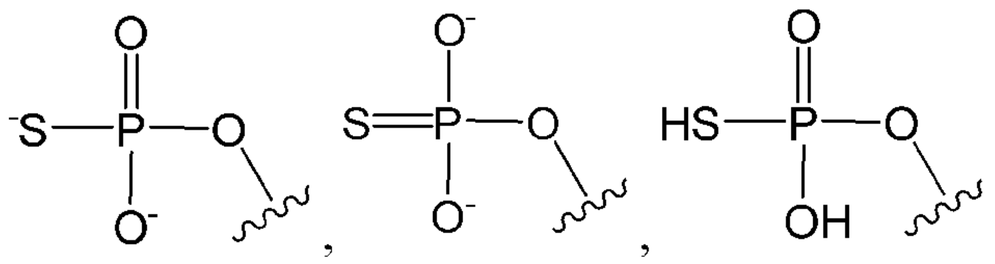
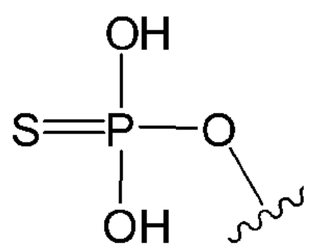
[0069] The term "pharmaceutically acceptable salt" refers to a salt of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. In some embodiments, the salt is an acid addition salt 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-toluensulfonic, salicylic or naphthalenesulfonic acid. Pharmaceutical salts can also be obtained by reacting a compound

with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, N-methyl-D-glucamine, tris(hydroxymethyl)methylamine, C_1-C_7 alkylamine, cyclohexylamine, triethanolamine, ethylenediamine, and salts with amino acids such as arginine and lysine.

[0070] 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.

[0071] 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.

[0072] 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.

[0073] Likewise, it is understood that, in any compound described, all tautomeric forms are also intended to be included. For example all tautomers of a phosphate and a phosphorothioate groups are intended to be included. Examples of tautomers of a phosphorothioate include the following: , . Furthermore, all tautomers of heterocyclic bases known in the art are intended to be included, including tautomers of natural and non-natural purine-bases and pyrimidine-bases.

[0074] 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).

[0075] 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.

[0076] 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.

[0077] 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:

[0078] Some embodiments described herein relate to a method of ameliorating and/or treating a norovirus infection, which can include administering an effective amount of one or more compounds described herein, or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), a compound of Formula (II) and/or a compound of Formula (III), or a pharmaceutically acceptable salt of the foregoing). Other embodiments described herein relate to a method of preventing a norovirus infection, which can include administering an effective amount of one or more compounds described herein, or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), a compound of Formula (II) and/or a compound of Formula (III), or a pharmaceutically acceptable salt of the foregoing).

[0079] Other embodiments described herein relate to a method of inhibiting viral replication of a norovirus virus, which can include contacting a cell infected with the norovirus virus with an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, an effective amount of a compound of Formula (II), or a pharmaceutically acceptable salt thereof, an effective amount of a compound of Formula (III), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), a compound of Formula (II) and/or a compound of Formula (III), or a pharmaceutically acceptable salt of the foregoing). Still other embodiments described herein related to a method of inhibiting at least one of the following in the norovirus replication: polymerase protease and helicase.

[0080] In some embodiments, an effective amount of one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof, an effective amount of one or more compounds of Formula (II), or a pharmaceutically acceptable salt thereof, an effective amount of one or more compounds of Formula (III), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutical composition that includes one or more compounds described herein (e.g., a compound of Formula (I), a compound of Formula (II) and/or a compound of Formula (III), or a pharmaceutically acceptable salt of the foregoing) can be used treat, ameliorate and/or prevent one more symptoms of an infection caused by a norovirus. For

example, a compound of Formulae (I), (II) and/or (III) can be used to treat, ameliorate and/or prevent one or more of the following symptoms caused by a norovirus infection: abdominal cramps, nausea, diarrhea, vomiting, dehydration, fever, headache, chills, myalgia and sore throat.

[0081] The one or more compounds of Formula (I) or a pharmaceutically acceptable salt thereof, one or more compounds of Formula (II), or a pharmaceutically acceptable salt thereof, and/or one or more compounds of Formula (III), or a pharmaceutically acceptable salt thereof, that can be used to treat, ameliorate and/or prevent a norovirus infection can be a compound of Formula (I), or pharmaceutically acceptable salt thereof, and/or a compound of Formula (II), or a pharmaceutically acceptable salt thereof, and/or a compound of Formula (III), or a pharmaceutically acceptable salt thereof, provided in any of the embodiments described in paragraphs [0094]-[0191].

[0082] As used herein, the terms "prevent" and "preventing," mean a subject does not develop an infection because the subject has an immunity against the infection, or if a subject becomes infected, the severity of the disease is less compared to the severity of the disease if the subject has not been administered/received the compound. Examples of forms of prevention include prophylactic administration to a subject who has been or may be exposed to an infectious agent, such as a norovirus.

[0083] As used herein, the terms "treat," "treating," "treatment," "therapeutic," and "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 subject's overall feeling of well-being or appearance.

[0084] The terms "therapeutically effective amount" and "effective amount" are used to indicate an amount of an active compound, or pharmaceutical agent, that elicits the biological or medicinal response indicated. For example, a therapeutically effective amount of compound can be the amount needed to prevent, alleviate or ameliorate symptoms of disease or prolong the survival of the subject being treated This response may occur in a tissue, system, animal or human and includes alleviation of the signs or symptoms of the disease being treated. Determination of an effective amount is well within the capability of

those skilled in the art, in view of the disclosure provided herein. The therapeutically effective amount of the compounds disclosed herein required as a dose will depend on the route of administration, the type of animal, including human, being treated, and the physical characteristics of the specific animal under consideration. The dose can be tailored to achieve a desired effect, but will depend on such factors as weight, diet, concurrent medication and other factors which those skilled in the medical arts will recognize.

[0085] Various indicators for determining the effectiveness of a method for treating a viral infection, such as a norovirus 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 of disease response.

[0086] In some embodiments, an effective amount of a compound of Formulae (I), (II) and/or (III), or a pharmaceutically acceptable salt of the foregoing, is an amount that is effective to reduce viral titers to undetectable levels, for example, to about 1000 to about 5000, to about 500 to about 1000, or to about 100 to about 500 genome copies/mL serum. In some embodiments, an effective amount of a compound of Formulae (I), (II) and/or (III), or a pharmaceutically acceptable salt of the foregoing, is an amount that is effective to reduce viral load compared to the viral load before administration of the compound of Formulae (I) ,(II) and/or (III), or a pharmaceutically acceptable salt of the foregoing. In some embodiments, an effective amount of a compound of Formulae (I), (II) and/or (III), or a pharmaceutically acceptable salt of the foregoing, is an amount that is effective to achieve a reduction in viral titer in the serum of the subject in the range of about 1.5-log to about a 2.5-log reduction, about a 3-log to about a 4-log reduction, or a greater than about 5-log reduction compared to the viral load before administration of the compound of Formulae (I), (II) and/or (III), or a pharmaceutically acceptable salt of the foregoing. For example, wherein the viral load is measure before administration of the compound of Formulae (I), (II) and/or (III), or a pharmaceutically acceptable salt of the foregoing, and again after completion of the treatment regime with the compound of Formulae (I), (II) and/or (III), or a pharmaceutically acceptable salt of the foregoing (for example, 1 week after completion). In some embodiments, a

compound of Formulae (I), (II) and/or (III), or a pharmaceutically acceptable salt of the foregoing, can result in at least a 1, 2, 3, 4, 5, 10, 15, 20, 25, 50, 75, 100-fold or more reduction in the replication of a norovirus relative to pre-treatment levels in a subject, as determined after completion of the treatment regime (for example, 1 week after completion). In some embodiments, a compound of Formulae (I), (II) and/or (III), or a pharmaceutically acceptable salt of the foregoing, can result in a reduction of the replication of a norovirus relative to pre-treatment levels in the range of about 2 to about 5 fold, about 10 to about 20 fold, about 15 to about 40 fold, or about 50 to about 100 fold.

[0087] 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.

[0088] 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.

[0089] 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.

[0090] 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.

[0091] 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.

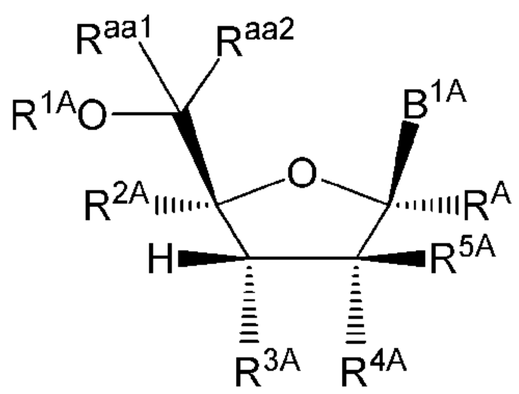
[0092] It should be noted that the attending physician would know how to and when to terminate, interrupt, or adjust administration due to toxicity or organ dysfunctions. Conversely, the attending physician would also know to adjust treatment to higher levels if the clinical response were not adequate (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.

[0093] 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*

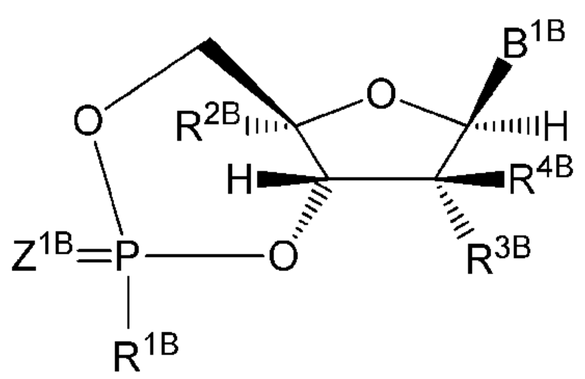
vitro toxicity towards a cell line, such as a mammalian, and preferably human, cell line. The results of such studies are often predictive of toxicity in animals, such as mammals, or more specifically, humans. Alternatively, the toxicity of particular compounds in an animal model, such as mice, rats, 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.

Compounds

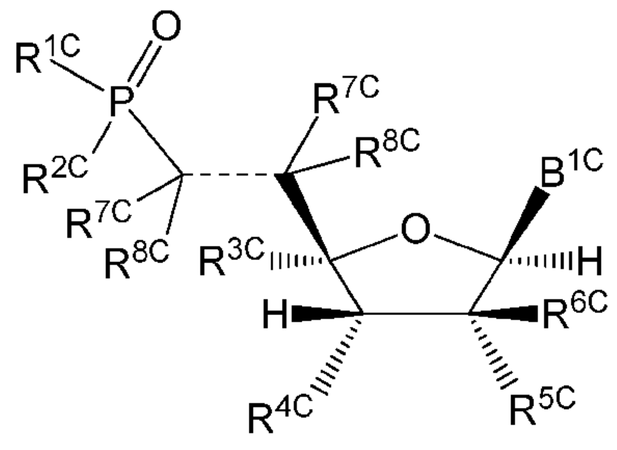
[0094] Some embodiments disclosed herein relate to a compound selected from Formula (I), Formula (II) and Formula (III), or a pharmaceutically acceptable salt of the foregoing:



(I)

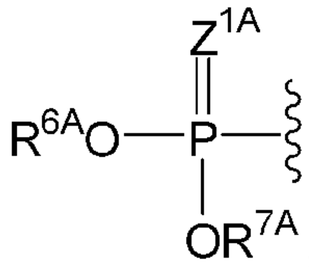
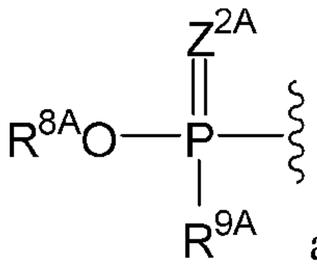
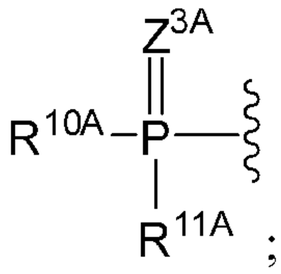
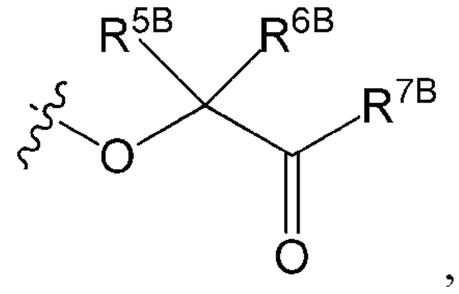
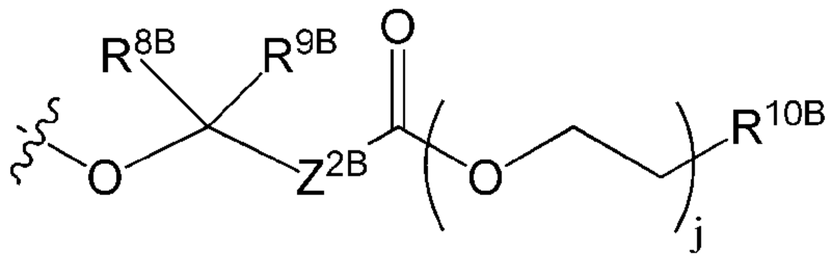
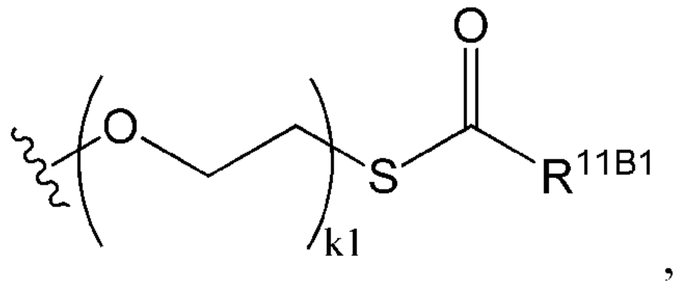
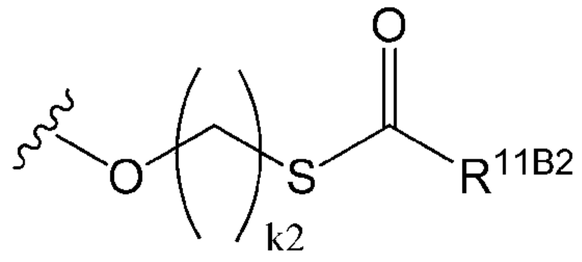
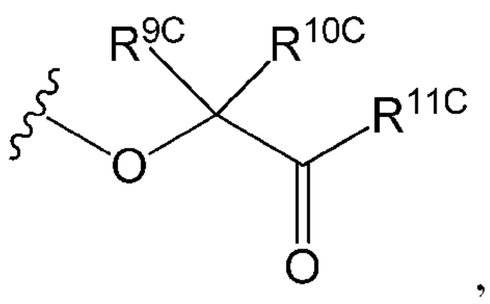
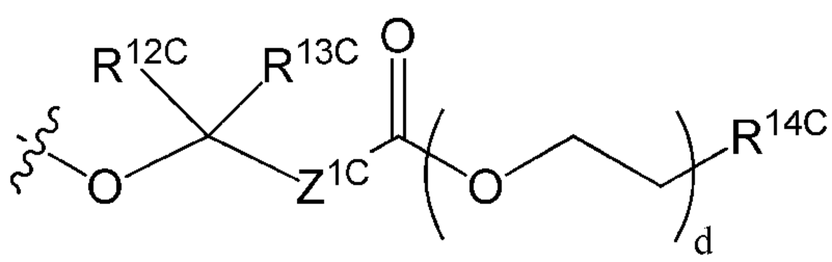
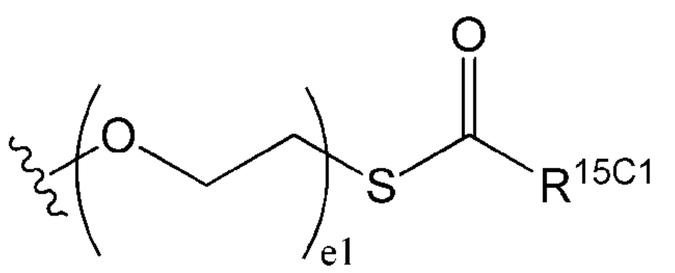
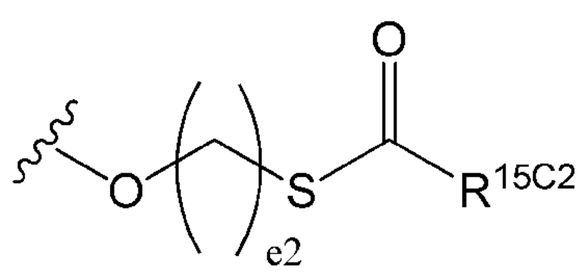


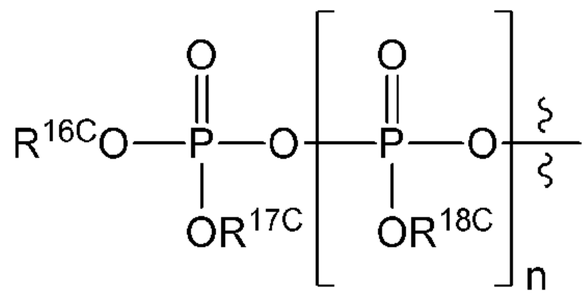
(II)



(III)

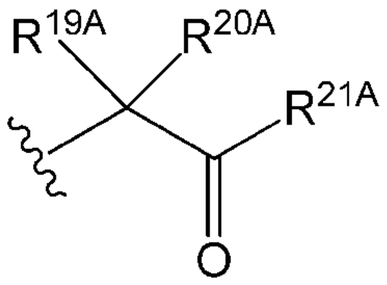
wherein: B^{1A}, B^{1B} and B^{1C} can be independently an optionally substituted heterocyclic base or an optionally substituted heterocyclic base with a protected amino group; R^{aa1} and R^{aa2} can be independently hydrogen or deuterium; R^{A} can be hydrogen, deuterium, an unsubstituted C_{1-3} alkyl, 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 selected from hydrogen, halogen, azido, 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 –O–C_{1-6} alkyl, an optionally substituted O–C_{3-6} alkenyl, an optionally substituted O–C_{3-6} alkynyl and cyano; R^{3A} can be selected from halogen, OH, -OC(=O)$R^{"A}$ and an optionally substituted O-linked amino acid; R^{1B} can be selected from O^-, OH, an optionally substituted C_{1-6} alkoxy, , , , , an optionally substituted N-linked amino acid and an optionally substituted N-linked amino acid ester derivative; R^{1C} and R^{2C} can be independently selected from O^-, OH, an optionally substituted C_{1-6} alkoxy, , , , , an optionally substituted N-linked amino acid and an optionally

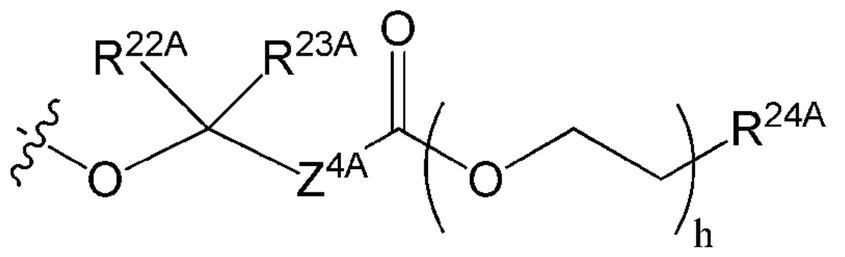


substituted N-linked amino acid ester derivative; or R^{1C} can be

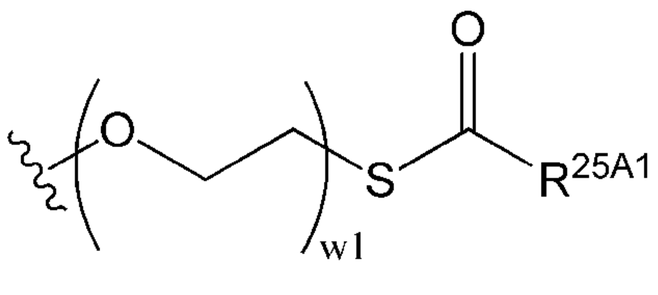
and R^{2C} can be O^- or OH; R^{2B} and R^{3C} can be independently selected from halogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{2-6} alkynyl, an optionally substituted –O–C_{1-6} alkyl, an optionally substituted –O–C_{3-6} alkenyl, an optionally substituted–O–C_{3-6} alkynyl, an optionally substituted C_{3-6} cycloalkyl and cyano; R^{4C} can be selected from OH, -OC(=O)$R^{"C}$ and an optionally substituted O-linked amino acid; R^{4A}, R^{3B} and R^{5C} can be independently selected from hydrogen, halogen, OR^{1D}, an optionally substituted O-linked amino acid, azido and $NR^{2D}R^{3D}$; R^{1D} can be hydrogen or –C(=O)$R^{"D}$; R^{2D} and R^{3D} can be independently hydrogen or an optionally substituted C_{1-6} alkyl; R^{5A}, R^{4B} and R^{6C} can be independently 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^{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,



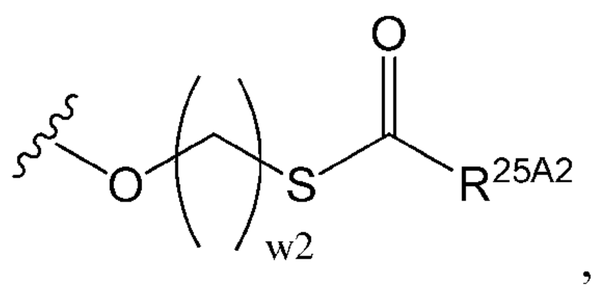
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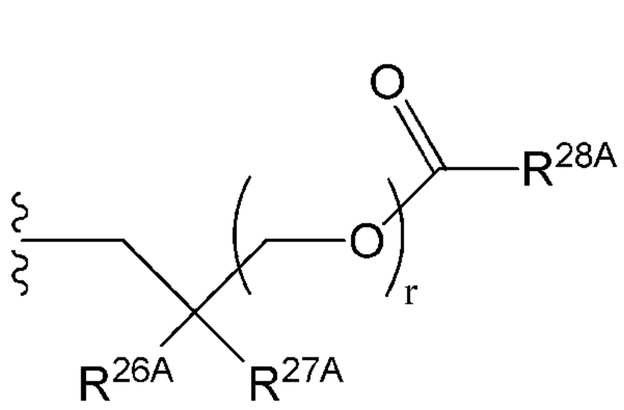
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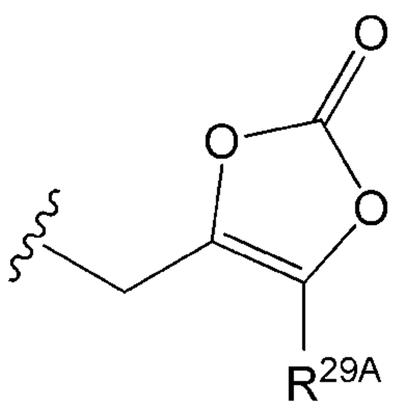


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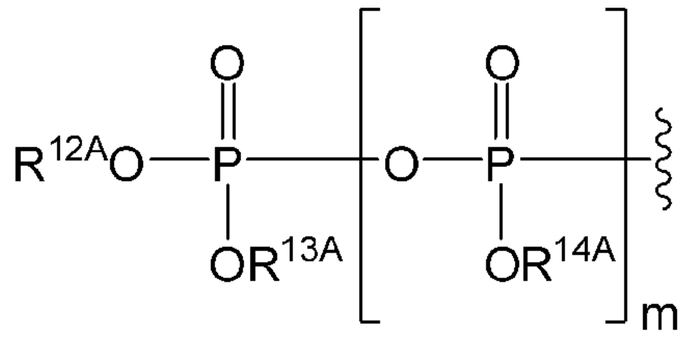


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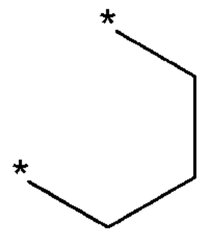




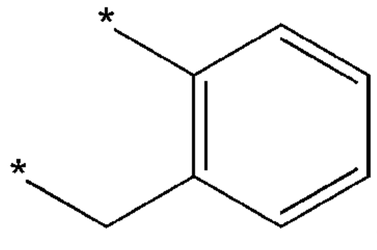
and ; or R^{6A} can be



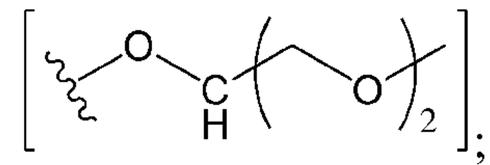
m and R^{7A} can be absent or hydrogen; or R^{6A} and R^{7A} can be taken together to form a moiety selected from an optionally substituted

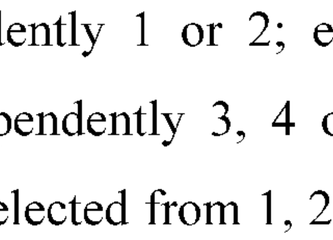
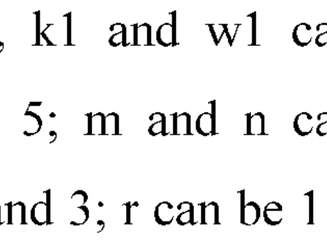


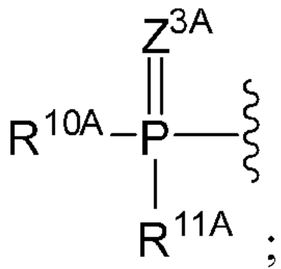
and an optionally substituted



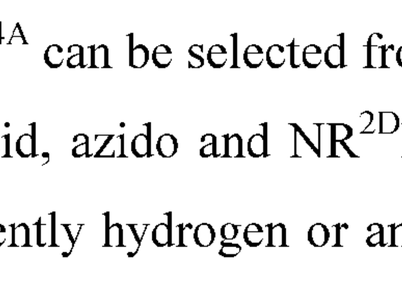
, wherein the oxygens connected to R^{6A} and R^{7A}, the phosphorus and the moiety form a six-membered to ten-membered ring system; R^{9A} can be independently selected from an optionally substituted C_{1-24} alkyl, an optionally substituted C_{2-24} alkenyl, an optionally substituted C_{2-24} alkynyl, 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}, R^{13A} and R^{14A} can be independently absent or hydrogen; 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 alkoxy; R^{19A}, R^{20A}, R^{22A}, R^{23A}, R^{5B}, R^{6B}, R^{8B}, R^{9B}, R^{9C}, R^{10C}, R^{12C} and R^{13C} can be independently selected from hydrogen, an optionally substituted C_{1-24} alkyl and an optionally substituted aryl; R^{21A}, R^{24A}, R^{7B}, R^{10B}, R^{11C} and R^{14C} 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, an optionally substituted –O–

monocyclic heterocyclyl and ; R^{25A1}, R^{25A2}, R^{29A}, R^{11B1}, R^{11B2}, R^{15C1} and R^{15C2} can be independently selected from hydrogen, an optionally substituted C_{1-24} alkyl and an optionally substituted aryl; R^{16C}, R^{17C} and R^{18C} can be independently absent or hydrogen; R^{26A} and R^{27A} 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; 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 and an optionally substituted C_{3-6} cycloalkenyl; for Formula (III), ------- can be a single bond or a double bond; when ------- is a single bond, each R^{7C} and each R^{8C} can be independently hydrogen or halogen; and when ------- is a double bond, each R^{7C} is absent and each R^{8C} can be independently hydrogen or halogen; $R^{"A}$, $R^{"C}$ and $R^{"D}$ can be independently an optionally substituted C_{1-24}-alkyl; d, j and h can be independently 1 or 2; e1, k1 and w1 can be independently 0 or 1; e2, k2 and w2 can be independently 3, 4 or 5; m and n can be independently 0 or 1; p and q can be independently selected from 1, 2 and 3; r can be 1 or 2; and Z^{1A}, Z^{2A}, Z^{3A}, Z^{4A}, Z^{1B}, Z^{2B} and Z^{1C} can be independently O or S.

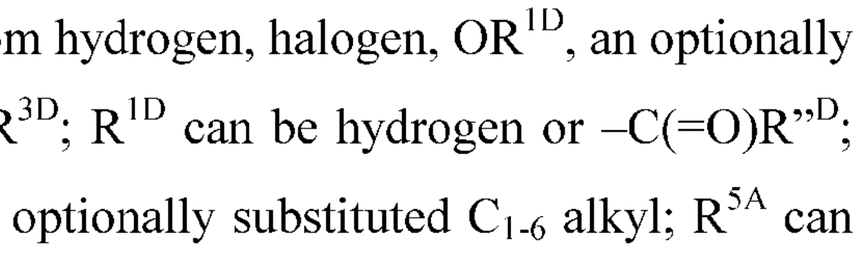
[0095] In some embodiments, the compound can be a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein: B^{1A} can be an optionally substituted heterocyclic base or an optionally substituted heterocyclic base with a protected amino group; R^{aa1} and R^{aa2} can be independently 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, ,  and



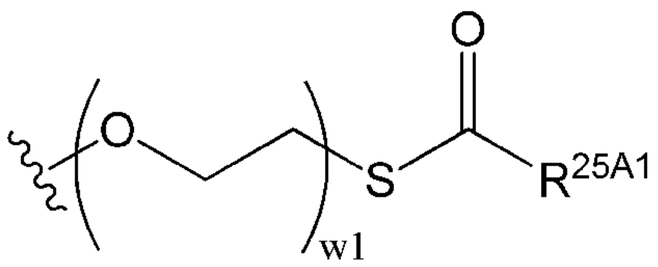
; R^{2A} can be selected from hydrogen, halogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{2-6} alkynyl, an optionally substituted –O–C_{1-6} alkyl, an optionally substituted –O–C_{3-6} alkenyl, an optionally substituted –O–C_{3-6} alkynyl and cyano; R^{3A} is halogen, OH, -OC(=O)R"^{A} and an optionally substituted O-linked amino; R^{4A} can be selected from hydrogen, halogen, OR^{1D}, an optionally substituted O-linked amino acid, azido and $NR^{2D}R^{3D}$; R^{1D} can be hydrogen or –C(=O)R"^{D}; R^{2D} and R^{3D} can be independently hydrogen or an optionally substituted C_{1-6} alkyl; R^{5A} can be selected from hydrogen, halogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl and an optionally substituted C_{2-6} alkynyl; R^{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,



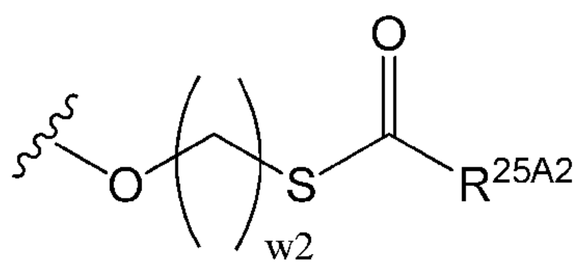
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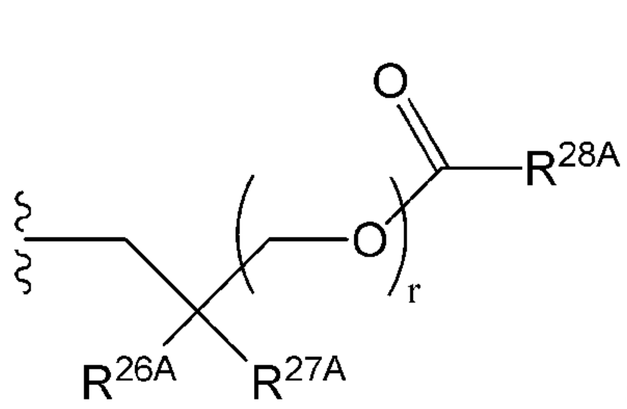
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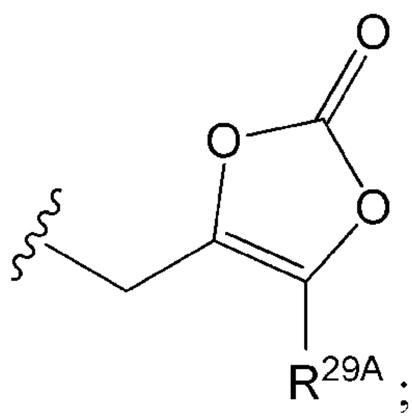
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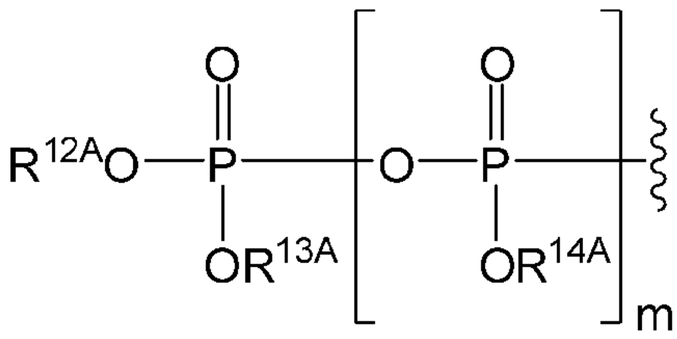
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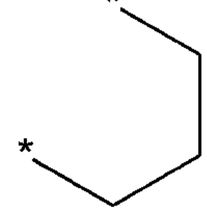
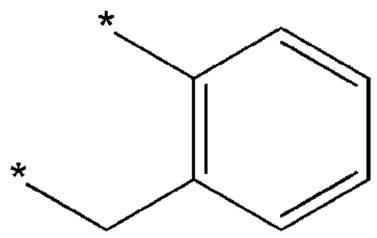
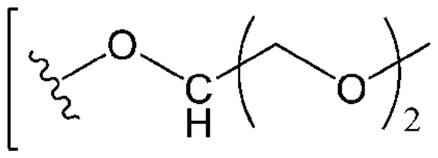


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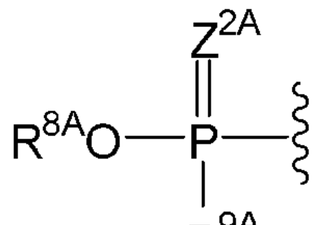


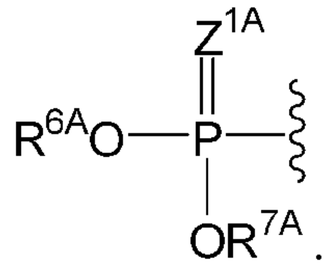
; or R^{6A} can be

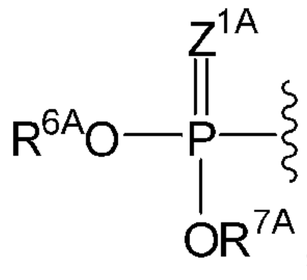


and R^{7A} can be absent or hydrogen; or R^{6A} and R^{7A} can be taken together to form a moiety selected from an optionally substituted  and an optionally substituted , wherein the oxygens connected to R^{6A} and R^{7A}, the phosphorus and the moiety form a six-membered to ten-membered ring system;. 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}, R^{13A} and R^{14A} can be independently absent or hydrogen; 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 alkoxy; R^{19A}, R^{20A}, R^{22A} and R^{23A} can be independently selected from hydrogen, an optionally substituted C_{1-24} alkyl and an optionally substituted aryl; R^{21A} and 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, an optionally substituted –O–monocyclic heterocyclyl and ; R^{25A1}, R^{25A2} and R^{29A} can be independently selected from hydrogen, an optionally substituted C_{1-24} alkyl and an optionally substituted aryl; R^{26A} and R^{27A} 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; 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 and an optionally substituted C_{3-6} cycloalkenyl; $R^{"A}$ and $R^{"D}$ can be independently an optionally substituted C_{1-24}-alkyl; h can be 1 or 2; w1 can be 0 or 1; w2 can be 3, 4 or 5; m can be 0 or 1; p and q can be independently selected from 1, 2 and 3; r can be 1 or 2; and Z^{1A}, Z^{2A}, Z^{3A} and Z^{4A} can be independently O or S.

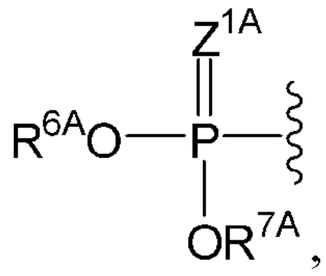
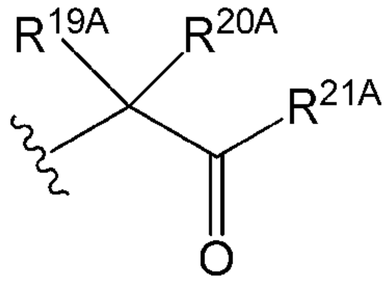
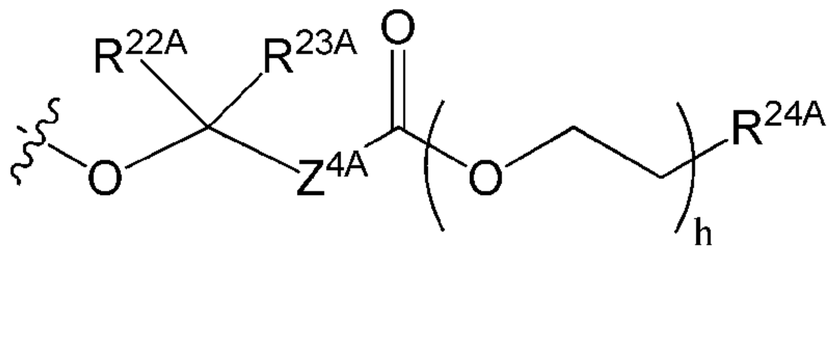
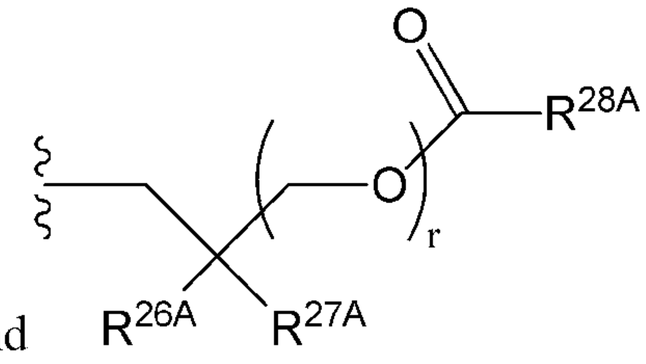
[0096] In some embodiments, a compound of Formula (I) can have a structure shown herein, provided that when R^{1A} is  wherein R^{8A} is an unsubstituted C_{1-4} alkyl or phenyl optionally para-substituted with a halogen or methyl and R^{9A} is methyl ester, ethyl ester, isopropyl ester, n-butyl ester, benzyl ester or phenyl ester of an amino acid selected from glycine, alanine, valine, leucine, phenylalanine, tryptophan, methionine and proline; R^{3A} is OH; R^{4A} is fluoro; R^{5A} is fluoro or hydrogen; and B^{1A} is an unsubstituted uracil; then R^{2A} cannot be $-OCH_3$. In some embodiments, a compound of Formula (I) can have a structure shown herein, provided that when R^{1A} is H; R^{3A} is OH; R^{4A} is fluoro; R^{5A} is fluoro; and B^{1A} is an unsubstituted cytosine; then R^{2A} cannot be allenyl. In some embodiments, a compound of Formula (I) can have a structure shown herein, provided that when R^{1A} is H; R^{3A} is OH; R^{4A} is fluoro; R^{5A} is hydrogen; and B^{1A} is an unsubstituted thymine; then R^{2A} cannot be C_1 alkyl substituted with an N-amido (for example, $-NC(=O)CF_3$). In some embodiments, a compound of Formula (I) can have a structure shown herein, provided that when R^{1A} is H; R^{3A} is OH; R^{4A} is fluoro; R^{5A} is fluoro; and B^{1A} is an unsubstituted cytosine; then R^{2A} cannot be ethynyl. In some embodiments, R^{2A} cannot be hydrogen. In some embodiments, when R^{2A} is hydrogen, then R^{5A} can be selected from halogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl and an optionally substituted C_{2-6} alkynyl.

[0097] 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.

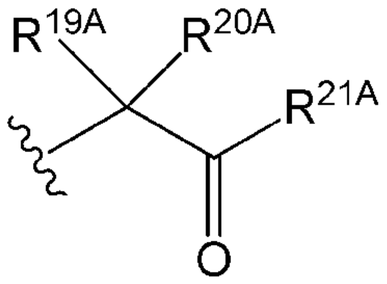
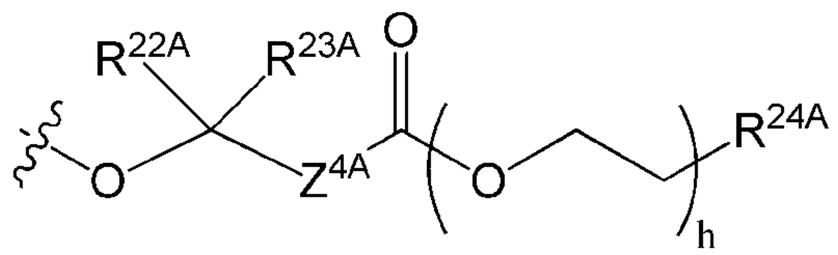
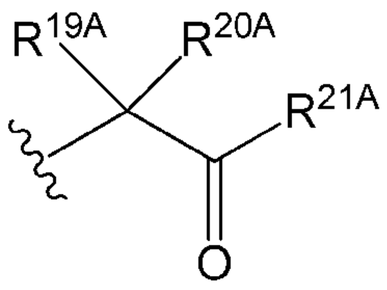
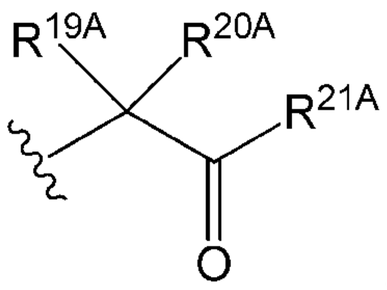
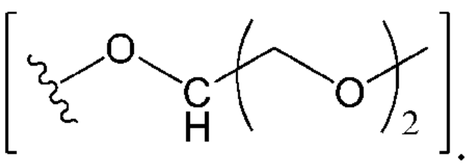
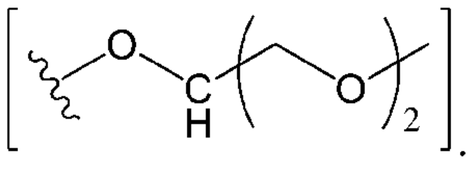
[0098] In some embodiments, when R^{1A} is , one of R^{6A} and R^{7A} can be hydrogen, and the other of R^{6A} and R^{7A} can be selected from an optionally substituted C_{1-24} alkyl, an optionally substituted C_{2-24} alkenyl, an optionally substituted C_{2-24} alkynyl, an optionally substituted C_{3-6} 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 version of 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.

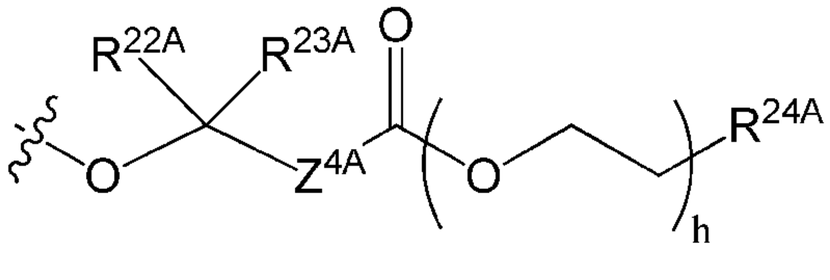
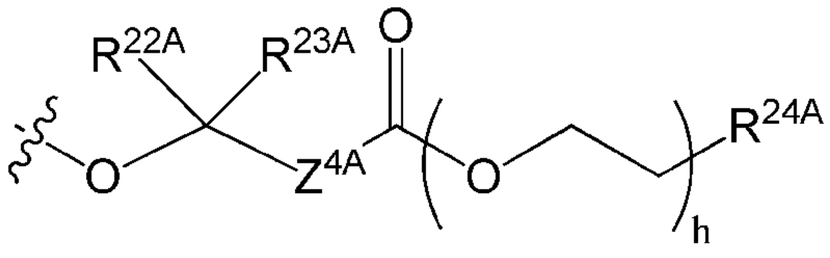
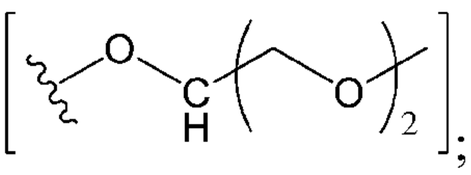
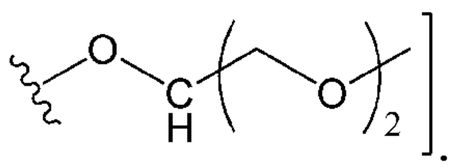
[0099] In some embodiments, at least one of R^{6A} and R^{7A} can be *–$(CR^{15A}R^{16A})_p$–O–C_{1-24} alkyl. In other embodiments, R^{6A} and R^{7A} can be both *–$(CR^{15A}R^{16A})_p$–O–C_{1-24} alkyl. In some embodiments, each R^{15A} and each R^{16A} can be hydrogen. In other embodiments, at least 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.

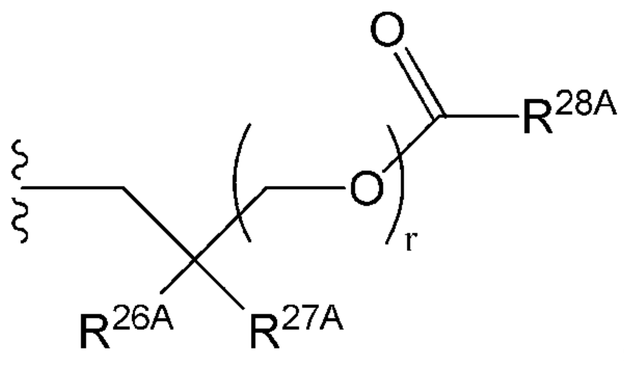
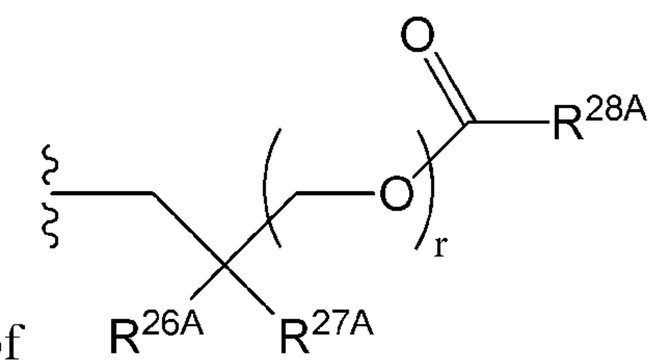
[0100] In some embodiments, at least one of R^{6A} and R^{7A} can be *–$(CR^{17A}R^{18A})_q$–O–C_{2-24} alkenyl. In other embodiments, R^{6A} and R^{7A} can be both *–$(CR^{17A}R^{18A})_q$–O–C_{2-24} alkenyl. In some embodiments, each R^{17A} and each R^{18A} can be hydrogen. In other embodiments, at 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.

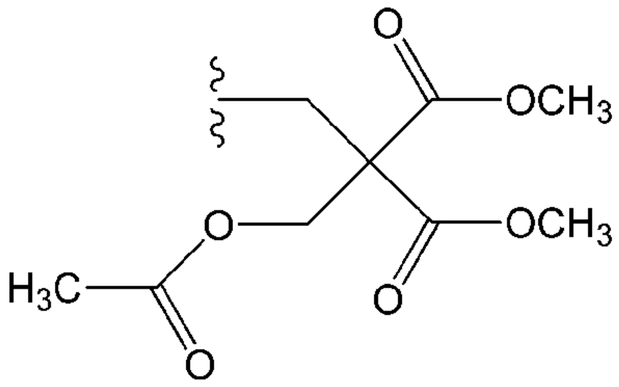
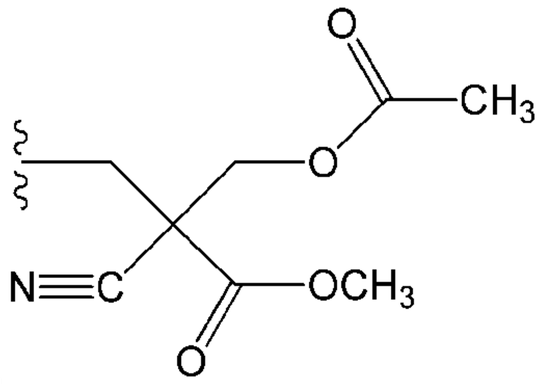
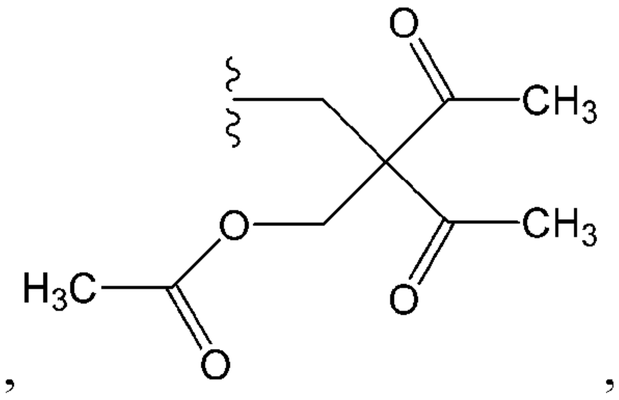
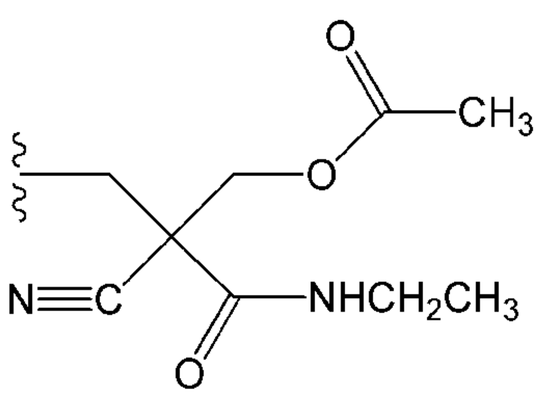
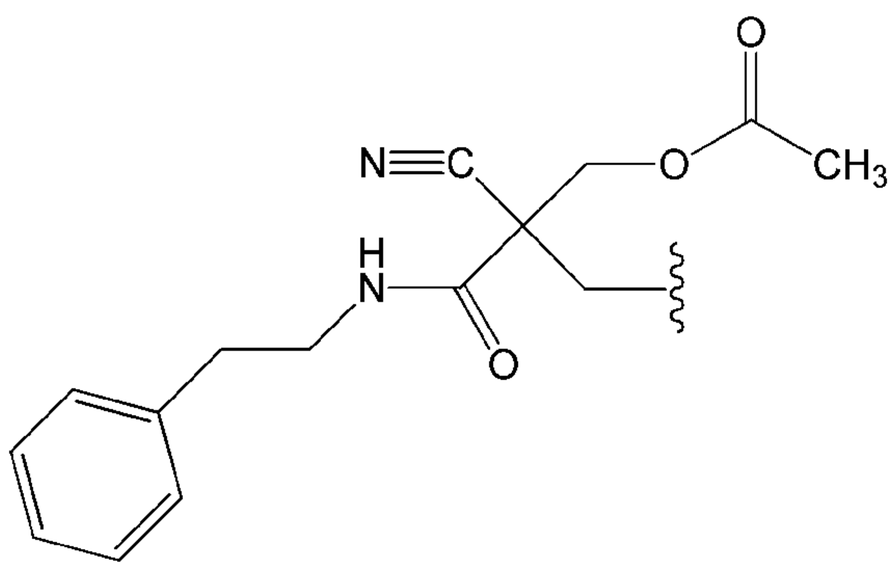
[0101] In some embodiments, when R^{1A} is , at least one of R^{6A} and R^{7A} can be selected from , ,  and ; and the other of R^{6A} and R^{7A} can be selected from absent, hydrogen, an optionally substituted C_{1-24} alkyl, an optionally substituted C_{2-24} alkenyl, an optionally substituted C_{2-24} alkynyl, an optionally substituted C_{3-6} cycloalkyl, an optionally

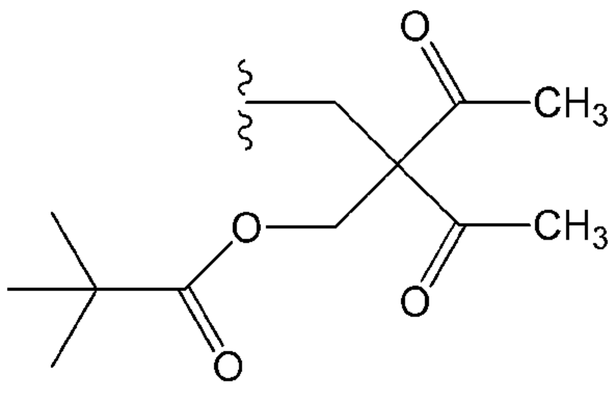
substituted C_{3-6} cycloalkenyl, an optionally substituted aryl, an optionally substituted heteroaryl and an optionally substituted aryl(C_{1-6} alkyl).

[0102] 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, an optionally substituted –O–monocyclic heterocyclyl and . 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 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 yet still other embodiments, R^{21A} can be .

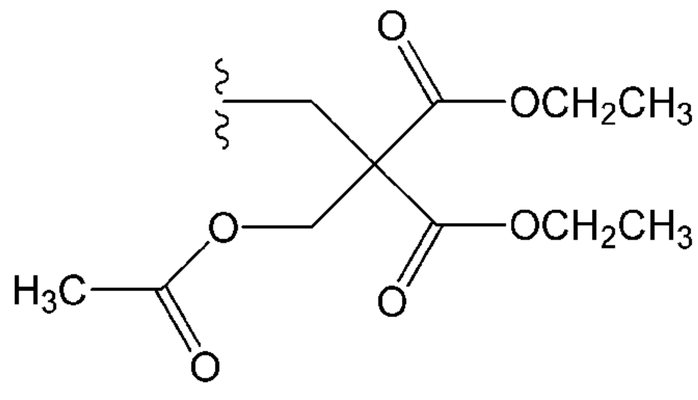
[0103] In some embodiments, both R^{6A} and R^{7A} can be . When one or both of R^{6A} and R^{7A} are , R^{22A} and R^{23A} can be independently selected from hydrogen, an optionally substituted $C_{1\text{-}24}$ alkyl and an optionally substituted aryl; R^{24A} can be independently selected from hydrogen, an optionally substituted $C_{1\text{-}24}$ alkyl, an optionally substituted aryl, an optionally substituted –O–$C_{1\text{-}24}$ alkyl, an optionally substituted –O–aryl, an optionally substituted –O–heteroaryl, an optionally substituted –O–monocyclic heterocyclyl and ; 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 $C_{1\text{-}24}$ alkyl or an optionally substituted aryl. In some embodiments, R^{24A} can be an optionally substituted $C_{1\text{-}24}$ alkyl. In other embodiments, R^{24A} can be an optionally substituted aryl. In still other embodiments, R^{24A} can be an optionally substituted –O–$C_{1\text{-}24}$ 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, h can be 1. In other embodiments, h can be 2. In some embodiments, Z^{4A} can be O (oxygen). In other embodiments, Z^{4A} can be or S (sulfur). In some embodiments, one or both of R^{6A} and R^{7A} can be isopropyloxycarbonyloxymethyl. In some embodiments, one or both of R^{6A} and R^{7A} can be pivaloyloxymethyl. In some embodiments, R^{6A} and R^{7A} can be both a isopropyloxycarbonyloxymethyl group, and form a bis(isopropyloxycarbonyloxymethyl) (bis(POC)) prodrug. In some embodiments, R^{6A} and R^{7A} can be both a pivaloyloxymethyl group, and form a bis(pivaloyloxymethyl) (bis(POM)) prodrug.

[0104] In some embodiments, both R^{6A} and R^{7A} can be , wherein R^{26A} and R^{27A} 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 r can be 1 or 2. Example of  include, but are not limited to the following:

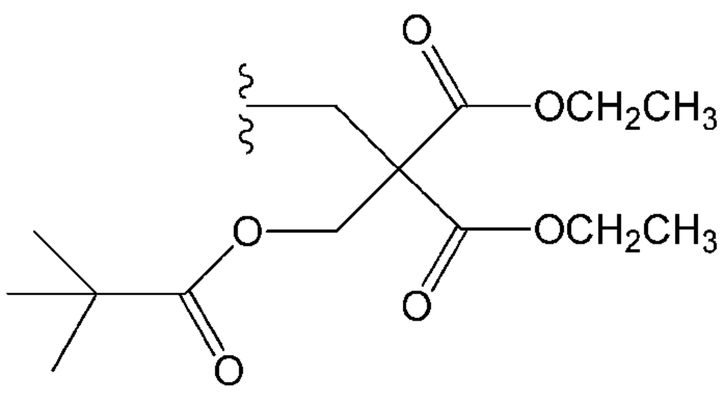
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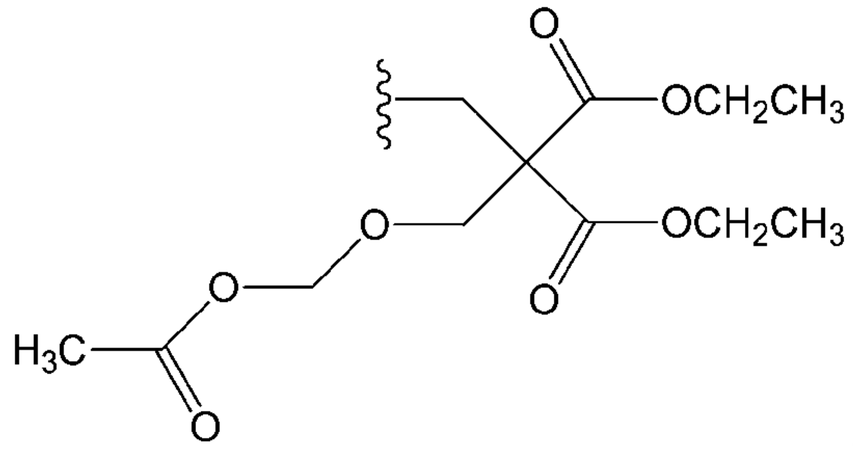
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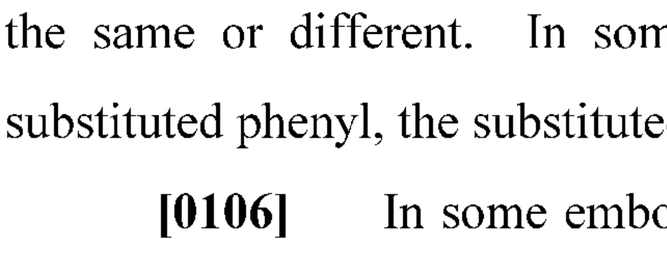


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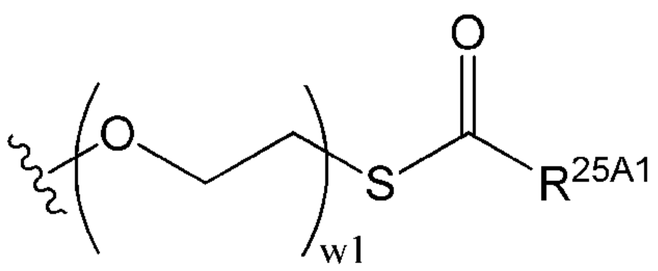
[0105] In some embodiments, R^{6A} and R^{7A} can be both an optionally substituted aryl. In some embodiments, at least one of R^{6A} and R^{7A} can be an optionally substituted aryl. For example, both R^{6A} and R^{7A} can be an optionally substituted phenyl or an optionally substituted naphthyl. When 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.

[0106] 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.

[0107] In some embodiments, R^{6A} and R^{7A} can be both

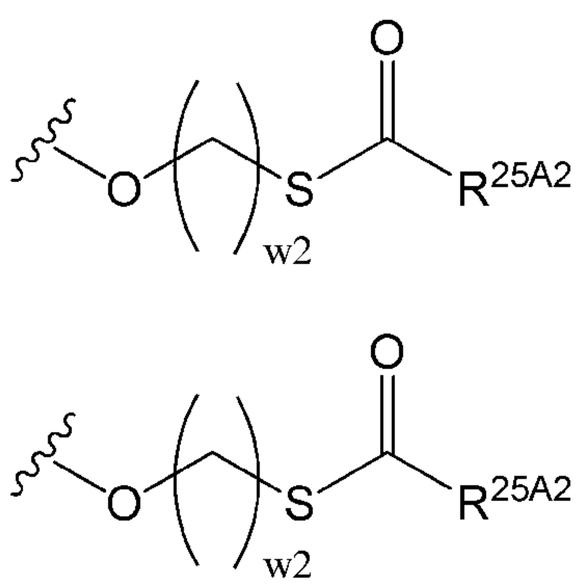


. In some embodiments, at least one of R^{6A} and R^{7A} can be



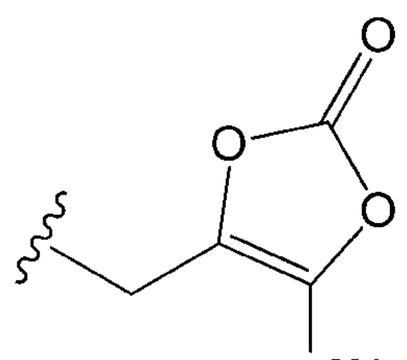
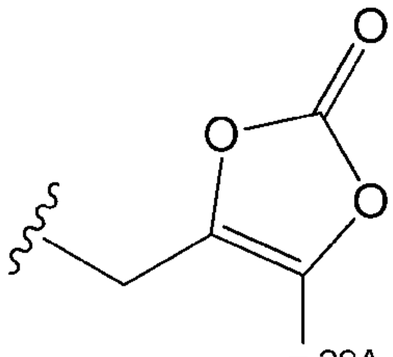
. In some embodiments, R^{25A1} can be hydrogen. In other embodiments, R^{25A1} can be an optionally substituted C_{1-24} alkyl. In still other embodiments, R^{25A1} can be an optionally substituted aryl. In some embodiments, R^{25A1} can be a C_{1-6} alkyl, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, pentyl (branched and straight-chained) and hexyl (branched and straight-chained). In some embodiments, w1 can be 0. In other embodiments, w1 can be 1. In some embodiments, R^{6A} and R^{7A} can be both a S-acylthioethyl (SATE) group and form a SATE ester prodrug.

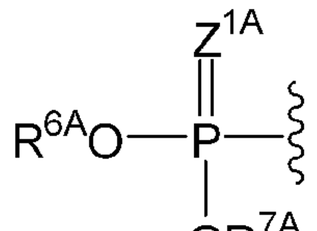
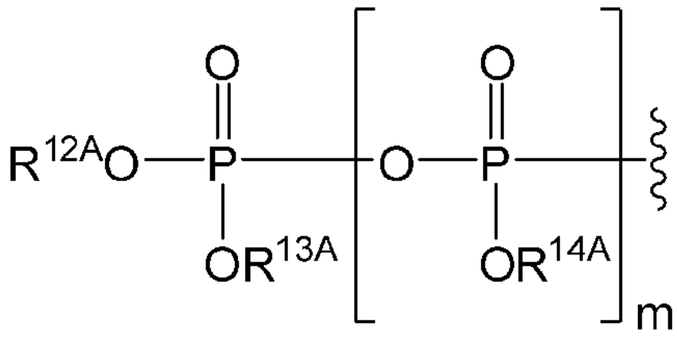
[0108] In some embodiments, R^{6A} and R^{7A} can be both

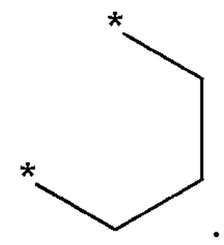
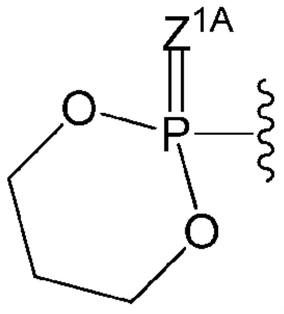
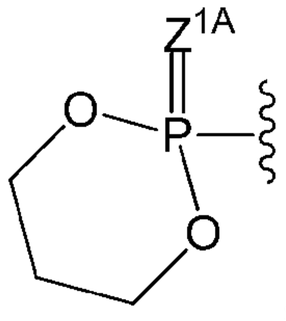
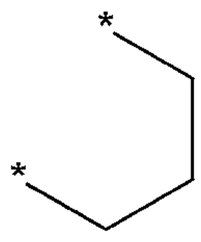
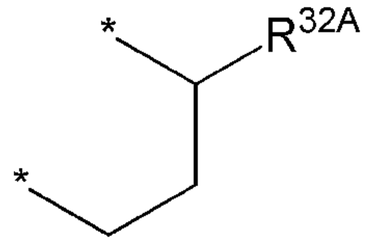


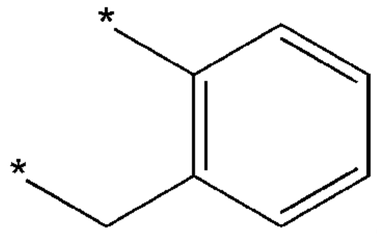
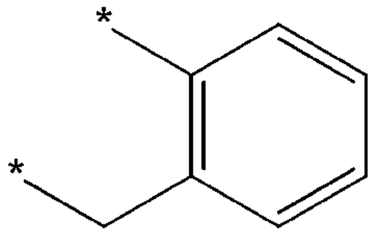
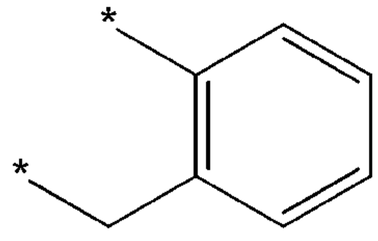
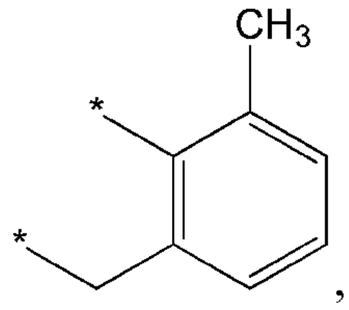
. In some embodiments, at least one of R^{6A} and R^{7A} can be

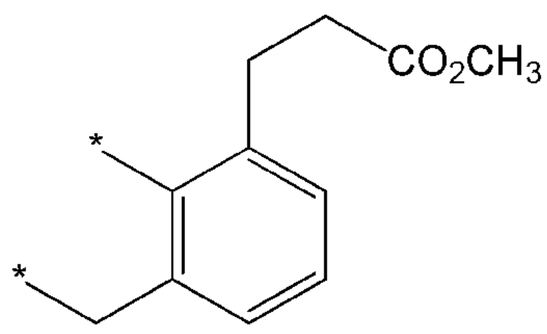
. In some embodiments, R^{25A2} can be hydrogen. In other embodiments, R^{25A2} can be an optionally substituted C_{1-24} alkyl. In still other embodiments, R^{25A2} can be an optionally substituted aryl, for example, an optionally substituted phenyl. In some embodiments, R^{25A2} can be an optionally substituted C_{1-6} alkyl. In some embodiments, R^{25A2} can be an unsubstituted C_{1-6} alkyl. In some embodiments, w2 can be 3. In other embodiments, w2 can be 4. In still other embodiments, w2 can be 5.

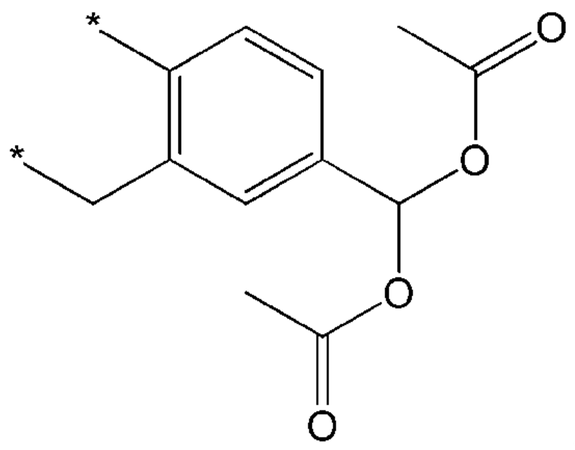
[0109] In some embodiments, R^{6A} and R^{7A} can be both . In some embodiments, at least one of R^{6A} and R^{7A} can be . In some embodiments, R^{29A} can be hydrogen. In other embodiments, R^{29A} can be an optionally substituted C_{1-24} alkyl. In some embodiments, R^{29A} can be a C_{1-4} alkyl, 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 a dioxolenone group and form a dioxolenone prodrug.

[0110] In some embodiments, R^{1A} can be ; R^{6A} can be ; R^{7A} can be absent or hydrogen; R^{12A}, R^{13A} and R^{14A} can be independently absent or hydrogen; 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}, R^{13A} and R^{14A} can be independently absent or hydrogen. Those skilled in the art understand that when m is 0, R^{6A} can be 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 triphosphate, when Z^{1A} is oxygen, or an alpha-thiotriphosphate, when Z^{1A} is sulfur.

[0111] 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 a cyclic 1-aryl-1,3-propanyl ester (HepDirect) prodrug moiety.

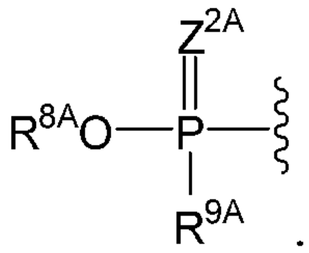
[0112] In some embodiments, R^{6A} and R^{7A} can be taken together to form an optionally substituted , wherein the oxygens connected to R^{6A} and R^{7A}, the phosphorus and the moiety form a six-membered to ten-membered ring system. Example of an optionally substituted  include , ,



and . In some embodiments, R^{6A} and R^{7A} can form a cyclosaligenyl (cycloSal) prodrug.

[0113] In some embodiments, R^{6A} and R^{7A} can be the same. In some embodiments, R^{6A} and R^{7A} can be different.

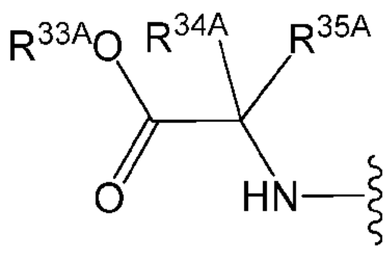
[0114] In some embodiments, Z^{1A} can be oxygen. In other embodiments, Z^{1A} can be sulfur.

[0115] 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.

[0116] 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^{30} and R^{31} 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 and an optionally substituted C_{3-6} cycloalkenyl.

[0117] 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

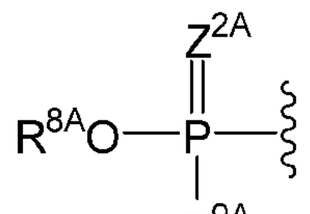
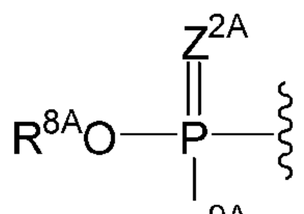
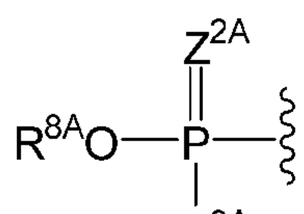
be an optionally substituted N-linked amino acid or an optionally substituted N-linked amino acid ester derivative. In still other embodiments, R^{8A} can be an optionally substituted heteroaryl; and R^{9A} can be an optionally substituted N-linked amino acid or an optionally substituted N-linked amino 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: alanine isopropyl ester, alanine cyclohexyl ester, alanine neopentyl ester, valine isopropyl ester and leucine isopropyl ester. In some embodiments, R^{9A} can have the structure

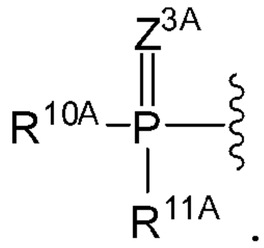
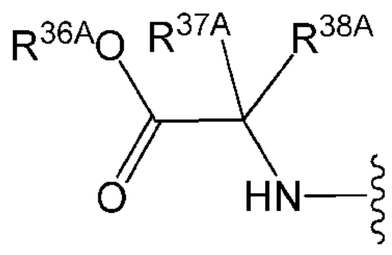


wherein R^{33A} can be selected from hydrogen, an optionally substituted C_{1-6}-alkyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted aryl, an optionally substituted aryl(C_{1-6} alkyl) and an optionally substituted haloalkyl; R^{34A} can be selected from hydrogen, an optionally 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.

[0118] 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,

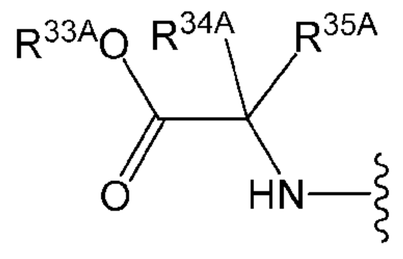
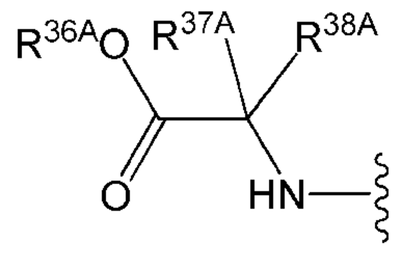
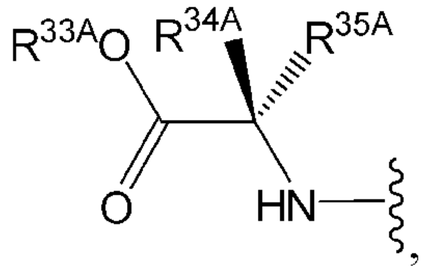
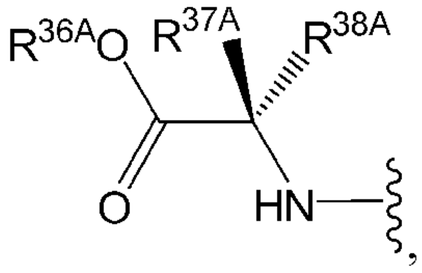
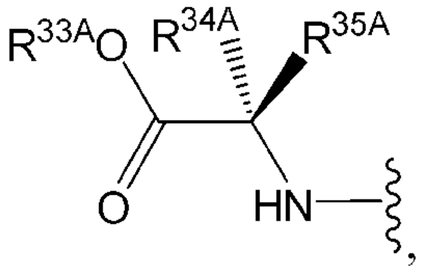
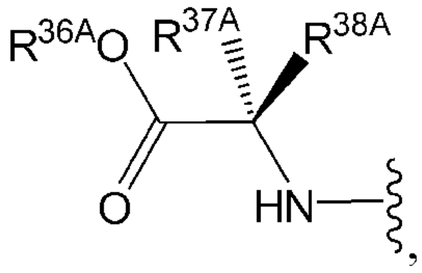
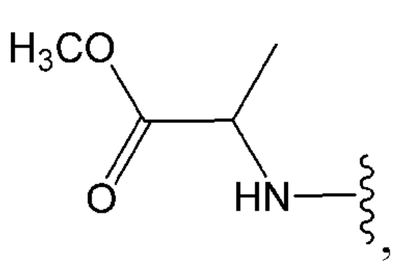
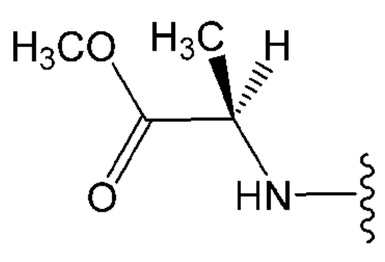
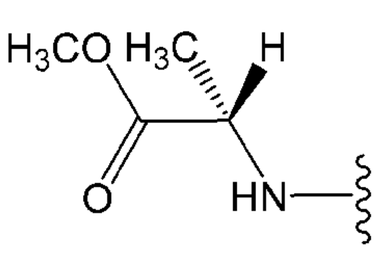
R^{33A} can be an optionally substituted C_{3-6} cycloalkyl. Examples of optionally substituted C_{3-6} cycloalkyl include optionally substituted variants of the following: cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. In an embodiment, R^{33A} can be an optionally substituted cyclohexyl. In 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 an embodiment, 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.

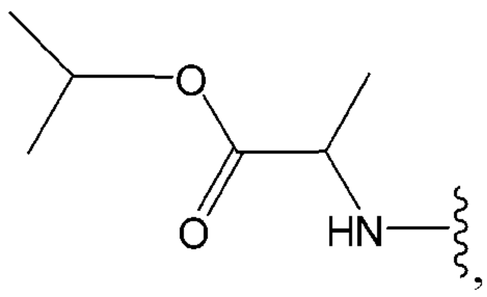
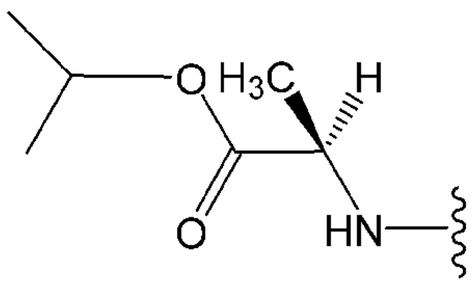
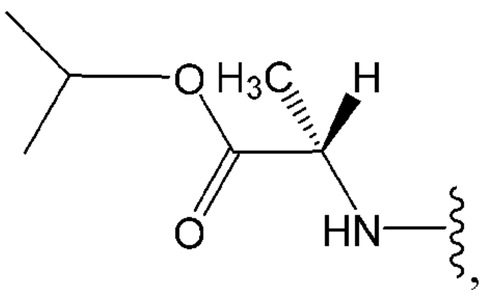
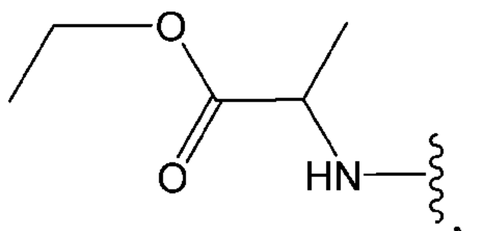
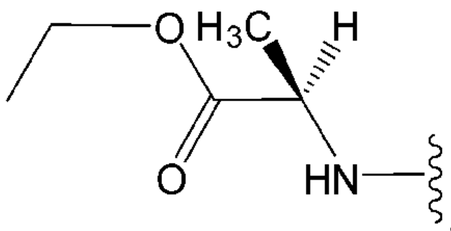
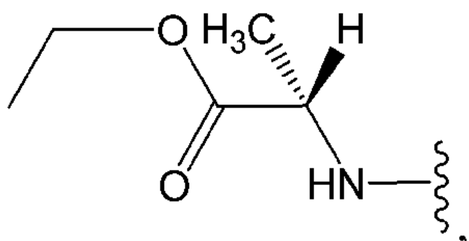
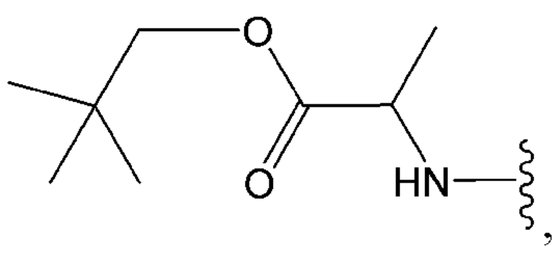
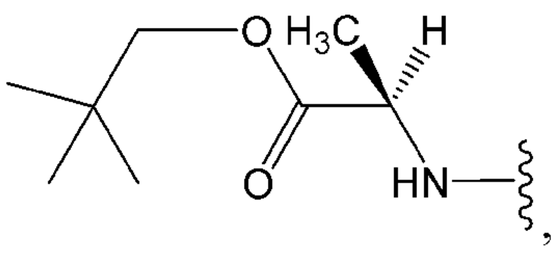
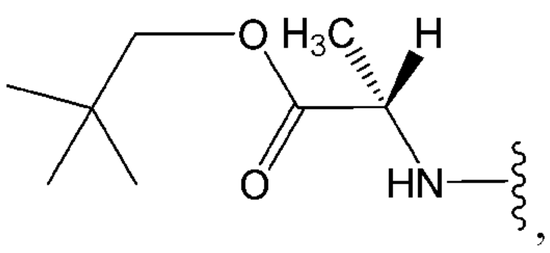
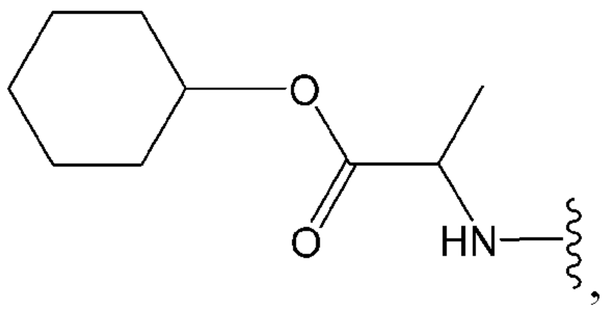
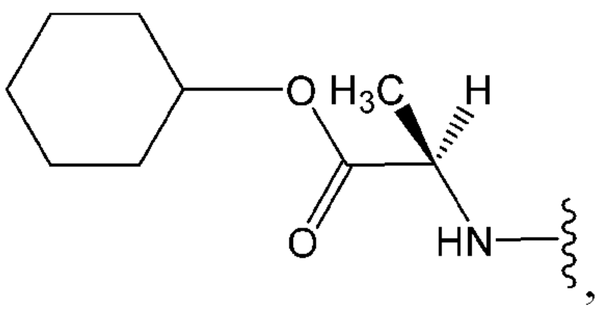
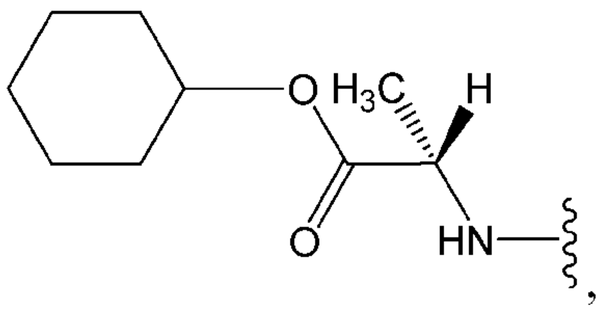
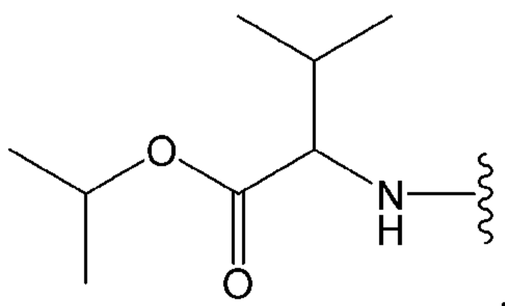
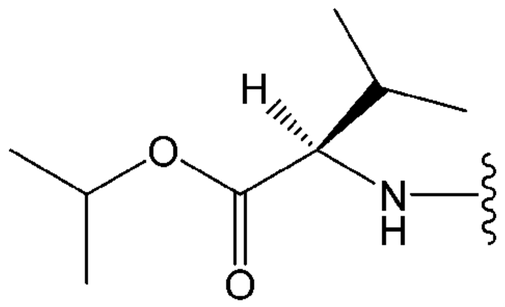
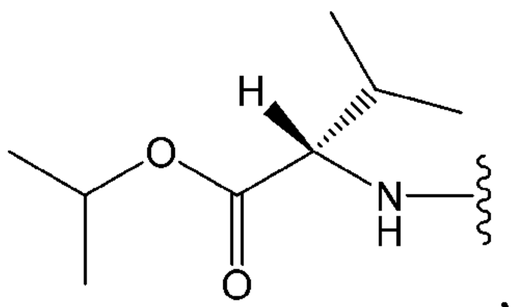
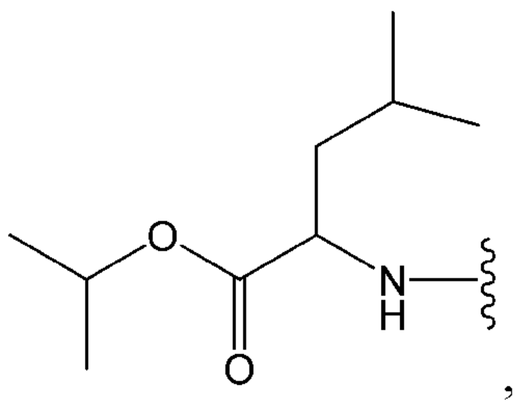
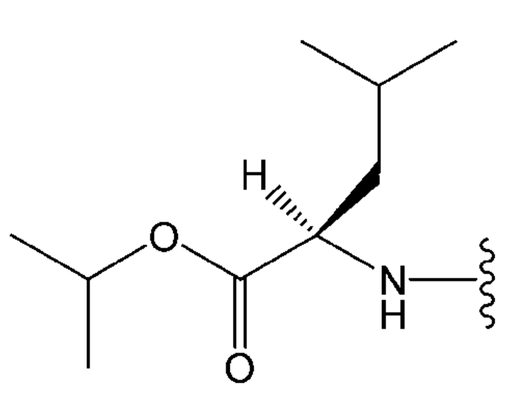
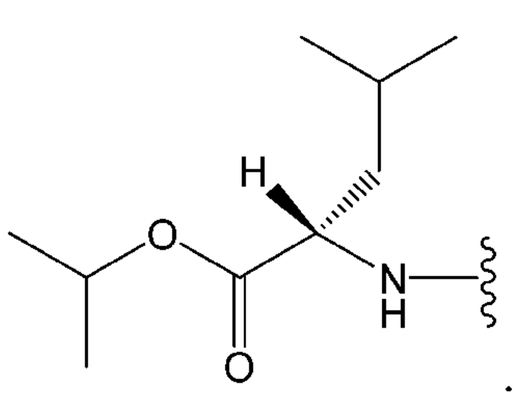
[0119] In some embodiments, when R^{1A} is , Z^{2A} can be O (oxygen). In other embodiments, when R^{1A} is , Z^{2A} can be S (sulfur). In some embodiments, when R^{1A} is , a compound of Formula (I) can be a phosphoramidate prodrug, such as an aryl phosphoramidate prodrug.

[0120] 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: alanine isopropyl ester, alanine cyclohexyl ester, alanine neopentyl ester, valine isopropyl ester and 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.

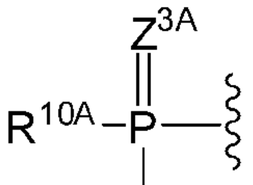
[0121] When R^{37A} is substituted, R^{37A} can be substituted with one or more substituents selected from N-amido, mercapto, alkylthio, an optionally substituted aryl, hydroxy, an optionally substituted heteroaryl, O-carboxy and amino. In some embodiments, R^{37A} can be an unsubstituted C_{1-6}-alkyl, 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 an embodiment, 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 an embodiment, 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.

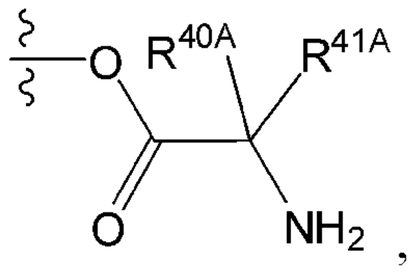
[0122] Examples of suitable  and  groups include the following: , , , , , , ,

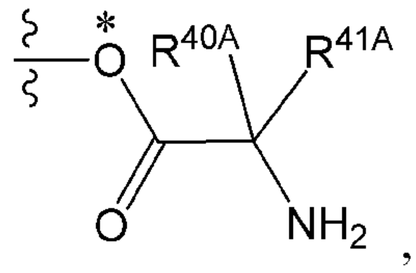

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[0123] In some embodiments, R^{10A} and R^{11A} can be the same. In some embodiments, R^{10A} and R^{11A} can be different.

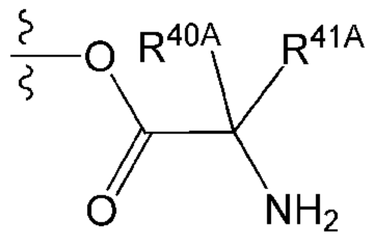
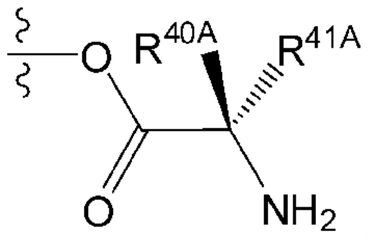
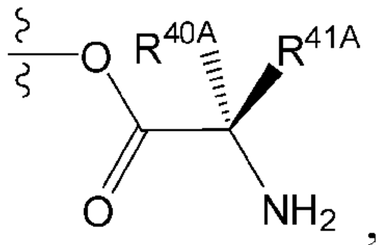
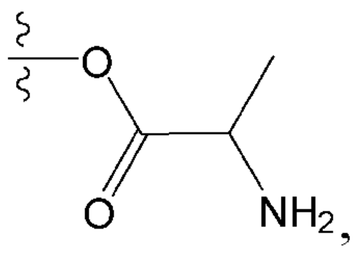
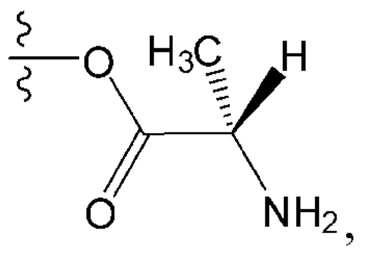
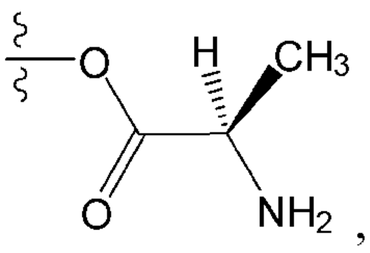
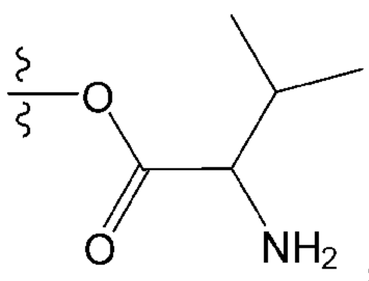
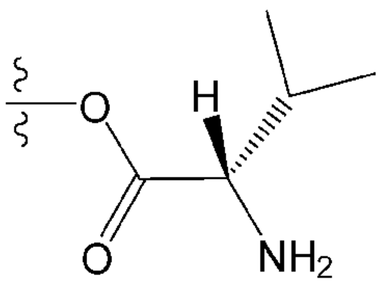
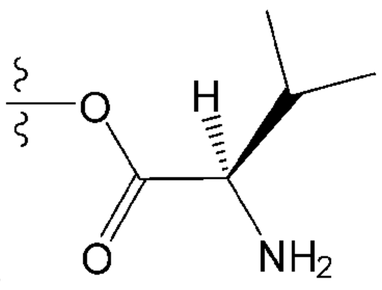
[0124] In some embodiments, Z^{3A} can be O (oxygen). In other embodiments, Z^{3A} can be S (sulfur). In some embodiments, when R^{1A} is , a compound of Formula (I) can be a phosphonic diamide prodrug.

[0125] In some embodiments, R^{1A} can be hydrogen. In some embodiments, R^{1A} can be an optionally substituted acyl. In other embodiments, 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 still other embodiments, R^{39A} can be an unsubstituted C_{2-12} alkyl. In yet still other embodiments, R^{39A} can be an unsubstituted C_{2-6} alkyl.

[0126] 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).

[0127] 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 an embodiment, 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.

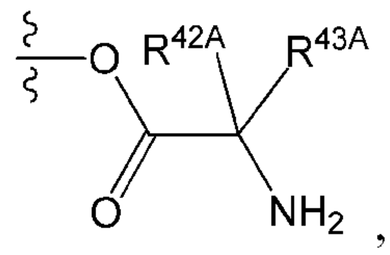
[0128] Examples of suitable  include the following:  ,  ,  ,  ,  ,  ,  and  .

[0129] In some embodiments, R^{2A} can be selected from an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{2-6} alkynyl, an optionally substituted $-O-C_{1-6}$ alkyl, an optionally substituted $-O-C_{3-6}$ alkenyl, an optionally

substituted –O–C_{3-6} alkynyl and cyano, and R^{3A} can be selected from OH, -OC(=O)$R^{"A}$ and an optionally substituted O-linked amino acid.

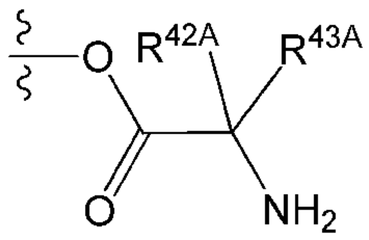
[0130] Various groups can be attached to the 4'-position of the pentose ring. In some embodiments, R^{2A} can be hydrogen. In other embodiments, R^{2A} can be halogen, such as fluoro. In still other embodiments, R^{2A} can be azido. In some embodiments, R^{2A} can be an optionally substituted C_{1-6} 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 some embodiments, R^{2A} can be an unsubstituted C_{1-6} alkyl. In other embodiments, R^{2A} can be a substituted C_{1-6} alkyl. For example, R^{2A} can be a halogen substituted C_{1-6} alkyl, a hydroxy substituted C_{1-6} alkyl (such as, CH_2OH), an alkoxy substituted C_{1-6} alkyl (such as, -C_{1-6} alkyl-O-C_{1-6} alkyl and CH_2OCH_3), a sulfenyl substituted C_{1-6} alkyl (for example, -C_{1-6} alkyl-S-C_{1-6} alkyl and CH_2SCH_3), an azido substituted C_{1-6} alkyl or amino substituted C_{1-6} alkyl. In some embodiments, R^{2A} can be a C_{1-6} haloalkyl. For example, R^{2A} can be a C_{1-6} bromoalkyl C_{1-6} chloroalkyl or a C_{1-6} fluoroalkyl, such as CH_2Br, CH_2Cl, CH_2F, CHF_2 or $CHFCH_3$. In other embodiments, R^{2A} can be a C_{1-6} azidoalkyl (for example, N_3CH_2-). In still other embodiments, R^{2A} can be a C_{1-6} aminoalkyl (for example, NH_2CH_2-). In some embodiments, R^{2A} can be an optionally substituted C_{2-6} alkenyl. In some embodiments, R^{2A} can be a substituted C_{2-6} alkenyl. In other embodiments, R^{2A} can be an unsubstituted C_{2-6} alkenyl. For example, R^{2A} can be ethenyl, propenyl or allenyl. In still other embodiments, R^{2A} can be an optionally substituted C_{2-6} alkynyl. In some embodiments, R^{2A} can be a substituted C_{2-6} alkynyl. In other embodiments, R^{2A} can be an unsubstituted C_{2-6} alkynyl. Suitable C_{2-6} alkynyls include ethynyl and propynyl. In yet still other embodiments, R^{2A} can be an optionally substituted C_{3-6} cycloalkyl. In some embodiments, R^{2A} can be a substituted C_{3-6} cycloalkyl. In other embodiments, R^{2A} can be an unsubstituted C_{3-6} cycloalkyl. A non-limiting list of C_{3-6} cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. In some embodiments, R^{2A} can be an optionally substituted –O–C_{1-6} alkyl. In some embodiments, R^{2A} can be a substituted –O–C_{1-6} alkyl. In other embodiments, R^{2A} can be an unsubstituted –O–C_{1-6} alkyl. Examples of suitable O–C_{1-6} alkyl groups include methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, isobutoxy, tert-butoxy, pentoxy (branched and straight-chained) and hexoxy (branched and straight-chained).

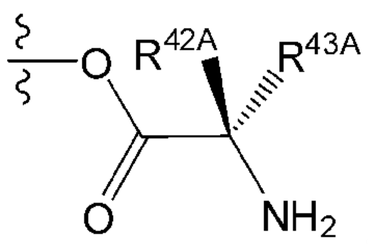
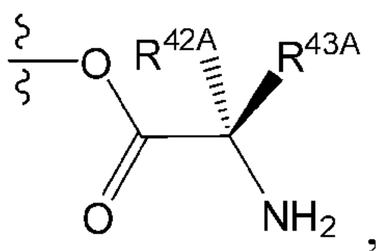
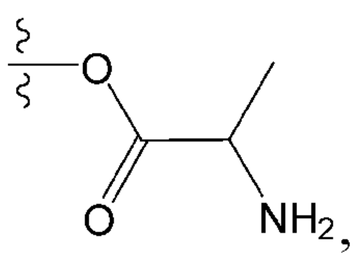
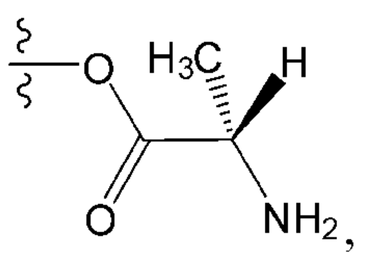
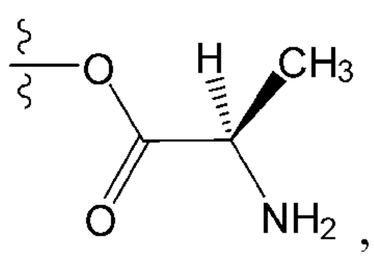
In other embodiments, R^{2A} can be an optionally substituted –O–C_{3-6} alkenyl. In some embodiments, R^{2A} can be a substituted –O–C_{3-6} alkenyl. In other embodiments, R^{2A} can be an unsubstituted –O–C_{3-6} alkenyl. In still other embodiments, R^{2A} can be an optionally substituted –O–C_{3-6} alkynyl. In some embodiments, R^{2A} can be a substituted –O–C_{3-6} alkynyl. In other embodiments, R^{2A} can be an unsubstituted –O–C_{3-6} alkynyl. In still other embodiments, R^{2A} can be cyano.

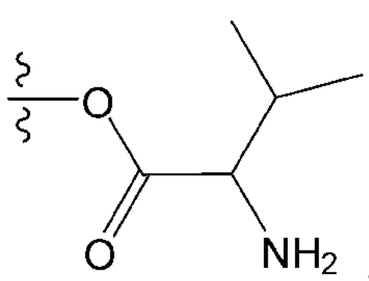
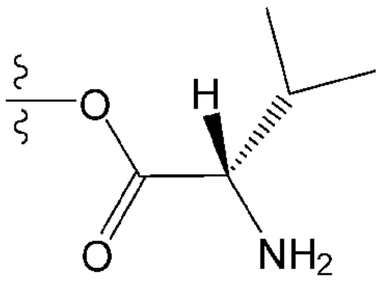
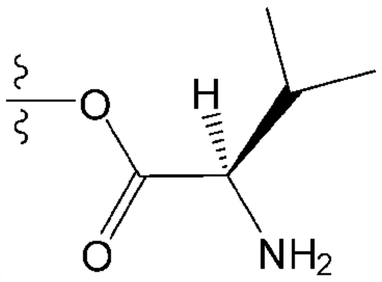
[0131] The groups attached to the 3'-position of the pentose ring can vary. In some embodiments, including those of paragraph [0130], R^{3A} can be halogen, for example, fluoro. In other embodiments, including those of paragraph [0130], R^{3A} can be OH. In still other embodiments, including those of paragraph [0130], R^{3A} 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^{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.

[0132] 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 an embodiment, 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.

[0133] Examples of suitable  include the following:

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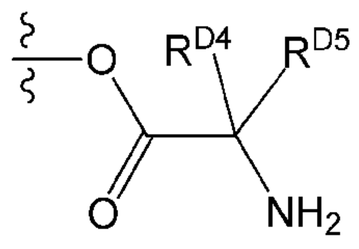
,  and .

[0134] In still other embodiments, including those of paragraph [0130], R^{3A} can be $-OC(=O)R^{"A}$, wherein $R^{"A}$ can be an optionally substituted C_{1-24} alkyl. In some embodiments, $R^{"A}$ can be a substituted C_{1-8} alkyl. In other embodiments, $R^{"A}$ can be an unsubstituted C_{1-8} alkyl. In still other embodiments, including those of paragraph [0130], R^{3A} can be an optionally substituted -O-acyl. In yet still other embodiments, including those of paragraph [0130], R^{3A} can be $-OC(=O)R^{44A}$, wherein R^{44A} 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^{44A} can be a substituted C_{1-12} alkyl. In other embodiments, R^{44A} can be an unsubstituted C_{1-12} alkyl.

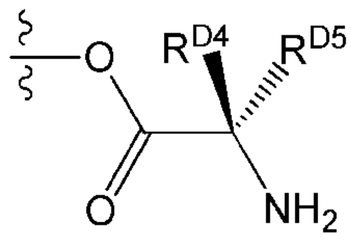
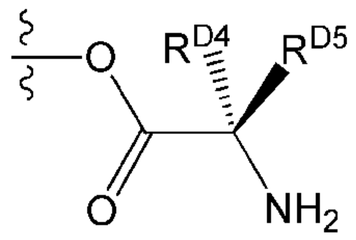
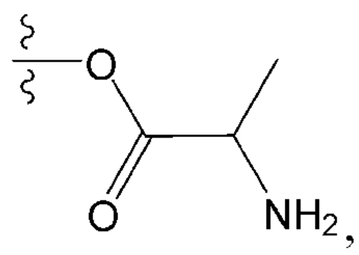
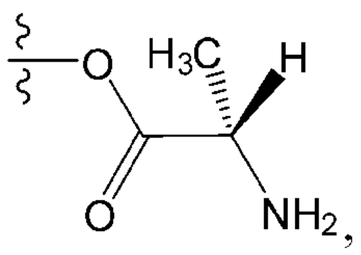
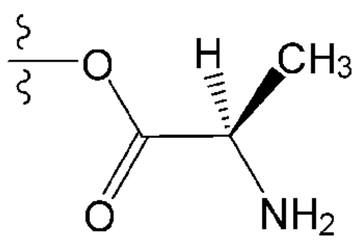
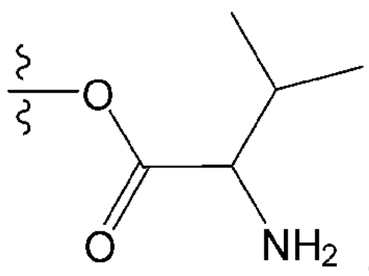
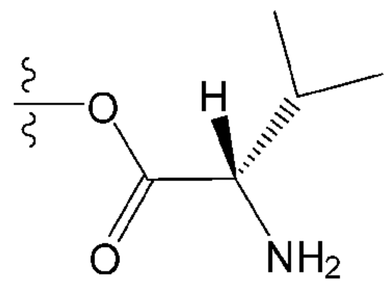
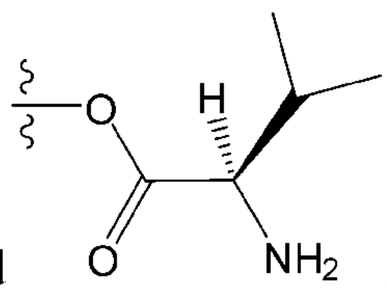
[0135] Various substituents can be present at the 2'-position of the pentose ring. In some embodiments, R^{5A} can be hydrogen. In other embodiments, R^{5A} can be halogen, for

example, fluoro. In still other embodiments, R^{5A} can be an optionally substituted C_{1-6} alkyl. In some embodiments, R^{5A} can be an unsubstituted C_{1-6} alkyl. In some embodiments, R^{5A} can be a substituted C_{1-6} alkyl. In yet still other embodiments, R^{5A} can be an optionally substituted C_{2-6} alkenyl. In some embodiments, R^{5A} can be an unsubstituted C_{2-6} alkenyl. In some embodiments, R^{5A} can be a substituted C_{2-6} alkenyl. In some embodiments, R^{5A} can be an optionally substituted C_{2-6} alkynyl. In some embodiments, R^{5A} can be an unsubstituted C_{2-6} alkynyl. In some embodiments, R^{5A} can be a substituted C_{2-6} alkynyl.

[0136] In some embodiments, R^{4A} can be hydrogen. In other embodiments, R^{4A} can be halogen, such as fluoro or chloro. In still other embodiments, R^{4A} can be OR^{1D}. For example, R^{4A} can be OH. In some embodiments, R^{4A} can be $OC(=O)R^{"D}$. In other embodiments, R^{4A} can be an optionally substituted O-linked amino acid. In still other embodiments, R^{4A} can be azido. In yet still other embodiments, R^{4A} can be $NR^{2D}R^{3D}$. For example, R^{4A} can be amino, a mono-substituted amine or a di-substituted amine. Examples of suitable O-linked amino acids for R^{4A} include, but are not limited to:



include the following:

and .

[0137] In some embodiments, R^{5A} can be hydrogen and R^{4A} can be halogen. In other embodiments, R^{4A} and R^{5A} can both be halogen.

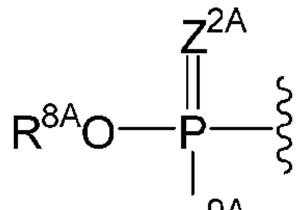
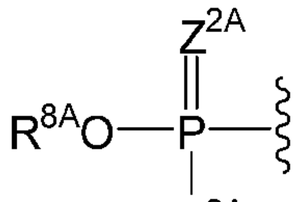
[0138] A variety of substituents can be present at the 1'-position of the pentose ring. In some embodiments, R^{A} can be hydrogen. In some embodiments, R^{A} can be

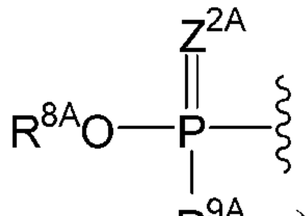
deuterium. In still other embodiments, R^A can be an unsubstituted C_{1-3} alkyl (such as methyl, ethyl, n-propyl and iso-propyl). In yet still other embodiments, R^A can be an unsubstituted C_{2-4} alkenyl (for example, ethenyl, propenyl (branched or straight) and butenyl (branched or straight)). In 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.

[0139] A variety of substituents can also be present at the 5'-position of the pentose ring. In some embodiments, both R^{aa1} and R^{aa2} can be hydrogen. In other embodiments, R^{aa1} can be hydrogen and R^{aa2} can be deuterium. In still other embodiments, both R^{aa1} and R^{aa2} can be deuterium.

[0140] In some embodiments, R^{2A} can be a C_{1-6} haloalkyl, R^{3A} can be OH or an optionally substituted acyl, R^{4A} can be a halogen (for example, fluoro or chloro). In some embodiments, R^{3A} and R^{5A} can each be an optionally substituted acyl.

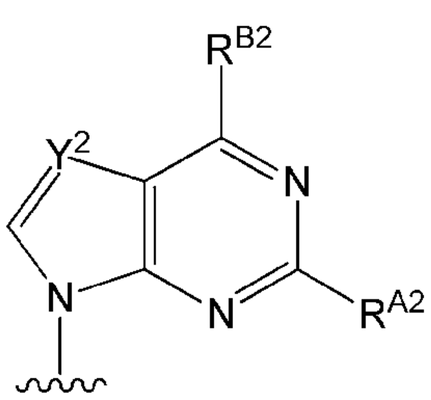
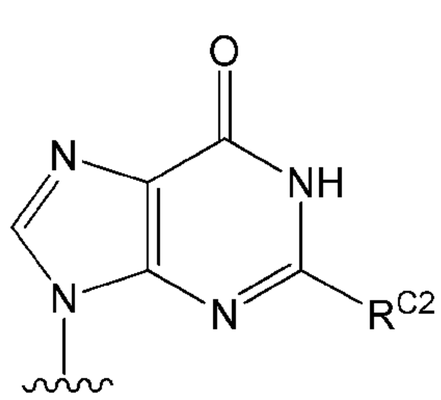
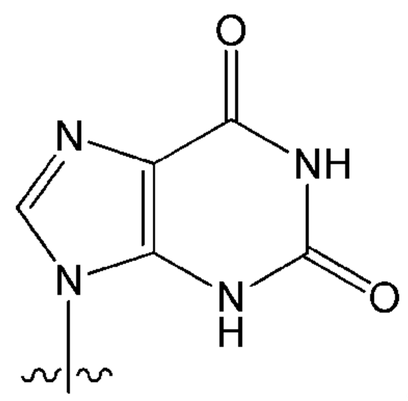
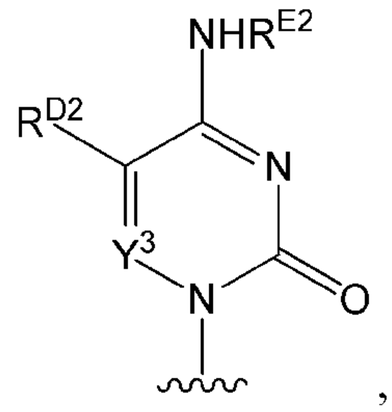
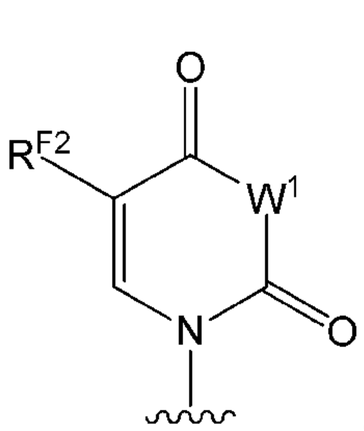
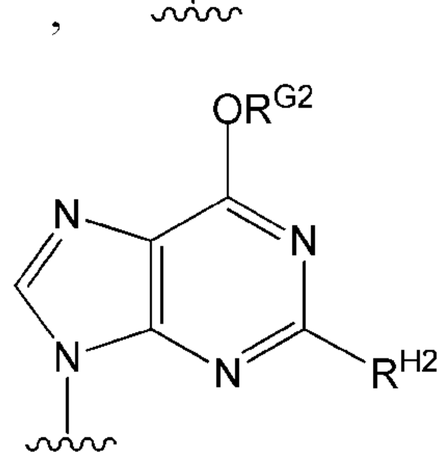
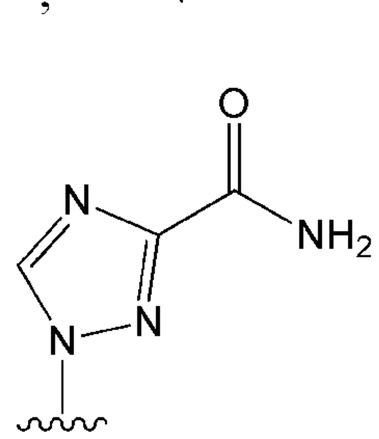
[0141] In some embodiments, R^{2A} cannot be hydroxy. In some embodiments, when R^{4A} is hydroxy, amino or fluoro and R^{5A} is hydrogen or methyl, then R^{2A} cannot be hydrogen. In some embodiments, R^{2A} cannot be hydrogen. In some embodiments, R^{2A} cannot be halogen (for example, fluoro). In some embodiments, R^{2A} cannot be azido. In some embodiments, R^{2A} cannot be methoxy. In some embodiments, R^{2A} cannot be methoxy when B^{1A} is substituted or unsubstituted uracil. In some embodiments, B^{1A} is a substituted or an unsubstituted cytosine. In other embodiments, B^{1A} is a substituted or an unsubstituted thymine. In still other embodiments, B^{1A} cannot be a substituted or an unsubstituted uracil.

In some embodiments, R^{2A} cannot be methoxy when Z^{1A} is , wherein R^{8A} is an unsubstituted C_{1-6} alkyl or a para-substituted phenyl; and R^{9A} is an optionally substituted N-linked amino acid or an optionally substituted N-linked amino acid ester derivative. In some embodiments, R^{2A} cannot be methoxy when Z^{1A} is . In some embodiments,

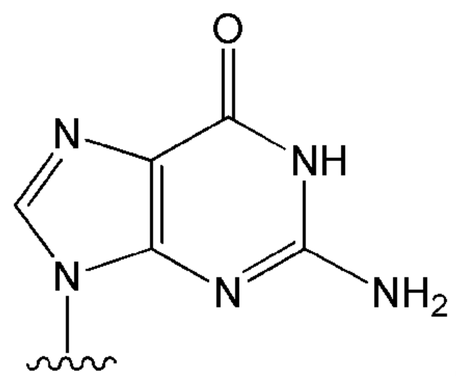
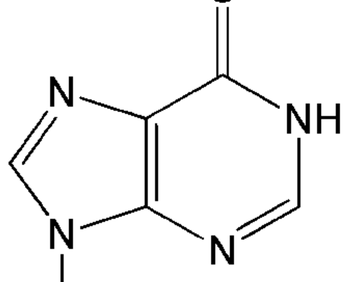
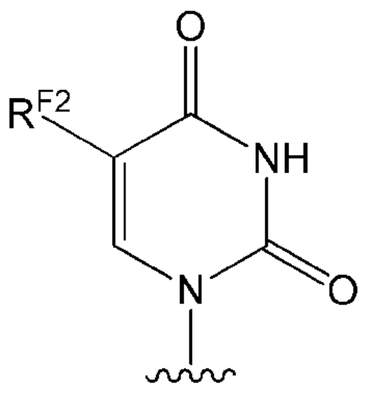
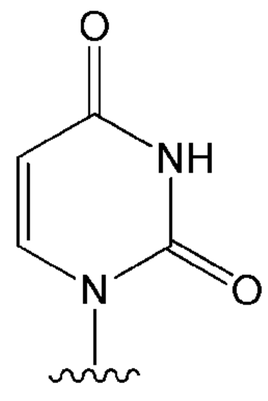
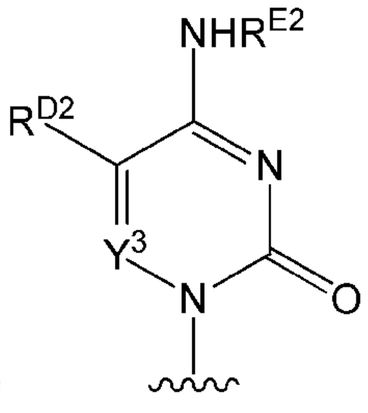
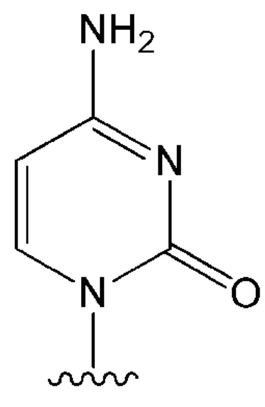
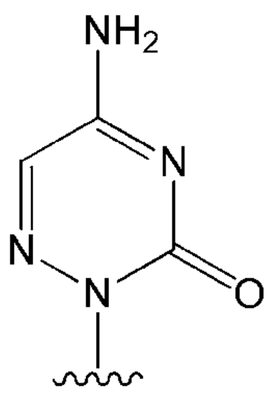
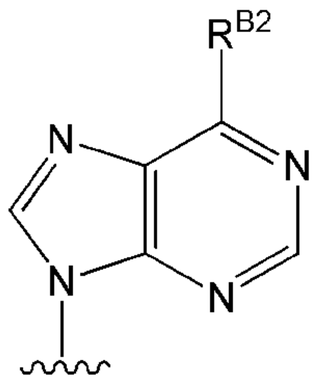


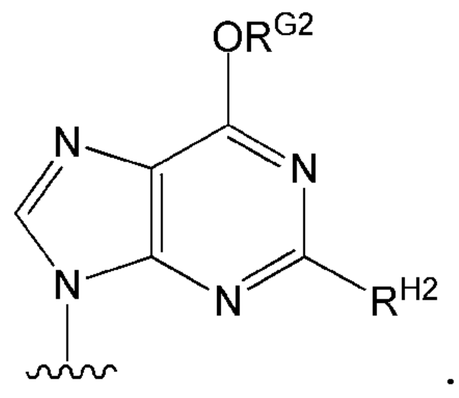
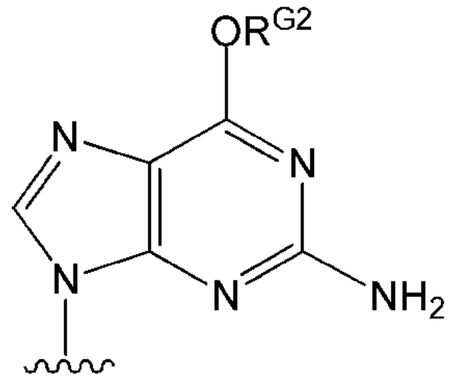
R^{2A} cannot be an alkoxy (for example, when Z^{1A} is). In some embodiments, B^{1A} cannot be cytosine when R^{2A} is an unsubstituted alkenyl or an unsubstituted alkynyl. In some embodiments, B^{1A} cannot be thymine when R^{2A} is an optionally substituted alkyl. In some embodiments, R^{2A} cannot be an unsubstituted alkoxy (such as methoxy), an optionally substituted alkenyl (such as allenyl), an unsubstituted alkynyl (such as ethynyl) or a C_1 alkyl substituted with a non-halogen substituent. In some embodiments, R^{2A} cannot be an unsubstituted alkoxy (such as methoxy), an optionally substituted alkenyl (such as allenyl), an optionally substituted alkynyl (such as ethynyl) or a C_{1-4} alkyl substituted with a non-halogen substituent. In some embodiments, R^{2A} cannot be an optionally substituted alkynyl (such as ethynyl), CH_3 or CF_3. In some embodiments, when B^{1A} is a substituted or unsubstituted cytosine, then R^{2A} can be azido. In some embodiments R^{1A} cannot be H. In some embodiments R^{1A} cannot be H when B^{1A} is an optionally substituted cytosine or an optionally substituted thymine. In some embodiments, R^{4A} cannot be bromo. In some embodiments, a compound of Formula (I), or a pharmaceutically acceptable salt, cannot be 2'-C-methylcytidine, ribavirin, β-d-N^4-hydroxycytidine, 2'-F-2'-methylcytidine, 2-thiouridine, 6-aza-uridine, 5-nitrocytidine and/or 2'-amino-2'-deoxycytidine, or a mono-, a di- and/or a tri-phosphate of the foregoing.

[0142] Various optionally substituted heterocyclic bases can be attached to the pentose ring. In some embodiments, one or more of the amine and/or amino groups may be protected with a suitable protecting group. For example, an amino group may be protected by transforming the amine and/or amino group to an amide or a carbamate. In some embodiments, an optionally substituted heterocyclic base or an optionally substituted heterocyclic base with one or more protected amino groups can have one of the following structures:

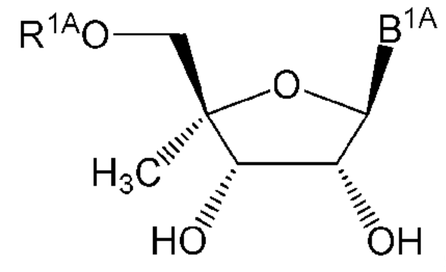
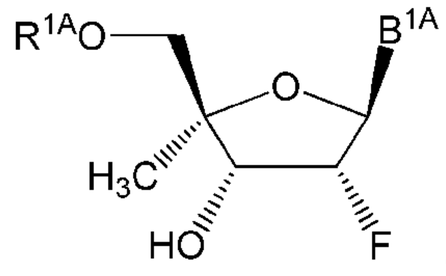
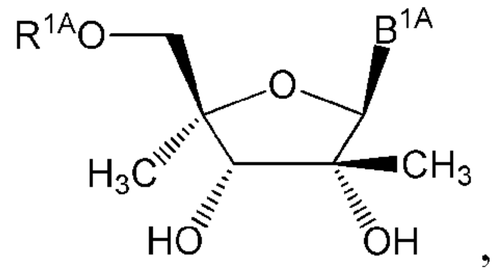
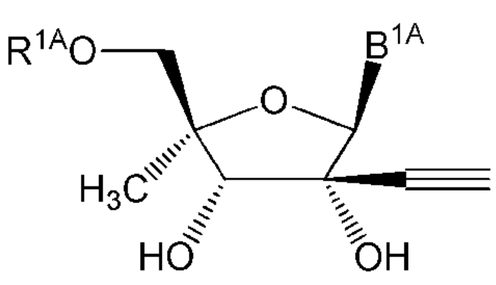
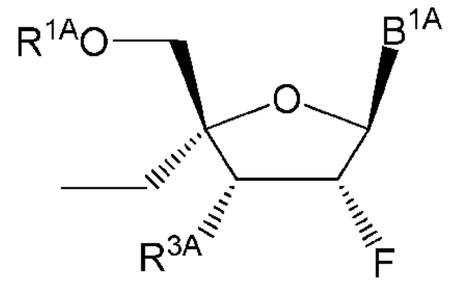
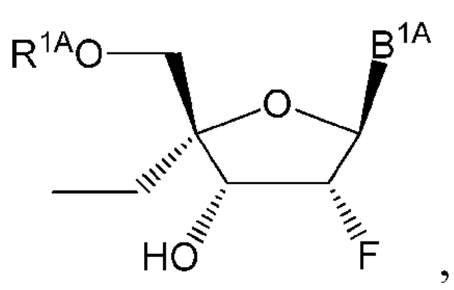
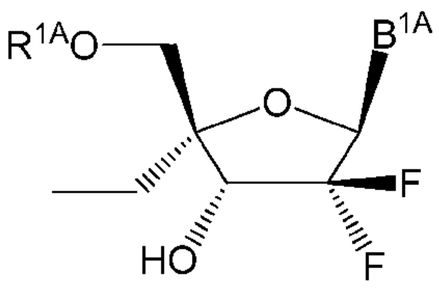
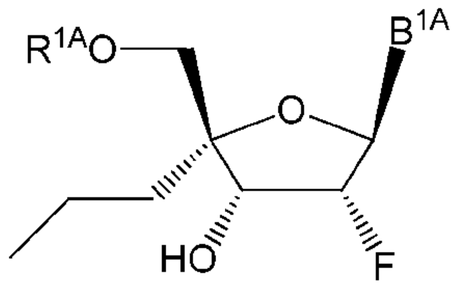
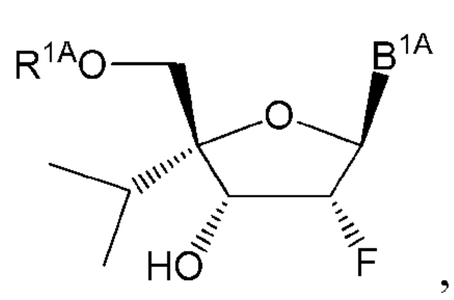
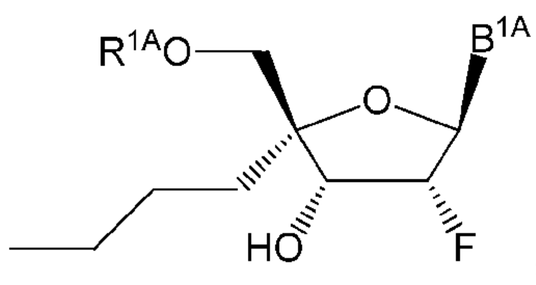
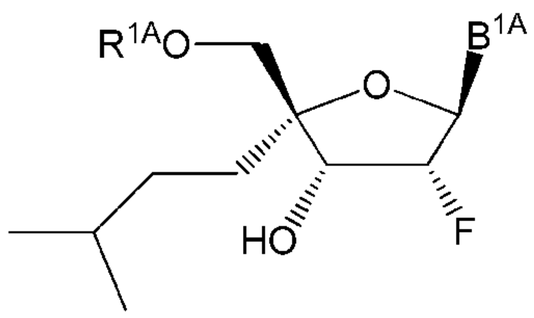
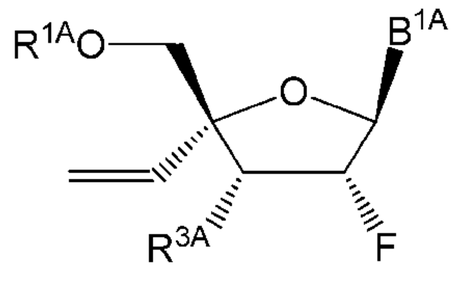
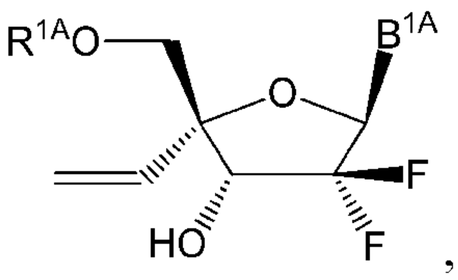
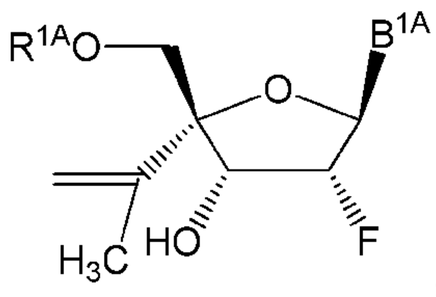
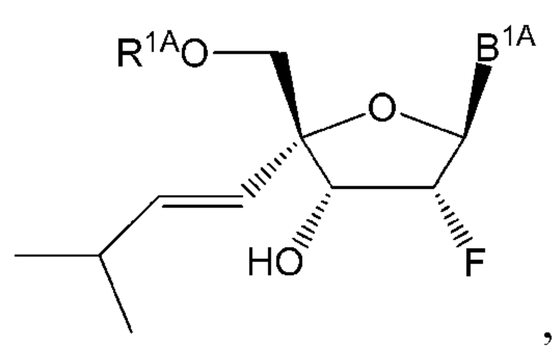

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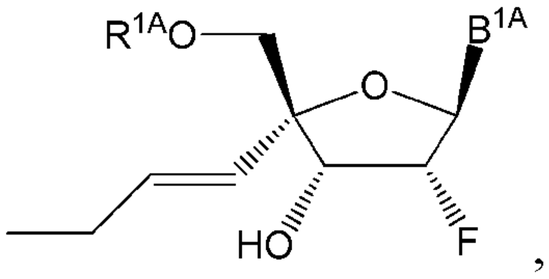
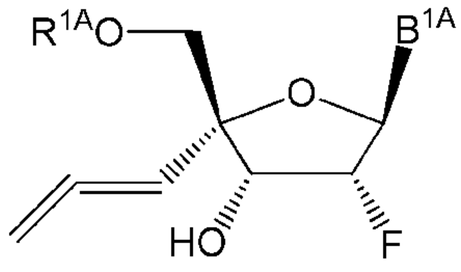
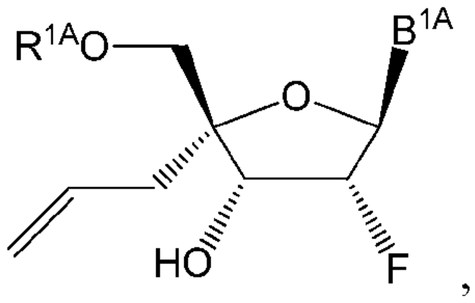
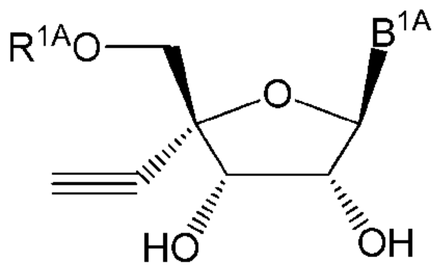
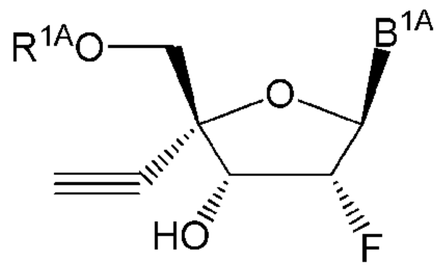
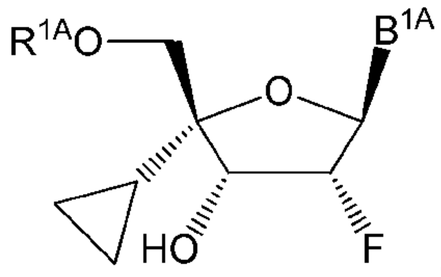
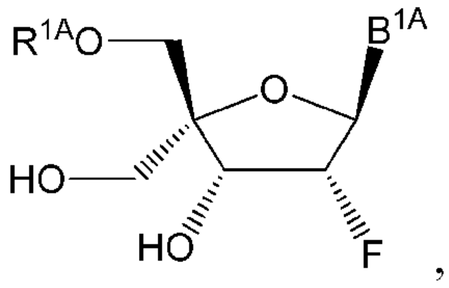
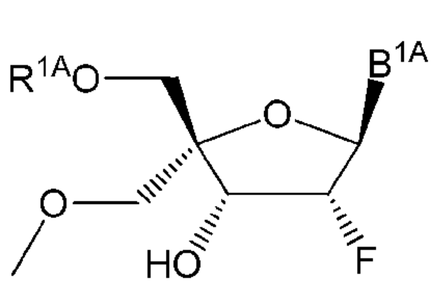
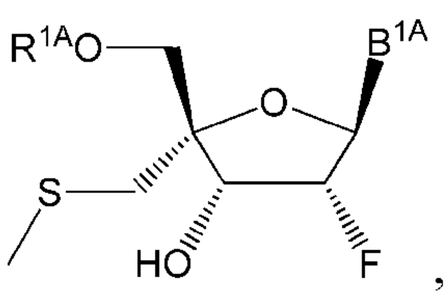
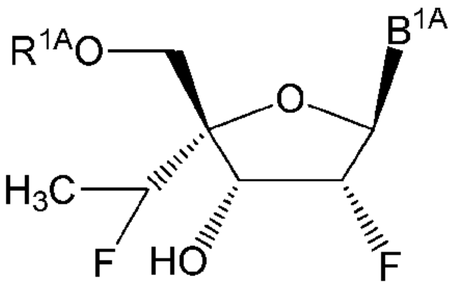
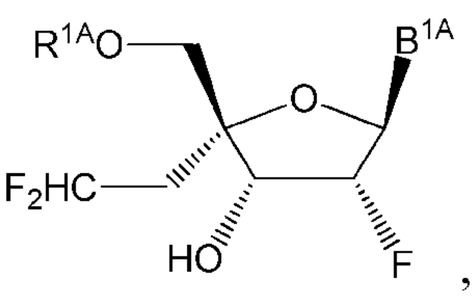
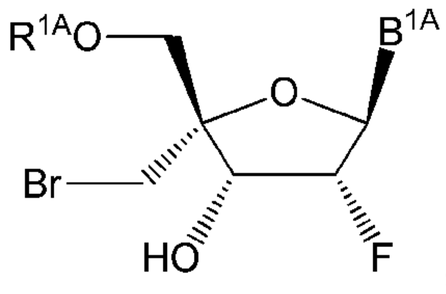
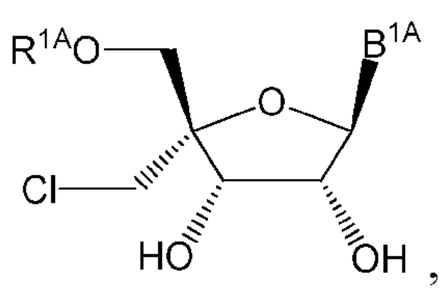
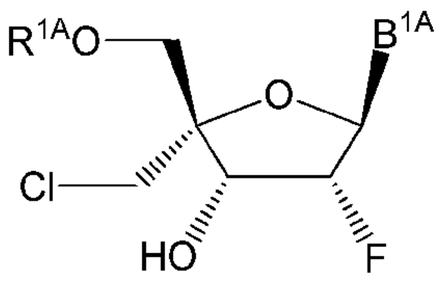
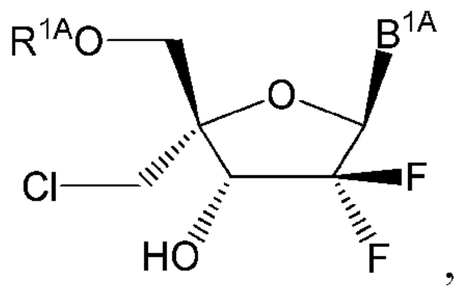
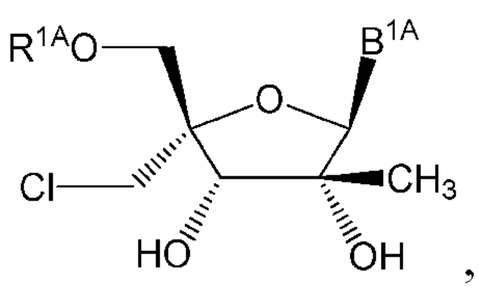
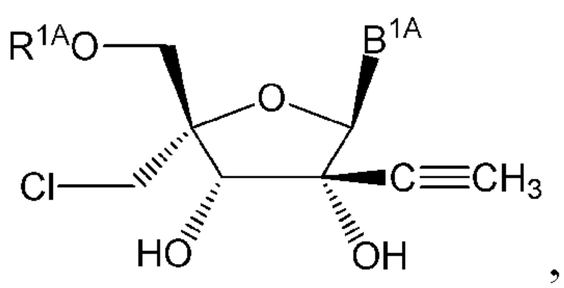
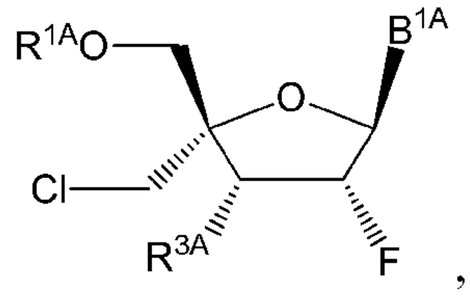
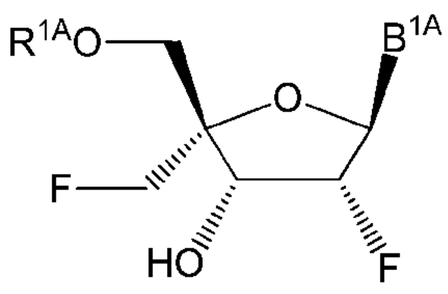
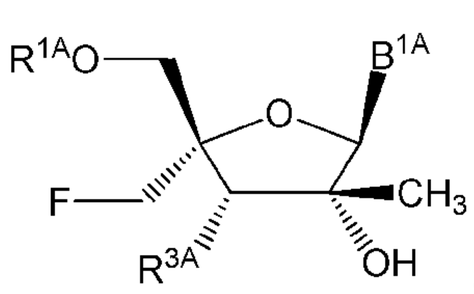
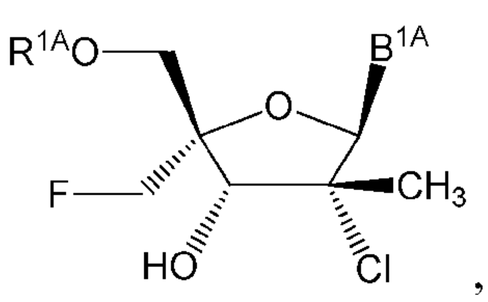
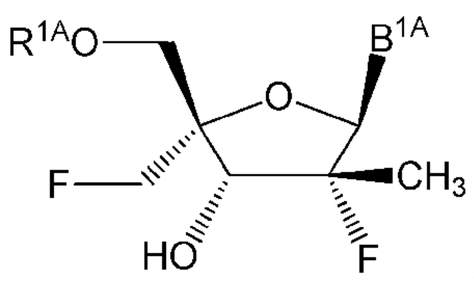
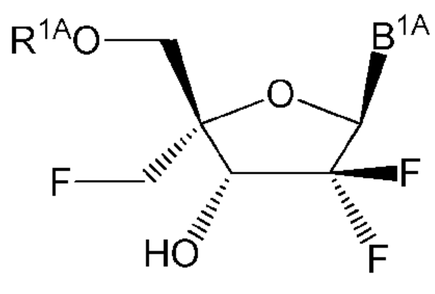
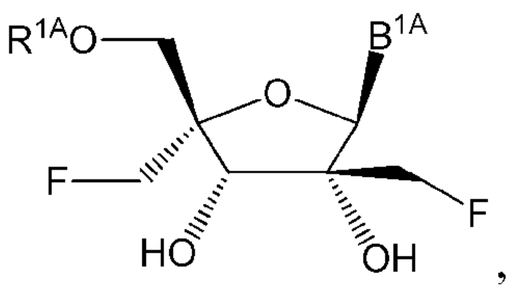
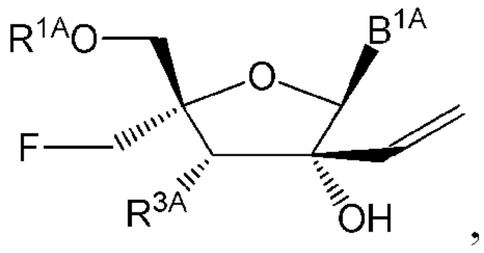
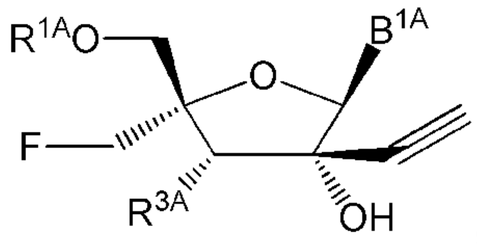
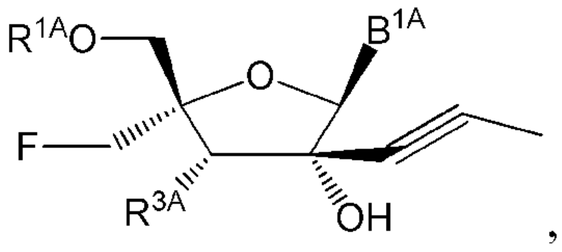
wherein: R^{A2} can be selected from hydrogen, halogen and NHR^{J2}, wherein R^{J2} can be selected from hydrogen, -C(=O)R^{K2} and –C(=O)OR^{L2}; R^{B2} can be halogen or NHR^{W2}, wherein R^{W2} can be selected from hydrogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} 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 or $–NCH_2$-OC(=O)CH(NH_2)-CH(CH_3)$_2$; 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, heteroalicyclyl, aryl(C_{1-6} alkyl), heteroaryl(C_{1-6} alkyl) and heteroalicyclyl(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."

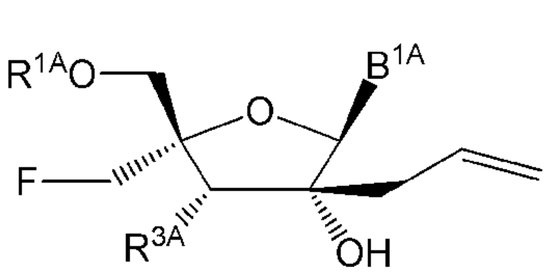
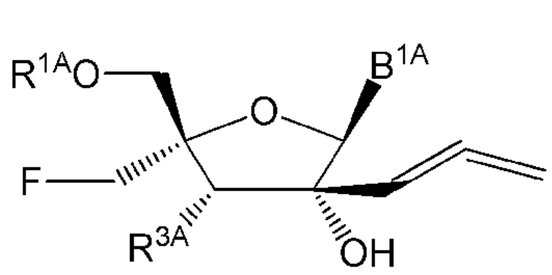
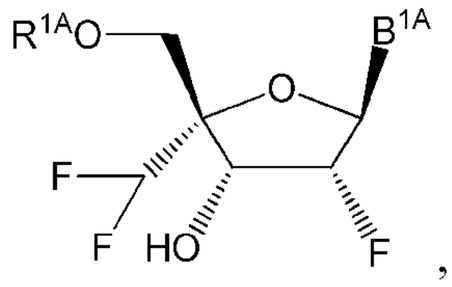
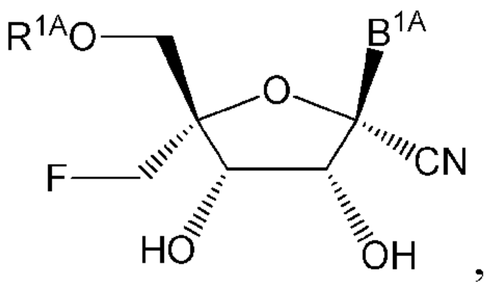
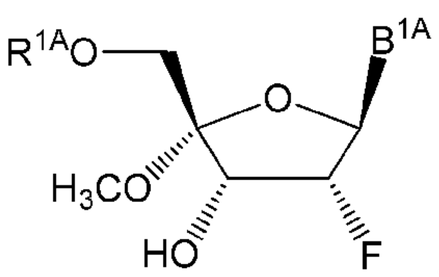
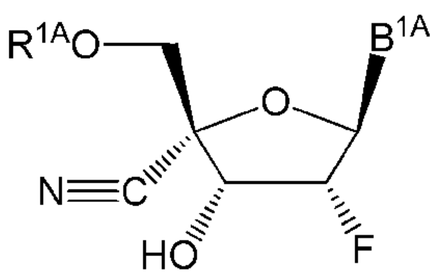
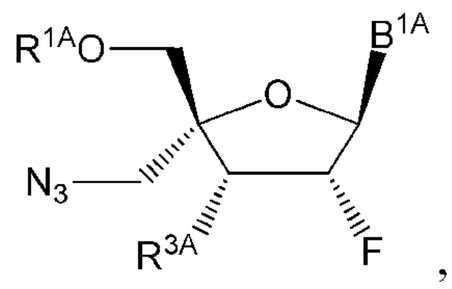
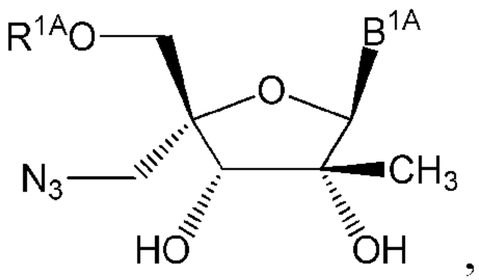
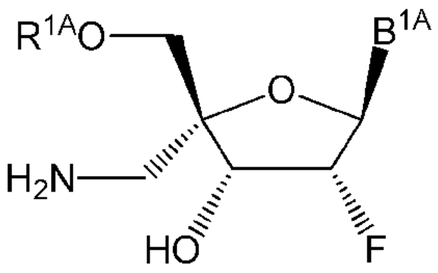
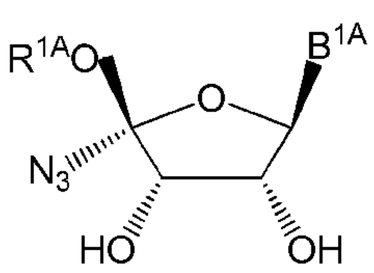
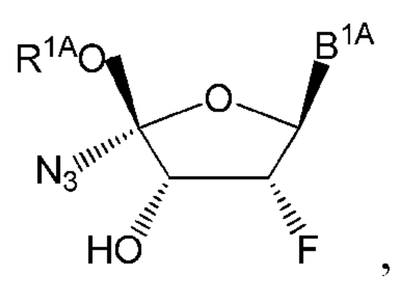
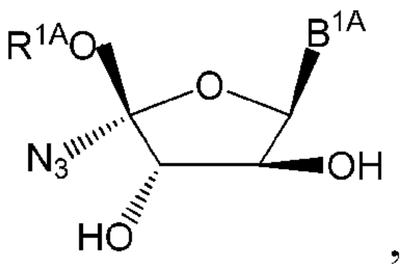
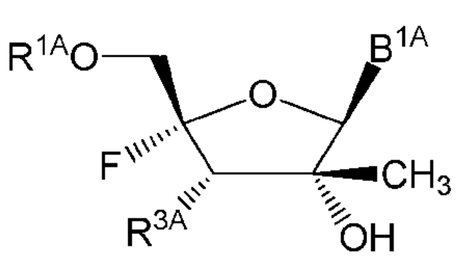
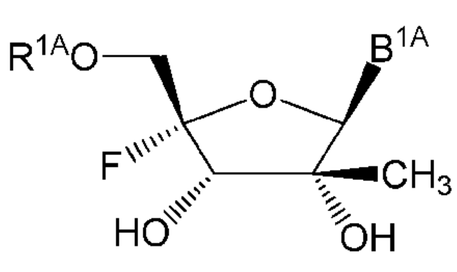
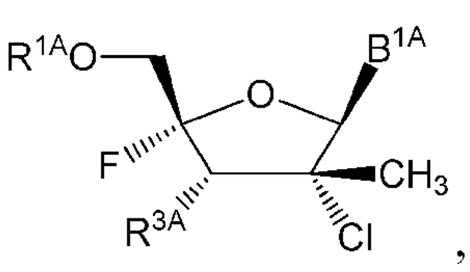
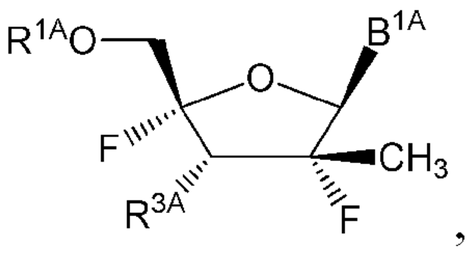
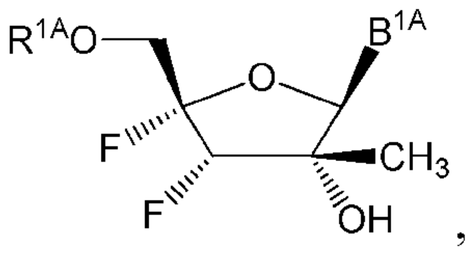
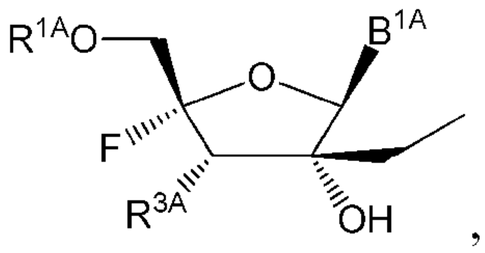
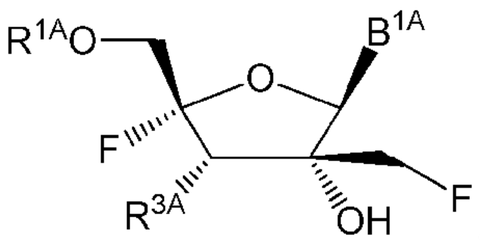
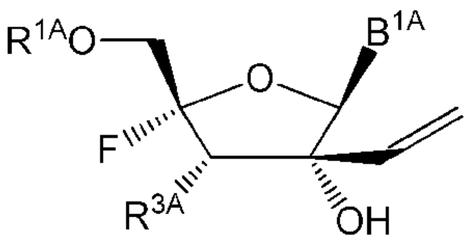
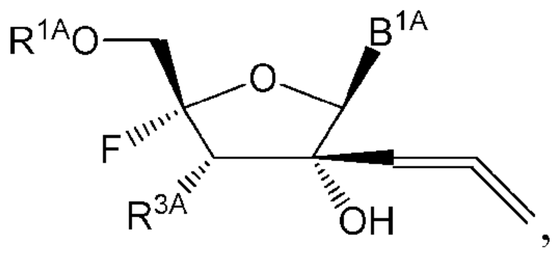
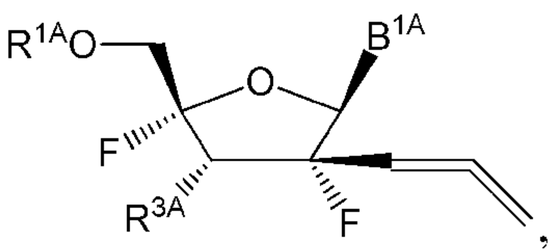
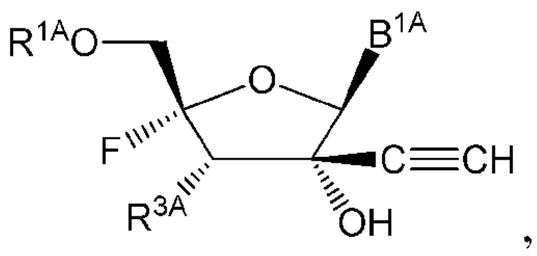
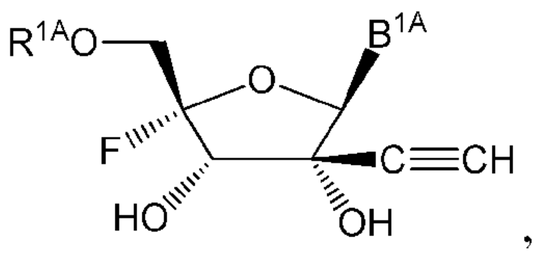
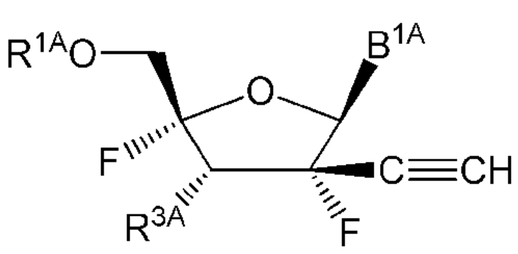
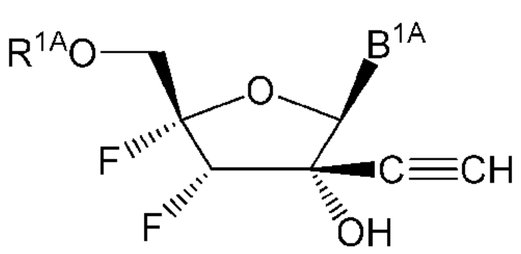
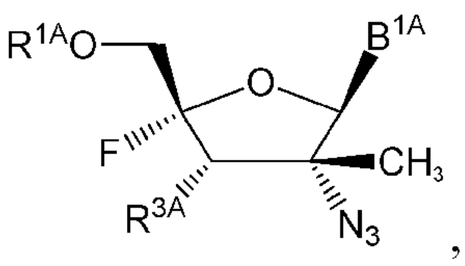
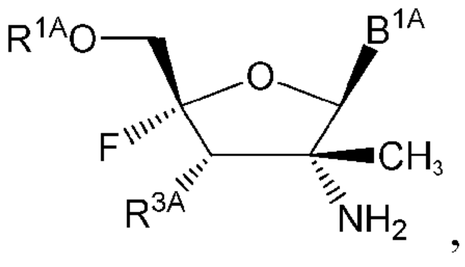
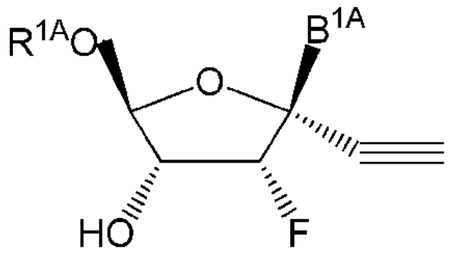
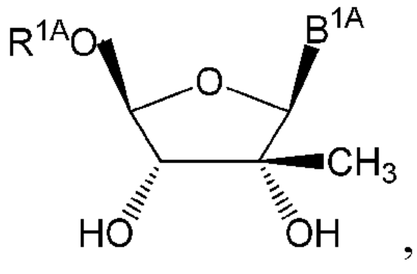
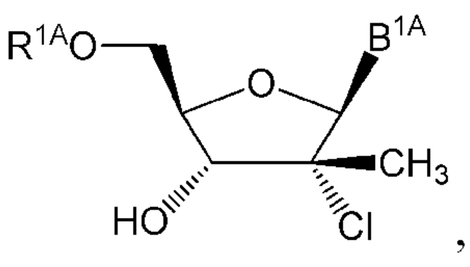
[0143] In some embodiments, B^{1A} can be . In other embodiments, B^{1A} can be . In still other embodiments, B^{1A} can be , such as . In yet still other embodiments, B^{1A} can be , for example,  or . In some embodiments, R^{D2} can be hydrogen. In other embodiments, B^{1A} can be . In some embodiments, R^{B2} can be NH_2. In other embodiments, R^{B2} can be NHR^{W2}, wherein R^{W2} can be $-C(=O)R^{M2}$

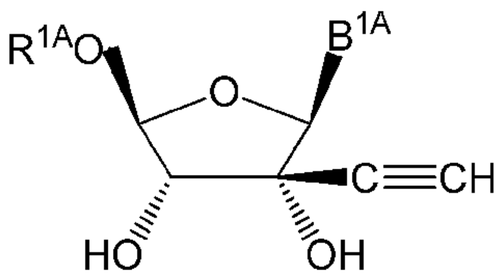
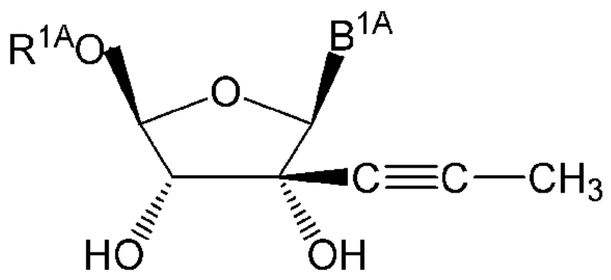
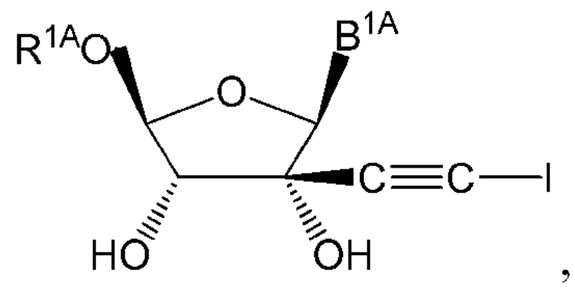
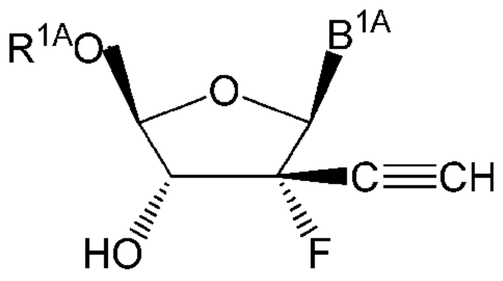
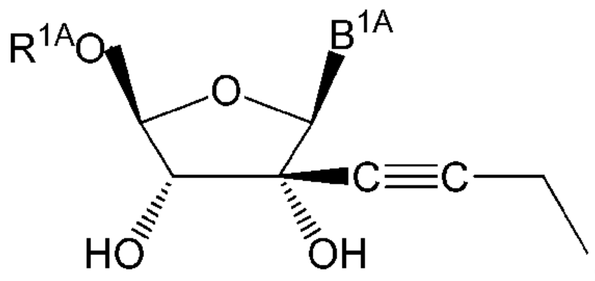
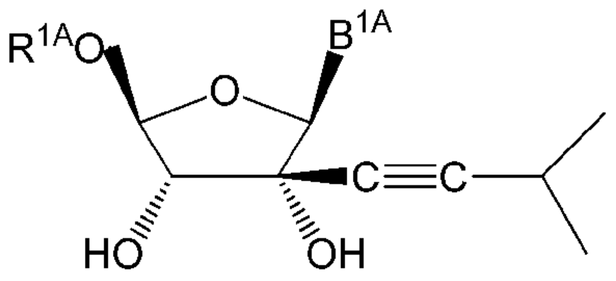
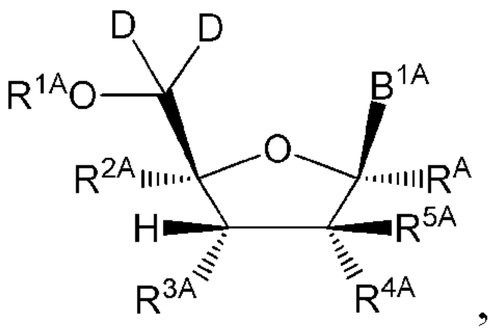
or –C(=O)OR^{N2}. In still other embodiments, B^{1A} can be  . In some embodiments, B^{1A} can be  .

[0144] In some embodiments, a compound of Formula (I) can have a structure selected from one of the following:

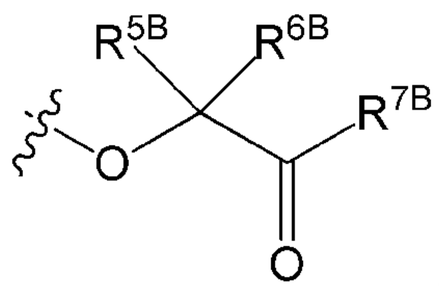
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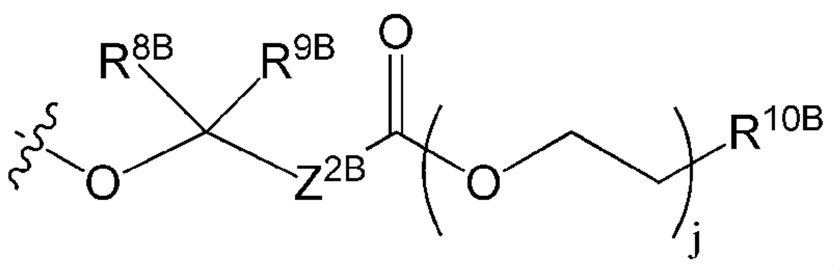

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and

, or a pharmaceutically acceptable salt of the foregoing. In some embodiments of this paragraph, B^{1A} can be an optionally substituted purine base. In other embodiments of this paragraph, B^{1A} can be an optionally substituted pyrimidine base. In some embodiments of this paragraph, B^{1A} can be guanine. In other embodiments of this paragraph, B^{1A} can be thymine. In still other embodiments of this paragraph, B^{1A} can be cytosine. In yet still other embodiments of this paragraph, B^{1A} can be uracil. In some embodiments of this paragraph, B^{1A} can be adenine. In some embodiments of this paragraph, R^{1A} can be hydrogen. In other embodiments of this paragraph, R^{1A} can be an optionally substituted acyl. In still other embodiments of this paragraph, R^{1A} can be mono-, di- or tri-phosphate. In yet other embodiments of this paragraph, R^{1A} can be phosphoramidate prodrug, such as an aryl phosphoramidate prodrug. In some embodiments of this paragraph, R^{1A} can be an acyloxyalkyl ester phosphate prodrug. In other embodiments of this paragraph, R^{1A} can be a S-acylthioethyl (SATE) prodrug. In still other embodiments, R^{1A} can be a phosphonic diamide prodrug. In yet still other embodiments, of this paragraph, R^{1A} can be a cyclic 1-aryl-1,3-propanyl ester (HepDirect) prodrug moiety. In some embodiments of this paragraph, R^{1A} be a cyclosaligenyl (cycloSal) prodrug.

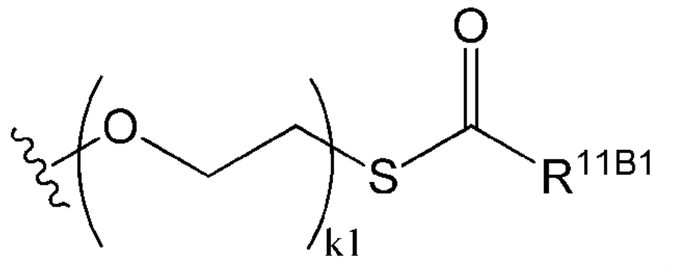
[0145] In some embodiments, the compound can be a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein: B^{1B} can be an optionally substituted heterocyclic base or an optionally substituted heterocyclic base with a protected amino group;



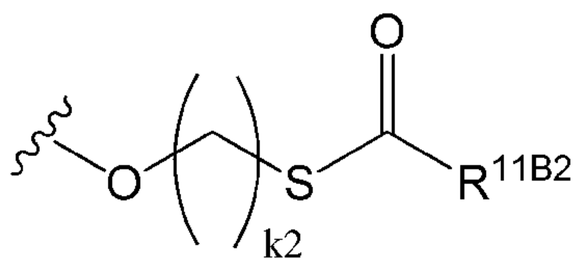
R^{1B} can be selected from O^-, OH, an optionally substituted C_{1-6} alkoxy, ,



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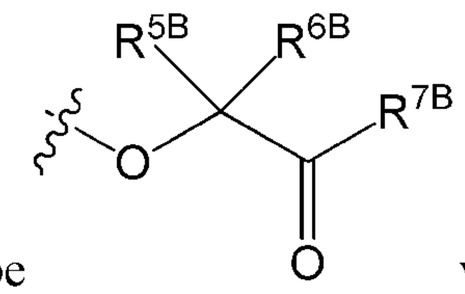


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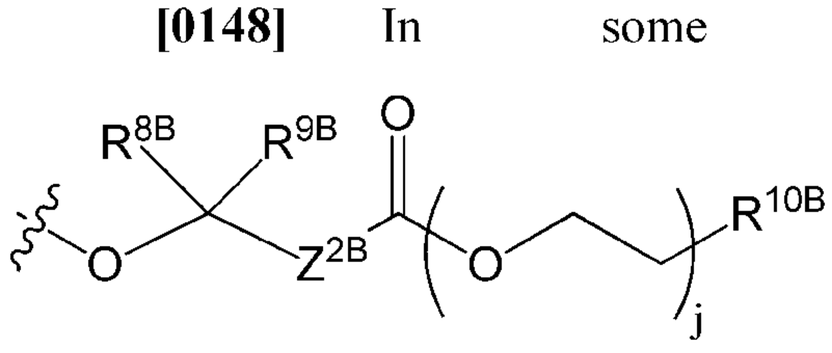
, an optionally substituted N-linked amino acid and an optionally substituted N-linked amino acid ester derivative; R^{2B} can be selected from an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{2-6} alkynyl, an optionally substituted –O–C_{1-6} alkyl, an optionally substituted –O–C_{3-6} alkenyl, an optionally substituted –O–C_{3-6} alkynyl and cyano; R^{3B} can be selected from hydrogen, halogen, OR^{1D}, an optionally substituted O-linked amino acid, azido and $NR^{2D}R^{3D}$; R^{1D} can be hydrogen or –C(=O)$R^{"D}$; R^{2D} and R^{3D} can be independently hydrogen or an optionally substituted C_{1-6} alkyl; R^{4B} can be selected from hydrogen, halogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl and an optionally substituted C_{2-6} alkynyl; R^{5B}, R^{6B}, R^{8B} and R^{9B} can be independently selected from hydrogen, an optionally substituted C_{1-24} alkyl and an optionally substituted aryl; R^{7B} and R^{10B} 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^{11B1} and R^{11B2} can be selected from hydrogen, an optionally substituted C_{1-24} alkyl and an optionally substituted aryl; j can be 1 or 2; k1 can be 0 or 1; k2 can be 3, 4 or 5; $R^{"D}$ can be an optionally substituted C_{1-24}-alkyl and Z^{1B} and Z^{2B} can be independently O or S.

[0146] In some embodiments, R^{1B} can be O^-. In other embodiments, R^{1B} can be OH. In still other embodiments, R^{1B} can be an optionally substituted C_{1-6} alkoxy. For example, R^{1B} can be methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, iso-butoxy, tert-butoxy, straight or branched pentoxy or straight or branched hexoxy.



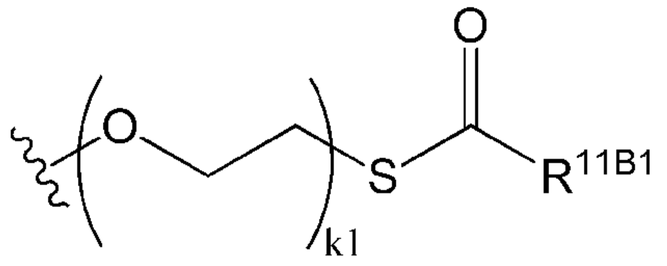
[0147] In some embodiments, R^{1B} can be wherein R^{5B} and R^{6B} can be independently selected from hydrogen, an optionally substituted C_{1-24} alkyl and an optionally substituted aryl; and R^{7B} can be selected from hydrogen, an optionally substituted C_{1-24} alkyl, an optionally substituted aryl, an optionally substituted –O–C_{1-24} alkyl, an optionally substituted –O–aryl, an optionally substituted –O–heteroaryl or an optionally substituted –O–monocyclic heterocyclyl. In some embodiments, R^{5B} and R^{6B} can be hydrogen. In other embodiments, at least one of R^{5B} and R^{6B} can be an optionally substituted C_{1-24} alkyl or an optionally substituted aryl. In some embodiments, R^{7B} can be an optionally substituted C_{1-24} alkyl. In other embodiments, R^{7B} can be an optionally substituted aryl. In still other embodiments, R^{7B} 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.

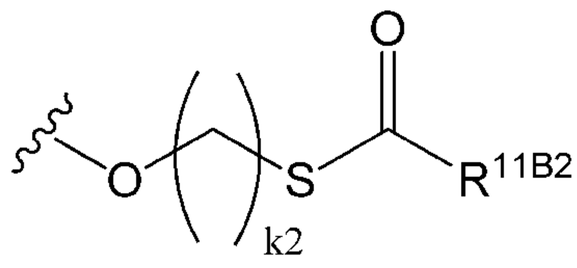
[0148] In some embodiments, R^{1B} can be



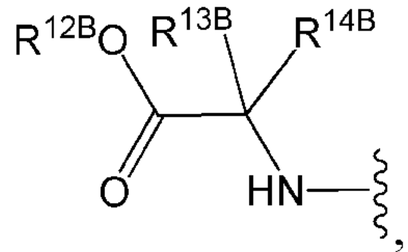
wherein R^{8B} and R^{9B} can be independently selected from hydrogen, an optionally substituted C_{1-24} alkyl and an optionally substituted aryl; R^{10B} can be independently selected from hydrogen, an optionally substituted C_{1-24} alkyl, an optionally substituted aryl, an optionally substituted –O–C_{1-24} alkyl, an optionally substituted –O–aryl, an optionally substituted –O–heteroaryl and an optionally substituted –O–monocyclic heterocyclyl; and Z^{2B} can be independently O (oxygen) or S (sulfur). In some embodiments, R^{8B} and R^{9B} can be hydrogen. In other embodiments, at least one of R^{8B} and R^{9B} can be an optionally substituted C_{1-24} alkyl or an optionally substituted aryl. In some embodiments, R^{10B} can be an optionally substituted C_{1-24} alkyl. In other embodiments, R^{10B} can be an optionally substituted aryl. In still other embodiments, R^{10B} 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, j

can be 1. In other embodiments, j can be 2. In some embodiments, Z^{2B} can be O (oxygen). In other embodiments, Z^{2B} can be or S (sulfur). In some embodiments, R^{1B} can be isopropyloxycarbonyloxymethyloxy, and form a bis(isopropyloxycarbonyloxymethyl) (bis(POC)) prodrug. In some embodiments, R^{1B} can be pivaloyloxymethyloxy, and form a bis(pivaloyloxymethyl) (bis(POM)) prodrug.

[0149] In some embodiments, R^{1B} can be . In some embodiments, R^{11B1} can be hydrogen. In other embodiments, R^{11B1} can be an optionally substituted C_{1-24} alkyl. In still other embodiments, R^{11B1} can be an optionally substituted aryl. In some embodiments, R^{11B1} 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, k1 can be 0. In other embodiments, k1 can be 1. In some embodiments, R^{1B} can be a S-acylthioethoxy (SATE) group and form a SATE ester prodrug.

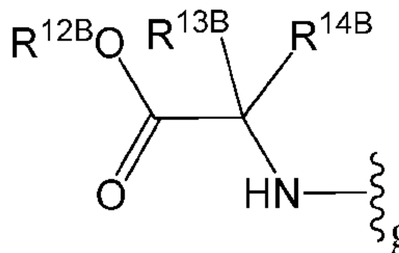
[0150] In some embodiments R^{1B} can be . In some embodiments, R^{11B2} can be hydrogen. In other embodiments, R^{11B2} can be an optionally substituted C_{1-24} alkyl. In still other embodiments, R^{11B2} can be an optionally substituted aryl, for example, an optionally substituted phenyl. In some embodiments, R^{11B2} can be an optionally substituted C_{1-6} alkyl. In some embodiments, R^{11B2} can be an unsubstituted C_{1-6} alkyl. In some embodiments, k2 can be 3. In other embodiments, k2 can be 4. In still other embodiments, k2 can be 5.

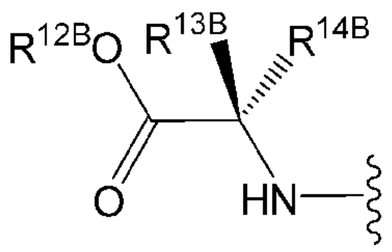
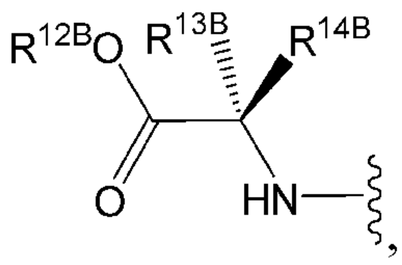
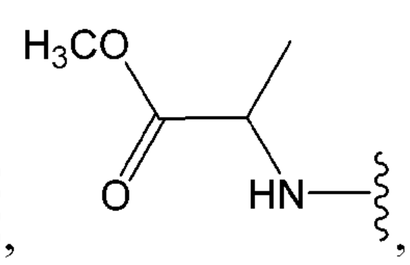
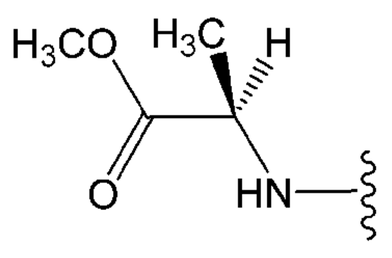
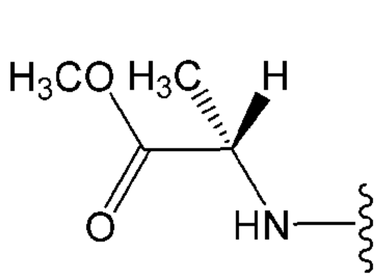
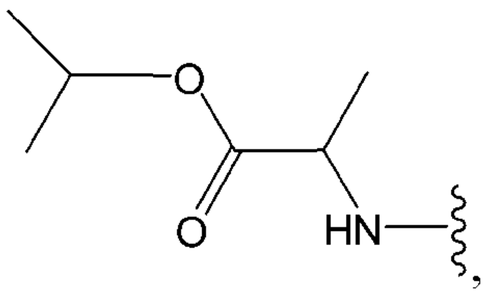
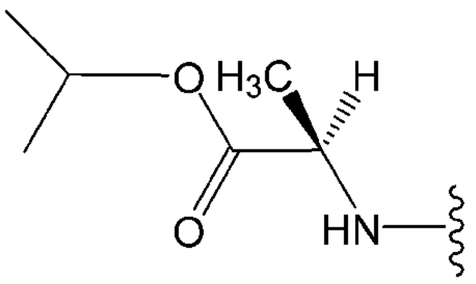
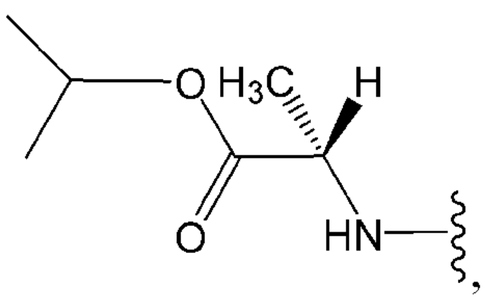
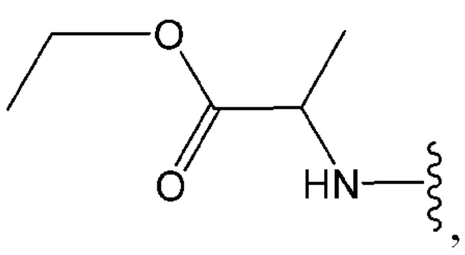
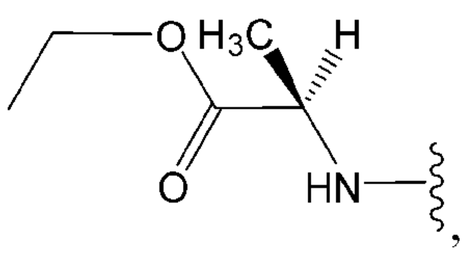
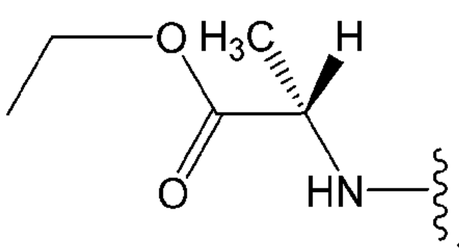
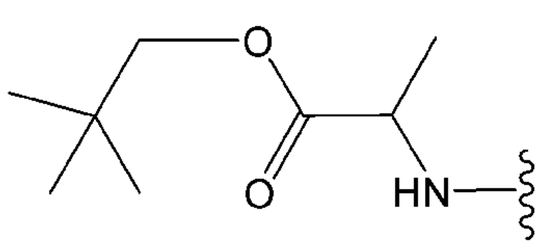
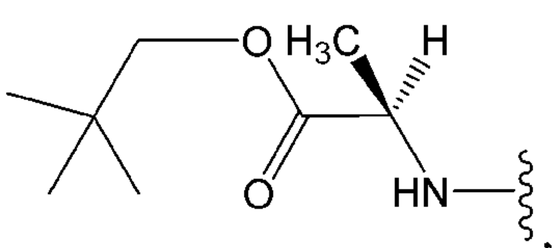
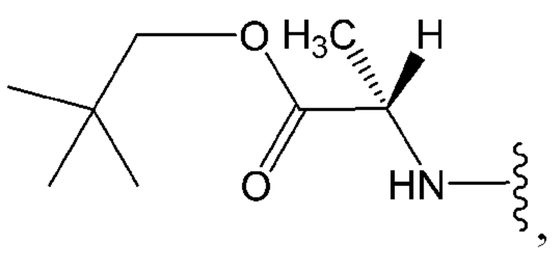
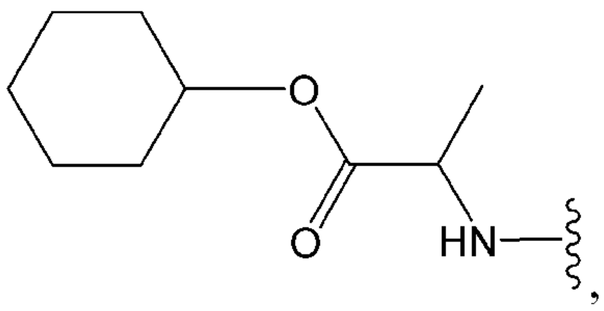
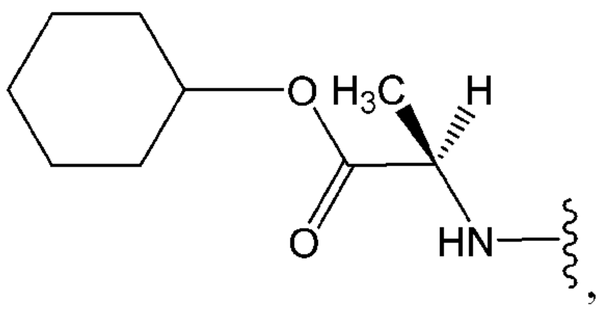
[0151] In some embodiments, R^{1B} can be an optionally substituted N-linked amino acid or an optionally substituted N-linked amino acid ester derivative. For example, R^{1B} can be optionally substituted version of the following: alanine, asparagine, aspartate, cysteine, glutamate, glutamine, glycine, proline, serine, tyrosine, arginine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, valine and ester

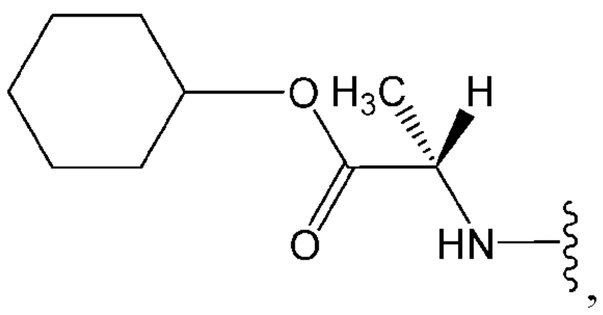
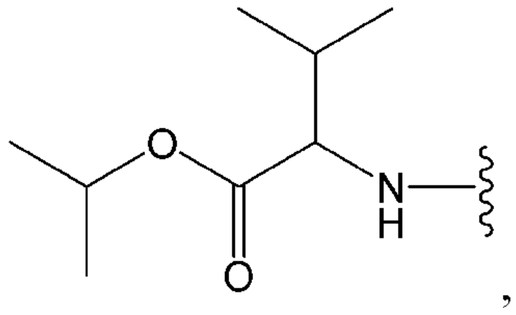
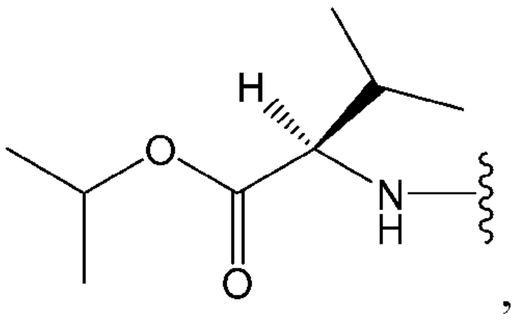
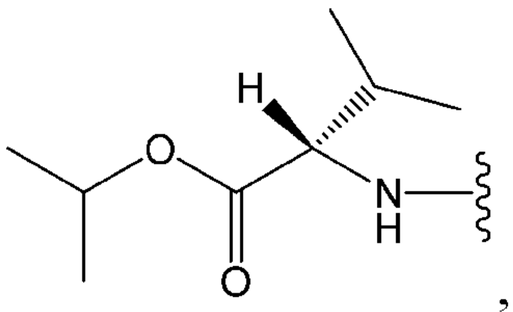
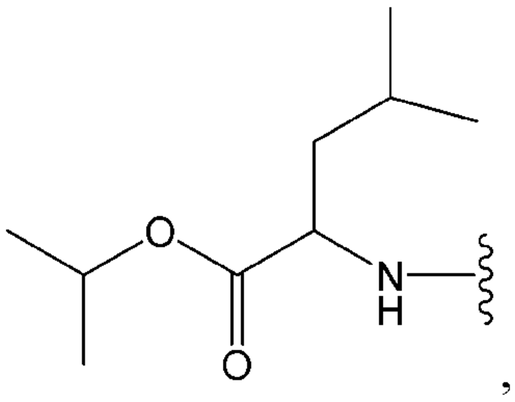
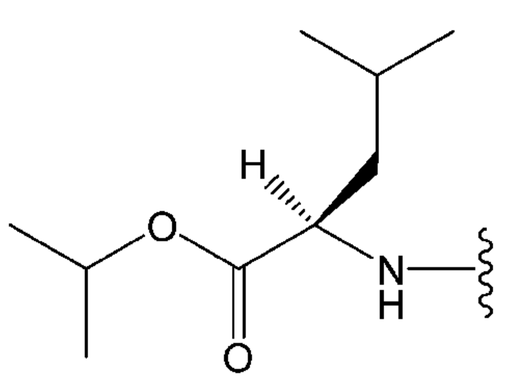
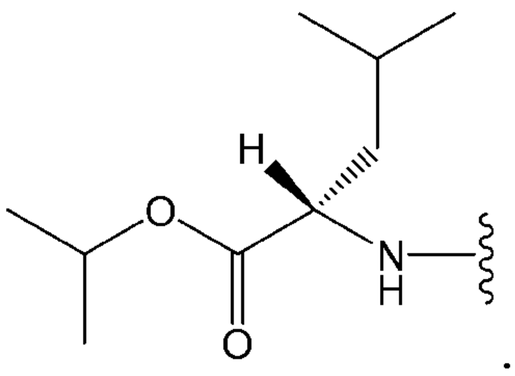
derivatives thereof. In some embodiments, R^{1B} can be selected from alanine isopropyl ester, alanine cyclohexyl ester, alanine neopentyl ester, valine isopropyl ester and leucine isopropyl ester. In some embodiments, R^{1B} can have the structure , wherein R^{12B} can be selected from hydrogen, an 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^{13B} 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^{14B} can be hydrogen or an optionally substituted C_{1-4}-alkyl; or R^{13B} and R^{14B} can be taken together to form an optionally substituted C_{3-6} cycloalkyl.

[0152] When R^{13B} is substituted, R^{13B} 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^{13B} can be an unsubstituted C_{1-6}-alkyl, such as those described herein. In some embodiments, R^{13B} can be hydrogen. In other embodiments, R^{13B} can be methyl. In some embodiments, R^{12B} 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^{12B} can be methyl or isopropyl. In some embodiments, R^{12B} can be ethyl or neopentyl. In other embodiments, R^{12B} can be an optionally substituted C_{3-6} cycloalkyl. Examples of optionally substituted C_{3-6} cycloalkyl include optionally substituted variants of the following: cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. In an embodiment, R^{12B} can be an optionally substituted cyclohexyl. In still other embodiments, R^{12B} can be an optionally substituted aryl, such as phenyl and naphthyl. In yet still other embodiments, R^{12B} can be an optionally substituted aryl(C_{1-6} alkyl). In some embodiments, R^{12B} can be an optionally substituted benzyl. In some embodiments, R^{12B} can be an optionally substituted C_{1-6} haloalkyl, for example, CF_3.

In some embodiments, R^{14B} can be hydrogen. In other embodiments, R^{14B} can be an optionally substituted C_{1-4}-alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and tert-butyl. In an embodiment, R^{14B} can be methyl. In some embodiments, R^{13B} and R^{14B} 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^{13B} and R^{14B}, the carbon to which R^{13B} and R^{14B} are attached may be a chiral center. In some embodiment, the carbon to which R^{13B} and R^{14B} are attached may be a (R)-chiral center. In other embodiments, the carbon to which R^{13B} and R^{14B} are attached may be a (S)-chiral center.

[0153] Examples of suitable  groups include the following:

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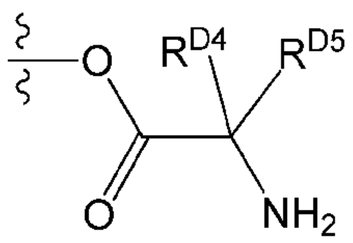
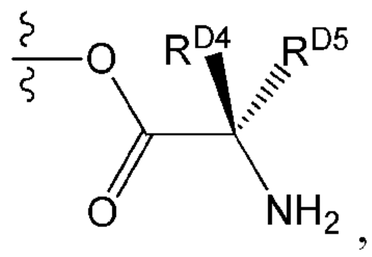
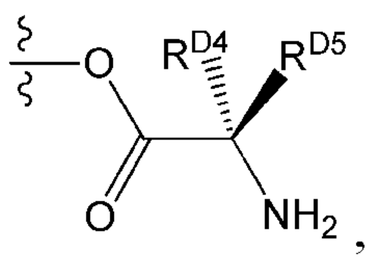
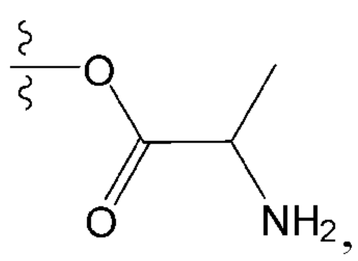
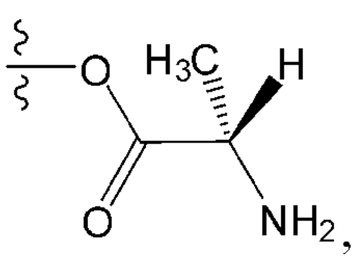
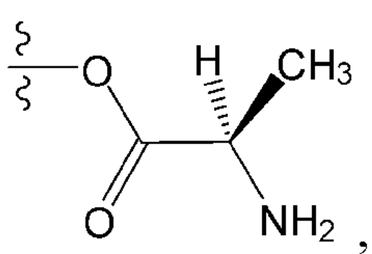
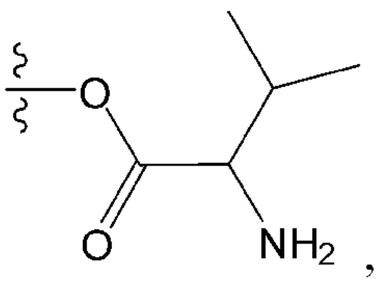
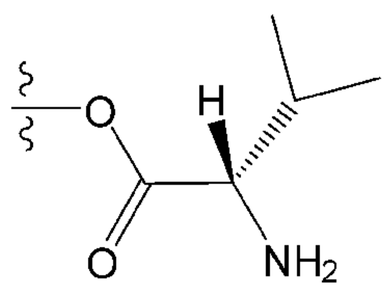
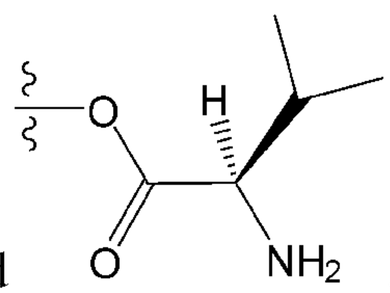

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[0154] A variety of substituents can be present at the 4'-position of the pentose ring. In some embodiments, R^{2B} can be an optionally substituted C_{1-6} alkyl. Examples of suitable C_{1-6} alkyls include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, pentyl (branched and straight-chained) and hexyl (branched and straight-chained). In some embodiments, R^{2B} can be an unsubstituted C_{1-6} alkyl. In other embodiments, R^{2B} can be a substituted C_{1-6} alkyl. For example, R^{2B} can be a halogen substituted C_{1-6} alkyl, a hydroxy substituted C_{1-6} alkyl (such as, CH_2OH), an alkoxy substituted C_{1-6} alkyl (such as, -C_{1-6} alkyl-O-C_{1-6} alkyl and CH_2OCH_3), a sulfenyl substituted C_{1-6} alkyl (for example, -C_{1-6} alkyl-S-C_{1-6} alkyl and CH_2SCH_3), an azido substituted C_{1-6} alkyl or amino substituted C_{1-6} alkyl. In some embodiments, R^{2B} can be a C_{1-6} haloalkyl. For example, R^{2B} can be a C_{1-6} bromoalkyl C_{1-6} chloroalkyl or a C_{1-6} fluoroalkyl, such as CH_2Br, CH_2Cl, CH_2F, CHF_2 or $CHFCH_3$. In other embodiments, R^{2B} can be a C_{1-6} azidoalkyl (for example, N_3CH_2-). In still other embodiments, R^{2B} can be a C_{1-6} aminoalkyl (for example, NH_2CH_2-). In some embodiments, R^{2B} can be an optionally substituted C_{2-6} alkenyl. In some embodiments, R^{2B} can be a substituted C_{2-6} alkenyl. In other embodiments, R^{2B} can be an unsubstituted C_{2-6} alkenyl. For example, R^{2B} can be ethenyl, propenyl or allenyl. In still other embodiments, R^{2B} can be an optionally substituted C_{2-6} alkynyl. In some embodiments, R^{2B} can be a substituted C_{2-6}

alkynyl. In other embodiments, R^{2B} can be an unsubstituted C_{2-6} alkynyl. Suitable C_{2-6} alkynyls include ethynyl and propynyl. In yet still other embodiments, R^{2B} can be an optionally substituted C_{3-6} cycloalkyl. In some embodiments, R^{2B} can be a substituted C_{3-6} cycloalkyl. In other embodiments, R^{2B} can be an unsubstituted C_{3-6} cycloalkyl. A non-limiting list of C_{3-6} cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. In some embodiments, R^{2B} can be an optionally substituted –O–C_{1-6} alkyl. In some embodiments, R^{2B} can be a substituted –O–C_{1-6} alkyl. In other embodiments, R^{2B} can be an unsubstituted –O–C_{1-6} alkyl. Examples of suitable O–C_{1-6} alkyl groups include methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, isobutoxy, tert-butoxy, pentoxy (branched and straight-chained) and hexoxy (branched and straight-chained). In other embodiments, R^{2B} can be an optionally substituted –O–C_{3-6} alkenyl. In some embodiments, R^{2B} can be a substituted – O–C_{3-6} alkenyl. In other embodiments, R^{2B} can be an unsubstituted –O–C_{3-6} alkenyl. In still other embodiments, R^{2B} can be an optionally substituted –O–C_{3-6} alkynyl. In some embodiments, R^{2B} can be a substituted –O–C_{3-6} alkynyl. In other embodiments, R^{2B} can be an unsubstituted –O–C_{3-6} alkynyl. In still other embodiments, R^{2B} can be cyano. In yet still other embodiments, R^{2B} can be halogen, such as fluoro.

[0155] Various substituents can be present at the 2'-position of the pentose ring. In some embodiments, R^{4B} can be hydrogen. In other embodiments, R^{4B} can be halogen, for example, fluoro. In still other embodiments, R^{4B} can be an optionally substituted C_{1-6} alkyl. In some embodiments, R^{4B} can be an unsubstituted C_{1-6} alkyl. In some embodiments, R^{4B} can be a substituted C_{1-6} alkyl. In yet still other embodiments, R^{4B} can be an optionally substituted C_{2-6} alkenyl. In some embodiments, R^{4B} can be an unsubstituted C_{2-6} alkenyl. In some embodiments, R^{4B} can be a substituted C_{2-6} alkenyl. In some embodiments, R^{4B} can be an optionally substituted C_{2-6} alkynyl. In some embodiments, R^{4B} can be an unsubstituted C_{2-6} alkynyl. In some embodiments, R^{4B} can be a substituted C_{2-6} alkynyl.

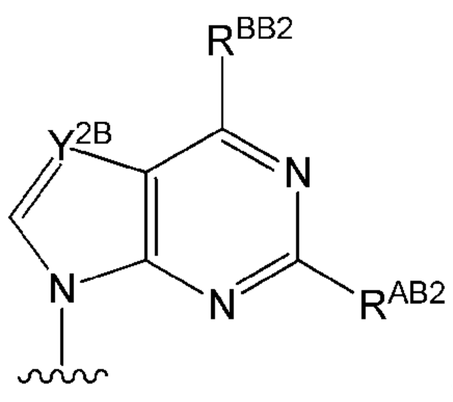
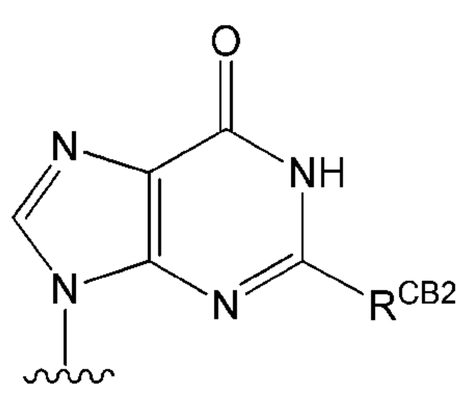
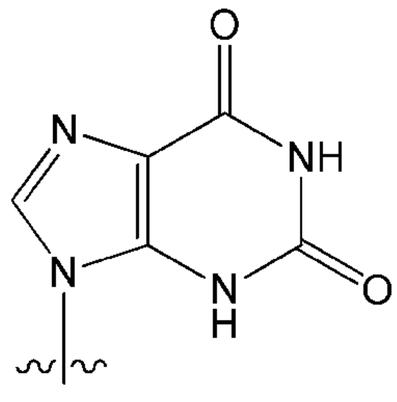
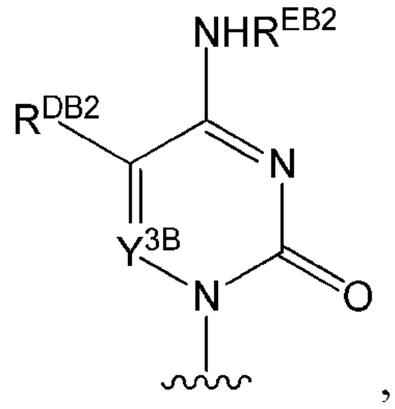
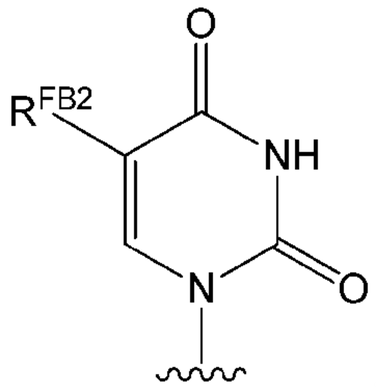
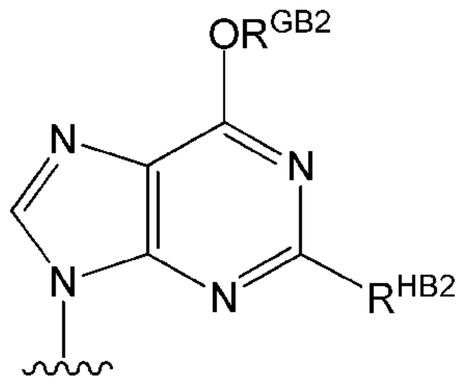
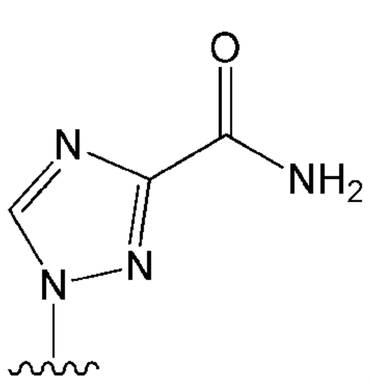
[0156] In some embodiments, R^{3B} can be hydrogen. In other embodiments, R^{3B} can be halogen, such as fluoro or chloro. In still other embodiments, R^{3B} can be OR^{1D}. For example, R^{3B} can be OH. In some embodiments, R^{3B} can be $OC(=O)R^{"D}$. In other embodiments, R^{3B} can be an optionally substituted O-linked amino acid. In still other embodiments, R^{3B} can be azido. In yet still other embodiments, R^{3B} can be $NR^{2D}R^{3D}$. For

example, R^{3B} can be amino, a mono-substituted amine or a di-substituted amine. When R^{3B} is an optionally substituted O-linked amino acid, in some embodiments, R^{D4} 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^{D5} can be hydrogen or an optionally substituted C_{1-4}-alkyl; or R^{D4} and R^{D5} can be taken together to form an optionally substituted C_{3-6} cycloalkyl. Examples of suitable O-linked amino acids for R^{3B} include, but are not limited to:  include the following: , , , , , ,  and .

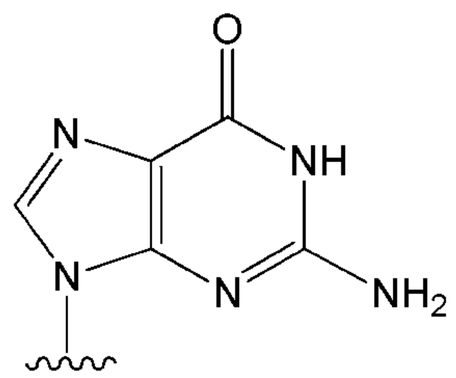
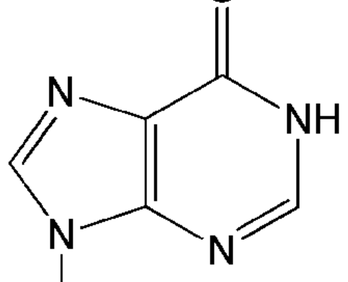
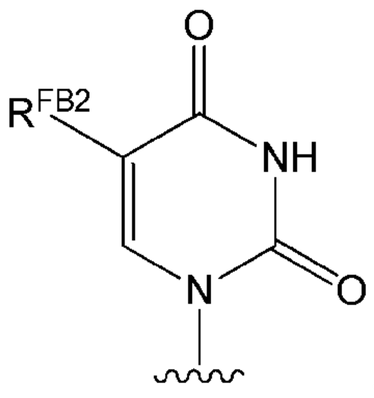
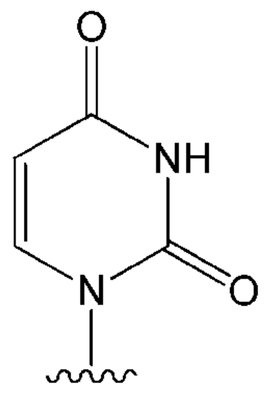
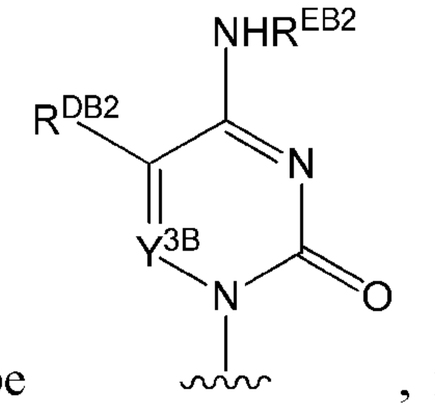
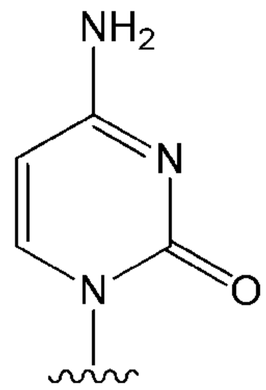
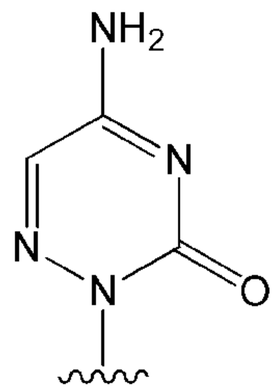
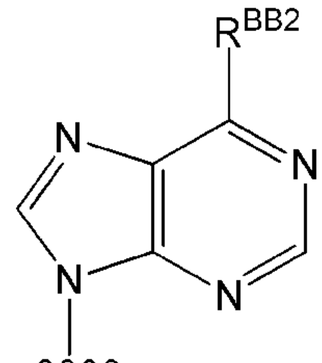
[0157] In some embodiments, R^{3B} can be halogen, such as fluoro or chloro. In some embodiments, R^{4B} can be hydrogen and R^{3B} can be halogen. In other embodiments, R^{3B} and R^{4B} can be both halogen. For example, R^{3B} and R^{4B} can be both fluoro.

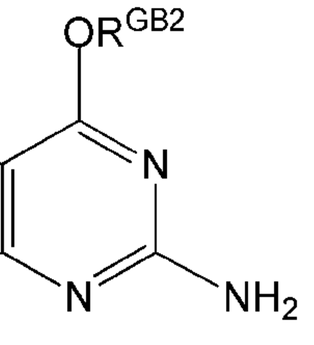
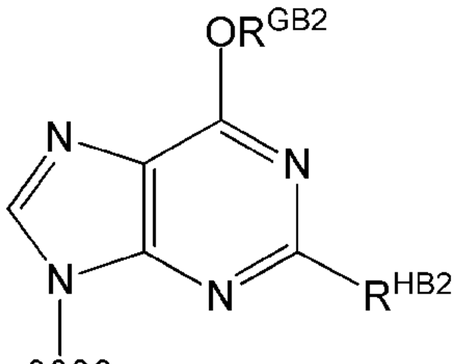
[0158] In some embodiments, Z^{1B} can be O (oxygen). In other embodiments, Z^{1B} can be S (sulfur).

[0159] Various optionally substituted heterocyclic bases can be attached to the pentose ring. In some embodiments, one or more of the amine and/or amino groups may be protected with a suitable protecting group. For example, an amino group may be protected by transforming the amine and/or amino group to an amide or a carbamate. In some embodiments, an optionally substituted heterocyclic base or an optionally substituted heterocyclic base with one or more protected amino groups can have one of the following structures:

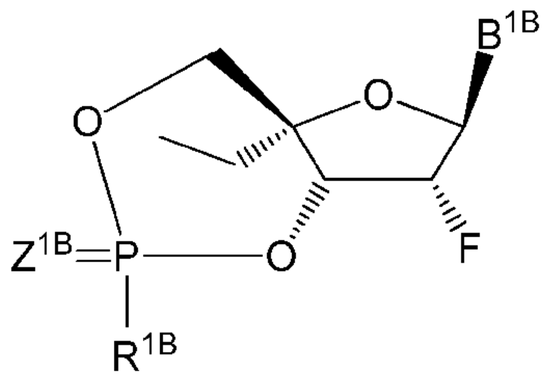
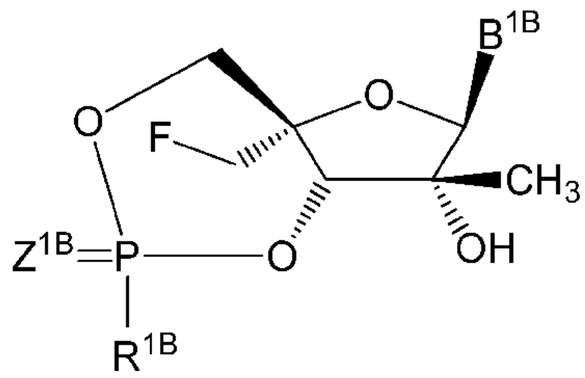
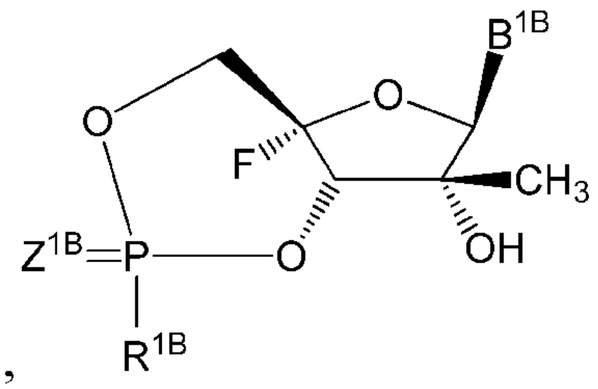

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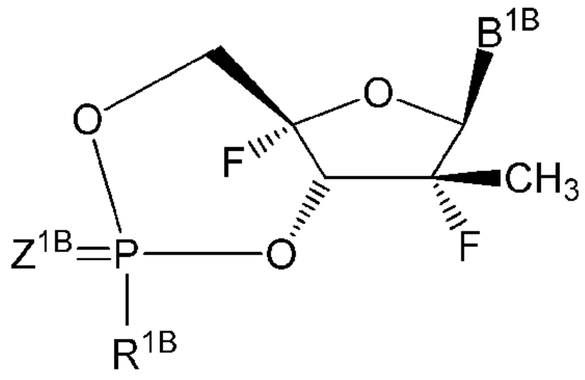
wherein: R^{AB2} can be selected from hydrogen, halogen and NHR^{JB2}, wherein R^{JB2} can be selected from hydrogen, -C(=O)R^{KB2} and –C(=O)OR^{LB2}; R^{BB2} can be halogen or NHR^{WB2}, wherein R^{WB2} can be selected from hydrogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{3-8} cycloalkyl, -C(=O)R^{MB2} and –C(=O)OR^{NB2}; R^{CB2} can be hydrogen or NHR^{OB2}, wherein R^{OB2} can be selected from hydrogen, -C(=O)R^{PB2} and –C(=O)OR^{QB2}; R^{DB2} 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^{EB2} can be selected from hydrogen, hydroxy, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{3-8} cycloalkyl, -C(=O)R^{RB2} and –C(=O)OR^{SB2}; R^{FB2} 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^{2B} and Y^{3B} can be independently N (nitrogen) or CR^{IB2}, wherein R^{IB2} can be selected from hydrogen, halogen, an optionally substituted C_{1-6}-alkyl, an optionally substituted C_{2-6}-alkenyl and an optionally substituted C_{2-6}-alkynyl; R^{GB2} can be an optionally substituted C_{1-6} alkyl; R^{HB2} can be hydrogen or NHR^{TB2}, wherein R^{TB2} can be independently selected from hydrogen, -C(=O)R^{UB2} and –C(=O)OR^{VB2}; and R^{KB2}, R^{LB2}, R^{MB2}, R^{NB2}, R^{PB2}, R^{QB2}, R^{RB2}, R^{SB2}, R^{UB2} and R^{VB2} can be independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkenyl, C_{6-10} aryl, heteroaryl, heteroalicyclyl, aryl(C_{1-6} alkyl), heteroaryl(C_{1-6} alkyl) and heteroalicyclyl(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."

[0160] In some embodiments, B^{1B} can be . In other embodiments, B^{1B} can be . In still other embodiments, B^{1B} can be , such as . In yet still other embodiments, B^{1B} can be , for example,  or . In some embodiments, 

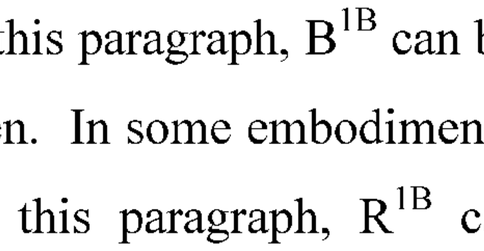
R^{DB2} can be hydrogen. In other embodiments, B^{1B} can be . In some embodiments, R^{BB2} can be NH_2. In other embodiments, R^{BB2} can be NHR^{WB2}, wherein R^{WB2} can be $-C(=O)R^{MB2}$ or $-C(=O)OR^{NB2}$. In still other embodiments, B^{1B} can be  . In some embodiments, B^{1B} can be .

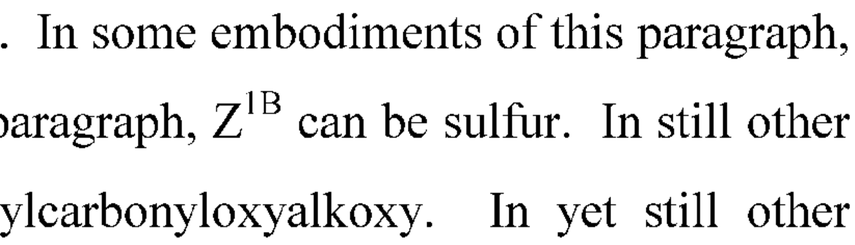
[0161] In some embodiments, a compound of Formula (II) can be selected from:

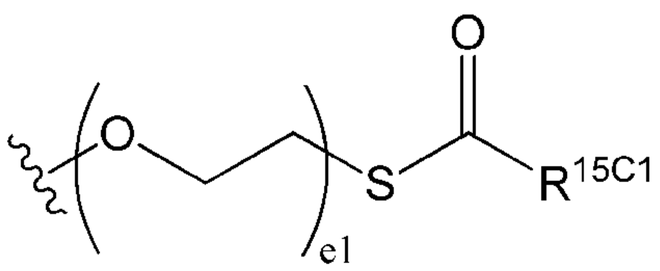
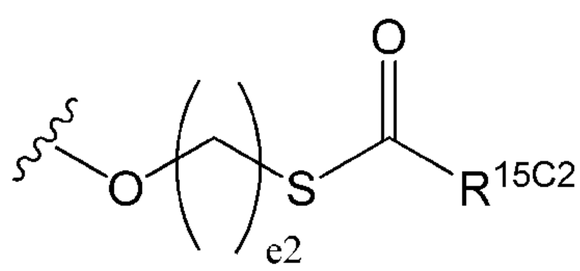



and


, or a pharmaceutically acceptable salt of the foregoing. In some embodiments of this paragraph, B^{1B} can be an optionally substituted purine base. In other embodiments of this paragraph, B^{1B} can be an optionally substituted pyrimidine base. In some embodiments of this paragraph, B^{1B} can be guanine. In other embodiments of this paragraph, B^{1B} can be thymine. In still other embodiments of this paragraph, B^{1B} can be cytosine. In yet still other embodiments of this paragraph, B^{1B} can be uracil. In some embodiments of this paragraph, B^{1B} can be adenine. In some embodiments of this paragraph, Z^{1B} can be oxygen. In some embodiments of this paragraph, Z^{1B} can be sulfur. In still other embodiments of this paragraph, R^{1B} can be alkylcarbonyloxyalkoxy. In yet still other embodiments of this paragraph, R^{1B} can be alkoxycarbonyloxyalkoxy. In some embodiments of this paragraph, R^{1B} can be a C_{1-6} alkoxy.

[0162] In some embodiments, the compound can be a compound of Formula (III), or a pharmaceutically acceptable salt thereof, wherein: B^{1C} can be an optionally substituted heterocyclic base or an optionally substituted heterocyclic base with a protected amino group; R^{1C} and R^{2C} can be independently selected from O^-, OH, an optionally substituted C_{1-6} alkoxy,

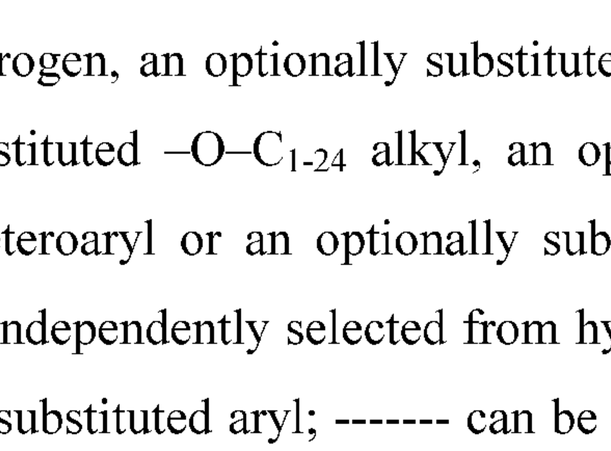

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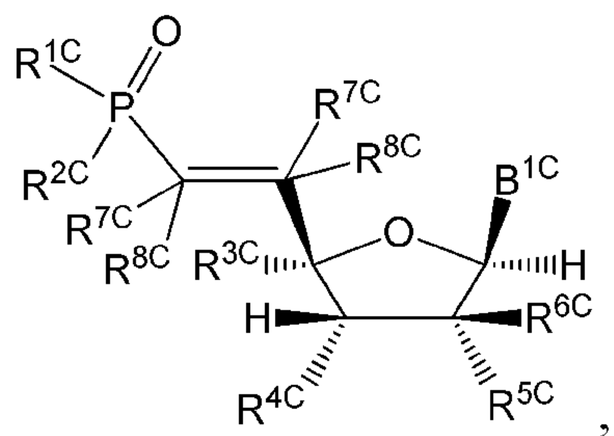
, an optionally substituted N-linked amino acid and an optionally substituted N-linked amino acid ester derivative; R^{3C} can be selected from an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{2-6} alkynyl, an optionally substituted –O–C_{1-6} alkyl, an optionally substituted –O–C_{3-6} alkenyl, an optionally substituted –O–C_{3-6} alkynyl, an optionally substituted C_{3-6} cycloalkyl and cyano; R^{4C} can be selected from OH, -OC(=O)$R^{"C}$ and an optionally substituted O-linked amino acid; R^{5C} can be selected from hydrogen, halogen, OR^{1D}, an optionally substituted O-linked amino acid, azido and $NR^{2D}R^{3D}$; R^{1D} can be hydrogen or –C(=O)$R^{"D}$; R^{2D} and R^{3D} can be independently hydrogen or an optionally substituted C_{1-6} alkyl; R^{6C} can be selected from hydrogen, halogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl and an optionally substituted C_{2-6} alkynyl; R^{9C}, R^{10C}, R^{12C} and R^{13C} can be independently selected from hydrogen, an optionally substituted C_{1-24} alkyl and an optionally substituted aryl; R^{11C} and R^{14C} 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 or an optionally substituted –O–monocyclic heterocyclyl; R^{15C1} and R^{15C2} can be independently selected from hydrogen, an optionally substituted C_{1-24} alkyl and an optionally substituted aryl; ------- can be a single bond or a double bond; when ------- is a single bond, each R^{7C} and each R^{8C} can be independently hydrogen or halogen; and when ------- is a double bond, each R^{7C} is absent and each R^{8C} can be independently hydrogen or halogen; d can be 1 or 2; e1 can be 0 or 1; e2 can be 3, 4 or 5; $R^{"C}$ and $R^{"D}$ can be independently an optionally substituted C_{1-24}-alkyl and Z^{1C} can be O (oxygen) or S (sulfur).

[0163] In some embodiments, ------- can be a single bond such that Formula (III) has the structure

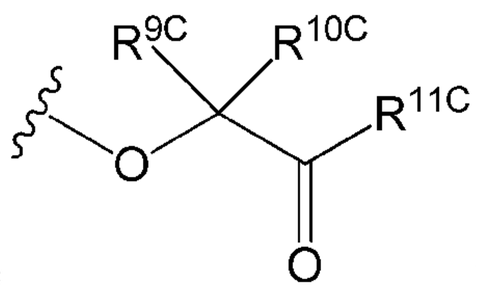


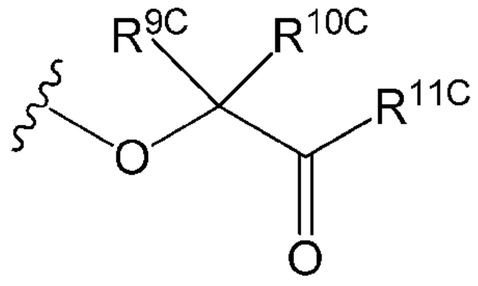
, wherein each R^{7C} and each R^{8C} can be

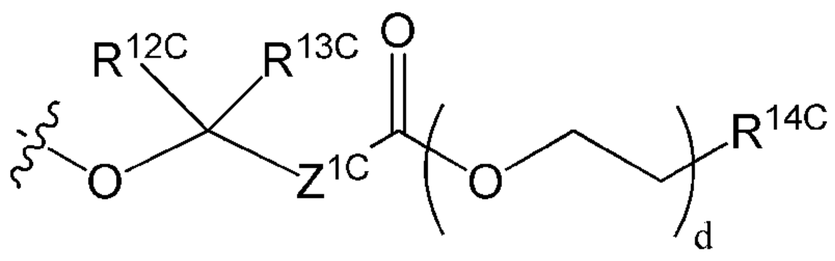
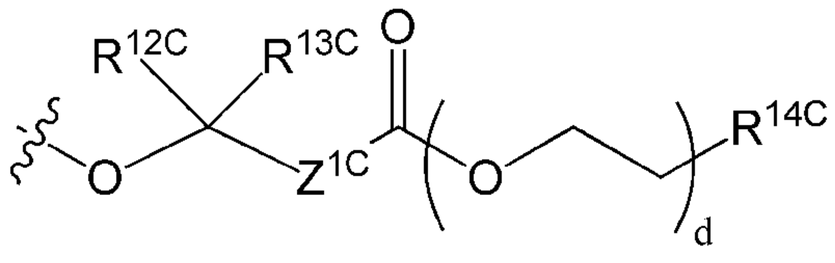
independently hydrogen or halogen. In some embodiments, the R^{7C} and the R^{8C} groups can all be hydrogen. In other embodiments, one R^{7C} can be halogen, one R^{7C} can be hydrogen and both R^{8C} groups can be hydrogen. In still other embodiments, one R^{7C} can be halogen, one R^{7C} can be hydrogen, one R^{8C} can be halogen and one R^{8C} can be hydrogen. In some embodiments, the carbon adjacent to the phosphorus and the 5'-carbon can each be independently a (S)-chiral center. In some embodiments, the carbon adjacent to the phosphorus and the 5'-carbon can each be independently a (R)-chiral center.

[0164] In some embodiments, ------- can be a double bond such that Formula (III) has the structure , wherein each R^{7C} is absent and each R^{8C} can be independently hydrogen or halogen. In some embodiments, both R^{8C} groups can be hydrogen. In other embodiments, one R^{8C} can be halogen and the other R^{8C} can be hydrogen. In some embodiments, both R^{8C} groups can be halogen. In some embodiments, the double bond has a (*Z*)-configuration. In some embodiments, the double bond has a (*E*)-configuration.

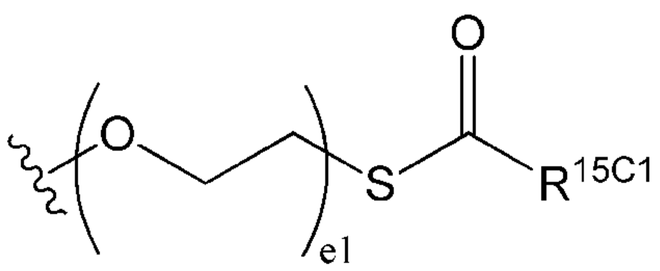
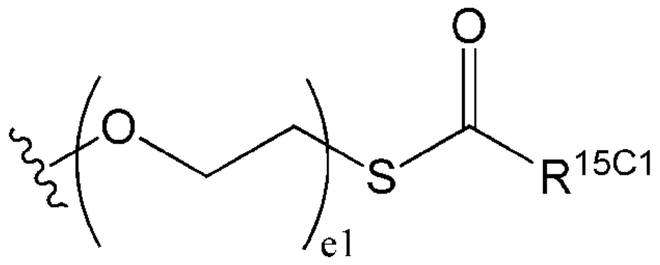
[0165] In some embodiments, R^{1C} and/or R^{2C} can be O^-. In other embodiments, R^{1C} and/or R^{2C} can be OH. In some embodiments, R^{1C} and R^{2C} can be both OH.

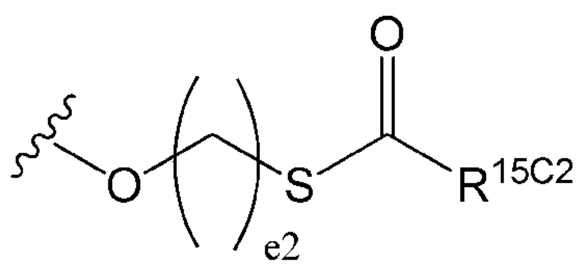
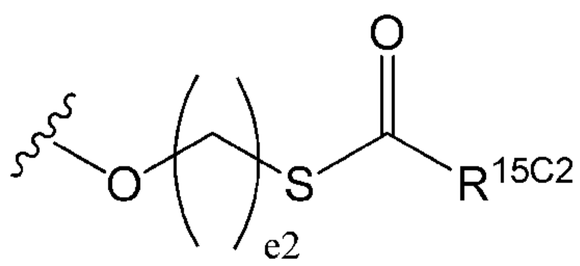
[0166] In some embodiments, R^{1C} and/or R^{2C} can be  wherein R^{9C} and R^{10C} can be independently selected from hydrogen, an optionally substituted $C_{1\text{-}24}$ alkyl and an optionally substituted aryl; and R^{11C} can be selected from hydrogen, an optionally substituted $C_{1\text{-}24}$ alkyl, an optionally substituted aryl, an optionally substituted –O–$C_{1\text{-}24}$ alkyl, an optionally substituted –O–aryl, an optionally substituted –O–heteroaryl and an optionally substituted –O–monocyclic heterocyclyl. In some embodiments, R^{9C} and R^{10C} can be hydrogen. In other embodiments, at least one of R^{9C} and R^{10C} can be an optionally substituted $C_{1\text{-}24}$ alkyl or an optionally substituted aryl. In some

embodiments, R^{11C} can be an optionally substituted C_{1-24} alkyl. In other embodiments, R^{11C} can be an optionally substituted aryl. In still other embodiments, R^{11C} 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^{1C} and R^{2C} can be both  .

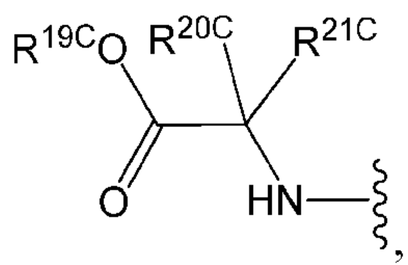
[0167] In some embodiments, R^{1C} and/or R^{2C} can be  wherein R^{12C} and R^{13C} can be independently selected from hydrogen, an optionally substituted C_{1-24} alkyl and an optionally substituted aryl; R^{14C} can be independently selected from hydrogen, an optionally substituted C_{1-24} alkyl, 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; and Z^{1C} can be independently O (oxygen) or S (sulfur). In some embodiments, R^{12C} and R^{13C} can be hydrogen. In other embodiments, at least one of R^{12C} and R^{13C} can be an optionally substituted C_{1-24} alkyl or an optionally substituted aryl. In some embodiments, R^{14C} can be an optionally substituted C_{1-24} alkyl. In other embodiments, R^{14C} can be an optionally substituted aryl. In still other embodiments, R^{14C} 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, d can be 1. In other embodiments, d can be 2. In some embodiments, Z^{1C} can be O (oxygen). In other embodiments, Z^{1C} can be or S (sulfur). In some embodiments, R^{1C} and/or R^{2C} can be isopropyloxycarbonyloxymethoxy. In some embodiments, R^{1C} and/or R^{2C} can be pivaloyloxymethoxy. In some embodiments, R^{1C} and R^{2C} can be both  . In some embodiments, R^{1C} and R^{2C} can be both

isopropyloxycarbonyloxymethoxy. In other embodiments, R^{1C} and R^{2C} can be both pivaloyloxymethoxy. In some embodiments, R^{1C} and R^{2C} can be both a isopropyloxycarbonyloxymethoxy group, and form a bis(isopropyloxycarbonyloxymethyl) (bis(POC)) prodrug. In some embodiments, R^{1C} and R^{2C} can be both a pivaloyloxymethoxy group, and form a bis(pivaloyloxymethyl) (bis(POM)) prodrug.

[0168] In some embodiments, R^{1C} and/or R^{2C} can be  . In some embodiments, R^{15C1} can be hydrogen. In other embodiments, R^{15C1} can be an optionally substituted C_{1-24} alkyl. In still other embodiments, R^{15C1} can be an optionally substituted aryl. In some embodiments, R^{15C1} 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, R^{1C} and R^{2C} can be both  . In some embodiments, e1 can be 0. In other embodiments, e1 can be 1. In some embodiments, R^{1C} and R^{2C} can be both a S-acylthioethoxy (SATE) group and form a SATE ester prodrug.

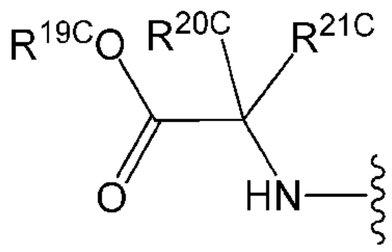
[0169] In some embodiments, R^{1C} and R^{2C} can be both  . In some embodiments, at least one of R^{1C} and R^{2C} can be  . In some embodiments, R^{15C2} can be hydrogen. In other embodiments, R^{15C2} can be an optionally substituted C_{1-24} alkyl. In still other embodiments, R^{15C2} can be an optionally substituted aryl, for example, an optionally substituted phenyl. In some embodiments, R^{15C2} can be an optionally substituted C_{1-6} alkyl. In some embodiments,

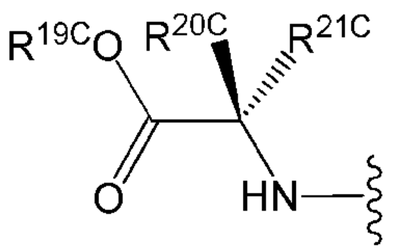
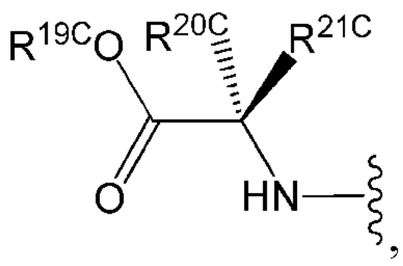
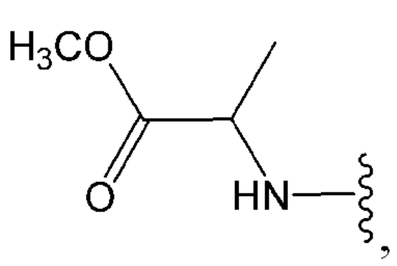
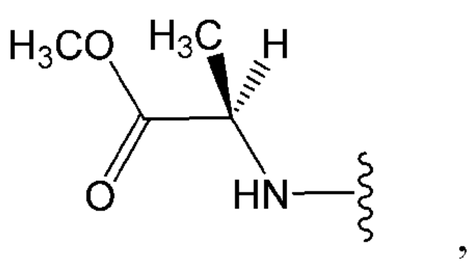
R^{15C2} can be an unsubstituted C_{1-6} alkyl. In some embodiments, e2 can be 3. In other embodiments, e2 can be 4. In still other embodiments, e2 can be 5.

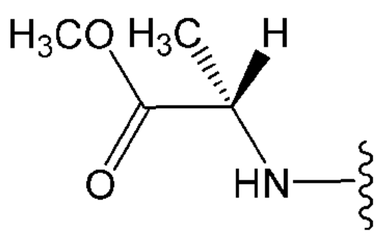
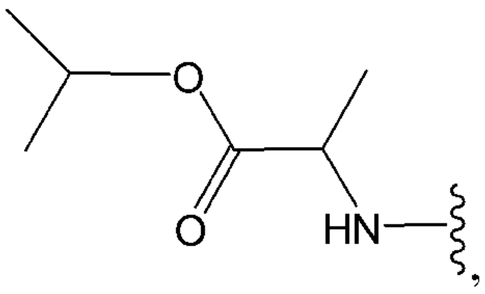
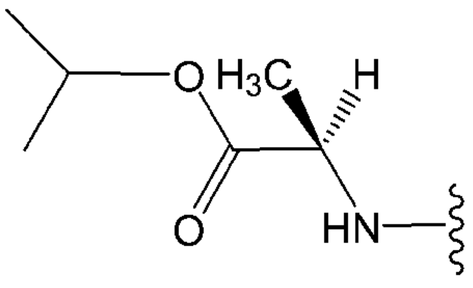
[0170] In some embodiments, R^{1C} and/or R^{2C} can be an optionally substituted N-linked amino acid or an optionally substituted N-linked amino acid ester derivative. For example, R^{1C} and/or R^{2C} can be optionally substituted version of the following: alanine, asparagine, aspartate, cysteine, glutamate, glutamine, glycine, proline, serine, tyrosine, arginine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, valine and ester derivatives thereof. In some embodiments, R^{1C} and/or R^{2C} can be selected from alanine isopropyl ester, alanine cyclohexyl ester, alanine neopentyl ester, valine isopropyl ester and leucine isopropyl ester. In some embodiments, R^{1C} and/or R^{2C} can have the structure , wherein R^{19C} 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^{20C} 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^{21C} can be hydrogen or an optionally substituted C_{1-4}-alkyl; or R^{20C} and R^{21C} can be taken together to form an optionally substituted C_{3-6} cycloalkyl.

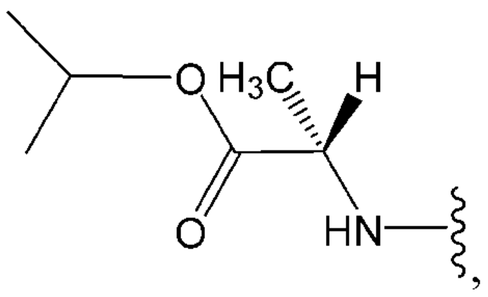
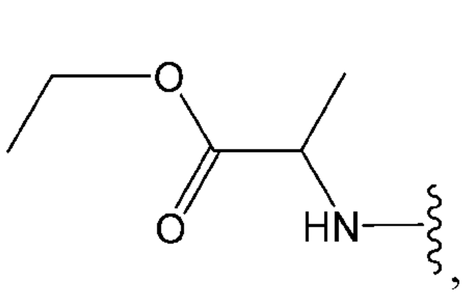
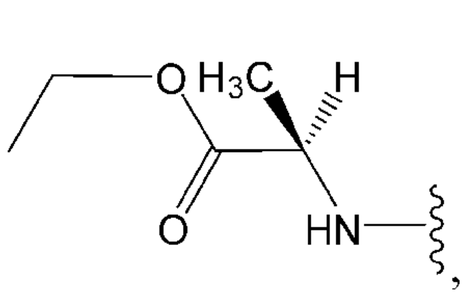
[0171] When R^{20C} is substituted, R^{20C} can be substituted with one or more substituents selected from N-amido, mercapto, alkylthio, an optionally substituted aryl, hydroxy, an optionally substituted heteroaryl, O-carboxy and amino. In some embodiments, R^{20C} can be an unsubstituted C_{1-6}-alkyl, such as those described herein. In some embodiments, R^{20C} can be hydrogen. In other embodiments, R^{20C} can be methyl. In some embodiments, R^{19C} 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^{19C} can be methyl or isopropyl. In some embodiments, R^{19C} can be ethyl or neopentyl. In other embodiments,

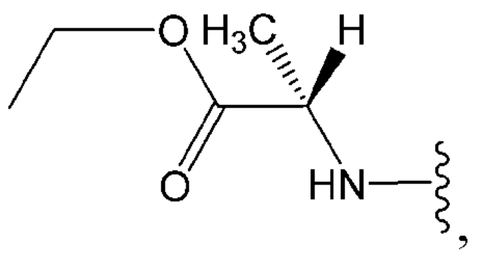
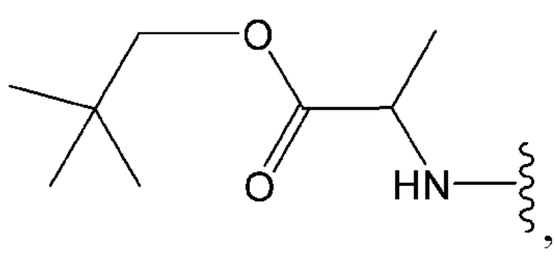
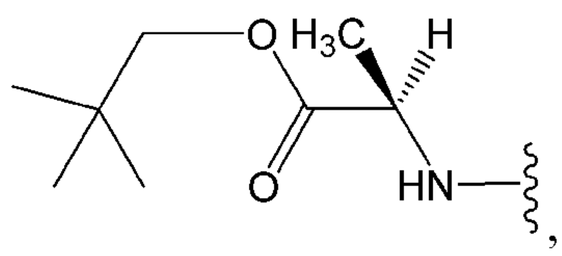
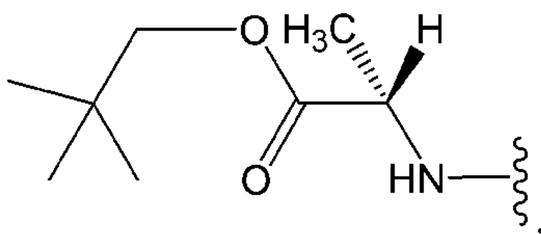
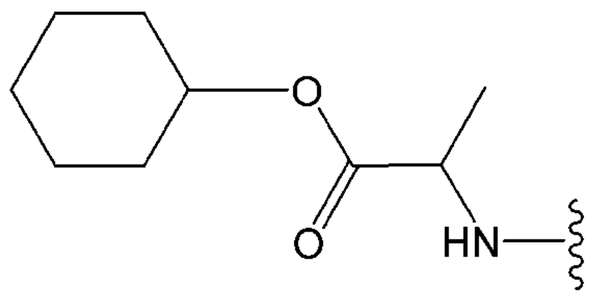
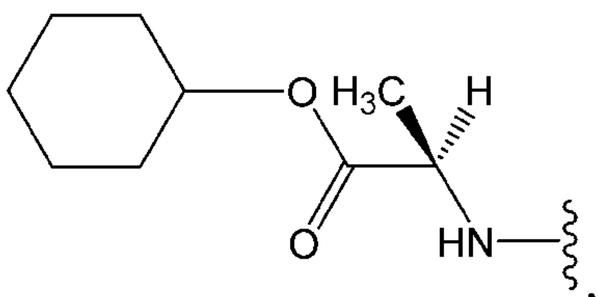
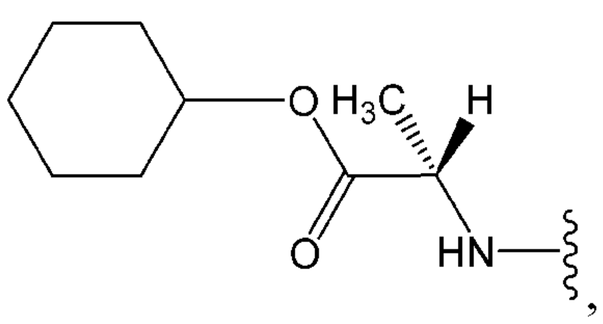
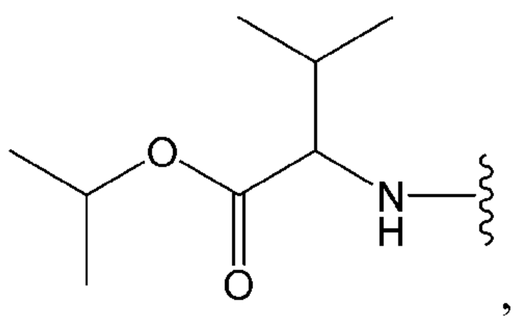
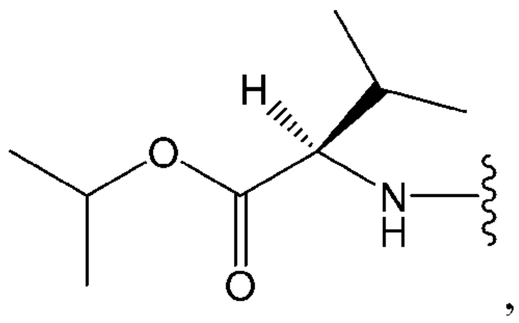
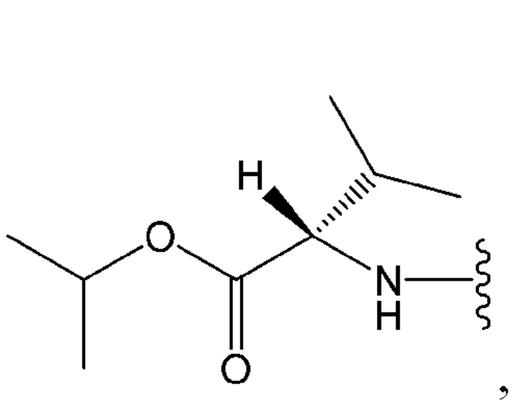
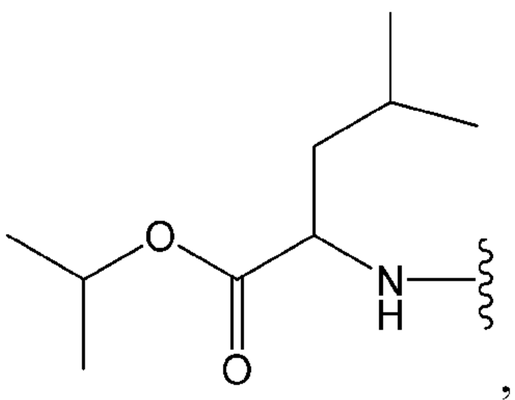
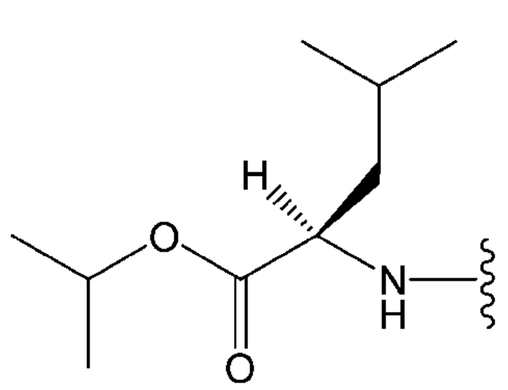
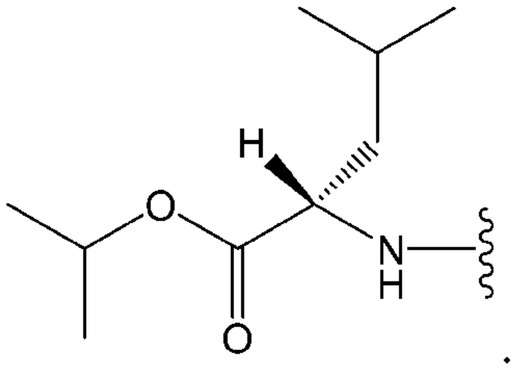
R^{19C} can be an optionally substituted C_{3-6} cycloalkyl. Examples of optionally substituted C_{3-6} cycloalkyl include optionally substituted variants of the following: cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. In an embodiment, R^{19C} can be an optionally substituted cyclohexyl. In still other embodiments, R^{19C} can be an optionally substituted aryl, such as phenyl and naphthyl. In yet still other embodiments, R^{19C} can be an optionally substituted aryl(C_{1-6} alkyl). In some embodiments, R^{19C} can be an optionally substituted benzyl. In some embodiments, R^{19C} can be an optionally substituted C_{1-6} haloalkyl, for example, CF_3. In some embodiments, R^{21C} can be hydrogen. In other embodiments, R^{21C} can be an optionally substituted C_{1-4}-alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and tert-butyl. In an embodiment, R^{21C} can be methyl. In some embodiments, R^{20C} and R^{21C} 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^{20C} and R^{21C}, the carbon to which R^{20C} and R^{21C} are attached may be a chiral center. In some embodiment, the carbon to which R^{20C} and R^{21C} are attached may be a (R)-chiral center. In other embodiments, the carbon to which R^{20C} and R^{21C} are attached may be a (S)-chiral center.

[0172] Examples of suitable  groups include the following:

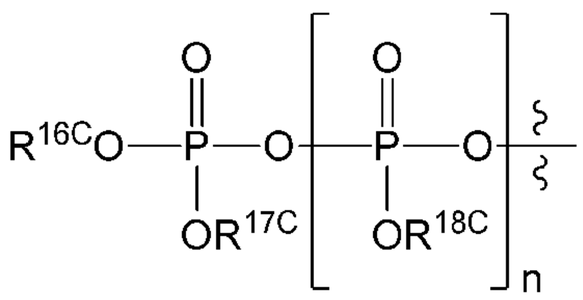
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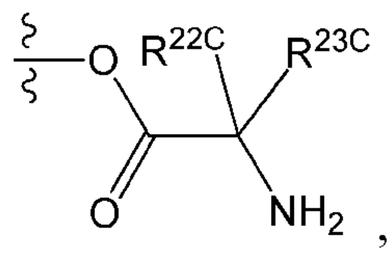

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and

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[0173] In some embodiments, R^{1C} and R^{2C} can be the same. In other embodiments, R^{1C} and R^{2C} can be different.

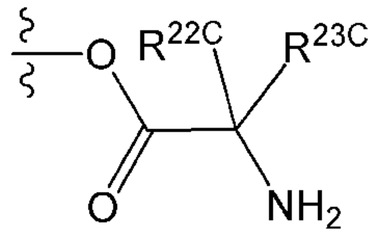
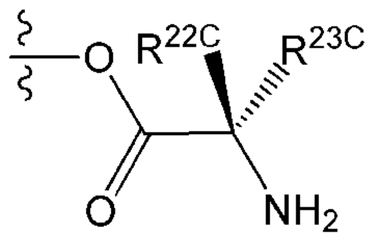
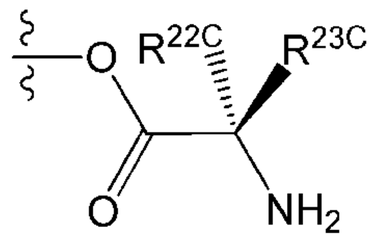
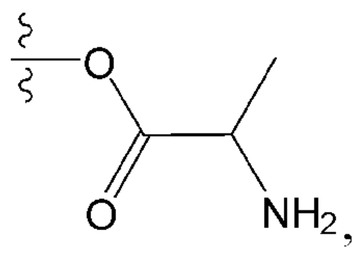
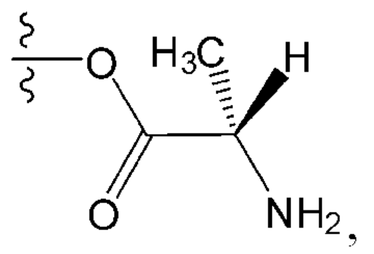
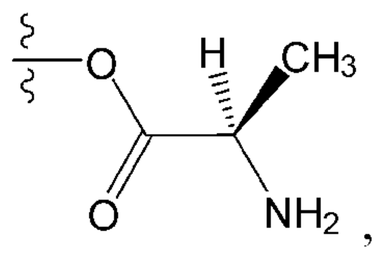
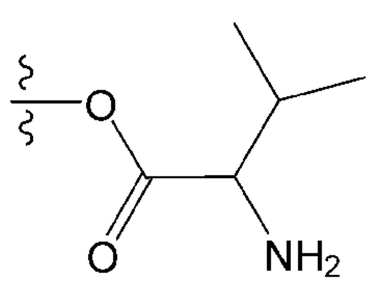
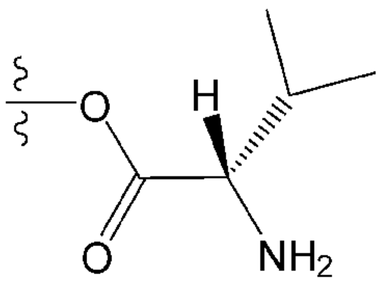
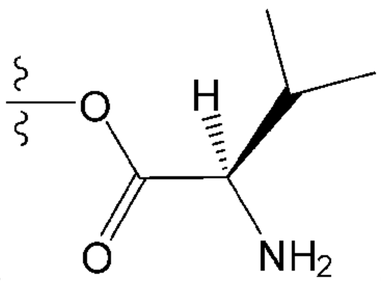
[0174] In some embodiments, R^{1C} can be  and R^{2C} can be O^- or OH, wherein R^{16C}, R^{17C} and R^{18C} can be absent or hydrogen; and n can be 0 or 1. Those skilled in the art understand that when R^{16C}, R^{17C} and/or R^{18C} are absent, the associated oxygen will be negatively charge. In some embodiments, when n is 0, the compound of Formula (III) will be a diphosphate. In other embodiments, when n is 1, the compound of Formula (III) will be a triphosphate.

[0175] A variety of substituents can be present at the 4'-position of the pentose ring. In some embodiments, R^{3C} 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 some embodiments, R^{3C} can be an unsubstituted C_{1-6} alkyl. In other embodiments, R^{3C} can be a substituted C_{1-6} alkyl. For example, R^{3C} can be a halogen substituted C_{1-6} alkyl, a hydroxy substituted C_{1-6} alkyl (such as, CH_2OH), an alkoxy substituted C_{1-6} alkyl (such as, -C_{1-6} alkyl-O-C_{1-6} alkyl and CH_2OCH_3), a sulfenyl substituted C_{1-6} alkyl (for example, -C_{1-6} alkyl-S-C_{1-6} alkyl and CH_2SCH_3), an azido substituted C_{1-6} alkyl or amino substituted C_{1-6} alkyl. In some embodiments, R^{3C} can be a C_{1-6} haloalkyl. For example, R^{3C} can be a C_{1-6} bromoalkyl C_{1-6} chloroalkyl or a C_{1-6} fluoroalkyl, such as CH_2Br, CH_2Cl, CH_2F, CHF_2 or $CHFCH_3$. In other embodiments, R^{3C} can be a C_{1-6} azidoalkyl (for example, N_3CH_2-). In still other embodiments, R^{3C} can be a C_{1-6} aminoalkyl (for example, NH_2CH_2-). In other embodiments, R^{3C} can be an optionally substituted C_{2-6} alkenyl. In some embodiments, R^{3C} can be a substituted C_{2-6} alkenyl. In other embodiments, R^{3C} can be an unsubstituted C_{2-6} alkenyl. For example, R^{3C} can be ethenyl, propenyl or allenyl. In still other embodiments, R^{3C} can be an optionally substituted C_{2-6} alkynyl. In some embodiments, R^{3C} can be a substituted C_{2-6} alkynyl. In other embodiments, R^{3C} can be an unsubstituted C_{2-6} alkynyl. Suitable C_{2-6} alkynyls include ethynyl and propynyl. In yet still other embodiments, R^{3C} can be an optionally substituted C_{3-6} cycloalkyl. In some embodiments, R^{3C} can be a substituted C_{3-6} cycloalkyl. In other embodiments, R^{3C} can be an unsubstituted C_{3-6} cycloalkyl. A non-limiting list of C_{3-6} cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. In some embodiments, R^{3C} can be an optionally substituted –O–C_{1-6} alkyl. In some embodiments, R^{3C} can be a substituted –O–C_{1-6} alkyl. In other embodiments, R^{3C} can be an unsubstituted –O–C_{1-6} alkyl. Examples of suitable O–C_{1-6} alkyl groups include methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, isobutoxy, tert-butoxy, pentoxy (branched and straight-chained) and hexoxy (branched and straight-chained). In other embodiments, R^{3C} can be an optionally substituted –O–C_{3-6} alkenyl. In some embodiments, R^{3C} can be a substituted –O–C_{3-6} alkenyl. In other embodiments, R^{3C} can be an unsubstituted –O–C_{3-6} alkenyl. In still other embodiments, R^{3C} can be an optionally substituted –O–C_{3-6} alkynyl. In

some embodiments, R^{3C} can be a substituted –O–C_{3-6} alkynyl. In other embodiments, R^{3C} can be an unsubstituted –O–C_{3-6} alkynyl. In still other embodiments, R^{3C} can be cyano.

[0176] The substituents that can be present on the 3'-position of the pentose ring can vary. In some embodiments, R^{4C} can be OH. In other embodiments, R^{4C} 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^{22C} 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^{23C} can be hydrogen or an optionally substituted C_{1-4}-alkyl; or R^{22C} and R^{23C} can be taken together to form an optionally substituted C_{3-6} cycloalkyl.

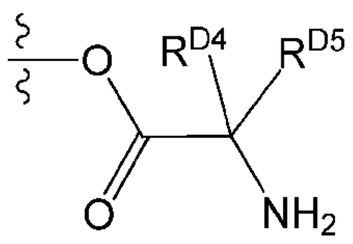
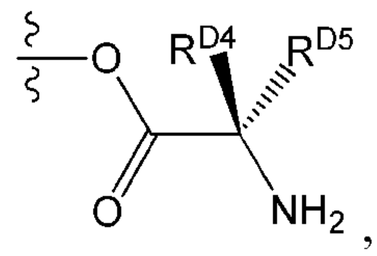
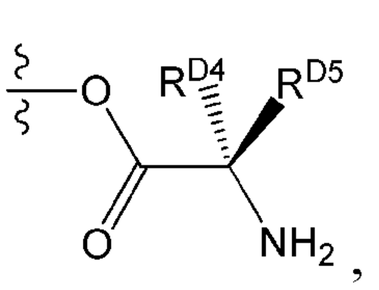
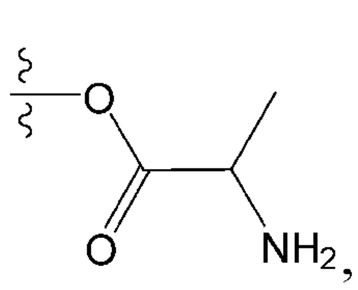
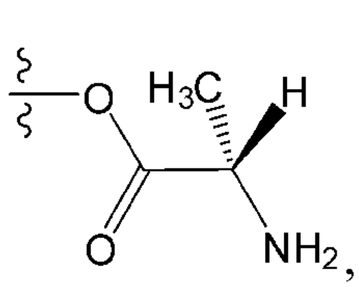
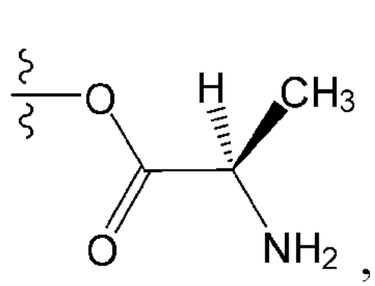
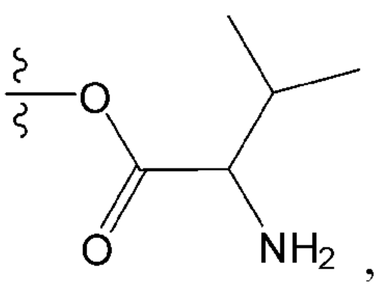
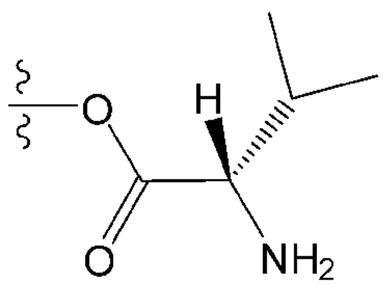
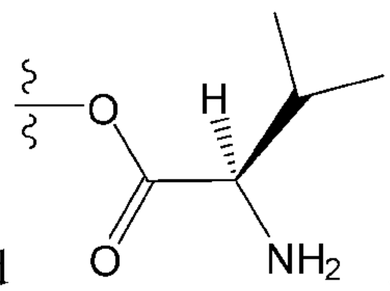
[0177] When R^{22C} is substituted, R^{22C} can be substituted with one or more substituents selected from N-amido, mercapto, alkylthio, an optionally substituted aryl, hydroxy, an optionally substituted heteroaryl, O-carboxy and amino. In some embodiments, R^{22C} can be an unsubstituted C_{1-6}-alkyl, such as those described herein. In some embodiments, R^{22C} can be hydrogen. In other embodiments, R^{22C} can be methyl. In some embodiments, R^{23C} can be hydrogen. In other embodiments, R^{23C} can be an optionally substituted C_{1-4}-alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and tert-butyl. In an embodiment, R^{23C} can be methyl. Depending on the groups that are selected for R^{22C} and R^{23C}, the carbon to which R^{22C} and R^{23C} are attached may be a chiral center. In some embodiment, the carbon to which R^{22C} and R^{23C} are attached may be a (R)-chiral center. In other embodiments, the carbon to which R^{22C} and R^{23C} are attached may be a (S)-chiral center.

[0178] Examples of suitable  include the following:        and .

[0179] In still other embodiments, R^{4C} can be –OC(=O)$R^{"C}$, wherein $R^{"C}$ can be an optionally substituted C_{1-24} alkyl. In some embodiments, $R^{"C}$ can be a substituted C_{1-12} alkyl. In other embodiments, $R^{"C}$ can be an unsubstituted C_{1-12} alkyl. In still other embodiments, $R^{"C}$ can be a substituted C_{1-8} alkyl. In yet still other embodiments, $R^{"C}$ can be an unsubstituted C_{1-8} alkyl. In some embodiments, R^{4C} can be an optionally substituted acyl. In other embodiments, R^{4C} can be –OC(=O)$R^{"C}$, wherein $R^{"C}$ 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, $R^{"C}$ can be a substituted C_{1-12} alkyl. In other embodiments, $R^{"C}$ can be an unsubstituted C_{1-12} alkyl.

[0180] Various substituents can be present at the 2'-position of the pentose ring. In some embodiments, R^{6C} can be hydrogen. In other embodiments, R^{6C} can be halogen, for example, fluoro. In still other embodiments, R^{6C} can be an optionally substituted C_{1-6} alkyl. In some embodiments, R^{6C} can be an unsubstituted C_{1-6} alkyl. In some embodiments, R^{6C} can be a substituted C_{1-6} alkyl. In yet still other embodiments, R^{6C} can be an optionally substituted C_{2-6} alkenyl. In some embodiments, R^{6C} can be an unsubstituted C_{2-6} alkenyl. In some embodiments, R^{6C} can be a substituted C_{2-6} alkenyl. In some embodiments, R^{6C} can be

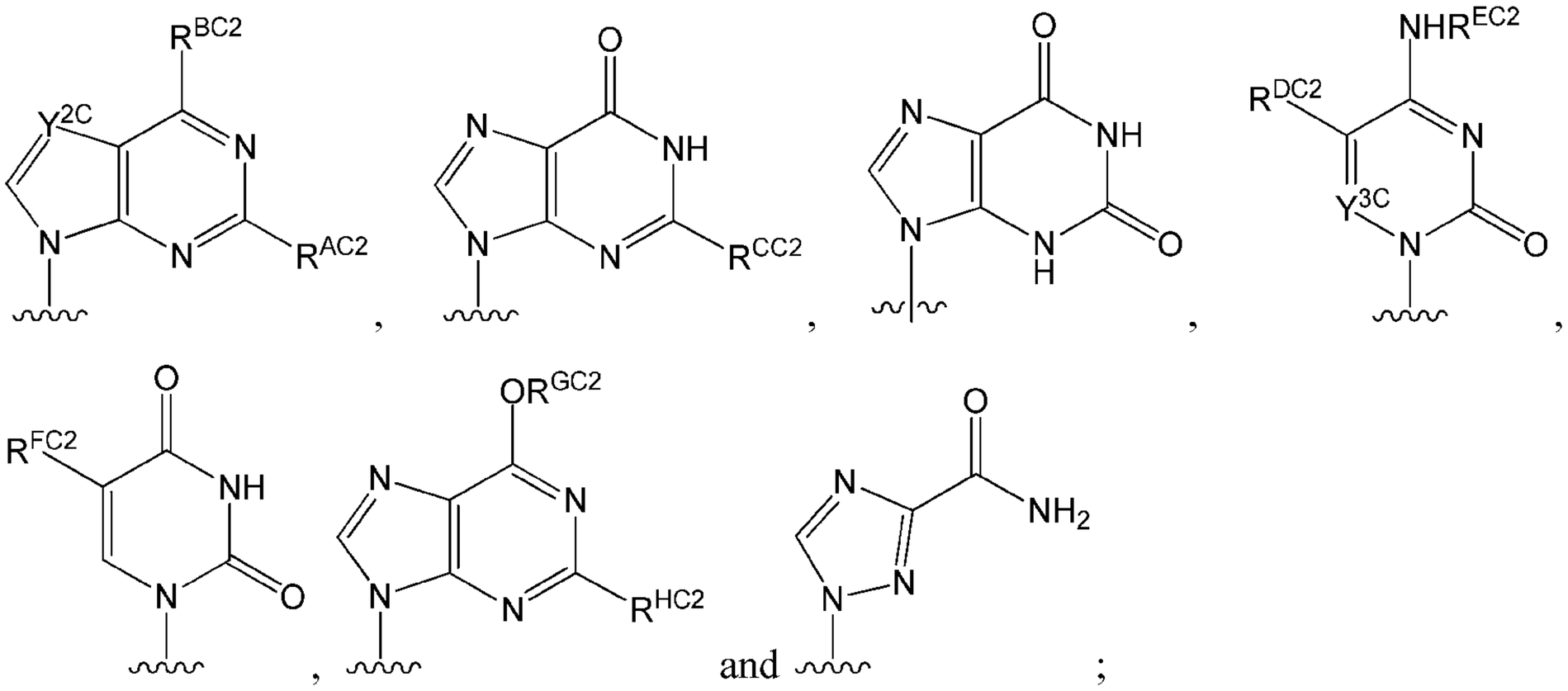
an optionally substituted C_{2-6} alkynyl. In some embodiments, R^{6C} can be an unsubstituted C_{2-6} alkynyl. In some embodiments, R^{6C} can be a substituted C_{2-6} alkynyl.

[0181] In some embodiments, R^{5C} can be hydrogen. In other embodiments, R^{5C} can be halogen, such as fluoro or chloro. In still other embodiments, R^{5C} can be OR^{1D}. For example, R^{5C} can be OH. In some embodiments, R^{5C} can be $OC(=O)R^{"D}$. In other embodiments, R^{5C} can be an optionally substituted O-linked amino acid. In still other embodiments, R^{5C} can be azido. In yet still other embodiments, R^{5C} can be $NR^{2D}R^{3D}$. For example, R^{5C} can be amino, a mono-substituted amine or a di-substituted amine. When R^{5C} is an optionally substituted O-linked amino acid, in some embodiments, R^{D4} 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^{D5} can be hydrogen or an optionally substituted C_{1-4}-alkyl; or R^{D4} and R^{D5} can be taken together to form an optionally substituted C_{3-6} cycloalkyl. Examples of suitable O-linked amino acids for R^{5C} include, but are not limited to:  include the following: , , , , , ,  and .

[0182] In some embodiments, R^{6C} can be hydrogen and R^{5C} can be halogen. In other embodiments, R^{5C} and R^{6C} can be both halogen. For example, R^{5C} and R^{6C} can be both fluoro.

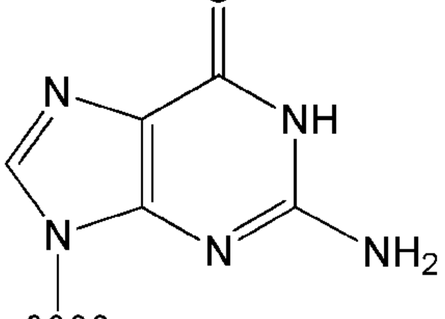
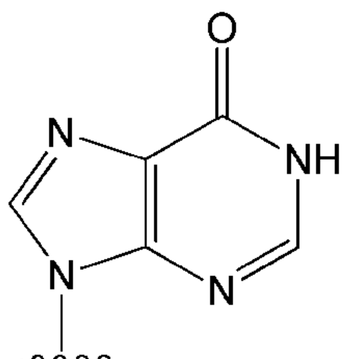
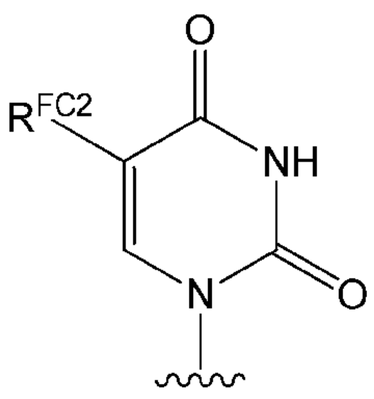
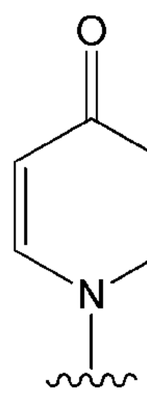
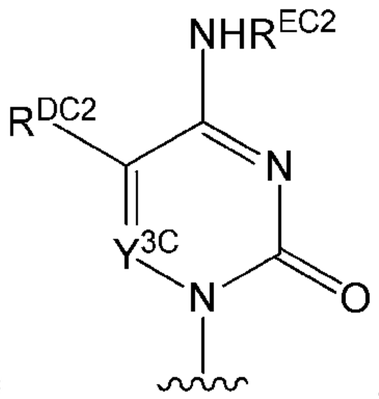
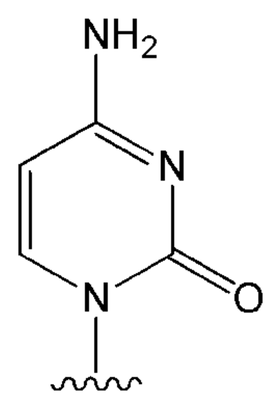
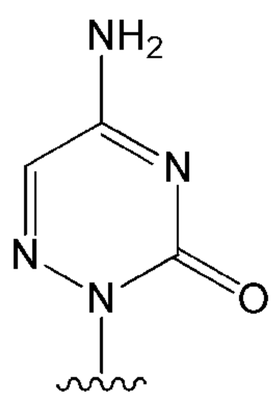
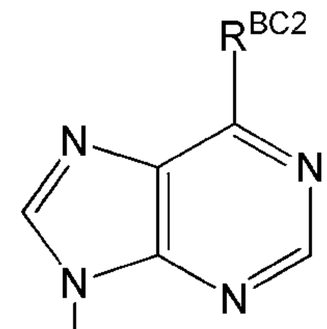
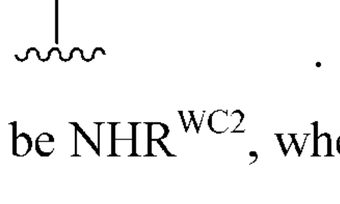
[0183] Various optionally substituted heterocyclic bases can be attached to the pentose ring. In some embodiments, one or more of the amine and/or amino groups may be protected with a suitable protecting group. For example, an amino group may be protected by

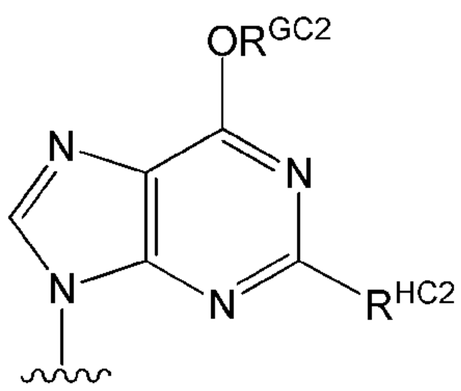
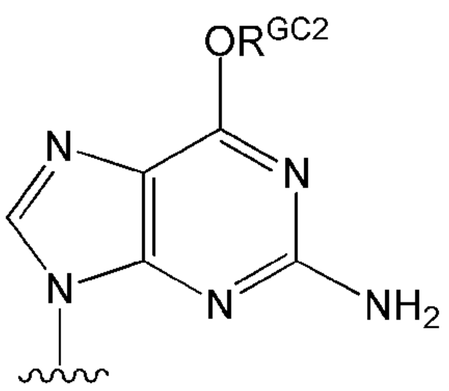
transforming the amine and/or amino group to an amide or a carbamate. In some embodiments, an optionally substituted heterocyclic base or an optionally substituted heterocyclic base with one or more protected amino groups can have one of the following structures:

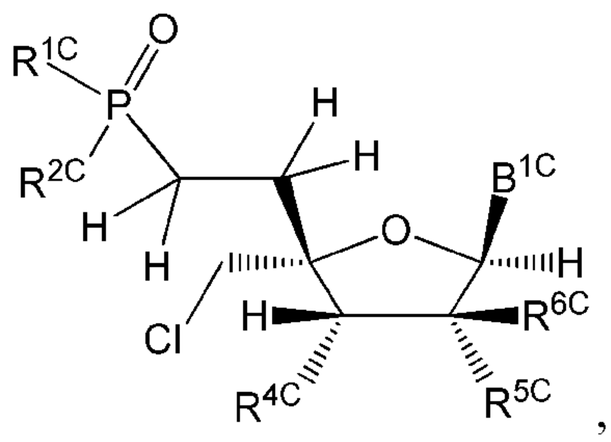
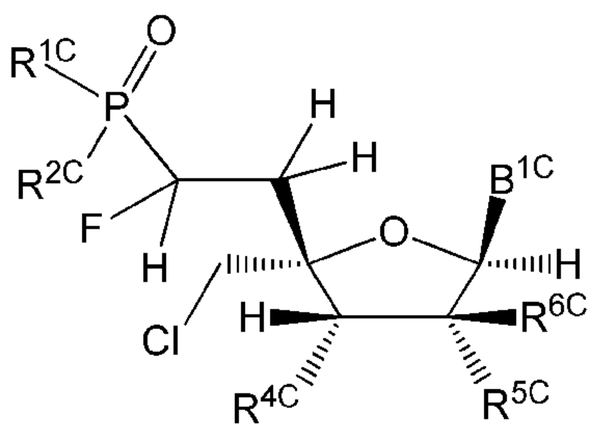
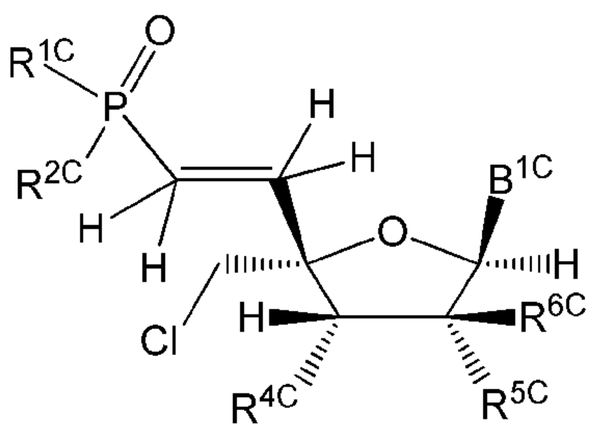
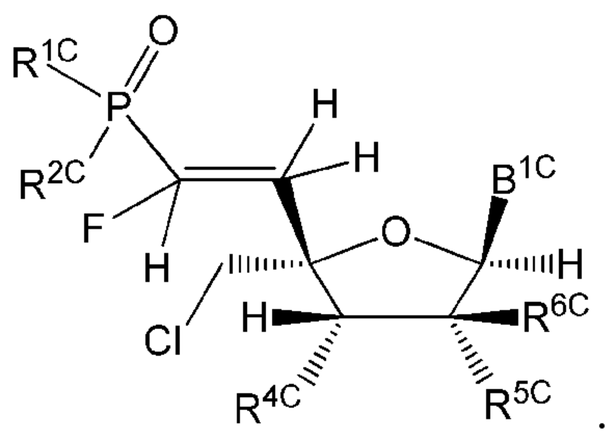


wherein: R^{AC2} can be selected from hydrogen, halogen and NHR^{JC2}, wherein R^{JC2} can be selected from hydrogen, -C(=O)R^{KC2} and –C(=O)OR^{LC2}; R^{BC2} can be halogen or NHR^{WC2}, wherein R^{WC2} can be selected from hydrogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{3-8} cycloalkyl, -C(=O)R^{MC2} and –C(=O)OR^{NC2}; R^{CC2} can be hydrogen or NHR^{OC2}, wherein R^{OC2} can be selected from hydrogen, -C(=O)R^{PC2} and –C(=O)OR^{QC2}; R^{DC2} can be selected from hydrogen, halogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl and an optionally substituted C_{2-6} alkynyl; R^{EC2} can be selected from hydrogen, hydroxy, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{3-8} cycloalkyl, -C(=O)R^{RC2} and –C(=O)OR^{SC2}; R^{FC2} 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^{2C} and Y^{3C} can be independently N (nitrogen) or CR^{IC2}, wherein R^{IC2} can be selected from hydrogen, halogen, an optionally substituted C_{1-6}-alkyl, an optionally substituted C_{2-6}-alkenyl and an optionally substituted C_{2-6}-alkynyl; R^{GC2} can be an optionally substituted C_{1-6} alkyl; R^{HC2} can be hydrogen or NHR^{TC2}, wherein R^{TC2} can be independently selected from hydrogen, -C(=O)R^{UC2} and –C(=O)OR^{VC2}; and R^{KC2}, R^{LC2}, R^{MC2}, R^{NC2}, R^{PC2}, R^{QC2}, R^{RC2}, R^{SC2}, R^{UC2} and R^{VC2} can be independently selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl,

C_{3-6} cycloalkyl, C_{3-6} cycloalkenyl, C_{6-10} aryl, heteroaryl, heteroalicyclyl, aryl(C_{1-6} alkyl), heteroaryl(C_{1-6} alkyl) and heteroalicyclyl(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."

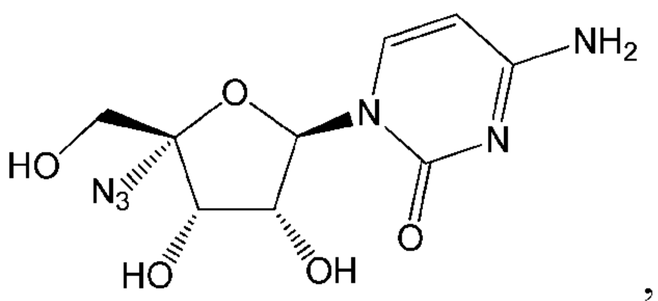
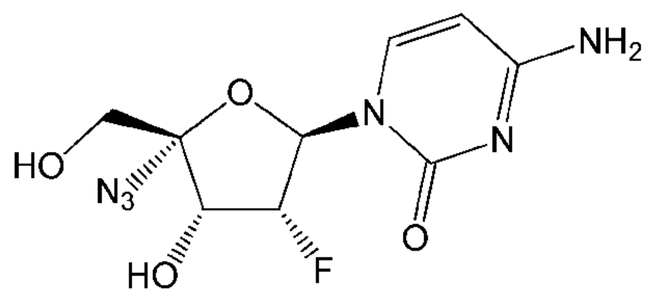
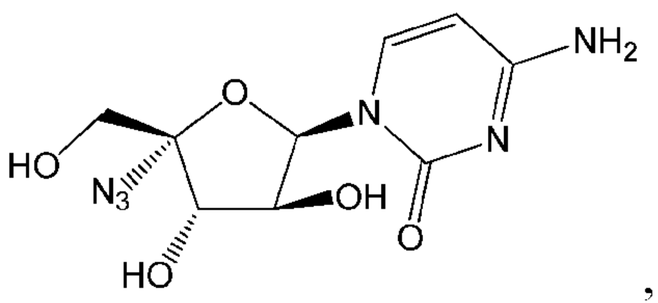
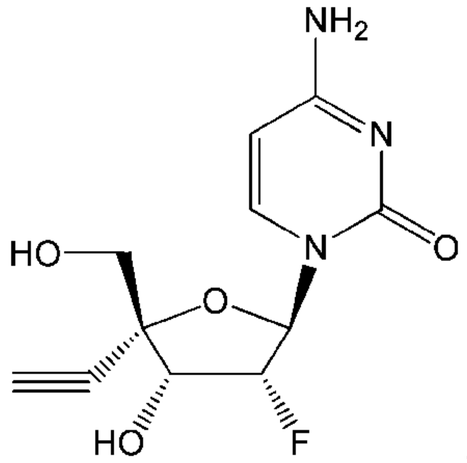
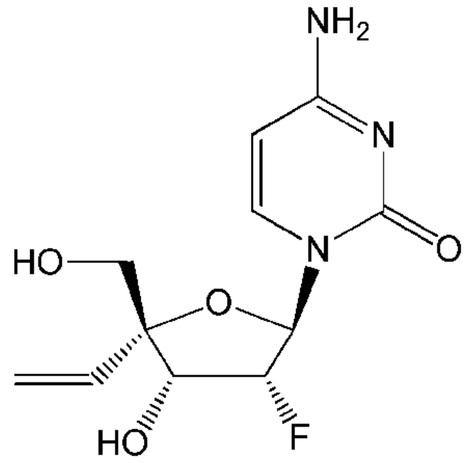
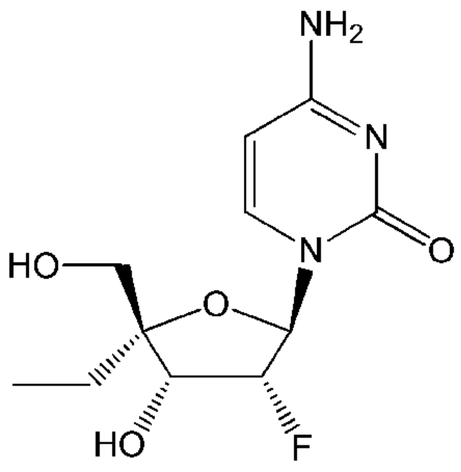
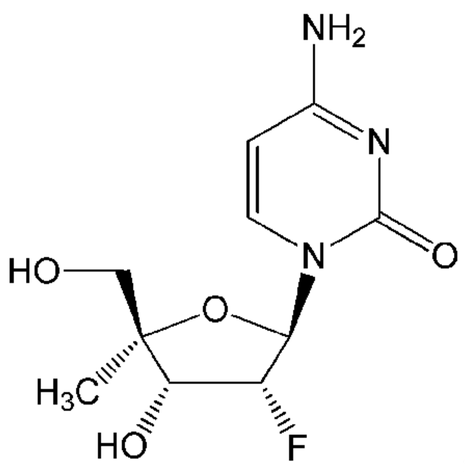
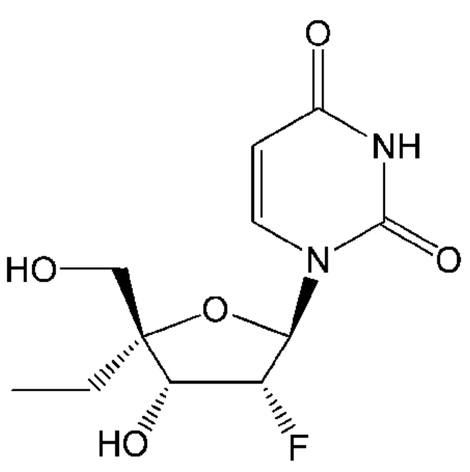
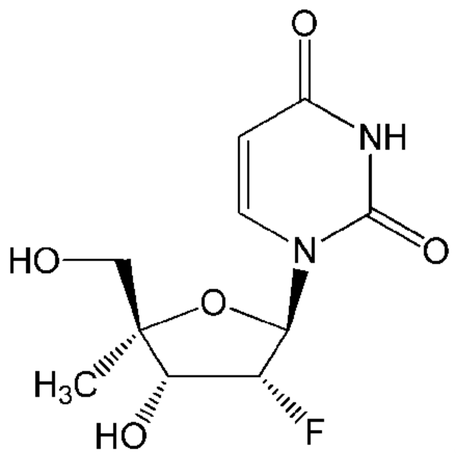
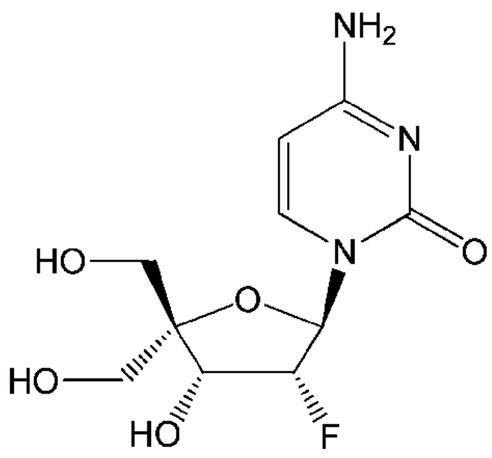
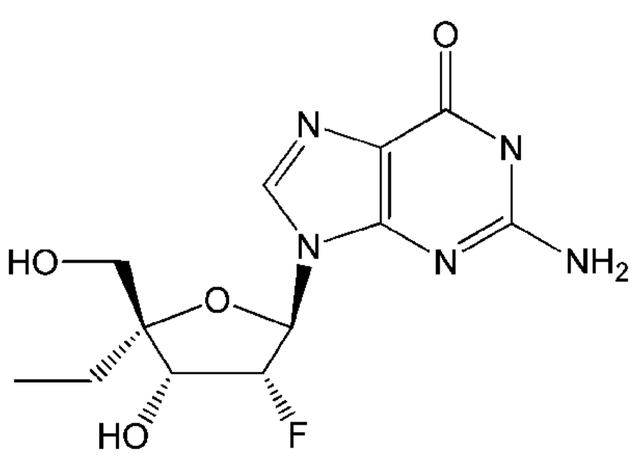
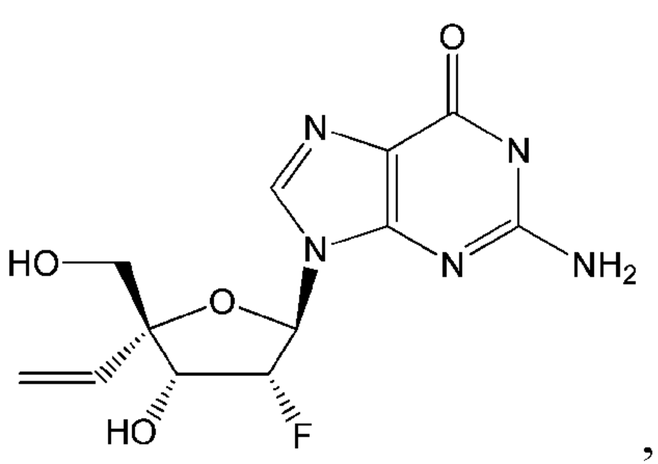
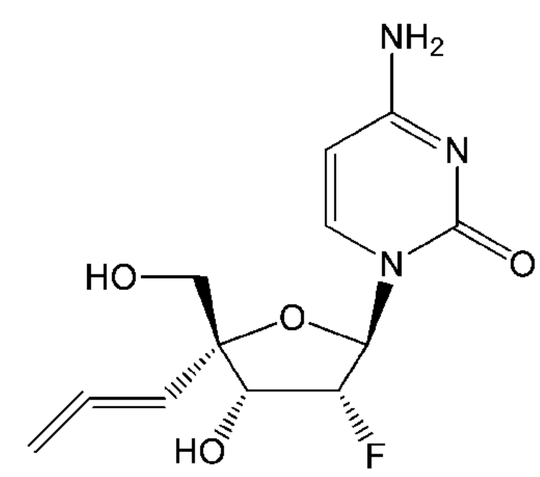
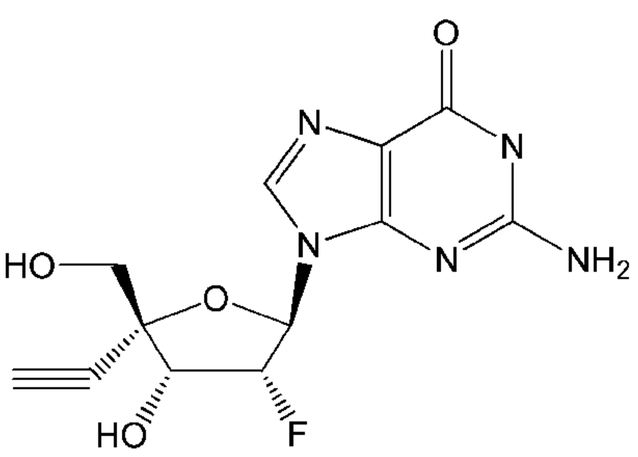
[0184] In some embodiments, B^{1C} can be . In other embodiments, B^{1C} can be . In still other embodiments, B^{1C} can be , such as . In yet still other embodiments, B^{1C} can be , for example,  or . In some embodiments,  R^{DC2} can be hydrogen. In other embodiments, B^{1C} can be . In some embodiments, R^{BC2} can be NH_2. In other embodiments, R^{BC2} can be NHR^{WC2}, wherein R^{WC2}

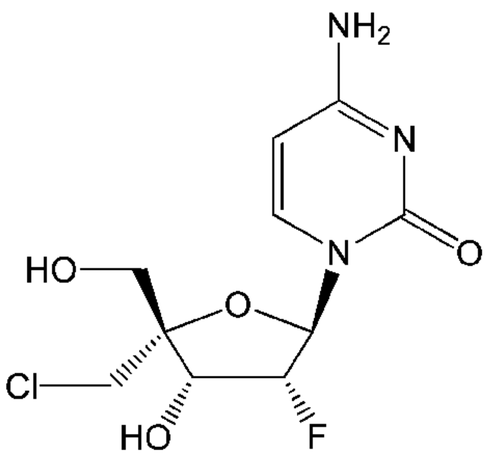
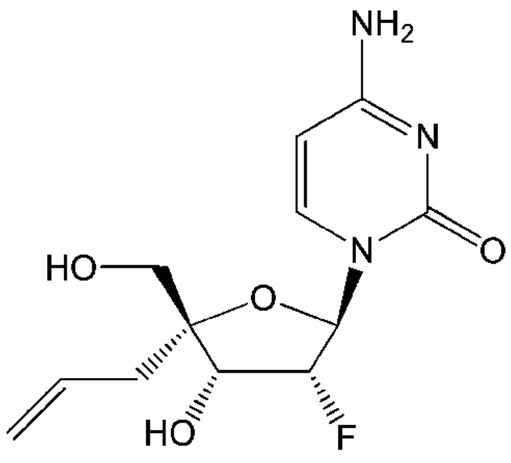
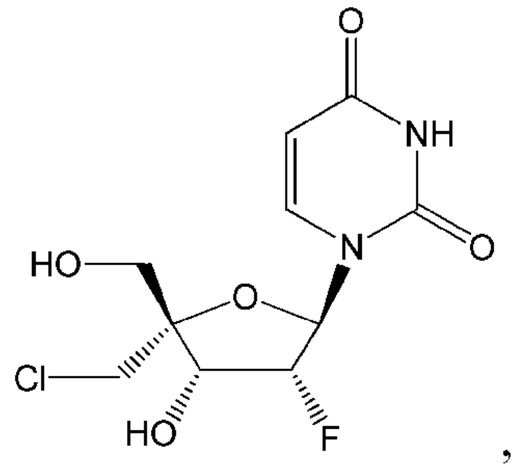
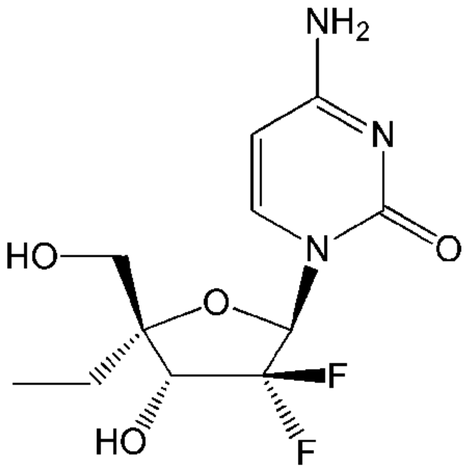
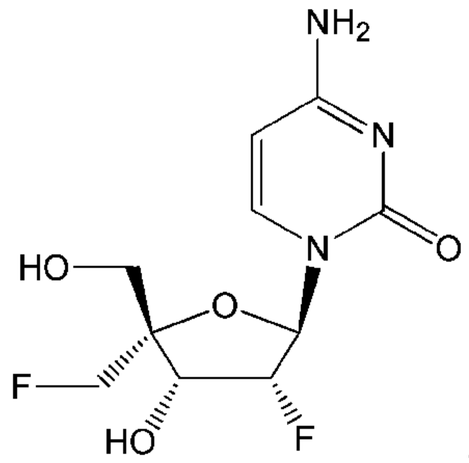
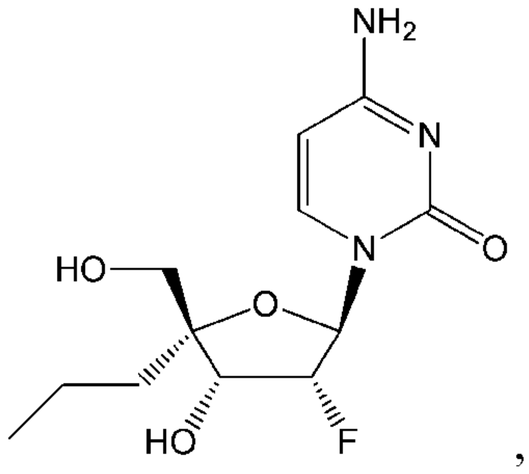
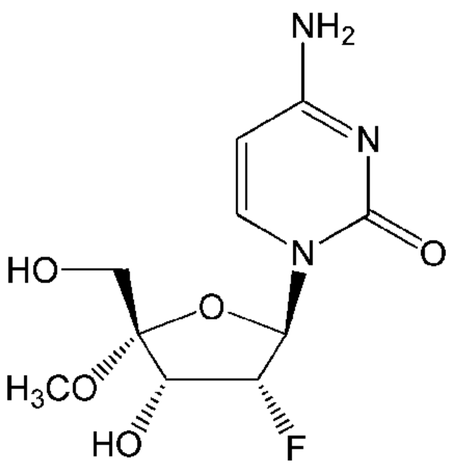
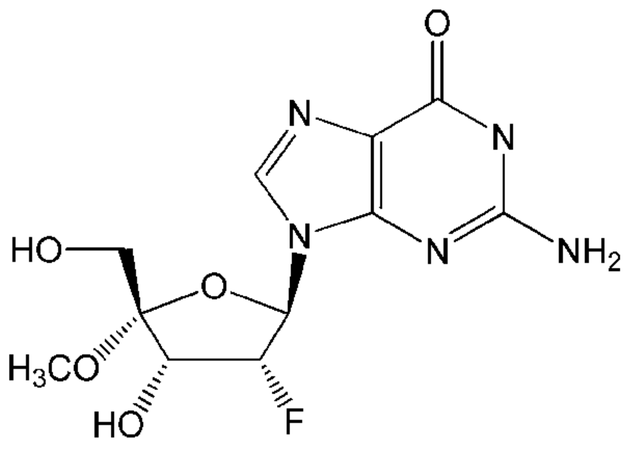
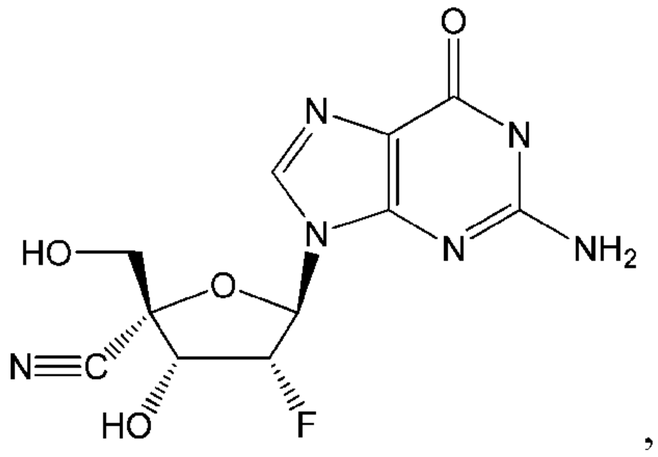
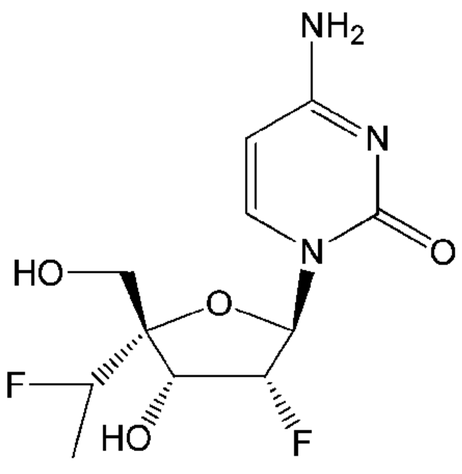
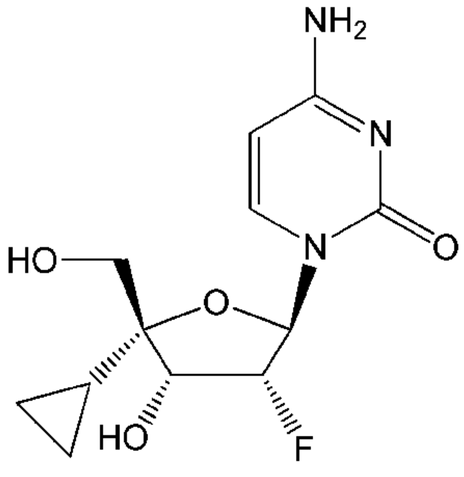
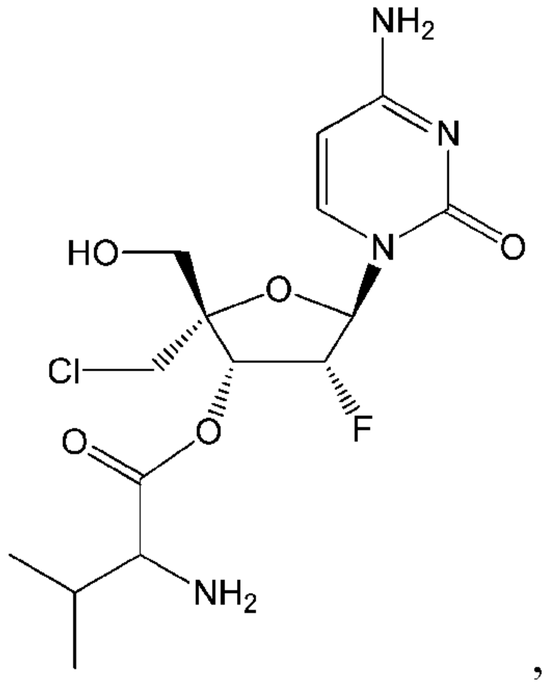
can be -C(=O)R^{MC2} or –C(=O)OR^{NC2}. In still other embodiments, B^{1C} can be  . In some embodiments, B^{1C} can be  .

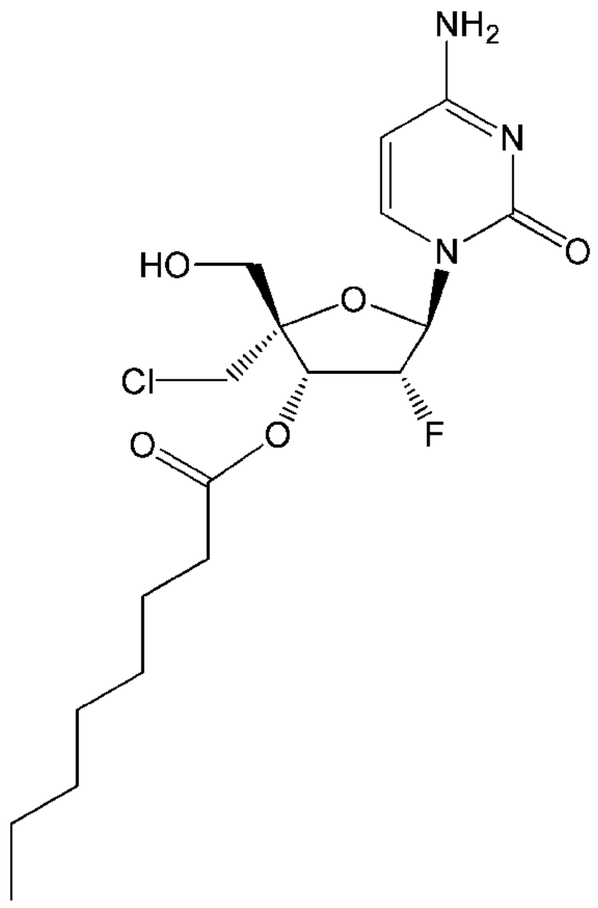
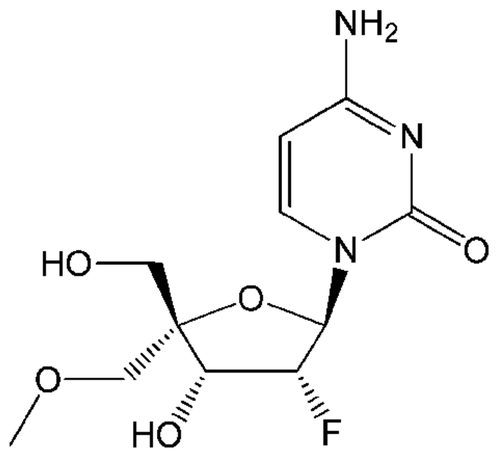
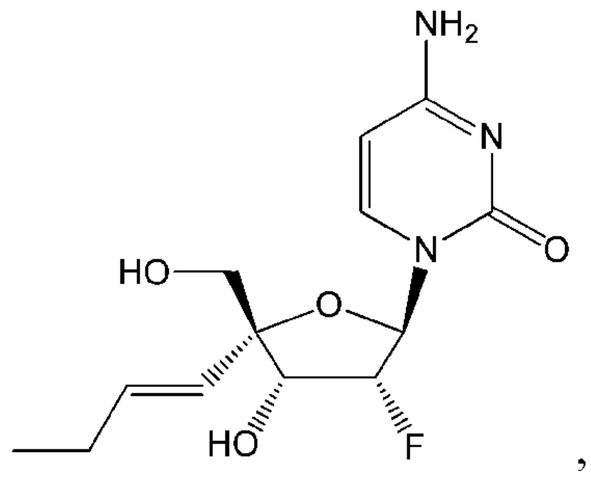
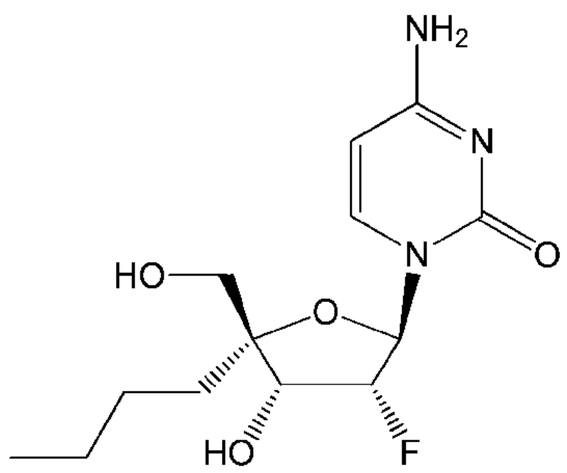
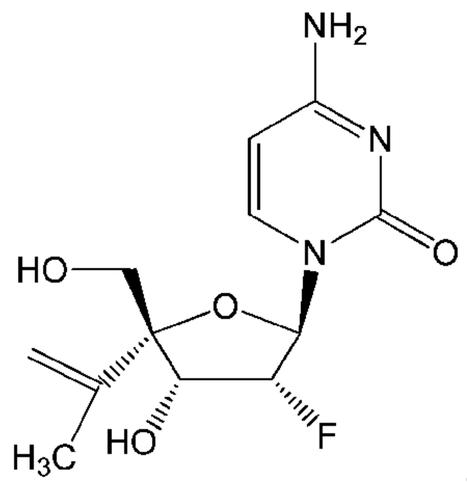
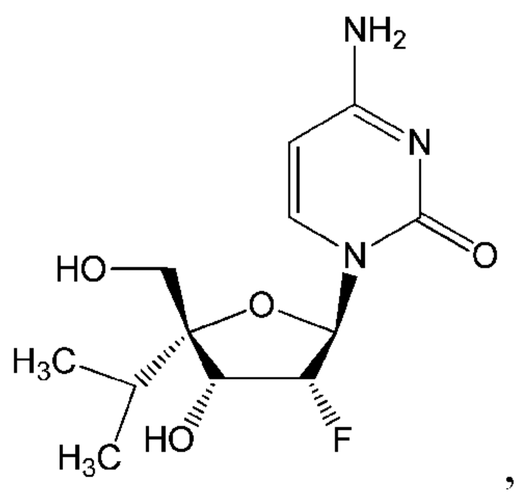
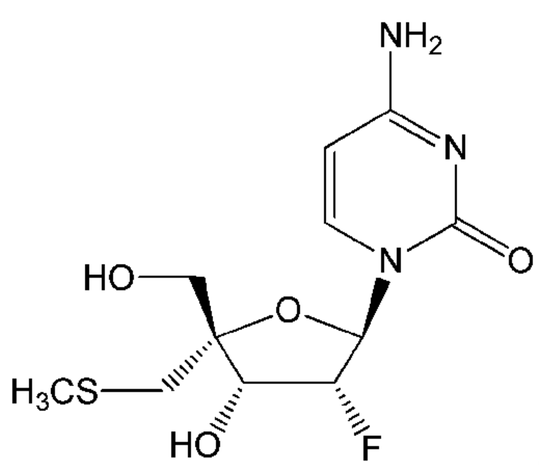
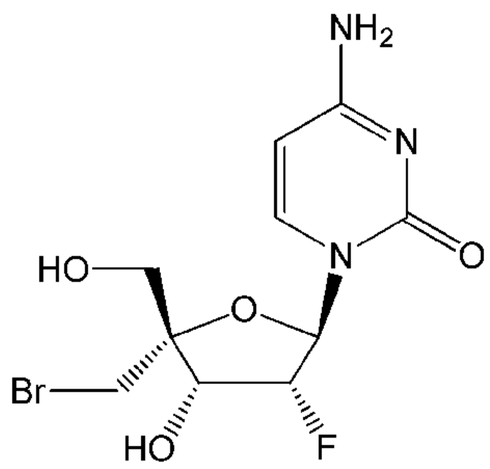
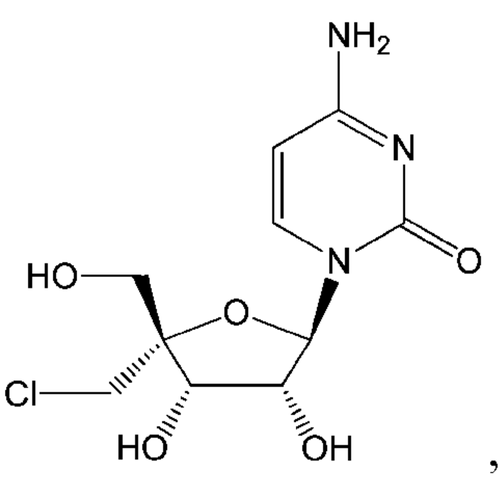
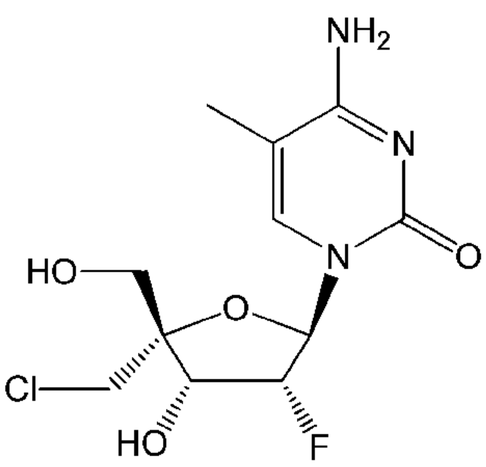
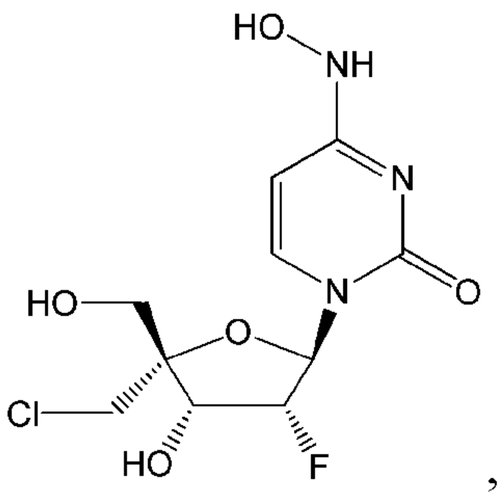
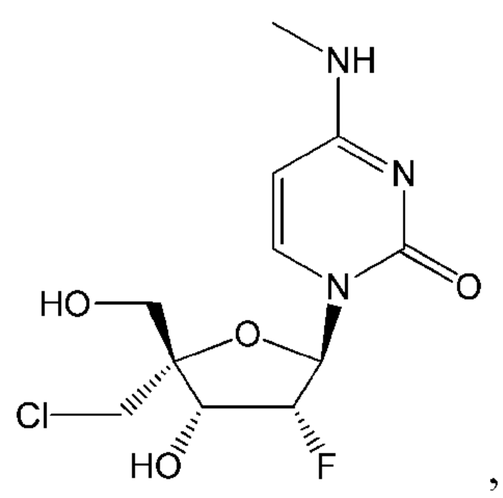
[0185] In some embodiments, the compound of Formula (III) can have one of the following structures:  ,   or  .

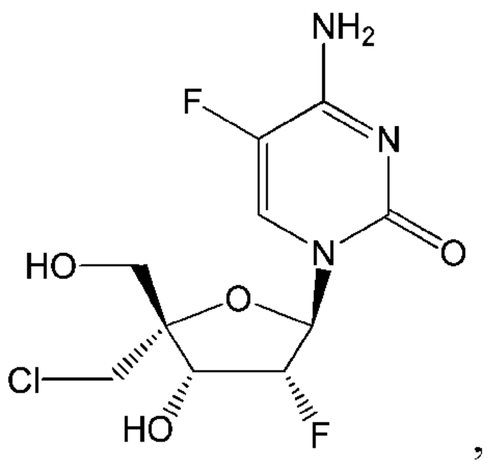
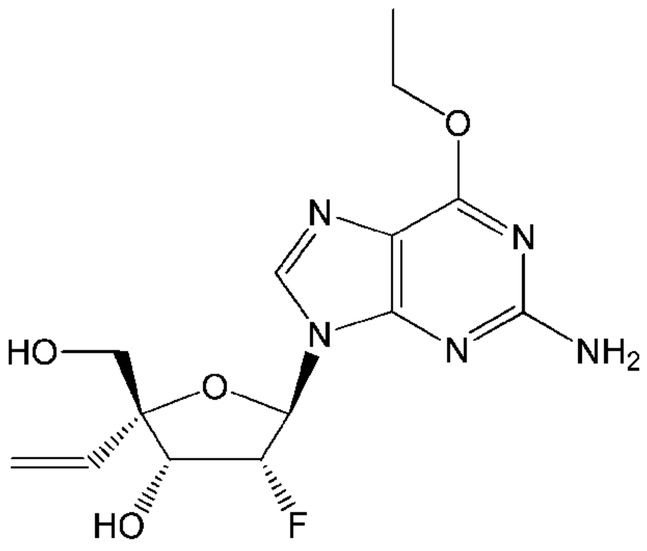
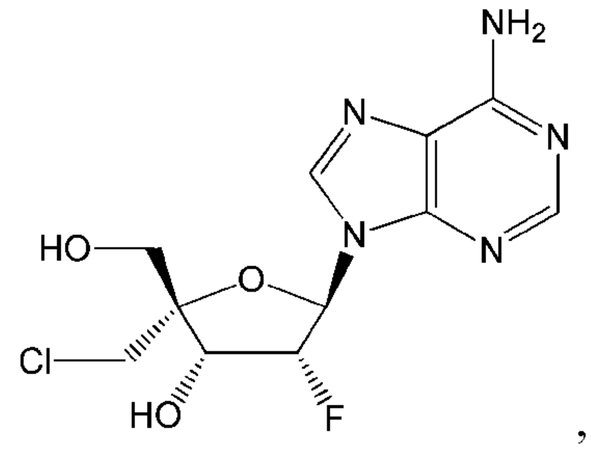
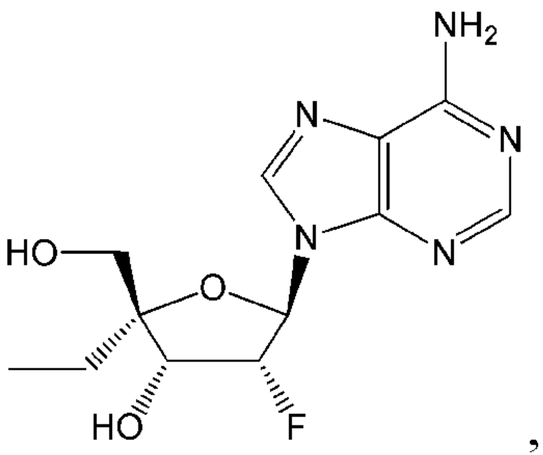
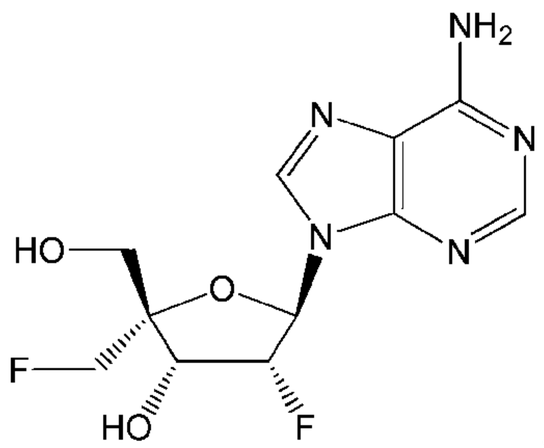
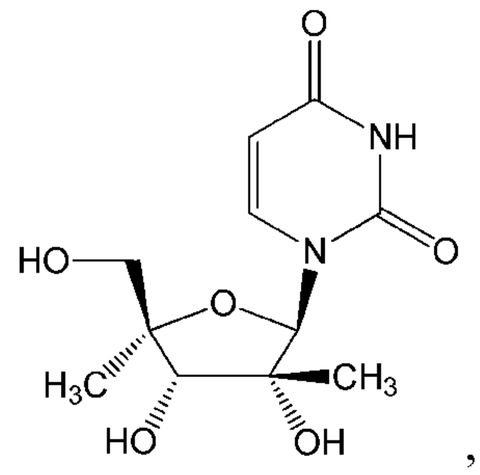
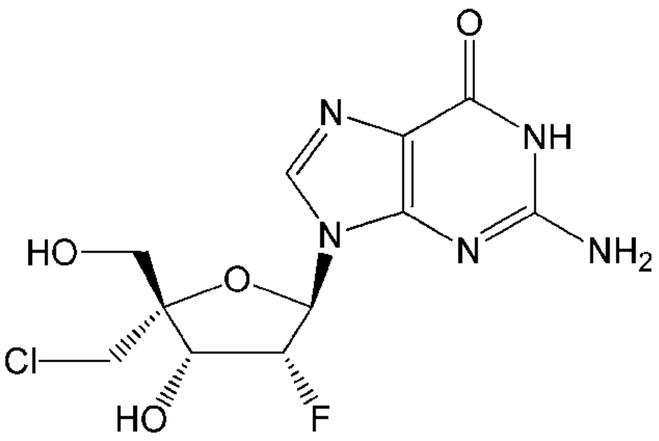
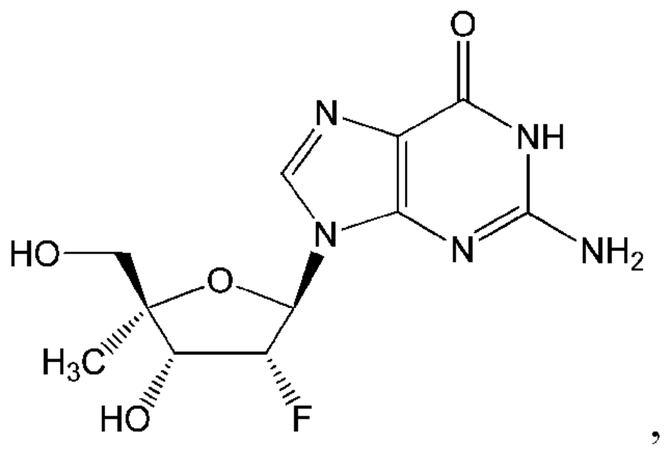
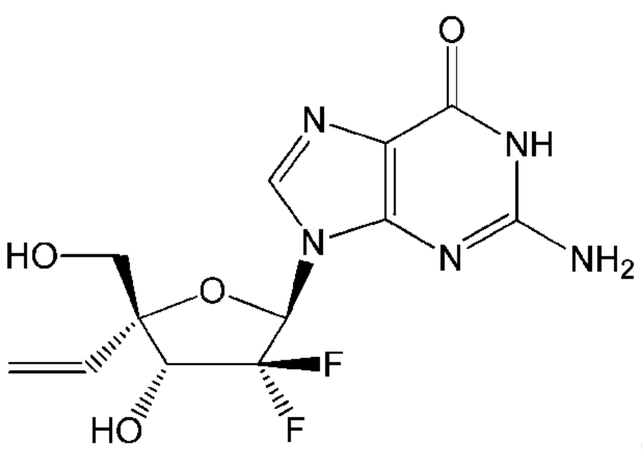
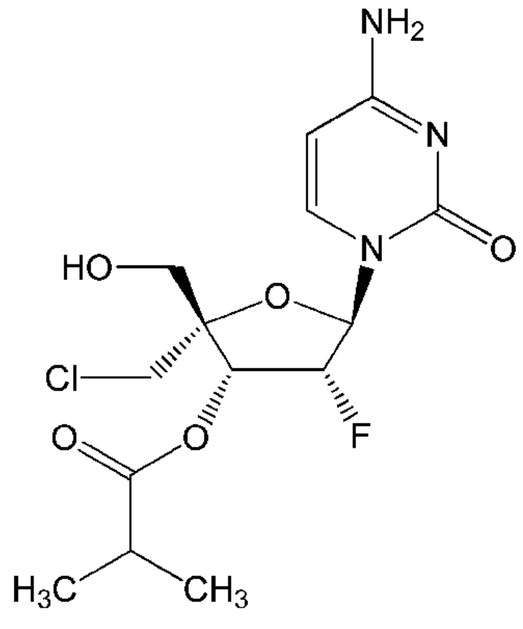
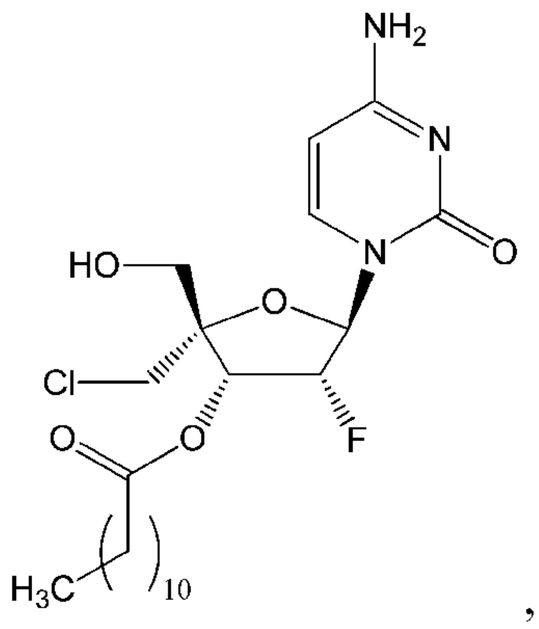
In some embodiments of this paragraph, B^{1C} can be an optionally substituted purine base. In other embodiments of this paragraph, B^{1C} can be an optionally substituted pyrimidine base. In some embodiments of this paragraph, B^{1C} can be guanine. In other embodiments of this paragraph, B^{1C} can be thymine. In still other embodiments of this paragraph, B^{1C} can be cytosine. In yet still other embodiments of this paragraph, B^{1C} can be uracil. In some embodiments of this paragraph, B^{1C} can be adenine. In some embodiments of this paragraph, R^{1C} and R^{2C} can each be an optionally substituted C_{1-4} alkyl. In other embodiments of this paragraph, R^{1A} can be an optionally substituted acyl. In still other embodiments of this paragraph, R^{1C} and R^{2C} can form a mono-, di- or tri-phosphate. In yet other embodiments of this paragraph, R^{1C} and R^{2C} can each be an alkylcarbonyloxyalkoxy. In some embodiments of this paragraph, R^{4C} can be OH. In some embodiments of this paragraph, R^{5C} can be F or Cl, and R^{6C} can be hydrogen.

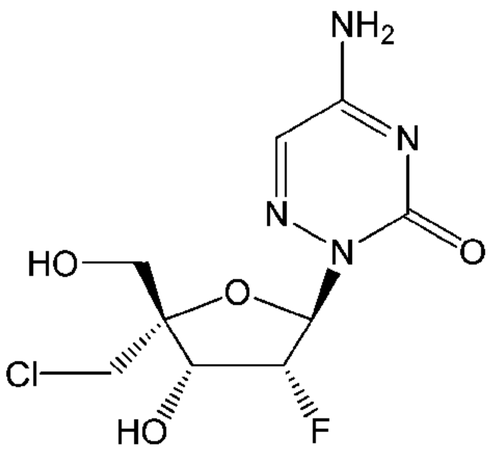
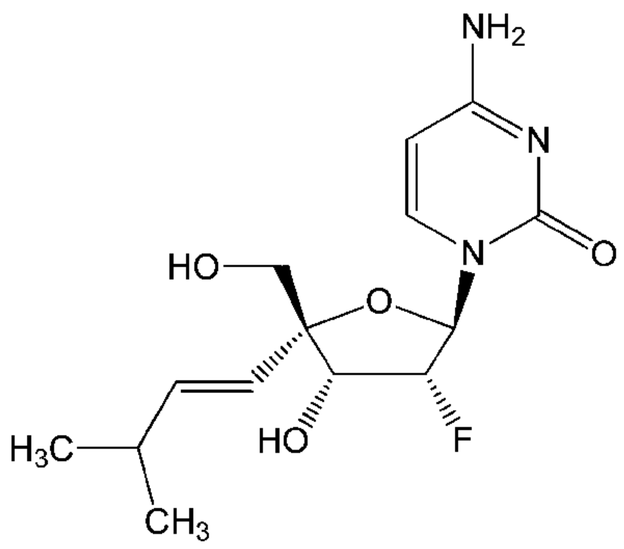
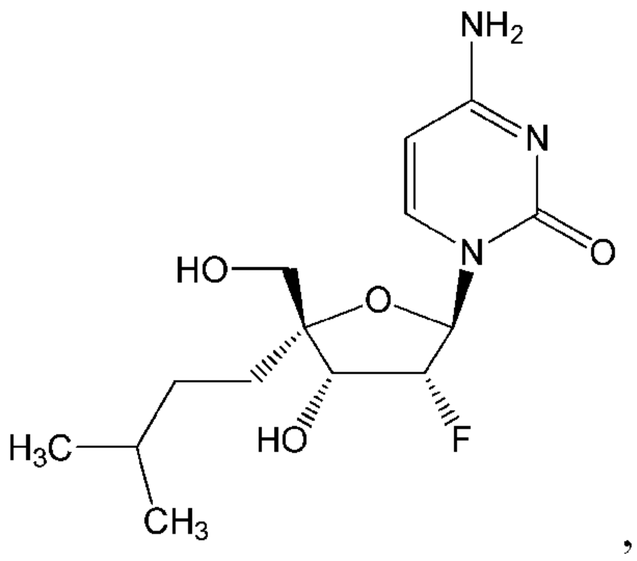
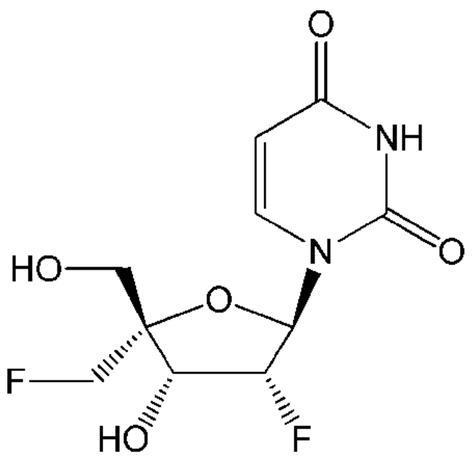
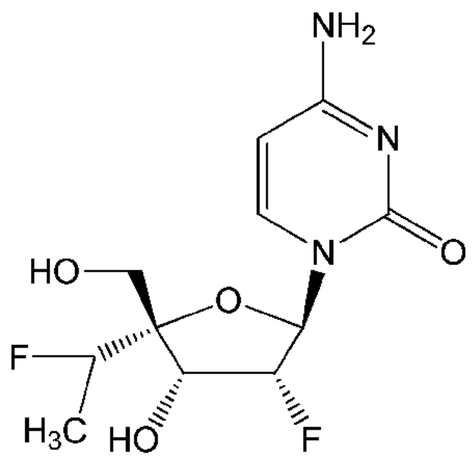
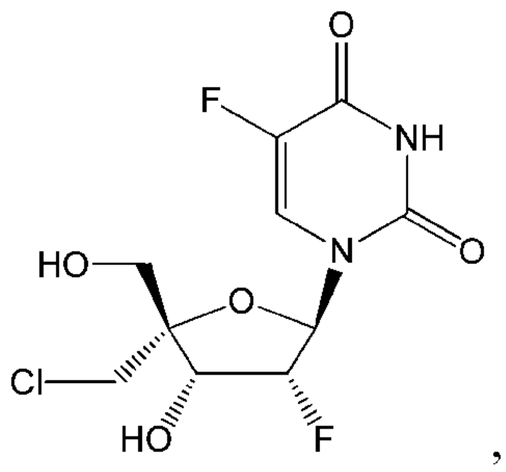
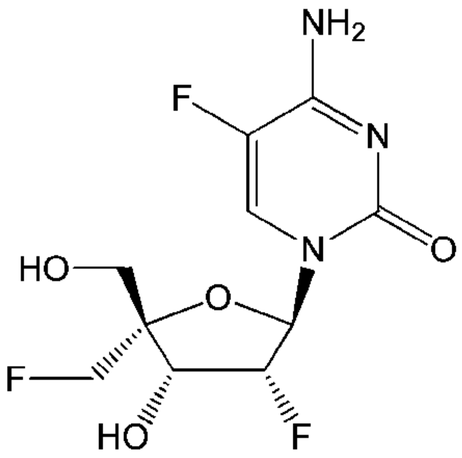
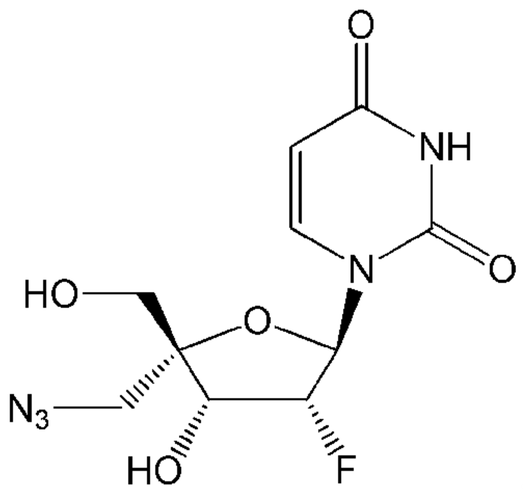
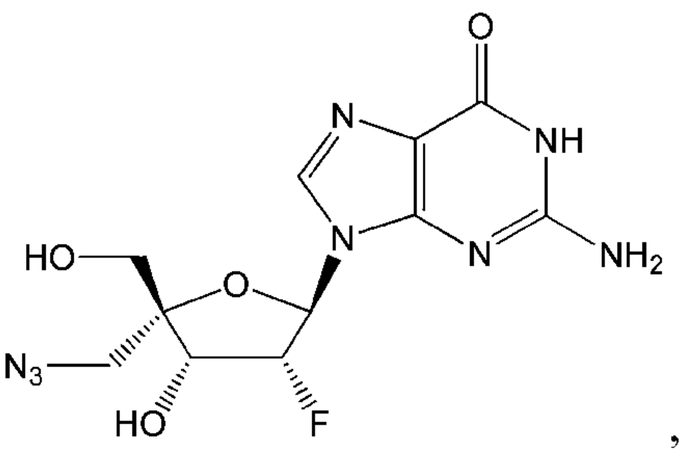
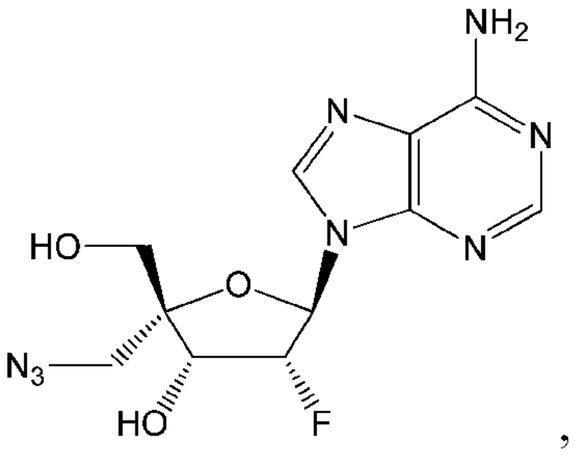
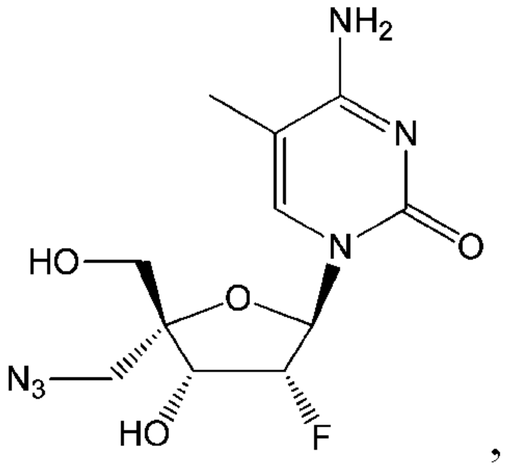
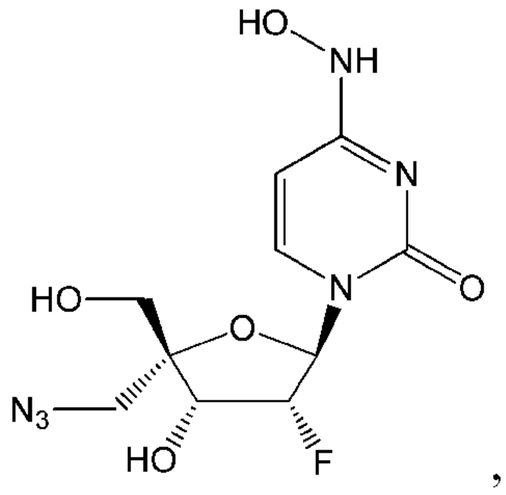
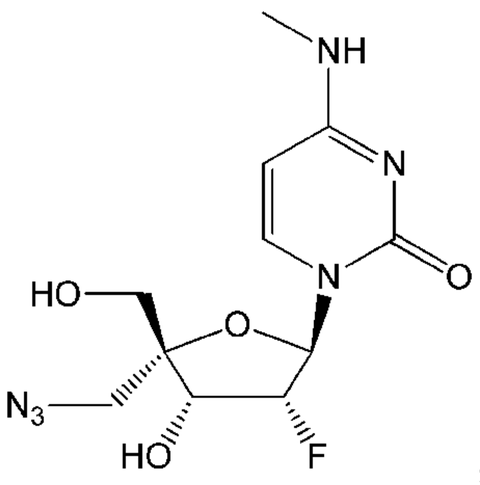
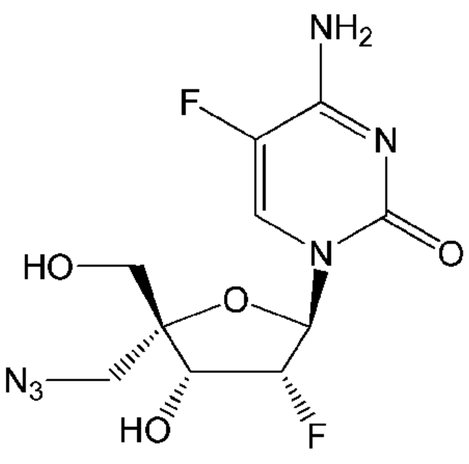
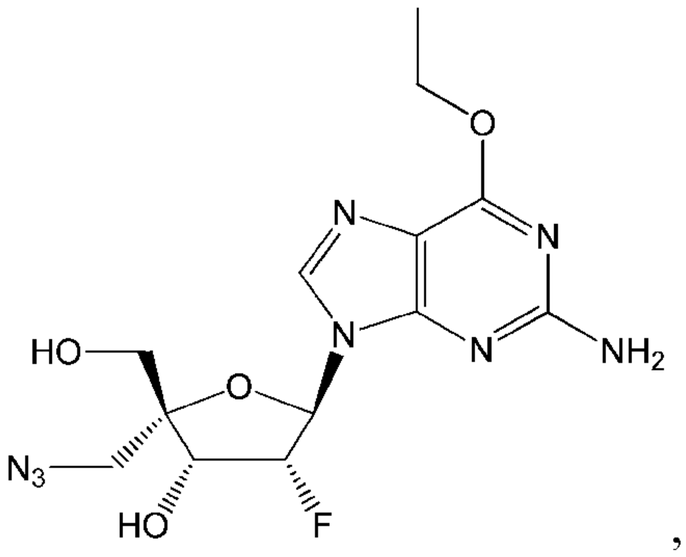
[0186] Examples of suitable compounds of Formula (I) include, but are not limited to the following:

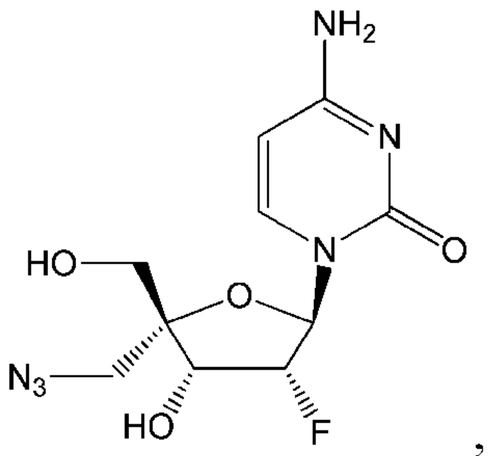
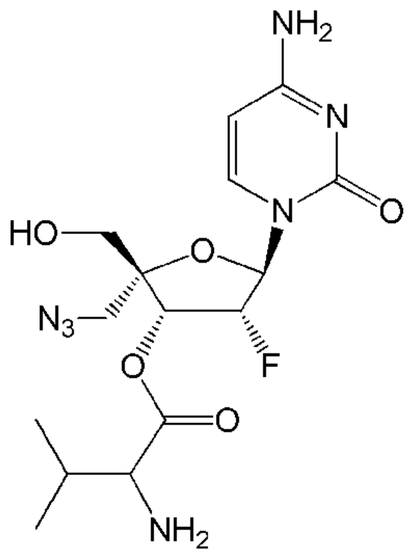
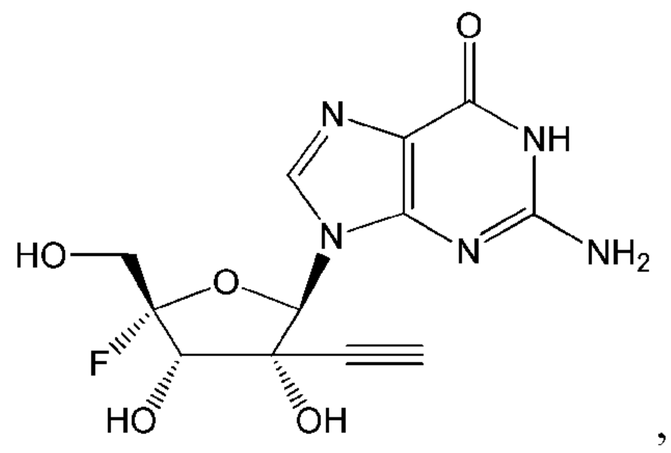
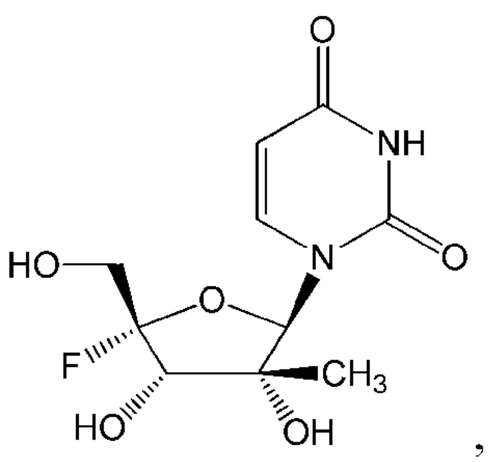
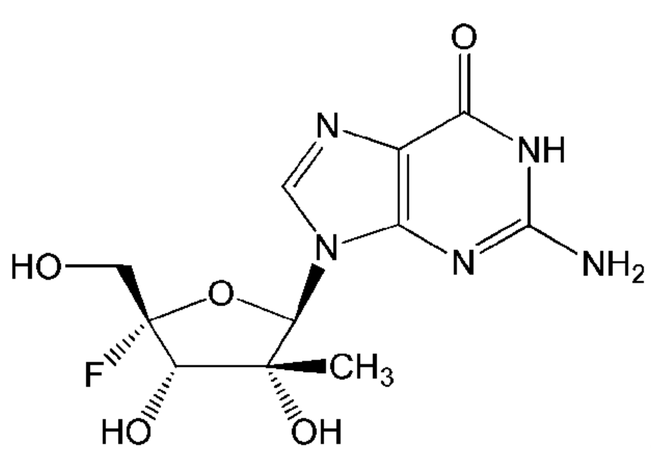
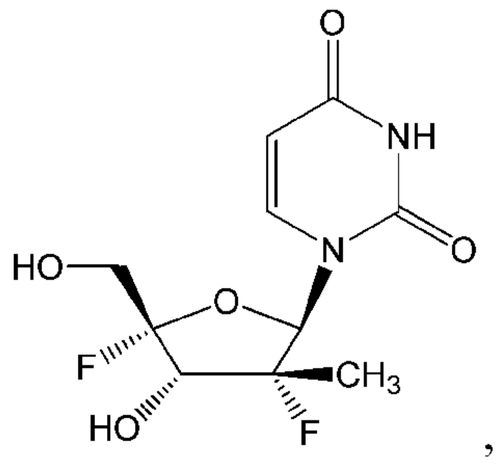
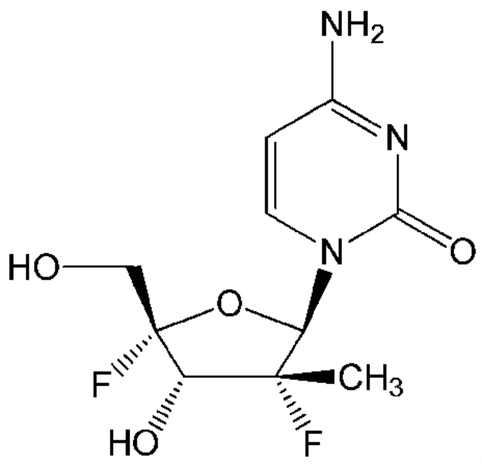
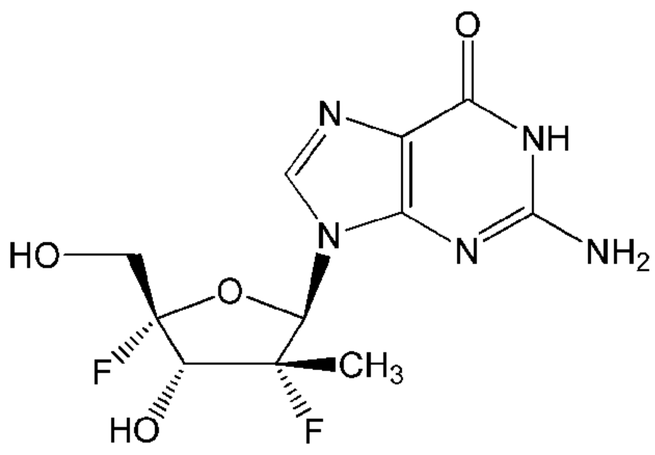
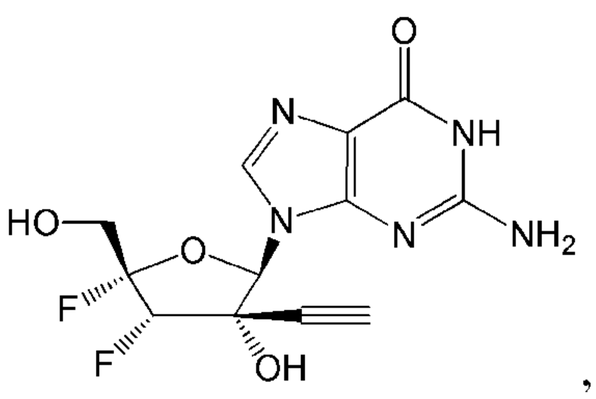
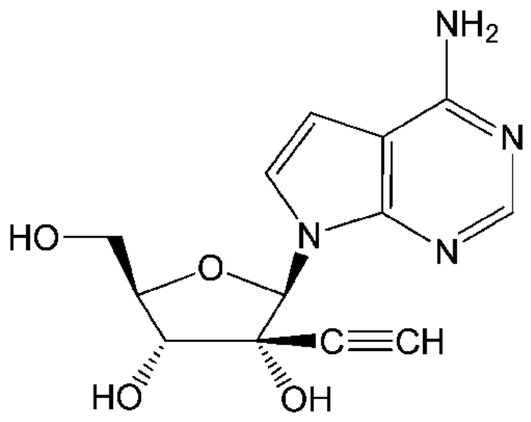
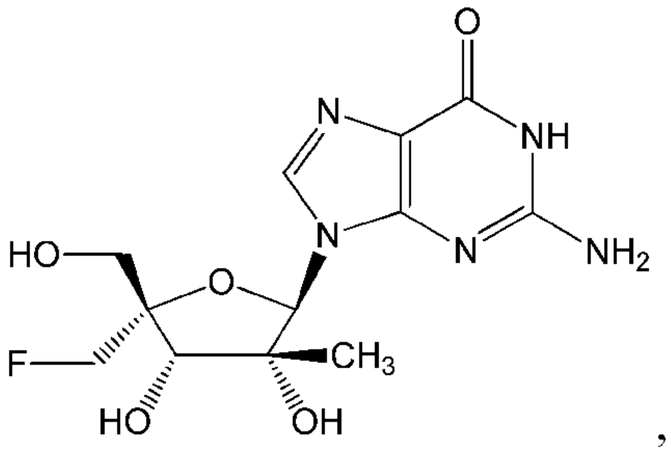
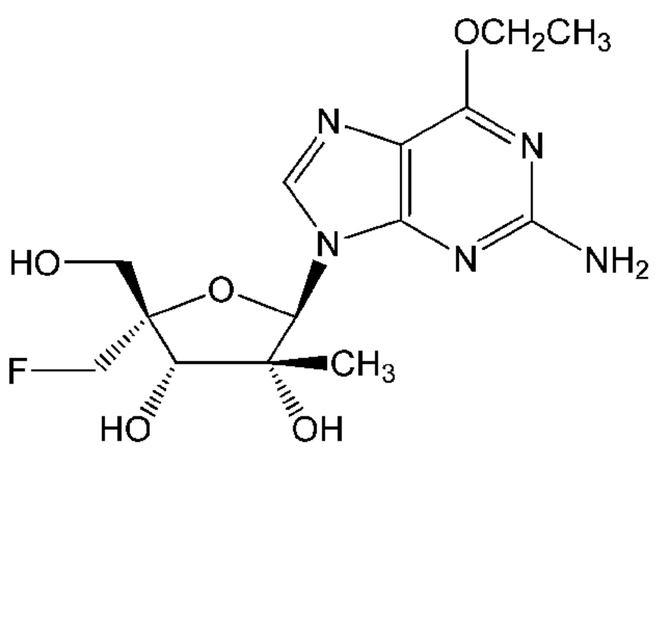
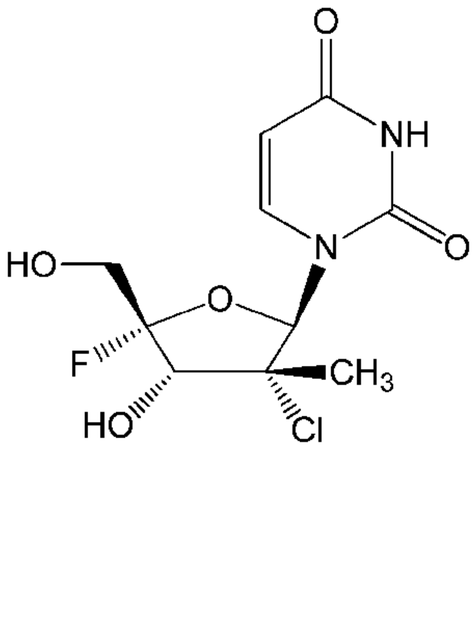
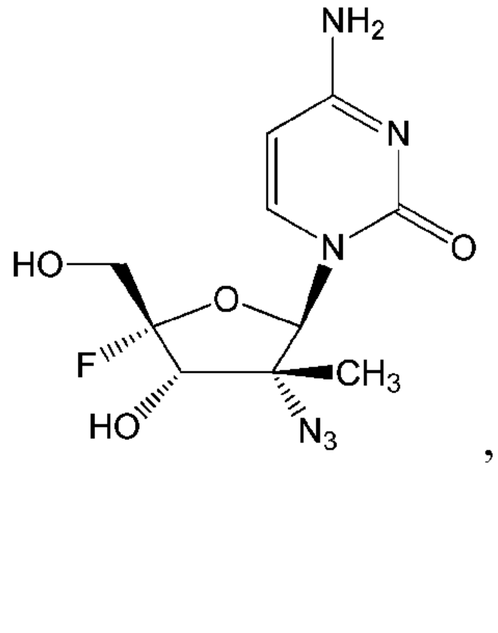

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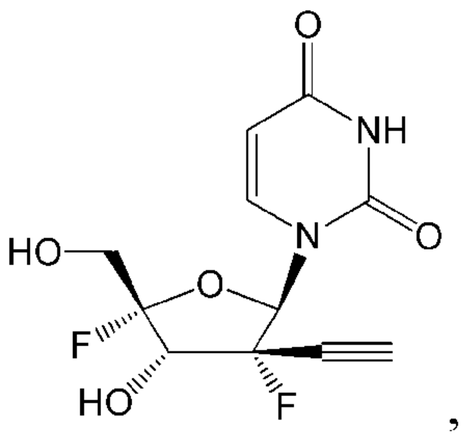
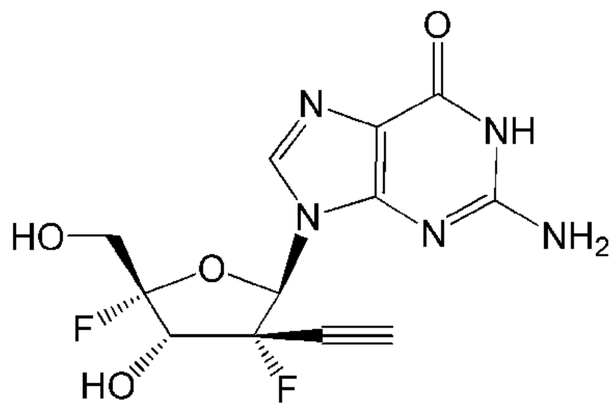
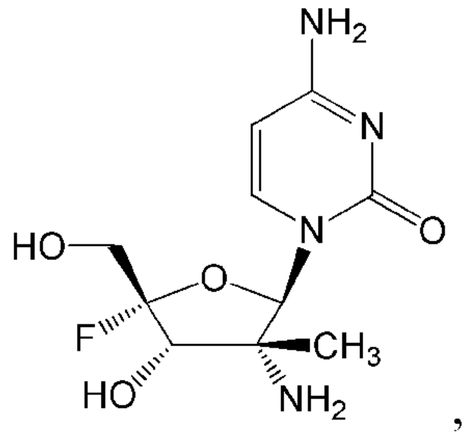
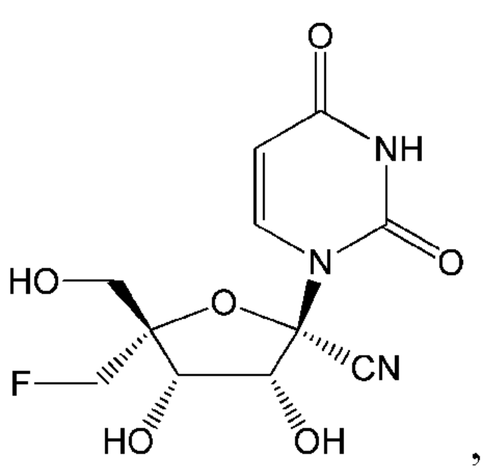
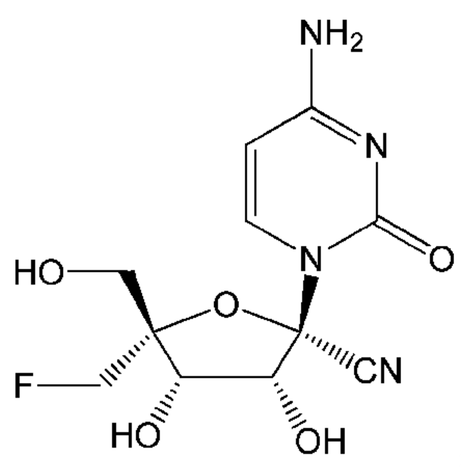
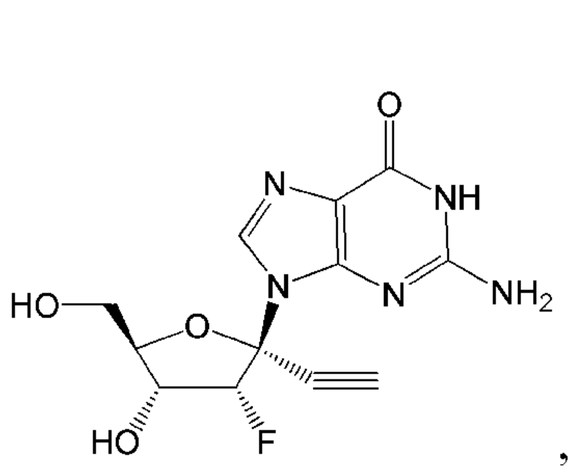
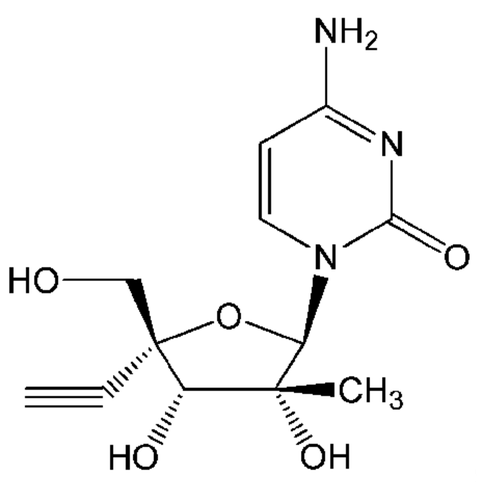
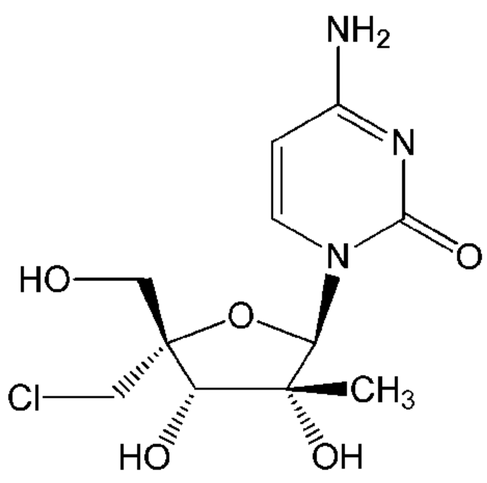
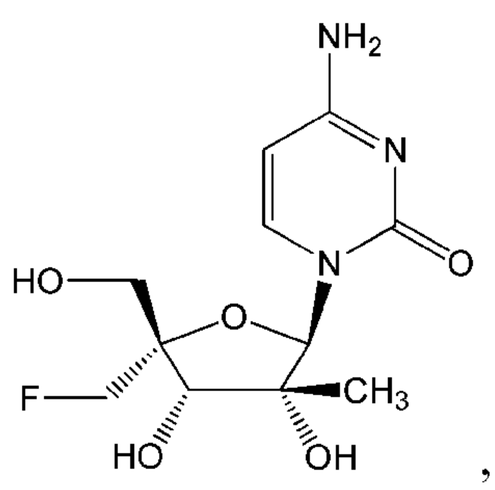
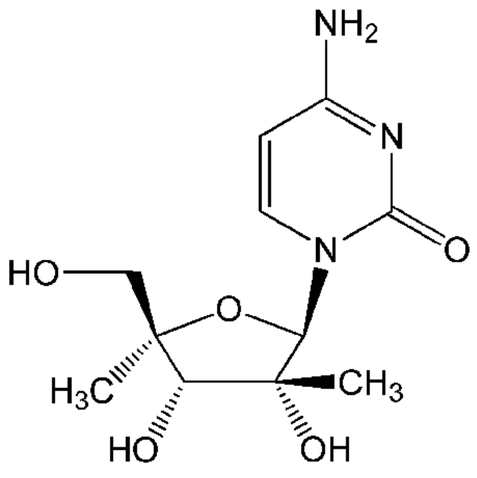
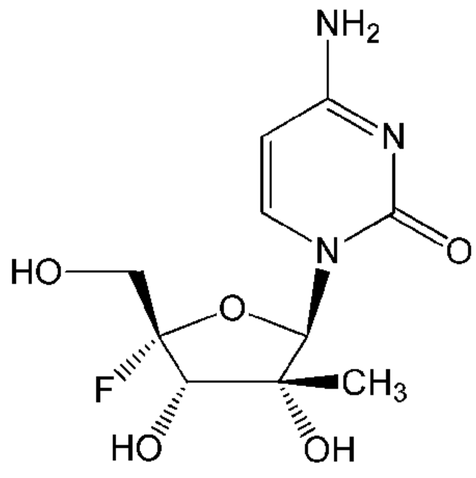
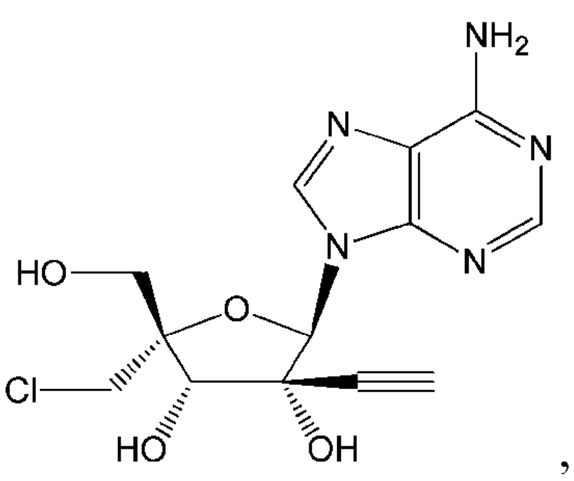
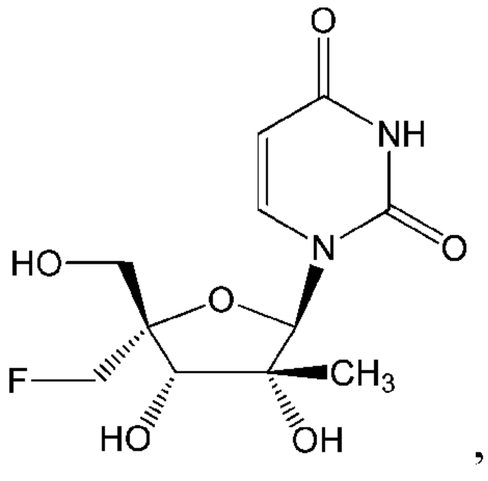
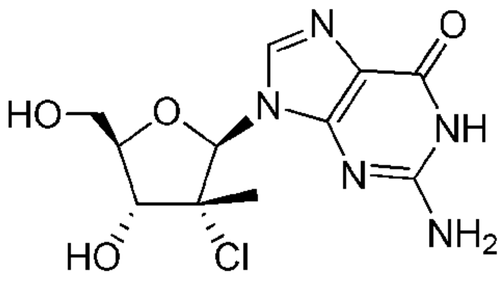
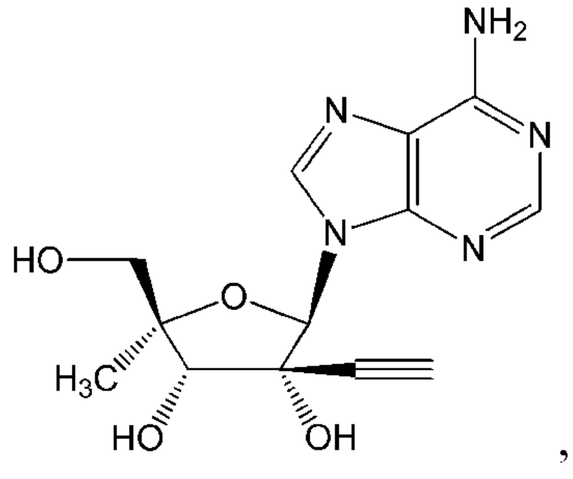

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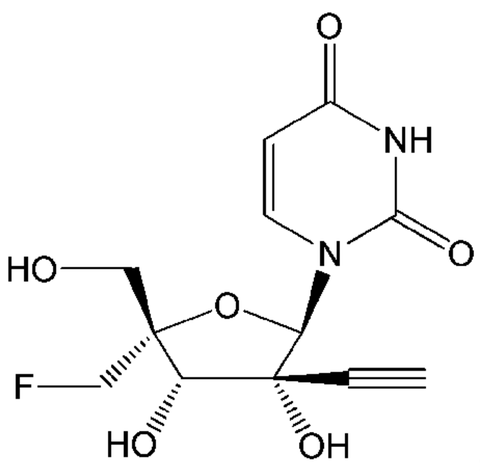
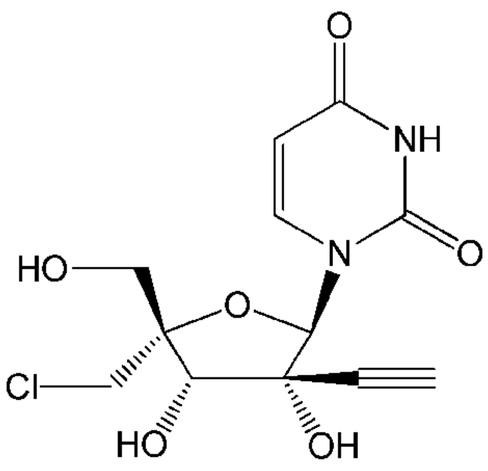
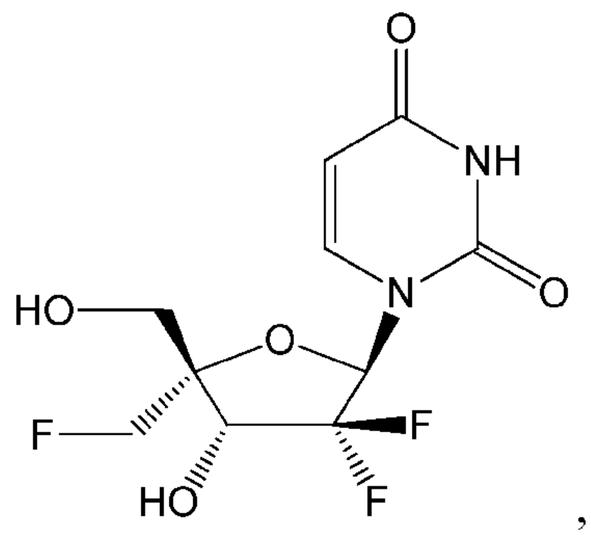
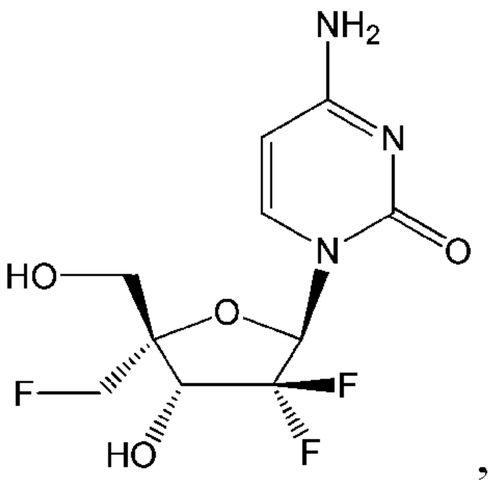
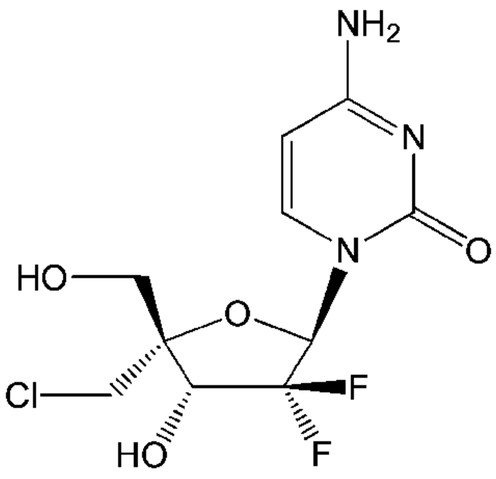
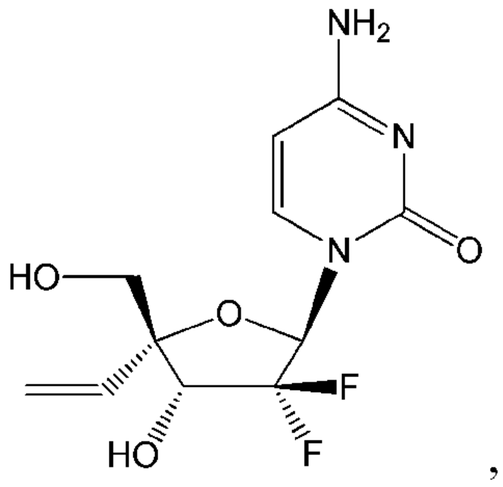
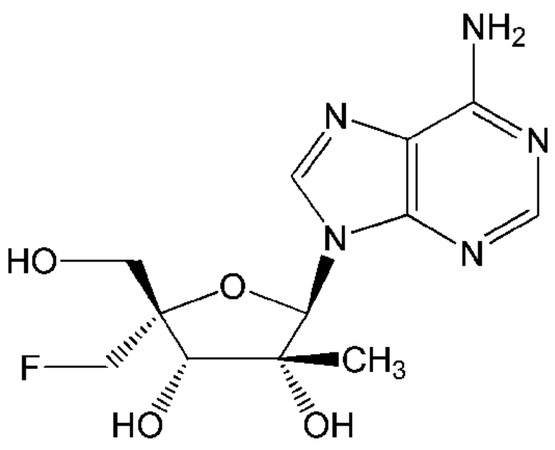
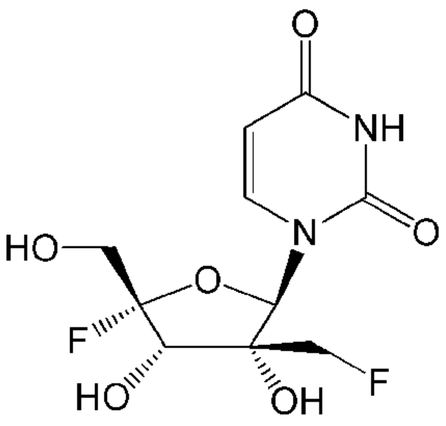
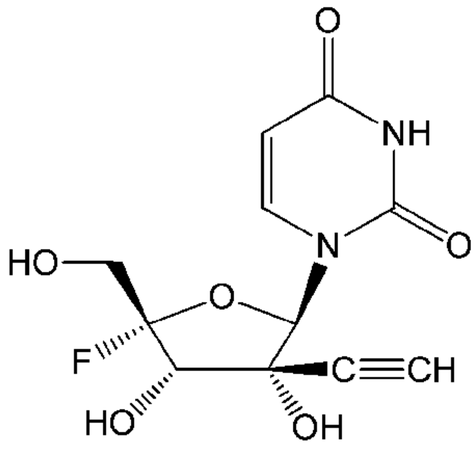
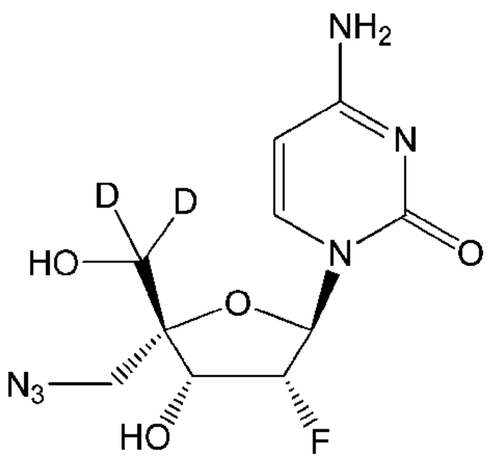














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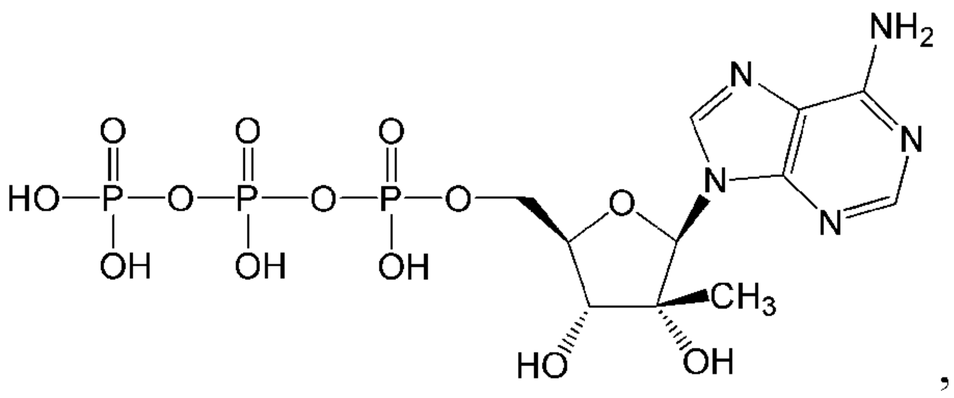

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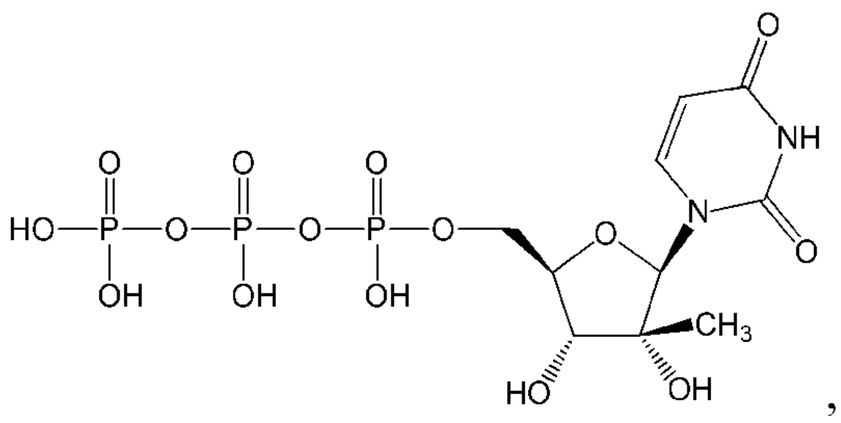

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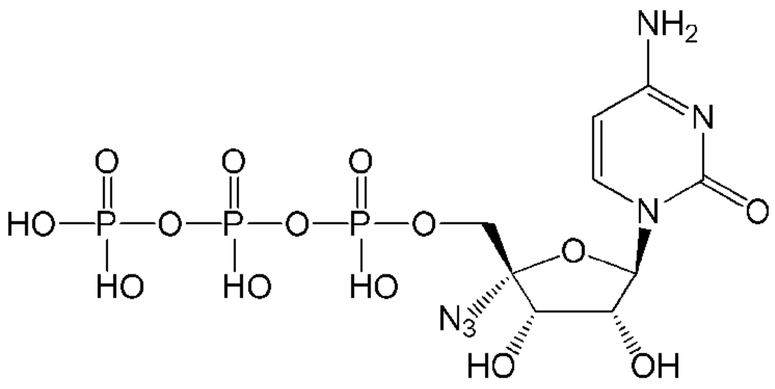

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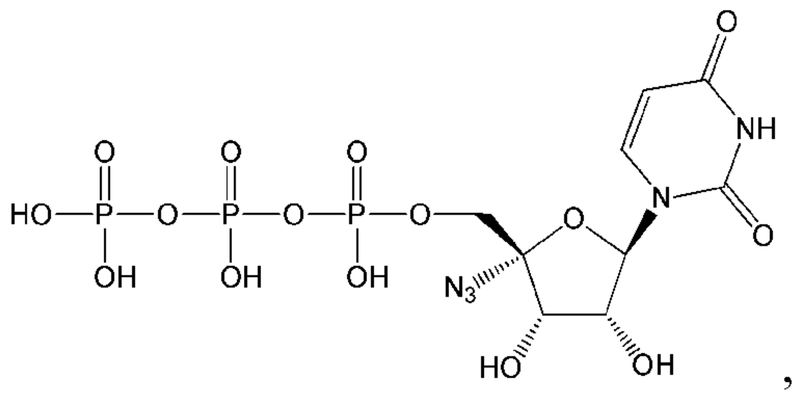

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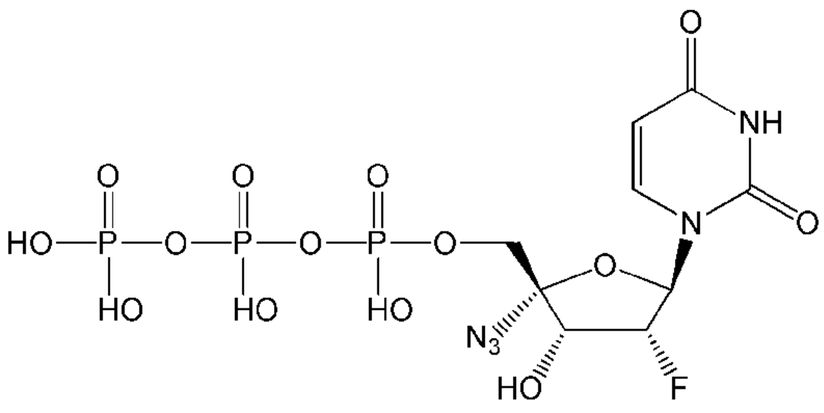
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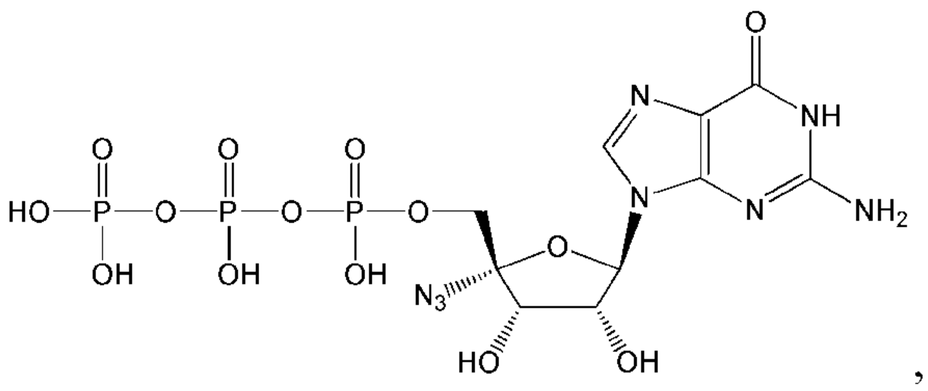

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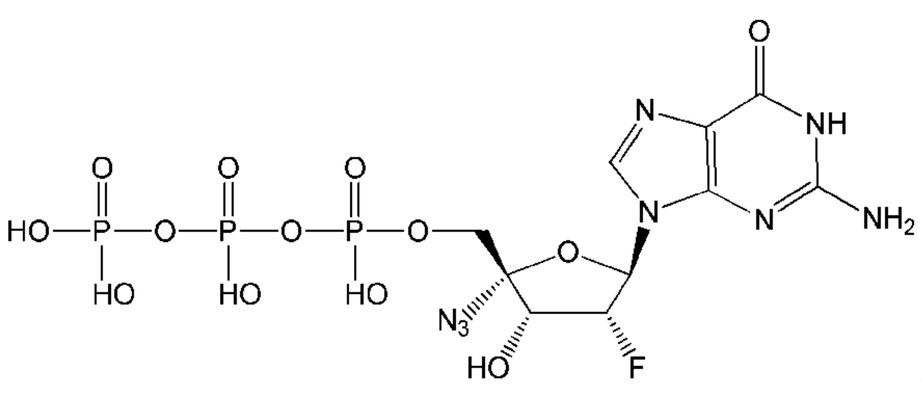

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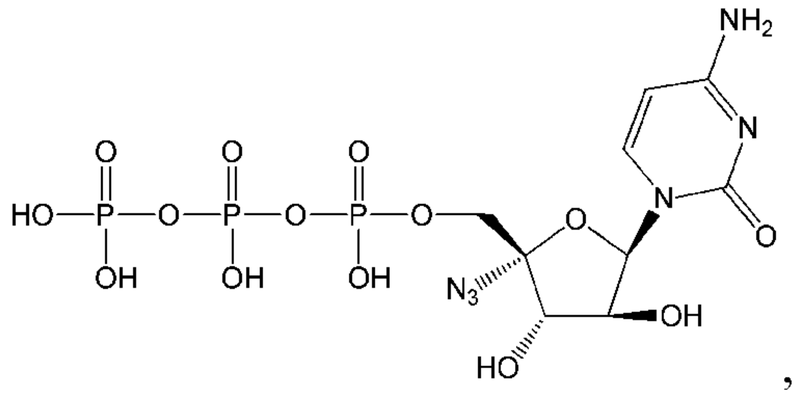

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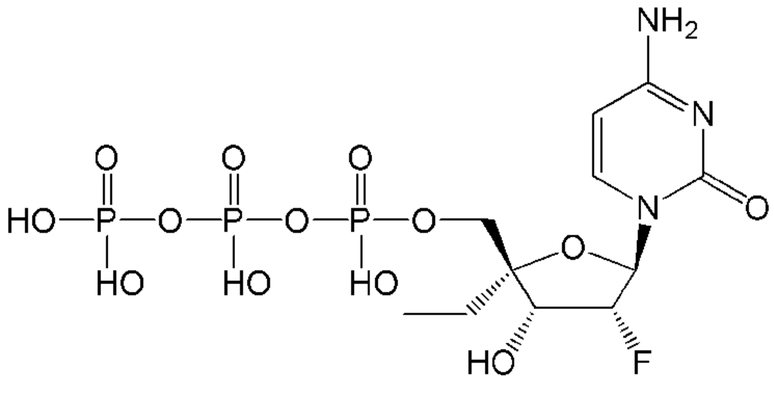

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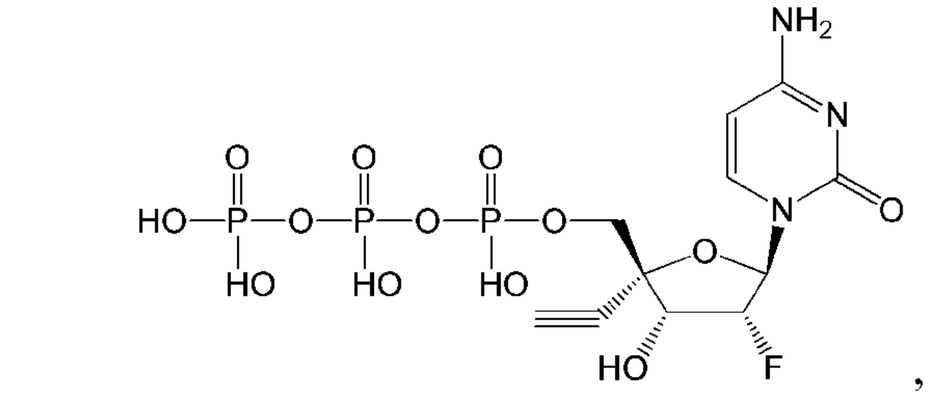

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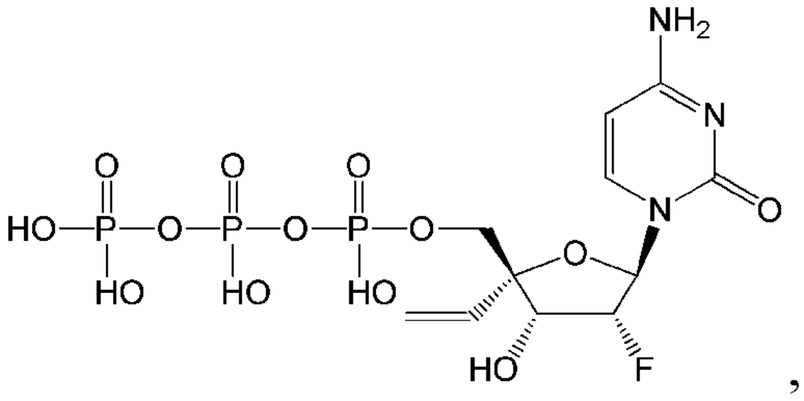

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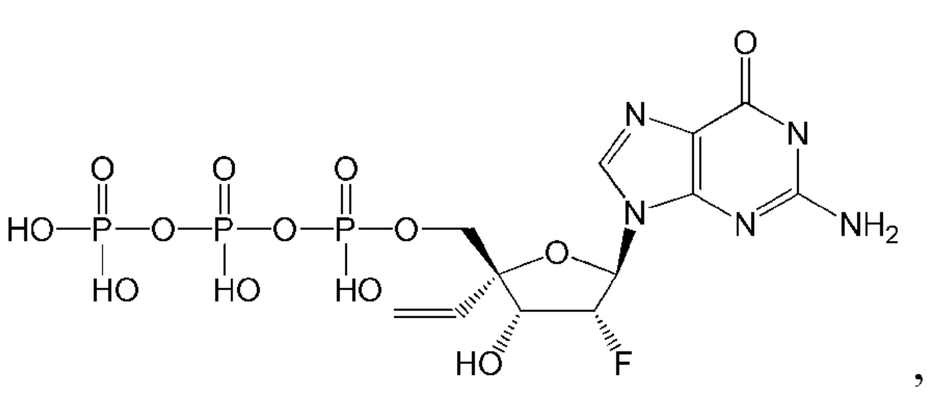

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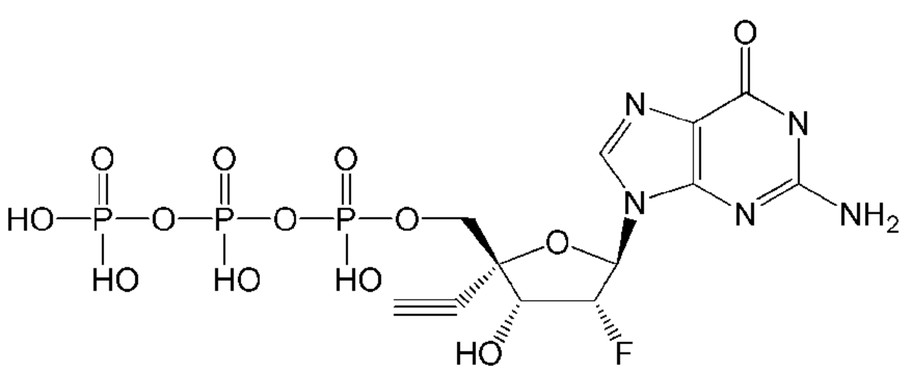

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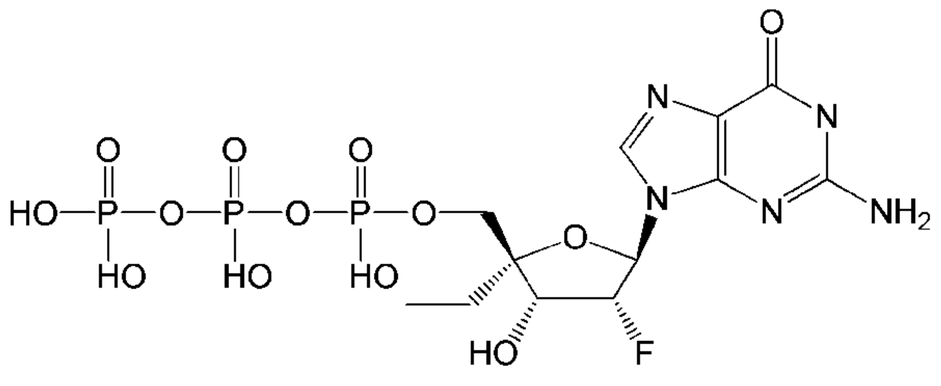

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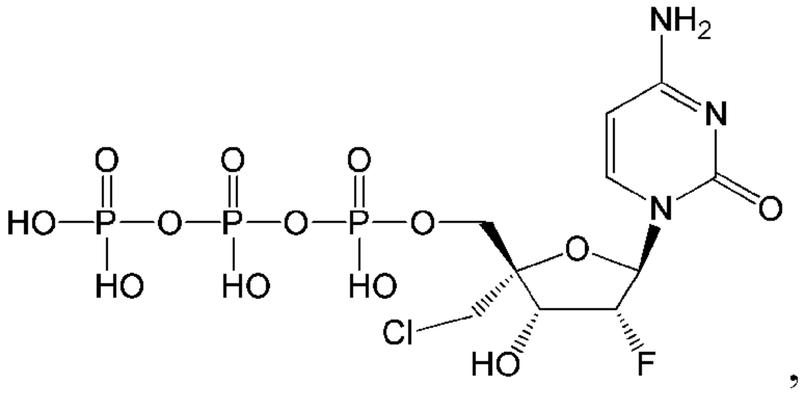

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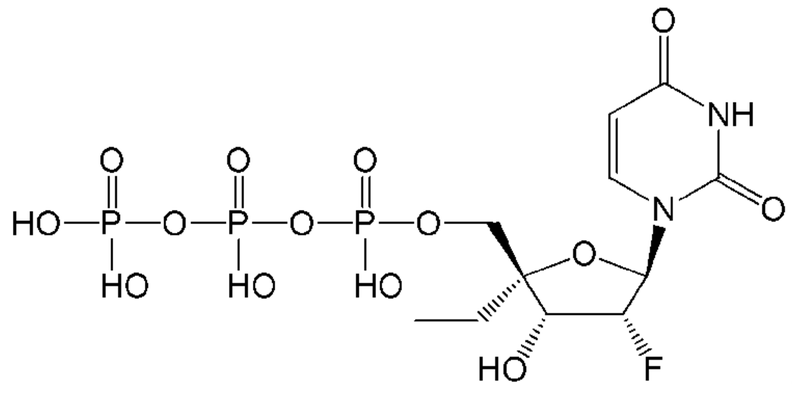
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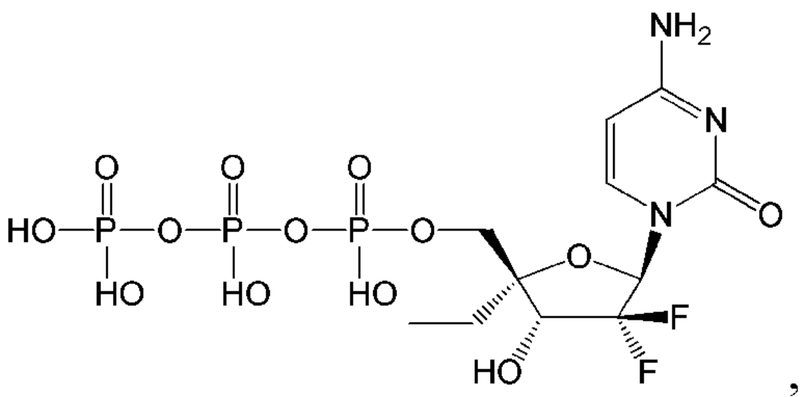
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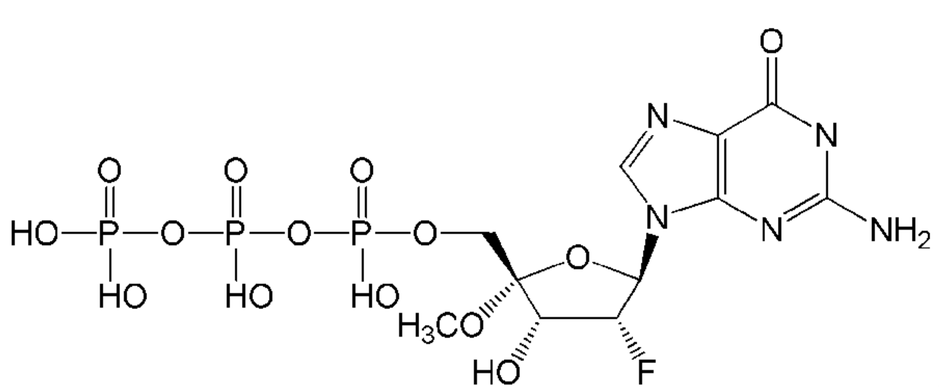
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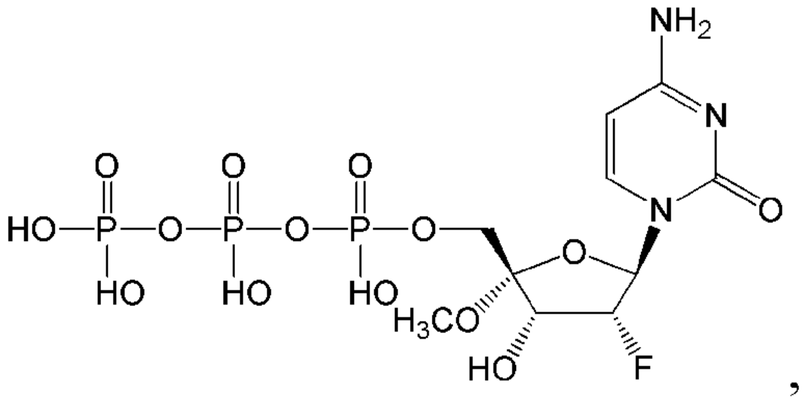
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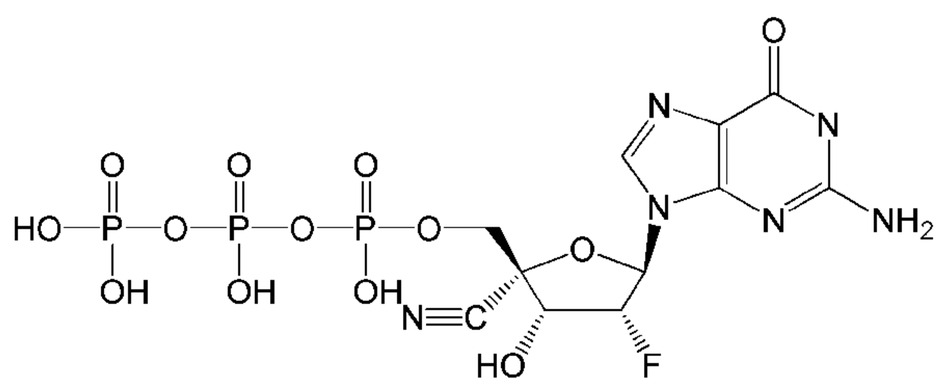
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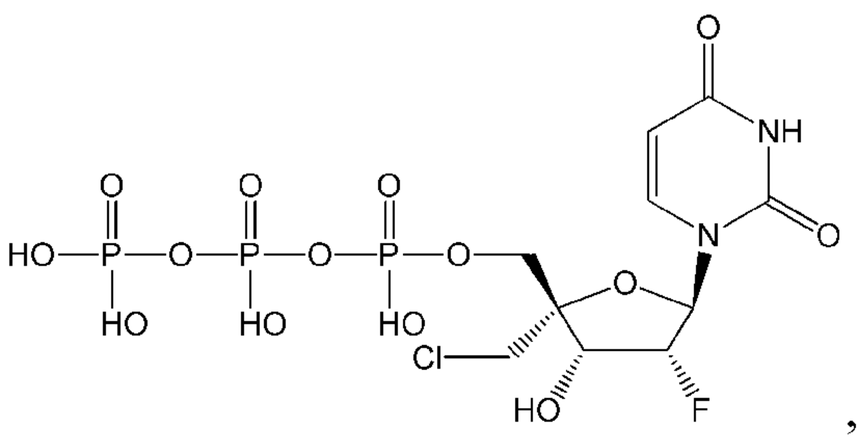
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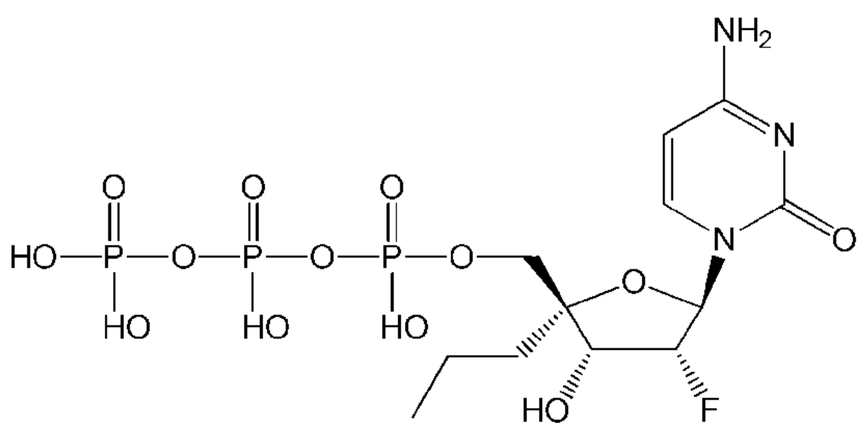
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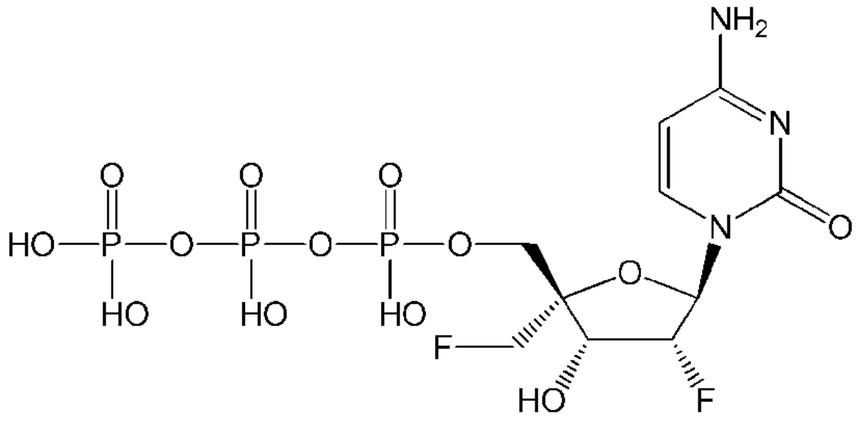
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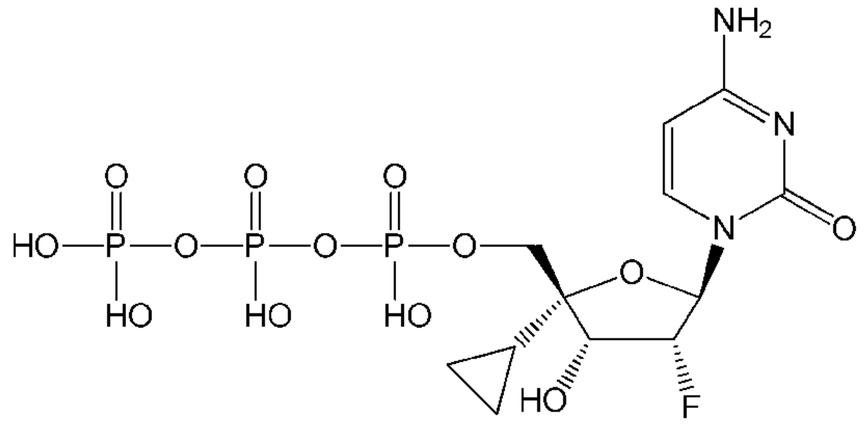
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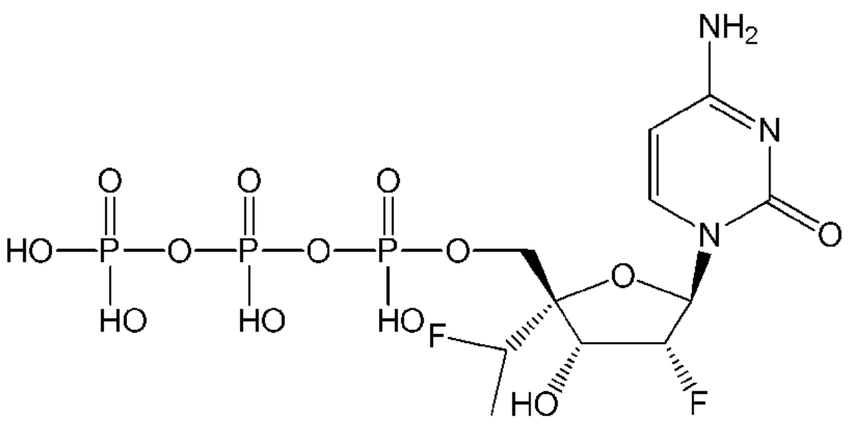
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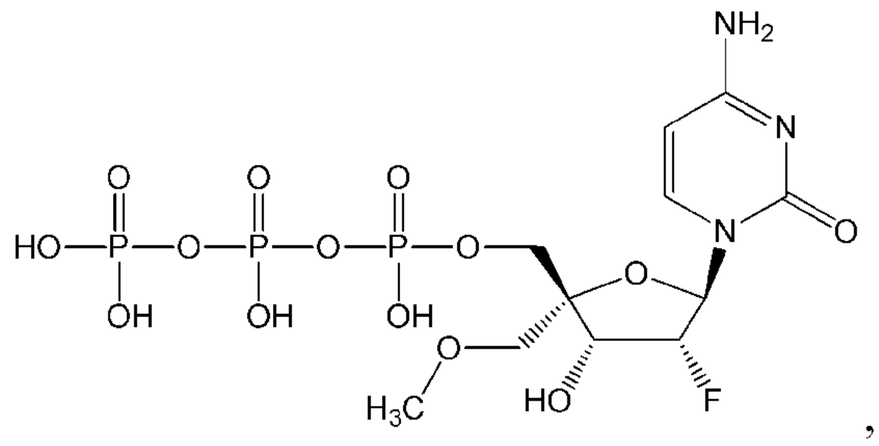
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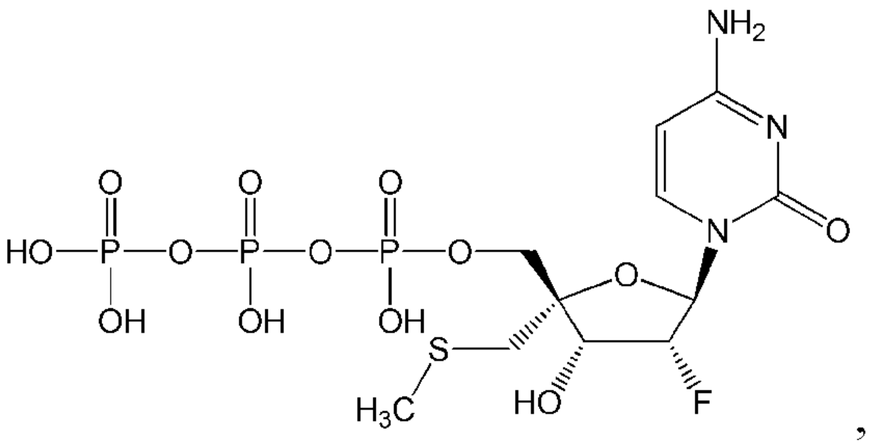
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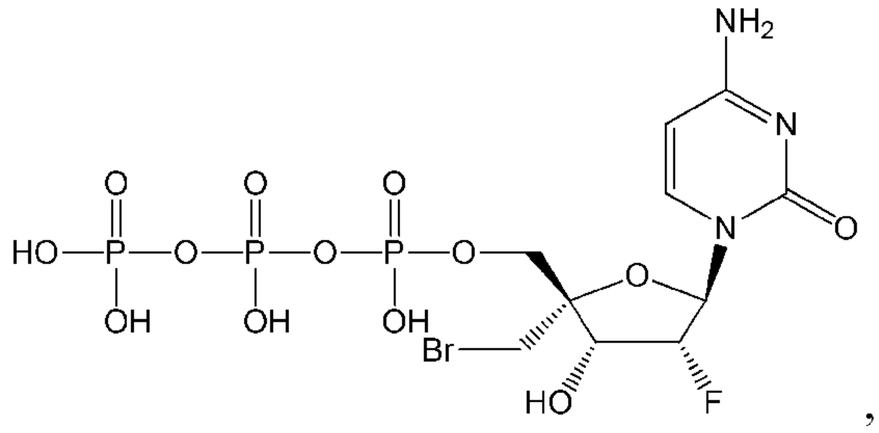
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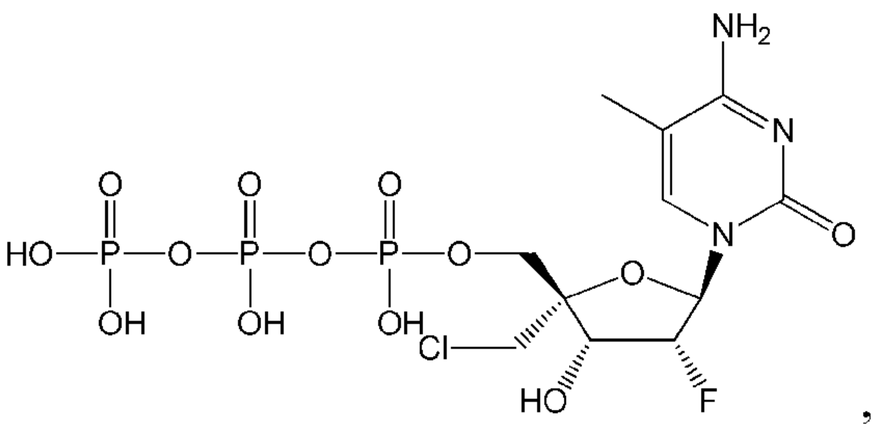
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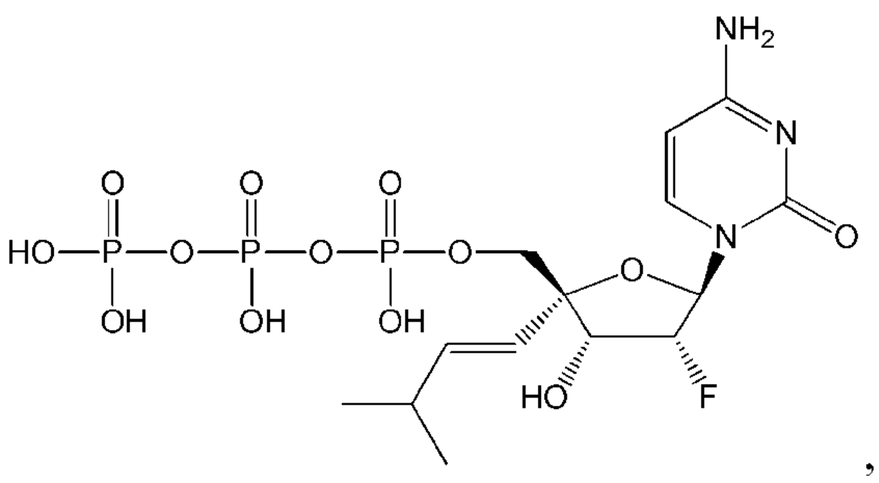
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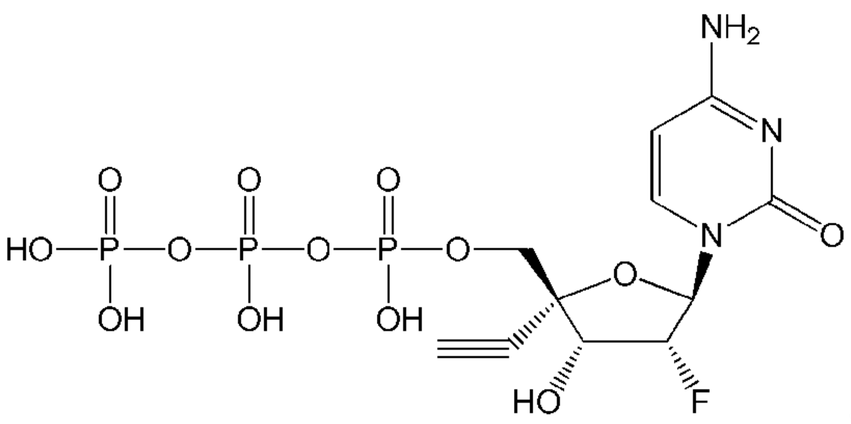
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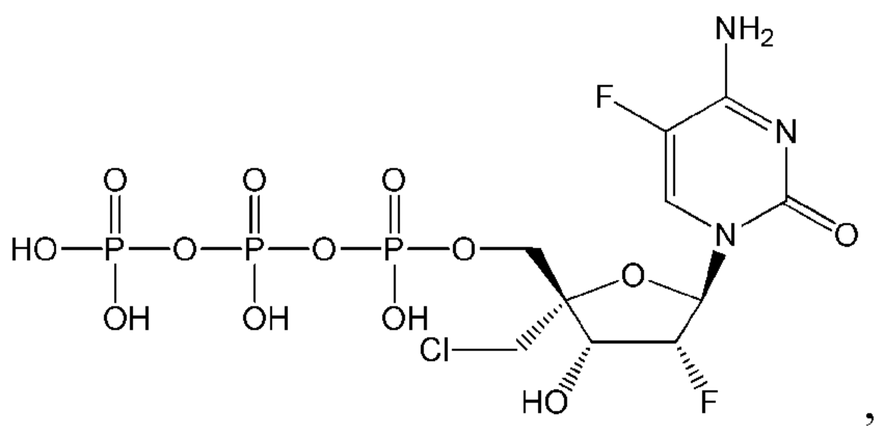
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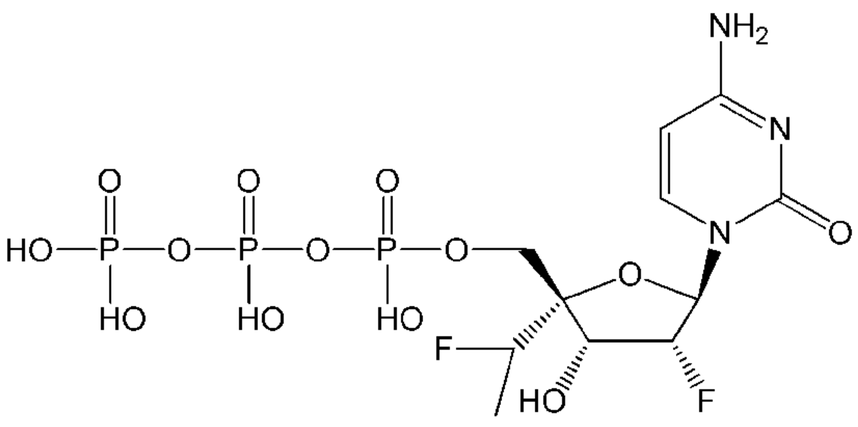
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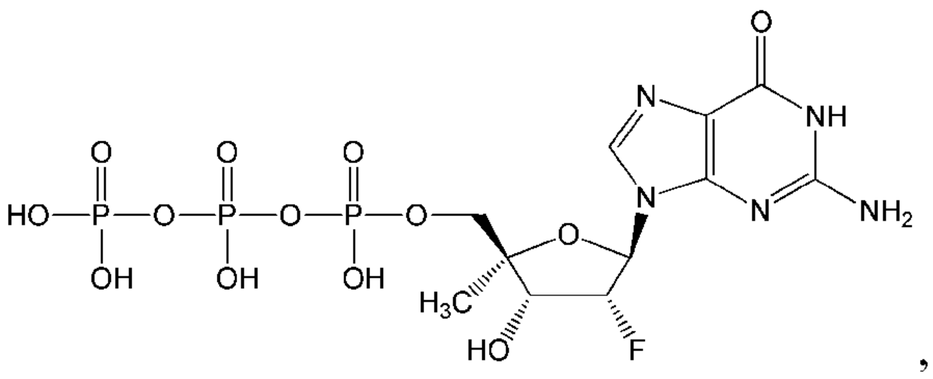
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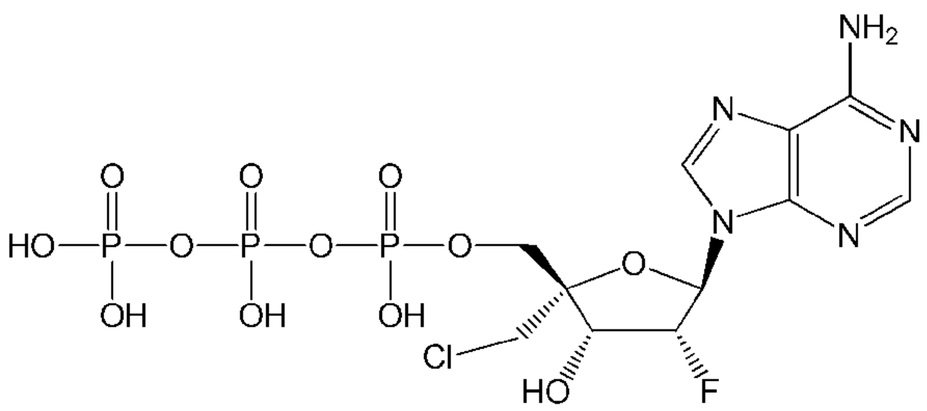
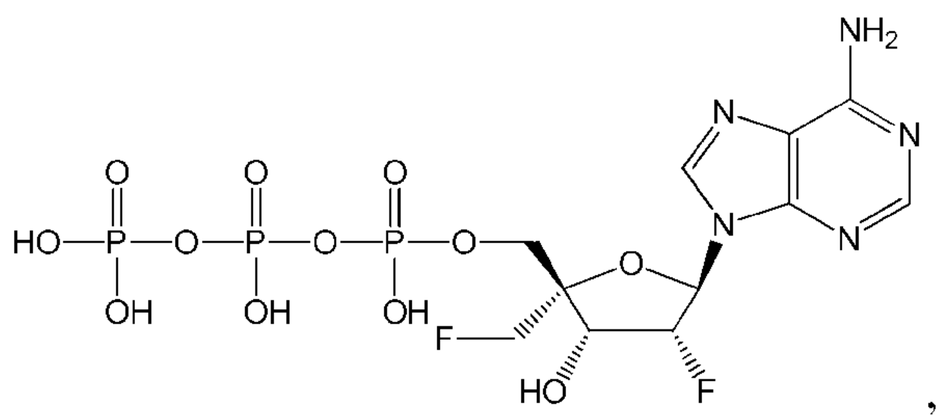
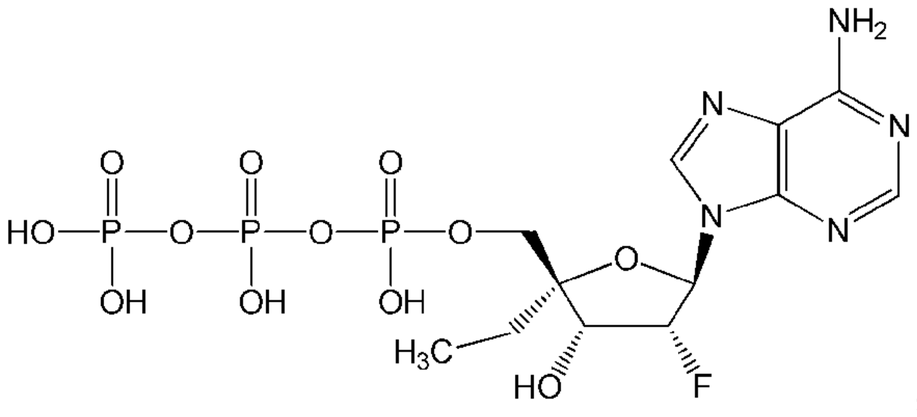
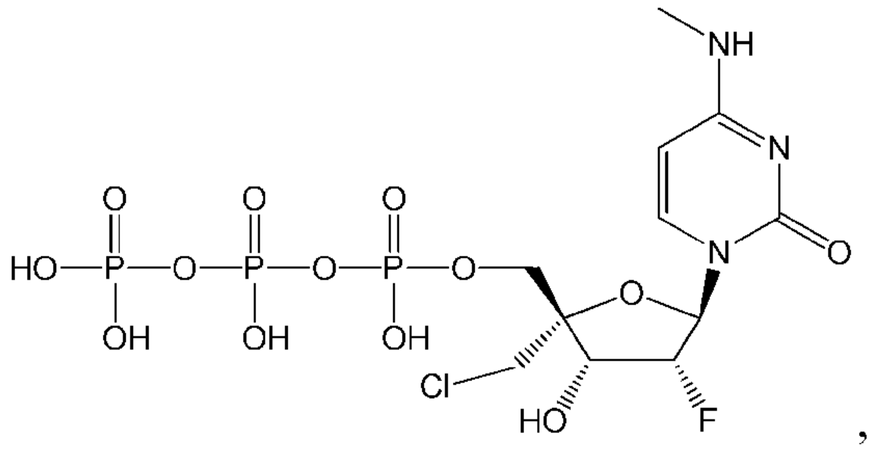
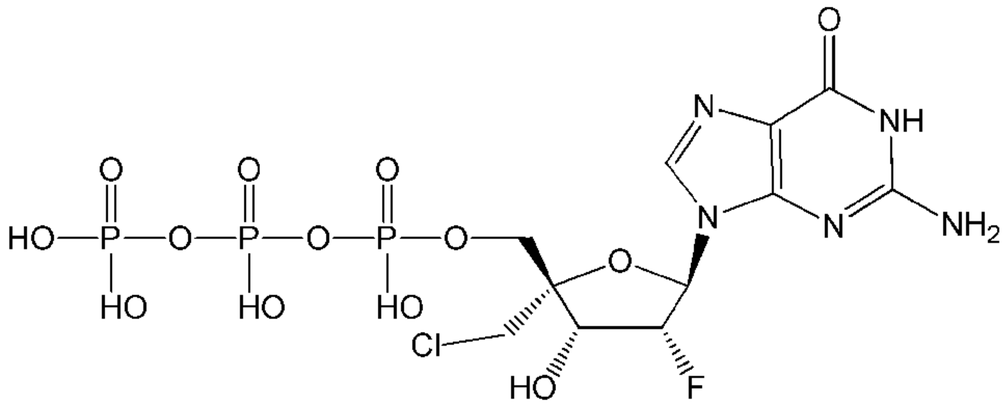
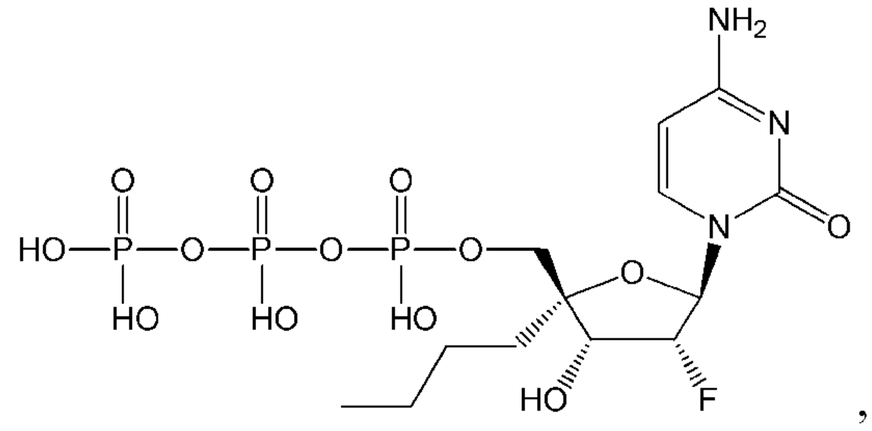
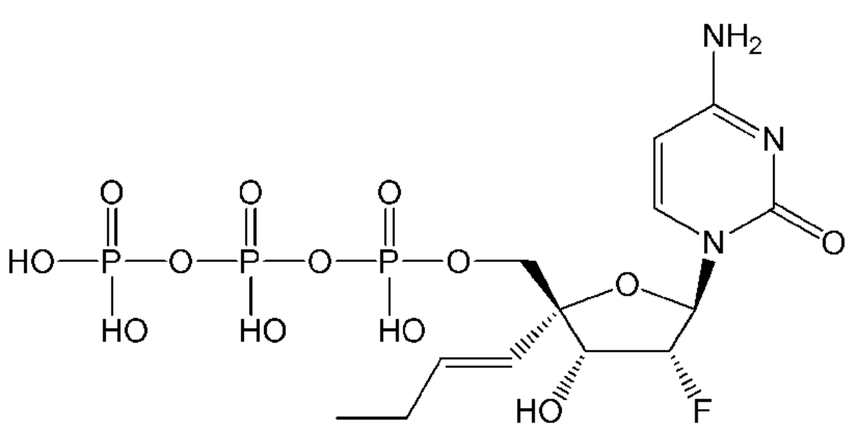
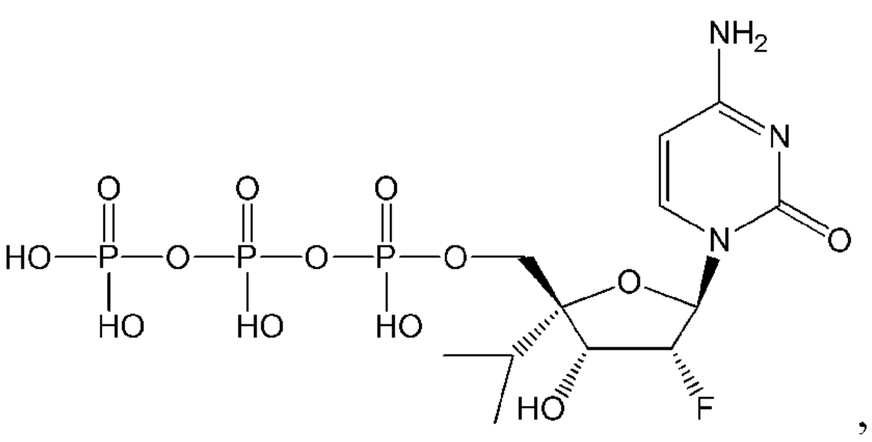
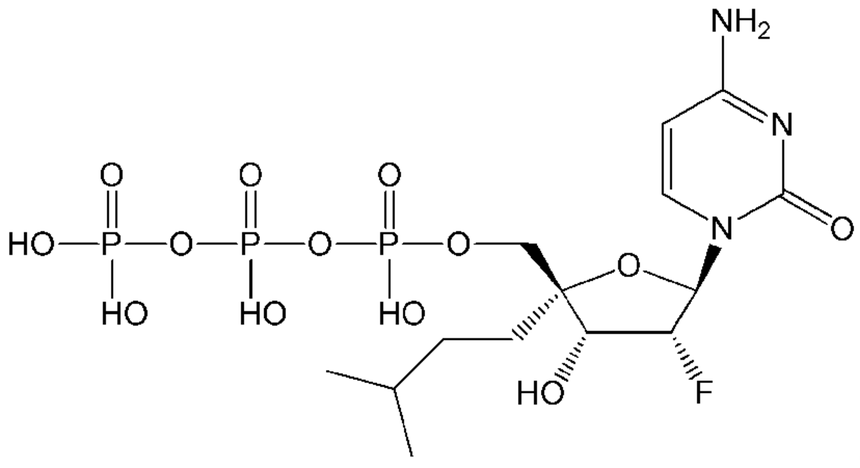
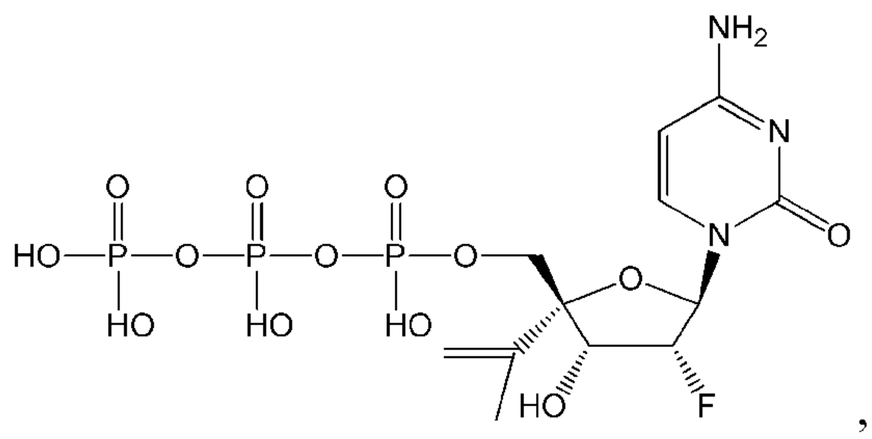
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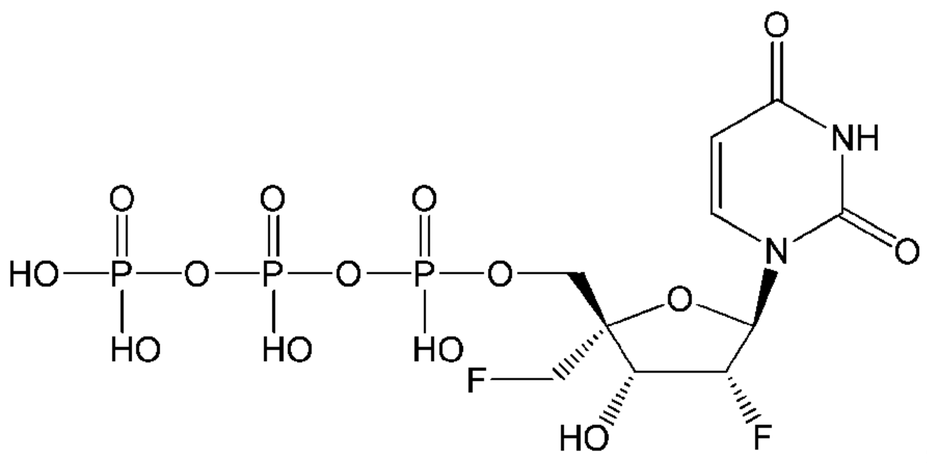
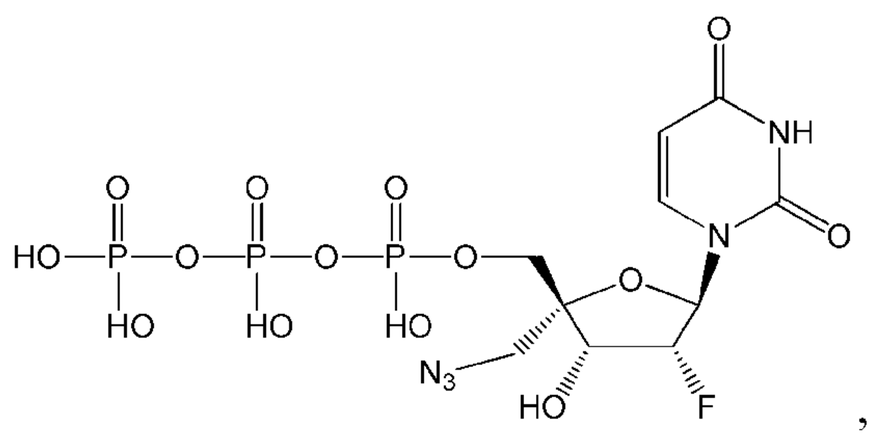
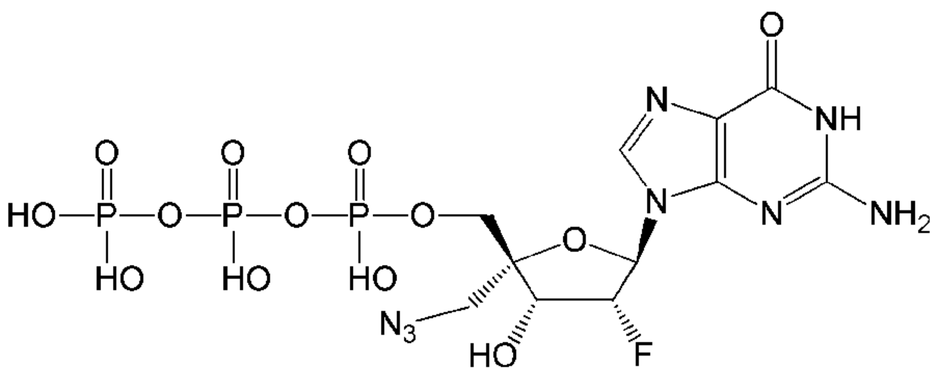
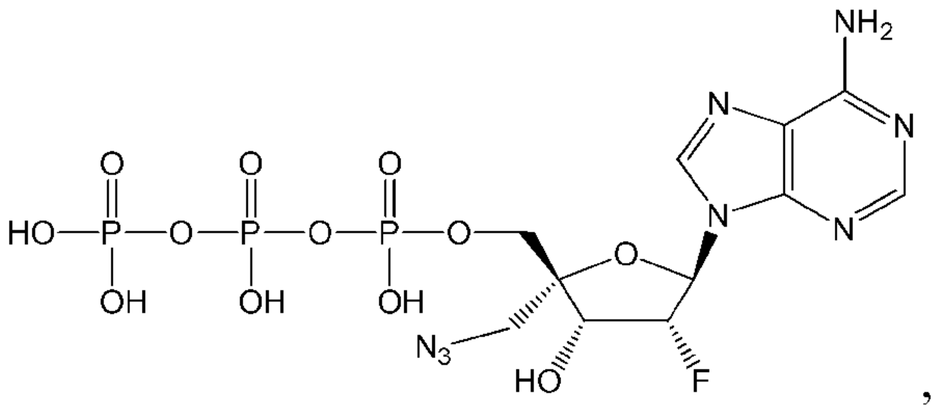
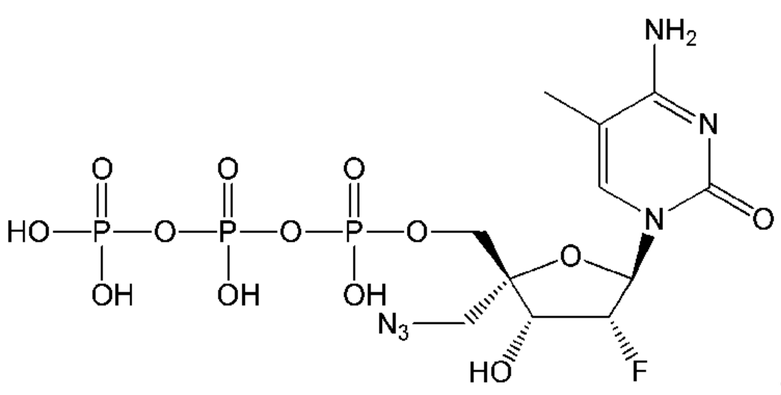
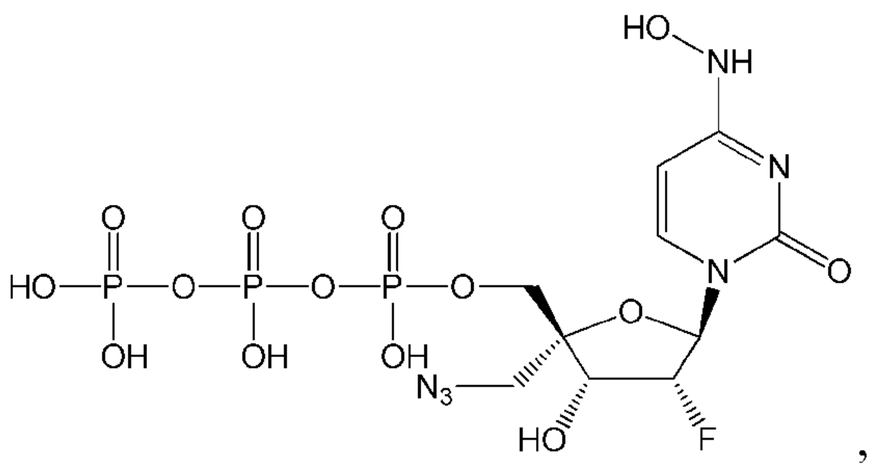
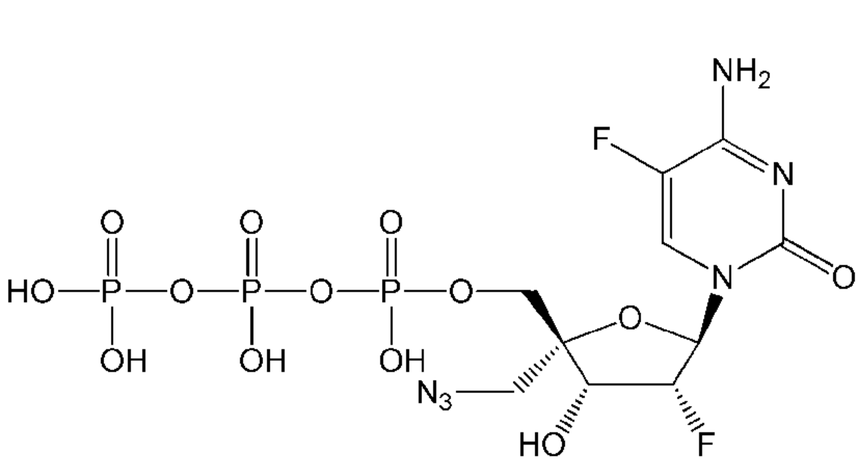
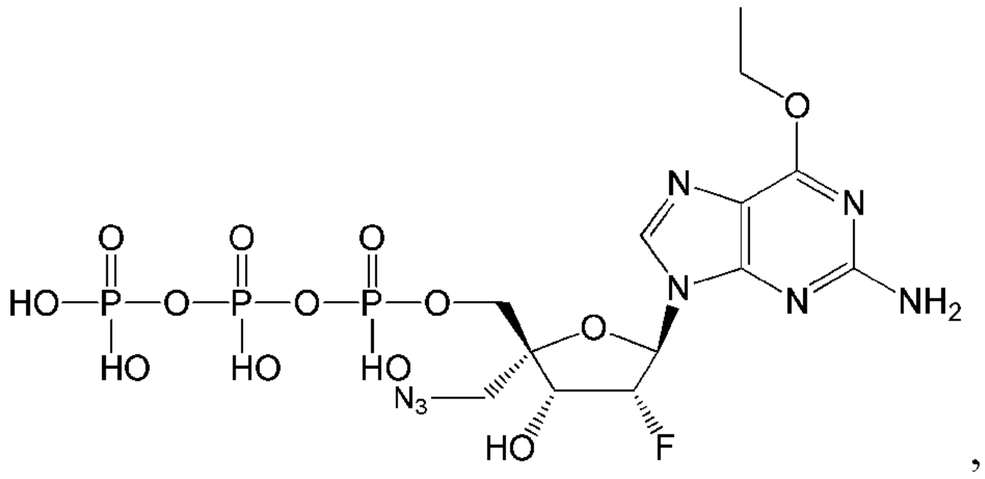
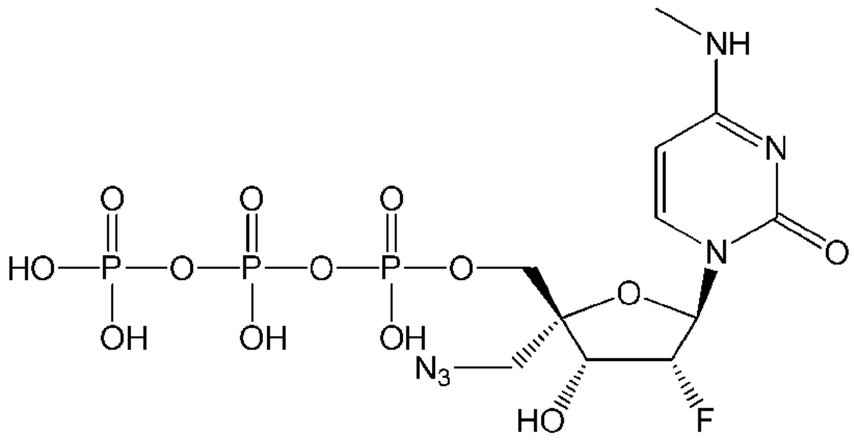
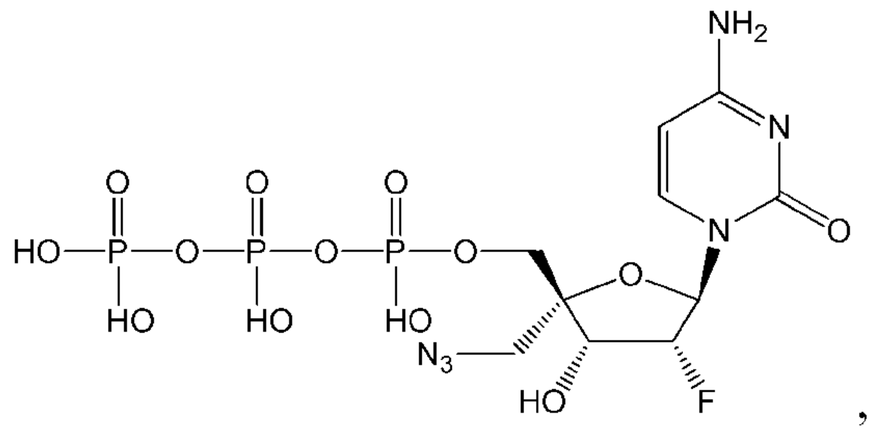


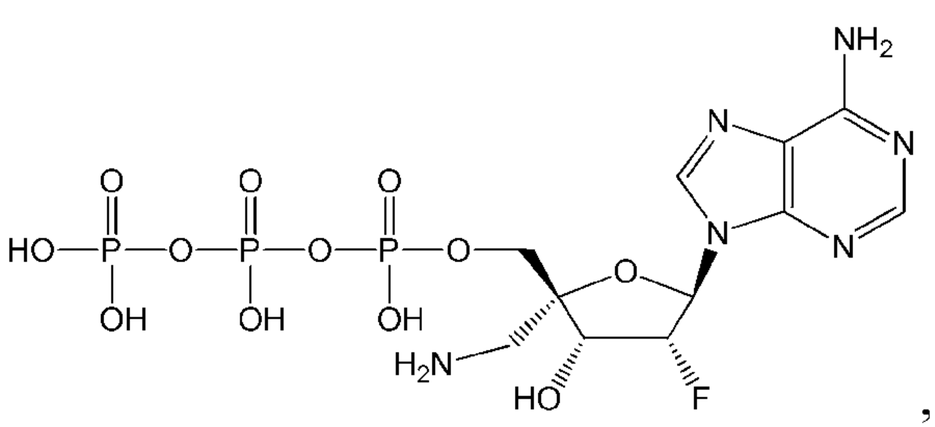
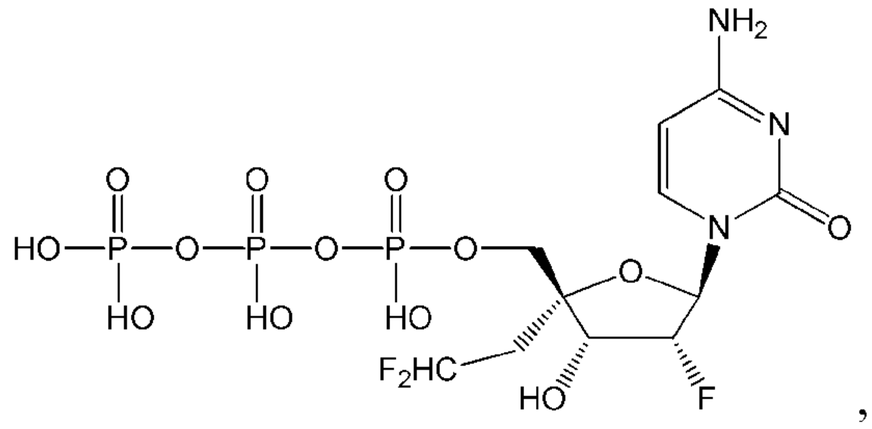
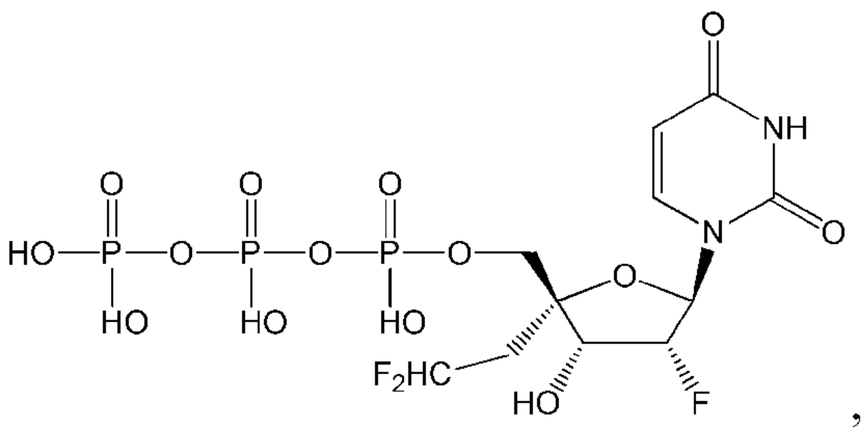
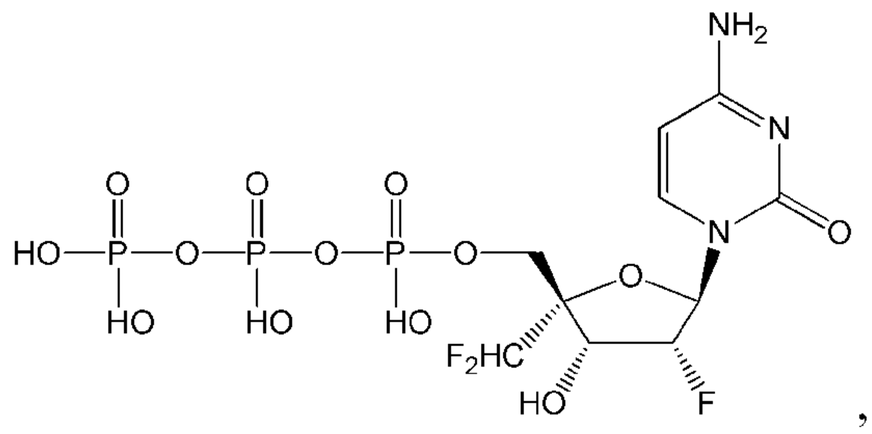
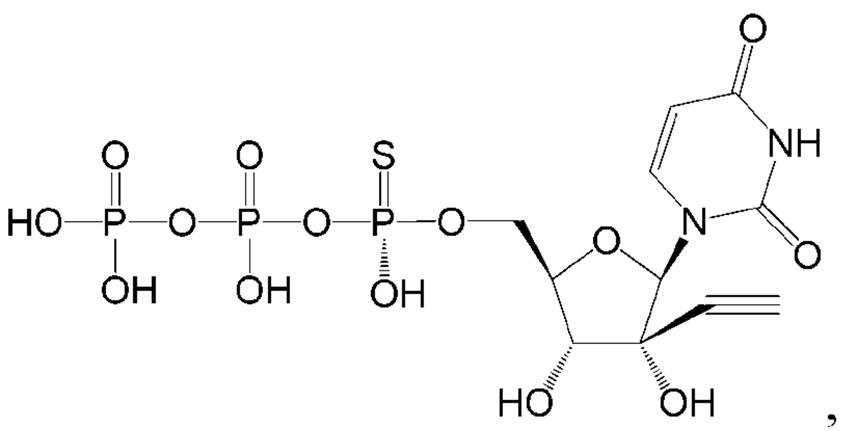
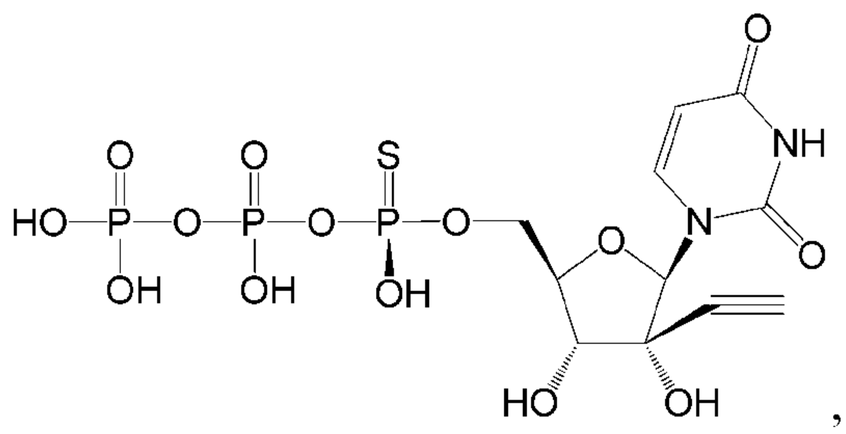
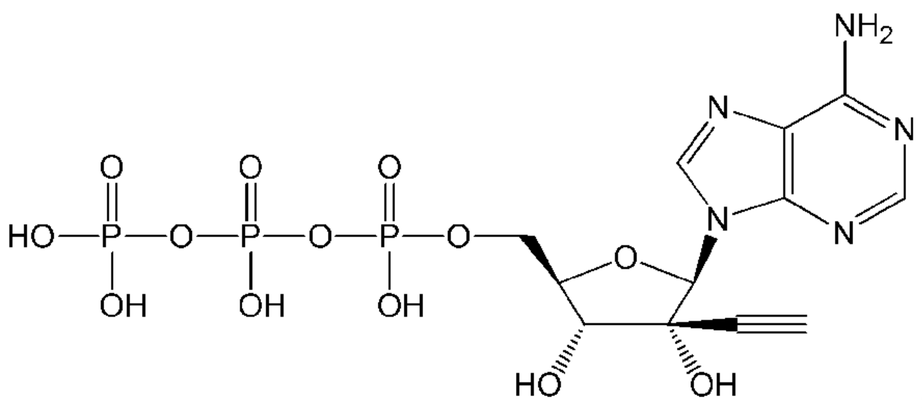
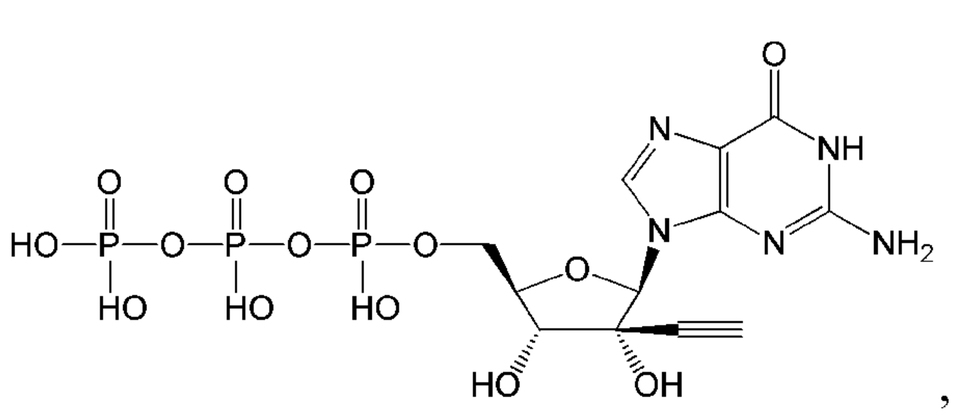
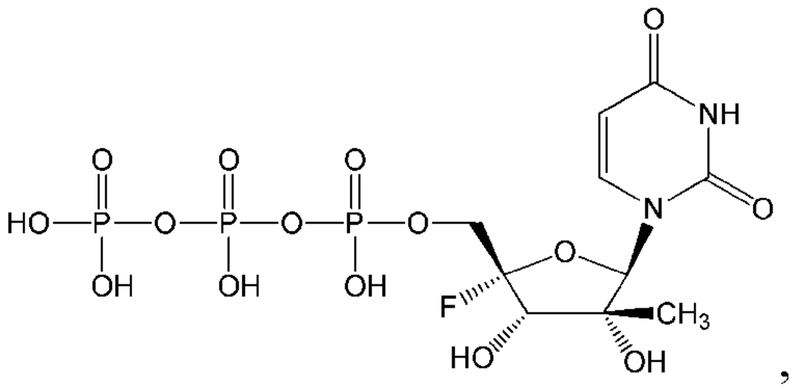
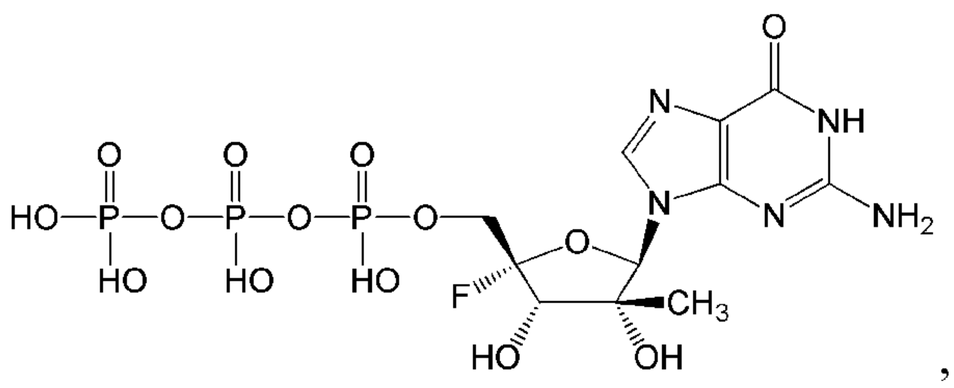
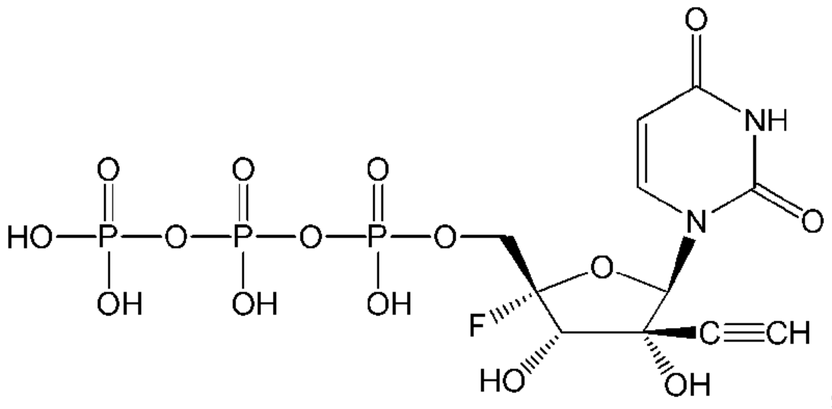
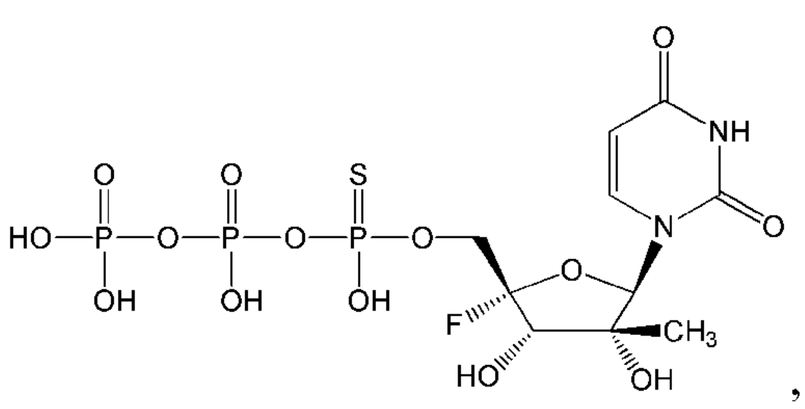
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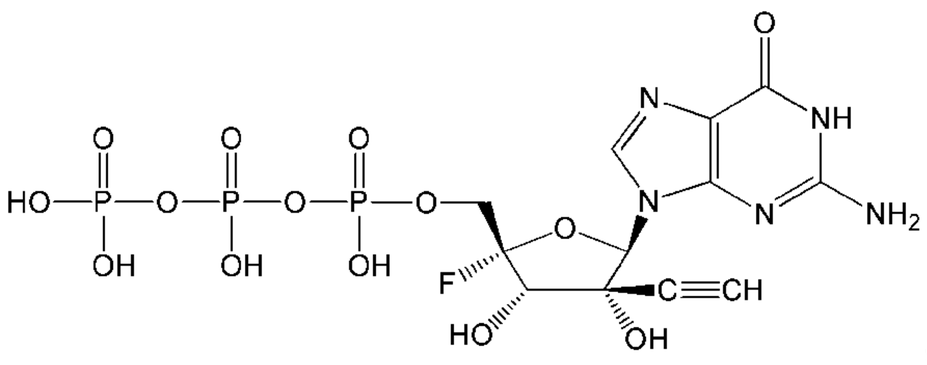
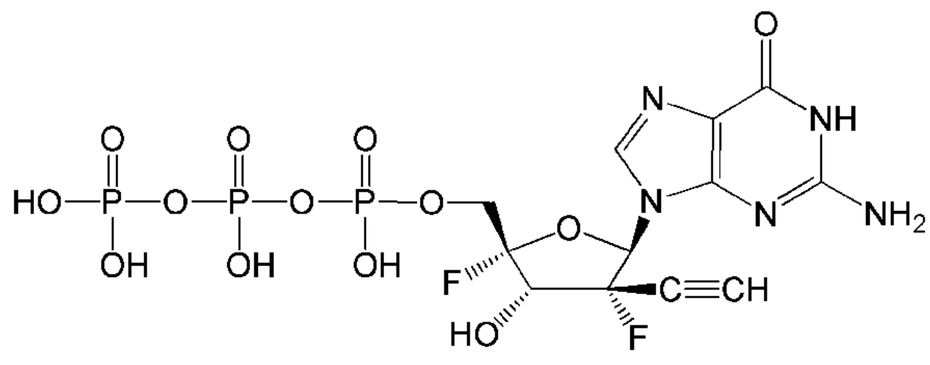
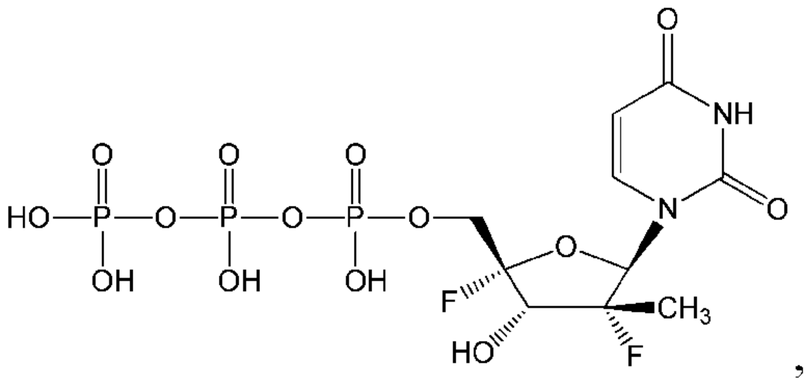
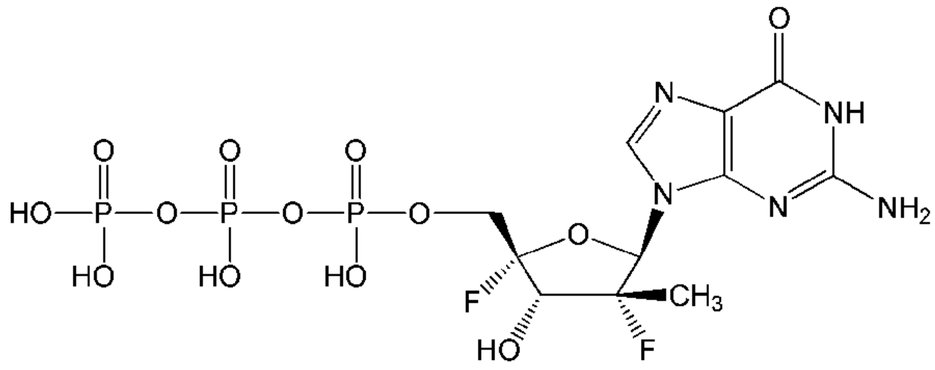
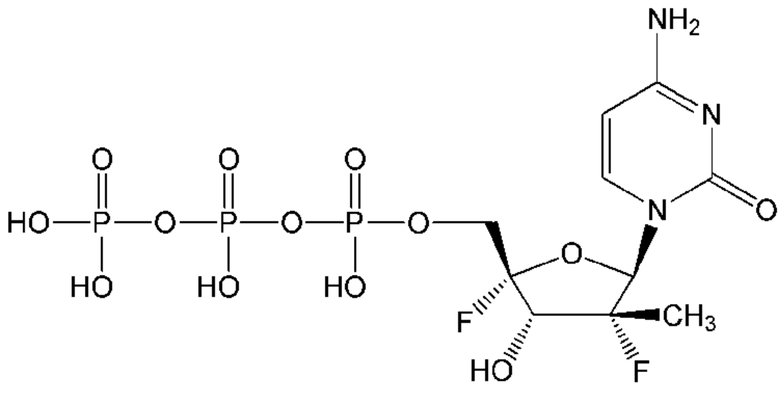
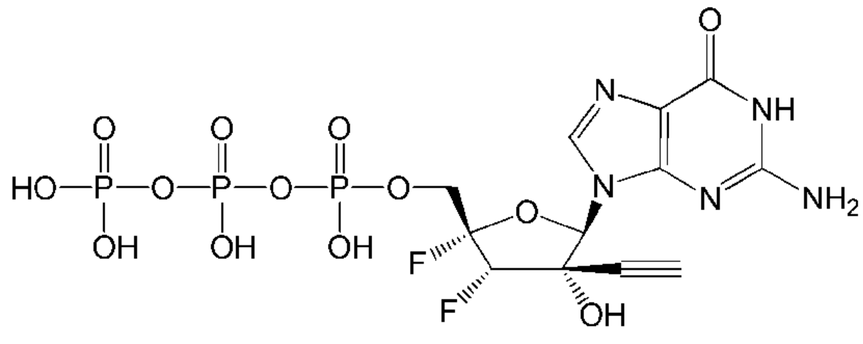
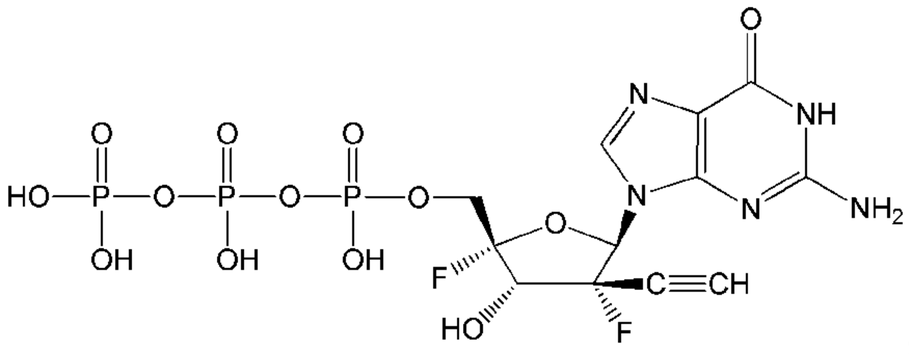
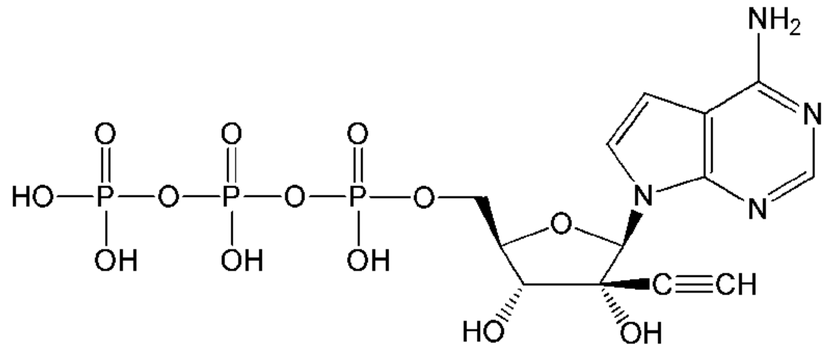
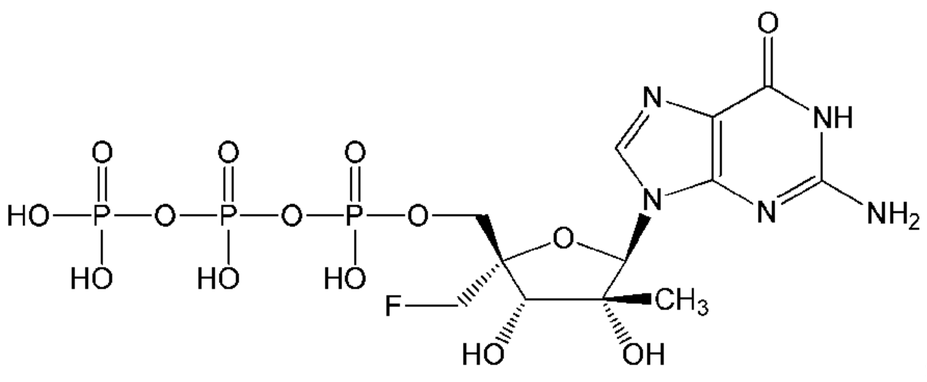
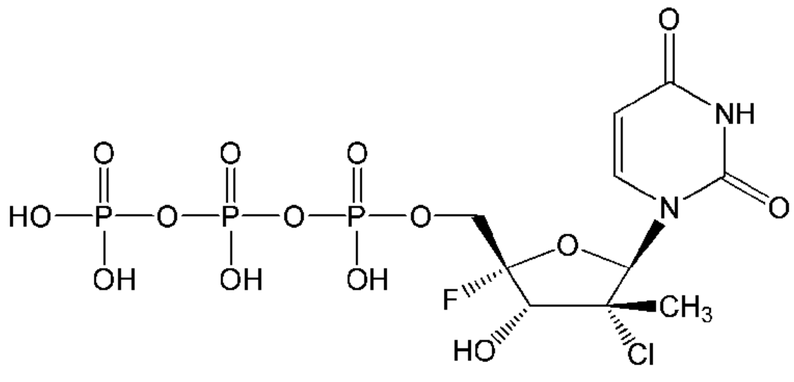
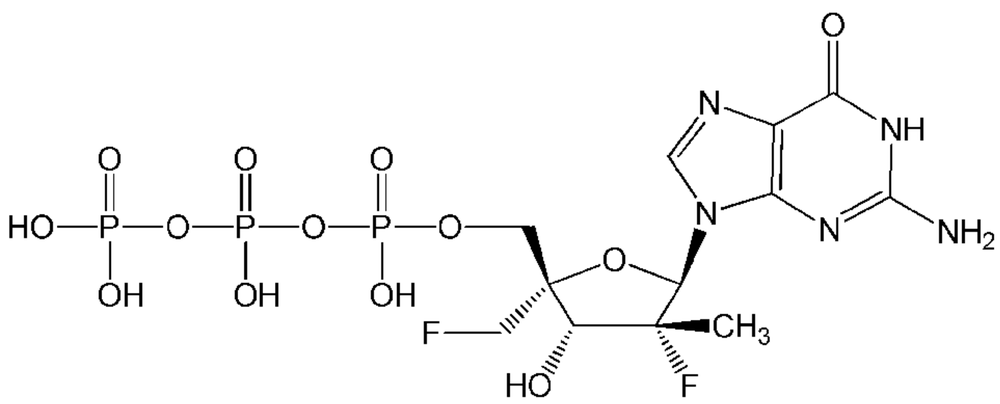
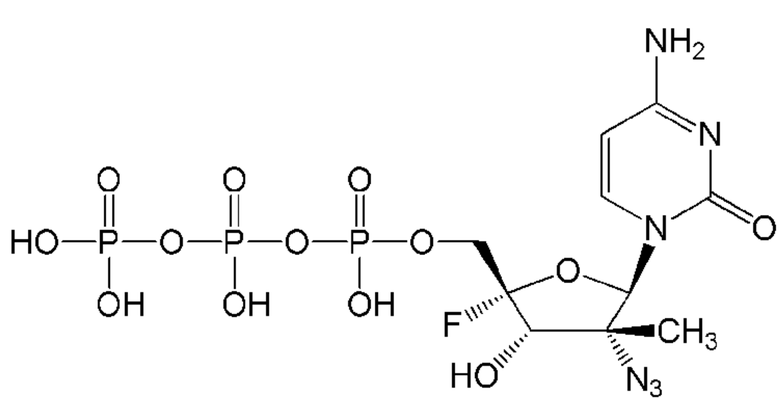


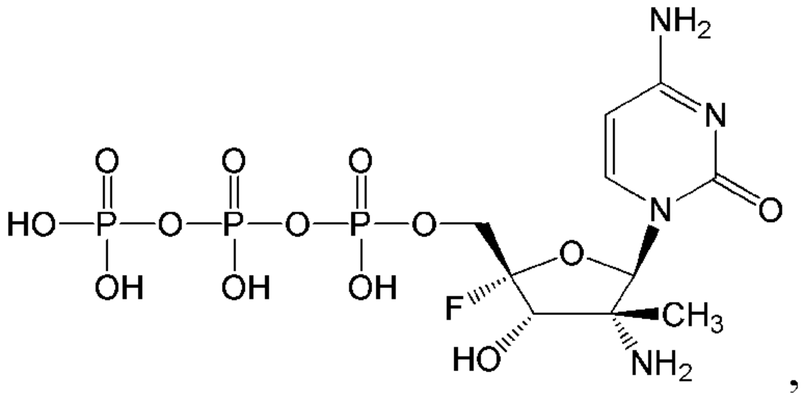
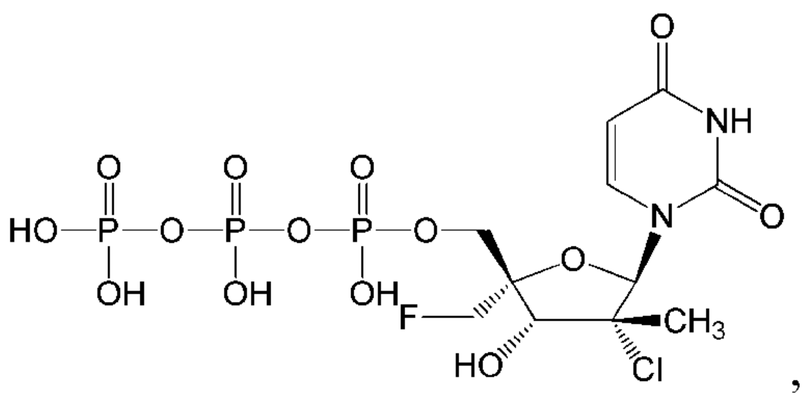
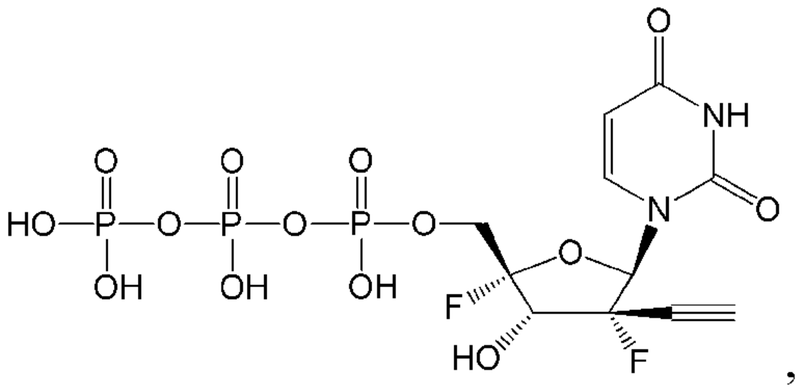
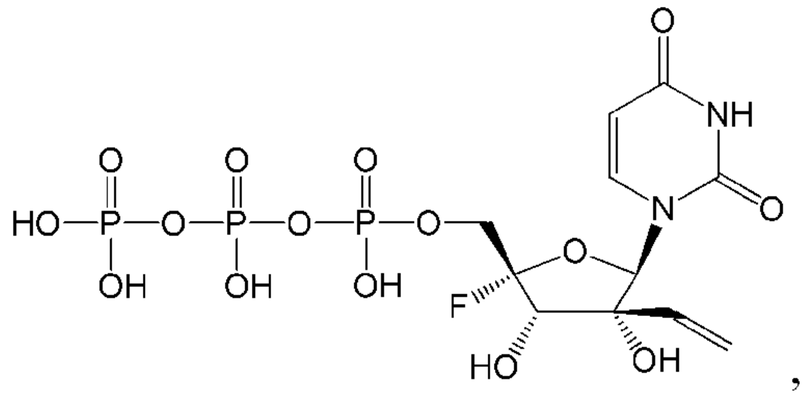
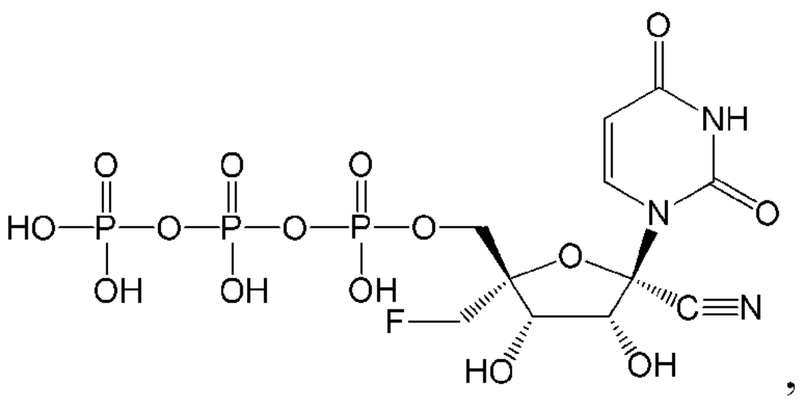
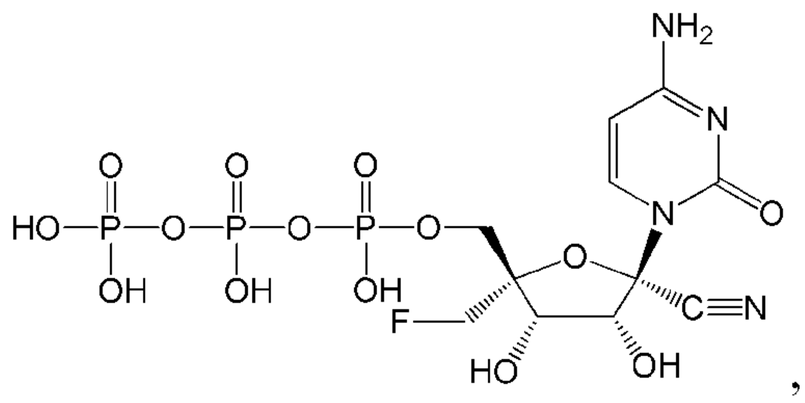
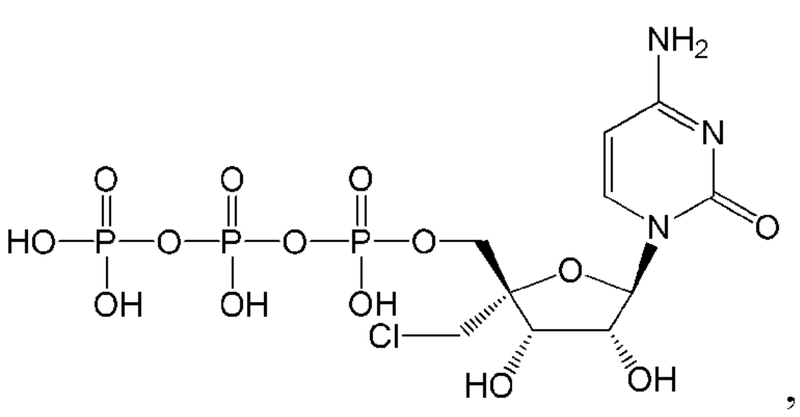
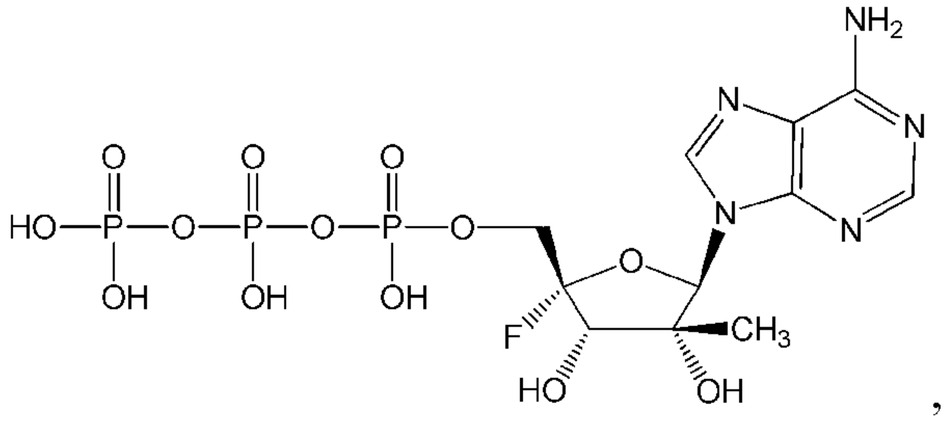
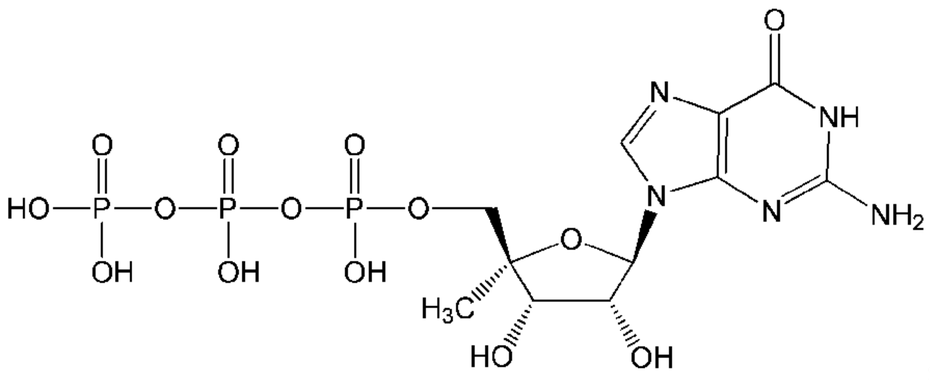
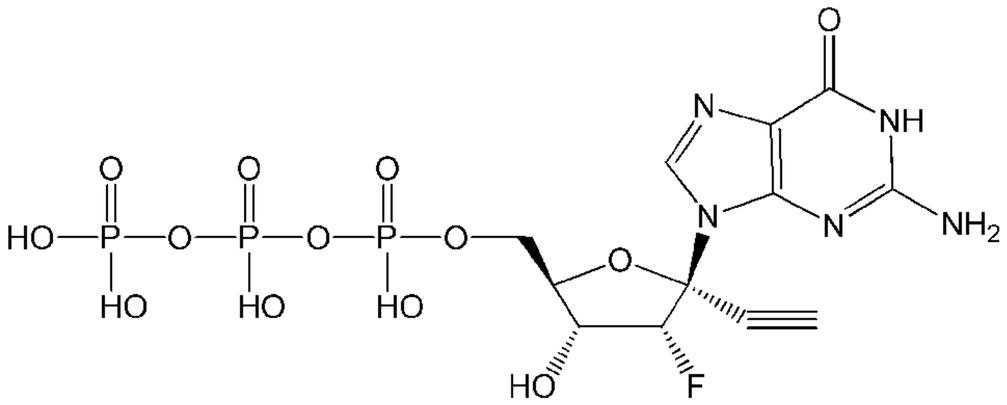
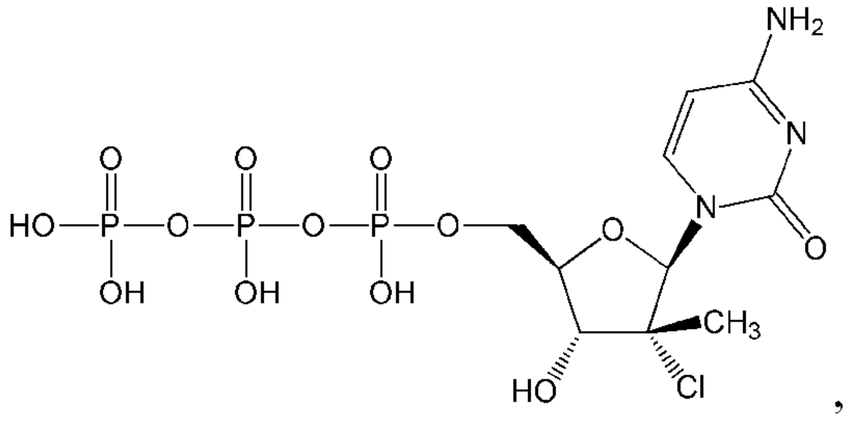
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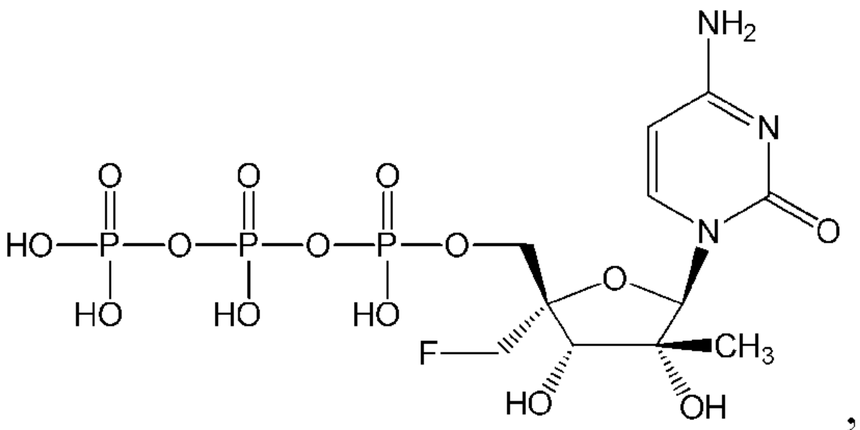
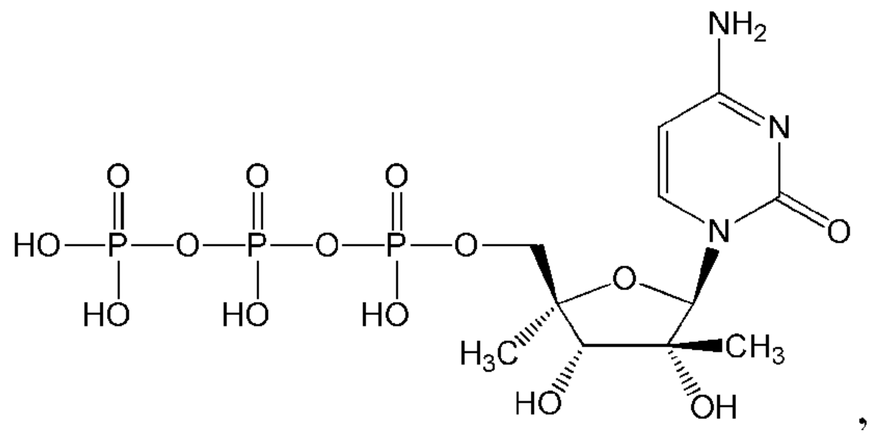
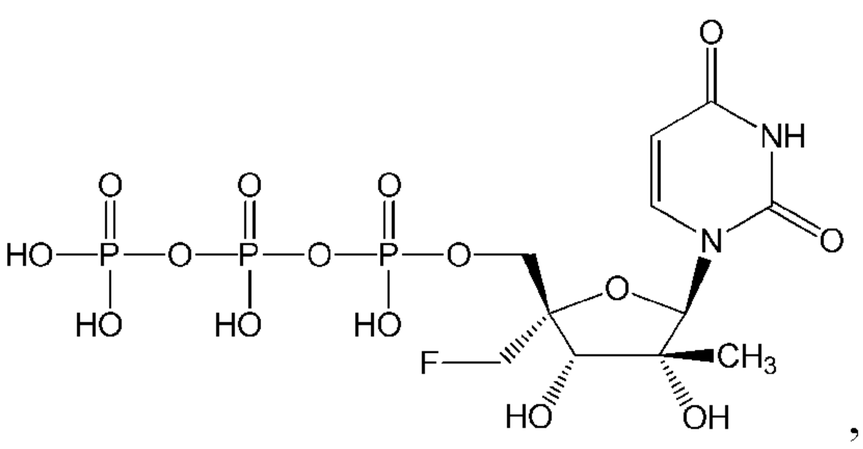
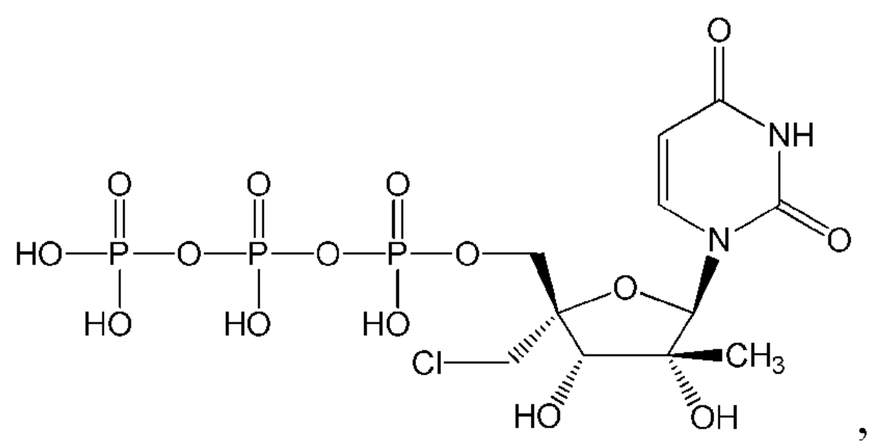
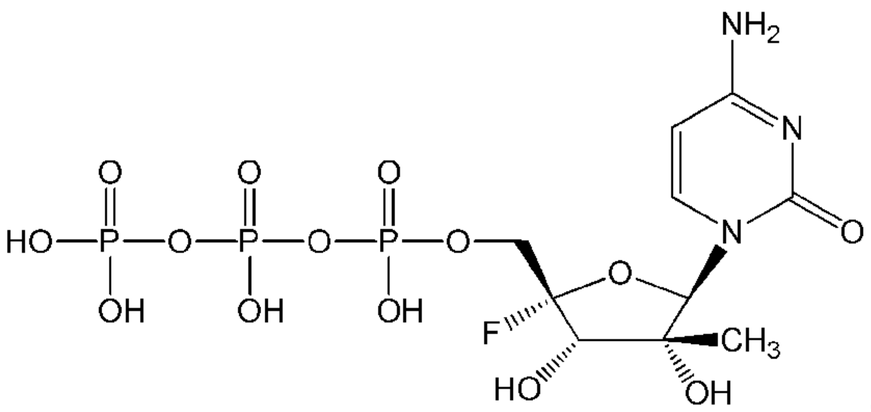
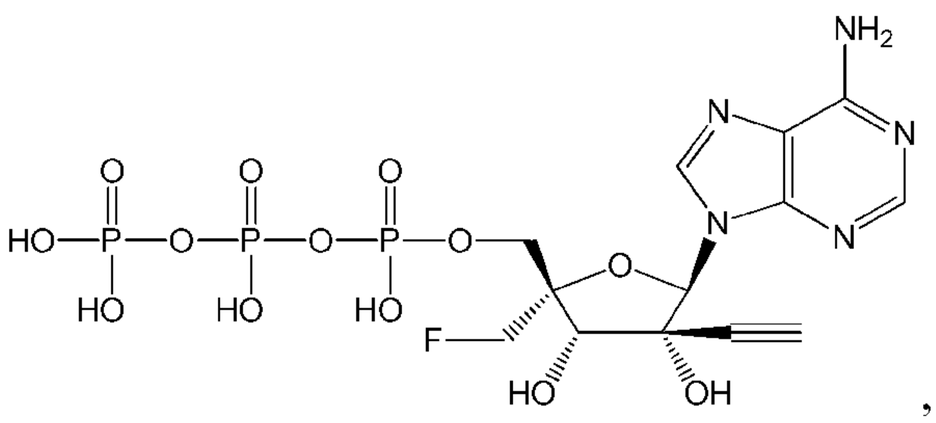
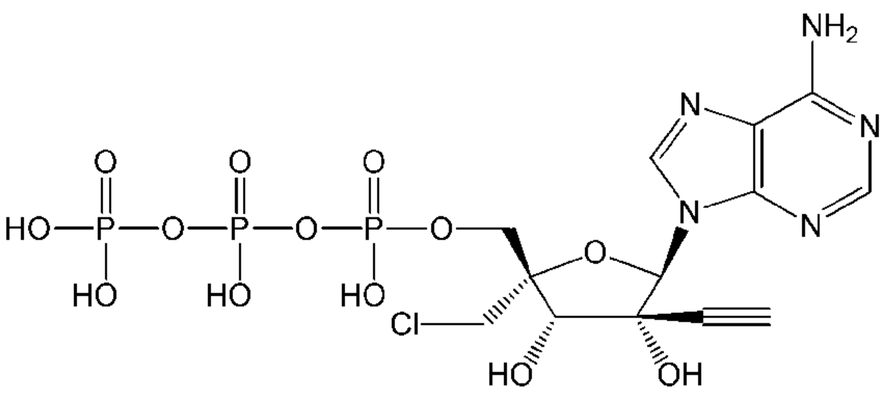
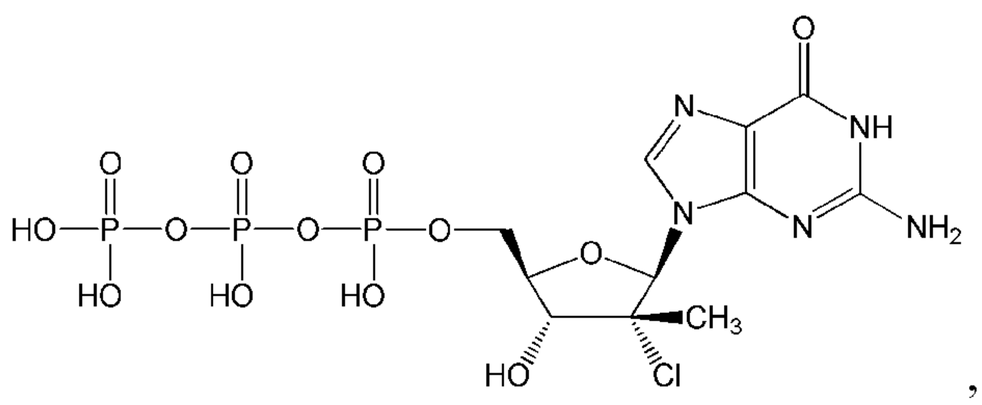
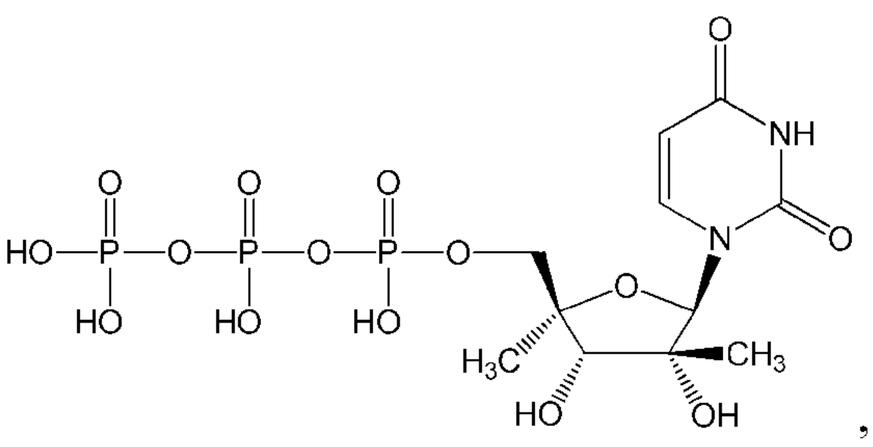
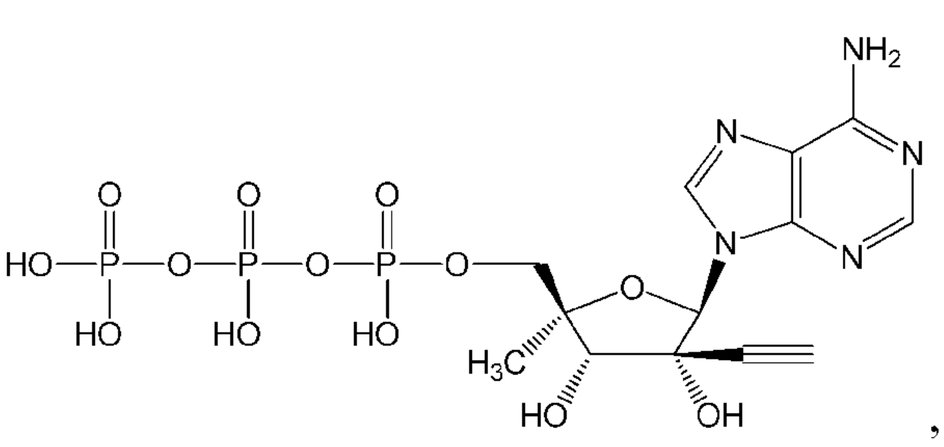
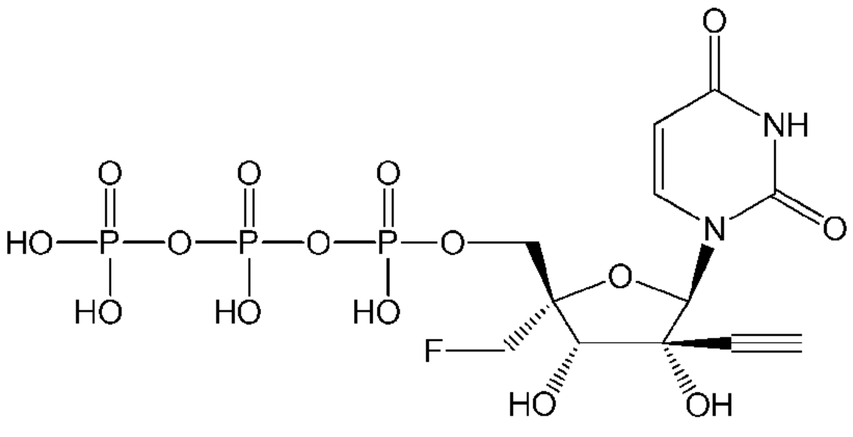
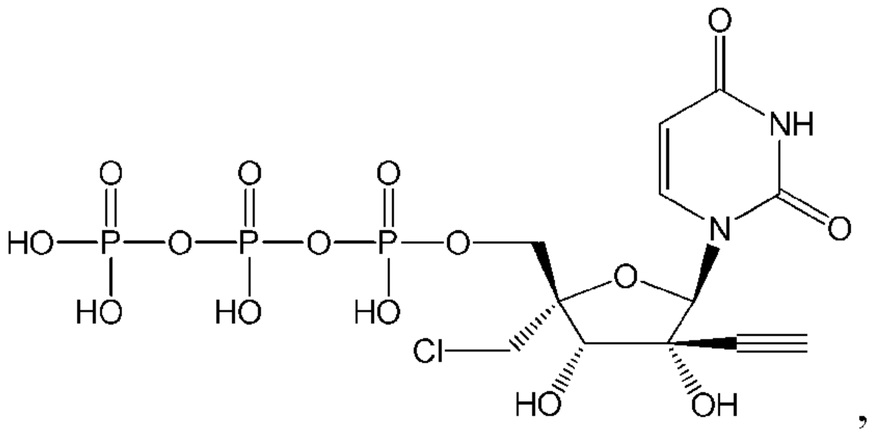

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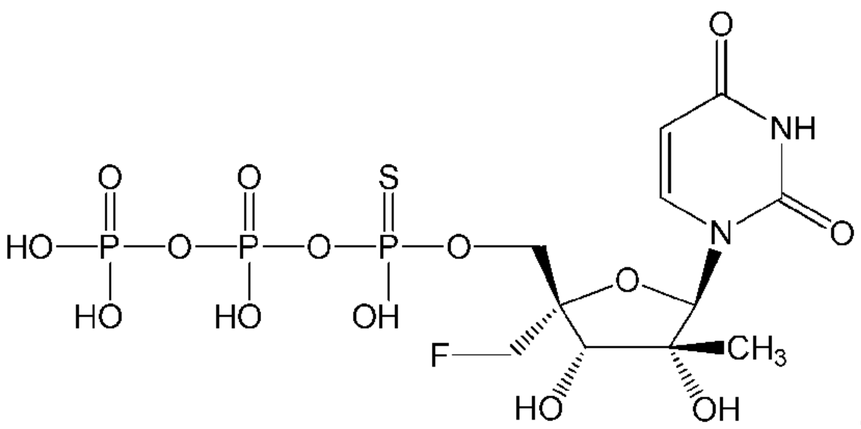
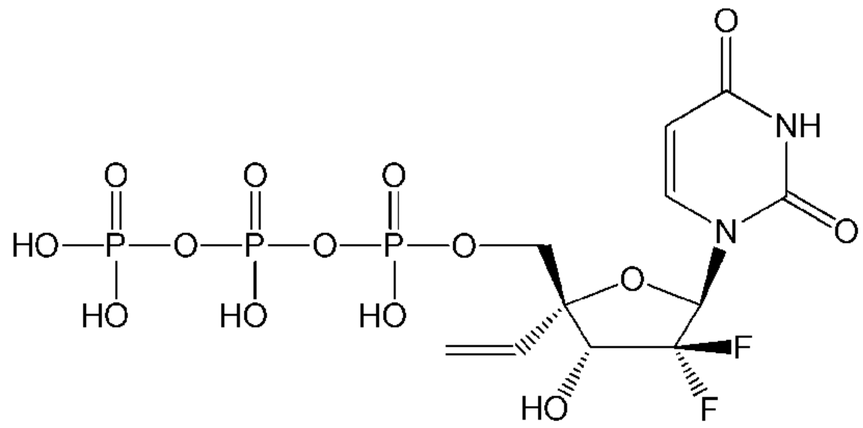
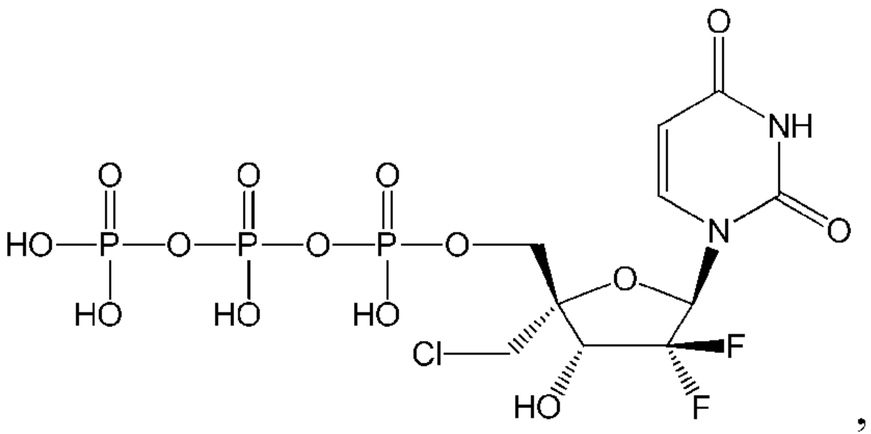
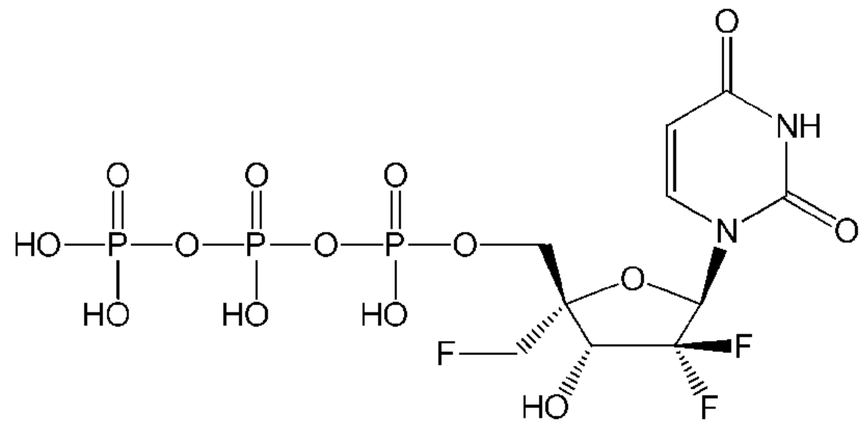
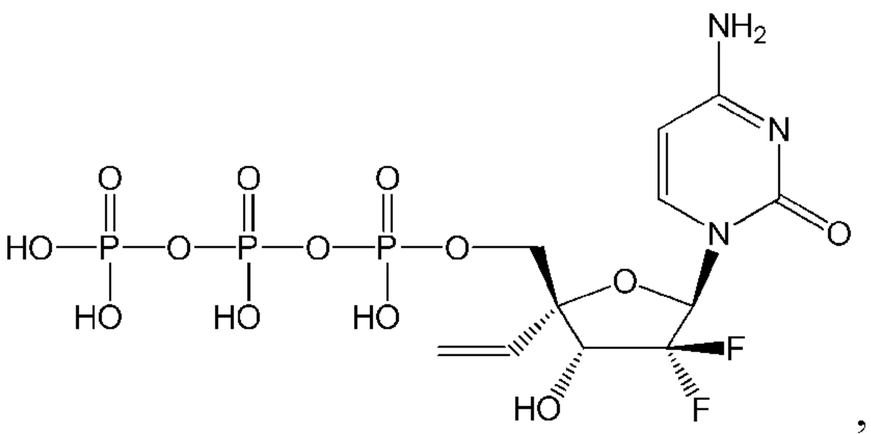
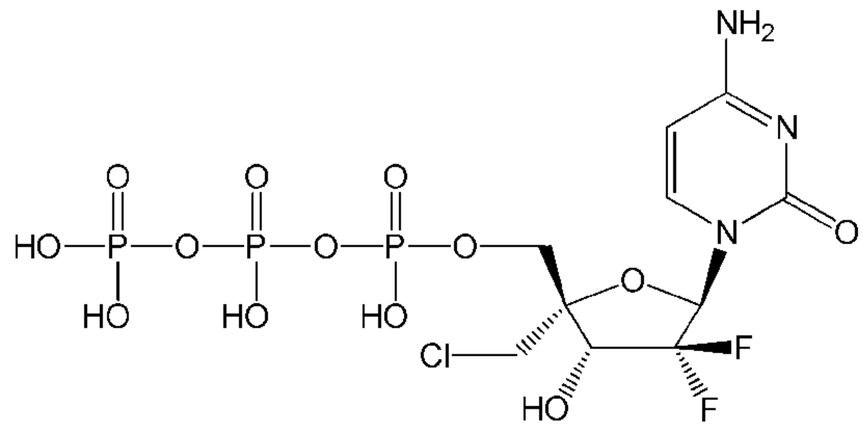
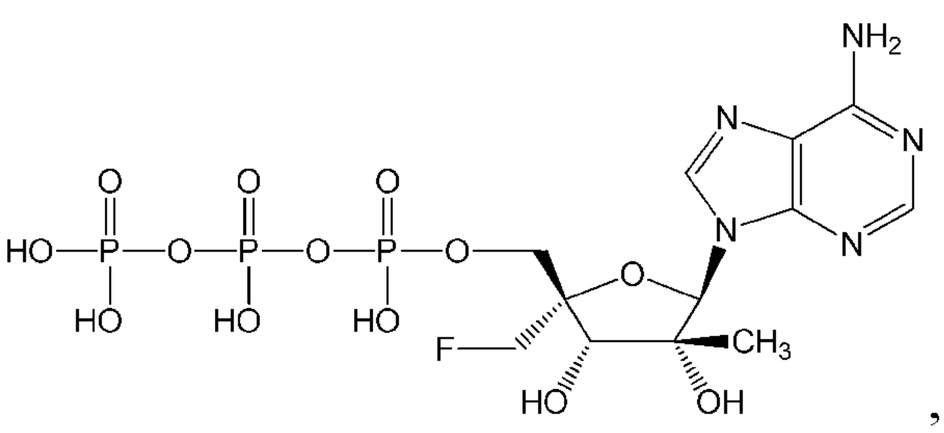
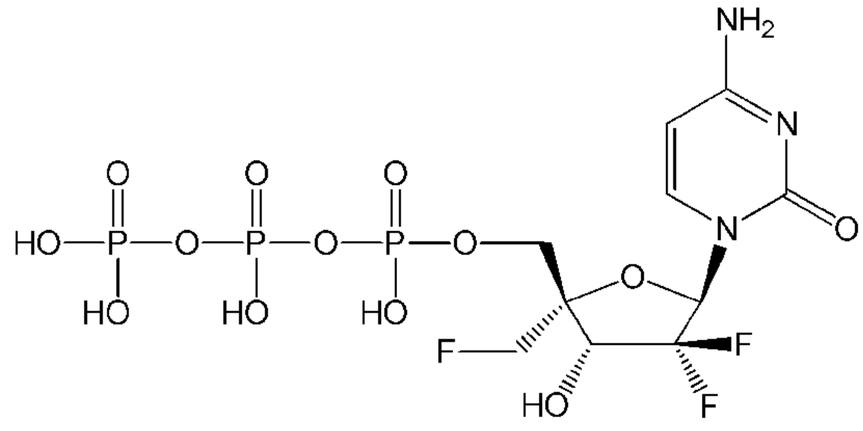
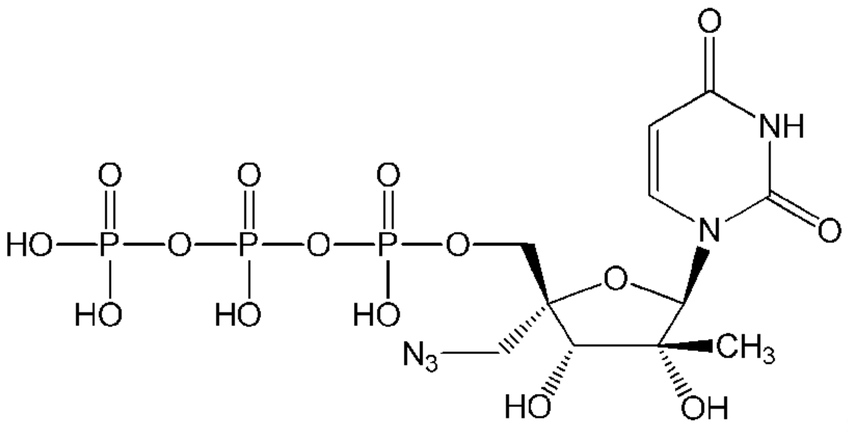
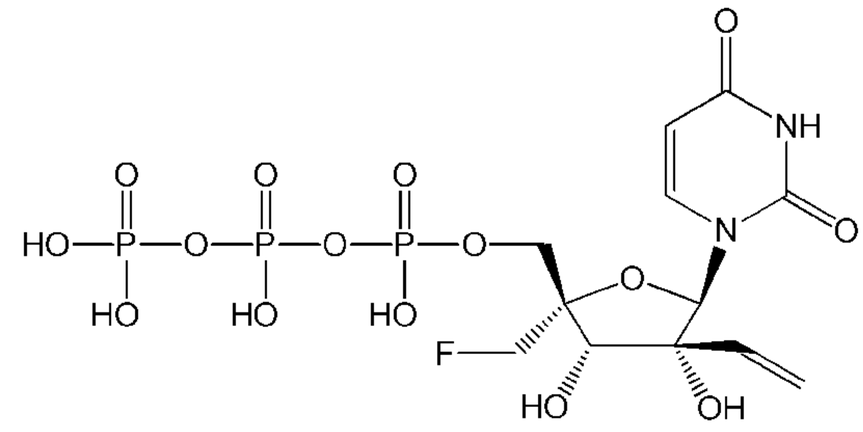

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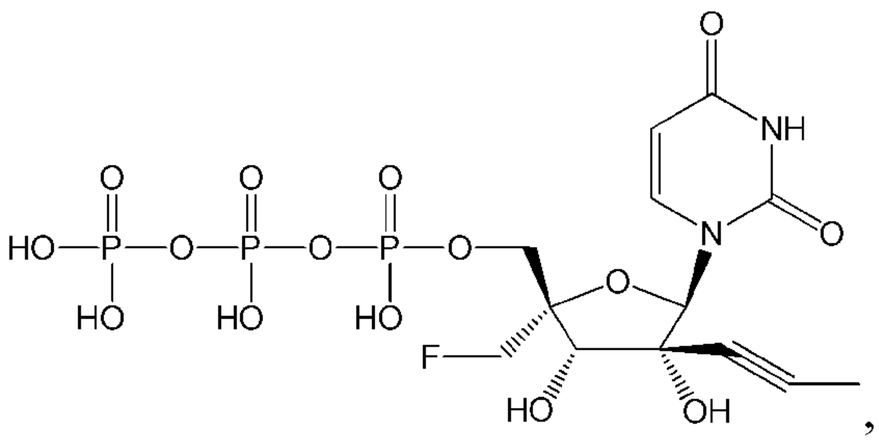
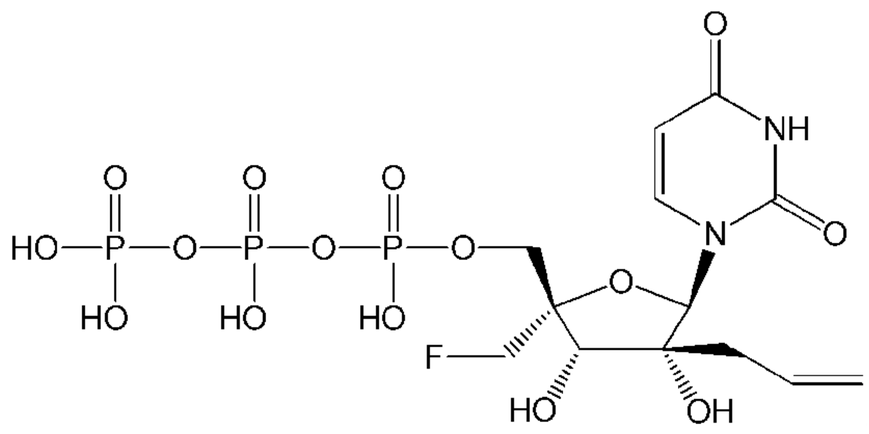
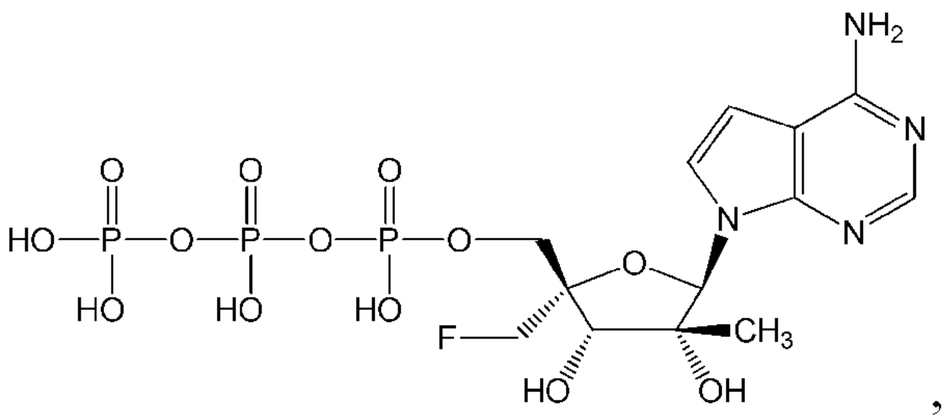
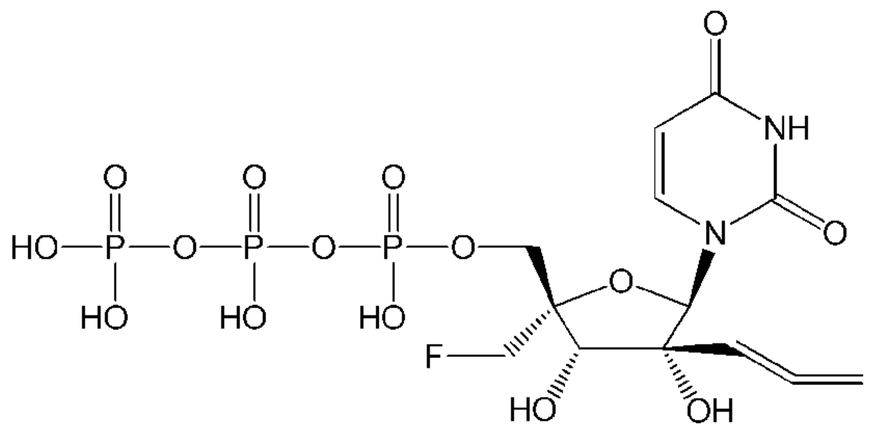
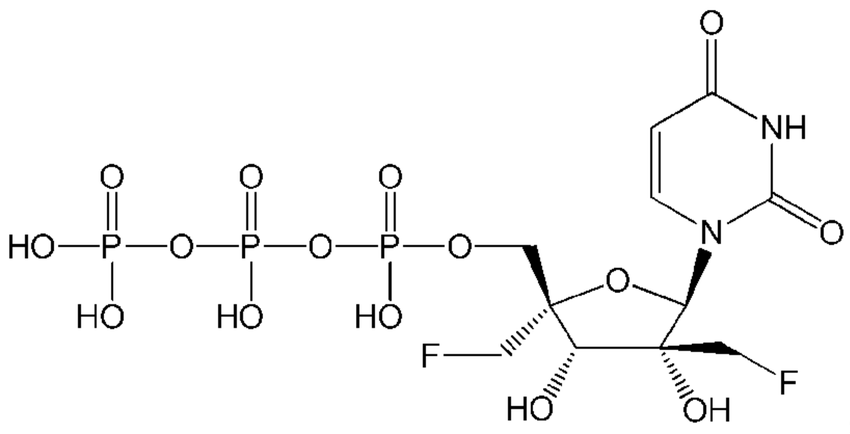
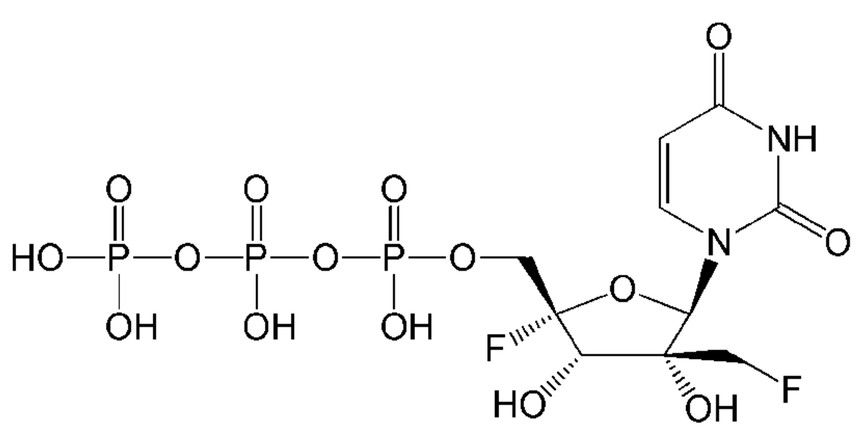
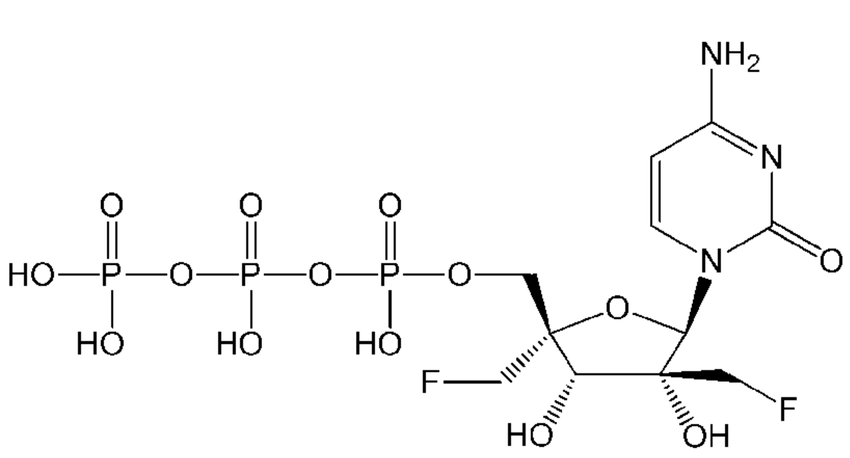
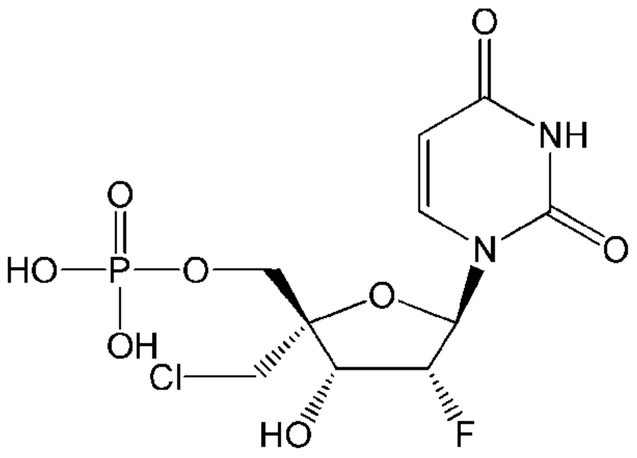
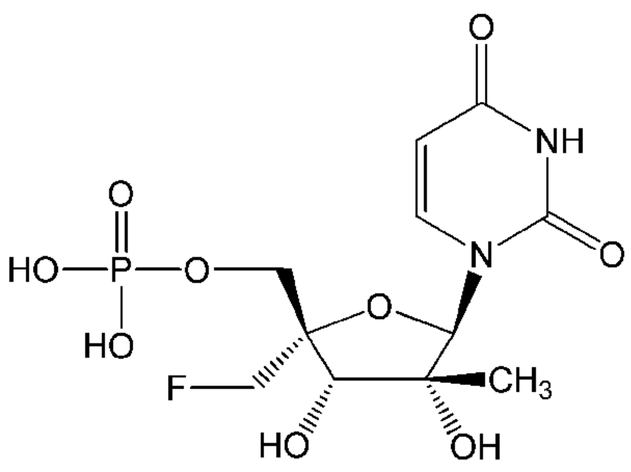
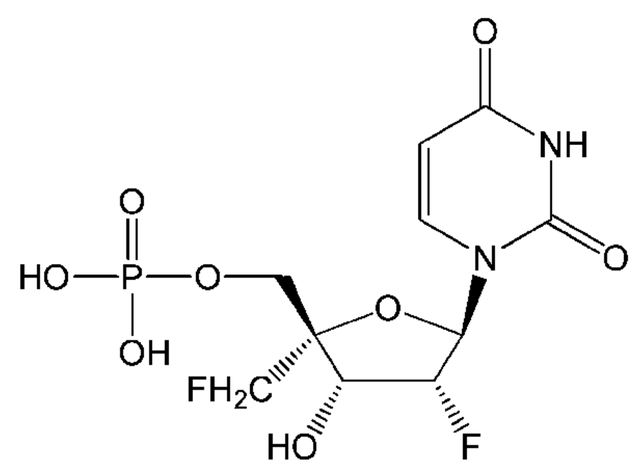

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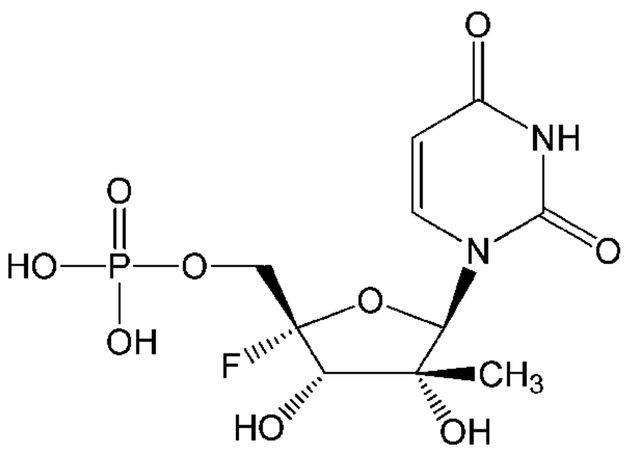

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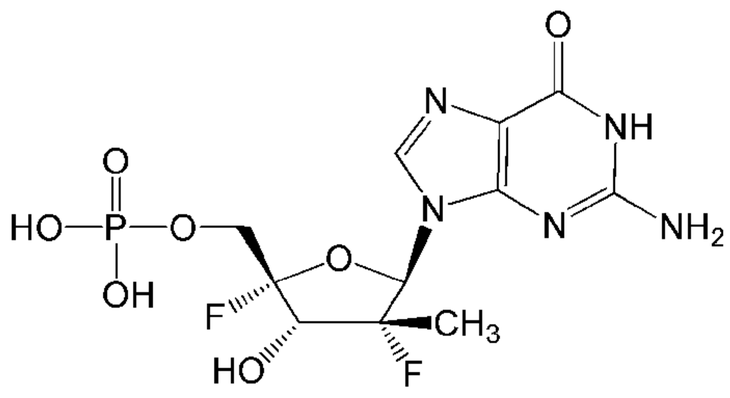

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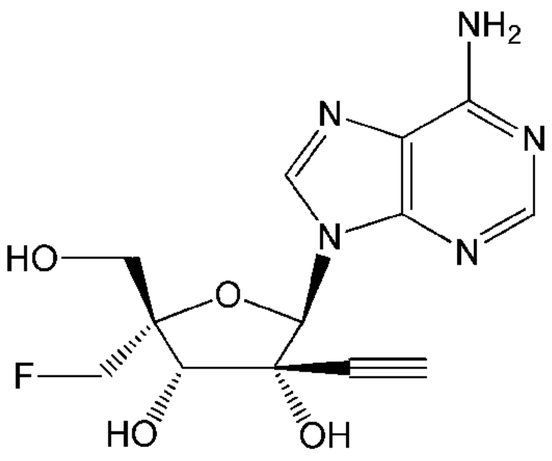

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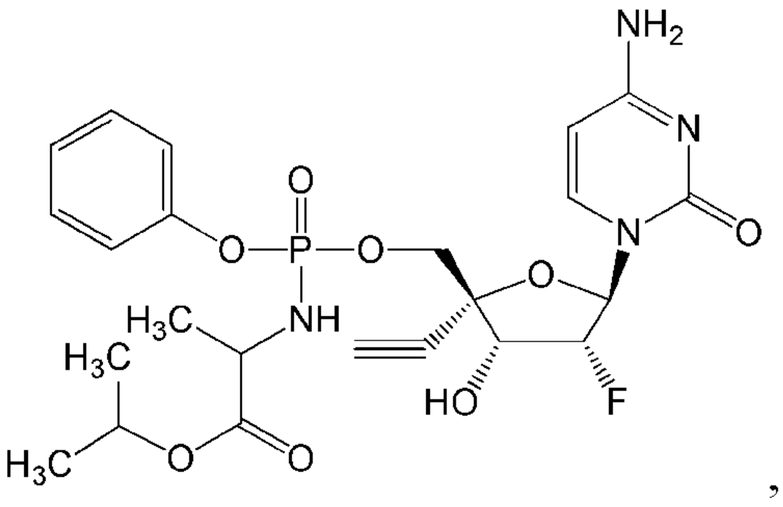


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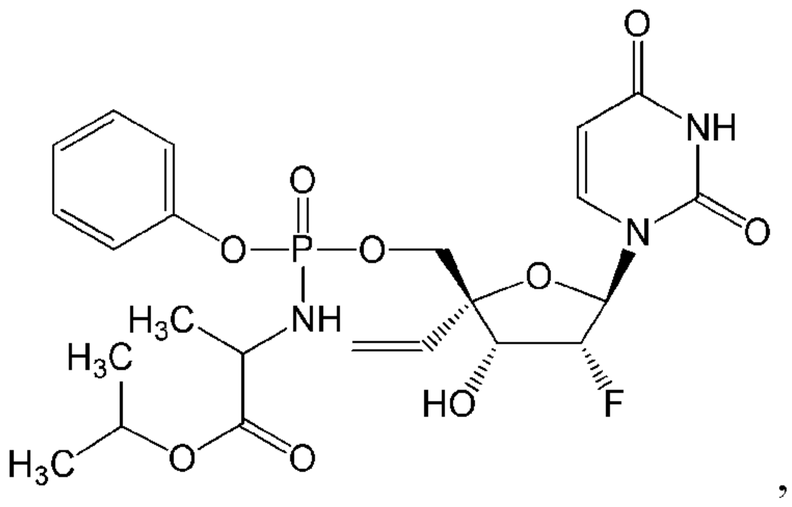


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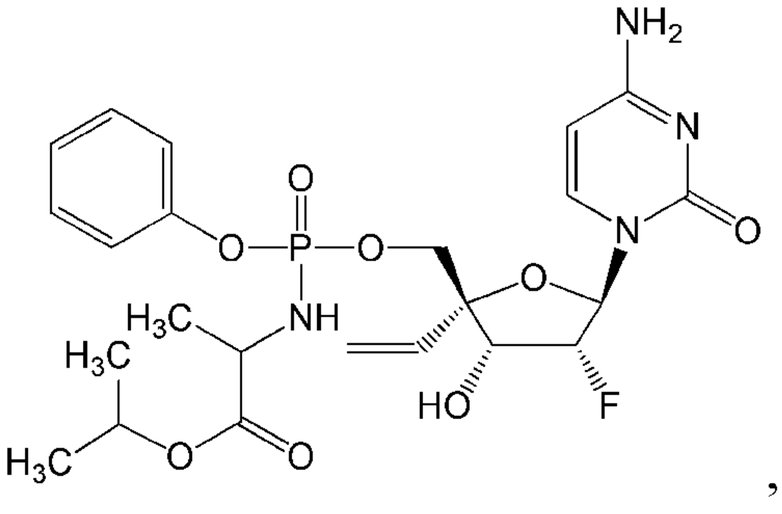
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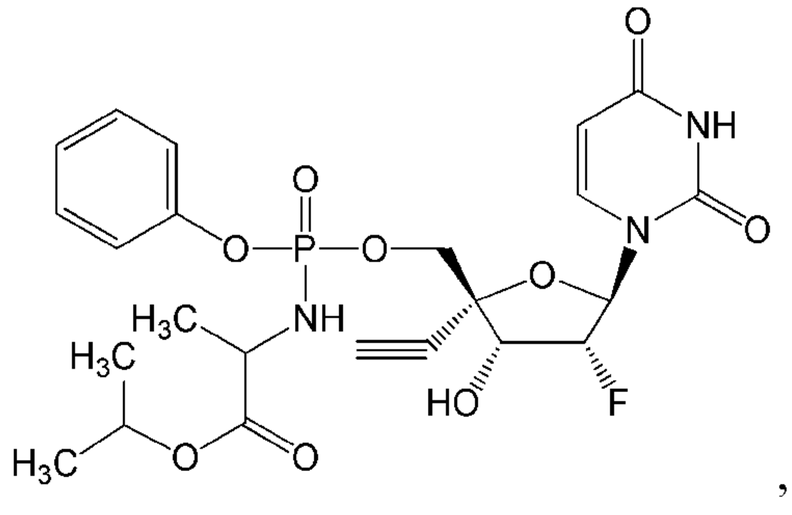
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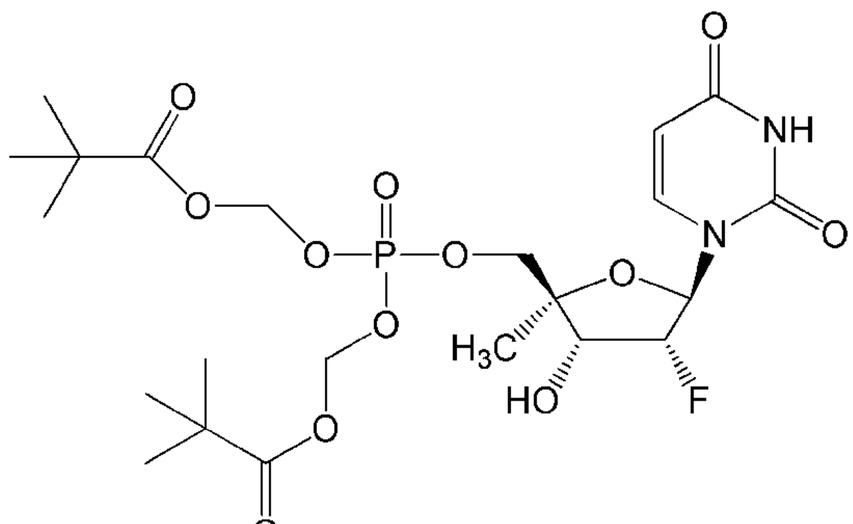
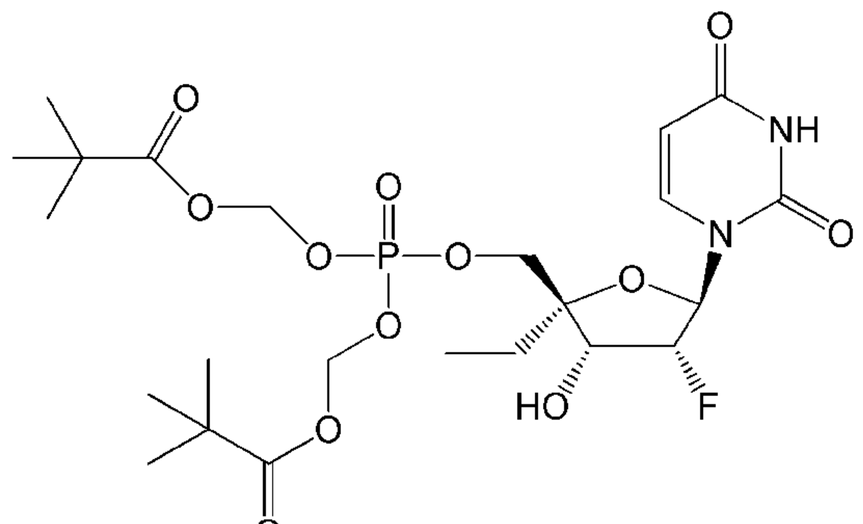
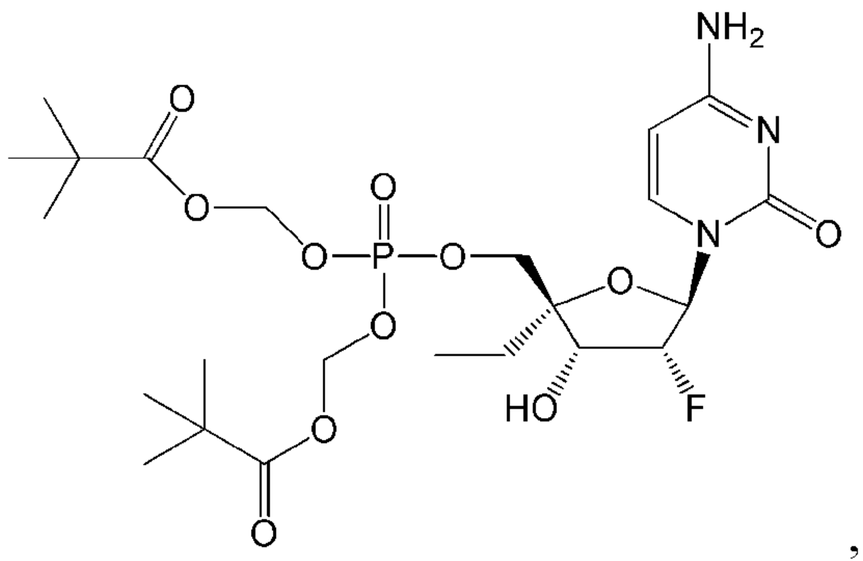
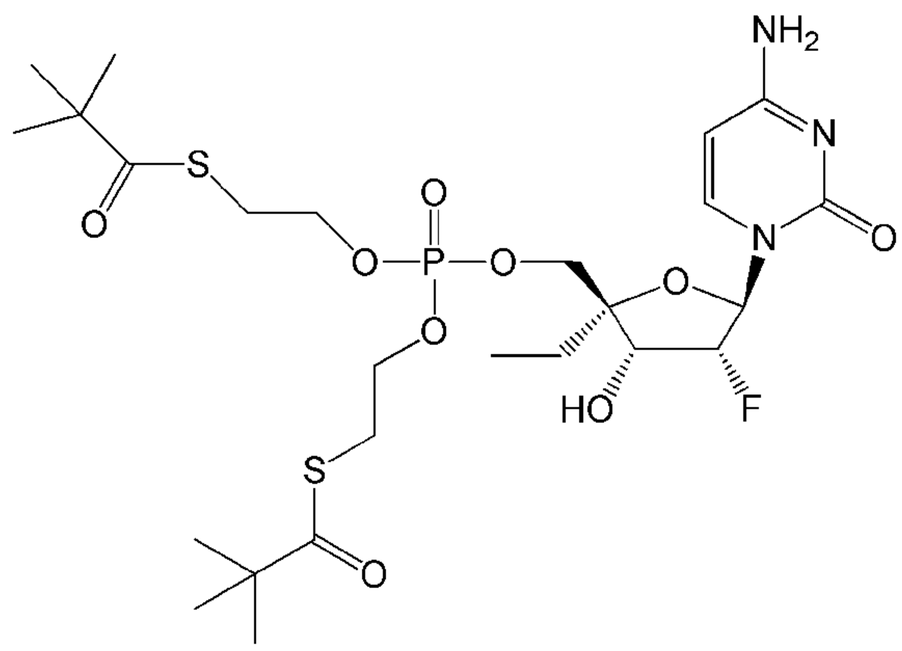
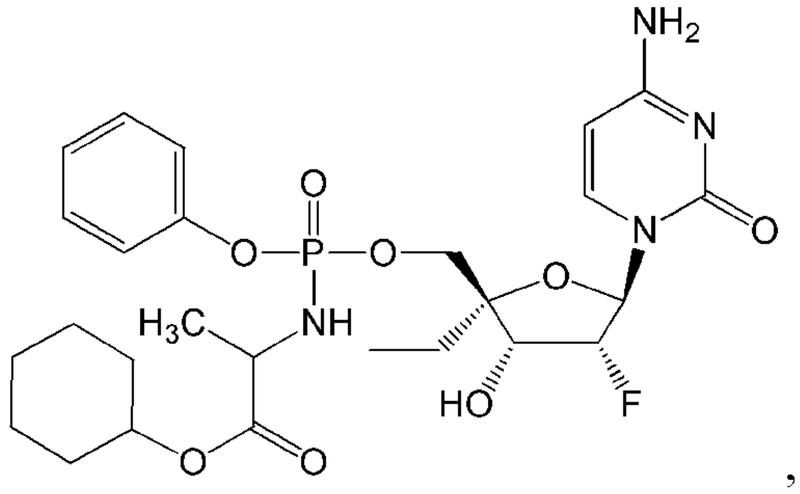
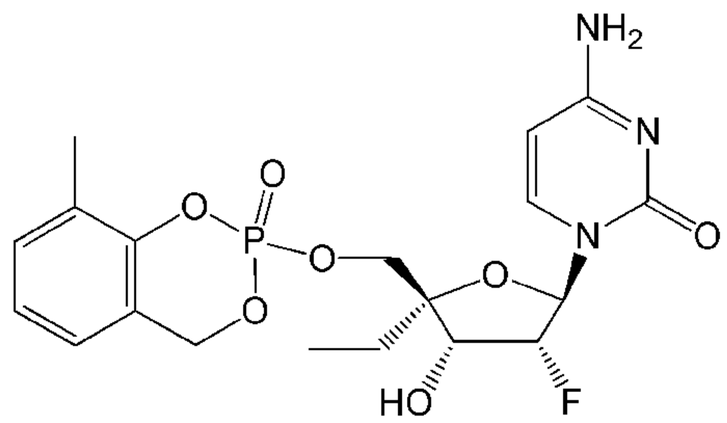
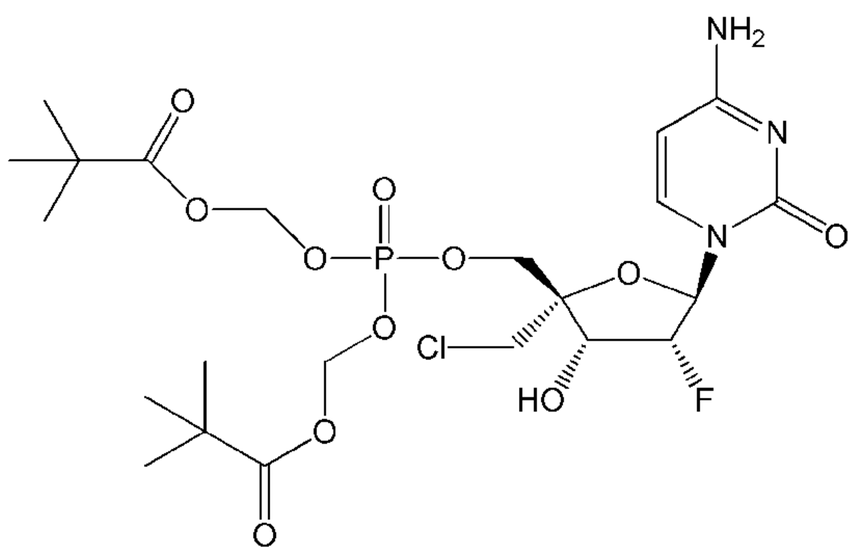
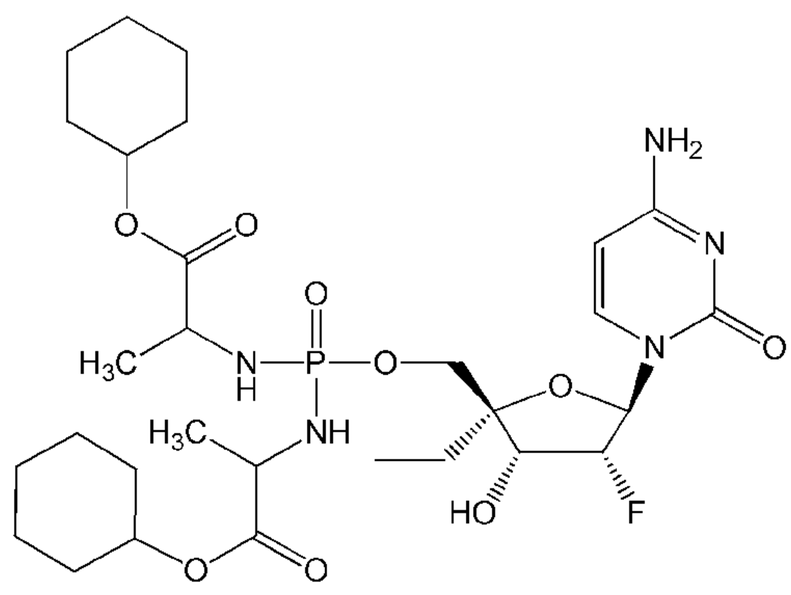
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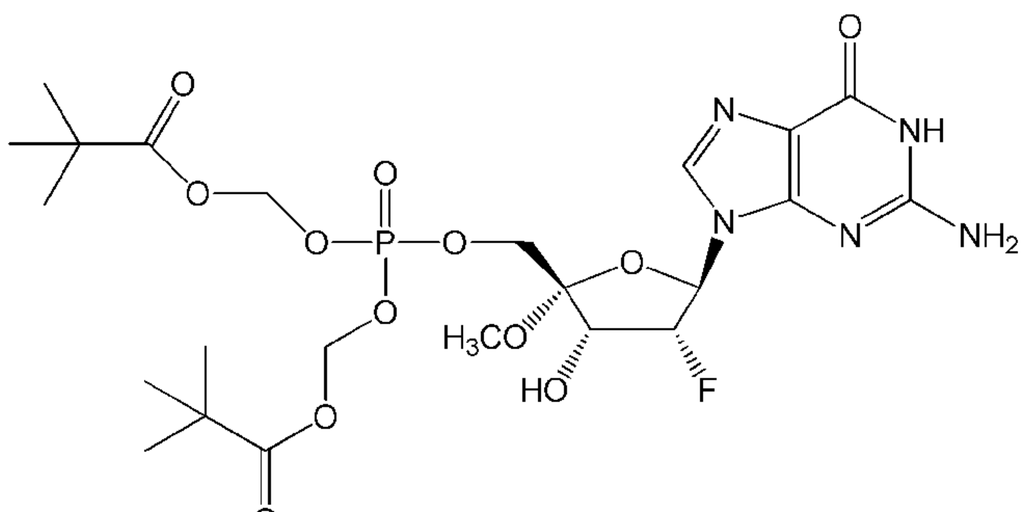


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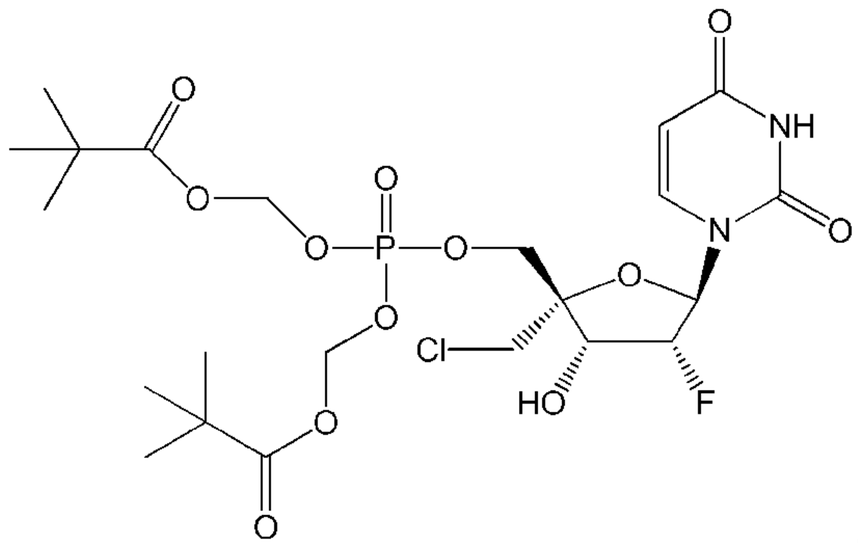


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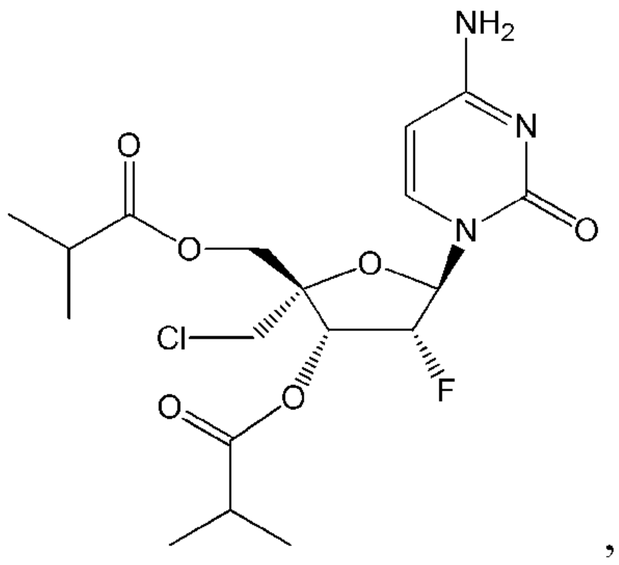

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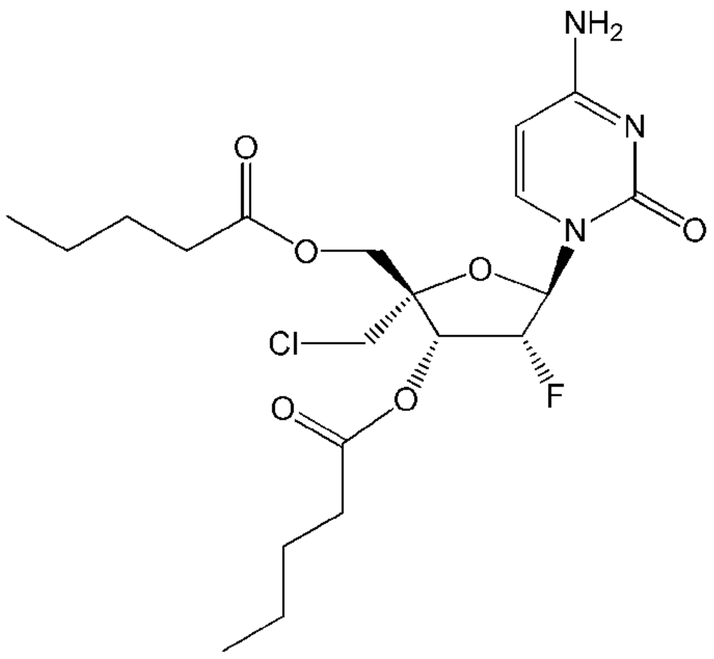


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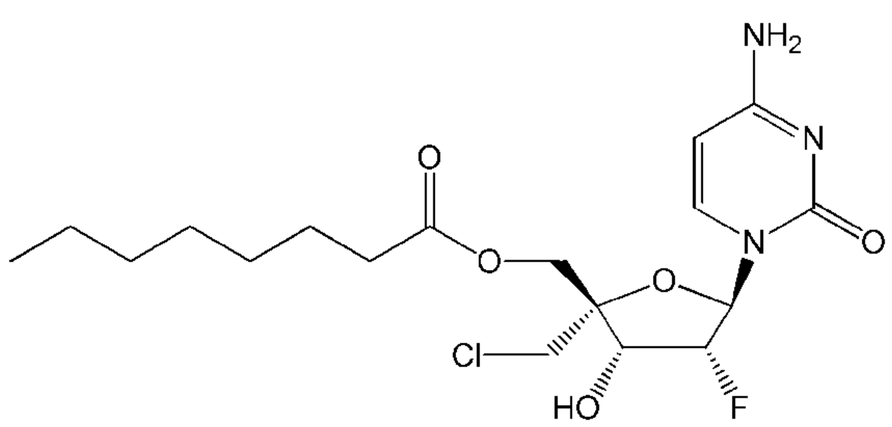


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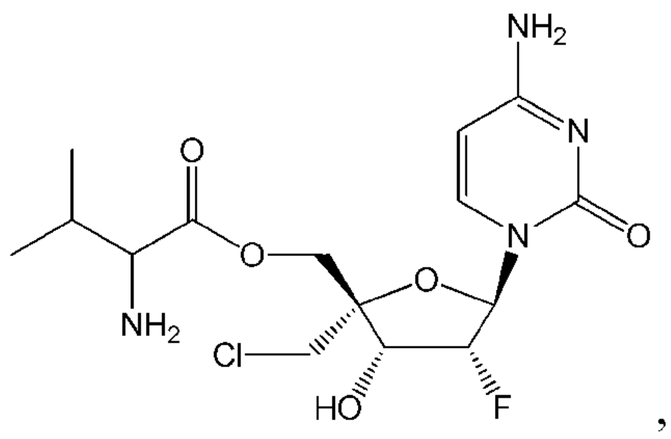
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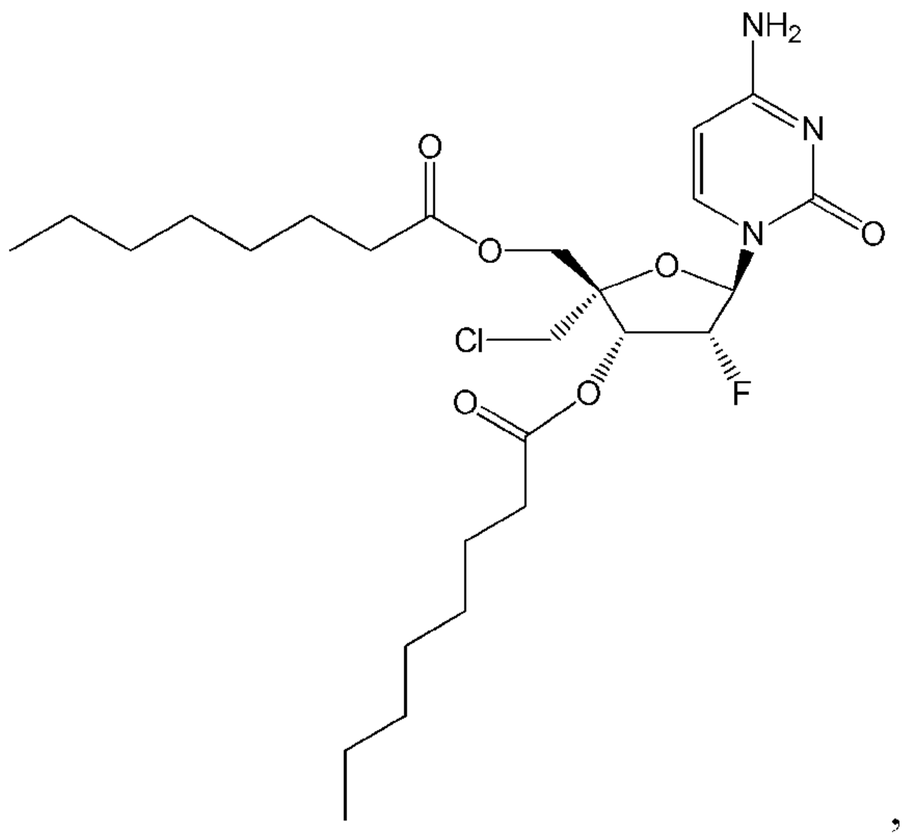
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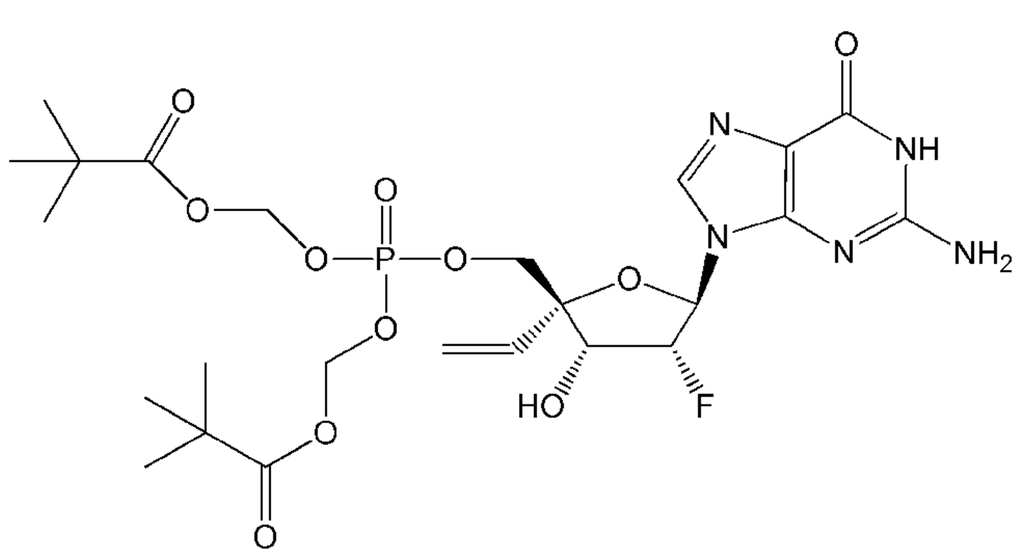
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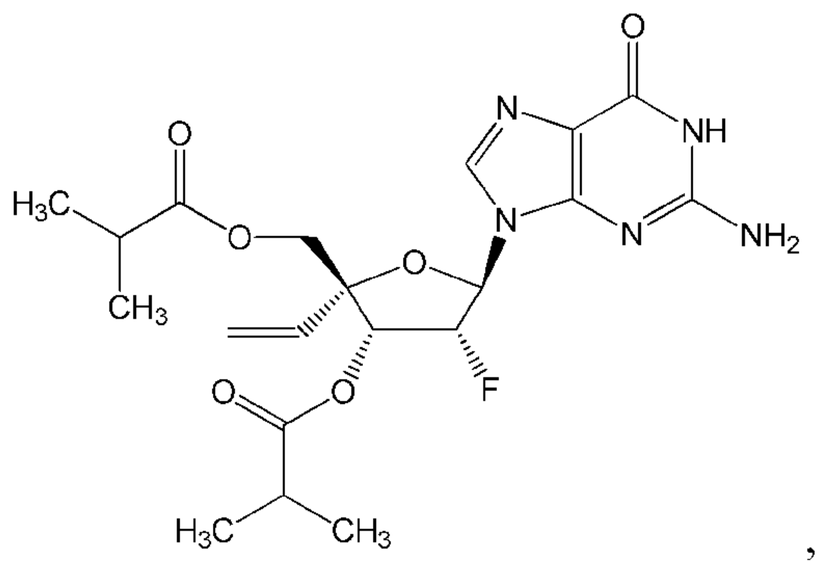
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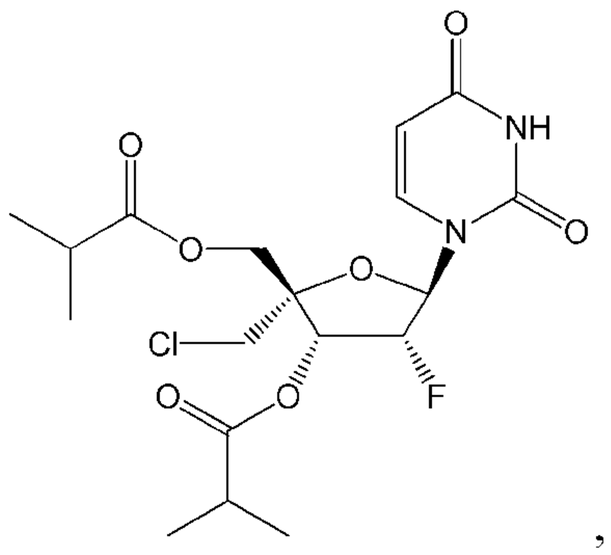
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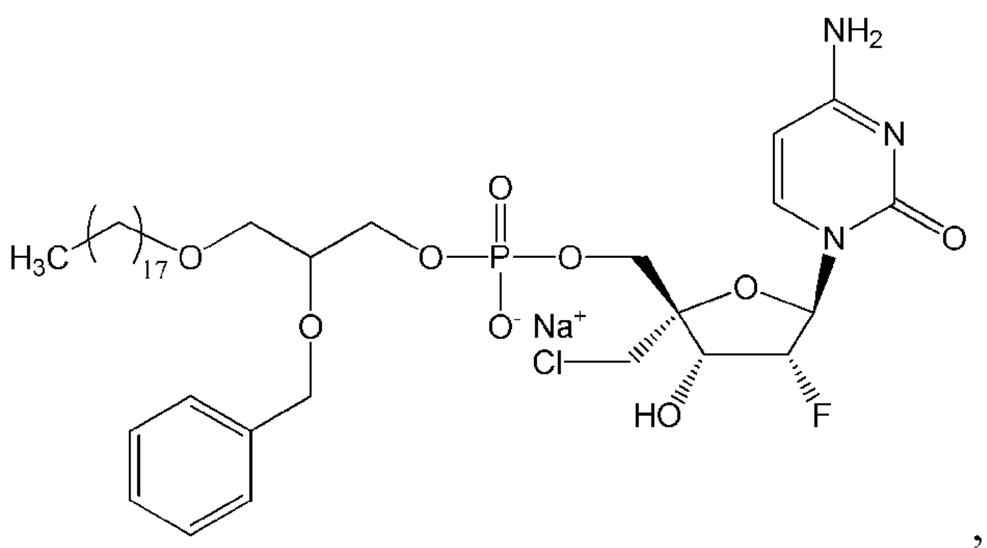
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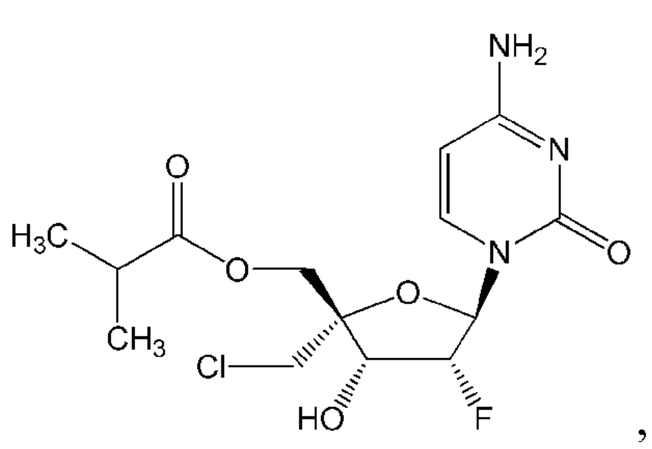
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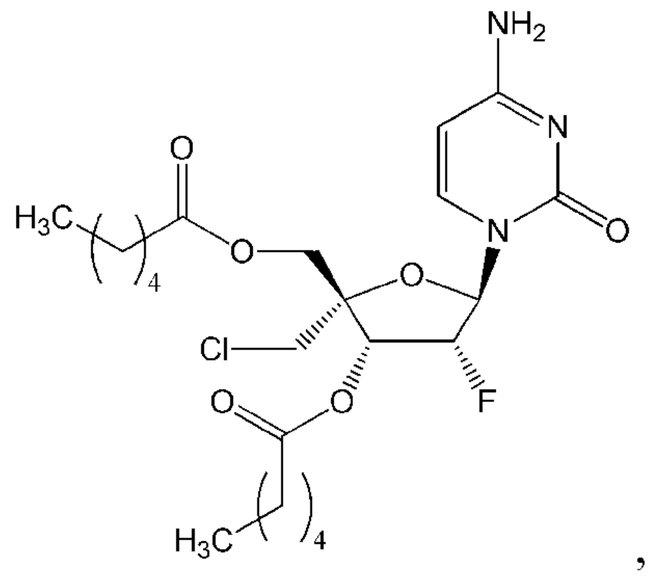
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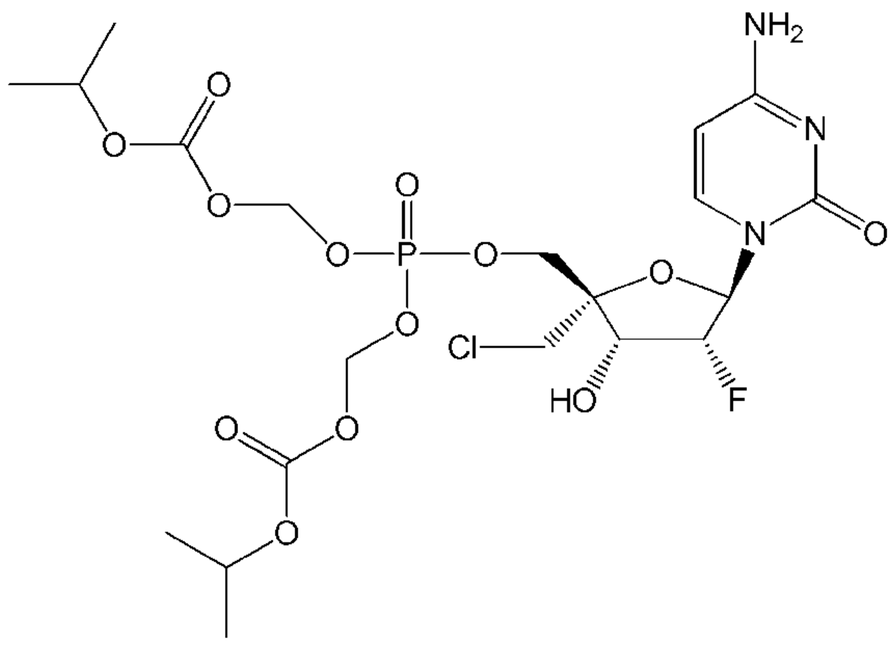
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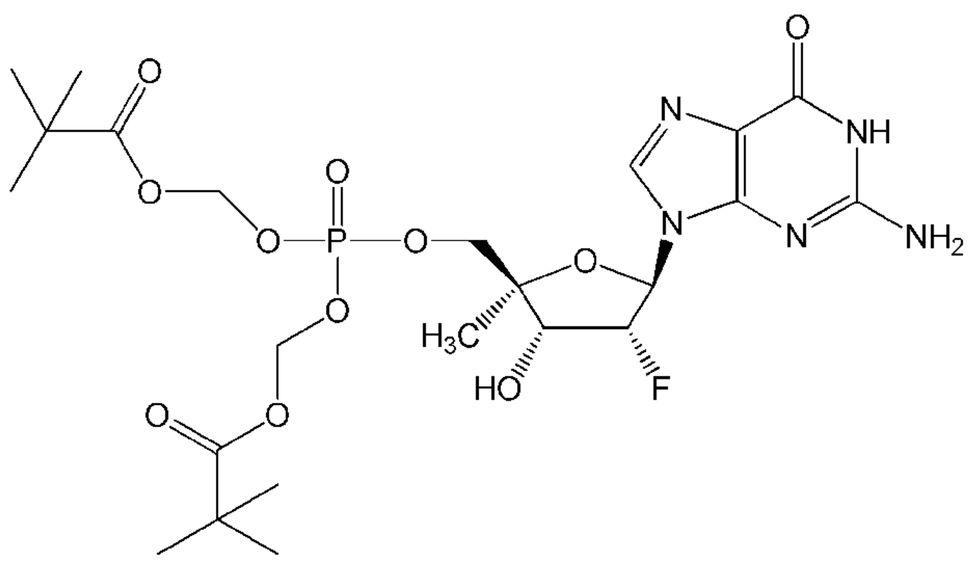
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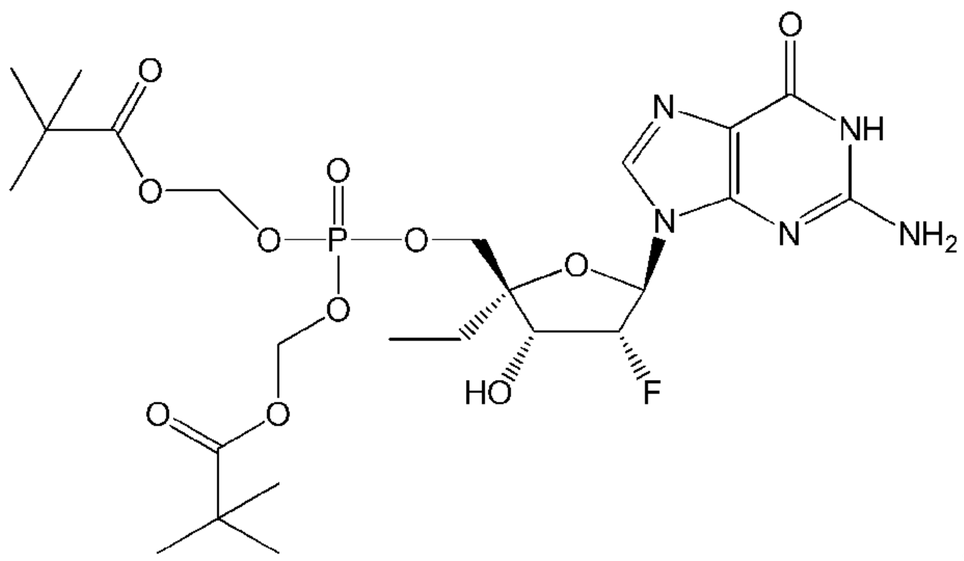
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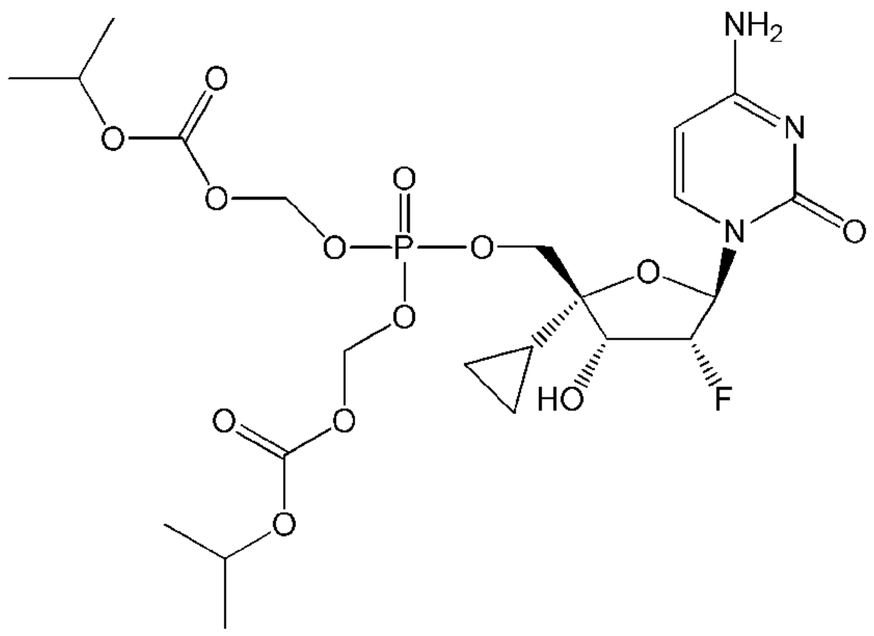
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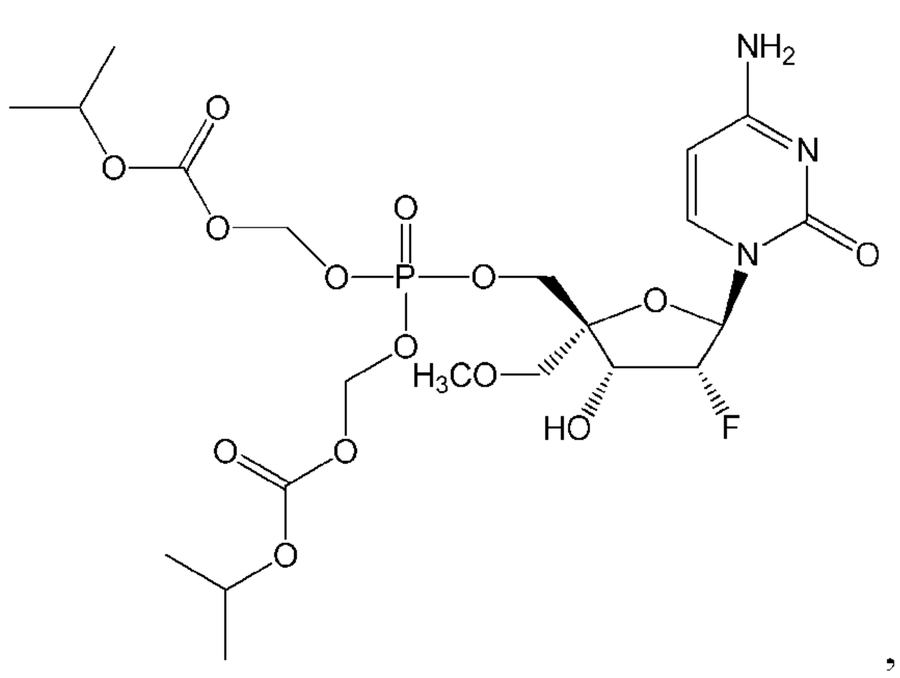
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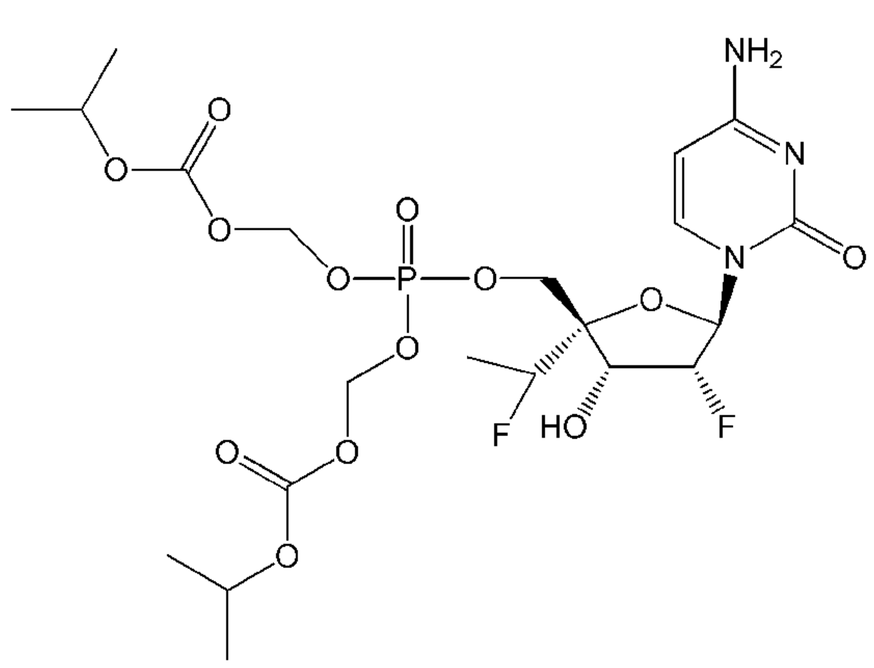
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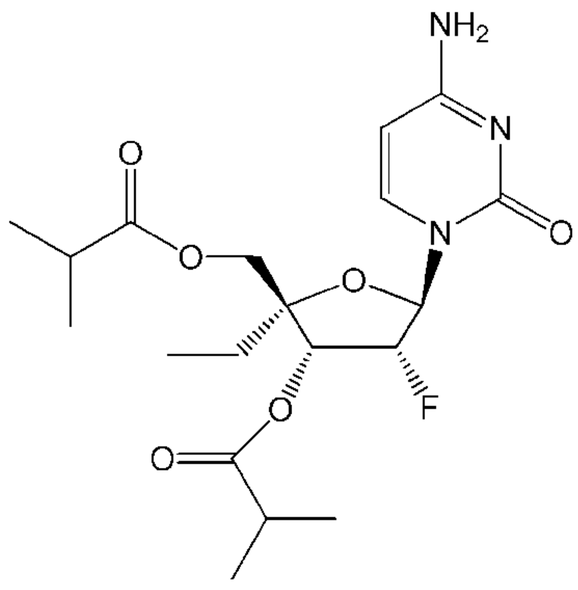
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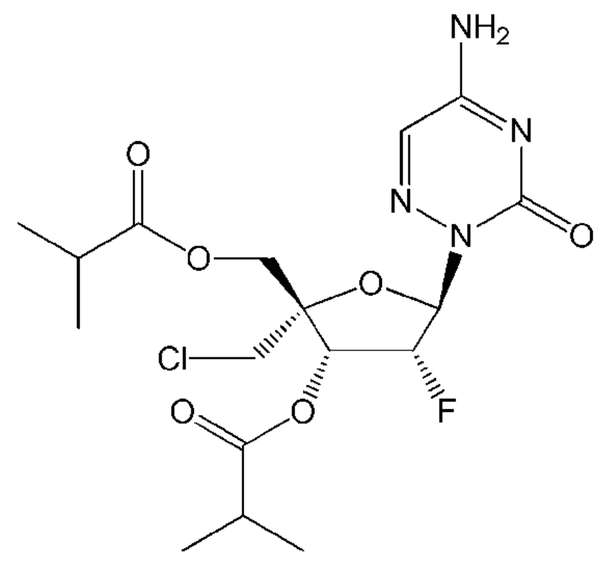
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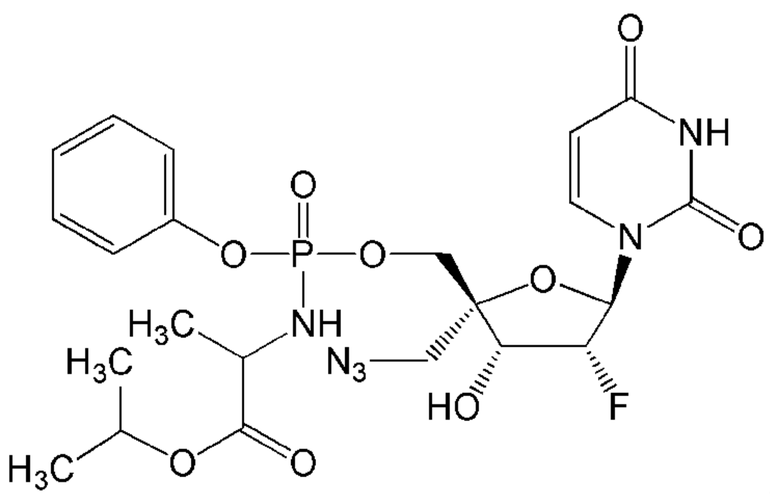
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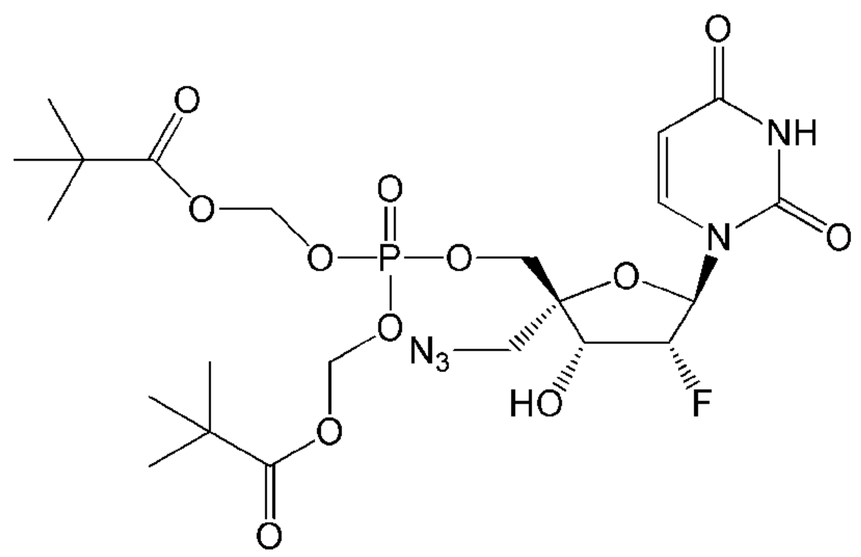
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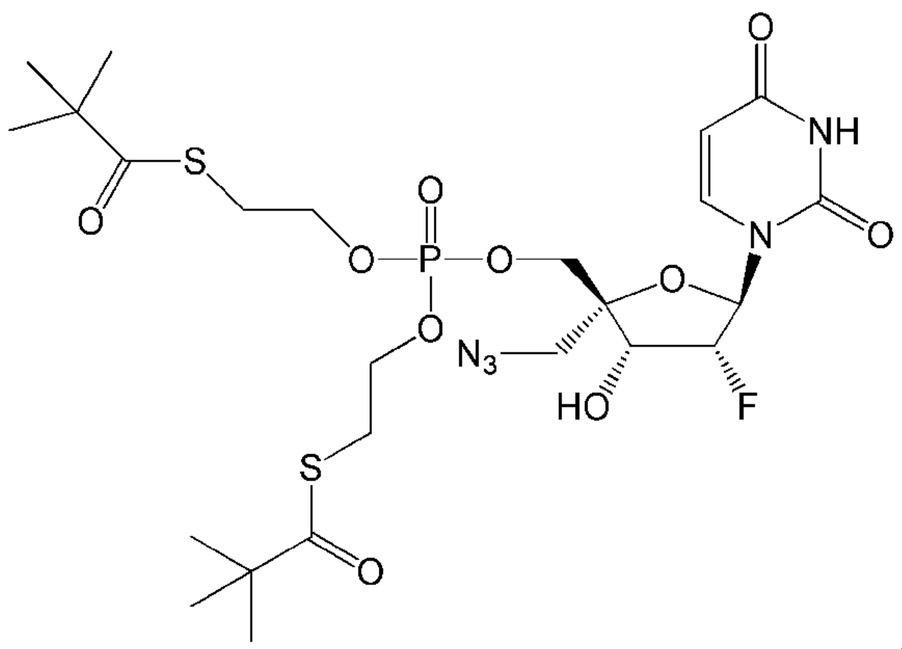
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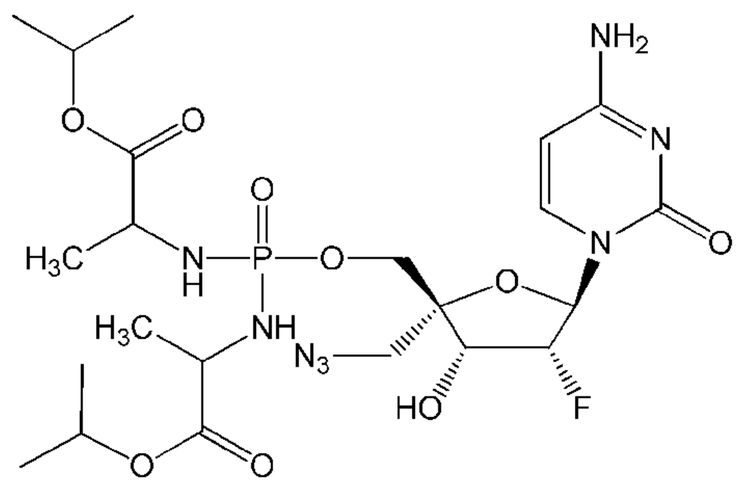
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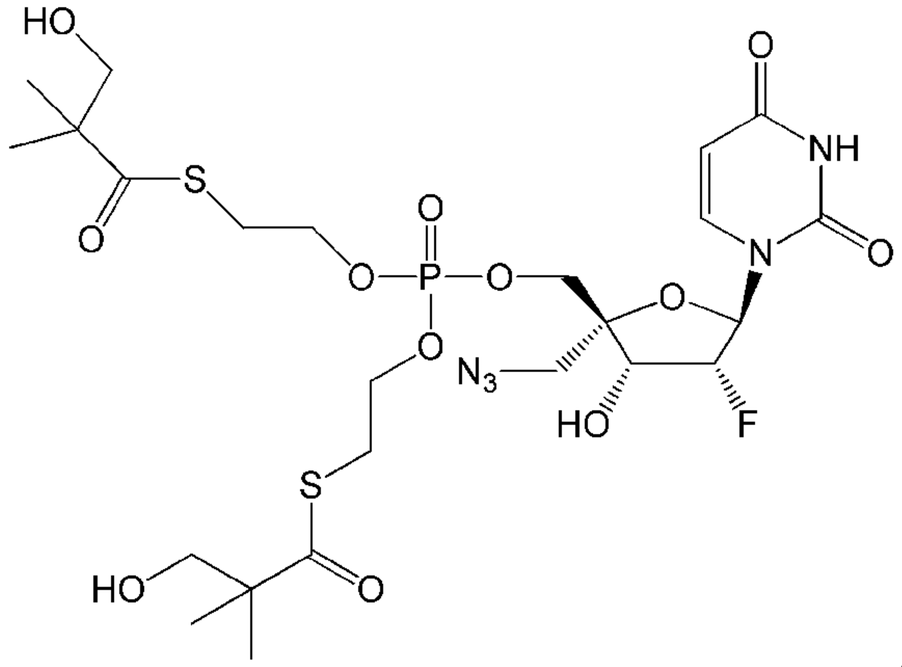
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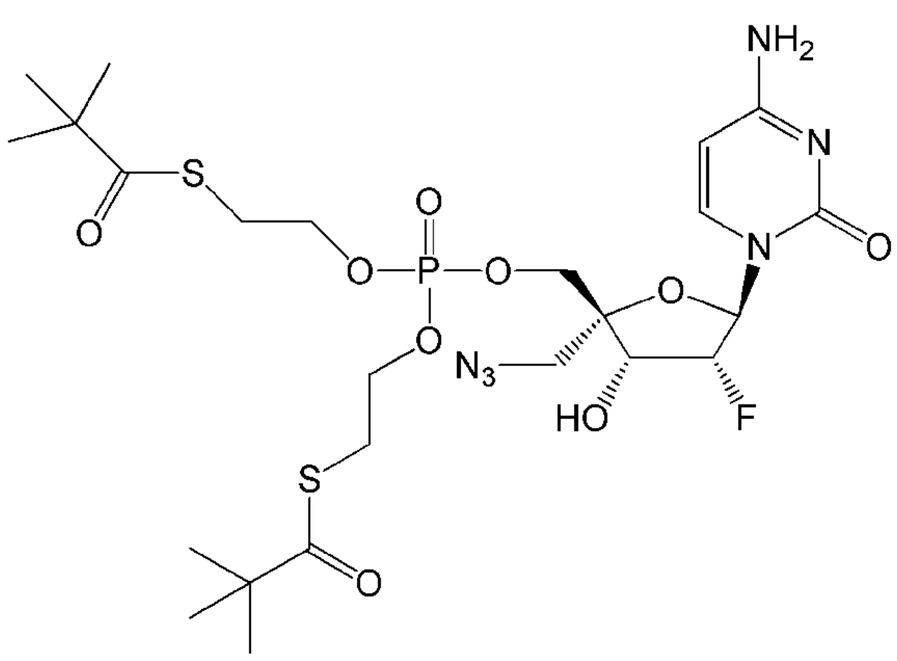
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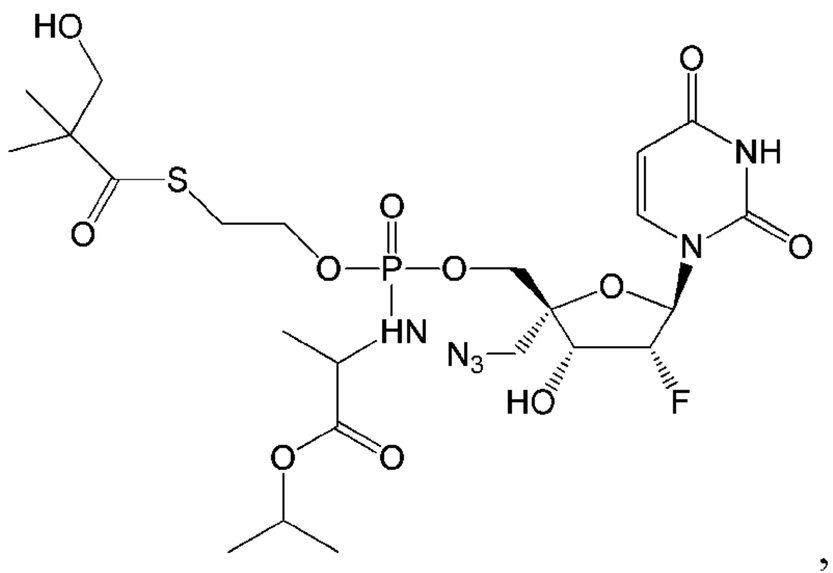
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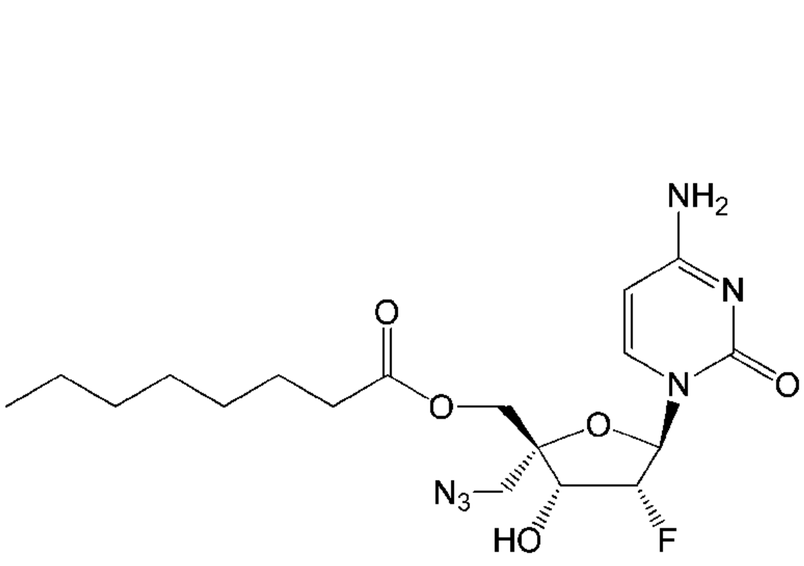
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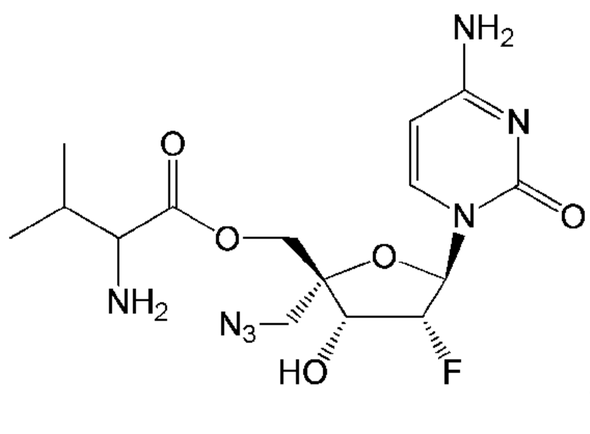
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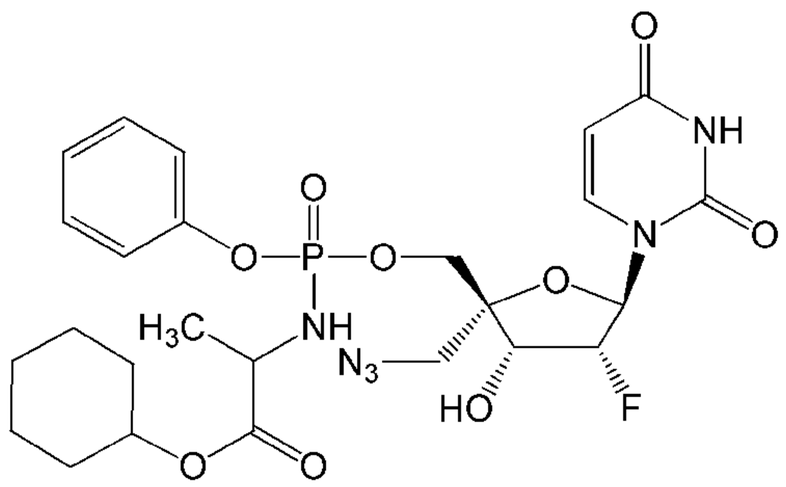
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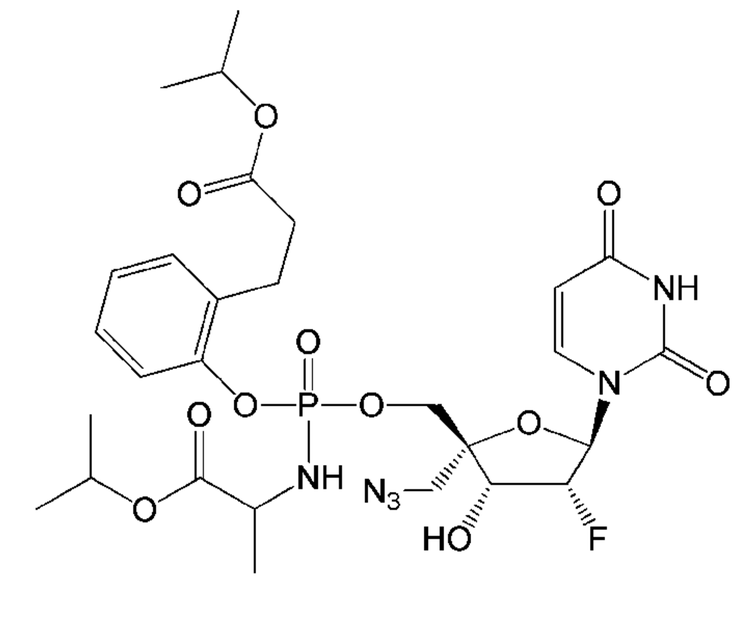
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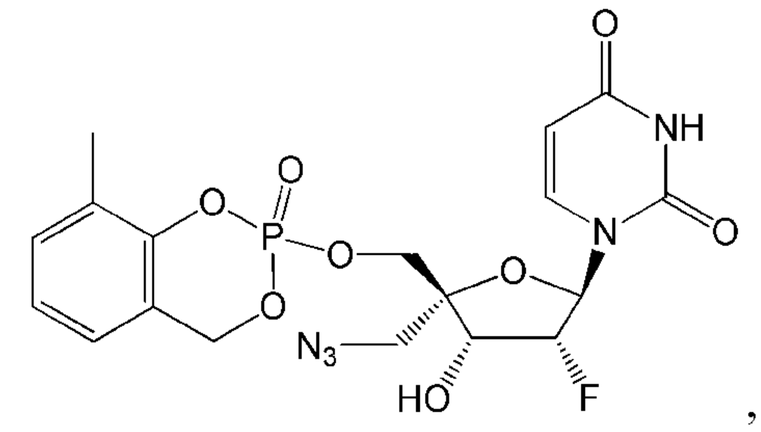
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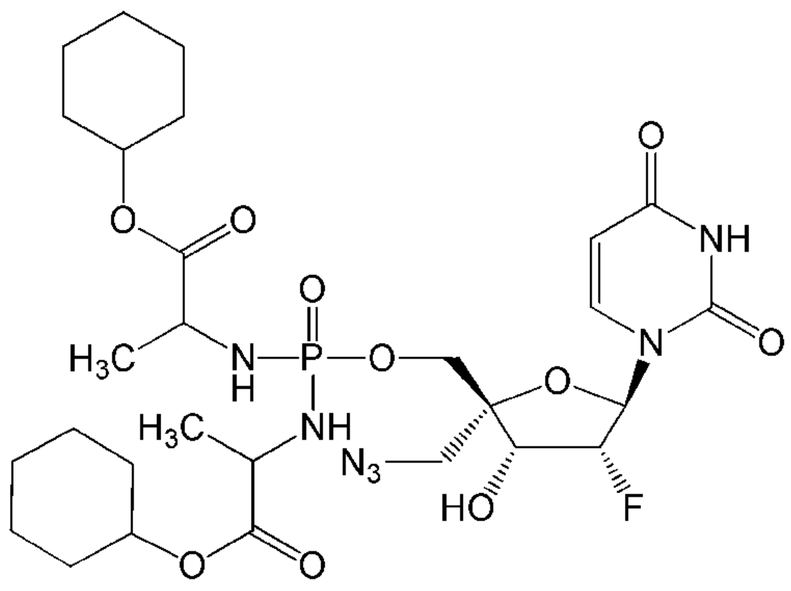
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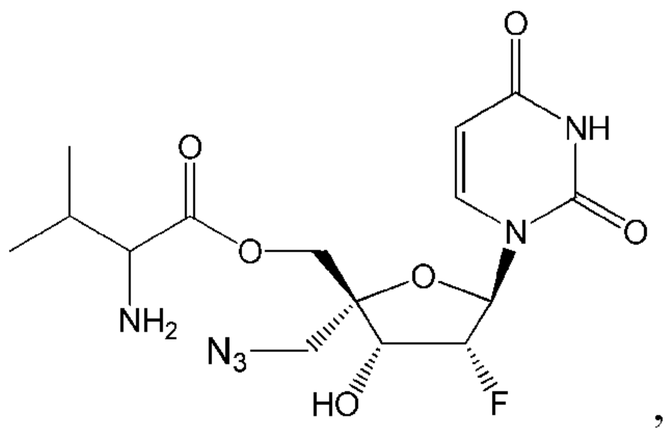
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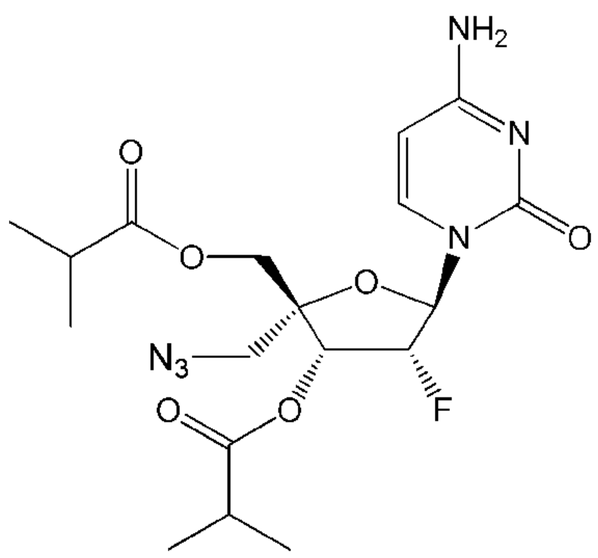
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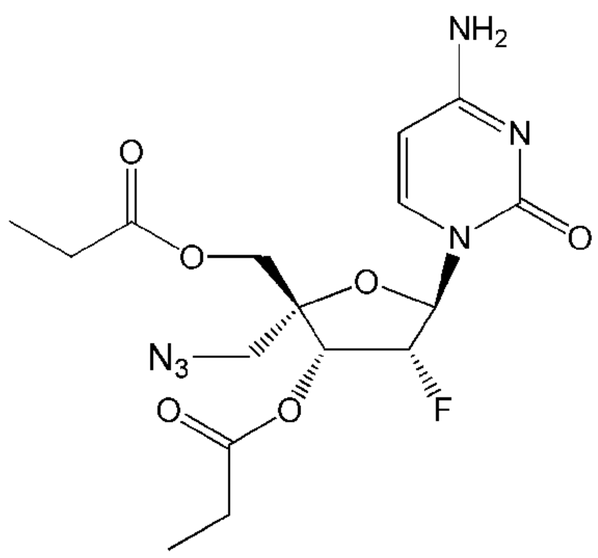
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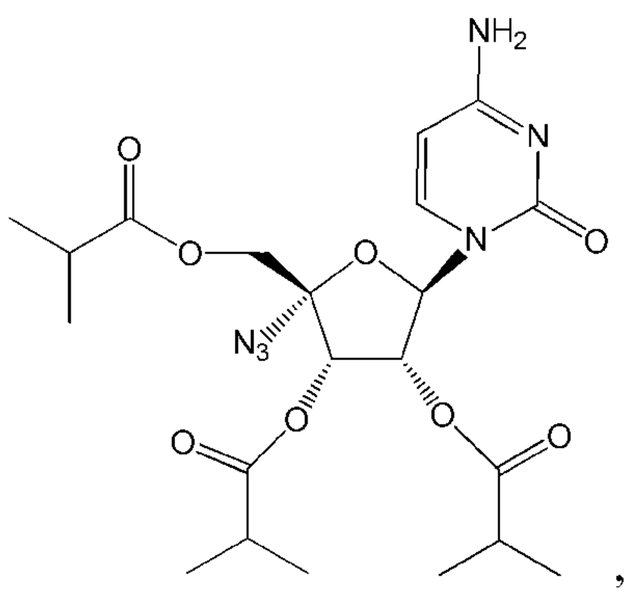
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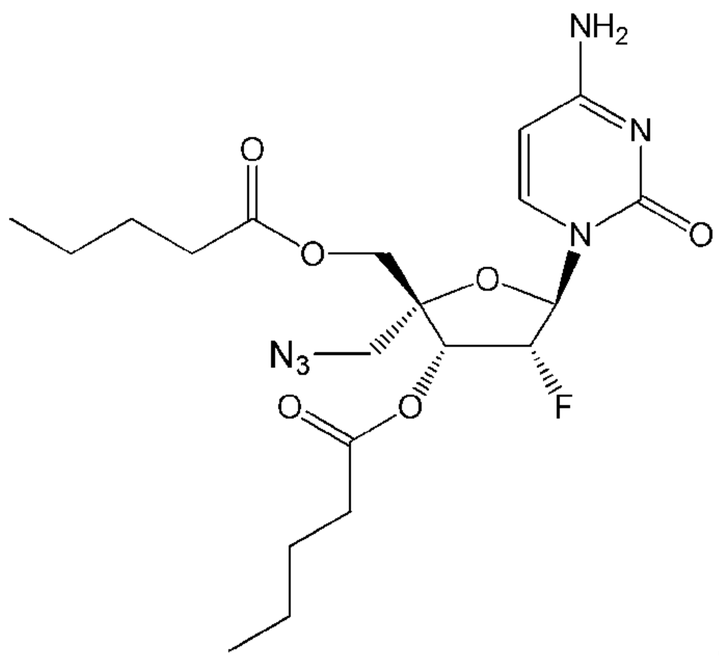
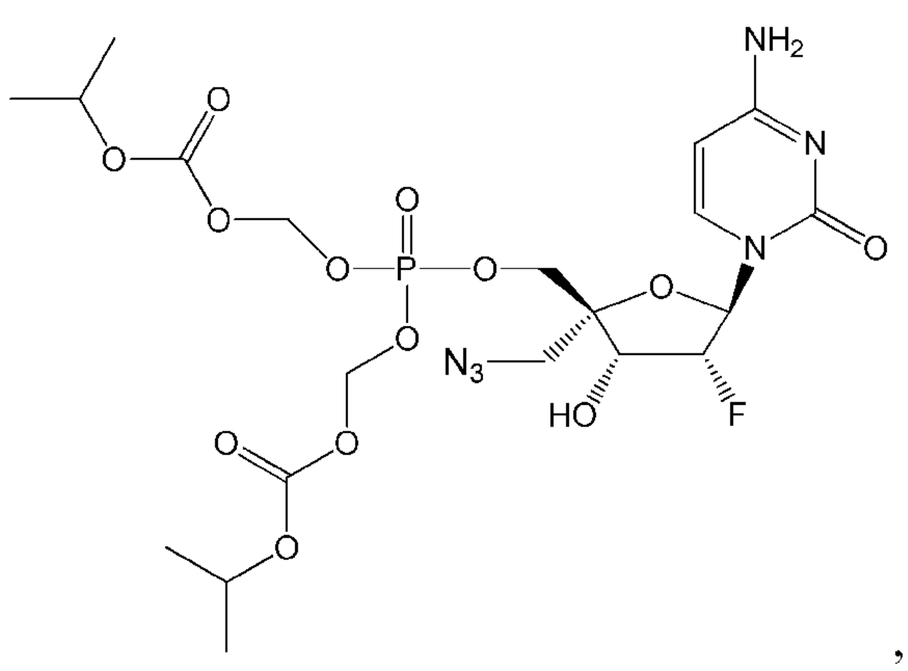
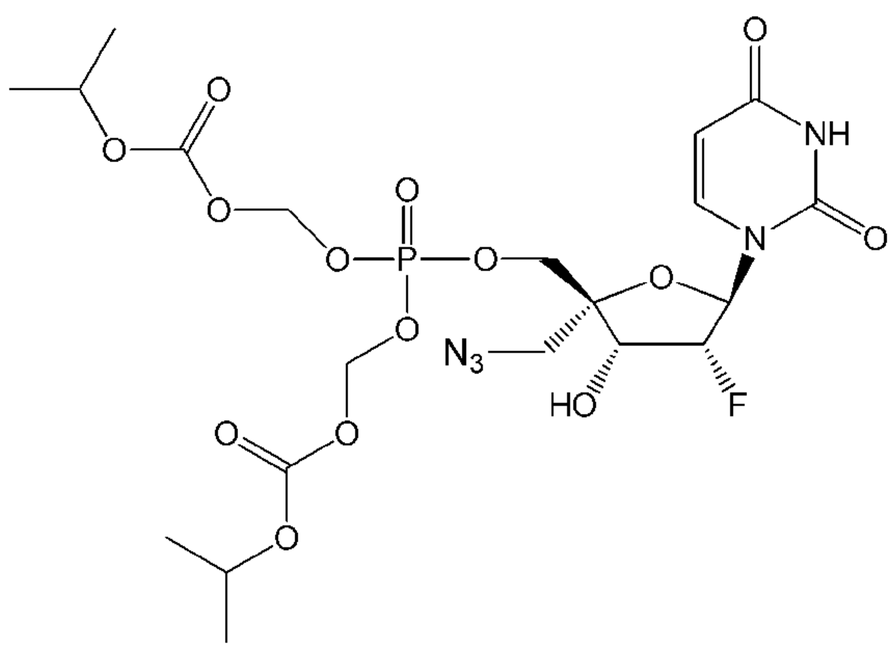
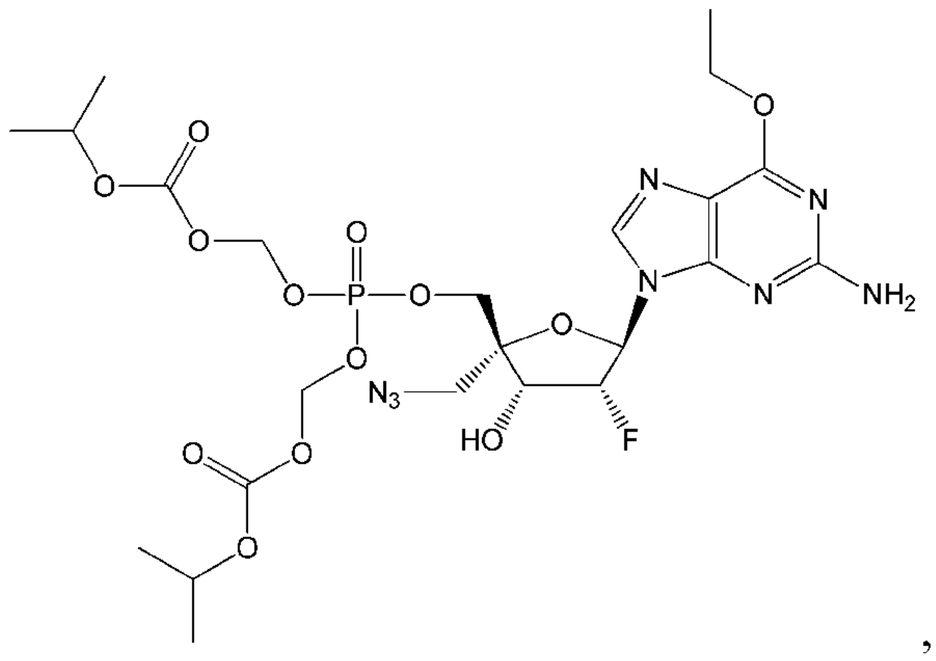
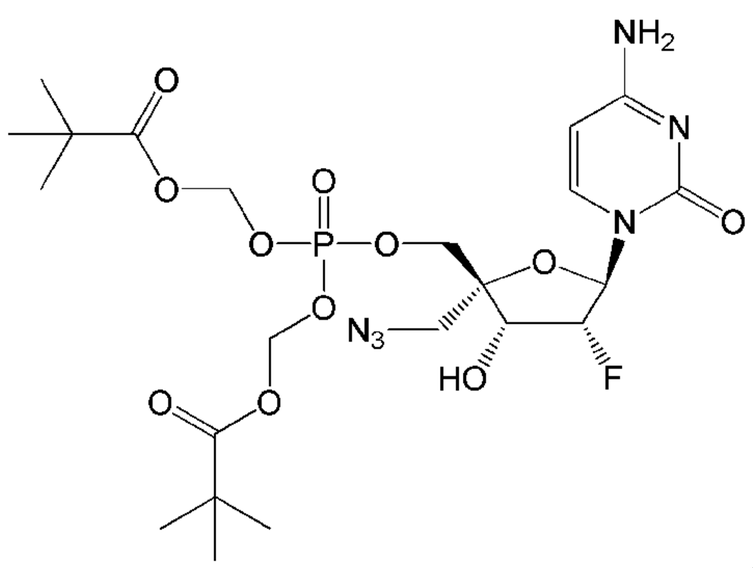
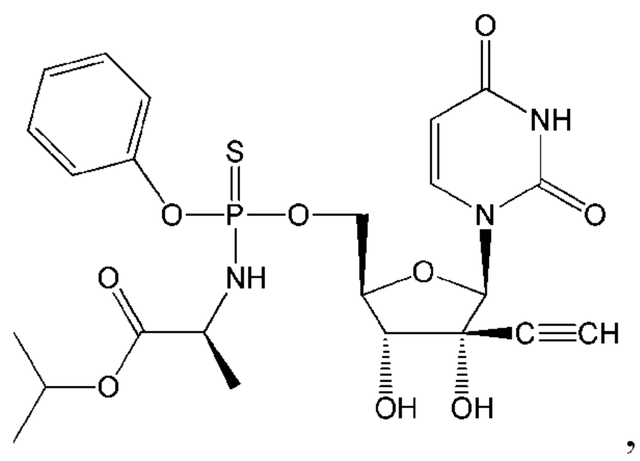
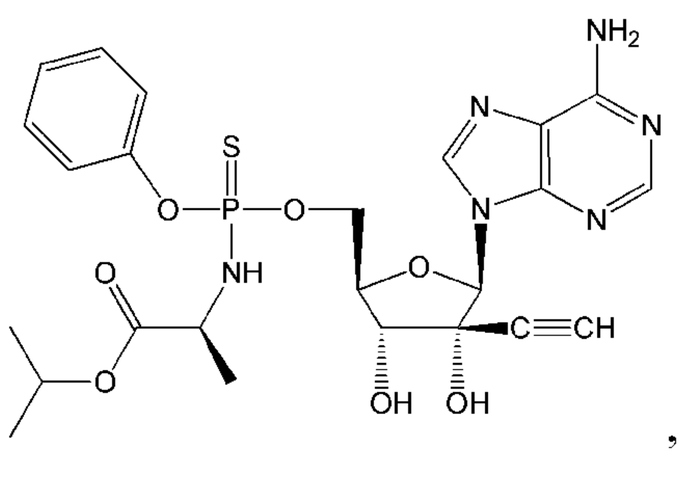
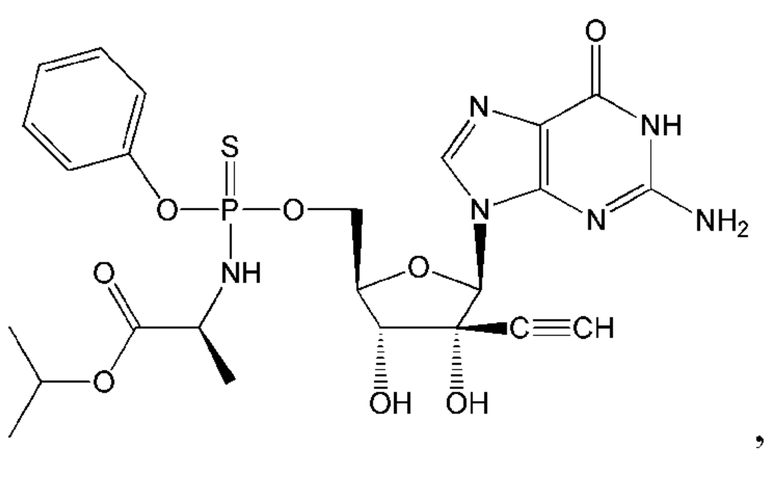
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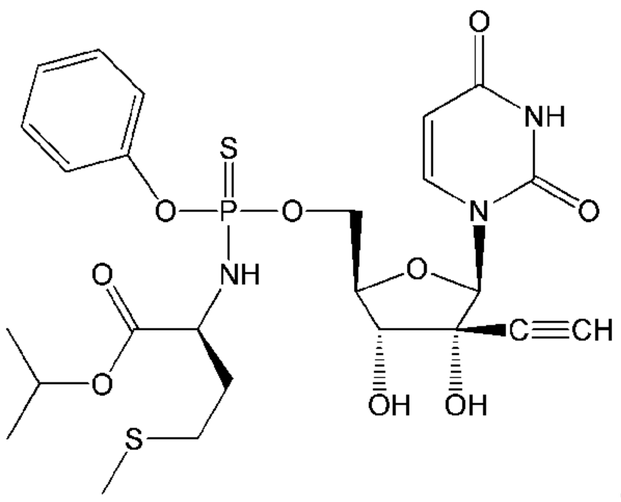


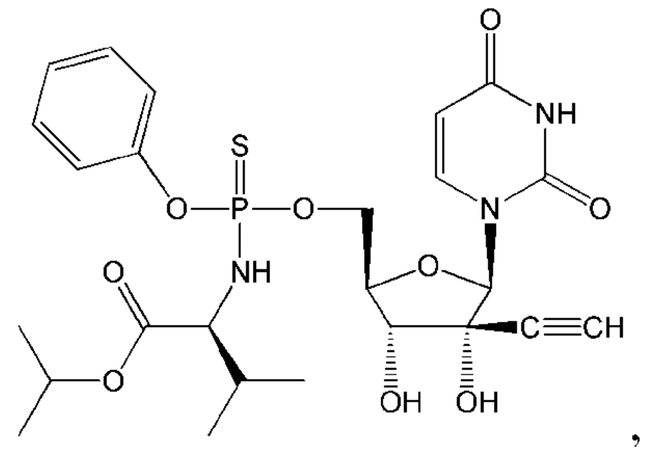
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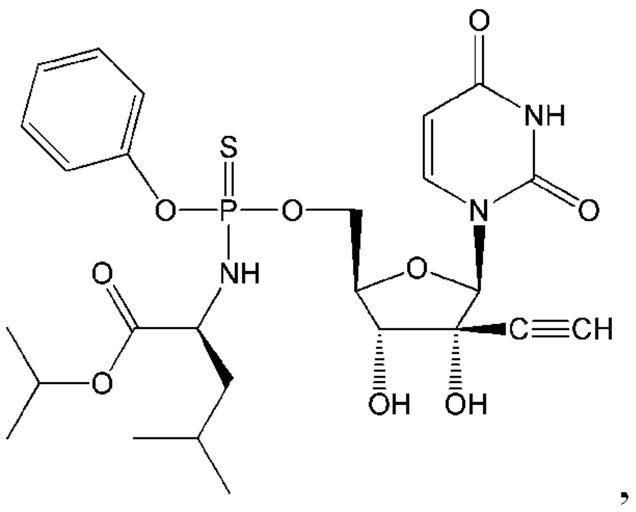


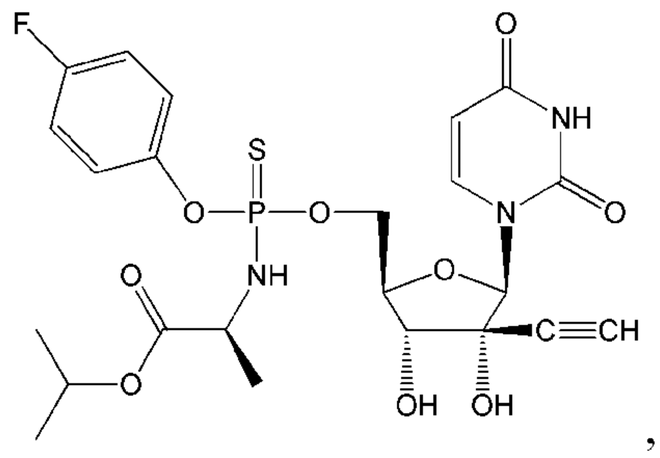
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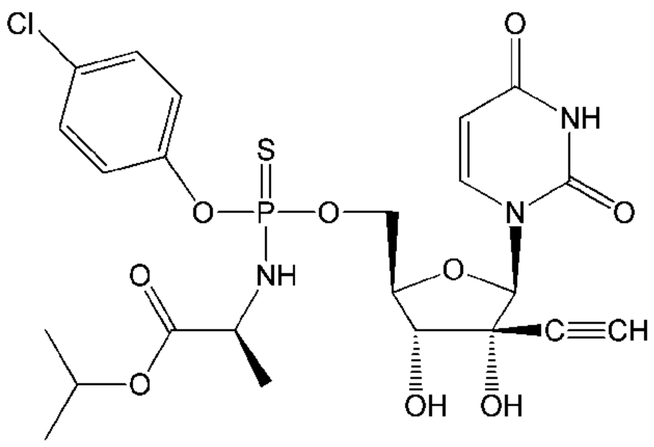









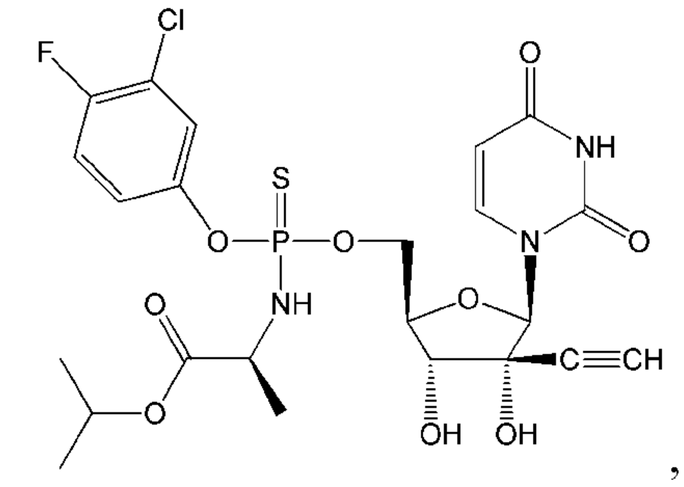

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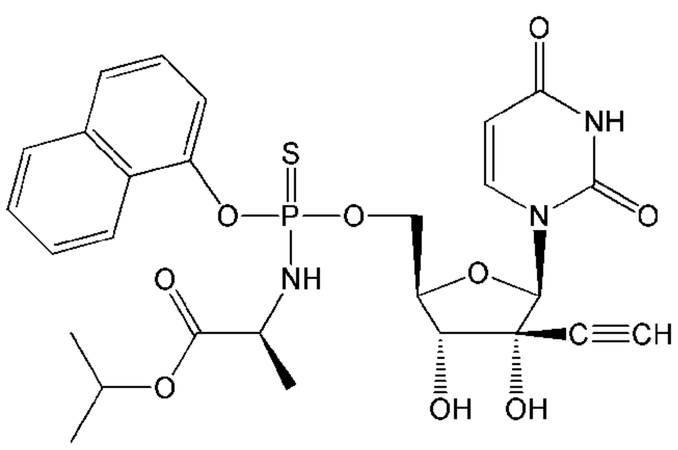

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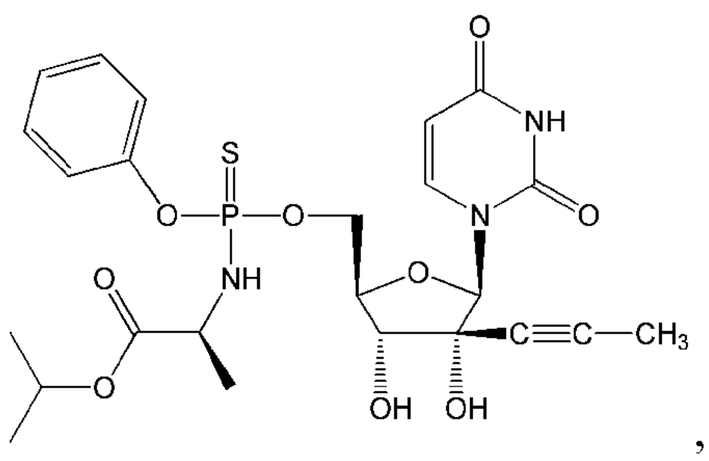

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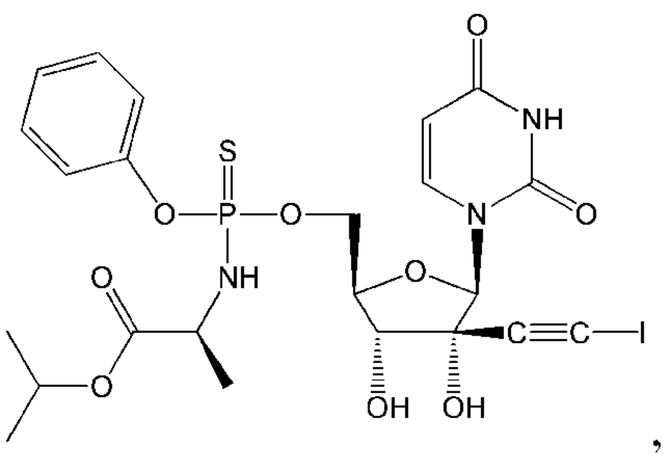

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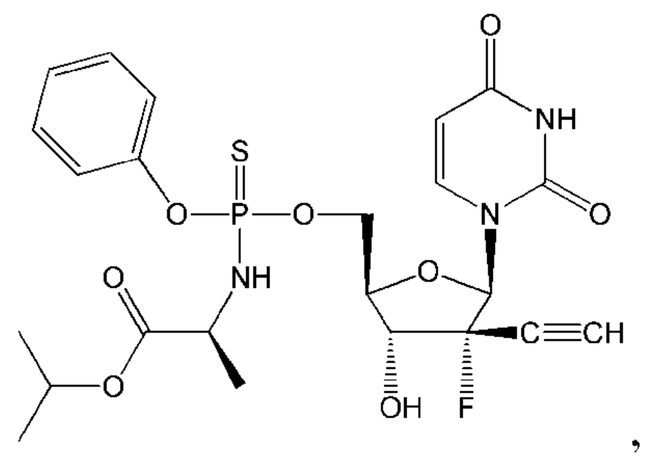

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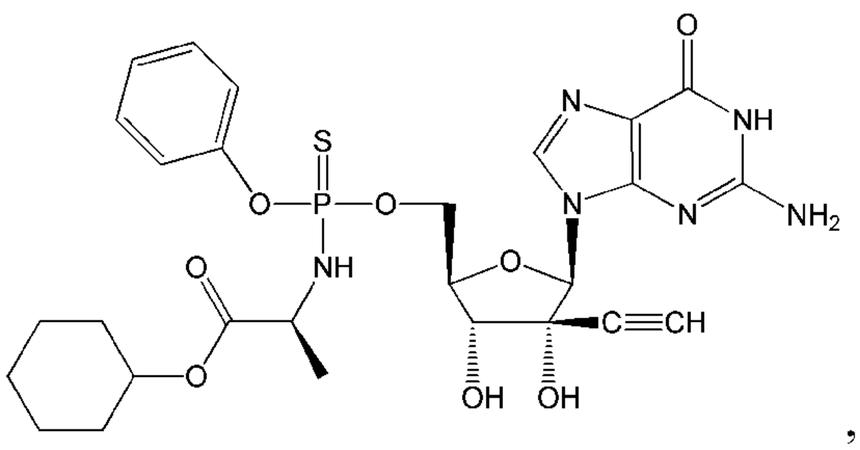

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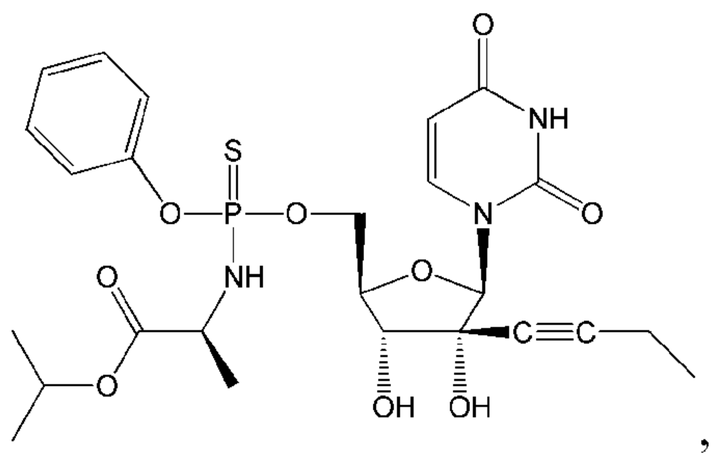

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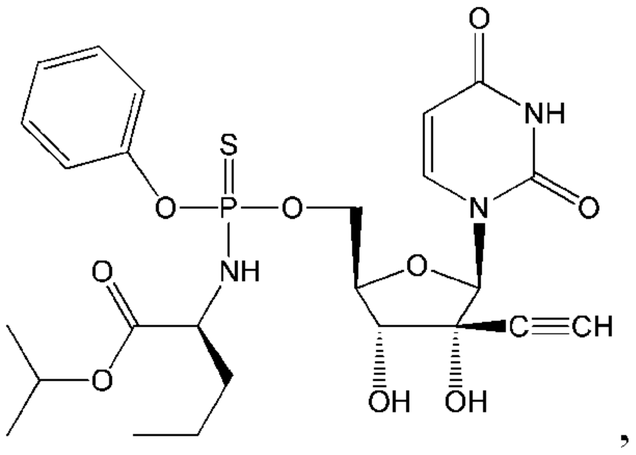

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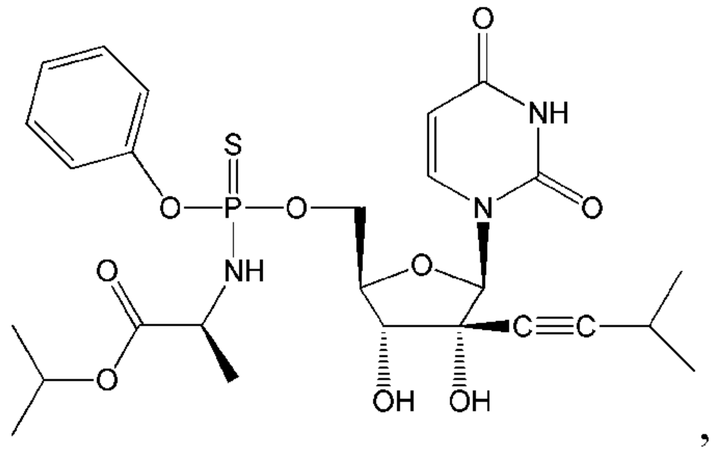

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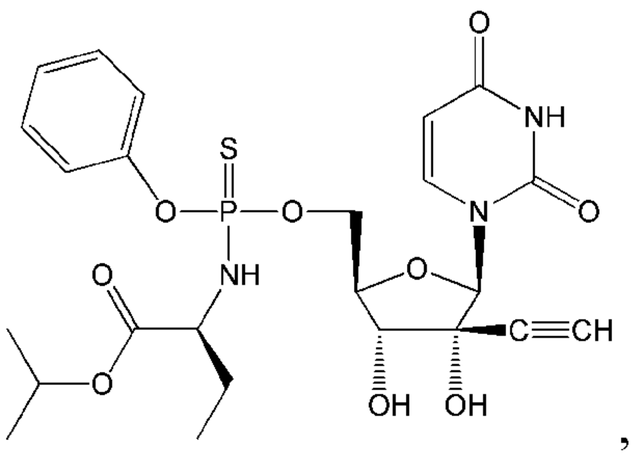

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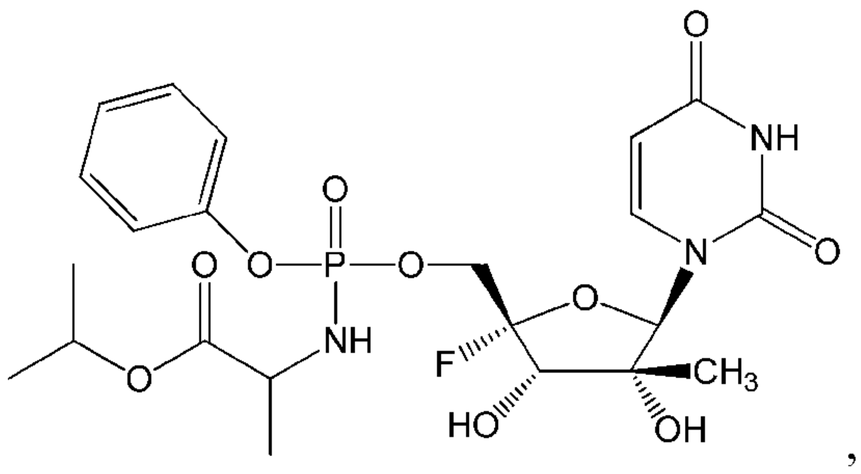

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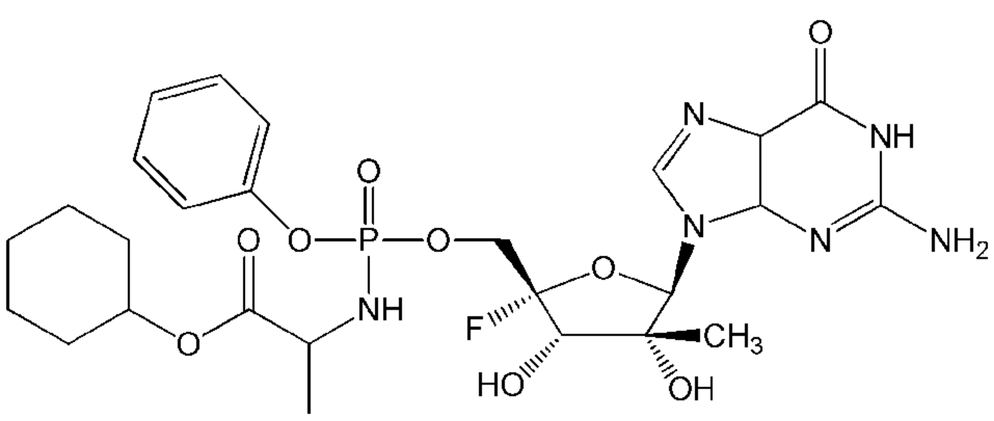

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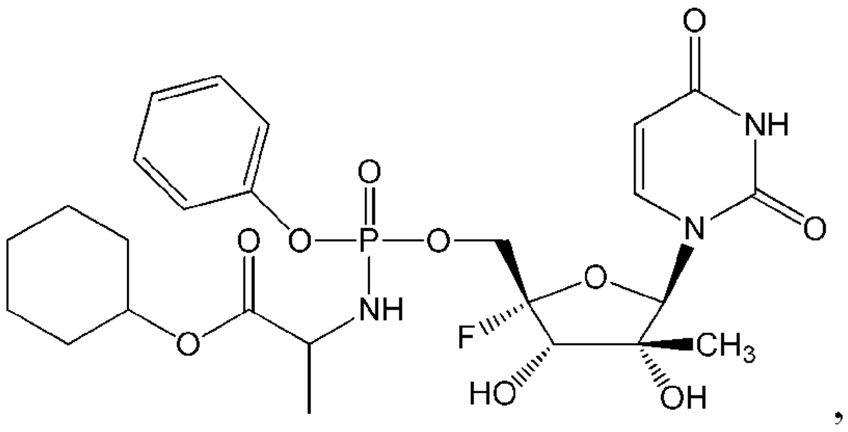

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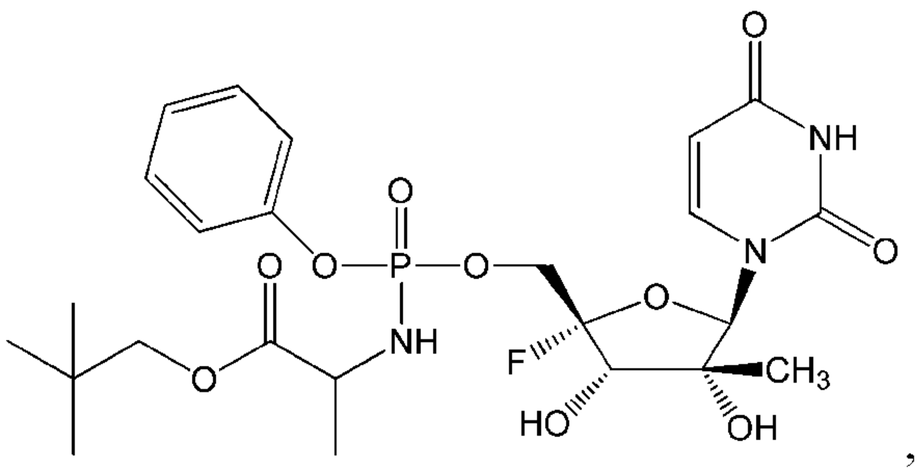

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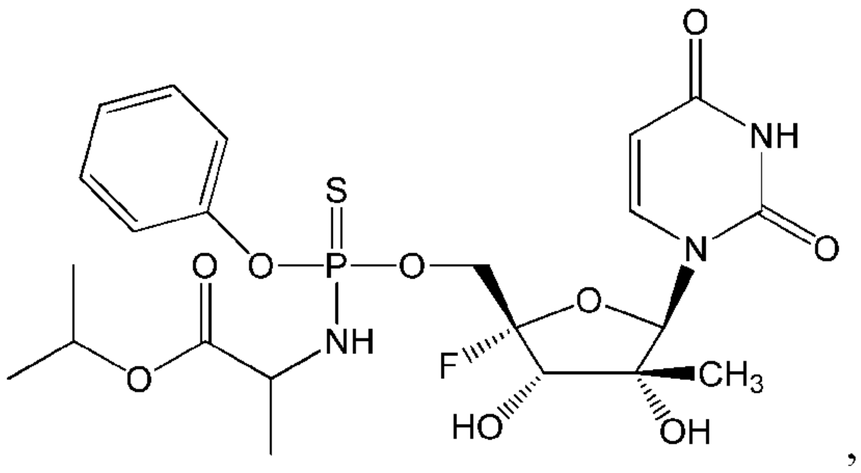

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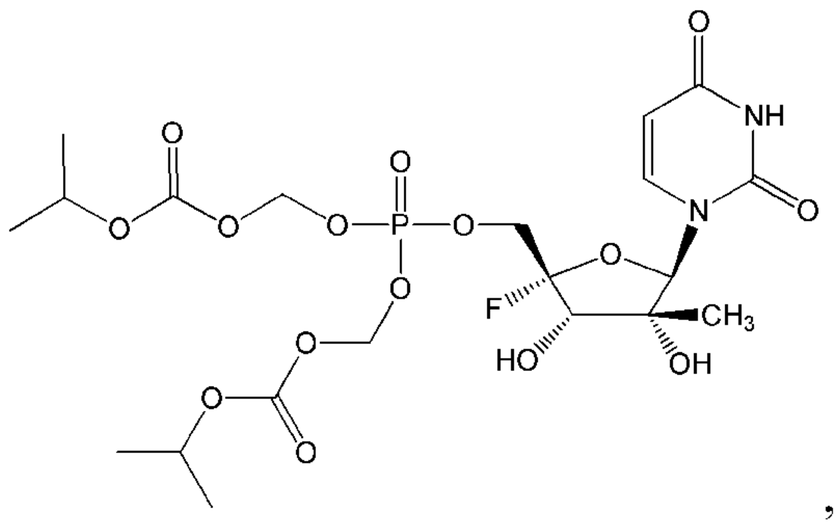
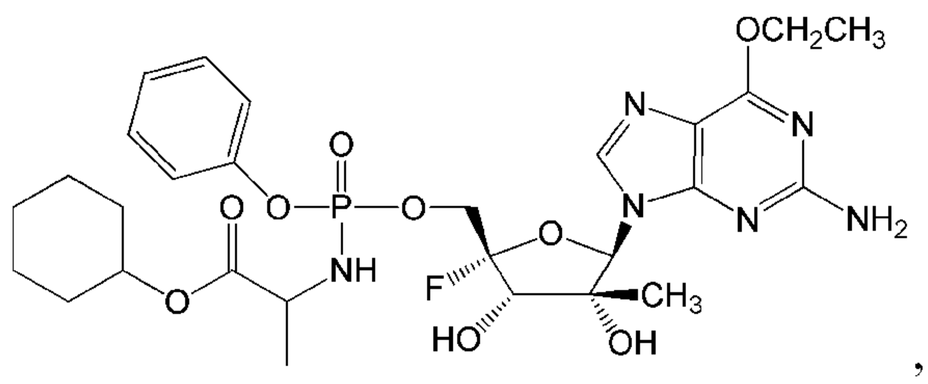
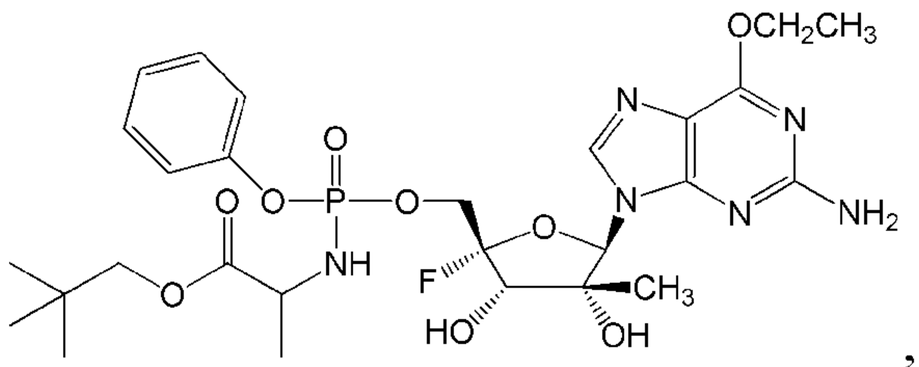
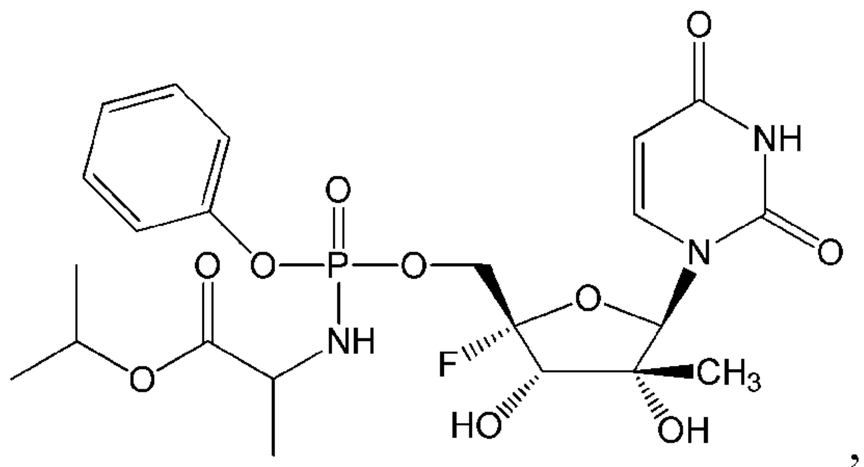
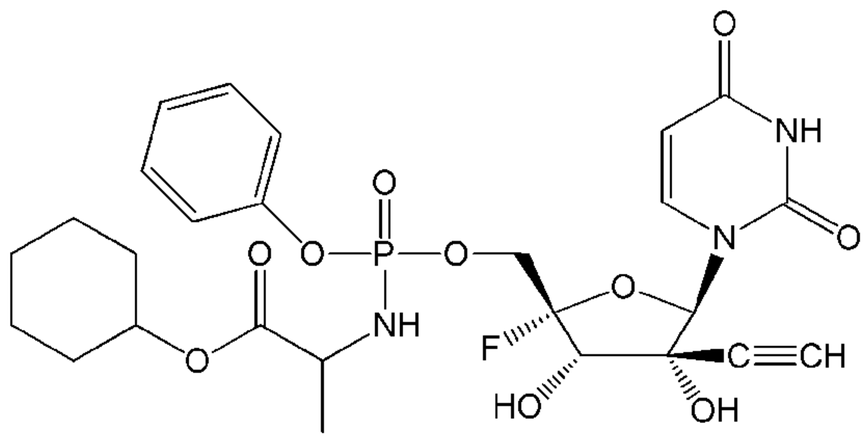
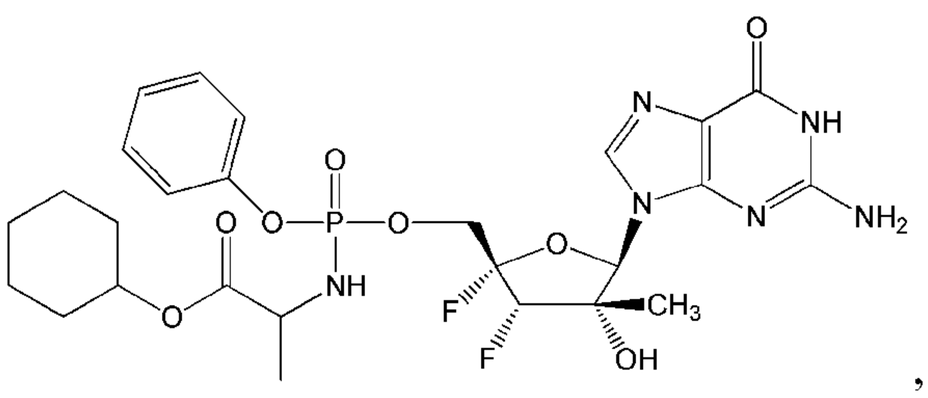
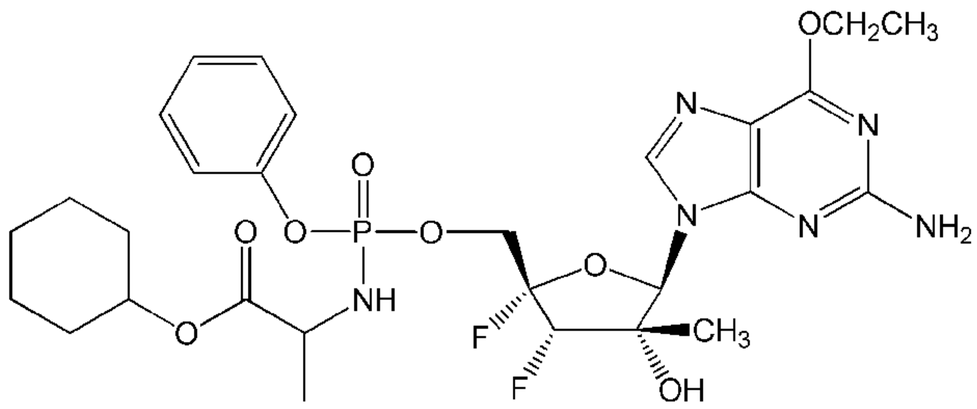
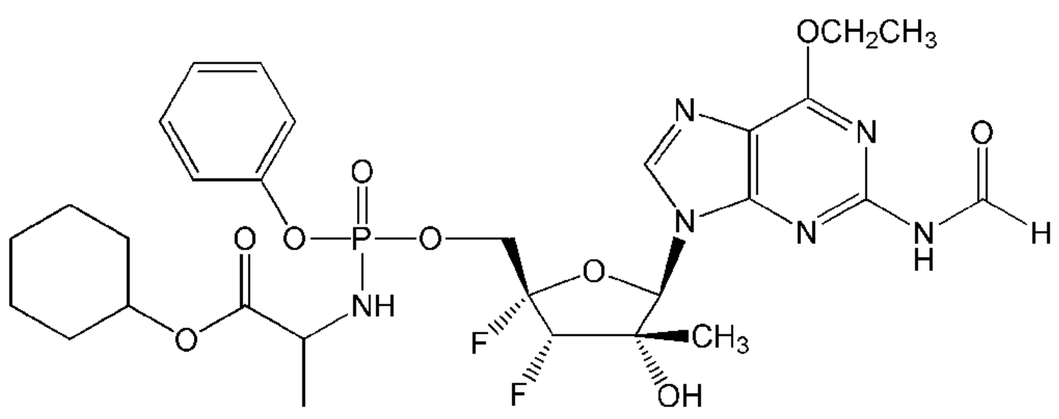

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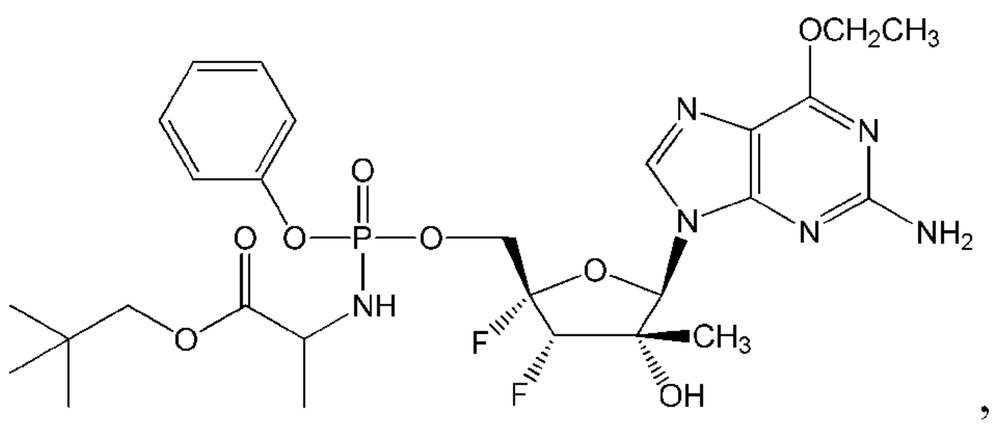

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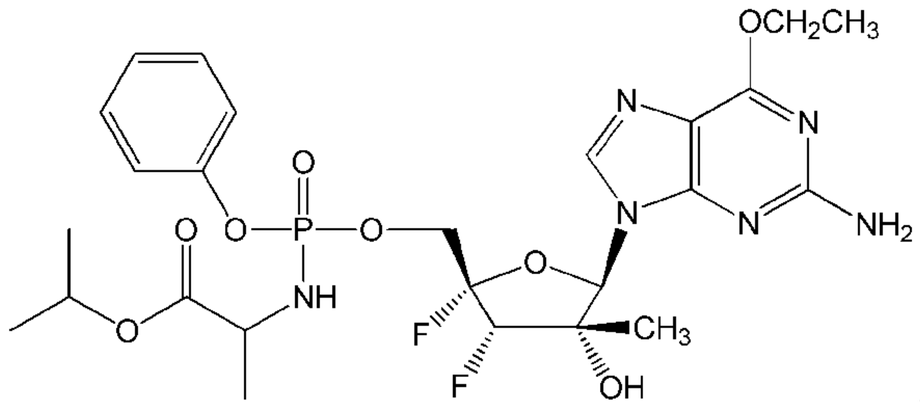

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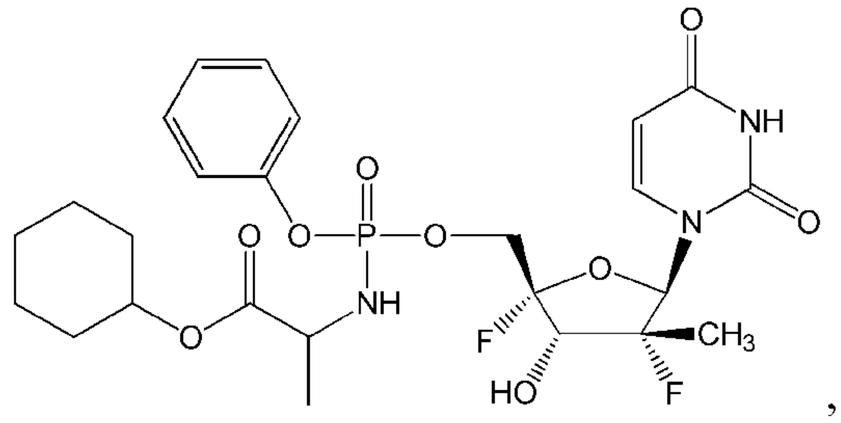

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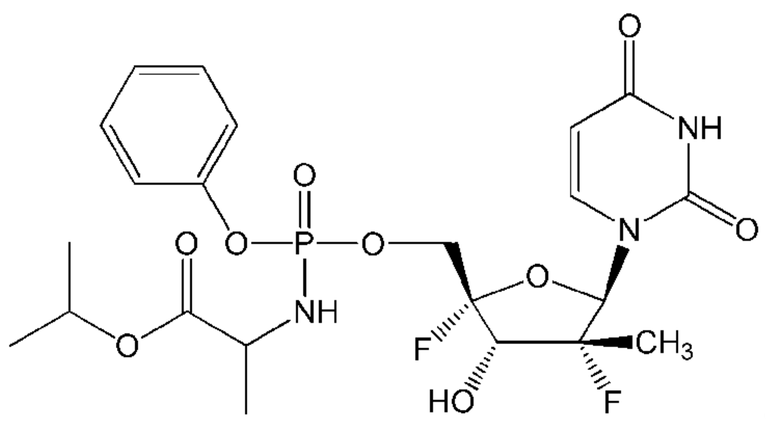
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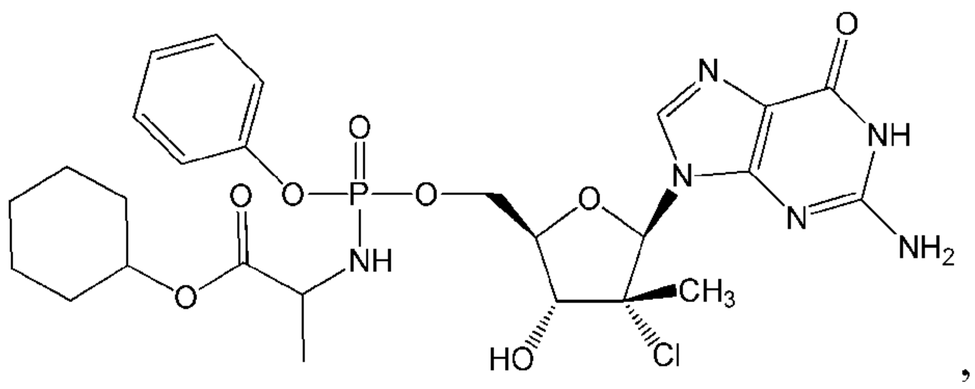
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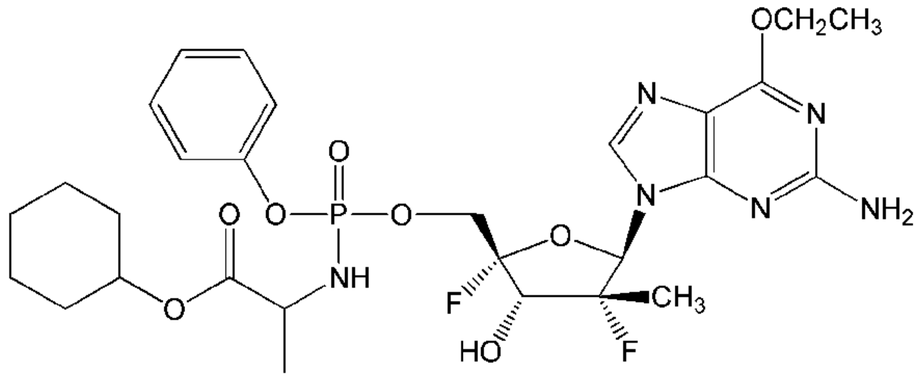
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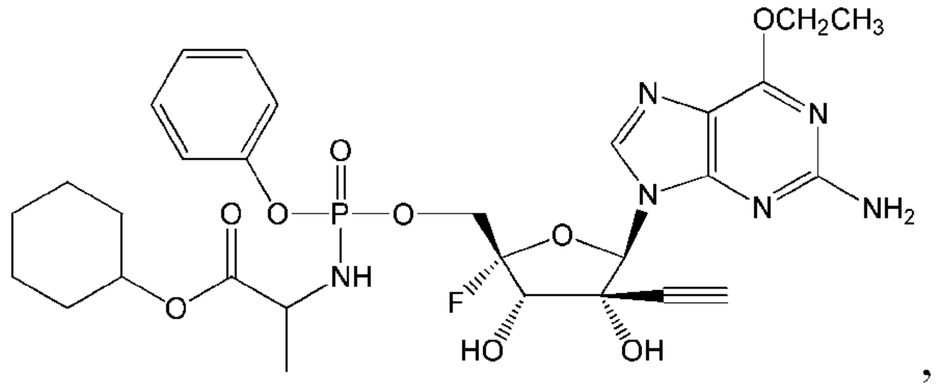
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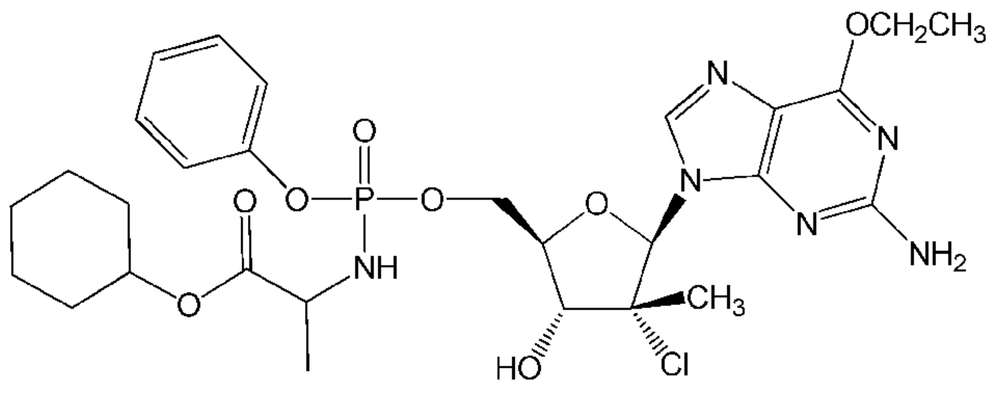
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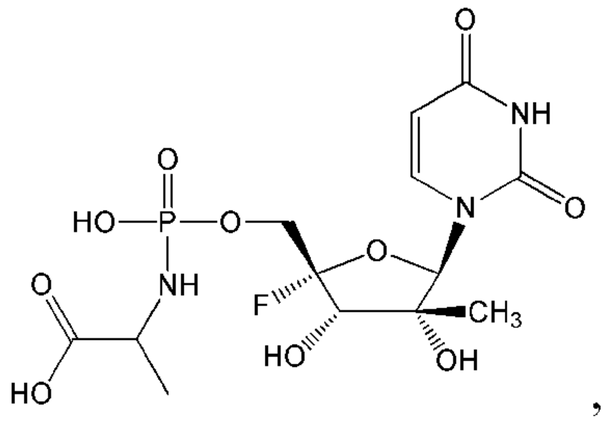
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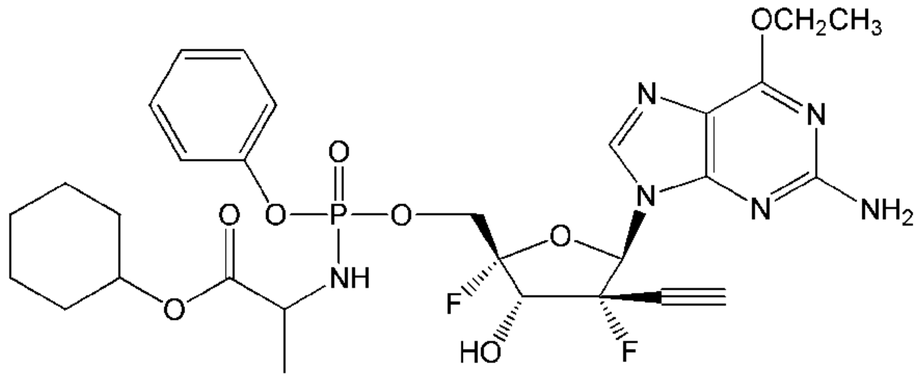
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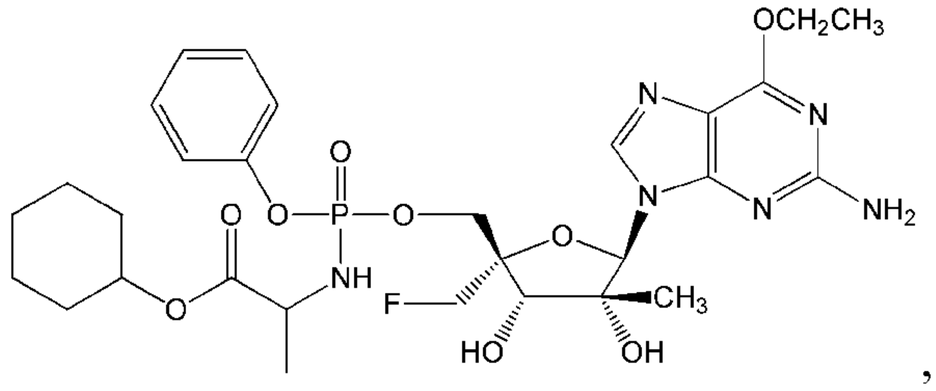
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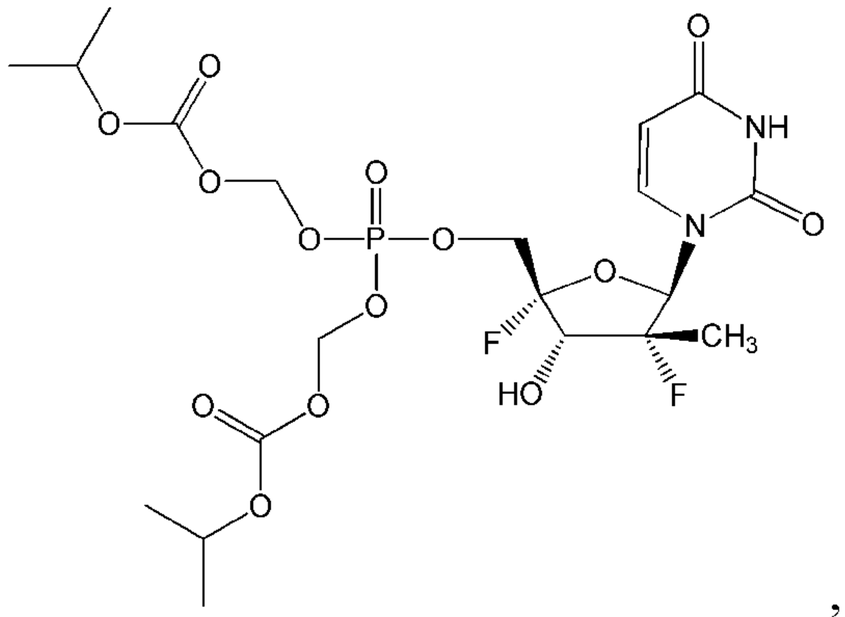
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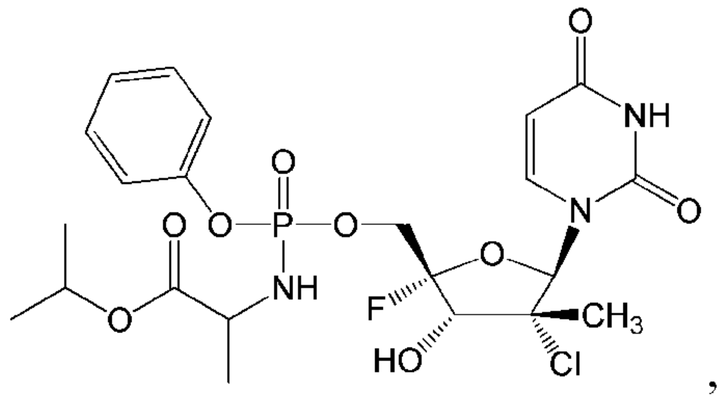


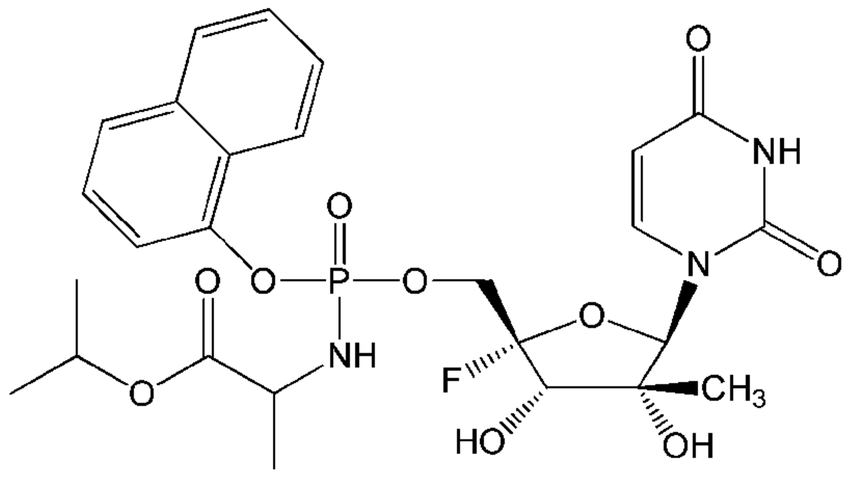
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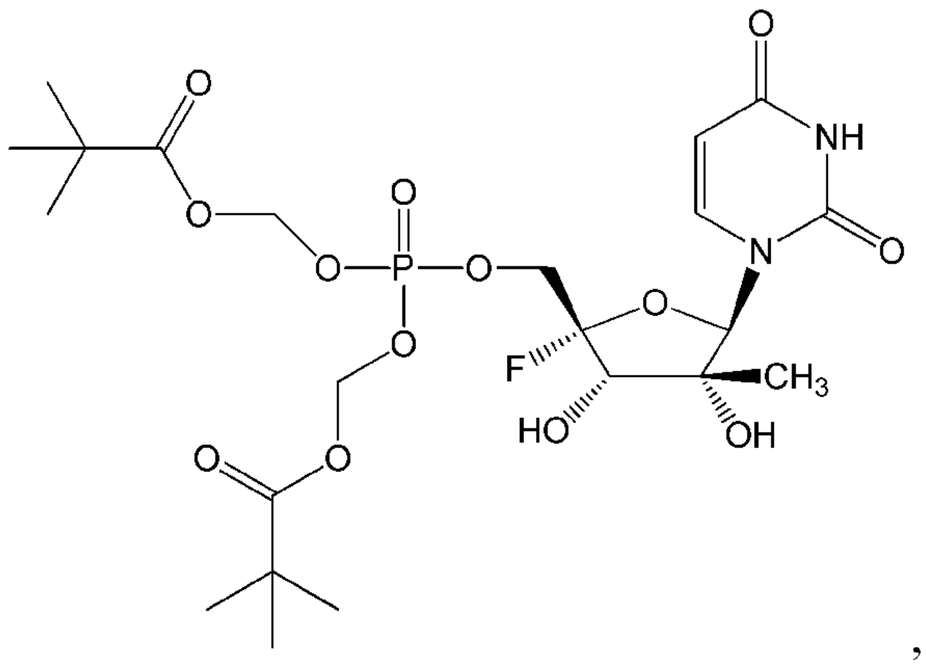


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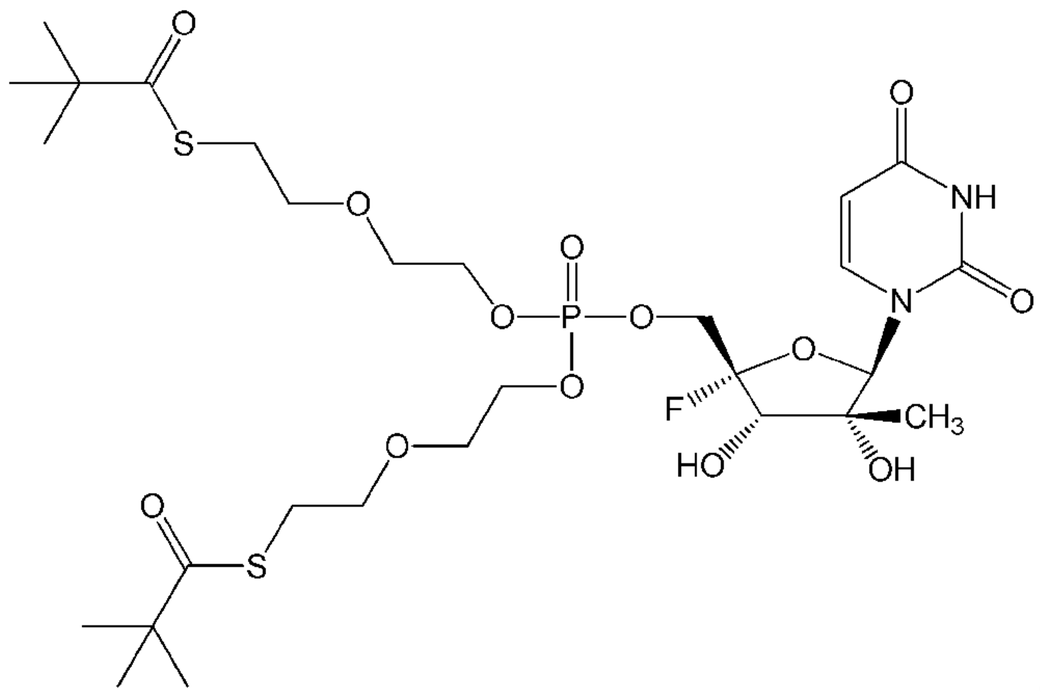

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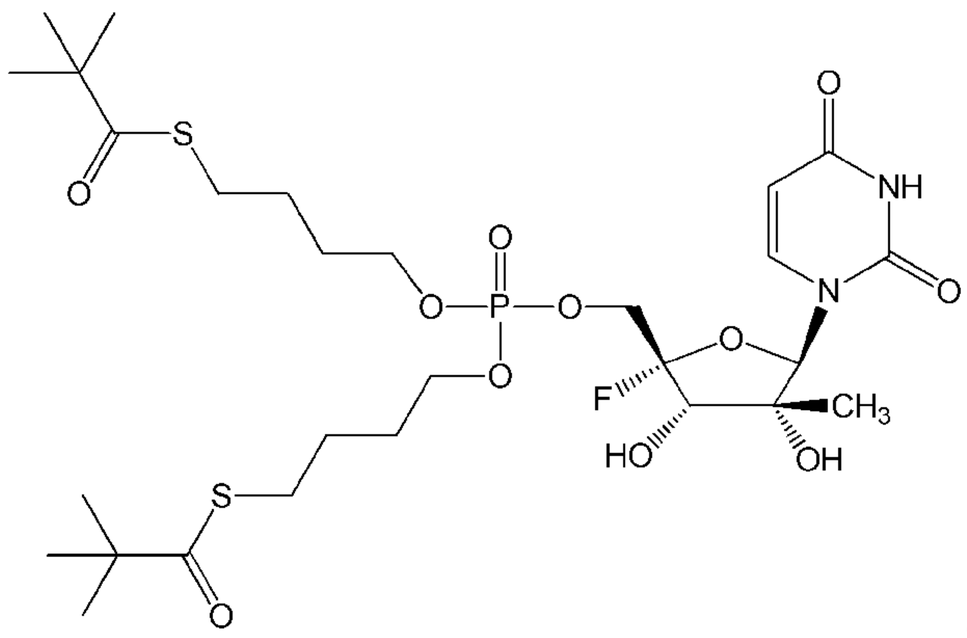
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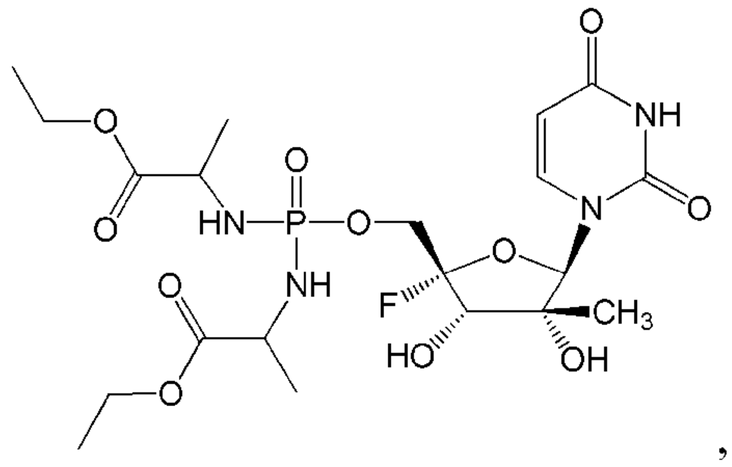
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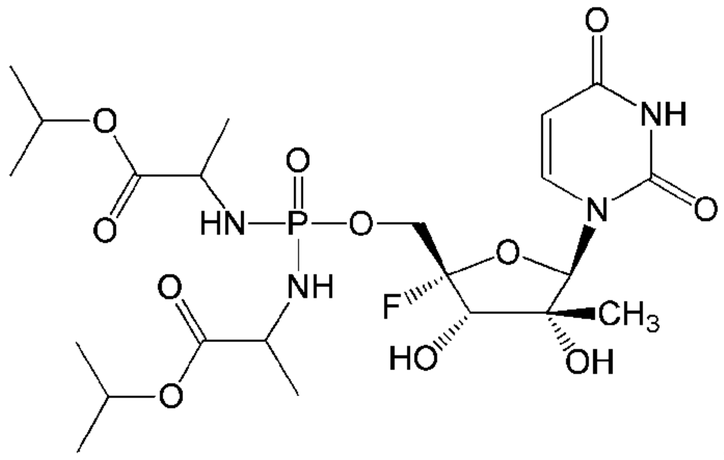
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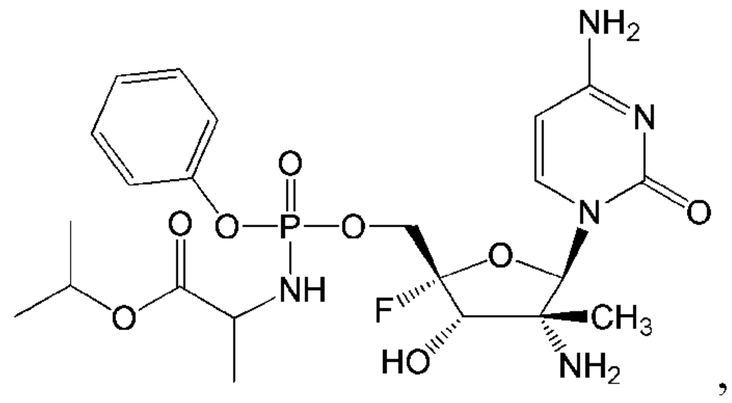
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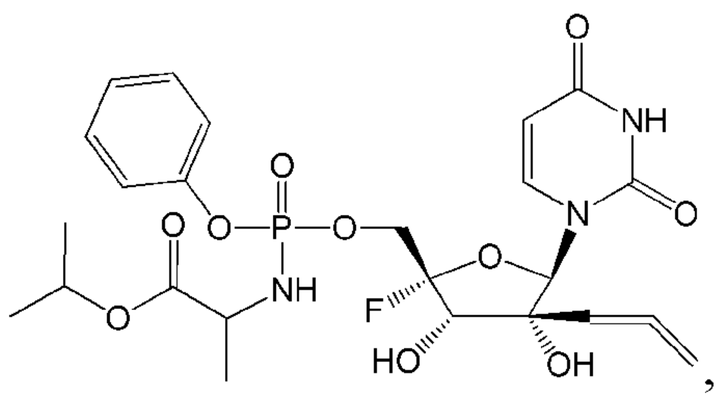
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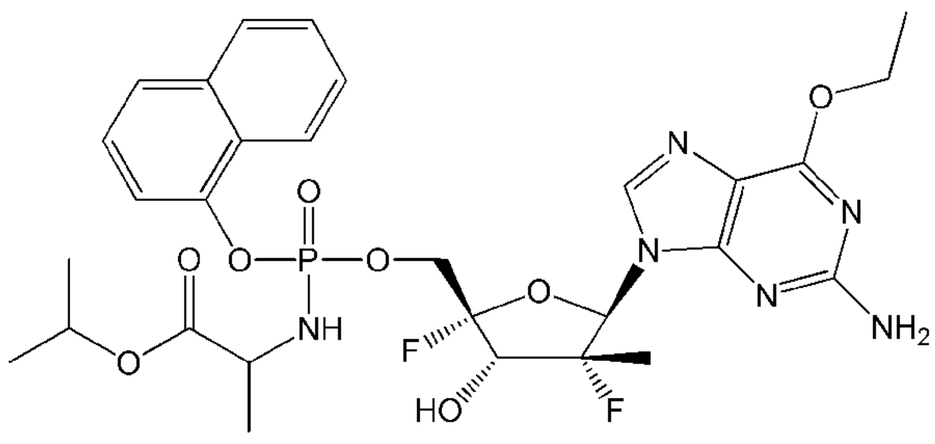
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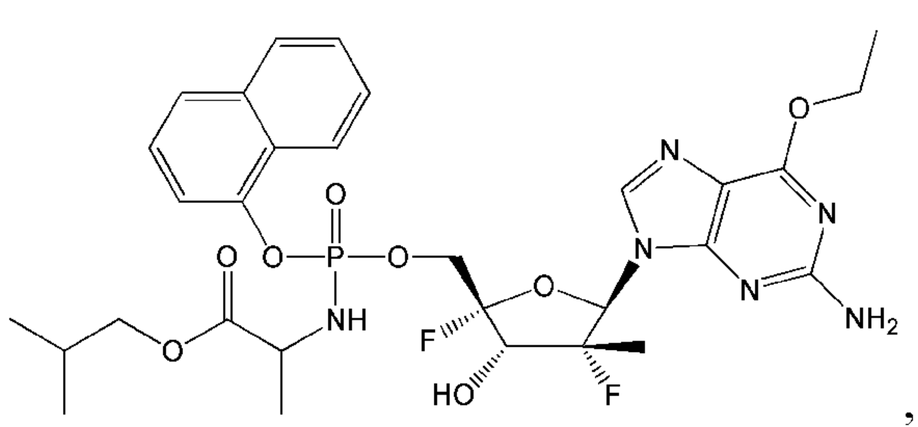
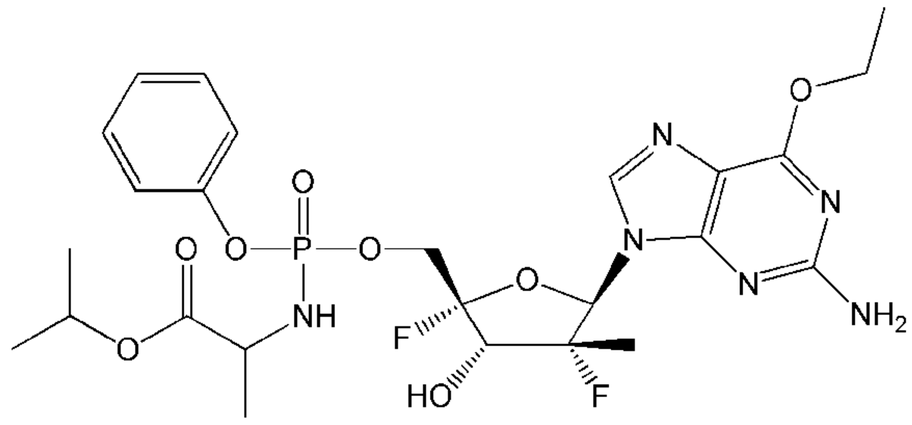
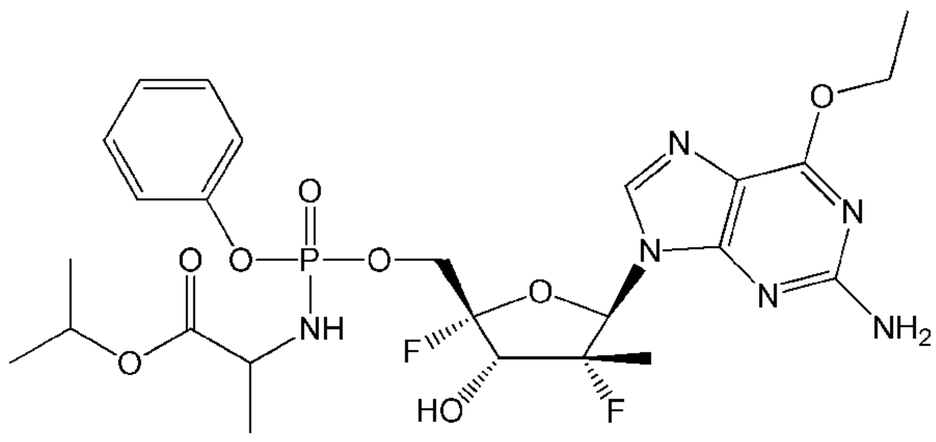
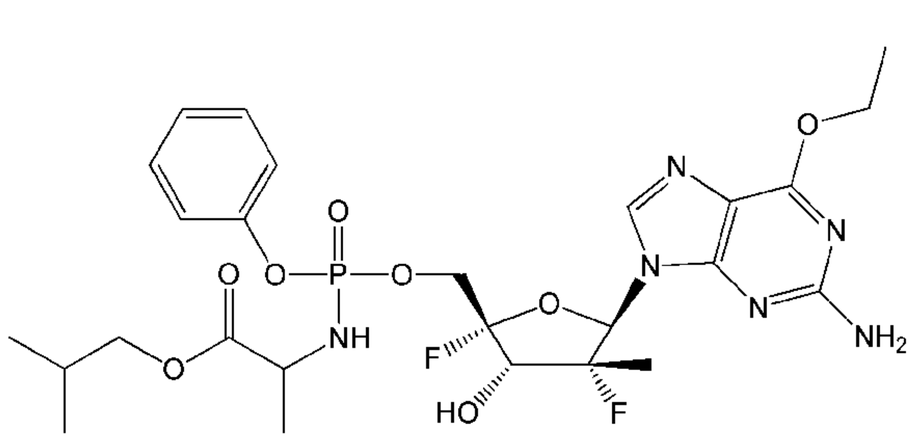
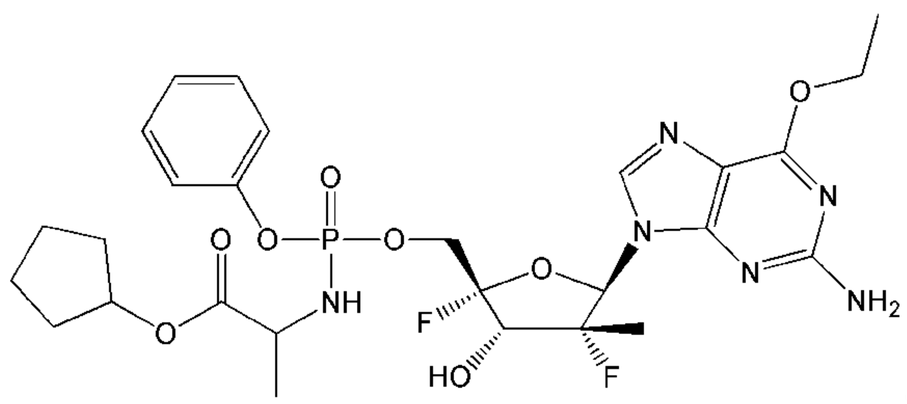
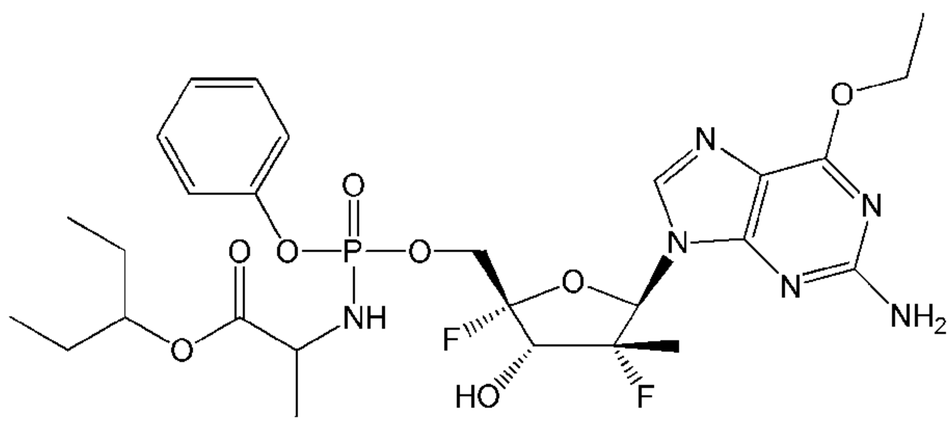
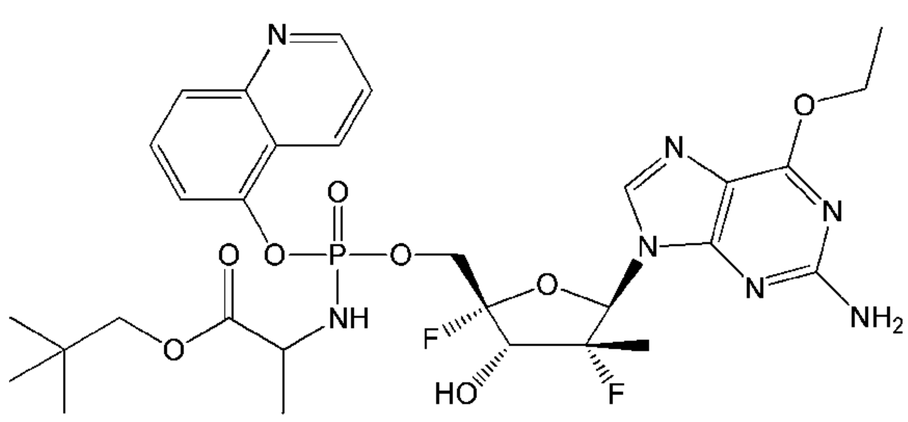
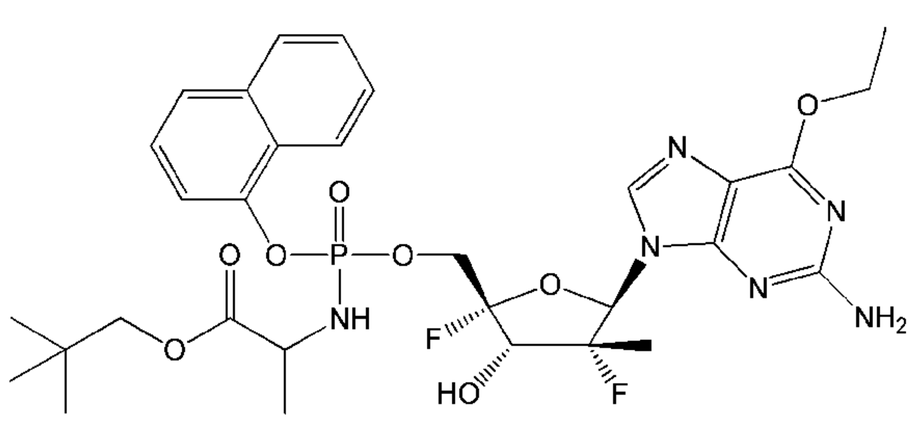
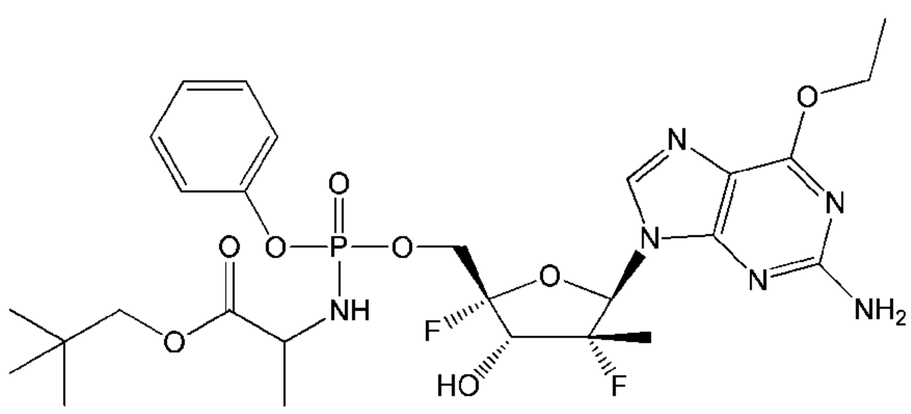
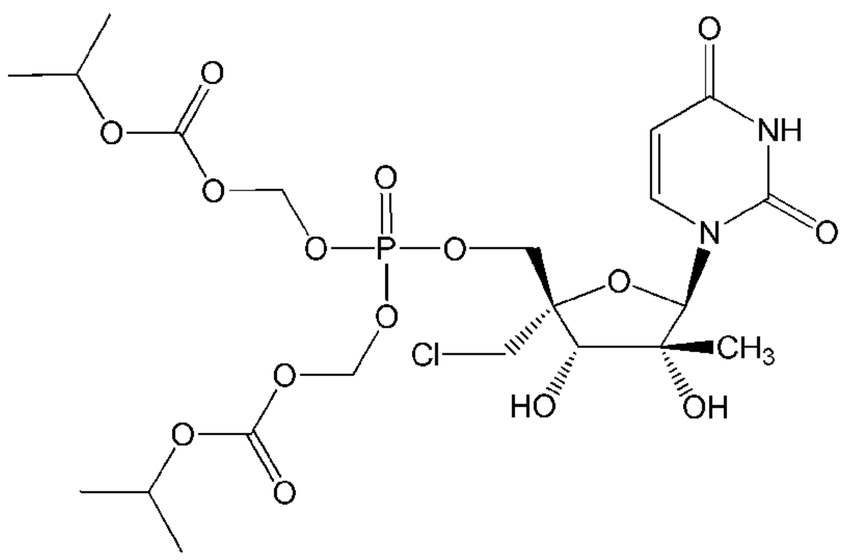
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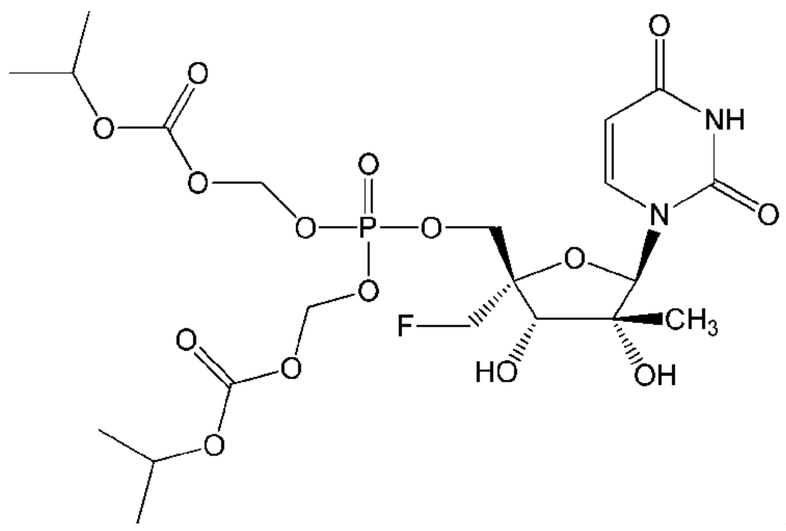


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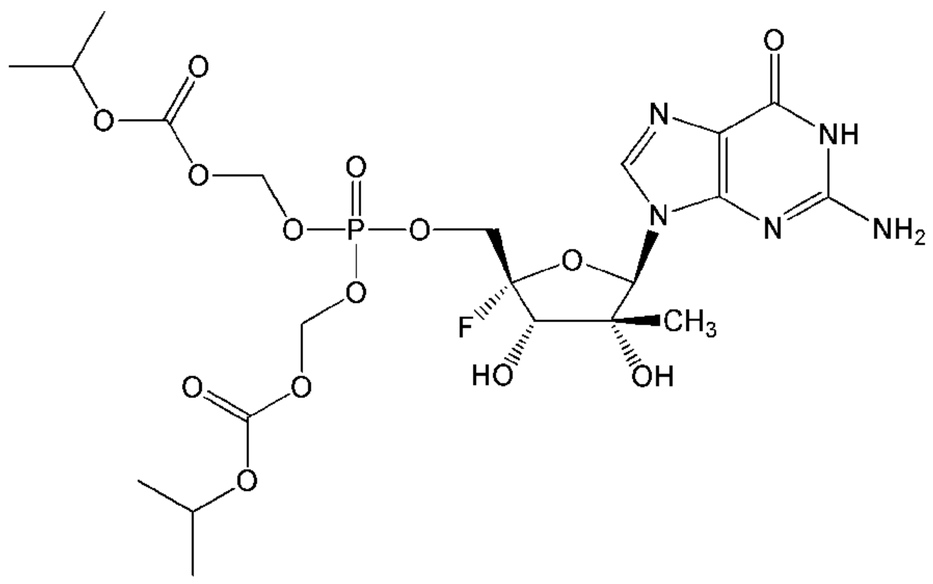


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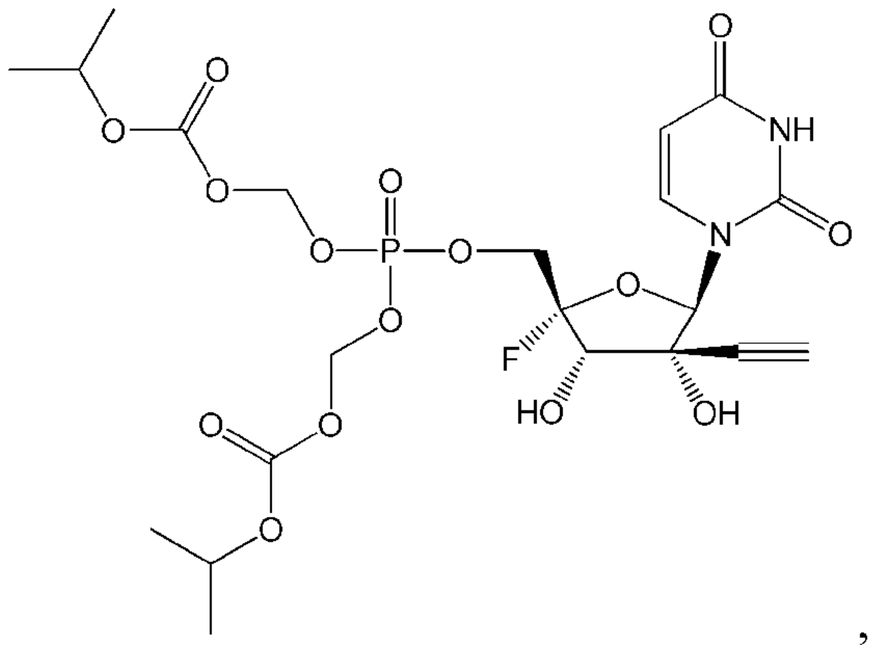

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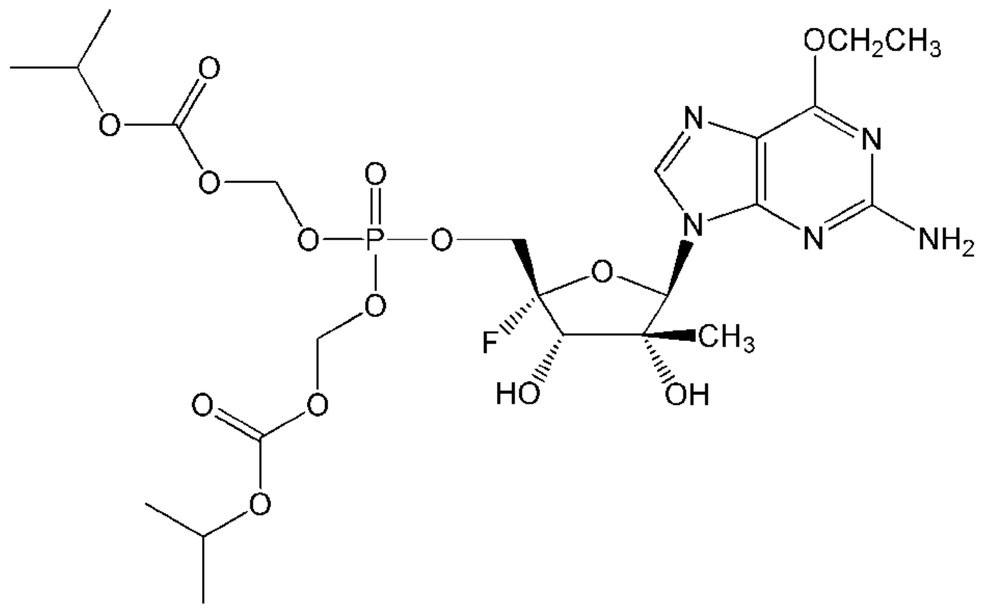
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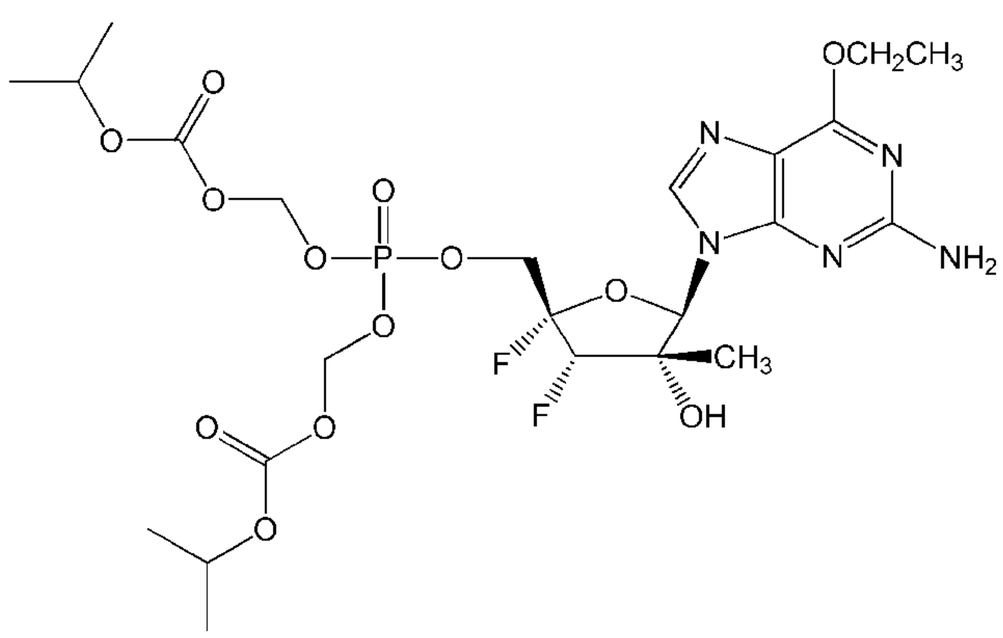
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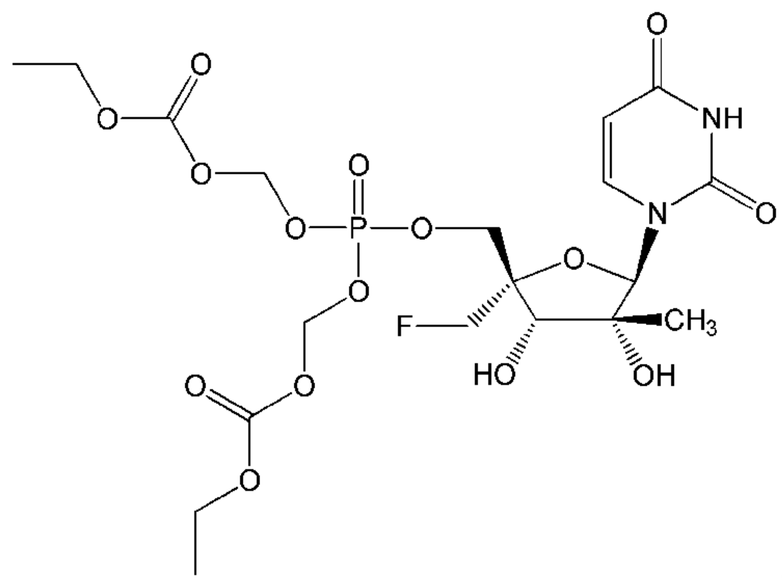
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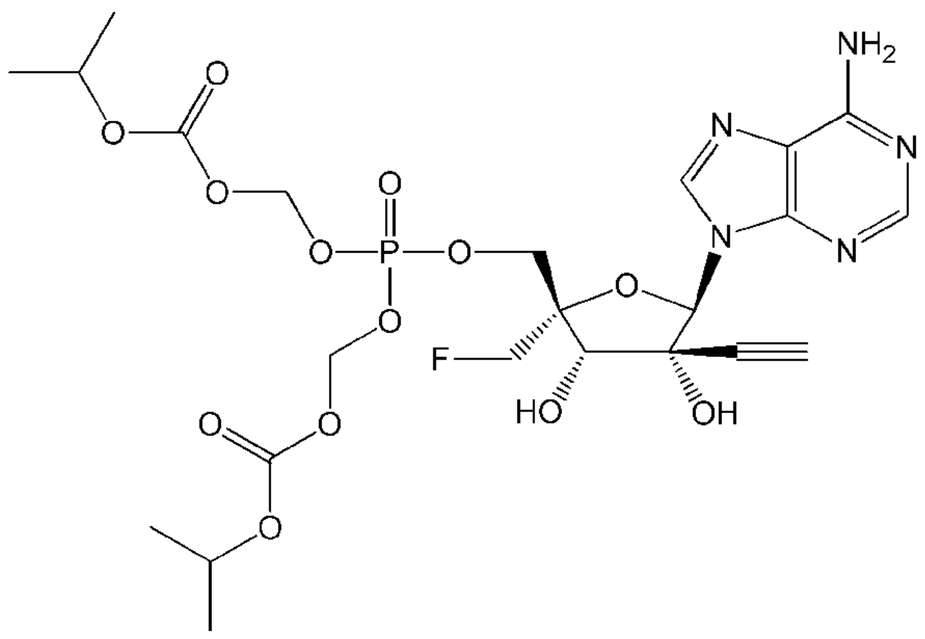
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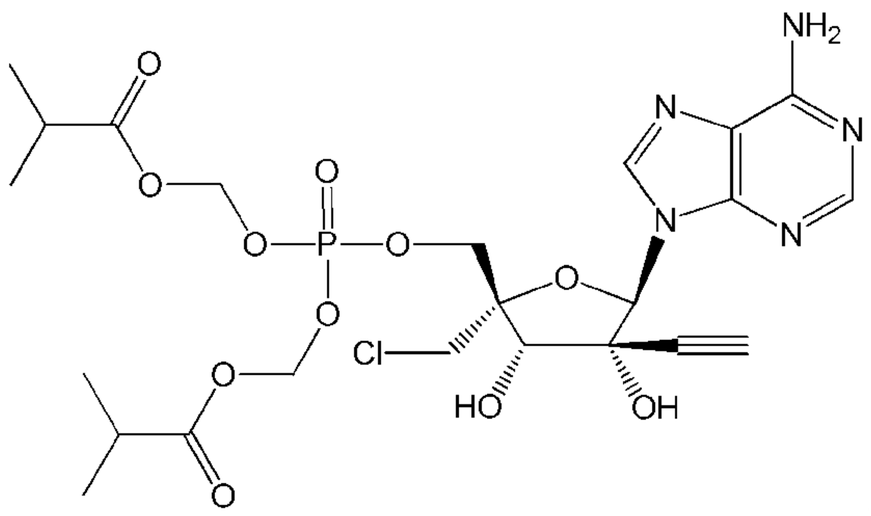
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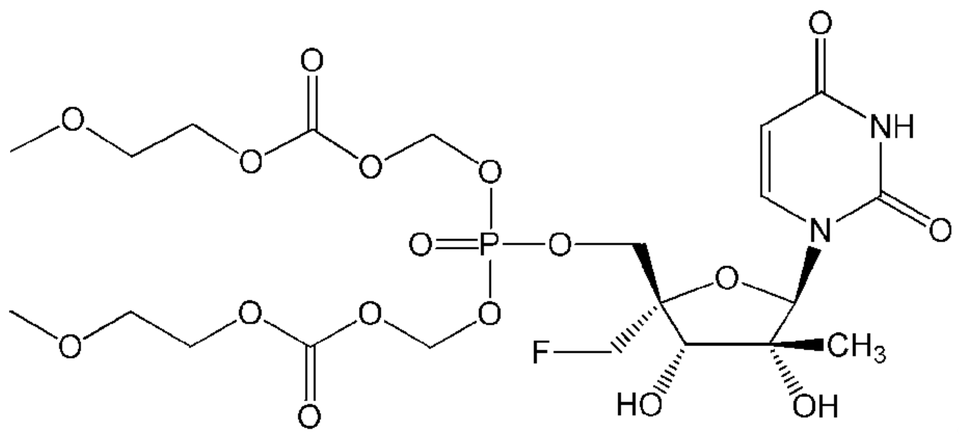
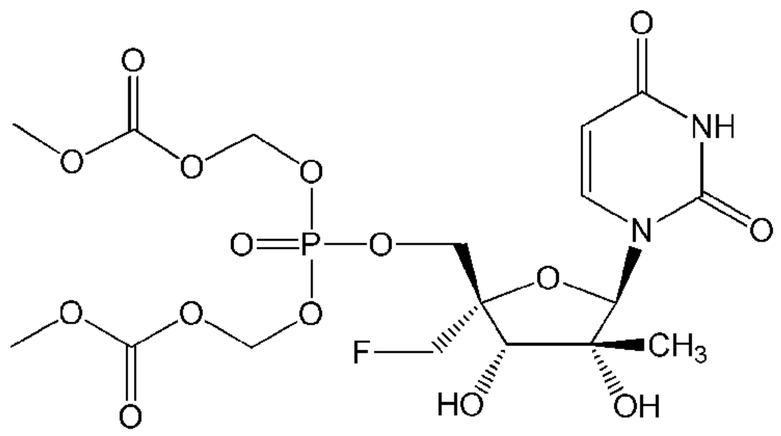
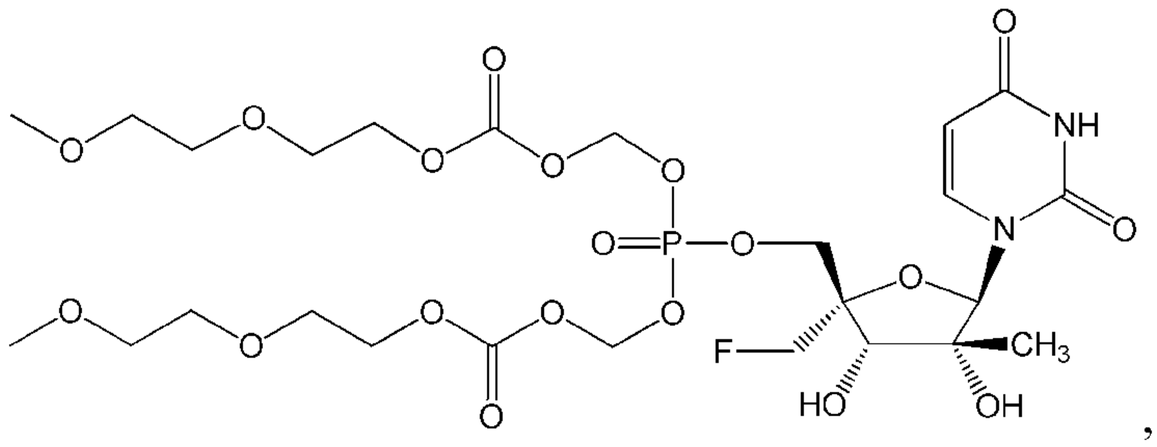
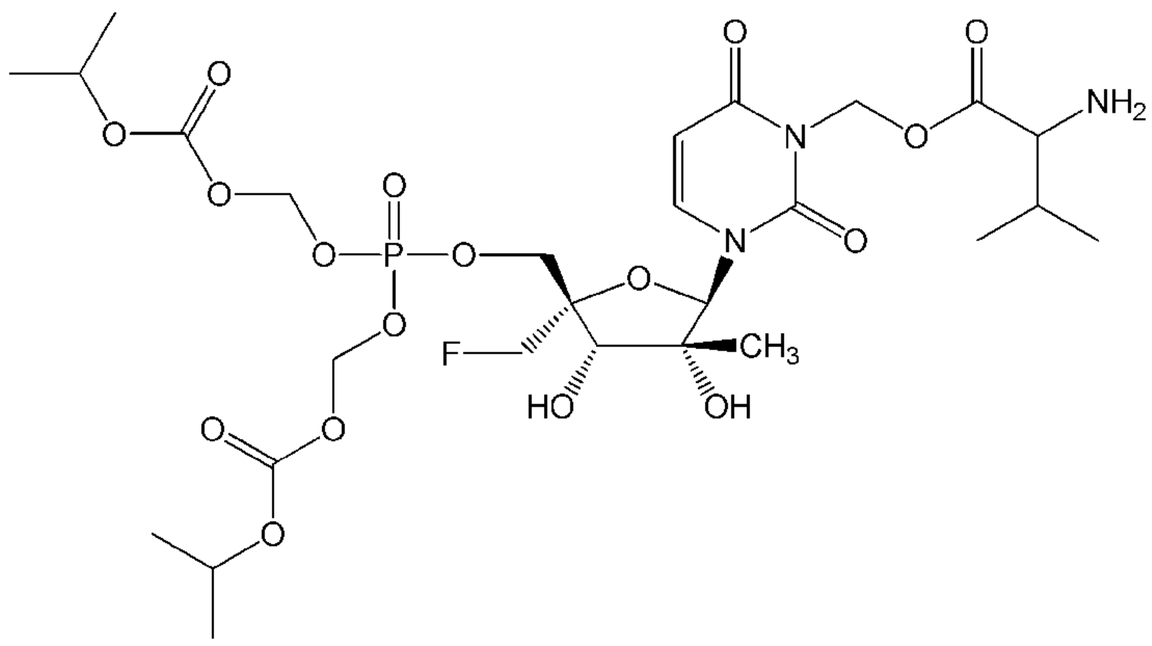
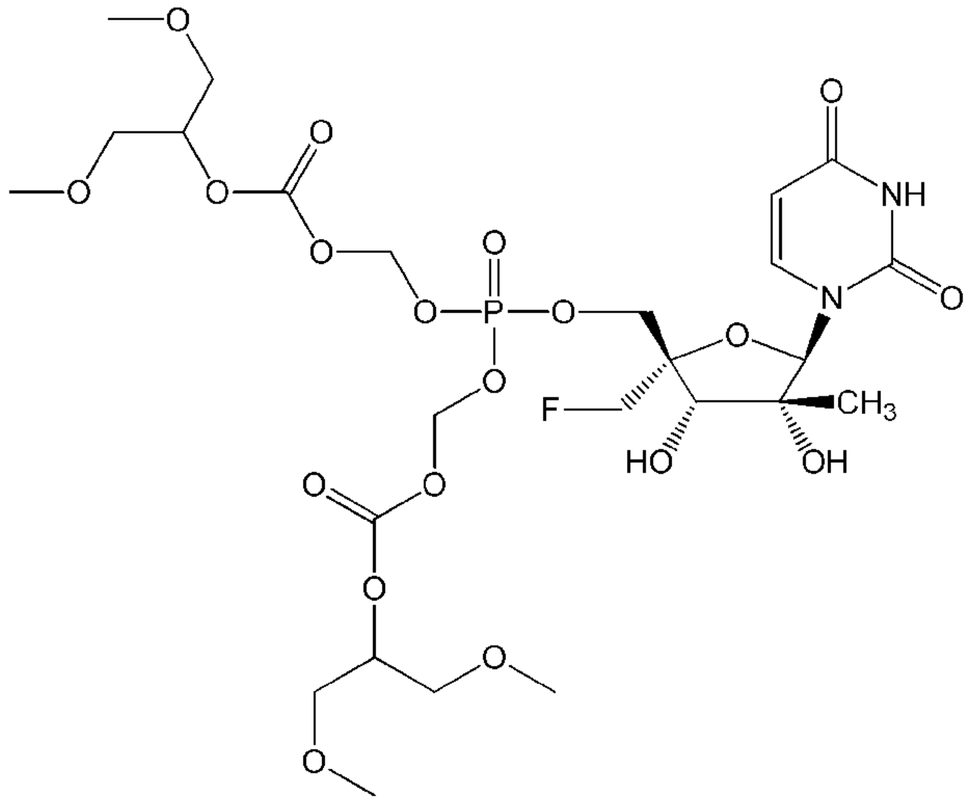
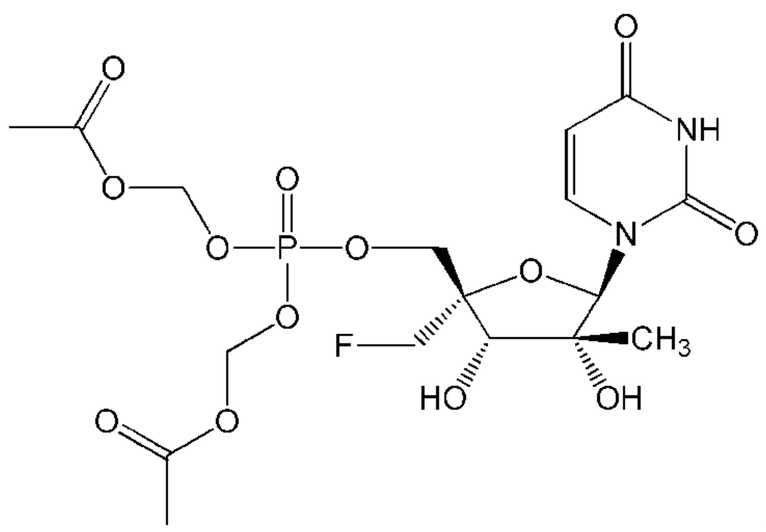
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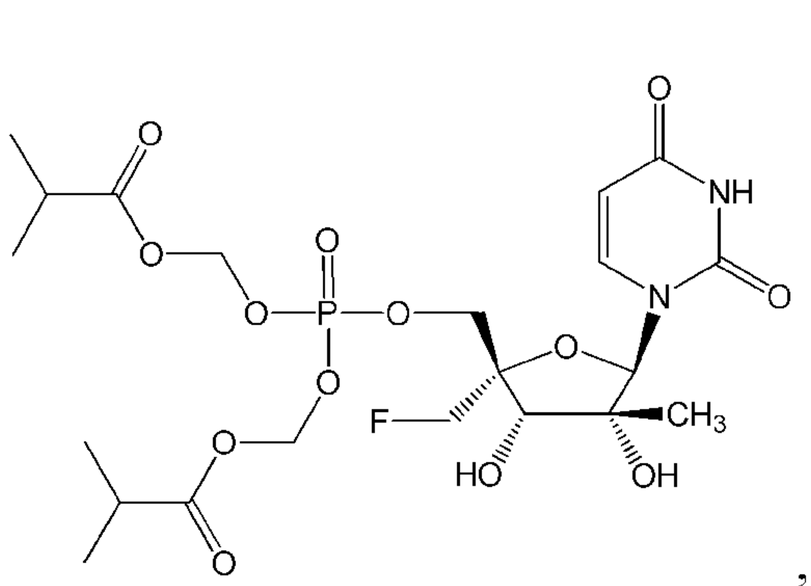
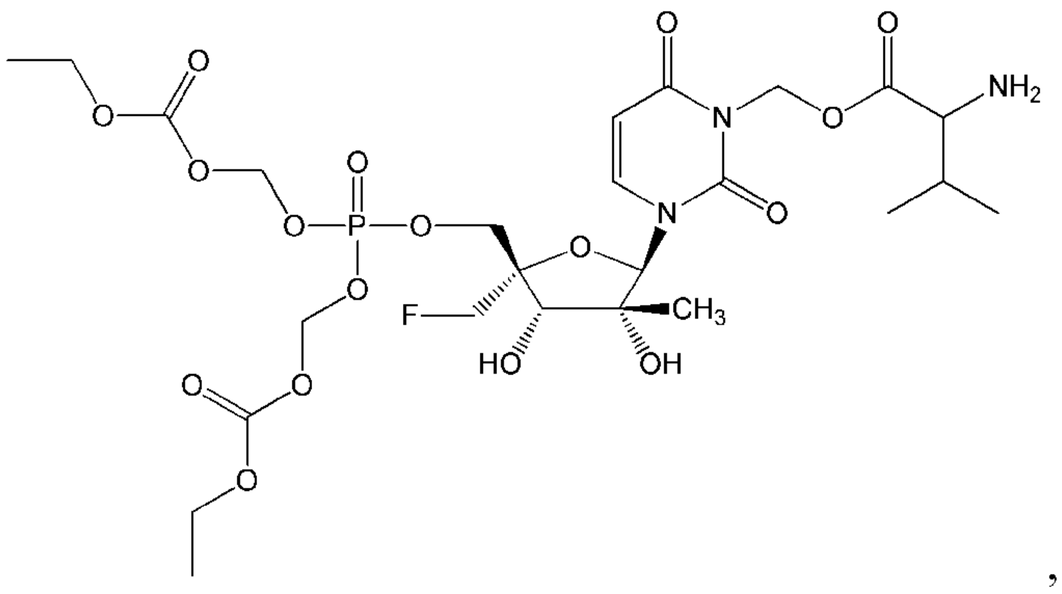
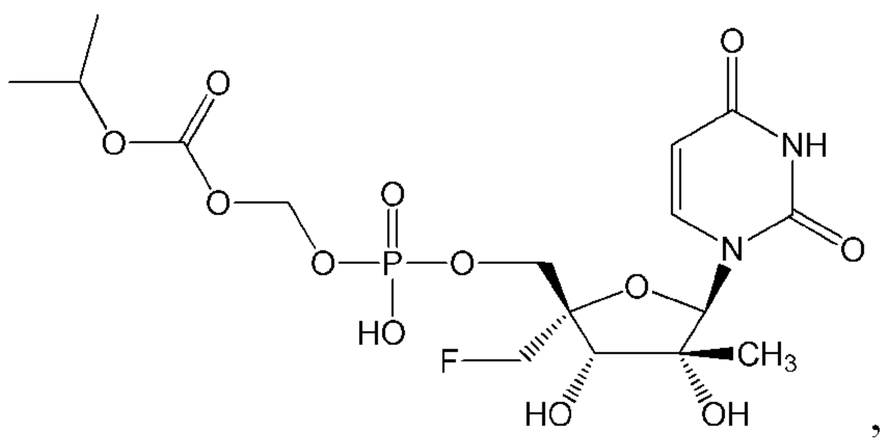
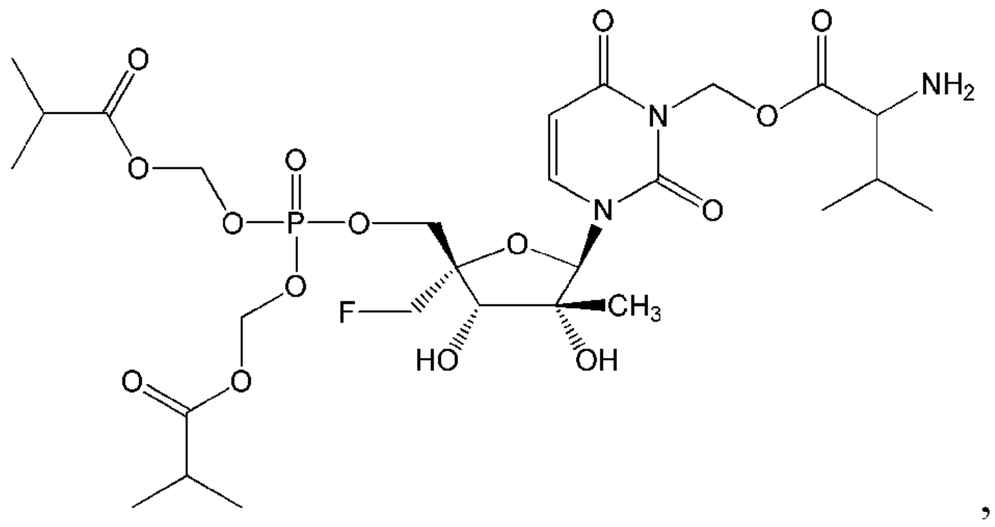
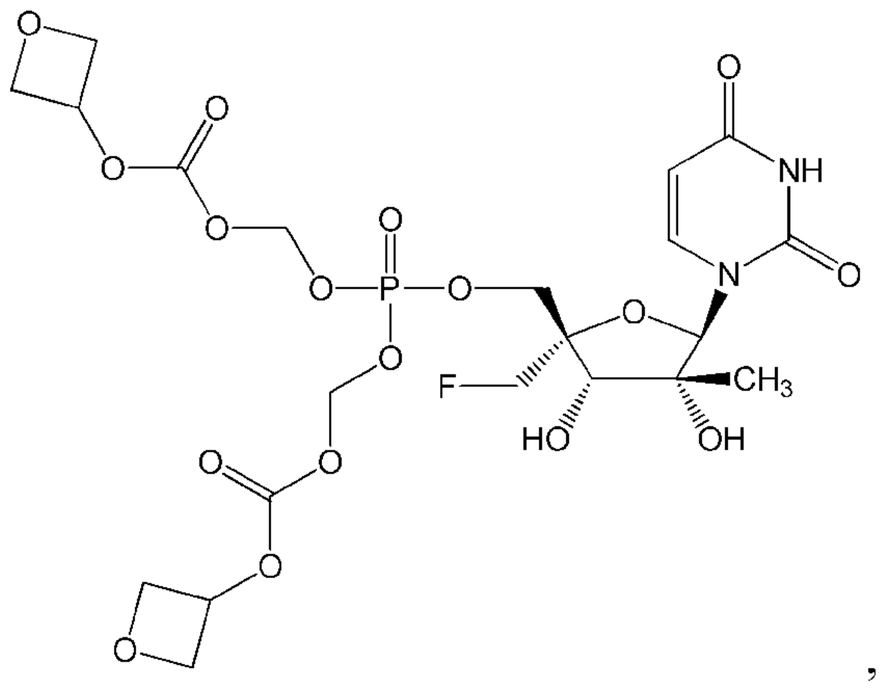
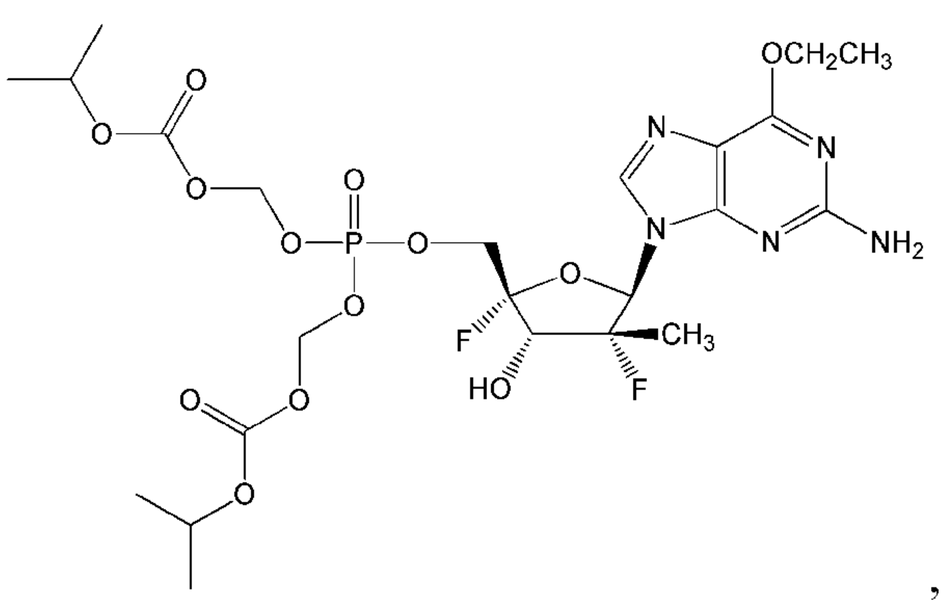
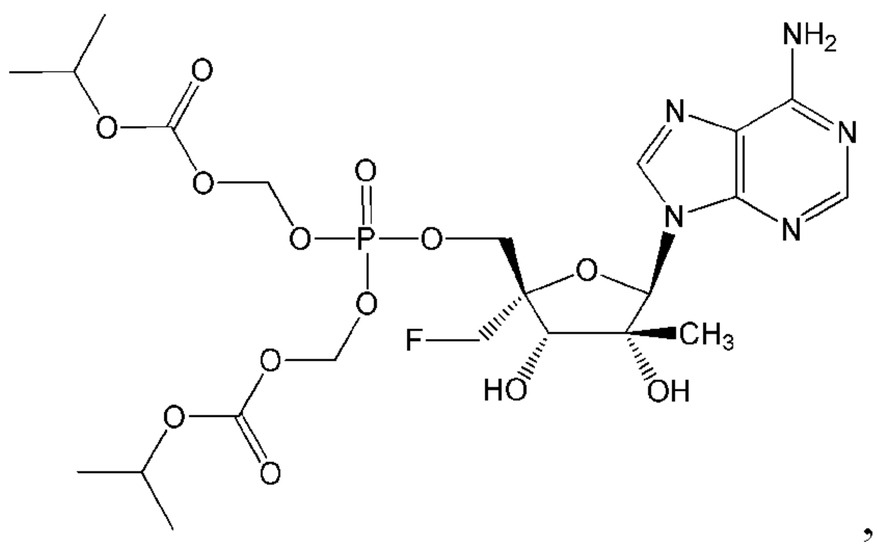
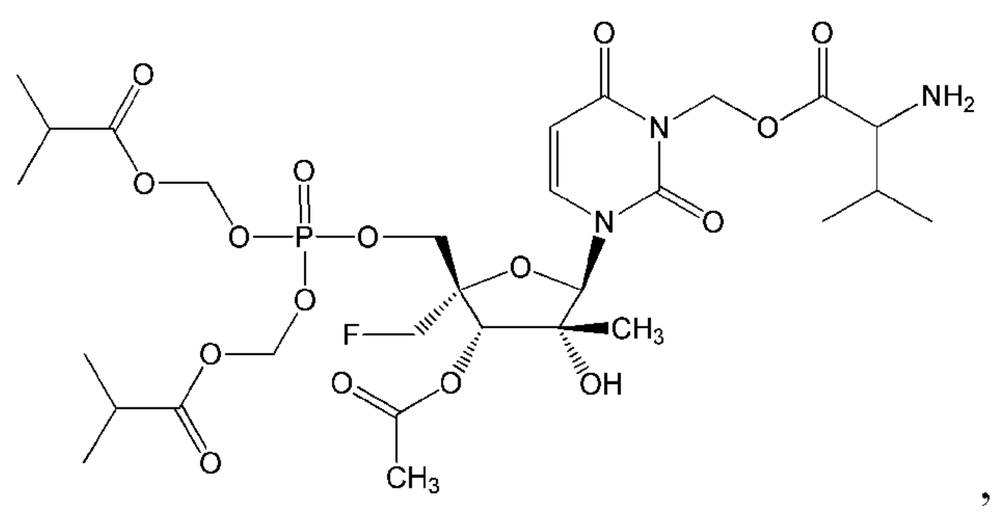


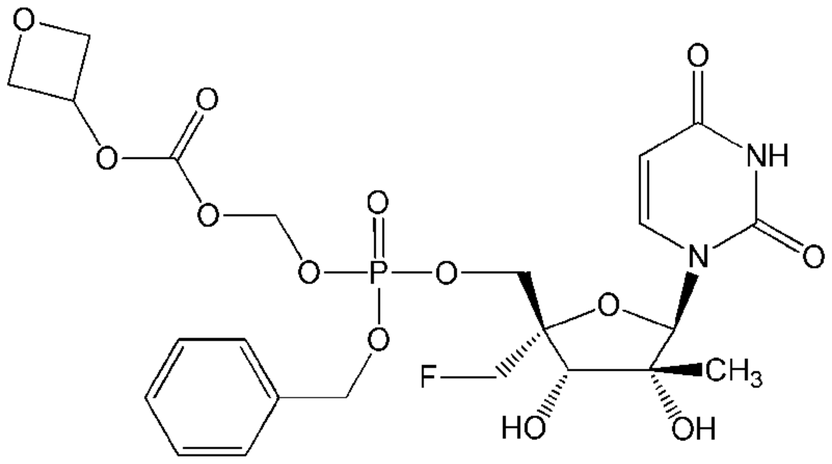
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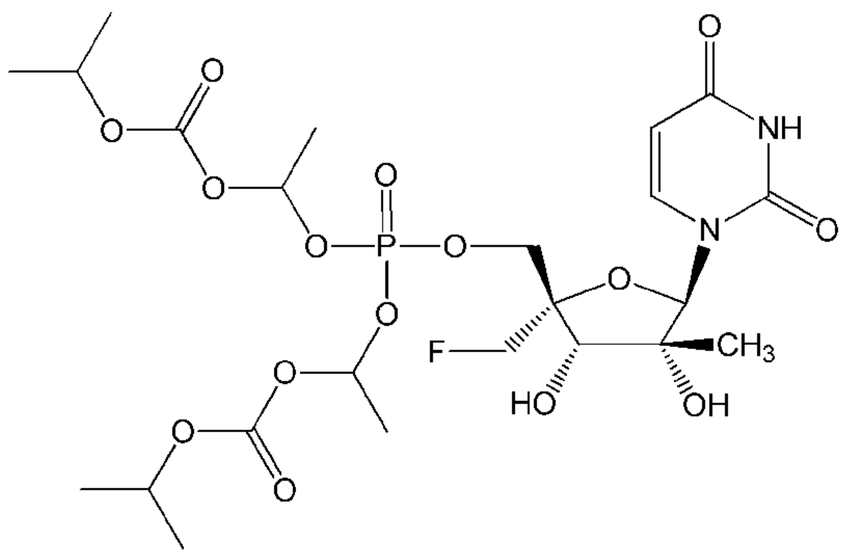
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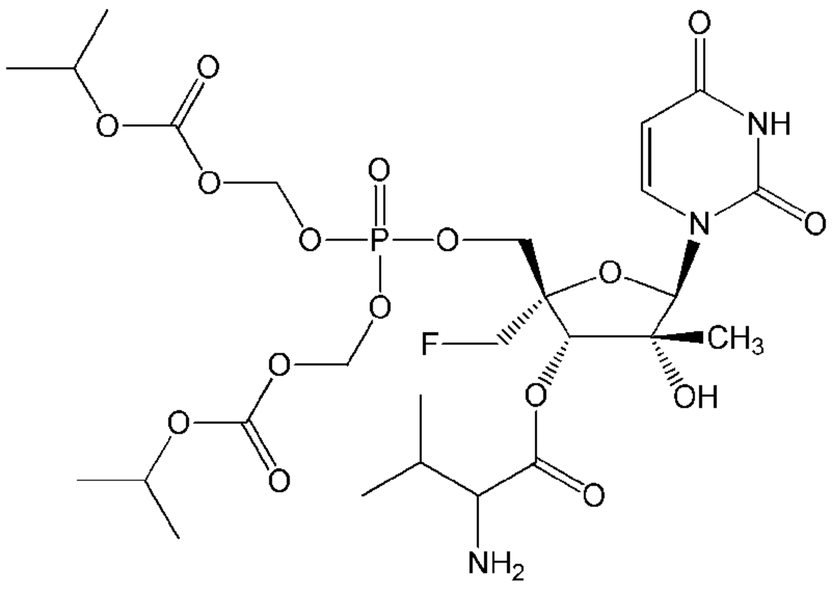











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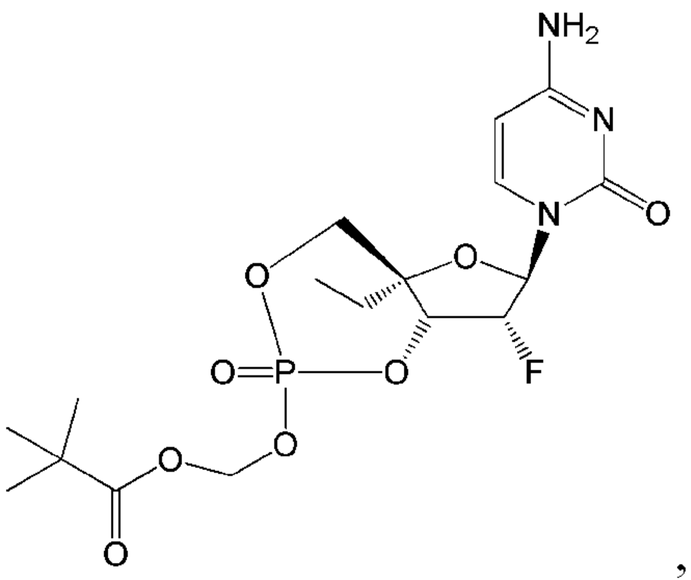


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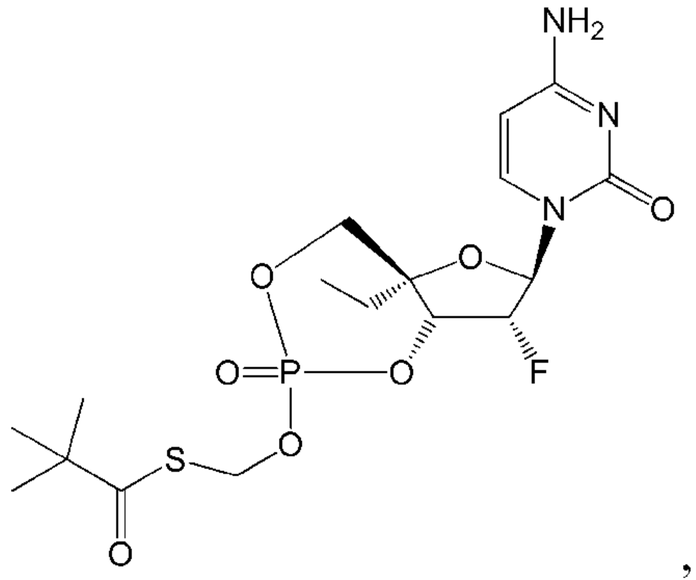


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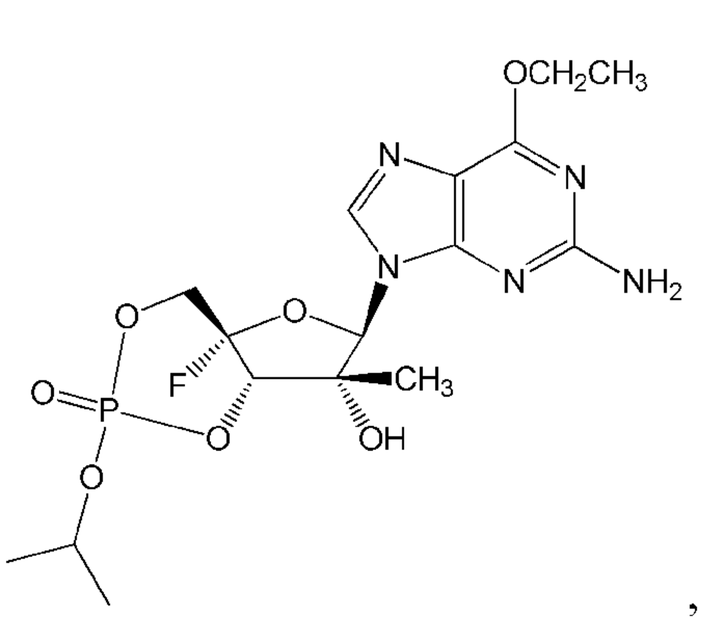
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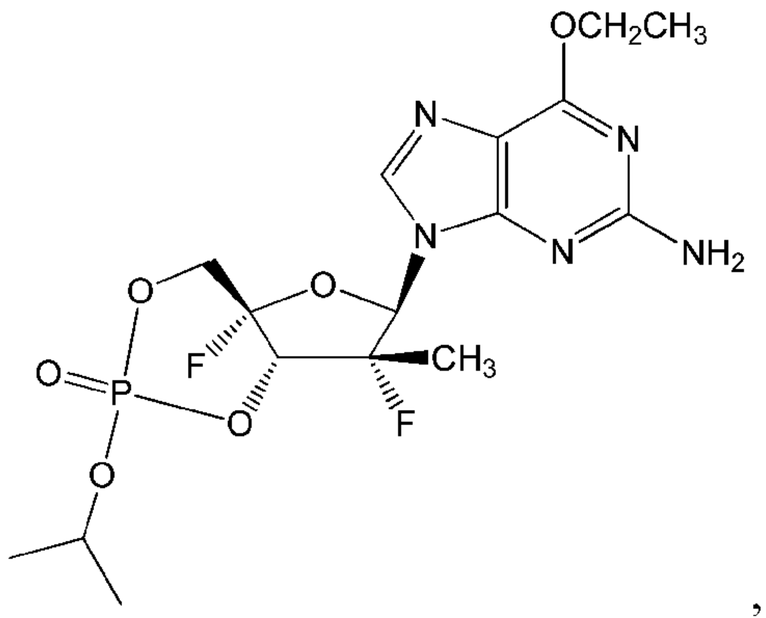
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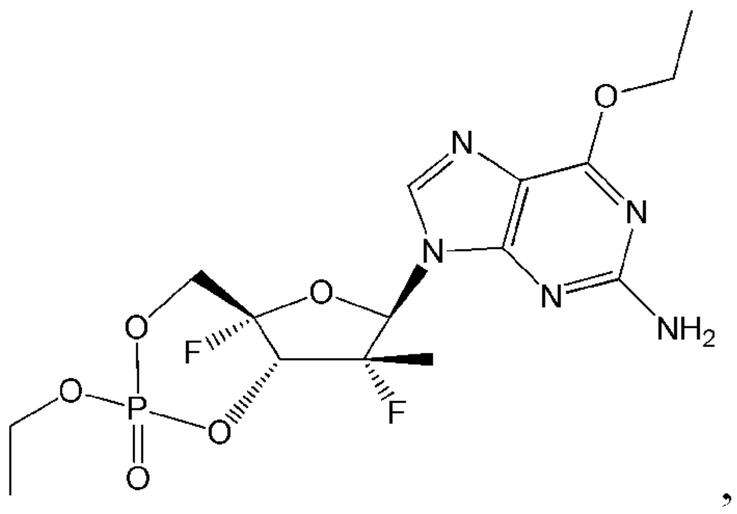
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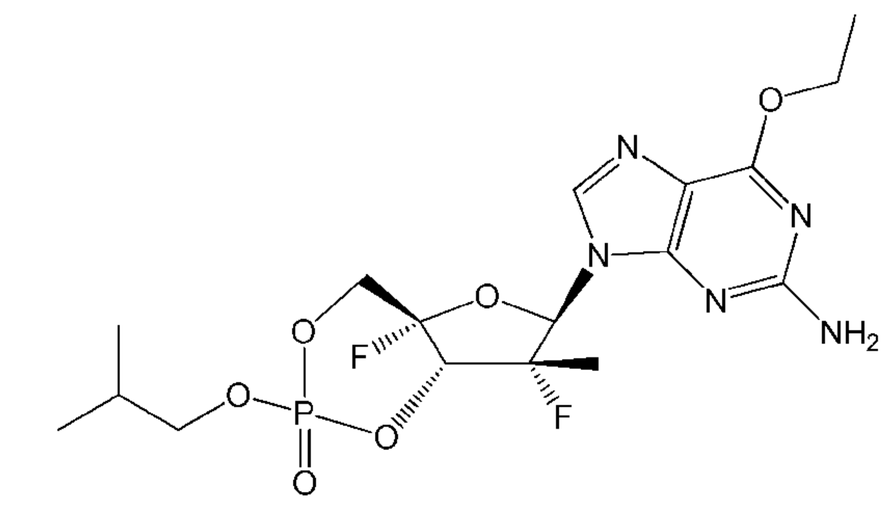


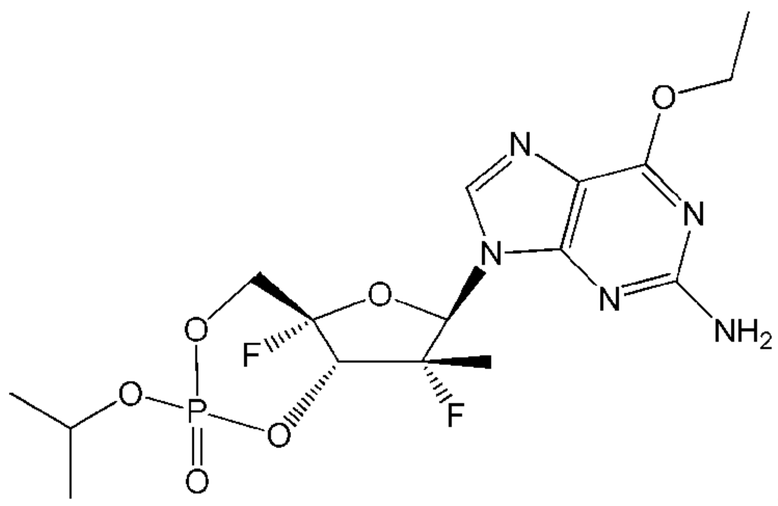
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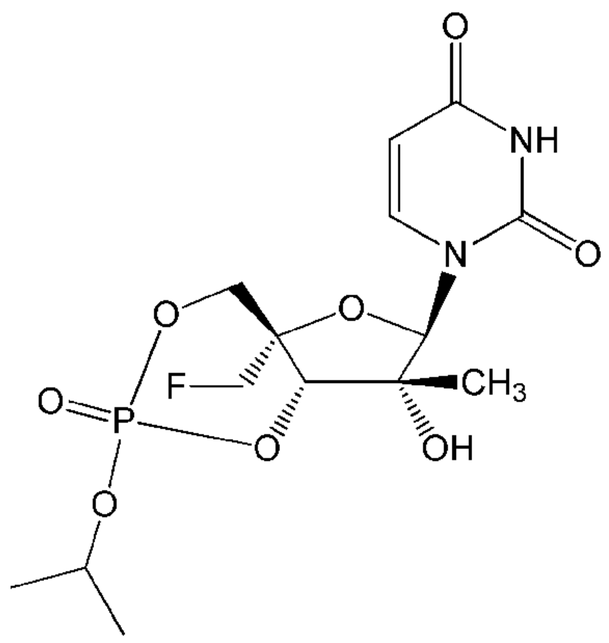


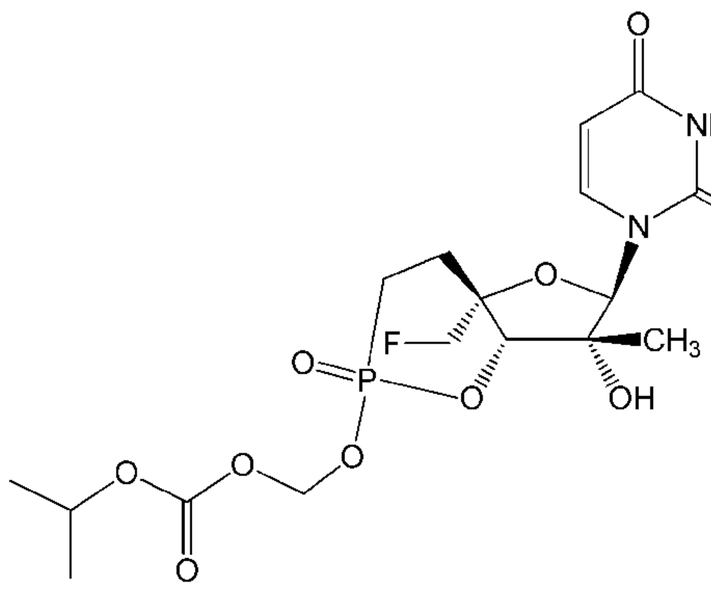
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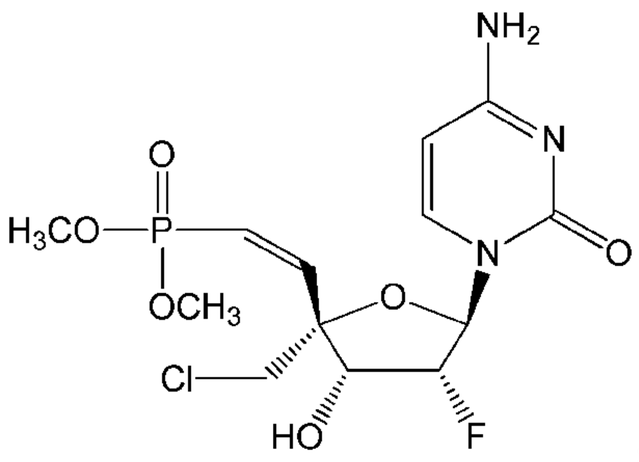

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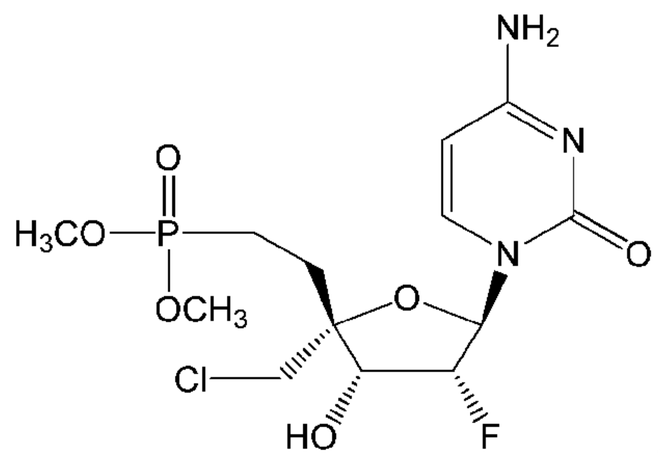

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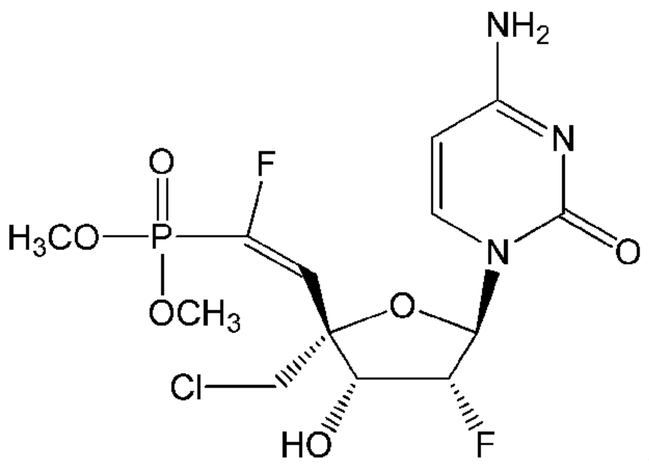

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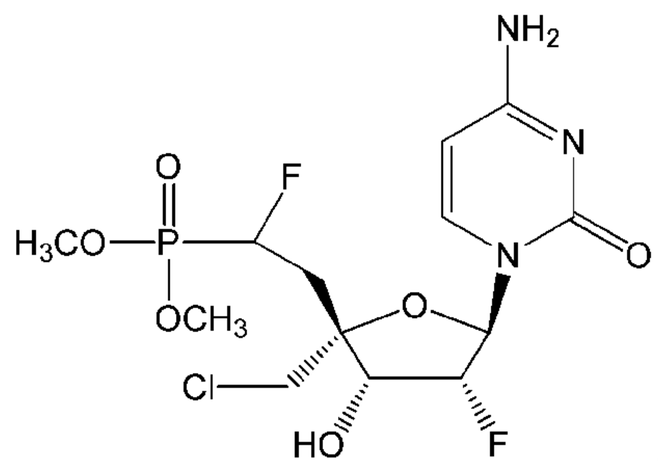

, or a pharmaceutically acceptable salt of the foregoing.

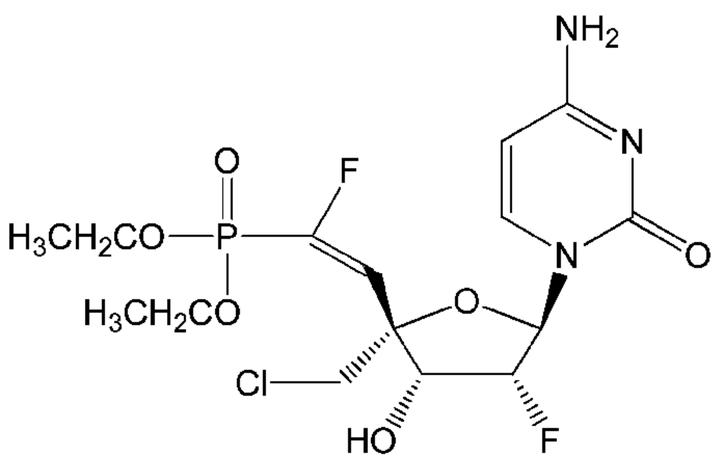
[0190] Examples of a compound of Formula (III) include, but are not limited to, the following:

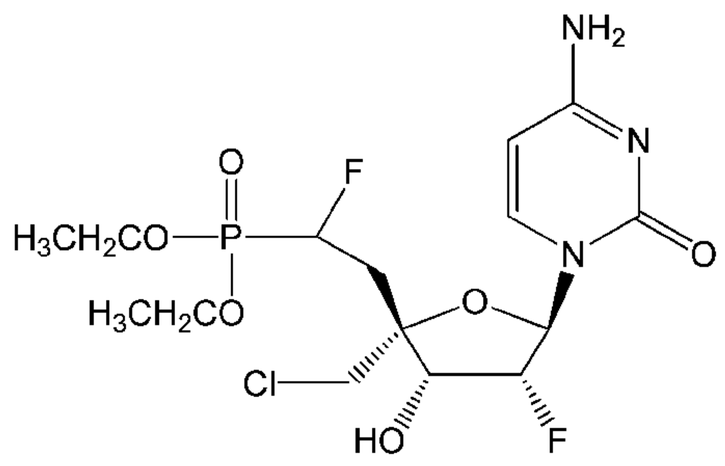

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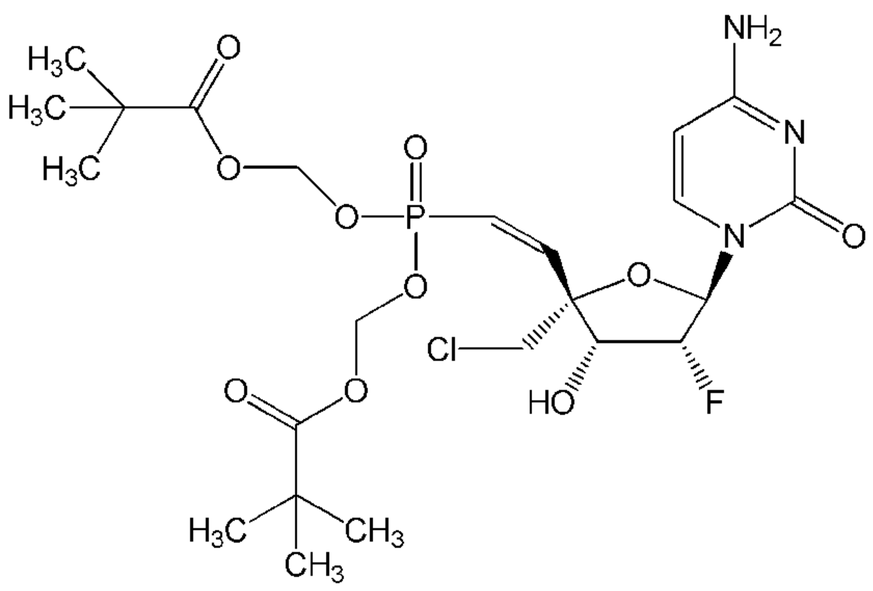

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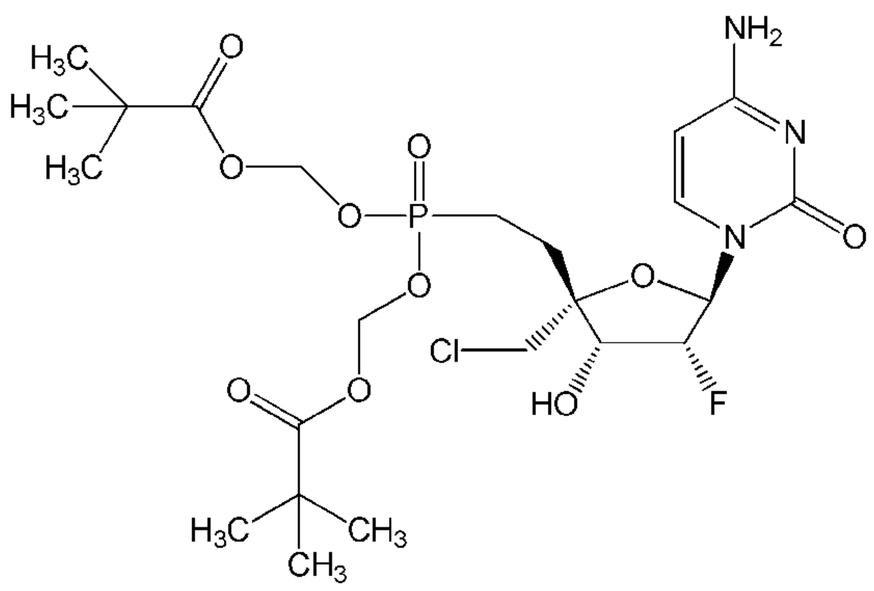

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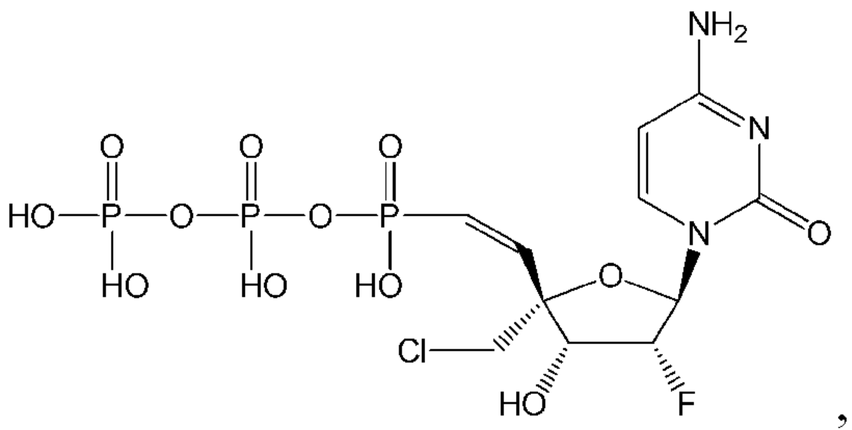
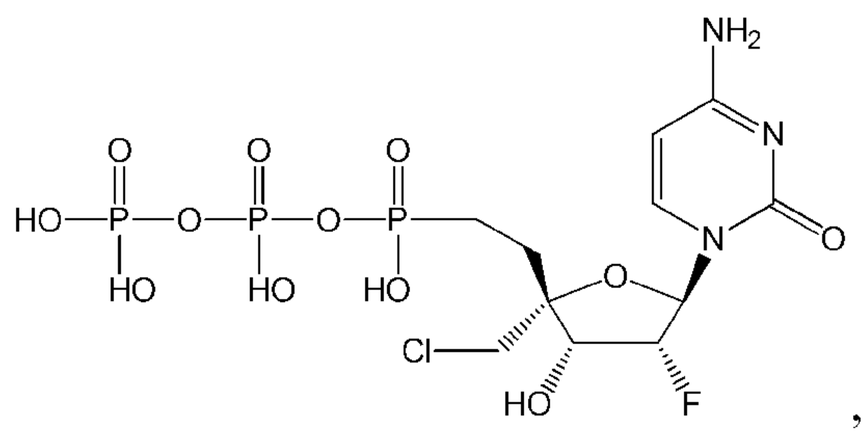
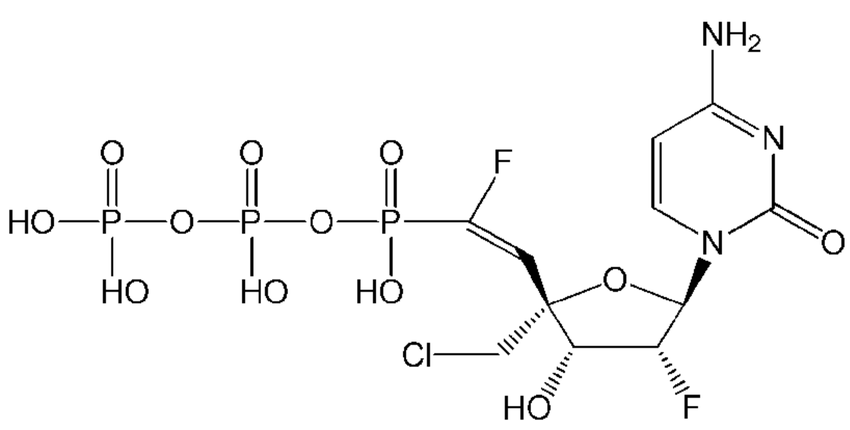
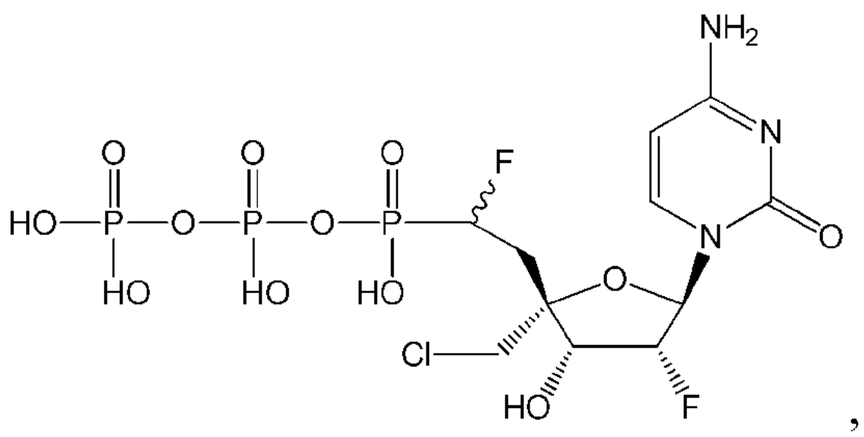

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and


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or a pharmaceutically acceptable salt of the foregoing.

[0191] Further examples of a compound of Formula (III) include, but are not limited to, the following:


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and

, or a pharmaceutically acceptable salt of the foregoing.

[0192] Compounds disclosed herein, for example compounds of Formulae (I), (II) and (III), and pharmaceutically acceptable salts of the foregoing, can be administered in various ways. Examples of suitable techniques for administration include, 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.

[0193] 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. In some embodiments, a compound described herein (such as a compound of Formula (I), a compound of Formula (II) and/or a compound of Formula (III), and pharmaceutically acceptable salts of the foregoing) can be administered intranasally. In other embodiments, a compound described herein (such as a compound of Formula (I), a compound of Formula (II) and/or a compound of Formula (III), and pharmaceutically acceptable salts of the foregoing) can be administered via an injection.

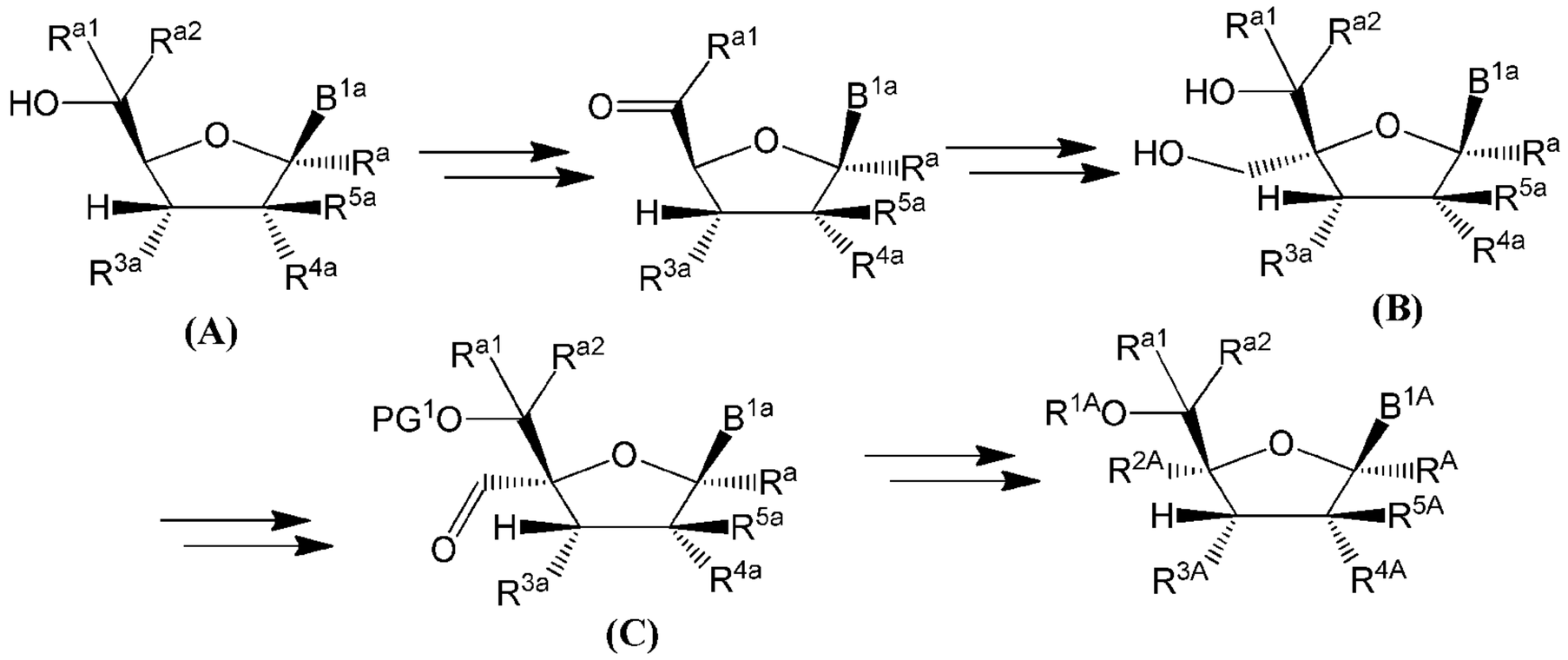
[0194] The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient.

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

[0195] Compounds of Formula (I), Formula (II) and Formula (III), and those described herein may be prepared in various ways. Some compounds of Formulae (I), (II) and (III) can be obtained commercially and/or prepared utilizing known synthetic procedures. General synthetic routes to the compounds of Formulae (I), (II) and (III), and some examples of starting materials used to synthesize the compounds of Formulae (I), (II) and (III) are shown and described herein. The routes shown and described herein are illustrative only and are not intended, nor are they to be construed, to limit the scope of the claims in any manner whatsoever. Those skilled in the art will be able to recognize modifications of the disclosed syntheses and to devise alternate routes based on the disclosures herein; all such modifications and alternate routes are within the scope of the claims.

Scheme 1

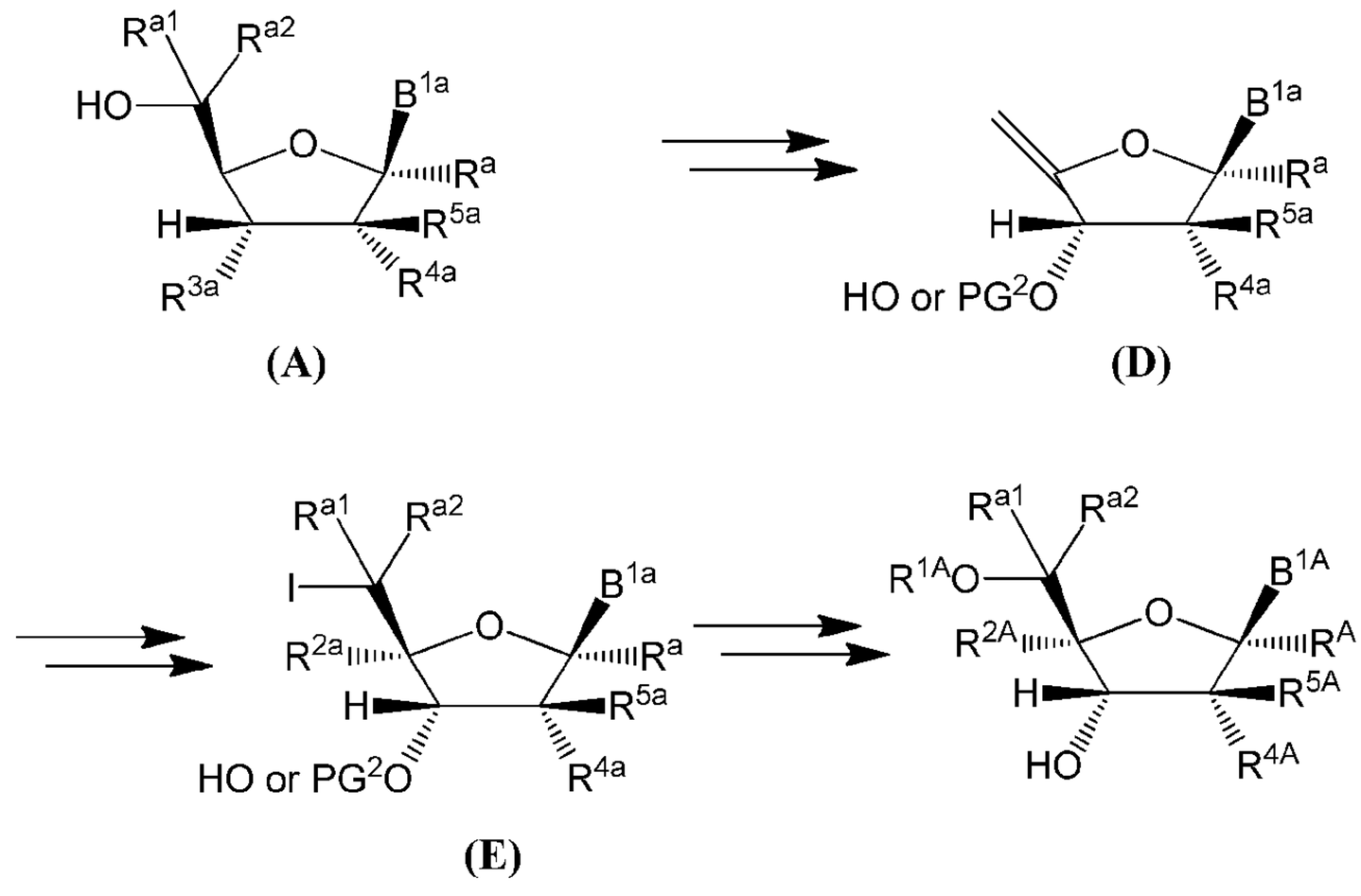


[0196] As shown in Scheme 1, compounds of Formula (I) can be prepared from a nucleoside, for example, a nucleoside of Formula (A). In Scheme 1, R^a, R^{3a}, R^{4a}, R^{5a}, and B^{1a} can be the same as R^A, R^{3A}, R^{4A}, R^{5A}, and B^{1A} as described herein for Formula (I), and PG^1 is a suitable protecting group. 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 $LiAlH_4$. The oxygen attached to the 5'-carbon of Formula (B) can be protected, and the hydroxymethyl group at the 4'-position can be oxidized to an aldehyde using a suitable oxidizing agent(s) to form a compound of Formula (C). Examples of suitable oxidizing agent(s) are described herein. An optionally substituted C_{2-6} alkenyl or an optionally

substituted C_{2-6} alkynyl can be formed at the 4'-position using methods known to those skilled in the art, for example, Wittig reagent and n-BuLi, Wittig-type reactions, Peterson olefination reaction, and Corey Fuchs reaction. An optionally substituted C_{1-6} alkyl can be obtained by hydrogenating the unsaturated group attached to the 4'-position, for example, using hydrogen over palladium on carbon.

[0197] Alternatively, 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). An iodoalkyl can be transformed to an unsubstituted C_{1-6} alkyl group using methods known to those skilled in the art, for example, hydrogen over palladium on carbon. A compound of Formula (C) can be reacted with hydroxylamine to form an oxime. The oxime can be transformed to a cyano group using methods known to those skilled in the art, for example, using methanesulfonyl chloride.

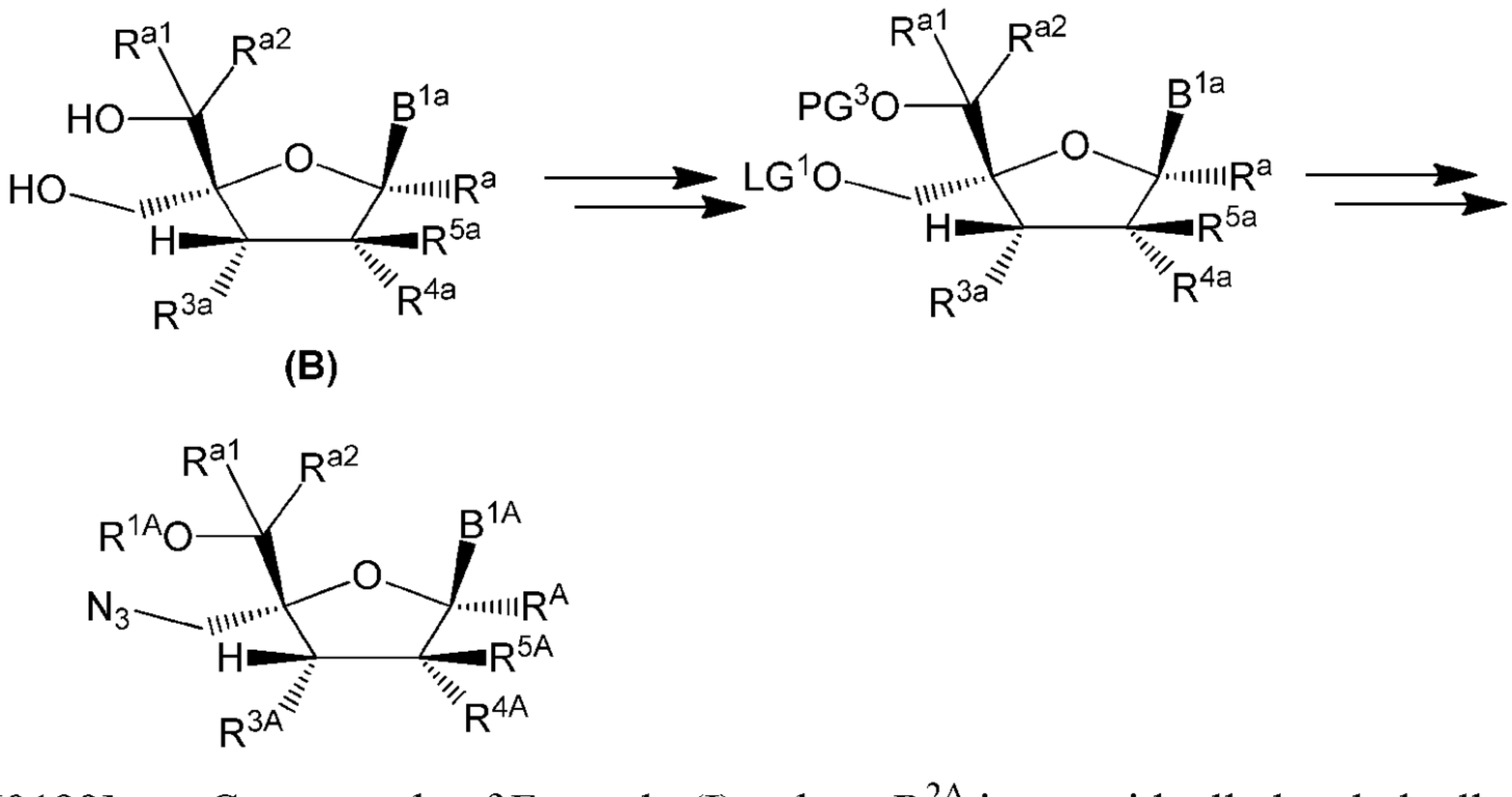
Scheme 2



[0198] As shown in Scheme 2, compounds of Formula (I), where R^{2A} is an optionally substituted –O–C_{1-6} alkyl, an optionally substituted –O–C_{3-6} alkenyl or an optionally substituted –O–C_{3-6} alkynyl, can be prepared from a nucleoside, for example, a nucleoside of Formula (A). In Scheme 2, 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 Formula (I), and PG^2 can be a suitable protecting group. The nucleoside can undergo elimination and form an olefin having the general formula of Formula (D). A compound of Formula (D) can be treated with an iodinating reagent in the presence of lead carbonate and an alkoxy source to form a compound of Formula (E). A compound of Formula (E) can then be transformed to a compound of Formula (I) through displacement of the iodide with an oxygen nucleophile.

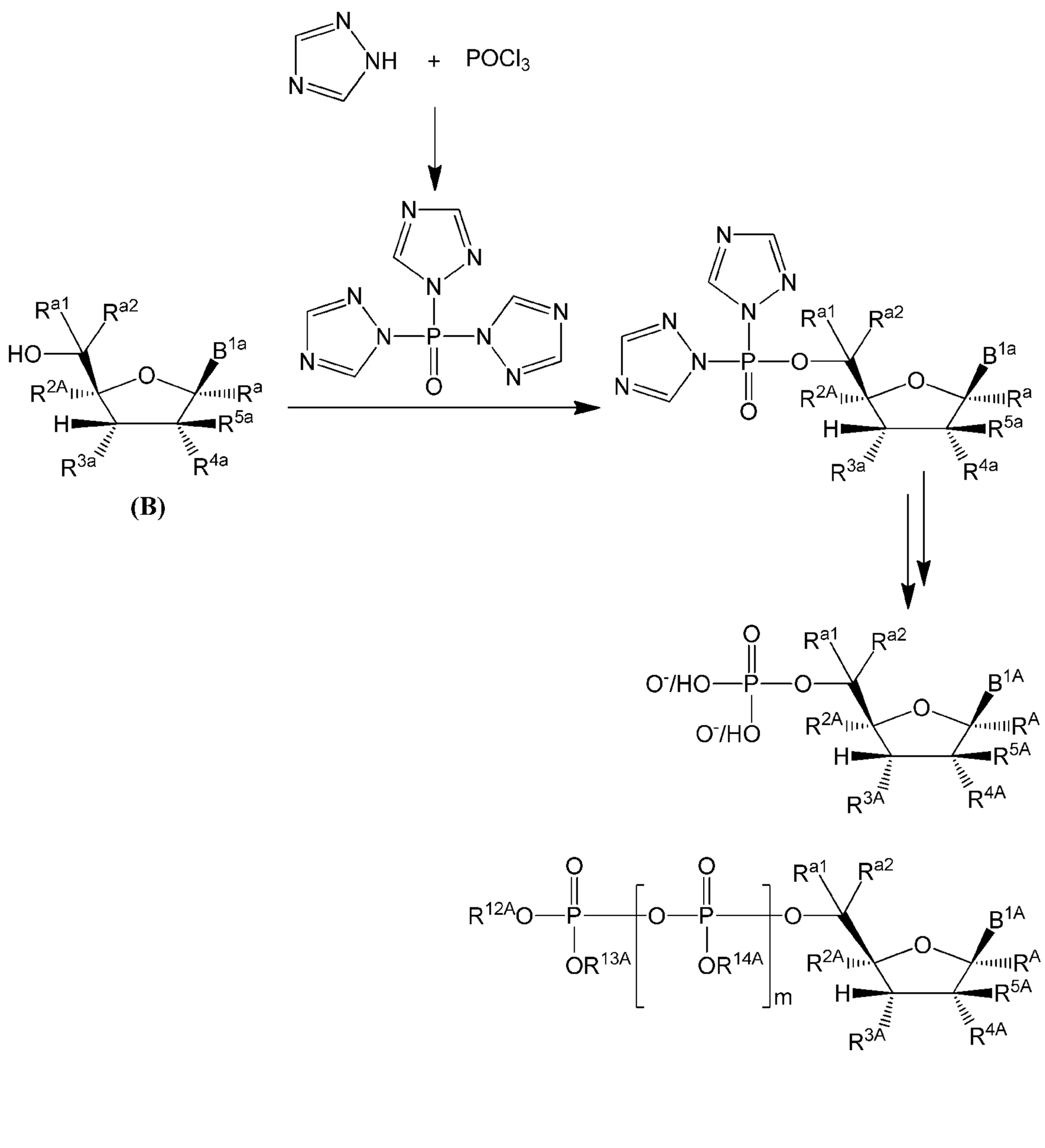
Scheme 3



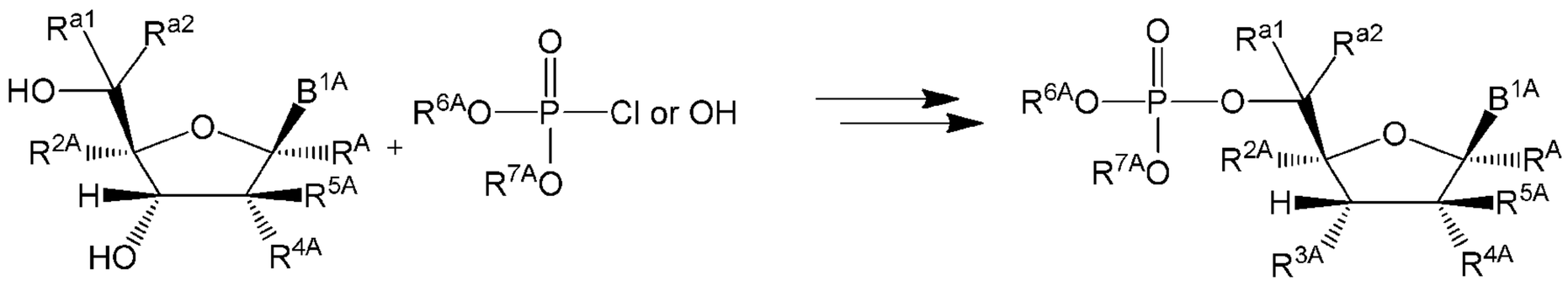
[0199] Compounds of Formula (I), where R^{2A} is an azidoalkyl or haloalkyl can be prepared from a compound of Formula (B). In Scheme 3, R^a, R^{3a}, R^{4a}, R^{5a} and B^{1a} can be the same as R^A, R^{3A}, R^{4A}, R^{5A} and B^{1A} as described herein for Formula (I), PG^3 can be a suitable protecting group and LG^1 can be a suitable leaving group. 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 or halo group using a metal azide reagent or metal halide, respectively. An example of a suitable metal azide is sodium azide. An example of a suitable metal halide is lithium chloride. 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.

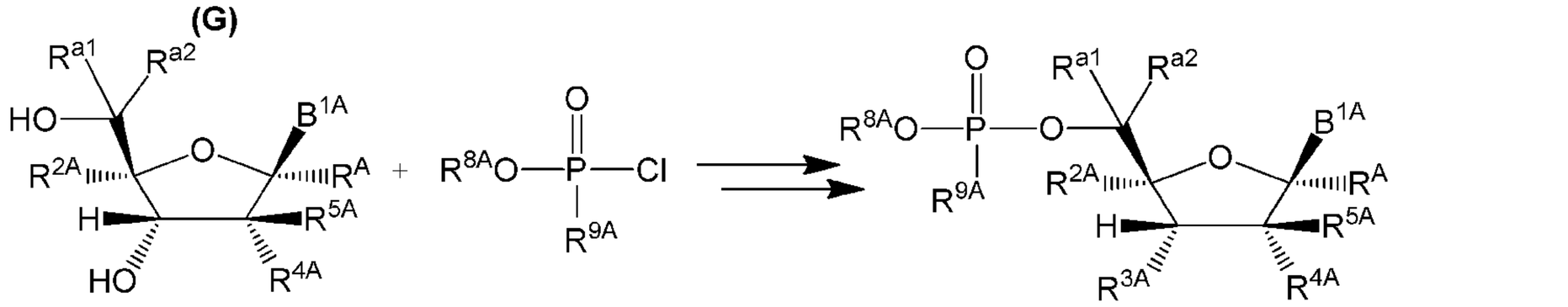
Scheme 4



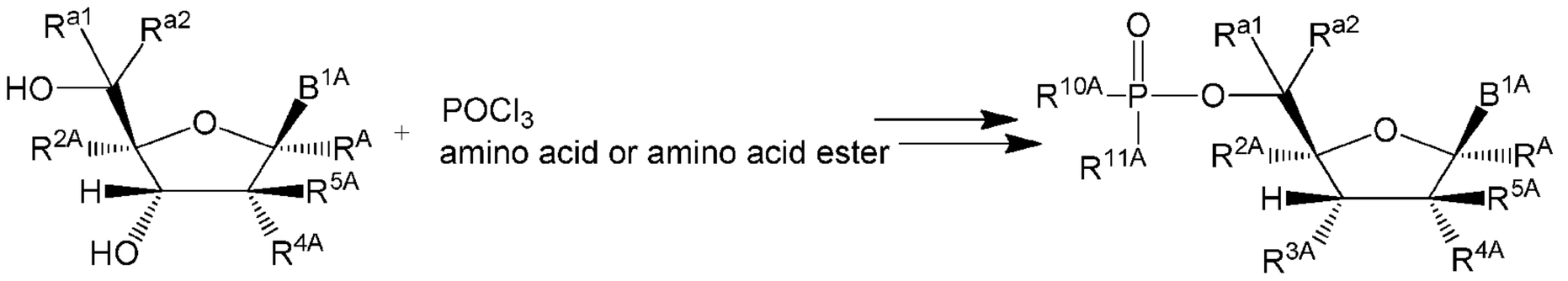
Scheme 5



(G)



(G)



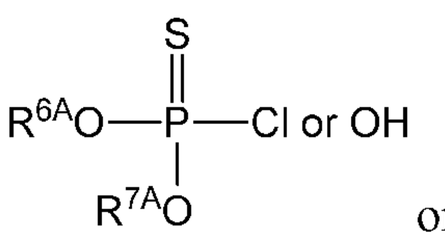
(G)

[0200] 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 4 and 5. In Schemes 4 and 5, 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 Formula (I). A phosphorus containing precursor can be coupled to the nucleoside, for example, a compound of Formula (F) or a compound of Formula (G). As shown in Scheme 4, 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.

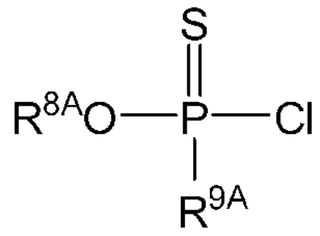
[0201] In some embodiments, an alkoxide can be generated from a compound of Formula (G) using an organometallic reagent, such as a Grignard reagent. The alkoxide can be coupled to the phosphorus containing precursor. Suitable Grignard reagents are known to those skilled in the art and include, but are 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.

[0202] 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,



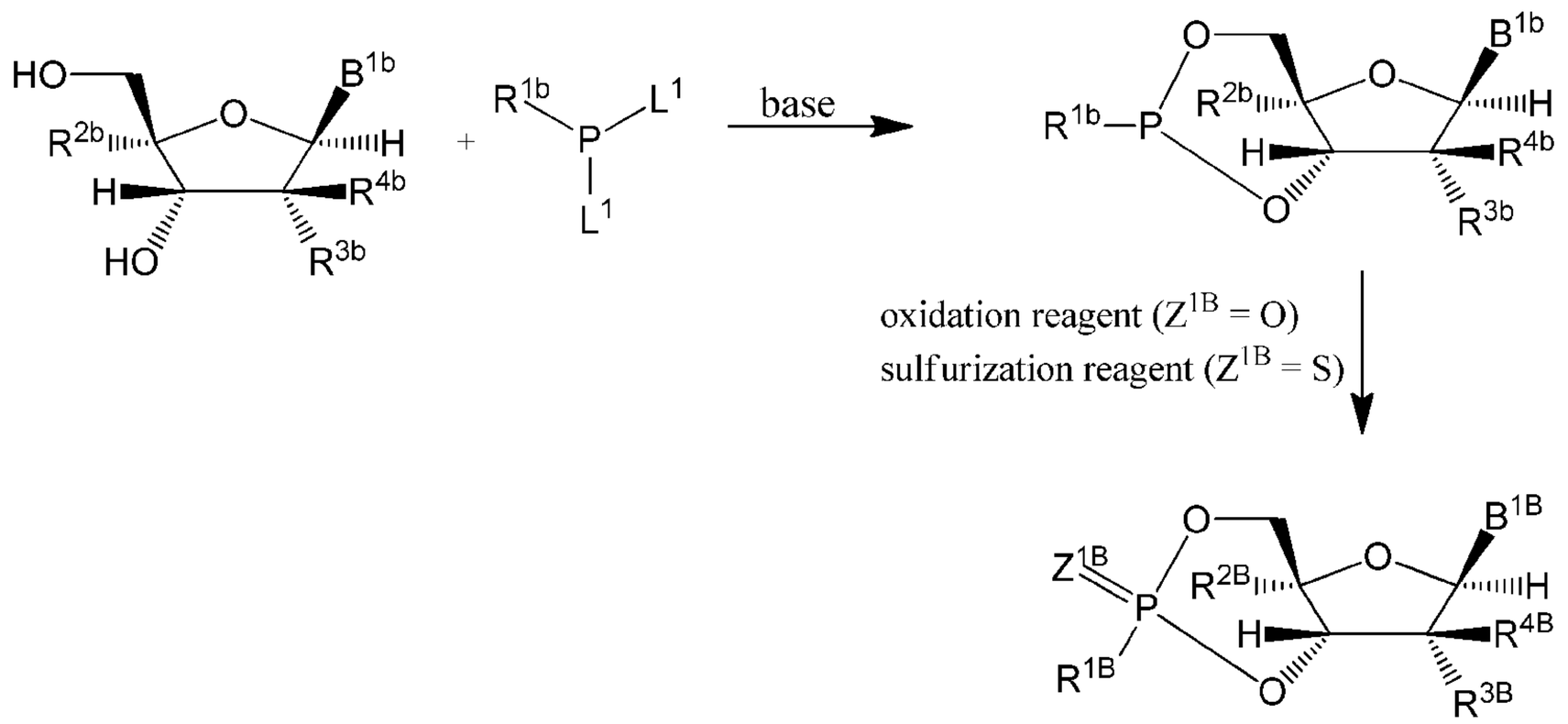
or



. 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).

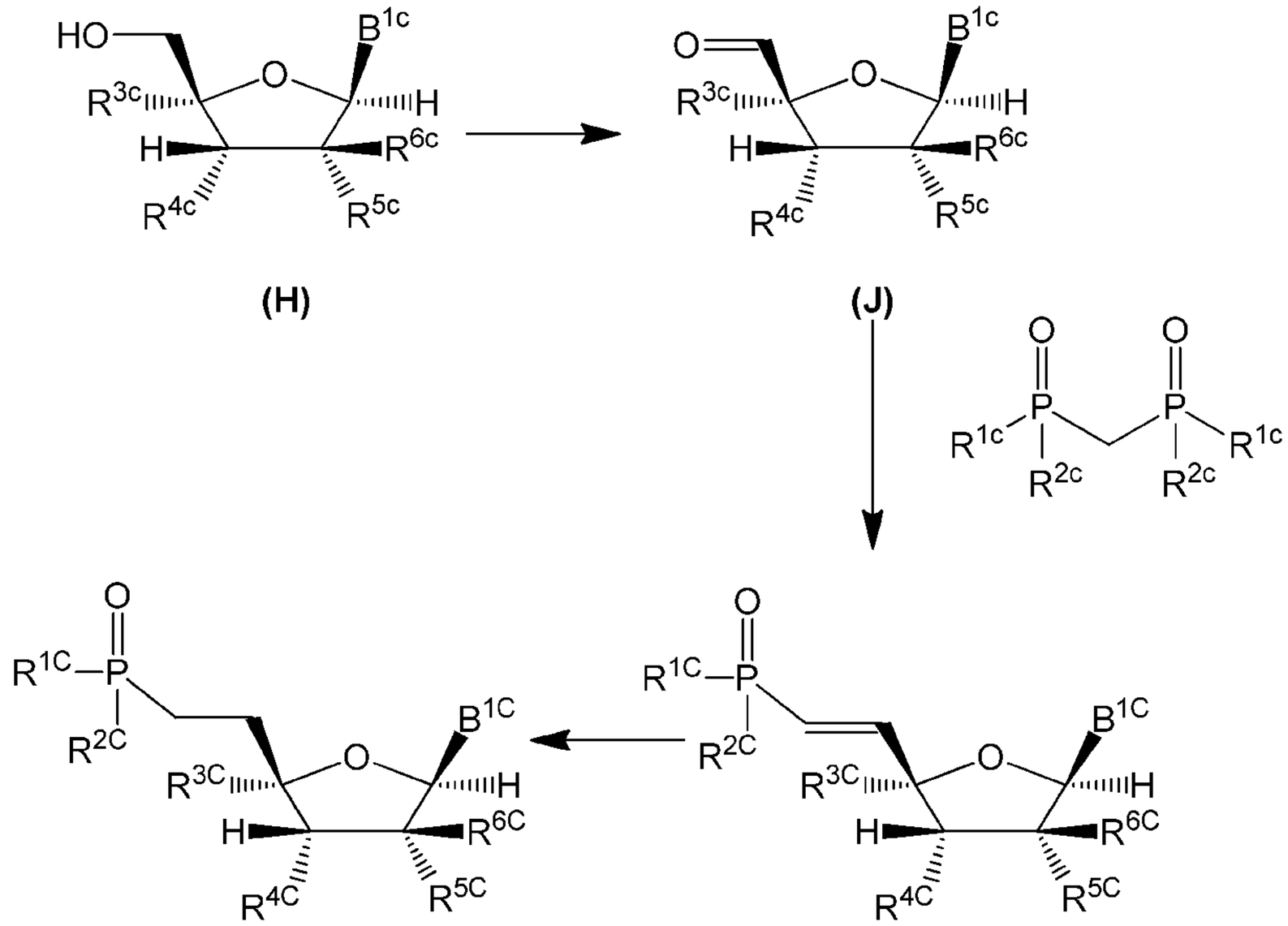
[0203] Suitable phosphorus containing precursors can be commercially obtained or prepared by synthetic methods known to those skilled in the art. Examples of general structures of phosphorus containing precursors are shown in Schemes 4 and 5.

Scheme 6:



[0204] A method for forming a compound of Formula (II) is shown in Scheme 6. In Scheme 6, R^{1b}, R^{2b}, R^{3b}, R^{4b} and B^{1b} can be the same as R^{1B}, R^{2B}, R^{3B}, R^{4B} and B^{1B} as described herein for Formula (II), each L^1 can be a halogen, a sulfonate ester or an amine (mono- or di-substituted), and X can be oxygen or sulfur. As shown in Scheme 6, a compound having a hydroxy group attached to the 3'-carbon and a hydroxy group attached to the 5'-carbon can be reacted with a compound having the formula, $(R^{1b})P(L^1)_2$, in the presence of a base, to produce a phosphite compound. Suitable bases are known to those skilled in the art and described herein. The phosphorus can then be oxidized to phosphorus(V) using a suitable oxidizing agent, to produce a compound where X is O (oxygen). Alternatively, the phosphite compound can be reacted with a sulfurization reagent to produce a compound where X is S (sulfur). Suitable oxidizing and sulfurization agents are known to those skilled in the art. For example, the oxidation can be carried out using iodine as the oxidizing agent and water as the oxygen donor. Suitable sulfurization agents are described herein.

Scheme 7



[0205] A method for forming a compound of Formula (III) is shown in Scheme 7. In Scheme 7, R^{1c}, R^{2c}, R^{3c}, R^{4c}, R^{5c}, R^{6c} and B^{1c} can be the same as R^{1C}, R^{2C}, R^{3C}, R^{4C}, R^{5C}, R^{6C} and B^{1C} as described herein for Formula (III), and R^{7C} and R^{8C} are not shown. The oxygen attached to the 5'-carbon of the compound of Formula (H) can be oxidized to a ketone using methods and reagents known to those skilled in the art. For example, an oxidizing agent, such as Dess-Martin periodinane, can be utilized. A phosphorus-containing reagent can then be added to a compound of Formula (J) in the presence of a strong base (e.g., sodium hydride). The double bond can be hydrogenated, for example using hydrogen gas or Pd/C, to a single bond. Additional phosphates can be added via phosphorylation to form a di- or tri-phosphate using suitable reagents, such as a pyrophosphate (e.g., tetrabutylammonium pyrophosphate).

[0206] An acyl group can be added to the 5'-position and/or the 3'-position of a compound of Formula (I) or (III) using methods known to those skilled in the art. One suitable method is using an anhydride in pyridine.

[0207] During the synthesis of any of the compounds described herein, if desired, any hydroxy groups attached to the pentose ring, and any –NH and/or NH_2 groups present on

the B^{1a}, B^{1b} and B^{1c} can be protected with one or more suitable protecting groups. Suitable protecting groups are described herein. For example, when R^{3a} and/or R^{4c} is a hydroxy group, R^{3a} and/or R^{4c} can be protected with a triarylmethyl group or a silyl group. Likewise, any –NH and/or NH_2 groups present on the B^{1a}, B^{1b} and B^{1c} can be protected, such as with a triarylmethyl and a silyl group(s). Examples of triarylmethyl groups include but are not limited to, trityl, monomethoxytrityl (MMTr), 4,4'-dimethoxytrityl (DMTr), 4,4',4"-trimethoxytrityl (TMTr),. 4,4',4"-tris- (benzoyloxy) trityl (TBTr), 4,4',4"-tris (4,5-dichlorophthalimido) trityl (CPTr), 4,4',4"-tris (levulinyloxy) trityl (TLTr), p-anisyl-1-naphthylphenylmethyl, di-o-anisyl-1-naphthylmethyl, p-tolyldipheylmethyl, 3-(imidazolylmethyl)-4,4'-dimethoxytrityl, 9-phenylxanthen-9-yl (Pixyl), 9-(p-methoxyphenyl) xanthen-9-yl (Mox), 4-decyloxytrityl, 4- hexadecyloxytrityl, 4,4'-dioctadecyltrityl, 9-(4-octadecyloxyphenyl) xanthen-9-yl, 1,1'-bis-(4-methoxyphenyl)-1'-pyrenylmethyl, 4,4',4"-tris-(tert-butylphenyl) methyl (TTTr) and 4,4'-di-3, 5-hexadienoxytrityl. Examples of silyl groups include, but are not limited to, trimethylsilyl (TMS), *tert*-butyldimethylsilyl (TBDMS), triisopropylsilyl (TIPS), tert-butyldiphenylsilyl (TBDPS), tri-*iso*-propylsilyloxymethyl and [2-(trimethylsilyl)ethoxy]methyl. Alternatively, R^{3a} and R^{4a} and/or R^{4c} and R^{5c} 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. Those skilled in the art will appreciate that groups attached to the pentose ring and any –NH and/or NH_2 groups present on the B^{1a}, B^{1b} and B^{1c} can be protected with various protecting groups, and any protecting groups present can be exchanged for other protecting groups. The selection and exchange of the protecting groups is within

the skill of those of ordinary skill in the art. Any protecting group(s) can be removed by methods known in the art, for example, with an acid (e.g., a mineral or an organic acid), a base or a fluoride source.

Pharmaceutical Compositions

[0208] Some embodiments described herein relates to the use of a pharmaceutical composition, that can include an effective amount of one or more compounds described herein (e.g., a compound of Formula (I), a compound of Formula (II) and/or a compound of Formula (III), or a pharmaceutically acceptable salt of the foregoing) and a pharmaceutically acceptable carrier, diluent, excipient or combination thereof.

[0209] 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.

[0210] The term "physiologically acceptable" defines a carrier, diluent or excipient that does not abrogate the biological activity and properties of the compound.

[0211] 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.

[0212] 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.

[0213] 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.

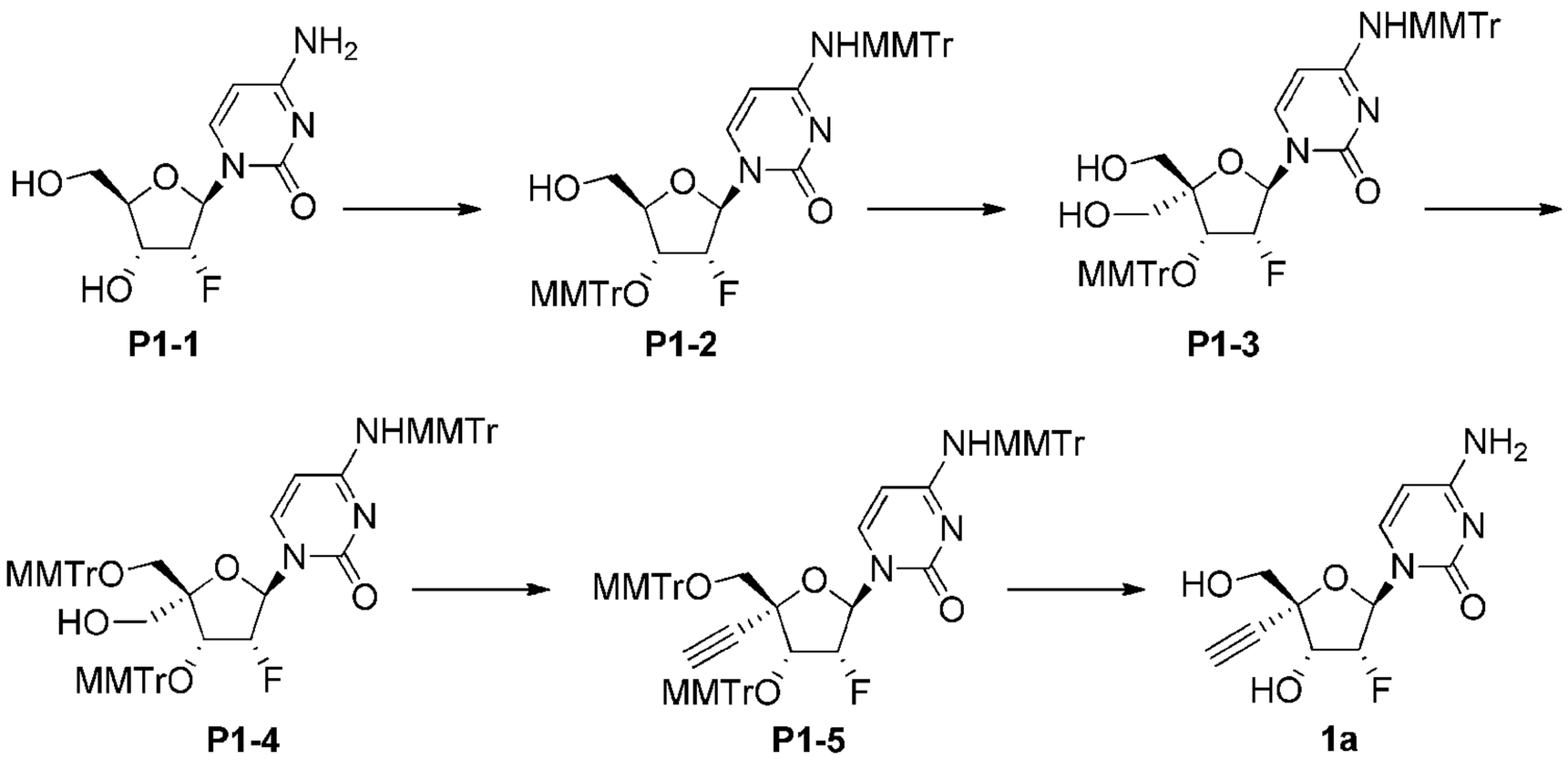
[0214] The pharmaceutical compositions described herein can be administered to a human patient *per se*, or in pharmaceutical compositions where they are mixed with other active ingredients, as in combination therapy, or carriers, diluents, excipients or combinations thereof. Proper formulation is dependent upon the route of administration chosen. Techniques for formulation and administration of the compounds described herein are known to those skilled in the art.

[0215] 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.

EXAMPLES

[0216] 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
Preparation of Compound 1a



[0217] To an ice cooled solution of **P1-1** (10.0 g, 40.8 mmol) in dry pyridine (100 mL) was added TBSCl in pyridine (1M, 53 mL) dropwise at room temperature (R.T.). The reaction mixture was stirred at R.T. for 16 hours. The reaction mixture was then quenched with water, concentrated to give a residue. The residue was separated by ethyl acetate (EA) and saturated $NaHCO_3$ aq. solution. The organic phase was dried and concentrated. The residue was purified on a silica gel column (5% MeOH in DCM) to give a crude 5'-O-TBS protected intermediate as a white solid (13.4 g, 91%). The intermediate was dissolved in anhydrous DCM (100 mL) and sym-collidine (17.9 g, 149.2 mmol), $AgNO_3$ (25 g, 149.2 mmol) and MMTrCl (45 g, 149.2 mmol) were added. The mixture was stirred at R.T. for 16 hours. The mixture was quenched with water, and the organic layer was separated and concentrated. The residue purified on a silica gel column (30% PE in EA) to give the crude product. The crude product was dissolved in 1M TBAF (50 mL) in THF. The mixture was stirred at R.T. for 2 hours. The solvent was removed, and the residue was purified on a silica gel column (50% PE in EA) to give **P1-2** as a white solid (21.4 g, 66% for three steps).

[0218] To a solution of pyridine (521 mg, 6.59 mmol) in anhydrous DMSO (5 mL) was added TFA (636 mg, 5.58 mmol) dropwise at 10°C under nitrogen. The reaction mixture was stirred until the solution became clear. The solution was then added into a mixture of **P1-2** (4.0 g, 5.07 mmol) and DCC (3.86 g, 18.76 mmol) in anhydrous DMSO (18 mL) at R.T. under nitrogen. The reaction mixture was stirred at 30°C overnight. Water (80

mL) was added into the mixture, diluted with EtOAc (100 mL) and filtered. The filtrate was extracted with DCM (100 mL x 6). The organic layer was washed with saturated aq. $NaHCO_3$, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified on a silica gel column eluted with 1% MeOH in DCM to give the intermediate (3.5 g, 87.7%) as a yellow solid. The intermediate (3.5 g, 4.45 mmol) was dissolved in dioxane (25 mL) and aq. HCHO (668 mg, 22.25 mmol) was added at R.T. 2N NaOH (4.5 mL, 8.9 mmol) was then added. The reaction mixture was stirred at 30°C overnight. $NaBH_4$ (593 mg, 15.6 mmol) was added in by portions at 5°C, and the mixture was stirred at R.T. for 15 min. The reaction was quenched with water, and the mixture was extracted with EtOAc (100 mL x 3). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified on a silica gel column eluted with 1% MeOH in DCM to give **P1-3** as a yellow solid (2.5 g, 67%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.82-7.50 (m, 29H), 5.40 (d, J = 23.2 Hz, 1H), 4.99 (d, J = 7.6 Hz, 1H), 4.46 (dd, J_1 = 6.0 Hz, J_2 = 54.4 Hz, 1H), 3.94 (dd, J_1 = 4.4 Hz, J_2 = 12.4 Hz, 1H), 3.78 (s, 6H), 3.42-3.69 (m, 2H), 2.71-3.05 (m, 2H), 2.45 (m, 1H).

[0219] To an ice cooled solution of **P1-3** (4.0 g, 4.9 mmol) in dry pyridine (20 mL) was added dropwise TBSCl in pyridine (1M, 5.88 mL). The reaction mixture was stirred at R.T. for 16 hours. The reaction mixture was then quenched with water, concentrated to give a residue. The residue was separated in EA and saturated aq. $NaHCO_3$. The organic layer was separated and dried, and then concentrated. The residue was purified on a silica gel column (1% MeOH in DCM) to give the intermediate as a yellow solid (3.2 g, 70%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.53-6.83 (m, 29H), 5.51 (d, J = 21.2 Hz, 1H), 4.98 (d, J = 7.6 Hz, 1H), 4.67 (dd, J_1 = 5.6 Hz, J_2 = 22.4 Hz, 1H), 4.22 (dd, J_1 = 5.6 Hz, J_2 = 53.2 Hz, 1H), 4.07 (m, 1H), 3.89 (m, 1H), 3.80 (s, 6H), 3.70-3.67 (m, 1H), 3.03-2.98 (m, 1H), 2.26 (m, 1H), 0.93 (s, 9H), 0.10 (s, 6H).

[0220] The obtained intermediate was dissolved in anhydrous DCM (20 mL) and collidine (360 mg, 3 mmol), and $AgNO_3$ (500 mg, 3 mmol) and MMTrCl (606 mg, 2 mmol) were added. The mixture was stirred at R.T. for 16 hours. The reaction mixture was quenched with water, and the organic layer was separated and concentrated. The residue was purified on a silica gel column (0.5% MeOH in DCM) to give the fully protected intermediate as a yellow solid (3.3 g, 80%). The intermediate was dissolved in 1M TBAF in

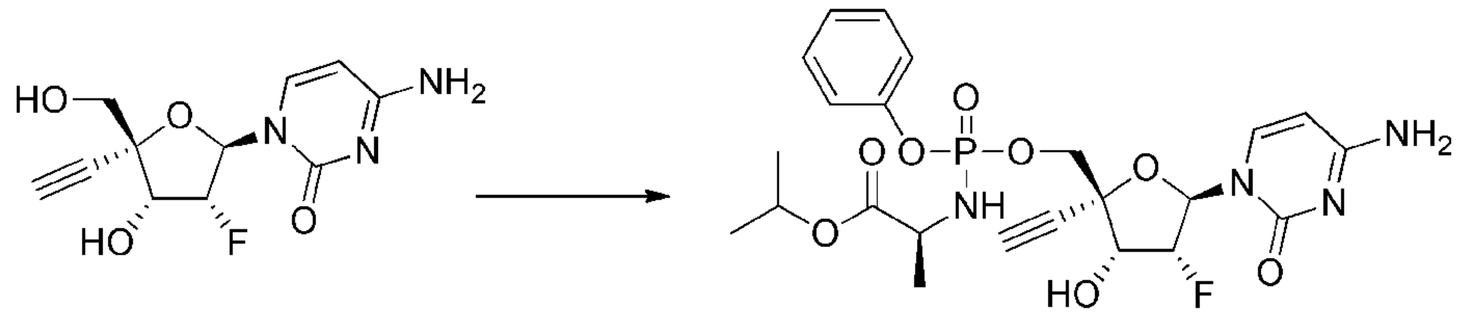
THF (5 mL) and was stirred at R.T. for 2 hours. The solution was concentrated, and the residue was purified on a silica gel column (1% MeOH in DCM) to give a mixture of **P1-3** and **P1-4**, which was separated by HPLC separation (MeCN and 0.1% HCOOH in water) to give **P1-4** as a white solid (1.5 g, 25%).

[0221] Compound **P1-4** (1.5 g, 1.22 mmol) was suspended in anhydrous DCM (50 mL), and Dess Martin periodinane (1.2 g, 2.73 mmol) was added at 0°C. The reaction mixture was stirred at R.T. for 3 hours. The reaction mixture was then quenched with saturated aq. $Na_2S_2O_3$ and Na_2CO_3. The organic layer was separated and dried, and then concentrated to give the aldehyde intermediate as a white solid.

[0222] A solution of $ClCH_2PPh_3Br$ (2.19 g, 5.6 mmol) in anhydrous THF (40 mL) was cooled to -78°C. n-BuLi (2.5 M, 2.3 mL) was added in dropwise. After the addition, the mixture was stirred at 0°C for 2 hours. A solution of the aldehyde in anhydrous THF (10 mL) was then added. The mixture was stirred at R.T. for 16 hours. The reaction was quenched with saturated NH_4Cl aq. and extracted by EA. The organic layer was separated, dried and concentrated. The residue was purified on a silica gel column (1% MeOH in DCM) to give the intermediate as a yellow solid (1.1 g, 73%). To a solution of the intermediate (1.1 g, 0.98 mmol) in anhydrous THF (40 mL) was added n-BuLi (2.5M, 6 mL) -78°C dropwise. The mixture was stirred at -78°C for 5 hours and then quenched with a saturated NH_4Cl aq. solution. The mixture was extracted with EA. The organic layer was separated, dried and concentrated. The residue was purified on a silica gel column (2% MeOH in DCM) to give **P1-5** as a yellow solid (910 mg, 86%).

[0223] Compound **P1-5** (910 mg, 0.84 mmol) was suspended in 80% CH_3COOH (50 mL), and the reaction mixture was stirred at 40°C for 15 hours. The solvents were evaporated, and the residue was co-evaporated with toluene to remove traces of acid and water. The residue was purified by HPLC separation (MeCN and 0.1% HCOOH in water) to give pure **1a** as a white solid (101 mg, 45%). ESI-TOF-MS: m/z 270.09 $[M+H]^+$, 539.17 $[2M+H]^+$.

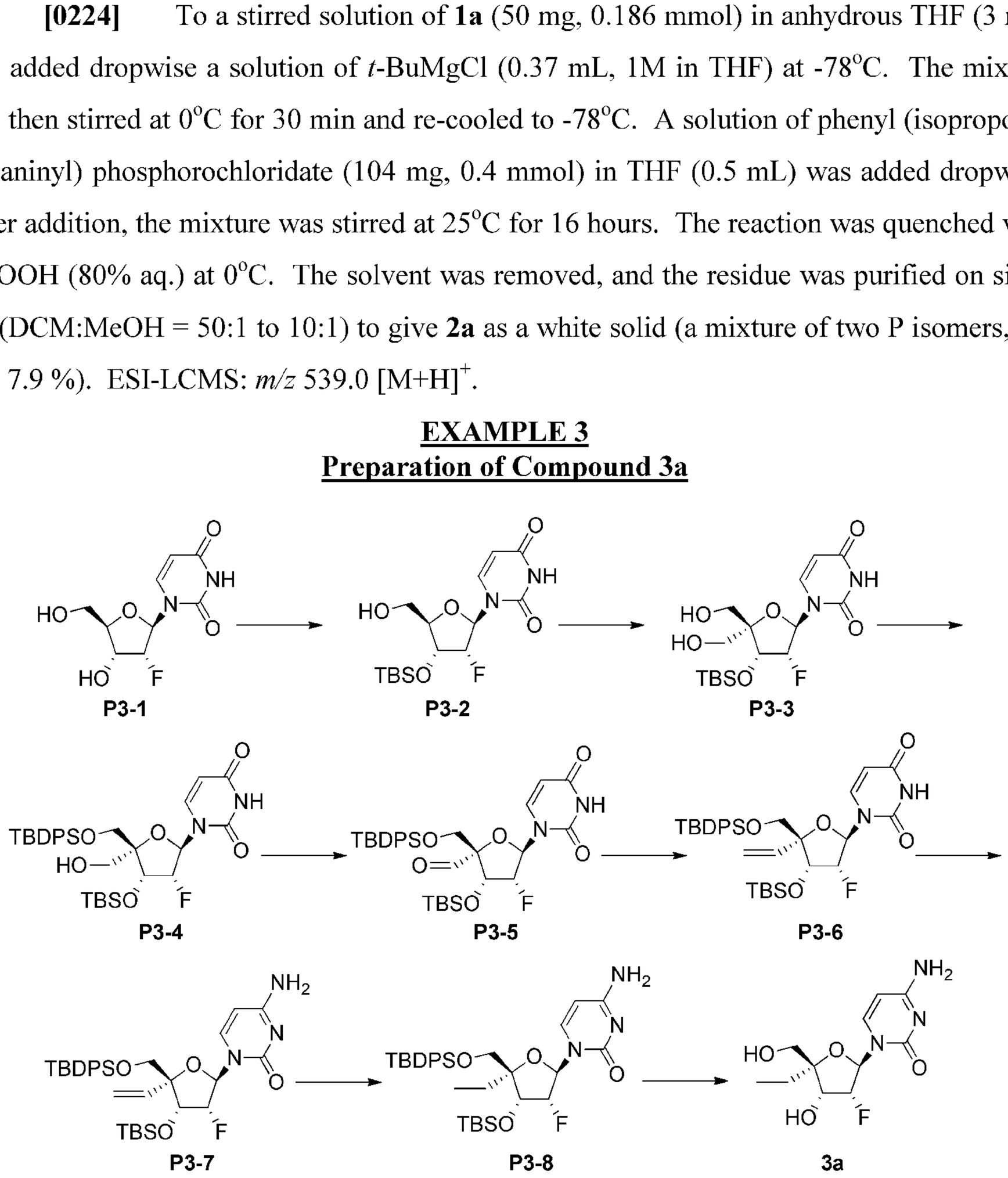
EXAMPLE 2
Preparation of Compound 2a



1a 2a

[0224] To a stirred solution of **1a** (50 mg, 0.186 mmol) in anhydrous THF (3 mL) was added dropwise a solution of *t*-BuMgCl (0.37 mL, 1M in THF) at -78°C. The mixture was then stirred at 0°C for 30 min and re-cooled to -78°C. A solution of phenyl (isopropoxy-L-alaninyl) phosphorochloridate (104 mg, 0.4 mmol) in THF (0.5 mL) was added dropwise. After addition, the mixture was stirred at 25°C for 16 hours. The reaction was quenched with HCOOH (80% aq.) at 0°C. The solvent was removed, and the residue was purified on silica gel (DCM:MeOH = 50:1 to 10:1) to give **2a** as a white solid (a mixture of two P isomers, 8.0 mg, 7.9 %). ESI-LCMS: *m/z* 539.0 $[M+H]^+$.

EXAMPLE 3
Preparation of Compound 3a



[0225] To a solution of **P3-1** (100.0 g, 406.5 mmol) in pyridine (750 mL) was added DMTrCl (164.9 g, 487.8 mmol). The solution was stirred at R.T. for 15 hours. MeOH (300 mL) was added, and the mixture 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 concentrated. The residue was dissolved in DCM (500 mL). Imidazole (44.3 g, 650.4 mmol) and TBSCl (91.9 g, 609.8 mmol) was added. The reaction mixture was stirred at R.T. for 14 hours. The reaction solution was washed with $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, and concentrated to give the crude as a light yellow solid. The crude (236.4 g, 356.6 mmol) was dissolved in 80% HOAc aq. solution (500mL). The mixture was stirred at R.T. for 15 hours. The mixture was diluted with EtOAc and washed with a $NaHCO_3$ 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 **P3-2** (131.2 g, 89.6%) as a light yellow solid. ESI-MS: m/z 802 $[M+H]^+$.

[0226] To a solution of **P3-2** (131.2 g, 364.0 mmol) in anhydrous CH_3CN (1200 mL) was added IBX (121.2 g, 432.8 mmol) at R.T. The reaction mixture was refluxed for 3 hours and then cooled to 0^oC. The precipitate was filtered-off, 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, 1.3536 mol) and 2M NaOH aq. solution (253.8 mL, 507.6 mmol) were added. The mixture was stirred at R.T. for 2 hours and then neutralized with AcOH to pH = 7. To the solution were added EtOH (400 mL) and $NaBH_4$ (51.2 g, 1.354 mol). The mixture was stirred at R.T. for 30 minutes. The mixture was quenched with saturated aq. NH_4Cl and 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 **P3-3** (51.4 g, 38.9 %) as a white solid.

[0227] To a solution of **P3-3** (51.4 g, 131.6 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 R.T. for 14 hours, 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 a mono-DMTr protected intermediate as a yellow foam (57.4 g, 62.9%). To the intermediate (57.4 g, 82.8 mmol) in CH_2Cl_2 (400 mL) was added imidazole (8.4 g, 124.2

mmol) and TBDPSCl (34.1 g, 124.2 mmol). The mixture was stirred at R.T. for 14 hours. The precipitate was filtered off, and the filtrate was washed with brine and dried over Na_2SO_4. The solvent was removed to give the residue (72.45 g) as a white solid. The solid was dissolved in 80% HOAc aq. solution (400 mL). The mixture was stirred at R.T. for 15 hours. The mixture was diluted with EtOAc 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 **P3-4** (37.6 g, 84.2%) as a white solid. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.76 (d, J = 4.0 Hz, 1H), 7.70 (dd, J_1 = 1.6 Hz, J_2 = 8.0 Hz, 2H), 7.66~7.64 (m, 2H), 7.48~7.37 (m, 6H), 6.12 (dd, J_1 = 2.8 Hz, J_2 = 16.8 Hz, 1H), 5.22 (d, J = 8.0 Hz, 1H).5.20~5.05 (m, 1H), 4.74 (dd, J_1 = 5.6 Hz, J_2 = 17.6 Hz, 1H), 4.16 (d, J = 12.0 Hz, 1H), 3.87~3.80 (m, 2H), 3.56 (d, J = 12.0 Hz, 1H), 1.16 (s, 9H), 0.92 (s, 9H), 0.14 (s, 6H).

[0228] To a solution of **P3-4** (11.8 g, 18.8 mmol) in anhydrous DCM (100 mL) was added Dess-Martin periodinane (16.3 g, 37.6 mmol) at 0°C under nitrogen. The reaction was stirred R.T. for 2.5 hours. Water (100 mL) was added, and the mixture was then filtered. The filtrate was washed with saturated aq. $NaHCO_3$ and concentrated. The crude residue was purified by silica gel column chromatography (20% EtOAc in hexane) to give **P3-5** as a white solid (10.1 g, 86.0%).

[0229] To a mixture of methyltriphenylphosphonium bromide (15.7 g, 48.5 mmol) in anhydrous THF (100 mL) was added n-BuLi (19.4 mL, 48.48 mmol) at -78°C under nitrogen. The reaction was stirred at 0°C for 30 minutes. A solution of **P3-5** (10.1 g, 16.2 mmol) in anhydrous THF (70 mL) was added dropwise at 0°C under nitrogen. The reaction was stirred at R.T. for 1.5 hours. The reaction was quenched by NH_4Cl and extracted with EtOAc. The crude product was purified by silica gel column chromatography (20% EtOAc in hexane) to give **P3-6** as a white solid (8.3 g, 82.2%).^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.16 (s, 1H), 8.81 (d, J = 8.0 Hz, 1H), 7.58-7.67 (m, 4H), 7.37-7.46 (m, 6H), 6.17 (d, J = 16.0 Hz, 1H), 5.91 (dd, J_1 = 10.8 Hz, J_2 = 17.6 Hz, 1H), 5.42 (d, J = 17.6 Hz, 1H), 5.22-5.30 (m, 2H), 4.60-4.84 (m, 2H), 3.69 (dd, J_1 = 11.6 Hz, J_2 = 21.2 Hz, 2H), 1.10 (s, 9H), 0.91 (s, 1H), 0.12 (d, J = 8.0 Hz, 6H).

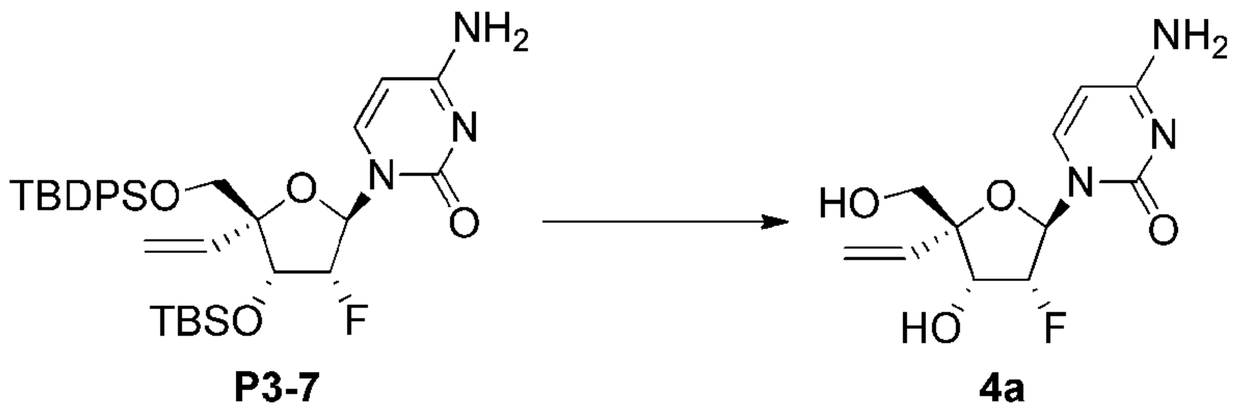
[0230] To a solution of **P3-6** (6.3 g, 10.09 mmol) in anhydrous CH_3CN (50 mL) were added TPSCl (6.1 g, 20.2 mmol), DMAP (2.5 g, 20.2 mmol) and NEt_3 (3 mL) at R.T.

The reaction was stirred at R.T. for 2 hours. NH_4OH (25 mL) was added, and the reaction was stirred for 1 hour. The mixture was diluted with DCM (150 mL) and washed with water, 0.1 M HCl and saturated aq. $NaHCO_3$. The solvent was removed, and the crude product was purified by silica gel column chromatography (2% MeOH in DCM) to give **P3-7** as a yellow solid (5.9 g, 93.6%).

[0231] To a solution of **P3-7** (5.9 g, 9.5 mmol) in MeOH (10 mL) was added Pd/C (1.5 g) at R.T. The reaction was stirred at R.T. for 2 hours under H_2 (balloon). The mixture was filtered, and the filtrate was concentrated *in vacuo* to give **P3-8** as a white solid (5.4 g, 91.3%).

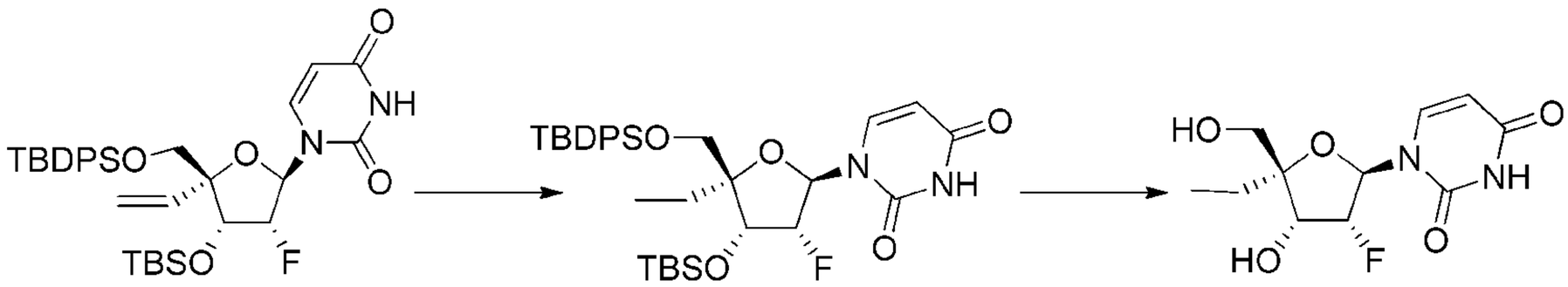
[0232] To a solution of **P3-8** (5.4 g, 8.6 mmol) in MeOH (60 mL) was added NH_4F (10.0 g), and the reaction mixture was refluxed overnight. After cooling to R.T., the mixture was filtered, and the filtrate was concentrated. The crude product was purified by silica gel column chromatography (10% MeOH in DCM) to give compound **3a** as a white solid (1.6 g, 67.8%). ESI-MS: m/z 274 $[M+H]^+$, 547 $[2M+H]^+$.

EXAMPLE 4
Preparation of Compound 4a



[0233] To a solution of **P3-7** (280 mg, 0.45 mmol) in MeOH (10 mL) was added NH_4F (1.0 g) at R.T. The reaction mixture was refluxed for 5 hours. After cooling to R.T., the mixture was filtered, and the filtrate was concentrated. The crude product was purified by silica gel column chromatography (10% MeOH in DCM) to give **4a** as a white solid (82 mg, 67.2%1.6 g, 67.8%). ESI-MS: m/z 272 $[M+H]^+$, 543 $[2M+H]^+$.

EXAMPLE 5
Preparation of Compound 5a

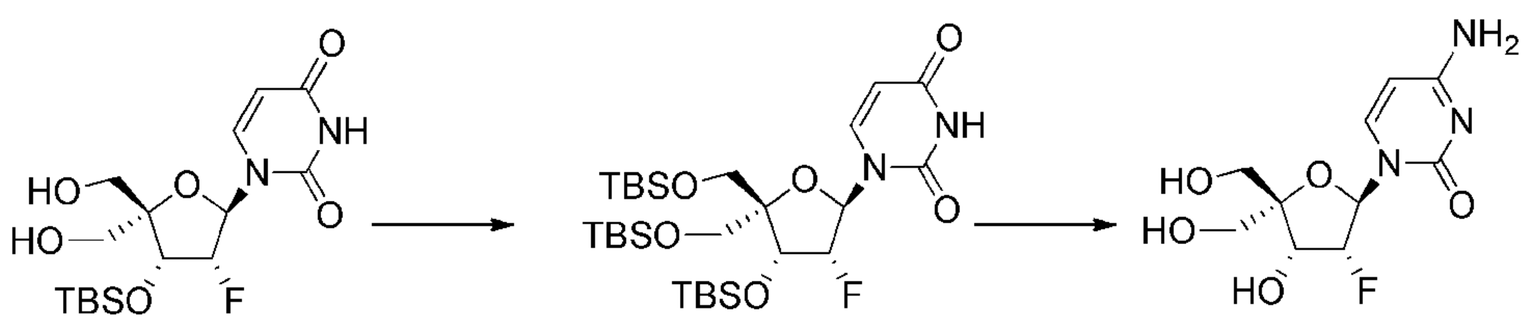


P3-6 P5-1 5a

[0234] To a solution of **P3-6** (600 mg, 0.96 mmol) in MeOH (30 mL) was added 10% Pd/C (320 mg) at R.T. The mixture was stirred under H_2 balloon at R.T. for 3 hours. The reaction mixture was filtered, and the filtrate was concentrated to give **P5-1** (540 mg, 89.8 %) as a colorless solid. The crude product was used directly for the next step without purification.

[0235] To a solution of **P5-1** (540 mg, 0.86 mmol) in MeOH (8 mL) was added NH_4F (1.2 g, 32.4 mmol) R.T. The mixture was refluxed for 30 hours. The solid was removed by filtration, and the filtrate was concentrated. The residue was purification by silica gel column chromatography (2.5%-9%MeOH in DCM) to give **5a** (190 mg, 80.6%) as a colorless solid. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.05 (d, J = 8.0 Hz, 1H), 6.09 (dd, J_1 =4.0 Hz, J_2 =14.8 Hz, 1H), 5.04-5.20 (m ,1H), 4.42 (dd, J_1 = 5.2 Hz, J_2 = 13.6 Hz, 1H), 3.71 (d, J = 11.6 Hz, 1H), 3.57 (d, J = 12.0 Hz, 1H), 1.61-1.82 (m , 2H), 0.94 (t, J = 7.2 Hz, 3H).

EXAMPLE 6
Preparation of Compound 6a



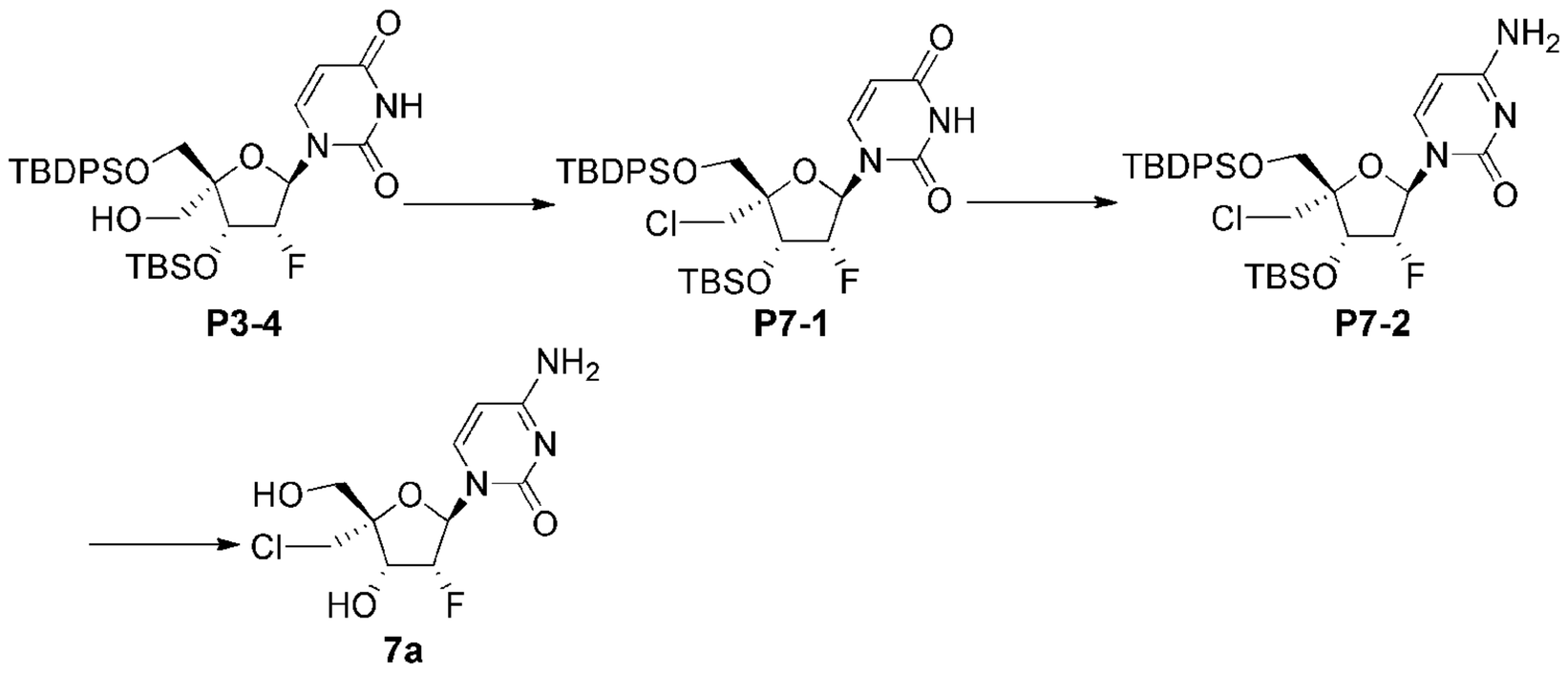
P3-3 P6-1 6a

[0236] To a solution of **P3-3** (800 mg, 2.05 mmol) in anhydrous DCM (15 mL) were added imidazole (558 mg, 8.2 mmol), TBSCl (1.2 g, 8.2 mmol) and $AgNO_3$ (700 mg, 4.1 mmol) at R.T. The reaction mixture was stirred at R.T. overnight. The mixture was filtered, and the filtrate was washed with brine and concentrated in vacuo. The residue was

purified by column chromatography on silica gel to give **P6-1** as a white solid (950 mg, 79.2%).

[0237] To a solution of **P6-1** (600 mg, 0.97 mmol) in anhydrous CH_3CN (18 mL) was added DMAP (239 mg, 2.91 mmol), NEt_3 (294 mg, 2.91 mmol) and TPSCl (879 mg, 2.91 mmol) at R.T. The reaction was stirred at R.T. for 1 hour. NH_4OH (9 mL) was added, and the reaction was stirred for 3 hours. The mixture was diluted with EtOAc (200 mL) and washed with water, 0.1 M HCl and saturated aq. $NaHCO_3$. The organic layer was separated, dried and concentrated to give a crude residue. The crude residue was purified by column chromatography on silica gel to give the product as a white solid (500 mg, 83.3%). The solid was treated with NH4F (1.0 g) in MeOH (20 mL) at refluxed temperature for 5 hours. The mixture was filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel (15% MeOH in DCM) to give **6a** as a white solid (132 mg, 59.3%). ESI-MS: m/z 276 $[M+H]^+$, 551 $[2M+H]^+$.

EXAMPLE 7
Preparation of Compound 7a



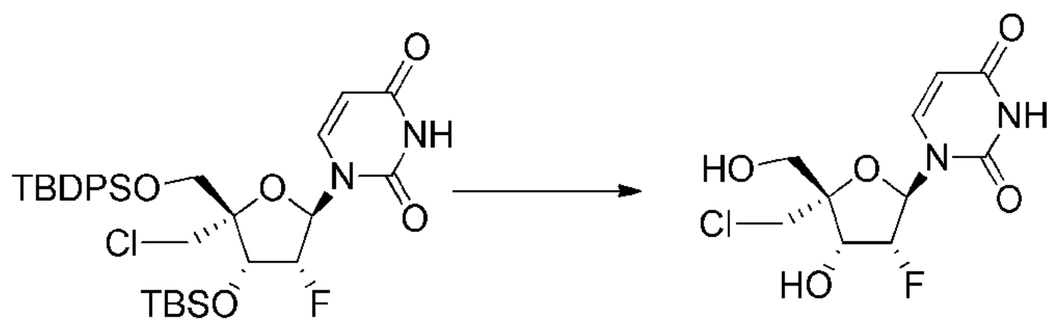
[0238] A mixture of **P3-4** (1.60 g, 2.5 mmol), PPh_3 (1.3 g, 5.0 mmol) and CCl_4 (0.76g, 5.0 mmol) in DCE (20 mL) was heated to 130°C under microwave irradiation under N_2 for 40 mins. After cooled to R.T., the solvent was removed, and the residue was purified on a silica gel column (PE/EA = 50/1 to 10/1) to give **P7-1** (1.1 g, 68.8%) as a white solid.

[0239] Compound **P7-1** (0.80 g, 1.3 mmol), DMAP (0.3 g, 2.6 mmol), TPSCl (0.8 g, 2.6 mmol) and Et_3N (0.3 g, 2.6 mmol) were dissolved in MeCN (30 mL). The mixture was stirred at R.T. for 14 hours. NH_3 in THF (saturated at 0°C, 100 mL) was added

to the mixture, and the mixture was stirred at R.T. for 2 hours. The solvent was removed, and the residue was purified by column (DCM/MeOH = 100:1 to 50:1) to give **P7-2** (0.63 g, 78.8%) as a white solid.

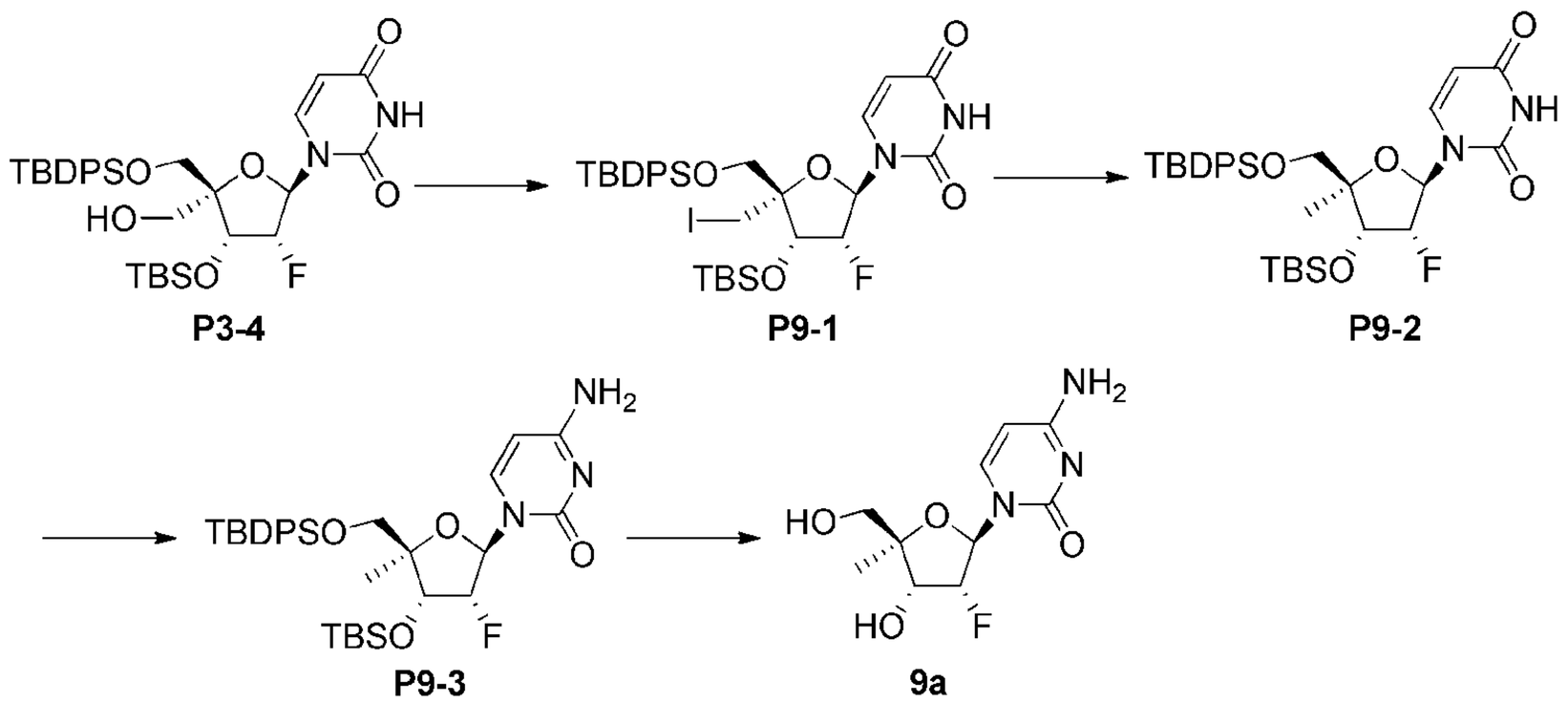
[0240] To a solution of **P7-2** (0.63 g, 0.98 mmol) in MeOH (10 mL) was added NH_4F (0.3 g), and the reaction was refluxed for 12 hours. The reaction was cooled to R.T., and the precipitate was filtered off. The filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (10% MeOH in DCM) to give **7a** as a white solid (153 mg, 53.5%). ESI-MS: m/z 294 $[M + H]^+$, 587 $[2M+H]^+$.

EXAMPLE 8
Preparation of Compound 8a



[0241] To a solution of **P7-1** (630 mg, 0.5 mmol) in MeOH (10 mL) was added NH_4F (0.1 g), and the reaction was refluxed for 12 hours. The mixture was filtered, and the filtrate was concentrated in vacuo. The crude product was purified by silica gel column chromatography (10% MeOH in DCM) to give **8a** as a white solid (153 mg, 53.5%). Negative-ESI-MS: m/z 293 $[M-H]^-$.

EXAMPLE 9
Preparation of Compound 9a



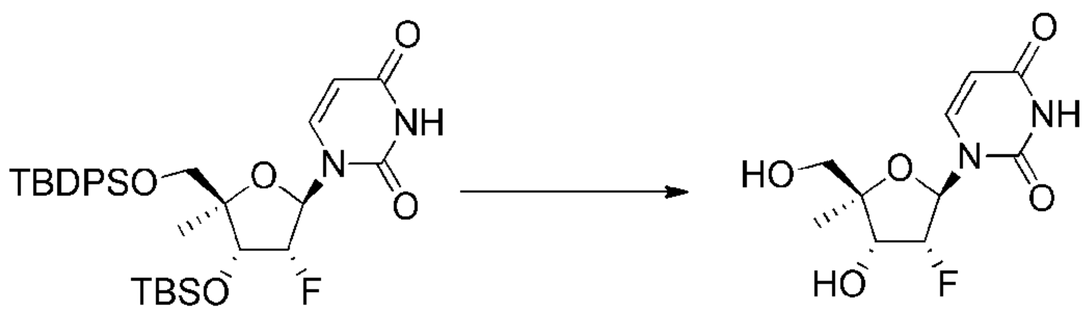
[0242] A mixture of **P3-4** (3.2 g, 5.0 mmol), Ph_3P (5.2 g, 20 mmol), iodine (2.60 g, 10.2 mmol) and imidazole (1.4 g, 20mmol) in anhydrous THF (40 mL) was stirred at 80°C for 14 hours. The reaction was cooled to R.T. and quenched with saturated aq. $Na_2S_2O_3$. The solution was extracted with EA. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (20-50% EA in PE) to give **P9-1** (1.6 g, 68.2%) as a white solid.

[0243] A mixture of **P9-1** (1.4 g, 0.2 mmol), Et_3N (40 mg, 0.4mmol) and Pd/C in EtOH (20 mL) was stirred at R.T. under H_2 (balloon) overnight. The precipitate was filtered off, and the filtrate was concentrated. The residue was purified on a silica gel column (20%-50% EtOAc in PE) to give **P9-2** as a white solid (1.1 g, 78%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.11 (br s, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.39-7.67 (m, 10H), 6.18 (dd, J_1 = 3.2 Hz, J_2 = 14.4 Hz, 1H), 5.26-5.30 (m, 1H), 4.86 (m, 1H), 4.42 (dd, J_1 = 5.2 Hz, J_2 = 15.2 Hz, 1H), 3.81 (d, J = 11.2 Hz, 1H), 3.58 (d, J = 11.2 Hz, 1H), 1.16 (s, 3H), 1.11 (s, 9H), 0.91 (s, 9H), 0.13 (s, 3H), 0.08 (s, 3H).

[0244] Compound **P9-2** (650 mg, 1.1 mmol), DMAP (270 mg, 2.2 mmol), TPSCl (664 mg, 2.2 mol) and Et_3N (222 mg, 2.2 mmol) were dissolved in MeCN (20 mL). The mixture was stirred at R.T. for 14 hours. The reaction was added NH_3 in THF (saturated at 0°C), and the mixture was stirred at R.T. for 2 hours. The solvent was removed, and the residue was purified on a silica gel column (1-10% MeOH in DCM) to give **P9-3** (430 mg, crude) as a light yellow syrup.

[0245] A mixture of **P9-3** (430 mg, 0.7 mmol) and NH_4F (97 mg, 2.1mmol) in MeOH (10 mL) was refluxed for 14 hours. The solvent was removed, and the residue was purified on a silica gel column (5%-10% MeOH in DCM) to give **9a** as a white solid (64.8 mg, 35.4%). ^{1}H NMR (CD_3OD, 400 MHz) δ 8.10 (d, J = 7.6 Hz, 1H), 6.03 (dd, J_1 =2.0 Hz, J_2 = 16.8 Hz, 1H), 5.87 (d , J = 7.6 Hz, 1H), 4.98 (m, 1H), 4.37 (dd, J_1 = 5.2 Hz, J_2 = 21.6 Hz, 1H), 3.59 (dd, J_1 = 12.0 Hz, J_2 = 28.4 Hz, 2H), 1.23 (d, J = 0.8 Hz, 3H).

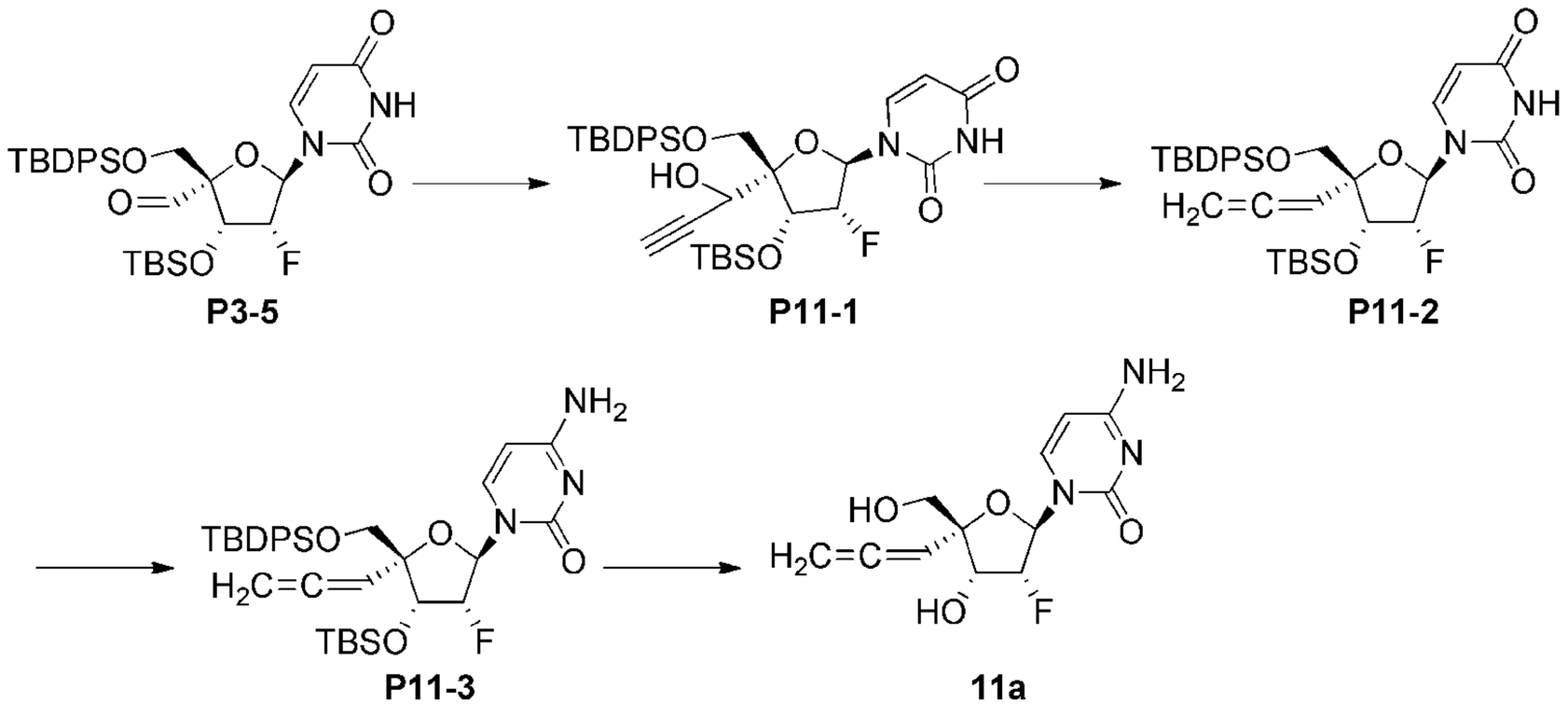
EXAMPLE 10
Preparation of Compound 10a



P9-2 10a

[0246] To a stirred solution of **P9-2** (400 mg, 0.65 mmol) in MeOH (20 mL) was added NH_4F (52 mg, 1.5 mmol). The mixture was refluxed overnight. The solvent was removed, and the residue was purified on a silica gel column (5~10% MeOH in DCM) to give **10a** (140 mg, 82.4%) as a white solid. ESI-TOF-MS: m/z 283 $[M+Na]^+$.

EXAMPLE 11
Preparation of Compound 11a



P3-5 P11-1 P11-2

P11-3 11a

[0247] To a solution of **P3-5** (2.1 g, 3.5 mmol) in anhydrous THF (25 mL) was added ethynylmagnesium bromide (5.1 mmol) at -78°C. The reaction was stirred at 0°C for 3 hours. The reaction was quenched with saturated aq. NH_4Cl (10 mL). The mixture was diluted with EtOAc (200 mL) and washed with water and brine. The organic layer was dried and concentrated to give a residue. The residue was purified by column chromatography on silica gel (eluting with DCM: MeOH = 60:1) to give **P11-1** as a white solid (870 mg, 83.3%).

[0248] Compound **P11-1** (870 mg, 1.34 mmol) was dissolved in anhydrous DCM (12 mL), and methyl chloroformate (2.3 mL) and pyridine (2.5 mL) were added at R.T. The reaction mixture was stirred at R.T. for 1 hour. The mixture was diluted with DCM and

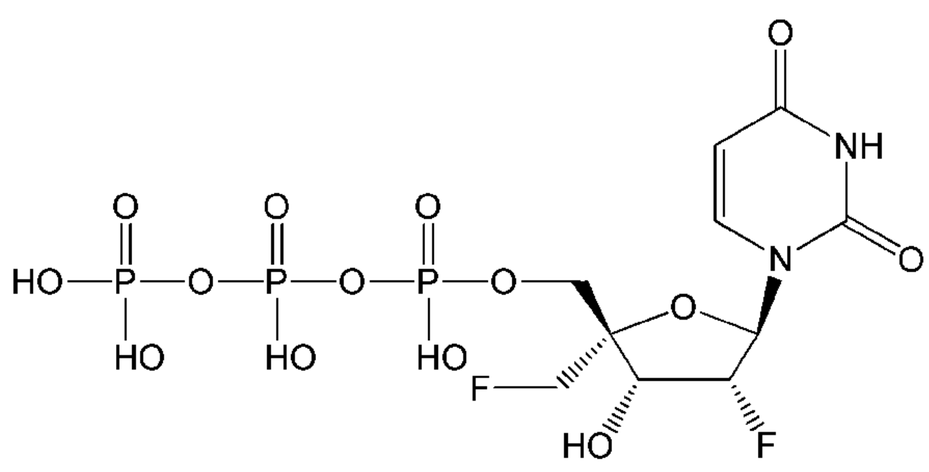
washed with saturated aq. $NaHCO_3$. The organic layer was separated, dried and concentrated to give a residue. The residue was purified by column chromatography on silica gel (eluting with PE: EtOAc = 8: 1) to give a crude product as a white solid (830 mg, 88.4%). To a mixture of $Pd_2(dba)_3$ (55 mg, 0.06 mmol) in anhydrous DMF (12 mL) was added $P(nBu)_3$ (35 mg, 0.17 mmol) and $HCOONH_4$ (108 mg, 1.7 mmol) at R.T. under nitrogen. The reaction mixture was stirred at R.T. for 30 min. A solution of the crude product (830 mg, 1.16 mmol) in anhydrous DMF (16 mL) was added, and the reaction mixture was stirred at 70°C for 3 hours. The reaction was diluted with EtOAc and washed with brine. The organic layer was separated, dried and concentrated to give a residue. The residue was purified by column chromatography on silica gel (eluting with PE: EtOAc = 9: 1) to give **P11-2** as a white solid (510 mg, 67.6%). ^{1}H NMR (CD_3OD, 400 M Hz) δ 7.61-7.75 (m, 5H), 7.36-7.47 (m, 6H), 6.04 (d, J = 18.8 Hz, 1H), 5.34 (t, J = 6.8 Hz, 1H), 5.21 (dd, J_1 = 1.2 Hz, J_2 = 7.2 Hz, 1H), 5.10 (q, J_1 = 5.2 Hz, J_2 = 53.6 Hz, 1H), 4.80-4.92 (m, 1H), 4.59-4.79 (m, 2H), 3.86 (d, J = 12.0 Hz, 1H), 3.75 (d, J = 12.0 Hz, 1H), 1.09 (s, 9H), 0.92 (d, J = 4.4 Hz, 9H), 0.15 (t, J = 4.0 Hz, 6H).

[0249] To a solution of **P11-2** (490 mg, 0.77 mmol) in anhydrous MeCN (15 mL) was added TPSCl (700 mg, 2.31 mmol), DMAP (282 mg, 2.31 mmol) and TEA (234 mg, 2.31 mmol) at R.T. The reaction mixture was stirred at room temperature for 1 hour. Then NH_4OH (8 mL) was added and the reaction mixture was stirred for another 4 hours. The mixture was diluted with EtOAc and washed with water, 1.0 M aq. HCl and saturated aq. $NaHCO_3$. The organic layer was separated and dried, concentrated to give the residue which was purified by HPLC separation (MeCN and 0.1% HCOOH in water) to give **P11-3** as a white solid (190 mg, 38.8%). ^{1}H NMR (CD_3OD, 400 MHz) δ 7.88 (d, J = 7.2 Hz, 1H), 7.63-7.70 (m, 4H), 7.37-7.48 (m, 6H), 6.12 (d, J = 18.4 Hz, 1H), 5.49 (d, J = 7.6 Hz, 1H), 5.34 (t, J = 6.8 Hz, 1H), 4.84-5.01 (m, 2H), 4.66-4.78 (m, 2H), 3.89 (d, J = 11.6 Hz, 1H), 3.75 (d, J = 11.6 Hz, 1H), 1.10 (s, 9H), 0.91 (d, J = 3.2 Hz, 9H), 0.13 (t, J = 5.2 Hz, 6H).

[0250] To a solution of **P11-3** (130 mg, 0.21 mmol) in MeOH (8 mL) was added NH_4F (1 g), and the reaction mixture was refluxed for 6 hours. The mixture was filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography

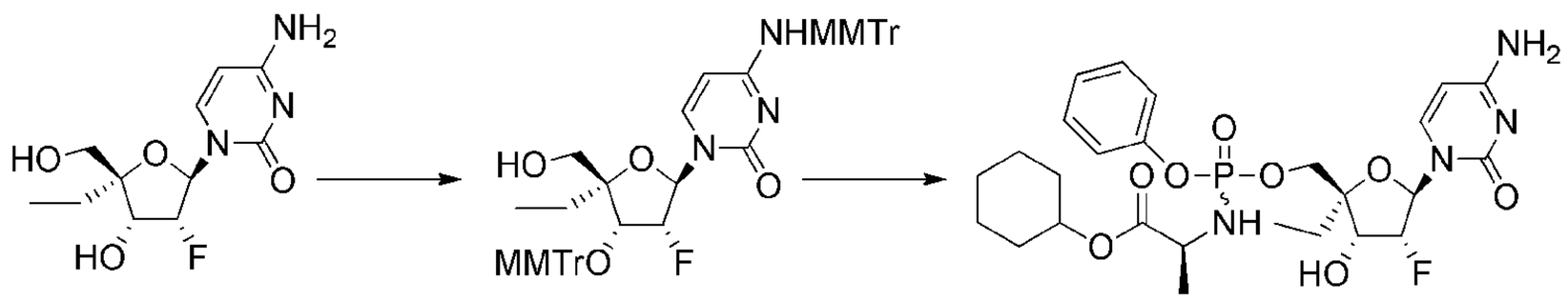
on silica gel (eluting with DCM:MeOH = 13:1) to give **11a** as a white solid (47 mg, 79.1%). ESI-MS: m/z 284.02 $[M+H]^+$, 567.08 $[2M+H]^+$.

EXAMPLE 12
Preparation of Compound 111a



[0251] The 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 bath temperature (42^0C), than cooled down to R.T. N-Methylimidazole (0.009 mL, 0.11 mmol) was added followed by $POCl_3$ (9ul, 0.11 mmol), and the mixture was kept at R.T. for 40 mins. The reaction was controlled by LCMS and monitored by the appearance of corresponding nucleoside 5'-monophosphate. After more than 50% of the transformation was achieved, 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 diluted with water (10 mL) and loaded on a 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 (pH7.5). 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. MS: m/z 517.2 [M-1].

EXAMPLE 13
Preparation of Compound 13a



3a P13-1 13a

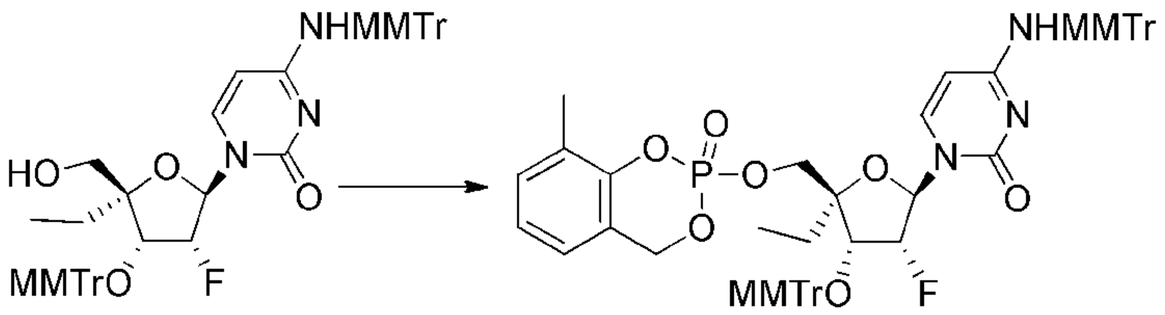
[0252] To a solution of **3a** (700 mg, 2.56 mmol) in anhydrous pyridine (5 mL) were added TBDPSCl (2.8 g, 10.24 mmol), imidazole (522 mg, 7.68 mmol) and $AgNO_3$ (870 mg, 5.12 mmol) at R.T. under N_2. The reaction mixture was stirred at R.T. for 3 hours. The mixture was diluted with MeOH and filtered. The mixture was concentrated, and the residue was purified by column chromatography on silica gel (eluting with DCM: MeOH = 80:1 ~ 40:1) to give the crude intermediate as a yellow solid (1.05 g, 80.8%).^{1}H NMR (DMSO-*d6*, 400 MHz) δ 7.75 (d, J = 7.6 Hz, 1H), 7.61-7.65 (m, 4H), 7.41-7.50 (m, 7H), 6.02 (dd, J_1 = 2.8 Hz, J_2 = 17.2 Hz, 1H), 5.69 (d, J = 6.0 Hz, 1H), 5.56 (d, J = 7.6 Hz, 1H), 4.96-5.11 (m, 1H), 4.37-4.46 (m, 1H), 3.82 (d, J = 10.8 Hz, 1H), 3.62 (d, J = 10.8 Hz, 1H), 1.70-1.78 (m, 1H), 1.53-1.59 (m, 1H), 1.02 (s, 9H),0.79 (t, J = 7.6 Hz, 3H). To a solution of the crude intermediate (1.0 g, 1.96 mmol) in anhydrous DCM (15 mL) were added *sym*-collidine (1.4 g, 11.76 mmol), $AgNO_3$ (1.0 g, 5.88 mmol) and MMTrCl (4.8 g, 15.6 mmol) at R.T. under N_2. The reaction mixture was stirred at R.T. overnight. The mixture was filtered and concentrated. The residue was purified by column chromatography on silica gel (eluting with PE:EtOAc=2: 1) to give crude full protected intermediates as a white solid(1.1 g, 53.1%). To a solution of the crude intermediate (600 mg, 0.57 mmol) in THF (5 mL) was added TBAF (446 mg, 1.71 mmol)) at R.T. The reaction was stirred at 40~50^{o}C overnight. The crude product was purified by column chromatography on silica gel eluted with PE:EtOAc = 3:2 to give crude **P13-1** (350 mg, 75.1%) as a yellow solid.

[0253] To a solution of **P13-1** (300 mg, 0.37 mmol) in CH_3CN (2.5 mL) were added NMI (2.5 mL) and a solution of phenyl(isopropoxy-L-alaninyl) phosphorochloridate (2.55 g, 7.4 mmol) in CH_3CN (2.5 mL) at R.T. under N_2. The reaction mixture was stirred at R.T. for 3 hours. The mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (PE:EtOAc = 1:1) to give crude product as a yellow oil

(500 mg, 81%). The crude product was further treated with 80% HCOOH (70 mL) at R.T. overnight. The mixture was concentrated in vacuo, and the crude product was purified by RP HPLC (MeCN and 0.1% HCOOH in water) to give **13a** as a white solid (a mixture of two P isomers, 86 mg, 40.3% two steps). ESI-MS: m/z 582.93 $[M+H]^+$.

EXAMPLE 14

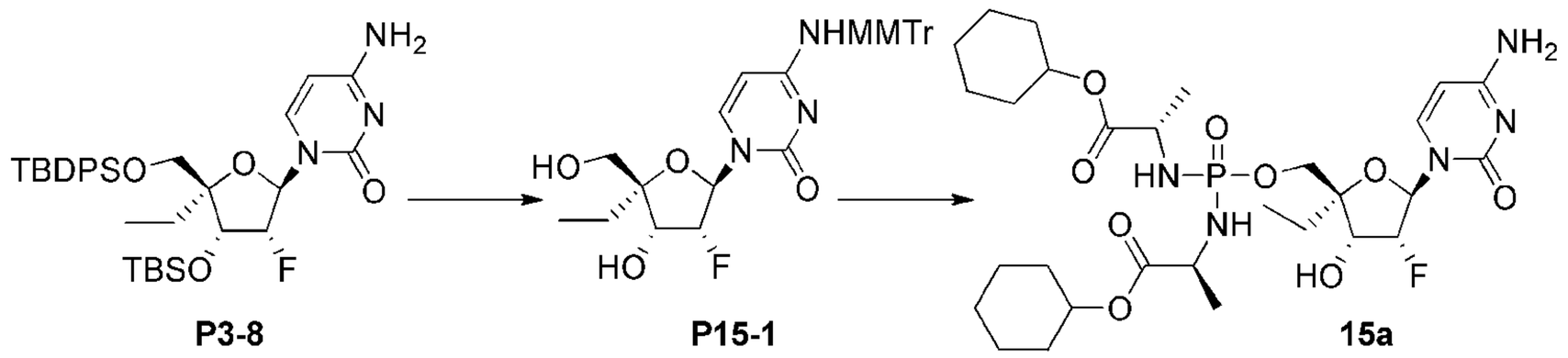
Preparation of Compound 14a



[0254] To a stirred solution of **P13-1** (451 mg, 0.55 mmol) and NMI (1mL) in anhydrous acetonitrile (2 mL) was added dropwise a solution of 2-chloro-8-methyl-4H-benzo[d][1,3,2]dioxaphosphinine (855 mg, 4.2 mmol) in acetonitrile (0.2 mL) at 0°C under N_2. The mixture was stirred at R.T. for 2 hours. Solution of I_2 (3.2 g, 12.6 mmol), pyridine (9 mL), H_2O(3 mL) and DCM(3 mL) was added. The reaction mixture was stirred for 30 mins. The reaction was quenched with NaS_2O_3 solution and extracted with EA. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by column on silica gel (PE: EA = 1:1 to 1:2) to give **P14-1** (205 mg, 37%) as a white solid.

[0255] Compound **P14-1 (**205 mg, 0.21 mmol**)** was dissolved in 80% HCOOH aq. solution, and the mixture was stirred at R.T. for 16 hours. The solvent was removed, and the residue was purified by RP HPLC (HCOOH system) to give **14a** as a mixture of 2 P-isomers (24 mg, 18%). ESI-LCMS: m/z 456 $[M+H]^+$.

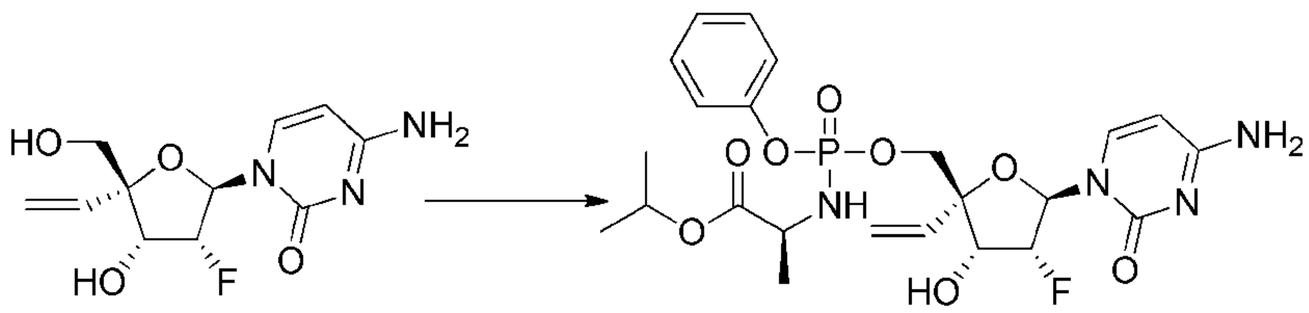
EXAMPLE 15
Preparation of Compound 15a



[0256] To a mixture of **P3-8** (2.2 g, 2.5 mmol), $AgNO_3$ (844 mg, 5.0 mmol) and collidine (907 mg, 7.5 mmol) in anhydrous DCM (10 mL) was added MMTrCl (1.54 g, 5.0 mmol) under N_2. The reaction mixture was stirred at R.T. overnight. The reaction mixture was filtered through a Buchner Funnel. The filtrate was washed with saturated $NaHCO_3$ solution and brine. The organic layer was separated, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated to dryness. The residue was purified by column on silica gel (PE:EA = 10:1 to 1:2) to give the intermediate (2.3 g, 84%), which was dissolved in a solution of TBAF in THF (1M, 2.6 mL) under N_2. The reaction mixture was stirred at R.T. overnight. The residue was dissolved in EA (200 mL) and washed with water and brine. The organic layer was separated, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated to dryness, and the residue was purified by column on silica gel (DCM/MeOH = 100:1 to 30:1) to give **P15-1** as a white foam (1.3 g, 94%).

[0257] To a stirred solution of **P15-1** (300 mg, 0.55 mmol) and proton sponge (235 mg, 1.1 mmol) in anhydrous MeCN (9 mL) was added with a solution of $POCl_3$ (169 mg, 1.1 mmol) in MeCN (1 mL) via syringe at 0°C. The mixture was stirred at R.T. for 40 mins. A mixture of (*S*)-cyclohexyl 2-aminopropanoate hydrochloride (525 mg, 2.55 mmol) and TEA (0.1 mL) was added at 0°C. The mixture was warmed to R.T. and stirred for 3 hours. The reaction mixture was quenched with saturated $NaHCO_3$, and extracted with EA (100 mL x 2). The combined organic layers was dried over Na_2SO_4, concentrated and purified by silica gel column (1~4% MeOH in DCM) to give the crude product (400 mg, 78.15%) as a yellow solid. The crude product was treated with 80% HCOOH (50mL) at R.T. for 16 hours. The solvent was removed, and the residue was purified by RP HPLC to give **15a** as a white solid (40 mg, 14%). ESI-LCMS: m/z 660 $[M+H]^+$.

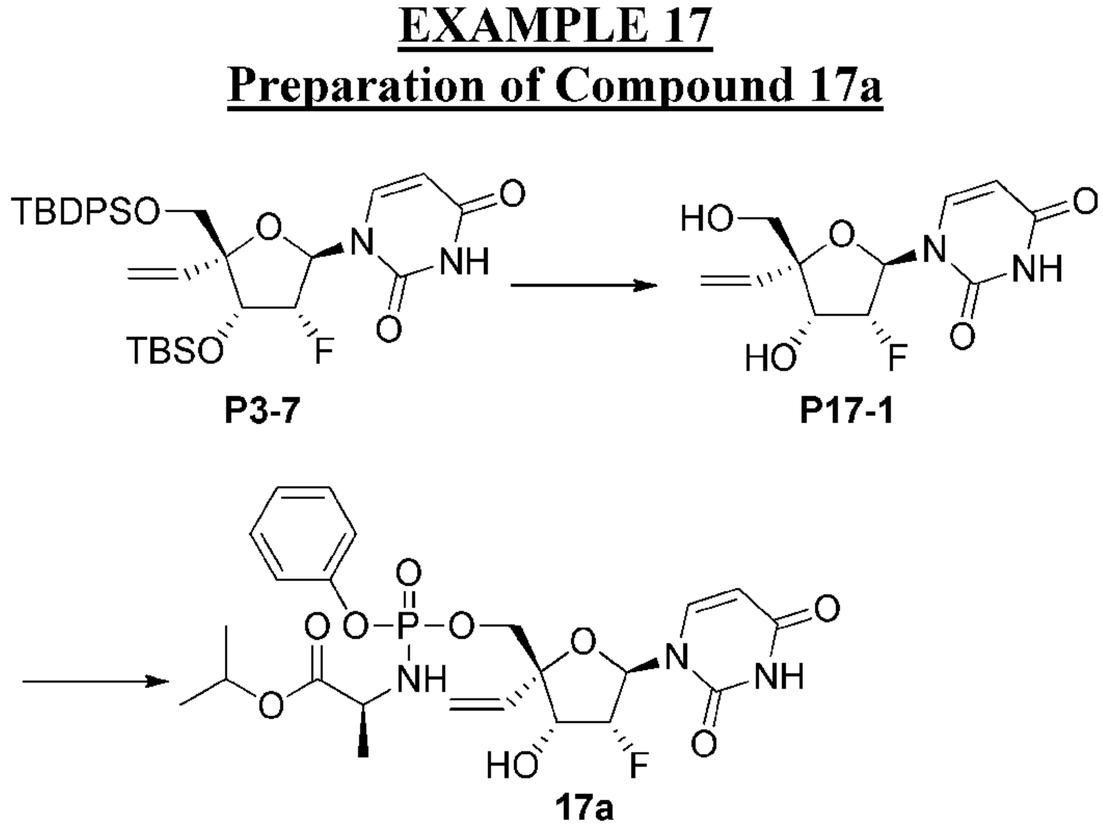
EXAMPLE 16
Preparation of Compound 16a



4a 16a

[0258] To a stirred solution of **4a** (150 mg, 0.56 mmol) in anhydrous THF (3 mL) was added dropwise a solution of *t*-BuMgCl (1.2 mL, 1M in THF) at -78°C. The mixture was stirred at 0°C for 30 min and re-cooled to -78°C. A solution of phenyl(isopropoxy-L-alaninyl) phosphorochloridate (312 mg, 1.2 mmol) in THF (1.0 mL) was added dropwise. After addition, the mixture was stirred at 25°C for 16 hours. The reaction was quenched with HCOOH (80% aq.) at 0°C. The solvent was removed, and the residue was purified on silica gel (DCM:MeOH = 50:1 to 10:1) to give **16a** as a white solid (24.0 mg, 15 %). ESI-LCMS: *m/z* 541.0$[M+H]^+$.

EXAMPLE 17
Preparation of Compound 17a



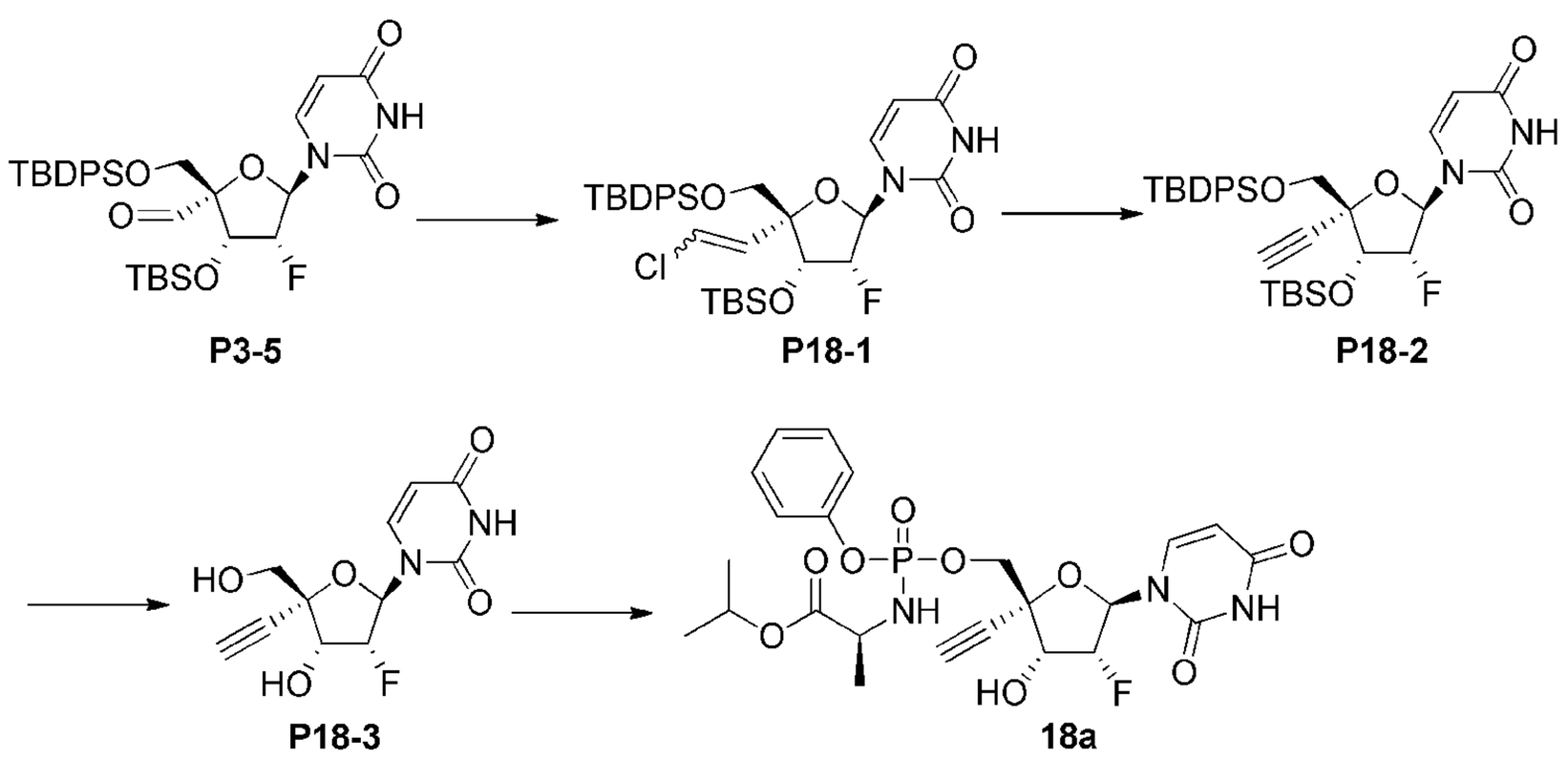
P3-7 P17-1

17a

[0259] To a solution of **P3-7** (1.4 g, 2.3 mmol) in MeOH (50 mL) was added NH_4F (8.0 g) at R.T. The reaction mixture was refluxed overnight. After cooling to R.T., the mixture was filtered, and the filtrate was concentrated. The crude product was purified by silica gel column chromatography (10% MeOH in DCM) to give **P17-1** as a white solid (410 mg, 77.8%).

[0260] To a stirred solution of **P17-1** (60 mg, 0.19 mmol) in anhydrous THF (3 mL) was added dropwise a solution of *t*-BuMgCl (0.38 mL, 1M in THF) at -78°C. The mixture was stirred at 0°C for 30 min and re-cooled to -78°C. A solution of phenyl(isopropoxy-L-alaninyl) phosphorochloridate (104 mg, 0.4 mmol) in THF (0.5 mL) was added dropwise. After addition, the mixture was stirred at 25°C for 16 hours. The reaction was quenched with HCOOH (80% aq.) at 0°C. The solvent was removed, and the residue was purified on silica gel (DCM:MeOH = 50:1 to 10:1) to give **17a** as a white solid (a mixture of two P isomers, 11.0 mg, 11 %). ESI-LCMS: m/*z* 542.0 $[M+H]^+$.

EXAMPLE 18
Preparation of Compound 18a



[0261] To a solution of (chloromethyl)triphenylphosphonium chloride (2.1 g, 6.0 mmol) in anhydrous THF (10 mL) was added dropwise n-BuLi (4.6 mL, 6.0 mmol) at -70°C under nitrogen. The reaction was stirred at -70°C for 50 mins. A solution of compound **P3-5** (950 mg, 1.5 mmol) in anhydrous THF (5 mL) was added at -70°C, and the reaction was stirred at 0°C for 3 hours. The reaction was quenched by saturated aq. NH_4Cl and extracted with EtOAc. The organic layer was separated, dried and concentrated to give a residue. The residue was purified by column chromatography on silica gel (eluting with PE:EtOAc = 6:1) to give **P18-1** as a yellow gum (900 mg, 91.2%).

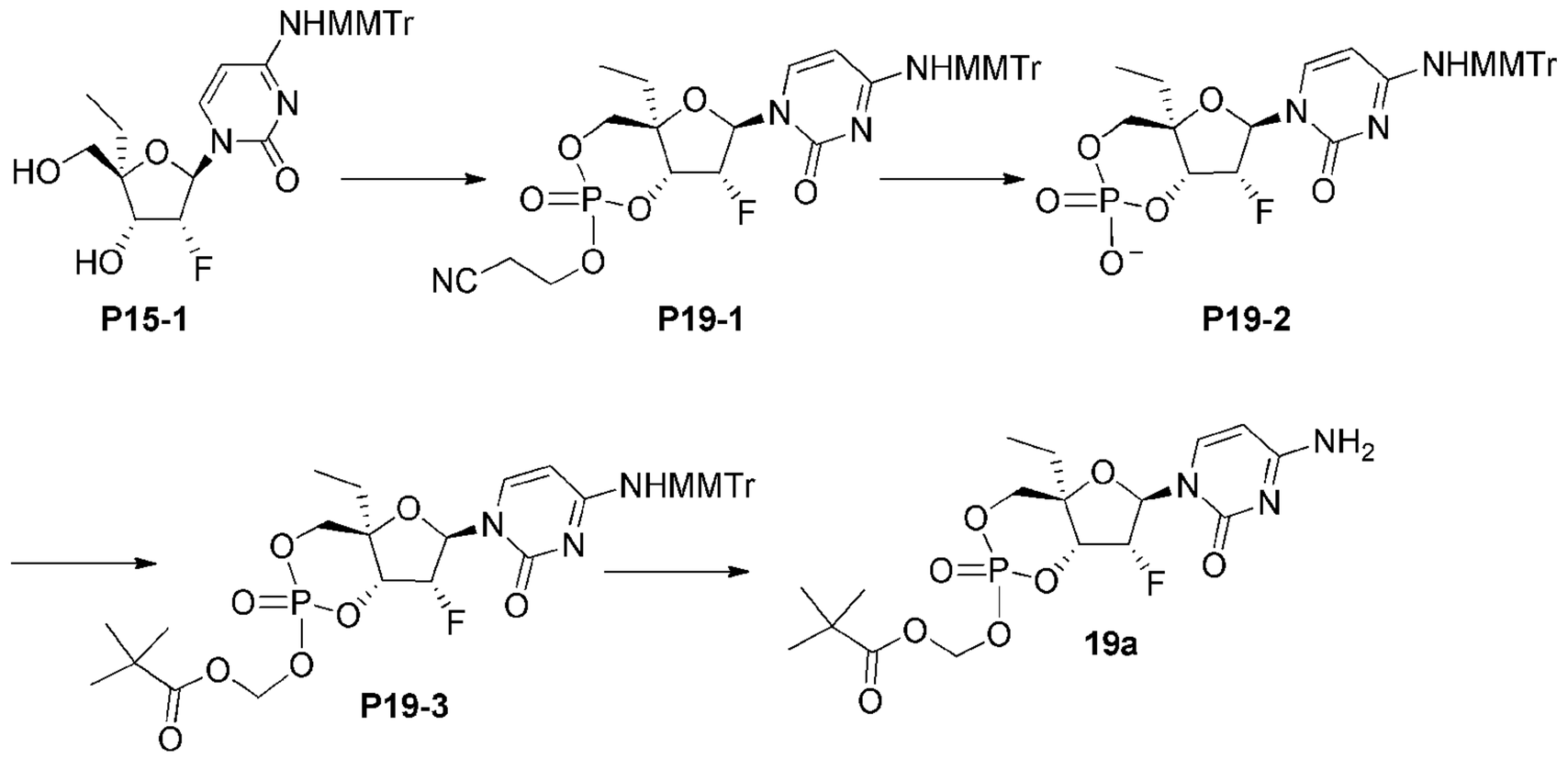
[0262] To a solution of compound **P18-1** (600 mg, 0.91 mmol) in anhydrous THF (18 mL) was added dropwise n-BuLi (4.7 mL, 10.9 mmol) at -70°C under nitrogen. The reaction was stirred at -70°C for 3 hours. The reaction was quenched by saturated aq. NH_4Cl

and extracted with EtOAc. The organic layer was separated, dried and concentrated to give a residue. The residue was purified by column chromatography on silica gel (eluting with PE:EtOAc = 8:1~5:1) to give **P18-2** as a white solid (300 mg, 53.0%).

[0263] To a solution of **P18-2** (300 mg, 0.44 mmol) in MeOH (10 mL) was added NH_4F (1.0 g) at R.T. The reaction was refluxed for 3 hours. After cooling R.T., the mixture was filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluting with DCM:MeOH = 50:1~30:1) to give **P18-3** as a white solid (135 mg, 78.1%).^{1}H NMR (CD_3OD, 400 MHz) δ 7.84 (d, J = 8.0 Hz, 1H), 6.06 (dd, J_1 = 1.6 Hz, J_2 =19.6 Hz, 1H), 5.67 (d, J = 8.4 Hz, 1H), 5.18-5.03 (m, 1H), 4.50 (dd, J_1 = 5.2 Hz, J_2 =21.6 Hz, 1H), 3.85 (d, J = 12.4 Hz, 1H), 3.72 (d, J = 12.4 Hz, 1H), 3.09 (s, 1H).

[0264] To a solution of **P18-3** (130 mg, 0.5 mmol) in anhydrous THF (4 mL) was added dropwise t-BuMgCl (1.0 mL, 1.0 mmol) at -70°C under nitrogen. The reaction was stirred at R.T. for 30 mins. A solution of phenyl(isopropoxy-L-alaninyl) phosphorochloridate in anhydrous THF(1M, 0.8 mL, 0.78 mmol) was added at -70°C, and the reaction mixture was stirred at R.T. for 5 hours. The reaction was quenched by HCOOH, and the mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (DCM:MeOH = 60:1) to give **18a** as a white solid (a mixture of two P isomers, 25 mg, 7.7%). ESI-MS: m/z 540.2 $[M+H]^+$.

EXAMPLE 19
Preparation of Compound 19a



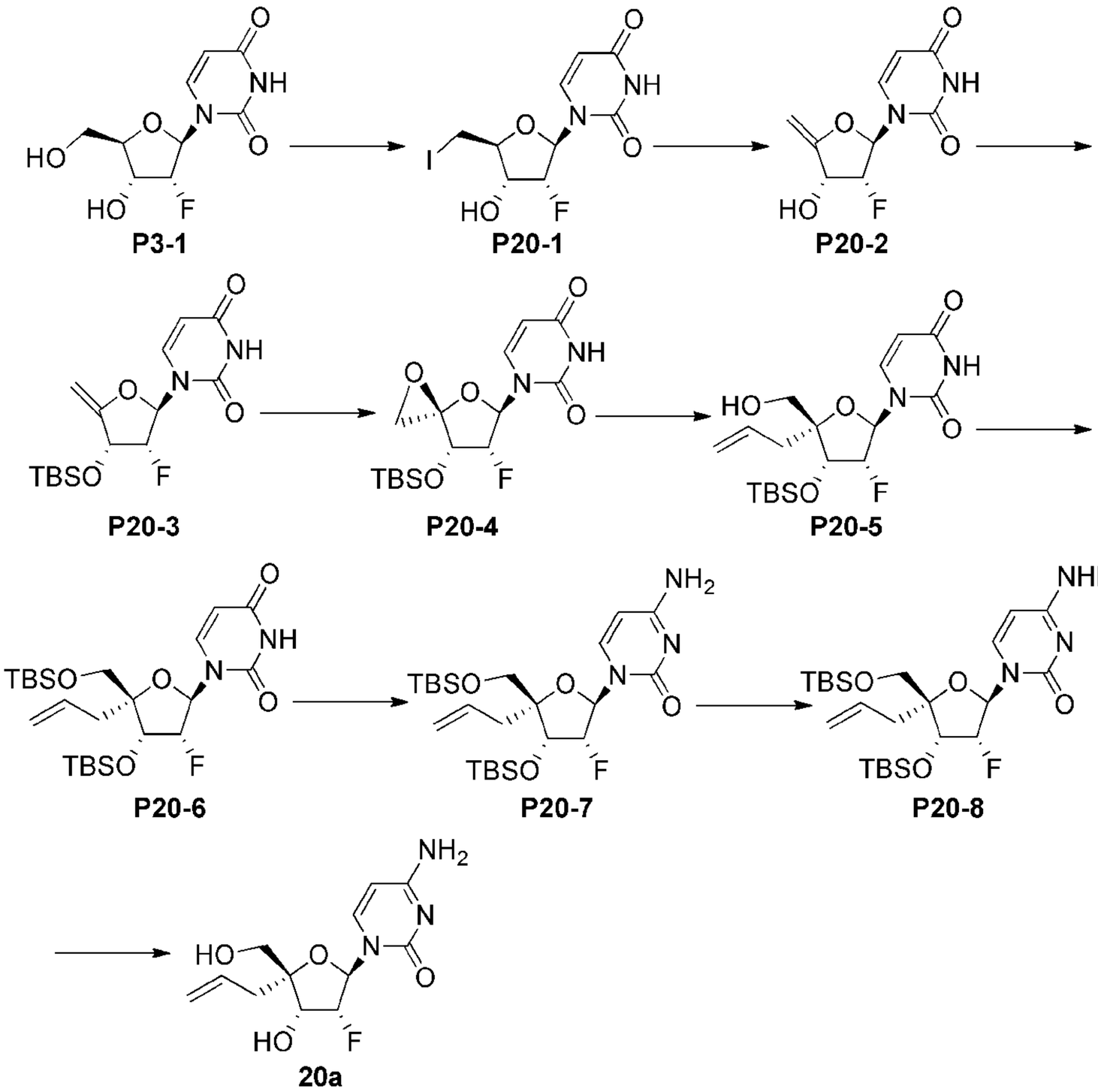
[0265] Compound **P15-1** (1.2 g, 2.2 mmol) was dissolved in dry acetonitrile (20 mL), and 0.45 M tetrazole (24.0 mL, 11.0 mmol) and 3-(bis(diisopropylamino)phosphinooxy)propanenitrile (1.13 g, 3.74 mmol) was added. The reaction mixture was stirred for 1 hour under N_2 at R.T. TBDPH (2.7 mL, 15 mmol) was added, and the mixture was stirred for 1 hour. The reaction was quenched by $Na_2S_2O_3$ solution and extracted with EA. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by column on silica gel (DCM:MeOH = 100:1 to 40:1) to give **P19-1** as a white solid (759 mg, 52%).

[0266] Compound **P19-1** (750 mg, 1.14 mmol) was dissolved in saturated NH_3 in MeOH solution. The mixture was stirred for 2 hours at R.T. The solution was concentrated to dryness to give crude **P19-2** as a yellow solid (662 mg, 100%). Negative-ESI-LCMS: m/z 606 $[M-H]^-$.

[0267] Compound **P19-2** (292 mg, 0.47 mmol) was co-evaporated with pyridine twice and dissolved in anhydrous DMF (0.5 mL). DIPEA (1.2 mL) was added and followed by 2,2-dimethyl-propionic acid iodomethyl ester (680 mg, 2.8 mmol). The reaction mixture was stirred at R.T. under N_2 for 16 hours. The reaction was quenched by $Na_2S_2O_3$ solution and extracted with EA. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by column on silica gel (DCM:MeOH = 100:1 to 30:1) to give **P19-3** as a white solid (95 mg, 30%).

[0268] Compound **P19-3** (95 mg, 0.13 mmol) was dissolved in a 80% HCOOH aq. solution, and the mixture was stirred at R.T. for 16 hours. The solvent was removed, and the residue was purified by RP HPLC (MeCN and 0.1% HCOOH in water) to give **19a** as a white solid (10 mg, 17%). ESI-LCMS: m/z 450 $[M+H]^+$.

EXAMPLE 20
Preparation of Compound 20a



[0269] To a stirred suspension of **P3-1** (20.0 g, 81.3mmol), imidazole (15.9 g, 234.0 mmol), PPh_3 (53.5 g, 203.3 mmol) and pyridine (90 mL) in anhydrous THF (360 mL) was added dropwise a solution of I_2 (41.3 g, 162.6mmol) in THF (350 mL) at 0°C. After addition, the mixture was warmed to R.T. and stirred for 14 hours. The solution was quenched with aq. $Na_2S_2O_3$ (150 mL) and extracted with EA. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified on a silica gel column (DCM:MeOH = 100:1 to 10:1) to afford **P20-1** as a white solid (22.1 g, 76.4%). ^{1}H NMR (CD_3OD, 400 MHz) δ 7.70 (d, J = 8.0 Hz, 1H), 5.88 (dd, J_1 = 1.6 Hz, J_2 = 20.8 Hz, 1H), 5.71 (d, J = 8.4 Hz, 1H), 5.24 (dd, J_1 = 2.0 Hz, J_2 = 5.2 Hz, 1H), 5.10 (dd, J_1 = 2.0 Hz, J_2 = 5.2 Hz 1H), 3.78-3.83 (m, 1H), 3.61-3.65 (m, 1H), 3.44 (dd, J_1 = J_2 = 6.0 Hz, 1H).

[0270] To a stirred solution of **P20-1** (22.1 g, 62.1 mmol) in anhydrous THF (200 mL) was added dropwise DBU (14.2 g, 93.1 mmol) in THF (50 mL) at 0°C over 10 mins.

The mixture was stirred at 60°C for 6 hours. The reaction was quenched with aq. $NaHCO_3$ (200 mL) and extracted with EA. The organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed, and the residue was purified on a silica gel column (MeOH:DCM = 1/100 to 1/30) to afford **P20-2** as a white solid (8.7 g, 61.5%). ^1H NMR (CD_3OD, 400 MHz) δ 7.51 (d, J = 8.0 Hz, 1H), 6.05 (dd, J_1 =1.2 Hz, J_2 = 17.2 Hz, 1H), 5.73 (d, J = 8.0 Hz, 1H), 5.26 (dd, J_1 = 1.2 Hz, J_2 = 4.8 Hz, 1H), 5.13 (dd, J_1 = 1.2 Hz, J_2 = 4.8 Hz, 1H), 4.63 (dd, J_1 =2.0 Hz, J_2 = 3.2 Hz, 1H), 4.41(dd, $J_1 = J_2$ = 2.0 Hz, 1H).

[0271] To a stirred solution of **P20-2** (3.2 g, 14.0 mmol) in anhydrous pyridine(10 mL) and DCM (100 mL) was added dropwise a solution of TBSCl (4.2 g, 28.0 mmol)at 0°C. Stirring was continued at R.T. for 18 hours. The mixture was diluted with DCM. The organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed, and the residue was purified on a silica gel column (10% MeOH in DCM) to afford **P20-3** as a white solid (3.4 g, 70.8%).

[0272] To a stirred solution of $NaHCO_3$ in H_2O (250 mL) and acetone (200 mL) was added oxone (30.0 x 4 g) at 0°C. The mixture was warmed to R.T., and the distillate was collected at -78°C (120 mL) under slightly reduced pressure to give a solution of DMDO in acetone. To a stirred solution of **P20-3** (250.0 mg, 0.7 mmol) in DCM (20 mL) were added a DMDO (120 mL) solution at -40°C and $MgSO_4$. The mixture was warmed to R.T. and then stirred for 2 hours. The solution was filtrated, and the filtrate was used for the next-step directly.

[0273] To a stirred solution of **P20-4** (500.0 mg, 1.4 mmol) in anhydrous DCM (50 mL) was added allyl-trimethyl-silane (760.0mg, 6.7mmol) and $SnCl_4$ (1.2 g, 4.5 mmol) at -40°C. The mixture was warmed and stirred at 0°C for 1 hour. The reaction was quenched with saturated $NaHCO_3$ and extracted with DCM. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified on a silica gel column (20~50% EA in PE) to give **P20-5** as a white foam (120 mg, 41%). ESI-LCMS: m/z = 422 $[M+Na]^+$.

[0274] To a stirred solution of **P20-5** (270.0 mg, 0.7 mmol) in dry DCM were added imidazole (400.0mg, 5.9mmol) and TBSCl (390.0 mg, 2.6 mmol) at R.T. The mixture was stirred at R.T. for 18 hours. The solution was diluted with EA. The solvent was washed with brine and dried over Na_2SO_4. The solvent was removed, and the residue was purified on

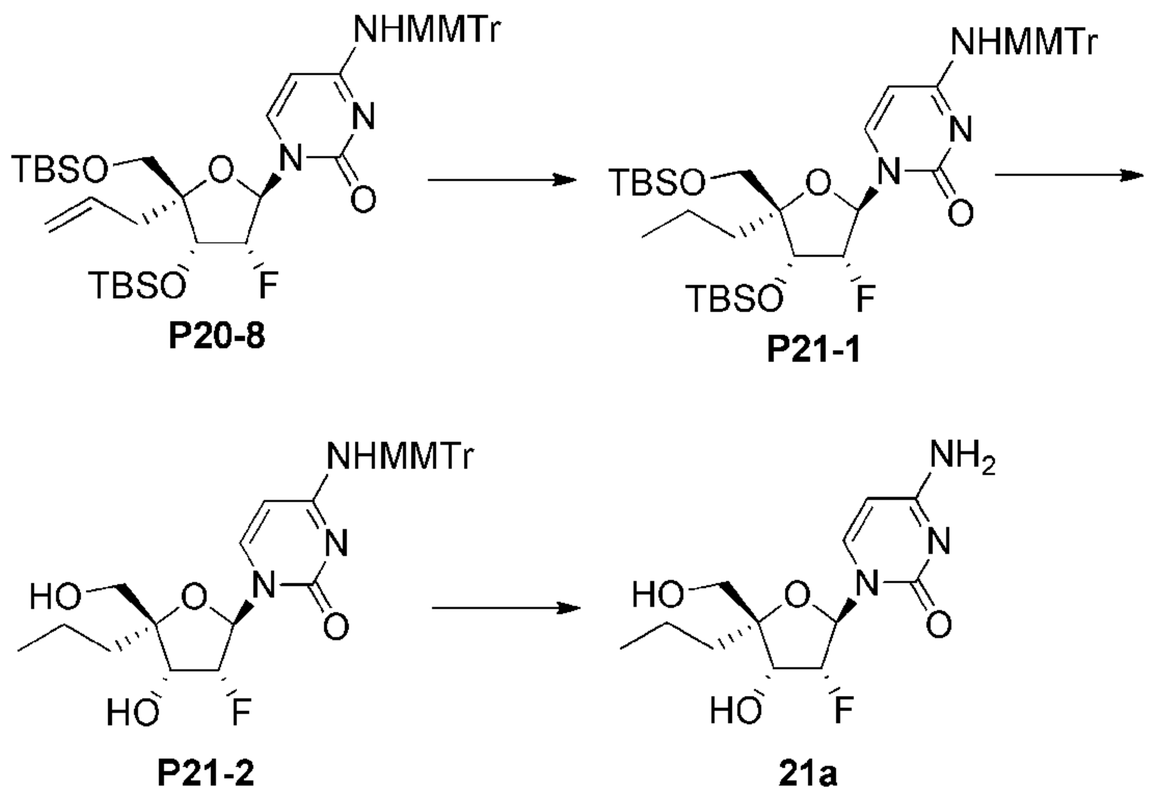
a silica gel column (20~40% EA in PE) to afford compound **P20-6** as a white foam (280 mg, 80.7%). ESI-LCMS: m/z 537 $[M+Na]^+$.

[0275] To a stirred solution of **P20-6** (280.0 mg, 0.5 mmol) in dry MeCN were added TPSCl (350.0 mg, 1.2 mmol), NEt_3 (400.0 mg, 4.0 mmol) and DMAP (270.0 mg, 2.2 mmol) at R.T. The mixture was stirred at R.T. for 18 hours. The solution was quenched with ammonium. The organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed, and the residue was purified by TLC (using EA) to afford compound **P20-7** as a white foam (240.0 mg, 85.7%). ESI-LCMS: m/z 514 $[M+H]^+$.

[0276] To a stirred solution of **P20-7** (270.0 mg, 0.5 mmol) in dry DCM were added $AgNO_3$ (1.5 g, 8.8mmol), MMTrCl (450.0 mg, 1.5 mmol) and collidine (500.0 mg, 4.1 mmol) at R.T. The mixture was stirred at R.T. for 18 hours. The solution was diluted with DCM. The organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed, and the residue was purified on a silica gel column (20~40% EA in PE) to afford compound **P20-8** as a white foam (300 mg, 81.6%). ESI-LCMS: m/z 786 $[M+H]^+$.

[0277] To a stirred solution of **P20-8** (170.0 mg, 0.3 mmol) in dry MeOH was added NH_4F (300.0 mg, 8.1 mmol), and the mixture was refluxed for 24 hours. The solvent was removed under reduced pressure, and the residue was purified on a silica gel column (2~5% MeOH in DCM) to give the crude product. The crude product was further purified by RP HPLC (water and 0.1% HCOOH in MeCN) to afford **20a** as a white solid (47.0 mg, 49.8%). ESI-LCMS: m/z 286 $[M+H]^+$.

EXAMPLE 21
Preparation of Compound 21a

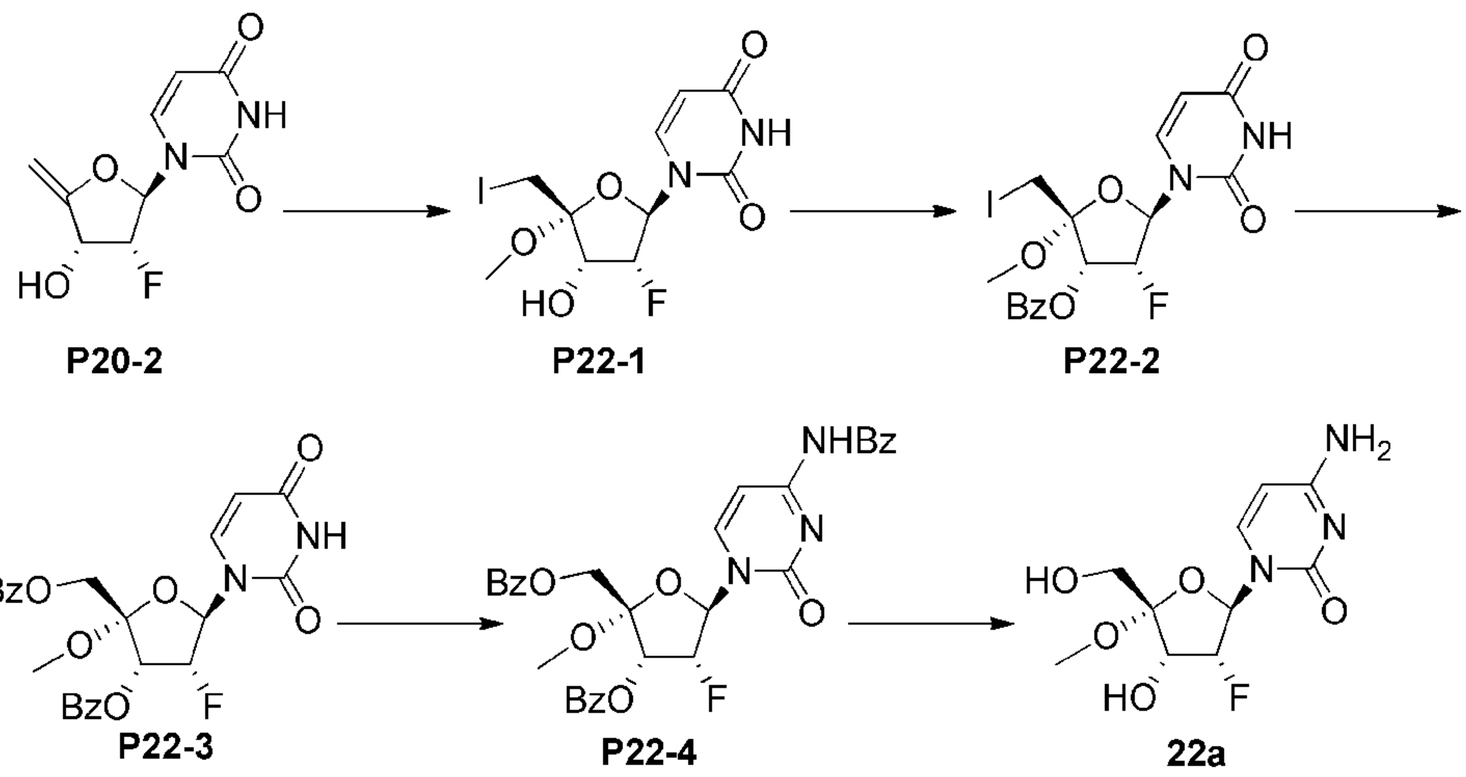


[0278] To a stirred solution of **P20-8** (250.0 mg, 0.3 mmol) in MeOH was added Pd/C (500.0 mg), and the mixture was stirred under H_2 (balloon) for 18 hours at R.T. The reaction was filtered, and the solvent removed under reduced pressure. The residue was purified by prep. TLC (30% EtOAc in PE) to afford **P21-1** as a white foam (210.0 mg, 84.0%).

[0279] To a stirred solution of **P21-1** (210.0 mg, 0.3 mmol) in dry THF was added TBAF (1 mL, 1mmol), and the mixture was stirred at R.T. for 18 hours. The solvent was removed under reduced pressure, and the residue was purified by prep. TLC (30% EtOAc in PE) to give **P21-2** as a white foam (111.2 mg, 74.6%). ESI-MS: m/z 560 $[M + H]^+$.

[0280] Compound **P21-2** (81 mg) was dissolved in a mixture (5 mL) of formic acid (80%) and water (20%). The resulting solution was stirred at R.T. for 3 hours and then concentrated. The residue was co-evaporated with methanol/toluene three times. Chromatography on silica gel with 5-12% methanol in DCM gave a mixture of two compounds, which was dissolved in methanol with a drop of concentrated aqueous ammonia and concentrated. The residue was purified on silica gel with 5-12% methanol in DCM to give **21a** (27 mg) as a white solid; MS: m/z 417 $[M+2\text{-methylheptylamine}]^+$.

EXAMPLE 22
Preparation of Compound 22a



[0281] To a solution of **P20-2** (5.23 g, 23.1 mmol) in anhydrous MeOH (50 mL) was added $PbCO_3$(12.7 g, 46.3 mmol) at R.T. A solution of I_2 (11.7 g, 46.3 mmol) in MeOH (10 mL) was then added dropwise at 0°C. The reaction mixture was stirred at R.T. for overnight. The reaction was quenched with $Na_2S_2O_3$ and dissolved in EA. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by column (DCM/MeOH = 100/1 to 20/1) to give **P22-1** as a white solid (5.6 g, 71.8%). ^{1}H NMR (CD_3OD, 400 MHz) δ 7.67 (d, J = 8.0 Hz, 1H), 5.88 (dd, J_1 = J_2 = 7.6 Hz, 1H), 5.73 (d, J = 8.0 Hz, 1H), 5.24 (dd, J_1 = 4.4 Hz, J_2 = 6.4 Hz, 1H), 5.11 (dd, J_1 = 6.4 Hz, J_2 = 6.0 Hz, 1H); 4.65 (dd, J_1 = 20.0 Hz, J_2 = 20.4 Hz, 1H), 3.67 (d, J = 11.6 Hz, 1H), 3.54 (d, J = 11.6 Hz, 1H), 3.43 (s, 3H).

[0282] To a stirred solution of **P22-1** (5.6 g, 14.5 mmol) in anhydrous pyridine (20 mL) was added dropwise BzCl (2.9 g, 20.9 mmol) at 0°C. The mixture was stirred at R.T. for 10 hours. The reaction was quenched with H_2O, and the solution was concentrated. The residue was dissolved in EA and washed with saturated $NaHCO_3$. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified on a silica gel column (20~40% EA in PE) to give **P22-2** as a white foam (4.9 g, 74.2%).

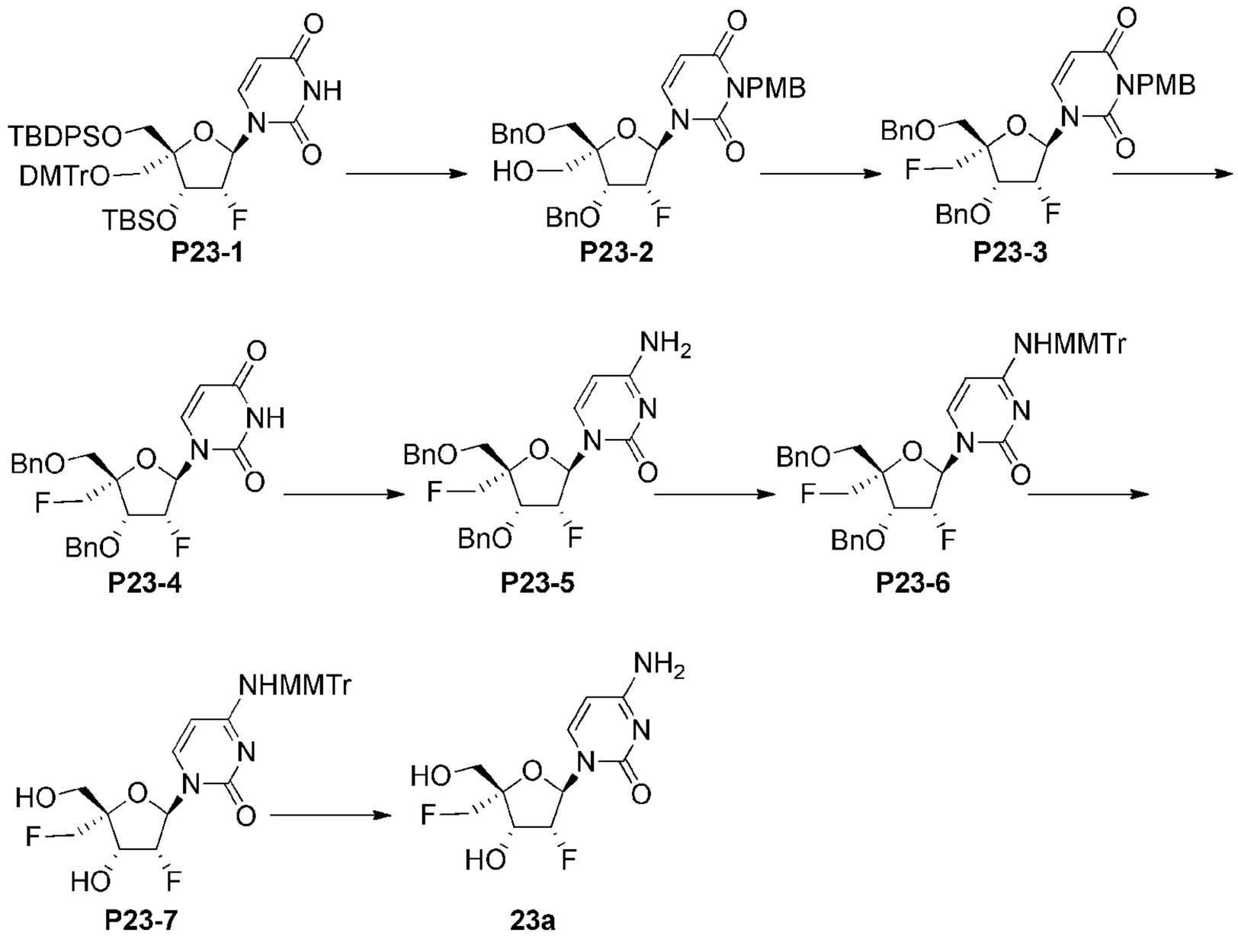
[0283] Compound **P22-2** (4.9 g, 10.0 mmol), BzONa (14.4 g, 100 mmol) and 15-crown-5 (22.0 g, 100 mmol) were suspended in DMF (200 mL). The mixture was stirred at 60-70°C for 3 days. The precipitate was removed by filtration, and the filtrate was diluted with EA. The solvent was washed with brine and dried over Na_2SO_4. The solvent was

removed, and the residue was purified on a silica gel column (20~60% EA in PE) to afford **P22-3** as a white foam (2.3 g, 47.9%).

[0284] Compound **P22-3** (2.3 g, 4.8 mmol), DMAP (1.2 g, 9.6 mmol), TPSCl (2.9 g, 9.6 mmol) and Et_3N (0.97 g, 9.6 mmol) were suspended in MeCN (10 mL). The mixture was stirred at R.T. for 14 hours. NH_3 in THF (saturated at 0°C, 100 mL) was added to the mixture, and the mixture stirred at R.T. for 2 hours. The solvent was removed, and the residue was purified by column (DCM/MeOH = 100:1 to 50:1) to give the crude product (1.2 g). The crude product was dissolved in pyridine, and BzCl (0.42 g, 3.0 mmol) was added. The mixture was stirred at R.T. for 16 hours and quenched with water. The solvent was removed, and the residue was purified on a silica gel column (PE:EA = 2:1 to 1:1) to give **P22-4** as a white foam (460 mg, 31%).

[0285] Compound **P22-4** (0.46 g, 0.8 mmol) was dissolved in saturated methanolic ammonia (100 mL), and the mixture was stirred at R.T. for 14 hours. The solvent was removed, and the residue was dissolved in H_2O and washed with DCM. The aqueous phase was lyophilized and further purified by prep. HPLC (0.1% formic acid in water/acetonitrile) to give **22a** as a white solid (145 mg, 78.9 %). ESI-MS: m/z 276 $[M+H]^+$.

EXAMPLE 23
Preparation of Compound 23a



P23-1 P23-2 P23-3

P23-4 P23-5 P23-6

P23-7 23a

[0286] To a solution of **P23-1** (3.1 g, 4.5 mmol) in DMF (30 mL) was added anhydrous K_2CO_3 (1.24 g, 9.03 mmol) and PMBCl (1.40 g, 9.03 mmol). The mixture was stirred at ambient temperature overnight. The reaction was quenched with water and extracted with EA. The organic layer was concentrated, and the residue was purified on a silica gel column (PE:EA = 10:1 to 4:1) to give the intermediate as a white solid (2.36 g, 74.8%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29-7.88 (m, 23H), 6.83-6.98 (m, 6H), 6.35-6.45 (m, 1H), 4.51-5.50 (m, 6H), 3.89-3.95 (m, 9H), 3.66-3.71 (m, 2H),3.03 (d, J =11.2Hz, 1H), 1.21 (s, 9H), 0.89 (m, 9H), 0.01-0.11 (m, 6H). The intermediate was used in the next step.

[0287] To a stirred solution of the intermediate (11.0 g, 10.47 mmol) in anhydrous THF (100 mL) was added TBAF (8.20 g, 31.42 mmol) at R.T., and the mixture was stirred at R.T. for 5 hours. The solution was removed, and the residue was purified on a silica gel column (PE: EA=5:1 to 1:1) to give a second intermediate as a white solid (5.99 g, 82%).

[0288] To a stirred solution of the second intermediate (500 mg, 0.716 mmol) in anhydrous DMF (10 mL) was added NaH (51.5 mg, 2.14 mmol) and BnBr (365 mg, 2.14 mmol) dropwise at 0°C. The mixture was stirred at R.T. for overnight. The solution was quenched with water and extracted with EA. The concentrated organic phase was purified on a silica gel column (PE:EA = 10:1 to 4:1) to give a third intermediate as a white solid (496 mg, 79%).

[0289] The third intermediate (2.5 g, 2.84 mmol) was dissolved in 80% HOAc (25 mL) at R.T., and the mixture was stirred at R.T. for overnight. The reaction was quenched with MeOH, and the solvent was removed. The crude was purified on a silica gel column (PE:EA = 5:1 to 1:1) to give **P23-2** as a white solid (1.2 g, 73%).

[0290] To a stirred solution of DAST (1.39 g, 8.68 mmol) in anhydrous toluene (15 mL) was added dropwise a solution of **P23-2** (1.0 g, 1.73 mmol) at -78°C. The mixture was stirred at -78°C for 30 mins. The solution was heated to 60°C gradually and then stirred overnight. The mixture was poured into saturated Na_2CO_3 solution. The concentrated organic phase was purified on a silica gel column (PE:EA = 10:1 to 4:1) to give **P23-3** as a white solid (449 mg, 45%). ^{1}H NMR (CD_3OD, 400 MHz) δ 7.87 (d, J = 8.4 Hz, 1H), 7.27-7.37 (m, 12H), 6.82-6.84 (m, 2H), 6.14 (dd, J = 16.8,2.0Hz, 1H), 5.18-5.50 (m, 4H), 4.96 (s, 2H), 4.45-4.88 (m, 7H), 3.67-3.89 (m, 5H).

[0291] A mixture of **P23-3** (1.20 g, 2.07 mmol) and CAN (3.41 g, 6.23 mmol) in a solution of MeCN:Water (3:1, 10 mL) was stirred at R.T. overnight. Brine (10 mL) was added, and the mixture was extracted with EA. The combined organic extracts were dried and evaporated under reduced pressure. The residue was purification by chromatography on silica gel (PE:EA = 10:1 to 2:1) to give **P23-4** as a yellow solid (475 mg, 49.8%).

[0292] To a stirred solution of **P23-4** (550 mg,210 mmol) in anhydrous MeCN (10 mL) were added TPSCl (725 mg, 2.40 mmol), DMAP (293 mg, 2.40 mmol) and TEA (242 mg, 2.40 mmol) at R.T., and the mixture was stirred at R.T. overnight. NH_4OH (25 mL) was added, and the mixture was stirred for 2 hours. The solvent was removed, and the residue was purified on a silica gel column (PE:EA = 8:1 to 2:1) to give **P23-5** as a white solid (700 mg crude).^{1}H NMR (CD_3OD, 400 MHz) δ 7.86 (d, J = 8.4 Hz, 1H), 7.27-7.36 (m, 10H), 6.13 (dd, J_1 = 17.2 Hz, J_2 = 2.0 Hz, 1H), 5.48-5.53 (m, 1H), 5.11-5.26 (m, 1H), 4.44-

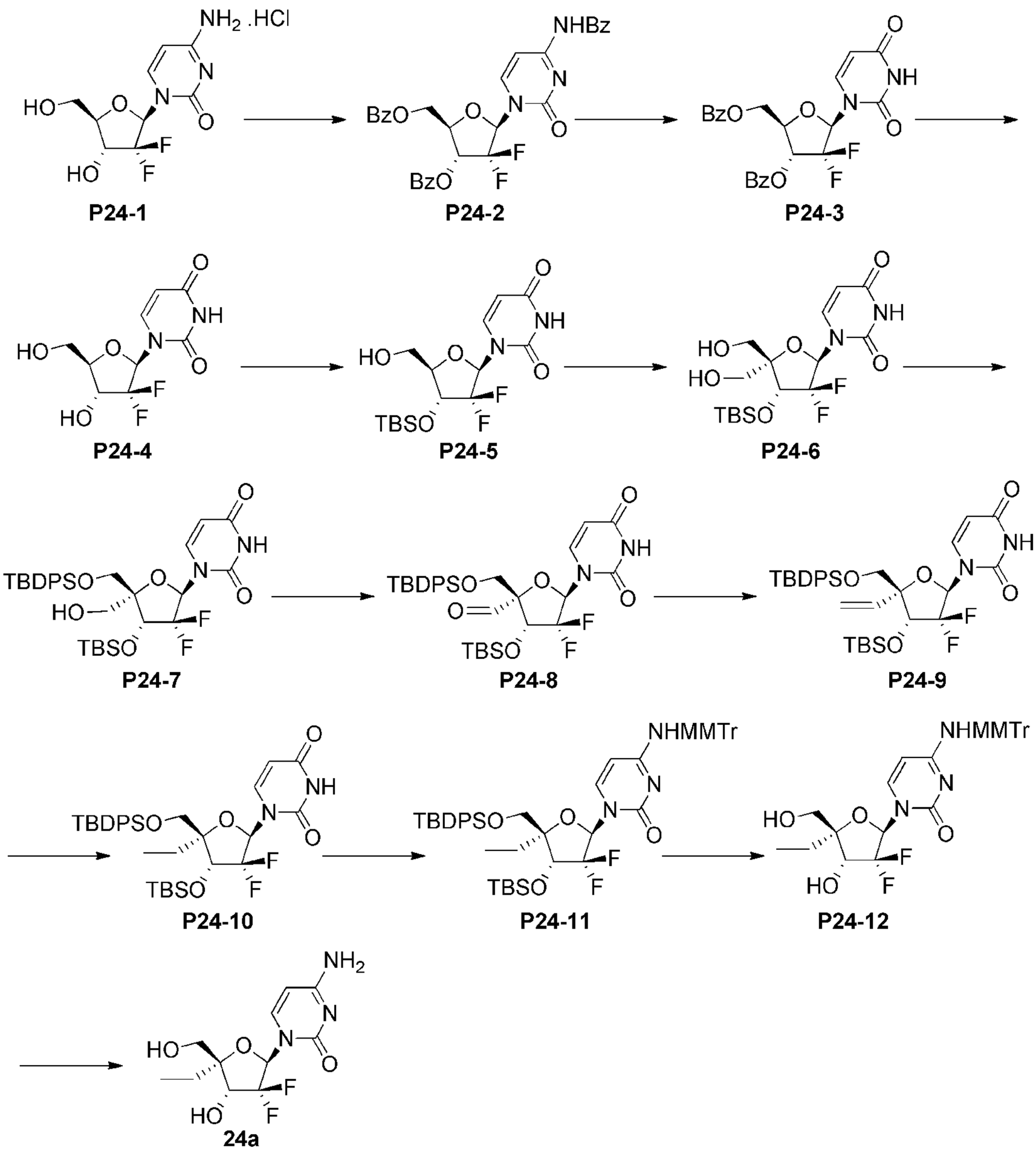
4.74 (m, 7H), 3.89 (dd, J_1 = 10.4 Hz, J_2 = 2.0 Hz, 1H), 3.69 (dd, J_1 = 10.8 Hz, J_2 =1.6 Hz, 1H).

[0293] To a stirred solution of **P23-5** (1.0 g, 2.18 mmol) in anhydrous DCM (15 mL) was added MMTrCl (2.02 g, 6.56 mmol) and $AgNO_3$ (1.11 g, 6.56 mmol) at R.T., and the mixture was stirred at R.T. overnight. The solid was filtered off and washed with DCM. The filtrate was washed with brine and dried over Na_2SO_4. The organic phase was concentrated, and the residue was purified on a silica gel column (PE:EA = 8:1 to 2:1) to give **P23-6** as a white solid (520 mg, 41%).

[0294] To a stirred solution of **P23-6** (520 mg, 0.713 mmol) in acetone were added ammonium formate (2.0 g, 31.7 mmol, in portions) and 10% palladium on carbon (1.0 g). The mixture was refluxed for 12 hours. The catalyst was filtered off and washed with solvent. The filtrate was added EA and washed with brine. The concentrated organic phase was purified by column chromatography (DCM:MeOH = 100:1 to 15:1)and prep. TLC to give **P23-7** as a white solid (270 mg, 69.0%). ESI-MS: m/z 549.6 $[M+H]^+$.

[0295] Compound **P23-7** (130 mg, 0.236 mmol) was dissolved in 80% HCOOH (20 mL) at R.T., and the mixture was stirred at 50°C for 12 hours. The solvent was removed, and the residue was co-evaporated with toluene twice. The residue was re-dissolved in MeOH (20 mL) at 60°C and stirring was continued for 48 hours. The solvent was removed, and the residue was purified by column chromatography (DCM:MeOH = 100:1 to 10:1) to give **23a** as a white solid (45 mg, 69.0%). ESI-MS: m/z 277.8 $[M+H]^+$, 554.8 $[2M+H]^+$.

EXAMPLE 24
Preparation of Compound 24a



[0296] To a solution of **P24-1** (30.0 g, 100.0 mmol) in pyridine (300 mL) was added BzCl (56.0 g, 400 mmol) at 25°C. The mixture was stirred at 25°C for 15 hours. The mixture was concentrated and purified by column chromatography (PE:EA = 20:1 to 2:1) to give crude **P24-2** (55.0 g, 81%).

[0297] Compound **P24-2**(55.0 g, 92 mmol) was dissolved in 80% HOAc aq. solution, and the mixture was refluxed for 14 hours. The solvent was removed under reduced

pressure, and the residue was co-evaporated with toluene. The residue was purified on a silica gel column (PE/EA = 4:1 to 2:1) to give **P24-3** as a white solid (39.2 g, 83%).

[0298] Compound **P24-3** (39.2 g, 83 mmol) was dissolved in saturated methanolic ammonia, and the resulting solution was stirred at R.T. for 15 hours. The solvent was removed, and the residue was purified on a silica gel column (DCM/MeOH = 50:1 to 20:1) to give **P24-4** (21.0 g, 95.8%).

[0299] To a solution of **P24-4** (21.0 g, 79.5 mmol) in pyridine (250 mL) was added DMTrCl (28.2 g, 83.5 mmol) at 0°C. The solution was stirred at R.T. for 15 hours. The reaction was quenched with MeOH and 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 concentrated. The residue was dissolved in DCM (300 mL). Imidazole (13.6 g, 200 mmol) and TBSCl (30.0 g, 200 mmol) were added. The reaction mixture was stirred at R.T. for 12 hours. The reaction mixture was washed with $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and concentrated. The residue (48.5 g, 79.5 mmol) was dissolved in 80% HOAc aq. solution (400 mL). The mixture was stirred at R.T. for 20 hours. The mixture was diluted with EtOAc 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 **P24-5** as a white solid (21.0 g, 70%). ESI-MS: m/z 379.1 $[M+H]^+$.

[0300] To a solution of **P24-5** (21.0 g, 55.6 mmol) in anhydrous CH_3CN (200 mL) was added IBX (17.1 g, 61.1 mmol) at R.T. The reaction mixture was refluxed for 1 hour and then cooled to 0°C. The precipitate was filtered off, and the filtrate was concentrated to give the aldehyde as a yellow solid (21.0 g, 55.6 mmol). To a solution of the aldehyde (21.0 g, 55.6 mmol) in dioxane (200 mL) were added 37% CH_2O (22.2 mL, 222.4 mmol) and 2N NaOH aq. solution (55.6 mL, 111.2 mmol). The mixture was stirred at R.T. for 2 hours and then neutralized with AcOH to pH = 7. To the reaction were added EtOH (50 mL) and $NaBH_4$ (12.7 g, 333.6 mmol). The mixture was stirred at R.T. for 30 mins. The reaction was quenched with saturated aq. NH_4Cl. 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 **P24-6** as a white solid (13.5 g, 59.5%).

[0301] To a solution of **P24-6** (13.5 g, 33.1 mmol) in DCM (100 mL) were added pyridine (20 mL) and DMTrCl (11.2 g, 33.1 mmol) at 0°C. The solution was stirred at 25°C for 3 hours, and then treated with MeOH (30 mL). The solvent was removed, and the residue was purified by silica gel column chromatography (DCM:MeOH = 300:1 to 100:1) to give a residue. The residue was dissolved in anhydrous pyridine (150 mL) and TBDPSCl (16.5 g, 60 mmol) and $AgNO_3$ (10.2 g, 60 mmol) were added. The mixture was stirred at 25°C for 15 hours, and then filtered and concentrated. The mixture was dissolved in EtOAc and washed with brine. The organic layer was dried over Na_2SO_4. Purified by silica gel column chromatography (DCM:MeOH = 300:1 to 100:1) gave the product as a yellow solid (16.2 g, 85.3%). The solid was dissolved in 80% HOAc aq. solution (400 mL). The mixture was stirred at R.T. for 15 hours. The mixture was diluted with EtOAc and washed with $NaHCO_3$ solution and brine. 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 **P24-7** as a white solid (9.5 g, 86.5%).^{1}H NMR (CD_3OD, 400 MHz) δ 7.39-7.70 (m, 11H), 6.34-6.38 (m, 1H), 5.12 (d, J = 8.0 Hz, 1H), 4.79 (dd, J_1 = 10.0 Hz, J_2 = 16.0 Hz, 1H), 4.14 (dd, J_1 = 1.6 Hz, J_2 = 11.6 Hz, 1H), 3.48-3.84 (m, 2H), 3.49 (dd, J_1 = 1.6 Hz, J_2 = 11.6 Hz, 1H),1.12 (s, 9H), 0.92 (s, 9H), 0.16 (s, 6H).

[0302] To a solution of **P24-7** (6.0 g, 9.3 mmol) in anhydrous DCM (80 mL) was added Dess-Martin periodinane (7.9 g, 18.6 mmol) at 0°C under nitrogen. The reaction was stirred at R.T. for 1 hour. The solvent was removed in vacuo, and the residue was triturated with diethyl ether (50 mL). The mixture was filtered through a pad of $MgSO_4$, and the organic solvent was stirred with an equal volume of $Na_2S_2O_3.5H_2O$ in saturated $NaHCO_3$ (50 mL) until the organic layer became clear (approx. 10 min). The organic layer was separated, washed with brine, and dried over $MgSO_4$. After concentration in vacuo, **P24-8** was obtained as a red solid (5.8 g.98%).

[0303] To a mixture of methyltriphenylphosphonium bromide (9.6 g, 27.0 mmol) in anhydrous THF (60 mL) was added n-BuLi (10.8 mL, 27.0 mmol) at -70°C under nitrogen. The reaction was stirred at 0°C for 30 mins. A solution of **P24-8** (5.8 g, 9.0 mmol) in anhydrous THF (20 mL) was added dropwise at 0°C under nitrogen. The reaction was stirred at R.T. for 12 hours. The reaction was quenched with NH_4Cl and extracted with EtOAc. The

organic layer was separated, dried and concentrated, and the residue was purified by silica gel column chromatography (DCM:MeOH = 300:1 to 100:1) to give **P24-9** as a white solid (3.0 g, 51%).

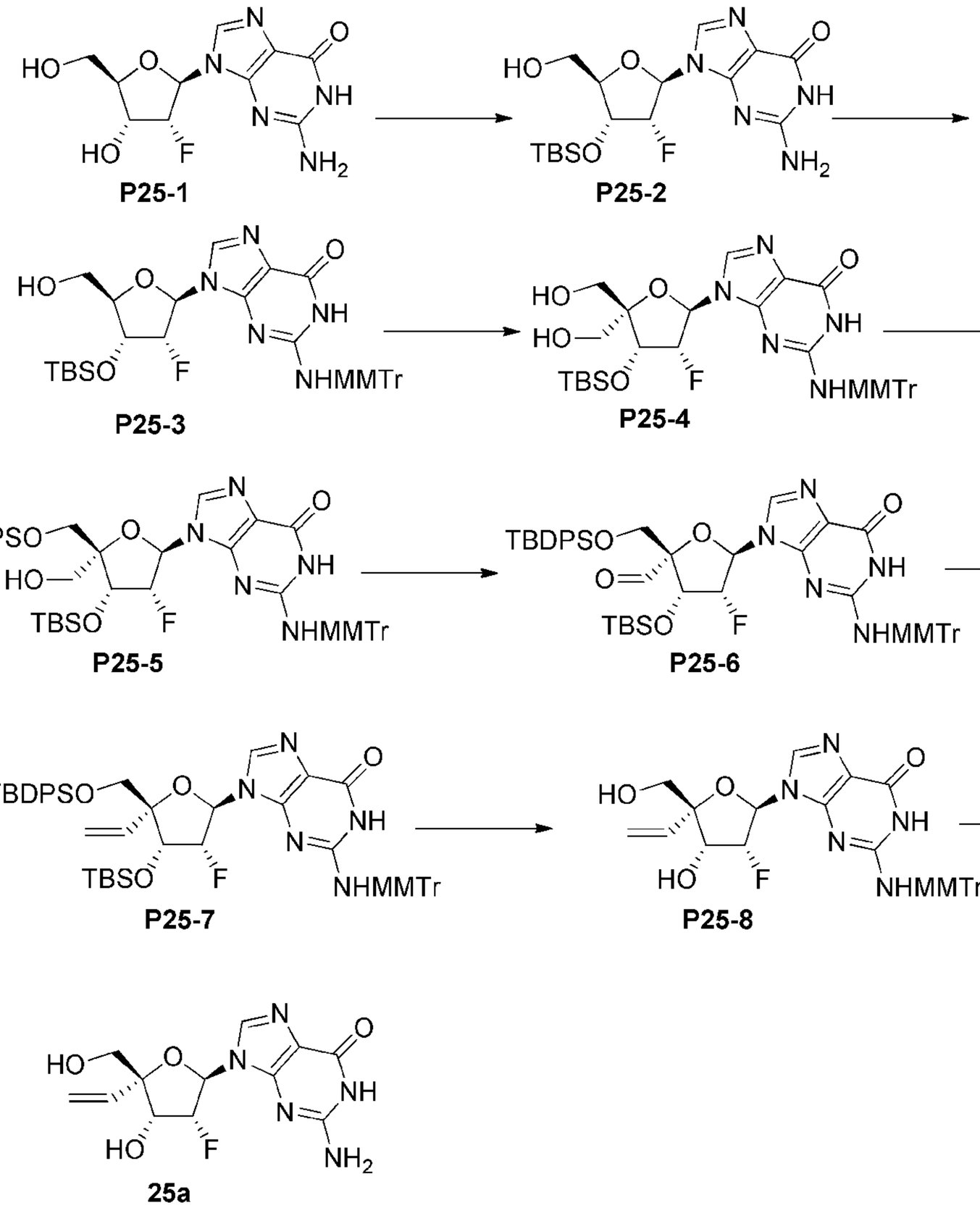
[0304] To a solution of **P24-9** (2.9 g, 4.5 mmol) in anhydrous MeOH (20 mL) was added Pd/C (1.4 g) at 25°C under hydrogen atmosphere. The mixture was stirred at 25°C for 1 hour. The solution was filtered, evaporated to dryness and purified on a silica gel column (DCM:MeOH =300:1 to 100:1) to give **P24-10** as a white solid (2.3 g, 79.3 %).

[0305] To a solution of **P24-10** (1.0 g, 1.55 mmol) in anhydrous CH_3CN (20 mL) were added TPSCl (940 mg, 3.1 mmol), DMAP (380 mg, 3.1 mmol) and NEt_3 (470 mg, 4.6 mmol) at R.T. The reaction was stirred at R.T. for 5 hours. NH_4OH (8 mL) was added, and the reaction was stirred for 1 hour. The mixture was diluted with DCM (150 mL) and washed with water, 0.1 M HCl and saturated aq. $NaHCO_3$. The solvent was removed, and the residue was purified by silica gel column chromatography (PE:EA = 10:1 to 1:1) to give the crude product as a yellow solid (900 mg, 90 %). To a solution of the crude product in DCM (10 mL) were added MMTrCl (930 mg, 3.0 mmol), $AgNO_3$ (510 mg, 3.0 mmol) and colliding (720 mg, 6.0 mmol) at R.T. The reaction was stirred for 12 hours at R.T. The reaction was filtered, concentrated and purified by silica gel column chromatography (DCM:MeOH=200:1 to 50:1) to give **P24-11** as a yellow solid (1.1 g, 77.6%).

[0306] To a solution of **P24-11** (1.1 g, 1.2 mmol) in MeOH (40 mL) was added NH_4F (1.0 g, 30 mmol) at 25°C and stirred at 70°C for 15 hours. The solution was filtered and evaporated to dryness, and the residue was purified by silica gel column (DCM:MeOH = 200:1 to 20:1) to give **P24-12** as a white solid (450 mg, 66.6%). ESI-LCMS: m/z 563.6 $[M+H]^+$.

[0307] Compound **P24-12** (250 mg, 0.44 mmol) was dissolved in 80% HCOOH in H_2O (6.0 g) at 25°C. The mixture was stirred at 35°C for 15 hours. The solution was evaporated to dryness, dissolved in MeOH (30 mL) and stirred at 60°C for 12 hours. The solution was evaporated to dryness and purified by silica gel column chromatography methylene chloride:methanol to give **24a** as a white solid (125.6 mg, 97%). ESI-LCMS: m/z 291.9 $[M+H]^+$.

EXAMPLE 25
Preparation of Compound 25a



[0308] To a solution of **P25-1** (20.0 g, 70.16 mmol) in anhydrous pyridine (200 mL) was added imidazole (19.08 g, 280.7 mmol) and TBSCl (42.10 g, 280.7 mmol) at 25°C. The solution was stirred at 25°C for 15 hours, and then concentrated to dryness under reduced pressure. The residue was washed with EtOAc to give the crude product as a white solid (36.4 g). The crude product was dissolved in THF (150 mL) and H_2O (100 mL), and then HOAc (300 mL) was added. The solution was stirred at 80°C for 13 hours. The reaction was cooled to R.T., and the mixture was concentrated to dryness under reduced pressure. The residue was dissolved washed with EtOAc and dried to give **P25-2** as a white solid (31.2 g, 60.9 %).

[0309] To a stirred solution of **P25-2** (31.2 g, 78.2 mmol) in anhydrous pyridine (300 mL) was added Ac_2O (11.96 g, 117.3 mmol). The mixture was stirred at 25°C for 18 hours. MMTrCl (72.3 g, 234.6 mmol) and $AgNO_3$ (39.9 g, 234.6 mmol) were then added. The solution was stirred at 25°C for 15 hours. And H_2O was added to quench the reaction. 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 vacuo to give a residue. The residue was purified by silica gel (DCM:MeOH = 200:1 to 50:1) to give the product. The product was dissolved in NH_3/MeOH (300 mL), and the mixture was stirred at 25°C for 20 hours. The solvent was removed, and the residue was purified on a silica gel column (DCM:MeOH = 100:1 to 50:1) to give **P25-3** as a yellow solid (28.6 g, 86.5 %). ^{1}H NMR (400 MHz, MeOD) δ 8.01 (s, 1H), 7.23-7.35(m, 12H), 6.85-6.87 (m, 2H), 5.60 (dd, J_1 = 11.2 Hz, J_2 = 5.6 Hz, 1H), 4.78-4.94 (m, 1H), 4.44 (dd, J_1 = 8.0 Hz, J_2 = 4.8 Hz, 1H), 3.78 (s, 3H), 3.60-3.63 (m, 1H), 3.50 (dd, J_1 = 32.0 Hz, J_2 = 12.0 Hz, 2H), 3.32 (s, 3H), 0.94 (s, 9H), 0.12-0.14 (m, 6H).

[0310] To a solution of **P25-3** (7.24 g, 10.79 mmol) in anhydrous CH_3CN (100 mL) was added IBX (3.93 g, 14.03 mmol) at 20°C. The reaction mixture was refluxed at 90°C for 1 hour. The reaction was filtered, and the filtrate was concentrated to give the aldehyde as a yellow solid (7.1 g). To a solution of the aldehyde (7.1 g, 10.6 mmol) in dioxane (80 mL) was added 37% CH_2O (4.2 mL, 42.4 mmol) and 2N NaOH aq. solution (8.0 mL, 15.9 mmol). The mixture was stirred at 25°C for 2 hours and then neutralized with AcOH to pH = 7. To reaction was added EtOH (30 mL) and $NaBH_4$ (2.4 g, 63.6 mmol), the reaction was then stirred for 30 mins. The mixture was quenched with saturated aq. NH_4Cl. The mixture was extracted with EA, and the organic layer was dried over Na_2SO_4. The solvent was removed, and the residue was purified by silica gel column chromatography (DCM:MeOH = 200:1 to 50:1) to give **P25-4** as a yellow solid (4.86 g, 65.4%).

[0311] To a solution of **P25-4** (3.8 g, 5.4 mmol) in DCM (40 mL) were added pyridine (10 mL) and DMTrCl (1.8 g, 5.4 mmol) at 0°C. The solution was stirred at 25°C for 1 hour. The reaction mixture was treated with MeOH (15 mL) and concentrated. The residue was purified by silica gel column chromatography (DCM:MeOH = 200:1 to 50:1) to give the mono-DMTr protected intermediate as a yellow solid (3.6 g, 66.4 %). To a solution

of the intermediate in anhydrous pyridine (30 mL) were 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 hours. The mixture was filtered and concentrated, and then dissolved in EtOAc and washed with brine. The organic layer was dried over Na_2SO_4, and then concentrated. The residue was purified by silica gel column chromatography (DCM:MeOH = 200:1 to 50:1) to give the pure intermediate as a white solid (3.8 g, 85.1%). To a solution of the intermediate (3.6 g, 2.9 mmol) in anhydrous DCM (50 mL) was added $Cl_2CHCOOH$ (1.8 mL) in anhydrous DCM (18 mL) at -78°C. The mixture was stirred at -10°C for 30 mins. The mixture was quenched with saturated aq. $NaHCO_3$ 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 **P25-5** as a white solid (2.2 g, 80.7%).

[0312] Compound **P25-5** (2.2 g, 2.3 mol) was added to a suspension of Dess-Martin periodinane (2.5 g, 5.8 mol) in anhydrous CH_2Cl_2 (30 mL) at 25°C. The mixture was stirred at 25°C for 4 hours. The solvent was removed in vacuo, and the residue triturated with diethyl ether (30 mL). The mixture was filtered through a pad of $MgSO_4$. The organic solvent was stirred with an equal volume of $Na_2S_2O_3.5H_2O$ in saturated $NaHCO_3$ (30 mL) until the organic layer became clear (approx. 10 min). The organic layer was separated, washed with brine, and dried over $MgSO_4$. The solvent was removed in vacuo to give **P25-6** as a yellow solid (2.1 g, 95%).

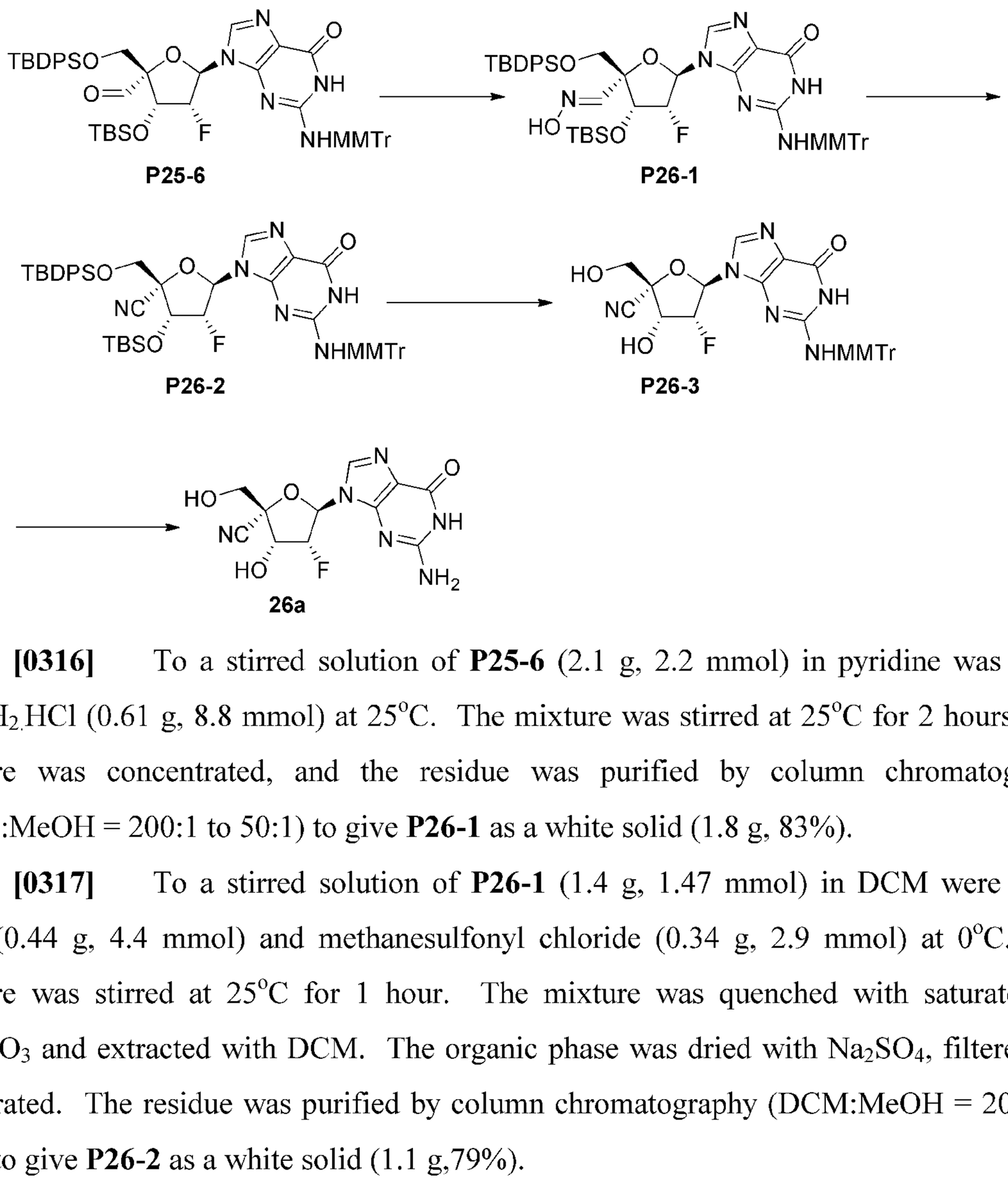
[0313] To a stirred solution of methyl-triphenyl-phosphonium bromide (2.3 g , 6.6 mmol) in anhydrous THF (30 mL) was added dropwise n-BuLi (2.6 mL, 6.6 mmol, 2.5 M in THF) at -78°C over 1 minute. Stirring was continued at 0°C for 1 hour. **P25-6** (2.1 g, 2.2 mmol) was added to the mixture, and then stirred at 25°C for 15 hours. The reaction was quenched with saturated NH_4Cl (50 mL). The mixture was extracted with EtOAc. The combined organic phase was dried with Na_2SO_4, filtered and evaporated to dryness to give a light yellow oil. The oil was purified by column chromatography (DCM:MeOH = 200:1 to 50:1) to give **P25-7** as a white solid (1.6 g, 76%).

[0314] To a solution of **P25-7** (1.6 g, 1.7 mmol) in MeOH (50 mL) was added NH_4F (1.5 g, 40 mmol), and the mixture was stirred at 70°C for 15 hours. The solution was filtered and evaporated to dryness. The residue was purified by silica gel column

(DCM:MeOH = 200:1 to 20:1) to give **P25-8** as a white solid (450 mg, 49%). ESI-LCMS: m/z 584.1 $[M+H]^+$.

[0315] Compound **P25-8** (130 mg, 0.22 mmol) was dissolved in 80% HCOOH and the mixture was stirred at 25°C for 1 hour. Then the solution was evaporated to dryness. The residue was dissolved in MeOH (30 mL) and stirred at 60°C for 12 hours. Then the solution was evaporated to dryness, and the residue was washed by EtOAc to give **25a** as a white solid (52.3 mg, 76%). ESI-MS: m/z 334.1 $[M+Na]^+$.

EXAMPLE 26
Preparation of Compound 26a



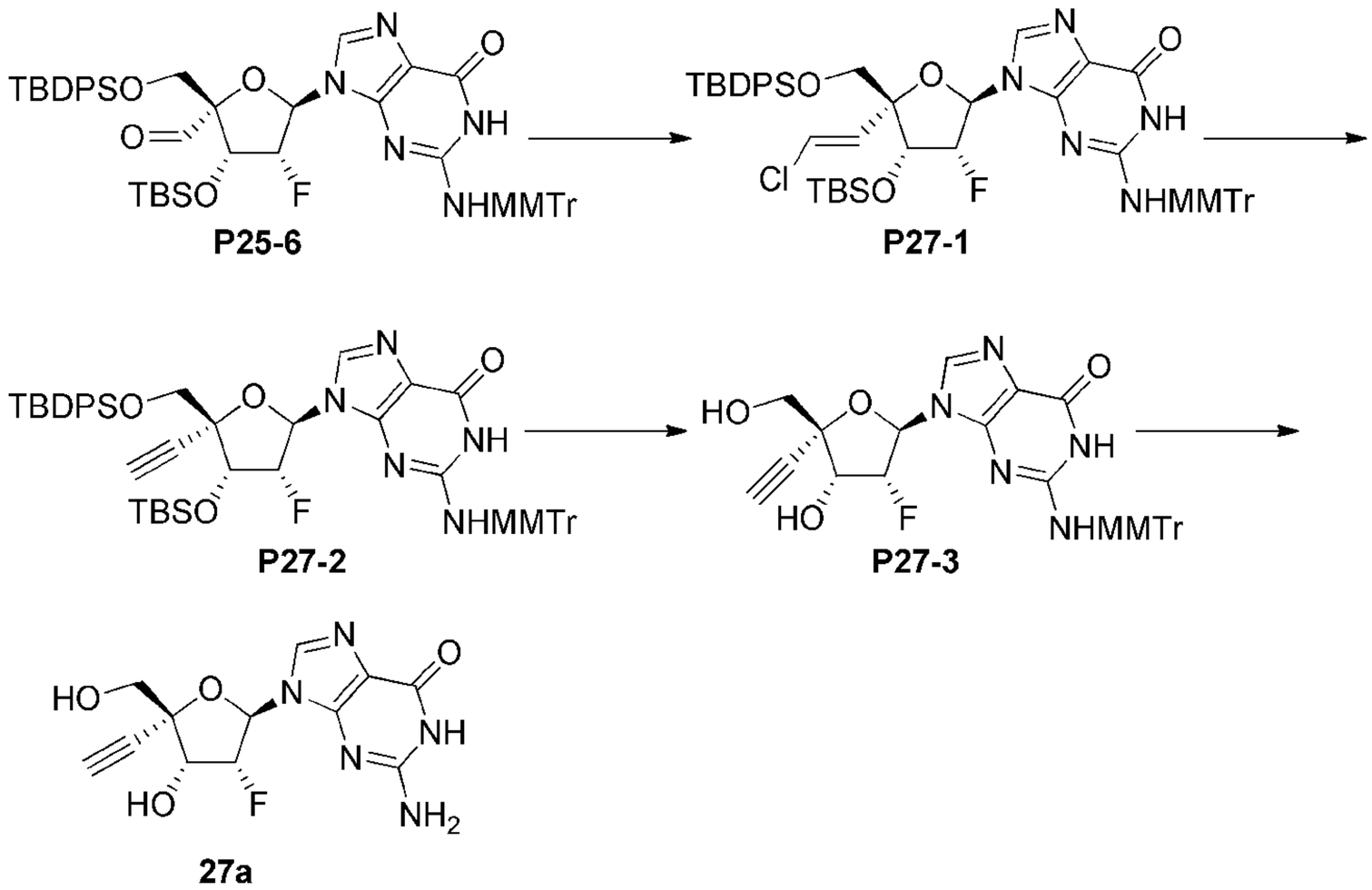
[0316] To a stirred solution of **P25-6** (2.1 g, 2.2 mmol) in pyridine was added $HONH_2.HCl$ (0.61 g, 8.8 mmol) at 25°C. The mixture was stirred at 25°C for 2 hours. The mixture was concentrated, and the residue was purified by column chromatography (DCM:MeOH = 200:1 to 50:1) to give **P26-1** as a white solid (1.8 g, 83%).

[0317] To a stirred solution of **P26-1** (1.4 g, 1.47 mmol) in DCM were added TEA (0.44 g, 4.4 mmol) and methanesulfonyl chloride (0.34 g, 2.9 mmol) at 0°C. The mixture was stirred at 25°C for 1 hour. The mixture was quenched with saturated aq. $NaHCO_3$ and extracted with DCM. The organic phase was dried with Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography (DCM:MeOH = 200:1 to 50:1) to give **P26-2** as a white solid (1.1 g,79%).

[0318] To a solution of **P26-2** (1.1 g, 1.18 mmol) in MeOH (50 mL) was added NH_4F (1.5 g, 40 mmol), and the mixture was stirred at 70°C for 15 hours. The solution was filtered and evaporated to dryness. The residue was purified by silica gel column (DCM:MeOH = 200:1 to 20:1) to give **P26-3** as a white solid (400 mg, 71%). ESI-LCMS: m/z 583.1 $[M+H]^+$.

[0319] Compound **P26-3** (200 mg, 0.34 mmol) was dissolved in 80% HCOOH aq. solution. The mixture was stirred at 25°C for 1 hour. The solution was evaporated to dryness, dissolved in MeOH (30 mL) and stirred at 60°C for 12 hours. The solvent was removed, and the residue was washed by EtOAc to give **26a** as a white solid (100.4 mg, 95%). ESI-MS: m/z 311.1 $[M+H]^+$.

EXAMPLE 27
Preparation of Compound 27a



[0320] To a stirred solution of chloromethyl-triphenyl-phosphonium chloride (1.9 g , 5.4 mmol) in anhydrous THF (30 mL) was added dropwise n-BuLi (2.16 mL, 5.4 mmol, 2.5 M in THF) at -78°C over 10 mins. Stirring was continued at -78°C for 2 hours. **P25-6** (1.7 g, 1.8 mmol) was added, and the mixture and stirred at 25°C for 15 hours. The reaction was quenched with saturated NH_4Cl (50 mL). The mixture was extracted with EtOAc. The combined organic phase was dried with Na_2SO_4, filtered and evaporated to dryness to give a

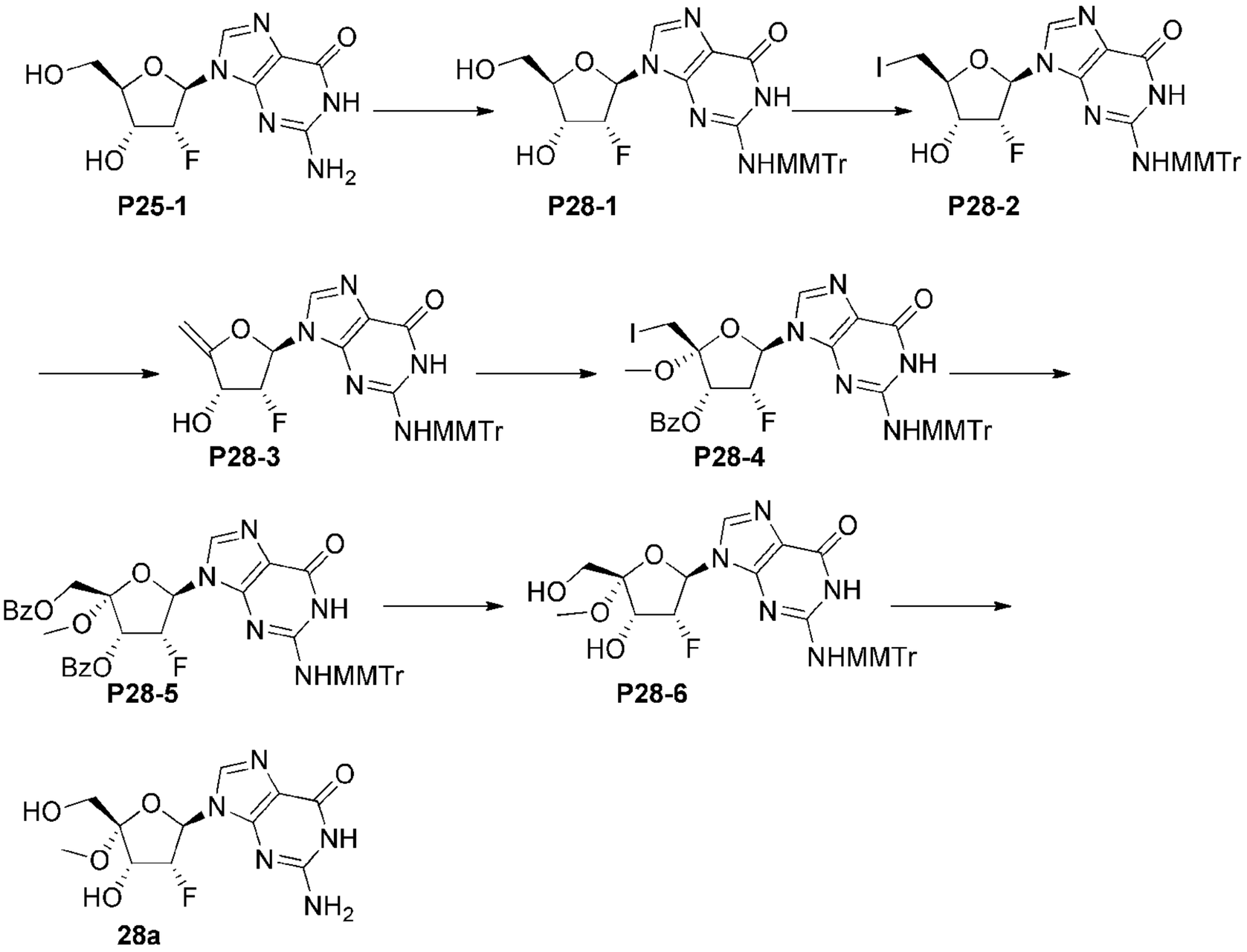
light yellow oil. The oil was purified by column chromatography (DCM:MeOH = 200:1 to 50:1) to give **P27-1** as a white solid (1.2 g, 70%).

[0321] To a stirred solution of **P27-1** (1.2 g, 1.3 mmol) in anhydrous THF (20 mL) was added dropwise n-BuLi (8.0 mL, 20 mmol, 2.5 M in THF) at -78°C over 10 minutes. Stirring was continued at -78°C for 4 hours. The reaction was quenched with saturated NH_4Cl (50 mL). The mixture was extracted with EtOAc (50 x 2 mL). The combined organic phase was dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by column chromatography (DCM:MeOH = 200:1 to 50:1) to give **P27-2** as a white solid (1.0 g, 83%).

[0322] To a solution of **P27-2** (1.0 g, 1.1 mmol) in MeOH (40 mL) was added NH_4F (1.5 g, 40 mmol), and the mixture was stirred at 70°C for 25 hours. The solution was filtered, and the filtrate was evaporated to dryness. The residue was purified on a silica gel column (DCM:MeOH = 200:1 to 20:1) to give **P27-3** as a white solid (240 mg, 38%). ESI-LCMS: m/z 582.1 $[M+H]^+$.

[0323] Compound **P27-3** (130 mg, 0.22 mmol) was dissolved in 80% HCOOH aq. solution. The mixture was stirred at 25°C for 1 hour. The solution was evaporated to dryness. The residue was dissolved in MeOH (30 mL) and stirred at 60°C for 12 hours. The solvent was removed, and the residue was washed with EtOAc to give **27a** as a white solid (43.0 mg, 63%). ESI-MS: m/z 310.1 $[M+H]^+$.

EXAMPLE 28
Preparation of Compound 28a



[0324] To a stirred solution of **P25-1** (5.7 g. 20 mmol) in anhydrous pyridine (20 mL) was added dropwise Ac_2O (5.8 mL, 60 mmol) at 0°C. The mixture was stirred at R.T. for 10 hours. AgNO3 (8.5 g, 50 mmol) and MMTrCl (15.5 g, 50 mmol) were added. The mixture was stirred at R.T. for 10 hours. The solution was quenched with saturated $NaHCO_3$ and extracted with EA. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified on a silica gel column (DCM/MeOH = 100:1 to 50:1) to afford the intermediate as a light yellow solid (12.1 g, 93.4%). The solid was treated with saturated NH_3 in MeOH at R.T. for 14 hours. The solvent was removed, and the residue was purified by silica gel column chromatography (DCM/MeOH = 80:1 to 30:1) to afford **P28-1** as a white solid (9.2 g, 87.5%).

[0325] To a stirred solution of **P28-1** (9.2 g, 16.5mmol) in dry THF (300 mL) were added imidazole (9.0 g, 132 mmol) and PPh_3 (34.8 g, 132 mmol). A solution of I_2 (26.0 g, 103 mmol) in THF (100 mL) was added dropwise under N_2 at 0°C. The mixture was stirred at R.T. for 18 hours. The reaction was quenched with $Na_2S_2O_3$ solution, and the

mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (DCM/MeOH = 80:1 to 30:1) to give **P28-2** as a light yellow solid (10.3 g, 93.4%).

[0326] To a stirred solution of **P28-2** (10.2 g, 15.3 mmol) in dry THF (300 mL) was added DBU (4.7 g, 30.1 mmol). The mixture was stirred at 60°C for 8 hours. The solution was diluted with $NaHCO_3$ solution and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc = 3:1 to 1:3) to afford **P28-3** as a light yellow foam (6.2 g, 75.6 %). ESI-MS: *m/z* 540 $[M + H]^+$.

[0327] To a stirred solution of **P28-3** (5.42 g, 10 mmol) in anhydrous CH_3OH (100 mL) were added $PbCO_3$ (13.7 g, 53.1mmol) followed by a solution of I_2 (12.3 g, 48.9 mmol) in CH_3OH (300 mL) at 0°C. The mixture was stirred at R.T. for 10 hours. The solution was quenched with a $Na_2S_2O_3$ solution and extracted with DCM. The organic layer was washed with $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated. The residue was purified by pre-HPLC (MeCN and 0.1% HCOOH in water) to give the pure product as a white foam (2.4 g, 34 %). The product was dissolved in dry pyridine (20 mL) and BzCl (723 mg, 5.2 mmol) was added dropwise at 0°C. The mixture was stirred at 0°C for 1 hour. The solution was quenched with $NaHCO_3$ solution, and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography using petroleum ether:ethyl acetate to afford **P28-4** as a white solid (2.1 g, 77.1%).

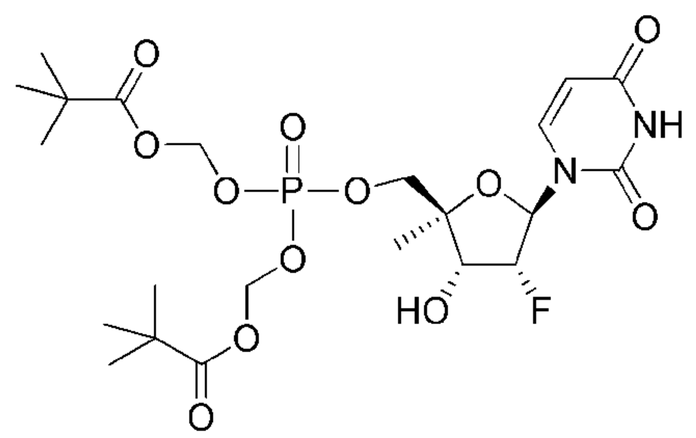
[0328] Compound **P28-4** (2.0 g, 2.5 mmol), BzONa (3.6 g, 25 mmol) and 15-crown-5 (5.5 g, 25 mmol) were suspended in DMF (50 mL). The mixture was stirred at 110-125°C for 5 days. The precipitate was removed by filtration, and the filtrate was diluted with EA. The solution was washed with brine and dried over Na_2SO_4. The solvent was removed, and the residue was purified on a silica gel column (PE/EA = 10/1 to 2/1) to afford crude **P28-5** as a light yellow foam (1.6 g, 80%).

[0329] Compound **P28-5** (1.6 g, 2.0mmol) was dissolved in methanolic ammonia (100 mL, saturated), and the mixture was stirred at R.T. for 20 hours. The solvent was

removed, and the residue was purified on a silica gel column (DCM/MeOH = 100:1 to 20:1) to give **P28-6** as a white solid (410 mg, 34.9%). ESI-LCMS: m/z 588.1 $[M+H]^+$.

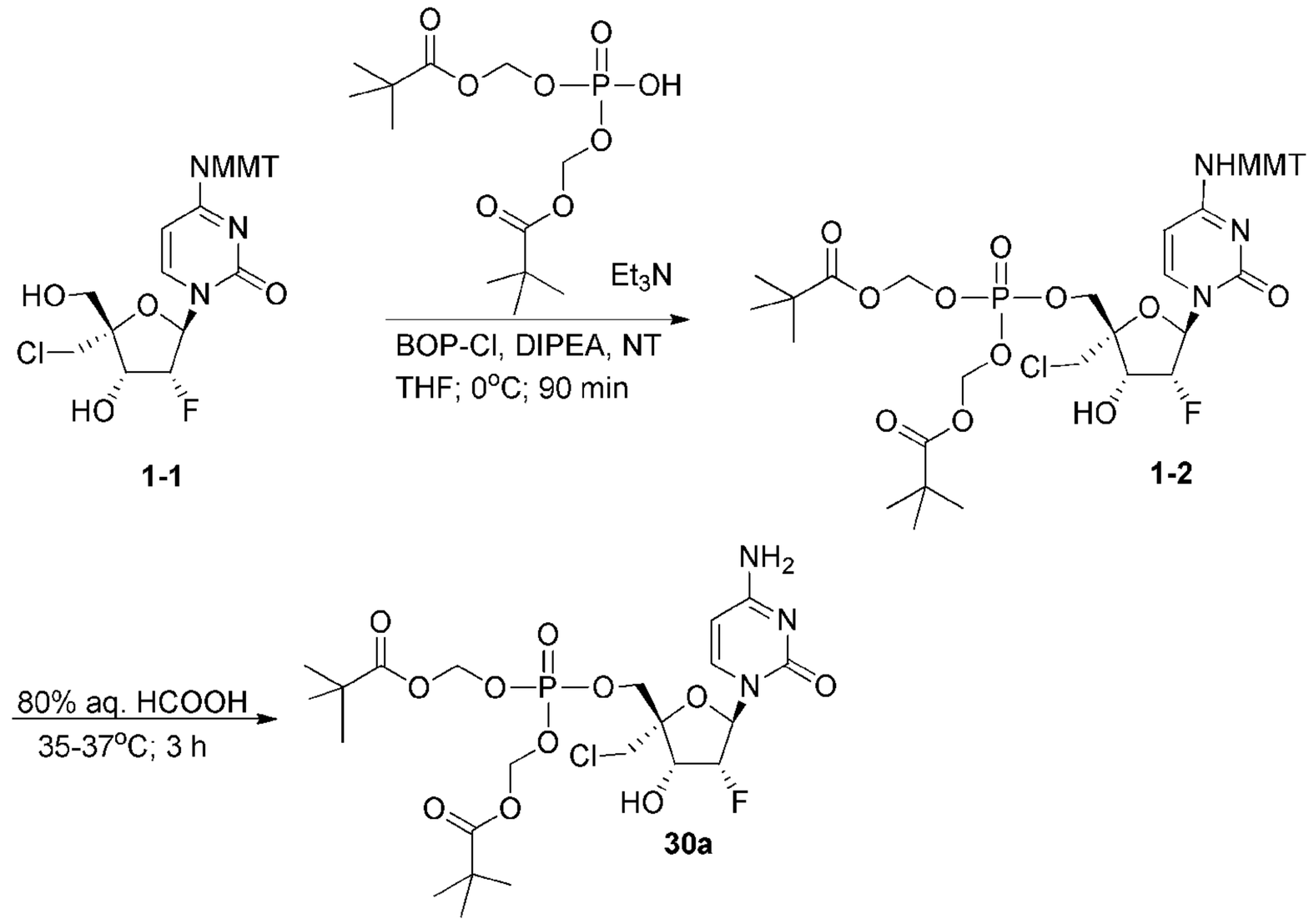
[0330] Compound **P28-6** (200 mg, 0.34 mmol) was dissolved in 80% HCOOH and the mixture was stirred at 25°C for 1 hour. The solution was evaporated to dryness, and the residue was dissolved in MeOH (30 mL) and stirred at 60°C for 12 hours. The solvent was removed, and the residue washed with EtOAc to give **28a** as a white solid (46.1 mg, 43%). ESI-MS: m/z 316.1 $[M+H]^+$.

EXAMPLE 29
Preparation of Compound 29a



[0331] DEAD (40% in toluene, 0.15 mL, 0.33 mmol) was added to a stirred solution of triphenylphosphine (78 mg, 0.3 mmol) in anhydrous 1,4-dioxane (0.5 mL) at 0°C under argon. The mixture was warmed up to R.T. and **10a** (26 mg, 0.1 mmol) and bis(pivaloyloxymethyl)phosphate (98 mg, 0.3 mmol) were added. The resulting mixture was stirred at 65°C for 3 days. Diisopropylethylamine (50 μL) was added, and the mixture was stirred at 70°C for 3 days. Another reaction of the same scale was conducted separately. The two reaction mixtures were combined and concentrated. Chromatography on silica gel with 5-10% methanol in DCM gave the desired product (20 mg) with a minor impurity. A second chromatography on silica gel, followed by RP HPLC with acetonitrile/water, gave **29a** (2.8 mg) as a colorless residue. MS: m/z 698 [M + 2-methylheptylamine]$^+$.

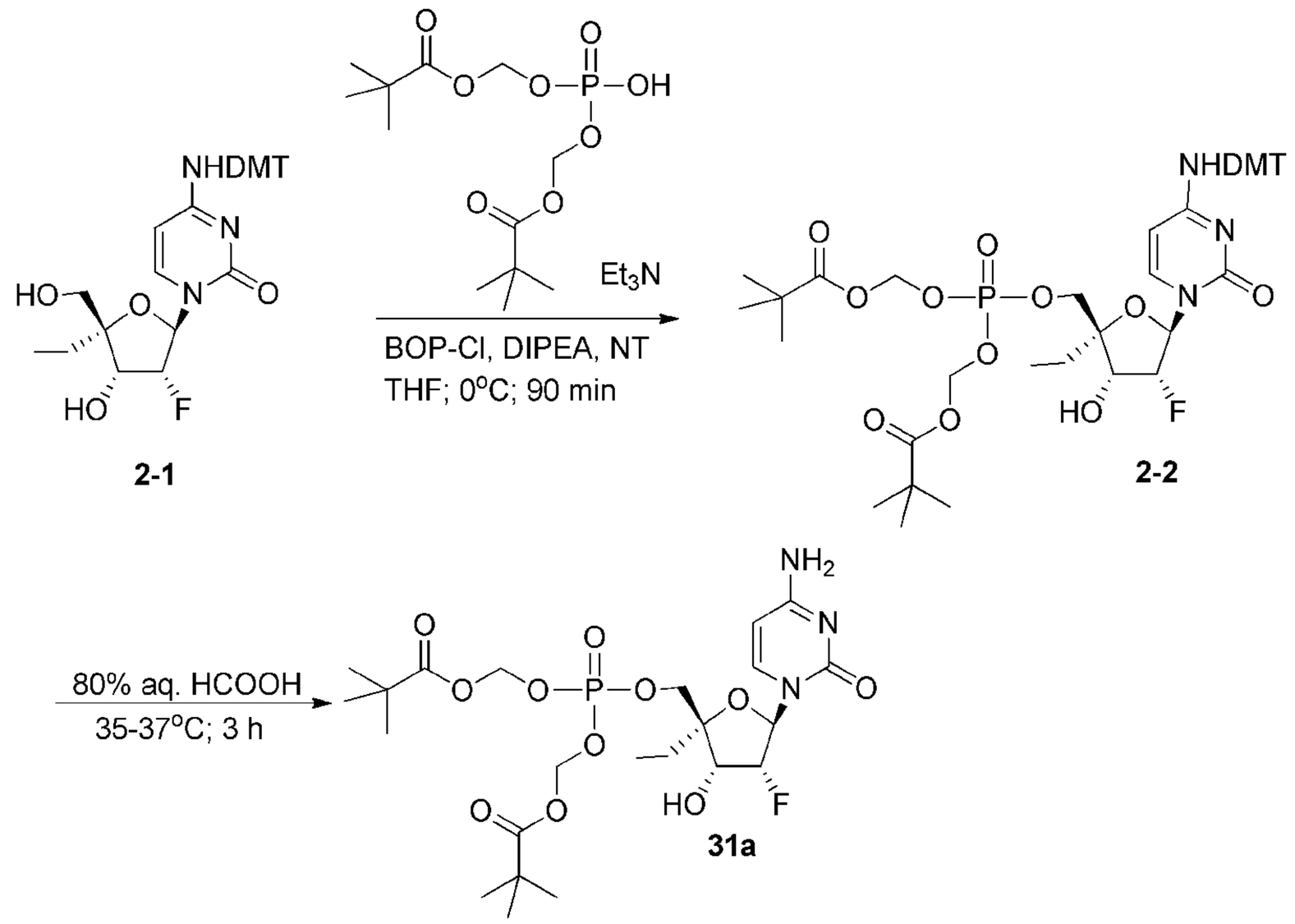
EXAMPLE 30
Preparation of Compound 30a



[0332] To a solution of **1-1** (313 mg; 0.55 mmol) in THF (8 mL) under Ar was added a solution of triethylammonium bis(POM)phosphate in THF (prepared from bis(POM)phosphate (215 mg ; 1.2 equiv), THF (2 mL) and Et_3N (0.1 mL; 1.3 equiv)). The resulting mixture cooled in an ice-bath. Diisopropylethyl amine (0.38 mL; 4 equiv) was added. BOP-Cl (280 mg; 2 equiv) and 3-nitro-1,2,4-triazole (125 mg; 2 equiv) was then added. The reaction mixture was stirred at 0°C for 90 mins. The mixture was diluted with CH_2Cl_2 (60 mL) and washed with saturated aq. $NaHCO_3$ (2 x 10 mL) and brine. The combined aqueous layers were back extracted with CH_2Cl_2 (~20 mL). The combined organic extract was dried (Na_2SO_4) and evaporated. The residue purified on silica (25 g column) with CH_2Cl_2 /i-PrOH solvent system (2-10% gradient). Yield: 140 mg (27%).

[0333] A solution of **1-2** (110 mg; 0.13 mmol) in 80% aq. formic acid was heated at 35-37°C for 3 hours. The mixture was evaporated to give an oily residue. The residue was co-evaporated 2 times with toluene. Purification on a silica gel column (10 g) with CH_2Cl_2 /MeOH solvent system (4-10% gradient) to afford **30a** (46 mg, 59% yield). ^{31}P-NMR (DMSO-d_6): δ -4.45. MS: m/z 646 [M+46-1].

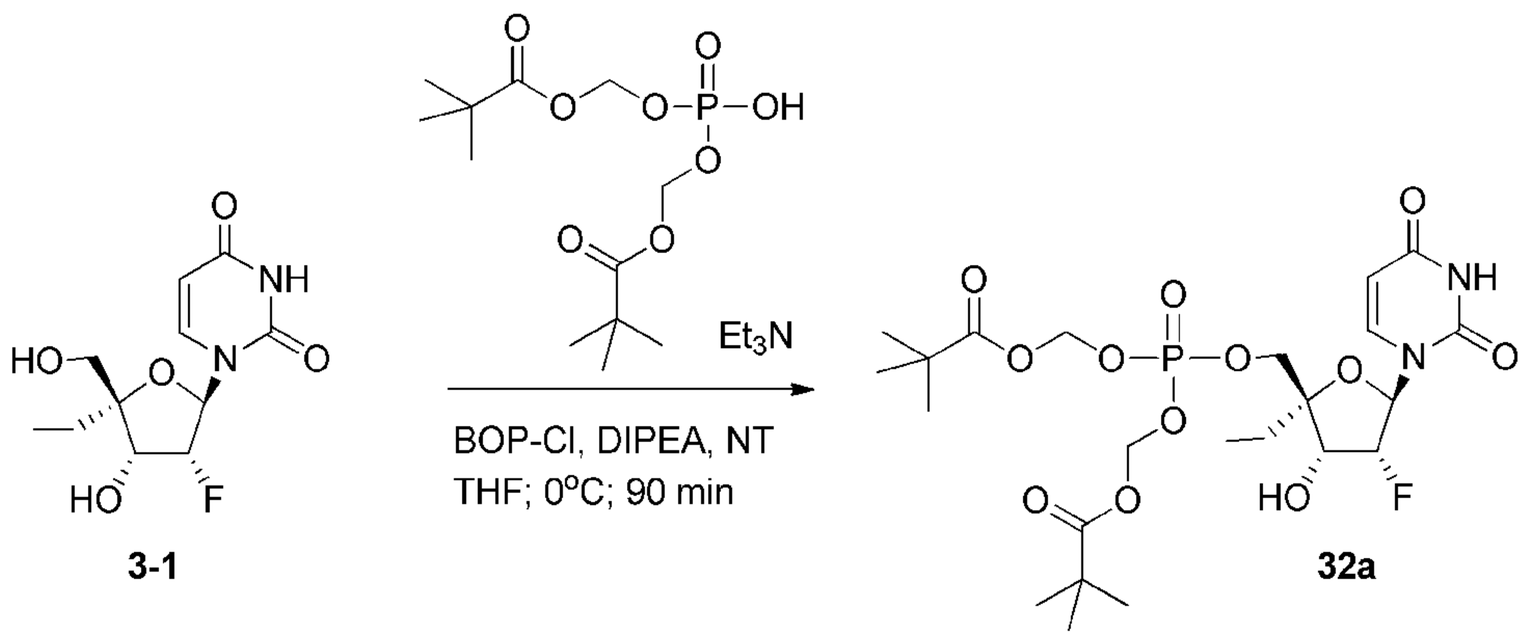
EXAMPLE 31
Preparation of Compound 31a



[0334] To a solution of **2-1** (370 mg; 0.64 mmol) in THF (10 mL) under Ar was added triethylammonium bis(POM)phosphate (330 mg; 1.2 equiv). The mixture cooled in ice-bath, and diisopropylethyl amine (0.42 mL; 4 equiv) was added. BOP-Cl (305 mg; 2 equiv) and 3-nitro-1,2,4-triazole (137 mg; 2 equiv) was then added. The reaction mixture was stirred at 0°C for 90 mins. The mixture was diluted with CH_2Cl_2 (50 mL) and washed with saturated aq. $NaHCO_3$ (2 x 10 mL) and brine. The combined aqueous layers were back extracted with CH_2Cl_2 (~20 mL). The combined organic extract was dried (Na_2SO_4), evaporated, and the residue purified on silica (25 g column) with CH_2Cl_2 /i-PrOH solvent system (2-10% gradient). Yield: 154 mg (27%).

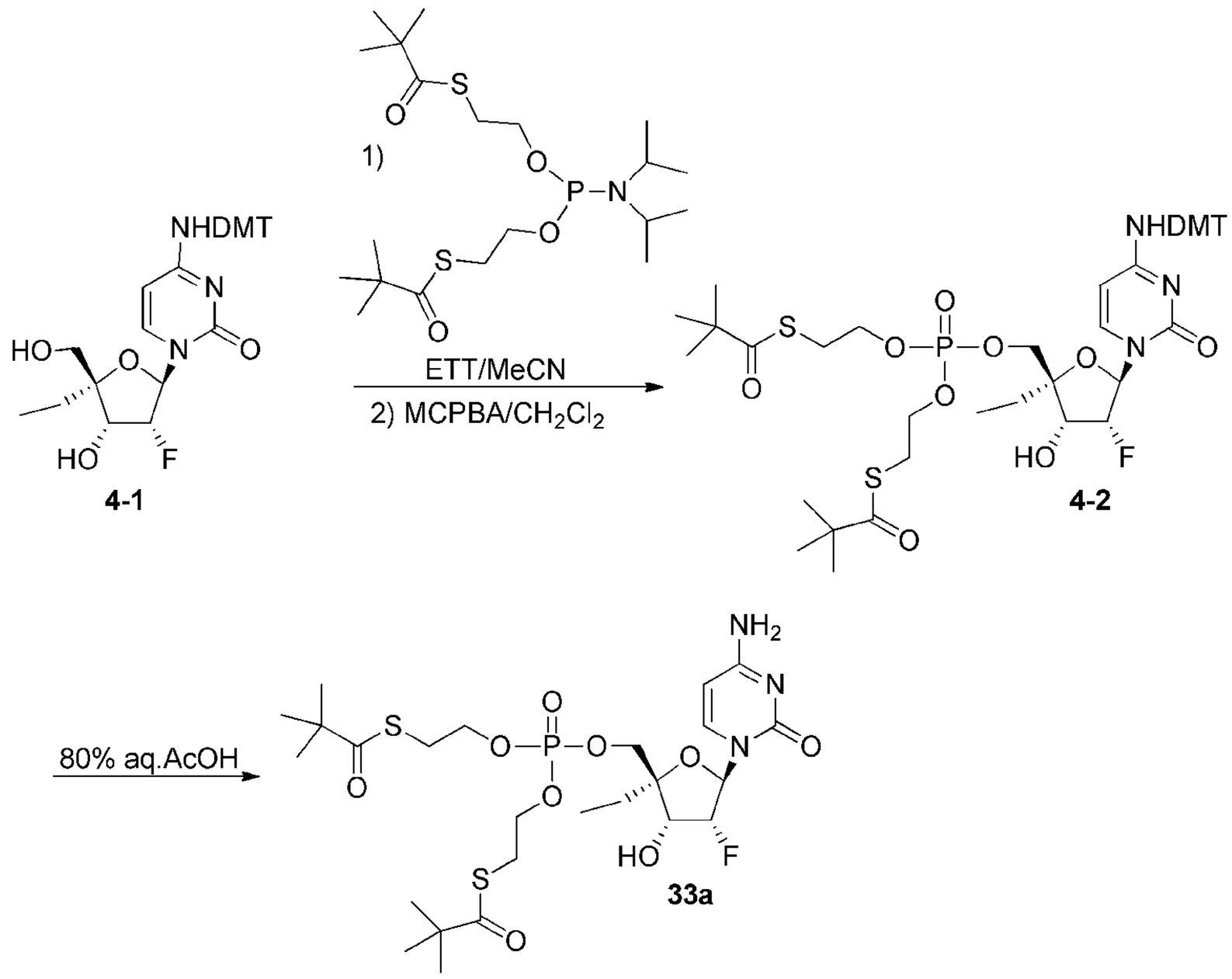
[0335] A solution of **2-2** (68 mg; 0.08 mmol) in 80% aq. formic acid was stirred at R.T. for 3 hours. The mixture was evaporated to an oily residue. The residue was co-evaporated 2 times with toluene. Purification on a silica gel column (10 g) with CH_2Cl_2 /MeOH solvent system (4-10% gradient; target compound eluted with 8% MeOH) afforded **31a** (35 mg, 78% yield). ^{31}P-NMR (DMSO-d_6): δ -4.19. MS: m/z 580 (M-1), 646 (M+46-1), 550 [M-30-1].

EXAMPLE 32
Preparation of Compound 32a



[0336] To a solution of **3-1** (71 mg; 0.26 mmol) in THF (4 mL) under Ar was added triethylammonium bis(POM)phosphate (144 mg; 1.2 equiv), and the resulting mixture was cooled in an ice-bath, and diisopropylethyl amine (0.18 mL; 4 equiv) was added. BOP-Cl (132 mg; 2 equiv) and 3-nitro-1,2,4-triazole (59 mg; 2 equiv) was then added. The reaction mixture was stirred at 0°C for 1 hour. The mixture was diluted with CH_2Cl_2 (50 mL) and washed with saturated aq. $NaHCO_3$ (2 x 10 mL) and brine. The combined aqueous layers were back extracted with CH_2Cl_2 (~20 mL). The combined organic extract was dried (Na_2SO_4), evaporated, and the residue was purified on silica (10 g column) with CH_2Cl_2/MeOH solvent system (4-10% gradient). Compound **32a** was repurified by RP-HPLC (35-90%B; A: water, B: MeOH). Yield 75 mg (50%). ^{31}P-NMR (DMSO-d_6): δ -4.14. MS: m/z 627 (M+46-1), 551 [M-30-1].

EXAMPLE 33
Preparation of Compound 33a



[0337] To a solution of **4-1** (0.29 g; 0.5 mmol) in MeCN (8 mL) was added 5-ethylthio-1H-tetrazole in MeCN (0.25 M; 2.4 mL; 1.2 equiv). BisSATE-phosphoramidate (0.24 g; 1.05 equiv.) in MeCN (1.5 mL) was added over 90 mins. The reaction mixture was stirred for 4 hours at R.T., and then cooled to -40°C. MCPBA (0.23 g; 2 equiv.) in CH_2Cl_2 (3 mL) was added. The mixture was allowed to warm to R.T. and diluted with EtOAc(50 mL). The mixture was washed with 10% aq. $NaHSO_3$ (2 x 10 mL), saturated aq. $NaHCO_3$ (2 x 10 mL) and brine. The mixture was then dried (Na_2SO_4). The evaporated residue was purified on silica (10 g column) with CH_2Cl_2 /MeOH solvent system (4-10% gradient) to afford **4-2** (0.26 g, 55% yield).

[0338] A solution of **4-2** (0.21 g; 0.22 mmol) in 80% aq. AcOH (15 mL) was stirred 4 hours at R.T. The mixture was evaporated and purified on silica (10 g column) with CH_2Cl_2/MeOH solvent system (4-10% gradient) to yield **33a** (0.13 g, 90%). ^{31}P-NMR (DMSO-d_6): δ -2.00. MS: m/z 686 [M+46-1].

EXAMPLE 34
Preparation of Compounds 34a-34e

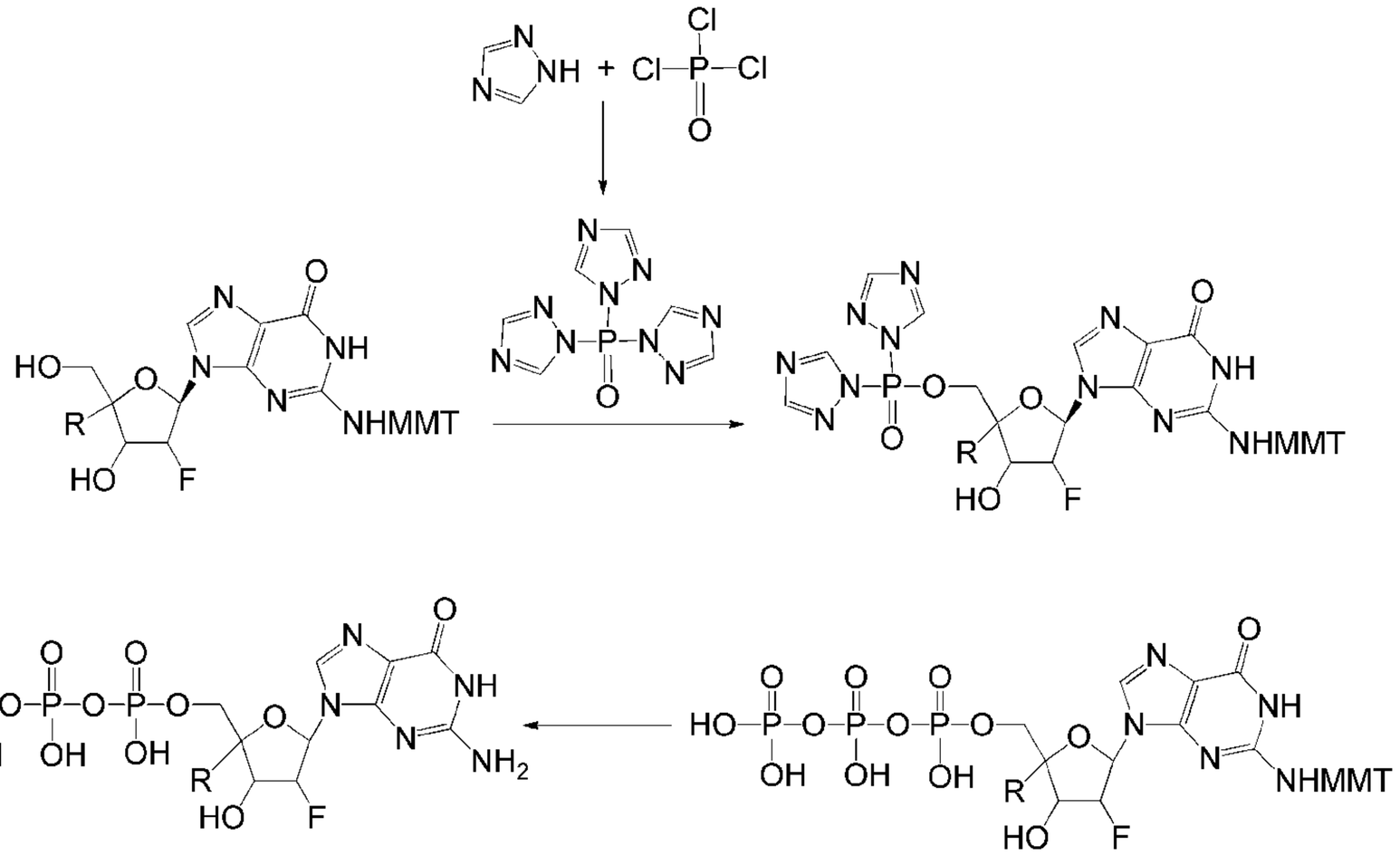
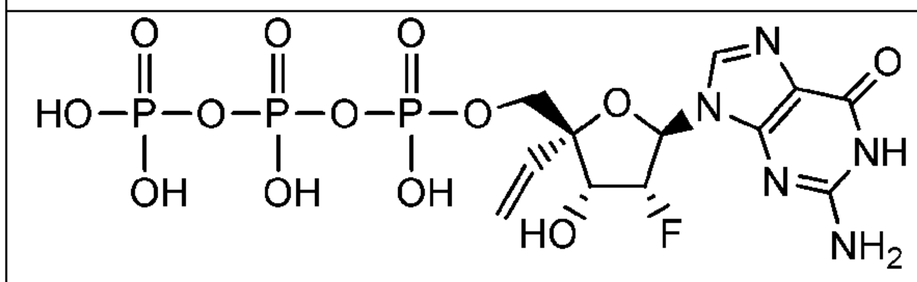
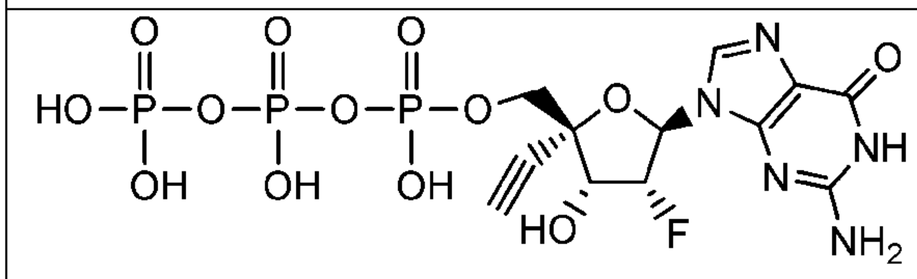
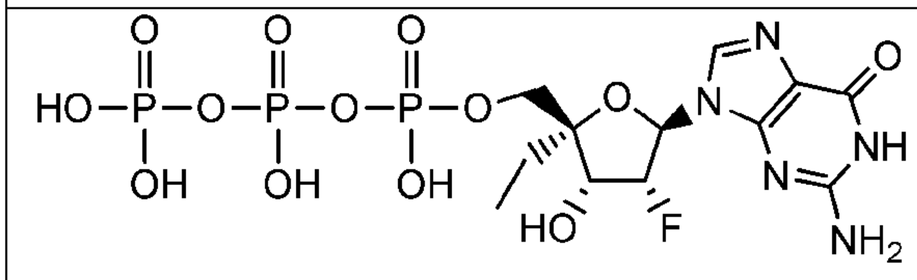
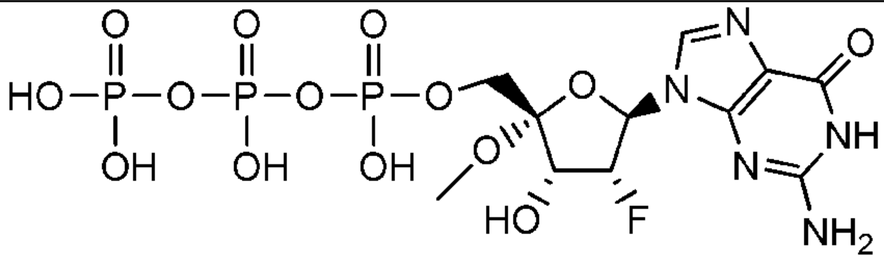
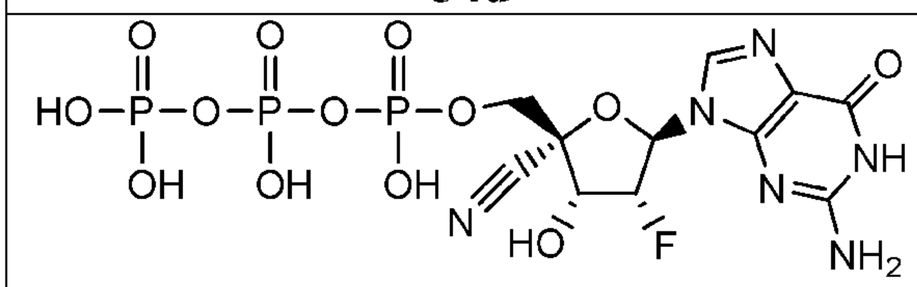
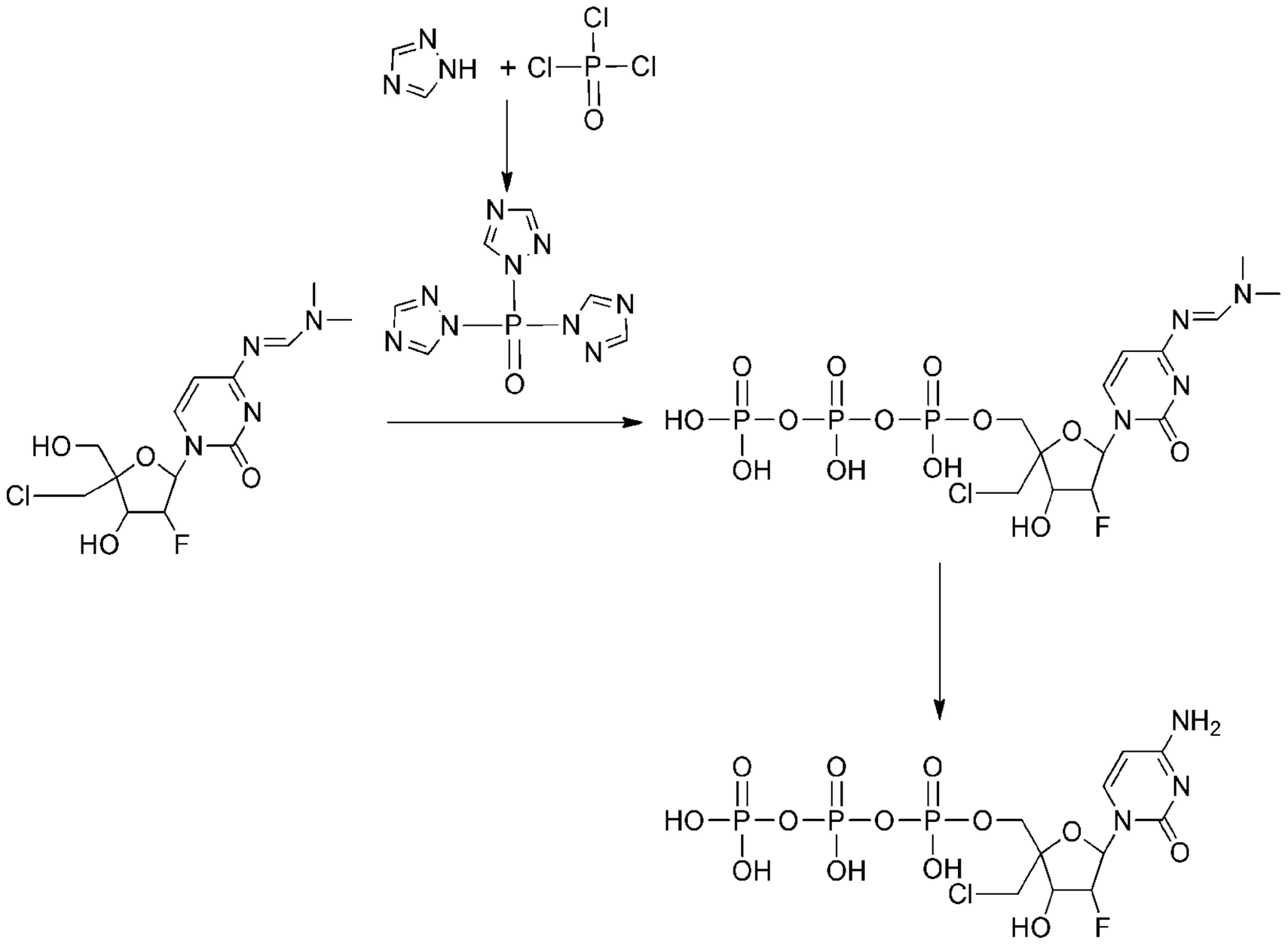

N
NH
Cl
Cl—P—Cl
O
HO
R
HO
F
NHMMT
N
N
N

Table 1 – Triphosphates obtained from Example 34

Compound	^{31}P NMR Pα	^{31}P NMR Pβ	^{31}P NMR Pγ	MS (M^-)
 **34a**	-11.31 d	-20.82 t	-5.48 d	550.2
 **34b**	-9.13 d	-18.18 t	-2.85 d	548.2
 **34c**	-10.95 d	-20.62 bs	-5.37 bs	552.2
 **34d**	-11.24 d	-20.82 t	-5.48 d	554.2
 **34e**	-12.06 d	-20.97 t	-5.69 d	549.2

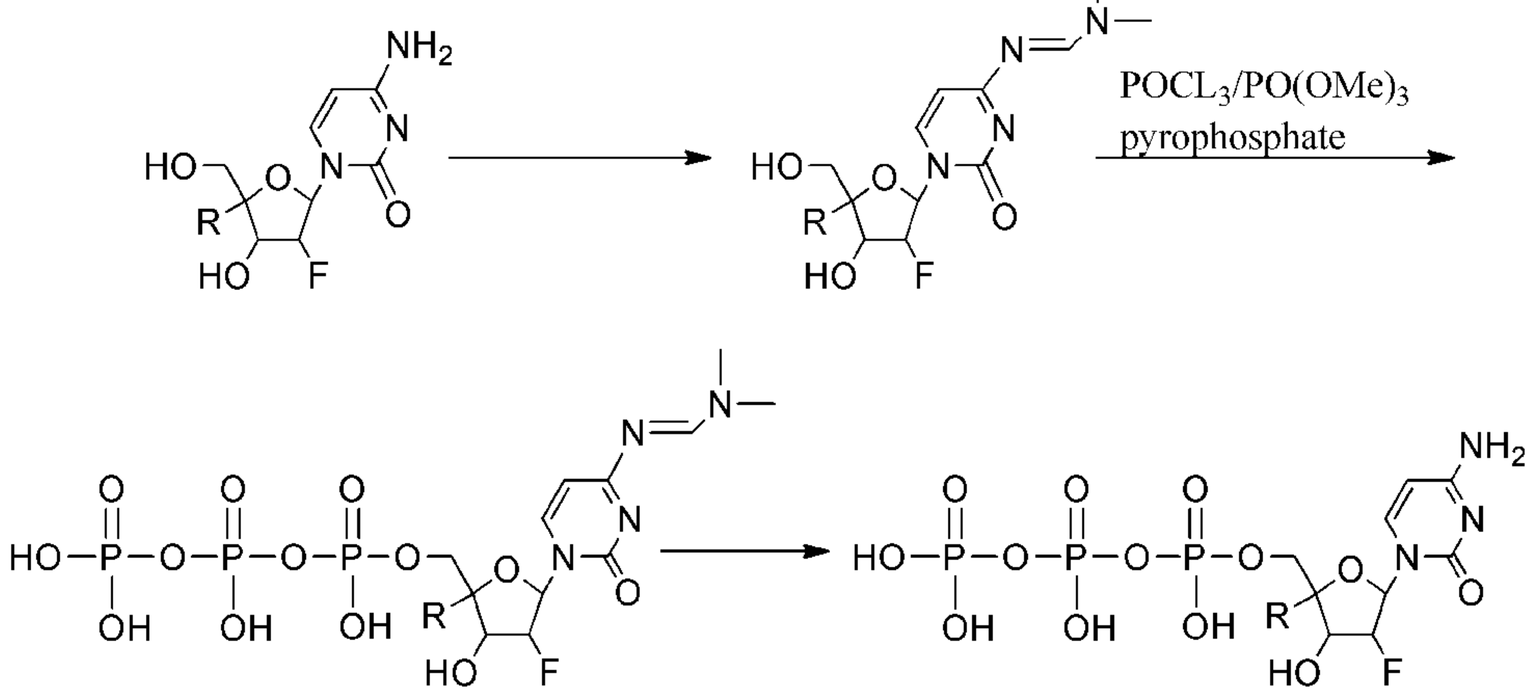
EXAMPLE 35
Preparation of Compound 35a



[0340] 1,2,4-Triazole (42 mg, 0.6 mmol) was suspended in dry CH_3CN (1 mL). Triethylamine was added (0.088 mL, 0.63 mmol), and the mixture was vortexed to obtain a clear solution. After addition of $POCl_3$ (0.01 mL, 0.1 mmol), the mixture was vortexed and left for 20 mins. The mixture was centrifugated, and the supernatant was added to the protected nucleoside (0.05 mmol). The mixture was kept at ambient temperature for 1 hour. Tris(tetrabutylammonium) hydrogen pyrophosphate (180 mg, 0.2 mmol) was added, and the mixture was kept for 2 hours at R.T. The reaction was quenched with water, evaporated, dissolved in ammonium hydroxide and left for 2 hours at R.T. The solvent was evaporated, and the residue dissolved in water (10 mL). The mixture was loaded onto a column HiLoad 16/10 with Q Sepharose High Performance. Separation was done in linear gradient of NaCl from 0 to 1N in 50mM TRIS-buffer (pH7.5). The fractions containing the product were combined, concentrated and desalted by RP HPLC on Synergy 4 micron Hydro-RP column (Phenominex). A linear gradient of methanol from 0 to 20% in 50mM triethylammonium

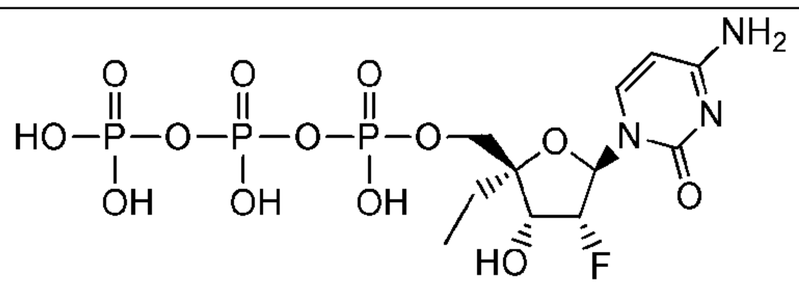
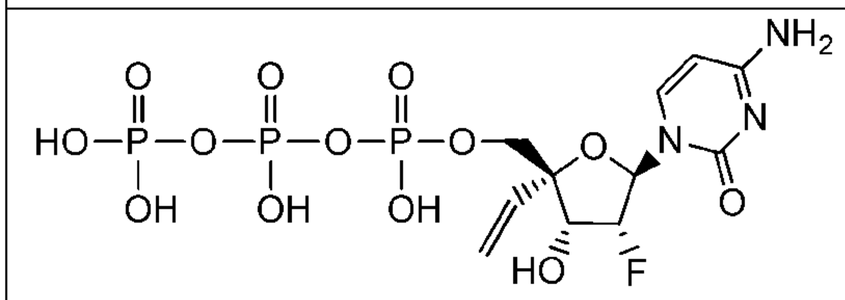
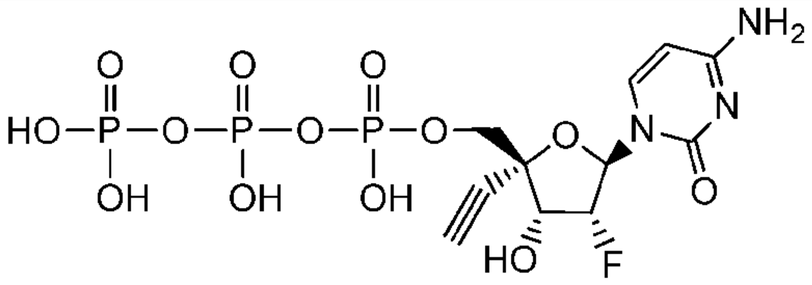
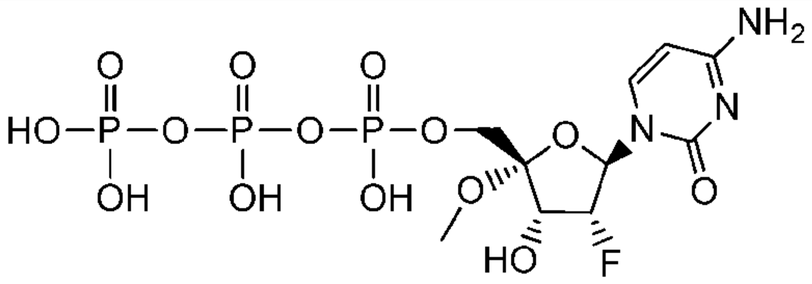
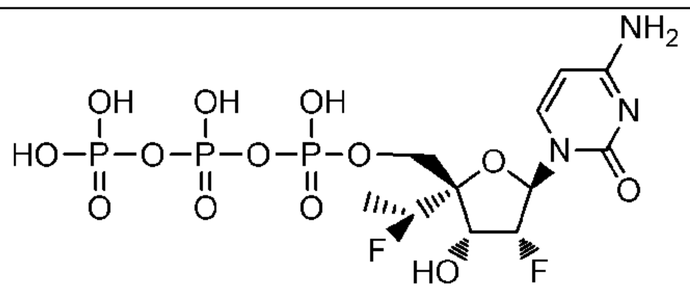
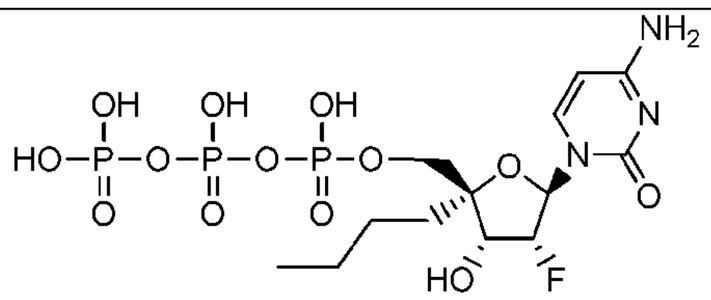
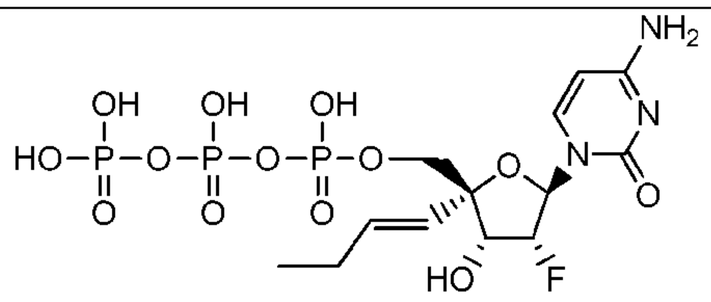
acetate buffer (pH 7.5) was used for elution. MS (M-1): 532.1. ^{31}P-NMR (δ ppm): -5.12 (d), -11.31 (d) and -20.43 (t).

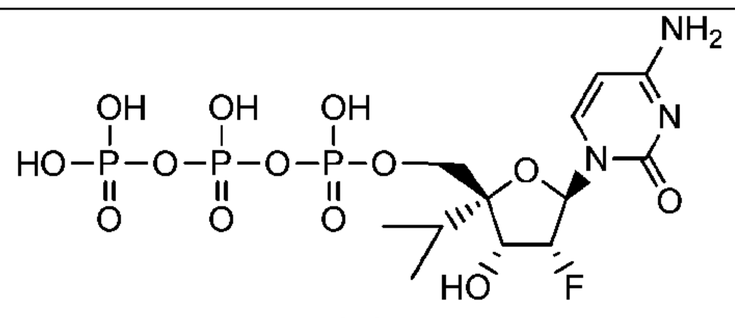
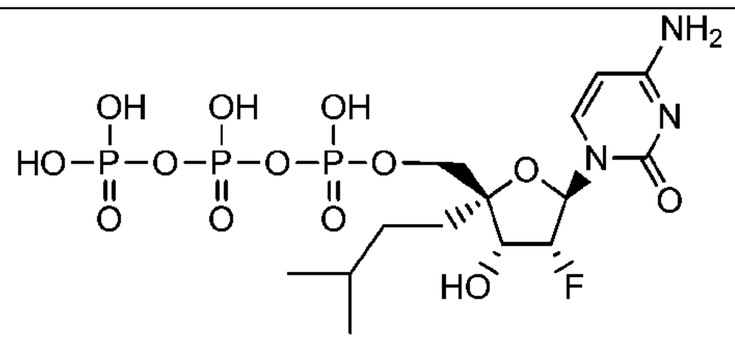
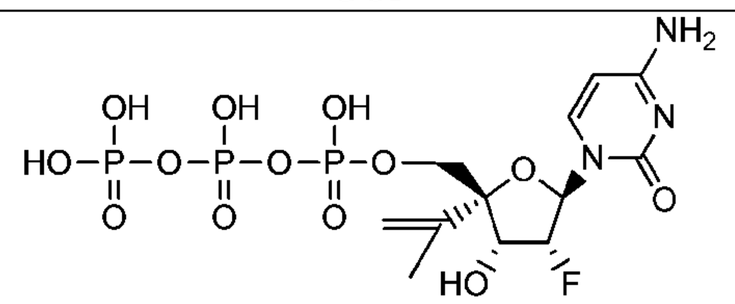
EXAMPLE 36
Preparation of Compounds 36a- 36d



[0341] 2'-Deoxy-2'-fluoro-4'-alkyl-cytidine (0.09 mmol) was dissolved in the mixture of DMF (5 mL) and N,N'-dimethylacetate in DMF (0.110 mL, 0.9 mmol). The reaction mixture left at R.T. overnight. The solvent was evaporated, and the residue purified by flash chromatography in gradient of methanol in DCM from 3% to 20%. The N-Protected nucleoside was concentrated in vacuum, dried and dissolved in dry trimethylphosphate (0.7 mL). The solution was cooled to 4°C and $POCl_3$ (0.017 mL, 0.18 mmol) was added. In 1 hour, tributylamine (0.102 mL, 0.3 mmol) was added at R.T. Tributylammonium pyrophosphate (156 mg, 0.34 mmol) was then added. Dry DMF (about 0.100 mL) was added to solubilize pyrophosphate. After 2 hours, the reaction was quenched with TEAB-buffer. The product was isolated by ion-exchange chromatography on AKTA Explorer as described in Example 35. The fractions containing the product were concentrated and treated with NH_4OH for 2 hours at R.T. The product was desalted by RP HPLC as described in Example 35.

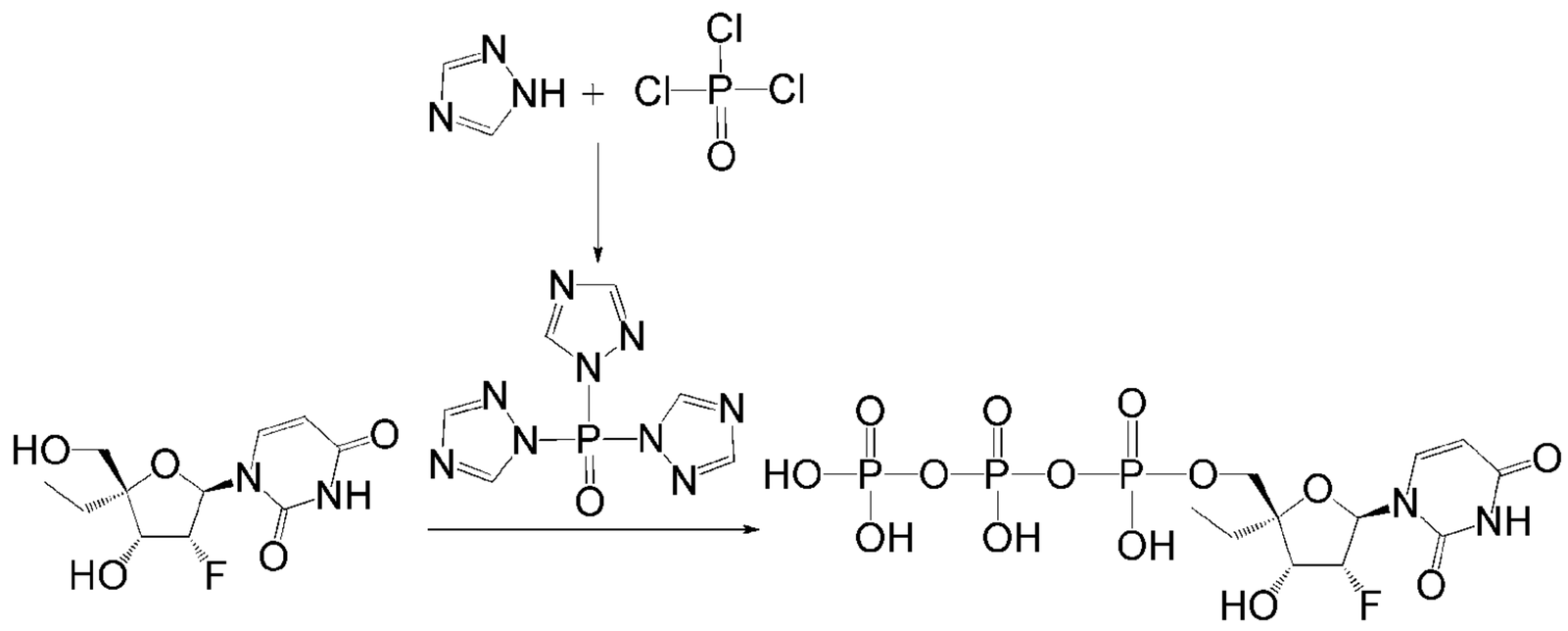
Table 2 – Triphosphates obtained from Example 36

Compound	^{31}P NMR Pα	^{31}P NMR Pβ	^{31}P NMR Pγ	MS (M^-)
 **36a**	-11.38 (bs)	-22.88 (bs)	-7.62 (bs)	512.1
 **36b**	-11.49 (bs)	-20.41 (bs)	-5.34 (bs)	510.0
 **36c**	-11.96 (bs)	-22.07 (t)	-5.66 (d)	508.3
 **36d**	-11.90 (d)	-23.23 (t)	-10.66 (d)	514.0
 **36e**	-11.77 (d)	-23.05 (t)	-9.70 (s)	529.9
 **36f**	-11.74 (d)	-23.37 (t)	-10.85 (d)	539.2
 **36g**	-11.87 (d)	-23.32 (t)	-10.83 (d)	523.9

Compound	^{31}P NMR Pα	^{31}P NMR Pβ	^{31}P NMR Pγ	MS (M^-)
 **36h**	-11.48 (d)	-23.26 (t)	-10.63 (d)	526.1
 **36i**	-11.67 (d)	-23.22 (t)	-10.77 (d)	554.1
 **36j**	-11.97 (d)	-23.34 (t)	-10.92 (d)	523.9

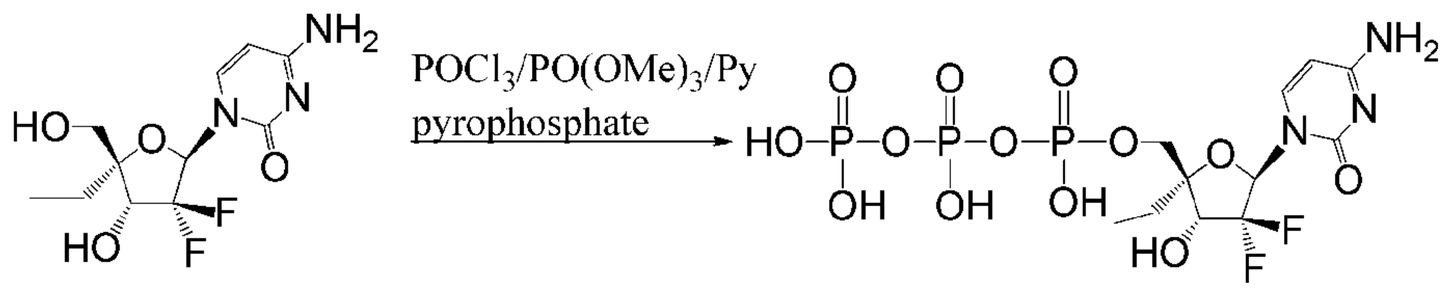
EXAMPLE 37

Preparation of Compounds 37a



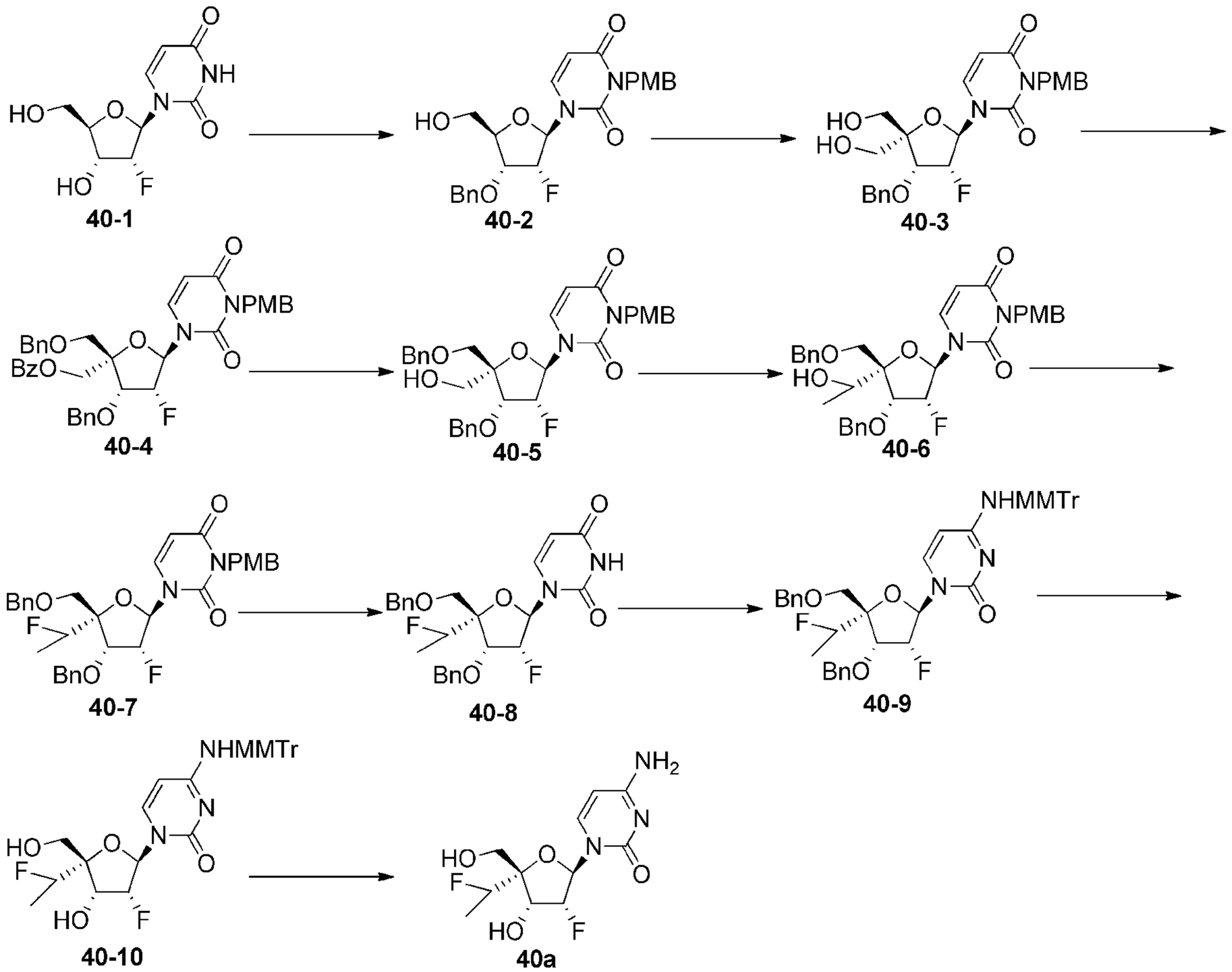
[0342] Compound **37a** was synthesized by reaction of phosphor(tris-triazolide) with 4'-ethyl-2'-deoxy-2'-fluoro-uridine as described Examples 34 and 35. ^{31}P-NMR (δ ppm): -9.43 (bs), -11.68 (d) and -23.09 (bs). MS: m/z 513.1 [M-1].

EXAMPLE 38
Preparation of Compounds 38a



[0343] The starting nucleoside (15 mg, 0.05 mmol) was dissolved in dry trimethylphosphate (3 mL). The solution was cooled to 4°C. $POCl_3$ (0.013 mL, 0.125 mmol) was added, followed by pyridine (0.01 mL, 0.125 mmol). In 1 hour, tributylamine (0.035mL, 0.125 mmol) was added at R.T. followed by tributylammonium pyrophosphate (156 mg, 0.34 mmol). Dry DMF (about 0.100 mL) was added to solubilize pyrophosphate. In 2 hours, the reaction was quenched with TEAB-buffer. The product was isolated by ion-exchange chromatography on AKTA Explorer as described in Example 35. The fractions containing the product were concentrated and treated with NH_4OH for 2 hours at R.T. The product was desalted by RP HPLC as described in Example 35. MS: m/z 529.9 [M-1]. ^{31}P-NMR (δ ppm): -9.42(d), -11.59(d) and -23.03(t).

EXAMPLE 39
Preparation of Compound 40a



[0344] To a solution of **40-1** (50.0 g, 205 mmol) in pyridine (250 mL) was added DMTrCl (75.0 g, 225.0 mmol). The solution was stirred at R.T. for 15 hours. MeOH (120 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 to give the crude 5'-O-DMTr intermediate (80.52g) as a light yellow solid. The intermediate was dissolved in anhydrous DMF (300 mL), and K_2CO_3 (80.52g, 583.2 mmol) was added followed by PMBCl (31.7 g, 109.2 mmol). The mixture was stirred at R.T. overnight. The reaction was diluted with EA and washed with brine. The organic phase was dried over Na_2SO_4 and concentrated to give crude 5'-O-DMTr-N3-PMB FdU (98.8 g) as a light yellow solid. The solid was dissolved in DMF (300 mL), and NaH (10.42 g, 260.5 mmol) was added followed by BnBr (73.8 g, 434.2 mmol). The reaction was

stirred at R.T. overnight and then was quenched with water. The solution was diluted with EA and washed with brine. The organic phase was dried over Na_2SO_4 and concentrated to give the crude fully blocked FdU intermediate, which was purified on a silica gel column (PE:EA = 10:1 to 3:1) to the pure fully blocked FdU (101.1 g). The intermediate was treated with 80% HOAc (900 mL) at R.T. overnight, and the solvent was removed. The residue was purified on a silica gel column to give **40-2** as a white foam (42.1 g, 30.2% for 4 steps).

[0345] To a solution of **40-2** (42.1 g, 92.6 mmol) in anhydrous CH_3CN (300 mL) was added IBX (28.5 g, 121.7 mmol) at R.T. The reaction mixture was refluxed for 1 hour and then cooled to 0°C. The precipitate was filtered-off, and the filtrate was concentrated to give the crude aldehyde (39.22 g) as a yellow solid. To a solution of the aldehyde (39.22 g) in 1,4-dioxane (250 mL) was added 37% CH_2O (28.1 mL, 345.6 mmol) and 2N NaOH aqueous solution (86.4 mL, 172.8 mmol). The mixture was stirred at R.T. for 2 hours and then neutralized with AcOH to pH = 7. EtOH (200 mL) and $NaBH_4$ (19.7 g, 518.6 mmol) were added, stirred at R.T. for 30 mins. The mixture was quenched with saturated aqueous NH_4Cl, and extracted with EA. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (PE:EA = 4:1 to 2:1) to give **40-3** (25.5 g, 55.7%) as a white solid.

[0346] To a stirred solution of **40-3** (25.5 g, 52.5 mmol) in anhydrous pyridine (150 mL) and anhydrous CH_3CN (150 mL) was added BzCl (6.6 g, 52.47 mmol) dropwise at 0°C. The mixture was stirred at R.T. for 14 hours. The reaction was quenched with H_2O, and the solution was concentrated. The residue was dissolved in EA and washed with saturated $NaHCO_3$. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified on a silica gel column (PE/EA = 5:4) to give the mono-Bz protected intermediate (18.1 g, 60.0%) as a white foam. To a stirred solution of this intermediate (18.1 g, 30.68 mmol) in DMF (100 mL) were added Cs_2CO_3 (30.0 g, 92.03 mmol) and BnBr (10.4 g, 61.36 mmol). The mixture was stirred at R.T. overnight. The reaction was quenched with saturated NH_4Cl aq., extracted with EA and washed with brine. The solvent was removed to give crude **40-4** (19.3g, 95.1%) as a light yellow solid.

[0347] To a stirred solution of **40-4** (19.3 g, 28.4 mmol) in anhydrous MeOH (230 mL) was added NaOMe (24.9 g, 460 mmol) at R.T. The mixture was stirred for 1 hour. The

reaction was quenched with AcOH (10 mL) and concentrated. The residue was purified on a silica gel column (PE/EA = 1/2) to afford **40-5** (11.2 g, 54.0%) as a white solid.

[0348] To a stirred solution of **40-5** (200 mg, 0.347 mmol) in anhydrous DCM (5 mL) was added DMP (168 mg, 0.674 mmol) at R.T. The mixture was stirred at R.T. for 2 hours. The solvent was removed, and the residue was purified on a silica gel column (PE:EA = 5:1 to 1:1) to give the aldehyde crude as a light yellow solid (200 mg). T o a stirred solution of the aldehyde (200 mg) in anhydrous THF (5 mL) was added MeMgBr (1.0 mL, 1.01 mmol) at -78°C. The mixture was stirred at -78°C for 1 hour. The reaction was quenched with saturated NH_4Cl aq .and extracted with EA. The concentrated organic phase was purified by column chromatography (PE: EA = 5:1 to 1:1) to give **40-6** (a mixture of stereomers, 135 mg, 65%) as a white solid.

[0349] To a stirred solution of DAST (1.64 g, 10.17 mmol) in anhydrous toluene (40 mL) was added dropwise a solution of **40-6** (1.2 g, 2.03 mmol) at -78°C. The mixture was stirred at -78°C for 30 mins. The solution was warmed to 60°C slowly and stirring was continued overnight. The mixture was poured into a saturated Na_2CO_3 solution. The concentrated organic phase was concentrated and purified on a silica gel column (PE:EA = 10:1 to 3:1) to afford **40-7** as a white solid (1.08 g, 83.88%). ^{1}H NMR (CD_3OD, 400 MHz) δ 7.87 (d, J = 8.4Hz, 1H), 7.27-7.37 (m, 12H), 6.82-6.84 (m, 2H), 6.14 (d, J =16.8, 2.0Hz, 1H), 5.18-5.50 (m, 4H), 4.96 (s, 2H), 4.45-4.88 (m, 7H), 3.67-3.89 (m, 5H).

[0350] A mixture of **40-7** (0.91g, 1.54 mmol) and CAN (2.53 g, 4.61 mmol) in a 3:1 solution of MeCN:water (10 m L) was stirred at R.T. overnight. Brine (10 mL) was added, and the mixture was extracted with EA. The combined organic extracts were dried and evaporated under reduced pressure. Purification by chromatography on silica gel column with PE: EA=10:1 to 2:1 afforded **40-8** as a yellow solid (305 mg, 41.96%).

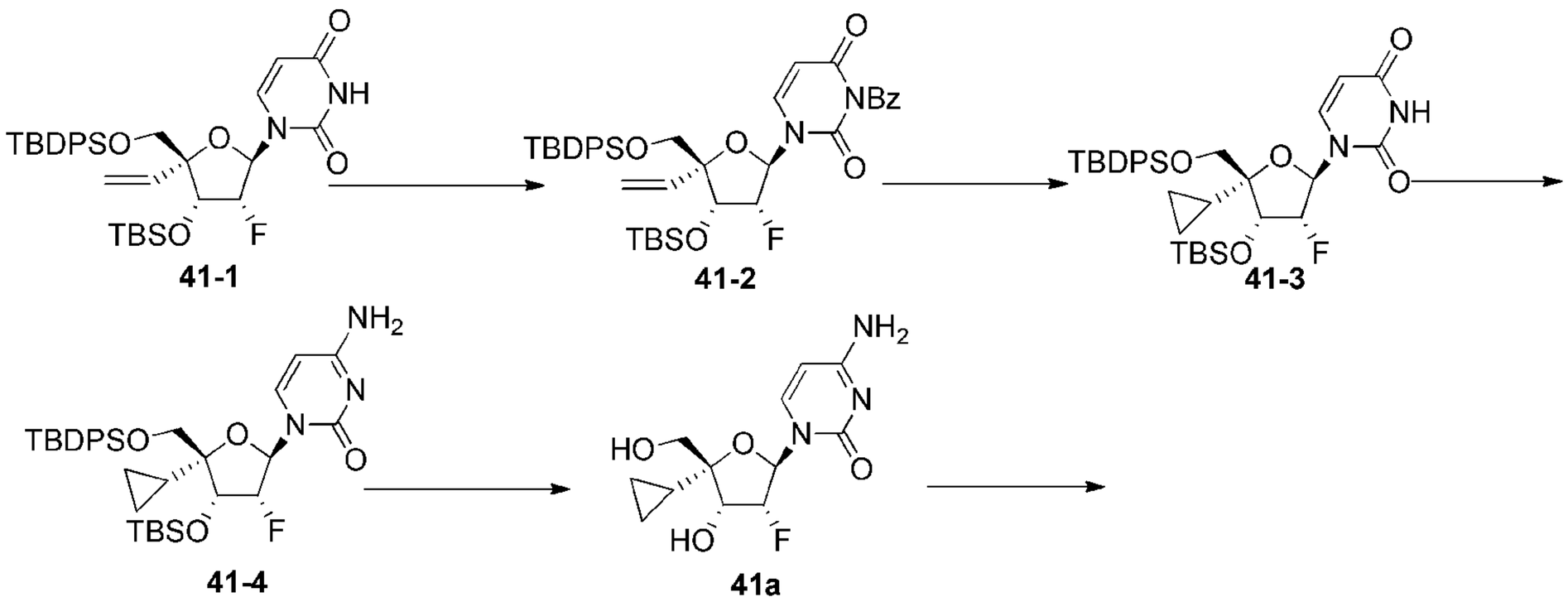
[0351] To a stirred solution of **40-8** (350 mg, 0.74 mmol) in anhydrous MeCN (8 mL) were added TPSCl (449 mg, 1.48 mmol), DMAP (180 mg, 1.48 mmol) and TEA (374 mg, 3.70 mmol) at R.T. The mixture was stirred at R.T. overnight. NH_4OH (15 mL) was added, and the mixture was stirred for 2 hours. The solvent was removed, and the residue was purified on a silica gel column with PE: EA=8:1 to 1:1 to afford the crude (380 mg crude), which was dissolved in anhydrous DCM (10 mL). A mixture of MMTrCl (695mg,

2.25mmol) and $AgNO_3$ (380mg, 2.25 mmol) was added at R.T., and the mixture was stirred at R.T. overnight. The solid was filtered off and washed with DCM. The filtrate was washed with brine and dried over Na_2SO_4. The concentrated organic phase was purified on a silica gel column (PE:EA = 8:1 to 2:1) to afford **40-9** as a yellow solid (460 mg, 81.33%).

[0352] To a stirred solution of **40-9** (450 mg, 0.61 mmol) in acetone were added ammonium formate (1.29 g, 20.6mmol, in portions) and 10% palladium on carbon (1.0 g). The mixture was refluxed for 12 h. The catalyst was filtered off and washed with acetone. The filtrate was diluted with EA and washed with brine. The concentrated organic phase was purified by column chromatography (DCM:MeOH = 100:1 to 15:1) to afford **40-10** as a white solid (250 mg, 72.8%). ESI-MS: m/z 563.50 $[M + H]^+$.

[0353] Compound **40-10** (101 mg, 0.179 mmol) was dissolved in 80% HOAc (20 mL) at R.T. The mixture was stirred at 50°C for 5 hours. The solvent was removed, and the residue was co-evaporated with toluene twice. The residue was purified by column chromatography (DCM:MeOH = 100:1 to 10:1) to afford **40a** as a white solid (36.6 mg, 70.26%). ESI-MS: m/z 291.84 $[M+H]^+$, 582.81 $[2M+H]^+$.

EXAMPLE 40
Preparation of Compound 41a



[0354] To a solution of **41-1** (3 g, 4.8 mmol) in anhydrous DCM (50 mL) were added BzCl (1.3 g, 9.6 mmol), DMAP (1.1 g, 9.6 mmol) and NEt_3 (4 mL) at R.T. The reaction was stirred at R.T. for 2 hours. Water was added, and the reaction was stirred for another 1 hour. The mixture was diluted with DCM (150 mL) and washed with water, 0.1 M HCl and saturated aqueous $NaHCO_3$. The solvent was removed, and the crude product was

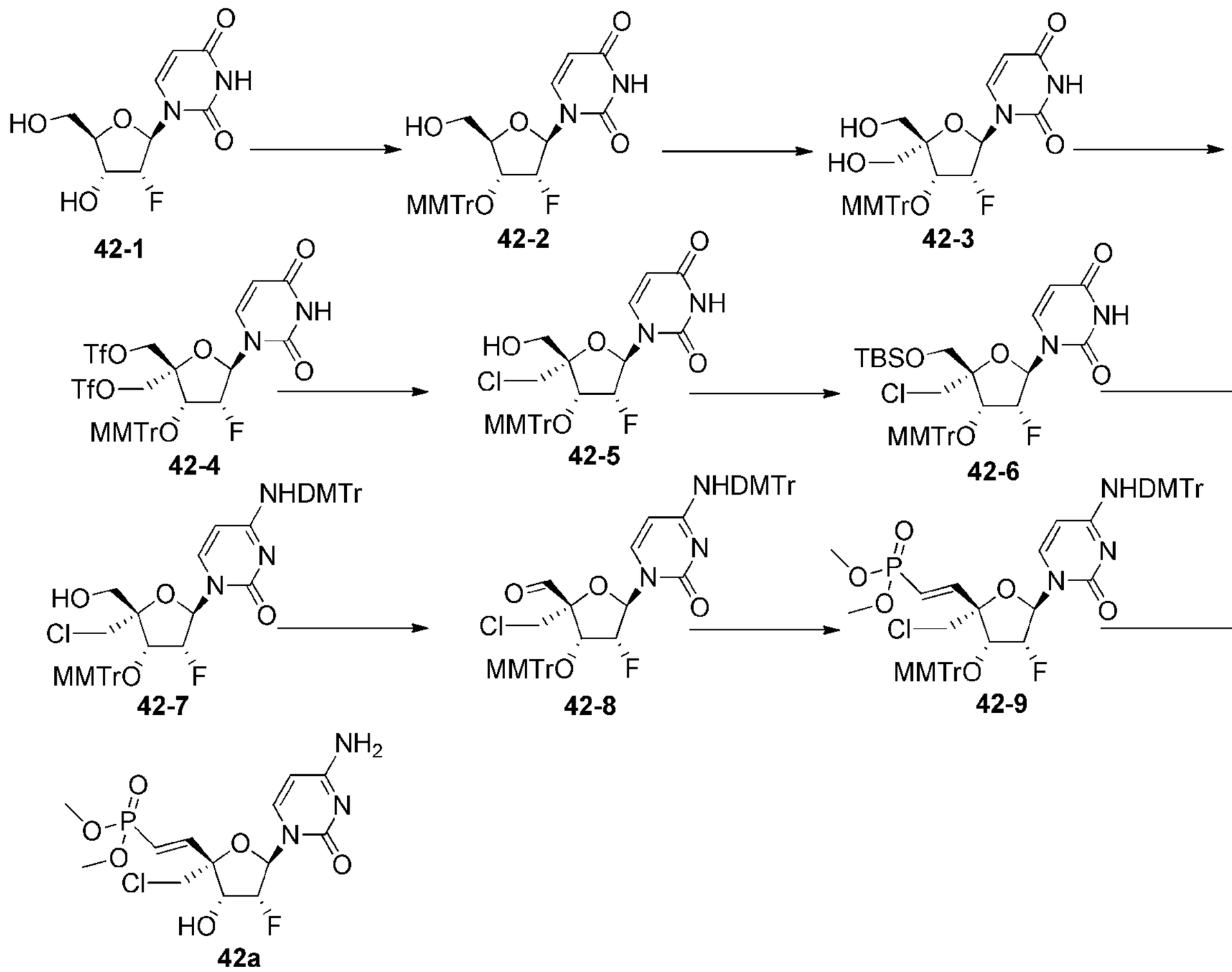
purified by silica gel column chromatography (25% EtOAc in PE) to give **41-2** as a yellow solid (2.8 g, 80.0%).

[0355] A mixture of **41-2** (2.6 g, 3.6 mmol) and $Pd(OAc)_2$ (100 mg) in DCM (50 mL) was suspended in a solution of CH_2N_2 in Et_2O (generated by standard procedure, 350 mL) at -78°C. The reaction was stirred to R.T. overnight. The mixture was quenched with HOAc, and the reaction was stirred for another 1 hour. The mixture was diluted with EtOAc (150 mL) and washed with water and saturated aqueous $NaHCO_3$. The solvent was removed, and the crude was dissolved in NH_3.MeOH (sat., 100 mL). The reaction was stirred to R.T. overnight. The crude product was purified by silica gel column chromatography (25% EtOAc in PE) to give **41-3** as a yellow solid (800 mg, 35.2%).

[0356] To a solution of **41-3** (800 mg, 1.3 mmol) in anhydrous CH_3CN (50 mL) were added TPSCl (755 mg, 2.5 mmol), DMAP (305 mg, 2.5 mmol) and NEt_3 (400 mg, 4 mmol) at R.T. The reaction was stirred at R.T. for 2 hours. NH_4OH (25 mL) was added, and the reaction was stirred for another 1 hour. The mixture was diluted with DCM (150 mL) and washed with water, 0.1 M HCl and saturated aqueous $NaHCO_3$. The solvent was removed, and the crude product was purified by silica gel column chromatography (25% EtOAc in PE) to give **41-4** as a yellow solid (340 mg, 42.5%).

[0357] To a solution of **41-4** (200.0 mg) in MeOH (10 mL) was added NH_4F (600 mg). The reaction was refluxed for 24 hours. The solvent was removed, and the residue was purified by column chromatography on silica gel (DCM: MeOH = 15: 1) to give **41a** (50.0 mg, 55.9%) as a white solid. ESI-MS: m/z 285.82 $[M + H]^+$, 570.84 $[2M+H]^+$.

EXAMPLE 41
Preparation of Compound 42a



[0358] To a solution of **42-1** (50 g, 203 mmol) in anhydrous pyridine (200 mL) was added TBDPSCl (83.7 g, 304 mmol, 1.5 eq). The reaction was stirred overnight at R.T. The solution was concentrated under reduced pressure to give a syrup, which was partitioned between ethyl acetate and water. The organic layer was separated, washed with brine, dried over magnesium sulfate and concentrated to give the 5'-OTBDPS ether as a white foam (94 g). The crude ether was dissolved in anhydrous DCM (300 mL), and silver nitrate (66.03 g, 388.4 mmol, 2.0 eq) and collidine (235 mL, 1.94 mol, 10 eq) were added. The mixture was stirred at R.T., and MMTrCl (239.3 g, 776.8 mmol, 4 eq) was added. After being stirred overnight at R.T., the mixture was filtered through Celite and filtrate was diluted with MTBE. 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. The crude

intermediate was dissolved in anhydrous THF (250 mL) and treated with TBAF (60 g, 233 mmol, 1.2 eq). The mixture was stirred for 2 hours at R.T., and the solvent was removed under reduced pressure. The residue was taken into ethyl acetate and washed brine. After drying over magnesium sulfate, the solvent was removed in vacuo. The residue was purified by column chromatography (PE:EA = 5:1 to 1:1) to give **42-2** as a white foam (91 g, 86.4%).

[0359] To a solution of **42-2** (13.5 g, 26 mmol) in DCM (100 mL) was added pyridine (6.17 mL, 78 mmol, 3 eq). The solution was cooled to 0ºC and Dess-Martin periodinane (33.8 g, 78 mmol, 3 eq) was added. The mixture was stirred for 4 hours at R.T. and quenched by the addition of a 4% $Na_2S_2O_3$/4% sodium bicarbonate aqueous solution (to pH 6, ~150 mL). The mixture was stirred for another 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 R.T. overnight. The reaction was quenched with saturated NH_4Cl (~150 mL), and the mixture was concentrated under reduced pressure. 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 (MeOH:DCM = 100:1~50:1) to give **42-3** as a white foam (9.2 g, 83.6%).

[0360] Compound **42-3** (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 -35°C. Triflic anhydride (24.9 g, 88.1 mmol, 2.1 eq) was added dropwise over 10 mins. At this temperature, the reaction was stirred for 40 mins and then was quenched with water (50 mL) at 0^0C. The mixture was stirred 30 mins, and extracted with EA (150 mL x 2). The organic phase was dried over Na_2SO_4, and filtered through a silica gel pad. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (PE:EA = 100:1~1:1) to give **42-4** as a brown foam (30.0 g, 88.3%).

[0361] Compound **42-4** (30 g, 36.9 mmol) was co-evaporated twice with toluene and dissolved in anhydrous DMF (150 mL). The solution was cooled to 0°C, and treated with sodium hydride (60% in mineral oil; 1.5 g, 40.6 mmol). The reaction was stirred at R.T.

for 1 h. Lithium chloride (4.6 g, 110.7 mmol, 3 eq) was added. Stirring was continued for 2 hours when LCMS indicated complete conversion of the anhydro triflate intermediate to anhydro-chloro compound. The mixture was taken into 100 mL of half saturated ammonium chloride and ethyl acetate. The organic phase was separated, washed with diluted brine and concentrated under reduced pressure. The residue was dissolved in THF (150 mL), and the solution was treated with 1N aqueous sodium hydroxide (~41 mL, 40.1 mmol, 1.1 eq). The mixture was stirred at R.T. for 1h. The reaction was diluted with half saturated sodium bicarbonate (~60 mL) and extracted with EA. The organic phase was dried (magnesium sulfate) and concentrated under reduced pressure. The residue was purified by column chromatography (DCM:MeOH = 300:1~60:1) to give **42-5** as a yellow foam (18.3 g, 87.6%).

[0362] To a solution of **42-5** (18.3 g, 32.33 mmol) in anhydrous DCM (150 mL) was added TBSCl (17.7 g, 64.6 mmol) and imidazole (6.6 g, 97 mmol). The reaction was stirred overnight at R.T. The reaction was diluted with water and extracted with DCM. The organic layer was separated, washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (DCM:MeOH = 300:1~80:1) to give **42-6** as a white foam (18.4 g, 83.7%).

[0363] A solution of **42-6** (18.4 g, 27.1 mmol), DMAP (6.6 g, 54.0 mmol) and TEA (5.4 g ,54.0 mmol) in MeCN (450 mL) was treated with 2,4,6-triispropylbenzenesulfonyl chloride (16.3 g, 54.0 mmol). The mixture was stirred at R.T. for 3 hours. NH_4OH (70 mL) was added, and the mixture was stirred for 2 hours. The solution was evaporated under reduced pressure, and the residue was purified on a silica gel column (DCM/MeOH = 100:1 to 15:1) to give the crude (18.0 g). The crude was dissolved in anhydrous DCM (150 mL). Collidine (8.1 g, 66.3 mmol, 2.5 eq), silver nitrate (4.5 g, 26.5 mmol, 1.0 eq) and DMTrCl (13.4 g, 39.7 mmol, 1.5 eq) were added. The reaction was stirred overnight at R.T. The mixture was filtered through Celite. The filtrate was washed with brine and extracted with DCM. The organic layer was separated, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (PE:EA = 60:1~3:1) as a yellow foam. The foam was dissolved in THF (150 mL) and TBAF (10.4 g, 39.7 mmol, 1.5 eq) was added. The reaction was stirred at R.T. After being concentrated, the mixture was washed with brine and extracted with EA. The organic layer was separated, dried over

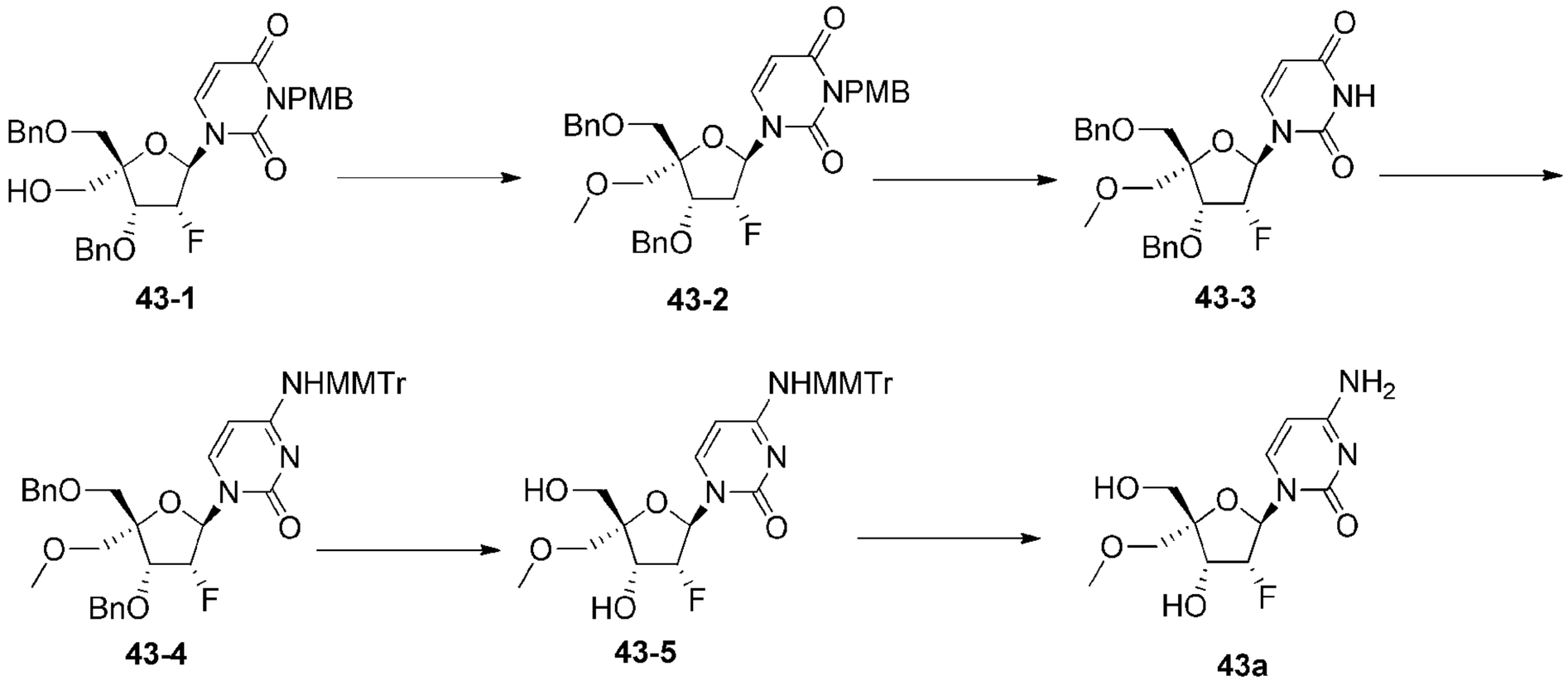
Na_2SO_4 and concentrated. The residue was purified by column chromatography (PE:EA =60:1~EA) to give **42-7** as a yellow foam (21.3 g, 92.4%).

[0364] To a solution of **42-7** (2.0 g, 2.3 mmol) in anhydrous DCM (20 mL) was added Dess-Martin periodinane (1.95 g, 4.6 mmol) at 0°C under nitrogen. The reaction was stirred at R.T. for 5 hours. The mixture was diluted with EtOAc (100 mL), and washed with a mixture of saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$. The crude product was purified by column chromatography on silica gel (PE: EtOAc = 2: 1) to give **42-8** (1.8 g, 90%) as a yellow solid.

[0365] To a solution of tetramethyl methylenediphosphonate (390 mg, 1.68 mmol) in anhydrous THF (10 mL) was added NaH (84 mg, 2.1 mmol) at 0°C under nitrogen. The reaction was stirred at 0°C for 30 min. A solution of **42-8** (1.2 g, 1.4 mmol) in anhydrous THF (10 mL) was added dropwise at 0°C. The mixture was stirred at R.T. for 1 h. The reaction was quenched with saturated aqueous NH_4Cl, and the crude product was purified by column chromatography on silica gel (DCM: MeOH = 150: 1) to give **42-9** (1.2 g, 88.2%) as a yellow solid. ESI-MS: m/z 971.59 $[M + H]^+$.

[0366] A solution of **42-9** (300 mg) in 80% HOAc (26 mL) was stirred at 80-90°C for 2 h. The solvent was removed, and the crude product was purified by column chromatography on silica gel (DCM: MeOH 20: 1) to give **42a** (70 mg, 57%) as a white solid. ESI-MS: m/z 397.81 $[M + H]^+$.

EXAMPLE 42
Preparation of Compound 43a



[0367] To a stirred solution of **43-1**(3.8 g, 6.6 mmol) in anhydrous DMF (100mL) was added NaH (2.2 g) followed by CH_3I (9.3 g, 66 mmol) at 0°C. Stirring was continued at R.T. overnight. The reaction was quenched with saturated NH_4Cl aq. The mixture was diluted with EA and washed with brine. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (PE:EA = 2:1) to give **43-2** (3.0 g, 70%) as a white solid.

[0368] A mixture of **43-2** (3.0 g, 5.1 mmol) and CAN (5.56 g, 10.2 mmol) in a 3:1 solution of MeCN:Water (16 mL) was stirred at R.T. overnight. The solution was diluted with brine (10 mL) and was extracted with EA. The combined organic extracts were dried and evaporated under reduced pressure. Purification by chromatography on silica (PE:EA = 1:1) gave **43-3** as a yellow solid (1.71 g, 72%).

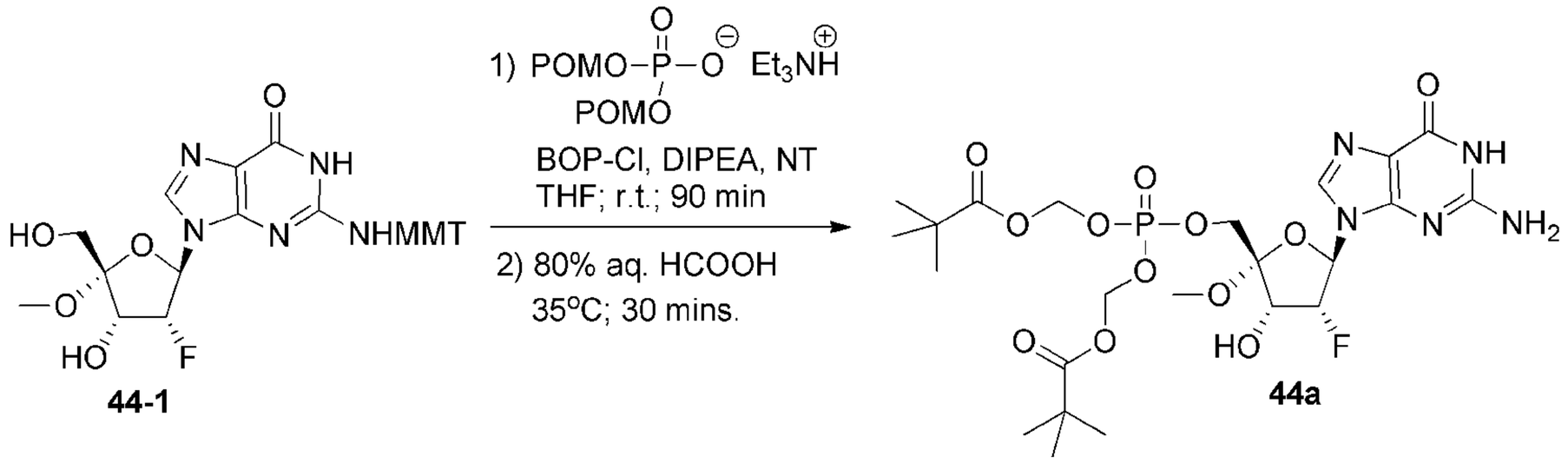
[0369] To a stirred solution of **43-3** (1.7 g, 3.6 mmol) in anhydrous MeCN (50 mL) were added TPSCl (2.2 g, 7.2 mmol), DMAP (880 mg, 7.2 mmol) and TEA (1.1 g ,10.8 mmol) at R.T. The mixture was stirred at R.T. overnight. NH_4OH (25 mL) was added, and the mixture was stirred for 2 hours. The solvent was removed, and the residue was purified on a silica gel column (PE:EA = 8:1 to 2:1) to give the intermediate (1.4 g). The intermediate was dissolved in anhydrous DCM (30 mL), and MMTrCl (1.6 g, 5.2 mmol), $AgNO_3$ (1.4 g, 7.8 mmol) and collidine (1.57 g, 13 mmol) were added. The mixture was stirred at R.T. overnight. The solid was filtered off and washed with DCM. The filtrate was washed with brine and dried over Na_2SO_4. The concentrated organic phase was purified on a silica gel column (PE:EA = 3:2) to give **43-4** (1.1 g, 57.9%) as a white solid.

[0370] To a stirred solution of **43-4** (550 mg, 0.74 mmol) in acetone were added ammonium formate (1.0 g, 15.8 mmol, in portions) and 10% palladium on carbon (1.0 g). The mixture was refluxed for 48 hours. The catalyst was filtered off and washed with the acetone. The filtrate was diluted with EA, washed with brine and dried. The concentrated organic phase was purified by column chromatography (DCM:MeOH = 50:1) to give **43-5** (330 mg, 72%).

[0371] Compound **43-5** (200 mg, 0.36 mmol) was dissolved in 80% CH_3COOH (20 mL) at R.T. The mixture was stirred at 60°C for 12 hours. The solvent was removed. The residue was purified by column chromatography (DCM:MeOH = 10:1), and the resulting

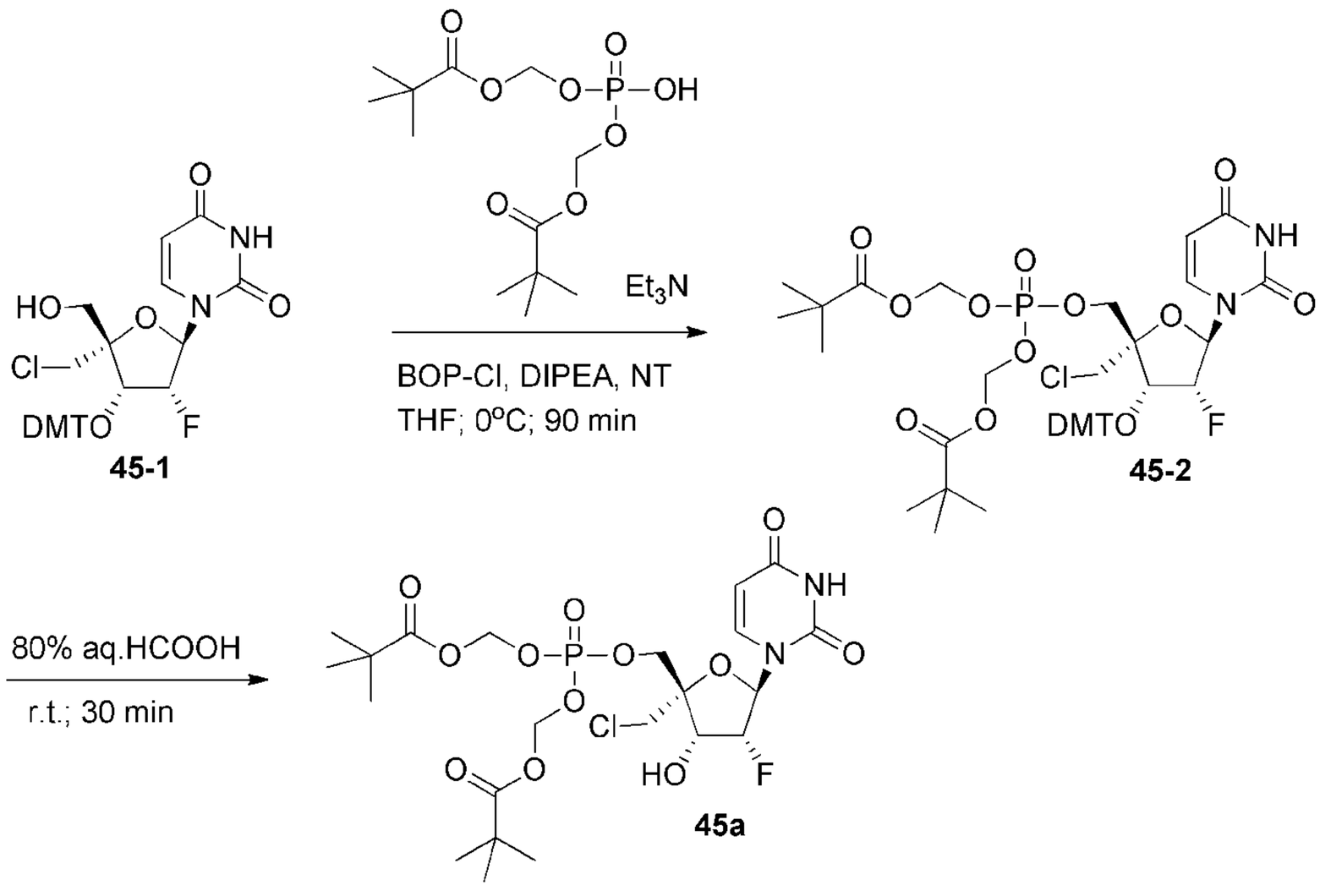
solid was washed with DCM to give pure **43a** as a white solid (44mg, 42%). ESI-MS: m/z 290 $[M+H]^+$.

EXAMPLE 43
Preparation of Compound 44a



[0372] To a solution of triethylammonium bis(POM)phosphate (0. 3 mmol, prepared from 100 mg of bis(POM)phosphate and 50 μL of Et_3N) in THF (3 mL) was added nucleoside **44-1** (150 mg; 0.26 mmol). The mixture was cooled in ice-bath. Diisopropylethyl amine (0.18 mL; 4 equiv) was added then, followed by BOP-Cl (132 mg; 2 equiv) and 3-nitro-1,2,4-triazole (59 mg; 2 equiv). The reaction mixture was stirred at 0°C for 90 mins., and then diluted with CH_2Cl_2 (30 mL) and washed with saturated aq. $NaHCO_3$ and brine. The combined aqueous layers were back extracted with CH_2Cl_2. The combined organic extract was dried (Na_2SO_4), evaporated, and the residue purified on silica (10 g column) with CH_2Cl_2 /i-PrOH solvent system (3-10% gradient). The obtained mixture of products were treated for 30 mins at 35°C with 80% aq. HCOOH, and then evaporated and coevaporated with toluene. The evaporated residue was purified on silica (10 g column) with CH_2Cl_2 /MeOH solvent system (5-10% gradient) to obtain **44a** (8 mg, 5%). ^{31}P-NMR (DMSO-d_6): δ -5.07. MS: m/z = 668 [M+46-1].

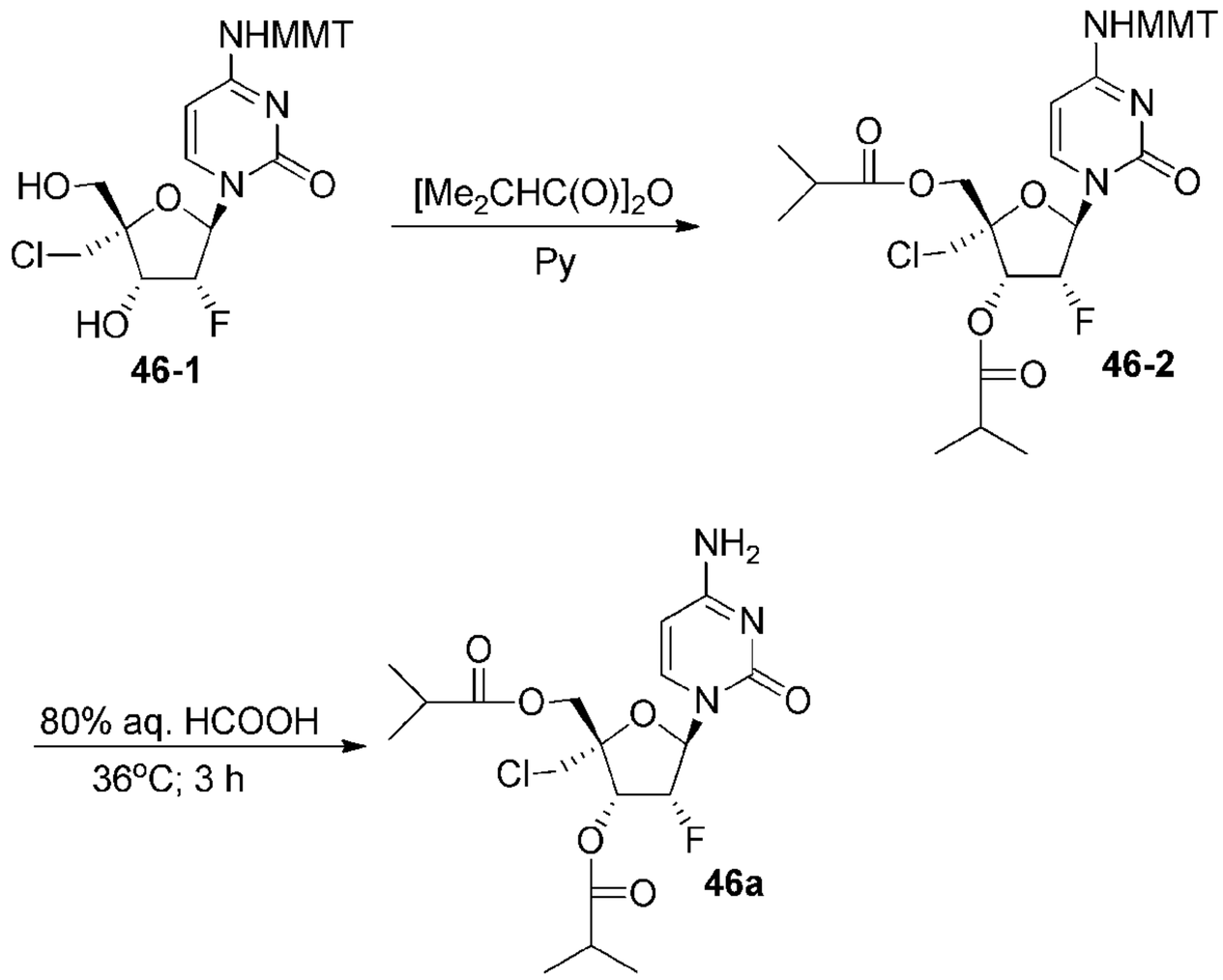
EXAMPLE 44
Preparation of Compound 45a



[0373] To a solution of triethylammonium bis(POM)phosphate (0. 7 mmol, prepared from 233 mg of bis(POM)phosphate and 0.1 mL of Et_3N) in THF (8 mL) was added nucleoside **45-1** (253 mg; 0.42 mmol), followed by diisopropylethyl amine (0.36 mL; 5 equiv), BOP-Cl (268 mg; 2.5 equiv) and 3-nitro-1,2,4-triazole (120 mg; 2.5 equiv). The reaction mixture was stirred at R.T. for 2 hours. The mixture was diluted with CH_2Cl_2 (40 mL) and washed with saturated aq. $NaHCO_3$ and brine. The combined aqueous layers were back extracted with CH_2Cl_2. The combined organic extract was dried (Na_2SO_4), evaporated, and the residue was purified on silica (10 g column) with hexanes/EtOAc solvent system (40-100% gradient) to yield **45-2** (180 mg, 47%).

[0374] A solution of **45-2** (0.12 g; 0.13 mmol) in 80% aq. HCOOH (8 mL) was stirred 30 mins. at R.T. The mixture was evaporated, coevaporated with toluene and purified on silica (10 g column) with CH_2Cl_2/MeOH solvent system (4-10% gradient) to yield **45a** (55 mg, 70%). ^{31}P-NMR (DMSO-d_6): δ -4.36. MS: m/z = 647 [M+46-1].

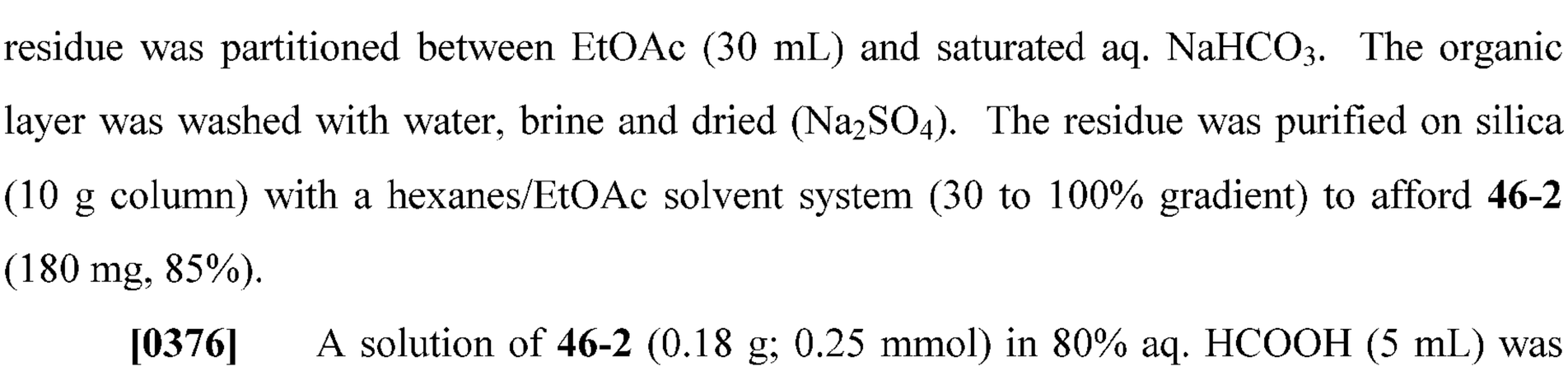
EXAMPLE 45
Preparation of Compound 46a



[0375] A mixture of **46-1** (170 mg; 0.3 mmol) in pyridine (3 mL) and isobutyric anhydride (0.1 mL; 2 equiv) was stirred o/n at R.T. The mixture was concentrated, and the residue was partitioned between EtOAc (30 mL) and saturated aq. $NaHCO_3$. The organic layer was washed with water, brine and dried (Na_2SO_4). The residue was purified on silica (10 g column) with a hexanes/EtOAc solvent system (30 to 100% gradient) to afford **46-2** (180 mg, 85%).

[0376] A solution of **46-2** (0.18 g; 0.25 mmol) in 80% aq. HCOOH (5 mL) was heated for 3 hours at 36°C. The mixture was then evaporated, coevaporated with toluene and purified on silica (10 g column) with a CH_2Cl_2/MeOH solvent system (4-10% gradient) to afford **46a** (75 mg, 70%). MS: m/z = 434 [M+1].

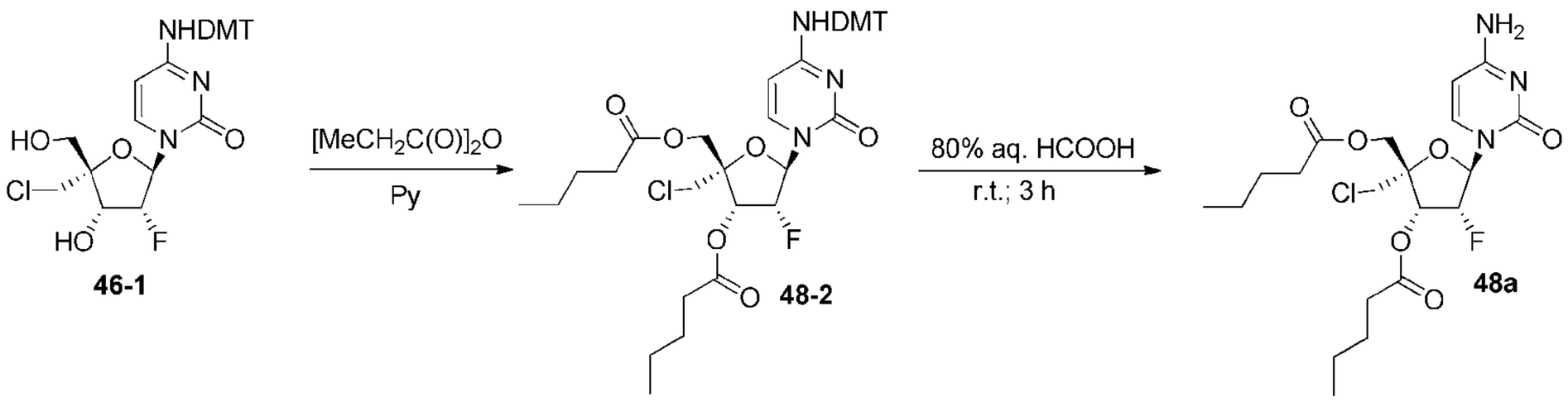
EXAMPLE 46
Preparation of Compound 47a



[0377] Compound **47-2** was prepared from **46-1** (274 mg, 0.46 mmol) and propyonic anhydride (0.12 mL, 2 equiv.) in pyridine (5 mL) in the same manner as described for **46-2** (260 mg, 80%).

[0378] Compound **47-2** (120 mg, 0.2 mmol) was treated with 80% aq. HCOOH at R.T. for 3 hours. The mixture was evaporated, coevaporated with toluene and purified on silica (10 g column) with a CH_2Cl_2/MeOH solvent system (4-10% gradient) to yield **47a** (62 mg, 75%). MS: m/z = 404 [M-1].

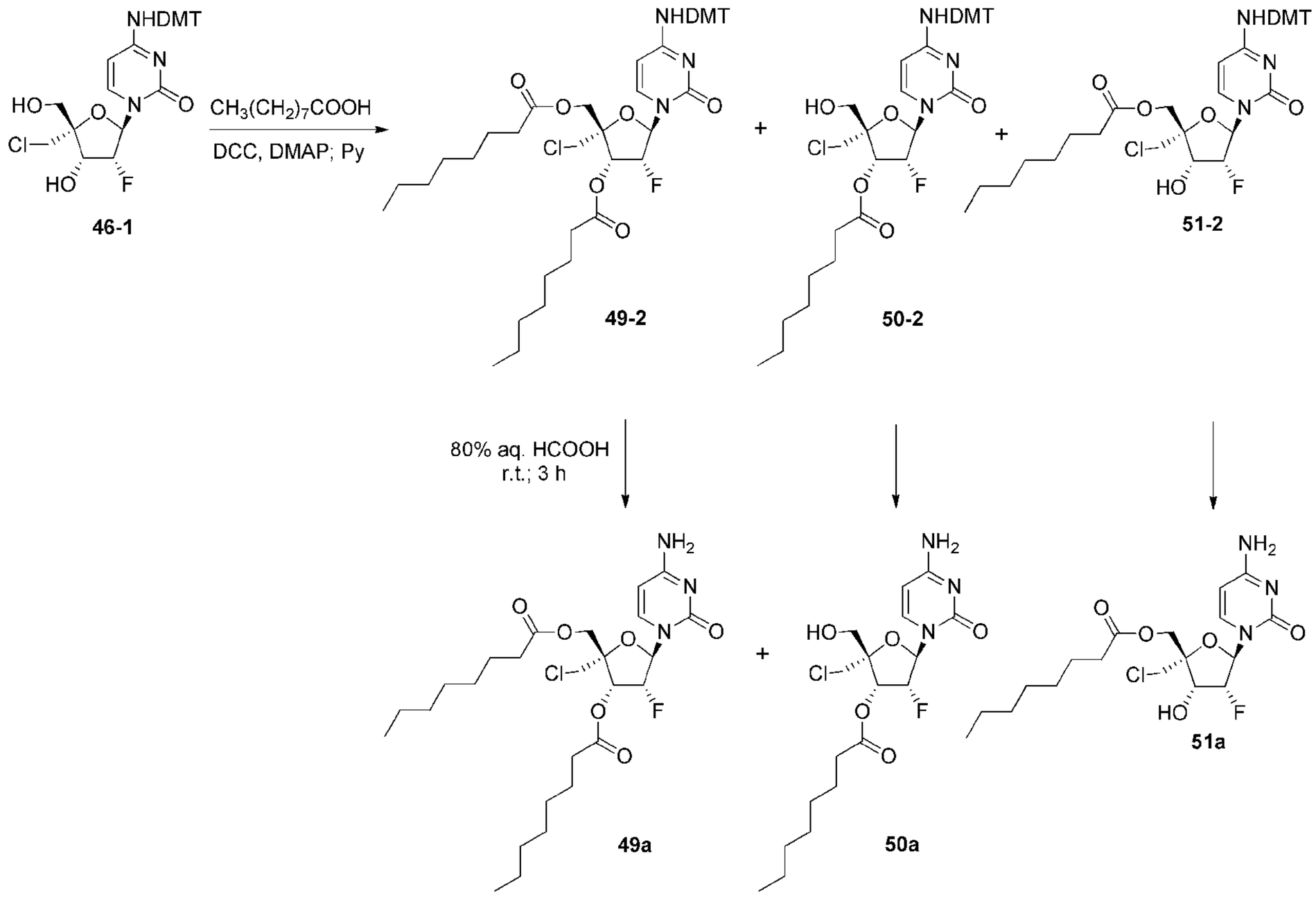
EXAMPLE 47
Preparation of Compound 48a



[0379] Compound **48-2** was prepared from **46-1** (150 mg, 0.27 mmol) and valeric anhydride (0.11 mL, 2 equiv.) in pyridine (3 mL) in the same manner as described for **46-2** (150 mg, 73%).

[0380] Compound **48-2** (140 mg, 0.18 mmol) was treated with 80% aq. HCOOH at R.T. for 3 h. The mixture was evaporated and purified on silica (10 g column) with a CH_2Cl_2/MeOH solvent system (4-10% gradient) to yield **48a** (70 mg, 84%). MS: m/z = 462 [M+1].

EXAMPLE 48
Preparation of Compounds 49a, 50a and 51a



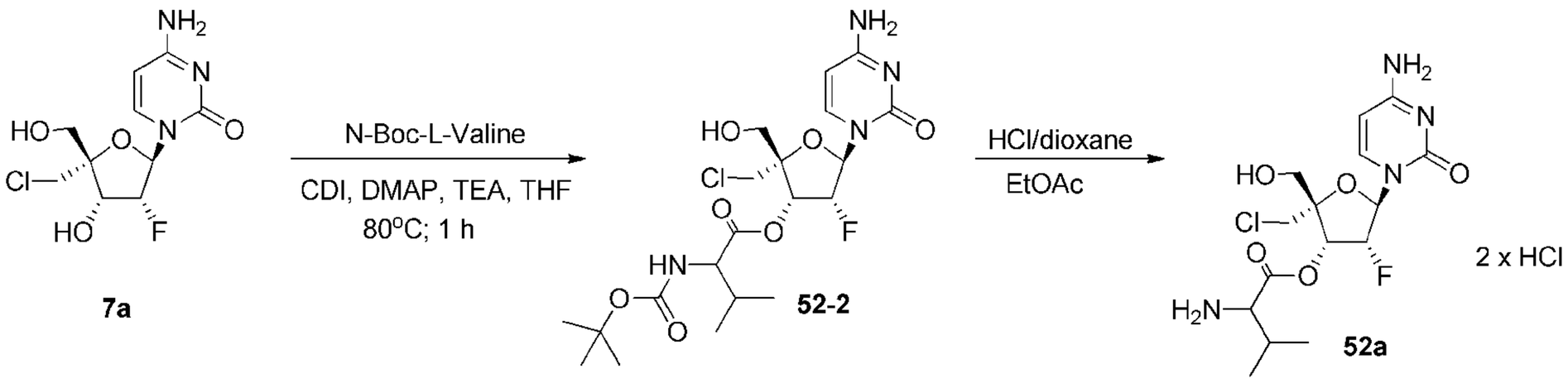
[0381] To a solution of **46-1** (1.26 g, 2.12 mmol) in pyridine (15 mL) were added n-octanoic acid (0.34 mL, 1.0 equiv.), DCC (60% in xylene; 0.81 mL, 1 equiv.) and DMAP (52 mg; 0.2 equiv.). The resulting mixture was stirred for 6 hours at R.T. The mixture was evaporated, and the residue partitioned between CH_2Cl_2 (100 mL) and saturated aq. $NaHCO_3$ (25 mL). The organic layer was washed with water, brine and dried (Na_2SO_4). The residue was treated with toluene. The solid material was filtered off, and the filtrate was purified on silica (25 g column) with a heaxanes/EtOAc solvent system (30-100% gradient) to yield **49-2** (0.57 g, 32%), **50-2** (0.18 g, 12%), and **51-2** (0.2 g, 13%).

[0382] A mixture of **49-2** (114 mg, 0.13 mmol) and 80% aq. formic acid was stirred for 3 hours at R.T. The mixture was evaporated and coevaporated with toluene and purified on silica (10 g column) with a CH_2Cl_2/MeOH solvent system (2-8% gradient) to yield **49a** (53 mg, 75%). MS: m/z = 544 (M-1).

[0383] Compound **50a** (44 mg, 75% yield) was prepared from **50-2** (104 mg, 0.14 mmol) in the same manner as described for **49a** by using a 4-10% gradient of MeOH in CH_2Cl_2 for purification. MS: m/z = 418 (M-1).

[0384] **51a** (60 mg, 71% yield) was prepared from **50-2** (140 mg, 0.2 mmol) in the same manner as described for **49a** by using a 4-10% gradient of MeOH in CH_2Cl_2 for purification. MS: m/z = 418 [M-1].

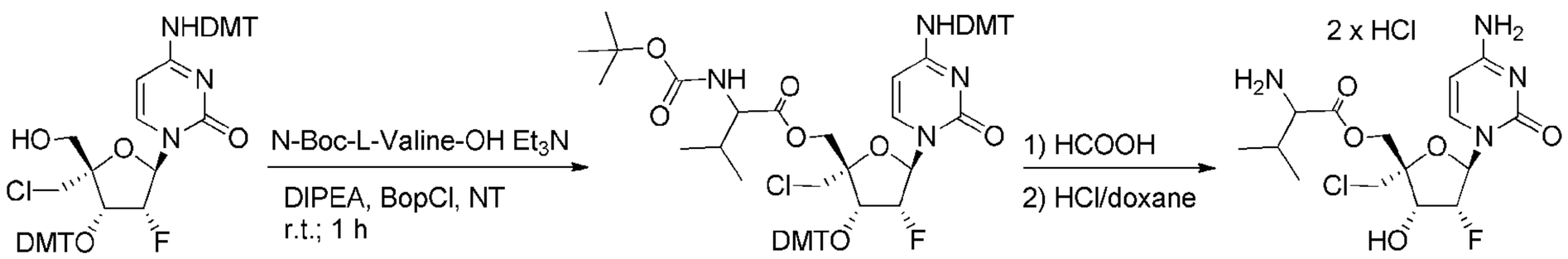
EXAMPLE 49
Preparation of Compound 52a



[0385] A solution of *N*-(*tert*-butoxycarbonyl)-L-valine (0.41 g, 1.9 mmol) and carbonyldiimidazole (0.31 g, 1.9 mmol) in THF (9 mL) was stirred at R.T. for 1.5 hours. The mixture was then stirred at 40°C for 20 mins. The mixture was added to a solution of **7a** (0.42 g, 1.43 mmol) and DMAP (25 mg, 0.2 mmol) in DMF (8 mL) and TEA (4 mL) at 80°C. The reaction mixture was stirred at 80°C for 1 h, then cooled and concentrated. The residue was partitioned between *tert*-butyl methyl ether (100 mL) and water. The organic layer was washed with water, brine and dried (Na_2SO_4). The residue was purified on silica (25 g column) with a CH_2Cl_2/MeOH solvent system (2-10% gradient) to yield **52-2** (0.32 g, 90% in the mixture with 5'-isomer), which was repurified by RP-HPLC (10-100% B; A: water, B: MeOH). Yield: 0.25 g (35%).

[0386] A solution of **52-2** (0.12 g; 0.24 mmol) in EtOAc (0.6 mL) was treated with HCl/dioxane (4 M; 0.6 mL) for 20 mins. with vigorous shaking. The white precipitate was filtered, washed with diethyl ether and dried to yield **52a** as the dihydrochloride salt (95 mg; 85%). MS: m/z = 391 [M-1].

EXAMPLE 50
Preparation of Compound 53a

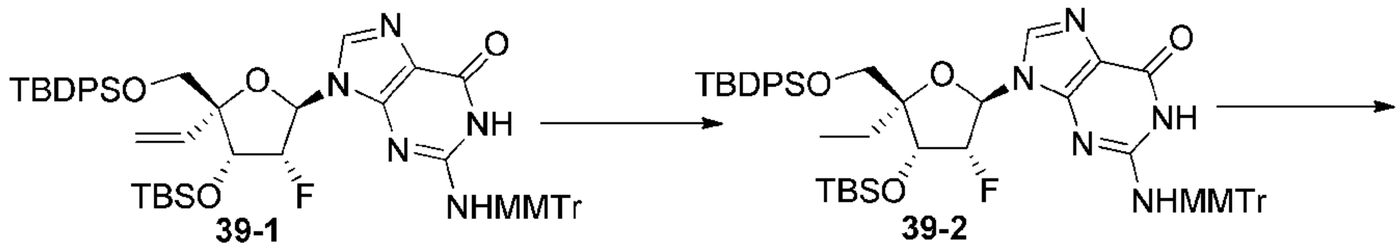


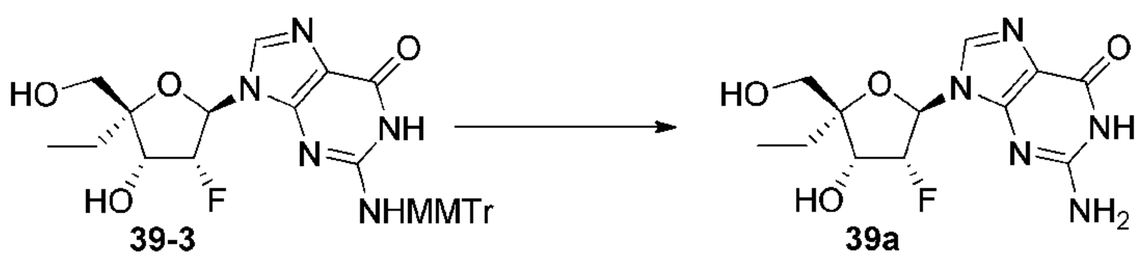
53-1 53-2 53a

[0387] To a solution of N-Boc-Val-OH (0.16 g, 0.74 mmol) and Et_3N (0.14 mL, 1.0 mmol) in THF was added **53-1**. The resulting mixture was evaporated, coevaporated with pyridine and toluene and dissolved in THF (4 mL). DIPEA (0.38 mL, 2.2 mmol) was added, followed by BOP-Cl (0.28 g, 1.1 mmol) and 3-nitro-1,2,4-triazole (0.13 g, 1.1 mmol). The reaction mixture was stirred at R.T. for 1 h. The mixture was diluted with CH_2Cl_2 (40 mL) and washed with saturated aq. $NaHCO_3$ and brine. The combined aqueous layers were back extracted with CH_2Cl_2. The combined organic extract was dried (Na_2SO_4), evaporated, and the residue was purified on silica (10 g column) with a hexanes/0.5 % Et_3N/EtOAc solvent system (20-100% gradient) to yield **53-2** (0.39 g, 81%).

[0388] A mixture of **53-2** (0.37 g, 0.33 mmol) and 80% aq. HCOOH (10 mL) was stirred at R.T. for 3 hours. The mixture was evaporated, and the residue was partitioned between water and CH_2Cl_2. The aqueous layer was washed with CH_2Cl_2 and evaporated. The solid residue was suspended in EtOAc (1.5 mL) and treated with 4N HCl in dioxane (1.5 mL) with vigorous shaking. The solid was filtered, washed with diethyl ether and purified by RP-HPLC (A: 0.5N HCOOH in water, B: 0.5 N HCOOH in acetonitrile). The resulting formic acid salt of 5'-O-valyn ester was converted into **53a** dihydrochloride salt (63 mg, 40%) by suspending in EtOAc (2 mL) and treatment with 4N HCl/dioxane (2 mL). MS: m/z = 391 [M-1].

EXAMPLE 51
Preparation of Compound 39a



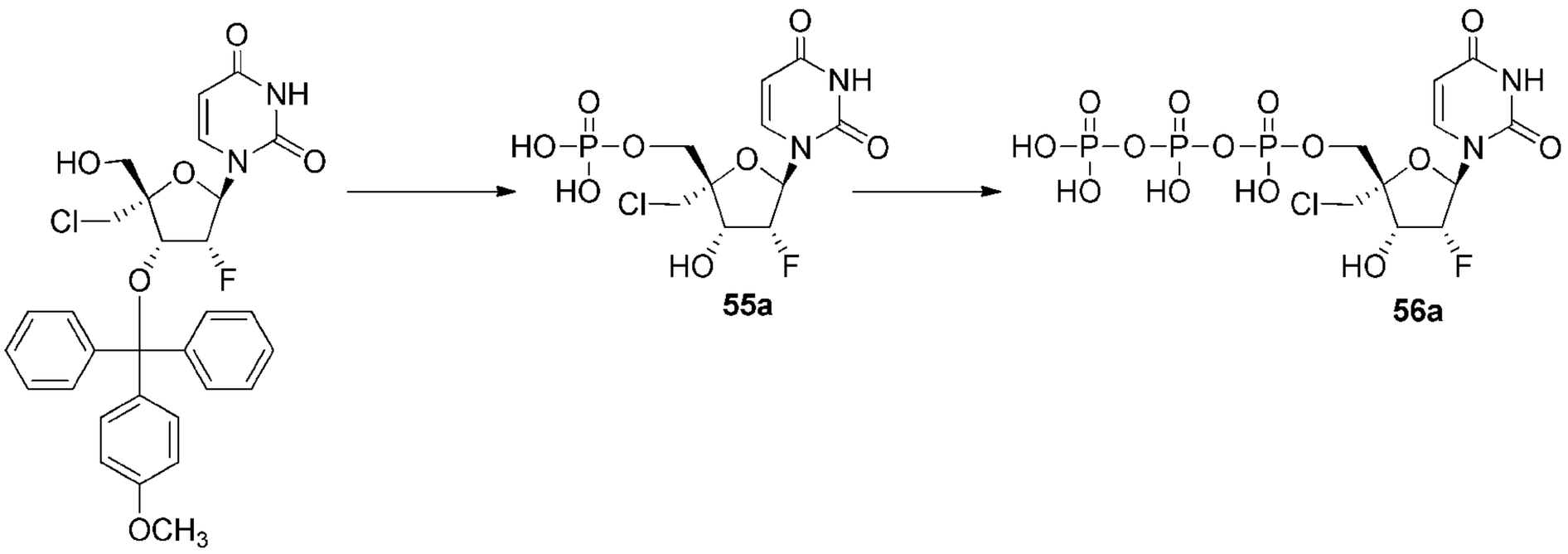


[0389] A solution of **39-1** (1.3 g, 1.4 mmol) in anhydrous MeOH (20 mL) was charged with Pd/C (1.3 g) and stirred at 25°C under hydrogen (1 atm) atmosphere for 1 hour. The solution was filtered, evaporated to dryness, and purified on a silica gel column (DCM:MeOH = 100:1 to 50:1) to give **39-2** (1.2 g, 92.3 %) as a white solid.

[0390] To a solution of **39-2** (1.2 g, 1.3 mmol) in MeOH (40 mL) was added NH_4F (370 mg, 10 mmol) at 25°C and stirred at 60°C for 6 hours. The solution was filtered, evaporated to dryness, and purified on a silica gel column (DCM:MeOH = 200:1 to 20:1) to give **39-3** as a white solid (249 mg, 30.7%). ESI-LCMS: m/z 586.1 $[M + H]^+$.

[0391] A solution of **39-3** of 80% formic acid/20% water (3 mL) stood at RT for 2 hours, and then was concentrated to dryness. The residue was co-evaporated with MeOH/toluene (3 times) and then ethyl acetate added. The suspension in ethyl acetate was heated at 70°C for 5 mins. The solvent was removed using a pipet. This washing was repeated 3 times. The resulting product (44mg) was further purified on reverse-phase HPLC using acetonitrile/water as mobile phase to give **39**a (20 mg) as an off-white solid. ESI-LCMS: m/z 443.6 $[M + 6\text{-methyl-2-heptylamine})]^+$.

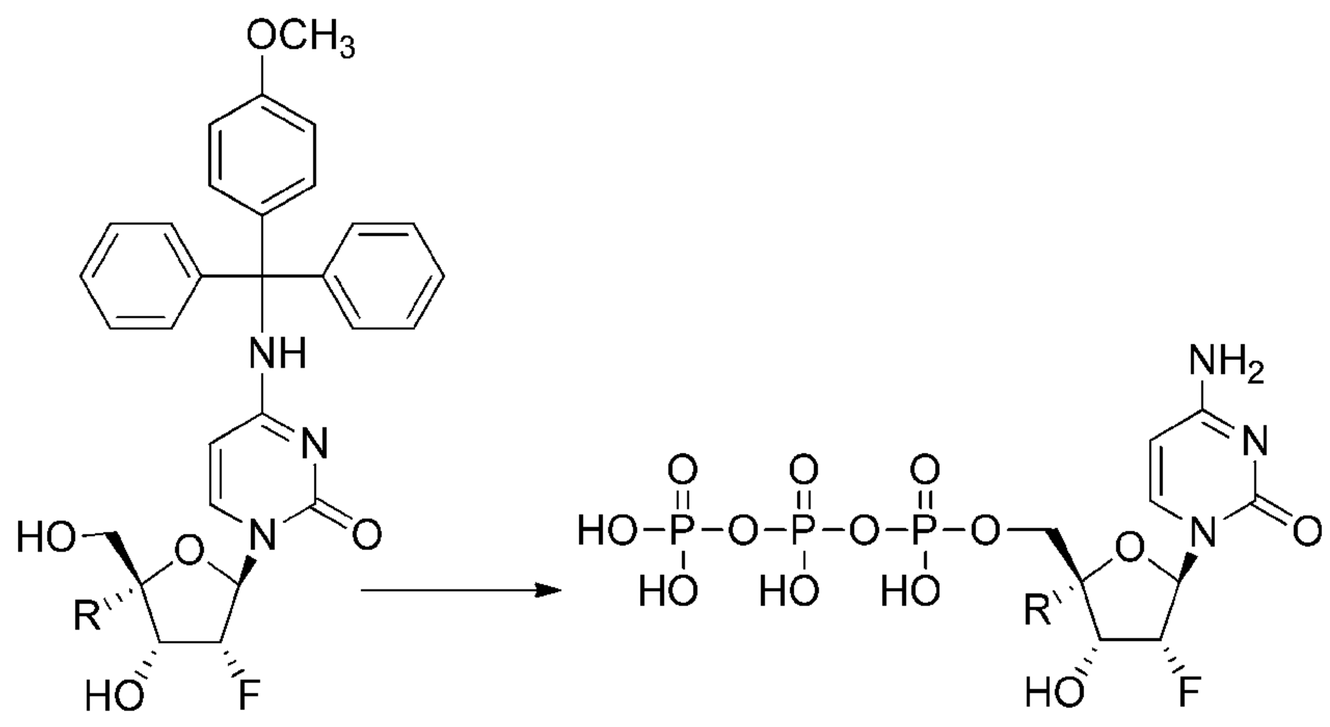
EXAMPLE 52
Preparation of Compounds 55a and 56a



55a 56a

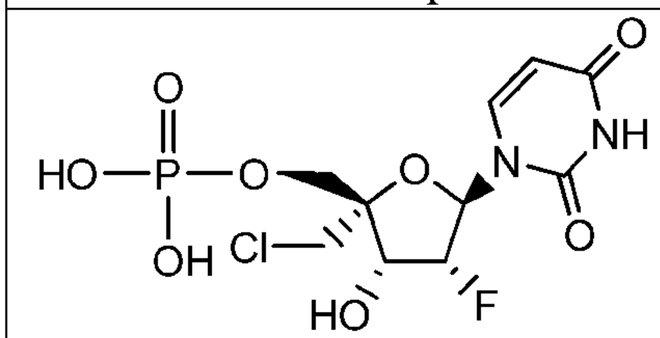
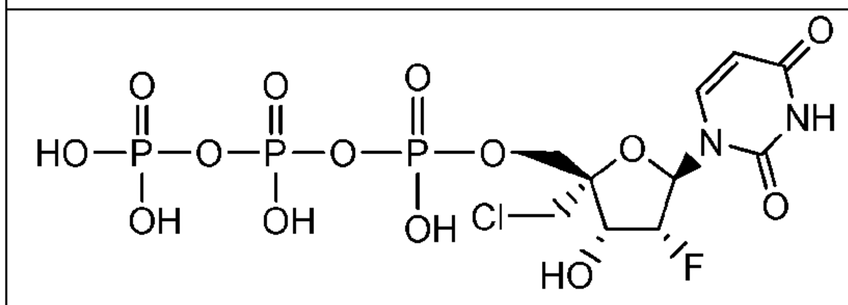
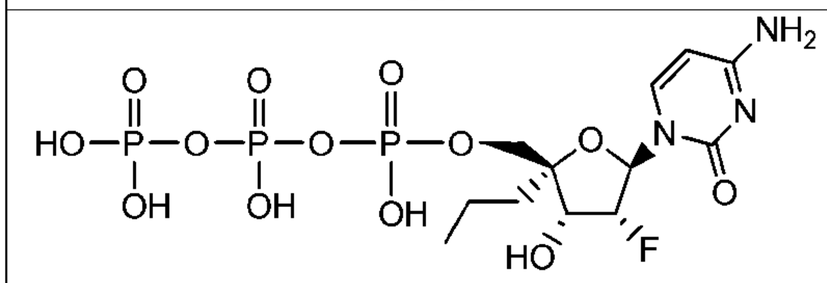
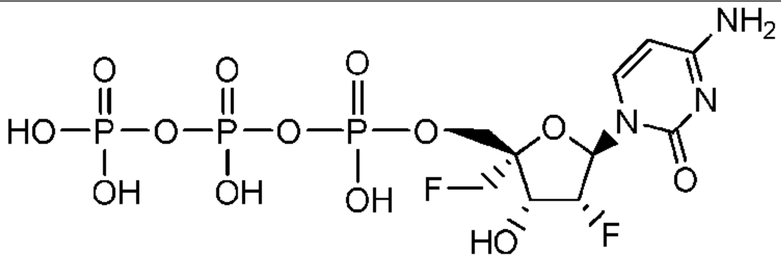
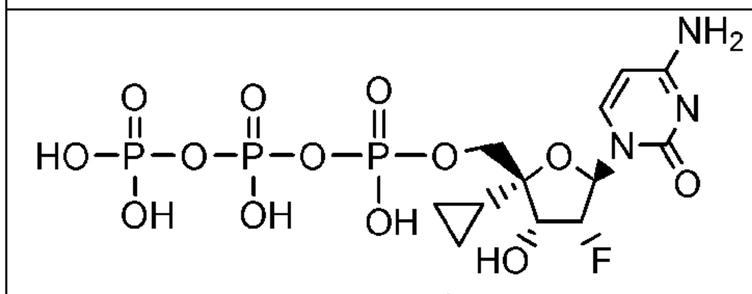
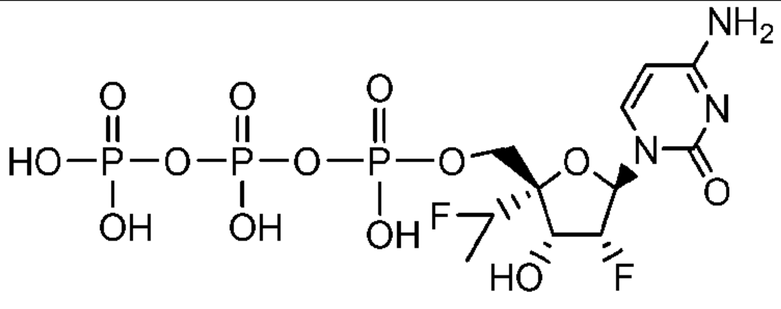
[0392] 1,2,4-Triazole (21 mg, 0.3 mmol) was dissolved in the mixture of CH_3CN (0.7 mL) and Et_3N (44 µL, 0.31 mmol). $POCl_3$ (9ul, 0.1 mmol) was added, and the mixture was kept at R.T. for 20 mins. The white precipitate was filtered, and the filtrate added to the dry nucleoside (28 mg, 0.05 mmol). The reaction was controlled by TLC and monitored by the disappearance of the starting nucleoside. 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 diluted with water (4 mL) and extracted with DCM (2 x 5 mL). The combined organic extracts were evaporated, dissolved in 5 mL of 80% HCOOH and left for 2 hours at R.T. The reaction mixture was concentrated and distributed between water (5 mL) and DCM (5 mL). The aqueous fraction was loaded on the column HiLoad 16/10 with Q Sepharose High Performance. Separation was done in a linear gradient of NaCl from 0 to 1N in 50mM TRIS-buffer (pH7.5). Two fractions were obtained. The first fraction, containing the monophosphate (**55a**) was eluted at 70-75%B. and triphosphate (**56a**) was eluted at 75-80%B. Both fractions were desalted by RP HPLC on Synergy 4 micron Hydro-RP column (Phenominex). A linear gradient of methanol from 0 to 30% in 50mM triethylammonium acetate buffer (pH 7.5) was used for elution. The corresponding fractions were combined, concentrated and lyophilized 3 times to remove excess of buffer.

EXAMPLE 53
Preparation of Compounds 56b-56e

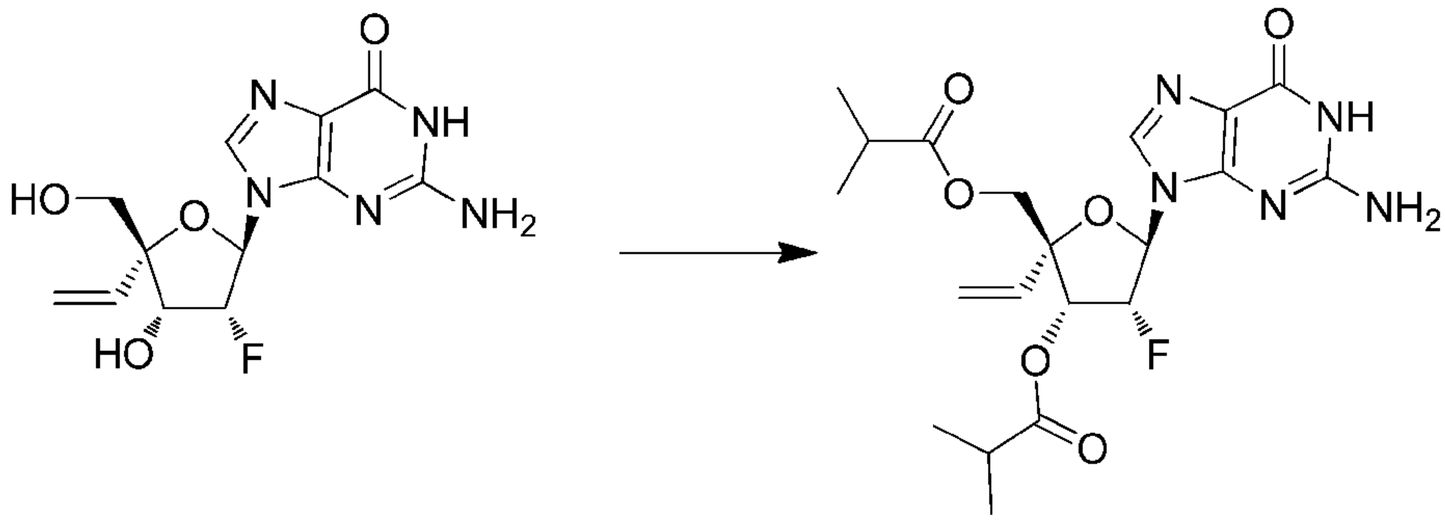


[0393] 1,2,4-Triazole (21 mg, 0.3 mmol) was dissolved in the mixture of CH_3CN (0.7 mL) and Et_3N (44 µL, 0.31 mmol). $POCl_3$ (9ul, 0.1 mmol) was added, and the mixture was kept at R.T. for 20 mins. The white precipitate was filtered, and the filtrate added to the dry nucleoside (28 mg, 0.05 mmol). The reaction was controlled by TLC and monitored by the disappearance of the starting nucleoside. 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 diluted with water (4 mL) and extracted with DCM (2 x 5 mL). The combined organic extracts were evaporated, dissolved in 5 mL of 80% HCOOH and left for 4 hours at 38°C. The reaction mixture was concentrated and distributed between water (5 mL) and DCM (5 mL). The aqueous fraction was 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 (pH7.5). Two fractions were obtained. The triphosphate (**56b-56e**) was eluted at 75-80%B. Desalting 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.

Table 3 – Triphosphates obtained from Example 53

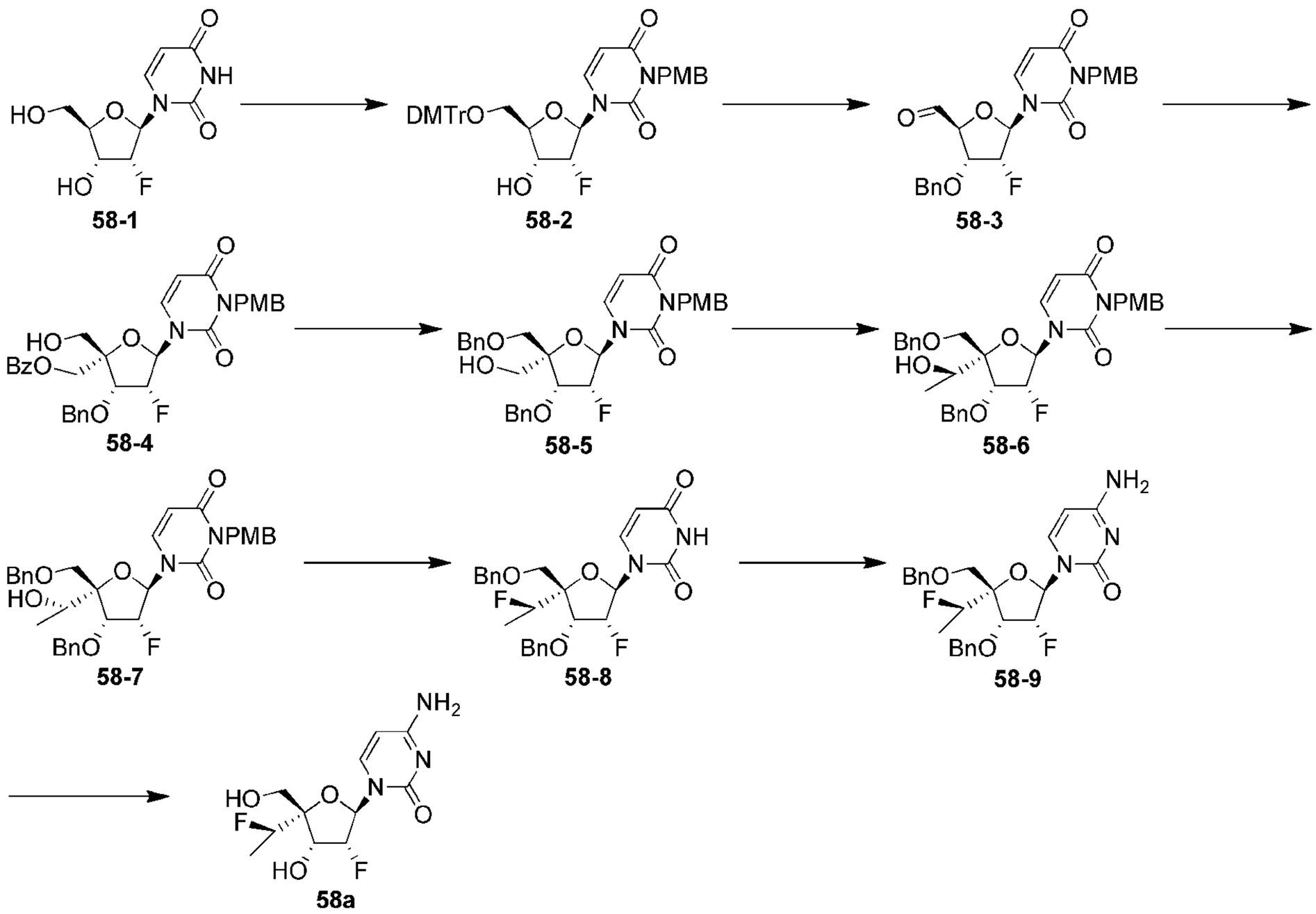
Compound	MS (M-1)	P(α)	P(β)	P(γ)
 **55a**	373.00	+3.64 (s)	NA	NA
 **56a**	532.95	-6.67 -6.74(d)	-21.87(t)	-11.51 -11.63(d)
 **56b**	526.05	-6.33 -6.47(d)	-22.48(t)	-11.53 -11.64(d)
 **56c**	516.00	-63.2(bs)	-22.45 (t)	-11.64(d)
 **56d**	524.4	-10.57 - 10.67(d)	-23.31(t)	-11.31 -11.94(d)
 **56e**	529.8	-6.17(bs)	- 21.96(bs)	- 11.42(bs)

EXAMPLE 54
Preparation of Compound 57a



[0394] 2'-Deoxy-2'-fluoro-4'-*C*-(ethenyl)guanosine (**25a**, 31 mg, 0.1 mmol) was dissolved in dry pyridine (3 mL). Isobutyric anhydrate (50 μL, 0.3 mmol) was added. The reaction mixture was kept at ambient temperature. After 40 hours, isobutyric anhydrate (100 μL, 0.6 mmol) was added, and the reaction mixture was left overnight. The pyridine was evaporated. The residue was purified by silica gel chromatography using a gradient of methanol in DCM from 3% to 10% to yield **57a** (20 mg, 50%). MS: m/z 452 [M+1].

EXAMPLE 55
Preparation of Compound 58a



[0395] To a solution of **58-1** (50.0 g, 205 mmol) in pyridine (250 mL) was added DMTrCl (75.0 g, 225.0 mmol). The solution was stirred at R.T. for 15 hours. MeOH (120 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 to give the crude DMTr protected derivative (80.5 g, 89%) as a light yellow solid. Dried K_2CO_3 (80.52 g, 583.2 mmol) and then PMBCl (31.7 g, 109.2 mmol) were added to a stirred solution of the DMTr protected derivative (80 g, 146 mmol) in anhydrous DMF (300 mL). The stirring was continued at ambient temperature for overnight. The reaction was monitored by TLC. The mixture was diluted with EA and washed with water. The organic layer was dried over Na_2SO_4 and concentrated to give **58-2** (98.8 g, 90%) as light yellow solid.

[0396] NaH (10.4 g, 260.5 mmol) and BnBr (73.8 g, 434.2 mmol) were added to a stirred solution of **58-2** (98.8 g, 147.9 mmol) in anhydrous DMF (300 mL), and the stirring

was continued at 25°C overnight. The reaction was monitored by TLC. The reaction was quenched with water, extracted with EA and washed with brine. The solvent was removed, and the residue was purified on silica gel (PE: EA= 10:1 to 3:1) to give the Bn protected derivative (101.1 g, 90%) as a light yellow solid. The Bn protected derivative (101.1 g, 133.4 mmol) was dissolved in 80% HOAc (900 mL) at 25°C. The mixture was stirred at 25°C overnight. The reaction was quenched with MeOH, and the solvent was removed to give the alcohol (42.1 g, 70%) as a white foam. To a solution of the alcohol (42.1 g, 92.6 mmol) in anhydrous CH_3CN (300 mL) was added IBX (28.5 g, 121.7 mmol) at 25°C. The reaction mixture was refluxed for 1 hour and then cooled to 0°C. The precipitate was filtered-off, and the filtrate was concentrated to give **58-3** (39.2 g, 93%) as a yellow solid.

[0397] To a solution of **58-3** (39.2 g, 86.39 mmol) in 1,4-dioxane (250 mL) was added 37% CH_2O (28.1 mL, 345.6 mmol) and 2N NaOH aqueous solution (86.4 mL, 172.8 mmol). The mixture was stirred at 25°C for 2 h and then neutralized with AcOH to pH = 7. To the reaction were added EtOH (200 mL) and $NaBH_4$ (19.7 g, 518.6 mmol). The mixture was stirred at 25°C for 30 mins. The reaction was quenched with saturated aqueous NH_4Cl. The mixture was extracted with EA, and the organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (PE: EA = 4:1 to 2:1) to give the diol derivative (25.5 g, 55%) as a white solid. To a stirred solution of the diol derivative (25.5 g, 52.5 mmol) in anhydrous pyridine (150 mL) and anhydrous CH_3CN (150 mL) was added BzCl (6.6 g, 52.47 mmol) dropwise at 0°C. The mixture was then stirred at 25°C for 14 h. The reaction was quenched with H_2O, and the solution was concentrated. The residue was dissolved in EA and washed with $NaHCO_3$. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified on a silica gel column (PE/EA = 5:4) to give **58-4** (18.1 g, 60%) as a white foam.

[0398] Cs_2CO_3 (30.0 g, 92.0 mmol) and BnBr (10.4 g, 61.3 mmol) were added to a stirred solution of **58-4** (18.1g, 30.6 mmol) in anhydrous DMF (300 mL), and stirring was continued at 25°C overnight. The reaction was quenched with NH_4Cl, extracted with EA and washed with brine. The solvent was removed to give the Bz protected derivative (19.3 g, 95%) as a light yellow solid. To a stirred solution of the Bz protected derivative (19.3 g, 28.4 mmol) in anhydrous MeOH (230 mL) was added NaOMe (24.9 g, 460 mmol) at 25°C for 1 h.

The reaction was quenched with AcOH (10 mL) and concentrated. The residue was purified on a silica gel column (PE/EA = 1/2) to afford **58-5** (11.2 g, 54%) as a white solid.

[0399] To a stirred solution of **58-5** (200 mg, 0.347 mmol) in anhydrous DCM (5 mL) was added DMP (168 mg, 0.674 mmol) at 25°C. The mixture was stirred at 25°C for 2 h. The solvent was removed, and the residue was purified on a silica gel column (PE: EA = 5:1 to 1:1) to give the aldehyde derivative (161 mg, 81%). To a stirred solution of the aldehyde derivative (200 mg, 0.348 mmol) in anhydrous THF (5 mL) was added MeMgBr (1.0 mL, 1.01 mmol) at -78°C. The mixture was stirred at -78°C for 1 h. The reaction was quenched with NH_4Cl and extracted with EA. The concentrated organic phase was purified by column chromatography (PE: EA = 5:1 to 1:1) to give **58-6** (135 mg, 65%).

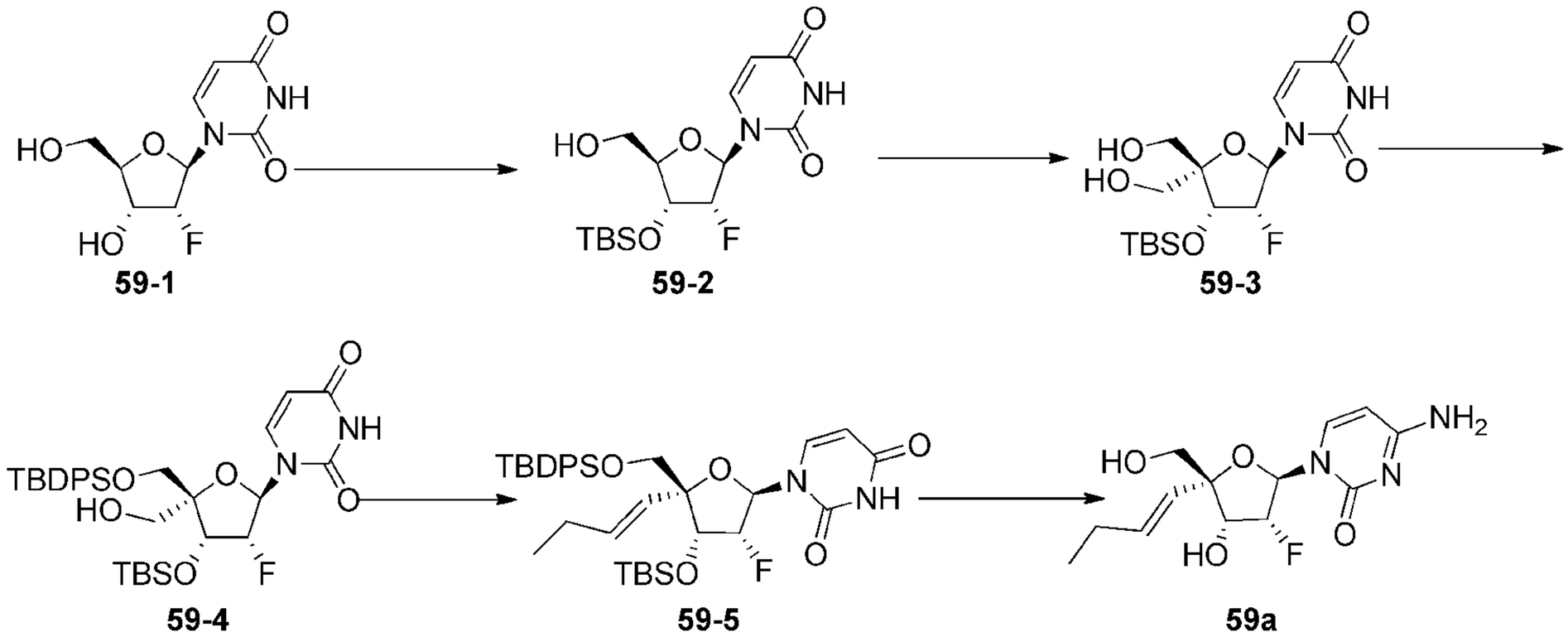
[0400] To a solution of **58-6** (900 mg, 1.5 mmol) in DCM was added DMP (2.5 g, 6.0 mmol) at 0°C. After stirring at 0°C for 1 h, the mixture was quenched with $Na_2S_2O_3$. The solvent was removed, and the residue was purified on a silica gel column (PE: EA = 5:1 to 1:1) to give the ketone derivative (700 mg, 78%). To a solution of the ketone derivative (700 mg, 1.52 mmol) in MeOH was added $NaBH_4$ in portions. After stirring at the same temperature for 1 h, the mixture was quenched with water. The solvent was removed, and the residue was purified on a silica gel column (PE: EA = 5:1 to 1:1) to give **58-7** (500 mg, 71%).

[0401] To a stirred solution of DAST (1.39 g, 8.68 mmol) in anhydrous toluene (15 mL) was added dropwise a solution of **58-7** (1.0 g, 1.73 mmol) at -78°C. The mixture was stirred at -78°C for 30 min. The solution was warmed to 25°C slowly and stirring continued overnight. The mixture was poured into a saturated Na_2CO_3 solution. The concentrated organic phase was purified on a silica gel column (PE: EA=10:1 to 4:1) to give the fluoride derivative (449 mg, 45%). A mixture of the fluoride derivative (1.20 g, 2.07 mmol) and CAN (3.41 g, 6.23 mmol) in a 3:1 solution of MeCN and water (10 mL) was stirred at 25°C overnight. Brine (10 mL) was added, and the mixture extracted with EA. The combined organic extracts were dried and evaporated under reduced pressure. Purification by chromatography on silica with PE: EA = 10:1 to 2:1 gave **58-8** as a yellow solid (475 mg, 50%).

[0402] To a stirred solution of **58-8** (550 mg, 210 mmol) in anhydrous MeCN (10 mL) were added TPSCl (725 mg, 2.40 mmol), DMAP (293 mg, 2.40 mmol) and TEA (242 mg, 2.40 mmol) at 25°C. The mixture was stirred at 25°C overnight. NH_4OH (25 mL) was added and stirred for 2 h. The solvent was removed, and the residue was purified on a silica gel column (DCM: MeOH = 10:1) to give **58-9** (300 mg). ESI-MS: m/z 472.1 $[M + H]^+$.

[0403] A 1 M boron trichloride solution in CH_2Cl_2 (3.2 mL; 3.2 mmol) was added dropwise to a solution of **58-9** (200 mg, 0.42 mmol) in anhydrous CH_2Cl_2 (10 mL) at -78°C. The mixture was slowly (in 4 h) warmed to -30 °C and stirred at -30 to -20°C for 3 h. Ammonium acetate (1 g) and MeOH (5 mL) were added, and the resulting mixture allowed to warm to ambient temperature. The solvent was removed, and residue purified by RP-HPLC (0-60% B; A: 50 mM aqueous TEAA, B: 50 mM TEAA in MeOH) to yield **58a** (75 mg). ESI-MS: m/z 290.4 $[M - H]^-$.

EXAMPLE 56
Preparation of Compound 59a



[0404] To a solution of **59-1** (100.0 g, 406.5 mmol) in pyridine (750 mL) was added DMTrCl (164.9 g, 487.8 mmol). The solution was stirred at R.T. for 15 h. MeOH (300 mL) was added, and the mixture 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 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 resulting reaction mixture was stirred at R.T. for 14 h. The reaction 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 product (236.4 g, 356.6 mmol) was dissolved in 80% HOAc aqueous solution (500 mL). The mixture was stirred at R.T. for 15 h. The mixture was diluted with EtOAc, 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 **59-2** (131.2 g, 89.6%) as a light yellow solid. ESI-MS: m/z 802 $[M + H]^+$.

[0405] To a solution of **59-2** (131.2 g, 364.0 mmol) in anhydrous CH_3CN (1200 mL) was added IBX (121.2 g, 432.8 mmol) at R.T. The reaction mixture was refluxed for 3 h and then cooled to 0°C. The precipitate was filtered-off, 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, 1.3536 mol) and 2M NaOH aqueous solution (253.8 mL, 507.6 mmol) were added. The mixture was stirred at R.T. 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, 1.354 mol). The mixture was stirred at R.T. for 30 mins and quenched with sat. aqueous 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 **59-3** (51.4 g, 38.9 %) as a white solid.

[0406] To a solution of **59-3** (51.4 g, 131.6 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 R.T. 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%). To the mono-DMTr protected intermediate (57.4 g, 82.8 mmol) in CH_2Cl_2 (400 mL) was added imidazole (8.4 g, 124.2 mmol) and TBDPSCl (34.1 g, 124.2 mmol). The mixture was stirred at R.T. for 14 h. The precipitated was filtered off, and the filtrate was washed with brine and dried over Na_2SO_4. The solvent was removed to give the residue (72.45 g) as a white solid, which was dissolved in 80% HOAc aqueous solution (400 mL). The mixture was stirred at R.T. for 15 h. The mixture was diluted with EtOAc, 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 **59-4** (37.6 g, 84.2%) as a white solid. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.76 (d, J = 4.0 Hz, 1H), 7.70 (dd, J = 1.6 Hz, J = 8.0 Hz, 2H), 7.66-7.64 (m, 2H), 7.48-7.37 (m, 6H), 6.12 (dd, J = 2.8 Hz, J = 16.8 Hz, 1H), 5.22 (d, J = 8.0 Hz, 1H).5.20-5.05 (m, 1H), 4.74 (dd, J = 5.6 Hz, J = 17.6 Hz, 1H), 4.16 (d, J = 12.0 Hz, 1H), 3.87-3.80 (m, 2H), 3.56 (d, J = 12.0 Hz, 1H), 1.16 (s, 9H), 0.92 (s, 9H), 0.14 (s, 6H).

[0407] To a solution of **59-4** (3.0 g, 4.78 mmol) in anhydrous DCM (100 mL) was added Dess-Martin periodinane (10.4 g, 23.9 mmol) at 0°C under nitrogen. The reaction mixture was stirred at R.T. for 5 h. The mixture was poured into $NaHCO_3$ and $Na_2S_2O_3$ (1:1) aqueous solution. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to give a residue. The residue was purified on a silica gel column (20% EtOAc in PE) to give the intermediate (2.5 g, 83.1 %) as a white solid.

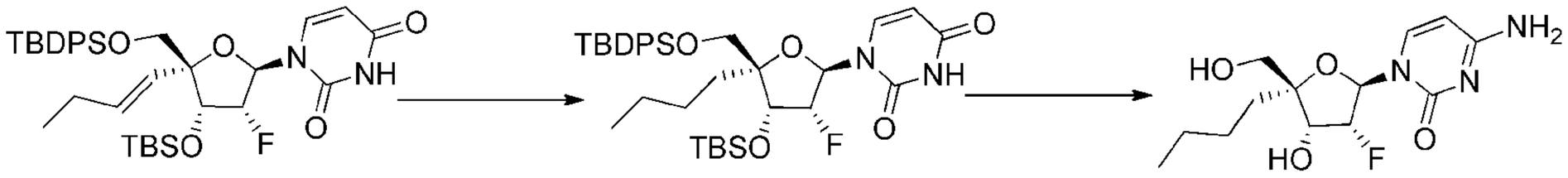
[0408] To a mixture of bromotriphenyl(propyl)phosphorane (6.45 g, 16.8 mmol) in anhydrous THF (3 mL) was added t-BuOK (16.8 mL, 16.8 mmol) at 0°C under nitrogen. The reaction mixture was stirred at 0°C for 50 mins. A solution of the above intermediate (1.5 g, 2.4 mmol) in anhydrous THF (3 mL) was added dropwise at 0°C under nitrogen. The reaction mixture was stirred at R.T. for 3 h. The reaction was quenched by NH_4Cl aqueous solution and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to give a residue. The residue was purified on a silica gel column (20% EtOAc in PE) to give **59-5** (1.3 g, 83%) as a white solid.

[0409] To a solution of **59-5** (300 mg, 0.45 mmol) in anhydrous CH_3CN (2 mL) were added TPSCl (341 mg, 1.13 mmol), DMAP (138 mg, 1.13 mmol) and NEt_3 (571 mg, 5.65 mmol) at R.T. The reaction mixture was stirred at R.T. for 2 h. NH_4OH (1 mL) was added, and the reaction mixture was stirred for 1 h. The mixture was diluted with EA and washed with water. The organic layer was dried and concentrated to give a residue. The residue was purified on a silica gel column (2% MeOH in DCM) to give the cytidine derivative (285 mg, 95.0%) as a white solid.

[0410] To a solution of the cytidine derivative (280 mg, 0.43 mmol) in MeOH (10 mL) was added NH_4F (1.0 g) at R.T. The reaction 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 **59a** (81 mg, 61%) as a white solid. ESI-TOF-MS: m/z 300.1 $[M+H]^+$.

EXAMPLE 57
Preparation of Compound 60a

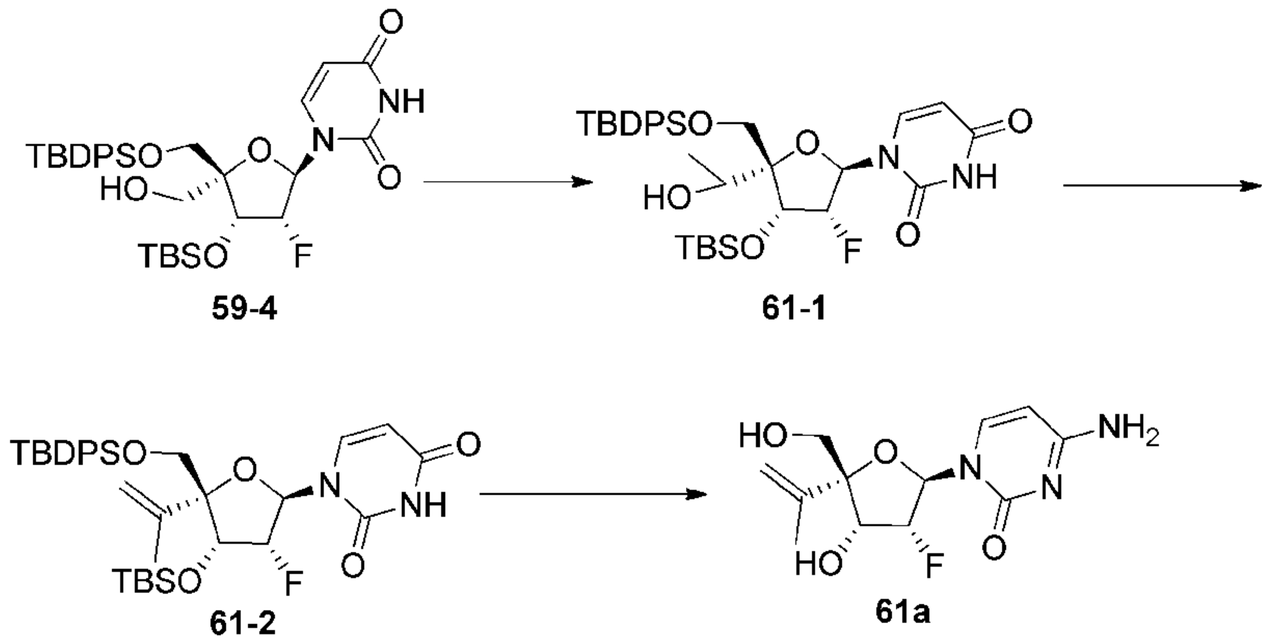


[0411] To a solution of **59-5** (450 mg, 0.69 mmol) in MeOH (10 mL) was added Pd/C (200 mg) at R.T. The reaction mixture was stirred R.T. for 1 h under H_2 (balloon). The mixture was filtered, and the filtrate was concentrated to give crude **60-1** (440 mg, 97.1%) as a white solid.

[0412] To a solution of **60-1** (440 mg, 0.67 mmol) in anhydrous CH_3CN (2 mL) were added TPSCl (510 mg, 1.68 mmol), DMAP (205 mg, 1.68 mmol) and NEt_3 (338 mg, 3.35 mmol) at R.T. The reaction mixture was stirred at R.T. for 2 h. NH_4OH (1 mL) was added, and the reaction was stirred for 1 h. The mixture was diluted with EA and washed with water. The solvent was removed. The crude product was purified on a silica gel column (2% MeOH in DCM) to give the cytidine derivative (205 mg, 46.5%) as a white solid.

[0413] To a solution of the cytidine derivative (205 mg, 0.31 mmol) in MeOH (6 mL) was added NH_4F (0.6 g) at R.T. The reaction mixture was refluxed overnight. After cooling to R.T., the mixture was filtered. The filtrate was concentrated, and the residue was purified on a silica gel column (10% MeOH in DCM) to give **60a** (59 mg, 62.8 %) as a white solid. ESI-MS: m/z 301.8 $[M+H]^+$.

EXAMPLE 58
Preparation of Compound 61a



[0414] To a solution of **59-4** (1.5 g, 2.39 mmol) in anhydrous DCM (100 mL) was added Dess-Martin periodinane (5.2 g, 11.95 mmol) at 0°C under nitrogen. The reaction mixture was stirred at R.T. for 5 h. The mixture was poured into $NaHCO_3$ and $Na_2S_2O_3$ solution and washed with brine. The organic layer was dried with anhydrous Na_2SO_4, and concentrated to give the crude intermediate (1.5 g) as a white solid.

[0415] To a solution of the crude intermediate (1.5 g, 2.39 mmol) in THF (12 mL) was added methylmagnesium bromide (2.4 mL, 7.2 mmol) dropwise at 0°C. The resulting mixture was stirred at 0°C for 2 h. After the starting material was consumed, the reaction was quenched with saturated NH_4Cl. The reaction mixture was extracted with DCM. The organic layer was washed with brine, dried and concentrated to give crude **61-1** (1.5 g).

[0416] To a solution of **61-1** (1.5 g, 2.39 mmol) in anhydrous DCM (50 mL) was added Dess-Martin periodinane (4.5 g, 10.6 mmol). The reaction mixture was stirred at R.T. overnight. The mixture was poured into $NaHCO_3$ and $Na_2S_2O_3$ aqueous solution. The organic layer was separated, washed with brine, dried and concentrated to give a residue. The residue was purified on a silica gel column (10% EtOAc in PE) to give the intermediate (907 mg, 58.6%) as a white solid.

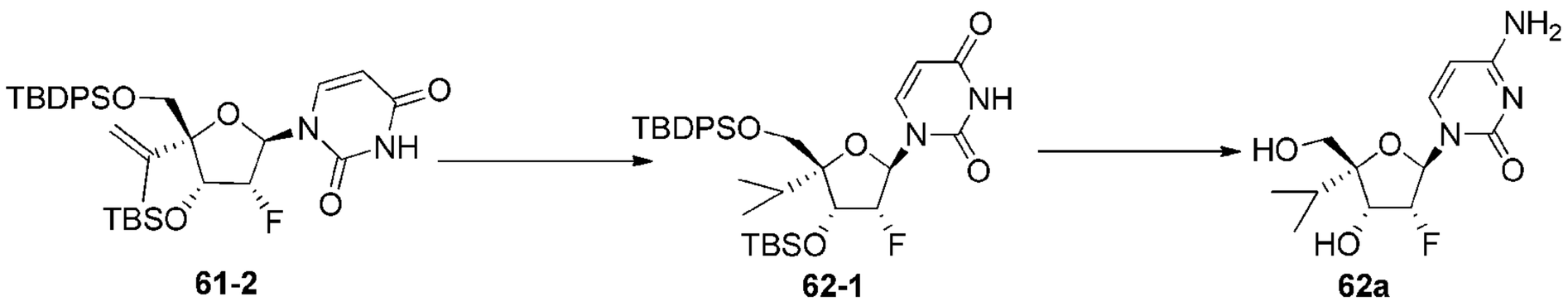
[0417] To a mixture of bromo(methyl)triphenylphosphorane (5.0 g, 14 mmol) in anhydrous THF (8 mL) was added t-BuOK (12.6 mL, 12.6 mmol) at 0°C under nitrogen. The mixture was stirred at R.T. for 50 mins. A solution of the above intermediate (900 mg, 1.4 mmol) in anhydrous THF (4 mL) was added dropwise at 0°C under nitrogen. The reaction mixture was stirred at R.T. for 3 h. The reaction mixture was quenched with NH_4Cl aqueous

solution and extracted with DCM. The organic layer was separated, washed with brine, dried and concentrated to give a residue. The residue was purified on a silica gel column (5% EtOAc in PE) to give **61-2** (700 mg, 78.0%) as a white solid.

[0418] To a solution of **61-2** (298 mg, 0.46 mmol) in anhydrous CH_3CN (5.5 mL) were added TPSCl (346.5 mg, 1.14 mmol), DMAP (139.6 mg, 1.14 mmol) and NEt_3 (115.6 mg, 1.14 mmol) at R.T. The reaction mixture was stirred at R.T. for 2 h. NH_4OH (1 mL) was added, and the mixture was stirred for another 1 h. The mixture was diluted with DCM and washed with water. The organic layer was separated, washed with brine, dried and concentrated to give a residue. The residue was purified on a silica gel column (2% MeOH in DCM) to give the cytidine derivative (250 mg, 85.0%) as a white solid.

[0419] To a solution of the cytidine derivative (250 mg, 0.39 mmol) in MeOH (10 mL) was added NH_4F (1.0 g) at R.T. The reaction 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 **61a** (55 mg, 49%) as a white solid. ESI-MS: m/z 285.9 $[M+H]^+$.

EXAMPLE 59
Preparation of Compound 62a



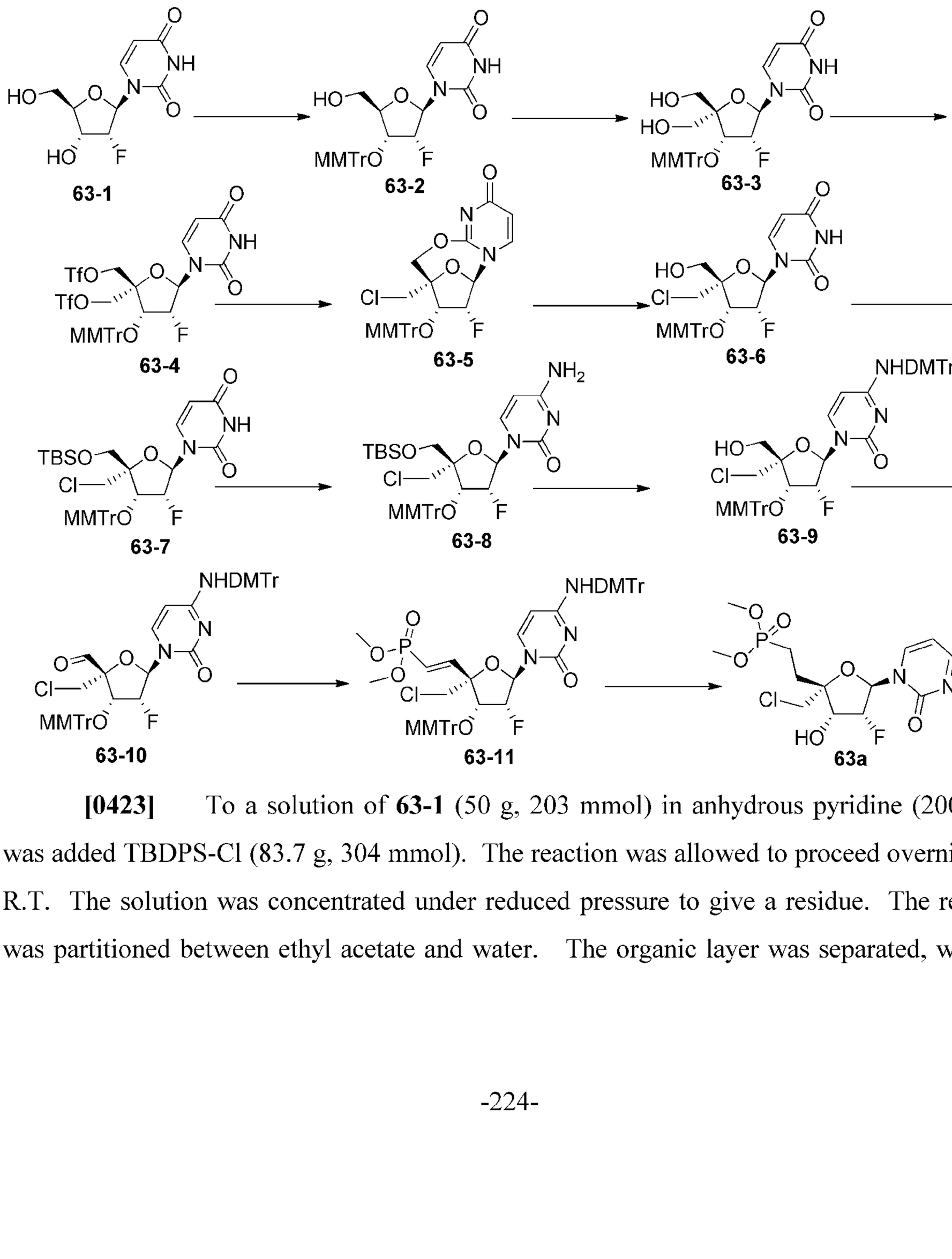
[0420] To a solution of **61-2** (400 mg, 0.63 mmol) in MeOH (10 mL) was added Pd/C (400 mg) at R.T. The reaction was stirred at R.T. for 5 h under H_2 (balloon). The mixture was filtered, and the filtrate was concentrated to give crude **62-1** (350 mg, 87%) as a white solid.

[0421] To a solution of **62-1** (350 mg, 0.55 mmol) in anhydrous CH_3CN (6 mL) were added TPSCl (414 mg, 1.4 mmol), DMAP (166.8 mg, 1.4 mmol) and NEt_3 (138.1 mg, 1.4 mmol) at R.T. The reaction mixture was stirred at R.T. for 2 h. NH_4OH (1 mL) was added, and the reaction was stirred for another 1 h. The mixture was diluted with EA and washed with water. The organic layer was separated, dried and concentrated to give a

residue. The residue was purified on a silica gel column (2% MeOH in DCM) to give the cytidine derivative (300 mg, 85%) as a white solid.

[0422] To a solution of the cytidine derivative (300 mg, 0.47mmol) in MeOH (10 mL) was added NH_4F (1.5g) at R.T. The reaction mixture was refluxed overnight. After cooling to R.T., the mixture was filtered. The filtrate was concentrated. The crude product was purified on a silica gel column (10% MeOH in DCM) to give **62a** (83 mg, 61%) as a white solid. ESI-MS: m/z 287.8 $[M+H]^+$.

EXAMPLE 60
Preparation of Compound 63a



[0423] To a solution of **63-1** (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 R.T. The solution was concentrated under reduced pressure to give a residue. The residue 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).

[0424] 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 R.T. After most of silver nitrate was dissolved (~15 min), the mixture was cooled to 0°C. Monomethoxytrityl chloride (239.3 g, 776.8 mmol) was added as a single portion, and the mixture was stirred overnight at R.T. The mixture was filtered through Celite, and the filtrate was diluted with MTBE. 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.

[0425] The 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 hours at R.T., and the solvent was removed under reduced pressure. The residue was taken into ethyl acetate, and the solution was washed with saturated sodium bicarbonate and brine. After drying over magnesium sulfate, the solvent was removed in vacuum. The residue was purified by column chromatography (PE: EA= 5:1, 1:1) to give **63-2** (91 g, 86.4%) as a white foam.

[0426] To a solution of **63-2** (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 R.T. The reaction was quenched with $Na_2S_2O_3$ solution (4%) and sodium bicarbonate aqueous solution (4%) (the solution was adjusted to pH 6, ~150 mL). The mixture was stirred for 15 min. 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 R.T. overnight. After stirring for 0.5 h at R.T., the excess of aqueous sodium hydroxide was neutralized with saturated with NH_4Cl (~150 mL). The mixture was concentrated under reduced pressure. 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 (MeOH: DCM= 100:1-50:1) to give **63-3** (9.2 g, 83.6%) as a white foam.

[0427] Compound **63-3** (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 -35°C. Triflic anhydride (24.9 g, 88.1 mmol) was added dropwise over 10 mins. The reaction was stirring for 40 min at -35°C. When TLC (PE: EA= 2:1 and DCM: MeOH= 15:1) showed that the reaction was complete, the reaction was quenched with water (50 mL) at 0°C. The mixture was stirred 30 mins, 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. The residue was purified by column chromatography (PE: EA= 100:1-1:1) to give **63-4** (30.0 g, 88.3%) as a brown foam.

[0428] Compound **63-4** (30 g, 36.9 mmol) was co-evaporated twice with toluene. The resulting bis-triflate was dissolved in anhydrous DMF (150 mL), cooled to 0°C and treated with sodium hydride (60% in mineral oil; 1.5 g, 40.6 mmol, 1.1 eq). The reaction mixture was stirred at R.T. for 1 h until TLC (DCM: MeOH = 15:1) showed the disappearance of the bis-triflate and formation of the 2,5'-anhydro intermediate. Lithium chloride (4.6 g, 110.7 mmol, 3 eq) was added, and the stirring was continued for 2 h. The mixture was taken into 100 mL of half saturated ammonium chloride and ethyl acetate. The organic phase was separated, washed with diluted brine and concentrated under reduced pressure to give **63-5**.

[0429] **63-5** was dissolved in THF (150 mL), and the solution was treated with 1N aqueous sodium hydroxide (~41 mL, 40.1 mmol, 1.1 eq). The mixture was stirred at R.T. for 1 h. The reaction was monitored by LCMS. The reaction was diluted with half saturated sodium bicarbonate (~60 mL) and extracted with ethyl acetate. The organic phase was dried (magnesium sulfate) and concentrated under reduced pressure. Purification of the residue by column chromatography (DCM: MeOH= 300:1-60:1) gave **63-6** (18.3 g, 87.6%) as a yellow foam.

[0430] To a solution of **63-6** (18.3 g, 32.33 mmol) in anhydrous DCM (150 mL) was added TBS-Cl (17.7 g, 64.6 mmol) and imidazole (6.6 g, 97 mmol). The reaction was allowed to proceed overnight at R.T. The reaction was diluted with water and extracted with DCM. The organic layer was separated, washed with brine, dried over Na_2SO_4 and concentrated. Purification of the residue by column chromatography (DCM: MeOH=300:1~80:1) gave **63-7** (18.4 g, 83.7%) as a white foam.

[0431] A solution of **63-7** (18.4 g, 27.1 mmol), DMAP (6.6 g, 54.0 mmol) and TEA (5.4 g,54.0 mmol) in MeCN (450 mL) was treated with 2,4,6-triispropylbenzenesulfonyl chloride (TPSCl, 16.3 g, 54.0 mmol). The mixture was stirred at R.T. for 3 h. $NH_3\,H_2O$ (70 mL) was added, and the mixture was stirred for 2 h. The solution was evaporated under reduced pressure, and the residue was purified on a silica gel column (DCM: MeOH= 100:1 to 15:1) to give **63-8** (18.0 g) as a light yellow solid.

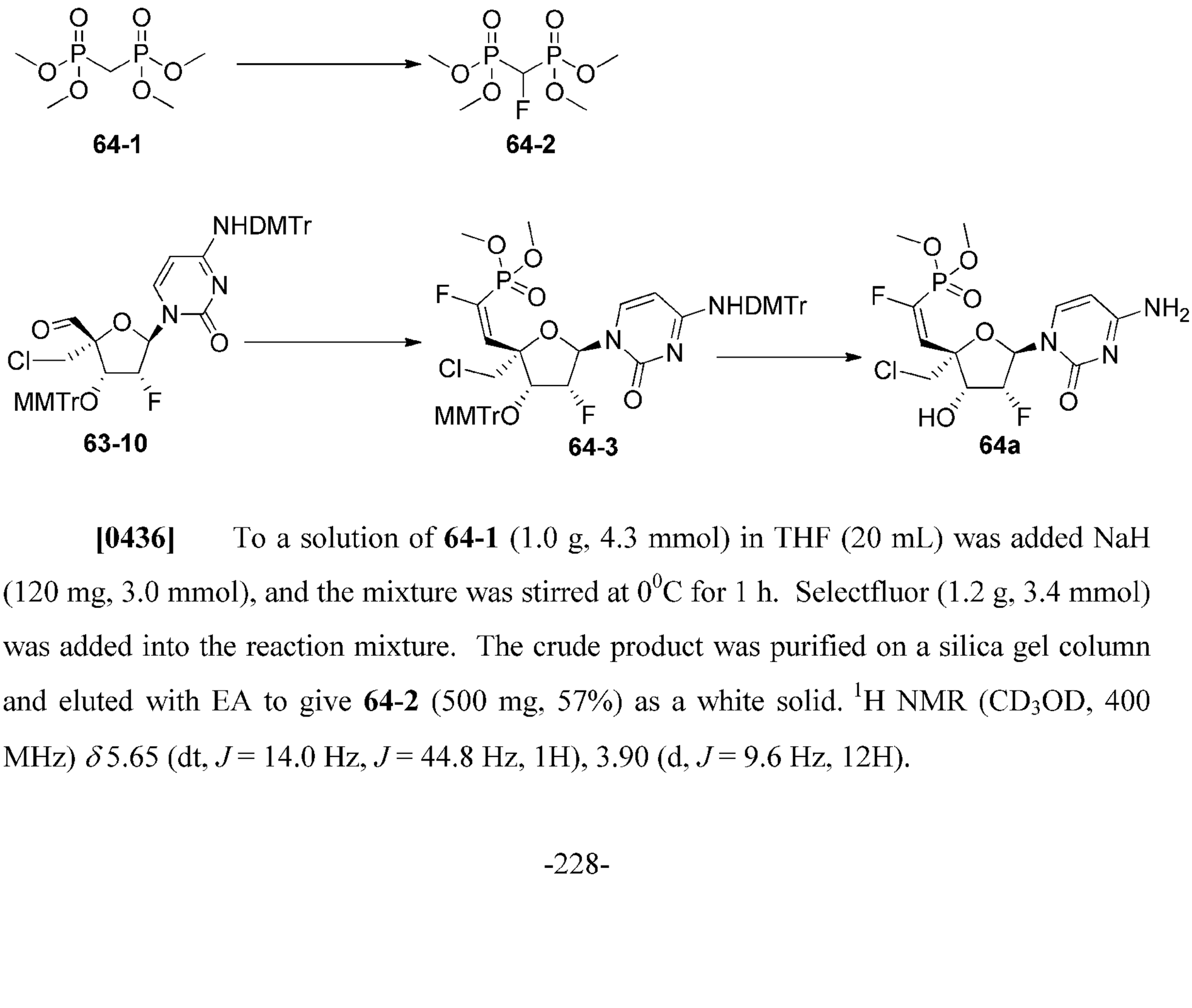
[0432] To a solution of **63-8** (18.0 g, 26.5 mmol) in anhydrous DCM (150 mL) was added collidine (8.1 g, 66.3 mmol, 2.5 eq), silver nitrate (4.5 g, 26.5 mmol, 1.0 eq) and DMTrCl (13.4 g, 39.7 mmol, 1.5 eq). The reaction was allowed to proceed overnight at R.T. The mixture was filtered. The filtrate was washed with brine and extracted with DCM. The organic layer was separated, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (PE: EA= 60:1~3:1) as a yellow foam. The foam was dissolved in THF (150 mL), and TBAF (10.4 g, 39.7 mmol, 1.5 eq) was added. The reaction was allowed to proceed overnight at R.T. The mixture was concentrated, washed with brine and extracted with EA. The organic layer was separated, dried over Na_2SO_4 and concentrated. Purification of the residue by column chromatography (PE: EA =60:1~EA) gave **63-9** (21.3 g, 92.4%) as a yellow foam.

[0433] To a solution of **63-9** (2.0 g, 2.3 mmol) in anhydrous DCM (20 mL) was added Dess-Martin periodinane (1.95 g, 4.6 mmol) at 0°C under nitrogen. The reaction was stirred at R.T. for 5 h. The mixture was diluted with EtOAc (100 mL) and washed with a mixture of saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$. The crude product was purified by column chromatography on silica gel (PE: EtOAc = 2: 1) to give **63-10** (1.8 g, 90%) as a yellow solid.

[0434] To a solution of tetramethyl methylenediphosphonate (390 mg, 1.68 mmol) in anhydrous THF (10 mL) was added NaH (84 mg, 2.1 mmol) at 0°C under nitrogen. The reaction was stirred at 0°C for 30 min. A solution of **63-10** (1.2 g, 1.4 mmol) in anhydrous THF (10 mL) was added dropwise at 0°C. The reaction mixture was stirred at R.T. for 1 h. The reaction was quenched by saturated aqueous NH_4Cl, and the crude product was purified by column chromatography on silica gel (DCM: MeOH = 150: 1) to give **63-11** (1.2 g, 88.2%) as a yellow solid. ESI-MS: m/z 971.59 $[M+H]^+$.

[0435] A solution of **63-11** (1.0 g, 1.03 mmol) in 80% HOAc (46 mL) was stirred at 80-90°C for 2 h. The solvent was removed, and the crude product was purified by column chromatography on silica gel (DCM: MeOH = 20: 1) to give an intermediate (337 mg, 82.3%) as a white solid. The intermediate was dissolved in MeOH and wet Pd/C (300 mg) was added. The reaction mixture was stirred under H_2 (1 atm) for 1 h and then filtered. The solvent was removed, and the residue was purified on a silica gel column (DCM: MeOH= 20:1) to give **63a** (192 mg, 63.9%) as a white solid. ESI-MS: m/z 400.0 $[M+H]^+$.

EXAMPLE 61
Preparation of Compound 64a

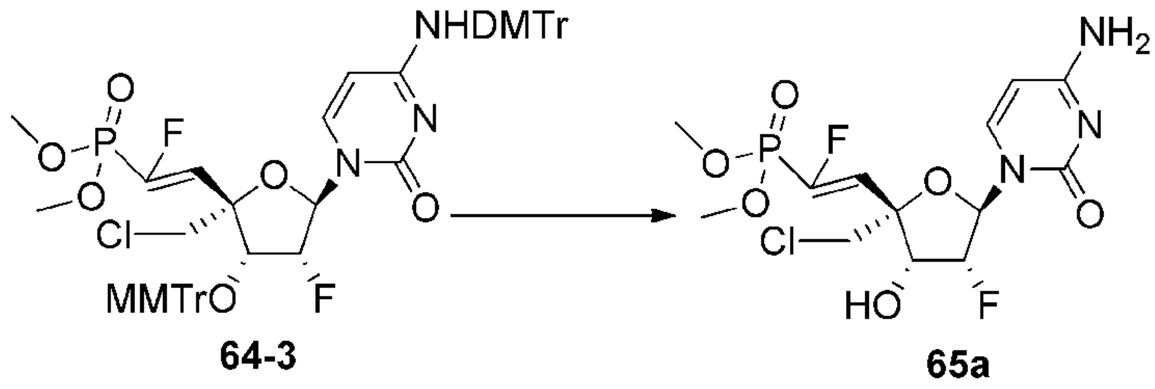


[0436] To a solution of **64-1** (1.0 g, 4.3 mmol) in THF (20 mL) was added NaH (120 mg, 3.0 mmol), and the mixture was stirred at 0°C for 1 h. Selectfluor (1.2 g, 3.4 mmol) was added into the reaction mixture. The crude product was purified on a silica gel column and eluted with EA to give **64-2** (500 mg, 57%) as a white solid. ^1H NMR (CD_3OD, 400 MHz) δ 5.65 (dt, J = 14.0 Hz, J = 44.8 Hz, 1H), 3.90 (d, J = 9.6 Hz, 12H).

[0437] To a solution of **64-2** (390 mg, 1.68 mmol) in anhydrous THF (10 mL) was added NaH (84 mg, 2.1 mmol) at 0^0C under nitrogen. The mixture was stirred at 0^0C for 30 mins. A solution of **63-10** (1.2 g, 1.4 mmol) in anhydrous THF (10 mL) was added dropwise at 0^0C. The mixture was stirred at R.T. for 1 h. The reaction was quenched with saturated aqueous NH_4Cl and concentrated to give a residue. The residue was purified on a silica gel column (DCM: MeOH= 150: 1) to give crude **64-3** (1.2 g, 88.2%) as a yellow solid.

[0438] A solution of crude **64-3** (230 mg, 0.23 mmol) in 80% HOAc (3 mL) was stirred at 80-90^0C for 2 h. The crude product was purified on a silica gel column (eluted with DCM: MeOH= 20:1) to give **64a** (54 mg, 53.7%) as a white solid. ESI-MS: m/z 416.3 $[M+H]^+$.

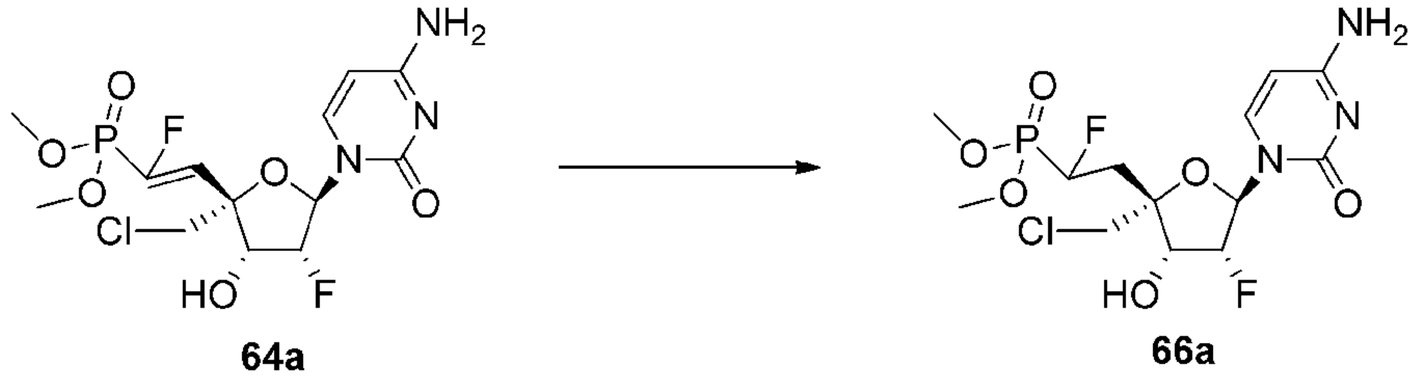
EXAMPLE 62
Preparation of Compound 65a



64-3 **65a**

[0439] A solution of crude **64-3** (230 mg, 0.23 mmol) in 80% HOAc (3 mL) was stirred at 80-90^0C for 2 h. The crude product was purified on a silica gel column (eluted with DCM: MeOH= 20:1) to give **65a** (52 mg, 33.7%) as a white solid. ^{1}H NMR (DMSO, 400 MHz) δ 7.59 (d, J = 7.2 Hz, 1H), 7.32 (s, 2H), 6.25-6.28 (m, 1H), 5.86-6.02 (m, 2H), 5.73 (s, 1H), 5.31 (d, J = 14.0 Hz, 1H), 4.72 (d, J = 16.4 Hz, 1H), 3.90 (d, J = 10.0 Hz, 1H), 3.73 (2d, J = 11.6 Hz, 6H).

EXAMPLE 63
Preparation of Compound 66a

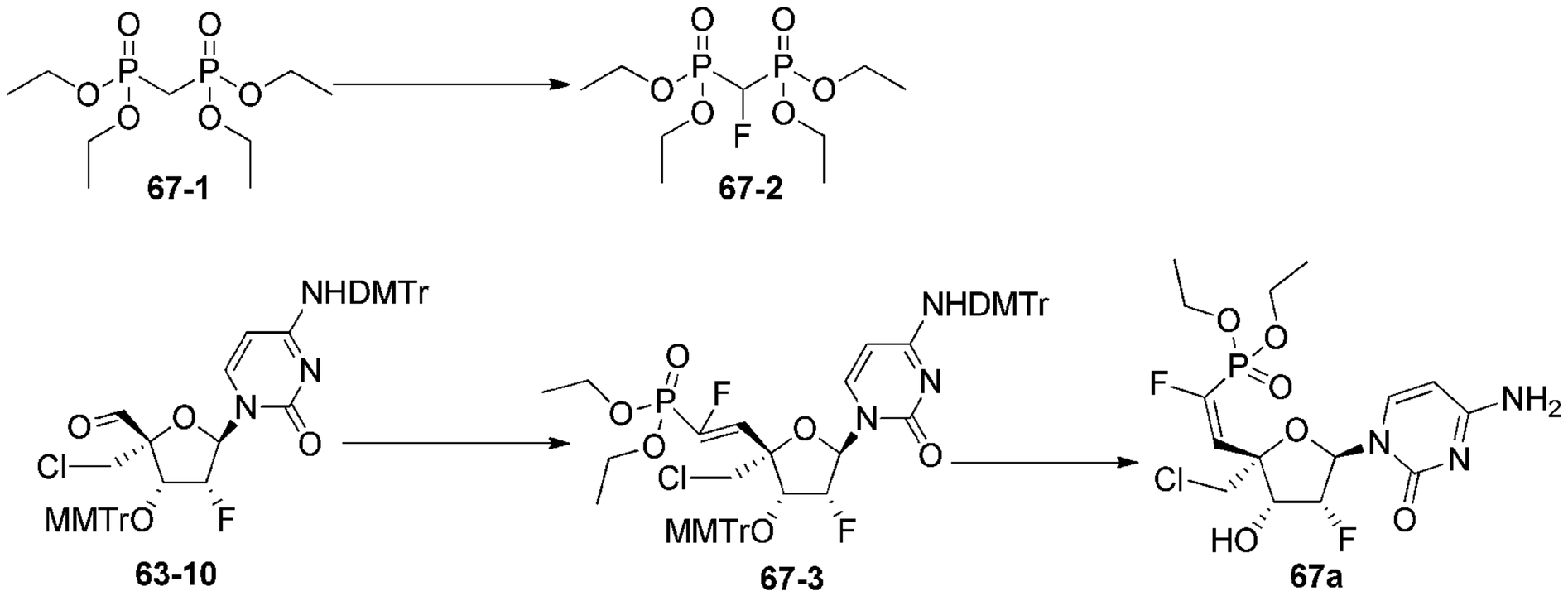


64a **66a**

[0440] A solution of **64a** (130 mg, 0.3 mmol) in EA:MeOH (5:1, 20 mL) was stirred under H_2 (15 Psi) at R.T. for 2 h. The mixture was filtered and concentrated to give a residue. The residue was purified on a silica gel column (DCM: MeOH= 20: 1) to give **66a** (70 mg, 54%) as a white solid. ESI-MS: m/z 418.3 $[M+H]^+$.

EXAMPLE 64

Preparation of Compound 67a



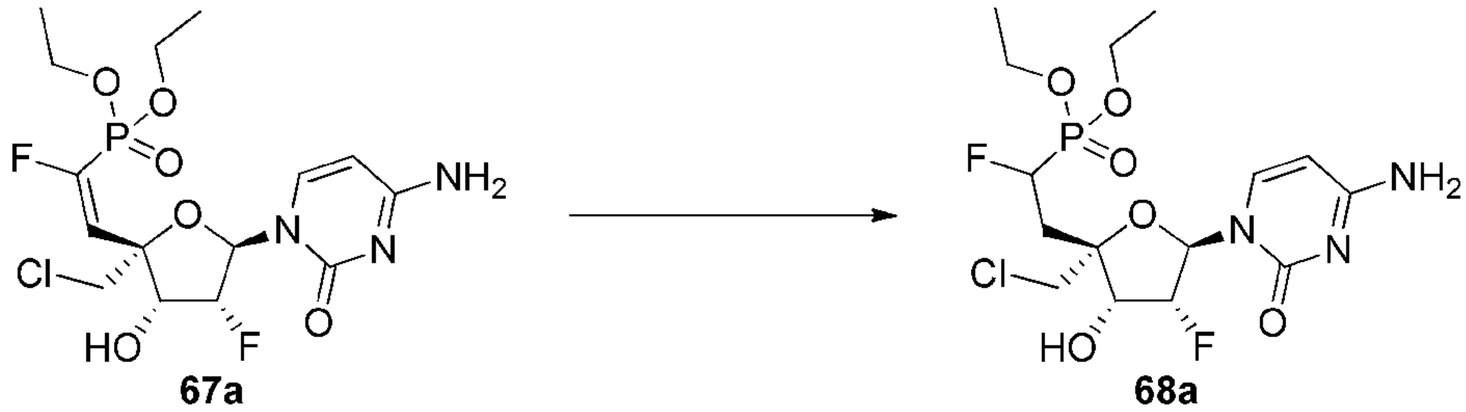
[0441] To a solution of **67-1** (2.0 g, 6.9 mmol) in THF (20 mL) was added NaH (110 mg, 2.8 mmol), and the mixture was stirred at 0^0C for 1 h. Selectfluor (5.0 g, 13.6 mmol) was added into the mixture. The reaction was quenched with saturated NH_4Cl and extracted with EA. The organic layer was separated, dried and concentrated to give the crude product. The crude product was purified on a silica gel column (eluted with EA) to give **67-2** (600 mg, 28.3%) as a white solid. ^{1}H NMR (CD_3OD, 400 MHz) δ 5.65 (dt, J = 14.0 Hz, J = 44.8 Hz, 1H), 4.24-4.46 (m, 8H), 1.35-1.39 (m, 12H).

[0442] To a solution of **67-2** (2.14 g, 7.0 mmol) in anhydrous THF (10 mL) was added NaH (84 mg, 2.1 mmol) at 0^0C under nitrogen. The reaction mixture was stirred at 0^0C for 30 mins. A solution of **63-10** (3.0 g, 3.5 mmol) in anhydrous THF (10 mL) was added in dropwise at 0^0C. The reaction mixture was stirred at R.T. for 1 h. The reaction was quenched with saturated aqueous NH_4Cl and concentrated to give a residue. The residue was purified on a silica gel column (DCM: MeOH=150: 1) to give crude **67-3** (2.9 g, 79.5%) as a yellow solid.

[0443] A solution of crude **67-3** (1.0 g, 0.98 mmol) in 80% HOAc (25 mL) was stirred at 80-90^0C for 2 h. The crude product was purified on a silica gel column (eluted with

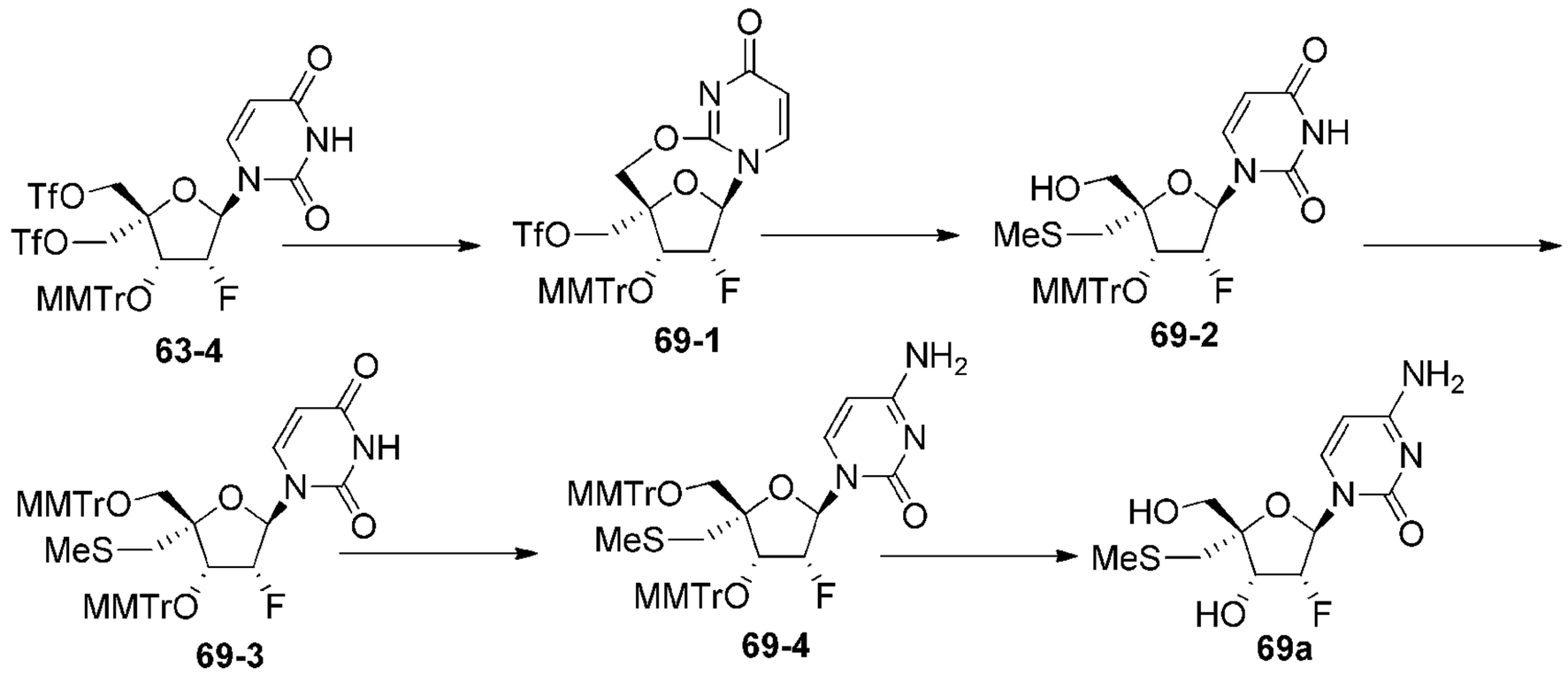
DCM: MeOH= 20:1) to give **67a** (133 mg, 32.5%) as a white solid. ESI-MS: m/z 466.1 $[M+Na]^+$.

EXAMPLE 65
Preparation of Compound 68a



[0444] To a solution of **67a** (130 mg, 0.29 mmol) in MeOH (20 mL) was stirred under H_2 (15 Psi) at R.T. for 2 h. The mixture was filtered and concentrated to give a residue. The residue was purified on a silica gel column (eluted with DCM: MeOH= 20:1) to give a mixture of diastereomers of **68a** (90 mg, 69.2%) as a white solid. ESI-MS: m/z 446.1 $[M+H]^+$

EXAMPLE 66
Preparation of Compound 69a



[0445] Compound **63-4** (3.0 g, 3.69 mmol) was co-evaporated twice with toluene. The resulting bis-triflate was dissolved in anhydrous DMF (20 mL). The solution was cooled to 0°C and treated with sodium hydride (60% in mineral oil; 177 mg, 0.43 mmol). The reaction was stirred at R.T. for 1 h (TLC (PE: EA =2:1) showed complete disappearance of the bis-triflate and clean formation of the 2',5'-anhydro intermediate). The mixture was used for the next step without any further workup

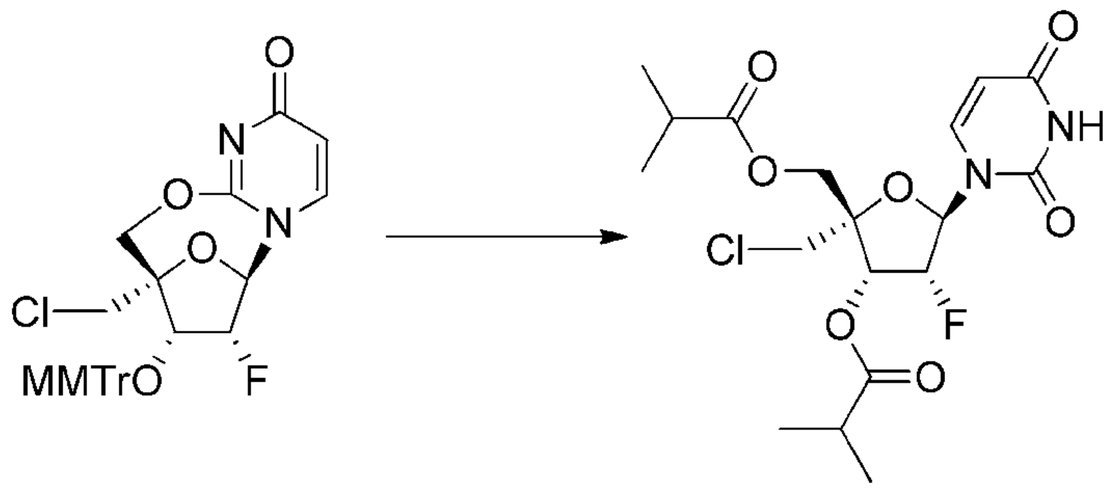
[0446] To the above stirred mixture was added NaSMe (9.0 g, 0.13 mmol) and 15-Crown-5 (4.87 g, 22.14 mmol) at 0°C under nitrogen. The solution was stirred at R.T. for 2 h (TLC (PE: EA= 1:1) showed the reaction was complete). The reaction was quenched with water. The mixture was extracted by EtOAc, washed with brine, and dried over $MgSO_4$. The mixture was filtered and concentrated to give a residue. The residue was purified on a silica gel column (PE: EA= 5:2) to give **69-2** (1.23 g, 59.0%) as a white foam.

[0447] To a stirred solution of **69-2** (1.34 g, 2.32 mmol) in anhydrous DCM (10 mL) was added MMTrCl (1.32 g, 4.64 mmol), AgNO3 (1.17 g, 6.96 mmol) and Collidine (1.41 g, 11.6 mmol) at R.T. under nitrogen. The reaction mixture was stirred at R.T. for 1 h (TLC (PE: EA= 1:1) showed the reaction was complete). The mixture was filtered and concentrated. The residue was purified on a silica gel column (PE: EA= 8:1) to give **69-3** (1.31g, 66.5%) as a white foam.

[0448] To a solution of **69-3** (900 mg, 1.06 mmol) in anhydrous MeCN (9 mL) was added DMAP (259 mg, 2.12 mmol), TEA (214 mg, 2.12 mmol) and TPSCl (640 mg, 2.12 mmol) at R.T. under nitrogen. The reaction mixture was stirred at R.T. for 2 h (TLC (DCM: MeOH=10:1) showed the reaction was complete). NH_4OH (10 mL) was added, and the reaction mixture was stirred for another 1 h (LCMS showed the reaction was complete). The solution was diluted with water, extracted with EtOAc. The organic layer was washed with 1M HCl, saturated $NaHCO_3$ and brine, and dried over $MgSO_4$. The mixture was filtered and concentrated to give a residue. The residue was purified on a silica gel column (DCM: MeOH= 70:1) to give **69-4** (870 mg, 68.5%) as a white solid.

[0449] Compound **69-4** (800 mg, 0.95 mmol) was dissolved in 80% HOAc aq. (50 mL). The reaction mixture was heated to 75°C overnight (LCMS showed the reaction was complete). The reaction mixture was concentrated and purified on a silica gel column (DCM: MeOH= 15:1) to give **69a** (180 mg, 62.5%) as a white solid. ESI-MS: m/z 305.8 $[M+H]^+$

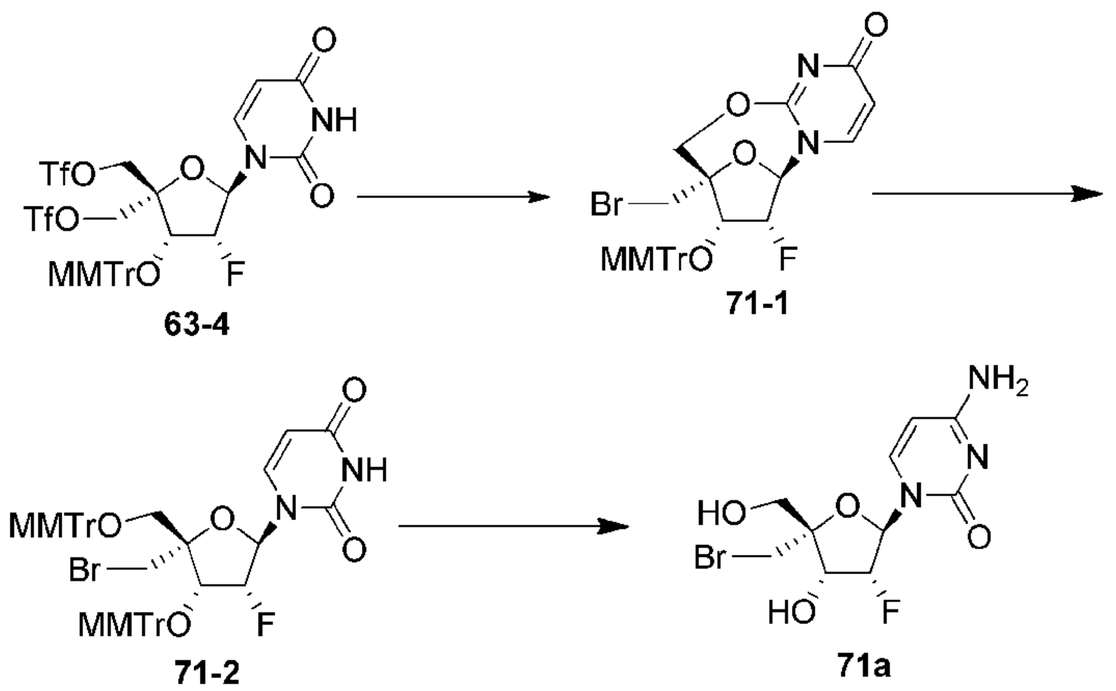
EXAMPLE 67
Preparation of Compound 70a



63-5 **70a**

[0450] To a solution of **63-5** (100 g, 182.5 mmol) in MeCN (2 L) was added 6N HCl aq. (15 g). The mixture was stirred at 40°C for 7 h, and then neutralized to pH = 5~6 with a 25% ammonia solution (~8 g). The mixture was filtered to give a solid, which was further washed by PE to give an intermediate (32.2 g, 60%) as a white solid. To a mixture of the intermediate (32.2 g, 109.5 mmol), TEA (22.1 g, 219 mmol) and DMAP (1.34 g, 11 mmol) in MeCN (1 L) was added with isobutyric anhydrous (69.2 g, 438 mmol). The mixture was stirred at R.T. for 3 h. The reaction was quenched by the addition of water (200 mL) and extracted with 2-Me-THF (800 mL). The organic layer was washed with saturated $NaHCO_3$ and brine. The organic layer was dried and concentrated to give a residue, which was purified by a silica gel column (10% toluene in heptane) to give **70a** (42.3 g, 89%) as a white solid. ^1H NMR (CD_3OD, 400 MHz) δ 7.65 (d, J = 8.0 Hz, 1H), 5.95 (dd, J = 2.8, 20.4 Hz, 1H), 5.55-5.74 (m, 3H), 4.33-4.41 (m, 2H), 3.88 (s, 2H), 2.57-2.72 (m, 2H), 1.14-1.22 (m, 12H).

EXAMPLE 68
Preparation of Compound 71a



[0451] To a solution of **63-4** (4.2 g, 5.17 mmol) in DMF (50 mL) at 0°C was added NaH (227 mg of 60% dispersion, 5.7 mmol). The mixture was stirred at 0°C for 2 h ,and then LiBr (1.34 g, 15.5 mmol) was added. The mixture was stirred overnight at R.T., diluted with EA (150 mL) and washed successively with water and brine. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified on a silica gel column eluted with 10% EA in PE to give **71-1** as a yellow solid (2 g, 66%)

[0452] To a solution of **71-1** (1.74 g, 2.9 mmol) in THF (20 mL) at 0°C was added 1N NaOH (3.2 mL, 3.2 mmol), and the mixture was stirred at 0°C for 2 h. The mixture was partitioned between EA (100 mL) and water (20 mL), and the organic layer was dried over Na_2SO_4 and evaporated to dryness. The residue was purified on a silica gel column eluted with 20% EA in PE to give the 5'-*OH* derivative as a yellow solid (1.6 g, 90%).

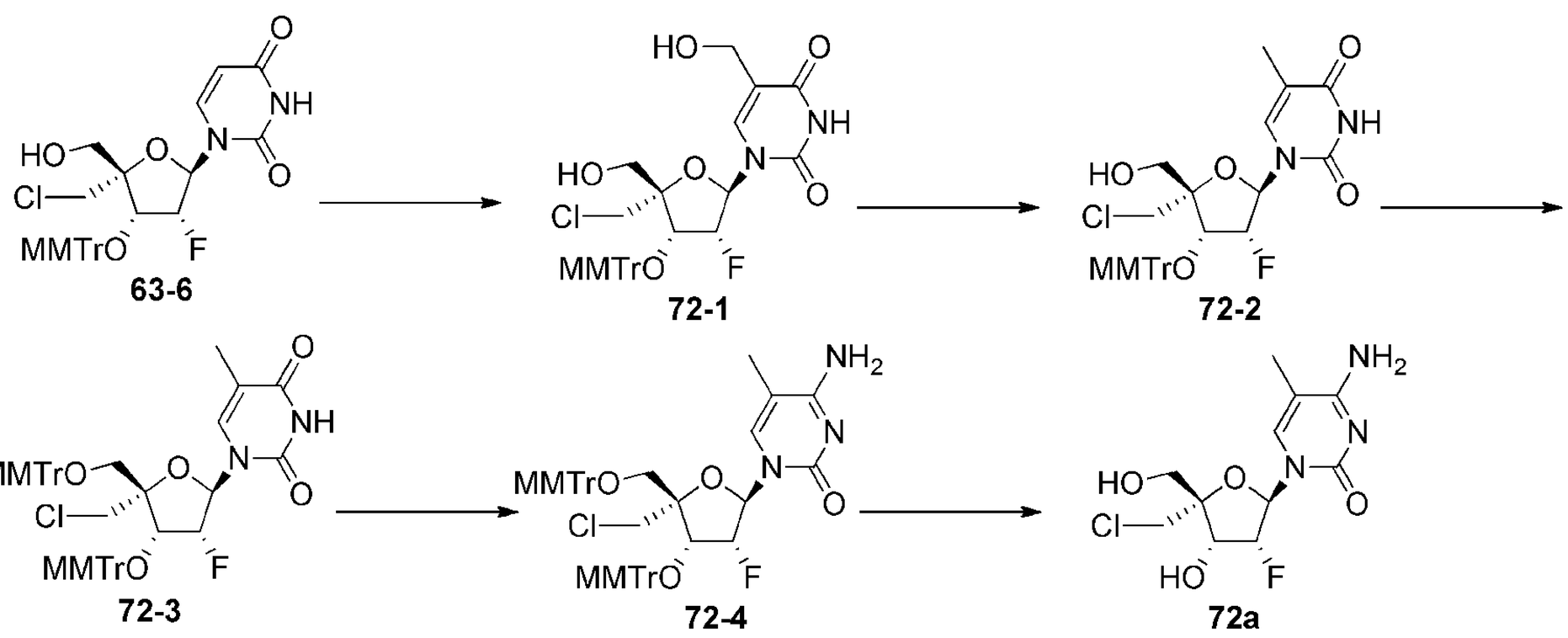
[0453] To a solution of 5'-*OH* derivative (2.3 g, 3.76 mmol) in anhydrous DCM (20 mL) were added collidine (0.8 g, 6.7 mol) and MMTrCl (2.7 g, 8.7 mmol). The reaction mixture was stirred at R.T. overnight. The mixture was filtered and washed successively with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated. The residue was purified on a silica gel column eluted with 10% EA in PE to give **71-2** as a yellow solid (2.4 g, 73%).

[0454] To a solution of **71-2** (2.4 g, 2.72 mmol) in anhydrous CH_3CN (30 mL) were added TPSCl (1.65 g, 5.44 mmol), DMAP (0.663 g, 5.44 mmol) and NEt_3 (1.5 mL) at R.T. The mixture was stirred at R.T. for 3 h, and 28% aqueous ammonia (30 mL) was added.

The mixture was stirred for 1 h. The mixture was diluted with EA (150 mL) and washed successively with water, saturated aqueous $NaHCO_3$ and brine. The solvent was removed, and the residue was purified on a silica gel column eluted with 2% MeOH in DCM to give a cytidine derivative as a yellow solid (1.5 g, 62%).

[0455] The cytidine derivative (1.35 g, 1.5 mmol) was dissolved in 80% AcOH (40 mL), and the mixture was stirred at 60°C for 2 h. The mixture was concentrated, and the residue was purified on a silica gel column using 5% MeOH in DCM as elute to give **71a** as a white solid (180 mg, 35 %). ESI-TOF-MS: m/z 337.9 $[M+H]^+$.

EXAMPLE 69
Preparation of Compound 72a



[0456] To a solution of **63-6** (1.0 g, 1.8 mmol) in 1, 4-dioxane (2 mL) was added TEA (3 mL) and 37% HCHO (3 mL). The reaction mixture was stirred for 10 h at 60°C. The reaction was concentrated to dryness under vacuum, and the residue was purified by column on a silica gel column (DCM: MeOH = 100:1-30:1) to give **72-1** (470 mg, 45%) as a white foam. ESI-TOF-MS: m/z 596.9 $[M+H]^+$.

[0457] To a solution of **72-1** (430 mg, 0.72 mmol) in dioxane (2 mL) was added 30% CH_3COOH (0.7 mL) and PtO_2 (290 mg). The reaction mixture was stirred under H_2 (1atm) at R.T. for 2 h. The mixture was filtered, and the filtrate was concentrated to dryness. The residue was purified on a silica gel column (DCM: MeOH = 100:1-30:1) to give **72-2** (268 mg, 64%) as a white foam. ESI-TOF-MS: m/z 580.9 $[M+H]^+$.

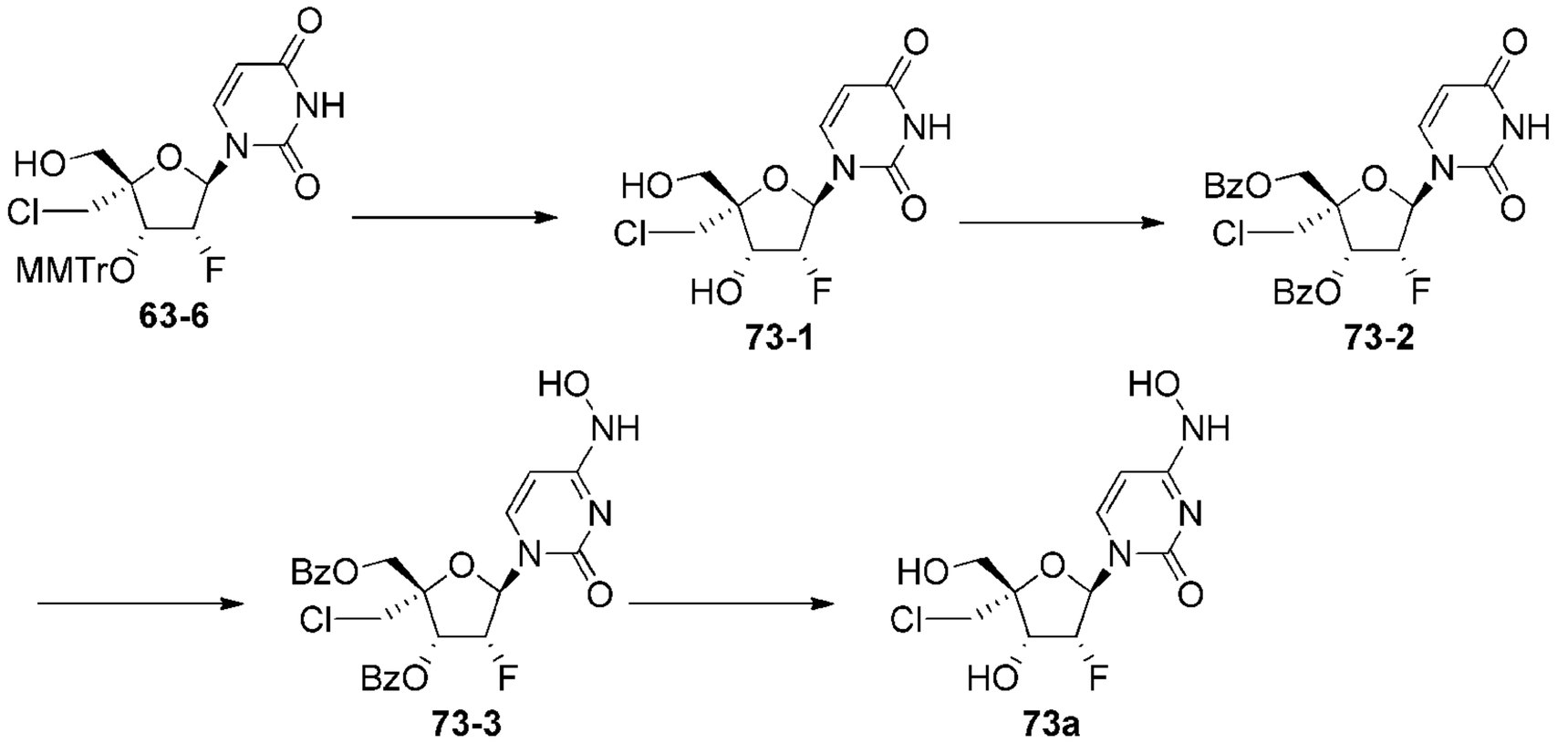
[0458] To a solution of **72-2** (260 mg, 0.45 mmol) in anhydrous DCM (3 mL) was added $AgNO_3$ (228 mg, 1.35 mmol), collidine (223 mg, 1.8 mmol) and MMTrCl (456 mg,

1.35 mmol). The mixture was stirred at R.T. for 10 h . The reaction mixture was filtered, and the filtrate was concentrated to dryness. The residue was purified on a silica gel column (PE: EA = 50:1-3:1) to give **72-3** (303 mg, 80%) as a white foam.

[0459] To a solution of **72-3** (300 mg, 0.35 mmol) in anhydrous CH_3CN (3 mL) was added DMAP (107 mg, 0.88 mmol), TEA (141 mg, 1.4 mmol) and TPSCl (106 mg, 0.35 mmol) at R.T. The reaction mixture was stirred at R.T. for 4 h. NH_4OH (1 mL) was added, and the mixture was stirred at R.T. for another 1 h. The solvent was removed, and the residue was partitioned by EA and water. The organic layer was washed by brine twice, dried and concentrated to give a residue. The residue was purified on a silica gel column (PE: EA = 50:1-3:1) to give **72-4** (270 mg, 90%) as a white foam.

[0460] Compound **72-4** (260 mg, 0.31 mmol) in 10 mL of 60% HCOOH was stirred at R.T. for 2 h. The solvent was removed, and the residue was washed with EA to give **72a** (31 mg, 32%) as a white powder. ESI-TOF-MS: m/z 307.9 $[M+H]^+$.

EXAMPLE 70
Preparation of Compound 73a



[0461] Compound **63-6** (600 mg, 1.06 mmol) in formic acid (5 mL, 80% in water) was stirred at R.T. overnight. Completion of the reaction was determined by TLC (DCM: MeOH= 10:1). The solvent was removed to give crude **73-1** (290 mg, 93.2%).

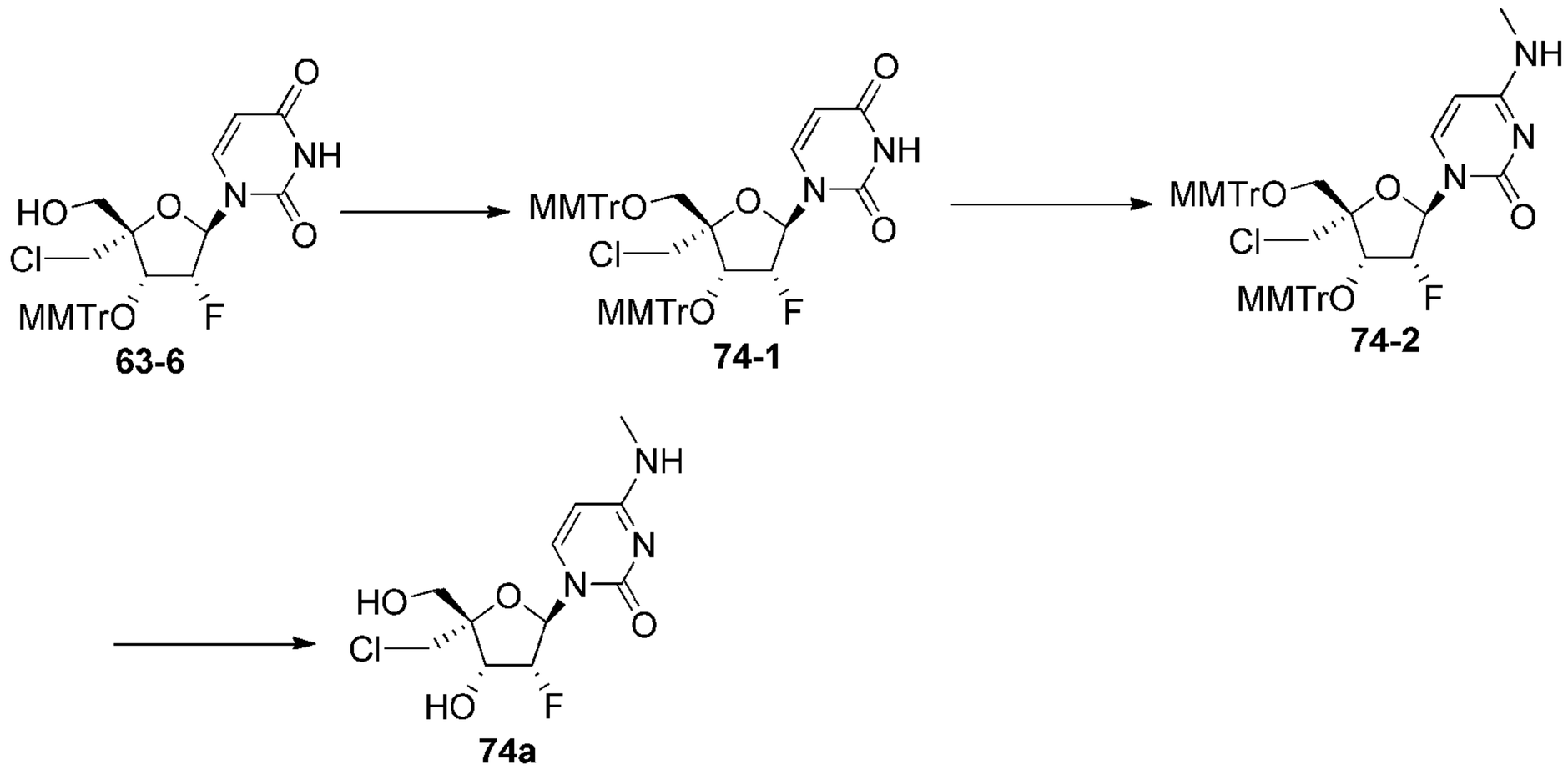
[0462] To a solution of **73-1** (290 mg, 0.98 mmol) in pyridine (5 mL) and acetonitrile (5 mL) was added BzCl (371 mg, 2.65 mmol). The reaction mixture was stirred at 0^oC for 0.5 h. The reaction was warmed to R.T. and stirred for 2 h. Completion of the

reaction was determined by LCMS. The reaction was quenched with water and extracted with EA. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified on a silica gel column (DCM: MeOH= 200:1) to give **73-2** (245 mg, 49.8%) as a white solid.

[0463] To a solution of **73-2** (245 mg, 0.49 mmol) in anhydrous acetonitrile (2.5 mL) was added TPSCl (394 mg, 0.98 mmol), DMAP (119.5 mg, 0.98 mmol) and TEA (98 mg, 0.98 mmol). The mixture was stirred at R.T. for 3 h. $NH_2OH \cdot HCl$ (68 mg, 0.98 mmol) and DBU (368 mg, 1.47 mmol) were added, and the reaction mixture was stirred at R.T. for 2 h. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic layer was washed with 1M HCl, saturated $NaHCO_3$ and brine, dried and concentrated. The residue was purified on a silica gel column (DCM: MeOH= 20:1) to give **73-3** (49 mg, 32.9%) as a white solid.

[0464] Compound **73-3** (49 mg, 0.1 mmol) in NH_3/MeOH (30 mL) was stirred at R.T. for 2 days. The solvent was removed. The residue was purified on a silica gel column (DCM: MeOH= 30:1) to give **73a** (12.9 mg, 44.0%) as a white solid. ESI-TOF-MS: m/z 308.1 $[M-H]^+$.

EXAMPLE 71
Preparation of Compound 74a



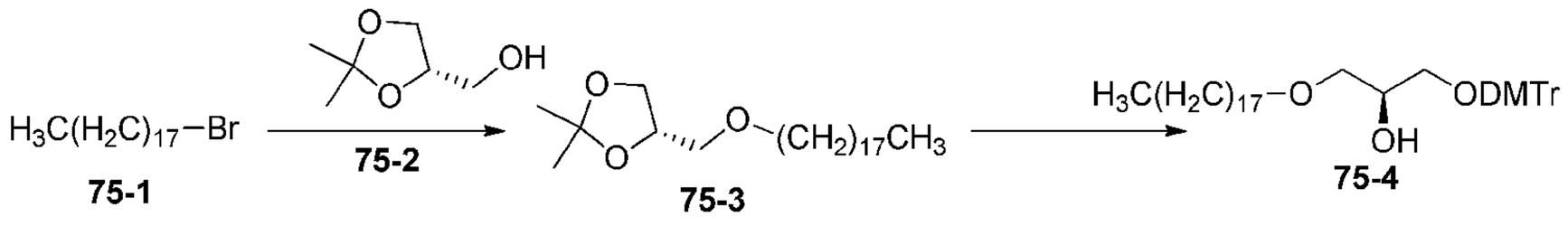
[0465] To a solution of **63-6** (1.2 g, 2.12 mmol) in anhydrous DCM (20 mL) were added collidine (750 mg, 6.51 mol) and MMTrCl (2.6 g, 8.5 mmol). The mixture was stirred

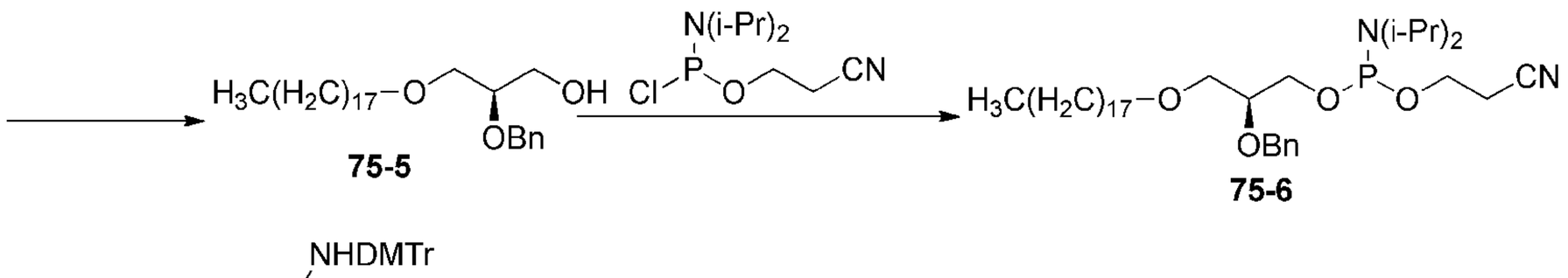
at R.T. overnight. The reaction was filtered and washed successively with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated. The residue was purified on a silica gel column eluted with 10% EA in PE to give **74-1** as a yellow solid (1.4 g, 72%).

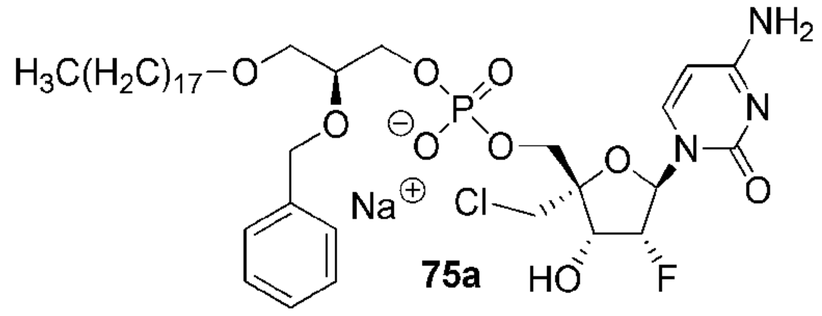
[0466] To a stirred solution of **74-1** (600 mg, 0.715 mmol) in anhydrous acetonitrile (6 mL) were added TPSCl (432 mg, 1.43 mmol), DMAP (174 mg, 1.43 mmol) and TEA (144 mg, 1.43 mmol). The mixture was stirred at R.T. for 2 h. Completion of the reaction was determined by TLC (DCM: MeOH= 10:1). CH_3NH_2 (310 mg, 10 mmol) was added dropwise at 0^oC. The reaction mixture was stirred at R.T. for 2 h. The mixture was diluted with water and extracted with EtOAc. The combined organic layer was washed with 1M HCl, saturated $NaHCO_3$ and brine. The solvent was removed, and the residue was purified by prep-TLC (DCM: MeOH= 10:1) to give **74-2** (307 mg, 50.45%) as a white solid.

[0467] **74-2** (300 mg, 0.352 mmol) in formic acid (10 mL, 80% in water) was stirred at R.T. overnight. Completion of the reaction was determined by TLC (DCM: MeOH= 10:1). The solvent was removed to dryness. The residue was dissolved in 20 mL of methanol. Ammonia (0.5 mL) was added, and the mixture was stirred at R.T. for 5 mins. The solvent was removed, and the residue was washed with PE (5X) to give **74a** (103 mg, 95.3%) as a white solid. ESI-TOF-MS: m/z 308.1 $[M+H]^+$.

EXAMPLE 72
Preparation of Compound 75a







[0468] To a stirred solution of **75-1** (20.0 g, 151 mmol) in anhydrous THF (200 mL)was added NaH (7.8 g, 196 mmol) in portions at 0°C. The mixture was stirred for 1 h, and **75-2** (65.0 g, 196 mmol) was added dropwise at 0°C. The mixture was stirred at R.T. for 10 h. The reaction was quenched with water and extracted with EA. The reaction was washed with brine, and the organic layer was concentrated to obtain crude **75-3** (72 g).

[0469] Crude **75-3** (72 g, 151 mmol) was dissolved with 80% CH_3COOH (300 mL) and stirred for 10 h. The solvent was removed under reduced pressure. The residue was dissolved in EA and washed with saturated $NaHCO_3$ and brine successively. The organic layer was dried over Na_2SO_4 and concentrated to dryness. The residue was purified on a silica gel column to give the crude intermediate, which was dissolved in anhydrous pyridine (80 mL) and DCM (400 mL). A solution of DMTrCl (56.0 g, 166 mmol) in DCM (150 mL) was added dropwise at 0°C. The mixture was stirred at R.T. for 10 h. The reaction mixture

was concentrated to dryness, and the residue was purified by column on silica gel (PE: EA= 2:1) to give **75-4** (58.5 g, 61%).

[0470] To a stirred solution of **75-4** (10.0 g, 15.5 mmol) in anhydrous DMF (80 mL) was added NaH (0.8 g, 20 mmol) at 0°C. The mixture was stirred at R.T. for 1 h, and BnBr (33.8 g, 20 mmol) was added. The reaction mixture was stirred at R.T. for 10 h. The reaction was quenched with water and extracted with EA. The reaction was washed with brine, and the organic layer was concentrated to give the crude intermediate (10.5 g, 92%) as a white foam. The crude intermediate (10.2 g, 13.8 mmol) in 80% CH_3COOH (100 mL) was stirred at R.T. for 12 h. The solvent was removed. The residue was dissolved in EA, washed with saturated $NaHCO_3$ and brine successively, dried and concentrated to give a residue. The residue was purified on a silica gel column twice (PE: EA= 3:1) to give **75-5** (4.2 g, 70%) as a white foam.

[0471] To a solution of **75-5** (4.0 g, 9.2 mmol) in anhydrous CH_3CN (30 mL) was added DIPEA (6.1 g, 47.6 mmol) and 2-cyanoethyl N,N-diisopropylchlorophosphoramidite (2.8 g, 11.9 mmol). The mixture was stirred at R.T. for 2 h. The solvent was removed, and residue was partitioned by EA and saturated $NaHCO_3$. The organic layer was dried over $MgSO_4$ and concentrated to give a residue. The residue was purified on a silica gel column (PE: EA= 3:1) to give **75-6** (5.1g, 88 %) as a white solid.

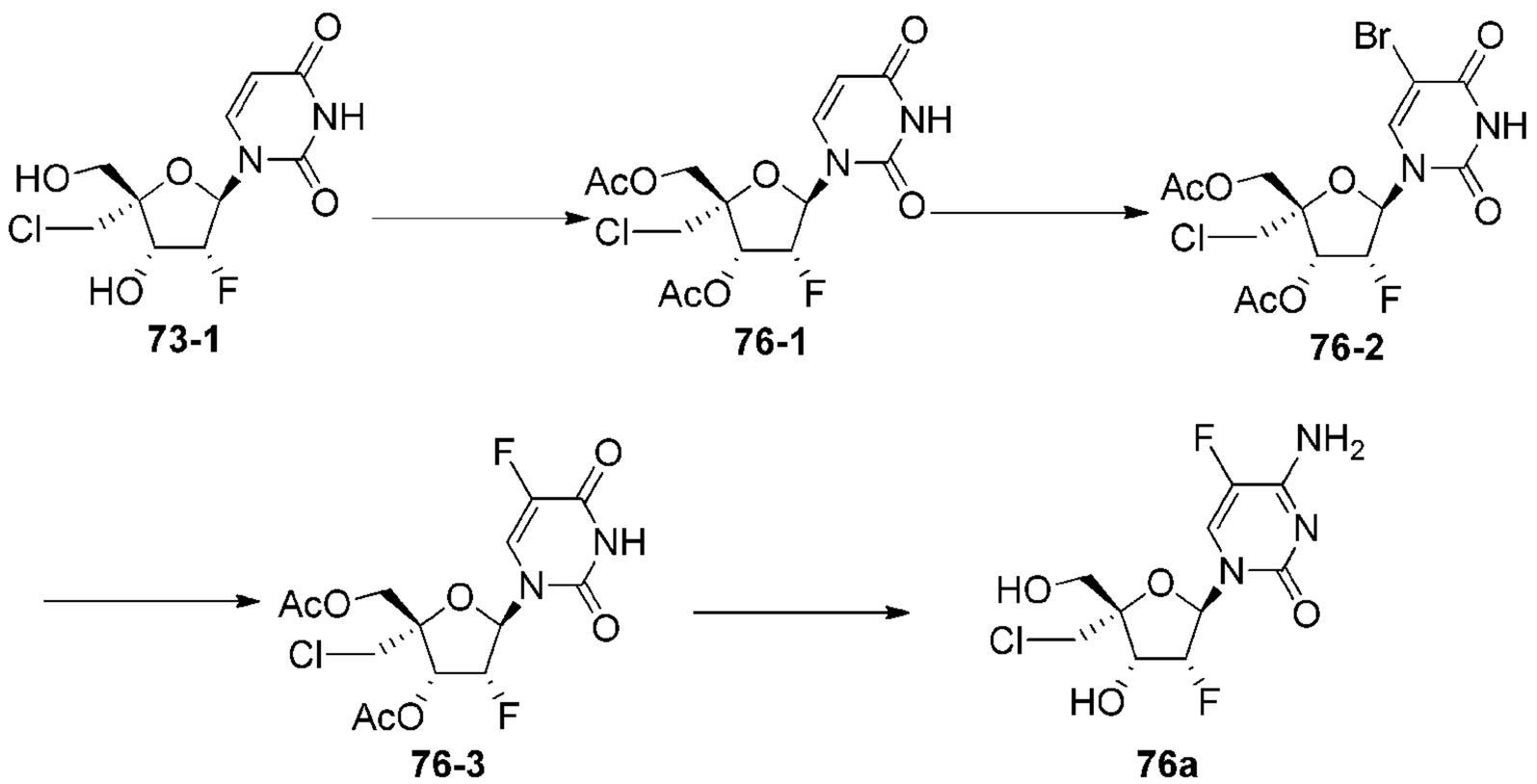
[0472] To a solution of **75-6** (1.0 g, 1.6 mmol) and **63-9** (925 mg, 1.1 mmol) in anhydrous MeCN (1 mL) was added tetrazole (12 mL, 0.45M in MeCN, 5.5 mmol) dropwise at R.T. After stirred for 3 h, TBDPH (0.96 mL, 5M 4.8 mmol) was added. The reaction mixture was stirred at R.T. for 1 h. The mixture was diluted with EA and washed with saturated Na_2SO_3 and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography (PE/EA = 50:1 to 1:1) to give **75-7** (1.1 g, 73.3%) as a white solid.

[0473] Compound **75-7** (1.0 g, 0.7 mmol) in 60% HCOOH (3 mL) was stirred at R.T. for 12 h. The solvent was removed. The residue was dissolved in EA and washed with saturated $NaHCO_3$ and brine successively, dried and concentrated to give a residue. The residue was purified twice on a silica gel column (DCM : MeOH= 30:1) to give crude **75a** (510 mg, 86%) as a white foam. To a solution of crude **75a** (275 mg, 0.33 mmol) in C_2H_5OH

was added a few drops 1N NaOH until pH~7.0. The mixture was stirred for 0.5 h. The mixture was concentrated to give a residue. The residue was purified by HPLC (MeCN and water, neutral system) to give **75a** (sodium salt, 170 mg, 64%) as a white solid. ESI-TOF-MS: m/z 788.3 $[M-H]^+$.

EXAMPLE 73

Preparation of Compound 76a



[0474] To a solution of **73-1** (4.1 g, 13.95 mmol) in pyridine (40 mL) was added Ac_2O (3.13 g, 30.68 mmol) at R.T., and the mixture was stirred overnight. The mixture was concentrated, and the residue was purified on a silica gel column (PE: EA= 3:1) to give **76-1** (4.0 g, 75.9%).

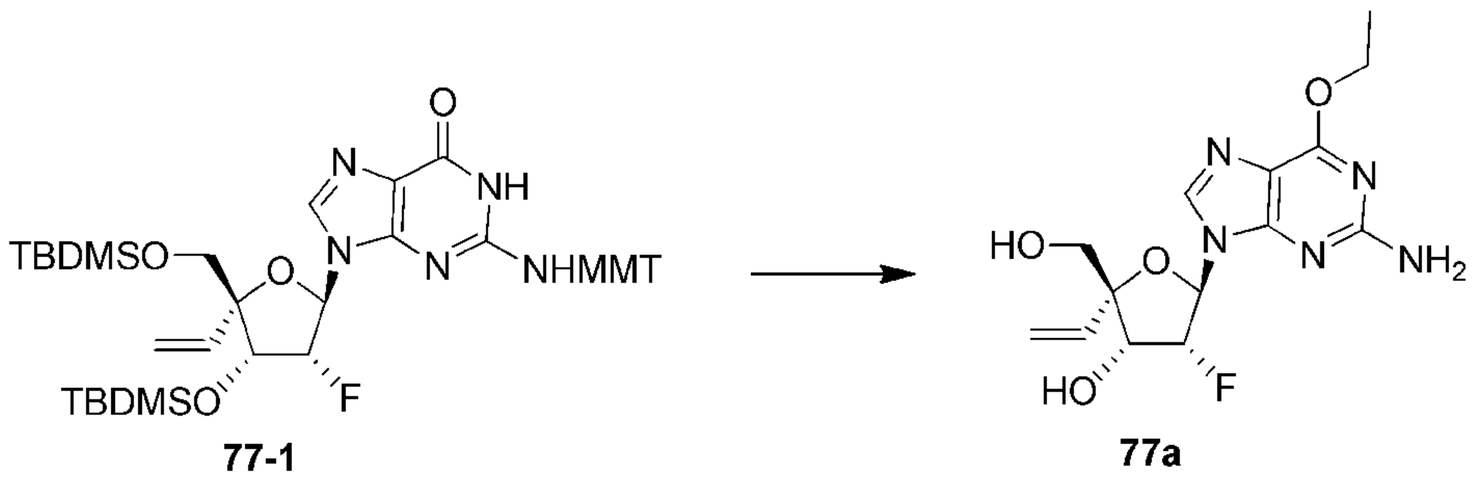
[0475] To a solution of **76-1** (1.3 g, 3.44 mmol) in pyridine (20 mL) was added NBS (1.22 g, 6.88mmol) at R.T., and the mixture was stirred overnight. The mixture was concentrated, and the residue was purified on a silica gel column (PE: EA= 4:1) to give **76-2** (1.43 g, 72.2%).

[0476] To a solution of **76-2** (770 mg, 1.68 mmol) in dioxane (10 mL) was added Me_6Sn_2 (1.1 g, 3.36 mmol) and $(PPh_3)_2PdCl_2$ (100 mg) under N_2 atmosphere. The mixture was heated at 80°C for 4 h. The mixture was concentrated, and the residue was purified on a silica gel column to give an intermediate (400 mg, 43.96%). To a solution of the intermediate (330 mg, 0.61 mmol) in anhydrous MeCN (3 mL) was added Selectflour® (462 mg, 1.34 mmol) at R.T. The mixture was stirred at R.T. for 2 days. The mixture was

concentrated, and the residue was purified on a silica gel column (PE: EA= 4:1) to give **76-3** (100 mg, 41.5%).

[0477] To a solution of **76-3** (100 mg, 0.25 mmol) in MeCN (2 mL) was added DMAP (62 mg, 0.51mmol), TEA (51 mg, 0.51 mmol) and TPSCl (153 mg, 0.51 mmol). The mixture was stirred at R.T. for 0.5 h. $NH_3.H_2O$ (0.75 mL) was added. The mixture was stirred at R.T. for 0.5 h. The mixture was extracted with EtOAc and washed with 1N HCl and brine. The organic layer was dried and concentrated. The residue was purified on a silica gel column (PE: EA= 1:1) to give an intermediate (60 mg, 60.1%). The intermediate (50 mg, 0.13 mmol) in NH_3/MeOH (5 mL) was stirred at R.T. for 3 h. The mixture was concentrated, and the residue was purified on a silica gel column (MeOH: DCM= 1:10) to give **76a** (30 mg, 76.2%). ESI-TOF-MS: m/z 312.1 $[M+H]^+$.

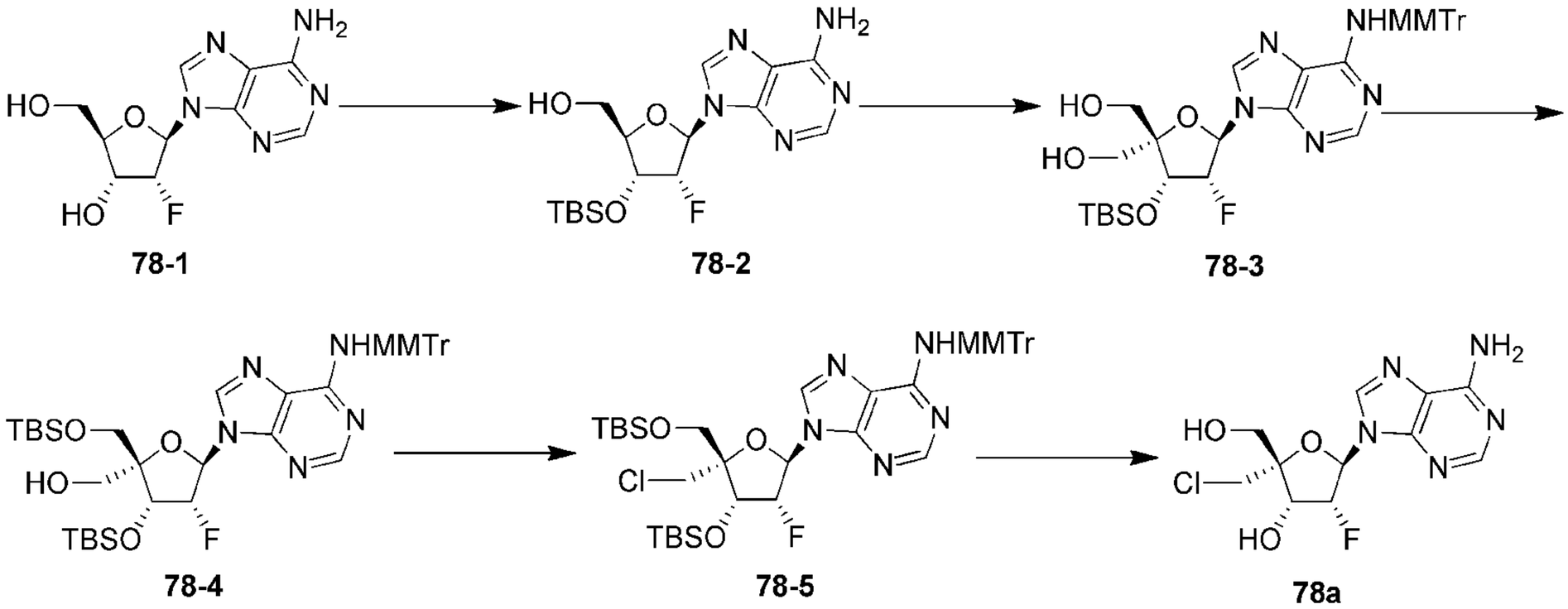
EXAMPLE 74
Preparation of Compound 77a



77-1 **77a**

[0478] Compound **77-1** (680 mg, 0.8 mmol) and triphenylphosphine (312 mg, 1.2 mmol) were dissolved in the mixture of 5 mL of dioxine and 0.25 mL of dry ethanol. A solution of diisopropyl azadicarboxylate (40% w solution in toluene, 1.28 mmol) in 3 mL of dioxane was added, and the mixture was stirred at R.T. for 2 h. The mixture was evaporated to dryness. The residue was dissolved in 10 mL of THF, cooled down to 4^0C and 2 equivalents of TBAF in THF were added. The mixture was warmed up to R.T. and the solvent was evaporated. The resulting nucleoside was treated with 80% HCOOH at R.T. for 3 h, and then the acid was evaporated. Isolated by isocratic silica gel chromatography using mixture of DCM (950 mL), MeOH (50 mL), and NH_4OH (2.5 mL) for elution gave **77a** (80mg, 30%). MS: 384 [M-1+HCOOH].

EXAMPLE 75
Preparation of Compound 78a



[0479] To a solution of **78-1** (10.0 g, 37.17 mmol) in anhydrous pyridine (100 mL) was added imidazole (9.54 g, 140.4 mmol) and TBSCl (21.1 g, 140.4 mmol) at 25°C. The solution was stirred at 25°C for 15 h. The solution was concentrated to dryness under reduced pressure. The residue was dissolved in EtOAc (200 mL) and washed with water and brine. The organic layer was separated, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated in vacuo to give a residue. The residue was purified by a silica gel column (PE/EA = 10:1 to 2:1) to give an intermediate (11.8 g, 64%). To an ice-cold solution of the intermediate (11.8 g, 23.7 mmol) in CH_2Cl_2 (150 mL) was added a solution of p-toluenesulfonic acid monohydrate (8.2 g, 47.5 mmol) in small portion under N_2. The mixture was stirred at 25°C for 30 min, and then washed with saturated aq. $NaHCO_3$. The organic layer was separated, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated in vacuum to give a residue, which was purified by silica gel (PE/EA = 10:1 to 1:1) to give **78-2** (6.7 g, 74%) as a solid.

[0480] To a solution of **78-2** (6.7 g, 17.5 mmol) in anhydrous pyridine (50 mL) was added TMSCl (2.8 g, 26.2 mmol) in small portions at 0°C under N_2. The reaction mixture was stirred at 25°C overnight. $AgNO_3$ (77.8 g, 510 mmol) and MMTrCl (156.8 g, 510 mmol) in anhydrous pyridine (50 mL) was added in small portions under N_2. The reaction mixture was stirred at 25°C overnight. Ammonia (30 mL) was added, and the reaction mixture was stirred for 30 min. The mixture was filtered through a Buchner funnel, and the filtrate was washed with saturated $NaHCO_3$ solution and brine. The organic layer

was separated, dried over anhydrous Na_2SO_4, filtered and concentrated. Chromatography on silica gel (PE:EA = 10:1 to 2:1) gave an amine protected derivative (6.1 g, 53%). To a solution of pyridine (142 mg, 1.8 mmol) in anhydrous DMSO (2 mL) at 0°C was added TFA (1.3 mg, 0.9 mmol) dropwise. The mixture was stirred at 25°C until a clear solution formed. The solution was then added into a solution of the amine protected derivative (1.0 g, 1.5 mmol) and DCC (0.95 g, 4.6 mmol) in anhydrous DMSO at 0°C dropwise. Stirring was continued at 25°C for 10 h. Water (10 mL) was added, and the mixture was stirred at 25°C for 1 h. The precipitate was removed by filtration, and the filtrate was extracted with EtOAc (20 mL). The organic layer was washed with brine (20 mL) and then dried over Na_2SO_4. The solvent was removed, and the residue was purified on a silica gel column (EA:PE = 10:1 to 2:1) to give the aldehyde derivative (850 mg, 85%). To a solution of the aldehyde derivative (2.6 g, 4.0 mmol) in 1,4-dioxane (30 mL) was added 37% CH_2O (1.3 g, 16.0 mmol) and 2N NaOH aqueous solution (3.0 mL, 6.0 mmol). The mixture was stirred at 25°C for 2 h and then neutralized with AcOH to pH=7. To the reaction were added EtOH (10 mL) and $NaBH_4$ (912 mg, 24.0 mmol). The reaction was stirred for 30 mins, and then quenched with saturated aqueous NH_4Cl. The mixture was extracted with EA, and the organic layer was dried over Na_2SO_4. Purification by silica gel column chromatography (EA: PE = 10:1 to 2:1) gave **78-3** (1.1 g, 40%) as a yellow solid.

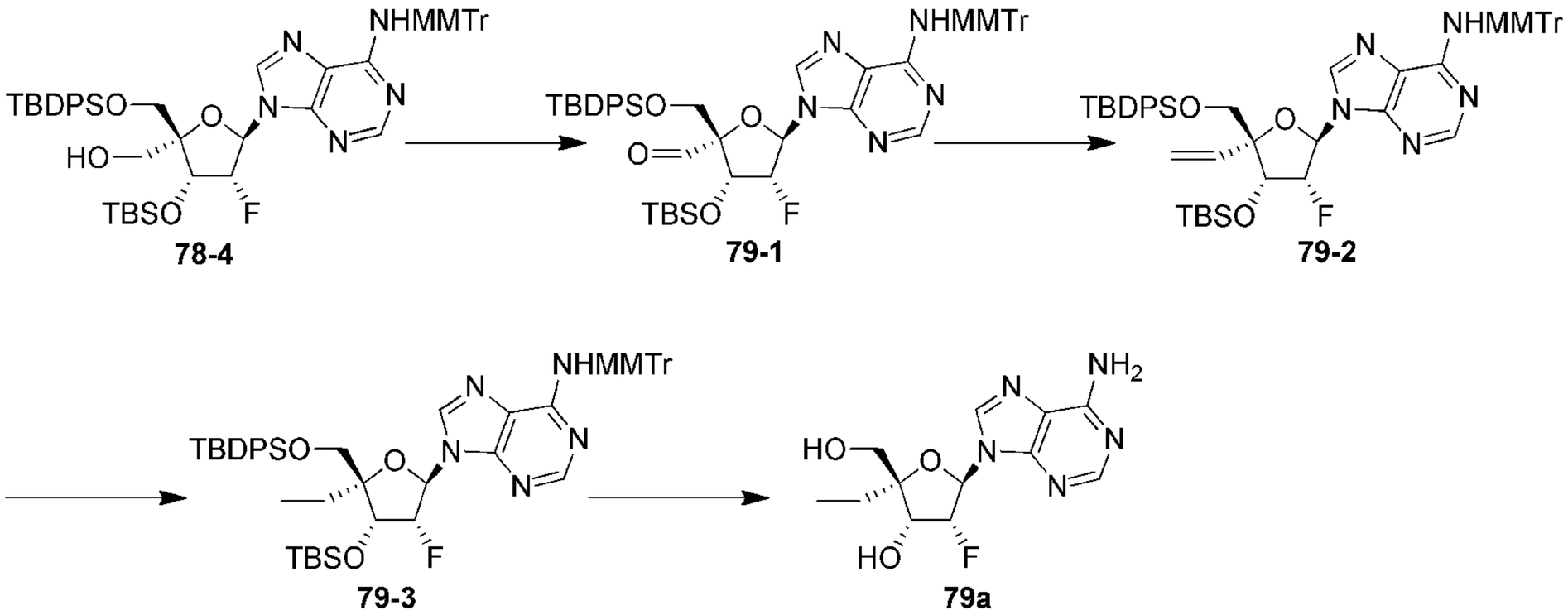
[0481] A stirred solution of **78-3** (685 mg, 1.0 mmol) in anhydrous CH_3CN (5 mL) and anhydrous pyridine (5 mL) was cooled to 0°C. BzCl (126 mg, 0.9 mmol) was added, and the reaction mixture was stirred at 25°C. After 1.5 h, water (5 mL) was added. The resulting mixture was extracted with DCM (2×30 mL). The combined extracts were washed with a saturated aqueous solution of $NaHCO_3$ (20 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (DCM: MeOH = 200:1 to 50:1) to give the Bz-protected derivative (679 mg, 86%). To a stirred solution of Bz-protected derivative (432 mg, 0.55 mmol) in anhydrous DMF (5 mL) was added imidazole (258 mg, 3.85 mmol) and TBSCl (240.0 mg, 1.65mmol). The mixture was stirred for 15 h. Water (10 mL) was added, and the mixture was extracted with EA. The combined extracts were washed with aqueous solution of $NaHCO_3$ (60 mL) and brine (60 mL), dried over $MgSO_4$, and evaporated under reduced pressure to give the

two-TBS protected derivative (680 mg, 137 %). The two-TBS protected derivative (680 mg, 0.75 mmol) was dissolved in anhydrous CH_3OH (5 mL), and $NaOCH_3$ (162 mg, 3.0 mmol) was added. The reaction mixture was stirred at 35°C for 2 h. The reaction was quenched with 80 % AcOH (3 mL) and extracted with DCM (2×50 mL). The combined extracts were washed with aqueous solution of $NaHCO_3$ (20 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EA: PE = 20:1 to 3:1) to give **78-4** (239 mg, 40%) as a white foam.

[0482] Compound **78-4** (239 mg, 0.30 mmol) was co-evaporated with toluene three times to remove H_2O. To a solution of **78-4** in DCM (5 mL) was added DMAP (182 mg, 1.50 mmol) and TfCl (69 mg, 0.45 mmol) at 0°C under N_2. The mixture was stirred 0°C for 40 mins. Completion of the reaction was determined by LCMS. The mixture was concentrated to give the crude Tf-derivative (353 mg). To a solution of the Tf-derivative in DMF (5 mL) was added LiCl (31 mg, 0.76 mmol) at 0°C under N_2. The mixture was stirred at 25°C for 40 mins. The mixture was washed with $NaHCO_3$ and extracted with EA. The combined organic layer was dried over Na_2SO_4 and concentrated to give crude **78-5** (268 mg) as a light yellow oil.

[0483] To a solution of **78-5** (268 mg, 0.328 mmol) in MeOH (5 mL) was added NH_4F (37 mg, 0.984 mmol) at 25°C for 4 h. The solution was filtered and evaporated to dryness. The residue was dissolved in HCOOH (20 mL) and H_2O (4 mL) at 25°C. The mixture was stirred at 25°C for 1 h and concentrated. The mixture was dissolved in MeCN and purified by prep-HPLC to give **78a** (32 mg) as a white solid. ESI-MS: m/z 317.9 $[M+H]^+$.

EXAMPLE 76
Preparation of Compound 79a



[0484] To a solution of **78-4** (1.1 g, 1.33 mmol) in anhydrous DCM (6.6 mL) at 0°C under nitrogen was added Dess-Martin periodinane (1.45 g, 3.33 mol). The mixture was stirred at 25°C for 4 h. The solvent was removed in vacuum, and the residue triturated with methyl-t-butyl ether (30 mL). The mixture was filtered through a pad of $MgSO_4$, and the organic solvent was stirred with an equal volume of $Na_2S_2O_3$ in 30 mL of saturated $NaHCO_3$ until the organic layer became clear (approx. 10 min). The organic layer was separated, washed with brine, and dried over $MgSO_4$. Prior to removing the solvent in vacuum, the residue was purified on a silica gel column (PE: EA= 7:1) to give **79-1** (750 mg, 75%) as a white solid.

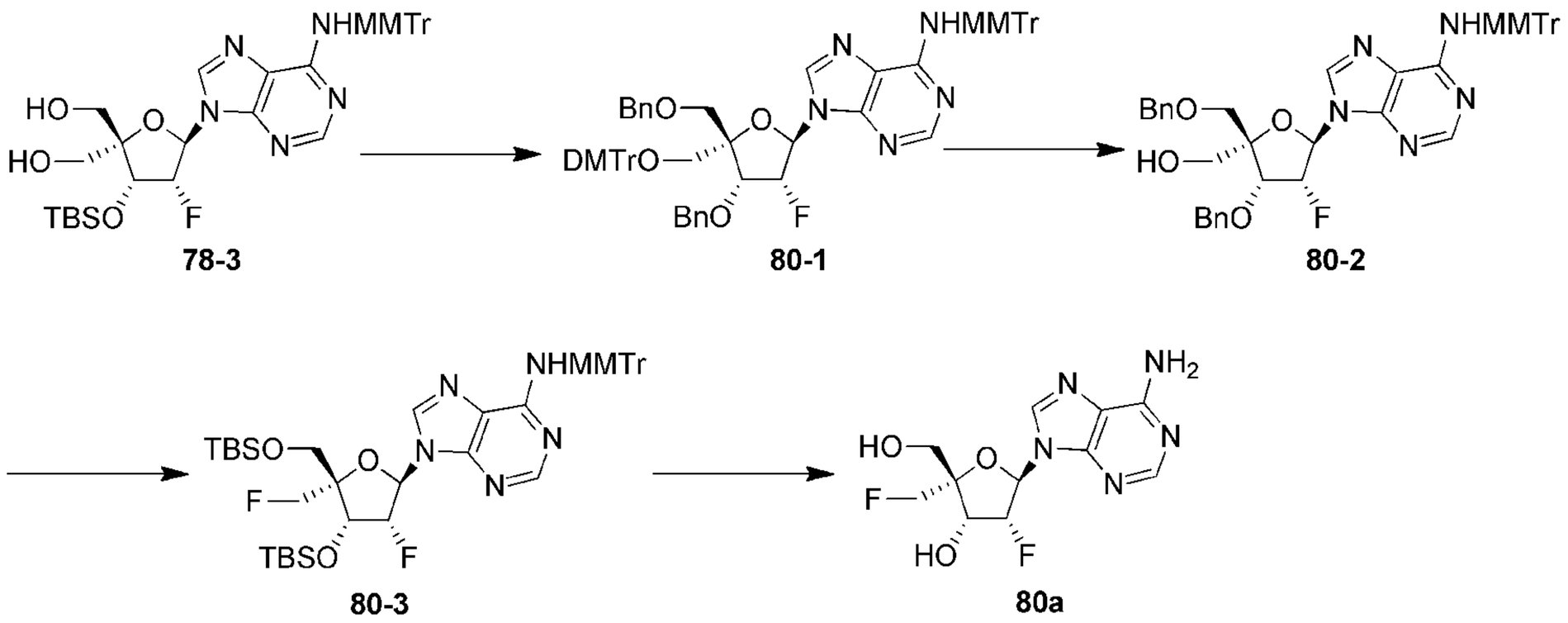
[0485] To a stirred solution of methyl-triphenyl-phosphonium bromide (1.74 g, 4.89 mmol) in anhydrous THF (8 mL) was added *n*-BuLi (1.91 mL, 4.89 mmol, 2.5 M in THF) at -78°C dropwise. The mixture was stirred at 0°C for 1 h. **79-1** (750 mg, 0.81 mmol) was added, and the mixture stirred at 25°C overnight. The reaction was quenched with saturated NH_4Cl (30 mL), and extracted with EtOAc (2×30 mL). The combined organic phase was washed with brine, dried with $MgSO_4$, filtered and evaporated to dryness to give a light white solid. The solid was purified by column chromatography (PE: EA = 5:1) to give **79-2** (440 mg, 60%).

[0486] To a solution of **79-2** (440 mg, 0.48 mmol) in MeOH (8 mL) was added Pd/C (500 mg, 10%) at R.T. under hydrogen atmosphere. The mixture was stirred at R.T. for

1.5 h. The mixture was filtered, and the filtrate was concentrated to dryness. Crude **79-3** (365 mg, 83%) was used for the next step without further purification.

[0487] **79-3** (365 mg, 0.40 mmol) in MeOH (50 mL) was added NH_4F (5.6 g, 0.15 mmol), and the solution was heated to refluxed overnight. Completion of the reaction was determined by LCMS. The mixture was filtered, and the filtrate was concentrated to dryness. The residue was purified on a silica gel column (PE: EA = 3:1) to give the amine protected derivative (173 mg, 77%) as a white solid. The amine protected derivative (100 mg, 0.18 mmol) in formic acid (4.4 mL) was stirred at 25°C overnight. The solution was concentration to dryness, and the residue was purified on a silica gel column (PE: EA = 1:3) to give **79a** (40 mg, 90%) as a white solid. ESI-MS: m/z 297.9 $[M+H]^+$.

EXAMPLE 77
Preparation of Compound 80a



[0488] To a solution of **78-3** (4.4 g, 6.4 mmol) in anhydrous pyridine (5 mL) and DCM (25 mL). A solution of DMTrCl (2.37 g, 7.04 mmol) in DCM (5 mL) was added dropwise at 0°C under N_2. After 2 h, the reaction was quenched with CH_3OH and concentrated to dryness. The residue was purified on a column of silica gel (PE: EA = 100:1 to 2:1) to obtain the DMTr protected derivative (4.3 g, 68%). The DMTr protected derivative (2.2 g, 2.5 mmol) in 1M TBAF (2.5 mL) of THF (2.5 mL) solution was stirred at 25°C for 3 h. The solvent was removed in vacuum, and the residue was purified by column chromatography (PE/EA= 50:1 to 1:2) to give the diol derivative (1.86 g, 96%). To a solution of the diol derivative (1.3 g, 1.5 mmol) in anhydrous THF (5 mL) was added NaH (132 mg, 3.3 mmol) at 0°C. The mixture was stirred for 1 h, and TBI (276 mg, 0.75 mmol),

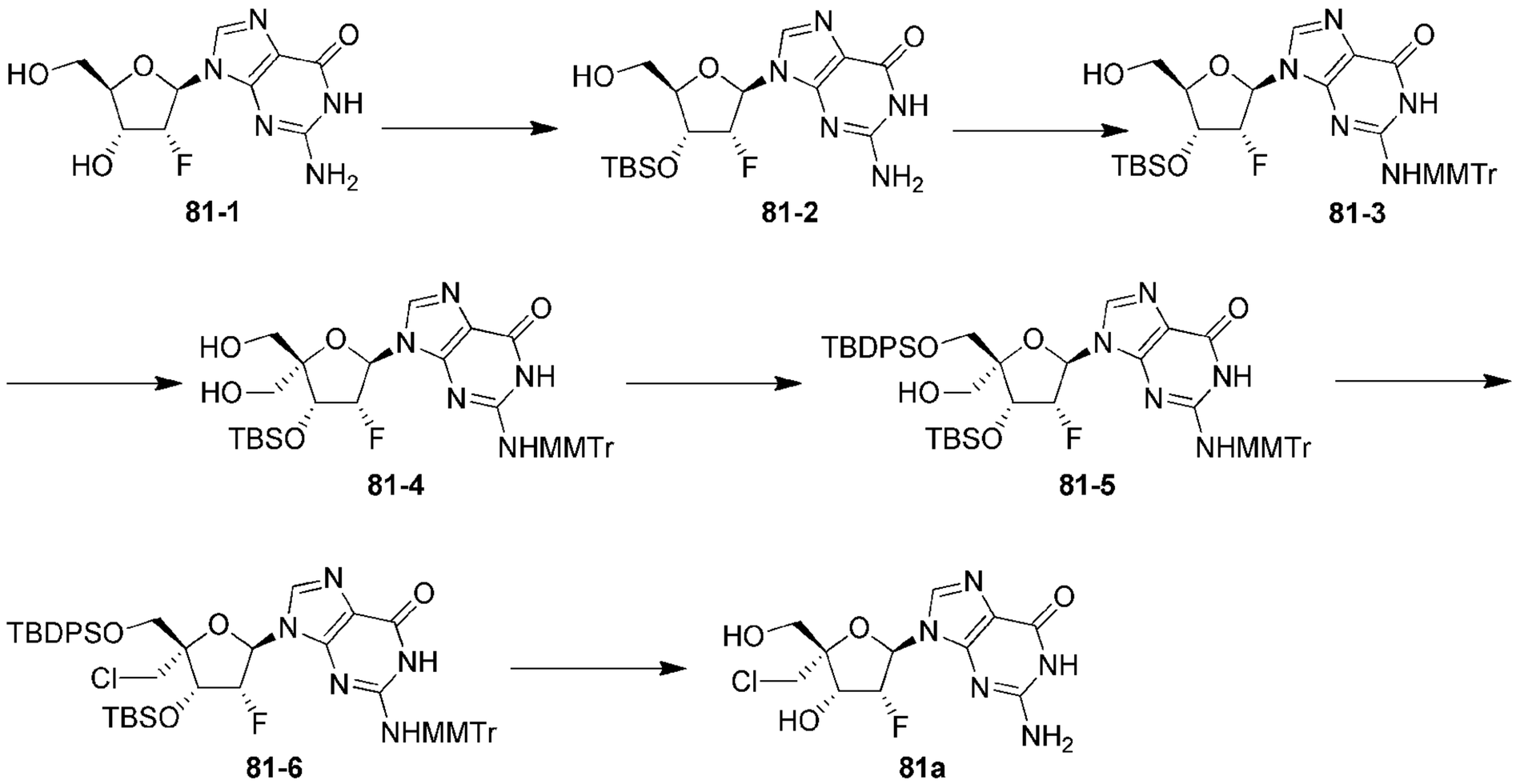
and BnBr (558 mg, 3.3 mmol) was added. The mixture was stirred for 10 h at 25°C. The reaction was quenched with water, and the solvent was evaporated. The mixture was extracted with EA and brine. The organic layer was dried over Na_2SO_4, and evaporated to afford the crude product. The product was purified by silica gel (PE/EA = 100:1 to 3:1) to afford **80-1** (1.4 g, 90%) as a white foam.

[0489] To a solution of **80-1** (1.3 g, 1.23 mmol) in anhydrous DCM (17 mL) was added $Cl_2CHCOOH$ (1.57 g, 12.3 mmol) at -78°C. The mixture was stirred at -20-10°C for 40 mins. The reaction was quenched with saturated $NaHCO_3$, and diluted with DCM (50 mL). The mixture was washed with brine, and the organic solution was dried over Na_2SO_4 and concentrated in vacuum. The residue was purified on a silica gel column (PE/EA = 100:1 to 1:1) to give **80-2** (652 mg, 70%) as a white foam.

[0490] Preparation of (**80-3**): To a solution of **80-2** (630 mg, 0.84 mmol) in anhydrous DCM (5 mL) was added DAST (1.35 g, 8.4 mmol) at -78°C. The mixture was gradually warmed to 0°C. The reaction was quenched with saturated $NaHCO_3$. The mixture was diluted with DCM (50 mL) and washed with brine. The organic solution was dried over Na_2SO_4 and concentrated in vacuum. The residue was purified on a silica gel column (PE/EA = 100:1 to 2:1) to give **80-3** as a white solid (302 mg, 48%).

[0491] A mixture of **80-3** (210 mg, 0.28 mmol) and $Pd(OH)_2$ (200 mg) in methanol (3 mL) was stirred at 0°C at 40 psi H_2 for 20 h. $Pd(OH)_2$ was filtered off, and the filtrate was concentrated to dryness. The residue was purified by column (DCM/MeOH = 10:1) to give **80a** (12 mg). ESI-MS: m/z 302.0 $[M+H]^+$.

EXAMPLE 78
Preparation of Compound 81a



[0492] To a solution of **81-1** (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 R.T., and then concentrated to dryness under reduced pressure to give **81-2** (31.2 g, 61%) as a white solid.

[0493] To a solution of **81-2** (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 **81-3** as a yellow solid (28.6 g, 87%).

[0494] To a solution of **81-3** (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 R.T. 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 **81-4** (7.5g, 59%) as a yellow solid.

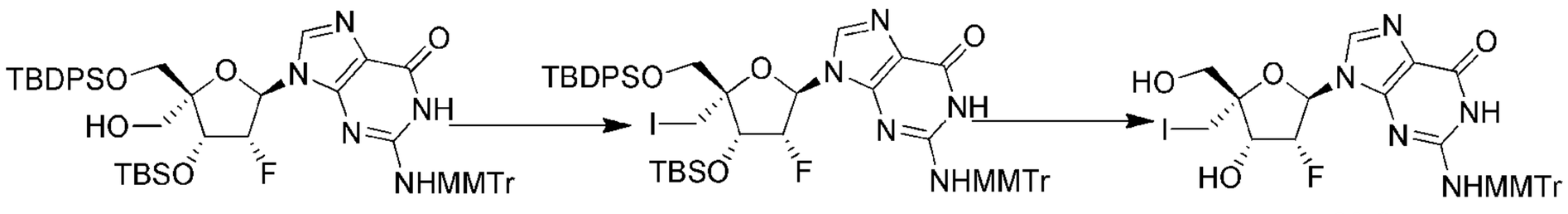
[0495] To a solution of **81-4** (3.8 g, 5.4 mmol) in DCM (40 mL) was added pyridine (10 mL) and DMTrCl (1.8 g, 5.4 mmol) at 0°C. The solution was stirred at 25°C for 1 h. MeOH (15 mL) was added, and the solution was concentrated. The residue was purified by silica gel column chromatography (DCM: MeOH = 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

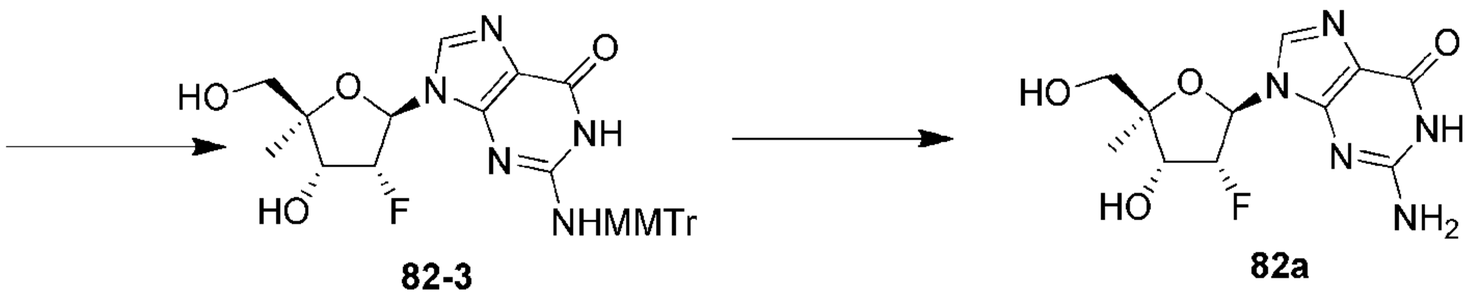
$NaHCO_3$ and extracted with DCM. The organic layer was dried over Na_2SO_4, and then purified by silica gel column chromatography (DCM: MeOH = 200:1 to 50:1) to give **81-5** (2.2 g, 80%).

[0496] To an ice cooled solution of **81-5** (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 **81-6** (430 mg, 61%).

[0497] To **81-6** (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 **81a** (58 mg, 81%) as a white solid. ESI-MS**:** *m/z* 333.8 $[M+H]^+$, 666.6 $[2M+H]^+$

EXAMPLE 79
Preparation of Compound 82a





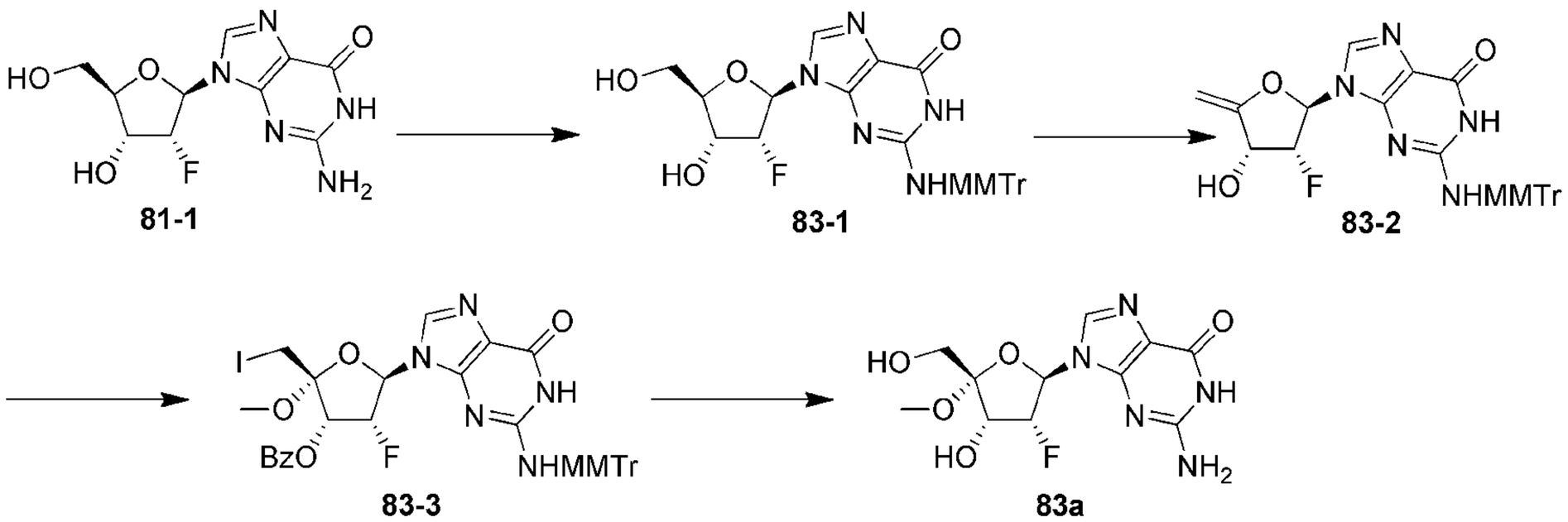
[0498] To a solution of **81-4** (310 mg, 0.33 mmol) in anhydrous DCM (10 mL) was added pyridine (130 mg, 1.65 mmol) and Tf_2O (139 mg, 0.49 mmol) diluted by DCM dropwise at 0°C. The mixture was stirred at 0°C for 15 mins. The reaction was quenched with ice cold water. The organic layer was separated and washed with brine. The organic layer was dried over Na_2SO_4 and evaporated to give to give the triflate derivative (420mg crude), which was used directly in the next step. To a solution of the triflate derivative (420 mg crude) in anhydrous pentan-2-one was added NaI (396 mg, 2.64 mmol). The mixture was stirred at 40°C for 3 h, and then dissolved with EtOAc. The organic layer were washed with $Na_2S_2O_3$ twice and washed with brine. The organic layer was dried over Na_2SO_4 and evaporated to give a residue. The residue was purified by a column (DCM: MeOH = 300:1 to 100:1) to give **82-1** (195 mg, 56% for two steps).

[0499] To a solution of **82-1** (650 mg, 0.62 mmol) in MeOH (10 mL) was added NH_4F (45.8 g, 12.4 mmol). The mixture was refluxed overnight. The mixture was filtered and evaporated to dryness. The residue was purified on a silica gel column (DCM/MeOH = 200:1 to 20:1) to give **82-2** (250 mg, 58%).

[0500] To a stirred solution of **82-2** (300 mg, 0.43 mmol), Et_3N (217 mg, 2.15 mmol) in anhydrous MeOH (10 mL) was added 10% Pd/C (50 mg). The mixture was stirred in a hydrogenation apparatus (30 psi hydrogen) at R.T. overnight. The catalyst was filtrated off, and the filtrate was evaporated to give a residue. The residue was purified on a silica gel column (DCM/MeOH = 200:1 to 20:1) to afford **82-3** as a white solid (180 mg, 73%).

[0501] Compound **82-3** (110 mg, 0.19 mmol) was dissolved in HCOOH (18 g) and H_2O (6 g) at 25°C, and stirred for 1 h. The solution was evaporated to dryness, dissolved in MeOH (30 mL). The mixture was stirred at 60°C for 12 h. The solution was evaporated to dryness, and dissolved in EtOAc (50 mL). The mixture was stirred at 60°C for 1 h. The mixture was filtered and washed with EtOAc to give **82a** as a white solid (45.3 mg, 80%). ESI-MS: m/z 299.76 $[M+1]^+$, 598.66 $[2M+1]^+$.

EXAMPLE 80
Preparation of Compound 83a



[0502] Compound **81-1** (5.7 g. 20 mmol) was co-evaporated with pyridine three times, and then dissolved in pyridine (20 mL). The mixture was cooled to 0°C and Ac_2O (5.8 mL, 60 mmol) was added dropwise. The mixture was stirred at 25°C for 10 h, and then cooled to 0°C. $AgNO_3$ (8.5 g, 50 mmol), and then MMTrCl (15.5 g, 50 mmol) were added in portions. The mixture was stirred at 25°C for 10 h. The reaction was quenched with saturated $NaHCO_3$ and extracted with EA. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (DCM/MeOH = 100:1 to 50:1) to afford the Ac protected derivative (12.1 g, 93%) as a light yellow solid. The Ac protected derivative (12.1 g) was dissolved in methanolic NH_3 (saturated). The mixture was stirred at 25°C for 14 h. The solvent was removed, and the residue was purified on a silica gel column (DCM/MeOH = 80:1 to 30:1) to give **83-1** (9.2 g, 87%).

[0503] To a stirred solution of **83-1** (9.2 g, 16.5 mmol) in dry THF (300 mL) was added imidazole (9.0 g, 132 mmol) and PPh_3 (34.8 g, 132 mmol). A solution of I_2 (26.0 g, 103 mmol) in THF (100 mL) was added dropwise under N_2 at 0°C. The mixture was stirred at 25°C for 18 h and then quenched with a $Na_2S_2O_3$ solution. The mixture was extracted with

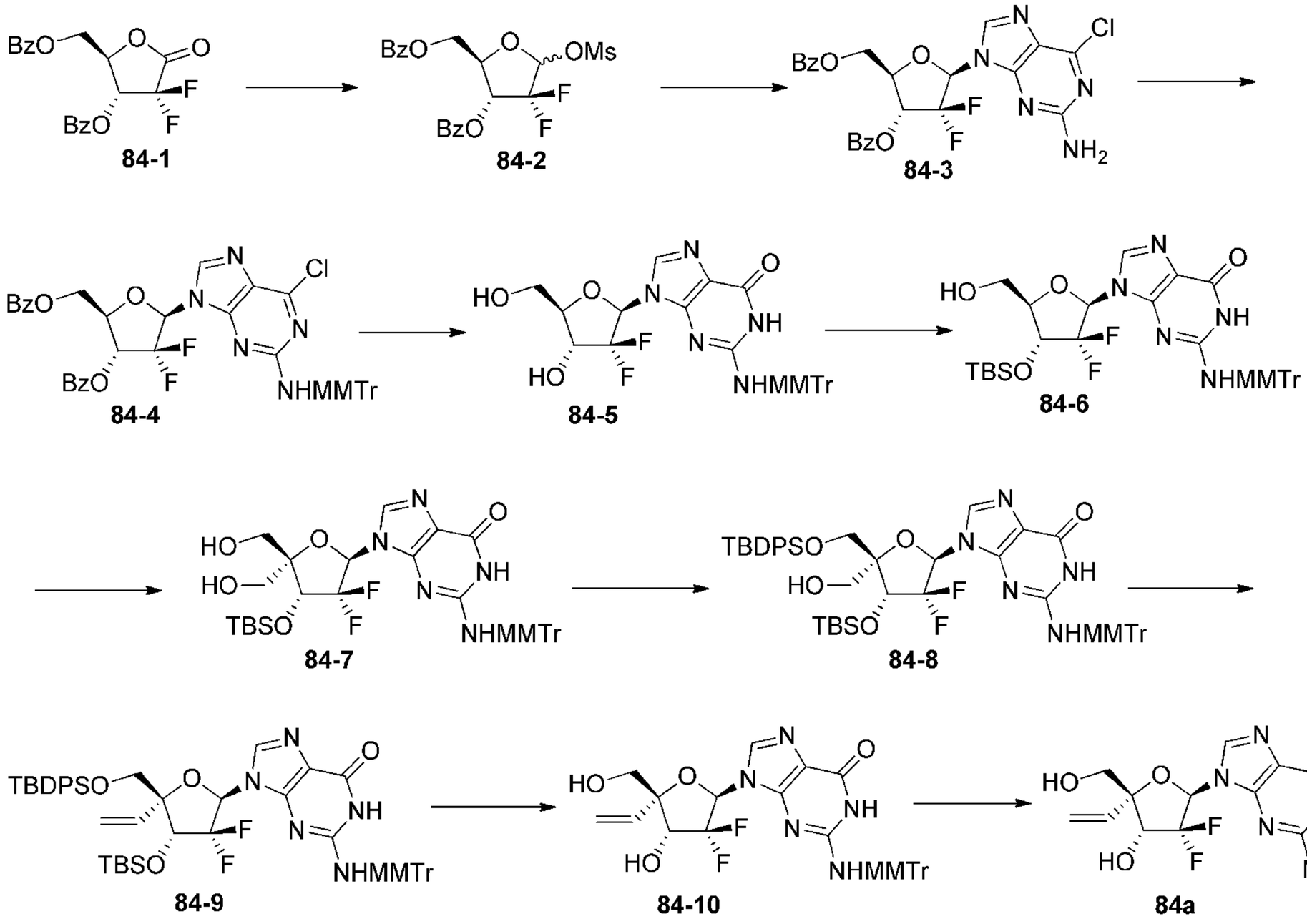
EtOAc. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified on a silica gel column (DCM/MeOH = 80:1 to 30:1) to give the iodide derivative (10.3 g, 93%) as a light yellow solid. To a stirred solution of the iodide derivative (10.2 g, 15.3 mmol) in dry THF (300 mL) was added DBU (4.7 g, 30.1 mmol). The mixture was stirred at 60°C for 8 h. The solution was diluted with a $NaHCO_3$ solution and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified on a silica gel column (PE/EtOAc= 3:1 to 1:3) to afford **83-2** (6.2 g, yield 76%).

[0504] To a stirred solution of **83-2** (5.42 g, 10 mmol) in anhydrous CH_3OH (100 mL) was added $PbCO_3$ (13.7 g, 53.1 mmol). A solution of I_2 (12.3 g, 48.9 mmol) in CH_3OH (300 mL) was added dropwise at 0°C. The mixture was stirred at 25°C for 10 h. The solution was quenched with a $Na_2S_2O_3$ solution and extracted with DCM. The organic layer was washed with a $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated to give a residue. The residue was purified by HPLC (0.1% HCOOH in water and MeCN) to give the desired methoxyl derivative (2.4 g, 34%). To a stirred solution of the methoxyl derivative (2.4 g, 3.4 mmol) in dry pyridine (20 mL) was added BzCl (723 mg, 5.2 mmol) dropwise at 0°C. The mixture was stirred at 0°C for 1 h. The solution was quenched with a $NaHCO_3$ solution and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated. Purified by a silica gel column (PE/EtOAc = 5:1 to 1:1) afforded **83-3** (2.1 g, 77%) as a white solid.

[0505] Compound **83-3** (2.0 g, 2.5 mmol), BzONa (3.6 g, 25 mmol) and 15-crown-5 (5.5 g, 25 mmol) were suspended in DMF (50 mL). The mixture was stirred at 110-125°C for 5 days. The precipitate was removed by filtration, and the filtrate was diluted with EA. The solution was washed with brine and dried over Na_2SO_4. The solvent was removed, and the residue was purified on a silica gel column (PE/EA = 10/1 to 2/1) to afford the crude Bz protected derivative (1.6 g, 80%). The Bz protected derivative (1.6 g, 2.0 mmol) was dissolved in methanolic ammonia (100 mL), and the mixture was stirred at 25°C for 20 h. The solvent was removed, and the residue was purified by a silica gel column (DCM/MeOH = 100:1 to 20:1) to the diol derivative as a white solid (410 mg, 35%). The diol derivative (200 mg, 0.34 mmol) was dissolved in HCOOH (24 g) and H_2O (6 g) at 25°C, and the mixture was stirred at 25°C for 1 h. The solution was evaporated to dryness, and dissolved in MeOH (30 mL). The mixture was stirred at 60°C for 12 h. The solution was evaporated to

dryness and dissolved in EtOAc (50 mL). The mixture was stirred at 60°C for 1 h. The mixture was then filtered and washed with EtOAc to give **83a** as a white solid (46.1 mg, 43%). ESI-MS: m/z 316.1 $[M+H]^+$.

EXAMPLE 81
Preparation of Compound 84a



[0506] To a stirred solution of **84-1** (100.0 g, 265.9 mmol) in dry THF (1000 mL) was added $Li(O\text{-}t\text{-}Bu)_3AlH$ (318.9 mL, 318.9 mmol) at -78°C under N_2. The mixture was stirred at -78°C for 1 h and then at R.T for 1 h. The reaction mixture was cooled to -50°C and quenched with ice and a saturated NH_4Cl solution. The mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated to afford the 1'-*OH* derivative (100.5 g) as a white solid. To a stirred solution of the 1'-*OH* derivative (100.5 g, 265.9 mmol) in dry DCM (600 mL), NEt_3 (110 mL) and MsCl (45.5 g, 298.0 mmol) were added dropwise at 0°C. The mixture was stirred at R.T. for 2 h. The mixture was quenched with ice water at 0°C and extracted with DCM. The organic layer was dried over Na_2SO_4, concentrated and purified on a silica gel column (PE: EA = 50:1 to 5:1) to afford **84-2** (113.4 g, yield: 93.9%) as a white solid.

[0507] To a suspension of compound 6-chloro-9*H*-purin-2-amine (70.1 g, 414.7 mmol), HMDS (480 mL) and $(NH_4)_2SO_4$ (0.8 g) was added dry DCE (400 mL). The mixture was refluxed under N_2 for 18 h and then cooled to R.T. To the silylated 2-amino-6-chloropurine solution was added **84-2** (78.0 g, 171.1mmol) and TMSOTf (60 mL, 331.9 mmol). The mixture was refluxed overnight, concentrated and neutralized with a $NaHCO_3$ solution. The resulting precipitate was filtered, and the filtrate was extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated. Chromatography on a silica gel column (PE: EA = 5:1 to 2:1) gave **84-3** (10.8 g, yield: 11.9%) as a light yellow solid.

[0508] To a suspension of **84-3** (30.0 g, 56.6 mmol) in DCM (300 mL) were added MMTrCl (34.9 g, 113.2 mmol) and $AgNO_3$ (19.3 g, 113.2 mmol). The reaction mixture was cooled to 0°C, and collidine (18.0 g, 150 mmol) was added. The resulting suspension was stirred at R.T. for 12 h. The suspension was filtered. The filtrate was extracted with DCM and washed with a $NaHCO_3$ solution. The organic layer was dried over Na_2SO_4 and concentrated. Purification by a silica gel column (PE: EA = 20:1 to 3:1) to give **84-4** (35.0 g, yield: 77.9%) as a light yellow solid. ESI-MS: m/z 802 $[M+H]^+$.

[0509] To a stirred solution of **84-4** (35.0 g, 43.6 mmol) in dry MeOH (400 mL) was added NaOMe (23.5 g, 436 mmol) and 2-mercapto-ethanol (30.6 g, 392.4 mmol). The mixture was refluxed overnight. The pH was adjusted to 9-10 with CO_2. The precipitate was filtered, and the filtrate was concentrated. Purification on a silica gel column (PE: EA = 10:1 to 1:1) gave pure **84-5** (24.0 g, yield 95.7%) as a light yellow solid.

[0510] To a solution of **84-5** (24.0 g, 41.7 mmol) in pyridine (250 mL) was added DMTrCl (28.2 g, 83.5 mmol) at 0°C. The solution was stirred at R.T. for 15 h. MeOH (50 mL) was added, and the mixture 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, filtered, concentrated and purified by a silica gel column (DCM: MeOH = 200:1 to 50:1) to give a first intermediate (27.6 g) as a yellow solid. To a solution of the first intermediate (27.6 g, 31.5 mmol) in DCM (200 mL) was added imidazole (4.3 g, 63 mmol) and TBSCl (9.5 g, 63 mmol). The mixture was stirred at R.T. for 12 h. The solution was washed with $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered, concentrated and purified by a silica gel column (DCM: MeOH = 200:1 to 100:1) to give a

second intermediate (30.2 g) as a yellow solid. To a solution of the second intermediate (30.2 g, 30.4 mmol) in anhydrous DCM (50 mL) was added $Cl_2CHCOOH$ (20 ml) in anhydrous DCM (500 mL). The mixture was stirred at -78°C for 1 h. $Cl_2CHCOOH$ (30 mL) was added at -78°C. The mixture was stirred at -20°C for 2 h. 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 a silica gel column (DCM: MeOH = 200:1 to 30:1) to give **84-6** (18.0 g, 62.5%) as a white solid. ESI-LCMS: m/z 690.0 $[M+H]^+$.

[0511] Compound **84-6** (7.0 g, 10.0 mmol) was added to a suspension of DMP (10.6 g, 25 mmol) in anhydrous CH_2Cl_2 (100 mL) at 0°C. The mixture was stirred at 25°C for 2 h. The solvent was removed in vacuo, and the residue triturated with diethyl ether (100 mL). The mixture was filtered through a pad of $MgSO_4$. The organic solvent was stirred with an equal volume of $Na_2S_2O_3.5H_2O$ in 100 mL of saturated $NaHCO_3$ until the organic layer became clear (10 min). The organic layer was separated, washed with brine, and dried over $MgSO_4$. The solvent was removed in vacuo to give a third intermediate as a red solid (6.5 g, 95%). To a solution of the third intermediate (6.5 g, 9.5 mmol) in 1,4-dioxane (80 mL) was added 37% CH_2O (6.0 mL, 60 mmol) and 2N NaOH aqueous solution (9.5 mL, 19 mmol). The mixture was stirred at 25°C for 2 h and then neutralized with AcOH to pH 7. EtOH (30 mL) and $NaBH_4$ (3.8 g, 100 mmol) were added, and the mixture 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_2SO4. Purification by a silica gel column (DCM: MeOH = 200:1 to 30:1) gave **84-7** (4.2 g, 58.3%) as a yellow solid.

[0512] To a solution of **84-7** (4.2 g, 5.8 mmol) in DCM (50 mL) was added pyridine (5 mL) and DMTrCl (1.9 g, 5.8 mmol) at -20°C. The solution was stirred at 0°C for 2 h. The reaction mixture was treated with MeOH (15 mL), and then concentrated. The residue was purified by a silica gel column (DCM: MeOH = 200:1 to 50:1) to give the fourth intermediate (1.3 g) as a yellow solid. To a solution of the fourth intermediate (1.3 g, 1.3 mmol) in anhydrous pyridine (15 mL) was added TBDPSCl (1.1 g, 3.9 mmol) and $AgNO_3$ (0.68 g, 4.0 mmol). The mixture was stirred at 25°C for 15 h. The mixture was filtered, concentrated, dissolved in EtOAc and washed with brine. The organic layer was dried over Na_2SO_4. Purification by a silica gel column (DCM: MeOH = 200:1 to 100:1) gave a fifth

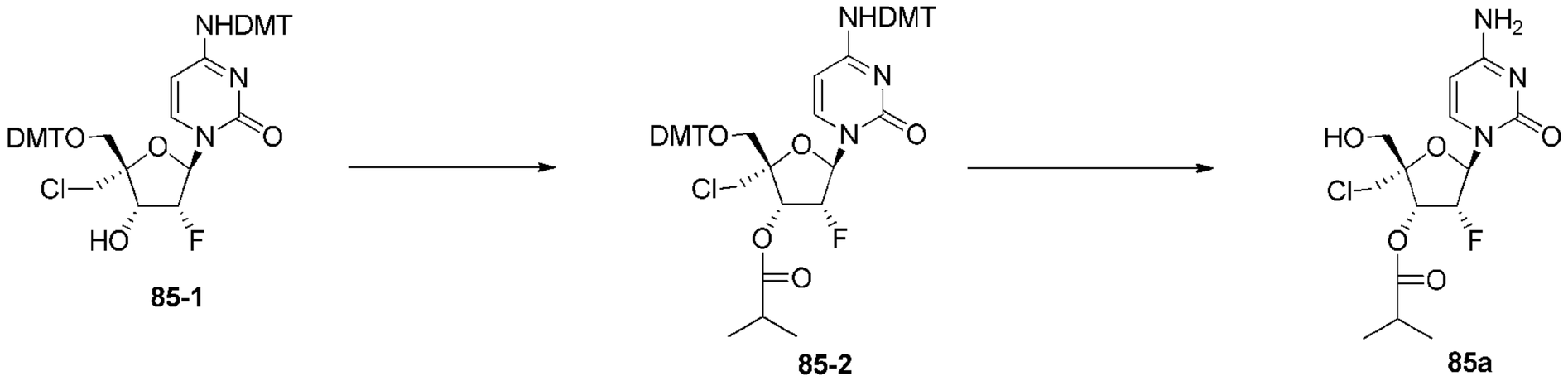
intermediate (1.4 g) as a solid. To a solution of the fifth intermediate (1.4 g, 1.1 mmol) in anhydrous DCM (50 mL) was added $Cl_2CHCOOH$ (0.7 ml) in anhydrous DCM (18 mL). The mixture was stirred at -78°C for 1 h. $Cl_2CHCOOH$ (1.5 ml) was added at -78°C, and the mixture was stirred at -20°C for 1.5 h. The mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with DCM. The organic layer was dried over Na_2SO_4. Purification by a silica gel column (DCM: MeOH = 200:1 to 50:1) gave **84-8** (650 mg, 11.6%) as a white solid.

[0513] To a solution of pyridine (521 mg, 6.59 mmol) in anhydrous DMSO (5 mL) was added TFA (636 mg, 5.58 mmol) dropwise at 10°C under N_2. The mixture was stirred until a clear solution formed. To this solution (0.8 mL) was added a mixture of **84-8** (650 mg, 0.68 mmol) and DCC (410 mg, 2.0 mmol) in anhydrous DMSO (5 mL) at R.T. under N_2. The mixture was stirred at 20 °C overnight. Water (30 mL) was added. The mixture was diluted with DCM (30 mL) and filtered. The filtrate was extracted with DCM. The organic layers were washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified on a silica gel column (PE: EA = 10:1 to 1:1) to give the sixth intermediate (600 mg) as a yellow solid. To a stirred solution of Methyl-triphenyl-phosphonium bromide (714 mg, 2.0 mmol) in anhydrous THF (5 mL) was added n-BuLi (0.8 mL, 2.0 mmol, 2.5 M in THF) at -78°C dropwise over 1 min. Stirring was continued at 0 °C for 1 h. The sixth intermediate (600 mg, 0.63 mmol) was added to the mixture, and the mixture was stirred at 25°C for 15 h. The reaction was quenched with saturated NH_4Cl (20 mL) and extracted with EtOAc. The combined organic phase was dried with Na_2SO_4, filtered and evaporated to dryness to give a light yellow oil. The oil was purified by column chromatography (DCM: MeOH = 200:1 to 50:1) to give **84-9** (250 mg, 38.5%) as a yellow solid.

[0514] Compound **84-9** (250 mg, 0.26 mmol) was dissolved in THF (5.0 mL). TBAF (131 mg, 0.5 mmol) was added at 20°C, and stirring was continued for 2 h. The solution was evaporated to dryness. The residue was dissolved in EA (50 mL) and washed with water (2X). The solution was evaporated to dryness, and purified by a silica gel column (PE: EA = 10:1 to 1:2) to give **84-10** (57.6 mg, 36.9%) as a white solid. ESI-LCMS: m/z 602.0 $[M+H]^+$.

[0515] A solution of **84-10** (27 mg) in 1.5 mL of 80% formic acid stood at R.T. for 4.5 h and then concentrated to dryness. The residue was mixed with water and lyophilized. MeOH (1.5 mL) and TEA (0.1 mL) were added, and the mixture was concentrated. The precipitate from MeOH and EtOAc was filtered and washed with EtOAc to give **84a** (9.3 mg) as a slightly-amber solid. ESI-MS: m/z 328.4 $[M-H]^-$.

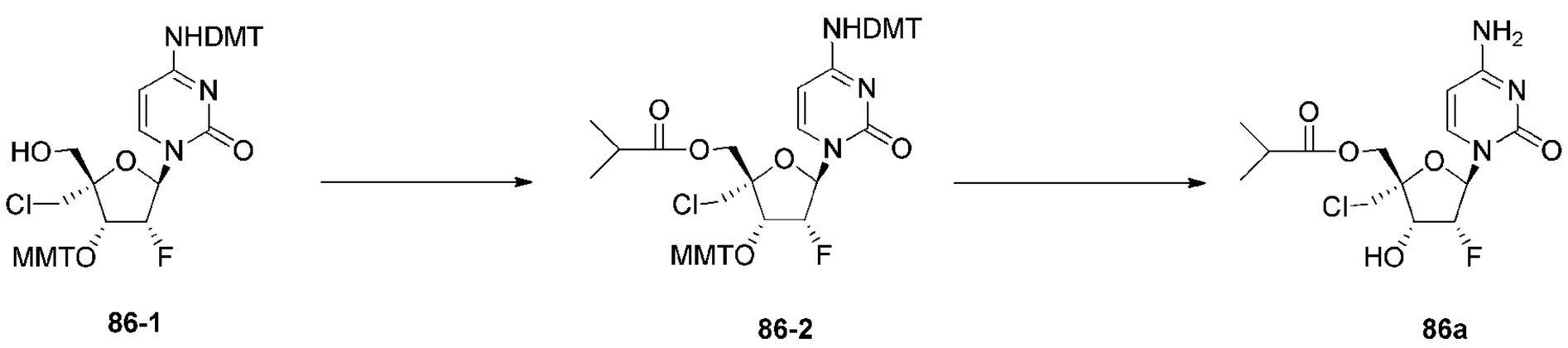
EXAMPLE 82
Preparation of Compound 85a



[0516] A mixture of **85-1** (200 mg; 0.22 mmol) in pyridine (2.5 mL) and isobutyric anhydride (44 μL; 1.2 equiv) was stirred R.T. overnight. The mixture was concentrated, and the residue partitioned between EtOAc (50 mL) and water. The organic layer was washed with 1N citric acid, water, saturated aqueous $NaHCO_3$ and brine. The mixture was dried with Na_2SO_4. The solvent was evaporated and the residue was purified on a silica column (10 g column) using hexanes/EtOAc (30 to 100% gradient) to give **85-2** (0.16 g, 75%).

[0517] A solution of **85-2** (0.16 g; 0.16 mmol) in 80% aq. HCOOH (5 mL) was stirred at R.T. for 3 h. The solvent was evaporated and then co-evaporated with toluene. Purification on a silica column (10 g column) with CH_2Cl_2 /MeOH (4-10% gradient) gave **85a** (43 mg, 74%). MS: m/z = 362.1 [M+1].

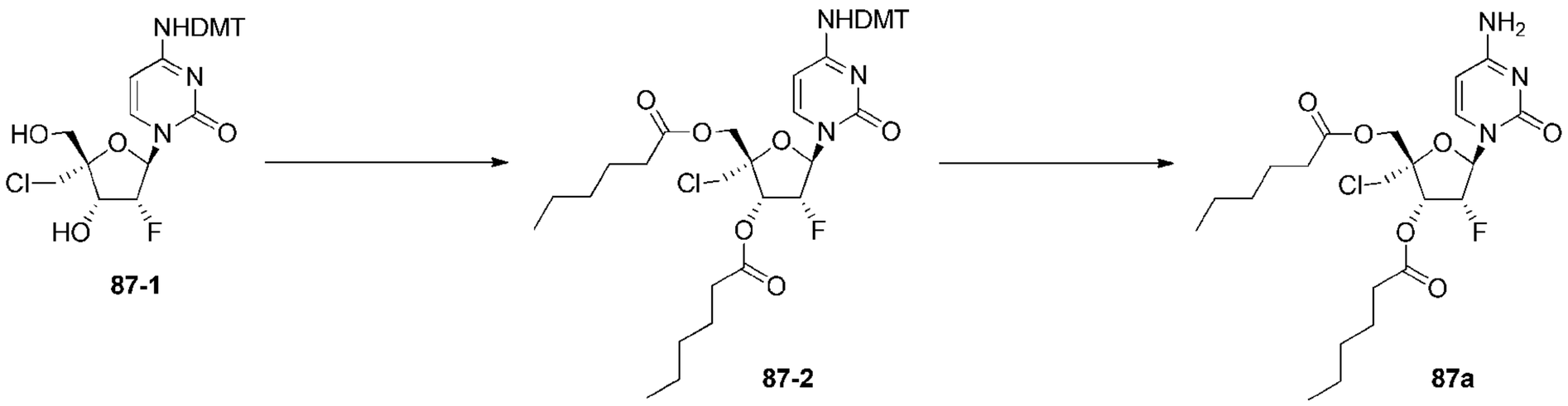
EXAMPLE 83
Preparation of Compound 86a



[0518] Compound **86-2** was prepared using a similar procedure for preparing **85-2** with the following: **86-1** (220 mg; 0.22 mmol), (2.5 mL), isobutyric anhydride (0.13 mL; 3.6 equiv), EtOAc (30 mL), and hexanes/EtOAc (30 to 100% gradient) to give **86-2** (175 mg, 85%).

[0519] Compound **86a** was prepared using a similar procedure for preparing **85a** with the following: **86-2** (117 mg; 0.13 mmol), 80% aq. HCOOH (4 mL) and CH_2Cl_2 /MeOH (4-10% gradient) to give **86a** (36 mg, 77%). MS: m/z = 364 [M+1].

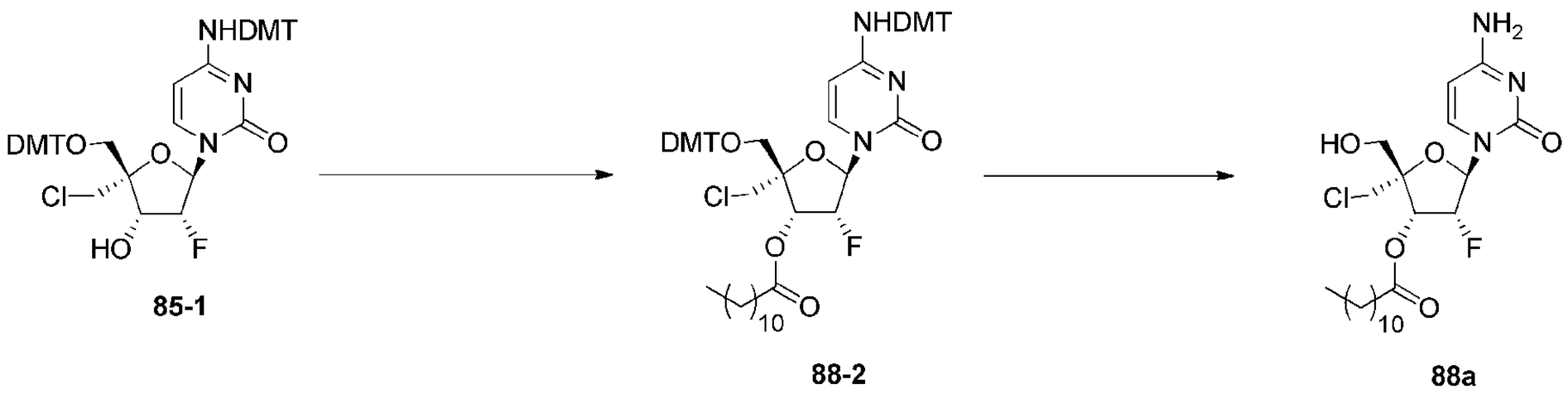
EXAMPLE 84
Preparation of Compounds 87a



[0520] Compound **87-2** was prepared using a similar procedure for preparing **46-2** with the following: **87-1** (178 mg, 0.3 mmol), hexanoic anhydride (0.14 mL, 2 equiv.), pyridine (3 mL) to give **87-2**. (120 mg, 50%).

[0521] Compound **87a** was prepared using a similar procedure for preparing **85a** with the following: **87-2** (120 mg, 0.15 mmol), 80% aq. HCOOH and CH_2Cl_2 /MeOH (4-10% gradient) to give **87a** (62mg, 85%). MS: m/z = 488 [M-1].

EXAMPLE 85
Preparation of Compound 88a

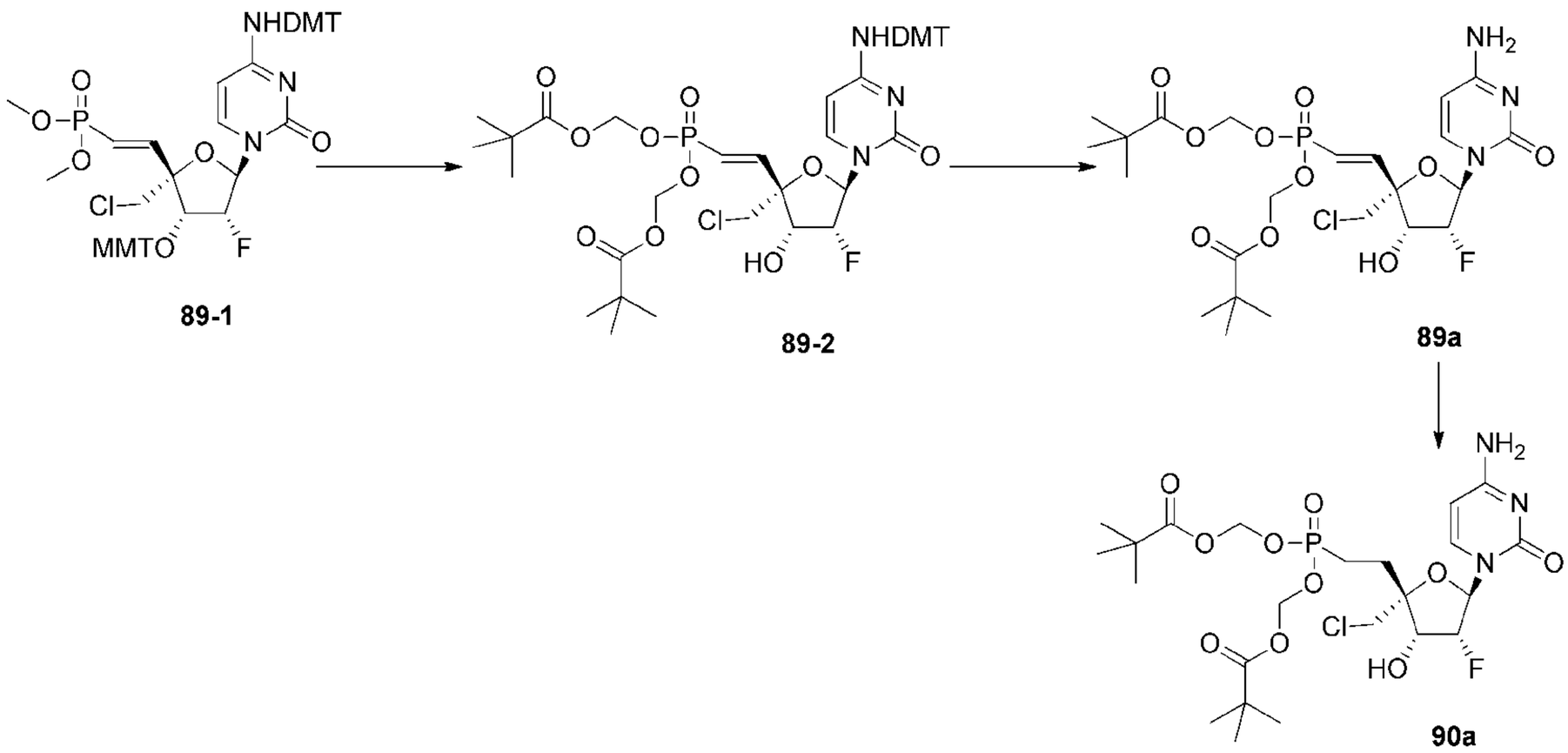


[0522] Compound **88-2** was prepared using a similar procedure for preparing **85-2** with the following: **85-1** (220 mg; 0.24 mmol), pyridine (3 mL), dodecanoyc anhydride (0.12

g; 1.3 equiv), EtOAc (50 mL) and hexanes/EtOAc (25 to 80% gradient) to give **88-2** (0.22 g, 85%).

[0523] Compound **88a** was prepared using a similar procedure for preparing **85a** with the following: **88-2** (0.19 g; 0.17 mmol), 80% aq. HCOOH (5 mL) and CH_2Cl_2 /MeOH (4-10% gradient) to give **88a** (66 mg, 82%). MS: m/z = 474 [M-1].

EXAMPLE 86
Preparation of Compounds 89a and 90a



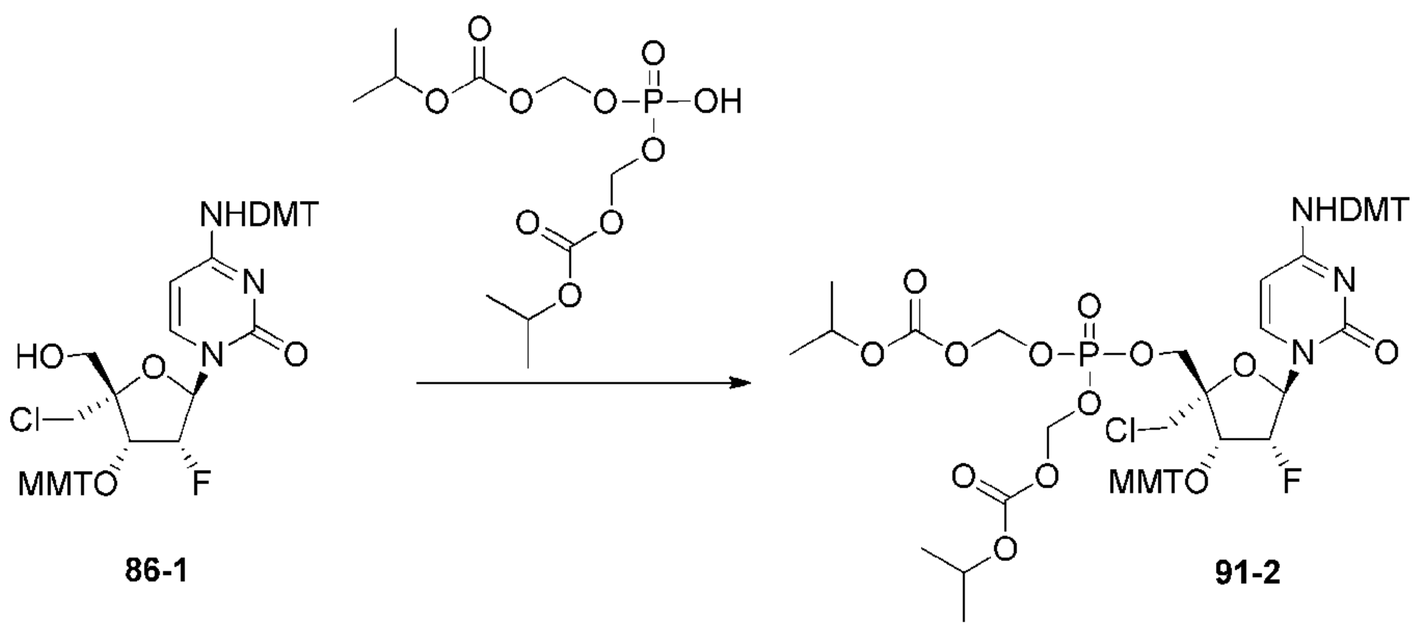
[0524] To a solution of **89-1** (175 mg; 0.18 mmol) in MeCN (2.5 mL) at 0°C was added TMSBr (0.28 mL; 10 equiv.). The mixture was stirred at R.T. for 1 h, evaporated and treated with water. The obtained white solid was filtered, dried and washed with CH_2Cl_2. The white solid was then dissolved in NMP (2 mL) and treated with DIPEA (94 µL; 3 equiv.) and pivaloyloxymethyliodide (84 µL; 3 equiv.). The mixture was stirred at R.T. for 1 day, and then partitioned between water (20 mL) and *tert*-butyl methyl ether (TBME; 60 mL). The organic layer was washed with saturated aqueous $NaHCO_3$, water and brine. The combined aqueous washings were back extracted with TBME (2 x 20 mL). The combined organic extract was dried and purified on a silica column (10 g column) with CH_2Cl_2 /i-PrOH (2-10% gradient) to give **89-2** (42 mg, 26%).

[0525] A solution of **89-2** in 80% aq. HCOOH was stirred at R.T. for 3 h. The solvent was evaporated and then co-evaporated with toluene. Purification on a silica column

(10 g column) with CH_2Cl_2 /MeOH (4-15% gradient) gave **89a** (17 mg, 74%). MS: m/z = 598 [M+1].

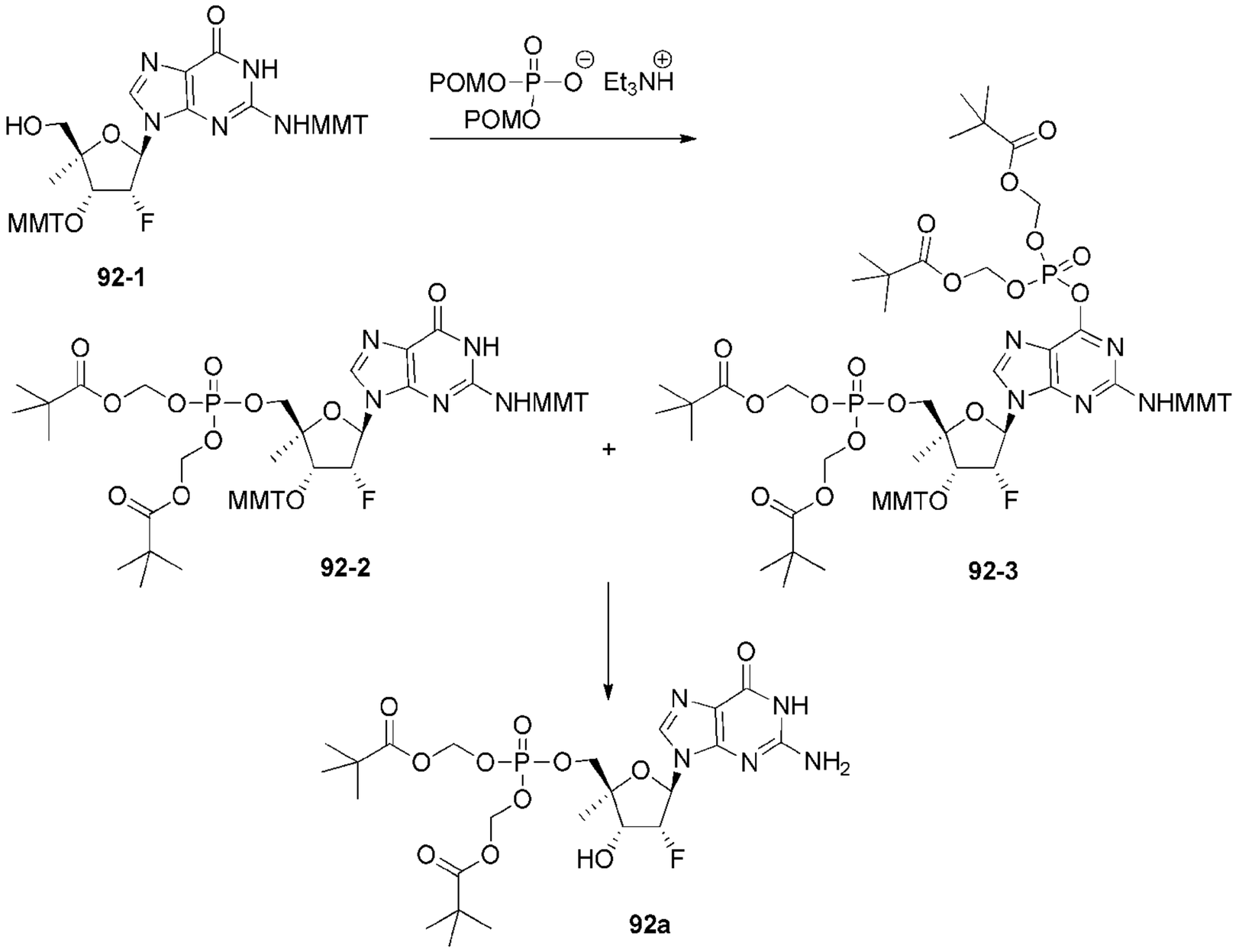
[0526] A mixture of **89a** (12 mg; 0.02 mmol) in EtOH (1 mL) and Pd/C (10%; 2.5 mg) was stirred overnight under an atmospheric pressure of hydrogen. The mixture was filtered through a Celite pad. The solvent was evaporated and the product was purified on a silica column (10 g column) with CH_2Cl_2 /MeOH (4-17% gradient) to give **90a** (6 mg, 50%). MS: m/z = 600 [M+1].

EXAMPLE 87
Preparation of Compound 91a


NHDMT
HO
Cl
MMTO
F
O
O
O

[0528] Compound **91a** was prepared using a similar procedure for preparing **85a** with the following: **91-2** (87 mg; 0.07 mmol), 80% aq. HCOOH (5 mL) and CH_2Cl_2 /MeOH (4-15% gradient) to give **91a** (36 mg, 85%). MS: m/z = 606 [M+1].

EXAMPLE 88
Preparation of Compound 92a

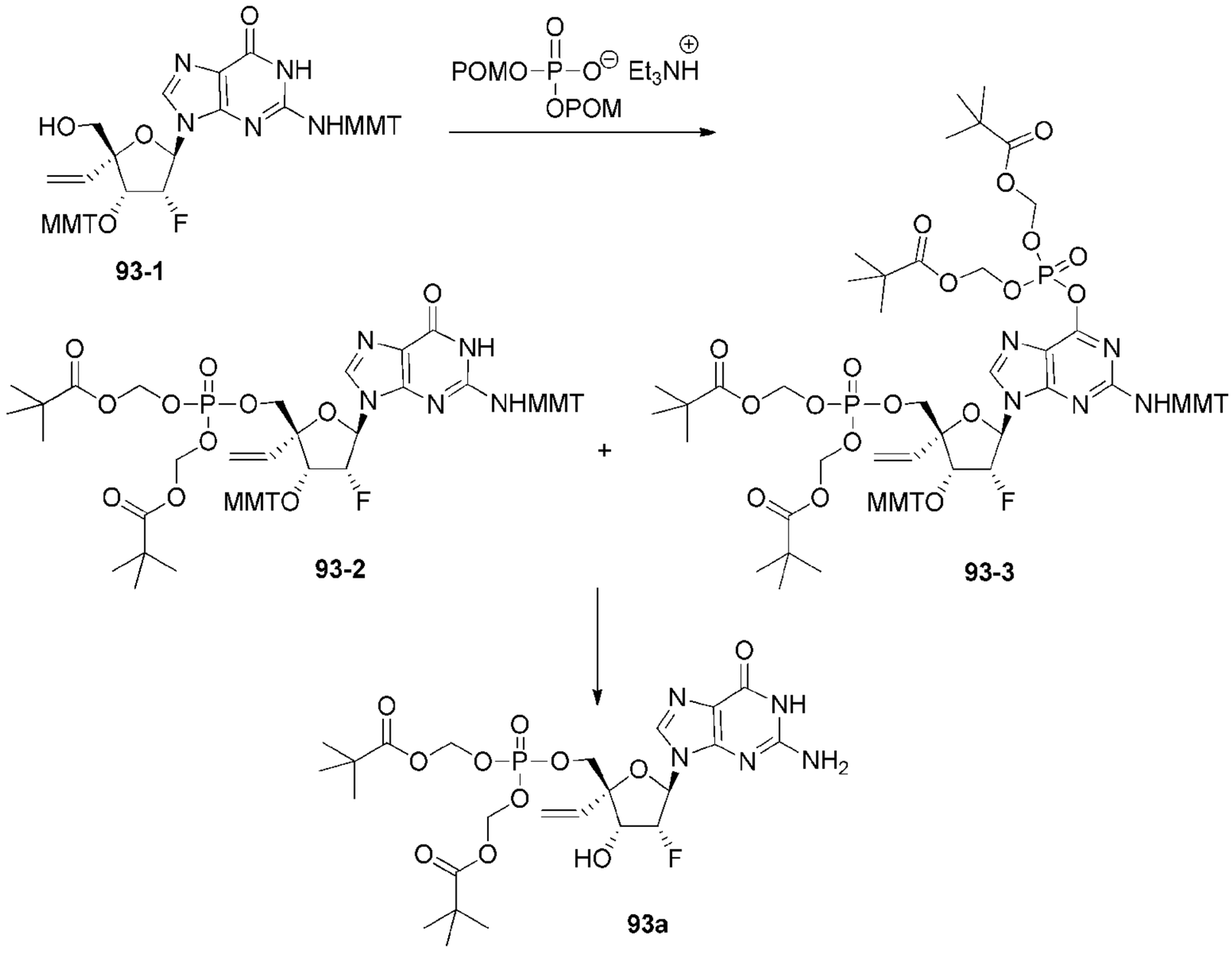


[0529] To a solution of triethylammonium bis(POM)phosphate (0. 48 mmol, prepared from 176 mg of bis(POM)phosphate and 0.15 mL of Et_3N) in THF (2 mL) was added **92-1** (150 mg; 0.18 mmol) followed by diisopropylethyl amine (0.31 mL; 10 equiv), BOP-Cl (229 mg; 5 equiv), and 3-nitro-1,2,4-triazole (103 mg; 5 equiv). The mixture was stirred at R.T. for 90 mins., and then diluted with CH_2Cl_2 (30 mL). The mixture was washed with saturated aqueous $NaHCO_3$ and brine. The mixture was dried with Na_2SO_4. The solvent was evaporated, and the residue was purified on a silica column (10 g column) with CH_2Cl_2 /i-PrOH (2-10% gradient) to obtain **92-2** (44 mg, 21%) and **92-3** (73 mg, 28%).

[0530] A mixture of **92-2** and **92-3** (73 mg and 44 mg) and 80% aq. HCOOH (3 mL) was heated for 30 mins., at 35°C. The solvent was evaporated and then coevaporated with toluene. The solvent was evaporated, and the residue was purified on a silica column

(10 g column) with CH_2Cl_2 /MeOH (4-10% gradient) to obtain **92a** (40 mg, 75%). MS: m/z = 608 [M+1].

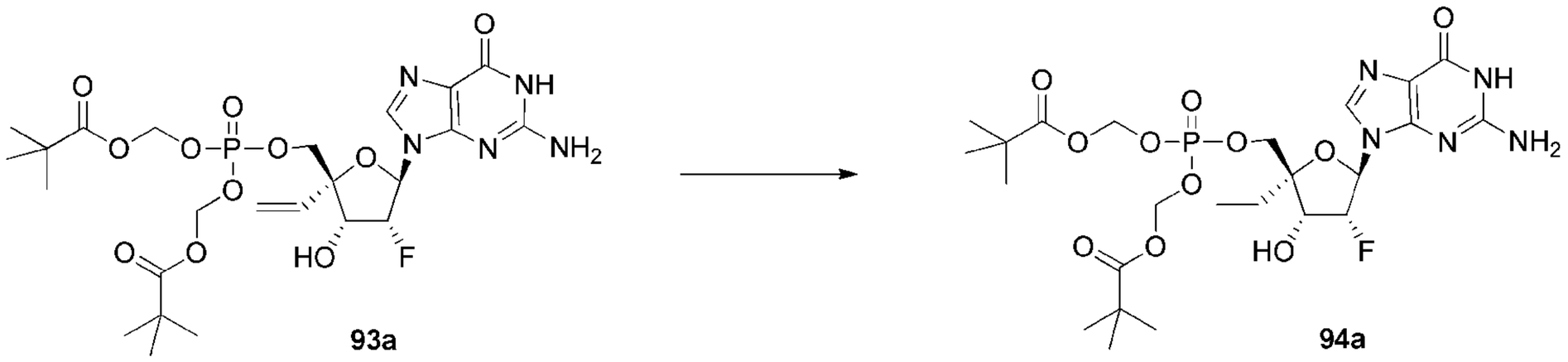
EXAMPLE 89
Preparation of Compound 93a



[0531] Compound **93-2** and **93-3** (68 mg and 80 mg, respectively) were prepared in the same manner from **93-1** (200 mg; 0.23 mmol) and bis(POM) phosphate (230 mg) with DIPEA (0.4 mL), BopCl (290 mg), and 3-nitro-1,2,4-triazole (130 mg) in THF (3 mL) as **92-2** and **92-3** from **92-1**.

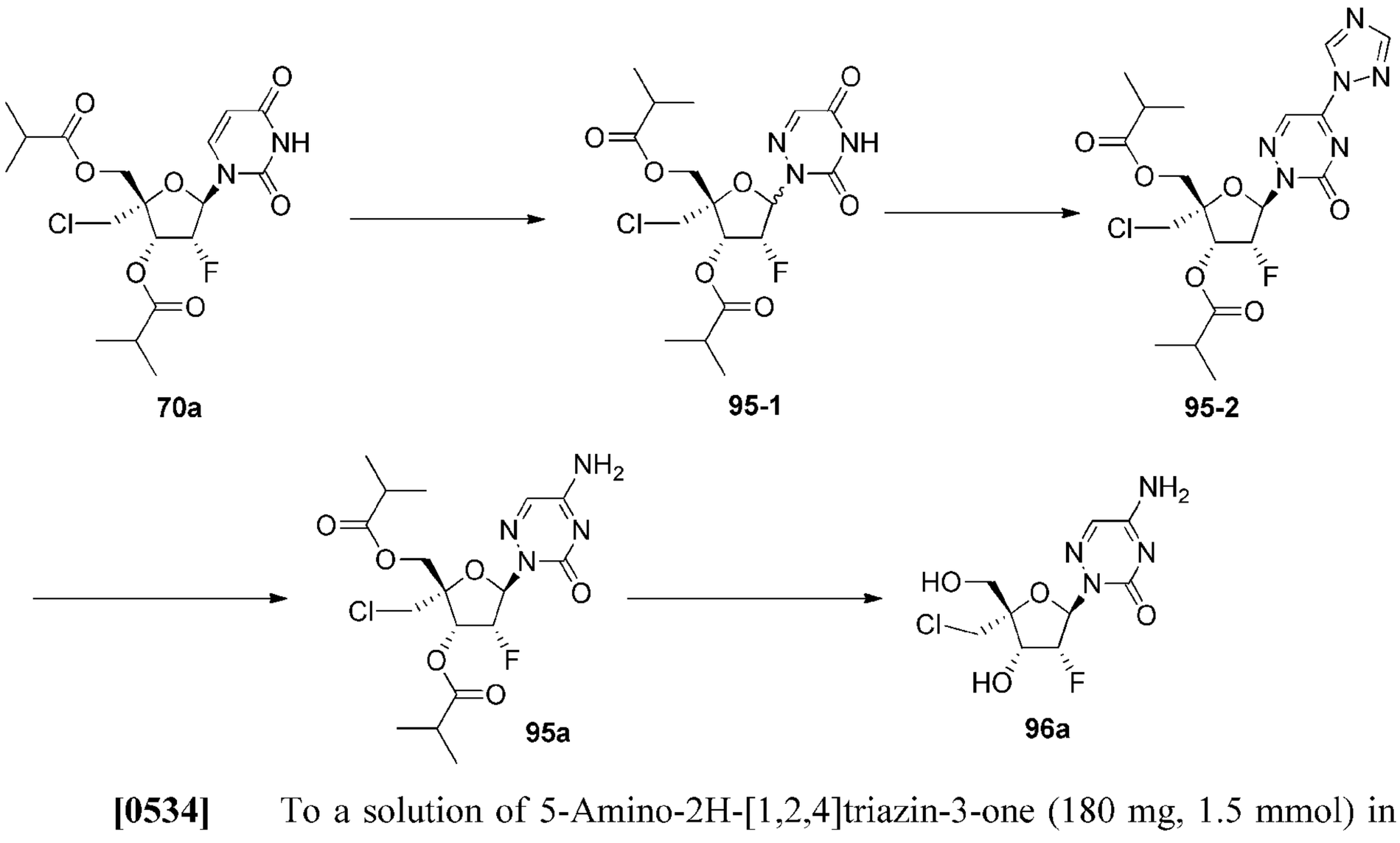
[0532] Compound **93-2** and **93-3** (68 mg and 80 mg, respectively) were converted into **93a** (42 mg) with formic acid in the same manner as **92a** from **92-2** and **92-3**. MS: m/z = 620 [M+1].

EXAMPLE 90
Preparation of Compound 94a



[0533] To a solution of **93a** (53 mg; 0.09 mmol) in EtOH (2 mL) was added 10% Pd/C (10 mg). The mixture stirred under hydrogen at atmospheric pressure for 1 h. The mixture was filtered through a Celite pad, and the filtrate evaporated. Purification on a silica column (10 g column) with CH_2Cl_2 /MeOH (4-11% gradient) yielded **94a** (45 mg, 81%). MS: m/z = 622 [M+1].

EXAMPLE 91
Preparation of Compounds 95a and 96a



[0534] To a solution of 5-Amino-2H-[1,2,4]triazin-3-one (180 mg, 1.5 mmol) in HMDS was added a catalytic amount of $(NH_4)_4SO_4$. The mixture was heated to reflux for 5 h. HMDS was evaporated to give a crude product. To a solution of the crude product in anhydrous CH_3CN was added **70a** (220 mg, 0.5 mmol) and TMSOTf (0.45 mL, 2.5 mmol).

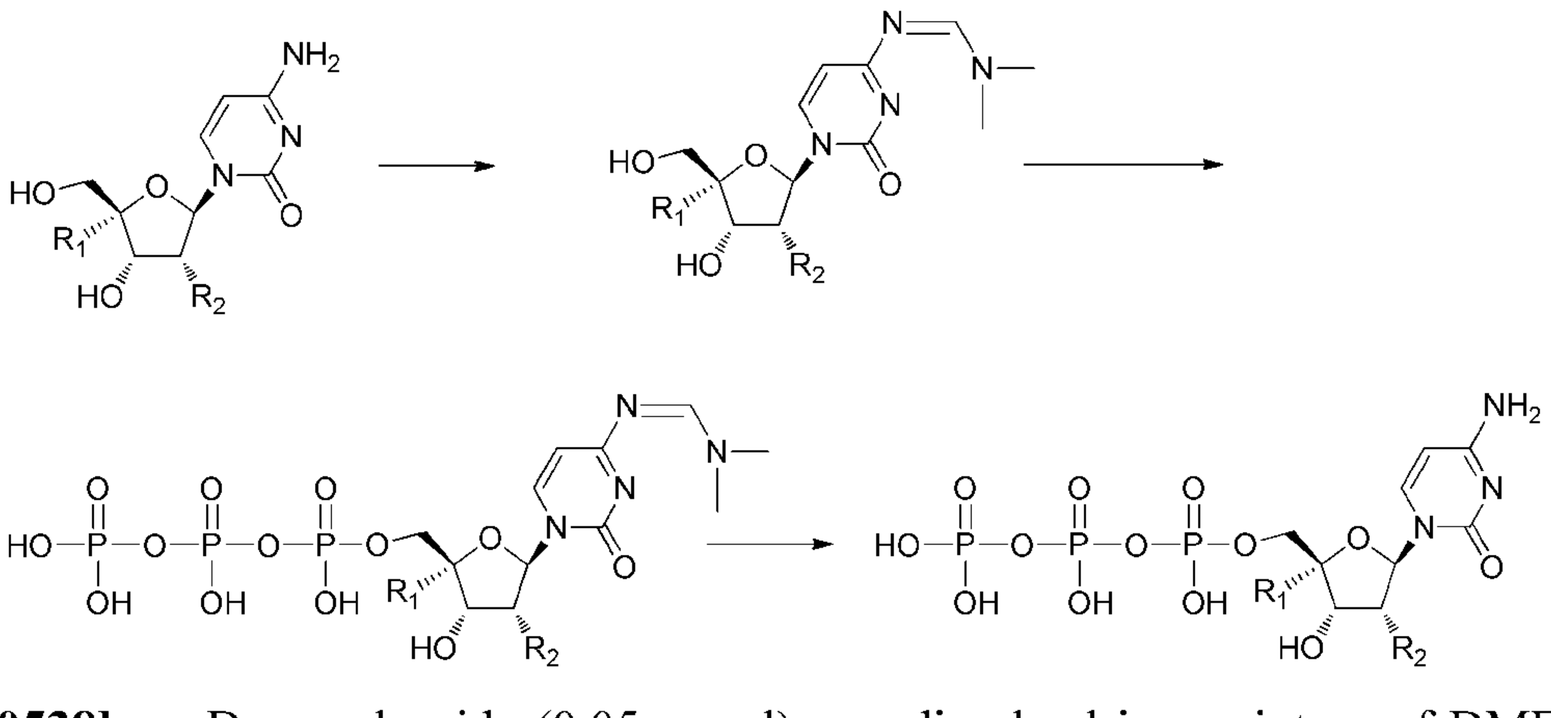
The mixture was heated to reflux for 24 h in a sealed tube. The reaction was quenched with $NaHCO_3$ and diluted with EA. The organic solvent was removed, and the residue was purified by prep-TLC first, and the by RP-HPLC (0.5% HCOOH in water and MeCN) to give the pure **95-1** (100 mg, 46%).

[0535] To a solution of **95-1** (80 mg, 0.18 mmol) in anhydrous CH_3CN was added 1,2,4-triazole (911 mg, 11.7 mmol) and TEA (1.45 g, 14.4 mmol). The mixture was cooled to 0°C and $POCl_3$ was added. The reaction mixture was stirred at 25°C for 24 h. The solvent was evaporated and partitioned with EA and water. The organic layer was concentrated to give the crude **95-2** (80 mg, 90%).

[0536] Compound **95-2** (90 mg, 0.18 mmol) was dissolved in 20 mL of saturated THF ammonia. The resulting solution was stirred at 25°C for 2 h. The solvent was removed, and the residue was purified on a silica gel column (EA: PE = 6:1) to give **95a** as a white solid (70 mg, 70%).

[0537] Compound **95a** (70 mg, 0.16 mmol) was dissolved in 20 mL of saturated MeOH ammonia. The resulting solution was stirred at 25°C for 2 h. The solvent was removed, and the residue was purified by RP-HPLC (0.5% HCOOH in water and MeCN) to give **96a** (5 mg, 11%) as a white solid. ESI-TOF-MS: m/z 295.1 $[M+H]^+$.

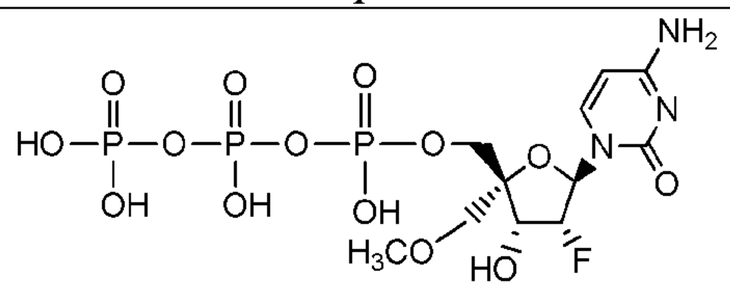
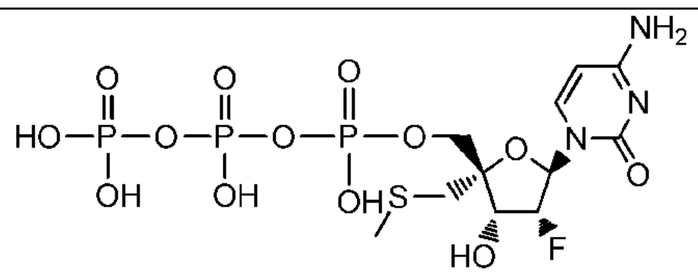
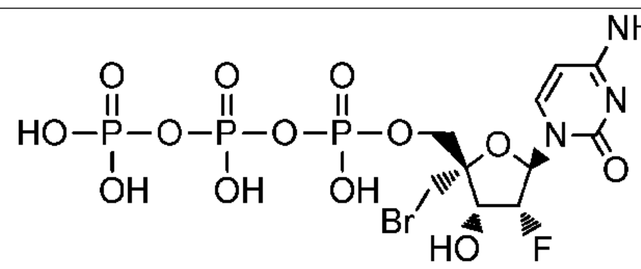
EXAMPLE 92
Preparation of Compounds 97a-97g

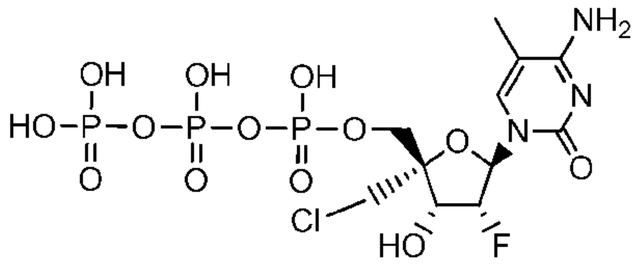
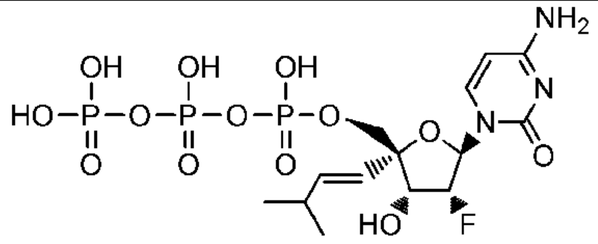
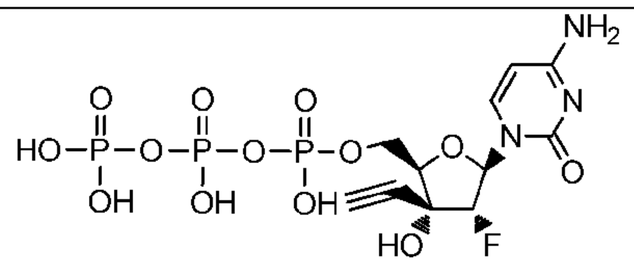
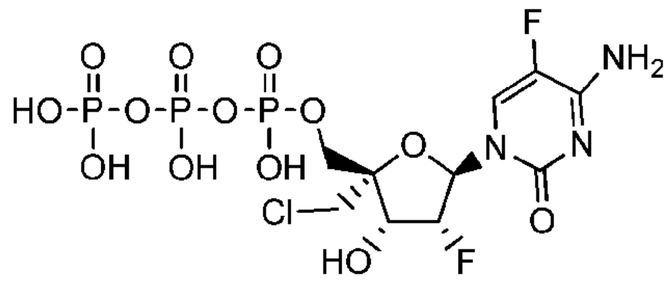


[0538] Dry nucleoside (0.05 mmol) was dissolved in a mixture of DMF (3 mL) and DMA-DMF (0.04 mL, 0.1 mmol). The reaction was kept at ambient temperature for 4 h and then evaporated to dryness. The residue was dissolved in a mixture of $PO(OMe)_3$ (0.7 mL) and pyridine (0.3 mL). The mixture was evaporated in vacuum for 15 min. at 42°C, than

cooled down to R.T. N-Methylimidazole (0.009 mL, 0.11 mmol) was added followed by $POCl_3$ (9µl, 0.11 mmol). The mixture was kept at R.T. for 20-40 mins. The reaction was controlled by LCMS and monitored by the appearance of the corresponding nucleoside 5'-monophosphate. 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 h at ambient temperature, the reaction was diluted with water (10 mL). The mixture was loaded on the column HiLoad 16/10 with Q Sepharose High Performance, and separation was done in a linear gradient of NaCl from 0 to 1N in 50mM TRIS-buffer (pH7.5). The triphosphate (**97a-f**) was eluted at 75-80%B. The corresponding fractions were concentrated. The residue was dissolved in 5% ammonium hydroxide, kept for 15 min. at R.T. and 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 50mM triethylammonium acetate buffer (pH 7.5) was used for elution. The corresponding fractions were combined, concentrated and lyophilized 3 times to remove excess of buffer.

Table 4 – Triphosphates obtained from Example 92

Compound	MS (M-1)	P(α)	P(β)	P(γ)
 **97a**	528.0	-6.71 -6.82(d)	-21.43(t)	-11.35 -11.47(d)
 **97b**	544.0	-6.25(bs)	-21.45(bs)	-11.44 -11.56(d)
 **97c**	575.7	-8.86 -9.00(d)	-22.95(t)	-11.81 -11.94(d)

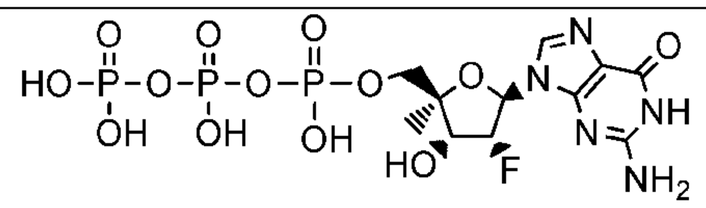
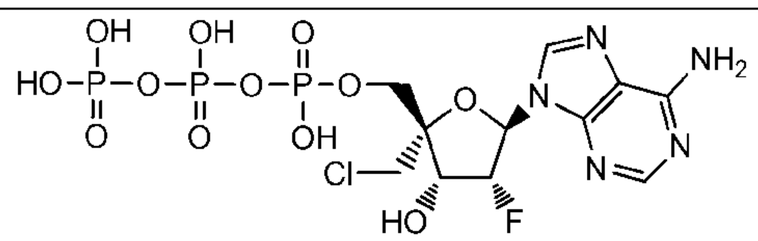
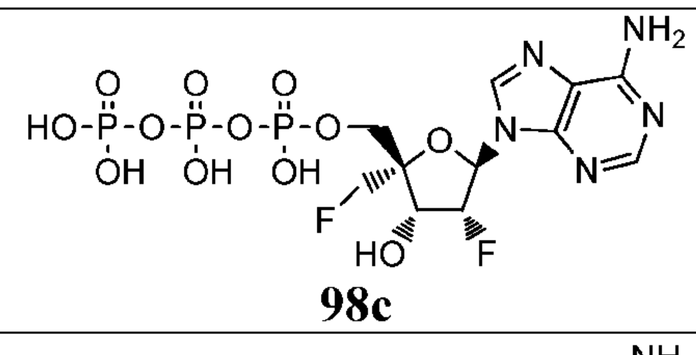
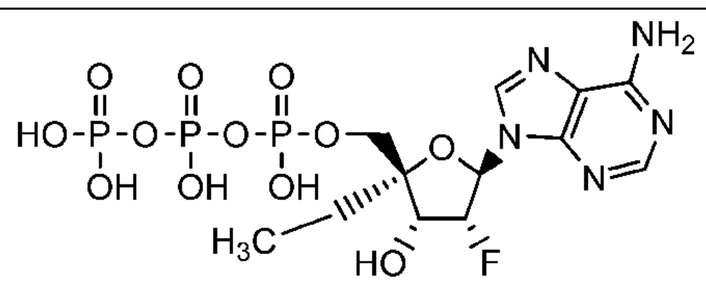
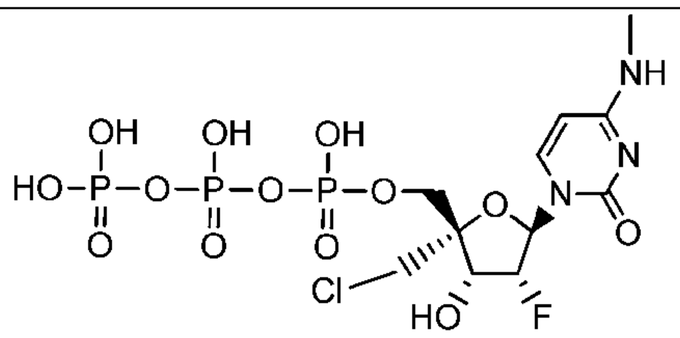
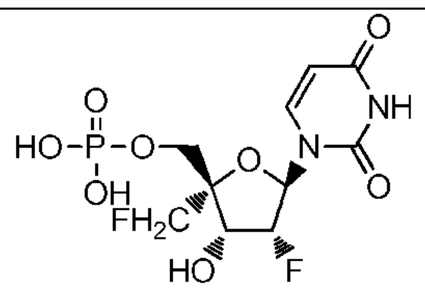
Compound	MS (M-1)	P(α)	P(β)	P(γ)
 **97d**	545.9	-9.41 -9.44(d)	-23.04 (t)	-12.00 -12.13(d)
 **97e**	552.1	-10.32 -10.44(d)	-23.26(t)	-11.84 -11.96(d)
 **97f**	508.4	-8.30 (bs)	-22.72(bs)	-11.51 -11.63(d)
 **97g**	550.1	-9.17 -9.29 (d)	-23.04 (t)	-11.97 -12.09(d)

EXAMPLE 93
Preparation of Compounds 98a-98e and 99a

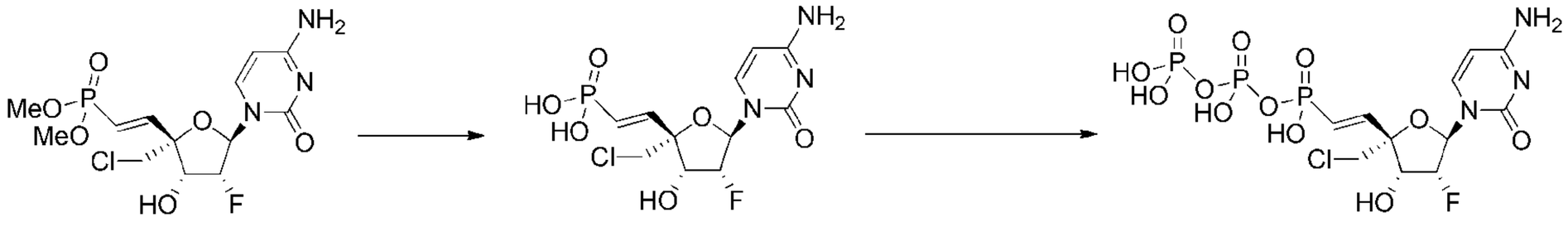
[0539] Dry nucleoside (0.05 mmol) was dissolved in a mixture of $PO(OMe)_3$ (0.7 mL) and pyridine (0.3 mL). The mixture was evaporated in vacuum for 15 mins. at 42^0C, than cooled down to R.T. N-Methylimidazole (0.009 mL, 0.11 mmol) was added followed by $POCl_3$ (9μl, 0.11 mmol). The mixture was kept at R.T. for 20-40 mins. The reaction was controlled by LCMS and monitored by the appearance of the corresponding nucleoside 5'-monophosphate. 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 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 50mM TRIS-buffer (pH7.5). The triphosphate (**98a-98e**) was eluted at 75-80%B. The 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 50mM triethylammonium acetate buffer (pH 7.5) was used for elution. The corresponding fractions were combined, concentrated and lyophilized 3 times to remove excess of buffer.

Table 5 – Compounds obtained from Example 93

Structure	MS (M-1)	P(α)	P(β)	P(γ)
 **98a**	538.0	-5.21 -5.33(d)	-20.56(t)	-11.09 -11.20(t)
 **98b**	556.2	-10.85(bs)	-23.11(bs)	-11.76 -11.88(d)
 **98c**	540.4	-8.86(bs)	-23.84(t)	-11.68 -11.80(d)
 **98d**	536.0	-9.35 -9.47(d)	-23.05(t)	-11.60 -11.72(d)
 **98e**	545.9	-10.54 -10.66	-23.26	-11.80 -11.93(d)
 **99a**	357.2	1.42(s)	NA	NA

EXAMPLE 94
Preparation of Compound 100a

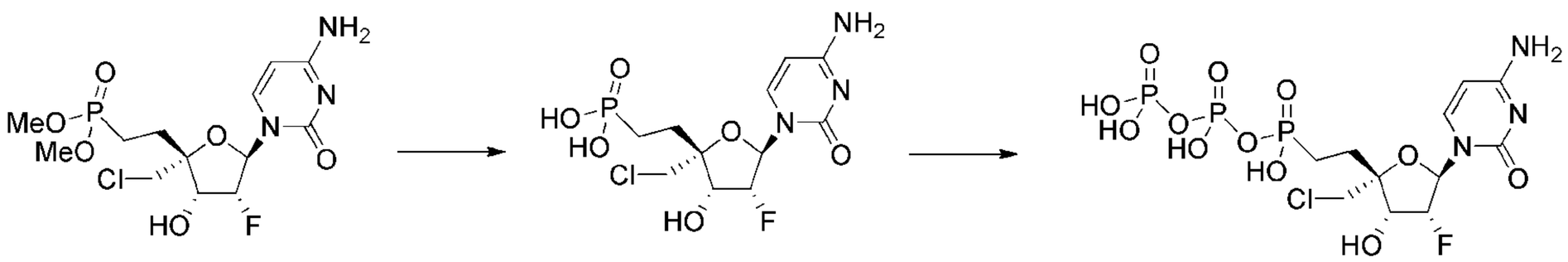


100-1 100-2 100a

[0540] To an ice-cold solution of **100-1** (22 mg; 0.055 mmol) in acetonitrile (0.5 mL) was added TMSBr (80 μL; 10 equiv.). The resulting mixture was stirred at R.T. for 1 h. The mixture was concentrated, and the residue was partitioned between water and diethyl ether. The aqueous layer was washed with Et_2O, neutralized with triethylammonium bicarbonate buffer and lyophilized to yield the triethylammonium salt of **100-2**.

[0541] Compound **100-2** was rendered anhydrous by coevaporating with pyridine and toluene. Anhydrous **100-2** was dissolved in HMPA (1 mL) and 1,1-carbonyldiimidazole (32 mg; 0.2 mmol) was added. The mixture was stirred at R.T. for 6 h. A solution of tetrabutylammonium pyrophosphate (0.22 g; ~0.2 mmol) in DMF (2 mL) was added. The mixture was stirred overnight at R.T. The mixture was diluted with triethylammonium acetate buffer and purified by RP-HPLC with a gradient 0-60% B (A: 50 mM aqueous TEAA, B: 50mM TEAA in MeOH) and repurified by RP-HPLC with a gradient 0-30% B to give **100a.** ^{31}P-NMR (D_2O): δ 3.22 (d, 1P), -8.21 (br, 1 P), -22.91 (br, 1 P). MS: m/z = 528 [M-1].

EXAMPLE 95
Preparation of Compound 100b

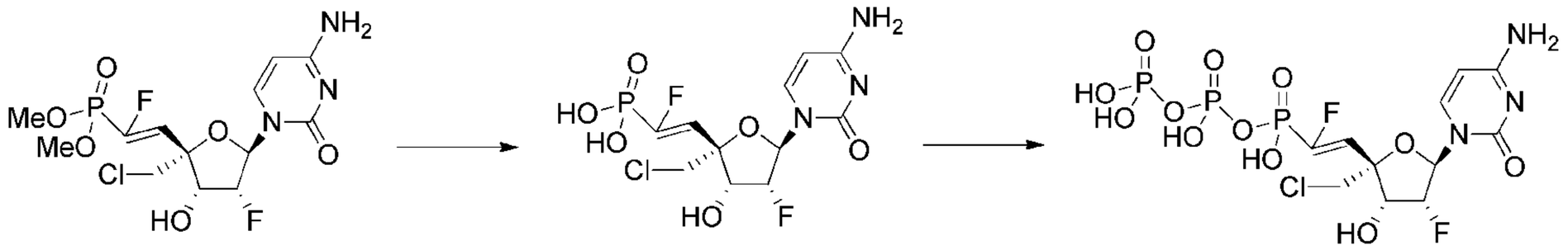


100-3 100-4 100b

[0542] Compound **100-4** was prepared from **100-3** (54 mg; 0.13 mmol) in acetonitrile (1.3 mL) with TMSBr (0.18 mL) using a similar procedure as described for the preparation of **100-2**.

[0543] Compound **100b** was prepared from **100-4** in HMPA (2 mL) with CDI (84 mg) and tetrabutylammonium pyrophosphate (0.5 g) in DMF (2 mL) using a similar procedure as described for the preparation of **100a**. ^{31}P-NMR (D_2O): δ 17.90 (d, 1P), -9.00 (d, 1 P), -22.91 (t, 1 P). MS: m/z = 530 [M-1].

EXAMPLE 96
Preparation of Compound 100c

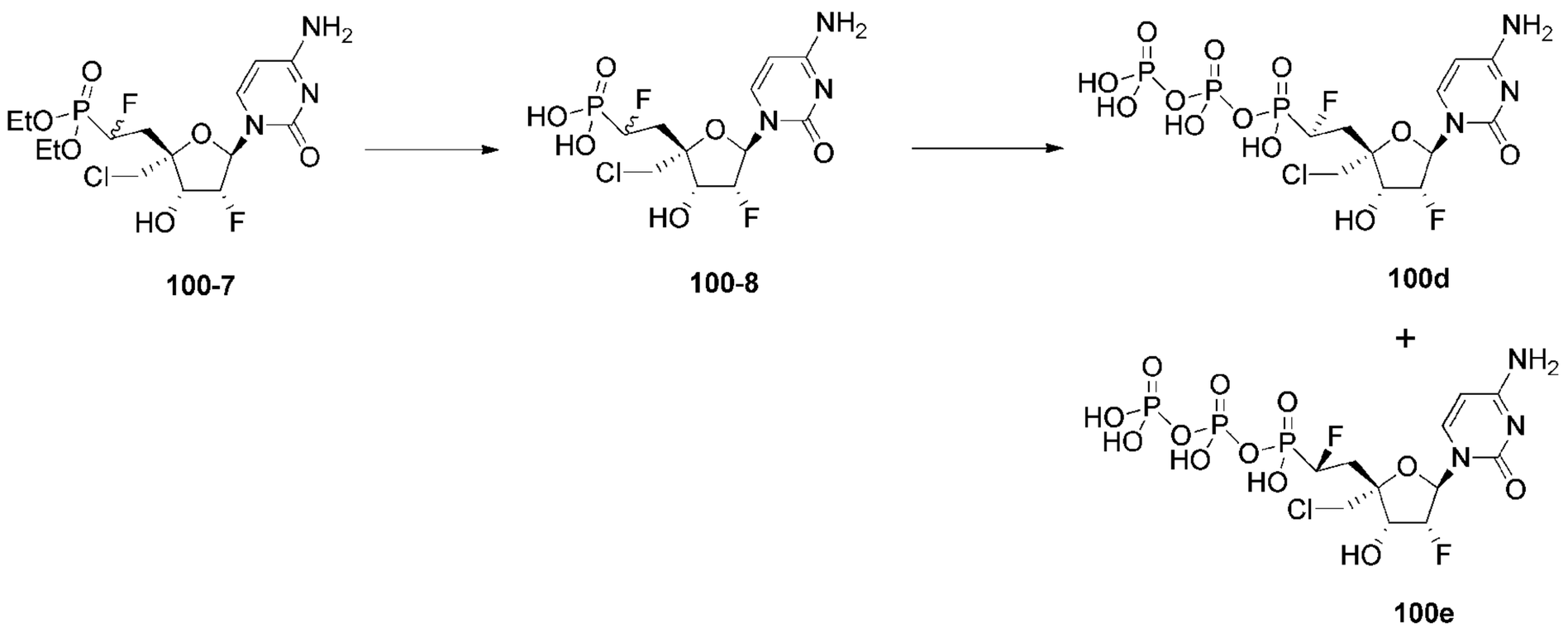


100-5 **100-6** **100c**

[0544] Compound **100-6** was prepared from **100-5** (40 mg; 0.09 mmol) in acetonitrile (1 mL) with TMSBr (0.1 mL) using a similar procedure as described for the preparation of **100-2**.

[0545] Compound **100c** was prepared from **100-6** in HMPA (1.5 mL) with CDI (50 mg) and tetrabutylammonium pyrophosphate (0.3 g) using a similar procedure as described for the preparation of **100a**. ^{31}P-NMR (D_2O): δ -7.13 (br, 1P), -10.14 (d, 1 P), -22.84 (br, 1 P). ^{19}F-NMR (D_2O): δ -117.53 (dd, 1 F), -197.8 (m, 1 F). MS: m/z = 545.5 [M-1].

EXAMPLE 97
Preparation of Compounds 100d and 100e

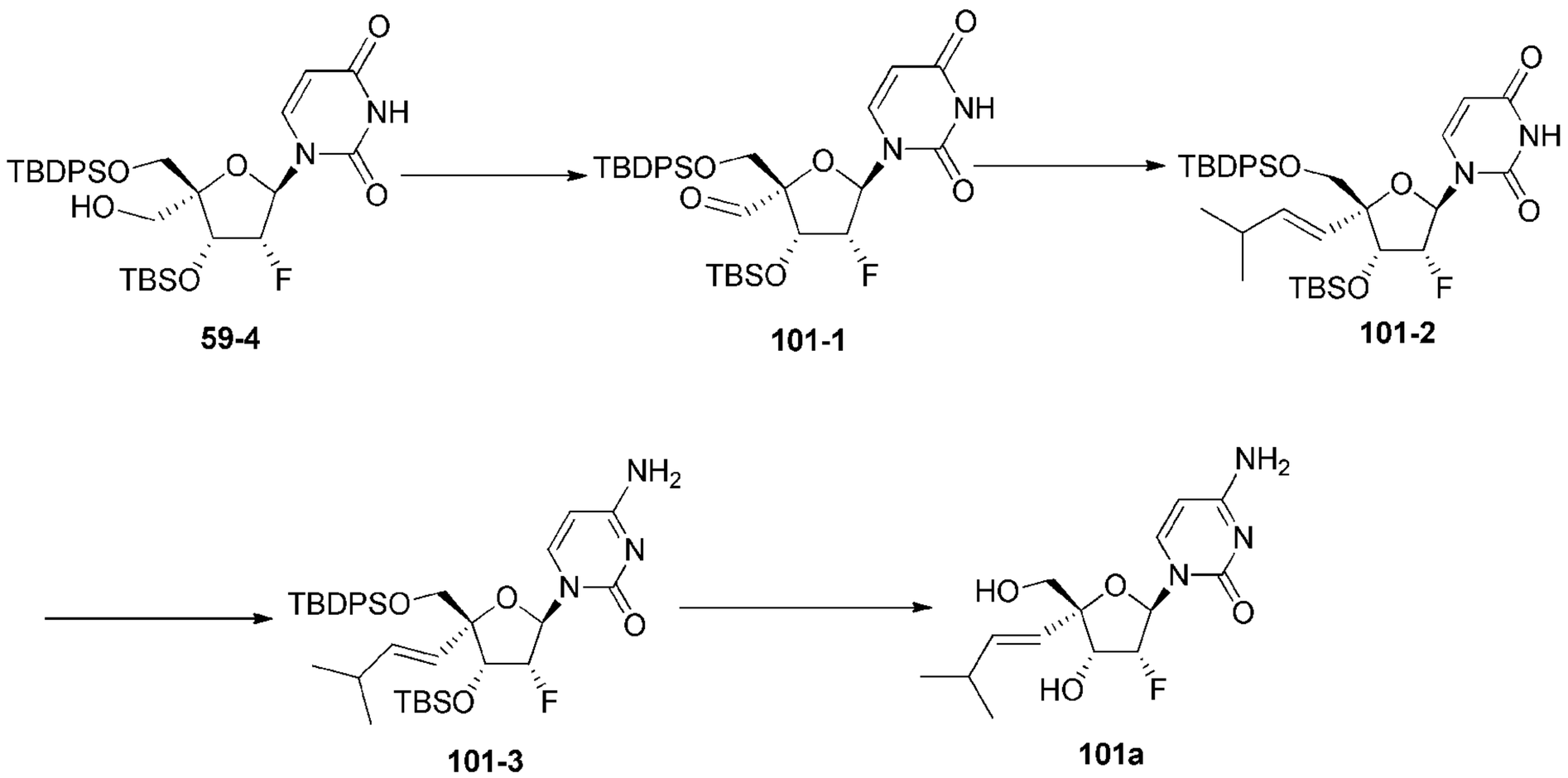


100-7 **100-8** **100d** + **100e**

[0546] To an ice-cold solution of diastereomers **100-7** (35 mg; 0.08 mmol) in acetonitrile (1 mL) was added TMSBr (0.1 mL; 10 equiv.). The resulting mixture was stirred overnight at R.T. and then concentrated. The residue was partitioned between water and CH_2Cl_2. The aqueous layer was washed with CH_2Cl_2, neutralized with triethylammonium bicarbonate buffer and lyophilized to yield the triethylammonium salt of **100-8**.

[0547] Compound **100-8** was rendered anhydrous by coevaporating with pyridine and toluene. Anhydrous **100-8** was dissolved in DMF (1.5 mL) and CDI (54 mg; 0.3 mmol) was added. The mixture was stirred at R.T. for 7 h. A solution of tetrabutylammonium pyrophosphate (0.3 g; ~0.3 mmol) in DMF (4 mL) was added. The mixture was stirred at R.T for 3 days. The mixture was diluted with triethylammonium acetate buffer. Two consecutive RP-HPLC purifications with a gradient 0-60% B (A: 50 mM aqueous TEAA, B: 50mM TEAA in MeOH) and 0-40% B gave **100d** and **100e** as single diastereomers. **100d**: ^{31}P-NMR (D_2O): δ 4.28 (dd, 1P), -6.37 (d, 1 P), -22.36 (t, 1 P). MS: m/z = 548.1 [M-1]. **100e**: ^{31}P-NMR (D_2O): δ 4.13 (dd, 1P), -6.38 (d, 1 P), -22.46 (t, 1 P). MS: m/z = 548.1 [M-1].

EXAMPLE 98
Preparation of Compound 101a



[0548] To a solution of **59-4** (1.5 g, 2.39 mmol) in anhydrous DCM (100 mL) was added Dess-Martin periodinane (5.2 g, 11.95 mmol) at 0°C under nitrogen. The mixture was

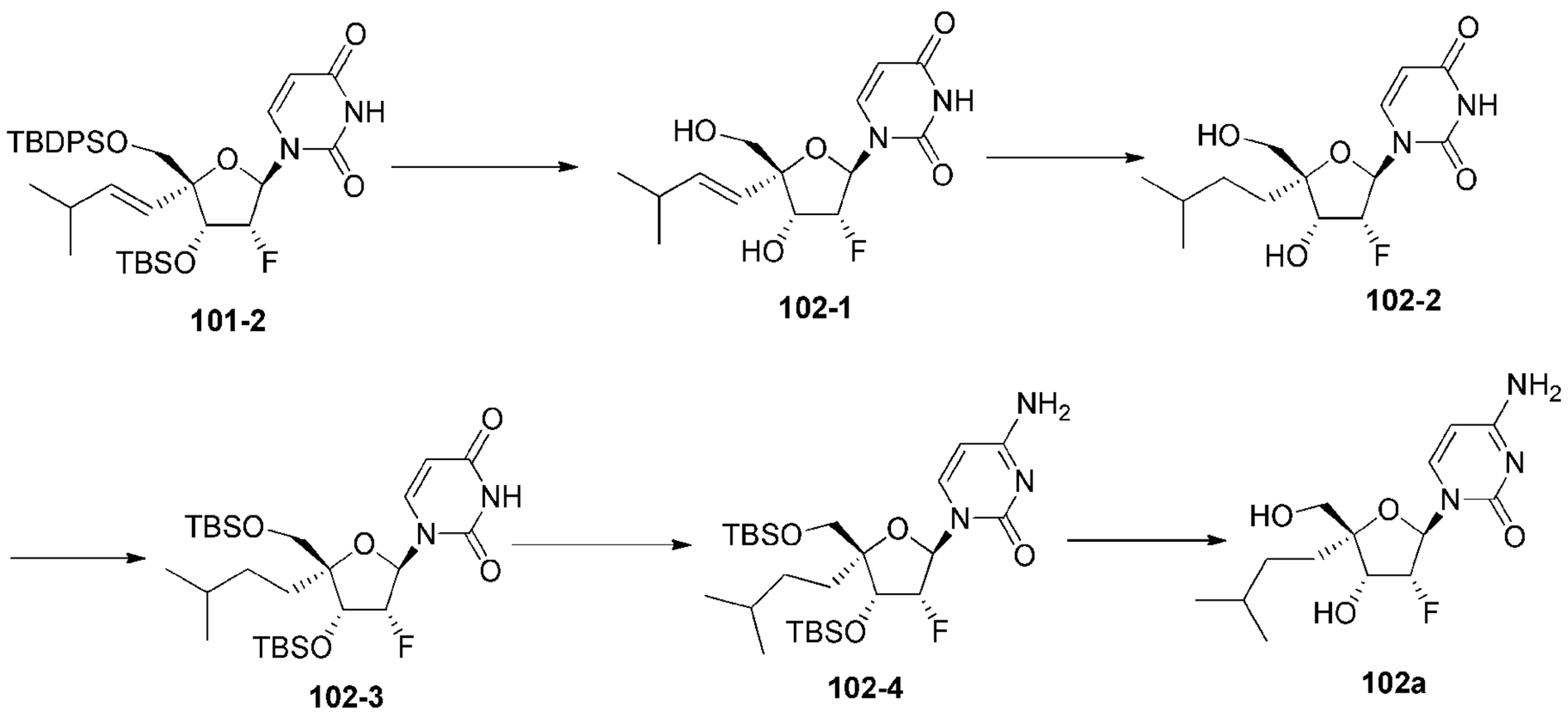
stirred at R.T. for 5 h. The mixture was poured into $NaHCO_3$ and $Na_2S_2O_3$ aq. Solution. The organic layer was washed with brine, dried over with anhydrous Na_2SO_4, and concentrated to dryness to give the crude **101-1** (1.5 g) as a white solid, which was used for the next step without further purification.

[0549] To a mixture of bromo(isobutyl)triphenylphosphorane (4.8 g, 12.03 mmol) in anhydrous THF (8 mL) was added t-BuOK(11.2 mL, 11.2 mmol) at 0°C under nitrogen. The mixture was stirred at R.T. for 1 h. A solution of **101-1** (1.0 g, 1.6 mmol) in anhydrous THF (4 mL) was added dropwise at 0°C. The mixture was stirred at R.T. for 3 h. The reaction was quenched with a NH_4Cl aq. solution and extracted with DCM. The organic layer was dried and concentrated to give a residue, which was purified by silica gel column chromatography (5% EtOAc in PE) to give **101-2** (793 mg, 74.4%) as a white solid.

[0550] To a solution of **101-2** (364 mg, 0.547 mmol) in anhydrous CH_3CN (6 mL) were added TPSCl (414 mg, 1.37 mmol), DMAP (167 mg, 1.37 mmol) and NEt_3 (138 mg, 1.37 mmol) at R.T. The mixture was stirred at R.T. for 2 h. NH_4OH (6 mL) was added, and the mixture was stirred for another 1 h. The mixture was diluted with DCM and washed with a $NaHCO_3$ aq. solution. The organic layer was separated and concentrated to give a residue, which was purified by silica gel column chromatography (2% MeOH in DCM) to give **101-3** (347 mg, 95.0%) as white solid.

[0551] To a solution of **101-3** (347 mg, 0.52 mmol) in MeOH (10 mL) was added NH_4F (1.5 g) at R.T. The reaction mixture was refluxed for 12 h, and then filtered. The filtrate was concentrated in vacuo**,** and the residue was purified by silica gel column chromatography (10% MeOH in DCM) to give **101a** (87 mg, 53%) as a white solid. ESI-MS: m/z 626.9 $[2M+H]^+$.

EXAMPLE 99
Preparation of Compound 102a



101-2 102-1 102-2

102-3 102-4 102a

[0552] To a solution of **101-2** (1.0 g, 1.5 mmol) in MeOH (20 mL) was added NH_4F (6 g) at R.T., and the mixture was refluxed overnight. After cooling to R.T., the mixture was filtered, and the filtrate was concentrated. The residue was purified by silica gel column chromatography (8 % MeOH in DCM) to give **102-1** (400 mg, 85%) as a white solid.

[0553] To a solution of **102-1** (400 mg, 1.27 mmol) in MeOH (10 mL) was added Pd/C (400 mg) at R.T. The mixture was stirred at R.T. under a balloon of H_2 for 1.5 h. The mixture was filtered, and the filtrate was concentrated in vacuo to give **102-2** (400 mg, 99 %) as a white solid.

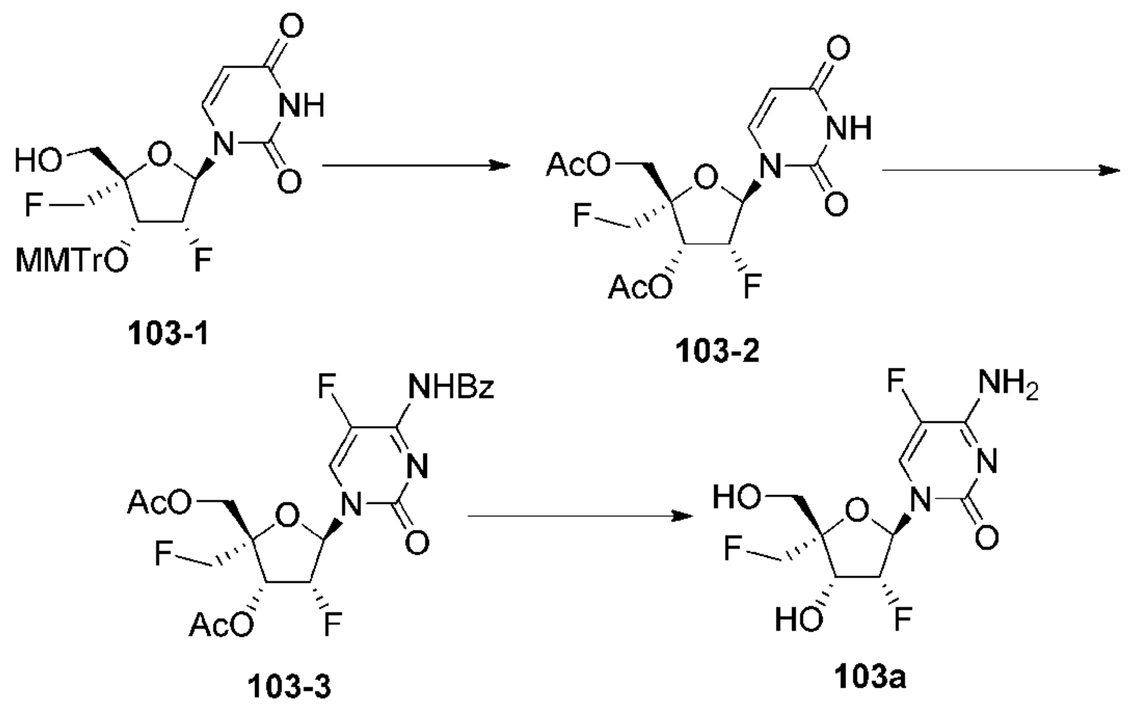
[0554] To a solution of **102-2** (400 mg, 1.26 mmol) in anhydrous DMF (5 mL) were added imidazole (968 mg, 14.2 mmol), and TBSCl (1.5 g, 10.0 mmol) at R.T. The mixture was stirred at 50°C overnight. The mixture was diluted with DCM and washed with a $NaHCO_3$ aq. solution. The organic layer was dried and concentrated. The residue was purified by silica gel column chromatography (10% EA in PE) to give **102-3** (676 mg, 98 %) as a white solid.

[0555] To a solution of **102-3** (676 mg, 1.24 mmol) in anhydrous CH_3CN (6 mL) were added TPSCl (941 mg, 13.11 mmol), DMAP (379 mg, 3.11 mmol) and NEt_3 (314 mg, 3.11 mmol) at R.T. The reaction was stirred at R.T. for 3 h. NH_4OH (1 mL) was added, and the reaction was stirred for 4 h. The mixture was diluted with DCM and washed with a

$NaHCO_3$ solution. The organic layer was dried and concentrated. The residue was purified by silica gel column chromatography (2% MeOH in DCM) to give **102-4** (450 mg, 67%) as a white solid.

[0556] To a solution of **102-4** (450 mg, 0.83 mmol) in MeOH (10 mL) was added NH_4F (2 g) at R.T. The reaction mixture was refluxed overnight. After cooling to R.T., the mixture was filtered, and the filtrate was concentrated. The residue was purified by silica gel column chromatography (8 % MeOH in DCM) to give **102a** (166.6 mg, 64%) as a white solid. ESI-MS: m/z 631.1 $[2M+H]^+$.

EXAMPLE 100
Preparation of Compound 103a



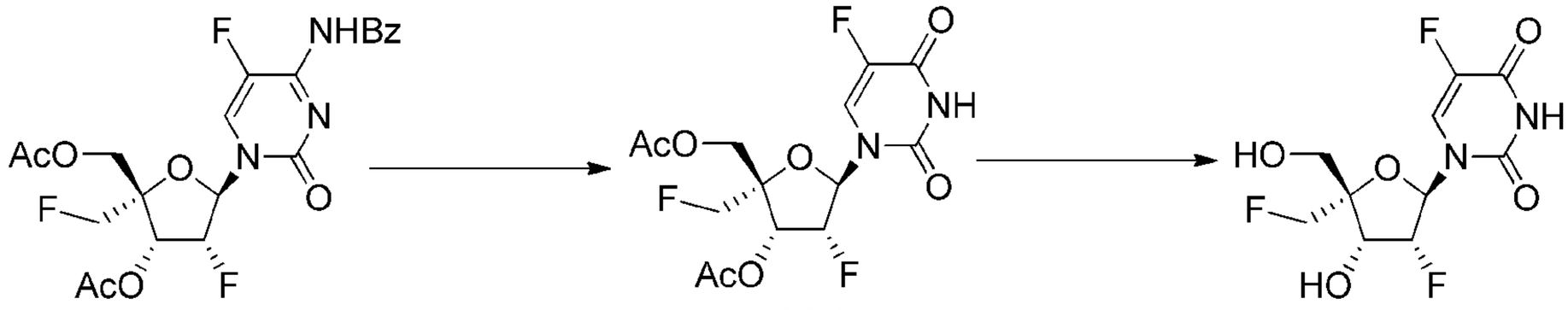
[0557] Compound **103-1** (3.8 g, 6.9 mmol) in 80% AcOH aq. was stirred at 50°C for 4 h. The mixture was concentrated to give a residue, which was purified by silica gel column chromatography (5% MeOH in DCM) to give the uridine derivative (1.5 g, 78.2%) as a white solid. To a solution of the uridine derivative (1.5 g, 5.4 mmol) in Py (10 mL) was added Ac_2O (1.38 g, 13.5 mmol) at R.T. The mixture was stirred at R.T. for 12 h. The mixture was concentrated to give a residue, which was purified by silica gel column chromatography (20% EA in PE) to give **103-2** (1.3 g, 68%) as a white solid.

[0558] To a solution of N-(5-fluoro-2-hydroxy-1,2-dihydropyrimidin-4-yl)benzamide (0.5 g, 2.1 mmol) in anhydrous PhCl (5 mL) was added ammonium sulfate (6 mg, 0.043 mmol), followed by HMDS (0.7 g, 4.3 mmol). The mixture was heated to 130°C for 8 h. The mixture was concentrated under vacuum to 2 mL, and then cooled to 0°C. TMSOTf (310 mg, 1.4 mmol) was then added. After stirring for 10 min at 0°C, **103-2** (150

mg, 0.4 mmol) in PhCl (5 mL) was added. The mixture was stirred at 130°C for 10 h. The mixture was concentrated, and the residue was re-dissolved in DCM (10 mL), washed with water (5 mL) and saturated $NaHCO_3$. The organic layer was dried over Na_2SO_4, evaporated to dryness and the crude product was purified by silica gel column chromatography (60% PE in EA) to give **103-3** (30 mg, 16%) as a white solid.

[0559] A solution of **103-3** (150 mg, 0.34 mmol) in NH_3/MeOH (10 mL) was stirred at R.T. for 3 h. The mixture was concentrated, and the residue was purified by HPLC separation (0.1% HCOOH in water and MeCN) to give **103a** (60 mg, 60%) as a white solid. ESI-MS: m/z 613.1 $[2M+Na]^+$.

EXAMPLE 101
Preparation of Compound 104a

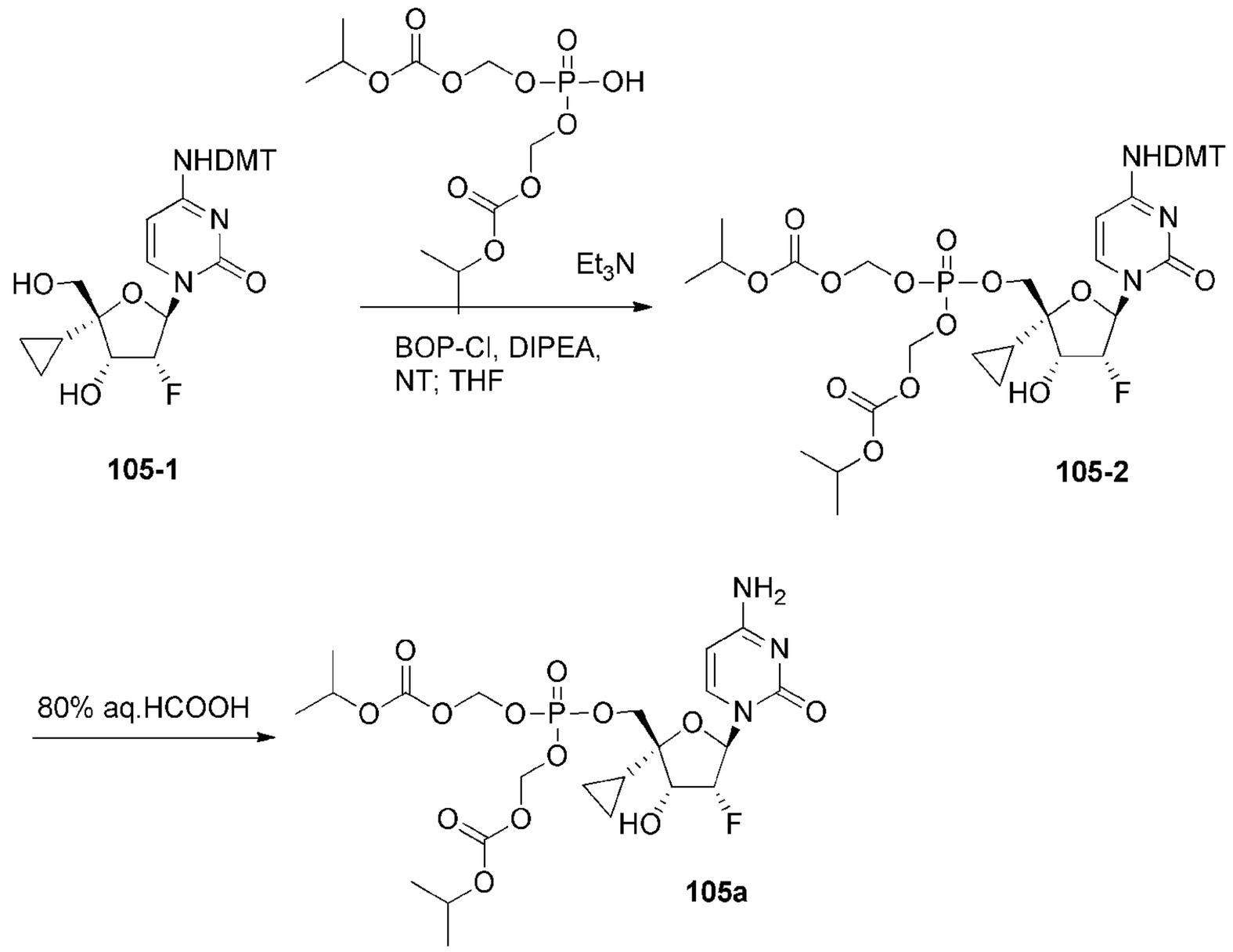


103-3 **104-1** **104a**

[0560] Compound **103-3** (150 mg, 0.31 mmol) was dissolved in 80% aqueous acetic acid (3 mL). The solution was heated to reflux for 2 h. The mixture was cooled to ambient temperature and diluted with water (5 mL), neutralized to pH>7 with saturated $NaHCO_3$ and extracted with EA. The organic layer was dried and evaporated to dryness. The residue was purified by silica gel column chromatography (50% EA in PE) to give **104-1** (80 mg, 70%) as a white solid.

[0561] Compound **104-1** (80 mg, 0.22 mmol) in saturated NH_3/MeOH (10 mL) was stirred at R.T. for 3 h. The mixture was concentrated, and the residue was purified by silica gel column chromatography (5% MeOH in DCM) to give **104a** (40 mg, 60%) as a white solid. ESI-MS: m/z 319.1 $[M+Na]^+$.

EXAMPLE 102
Preparation of Compound 105a

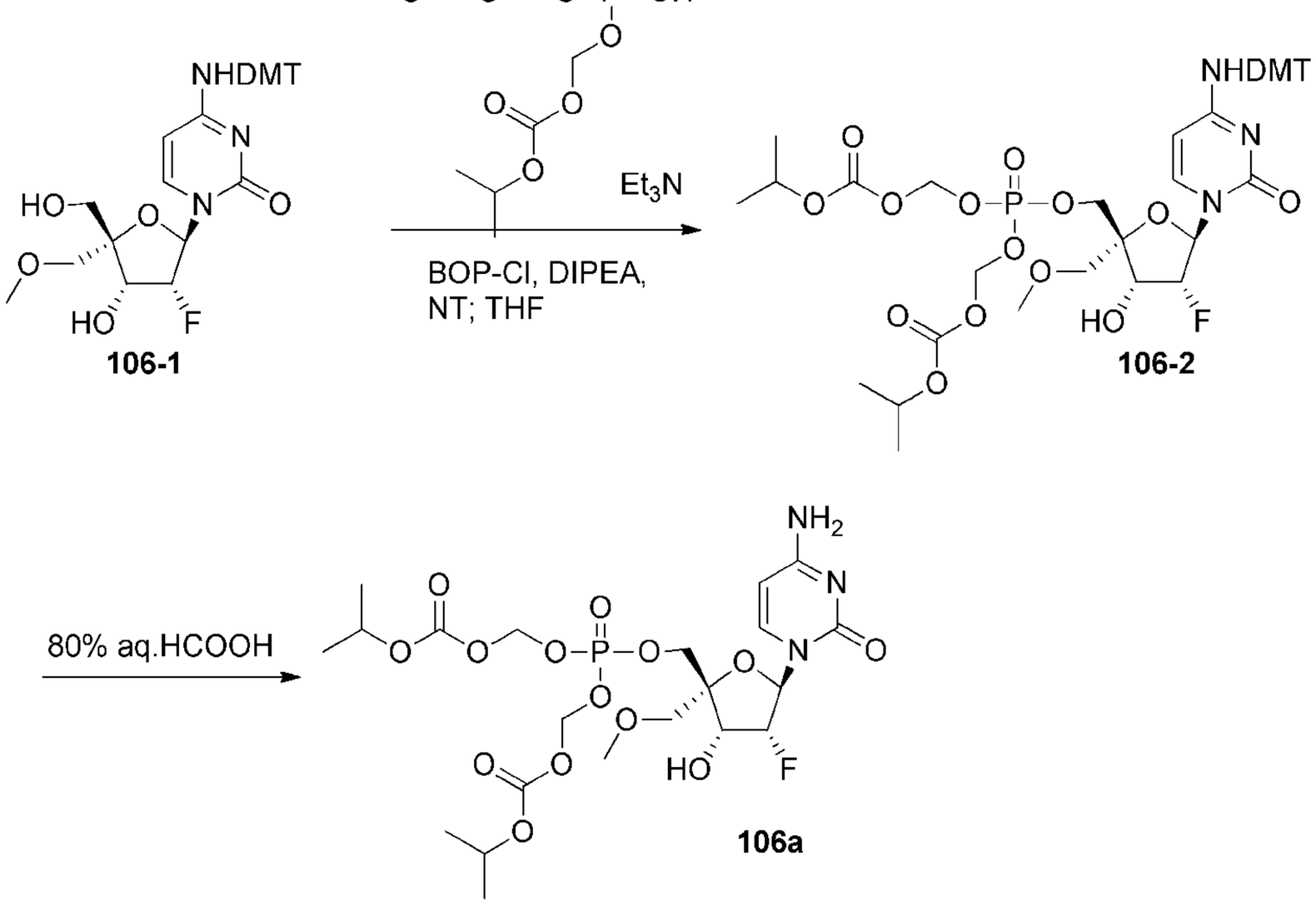


[0562] To a solution of triethylammonium bis(isopropyloxycarbonyloxymethyl)phosphate (0. 065 mmol, prepared from 22 mg of bis(POC)phosphate and Et_3N) in THF was added **105-1** (31 mg; 0.05 mmol). The resulting mixture evaporated, and the residue was rendered anhydrous by coevaporation with pyridine, followed by toluene. The anhydrous evaporated residue was dissolved THF (1 mL) and cooled in an ice-bath. To the solution was added diisopropylethyl amine (35 μL; 4 equiv), followed by BOP-Cl (25 mg; 2 equiv) and 3-nitro-1,2,4-triazole (11 mg; 2 equiv). The mixture was stirred at 0°C for 90 min. The mixture was diluted with CH_2Cl_2, washed with saturated aq. $NaHCO_3$ and brine, and dried with Na_2SO_4. The evaporated residue was purified on silica (10 g column) with a CH_2Cl_2 /i-PrOH solvent system (3-10% gradient) to give **105-2** (13 mg, 28%).

[0563] A solution of **105-2** (13 mg; 0.014 mmol) in 80% aq. HCOOH (2 mL) was stirred at R. T. for 3 h. The mixture was evaporated and then coevaporated with toluene.

The product was purified on silica (10 g column) with a CH_2Cl_2/MeOH solvent system (4-15% gradient) to give **105a** (7 mg, 78%). MS: m/z = 598.4 [M+1].

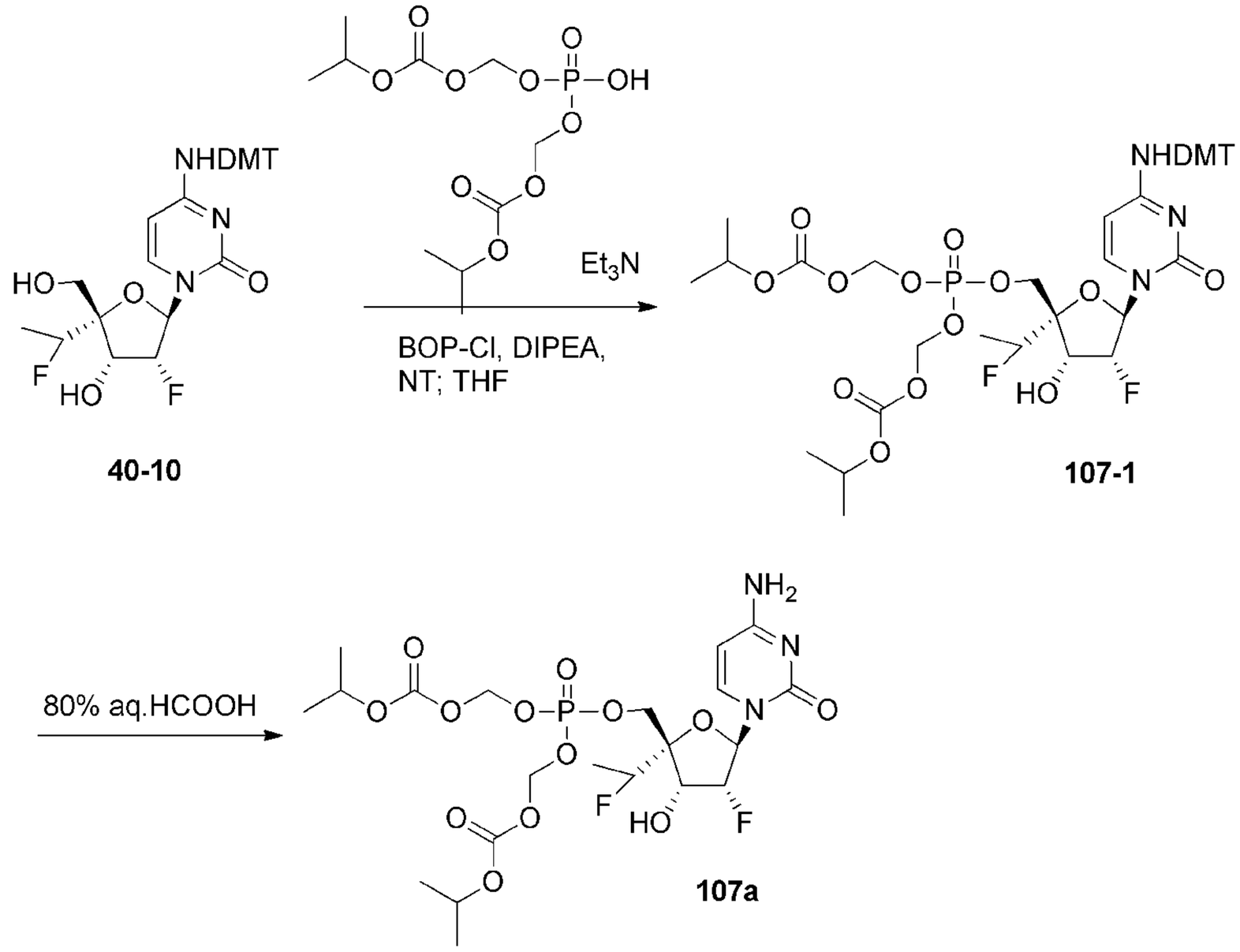
EXAMPLE 103
Preparation of Compound 106a



[0564] Compound **106-2** (15 mg; 30% yield) was prepared in the same manner from **106-1** (32 mg; 0.057 mmol) and bis(POC)phosphate (24 mg) with DIPEA (40 μL), BopCl (29 mg) and 3-nitro-1,2,4-triazole (13 mg) as **105-2** from **105-1**.

[0565] Compound **106-1** (15 mg) was converted in formic acid to **106a** (8 mg; 78% yield) in the same manner as **105-2** to **105a**. MS: m/z = 602.4 [M+1].

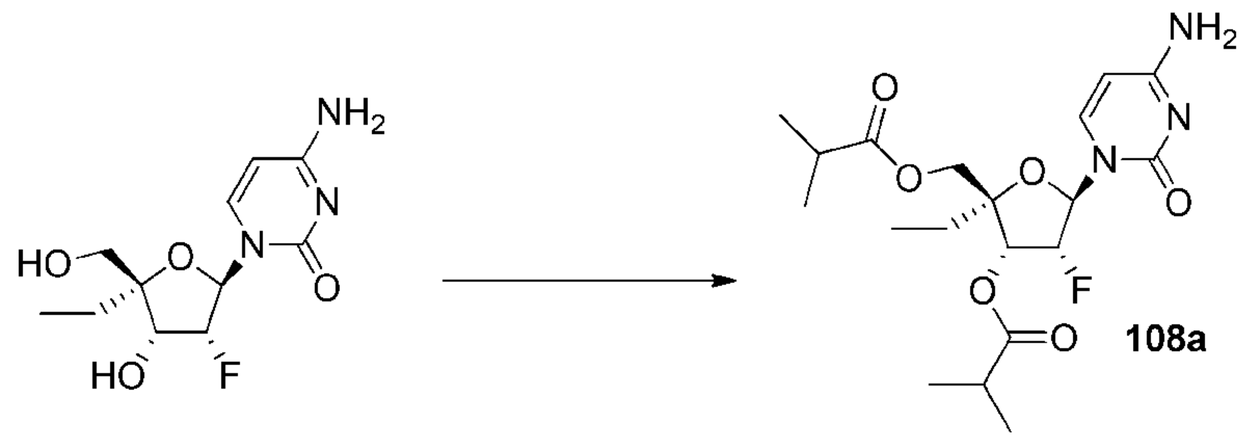
EXAMPLE 104
Preparation of Compound 107a



[0566] Compound **107-1** (30 mg; 30% yield) was prepared in the same manner from **40-10** (65 mg; 0.115 mmol) and bis(POC)phosphate (49 mg) with DIPEA (80 µL), BopCl (58 mg) and 3-nitro-1,2,4-triazole (26 mg) as **105-2** from **105-1**.

[0567] Compound **107-1** (30 mg) was converted in formic acid to **107a** (15 mg; 73% yield) in the same manner as **105-2** to **105a**. MS: m/z = 604.3 [M+1].

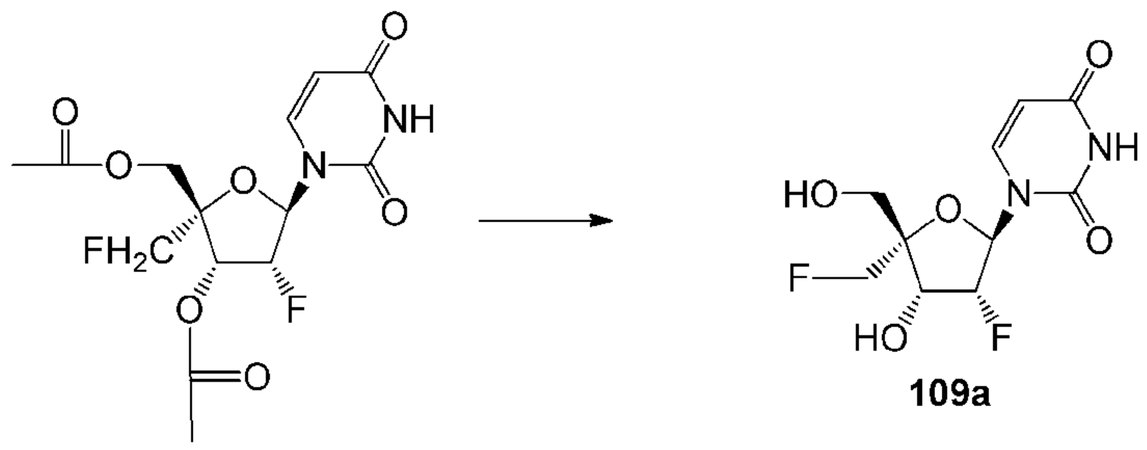
EXAMPLE 105
Preparation of Compound 108a



[0568] To a solution of 4'-ethyl-2'-fluorocytidine (50 mg, 0.183 mmol) in DMF (1 mL) were added DCC (113 mg, 0.55 mmol), isobutyric acid (48.5 µl, 0.55 mmol) and DMAP

(22 mg, 0.183 mmol). The mixture was stirred at R.T. overnight. The mixture was filtered, and the filtrate was concentrated with a rotary evaporator until half of its original volume was achieved. EA was added to the mixture. The mixture was washed with water, followed by brine. The mixture was dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a residue, which was purified by silica gel with DCM/ MeOH=95:5 to give **108a** (40.8 mg, 54%) as a white solid. MS: m/z 414 $[M-H]^+$, 829 $[2M+H]^+$.

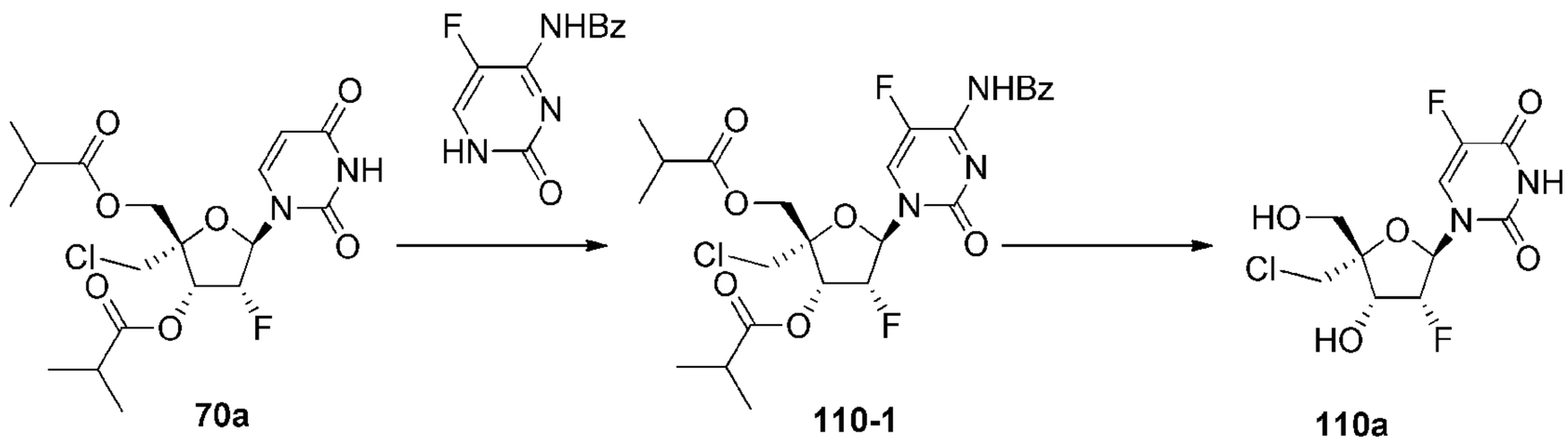
EXAMPLE 106
Preparation of Compound 109a



109a

[0569] 3',5'-diacetylnucleoside (36 mg, 1 mmol) was dissolved in methanol saturated with NH_4OH and kept overnight at R.T. The solvent was evaporated, and the product isolated by column chromatography in gradient of methanol in DCM from 0 to 15% on a 10g Biotage cartridge. The product was **109a** obtained (20 mg, 73%). MS: m/z 277.2 [M-H].

EXAMPLE 107
Preparation of Compound 110a



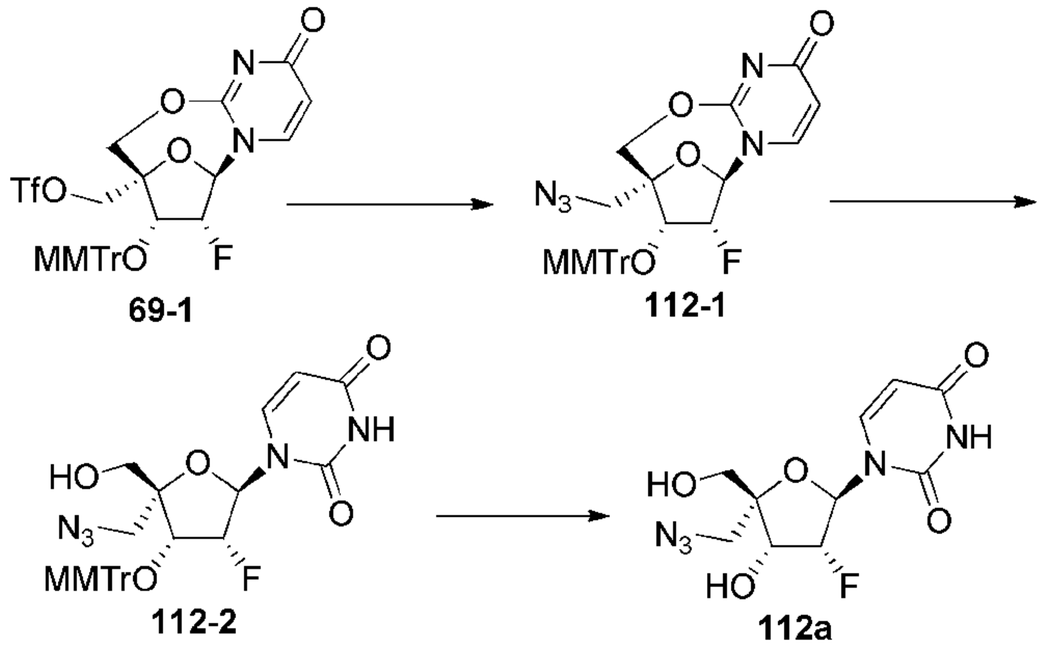
70a 110-1 110a

[0570] To a solution of **70a** (6.55 g, 2.1 mmol) and the benzoyl protected base moiety (2.3 g, 5.3 mmol) in PhCl (50 mL) was added TMSOTf (3.6 g, 16.1 mmol). After addition, the mixture was heated to 140°C for 8 h. The mixture was cooled to R.T., and evaporated to give a residue. The residue was re-dissolved in DCM and washed with

saturated $NaHCO_3$ and brine. The organic layer was dried and concentrated to give a residue, which was purified by silica gel column (40% EA in PE) to give **110-1** (300 mg, 10%) as a white solid.

[0571] Compound **110-1** (300 mg, 0.55 mmol) in 80% aqueous acetic acid (5 mL) was heated to reflux for 2 h. The mixture was cooled to ambient temperature and diluted with water (5 mL), and then extracted with EA. The organic layer was washed with saturated $NaHCO_3$ and brine. The mixture was dried and concentrated to give a residue, which was purified by silica gel column (10% EA in PE) to give the protected uridine derivative (180 mg, 70%) as a white solid. The protected uridine derivative (180 mg, 0.4 mmol) in saturated NH_3/MeOH (10 mL) was stirred at R.T. for 3 h. The mixture was concentrated to give a residue, which was purified by preparative HPLC (0.1% HCOOH in water and MeCN) to give **110a** (80 mg, 60%) as a white solid. ESI-TOF-MS: m/z 334.7 $[M+Na]^+$.

EXAMPLE 108
Preparation of Compound 112a



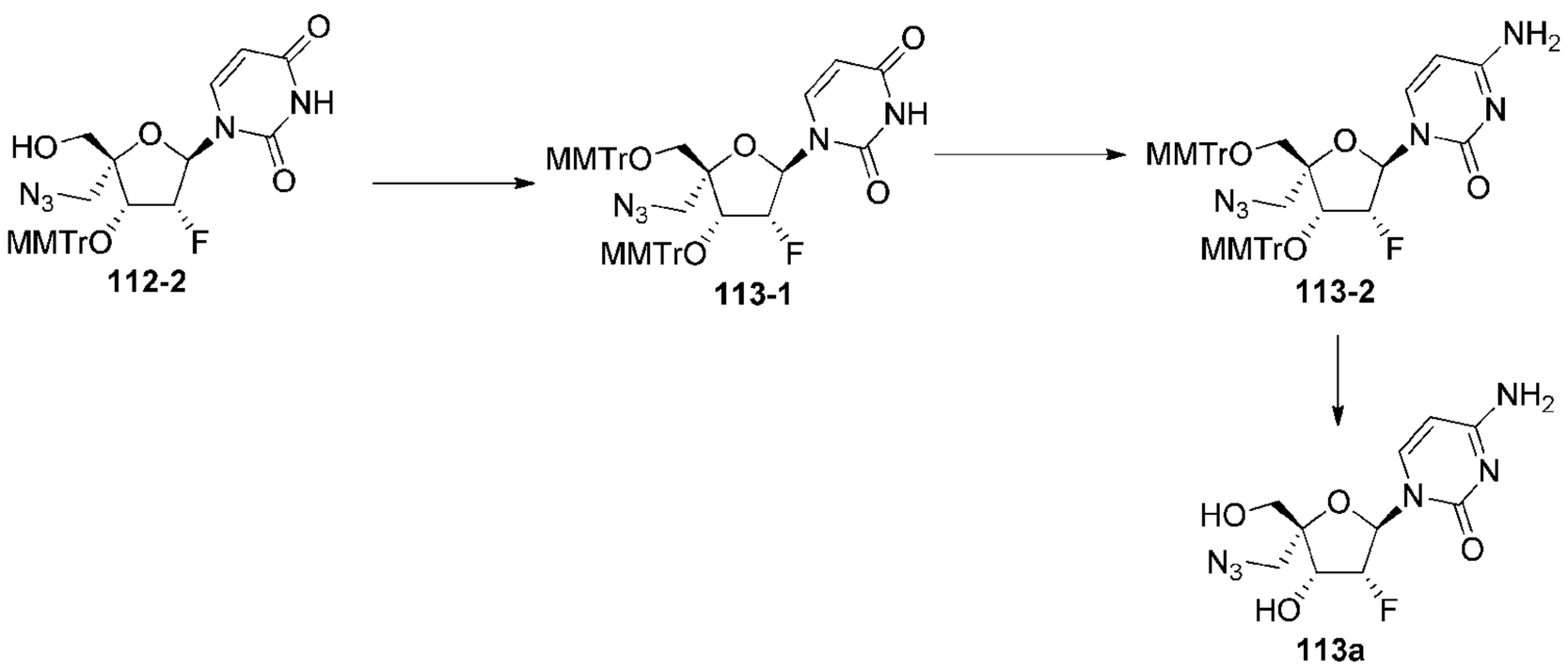
[0572] To the stirred solution of **69-1** was added NaN_3 (1.5 g, 21.68 mmol) at 0°C under nitrogen atmosphere, and the resulting solution was stirred at R.T. for 1.5 h. The reaction was quenched with water, extracted with EA, washed with brine, and dried over $MgSO_4$. The concentrated organic phase was used for the next step without further purification.

[0573] To a solution of **112-1** (3.0 g, 5.4 mmol) in anhydrous 1,4-dioxane (18 mL) was added NaOH (5.4 mL, 2M in water) at R.T. The reaction mixture was stirred at R.T. 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 **112-2** (2.9 g, 93%) as a white foam.

[0574] Compound **112-2** (520 mg, 0.90 mmol) was dissolved in 80% of HCOOH (20 mL) at R.T. 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 R.T., for 5 mins. The solvent was concentrated to dryness and the residue was purified by column chromatography to give **112a** (120 mg, 44.4%) as a white solid. ESI-LCMS: m/z 302.0 $[M+H]^+$, 324.0$[M+Na]^+$.

EXAMPLE 109
Preparation of Compound 113a

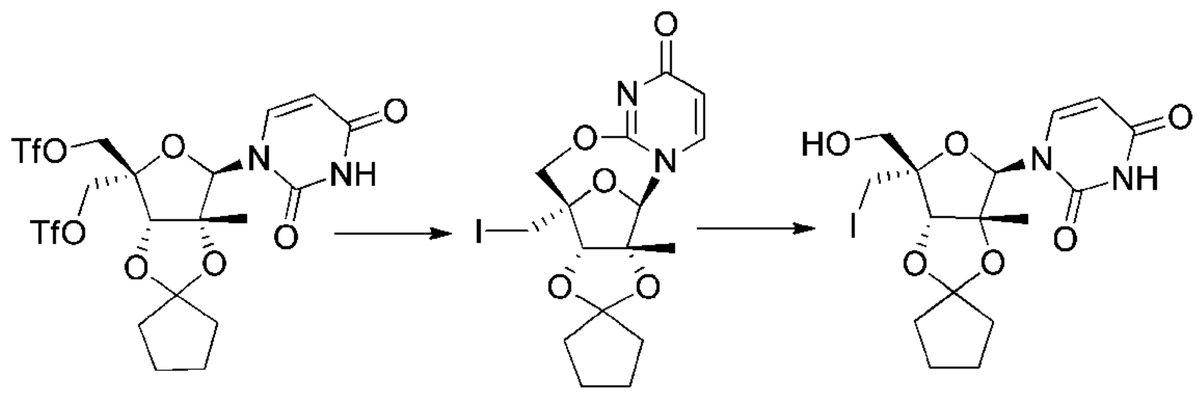


[0575] To a stirred solution of **112-2** (1.1 g, 2.88 mmol) in anhydrous DCM (10 mL) was added MMTrCl (1.77 g, 5.76 mmol), $AgNO_3$ (1.47 g, 8.64 mmol) and collidine (1.05 g, 8.64 mmol) at 25°C under a N_2 atmosphere. The reaction was refluxed for 12 h. MeOH (20 mL) was added and the solvent was removed to dryness. The residue was purified on a silica gel column (20% EA in PE) to give **113-1** (1.6 g, 85.1%) as a white foam.

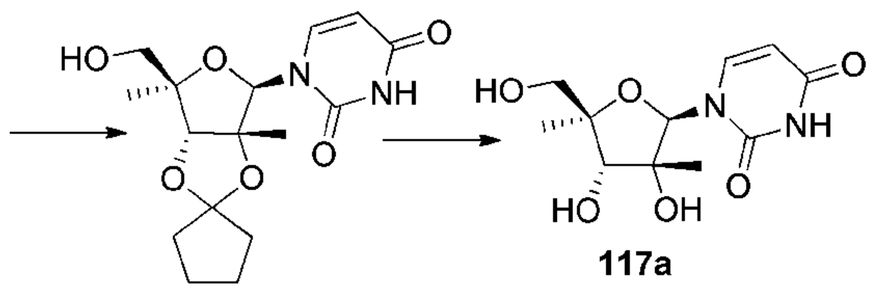
[0576] To a stirred solution of **113-1** (800 mg, 0.947 mmol) in anhydrous MeCN (10 mL) were added TPSCl (570 mg, 1.89 mmol), DMAP (230 mg, 1.89 mmol) and TEA (190 mg, 1.89 mmol) at R.T. The mixture was stirred for 12 h. NH_4OH (25 mL) was added and the mixture was stirred for 2 h. The solvent was removed, and the residue was purified on a silica gel column as a yellow foam. Further purification by prep-TLC gave **113-2** (700 mg, 87.1%) as a white solid.

[0577] Compound **113-2** (300 mg, 0.355 mmol) was dissolved in 80% of HCOOH (5 mL) at R.T. 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 R.T., for 5 mins. The solvent was removed and the residue was purified by column chromatography to give **113a** (124 mg, 82.6%) as a white solid. ESI-LCMS: m/z 301.0 $[M+H]^+$, 601.0$[2M+H]^+$.

EXAMPLE 110
COMPOUND 117a



117-1 117-2 117-3



117a

117-4

[0578] To a solution of **117-1** (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 **117-2** (1.7 g, 94%) as a yellow solid.

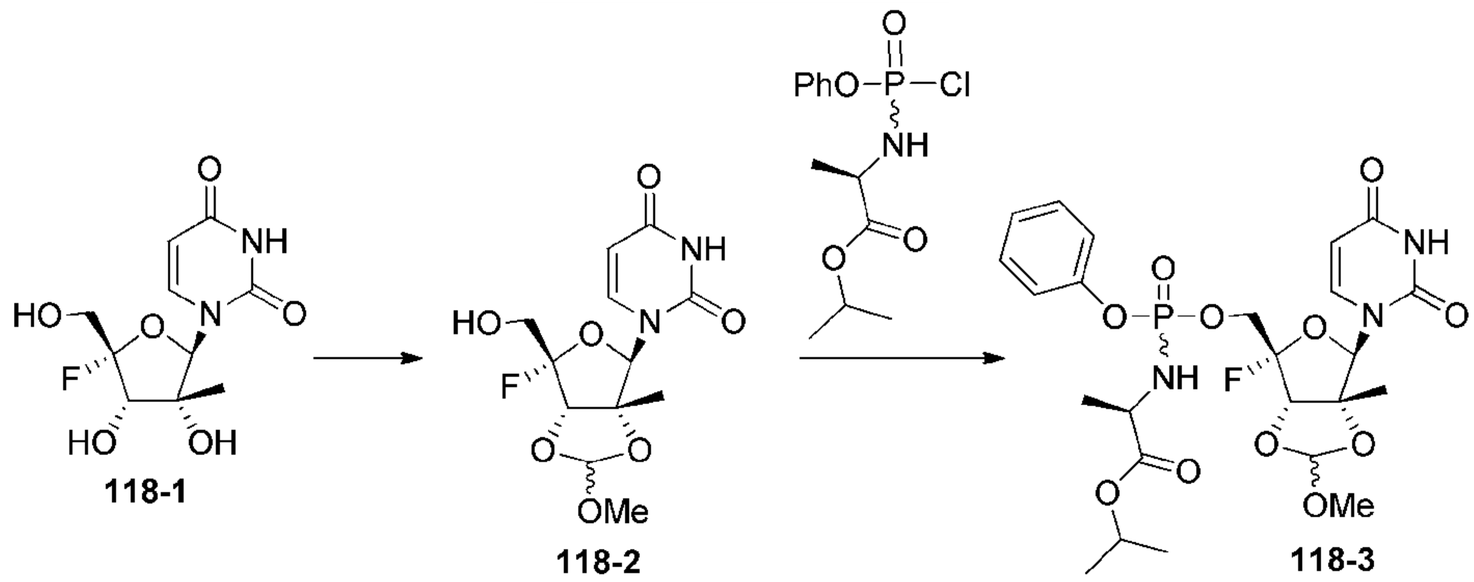
[0579] To a solution of **117-2** (1.7 g, 3.81 mmol) in THF (5 mL) was added 2 M NaOH solution (4.5 mL) at 0 °C. The solution was stirred for 2 h at RT. The mixture was adjusted to pH = 7, and concentrated under reduced pressure. The mixture was partitioned between DCM and water. The DCM layer was dried with high vacuum to give **117-3** (1.2 g, 68%) as a white solid, which was used without further purification.

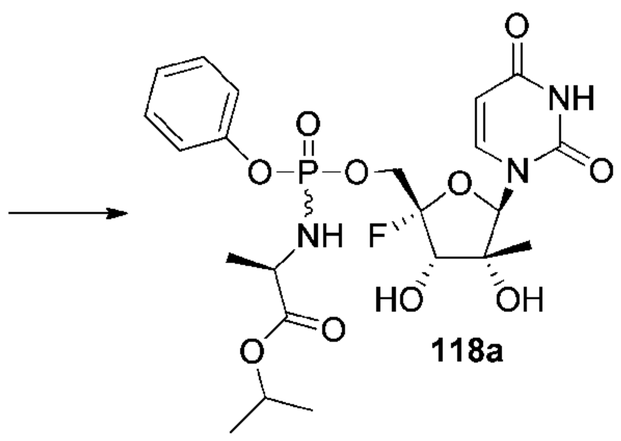
[0580] To a solution of **117-3** (1.2 g, 2.58 mmol) in EtOH (20 mL) was added NH_4COOH(650 mg, 7.75 mmol) and Pd/C (120 mg). The mixture was stirred under H_2 (30

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 **117-4** (545 mg, 62%). ESI-MS: m/z 361.2 $[M + 23]^+$.

[0581] Compound **117-4** 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 **117a** (14 mg) as a white solid.

EXAMPLE 111
COMPOUND 118a





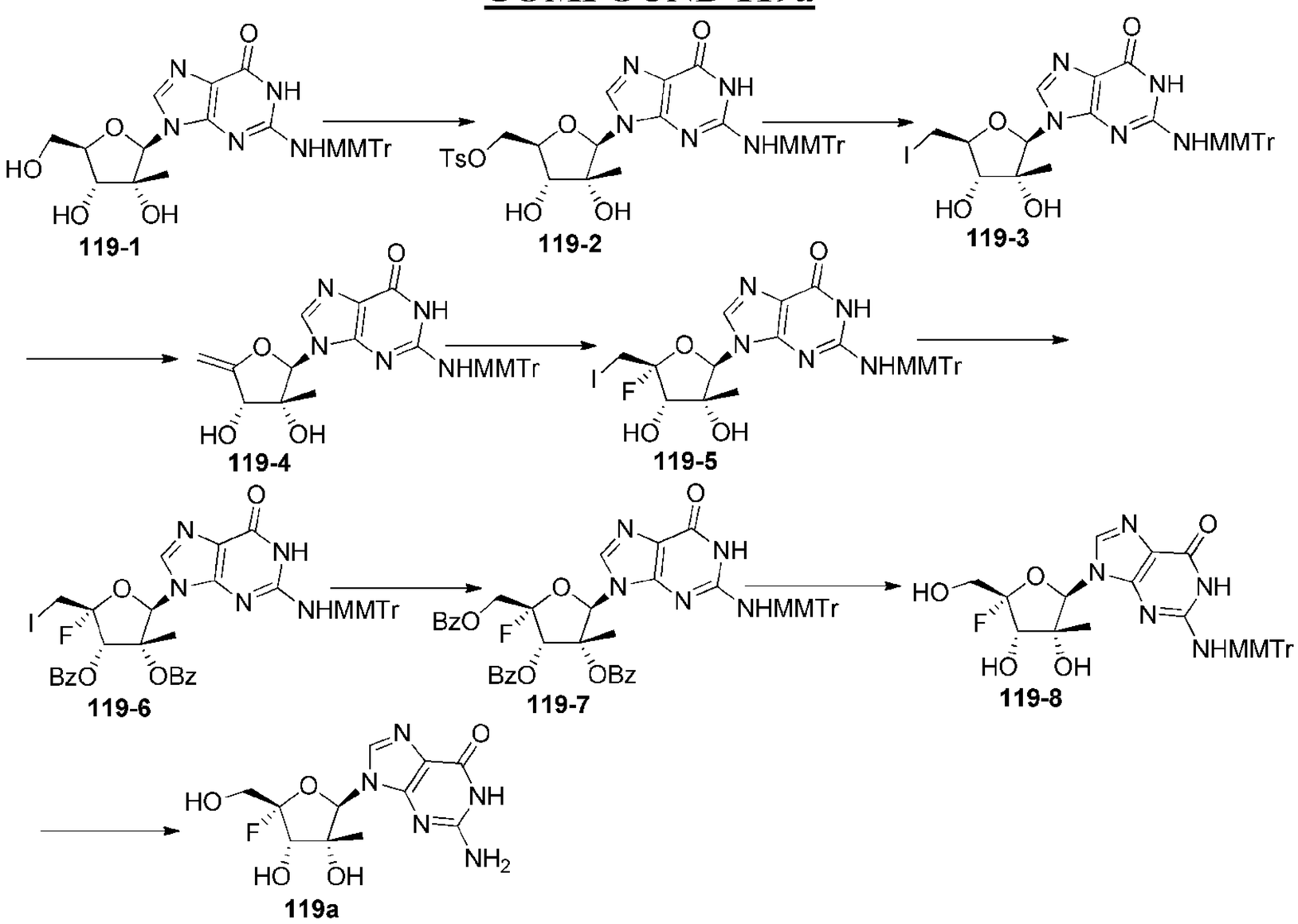
[0582] To a solution of **118-1** (1.2 g; 4.3 mmol) in dioxane (30 mL) were added p-toluenesulphonic acid monohydrate (820 mg; 1 eq.) and trimethyl orthoformate (14 mL; 30 eq.). The mixture was stirred overnight at RT. The mixture was then neutralized with methanolic ammonia and the solvent evaporated. Purification on silica gel column with CH_2Cl_2-MeOH solvent system (4-10% gradient) yielded **118-2** (1.18 g, 87%).

[0583] To an ice cooled solution of **118-2** (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 **118-3** (1.59 g; 93%).

[0584] A mixture of **118-3** (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 **118a** (950 mg; 70%). ^{31}P-NMR (DMSO-d_6): δ 3.52, 3.37. MS: m/z = 544 [M-1].

EXAMPLE 112
COMPOUND 119a



[0585] Compound **119-1** (5 g, 8.79 mmol) was co-evaporated with anhydrous pyridine. To an ice cooled solution of **119-1** 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 **119-2** (6.35 g, 100%) was used for next step directly.

[0586] To a solution of **119-2** (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 **119-3** (11.5g, 38%) as a white solid.

[0587] To a solution of **119-3** (11.5 g, 16.94 mmol) in dry THF (120 mL) was added DBU (12.87 g, 84.68 mmol), and heated to 60 ^oC. 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 **119-4** (5.5 g, 54%) as a white solid.

[0588] To an ice cooled solution of **119-4** (500 mg, 0.90 mmol) in dry DCM (20ml) 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 **119-5** (420 mg, 66%).

[0589] To a solution of crude **119-5** (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 **119-6** (150 mg, 46%).

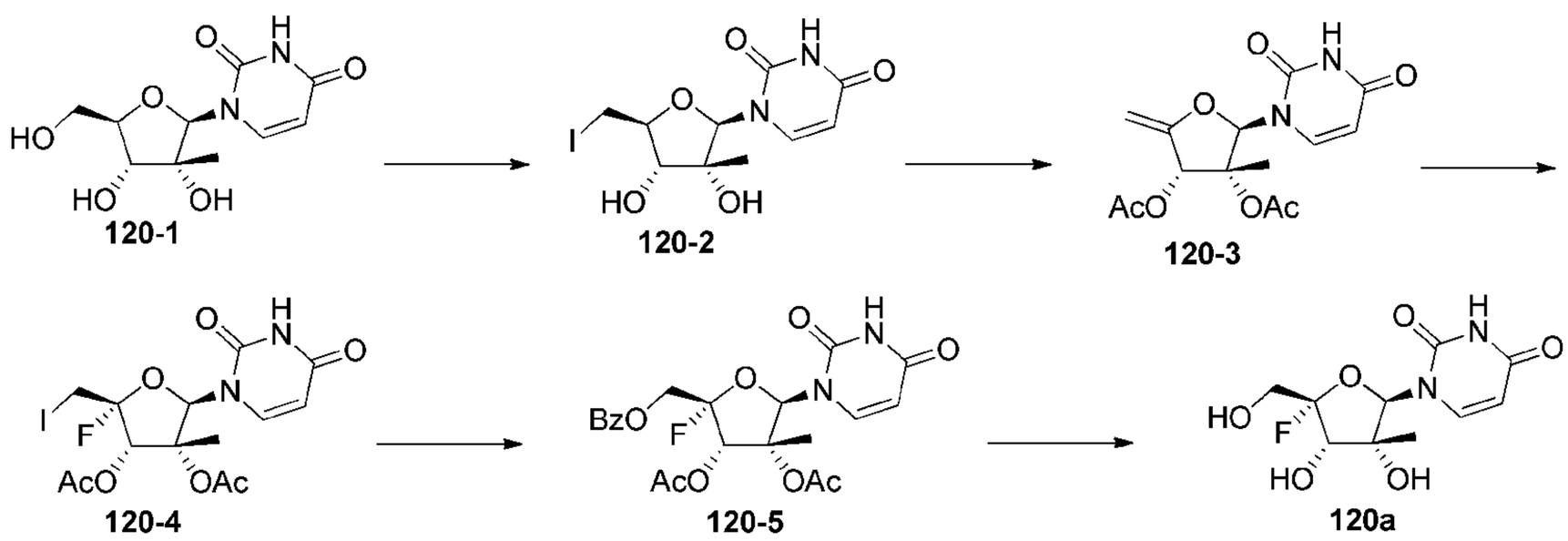
[0590] To a solution of crude **119-6** (650 mg, 0.72 mmol) in dry HMPA (20 mL) was added NaOBz (1.03 g, 7.2 mmol) and 15-crown-5 (1.59 g, 7.2 mmol). The reaction was stirred for 2 d at 60 ^oC. The mixture was diluted with H_2O, and extracted with EA. The

organic layer was evaporated at low pressure. The residue was purified by prep-TLC to give **119-7** (210 mg, 32.4%). ESI-MS: m/z: 900.4 $[M+H]^+$.

[0591] A mixture of **119-7** (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 **119-8** (15 mg, 91%).

[0592] A mixture of **119-8** (15 mg, 0.02 mmol) in ACN (0.25 mL) and 4 N HCL/dioxane (19 uL) 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 **119a** (7 mg). MS: m/z = 314 [M-1].

EXAMPLE 113
COMPOUND 120a



[0593] To a stirred suspension of **120-**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 **120-2** (22.5 g, 78.9%) as a white solid. ^1H 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).

[0594] To a stirred solution of **120-2** (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

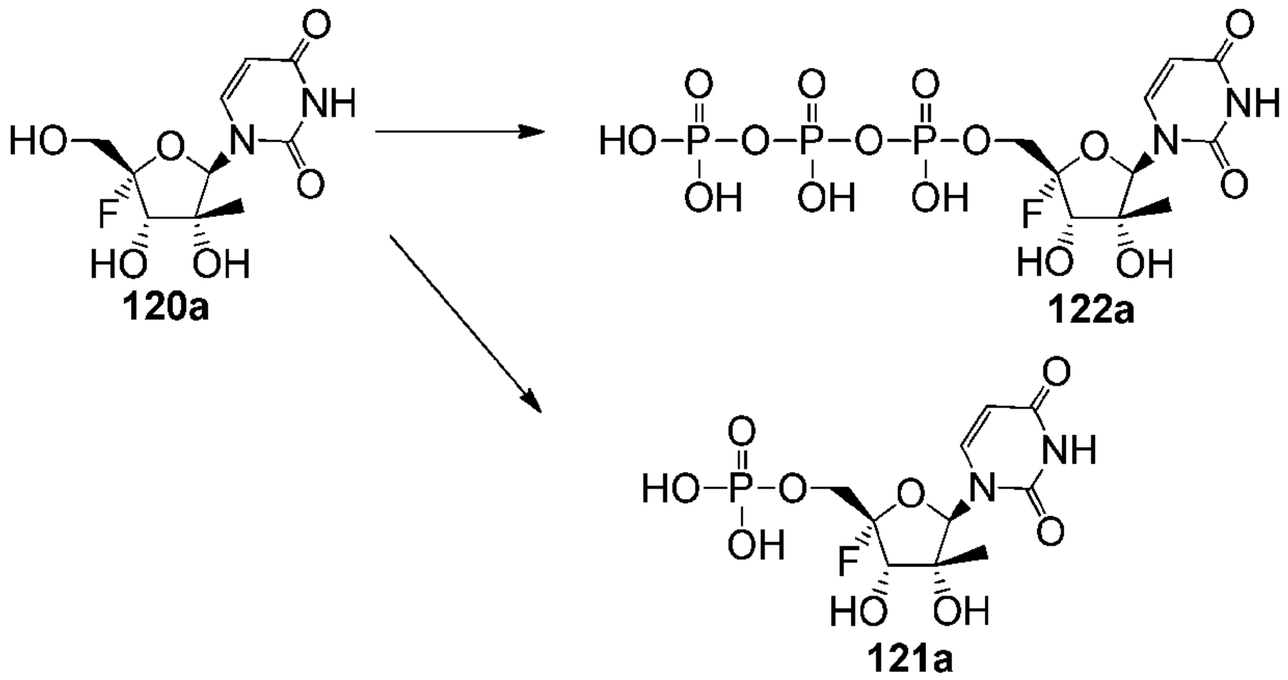
refluxed for 3 h. The solvent was removed, and the residue was re-dissolved in anhydrous pyridine (200 mL). To the mixture was added Ac_2O (84.9 g, 833.3 mmol) at 0 °C. The mixture was warmed to 60 °C and stirred for 10 h. The solvent was removed, and the residue was diluted with DCM, washed with saturated $NaHCO_3$ and brine. The organic layer was concentrated and purified on a silica gel column (10-50% EA in PE) to give **120-3** (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).

[0595] To an ice cooled solution of **120-3** (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 **120-4** (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).

[0596] To a solution of **120-4** (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 **120-5** (2.8 g, 40.5%). ESI-MS: m/z 444.9 $[M-F+H]^+$.

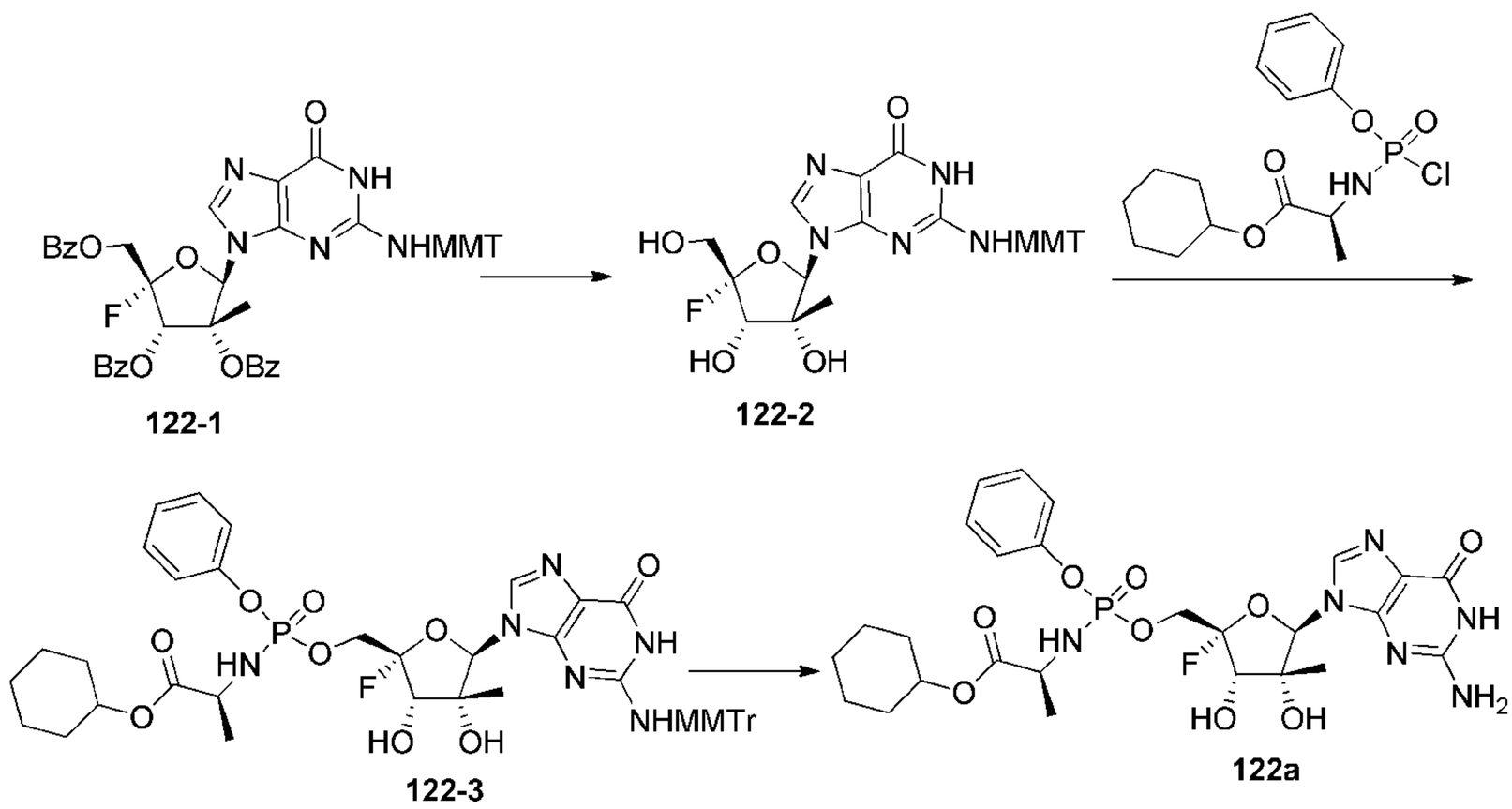
[0597] A mixture of **120-5** (4.0 g; 8.6 mmol) and liquid ammonia was kept overnight at RT in a high-pressure stainless-steel vessel. Ammonia was then evaporated, and the residue purified on silica (50g column) with a CH_2Cl_2/MeOH solvent mixture (4-12% gradient) to yield **120a** as a colorless foam (2.0 g; 84% yield). ESI-MS: m/z 275.1 $[M-H]^-$.

EXAMPLE 114
COMPOUNDS 121a AND 122a



[0598] Dry **120a** (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 50mM TRIS-buffer (pH7.5). The fractions eluted at 60% buffer B contained **121a** and at 80% buffer B contained **122a**. 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 50mM triethylammonium acetate buffer (pH 7.5) was used for elution. The corresponding fractions were combined, concentrated and lyophilized 3 times to remove excess of buffer. **121a**: P^{31}-NMR (D_20): -3.76 (s); MS: 378.2 [M-1]. **122a**: 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 115
COMPOUND 263a

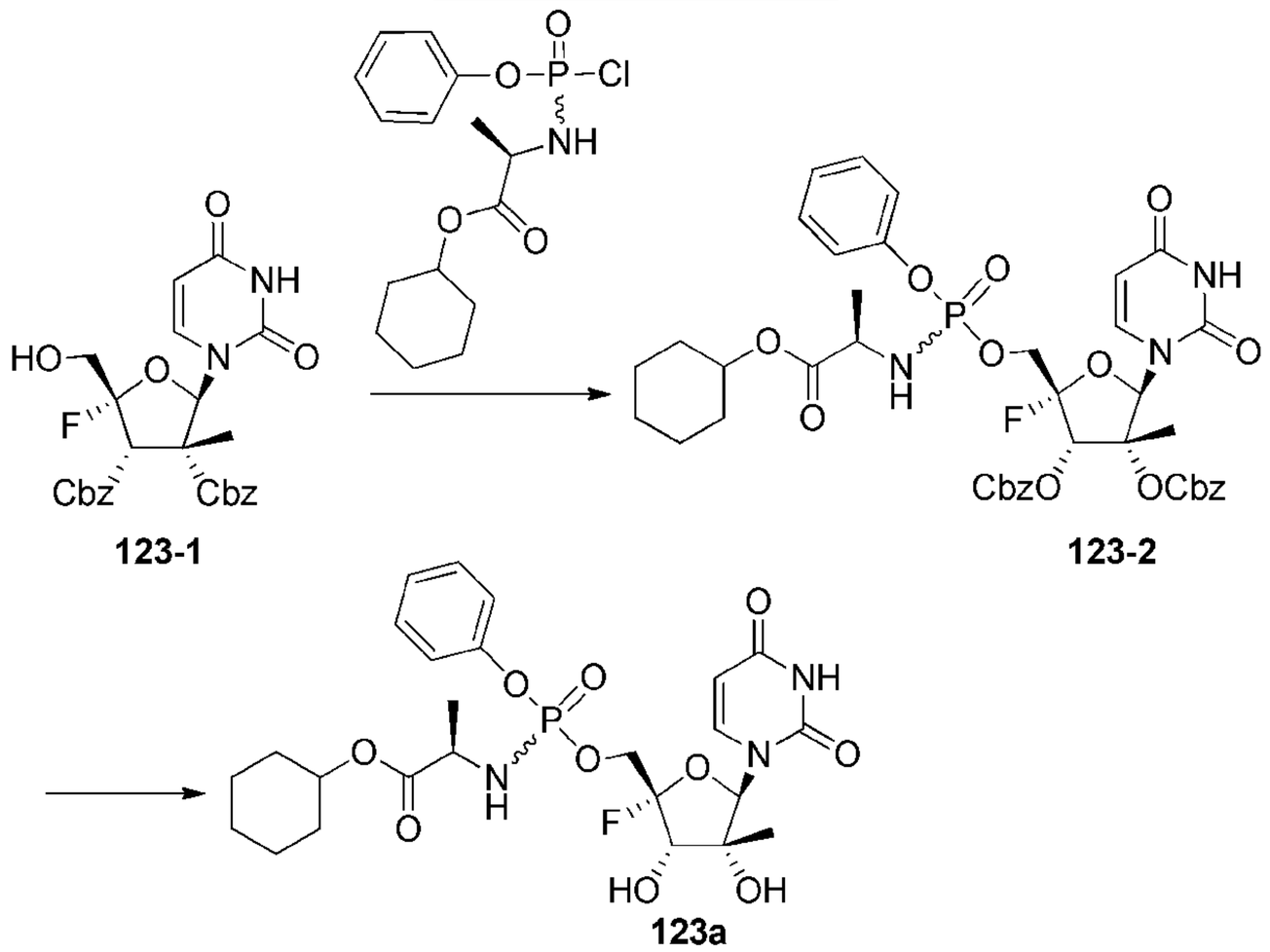


[0599] A mixture of **122-1** (170 mg, 0.19 mmol) and methanolic ammonia (7 N; 3 mL) was stirred at RT for 8 h, concentrated and purified on silica gel (10 g column) with CH_2Cl_2/MeOH (4-11% gradient) to give **122-2** (100 mg, 90%).

[0600] Compound **122-2** was rendered anhydrous by co-evaporating with pyridine, followed by toluene. To a solution of **122-2** (24 mg, 0.04 mmol), and N-methylimidazole (17 μL, 5 equiv) in acetonitrile (1 mL) was added the phosphochloridate (50 mg, 3.5 equiv.) 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 **122-3** (10 mg, 28%).

[0601] A solution of **122-3** (9 mg, 0.01 mmol) in 80% formic acid was stirred 3 h at R. T. The mixture was evaporated and purified on silica (10 g column) with CH_2Cl_2/MeOH (5-15% gradient) to give **122a** (3 mg, 50%). MS: m/z = 624 [M-1].

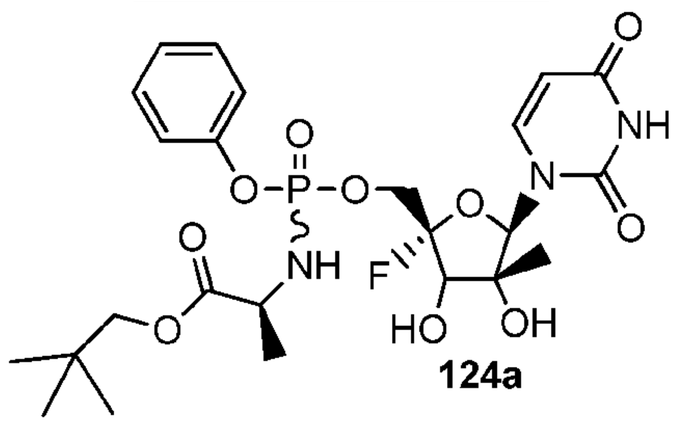
EXAMPLE 116
COMPOUND 123a



[0602] To an ice cooled solution of **123-1** (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 **123-2** (102 mg; 80%).

[0603] A mixture of **123-2** (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 **123a** (52 mg, 74%). MS: m/z = 584 [M-1].

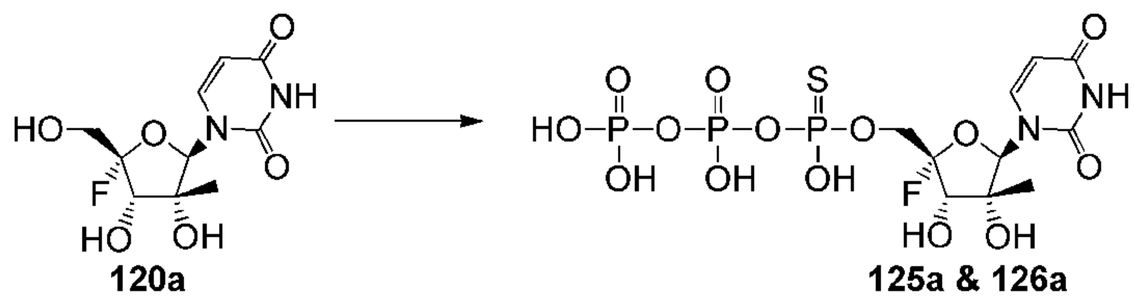
EXAMPLE 117
COMPOUND 124a



124a

[0604] Compound **124a** (36 mg, 63%) was synthesized as described for **117a** using a neopentyl ester phosphorochloridate reagent. MS: 572.6 [M-1].

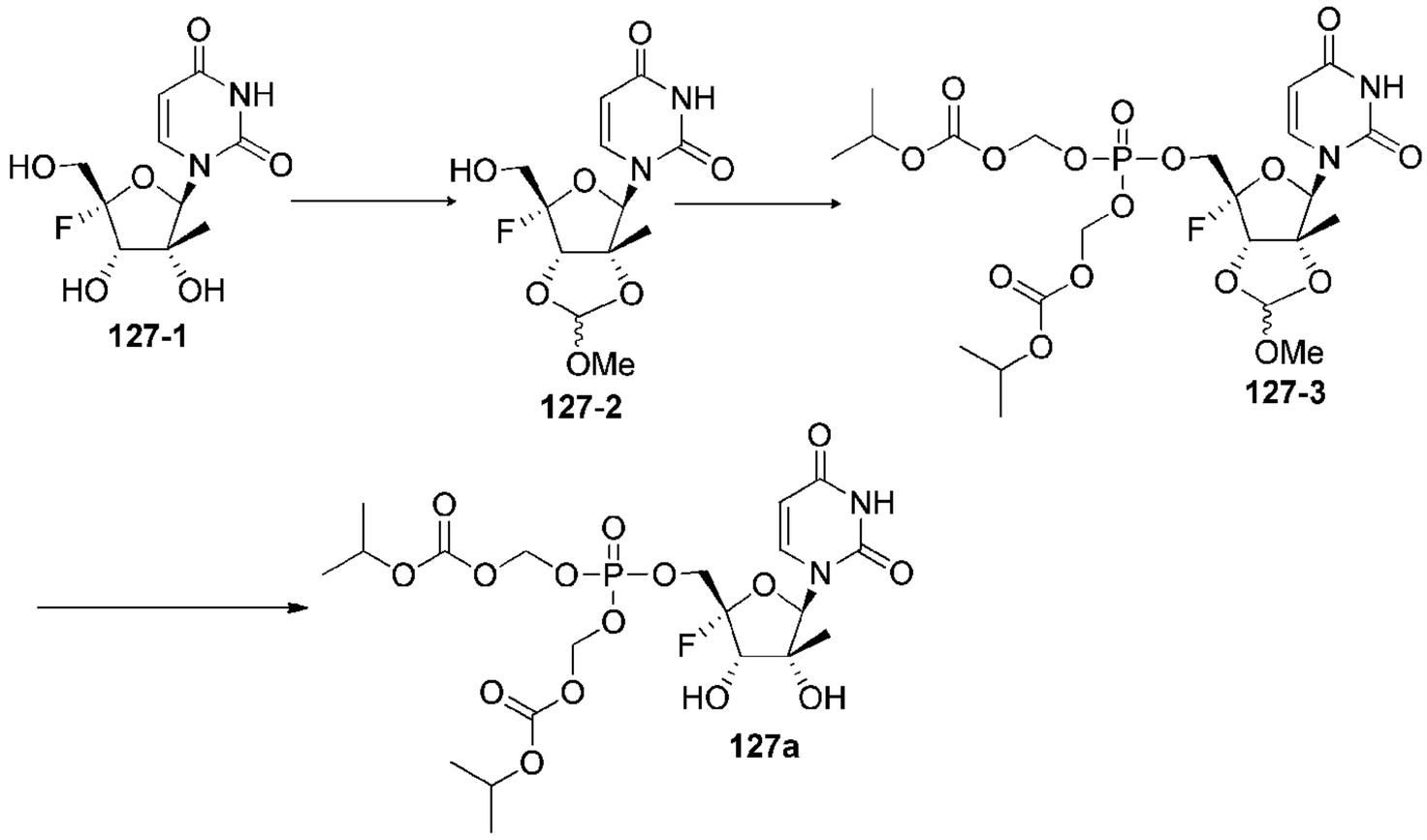
EXAMPLE 118
COMPOUNDS 125a AND 126a



120a **125a & 126a**

[0605] Dry **120a** (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 **125a** and **126a.** 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 50mM 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: m/z 530.9.0 [M-1].

EXAMPLE 119
COMPOUND 127a

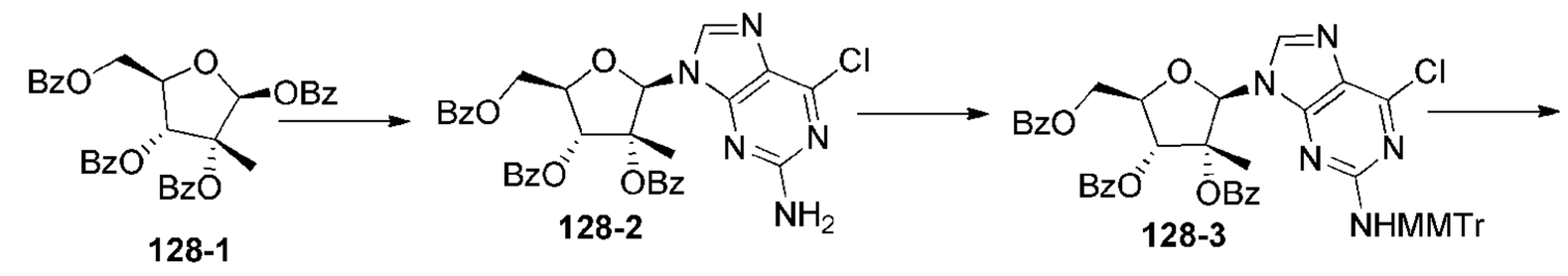


[0606] A mixture of **127-1** (1.2 g, 4.3 mmol), PTSA monohydrate (0.82 g, 1 equiv.), and trimethyl orthoformate (14 mL, 30 equiv.) in dioxane (30 mL) was stirred overnight at RT. The reaction was neutralized with 7 N NH_3/MeOH and a white solid removed by filtration. The residue was dissolved in THF (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 **127-2** (1.18 g, 87%).

[0607] Compound **127-3** (137 mg, 75%) was prepared from **127-2** (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).

[0608] A solution of **127-3** (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 **127a** (100 mg, 77%). MS: m/z = 1175 [2M-1].

EXAMPLE 120
COMPOUND 128a



[0609] Compound **128-1** (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 **128-1** 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 **128-2** (48.0 g, yield: 88.7%) as a yellow foam. ESI-MS: m/z 628 $[M+H]^+$.

[0610] To a solution of **128-2** (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 **128-3** (68 g, 98%). ESI-MS: m/z 900.1 $[M+H]^+$.

[0611] Sodium (8.7 g, 378.0 mmol) was dissolved in dry EtOH (100 mL) at 0 °C, and slowly warmed to RT. Compound **128-3** (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 **128-4** (34.0 g, 75.2%) as a yellow solid. ESI-MS: m/z 598 $[M+H]^+$.

[0612] Compound **128-4** (32.0 g, 53.5 mmol) was co-evaporated with anhydrous pyridine 3 times. To an ice cooled solution of **128-4** 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 **128-5** (25.0 g, 62.2%) as a yellow solid. ESI-MS: m/z 752 $[M+H]^+$.

[0613] To a solution of **128-5** (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 **128-6** (12.0 g, 67.4%) as a yellow solid. ESI-MS: m/z 580 $[M+H]^+$.

[0614] To an ice cooled solution of **128-6** (8.0 g, 13.8 mmol) in dry MeCN (100mL) 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 **128-7**(7.2 g, 72.0%) as a solid. ESI-MS: m/z 726 $[M+H]^+$.

[0615] To a solution of crude **128-7** (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 **128-8** (8.0 g, 86.4%) as a solid. ESI-MS: m/z 934 $[M+H]^+$.

[0616] To a solution of **128-8** (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 **128-9** (6.0 g, 80.0%) as a solid. ESI-MS: m/z 928 $[M+H]^+$.

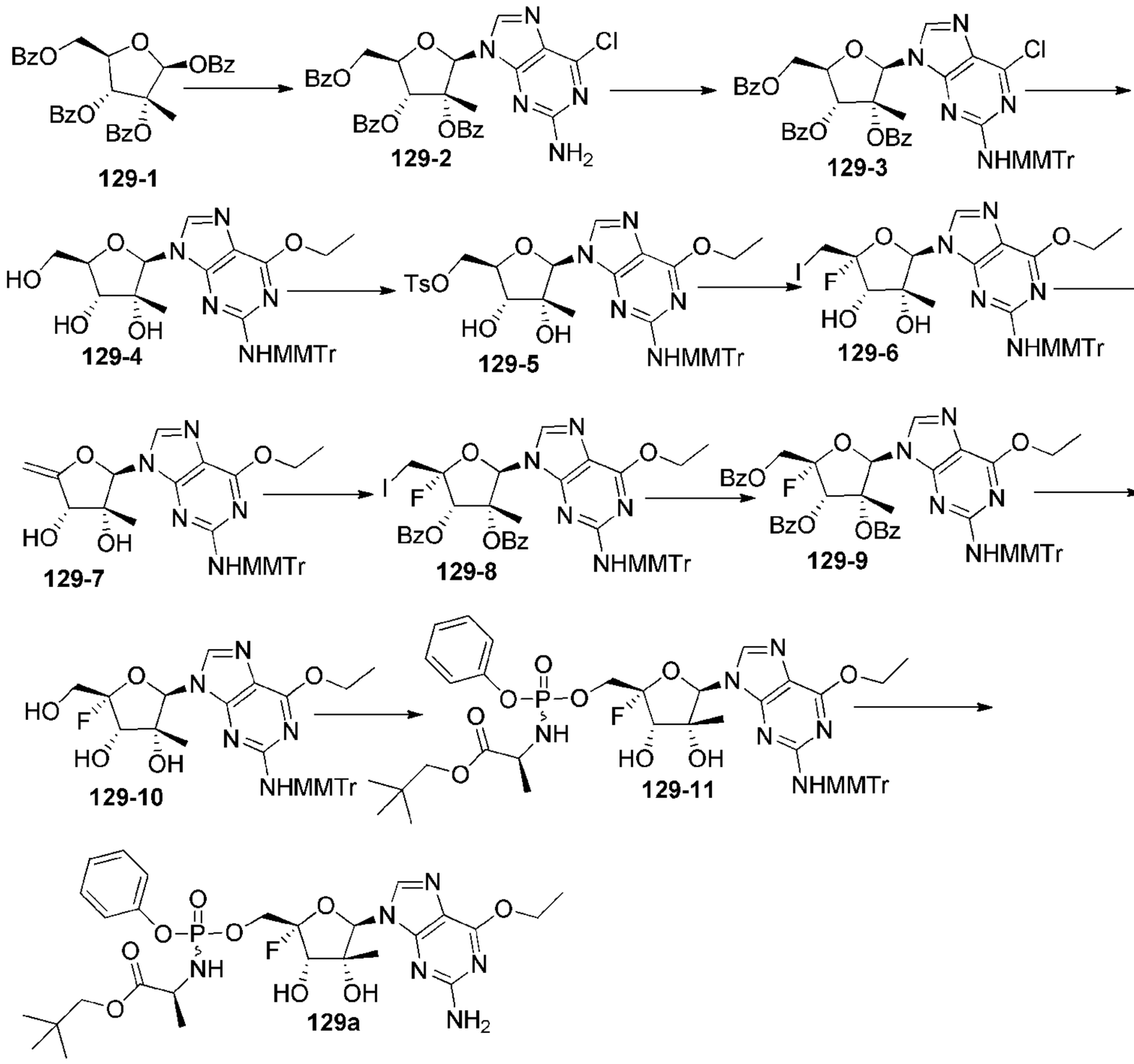
[0617] Compound **128-9** (4.0 g, 4.3 mmol) was co-evaporated with anhydrous toluene 3 times, and treated with NH_3/MeOH (50 mL, 4N) at RT. The mixture was stirred for 18 h at RT. The reaction was monitored by LCMS, and the mixture was concentrated at

low pressure. The residue was purified by silica gel column chromatography (EA in PE from 30% to 50%) to give **128-10** (1.9 g, 71.7%) as a solid. ESI-MS: m/z 616 $[M+H]^+$.

[0618] Compound **128-10** (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 **128-11** (240 mg, 53.3%) as a solid. ESI-MS: m/z 925 $[M+H]^+$.

[0619] Compound **128-11** (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 **128a** (87.6 mg, 51.7%) as a solid. ESI-MS: m/z 653 $[M+H]^+$.

EXAMPLE 121
COMPOUND 129a



[0620] Compound **129-1** (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 **129-1** (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 **129-2** (48.0 g, 88.7%) as a yellow foam. ESI-MS: m/z 628 $[M+H]^+$.

[0621] To a solution of **129-2** (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 **129-3** (68 g, 98%). ESI-MS: m/z 900.1 $[M+H]^+$.

[0622] Sodium (8.7 g, 378.0 mmol) was dissolved in dry EtOH (100 mL) at 0 °C, and slowly warmed to RT. Compound **129-3** (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 **129-4** (34.0 g, 75.2%) as a yellow solid. ESI-MS: m/z 598 $[M+H]^+$.

[0623] Compound **129-4** (32.0 g, 53.5 mmol) was co-evaporated with anhydrous pyridine 3 times. To an ice cooled solution of **129-4** (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 **129-5** (25.0 g, 62.2%) as a yellow solid. ESI-MS: m/z 752 $[M+H]^+$.

[0624] To a solution of **129-5** (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 **129-6** (12.0 g, 67.4%) as a yellow solid. ESI-MS: m/z 580 $[M+H]^+$.

[0625] To an ice cooled solution of **129-6** (8.0 g, 13.8 mmol) in anhydrous MeCN (100mL) 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 **129-7** (7.2 g, 72.0%) as a solid. ESI-MS: m/z 726 $[M+H]^+$.

[0626] To a solution of **129-7** (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 **129-8** (8.0 g, 86.4%) as a solid. ESI-MS: m/z 934 $[M+H]^+$.

[0627] To a solution of **129-8** (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 **129-9** (6.0 g, 80.0%) as a solid. ESI-MS: m/z 928 $[M+H]^+$.

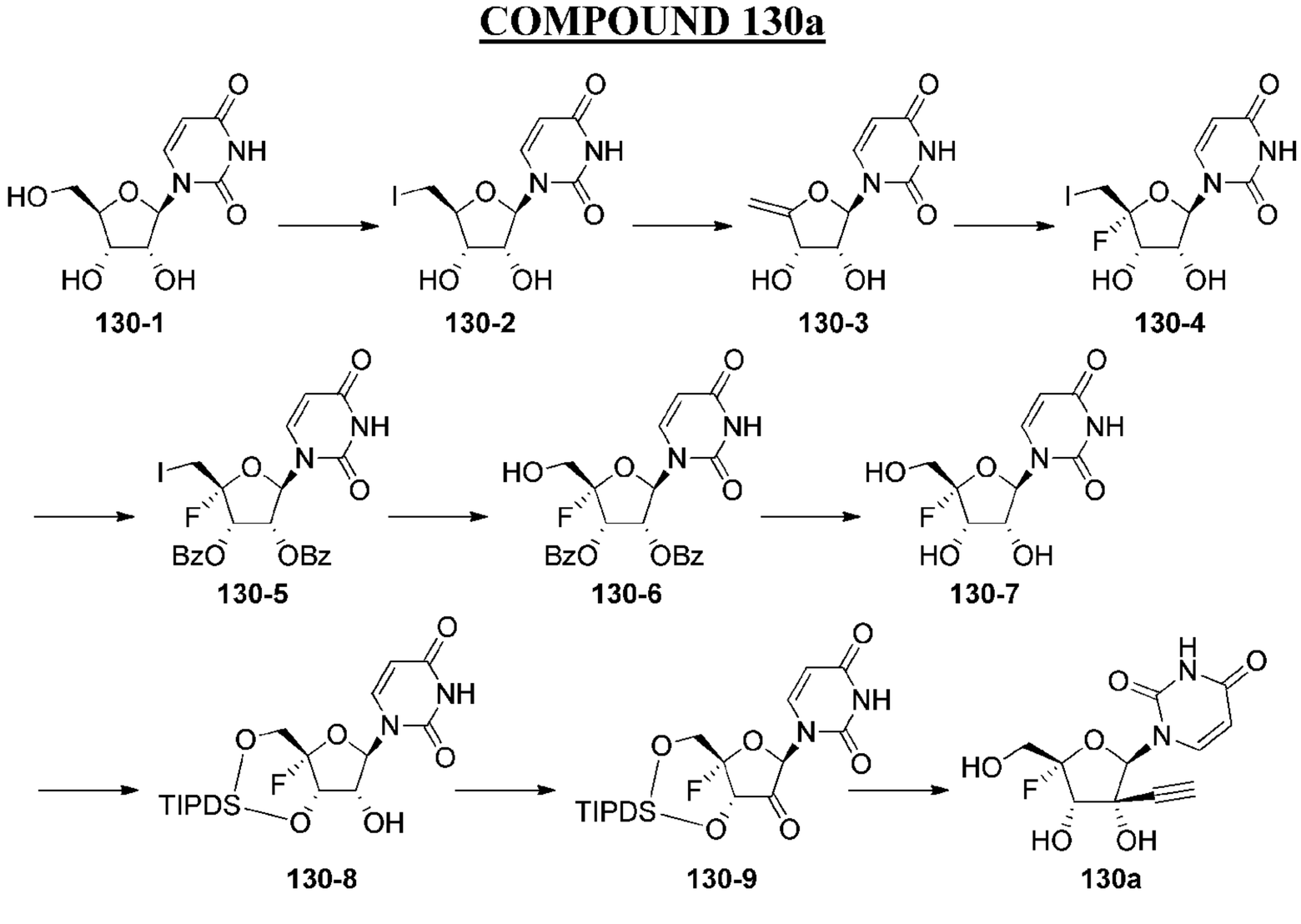
[0628] Compound **129-9** (4.0 g, 4.3 mmol) was co-evaporated with anhydrous toluene 3 times, and treated with NH_3/MeOH (50 mL, 4N) at RT. The mixture was stirred for 18 h. at RT. Completion of the reaction was determined by LCMS. The mixture was concentrated at low pressure, and the residue was purified by silica gel column

chromatography (EA in PE from 30% to 50%) to give product **129-10** (1.9 g, 71.7%) as a solid. ESI-MS: m/z 616 $[M+H]^+$.

[0629] Compound **129-10** (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 **129-11** (210 mg, 47.5%) as a solid. ESI-MS: m/z 913.0 $[M+H]^+$.

[0630] Compound **129-11** (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 **129a** (71.8 mg, 48.7%) as a solid. ESI-MS: m/z 641.3 $[M+H]^+$.

EXAMPLE 122
COMPOUND 130a



[0631] To a stirred suspension of **130-1** (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 **130-2** (23 g, 79%) as a white solid.

[0632] To a stirred solution of **130-2** (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 **130-3** (13.1 g, 92.5%) as a white foam solid.

[0633] To a stirred solution of **130-3** (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 **130-4 (**14 g, 73%) as a yellow solid. ESI-MS: m/z 373.0 $[M+H]^+$.

[0634] To a stirred solution of **130-4** (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 **130-5** (15 g, 81%) as a white solid. ESI-TOF-MS: m/z 581.0 $[M+H]^+$.

[0635] 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 **130-5** (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 **130-6** (7.5 g, 68%)

[0636] Compound **130-6** (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

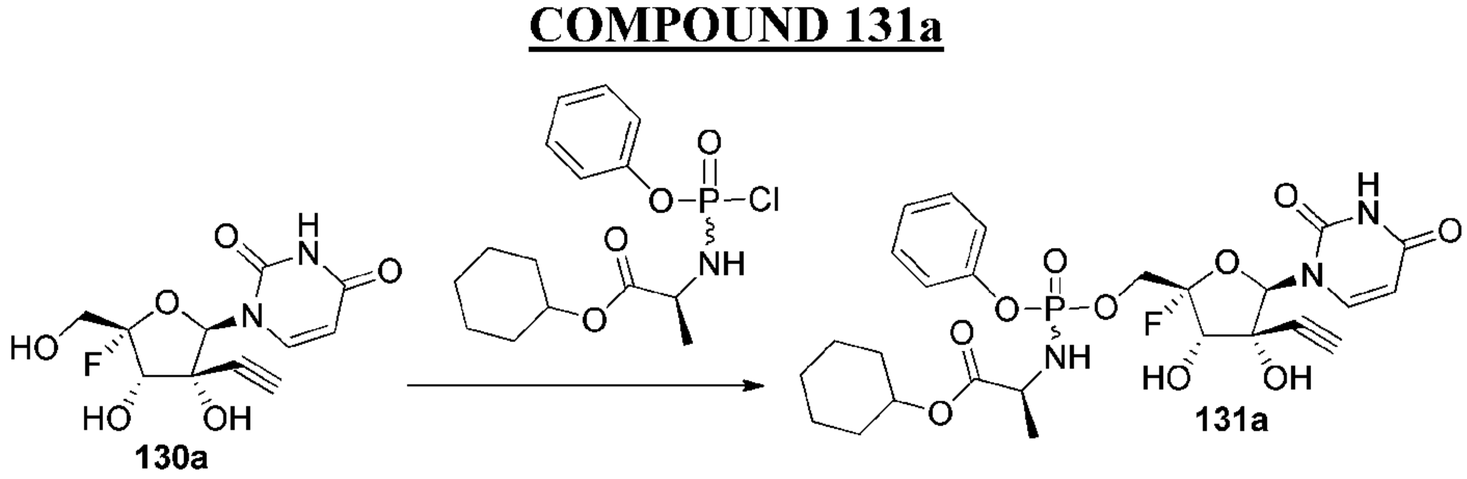
at low pressure. The residue was washed with DCM, and the solid was filtered to give **130-7** (2.1 g, 75%) as a white foam. ESI-MS: m/z 263.0 $[M+H]^+$.

[0637] To a solution of **130-7** (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 **130-8** (1.6 g, 40%) as a white foam.

[0638] A solution of **130-8** (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 **130-9** (1.2 g, 80%) as a white foam. ESI-MS: m/z 503.0 $[M+H]^+$

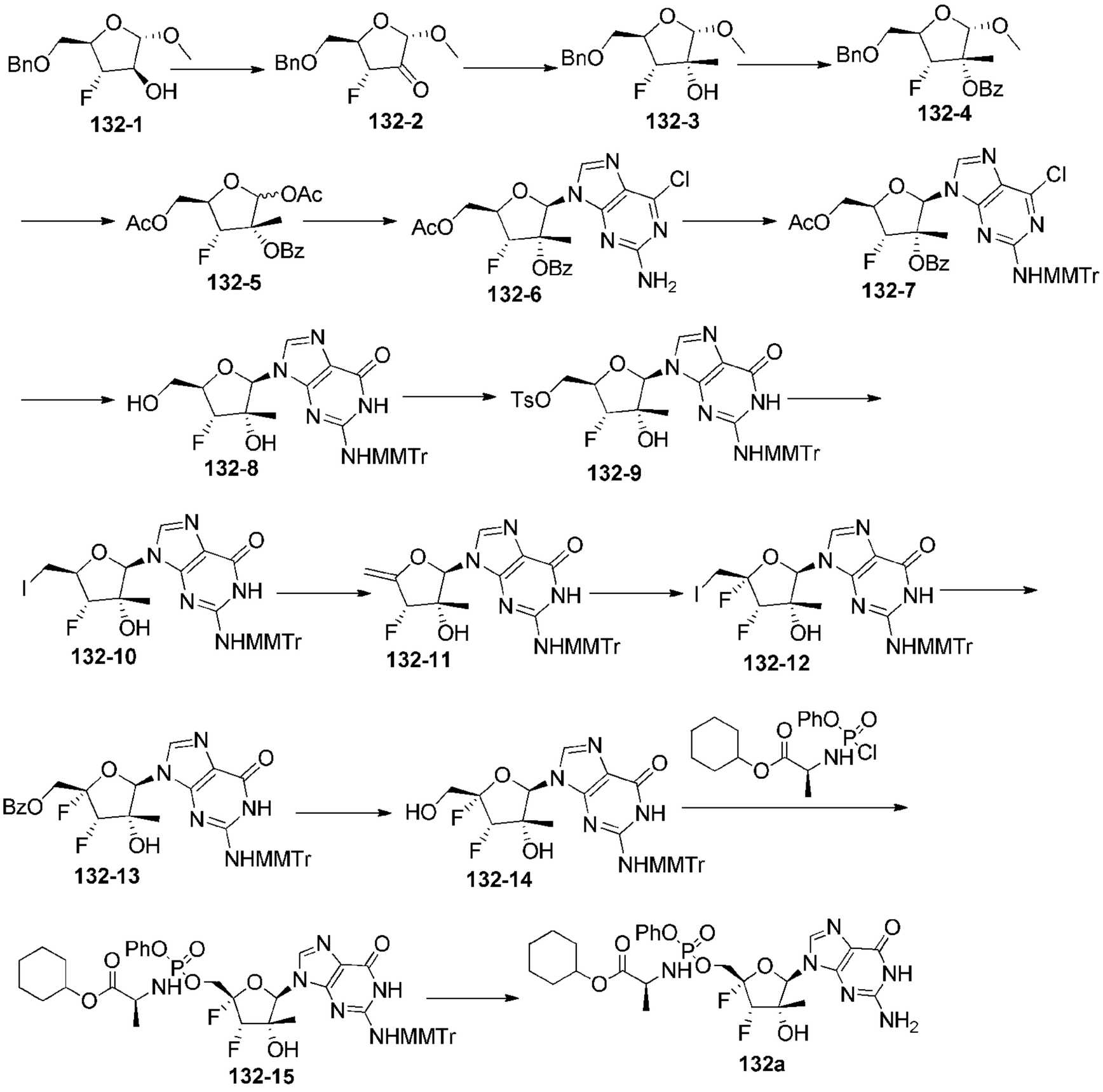
[0639] Compound **130-9** (500 mg, 1 mmol) was dissolved in dry THF (8 mL). Ethynyl magnesium bromide (8 mL of 0.5M solution in cyclohexane) was added at RT. After 30 mins, additional ethynyl magnesium bromide (8 mL) was added. The mixture was left for 30 mins, and then quenched with sat. solution of 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 **130a** (110 mg). MS: 285.1 [M-1].

EXAMPLE 123
COMPOUND 131a



[0640] Compound **130a** (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 **131a** was obtained (46 mg, 39%). MS: m/z 593.9 [M-1].

EXAMPLE 124
COMPOUND 132a



[0641] To a stirred solution of **132-1** (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 ^{o}C for 12 h, and

then slowly cooled to RT. After filtration, the filtrate was concentrated to give crude **132-2** (4.87 g, 98%).

[0642] To a solution of **132-2** (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 **132-3** (4.37 g, 83%) as a white solid.

[0643] To a solution of **132-3** (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 **132-4** (5.3 g, 87%) as a white solid.

[0644] To a solution of **132-4** (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 **132-5** (2.3 g, 81%)) as a white solid.

[0645] To a stirred solution of 6-Cl-guanine (560 mg, 3.31 mmol) and **132-5** (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 **132-6** (800 mg, 70%) as a white solid.

[0646] To a solution of **132-6** (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 **132-7** (1.3 g, 72.5%) as a white solid.

[0647] 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 **132-7** (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 **132-8** (600 mg, 85%) as a white solid.

[0648] To a solution of **132-8** (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 **132-9** (6.0 g, 76%) as a white solid.

[0649] To a solution of **132-9** (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 **132-10** (5.43 g, 96.4%) as a white solid.

[0650] To a solution of **132-10** (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 **132-11** (3.5 g, 85%) as a white solid.

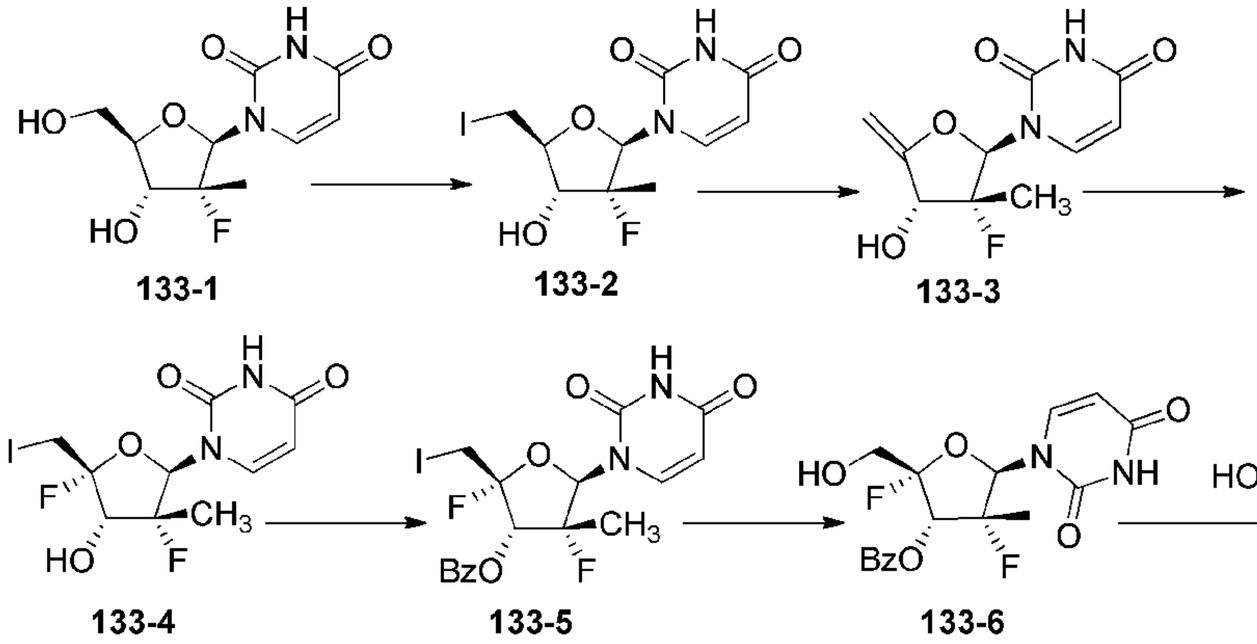
[0651] To a solution of **132-11** (3.5 g, 6.33 mmol) and AgF (4.42 g, 34.81 mmol) in anhydrous DCM (20 mL) was added a solution of iodine (3.54 g, 13.93 mmol) in anhydrous DCM (5 mL) dropwise at 0°C. The mixture was stirred for 3 h. The reaction mixture was washed with sat. $NaHCO_3$ solution (40 mL) 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 **132-12** (1.37g, 31%) as a white solid.

[0652] To a solution of **132-12** (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 **132-13** (250 mg, 20%). ESI-MS: m/z: 694 $[M+H]^+$

[0653] A mixture of **132-13** (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 **132-14** (180 mg, 85%).

[0654] Compound **132a** (85 mg, 56%) was prepared from **132-14** (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 125
COMPOUND 133a



[0655] To a solution of **133-1** (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 **133-2** (190 mg, 85%) as a white solid.

[0656] To a solution of **133-2** (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 ^oC 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 **133-3** (75 mg, 52%) as a white solid.

[0657] To a solution of **133-3** (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 **133-4** (300 mg, 62%) as a white solid.

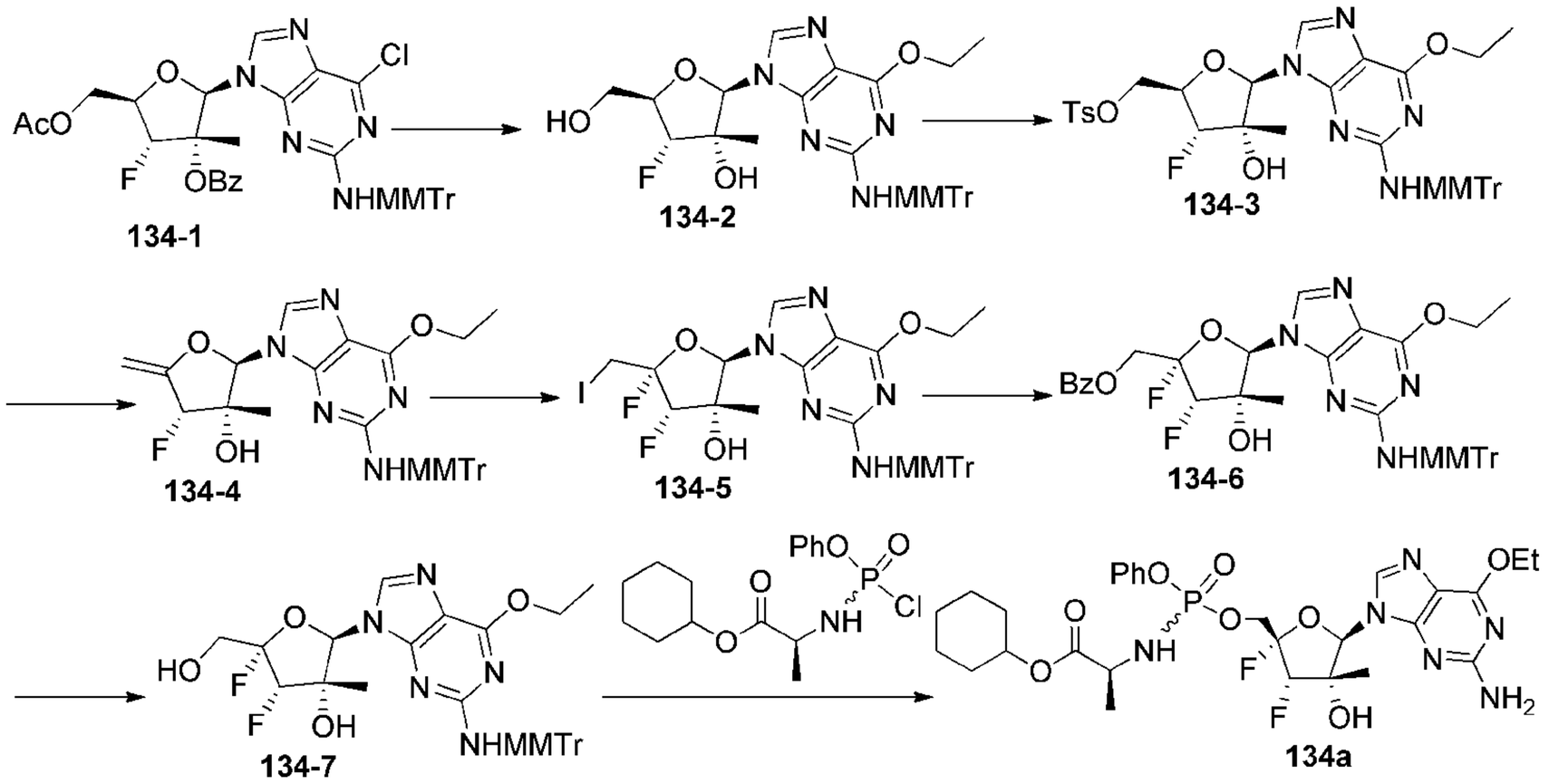
[0658] To a solution of **133-4** (194 mg, 0.5 mmol) in pyridine(5 mL) was added BzCl (92 mg, 0.55 mmol) at 0 ^oC. The mixture was stirred at RT for 5 h, and the reaction was quenched with water. The mixture was concentrated at low pressure, and the residue was purified by silica gel column (20% EA in PE) to give **133-5** (397 mg, 81%) as a white solid.

[0659] To a solution of **133-5** (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 **133-6** (450 mg, 63%) as a white solid.

[0660] Compound **133-6** (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 **133a** (120 mg, 66%) as a white powder. ESI-MS: m/z 279.0 $[M+H]^+$.

EXAMPLE 126
COMPOUND 134a



[0661] Sodium (6.0 g, 261.2 mmol) was dissolved in dry EtOH (400ml) at 0 °C, and slowly warmed to RT. Compound **134-1** (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 **134-2** (20.0 g, 76.6%) as a white solid.

[0662] Compound **134-2** (20.0 g, 33.3 mmol) was co-evaporated with anhydrous pyridine 3 times. To an ice cooled solution of **134-2** 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 **134-3** (20.0 g, 80%) as a yellow solid.

[0663] To a solution of **134-3** (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 **134-4** (12.0 g, 77.9%) as a yellow solid.

[0664] To an ice-clod solution of **134-4** (11.0 g, 18.9 mmol) in dry MeCN (100mL) 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 **134-5** (11.0 g, 79.9%).

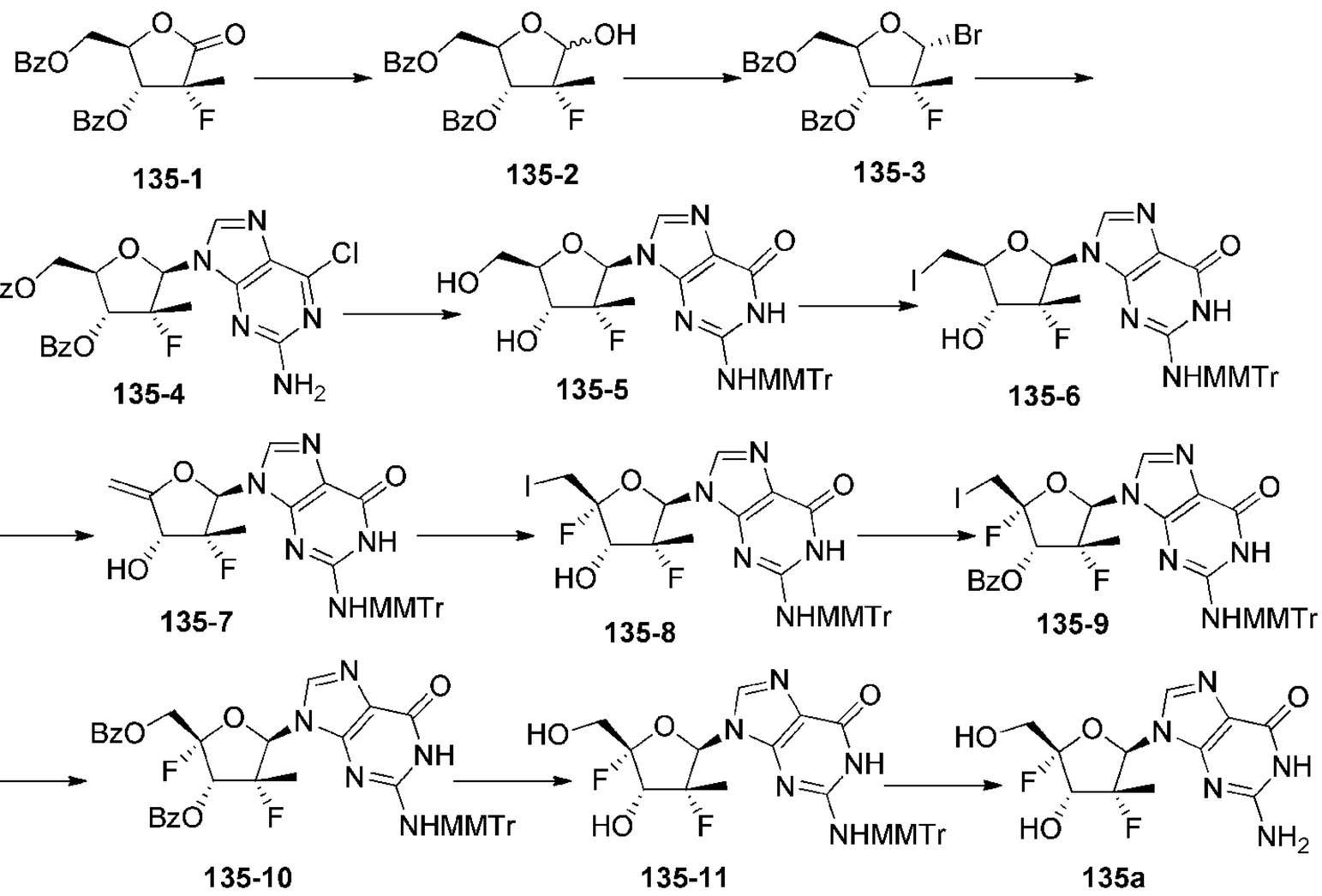
[0665] To a solution of **134-5** (10.0 g, 13.7 mmol) in dry DMF (100 mL) was added NaOBz (19.8 g, 137 mmol) and 15-crown-5 (30.2 g, 137 mmol). The reaction was stirred for 48 h at 90 °C, and diluted with EA. The solution was washed with water and brine, and dried over $MgSO_4$. The organic layer was evaporated at low pressure, and the residue was purified by silica gel column chromatography (EA in PE from 12% to 50%) to give **134-6** (8.0 g, 80.0%).

[0666] Compound **134-6** (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 **134-7** (4.5 g, 87.8%). ESI-MS: m/z 617.9 $[M+H]^+$.

[0667] To an ice cooled mixture of **134-7** (25 mg, 0.07 mmol) and NMI (46 μL, 8 equiv.) in acetonitrile (0.7 mL) was added the phosphorochloridate reagent (73 mg, 3 equiv.) 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 **134a** (18 mg, 40%). MS: m/z = 655 [M+1].

EXAMPLE 127
COMPOUND 135a



[0668] To a solution of compound **135-1** (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 **135-2** (26 g, 86%) as a colorless oil.

[0669] To a stirred solution of PPh_3 (37.7 g, 0.144 mol) in DCM (100 mL) was added compound **135-2** (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 **135-3** (α-isomer, 17 g, 55%) as a colorless oil.

[0670] 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 **135-3** (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 **135-4** (6 g, 42%) as a yellow solid.

[0671] To a solution of **135-4** (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 **135-5** (5.8 g, 77%) as a yellow solid.

[0672] 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 **135-5** (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 **135-6** (7 g, 66%) as a yellow solid.

[0673] To a solution of **135-6** (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 **135-7** (4.0 g, 67%) as a white solid.

[0674] To an ice-cooled solution of **135-7** (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 **135-8** (0.6 g, 16%) as a white solid.

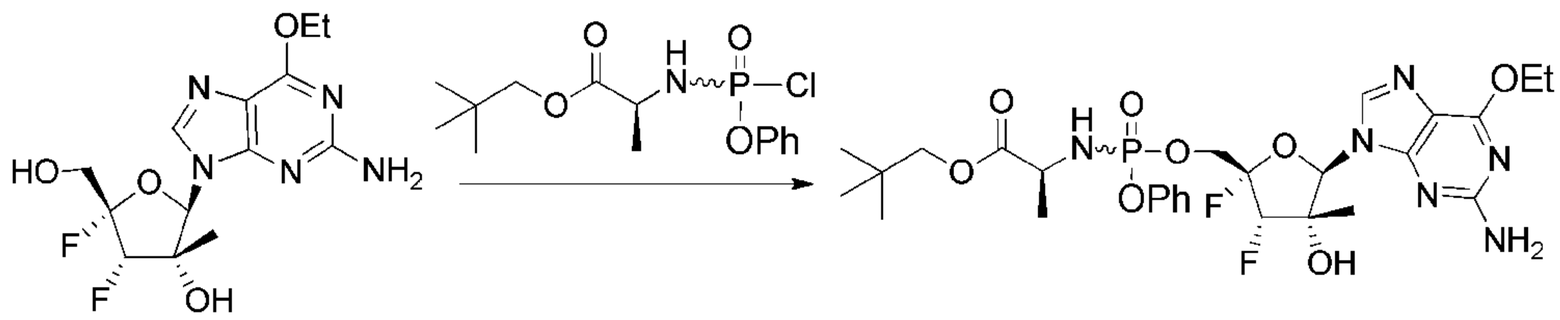
[0675] To a solution of **135-8** (0.7 g, 1 mmol) in dry pyridine (10 mL) was added BzCl (147 mg, 1.05 mmol) at 0 °C. The mixture was stirred at RT for 3 h. The mixture was then diluted with EA, and washed with sat. $NaHCO_3$ aq. and brine. The organic layer was dried over Na_2SO_4, and evaporated at low pressure. The residue was purified by silica gel column (20% EA in PE) to give **135-9** (0.65 g, 81%) as a white solid.

[0676] To a solution of **135-9** (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 **135-10** (500 mg, 78%) as a white solid.

[0677] Compound **135-10** (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 **135-11** (220 mg, 63%) as a white solid. ESI-MS: m/z 590.3 $[M+H]^+$.

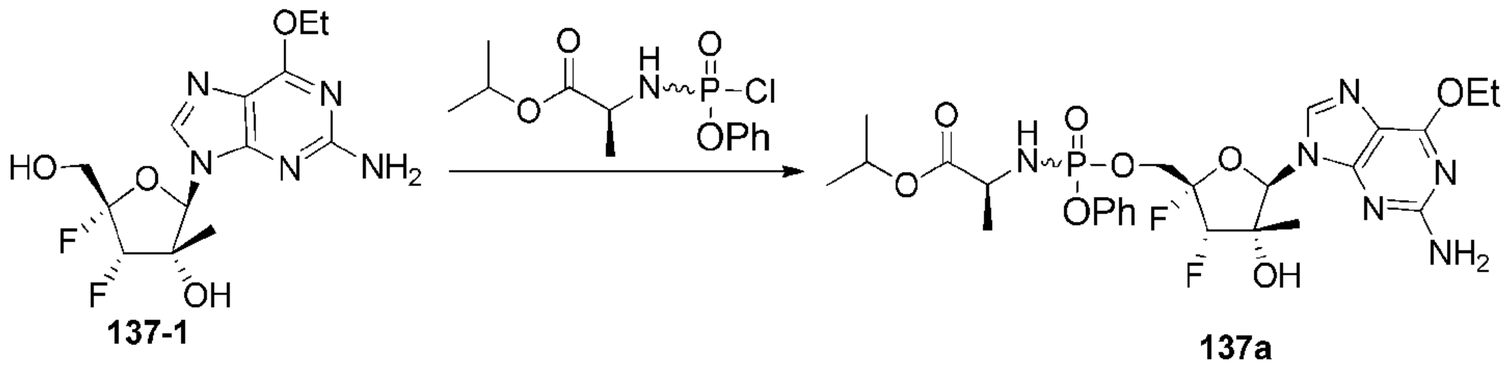
[0678] Compound **135-11** (59 mg, 0.1 mmol) was dissolved in 50% TFA in methanol (10 mL), and the mixture was kept at RT for 2 h. The solvent was evaporated and co-evaporated with a methanol/toluene mixture to remove traces of the acid. The residue was suspended in CH_3CN (1 mL) and centrifuged. The precipitate was washed with CH_3CN (1mL) and dried. Compound **135a** was obtained as a colorless solid (21 mg, 65%. MS: m/z 316.2 [M-1].

EXAMPLE 128
COMPOUND 136a



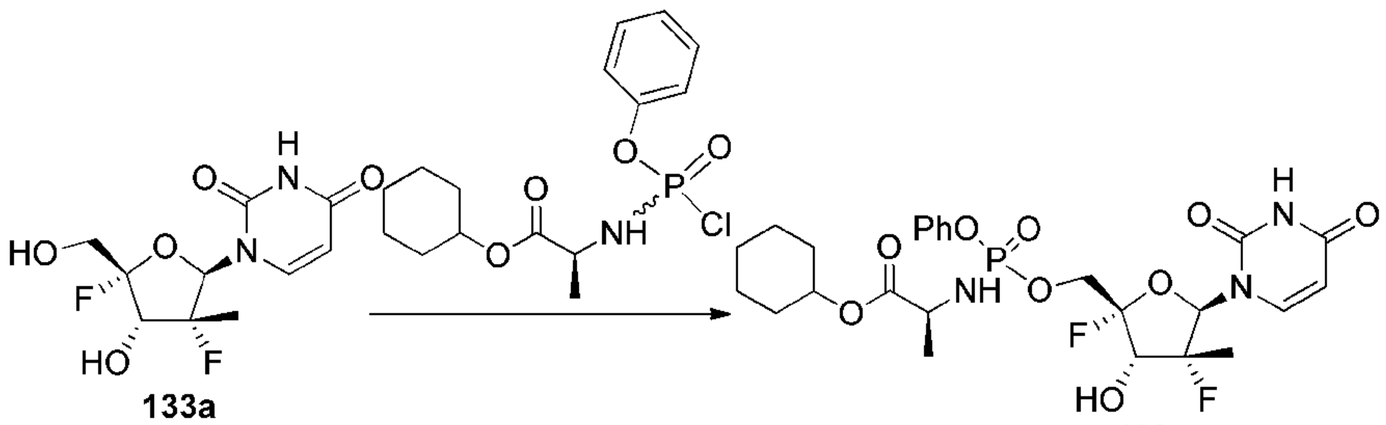
[0679] Compound **136a** (15 mg, 16%) was prepared from **136-1** (50 mg) in acetonitrile (2 mL) with the phosphorochloridate reagent (0.14 g) and NMI (0.1 mL) in the same manner as compound **7**. MS: m/z = 643 [M+1].

EXAMPLE 129
COMPOUND 137a



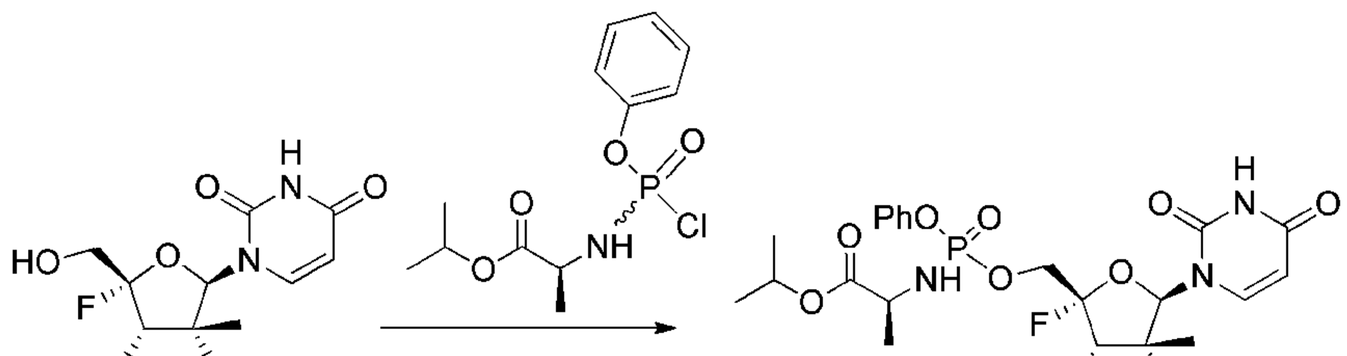
[0680] Compound **137a** (30 mg, 32%) was prepared from **137-1** (50 mg) in acetonitrile (2 mL) with the phosphorochloridate reagent (0.14 g) and NMI (0.1 mL) in the same manner as compound **7**. MS: m/z = 615 [M+1].

EXAMPLE 130
COMPOUND 138a



[0681] To a stirred solution of **133a** (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 ^{o}C for 1 h, and the temperature was raised up-to 10 ^{o}C over the next 1 h. The reaction left at 10 ^{o}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 **138a** (6.3 mg). MS *m/z* 586.05 [M-H].

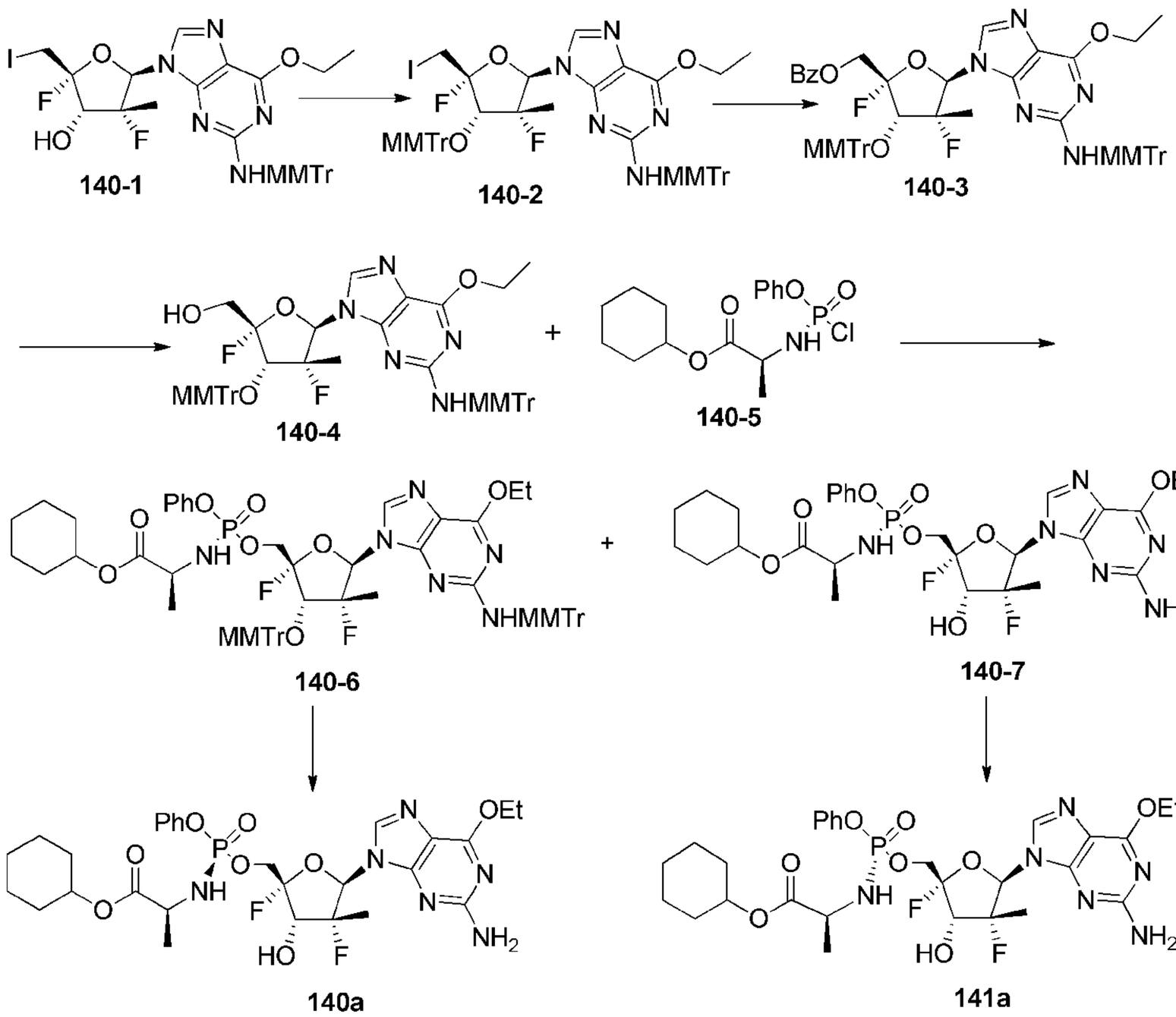
EXAMPLE 131
COMPOUND 139a



[0682] To a stirred solution of **133a** (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 °C for 1 h, the reaction temperature was raised up-to 10 °C during the next 1 h, and the solution was left at 10 °C for the next 4 h. The mixture was cooled to 0 to 5 °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 **139a** (17.5 mg). MS *m/z* 546.05 [M-H].

EXAMPLE 132
COMPOUNDS 140a AND 141a



[0683] To a solution of **140-1** (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 **140-2** (0.55, 85%) as a white solid.

[0684] To a solution of **140-2** (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 ^{o}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 **140-3** (0.3 g, 60%) as a white solid.

[0685] Compound **140-3** (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 **140-4** (145 mg, 56%) as a white solid. ESI-LCMS: m/z 890.5 $[M+H]^+$.

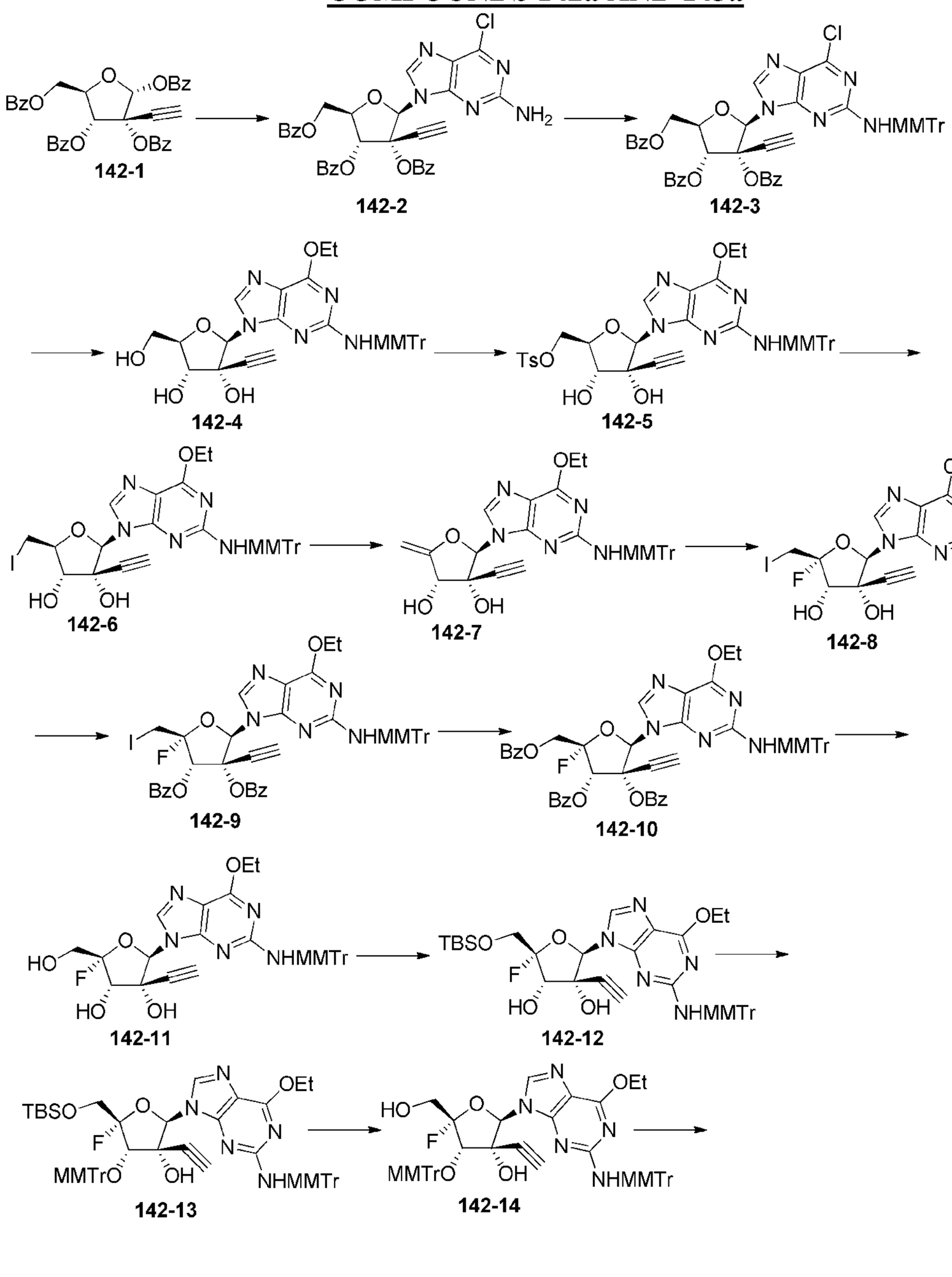
[0686] To a stirred solution of **140-4** (161 mg, 0.16 mmol) in anhydrous CH_3CN (2.0 mL) was added N-methylimidazole (118 μL, 2.87 mmol) at 0 to 5 ^{0}C (ice/water bath) followed by solution of **140-5** (186 mg, 0.54 mmol, dissolved in 2mL of CH_3CN). The solution was stirred at 0 to 5 ^{o}C for 4 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 **140-6** (82.6 mg) as the faster eluting isomer and **140-7** (106 mg) as the slower eluting isomer.

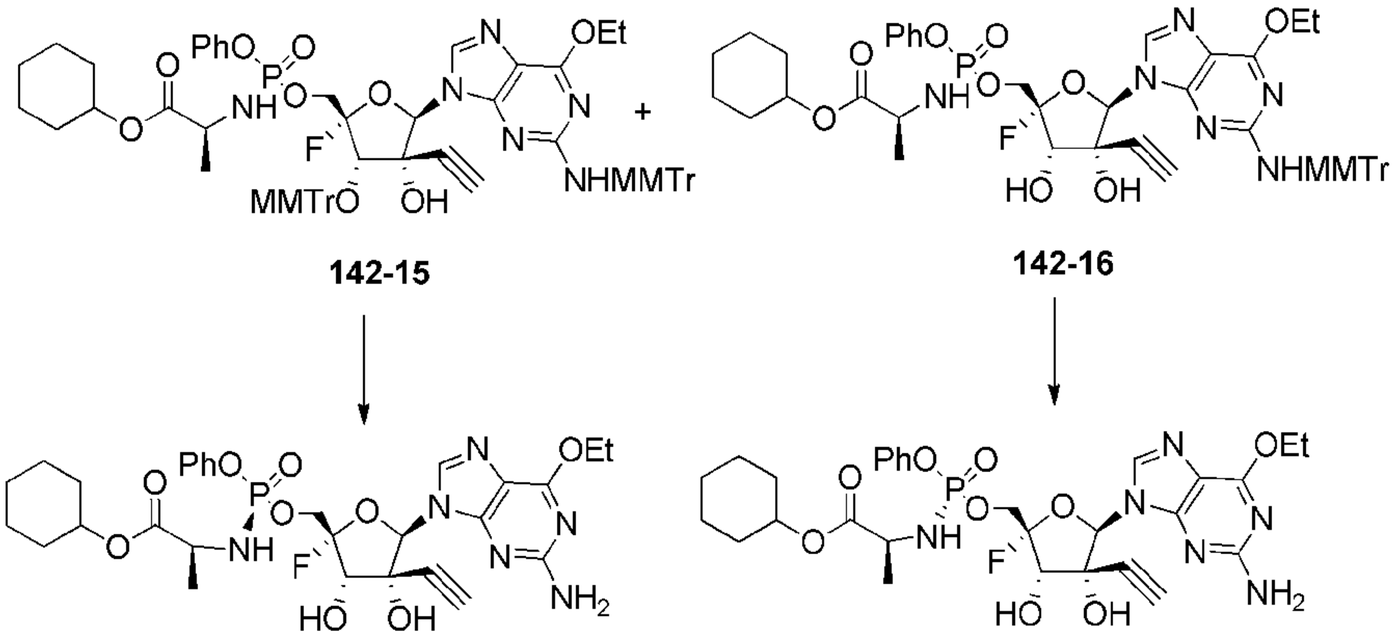
[0687] Compound **140-6** (82.6 mg, 0.07 mmol) was dissolved in_anhydrous CH_3CN (0.5 mL), and 4N HCl in dioxane (35 μL) was added at 0 to 5 ^{o}C. The mixture was stirred at RT for 1 h, and anhydrous EtOH (100 μL) was added. The solvents were evaporated at RT and co-evaporated with toluene 3 times. 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 **140a** (19.4 mg). ESI-LCMS: m/z = 655.2 $[M+H]^+$, 653.15 $[M-H]^-$.

[0688] Compound **140-7** (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 ^{o}C. Following the

procedure for obtaining **140a**, **141a** (31.8 mg) was obtained. ESI-LCMS: m/z = 655.2 $[M+H]^+$, 653.1 $[M-H]^-$.

EXAMPLE 133
COMPOUNDS 142a AND 143a





142-15 142-16 142a 143a

[0689] To a stirred suspension of **142-1** (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 **142-2** (30 g, 55.5%) as a white solid.

[0690] To a solution of **142-2** (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 **142-3** (35 g, 82%) as a white solid.

[0691] To a stirred solution of **142-3** (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 **142-4** (19 g, 81%) as a white solid.

[0692] Compound **142-4** (19 g, 31.3 mmol) was co-concentrated with anhydrous pyridine for 3 times. To an ice cooled solution of **142-4** 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 **142-5** (16 g, 67 %) as a yellow solid.

[0693] To a solution of **142-5** (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 **142-6** (9 g, 63.7%) as a white solid.

[0694] To a solution of **142-6** (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 **142-7** (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).

[0695] To an ice cooled solution of **142-7** (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 **142-8** (4.4 g, 79.8%) as a white solid.

[0696] To a solution of **142-8** (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 **142-9** (5.6 g, 81.3%) as a white solid.

[0697] To a solution of **142-9** (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 ^{o}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 **142-10** (3.9 g, 78.5%) as a white solid.

[0698] Compound **142-10** 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 **142-11** (500 mg, 74.7%) as a white solid. ESI-MS: m/z 626.3 $[M+H]^+$.

[0699] To a solution of **142-11** (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 ^{o}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 **142-12** (338 mg, 81.8%) as a white solid.

[0700] To a solution of **142-12** (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 **142-13** (337 mg).

[0701] To a solution of **142-13** (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^{o}C. The reaction was slowly warmed to RT, and stirred for 1 h. The mixture was quenched with silica gel, and

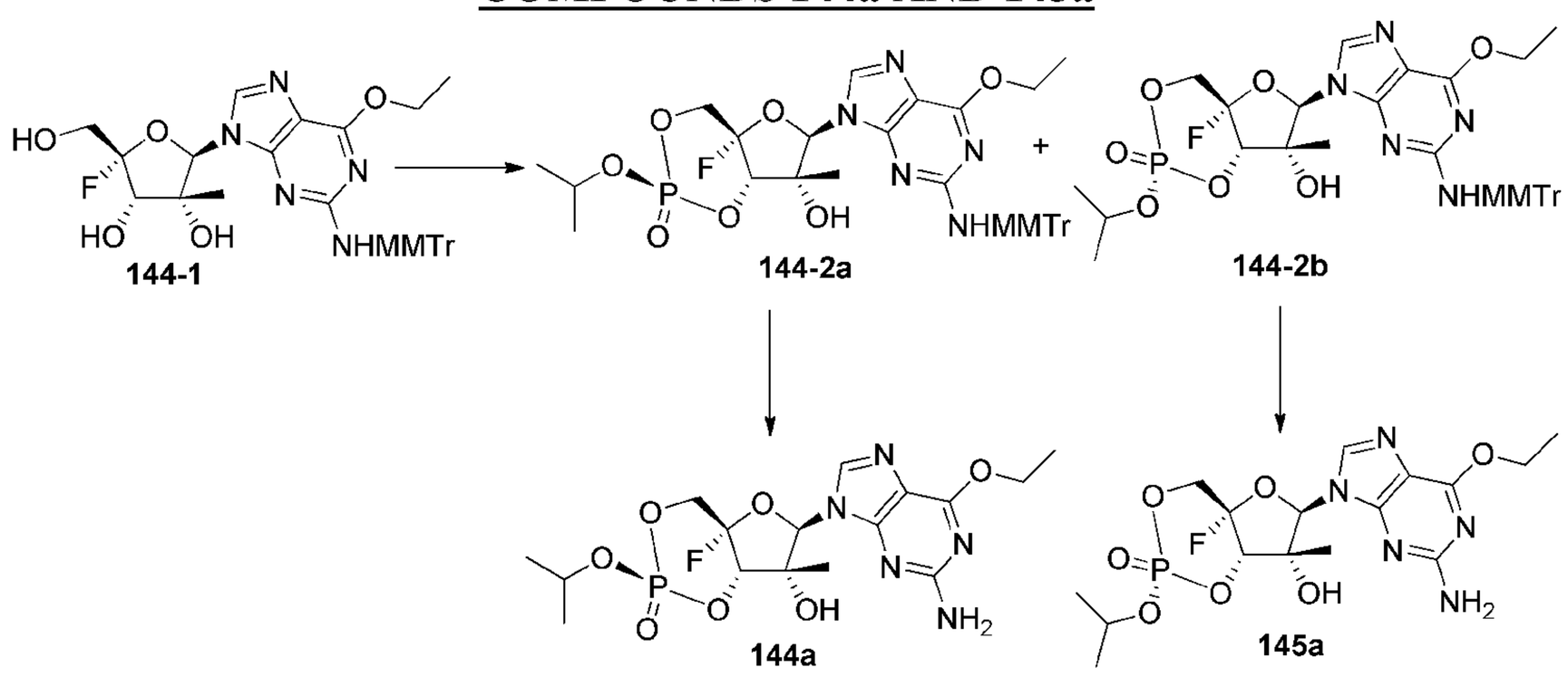
filtered. The solvents were evaporated to give the crude product, which was purified by silica gel column (EA in hexanes from 0% to 50%) to give **142-14** (188 mg).

[0702] To a stirred solution of **142-14** (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 **142-15** (75.8 mg) and **27-15** (108 mg) as a slower eluting isomer.

[0703] Compound **142-15** (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 **142a** (26.6 mg). ESI-LCMS: m/z = 663.3 $[M+H]^+$.

[0704] Compound **142-16** (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 **143a** (40.3 mg). ESI-LCMS: m/z = 663.2 $[M+H]^+$.

EXAMPLE 134
COMPOUNDS 144a AND 145a

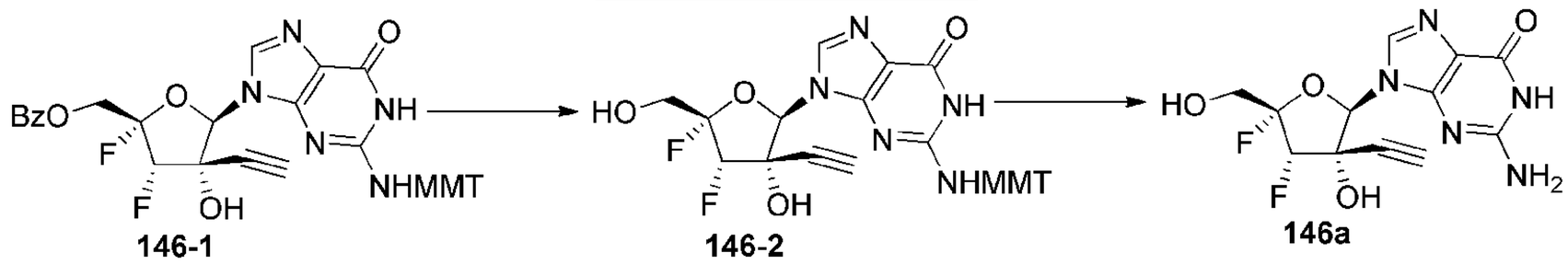


[0705] To a solution of **144-1** (150 mg, 0.24 mmol) in DCM (2.0 mL), triethylamine (141 µL, 2.0 mmol) was added at RT. The mixture was cooled to 0 to 5°C (ice/water bath), and freshly prepared and distilled isopropyl phosphorodichloridate (45 µL, 0.26 mmol, prepared according to a procedure , Reddy *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 **144-1.** 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 **144-2a** (16.9 mg, faster eluting isomer) and **144-2b** (72.7 mg, slower eluting isomer).

[0706] Compounds **144-2a** and **144-2b** were deprotected using a procedure described herein. **144a** (7.3 mg, single isomers from **144-2a** (16.5 mg, 0.0235 mmol)) and **145a** (29.0 mg. single isomers from **144-2b** (72.7 mg, 0.1 mmol)) were obtained.

[0707] **144a**: ESI-LCMS: m/z = 448.05 $[M+H]^+$. Compound **145a**: ESI-LCMS: m/z = 448.05 $[M+H]^+$.

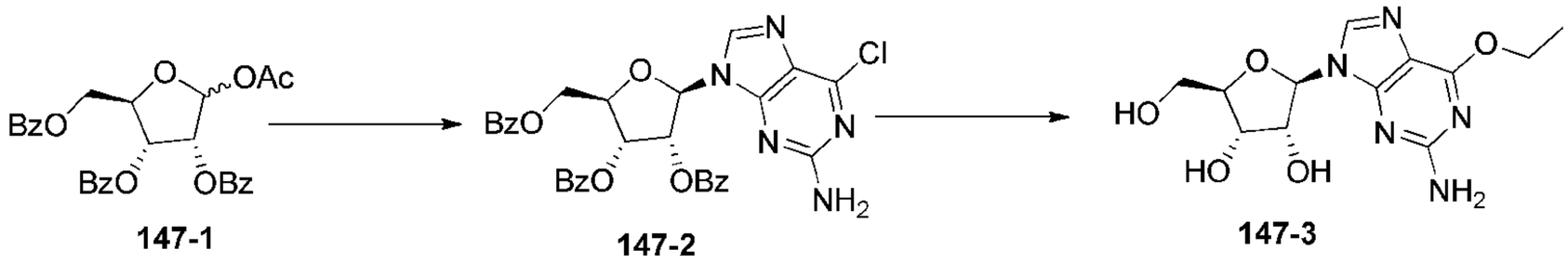
EXAMPLE 135
COMPOUND 146a

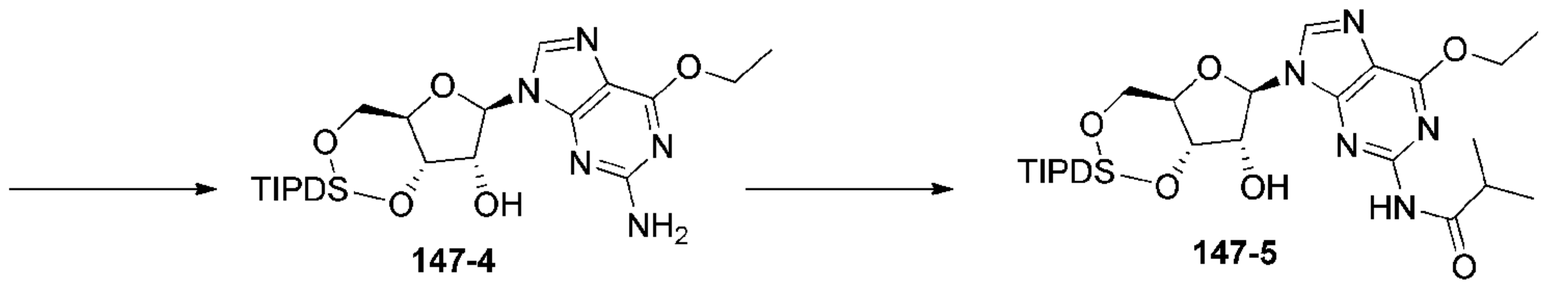


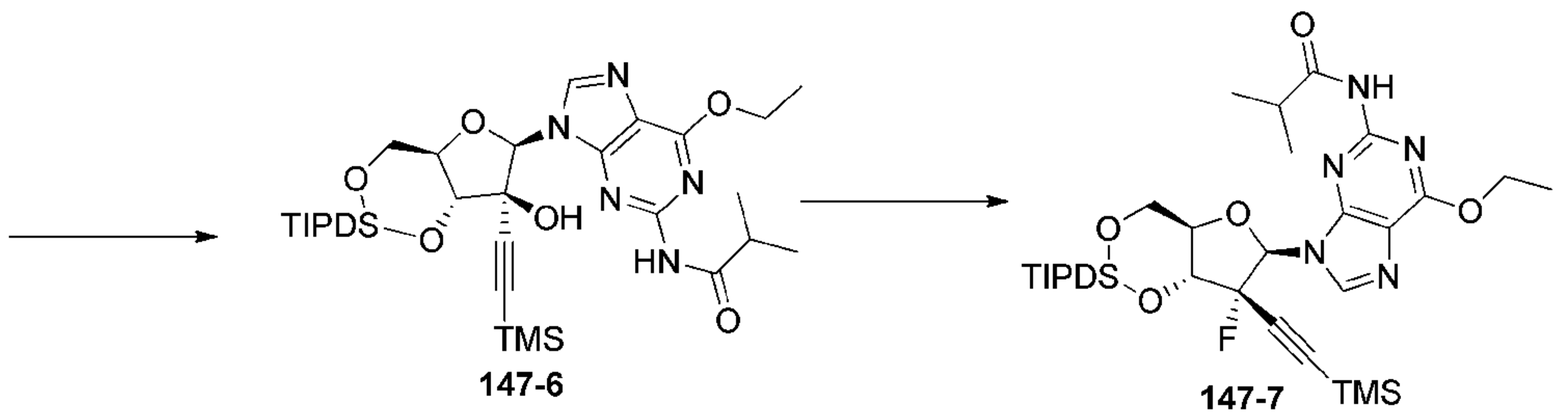
[0708] A mixture of **146-1** (45 mg, 0.06 mmol) and butylamine (0.4 mL) was kept overnight at RT and then evaporated. The crude residue was purified on silica gel (10 g column) with CH_2Cl_2/MeOH (4-12% gradient) to yield **146-2** as a colorless glass (20 mg, 56%).

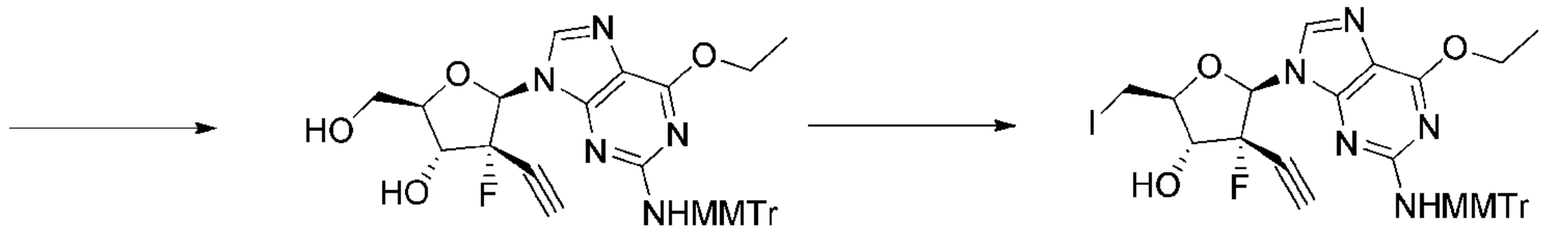
[0709] To a solution of **146-2** (20 mg, 0.03 mmol) in ACN (0.5 mL) was added 4N HCl in dioxane (35 μL). The mixture was stirred at RT for 4 h and then quenched with MeOH. The residue was treated with ACN to yield **146a** as an off-white solid (9 mg, 80%). MS m/z = 328 [M+1].

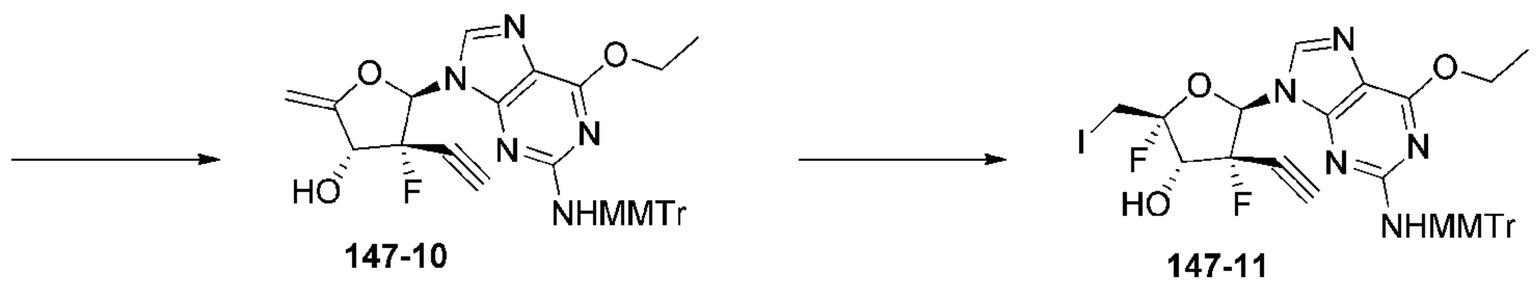
EXAMPLE 136
COMPOUNDS 147a AND 148a

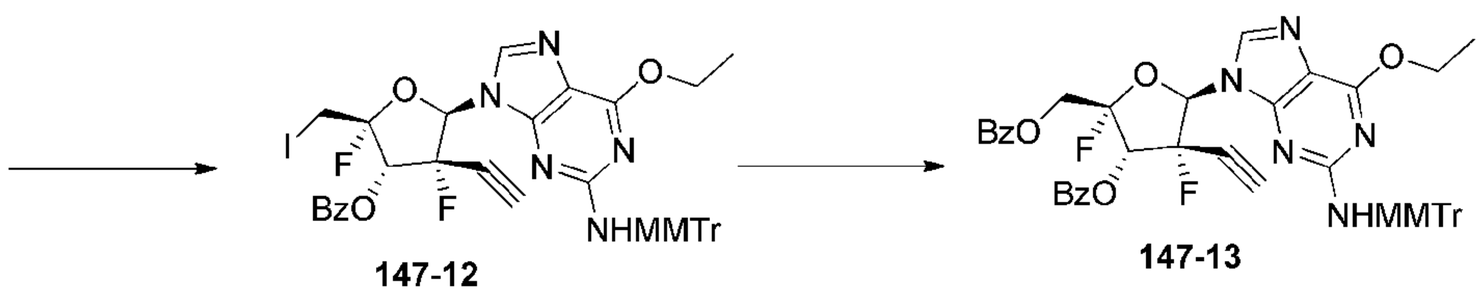


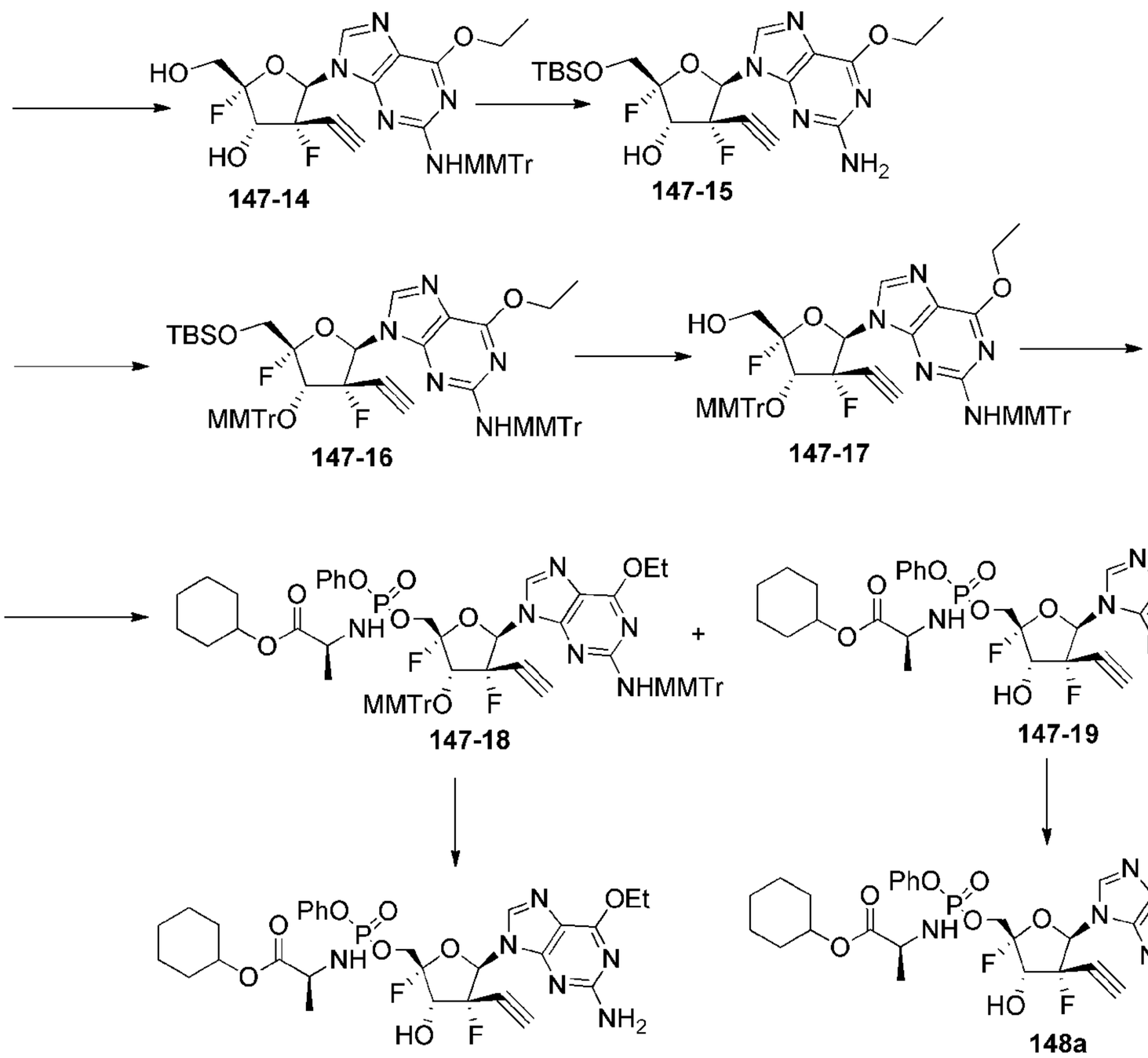












[0710] To a mixture of pre-silylated 6-Cl-guanine (using HMDS and $(NH_4)_2SO_4$) (25.2 g, 150 mmol) in DCE (300 mL) was added **147-1** (50 g, 100 mmol) and TMSOTf (33.3 g, 150 mmol) at 0 °C. The mixture was stirred at 70 °C for 16 h, and then concentrated at low pressure. The residue was re-dissolved 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 **147-2** (45 g, 73%) as a white solid.

[0711] To a solution of **147-2** (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 **147-3** (19 g, 83%) as a white solid.

[0712] To a solution of **147-3** (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 **147-4** (22 g, 65%) as a white solid.

[0713] To a solution of **147-4** (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 **147-5** (15 g, 60%) as a white solid.

[0714] To a solution of **147-5** (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 Na_2SO_4, 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 **147-6** (3.1 g, 18%) as a white solid.

[0715] To a solution of **147-6** (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 **147-7** (3.1 g, 18%) as a white solid.

[0716] Compound **147-7** (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 **147-8** (3.0 g, 86%) as a white solid.

[0717] To a solution of **147-8** (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 ^oC. 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 **147-9** (4.2 g, >100%, containing TPPO) as a white solid.

[0718] To a solution of crude **147-9** in anhydrous THF (30 mL) was added DBU (2.7 g, 18 mmol), and heated to 80 ^oC. 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 **147-10** (2.0 g, 69%) as a white solid.

[0719] To an ice cooled solution of **147-10** (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 ^oC. 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 **147-11** (2.1 g, 84.0%) as a white solid.

[0720] To a solution of crude **147-11** (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 ^oC. 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 **147-12** (2.0 g, 83.4%) as a white solid.

[0721] To a solution of **147-12** (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 ^{o}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 **147-13** (830 mg, 42.0%) as a white solid. ESI-MS: m/z 836.11 $[M+H]^+$.

[0722] A solution of **147-13** (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 **147-14** as a light pink solid (563 mg).

[0723] To a solution of **147-14** (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 ^{o}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 **147-15** (303 mg) as a white solid.

[0724] To a solution of **147-15** (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 **147-16** (374 mg, 90%).

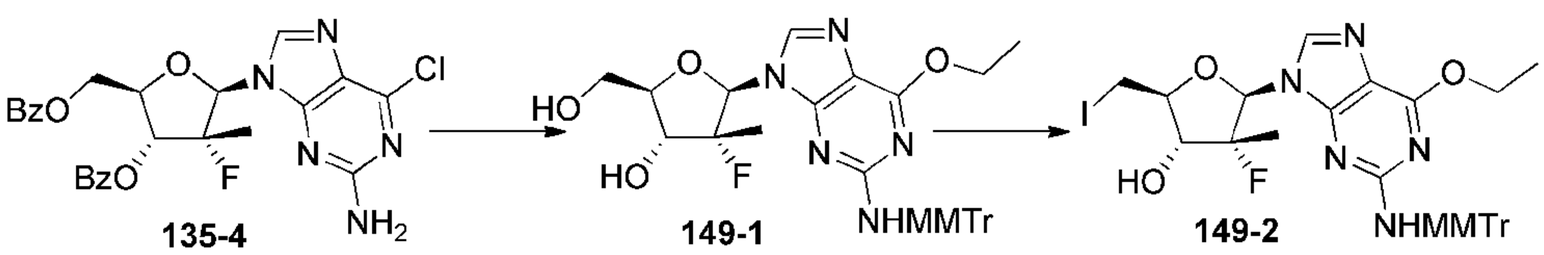
[0725] To a solution of **147-16** (374 mg, 0.37 mmol) in anhydrous THF (4 mL) was added 1.0 M solution of TBAF (0.74 mL, 0.74 mmol) at 0 to 5°C. The mixture was stirred at RT for 1 h. The mixture was quenched with silica gel, and filtered. The solvents were evaporated to give the crude product, which was purified by silica gel column (EA in hexanes from 0% to 50%) to give **147-17** (265 mg).

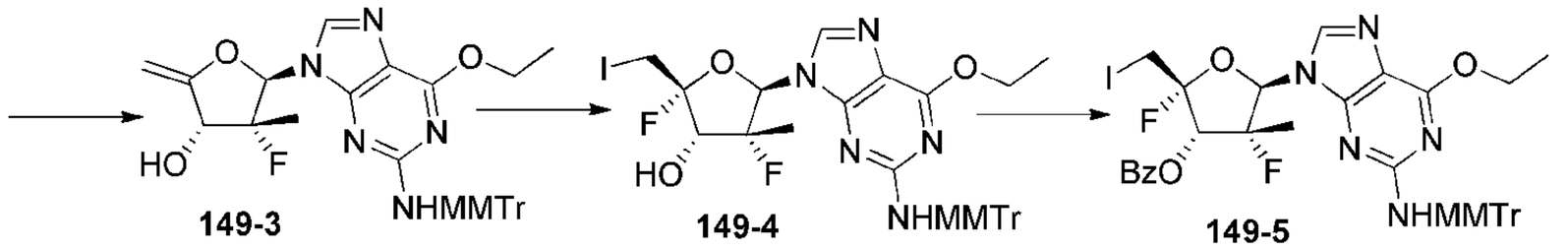
[0726] To a stirred solution of **147-17** (187.5 mg, 0.16 mmol) in anhydrous CH_3CN (2.5 mL) was added N-methylimidazole (136 μL, 1.66 mmol) at 0-5 ^{0}C (ice/water bath) followed by solution of phenyl (cyclohexanoxy-L-alaninyl) phosphorochloridate (214 mg, 0.62 mmol, dissolved in 0.5 mL of CH_3CN). 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 **147-18 (**108 mg) Elution of the latter fraction gave (single isomers) of **147-19** (120 mg) as glassy solid.

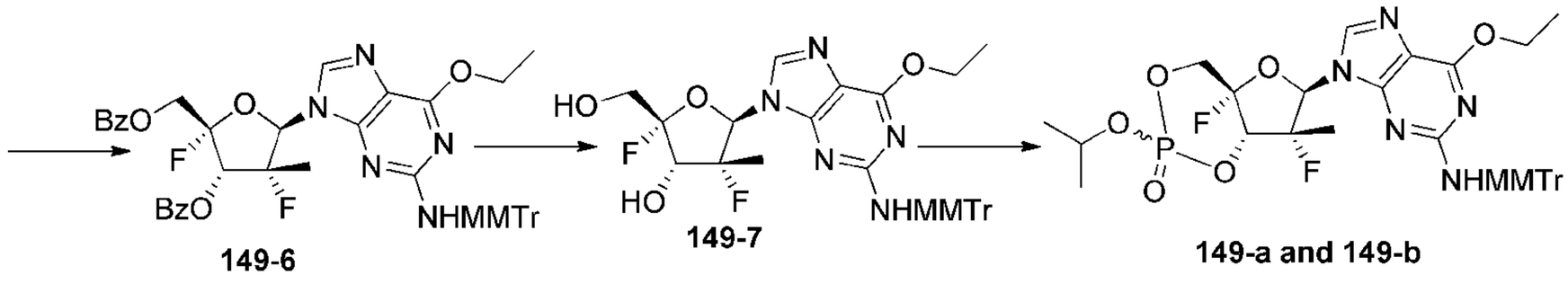
[0727] Compound **147-18** (108mg, 0.089 mmol) was dissolved in_anhydrous CH_3CN (0.5 mL), and 4N HCl in dioxane (67 μL) was added at 0 to 5 °C (ice/ water bath). The mixture was stirred at RT for 40 mins, and anhydrous EtOH (200 μL) was added. The solvents were evaporated at RT and co-evaporated with 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 **147a** (26.6 mg) as a white foam. ESI-LCMS: m/z = 665.2 $[M+H]^+$.

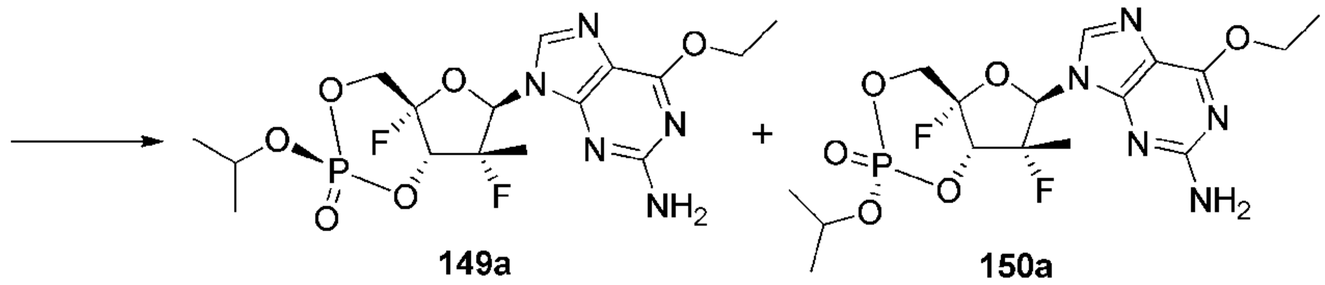
[0728] Compound **148a** (44.4 mg, single isomer) was obtained according to the procedure described for **147a** using **147-19.** ESI-LCMS: m/z = 665.15 $[M+H]^+$.

EXAMPLE 137
COMPOUNDS 149a AND 150a









[0729] A freshly prepared EtONa in dry EtOH (2N, 150 mL) was added to a solution of **135-4** (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 **149-1** (10 g, 98%) as a yellow solid.

[0730] 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 **149-1** (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 **149-2** (3.0 g, 75%) as a yellowed solid.

[0731] To a solution of **149-2** 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 **149-3** (0.6 g, 37.5%) as a white solid.

[0732] To an ice-cooled solution of **149-3** (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 ^oC. 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 **149-4** (1.5 g, 60%) as a white solid.

[0733] To a solution of **149-4** (1 g, 1.37 mmol) in dry pyridine (100 mL) was added BzCl (0.23 g, 1.65 mmol) at 0 ^oC. 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 **149-5** (0.9 g, 78%) as a white solid.

[0734] To a solution of **149-5** (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 ^oC 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 **149-6** (1.5 g, 75%) as a white solid.

[0735] Compound **149-6** (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 **149-7** (0.9 g, 90%) as a white solid. ESI-MS: m/z 618.3 $[M+H]^+$.

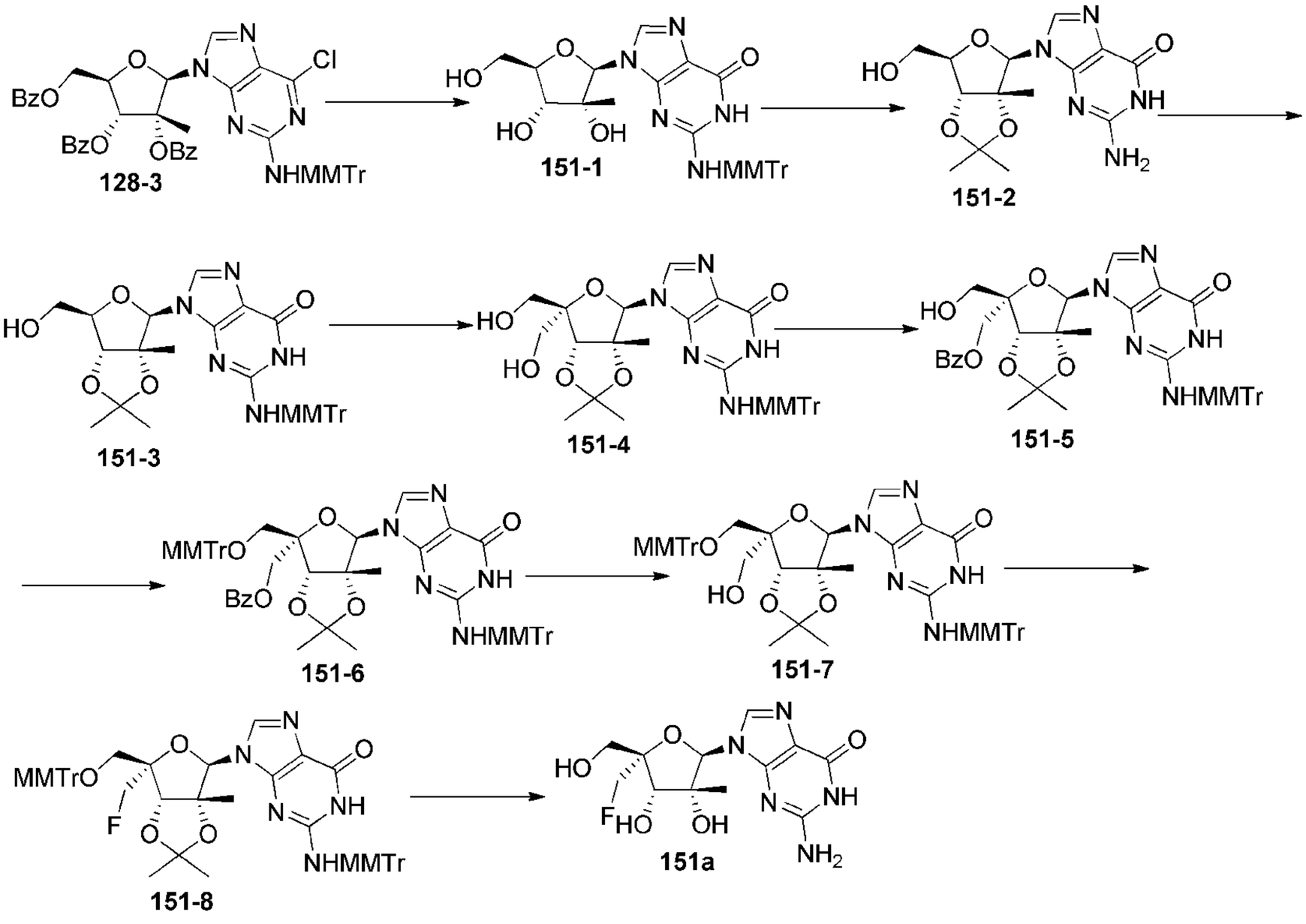
[0736] To a solution of **149-7** (99 mg, 0.16 mmol) in DCM (1.0 mL), triethylamine (92.7 μL, 0.64 mmol) was added at RT. The mixture was cooled to 0 to 5^oC (ice/ water bath), and freshly prepared and distilled isopropyl phosphorodichloridate (36.6 μL, 0.2 mmol, prepared according to a procedure , Reddy *et al. J. Org. Chem.* **2011**, *76 (10)*, 3782-3790) was added to the mixture. The mixture was stirred 0 to 5^oC (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 **149-7.** 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 **149-a** and **149-b** (61.5 mg).

[0737] A mixture of **149-a** and **149-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 **149a** (1.8 mg) and **150a** (14.5 mg).

[0738] **149a:** ESI-LCMS: m/z = 450.1 $[M+H]^+$; **150a:** ESI-LCMS: m/z = 450. $[M+H]^+$.

EXAMPLE 138
COMPOUND 151a



[0739] 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 **128-3** (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 **151-1** (9.38 g, 55%).

[0740] To a solution of **151-1** (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 **151-2** (520 mg, 87%).

[0741] To a stirred solution of **151-2** (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 **151-3** (4.8 g, 80%).

[0742] To a solution of **151-3** (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 **151-4** (125 mg, 60%).

[0743] To a solution of **151-4** (4 g, 6.25 mmol) in DCM (40 mL) was added pyridine (10 mL) and BzCl (920 mg, 15.6 mmol) at -78 ^{o}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 **151-5** (3.25 g, 70%).

[0744] To a solution of **151-5** (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 **151-6** (6.25 g, 80%).

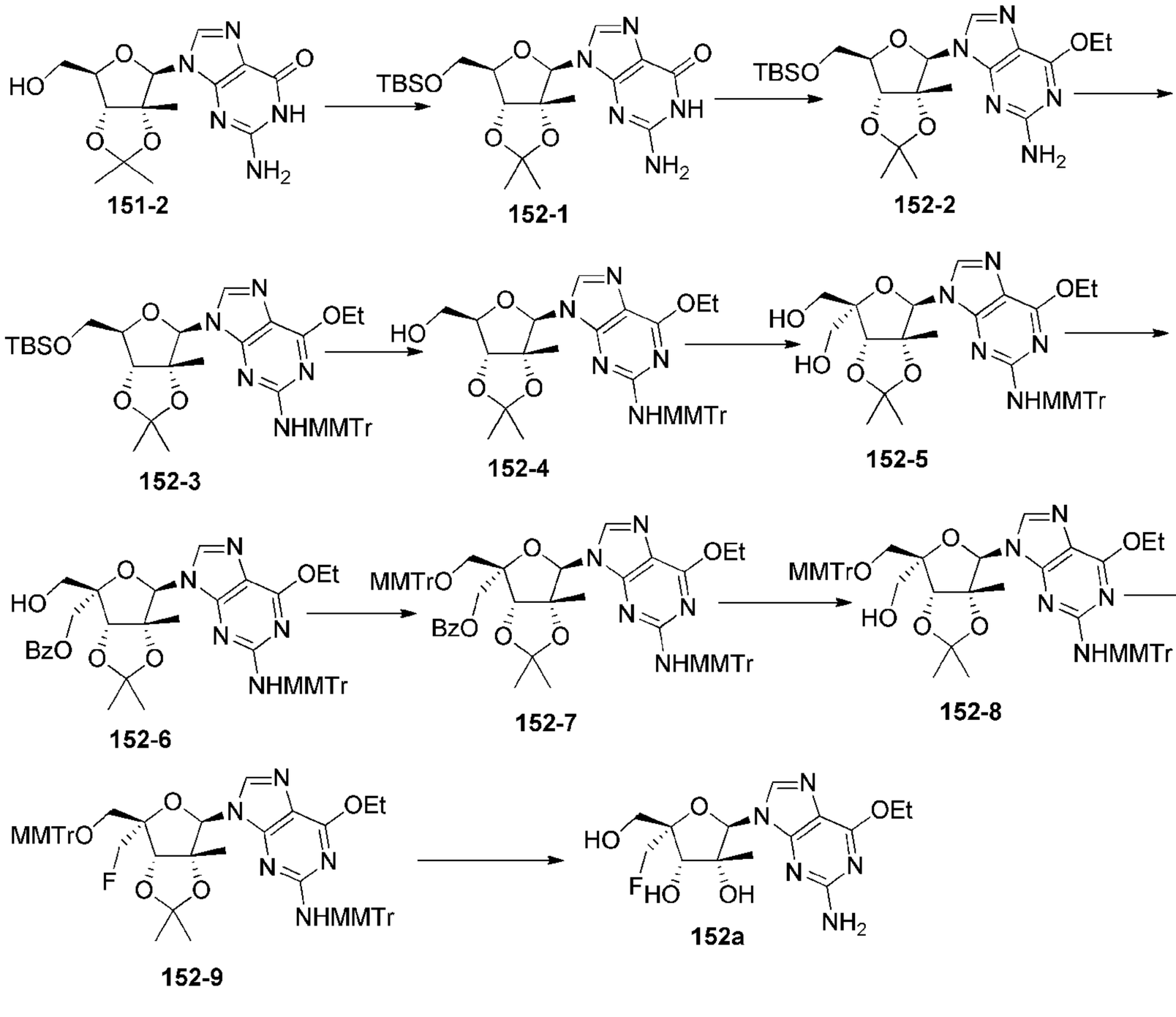
[0745] To a solution of **151-6** (4.3 g, 4.23 mmol) in MeOH (40 mL) was added NaOMe (0.82 g, 12.6 mmol) at RT, and stirred for 3 h. The mixture was concentrated at low pressure. The residue was dissolved in EA (30 mL), and washed with brine. The organic layer was dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified by silica gel column to give **151-7** (2.89 g, 75%).

[0746] To a solution of **151-7** (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 ^{o}C. The mixture was warmed up to -5 ^{0}C 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 **151-8** (221 mg, 45%). ESI-MS: m/z 914.4 $[M+H]^+$.

[0747] Compound **151-8** (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 **151a** was obtained (370 mg, 48%). MS: m/z 316.2 [M-1].

EXAMPLE 139
COMPOUND 152a



[0748] To a stirred solution of **151-2** (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 **152-1** (5.69 g, 85.1%).

[0749] 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 **152-1** (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 **152-2** (2 g, 78.4%) as a white solid.

[0750] To a solution of **152-2** (8 g, 16.9 mmol) in dichloride methane (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 ^oC. 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 **152-3** (10 g, 80%) as a white solid.

[0751] To a solution of **152-3** (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 **152-4** as a white solid (5 g, 59%).

[0752] To a solution of **152-4** (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 ^oC overnight. $NaBH_4$ (0.7 g, 18.9 mmol) was added in portions at 5 ^oC, 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 **152-5** (2.5 g, 60%) as a white solid.

[0753] To a solution of **152-5** (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 **152-6** (1.62 mg, 62%).

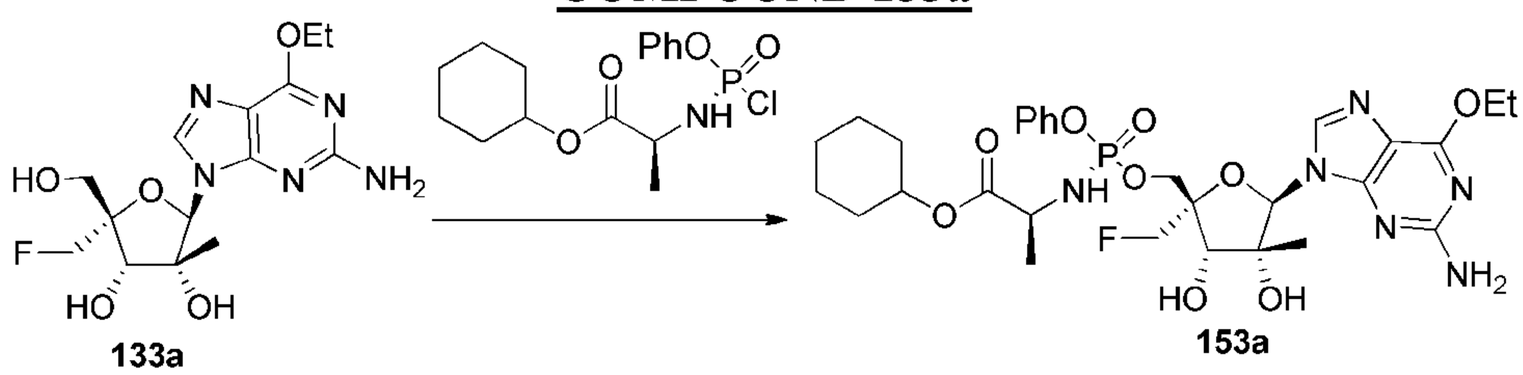
[0754] To a solution of **152-6** (1.62 g, 2.1 mmol) in dichloride methane (20 mL) was added $AgNO_3$ (714 mg, 4.2 mmol), collidine (508 mg, 4.2 mmol) and MMTrCl (970 mg, 3.2 mmol) in small portions under N_2 at 0 °C. The mixture was stirred at RT overnight. The reaction was monitored by TLC. After filtration, 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 **152-7** (2 g, 91.3%) as a white solid.

[0755] To a solution of **152-7** (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 **152-8** (1.3 g, 69%) as a white solid.

[0756] To a solution of **152-8** (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 **152-9** (1.25 g, 96%) as a white solid. ESI-LCMS: m/z 942.4 $[M+H]^+$.

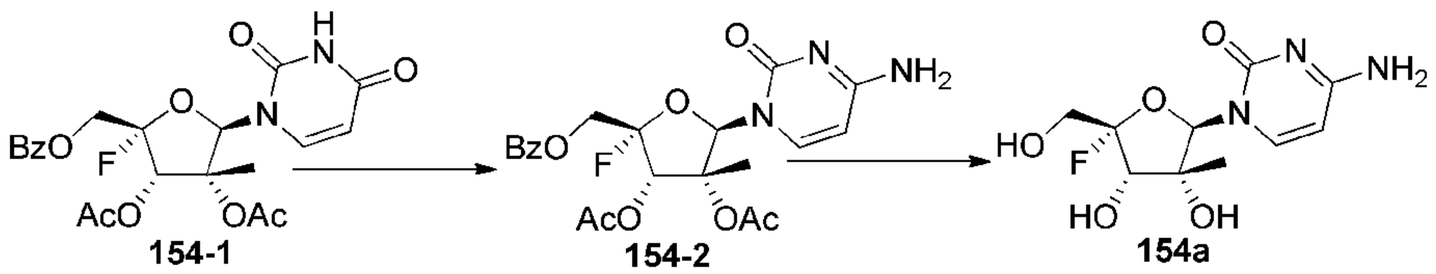
[0757] Compound **152-9** (0.55g, 0.58 mmol) was added into ice cooled 80% aq. TFA (5 mL) and kept overnight at 5 °C. The mixture was concentrated under reduced pressure at 5 °C. Thick oily residue was coevaporated several times with toluene and purified on silica gel (10 g column) with CH_2Cl_2/MeOH (4-15% gradient) to yield **152a** (75 mg, 36%). MS: m/z = 358 [M+1].

EXAMPLE 140
COMPOUND 153a



[0758] Compound **153a** (8 mg, 10%) was prepared from **133a** (48 mg) in acetonitrile (1.5 mL) with the phosphorochloridate reagent (0.14 g) and NMI (0.17 mL) in the same manner as **122a**. Purification was done by RP-HPLC (30-100% B, A: 50 mM TEAA in water, B: 50mM TEAA in MeCN). MS: m/z = 665 [M-1].

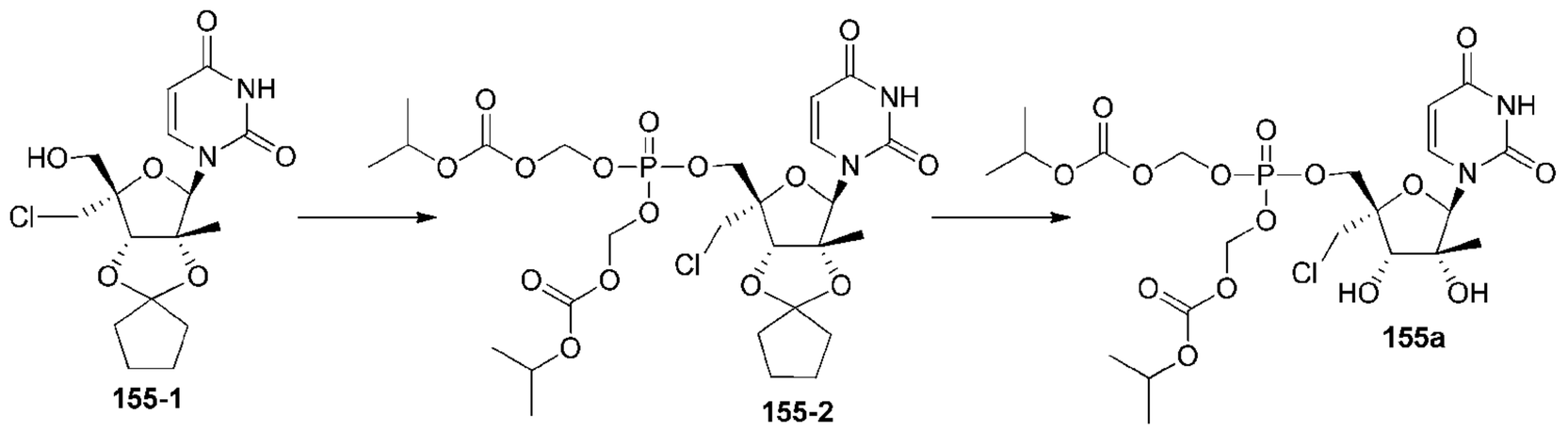
EXAMPLE 141
COMPOUND 154a



[0759] To a solution of **154-1** (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 **154-2** (370 mg, 62%) as a white foam solid.

[0760] Compound **154-2** (370 mg, 1.48 mmol) in methanolic ammonium was stirred at RT for 4 h. The solution was concentrated to dryness to give **154a** (200 mg, 91%) as a white solid. ESI-MS: m/z 275.9 $[M+H]^+$.

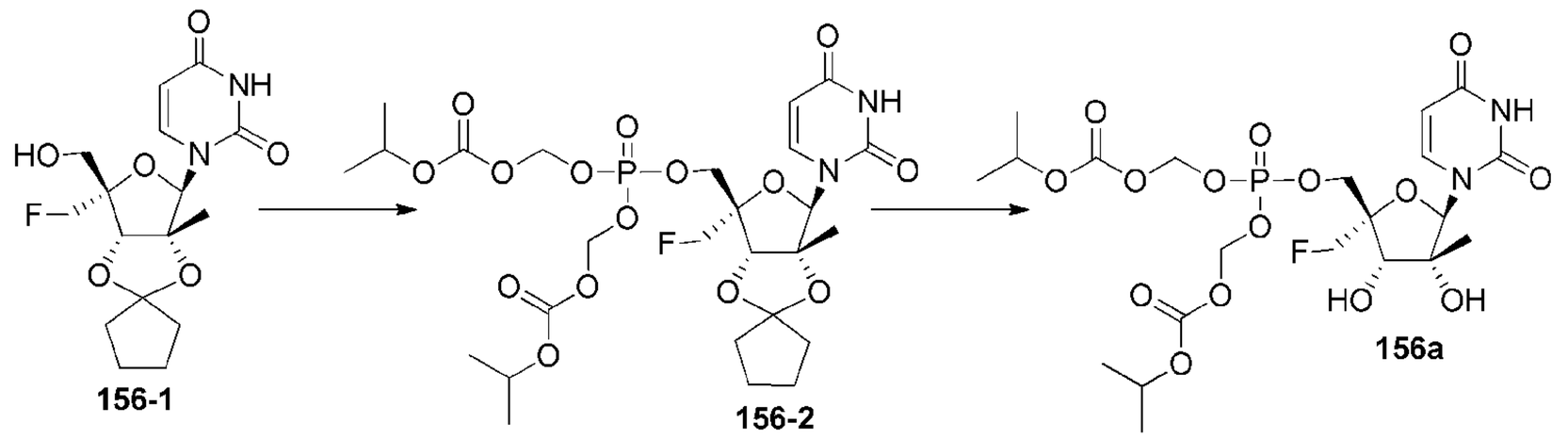
EXAMPLE 142
COMPOUND 155a



[0761] 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 **155-1** (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 **155-2**.

[0762] A solution of **155-2** (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 **155a** (35 mg ,91%). MS: m/z = 619 [M+1].

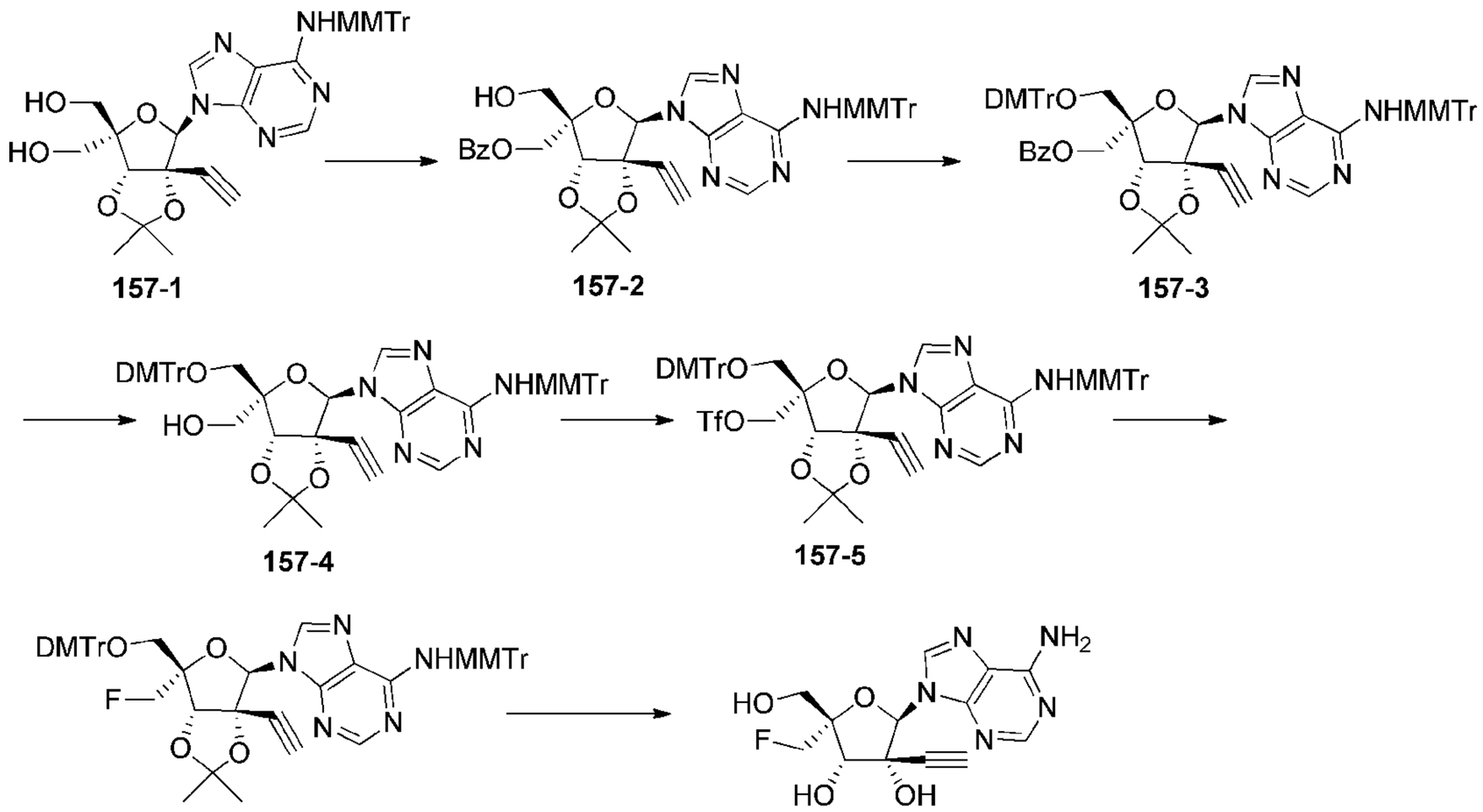
EXAMPLE 143
COMPOUND 156a



[0763] Compound **156-2** was prepared from **156-1** following a similar procedure for the preparation of **155-2**. The residue was purified on silica (10 g column) with hexanes/EtOAc (35-100% gradient) to yield **156-2** (0.45 g, 75%).

[0764] A solution of **156-2** (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 **156a** (0.27 g, 75%). MS: m/z = 603 [M+1].

EXAMPLE 144
COMPOUND 157a



157-1 157-2 157-3 157-4 157-5 157-6 157a

[0765] To a solution of **157-1** (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 **157-2** (2.6 g, 72%) as a solid.

[0766] To a solution of **157-2** (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 **157-3** (1.5 g), which was used without further purification.

[0767] To a solution of **157-3** (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

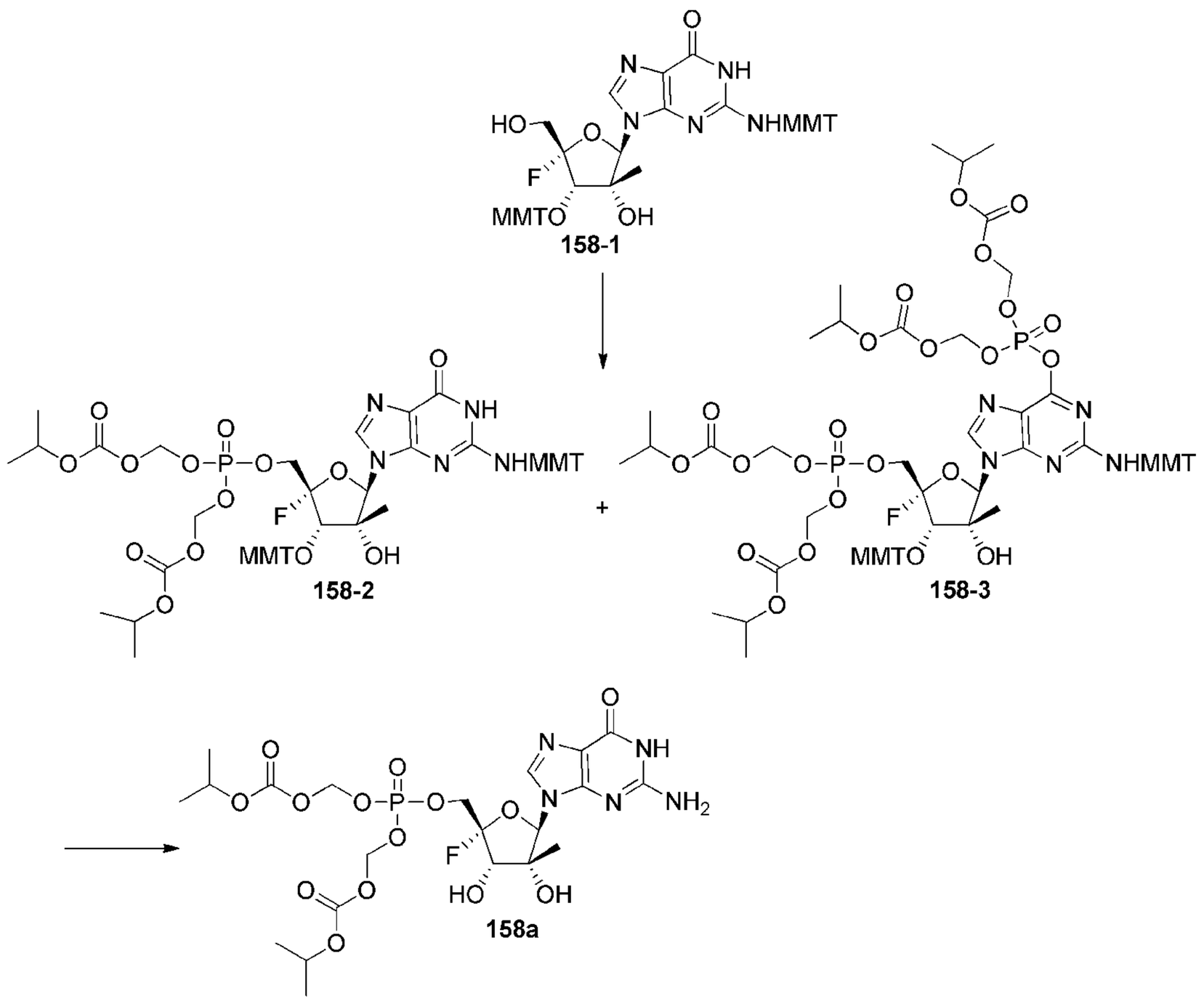
by TLC. The reaction was quenched with dry ice, and concentrated to dryness at low pressure. The residue was dissolved in DCM (100 mL). The solution was washed with brine, dried over anhydrous Na_2SO_4, and concentrated at low pressure. The residue was purified on silica gel column (EA in PE from 2% to 50%) to provide **157-4** (1.0 g, 79%).

[0768] To a solution of **157-4** (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 ^oC 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 **157-5** (1.08 g, 1.02 mmol), which was used without further purification.

[0769] To a solution of **157-5** (1.08 g, 1.02 mmol) in THF (6 mL) was added TBAF (0.8 g, 3 mmol), and stirred at 30-40 ^oC 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 **157-6** (0.62 g, 65%).

[0770] A mixture of **157-6** (0.55 g, 0.59 mmol) in TFA (90%, 5 mL) was stirred at 50-60 ^oC for 16 h. The mixture was treated with MeOH, and concentrated at low pressure. The residue was purified by prep-HPLC to afford **157a** (60 mg, 31%). ESI-MS: m/z 324.0 $[M+H]^+$.

EXAMPLE 145
COMPOUND 158a

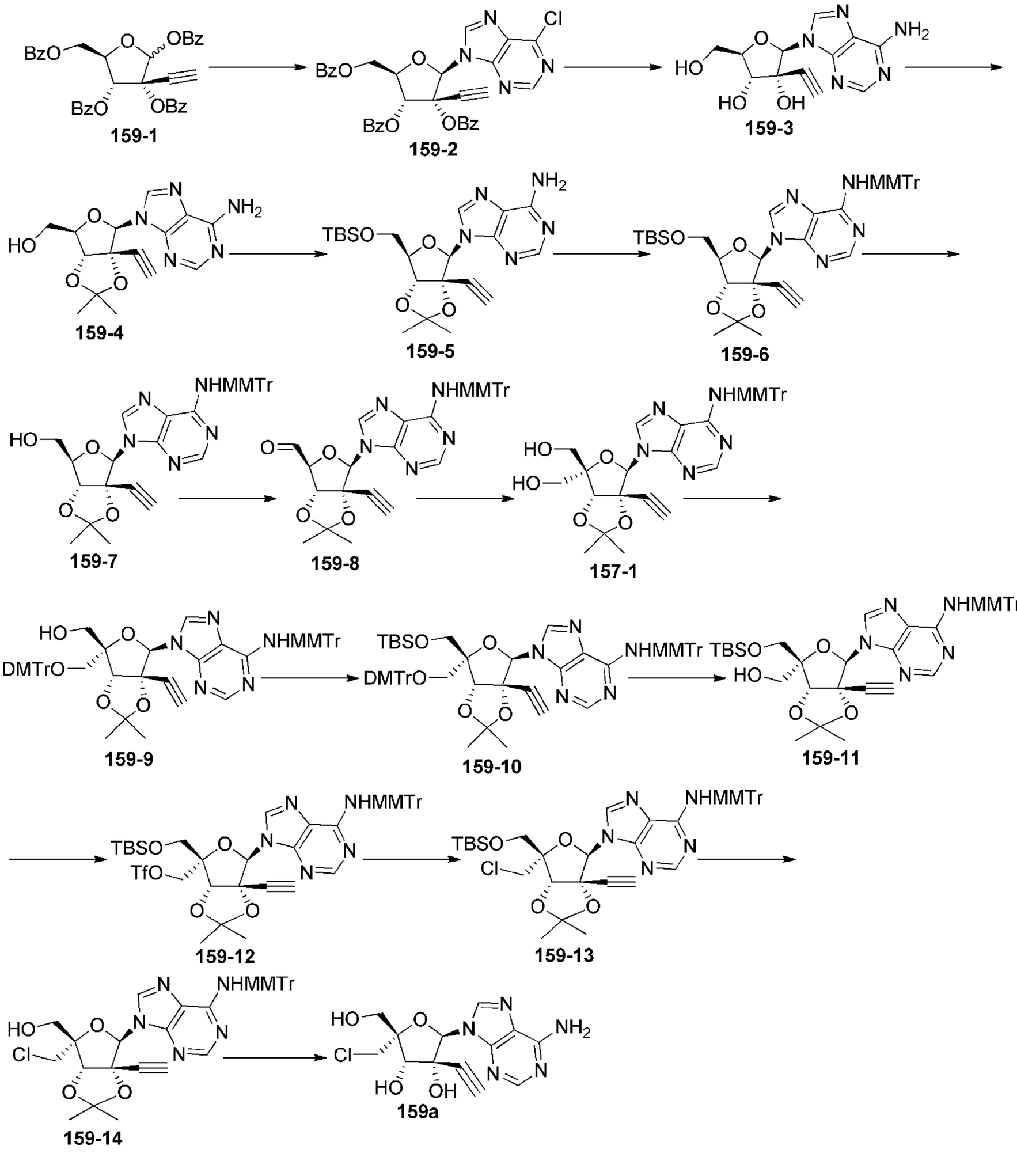


[0771] To a solution of triethylammonium bis(isopropyloxycarbonyloxymethyl)phosphate (0.33 mmol, prepared from 110 mg of bis(POC)phosphate and 46 μL of Et_3N) in THF was added **158-1** (91 mg, 0.11 mmol). The mixture evaporated and rendered anhydrous by co-evaporating with pyridine follow by toluene. 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 ^oC 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 **158-2** (13 mg, 10%) and **158-3** (95 mg, 58%).

[0772] A solution of **158-2** and **158-3** (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 **158a** in (42 mg, 94%) yield. MS: m/z=628 [M+1].

EXAMPLE 146
COMPOUND 159a



[0773] Compound **159-1** (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 ^{o}C. The mixture was stirred at 0 ^{o}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 **159-2** (2.5 g, 46.3%) as a white foam.

[0774] Compound **159-2** (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 **159-3** (1.0 g, 71%) as a white foam.

[0775] To a solution of **159-3** (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 **159-4** (5.0 g, 83%).

[0776] To a solution of **159-4** (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 **159-5** (8.4 g, 60%), which used without further purification.

[0777] Compound **159-5** (8.4 g, 18.8 mmol) was co-evaporated with pyridine. To a stirred solution of **159-5** (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 **159-6** (10.8 g, 80%) as a solid

[0778] To a solution of **159-6** (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 **159-7** (8.8 g, 91%). ESI-MS: m/z 604.4 $[M+H]^+$.

[0779] To a solution of **159-7** (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 **159-8** (4.4 g, 7.3 mmol), which was used without further purification.

[0780] To a solution of **159-8** 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 **157-1** (3.0 g, 65%). ESI-MS: m/z 633.9 $[M+H]^+$.

[0781] To a solution of **157-1** (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 **159-9** (3 g, 45%) as a yellow solid

[0782] To a solution of **159-9** (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 **159-10** (0.83 g, 67%)

[0783] To a solution of **159-10** (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 **159-11** (0.58 g, 74%).

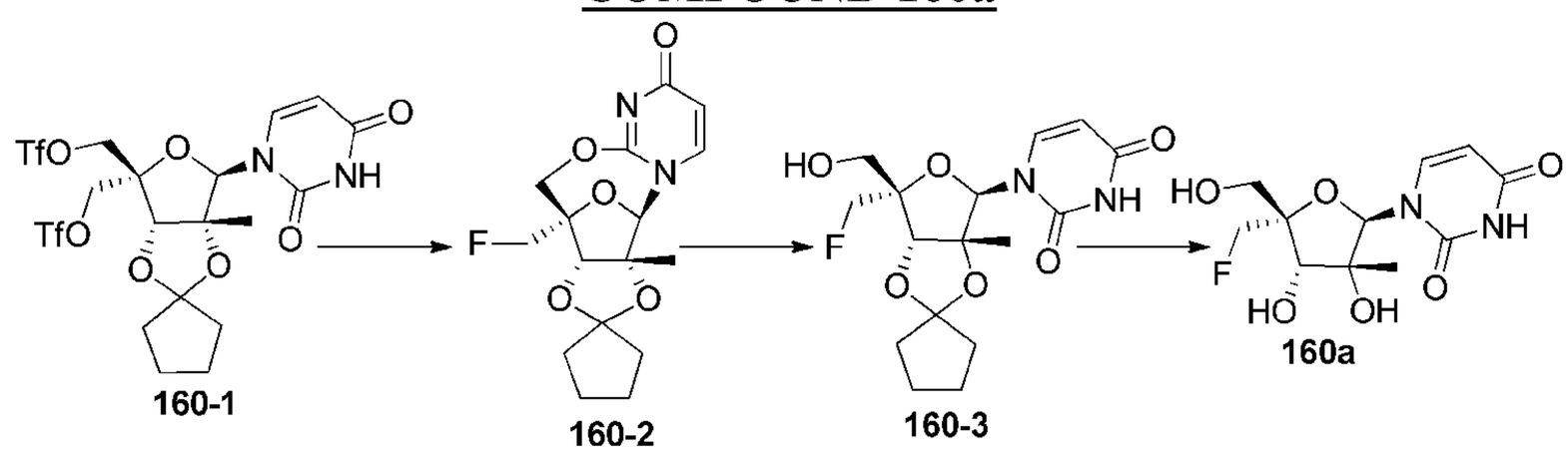
[0784] To a solution of **159-11** (200 mg, 0.268 mmol) and pyridine (53 mg, 0.67 mmol) in anhydrous DCM (5 mL) was added Tf_2O (90 mg, 0.32 mmol) at -30 ^oC. The mixture was stirred for 1 h, and slowly warmed to RT. Completion of the reaction was determined by TLC. The reaction was quenched with sat. $NaHCO_3$ 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 **159-12** (200 mg, 0.27 mmol) was used without further purification.

[0785] To a solution of **159-12** (200 mg, 0.27 mmol) in DMF (5 mL) was added LiCl (45 mg, 1.07 mmol), and stirred at 30-40 ^oC 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 **159-13** was used without further purification.

[0786] A mixture of **159-13** (245 mg, 0.32 mmol) and TBAF (200 mg, 0.7 mmol) in THF was stirred at 30 ^oC 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 **159-14** (150 mg, 72%). ESI-MS: m/z 652.3 $[M + H]^+$.

[0787] Compound **159-14** (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 50mM triethylammonium acetate buffer (pH 7.5) was used for elution. The corresponding fractions were combined, concentrated and lyophilized 3 times to remove excess buffer. **159a** was obtained (45 mg, 67%). MS: m/z 338.0 (M-1).

EXAMPLE 147
COMPOUND 160a

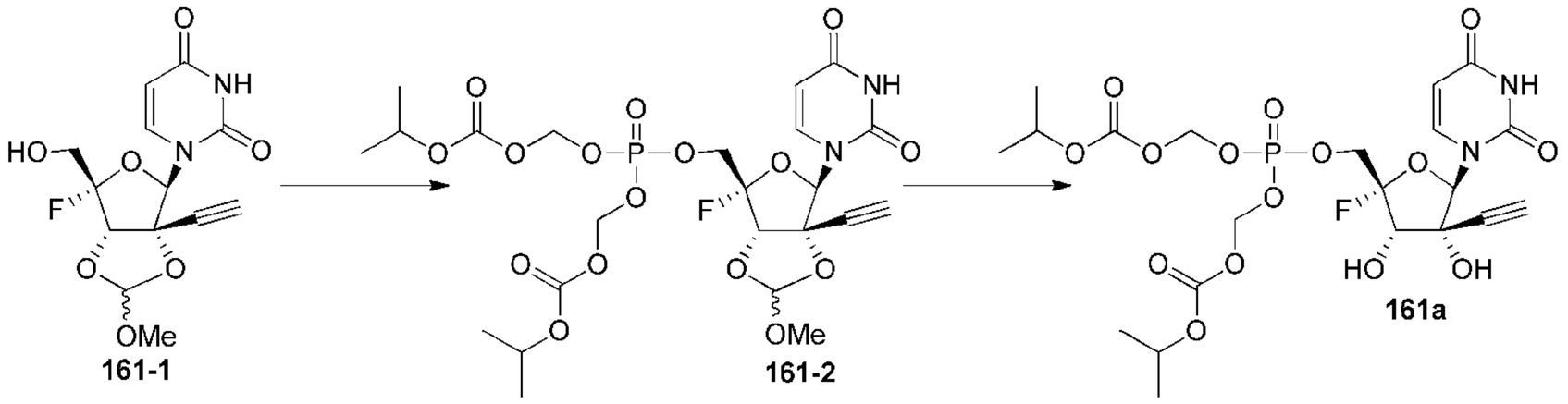


[0788] To a solution of **160-1** (12.3 g, 19.9 mmol) in DMF (50 mL) was added NaH (800 mg, 20 mmol) at 0 °C. The mixture was stirred at RT for 3 h. The mixture was treated with CsF (30.4 g, 200 mmol), and then stirred at RT for 3 h. The reaction was quenched with water, and extracted with EA. The organic 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 **160-2** (4.1 g, 61%) as a white solid.

[0789] To a solution of **160-2** (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 **160-3** (3.1 g, 72%) as a white solid. ESI-MS:m/z 379.1 $[M+Na]^+$.

[0790] Compound **160-3** (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. **160a** (68%) was isolated by silica gel chromatography in gradient of methanol in DCM from 5% to 20%. MS: m/z 289.0 [M-1].

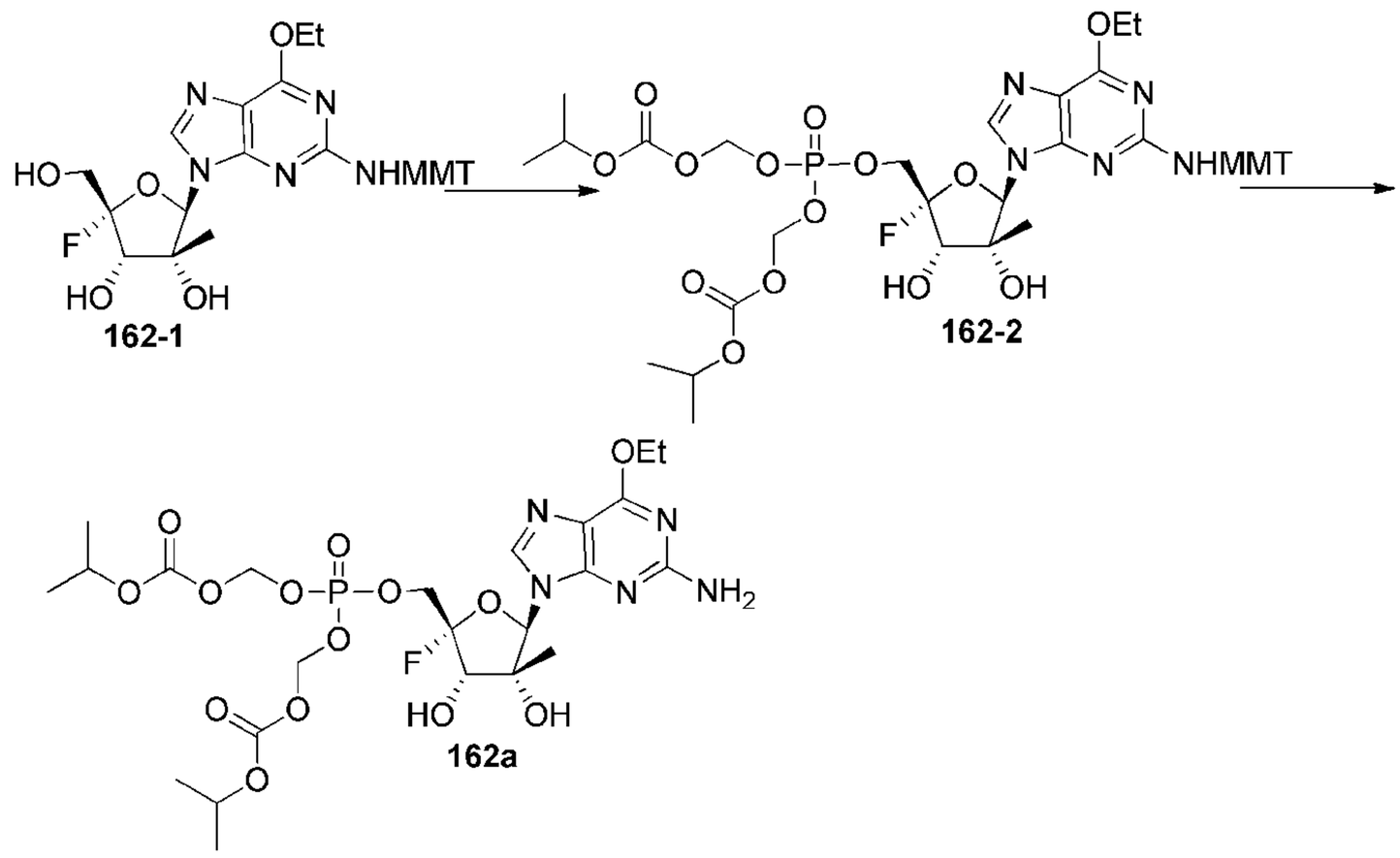
EXAMPLE 148
COMPOUND 161a



[0791] Compound **161-2** (0.20 g, 64%) was prepared in the same manner from **161-1** (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 **176-4**.

[0792] A solution of **161-2** (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 50mM TEAA. Gradient was 25-75% ACN in 20 mins at 24mL/min, 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 **161a** (18 mg). MS: m/z = 1197 [2M+1].

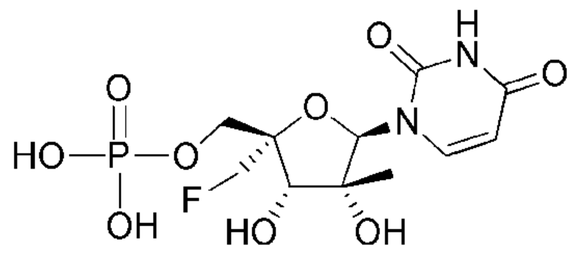
EXAMPLE 149
COMPOUND 162a



[0793] Compound **162-2** (158 mg, 50%) was prepared from **162-1** (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).

[0794] A solution of **162-2** (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 **162a** (85 mg, 76%). MS: m/z = 656 [M+1].

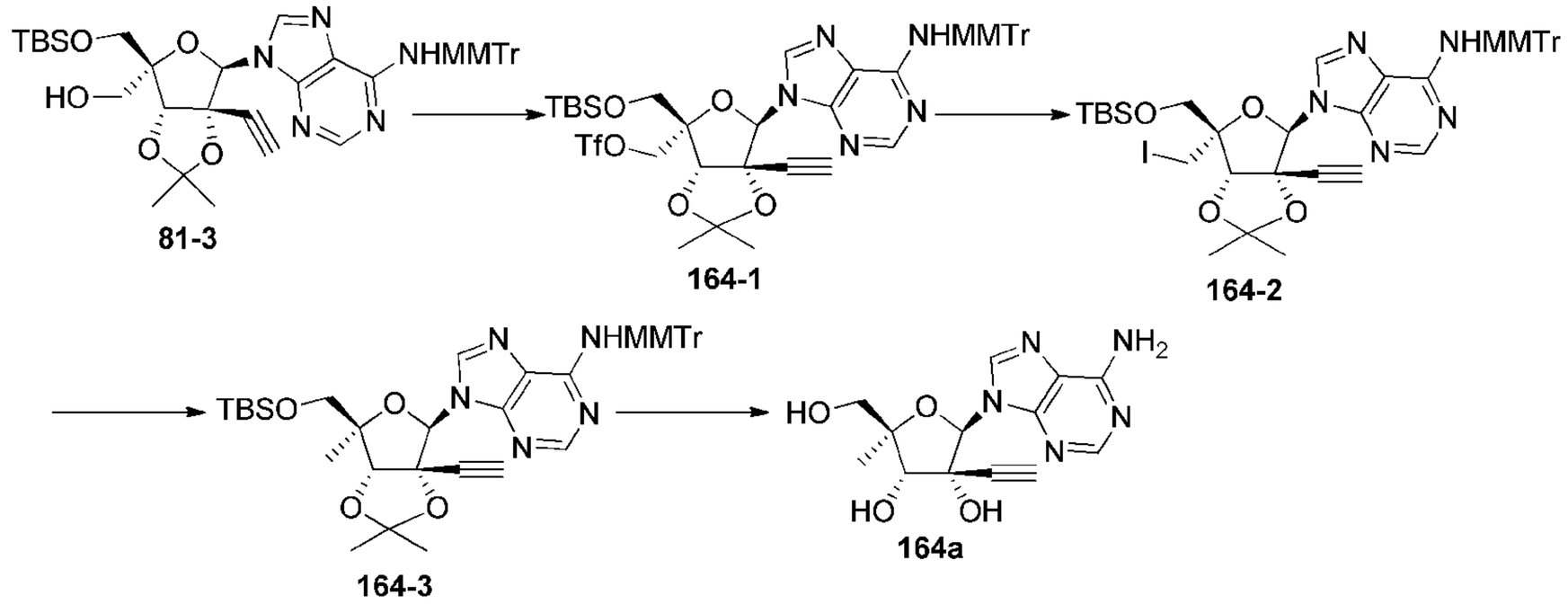
EXAMPLE 150
COMPOUND 163a



[0795] Dry **160a** (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 $POCl_3$ (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 compound **163a**. Isolation was performed by RP HPLC on Synergy 4 micron Hydro-RP column (Phenominex). A linear gradient of methanol from 0 to 30% in 50mM triethylammonium

acetate buffer (pH 7.5) was used for elution. The corresponding fractions were combined, concentrated and lyophilized 3 times to remove excess of buffer to yield **163a**. MS: m/z 369.0 (M-1).

EXAMPLE 151
COMPOUND 164a



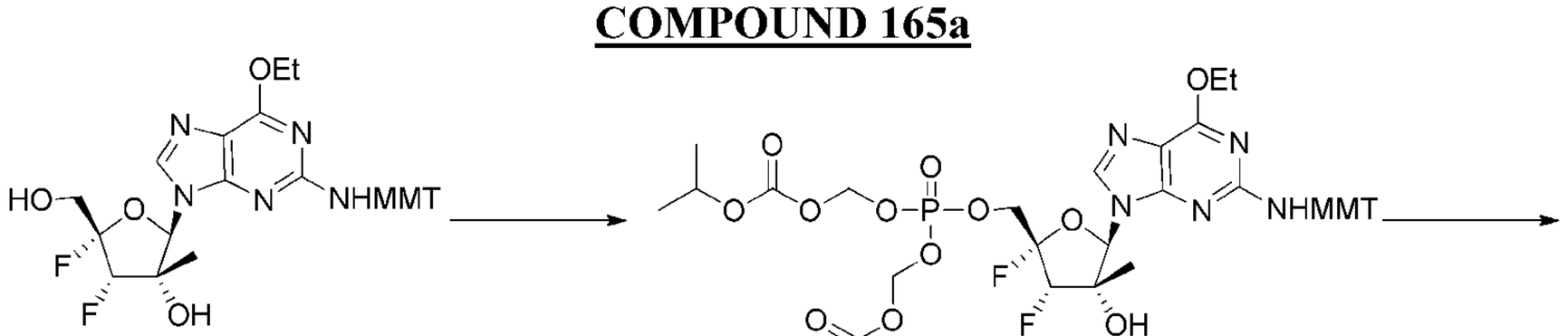
[0796] To a solution of **81-3** (300 mg, 0.4 mmol) and pyridine (80 mg, 1.0 mmol) in DCM (5 mL) was added Tf_2O (136 mg, 0.48 mol) in a solution of DCM (1mL) dropwise at -30 °C. The mixture was stirred at -30 °C to 0 °C for 20 mins. The reaction was quenched with water, and extracted with DCM (20 mL). The organic phase was dried over anhydrous Na_2SO_4, and evaporated to give crude **164-1** (352.8 mg, 0.4 mmol), which was used without further purification.

[0797] To a solution of **164-1** (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 **164-2** (270 mg, 31%).

[0798] To a solution of **164-2** (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 **164-3** and a by-product (400 mg, 72%).

[0799] A mixture of **164-3** (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 **164a** (46 mg, 27%). ESI-MS: m/z 306.1 $[M+H]^+$.

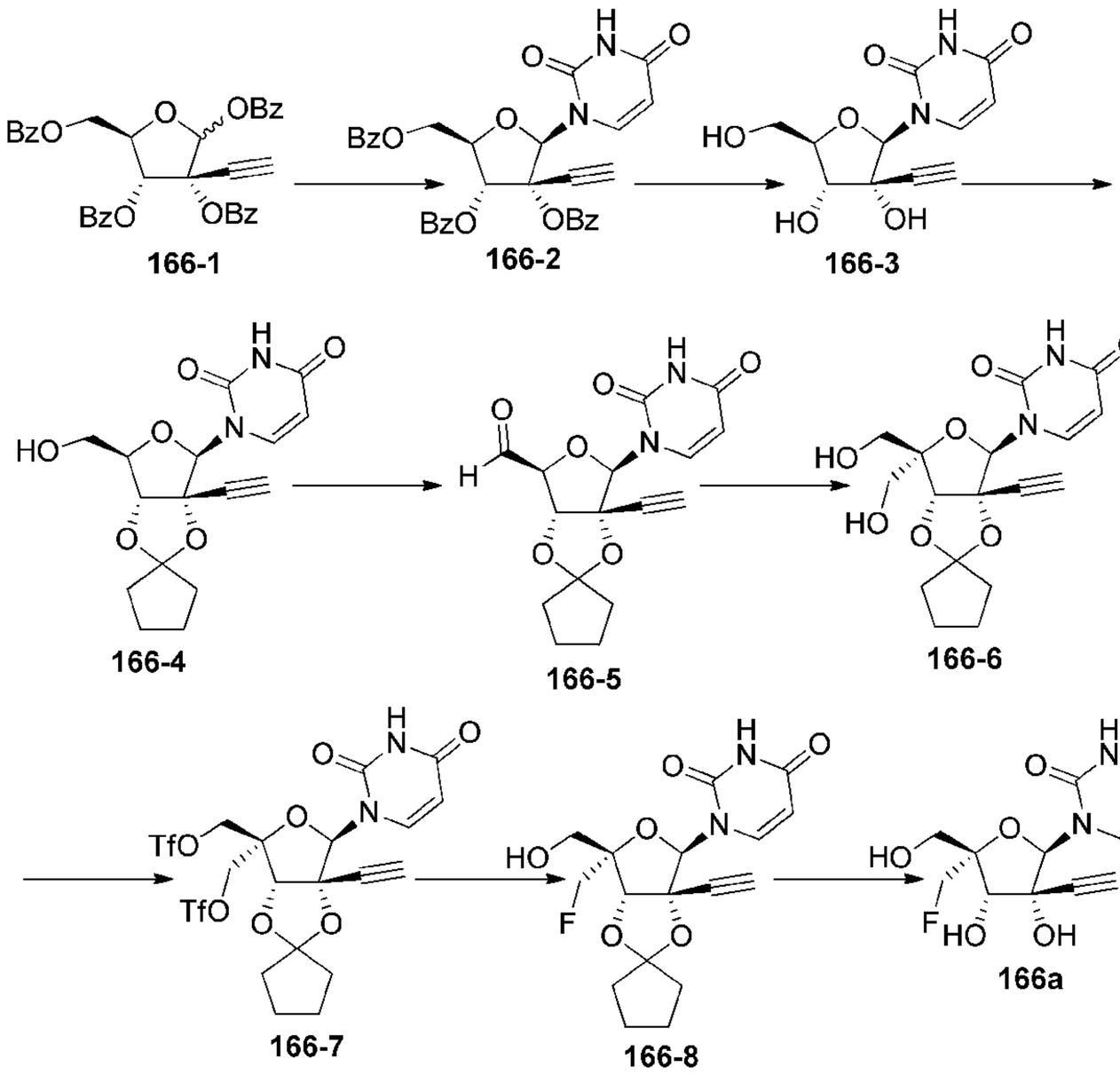
EXAMPLE 152
COMPOUND 165a



[0800] Compound **165-2** (120 mg, 72%) was prepared in the same manner from **165-1** (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 **176-4** from **176-3**.

[0801] Compound **165a** (14 mg, 77%) was prepared from **165-2** (25 mg) in acetonitrile (0.1 mL) and 4 N HCl/dioxane (8 μL) using the method as described for **209a**. MS: m/z = 658 [M+1].

EXAMPLE 153
COMPOUND 166a



[0802] 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 **166-1**(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 **166-2** (38 g, 70%) as a white sold.

[0803] Compound **166-2** (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 **166-3** (13 g, 81%) as a white solid.

[0804] 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 **166-3** (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 **166-4** (30 g, 82%).

[0805] To a solution of **166-4** (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 **166-5** (10 g, 100%) as a yellow solid.

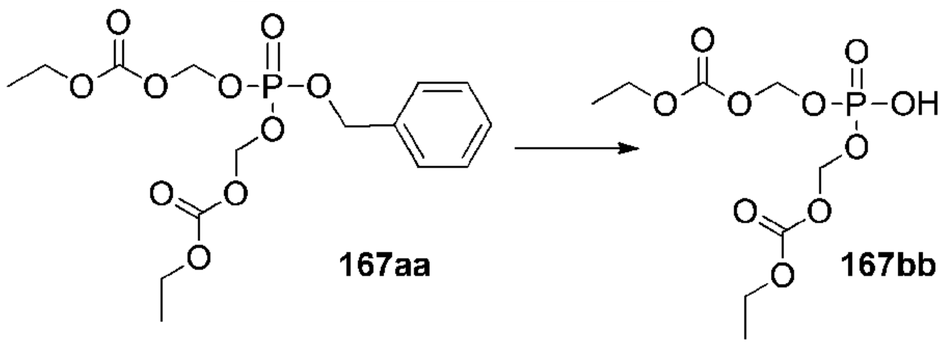
[0806] Crude **166-5** (10 g, 30 mmol) was dissolved in 1,4-dioxane (100 mL). 37% HCHO (10 mL) and 2N NaOH aqueous solution (20 mL) were added at RT. The mixture was stirred at RT overnight, and adjusted to pH = 7. The mixture was treated with $NaBH_4$ (4.44 g, 120 mmol) at 0 °C. The reaction was stirred 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 **166-6** (5.5 g, 50 %) as a white solid.

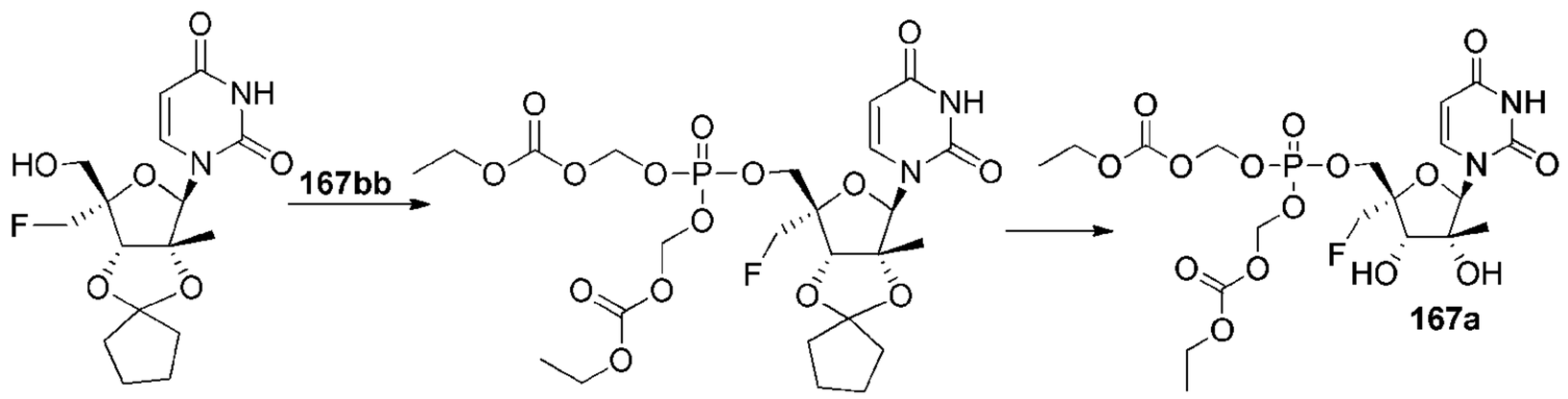
[0807] To a stirred solution of **166-6** (5.0 g, 13.8 mmol) and pyridine (5 mL) in DCM (20 mL) was added Tf_2O (8.5 g, 30.3 mmol) dropwise at -70 °C. The solution was warmed to 0 °C slowly, stirred at 0 °C for 0.5 h, and washed with HCl (0.5 M). The DCM layer was concentrated to dryness at low pressure, and the residue was purified on silica gel column to give **166-7** (4.5 g, 52 %) as a white solid.

[0808] To a solution of **166-7** (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 **166-8** (0.8 g, 46 %) as a white solid. ESI-MS: m/z 367.0 $[M+H]^+$, 389.0 $[M+Na]^+$.

[0809] Compound **166-8** (0.2 mmol) was dissolved in 80% HCOOH (10 mL), and the mixture was heated at 45^0C 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 **166a** (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 154
COMPOUNDS 167a





167-1 167-2

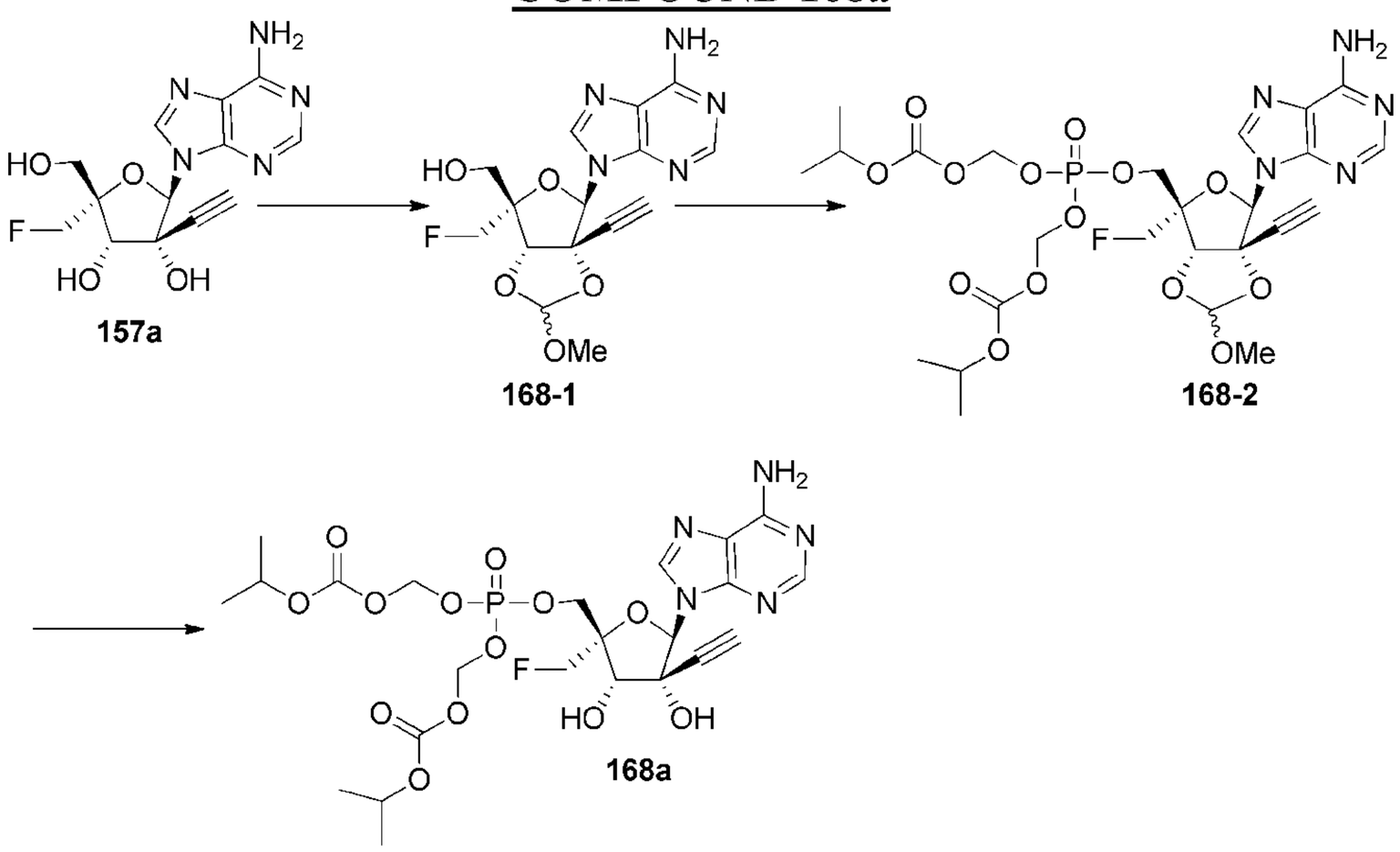
[0810] To a solution of **167aa** (0.31 g, 0.8 mmol) in anhydrous methanol (2 mL), was added 10 % Pd/C (30 mg), and the mixture was stirred under H_2 atmosphere for 1 h. After completion, the mixture was filtered, and the catalyst cake was washed with methanol. The washing and filtrate were combined. The solvent was removed under vacuum to give **167bb** 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).

[0811] To a solution of triethylammonium bis (EOC) phosphate (0.7 mmol, prepared from 213 mg of **167bb** and 0.2 mL of TEA) in THF (3 mL) was added **167-1** (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 **167-2** (189 mg, 66 %).

[0812] To a solution of **167-2** (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 **167a** (97.3 mg) as a white foam after lypholization. MS: m/z = 575.1 $[M+H]^+$.

EXAMPLE 155
COMPOUND 168a

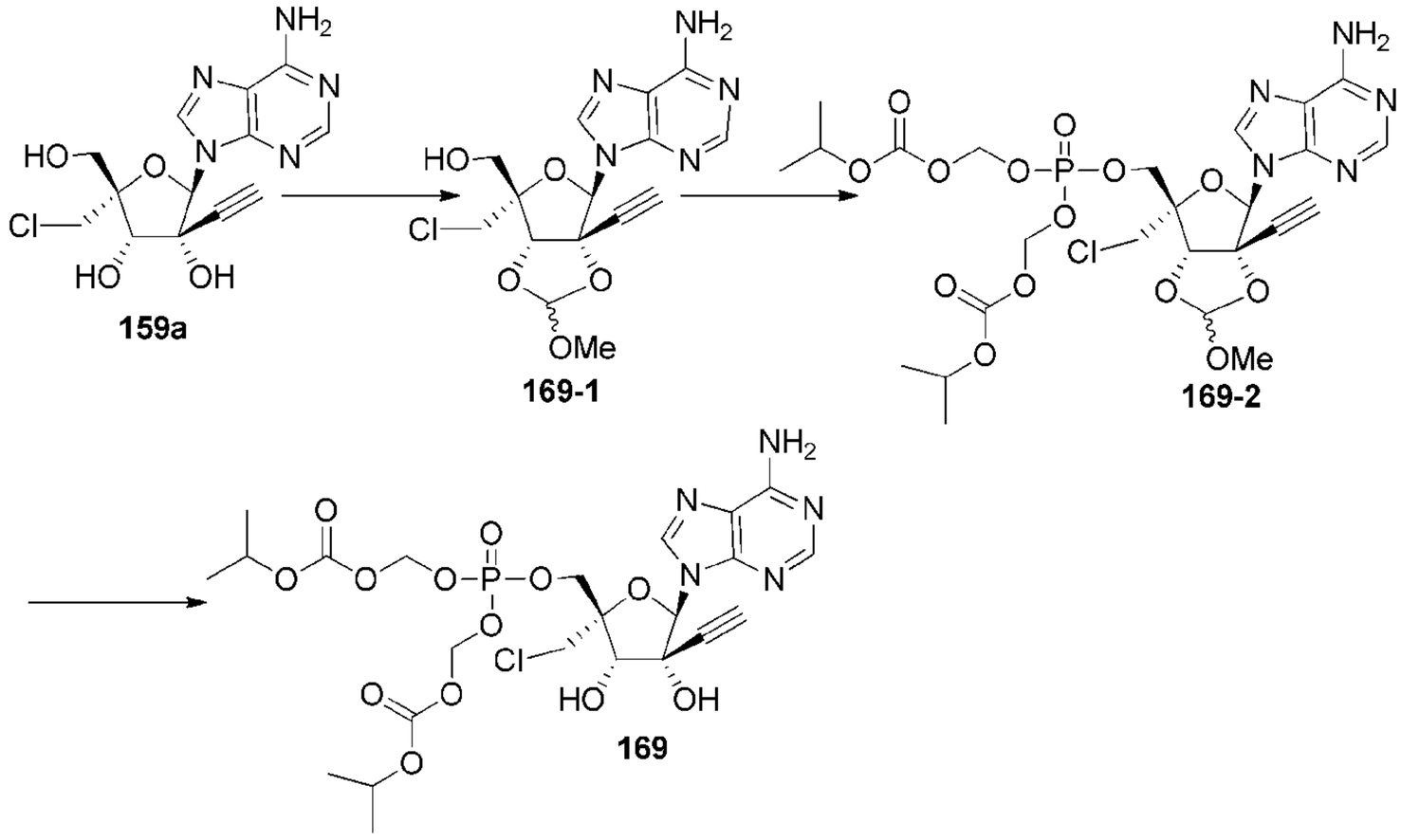


[0813] A mixture of compound **157a** (30 mg, 0.09 mmol), PTSA monohydrate (18 mg, 1 equiv.), and trimethyl orthoformate (0.3 mL; 30 equiv.) in dioxane (1 mL) was stirred 1 d at RT. The reaction was neutralized with NH_3/MeOH and then filtered. The filtrate was dissolved in a mixture of THF (0.5 mL) 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 **168-1** (30 mg, 91%).

[0814] Compound **168-2** (28 mg, 52%) was prepared in the same manner from **168-1** (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 **176-4** from **176-3**. Purification was done with CH_2Cl_2/MeOH (4-10% gradient).

[0815] Compound **168a** (15 mg, 67%) was prepared from **168-2** (24 mg) using the method for preparing **176-5**. Purification was done with CH_2Cl_2/MeOH (4-10% gradient). MS: m/z = 636 [M+1].

EXAMPLE 156
COMPOUND 169a

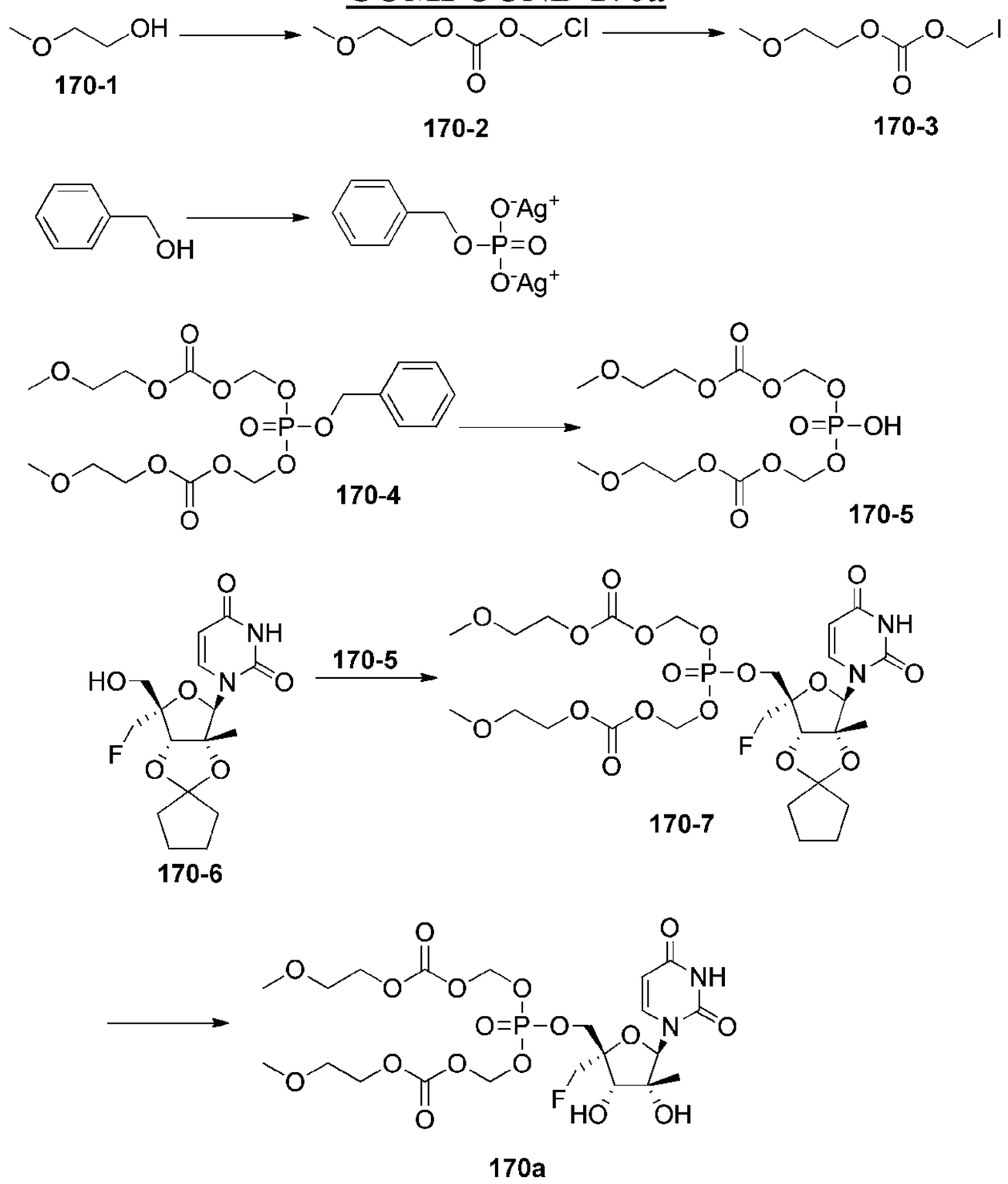


[0816] Compound **169-1** (8 mg, 40%) was prepared from **159a** (17 mg) and trimethylorthoformate (0.15 mL) with PTSA monohydrate (9 mg) in dioxane (0.5 mL) in the same manner as **168-1.**

[0817] Compound **169-2** (10 mg, 72%) was prepared in the same manner from **169-1** (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 **168-2**.

[0818] Compound **169a** (15 mg, 67%) was prepared from **169-2** (24 mg) in the same manner as **63**. MS: m/z = 652 [M+1].

EXAMPLE 157
COMPOUND 170a



[0819] 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 **170-2** as a colorless oil (13.0 g).

[0820] Compound **170-2** (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 **170-3** as a light yellow oil of **170-3** (8.5 g), which was used without further purification.

[0821] 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.

[0822] Dry acetonitrile (25 mL) was added to benzylphosphoric acid (silver salt) followed by addition of **170-3** (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 **170-4** as a colorless liquid (860 mg, 50%).

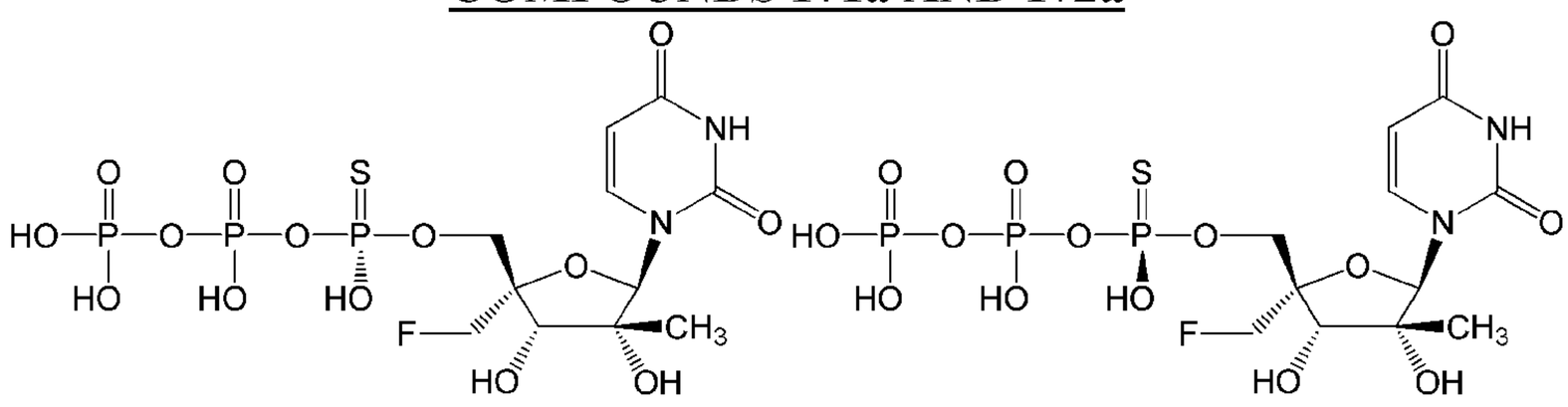
[0823] Compound **170-4** (750 mg; 1.65 mmol) was dissolved in methanol (10 mL). Pd-on-carbon (85 mg) and TEA (1 eq.) were added. The flask was charged with hydrogen gas for 1 h. The catalyst was filtered, and the solvent removed in vacuo to give **170-**5 (triethylammonium salt) (510 mg) which was used immediately without further purification.

[0824] Compound **170-6** (320 mg; 0.9 mmol) and **170-5** (510 mg, 1.35 mmol; 1.5x) were co-evaporated twice with pyridine and twice with toluene. Compounds **170-5** and **170-6** 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 **170-7** (430 mg, 0.6 mmol).

[0825] Purified **170-7** 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 **170a** (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 158
COMPOUNDS 171a AND 172a

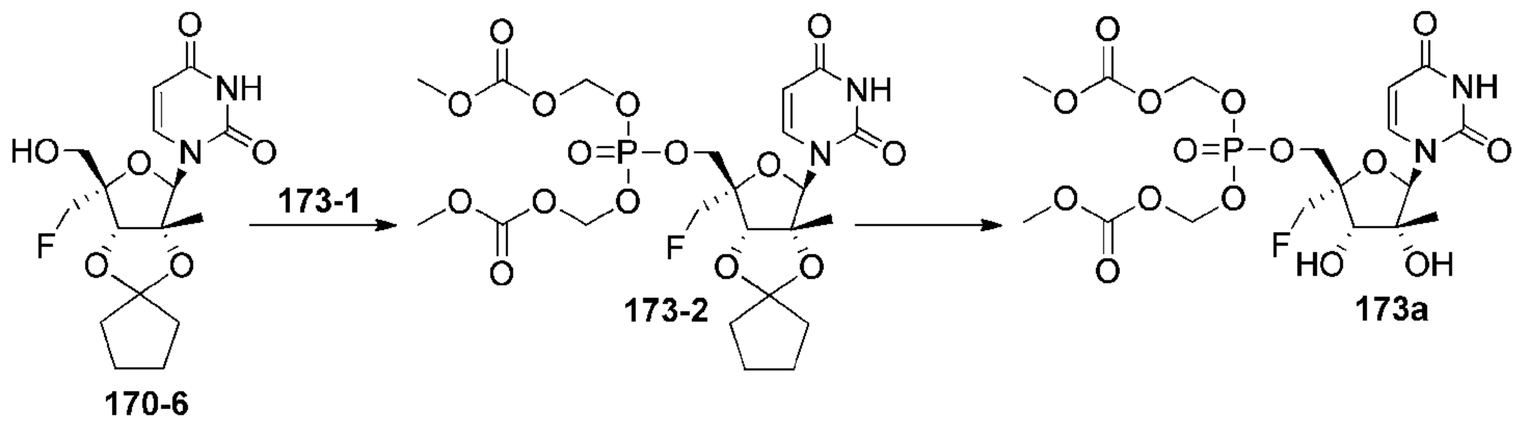


171a **172a**

[0826] Dry **160a** (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 50mM 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 50mM triethylammonium buffer was used for elution over 20 min, flow 10mL/min.

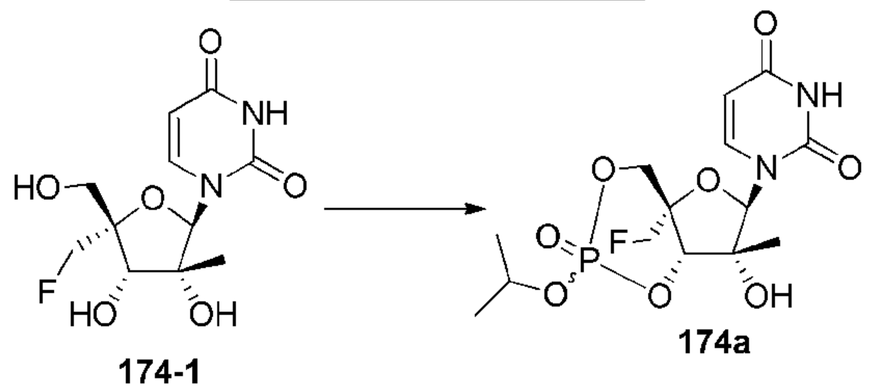
Compounds **171a** and **172a** were collected. Analytical RP HPLC was done in 50 mM triethylammonium acetate buffer, pH 7.5 containing linear gradient of acetonitrile from 0% to 25% in 7 min on Synergy 4 micron Hydro-RP column (Phenominex). **171a**: RT 5.50 min. ^{31}P NMR: δ +42.45(1P, d), -6.80 (1P, d), -23.36 (1P, q). MS: m/z 544.9 [M-1]. **172a**: RT 6.01 min. ^{31}P NMR: δ +41.80(1P, d), -6.57 (1P, d), -23.45 (1P, q). MS: m/z 544.9 [M-1].

EXAMPLE 159
COMPOUND 173a



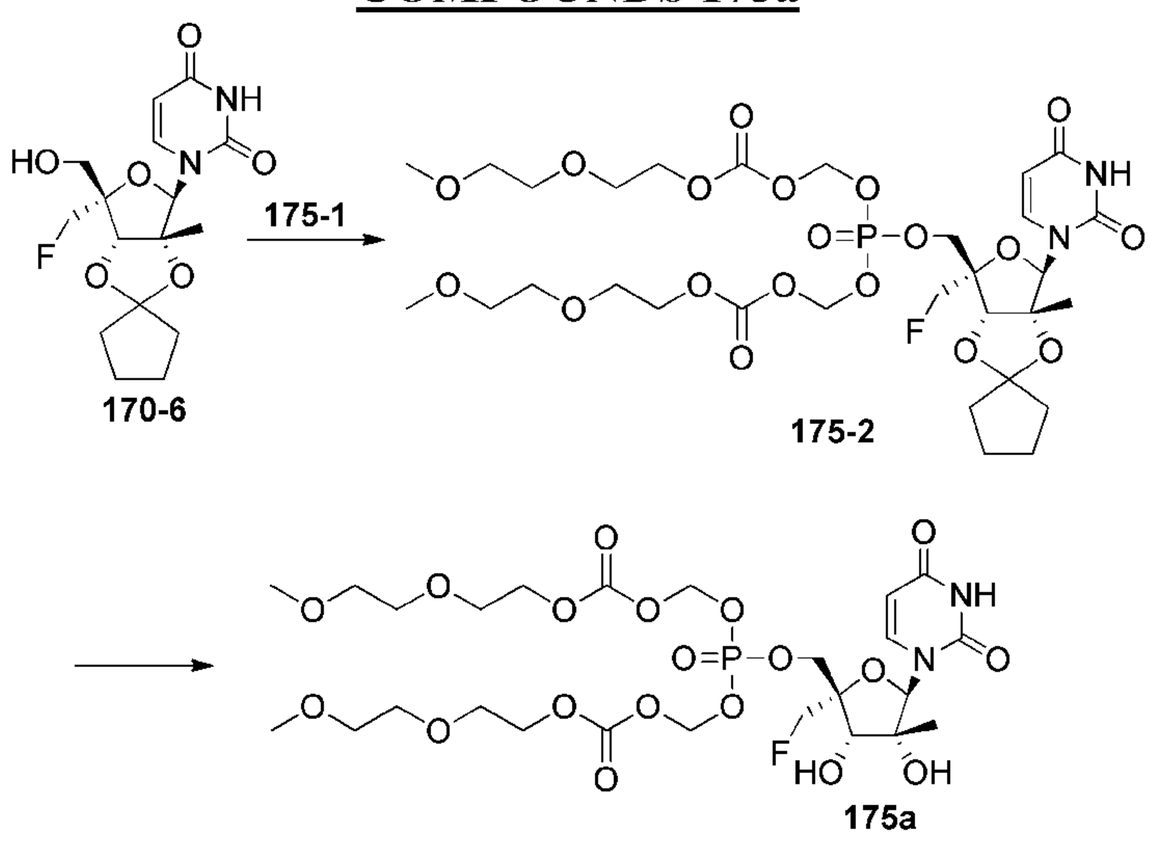
[0827] Commercially available chloromethyl methyl carbonate (5.0 g) was treated with NaI to give **170aa** (5.38 g). Benzylphosphate (silver salt) and **170aa** were reacted to yield purified **170bb** (1.5 g). ^{1}H-NMR (CD_3CN): δ 7.39-7.42 (m, 5H), 5.60 (d, 4H), 5.11 (d, 2H), 3.8 (s, 6H). ^{31}P-NMR (CD_3CN): δ - 4.47 ppm. Compound **170bb** (415 mg; 1.7 mmol) was deprotected to give **173-1** (triethylammonium salt) (510 mg), which was used immediately without further purification. Compound **170-6** (320 mg; 0.9 mmol) and **173-1** (510 mg) were reacted to purified **173-2** (400 mg). Compound **173-2** (230 mg) was deprotected to give purified **173a** (250 mg). The aforementioned reactions were conducted using a method described in the preparation of **170a**. ^{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 160
COMPOUND 174a



[0828] To a stirred solution of **174-1** (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 **174a** (43.6 mg). MS: m/z = 395.05 $[M+H]^+$, 393.0 $[M-H]^-$, 787.05.0 $[2M-H]^-$.

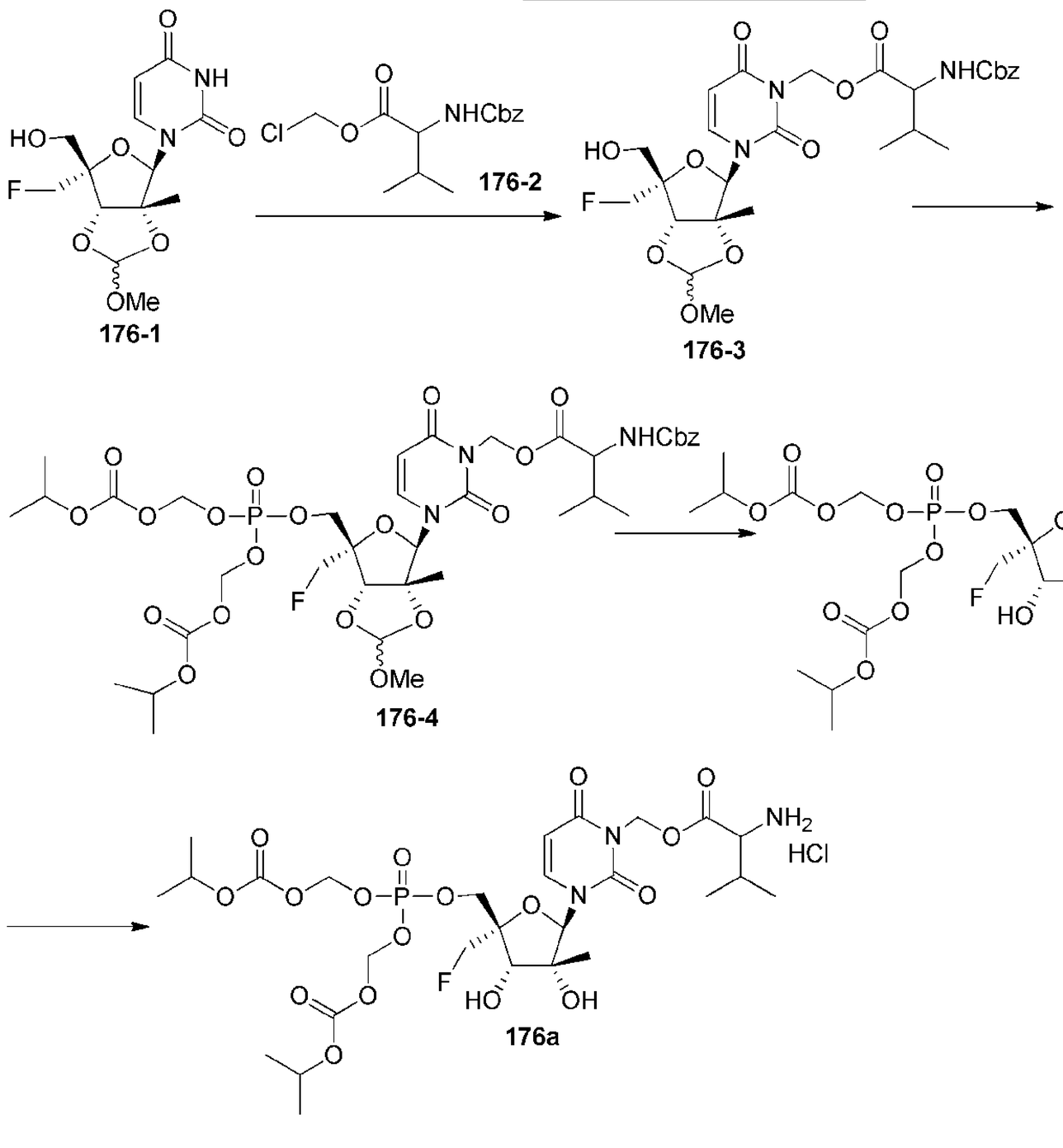
EXAMPLE 161
COMPOUNDS 175a



[0829] Compound **175aa** was prepared from commercially available 2-(2-methoxyethoxy)-ethanol (11.56 mL). Compound **175aa** (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 **175bb** (9.6 g) was prepared from **175aa**, 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 **175bb** (2.4 g) were reacted and yielded purified **175cc** (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 **175cc** (620 mg; 1.15 mmol) was deprotected to give **175-1** (triethylammonium salt), which was used immediately without further purification. Compound **170-6** (356 mg; 1.0 mmol) and **175-1** were reacted to give purified **175-2** (250 mg). Compound **175-2** (250 mg) was deprotected to yield purified **175a** (110 mg , 0.14 mmol). The aforementioned reactions were conducted using a method described in the preparation of **170a**. ^{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 162
COMPOUND 176a



[0830] A mixture of **176-2** (1.2 g; 4 mmol) and NaI (0.6 g; 4 mmol) in acetone (13 mL) was stirred at RT for 1 h. Compound **176-1** (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

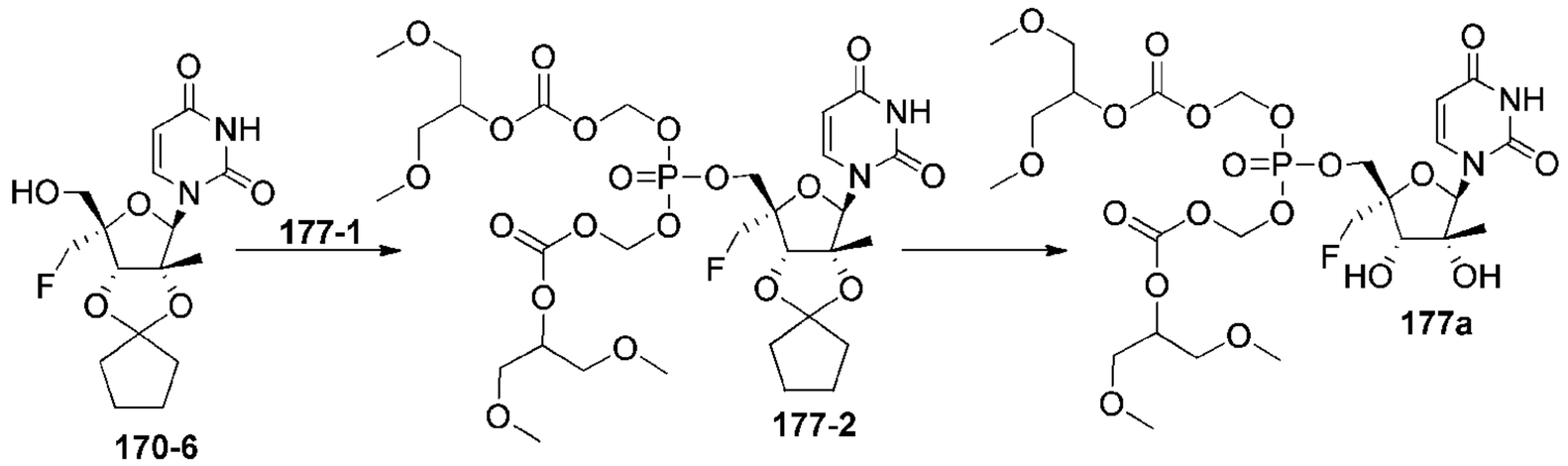
the filtrate was evaporated. Purification of the residue on silica (25 g column) with hexanes/EtOAc (30-100% gradient) yielded **176-3** as a colorless foam (1.14 g; 64%).

[0831] 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 **176-3** (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 ^oC 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 **176-4**.

[0832] A solution of **176-4** (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 **176-5** (0.96 g, 85%).

[0833] To a solution of **176-5** (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 **176a** as its HCl salt (4.2 g; 96%). MS: m/z = 732 [M+1].

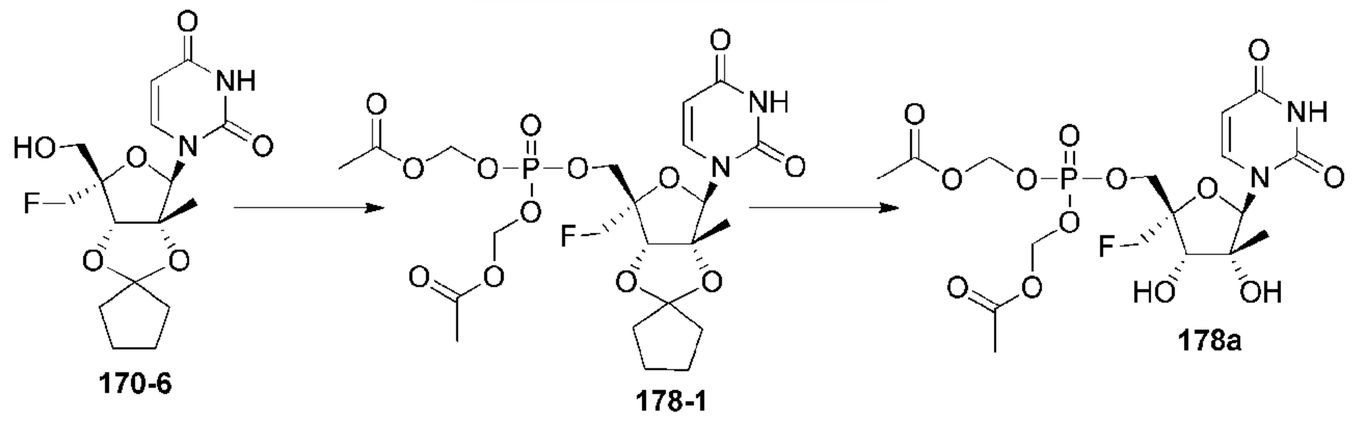
EXAMPLE 163
COMPOUND 177a



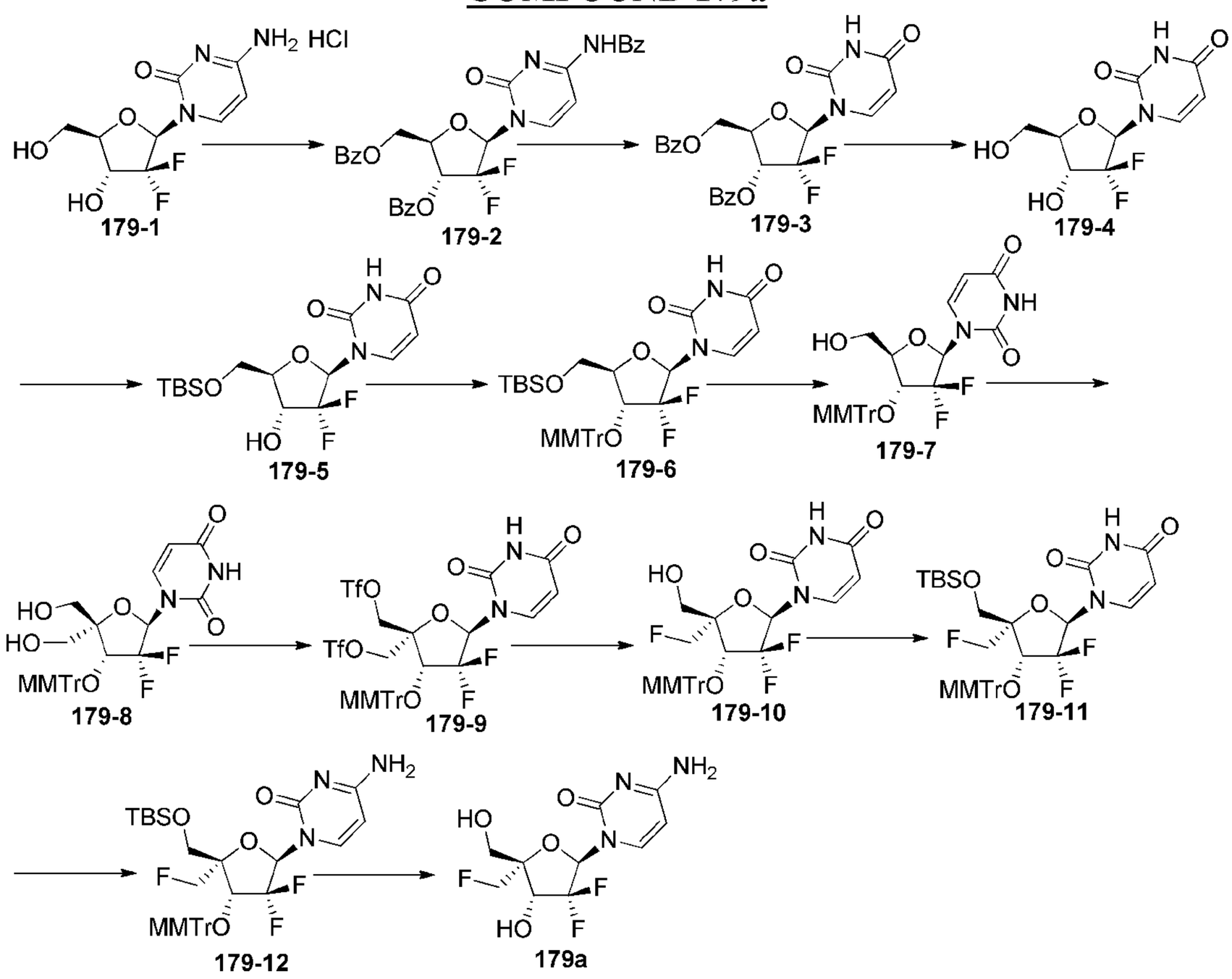
[0834] Compound **177aa** was prepared from 1,3-dimethoxypropan-2-ol. ^1H-NMR ($CDCl_3$) δ 5.73 (s,2H) , 5.03-5.06 (m,1H), 3.59 (d,4H), 3.38 (s,6H). Dry ACN (25 mL) was added to benzylphosphate (silver salt) (5 mmol) followed by addition of **177aa** (3.12 g;

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 **177bb** 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 **177bb** (540 mg; 1.0 mmol) was deprotected to give **177-1** (triethylammonium salt), which was used immediately without further purification. Compound **170-6** (285 mg; 0.8 mmol) and **177-1** were reacted to give purified **177-2** (300 mg). Compound **177-2** (300 mg) was deprotected to give purified **177a** (290 mg). The aforementioned reactions were conducted using a method described in the preparation of **170a**. ^{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 164
COMPOUND 178a


HO
F
NH
O
N
O
O
O

EXAMPLE 165
COMPOUND 179a



[0837] To a solution of **179-1** (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 **179-2** (27 g, 93.5%) as a white solid.

[0838] Compound **179-2** (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 **179-3.**

[0839] Compound **179-3** 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 **179-4** (12 g, 99%) as a white solid.

[0840] To a solution of **179-4** (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 **179-5.**

[0841] To a solution of **179-5** 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 **179-6** (32 g, 87%).

[0842] Compound **179-6** (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 **179-7** (21 g, 79%).

[0843] To a solution of **179-7** (21 g, 38.8 mmol) in DCM (200 mL) was added pyridine (9.2 mL, 116.4 mmol). The solution was cooled to 0 ^{o}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 **179-8** (10 g, 50.5%) as a white foam.

[0844] Compound **179-8** (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 **179-9** (6.1 g, 86.4%) as a brown foam.

[0845] Compound **179-9** (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 **179-10** (2.1 g, 50.6%).

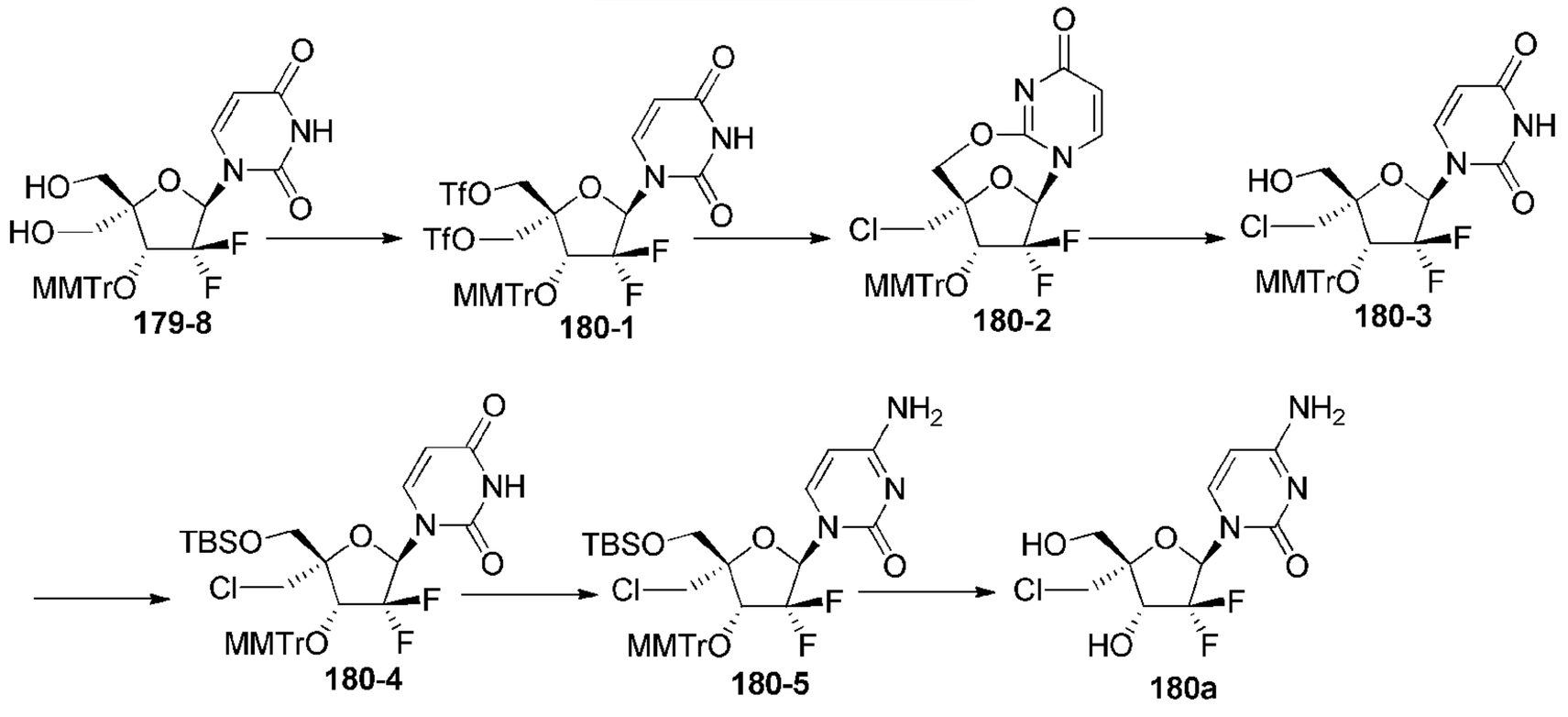
[0846] To a solution of **179-10** (1.5 g, 2.6 mmol) in anhydrous pyridine (15 mL) was added imidazole (530 mg, 7.8 mmol) and TBSCl (585 mg, 3.9 mmol) at RT. The mixture was stirred for 2 h. The solvent was removed and diluted with EA. The mixture was washed with $NaHCO_3$ aq. solution and brine. The organic layer was dried and concentrated to give the residue, which was purified by silica gel column chromatography (10% EA in PE) to give **179-11**(1.5 g, 84.5%).

[0847] To a solution of **179-11** (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 **179-12,** which was purified by prep-TLC to give **179-12** (1.2 g, 80%) as a white solid.

[0848] A solution of **179-12** (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 **179a** (480 mg, 92%) as a white solid. ESI-MS: m/z 591 $[2M+H]^+$.

EXAMPLE 166
COMPOUND 180a



[0849] A solution of **179-8** (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 **180-1** (2.60 g, 67%).

[0850] A solution of **180-1** (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 **180-2**.

[0851] To a solution **180-2** (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 **180-3**. (1.34 g, 72%).

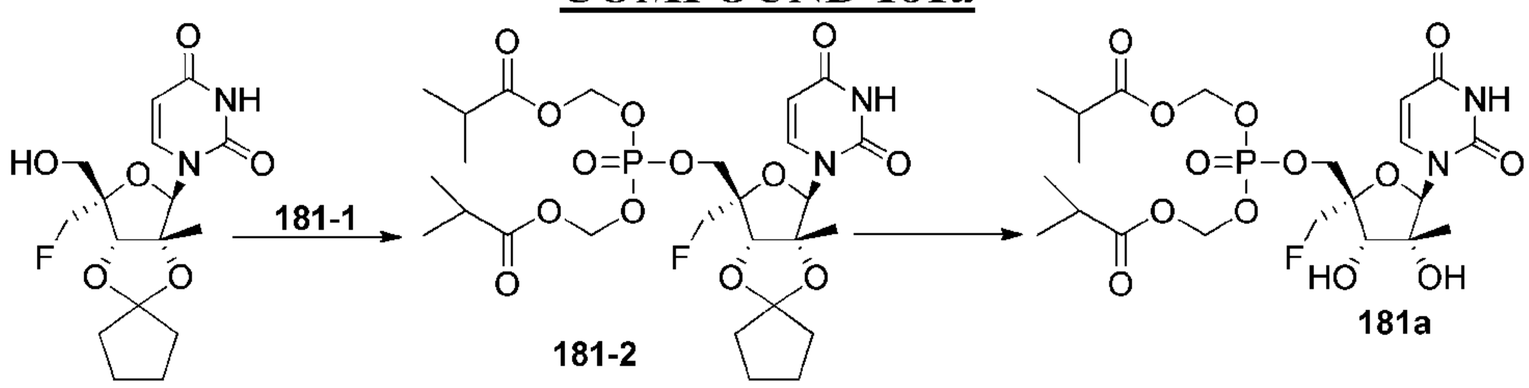
[0852] A solution of **180-3** (925 mg, 1.58 mmol) in dichloromethane (10 mL) was added TBSCl (713 mg, 4.75 mmol) and imidazole (323 mg, 4.74 mmol), and stirred at RT overnight. The mixture was diluted with EA (20 mL), and washed with brine. T he organic

phase was concentrated at low pressure to give the crude product. The residue was purified by column chromatography to give **180-4** (1.0 g, 90%).

[0853] A solution of **180-4** (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 **180-5** (1.0 g, 81%) as a white solid.

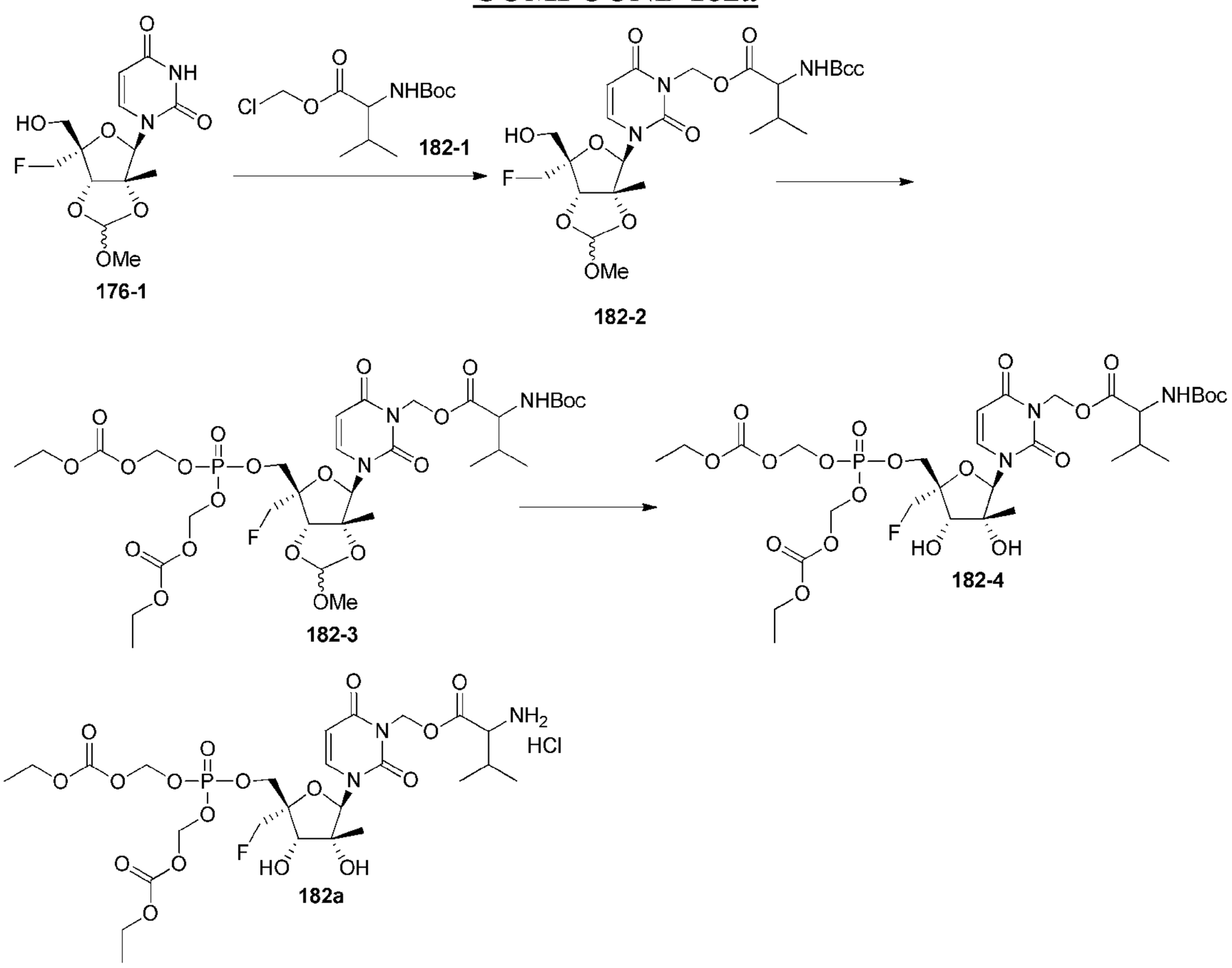
[0854] Compound **180-5** (1.0 g, 1.43 mmol) was treated with 80% HCOOH (10 mL), and stirred at RT overnight. The solvent was removed under reduced pressure, and the residue was purified on silica gel using 5% MeOH in CH_2Cl_2 to give **180a** (264 mg, 60%). ESI-MS: m/z 311.9 $[M+H]^+$.

EXAMPLE 167
COMPOUND 181a



[0855] Benzylphosphate (silver salt) and commercially available chloromethyl isobutylrate (5.0 g) yielded purified **181aa** (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 **181aa** (780 mg; 2.0 mmol) was deprotected to give **181-1** (triethylammonium salt), which was used immediately without further purification. Compound **170-6** (356 mg; 1.0 mmol) and **181-1** were reacted to give purified **181-2** (230 mg). Compound **181-2** (230 mg) was deprotected to yield purified **181a** (80 mg, 0.14 mmol). The aforementioned reactions were conducted using a method described in the preparation of **170a** and **177a**. ^{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 168
COMPOUND 182a



[0856] Compound **182-2** (0.34 g, 60%) was prepared from **176-1** (0.33 g) and **182-1** (0.34 g) in acetone (6 mL) with NaI (0.19 g) and K_2CO_3 (0.69 g).

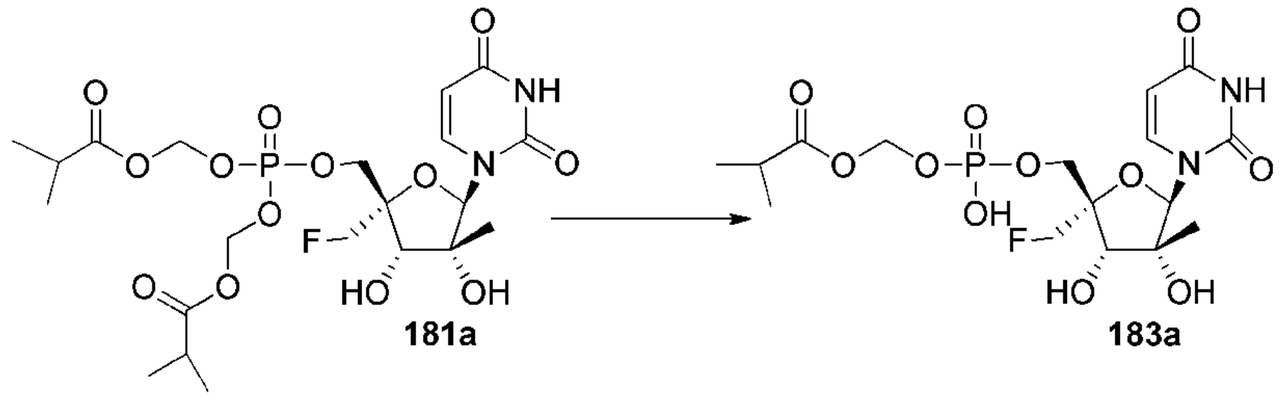
[0857] Compound **182-3** (0.28 g, 74%) was prepared in the same manner from **182-2** (0.25 g, 0.45 mmol) and triethylammonium bis(ethoxycarbonyloxymethyl)phosphate (0.9 mmol) with DIPEA (0.35 mL), BopCl (0.25 g), and 3-nitro-1,2,4-triazole (0.11 g) in THF (5 mL). Purification was done with hexanes/EtOAc (30-100% gradient).

[0858] A solution of **182-3** (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 **182-4** (0.22 g, 84%).

[0859] To a solution of **182-4** (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 **182a** precipitated. The mixture was filtered and washed with ether to give **182a** (100

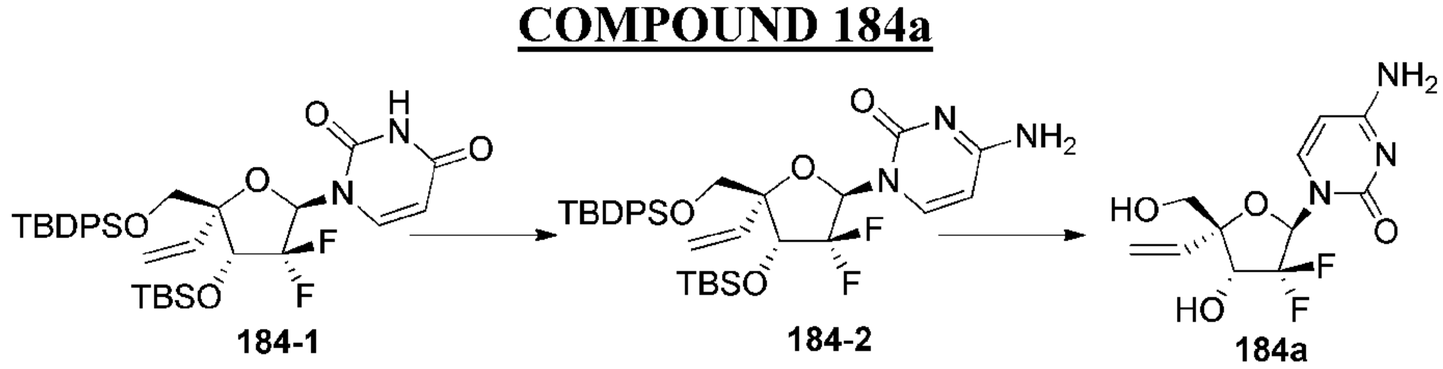
mg, 75%). The aforementioned reactions were conducted using a method described in the preparation of **176a**. MS: m/z=704 [M+1].

EXAMPLE 169
COMPOUNDS 183a



[0860] Compound **181a** (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 min. Pure fractions were pooled and lyophilized to yield **183a** (0.005g, 63%). MS: m/z = 487 [M+1].

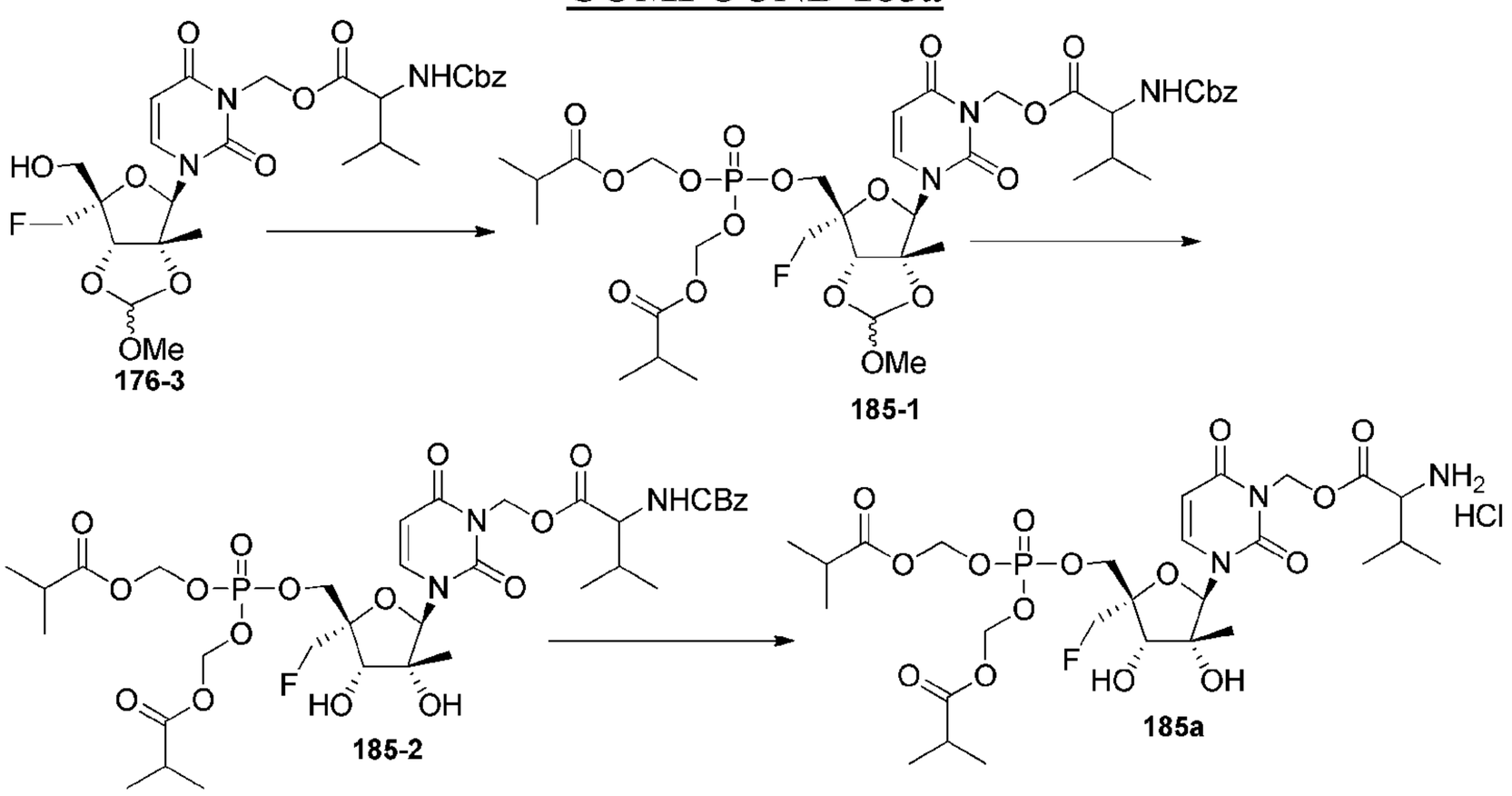
EXAMPLE 170
COMPOUND 184a



[0861] A mixture solution of **184-1** (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 **184-2** (200 mg, 63%).

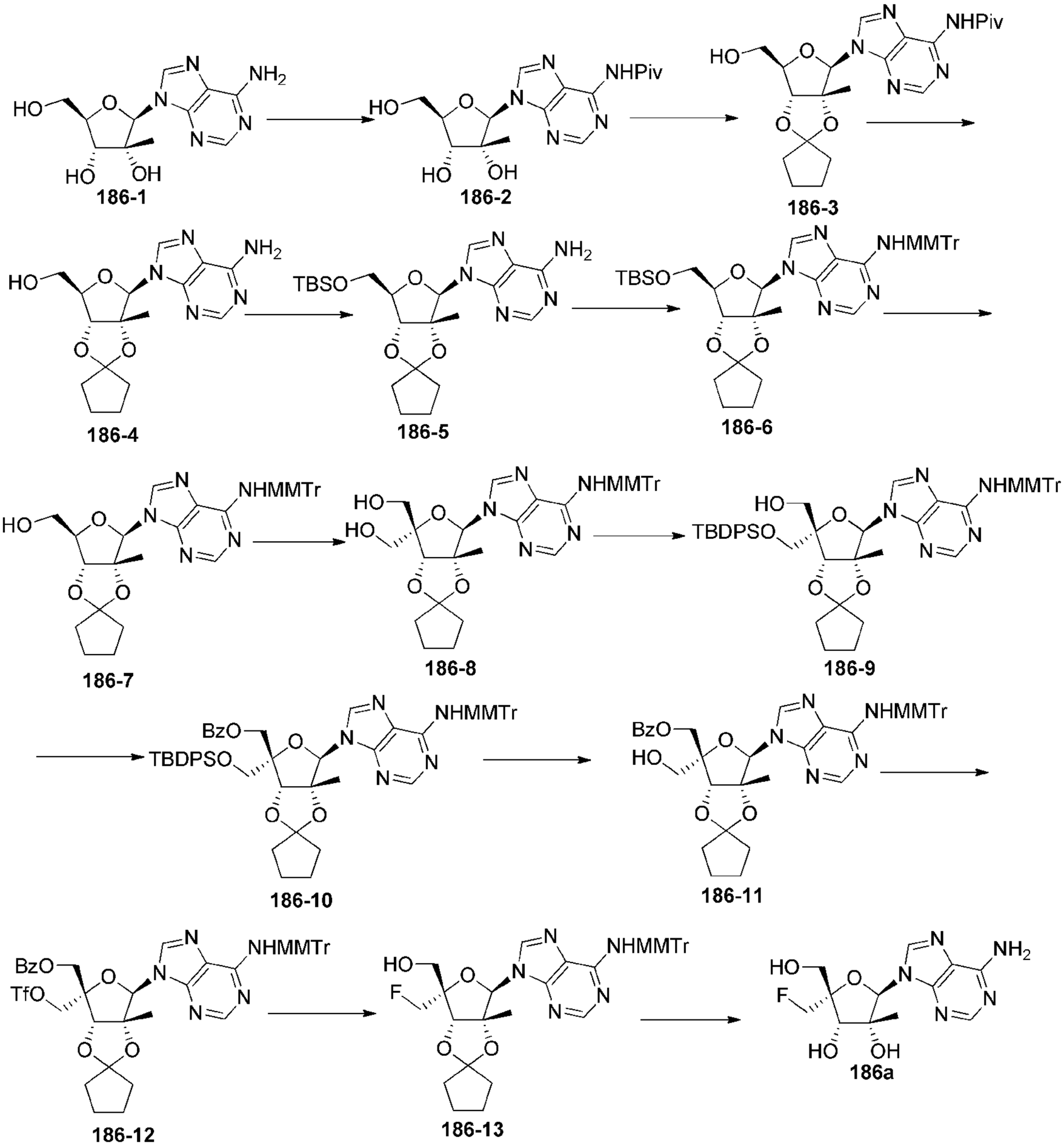
[0862] A solution of **184-2** (286 mg, 0.45 mmol) and ammonium fluoride (500 mg, 13.5 mmol) in methanol (10 mL) was refluxed overnight. The solvent was removed under reduced pressure and the residue was purified on silica gel to give **184a** (75 mg, 57%). ESI-MS: m/z 289.9 $[M+H]^+$.

EXAMPLE 171
COMPOUND 185a



[0863] Compound **185-1** (0.44 g, 34%) was prepared from **176-3** (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 **185-2** (0.43 g, 85%) was prepared from **185-1** (0.44 g); and **185a** (0.19 g, 98%) was prepared from **185-2** (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 **176a**. MS: m/z = 700 [M+1].

EXAMPLE 172
COMPOUND 186a



[0864] To a stirred solution of **186-1** (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 **186-2** (2.2 g, 85%).

[0865] To a solution of **186-2** (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 **186-3** (6.5 g, 65%).

[0866] To a stirred solution of **186-3** (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 **186-4** (4.4 g, 92%).

[0867] To a stirred solution of **186-4** (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 **186-5** (5.44 g, 82%).

[0868] To a stirred solution of **186-5** (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 **186-6** (7.1 g, 89%).

[0869] To a stirred solution of **186-6** (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 **186-7** (5.1 g, 87%).

[0870] To a stirred solution of **186-7** (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 **186-8** (2.01 g, 61%).

[0871] To a stirred solution of **186-8** (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 **186-9** (175 mg, 64%).

[0872] To a stirred solution of **186-9** (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 **186-10** (250 mg, 83.3%).

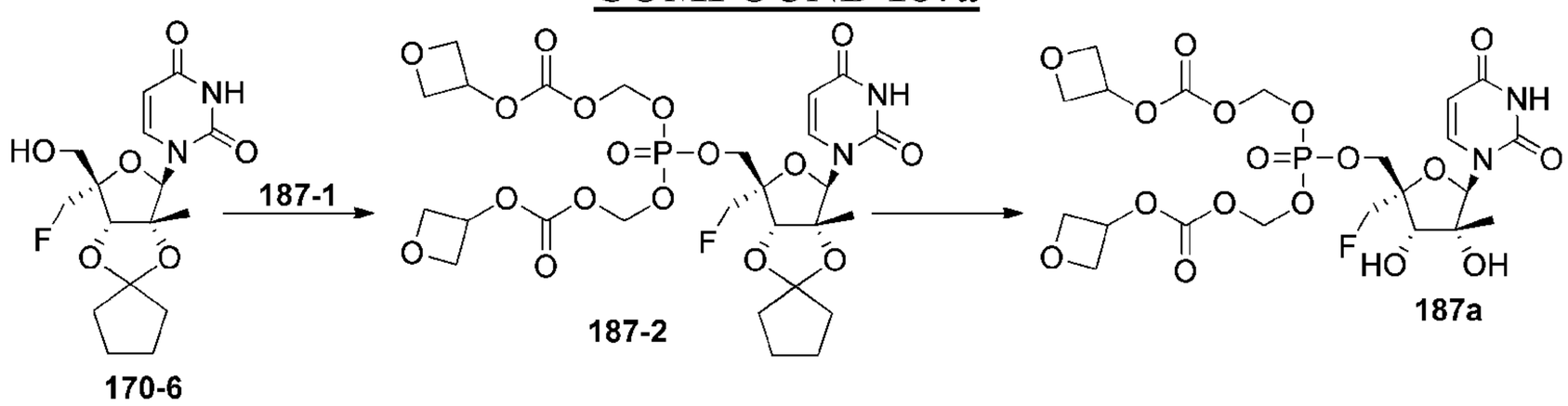
[0873] Compound **186-10** (300 mg, 0.302 mmol) in THF (5 mL) was treated with a solution of TBAF (0.61 mL, 0.61 mmol, 1M in THF) and HOAc (0.2 mL) at RT. The mixture was stirred at RT for 12 h. The mixture was concentrated at low pressure, and the residue was purified by column chromatography to give **186-11** (170 mg, 75%).

[0874] To a stirred solution of **186-11** (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 **186-12** (401 mg, 85%).

[0875] Compound **186-12** (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 **186-13** (150 mg, 40.8%) as a white solid. ESI-MS: m/z 652.1 $[M + H]^+$.

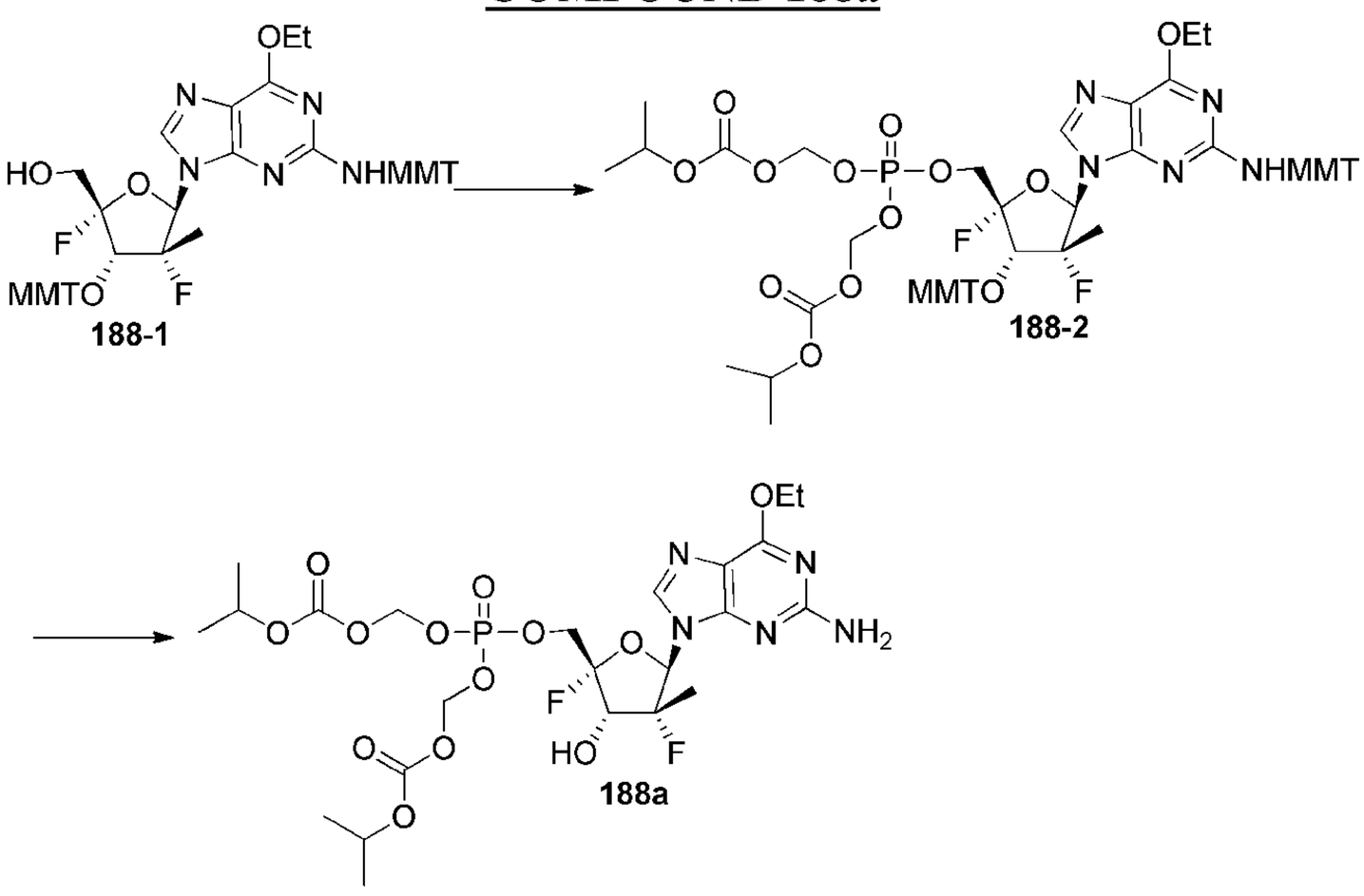
[0876] Compound **186-13** (50 mg) was dissolved in 80% HCOOH (10 mL), and the mixture was heated at 45^0C for 24 h. The solvent was evaporated and co-evaporated with methanol/toluene to remove traces of acid. The residue was dissolved in 20% triethylamine in methanol, kept for 15 mins and then evaporated. Compound **186a** (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 173
COMPOUND 187a



[0877] Compound **187aa** 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 **187bb** (8.0 g) was prepared from **187aa**. ^{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 **187bb** (8.0 g) were reacted to yield purified **187cc** (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 **187cc** was deprotected to give **187-1** (triethylammonium salt), which was used immediately without further purification. Compound **170-6** (356 mg; 1.0 mmol) and **187-1** were reacted to give purified **187-2** (230 mg). Compound **187-2** (230 mg) was deprotected to yield purified **187a** (12.5 mg, 0.02 mmol). The aforementioned reactions were conducted using a method described in the preparation of **170a**. ^{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.

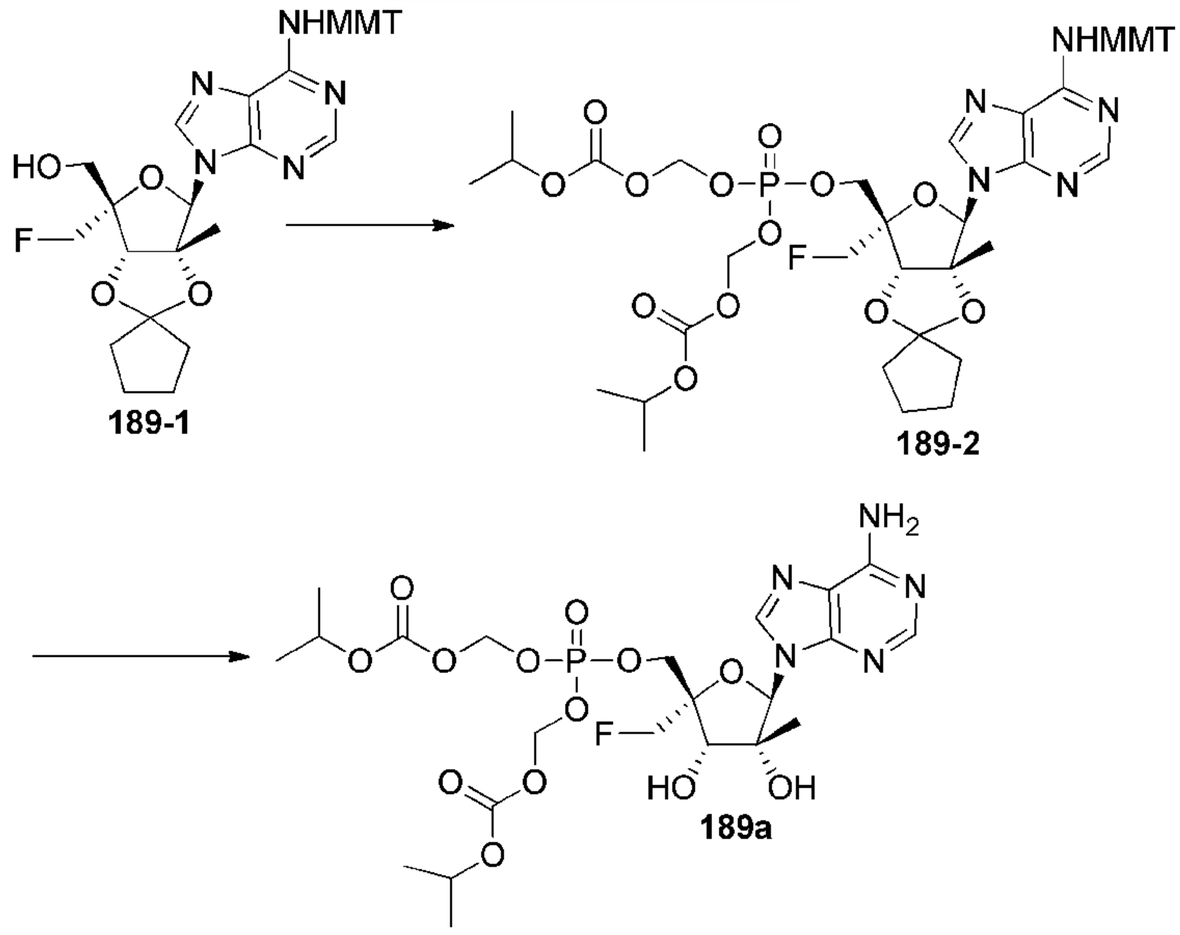
EXAMPLE 174
COMPOUND 188a



[0878] Compound **188-2** (70 mg, 58%) was prepared in the same manner from compound **188-1** (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 **156a**. Purification was done with hexanes/EtOAc with a 20-80% gradient.

[0879] Compound **188a** (25 mg, 64%) was prepared from **188-2** (70 mg) in acetonitrile (0.6 mL) and 4 N HCl/dioxane (50 μL) as described in the preparation of **209a**. MS: m/z = 658 [M+1].

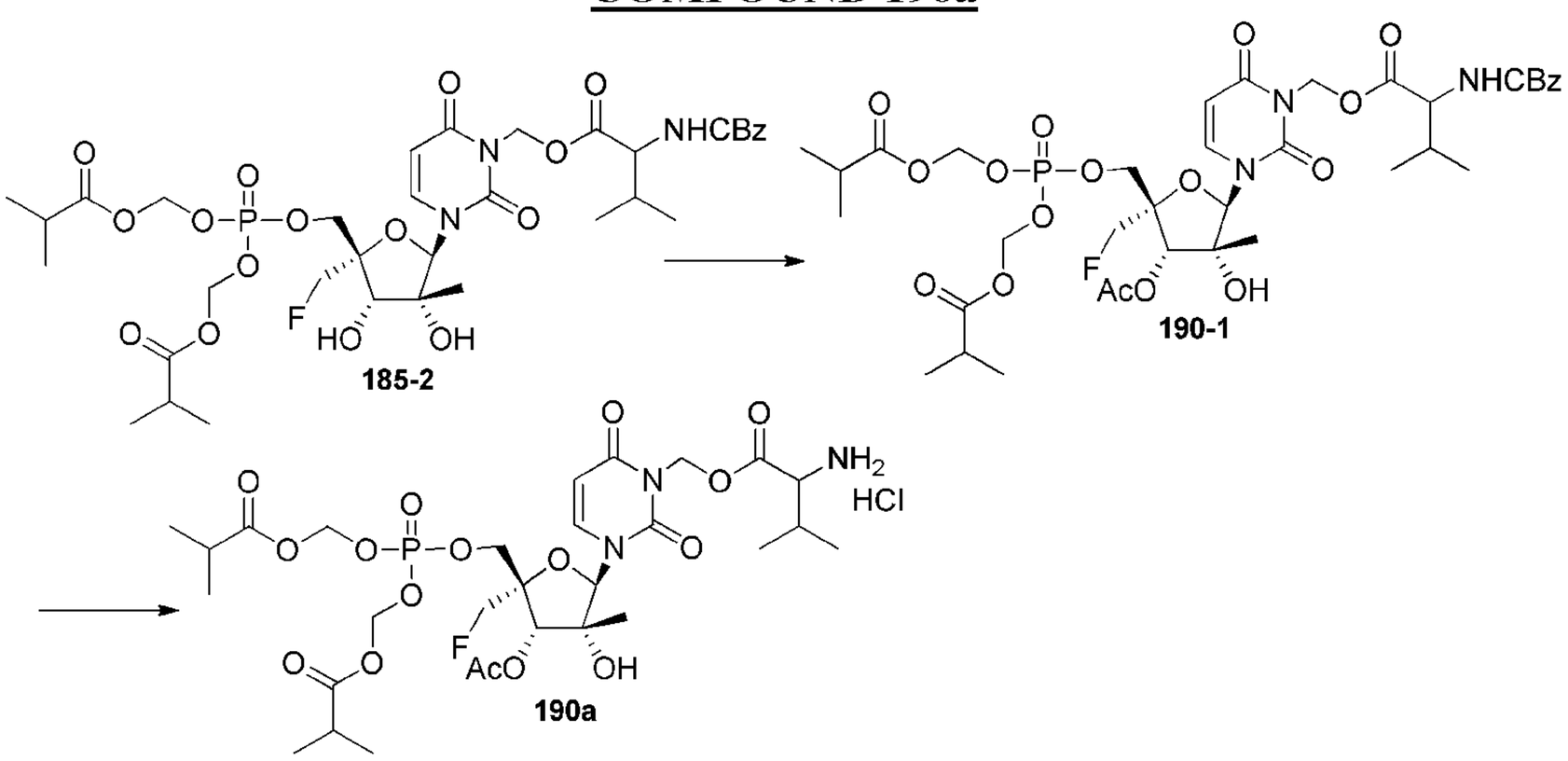
EXAMPLE 175
COMPOUND 189a



[0880] Compound **189-2** (69 mg, 90%) was prepared from compound **189-1** (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 **156a**. Purification was done with hexanes/EtOAc with a 20-100% gradient.

[0881] Compound **189a** (27 mg, 62%) was prepared from **189-2** (65 mg) as described in the preparation of **156a**. MS: m/z = 626 [M+1].

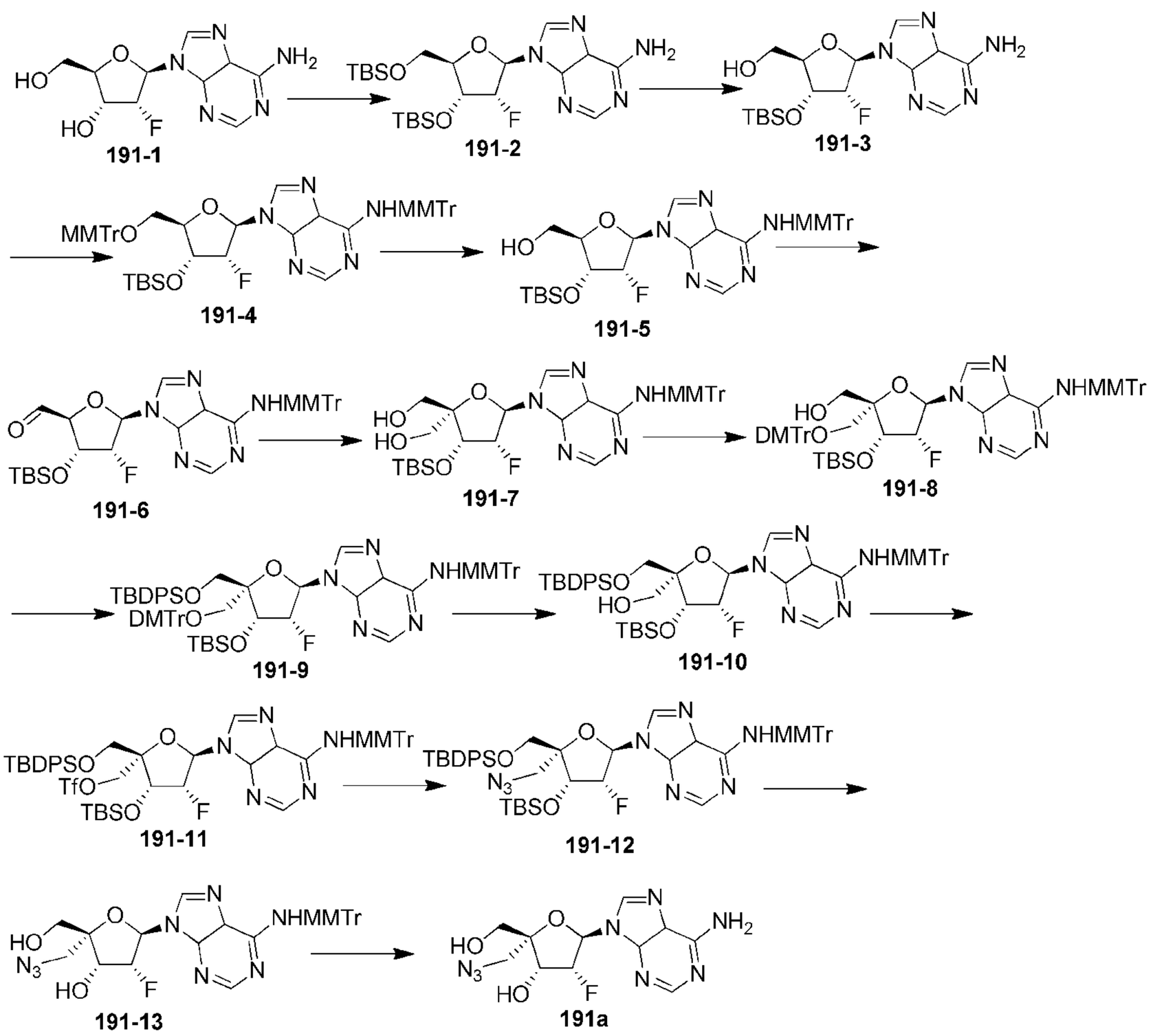
EXAMPLE 176
COMPOUND 190a



[0882] A mixture of **185-2** 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 **190-1** (12 mg, 69%).

[0883] Compound **190a** (10 mg, 92%) was prepared from **190-1** (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 **176a**. MS: m/z=742 [M+1].

EXAMPLE 177
COMPOUND 191a



[0884] To a solution of **191-1** (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 **191-2** (4.49 g, 90 %) as a white solid.

[0885] To a stirred solution of **191-2** (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 **191-3** (1.75 g, 65%) as a white foam.

[0886] To a solution of **191-3** (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 **191-4** (5.76 g, 70%) as a white foam.

[0887] To a solution of **191-4** (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 **191-5** (0.99 g, 70%) as a white foam.

[0888] To a stirred solution of **191-5** (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 **191-6** (3.5 g) as a yellow oil.

[0889] To a stirred solution of **191-6** (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 **191-7** (1.46 g, 40%) as a white solid.

[0890] To a stirred solution of **191-7** (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 **191-8** (1.60 g, 60 %) as a white solid.

[0891] To a solution of **191-8** (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 **191-9** (0.93 g, 70%) as a white foam.

[0892] To a stirred solution of **191-9** (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 **191-10** (0.48 g, 65%) as a solid.

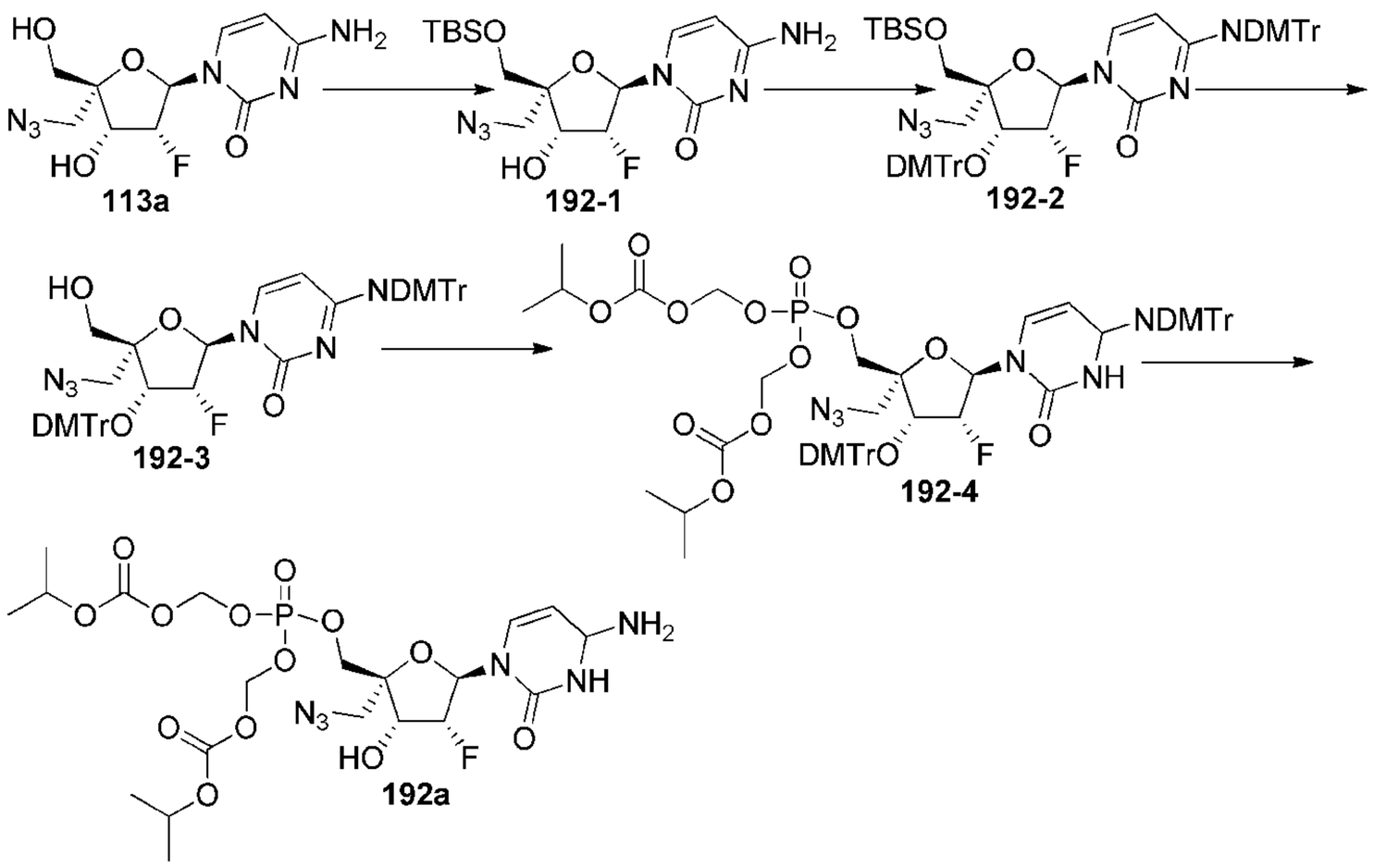
[0893] To an ice cold solution of **191-10** (0.4 g, 0.433 mmol) in anhydrous DCM (2.7 mL) was added pyridine (171 mg, 2.17 mmol) and Tf_2O (183 mg, 0.65 mmol) by dropwise at -35 °C. The mixture was stirred at -10 °C for 20 mins. The reaction was quenched with ice water and stirred for 30 mins. The mixture 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 **191-11** (0.46 g), which was used for next step without further purification.

[0894] To a solution of **191-11** (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 **191-12** (0.31 g, 70%) as a solid.

[0895] To a solution of **191-12** (0.31 g, 0.33 mmol) in MeOH (5 mL) was added NH_4F (0.36 g, 9.81 mmol) at 70 ^oC. 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 **191-13** (117 mg, 60%) as a white solid.

[0896] Compound **191-13** (300 mg, 0.50mmol) 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 **191a** (100 mg, 61.3 %) as a white solid. ESI-LCMS: m/z 325.1 $[M+H]^+$.

EXAMPLE 178
COMPOUND 192a



[0897] To a solution of **113a** (200 mg, 0.67 mmol) in anhydrous pyridine (5 mL) was added TBSCl (120 mg, 0.8 mmol) at R.T. 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 **192-1** (153 mg, 55%) as a white solid.

[0898] To a solution of **192-1** (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 R.T. The mixture was stirred overnight, and then diluted wit DCM (5 mL). The mixture was filtered through a pre-packed celite funnel, and the filtrate was washed with

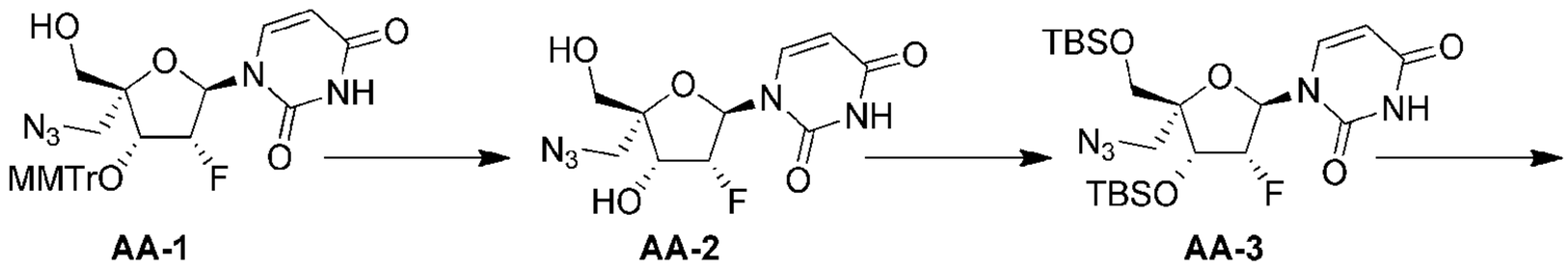
$NaHCO_3$ aq. solution, 1.0 M citric acid solution and then brine. The organic layer was dried over Na_2SO_4, and concentrated at low pressure to give a residue. The residue was purified by silica gel column chromatography (25% EA in PE to 100 %EA) to give **192-2** (83.5 mg, 63.6%).

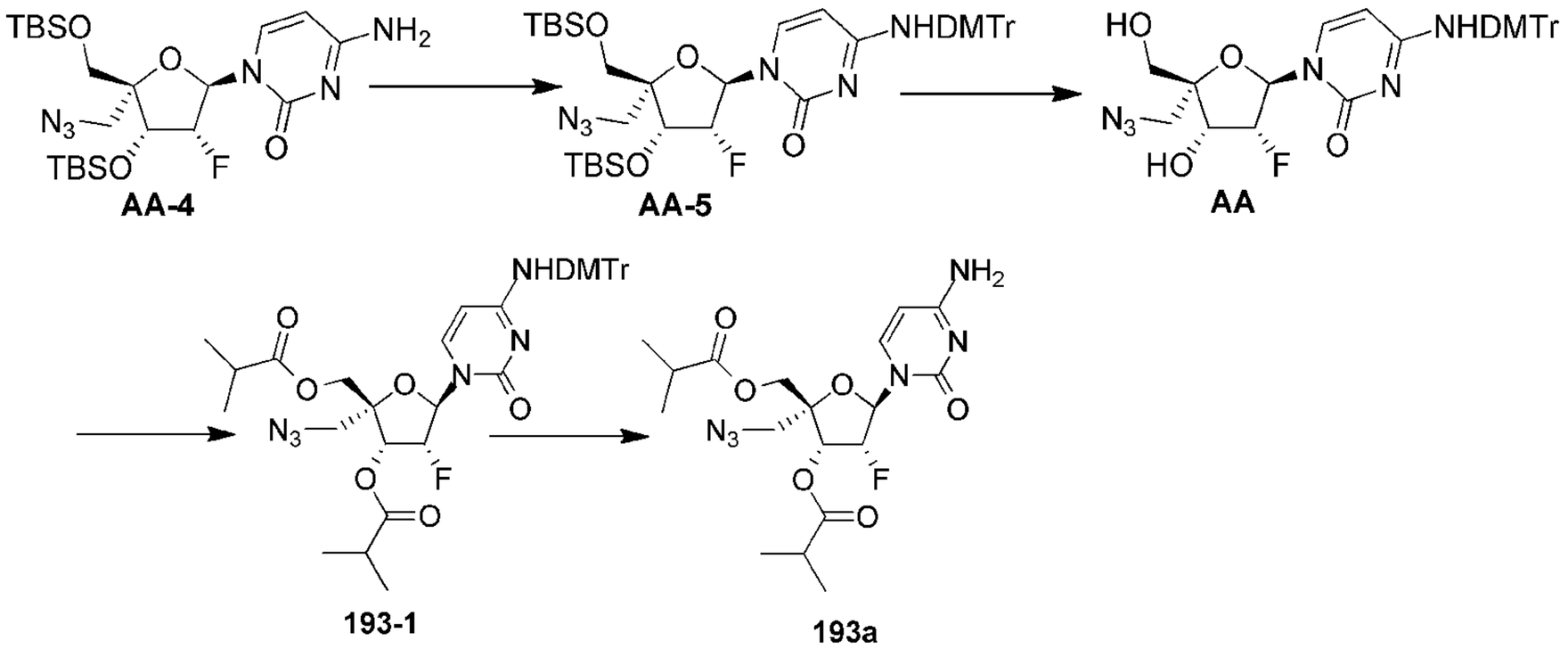
[0899] To a solution of **192-2** (83 mg, 0.081 mmol) in THF (1 mL), was added a 1M solution of TBAF in THF (0.122 mL, 0.122 mmol) at ice bath temperature. The mixture was stirred for 1.5 h. The mixture was diluted with EA, and washed with water and brine. The organic layer was dried and concentrated to give the crude product, which was purified by silica gel column chromatography (DCM to 5% MeOH in DCM) to give **192-3** (66.6 mg, 91%) as a white foam.

[0900] Compound **192-3** (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 **192-4** (68 mg, 76%) as a white solid.

[0901] Compound **192-4** (68 mg, 0.07 mmol) was dissolved in 80% HCOOH. The mixture was stirred at R.T. for 2 h. The solvents were evaporated at R.T. 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 **192a** (4.8 mg, 14%) as a white foam. ESI-LCMS: m/z = 613.1 $[M+H]^+$, 1225.2 $[2M+H]^+$.

EXAMPLE 179
COMPOUND 193a





[0902] Compound **AA-1** (2.20 g, 3.84 mmol) was dissolved in 80% HCOOH (40 mL) at R.T. (18 °C). The mixture was stirred at R.T. 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.

[0903] 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 R.T. (16 °C) under N_2 atmosphere. The mixture was stirred at R.T. 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.

[0904] 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 R.T. (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.

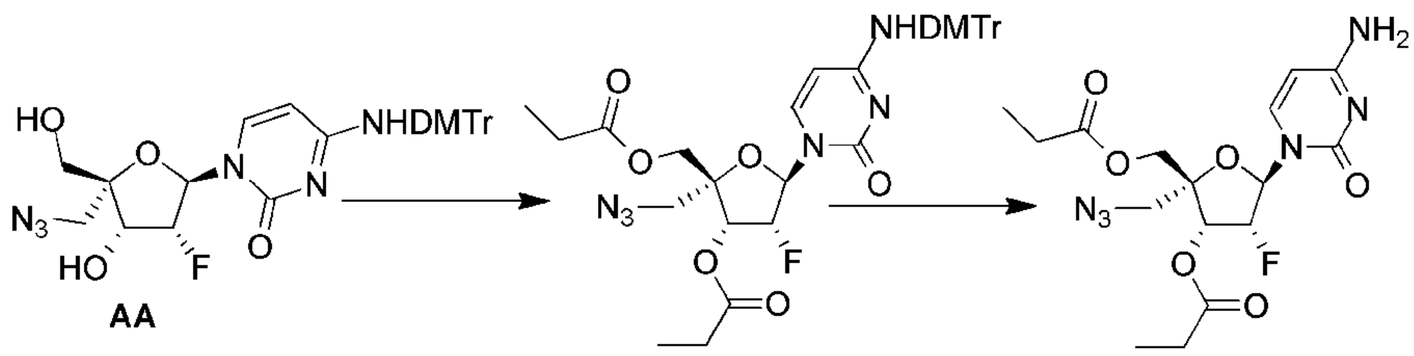
[0905] To a stirred solution of **AA-4** (1.90 g, 2.34 mmol) in anhydrous DCM (20 mL) was added DMTrCl (1.82 g, 3.49 mmol) and 2,4,6-trimethylpyridine (1.00 g, 8.25 mmol) at R.T. (15 °C) under N_2 atmosphere. The mixture was stirred at R.T. for 12 h. MeOH (20 mL) was added. The mixture was filtered, 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.

[0906] Compound **AA-5** (2.40 g, 2.60 mmol) was dissolved in TBAF (10 mL, 1M in THF). The mixture was stirred at R.T. (15 ^{o}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 $[M + Na]^+$.

[0907] 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 R.T. (15 ^{o}C) under N_2 atmosphere. The mixture was stirred at R.T. 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 **193-1** (59.00 mg, 79.77%) as a white solid.

[0908] Compound **193-1** (57.00 mg, 76.74 μmol, 1.00 eq.) was dissolved in 80% CH_3COOH (8 mL). The solution was stirred at R.T. (15 ^{o}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 **193a** (23.00 mg, 68.05%) as a white foam. ESI-MS: m/z 441.2 $[M+H]^+$, 463.2$[M+Na]^+$.

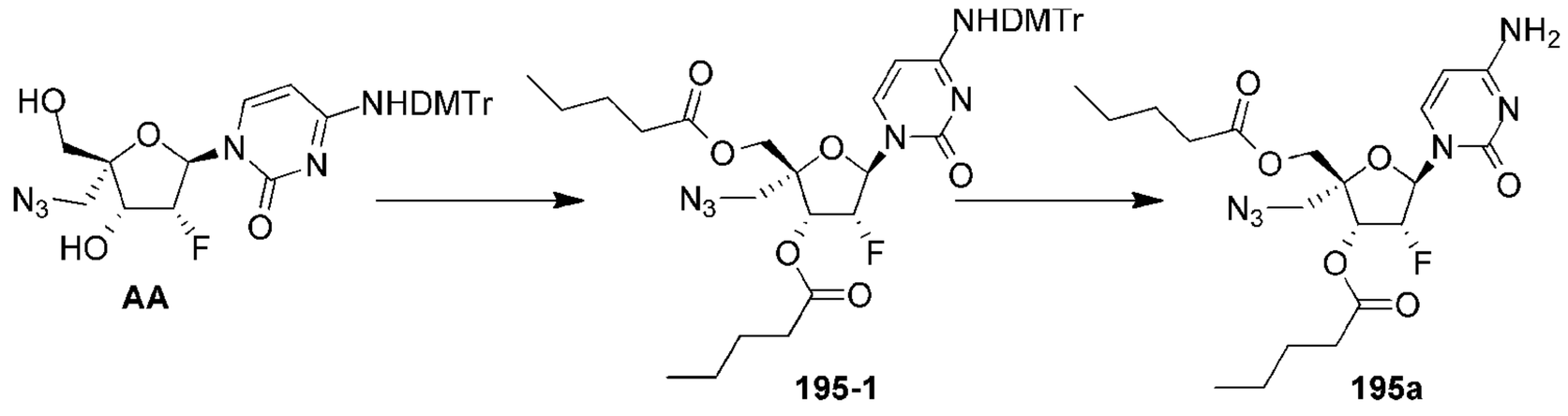
EXAMPLE 180
COMPOUND 194a



[0909] Compound **194-1** was prepared in similar manner as **193-1** 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.). **194-1** (white solid, 56.00 mg, 78.69%).

[0910] Compound **194a** was prepared in similar manner as **193a** using **194-1** (54.00 mg, 75.55 μmol, 1.00 eq.) Compound **194a** (white foam, 18.00 mg, 57.78%). ESI-MS: m/z 413.1 $[M+H]^+$.

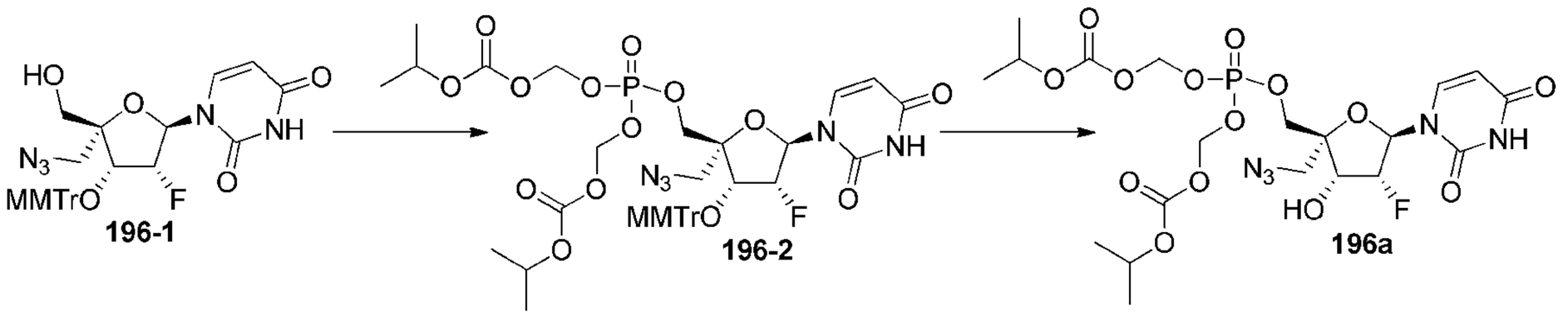
EXAMPLE 181
COMPOUND 195a



[0911] Compound **195-1** was prepared in similar manner as **193-1** 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.). Compound **195-1** (white solid, 60.00 mg, 75.65%).

[0912] Compound **195a** was prepared in similar manner as **193a** using **195-1** (75.00 mg, 97.30 μmol, 1.00 eq.) Compound **195a** (white foam, 28.00 mg, 61.43%). ESI-MS: m/z 469.2 $[M+H]^+$.

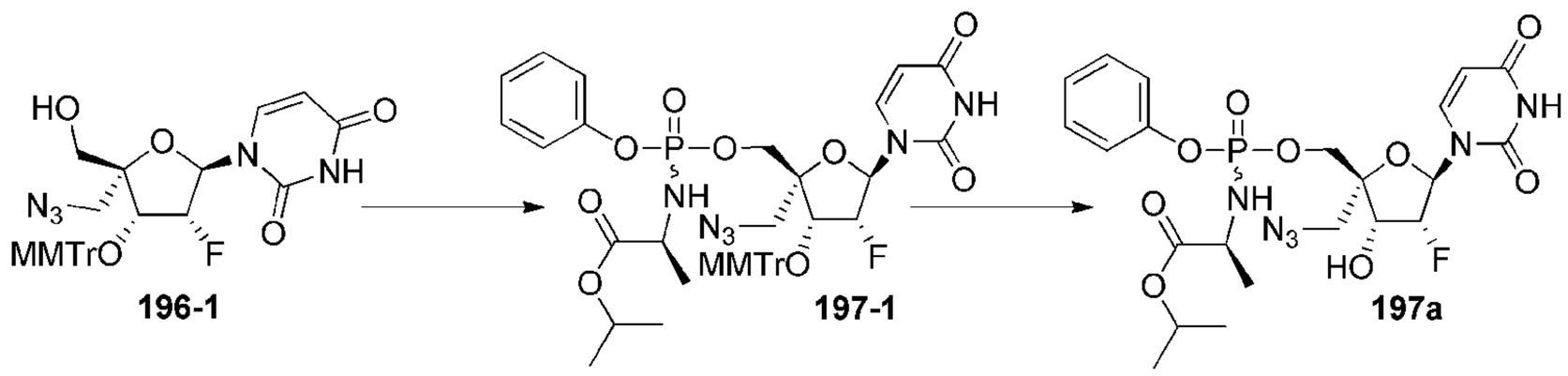
EXAMPLE 182
COMPOUND 196a



[0913] Compound **196-2** (40.7 mg, 53%) was prepared in the same manner from **196-1** (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 **192-4**.

[0914] Compound **196-2** (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 ^oC. The mixture was stirred at R.T. for 3 h. Anhydrous EtOH (200 μL) was added. The solvents were evaporated at R.T. and co-evaporated with toluene (3x). The residue was purified on silica (10 g column) with MeOH/CH_2Cl_2 (5-7% gradient) and lypholized give **196a** (15.4 mg, 76%) as a white foam. ESI-LCMS: m/z = 614.15 $[M+H]^+$, 1227.2 $[2M+H]^+$.

EXAMPLE 183
COMPOUND 197a

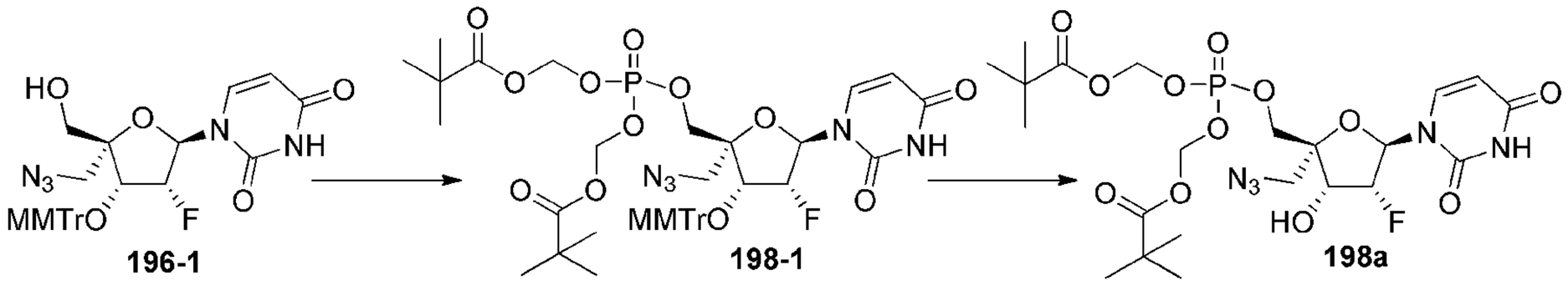


[0915] To a stirred solution of **196-1** (80 mg, 0.14 mmol) in anhydrous CH_3CN (2.0 mL) was added N-methylimidazole (0.092 mL, 1.12 mmol) at 0 ^0C (ice/water bath). A solution of phenyl (isopropoxy-L-alaninyl) phosphorochloridate (128 mg, 0.42 mmol, dissolved in CH_3CN (0.5 mL)) was then added (prepared 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 ^oC for h and then stirred at R.T. for 16 h. The mixture was cooled to 0 to 5 ^0C, 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 **197-1** (57.3 mg, 49 %) as a foam.

[0916] Compound **197-1** (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 ^oC. The mixture was stirred at R.T. for 2 h, and anhydrous EtOH (100 μL) was added. The solvents were evaporated at R.T. 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 **197a** (27.8 mg, 72%) as a white foam. ESI-LCMS: m/z = 571.1 $[M+H]^+$, 1141.2 $[2M+H]^+$.

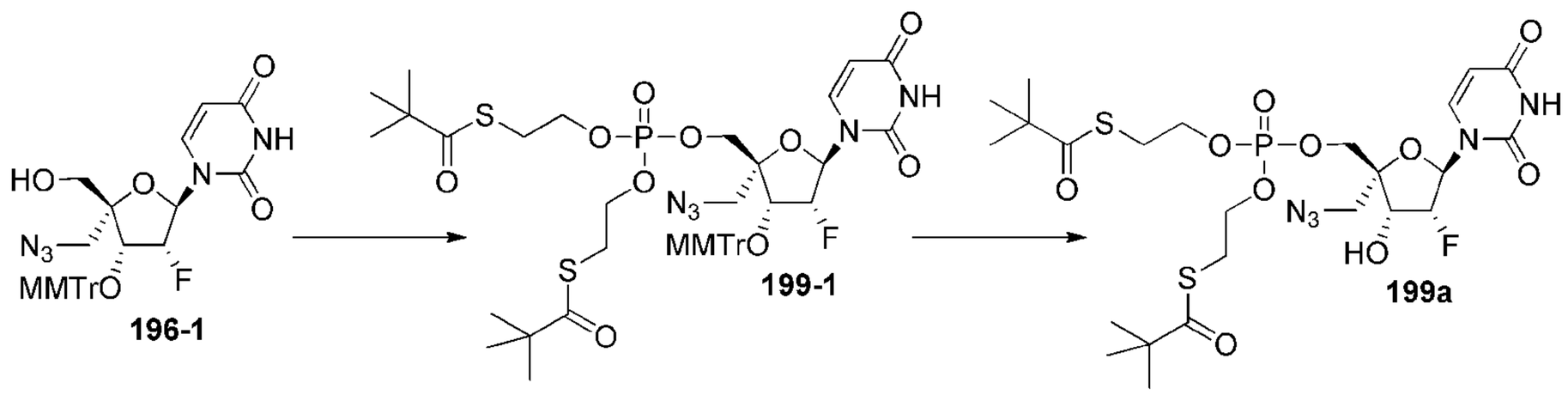
EXAMPLE 184
COMPOUND 198a



[0917] Compound **198-1** (68.4 mg, 44.7 %) was prepared from **196-1** (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 **192-4**.

[0918] Compound_**198a** (31.4 mg, 67%) was prepared from **198-1** (68 mg, 0.077 mmol) in the same manner as **196a**. ESI-LCMS: m/z = 627.15 $[M+Na]^+$, 1219.25 $[2M+H]^+$.

EXAMPLE 185
COMPOUND 199a

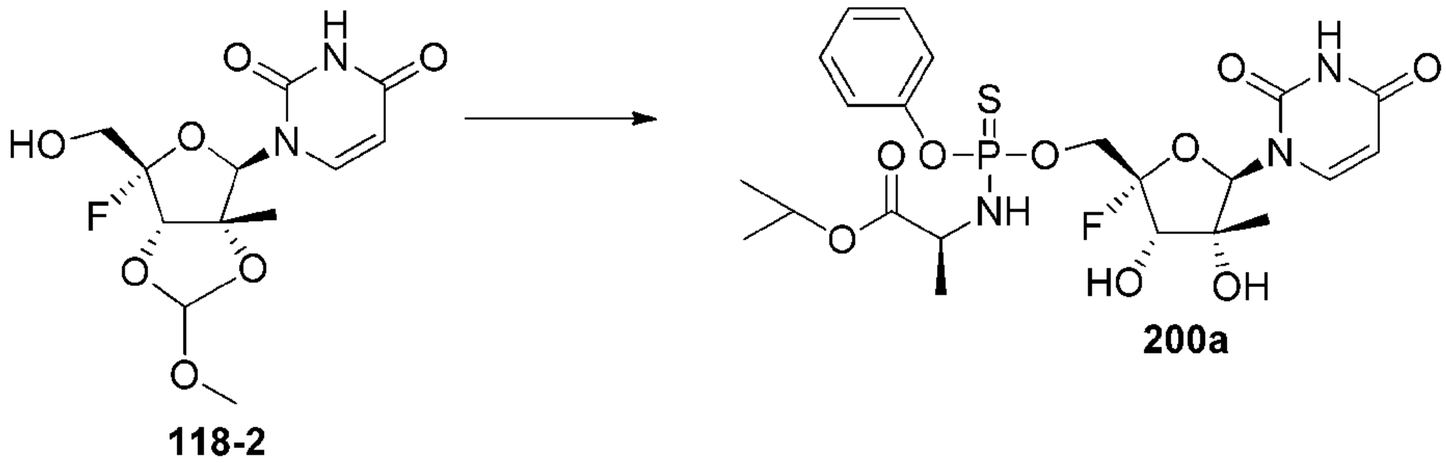


[0919] To a solution of **196-1** (100mg, 0.175 mmol) in anhydrous CH_3CN (2 mL) was added 5-ethylthio-1H-tetrazole in CH_3CN (0.25M; 0.84 mL, 0.21 mmol). Bis-SATE-phosphoramidate (95 mg, 0.21 mmol) in CH_3CN (1 mL) was added at 0 to 5 ^0C dropwise.

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 **199-1** (105 mg, 63.6 %) as a white foam.

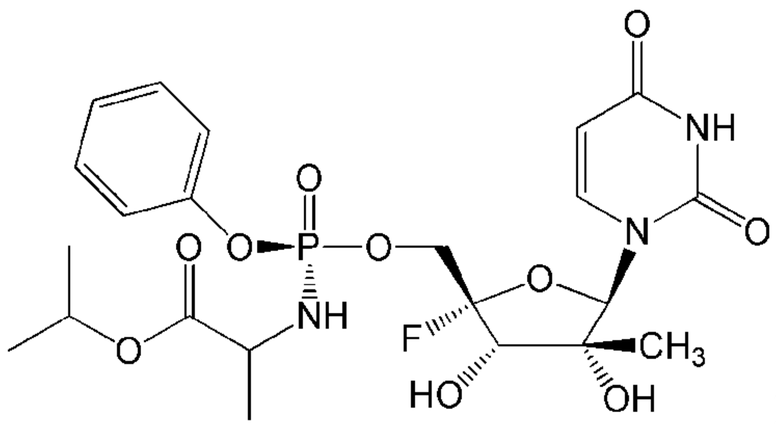
[0920] Compound **199-1** (105 mg, 0.112 mmol) was dissolved in_anhydrous CH_3CN (0.8 mL), and 4N HCl in dioxane (84 µL, 0.334 mmol) was added at 0 to 5 °C. The mixture was stirred at R.T. for 2 h. Anhydrous EtOH (100 µL) was added. The solvents were evaporated at R.T., and co-evaporated with toluene (3x). The residue was purified on silica (10 g column) with MeOH/CH_2Cl_2 (1-7% gradient) and lypholized to give **199a** (42.7 mg, 57%) as a white foam. ESI-LCMS: m/z = 692.15 $[M+Na]^+$, 1339.30 $[2M+H]^+$.

EXAMPLE 186
COMPOUND 200a

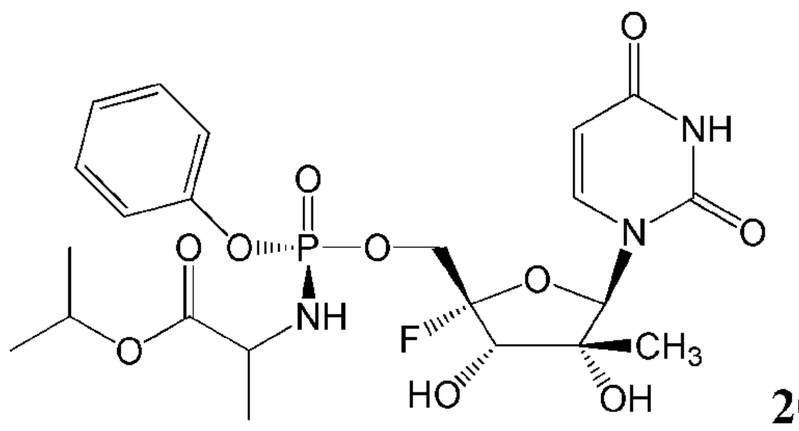


[0921] Compound **118-2** (32 mg, 0.1 mmol) was dissolved in dry THF (3 mL) and 2M solution of isopropylmagnesium bromide in THF (0.1 mL) was added at 0 ^{0}C. The reaction was left for 1 h at RT, and phenyl(isopropy*l*-L-alaninyl) thiophosphorochloridate was added (0.3 mmol). The mixture was left overnight 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. **200a** 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. **200a** (7 mg, yield 12.5%). MS m/z = 560.0 [M-H].

EXAMPLE 187
COMPOUNDS 201a AND 202a



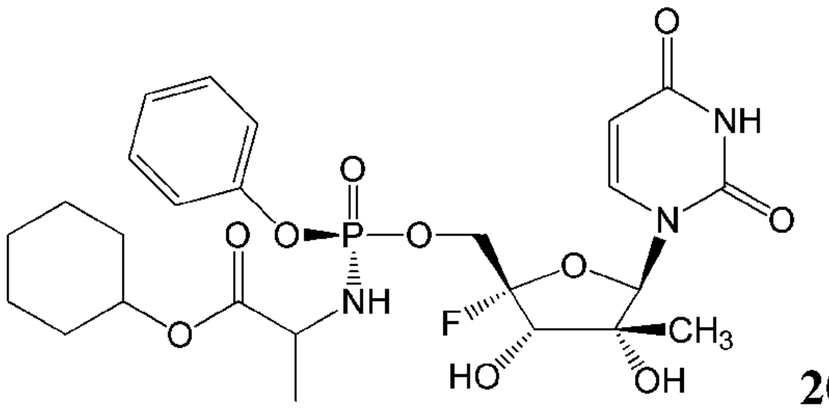
201a



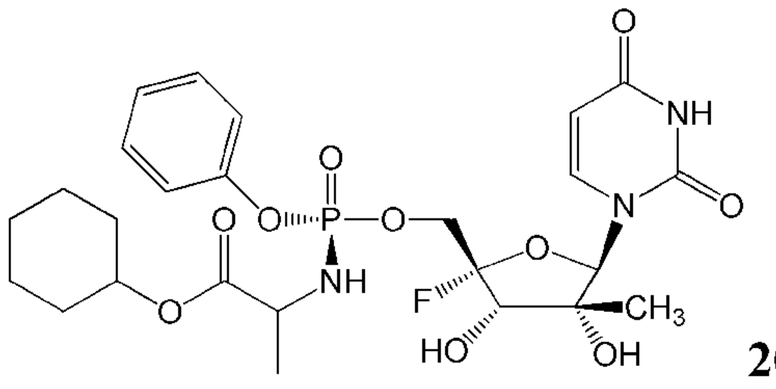
202a

[0922] The diastereomers of **118a** 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 **202a** (29.5 mins) and **201a** (30.1 mins). Pure fractions were lyophilized to produce a white powder. **202a**: ^{31}P-NMR (DMSO-d6) 3.448 ppm; MS m/z = 544 [M-1]; **201a**: ^{31}P-NMR (DMSO-d6) 3.538 ppm; MS m/z = 544 [M-1].

EXAMPLE 188
COMPOUNDS 203a AND 204a



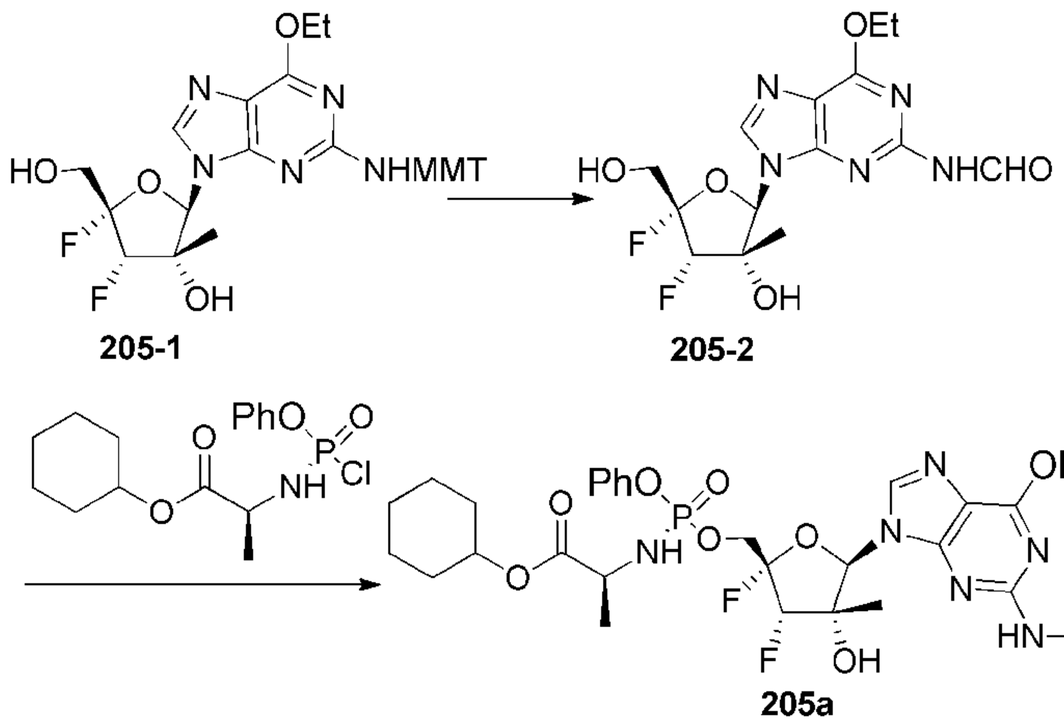
204a



203a

[0923] The diastereomers of **123a** were separated by RP-HPLC. A gradient of 25-52%ACN in H_2O over 26 minutes on a Synergi Hydro RP 30x250m 4u particle column (Phenomenex PN 00G-4375-U0-AX) eluted **203a** (24.8 mins) and **204a** (25.3 mins). Pure fractions were lyophilized to produce a white powder. **203a**: ^{31}P-NMR (DMSO-d6) 3.492 ppm; MS m/z = 584 M-1. **204a**: ^{31}P-NMR (DMSO-d6) 3.528 ppm; MS m/z = 584 [M-1].

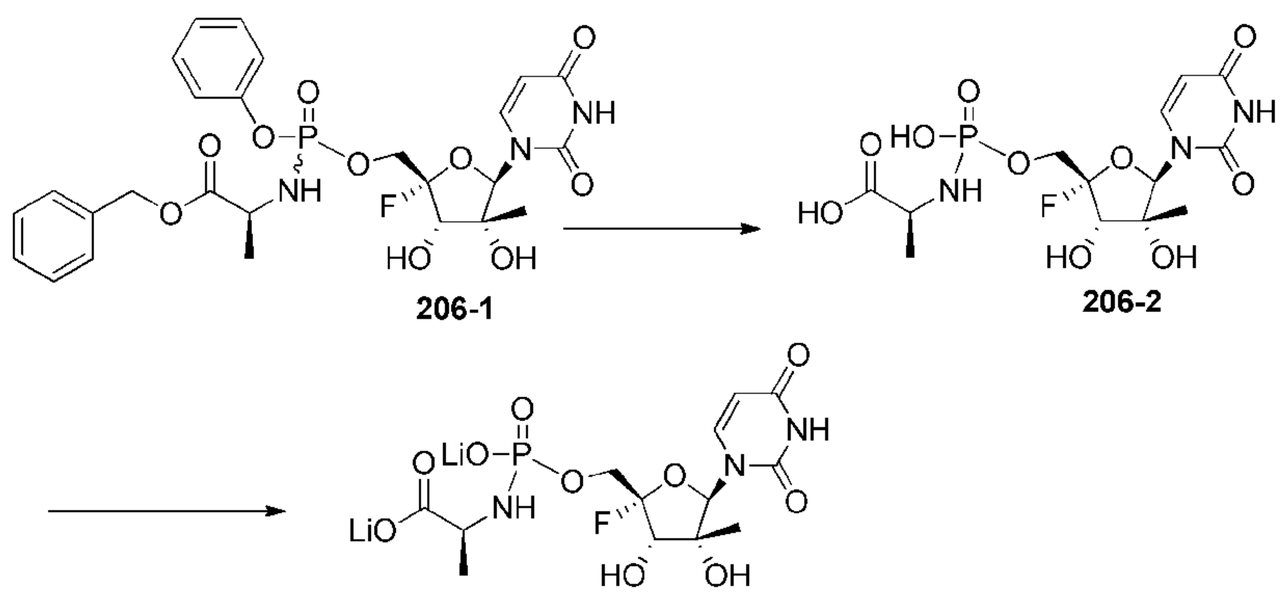
EXAMPLE 189
COMPOUND 205a



[0924] A solution of **205-1** (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 **205-2** (8 mg, 54%).

[0925] A mixture of **205-2** (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 **205a** (9 mg, 66%). MS: m/z = 683 [M+1].

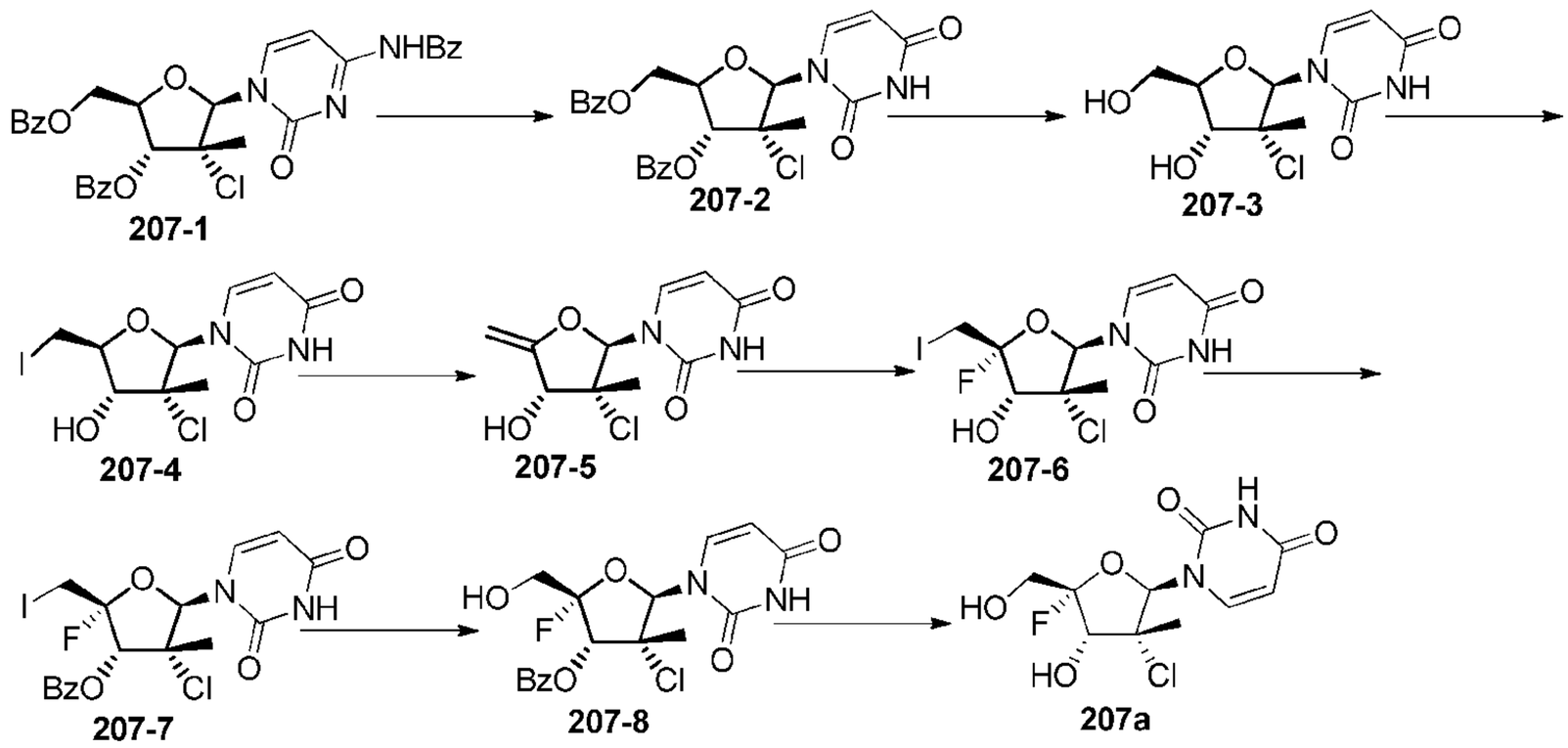
EXAMPLE 190
COMPOUND 206a, Bis-lithium Salt



[0926] Compound **206-1** was synthesized using a procedure similar for preparing compound **117a** using alanine benzyl ester hydrochloride. LCMS: m/z = 592 $[M-1]^-$.

[0927] To a solution of **206-1** (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 **206a** (bis-lithium salt) (731 mg, 90%). LCMS: m/z 426 = $[M-1]^-$.

EXAMPLE 191
COMPOUND 207a



[0928] Compound **207-1** (15.0 g, 25.55 mmol) was treated with 90% HOAc (150 mL) at RT. The mixture was stirred at 110 °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 **207-2** (11.0 g, 88.9%) as a white solid.

[0929] Compound **207-2** (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 **207-3** (6.5 g, 95.0%) as a white solid.

[0930] To a stirred suspension of **207-3** (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 **207-4** (5.1 g, 85.0%) as a white solid.

[0931] Compound **207-4** (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 **207-5** (240 mg, 44.9%) as a white solid.

[0932] To an ice-cooled solution of **207-5** (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 **207-6** (0.91 g, 48.6%) as a white solid.

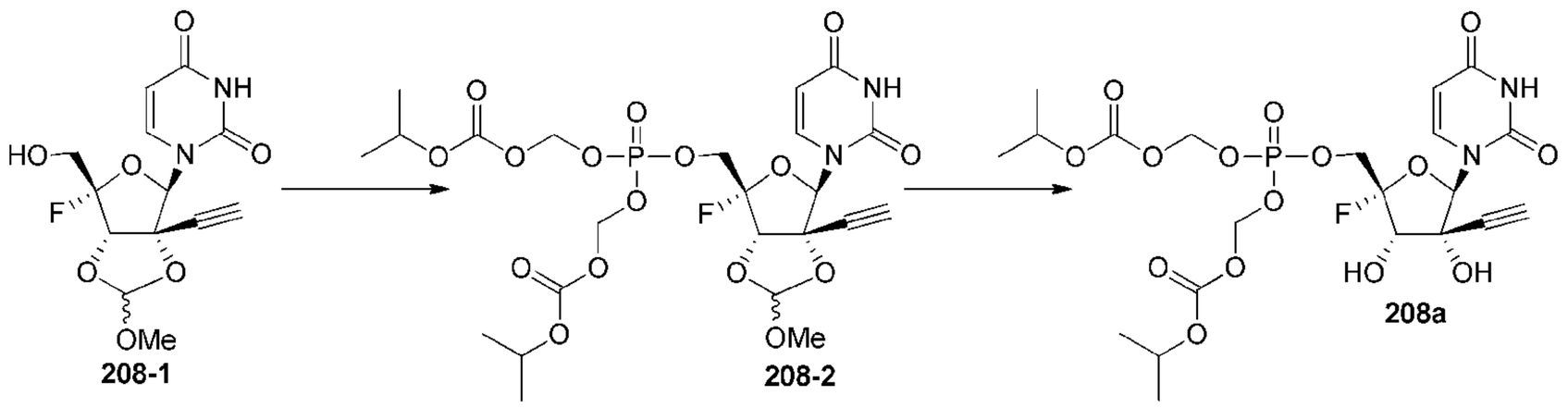
[0933] To a stirred solution of **207-6** (1.2 g, 2.97 mmol) in anhydrous DCM (12 mL) was added BzCl (0.83 g, 5.94 mmol), TEA (0.6 g, 5.94 mmol) and DMAP (0.72 g, 5.94 mmol) successively at RT. The mixture was stirred at RT for 12 h. The reaction was quenched with water, and extracted with EA (3 x 60 mL). The organic phase was concentrated at low pressure. The residue was purified by column chromatography (0-5% MeOH in DCM) to give **207-7** (1.2 g, 66.2%) as a white solid.

[0934] 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 **207-7**

(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 **207-8** (350 mg, 41.1%) as a white solid.

[0935] Compound **207-8** (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 **207a** (110 mg, 53.1%) as a white solid. ESI-LCMS: m/z 295.1 $[M+H]^+$.

EXAMPLE 192
COMPOUND 208a

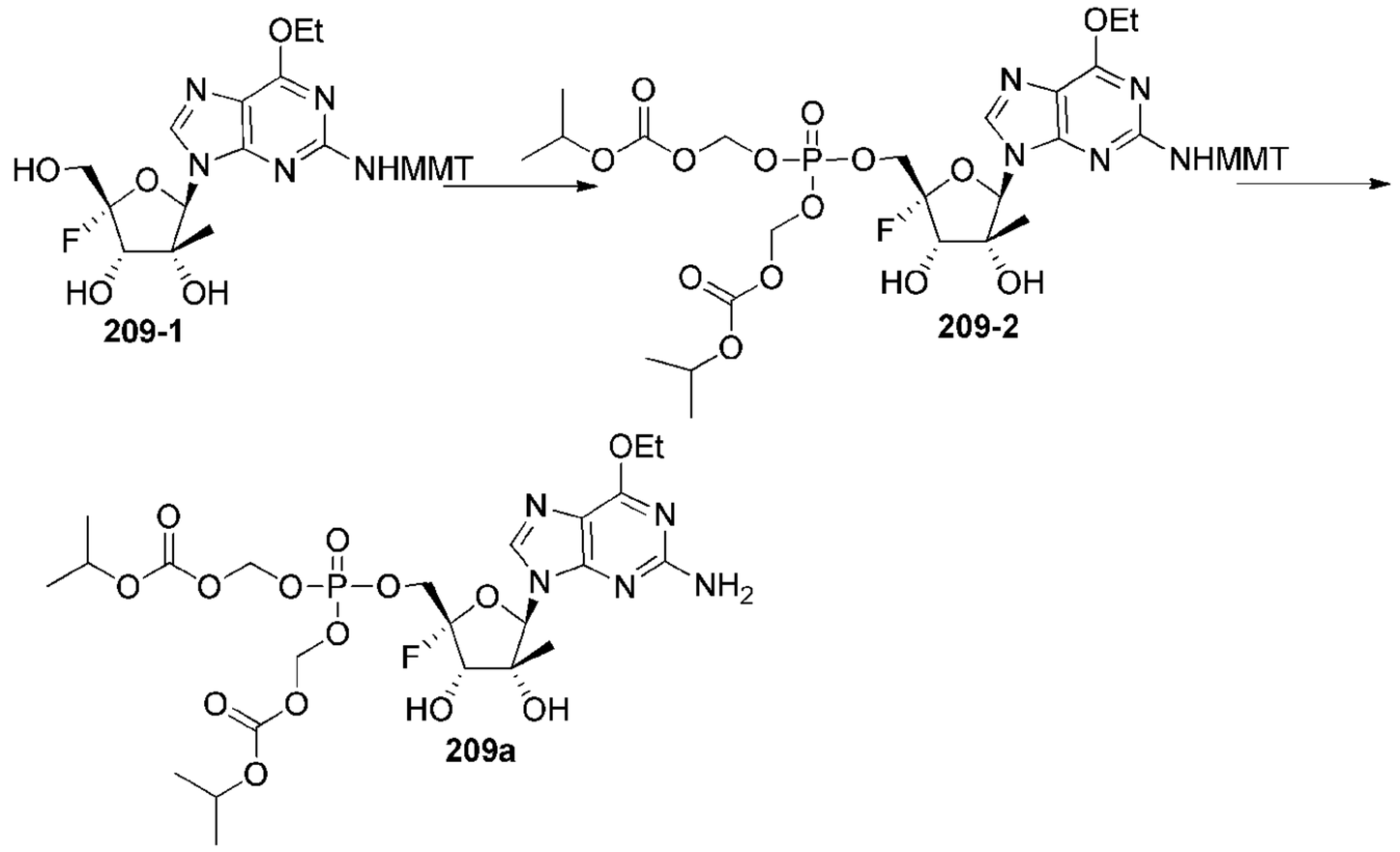


[0936] Compound **208-2** (0.20 g, 64%) was prepared in the same manner from **208-1** (0.16 g; 0.49 mmol) and triethylammonium bis(isopropyloxycarbonyloxymethyl)phosphate (0.74 mmol) with DIPEA (0.34 mL), BopCl (250 mg), and 3-nitro-1,2,4-triazole (112 mg) in THF (5 mL) following the procedure for the preparation of **176-4**.

[0937] A solution of **208-2** (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 50mM TEAA. Gradient was 25-75% ACN in 20 mins at 24mL/min, 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 **208a** (18 mg). MS: m/z = 1197 [2M+1].

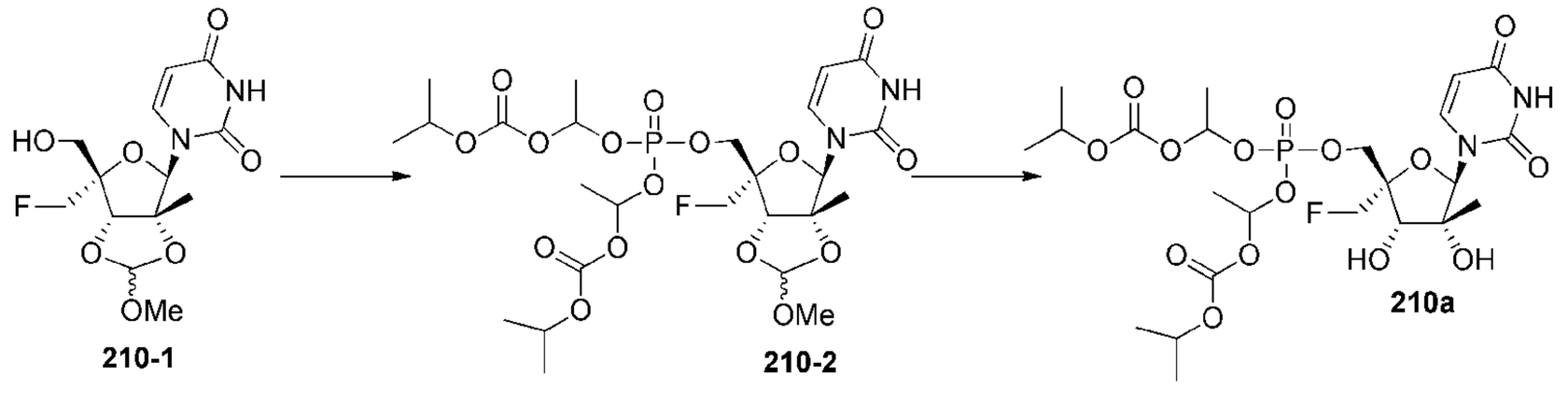
EXAMPLE 193
COMPOUND 209a



[0938] Compound **209-2** (158 mg, 50%) was prepared from **209-1** (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).

[0939] A solution of **209-2** (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 **209a** (85 mg, 76%). MS: m/z = 656 [M+1].

EXAMPLE 194
COMPOUND 210a

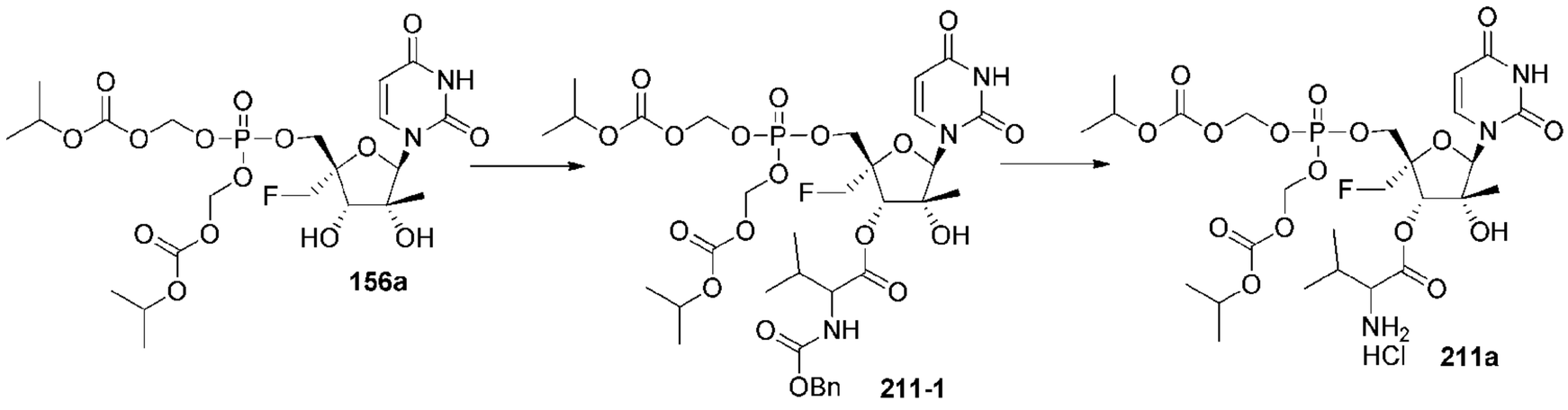


[0940] To a solution of triethylammonium bis(isopropyloxycarbonyloxyethyl-1)phosphate (0.28 mmol, prepared from 100 mg of bis(isopropyloxycarbonyloxyethyl-1)phosphate and 40 μL of Et_3N) in THF was added **210-1** (60 mg, 0.18 mmol). The mixture

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 **210-2** (19 mg, 17%).

[0941] A solution of **210-2** (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 **210a** (5 mg, 26%). MS: m/z = 629 [M-1].

EXAMPLE 195
COMPOUND 211a



[0942] 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 **156a** (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 **211-1** (83 mg, 50%) as a colorless foam.

[0943] To a solution of **211-1** (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 **211a** (50 mg) as a white solid. MS: m/z = 702 [M+1].

EXAMPLE 196
Preparation of Triphosphates

[0944] 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 a bath temperature of 42^0C, and then cooled down to R.T. 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 R.T. for 40 mins. The reaction was controlled by LCMS and monitored by the appearance of the corresponding nucleoside 5'-monophosphate. After more than 50% of transformation was achieved, 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 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.

[0945] Compound **213a**: Nucleoside 5'-triphosphates with a 4'-azidoalkyl group were dissolved in water (0.1 mL), methanol (3 mL) was added followed by 10% Pd/C (3 mg). Hydrogen was bubbled through the solution for 2 h. 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 methanol from 0 to 20% in 50mM triethylammonium acetate buffer (pH 7.5) was used for elution. The corresponding fractions were combined, concentrated and lyophilized 3 times to remove excess of buffer.

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CONTENANT LES PAGES	1	À	398

NOTE : Pour les tomes additionels, veuillez contacter le Bureau canadien des brevets

JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME	1	OF	2
CONTAINING PAGES	1	TO	398

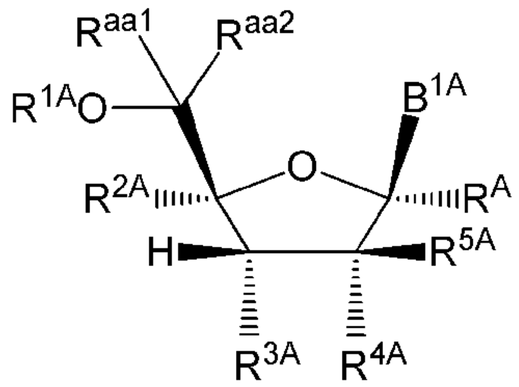
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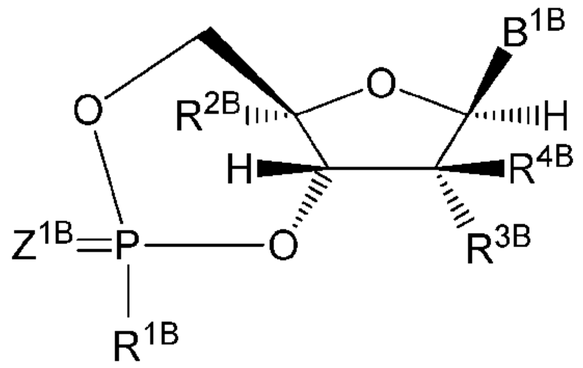
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WHAT IS CLAIMED IS:

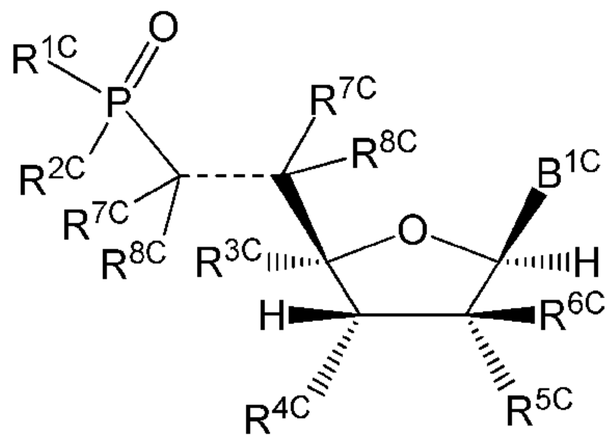
1. Use of an effective amount of a compound selected from Formula (I), Formula (II) and Formula (III), or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition of containing a compound selected from Formula (I), Formula (II) and Formula (III), or a pharmaceutically acceptable salt of the foregoing, in the preparation of a medicament for ameliorating, treating or preventing a norovirus infection:



(I)



(II)



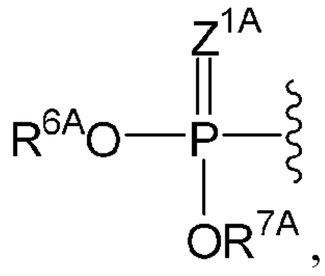
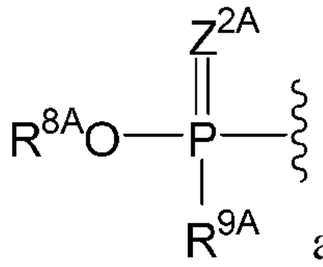
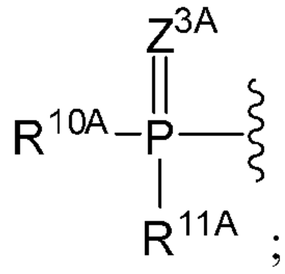
(III)

wherein:

B^{1A}, B^{1B} and B^{1C} are independently an optionally substituted heterocyclic base or an optionally substituted heterocyclic base with a protected amino group;

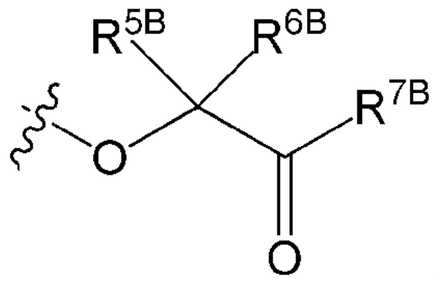
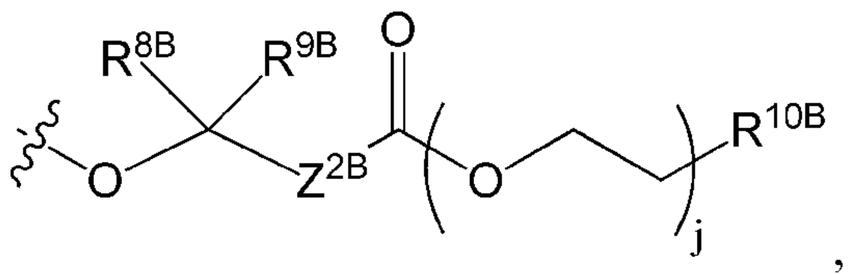
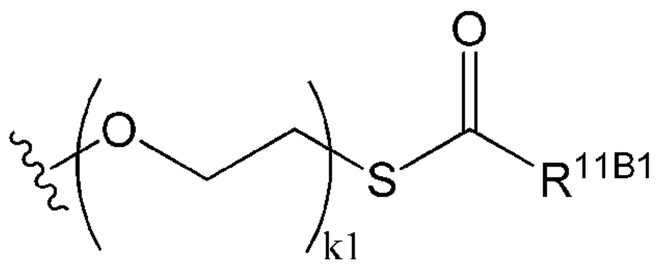
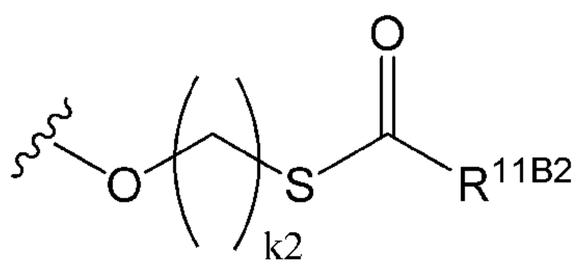
R^{aa1} and R^{aa2} are independently hydrogen or deuterium;

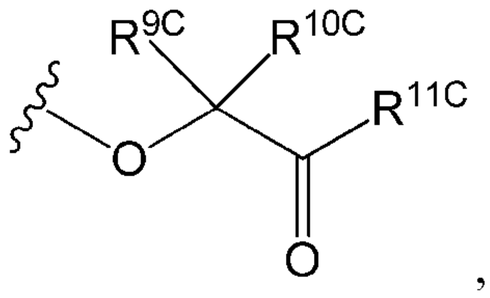
R^{A} is hydrogen, deuterium, an unsubstituted C_{1-3} alkyl, an unsubstituted C_{2-4} alkenyl, an unsubstituted C_{2-3} alkynyl or cyano;

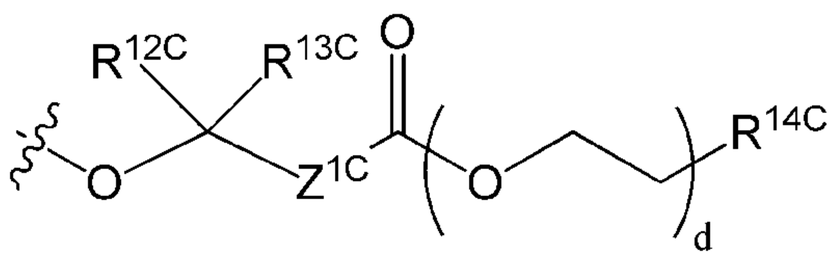
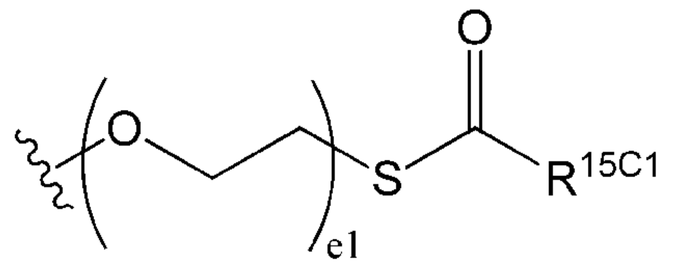
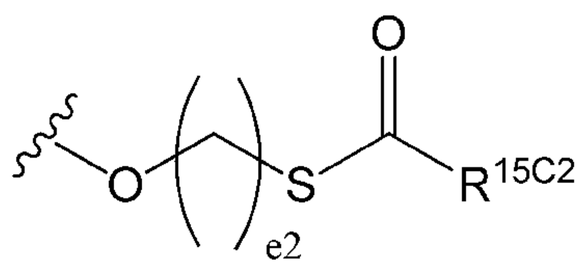
R^{1A} is selected from the group consisting of hydrogen, an optionally substituted acyl, an optionally substituted O-linked amino acid, ,  and ;

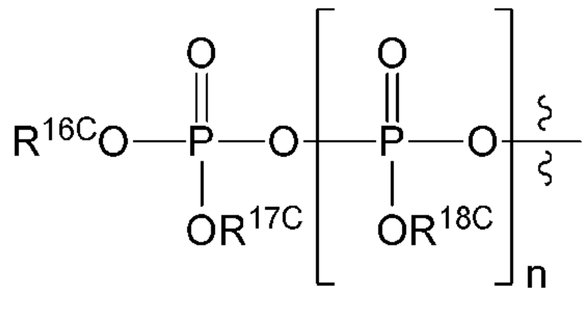
R^{2A} is selected from the group consisting of hydrogen, halogen, azido, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{2-6} alkynyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted –O–C_{1-6} alkyl, an optionally substituted –O–C_{3-6} alkenyl, an optionally substituted –O–C_{3-6} alkynyl and cyano;

R^{3A} is selected from the group consisting of halogen, OH, –OC(=O)$R^{"A}$ and an optionally substituted O-linked amino acid;

R^{1B} is selected from the group consisting of O^-, OH, an optionally substituted C_{1-6} alkoxy, , , , , an optionally substituted N-linked amino acid and an optionally substituted N-linked amino acid ester derivative;

R^{1C} and R^{2C} are independently selected from the group consisting of O^-, OH, an optionally substituted C_{1-6} alkoxy, ,


,

,

, an optionally substituted N-linked amino acid and an optionally substituted N-linked amino acid ester derivative; or

R^{1C} is  and R^{2C} is O^- or OH;

R^{2B} and R^{3C} are independently selected from the group consisting of halogen, 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 –O–C_{1-6} alkyl, an optionally substituted –O–C_{3-6} alkenyl, an optionally substituted –O–C_{3-6} alkynyl and cyano;

R^{4C} is selected from the group consisting of OH, –OC(=O)$R^{"C}$ and an optionally substituted O-linked amino acid;

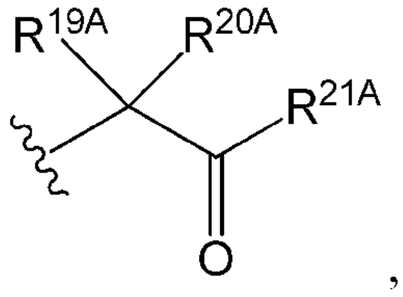
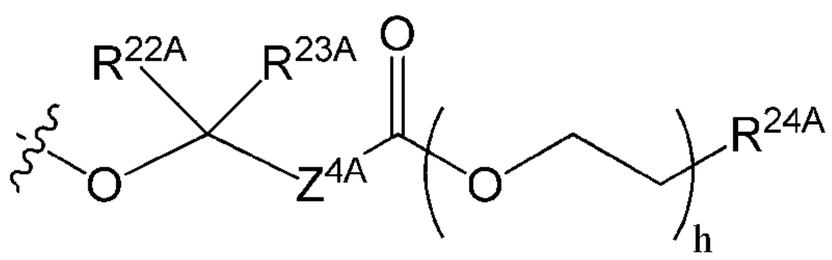
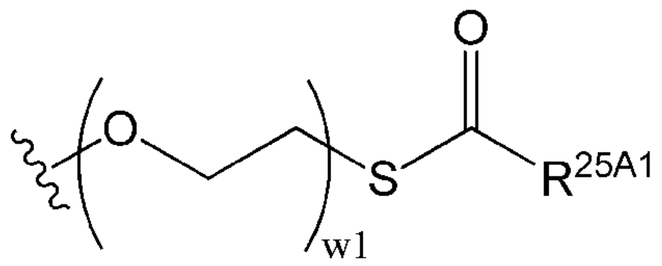
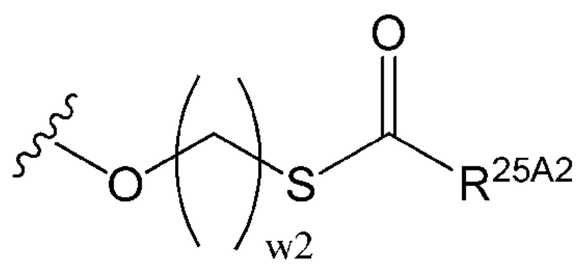
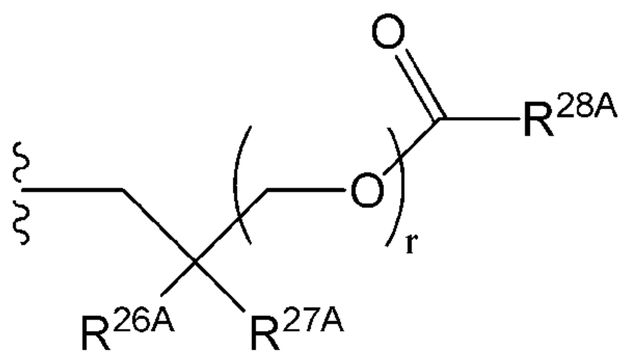
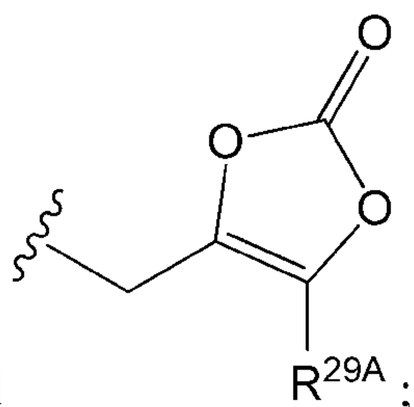
R^{4A}, R^{3B} and R^{5C} are independently selected from the group consisting of hydrogen, halogen, OR^{1D}, an optionally substituted O-linked amino acid, azido and $NR^{2D}R^{3D}$;

R^{1D} is hydrogen or –C(=O)$R^{"D}$;

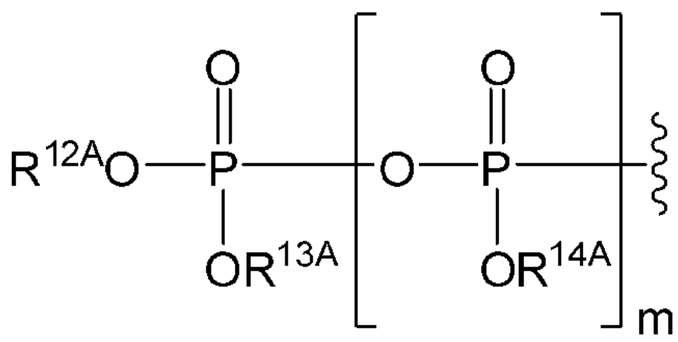
R^{2D} and R^{3D} are independently hydrogen or an optionally substituted C_{1-6} alkyl;

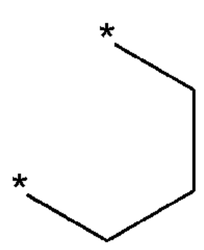
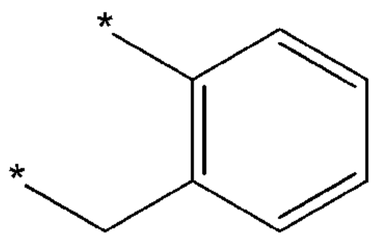
R^{5A}, R^{4B} and R^{6C} are independently selected from the group consisting of hydrogen, halogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl and an optionally substituted C_{2-6} alkynyl;

R^{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;.

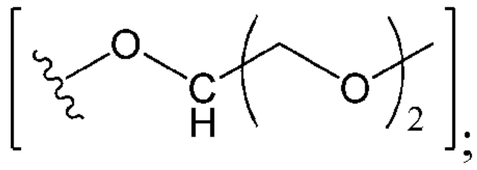
R^{9A} is independently selected from the group consisting of an optionally substituted C_{1-24} alkyl, an optionally substituted C_{2-24} alkenyl, an optionally substituted C_{2-24} alkynyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted C_{3-6} cycloalkenyl, $NR^{30A}R^{31A}$, 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}, R^{13A} and R^{14A} are independently absent or hydrogen;

each R^{15A}, each R^{16A}, each R^{17A} and each R^{18A} are independently hydrogen, an optionally substituted C_{1-24} alkyl or alkoxy;

R^{19A}, R^{20A}, R^{22A}, R^{23A}, R^{5B}, R^{6B}, R^{8B}, R^{9B}, R^{9C}, R^{10C}, R^{12C} and R^{13C} are independently selected from the group consisting of hydrogen, an optionally substituted C_{1-24} alkyl and an optionally substituted aryl;

R^{21A}, R^{24A}, R^{7B}, R^{10B}, R^{11C} and R^{14C} 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^{25A1}, R^{25A2}, R^{29A}, R^{11B1}, R^{11B2}, R^{15C1} and R^{15C2} are independently selected from the group consisting of hydrogen, an optionally substituted C_{1-24} alkyl and an optionally substituted aryl;

R^{16C}, R^{17C} and R^{18C} are independently absent or hydrogen;

R^{26A} and R^{27A} are independently -C≡N or an optionally substituted substituent selected from the group consisting of C_{2-8} organylcarbonyl, C_{2-8} alkoxycarbonyl and 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 and an optionally substituted C_{3-6} cycloalkenyl;

for Formula (III), ------- is a single bond or a double bond;

when ------- is a single bond, each R^{7C} and each R^{8C} is independently hydrogen or halogen; and

when ------- is a double bond, each R^{7C} is absent and each R^{8C} is independently hydrogen or halogen;

$R^{"A}$, $R^{"C}$ and $R^{"D}$ are independently an optionally substituted C_{1-24}-alkyl;

d, j and h are independently 1 or 2;

e1, k1 and w1 are independently 0 or 1;

e2, k2 and w2 are independently 3, 4 or 5;

m and n are independently 0 or 1;

p and q are independently selected from the group consisting of 1, 2 and 3;

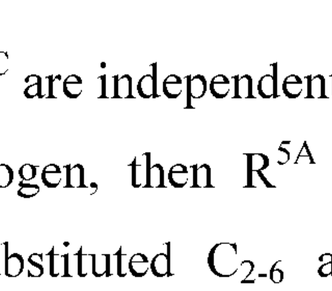
r is 1 or 2;

Z^{1A}, Z^{2A}, Z^{3A}, Z^{4A}, Z^{1B}, Z^{2B} and Z^{1C} are independently O or S;. and

provided that when R^{2A} is hydrogen, then R^{5A} is halogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl and an optionally substituted C_{2-6} alkynyl; and

provided that the compound of Formula (I), or a pharmaceutically acceptable salt thereof, cannot be selected from the group consisting of 2'-C-methylcytidine, ribavirin, β-d-N^4-hydroxycytidine, 2'-F-2'-methylcytidine, 2-thiouridine, 6-aza-uridine, 5-nitrocytidine and 2'-amino-2'-deoxycytidine, or a mono-, a di- or a tri-phosphate of the foregoing.

2. The use of Claim 1, wherein the compound is a compound of Formula (I).

3. The use of Claim 2, wherein R^{1A} is .

4. The use of Claim 3, wherein R^{6A} and R^{7A} are both hydrogen or absent.

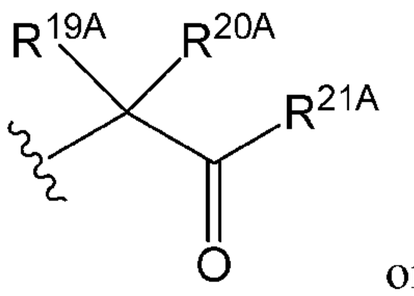
5. The use of Claim 3, wherein one of R^{6A} and R^{7A} is hydrogen, and the other of R^{6A} and R^{7A} is selected from the group consisting of an optionally substituted C_{1-24} alkyl, an optionally substituted C_{2-24} alkenyl, an optionally substituted C_{2-24} alkynyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted C_{3-6} cycloalkenyl, an optionally substituted aryl, an optionally substituted heteroaryl and an optionally substituted aryl(C_{1-6} alkyl).

6. The use of Claim 5, wherein the other of R^{6A} and R^{7A} is an optionally substituted C_{1-24} alkyl.

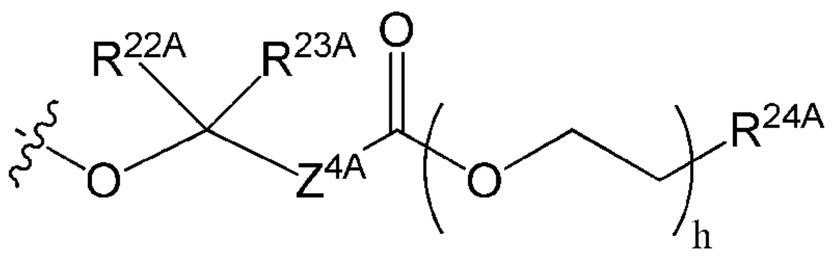
7. The use of Claim 3, wherein both R^{6A} and R^{7A} are independently selected from the group consisting of an optionally substituted C_{1-24} alkyl, an optionally substituted C_{2-24} alkenyl, an optionally substituted C_{2-24} alkynyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted C_{3-6} cycloalkenyl, an optionally substituted aryl, an optionally substituted heteroaryl and an optionally substituted aryl(C_{1-6} alkyl).

8. The use of Claim 7, wherein both R^{6A} and R^{7A} are an optionally substituted C_{1-24} alkyl.

9. The use of Claim 3, wherein at least one of R^{6A} and R^{7A} is

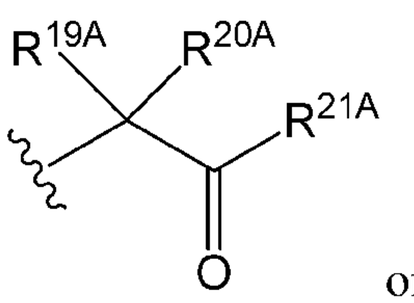


or

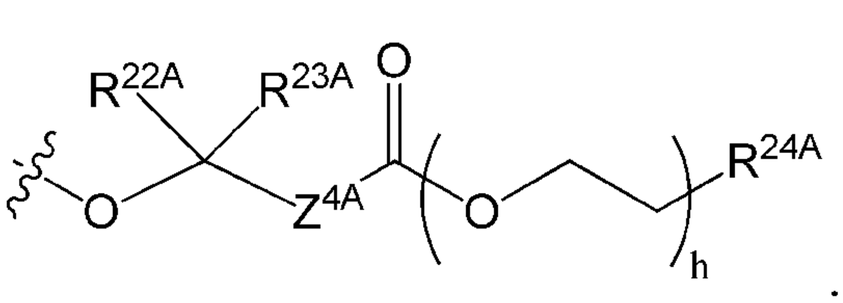


; and the other of R^{6A} and R^{7A} is selected from the group consisting of absent, hydrogen, an optionally substituted C_{1-24} alkyl, an optionally substituted C_{2-24} alkenyl, an optionally substituted C_{2-24} alkynyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted C_{3-6}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

10. The use of Claim 3, wherein both R^{6A} and R^{7A} are independently



or



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11. The use of Claim 3, wherein R^{6A} and R^{7A} are both an optionally substituted C_{1-24} alkyl.

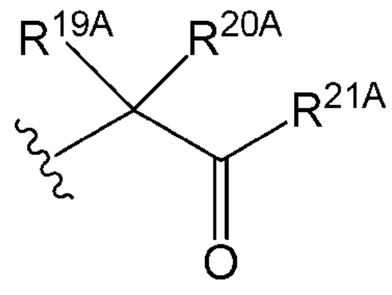
12. The use of Claim 3, wherein R^{6A} and R^{7A} are both an optionally substituted C_{2-24} alkenyl.

13. The use of Claim 3, wherein R^{6A} and R^{7A} are both *–$(CR^{15A}R^{16A})_p$–O–C_{1-24} alkyl.

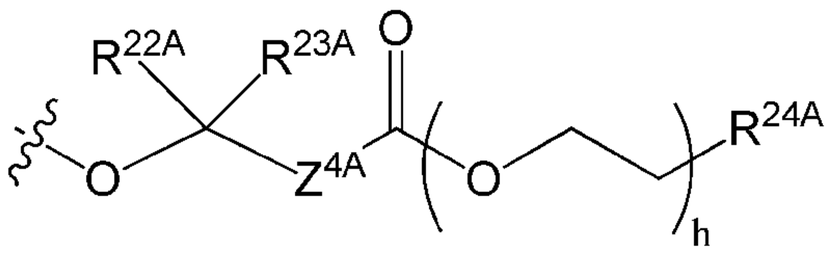
14. The use of Claim 3, wherein R^{6A} and R^{7A} are both *–$(CR^{17A}R^{18A})_q$–O–C_{2-24} alkenyl.

15. The use of Claim 3, wherein R^{6A} and R^{7A} are both an optionally substituted aryl.

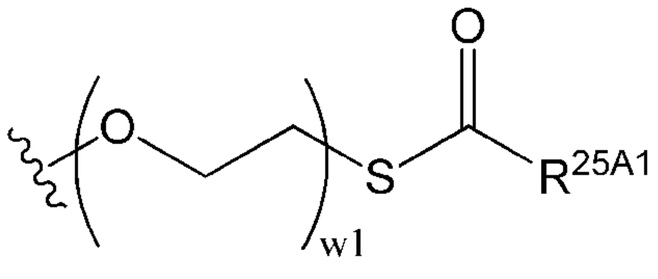
16. The use of Claim 3, wherein R^{6A} and R^{7A} are both an optionally substituted aryl(C_{1-6} alkyl).

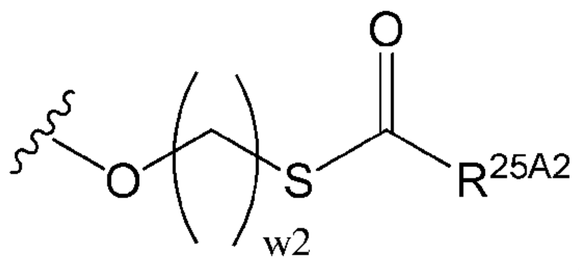
17. The use of Claim 3, wherein R^{6A} and R^{7A} are both 

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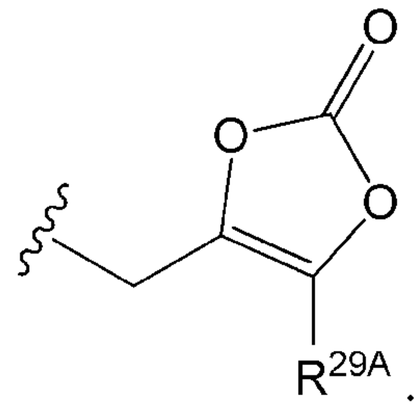
18. The use of Claim 3, wherein R^{6A} and R^{7A} are both 

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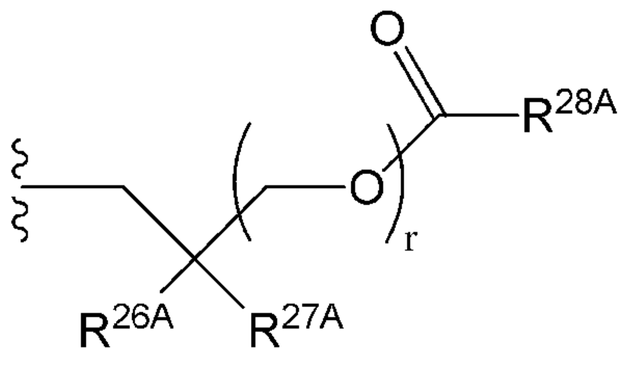
19. The use of Claim 3, wherein R^{6A} and R^{7A} are both 

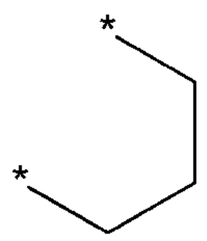
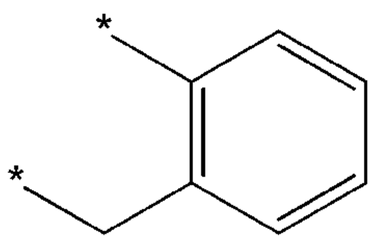
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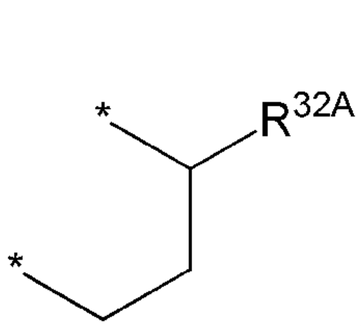
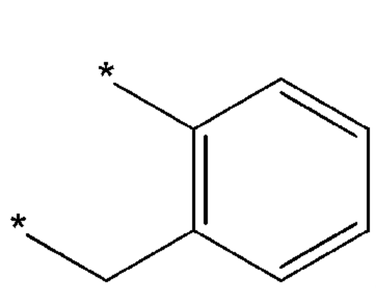
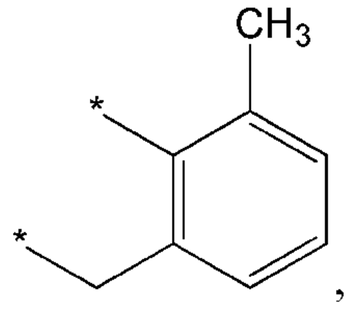
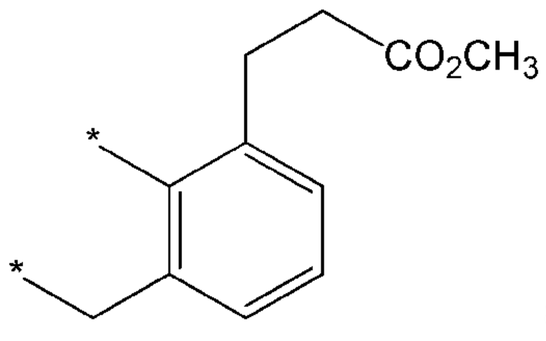
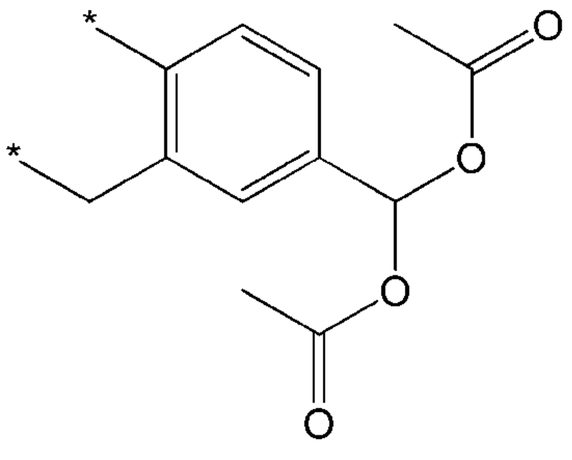
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20. The use of Claim 3, wherein R^{6A} and R^{7A} are both 

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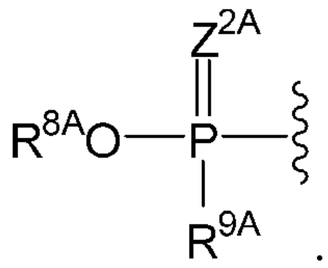
21. The use of Claim 3, wherein R^{6A} and R^{7A} are both .

22. The use of Claim 3, 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.

23. The use of Claim 22, wherein R^{6A} and R^{7A} are taken together to form a moiety selected from the group consisting of , , ,  and , wherein R^{32A} is an optionally substituted aryl, an optionally substituted heteroaryl or an optionally substituted heterocyclyl.

24. The use of any one of Claims 2 to 23, wherein Z^{1A} is O.

25. The use of any one of Claims 2 to 23, wherein Z^{1A} is S.

26. The use of Claim 2, wherein R^{1A} is .

27. The use of Claim 26, wherein R^{8A} is 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 and an optionally substituted C_{3-6} cycloalkenyl; and 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 and an optionally substituted C_{3-6} cycloalkenyl.

28. The use of Claim 27, wherein R^{8A} is hydrogen, and R^{9A} is an optionally substituted C_{1-6} alkyl.

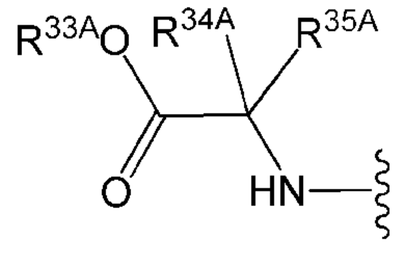
29. The use of Claim 26, wherein R^{8A} is hydrogen, and R^{9A} is $NR^{30A}R^{31A}$, wherein R^{30} and R^{31} are independently selected from the group consisting of hydrogen, an optionally substituted C_{1-24} alkyl, an optionally substituted C_{2-24} alkenyl, an optionally substituted C_{2-24} alkynyl, an optionally substituted C_{3-6} cycloalkyl and an optionally substituted C_{3-6} cycloalkenyl.

30. The use of Claim 26, wherein R^{8A} is absent or hydrogen; and R^{9A} is an optionally substituted N-linked amino acid or an optionally substituted N-linked amino acid ester derivative.

31. The use of Claim 26, wherein R^{8A} is an optionally substituted aryl; and R^{9A} is an optionally substituted N-linked amino acid or an optionally substituted N-linked amino acid ester derivative.

32. The use of Claim 30 or 31, wherein R^{9A} is selected from the group consisting of alanine, asparagine, aspartate, cysteine, glutamate, glutamine, glycine, proline, serine, tyrosine, arginine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, valine and ester derivatives thereof.

33. The use of Claim 32, wherein R^{9A} is selected from the group consisting of alanine isopropyl ester, alanine cyclohexyl ester, alanine neopentyl ester, valine isopropyl ester and leucine isopropyl ester.

34. The use of Claim 30 or 31, wherein R^{9A} has the structure 

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.

35. The use of Claim 34, wherein R^{34A} is an optionally substituted C_{1-6}-alkyl.

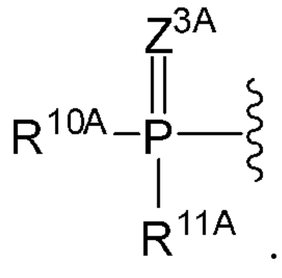
36. The use of Claim 35, wherein the optionally substituted C_{1-6}-alkyl is methyl.

37. The use of any one of Claims 34 to 36, wherein R^{35A} is hydrogen.

38. The use of any one of Claims 34 to 37, wherein R^{33A} is an optionally substituted C_{1-6} alkyl, an optionally substituted C_{3-6} cycloalkyl or an optionally substituted benzyl.

39. The use of any one of Claims 26 to 38, wherein Z^{2A} is O.

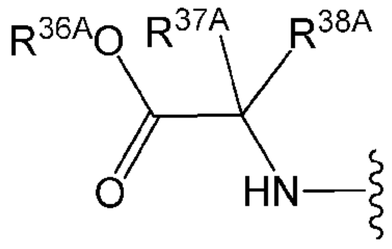
40. The use of any one of Claims 26 to 38, wherein Z^{2A} is S.

41. The use of Claim 2, wherein R^{1A} is  .

42. The use of Claim 41, wherein R^{10A} and R^{11A} are both an optionally substituted N-linked amino acid or an optionally substituted N-linked amino acid ester derivative.

43. The use of Claim 42, wherein R^{10A} and R^{11A} are independently selected from the group consisting of alanine, asparagine, aspartate, cysteine, glutamate, glutamine, glycine, proline, serine, tyrosine, arginine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, valine and ester derivatives thereof.

44. The use of Claim 43, wherein R^{10A} and R^{11A} are independently selected from the group consisting of alanine isopropyl ester, alanine cyclohexyl ester, alanine neopentyl ester, valine isopropyl ester and leucine isopropyl ester.

45. The use of Claim 42, wherein R^{10A} and R^{11A} are independently have the structure  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.

46. The use of Claim 45, wherein R^{37A} is an optionally substituted C_{1-6}-alkyl.

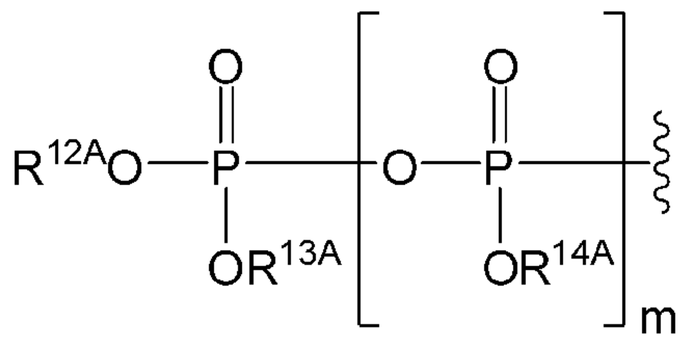
47. The use of Claim 46, wherein the optionally substituted C_{1-6}-alkyl is methyl.

48. The use of any one of Claims 45 to 47, wherein R^{38A} is hydrogen.

49. The use of any one of Claims 45 to 48, wherein R^{36A} is an optionally substituted C_{1-6} alkyl, an optionally substituted C_{3-6} cycloalkyl or an optionally substituted benzyl.

50. The use of any one of Claims 41 to 49, wherein Z^{3A} is O.

51. The use of any one of Claims 41 to 49, wherein Z^{3A} is S.

52. The use of Claim 2, wherein R^{1A} is .

53. The use of Claim 52, wherein m is 0, and R^{12A} and R^{13A} are independently absent or hydrogen.

54. The use of Claim 52, wherein m is 1, and R^{12A}, R^{13A} and R^{14A} are independently absent or hydrogen.

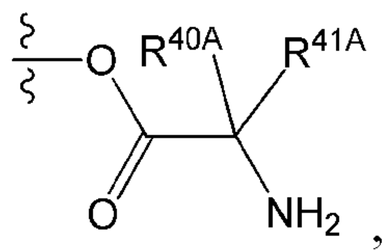
55. The use of Claim 2, wherein R^{1A} is H.

56. The use of Claim 2, wherein R^{1A} is an optionally substituted acyl.

57. The use of Claim 56, wherein the optionally substituted acyl is $-C(=O)R^{39A}$, wherein R^{39A} is selected from the group consisting of 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).

58. The use of Claim 57, wherein R^{39A} is substituted or unsubstituted C_{1-12} alkyl.

59. The use of Claim 2, wherein R^{1A} is an optionally substituted O-linked amino acid.

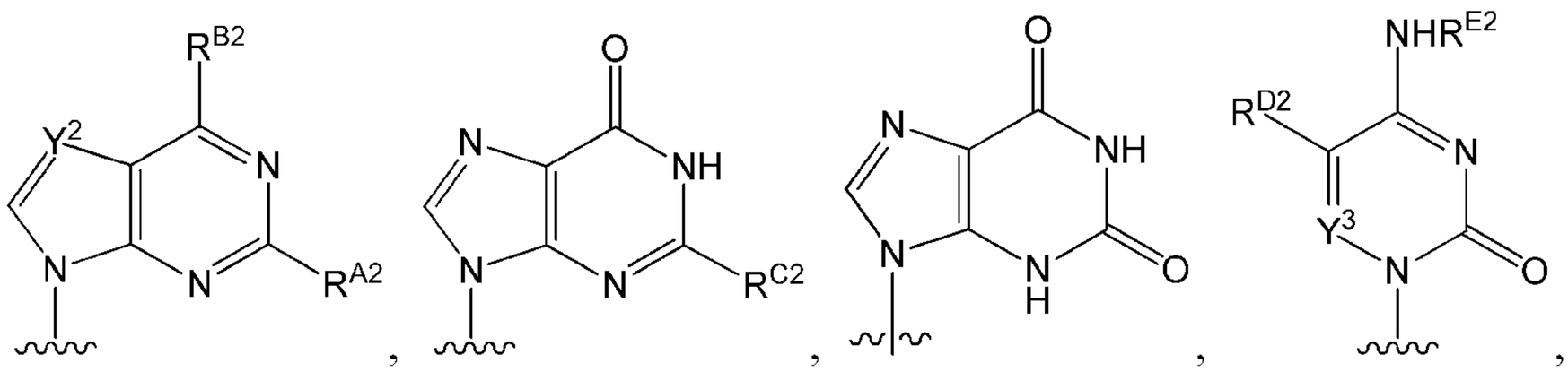
60. The use of Claim 2, wherein R^{1A} is , wherein R^{40A} is selected from the group consisting of hydrogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{1-6} haloalkyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted C_6 aryl, an optionally substituted C_{10} aryl and an optionally substituted aryl(C_{1-6} alkyl); and R^{41A} is hydrogen or an optionally substituted C_{1-4}-alkyl; or R^{40A} and R^{41A} are taken together to form an optionally substituted C_{3-6} cycloalkyl.

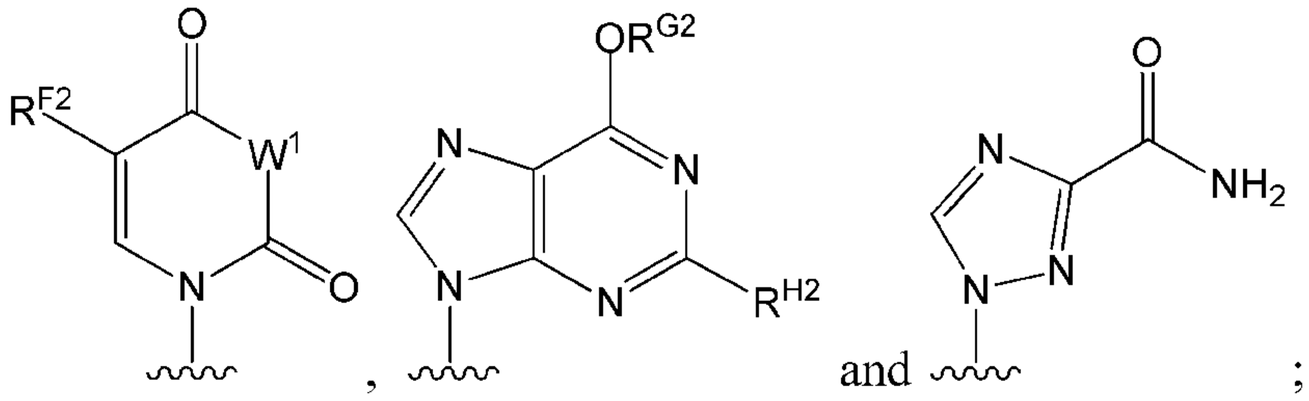
61. The use of Claim 60, wherein R^{40A} is an optionally substituted C_{1-6}-alkyl.

62. The use of Claim 61, wherein the optionally substituted C_{1-6}-alkyl is methyl.

63. The use of any one of Claims 60 to 62, wherein R^{41A} is hydrogen.

64. The use of any one of Claims 2 to 63, 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;

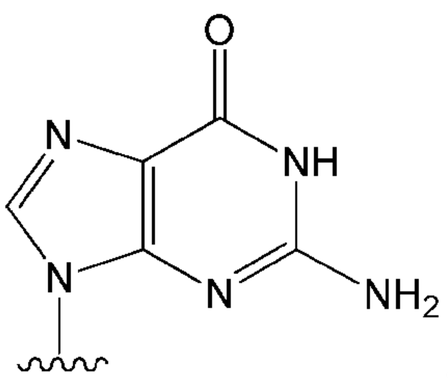
Y^2 and Y^3 are independently N or CR^{I2}, wherein R^{I2} is selected from the group consisting of hydrogen, halogen, an optionally substituted C_{1-6}-alkyl, an optionally substituted C_{2-6}-alkenyl and an optionally substituted C_{2-6}-alkynyl;

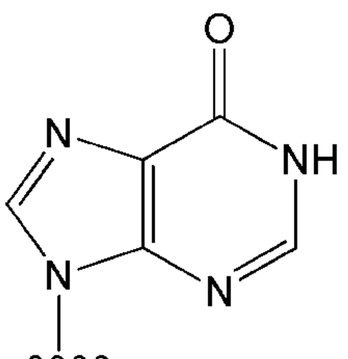
W^1 is NH or $–NCH_2$-OC(=O)$CH(NH_2)$-$CH(CH_3)_2$;

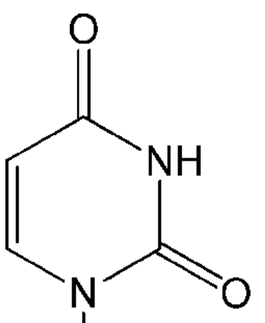
R^{G2} is an optionally substituted C_{1-6} alkyl;

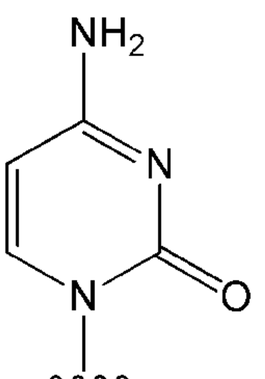
R^{H2} is hydrogen or NHR^{T2}, wherein R^{T2} is independently selected from the group consisting of hydrogen, -C(=O)R^{U2} and $–C(=O)OR^{V2}$; and

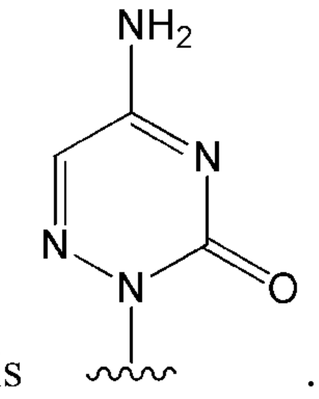
R^{K2}, R^{L2}, R^{M2}, R^{N2}, R^{P2}, R^{Q2} R^{R2}, $R^{S2,}$ R^{U2} and R^{V2} are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkenyl, C_{6-10} aryl, heteroaryl, heteroalicyclyl, aryl(C_{1-6} alkyl),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

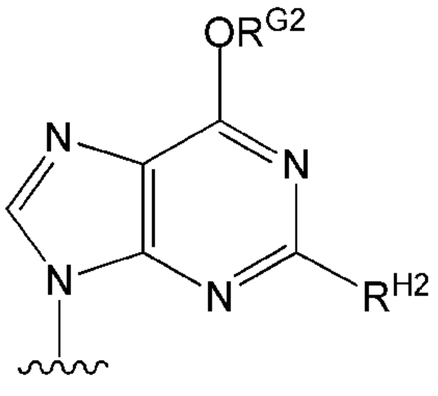
65. The use of Claim 64, wherein B^{1A} is .

66. The use of Claim 64, wherein B^{1A} is .

67. The use of Claim 64, wherein B^{1A} is .

68. The use of Claim 64, wherein B^{1A} is .

69. The use of Claim 64, wherein B^{1A} is .

70. The use of Claim 64, wherein B^{1A} is .

71. The use of any one of Claims 2 to 70, wherein R^{2A} is hydrogen.

72. The use of any one of Claims 2 to 70, wherein R^{2A} is halogen.

73. The use of any one of Claims 2 to 70, wherein R^{2A} is azido.

74. The use of any one of Claims 2 to 70, wherein R^{2A} is an optionally substituted C_{1-6} alkyl.

75. The use of any one of Claims 2 to 70, wherein R^{2A} is an optionally substituted C_{2-6} alkenyl.

76. The use of any one of Claims 2 to 70, wherein R^{2A} is an optionally substituted C_{2-6} alkynyl.

77. The use of any one of Claims 2 to 70, wherein R^{2A} is an optionally substituted C_{3-6} cycloalkyl.

78. The use of any one of Claims 2 to 70, wherein R^{2A} is an optionally substituted $-O-C_{1-6}$ alkyl.

79. The use of any one of Claims 2 to 70, wherein R^{2A} is an optionally substituted $-O-C_{3-6}$ alkenyl.

80. The use of any one of Claims 2 to 70, wherein R^{2A} is an optionally substituted $-O-C_{3-6}$ alkynyl.

81. The use of any one of Claims 2 to 70, wherein R^{2A} is unsubstituted C_{1-6} alkyl, unsubstituted C_{2-6} alkenyl, unsubstituted C_{2-6} alkynyl, unsubstituted $-O-C_{1-6}$ alkyl, unsubstituted $-O-C_{3-6}$ alkenyl or unsubstituted $-O-C_{3-6}$ alkynyl.

82. The use of any one of Claims 2 to 70, wherein R^{2A} is cyano.

83. The use of any one of Claims 2 to 82, wherein R^{3A} is halogen.

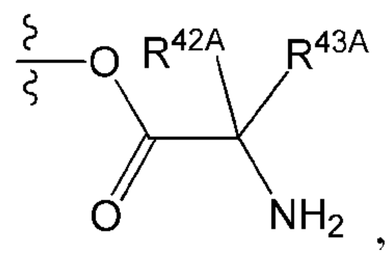
84. The use of any one of Claims 2 to 82, wherein R^{3A} is OH.

85. The use of any one of Claims 2 to 82, wherein R^{3A} is $-OC(=O)R^{"A}$.

86. The use of Claim 85, wherein $R^{"A}$ is an optionally substituted C_{1-8} alkyl.

87. The use of any one of Claims 2 to 82, wherein R^{3A} is O-linked amino acid.

88. The use of Claim 87, wherein the O-linked amino acid is selected from the group consisting of alanine, asparagine, aspartate, cysteine, glutamate, glutamine, glycine, proline, serine, tyrosine, arginine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, valine, ornithine, hypusine, 2-aminoisobutyric acid, dehydroalanine, gamma-aminobutyric acid, citrulline, beta-alanine, alpha-ethyl-glycine, alpha-propyl-glycine and norleucine.

89. The use of any one of Claims 2 to 82, wherein R^{3A} is , wherein R^{42A} 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^{43A} is hydrogen or an optionally substituted C_{1-4}-alkyl; or R^{42A} and R^{43A} are taken together to form an optionally substituted C_{3-6} cycloalkyl.

90. The use of Claim 89, wherein R^{42A} is an optionally substituted C_{1-6}-alkyl.

91. The use of Claim 90, wherein the optionally substituted C_{1-6}-alkyl is methyl.

92. The use of any one of Claims 89 to 91, wherein R^{43A} is hydrogen.

93. The use of any one of Claims 2 to 92, wherein R^{5A} is hydrogen.

94. The use of any one of Claims 2 to 92, wherein R^{5A} is halogen.

95. The use of Claim 94, wherein R^{5A} is fluoro.

96. The use of any one of Claims 2 to 92, wherein R^{5A} is an optionally substituted C_{1-6} alkyl.

97. The use of any one of Claims 2 to 92 wherein R^{5A} is an optionally substituted C_{2-6} alkenyl.

98. The use of any one of Claims 2 to 92, wherein R^{5A} is an optionally substituted C_{2-6} alkynyl.

99. The use of any one of Claims 2 to 98, wherein R^{4A} is hydrogen.

100. The use of any one of Claims 2 to 98, wherein R^{4A} is halogen.

101. The use of Claim 100, wherein R^{4A} is fluoro or chloro.

102. The use of any one of Claims 2 to 98, wherein R^{4A} is OR^{1D}.

103. The use of Claim 102, wherein R^{4A} is OH.

104. The use of Claim 102, wherein R^{4A} is $-OC(=O)R^{"D}$.

105. The use of any one of Claims 2 to 98, wherein R^{4A} is an optionally substituted O-linked amino acid.

106. The use of any one of Claims 2 to 98, wherein R^{4A} is azido.

107. The use of any one of Claims 2 to 98, wherein R^{4A} is $NR^{2D}R^{3D}$.

108. The use of any one of Claims 2 to 98, wherein R^{4A} is NH_2.

109. The use of any one of Claims 2 to 108, wherein R^{A} is hydrogen.

110. The use of any one of Claims 2 to 108, wherein R^{A} is deuterium.

111. The use of any one of Claims 2 to 108, wherein R^{A} is an unsubstituted C_{1-3} alkyl.

112. The use of any one of Claims 2 to 108, wherein R^{A} is an unsubstituted C_{2-4} alkenyl.

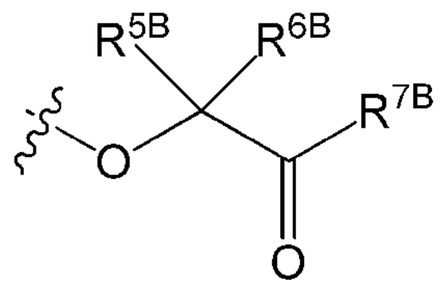
113. The use of any one of Claims 2 to 108, wherein R^{A} is an unsubstituted C_{2-3} alkynyl.

114. The use of any one of Claims 2 to 108, wherein R^{A} is cyano.

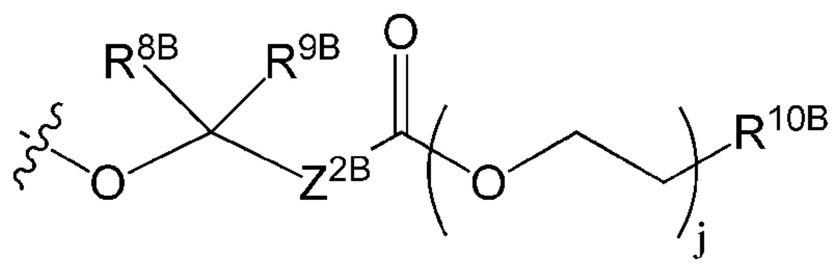
115. The use of Claim 1, wherein the compound is a compound of Formula (II).

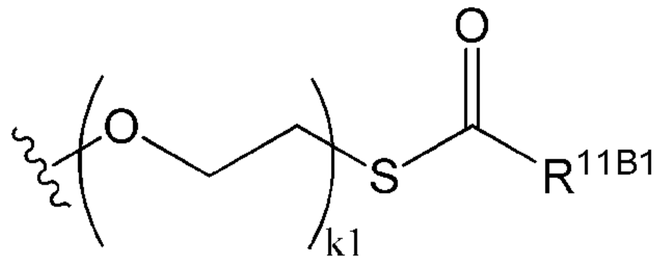
116. The use of Claim 115, wherein R^{1B} is O^{-} or OH.

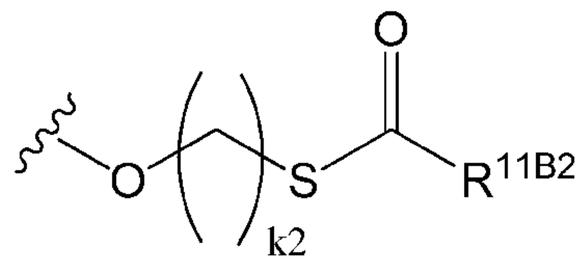
117. The use of Claim 115, wherein R^{1B} is an optionally substituted C_{1-6} alkoxy.

118. The use of Claim 115, wherein R^{1B} is 

.

119. The use of Claim 115, wherein R^{1B} is .

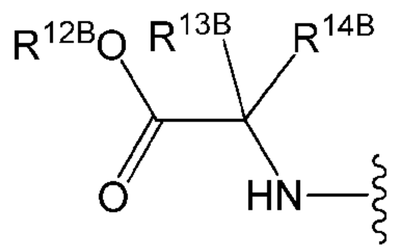
120. The use of Claim 115, wherein R^{1B} is .

121. The use of Claim 115, wherein R^{1B} is .

122. The use of Claim 115, wherein R^{1B} is an optionally substituted N-linked amino acid or an optionally substituted N-linked amino acid ester derivative.

123. The use of Claim 115, wherein R^{1B} is selected from the group consisting of alanine, asparagine, aspartate, cysteine, glutamate, glutamine, glycine, proline, serine, tyrosine, arginine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, valine and ester derivatives thereof.

124. The use of Claim 115, wherein R^{1B} is selected from the group consisting of alanine isopropyl ester, alanine cyclohexyl ester, alanine neopentyl ester, valine isopropyl ester and leucine isopropyl ester.

125. The use of Claim 115, wherein R^{1B} has the structure  wherein R^{12B} 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^{13B} 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^{14B} is

hydrogen or an optionally substituted C_{1-4}-alkyl; or R^{13B} and R^{14B} are taken together to form an optionally substituted C_{3-6} cycloalkyl.

126. The use of Claim 125, wherein R^{13B} is an optionally substituted C_{1-6}-alkyl.

127. The use of Claim 126, wherein the optionally substituted C_{1-6}-alkyl is methyl.

128. The use of any one of Claims 125 to 127, wherein R^{14B} is hydrogen.

129. The use of any one of Claims 125 to 128, wherein R^{12B} is an optionally substituted C_{1-6} alkyl, an optionally substituted C_{3-6} cycloalkyl or an optionally substituted benzyl.

130. The use of any one of Claims 115 to 129, wherein R^{2B} is halogen.

131. The use of any one of Claims 115 to 129, wherein R^{2B} is an optionally substituted C_{1-6} alkyl.

132. The use of any one of Claims 115 to 129, wherein R^{2B} is an optionally substituted C_{2-6} alkenyl.

133. The use of any one of Claims 115 to 129, wherein R^{2B} is an optionally substituted C_{2-6} alkynyl.

134. The use of any one of Claims 115 to 129, wherein R^{2B} is an optionally substituted –O–C_{1-6} alkyl.

135. The use of any one of Claims 115 to 129, wherein R^{2B} is an optionally substituted –O–C_{3-6} alkenyl.

136. The use of any one of Claims 115 to 129, wherein R^{2B} is an optionally substituted –O–C_{3-6} alkynyl.

137. The use of any one of Claims 115 to 129, wherein R^{2B} is an optionally substituted C_{3-6} cycloalkyl.

138. The use of any one of Claims 115 to 129, wherein R^{2B} is unsubstituted C_{1-6} alkyl, unsubstituted C_{2-6} alkenyl, unsubstituted C_{2-6} alkynyl, unsubstituted –O–C_{1-6} alkyl, unsubstituted –O–C_{3-6} alkenyl or unsubstituted –O–C_{3-6} alkynyl.

139. The use of any one of Claims 115 to 129, wherein R^{2B} is cyano.

140. The use of any one of Claims 115 to 139, wherein R^{4B} is hydrogen.

141. The use of any one of Claims 115 to 139, wherein R^{4B} is halogen.

142. The use of Claim 141, wherein R^{4B} is fluoro.

143. The use of any one of Claims 115 to 139, wherein R^{4B} is an optionally substituted C_{1-6} alkyl.

144. The use of any one of Claims 115 to 139, wherein R^{4B} is an optionally substituted C_{2-6} alkenyl.

145. The use of any one of Claims 115 to 139, wherein R^{4B} is an optionally substituted C_{2-6} alkynyl.

146. The use of any one of Claims 115 to 145, wherein R^{3B} is hydrogen.

147. The use of any one of Claims 115 to 145, wherein R^{3B} is halogen.

148. The use of Claim 147, wherein R^{3B} is fluoro or chloro.

149. The use of any one of Claims 115 to 145, wherein R^{3B} is OR^{1D}.

150. The use of Claim 149, wherein R^{3B} is OH.

151. The use of Claim 149, wherein R^{3B} is $-OC(=O)R^{"D}$.

152. The use of any one of Claims 115 to 145, wherein R^{3B} is an optionally substituted O-linked amino acid.

153. The use of any one of Claims 115 to 145, wherein R^{3B} is azido.

154. The use of any one of Claims 115 to 145, wherein R^{3B} is $NR^{2D}R^{3D}$.

155. The use of any one of Claims 115 to 145, wherein R^{3B} is NH_2.

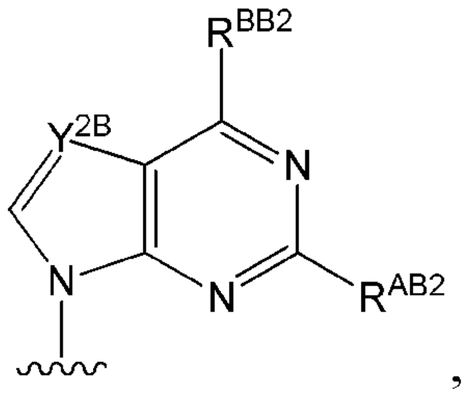
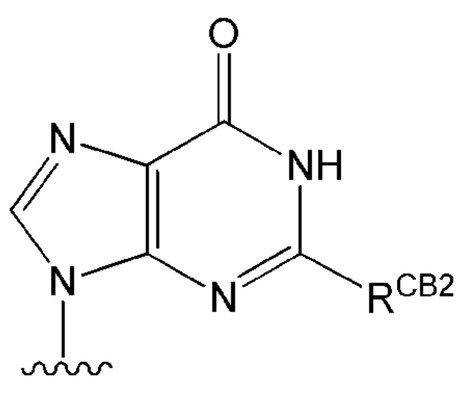
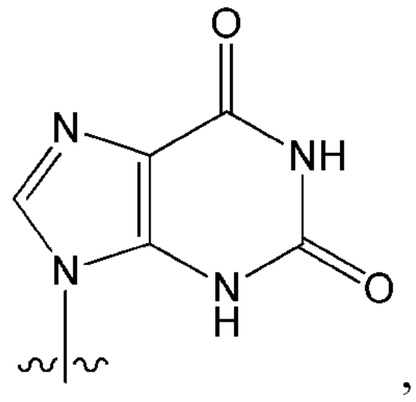
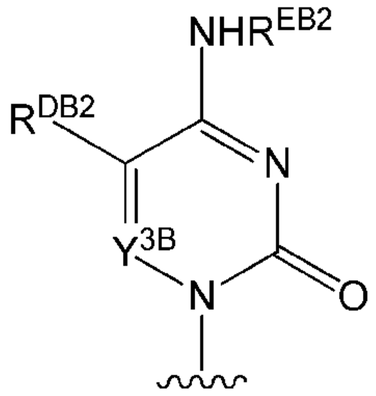
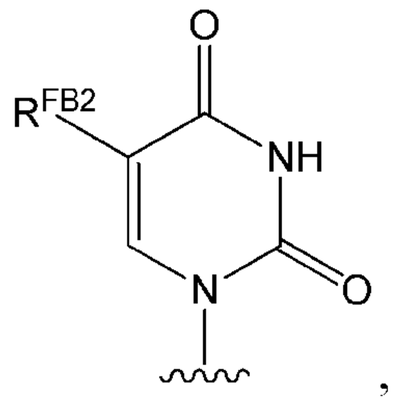
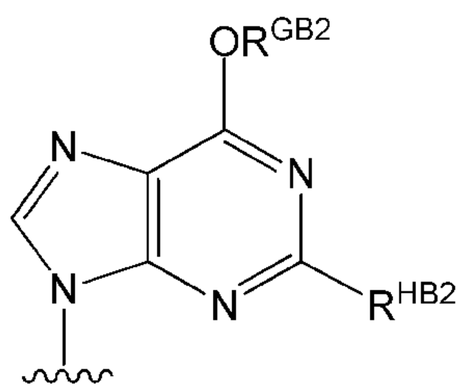
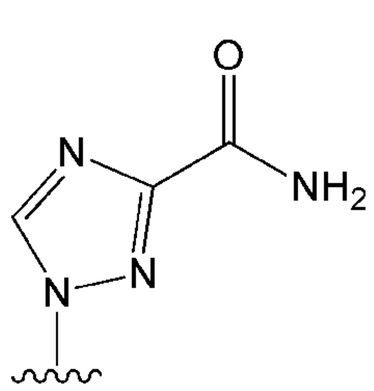
156. The use of any one of Claims 115 to 155, wherein R^{a1} and R^{a2} are both hydrogen.

157. The use of any one of Claims 115 to 155, wherein R^{a1} and R^{a2} are both deuterium.

158. The use of any one of Claims 115 to 157, wherein Z^{1B} is O.

159. The use of any one of Claims 115 to 157, wherein Z^{1B} is S.

160. The use of any one of Claims 115 to 159, wherein B^{1B} is selected from the group consisting of:


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,

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and

;

wherein:

R^{AB2} is selected from the group consisting of hydrogen, halogen and NHR^{JB2}, wherein R^{JB2} is selected from the group consisting of hydrogen, $-C(=O)R^{KB2}$ and $-C(=O)OR^{LB2}$;

R^{BB2} is halogen or NHR^{WB2}, wherein R^{WB2} 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, $-C(=O)R^{MB2}$ and $-C(=O)OR^{NB2}$;

R^{CB2} is hydrogen or NHR^{OB2}, wherein R^{OB2} is selected from the group consisting of hydrogen, $-C(=O)R^{PB2}$ and $-C(=O)OR^{QB2}$;

R^{DB2} 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^{EB2} is selected from the group consisting of hydrogen, hydroxy, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{3-8} cycloalkyl, $-C(=O)R^{RB2}$ and $-C(=O)OR^{SB2}$;

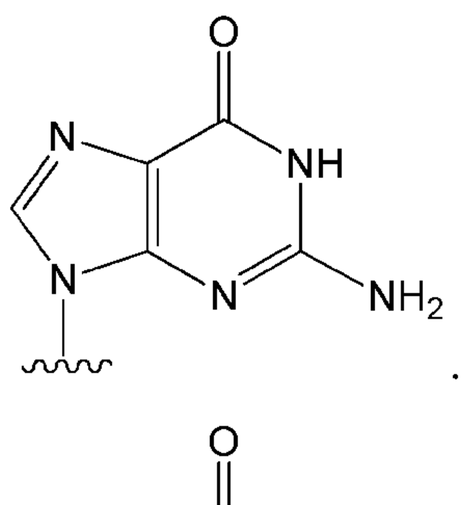
R^{FB2} is selected from the group consisting of hydrogen, halogen, an optionally substituted C_{1-6}alkyl, an optionally substituted C_{2-6} alkenyl and an optionally substituted C_{2-6} alkynyl;

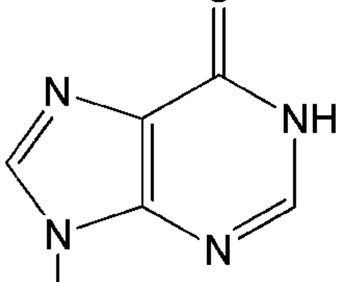
Y^{2B} and Y^{3B} are independently N or CR^{IB2}, wherein R^{IB2} is selected from the group consisting of hydrogen, halogen, an optionally substituted C_{1-6}-alkyl, an optionally substituted C_{2-6}-alkenyl and an optionally substituted C_{2-6}-alkynyl;

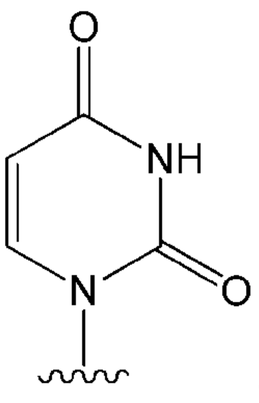
R^{GB2} is an optionally substituted C_{1-6} alkyl;

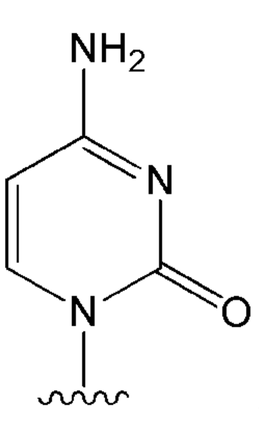
R^{HB2} is hydrogen or NHR^{TB2}, wherein R^{TB2} is independently selected from the group consisting of hydrogen, $-C(=O)R^{UB2}$ and $-C(=O)OR^{VB2}$; and

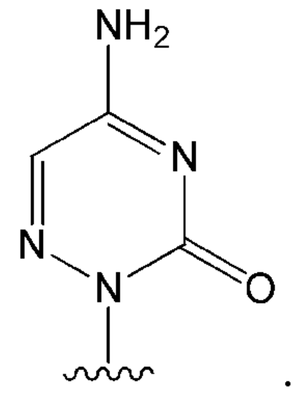
R^{KB2}, R^{LB2}, R^{MB2}, R^{NB2}, R^{PB2}, R^{QB2} R^{RB2}, $R^{SB2,}$ R^{UB2} and R^{VB2} are independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkenyl, C_{6-10} aryl, heteroaryl, heteroalicyclyl, aryl(C_{1-6} alkyl), heteroaryl(C_{1-6} alkyl) and heteroalicyclyl(C_{1-6} alkyl).

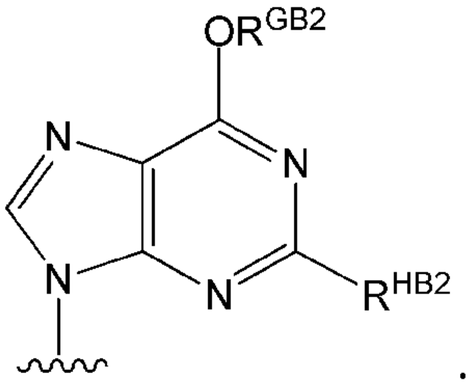
161. The use of Claim 160, wherein B^{1B} is .

162. The use of Claim 160, wherein B^{1B} is .

163. The use of Claim 160, wherein B^{1B} is .

164. The use of Claim 160, wherein B^{1B} is .

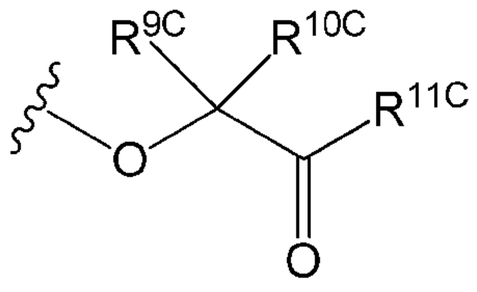
165. The use of Claim 160, wherein B^{1B} is .

166. The use of Claim 160, wherein B^{1B} is .

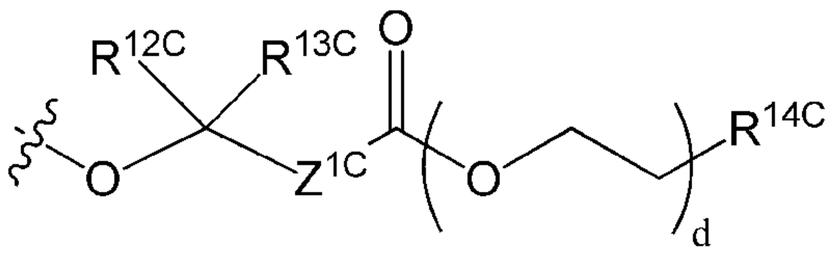
167. The use of Claim 1, wherein the compound is a compound of Formula (III).

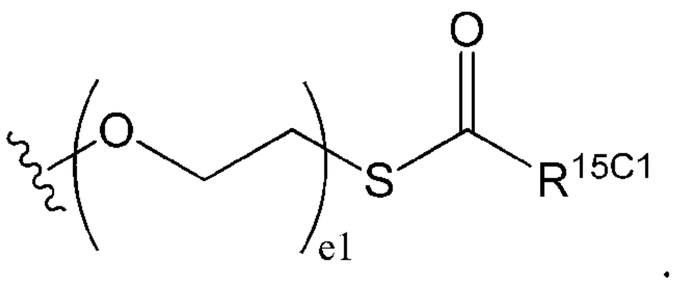
168. The use of Claim 167, wherein R^{1C} is O^- or OH.

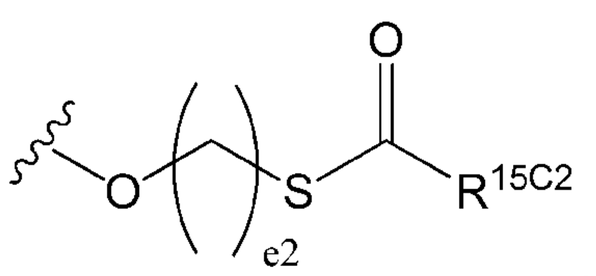
169. The use of Claim 167, wherein R^{1C} is an optionally substituted C_{1-6} alkoxy.

170. The use of Claim 167, wherein R^{1C} is .

171. The use of Claim 167, wherein R^{1C} is

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172. The use of Claim 167, wherein R^{1C} is .

173. The use of Claim 167, wherein R^{1C} is .

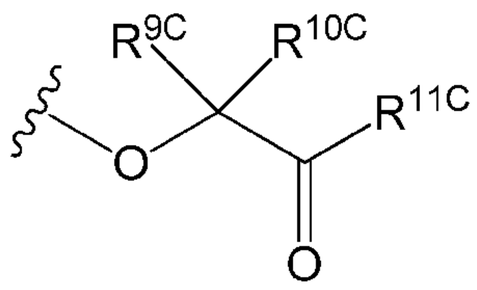
174. The use of Claim 167, wherein R^{1C} is an optionally substituted N-linked amino acid.

175. The use of Claim 167, wherein R^{1C} is an optionally substituted N-linked amino acid ester derivative.

176. The use of any one of Claims 167 to 175, wherein R^{2C} is O^- or OH.

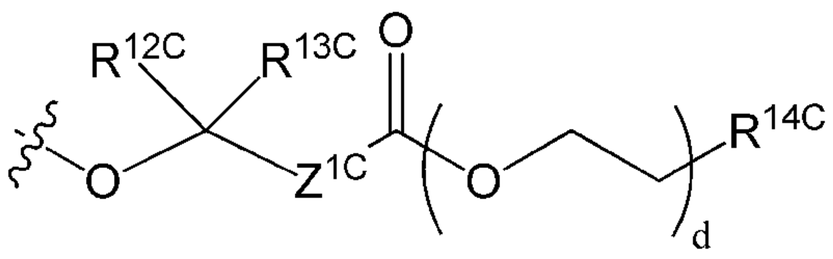
177. The use of any one of Claims 167 to 175, wherein R^{2C} is an optionally substituted C_{1-6} alkoxy.

178. The use of any one of Claims 167 to 175, wherein R^{2C} is



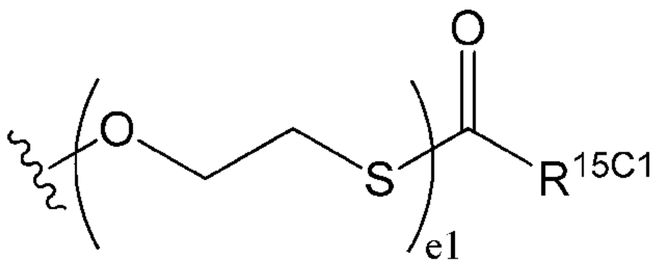
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179. The use of any one of Claims 167 to 175, wherein R^{2C} is



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180. The use of any one of Claims 167 to 175, wherein R^{2C} is

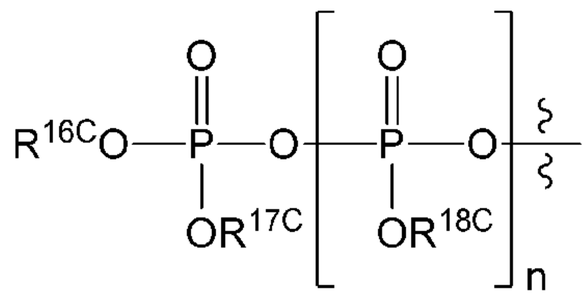


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181. The use of any one of Claims 167 to 175, wherein R^{2C} is an optionally substituted N-linked amino acid.

182. The use of any one of Claims 167 to 175, wherein R^{2C} is an optionally substituted N-linked amino acid ester derivative.

183. The use of any one of Claim 167, wherein R^{1C} is



and R^{2C} is O^- or OH; wherein R^{16C}, R^{17C} and R^{18C} is absent or hydrogen; and n is 0 or 1.

184. The use of any one of Claims 167 to 183, wherein R^{3C} is an optionally substituted C_{1-6} alkyl.

185. The use of any one of Claims 167 to 183, wherein R^{3C} is an optionally substituted C_{2-6} alkenyl.

186. The use of any one of Claims 167 to 183, wherein R^{3C} is an optionally substituted C_{2-6} alkynyl.

187. The use of any one of Claims 167 to 183, wherein R^{3C} is an optionally substituted –O–C_{1-6} alkyl.

188. The use of any one of Claims 167 to 183, wherein R^{3C} is an optionally substituted –O–C_{3-6} alkenyl.

189. The use of any one of Claims 167 to 183, wherein R^{3C} is an optionally substituted –O–C_{3-6} alkynyl.

190. The use of any one of Claims 167 to 183, wherein R^{3C} is an optionally substituted C_{3-6} cycloalkyl.

191. The use of any one of Claims 167 to 183, wherein R^{3C} is unsubstituted C_{1-6} alkyl. unsubstituted C_{2-6} alkenyl, unsubstituted C_{2-6} alkynyl, unsubstituted –O–C_{1-6} alkyl, unsubstituted –O–C_{3-6} alkenyl or unsubstituted –O–C_{3-6} alkynyl.

192. The use of any one of Claims 167 to 183, wherein R^{3C} is cyano.

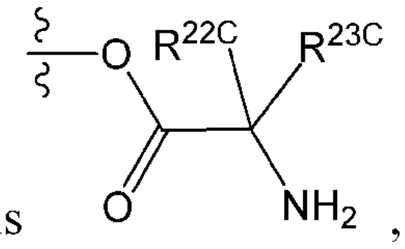
193. The use of any one of Claims 167 to 192, wherein R^{4C} is OH.

194. The use of any one of Claims 167 to 192, wherein R^{4C} is –OC(=O)$R^{"C}$.

195. The use of Claim 194, wherein $R^{"C}$ is an optionally substituted C_{1-8} alkyl.

196. The use of any one of Claims 167 to 192, wherein R^{4C} is O-linked amino acid.

197. The use of Claim 196, wherein the O-linked amino acid is selected from the group consisting of alanine, asparagine, aspartate, cysteine, glutamate, glutamine, glycine, proline, serine, tyrosine, arginine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, valine, ornithine, hypusine, 2-aminoisobutyric acid, dehydroalanine, gamma-aminobutyric acid, citrulline, beta-alanine, alpha-ethyl-glycine, alpha-propyl-glycine and norleucine.

198. The use of any one of Claims 167 to 192, wherein R^{4C} is , wherein R^{22C} 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^{23C} is hydrogen or an optionally substituted C_{1-4}-alkyl; or R^{22C} and R^{23C} are taken together to form an optionally substituted C_{3-6} cycloalkyl.

199. The use of Claim 198, wherein R^{22C} is an optionally substituted C_{1-6}-alkyl.

200. The use of Claim 199, wherein the optionally substituted C_{1-6}-alkyl is methyl.

201. The use of any one of Claims 198 to 200, wherein R^{23C} is hydrogen.

202. The use of any one of Claims 167 to 201, wherein R^{6C} is halogen.

203. The use of any one of Claims 167 to 201, wherein R^{6C} is hydrogen.

204. The use of any one of Claims 167 to 201, wherein R^{6C} is an optionally substituted C_{1-6} alkyl.

205. The use of any one of Claims 167 to 201, wherein R^{6C} is an optionally substituted C_{2-6} alkenyl.

206. The use of any one of Claims 167 to 201, wherein R^{6C} is an optionally substituted C_{2-6} alkynyl.

207. The use of any one of Claims 167 to 206, wherein R^{5C} is hydrogen.

208. The use of any one of Claims 167 to 206, wherein R^{5C} is halogen.

209. The use of Claim 208, wherein R^{5C} is fluoro or chloro.

210. The use of any one of Claims 167 to 206, wherein R^{5C} is OR^{1D}.

211. The use of Claim 210, wherein R^{5C} is OH.

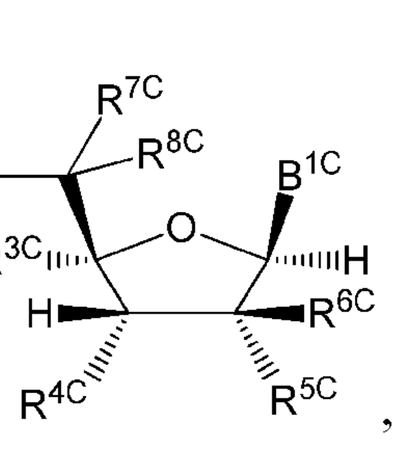
212. The use of Claim 210, wherein R^{5C} is $-OC(=O)R^{"D}$.

213. The use of any one of Claims 167 to 206, wherein R^{5C} is an optionally substituted O-linked amino acid.

214. The use of any one of Claims 167 to 206, wherein R^{5C} is azido.

215. The use of any one of Claims 167 to 206, wherein R^{5C} is $NR^{2D}R^{3D}$.

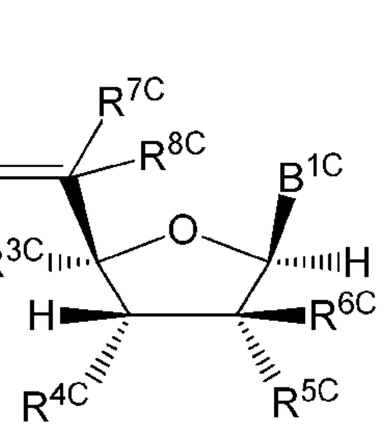
216. The use of any one of Claims 167 to 206, wherein R^{5C} is NH_2.

217. The use of any one of Claims 167 to 216, wherein ------- is a single bond such that Formula (III) has the structure , wherein each R^{7C} and each R^{8C} is independently hydrogen or halogen.

218. The use of Claim 217, wherein the R^{7C} and the R^{8C} groups are all hydrogen.

219. The use of Claim 217, wherein one R^{7C} is halogen, one R^{7C} is hydrogen and both R^{8C} groups are all hydrogen.

220. The use of Claim 217, wherein one R^{7C} is halogen, one R^{7C} is hydrogen, one R^{8C} is halogen and one R^{8C} is hydrogen.

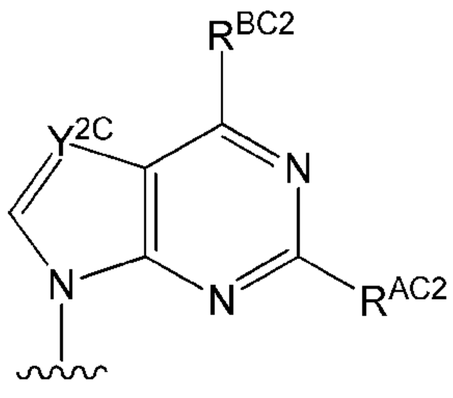
221. The use of any one of Claims 167 to 216, wherein ------- is a double bond such that Formula (III) has the structure , wherein each R^{7C} is absent and each R^{8C} is independently hydrogen or halogen.

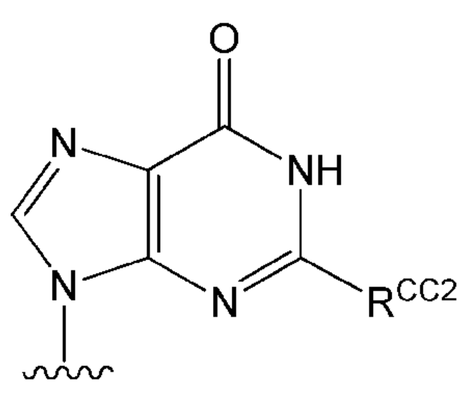
222. The use of Claim 221, wherein both R^{8C} groups are hydrogen.

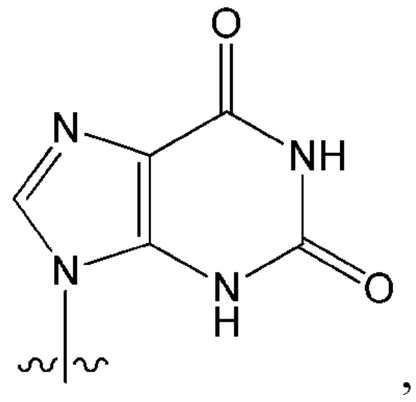
223. The use of Claim 221, wherein one R^{8C} is halogen and the other R^{8C} is hydrogen.

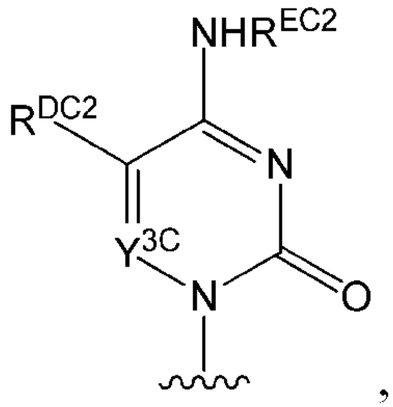
224. The use of Claim 221, wherein both R^{8C} groups are halogen.

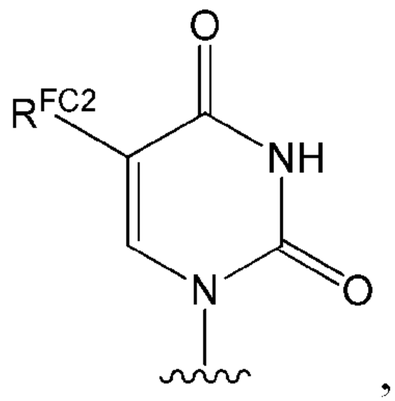
225. The use of any one of Claims 167 to 224, wherein B^{1C} is selected from the group consisting of:

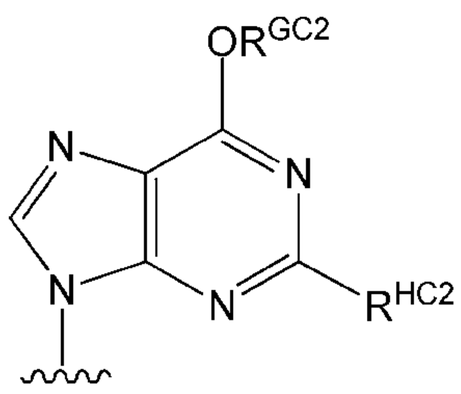


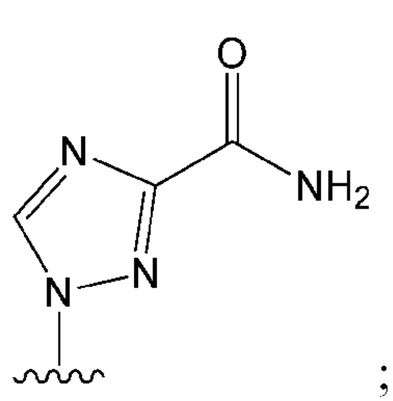
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and


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wherein:

R^{AC2} is selected from the group consisting of hydrogen, halogen and NHR^{JC2}, wherein R^{JC2} is selected from the group consisting of hydrogen, $-C(=O)R^{KC2}$ and $-C(=O)OR^{LC2}$;

R^{BC2} is halogen or NHR^{WC2}, wherein R^{WC2} 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, $-C(=O)R^{MC2}$ and $-C(=O)OR^{NC2}$;

R^{CC2} is hydrogen or NHR^{OC2}, wherein R^{OC2} is selected from the group consisting of hydrogen, $-C(=O)R^{PC2}$ and $-C(=O)OR^{QC2}$;

R^{DC2} is selected from the group consisting of hydrogen, halogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl and an optionally substituted C_{2-6} alkynyl;

R^{EC2} is selected from the group consisting of hydrogen, hydroxy, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{3-8} cycloalkyl, $-C(=O)R^{RC2}$ and $-C(=O)OR^{SC2}$;

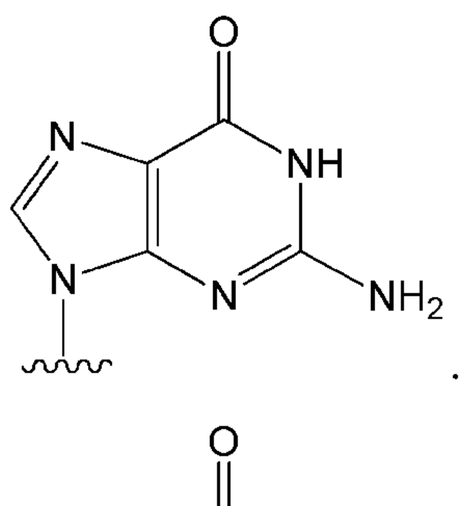
R^{FC2} is selected from the group consisting of hydrogen, halogen, an optionally substituted C_{1-6}alkyl, an optionally substituted C_{2-6} alkenyl and an optionally substituted C_{2-6} alkynyl;

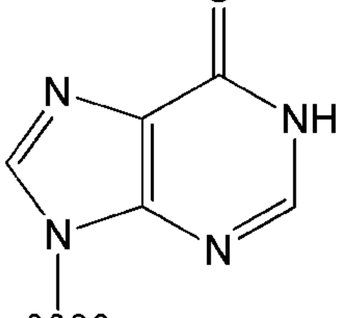
Y^{2C} and Y^{3C} are independently N or CR^{IC2}, wherein R^{IC2} is selected from the group consisting of hydrogen, halogen, an optionally substituted C_{1-6}-alkyl, an optionally substituted C_{2-6}-alkenyl and an optionally substituted C_{2-6}-alkynyl;

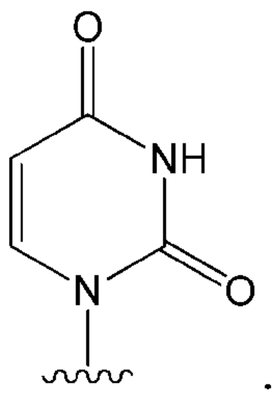
R^{GC2} is an optionally substituted C_{1-6} alkyl;

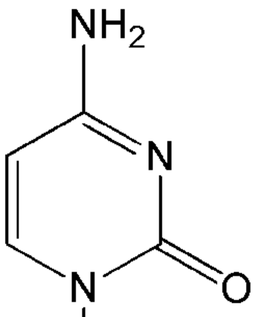
R^{HC2} is hydrogen or NHR^{TC2}, wherein R^{TC2} is independently selected from the group consisting of hydrogen, $-C(=O)R^{UC2}$ and $-C(=O)OR^{VC2}$; and

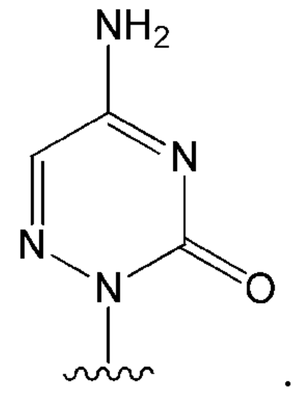
R^{KC2}, R^{LC2}, R^{MC2}, R^{NC2}, R^{PC2}, R^{QC2} R^{RC2}, $R^{SC2,}$ R^{UC2} and R^{VC2} are independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkenyl, C_{6-10} aryl, heteroaryl, heteroalicyclyl, aryl(C_{1-6} alkyl), heteroaryl(C_{1-6} alkyl) and heteroalicyclyl(C_{1-6} alkyl).

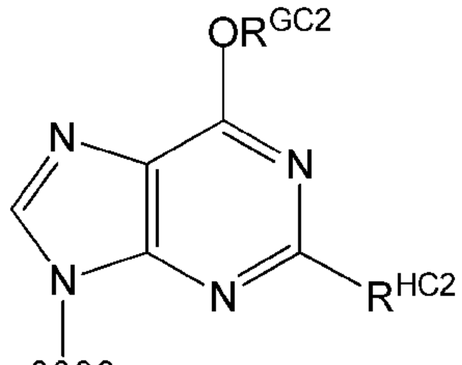
226. The use of Claim 225, wherein B^{1C} is .

227. The use of Claim 225, wherein B^{1C} is .

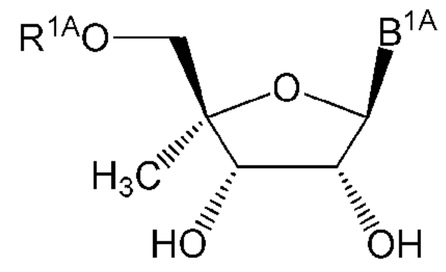
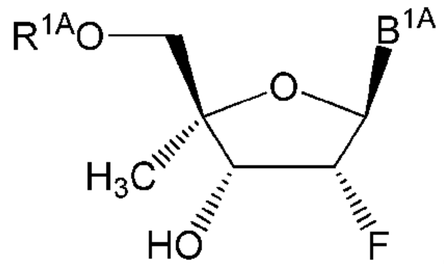
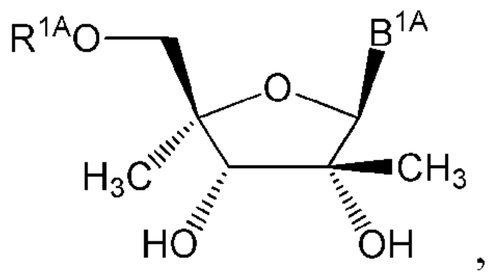
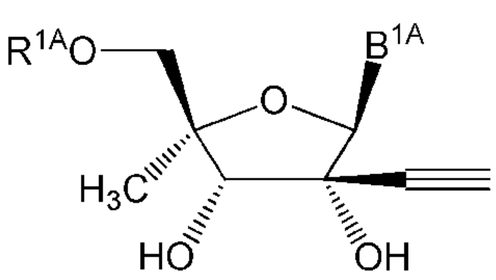
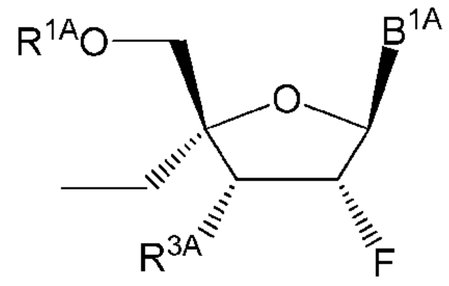
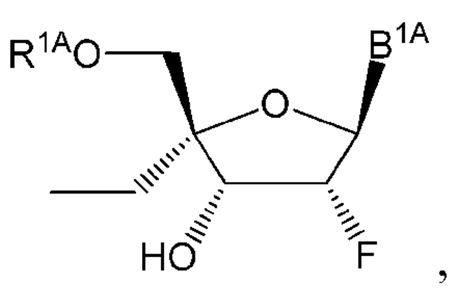
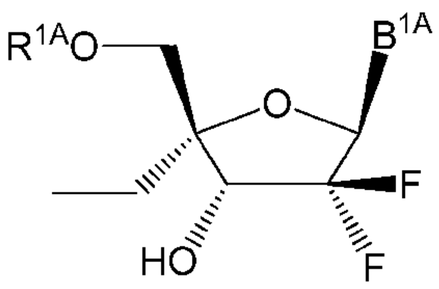
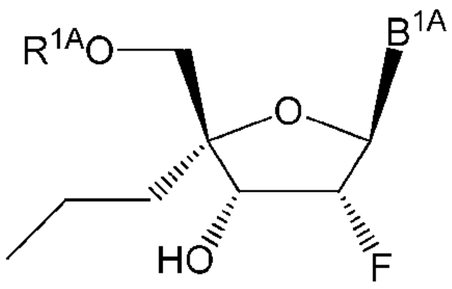
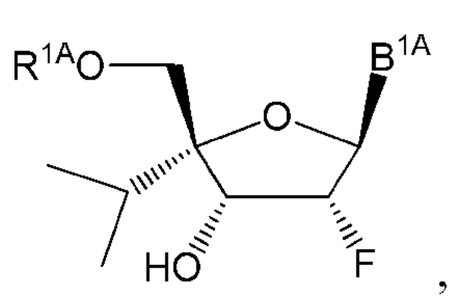
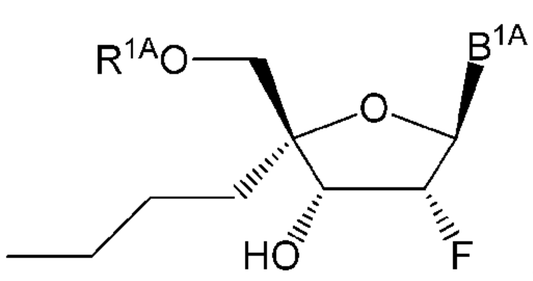
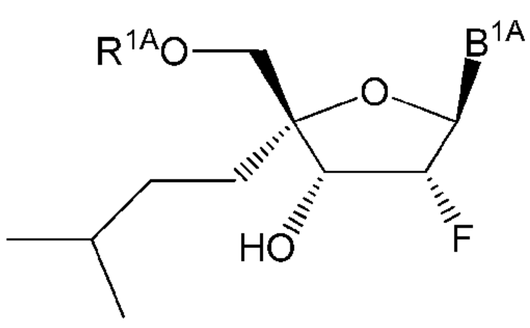
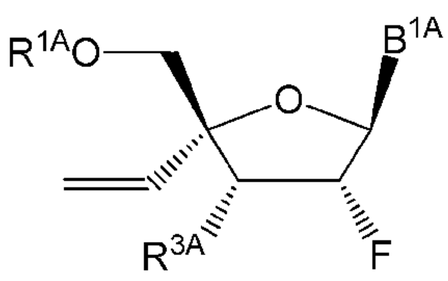
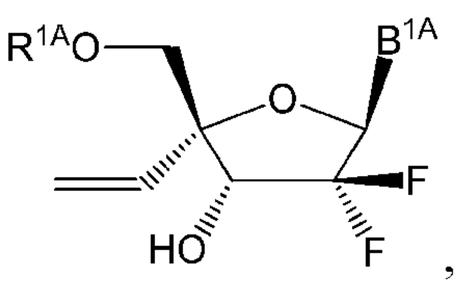
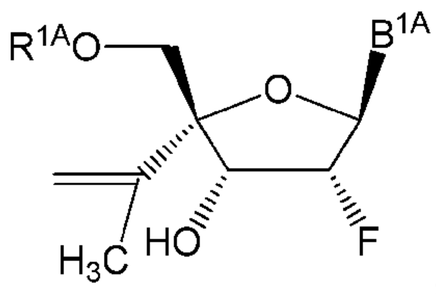
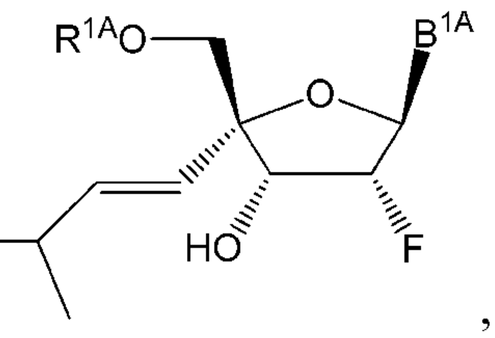
228. The use of Claim 225, wherein B^{1C} is .

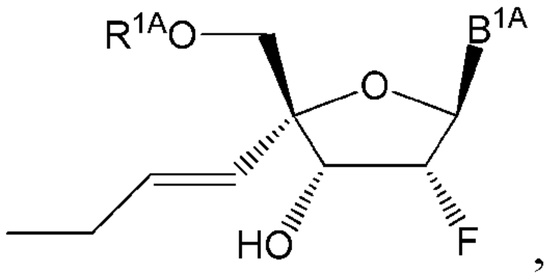
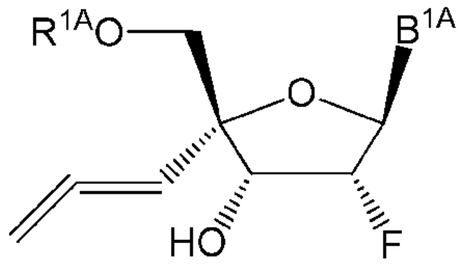
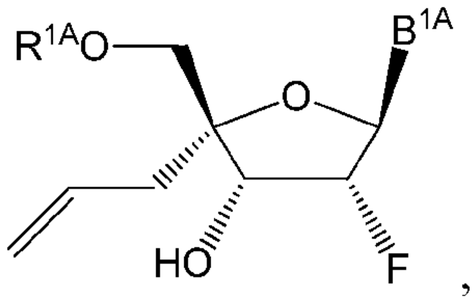
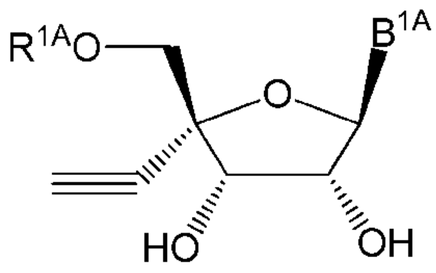
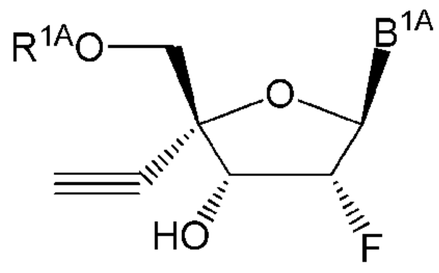
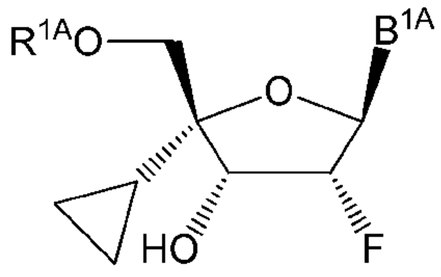
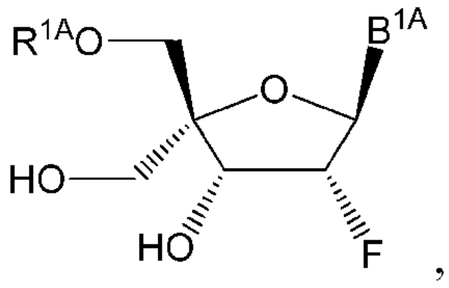
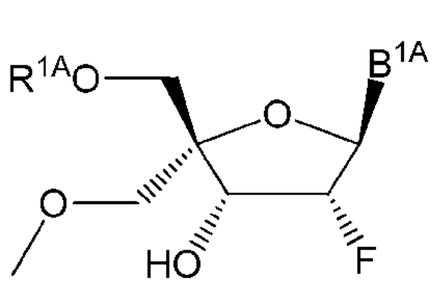
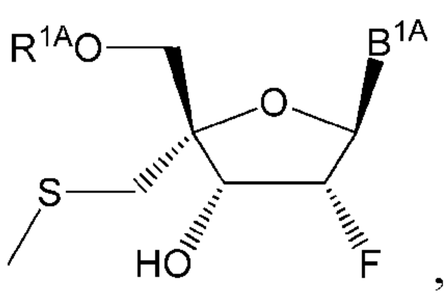
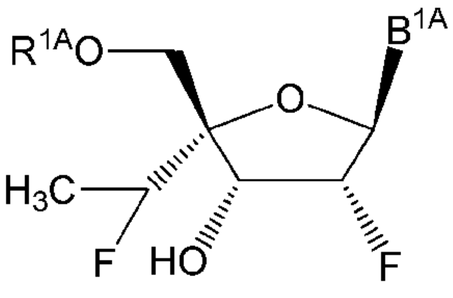
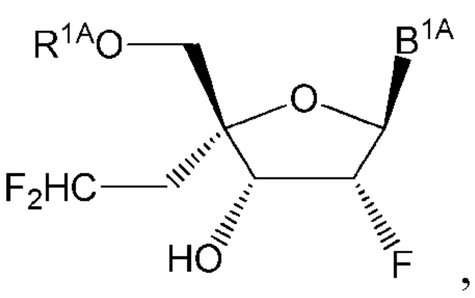
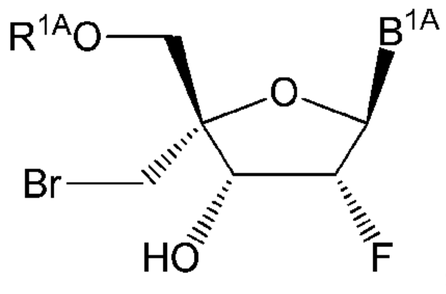
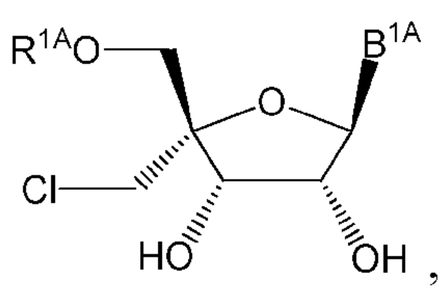
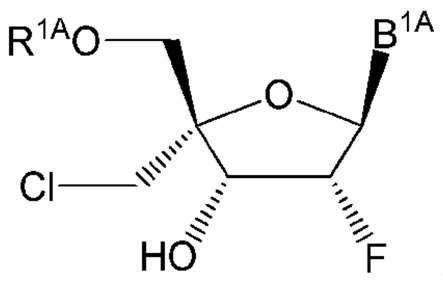
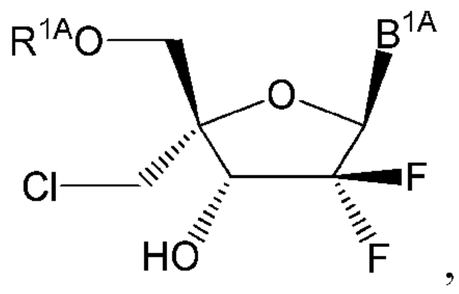
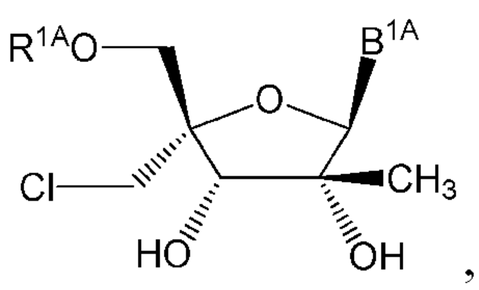
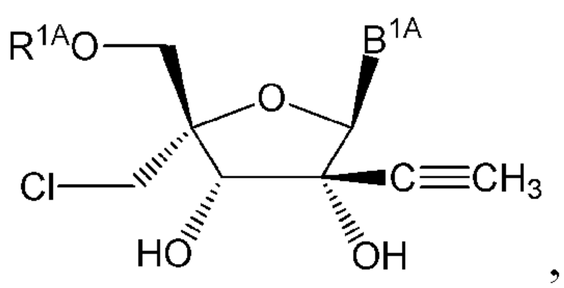
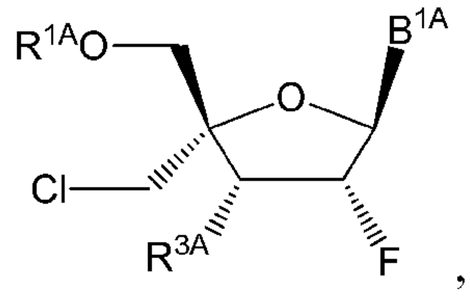
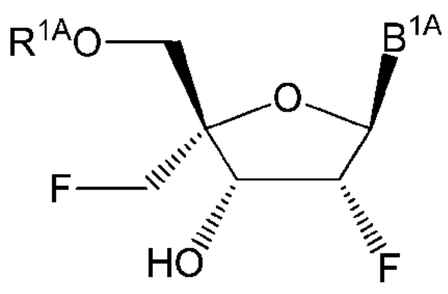
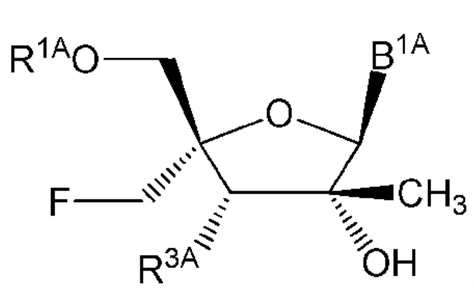
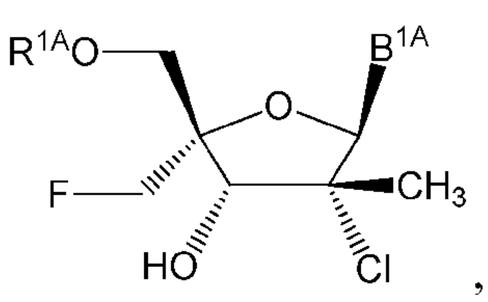
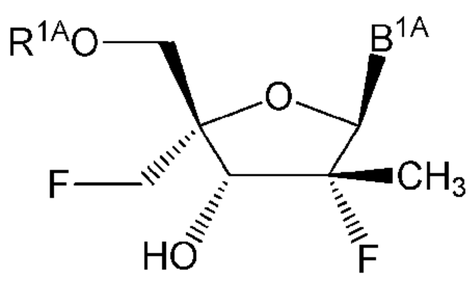
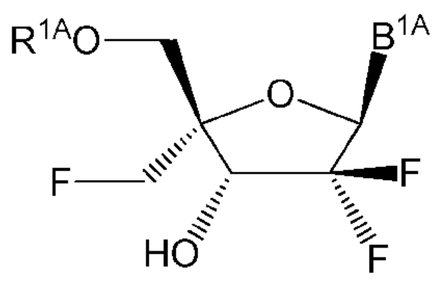
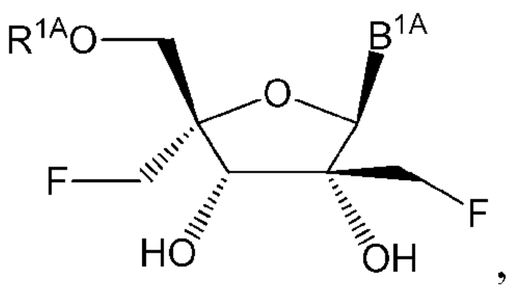
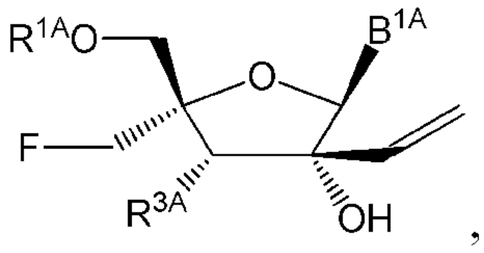
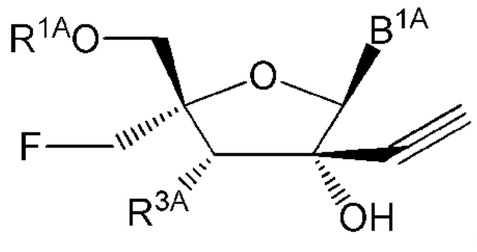
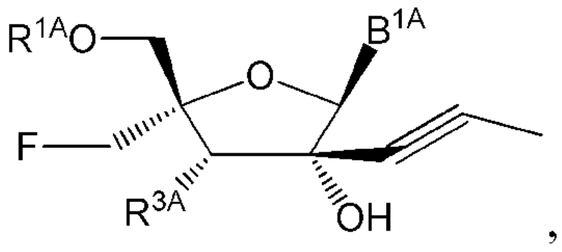
229. The use of Claim 225, wherein B^{1C} is .

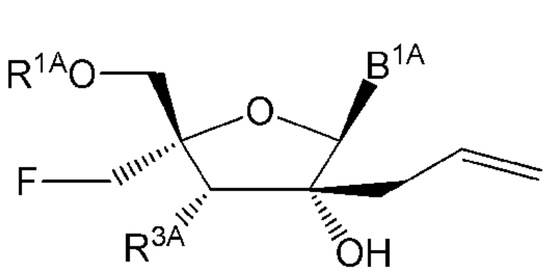
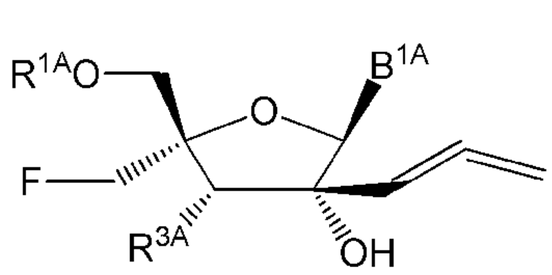
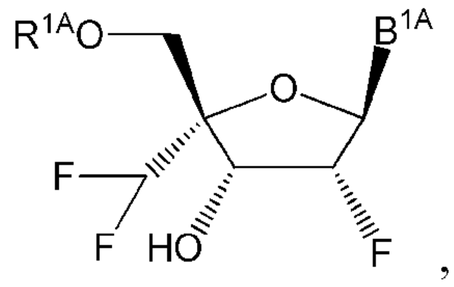
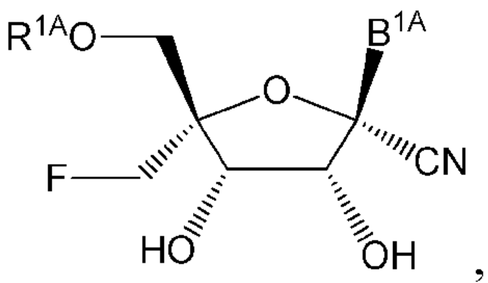
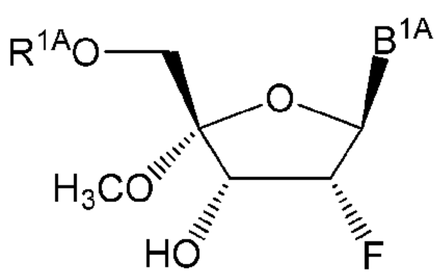
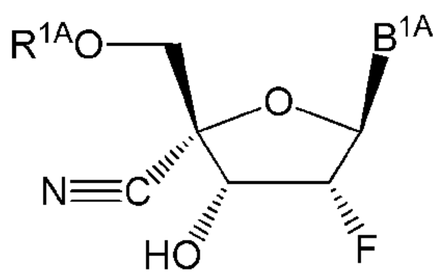
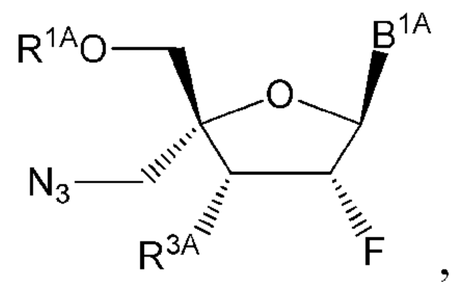
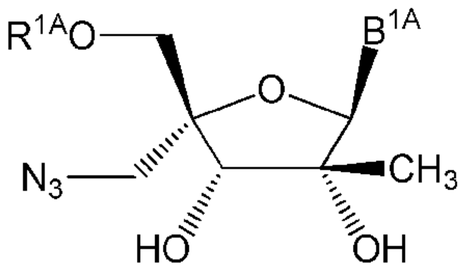
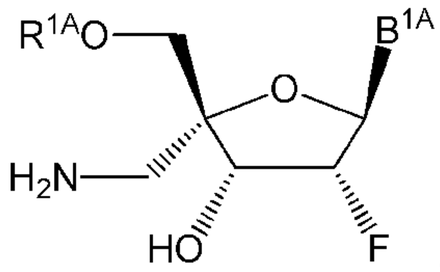
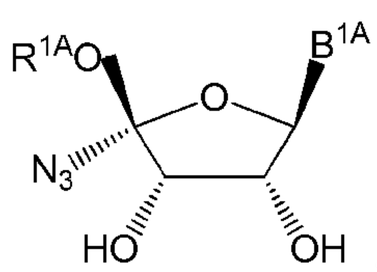
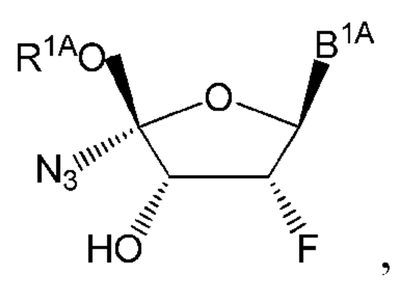
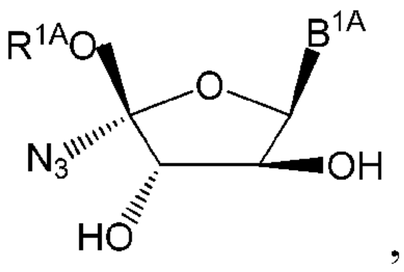
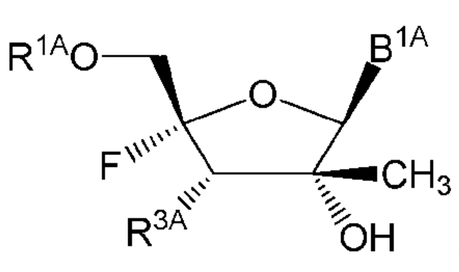
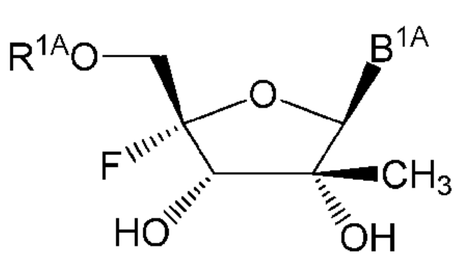
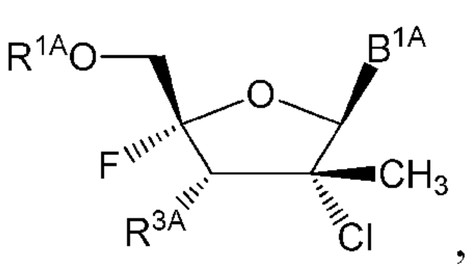
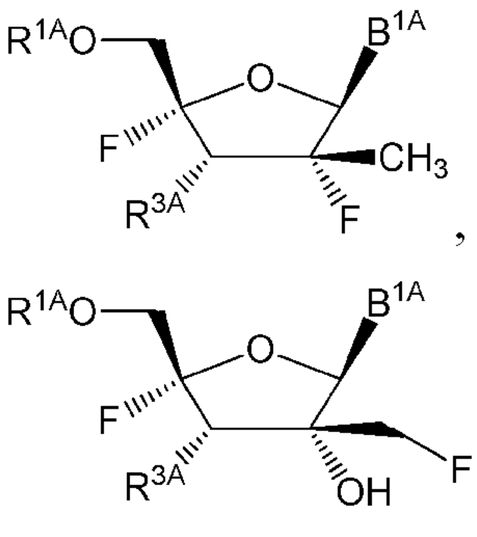
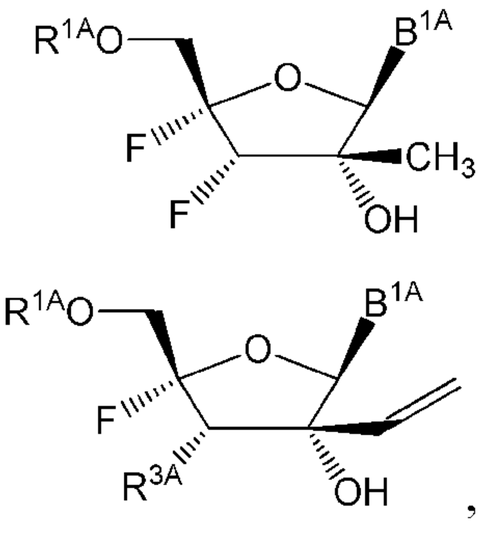
230. The use of Claim 225, wherein B^{1C} is .

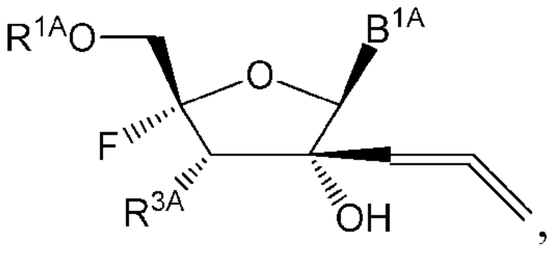
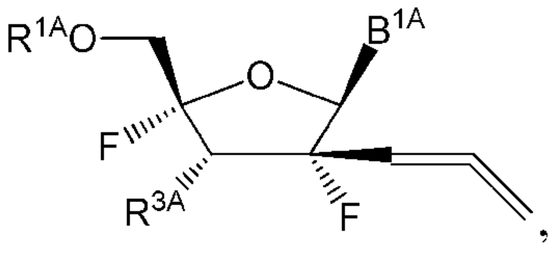
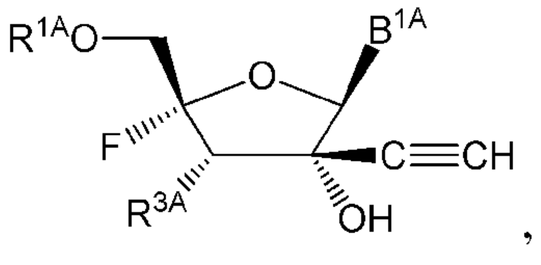
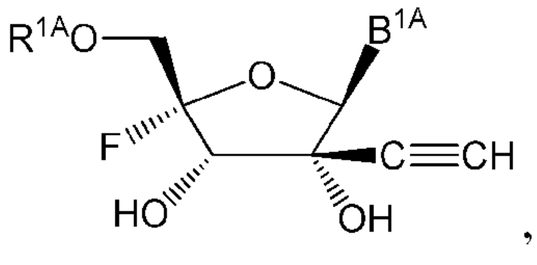
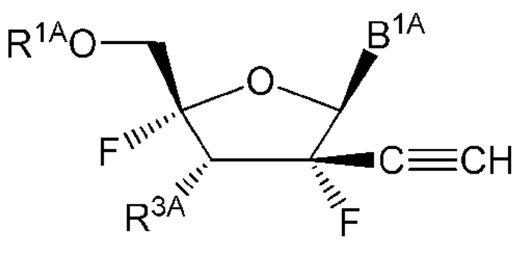
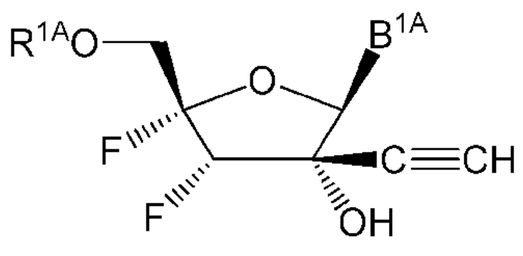
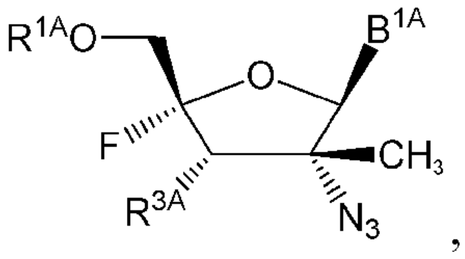
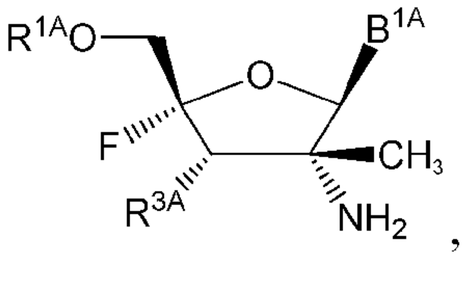
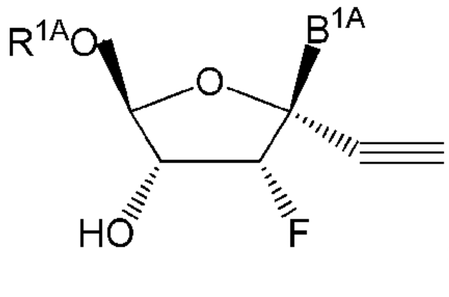
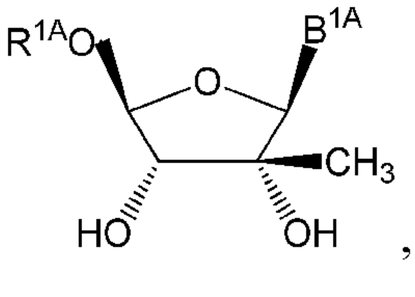
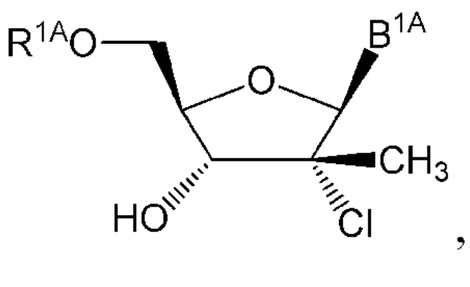
231. The use of Claim 225, wherein B^{1C} is .

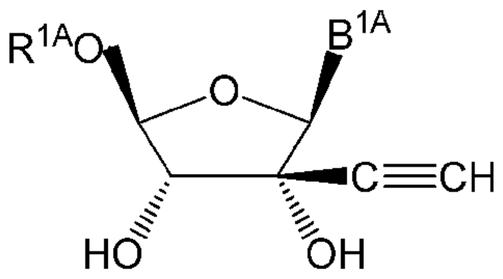
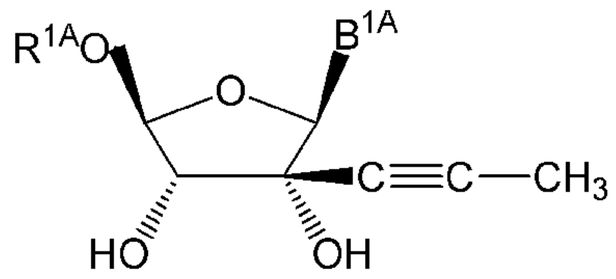
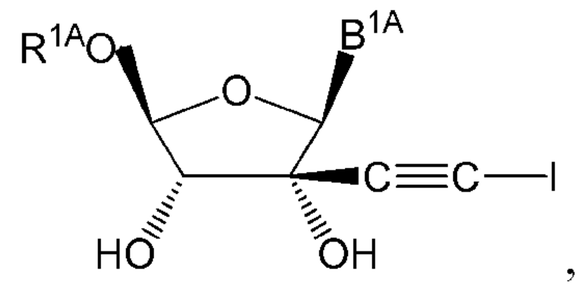
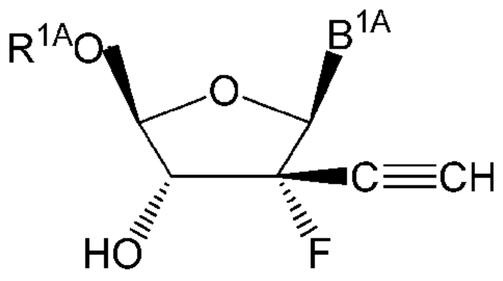
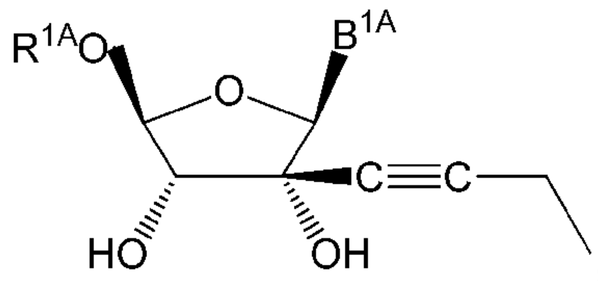
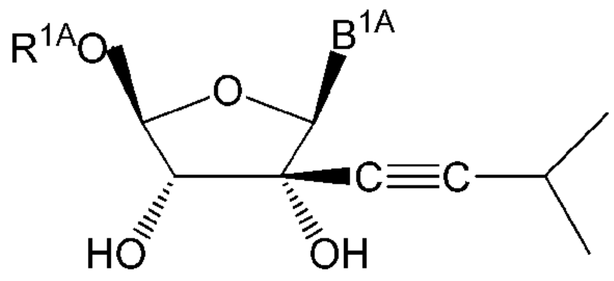
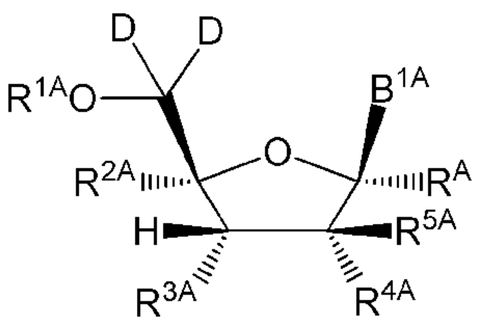
232. The use of Claim 1, wherein the compound of Formula (I) is selected from the group consisting of:

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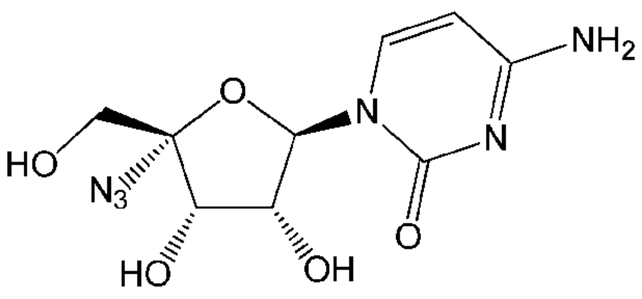
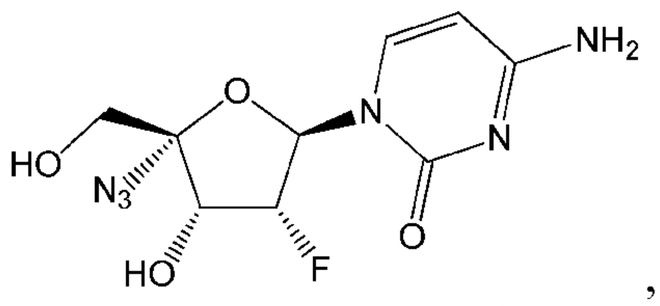
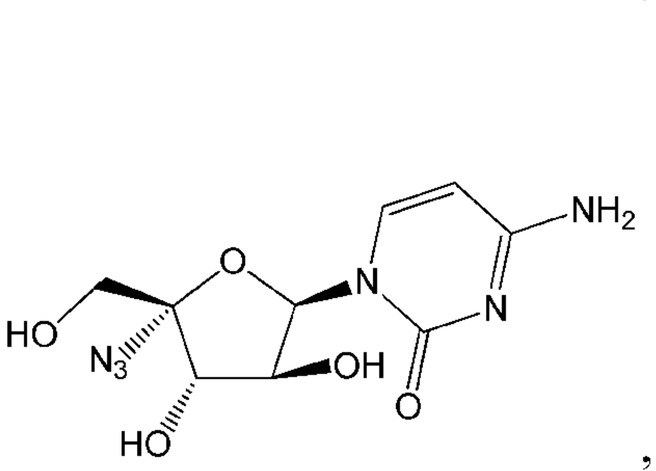
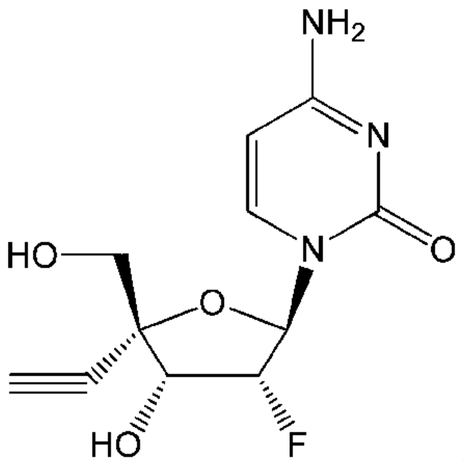
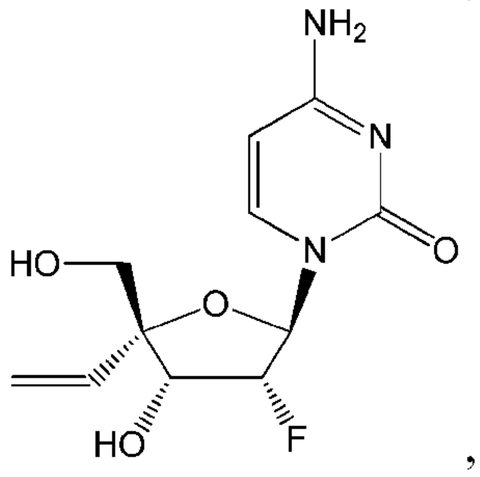
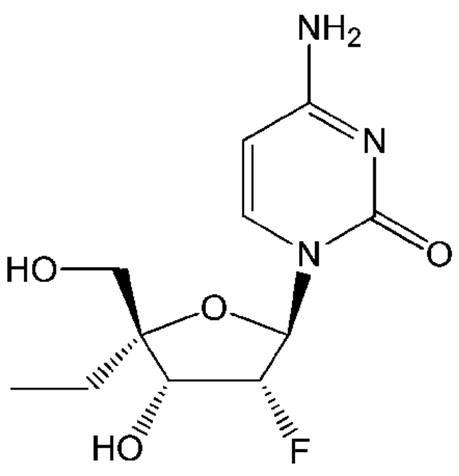
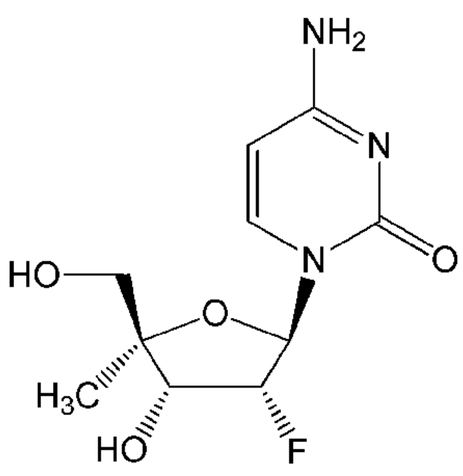
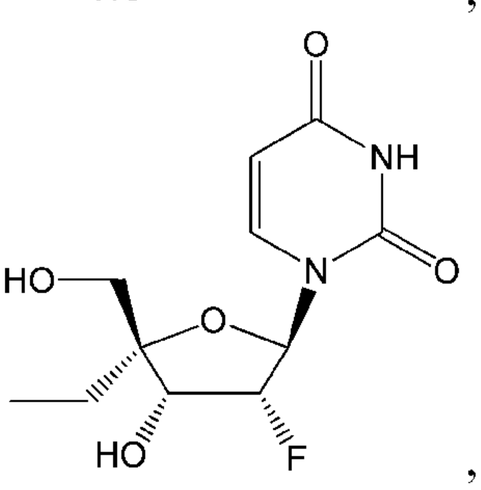

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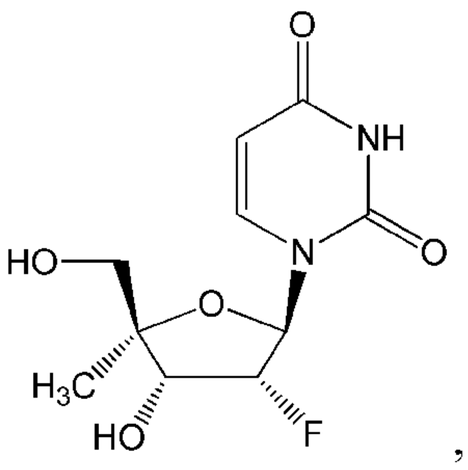
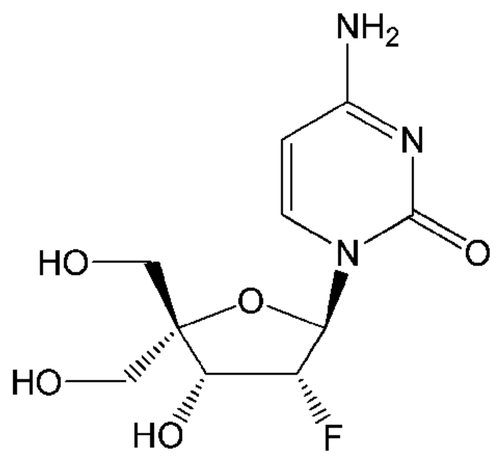
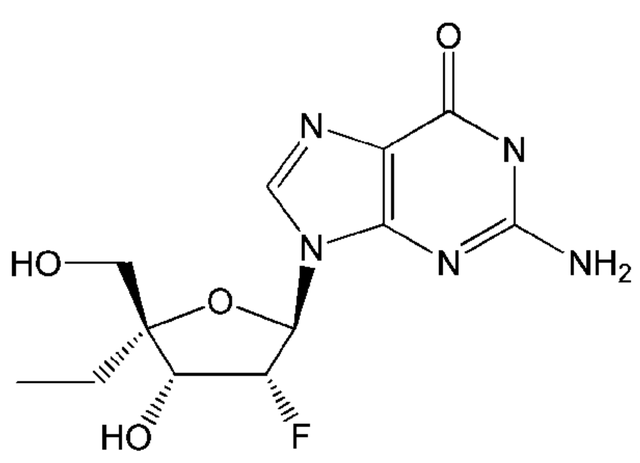
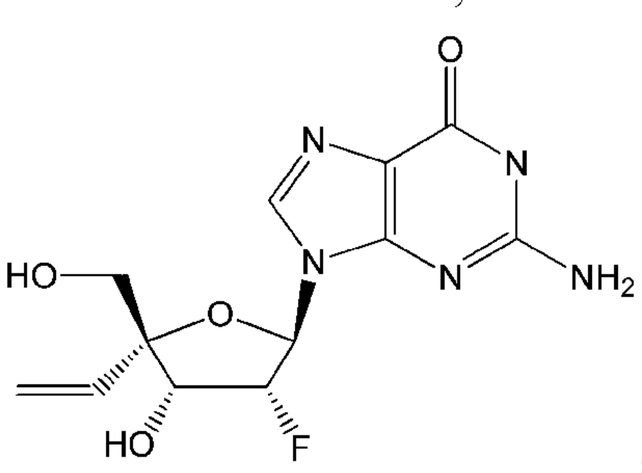
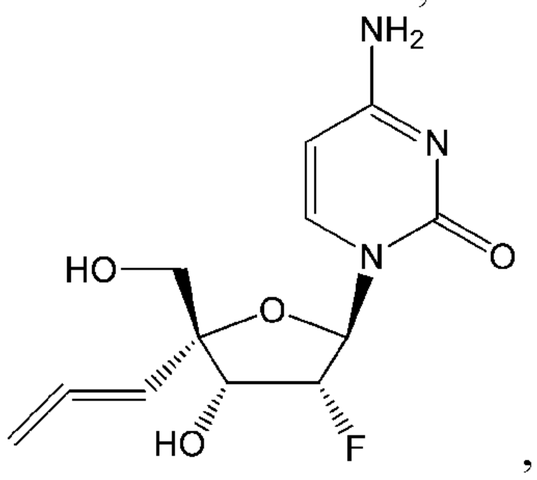
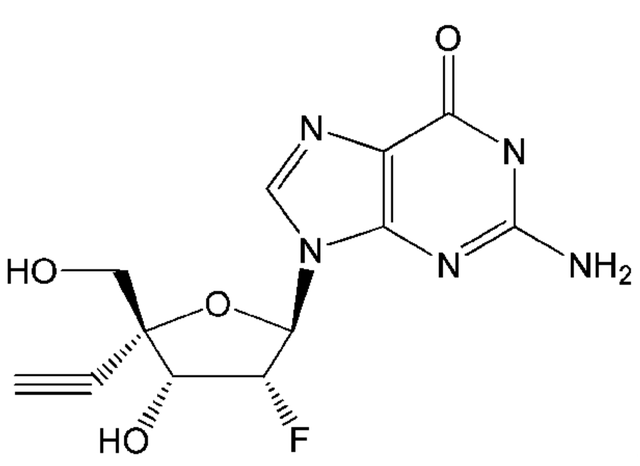
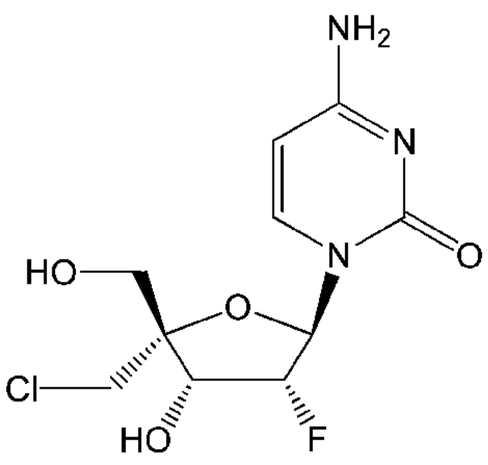
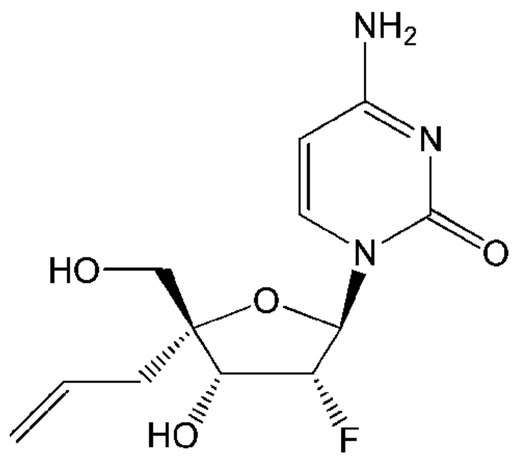
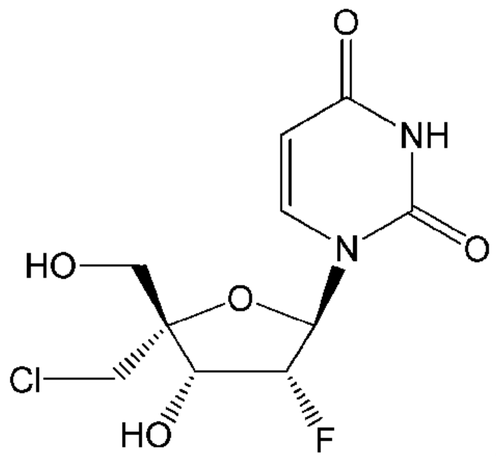
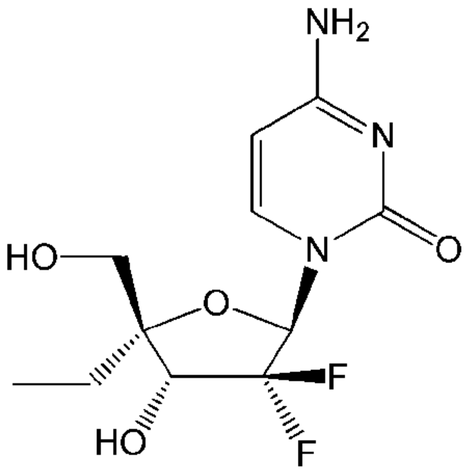
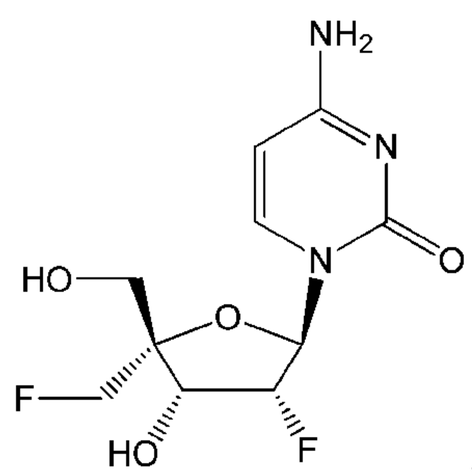
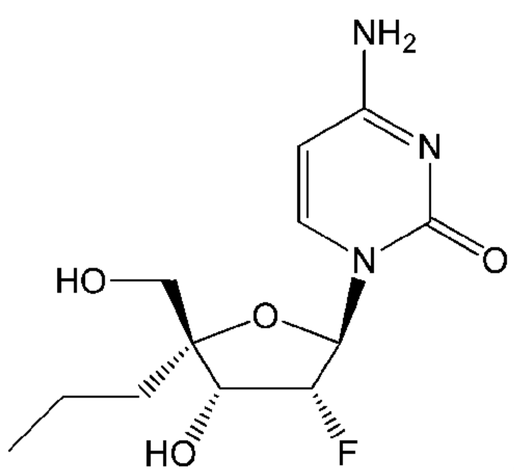
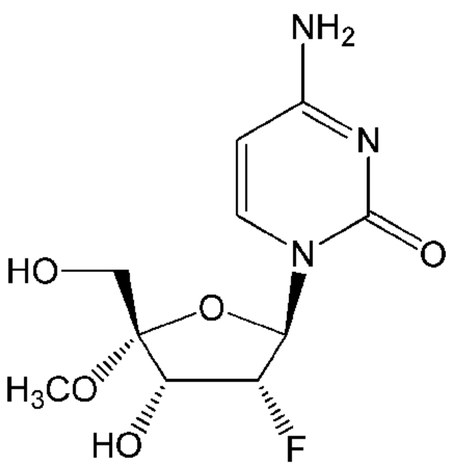
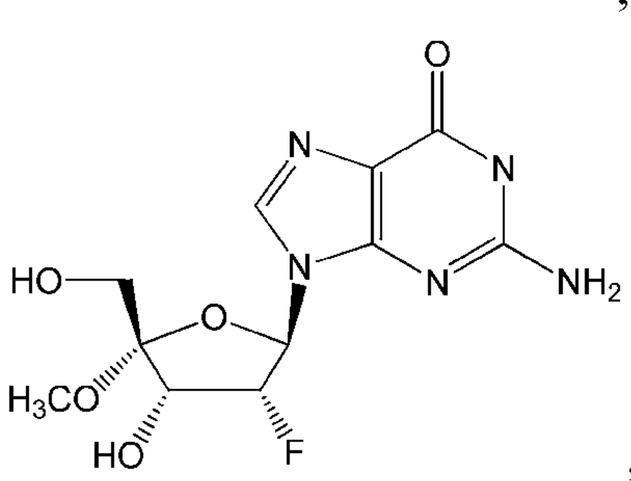
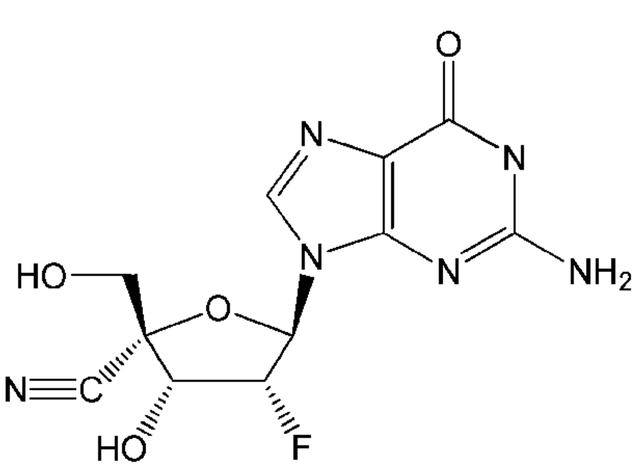


















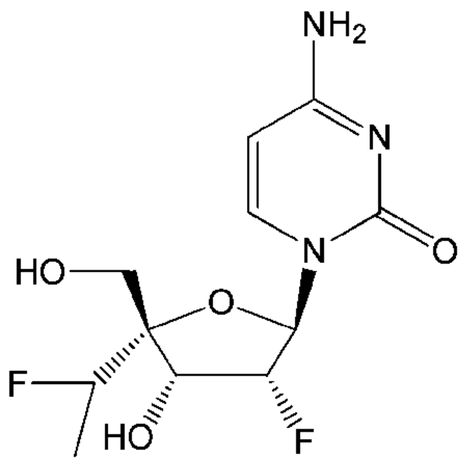
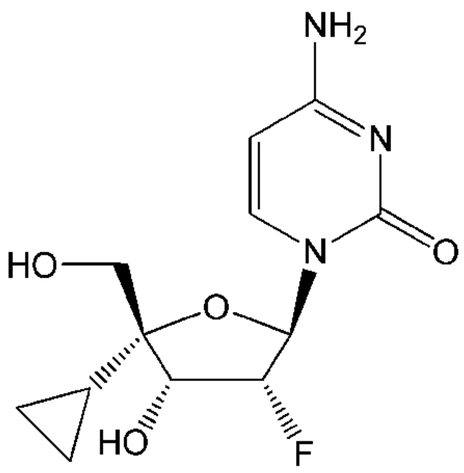
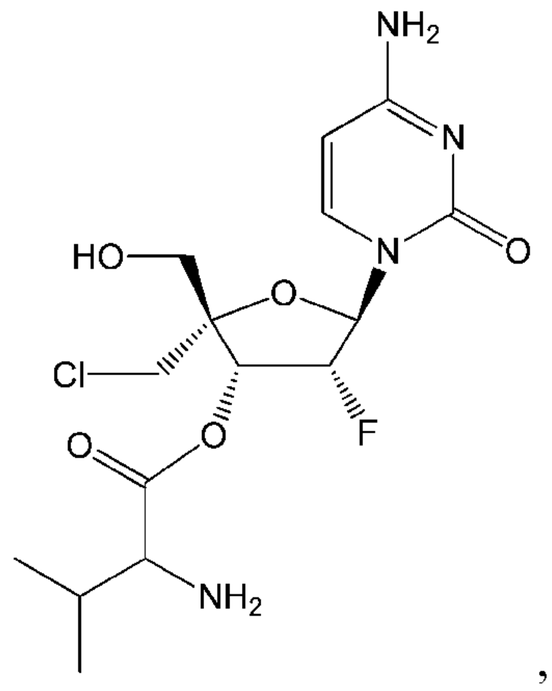
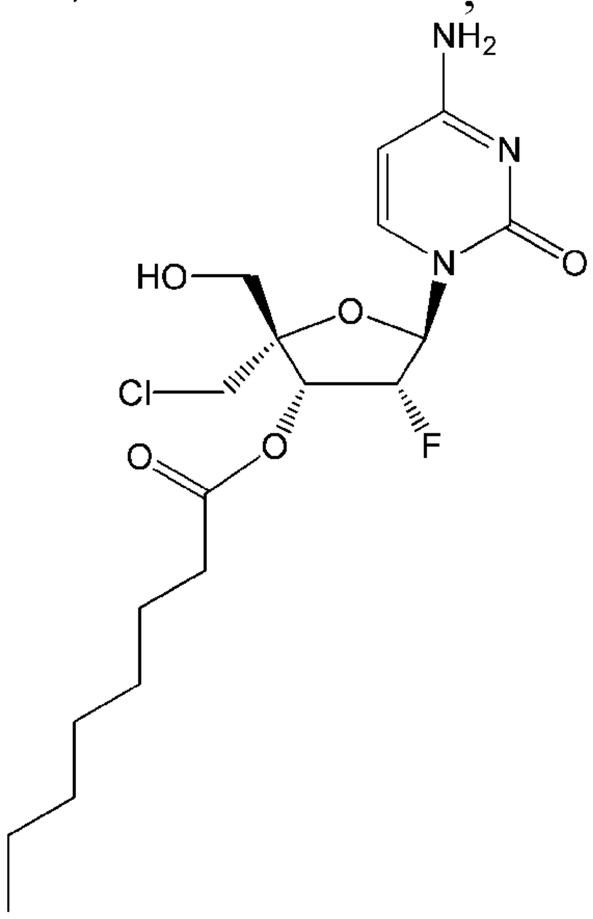
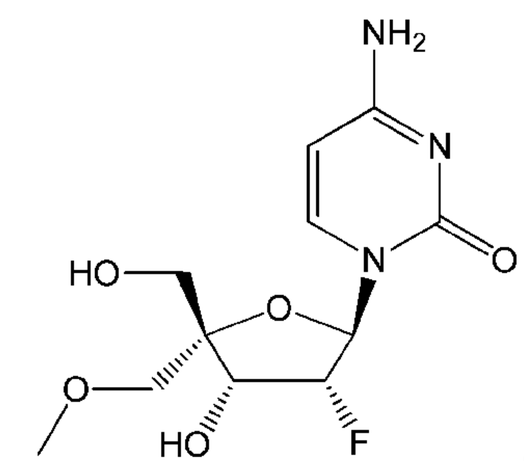
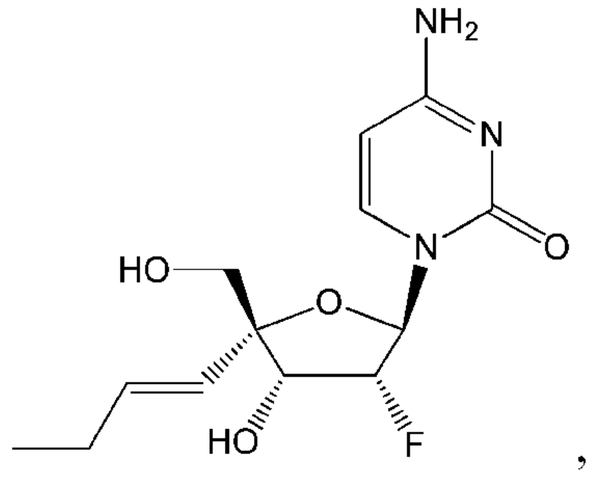
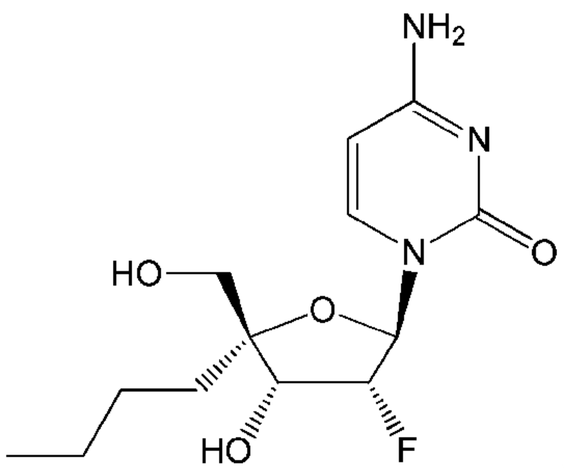
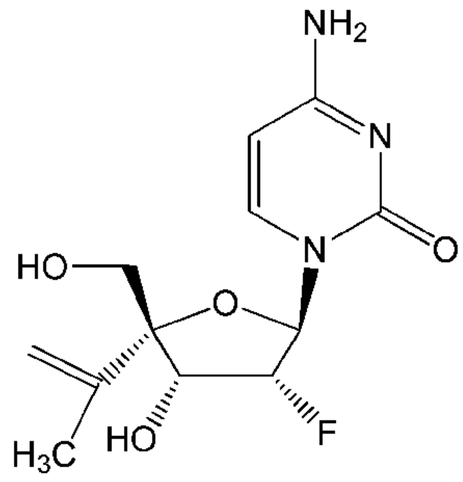
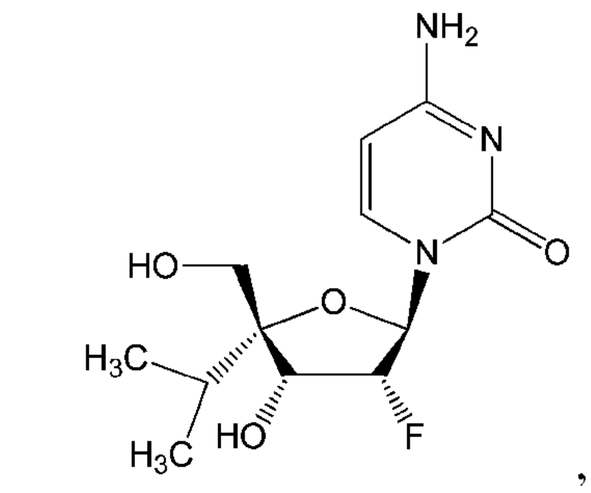
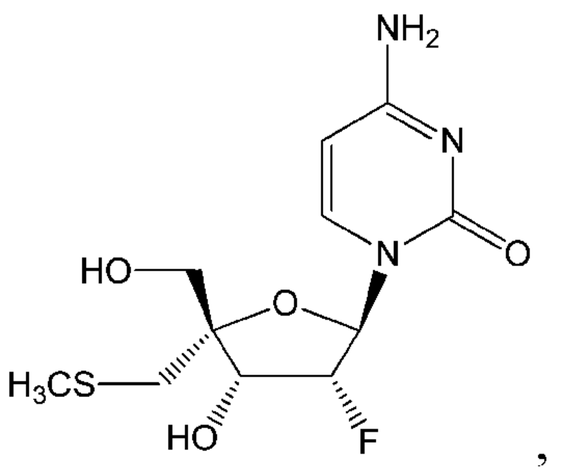
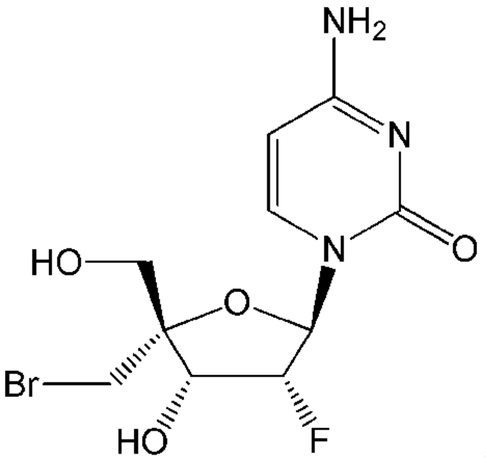
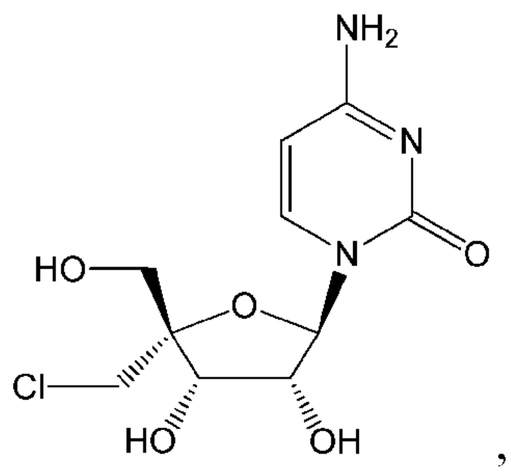












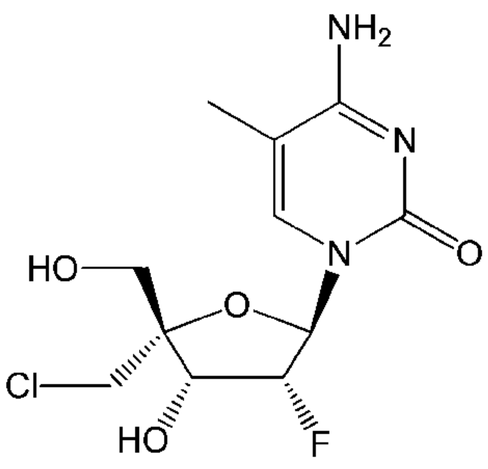
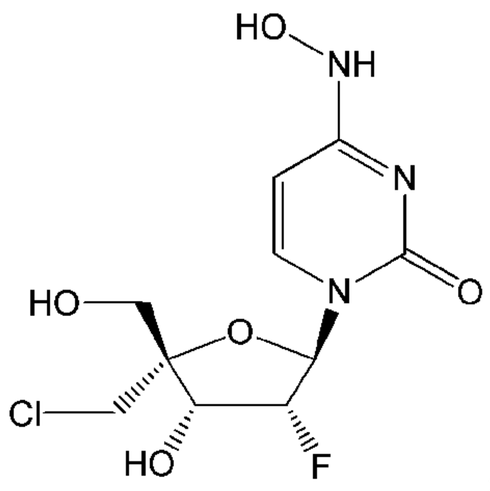
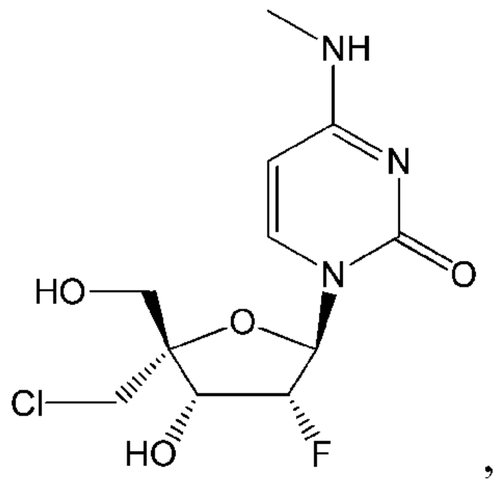
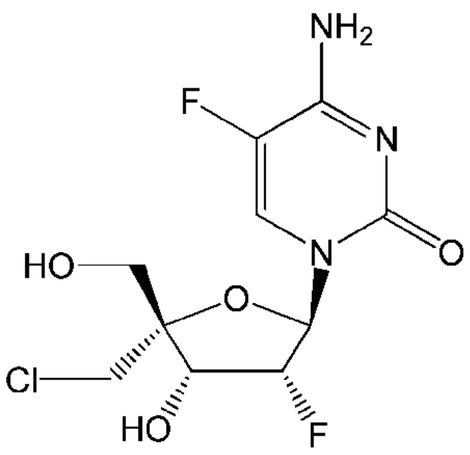
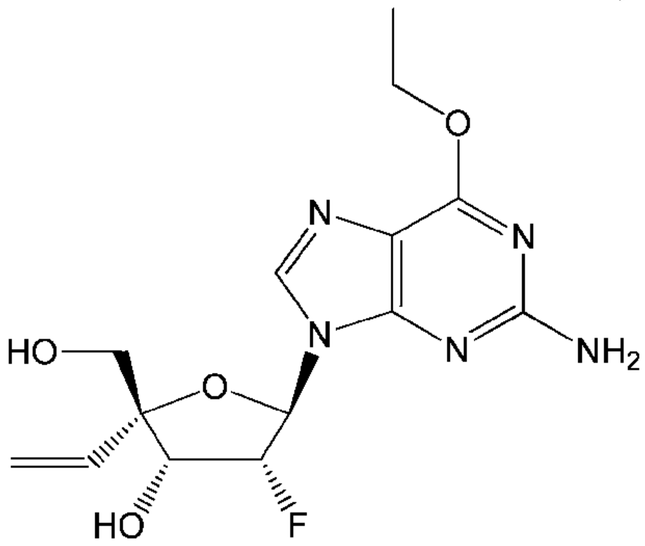
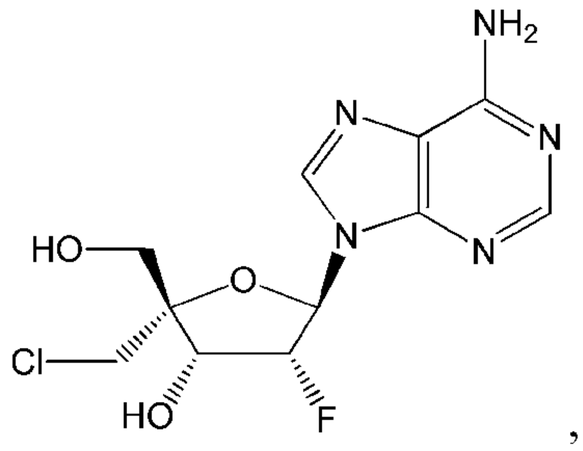
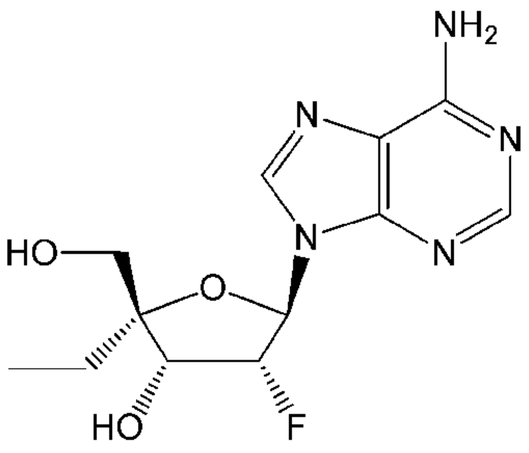
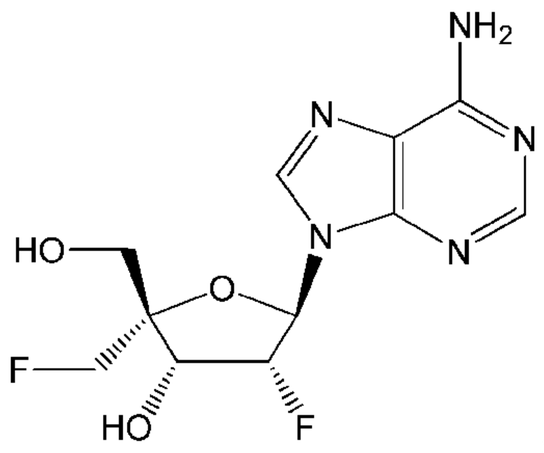
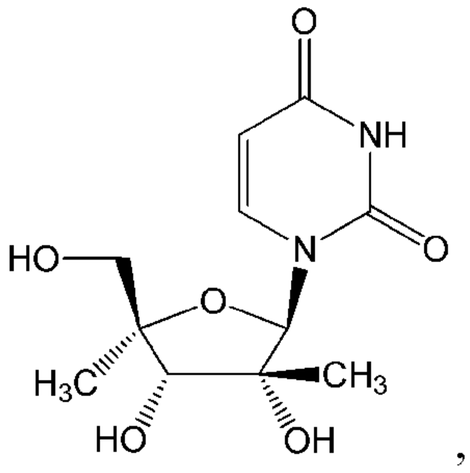
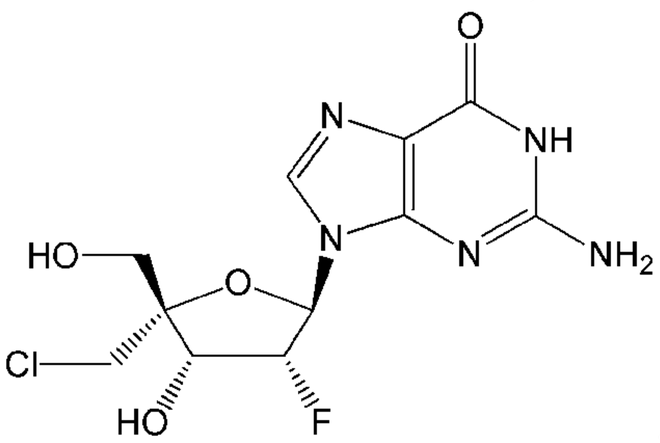
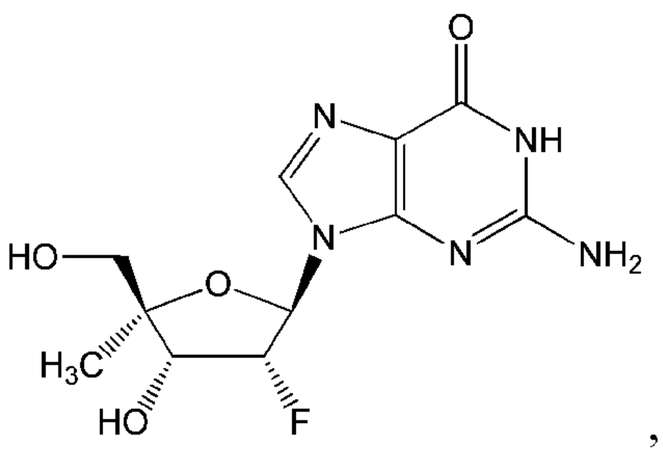
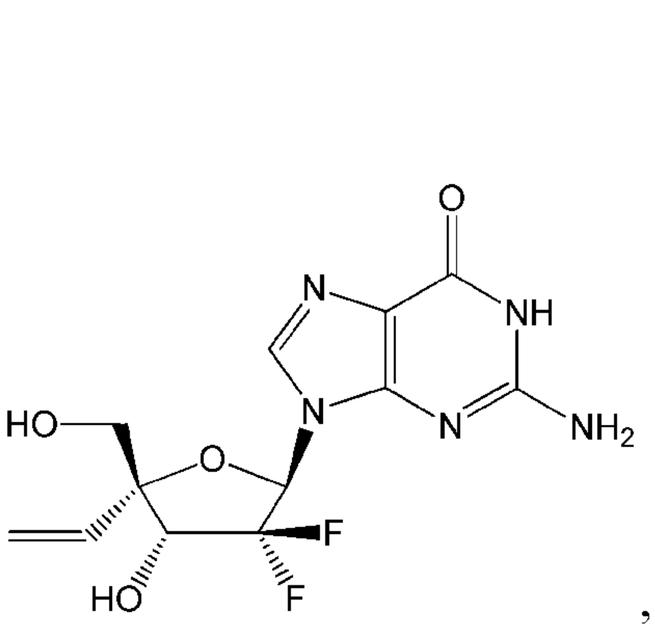
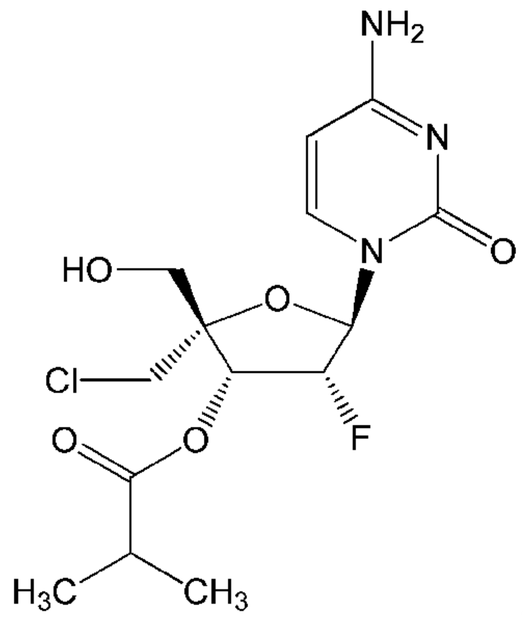
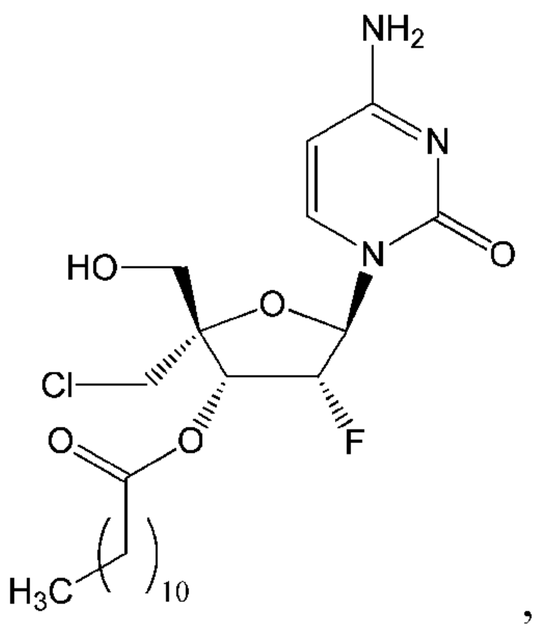

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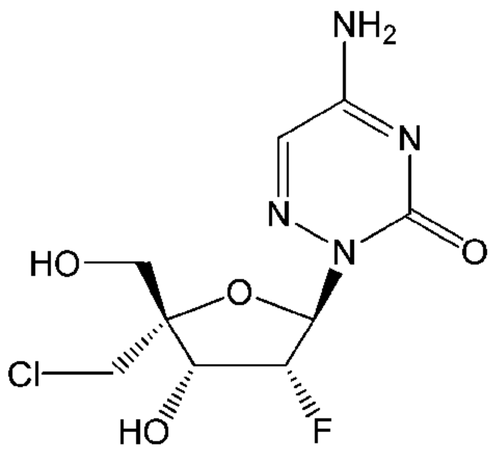
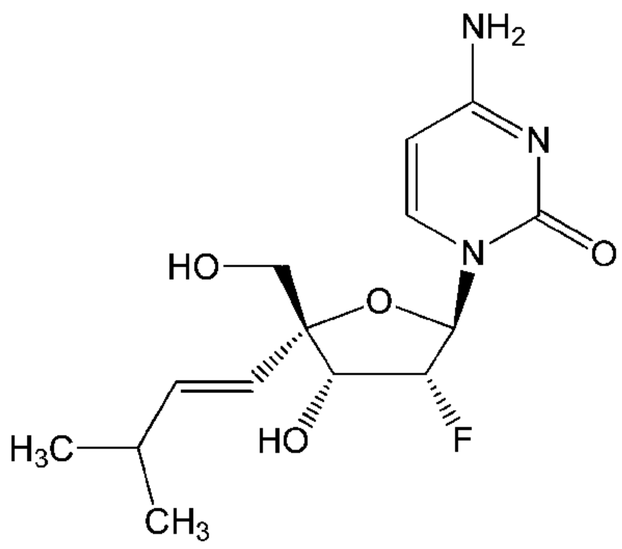
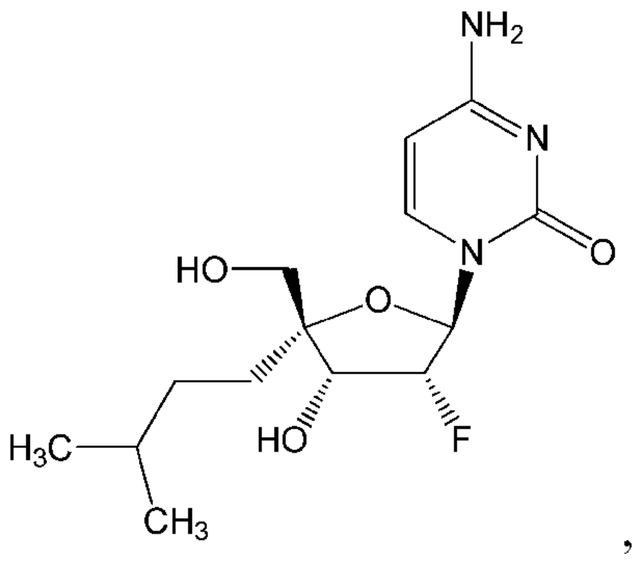
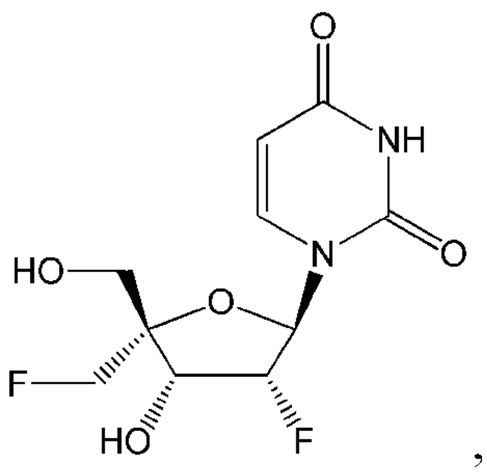
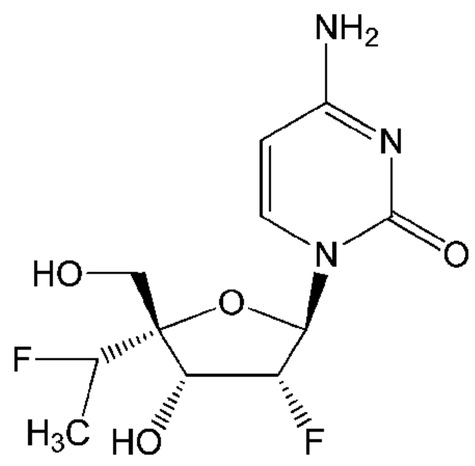
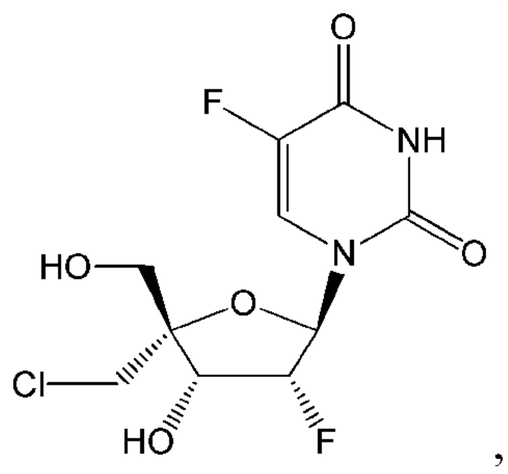
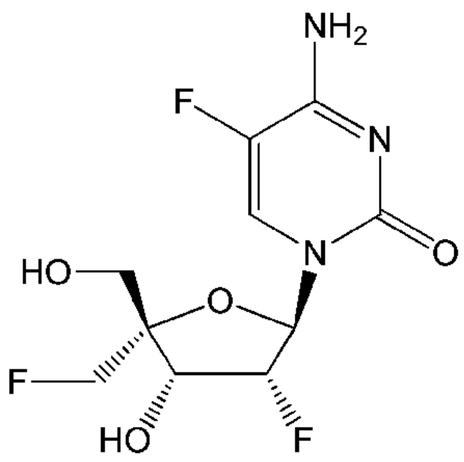
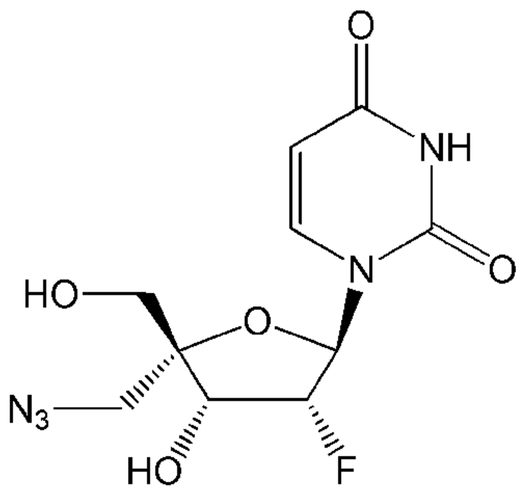
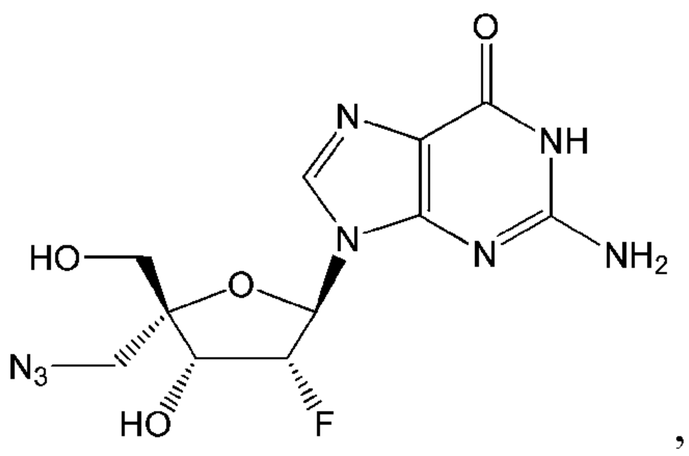
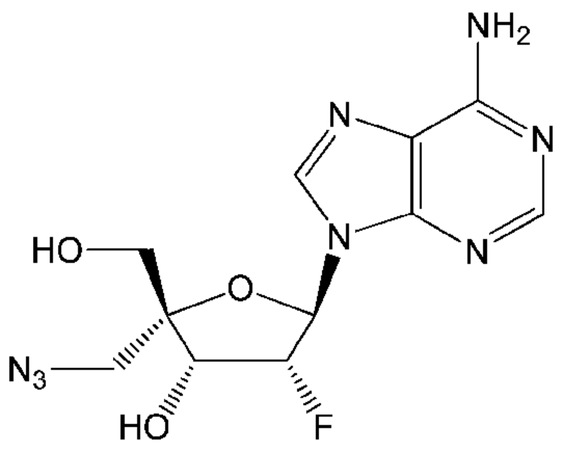
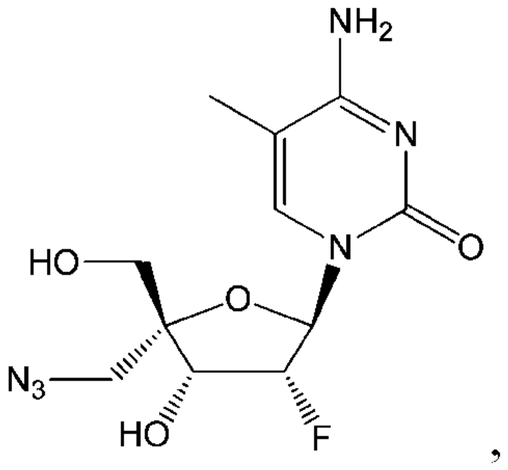
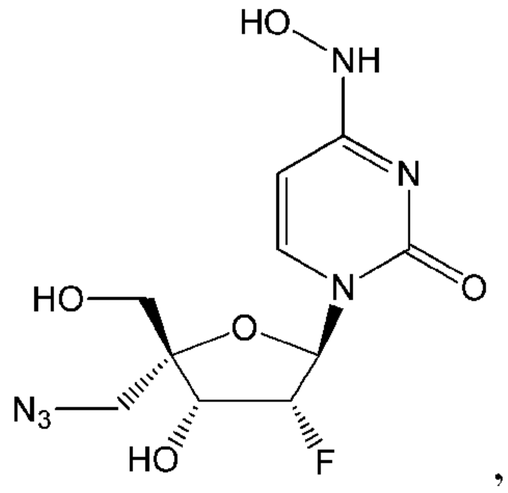
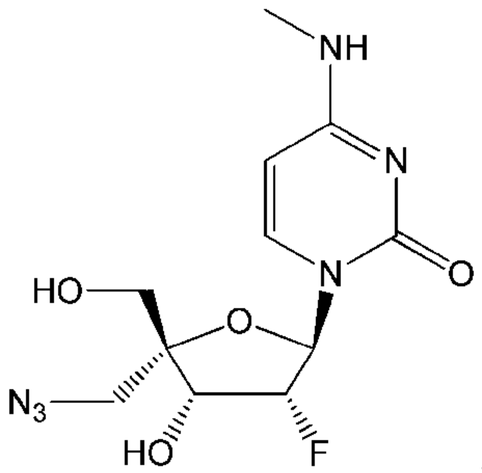
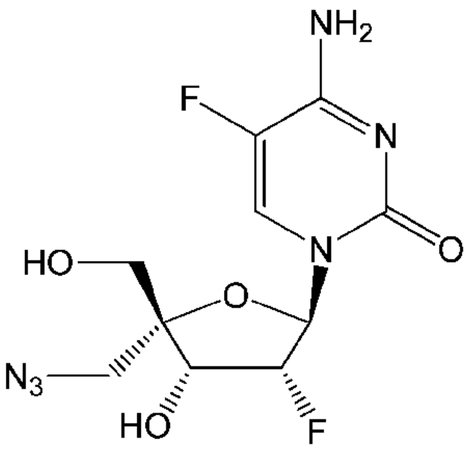
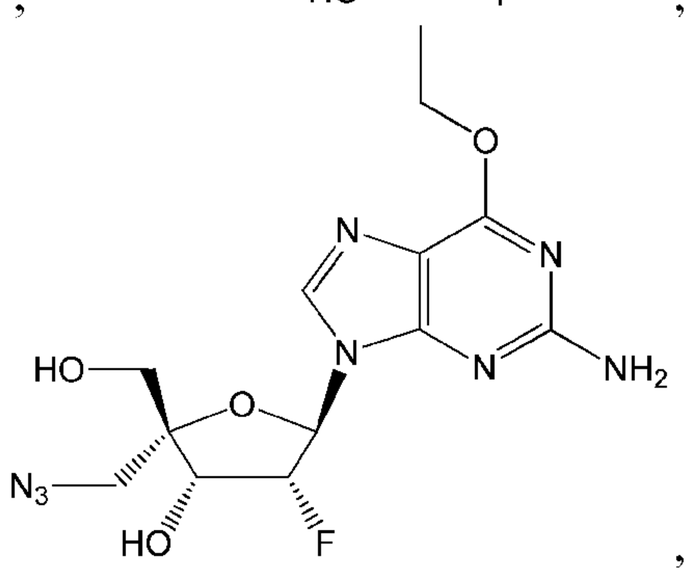
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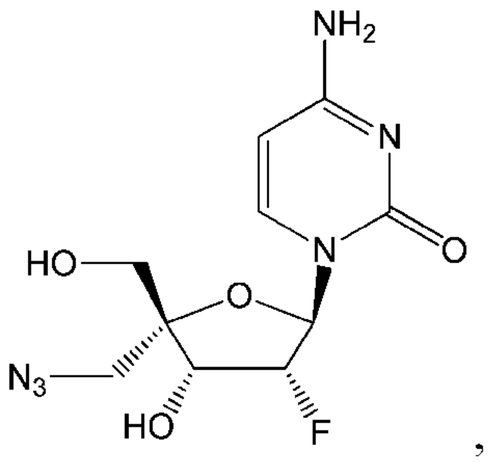
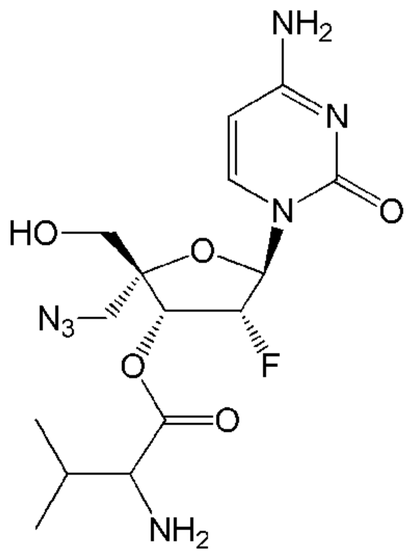
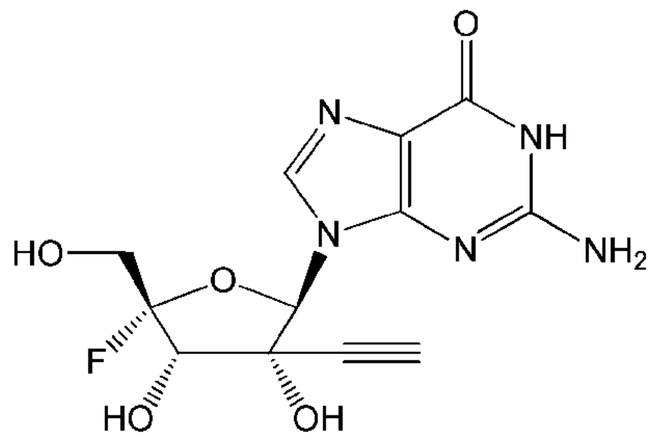
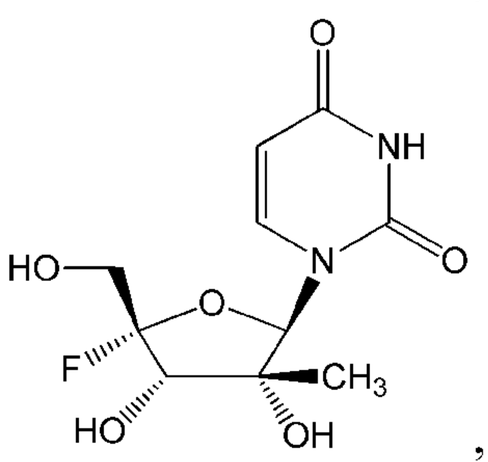
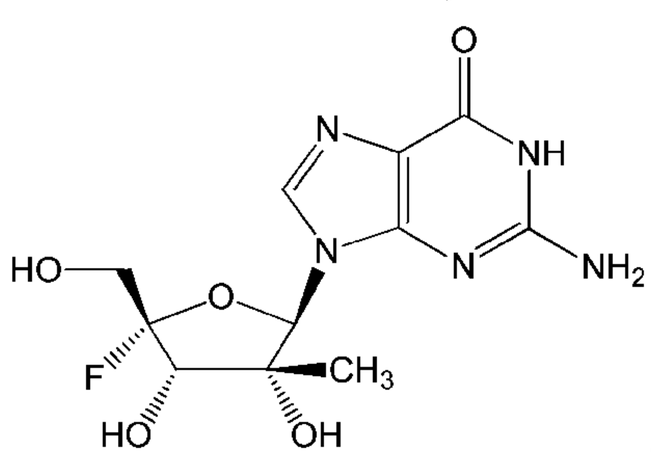
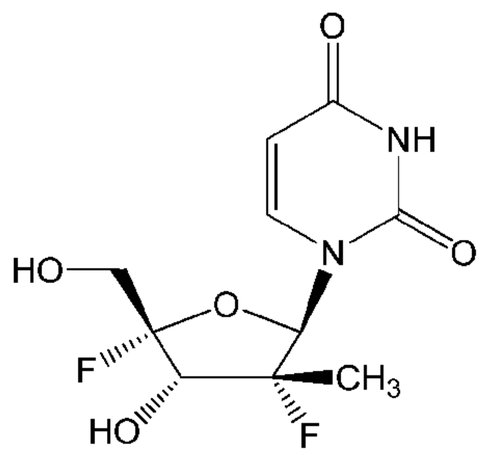
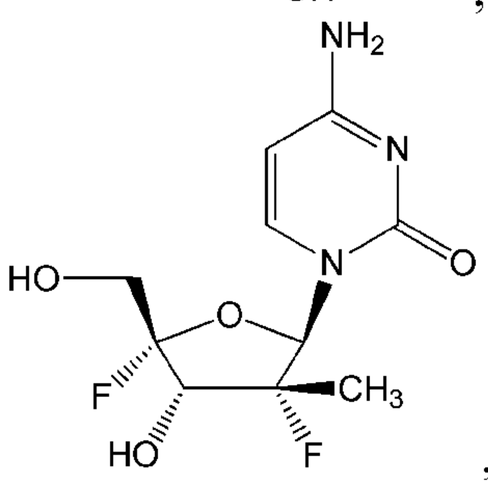
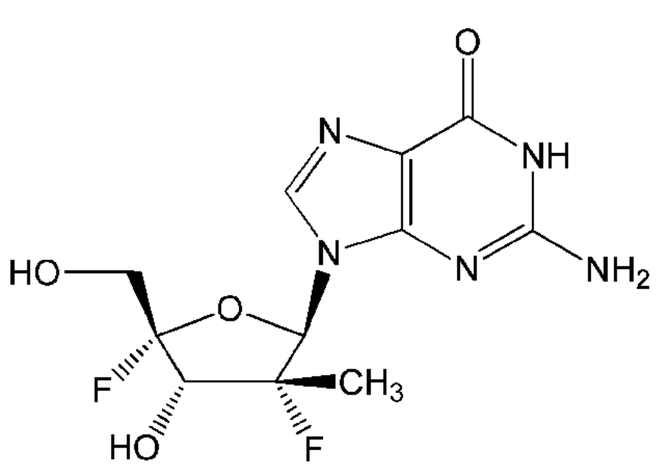
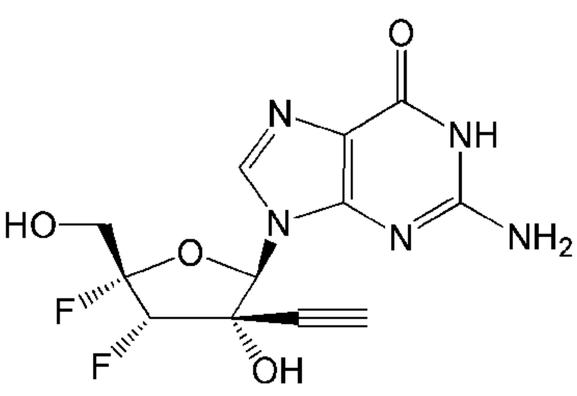
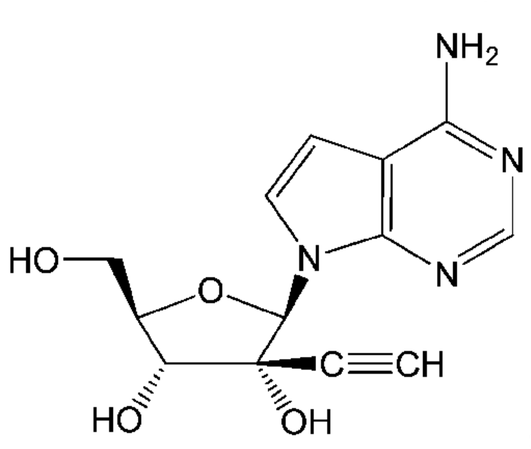
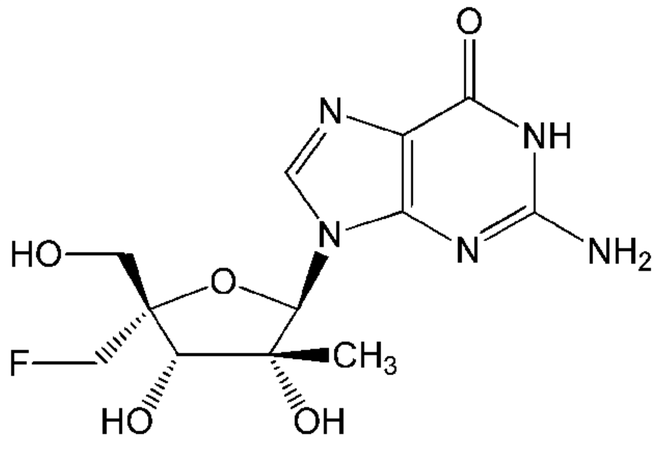
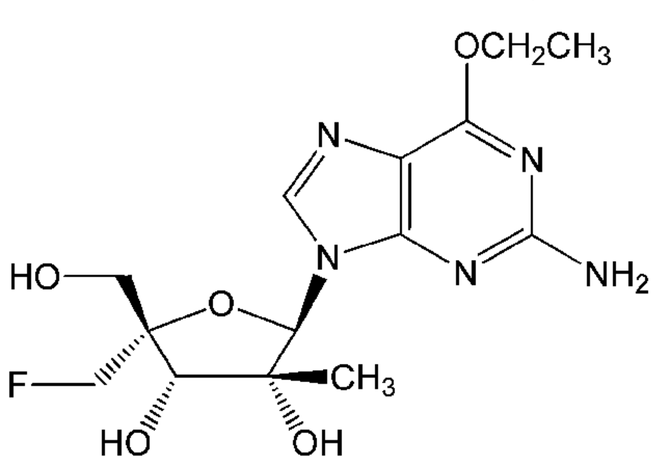
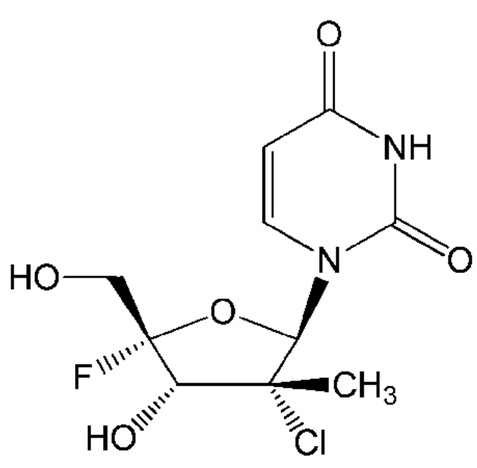
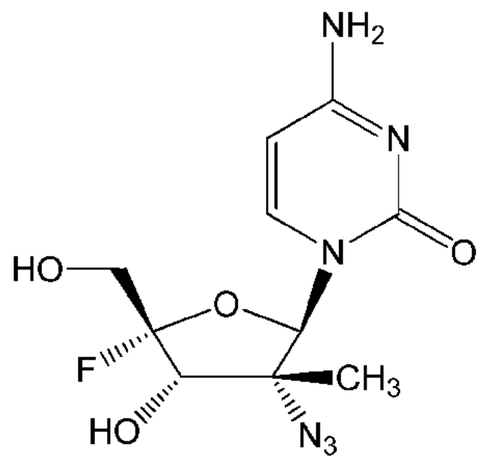

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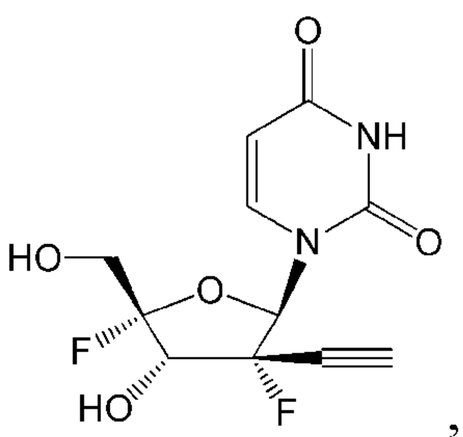
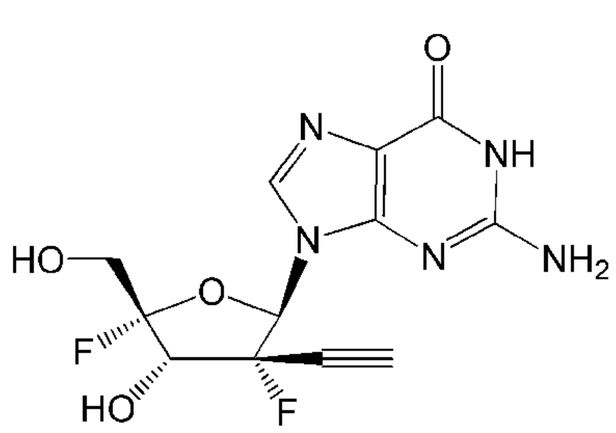
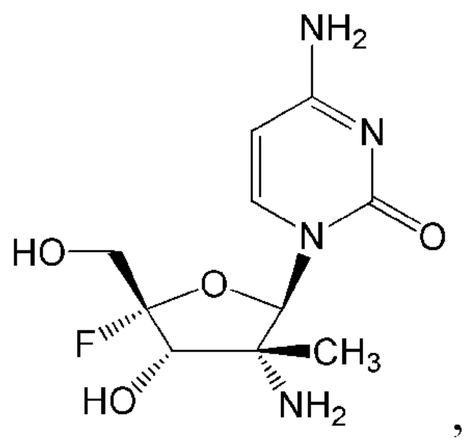
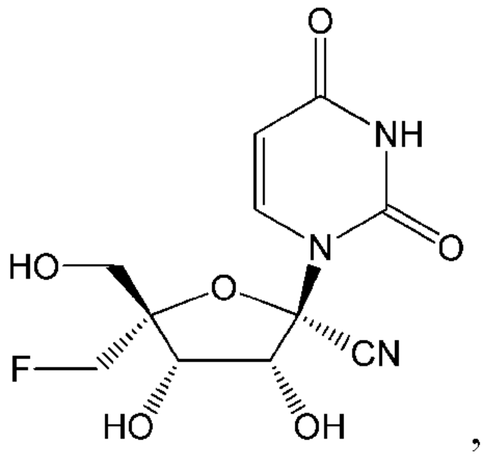
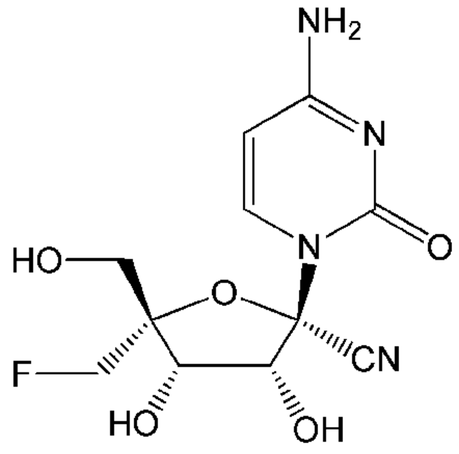
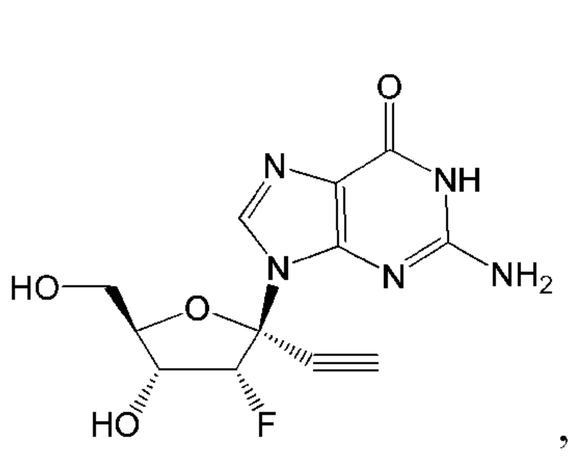
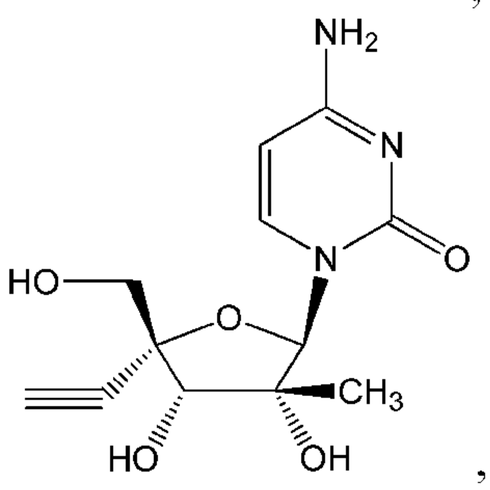
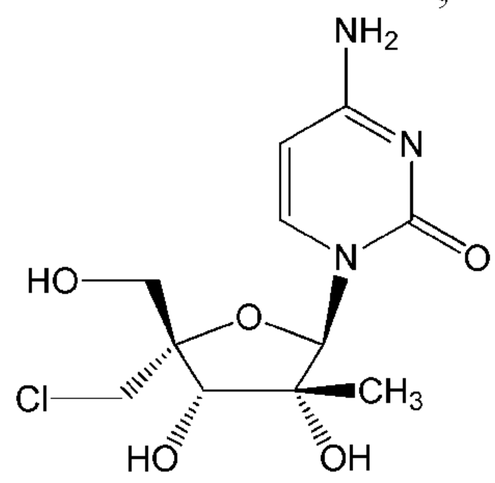
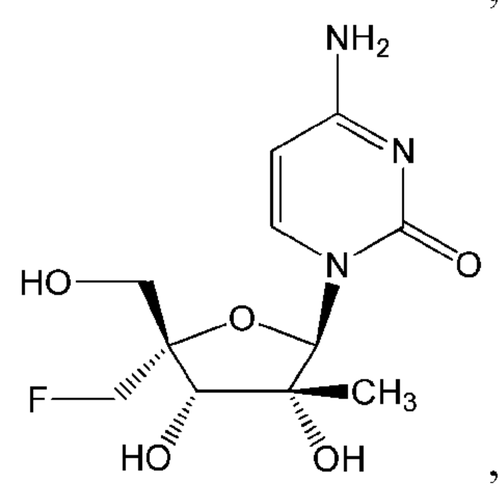
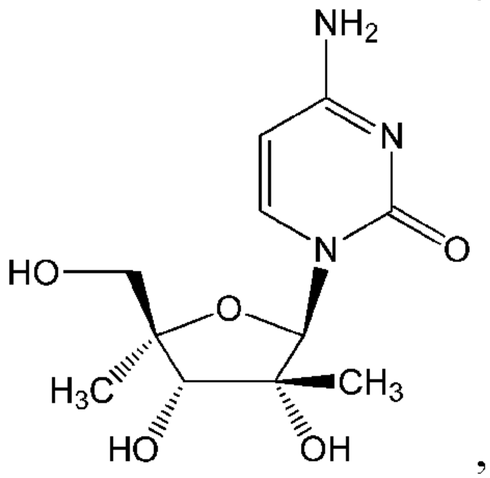
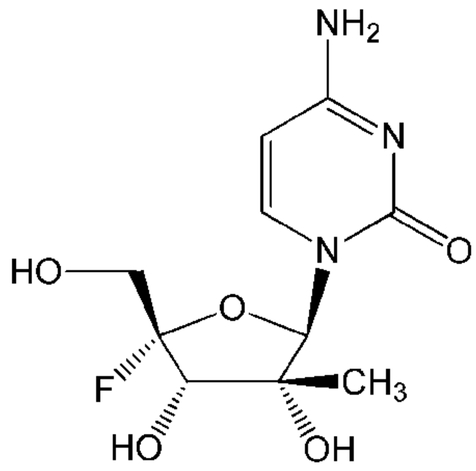
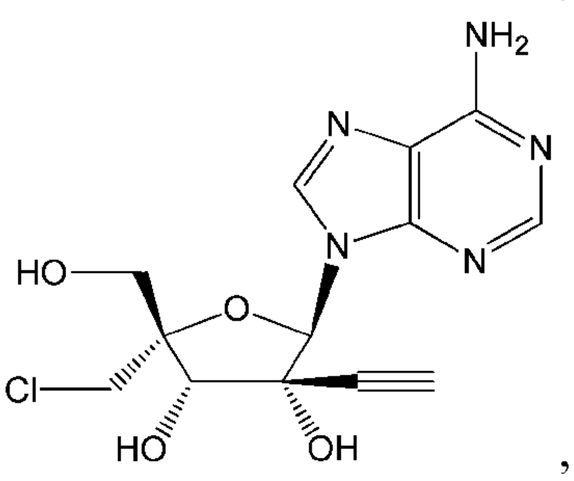
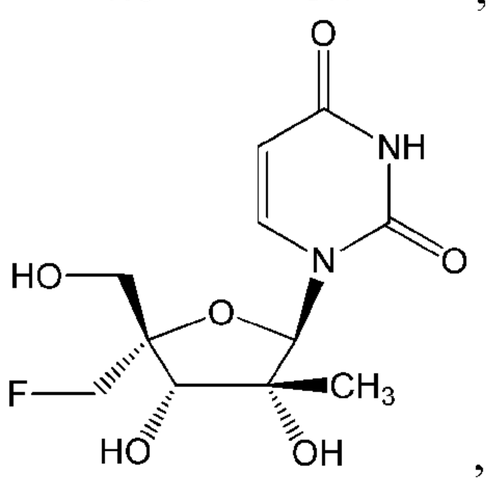
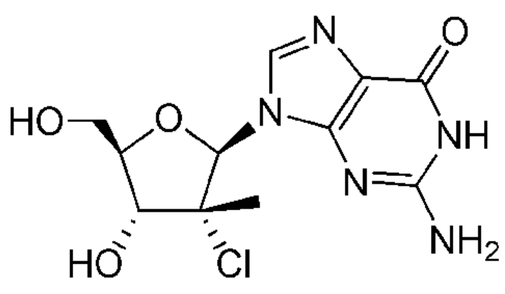
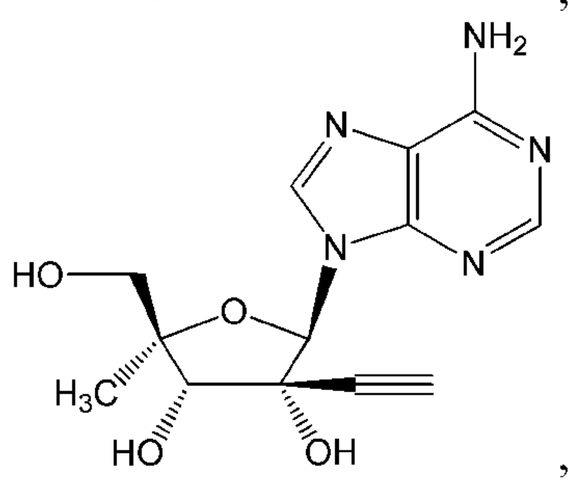

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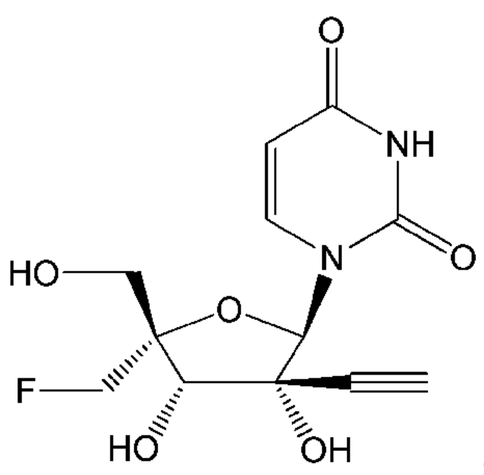
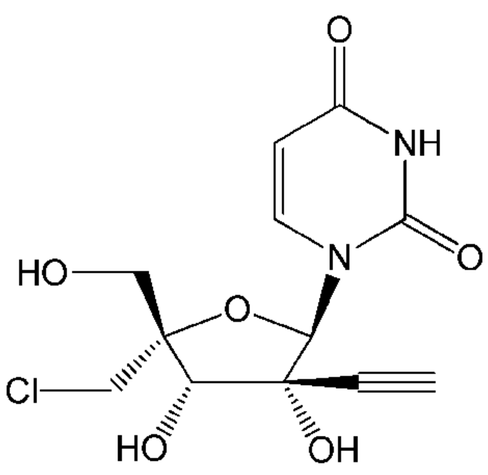
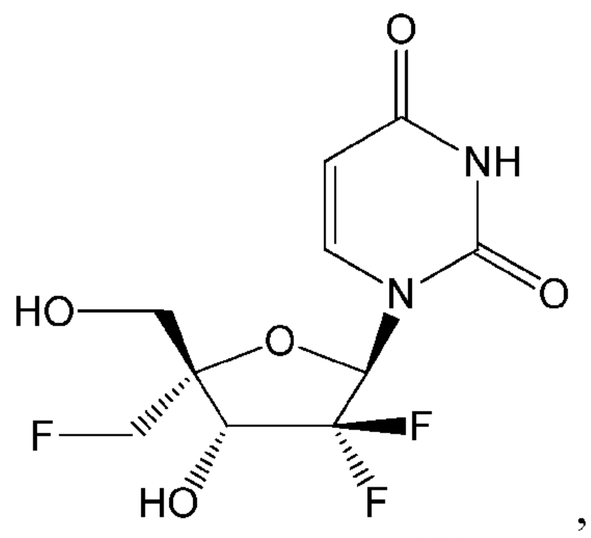
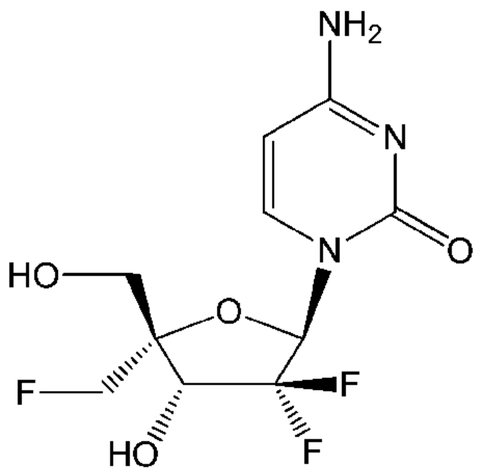
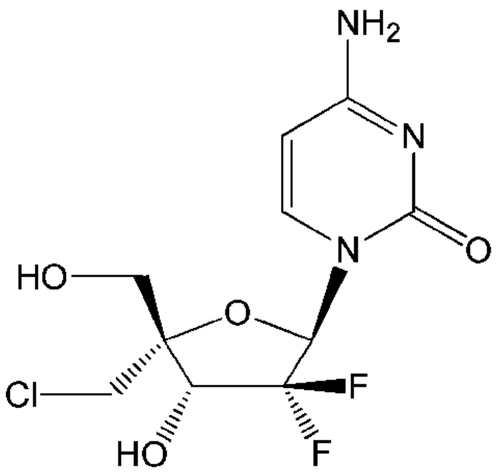
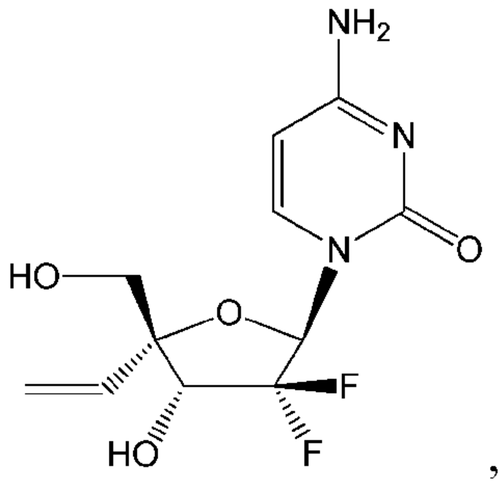
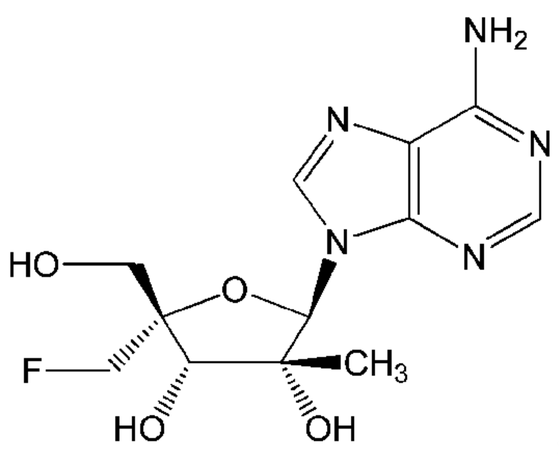
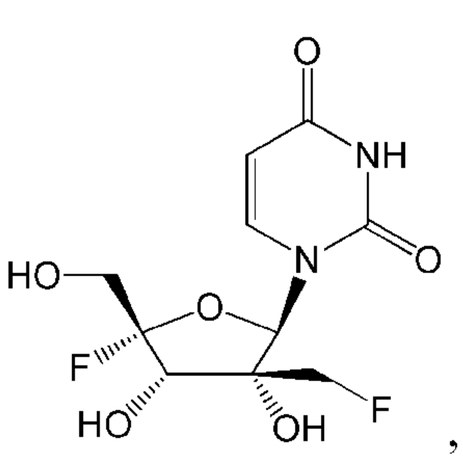
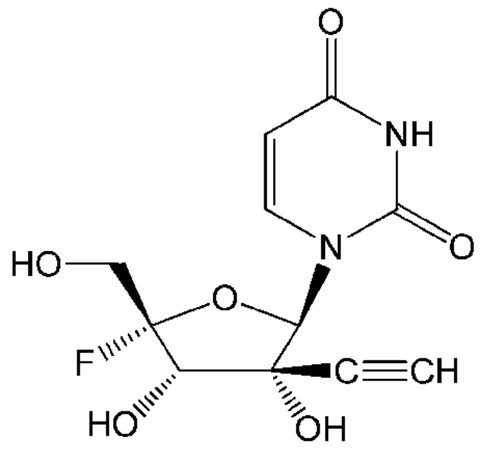
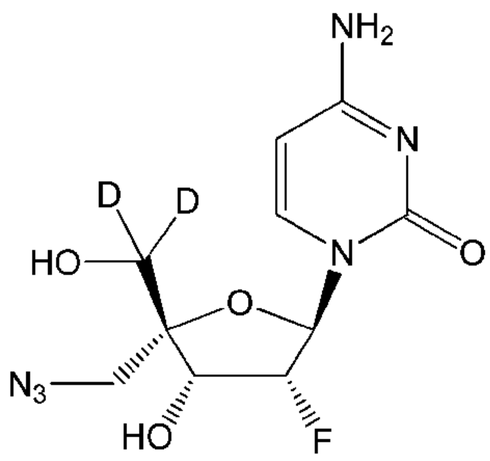














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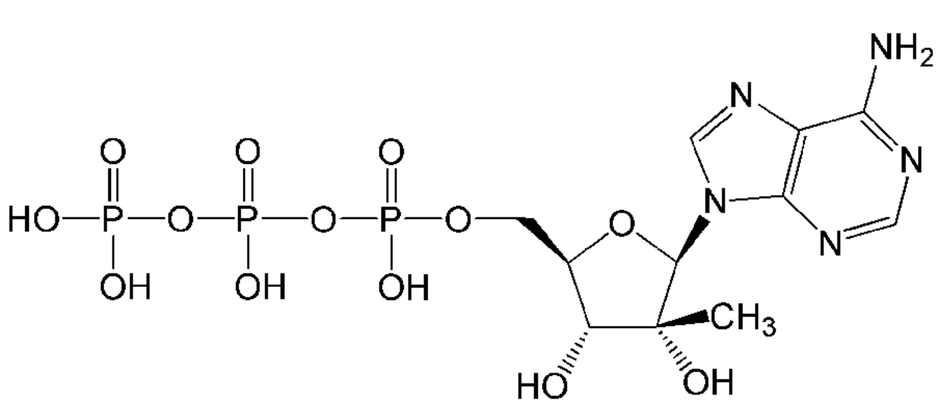
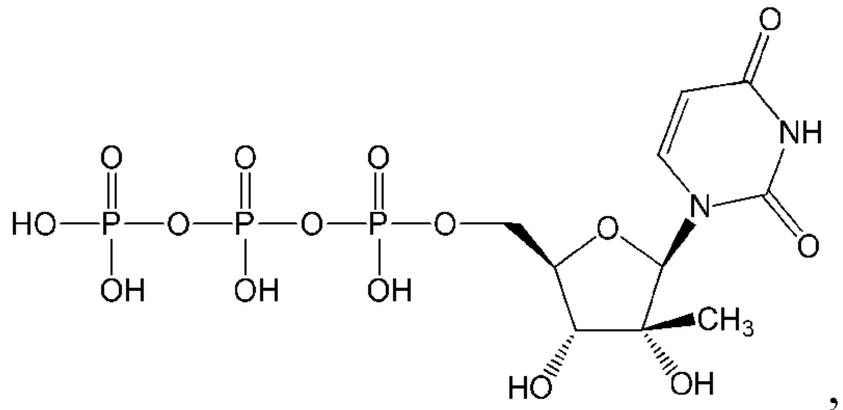
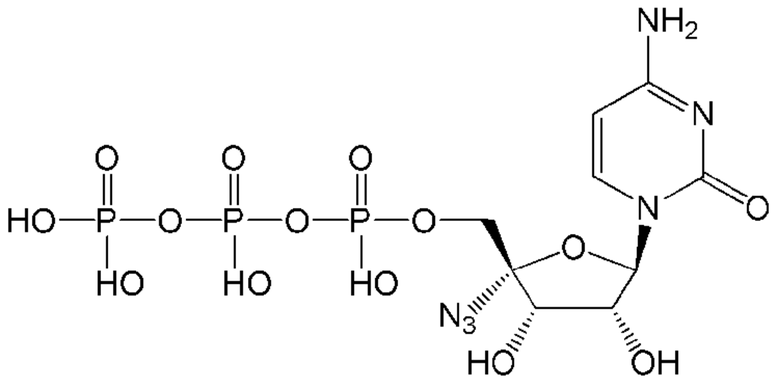
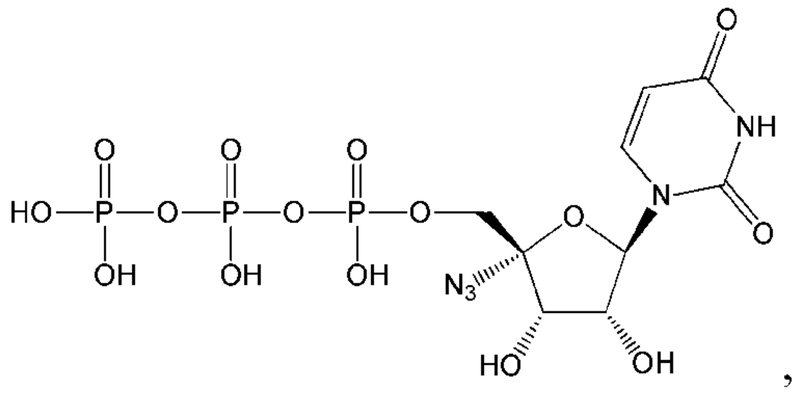
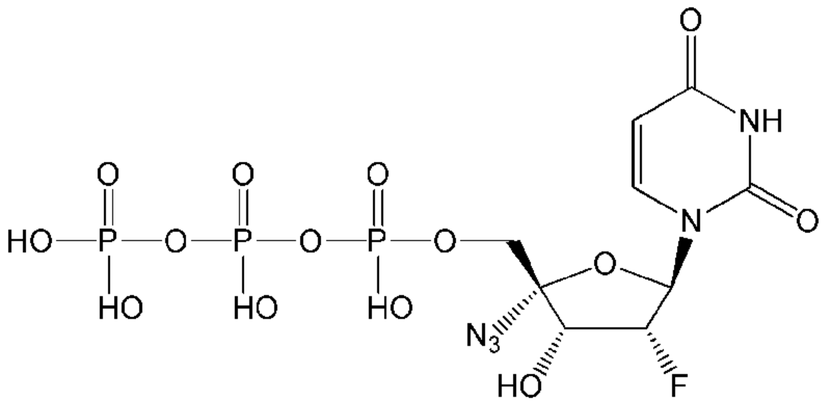
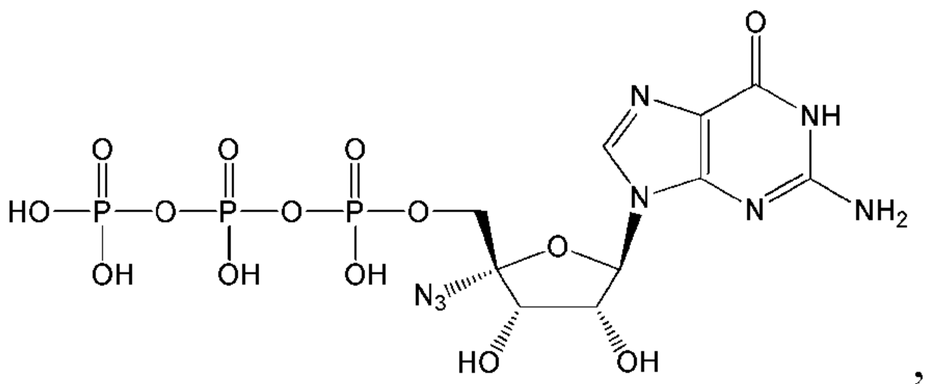
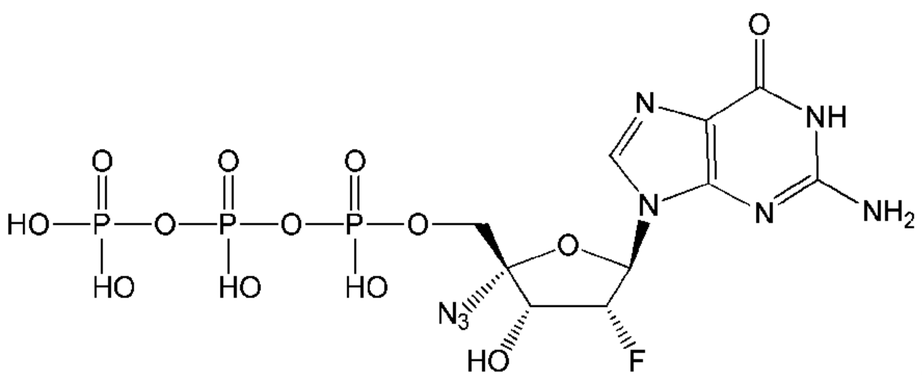
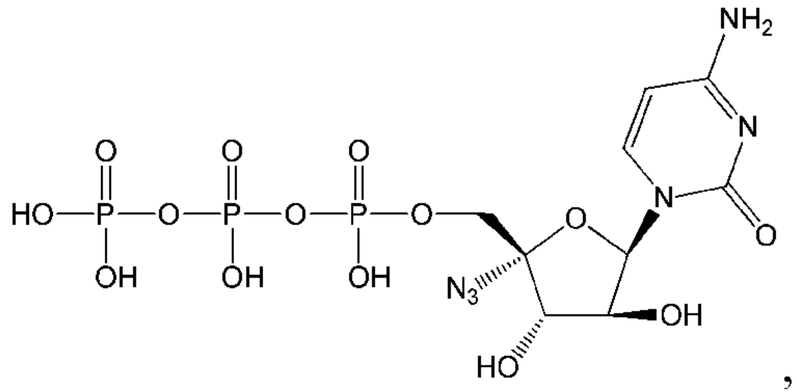
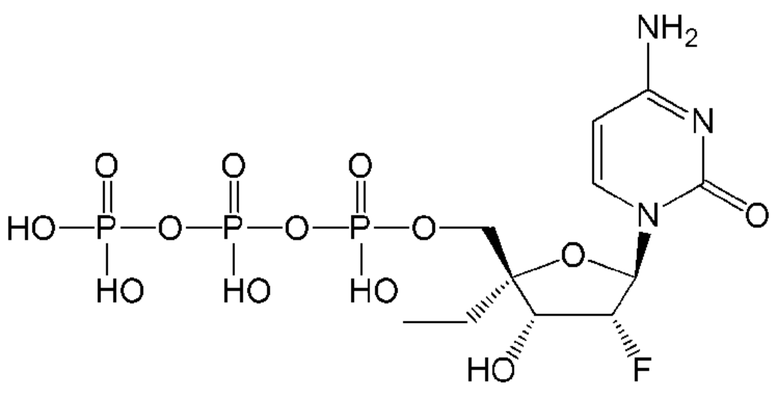
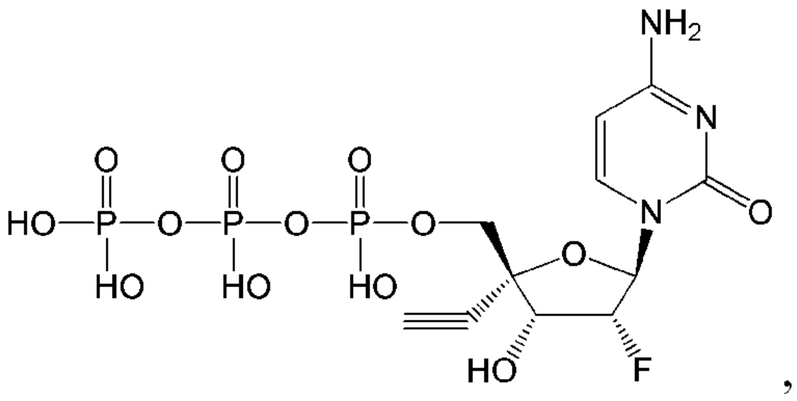
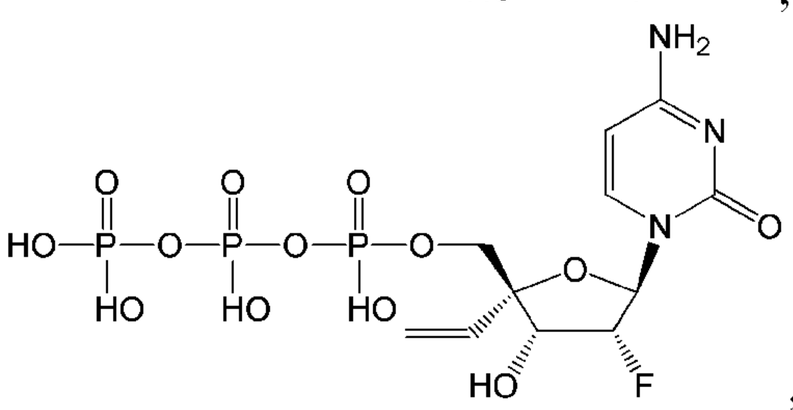
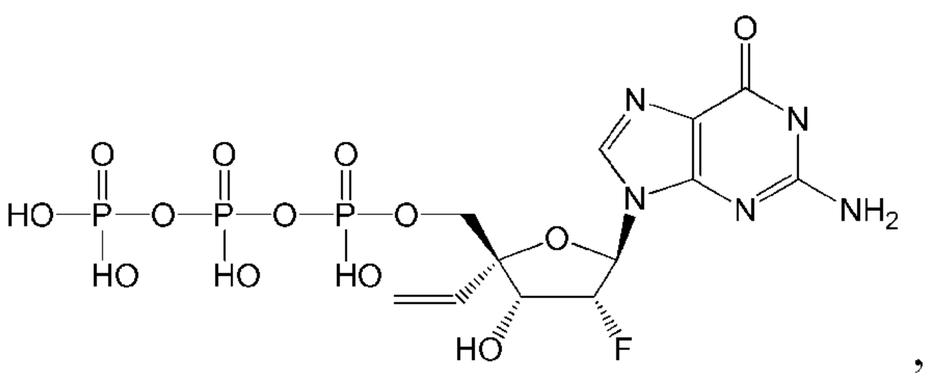

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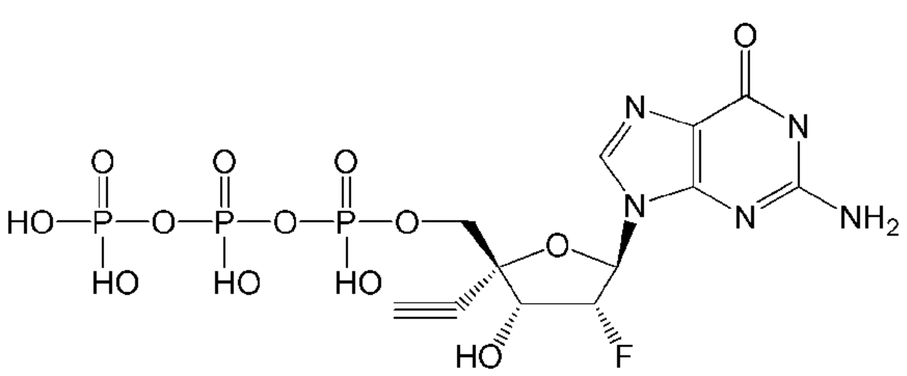
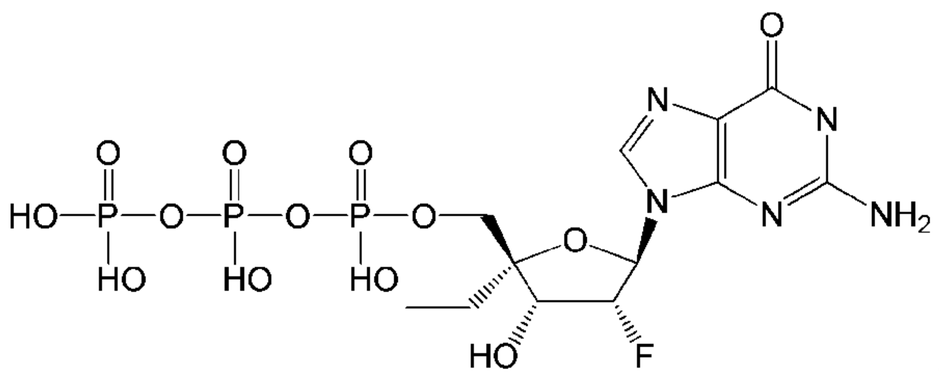
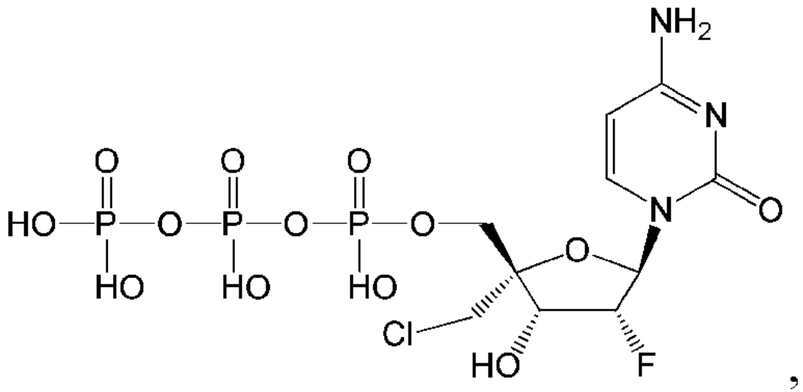
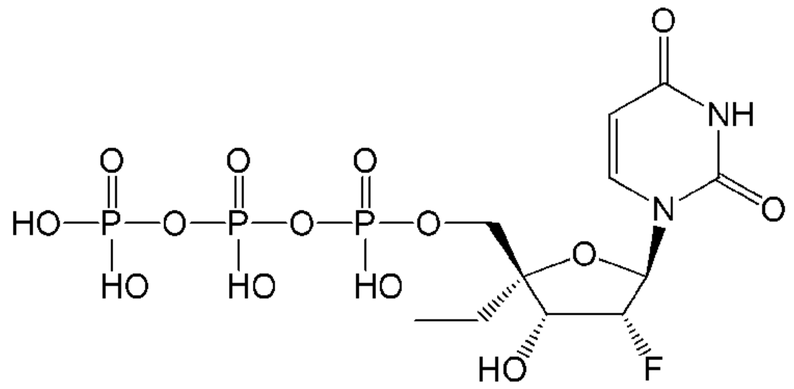
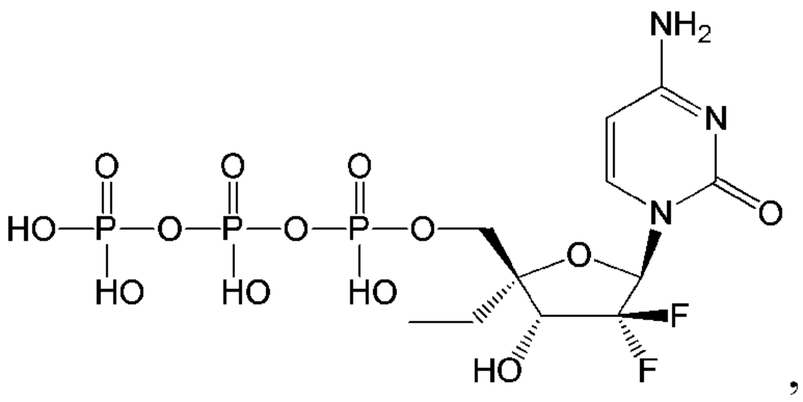
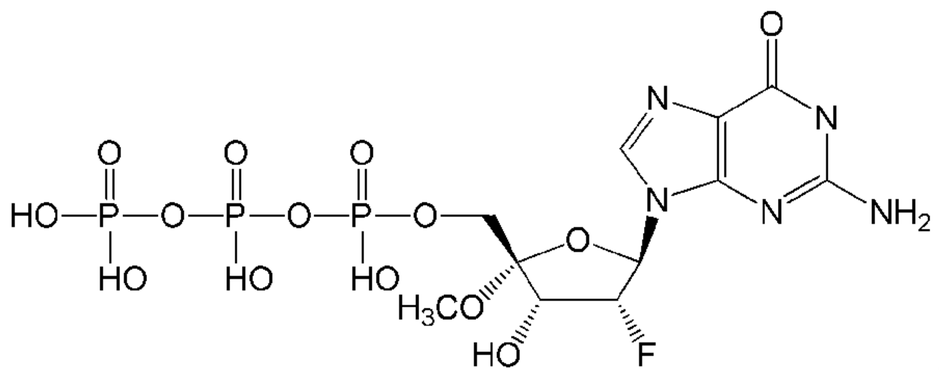
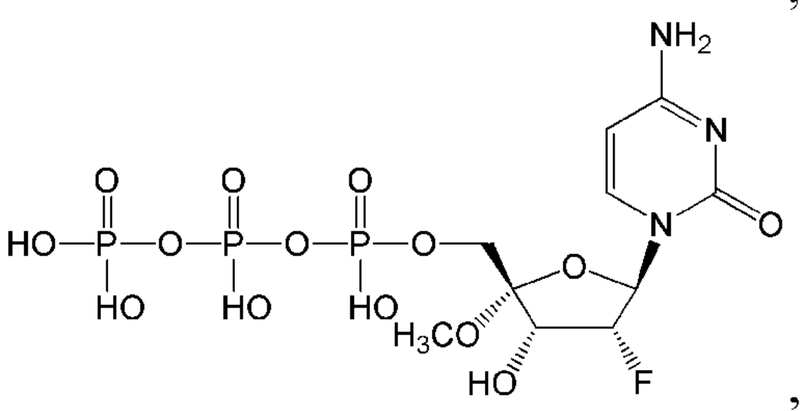
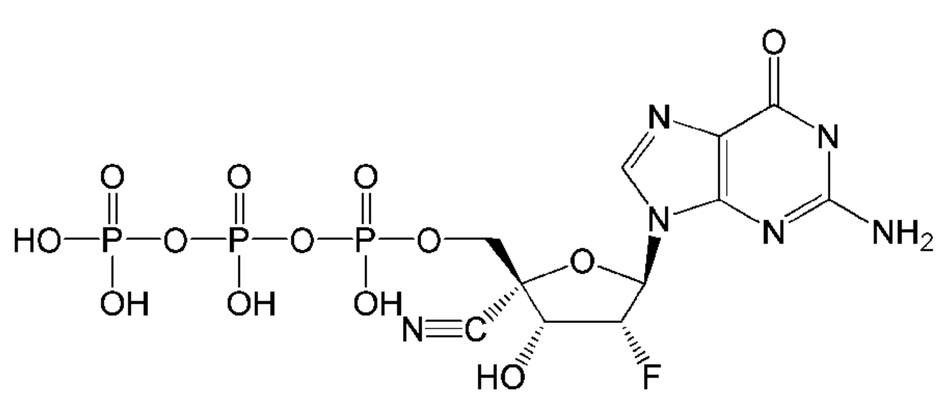
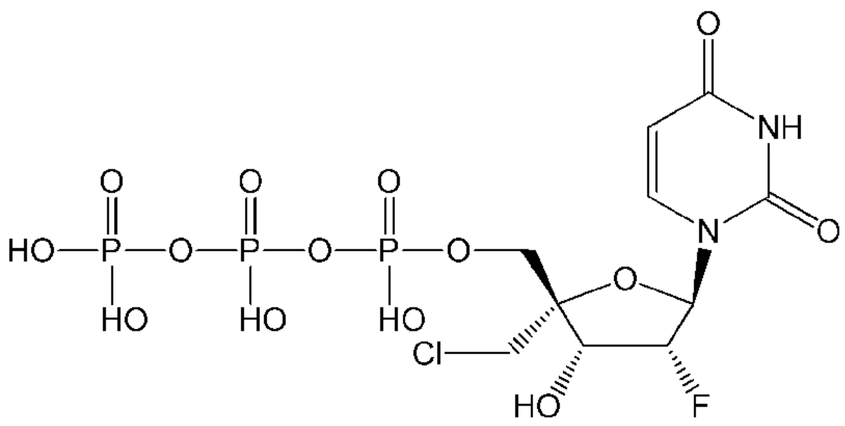
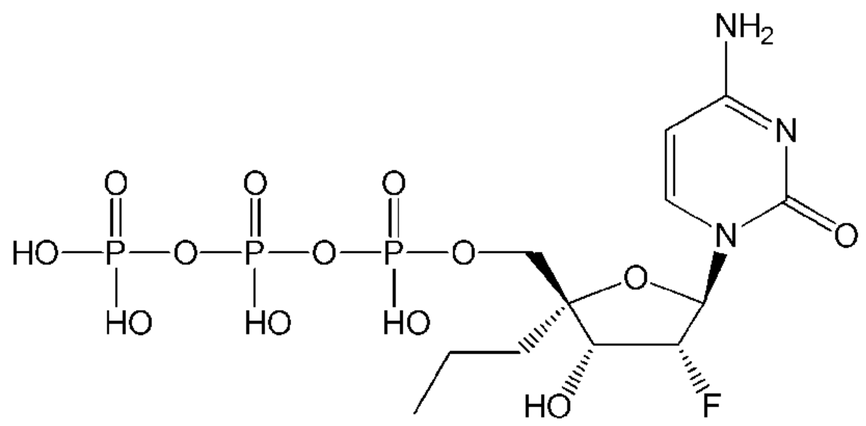
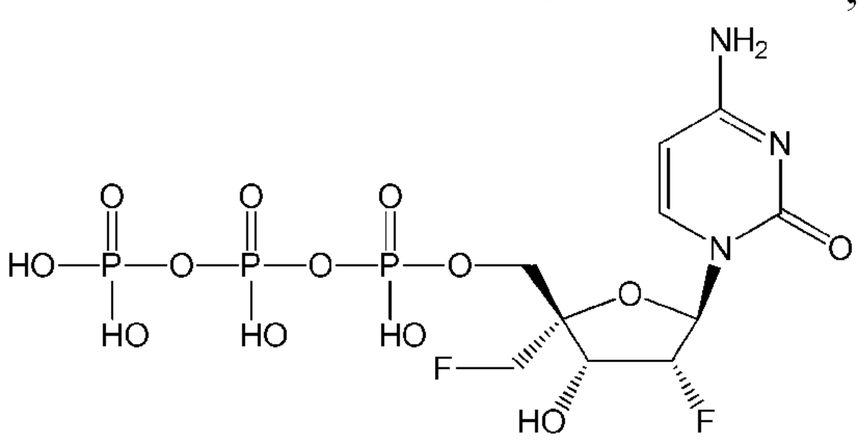
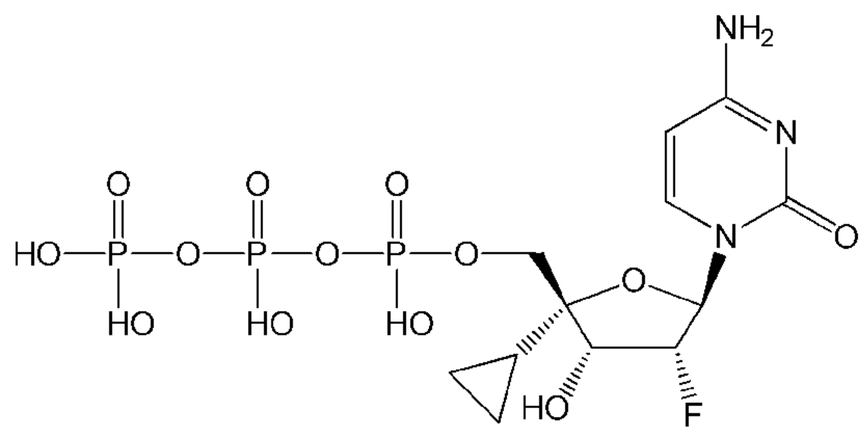

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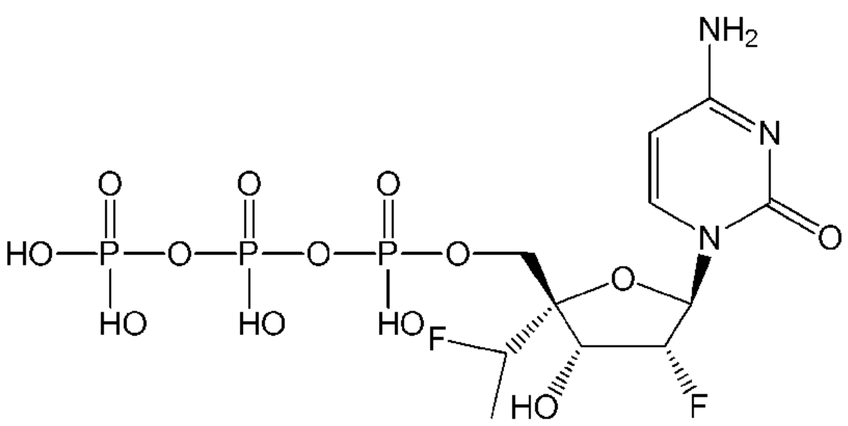

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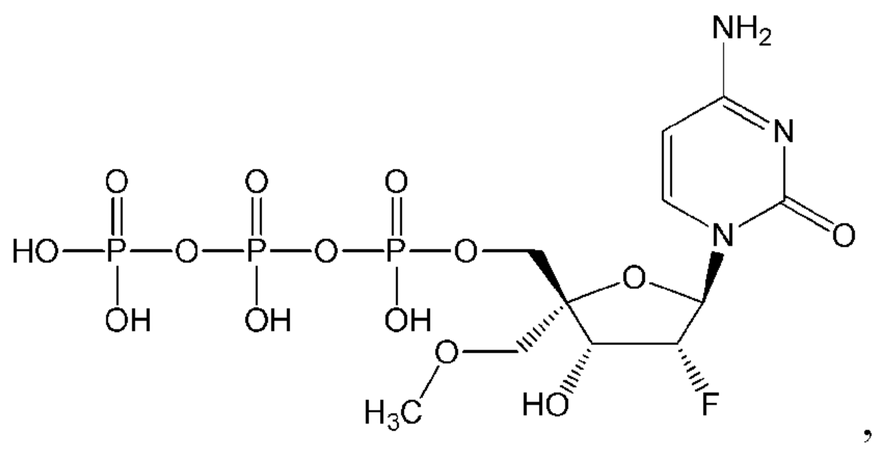

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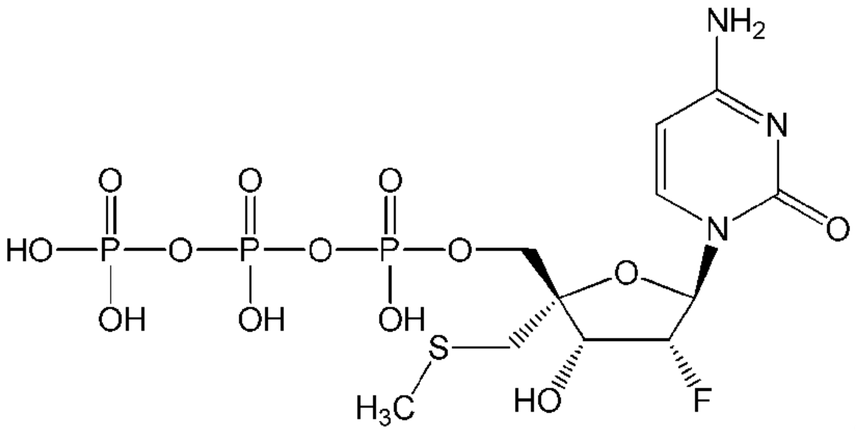
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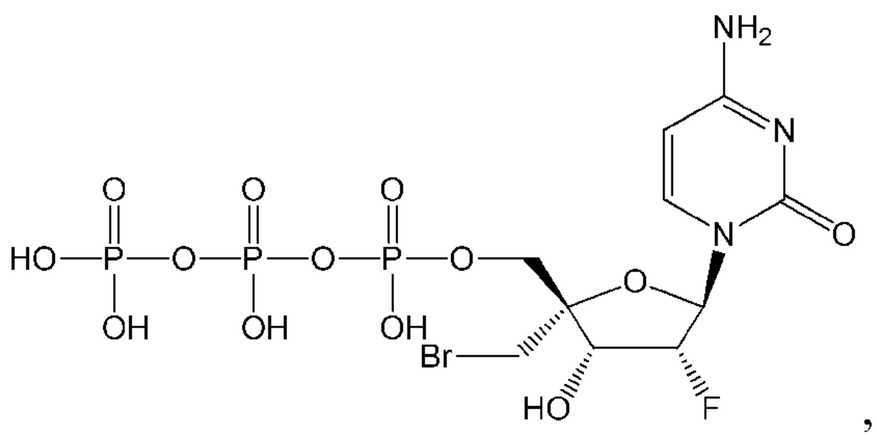

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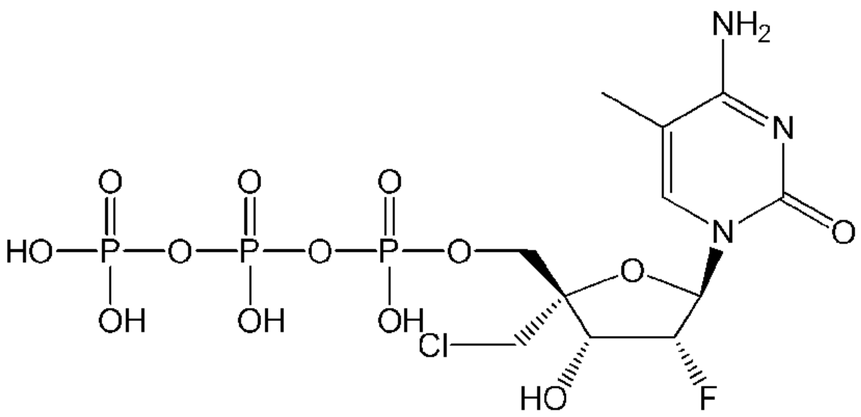

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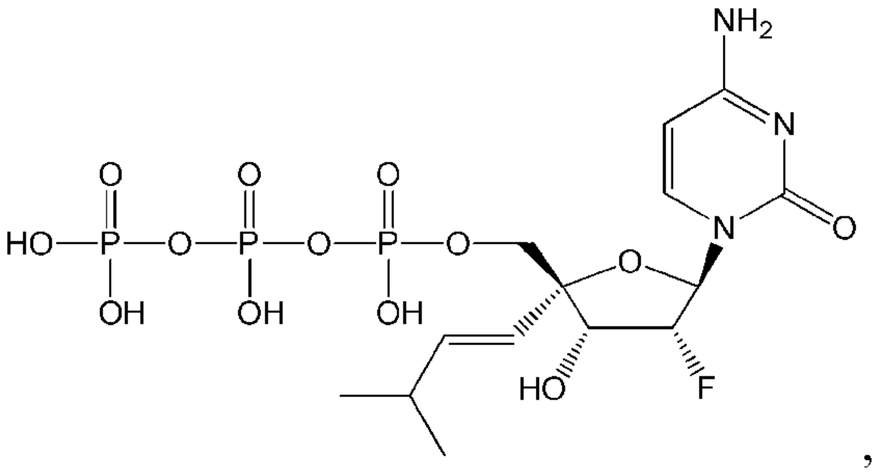

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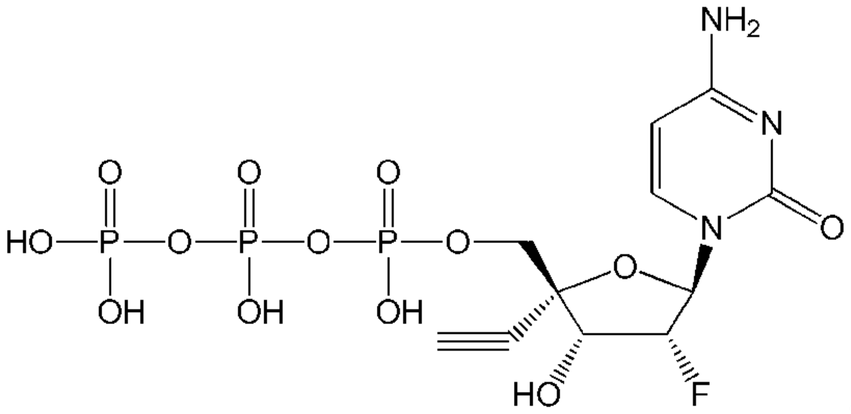

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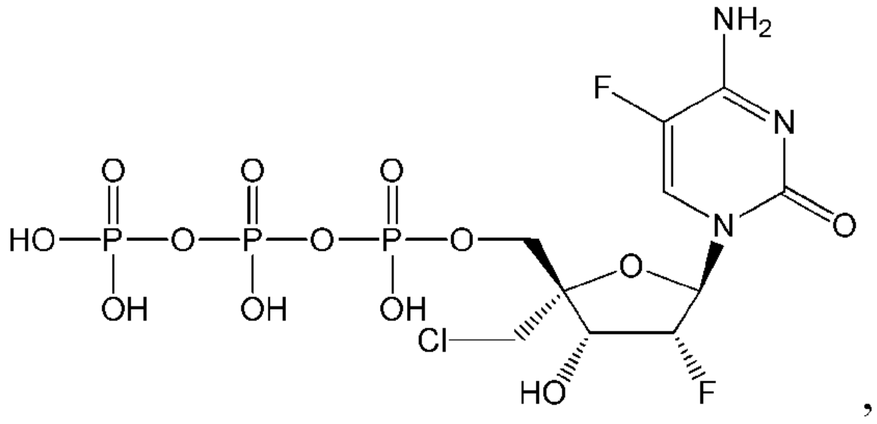

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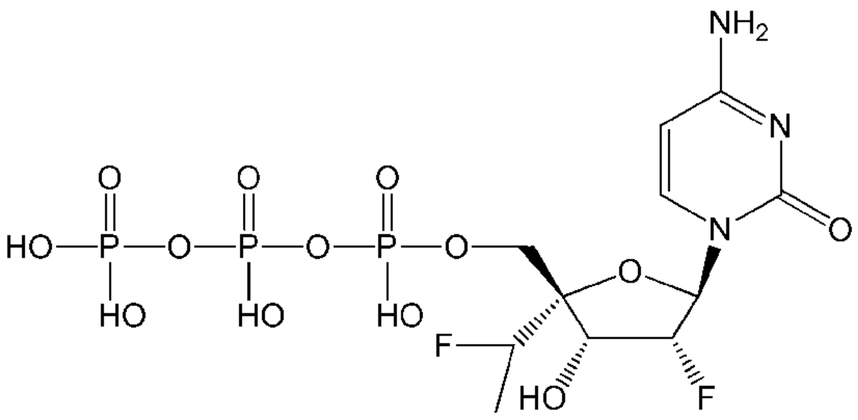

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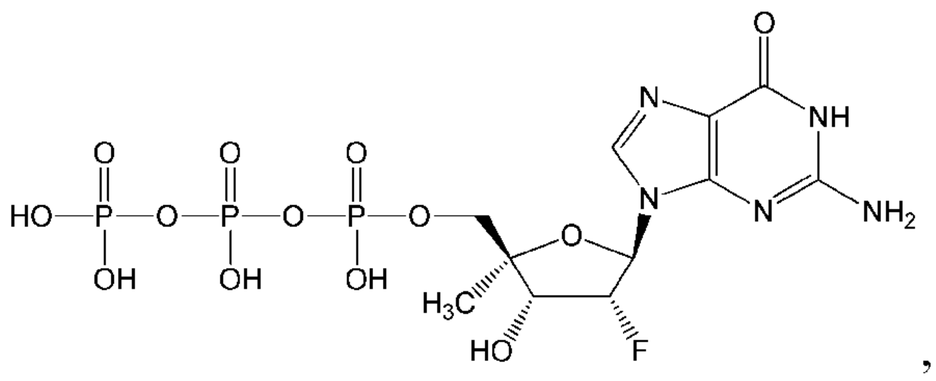

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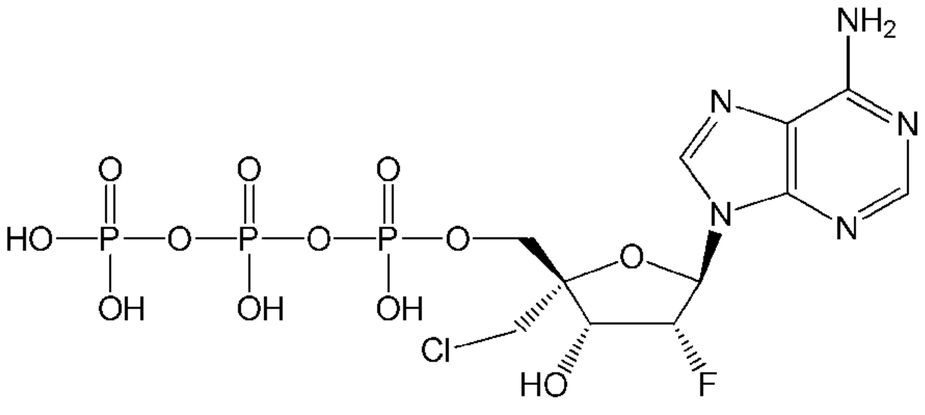

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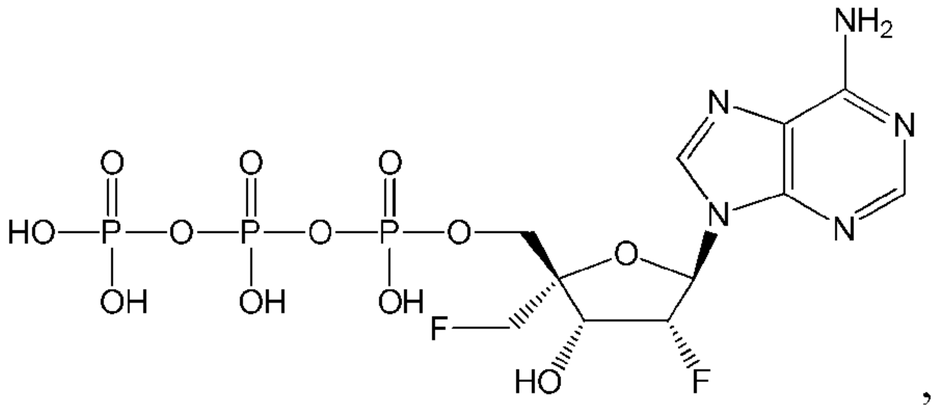

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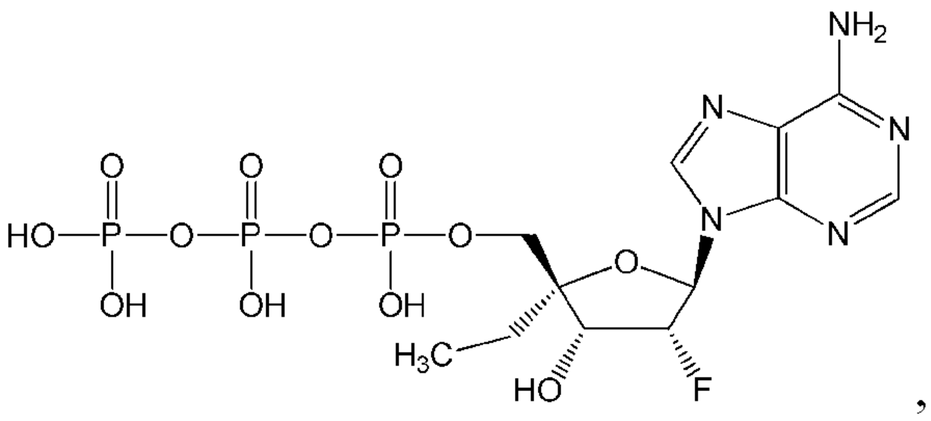
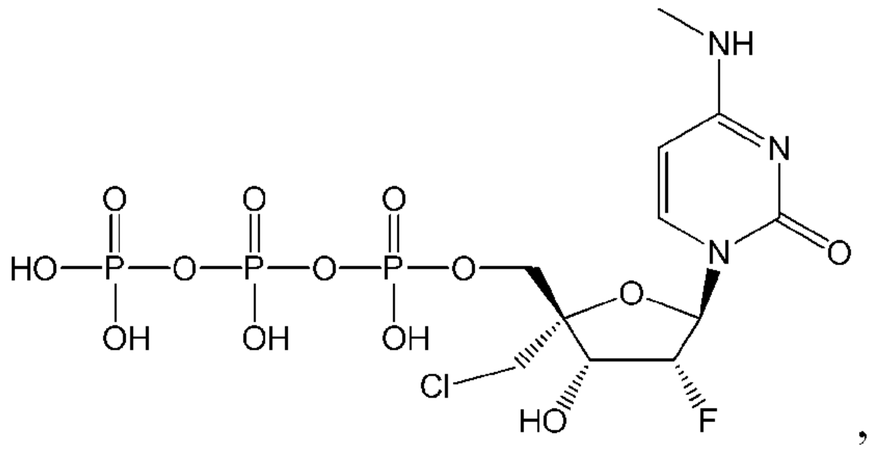
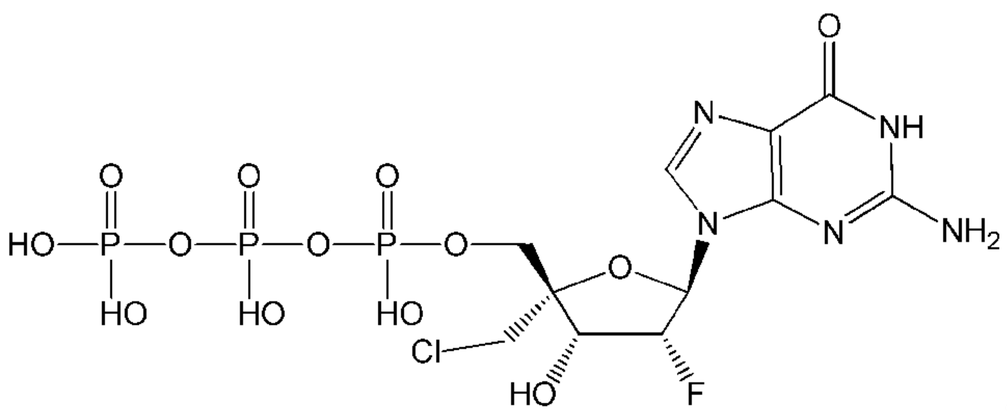
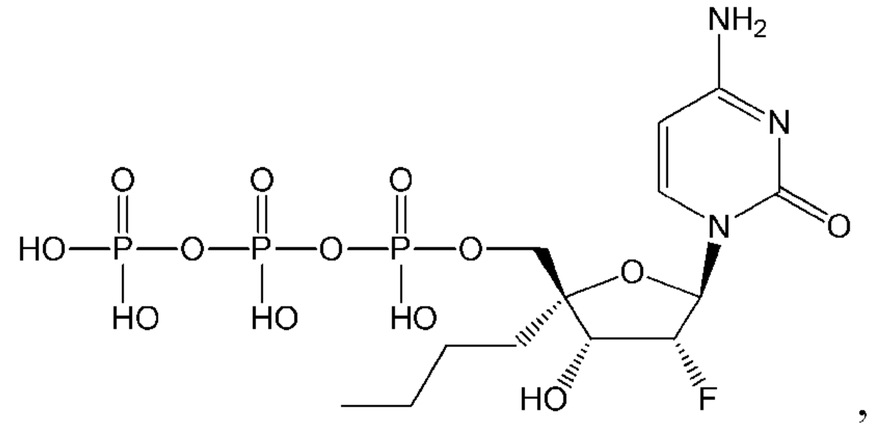
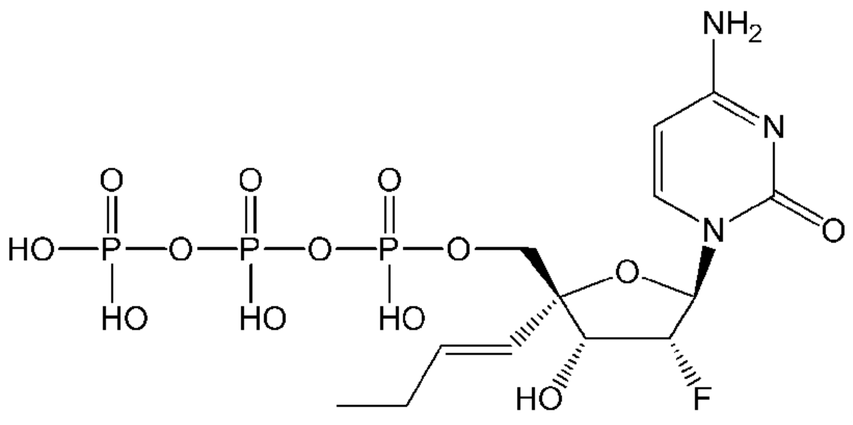
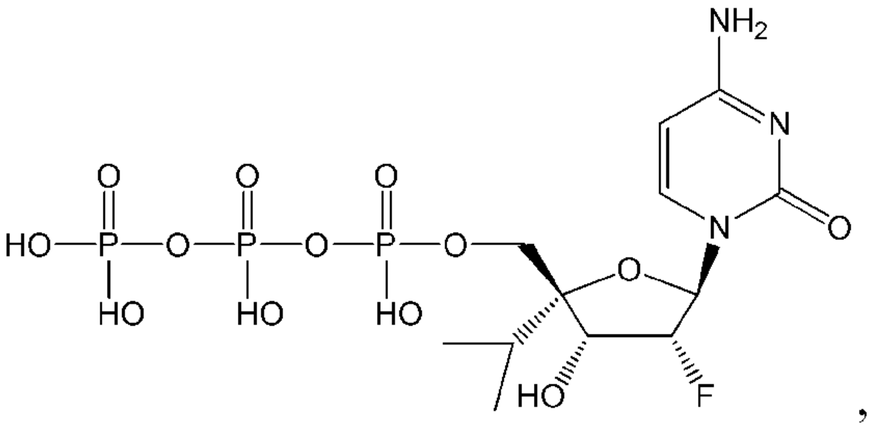
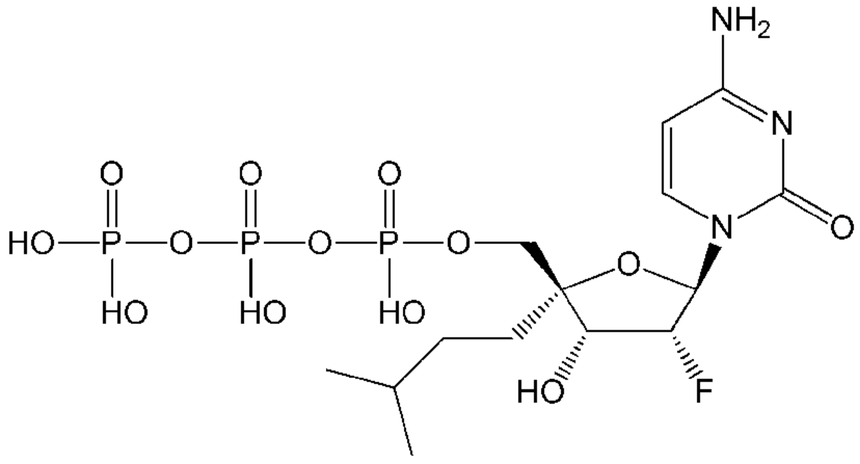
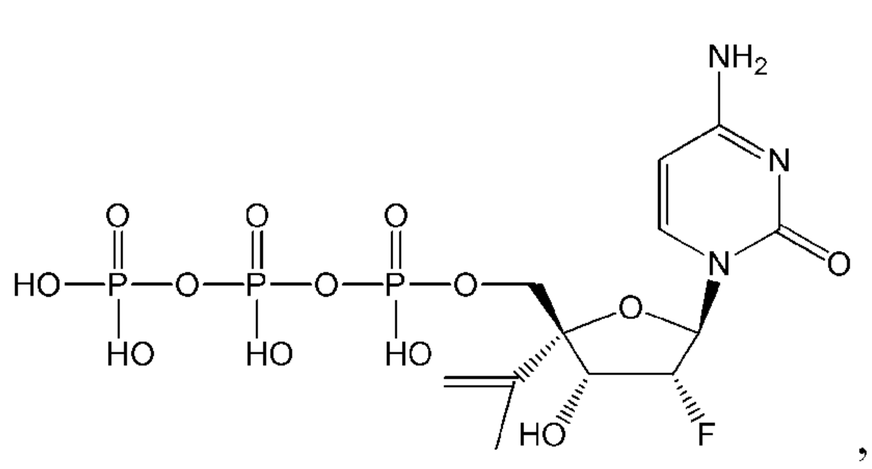
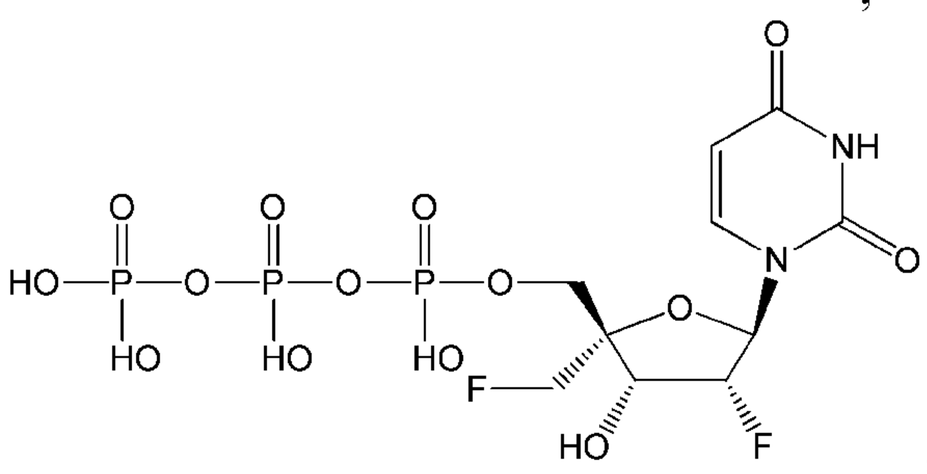
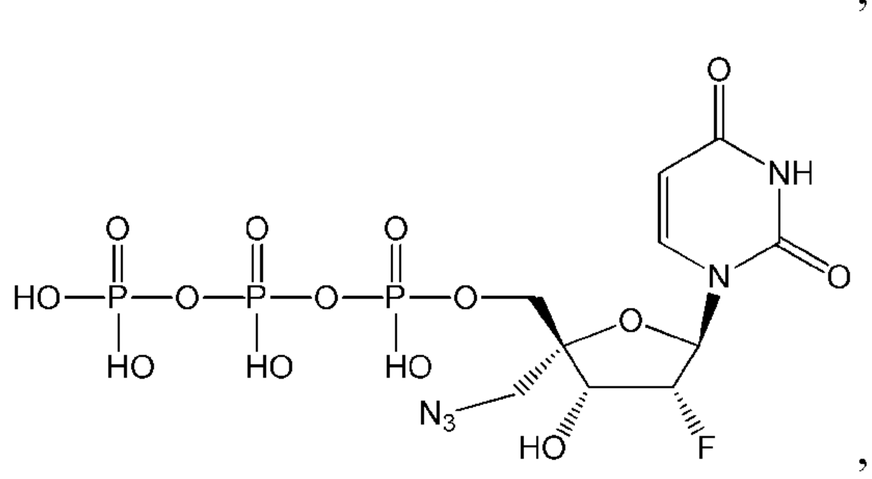
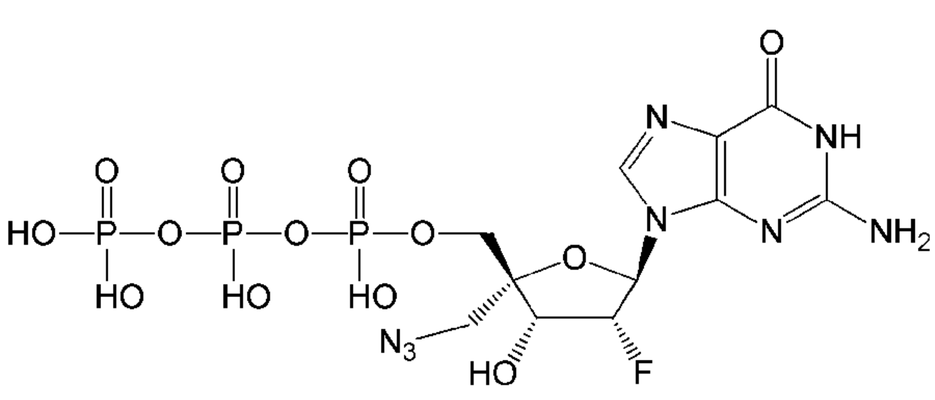
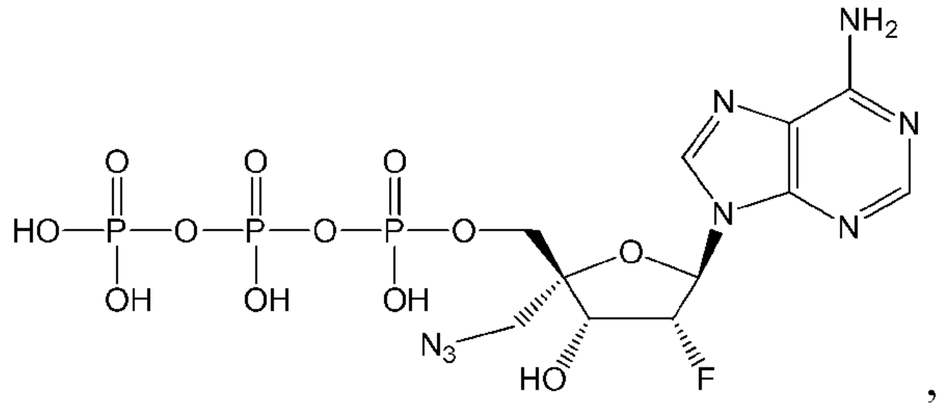

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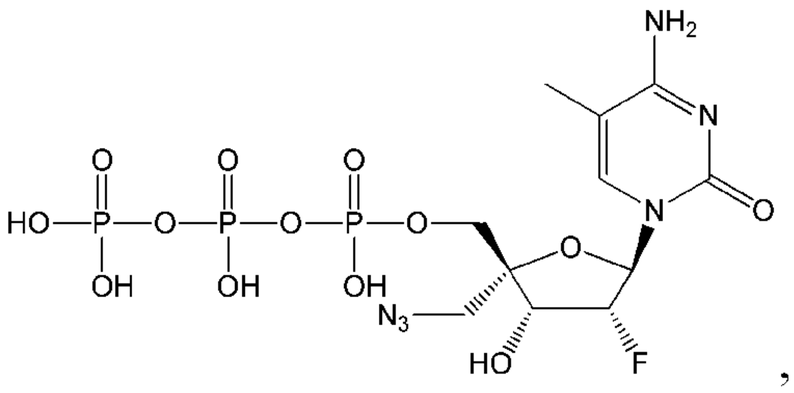

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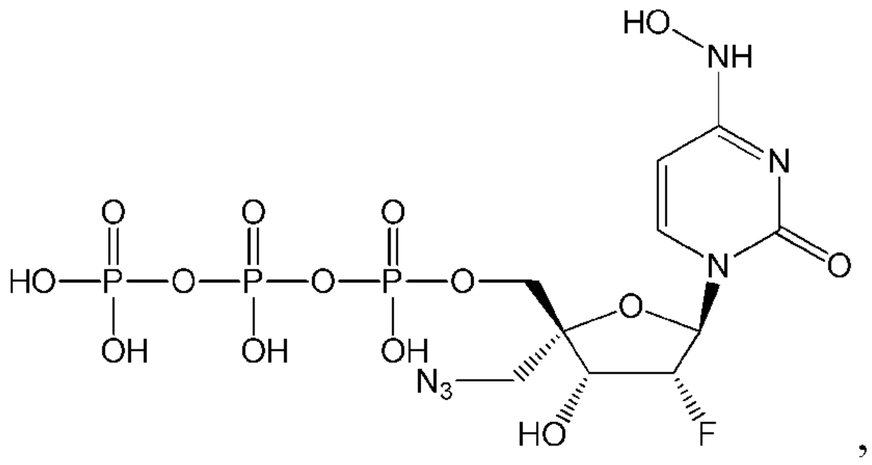

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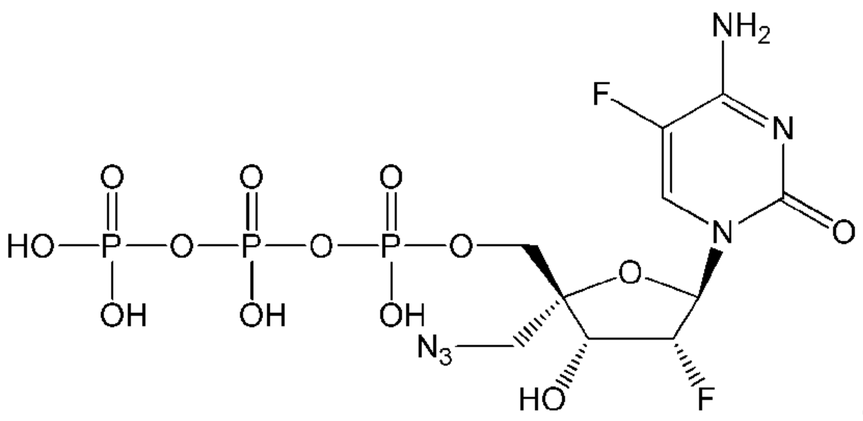

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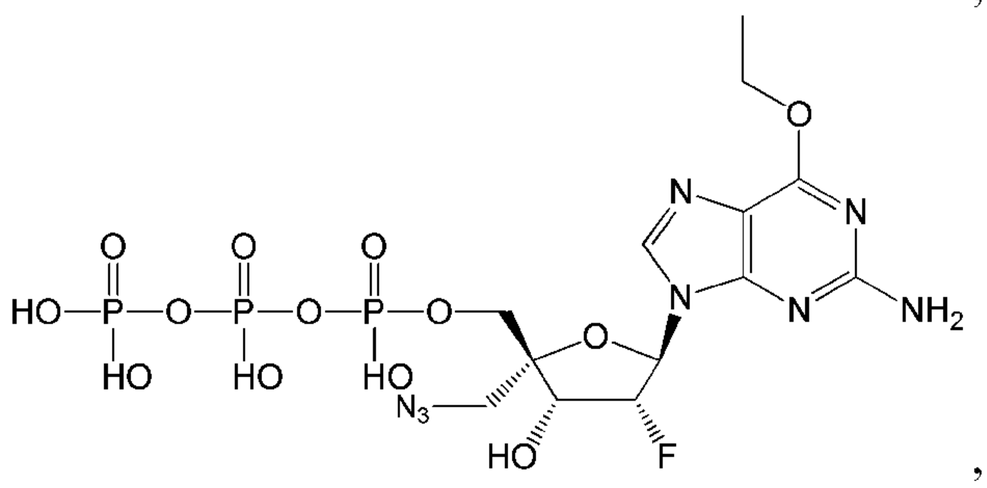
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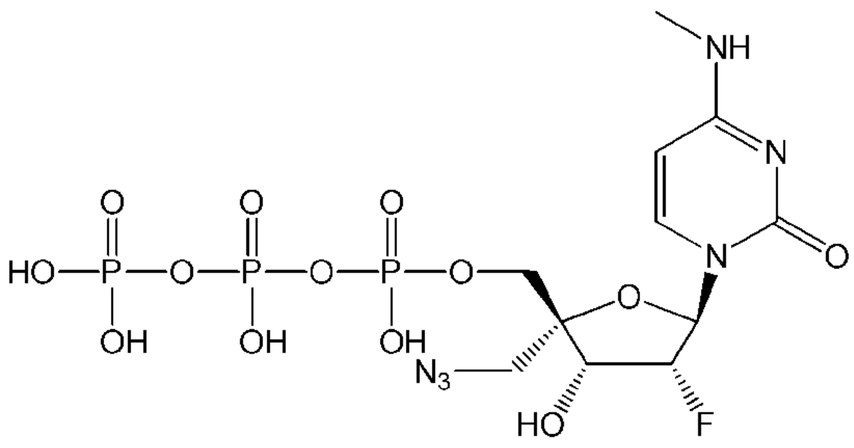
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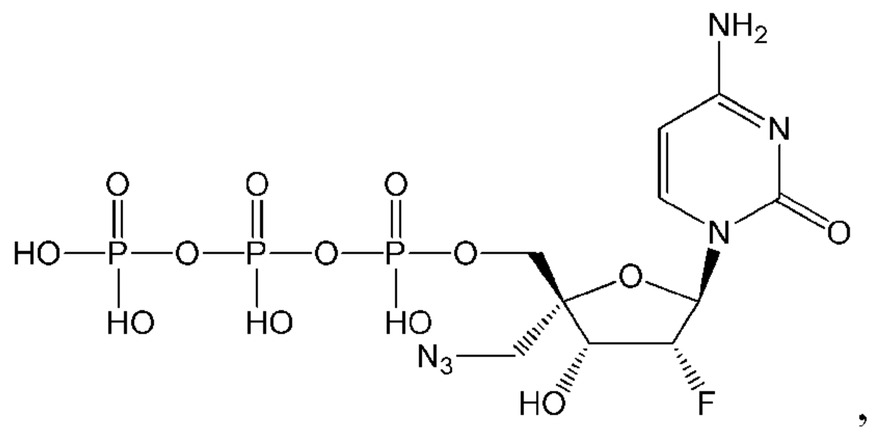
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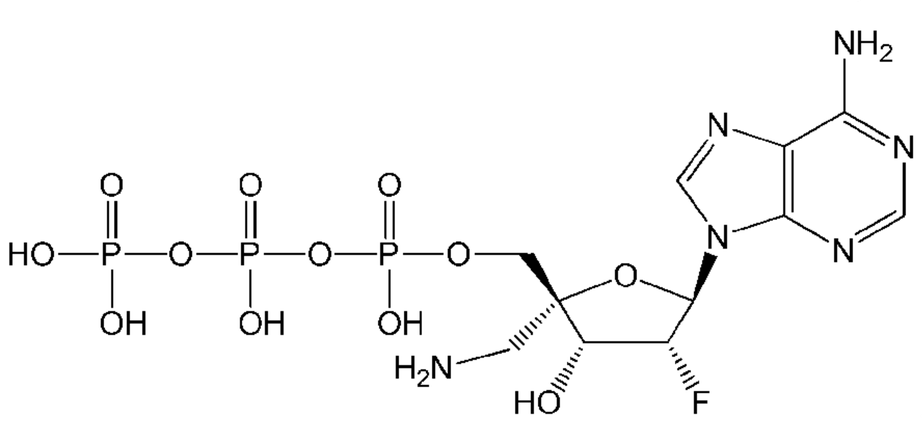
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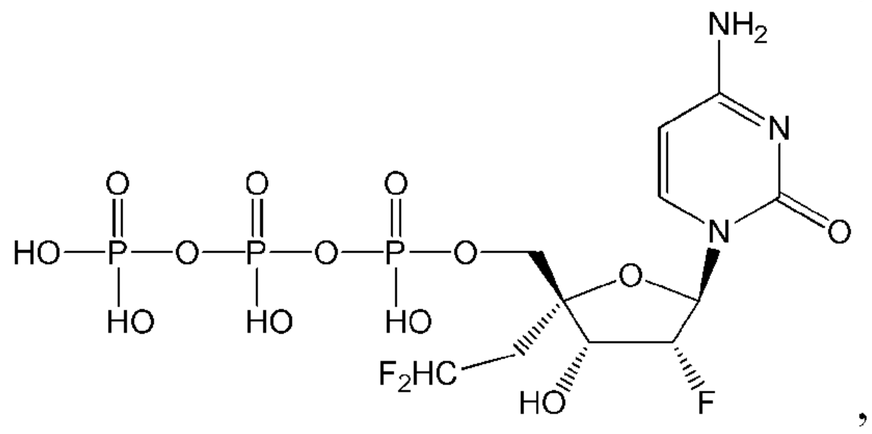
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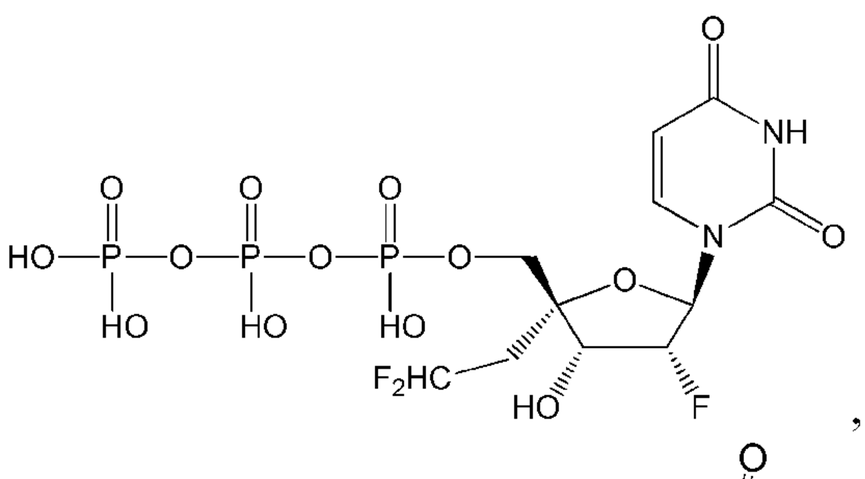
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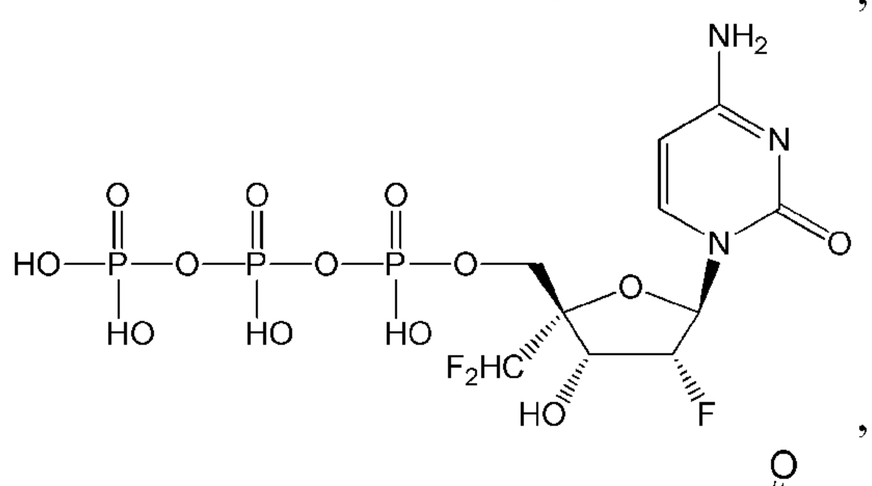
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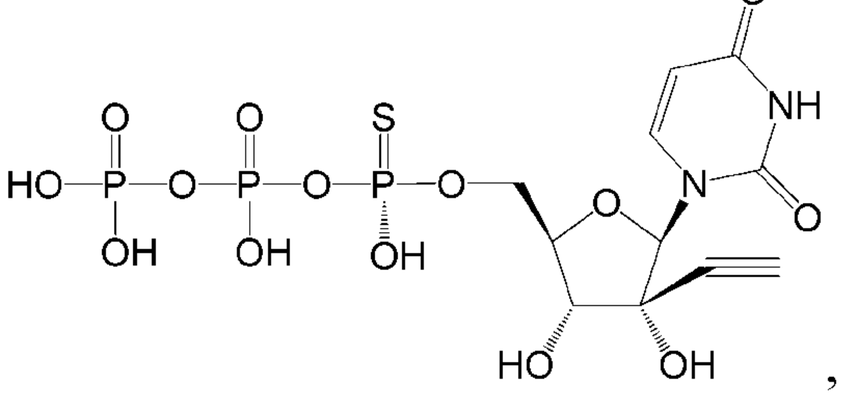
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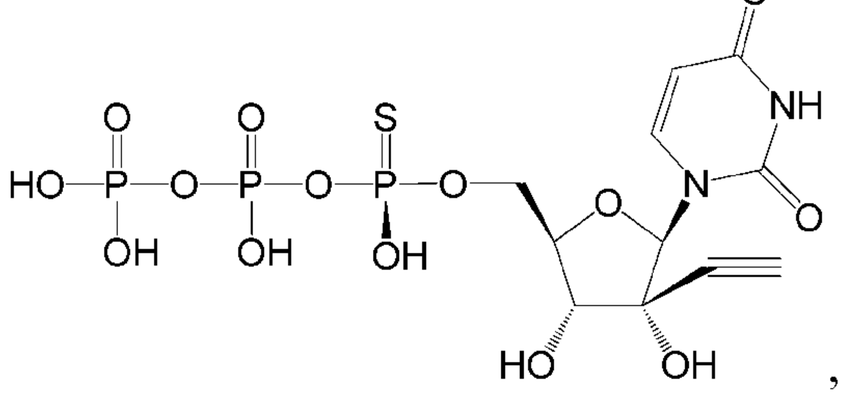
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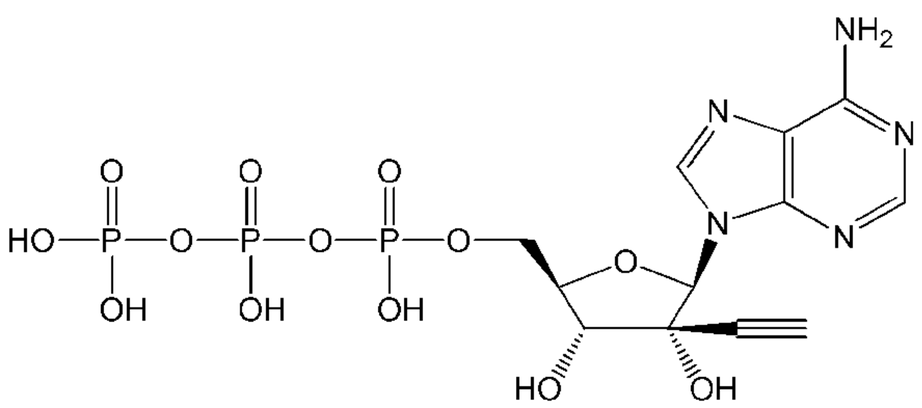
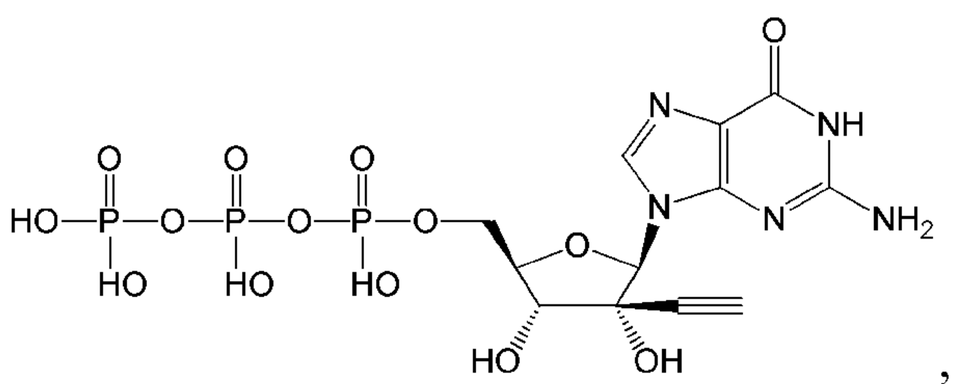
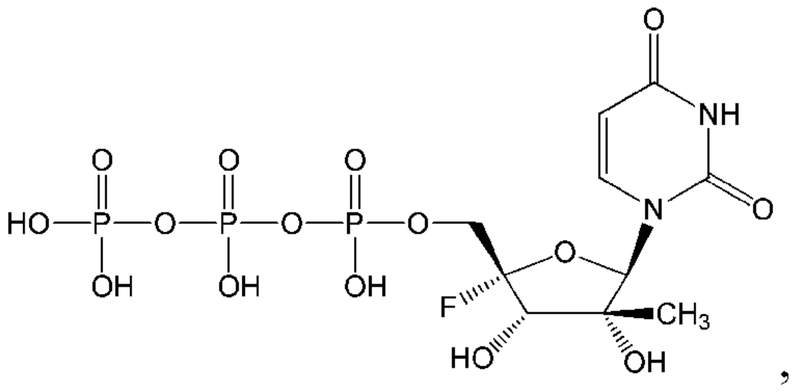
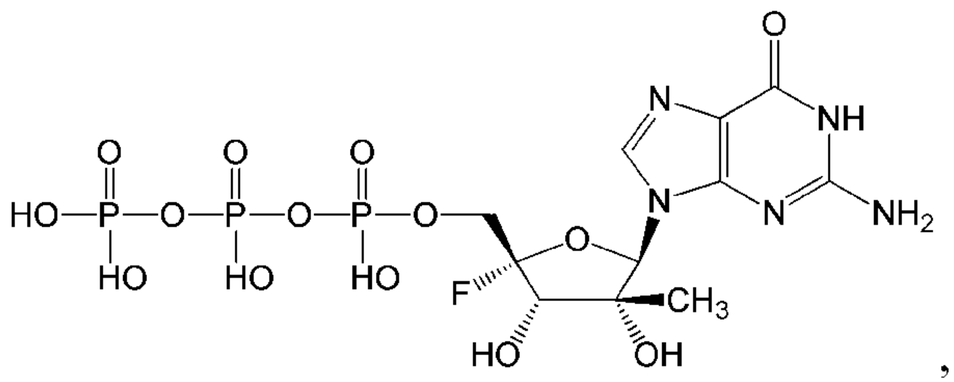
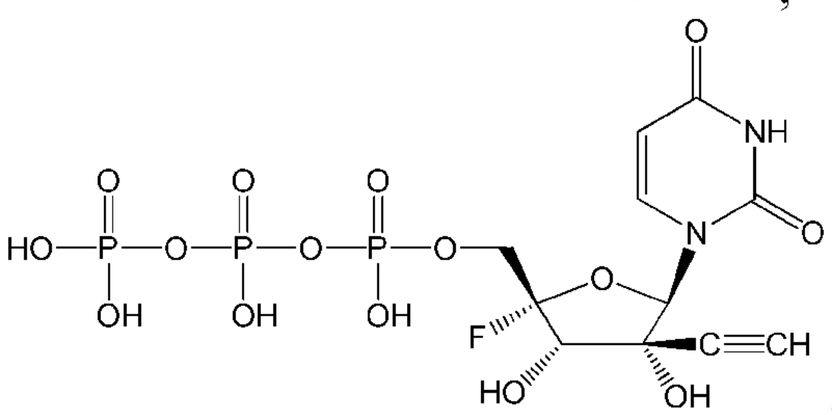
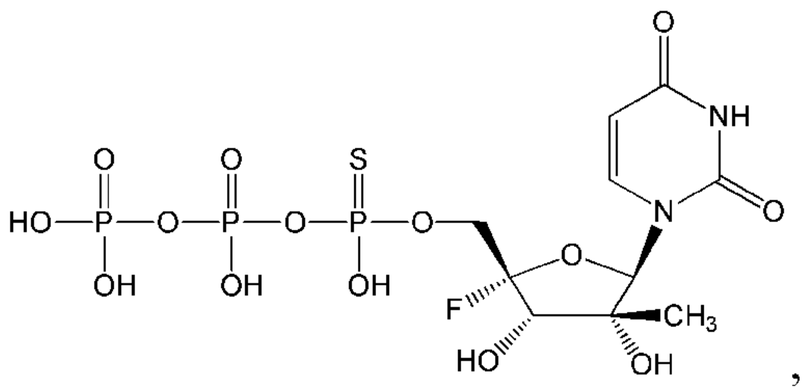
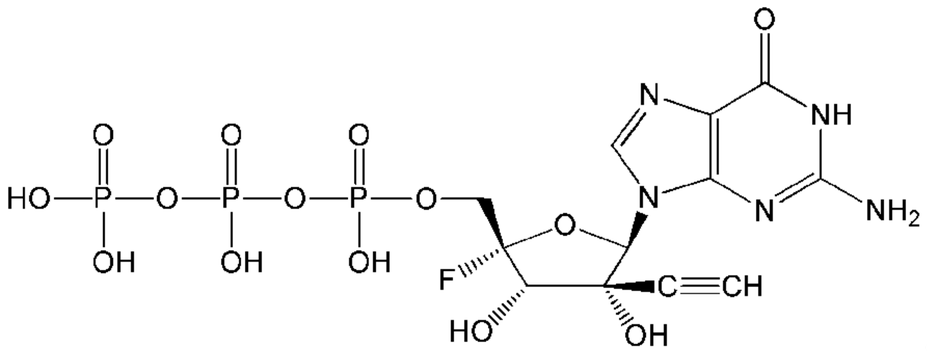
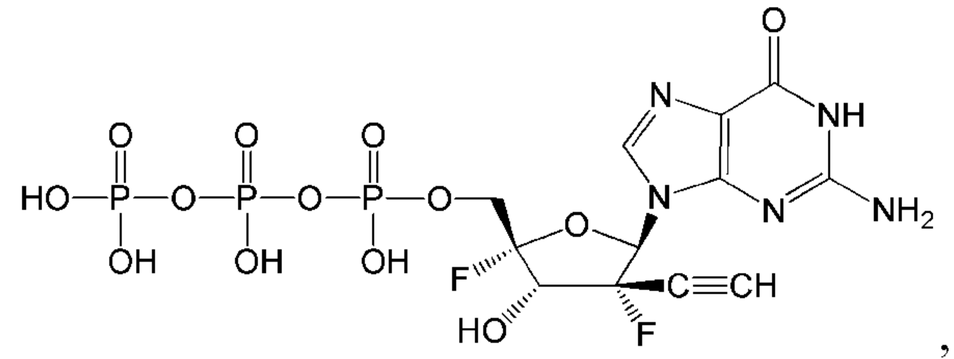
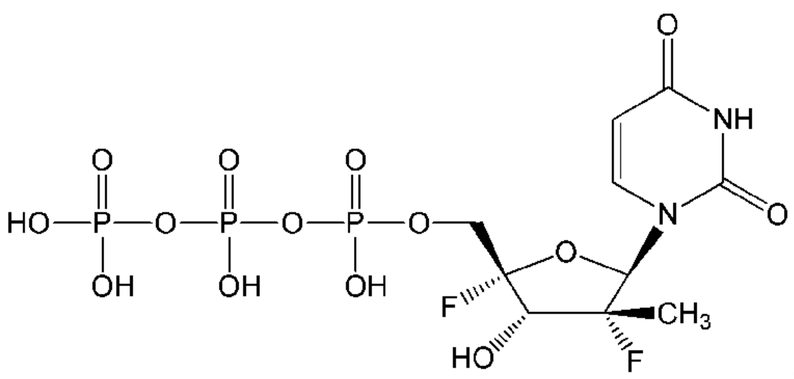
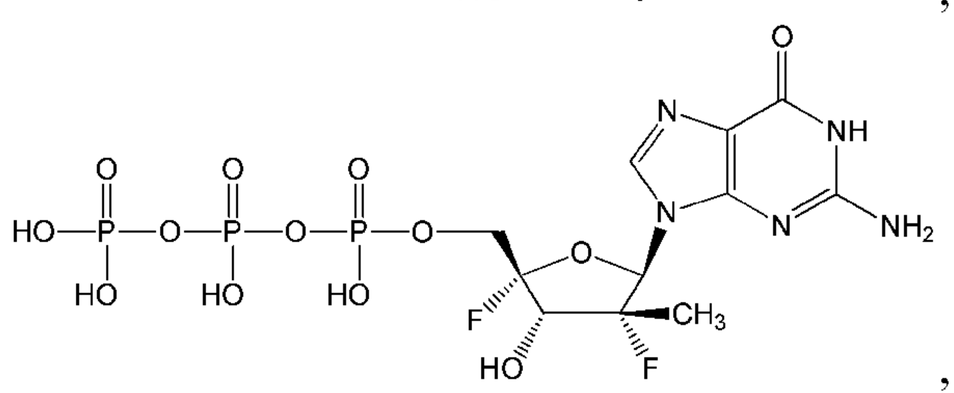
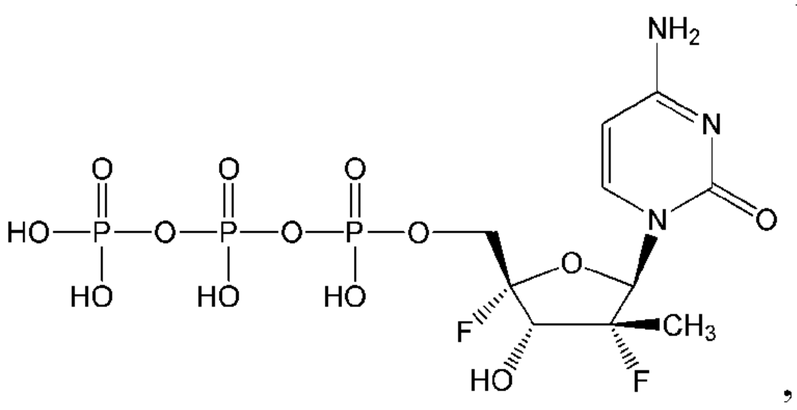
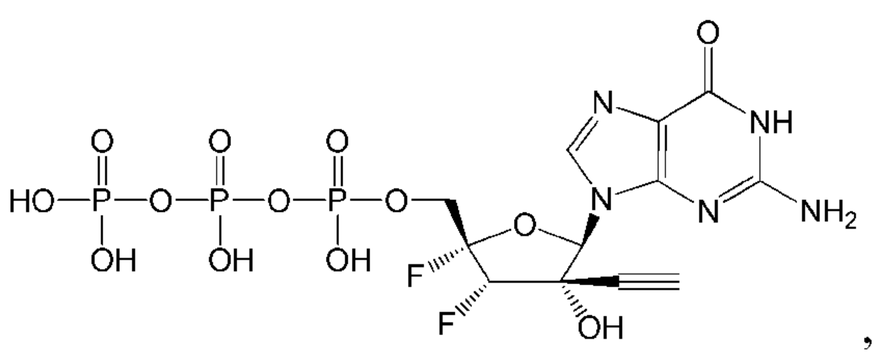
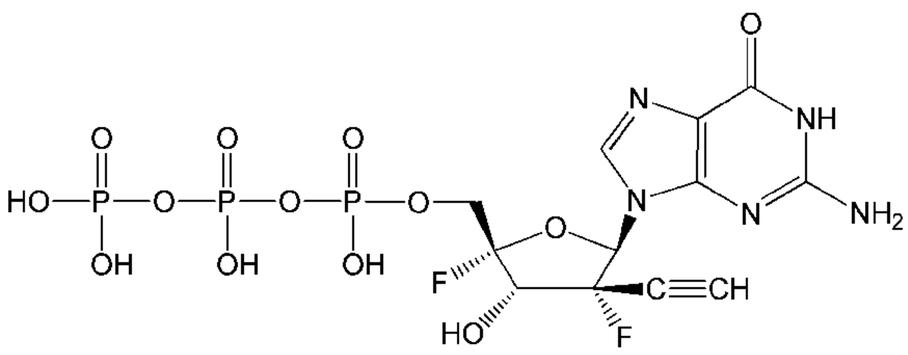
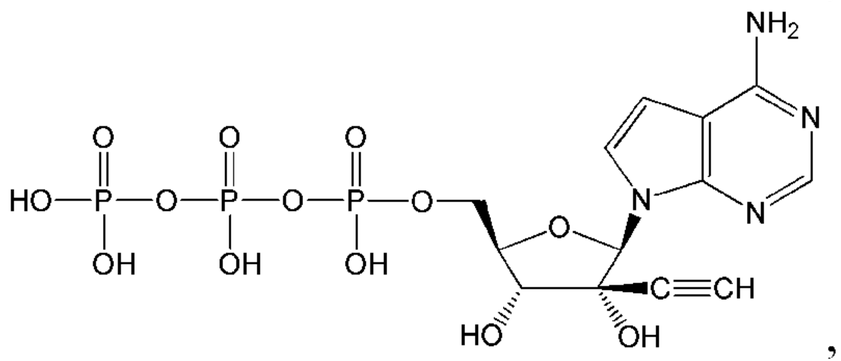
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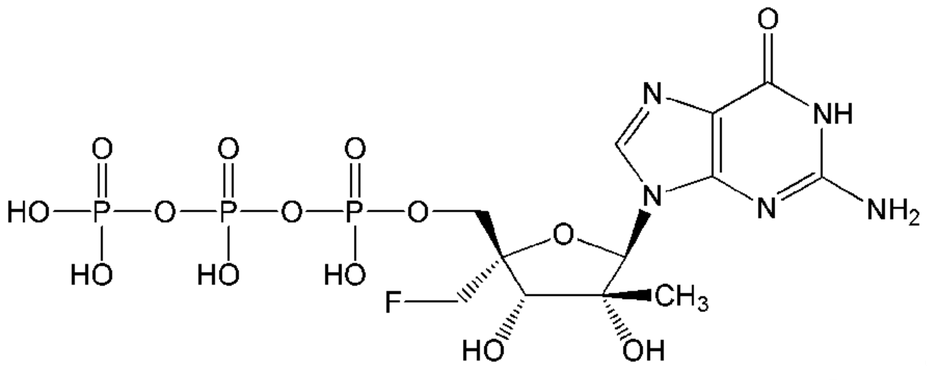
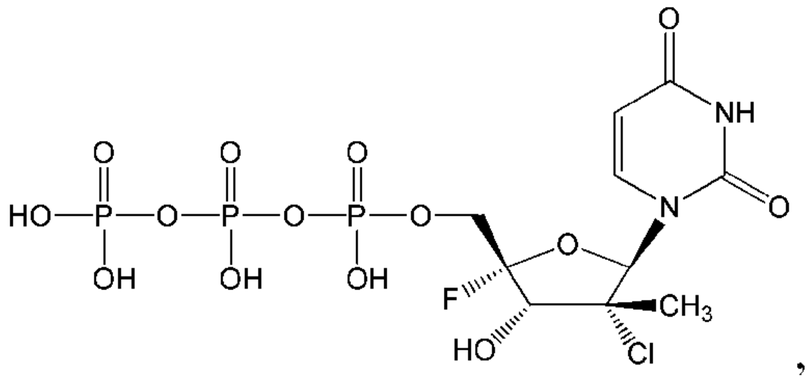
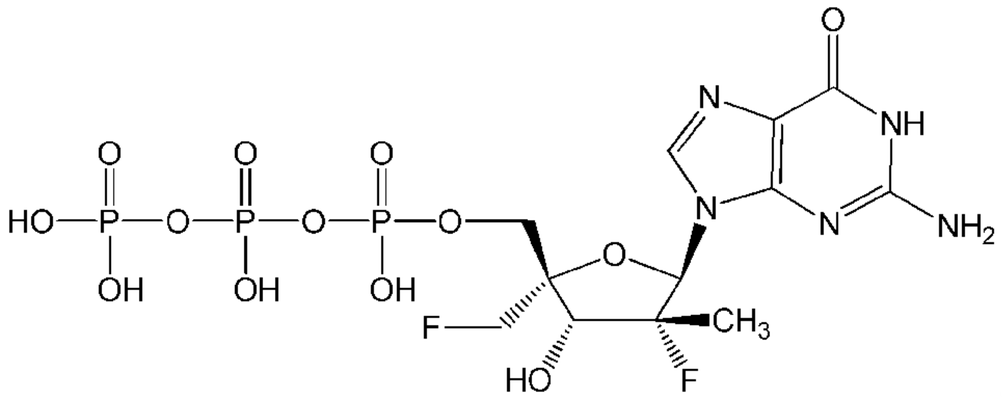
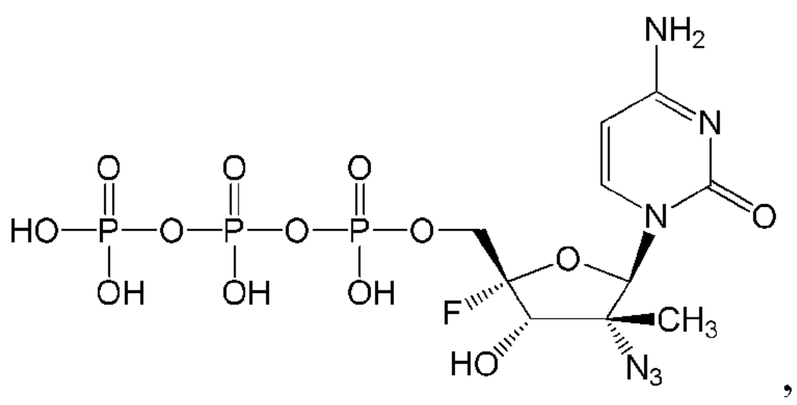
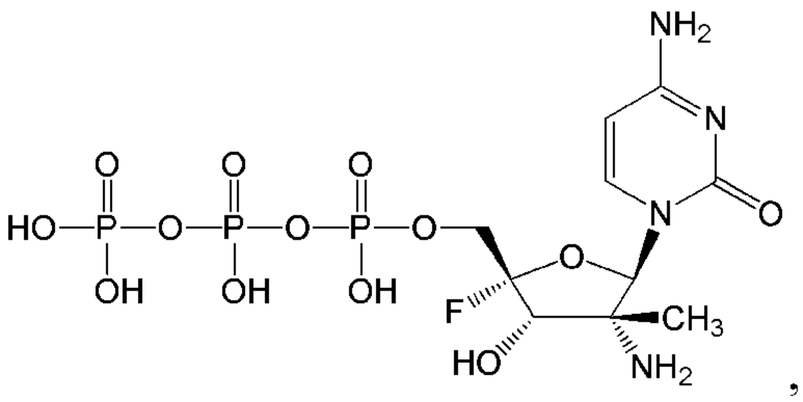
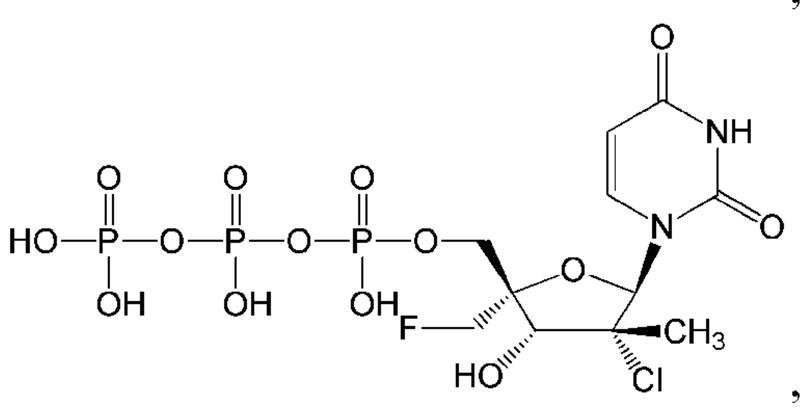
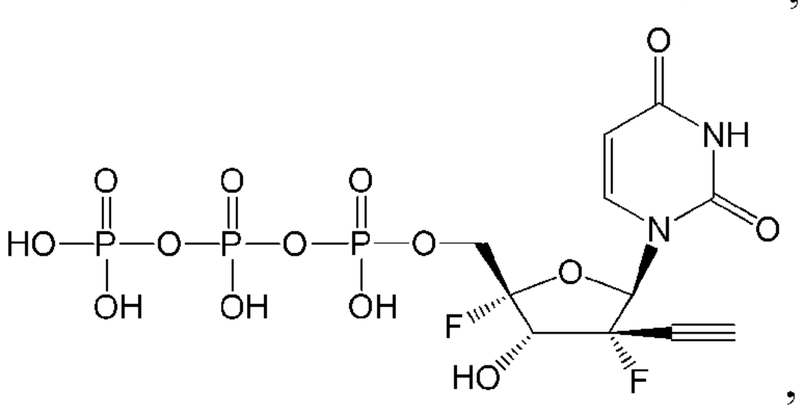
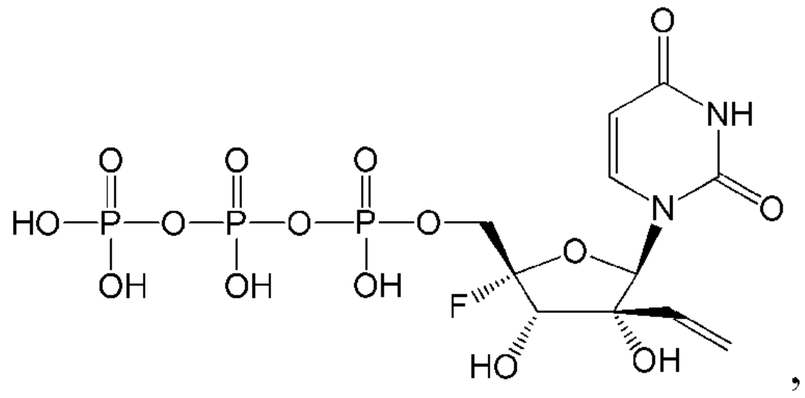
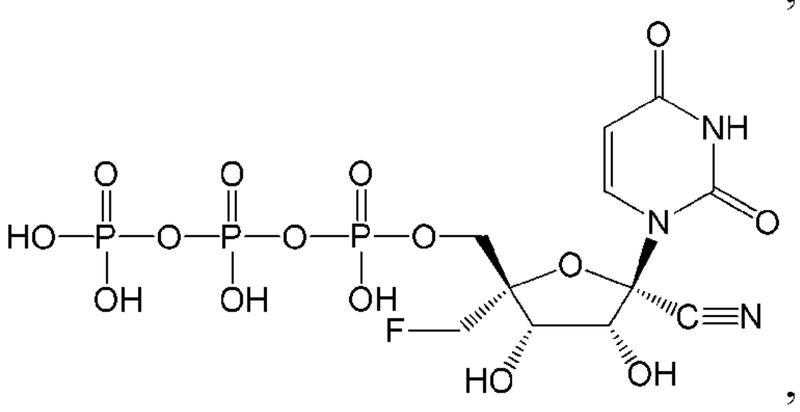
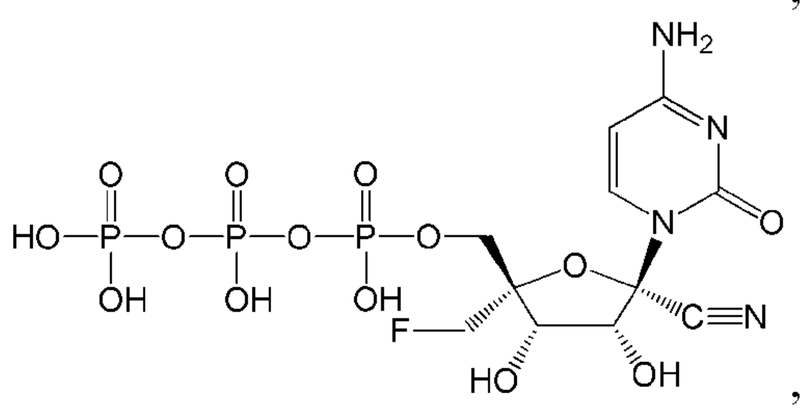
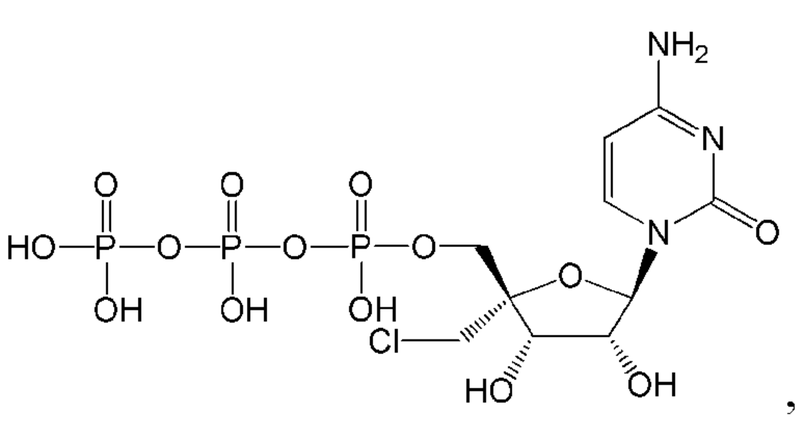
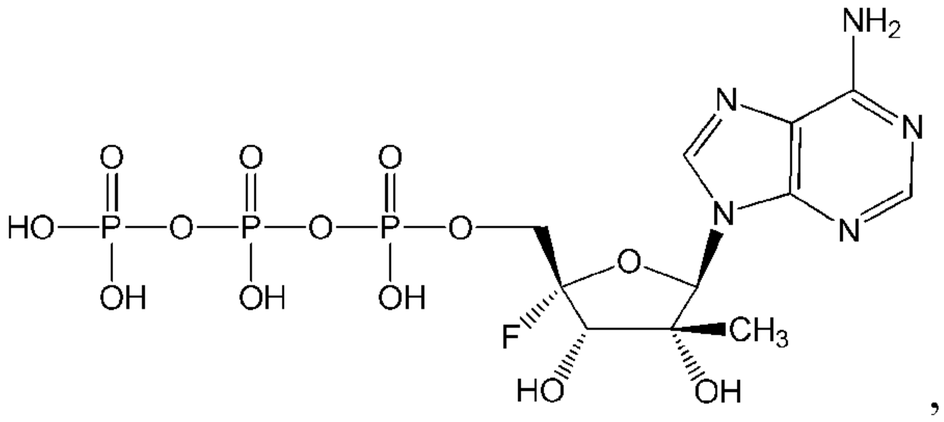


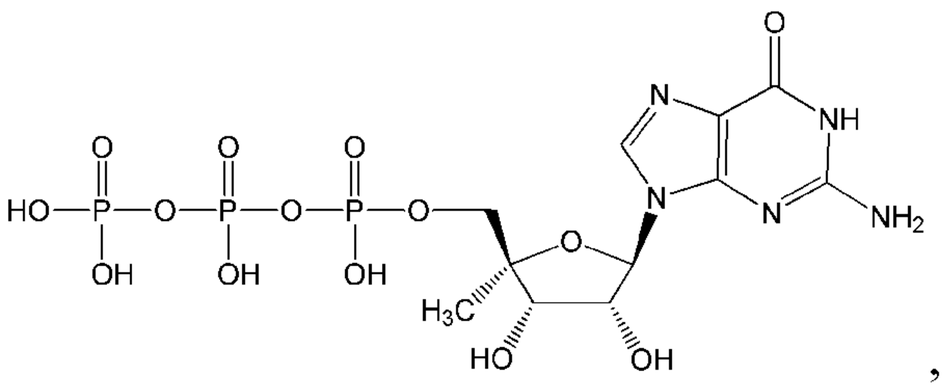
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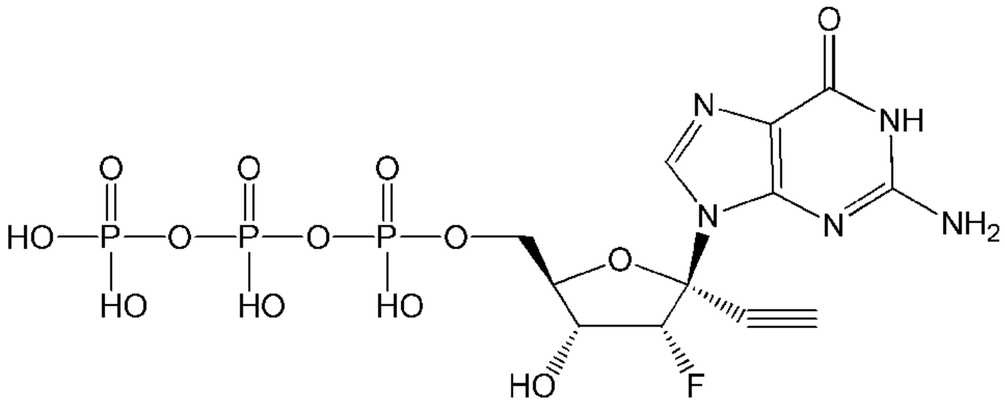
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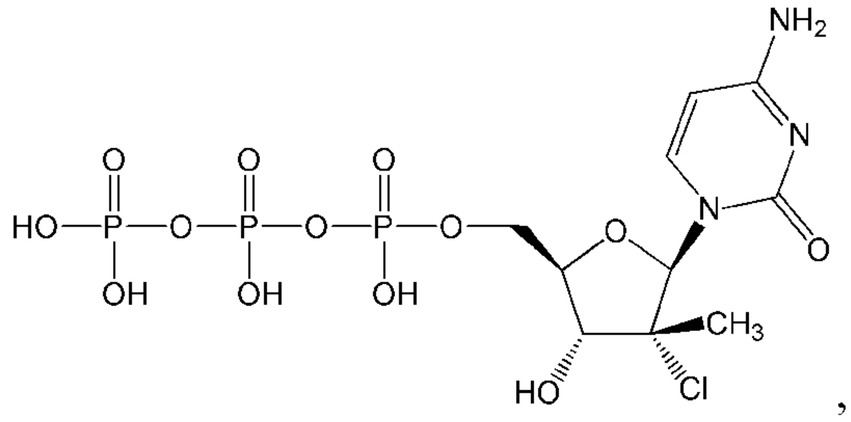

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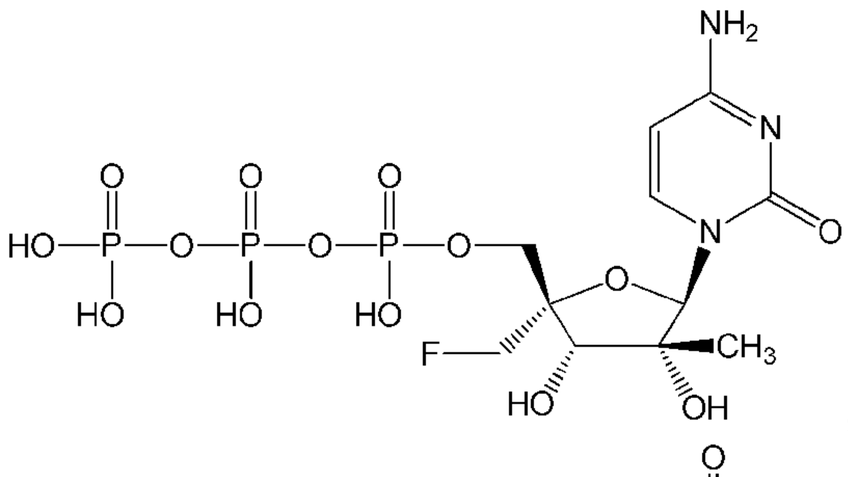
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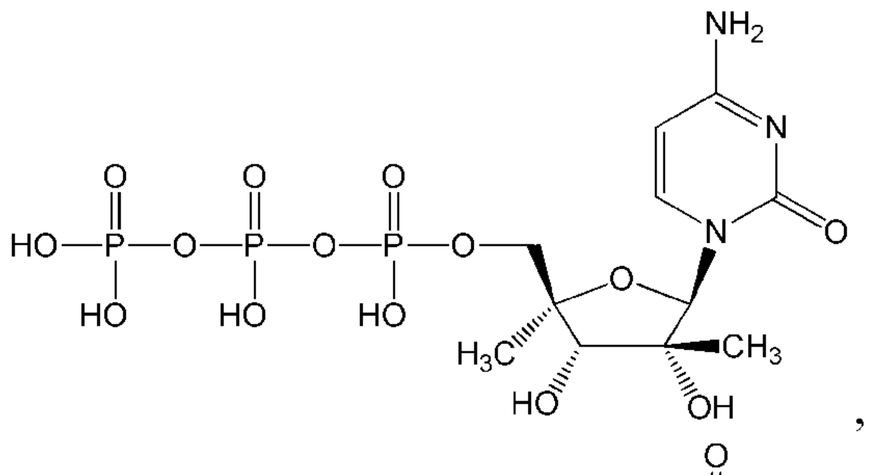
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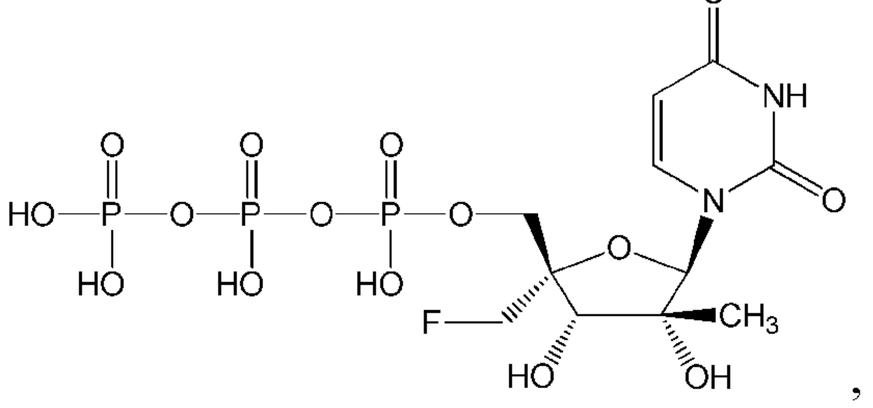
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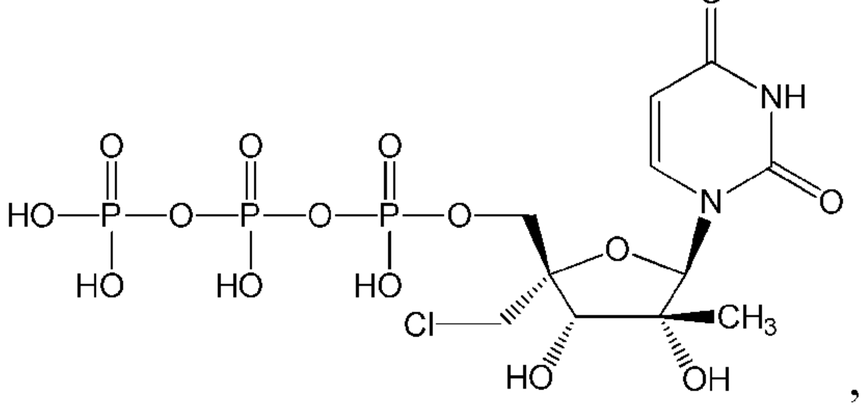
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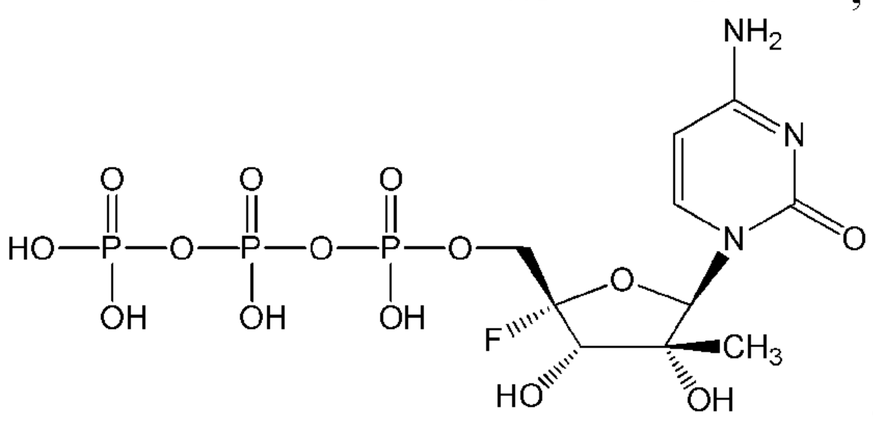
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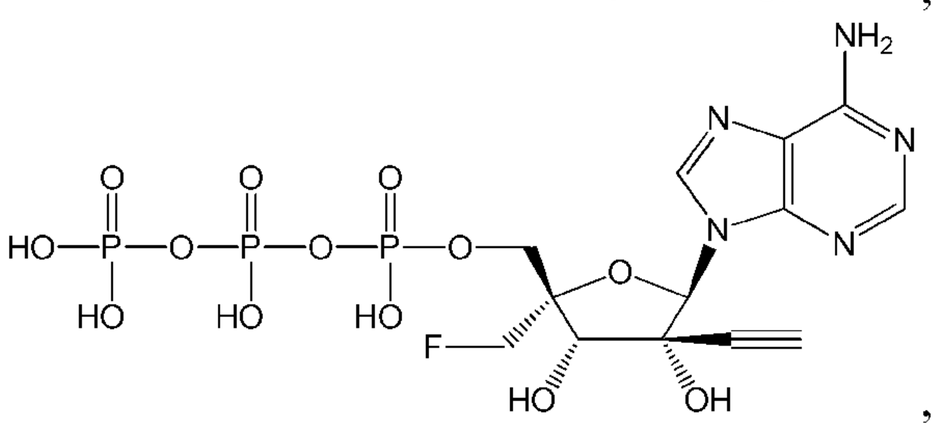
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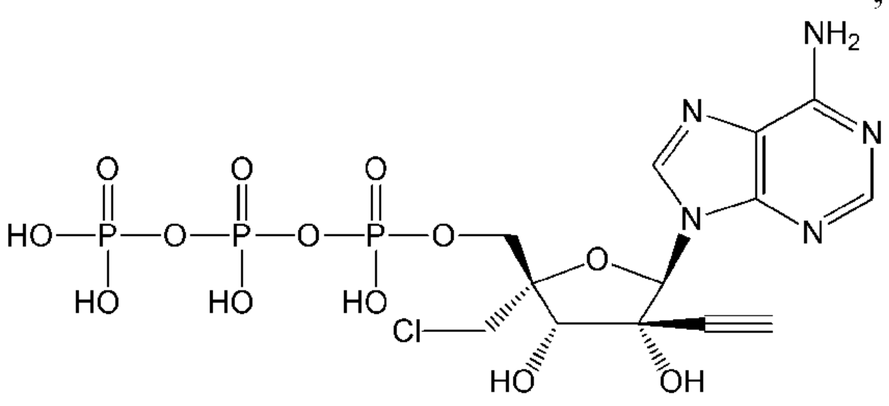
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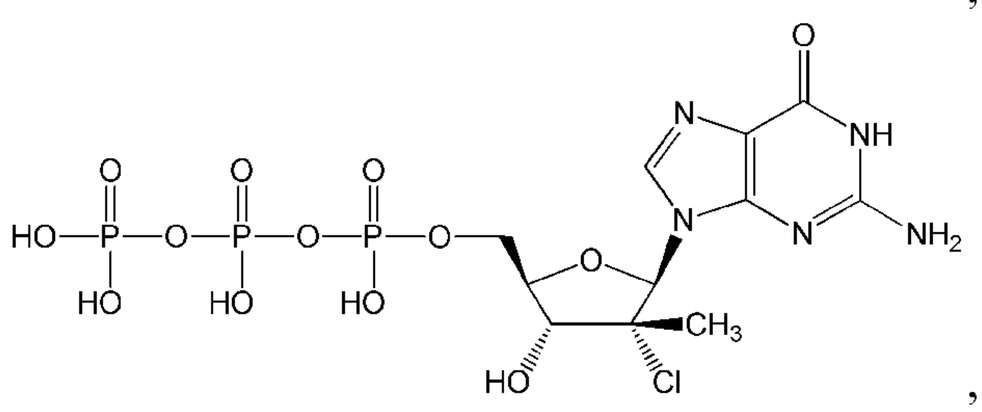
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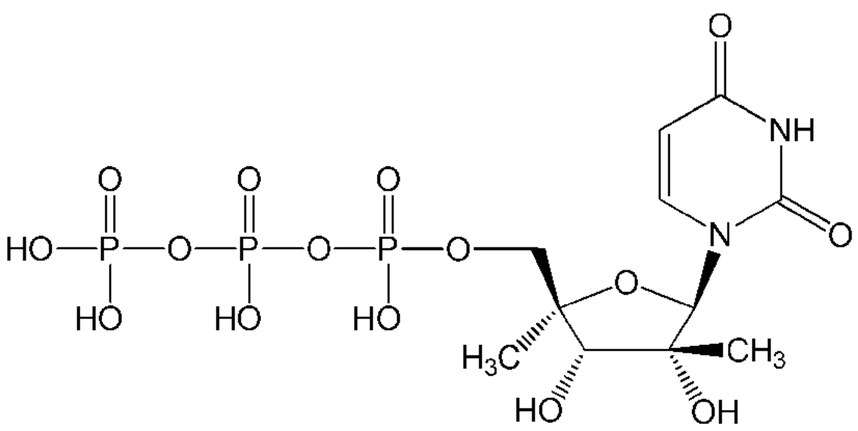
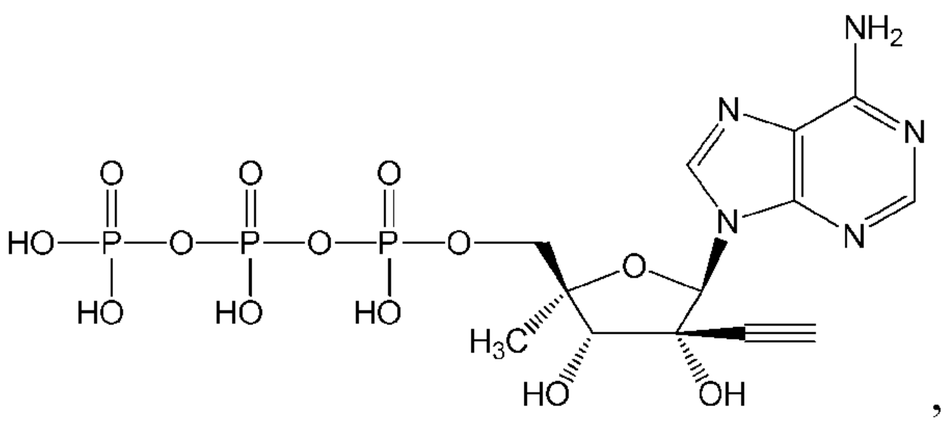
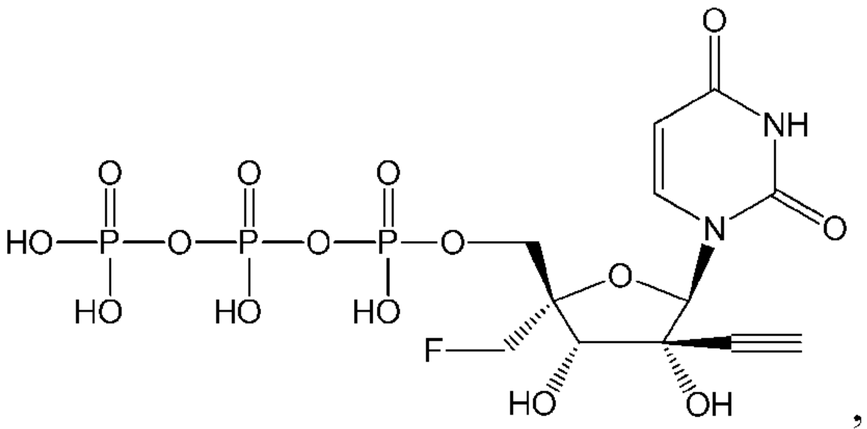
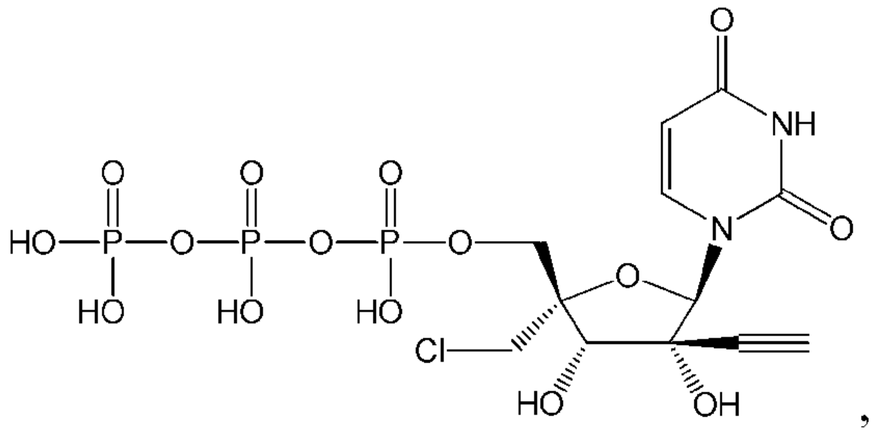
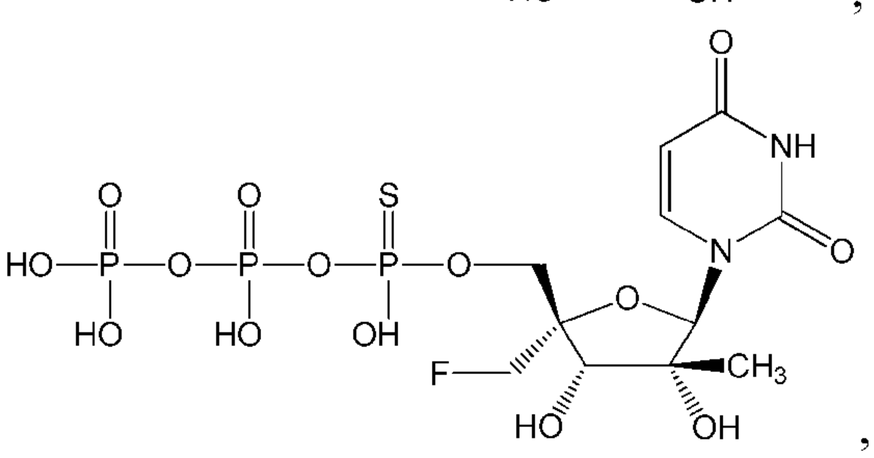
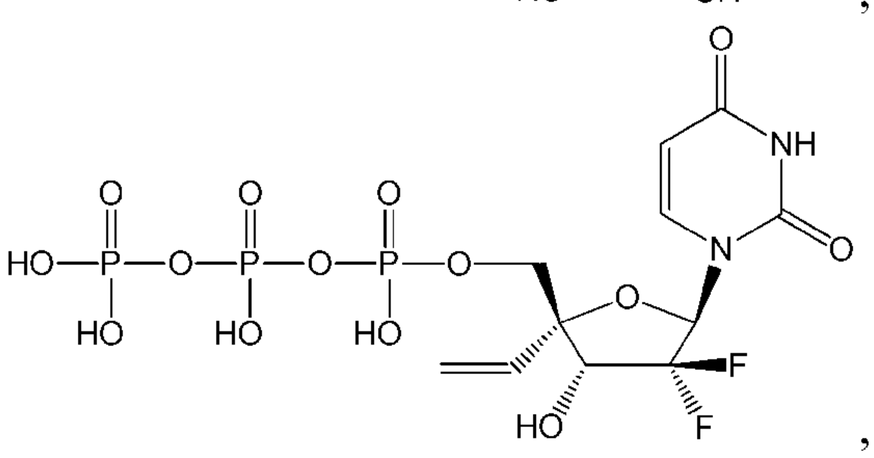
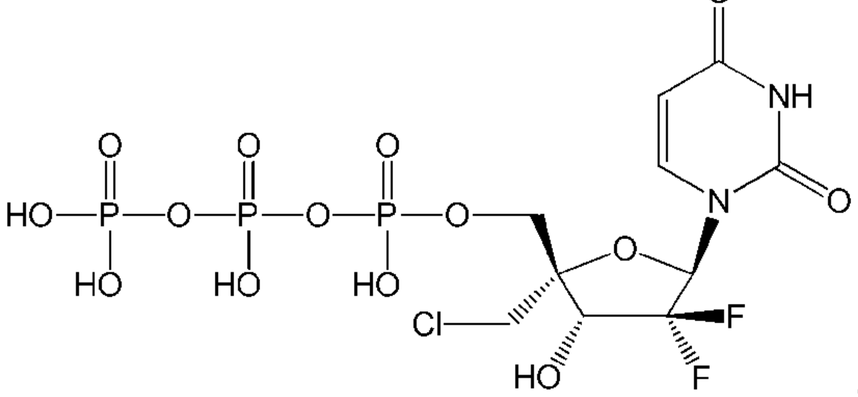
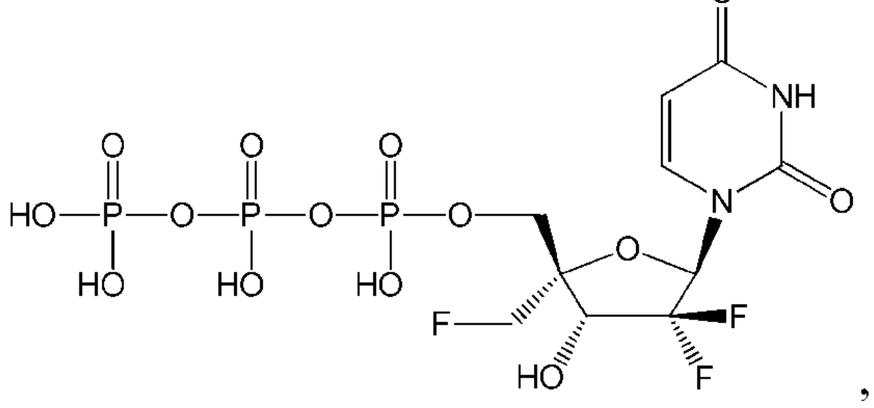
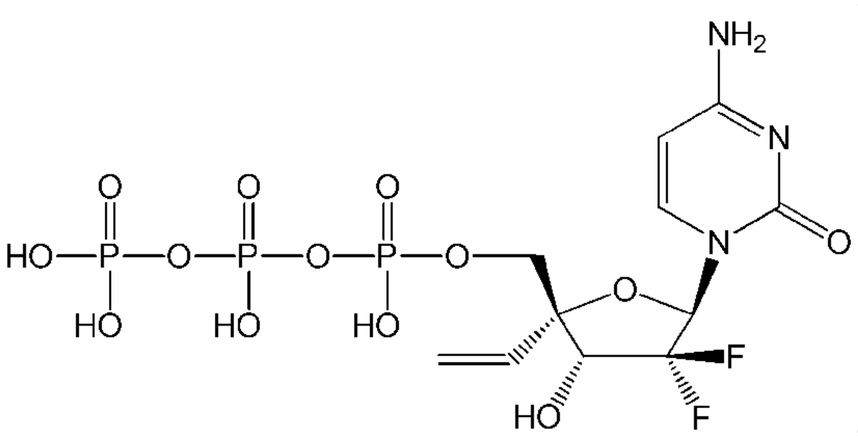
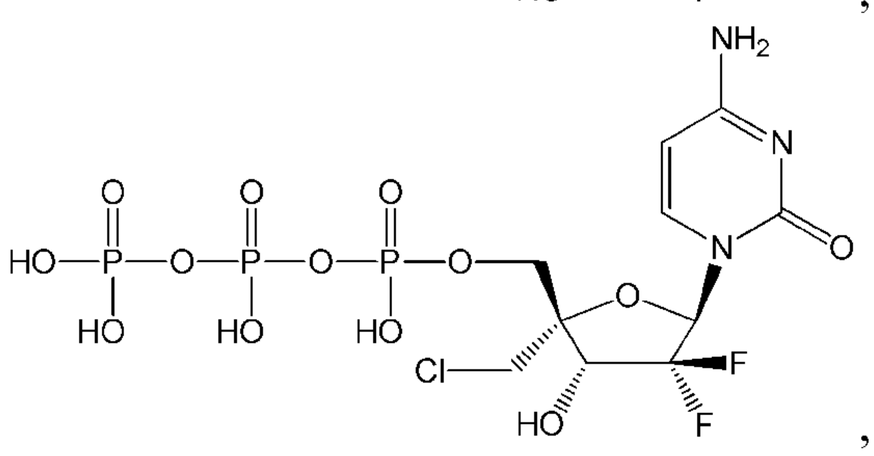
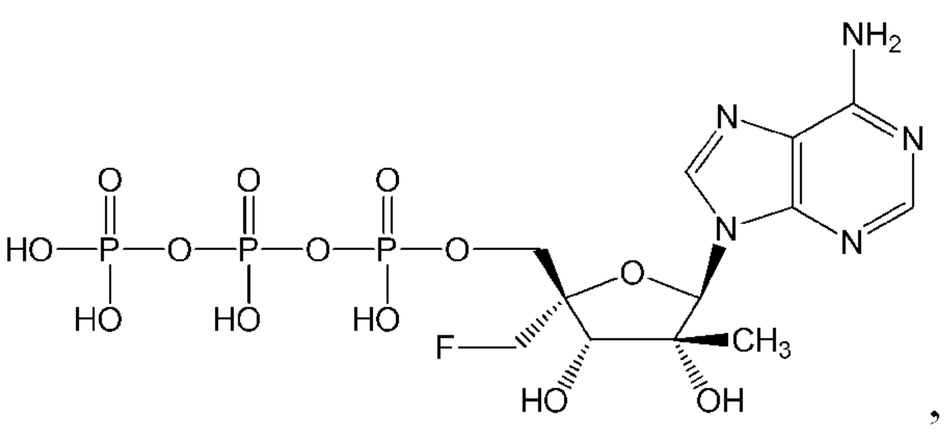
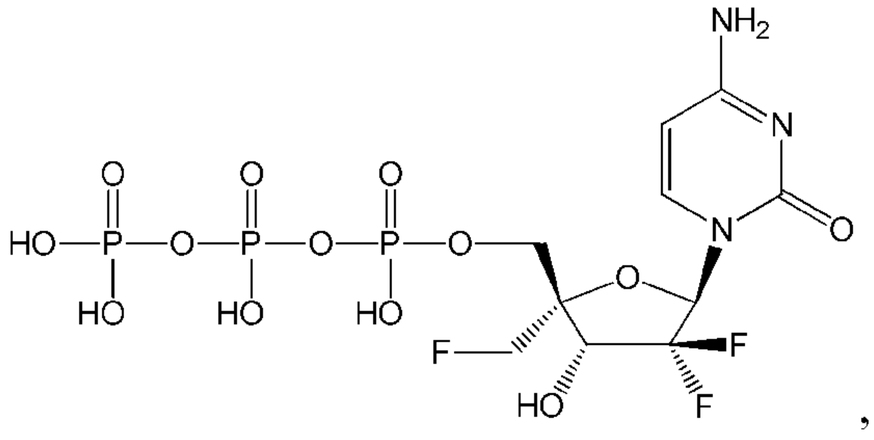
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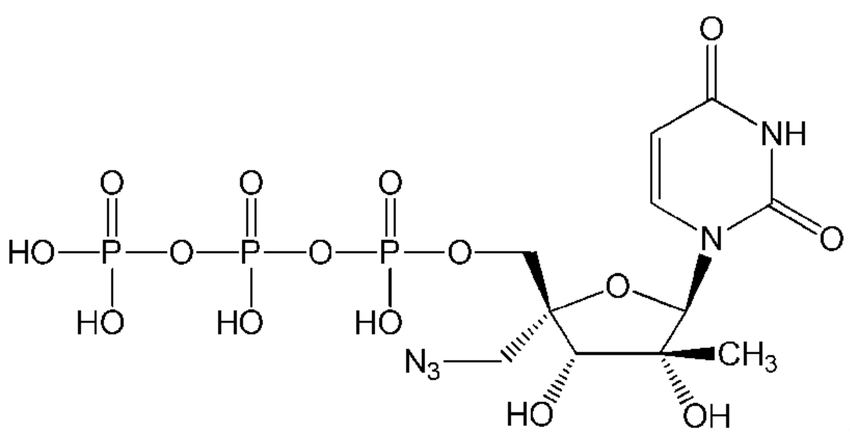


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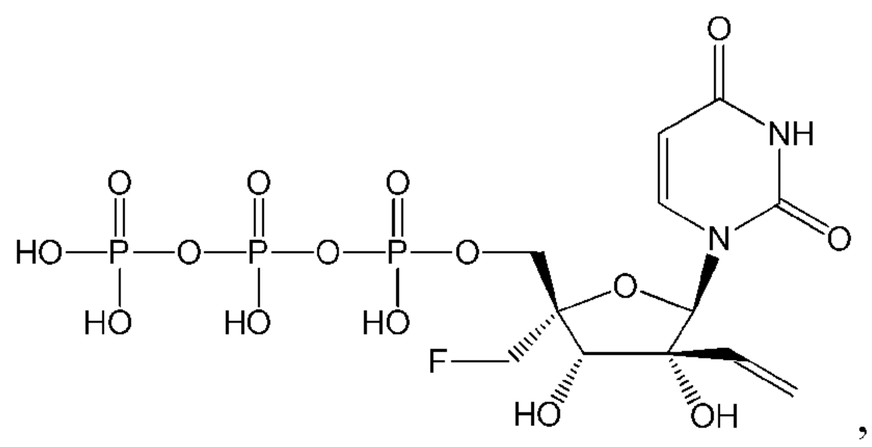


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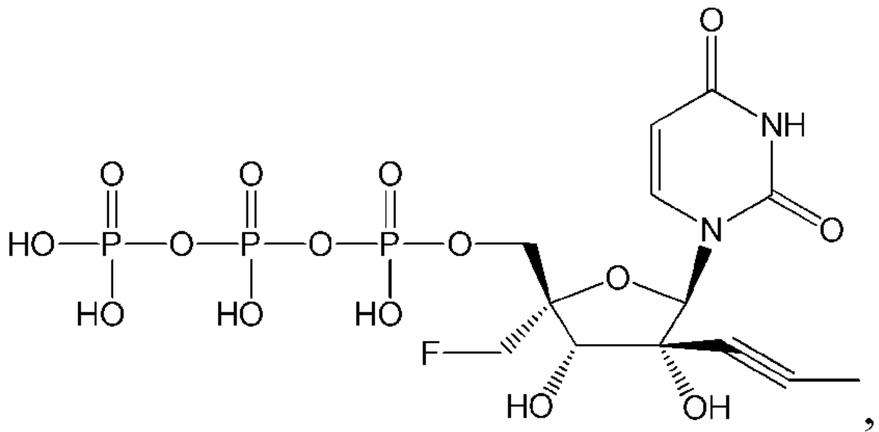

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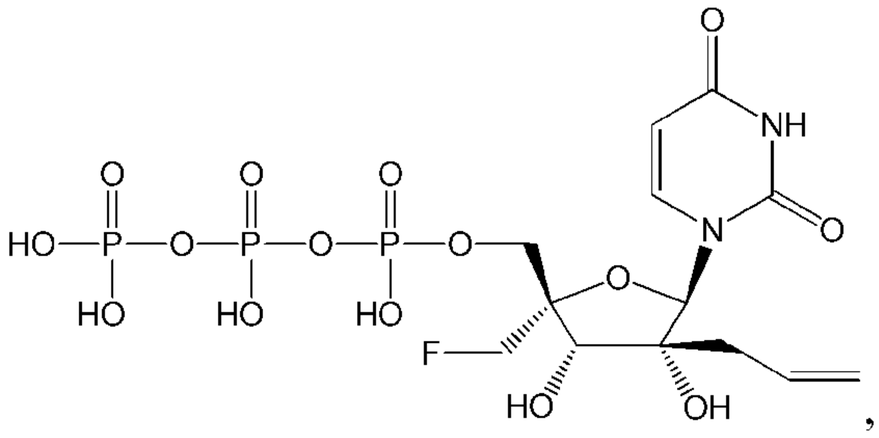
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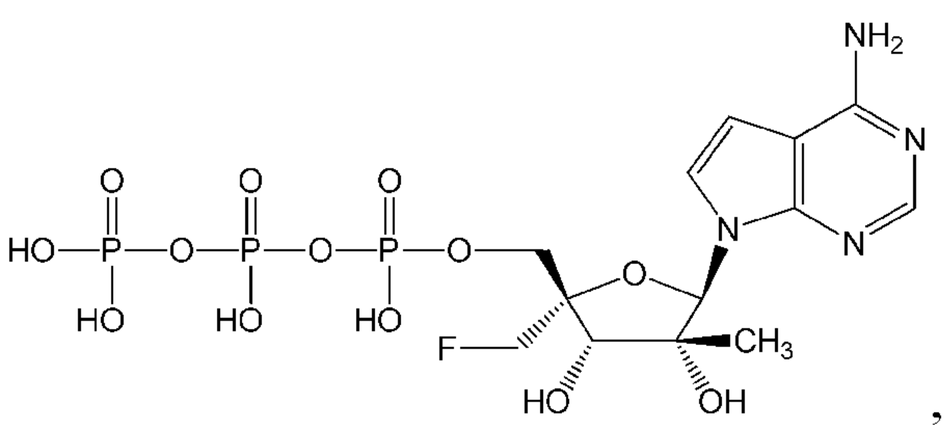
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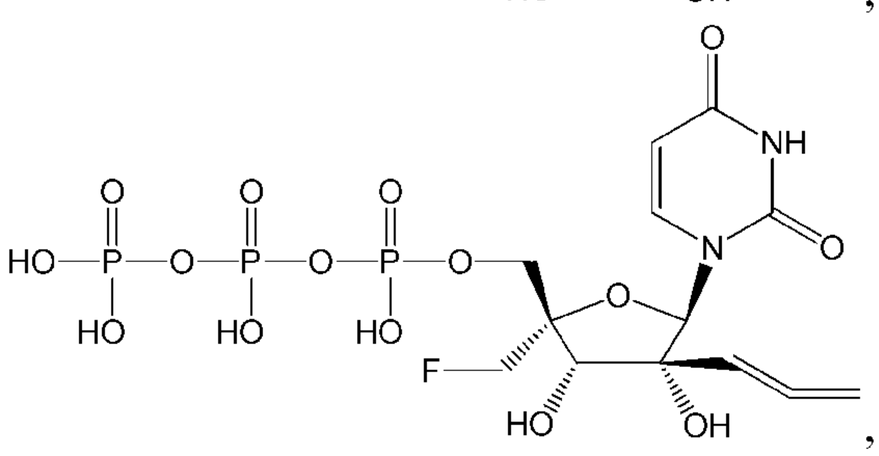
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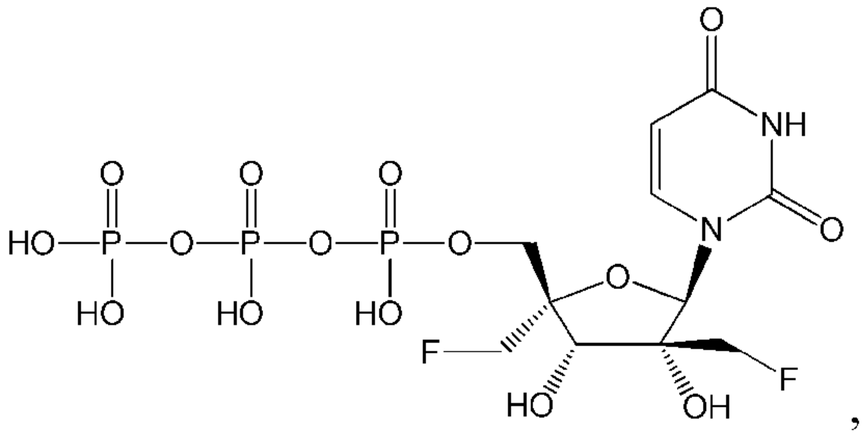
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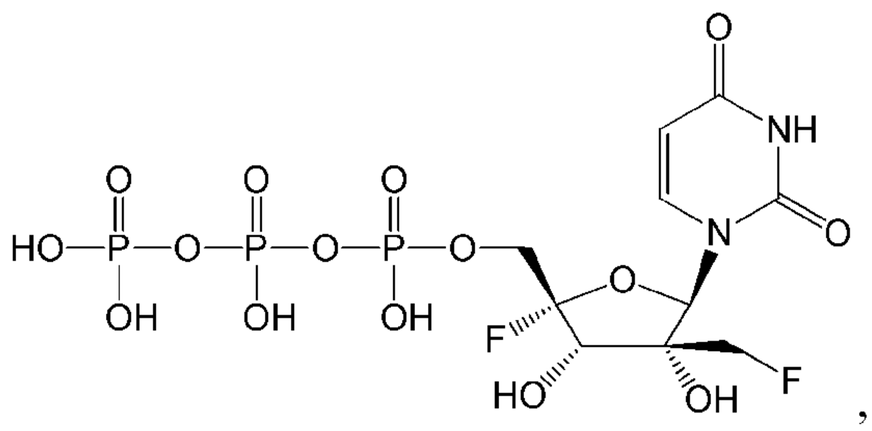
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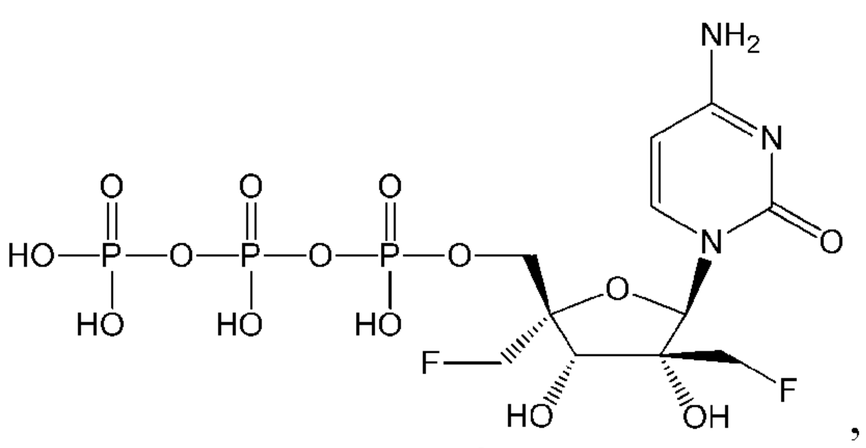
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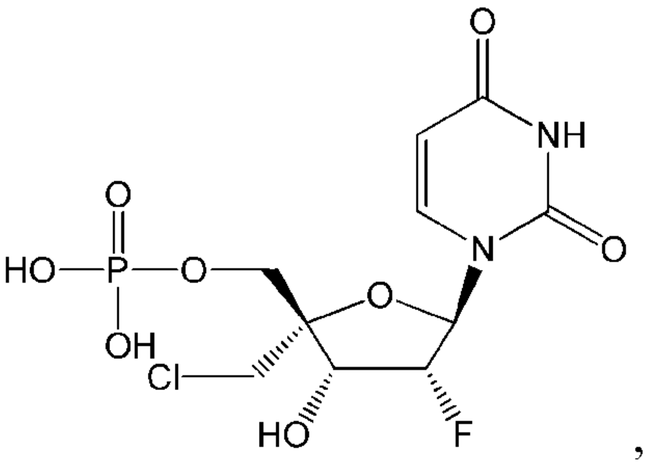
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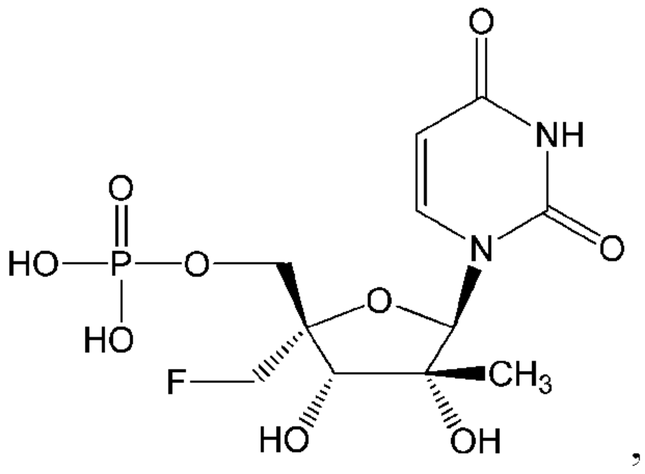
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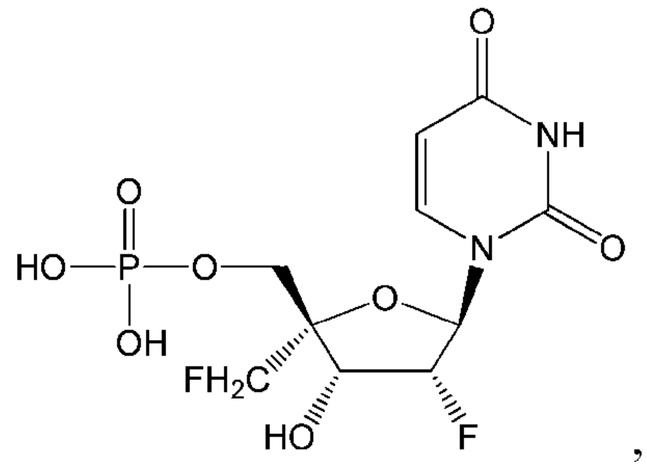
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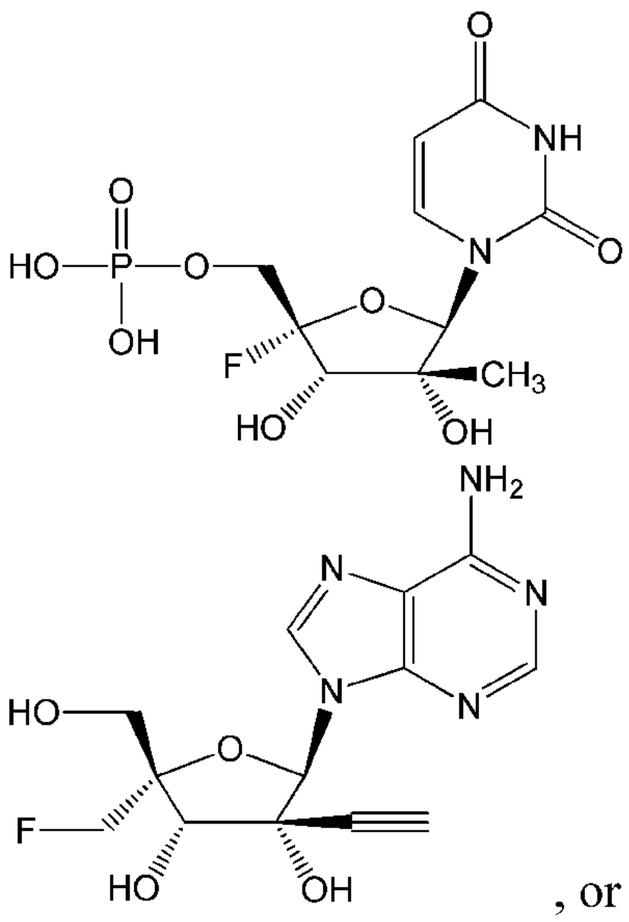
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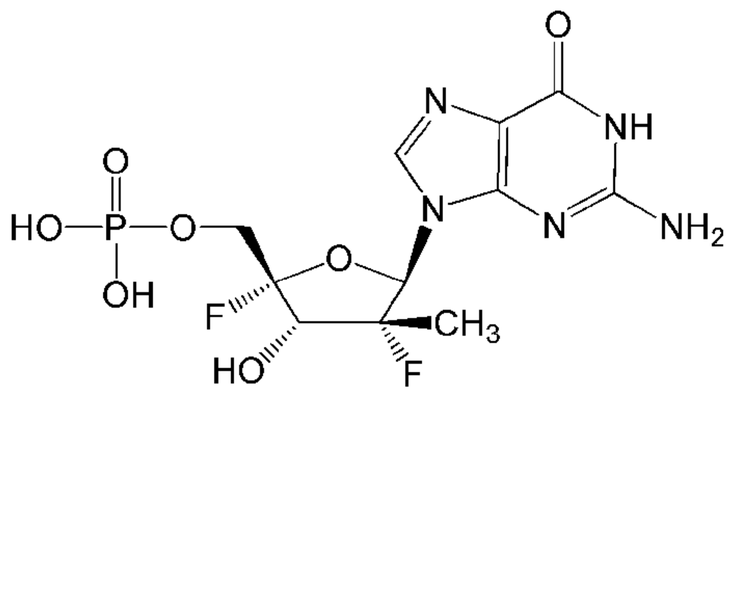
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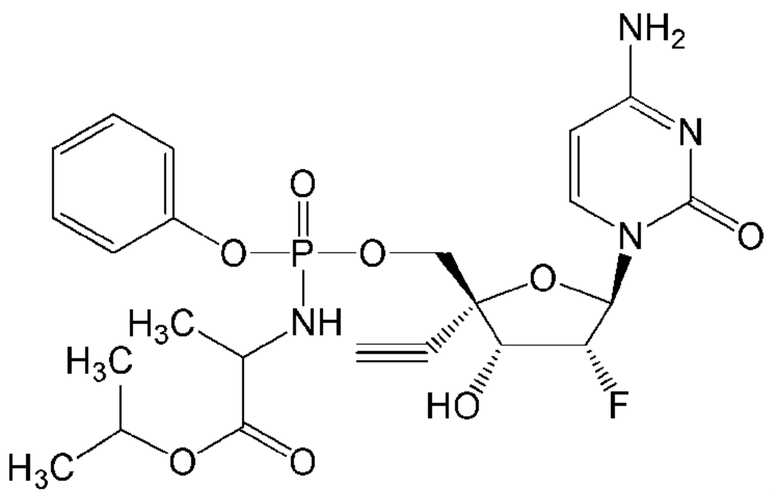
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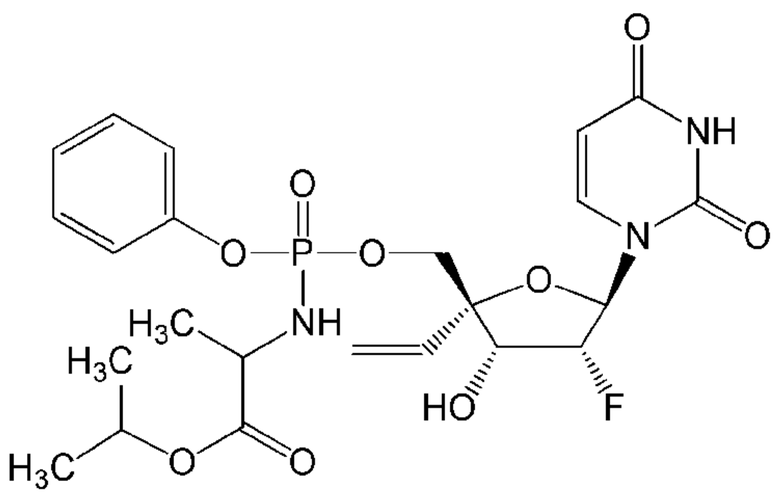
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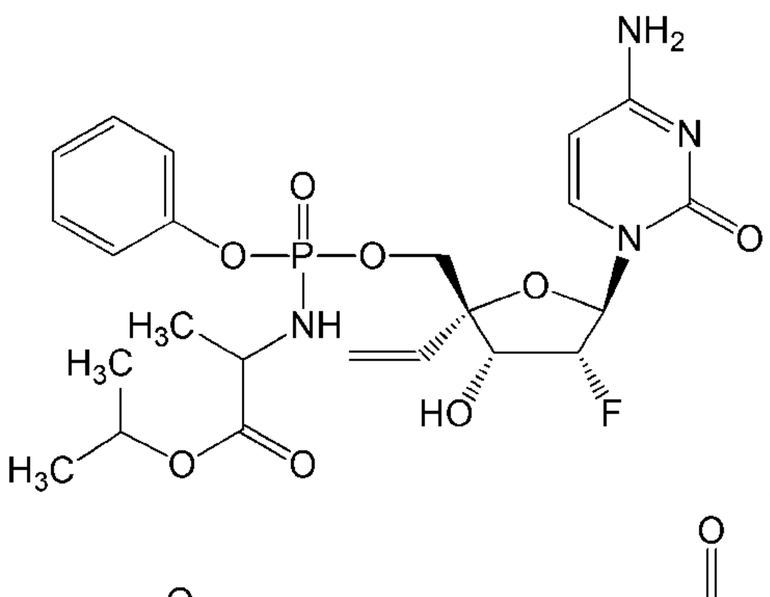
235. The use of Claim 1, wherein the compound of Formula (II) is selected from the group consisting of:



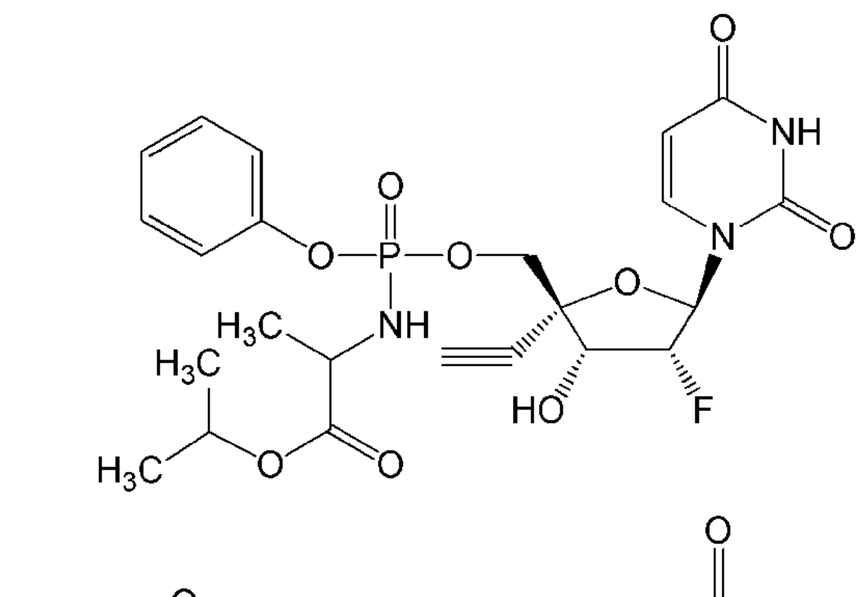
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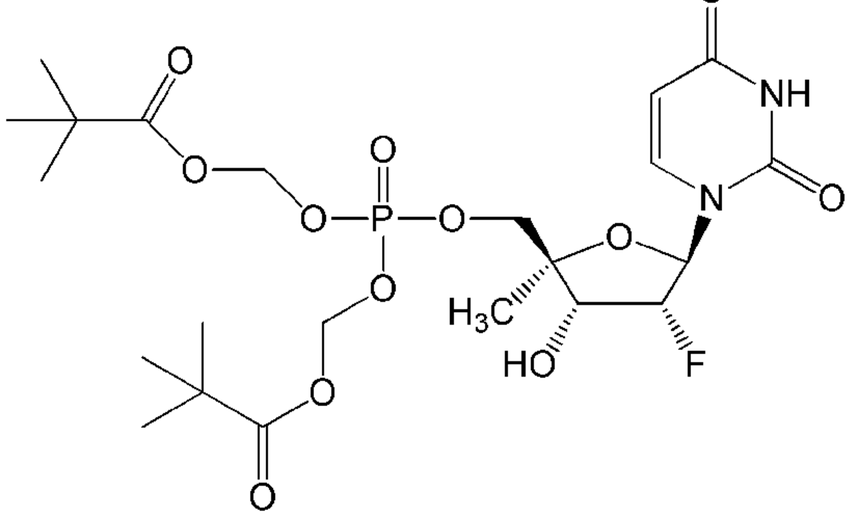
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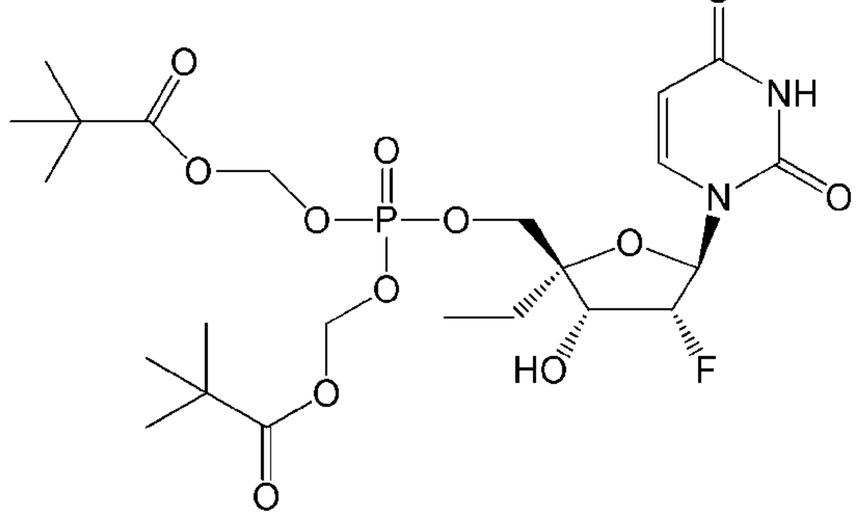
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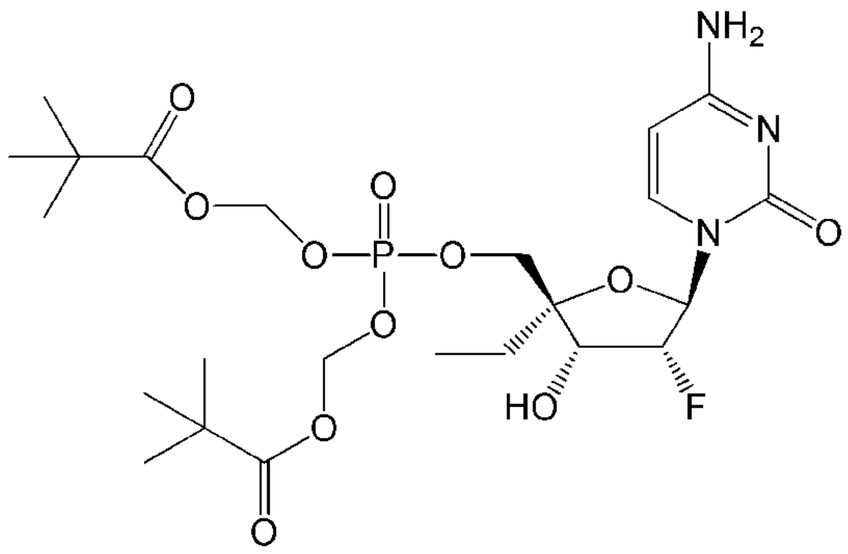
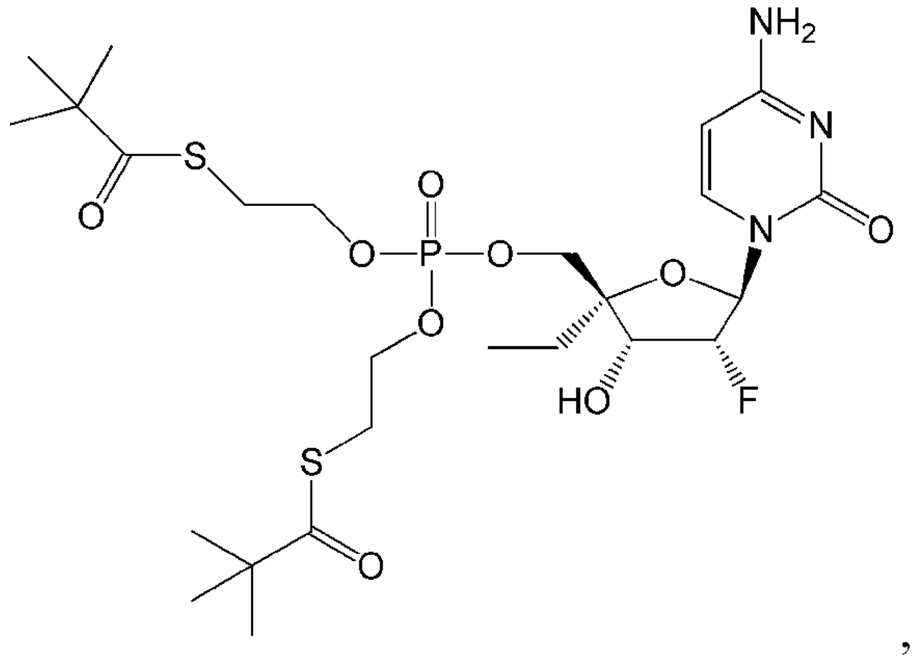
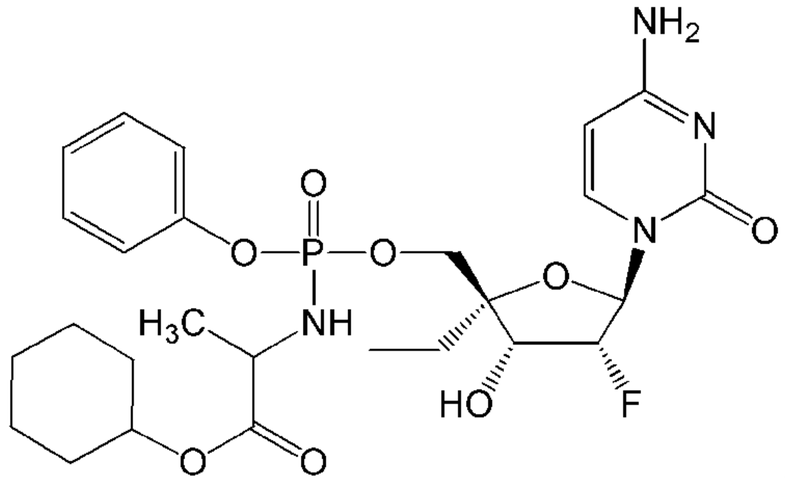
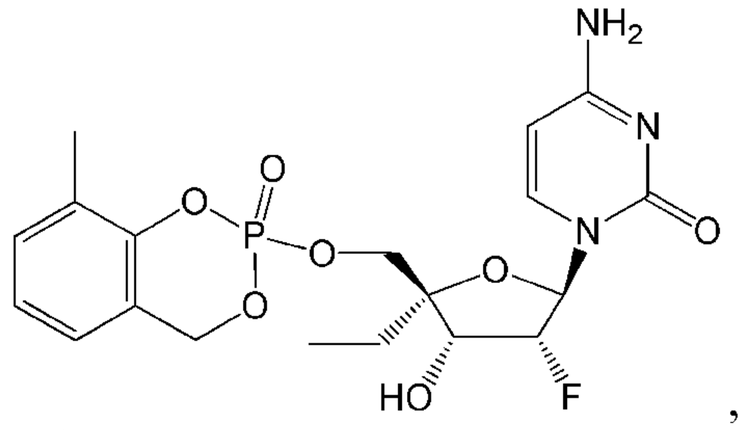
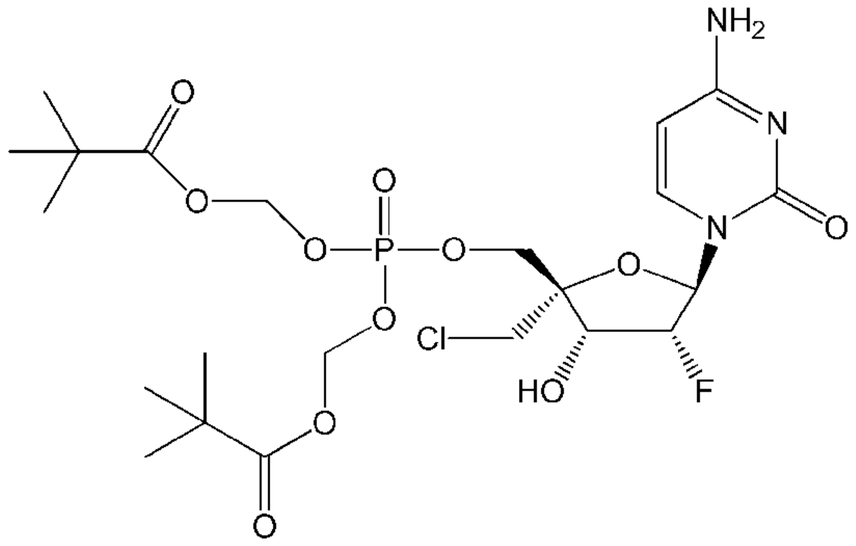
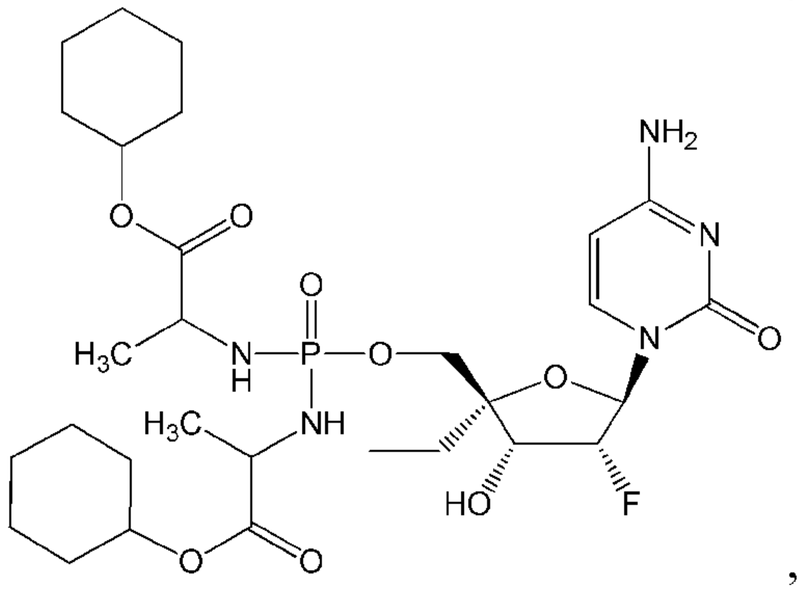
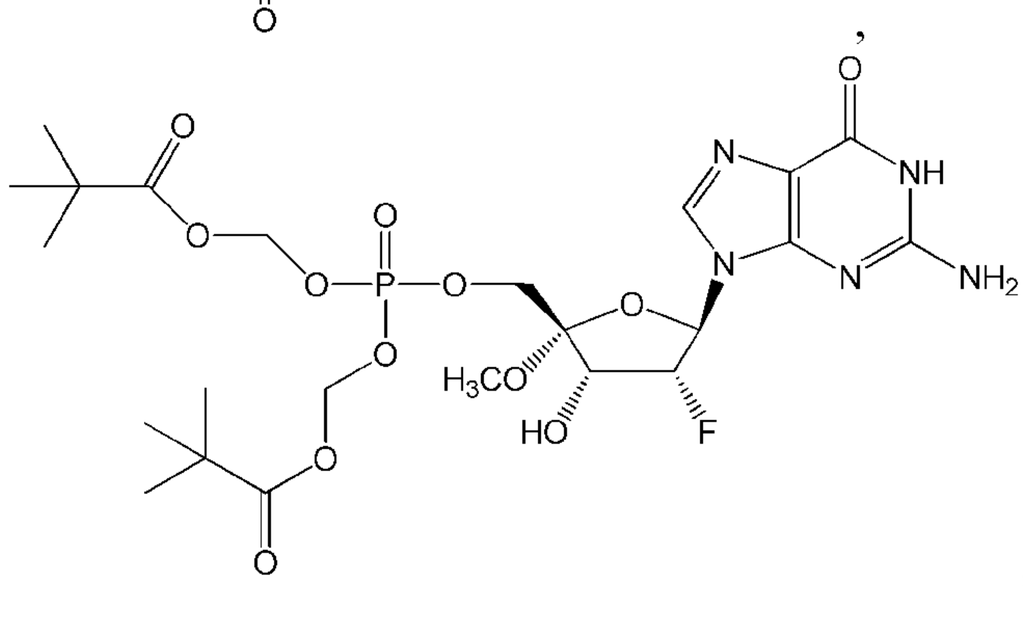
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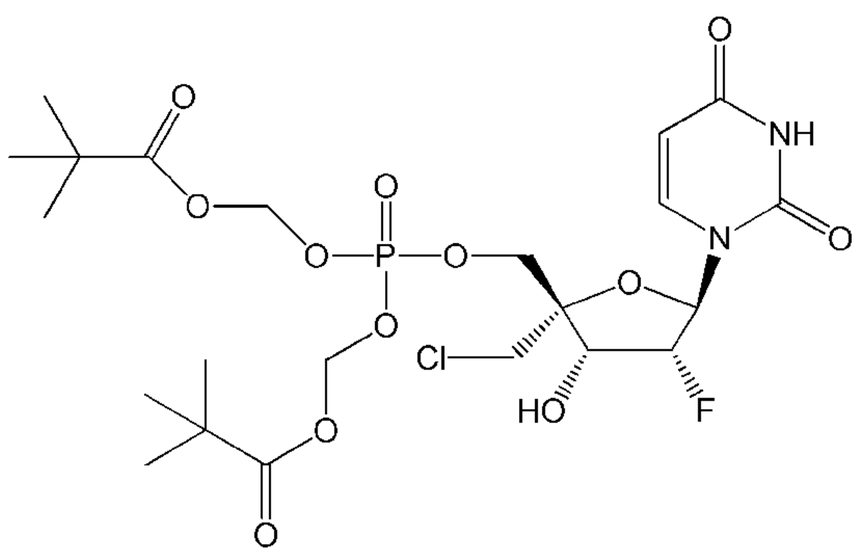


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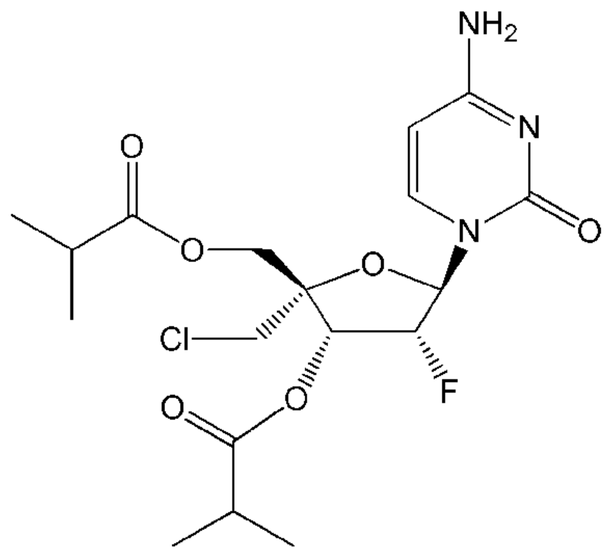


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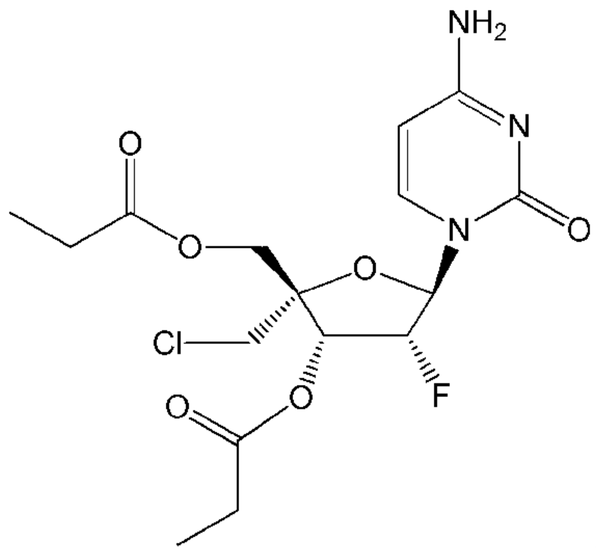

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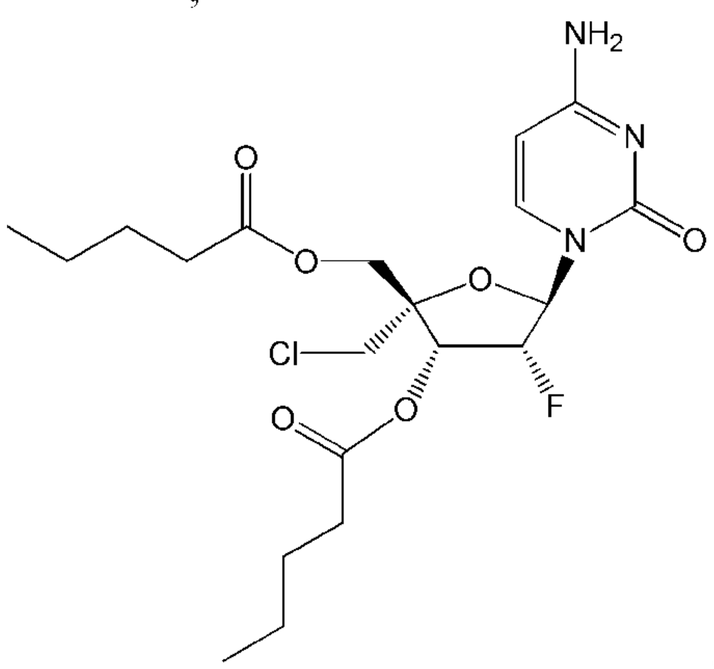
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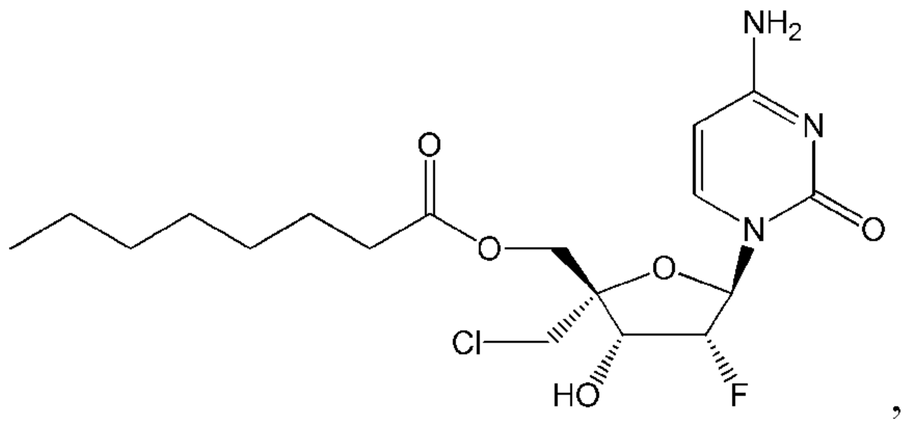
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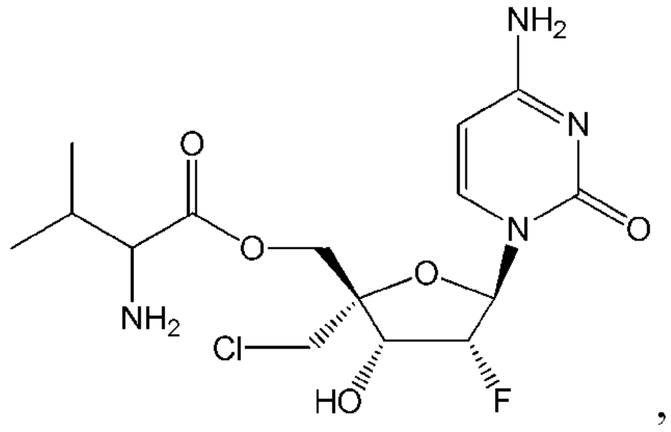
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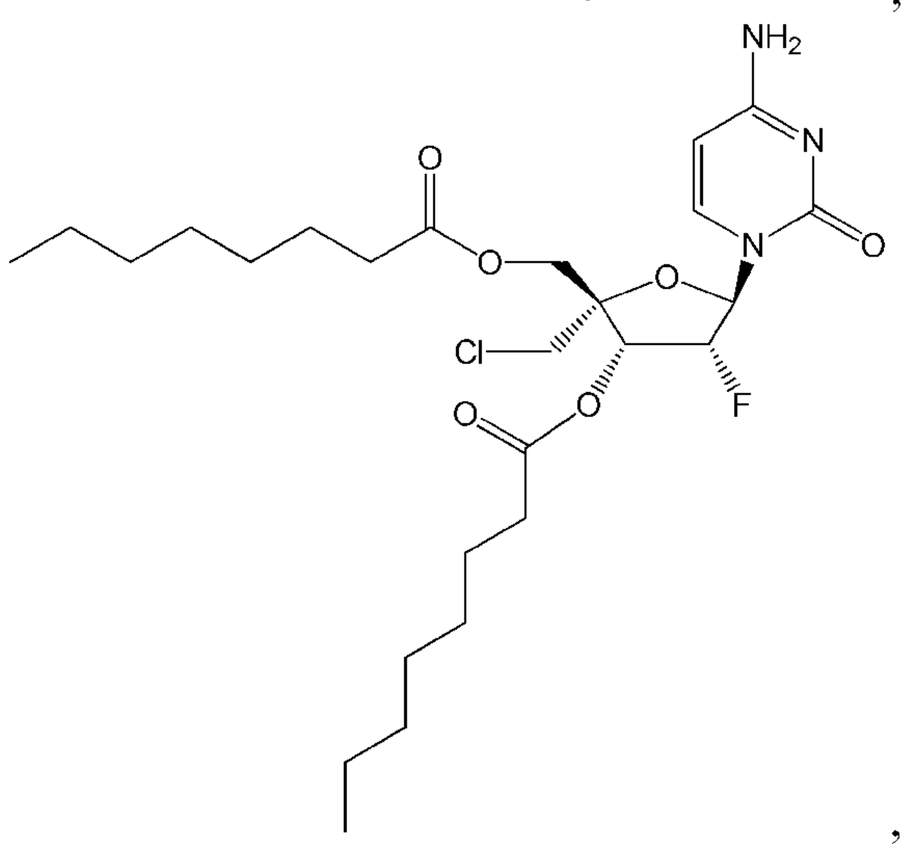
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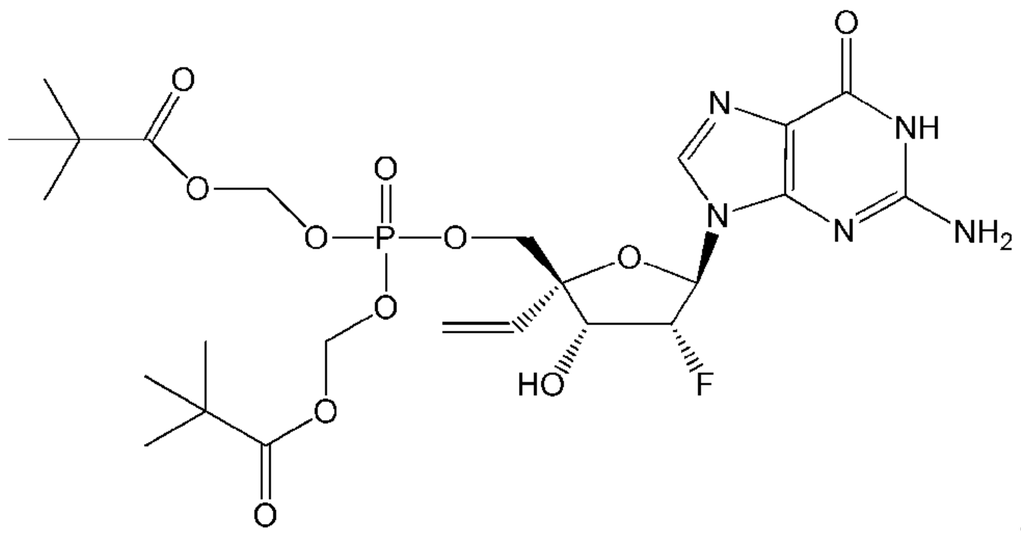
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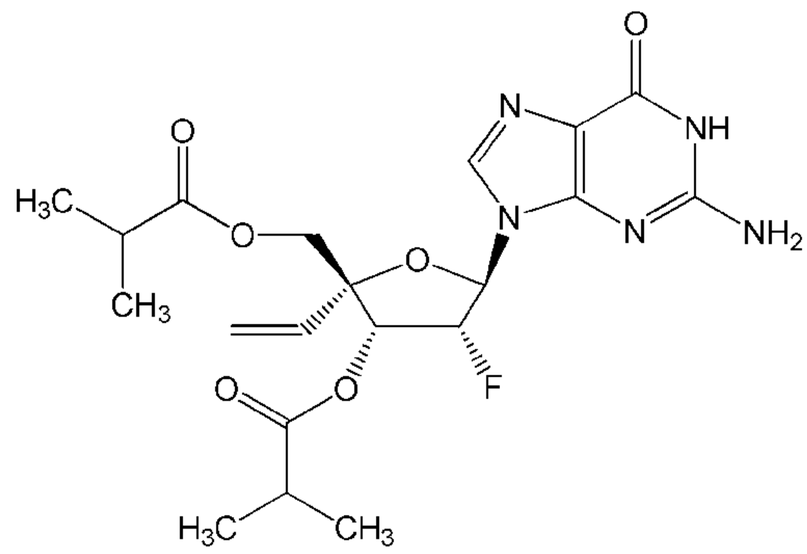
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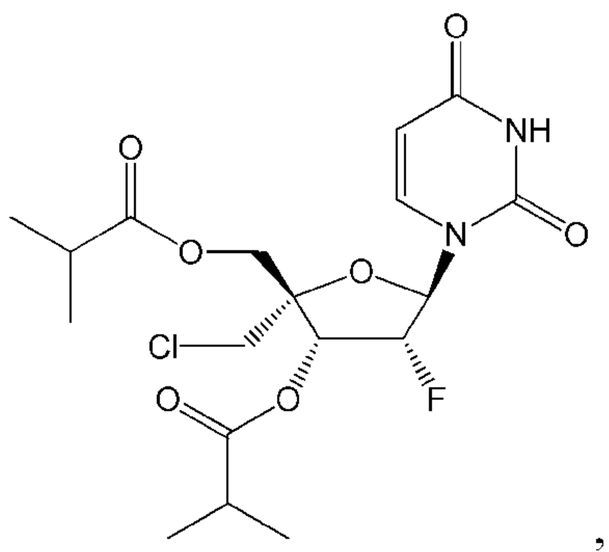
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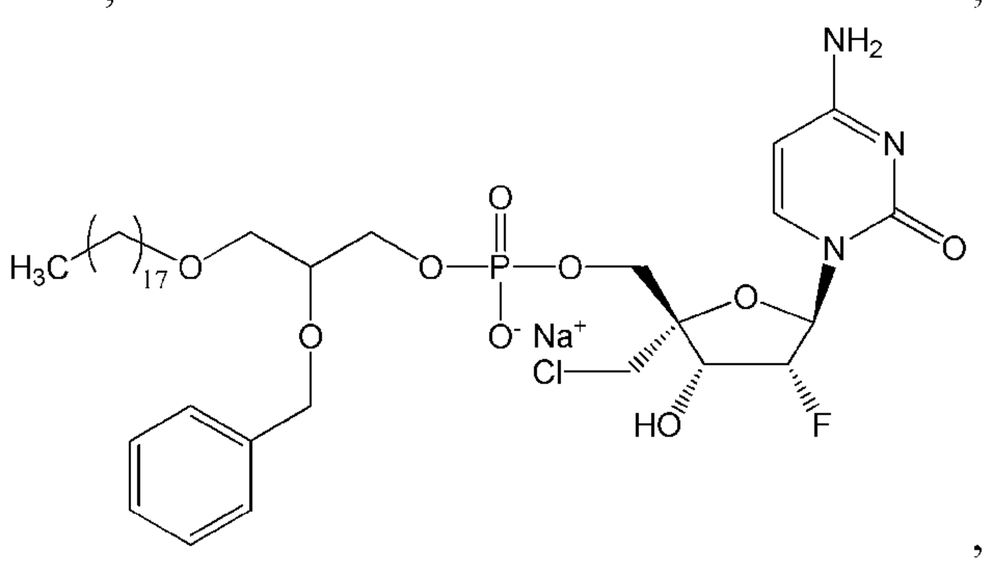
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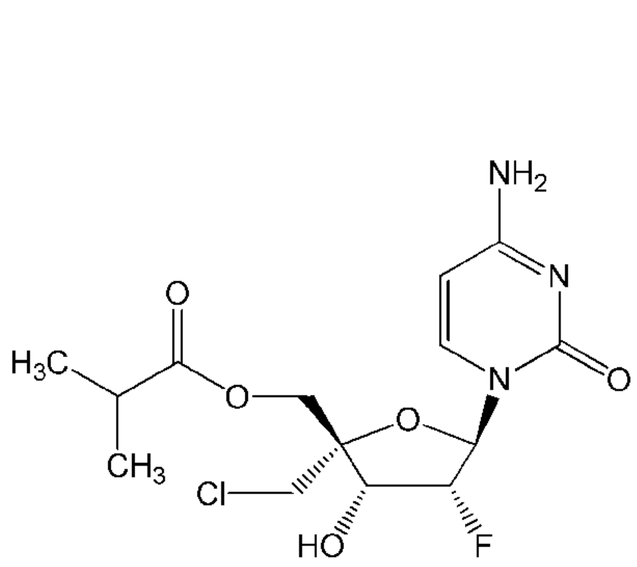
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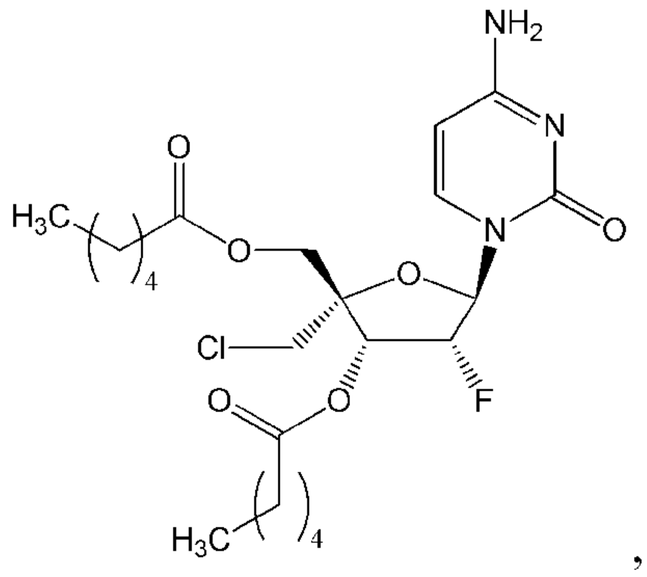
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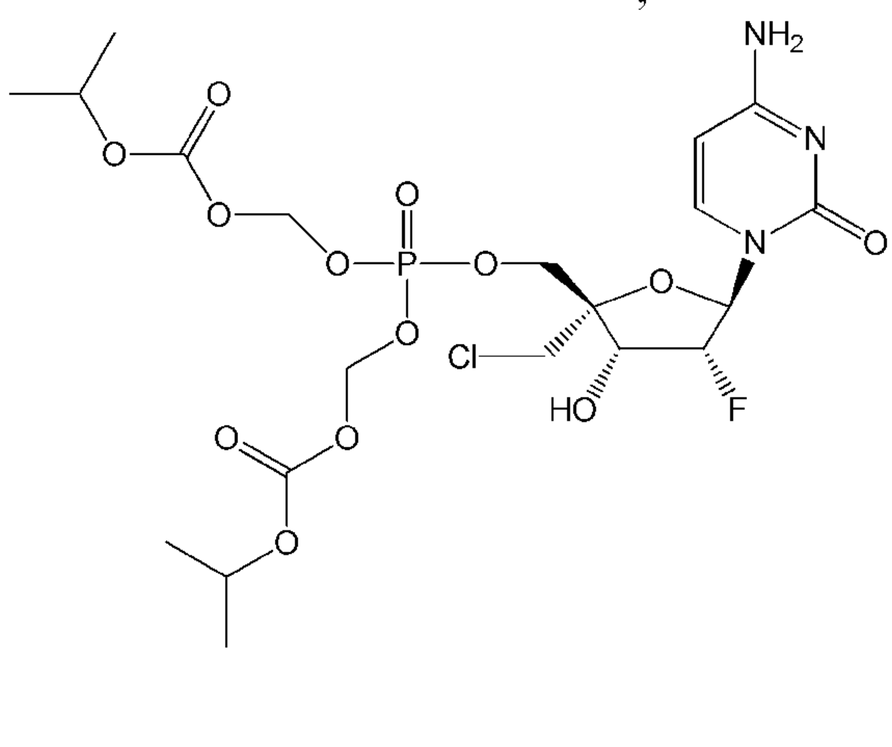
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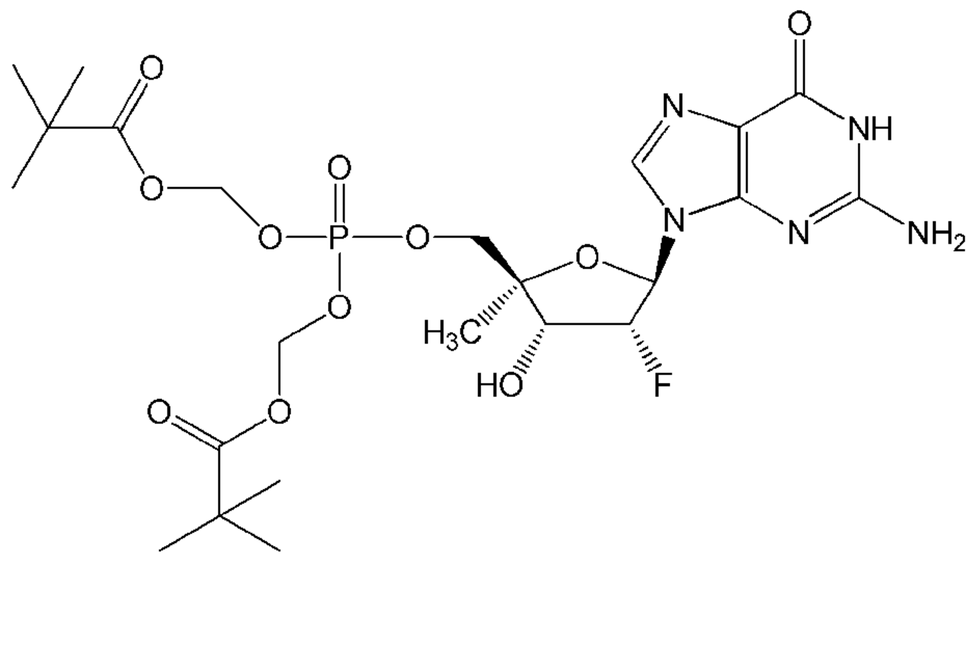
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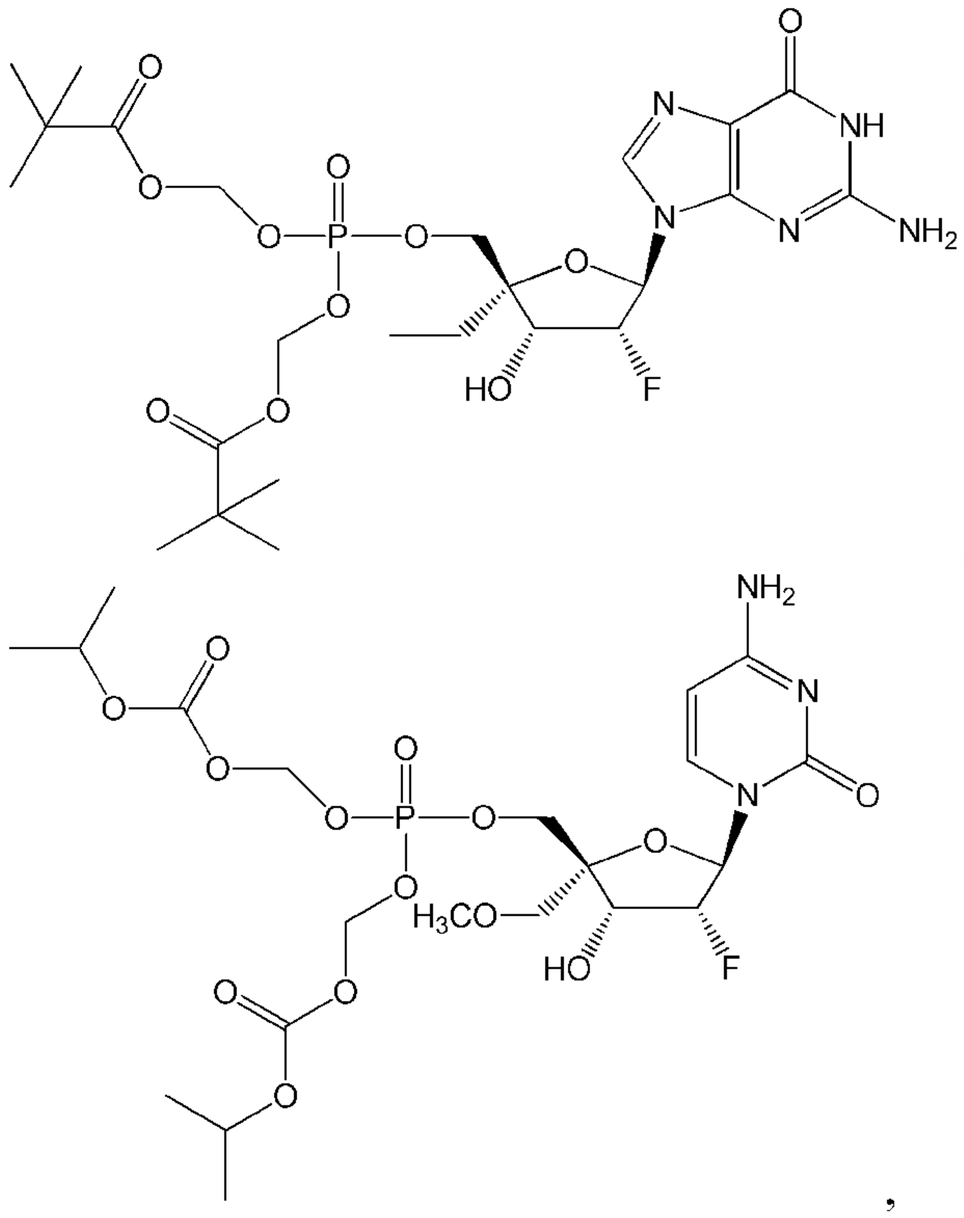
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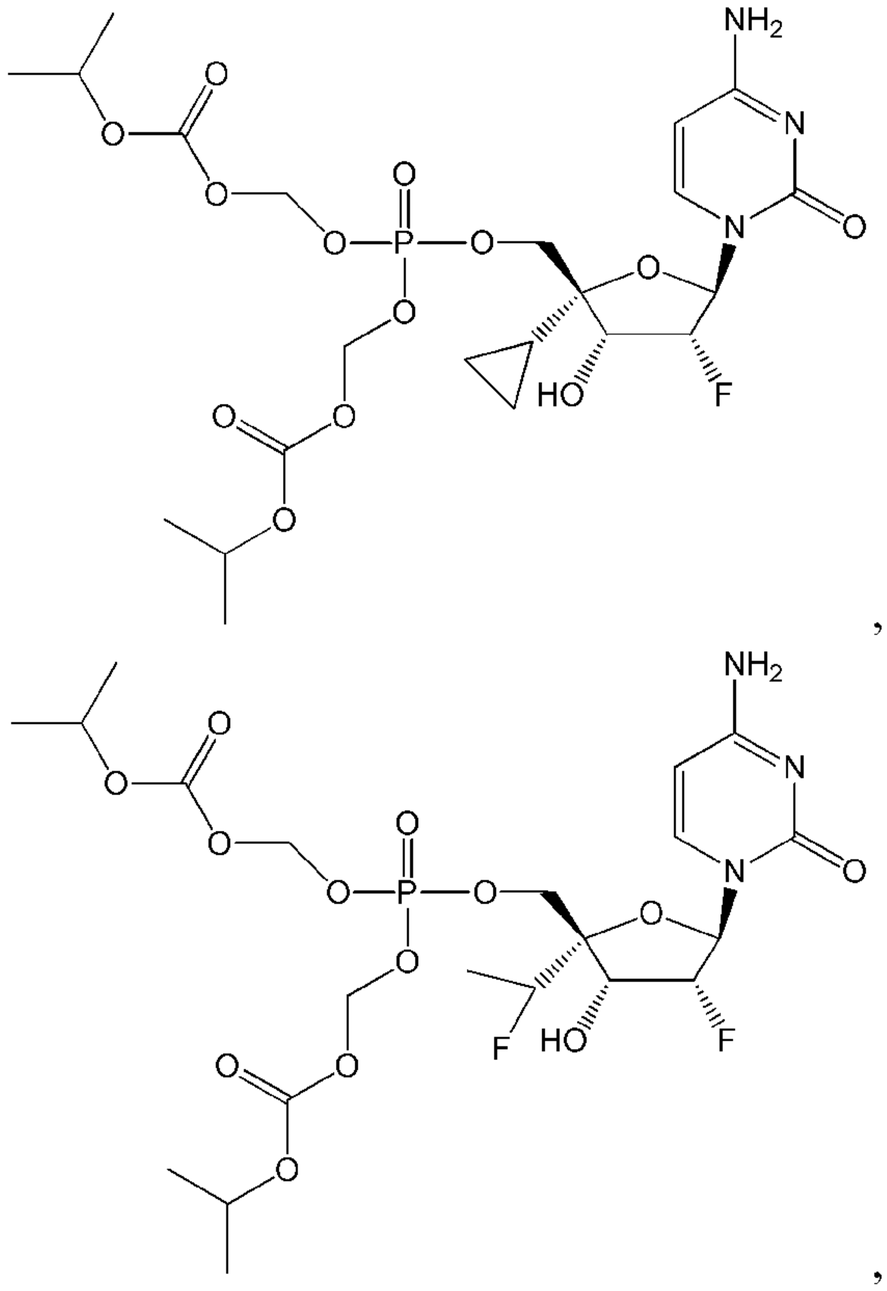
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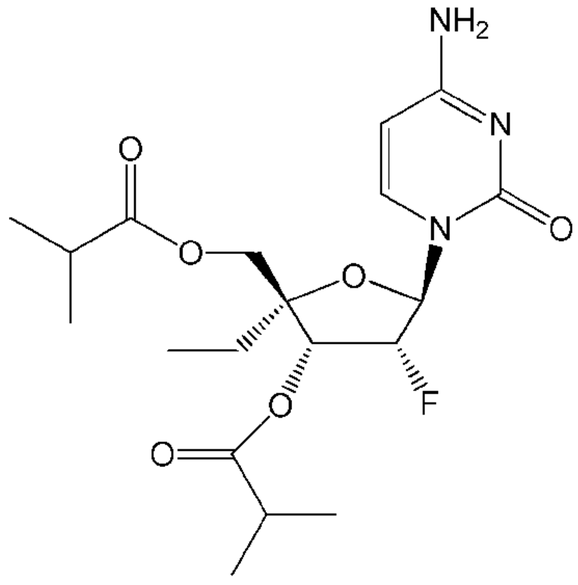
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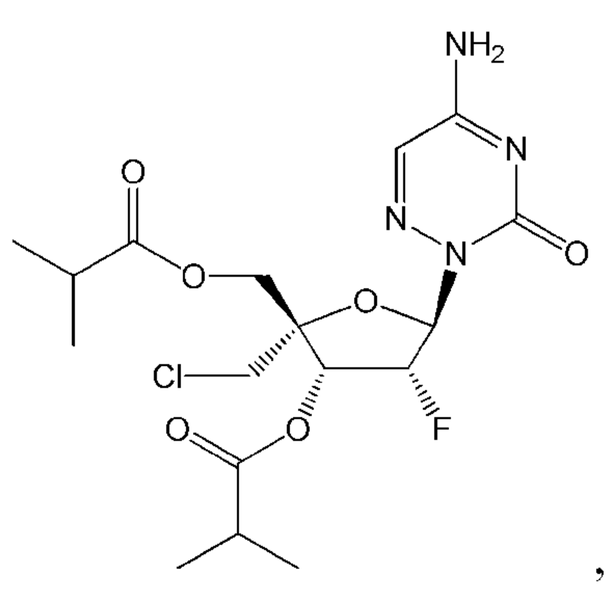
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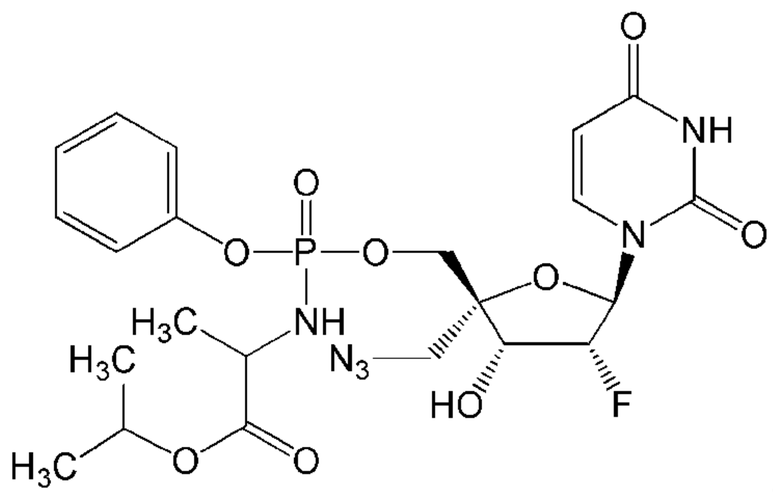
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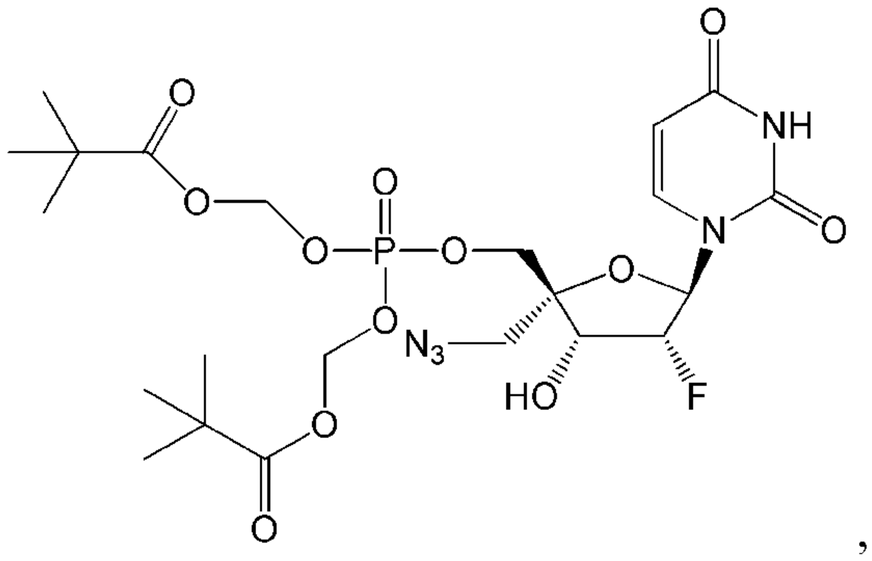
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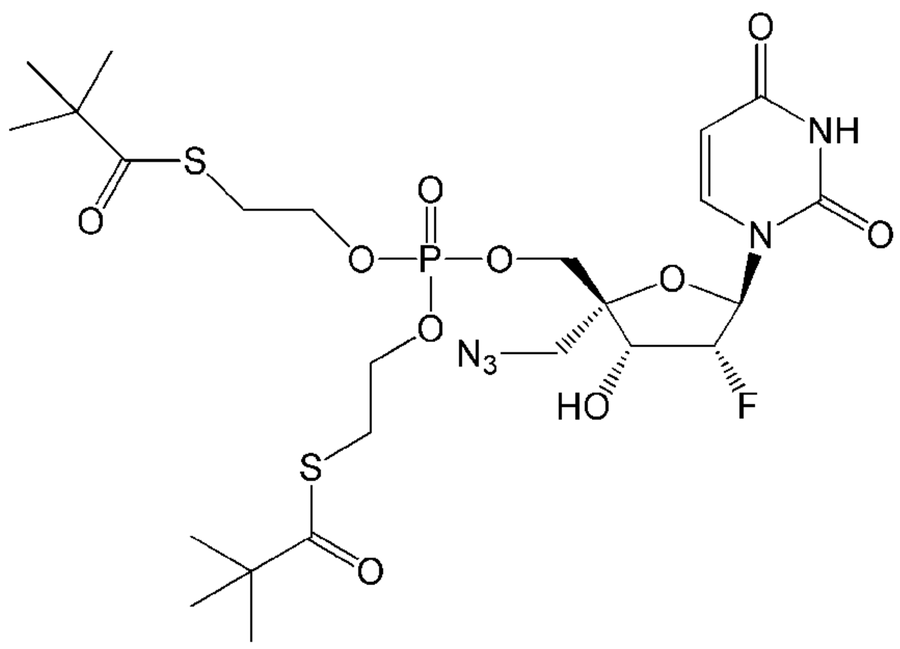
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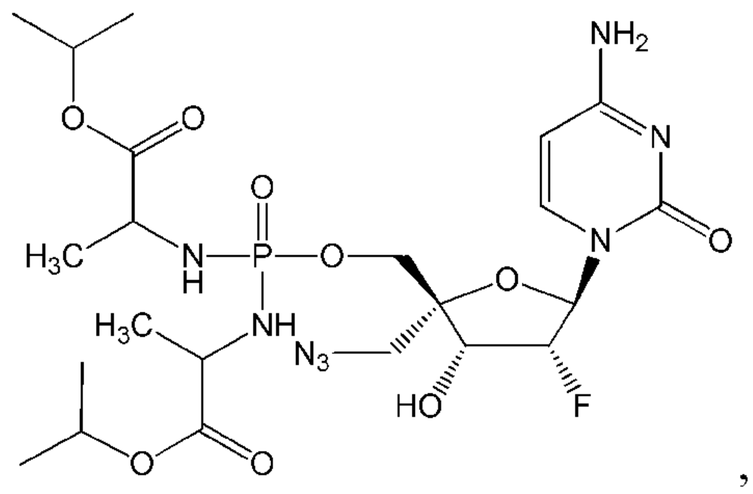
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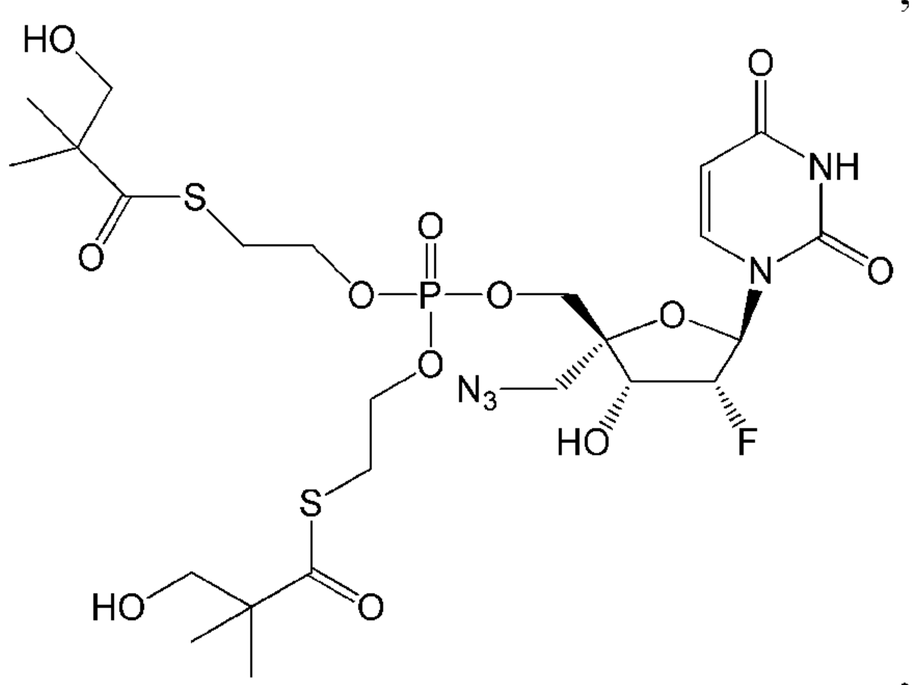
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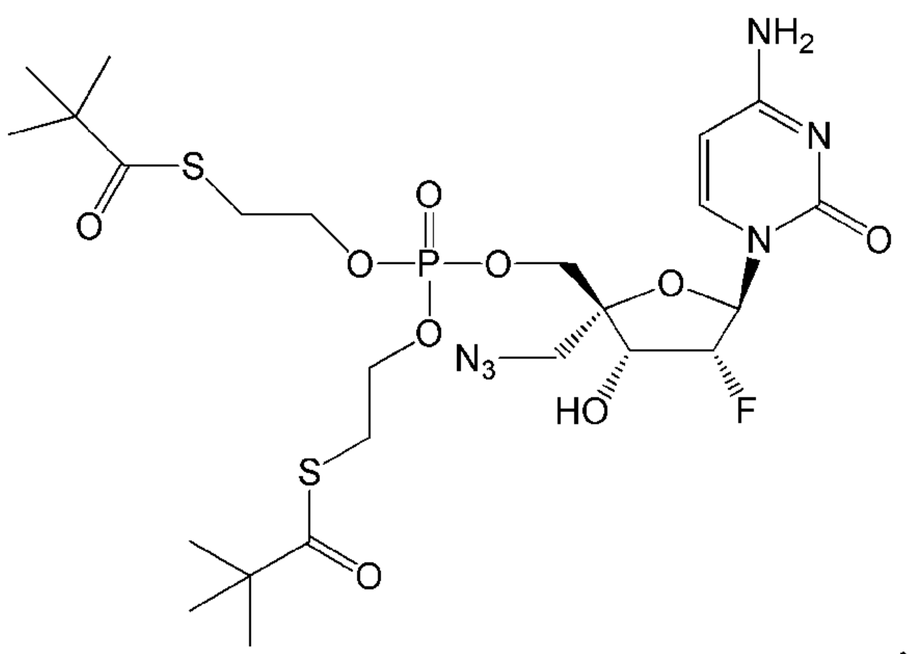
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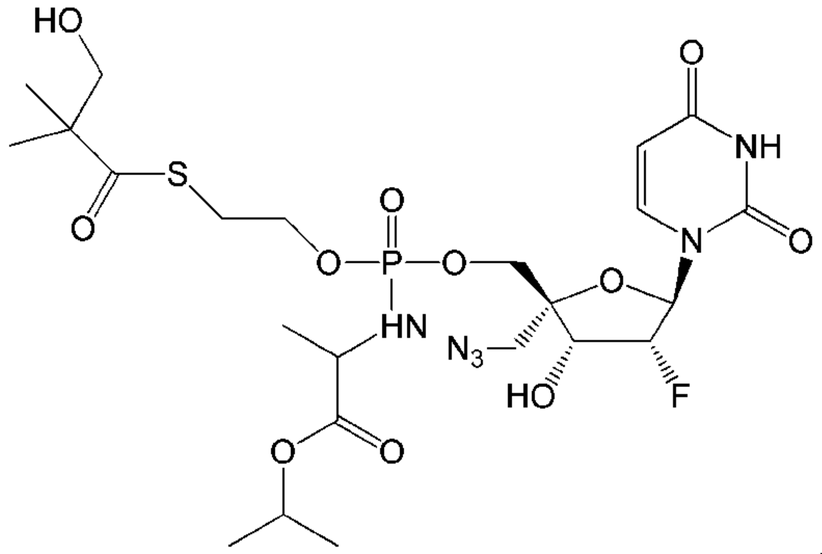
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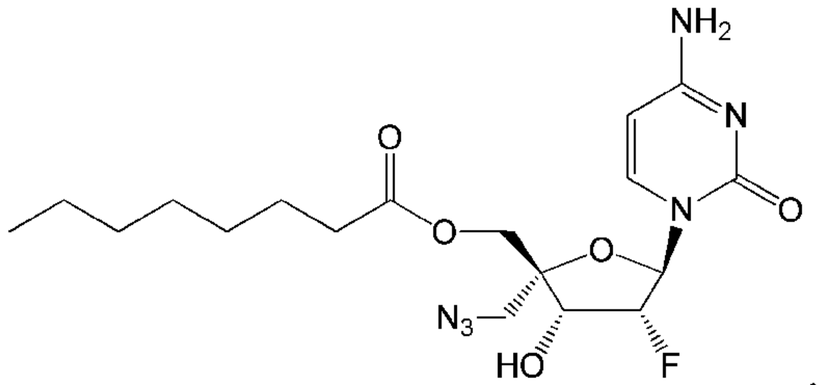
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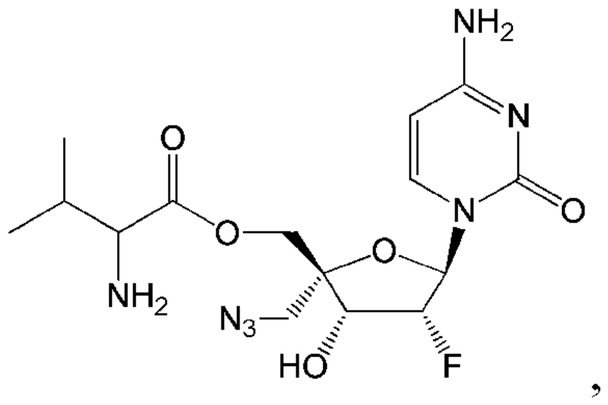
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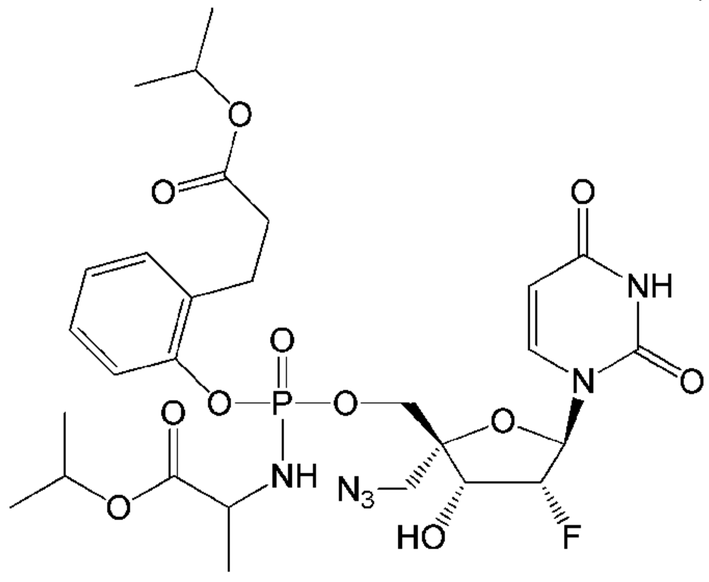
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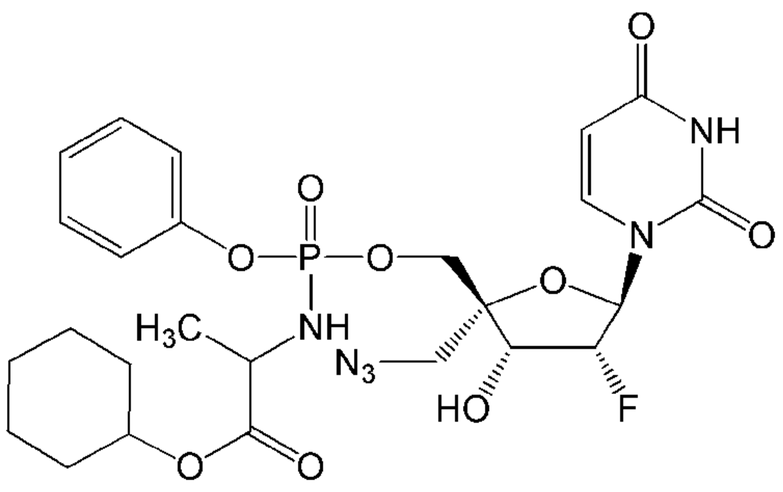
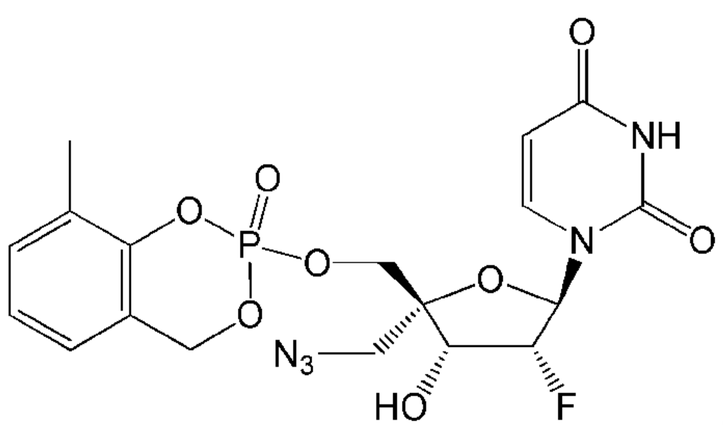
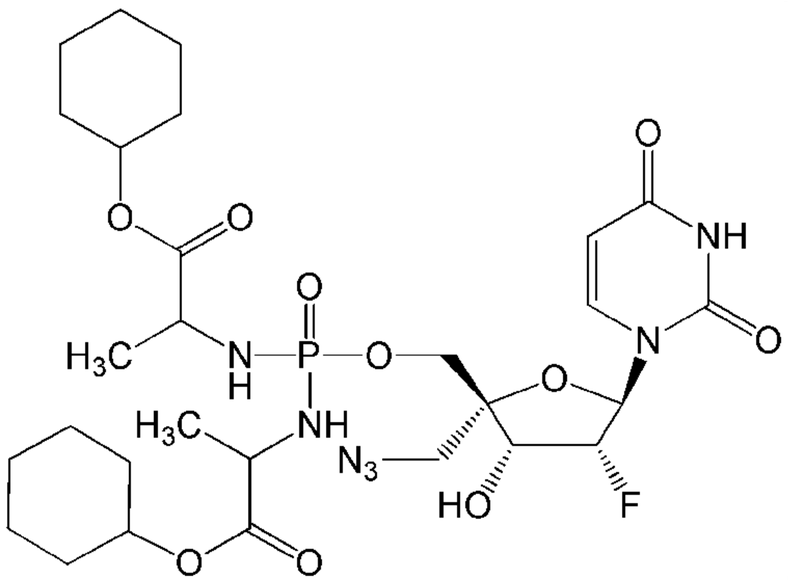
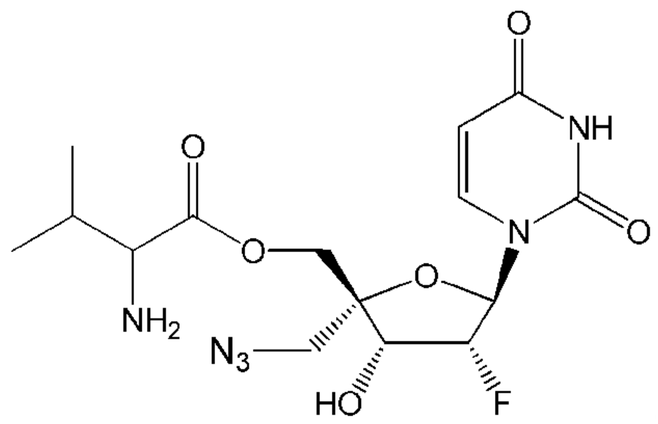
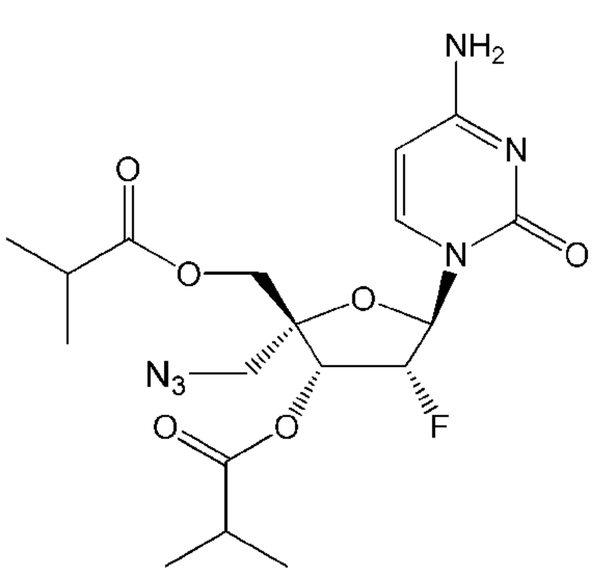
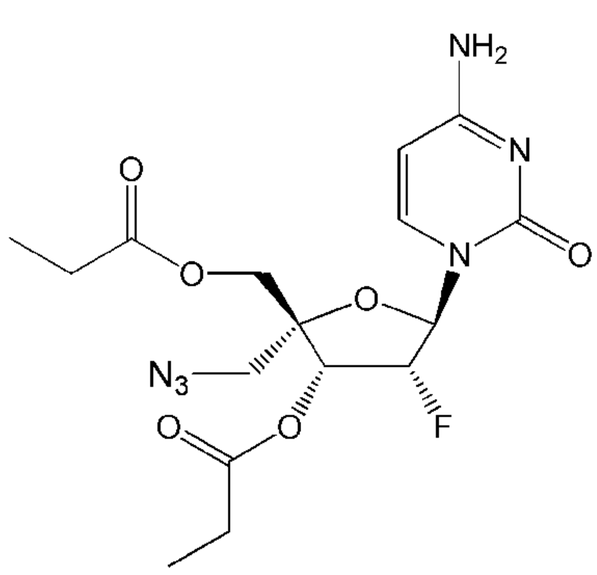
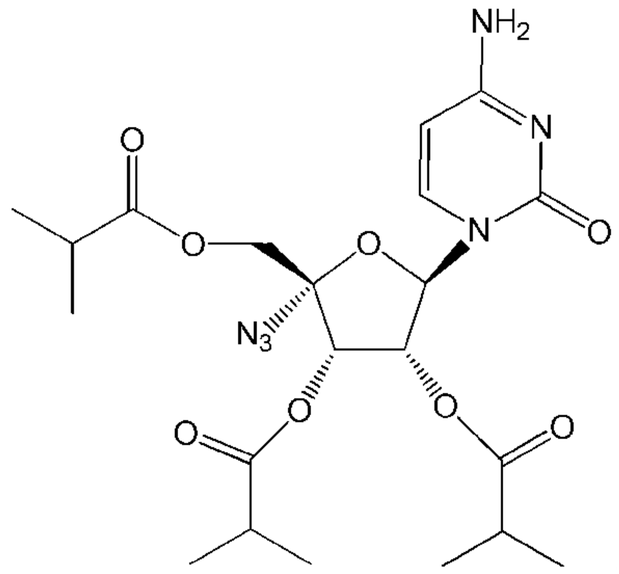
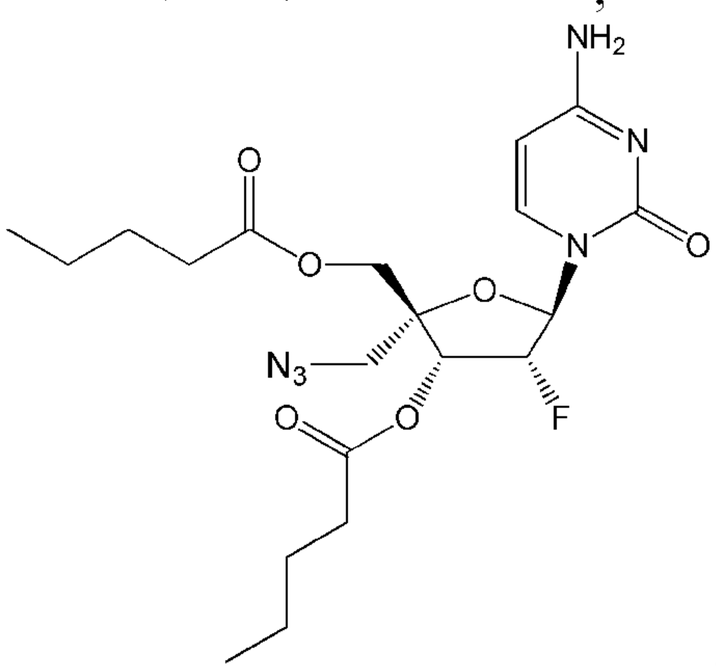
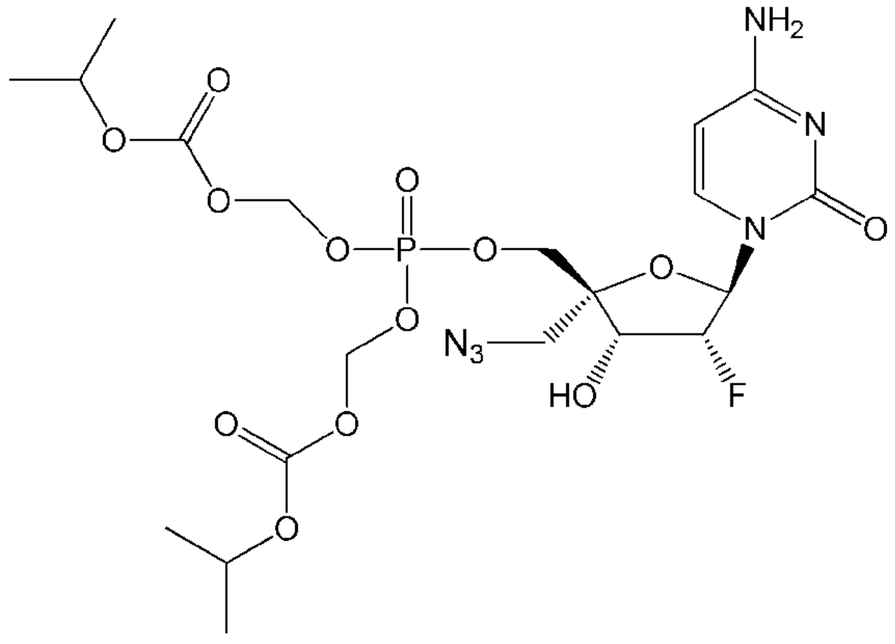


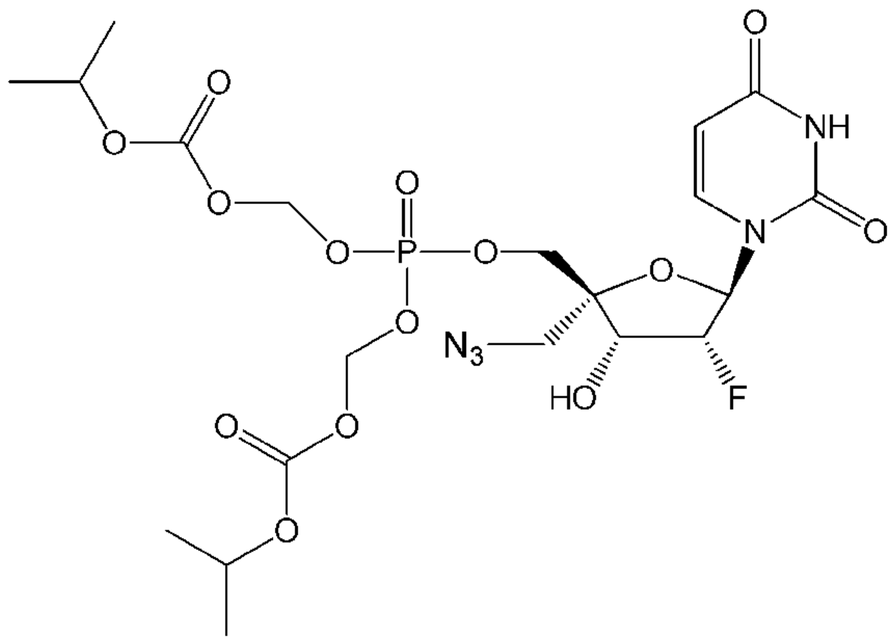
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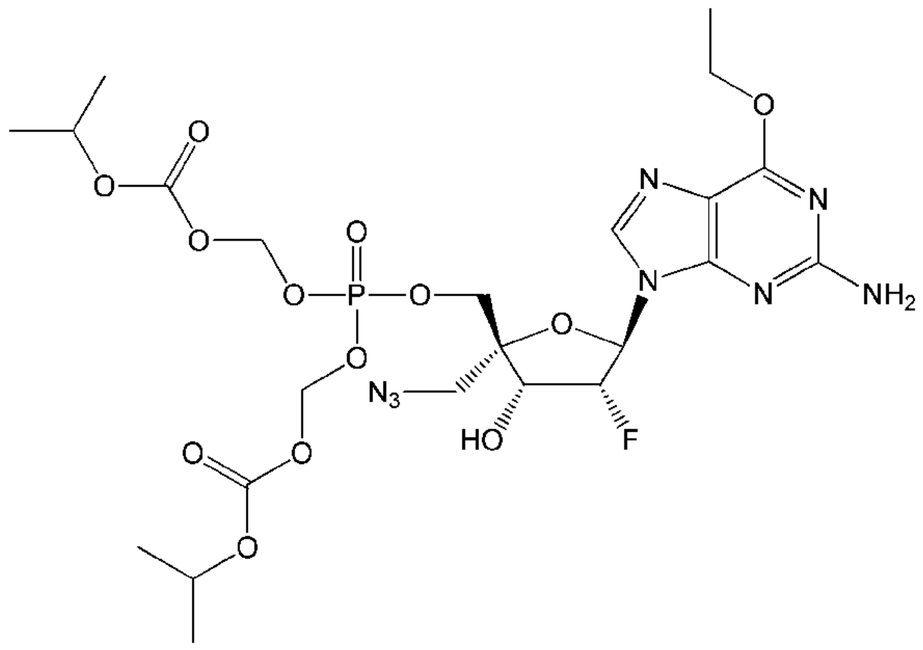
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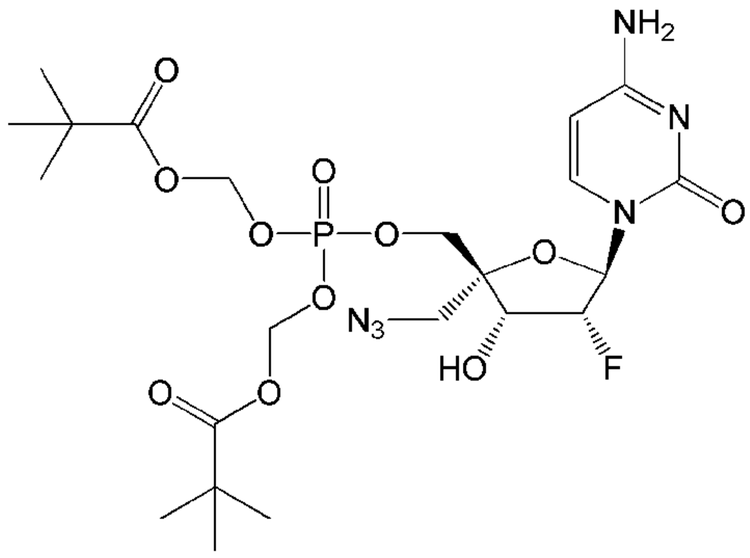

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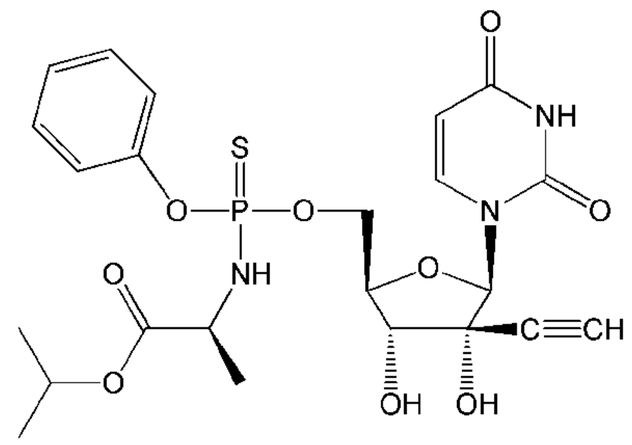
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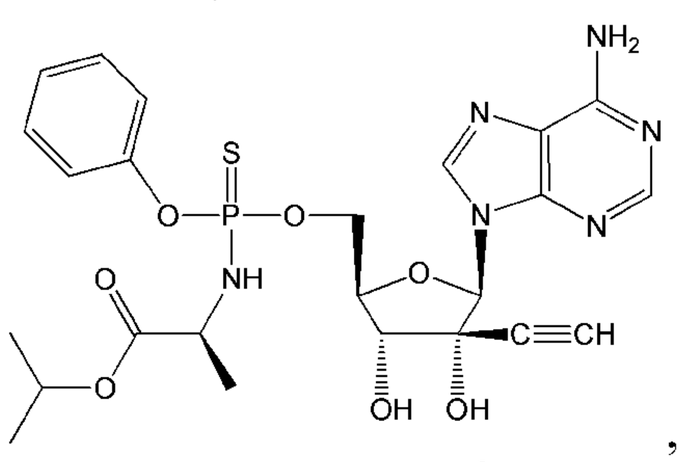
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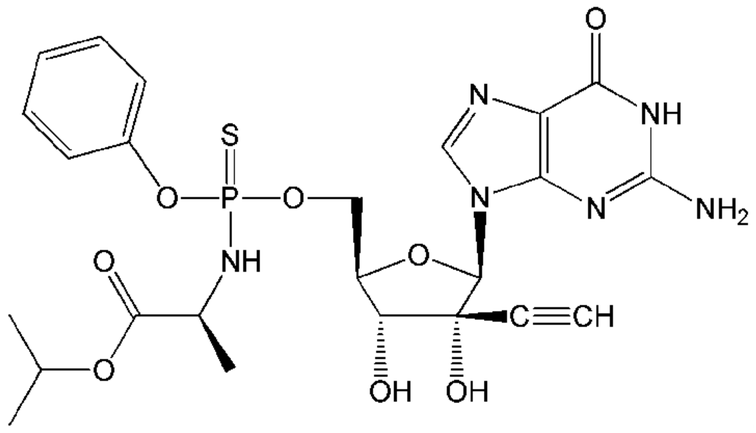
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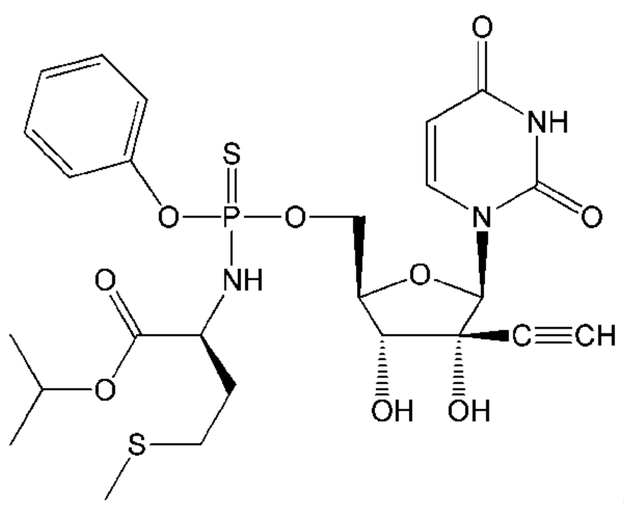
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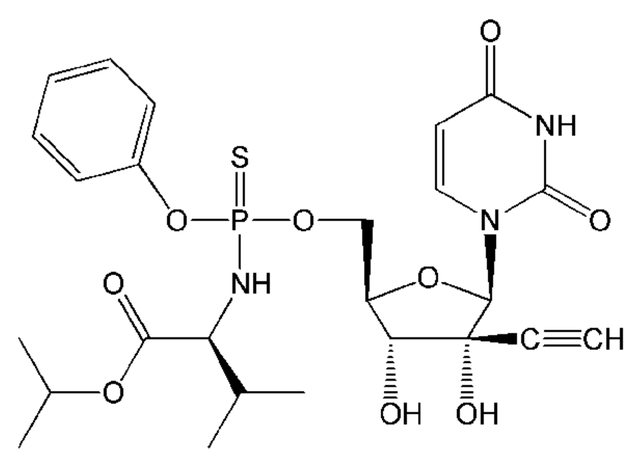
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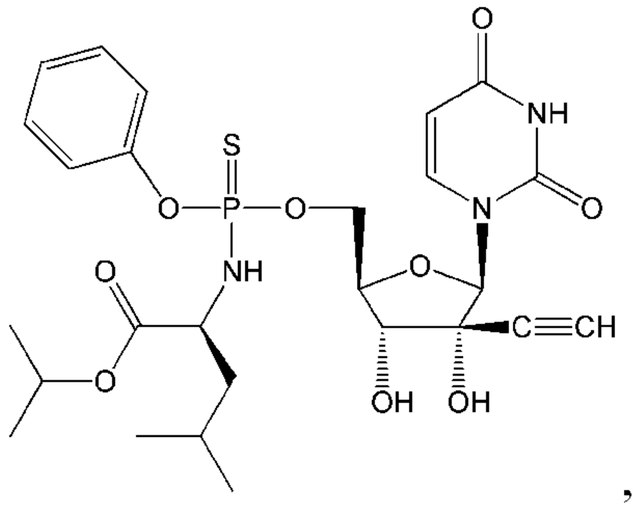
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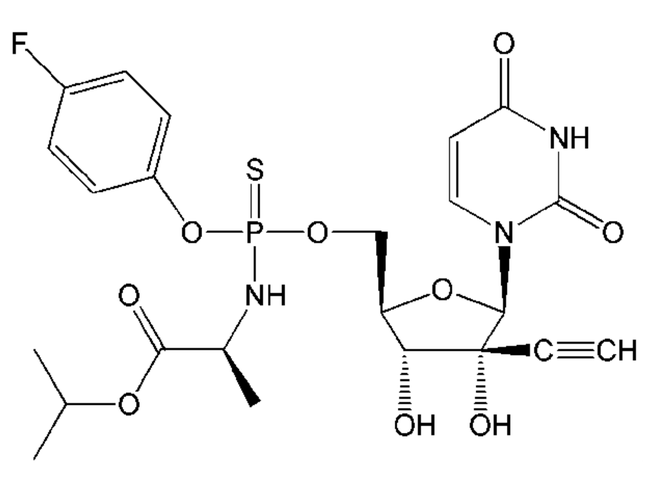
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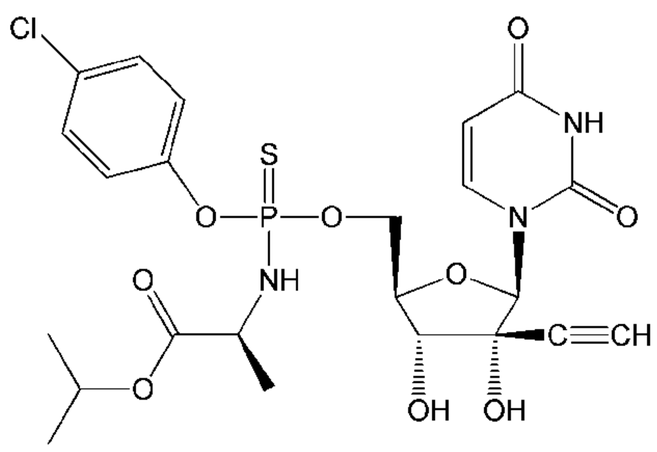
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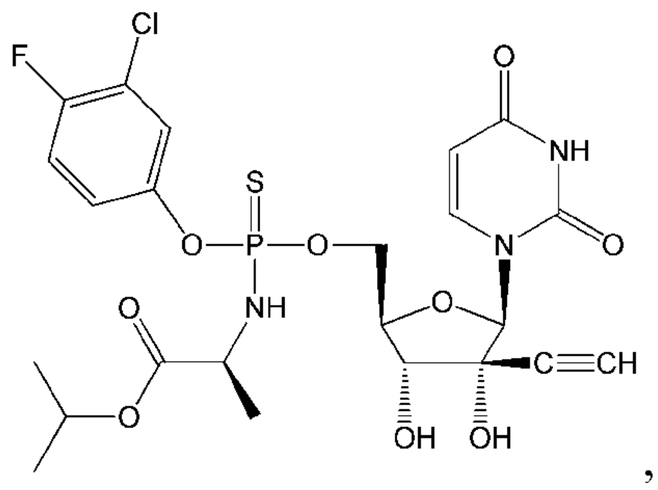
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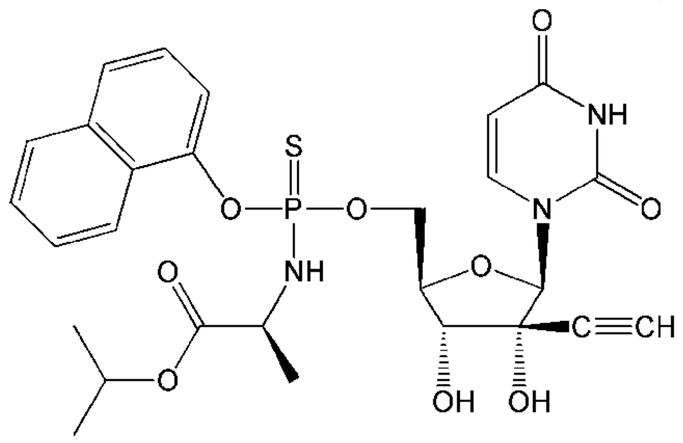
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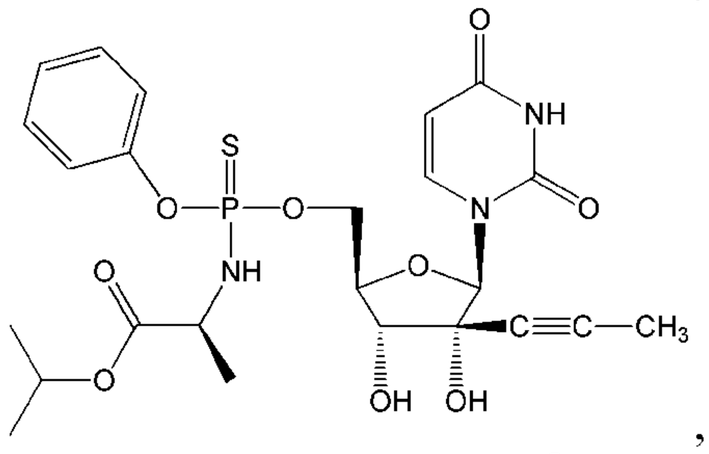
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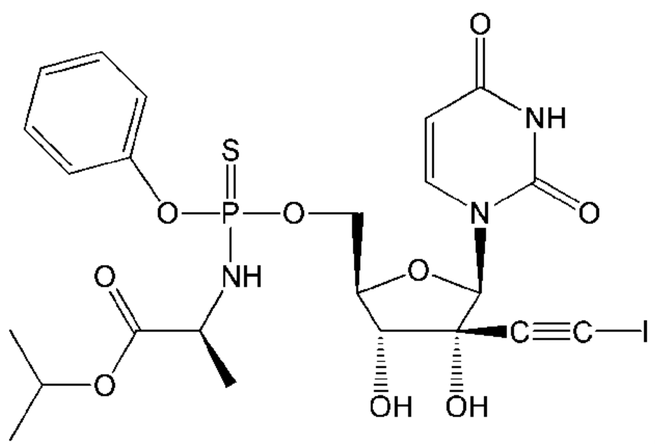
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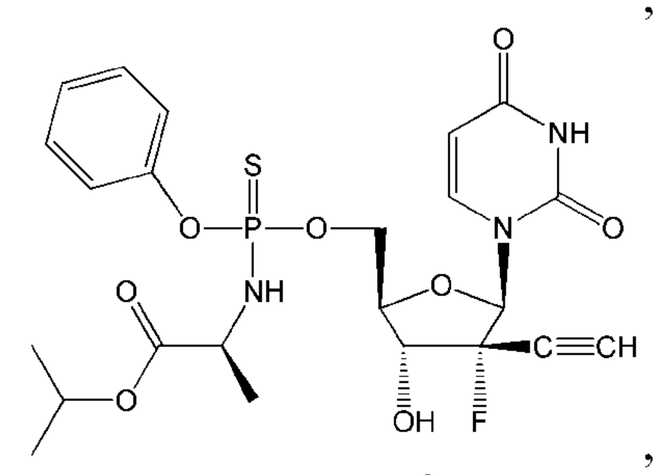
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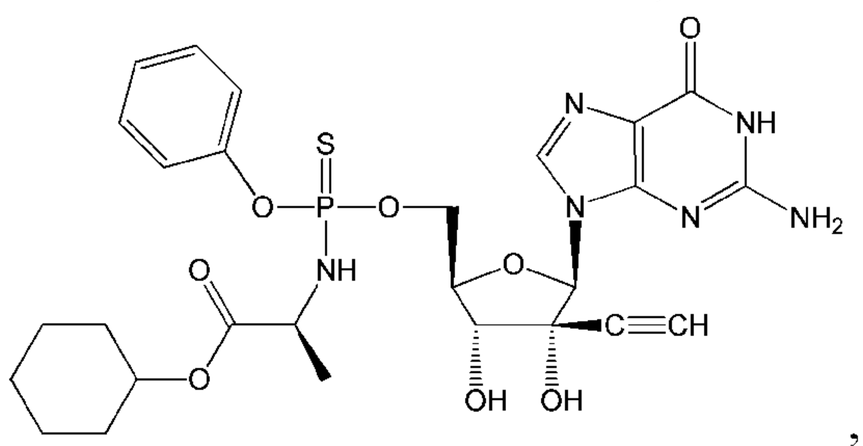
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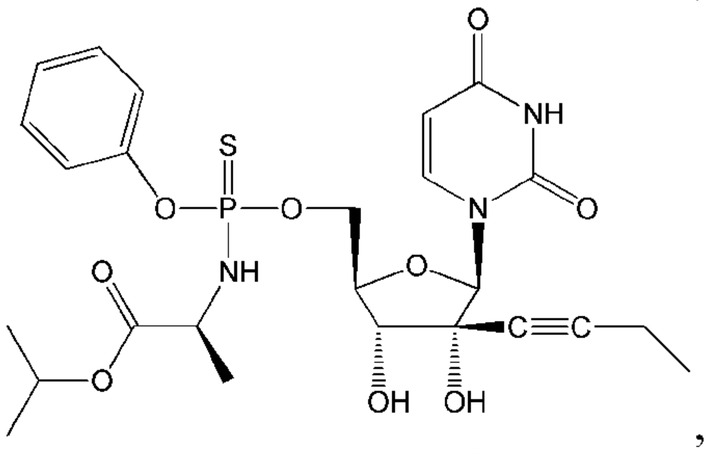
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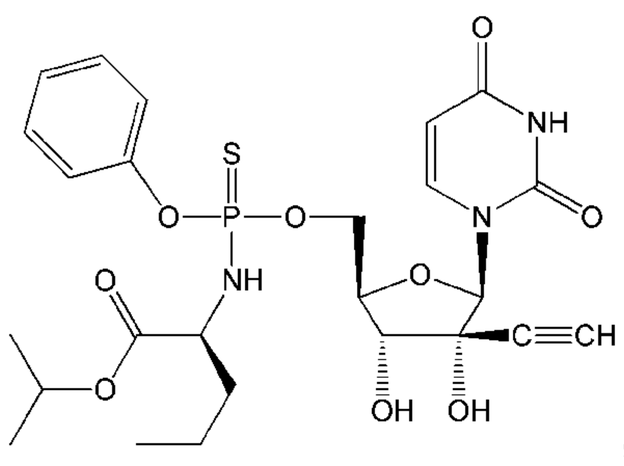
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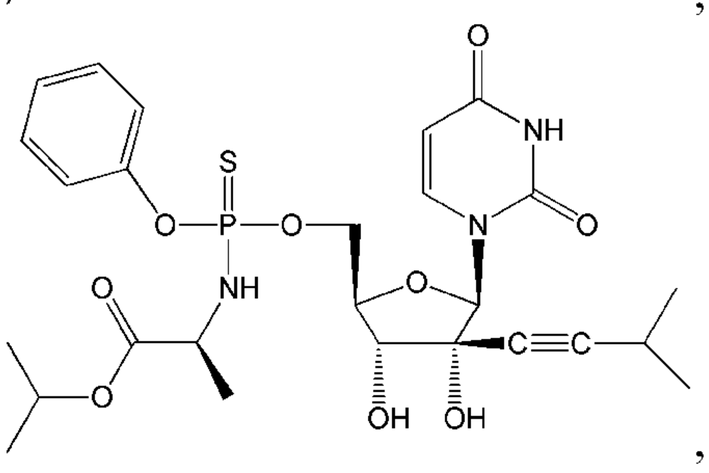
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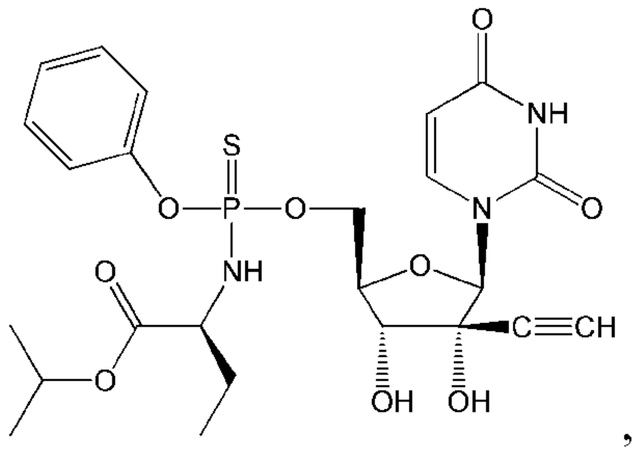
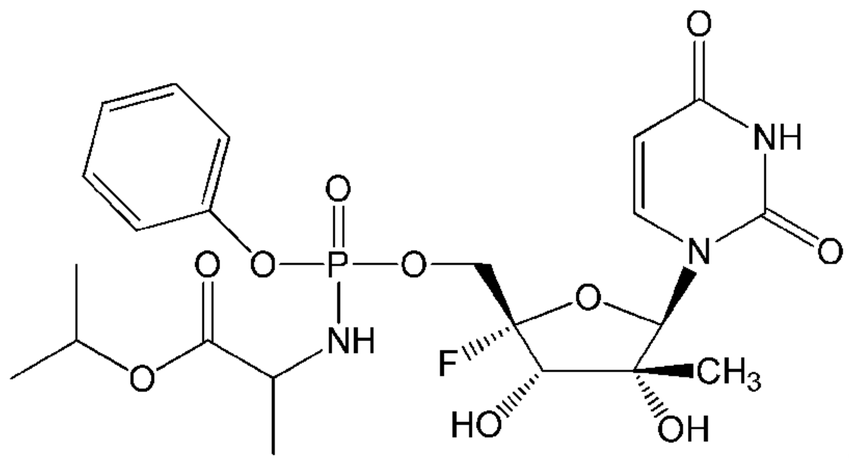
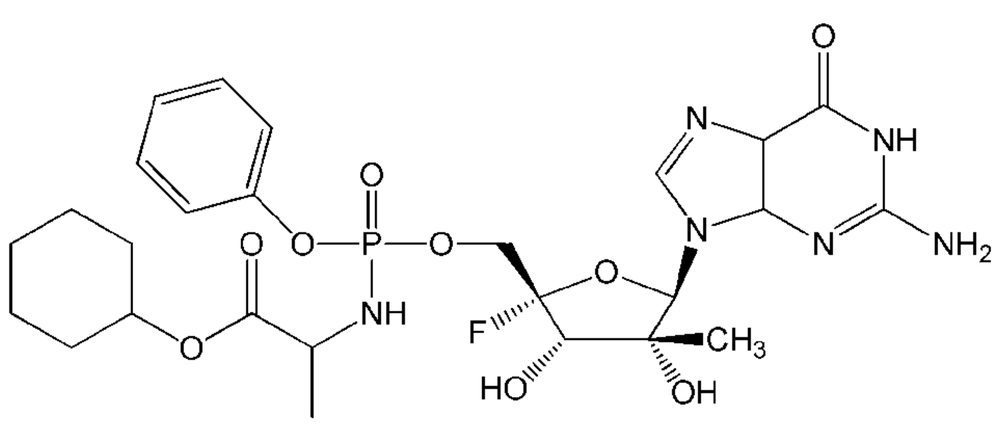
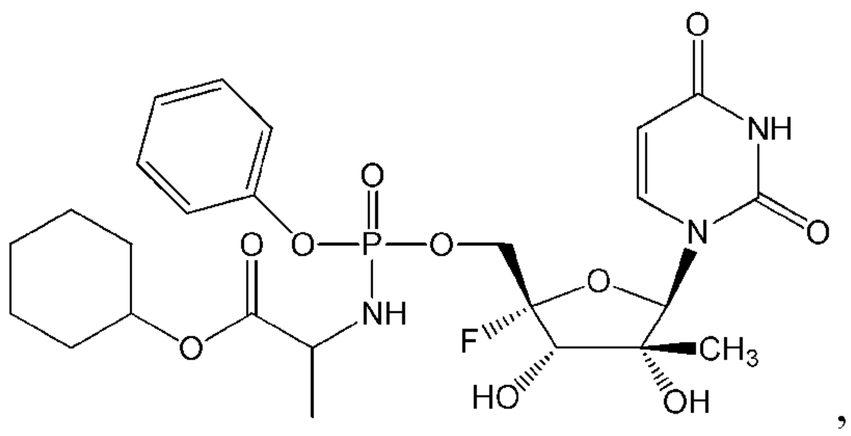
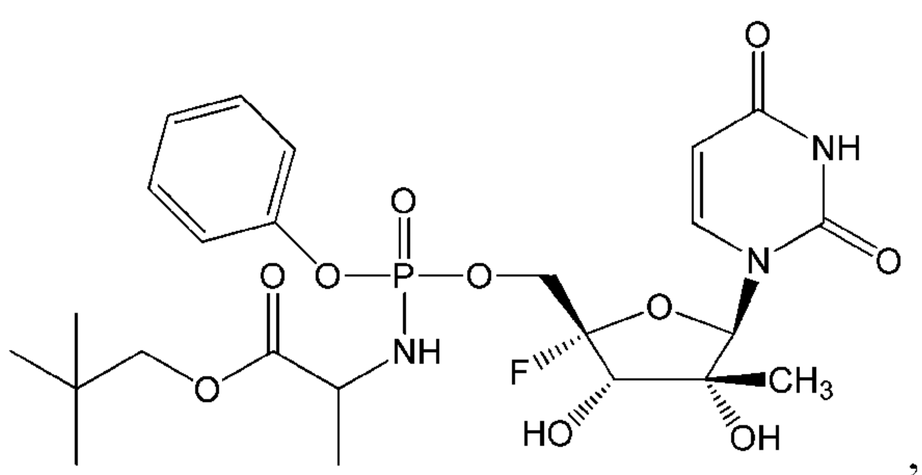
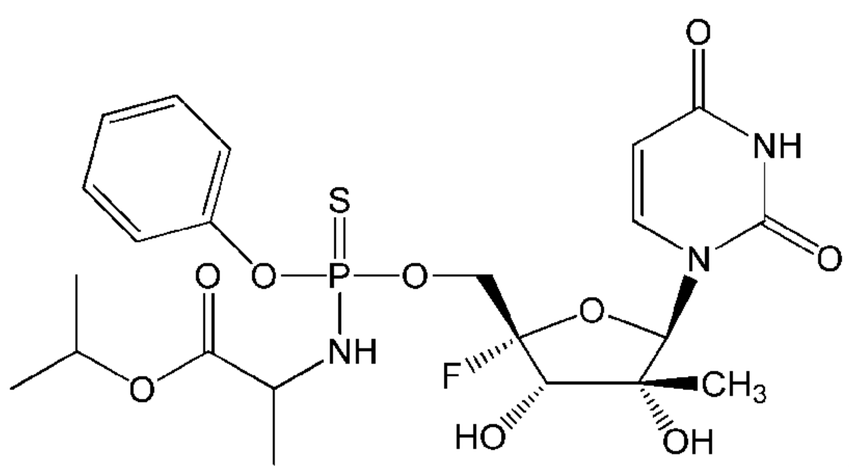
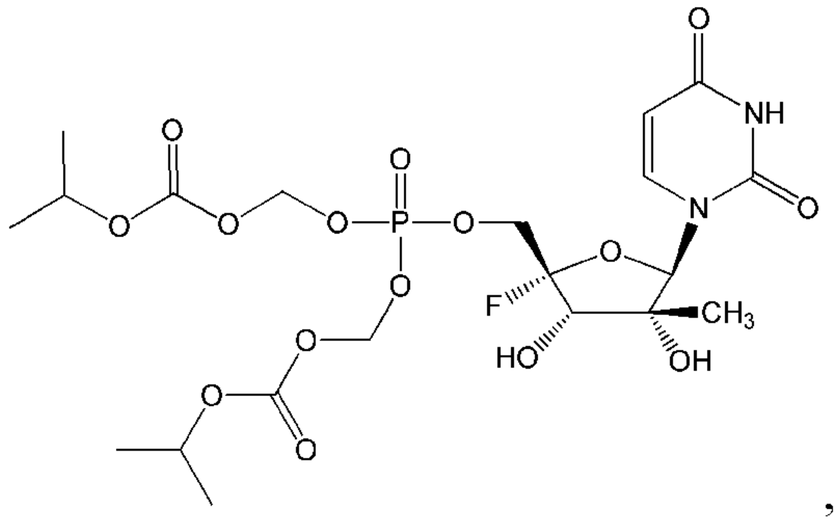
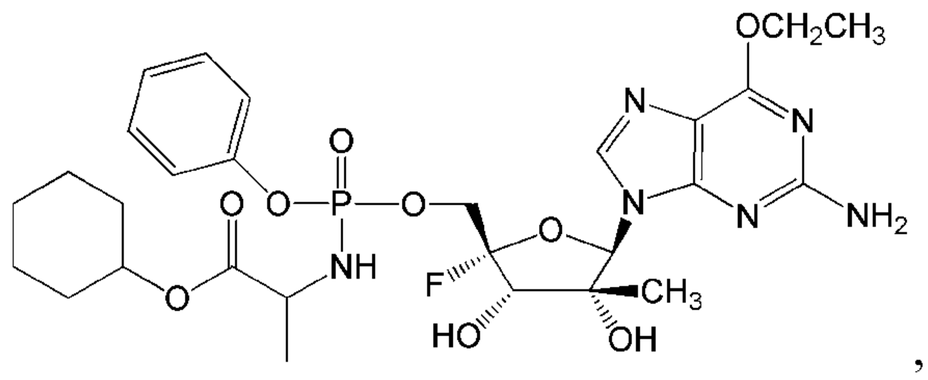
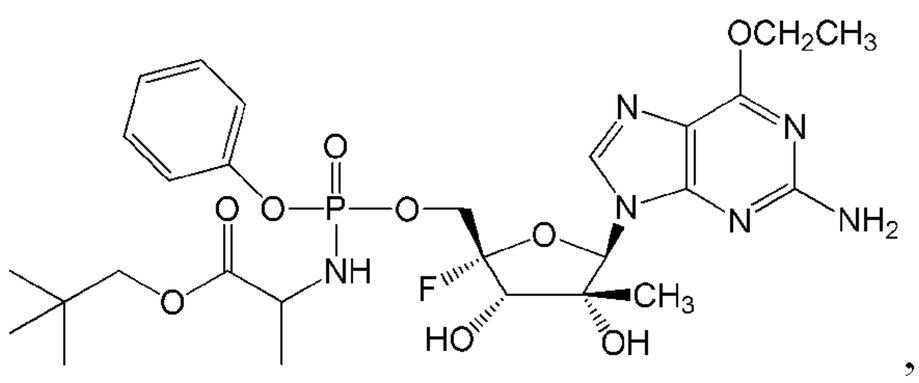
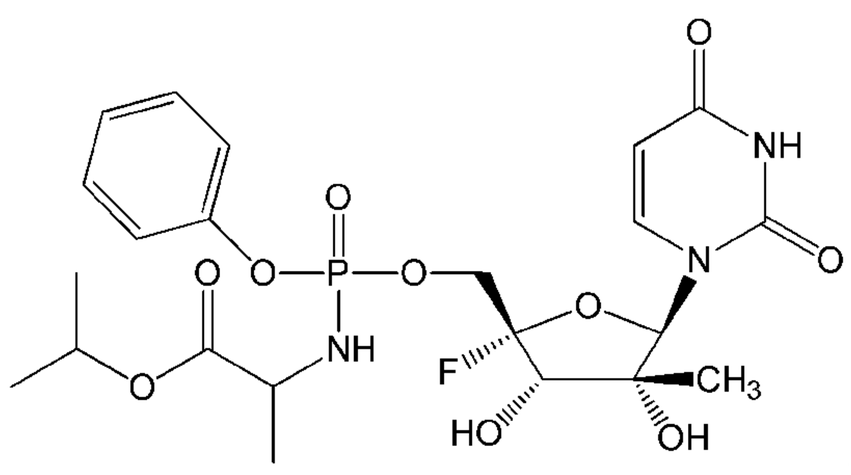
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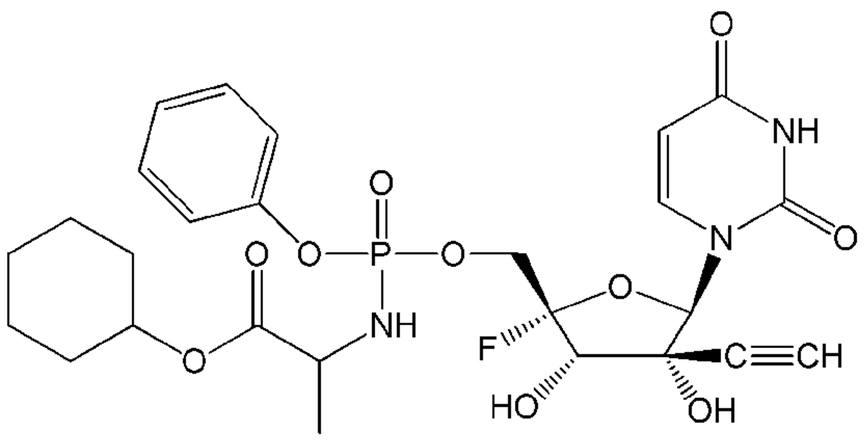
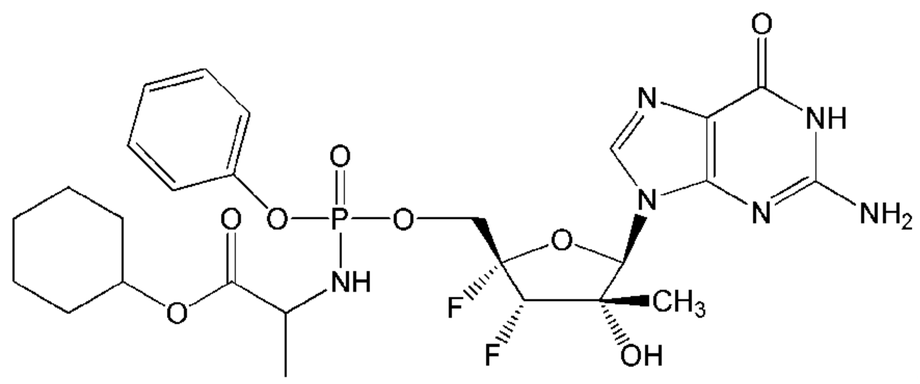
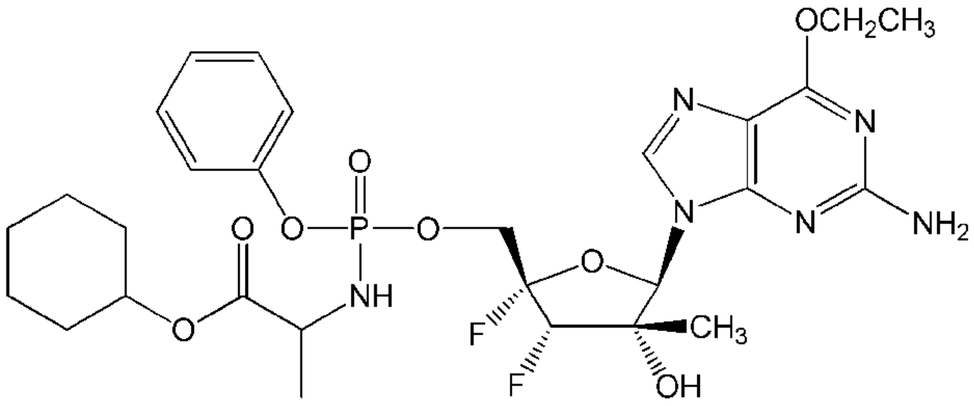
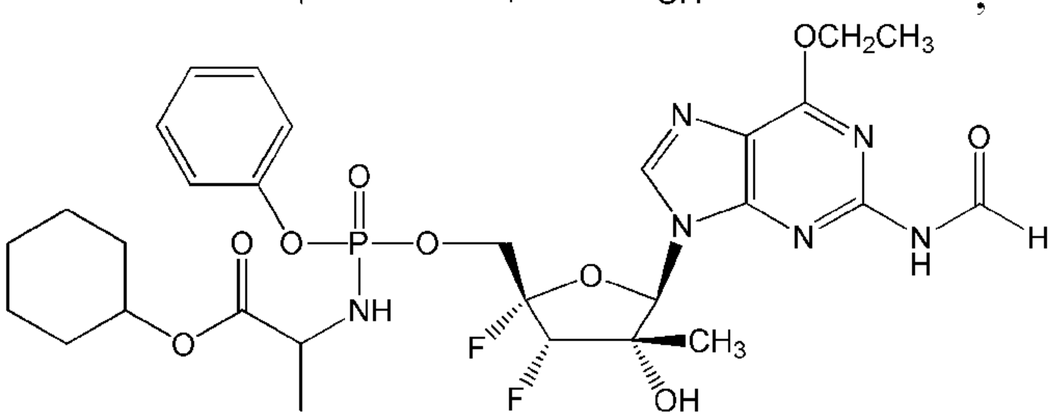
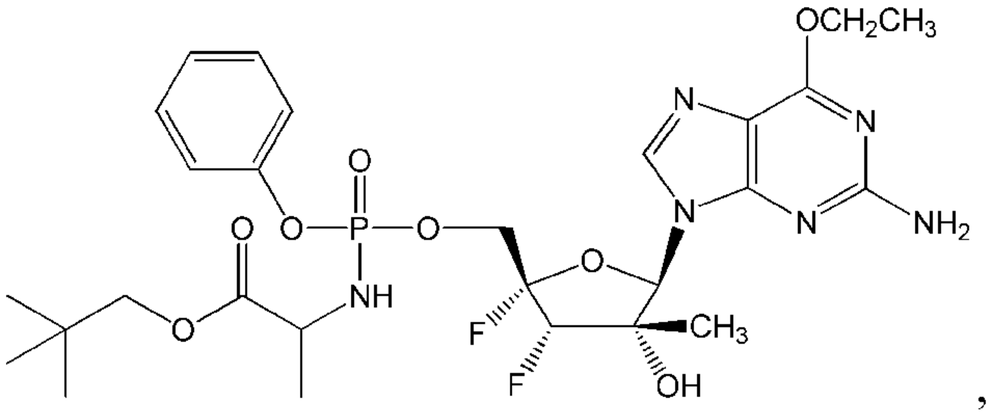
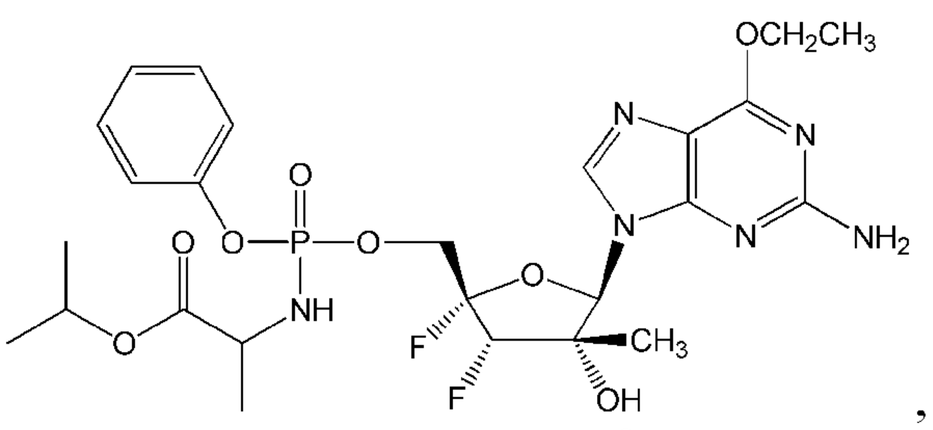
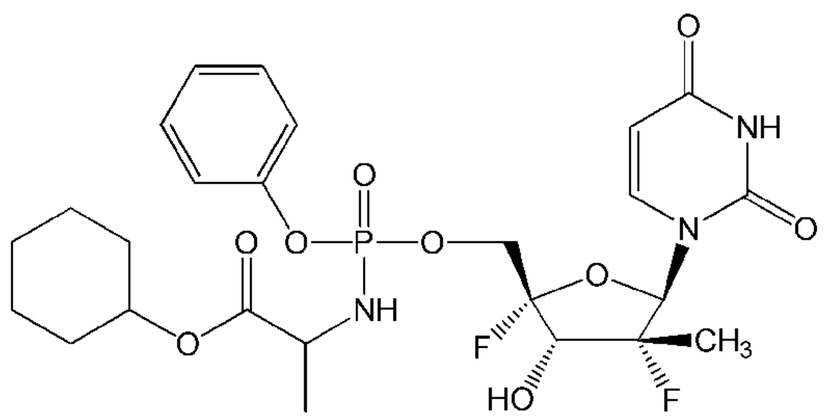
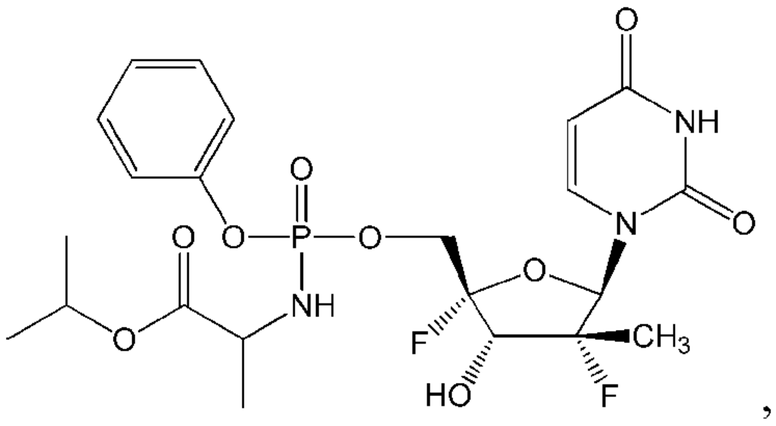
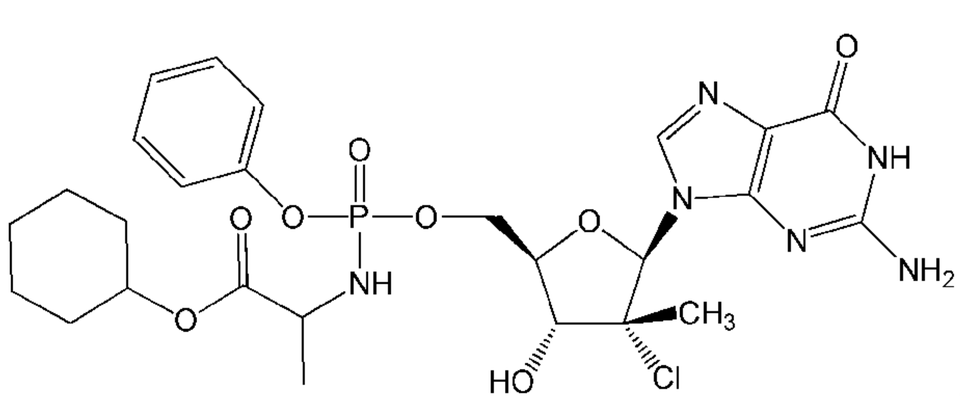


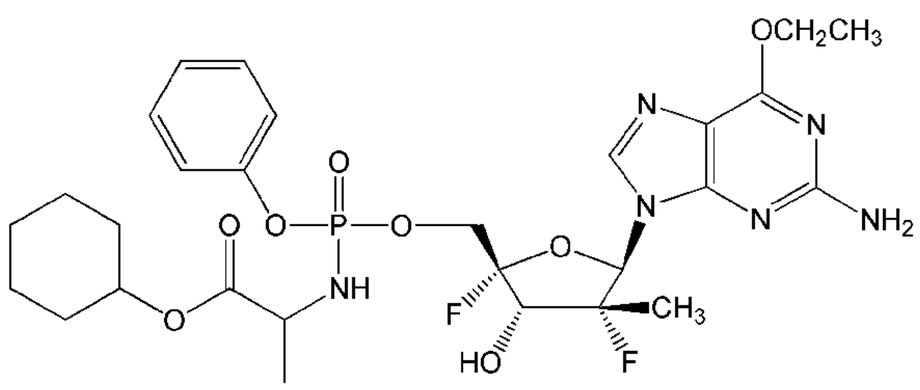
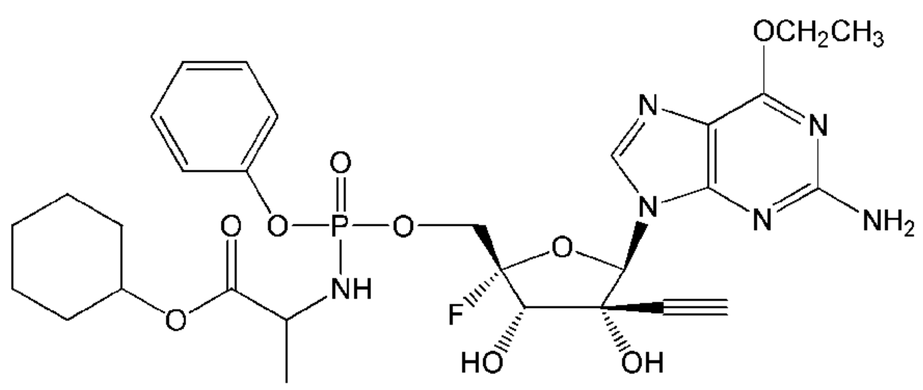
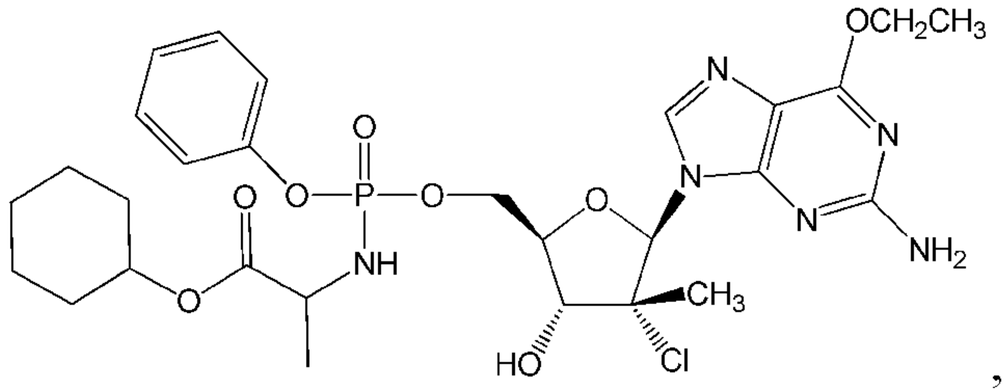
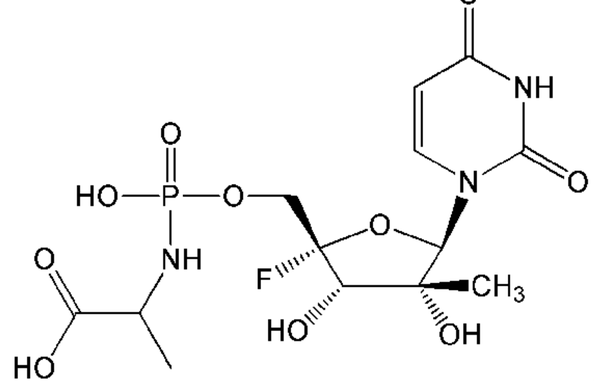
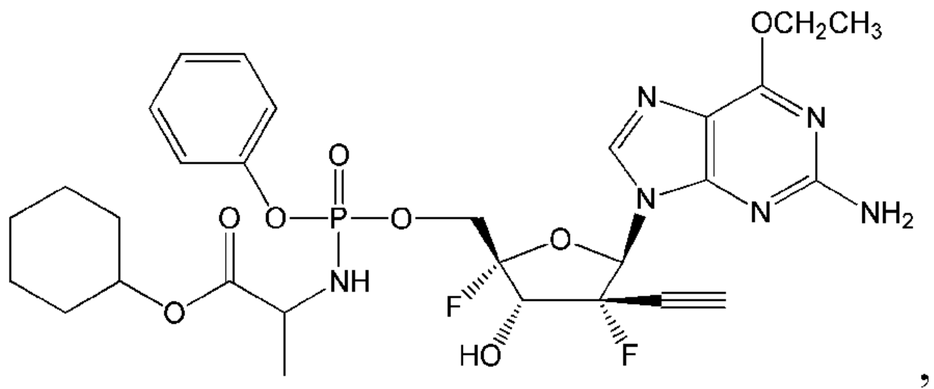
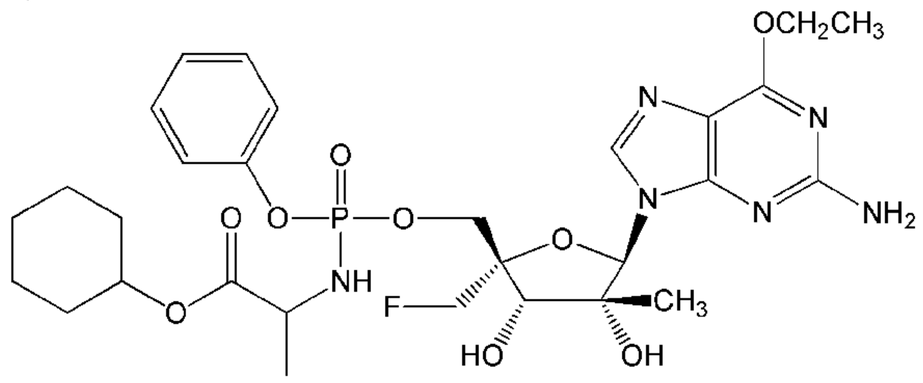
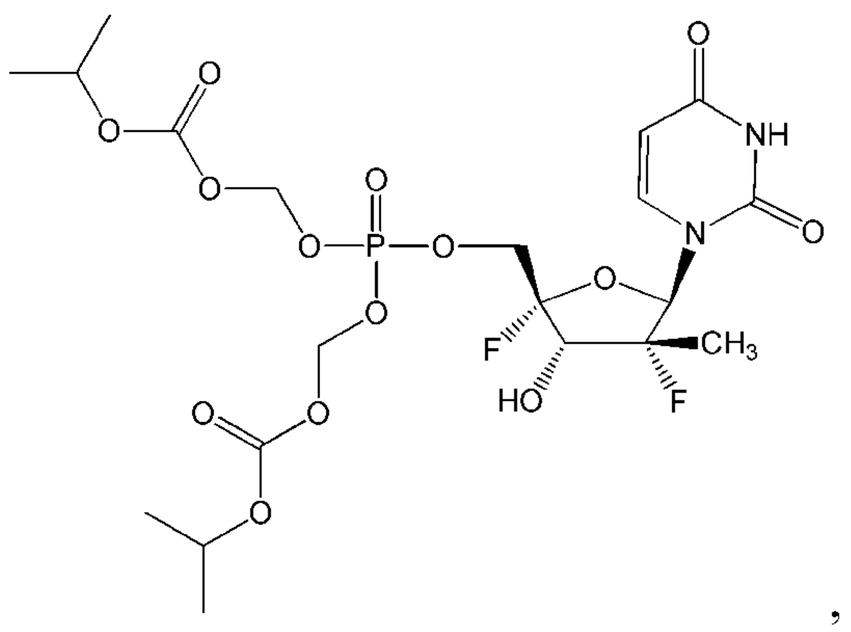
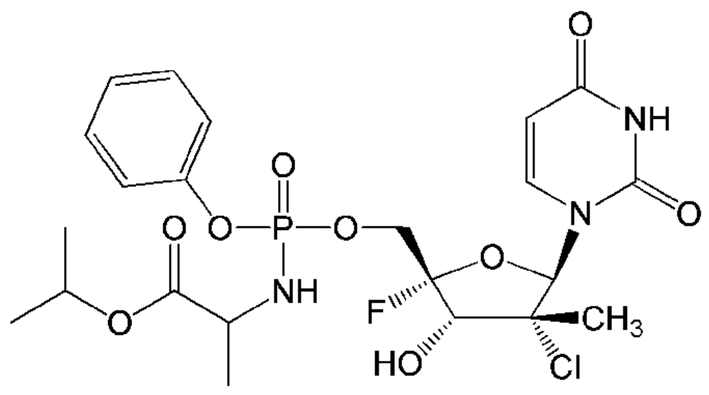
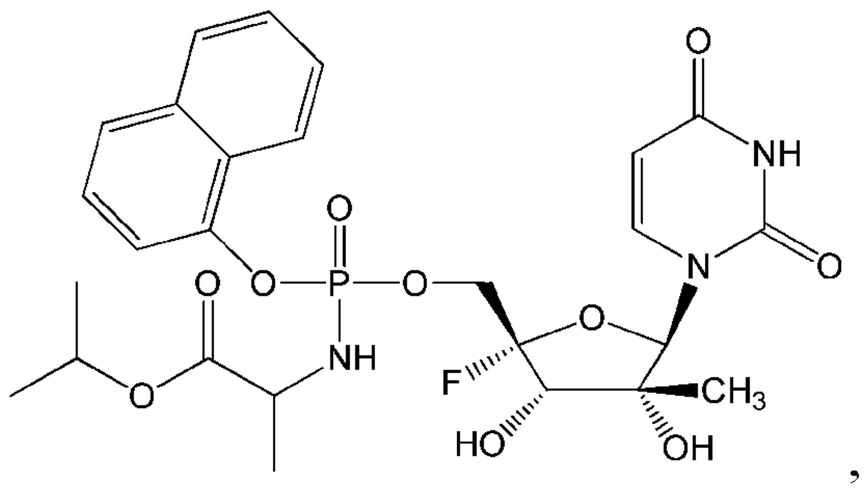
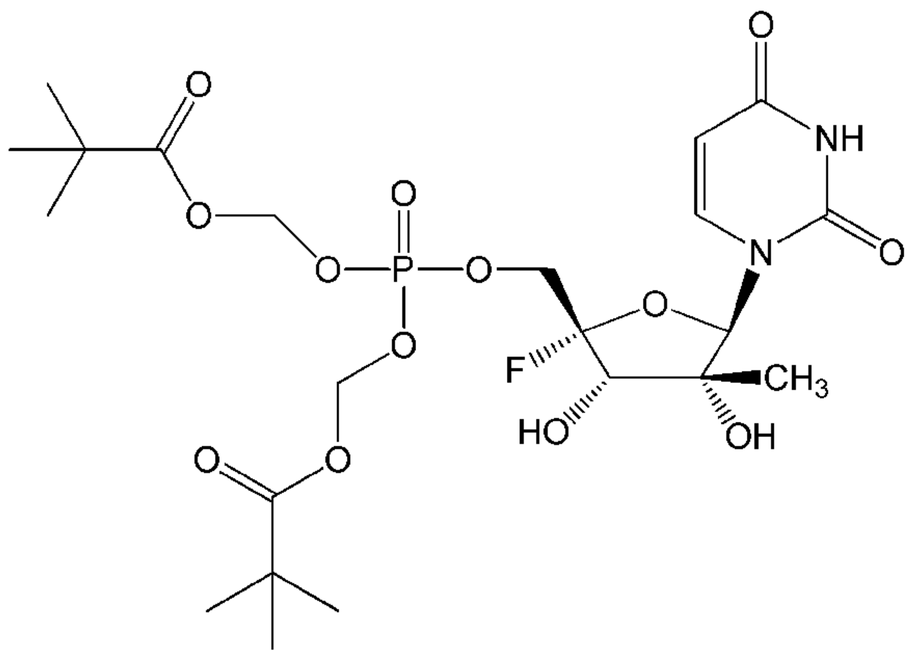
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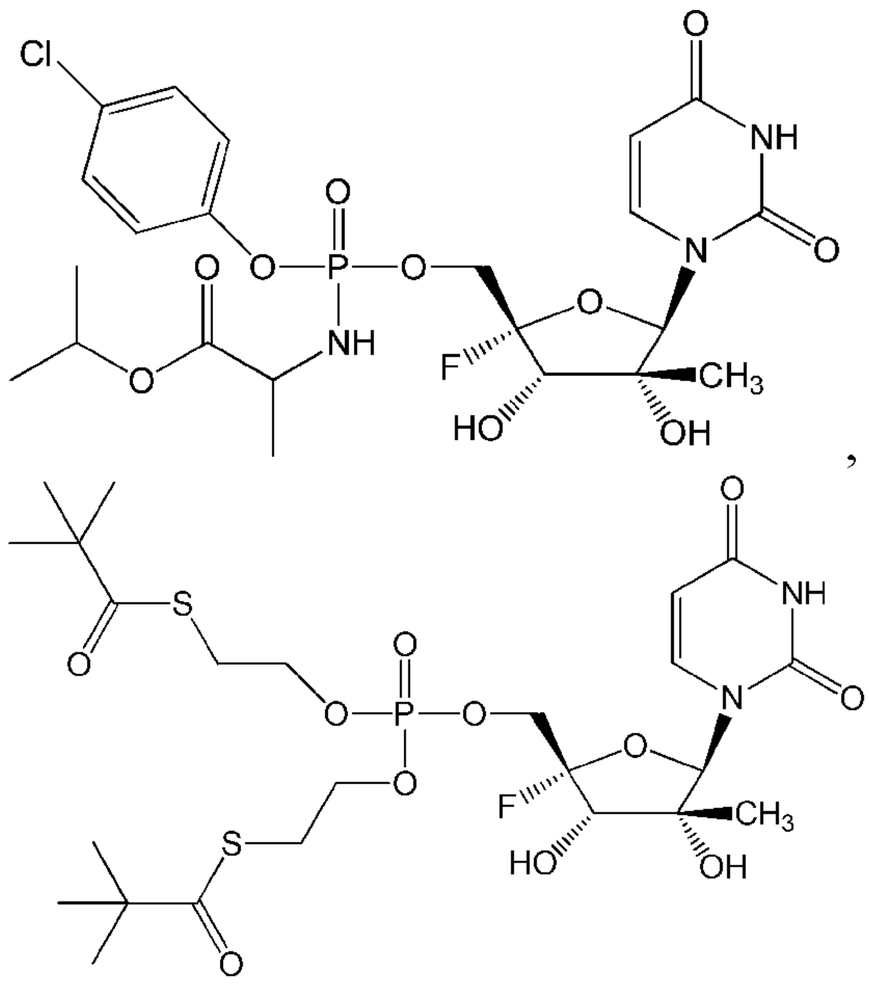


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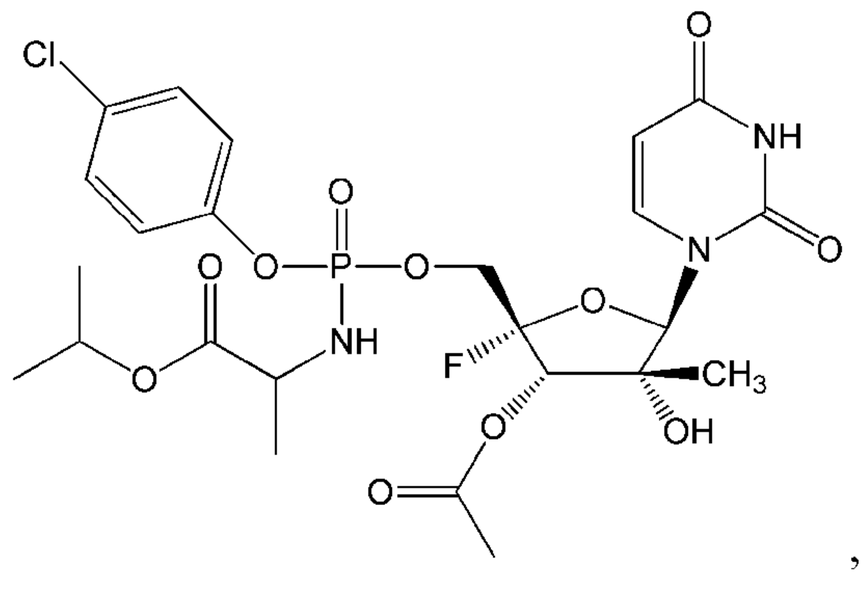

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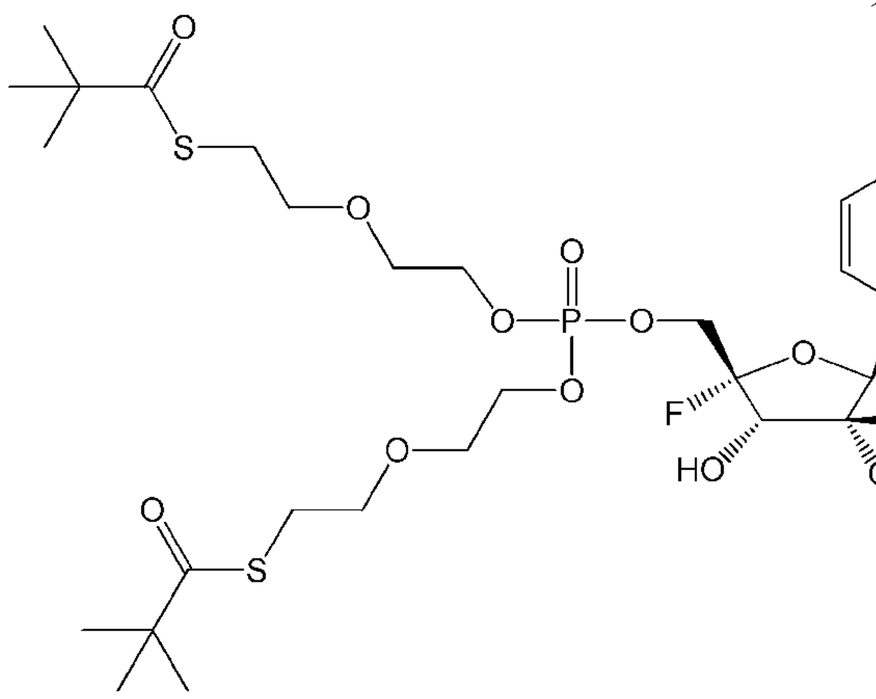

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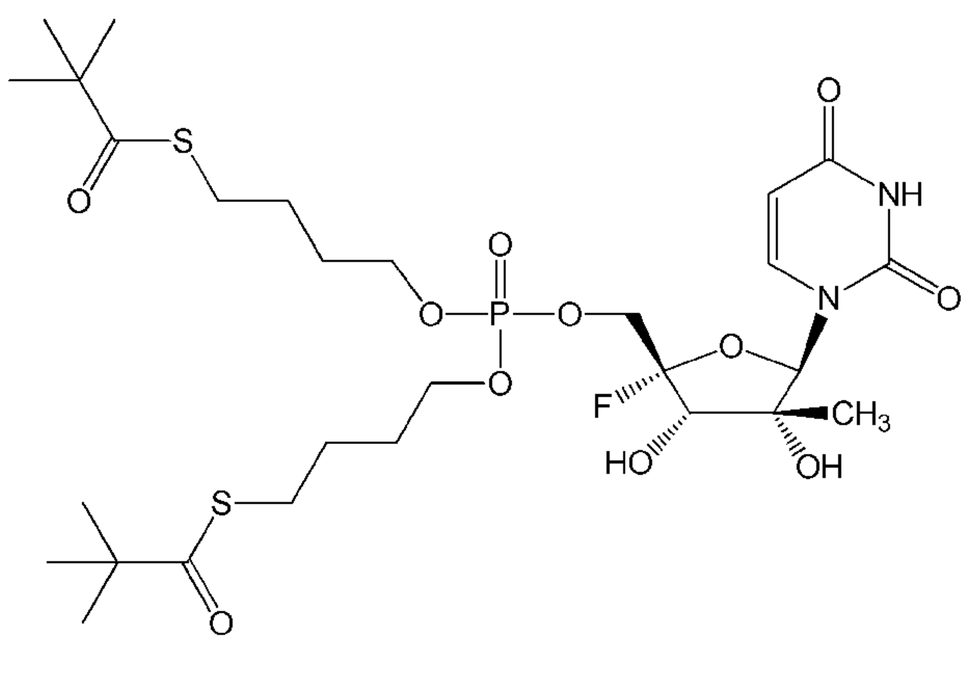


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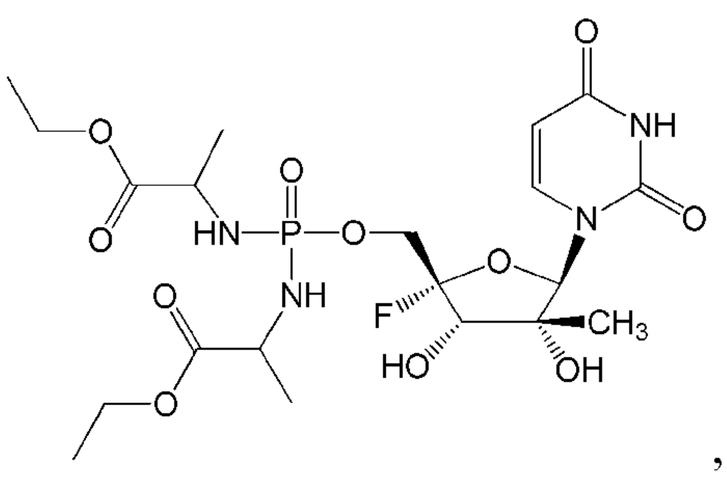


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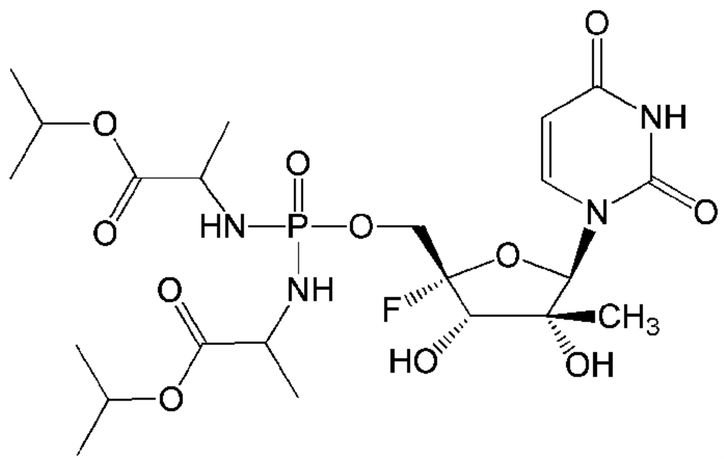
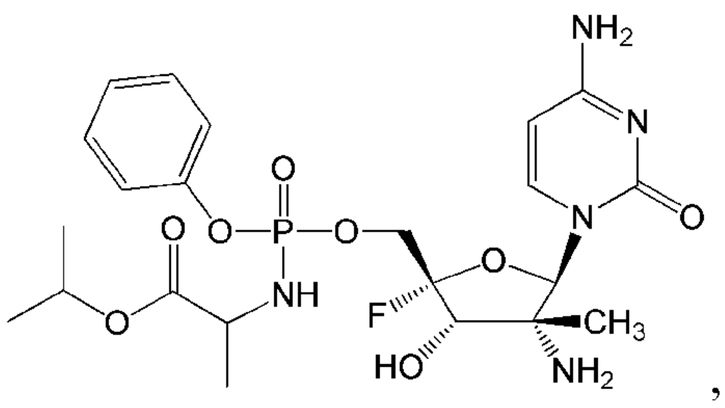
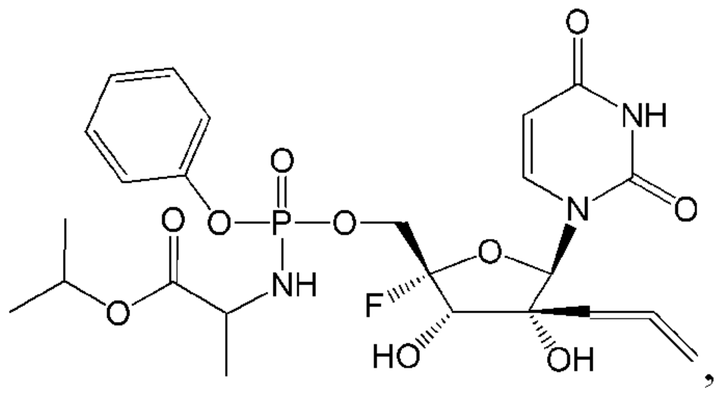
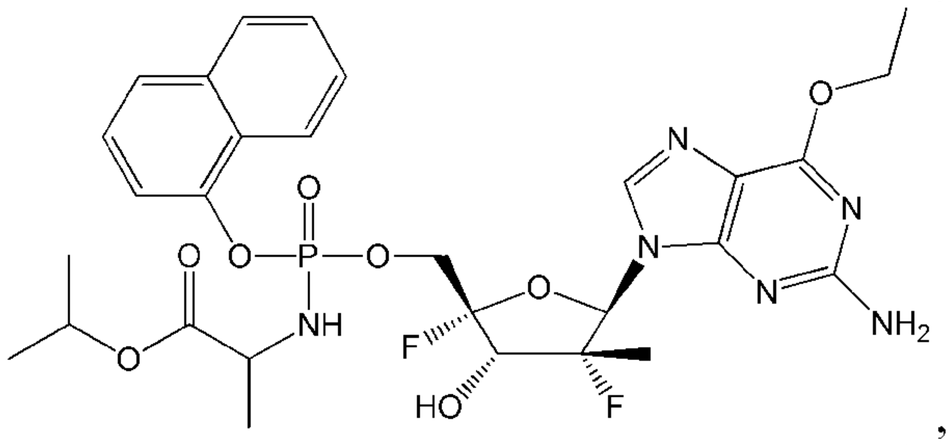
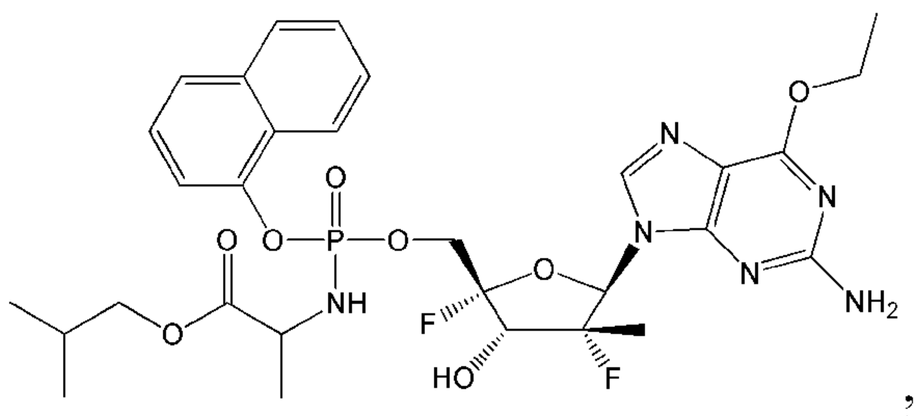
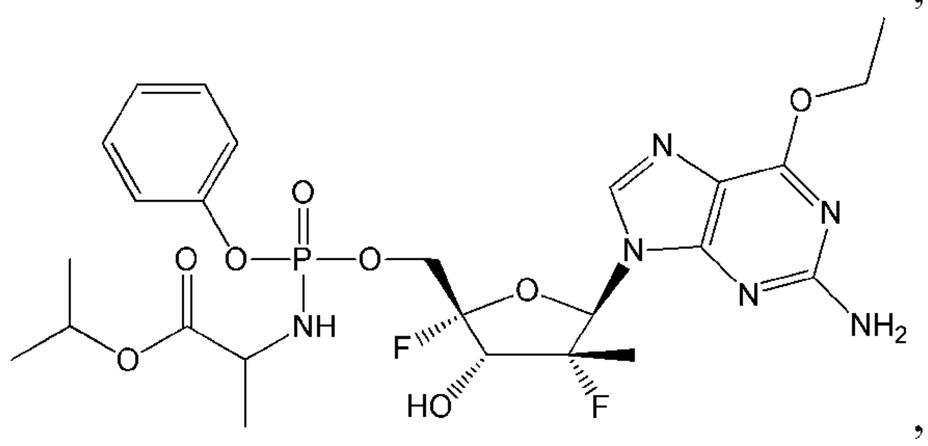
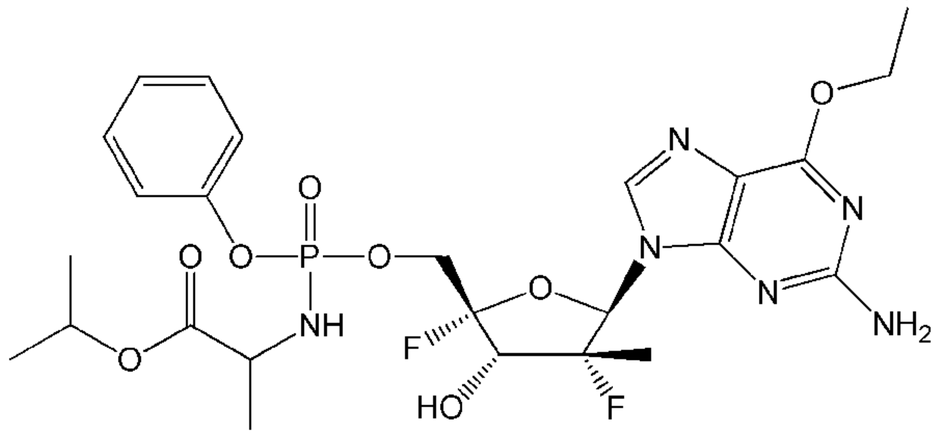
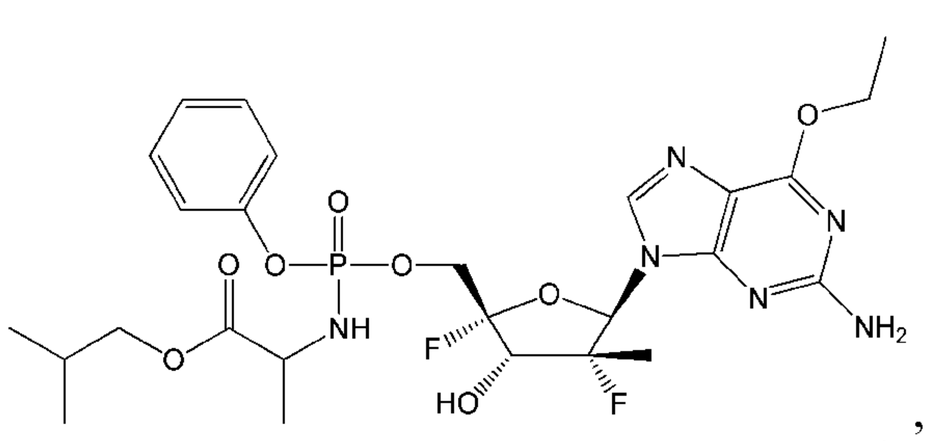
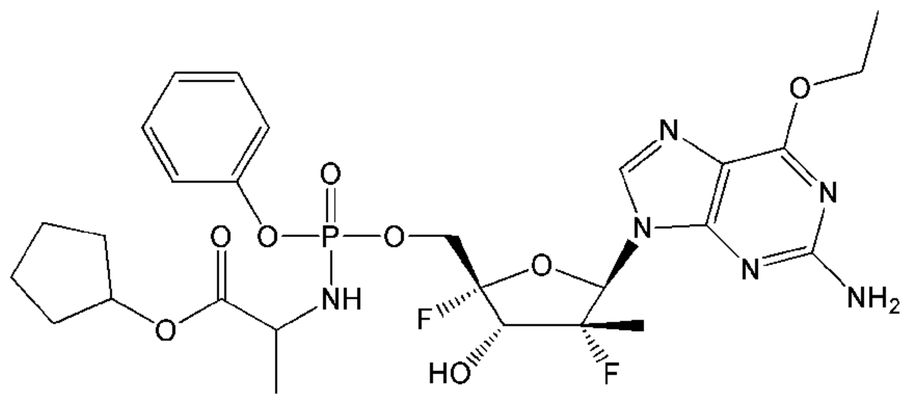
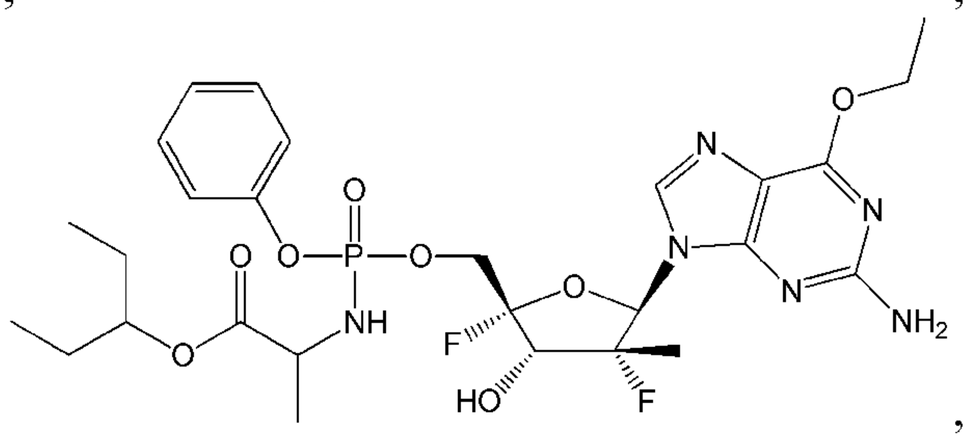
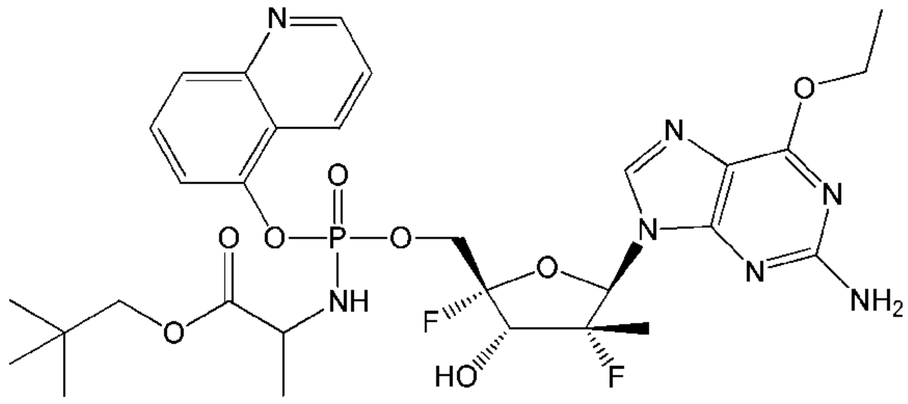
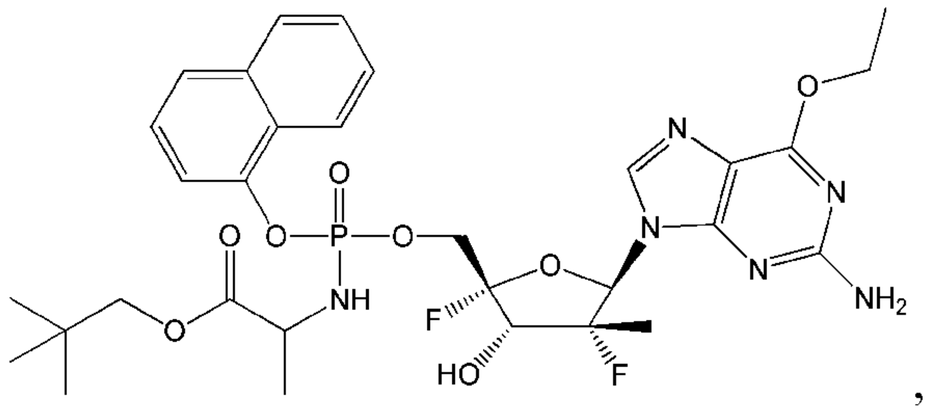
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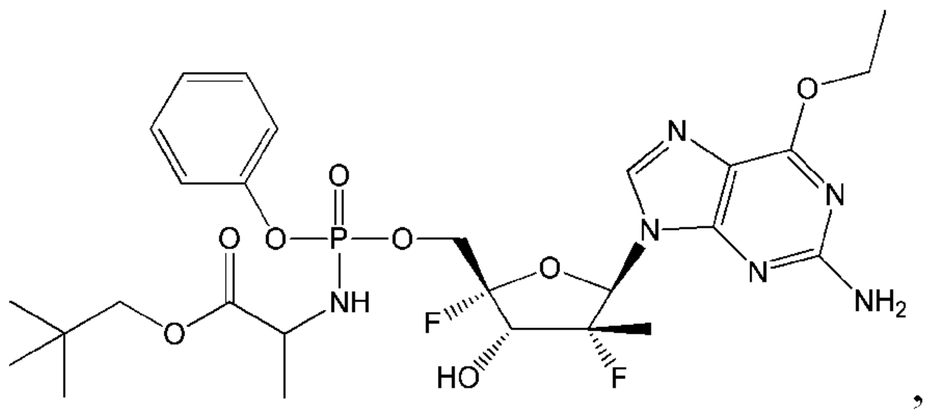


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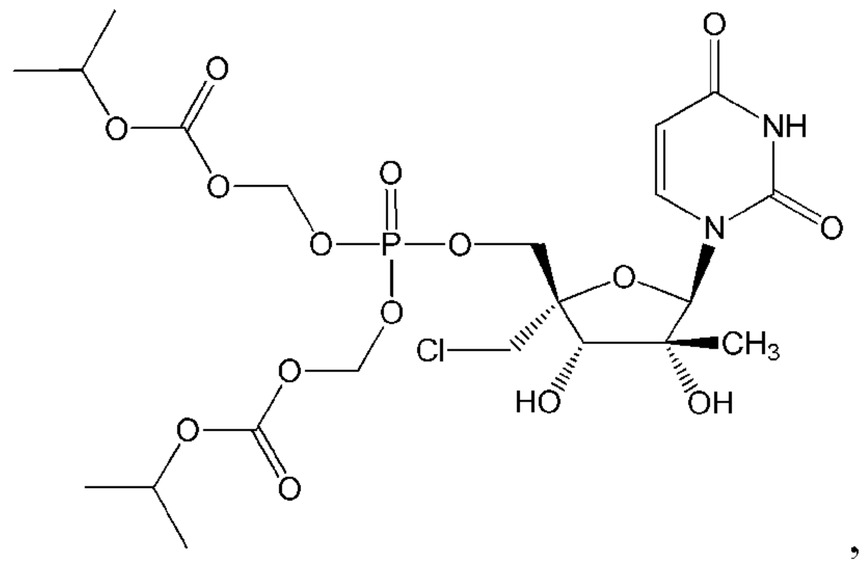


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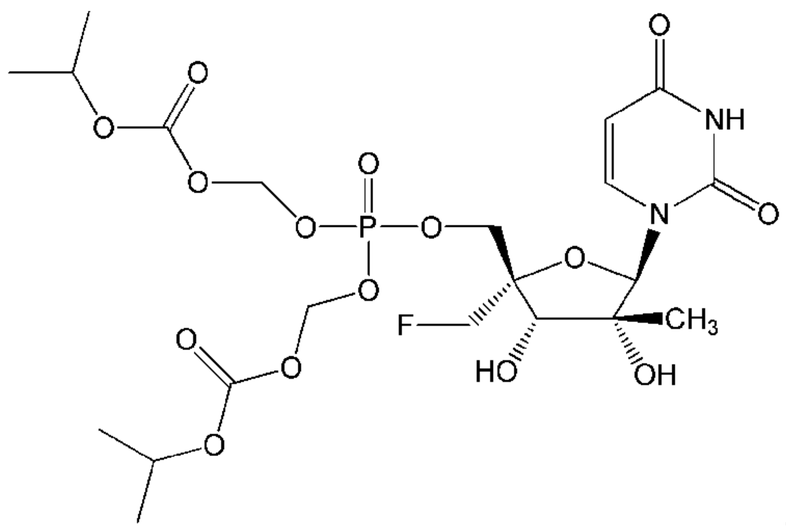

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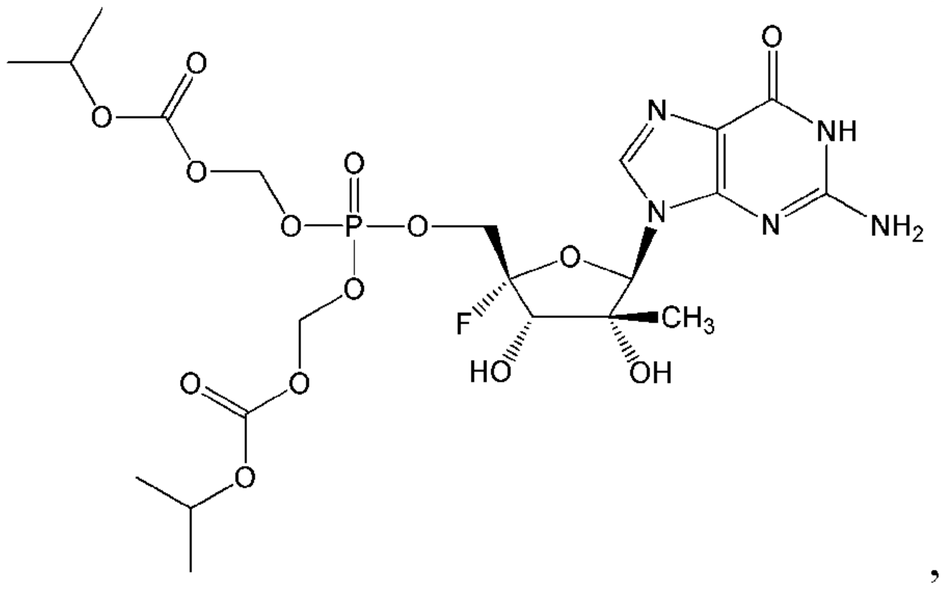
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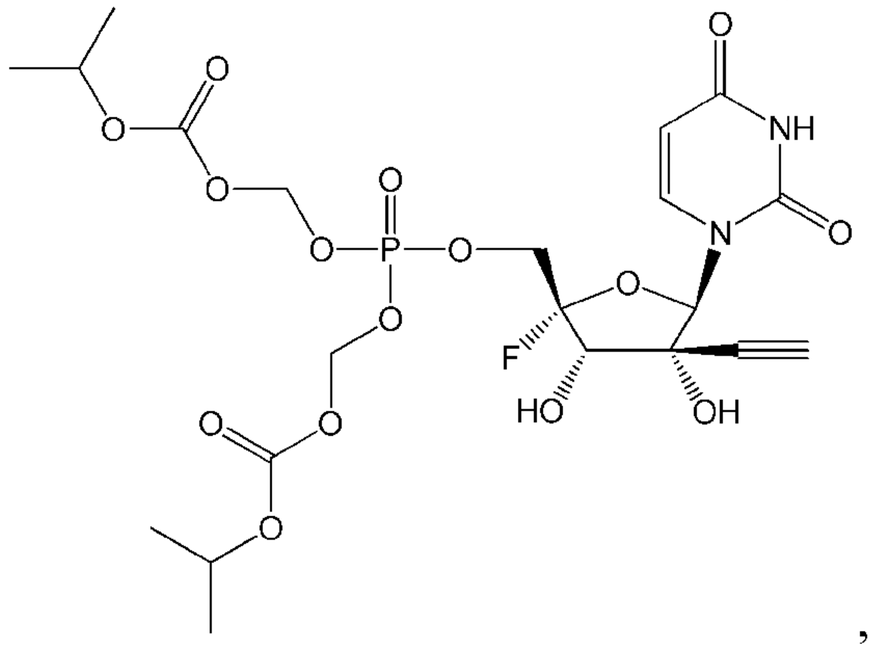
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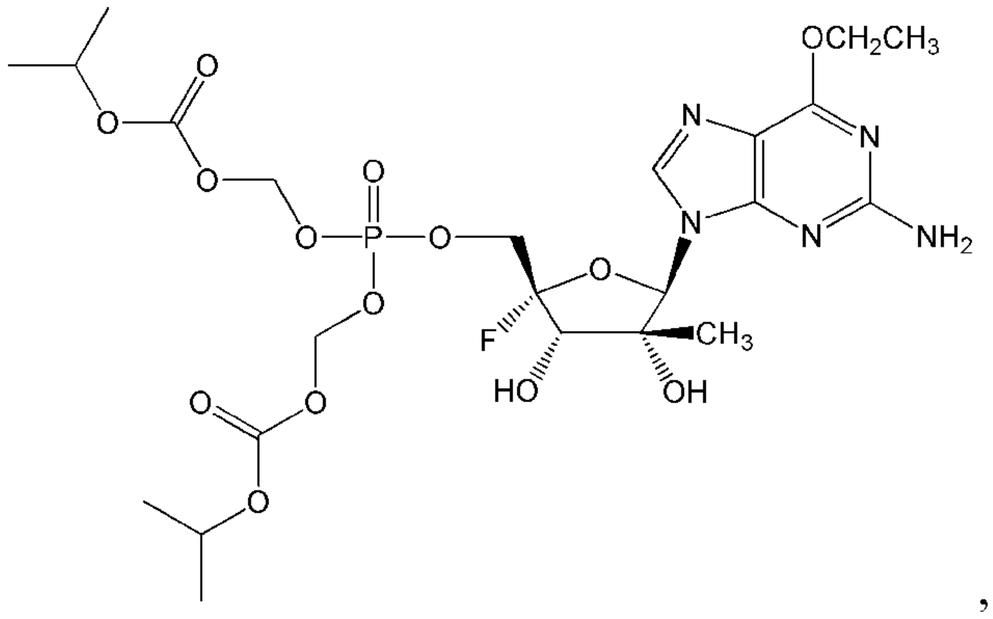
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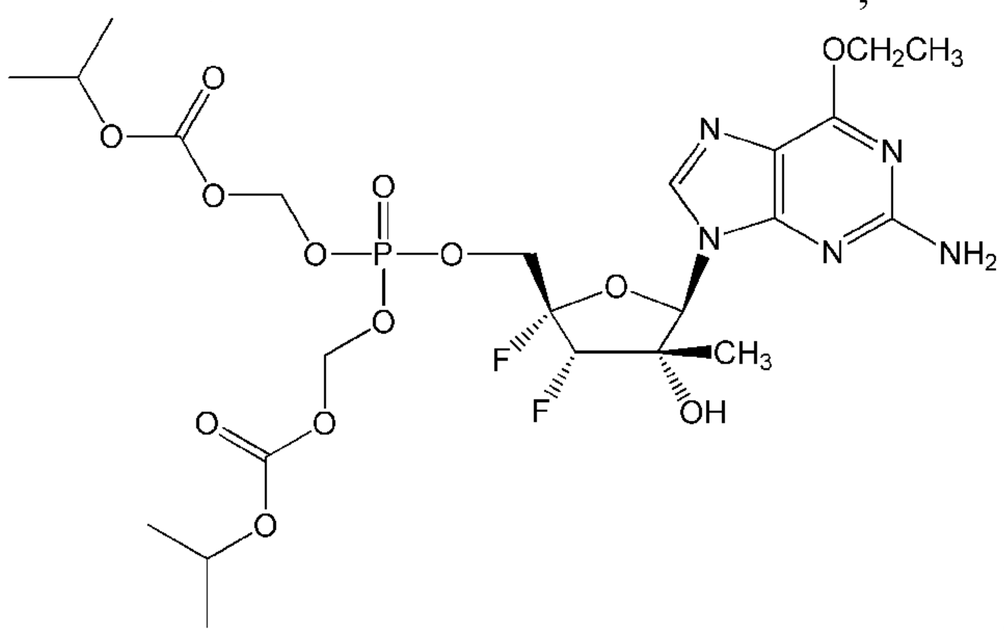
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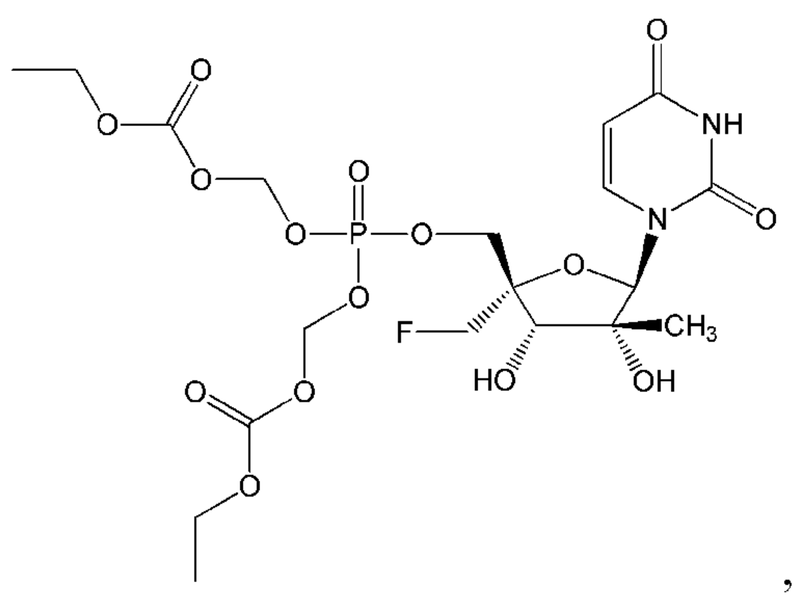
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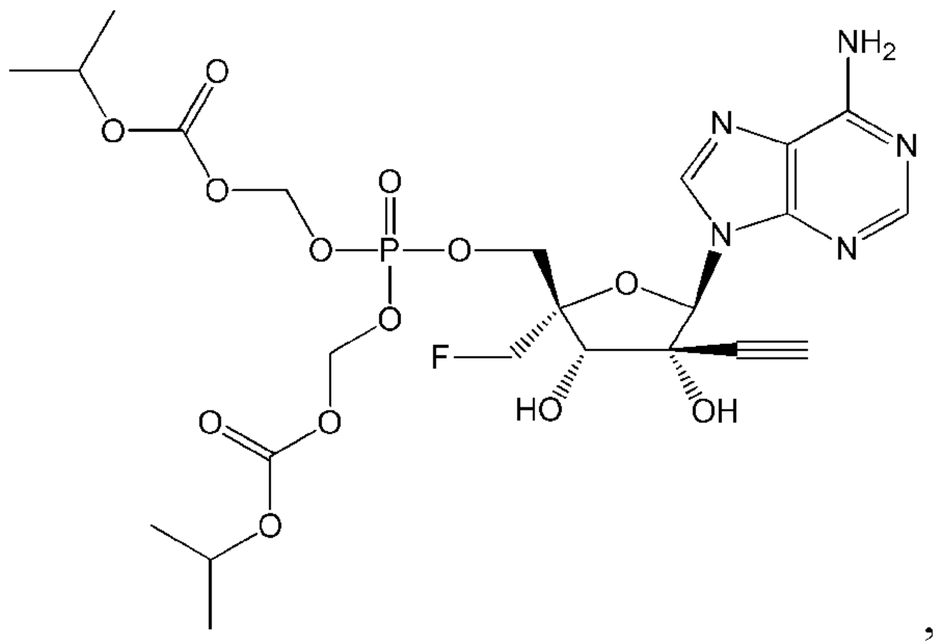
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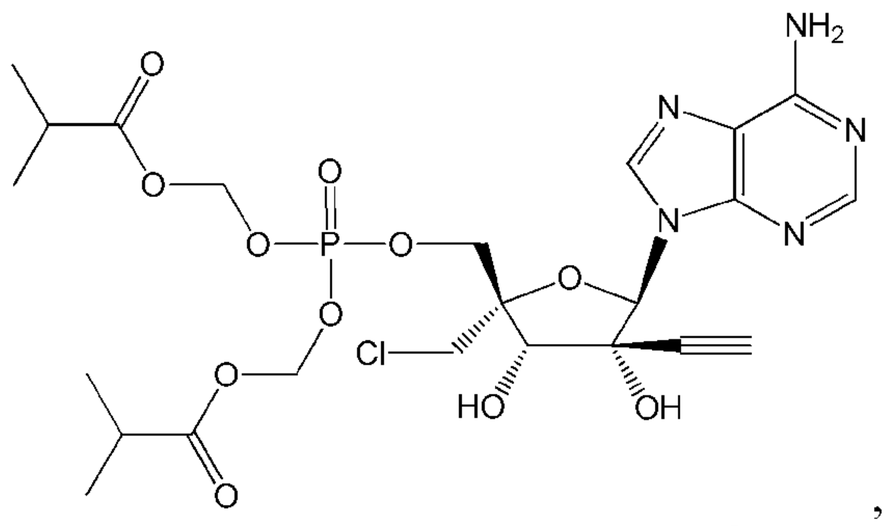
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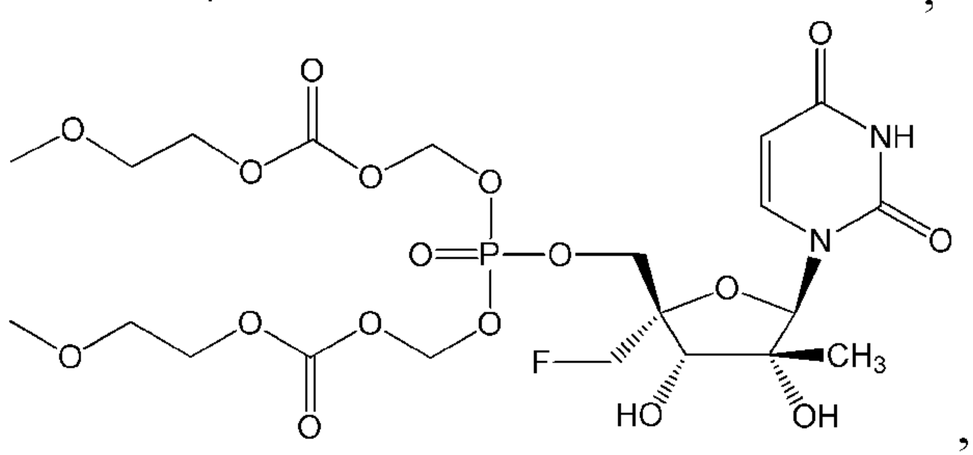
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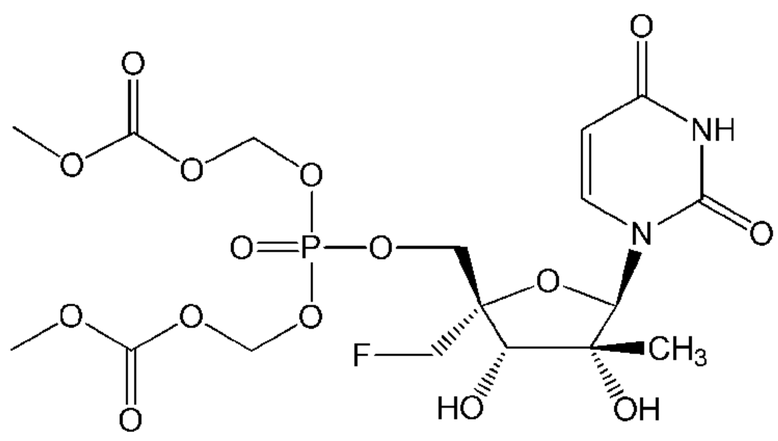
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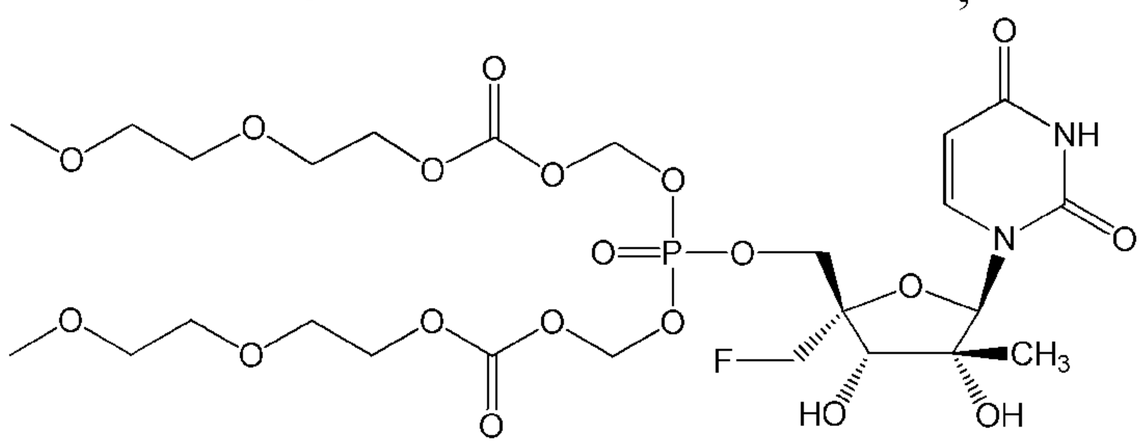
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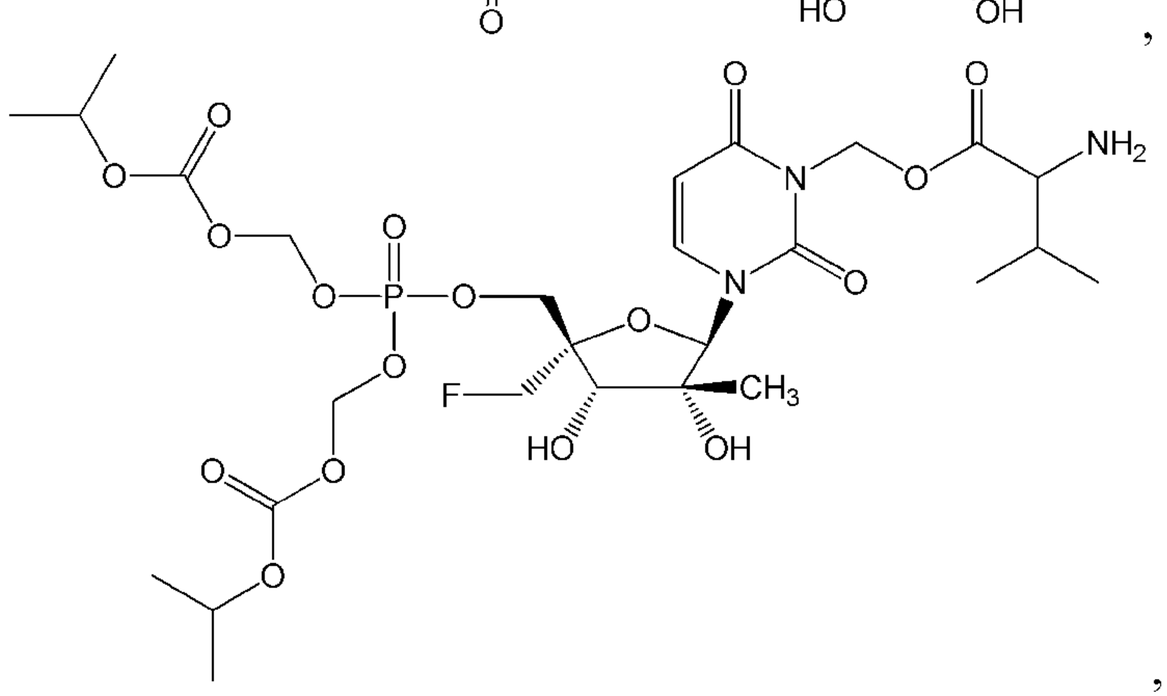
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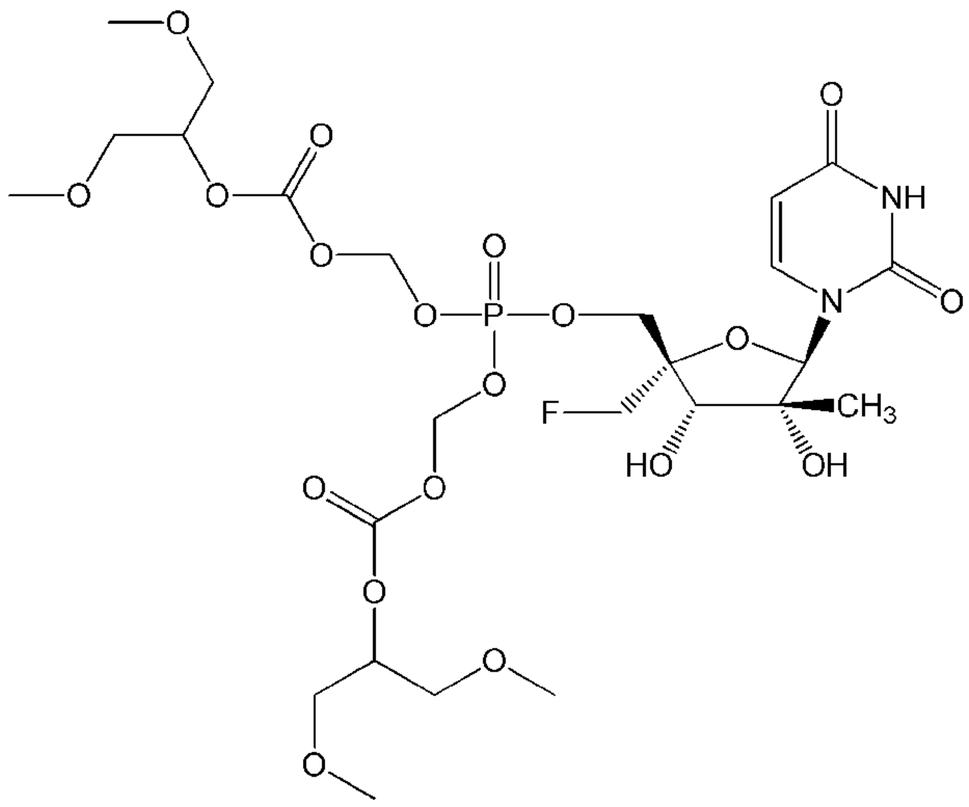
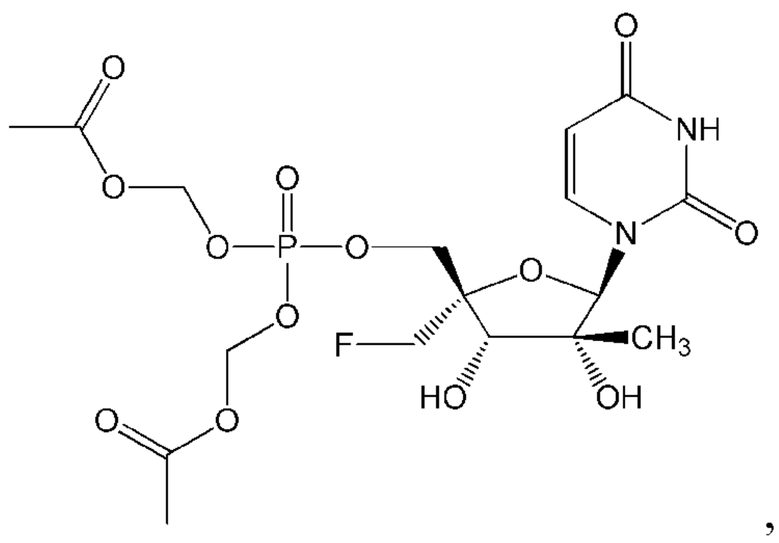
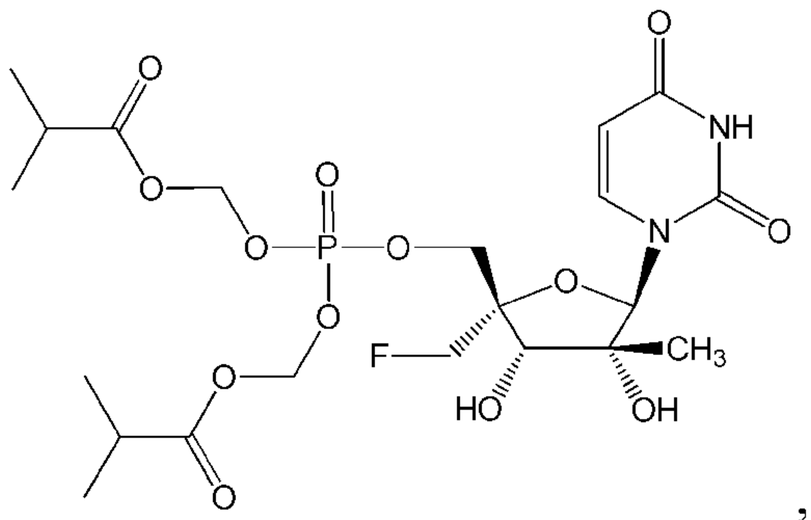
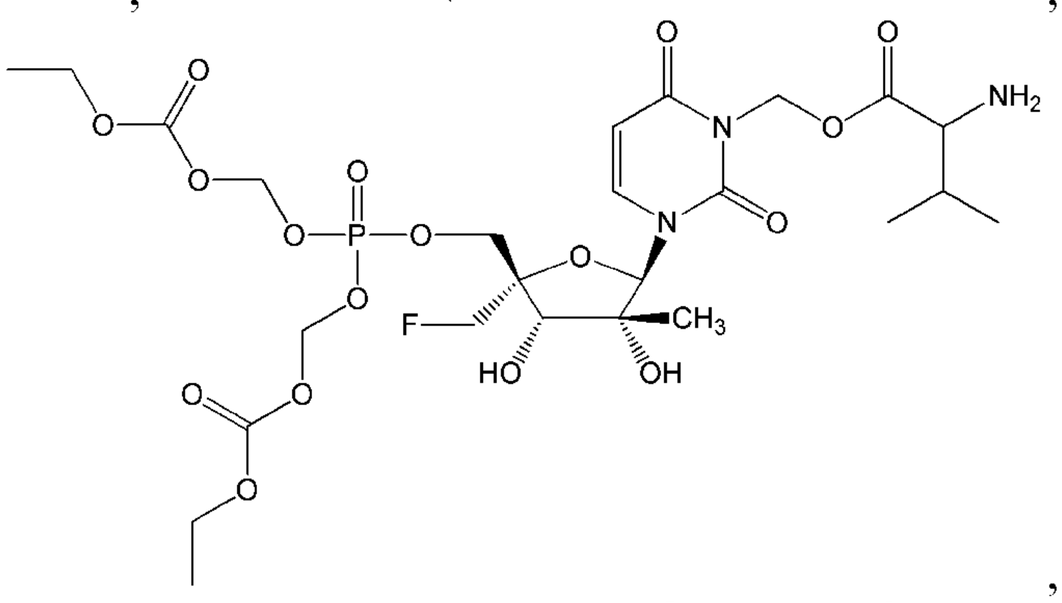
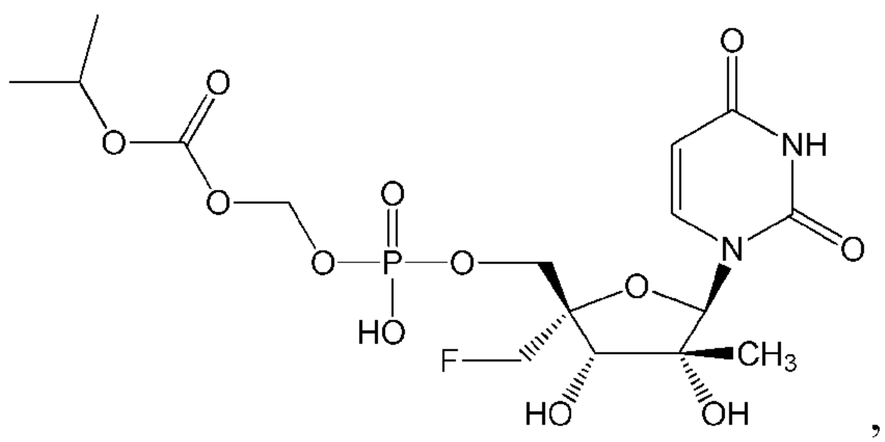
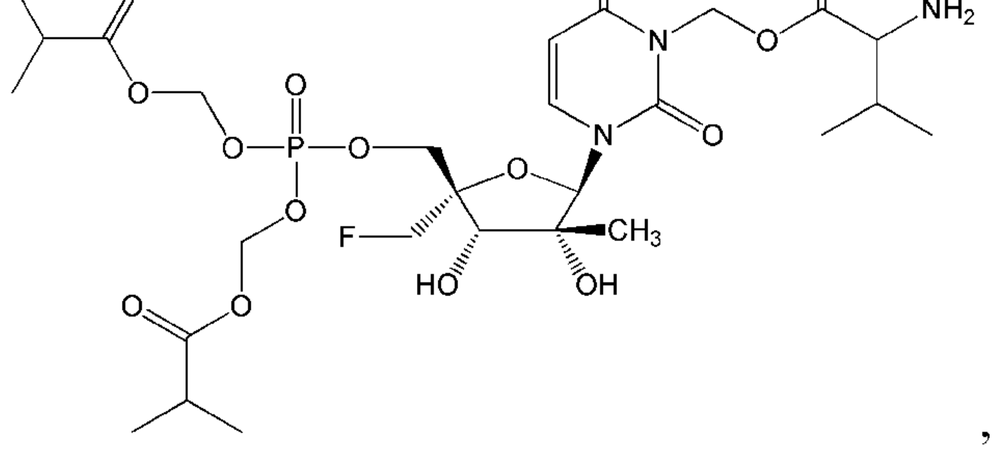
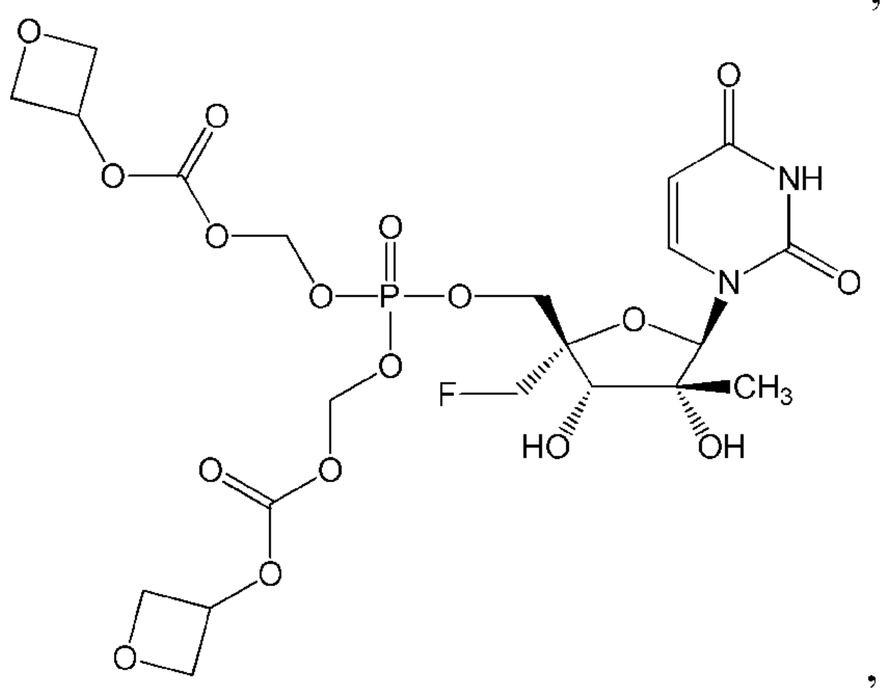
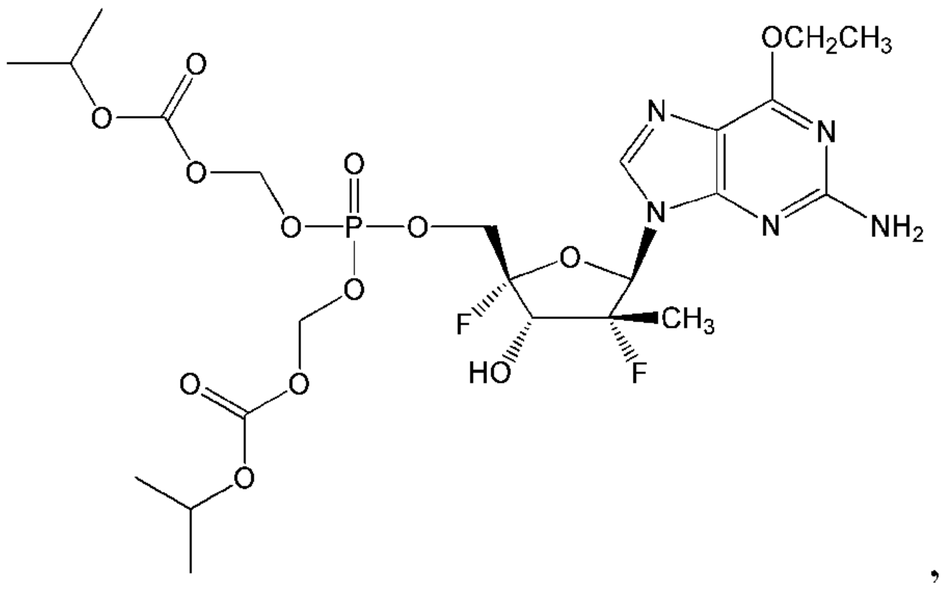
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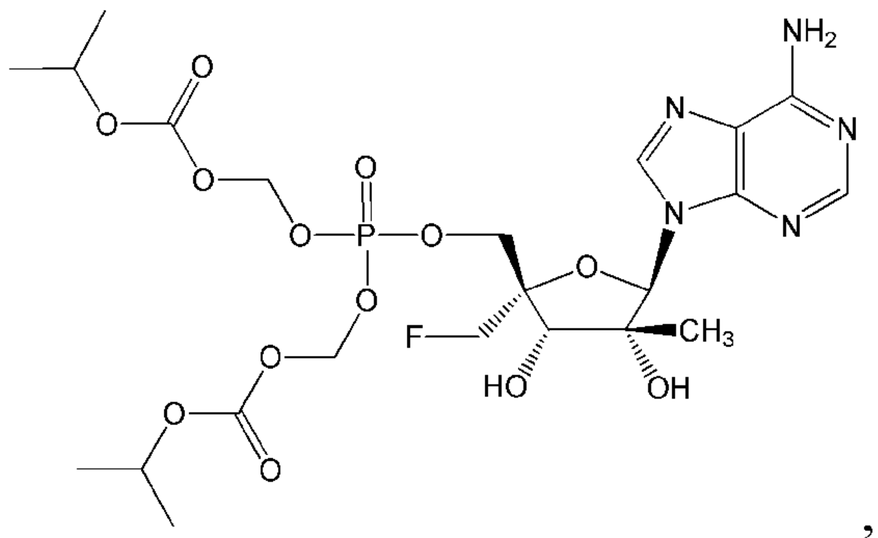


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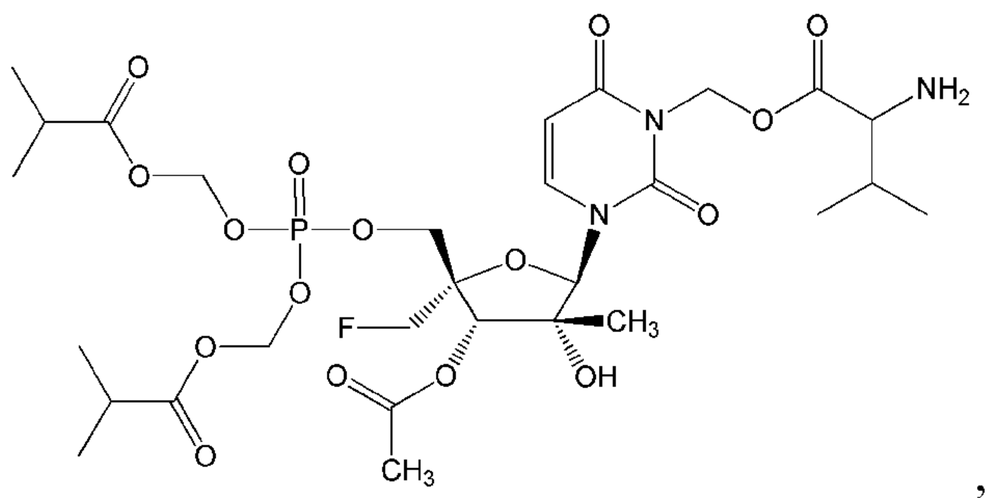


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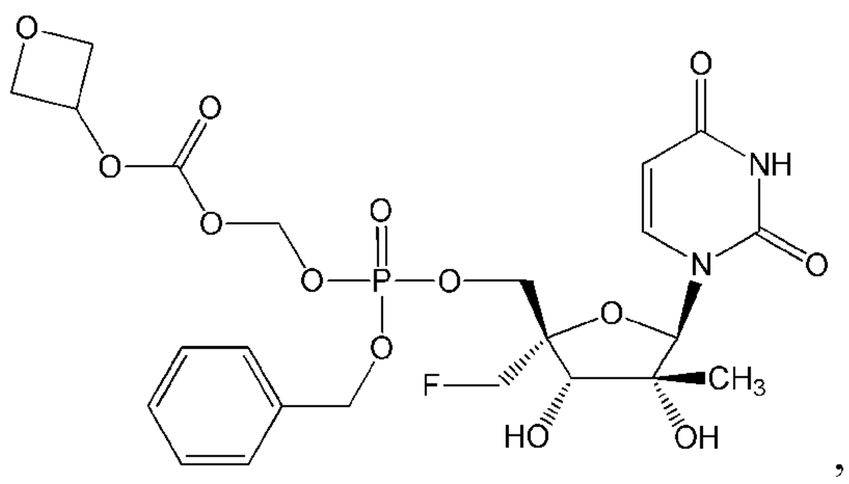

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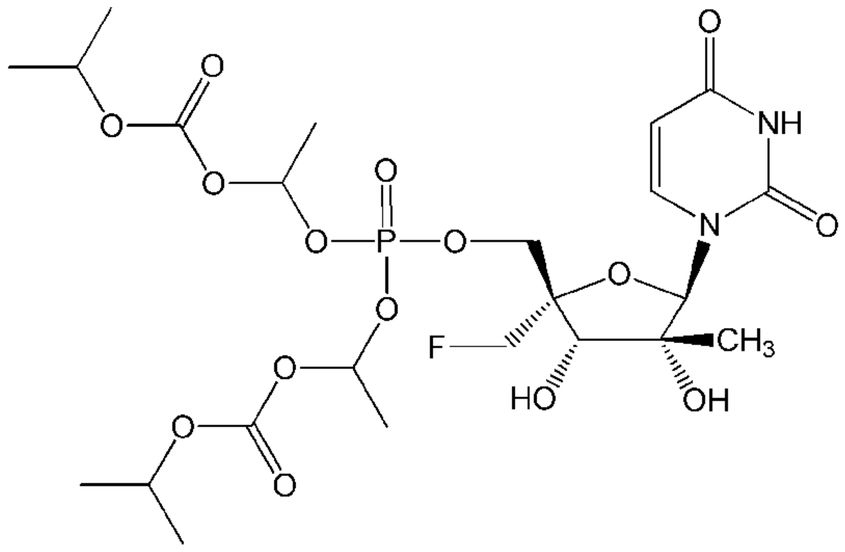
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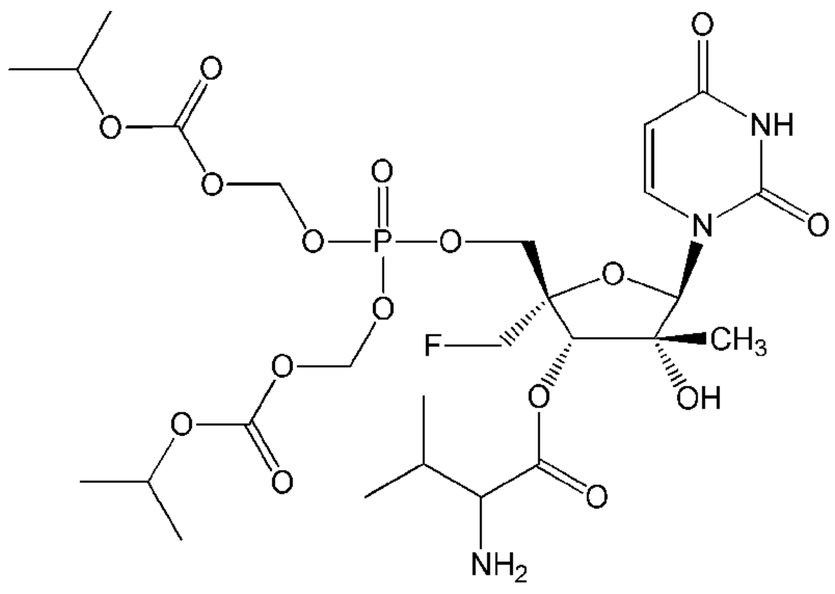
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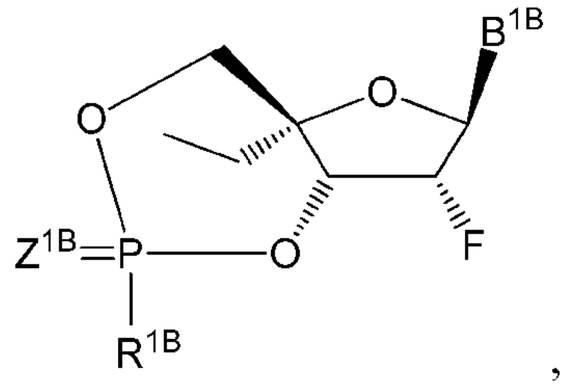


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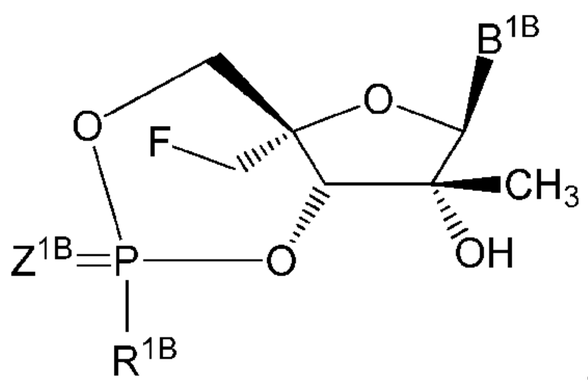
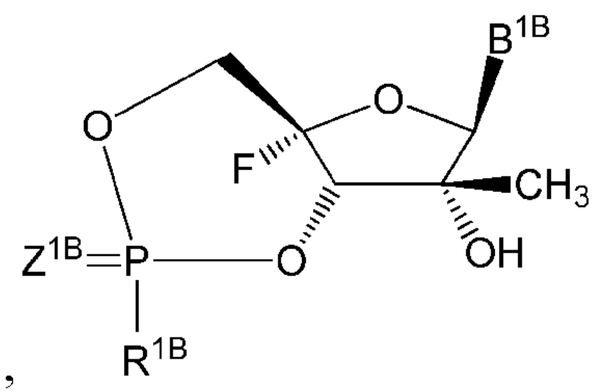
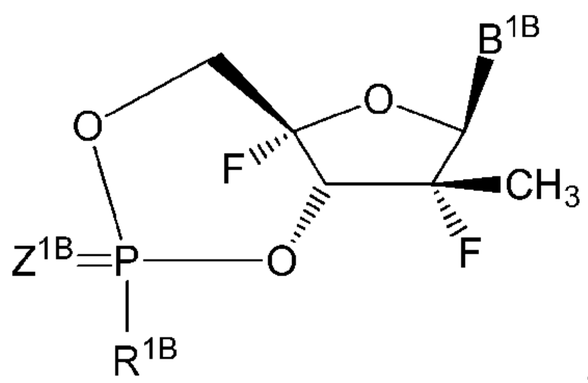


, or a pharmaceutically acceptable salt of the foregoing.

236. The use of Claim 116, wherein the compound of Formula (II) is selected from the group consisting of:

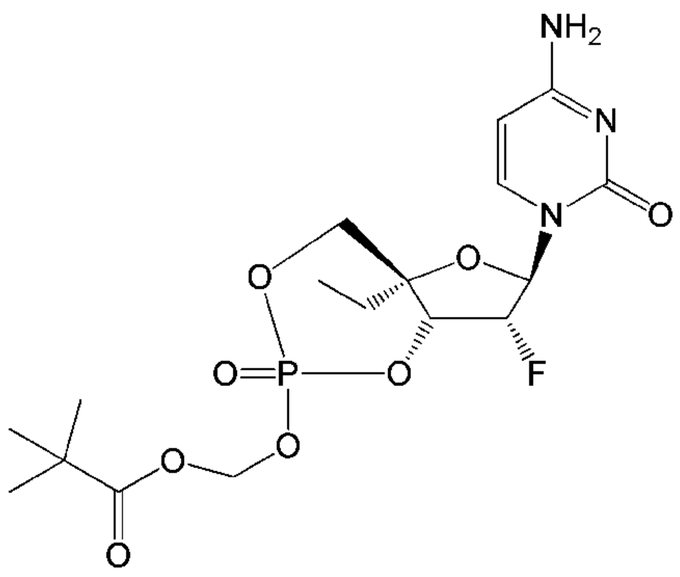
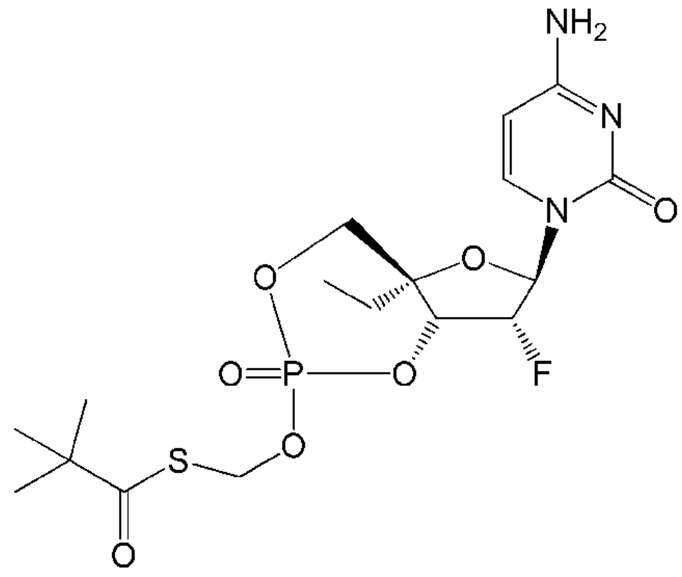


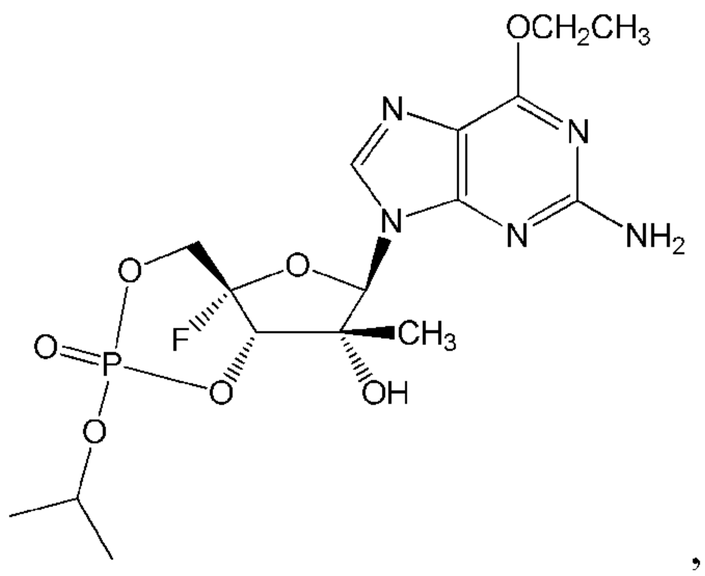
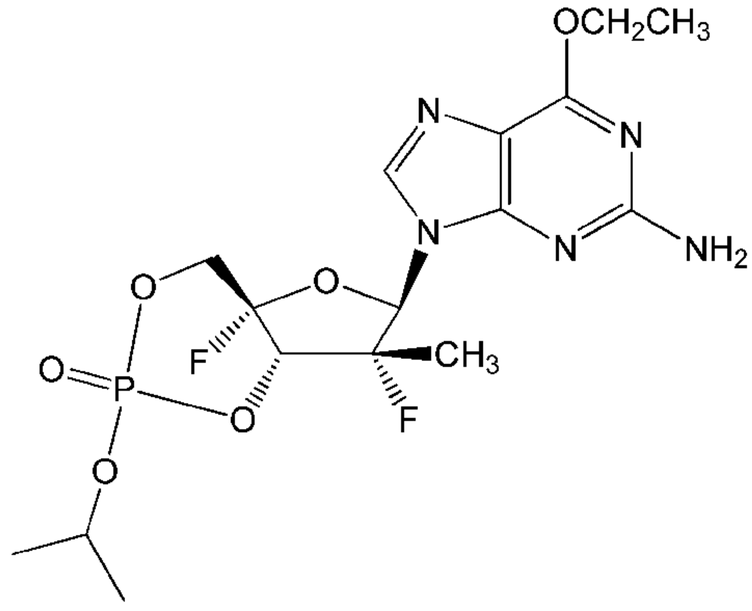
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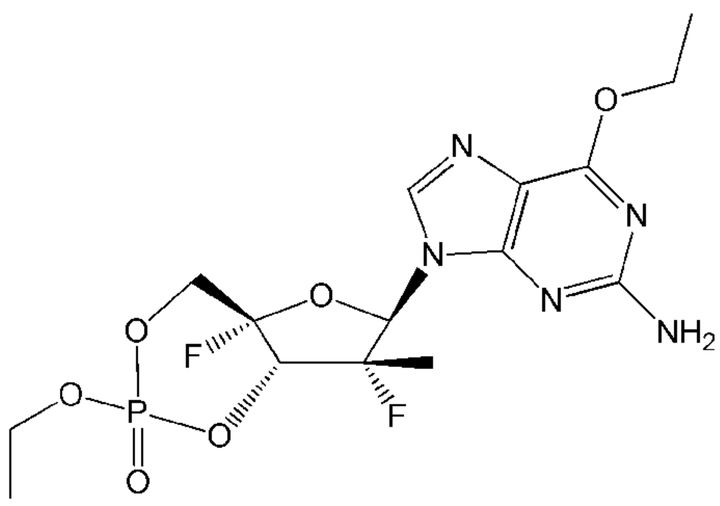
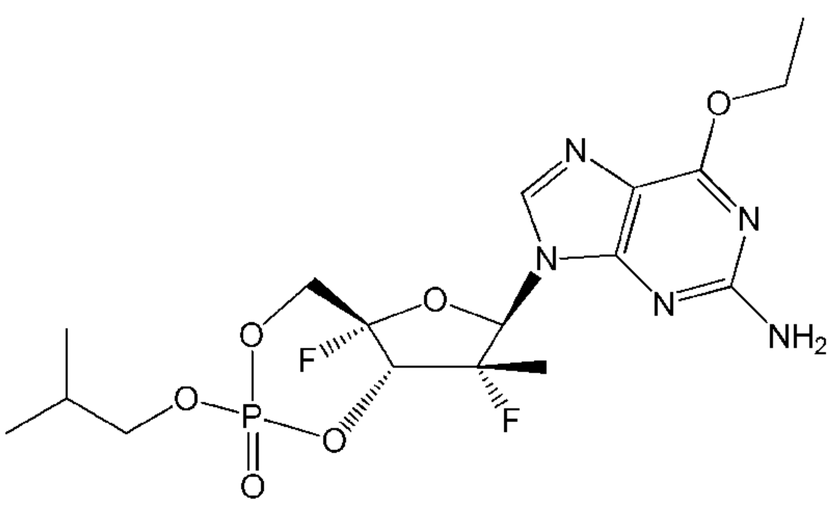

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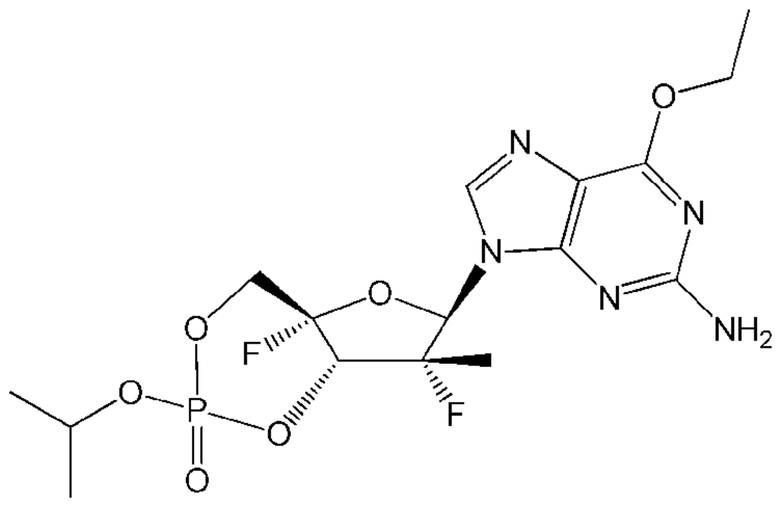
or a pharmaceutically acceptable salt thereof.

237. The use of Claim 116, wherein the compound of Formula (II) is selected from the group consisting of:

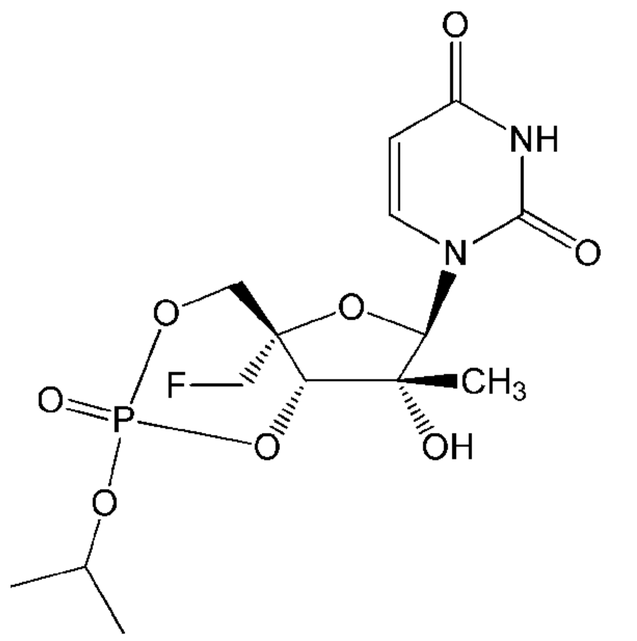

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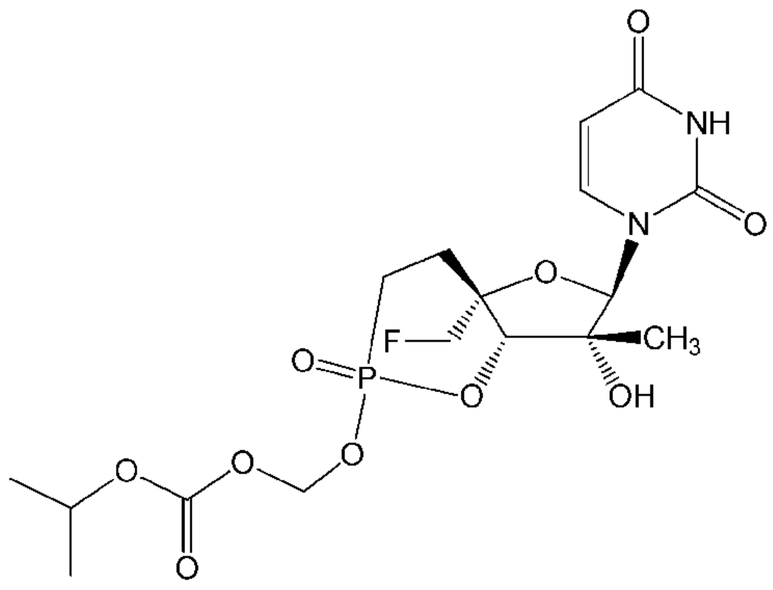

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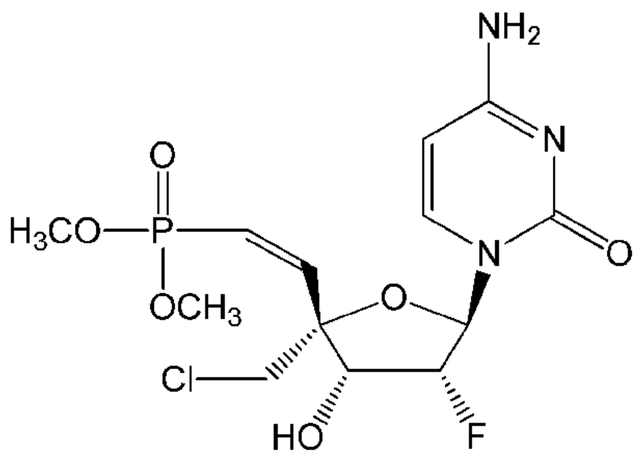


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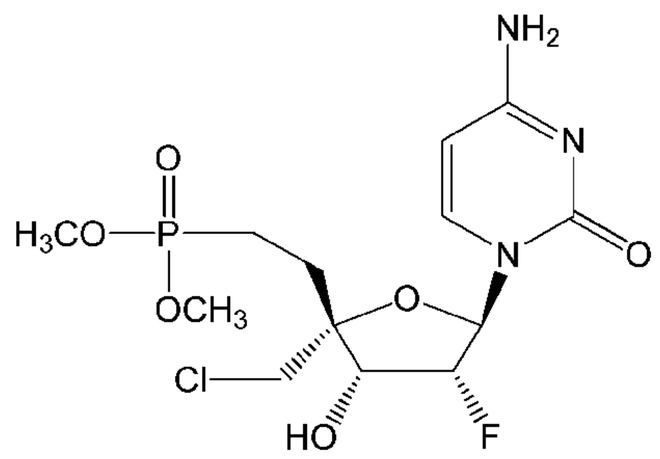


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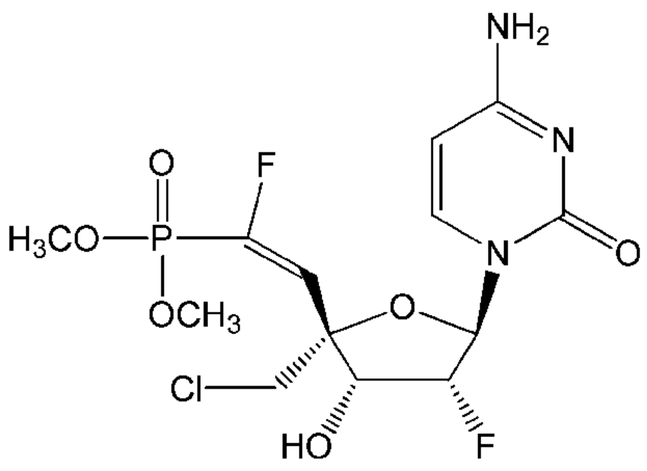
238. The use of Claim 166, wherein the compound of Formula (III) is selected from the group consisting of:



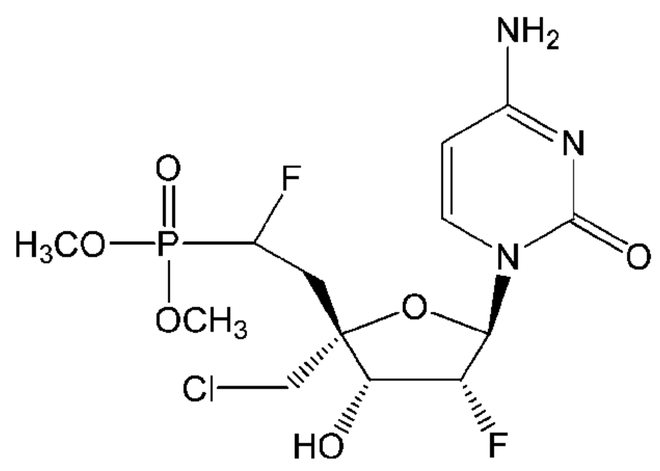
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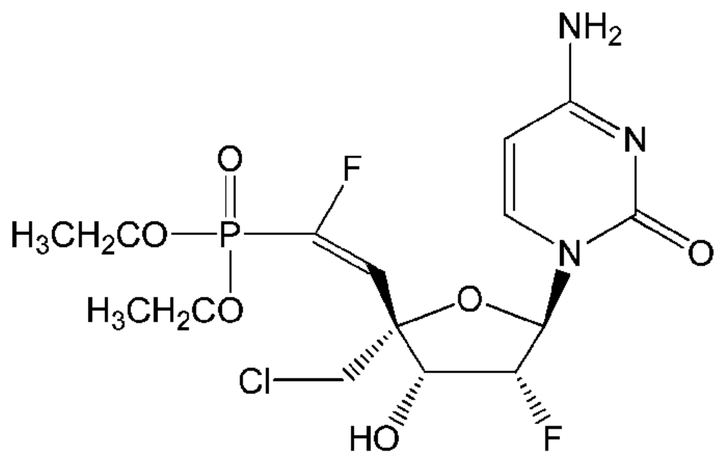
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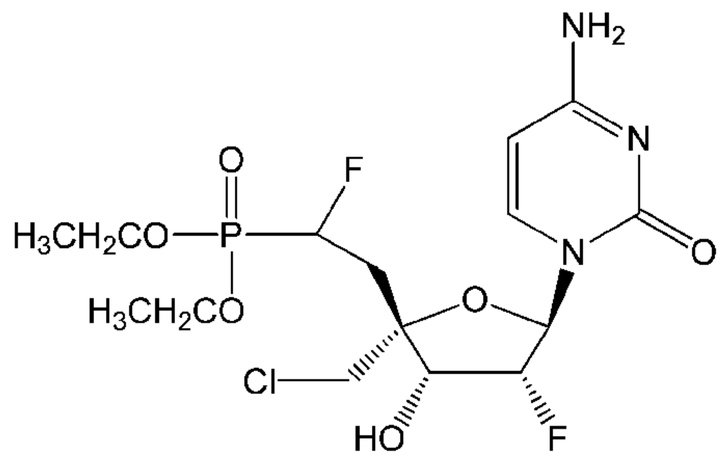
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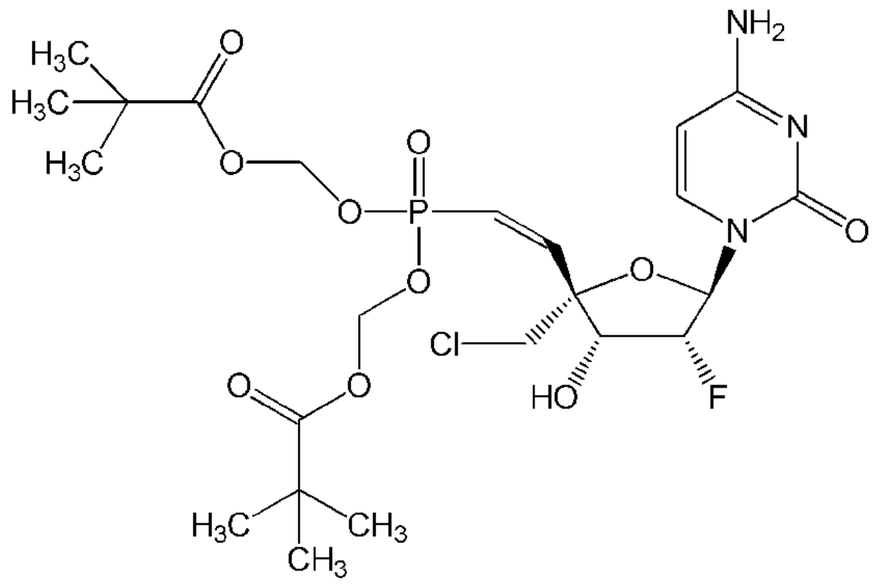
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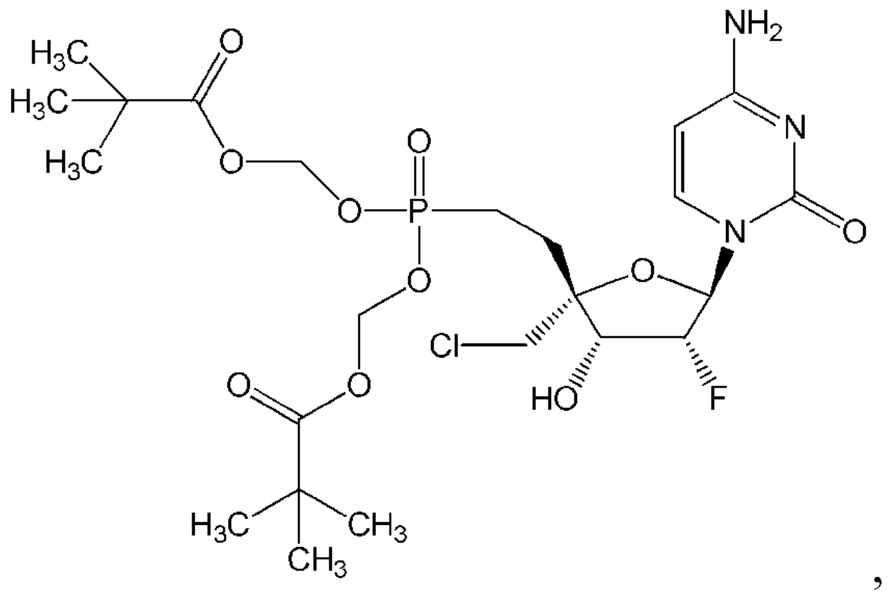
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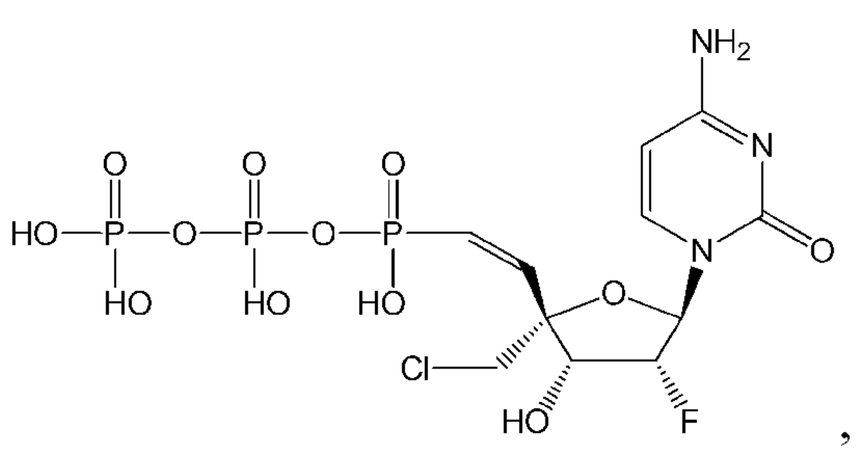
and



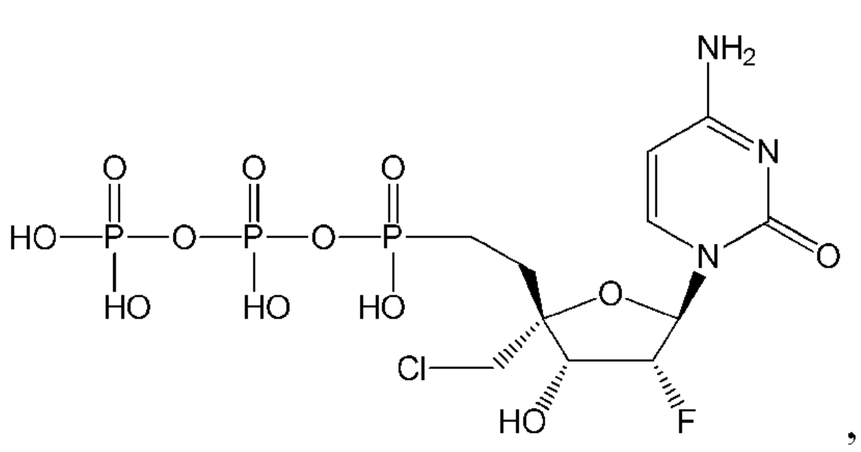
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or a pharmaceutically acceptable salt of the foregoing.

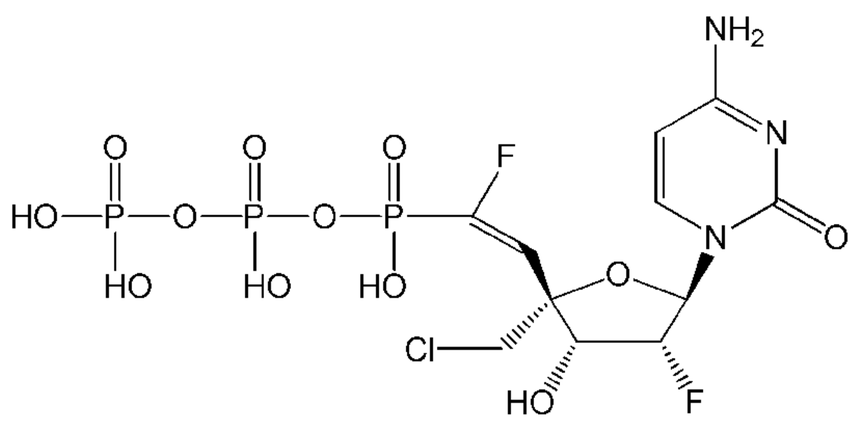
239. The use of Claim 166, wherein the compound of Formula (III) is selected from the group consisting of:



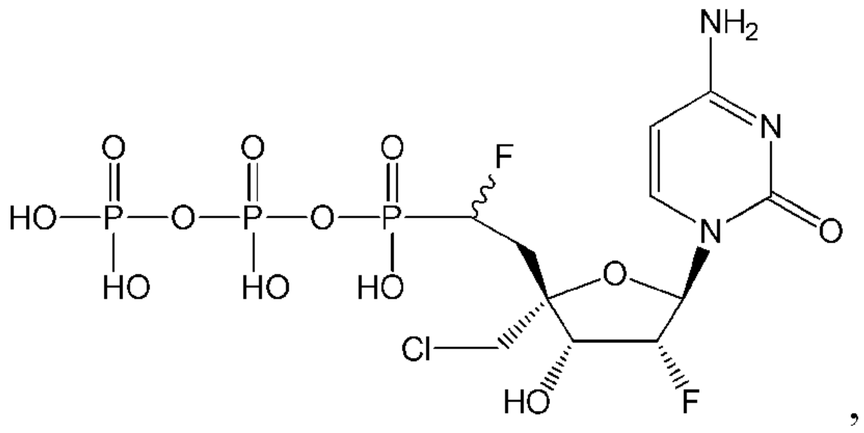
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and



, or a pharmaceutically acceptable salt of the foregoing..

240. Use of an effective amount of a compound selected from Formula (I), Formula (II) and Formula (III), or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition of containing a compound selected from Formula (I), Formula

(II) and Formula (III), or a pharmaceutically acceptable salt of the foregoing, in the preparation of a medicament for inhibiting replication of a norovirus.

241. Use of an effective amount of a compound selected from Formula (I), Formula (II) and Formula (III), or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition of containing a compound selected from Formula (I), Formula (II) and Formula (III), or a pharmaceutically acceptable salt of the foregoing, in the preparation of a medicament for contacting a cell infected with a norovirus.

242. A method for ameliorating, treating or preventing a norovirus infection comprising administering an effective amount of a compound selected from Formula (I), Formula (II) and Formula (III), or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition of containing a compound selected from Formula (I), Formula (II) and Formula (III), or a pharmaceutically acceptable salt of the foregoing.

243. A method for inhibiting replication of a norovirus comprising contacting a cell infected with the virus with an effective amount of a compound selected from Formula (I), Formula (II) and Formula (III), or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition of containing a compound selected from Formula (I), Formula (II) and Formula (III), or a pharmaceutically acceptable salt of the foregoing.

244. A method for ameliorating, treating or preventing a norovirus infection comprising contacting a cell infected with the norovirus with an effective amount of a compound selected from Formula (I), Formula (II) and Formula (III), or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition of containing a compound selected from Formula (I), Formula (II) and Formula (III), or a pharmaceutically acceptable salt of the foregoing.

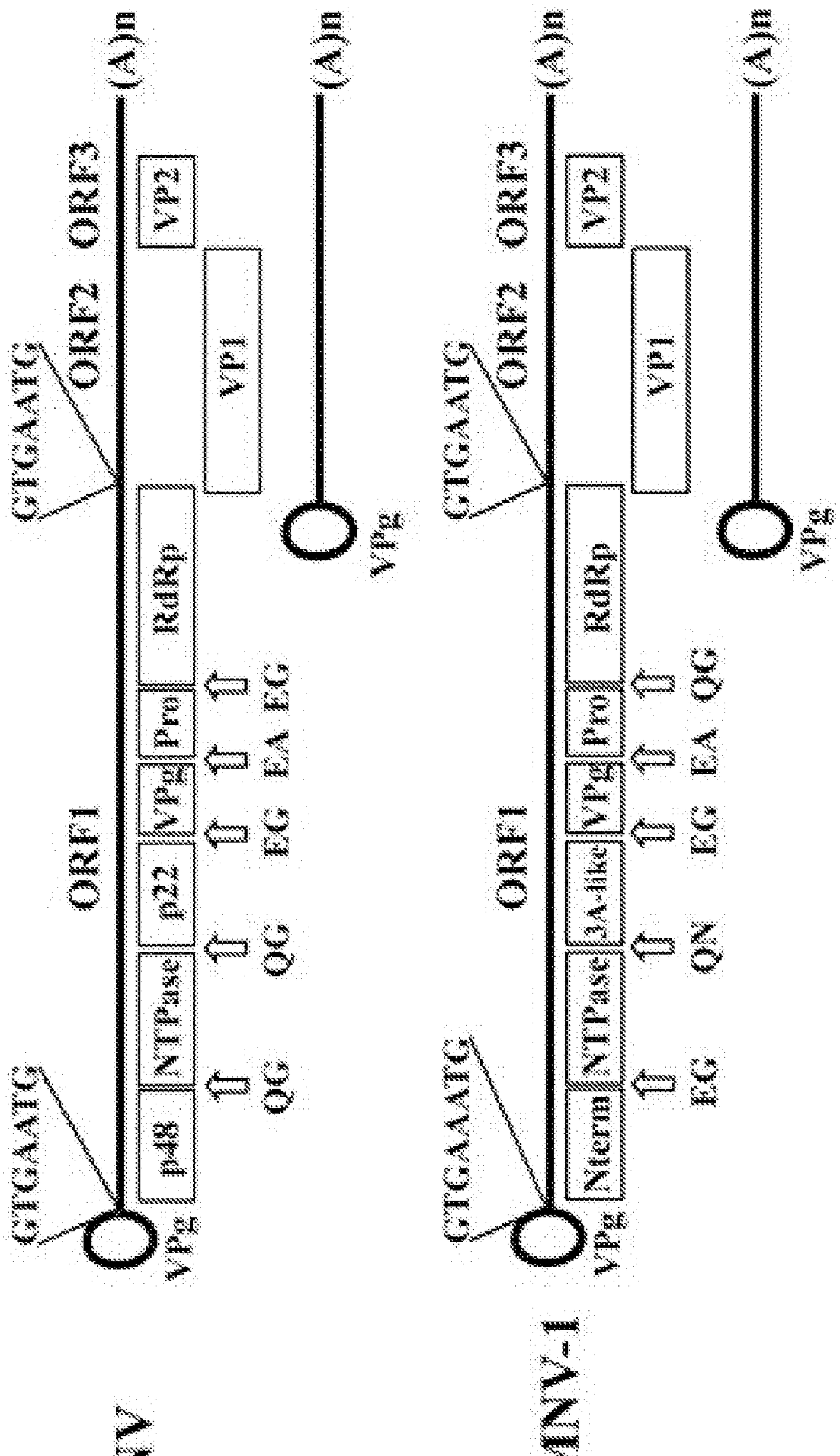
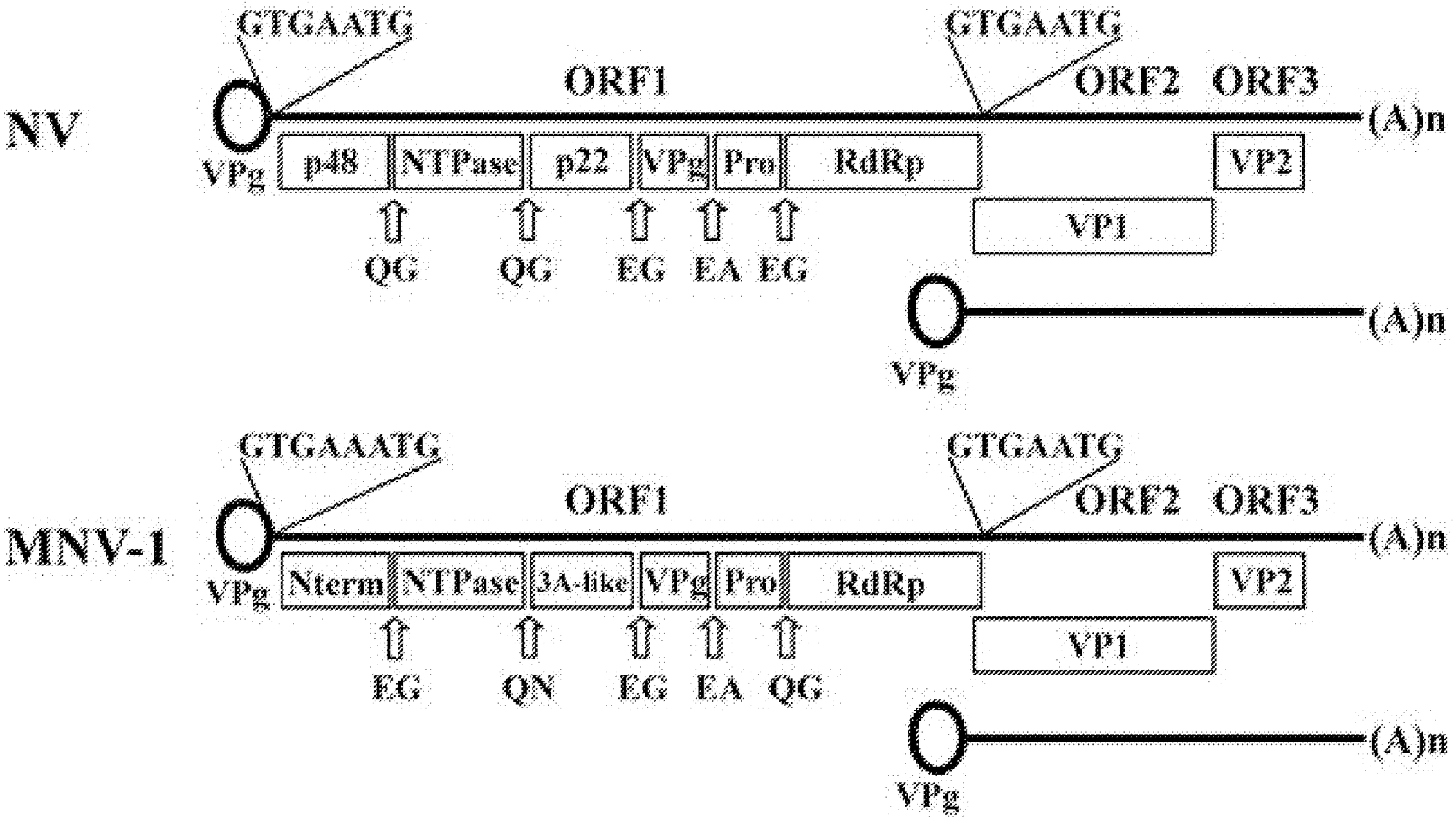

CITCAATG
ORF2
ORF3
VP2
VP1
RdRp
VPg
CITCAATG
ORF1
p48
NTPase
p22
VPg
Pro
QG
EG
EA
Nterm
3A-like
Figure 1

Figure 1


NV
GTGAATG
ORF1
GTGAATG
ORF2
ORF3
(A)n
VPg
p48
NTPase
p22
VPg
Pro
RdRp
VP2
VP1
QG
QG
EG
EA
EG
(A)n
VPg
MNV-1
GTGAAATG
ORF1
GTGAATG
ORF2
ORF3
(A)n
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