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[Continued on next page]

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

Figure 1

Compound	Structure
BMS-433771	
TMC-353121	

(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 paramyxovirus and/or an orthomyxovirus, with a nucleoside, a nucleotide and an analog thereof.



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SUBSTITUTED NUCLEOSIDES, NUCLEOTIDES AND ANALOGS THEREOF**BACKGROUND**Field

[0001] 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 paramyxovirus and/or an orthomyxovirus viral infection with one or more nucleosides, nucleotides and analogs thereof.

Description

[0002] Respiratory viral infections, including upper and lower respiratory tract viral infections, infects and is the leading cause of death of millions of people each year. Upper respiratory tract viral infections involve the nose, sinuses, pharynx and/or larynx. Lower respiratory tract viral infections involve the respiratory system below the vocal cords, including the trachea, primary bronchi and lungs.

[0003] 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

[0004] Some embodiments disclosed herein relate to a compound of Formula (I), Formula (II) and/or Formula (III), or a pharmaceutically acceptable salt of the foregoing.

[0005] Some embodiments disclosed herein relate to methods of ameliorating and/or treating a paramyxovirus viral infection that can include administering to a subject suffering from the paramyxovirus viral infection 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 and/or treating a paramyxovirus viral 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 and/or treating a paramyxovirus viral infection. Yet still other embodiments disclosed herein relate to methods of ameliorating and/or treating a paramyxovirus viral infection that can include contacting a cell infected with the paramyxovirus 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 paramyxovirus that can include contacting a cell infection with the paramyxovirus 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. For example, the paramyxovirus viral infection can be caused by a henipavirus, a morbillivirus, a respirovirus, a rubulavirus, a pneumovirus (including a respiratory syncytial viral infection), a metapneumovirus, hendravirus, nipahvirus, measles, sendai virus, mumps, a human parainfluenza virus (HPIV-1, HPIV-2, HPIV-3 and HPIV-4) and/or a metapneumovirus.

[0006] Some embodiments disclosed herein relate to methods of ameliorating and/or treating an orthomyxovirus viral infection that can include administering to a subject suffering from the orthomyxovirus viral infection 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 and/or treating an orthomyxovirus viral 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 and/or treating an orthomyxovirus viral infection. Yet still other embodiments disclosed herein relate to methods of ameliorating and/or treating an orthomyxovirus viral

infection that can include contacting a cell infected with the orthomyxovirus 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 an orthomyxovirus that can include contacting a cell infection with the orthomyxovirus 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. For example, the orthomyxovirus viral infection can be an influenza viral infection (such as influenza A, B and/or C).

[0007] Some embodiments disclosed herein relate to methods of ameliorating and/or treating a paramyxovirus viral infection and/or an orthomyxovirus viral infection that can include administering to a subject suffering from the viral infection an effective amount of a compound described herein or a pharmaceutically acceptable salt thereof (for example, one or more compounds of Formulae (I), (II) and/or (III), or a pharmaceutically acceptable salt of the foregoing), or a pharmaceutical composition that includes one or more compounds described herein, in combination with one or more agents described herein. Some embodiments disclosed herein relate to methods of ameliorating and/or treating a paramyxovirus viral infection and/or an orthomyxovirus viral infection that can include contacting a cell infected with the virus with an effective amount of a compound described herein or a pharmaceutically acceptable salt thereof (for example, one or more compounds of Formulae (I), (II) and/or (III), or a pharmaceutically acceptable salt of the foregoing), or a pharmaceutical composition that includes one or more compounds described herein, in combination with one or more agents described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0008] Figure 1 shows example RSV agents.

DETAILED DESCRIPTION

[0009] *Paramyxoviridae* family is a family of single stranded RNA viruses. Several genera of the *paramyxoviridae* family include henipavirus, morbillivirus, respirovirus, rubulavirus, pneumovirus and metapneumovirus. These viruses can be transmitted person to

person via direct or close contact with contaminated respiratory droplets or fomites. Species of henipavirus include hendravirus and nipahvirus. A species of morbillivirus is measles. Species of respirovirus include sendai virus and human parainfluenza viruses 1 and 3; and species of rubulavirus include mumps virus and human parainfluenza viruses 2 and 4. A species of metapneumovirus is human metapneumovirus.

[0010] Human Respiratory Syncytial Virus (RSV), a species of pneumovirus, can cause respiratory infections, and can be associated with bronchiolitis and pneumonia. Symptoms of an RSV infection include coughing, sneezing, runny nose, fever, decrease in appetite, and wheezing. RSV is the most common cause of bronchiolitis and pneumonia in children under one year of age in the world, and can be the cause of tracheobronchitis in older children and adults. In the United States, between 75,000 and 125,000 infants are hospitalized each year with RSV. Among adults older than 65 years of age, an estimated 14,000 deaths and 177,000 hospitalizations have been attributed to RSV.

[0011] Treatment options for people infected with RSV are currently limited. Antibiotics, usually prescribed to treat bacterial infections, and over-the-counter medication are not effective in treating RSV and may help only to relieve some of the symptoms. In severe cases, a nebulized bronchodilator, such as albuterol, may be prescribed to relieve some of the symptoms, such as wheezing. RespiGram® (RSV-IGIV, MedImmune, approved for high risk children younger than 24 months of age), Synagis® (palivizumab, MedImmune, approved for high risk children younger than 24 months of age), and Virzole® (ribavirin by aerosol, ICN pharmaceuticals) have been approved for treatment of RSV.

[0012] Symptoms of the measles include fever, cough, runny nose, red eyes and a generalized rash. Some individuals with measles can develop pneumonia, ear infections and bronchitis. Mumps leads to swelling of the salivary glands. Symptoms of mumps include fever, loss of appetite and fatigue. Individuals are often immunized against measles and mumps via a three-part MMR vaccine (measles, mumps, and rubella). Human parainfluenza virus includes four serotypes types, and can cause upper and lower respiratory tract infections. Human parainfluenza virus 1 (HPIV-1) can be associated with croup; human parainfluenza virus 3 (HPIV-3) can be associated with bronchiolitis and pneumonia. According to the Centers of Disease Control and Prevention (CDC), there are no vaccines against human parainfluenza virus.

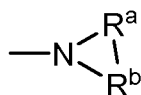
[0013] Influenza is a single stranded RNA virus and a member of the *Orthomyxoviridae* family. There are currently three species of influenza; influenza A, influenza B and influenza C. Influenza A has been further classified based on the viral surface proteins

into hemagglutinin (H or HA) and neuramididase (N). There are approximately 16 H antigens (H1 to H16) and 9 N antigens (N1 to N9). Influenza A includes several subtype, including H1N1, H1N2, H2N2, H3N1, H3N2, H3N8, H5N1, H5N2, H5N3, H5N8, H5N9, H7N1, H7N2, H7N3, H7N4, H7N7, H9N2, H10N7. As with RSV, influenza viruses can be transmitted from person to person via direct contact with infected secretions and/or contaminated surfaces or objections. Complications from an influenza viral infection include pneumonia, bronchitis, dehydration, and sinus and ear infections. Medications currently approved by the FDA against an influenza infection include amantadine, rimantadine, Relenza® (zanamivir, GlaxoSmithKline) and Tamiflu® (oseltamivir, Genentech).

Definitions

[0014] 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.

[0015] As used herein, any "R" group(s) such as, without limitation, 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^{25A}, 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^{11B}, 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^{15C}, 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, cycloalkynyl, aryl, heteroaryl or heterocycle. For example, without limitation, if R^a and R^b of an NR^aR^b group are indicated to be "taken together," it means that they are covalently bonded to one another to form a ring:



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

[0016] Whenever a group is described as being "optionally substituted" that group may be unsubstituted or substituted with one or more of the indicated substituents. Likewise,

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

[0017] As used herein, “C_a to C_b” in which “a” and “b” are integers refer to the number of carbon atoms in an alkyl, alkenyl or alkynyl group, or the number of carbon atoms in the ring of a cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl or heteroalicycyl group. That is, the alkyl, alkenyl, alkynyl, ring of the cycloalkyl, ring of the cycloalkenyl, ring of the cycloalkynyl, ring of the aryl, ring of the heteroaryl or ring of the heteroalicycyl can contain from “a” to “b”, inclusive, carbon atoms. Thus, for example, a “C₁ to C₄ alkyl” group refers to all alkyl groups having from 1 to 4 carbons, that is, CH₃-, CH₃CH₂-, CH₃CH₂CH₂-, (CH₃)₂CH-, CH₃CH₂CH₂CH₂-, CH₃CH₂CH(CH₃)- and (CH₃)₃C-. If no “a” and “b” are designated with regard to an alkyl, alkenyl, alkynyl, cycloalkyl cycloalkenyl, cycloalkynyl, aryl, heteroaryl or heteroalicycyl group, the broadest range described in these definitions is to be assumed.

[0018] As used herein, “alkyl” refers to a straight or branched hydrocarbon chain that comprises a fully saturated (no double or triple bonds) hydrocarbon group. The alkyl group may have 1 to 20 carbon atoms (whenever it appears herein, a numerical range such as “1 to 20” refers to each integer in the given range; *e.g.*, “1 to 20 carbon atoms” means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 20 carbon atoms, although the present definition also covers the occurrence of the term “alkyl” where no numerical range is designated). The alkyl group may also be a medium size alkyl having 1 to 10 carbon atoms. The alkyl group could also be a lower alkyl having 1 to 6 carbon atoms. The alkyl group of the compounds may be designated as “C₁-C₄ alkyl” or similar designations. By way of example only, “C₁-C₄ alkyl” indicates that there are one to four carbon atoms in the alkyl chain, *i.e.*, the alkyl chain is selected from methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, and t-butyl. Typical alkyl groups include, but are in no way limited

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

[0019] As used herein, “alkenyl” refers to an alkyl group that contains in the straight or branched hydrocarbon chain one or more double bonds. An alkenyl group may be unsubstituted or substituted.

[0020] As used herein, “alkynyl” refers to an alkyl group that contains in the straight or branched hydrocarbon chain one or more triple bonds. An alkynyl group may be unsubstituted or substituted.

[0021] 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.

[0022] As used herein, “cycloalkenyl” refers to a mono- or multi- cyclic hydrocarbon ring system that contains one or more double bonds in at least one ring; although, if there is more than one, the double bonds cannot form a fully delocalized pi-electron system throughout all the rings (otherwise the group would be “aryl,” as defined herein). When composed of two or more rings, the rings may be connected together in a fused fashion. A cycloalkenyl group may be unsubstituted or substituted.

[0023] As used herein, “cycloalkynyl” refers to a mono- or multi- cyclic hydrocarbon ring system that contains one or more triple bonds in at least one ring. If there is more than one triple bond, the triple bonds cannot form a fully delocalized pi-electron system throughout all the rings. When composed of two or more rings, the rings may be joined together in a fused fashion. A cycloalkynyl group may be unsubstituted or substituted.

[0024] As used herein, “aryl” refers to a carbocyclic (all carbon) monocyclic or polycyclic aromatic ring system (including fused ring systems where two carbocyclic rings share a chemical bond) that has a fully delocalized pi-electron system throughout all the rings. The number of carbon atoms in an aryl group can vary. For example, the aryl group can be a C₆-C₁₄ aryl group, a C₆-C₁₀ aryl group, or a C₆ aryl group. Examples of aryl groups include, but are not limited to, benzene, naphthalene and azulene. An aryl group may be substituted or unsubstituted.

[0025] As used herein, “heteroaryl” refers to a monocyclic or polycyclic aromatic ring system (a ring system with fully delocalized pi-electron system) that contain(s) one or more

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

[0026] 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).

[0027] As used herein, “aralkyl” and “aryl(alkyl)” refer to an aryl group connected, as a substituent, via a lower alkylene group. The lower alkylene and aryl group of an aralkyl may be substituted or unsubstituted. Examples include but are not limited to benzyl, 2-phenylalkyl, 3-phenylalkyl, and naphthylalkyl.

[0028] As used herein, “heteroaralkyl” and “heteroaryl(alkyl)” refer to a heteroaryl group connected, as a substituent, via a lower alkylene group. The lower alkylene and heteroaryl group of heteroaralkyl may be substituted or unsubstituted. Examples include but are not limited to 2-thienylalkyl, 3-thienylalkyl, furylalkyl, thienylalkyl, pyrrolylalkyl, pyridylalkyl, isoxazolylalkyl, imidazolylalkyl, and their benzo-fused analogs.

[0029] A “(heteroalicycyl)alkyl” and “(heterocyclyl)alkyl” refer to a heterocyclic or a heteroalicyclic group connected, as a substituent, via a lower alkylene group. The lower alkylene and heterocyclyl of a (heteroalicycyl)alkyl may be substituted or unsubstituted. Examples include but are not limited tetrahydro-2H-pyran-4-yl)methyl, (piperidin-4-yl)ethyl, (piperidin-4-yl)propyl, (tetrahydro-2H-thiopyran-4-yl)methyl, and (1,3-thiazinan-4-yl)methyl.

[0030] “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.”

[0031] As used herein, “alkoxy” refers to the formula $-OR$ wherein R is an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, a cycloalkynyl, aryl, heteroaryl, heteroalicycyl, aralkyl, (heteroaryl)alkyl or (heteroalicycyl)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.

[0032] As used herein, “acyl” refers to a hydrogen, alkyl, alkenyl, alkynyl, or aryl connected, as substituents, via a carbonyl group. Examples include formyl, acetyl, propanoyl, benzoyl, and acryl. An acyl may be substituted or unsubstituted.

[0033] 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.

[0034] 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.

[0035] As used herein, “haloalkoxy” refers to an alkoxy group in which one or more of the hydrogen atoms are replaced by a halogen (e.g., mono-haloalkoxy, di-haloalkoxy and tri-haloalkoxy). Such groups include but are not limited to, chloromethoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, 1-chloro-2-fluoromethoxy and 2-fluoroisobutoxy. A haloalkoxy may be substituted or unsubstituted.

[0036] As used herein, “arylthio” refers to RS-, in which R is an aryl, such as, but not limited to, phenyl. An arylthio may be substituted or unsubstituted.

[0037] A “sulfenyl” group refers to an “-SR” group in which R can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicycyl, aralkyl, (heteroaryl)alkyl or (heteroalicycyl)alkyl. A sulfenyl may be substituted or unsubstituted.

[0038] 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.

[0039] A “sulfonyl” group refers to an “-SO₂R” group in which R can be the same as defined with respect to sulfenyl. A sulfonyl may be substituted or unsubstituted.

[0040] An “O-carboxy” group refers to a “RC(=O)O-” group in which R can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicycyl, aralkyl, (heteroaryl)alkyl or (heteroalicycyl)alkyl, as defined herein. An O-carboxy may be substituted or unsubstituted.

[0041] 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.

[0042] 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.

[0043] A “trihalomethanesulfonyl” group refers to an “X₃CSO₂-” group wherein each X is a halogen.

[0044] A “trihalomethanesulfonamido” group refers to an “X₃CS(O)₂N(R_A)-” group wherein each X is a halogen, and R_A hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl,

cycloalkynyl, aryl, heteroaryl, heteroalicycyl, aralkyl, (heteroaryl)alkyl or (heteroalicycyl)alkyl.

[0045] The term “amino” as used herein refers to a -NH_2 group.

[0046] As used herein, the term “hydroxy” refers to a -OH group.

[0047] A “cyano” group refers to a “ -CN ” group.

[0048] The term “azido” as used herein refers to a -N_3 group.

[0049] An “isocyanato” group refers to a “ -NCO ” group.

[0050] A “thiocyanato” group refers to a “ -CNS ” group.

[0051] An “isothiocyanato” group refers to an “ -NCS ” group.

[0052] A “mercapto” group refers to an “ -SH ” group.

[0053] A “carbonyl” group refers to a C=O group.

[0054] An “S-sulfonamido” group refers to a “ $\text{-SO}_2\text{N(R}_A\text{R}_B\text{)}$ ” group in which R_A and R_B can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicycyl, aralkyl, (heteroaryl)alkyl or (heteroalicycyl)alkyl. An S-sulfonamido may be substituted or unsubstituted.

[0055] An “N-sulfonamido” group refers to a “ $\text{RSO}_2\text{N(R}_A\text{)-}$ ” group in which R and R_A can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicycyl, aralkyl, (heteroaryl)alkyl or (heteroalicycyl)alkyl. An N-sulfonamido may be substituted or unsubstituted.

[0056] An “O-carbamyl” group refers to a “ $\text{-OC(=O)N(R}_A\text{R}_B\text{)}$ ” group in which R_A and R_B can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicycyl, aralkyl, (heteroaryl)alkyl or (heteroalicycyl)alkyl. An O-carbamyl may be substituted or unsubstituted.

[0057] An “N-carbamyl” group refers to an “ $\text{ROC(=O)N(R}_A\text{)-}$ ” group in which R and R_A can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicycyl, aralkyl, (heteroaryl)alkyl or (heteroalicycyl)alkyl. An N-carbamyl may be substituted or unsubstituted.

[0058] An “O-thiocarbamyl” group refers to a “ $\text{-OC(=S)-N(R}_A\text{R}_B\text{)}$ ” group in which R_A and R_B can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicycyl, aralkyl, (heteroaryl)alkyl or (heteroalicycyl)alkyl. An O-thiocarbamyl may be substituted or unsubstituted.

[0059] An “N-thiocarbamyl” group refers to an “ $\text{ROC(=S)N(R}_A\text{)-}$ ” group in which R and R_A can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl,

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

[0060] A “C-amido” group refers to a “-C(=O)N(R_AR_B)” group in which R_A and R_B can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicycyl, aralkyl, (heteroaryl)alkyl or (heteroalicycyl)alkyl. A C-amido may be substituted or unsubstituted.

[0061] An “N-amido” group refers to a “RC(=O)N(R_A)-” group in which R and R_A can be independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicycyl, aralkyl, (heteroaryl)alkyl or (heteroalicycyl)alkyl. An N-amido may be substituted or unsubstituted.

[0062] 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.

[0063] Where the numbers of substituents is not specified (e.g. haloalkyl), there may be one or more substituents present. For example “haloalkyl” may include one or more of the same or different halogens. As another example, “C₁-C₃ alkoxyphenyl” may include one or more of the same or different alkoxy groups containing one, two or three atoms.

[0064] 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)).

[0065] 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.

[0066] 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.

[0067] As used herein, the term “heterocyclic base” refers to an optionally substituted nitrogen-containing heterocyclyl that can be attached to an optionally substituted pentose moiety or modified pentose moiety. In some embodiments, the heterocyclic base can be selected from an optionally substituted purine-base, an optionally substituted pyrimidine-base and an optionally substituted triazole-base (for example, a 1,2,4-triazole). The term “purine-base” is used herein in its ordinary sense as understood by those skilled in the art, and includes its tautomers. Similarly, the term “pyrimidine-base” is used herein in its ordinary sense as understood by those skilled in the art, and includes its tautomers. A non-limiting list of optionally substituted purine-bases includes purine, adenine, guanine, hypoxanthine, xanthine, alloxanthine, 7-alkylguanine (e.g. 7-methylguanine), theobromine, caffeine, uric acid and isoguanine. Examples of pyrimidine-bases include, but are not limited to, cytosine, thymine, uracil, 5,6-dihydrouracil and 5-alkylcytosine (e.g., 5-methylcytosine). An example of an optionally substituted triazole-base is 1,2,4-triazole-3-carboxamide. Other non-limiting examples of heterocyclic bases include diaminopurine, 8-oxo-N⁶-alkyladenine (e.g., 8-oxo-N⁶-methyladenine), 7-deazaxanthine, 7-deazaguanine, 7-deazaadenine, N⁴,N⁴-ethanocytosine, N⁶,N⁶-ethano-2,6-diaminopurine, 5-halouracil (e.g., 5-fluorouracil and 5-bromouracil), pseudoisocytosine, isocytosine, isoguanine, and other heterocyclic bases described in U.S. Patent Nos. 5,432,272 and 7,125,855, which are incorporated herein by reference for the limited purpose of disclosing additional heterocyclic bases. In some embodiments, a heterocyclic base can be optionally substituted with an amine or an enol protecting group(s).

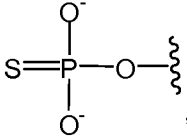
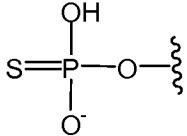
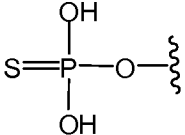
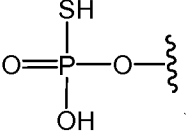
[0068] The term “-N-linked amino acid” refers to an amino acid that is attached to the indicated moiety via a main-chain amino or mono-substituted amino group. When the amino acid is attached in an -N-linked amino acid, one of the hydrogens that is part of the main-chain amino or mono-substituted amino group is not present and the amino acid is attached via the nitrogen. N-linked amino acids can be substituted or unsubstituted.

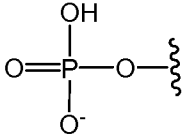
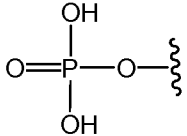
[0069] The term “-N-linked amino acid ester derivative” refers to an amino acid in which a main-chain carboxylic acid group has been converted to an ester group. In some embodiments, the ester group has a formula selected from alkyl-O-C(=O)-, cycloalkyl-O-C(=O)-, aryl-O-C(=O)- and aryl(alkyl)-O-C(=O)-. 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.

[0070] 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.

[0071] 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.

[0072] The terms “phosphorothioate” and “phosphothioate” refer to a compound of the general formula , its protonated forms (for example,  and ) and its tautomers (such as ).

[0073] 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.

[0074] The terms “protecting group” and “protecting groups” as used herein refer to any atom or group of atoms that is added to a molecule in order to prevent existing groups in the molecule from undergoing unwanted chemical reactions. Examples of protecting group moieties are described in T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 3.

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

[0075] 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, C₁-C₇ alkylamine, cyclohexylamine, triethanolamine, ethylenediamine, and salts with amino acids such as arginine and lysine.

[0076] Terms and phrases used in this application, and variations thereof, especially in the appended claims, unless otherwise expressly stated, should be construed as open ended as

opposed to limiting. As examples of the foregoing, the term 'including' should be read to mean 'including, without limitation,' 'including but not limited to,' or the like; the term 'comprising' as used herein is synonymous with 'including,' 'containing,' or 'characterized by,' and is inclusive or open-ended and does not exclude additional, unrecited elements or method steps; the term 'having' should be interpreted as 'having at least;' the term 'includes' should be interpreted as 'includes but is not limited to;' the term 'example' is used to provide exemplary instances of the item in discussion, not an exhaustive or limiting list thereof; and use of terms like 'preferably,' 'preferred,' 'desired,' or 'desirable,' and words of similar meaning should not be understood as implying that certain features are critical, essential, or even important to the structure or function of the invention, but instead as merely intended to highlight alternative or additional features that may or may not be utilized in a particular embodiment. In addition, the term "comprising" is to be interpreted synonymously with the phrases "having at least" or "including at least". When used in the context of a process, the term "comprising" means that the process includes at least the recited steps, but may include additional steps. When used in the context of a compound, composition or device, the term "comprising" means that the compound, composition or device includes at least the recited features or components, but may also include additional features or components. Likewise, a group of items linked with the conjunction 'and' should not be read as requiring that each and every one of those items be present in the grouping, but rather should be read as 'and/or' unless expressly stated otherwise. Similarly, a group of items linked with the conjunction 'or' should not be read as requiring mutual exclusivity among that group, but rather should be read as 'and/or' unless expressly stated otherwise.

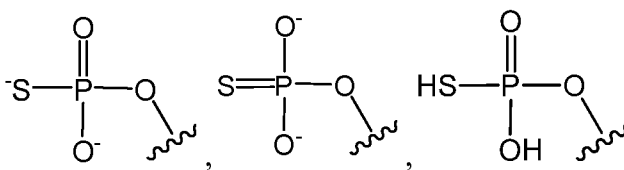
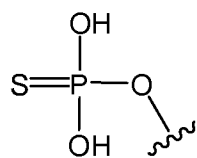
[0077] With respect to the use of substantially any plural and/or singular terms herein, those having skill in the art can translate from the plural to the singular and/or from the singular to the plural as is appropriate to the context and/or application. The various singular/plural permutations may 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.

[0078] 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.

[0079] 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.

[0080] 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).

[0081] 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.

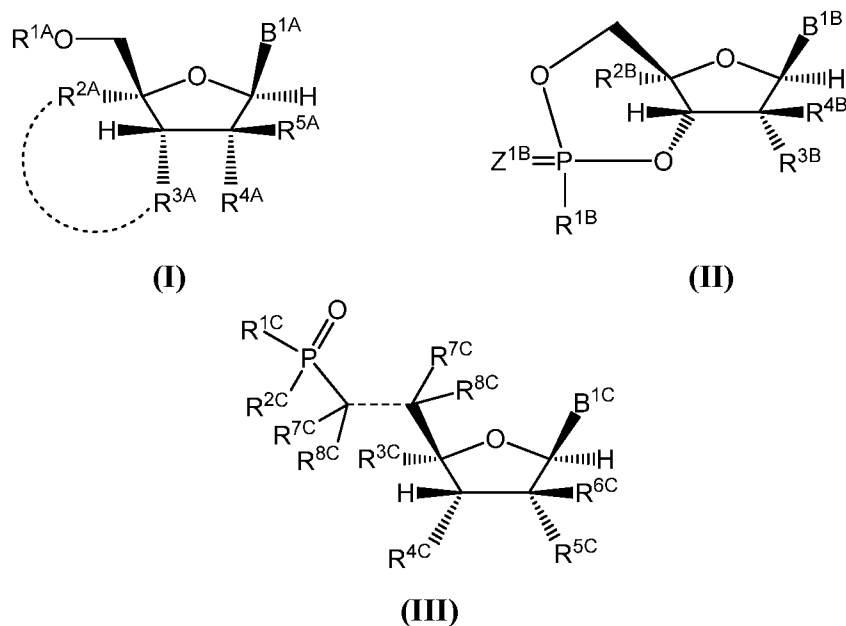
[0082] It is understood that the methods and combinations described herein include crystalline forms (also known as polymorphs, which include the different crystal packing arrangements of the same elemental composition of a compound), amorphous phases, salts, solvates, and hydrates. In some embodiments, 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.

[0083] Where a range of values is provided, it is understood that the upper and lower limit, and each intervening value between the upper and lower limit of the range is encompassed within the embodiments.

Compounds

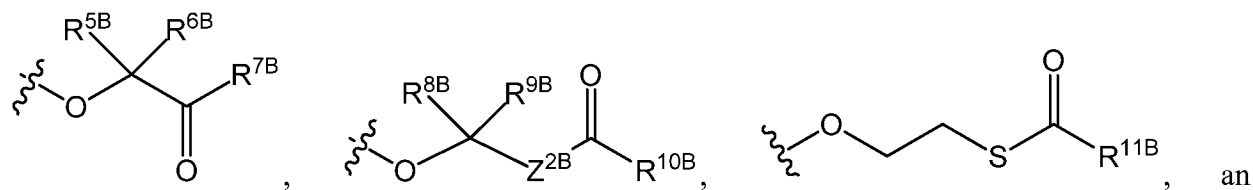
[0084] Some embodiments disclosed herein relate to a compound selected from Formula (I), Formula (II) and Formula (III), or a pharmaceutically acceptable salt of the foregoing:



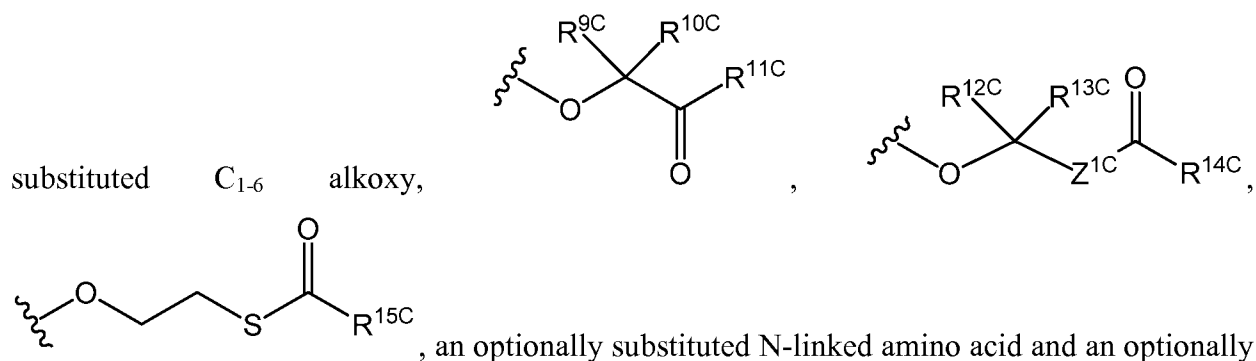
wherein: B^{1A}, B^{1B} and B^{1C} can be independently an optionally substituted heterocyclic base or an optionally substituted heterocyclic base with a protected amino group; R^{1A} can be selected from hydrogen, an optionally substituted acyl, an optionally substituted O-linked amino acid,

$$\begin{array}{c} \text{Z}^{1A} \\ \parallel \\ \text{R}^{6A}\text{O}-\text{P}-\text{OR}^{7A} \\ | \\ \text{OR}^{7A} \end{array}, \quad \begin{array}{c} \text{Z}^{2A} \\ \parallel \\ \text{R}^{8A}\text{O}-\text{P}-\text{R}^{9A} \\ | \\ \text{R}^{9A} \end{array} \quad \text{and} \quad \begin{array}{c} \text{Z}^{3A} \\ \parallel \\ \text{R}^{10A}-\text{P}-\text{R}^{11A} \\ | \\ \text{R}^{11A} \end{array};$$
 when the dashed line (-----) of Formula (I) is a single bond, R^{2A} can be CH₂, and R^{3A} can be O (oxygen); when the dashed line (-----) of Formula (I) is absent, R^{2A} can be selected from an optionally substituted C₁₋₆ alkyl, an optionally

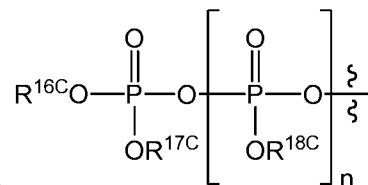
substituted C₂₋₆ alkenyl, an optionally substituted C₂₋₆ alkynyl, an optionally substituted C₃₋₆ cycloalkyl, an optionally substituted -O-C₁₋₆ alkyl, an optionally substituted O-C₃₋₆ alkenyl, an optionally substituted O-C₃₋₆ alkynyl and cyano, and R^{3A} can be selected from OH, -OC(=O)R^{3A} and an optionally substituted O-linked amino acid; R^{1B} can be selected from O⁻, OH,



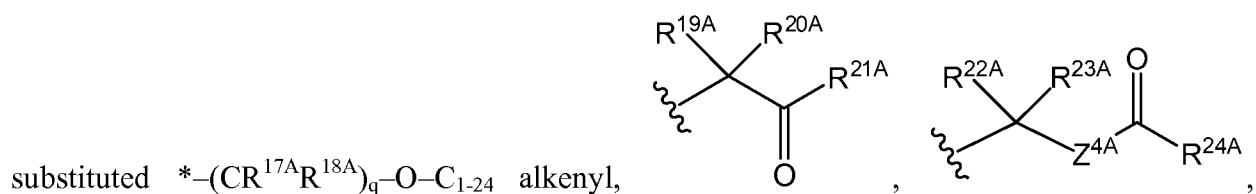
an optionally substituted N-linked amino acid and an optionally substituted N-linked amino acid ester derivative; R^{1C} and R^{2C} can be independently selected from O⁻, OH, an optionally



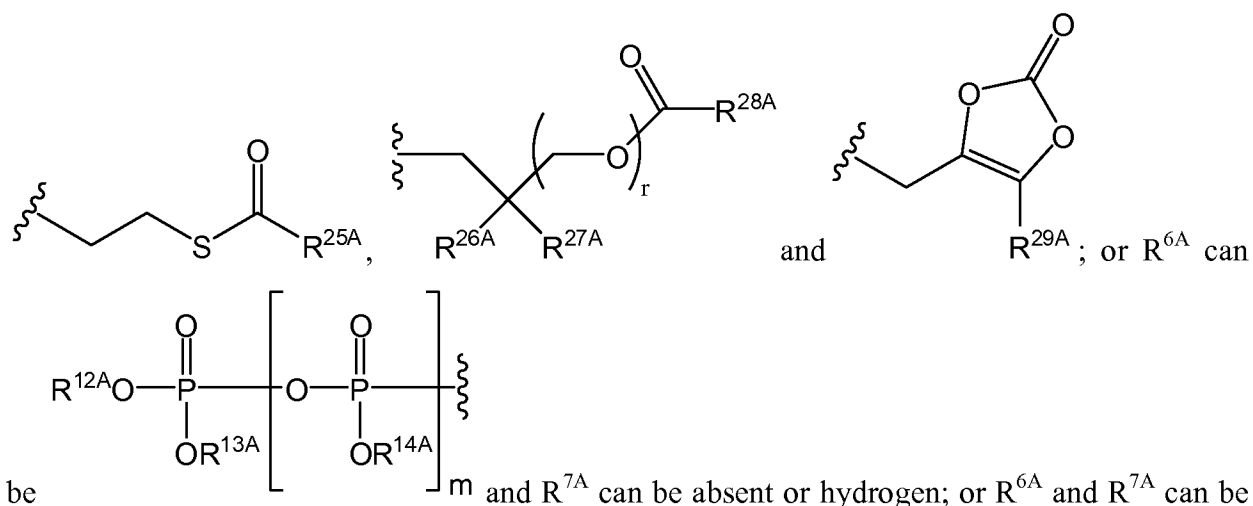
, an optionally substituted N-linked amino acid and an optionally

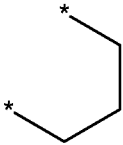


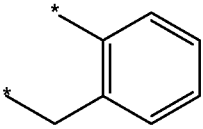
substituted N-linked amino acid ester derivative; or R^{1C} can be R^{2C} can be O⁻ or OH; R^{2B} and R^{3C} can be independently selected from an optionally substituted C₁₋₆ alkyl, an optionally substituted C₂₋₆ alkenyl, an optionally substituted C₂₋₆ alkynyl, an optionally substituted -O-C₁₋₆ alkyl, an optionally substituted -O-C₃₋₆ alkenyl, an optionally substituted -O-C₃₋₆ alkynyl, an optionally substituted C₃₋₆ cycloalkyl and cyano; R^{4C} can be selected from OH, -OC(=O)R^{4C} and an optionally substituted O-linked amino acid; R^{4A}, R^{3B} and R^{5C} can be independently a halogen; R^{5A}, R^{4B} and R^{6C} can be independently hydrogen or halogen; R^{6A}, R^{7A} and R^{8A} can be independently selected from absent, hydrogen, an optionally substituted C₁₋₂₄ alkyl, an optionally substituted C₂₋₂₄ alkenyl, an optionally substituted C₂₋₂₄ alkynyl, an optionally substituted C₃₋₆ cycloalkyl, an optionally substituted C₃₋₆ cycloalkenyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aryl(C₁₋₆ alkyl), an optionally substituted ^{*}-(CR^{15A}R^{16A})_p-O-C₁₋₂₄ alkyl, an optionally



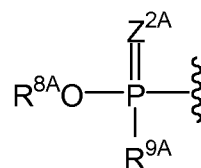
substituted ^{*}-(CR^{17A}R^{18A})_q-O-C₁₋₂₄ alkenyl,



taken together to form a moiety selected from an optionally substituted  and an

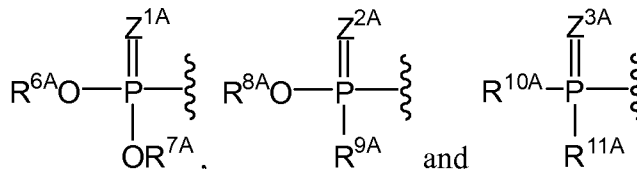
optionally substituted , wherein the oxygens connected to R^{6A} and R^{7A}, the phosphorus and the moiety form a six-membered to ten-membered ring system; R^{9A} can be independently selected from an optionally substituted C₁₋₂₄ alkyl, an optionally substituted C₂₋₂₄ alkenyl, an optionally substituted C₂₋₂₄ alkynyl, an optionally substituted C₃₋₆ cycloalkyl, an optionally substituted C₃₋₆ 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 C₁₋₂₄ 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 C₁₋₂₄ 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 C₁₋₂₄ alkyl, an optionally substituted aryl, an optionally substituted -O-C₁₋₂₄ alkyl and an optionally substituted -O-aryl; R^{25A}, R^{29A}, R^{11B} and R^{15C} can be independently selected from hydrogen, an optionally substituted C₁₋₂₄ 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 C₂₋₈ organylcarbonyl, C₂₋₈ alkoxycarbonyl and C₂₋₈ organylaminocarbonyl; R^{28A} can be selected from hydrogen, an optionally substituted C₁₋₂₄-alkyl, an optionally substituted C₂₋₂₄ alkenyl, an optionally substituted C₂₋₂₄ alkynyl, an optionally substituted C₃₋₆ cycloalkyl and an optionally

substituted C₃₋₆ cycloalkenyl; R^{30A} and R^{31A} can be independently selected from hydrogen, an optionally substituted C₁₋₂₄-alkyl, an optionally substituted C₂₋₂₄ alkenyl, an optionally substituted C₂₋₂₄ alkynyl, an optionally substituted C₃₋₆ cycloalkyl and an optionally substituted C₃₋₆ 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^{7A} and R^{7C} can be independently an optionally substituted C₁₋₂₄-alkyl, 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; Z^{1A}, Z^{2A}, Z^{3A}, Z^{4A}, Z^{1B}, Z^{2B} and Z^{1C} can be independently O or S; and provided that when the



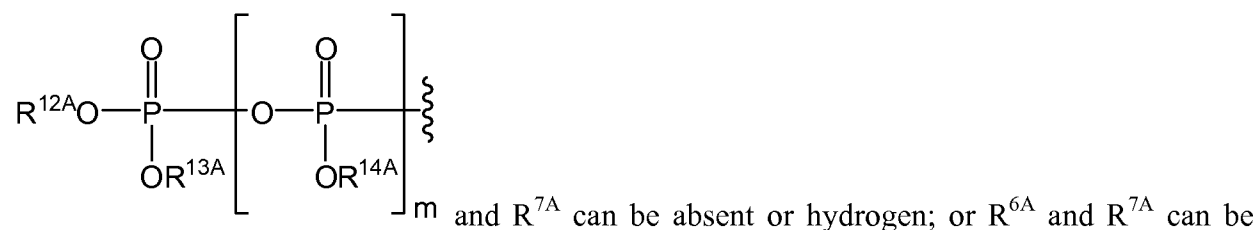
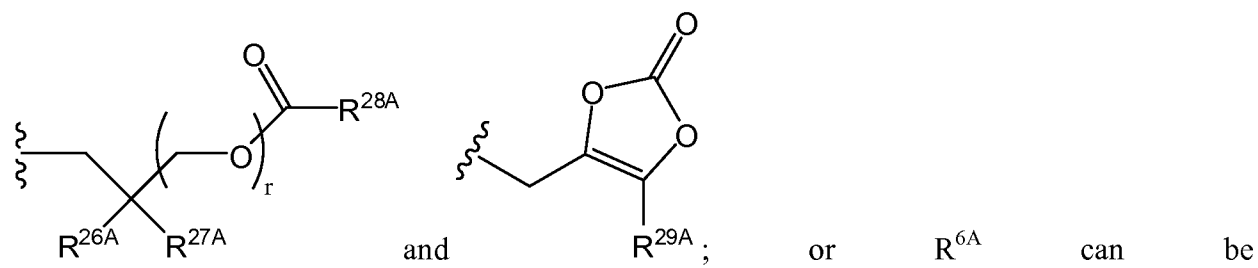
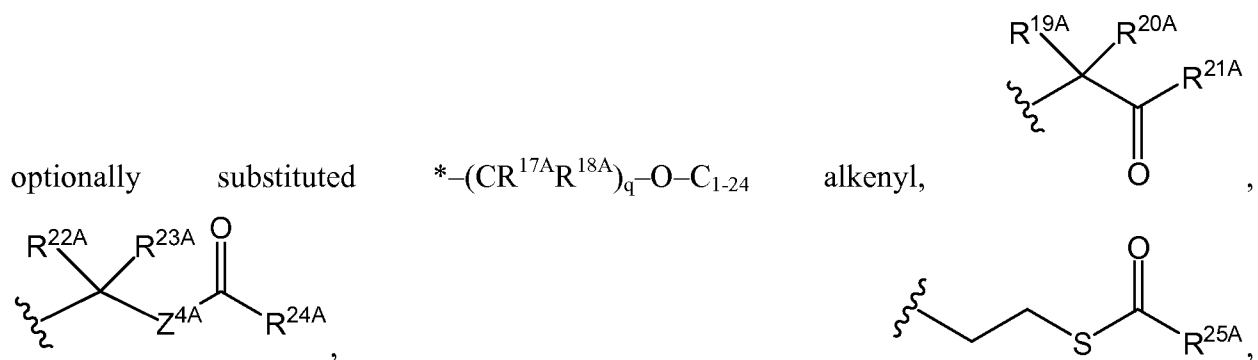
dashed line (-----) of Formula (I) is absent; R^{1A} is $\text{R}^{8A}-\text{O}-\text{P}(\text{R}^{9A})_2$ wherein R^{8A} is an unsubstituted C₁₋₄ alkyl or phenyl optionally para-substituted with a halogen or methyl and R^{9A} is methyl ester, ethyl ester, isopropyl ester, n-butyl ester, benzyl ester 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 -OCH₃; provided that when the dashed line (-----) of Formula (I) is absent; 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; provided that when the dashed line (-----) of Formula (I) is absent; 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 C₁ alkyl substituted with an optionally substituted N-amido (for example, -NC(=O)CF₃); and provided that when the dashed line (-----) of Formula (I) is absent; 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.

[0085] 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^{1A} can be selected from hydrogen, $\text{R}^{6A}-\text{O}-\text{P}(\text{OR}^{7A})(\text{Z}^{1A})$, $\text{R}^{8A}-\text{O}-\text{P}(\text{R}^{9A})(\text{Z}^{2A})$ and $\text{R}^{10A}-\text{P}(\text{R}^{11A})(\text{Z}^{3A})$; when the dashed line (-----) of Formula (I) is a single bond, R^{2A} is CH₂, and R^{3A} is O (oxygen); when the dashed line (-----) of Formula (I) is absent, R^{2A} can be selected from an optionally substituted C₁₋₆ alkyl, an optionally substituted C₂₋₆ alkenyl, an optionally substituted C₂₋₆ alkynyl, an optionally substituted -O-C₁₋₆ alkyl, an optionally substituted -O-C₃₋₆ alkenyl, an optionally

substituted $-O-C_{3-6}$ alkynyl and cyano, and R^{3A} is OH; R^{4A} can be a halogen; R^{5A} can be hydrogen or halogen; 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

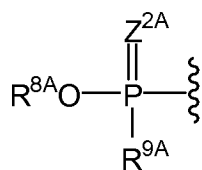


taken together to form a moiety selected from an optionally substituted

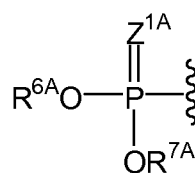
and an

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 and an optionally substituted $-O$ -aryl; R^{25A} 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 $-C\equiv N$ or an optionally substituted substituent selected from C_{2-8} organylcarbonyl, C_{2-8} alkoxy carbonyl 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; m can be 0 or 1; p and q can be independently selected from 1, 2 and 3; r can be 1 or 2; Z^{1A} , Z^{2A} , Z^{3A} and Z^{4A} can be independently O or S. In some embodiments, a compound of Formula (I) can have a structure shown herein, provided that when the dashed line (-----) of Formula (I) is

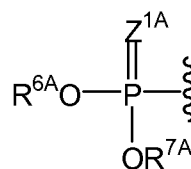


absent; R^{1A} is R^{9A} wherein R^{8A} is an unsubstituted C_{1-4} alkyl or phenyl optionally para-substituted with a halogen or methyl and R^{9A} is methyl ester, ethyl ester, isopropyl ester, n-butyl ester, benzyl ester or phenyl ester of an amino acid selected from glycine, alanine, valine, leucine, 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 $-OCH_3$; provided that when the dashed line (-----) of Formula (I) is absent; 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; provided that when the dashed line (-----) of Formula (I) is absent; 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; and provided that when the dashed line (-----) of Formula (I) is absent; 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.



[0086] In some embodiments, R^{1A} can be OR^{7A} . 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.

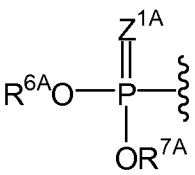


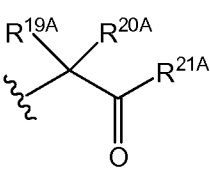
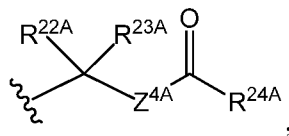
[0087] In some embodiments, when R^{1A} is OR^{7A} , one of R^{6A} and R^{7A} can be hydrogen, and the other of R^{6A} and R^{7A} is selected from an optionally substituted C_{1-24} alkyl, an optionally substituted C_{2-24} alkenyl, an optionally substituted C_{2-24} alkynyl, an optionally substituted 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.

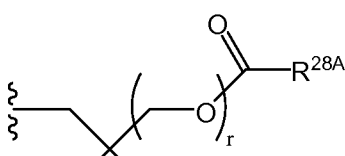
[0088] In some embodiments, at least one of R^{6A} and R^{7A} can be $*(CR^{15A}R^{16A})_p-O-C_{1-24}$ alkyl. In other embodiments, R^{6A} and R^{7A} can be both $*(CR^{15A}R^{16A})_p-O-C_{1-24}$ alkyl. In some embodiments, each R^{15A} and each R^{16A} are hydrogen. In other embodiments, at least one of R^{15A} and R^{16A} is an optionally substituted C_{1-24} alkyl. In other embodiments, at least one of R^{15A} and R^{16A} is 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.

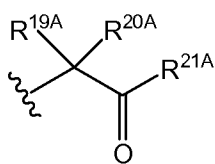
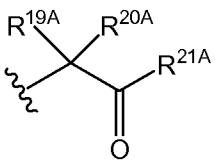
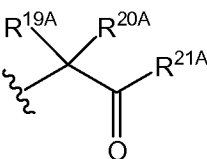
[0089] In some embodiments, at least one of R^{6A} and R^{7A} can be $*(CR^{17A}R^{18A})_q-O-C_{2-24}$ alkenyl. In other embodiments, R^{6A} and R^{7A} can be both $*(CR^{17A}R^{18A})_q-O-C_{2-24}$ alkenyl. In some embodiments, each R^{17A} and each R^{18A} are hydrogen. In other embodiments, at least

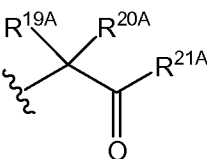
one of R^{17A} and R^{18A} is an optionally substituted C_{1-24} alkyl. In some embodiments, q can be 1. In other embodiments, q can be 2. In still other embodiments, q can be 3. When at least one of R^{6A} and R^{7A} is $-(CR^{15A}R^{16A})_p-O-C_{1-24}$ alkyl or $-(CR^{17A}R^{18A})_q-O-C_{2-24}$ alkenyl, 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 docosaheptaenyl.

[0090] In some embodiments, when R^{1A} is , at least one of R^{6A} and

R^{7A} can be selected from , ,

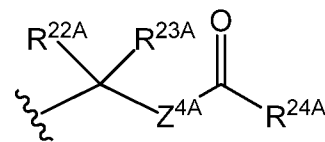
and ; and the other of R^{6A} and R^{7A} can be selected from absent, hydrogen, an optionally substituted C_{1-24} alkyl, an optionally substituted C_{2-24} alkenyl, an optionally substituted C_{2-24} alkynyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted C_{3-6} cycloalkenyl,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

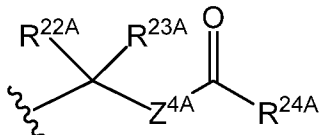
[0091] In some embodiments, at least one of R^{6A} and R^{7A} can be  or . In some embodiments, both R^{6A} and R^{7A} can be .

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 and an optionally substituted $-O$ -aryl.

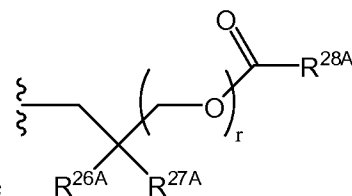
In some embodiments, R^{19A} and R^{20A} can be hydrogen. In other embodiments, at least one of R^{19A} and R^{20A} can be an optionally substituted C_{1-24} alkyl or an optionally substituted aryl. In some embodiments, R^{21A} can be an optionally substituted C_{1-24} alkyl. In other embodiments, R^{21A} can be an optionally substituted aryl. In still other embodiments, R^{21A} can be an optionally substituted $-O-C_{1-24}$ alkyl or an optionally substituted $-O$ -aryl.

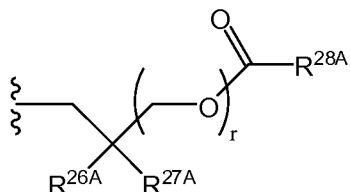
[0092] In some embodiments, both R^{6A} and R^{7A} can be



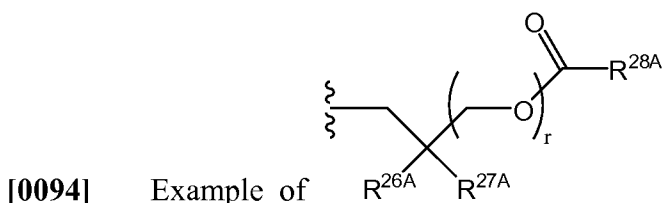
When one or both of R^{6A} and R^{7A} are , R^{22A} and R^{23A} can be independently selected from hydrogen, an optionally substituted C_{1-24} alkyl and an optionally substituted aryl; R^{24A} can be independently selected from hydrogen, an optionally substituted C_{1-24} alkyl, an optionally substituted aryl, an optionally substituted $-O-C_{1-24}$ alkyl and an optionally substituted $-O$ -aryl; and Z^{4A} can be independently O (oxygen) or S (sulfur). In some embodiments, R^{22A} and R^{23A} can be hydrogen. In other embodiments, at least one of R^{22A} and R^{23A} can be an optionally substituted C_{1-24} alkyl or an optionally substituted aryl. In some embodiments, R^{24A} can be an optionally substituted C_{1-24} alkyl. In other embodiments, R^{24A} can be an optionally substituted aryl. In still other embodiments, R^{24A} can be an optionally substituted $-O-C_{1-24}$ alkyl or an optionally substituted $-O$ -aryl. In some embodiments, Z^{4A} can be O (oxygen). In other embodiments, Z^{4A} can be S (sulfur). In some embodiments, one or both of R^{6A} and R^{7A} can be isopropylcarbonyloxymethyl. In some embodiments, one or both of R^{6A} and R^{7A} can be pivaloyloxymethyl.

[0093] In some embodiments, both R^{6A} and R^{7A} can be



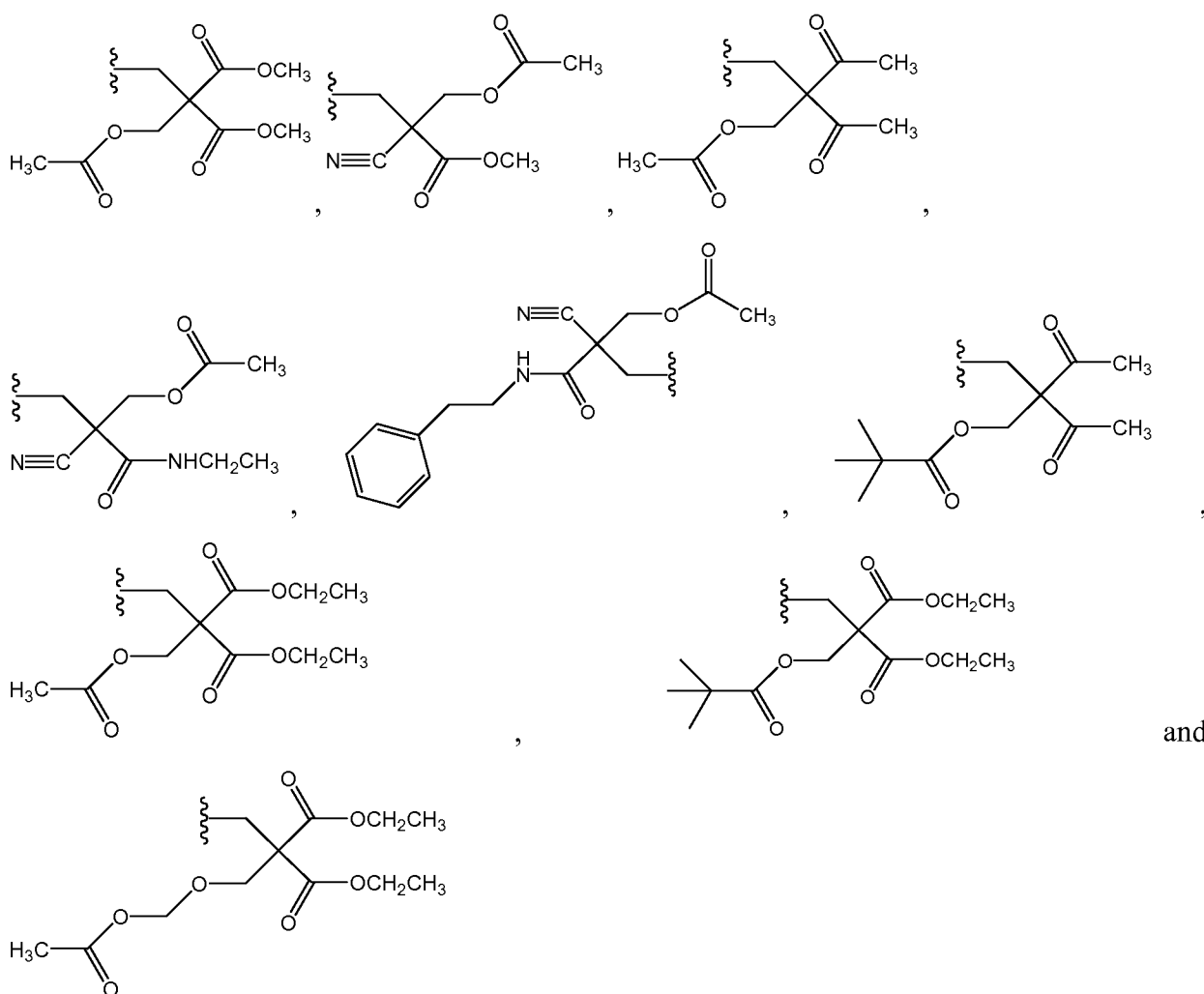
When one or both of R^{6A} and R^{7A} are , R^{26A} and R^{27A} can be independently $-C\equiv N$ or an optionally substituted substituent selected from C_{2-8} organylcarbonyl, C_{2-8} alkoxy carbonyl and C_{2-8} organylaminocarbonyl; R^{28A} can be selected from hydrogen, an optionally substituted 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

C₃₋₆ cycloalkenyl; and r can be 1 or 2. In some embodiments, R^{26A} can be -C≡N and R^{27A} can be an optionally substituted C₂₋₈ alkoxy carbonyl, such as -C(=O)OCH₃. In other embodiments, R^{26A} can be -C≡N and R^{27A} can be an optionally substituted C₂₋₈ organylaminocarbonyl, for example, -C(=O)NHCH₂CH₃ and -C(=O)NHCH₂CH₂phenyl. In some embodiments, both R^{26A} and R^{27A} can be an optionally substituted C₂₋₈ organylcarbonyl, such as -C(=O)CH₃. In some embodiments, both R^{26A} and R^{27A} can be an optionally substituted C₁₋₈ alkoxy carbonyl, for example, -C(=O)OCH₂CH₃ and -C(=O)OCH₃. In some embodiments, including those described in this paragraph, R^{28A} can be an optionally substituted C₁₋₄-alkyl. In some embodiment, R^{28A} can be methyl or tert-butyl. In some embodiments, r can be 1. In other embodiments, r can be 2.



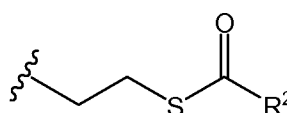
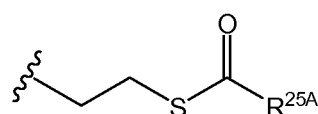
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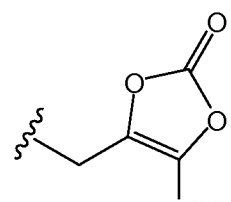
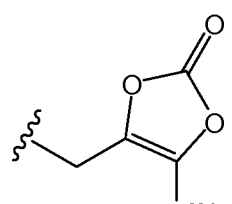
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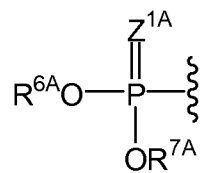
[0095] In some embodiments, R^{6A} and R^{7A} can be both an optionally substituted aryl. In some embodiments, at least one of R^{6A} and R^{7A} can be an optionally substituted aryl. For example, both R^{6A} and R^{7A} can be an optionally substituted phenyl or an optionally substituted naphthyl. When 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.

[0096] 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.

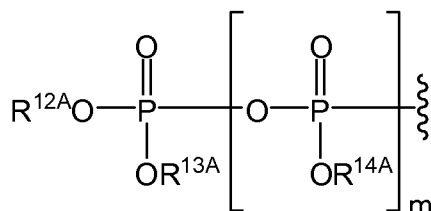
[0097] In some embodiments, R^{6A} and R^{7A} can be both . In some embodiments, at least one of R^{6A} and R^{7A} can be . In some embodiments, R^{25A} can be hydrogen. In other embodiments, R^{25A} can be an optionally substituted C_{1-24} alkyl. In still other embodiments, R^{25A} can be an optionally substituted aryl. In some embodiments, R^{25A} can be a C_{1-6} alkyl, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, pentyl (branched and straight-chained), and hexyl (branched and straight-chained).

[0098] 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.

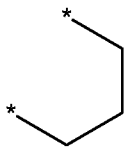


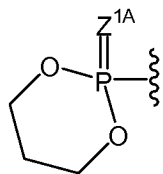
[0099] In some embodiments, R^{1A} can be



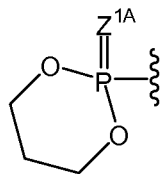
R^{7A} can be absent or hydrogen; R^{12A} , R^{13A} and R^{14A} can be independently absent or hydrogen; and m can be 0 or 1. In some embodiments, m can be 0, and R^{7A} , R^{12A} and R^{13A} can be independently absent or hydrogen. In other embodiments, m can be 1, and R^{7A} , R^{12A} , R^{13A} and 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.

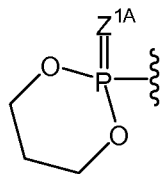
[0100] In some embodiments, R^{6A} and R^{7A} can be taken together to form an

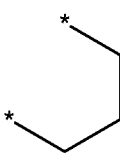
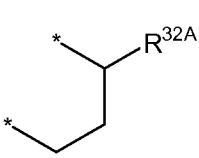
optionally substituted . For example, R^{1A} can be an optionally substituted



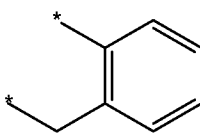
. When substituted, the ring can be substituted 1, 2, 3 or 3 or more times. When substituted with multiple substituents, the substituents can be the same or different. In some

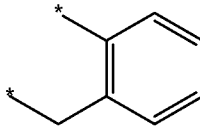
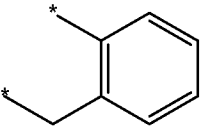
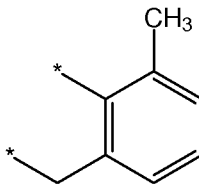
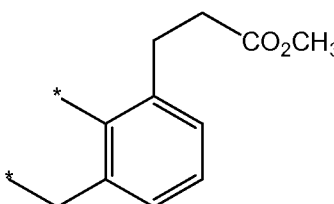
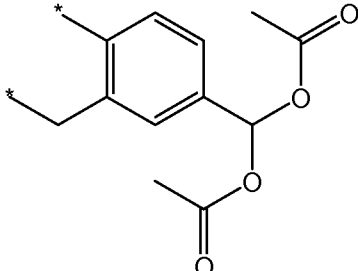


embodiments, when R^{1A} is , the ring can be substituted with an optionally substituted aryl group and/or an optionally substituted heteroaryl. An example of a suitable heteroaryl is pyridinyl. In some embodiments, R^{6A} and R^{7A} can be taken together to form an

optionally substituted  such as , wherein R^{32A} can be an optionally substituted aryl, an optionally substituted heteroaryl or an optionally substituted heterocyclyl.

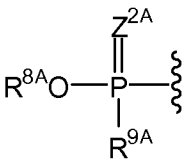
[0101] In some embodiments, R^{6A} and R^{7A} can be taken together to form an

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 .

[0102] In some embodiments, R^{6A} and R^{7A} can be the same. In some embodiments, R^{6A} and R^{7A} can be the different.

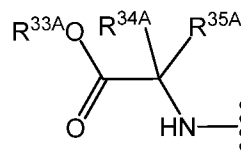
[0103] In some embodiments, Z^{1A} can be oxygen. In other embodiments, Z^{1A} can be sulfur.

[0104] In some embodiments, R^{1A} can be . In some embodiments, R^{8A} can be selected from absent, hydrogen, an optionally substituted C₁₋₂₄ alkyl, an optionally substituted C₂₋₂₄ alkenyl, an optionally substituted C₂₋₂₄ alkynyl, an optionally substituted C₃₋₆ cycloalkyl and an optionally substituted C₃₋₆ cycloalkenyl; and R^{9A} can be independently selected from an optionally substituted C₁₋₂₄ alkyl, an optionally substituted C₂₋₂₄ alkenyl, an optionally substituted C₂₋₂₄ alkynyl, an optionally substituted C₃₋₆ cycloalkyl and an optionally substituted C₃₋₆ cycloalkenyl.

[0105] In some embodiments, R^{8A} can be hydrogen, and R^{9A} can be an optionally substituted C₁₋₆ alkyl. Examples of suitable C₁₋₆ 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.

[0106] 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.

[0107] 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-

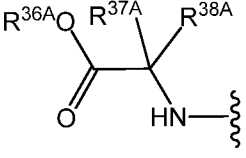
chained). In some embodiments, R^{33A} can be methyl or isopropyl. In some embodiments, R^{33A} can be ethyl or neopentyl. In other embodiments, R^{33A} can be an optionally substituted C_{3-6} cycloalkyl. Examples of optionally substituted C_{3-6} cycloalkyl include optionally substituted variants of 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.

[0108] In some embodiments, when R^{1A} is $\begin{array}{c} Z^{2A} \\ || \\ R^8O-P \\ | \\ R^9A \end{array}$, Z^{2A} can be O (oxygen).

In other embodiments, when R^{1A} is $\begin{array}{c} Z^{2A} \\ || \\ R^8O-P \\ | \\ R^9A \end{array}$, Z^{2A} can be S (sulfur).

[0109] In some embodiments, R^{1A} can be $\begin{array}{c} Z^{3A} \\ || \\ R^{10A}-P \\ | \\ R^{11A} \end{array}$. 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

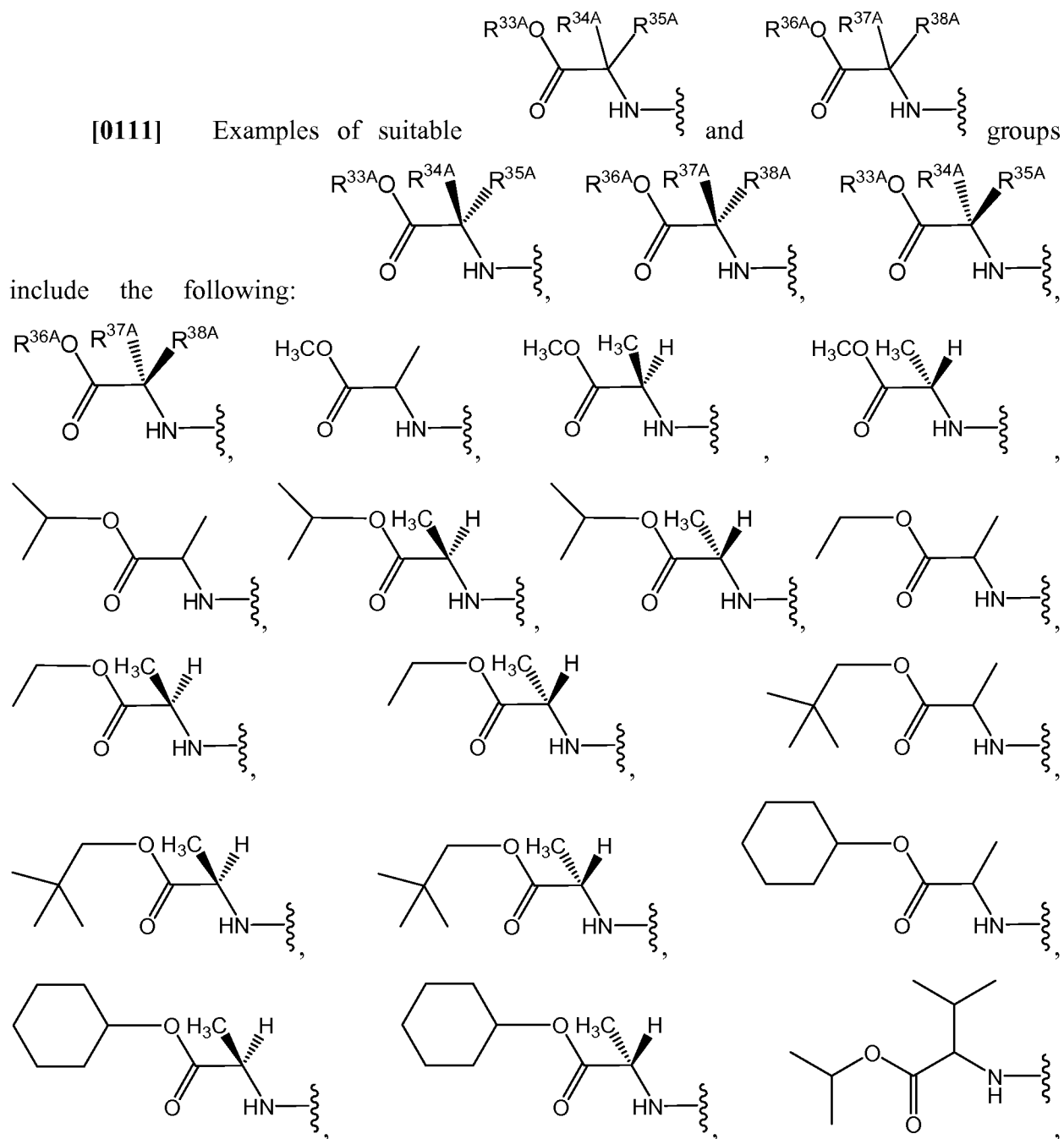
structure  wherein R^{36A} can be selected from hydrogen, an optionally substituted C_{1-6} -alkyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted aryl, an optionally substituted aryl(C_{1-6} alkyl) and an optionally substituted haloalkyl; R^{37A} can be selected from hydrogen, 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.

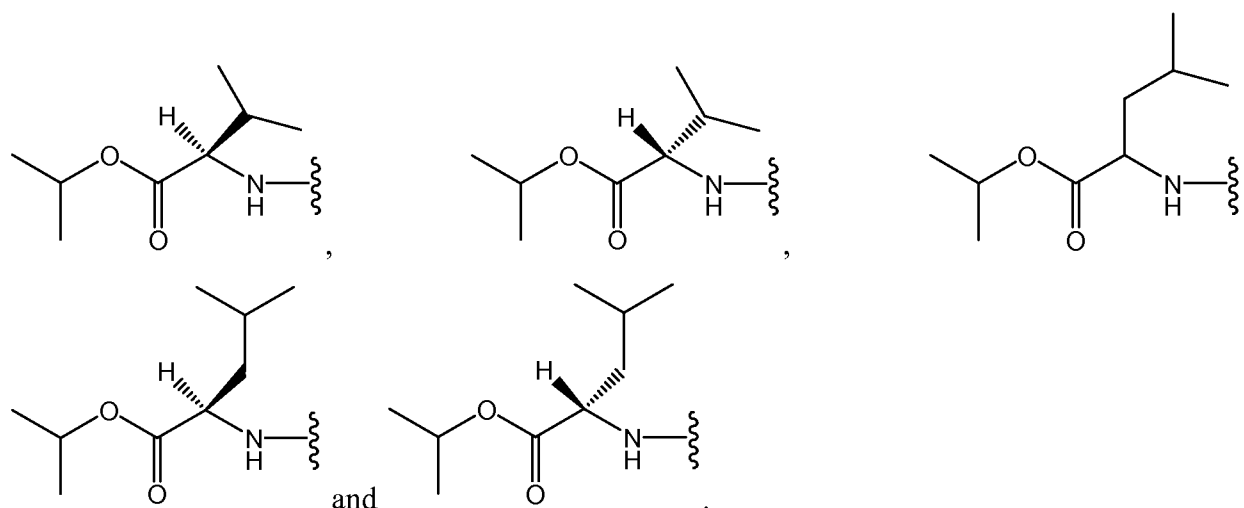
[0110] When R^{37A} is substituted, R^{37A} can be substituted with one or more substituents selected from N-amido, mercapto, alkylthio, an optionally substituted aryl, hydroxy, an optionally substituted heteroaryl, O-carboxy, and amino. In some embodiments, R^{37A} can be an unsubstituted C_{1-6} -alkyl, 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.

[0111] Examples of suitable

include the following:



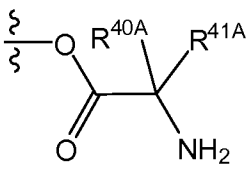


[0112] In some embodiments, R^{10A} and R^{11A} can be the same. In some embodiments, R^{10A} and R^{11A} can be the different.

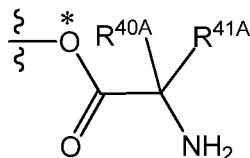
[0113] In some embodiments, Z^{3A} can be O (oxygen). In other embodiments, Z^{3A} can be S (sulfur).

[0114] 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.

[0115] 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

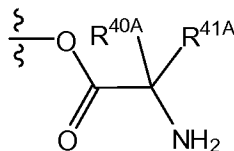
acid can have the structure , wherein R^{40A} can be selected from hydrogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{1-6} haloalkyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted C_6 aryl, an optionally substituted C_{10} aryl

and an optionally substituted aryl(C₁₋₆ alkyl); and R^{41A} can be hydrogen or an optionally substituted C₁₋₄-alkyl; or R^{40A} and R^{41A} can be taken together to form an optionally substituted C₃₋₆ 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-

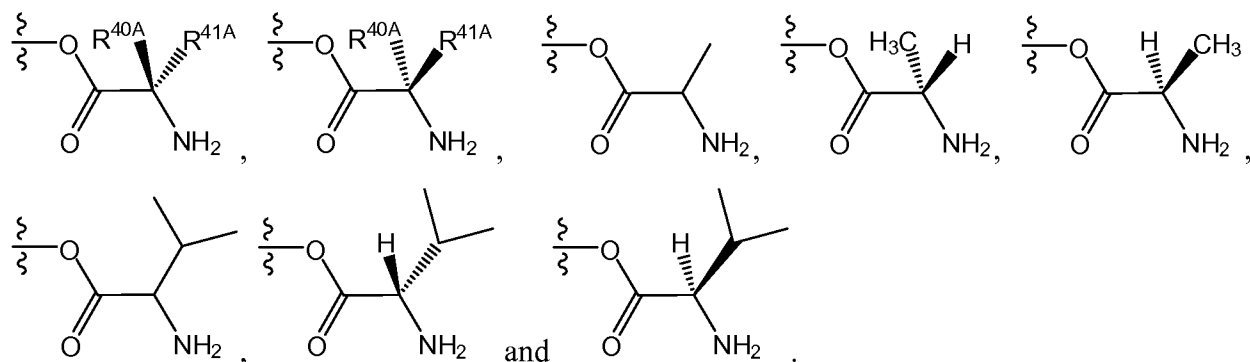


linked amino acid. For example, when R^{1A} is the oxygen indicated with “*” is the oxygen of R^{1A}O- of Formula (I).

[0116] 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 C₁₋₆-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 C₁₋₄-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.



[0117] Examples of suitable include the following:



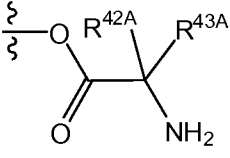
[0118] In some embodiments, the dashed line (-----) can be a single bond, R^{2A} can be CH₂, and R^{3A} can be O (oxygen). When the dashed line (-----) is a single bond, R^{2A} is CH₂, and R^{3A} is O (oxygen), a 4-membered ring is formed that includes the 4'-carbon and 3'-carbon of the pentose ring. In other embodiments, the dashed line (-----) can be absent, R^{2A} can be selected from an optionally substituted C₁₋₆ alkyl, an optionally substituted C₂₋₆ 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, $-OC(=O)R^{2A}$ and an optionally substituted O-linked amino acid.

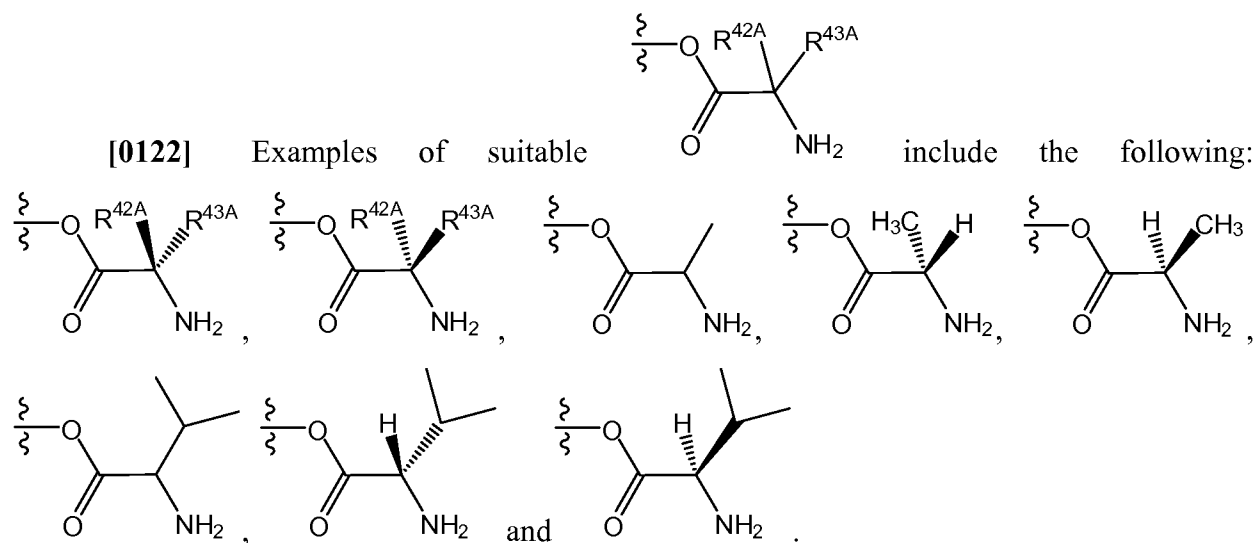
[0119] Various groups can be attached to the 4'-position of the pentose ring. In some embodiments, R^{2A} can be an optionally substituted C_{1-6} alkyl. Examples of suitable C_{1-6} alkyls include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, pentyl (branched and straight-chained), 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, an alkoxy substituted C_{1-6} alkyl or a sulfenyl substituted C_{1-6} alkyl (for example, $-C_{1-6}$ alkyl-S- C_{1-6} alkyl). In other embodiments, R^{2A} can be a C_{1-6} haloalkyl. In other 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 yet still other embodiments, R^{2A} can be cyano.

[0120] The groups attached to the 3'-position of the pentose ring can vary. In some embodiments, including those of paragraph [0119], R^{3A} can be OH. In other embodiments, including those of paragraph [0119], 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 C₁₋₆ alkyl, an optionally substituted C₁₋₆ haloalkyl, an optionally substituted C₃₋₆ cycloalkyl, an optionally substituted C₆ aryl, an optionally substituted C₁₀ aryl and an optionally substituted aryl(C₁₋₆ alkyl); and R^{43A} can be hydrogen or an optionally substituted C₁₋₄-alkyl; or R^{42A} and R^{43A} can be taken together to form an optionally substituted C₃₋₆ cycloalkyl.

[0121] 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 C₁₋₆-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 C₁₋₄-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.

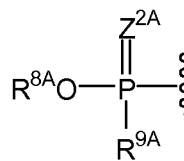


[0123] In still other embodiments, including those of paragraph [0119], R^{3A} can be $-OC(=O)R^{''A}$, wherein $R^{''A}$ can be an optionally substituted C_{1-24} alkyl. In some embodiments, $R^{''A}$ can be a substituted C_{1-8} alkyl. In other embodiments, $R^{''A}$ can be an unsubstituted C_{1-8} alkyl. In still other embodiments, including those of paragraph [0119], R^{3A} can be an optionally substituted $-O$ -acyl. In yet still other embodiments, including those of paragraph [0119], 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.

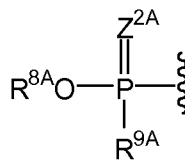
[0124] Various substituents can be present at the 2'-position of the pentose ring. In some embodiments, R^{5A} can be hydrogen. In other embodiments, R^{5A} can be halogen, for example, fluoro. In some embodiments, R^{4A} can be halogen, such as fluoro. In some embodiments, R^{5A} can be hydrogen and R^{4A} can be halogen. In other embodiments, R^{4A} and R^{5A} can both be halogen.

[0125] In some embodiments, ---- can be a single bond, R^{4A} can be fluoro, R^{5A} can be hydrogen and R^{2A} can be a C_{1-6} haloalkyl. In some embodiments, ---- can be a single bond, R^{4A} can be fluoro, R^{5A} can be hydrogen, R^{2A} can be a C_{1-6} haloalkyl and B^{1A} can be cytosine.

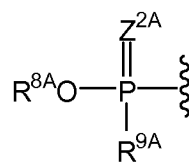
[0126] In some embodiments, R^{2A} cannot be methoxy. In some embodiments, R^{2A} cannot be methoxy when B^{1A} is substituted or unsubstituted uracil. In some embodiments, B^{1A} is substituted or unsubstituted cytosine. In other embodiments, B^{1A} is substituted or unsubstituted thymine. In still other embodiments, B^{1A} cannot be an unsubstituted uracil. In



some embodiments, R^{2A} cannot be methoxy when Z^{1A} is R^{8A} , 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

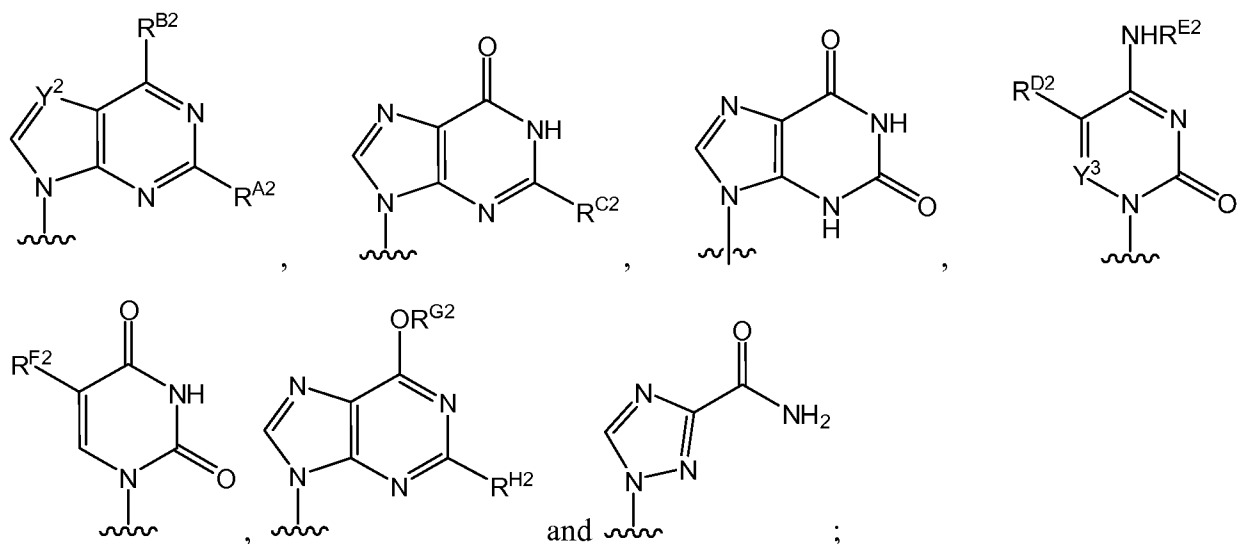


embodiments, R^{2A} cannot be methoxy when Z^{1A} is R^{9A} . In some embodiments, R^{2A}



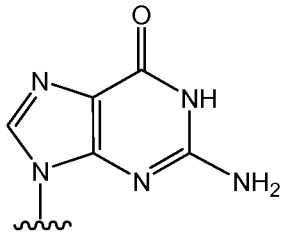
cannot be an alkoxy (for example, when Z^{1A} is $\text{P}(=\text{O})(\text{OR}^{9A})(\text{wavy line})$). In some embodiments, B^{1A} cannot be cytosine when R^{2A} is an unsubstituted alkenyl or an unsubstituted alkynyl. In some embodiments, B^{1A} cannot be thymine when R^{2A} is an optionally substituted 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^{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.

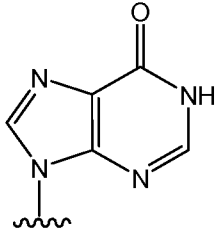
[0127] Various optionally substituted heterocyclic bases can be attached to the pentose ring. In some embodiments, one or more of the amine and/or amino groups may be protected with a suitable protecting group. For example, an amino group may be protected by transforming the amine and/or amino group to an amide or a carbamate. In some embodiments, an optionally substituted heterocyclic base or an optionally substituted heterocyclic base with one or more protected amino groups can have one of the following structures:

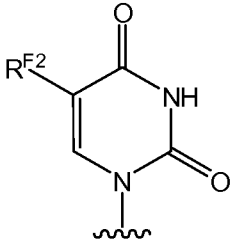
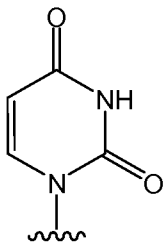


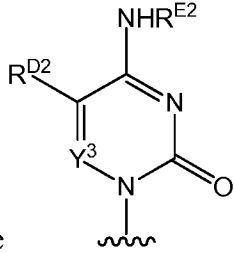
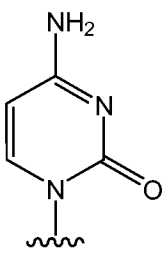
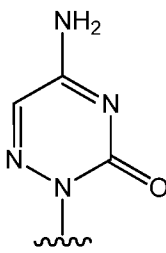
wherein: R^{A2} can be selected from hydrogen, halogen and NHR^{J2} , wherein R^{J2} can be selected from hydrogen, $-\text{C}(=\text{O})\text{R}^{K2}$ and $-\text{C}(=\text{O})\text{OR}^{L2}$; R^{B2} can be halogen or NHR^{W2} , wherein R^{W2} can be selected from hydrogen, an optionally substituted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

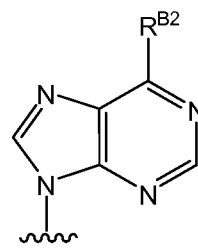
substituted C₂₋₆ alkenyl and an optionally substituted C₂₋₆ alkynyl; R^{E2} can be selected from hydrogen, hydroxy, an optionally substituted C₁₋₆ alkyl, an optionally substituted C₃₋₈ cycloalkyl, -C(=O)R^{R2} and -C(=O)OR^{S2}; R^{F2} can be selected from hydrogen, halogen, an optionally substituted C₁₋₆ alkyl, an optionally substituted C₂₋₆ alkenyl and an optionally substituted C₂₋₆ alkynyl; Y² and Y³ can be independently N (nitrogen) or CR^{I2}, wherein R^{I2} can be selected from hydrogen, halogen, an optionally substituted C₁₋₆-alkyl, an optionally substituted C₂₋₆-alkenyl and an optionally substituted C₂₋₆-alkynyl; R^{G2} can be an optionally substituted C₁₋₆ 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 C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkenyl, C₆₋₁₀ aryl, heteroaryl, heteroalicycyl, aryl(C₁₋₆ alkyl), heteroaryl(C₁₋₆ alkyl) and heteroalicycyl(C₁₋₆ alkyl). In 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.”

[0128] In some embodiments, B^{1A} can be . In other

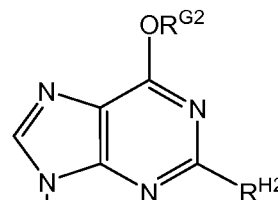
embodiments, B^{1A} can be . In still other embodiments, B^{1A} can be

, such as . In yet still other embodiments, B^{1A} can

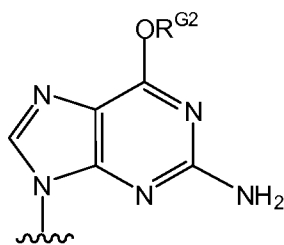
be , for example,  or . In some embodiments, R^{D2}



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

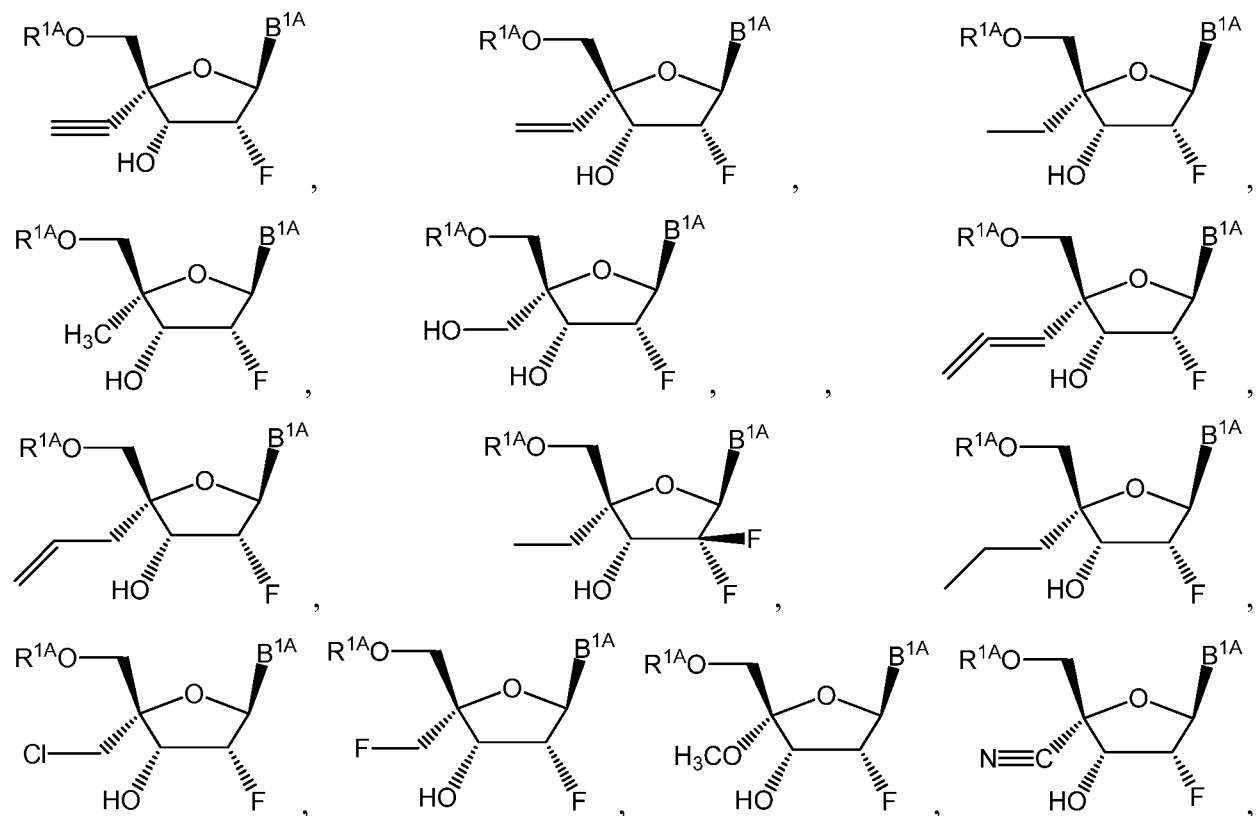


$-C(=O)OR^{N2}$. In still other embodiments, B^{1A} can be . In some

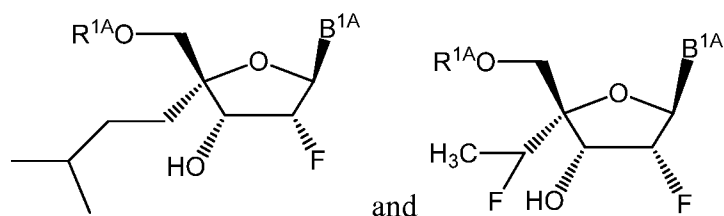


embodiments, B^{1A} can be .

[0129] In some embodiments, a compound of Formula (I) can have a structure selected from one of the following:

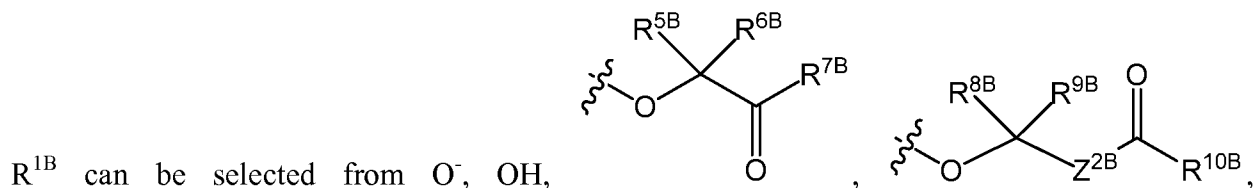




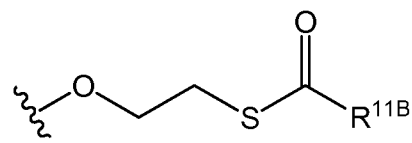


, or a pharmaceutically acceptable salt of the foregoing. In some embodiments of this paragraph, B^{1A} can be an optionally substituted purine base. In other embodiments of this paragraph, B^{1A} can be an optionally substituted pyrimidine base. In some embodiments of this paragraph, B^{1A} can be guanine. 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. In some embodiments of this paragraph, R^{1A} can be an acyloxyalkyl ester phosphate prodrug.

[0130] 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;

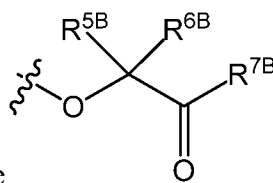


R^{1B} can be selected from O^- , OH ,

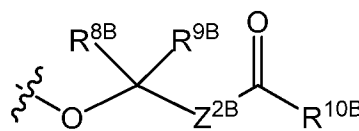


, an optionally substituted N-linked amino acid and an optionally substituted N-linked amino acid ester derivative; R^{2B} can be selected from an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{2-6} alkynyl, an optionally substituted $-O-C_{1-6}$ alkyl, an optionally substituted $-O-C_{3-6}$ alkenyl, an optionally substituted $-O-C_{3-6}$ alkynyl and cyano; R^{3B} can be a halogen; R^{4B} can be hydrogen or halogen; 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 and an optionally substituted $-O$ -aryl; R^{11B} can be selected from hydrogen, an optionally substituted C_{1-24} alkyl and an optionally substituted aryl; Z^{1B} and Z^{2B} can be independently O or S.

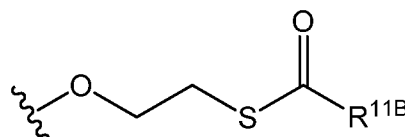
[0131] In some embodiments, R^{1B} can be O^- . In other embodiments, R^{1B} can be OH .



[0132] 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 and an optionally substituted $-O$ -aryl. 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 or an optionally substituted $-O$ -aryl.

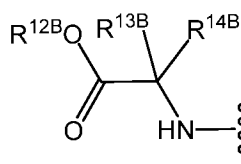


[0133] In some embodiments, R^{1B} can be wherein R^{8B} and R^{9B} can be independently selected from hydrogen, an optionally substituted C_{1-24} alkyl and an optionally substituted aryl; R^{10B} can be independently selected from hydrogen, an optionally substituted C_{1-24} alkyl, an optionally substituted aryl, an optionally substituted $-O-C_{1-24}$ alkyl and an optionally substituted $-O$ -aryl; 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 or an optionally substituted $-O$ -aryl. In some embodiments, Z^{2B} can be O (oxygen). In other embodiments, Z^{2B} can be S (sulfur). In some embodiments, R^{1B} can be isopropylcarbonyloxymethoxy. In some embodiments, R^{1B} can be pivaloyloxymethoxy.



[0134] In some embodiments, R^{1B} can be . In some embodiments, R^{11B} can be hydrogen. In other embodiments, R^{11B} can be an optionally substituted C_{1-24} alkyl. In still other embodiments, R^{11B} can be an optionally substituted aryl. In some embodiments, R^{11B} 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).

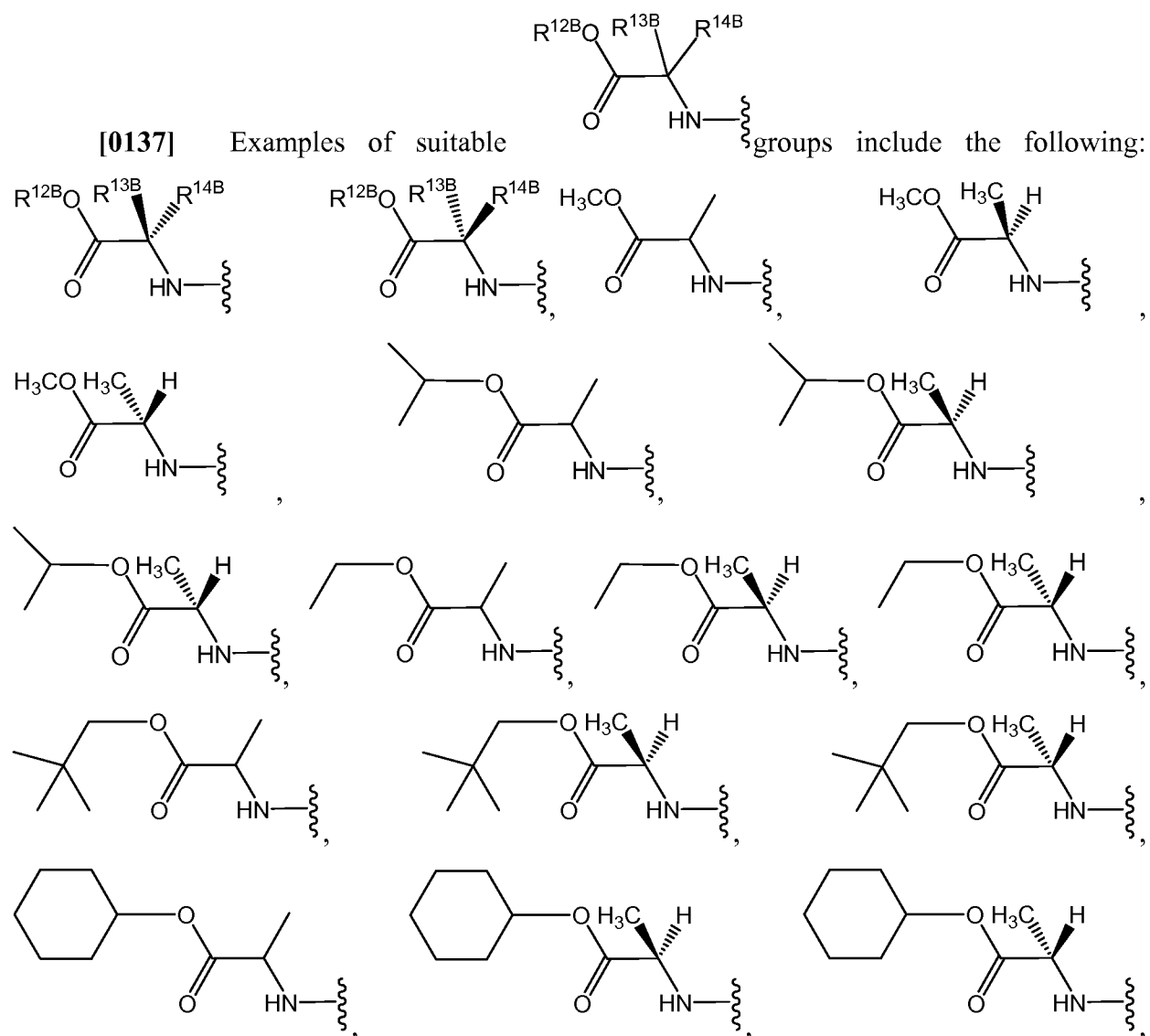
[0135] In some embodiments, R^{1B} can be an optionally substituted N-linked amino acid or an optionally substituted N-linked amino acid ester derivative. For example, R^{1B} can be optionally substituted version of the following: alanine, asparagine, aspartate, cysteine, glutamate, glutamine, glycine, 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

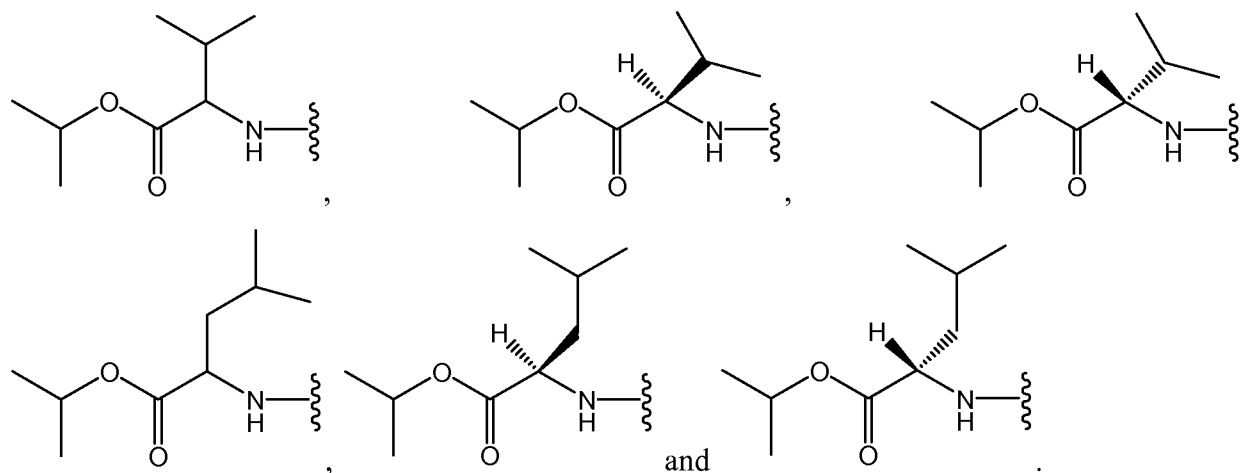


embodiments, R^{1B} can have the structure wherein R^{12B} can be selected from hydrogen, an optionally substituted C_{1-6} -alkyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted aryl, an optionally substituted aryl(C_{1-6} alkyl) and an optionally substituted haloalkyl; R^{13B} 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.

[0136] 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 C₁₋₄-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 C₃₋₆ cycloalkyl. Examples of optionally substituted C₃₋₆ 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.





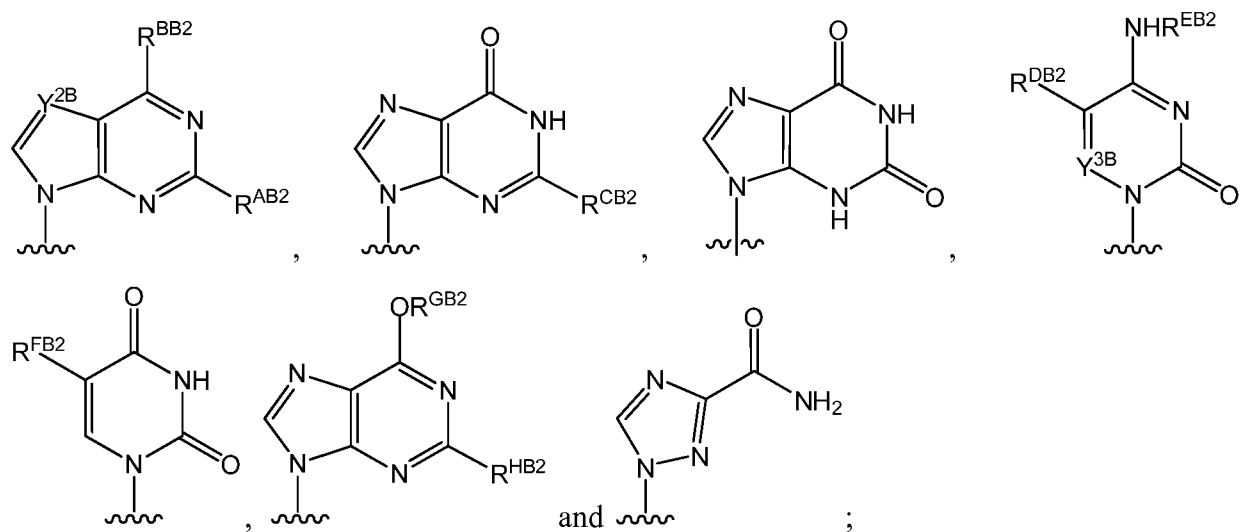
[0138] A variety of substituents can be present at the 4'-position of the pentose ring. In some embodiments, R^{2B} can be an optionally substituted C_{1-6} alkyl. Examples of suitable C_{1-6} alkyls include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, pentyl (branched and straight-chained), 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, an alkoxy substituted C_{1-6} alkyl or a sulfenyl substituted C_{1-6} alkyl (for example, $-C_{1-6}$ alkyl-S- C_{1-6} alkyl). In other embodiments, R^{2B} can be a C_{1-6} haloalkyl. In other 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, isopropoxy, 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-C₃₋₆ alkynyl. In other embodiments, R^{2B} can be an unsubstituted -O-C₃₋₆ alkynyl. In yet still other embodiments, R^{2B} can be cyano.

[0139] Variety of 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, such as fluoro. In some embodiments, R^{3B} can be halogen, such as fluoro. 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.

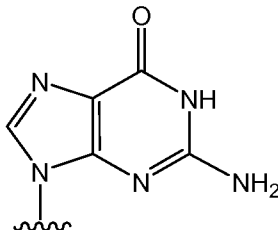
[0140] In some embodiments, Z^{1B} can be O (oxygen). In other embodiments, Z^{1B} can be S (sulfur).

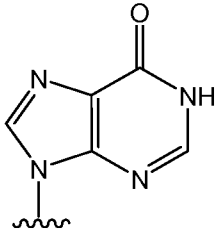
[0141] Various optionally substituted heterocyclic bases can be attached to the pentose ring. In some embodiments, one or more of the amine and/or amino groups may be protected with a suitable protecting group. For example, an amino group may be protected by transforming the amine and/or amino group 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:

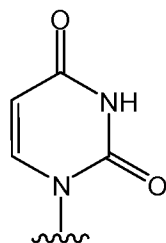
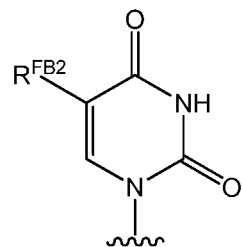


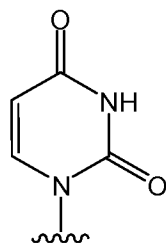
wherein: R^{AB2} can be selected from hydrogen, halogen and NHR^{JB2}, wherein R^{JB2} can be selected from hydrogen, -C(=O)R^{KB2} and -C(=O)OR^{LB2}; R^{BB2} can be halogen or NHR^{WB2}, wherein R^{WB2} can be selected from hydrogen, an optionally substituted C₁₋₆ alkyl, an optionally substituted C₂₋₆ alkenyl, an optionally substituted C₃₋₈ 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, halogen, an optionally substituted C₁₋₆ alkyl, an optionally substituted C₂₋₆ alkenyl and an optionally substituted C₂₋₆ alkynyl; R^{EB2} can be selected from hydrogen, hydroxy, an optionally substituted C₁₋₆ alkyl, an optionally substituted C₃₋₈ cycloalkyl, -C(=O)R^{RB2} and -C(=O)OR^{SB2}; R^{FB2} can be selected from hydrogen, halogen, an optionally substituted C₁₋₆ alkyl, an optionally substituted C₂₋₆ alkenyl and

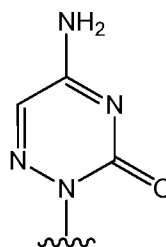
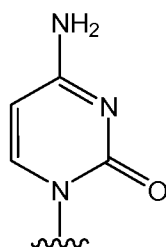
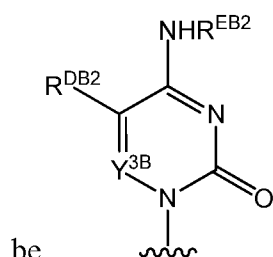
an optionally substituted C₂₋₆ alkynyl; Y^{2B} and Y^{3B} can be independently N (nitrogen) or CR^{IB2}, wherein R^{IB2} can be selected from hydrogen, halogen, an optionally substituted C₁₋₆-alkyl, an optionally substituted C₂₋₆-alkenyl and an optionally substituted C₂₋₆-alkynyl; R^{GB2} can be an optionally substituted C₁₋₆ 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 C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkenyl, C₆₋₁₀ aryl, heteroaryl, heteroalicycyl, aryl(C₁₋₆ alkyl), heteroaryl(C₁₋₆ alkyl) and heteroalicycyl(C₁₋₆ alkyl). In 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.”

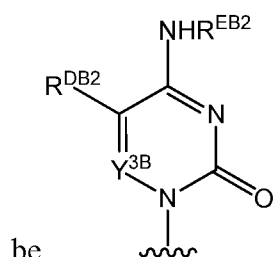
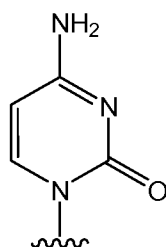
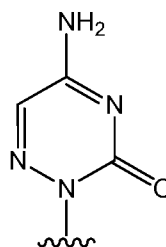
[0142] In some embodiments, B^{1B} can be . In other

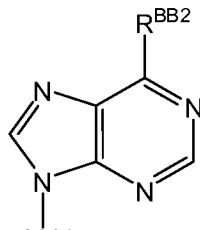
embodiments, B^{1B} can be . In still other embodiments, B^{1B} can be



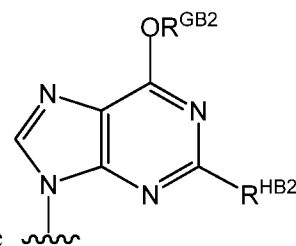
, such as . In yet still other embodiments, B^{1B} can



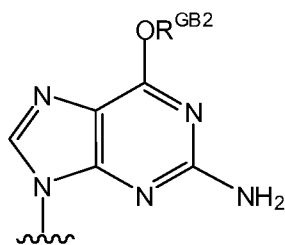
be , for example,  or . In some embodiments, R^{DB2}

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 -

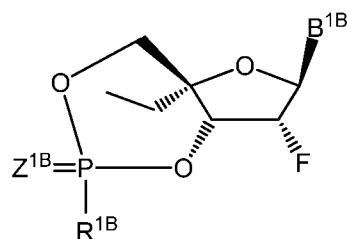


$C(=O)R^{MB2}$ or $-C(=O)OR^{NB2}$. In still other embodiments, B^{1B} can be . In



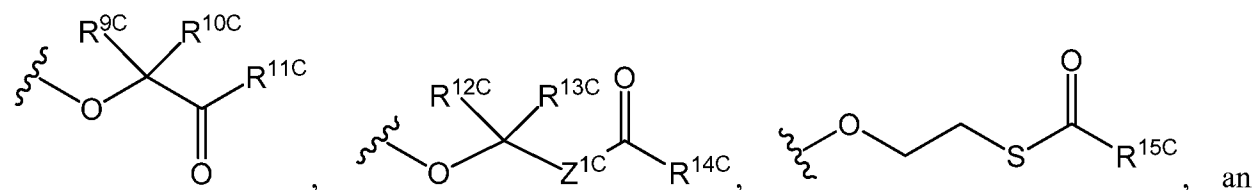
some embodiments, B^{1B} can be .

[0143] In some embodiments, a compound of Formula (II) can have the following structure:



, 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.

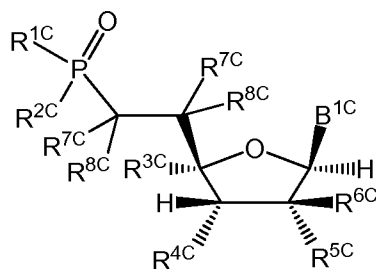
[0144] In some embodiments, the compound can be a compound of Formula (III), or a pharmaceutically acceptable salt thereof, wherein: B^{1C} can be an optionally substituted heterocyclic base or an optionally substituted heterocyclic base with a protected amino group; R^{1C} and R^{2C} can be independently selected from O^- , OH , an optionally substituted C_{1-6} alkoxy,



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

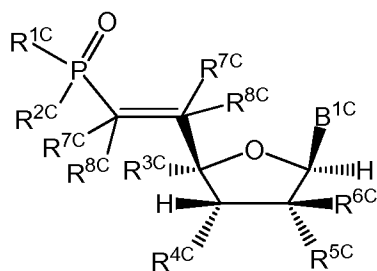
substituted C₂₋₆ alkenyl, an optionally substituted C₂₋₆ alkynyl, an optionally substituted -O-C₁₋₆ alkyl, an optionally substituted -O-C₃₋₆ alkenyl, an optionally substituted -O-C₃₋₆ alkynyl, an optionally substituted C₃₋₆ cycloalkyl and cyano; R^{4C} can be selected from OH, -OC(=O)R^{7C} and an optionally substituted O-linked amino acid; R^{5C} can be a halogen; R^{6C} can be hydrogen or halogen; R^{9C}, R^{10C}, R^{12C} and R^{13C} can be independently selected from hydrogen, an optionally substituted C₁₋₂₄ alkyl and an optionally substituted aryl; R^{11C} and R^{14C} can be independently selected from hydrogen, an optionally substituted C₁₋₂₄ alkyl, an optionally substituted aryl, an optionally substituted -O-C₁₋₂₄ alkyl and an optionally substituted -O-aryl; R^{15C} can be selected from hydrogen, an optionally substituted C₁₋₂₄ 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; Z^{1C} can be O (oxygen) or S (sulfur); and R^{7C} can be an optionally substituted C₁₋₂₄-alkyl.

[0145] 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 all 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.

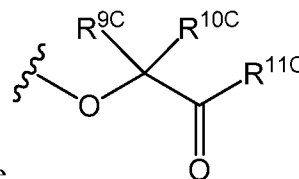
[0146] In some embodiments, ----- can be a double bond such that Formula (III)



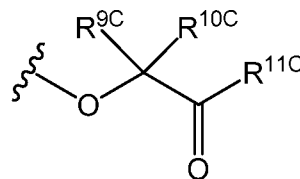
has the structure $\text{R}^{4\text{C}}-\text{C}-\text{C}-\text{R}^{5\text{C}}$, wherein each $\text{R}^{7\text{C}}$ is absent and each $\text{R}^{8\text{C}}$ can be independently hydrogen or halogen. In some embodiments, both $\text{R}^{8\text{C}}$ groups can be hydrogen. In other embodiments, one $\text{R}^{8\text{C}}$ can be halogen and the other $\text{R}^{8\text{C}}$ 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.

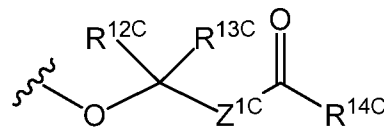
[0147] In some embodiments, R^{1C} and/or R^{2C} can be O^- . In other embodiments, R^{1C} and/or R^{2C} can be OH. In some embodiments, R^{1C} and R^{2C} can be both OH.



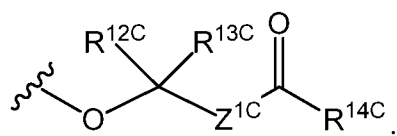
[0148] In some embodiments, R^{1C} and/or R^{2C} can be R^{9C} and R^{10C} can be independently selected from hydrogen, an optionally substituted C_{1-24} alkyl and an optionally substituted aryl; and R^{11C} can be selected from hydrogen, an optionally substituted C_{1-24} alkyl, an optionally substituted aryl, an optionally substituted $-O-C_{1-24}$ alkyl and an optionally substituted $-O$ -aryl. 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_{1-24} 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 or an optionally substituted $-$



O -aryl. In some embodiments, R^{1C} and R^{2C} can be both

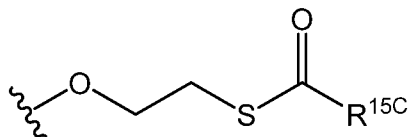


[0149] In some embodiments, R^{1C} and/or R^{2C} can be R^{12C} and R^{13C} can be independently selected from hydrogen, an optionally substituted C_{1-24} alkyl and an optionally substituted aryl; R^{14C} can be independently selected from hydrogen, an optionally substituted C_{1-24} alkyl, an optionally substituted aryl, an optionally substituted $-O-C_{1-24}$ alkyl and an optionally substituted $-O$ -aryl; 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 or an optionally substituted $-O$ -aryl. 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 isopropylcarbonyloxymethoxy. In some embodiments, R^{1C} and/or R^{2C} can be pivaloyloxymethoxy. In some embodiments, R^{1C} and R^{2C} can be both

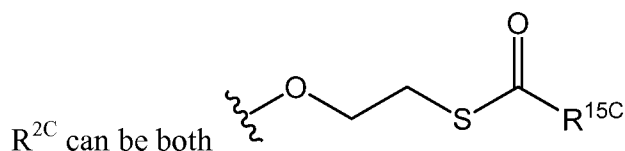


In some embodiments, R^{1C} and R^{2C} can be both isopropylcarbonyloxymethoxy. In other embodiments, R^{1C} and R^{2C} can be both pivaloyloxymethoxy.

[0150] In some embodiments, R^{1C} and/or R^{2C} can be

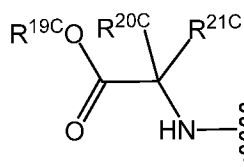


In some embodiments, R^{15C} can be hydrogen. In other embodiments, R^{15C} can be an optionally substituted C_{1-24} alkyl. In still other embodiments, R^{15C} can be an optionally substituted aryl. In some embodiments, R^{15C} can be a C_{1-6} alkyl, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, pentyl (branched and straight-chained), and hexyl (branched and straight-chained). In some embodiments, R^{1C} and



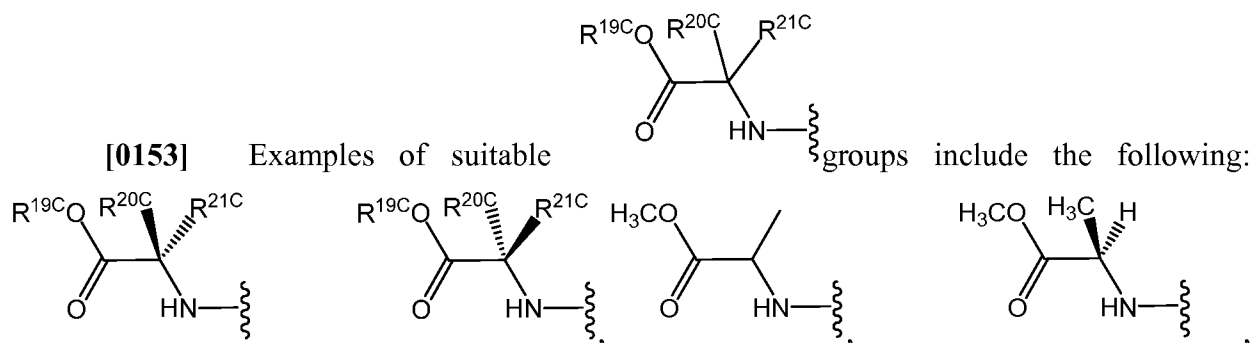
R^{2C} can be both

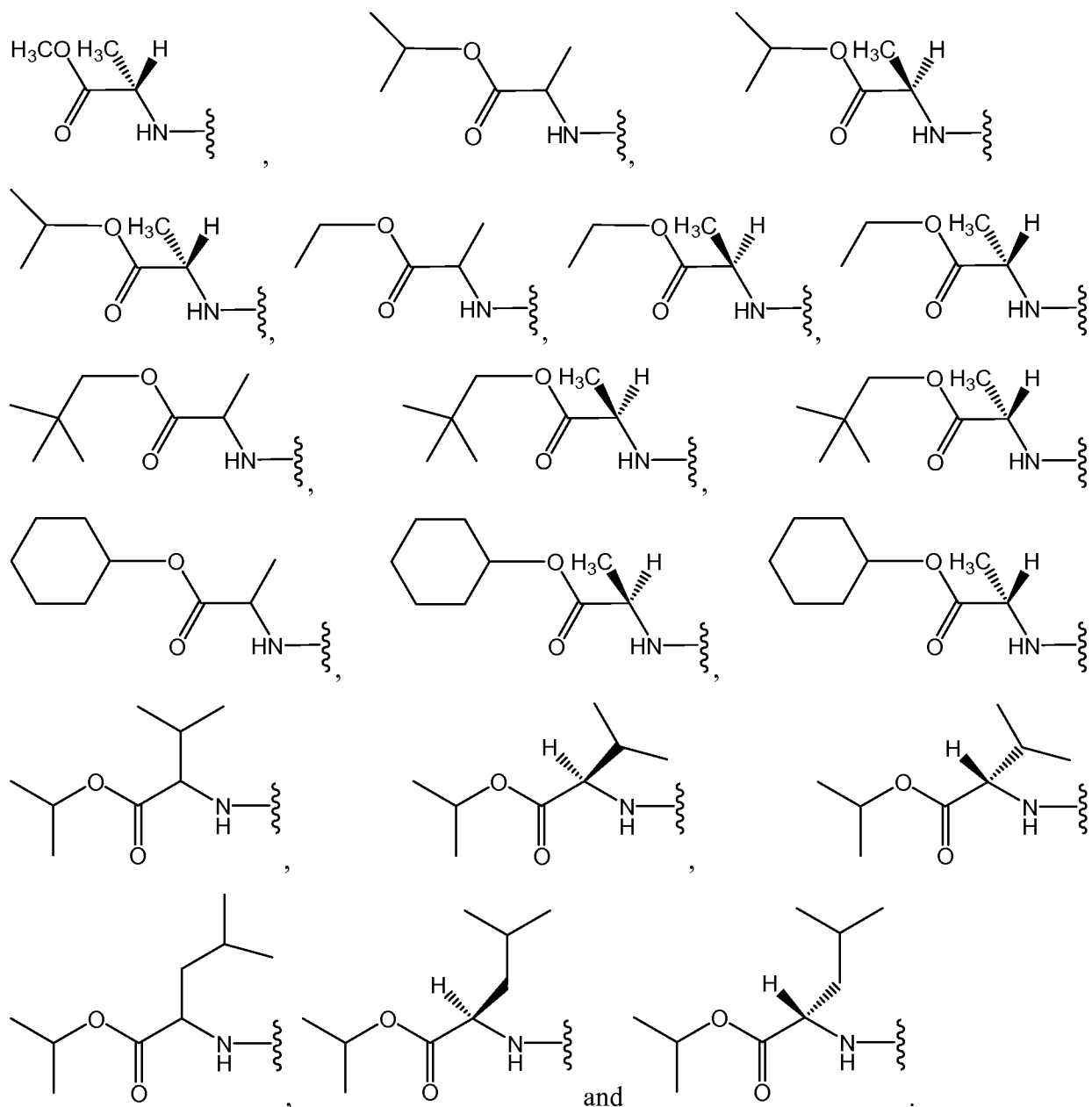
[0151] In some embodiments, R^{1C} and/or R^{2C} can be an optionally substituted N-linked amino acid or an optionally substituted N-linked amino acid ester derivative. For example, R^{1C} and/or R^{2C} can be optionally substituted version of the following: alanine, asparagine, aspartate, cysteine, 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



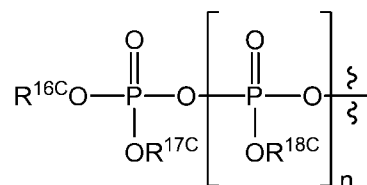
, wherein R^{19C} can be selected from hydrogen, an optionally substituted C_{1-6} -alkyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted aryl, an optionally substituted aryl(C_{1-6} alkyl) and an optionally substituted haloalkyl; R^{20C} can be selected from hydrogen, an optionally 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.

[0152] 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.





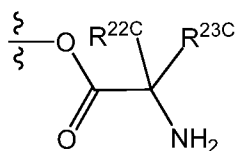
[0154] In some embodiments, R^{1C} and R^{2C} can be the same. In other embodiments, R^{1C} and R^{2C} can be different.

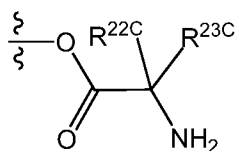


[0155] In some embodiments, R^{1C} can be O^- or OH , wherein R^{16C} , R^{17C} and R^{18C} can be absent or hydrogen; and n can be 0 or 1. Those skilled in the art understand that when R^{16C} , R^{17C} and/or R^{18C} are absent, the associated oxygen will be negatively charged. In some embodiments, 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.

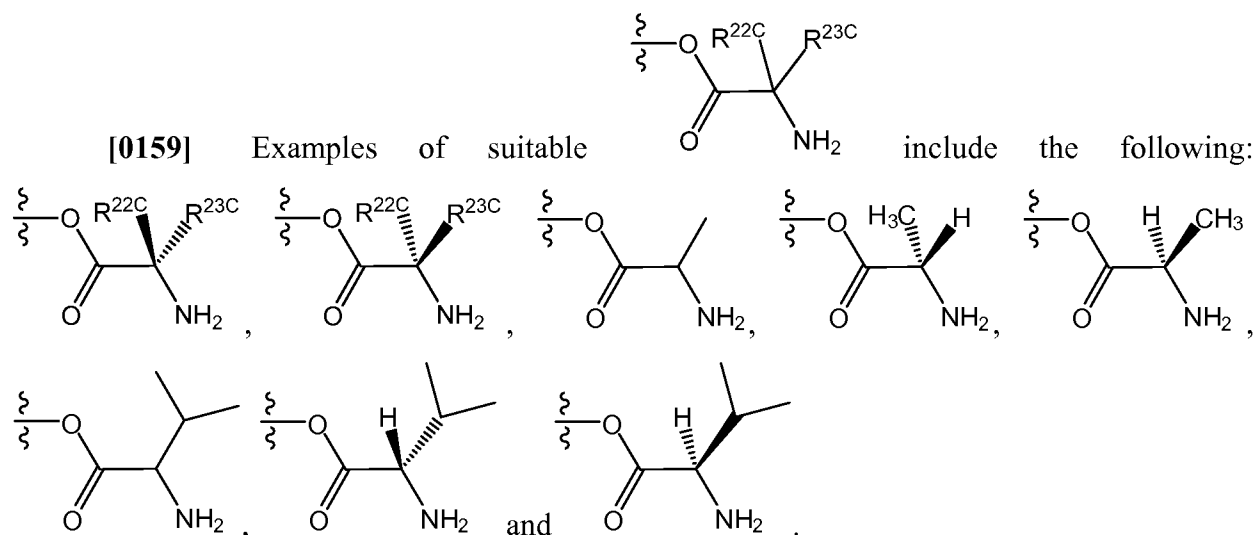
[0156] A variety of substituents can be present at the 4'-position of the pentose ring. In some embodiments, R^{3C} can be an optionally substituted C_{1-6} alkyl. Examples of suitable C_{1-6} alkyls include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, pentyl (branched and straight-chained), 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. 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 yet still other embodiments, R^{3C} can be cyano.

[0157] 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 C₁₋₆ alkyl, an optionally substituted C₁₋₆ haloalkyl, an optionally substituted C₃₋₆ cycloalkyl, an optionally substituted C₆ aryl, an optionally substituted C₁₀ aryl and an optionally substituted aryl(C₁₋₆ alkyl); and R^{23C} can be hydrogen or an optionally substituted C₁₋₄-alkyl; or R^{22C} and R^{23C} can be taken together to form an optionally substituted C₃₋₆ cycloalkyl.

[0158] 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 C₁₋₆-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 C₁₋₄-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.

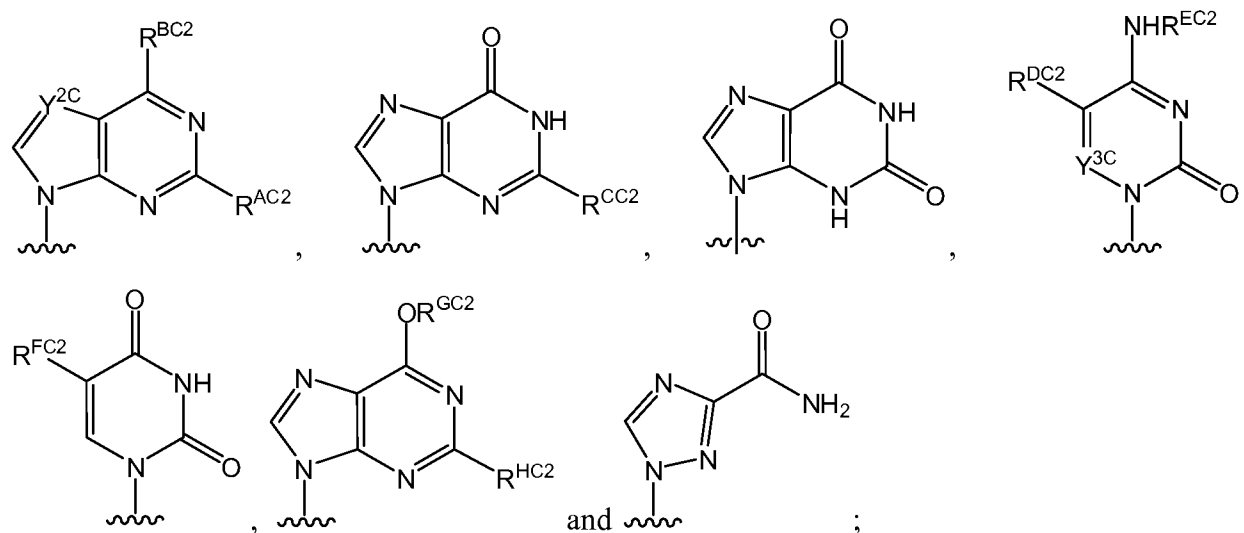


[0160] In still other embodiments, R^{4C} can be -OC(=O)R^{''C}, wherein R^{''C} can be an optionally substituted C₁₋₂₄ alkyl. In some embodiments, R^{''C} can be a substituted C₁₋₁₂ alkyl. In other embodiments, R^{''C} can be an unsubstituted C₁₋₁₂ alkyl. In still other embodiments, R^{''C} can be a substituted C₁₋₈ alkyl. In yet still other embodiments, R^{''C} can be an unsubstituted C₁₋₈ alkyl. In some embodiments, R^{4C} can be an optionally substituted acyl. In other embodiments,

R^{4C} can be $-OC(=O)R^{7C}$, wherein R^{7C} 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^{7C} can be a substituted C_{1-12} alkyl. In other embodiments, R^{7C} can be an unsubstituted C_{1-12} alkyl.

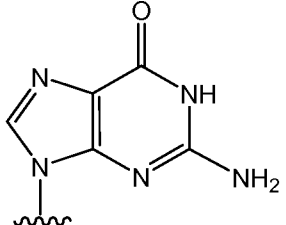
[0161] A variety of substituents can also be present at the 2'-position of the pentose ring. In some embodiments, R^{6C} can be hydrogen. In other embodiments, R^{6C} can be halogen, such as fluoro. In some embodiments, R^{5C} can be halogen, such as fluoro. In some embodiments, R^{6C} can be hydrogen 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.

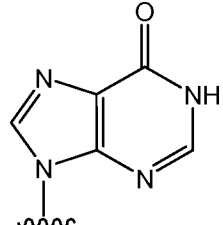
[0162] Various optionally substituted heterocyclic bases can be attached to the pentose ring. In some embodiments, one or more of the amine and/or amino groups may be protected with a suitable protecting group. For example, an amino group may be protected by transforming the amine and/or amino group 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:

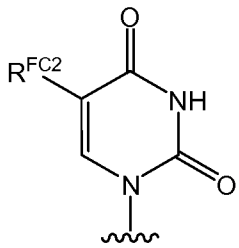
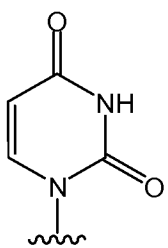


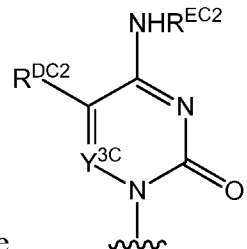
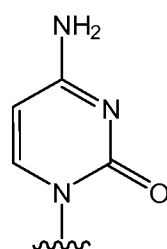
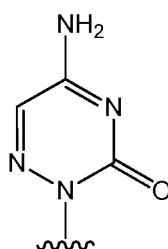
wherein: R^{AC2} can be selected from hydrogen, halogen and NHR^{JC2} , wherein R^{JC2} can be selected from hydrogen, $-C(=O)R^{KC2}$ and $-C(=O)OR^{LC2}$; R^{BC2} can be halogen or NHR^{WC2} , wherein R^{WC2} can be selected from hydrogen, an optionally substituted C_{1-6} alkyl, an optionally substituted 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}

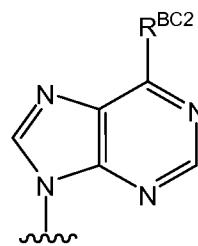
alkynyl; R^{EC2} can be selected from hydrogen, hydroxy, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{3-8} cycloalkyl, $-C(=O)R^{RC2}$ and $-C(=O)OR^{SC2}$; R^{FC2} can be selected from hydrogen, halogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} 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, heteroalicycyl, aryl(C_{1-6} alkyl), heteroaryl(C_{1-6} alkyl) and heteroalicycyl(C_{1-6} alkyl). In some embodiments, the structures shown above can be modified by replacing one or more hydrogens with substituents selected from the list of substituents provided for the definition of "substituted."

[0163] In some embodiments, B^{1C} can be . In other

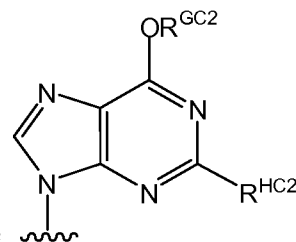
embodiments, B^{1C} can be . In still other embodiments, B^{1C} can be

, such as . In yet still other embodiments, B^{1C} can

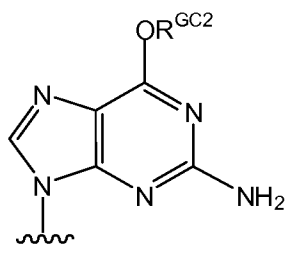
be , for example,  or . In some embodiments, R^{DC2}



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 -

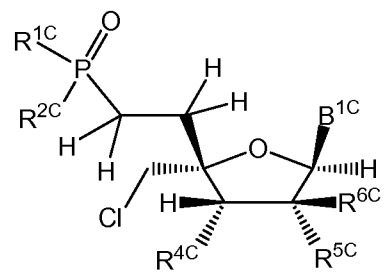


$C(=O)R^{MC2}$ or $-C(=O)OR^{NC2}$. In still other embodiments, B^{1C} can be . In



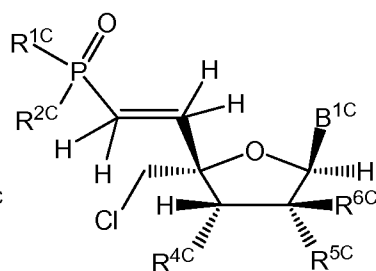
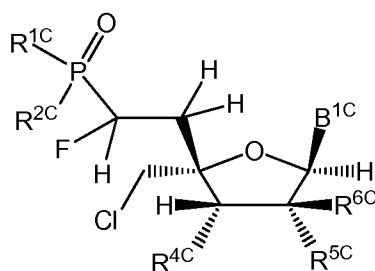
some embodiments, B^{1C} can be .

[0164] In some embodiments, the compound of Formula (III) can have one of the

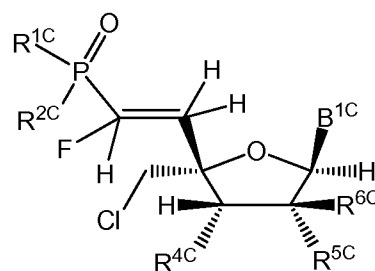


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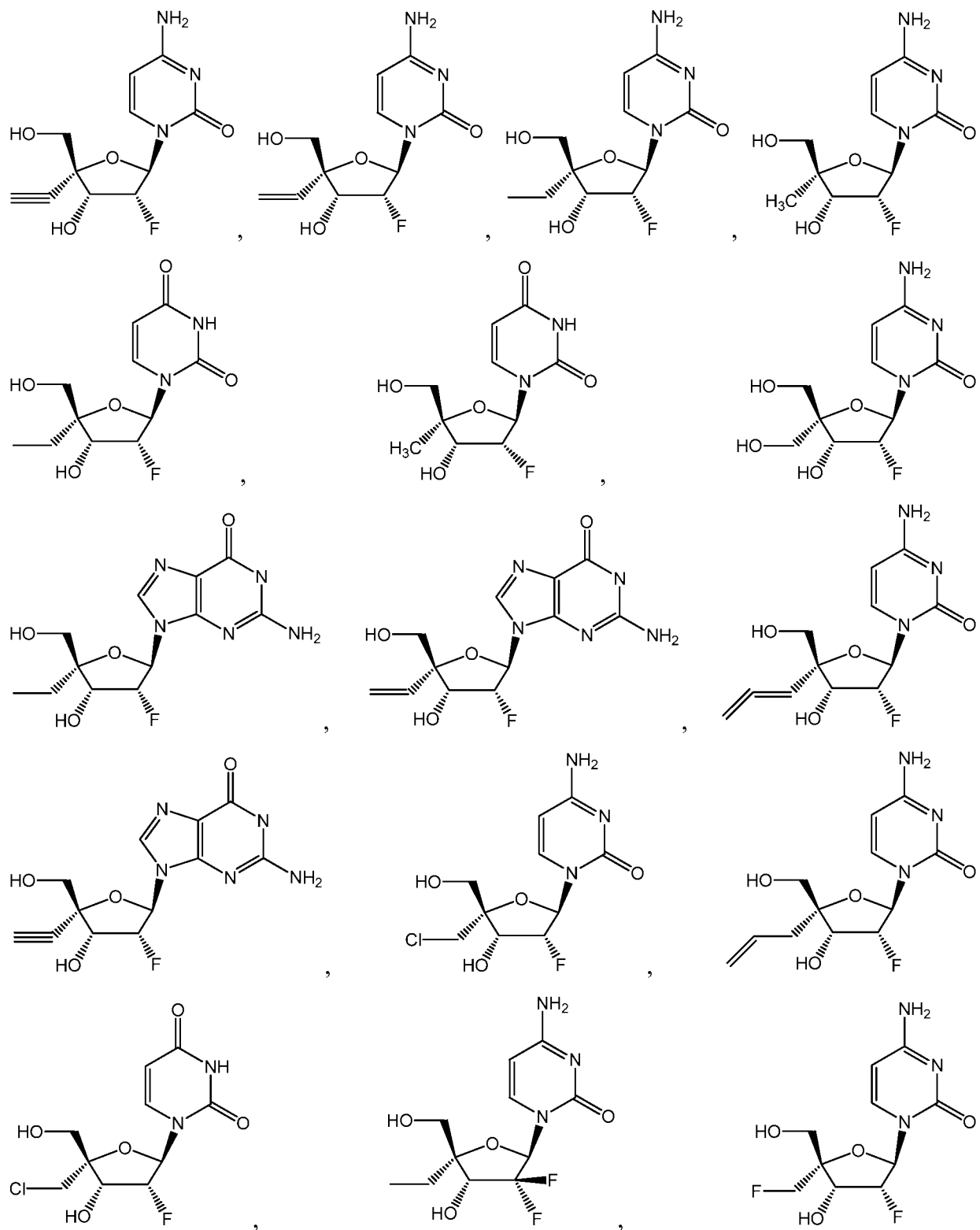


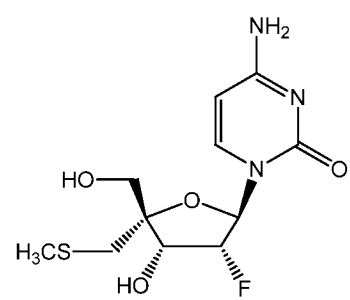
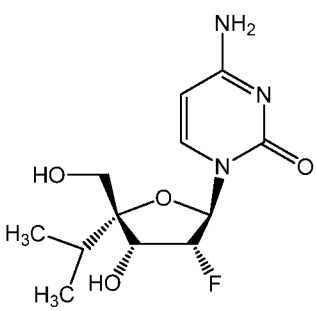
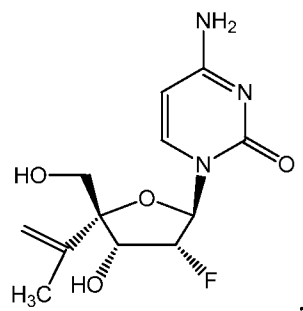
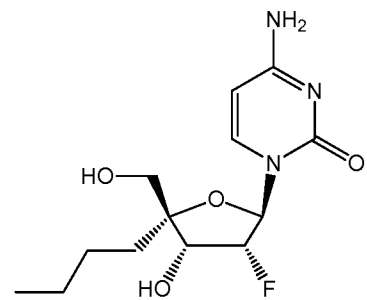
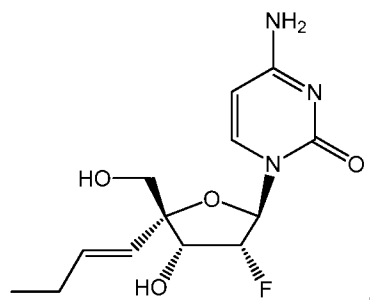
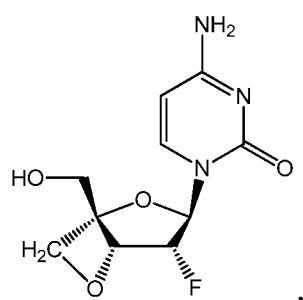
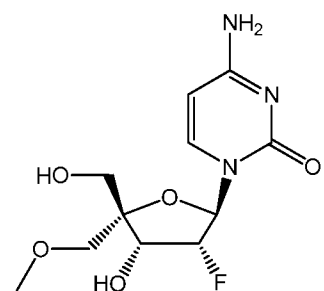
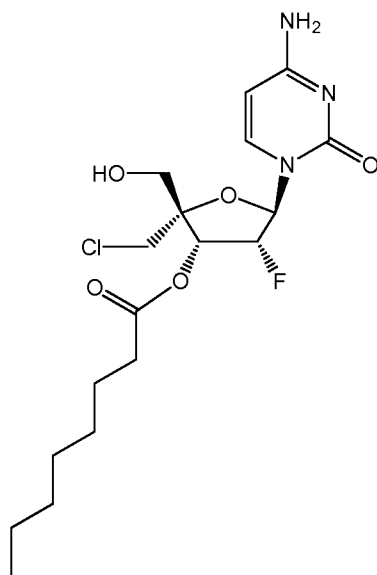
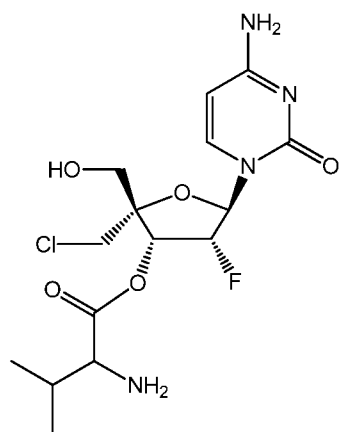
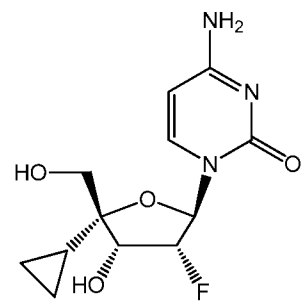
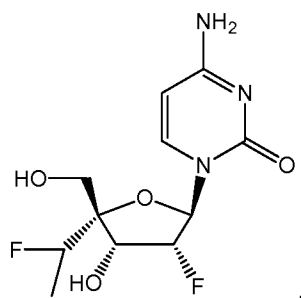
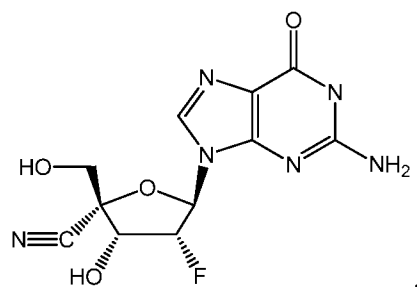
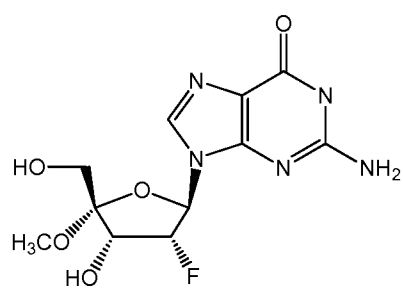
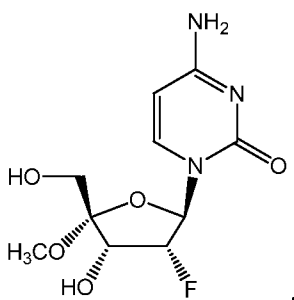
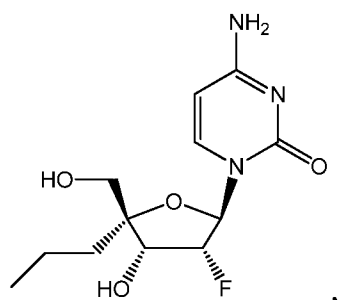
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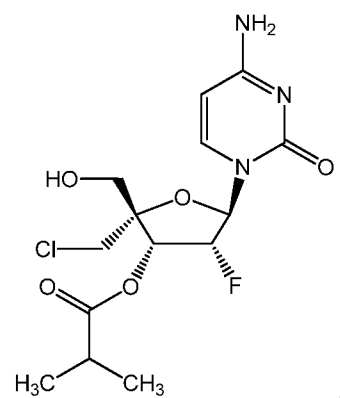
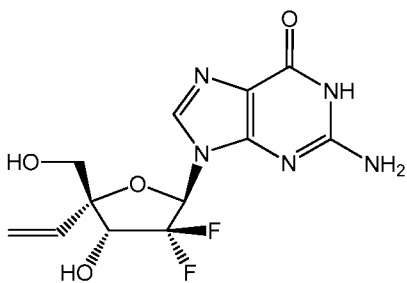
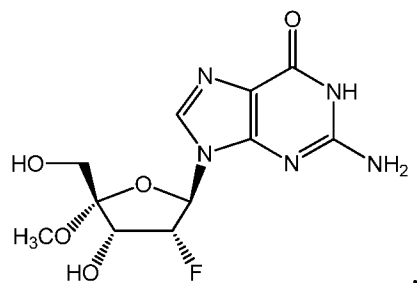
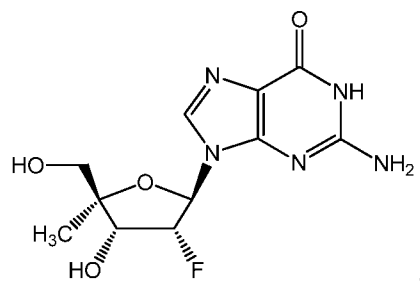
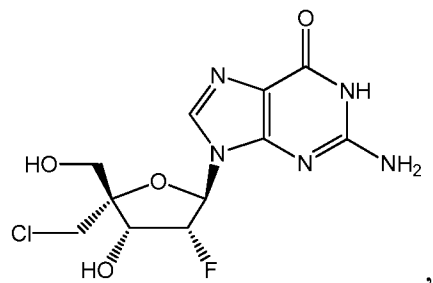
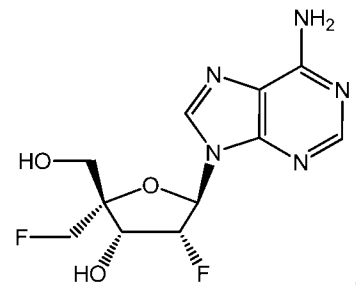
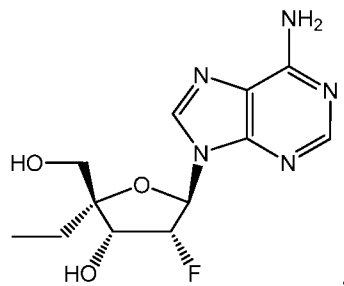
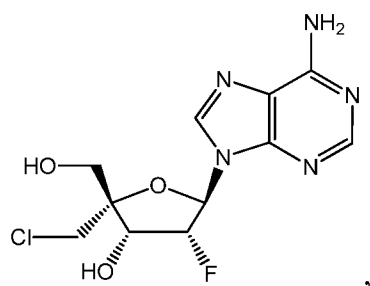
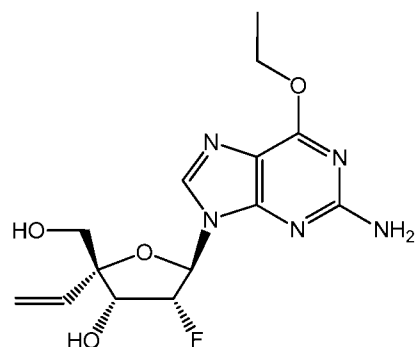
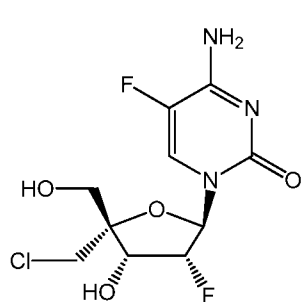
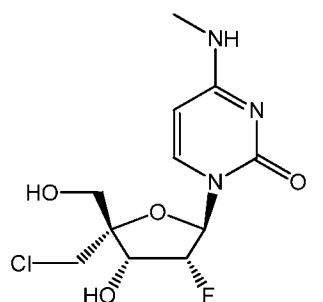
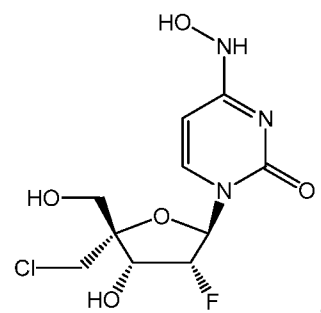
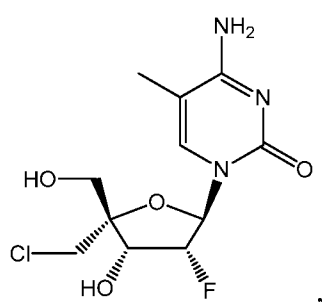
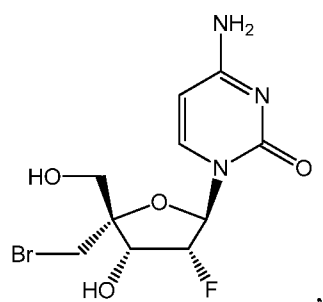
some embodiments of this paragraph, B^{1C} can be an optionally substituted purine base. In other embodiments of this paragraph, B^{1C} can be an optionally substituted pyrimidine base. In some embodiments of this paragraph, B^{1C} can be guanine. In other embodiments of this paragraph, B^{1C} can be 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

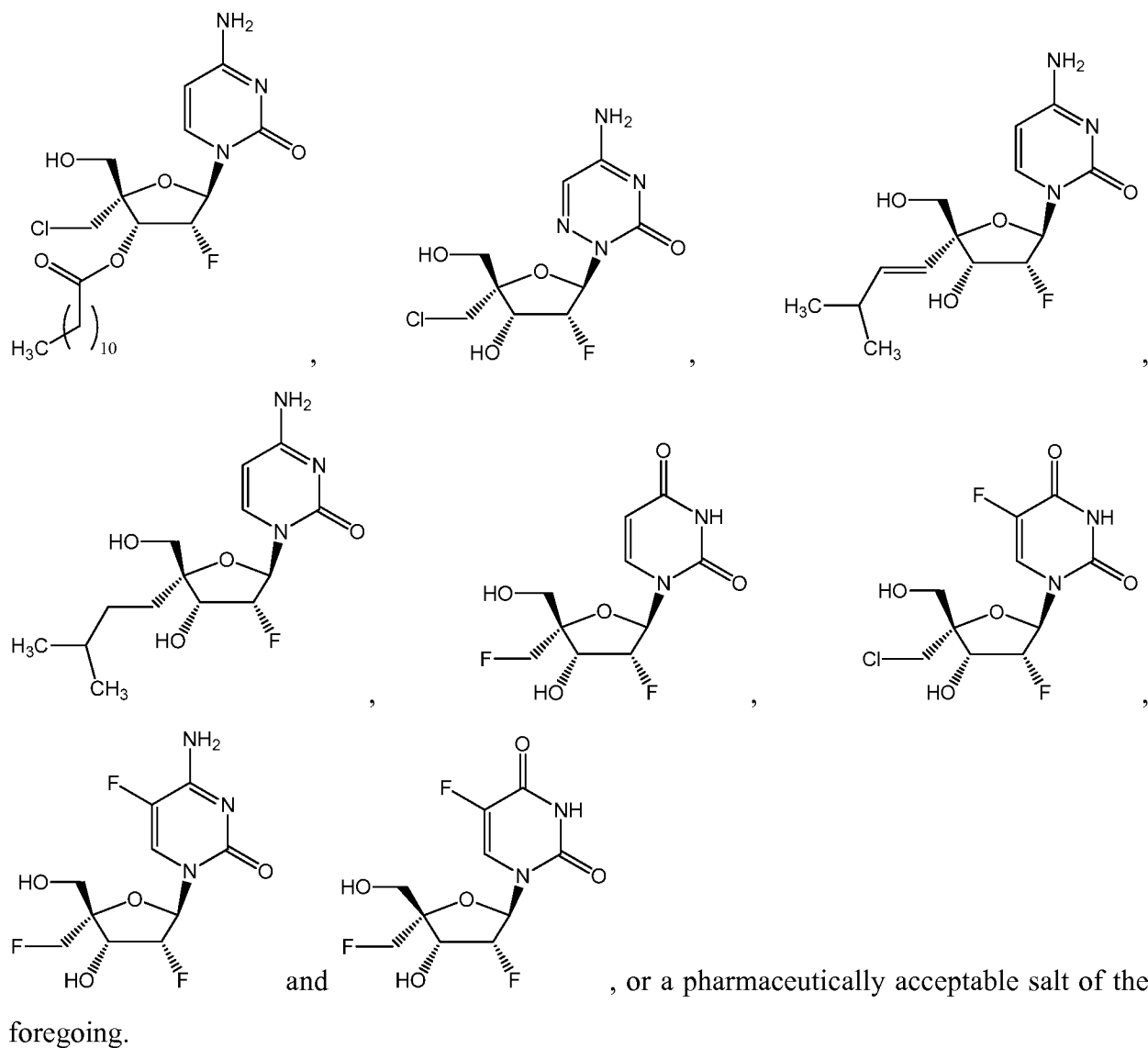
optionally substituted acyl. In still other embodiments of this paragraph, R^{1C} and R^{2C} can form a mono-, di- or tri-phosphate. In yet other embodiments of this paragraph, R^{1C} and R^{2C} can each be an alkylcarbonyloxyalkoxy. In some embodiments of this paragraph, R^{4C} can be OH. In some embodiments of this paragraph, R^{5C} can be F and R^{6C} can be hydrogen.

[0165] Examples of suitable compounds of Formula (I) include, but are not limited to the following:

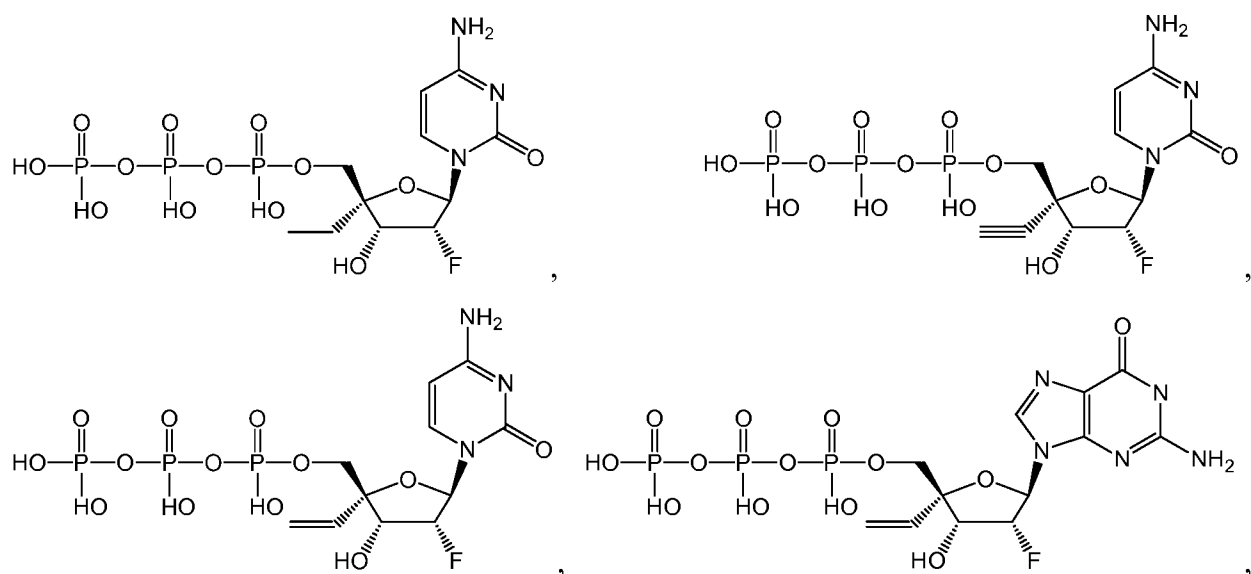


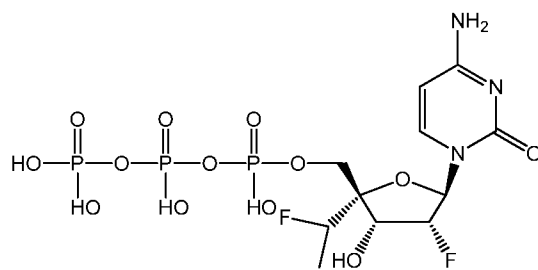
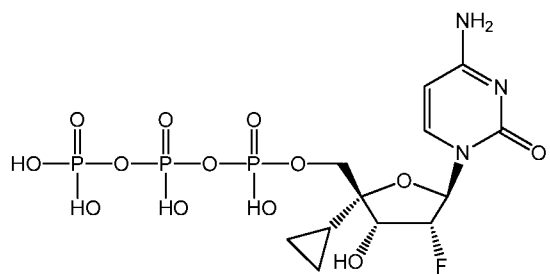
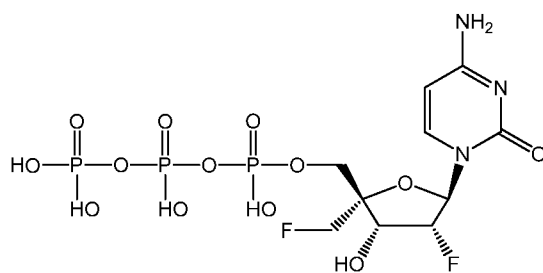
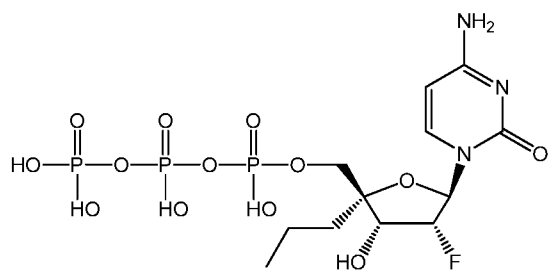
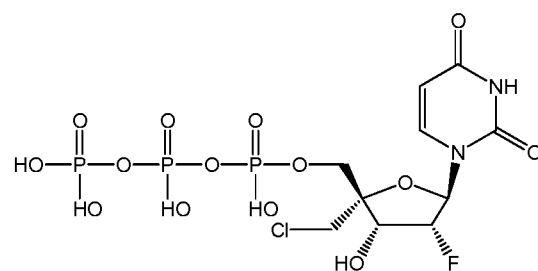
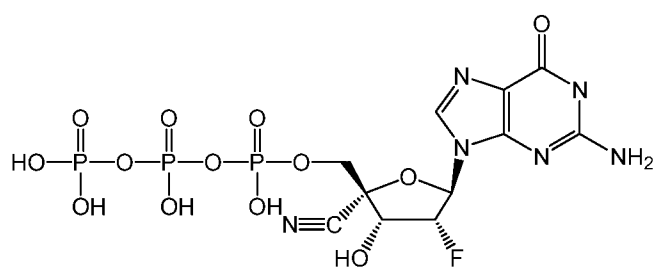
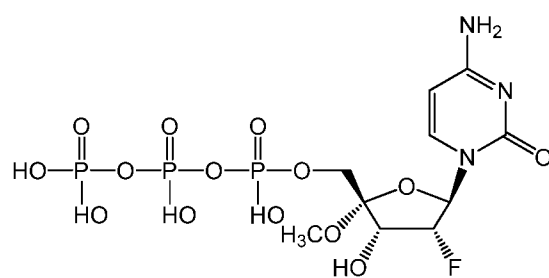
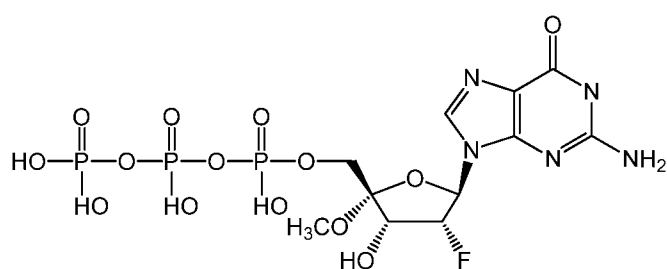
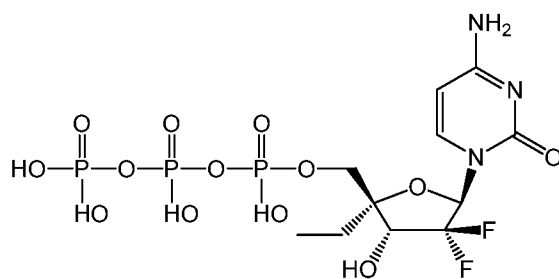
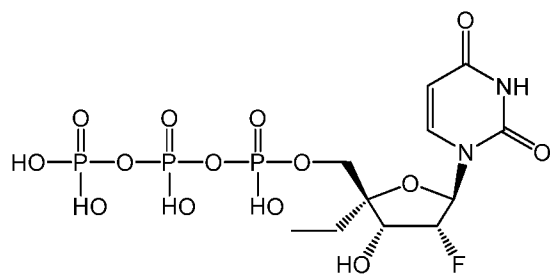
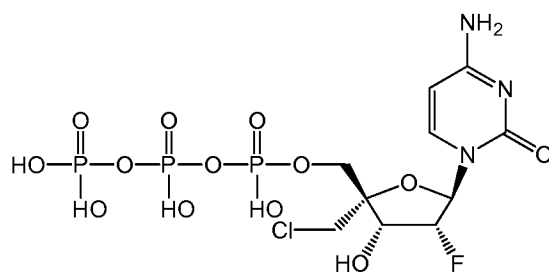
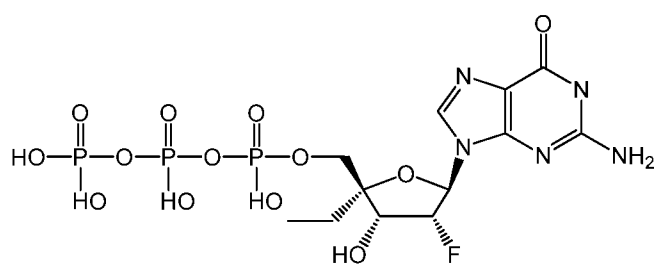


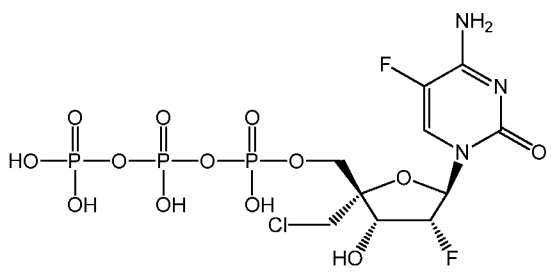
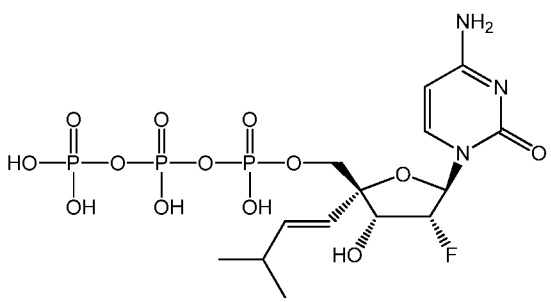
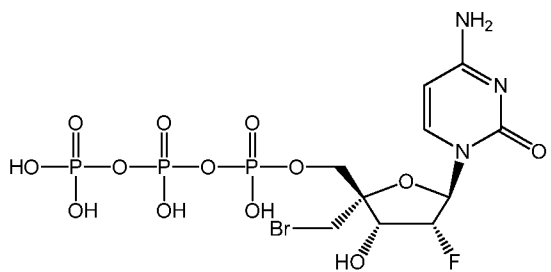
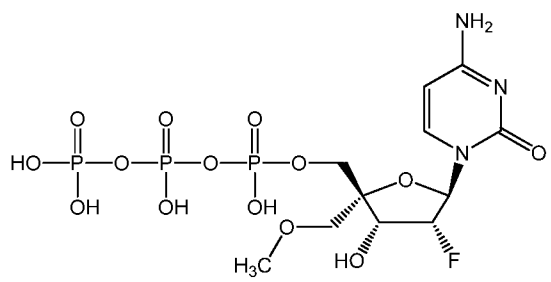


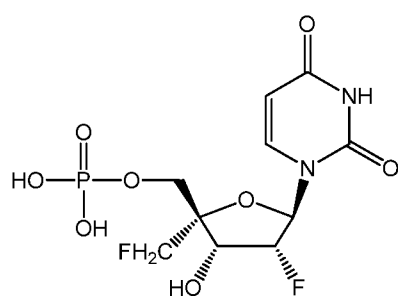
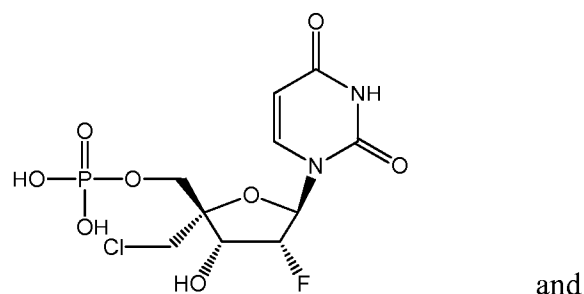
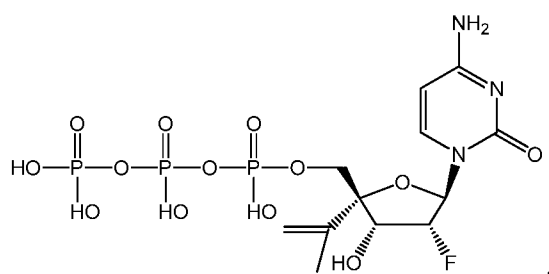
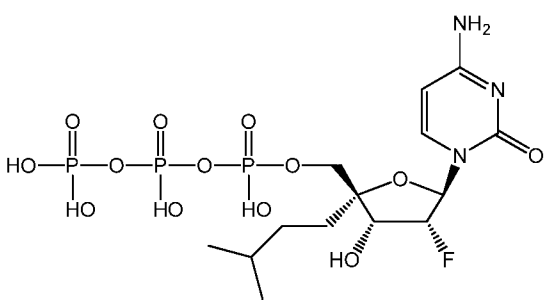
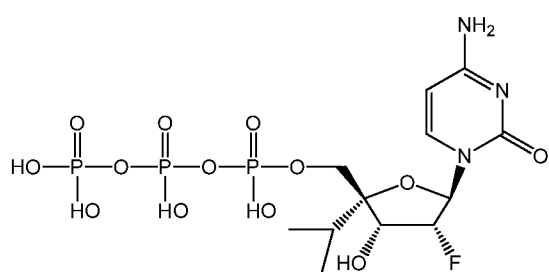
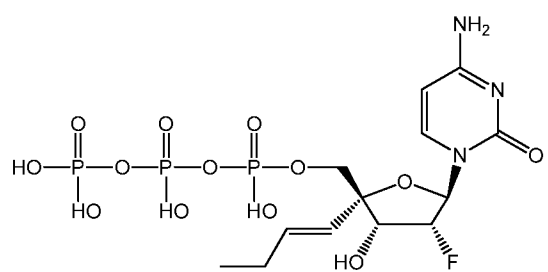
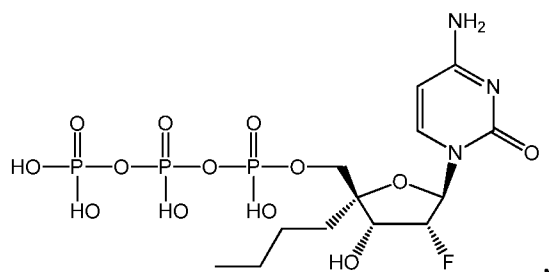
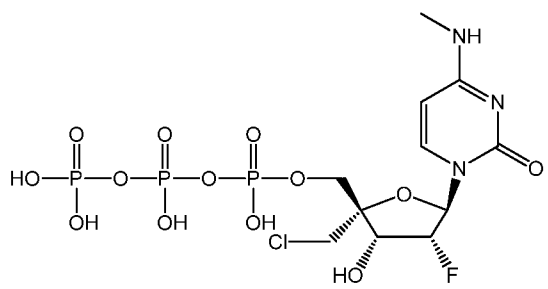
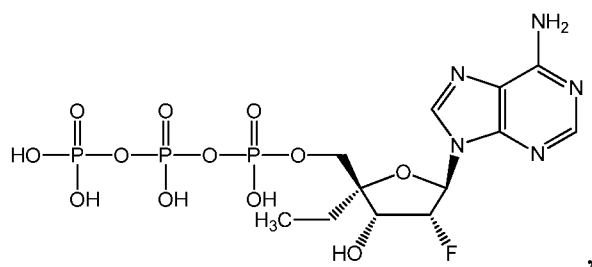


[0166] Additional examples of a compound of Formula (I) include the following:



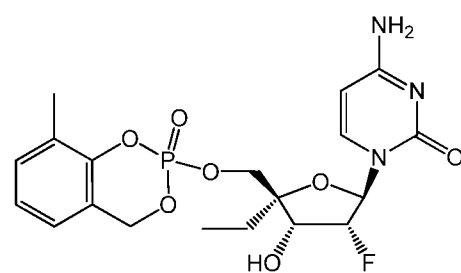
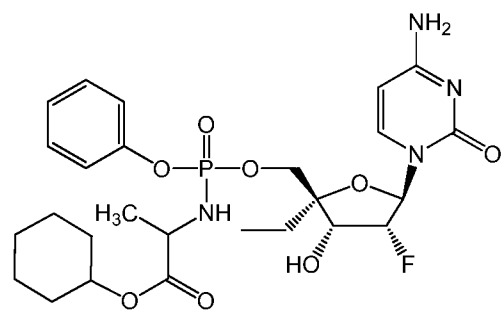
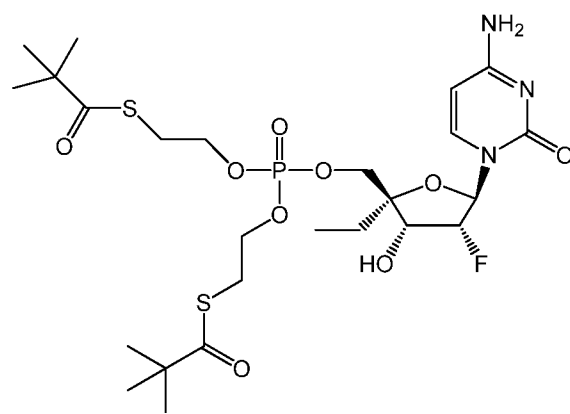
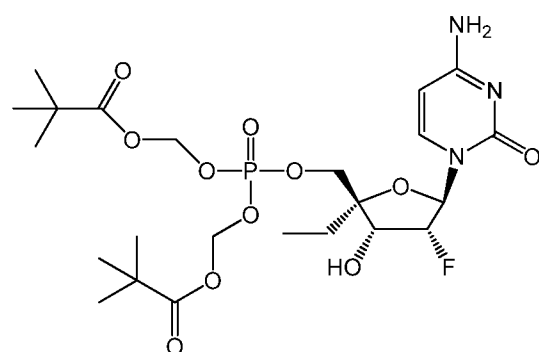
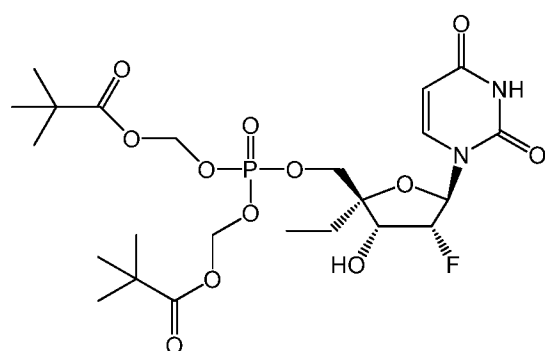
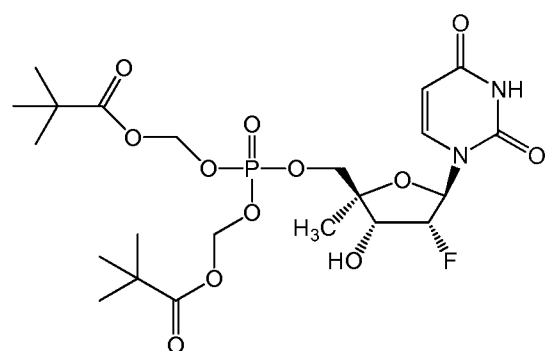
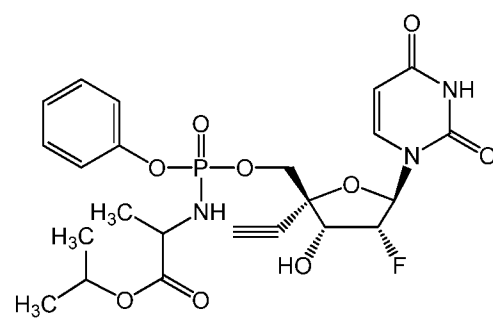
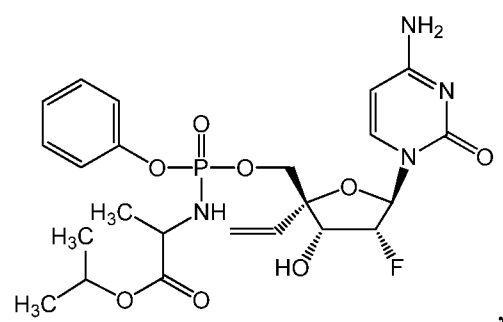


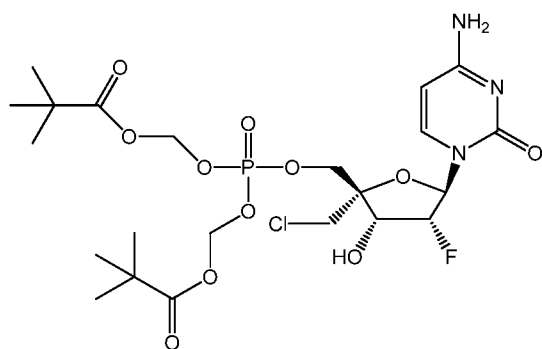




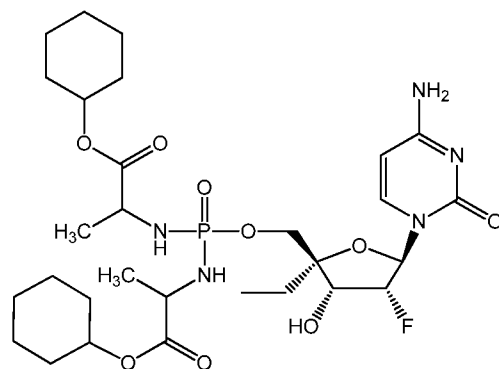
, or a pharmaceutically acceptable salt of the foregoing.

[0167] Further examples of a compound of Formula (I) include, but are not limited to the following:

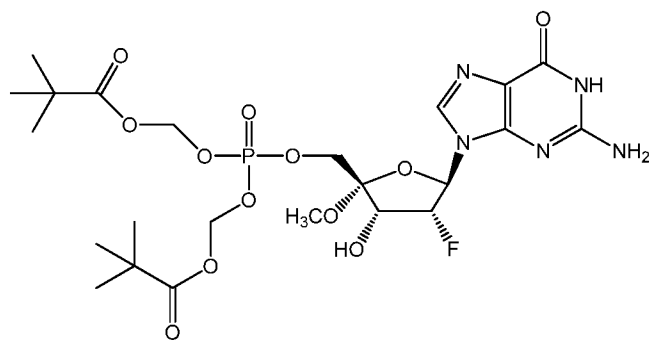




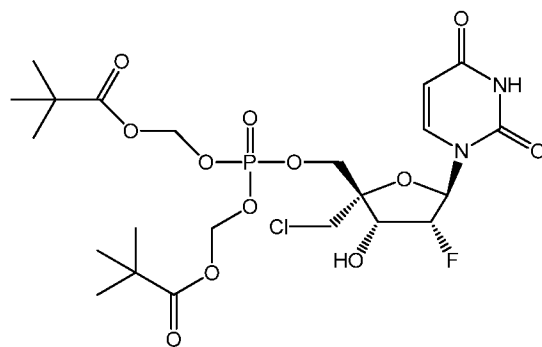
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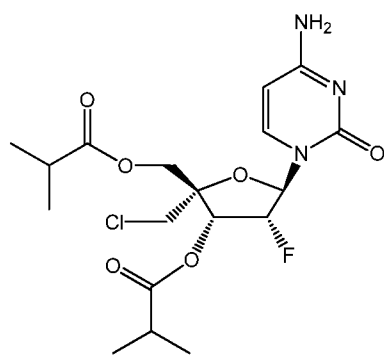
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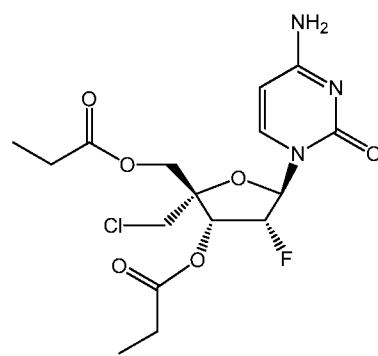
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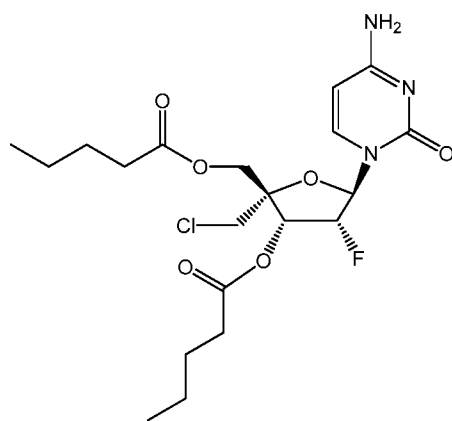
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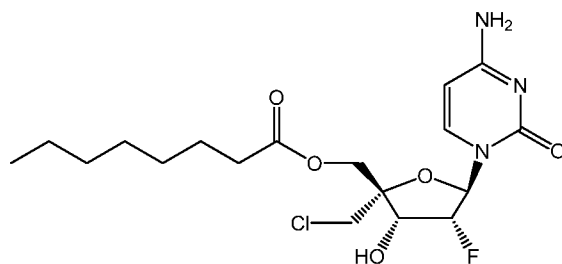


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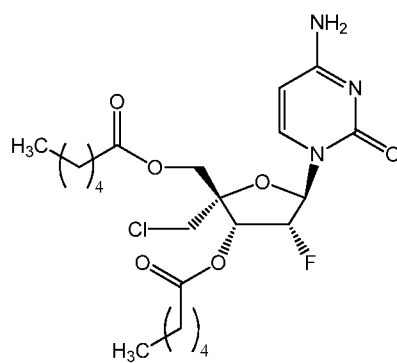
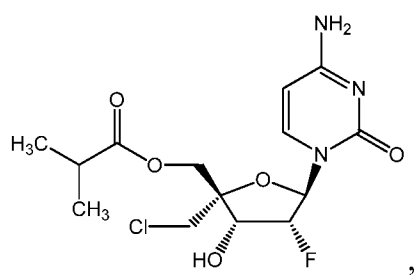
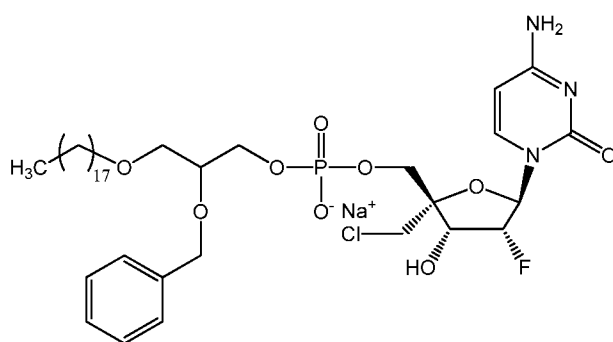
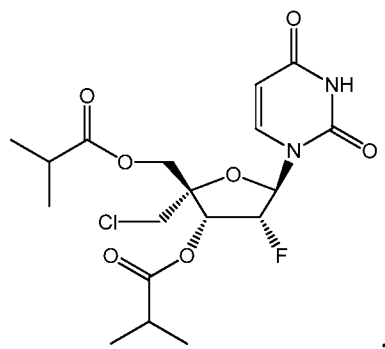
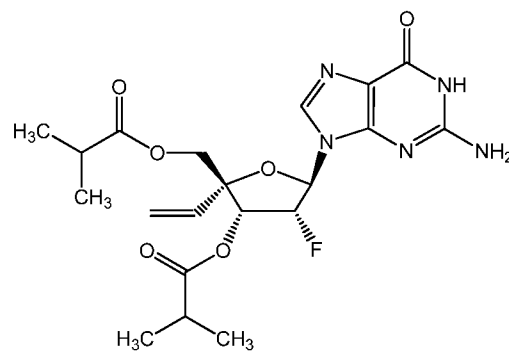
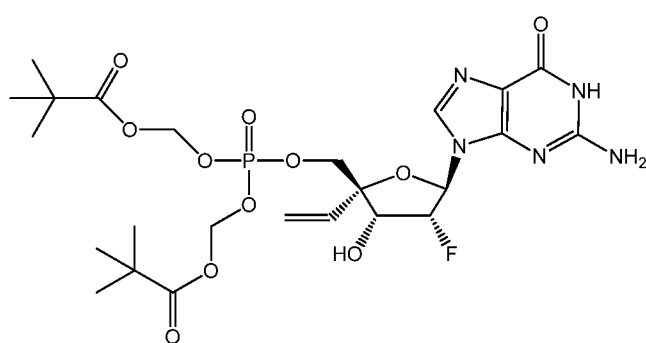
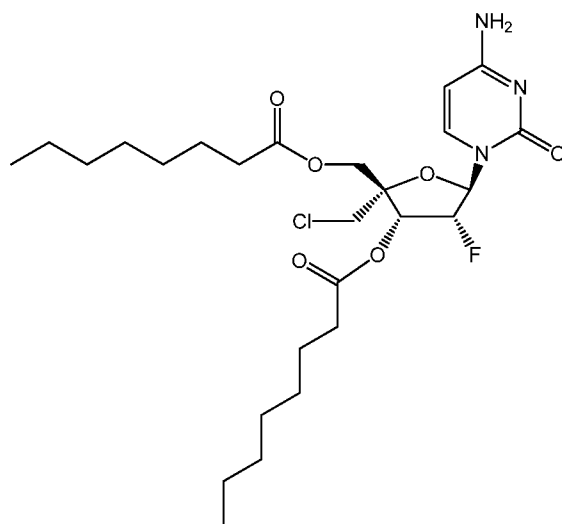
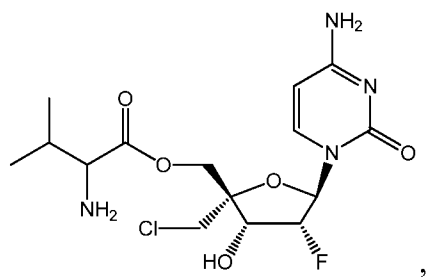


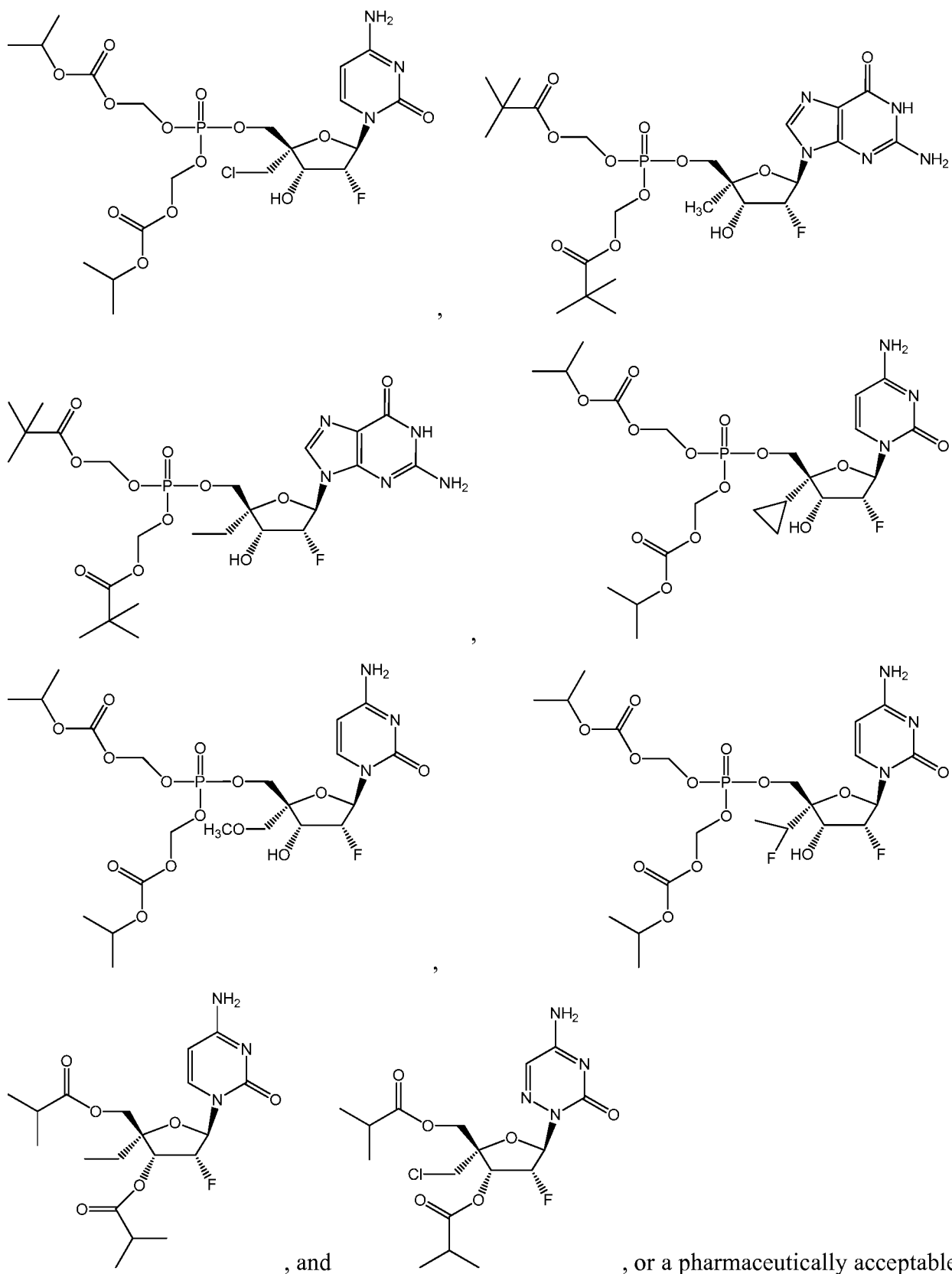
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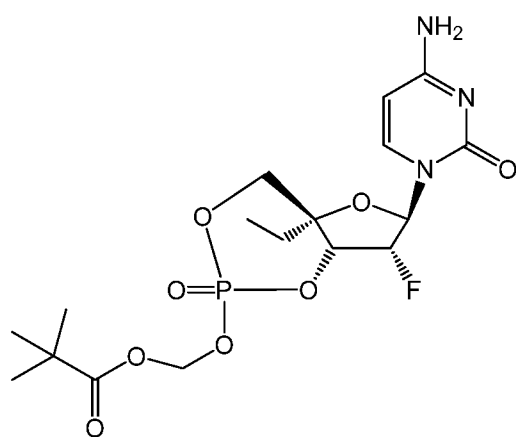


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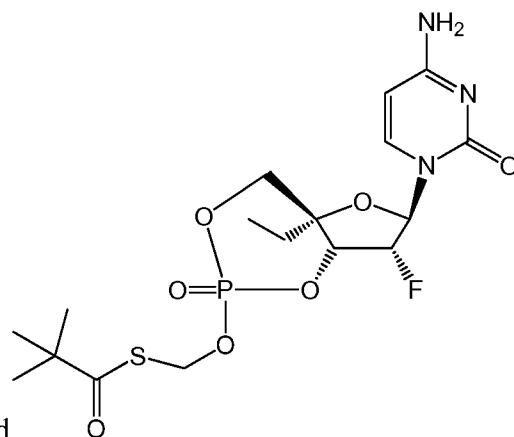




[0168] Examples of a compound of Formula (II) include, but are not limited to, the following:



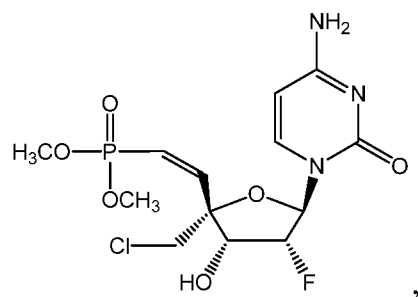
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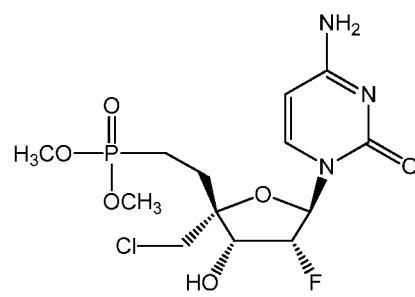
, or a

pharmaceutically acceptable salt of the foregoing.

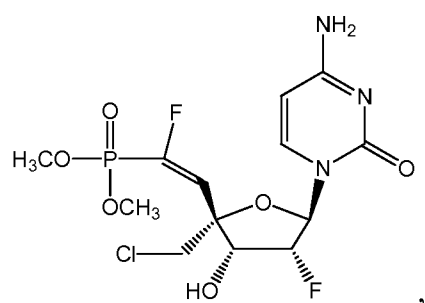
[0169] Examples of a compound of Formula (III) include, but are not limited to, the following:



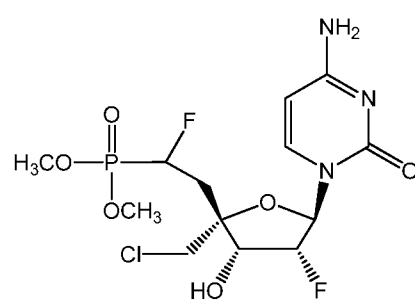
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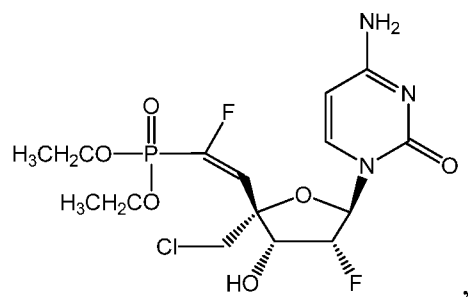
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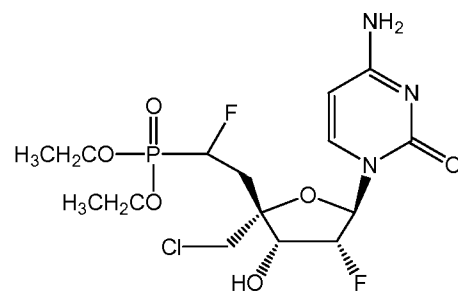
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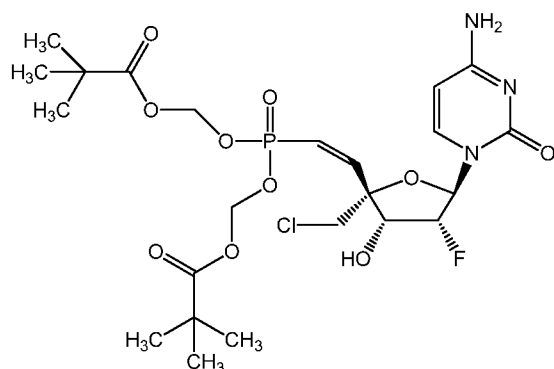
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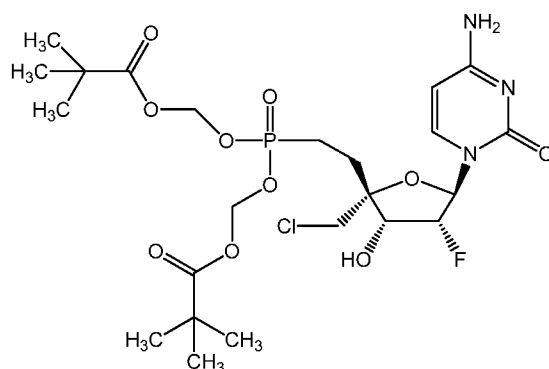
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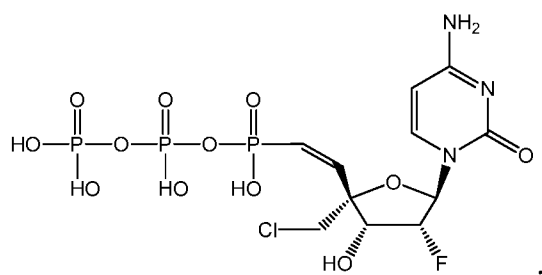
and



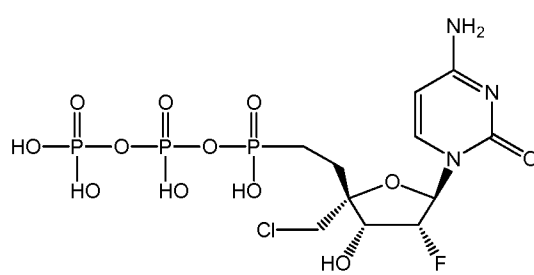
, or a

pharmaceutically acceptable salt of the foregoing.

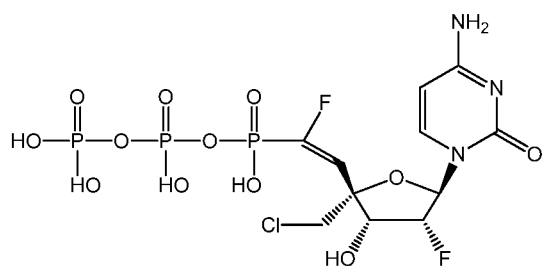
[0170] Further examples of a compound of Formula (III) include, but are not limited to, the following:



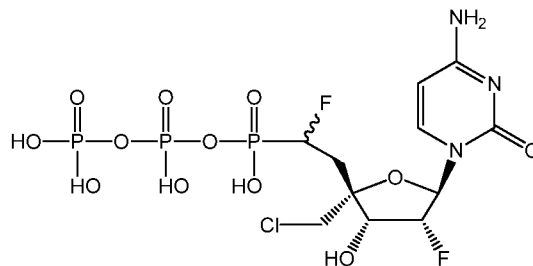
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and



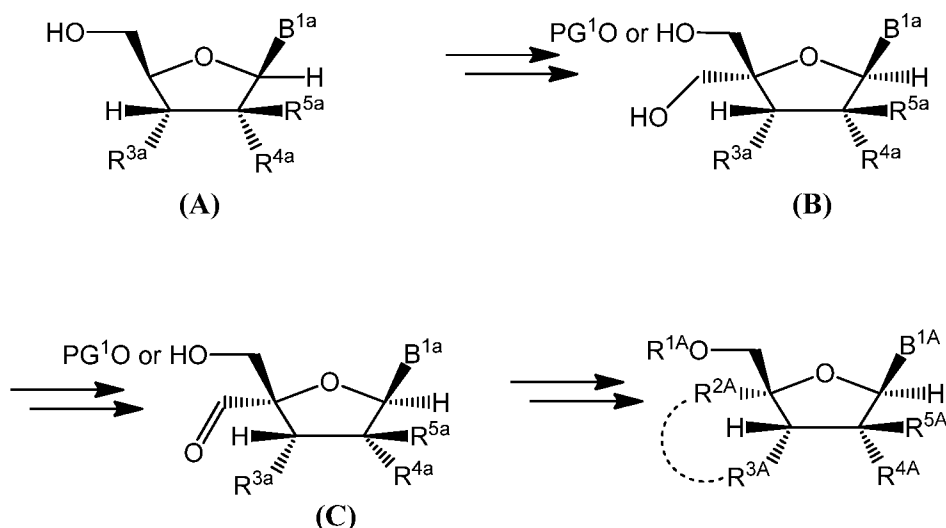
, or a

pharmaceutically acceptable salt of the foregoing.

Synthesis

[0171] 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.

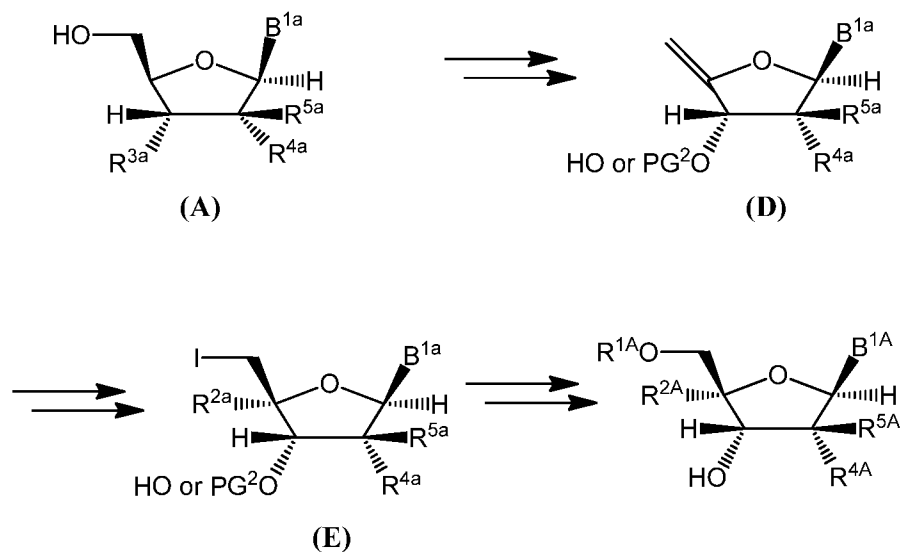
Scheme 1



[0172] 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^{3a} , R^{4a} , R^{5a} , and B^{1a} can be the same as R^{3A} , R^{4A} , R^{5A} , and B^{1A} as described herein for Formula (I), and PG^1 is a suitable protecting group. A hydroxyalkyl group can be formed at the 4'-position of the pentose ring using suitable conditions known to those skilled in the art. Examples of suitable conditions for forming a hydroxyalkyl include the use of 2-iodoxybenzoic acid (IBX) aqueous formaldehyde and sodium borohydride. A compound of Formula (B) can be oxidized to an aldehyde using a suitable oxidizing agent(s) to form a compound of Formula (C). An example of suitable oxidizing agent is Dess-Martin periodinane. 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 $n\text{-BuLi}$, 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.

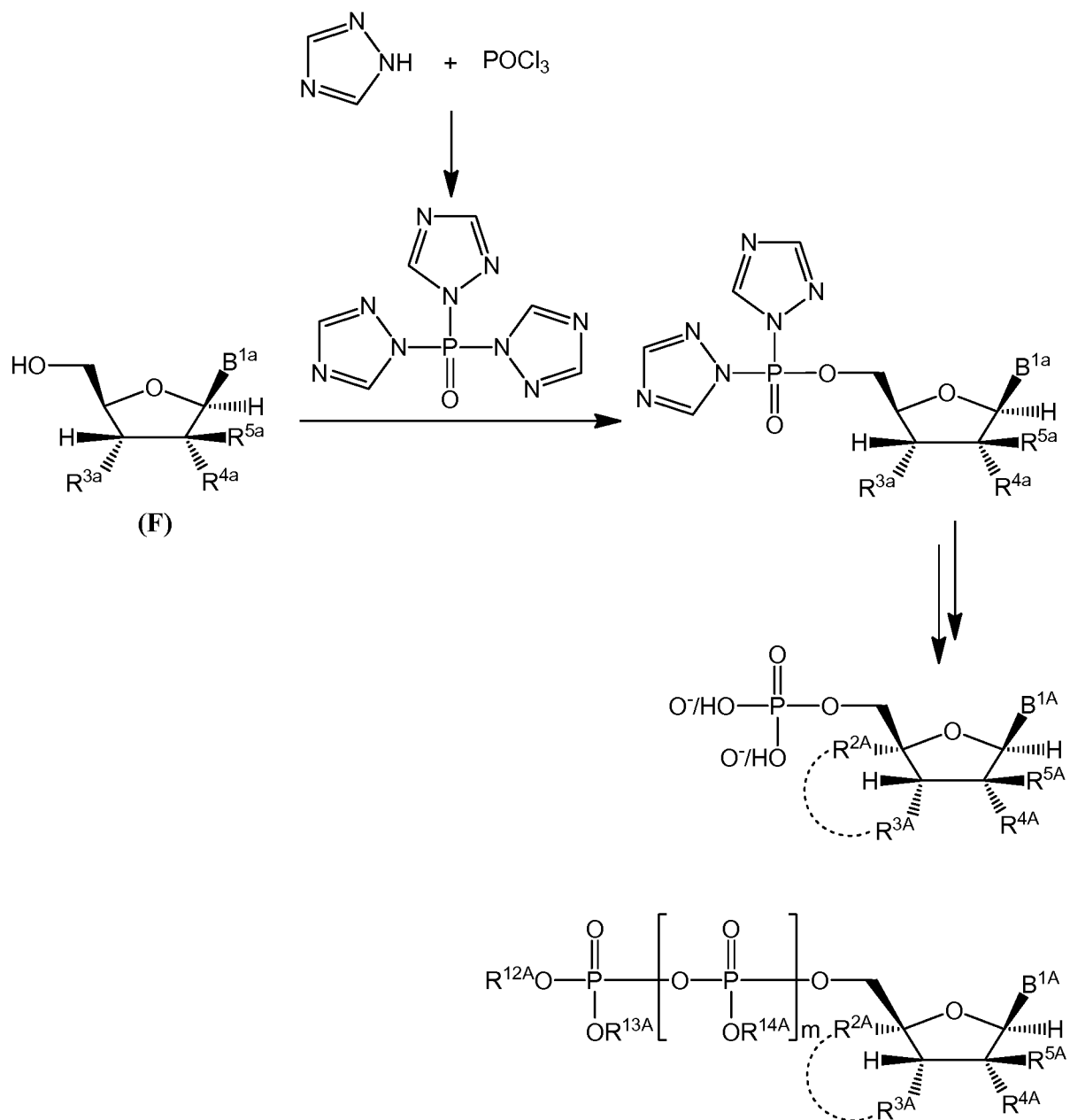
[0173] Alternatively, a compound of Formula (B) can be transformed to a haloalkyl using a suitable agent(s), for example, to an iodide using imidazole, triphenylphosphine and iodine; to a fluoro using diethylaminosulfur trifluoride (DAST); or to a chloro using triphenylphosphine and carbontetrachloride 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

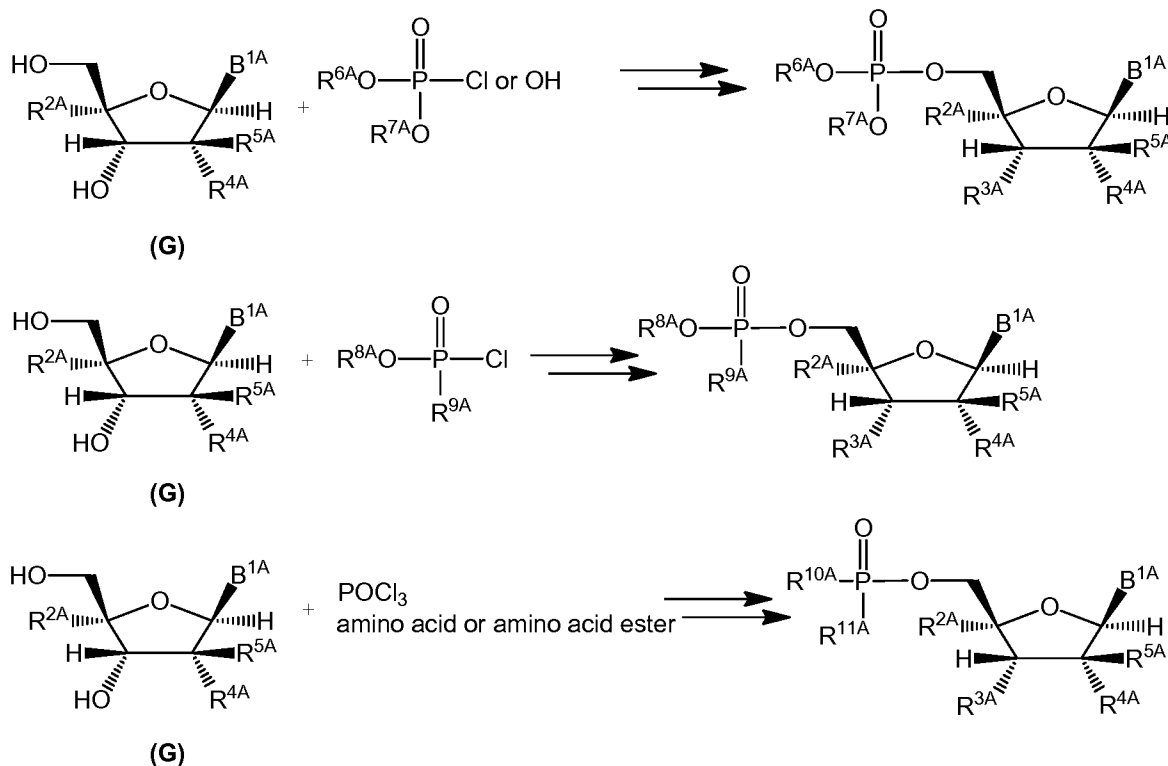


[0174] As shown in Scheme 2, compounds of Formula (I), where R^{2A} is an optionally substituted $-O-C_{1-6}$ alkyl, an optionally substituted $-O-C_{3-6}$ alkenyl or an optionally substituted $-O-C_{3-6}$ alkynyl, can be prepared from a nucleoside, for example, a nucleoside of Formula (A). In Scheme 2, R^{2a} , R^{3a} , R^{4a} , R^{5a} and B^{1a} can be the same as 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



Scheme 4



[0175] Compounds of Formula (I) having a phosphorus containing group attached to the 5'-position of the pentose ring can be prepared using various methods known to those skilled in the art. Examples of methods are shown in Schemes 3 and 4. 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 3, 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.

[0176] 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.

[0177] 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,

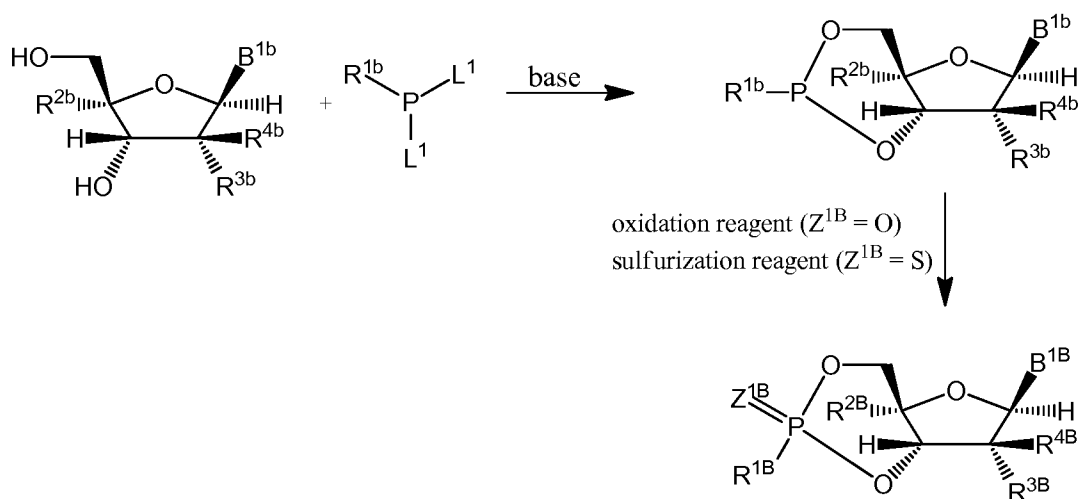
$$\begin{array}{c} \text{S} \\ \parallel \\ \text{R}^{6A}\text{O}-\text{P}-\text{Cl or OH} \\ | \\ \text{R}^{7A}\text{O} \end{array} \quad \text{or}$$

$$\begin{array}{c} \text{S} \\ \parallel \\ \text{R}^{8A}\text{O}-\text{P}-\text{Cl} \\ | \\ \text{R}^{9A} \end{array}$$

. 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).

[0178] 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 3 and 4.

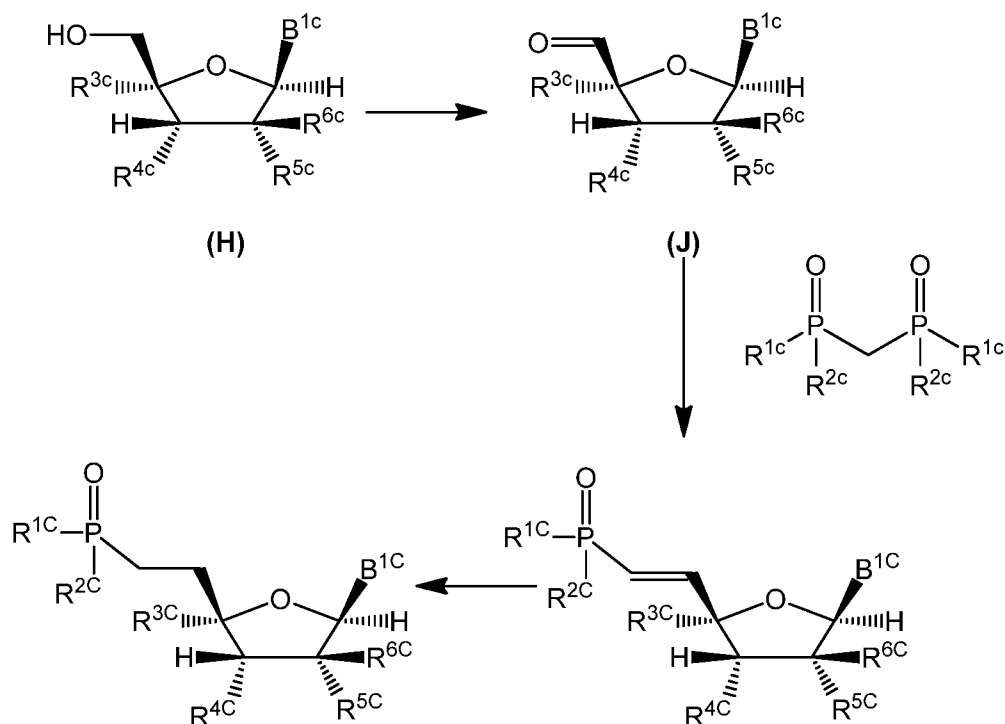
Scheme 5:



[0179] A method for forming a compound of Formula (II) is shown in Scheme 5. In Scheme 5, 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 5, 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, $(\text{R}^{1b})\text{P}(\text{L}^1)_2$, 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 6



[0180] A method for forming a compound of Formula (III) is shown in Scheme 6. In Scheme 6, 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).

[0181] 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.

[0182] 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 NH₂ 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 NH₂ 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-tolyldiphenylmethyl, 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 NH₂ 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

[0183] Some embodiments described herein relates to a pharmaceutical composition, that can include an effective amount of one or more compounds described herein (e.g., a compound of Formula (I), 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.

[0184] 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.

[0185] The term “physiologically acceptable” defines a carrier, diluent or excipient that does not abrogate the biological activity and properties of the compound.

[0186] 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.

[0187] 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.

[0188] 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.

[0189] 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.

[0190] 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.

[0191] Multiple techniques of administering a compound exist in the art including, but not limited to, oral, rectal, topical, aerosol, injection and parenteral delivery, including intramuscular, subcutaneous, intravenous, intramedullary injections, intrathecal, direct intraventricular, intraperitoneal, intranasal and intraocular injections.

[0192] 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.

[0193] The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. The pack or dispenser may also be accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. Such notice, for example, may be the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. Compositions that can include a compound described herein formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

Methods of Use:

[0194] Some embodiments described herein relate to a method of ameliorating, treating and/or preventing a viral infection selected from a paramyxovirus viral infection and an orthomyxovirus viral infection, which can include administering to a subject 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). In some embodiments, the subject is identified as suffering from the viral infection (for example, a paramyxovirus viral infection or an orthomyxovirus viral infection).

[0195] Other embodiments described herein relate to a method of inhibiting viral replication of a virus selected from a paramyxovirus and an orthomyxovirus, which can include contacting a cell infected with the 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).

[0196] Other embodiments described herein relate to the 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, for ameliorating or treating a viral infection caused by a virus selected from a henipavirus, a morbillivirus, a respirovirus, a rubulavirus and a metapneumovirus. Still other embodiments described herein relate to a method for ameliorating or treating a viral infection caused by a virus that can include administering to or contacting a cell in a subject with an effective amount of a compound selected from Formula (I), Formula (II), and Formula (III), or a pharmaceutically acceptable salt of the foregoing, wherein the virus can be selected from a henipavirus, a morbillivirus, a respirovirus, a rubulavirus and a metapneumovirus. Yet still other embodiments described herein relate to using an effective amount of a compound selected from Formula (I), Formula (II), and Formula (III), or a pharmaceutically acceptable salt of the foregoing, for inhibiting replication of a virus selected from a henipavirus, a morbillivirus, a respirovirus, a rubulavirus and a metapneumovirus (for example by inhibiting the virus' polymerase complex).

[0197] In some embodiments, an effective amount of 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, 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 to treat and/or ameliorate a respiratory syncytial viral (RSV) infection. In some embodiments, an effective amount of 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, 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 to prevent a respiratory syncytial viral infection. In some embodiments, an effective amount of 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, 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 to inhibit the replication of a respiratory syncytial virus. In some embodiments, an effective amount of 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, 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 to inhibit the RSV polymerase complex.

[0198] In other embodiments, an effective amount of 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, 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 to treat and/or ameliorate an

influenza viral infection. In other embodiments, an effective amount of 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, 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 to prevent an influenza viral infection. In some embodiments, an effective amount of 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, 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 to inhibit the replication of an influenza virus. In some embodiments, an effective amount of 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, 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 to inhibit the influenza polymerase complex.

[0199] In some embodiments, an effective amount of 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, 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 to treat and/or ameliorate a henipaviral infection. In some embodiments, an effective amount of 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, 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 to prevent a henipaviral infection and/or nipahviral infection. In some embodiments, an effective amount of 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, 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 to inhibit the replication of a henipavirus. In some embodiments, an effective amount of 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, 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 to inhibit the henipavirus polymerase complex and/or nipahvirus polymerase complex.

[0200] In some embodiments, an effective amount of 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, 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 to treat and/or ameliorate a hendraviral infection and/or nipahviral infection. In some embodiments, an effective amount of 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, 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 to prevent a hendraviral infection and/or nipahviral infection. In some embodiments, an effective amount of 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, 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 to inhibit the replication of a hendravirus and/or nipahvirus. In some embodiments, an effective amount of 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, 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 to inhibit the hendravirus polymerase complex and/or nipahvirus polymerase complex.

[0201] In some embodiments, an effective amount of 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, 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 to treat and/or ameliorate a morbilliviral infection. In some embodiments, an effective amount of 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, 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 to prevent morbilliviral infection. In some embodiments, an effective amount of 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, 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 to inhibit the replication of a morbillivirus. In some embodiments, an effective amount of 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, 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 to inhibit the morbillivirus polymerase complex.

[0202] In some embodiments, an effective amount of 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, 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 to treat and/or ameliorate measles. In some embodiments, an effective amount of 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, 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 to prevent measles. In some embodiments, an effective amount of 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, 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 to inhibit the replication of a measles virus. In some embodiments, an effective amount of 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, 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 to inhibit the measles polymerase complex.

[0203] In some embodiments, an effective amount of 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, 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 to treat and/or ameliorate a rubulaviral infection. In some embodiments, an effective amount of 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, 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 to prevent a rubulaviral infection. In some embodiments, an effective amount of 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, 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 to inhibit the replication of a rubulavirus. In some embodiments, an effective amount of 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, 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 to inhibit the rubulavirus polymerase complex.

[0204] In some embodiments, an effective amount of 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, 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 to treat and/or ameliorate mumps. In some embodiments, an effective amount of 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, 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 to prevent mumps. In some embodiments, an effective amount of 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, 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 to inhibit the replication of a mumps virus. In some embodiments, an effective amount of 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, 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 to inhibit the mumps polymerase complex.

[0205] In some embodiments, an effective amount of 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, 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 to treat and/or ameliorate a sendai viral infection. In some embodiments, an effective amount of 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, 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 to prevent a sendai viral infection. In some embodiments, an effective amount of 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, 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 to inhibit the replication of a sendai virus. In some embodiments, an effective amount of 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, 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 to inhibit the sendai virus polymerase complex.

[0206] In some embodiments, an effective amount of 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, 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 to treat and/or ameliorate a respiroviral infection. In some embodiments, an effective amount of 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, 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 to prevent a respiroviral infection. In some embodiments, an effective amount of 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, 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 to inhibit the replication of a respirovirus. In some embodiments, an effective amount of 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, 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 to inhibit the respirovirus polymerase complex.

[0207] In some embodiments, an effective amount of 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, 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 to treat and/or ameliorate a HPIV-1 infection and/or HPIV-3 infection. In some embodiments, an effective amount of 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, 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 to prevent a HPIV-1 infection and/or HPIV-3 infection. In some embodiments, an effective amount of 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, 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 to inhibit the replication of HPIV-1 and/or HPIV-3. In some embodiments, an effective amount of 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, 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 to inhibit the HPIV-1 polymerase complex and/or HPIV-3 polymerase complex.

[0208] In some embodiments, an effective amount of 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, 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 to treat and/or ameliorate a HPIV-2 infection and/or HPIV-4 infection. In some embodiments, an effective amount of 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, 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 to prevent a HPIV-2 infection and/or HPIV-4 infection. In some embodiments, an effective amount of 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, 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 to inhibit the replication of HPIV-2 and/or HPIV-4. In some embodiments, an effective amount of 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, 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 to inhibit the HPIV-2 polymerase complex and/or HPIV-4 polymerase complex.

[0209] In some embodiments, an effective amount of 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, 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 to treat and/or ameliorate a metapneumoviral infection. In some embodiments, an effective amount of 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, 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 to prevent a metapneumoviral infection. In some embodiments, an effective amount of 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, 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 to inhibit the replication of a metapneumovirus. In some embodiments, an effective amount of 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, 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 to inhibit the metapneumovirus

polymerase complex. In some embodiments, including those of this paragraphs, the metapneumovirus can be a human metapneumovirus.

[0210] In some embodiments, an effective amount of 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, 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 and/or ameliorate an upper respiratory viral infection caused by a virus selected from a henipavirus, a morbillivirus, a respirovirus, a rubulavirus, a pneumovirus, a metapneumovirus and influenza virus. In some embodiments, an effective amount of 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, 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 and/or ameliorate a lower respiratory viral infection caused by a virus selected from a henipavirus, a morbillivirus, a respirovirus, a rubulavirus, a pneumovirus, a metapneumovirus and influenza virus. In some embodiments, an effective amount of 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, 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 and/or ameliorate one or more symptoms of an infection caused by a virus selected from a henipavirus, a morbillivirus, a respirovirus, a rubulavirus, a pneumovirus, a metapneumovirus and influenza virus (such as those described herein).

[0211] In some embodiments, an effective amount of 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, 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 and/or ameliorate an upper respiratory viral infection caused by RSV infection, measles, mumps, parainfluenza infection, metapneumovirus and/or influenza infection. In some embodiments, an effective amount of 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, 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 and/or ameliorate a lower respiratory viral infection caused by RSV infection, measles, mumps, parainfluenza infection, metapneumovirus and/or influenza infection. In some embodiments, an effective amount of 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, 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 and/or ameliorate one or more symptoms of an infection caused by RSV infection, measles, mumps, parainfluenza infection, metapneumovirus and/or influenza infection (such as those described herein).

[0212] In some embodiments, an effective amount of 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, 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 and/or ameliorate bronchiolitis and/or tracheobronchitis due to a RSV infection, influenza infection and/or human parainfluenza virus 3 (HPIV-3) infection. In some embodiments, an effective amount of 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, 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 and/or ameliorate pneumonia due to a RSV infection, influenza infection and/or human parainfluenza virus 3 (HPIV-3) infection. In some embodiments, an effective amount of 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, 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 and/or ameliorate croup due to a RSV infection, influenza infection and/or human parainfluenza virus 1 (HPIV-1) infection.

[0213] In some embodiments, an effective amount of 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, 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 and/or ameliorate a fever, cough, runny nose, red eyes, a generalized rash, pneumonia, an ear infection and/or bronchitis due to measles. In some embodiments, an effective amount of 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, 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 and/or ameliorate swelling of the salivary glands, fever, loss of appetite and/or fatigue due to mumps.

[0214] In some embodiments, an effective amount of 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, 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 to prevent an influenza viral

infection. In some embodiments, the influenza viral infection can be an influenza A viral infection. In other embodiments, the influenza viral infection can be an influenza B viral infection. In still other embodiments, the influenza viral infection can be an influenza C viral infection. In some embodiments, 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, can be used to treat and/or ameliorate one or more subtypes of influenza. For example, 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, can be used to treat H1N1 and/or H3N2.

[0215] In some embodiments, an effective amount of 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, 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 to prevent a human parainfluenza viral infection. In some embodiments, the human parainfluenza viral infection can be a human parainfluenza virus 1 (HPIV-1). In other embodiments, the human parainfluenza viral infection can be a human parainfluenza virus 2 (HPIV-2). In other embodiments, the human parainfluenza viral infection can be a human parainfluenza virus 3 (HPIV-3). In other embodiments, the human parainfluenza viral infection can be a human parainfluenza virus 4 (HPIV-4). In some embodiments, 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, can be used to treat and/or ameliorate one or more subtypes of human parainfluenza virus. For example, 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, can be used to treat HPIV-1 and/or HPIV-3.

[0216] 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 paramyxovirus and/or or an orthomyxovirus viral 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 [0084]-[0170].

[0217] 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 paramyxovirus (e.g., RSV) and/or an orthomyxovirus (e.g., influenza).

[0218] 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.

[0219] 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.

[0220] Various indicators for determining the effectiveness of a method for treating a viral infection, such as a paramyxovirus and/or an orthomyxovirus 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.

[0221] 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. 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, an effective amount of a compound of Formulae (I), (II) and/or (III), or a pharmaceutically acceptable salt of the foregoing, can be an amount that is effective to reduce viral load to lower than about 100 genome copies/mL serum. In some embodiments, an effective amount of a compound of 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).

[0222] 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 paramyxovirus and/or an orthomyxovirus 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 paramyxovirus and/or an

orthomyxovirus relative to pre-treatment levels in the range of about 2 to about 5 fold, about 10 to about 20 fold, about 15 to about 40 fold, or about 50 to about 100 fold. In some embodiments, a compound of Formulae (I), (II) and/or (III), or a pharmaceutically acceptable salt of the foregoing, can result in a reduction of paramyxovirus replication in the range of 1 to 1.5 log, 1.5 log to 2 log, 2 log to 2.5 log, 2.5 to 3 log, 3 log to 3.5 log or 3.5 to 4 log more reduction of paramyxovirus replication compared to the reduction of paramyxovirus reduction achieved by ribavirin (Virazole®), or may achieve the same reduction as that of ribavirin (Virazole®) therapy in a shorter period of time, for example, in one week, two weeks, one month, two months, or three months, as compared to the reduction achieved after six months of ribavirin (Virazole®) therapy. 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 orthomyxovirus replication in the range of 1 to 1.5 log, 1.5 log to 2 log, 2 log to 2.5 log, 2.5 to 3 log, 3 log to 3.5 log or 3.5 to 4 log more reduction of orthomyxovirus replication compared to the reduction of orthomyxovirus reduction achieved by oseltamivir (Tamiflu®), or may achieve the same reduction as that of oseltamivir (Tamiflu®) therapy in a shorter period of time, for example, in one week, two weeks, one month, two months, or three months, as compared to the reduction achieved after six months of oseltamivir (Tamiflu®) therapy.

[0223] In some embodiments, an effective amount of 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, is an amount that is effective to achieve a sustained viral response, for example, non-detectable or substantially non-detectable paramyxovirus and/or orthomyxovirus RNA (e.g., less than about 500, less than about 400, less than about 200, or less than about 100 genome copies per milliliter serum) is found in the subject's serum for a period of at least about one week, two weeks, one month, at least about two months, at least about three months, at least about four months, at least about five months, or at least about six months following cessation of therapy.

[0224] After a period of time, infectious agents can develop resistance to one or more therapeutic agents. The term "resistance" as used herein refers to a viral strain displaying a delayed, lessened and/or null response to a therapeutic agent(s). For example, after treatment with an antiviral agent, the viral load of a subject infected with a resistant virus may be reduced to a lesser degree compared to the amount in viral load reduction exhibited by a subject infected with a non-resistant strain. In some embodiments, a compound of Formula (I), a compound of Formula (II) and/or a compound of Formula (III), or a pharmaceutically acceptable salt of the foregoing, can be administered to a subject infected with RSV that is resistant to one or more

different anti-RSV agents (for example, ribavirin). In some embodiments, development of resistant RSV strains can be delayed when subjects are treated with 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, compared to the development of RSV strains resistant to other RSV drugs. In some embodiments, 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 administered to a subject infected with an influenza virus that is resistant to one or more different anti-influenza agents (for example, amantadine and rimantadine). In some embodiments, development of resistant influenza strains can be delayed when subjects are treated with 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, compared to the development of influenza strains resistant to other influenza drugs.

[0225] In some embodiments, 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 decrease the percentage of subjects that experience complications from a RSV viral infection compared to the percentage of subjects that experience complication being treated with ribavirin. In some embodiments, 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 decrease the percentage of subjects that experience complications from an influenza viral infection compared to the percentage of subjects that experience complication being treated with oseltamivir. For example, the percentage of subjects being treated with 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, that experience complications can be 10% , 25%, 40%, 50%, 60%, 70%, 80% and 90% less compared to subjects being treated with ribavirin or oseltamivir.

[0226] In some embodiments, 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, or a pharmaceutical composition that includes a compound described herein, can be used in combination with one or more additional agent(s). In some embodiments, 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 in combination with one or more agents currently used for treating RSV. For example, the additional agent can be ribavirin, palivizumab and RSV-IGIV. For the treatment of RSV, additional agents include but are not limited to ALN-RSV01 (Alnylam Pharmaceuticals), BMS-433771 (1-cyclopropyl-3-[[1-(4-hydroxybutyl)benzimidazol-2-yl]methyl]imidazo[4,5-c]pyridin-2-one), RFI-641 ((4,4"-bis-{4,6-

bis-[3-(bis-carbamoylmethyl-sulfamoyl)-phenylamino]-(1,3,5)triazin-2-ylamino}-biphenyl-2,2"-disulfonic-acid)), RSV604 ((S)-1-(2-fluorophenyl)-3-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]di-azepin-3-yl)-urea), MDT-637 ((4Z)-2-methylsulfanyl-4-[(E)-3-thiophen-2-ylprop-2-enylidene]-1,3-thiazol-5-one), BTA9881, TMC-353121 (Tibotec), MBX-300, YM-53403 (N-cyclopropyl-6-[4-[(2-phenylbenzoyl)amino]benzoyl]-4,5-dihydrothieno[3,2-d][1]benzazepine-2-carboxamide), motavizumab (Medi-524, MedImmune), Medi-559, Medi-534, Medi-557, RV568 and a RSV-F Particle Vaccine (Novavax). In some embodiments, 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 in combination with one or more agents currently used for treating influenza. For example, the additional agent can be amantadine, rimantadine, zanamivir and oseltamivir. For the treatment of influenza, additional agents include but are not limited to peramivir ((1S,2S,3S,4R)-3-[(1S)-1-acetamido-2-ethylbutyl]-4-(diaminomethylideneamino)-2-hydroxycyclopentane-1-carboxylic acid), laninamivir ((4S,5R,6R)-5-acetamido-4-carbamimidamido-6-[(1R,2R)-3-hydroxy-2-methoxypropyl]-5,6-dihydro-4H-pyran-2-carboxylic acid), favipiravir (T-705, 6-fluoro-3-hydroxy-2-pyrazinecarboxamide), fludase (DAS181, NexBio), ADS-8902 (Adamas Pharmaceuticals), IFN- β (Synairgen), beraprost (4-[2-hydroxy-1-[(E)-3-hydroxy-4-methyloct-1-en-6-ynyl]-2,3,3a,8b-tetrahydro-1H-cyclopenta[b][1]benzofuran-5-yl]butanoic acid), Neugene® and VGX-3400X (Inovio).

[0227] In some embodiments, 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 administered with one or more additional agent(s) together in a single pharmaceutical composition. In some embodiments, 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 administered with one or more additional agent(s) as two or more separate pharmaceutical compositions. For example, 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 administered in one pharmaceutical composition, and at least one of the additional agents can be administered in a second pharmaceutical composition. If there are at least two additional agents, one or more of the additional agents can be in a first pharmaceutical composition that includes a compound of Formula (I), a compound of Formula (II) and/or a compound of Formula (III), or a pharmaceutically acceptable salt of the foregoing, and at least one of the other additional agent(s) can be in a second pharmaceutical composition.

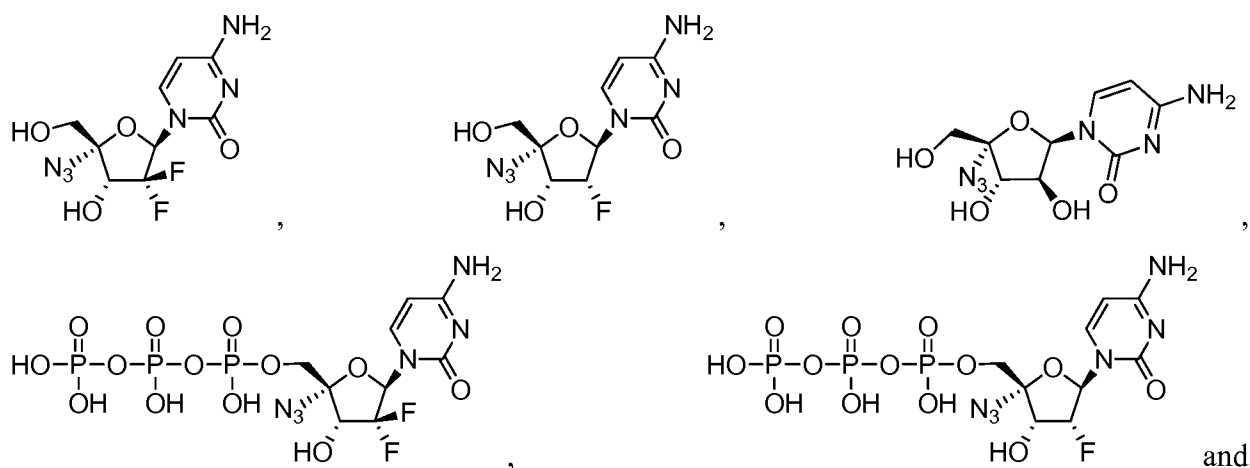
[0228] The order of administration of a compound of Formula (I), a compound of Formula (II) and/or a compound of Formula (III), or a pharmaceutically acceptable salt of the foregoing, with one or more additional agent(s) can vary. In some embodiments, a compound of Formula (I), a compound of Formula (II) and/or a compound of Formula (III), or a pharmaceutically acceptable salt of the foregoing, can be administered prior to all additional agents. In other embodiments, 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 administered prior to at least one additional agent. In still other embodiments, 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 administered concomitantly with one or more additional agent(s). In yet still other embodiments, 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 administered subsequent to the administration of at least one additional agent. In some embodiments, 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 administered subsequent to the administration of all additional agents.

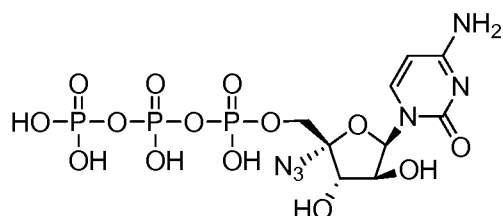
[0229] A potential advantage of utilizing a compound of Formula (I), a compound of Formula (II) and/or a compound of Formula (III), or a pharmaceutically acceptable salt of the foregoing, in combination with one or more additional agent(s) described in paragraph [0226], including pharmaceutically acceptable salts and prodrugs thereof, may be a reduction in the required amount(s) of one or more compounds of paragraph [0226] (including pharmaceutically acceptable salts and prodrugs thereof) that is effective in treating a disease condition disclosed herein (for example, RSV and/or influenza), as compared to the amount required to achieve same therapeutic result when one or more compounds described in paragraph [0226], including pharmaceutically acceptable salts and prodrugs thereof, are administered without a compound of Formula (I), a compound of Formula (II) and/or a compound of Formula (III), or a pharmaceutically acceptable salt the foregoing. For example, the amount of a compound described in paragraph [0226], including a pharmaceutically acceptable salt and prodrug thereof, can be less compared to the amount of the compound described in paragraph [0226], including a pharmaceutically acceptable salt and prodrug thereof, needed to achieve the same viral load reduction when administered as a monotherapy. Another potential advantage of utilizing a compound of Formula (I), a compound of Formula (II) and/or a compound of Formula (III), or a pharmaceutically acceptable salt of the foregoing, in combination with one or more additional agent(s) described in paragraph [0226], including pharmaceutically acceptable salts and

prodrugs thereof, is that the use of two or more compounds having different mechanism of actions can create a higher barrier to the development of resistant viral strains compared to the barrier when a compound is administered as monotherapy.

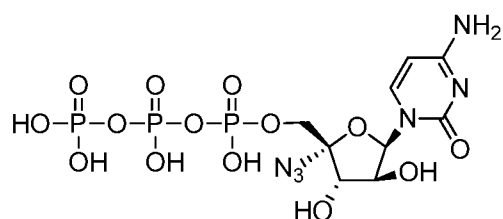
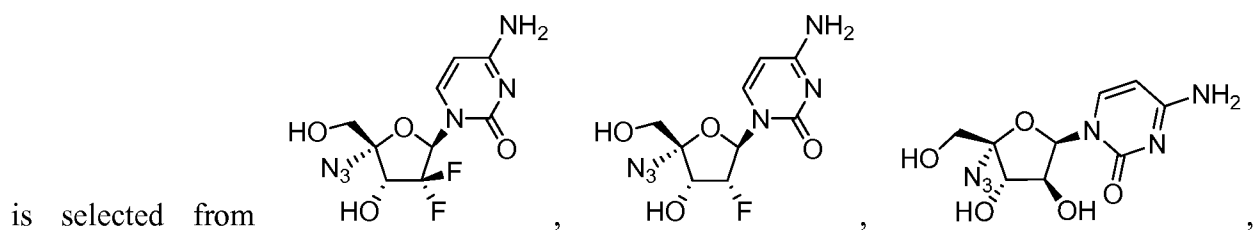
[0230] Additional advantages of utilizing a compound of Formula (I), a compound of Formula (II) and/or a compound of Formula (III), or a pharmaceutically acceptable salt the foregoing, in combination with one or more additional agent(s) described in paragraph [0226], including pharmaceutically acceptable salts and prodrugs thereof, may include little to no cross resistance between a compound of Formula (I), a compound of Formula (II) and/or a compound of Formula (III), or a pharmaceutically acceptable salt the foregoing, and one or more additional agent(s) described in paragraph [0226] (including pharmaceutically acceptable salts and prodrugs thereof); different routes for elimination of a compound of Formula (I), a compound of Formula (II) and/or a compound of Formula (III), or a pharmaceutically acceptable salt the foregoing, and one or more additional agent(s) described in paragraph [0226] (including pharmaceutically acceptable salts and prodrugs thereof); little to no overlapping toxicities between a compound of Formula (I), a compound of Formula (II) and/or a compound of Formula (III), or a pharmaceutically acceptable salt the foregoing, and one or more additional agent(s) described in paragraph [0226] (including pharmaceutically acceptable salts and prodrugs thereof); little to no significant effects on cytochrome P450; and/or little to no pharmacokinetic interactions between a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and one or more additional agent(s) described in paragraph [0226] (including pharmaceutically acceptable salts and prodrugs thereof).

[0231] Some embodiments described herein relate to the use of an effective amount of a compound, or a pharmaceutically acceptable salt thereof, for ameliorating or treating a viral infection caused by a virus selected from a henipavirus, a morbillivirus, a respirovirus, a rubulavirus and a metapneumovirus, wherein the compound can be selected from:

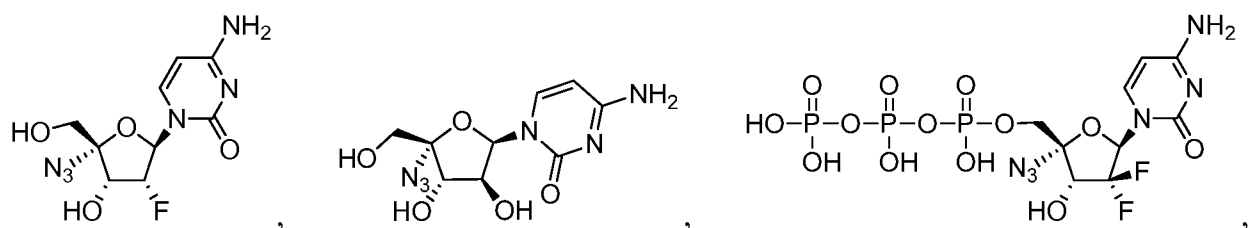
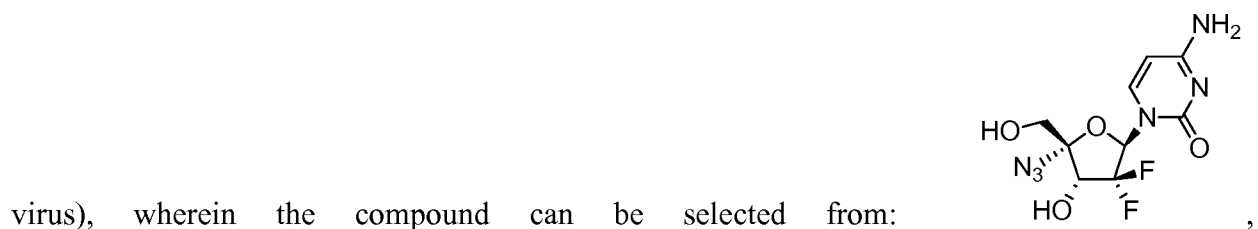


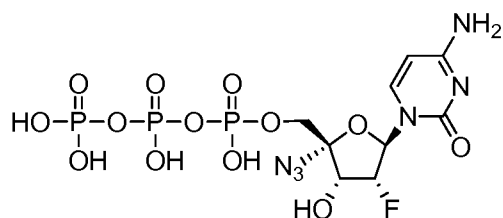


. Other embodiments described herein related to a method for ameliorating or treating a viral infection caused by a virus that can include administering to or contacting a cell in a subject with an effective amount of a compound, or a pharmaceutically acceptable salt of thereof, wherein the virus is selected from a henipavirus, a morbillivirus, a respirovirus, a rubulavirus and a metapneumovirus, and wherein the compound

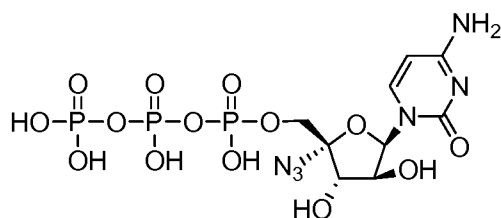


. Still other embodiments described herein relate to using an effective amount of a compound, or a pharmaceutically acceptable salt thereof, for inhibiting the replication of a virus selected from a henipavirus, a morbillivirus, a respirovirus, a rubulavirus and a metapneumovirus (for example, by inhibiting the polymerase complex of the





and



. In some embodiments of this paragraph, the virus can be a henipavirus (for example, a nipahvirus). In other embodiments of this paragraph, the virus can be a morbillivirus, such as measles virus. In still other embodiments of this paragraph, the virus can be a respirovirus. In some embodiments, the respirovirus can be human parainfluenza virus 1. In other embodiments, the respirovirus can be human parainfluenza virus 3. In yet still other embodiments of this paragraph, the virus can be a rubulavirus. . In some embodiments, the rubulavirus can be human parainfluenza virus 2. . In other embodiments, the rubulavirus can be human parainfluenza virus 4. . In still other embodiments, the rubulavirus can be the mumps virus. In some embodiments of this paragraph, the virus can be a metapneumovirus, such as the human metapneumovirus.

[0232] 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.

[0233] 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.

[0234] In instances where human dosages for compounds have been established for at least some condition, those same dosages may be used, or dosages that are between about 0.1% and 500%, more preferably between about 25% and 250% of the established human

dosage. Where no human dosage is established, as will be the case for newly-discovered pharmaceutical compositions, a suitable human dosage can be inferred from ED₅₀ or ID₅₀ values, or other appropriate values derived from *in vitro* or *in vivo* studies, as qualified by toxicity studies and efficacy studies in animals.

[0235] 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.

[0236] 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.

[0237] It should be noted that the attending physician would know how to and when to terminate, interrupt, or adjust administration due to toxicity or organ dysfunctions. Conversely, the attending physician would also know to adjust treatment to higher levels if the clinical response were not adequate (precluding toxicity). The magnitude of an administered dose in the management of the disorder of interest will vary with the severity of the condition to be treated and to the route of administration. The severity of the condition may, for example, be evaluated, in part, by standard prognostic evaluation methods. Further, the dose and perhaps dose frequency, will also vary according to the age, body weight, and response of the individual patient. A program comparable to that discussed above may be used in veterinary medicine.

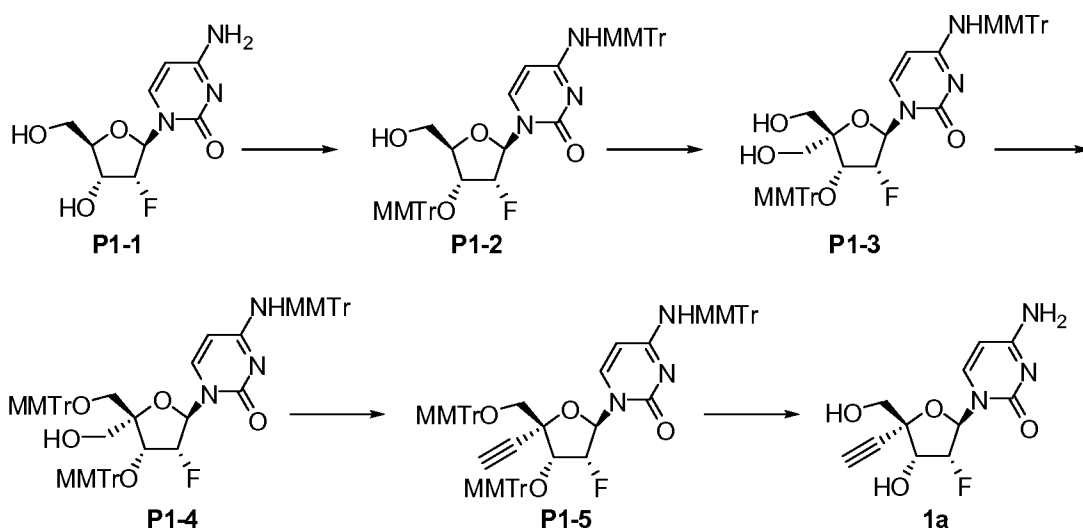
[0238] Compounds disclosed herein can be evaluated for efficacy and toxicity using known methods. For example, the toxicology of a particular compound, or of a subset of the compounds, sharing certain chemical moieties, may be established by determining *in vitro* toxicity towards a cell line, such as 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.

EXAMPLES

[0239] 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)



[0240] Preparation of (P1-2): 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 NaHCO₃ 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), AgNO₃ (25 g, 149.2 mmol) and MMTroCl (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).

[0241] Preparation of (P1-3): 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. NaHCO₃, dried over Na₂SO₄ 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. NaBH₄ (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 Na₂SO₄ 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%). ¹H NMR (CDCl₃, 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).

[0242] Preparation of (P1-4): 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. NaHCO₃. 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%). ¹H NMR (CDCl₃, 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).

[0243] The obtained intermediate was dissolved in anhydrous DCM (20 mL) and collidine (360 mg, 3 mmol), and AgNO₃ (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

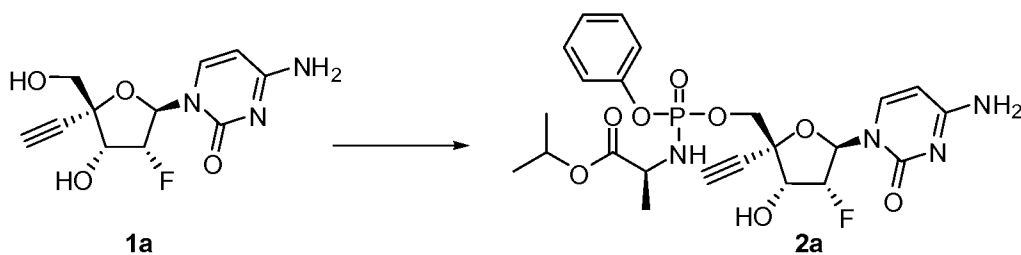
with water, and the organic layer was separated and concentrated. The residue was purified on a silica gel column (0.5% MeOH in DCM) to give the fully protected intermediate as a yellow solid (3.3 g, 80%). The intermediate was dissolved in 1M TBAF in THF (5 mL) and was stirred at R.T. for 2 hours. The 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%).

[0244] Preparation of (P1-5): **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. Na₂S₂O₃ and Na₂CO₃. The organic layer was separated and dried, and then concentrated to give the aldehyde intermediate as a white solid.

[0245] A solution of ClCH₂PPh₃Br (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 NH₄Cl 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 NH₄Cl 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%).

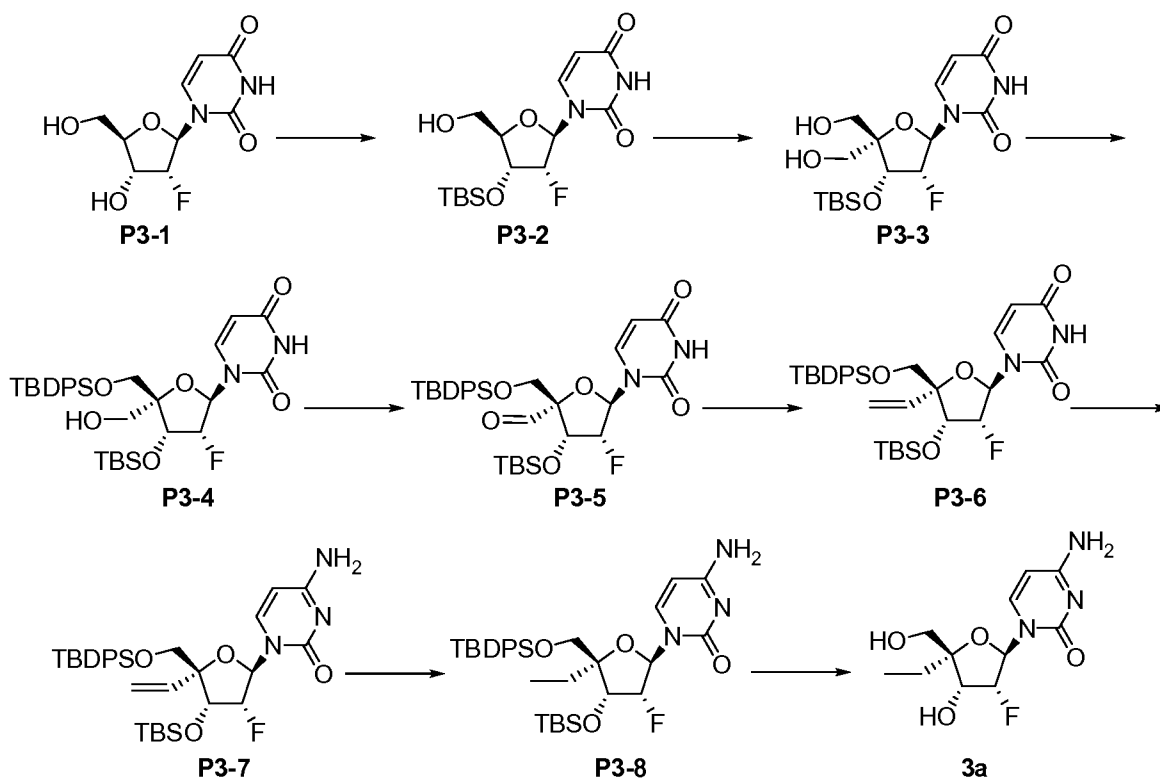
[0246] Preparation of (1a): **P1-5** (910 mg, 0.84 mmol) was suspended in 80% CH₃COOH (50 mL), and the reaction mixture was stirred at 40°C for 15 hours. The solvents were evaporated, and the residue was co-evaporated with toluene to remove traces of acid and water. The residue was purified by HPLC separation (MeCN and 0.1% HCOOH in water) to give pure compound **1a** as a white solid (101 mg, 45%). ¹H NMR (MeOD, 400 MHz) δ 7.90 (d, *J* = 7.2 Hz, 1H), 6.04 (d, *J* = 19.6 Hz, 1H), 5.87 (d, *J* = 7.6 Hz, 1H), 5.00 (dd, *J*₁ = 5.2 Hz, *J*₂ = 53.6 Hz, 1H), 4.47 (dd, *J*₁ = 5.2 Hz, *J*₂ = 22.8 Hz, 1H), 3.86 (d, *J* = 12.4 Hz, 1H), 3.73 (d, *J* = 12.4 Hz, 1H), 3.08 (s, 1H); ESI-TOF-MS: *m/z* 270.09 [M + H]⁺, 539.17 [2M + H]⁺.

EXAMPLE 2
Preparation of Compound (2a)



[0247] To a stirred solution of compound **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 compound **2a** as a white solid (a mixture of two P isomers, 8.0 mg, 7.9 %). ¹H NMR (MeOD, 400 MHz) δ 7.71, 7.68 (2d, *J* = 7.6 Hz, 1H), 7.17-7.37 (m, 5H), 6.02, 6.00 (2d, *J* = 20.4 Hz, 1H), 5.90, 5.86 (2d, *J* = 7.6 Hz, 1H), 5.03-5.18 (m, 1H), 4.91-4.99 (m, 1H), 4.45-4.55 (m, 1H), 4.34-4.43 (m, 1H), 4.26-4.33 (m, 1H), 3.87-3.95 (m, 1H), 3.25, 3.22 (2s, 1H), 1.29-1.34 (m, 3H), 1.20-1.22 (m, 6H). ³¹P NMR (MeOD, 162 MHz) δ 3.44, 3.27. ESI-LCMS: *m/z* 539.0 [M + H]⁺.

EXAMPLE 3
Preparation of Compound (3a)



[0248] Preparation of (P3-2): 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 Na₂SO₄ 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 NaHCO₃ and brine. The organic layer was dried over Na₂SO₄, 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 NaHCO₃ solution and brine. The organic layer was dried over Na₂SO₄ 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. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 11.39 (s, 1H), 7.88 (d, *J* = 7.2 Hz, 1H), 5.89 (dd, *J*₁ = 18.0 Hz, *J*₂ = 2.0 Hz, 1H), 5.64 (d, *J* = 8.0 Hz, 1H), 5.21 (dd, *J*₁ = *J*₂ = 7.2 Hz, 1H), 5.18~5.03 (m, 1H), 4.37~4.29 (m, 1H), 3.86 (dd, *J*₁ = *J*₂ = 3.2 Hz, 3H), 3.78~3.73 (m, 1H), 3.51~3.56 (m, 1H), 3.31 (s, 1H), 0.89 (s, 9H), 0.11 (s, 6H); ESI-MS: *m/z* 802 [M + H]⁺.

[0249] Preparation of (P3-3): To a solution of **P3-2** (131.2 g, 364.0 mmol) in anhydrous CH₃CN (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°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% CH₂O (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 NaBH₄ (51.2 g, 1.354 mol). The mixture was stirred at R.T. for 30 minutes. The mixture was quenched with saturated aq. NH₄Cl and extracted with EA. The organic layer was dried over Na₂SO₄ 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.

[0250] Preparation of (P3-4): 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 CH₂Cl₂ (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 Na₂SO₄. 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 NaHCO₃ solution and brine. The organic layer was dried over Na₂SO₄ 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. ¹H NMR (CD₃OD, 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).

[0251] Preparation of (P3-5): 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. NaHCO₃ 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%).

[0252] Preparation of (P3-6): 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

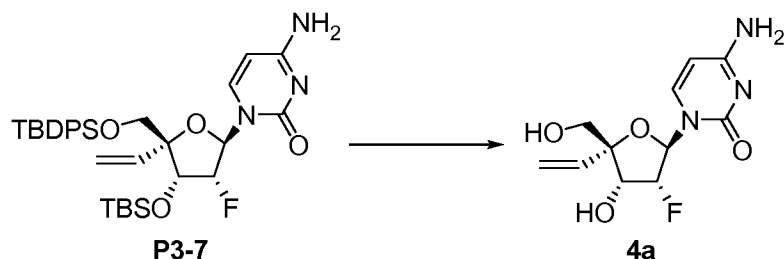
mmol) at -78°C under nitrogen. The reaction was stirred at 0°C for 30 minutes. A solution of **P3-5** (10.1 g, 16.2 mmol) in anhydrous THF (70 mL) was added dropwise at 0°C under nitrogen. The reaction was stirred at R.T. for 1.5 hours. The reaction was quenched by NH_4Cl and extracted with EtOAc. The 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%). ^1H 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).

[0253] Preparation of (P3-7): 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%).

[0254] Preparation of (P3-8): 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%).

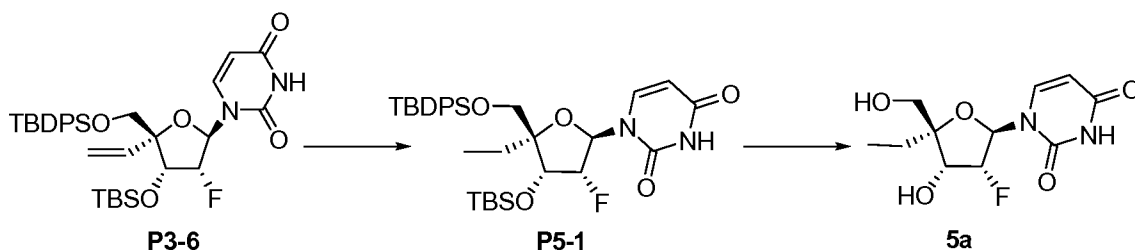
[0255] Preparation of (3a): To a solution of **P3-8** (5.4 g, 8.6 mmol) in MeOH (60 mL) was added NH_4F (10.0 g), and the reaction mixture was refluxed overnight. After cooling to R.T., the mixture was filtered, and the filtrate was concentrated. The crude product was purified by silica gel column chromatography (10% MeOH in DCM) to give compound **3a** as a white solid (1.6 g, 67.8%). ^1H NMR (CD_3OD , 400 MHz) δ 8.08 (d, $J = 7.6$ Hz, 1H), 6.07 (dd, $J_1 = 3.2$ Hz, $J_2 = 15.6$ Hz, 1H), 5.88 (d, $J = 7.2$ Hz, 1H), 5.04 (ddd, $J_1 = 3.2$ Hz, $J_2 = 5.2$ Hz, $J_3 = 54.0$ Hz, 1H), 4.45 (dd, $J_1 = 5.2$ Hz, $J_2 = 17.2$ Hz, 1H), 3.76 (d, $J = 12.0$ Hz, 1H), 3.57 (d, $J = 12.0$ Hz, 1H), 1.78-1.85 (m, 1H), 1.58-1.67 (m, 1H), 0.95 (t, $J = 7.6$ Hz, 3H); ESI-MS: m/z 274 $[\text{M} + \text{H}]^+$, 547 $[2\text{M} + \text{H}]^+$.

EXAMPLE 4
Preparation of Compound (4a)



[0256] 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 compound **4a** as a white solid (82 mg, 67.2% $\pm$ 1.6 g, 67.8%). ^1H NMR (CD_3OD , 400 MHz) δ 8.11 (d, $J = 7.6$ Hz, 1H), 5.99-6.08 (m, 2H), 5.88 (d, $J = 7.6$ Hz, 1H), 5.47 (dd, $J_1 = 1.2$ Hz, $J_2 = 17.2$ Hz, 1H), 5.26 (dd, $J_1 = 1.6$ Hz, $J_2 = 11.2$ Hz, 1H), 4.97 (d, $J = 5.2$ Hz, 0.5H), 4.82 (d, $J = 7.6$ Hz, 0.5H), 4.52 (dd, $J_1 = 5.2$ Hz, $J_2 = 23.2$ Hz, 1H), 3.65 (d, $J = 12.4$ Hz, 1H), 3.54 (d, $J = 12.4$ Hz, 1H); ESI-MS: m/z 272 $[\text{M} + \text{H}]^+$, 543 $[2\text{M} + \text{H}]^+$.

EXAMPLE 5
Preparation of Compound (5a)

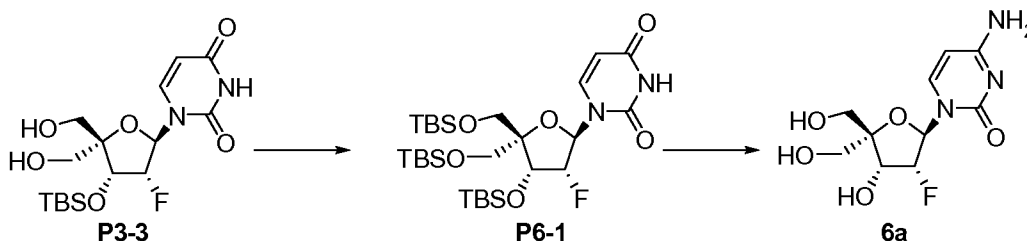


[0257] Preparation of (P5-1): To a solution of **P3-6** (600 mg, 0.96 mmol) in MeOH (30 mL) was added 10% Pd/C (320 mg) at R.T. The mixture was stirred under H_2 balloon at R.T. for 3 hours. The reaction mixture was filtered, and the filtrate was concentrated to give **P5-1** (540 mg, 89.8 %) as a colorless solid. The crude product was used directly for the next step without purification.

[0258] Preparation of (5a): 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 compound **5a** (190 mg, 80.6%) as a colorless solid. ^1H 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).

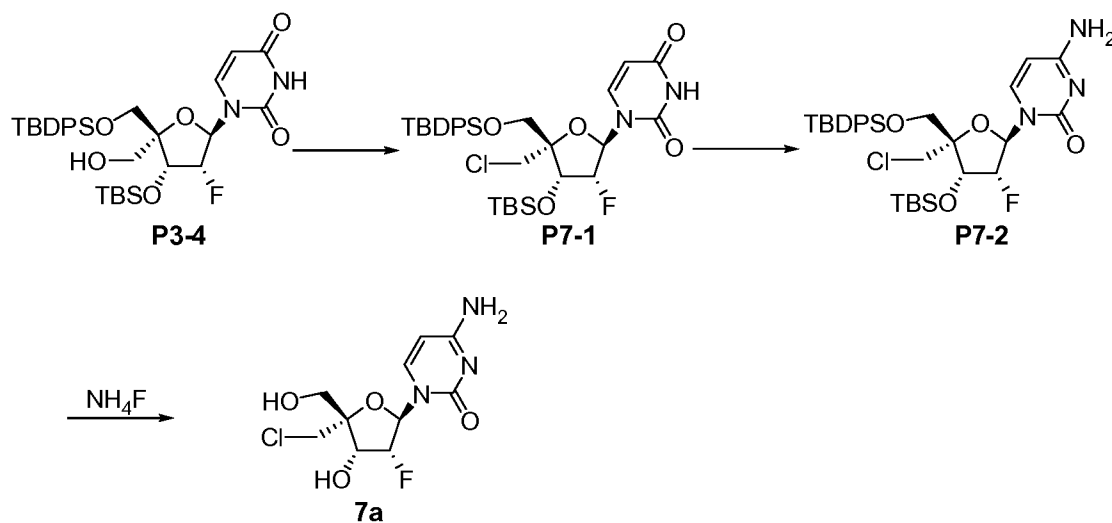
EXAMPLE 6 **Preparation of Compound (6a)**



[0259] Preparation of (P6-1): 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 AgNO₃ (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%).

[0260] Preparation of (6a): To a solution of **P6-1** (600 mg, 0.97 mmol) in anhydrous CH₃CN (18 mL) was added DMAP (239 mg, 2.91 mmol), NEt₃ (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. NH₄OH (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. NaHCO₃. 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 compound **6a** as a white solid (132 mg, 59.3%). ¹H NMR (DMSO-*d*₆, 400 MHz) δ 7.89 (d, $J = 7.6$ Hz, 1H), 7.22 (d, $J = 18.8$ Hz, 2H), 6.09 (dd, $J_1 = 4.4$ Hz, $J_2 = 14.8$ Hz, 1H), 5.73 (d, $J = 5.2$ Hz, 1H), 5.52 (d, $J = 5.6$ Hz, 1H), 5.12 (t, $J = 4.8$ Hz, 1H), 4.90-5.06 (m, 1H), 4.50 (t, $J = 6.0$ Hz, 1H), 4.27-4.33 (m, 1H), 3.66 (dd, $J_1 = 5.2$ Hz, $J_2 = 12.0$ Hz, 1H), 3.47-3.58 (m, 3H); ESI-MS: m/z 276 [M + H]⁺, 551 [2M + H]⁺.

EXAMPLE 7
Preparation of Compound (7a)

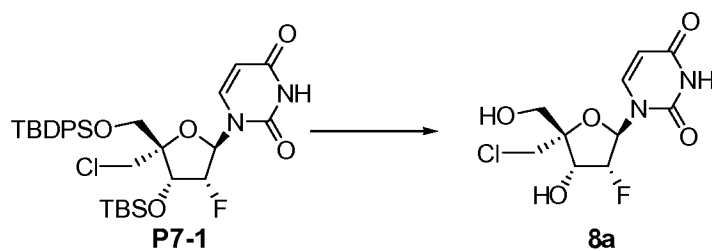


[0261] Preparation of (P7-1): A mixture of **P3-4** (1.60 g, 2.5 mmol), PPh_3 (1.3 g, 5.0 mmol) and CCl_4 (0.76g, 5.0 mmol) in DCE (20 mL) was heated to 130°C under microwave irradiation under N_2 for 40 mins. After cooled to R.T., the solvent was removed, and the residue was purified on a silica gel column (PE/EA = 50/1 to 10/1) to give **P7-1** (1.1 g, 68.8%) as a white solid.

[0262] Preparation of (P7-2): **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.

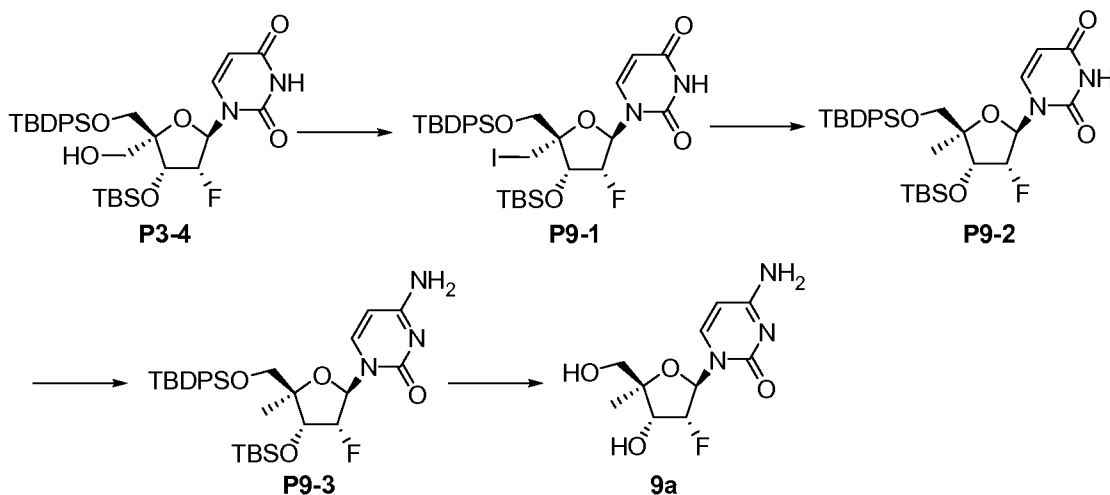
[0263] Preparation of (7a): To a solution of **P7-2** (0.63 g, 0.98 mmol) in MeOH (10 mL) was added NH_4F (0.3 g), and the reaction was refluxed for 12 hours. The reaction was cooled to R.T., and the precipitate was filtered off. The filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (10% MeOH in DCM) to give compound **7a** as a white solid (153 mg, 53.5%). ^1H NMR (CD_3OD , 400 MHz) δ 8.05 (d, $J = 7.2$ Hz, 1H), 6.14 (dd, $J_1 = 3.6$ Hz, $J_2 = 15.2$ Hz, 1H), 5.92 (d, $J = 7.2$ Hz, 1H), 5.15 (ddd, $J_1 = 4.0$ Hz, $J_2 = 5.2$ Hz, $J_3 = 53.6$ Hz, 1H), 4.57 (dd, $J_1 = 4.8$ Hz, $J_2 = 15.2$ Hz, 1H), 3.93 (d, $J = 11.6$ Hz, 1H), 3.75-3.84 (m, 3H); ESI-MS: m/z 294 $[\text{M} + \text{H}]^+$, 587 $[2\text{M} + \text{H}]^+$.

EXAMPLE 8
Preparation of Compound (8a)



[0264] 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 compound **8a** as a white solid (153 mg, 53.5%). ^1H NMR (CD_3OD , 400 MHz) δ 7.99 (d, $J = 8.0$ Hz, 1H), 6.17 (dd, $J_1 = 4.4$ Hz, $J_2 = 14.4$ Hz, 1H), 5.70 (d, $J = 8.0$ Hz, 1H), 5.22 (ddd, $J_1 = J_2 = 4.8$ Hz, $J_3 = 53.2$ Hz, 1H), 4.55 (dd, $J_1 = 5.2$ Hz, $J_2 = 12.4$ Hz, 1H), 3.88 (d, $J = 12.0$ Hz, 1H), 3.76-3.79 (m, 3H); Negative-ESI-MS: m/z 293 $[\text{M} - \text{H}]^-$.

EXAMPLE 9
Preparation of Compound (9a)



[0265] Preparation of (P9-1): 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, 20 mmol) 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. $\text{Na}_2\text{S}_2\text{O}_3$. 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.

[0266] Preparation of (P9-2): A mixture of **P9-1** (1.4 g, 0.2 mmol), Et_3N (40 mg, 0.4 mmol) and Pd/C in EtOH (20 mL) was stirred at R.T. under H_2 (balloon) overnight. The

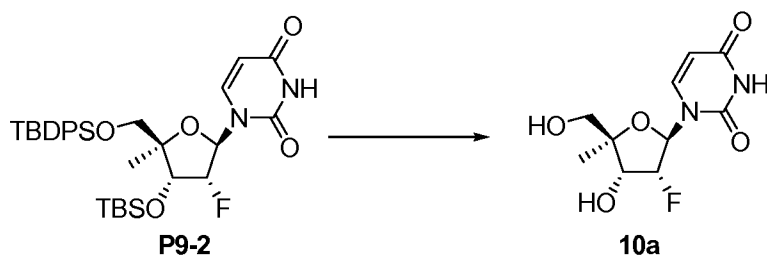
precipitate was filtered off, and the filtrate was concentrated. The residue was purified on a silica gel column (20%-50% EtOAc in PE) to give **P9-2** as a white solid (1.1 g, 78%). ^1H NMR (CDCl_3 , 400 MHz) δ 8.11 (br s, 1H), 7.76 (d, $J = 8.0$ Hz, 1H), 7.39-7.67 (m, 10H), 6.18 (dd, $J_1 = 3.2$ Hz, $J_2 = 14.4$ 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).

[0267] Preparation of (P9-3): **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.

[0268] Preparation of (9a): A mixture of **P9-3** (430 mg, 0.7 mmol) and NH_4F (97 mg, 2.1 mmol) 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 compound **9a** as a white solid (64.8 mg, 35.4%). ^1H 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).

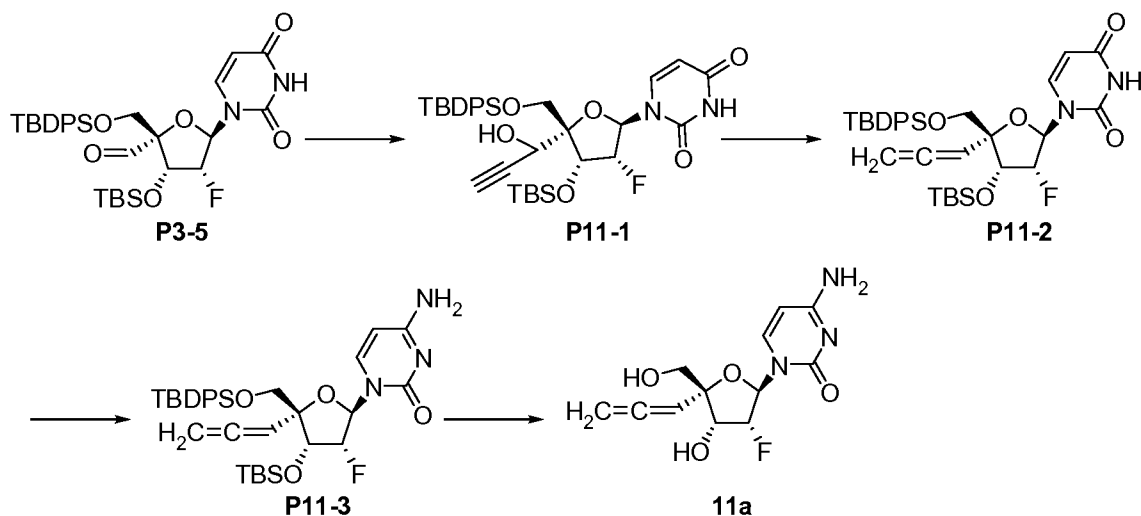
EXAMPLE 10

Preparation of Compound (10a)



[0269] 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 compound **10a** (140 mg, 82.4%) as a white solid. ^1H NMR (CD_3OD , 400 MHz) δ 8.05 (d, $J = 8.4$ Hz, 1H), 6.06 (dd, $J_1 = 2.8$ Hz, $J_2 = 16.4$ Hz, 1H), 5.67 (d, $J = 8.0$ Hz, 1H), 5.08 (m, 1H), 4.37 (d, $J_1 = 5.2$ Hz, $J_2 = 18.8$ Hz, 1H), 3.59 (dd, $J_1 = 12.0$ Hz, $J_2 = 26.4$ Hz, 2H), 1.23 (s, 3H). ESI-TOF-MS: m/z 283 $[\text{M} + \text{Na}]^+$.

EXAMPLE 11
Preparation of Compound (11a)



[0270] Preparation of (P11-1): 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%).

[0271] Preparation of (P11-2): **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 $\text{Pd}_2(\text{dba})_3$ (55 mg, 0.06 mmol) in anhydrous DMF (12 mL) was added $\text{P}(\text{nBu})_3$ (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%). ^1H 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, $J_2 = 53.6$

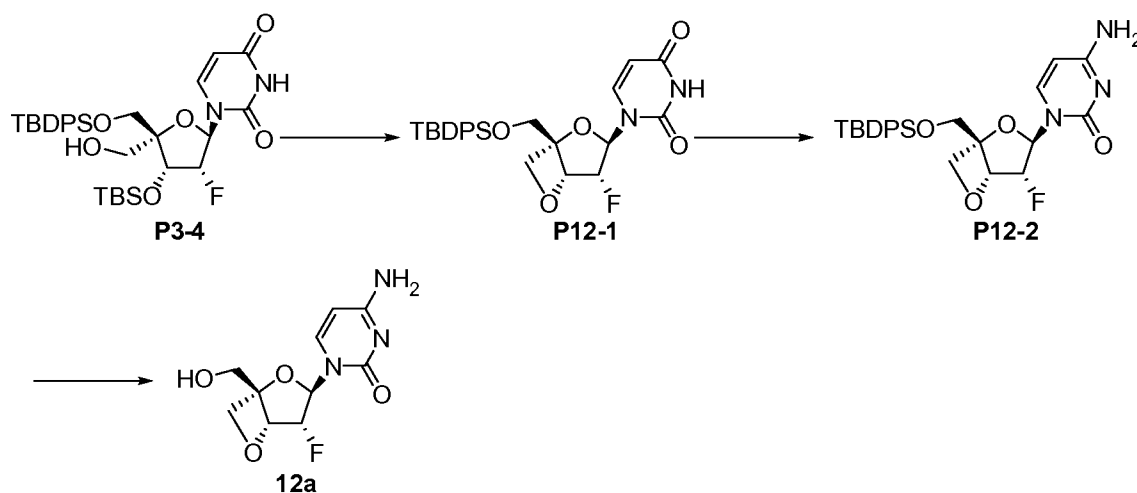
Hz, 1H), 4.80-4.92 (m, 1H), 4.59-4.79 (m, 2H), 3.86 (d, $J = 12.0$ Hz, 1H), 3.75 (d, $J = 12.0$ Hz, 1H), 1.09 (s, 9H), 0.92 (d, $J = 4.4$ Hz, 9H), 0.15 (t, $J = 4.0$ Hz, 6H).

[0272] Preparation of (P11-3): 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%). ^1H 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).

[0273] Preparation of (11a): 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 compound **11a** as a white solid (47 mg, 79.1%). ^1H NMR (CD_3OD , 400 MHz) δ 8.07 (d, $J = 7.6$ Hz, 1H), 6.05 (dd, $J_1 = 1.2$ Hz, $J_2 = 16.8$ Hz, 1H), 5.86 (d, $J = 7.6$ Hz, 1H), 5.40 (dd, $J_1 = J_2 = 6.8$ Hz, 1H), 4.87-4.99 (m, 3H), 4.46-4.80 (m, 1H), 3.75 (d, $J = 12.4$ Hz, 1H), 3.68 (d, $J = 12.4$ Hz, 1H); ESI-MS: m/z 284.02 $[\text{M} + \text{H}]^+$, 567.08 $[2\text{M} + \text{H}]^+$.

EXAMPLE 12

Preparation of Compound (12a)



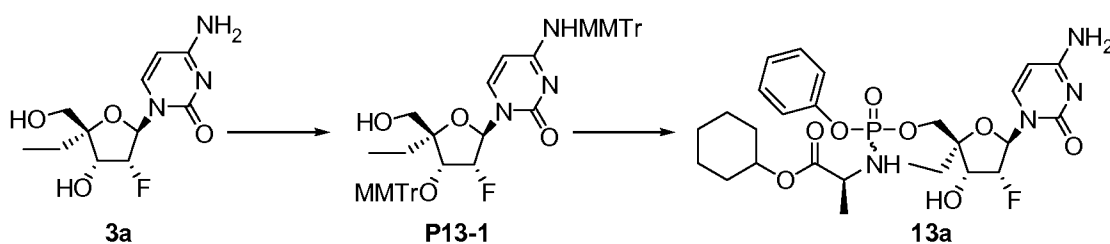
[0274] Preparation of (P12-1): To a solution of **P3-4** (500 mg, 0.8 mmol) in anhydrous toluene (12 mL) was added DAST (0.3 mL, 2 mmol) at -65°C under nitrogen. The reaction mixture was stirred at R.T. for 2 hours. The reaction was quenched with saturated aq. NaHCO₃ and extracted with EtOAc. The organic layer was separated, dried and concentrated to give the residue. The residue was purified by column chromatography on silica gel (eluting with PE: EtOAc = 9: 1) to give **P12-1** as a yellow solid (170 mg, 42.5%). ¹H NMR (CD₃OD, 400 MHz) δ 7.66 (dd, $J_1 = 1.6$ Hz, $J_2 = 18.0$ Hz, 4H), 7.54 (d, $J = 7.6$ Hz, 1H), 7.35-7.47 (m, 6H), 6.59 (dd, $J_1 = 5.6$ Hz, $J_2 = 14.0$ Hz, 1H), 5.78 (d, $J = 7.6$ Hz, 1H), 5.05-5.24 (m, 2H), 4.93 (d, $J = 7.6$ Hz, 1H), 4.57 (d, $J = 7.6$ Hz, 1H), 3.93-4.00 (m, 2H), 1.07 (d, $J = 2.4$ Hz, 9H).

[0275] Preparation of (P12-2): To a solution of **P12-1** (100 mg, 0.2 mmol) in anhydrous MeCN (5 mL) was added TPSCl (182 mg, 0.6 mmol), DMAP (68 mg, 0.6 mmol) and TEA (61 mg, 0.6 mmol) at R.T. under nitrogen. The reaction mixture was stirred at R.T. for 1 hour. NH₄OH (3mL) was added, and the reaction was stirred for 2 hours. The mixture was diluted with EtOAc and washed with water, 1.0 M HCl and saturated aq. NaHCO₃. The organic layer was separated, dried and concentrated to give a residue. The residue was purified by column chromatography on silica gel (DCM:MeOH = 50:1) to give **P12-2** as a yellow solid (96 mg, 96%).

[0276] Preparation of (12a): To a solution of **P12-2** (96 mg, 0.2 mmol) in MeOH (5 mL) was added NH₄F (500 mg) at R.T. The reaction was refluxed for 3 hours. The mixture was filtered, and the residue was purified by RP HPLC (MeCN and 0.1% HCOOH in water) to give compound **12a** as a white solid (25 mg, 48.7%). ¹H NMR (CD₃OD, 400 MHz) δ 7.85 (d, $J = 7.6$ Hz, 1H), 6.59 (dd, $J_1 = 5.2$ Hz, $J_2 = 12.8$ Hz, 1H), 6.04 (d, $J = 7.6$ Hz, 1H), 5.10-5.26 (m, 2H), 4.79-4.90 (m, 1H), 4.57 (d, $J = 7.6$ Hz, 1H), 3.82 (d, $J = 12.4$ Hz, 1H), 3.76 (dd, $J_1 = 1.6$ Hz, $J_2 = 12.4$ Hz, 1H); ESI-MS: m/z 257.9 [M + H]⁺, 514.8 [2M + H]⁺.

EXAMPLE 13

Preparation of Compound (13a)

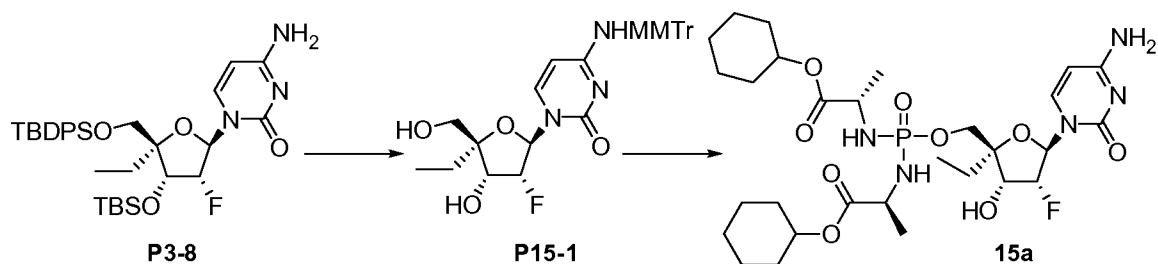


[0277] Preparation of (P13-1): To a solution of compound **3a** (700 mg, 2.56 mmol) in anhydrous pyridine (5 mL) were added TBDPSCl (2.8 g, 10.24 mmol), imidazole (522 mg, 7.68 mmol) and AgNO₃ (870 mg, 5.12 mmol) at R.T. under N₂. The reaction mixture was

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%). ^1H NMR (DMSO- d_6 , 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°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.

[0278] Preparation of (13a): 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 compound **13a** as a white solid (a mixture of two P isomers, 86 mg, 40.3% two steps). ^1H NMR (CD_3OD , 400 MHz) δ 7.75, 7.71 (2d, J = 7.6 Hz, 1H), 7.33-7.38 (m, 2H), 7.19-7.26 (m, 3H), 6.02-6.10 (m, 1H), 5.87, 5.82 (2d, J = 7.6 Hz, 1H), 4.99-5.02 (m, 0.5H), 4.72-4.82 (m, 1.5H), 4.14-4.43 (m, 3H), 3.89-3.94 (m, 1H), 1.68-1.81 (m, 6H), 1.51-1.56 (m, 1H), 1.30-1.43 (m, 8H), 0.96-1.01 (m, 3H); ESI-MS: m/z 582.93 $[\text{M} + \text{H}]^+$.

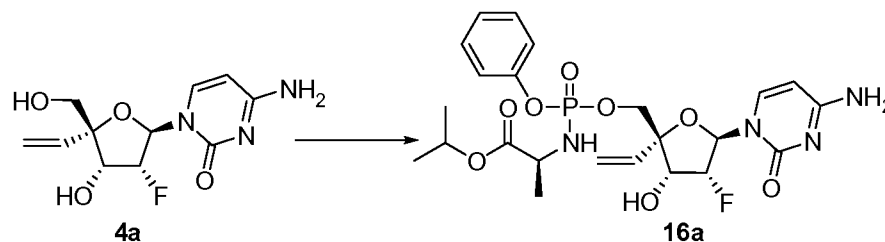
EXAMPLE 15
Preparation of Compound (15a)



[0281] Step1. Preparation of (P15-1): To a mixture of **P3-8** (2.2 g, 2.5 mmol), AgNO₃ (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 N₂. The reaction mixture was stirred at R.T. overnight. The reaction mixture was filtered through a Buchner Funnel. The filtrate was washed with saturated NaHCO₃ solution and brine. The organic layer was separated, dried over anhydrous Na₂SO₄ 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 N₂. 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 Na₂SO₄ 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%).

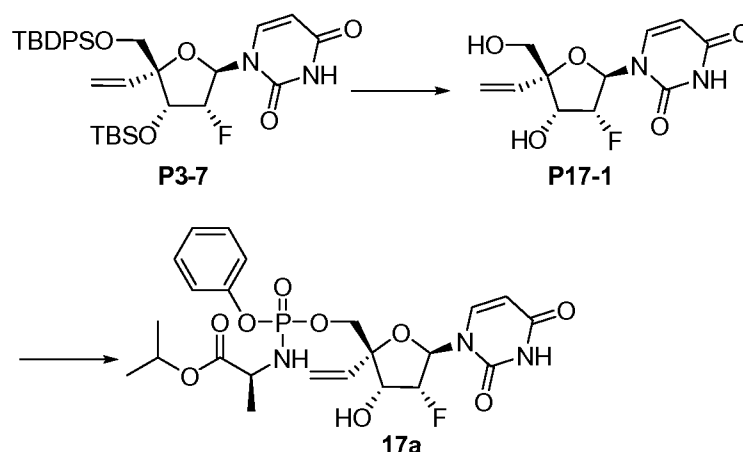
[0282] Preparation of (15a): To a stirred solution of **P15-1** (300 mg, 0.55 mmol) and proton sponge (235 mg, 1.1 mmol) in anhydrous MeCN (9 mL) was added with a solution of POCl₃ (169 mg, 1.1 mmol) in MeCN (1 mL) via syringe at 0°C. The mixture was stirred at R.T. for 40 mins. A mixture of (*S*)-cyclohexyl 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 NaHCO₃, and extracted with EA (100 mL x 2). The combined organic layers was dried over Na₂SO₄, 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 compound **15a** as a white solid (40 mg, 14%). ¹H NMR (MeOD, 400 MHz) δ 7.82 (d, *J* = 7.6 Hz, 1H), 6.09 (dd, *J*₁ = 2.8 Hz, *J*₂ = 14.0 Hz, 1H), 5.98 (d, *J* = 7.6 Hz, 1H), 5.04 (ddd, *J*₁ = 3.2 Hz, *J*₂ = 5.6 Hz, *J*₃ = 53.6 Hz, 1H), 4.71-4.77 (m, 2H), 4.45 (dd, *J*₁ = 5.6 Hz, *J*₂ = 12.4 Hz, 1H), 4.14-4.18 (m, 1H), 3.97-4.01 (m, 1H), 3.84-3.92 (m, 2H), 1.31-1.87 (m, 28H), 0.99 (t, *J* = 7.2 Hz, 3H). ³¹P NMR (CD₃OD, 162 MHz) δ 13.94; ESI-LCMS: *m/z* 660 [M + H]⁺.

EXAMPLE 16
Preparation of Compound (16a)



[0283] To a stirred solution of compound **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 compound **16a** as a white solid (24.0 mg, 15 %). ^1H NMR (MeOD, 400 MHz) δ 7.76 (d, J = 7.2 Hz, 1H), 7.17-7.38 (m, 5H), 6.01-6.08 (m, 2H), 5.81 (d, J = 7.6 Hz, 1H), 5.54-5.58 (m, 1H), 5.35-5.38 (m, 1H), 4.92-4.97 (m, 2H), 4.45-4.52 (m, 1H), 4.08-4.19 (m, 2H), 3.88-3.92 (m, 1H), 1.28-1.33 (m, 3H), 1.20-1.22 (m, 6H); ^{31}P NMR (CD_3OD , 162 MHz) δ 7.36; ESI-LCMS: m/z 541.0 $[\text{M} + \text{H}]^+$.

EXAMPLE 17
Preparation of Compound (17a)

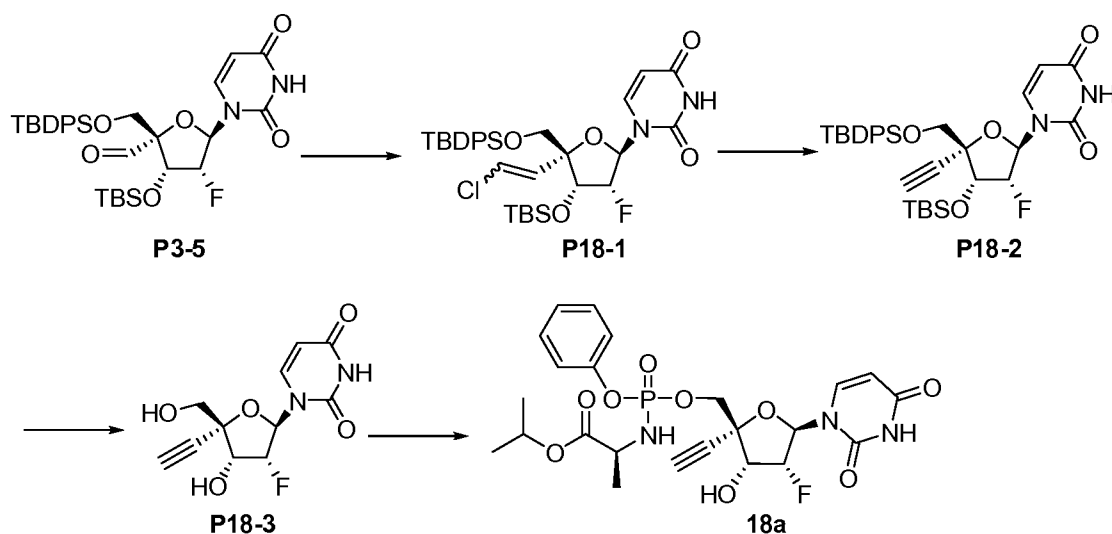


[0284] **Preparation of (P17-1):** To a solution of **P3-7** (1.4 g, 2.3 mmol) in MeOH (50 mL) was added NH_4F (8.0 g) at R.T. The reaction mixture was refluxed overnight. After cooling to R.T., the mixture was filtered, and the filtrate was concentrated. The crude product

was purified by silica gel column chromatography (10% MeOH in DCM) to give **P17-1** as a white solid (410 mg, 77.8%).

[0285] Preparation of (P17): 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 compound **17a** as a white solid (a mixture of two P isomers, 11.0 mg, 11 %). ¹H NMR (MeOD, 400 MHz) δ 7.71 (2d, *J* = 8.0 Hz, 1H), 7.17-7.37 (m, 5H), 5.98-6.07 (m, 2H), 5.61, 5.68 (2d, *J* = 8.0 Hz, 1H), 5.53-5.58 (m, 1H), 5.35-5.40 (m, 1H), 5.08-5.10 (m, 1H), 4.93-4.99 (m, 1H), 4.52-4.53 (m, 1H), 4.16-4.21 (m, 1H), 4.06-4.11 (m, 1H), 3.86-3.94 (m, 1H), 1.28-1.34 (m, 3H), 1.20-1.22 (m, 6H). ³¹P NMR (MeOD, 162 MHz) δ 3.72, 3.45. ESI-LCMS: *m/z* 542.0 [*M* + *H*]⁺.

EXAMPLE 18 **Preparation of Compound (18a)**



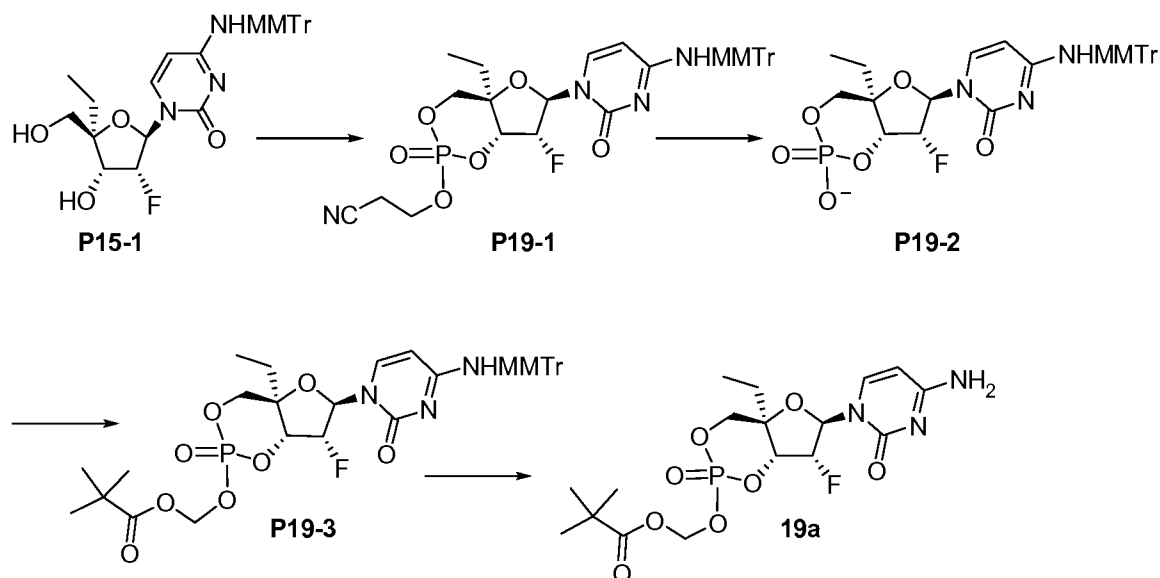
[0286] Preparation of (P18-1): To a solution of (chloromethyl)triphenylphosphonium chloride (2.1 g, 6.0 mmol) in anhydrous THF (10 mL) was added dropwise *n*-BuLi (4.6 mL, 6.0 mmol) at -70°C under nitrogen. The reaction was stirred at -70°C for 50 mins. A solution of compound **P3-9** (950 mg, 1.5 mmol) 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. NH₄Cl 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%).

[0287] Preparation of (P18-2): 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. NH₄Cl 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%).

[0288] Preparation of (P18-3): To a solution of **P18-2** (300 mg, 0.44 mmol) in MeOH (10 mL) was added NH₄F (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%). ¹H NMR (CD₃OD, 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).

[0289] Preparation of (18a): 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 compound **18a** as a white solid (a mixture of two P isomers, 25 mg, 7.7%). ¹H NMR (CD₃OD, 400 MHz) δ 7.64, 7.60 (2d, J = 7.6 Hz, 1H), 7.32-7.36 (m, 2H), 7.16-7.25 (m, 3H), 5.95-6.01 (m, 1H), 5.67, 5.62 (2d, J = 8.0 Hz, 1H), 5.10-5.25 (m, 1H), 4.93-4.97 (m, 1H), 4.49-4.59 (m, 1H), 4.33-4.42 (m, 1H), 4.24-4.29 (m, 1H), 3.86-3.94 (m, 1H), 3.25, 3.22 (2s, 1H), 1.28-1.34 (m, 3H), 1.20-1.23 (m, 6H); ESI-MS: m/z 540.2 [M + H]⁺.

EXAMPLE 19
Preparation of Compound (19a)



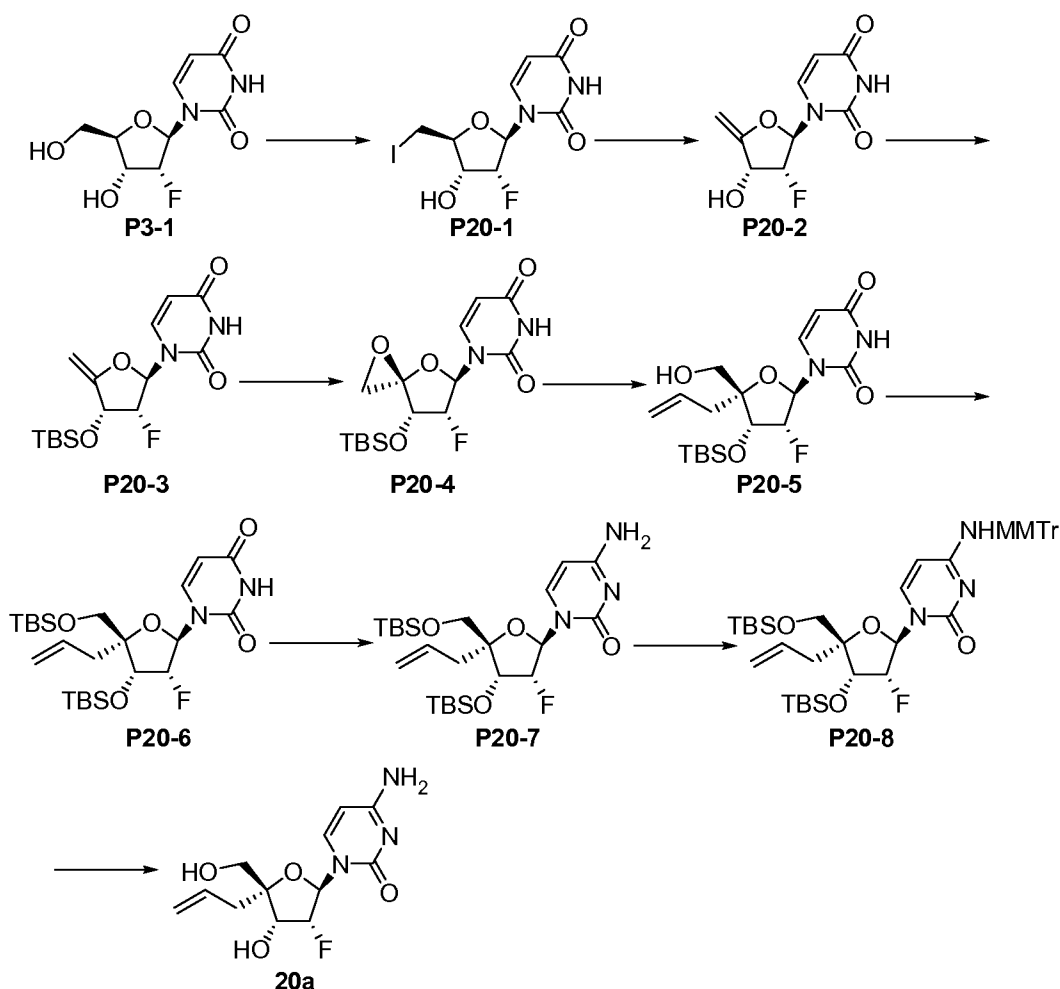
[0290] Preparation of (P19-1): **P15-2** (1.2 g, 2.2 mmol) was dissolved in dry acetonitrile (20 mL), and 0.45 M tetrazole (24.0 mL, 11.0 mmol) and 3-(bis(diisopropylamino)phosphinoxy)propanenitrile (1.13 g, 3.74 mmol) was added. The reaction mixture was stirred for 1 hour under N₂ at R.T. TBDPH (2.7 mL, 15 mmol) was added, and the mixture was stirred for 1 hour. The reaction was quenched by Na₂S₂O₃ solution and extracted with EA. The organic layer was dried over Na₂SO₄ 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%).

[0291] Preparation of (P19-2): **P19-1** (750 mg, 1.14 mmol) was dissolved in saturated NH₃ 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%). ¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.60 (s, 1H), 8.28 (s, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.12-7.29 (m, 12H), 6.83 (d, *J* = 8.8 Hz, 2H), 6.29 (d, *J* = 7.6 Hz, 1H), 5.88 (d, *J* = 8.8 Hz, 1H), 5.10 (d, *J* = 4.8 Hz, 1H), 4.42-4.45 (m, 1H), 3.72 (s, 3H), 1.64-1.91 (m, 2H), 1.10-1.13 (m, 2H), 0.83-0.86 (m, 3H). ³¹P NMR (CD₃OD, 400 MHz) δ -4.48; Negative-ESI-LCMS: *m/z* 606 [M - H]⁻.

[0292] Preparation of (P19-3): **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 N₂ for 16 hours. The reaction was quenched by Na₂S₂O₃ solution and extracted with EA. The organic layer was dried over Na₂SO₄ 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%).

[0293] Preparation of (19a): **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 compound **19a** as a white solid (10 mg, 17%). ¹H NMR (CD₃OD, 400 MHz) δ 7.69 (d, J = 7.2 Hz, 1H), 5.91 (d, J = 7.6 Hz, 1H), 5.84 (d, J = 22.0 Hz, 1H), 5.73 (d, J = 14.0 Hz, 2H), 5.52 (d, J = 5.2 Hz, 1H), 5.13-5.22 (m, 1H), 4.53-4.61 (m, 1H), 4.31 (d, J = 9.6 Hz, 1H), 1.92-2.08 (m, 2H), 1.23 (s, 9H), 1.03-1.07 (m, 3H); ³¹P NMR (CD₃OD, 162 MHz) δ -7.93; ESI-LCMS: m/z 450 [M + H]⁺.

EXAMPLE 20
Preparation of Compound (20a)



[0294] Preparation of (P20-1): To a stirred suspension of **P3-1** (20.0 g, 81.3mmol), imidazole (15.9 g, 234.0 mmol), PPh₃ (53.5 g, 203.3 mmol) and pyridine (90 mL) in anhydrous THF (360 mL) was added dropwise a solution of I₂ (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. Na₂S₂O₃ (150 mL) and extracted with EA. The organic layer was dried over

Na₂SO₄ 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%). ¹H NMR (CD₃OD, 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).

[0295] Preparation of (P20-2): 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. NaHCO₃ (200 mL) and extracted with EA. The organic layer was washed with brine and dried over Na₂SO₄. 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 (CD₃OD, 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).

[0296] Preparation of (P20-3): 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 Na₂SO₄. 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%).

[0297] Preparation of (P20-4): To a stirred solution of NaHCO₃ in H₂O (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 MgSO₄. 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.

[0298] Preparation of (P20-5): 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 SnCl₄ (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 NaHCO₃ and extracted with DCM. The organic layer was dried over Na₂SO₄ 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%). ¹H NMR (CD₃OD, 400 MHz) δ 8.01 (d, J = 8.4 Hz, 1H), 6.12 (dd, J_1 = 3.6 Hz, J_2 = 15.2 Hz, 1H), 5.87-5.96 (m, 1H), 5.71 (d, J = 8.4 Hz,

1H), 5.06-5.22 (m, 3H), 4.60 (dd, $J_1 = 5.6$ Hz, $J_2 = 14.4$ Hz, 1H), 3.72 (d, $J = 11.6$ Hz, 1H), 3.48 (d, $J = 11.6$ Hz, 1H), 2.62-2.67 (m, 1H), 2.23-2.29 (m, 1H); ESI-LCMS: $m/z = 422$ $[M + Na]^+$.

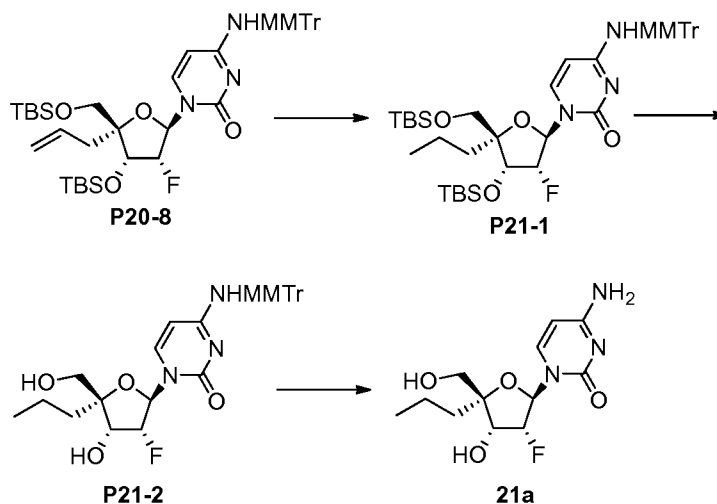
[0299] Preparation of (P20-6): To a stirred solution of **P20-5** (270.0 mg, 0.7 mmol) in dry DCM were added imidazole (400.0mg, 5.9mmol) and TBSCl (390.0 mg, 2.6 mmol) at R.T. The mixture was stirred at R.T. for 18 hours. The solution was diluted with EA. The solvent was washed with brine and dried 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 $[M + Na]^+$.

[0300] Preparation of (P20-7): 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 $[M + H]^+$.

[0301] Preparation of (P20-8): 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 $[M + H]^+$.

[0302] Preparation of (20a): 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 compound **20a** as a white solid (47.0 mg, 49.8%). ^1H NMR (CD_3OD , 400 MHz) δ 8.13 (d, $J = 8.4$ Hz, 1H), 6.12 (dd, $J_1 = 3.2$ Hz, $J_2 = 12.0$ Hz, 1H), 5.87-5.97 (m, 2H), 4.98-5.14 (m, 3H), 4.45 (dd, $J_1 = 5.2$ Hz, $J_2 = 17.6$ Hz, 1H), 3.71 (d, $J = 11.6$ Hz, 1H), 3.54 (d, $J = 11.6$ Hz, 1H), 2.54-2.59 (m, 1H), 2.33-2.39 (m, 1H); ESI-LCMS: m/z 286 $[M + H]^+$.

EXAMPLE 21
Preparation of Compound (21a)



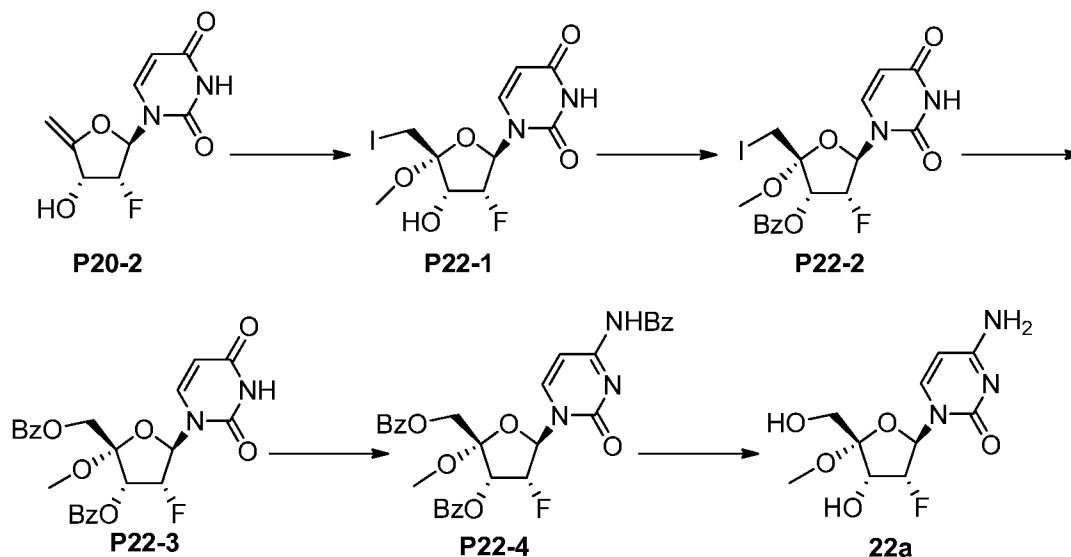
[0303] Preparation of (P21-1): To a stirred solution of **P20-8** (250.0 mg, 0.3 mmol) in MeOH was added Pd/C (500.0 mg), and the mixture was stirred under H₂ (balloon) for 18 hours at R.T. The reaction was filtered, and the solvent removed under reduced pressure. The residue was purified by prep. TLC (30% EtOAc in PE) to afford **P21-1** as a white foam (210.0 mg, 84.0%).

[0304] Preparation of (P21-2): 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 compound **21a** as a white foam (111.2 mg, 74.6%). ¹H NMR (DMSO-*d*₆, 400 MHz) δ 8.49 (s, 1H), 7.75 (d, *J* = 6.8 Hz, 1H), 6.83-7.32 (m, 14H), 6.25 (d, *J* = 7.6 Hz, 1H), 5.95 (dd, *J*₁ = 4.8 Hz, *J*₂ = 14.8 Hz, 1H), 5.48 (d, *J* = 5.6 Hz, 1H), 4.86-5.15 (m, 2H), 4.15-4.21 (m, 1H), 3.72 (s, 3H), 3.38-3.49 (m, 2H), 1.24-1.58 (m, 4H), 0.84 (t, *J* = 7.2 Hz, 3H); ESI-MS: *m/z* 560 [M + H]⁺.

[0305] Preparation of (P21): 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 compound **21a** (27 mg) as a white solid; ¹H NMR (CD₃OD, 400 MHz) δ 8.05 (d, *J* = 7.6 Hz, 1H), 6.06 (dd, *J*₁ = 2.8 Hz, *J*₂ = 16 Hz, 1H), 5.87 (d, *J* = 7.6 Hz, 1H), 5.10 (dd, *J* = 3.2, 5.2 Hz, 0.5H), 4.96 (dd, 3.2, 5.2 Hz, 0.5H), 4.42 (dd, *J* = 5.6, 17.2 Hz, 1H), 3.67 (dd, *J* = 11.6, 76 Hz,

2H), 1.70-1.79 (m, 1H), 1.31-1.61 (m, m, 3H), 0.94 (t, $J = 6.8$ Hz, 3H). MS: m/z 417 $[M + 2\text{-methylheptylamine}]^+$.

EXAMPLE 22
Preparation of Compound (22a)



[0306] Preparation of (P22-1): 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 $\text{Na}_2\text{S}_2\text{O}_3$ 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%). ^1H 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).

[0307] Preparation of (P22-2): 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%).

[0308] Preparation of (P22-3): **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 $60\text{--}70^\circ\text{C}$ for 3 days. The precipitate was removed by filtration, and the filtrate was

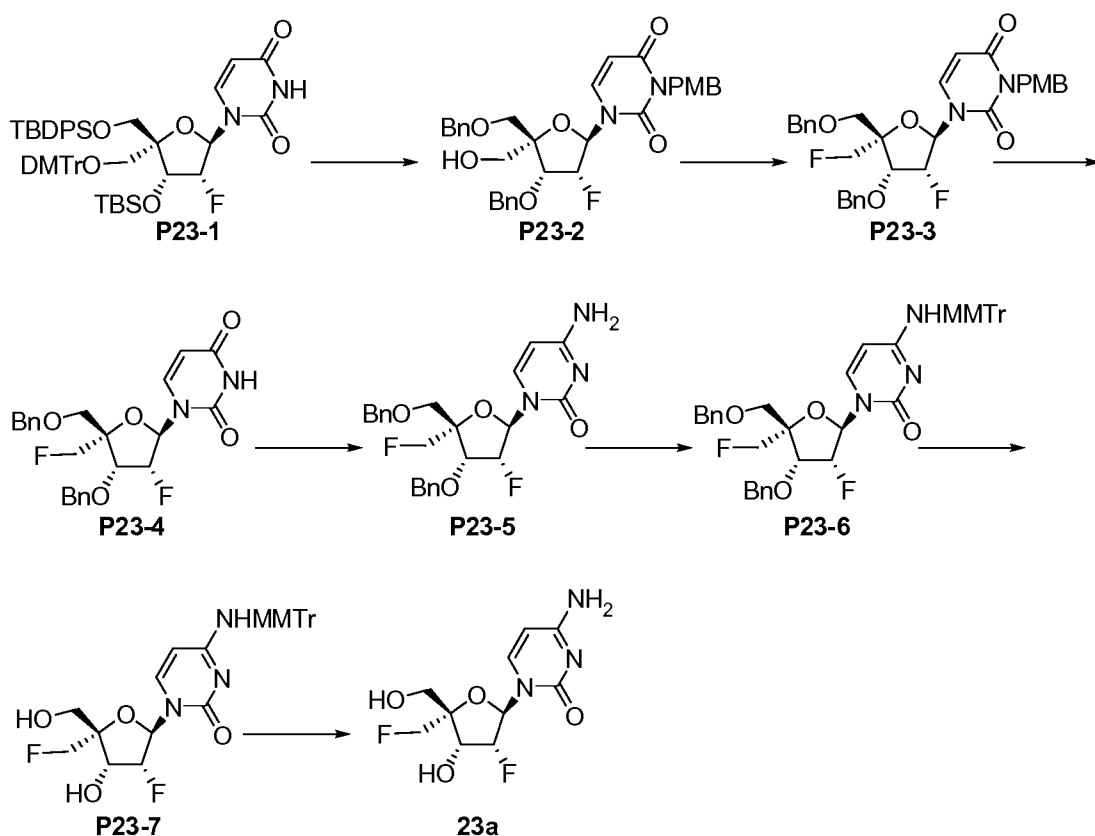
diluted with EA. The solvent was washed with brine and dried over Na₂SO₄. The solvent was removed, and the residue was purified on a silica gel column (20~60% EA in PE) to afford **P22-3** as a white foam (2.3 g, 47.9%).

[0309] Preparation of (P22-4): **P22-3** (2.3 g, 4.8 mmol), DMAP (1.2 g, 9.6 mmol), TPSCl (2.9 g, 9.6 mmol) and Et₃N (0.97 g, 9.6 mmol) were suspended in MeCN (10 mL). The mixture was stirred at R.T. for 14 hours. NH₃ 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%).

[0310] Preparation of (22a): **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 H₂O and washed with DCM. The aqueous phase was lyophilized and further purified by prep. HPLC (0.1% formic acid in water/acetonitrile) to give compound **22a** as a white solid (145 mg, 78.9 %). ¹H NMR (CD₃OD, 400 MHz) δ 7.88 (d, J = 7.6 Hz, 1H), 6.03 (d, J = 18.4 Hz, 1H), 5.87 (d, J = 7.6 Hz, 1H), 4.86-5.00 (m, 1H), 4.49 (dd, J_1 = 23.2 Hz, J_2 = 22.8 Hz, 1H), 3.90 (d, J = 12.0 Hz, 1H), 3.66 (d, J = 12.0 Hz, 1H), 3.41 (s, 3H); ESI-MS: m/z 276 [M + H]⁺.

EXAMPLE 23

Preparation of Compound (23a)



[0311] Preparation of (P23-2): To a solution of **P23-1** (3.1 g, 4.5 mmol) in DMF (30 mL) was added anhydrous K₂CO₃ (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%). ¹H NMR (CDCl₃, 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.

[0312] 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%).

[0313] 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%).

[0314] 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%).

[0315] Preparation of (P23-3): 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 Na₂CO₃ 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%). ¹H NMR (CD₃OD, 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, 2.0 Hz, 1H), 5.18-5.50 (m, 4H), 4.96 (s, 2H), 4.45-4.88 (m, 7H), 3.67-3.89 (m, 5H).

[0316] Preparation of (P23-4): 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%).

[0317] Preparation of (P23-5): 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. NH₄OH (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). ¹H NMR (CD₃OD, 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).

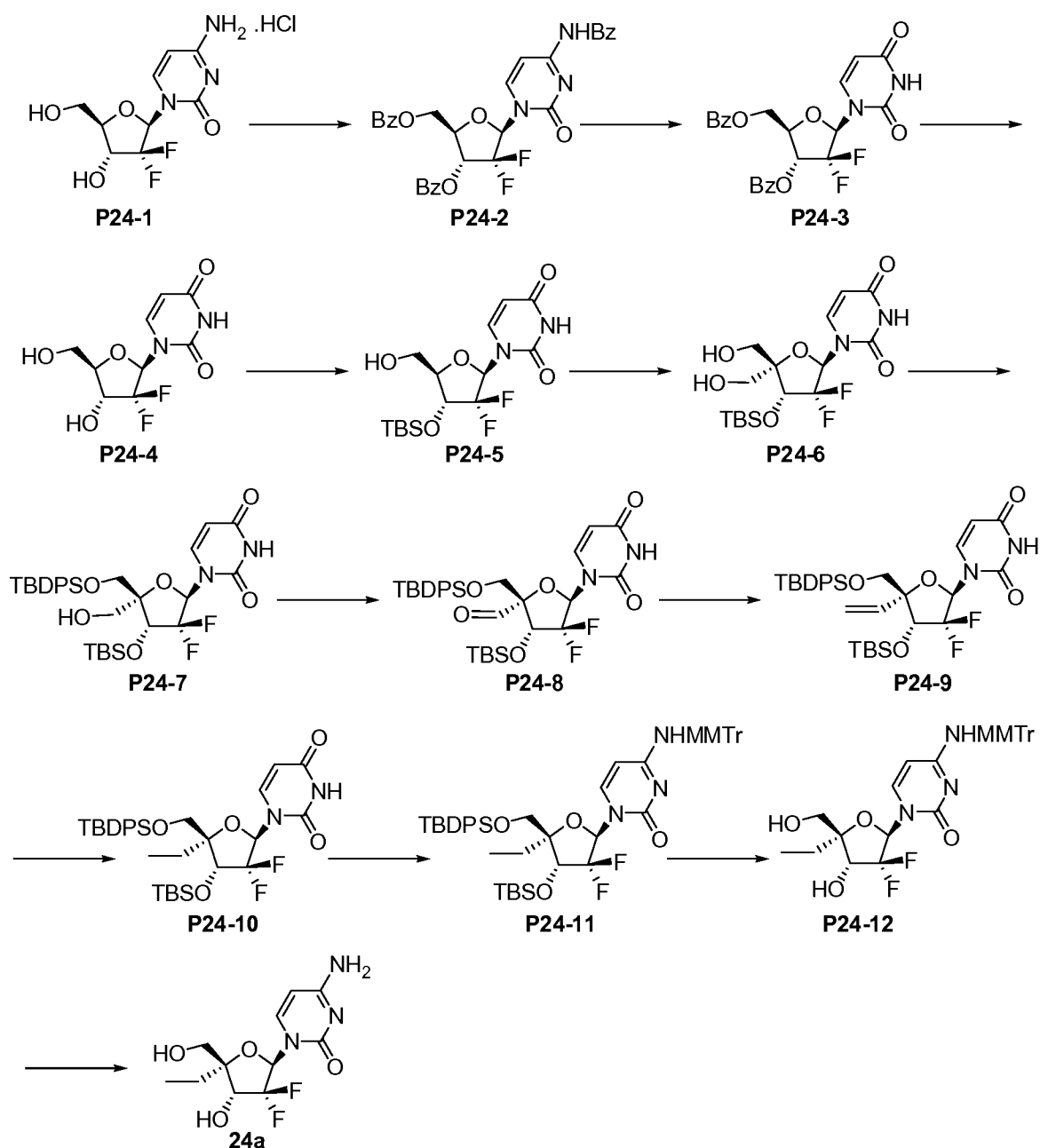
[0318] Preparation of (P23-6): To a stirred solution of **P23-5** (1.0 g, 2.18 mmol) in anhydrous DCM (15 mL) was added MMTrCl (2.02 g, 6.56 mmol) and AgNO₃ (1.11 g, 6.56 mmol) at R.T., and the mixture was stirred at R.T. overnight. The solid was filtered off and washed with DCM. The filtrate was washed with brine and dried over Na₂SO₄. 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%).

[0319] Preparation of (P23-7): 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%). ^1H NMR (CD_3OD , 400 MHz) δ 8.54 (s, 1H), 7.73 (d, $J = 7.6$ Hz, 1H), 7.13-7.32 (m, 12H), 6.83 (d, $J = 8.4$ Hz, 2H), 6.29 (d, $J = 7.6$ Hz, 1H), 5.99-6.04 (m, 1H), 5.82 (d, $J = 5.6$ Hz, 1H), 5.39 (t, $J = 5.2$ Hz, 1H), 5.09 (t, $J = 5.2$ Hz, 1H), 4.32-4.58 (m, 3H), 3.54-3.72 (m, 5H). ESI-MS: m/z 549.6 $[\text{M} + \text{H}]^+$.

[0320] Preparation of (23a): **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 compound **23a** as a white solid (45 mg, 69.0%). ^1H NMR (CD_3OD , 400 MHz) δ 8.00 (d, $J = 7.6$ Hz, 1H), 6.13 (dd, $J_1 = 16.0$ Hz, $J_2 = 4.0$ Hz, 1H), 5.89 (d, $J = 7.6$ Hz, 1H), 5.18-5.21 (m, 1H), 5.05-5.07 (m, 1H), 4.60 (s, 1H), 4.51-4.57 (m, 2H), 3.84 (dd, $J_1 = 12.0$ Hz, $J_2 = 2.0$ Hz, 1H), 3.75 (dd, $J_1 = 12.0$ Hz, $J_2 = 2.0$ Hz, 1H). ESI-MS: m/z 277.8 $[\text{M} + \text{H}]^+$, 554.8 $[2\text{M} + \text{H}]^+$.

EXAMPLE 24
Preparation of Compound (24a)



[0321] Preparation of (P24-2): 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%).

[0322] Preparation of (P24-3): **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%).

[0323] Preparation of (P24-4): **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%).

[0324] Preparation of (P24-5): 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 Na₂SO₄ 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 NaHCO₃ and brine. The organic layer was dried over Na₂SO₄ 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 NaHCO₃ solution and brine. The organic layer was dried over Na₂SO₄ and purified by silica gel column chromatography (1-2% MeOH in DCM) to give **P24-5** as a white solid (21.0 g, 70%). ¹H NMR (400 MHz, MeOD) δ 7.83 (d, J = 8.0 Hz, 1H), 6.14 (dd, J_1 = 6.0 Hz, J_2 = 10.0 Hz, 1H), 5.73 (d, J = 8.4 Hz, 1H), 4.38-4.46 (m, 1H), 3.89-3.91 (m, 1H), 3.88 (dd, J_1 = 2.8 Hz, J_2 = 5.2 Hz, 1H), 3.72 (dd, J_1 = 2.8 Hz, J_2 = 5.2 Hz, 1H), 0.93 (s, 9H), 0.15 (m, 6H). ESI-MS: m/z 379.1 [M + H]⁺.

[0325] Preparation of (P24-6): To a solution of **P24-5** (21.0 g, 55.6 mmol) in anhydrous CH₃CN (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% CH₂O (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 NaBH₄ (12.7 g, 333.6 mmol). The mixture was stirred at R.T. for 30 mins. The reaction was quenched with saturated aq. NH₄Cl, extracted with EA. The organic layer was dried over Na₂SO₄ 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%).

[0326] Preparation of (P24-7): 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 AgNO₃ (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 Na₂SO₄. 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 NaHCO₃ solution and brine. The organic layer was dried over Na₂SO₄ 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%). ¹H NMR (CD₃OD, 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).

[0327] Preparation of (P24-8): 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 MgSO₄, and the organic solvent was stirred with an equal volume of Na₂S₂O₃·5H₂O in saturated NaHCO₃ (50 mL) until the organic layer became clear (approx. 10 min). The organic layer was separated, washed with brine, and dried over MgSO₄. After concentration in vacuo, **P24-8** was obtained as a red solid (5.8 g, 98%).

[0328] Preparation of (P24-9): 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 NH₄Cl 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%).

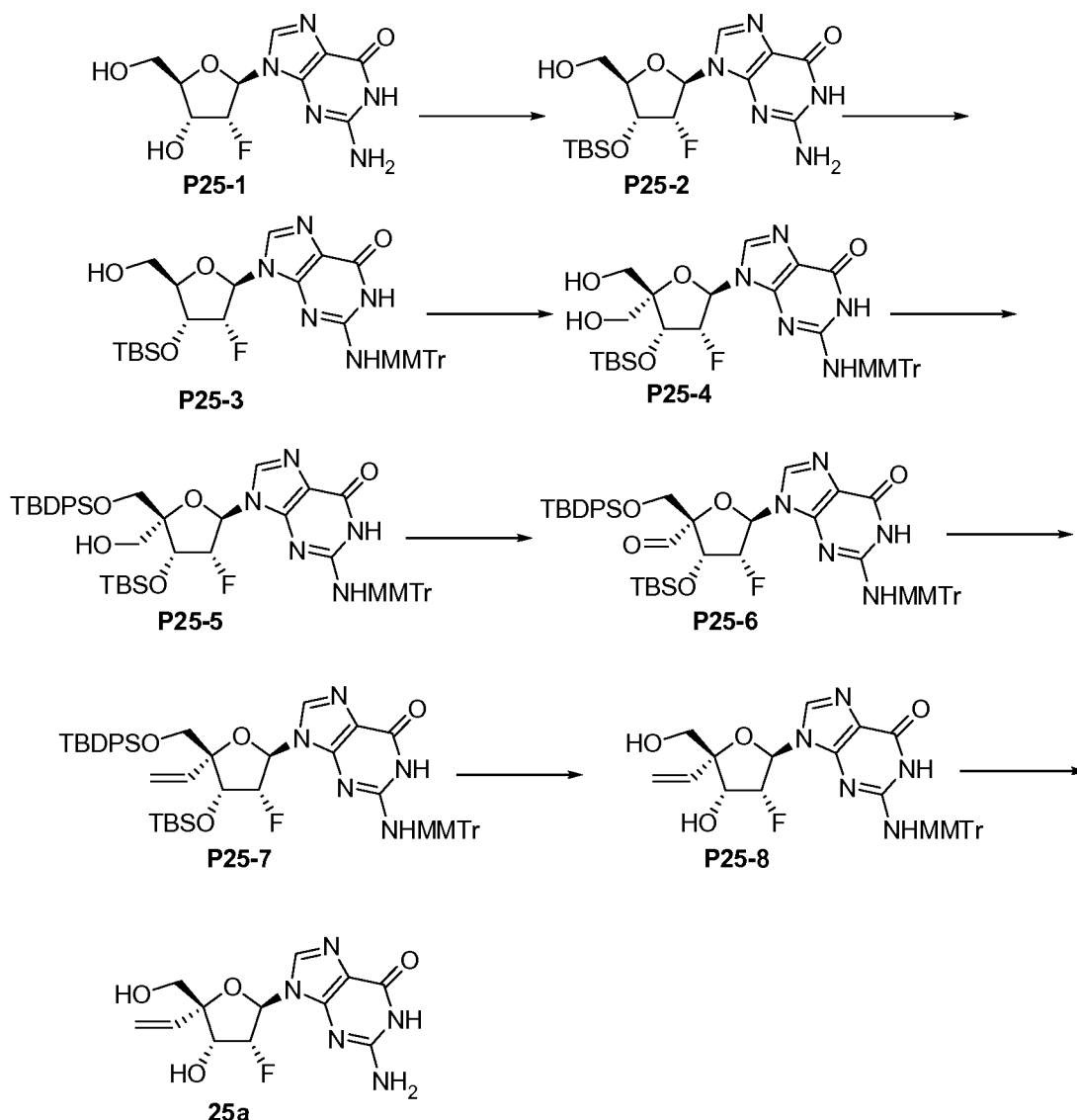
[0329] Preparation of (P24-10): To a solution of **P24-9** (2.9 g, 4.5 mmol) in anhydrous MeOH (20 mL) was added Pd/C (1.4 g) at 25°C under hydrogen atmosphere. The mixture was stirred at 25°C for 1 hour. The solution was filtered, evaporated to dryness and purified on a silica gel column (DCM:MeOH = 300:1 to 100:1) to give **P24-10** as a white solid (2.3 g, 79.3 %).

[0330] Preparation of (P24-11): To a solution of **P24-10** (1.0 g, 1.55 mmol) in anhydrous CH₃CN (20 mL) were added TPSCl (940 mg, 3.1 mmol), DMAP (380 mg, 3.1 mmol) and NEt₃ (470 mg, 4.6 mmol) at R.T. The reaction was stirred at R.T. for 5 hours. NH₄OH (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. NaHCO₃. 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), AgNO₃ (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%).

[0331] Preparation of (P24-12): To a solution of **P24-11** (1.1 g, 1.2 mmol) in MeOH (40 mL) was added NH₄F (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%). ¹H NMR (400 MHz, MeOD) δ 8.58 (s, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.13-7.30 (m, 12H), 6.83-6.85 (m, 2H), 6.29 (d, *J* = 7.6 Hz, 1H), 6.18 (d, *J* = 6.0 Hz, 1H), 5.94 (t, *J* = 8.0 Hz, 1H), 5.22 (t, *J* = 5.2 Hz, 1H), 4.28-4.37 (m, 1H), 3.72 (s, 3H), 3.57-3.62 (m, 1H), 1.39-1.60 (m, 2H), 0.79-0.84 (m, 3H). ESI-LCMS: *m/z* 563.6 [M + H]⁺.

[0332] Preparation of (24a): **P24-12** (250 mg, 0.44 mmol) was dissolved in 80% HCOOH in H₂O (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 (DCM:MeOH = 100:1 to 100:1) to give compound **24a** as a white solid (125.6 mg, 97%). ¹H NMR (400 MHz, MeOD) δ 7.91 (d, *J* = 7.6 Hz, 1H), 6.19 (t, *J* = 7.6 Hz, 1H), 5.90 (d, *J* = 7.2 Hz, 1H), 4.47 (t, *J* = 13.6 Hz, 1H), 3.67 (d, *J* = 12.0 Hz, 1H), 3.52 (d, *J* = 12.0 Hz, 1H), 1.73-1.82 (m, 1H), 1.53-1.63 (m, 1H), 0.95 (t, *J* = 7.6 Hz, 3H). ESI-LCMS: *m/z* 291.9 [M + H]⁺.

EXAMPLE 25
Preparation of Compound (25a)



[0333] Preparation of (P25-2): 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 H₂O (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 %).

[0334] Preparation of (P25-3): To a stirred solution of **P25-2** (31.2 g, 78.2 mmol) in anhydrous pyridine (300 mL) was added Ac₂O (11.96 g, 117.3 mmol). The mixture was stirred at 25°C for 18 hours. MMTTrCl (72.3 g, 234.6 mmol) and AgNO₃ (39.9 g, 234.6 mmol)

were then added. The solution was stirred at 25°C for 15 hours. And H₂O 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 Na₂SO₄ 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 NH₃/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 %). ¹H 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).

[0335] Preparation of (P25-4): To a solution of **P25-3** (7.24 g, 10.79 mmol) in anhydrous CH₃CN (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% CH₂O (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 NaBH₄ (2.4 g, 63.6 mmol), the reaction was then stirred for 30 mins. The mixture was quenched with saturated aq. NH₄Cl. The mixture was extracted with EA, and the organic layer was dried over Na₂SO₄. 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%).

[0336] Preparation of (P25-5): 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 AgNO₃ (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 Na₂SO₄, 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 Cl₂CHCOOH (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. NaHCO₃ and extracted with DCM. The organic layer was dried over Na₂SO₄, 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%).

[0337] Preparation of (P25-6): **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 CH₂Cl₂ (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 MgSO₄. The organic solvent was stirred with an equal volume of Na₂S₂O₃·5H₂O in saturated NaHCO₃ (30 mL) until the organic layer became clear (approx. 10 min). The organic layer was separated, washed with brine, and dried over MgSO₄. The solvent was removed in vacuo to give **P25-6** as a yellow solid (2.1 g, 95%).

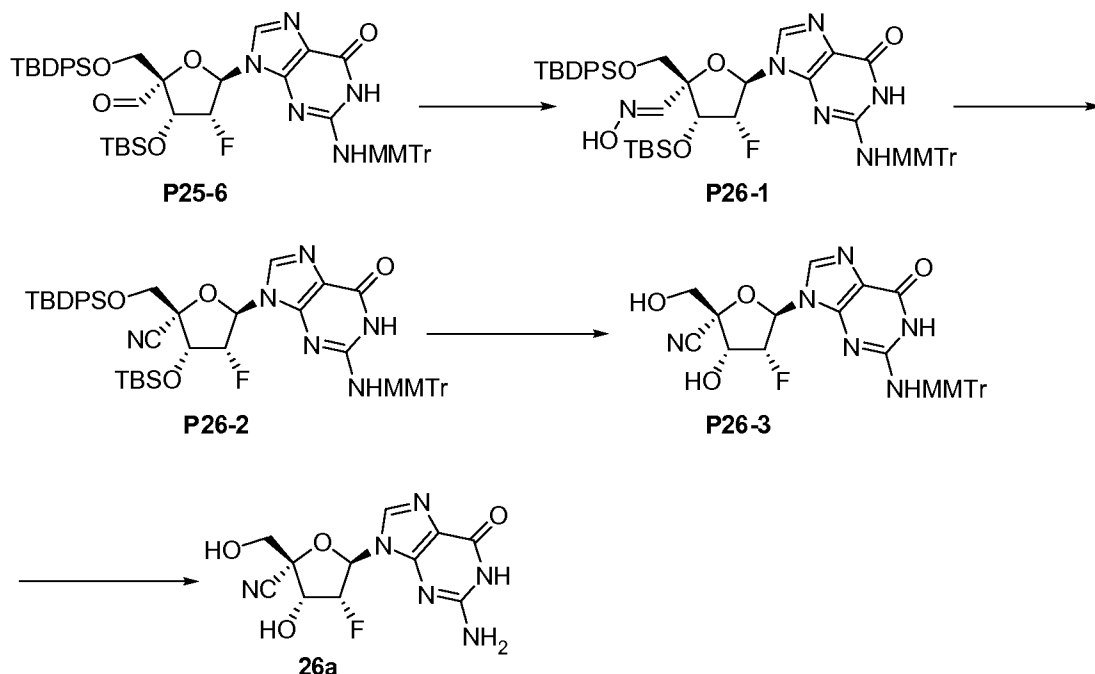
[0338] Preparation of (P25-7): To a stirred solution of methyl-triphenylphosphonium bromide (2.3 g, 6.6 mmol) in anhydrous THF (30 mL) was added dropwise n-BuLi (2.6 mL, 6.6 mmol, 2.5 M in THF) at -78°C over 1 minute. Stirring was continued at 0°C for 1 hour. **P25-6** (2.1 g, 2.2 mmol) was added to the mixture, and then stirred at 25°C for 15 hours. The reaction was quenched with saturated NH₄Cl (50 mL). The mixture was extracted with EtOAc. The combined organic phase was dried with Na₂SO₄, 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%).

[0339] Preparation of (P25-8): To a solution of **P25-7** (1.6 g, 1.7 mmol) in MeOH (50 mL) was added NH₄F (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%). ¹H NMR (400 MHz, MeOD) δ 7.95 (s, 1H), 7.21-7.33 (m, 12H), 6.82-6.84 (m, 2H), 5.92 (dd, *J*₁ = 11.2 Hz, *J*₂ = 17.6 Hz, 1H), 5.55-5.59 (m, 1H), 5.18-5.31 (m, 2H), 4.54-4.68 (m, 1H), 4.26-4.33 (m, 1H), 3.76 (s, 3H), 3.43 (dd, *J*₁ = 12.4 Hz, *J*₂ = 36.4 Hz, 2H). ESI-LCMS: *m/z* 584.1 [M + H]⁺.

[0340] Preparation of (25a): **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 **P25** as a white solid (52.3 mg, 76%). ¹H NMR (400 MHz, MeOD) δ 8.03 (s, 1H), 6.17 (dd, *J*₁ = 3.2 Hz, *J*₂ = 16.8 Hz, 1H), 6.03 (dd, *J*₁ = 11.2 Hz, *J*₂ = 17.2 Hz, 1H), 5.50 (dd, *J*₁ = 1.6 Hz, *J*₂ = 17.2 Hz,

1H), 5.23-5.38 (m, 2H), 4.76 (dd, $J_1 = 4.8$ Hz, $J_2 = 18.0$ Hz, 1H), 3.60 (dd, $J_1 = 12.0$ Hz, $J_2 = 44.8$ Hz, 2H). ESI-MS: m/z 334.1 $[M + Na]^+$.

EXAMPLE 26
Preparation of Compound (26a)



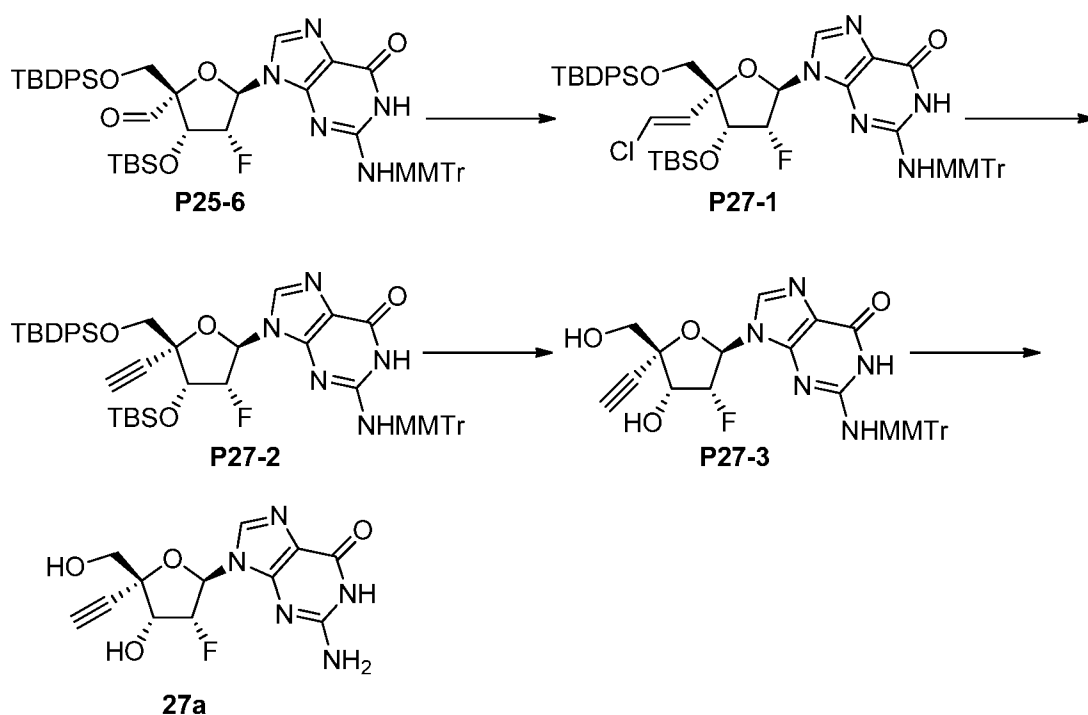
[0341] **Preparation of (P26-1):** To a stirred solution of **P25-6** (2.1 g, 2.2 mmol) in pyridine was added $HONH_2 \cdot HCl$ (0.61 g, 8.8 mmol) at 25°C. The mixture was stirred at 25°C for 2 hours. The mixture was concentrated, and the residue was purified by column chromatography (DCM:MeOH = 200:1 to 50:1) to give **P26-1** as a white solid (1.8 g, 83%).

[0342] **Preparation of (P26-2):** 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%).

[0343] **Preparation of (P26-3):** 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%). ^1H NMR (400 MHz, MeOD) δ 7.80 (s, 1H), 7.20-7.32 (m, 12H), 6.86-6.88 (m, 2H), 5.82 (dd, $J_1 = 2.0$ Hz, $J_2 = 20.0$ Hz, 1H), 4.51-4.66 (m, 1H), 3.94 (dd, $J_1 = 5.2$ Hz, $J_2 = 20.8$ Hz, 1H), 3.78 (s, 3H), 3.56 (dd, $J_1 = 12.4$ Hz, $J_2 = 42.0$ Hz, 2H). ESI-LCMS: m/z 583.1 $[M + H]^+$.

[0344] Preparation of (26a): **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 compound **26a** as a white solid (100.4 mg, 95%). ¹H NMR (400 MHz, MeOD) δ 7.90 (s, 1H), 6.34 (dd, $J_1 = 2.0$ Hz, $J_2 = 19.6$ Hz, 1H), 5.49 (ddd, $J_1 = 1.6$ Hz, $J_2 = 4.4$ Hz, $J_3 = 52.4$ Hz, 1H), 5.01 (dd, $J_1 = 4.8$ Hz, $J_2 = 20.8$ Hz, 1H), 3.93 (dd, $J_1 = 12.4$ Hz, $J_2 = 44.8$ Hz, 2H). ESI-MS: m/z 311.1 [M + H]⁺.

EXAMPLE 27
Preparation of Compound (27a)



[0345] Preparation of (P27-1): To a stirred solution of chloromethyl-triphenylphosphonium 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 NH₄Cl (50 mL). The mixture was extracted with EtOAc. The combined organic phase was dried with Na₂SO₄, 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%).

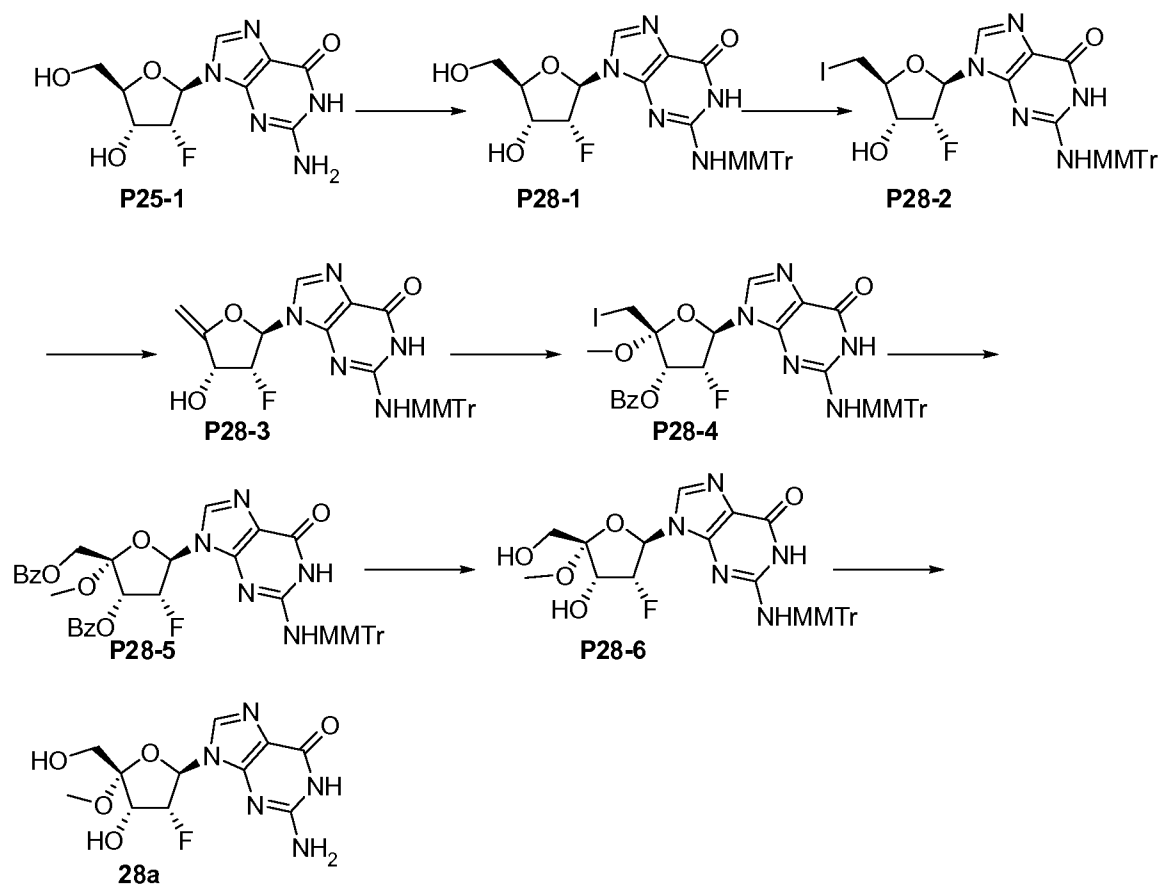
[0346] Preparation of (P27-2): To a stirred solution of **P27-1** (1.2 g, 1.3 mmol) in anhydrous THF (20 mL) was added dropwise n-BuLi (8.0 mL, 20 mmol, 2.5 M in THF) at -78°C over 10 minutes. Stirring was continued at -78°C for 4 hours. The reaction was quenched

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%).

[0347] Preparation of (P27-3): 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%). ^1H NMR (400 MHz, MeOD) δ 7.85 (s, 1H), 7.21-7.31 (m, 12H), 6.84~6.87 (m, 2H), 5.67 (dd, $J_1 = 1.6$ Hz, $J_2 = 19.2$ Hz, 1H), 4.47-4.62 (m, 1H), 3.94 (dd, $J_1 = 5.2$ Hz, $J_2 = 22.4$ Hz, 1H), 3.77 (s, 3H), 3.56 (dd, $J_1 = 12.4$ Hz, $J_2 = 47.2$ Hz, 2H), 3.04 (s, 1H). ESI-LCMS: m/z 582.1 $[\text{M} + \text{H}]^+$.

[0348] Preparation of (27a): **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 compound **27a** as a white solid (43.0 mg, 63%). ^1H NMR (400 MHz, MeOD) δ 7.95 (s, 1H), 6.22 (dd, $J_1 = 2.4$ Hz, $J_2 = 18.4$ Hz, 1H), 5.49 (ddd, $J_1 = 2.0$ Hz, $J_2 = 4.8$ Hz, $J_3 = 53.2$ Hz, 1H), 4.77 (dd, $J_1 = 5.2$ Hz, $J_2 = 20.0$ Hz, 1H), 3.79 (dd, $J_1 = 12.4$ Hz, $J_2 = 46.8$ Hz, 2H), 3.12 (s, 3H). ESI-MS: m/z 310.1 $[\text{M} + \text{H}]^+$.

EXAMPLE 28
Preparation of Compound (28a)



[0349] Preparation of (P28-1): To a stirred solution of **P25-1** (5.7 g, 20 mmol) in anhydrous pyridine (20 mL) was added dropwise Ac₂O (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 NaHCO₃ and extracted with EA. The organic layer was dried over Na₂SO₄ 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 NH₃ 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%).

[0350] Preparation of (P28-2): To a stirred solution of **P28-1** (9.2 g, 16.5 mmol) in dry THF (300 mL) were added imidazole (9.0 g, 132 mmol) and PPh₃ (34.8 g, 132 mmol). A solution of I₂ (26.0 g, 103 mmol) in THF (100 mL) was added dropwise under N₂ at 0°C. The mixture was stirred at R.T. for 18 hours. The reaction was quenched with Na₂S₂O₃ solution, and the mixture was extracted with EtOAc. The organic layer was dried over Na₂SO₄ 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%).

[0351] Preparation of (P28-3): 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 NaHCO₃ solution and extracted with EtOAc. The organic layer was dried over Na₂SO₄ 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 %). ¹H NMR (CD₃OD, 400 MHz) δ 7.71(s, 1H), 7.23-7.76 (m, 14H), 6.74 (d, J = 0.8 Hz, 2H), 5.83-5.88 (dd, J_1 = 2.8 Hz, J_2 = 16.0 Hz, 2H), 4.57-4.89 (m, 2H), 4.30-4.35(m, 1H), 4.79 (s, 3H). ESI-MS: m/z 540 [M + H]⁺.

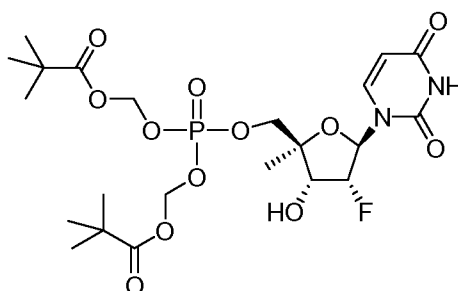
[0352] Preparation of (P28-4): To a stirred solution of **P28-4** (5.42 g, 10 mmol) in anhydrous CH₃OH (100 mL) were added PbCO₃ (13.7 g, 53.1mmol) followed by a solution of I₂ (12.3 g, 48.9 mmol) in CH₃OH (300 mL) at 0°C. The mixture was stirred at R.T. for 10 hours. The solution was quenched with a Na₂S₂O₃ solution and extracted with DCM. The organic layer was washed with NaHCO₃ solution, dried over Na₂SO₄ 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 NaHCO₃ solution, and extracted with EtOAc. The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by silica gel column chromatography (PE/EtOAc = 5:1 to 1:1) to afford **P28-4** as a white solid (2.1 g, 77.1%).

[0353] Preparation of (P28-5): **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 Na₂SO₄. 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%).

[0354] Preparation of (P28-6): **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%). ¹H NMR (400 MHz, MeOD) δ 7.84 (s, 1H), 7.20-7.33 (m, 12H), 6.83-6.86 (m, 2H), 5.64 (dd, J_1 = 1.6 Hz, J_2 = 18.4 Hz, 1H), 4.46-4.62 (m, 1H), 4.08 (dd, J_1 = 6.0 Hz, J_2 = 22.0 Hz, 1H), 3.76 (s, 3H), 3.58 (dd, J_1 = 12.4 Hz, J_2 = 30.4 Hz, 2H), 3.31 (s, 3H). ESI-LCMS: m/z 588.1 [M + H]⁺.

[0355] Preparation of (28a): **P28-8** (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 compound **28a** as a white solid (46.1 mg, 43%). ¹H NMR (400 MHz, MeOD) δ 7.92 (s, 1H), 6.22 (dd, $J_1 = 1.6$ Hz, $J_2 = 18.8$ Hz, 1H), 5.25 (ddd, $J_1 = 1.6$ Hz, $J_2 = 6.0$ Hz, $J_3 = 54.0$ Hz, 1H), 4.89-4.91 (m, 1H), 3.87 (d, $J = 11.6$ Hz, 1H), 3.67 (d, $J = 12.0$ Hz, 1H), 3.44 (s, 3H). ESI-MS: m/z 316.1 [M + H]⁺.

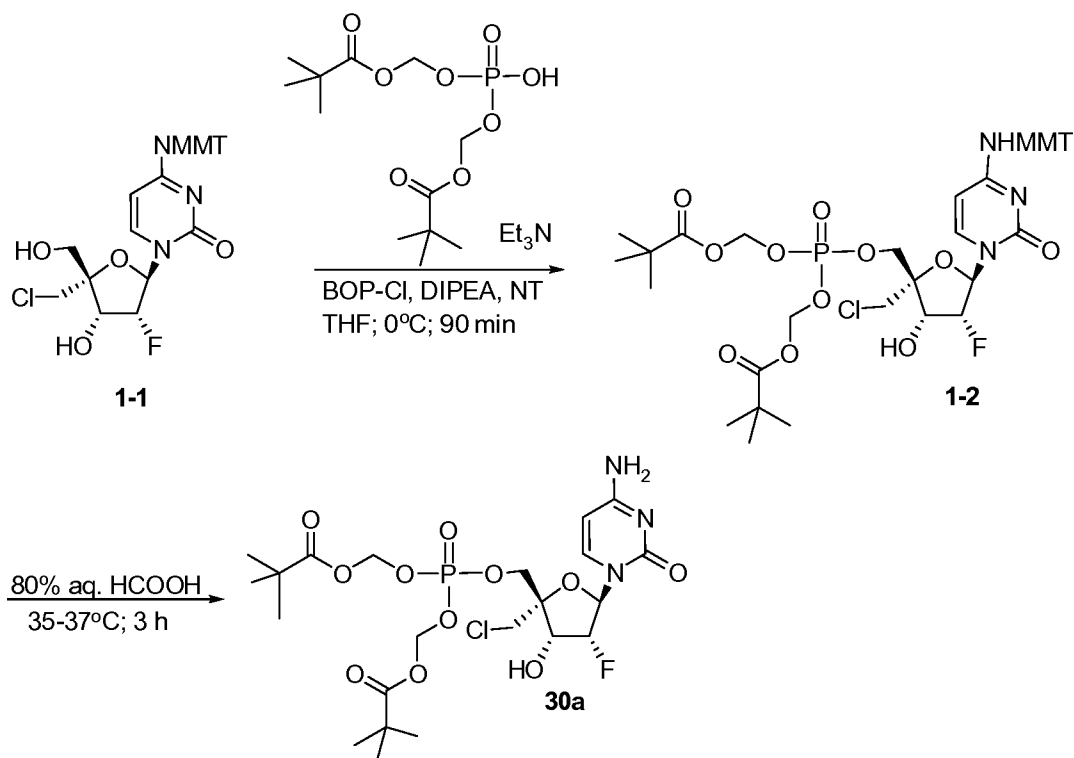
EXAMPLE 29
Preparation of Compound (29a)



[0356] 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 compound **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 μ L) 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 the compound (2.8 mg) as a colorless residue; ¹H NMR (CD₃OD, 400 MHz) δ 7.65 (d, $J = 8.0$ Hz, 1H), 5.94 (dd, $J_1 = 2.4$ Hz, $J_2 = 18.8$ Hz, 1H), 5.70 (d, $J = 8.0$ Hz, 1H), 5.69 (d, $J = 0.8$ Hz, 1H), 5.68 (s, 1H), 5.654 (d, $J = 1.2$ Hz, 1H), 5.650 (s, 1H), 5.21 (dd, $J = 2.0, 5.2$ Hz, 0.5H), 5.07 (dd, 2.0, 5.2 Hz, 0.5H), 4.42 (dd, $J = 5.6, 20.8$ Hz, 1H), 4.14 (m, 2H), 1.223 (s, 9H), 1.220 (m, 9H); ³¹P NMR (CD₃OD) 4.92 (s); MS: m/z 698 [M + 2-methylheptylamine]⁺.

EXAMPLE 30

Preparation of Compound (30a)

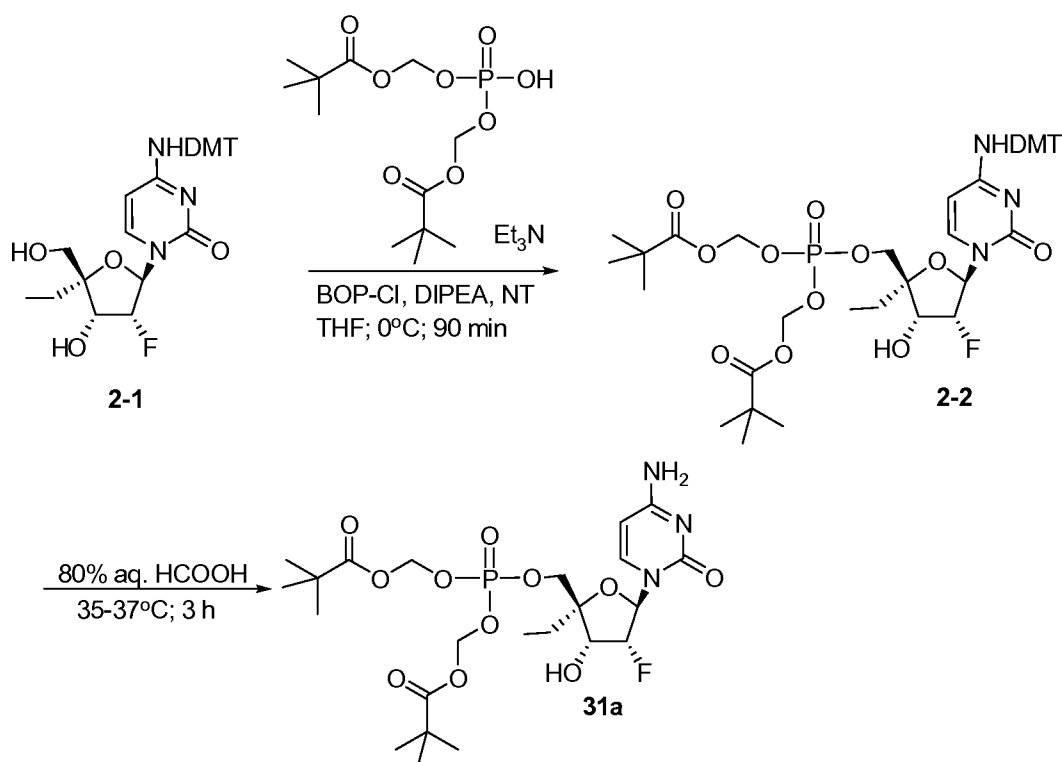


[0357] Preparation of (1-2): To a solution of **1-1** (313 mg; 0.55 mmol) in THF (8 mL) under Ar was added a solution of triethylammonium bis(POM)phosphate in THF (prepared from bis(POM)phosphate (215 mg ; 1.2 equiv), THF (2 mL) and Et₃N (0.1 mL; 1.3 equiv)). The resulting mixture cooled in an ice-bath. 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 CH₂Cl₂ (60 mL) and washed with saturated aq. NaHCO₃ (2 x 10 mL) and brine. The combined aqueous layers were back extracted with CH₂Cl₂ (~20 mL). The combined organic extract was dried (Na₂SO₄) and evaporated. The residue purified on silica (25 g column) with CH₂Cl₂ /i-PrOH solvent system (2-10% gradient). Yield: 140 mg (27%).

[0358] Preparation of (30a): 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 CH₂Cl₂ /MeOH solvent system (4-10% gradient) to afford compound **30a** (46 mg, 59% yield). ³¹P-NMR (DMSO-d₆): δ -4.45. MS: m/z 646 (M+46-1).

EXAMPLE 31

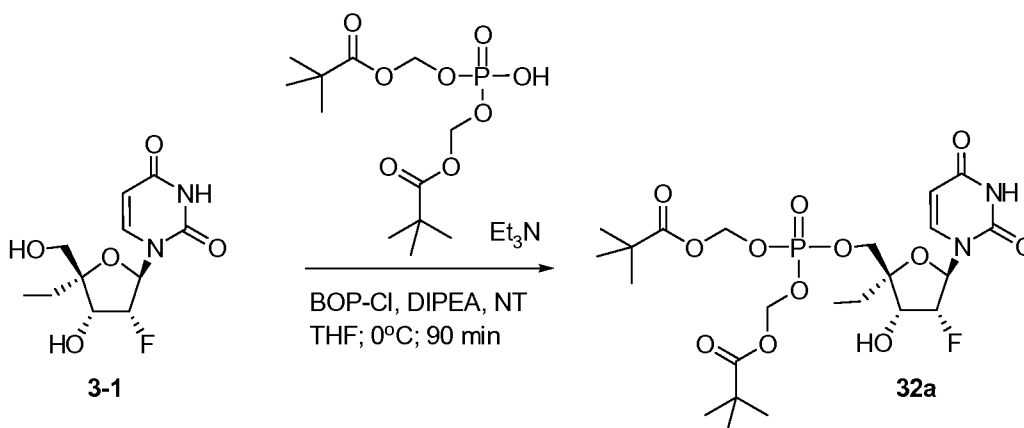
Preparation of Compound (31a)



[0359] Preparation of (2-2): 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 CH₂Cl₂ (50 mL) and washed with saturated aq. NaHCO₃ (2 x 10 mL) and brine. The combined aqueous layers were back extracted with CH₂Cl₂ (~20 mL). The combined organic extract was dried (Na₂SO₄), evaporated, and the residue purified on silica (25 g column) with CH₂Cl₂ /i-PrOH solvent system (2-10% gradient). Yield: 154 mg (27%).

[0360] Preparation of (31a): 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 CH₂Cl₂ /MeOH solvent system (4-10% gradient; target compound eluted with 8% MeOH) afforded **31a** (35 mg, 78% yield). ³¹P-NMR (DMSO-d₆): δ -4.19. MS: m/z 580 (M-1), 646 (M+46-1), 550 (M-30-1).

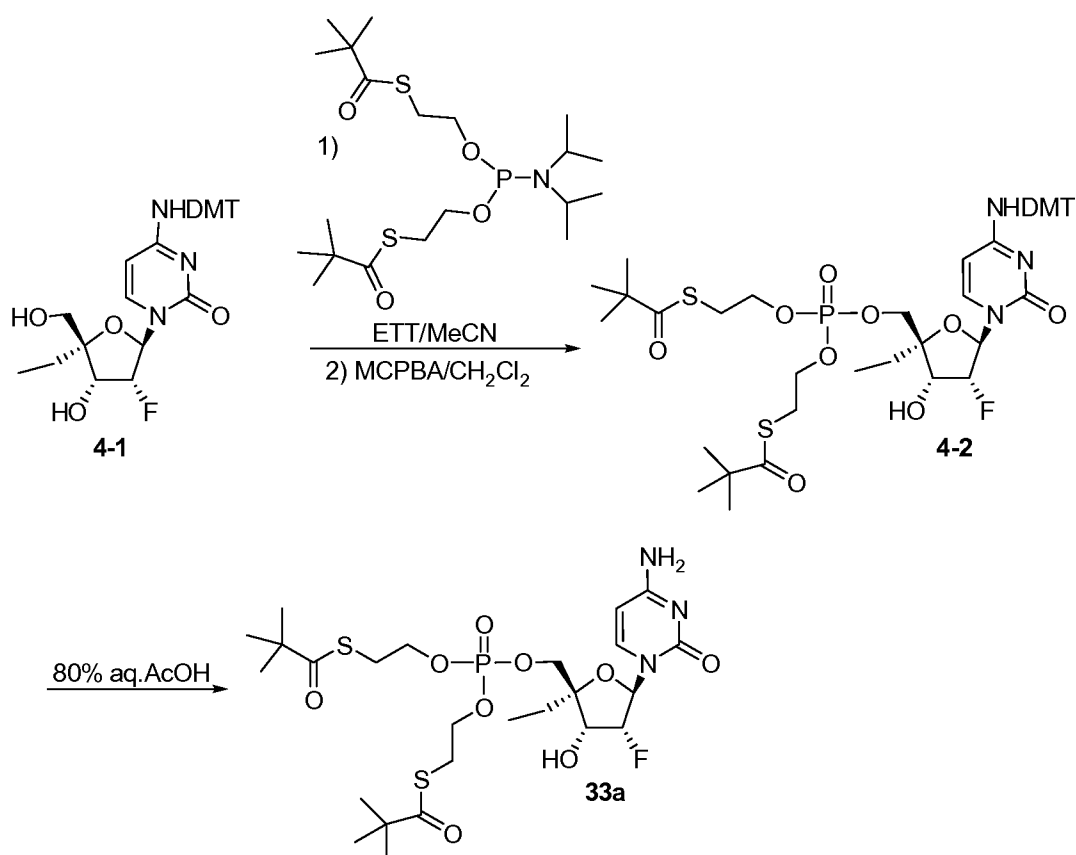
EXAMPLE 32
Preparation of Compound (32a)



[0361] 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 CH₂Cl₂ (50 mL) and washed with saturated aq. NaHCO₃ (2 x 10 mL) and brine. The combined aqueous layers were back extracted with CH₂Cl₂ (~20 mL). The combined organic extract was dried (Na₂SO₄), evaporated, and the residue was purified on silica (10 g column) with CH₂Cl₂/MeOH solvent system (4-10% gradient). Compound **32a** was repurified by RP-HPLC (35-90%B; A: water, B: MeOH). Yield 75 mg (50%). ³¹P-NMR (DMSO-d₆): δ -4.14. MS: m/z 627 (M+46-1), 551 (M-30-1).

EXAMPLE 33

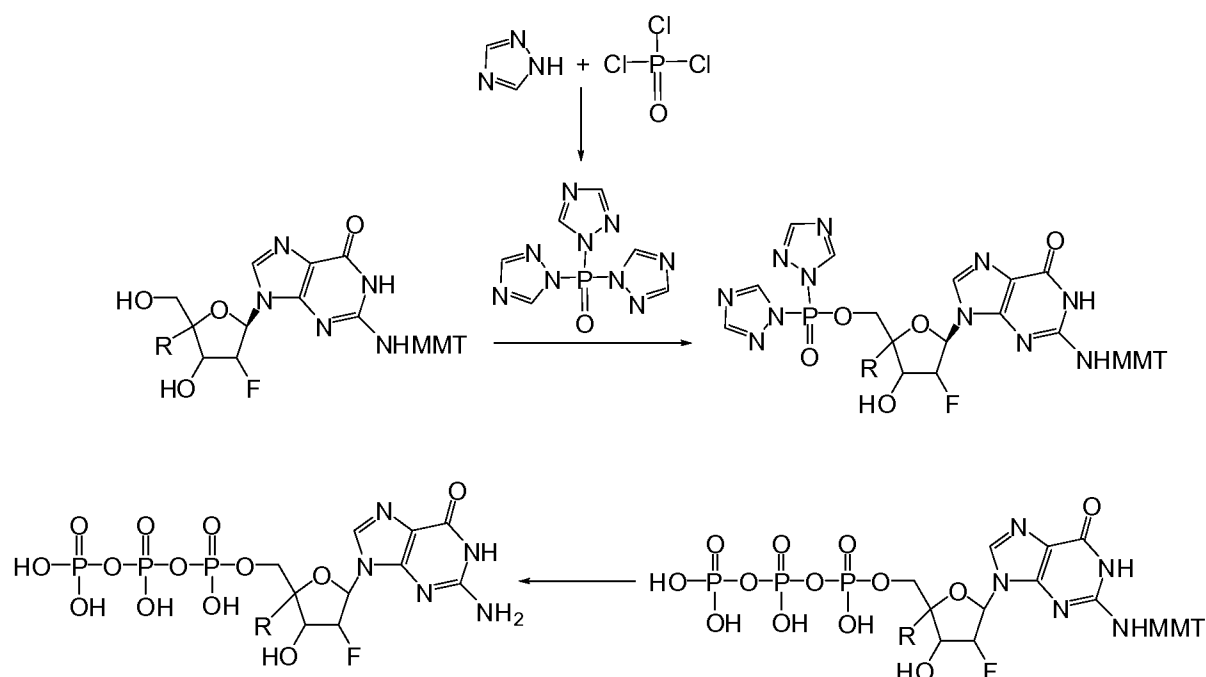
Preparation of Compound (33a)



[0362] Preparation of (4-2): 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 CH₂Cl₂ (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. NaHSO₃ (2 x 10 mL), saturated aq. NaHCO₃ (2 x 10 mL) and brine. The mixture was then dried (Na₂SO₄). The evaporated residue was purified on silica (10 g column) with CH₂Cl₂ /MeOH solvent system (4-10% gradient) to afford **4-2** (0.26 g, 55% yield).

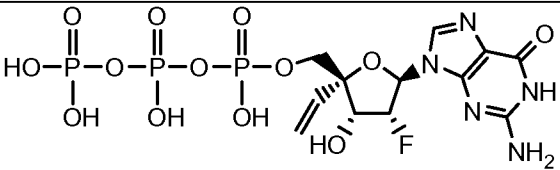
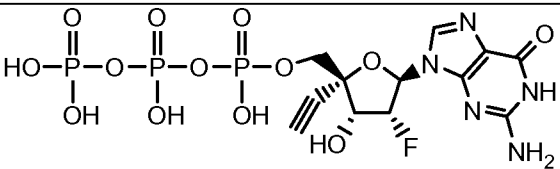
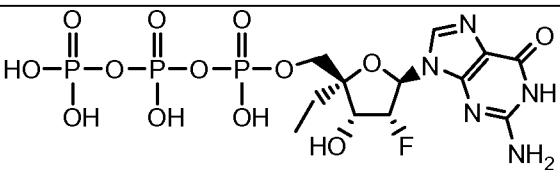
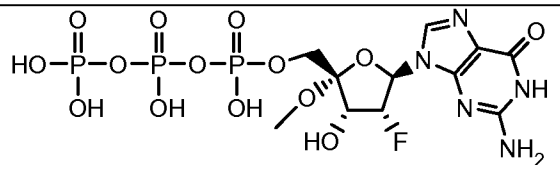
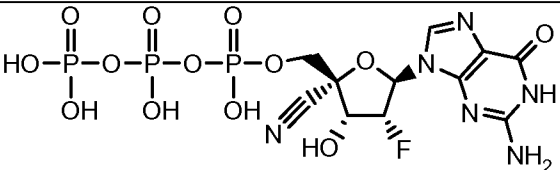
[0363] Preparation of (33a): A solution of **4-2** (0.21 g; 0.22 mmol) in 80% aq. AcOH (15 mL) was stirred 4 hours at R.T. The mixture was evaporated and purified on silica (10 g column) with CH₂Cl₂ /MeOH solvent system (4-10% gradient). Yield: 0.13 g (90%). ³¹P-NMR (DMSO-d₆): δ -2.00. MS: m/z 686 (M+46-1).

EXAMPLE 34
Preparation of Compounds (34a)-(34e)

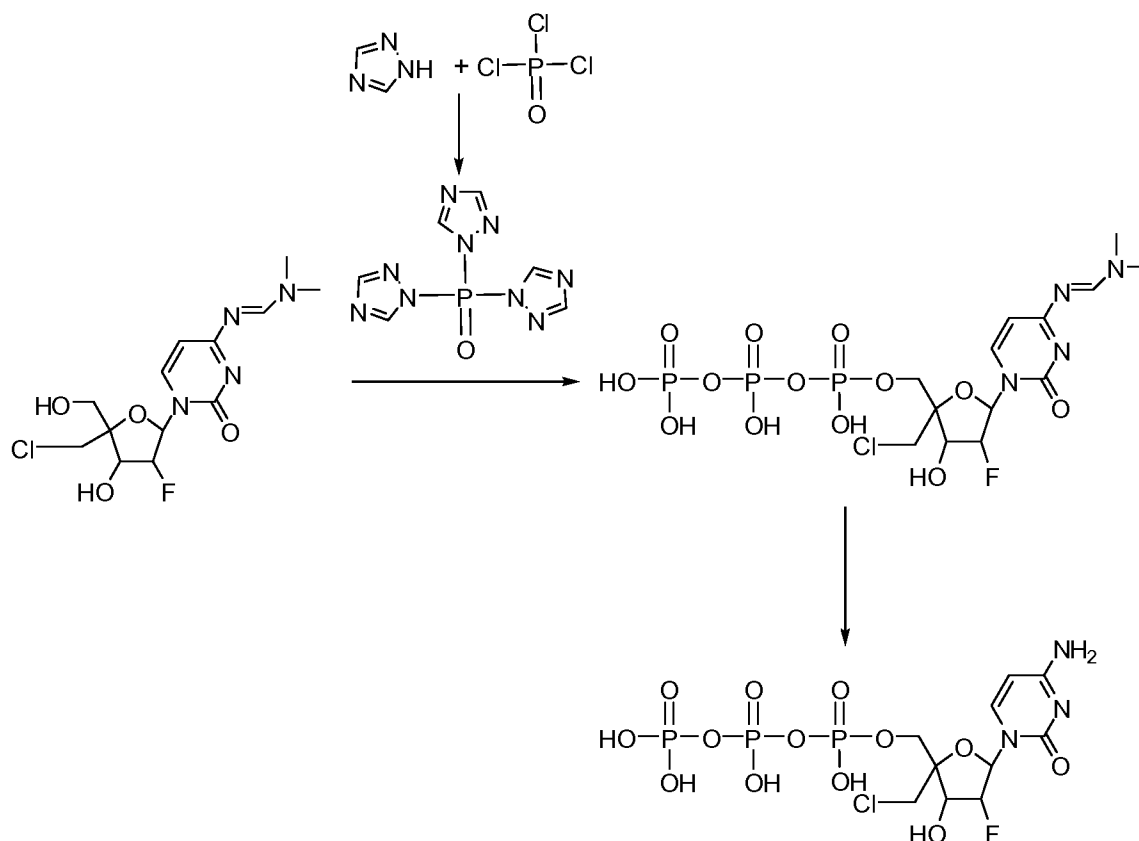


[0364] 1,2,4-Triazol (42 mg, 0.6 mmol) was suspended of dry CH₃CN (1 mL). Triethylamine was added (0.088 mL, 0.63 mmol), and the mixture was vortexed to obtain a clear solution. After addition of POCl₃ (0.01 mL, 0.1 mmol), the mixture was vortexed and left for 20 min. The mixture was then centrifugated. The supernatant was added to the protected nucleoside (0.05 mmol), and the mixture was kept at ambient temperature for 1 hour. Tris(tetrabutylammonium) hydrogen pyrophosphate (180 mg, 0.2 mmol) was added, and the mixture was kept for 2 hours at R.T. The reaction was quenched with water, evaporated, dissolved in 80% formic acid and left for 2 hours at R.T. Formic acid was evaporated, and the residue dissolved in water (5 mL) and extracted with EA (2 x 2 mL). The aqueous fraction was loaded onto column HiLoad 16/10 with Q Sepharose High Performance (linear gradient of NaCl from 0 to 1N in 50mM TRIS-buffer (pH = 7.5)). Fractions containing the triphosphate were combined, concentrated and desalted by RP HPLC on Synergy 4 micron Hydro-RP column (Phenominex) using a linear gradient of methanol from 0 to 20% in 50mM triethylammonium acetate buffer (pH 7.5) for elution. The following compounds shown in Table 1 were synthesized according this procedure:

Table 1 – Triphosphates obtained from Example 34

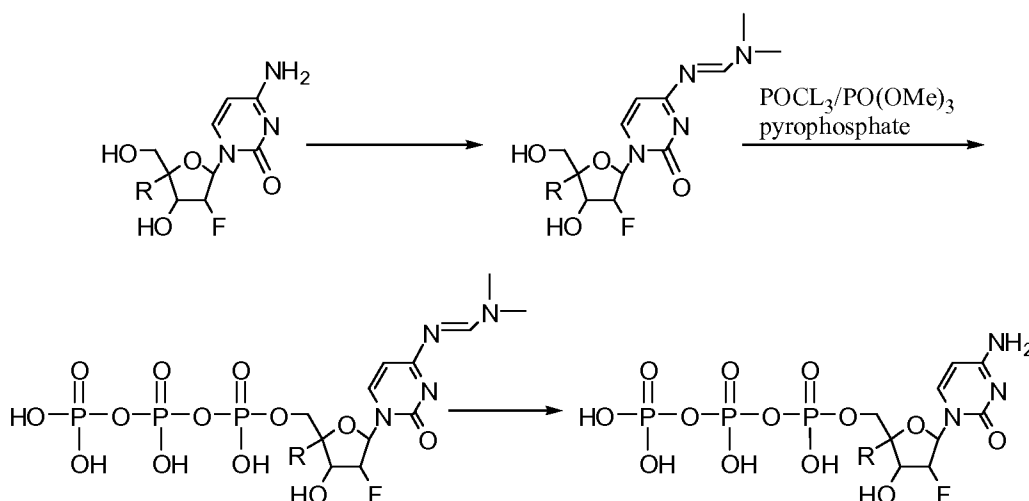
Compound	^{31}P NMR $\text{P}\alpha$	^{31}P NMR $\text{P}\beta$	^{31}P NMR $\text{P}\gamma$	MS (M ⁺)
 34a	-11.31 d	-20.82 t	-5.48 d	550.2
 34b	-9.13 d	-18.18 t	-2.85 d	548.2
 34c	-10.95 d	-20.62 bs	-5.37 bs	552.2
 34d	-11.24 d	-20.82 t	-5.48 d	554.2
 34e	-12.06 d	-20.97 t	-5.69 d	549.2

EXAMPLE 35
Preparation of Compound (35a)



[0365] 1,2,4-Triazol (42 mg, 0.6 mmol) was suspended in dry CH₃CN (1 mL). Triethylamine was added (0.088 mL, 0.63 mmol), and the mixture was vortexed to obtain a clear solution. After addition of POCl₃ (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 (Phenomenex). 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. ³¹P-NMR (δ ppm): -5.12 (d), -11.31 (d) and -20.43 (t).

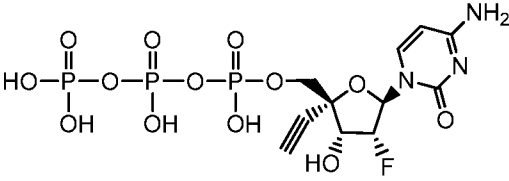
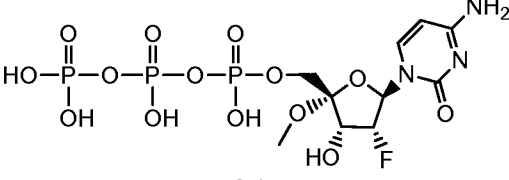
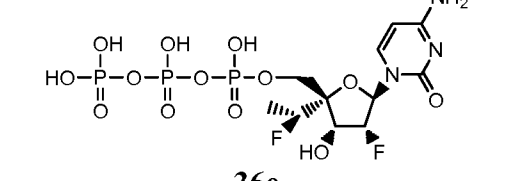
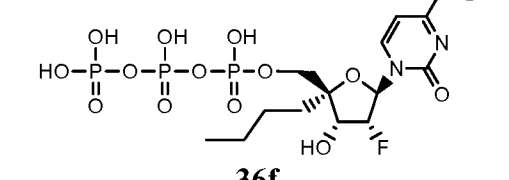
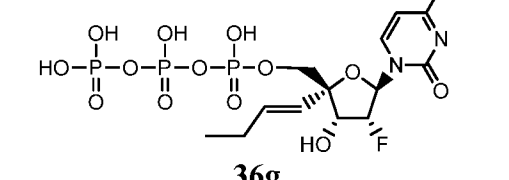
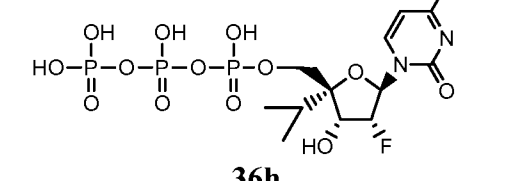
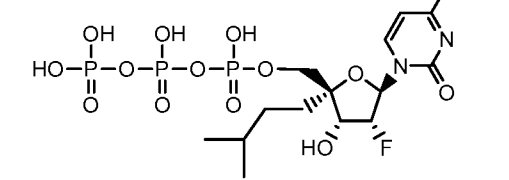
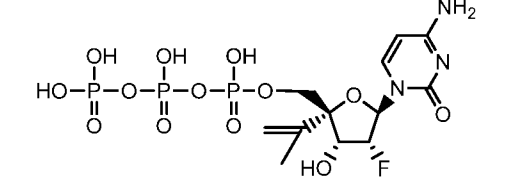
EXAMPLE 36
Preparation of Compounds (36a)-(36d)



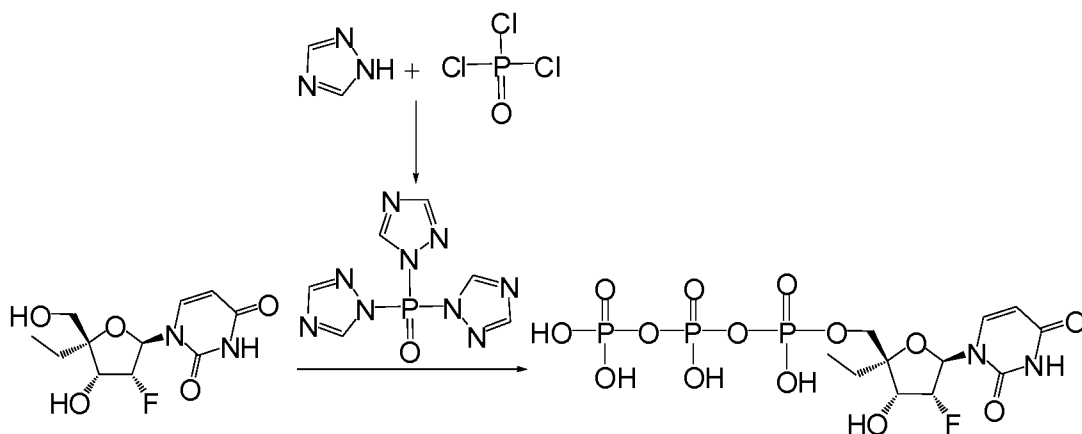
[0366] 2'-Deoxy-2'-fluoro-4'-alkyl-cytidine (0.09 mmol) was dissolved in the mixture of DMF (5 mL) and N,N'-dimethylacetate in DMF (0.110 mL, 0.9 mmol). The reaction mixture left at R.T. overnight. The solvent was evaporated, and the residue purified by flash chromatography in gradient of methanol in 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 POCl₃ (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 NH₄OH 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 P _α	³¹ P NMR P _β	³¹ P NMR P _γ	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

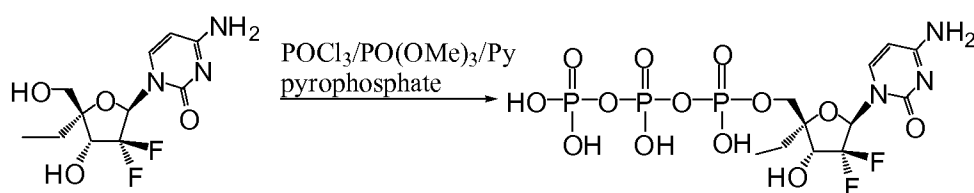
Compound	^{31}P NMR $\text{P}\alpha$	^{31}P NMR $\text{P}\beta$	^{31}P NMR $\text{P}\gamma$	MS (M^-)
 36c	-11.96 bs	-22.07 t	-5.66 d	508.3
 36d	-11.90 d	-23.23 t	-10.66 d	514.0
 36e	-11.77 d	-23.05 t	-9.70 s	529.9
 36f	-11.74 d	-23.37 t	-10.85 d	539.2
 36g	-11.87 d	-23.32 t	-10.83 d	523.9
 36h	-11.48 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)



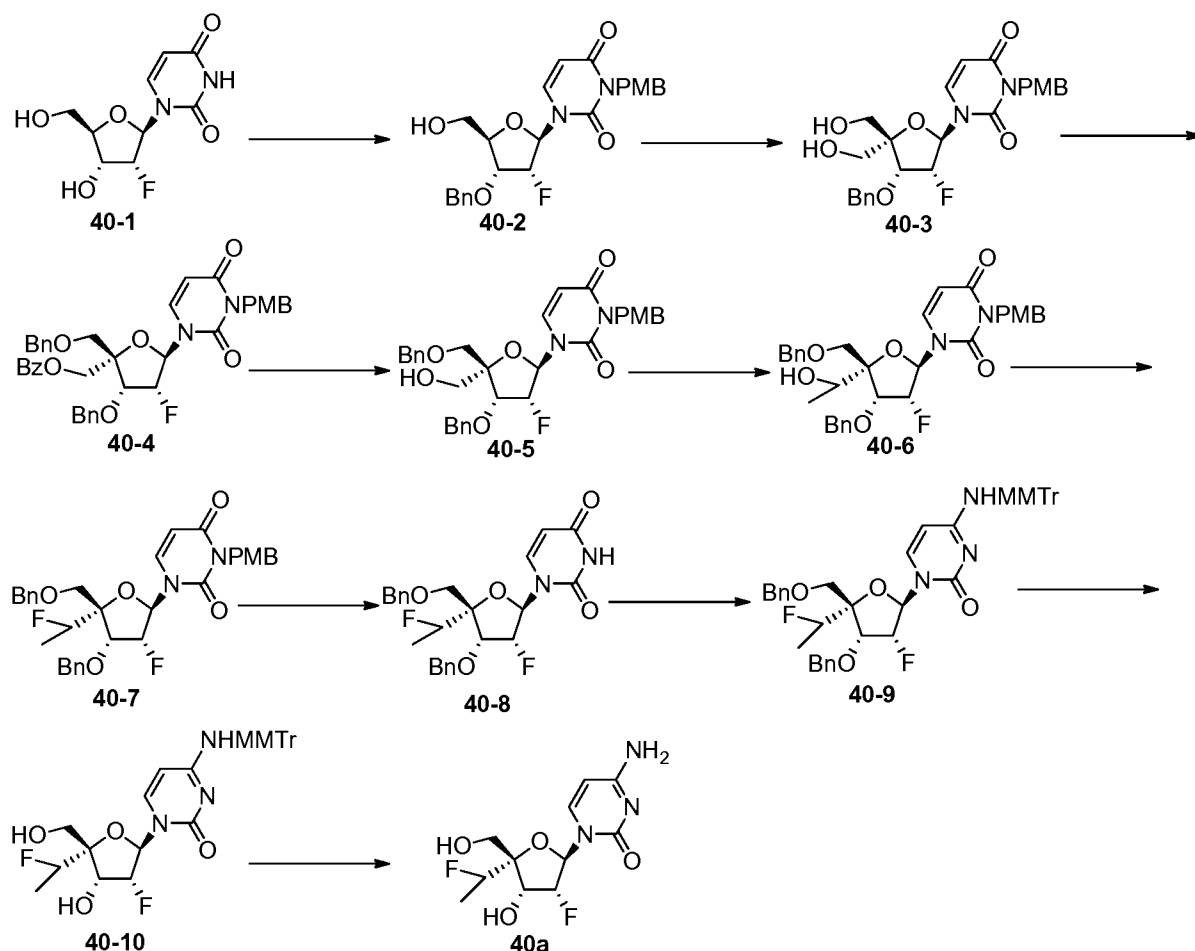
[0367] Compound **37a** was synthesized by reaction of phosphor(tris-triazolide) with 4'-ethyl-2'-deoxy-2'-fluoro-uridine as described Examples 34 and 35. MS (M-1): 513.1. ³¹P-NMR (δ ppm): -9.43 (bs), -11.68 (d) and -23.09 (bs).

EXAMPLE 38
Preparation of Compounds (38a)



[0368] The starting nucleoside (15 mg, 0.05 mmol) was dissolved in dry trimethylphosphate (3 mL). The solution was cooled to 4°C. POCl₃ (0.013 mL, 0.125 mmol) was added, followed by pyridine (0.01 mL, 0.125 mmol). In 1 hour, tributylamine (0.035 mL, 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 NH₄OH for 2 hours at R.T. The product was desalted by RP HPLC as described in Example 35. MS (M-1): 529.9. ³¹P-NMR (δ ppm): -9.42(d), -11.59(d) and -23.03(t).

EXAMPLE 39
Preparation of Compound (40a)



[0369] **Preparation of (40-2):** 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 Na₂SO₄ 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 K₂CO₃ (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 Na₂SO₄ 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 Na₂SO₄ 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).

[0370] Preparation of (40-3): To a solution of **40-2** (42.1 g, 92.6 mmol) in anhydrous CH₃CN (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% CH₂O (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 NaBH₄ (19.7 g, 518.6 mmol) were added, stirred at R.T. for 30 mins. The mixture was quenched with saturated aqueous NH₄Cl, and extracted with EA. The organic layer was dried over Na₂SO₄ 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.

[0371] Preparation of (40-4): To a stirred solution of **40-3** (25.5 g, 52.5 mmol) in anhydrous pyridine (150 mL) and anhydrous CH₃CN (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 H₂O, and the solution was concentrated. The residue was dissolved in EA and washed with saturated NaHCO₃. The organic layer was dried over Na₂SO₄ 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 Cs₂CO₃ (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 NH₄Cl 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.

[0372] Preparation of (40-5): 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.

[0373] Preparation of (40-6): To a stirred solution of compound **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). To 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.

[0374] Preparation of (40-7): To a stirred solution of DAST (1.64 g, 10.17 mmol) in anhydrous toluene (40 mL) was added dropwise a solution of compound **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%). ^1H 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 (d, J = 16.8, 2.0 Hz, 1H), 5.18-5.50 (m, 4H), 4.96 (s, 2H), 4.45-4.88 (m, 7H), 3.67-3.89 (m, 5H).

[0375] Preparation of (40-8): A mixture of compound **40-7** (0.91 g, 1.54 mmol) and CAN (2.53 g, 4.61 mmol) in a 3:1 solution of MeCN:water (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. 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%).

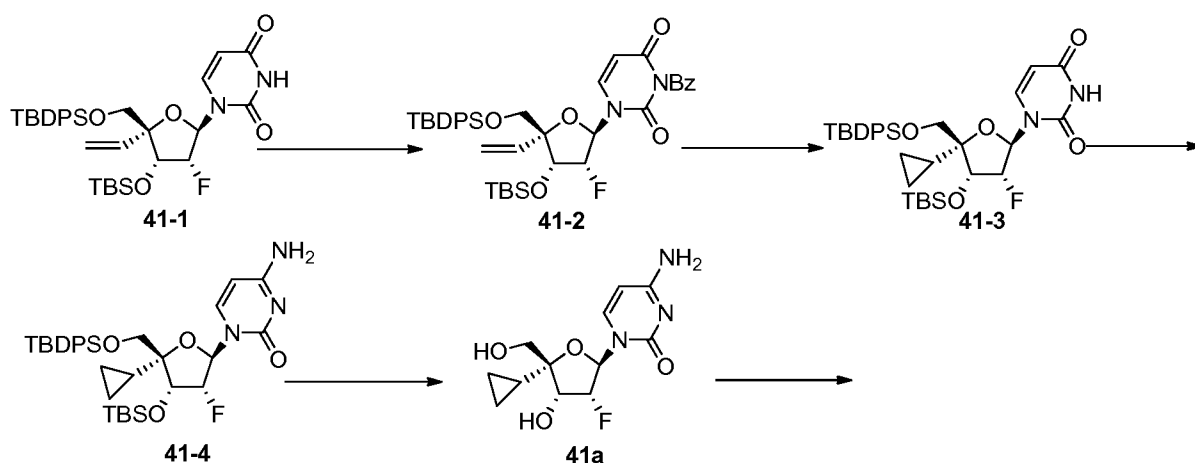
[0376] Preparation of (40-9): To a stirred solution of **40-8** (350 mg, 0.74 mmol) in anhydrous MeCN (8 mL) were added TPSCl (449 mg, 1.48 mmol), DMAP (180 mg, 1.48 mmol) and TEA (374 mg, 3.70 mmol) at R.T. The mixture was stirred at R.T. overnight. NH_4OH (15 mL) was added, and the mixture was stirred 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 (695 mg, 2.25 mmol) and AgNO_3 (380 mg, 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%).

[0377] Preparation of (40-10): To a stirred solution of compound **40-9** (450 mg, 0.61 mmol) in acetone were added ammonium formate (1.29 g, 20.6 mmol, 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%). ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 8.56

(s, 1H), 7.73 (d, $J = 7.6$ Hz, 1H), 7.14-7.28 (m, 12H), 6.84 (d, $J = 8.8$ Hz, 2H), 6.30 (d, $J = 7.6$ Hz, 1H), 6.03-6.08 (m, 1H), 5.84 (d, $J = 5.2$ Hz, 1H), 5.33-5.35 (m, 1H), 4.97-5.18 (m, 1H), 4.86-4.90 (m, 1H), 4.34 (d, $J = 4.4$ Hz, 1H), 3.72 (s, 3H), 3.54-3.57 (m, 2H), 1.28 (dd, $J_1 = 6.4$ Hz, $J_2 = 25.6$ Hz, 3H). ESI-MS: m/z 563.50 $[M + H]^+$.

[0378] Preparation of (40a): **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%). ^1H NMR (CD_3OD , 400 MHz) δ 7.98 (d, $J = 7.6$ Hz, 1H), 6.20-6.24 (m, 1H), 5.92 (d, $J = 7.2$ Hz, 1H), 5.17-5.30 (m, 1H), 4.99-5.14 (m, 1H), 4.51-4.86 (m, 1H), 3.78 (d, $J = 1.6$ Hz, 2H), 1.35-1.43 (m, 3H). ESI-MS: m/z 291.84 $[M + H]^+$, 582.81 $[2M + H]^+$.

EXAMPLE 40 Preparation of Compound (41a)



[0379] Preparation of (41-2): 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%).

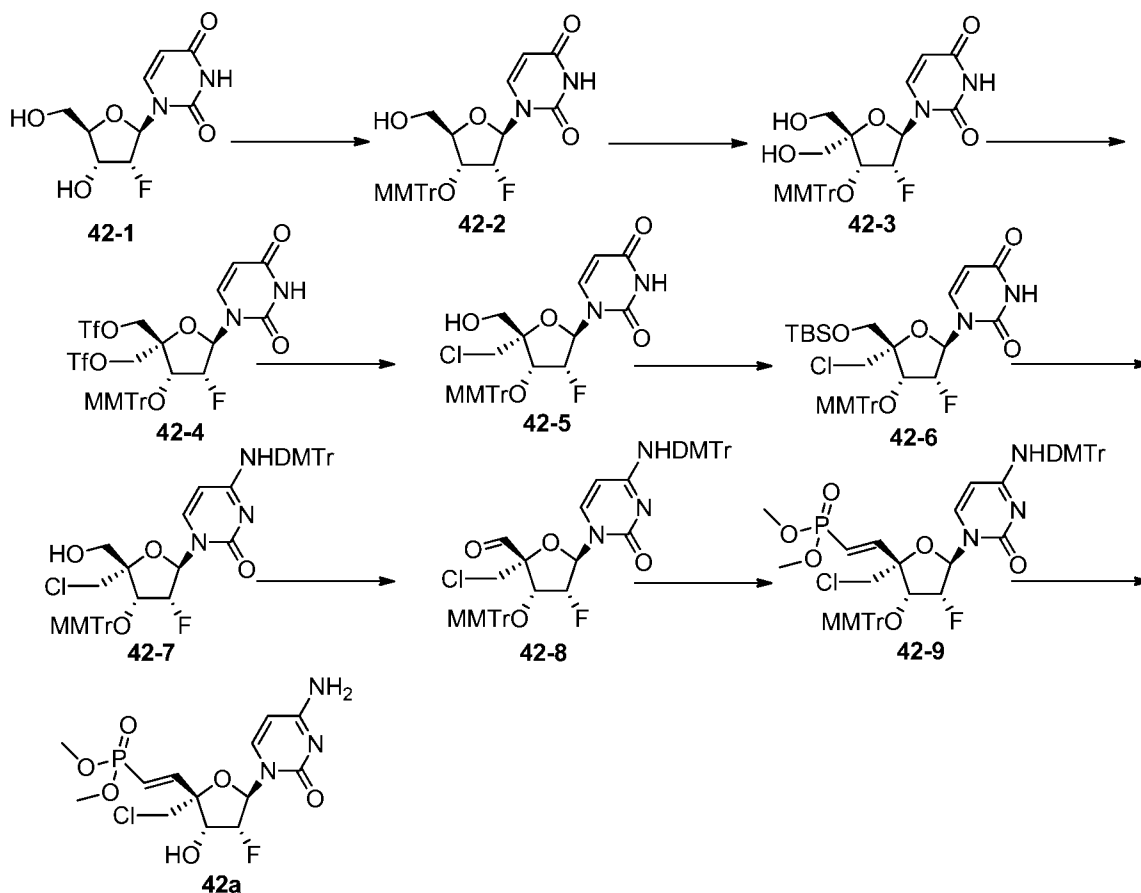
[0380] Preparation of (41-3): A mixture of **41-2** (2.6 g, 3.6 mmol) and $\text{Pd}(\text{OAc})_2$ (100 mg) in DCM (50 mL) was suspended in a solution of CH_2N_2 in Et_2O (generated by standard procedure, 350 mL) at -78°C. The reaction was stirred to R.T. overnight. The mixture was quenched with HOAc, 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 $\text{NH}_3\cdot\text{MeOH}$ (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%).

[0381] Preparation of (41-4): 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%).

[0382] Preparation of (41a): 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. ^1H NMR (CD_3OD , 400 M Hz) δ 8.13 (d, J = 7.6 Hz, 1H), 6.01 (dd, J_1 = 2.4 Hz, J_2 = 15.6 Hz, 1H), 5.85 (d, J = 7.6 Hz, 1H), 5.04-4.89 (m, 1H), 4.52 (dd, J_1 = 5.2 Hz, J_2 = 19.6 Hz, 1H), 3.66 (s, 2H), 1.00-0.94 (m, 1H), 0.54-0.30 (m, 4H); ESI-MS: m/z 285.82 $[\text{M} + \text{H}]^+$, 570.84 $[2\text{M} + \text{H}]^+$.

EXAMPLE 41
Preparation of Compound (42a)



[0383] Preparation of (42-2): 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 MMTroCl (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%).

[0384] Preparation of (42-3): 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 0°C 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% Na₂S₂O₃/4% 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 NH₄Cl (~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%).

[0385] Preparation of (42-4): **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°C. The mixture was stirred 30 mins, and extracted with EA (150 mL x 2). The organic phase was dried over Na₂SO₄, 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%).

[0386] Preparation of (42-5): **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%).

[0387] Preparation of (42-6): 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 Na₂SO₄ 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%).

[0388] Preparation of (42-7): 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-triisopropylbenzenesulfonyl chloride (16.3 g, 54.0 mmol). The mixture was stirred at R.T. for 3 hours. NH₄OH (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 Na₂SO₄ 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 Na₂SO₄ 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%).

[0389] Preparation of (42-8): 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 Na₂S₂O₃ and saturated aqueous NaHCO₃. 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.

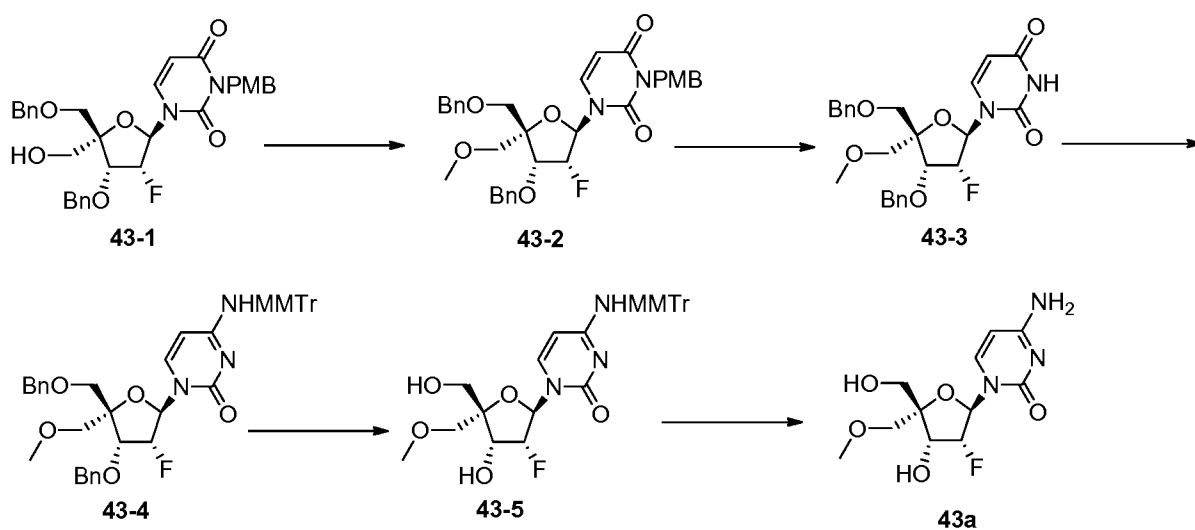
[0390] Preparation of (42-9): To a solution of tetramethyl methylenediphosphonate (390 mg, 1.68 mmol) in anhydrous THF (10 mL) was added NaH (84 mg, 2.1 mmol) at 0°C under nitrogen. The reaction was stirred at 0°C for 30 min. A solution of **42-8** (1.2 g, 1.4 mmol) in anhydrous THF (10 mL) was added 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. ^1H NMR (DMSO- d_6 , 400 M Hz) δ 8.51 (s, 1H), 7.46-7.09 (m, 22H), 6.88-6.82 (m, 6H), 6.62 (q, $J_1 = 17.2$ Hz, $J_2 = 22.4$ Hz, 1H), 6.12 (d, $J = 7.2$ Hz, 1H), 5.86-5.75 (m, 2H), 5.43 (d, $J = 25.2$ Hz, 1H), 4.63 (dd, $J_1 = 4.8$ Hz, $J_2 = 21.2$ Hz, 1H), 4.45 (d, $J = 12.0$ Hz, 1H), 3.94 (d, $J = 12.0$ Hz, 1H), 3.72 (s, 9H), 3.53 (q, $J_1 = 11.2$ Hz, $J_2 = 16.0$ Hz, 6H); ESI-MS: m/z 971.59 $[\text{M} + \text{H}]^+$.

[0391] Preparation of (42a): 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. ^1H NMR (DMSO- d_6 , 400 M Hz) δ 7.61 (d, $J = 7.6$ Hz, 1H), 7.35 (d, $J = 15.2$ Hz, 2H), 6.72 (q, $J_1 = 17.6$ Hz, $J_2 = 24.4$ Hz, 1H), 6.23 (d, $J = 6.0$ Hz, 1H), 5.99-5.85 (m, 2H), 5.74 (q, $J = 7.2$ Hz, 1H), 5.37-5.21 (m, 1H), 4.69-4.61 (m, 1H), 3.96 (d, $J = 12.4$ Hz, 1H), 3.82 (d, $J = 12.0$ Hz, 1H), 6.72 (q, $J_1 = 5.2$ Hz, $J_2 = 10.8$ Hz, 6H); ESI-MS: m/z 397.81 $[\text{M} + \text{H}]^+$.

EXAMPLE 42

Preparation of Compound (43a)



[0392] Preparation of (43-2): 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.

[0393] Preparation of (43-3): 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

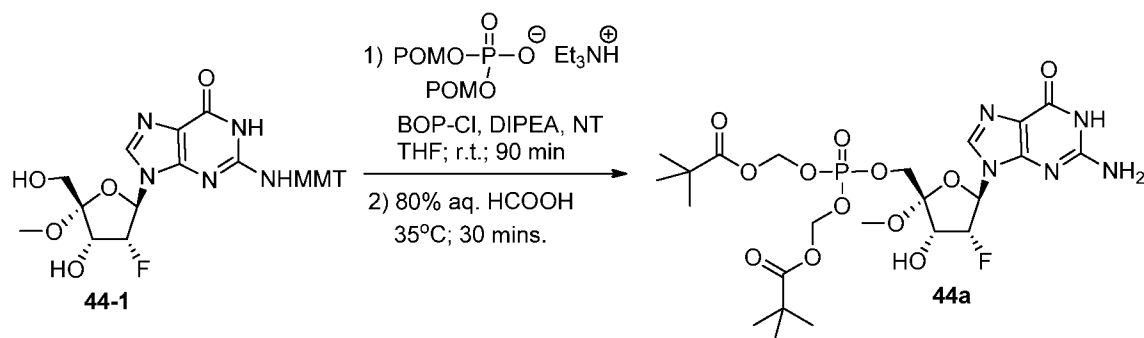
solution was diluted with brine (10 mL) and was extracted with EA. The combined organic extracts were dried and evaporated under reduced pressure. Purification by chromatography on silica (PE:EA = 1:1) gave **43-3** as a yellow solid (1.71 g, 72%).

[0394] Preparation of (43-4): 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. NH₄OH (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), AgNO₃ (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 Na₂SO₄. 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.

[0395] Preparation of (43-5): 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%).

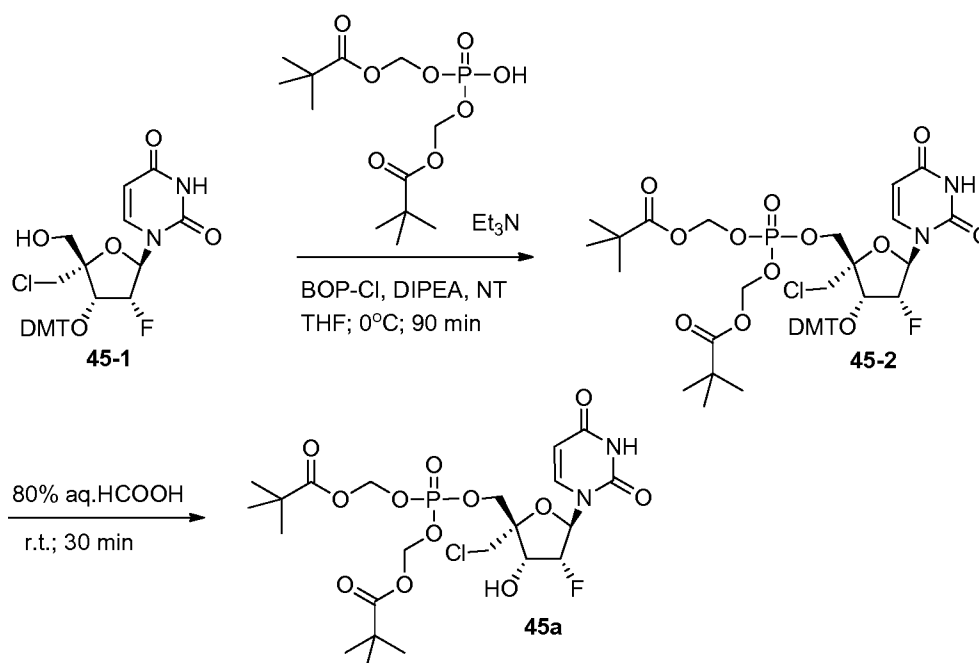
[0396] Preparation of (43a): **43-5** (200 mg, 0.36 mmol) was dissolved in 80% CH₃COOH (20 mL) at R.T. The mixture was stirred at 60°C for 12 hours. The solvent was removed. The residue was purified by column chromatography (DCM:MeOH = 10:1), and the resulting solid was washed with DCM to give pure **43a** as a white solid (44mg, 42%). ¹H NMR (CD₃OD, 400 MHz) δ 8.02 (d, J = 7.2 Hz, 1H), 6.14 (dd, J_1 = 3.6 Hz, J_2 = 15.2 Hz, 1H), 5.88 (d, J = 7.2 Hz, 1H), 5.10 (ddd, J_1 = 4.0 Hz, J_2 = 5.2 Hz, J_3 = 53.6 Hz, 1H), 4.47 (dd, J_1 = 5.2 Hz, J_2 = 14.8 Hz, 1H), 3.84 (d, J = 12.0 Hz, 1H), 3.70 (d, J = 12.0 Hz, 1H), 3.58-3.64 (m, 2H), 3.36 (s, 3H). ESI-MS: m/z 290 [M + H]⁺.

EXAMPLE 43
Preparation of Compound (44a)



[0397] 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 ($\text{DMSO}-d_6$): δ -5.07. MS: m/z = 668 ($M+46-1$).

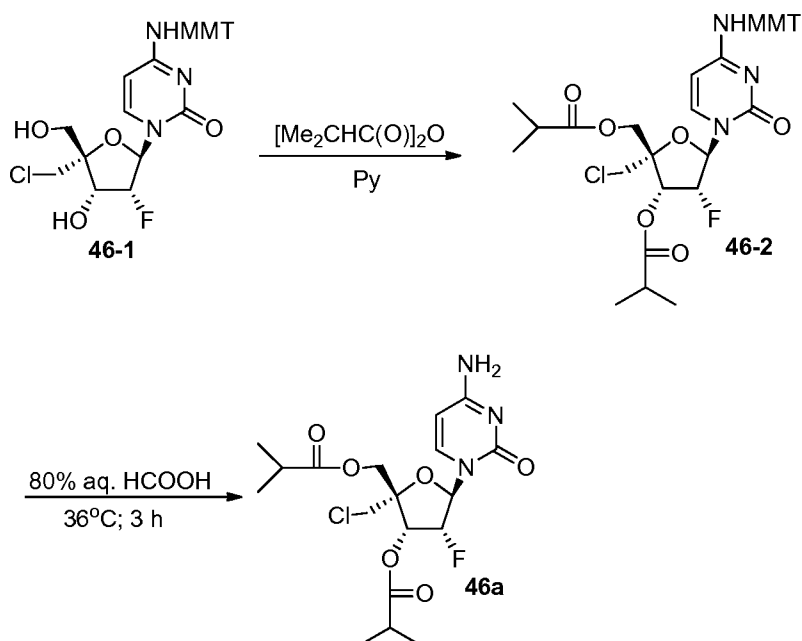
EXAMPLE 44
Preparation of Compound (45a)



[0398] Preparation of (45-2): To a solution of triethylammonium bis(POM)phosphate (0.7 mmol, prepared from 233 mg of bis(POM)phosphate and 0.1 mL of Et₃N) 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 CH₂Cl₂ (40 mL) and washed with saturated aq. NaHCO₃ and brine. The combined aqueous layers were back extracted with CH₂Cl₂. The combined organic extract was dried (Na₂SO₄), evaporated, and the residue was purified on silica (10 g column) with hexanes/EtOAc solvent system (40-100% gradient) to yield **45a** (180 mg, 47%).

[0399] Preparation of (45a): A solution of compound **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 CH₂Cl₂/MeOH solvent system (4-10% gradient) to yield **45a** (55 mg, 70%). ³¹P-NMR (DMSO-d₆): δ -4.36. MS: m/z = 647 (M+46-1).

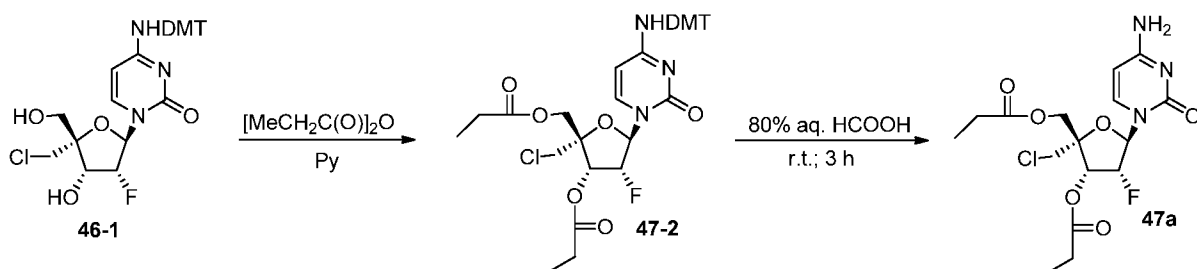
EXAMPLE 45
Preparation of Compound (46a)



[0400] Preparation of (46-2): 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%).

[0401] Preparation of (46a): 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 $\text{CH}_2\text{Cl}_2/\text{MeOH}$ solvent system (4-10% gradient) to afford **46a** (75 mg, 70%). MS: $m/z = 434$ ($\text{M}+1$).

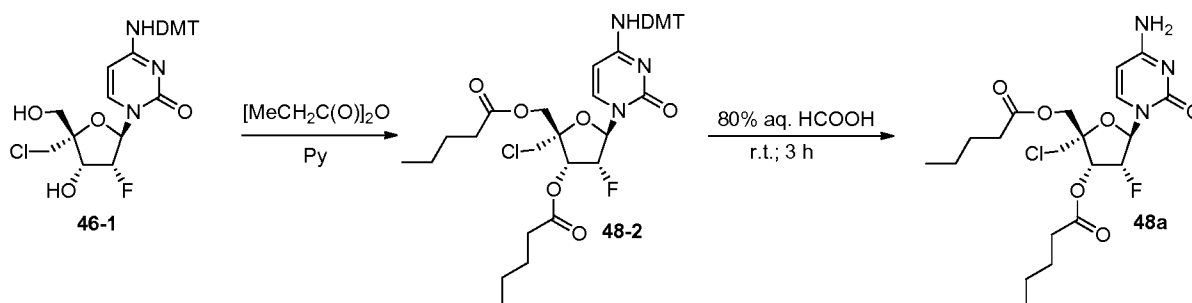
EXAMPLE 46
Preparation of Compound (47a)



[0402] Preparation of (47-2): **47-2** was prepared from **46-1** (274 mg, 0.46 mmol) and propionic anhydride (0.12 mL, 2 equiv.) in pyridine (5 mL) in the same manner as described for **46-2** (260 mg, 80%).

[0403] Preparation of (47a): **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 CH₂Cl₂/MeOH solvent system (4-10% gradient) to yield **47a** (62 mg, 75%). MS: m/z = 404 (M-1).

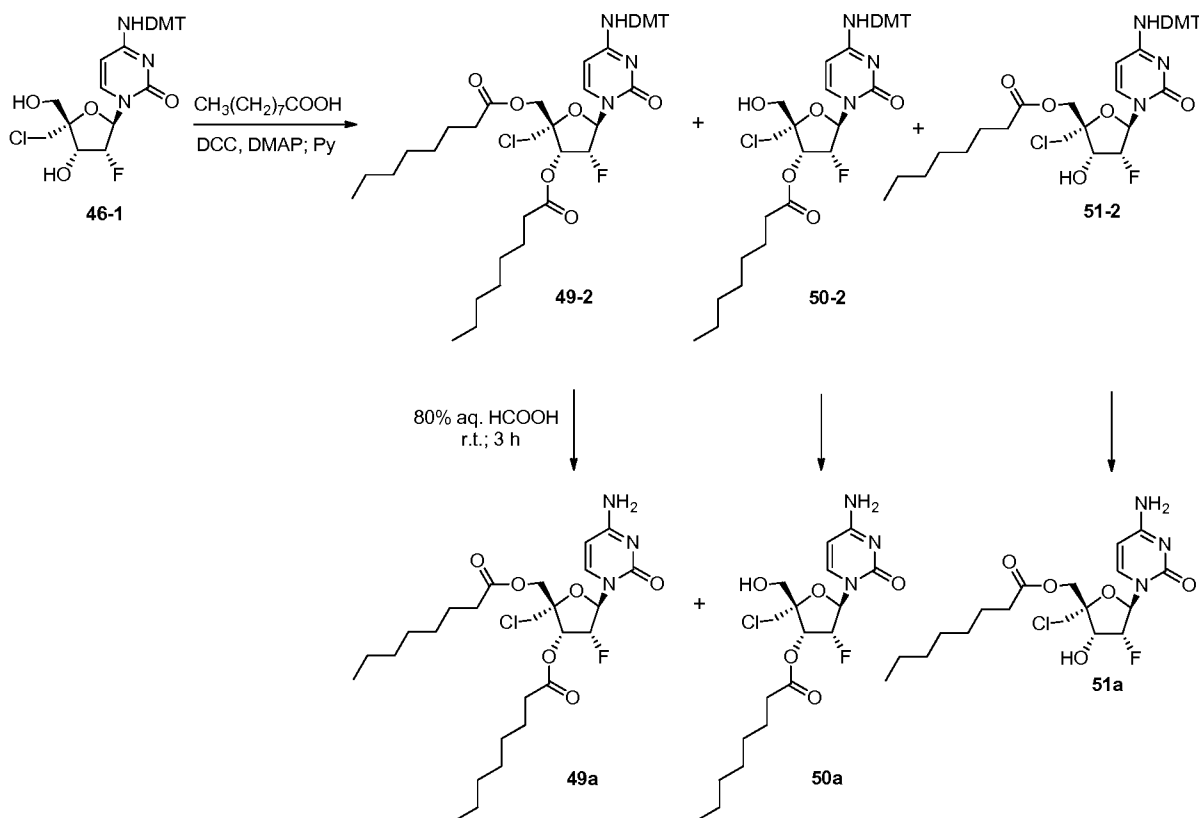
EXAMPLE 47
Preparation of Compound (48a)



[0404] Preparation of (48-2): **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%).

[0405] Preparation of (48a): **48-2** (140 mg, 0.18 mmol) was treated with 80% aq. HCOOH at R.T. for 3 hours. The mixture was evaporated and purified on silica (10 g column) with a CH₂Cl₂/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)



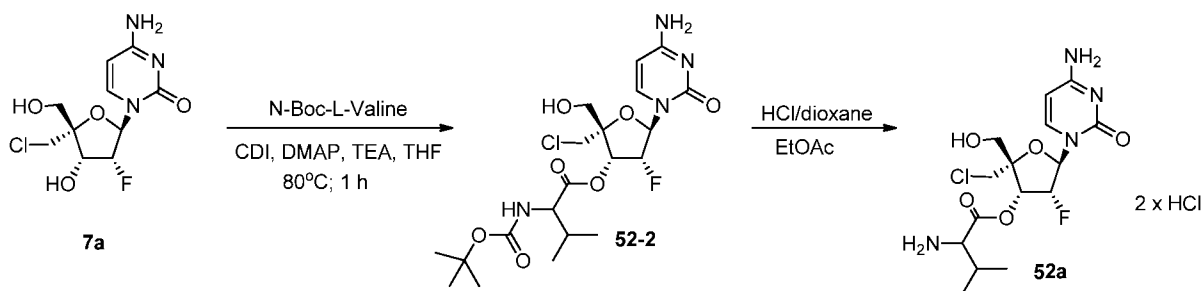
[0406] Preparation of (49-2), (50-2) and (51-2): To a solution of **46-1** (1.26 g, 2.12 mmol) in pyridine (15 mL) were added n-octanoic acid (0.34 mL, 1.0 equiv.), DCC (60% in xylene; 0.81 mL, 1 equiv.) and DMAP (52 mg; 0.2 equiv.). The resulting mixture was stirred for 6 hours at R.T. The mixture was 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%).

[0407] Preparation of (49a): 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 $\text{CH}_2\text{Cl}_2/\text{MeOH}$ solvent system (2-8% gradient) to yield **49a** (53 mg, 75%). MS: $m/z = 544$ (M-1).

[0408] Preparation of (50a): **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).

[0409] Preparation of (51a): **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).

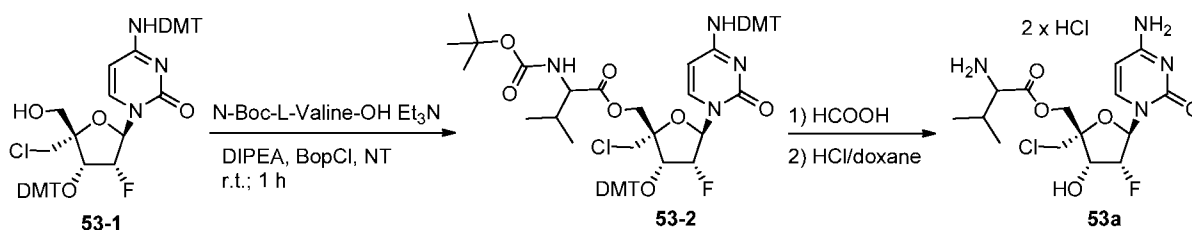
EXAMPLE 49
Preparation of Compound (52a)



[0410] **Preparation of (52-2):** 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 (Na₂SO₄). The residue was purified on silica (25 g column) with a CH₂Cl₂/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%).

[0411] **Preparation of (52a):** 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)



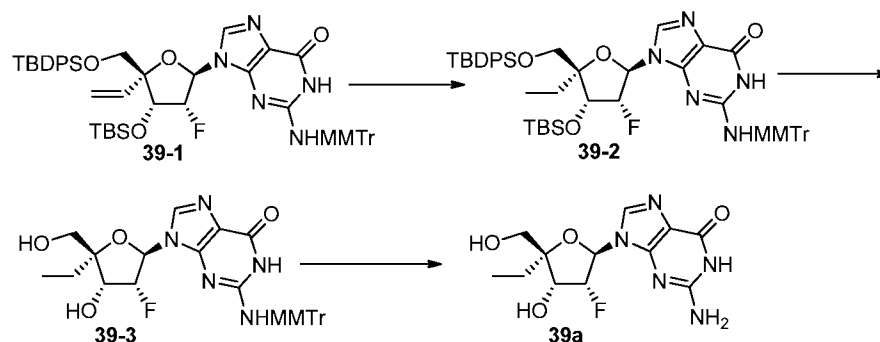
[0412] **Preparation of (53-2):** To a solution of *N*-Boc-Val-OH (0.16 g, 0.74 mmol) and Et₃N (0.14 mL, 1.0 mmol) in THF was added **53-1**. The resulting mixture was evaporated, coevaporated with pyridine and toluene and dissolved in THF (4 mL). DIPEA (0.38 mL, 2.2 mmol) was added, followed by BOP-Cl (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 CH₂Cl₂

(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 % $\text{Et}_3\text{N}/\text{EtOAc}$ solvent system (20-100% gradient) to yield **53-2** (0.39 g, 81%).

[0413] Preparation of (53a): A mixture of **14-2** (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)

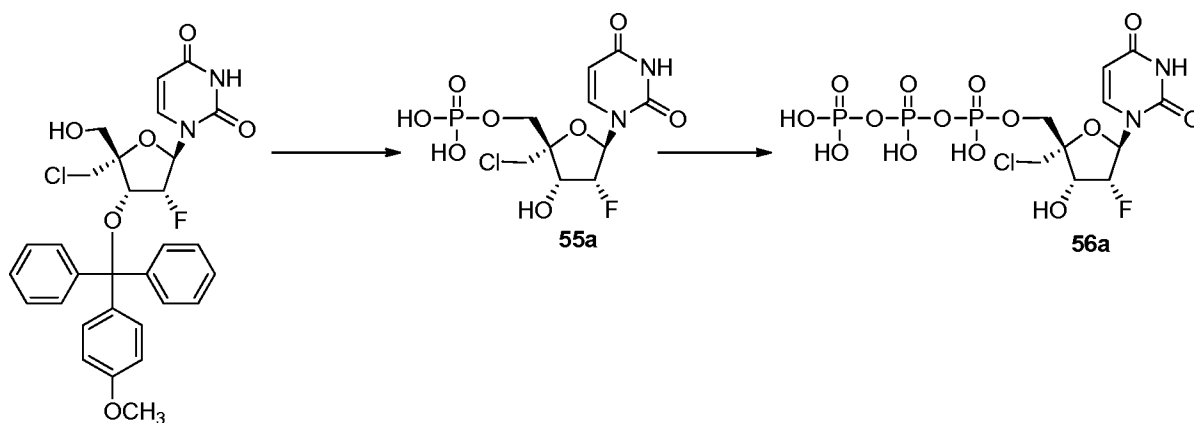


[0414] Preparation of (39-2): A solution of **39-1** (1.3 g, 1.4 mmol) in anhydrous MeOH (20 mL) was charged with Pd/C (1.3 g) and stirred at 25°C under hydrogen (1 atm) atmosphere for 1 hour. The solution was filtered, evaporated to dryness, and purified on a silica gel column ($\text{DCM}:\text{MeOH} = 100:1$ to $50:1$) to give **39-2** (1.2 g, 92.3 %) as a white solid.

[0415] Preparation of (39-3): 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 ($\text{DCM}:\text{MeOH} = 200:1$ to $20:1$) to give **39-3** as a white solid (249 mg, 30.7%). ^1H NMR (MeOD , 400 MHz) δ 7.92 (s, 1H), 7.19-7.33 (m, 12H), 6.83-6.85 (m, 2H), 5.50 (dd, $J_1 = 4.0$ Hz, $J_2 = 14.8$ Hz, 1H), 4.19-4.88 (m, 1H), 4.22 (dd, $J_1 = 5.2$ Hz, $J_2 = 16.0$ Hz, 1H), 3.76 (s, 3H), 3.41 (dd, $J_1 = 12.0$ Hz, $J_2 = 36.8$ Hz, 2H), 1.52-1.74 (m, 2H), 0.87 (t, $J = 7.6$ Hz, 3H); ESI-LCMS: m/z 586.1 $[\text{M} + \text{H}]^+$.

[0416] Preparation of (39a): 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 **39a** (20 mg) as an off-white solid. ¹H NMR (DMSO, 400 MHz) δ 7.92 (s, 1H), 10.82 br, 1H), 7.96 (s, 1H), 6.56 (s, 2H), 5.99 (dd, J = 6.0, 12.8 Hz, 1H), 5.65 (d, J = 4.8 Hz, 1H), 5.58, 5.45 (2t, J = 5.2 Hz, 0.5H, 0.5H), 5.25 (br, 1H), 4.19-4.88 (m, 1H), 4.22 (dd, J_1 = 5.2 Hz, J_2 = 16.0 Hz, 1H), 3.76 (s, 3H), 3.41 (dd, J_1 = 12.0 Hz, J_2 = 36.8 Hz, 2H), 1.52-1.74 (m, 2H), 0.87 (t, J = 7.6 Hz, 3H); ESI-LCMS: m/z 443.6 [M + 6-methyl-2-heptylamine)]⁺.

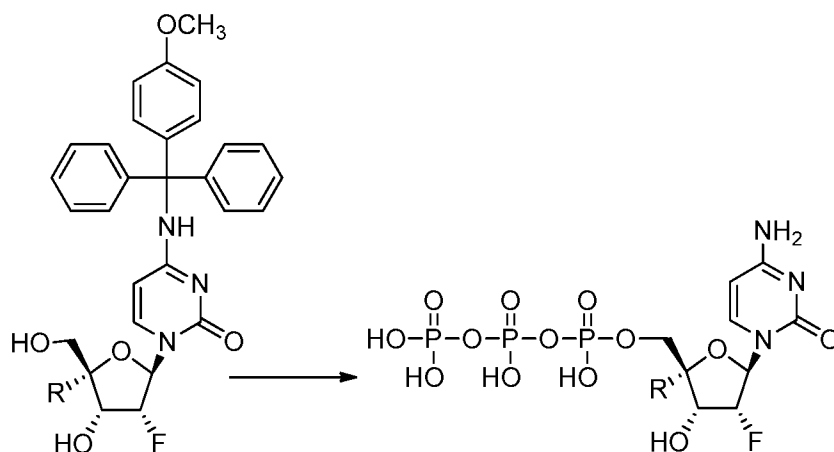
EXAMPLE 52
Preparation of Compounds (55a) and (56a)



[0417] 1,2,4-Triazol (21 mg, 0.3 mmol) was dissolved in the mixture of CH₃CN (0.7 mL) and Et₃N (44 μ L, 0.31 mmol). POCl₃ (9 μ L, 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

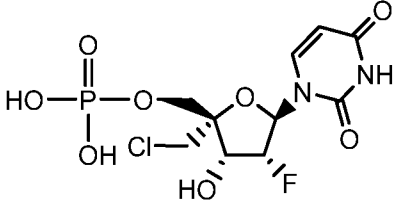
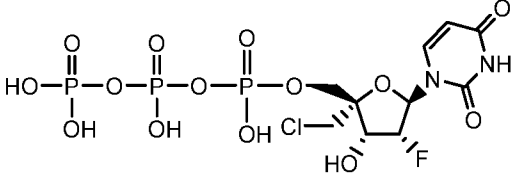
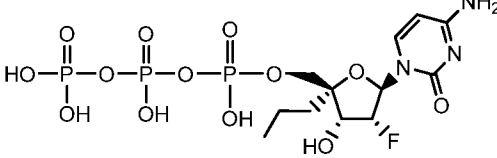
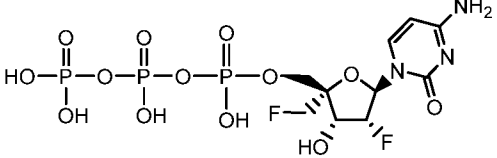
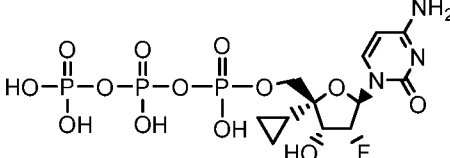
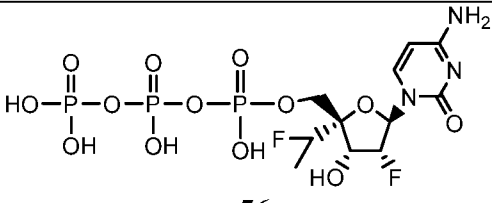
(**56a**) was eluted at 75-80%B. Both fractions were desalted by RP HPLC on Synergy 4 micron Hydro-RP column (Phenomenex). A linear gradient of methanol from 0 to 30% in 50mM triethylammonium acetate buffer (pH 7.5) was used for elution. The corresponding fractions were combined, concentrated and lyophilized 3 times to remove excess of buffer.

EXAMPLE 53
Preparation of Compounds (56b-e)

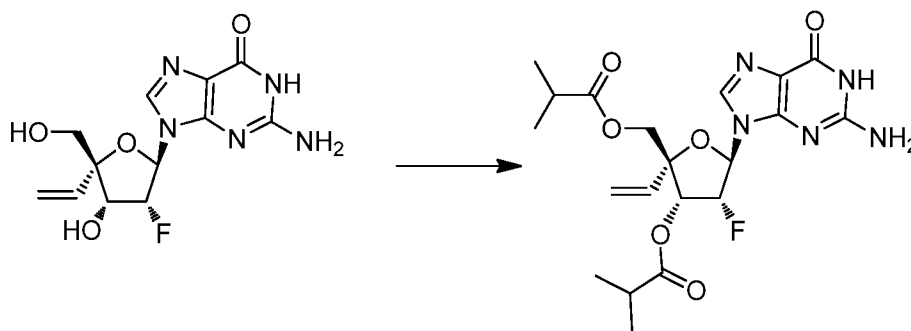


[0418] 1,2,4-Triazol (21 mg, 0.3 mmol) was dissolved in the mixture of CH₃CN (0.7 mL) and Et₃N (44 μ L, 0.31 mmol). POCl₃ (9 μ L, 0.1 mmol) was added, and the mixture was kept at R.T. for 20 mins. The white precipitate was filtered, and the filtrate added to the dry nucleoside (28 mg, 0.05 mmol). The 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-e**) was eluted at 75-80%B. Desaltin was performed by RP HPLC on Synergy 4 micron Hydro-RP column (Phenomenex). 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

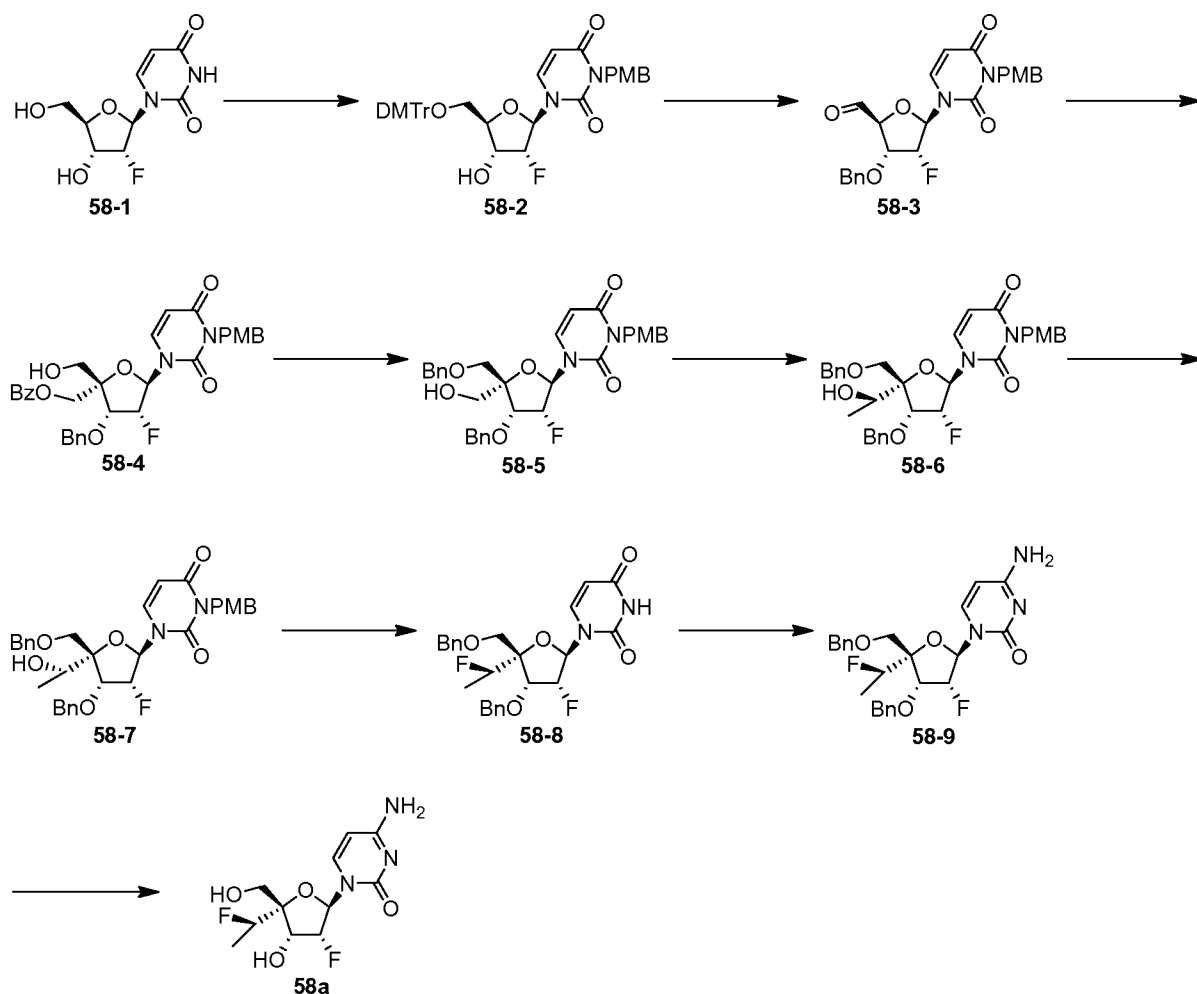
Compound	MS (M-1)	³¹ P NMR P _α	³¹ P NMR P _β	³¹ P NMR P _γ
 55a	373.00	+3.64 (s)	NA	NA
 56a	532.95	-6.67 -6.74(d)	-21.87(t)	-11.51 -11.63(d)
 56b	526.05	-6.33 -6.47(d)	-22.48(t)	-11.53 -11.64(d)
 56c	516.00	-63.2(bs)	-22.45 (t)	-11.64(d)
 56d	524.4	-10.57 -10.67(d)	-23.31(t)	-11.31 -11.94(d)
 56e	529.8	-6.17(bs)	-21.96(bs)	-11.42(bs)

EXAMPLE 54
Preparation of Compound (57a)



[0419] 2'-Deoxy-2'-fluoro-4'-C-(ethenyl)guanosine (**25a**, 31 mg, 0.1 mmol) was dissolved in dry pyridine (3 mL). Isobutyric anhydride (50 μ L, 0.3 mmol) was added. The reaction mixture was kept at ambient temperature. After 40 hours, isobutyric anhydride (100 μ L, 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%). ^1H NMR (DMSO- d_6) δ : 10.72 (s, 1H), 7.88 (s, 1H), 6.47 (s, 2H), 6.18-6.13 (dd, 1H), 5.90-5.83 (dd, 1H), 5.79-5.62 (m, 2H), 5.49-5.44 (d, 1H), 5.35-5.32 (d, 1H), 4.28-4.25 (d, 1H), 4.12-4.10 (d, 1H), 2.60-2.45 (m, 2H), 1.12-1.09 (m, 6H), 1.02-0.96 (m, 6H); m/z 452 ($M+1$).

EXAMPLE 55
Preparation of Compound (58a)



[0420] Preparation of (58-2): 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 Na₂SO₄ and concentrated to give the crude DMTr protected derivative (80.5 g, 89%) as a light yellow solid. Dried K₂CO₃ (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 Na₂SO₄ and concentrated to give **58-2** (98.8 g, 90%) as light yellow solid.

[0421] Preparation of (58-3): 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 CH₃CN (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.

[0422] Preparation of (58-4): To a solution of **58-3** (39.2 g, 86.39 mmol) in 1,4-dioxane (250 mL) was added 37% CH₂O (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 NaBH₄ (19.7 g, 518.6 mmol). The mixture was stirred at 25°C for 30 mins. The reaction was quenched with saturated aqueous NH₄Cl. The mixture was extracted with EA, and the organic layer was dried over Na₂SO₄ 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 CH₃CN (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 H₂O, and the solution was concentrated. The residue was dissolved in EA and washed with NaHCO₃. The organic layer was dried over Na₂SO₄ 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.

[0423] Preparation of (58-5): Cs₂CO₃ (30.0 g, 92.0 mmol) and BnBr (10.4 g, 61.3 mmol) were added to a stirred solution of compound **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 NH₄Cl, 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.

[0424] Preparation of (58-6): 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 NH₄Cl 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%).

[0425] Preparation of (58-7): 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 Na₂S₂O₃. 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 NaBH₄ 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%).

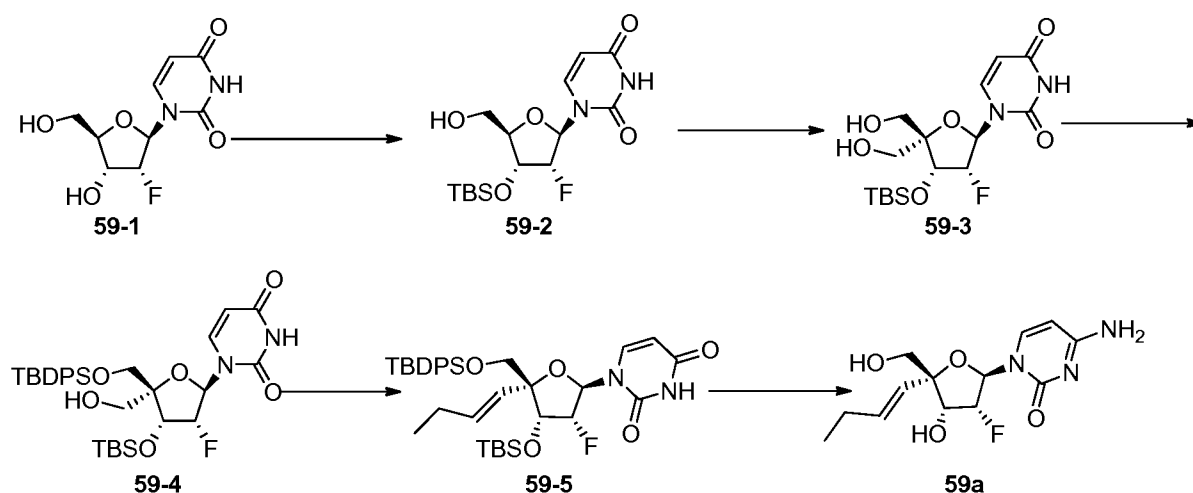
[0426] Preparation of (58-8): To a stirred solution of DAST (1.39 g, 8.68 mmol) in anhydrous toluene (15 mL) was added dropwise a solution of **58-6** (1.0 g, 1.73 mmol) at -78°C. The mixture was stirred at -78°C for 30 min. The solution was warmed to 25°C slowly and stirring continued overnight. The mixture was poured into a saturated Na₂CO₃ 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%).

[0427] Preparation of (58-9): 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. NH₄OH (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). ¹H NMR (CD₃OD, 400 MHz) δ 7.70 (d, *J* = 8.4 Hz, 1H), 7.25-7.36 (m, 10H), 6.13 (dd, *J* = 2.8, 16.8 Hz, 1H), 5.40 (d, *J* = 7.6 Hz, 1H), 5.15 (m, 1H), 4.81 (d, *J* = 11.6 Hz, 1H), 4.40-4.52 (m, 4H), 3.82 (d, *J* = 8.8 Hz, 7H), 3.62 (d, *J* = 9.6 Hz, 7H), 1.35 (dd, *J* = 2.8, 14.4 Hz, 3H). ESI-MS: *m/z* 472.1 [M + H]

+

[0428] Preparation of (58a): 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). ^1H NMR (CD_3OD) δ 7.97 (d, 1H), 6.20 (dd, 1 H), 5.92 (d, 1 H), 5.22 (dt, 1 H), 4.98 (dq, 1 H), 4.58 (dd, 1 H), 3.73 (m, 2 H), 1.40 (dd, 3 H). ^{19}F NMR (CD_3OD) δ -205.80 (m, 1 F), -188.54 (m, 1 F). ESI-MS: m/z 290.4 $[\text{M} - \text{H}]^-$.

EXAMPLE 56 Preparation of Compound (59a)



[0429] Preparation of (59-2): 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. ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 11.39 (s, 1H),

7.88 (d, $J = 7.2$ Hz, 1H), 5.89 (dd, $J = 18.0$ Hz, $J = 2.0$ Hz, 1H), 5.64 (d, $J = 8.0$ Hz, 1H), 5.21 (dd, $J_1 = J_2 = 7.2$ Hz, 1H), 5.18-5.03 (m, 1H), 4.37~4.29 (m, 1H), 3.86 (dd, $J = 3.2$ Hz, $J = 3.2$ Hz, 3H), 3.78-3.73 (m, 1H), 3.51-3.56 (m, 1H), 3.31 (s, 1H), 0.89 (s, 9H), 0.11 (s, 6H); ESI-MS: m/z 802 $[M + H]^+$.

[0430] Preparation of (59-3): 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.

[0431] Preparation of (59-4): 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. ^1H 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).

[0432] Preparation of (59-5): 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 $\text{Na}_2\text{S}_2\text{O}_3$ (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.

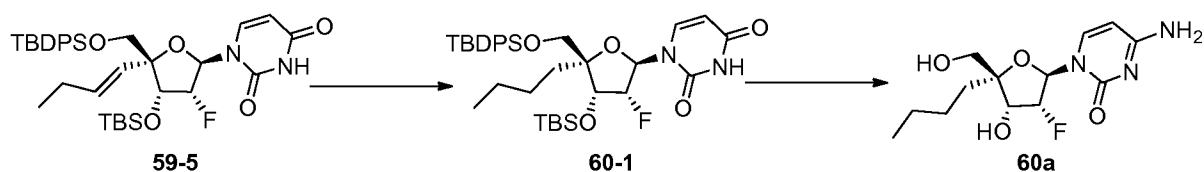
[0433] To a mixture of bromotriphenyl(propyl)phosphorane (6.45 g, 16.8 mmol) in anhydrous THF (3 mL) was added t-BuOK (16.8 mL, 16.8 mmol) at 0°C under nitrogen. The reaction mixture was stirred at 0°C for 50 mins. A solution of the above intermediate (1.5 g, 2.4 mmol) in anhydrous THF (3 mL) was added 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.

[0434] Preparation of (59a): 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.

[0435] 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. ^1H NMR (CD_3OD , 400 MHz) δ 8.11 (d, $J = 8.0$ Hz, 1H), 5.91 (dd, $J = 1.2$ Hz, $J = 17.6$ Hz, 1H), 5.90 (d, $J = 7.6$ Hz, 1H), 5.57-5.59 (m, 2H), 4.82-4.96 (m, 1H), 4.42 (dd, $J = 4.8$ Hz, $J = 24.4$ Hz, 1H), 3.72 (d, $J = 12.4$ Hz, 1H) 3.58 (d, $J = 12.4$ Hz, 1H), 2.31-2.41 (m, 2H), 0.99 (t, $J = 7.6$ Hz, 3H). ESI-TOF-MS: m/z 300.1 $[\text{M} + \text{H}]^+$.

EXAMPLE 57

Preparation of Compound (60a)

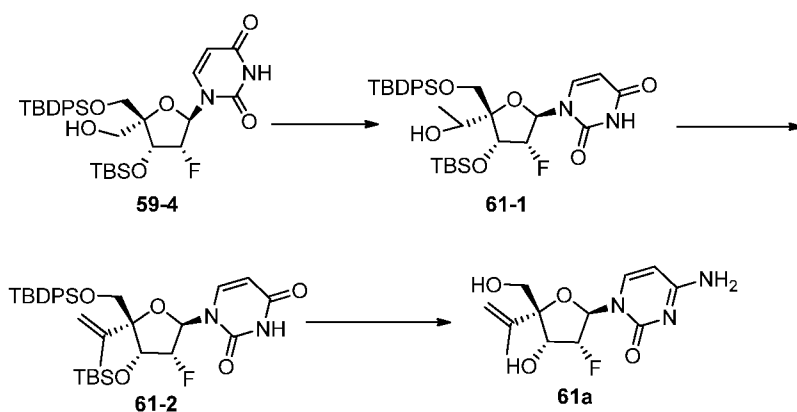


[0436] Preparation of (60-1): To a solution of **59-5** (450 mg, 0.69 mmol) in MeOH (10 mL) was added Pd/C (200 mg) at R.T. The reaction mixture was stirred R.T. for 1 h under H₂ (balloon). The mixture was filtered, and the filtrate was concentrated to give crude **60-1** (440 mg, 97.1%) as a white solid.

[0437] Preparation of (60a): To a solution of **60-1** (440 mg, 0.67 mmol) in anhydrous CH₃CN (2 mL) were added TPSCl (510 mg, 1.68 mmol), DMAP (205 mg, 1.68 mmol) and NEt₃ (338 mg, 3.35 mmol) at R.T. The reaction mixture was stirred at R.T. for 2 h. NH₄OH (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.

[0438] To a solution of the cytidine derivative (205 mg, 0.31 mmol) in MeOH (6 mL) was added NH₄F (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. ¹H NMR (CD₃OD, 400 MHz) δ 8.09 (d, J = 7.6 Hz, 1H), 6.01 (dd, J = 3.2 Hz, J = 15.6 Hz, 1H), 5.89 (d, J = 7.2 Hz, 1H), 4.95-5.12 (m, 1H), 4.41 (dd, J = 5.2 Hz, J = 17.2 Hz, 1H), 3.75 (d, J = 12.0 Hz, 1H) 3.56 (d, J = 11.6 Hz, 1H), 1.73-1.80 (m, 1H), 1.55-1.63 (m, 1H), 1.40-1.46 (m, 4H), 0.92 (t, J = 7.6 Hz, 3H). ESI-MS: m/z 301.8 [M + H]⁺.

EXAMPLE 58 **Preparation of Compound (61a)**



[0439] Preparation of (61-1): 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 NaHCO₃ and Na₂S₂O₃ solution and washed with brine. The organic layer was dried with anhydrous Na₂SO₄, and concentrated to give the crude intermediate (1.5 g) as a white solid.

[0440] 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 NH₄Cl. 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).

[0441] Preparation of (61-2): 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 NaHCO₃ and Na₂S₂O₃ 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.

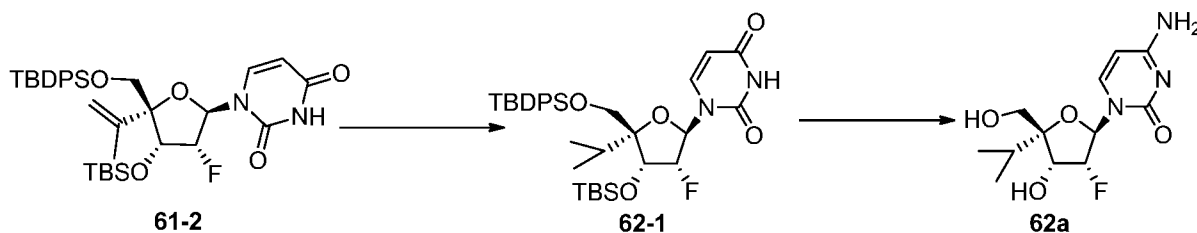
[0442] To a mixture of bromo(methyl)triphenylphosphorane (5.0 g, 14 mmol) in anhydrous THF (8 mL) was added t-BuOK (12.6 mL, 12.6 mmol) at 0°C under nitrogen. The mixture was stirred at R.T. for 50 mins. A solution of the above intermediate (900 mg, 1.4 mmol) in anhydrous THF (4 mL) was added dropwise at 0°C under nitrogen. The reaction mixture was stirred at R.T. for 3 h. The reaction mixture was quenched with NH₄Cl 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.

[0443] Preparation of (61a): To a solution of **61-2** (298 mg, 0.46 mmol) in anhydrous CH₃CN (5.5 mL) were added TPSCl (346.5 mg, 1.14 mmol), DMAP (139.6 mg, 1.14 mmol) and NEt₃ (115.6 mg, 1.14 mmol) at R.T. The reaction mixture was stirred at R.T. for 2 h. NH₄OH (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.

[0444] To a solution of the cytidine derivative (250 mg, 0.39 mmol) in MeOH (10 mL) was added NH₄F (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. ¹H NMR (CD₃OD, 400 MHz) δ 8.11 (d, *J* = 7.6 Hz, 1H), 6.21 (dd, *J* = 4.2 Hz, *J* = 14.0 Hz, 1H), 5.91 (d, *J* = 7.6 Hz, 1H), 5.10 (dt, *J* = 4.8 Hz, *J* = 53.6 Hz, 1H), 5.13 (brs, 1H), 5.00 (brs, 1H), 4.46 (dd, *J* = 4.8 Hz, *J* = 11.6 Hz, 1H), 3.83 (d, *J* = 11.6 Hz, 1H), 3.54 (d, *J* = 11.6 Hz, 1H), 1.84 (s, 3H). ESI-MS: *m/z* 285.9 [M + H]⁺.

EXAMPLE 59

Preparation of Compound (62a)

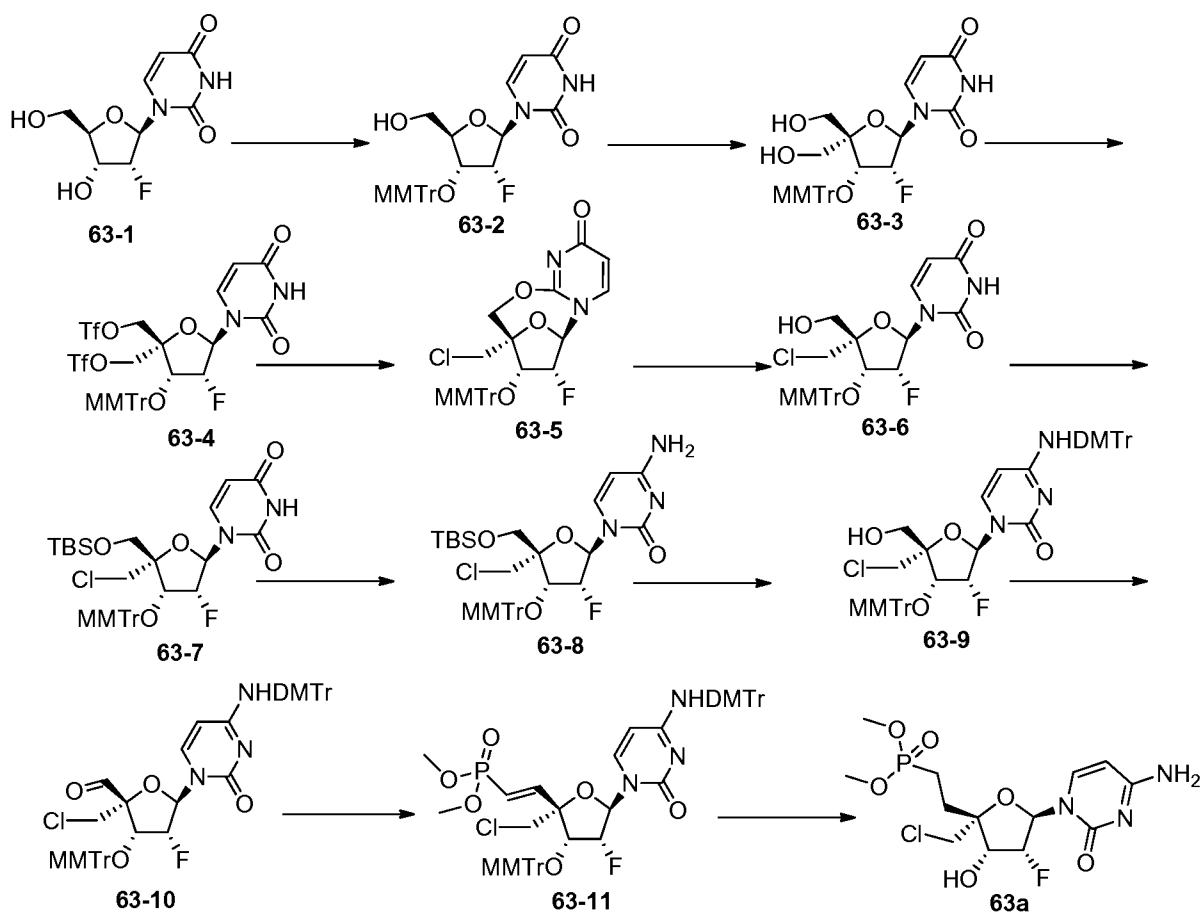


[0445] Preparation of (62-1): To a solution of **61-2** (400 mg, 0.63 mmol) in MeOH (10 mL) was added Pd/C (400 mg) at R.T. The reaction was stirred at R.T. for 5 h under H₂ (balloon). The mixture was filtered, and the filtrate was concentrated to give crude **62-2** (350 mg, 87%) as a white solid.

[0446] Preparation of (62a): To a solution of **62-1** (350 mg, 0.55 mmol) in anhydrous CH₃CN (6 mL) were added TPSCl (414 mg, 1.4 mmol), DMAP (166.8 mg, 1.4 mmol) and NEt₃ (138.1 mg, 1.4 mmol) at R.T. The reaction mixture was stirred at R.T. for 2 h. NH₄OH (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.

[0447] To a solution of the cytidine derivative (300 mg, 0.47mmol) in MeOH (10 mL) was added NH₄F (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. ¹H NMR (CD₃OD, 400 MHz) δ 8.12 (d, J = 7.6 Hz, 1H), 6.22 (dd, J = 6.4 Hz, J = 12.4 Hz, 1H), 5.94 (d, J = 7.6 Hz, 1H), 5.25 (dt, J = 5.6 Hz, J = 54.0 Hz, 1H), 4.38 (t, J = 4.8 Hz, 1H), 3.72 (d, J = 11.6 Hz, 1H), 3.67 (d, J = 11.6 Hz, 1H), 2.31-2.42 (m, 1H), 0.99 (2d, J = 7.2 Hz, 6H). ESI-MS: m/z 287.8 [M + H]⁺.

EXAMPLE 60
Preparation of Compound (63a)



[0448] **Preparation of (63-2):** 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).

[0449] 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.

[0450] 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.

[0451] Preparation of (63-3): 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 Na₂S₂O₃ 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 NH₄Cl (~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.

[0452] Preparation of (63-4): **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 Na₂SO₄ 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.

[0453] Preparation of (63-5): **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**.

[0454] Preparation of (63-6): **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.

[0455] Preparation of (63-7): 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 Na₂SO₄ 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.

[0456] Preparation of (63-8): 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-triisopropylbenzenesulfonyl chloride (TPSCl, 16.3 g, 54.0 mmol). The mixture was stirred at R.T. for 3 h. NH₃ H₂O (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.

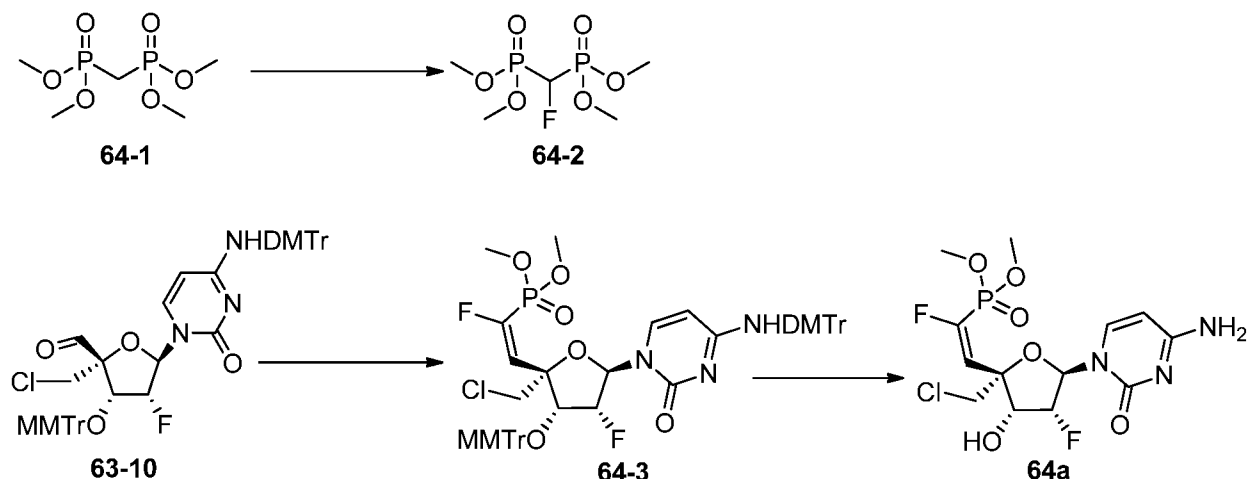
[0457] Preparation of (63-9): To a solution of **63-8** (18.0 g, 26.5 mmol) in anhydrous DCM (150 mL) was added collidine (8.1 g, 66.3 mmol, 2.5 eq), silver nitrate (4.5 g, 26.5 mmol, 1.0 eq) and DMTrCl (13.4 g, 39.7 mmol, 1.5 eq). The reaction was allowed to proceed overnight at R.T. The mixture was filtered. The filtrate was washed with brine and extracted with DCM. The organic layer was separated, dried over Na₂SO₄ 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 Na₂SO₄ 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.

[0458] Preparation of (63-10): 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 Na₂S₂O₃ and saturated aqueous NaHCO₃. 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.

[0459] Preparation of (63-11): 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 NH₄Cl, 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. ¹H NMR (DMSO-d₆, 400 MHz) δ 8.51 (s, 1H), 7.46-7.09 (m, 22H), 6.88-6.82 (m, 6H), 6.62 (q, *J*₁ = 17.2 Hz, *J*₂ = 22.4 Hz, 1H), 6.12 (d, *J* = 7.2 Hz, 1H), 5.86-5.75 (m, 2H), 5.43 (d, *J* = 25.2 Hz, 1H), 4.63 (dd, *J* = 4.8 Hz, *J* = 21.2 Hz, 1H), 4.45 (d, *J* = 12.0 Hz, 1H), 3.94 (d, *J* = 12.0 Hz, 1H), 3.72 (s, 9H), 3.53 (q, *J* = 11.2 Hz, *J* = 16.0 Hz, 6H). ESI-MS: *m/z* 971.59 [M + H]⁺.

[0460] Preparation of (63a): 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 H₂ (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. ¹H NMR (CD₃OD, 400 MHz) δ 7.60 (d, *J* = 7.6 Hz, 1H), 5.87 (d, *J* = 7.2 Hz, 1H), 5.70 (dd, *J* = 2.0 Hz, *J* = 21.6 Hz, 1H), 5.31 (m, 1H), 4.67 (dd, *J* = 5.6 Hz, *J* = 19.6 Hz, 1H), 3.80 (m, 2H), 3.75 (2d, *J* = 2.4 Hz, 6H), 1.92-2.20 (m, 4H). ³¹P NMR (CD₃OD, 162 MHz) δ 35.77. ESI-MS: *m/z* 400.0 [M + H]⁺.

EXAMPLE 61
Preparation of Compound (64a)

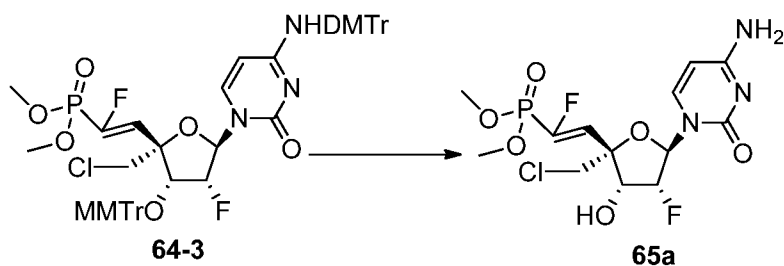


[0461] Preparation of (64-2): To a solution of **64-1** (1.0 g, 4.3 mmol) in THF (20 mL) was added NaH (120 mg, 3.0 mmol), and the reaction mixture was stirred at 0°C for 1 h. Selectfluor (1.2 g, 3.4 mmol) was added into the reaction mixture. The crude product was purified on a silica gel column and eluted with EA to give **64-2** (500 mg, 57%) as a white solid. ¹H NMR (CD₃OD, 400 MHz) δ 5.65 (dt, J = 14.0 Hz, J = 44.8 Hz, 1H), 3.90 (d, J = 9.6 Hz, 12H).

[0462] Preparation of (64-3): To a solution of compound **64-2** (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 mixture was stirred at 0°C for 30 mins. 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 with saturated aqueous NH₄Cl 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.

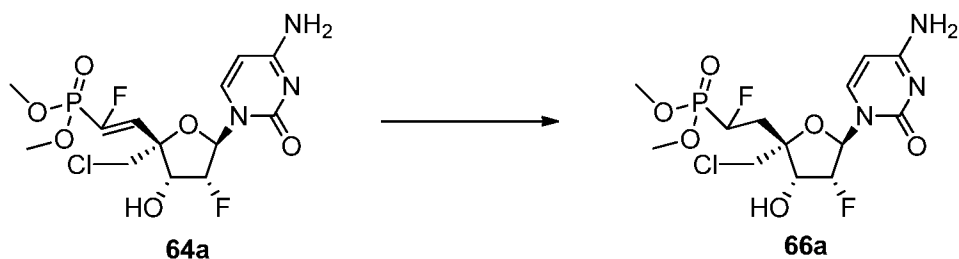
[0463] Preparation of (64a): A solution of crude **64-3** (230 mg, 0.23 mmol) in 80% HOAc (3 mL) was stirred at 80-90°C for 2 h. The crude product was purified on a silica gel column (eluted with DCM: MeOH= 20:1) to give **64a** (54 mg, 53.7%) as a white solid. ¹H NMR (DMSO, 400 MHz) δ 7.69 (d, J = 7.2 Hz, 1H), 7.37 (d, J = 1.6 Hz, 2H), 6.62-6.78 (m, 1H), 6.40 (d, J = 5.6 Hz, 1H), 6.03-6.07 (m, 1H), 5.77 (d, J = 7.6 Hz, 1H), 5.61-5.64 (m, 1H), 5.48-5.51 (m, 1H), 4.60-4.64 (m, 1H), 4.38 (d, J = 11.6 Hz, 1H), 3.98 (d, J = 11.6 Hz, 1H), 3.75 (2d, J = 11.6 Hz, 6H). ESI-MS: m/z 416.3 [M + H]⁺.

EXAMPLE 62
Preparation of Compound (65a)



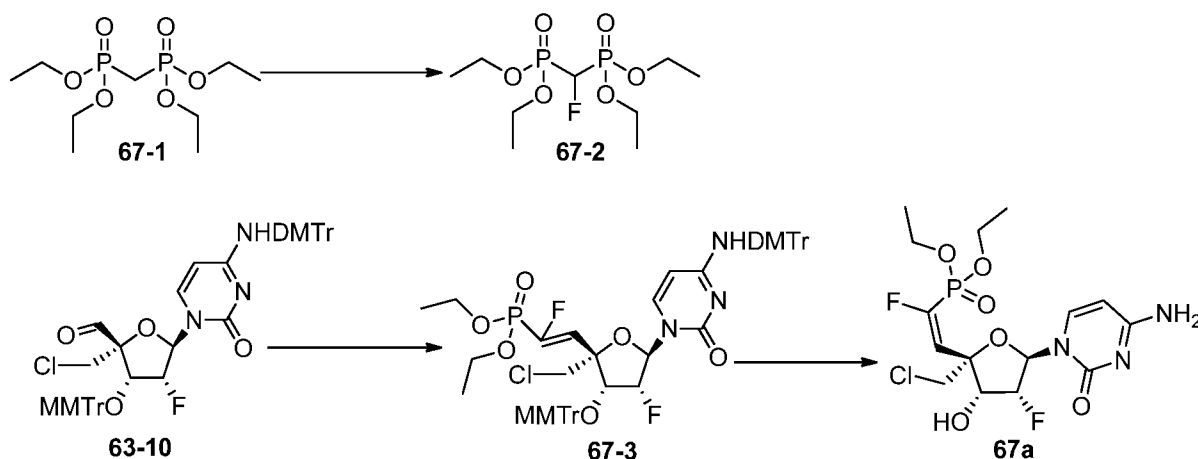
[0464] A solution of crude **64-3** (230 mg, 0.23 mmol) in 80% HOAc (3 mL) was stirred at 80-90°C for 2 h. The crude product was purified on a silica gel column (eluted with DCM: MeOH= 20:1) to give **64a** (52 mg, 33.7%) as a white solid. ¹H NMR (DMSO, 400 MHz) δ 7.59 (d, J = 7.2 Hz, 1H), 7.32 (s, 2H), 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)



[0465] A solution of **64a** (130 mg, 0.3 mmol) in EA:MeOH (5:1, 20 mL) was stirred under H₂ (15 Psi) at R.T. for 2 h. The reaction 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. ¹H NMR (DMSO, 400 MHz) δ 7.61 (d, J = 7.2 Hz, 1H), 5.87 (d, J = 7.2 Hz, 1H), 5.58-5.80 (m, 1H), 5.26-5.47 (m, 2H), 4.97-5.03 (m, 1H), 5.58-5.80 (m, 1H), 3.73-3.94 (m, 6H), 2.33-2.59 (m, 2H). ESI-MS: m/z 418.3 [M + H]⁺.

EXAMPLE 64
Preparation of Compound (67a)

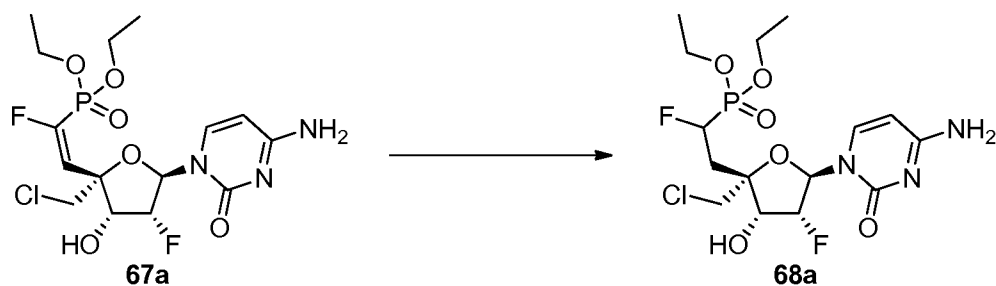


[0466] Preparation of (67-2): To a solution of **67-1** (2.0 g, 6.9 mmol) in THF (20 mL) was added NaH (110 mg, 2.8 mmol), and the reaction mixture was stirred at 0°C for 1 h. Selectfluor (5.0 g, 13.6 mmol) was added into the reaction mixture. The reaction was quenched with saturated NH₄Cl and extracted 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. ¹H NMR (CD₃OD, 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).

[0467] Preparation of (67-3): 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°C under nitrogen. The reaction mixture was stirred at 0°C 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°C. The reaction mixture was stirred at R.T. for 1 h. The reaction was quenched with saturated aqueous NH₄Cl 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.

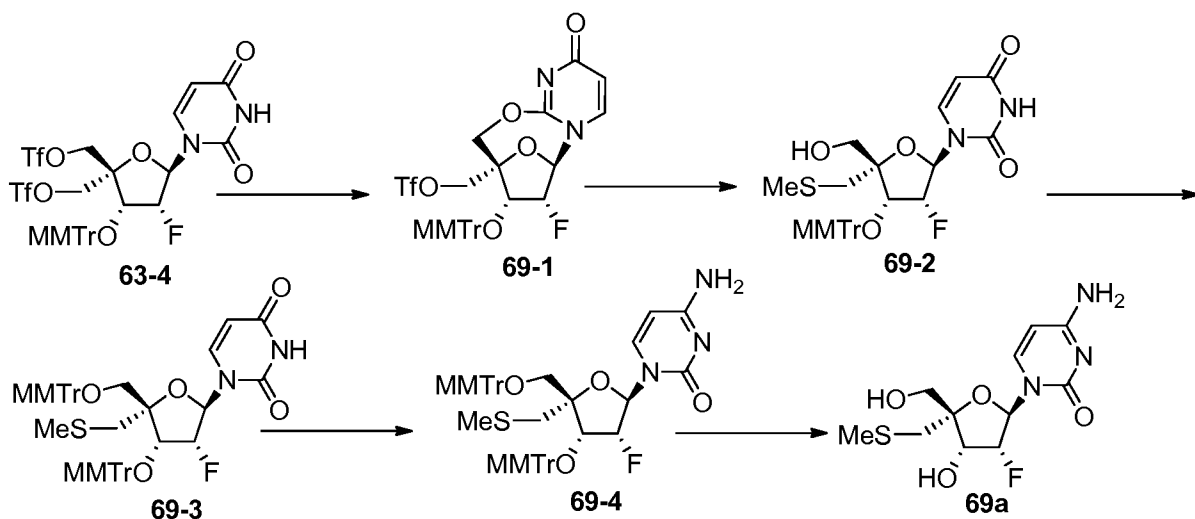
[0468] Preparation of (67a): A solution of crude **67-3** (1.0 g, 0.98 mmol) in 80% HOAc (25 mL) was stirred at 80-90°C for 2 h. The crude product was purified on a silica gel column (eluted with DCM: MeOH= 20:1) to give **67a** (133 mg, 32.5%) as a white solid. ¹H NMR (DMSO, 400 MHz) δ 7.67 (d, $J = 7.2$ Hz, 1H), 7.34 (d, $J = 12.8$ Hz, 2H), 6.33-6.69 (m, 1H), 6.05 (d, $J = 6.8$ Hz, 1H), 6.00-6.05 (m, 1H), 5.76 (d, $J = 7.6$ Hz, 1H), 5.45-5.61 (m, 1H), 4.60-4.63 (m, 1H), 4.08-4.14 (m, 5H), 1.23-1.29 (m, 6H). ³¹P NMR (DMSO, 162 MHz) δ 1.93, 1.30. ESI-MS: m/z 466.1 [M + Na]⁺.

EXAMPLE 65
Preparation of Compound (68a)



[0469] To a solution of **67a** (130 mg, 0.29 mmol) in MeOH (20 mL) was stirred under H₂ (15 Psi) at R.T. for 2 h. The reaction 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. ¹H NMR (DMSO, 400 MHz) δ 7.61-7.68 (m, 1H), 7.28-7.38 (m, 2H), 5.89-5.95 (m, 1H), 5.58-5.79 (m, 2H), 5.18-5.39 (m, 2H), 4.53-4.85 (m, 1H), 4.04-4.39 (m, 4H), 3.71-3.83 (m, 2H), 2.21-2.35 (m, 2H), 1.21-1.27 (m, 6H). ³¹P NMR (DMSO, 162 MHz) δ 18.2, 18.02, 17.73, 17.56. ESI-MS: m/z 446.1 [M + H]⁺

EXAMPLE 66
Preparation of Compound (69a)



[0470] **Preparation of (69-1):** **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 reaction mixture was used for the next step without any further workup

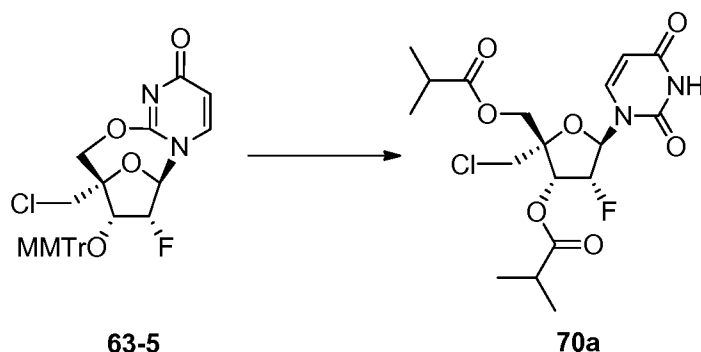
[0471] Preparation of (69-2): To the above stirred reaction mixture was added NaSMe (9.0 g, 0.13 mmol) and 15-Crown-5 (4.87 g, 22.14 mmol) at 0°C under nitrogen. The solution was stirred at R.T. for 2 h (TLC (PE: EA= 1:1) showed the reaction was complete). The reaction was quenched with water. The mixture was extracted by EtOAc, washed with brine, and dried over MgSO₄. 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.

[0472] Preparation of (69-3): To a stirred solution of **69-2** (1.34 g, 2.32 mmol) in anhydrous DCM (10 mL) was added MMTTrCl (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.

[0473] Preparation of (69-4): 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). NH₄OH (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 NaHCO₃ and brine, and dried over MgSO₄. 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.

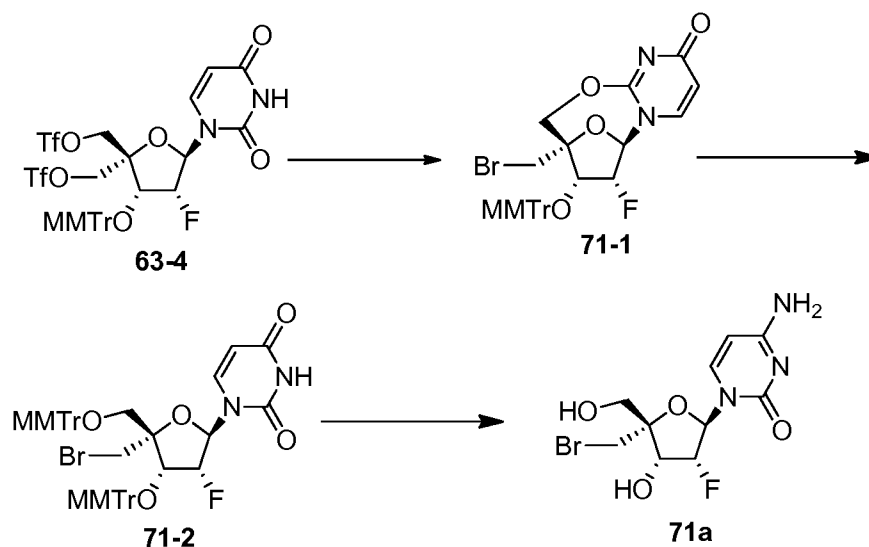
[0474] Preparation of (69a): **69-4** (800 mg, 0.95 mmol) was dissolved in 80% HOAc aq. (50 mL). The reaction mixture was heated to 75°C overnight (LCMS showed the reaction was complete). The reaction mixture was concentrated and purified on a silica gel column (DCM: MeOH= 15:1) to give **69a** (180 mg, 62.5%) as a white solid. ¹H NMR (CD₃OD, 400 MHz) δ 8.05 (d, *J* = 7.2 Hz, 1H), 6.11 (dd, *J* = 3.2 Hz *J* = 15.6 Hz, 1H), 5.87 (d, *J* = 7.6 Hz, 1H), 5.05 (dt, *J* = 4.8 Hz, *J* = 53.6 Hz, 1H), 4.47 (dd, *J* = 5.2 Hz *J* = 17.6 Hz, 1H), 3.83 (d, *J* = 12.0 Hz, 2H), 2.84 (d, *J* = 14.4 Hz, 2H), 2.15 (s, 3H). ESI-MS: *m/z* 305.8 [M + H]⁺

EXAMPLE 67
Preparation of Compound (70a)



[0475] 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 NaHCO₃ 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 (CD₃OD, 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)



[0476] Preparation of (71-1): 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 Na₂SO₄ 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%)

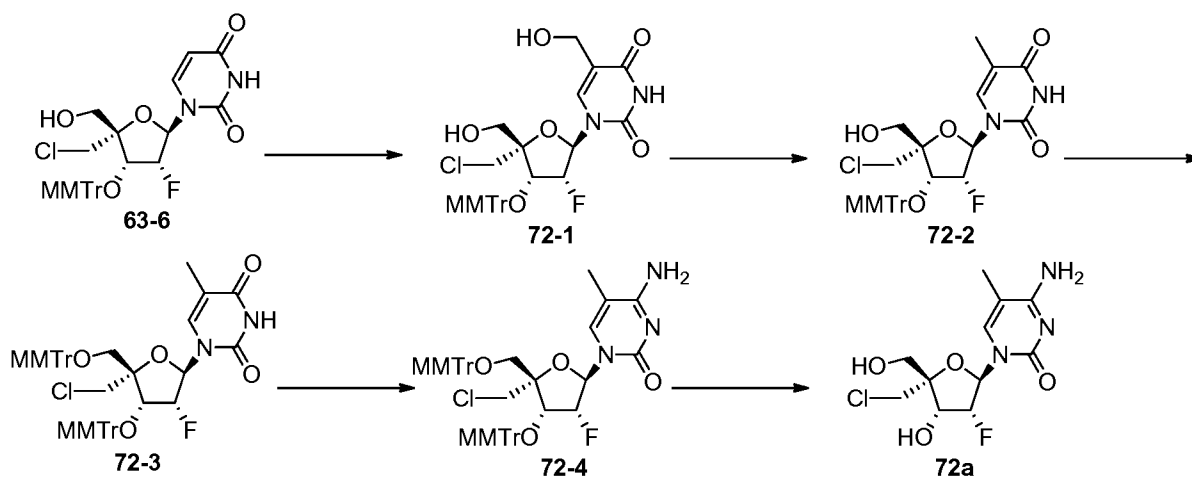
[0477] Preparation of (71-2): To a solution of **71-1** (1.74 g, 2.9 mmol) in THF (20 mL) at 0°C was added 1N NaOH (3.2 mL, 3.2 mmol), and the mixture was stirred at 0°C for 2 h. The mixture was partitioned between EA (100 mL) and water (20 mL), and the organic layer was dried over Na₂SO₄ and evaporated 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%).

[0478] 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 NaHCO₃ and brine, dried over Na₂SO₄ 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%).

[0479] Preparation of (71a): To a solution of **71-2** (2.4 g, 2.72 mmol) in anhydrous CH₃CN (30 mL) were added TPSCl (1.65 g, 5.44 mmol), DMAP (0.663 g, 5.44 mmol) and NEt₃ (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 NaHCO₃ 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%).

[0480] 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 %). ¹H NMR (MeOD, 400 MHz) δ 8.00 (d, J = 7.2 Hz, 1H), 6.12 (dd, J = 3.6 Hz, J = 15.6 Hz, 1H), 5.88 (d, J = 7.6 Hz, 1H), 5.10 (dd, J = 4.8 Hz, J = 53.2 Hz, 1H), 4.59 (dd, J = 5.2 Hz, J = 16.4 Hz, 1H), 3.95 (d, J = 11.6 Hz, 1H), 3.76 (d, J = 11.6 Hz, 1H), 3.70 (d, J = 11.6 Hz, 1H), 3.63 (d, J = 11.2 Hz, 1H); ESI-TOF-MS: m/z 337.9 [M + H]⁺.

EXAMPLE 69
Preparation of Compound (72a)



[0481] Preparation of (72-1): 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. ¹H NMR (DMSO-d₆, 400 MHz) δ 11.4 (s, 1H), 7.27-7.49 (m, 13H), 6.89 (d, J = 8.8 Hz, 2H), 4.90-4.95 (m, 1H), 4.58 (dd, J = 5.2 Hz, J = 23.6 Hz, 1H), 3.96-4.07 (m, 4H), 3.73 (s, 3H), 3.50-3.62 (m, 1H), 3.37-3.39 (m, 1H), ESI-TOF-MS: m/z 596.9 [M + H]⁺.

[0482] Preparation of (72-2): To a solution of **72-1** (430 mg, 0.72 mmol) in dioxane (2 mL) was added 30% CH₃COOH (0.7 mL) and PtO₂ (290 mg). The reaction mixture was stirred under H₂ (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. ¹H NMR (DMSO-d₆, 400 MHz) δ 11.3 (s, 1H), 7.27-7.46 (m, 13H), 6.88 (d, J = 8.8 Hz, 2H), 5.78 (d, J = 20.8 Hz, 1H), 5.06-5.08 (t, J = 20.8 Hz, 1H), 4.49 (dd, J = 4.2 Hz, J = 24.4 Hz, 1H), 3.94-4.04 (m, 2H), 3.70 (s, 3H), 3.59-3.63 (m, 1H), 3.52-3.53 (m, 1H), 3.34-3.40 (m, 1H), 1.66 (s, 3H). ESI-TOF-MS: m/z 580.9 [M + H]⁺.

[0483] Preparation of (72-3): To a solution of **72-2** (260 mg, 0.45 mmol) in anhydrous DCM (3 mL) was added AgNO₃ (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.

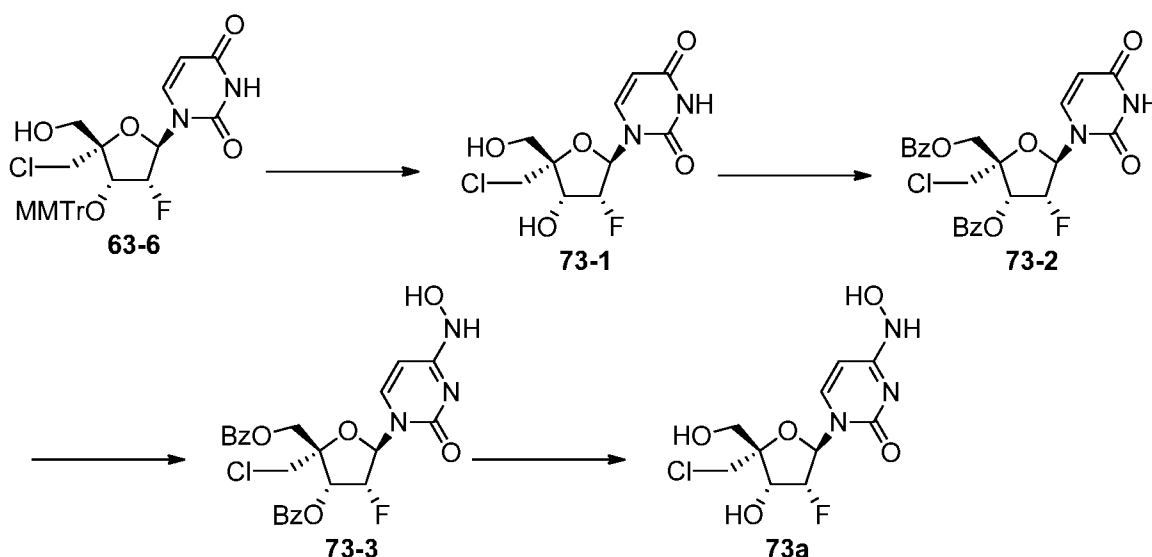
[0484] Preparation of (72-4): To a solution of **72-3** (300 mg, 0.35 mmol) in anhydrous CH₃CN (3 mL) was added DMAP (107 mg, 0.88 mmol), TEA (141 mg, 1.4 mmol)

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.

[0485] Preparation of (72a): **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. ^1H NMR (MeOD, 400 MHz) δ 7.85 (d, $J = 0.8$ Hz, 1H), 6.12 (dd, $J = 4.0$ Hz, $J = 15.2$ Hz, 1H), 5.08-5.22 (m, 1H), 4.58 (dd, $J = 4.8$ Hz, $J = 14.8$ Hz, 1H), 3.92 (d, $J = 15.6$ Hz, 1H), 3.74-3.84 (m, 3H), 1.94 (d, $J = 0.8$ Hz, 1H). ESI-TOF-MS: m/z 307.9 $[\text{M} + \text{H}]^+$.

EXAMPLE 70

Preparation of Compound (73a)



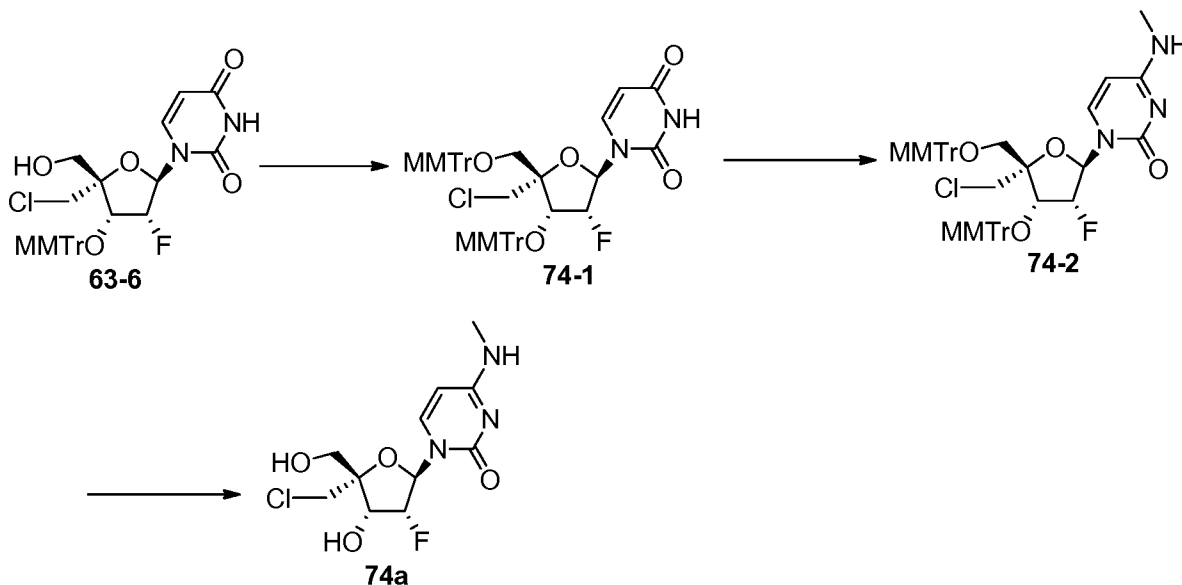
[0486] Preparation of (73-1): **63-6** (600 mg, 1.06 mmol) in formic acid (5 mL, 80% in water) was stirred at R.T. overnight. Completion of the reaction was determined by TLC (DCM: MeOH= 10:1). The solvent was removed to give crude **73-1** (290 mg, 93.2%).

[0487] Preparation of (73-2): 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°C 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.

[0488] Preparation of (73-3): 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. $\text{NH}_2\text{OH}\cdot\text{HCl}$ (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.

[0489] Preparation of (73a): **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. ^1H NMR ($\text{DMSO-}d_6$, 400 MHz) δ 10.07 (brs, 1H), 9.68 (brs, 1H), 7.02 (d, J = 8.0 Hz, 1H), 6.06 (dd, J = 6.4 Hz, J = 13.6 Hz, 1H), 5.94 (d, J = 5.6 Hz, 1H), 5.60 (d, J = 8.4 Hz, 1H), 5.36 (t, J = 5.2 Hz, 1H), 5.16 (dt, J = 5.2 Hz, J = 53.6 Hz, 1H), 4.31-4.35 (m, 1H), 3.58-3.76 (m, 2H), 3.57-3.58 (m, 2H). ESI-TOF-MS: m/z 308.1 $[\text{M} - \text{H}]^+$.

EXAMPLE 71 Preparation of Compound (74a)

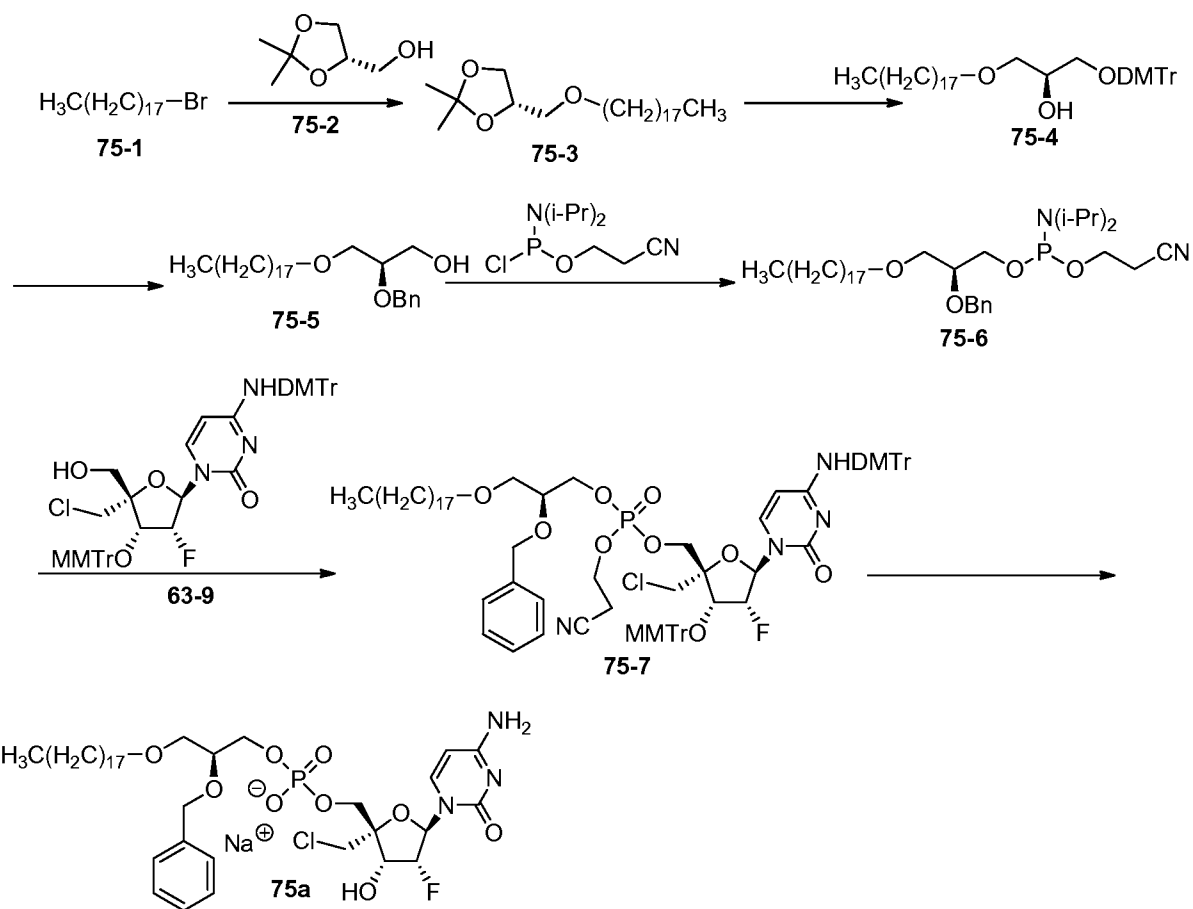


[0490] Preparation of (74-1): To a solution of **63-6** (1.2 g, 2.12 mmol) in anhydrous DCM (20 mL) were added collidine (750 mg, 6.51 mol) and MMTrCl (2.6 g, 8.5 mmol). The reaction mixture was stirred at R.T. overnight. The reaction was filtered and washed successively with saturated aqueous NaHCO_3 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%).

[0491] Preparation of (74-2): 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). CH₃NH₂ (310 mg, 10 mmol) was added dropwise at 0°C. 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 NaHCO₃ 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.

[0492] Preparation of (74a): **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. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 7.79 (d, *J* = 4.8 Hz, 1H), 7.72 (d, *J* = 5.2 Hz, 1H), 6.10 (dd, *J* = 4.4 Hz, *J* = 14.8 Hz, 1H), 5.97 (brs, 1H), 5.73 (d, *J* = 7.6 Hz, 1H), 5.39 (brs, 1H), 5.08 (dt, *J* = 4.2 Hz, *J* = 53.2 Hz, 1H), 4.37-4.40 (m, 1H), 3.73 (s, 2H), 3.54-3.70 (m, 2H), 2.73 (d, *J* = 4.4 Hz, 3H). ESI-TOF-MS: *m/z* 308.1 [M + H]⁺.

EXAMPLE 72
Preparation of Compound (75a)



[0493] Preparation of (75-3): 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).

[0494] Preparation of (75-4): Crude **75-3** (72 g, 151 mmol) was dissolved with 80% CH₃COOH (300 mL) and stirred for 10 h. The solvent was removed under reduced pressure. The residue was dissolved in EA and washed with saturated NaHCO₃ and brine successively. The organic layer was dried over Na₂SO₄ 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%).

[0495] Preparation of (75-5): 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% CH₃COOH (100 mL) was stirred at R.T. for 12 h. The solvent was removed. The residue was dissolved in EA, washed with saturated NaHCO₃ 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.

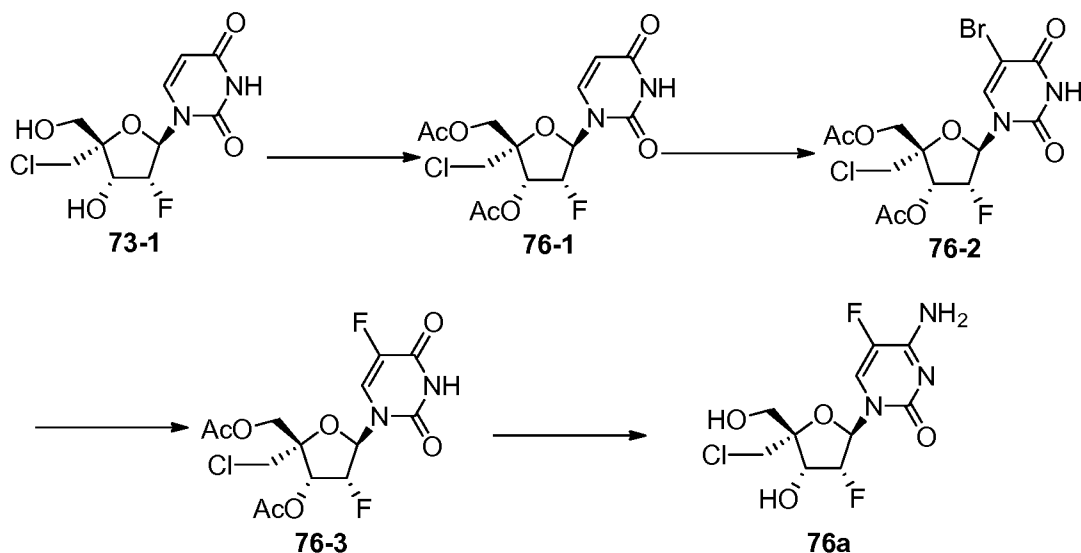
[0496] Preparation of (75-6): To a solution of **75-5** (4.0 g, 9.2 mmol) in anhydrous CH₃CN (30 mL) was added DIPEA (6.1 g, 47.6 mmol) and 2-cyanoethyl N,N-diisopropylchlorophosphoramidite (2.8 g, 11.9 mmol). The mixture was stirred at R.T. for 2 h. The solvent was removed, and residue was partitioned by EA and saturated NaHCO₃. The organic layer was dried over MgSO₄ 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.

[0497] Preparation of (75-7): 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 Na₂SO₃ and brine, dried over anhydrous Na₂SO₄ 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.

[0498] Preparation of (75a): **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 NaHCO₃ 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 C₂H₅OH 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. ¹H NMR (CD₃OD, 400 MHz) δ 8.01 (d, *J* = 7.6 Hz, 1H), 7.23-7.37 (m, 5H), 6.22 (dd, *J* = 3.6 Hz, *J* = 14.4 Hz, 1H), 6.01 (d, *J* = 7.6 Hz, 1H), 5.01-5.16 (m, 1H), 4.63-4.72 (m, 2H), 4.52-4.11 (m, 1H), 4.23-4.29 (m, 1H), 3.91-4.09 (m, 3H), 3.69-3.81 (m, 3H), 3.51-3.60 (m, 2H), 3.41-3.45 (m, 2H), 1.48-1.55 (m, 2H),

1.21-1.35 (m, 32H), 0.87-0.91 (m, 3H). ^{31}P NMR (CD_3OD , 162 MHz) δ -0.223. ESI-TOF-MS: m/z 788.3 $[\text{M} - \text{H}]^+$.

EXAMPLE 73
Preparation of Compound (76a)



[0499] Preparation of (76-1): 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%).

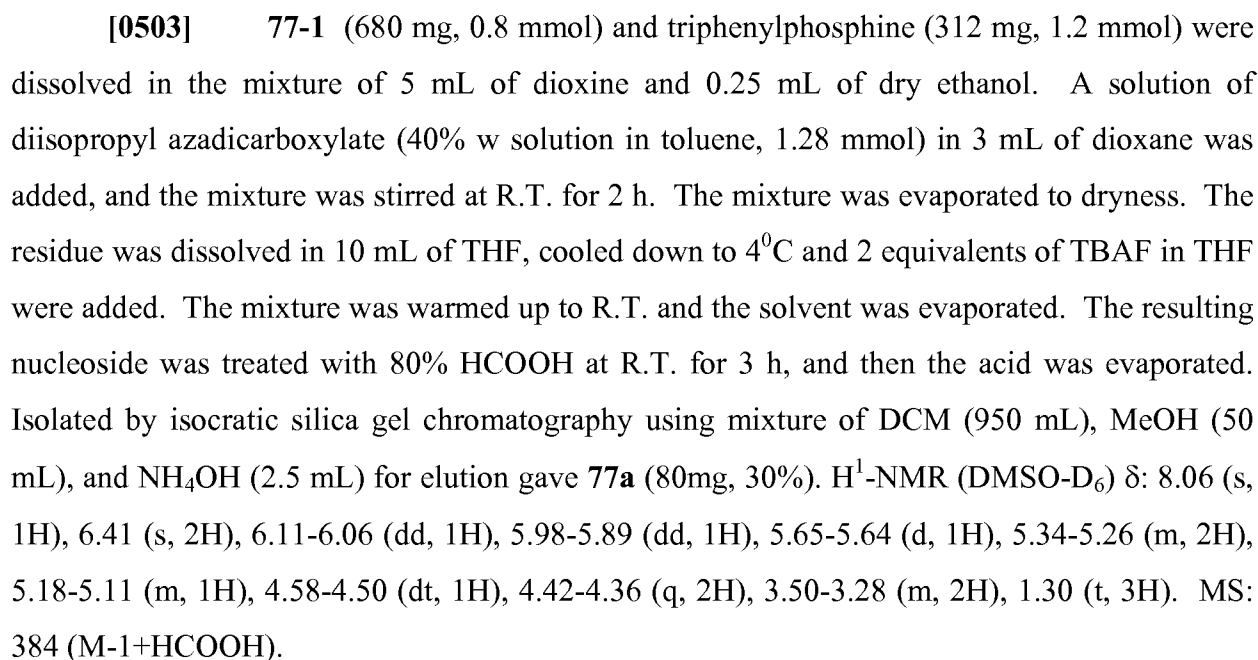
[0500] Preparation of (76-2): To a solution of **76-1** (1.3 g, 3.44 mmol) in pyridine (20 mL) was added NBS (1.22 g, 6.88 mmol) at R.T., and the mixture was stirred overnight. The mixture was concentrated, and the residue was purified on a silica gel column (PE: EA= 4:1) to give **76-2** (1.43 g, 72.2%).

[0501] Preparation of (76-3): 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 $(\text{PPh}_3)_2\text{PdCl}_2$ (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 Selectfluor® (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%).

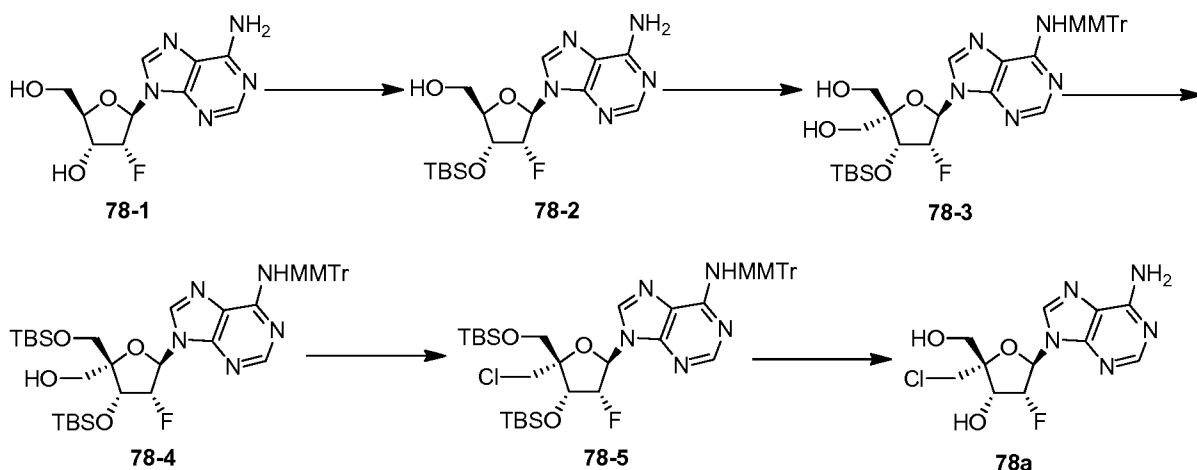
[0502] Preparation of (76a): To a solution of **76-3** (100 mg, 0.25 mmol) in MeCN (2 mL) was added DMAP (62 mg, 0.51 mmol), TEA (51 mg, 0.51 mmol) and TPSCl (153 mg, 0.51 mmol). The mixture was stirred at R.T. for 0.5 h. $\text{NH}_3\cdot\text{H}_2\text{O}$ (0.75 mL) was added. The

EXAMPLE 74

Preparation of Compound (77a)



EXAMPLE 75
Preparation of Compound (78a)



[0504] Preparation of (78-2): 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 Na₂SO₄ 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 CH₂Cl₂ (150 mL) was added a solution of p-toluenesulfonic acid monohydrate (8.2 g, 47.5 mmol) in small portion under N₂. The mixture was stirred at 25°C for 30 min, and then washed with saturated aq. NaHCO₃. The organic layer was separated, dried over anhydrous Na₂SO₄ 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.

[0505] Preparation of (78-3): 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 N₂. The reaction mixture was stirred at 25°C overnight. AgNO₃ (77.8 g, 510 mmol) and MMTTrCl (156.8 g, 510 mmol) in anhydrous pyridine (50 mL) was added in small portions under N₂. 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 NaHCO₃ solution and brine. The organic layer was separated, dried over anhydrous Na₂SO₄, 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 Na₂SO₄. 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% CH₂O (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 NaBH₄ (912 mg, 24.0 mmol). The reaction was stirred for 30 mins, and then quenched with saturated aqueous NH₄Cl. The mixture was extracted with EA, and the organic layer was dried over Na₂SO₄. Purification by silica gel column chromatography (EA: PE = 10:1 to 2:1) gave **78-3** (1.1 g, 40%) as a yellow solid.

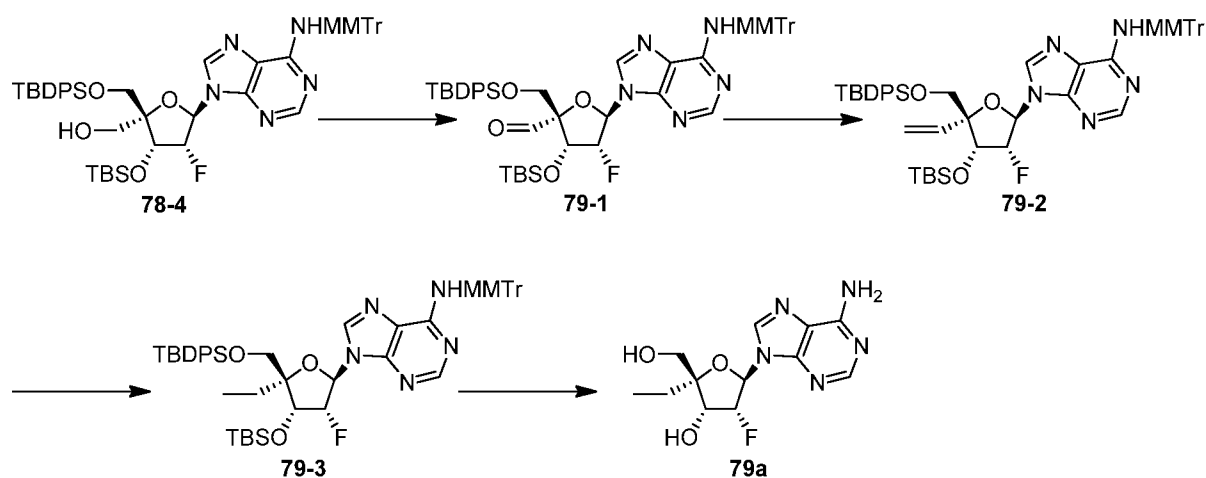
[0506] Preparation of (78-4): A stirred solution of **78-3** (685 mg, 1.0 mmol) in anhydrous CH₃CN (5 mL) and anhydrous pyridine (5 mL) was cooled to 0°C. BzCl (126 mg, 0.9 mmol) was added, and the reaction mixture was stirred at 25°C. After 1.5 h, water (5 mL) was added. The resulting mixture was extracted with DCM (2×30 mL). The combined extracts were washed with a saturated aqueous solution of NaHCO₃ (20 mL), dried over MgSO₄, 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, 1.65 mmol). 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 NaHCO₃ (60 mL) and brine (60 mL), dried over MgSO₄, 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 CH₃OH (5 mL), and NaOCH₃ (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 NaHCO₃ (20 mL), dried over MgSO₄, 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.

[0507] Preparation of (78-5): **78-4** (239 mg, 0.30 mmol) was co-evaporated with toluene three times to remove H₂O. 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 N₂. The mixture was stirred at 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 N₂. The mixture was stirred at 25°C for 40 mins. The mixture was washed with NaHCO₃ and extracted with EA. The combined organic layer was dried over Na₂SO₄ and concentrated to give crude **78-5** (268 mg) as a light yellow oil.

[0508] Preparation of (78a): To a solution of **78-5** (268 mg, 0.328 mmol) in MeOH (5 mL) was added NH₄F (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 H₂O (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. ¹H NMR (MeOD, 400 MHz) δ 8.33 (s, 1H), 8.20 (s, 1H), 6.32 (dd, J = 5.6, 12.4 Hz, 1H), 5.77 (m, 1H), 4.69 (m, 1H), 3.85 (m, 1H). ESI-MS: m/z 317.9 [M + H]⁺.

EXAMPLE 76 **Preparation of Compound (79a)**



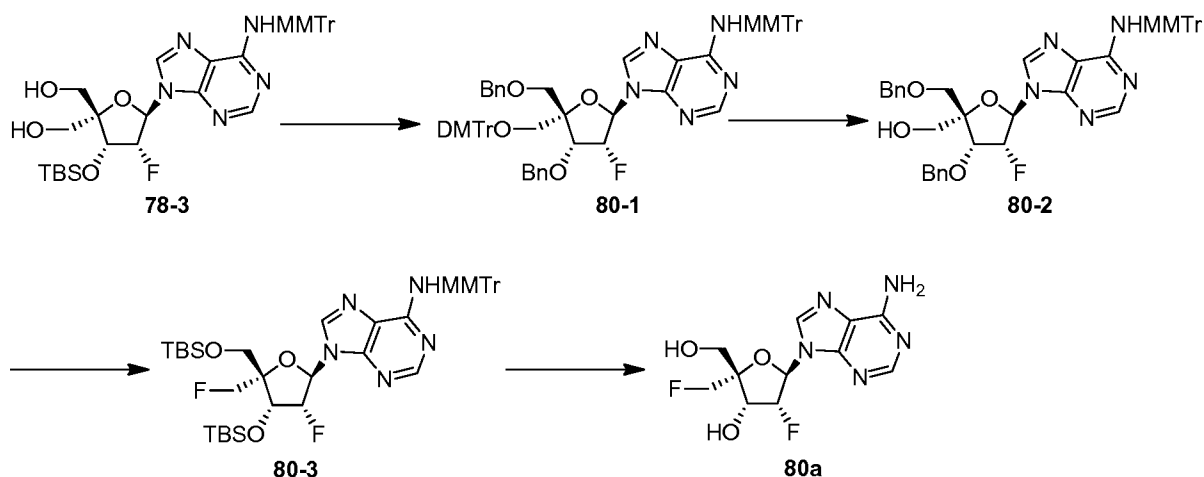
[0509] Preparation of (79-1): To a solution of **78-4** (1.1 g, 1.33 mmol) in anhydrous DCM (6.6 mL) at 0°C under nitrogen was added Dess-Martin periodinane (1.45 g, 3.33 mol). The mixture was stirred at 25°C for 4 h. The solvent was removed in vacuum, and the residue triturated with methyl-*t*-butyl ether (30 mL). The mixture was filtered through a pad of MgSO₄, and the organic solvent was stirred with an equal volume of Na₂S₂O₃ in 30 mL of saturated NaHCO₃ until the organic layer became clear (approx. 10 min). The organic layer was separated, washed with brine, and dried over MgSO₄. 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.

[0510] Preparation of (79-2): To a stirred solution of methyl-triphenylphosphonium 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 NH₄Cl (30 mL), and extracted with EtOAc (2×30 mL). The combined organic phase was washed with brine, dried with MgSO₄, 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%).

[0511] Preparation of (79-3): 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.

[0512] Preparation of (79a): **79-3** (365 mg, 0.40 mmol) in MeOH (50 mL) was added NH₄F (5.6 g, 0.15 mmol), and the solution was heated to reflux 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. ¹H NMR (400MHz, CD₃OD) δ 8.25 (s, 1H), 8.09 (s, 1H), 6.14 (dd, *J* = 6.0, 12.8 Hz, 1H), 5.58 (m, 1H), 4.45-4.48 (m, 1H), 3.60 (q, 2H), 1.66-1.74 (m, 2H), 0.88(t, 3H); ESI-MS: *m/z* 297.9 [M + H]⁺.

EXAMPLE 77 Preparation of Compound (80a)



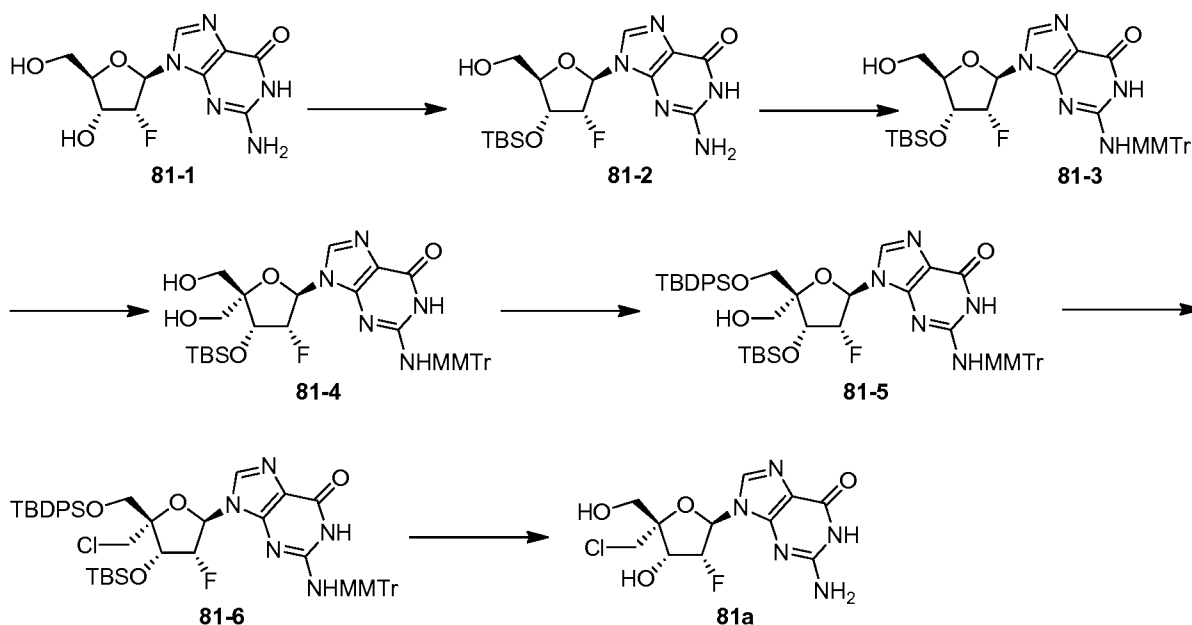
[0513] Preparation of (80-1): To a solution of **78-3** (4.4 g, 6.4 mmol) in anhydrous pyridine (5 mL) and DCM (25 mL). A solution of DMTrCl (2.37 g, 7.04 mmol) in DCM (5 mL) was added dropwise at 0°C under N₂. After 2 h, the reaction was quenched with CH₃OH and concentrated to dryness. The residue was 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 Na₂SO₄, 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.

[0514] Preparation of (80-2): To a solution of **80-1** (1.3 g, 1.23 mmol) in anhydrous DCM (17 mL) was added Cl₂CHCOOH (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 NaHCO₃, and diluted with DCM (50 mL). The mixture was washed with brine, and the organic solution was dried over Na₂SO₄ 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.

[0515] 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 NaHCO₃. The mixture was diluted with DCM (50 mL) and washed with brine. The organic solution was dried over Na₂SO₄ 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%).

[0516] Preparation of (80a): 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 H₂ 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). ¹H NMR (400MHz, CD₃OD) δ 8.33 (s, 1H), 8.20 (s, 1H), 6.33 (dd, *J* = 6.0, 13.2 Hz, 1H), 5.79 (t, *J* = 5.6 Hz, 1H), 5.66 (t, *J* = 5.2 Hz, 1H), 4.52-4.80 (m, 3H), 3.80-3.82 (m, 2H). ESI-MS: *m/z* 302.0 [M + H]⁺.

EXAMPLE 78
Preparation of Compound (81a)



[0517] Preparation of (81-2): 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). H₂O (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.

[0518] Preparation of (81-3): To a solution of **81-2** (31.2 g, 78.2 mmol) in anhydrous pyridine (300 mL) was added Ac₂O (11.9 g, 117.3 mmol). The mixture was stirred at 25°C for 18 h. MMTrCl (72.3 g, 234.6 mmol) and AgNO₃ (39.9 g, 234.6 mmol) were added, and the solution was stirred at 25°C for 15 h. H₂O 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 Na₂SO₄ 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 NH₃/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%).

[0519] Preparation of (81-4): 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 NaHCO₃ and Na₂S₂O₃ solution. The organic layer was washed with brine (2X) and dried over anhydrous Na₂SO₄. 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 NaBH₄ (10.9 g, 288 mmol) were added, and the reaction was stirred for 30 mins. The mixture was quenched with saturated aqueous NH₄Cl, and then extracted with EA. The organic layer was dried over Na₂SO₄, 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.

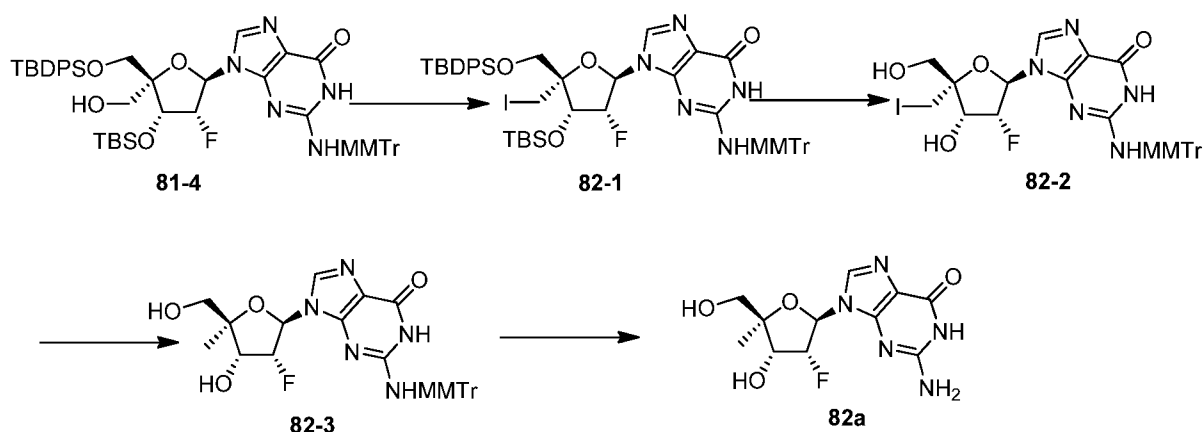
[0520] Preparation of (81-5): To a solution of **81-4** (3.8 g, 5.4 mmol) in DCM (40 mL) was added pyridine (10 mL) and DMTrCl (1.8 g, 5.4 mmol) at 0°C. The solution was stirred at 25°C for 1 h. MeOH (15 mL) was added, and the solution was concentrated. The residue was purified by silica gel column chromatography (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 AgNO₃ (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 Na₂SO₄, 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 Cl₂CHCOOH (1.8 mL) in anhydrous DCM (18 mL). The mixture was stirred at -78°C for 1 h. Cl₂CHCOOH (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 NaHCO₃ and extracted with DCM. The organic layer was dried over Na₂SO₄, and then purified by silica gel column chromatography (DCM: MeOH = 200:1 to 50:1) to give **81-5** (2.2 g, 80%).

[0521] Preparation of (81-6): 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 Tf₂O (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 MgSO₄. 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 MgSO₄, and the residue was purified on a silica gel column (DCM/MeOH = 100:1) to give **81-6** (430 mg, 61%).

[0522] Preparation of (81a): To **81-6** (470 mg, 0.49 mmol) in MeOH (85 mL) was added NH₄F (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. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 10.73 (br, 1H), 7.98 (s, 1H), 6.58 (br, 2H), 6.08 (q, *J* = 4.8, 9.2 Hz, 2H), 5.64 (dt, *J* = 5.6, 52.8 Hz, 1H), 5.40 (m, 1H), 4.52 (m, 1H), 3.80-3.82 (m, 2H), 3.64 (q, 2H). ESI-MS: *m/z* 333.8 [M + H]⁺, 666.6 [2M + H]⁺

EXAMPLE 79 **Preparation of Compound (82a)**



[0523] Preparation of (82-1): 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 Tf₂O (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 Na₂SO₄ 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 Na₂S₂O₃ twice and washed with brine. The organic layer was dried over Na₂SO₄ 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).

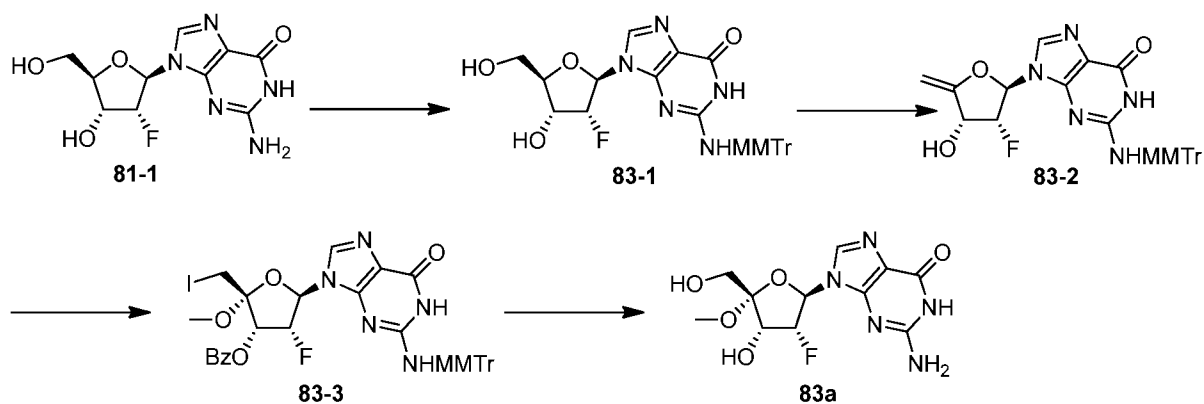
[0524] Preparation of (82-2): To a solution of **82-1** (650 mg, 0.62 mmol) in MeOH (10 mL) was added NH₄F (45.8 g, 12.4 mmol). The mixture was refluxed overnight. The mixture was filtered and evaporated to dryness. The residue was purified on a silica gel column (DCM/MeOH = 200:1 to 20:1) to give **82-2** (250 mg, 58%).

[0525] Preparation of (82-3): To a stirred solution of **82-2** (300 mg, 0.43 mmol), Et₃N (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%).

[0526] Preparation of (82a): **82-3** (110 mg, 0.19 mmol) was dissolved in HCOOH (18 g) and H₂O (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%). ¹H NMR (400MHz, MeOD) δ 8.00 (s, 1H), 6.11-6.15 (m, 1H), 5.35-5.50 (m, 1H), 4.53-4.59 (m, 1H), 3.54-3.64 (m, 2H), 1.26 (s, 3H). ESI-MS: m/z 299.76 [M + 1]⁺, 598.66 [2M + 1]⁺.

EXAMPLE 80

Preparation of Compound (83a)



[0527] Preparation of (83-1): **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 Ac₂O (5.8 mL, 60 mmol) was added dropwise. The mixture was stirred at 25°C for 10 h,

and then cooled to 0°C. AgNO₃ (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 NaHCO₃ and extracted with EA. The organic layer was dried over Na₂SO₄ 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 NH₃ (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%).

[0528] Preparation of (83-2): 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 PPh₃ (34.8 g, 132 mmol). A solution of I₂ (26.0 g, 103 mmol) in THF (100 mL) was added dropwise under N₂ at 0°C. The mixture was stirred at 25°C for 18 h and then quenched with a Na₂S₂O₃ solution. The mixture was extracted with EtOAc. The organic layer was dried over Na₂SO₄ 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 NaHCO₃ solution and extracted with EtOAc. The organic layer was dried over Na₂SO₄ 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%).

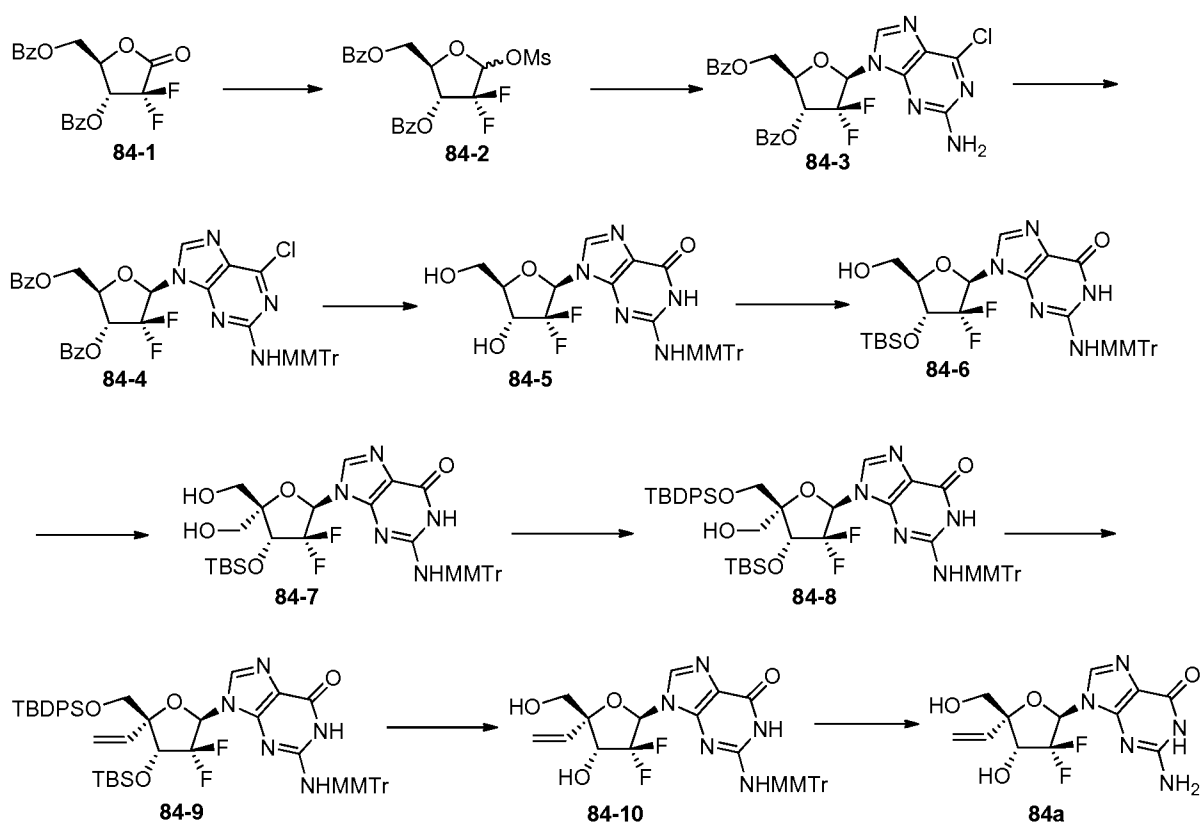
[0529] Preparation of (83-3): To a stirred solution of **83-2** (5.42 g, 10 mmol) in anhydrous CH₃OH (100 mL) was added PbCO₃ (13.7 g, 53.1 mmol). A solution of I₂ (12.3 g, 48.9 mmol) in CH₃OH (300 mL) was added dropwise at 0°C. The mixture was stirred at 25°C for 10 h. The solution was quenched with a Na₂S₂O₃ solution and extracted with DCM. The organic layer was washed with a NaHCO₃ solution, dried over Na₂SO₄ 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 NaHCO₃ solution and extracted with EtOAc. The organic layer was dried over Na₂SO₄ 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.

[0530] Preparation of (83a): **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 Na₂SO₄. 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 H₂O (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%). ¹H NMR (CD₃OD, 400MHz) δ 7.92 (s, 1H), 6.22 (dd, *J* = 1.6, 18.8 Hz, 1H), 5.17-5.32 (m, 1H), 4.89-4.91 (m, 1H), 3.77 (m, 2H), 3.44 (s, 3H). ESI-MS: *m/z* 316.1 [M + H]⁺.

EXAMPLE 81

Preparation of Compound (84a)



[0531] Preparation of (84-2): To a stirred solution of **84-1** (100.0 g, 265.9 mmol) in dry THF (1000 mL) was added Li(O-*t*-Bu)₃AlH (318.9 mL, 318.9 mmol) at -78°C under N₂. 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 NH₄Cl solution. The mixture was extracted with EtOAc. The organic layer was dried over Na₂SO₄ 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), NEt₃ (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 Na₂SO₄, 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.

[0532] Preparation of (84-3): To a suspension of compound 6-chloro-9H-purin-2-amine (70.1 g, 414.7 mmol), HMDS (480 mL) and (NH₄)₂SO₄ (0.8 g) was added dry DCE (400 mL). The mixture was refluxed under N₂ for 18 h and then cooled to R.T. To the silylated 2-amino-6-chloropurine solution was added **84-2** (78.0 g, 171.1 mmol) and TMSOTf (60 mL, 331.9 mmol). The mixture was refluxed overnight, concentrated and neutralized with a NaHCO₃ solution. The resulting precipitate was filtered, and the filtrate was extracted with EtOAc. The organic layer was dried over Na₂SO₄ 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.

[0533] Preparation of (84-4): 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 AgNO₃ (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 NaHCO₃ solution. The organic layer was dried over Na₂SO₄ 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. ¹H NMR (CDCl₃, 400 MHz) δ 7.94-7.96 (m, 4H), 7.05-7.58 (m, 18H), 6.62-6.67 (m, 2H), 6.55 (dd, *J* = 6.0 Hz, *J* = 9.6 Hz, 1H), 5.60-5.66 (m, 1H), 4.69-4.76 (m, 2H), 4.55-4.58 (m, 1H), 3.64 (s, 1H). ESI-MS: *m/z* 802 [M + H]⁺.

[0534] Preparation of (84-5): 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 CO₂. 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.

[0535] Preparation of (84-6): 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 Na₂SO₄, 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 NaHCO₃ and brine. The organic layer was dried over Na₂SO₄, 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 Cl₂CHCOOH (20 mL) in anhydrous DCM (500 mL). The mixture was stirred at -78°C for 1 h. Cl₂CHCOOH (30 mL) was added at -78°C. The mixture was stirred at -20°C for 2 h. The mixture was quenched with saturated aqueous NaHCO₃ and extracted with DCM. The organic layer was dried over Na₂SO₄, 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. ¹H NMR (400MHz, MeOD) δ 8.27 (s, 1H), 7.16-7.38 (m, 12H), 6.79-6.83 (m, 2H), 6.42 (dd, *J* = 4.4 Hz, *J* = 10.0 Hz, 1H), 4.54-4.62 (m, 1H), 3.92 (d, *J* = 8.8 Hz, 2H), 3.74 (s, 3H), 3.70-3.72 (m, 1H), 0.92 (s, 9H), 0.11-0.13 (m, 6H). ESI-LCMS: *m/z* 690.0 [M + H]⁺.

[0536] Preparation of (84-7): **84-6** (7.0 g, 10.0 mmol) was added to a suspension of DMP (10.6 g, 25 mmol) in anhydrous CH₂Cl₂ (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 MgSO₄. The organic solvent was stirred with an equal volume of Na₂S₂O₃·5H₂O in 100 mL of saturated NaHCO₃ until the organic layer became clear (10 min). The organic layer was separated, washed with brine, and dried over MgSO₄. 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% CH₂O (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 NaBH₄ (3.8 g, 100 mmol) were added, and the mixture was stirred for 30 mins. The mixture was quenched with saturated aqueous NH₄Cl, and then extracted with EA. The organic layer was dried over Na₂SO₄. 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.

[0537] Preparation of (84-8): 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 AgNO₃ (0.68 g, 4.0 mmol). The mixture was stirred at 25°C for 15 h. The mixture was filtered,

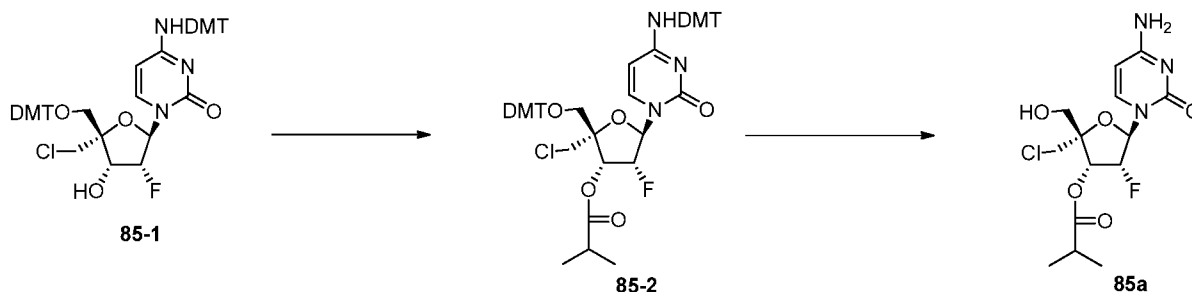
concentrated, dissolved in EtOAc and washed with brine. The organic layer was dried over Na₂SO₄. Purification by a silica gel column (DCM: MeOH = 200:1 to 100:1) gave a fifth intermediate (1.4 g) as a solid. To a solution of the fifth intermediate (1.4 g, 1.1 mmol) in anhydrous DCM (50 mL) was added Cl₂CHCOOH (0.7 ml) in anhydrous DCM (18 mL). The mixture was stirred at -78°C for 1 h. Cl₂CHCOOH (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 NaHCO₃ and extracted with DCM. The organic layer was dried over Na₂SO₄. Purification by a silica gel column (DCM: MeOH = 200:1 to 50:1) gave **84-8** (650 mg, 11.6%) as a white solid.

[0538] Preparation of (84-9): 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 N₂. 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 N₂. 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 NaHCO₃, dried over Na₂SO₄ 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 Methyltriphenyl-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 NH₄Cl (20 mL) and extracted with EtOAc. The combined organic phase was dried with Na₂SO₄, 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.

[0539] Preparation of (84-10): **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. ¹H NMR (400MHz, MeOD) δ 8.34 (s, 1H), 7.15-7.38 (m, 12H), 6.79-6.82 (m, 2H), 6.44 (dd, *J* = 2.0 Hz, *J* = 10.0 Hz, 1H), 6.01 (dd, *J* = 11.2 Hz, *J* = 17.6 Hz, 1H), 5.51 (dd, *J* = 1.6 Hz, *J* = 17.2 Hz, 1H), 5.35 (dd, *J* = 1.6 Hz, *J* = 17.2 Hz, 1H), 4.68-4.76 (m, 1H), 3.74 (s, 3H), 3.63(dd, *J* = 2.0 Hz, *J* = 12.8 Hz, 1H) 3.52(dd, *J* = 2.0 Hz, *J* = 12.8 Hz, 1H). ESI-LCMS: *m/z* 602.0 [M + H]⁺.

[0540] Preparation of (84a): 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 **84** (9.3 mg) as a slightly-amber solid. ^1H NMR (CD_3OD , 400 MHz) δ 8.44 (s, 1H), 6.57 (d, $J = 10.8$ Hz, 1H), 6.05 (dd, $J = 17.6$ Hz, 10.8 Hz, 1H), 5.45 (dd, $J = 17.6$ Hz, $J = 1.6$ Hz, 1H), 5.37 (dd, $J = 10.8$ Hz, 1.6 Hz, 1H), 4.78 (dd, $J = 18.4$ Hz, 17.2 Hz, 1H), 3.67 (d, $J = 12.4$ Hz, 1H), 3.56 (dd, $J = 12.4$ Hz, 2.0 Hz, 1H); ESI-MS: m/z 328.4 $[\text{M} - \text{H}]^-$.

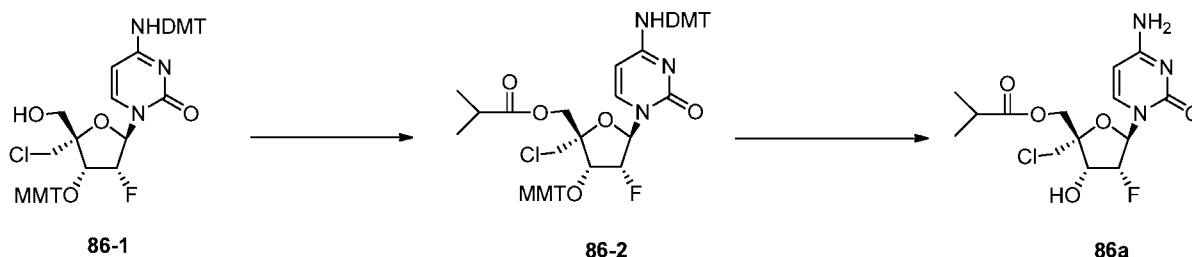
EXAMPLE 82
Preparation of Compound (85a)



[0541] Preparation of (85-2): 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%).

[0542] Preparation of (85a): 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%). ^1H -NMR ($\text{DMSO}-d_6$): δ 7.75 (d, 1 H), 7.33 (d, 2 H), 6.07 (dd, 1 H), 5.75 (d, 1 H), 5.55 (dd, 1 H), 5.43 (dt, 1 H), 5.43 (t, 1 H), 3.79 (dd, 2 H), 3.63 (ddd, 2 H), 2.64 (sept, 1 H), 1.12 (d, 6 H). MS: $m/z = 362.1$ $[\text{M} + 1]$

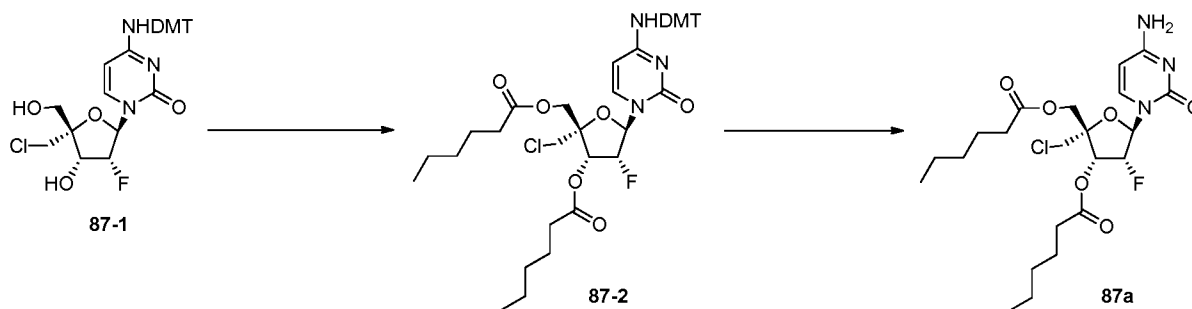
EXAMPLE 83
Preparation of Compound (86a)



[0543] Preparation of (86-2): **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%).

[0544] Preparation of (86a): **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 CH₂Cl₂ /MeOH (4-10% gradient) to give **86a** (36 mg, 77%). ¹H-NMR (DMSO-d₆): δ 7.58 (d, 1 H), 7.29 (d, 2 H), 6.00 (s, 1 H), 5.73 (d, 1 H), 5.24 (ddd, 1 H), 4.55 (dd, 1 H), 4.22 (dd, 2 H), 3.80 (dd, 2 H), 2.58 (sept, 1 H), 1.08, 1.07 (2d, 6 H). MS: m/z = 364 [M+1].

EXAMPLE 84
Preparation of Compounds (87a)

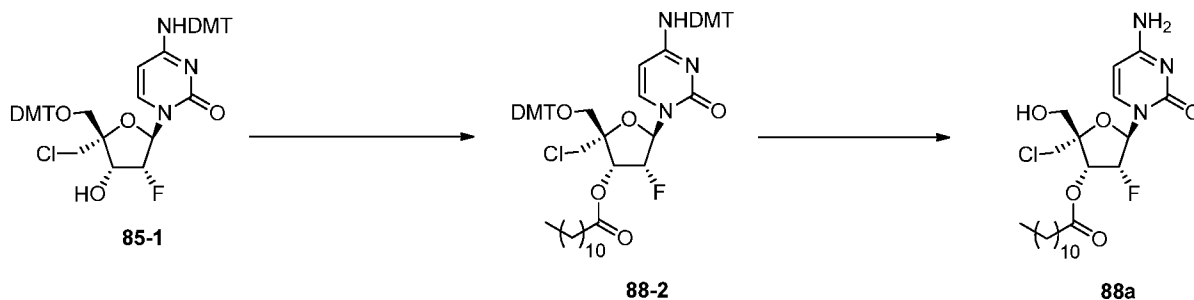


[0545] Preparation of (87-2): **87-2** was prepared using a similar procedure for preparing **46-2** with the following: **87-1** (178 mg, 0.3 mmol), hexanoic anhydride (0.14 mL, 2 equiv.), pyridine (3 mL) to give **87-2**. (120 mg, 50%).

[0546] Preparation of (87a): **87a** was prepared using a similar procedure for preparing **85a** with the following: **87-2** (120 mg, 0.15 mmol), 80% aq. HCOOH and CH₂Cl₂ /MeOH (4-10% gradient) to give **87a** (62mg, 85%). ¹H-NMR (CDCl₃): δ 8.2 (br, 1 H), 7.42 (d, 1 H), 6.8 (br, 1 H), 6.03 (d, 1 H), 5.77 (dd, 1 H), 5.64 (dd, 1 H), 5.51 (ddd, 1 H), 4.43 (dd, 2 H), 3.82 (dd, 2 H), 2.41 (m, 2 H), 2.33 (m, 2 H), 1.64 (m, 4 H), 1.31 (m, 8 H), 0.82 (m, 6 H). MS: m/z = 488 [M-1].

EXAMPLE 85

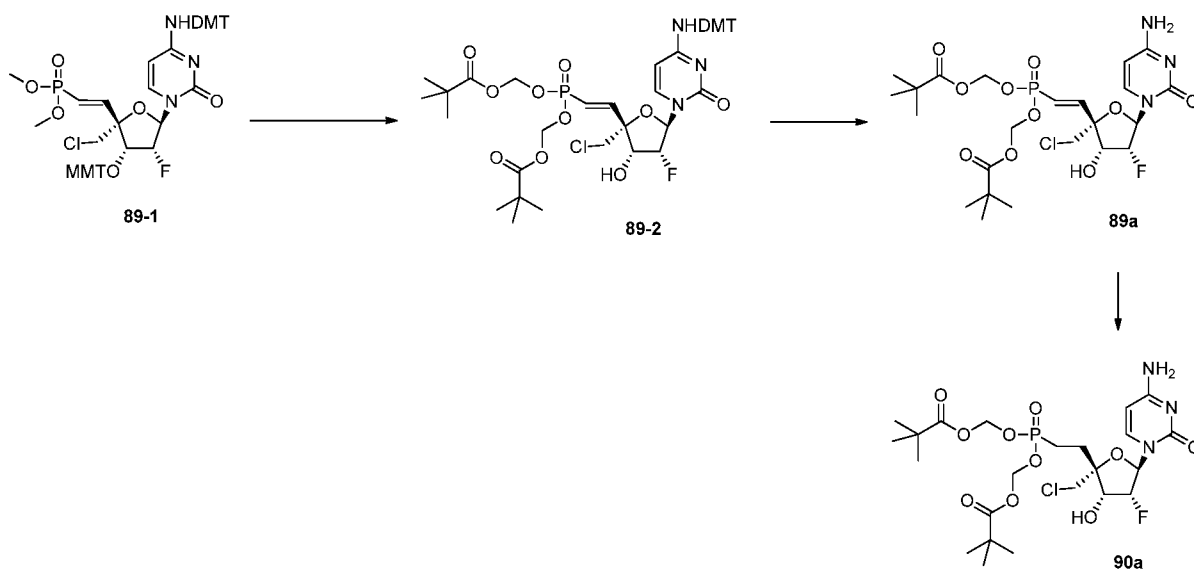
Preparation of Compound (88a)



[0547] Preparation of (88-2): **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), dodecanoyl 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%).

[0548] Preparation of (88a): **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 CH₂Cl₂ /MeOH (4-10% gradient) to give **88a** (66 mg, 82%). ¹H-NMR (DMSO-d₆): δ 7.77 (d, 1 H), 7.35 (d, 2 H), 6.07 (dd, 1 H), 5.77 (d, 1 H), 5.60 (dd, 1 H), 5.55 (ddd, 1 H), 5.43 (t, 1 H), 3.78 (dd, 2 H), 3.65 (ddd, 2 H), 2.41 (m, 2 H), 1.56 (m, 2 H), 1.24 (m, 16 H), 0.85 (m, 3 H). MS: m/z = 474 [M-1].

EXAMPLE 86
Preparation of Compounds (89a) and (90a)



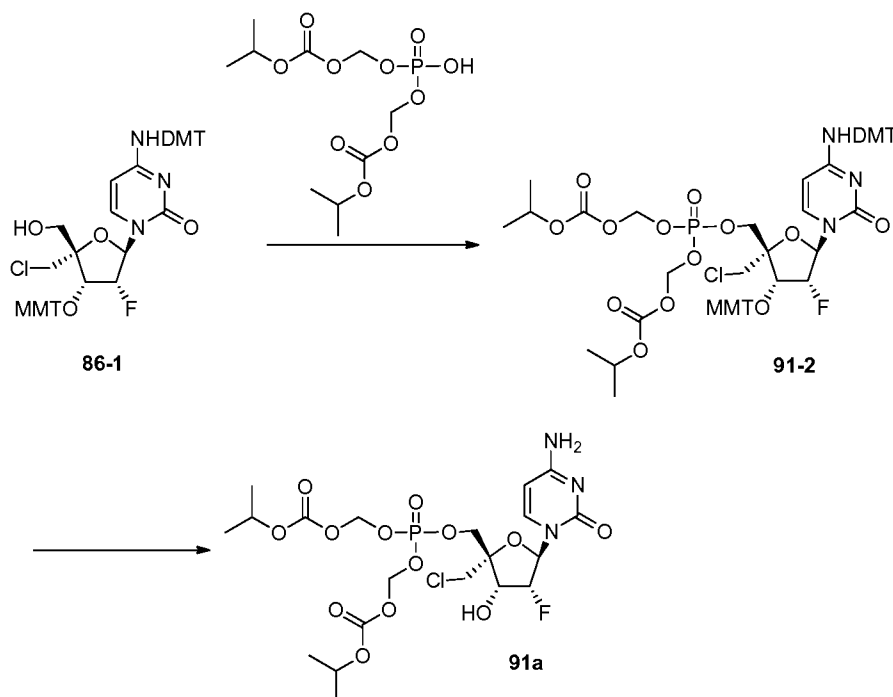
[0549] Preparation of (89-2): To a solution of **89-1** (175 mg; 0.18 mmol) in MeCN (2.5 mL) at 0°C was added TMSBr (0.28 mL; 10 equiv.). The mixture was stirred at R.T. for 1 h, evaporated and treated with water. The obtained white solid was filtered, dried and washed

with CH₂Cl₂. The white solid was then dissolved in NMP (2 mL) and treated with DIPEA (94 µL; 3 equiv.) and pivaloyloxymethyl iodide (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 NaHCO₃, 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 CH₂Cl₂ /i-PrOH (2-10% gradient) to give **89-2** (42 mg, 26%).

[0550] Preparation of (89a): 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 CH₂Cl₂ /MeOH (4-15% gradient) gave **89a** (17 mg, 74%). ¹H-NMR (CD₃OD): δ 7.47 (d, 1 H), 6.28 (dd, 1 H), 6.04 (dd, 1 H), 5.77-5.71 (m, 2 H), 5.53 (m, 4 H), 5.18 (ddd, 1 H), 5.60 (dd, 1 H), 3.77 (dd, 2 H), 1.08 (m, 18 H). ³¹P-NMR (CD₃OD): δ 17.64. MS: m/z = 598 [M+1].

[0551] Preparation of (90a): 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 CH₂Cl₂ /MeOH (4-17% gradient) to give **90a** (6 mg, 50%). ¹H-NMR (CD₃OD): δ 7.51 (d, 1 H), 5.79 (d, 1 H), 5.65-5.54 (m, 5 H), 5.20 (ddd, 1 H), 5.60 (dd, 1 H), 3.70 (dd, 2 H), 2.17-2.06 (m, 1 H), 2.02-1.87 (m, 3 H), 1.13 (m, 18 H). ³¹P-NMR (CD₃OD): δ 33.16. MS: m/z = 600 [M+1].

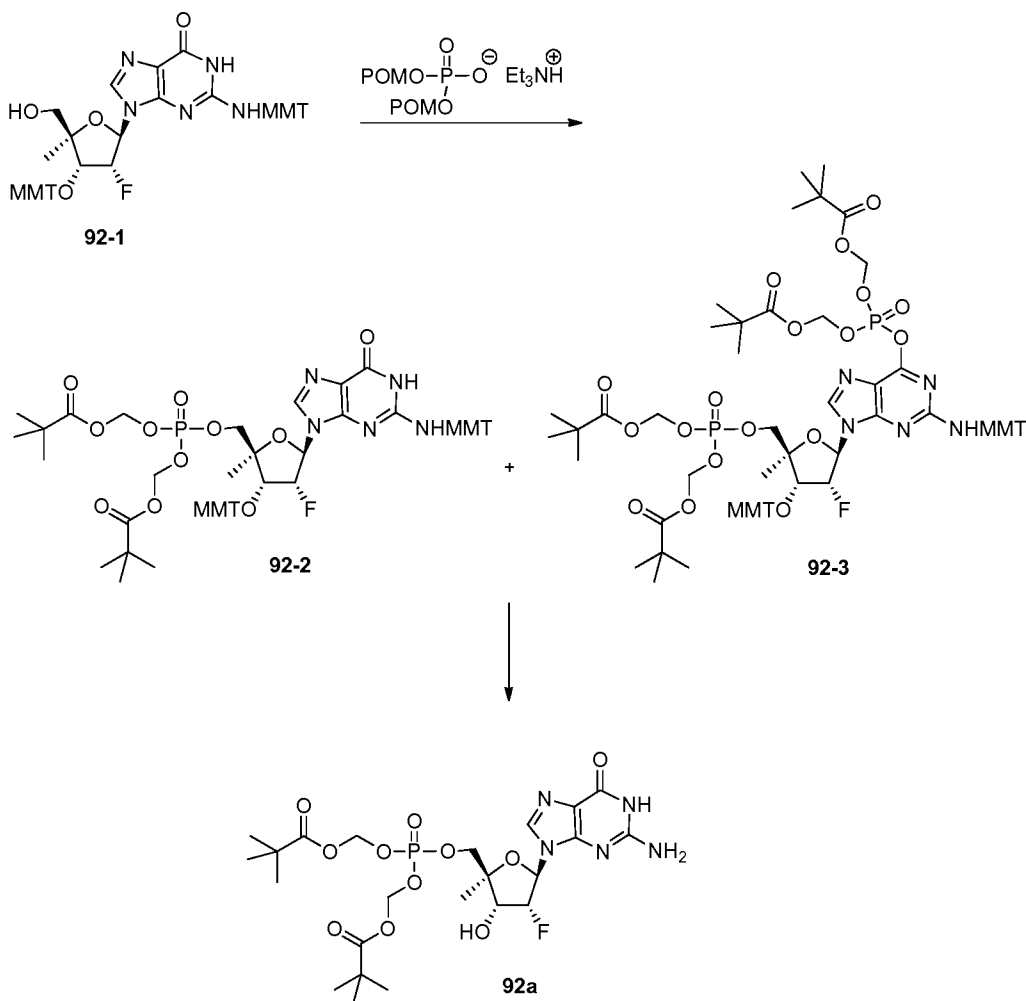
EXAMPLE 87
Preparation of Compound (91a)



[0552] Preparation of (91-2): To a solution of triethylammonium bis(isopropoxycarbonyloxymethyl)phosphate (0.33mmol, prepared from 110 mg of bis(POC)phosphate and 0.1 mL of Et₃N) in THF (2 mL) was added **86-1** (100 mg; 0.11 mmol), followed by diisopropylethyl amine (0.19 mL; 10 equiv), BOP-Cl (140 mg; 5 equiv) and 3-nitro-1,2,4-triazole (63 mg; 5 equiv). The mixture was stirred at R.T. for 90 mins., and then diluted with CH₂Cl₂ (30 mL). The mixture was washed with saturated aqueous NaHCO₃ and brine. The mixture was dried with Na₂SO₄. The solvent was evaporated, and the residue was purified on a silica column (10 g column) with hexanes/EtOAc (40-100% gradient) to give **91-2** (117 mg, 90%).

[0553] Preparation of (91a): **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 CH₂Cl₂ /MeOH (4-15% gradient) to give **91a** (36 mg, 85%). ¹H-NMR (CD₃CN): δ 7.67 (dd, 1 H), 6.35 (dd, 1 H), 6.1 (br, 2 H), 5.82 (d, 1 H), 5.62 (m, 4 H), 5.22 (dm, 1 H), 4.98 (br, 1H), 4.89 (m, 2 H), 4.49 (d, 1 H), 4.34 (m, 2 H), 3.88 (dd, 2H), 1.29 (d, 6 H), 1.28 (d, 6 H); ³¹P-NMR (CD₃CN): δ -4.49. MS: m/z = 606 [M+1].

EXAMPLE 88
Preparation of Compound (92a)

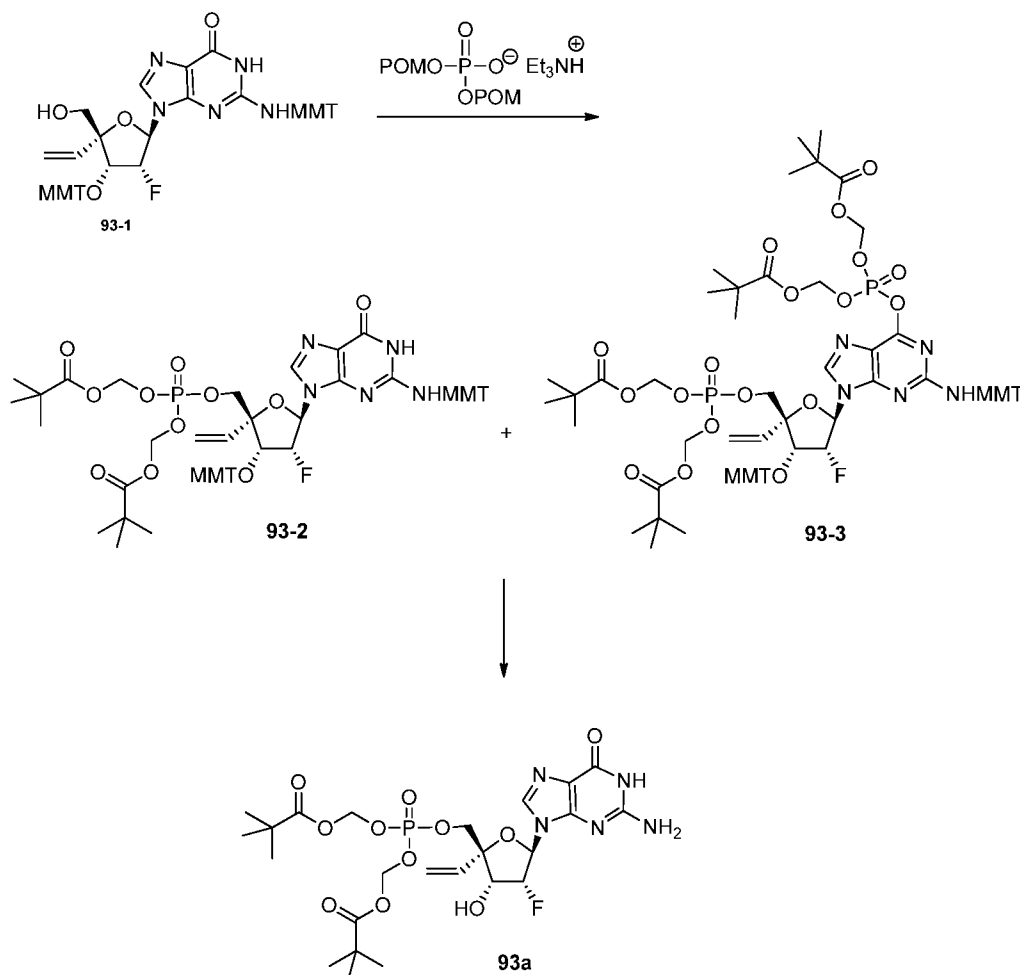


[0554] Preparation of (92-2) and (92-3): To a solution of triethylammonium bis(POM)phosphate (0.48 mmol, prepared from 176 mg of bis(POM)phosphate and 0.15 mL of Et₃N) in THF (2 mL) was added **92-1** (150 mg; 0.18 mmol) followed by diisopropylethyl amine (0.31 mL; 10 equiv), BOP-Cl (229 mg; 5 equiv), 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 CH₂Cl₂ (30 mL). The mixture was washed with saturated aqueous NaHCO₃ and brine. The mixture was dried with Na₂SO₄. The solvent was evaporated, and the residue was purified on a silica column (10 g column) with CH₂Cl₂ /i-PrOH (2-10% gradient) to obtain **92-2** (44 mg, 21%) and **92-3** (73 mg, 28%).

[0555] Preparation of (92a): 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 CH₂Cl₂ /MeOH (4-10% gradient) to obtain **92a** (40 mg, 75%).
¹H-NMR (DMSO-D₆): δ 10.6 (br, 1 H), 7.76 (s, 1 H), 6.44 (br, 2 H), 5.99 (dd, 1 H), 5.83 (d, 1

H), 5.53-5.27 (2 m, 6 H), 4.39 (dt, 1 H), 4.04 (m, 2 H), 1.17 (s, 3 H), 1.06, 1.08 (2 s, 18 H). ^{31}P -NMR (DMSO- d_6): δ -4.09. MS: m/z = 608 [M+1].

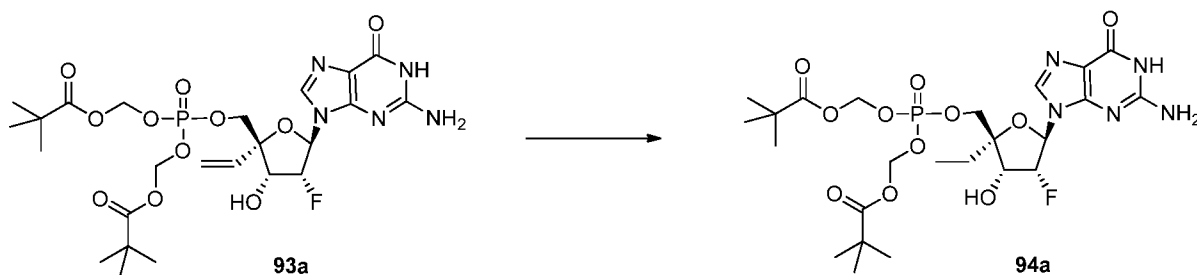
EXAMPLE 89
Preparation of Compound (93a)



[0556] Preparation of (93-2) and (93-3): 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.

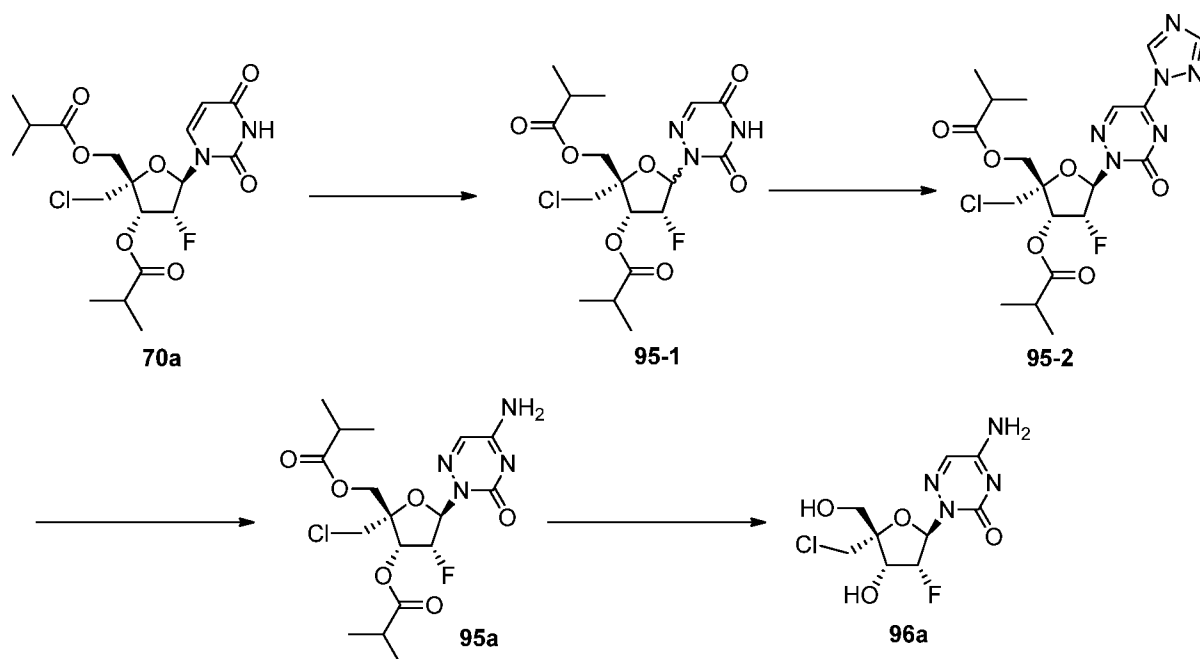
[0557] Preparation of (93a): 93-2 and 93-3 (68 mg and 80 mg, respectively) were converted into 93 (42 mg) with formic acid in the same manner as 92 from 92-2 and 92-3. ^1H -NMR (DMSO- D_6): δ 7.73 (s, 1 H), 6.46 (br, 2 H), 6.04 (dd, 1 H), 5.91 (dd, 1 H), 5.87 (d, 1 H), 5.48 (d, 4 H), 5.33 (m, 1 H), 5.24 (ddd, 1 H), 4.60 (dt, 1 H), 4.07 (m, 2 H), 1.07, 1.06, 1.05 (4 s, 18 H). ^{31}P -NMR (DMSO- d_6): δ -4.37. MS: m/z = 620 [M+1].

EXAMPLE 90
Preparation of Compound (94a)



[0558] 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 CH₂Cl₂ /MeOH (4-11% gradient) yielded **94a** (45 mg, 81%). ¹H-NMR (DMSO-D₆): δ 10.6 (br, 1 H), 7.81 (s, 1 H), 6.4 (br, 2 H), 5.97 (dd, 1 H), 5.85 (d, 1 H), 5.60-5.44 (m, 5 H), 4.37 (m, 1 H), 4.11 (ddd, 2 H), 1.66 (m, 2 H), 1.09, 1.06 (2 s, 18 H), 0.81 (7, 3 H); ³¹P-NMR (DMSO-d₆): δ -4.10. MS: m/z = 622 [M+1].

EXAMPLE 91
Preparation of Compounds (95a) and (96a)



[0559] Preparation of (95-1): 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 (NH₄)₄SO₄. 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 CH₃CN 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

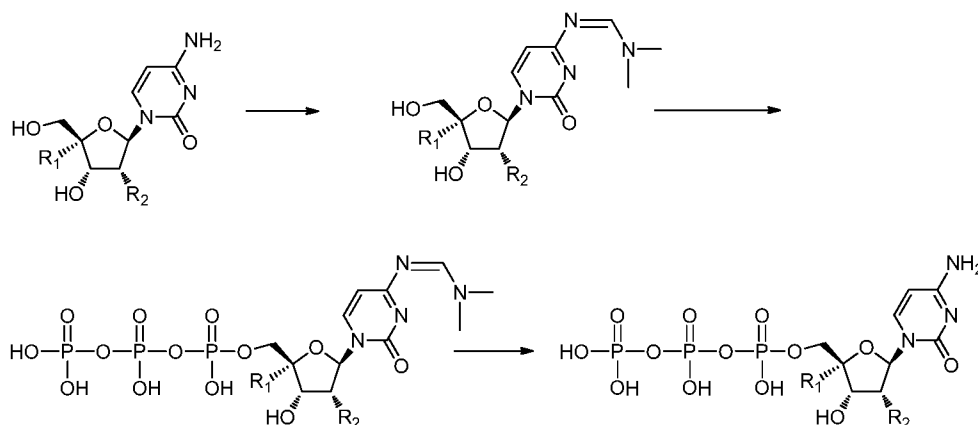
quenched with NaHCO_3 and diluted with EA. The organic solvent was removed, and the residue was purified by prep-TLC first, and the by RP-HPLC (0.5% HCOOH in water and MeCN) to give the pure **95-1** (100 mg, 46%).

[0560] Preparation of (95-2): 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%).

[0561] Preparation of (95a): **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%).

[0562] Preparation of (96a): **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. ^1H NMR (CD_3OD , 400 MHz) δ 7.57 (s, 1H), 6.35 (dd, $J = 3.6$ Hz, $J = 15.6$ Hz, 1H), 5.45-5.47 (m, 1H), 4.70 (dd, $J = 4.8$ Hz, $J = 16.2$ Hz, 1H), 3.83 (s, 2H), 3.71 (d, $J = 1.6$ Hz, 2H). ESI-TOF-MS: m/z 295.1 $[\text{M} + \text{H}]^+$.

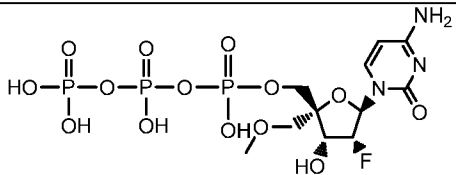
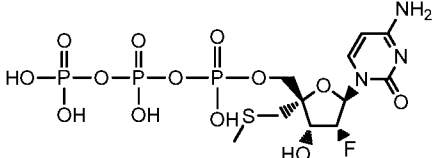
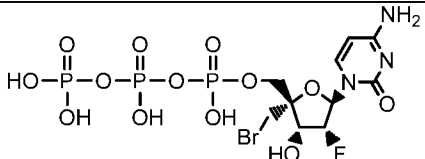
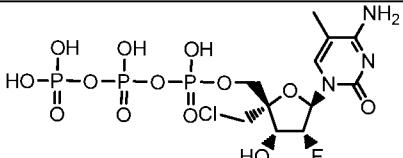
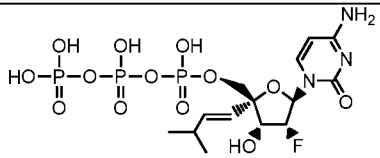
EXAMPLE 92 **Preparation of Compounds (97a-g)**

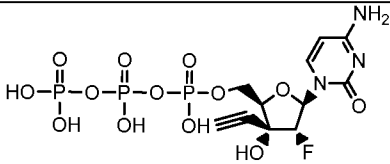
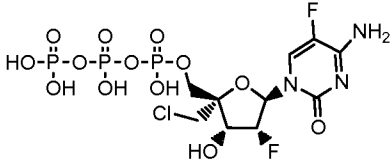


[0563] Dry nucleoside (0.05 mmol) was dissolved in a mixture of DMF (3 mL) and DMA-DMF (0.04 mL, 0.1 mmol). The reaction was kept at ambient temperature for 4 h and then evaporated to dryness. The residue was dissolved in a mixture of $\text{PO}(\text{OMe})_3$ (0.7 mL) and pyridine (0.3 mL). The mixture 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 (9 μL , 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 (Phenomenex). A linear gradient of methanol from 0 to 30% in 50mM triethylammonium acetate buffer (pH 7.5) was used for elution. The corresponding fractions were combined, concentrated and lyophilized 3 times to remove excess of buffer.

Table 4 – Triphosphates obtained from Example 92

Compound	MS (M-1)	³¹ P NMR P α	³¹ P NMR P β	³¹ P NMR 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)
 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)

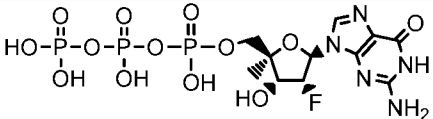
Compound	MS (M-1)	³¹ P NMR P α	³¹ P NMR P β	³¹ P NMR P γ
 97f	508.4	-8.30 (bs)	-22.72(bs)	-11.51 -11.63(d)
 97g	550.1	-9.17 -9.29 (d)	-23.04 (t)	-11.97 -12.09(d)

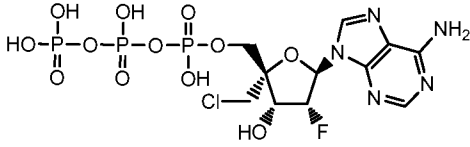
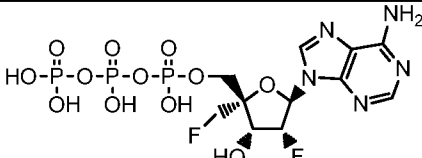
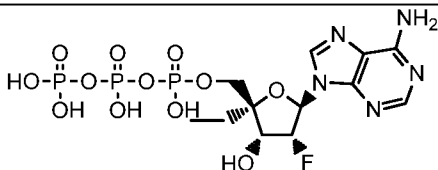
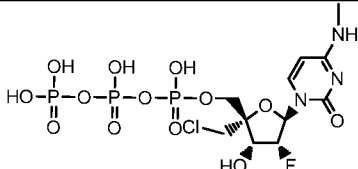
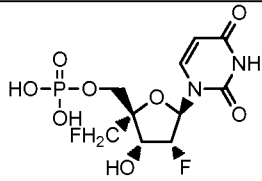
EXAMPLE 93

Preparation of Compounds (98a-e) and (99a)

[0564] 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 42⁰C, than cooled down to R.T. N-Methylimidazole (0.009 mL, 0.11 mmol) was added followed by POCl₃ (9 μ l, 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-e**) was eluted at 75-80%B. The corresponding fractions were concentrated. Desalting was achieved by RP HPLC on Synergy 4 micron Hydro-RP column (Phenomenex). A linear gradient of methanol from 0 to 30% in 50mM triethylammonium acetate buffer (pH 7.5) was used for elution. The corresponding fractions were combined, concentrated and lyophilized 3 times to remove excess of buffer.

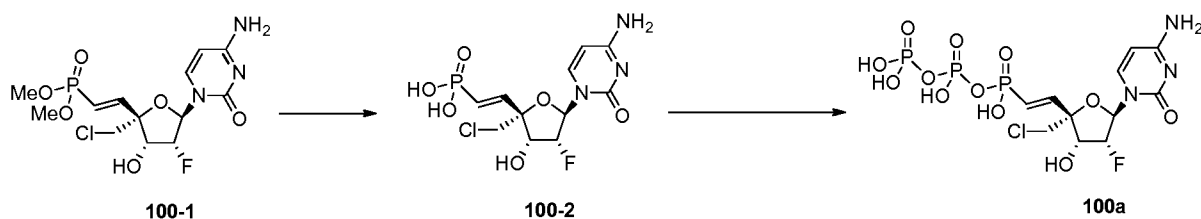
Table 5 – Compounds obtained from Example 93

Compound	MS (M-1)	³¹ P NMR P α	³¹ P NMR P β	³¹ P NMR P γ
 98a	538.0	-5.21 -5.33(d)	-20.56(t)	-11.09 -11.20(t)

Compound	MS (M-1)	³¹ P NMR P α	³¹ P NMR P β	³¹ P NMR P γ
 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

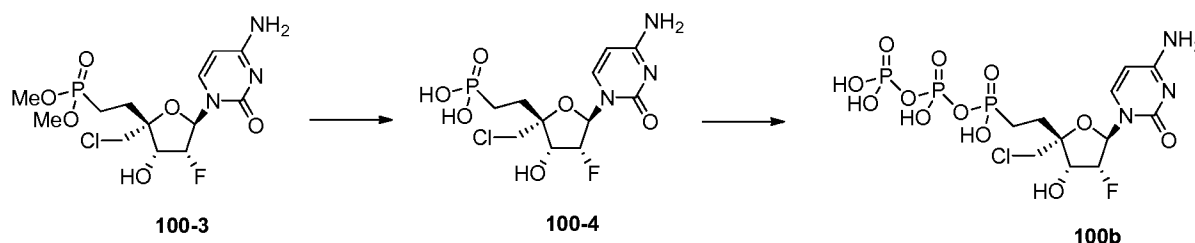
Preparation of Compound (100a)



[0565] Preparation of (100-2): To an ice-cold solution of **100-1** (22 mg; 0.055 mmol) in acetonitrile (0.5 mL) was added TMSBr (80 μ L; 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 Et₂O, neutralized with triethylammonium bicarbonate buffer and lyophilized to yield the triethylammonium salt of **100-2**.

[0566] Preparation of (100a): **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).

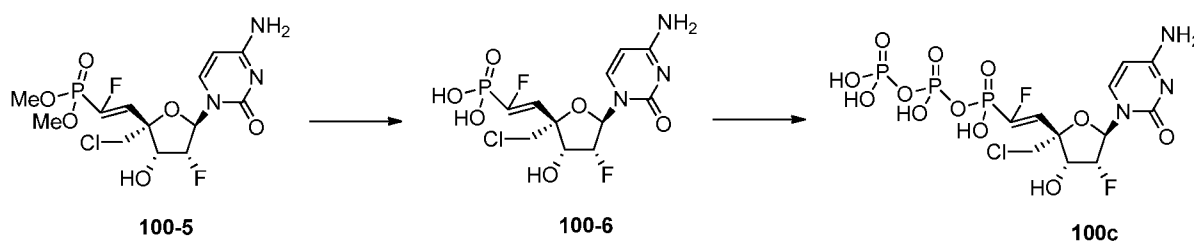
EXAMPLE 95
Preparation of Compound (100b)



[0567] Preparation of (100-4): **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**.

[0568] Preparation of (100b): **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).

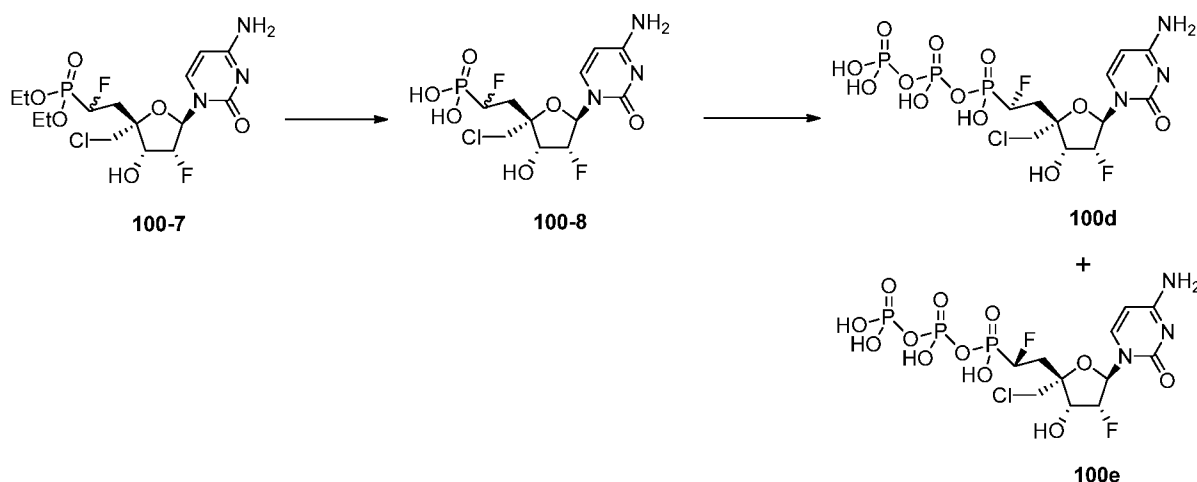
EXAMPLE 96
Preparation of Compound (100c)



[0569] Preparation of (100-6): **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**.

[0570] Preparation of (100c): **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).

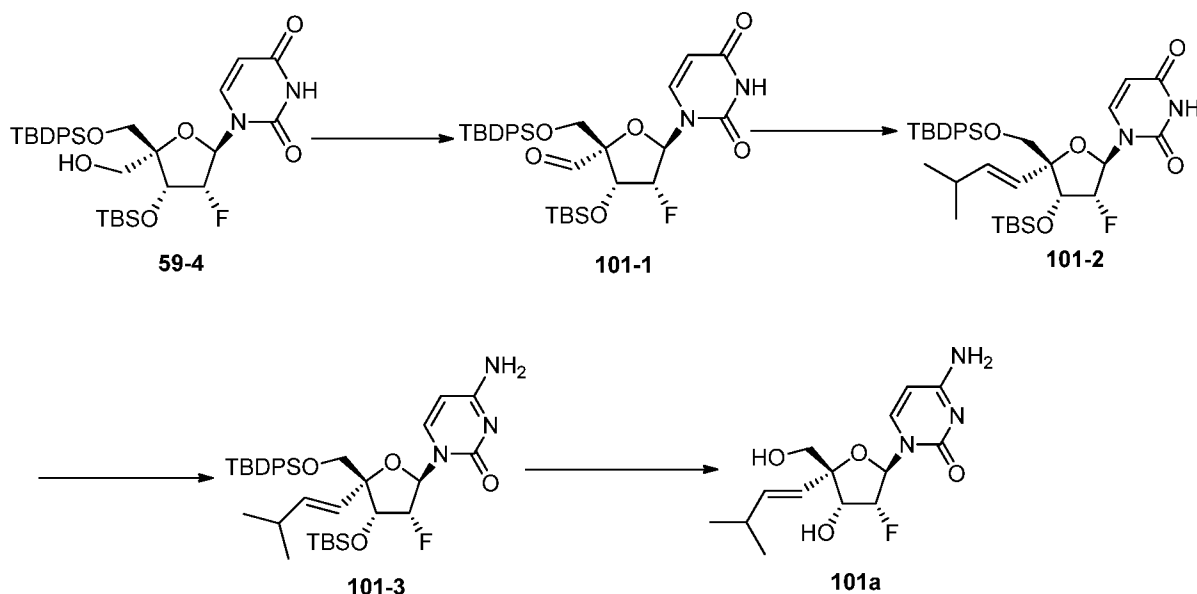
EXAMPLE 97
Preparation of Compounds (100d) and (100e)



[0571] Preparation of (100-8): 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**.

[0572] Preparation of (100d) and (100e): **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)



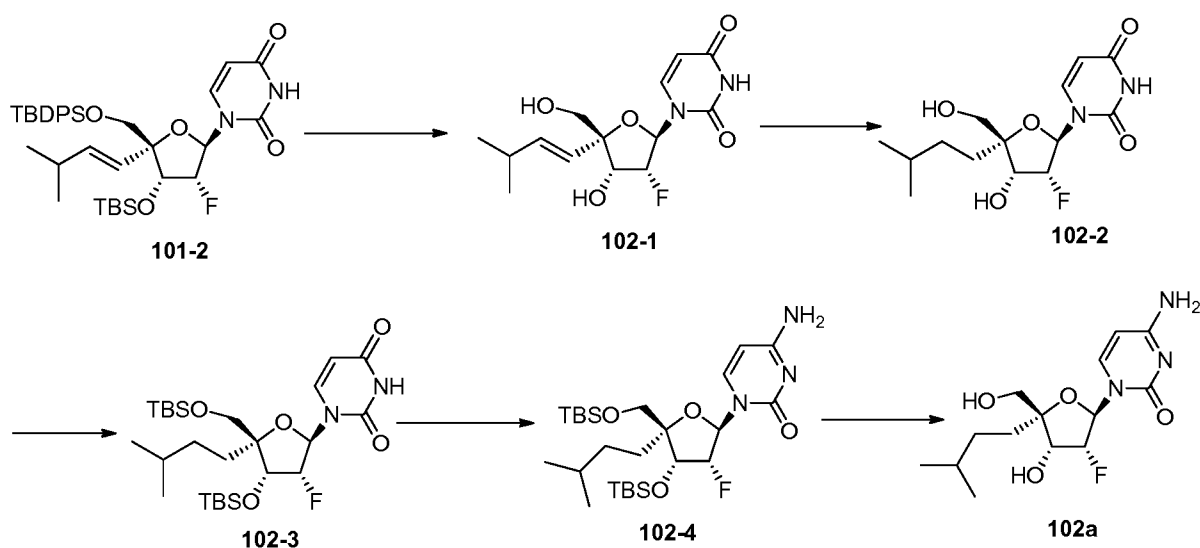
[0573] Preparation of (101-1): To a solution of **59-4** (1.5 g, 2.39 mmol) in anhydrous DCM (100 mL) was added Dess-Martin periodinane (5.2 g, 11.95 mmol) at 0°C under nitrogen. The mixture was stirred at R.T. for 5 h. The mixture was poured into NaHCO₃ and Na₂S₂O₃ aq. Solution. The organic layer was washed with brine, dried over with anhydrous Na₂SO₄, 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.

[0574] Preparation of (101-2): 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 NH₄Cl 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.

[0575] Preparation of (101-3): To a solution of **101-2** (364 mg, 0.547 mmol) in anhydrous CH₃CN (6 mL) were added TPSCl (414 mg, 1.37 mmol), DMAP (167 mg, 1.37 mmol) and NEt₃ (138 mg, 1.37 mmol) at R.T. The mixture was stirred at R.T. for 2 h. NH₄OH (6 mL) was added, and the mixture was stirred for another 1 h. The mixture was diluted with DCM and washed with a NaHCO₃ 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.

[0576] Preparation of (101a): To a solution of **27-3** (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. ^1H NMR (CD_3OD , 400MHz) δ 8.11 (d, $J = 7.6$ Hz, 1H), 6.03 (dd, $J = 1.2, 17.6$ Hz, 1H), 5.88 (d, $J = 7.2$ Hz, 1H), 6.03 (dd, $J = 1.6, 11.6$ Hz, 1H), 5.39 (d, $J = 10.8$ Hz, 1H), 4.88 (dd, $J = 3.2, 60.0$ Hz, 1H), 4.41 (dd, $J = 4.8, 24.4$ Hz, 1H), 3.70 (d, $J = 12.4$ Hz, 1H), 3.57 (d, $J = 12.0$ Hz, 1H), 3.08-3.14 (m, 1H), 0.94-0.98 (m, 6H). ESI-MS: m/z 626.9 $[2\text{M} + \text{H}]^+$.

EXAMPLE 99
Preparation of Compound (102a)



[0577] Preparation of (102-1): 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.

[0578] Preparation of (102-2): 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.

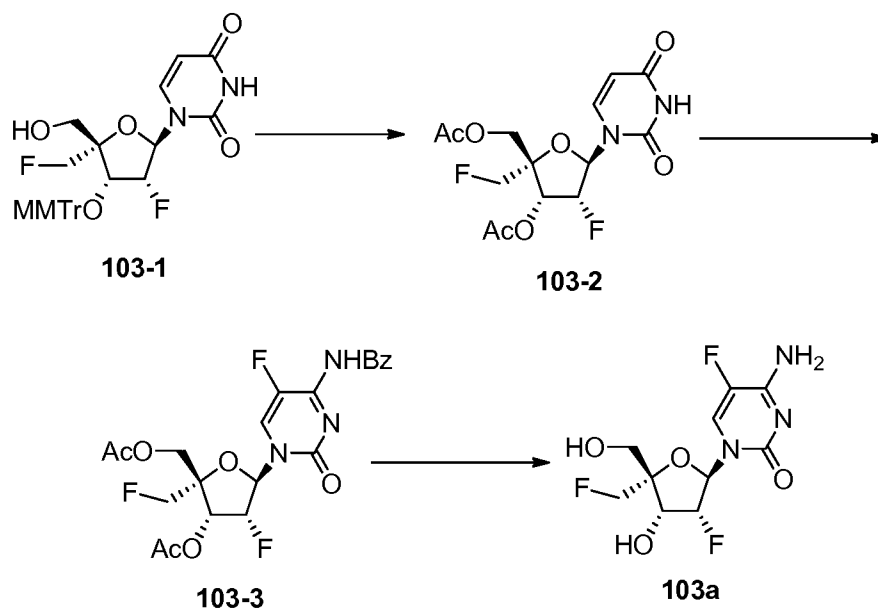
[0579] Preparation of (102-3): To a solution of **102-2** (400 mg, 1.26 mmol) in anhydrous DMF (5 mL) were added imidazole (968 mg, 14.2 mmol), and TBSCl (1.5 g, 10.0 mmol) at R.T. The mixture was stirred at 50°C overnight. The mixture was diluted with DCM and washed with a NaHCO_3 aq. solution. The 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.

[0580] Preparation of (102-4): To a solution of **102-3** (676 mg, 1.24 mmol) in anhydrous CH₃CN (6 mL) were added TPSCl (941 mg, 13.11 mmol), DMAP (379 mg, 3.11 mmol) and NEt₃ (314 mg, 3.11 mmol) at R.T. The reaction was stirred at R.T. for 3 h. NH₄OH (1 mL) was added, and the reaction was stirred for 4 h. The mixture was diluted with DCM and washed with a NaHCO₃ 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.

[0581] Preparation of (102a): To a solution of **102-4** (450 mg, 0.83 mmol) in MeOH (10 mL) was added NH₄F (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. ¹H NMR (CD₃OD, 400MHz) δ 8.09 (d, *J* = 7.6 Hz, 1H), 6.07 (d, *J* = 3.6 Hz, 1H), 6.05 (d, *J* = 2.8 Hz, 1H), 5.89 (d, *J* = 7.6 Hz, 1H), 5.03 (dd, *J* = 5.2, 57.2 Hz, 1H), 4.41 (dd, *J* = 4.2, 17.2 Hz, 1H), 3.74 (d, *J* = 12.0 Hz, 1H), 3.54 (d, *J* = 12.0 Hz, 1H), 1.23-1.78 (m, 5H), 0.90 (d, *J* = 6.4 Hz, 6H). ESI-MS: *m/z* 631.1 [2M + H]⁺.

EXAMPLE 100 **Preparation of Compound (103a)**



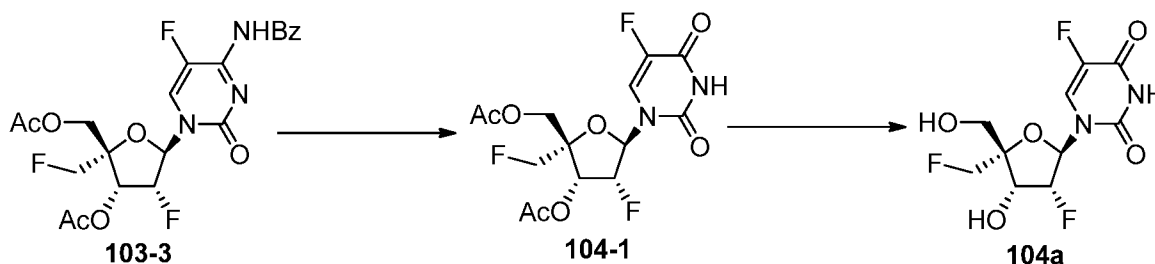
[0582] Preparation of (103-2): **103-1** (3.8 g, 6.9 mmol) in 80% AcOH aq. was stirred at 50°C for 4 h. The mixture was concentrated to give a residue, which was purified by silica gel column chromatography (5% MeOH in DCM) to give the uridine derivative (1.5 g,

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 Ac₂O (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.

[0583] Preparation of (103-3): 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 NaHCO₃. The organic layer was dried over Na₂SO₄, 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.

[0584] Preparation of (103a): A solution of **103-3** (150 mg, 0.34 mmol) in NH₃/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. ¹H NMR (CD₃OD, 400MHz) δ 8.28 (d, *J* = 6.8 Hz, 1H), 6.10 (dd, *J* = 2.0, 15.2 Hz, 1H), 4.99-5.15 (m, 1H), 4.62-4.65 (m, 1H), 4.49-4.55 (m, 2H), 3.89 (dd, *J* = 1.6, 12.0 Hz, 1H), 3.75 (dd, *J* = 1.2, 12.0 Hz, 1H). ESI-MS: *m/z* 613.1 [2M + Na]⁺.

EXAMPLE 101 **Preparation of Compound (104a)**

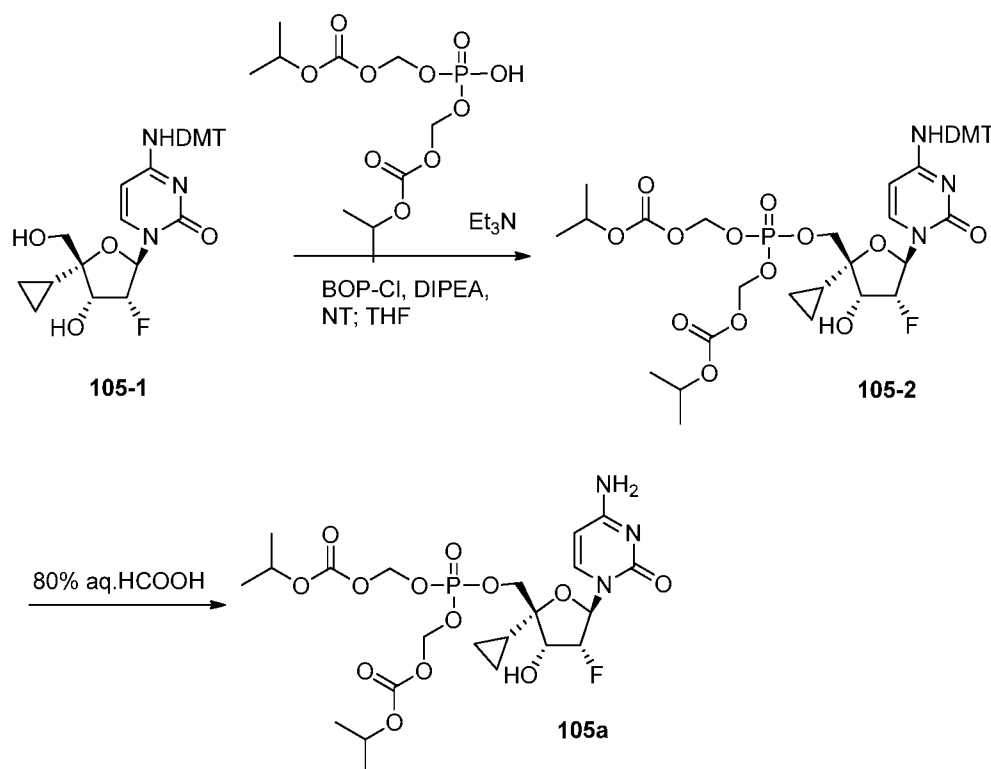


[0585] Preparation of (104-1): **103-3** (150 mg, 0.31 mmol) was dissolved in 80% aqueous acetic acid (3 mL). The solution was heated to reflux for 2 h. The mixture was cooled to ambient temperature and diluted with water (5 mL), neutralized to pH > 7 with saturated NaHCO₃ and extracted with EA. The 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.

[0586] Preparation of (104a): **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. ^1H NMR (CD_3OD , 400MHz) δ 8.30 (d, $J = 6.8$ Hz, 1H), 6.18 (dd, $J = 4.0, 14.0$ Hz, 1H), 5.13-5.65 (m, 1H), 4.52-4.56 (m, 1H), 3.980-3.95 (m, 2H), 3.76 (s, 3H). ESI-MS: m/z 319.1 $[\text{M} + \text{Na}]^+$.

EXAMPLE 102

Preparation of Compound (105a)

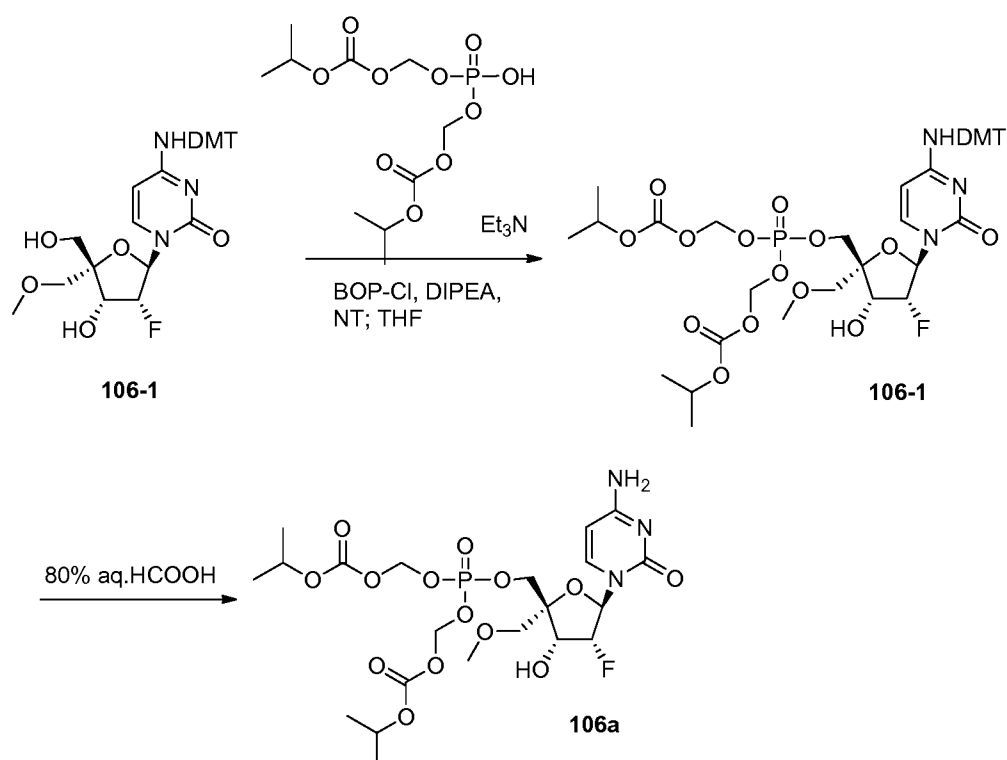


[0587] Preparation of (105-2): To a solution of triethylammonium bis(isopropoxycarbonyloxymethyl)phosphate (0.065 mmol, prepared from 22 mg of bis(POC)phosphate and Et_3N) in THF was added **105-1** (31 mg; 0.05 mmol). The resulting mixture evaporated, and the residue was rendered anhydrous by coevaporation 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%).

[0588] Preparation of (105a): 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 CH₂Cl₂/MeOH solvent system (4-15% gradient) to give **105a** (7 mg, 78%). ¹H-NMR (DMSO-d₆): δ 7.52 (d, 1 H), 7.28, 7.24 (2 br s, 2 H) 5.92 (dd, 1 H), 5.74 (d, 1 H), 5.69 (d, 1 H), 5.62 (d, 4 H), 4.97 (ddd, 1 H), 4.82 (m, 2 H), 4.38 (dt, 1 H), 4.07 (m, 2 H), 1.23 (m, 12 H), 1.04 (m, 1H), 0.37 (m, 4 H). ³¹P-NMR (DMSO-d₆): δ -4.51. ¹⁹F-NMR (DMSO-d₆): δ -199.23 (dt). MS: m/z = 598.4 (M+1).

EXAMPLE 103

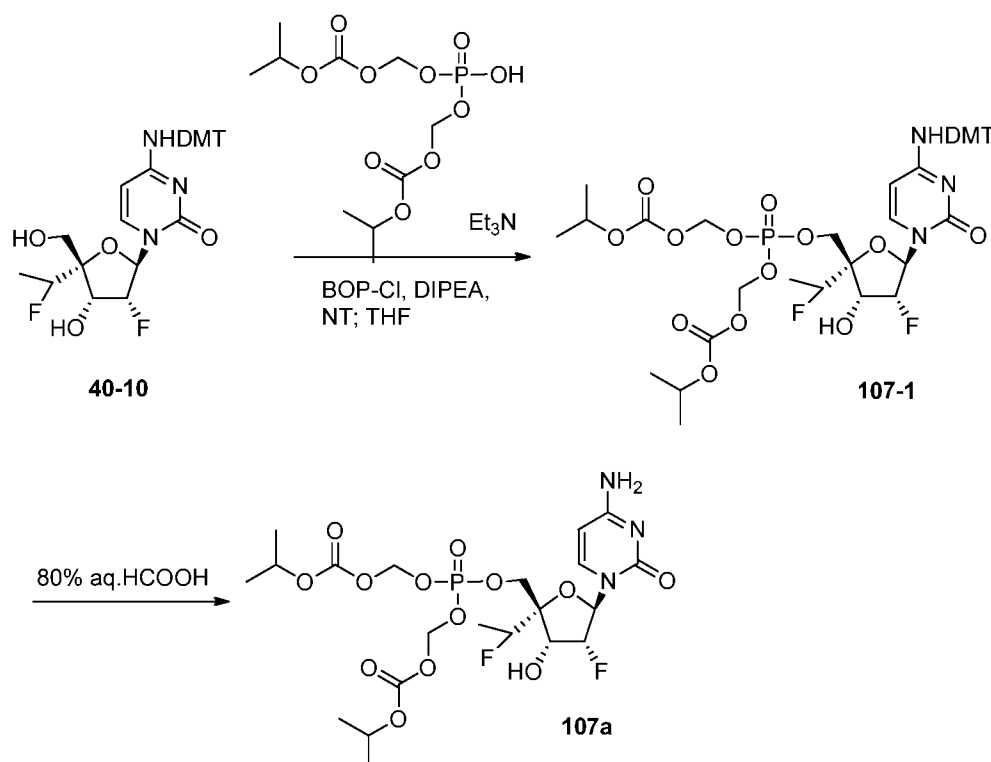
Preparation of Compound (106a)



[0589] Preparation of (106-1): **106-1** (15 mg; 30% yield) was prepared in the same manner from **43-5** (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**.

[0590] Preparation of (106a): **106-1** (15 mg) was converted in formic acid to **106a** (8 mg; 78% yield) in the same manner as **105-2** to **105a**. ¹H-NMR (DMSO-d₆): δ 7.55 (d, 1 H), 7.32, 7.27 (2 br s, 2 H) 6.06 (dd, 1 H), 5.84 (d, 1 H), 5.73 (d, 1 H), 5.61 (d, 4 H), 5.08 (ddd, 1 H), 4.83 (m, 2 H), 4.36 (m, 1 H), 4.21 (dd, H), 4.16 (dd, 1 H), 3.56 (d, 1 H), 3.49 (d, 1 H), 3.28 (s, 3 H), 1.25, 1.24 (2 d, 12 H). ³¹P-NMR (DMSO-d₆): δ -4.45. MS: m/z = 602.4 (M+1).

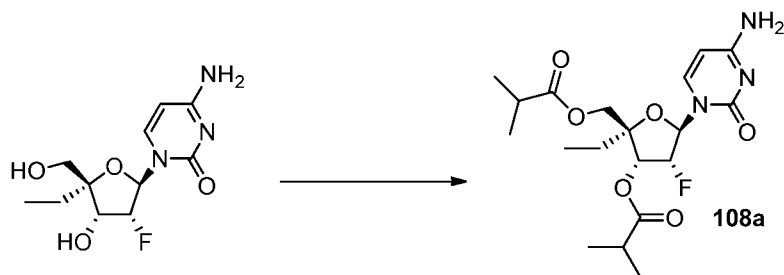
EXAMPLE 104
Preparation of Compound (107a)



[0591] **Preparation of (107-1):** 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 μ L), BopCl (58 mg) and 3-nitro-1,2,4-triazole (26 mg) as 105-2 from 105-1.

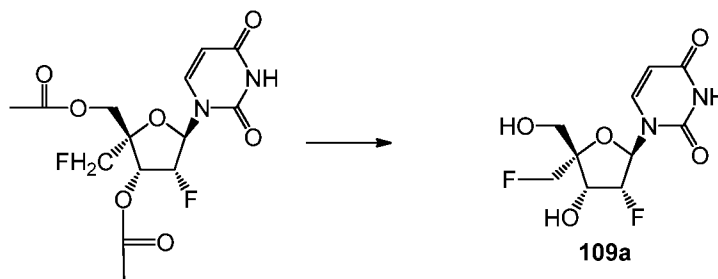
[0592] **Preparation of (106a):** 107-1 (30 mg) was converted in formic acid to 107a (15 mg; 73% yield) in the same manner as 105-2 to 105a. $^1\text{H-NMR}$ (DMSO- d_6): δ 7.60 (d, 1 H), 7.36, 7.32 (2 br s, 2 H) 6.02 (m, 2 H), 5.74 (d, 1 H), 5.62 (m, 4 H), 5.17 (ddd, 1 H), 4.99 (dq, 1 H), 4.83 (m, 2 H), 4.61 (m, 1 H), 4.19 (m, 2 H), 1.40 (dd, 3 H), 1.24, 1.23 (2 d, 12 H). $^{31}\text{P-NMR}$ (DMSO- d_6): δ -4.52. $^{19}\text{F-NMR}$ (DMSO- d_6): δ -185.92 (m, 1 F), -200.48 (d, 1 F). MS: m/z = 604.3 (M+1).

EXAMPLE 105
Preparation of Compound (108a)



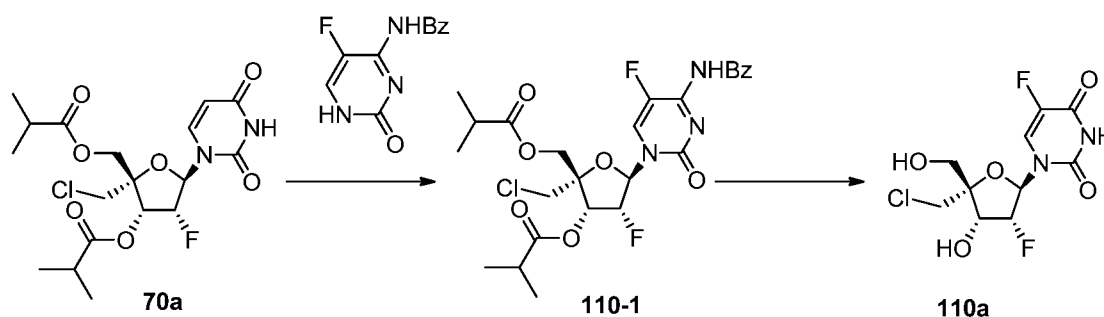
[0593] To a solution of 4'-ethyl-2'-fluorocytidine (50 mg, 0.183 mmol) in DMF (1 mL) were added DCC (113 mg, 0.55 mmol), isobutyric acid (48.5 μ L, 0.55 mmol) and DMAP (22 mg, 0.183 mmol). The mixture was stirred at R.T. overnight. The mixture was filtered, and the filtrate was concentrated with a rotary 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. ^1H NMR ($\text{DMSO-}d_6$, 400 MHz) δ 7.67 (d, J = 7.2 Hz, 1H), 7.34 (br s, 2H), 5.85, 5.8 (2d, J = 21.2, 22 Hz, 1H), 5.72 (d, J = 7.6 Hz, 1H), 5.55-5.41 (m, 2H), 4.1 (q, 2H), 2.68-2.52 (m, 2H), 1.77-1.64 (m, 2H), 1.13, 1.14 (2s, 2 x 3H), 1.09-1.07 (m, 6H), 0.96 (t, J = 7.6 Hz, 3H); MS m/z 414 (M-H^+), 829 ($2\text{M}+\text{H}^+$).

EXAMPLE 106
Preparation of Compound (109a)



[0594] 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%). ^1H -NMR ($\text{DMSO-}d_6$): δ 11.4 (s, 1H), 11.84-11.82 (d, 1H); 6.10-6.05 (m, 1H), 5.95-5.83 (d, 1H), 5.71 (s, 1H), 5.65-5.63 (d, 1H), 5.37-3.36 (t, 1H), 5.26-5.20 (t, 1H), 5.11-5.07 (t, 1H), 4.56-4.55 (m, 1H), 4.46-4.33 (m, 2H), 3.58-3.56 (m, 2H). MS 277.2 (M-H).

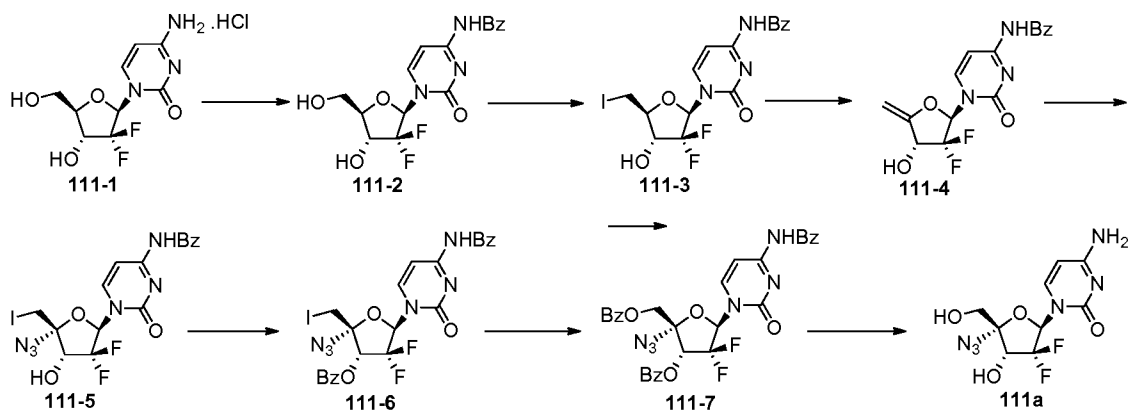
EXAMPLE 107
Preparation of Compound (110a)



[0595] Preparation of (110-1): 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 NaHCO₃ 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.

[0596] Preparation of (110a): **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 NaHCO₃ 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 NH₃/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. ¹H NMR (CD₃OD, 400MHz) δ 8.31 (d, J = 6.8 Hz, 1H), 6.17 (dd, J = 4.0, 14.0 Hz, 1H), 5.13-5.27 (m, 1H), 4.52-4.56 (m, 1H), 3.92 (dd, J = 12.0, 58.8 Hz, 2H). ESI-TOF-MS: m/z 334.7 [M + Na]⁺.

EXAMPLE 108
Preparation of Compound (111a)



[0597] Preparation of (111-2): Compound **111-1** (30.0 g, 0.1 mol) was suspended in anhydrous pyridine (300 mL) and stirred at room temperature (R.T.) for 1 hour. The suspension was cooled to 0°C and TMSCl (27.3 g, 0.25 mmol) was added dropwise. After addition was complete, the mixture was warmed to R.T. and stirred for 30 min. The mixture was then re-cooled to 0°C and BzCl (15.5 g, 0.11 mol) was added dropwise. The mixture was warmed to R.T. and stirred overnight. The reaction was cooled to 0°C and quenched with H₂O. Aqueous ammonia was added, and the reaction was stirred at R.T. for 2 hours. The solution was concentrated and the residue was taken up into ethyl acetate (EA) and H₂O. The aqueous phase was extracted with EA several times, and the combined organic layers were dried over Na₂SO₄ and concentrated. The residue was purified on a silica gel column to give compound **111-2** as a white solid (28.2 g, 76%). ESI-LCMS: m/z=368 [M+Na]⁺.

[0598] Preparation of (111-3): To a stirred suspension of compound **111-2** (18.4 g, 50 mmol), PPh₃ (22.3 g, 85 mmol) and pyridine (25 mL) in anhydrous THF (300 mL) was added a solution of I₂ (19.05 g, 75 mmol) in THF (80 mL) dropwise at 0°C. After addition, the mixture was warmed to R.T. and stirred for 60 hours. The precipitate was removed by filtration, and the filtrate was concentrated. The residue was dissolved in dichloromethane (DCM) and washed with saturated Na₂S₂O₃ aqueous solution and then brine. The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified on a silica gel column to afford compound **111-3** (16.4 g, 69%). ESI-LCMS: m/z=478 [M+H]⁺.

[0599] Preparation of (111-4): To a stirred solution of compound **111-3** (17.0 g, 35.6 mmol) in anhydrous dimethylformamide (DMF) (300 mL) was added dropwise a solution of t-BuOK (10.0 g, 89.1 mmol) in DMF (120 mL) at 0°C over 20 min. Stirring was continued at 0°C for 45 min, and then concentrated hydrochloric acid (4.5 mL) was added. A pH value of 8-9 was achieved by adding a saturated NaHCO₃ solution. The precipitate was removed by

filtration, and the filtrate was diluted with ethyl acetate. 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 to afford compound **111-4** as a white solid (8.6 g, 69%). ESI-LCMS: $m/z=350$ $[\text{M}+\text{H}]^+$.

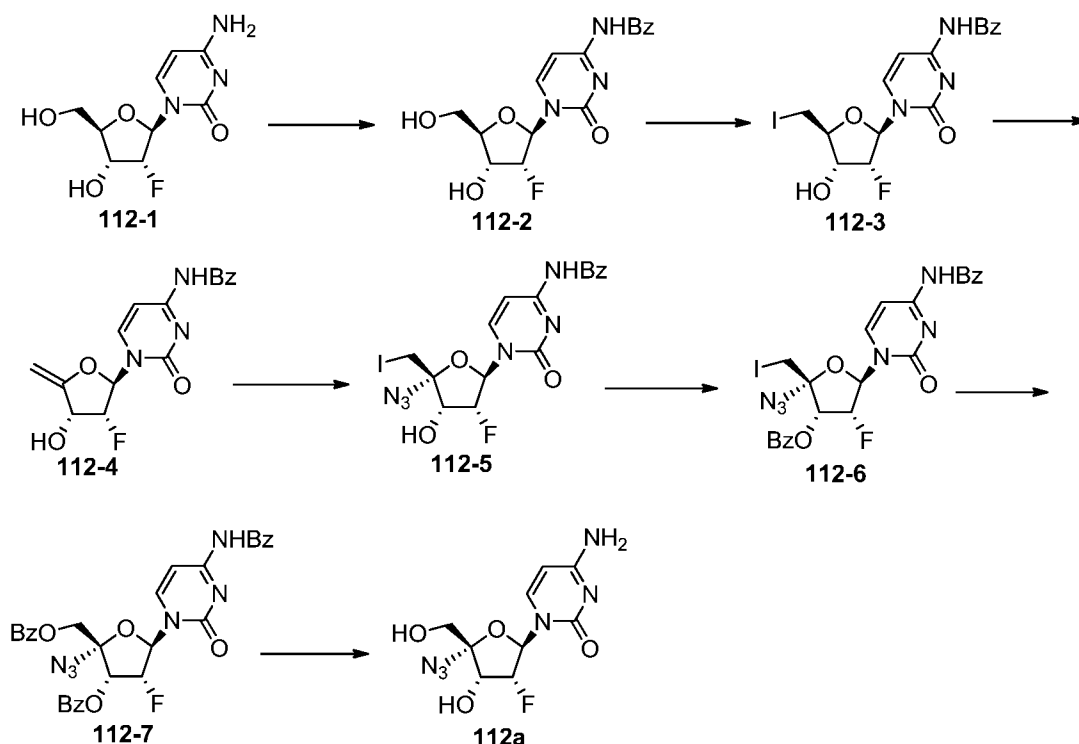
[0600] Preparation of (111-5): To a stirred solution of Bn Et_3NCl (37.4 g, 0.16 mol) in MeCN (600 mL) was added NaN_3 (10.8 g, 0.16 mol). The mixture was sonicated for 20 min, and then stirred at R.T. for 16 hours. The solution was filtrated into a solution of compound **111-4** (11.5 g, 32.9 mmol) and N-methylmorpholine (3.5 g) in anhydrous THF (200 mL). The mixture was cooled to 0°C and a solution of I_2 (33.6 g, 0.14 mol) in THF (100 mL) was added dropwise. Stirring was continued at $0-10^\circ\text{C}$ for 20 hours. N-Acetyl cystein was added until no gas evolved. Saturated $\text{Na}_2\text{S}_2\text{O}_3$ aq. was added until a light yellow solution was achieved. The solution was concentrated and then diluted with EA. The organic phase was washed with brine and dried over Na_2SO_4 . The solvent was removed, and the residue was purified on a silica gel column to give compound **111-5** (14.7 g, 84%). ESI-LCMS: $m/z=519$ $[\text{M}+\text{H}]^+$.

[0601] Preparation of (111-6): To a stirred solution of compound **111-5** (12.5 g, 24.8 mmol) in anhydrous pyridine (200 mL) was added BzCl (4.3 g, 30 mmol) dropwise at 0°C . The mixture was then 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 to give compound **111-6** as a white foam (11.2 g). ESI-LCMS: $m/z=623$ $[\text{M}+\text{H}]^+$.

[0602] Preparation of (111-7): Compound **111-6** (9.43 g, 15.2 mmol), BzONa (21.9 g, 152 mmol) and 15-crown-5 (33.4 g, 152 mmol) were suspended in 200 mL DMF. The mixture was stirred at $60-70^\circ\text{C}$ 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 to afford compound **111-7** as a white foam (4.4 g, 46%). ESI-LCMS: $m/z=617$ $[\text{M}+\text{H}]^+$.

[0603] Preparation of (111a): Compound **111-7** (4.4 g, 7.13 mmol) was dissolved in 100 mL of saturated methanolic ammonia, and the resulting solution was stirred at R.T. for 14 hours. The solvent was removed, and the residue was purified on a silica gel column (DCM/MeOH = 30:1 to 10:1) to give **111a** as a white solid (1.9 g, 88%). ^1H NMR (CD_3OD , 400 MHz) δ 7.70 (d, $J = 7.6$ Hz, 1H), 6.40 (t, $J = 7.2$ Hz, 1H), 5.93 (d, $J = 7.6$ Hz, 1H), 4.50 (t, $J = 13.2$ Hz, 1H), 3.88 (dd, $J_1 = 12.0$ Hz, $J_2 = 26.8$ Hz, 2H); ESI-MS: $m/z=305$ $[\text{M}+\text{H}]^+$, 609 $[\text{2M}+\text{H}]^+$.

EXAMPLE 109
Preparation of Compound (112a)



[0604] Preparation of (112-2): To a stirred solution of compound **112-1** (21.0 g, 85.7 mmol) in DMF (100 mL) was added benzoyl anhydride (9.66 g, 87 mmol) in portions. The mixture was stirred at R.T. overnight. The solvent was removed under reduced pressure, and the residue was triturated with CH₂Cl₂ to give compound **112-2** as a white solid (29.90 g, 100%).

[0605] Preparation of (112-3): To a stirred suspension of compound **112-2** (10.0 g, 28.65 mmol), PPh₃ (15.01 g, 57.30 mmol) and pyridine (20 mL) in anhydrous THF (100 mL) was added dropwise a solution of I₂ (14.55 g, 57.30 mmol) in THF (50 mL) at 0°C. After addition, the mixture was warmed to R.T. and stirred for 14 hours. The reaction was quenched with saturated aqueous Na₂S₂O₃ (150 mL) and extracted with EA (100 mL, 3 times). The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified on a silica gel column (DCM/MeOH = 100:1 to 50:1) to afford compound **112-3** (4.61 g, 35.1%) as a white solid.

[0606] Preparation of (112-4): To a stirred solution of compound **112-3** (4.6 g, 10.02 mmol) in anhydrous DMF (100 mL) was added dropwise a suspension of t-BuOK (3.36 g, 30.06 mmol) in DMF (20 mL) at 0°C over 10 min. The mixture was stirred at R.T. for 2 hours. The mixtures was then quenched with saturated aqueous NH₄Cl (50 mL), and extracted with THF and EA. The organic layer was washed with brine and dried over Na₂SO₄. The solvent

was removed, and the residue was purified on a silica gel column (MeOH/DCM = 1/100 to 1/30) to afford compound **112-4** as white solid (3.30 g, 99.6%).

[0607] Preparation of (112-5): To a stirred solution of BnEt_3NCl (11.69 g, 50.2 mmol) in MeCN (50 mL) was added NaN_3 (3.26 g, 50.2 mmol). The mixture was sonicated for 20 min and then stirred at R.T. for 16 hours. The solution was filtrated into a solution of compound **112-4** (3.31 g, 10.02 mmol) and NMM (5.02 g, 50.2 mmol) in anhydrous THF (80 mL). The mixture was cooled to 0°C, and a solution of I_2 (12.5 g, 50.2 mmol) in THF (40 mL) was added dropwise. Stirring was continued at 0-10°C for 20 hours. N-Acetyl cystein was added until no gas evolved. Saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ was added until a light yellow solution achieved. The solution was concentrated and then diluted with EA. The organic phase 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:DCM = 1:1:1) to give compound **112-5** (14.7 g, 84%) as a white foam. ^1H NMR (CD_3OD , 400 MHz) δ 11.41 (s, 1H), 8.19 (d, $J = 7.2$ Hz, 1H), 8.00 (d, $J = 7.2$ Hz, 1H), 7.62-7.66 (m, 1H), 7.50-7.54 (m, 2H), 7.39 (d, $J = 7.2$ Hz, 1H), 6.44 (d, $J = 6.8$ Hz, 1H), 6.13 (d, $J = 20.4$ Hz, 1H), 5.36-5.41 (m, 1H), 4.70-4.76 (m, 1H), 3.72 (dd, $J_1 = 17.6$ Hz, $J_2 = 11.6$ Hz, 2H).

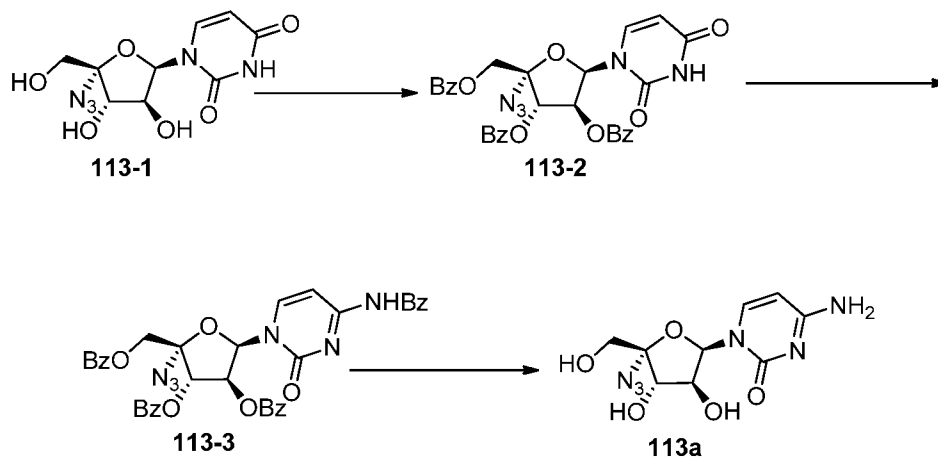
[0608] Preparation of (112-6): To a stirred solution of compound **112-5** (3.6 g, 7.20 mmol) in anhydrous pyridine (80 mL) was added BzCl (1.31 g, 9.36 mmol) dropwise at 0°C. The mixture was stirred at R.T. for 10 hours. The reaction was quenched with H_2O , and the solution was concentrated. The residue was dissolved in EA and washed with saturated aqueous NaHCO_3 . The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified on a silica gel column (PE/EA = 10/1 to 1/1) to give compound **112-6** (3.2 g, 73.7%) as a pale yellow foam.

[0609] Preparation of (112-7): Compound **112-6** (2.0 g, 3.31 mmol), BzONa (4.76 g, 33.1 mmol) and 15-crown-5 (7.28 g, 33.1 mmol) were suspended in DMF (100 mL). The mixture was stirred at 60-70°C for 3 days. The precipitate 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 = 4/1 to 2/1) to afford compound **112-7** as a light yellow foam (1.0 g, 50.7%).

[0610] Preparation of (112a): Compound **112-7** (0.5 g, 0.84 mmol) was dissolved in methanolic ammonia (30 mL), and the mixture was stirred at R.T. for 14 hours. The solvent was removed, and the residue was purified on a silica gel column (DCM/MeOH = 30:1 to 10:1) to give **112a** as white solids (0.11 g, 41.8%). ^1H NMR (CD_3OD , 400 MHz) δ 7.83 (d, $J = 7.6$ Hz, 1H), 6.10 (dd, $J_1 = 19.6$ Hz, $J_2 = 1.6$ Hz, 1H), 5.94 (d, $J = 7.6$ Hz, 1H), 5.10 (ddd, $J_1 = 53.6$

Hz, $J_2 = 5.2$ Hz, $J_3 = 1.2$ Hz, 1H), 4.57 (t, $J = 5.2$ Hz, 1H), 3.82 (dd, $J_1 = 38.0$ Hz, $J_2 = 12.4$ Hz, 2H); ESI-MS: $m/z = 287$ $[M + H]^+$, 573 $[2M + H]^+$.

EXAMPLE 110
Preparation of Compound (113a)



[0611] Preparation of (113-2): To a stirred solution of compound **113-1** (4.6 g, 16.2 mmol) in anhydrous pyridine (40 mL) was added BzCl (7.3 g, 51.8 mmol) dropwise at 0°C. The mixture was stirred at R.T. for 14 hours. The reaction was quenched with H₂O and the solution was concentrated. The residue was dissolved in EA and washed with saturated NaHCO₃. The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified on a silica gel column (PE/EA = 10/1 to 1/1) to give compound **113-2** (7.4 g, 84.1%).

[0612] Preparation of (113-3): Compound **113-2** (7.4 g, 12.4 mmol), DMAP (3.1 g, 24.8 mmol), TPSCl (7.5 g, 24.8 mol) and Et₃N (2.5 g, 24.8 mmol) were suspended in MeCN (50 mL). The mixture was stirred at R.T. for 14 hours. The solvent was removed, and the residue was dissolved in NH₃ (200 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 (DCM/MeOH = 100:1 to 50:1) to give the crude product. The crude product was dissolved in anhydrous pyridine (50 mL), and BzCl (1.7g, 12.2 mmol) was added dropwise at 0°C. The mixture was stirred at R.T. for 14 hours. The reaction was quenched with H₂O, and the solution was concentrated. The residue was dissolved in EA and washed with saturated NaHCO₃. The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified on a silica gel column (PE/EA = 10/1 to 1/1) to give compound **113-3** as a white foam (4.2 g, 48.4%).

[0613] Preparation of (113a): Compound **113-3** (4.2 g, 6.0 mmol) was dissolved in 200 mL of saturated methanolic ammonia, and the mixture was stirred at R.T. for 14 hours. The solvent was removed and then water added. The aqueous mixture was washed with DCM several times and lyophilized to give **113a** as a white solid (1.5 g, 88%). ¹H NMR (CD₃OD, 400

MHz) δ 7.74 (d, J = 7.2 Hz, 1H), 6.43 (d, J = 5.6 Hz, 1H), 5.87 (d, J = 7.6 Hz, 1H), 4.39 (dd, J_1 = 2.4 Hz, J_2 = 5.6 Hz, 1H), 4.15 (d, J = 5.6 Hz, 1H), 3.80 (s, 1H). ESI-MS: m/z =285 $[M+H]^+$.

EXAMPLE 111

RSV Antiviral Assays

[0614] CPE reduction assays are performed as described by Sidwell and Huffman et al., *Appl Microbiol.* (1971) 22(5):797–801 with slight modifications. HEp-2 cells (ATCC) at a concentration of 6000 cell/well are infected with RSV Long strain (ATCC) at a multiplicity of infection (m.o.i.) of 0.01, and each of the test compounds are provided to duplicate wells at final concentrations starting from 100 μ M using 1/3 stepwise dilutions. For each compound, two wells are set aside as uninfected, untreated cell controls (CC), and two wells per test compound receive virus only as a control for virus replication (VC). The assay is stopped after 6 days, before all of the cells in the virus-infected untreated control wells exhibited signs of virus cytopathology (giant cell formation, syncytia). At the end of the incubation, 20 μ L of cell counting kit-8 reagent (CCK-8, Dojindo Molecular Technologies, Inc.) are added to each well. After 4 hour incubation, the absorbance is measured in each well according to manufacturer's instruction, and the 50% effective concentration (EC_{50}) is calculated by using regression analysis, based on the mean O.D. at each concentration of compound.

[0615] RT-PCR based assays were performed in HEp-2 cells (ATCC: CCL-23) at a concentration of 20000 cell/well were plated in 96 well plates and incubated overnight. Each of the test compounds were 1/3 serially diluted and dosed to HEp-2 cells in duplicates. The highest final concentration for each compound was 100 μ M. After 24 hour compound pre-incubation, RSV A2 (ATCC: VR-1540) at MOI of 0.1 was added. Two wells per compound were set aside as uninfected, untreated cell controls (CC), and four wells per test compound received virus only as a control for virus replication (VC). The assay was stopped 4 days after virus infection and conditioned media was removed for viral RNA isolation. The quantities of the RSV virus were measured by real-time PCR using a set of RSV specific primers and probe. The data was analyzed with Prism software with EC_{50} defined as drug concentration that reduced the viral load 50% from the viral control (VC).

[0616] Standard RSV polymerase assays were conducted in the presence of 3 μ L extract of RSV-infected cells in a reaction buffer containing 50mM tris-acetate pH 8, 120mM K-acetate, 4.5mM $MgCl_2$, 5% glycerol, 2mM EDTA, 50 μ g/mL BSA, and 3mM DTT. Varying concentration of test compounds were used to initiate RNA synthesis for 120 mins at 30°C., and radioactive ^{33}P GTP (15 uCi) was used as tracer. The reaction was stopped by adding 50 mM EDTA, and RNA samples were purified through G-50 size exclusion spin columns and phenol-

chloroform extraction. The radio-labeled RNA products were resolved by electrophoresis on a 6% polyacrylamide TBE gel, and visualized and quantitated after being exposed on a phosphorImager screen. Polymerase inhibition experiments (IC_{50}) were conducted the same way in the presence of increasing concentration of test compounds.

[0617] Compounds of Formula (I), Formula (II) and Formula (III) are active in the assay as noted in Tables 6 and 7. In Table 6, 'A' indicates an $EC_{50} < 2 \mu M$, 'B' indicates an EC_{50} of $\geq 2 \mu M$ and $< 10 \mu M$ and 'C' indicates an $EC_{50} \geq 10 \mu M$ and $< 50 \mu M$. In Table 7, 'A' indicates an $EC_{50} < 1 \mu M$, 'B' indicates an EC_{50} of $\geq 1 \mu M$ and $< 10 \mu M$ and 'C' indicates an $EC_{50} \geq 10 \mu M$ and $< 100 \mu M$.

Table 6 – Activity of compounds as determined by RSV polymerase assay

No.	EC_{50}	No.	EC_{50}	No.	EC_{50}	No.	EC_{50}	No.	EC_{50}
35a	A	36i	B	56c	A	97b	A	97g	A
36a	A	36j	B	56da	A	97c	A	98b	A
36c	A	56a	B	56e	A	97d	A	98c	A
36e	A	56a	B	97a	A				

Table 7 - Activity of compounds as determined by RT-PCR assay

No.	EC_{50}	No.	EC_{50}	No.	EC_{50}	No.	EC_{50}	No.	EC_{50}	No.	EC_{50}
1a	C	14a	A	28a	B	48a	B	81a	B	106a	C
2a	C	20a	B	30a	A	50a	A	82a	A	108a	B
3a	A	21a	A	31a	B	52a	A	83a	B	-	-
4a	C	22a	C	33a	A	58a	C	85a	A	-	-
7a	A	23a	A	39a	B	69a	A	86a	A	-	-
9a	C	25a	C	41a	B	71a	A	87a	A	-	-
11a	B	26a	B	46a	B	73a	C	92a	C	-	-
13a	C	27a	B	45a	C	76a	A	105a	C	-	-

EXAMPLE 112

Influenza Antiviral Assay

[0618] Human lung carcinoma A549 cells (ATCC, Manassas, VA) were plated at a density of 5×10^4 cells/mL (5×10^3 cells/well) in assay media (Ham's F12 media supplemented with 0.3% FBS, 1% penicillin/streptomycin (all Mediatech, Manassas, VA) and 1% DMSO (Sigma-Aldrich, St Louis, MO)) in black 96-well plates. After 24 hours, serially diluted test

compounds were added to cells and incubated for an additional 24 hours. Cells were infected with 250 IU/well of Influenza strain A/WSN/33 (H1N1) (Virapur, San Diego CA) and incubated for 20 hours at 37°C, 5% CO₂. The cell culture supernatant was aspirated off and 50 µL of 25 µM 2'-(4-Methylumbelliferyl)-α-D-N-acetylneuraminic acid (Sigma-Aldrich) dissolved in 33 mM MES, pH 6.5 (Emerald Biosystems, Bainbridge Island, WA) was added to the cells. After incubation for 45 mins at 30°C, reactions were stopped by addition of 150 µL stop solution (100 mM glycine, pH 10.5, 25% ethanol, all Sigma-Aldrich). Fluorescence was measured with excitation and emission filters of 355 and 460 nm, respectively, on a Victor X3 multi-label plate reader (Perkin Elmer, Waltham, MA). Cytotoxicity of uninfected parallel cultures was determined by addition of 100 µL of CellTiter-Glo® reagent (Promega, Madison, WI), and incubation for 10 mins at R.T. Luminescence was measured on a Victor X3 multi-label plate reader.

[0619] Compounds of Formula (I), Formula (II) and Formula (III) are active in the assay as noted in Table 8, where 'A' indicates an EC₅₀ < 20 µM, 'B' indicates an EC₅₀ of ≥20 µM and < 100 µM and 'C' indicates an EC₅₀ ≥ 100 µM and < 250 µM.

Table 8 – Activity of compounds

No.	% Inhibition	No.	% Inhibition
1a	C	20a	C
2a	C	21a	C
3a	C	22a	C
4a	C	23a	C
6a	C	25a	A
7a	C	26a	C
9a	C	27a	B
12a	C	28a	C
16a	C	30a	C
17a	C	31a	C
18a	C	39a	B

EXAMPLE 113 **Influenza Pol Assay**

[0620] Recombinant influenza polymerase trimer is obtained as described (Aggarwal S. et al., PLoS ONE 2010). Standard RNA polymerization assays are conducted in the presence

of 0.15 μ M enzyme, 1.5 μ M 50-mer oligonucleotide template, 400 μ M AG primer and varying concentration of the test compounds are incubated together for 40 minutes at 30°C. Radioactive ^{33}P GTP are used as the tracer and the radio-labeled RNA products are resolved by electrophoresis on a 15% polyacrylamide TBE gel, and is visualized and quantitated after being exposed on a phosphorImager screen. Polymerase inhibition experiments (IC_{50}) are conducted the same way in the presence of increasing concentration of test compounds.

EXAMPLE 114

Parainfluenza virus-3 (PIV-3) RT-PCR Assays

[0621] RT-PCR based assays were performed in A549 cells (ATCC: CCL-185). A549 cells at a concentration of 20,000 cells/well were plated in 96 well plates and incubated overnight. Each of the test compounds were 1/3 serially diluted and dosed to A549 cells in duplicates. The highest final concentration for each compound was 100 μ M. After 24 hour compound pre-incubation, human parainfluenza virus 3 (hPIV3, ATCC: VR-93) at multiplicity of infection (MOI) of 0.1 was added. Two wells per compound were set aside as uninfected, untreated cell controls (CC), and four wells per test compound received virus only as a control for virus replication (VC). The assay was stopped 7 days after virus infection and conditioned media was removed for viral RNA isolation. The quantities of the hPIV3 virus were measured by real-time PCR using a set of hPIV3 specific primers and probe. The data was analyzed with Prism software with EC_{50} defined as drug concentration that reduced the viral load 50% from the viral control (VC). The results are provided in Table 9 and show Compounds of Formula (I), Formula (II) and Formula (III) are active against PIV-3, where 'A' indicates an $\text{EC}_{50} < 20$ μ M, 'B' indicates an EC_{50} of ≥ 20 μ M and < 100 μ M and 'C' indicates an $\text{EC}_{50} \geq 100$ μ M.

Table 9

No.	EC_{50} (μ M)	No.	EC_{50} (μ M)	No.	EC_{50} (μ M)
3a	A	22a	C	71a	C
6a	C	23a	C	111a	A
7a	A	40a	C	112a	A
9a	C	43a	C	113a	C
20a	C	69a	A		

EXAMPLE 115

Parainfluenza virus-3 (PIV-3) Enhanced Green Fluorescent Protein (eGFP) Assay

[0622] HPIV3-eGFP based assays were performed in A549 cells (ATCC: CCL-185). A549 cells at a concentration of 20,000 cells/well were plated in 96 well plates and incubated overnight. Each of the test compounds were 1/3 serially diluted and dosed to A549 cells in

duplicates. The highest final concentration for each compound was 100 μ M. After 24 hour compound pre-incubation, hPIV3-eGFP, (Roth et. al., *Antiviral Res.* (2009) 82(1):12–21.) at MOI of 0.1 was added. Two wells per compound were set aside as uninfected, untreated cell controls (CC), and four wells per test compound received virus only as a control for virus replication (VC). The assay was stopped 3 days after virus infection by removing the conditioned media and adding RIPA lysis buffer at 50 μ l/well. The eGFP fluorescence signal in the lysis buffer was detected in a Victor 3 plate reader. The data was analyzed with Prism software with EC₅₀ defined as drug concentration that reduced the viral load 50% from the viral control (VC). The results are provided in Table 10 and show Compounds of Formula (I), Formula (II) and Formula (III) are active against PIV-3, where ‘A’ indicates an EC₅₀ < 20 μ M, ‘B’ indicates an EC₅₀ of ≥ 20 μ M and < 100 μ M and ‘C’ indicates an EC₅₀ ≥ 100 μ M.

Table 10

No.	EC ₅₀ (μ M)	No.	EC ₅₀ (μ M)
3a	A	40a	C
4a	C	43a	C
6a	C	69a	B
7a	A	71a	C
9a	C	111a	A
20a	C	112a	A
22a	C	113a	C
23a	C		

EXAMPLE 116**Parainfluenza virus-3 (PIV-3) Plaque Assay**

[0623] MA-104 cells were grown in 24-well plates to a confluency of 90% in the presence of minimal essential medium (MEM) supplemented with 10% fetal bovine serum and antibiotics (C-EMEM). The cells were then washed twice with non-complete minimal essential medium (NC-EMEM). Test articles were dissolved in DMSO to a stock concentration of 10 mM.

[0624] An aliquot of 0.5mL of the test article at various concentrations was then inoculated in triplicate wells and incubated for 60 minutes at 37°C with 5% CO₂ for the diffusion of test article into MA-104 cells. After the incubation period, a stock of human PIV type 3 was thawed and diluted with NC-EMEM to achieve a viral concentration of 10⁴ pfu/mL. An aliquot of 0.1 mL was then inoculated into all the wells except for the negative and test article toxicity control wells. Upon infection, the plates were incubated for 72 hours at 37°C at 5% CO₂. After incubation, the plates were examined under microscopy to record cytotoxicity.

The supernatants collected for viral quantification using a standard plaque assay using MA-104 cells as the indicator cells.

[0625] To perform the plaques assay, MA-104 cells were grown to confluence in 24-well plates. The cells were washed with serum-free medium prior to inoculation of duplicate wells with serial 10-fold dilutions of supernatant sample. After 1 hour incubation at 37°C, the samples were aspirated and 1.0 mL of methyl cellulose overlay media was added to each well. After 6 days of culture, the cells were fixed and stained with 0.06% crystal violet in 1% glutaraldehyde and viral plaques enumerated. The data was analyzed with Prism software with EC₅₀ defined as drug concentration that reduced the viral load 50% from the viral control (VC). Table 11 provides the results and show Compounds of Formula (I), Formula (II) and Formula (III) are active against PIV-3, where 'A' indicates an EC₅₀ < 20 µM.

Table 11

No.	EC ₅₀ (µM)
3a	A
7a	A
111a	A

EXAMPLE 117

Human metapneumovirus (hMPV) TCID₅₀ Assay

[0626] LLC-MK2 cells were grown in 24-well plates to a confluency of 90% in the presence of minimal essential medium (MEM) supplemented with 10% fetal bovine serum and antibiotics (C-EMEM). The cells were then washed twice with non-complete minimal essential medium (NC-EMEM). Test articles were dissolved in DMSO to a stock concentration of 10 mM.

[0627] An aliquot of 0.5mL of the test article at various concentrations was then inoculated in triplicate wells and incubated for 60 minutes at 37°C with 5% CO₂ for the diffusion of test article into LLC-MK2 cells. After the incubation period, a stock of human metapneumovirus was thawed and diluted with NC-EMEM to achieve a viral concentration of 10⁴ pfu/mL. An aliquot of 0.1 mL was then inoculated into all the wells except for the negative and test article toxicity control wells. Upon infection, the plates were incubated for 7 days at 37°C at 5% CO₂. After incubation, the plates were examined under microscopy to record cytotoxicity. The supernatants collected for viral quantification using a standard TCID₅₀ assay using LLC-MK2 cells as the indicator cells. The data was analyzed with Prism software with EC₅₀ defined as drug concentration that reduced the viral load 50% from the viral control (VC). The results of the assay are shown in Table 12 and show Compounds of Formula (I), Formula

(II) and Formula (III) are active against human metapneumovirus, where 'A' indicates an $EC_{50} < 20 \mu\text{M}$.

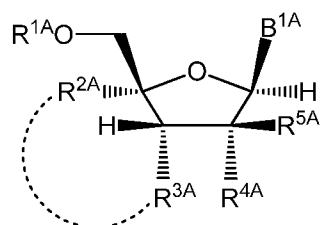
Table 12

No.	EC_{50} (μM)
3a	A
7a	A
111a	A

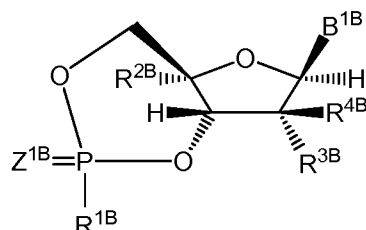
[0628] Although the foregoing has been described in some detail by way of illustrations and examples for purposes of clarity and understanding, it will be understood by those of skill in the art that numerous and various modifications can be made without departing from the spirit of the present disclosure. Therefore, it should be clearly understood that the forms disclosed herein are illustrative only and are not intended to limit the scope of the present disclosure, but rather to also cover all modification and alternatives coming within the true scope and spirit of the invention.

WHAT IS CLAIMED IS:

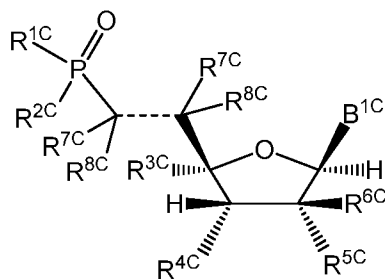
1. Use of an effective amount of a compound selected from Formula (I), Formula (II), and Formula (III), or a pharmaceutically acceptable salt of the foregoing, for ameliorating or treating a viral infection caused by a virus selected from a henipavirus, a morbillivirus, a respirovirus, a rubulavirus and a metapneumovirus, wherein the compound is selected from Formula (I), Formula (II), and Formula (III) has one of the following structures:



(I)



(II)



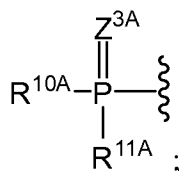
(III)

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^{1A} is selected from the group consisting of hydrogen, an optionally substituted

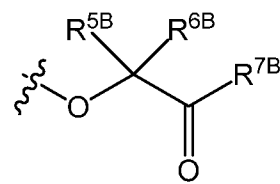
acyl, an optionally substituted O-linked amino acid, $R^{6A}O-P(=Z^{1A})(OR^{7A})$, $R^{8A}O-P(=Z^{2A})(R^{9A})$ and



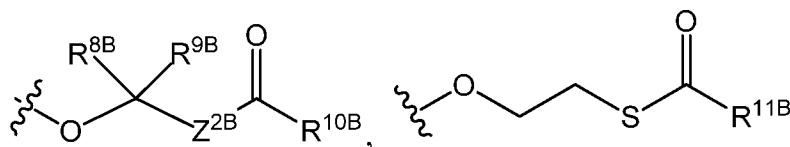
when the dashed line (-----) of Formula (I) is a single bond, R^{2A} is CH_2 , and R^{3A} is O (oxygen);

when the dashed line (-----) of Formula (I) is absent, R^{2A} is selected from the group consisting of an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{2-6} alkynyl, an optionally substituted C_{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, and R^{3A} is selected from the group consisting of OH, $-OC(=O)R^{''A}$ and an optionally substituted O-linked amino acid;

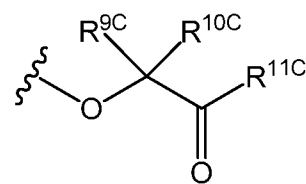


R^{1B} is selected from the group consisting of O^- , OH,

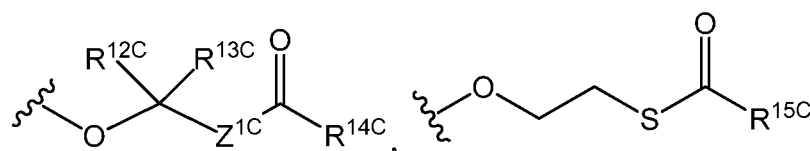


, an optionally substituted N-linked amino acid and an optionally substituted N-linked amino acid ester derivative;

R^{1C} and R^{2C} are independently selected from the group consisting of O^- , OH, an

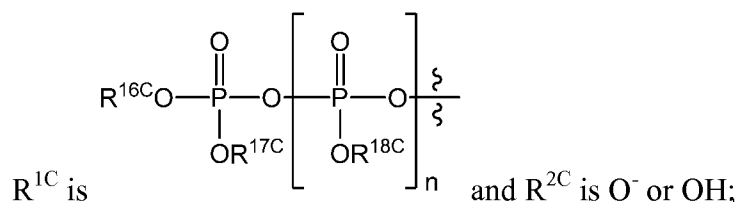


optionally substituted C_{1-6} alkoxy,



, an optionally substituted N-linked amino acid and an optionally substituted N-linked amino acid ester derivative;

or



R^{2B} and R^{3C} are independently selected from the group consisting of an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{2-6} alkynyl, an optionally substituted C_{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;

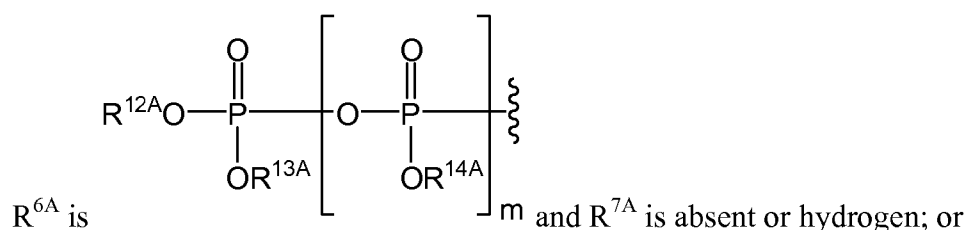
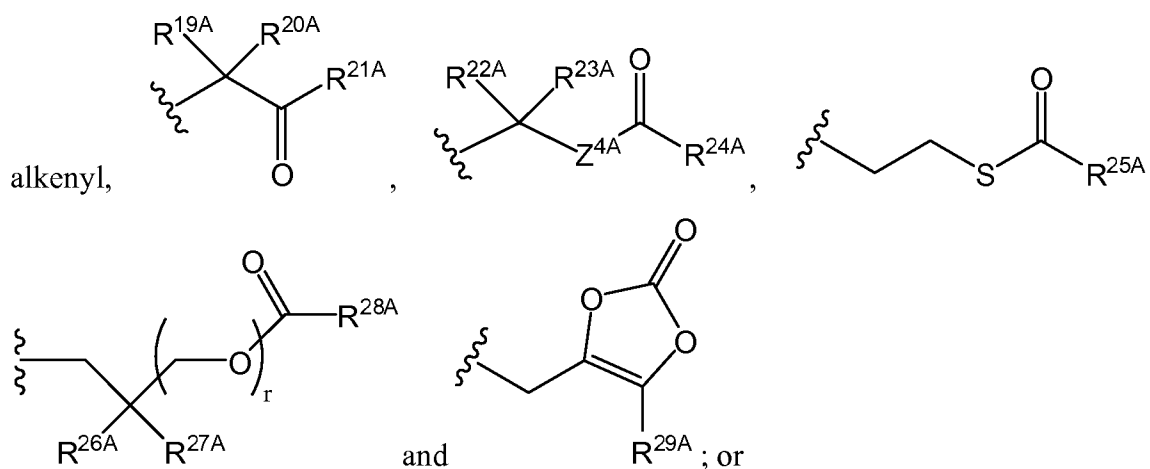
R^{4C} is selected from the group consisting of OH, $-OC(=O)R^{''C}$ and an optionally substituted O-linked amino acid;

R^{4A} , R^{3B} and R^{5C} are independently a halogen;

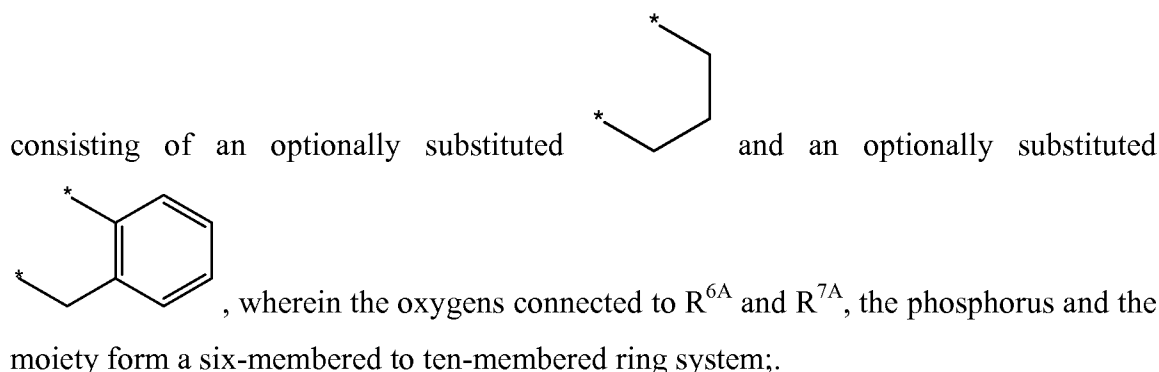
R^{5A} , R^{4B} and R^{6C} are independently hydrogen or halogen;

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 C₂₋₂₄ alkynyl, an optionally substituted C₃₋₆ cycloalkyl, an optionally substituted C₃₋₆ cycloalkenyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aryl(C₁₋₆ alkyl), an optionally substituted $^{*-(CR^{15A}R^{16A})_p-O-C_{1-24}}$ alkyl, an optionally substituted $^{*-(CR^{17A}R^{18A})_q-O-C_{1-24}}$



R^{6A} and R^{7A} are taken together to form a moiety selected from the group



R^{9A} is independently selected from the group consisting of an optionally substituted C₁₋₂₄ alkyl, an optionally substituted C₂₋₂₄ alkenyl, an optionally substituted C₂₋₂₄ alkynyl, an optionally substituted C₃₋₆ cycloalkyl, an optionally substituted C₃₋₆ 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 C₁₋₂₄ 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 and an optionally substituted $-O$ -aryl;

R^{25A} , R^{29A} , R^{11B} and R^{15C} 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 $-C\equiv N$ 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^{9A} and R^{9C} are independently an optionally substituted C_{1-24} -alkyl;

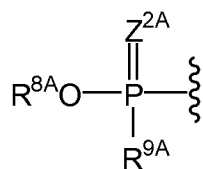
m and n are independently 0 or 1;

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 the dashed line (-----) of Formula (I) is absent; R^{1A} is



wherein R^{8A} is an unsubstituted C_{1-4} alkyl or phenyl optionally para-

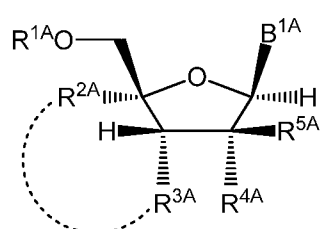
substituted with a halogen or methyl and R^{9A} is methyl ester, ethyl ester, isopropyl ester, n-butyl ester, benzyl ester or phenyl ester of an amino acid selected from the group consisting of glycine, alanine, valine, leucine, phenylalanine, tryptophan, methionine and proline; R^{3A} is OH; R^{4A} is fluoro; R^{5A} is fluoro or hydrogen; and B^{1A} is an unsubstituted uracil; then R^{2A} cannot be $-OCH_3$;

provided that when the dashed line (-----) of Formula (I) is absent; 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;

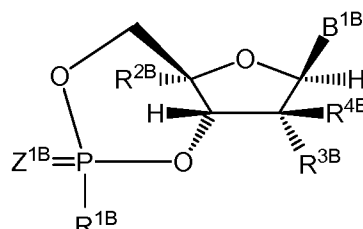
provided that when the dashed line (-----) of Formula (I) is absent; R^{1A} is H; R^{3A} is OH; R^{4A} is fluoro; R^{5A} is hydrogen; and B^{1A} is an unsubstituted thymine; then R^{2A} cannot be C_1 alkyl substituted with an N-amido; and

provided that when the dashed line (-----) of Formula (I) is absent; 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.

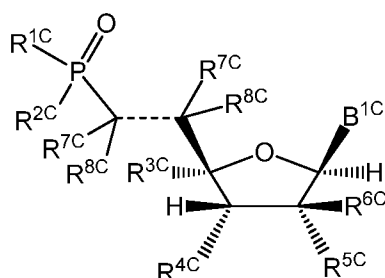
2. A method for ameliorating or treating a viral infection caused by a virus comprising administering to or contacting a cell in a subject with an effective amount of a compound selected from Formula (I), Formula (II), and Formula (III), or a pharmaceutically acceptable salt of the foregoing, wherein the virus is selected from a henipavirus, a morbillivirus, a respirovirus, a rubulavirus and a metapneumovirus, and wherein the compound is selected from Formula (I), Formula (II), and Formula (III) has one of the following structures:



(I)



(II)

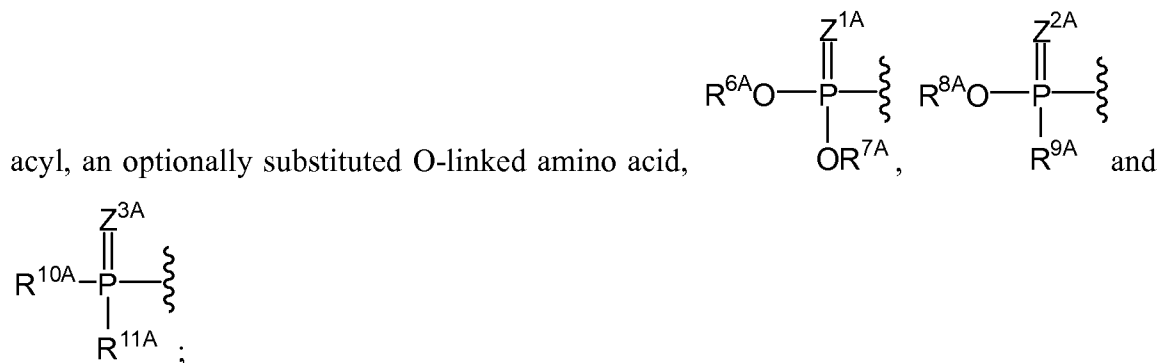


(III)

wherein:

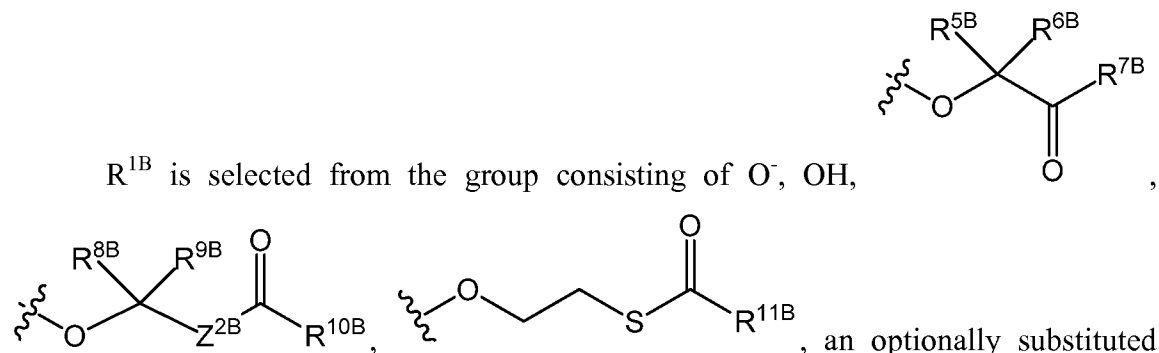
B^{1A} , B^{1B} and B^{1C} are independently an optionally substituted heterocyclic base or an optionally substituted heterocyclic base with a protected amino group;

R^{1A} is selected from the group consisting of hydrogen, an optionally substituted



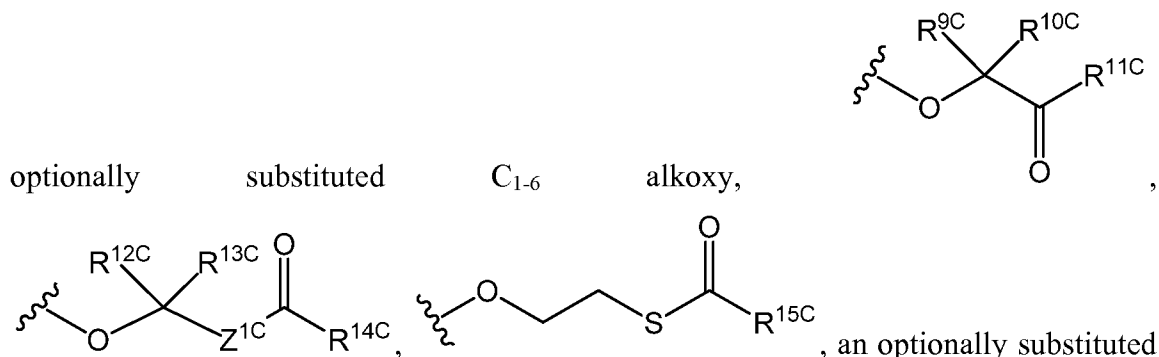
when the dashed line (-----) of Formula (I) is a single bond, R^{2A} is CH_2 , and R^{3A} is O (oxygen);

when the dashed line (-----) of Formula (I) is absent, R^{2A} is selected from the group consisting of an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{2-6} alkynyl, an optionally substituted C_{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, and R^{3A} is selected from the group consisting of OH, $-OC(=O)R^{3A}$ and an optionally substituted O-linked amino acid;



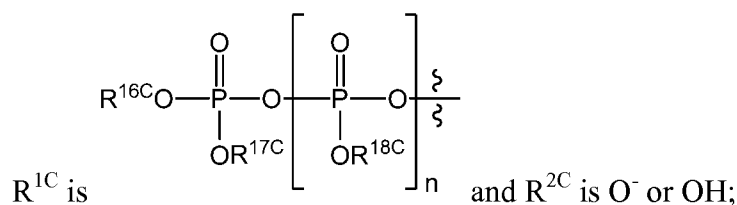
N-linked amino acid and an optionally substituted N-linked amino acid ester derivative;

R^{1C} and R^{2C} are independently selected from the group consisting of O^- , OH, an



N-linked amino acid and an optionally substituted N-linked amino acid ester derivative;

or



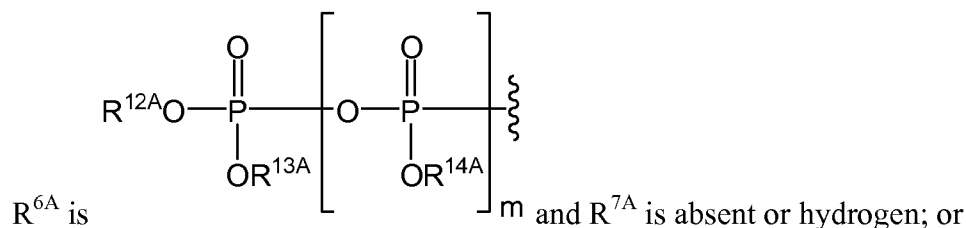
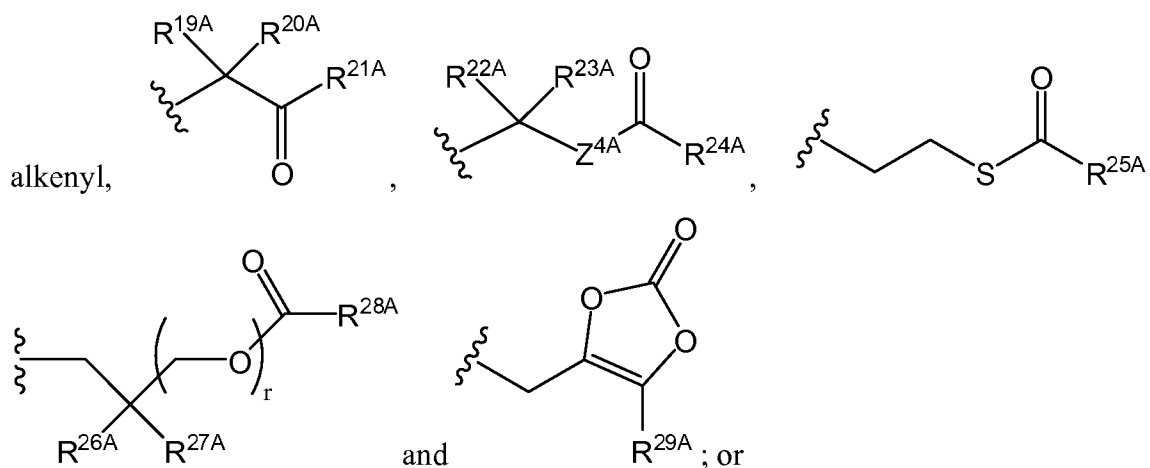
R^{2B} and R^{3C} are independently selected from the group consisting of an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{2-6} alkynyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted $-O-C_{1-6}$ alkyl, an optionally 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;

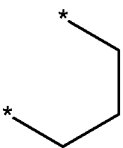
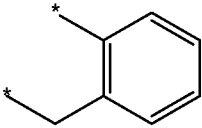
R^{4A} , R^{3B} and R^{5C} are independently a halogen;

R^{5A} , R^{4B} and R^{6C} are independently hydrogen or halogen;

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 $*(CR^{17A}R^{18A})_q-O-C_{1-24}$



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 and an optionally substituted $-O$ -aryl;

R^{25A} , R^{29A} , R^{11B} and R^{15C} 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 $-C\equiv N$ or an optionally substituted substituent selected from the group consisting of C_{2-8} organylcarbonyl, C_{2-8} alkoxy carbonyl 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^{7A} and R^{7C} are independently an optionally substituted C_{1-24} -alkyl;

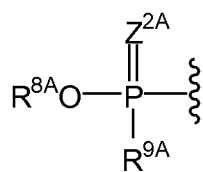
m and n are independently 0 or 1;

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 the dashed line (-----) of Formula (I) is absent; 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 the group consisting of 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 $-OCH_3$;

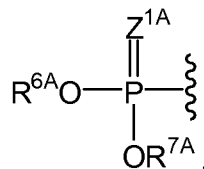
provided that when the dashed line (-----) of Formula (I) is absent; R^{1A} is H; R^{3A} is OH; R^{4A} is fluoro; R^{5A} is fluoro; and B^{1A} is an unsubstituted cytosine; then R^{2A} cannot be allenyl;

provided that when the dashed line (-----) of Formula (I) is absent; 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; and

provided that when the dashed line (-----) of Formula (I) is absent; 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.

3. The use of Claim 1 or the method of Claim 2, wherein the virus is a henipavirus.
4. The use or method of Claim 3, wherein the henipavirus is a nipahvirus.

5. The use of Claim 1 or the method of Claim 2, wherein the virus is a morbillivirus.
6. The use or method of Claim 5, wherein the morbillivirus is the measles virus.
7. The use of Claim 1 or the method of Claim 2, wherein the virus is a respirovirus.
8. The use or method of Claim 7, wherein the respirovirus is human parainfluenza virus 1.
9. The use or method of Claim 7, wherein the respirovirus is human parainfluenza virus 3.
10. The use of Claim 1 or the method of Claim 2, wherein the virus is a rubulavirus.
11. The use or method of Claim 10, wherein the rubulavirus is the mumps virus.
12. The use or method of Claim 10, wherein the rubulavirus is human parainfluenza virus 2.
13. The use or method of Claim 10, wherein the rubulavirus is human parainfluenza virus 4.
14. The use of Claim 1 or the method of Claim 2, wherein the virus is a metapneumovirus.
15. The use or method of Claim 14, wherein the metapneumovirus is human metapneumovirus.
16. The use of any one of Claim 1 or 3-15 or the method of any one of Claims 2-15, wherein the compound is a compound of Formula (I).



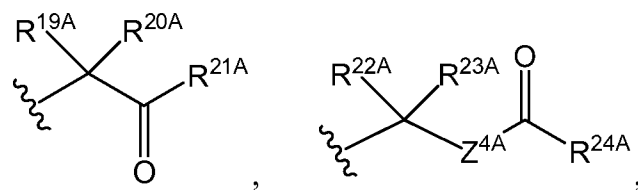
17. The use or method of Claim 16, wherein R^{1A} is
18. The use or method of Claim 17, wherein R^{6A} and R^{7A} are both hydrogen.
19. The use or method of Claim 17, wherein R^{6A} and R^{7A} are both absent.
20. The use or method of Claim 17, wherein one of R^{6A} and R^{7A} is hydrogen, and the other of R^{6A} and R^{7A} is selected from the group consisting of an optionally substituted C₁₋₂₄ alkyl, an optionally substituted C₂₋₂₄ alkenyl, an optionally substituted C₂₋₂₄ alkynyl, an optionally substituted C₃₋₆ cycloalkyl, an optionally substituted C₃₋₆ cycloalkenyl, an optionally substituted aryl, an optionally substituted heteroaryl and an optionally substituted aryl(C₁₋₆ alkyl).
21. The use or method of Claim 20, wherein the other of R^{6A} and R^{7A} is an optionally substituted C₁₋₂₄ alkyl.
22. The use or method of Claim 17, wherein both R^{6A} and R^{7A} are independently selected from the group consisting of an optionally substituted C₁₋₂₄ alkyl, an optionally

substituted C₂₋₂₄ alkenyl, an optionally substituted C₂₋₂₄ alkynyl, an optionally substituted C₃₋₆ cycloalkyl, an optionally substituted C₃₋₆ cycloalkenyl, an optionally substituted aryl, an optionally substituted heteroaryl and an optionally substituted aryl(C₁₋₆ alkyl).

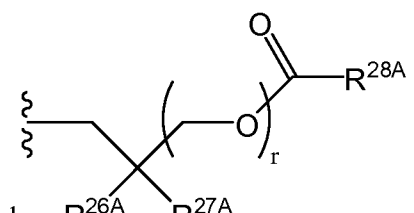
23. The use or method of Claim 22, wherein both R^{6A} and R^{7A} are an optionally substituted C₁₋₂₄ alkyl.

24. The use or method of Claim 17, wherein at least one of R^{6A} and R^{7A} are selected

from the group consisting of



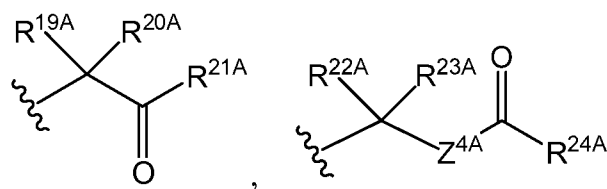
and



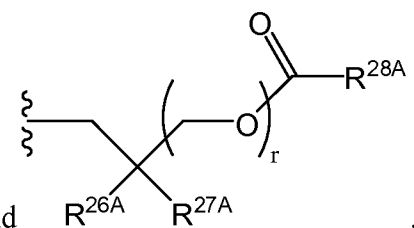
; and the other of R^{6A} and R^{7A} is selected from the group consisting of absent, hydrogen, an optionally substituted C₁₋₂₄ alkyl, an optionally substituted C₂₋₂₄ alkenyl, an optionally substituted C₂₋₂₄ alkynyl, an optionally substituted C₃₋₆ cycloalkyl, an optionally substituted C₃₋₆ cycloalkenyl, an optionally substituted aryl, an optionally substituted heteroaryl and an optionally substituted aryl(C₁₋₆ alkyl).

25. The use or method of Claim 17, wherein both R^{6A} and R^{7A} are independently

selected from the group consisting of



and



.

26. The use or method of any one of Claims 24-25, wherein both R^{26A} and R^{27A} are an optionally substituted C₂₋₈ organylcarbonyl.

27. The use or method of Claim 26, wherein the optionally substituted C₁₋₈ organylcarbonyl is -C(=O)CH₃.

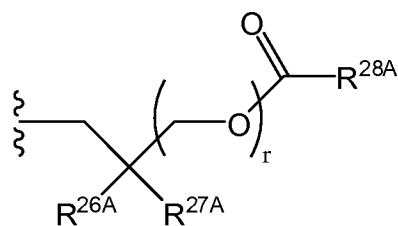
28. The use or method of any one of Claims 24-25, wherein both R^{26A} and R^{27A} are an optionally substituted C₂₋₈ alkoxy carbonyl.

29. The use or method of Claim 28, wherein the optionally substituted C₁₋₈ alkoxycarbonyl is $-\text{C}(=\text{O})\text{OCH}_2\text{CH}_3$.

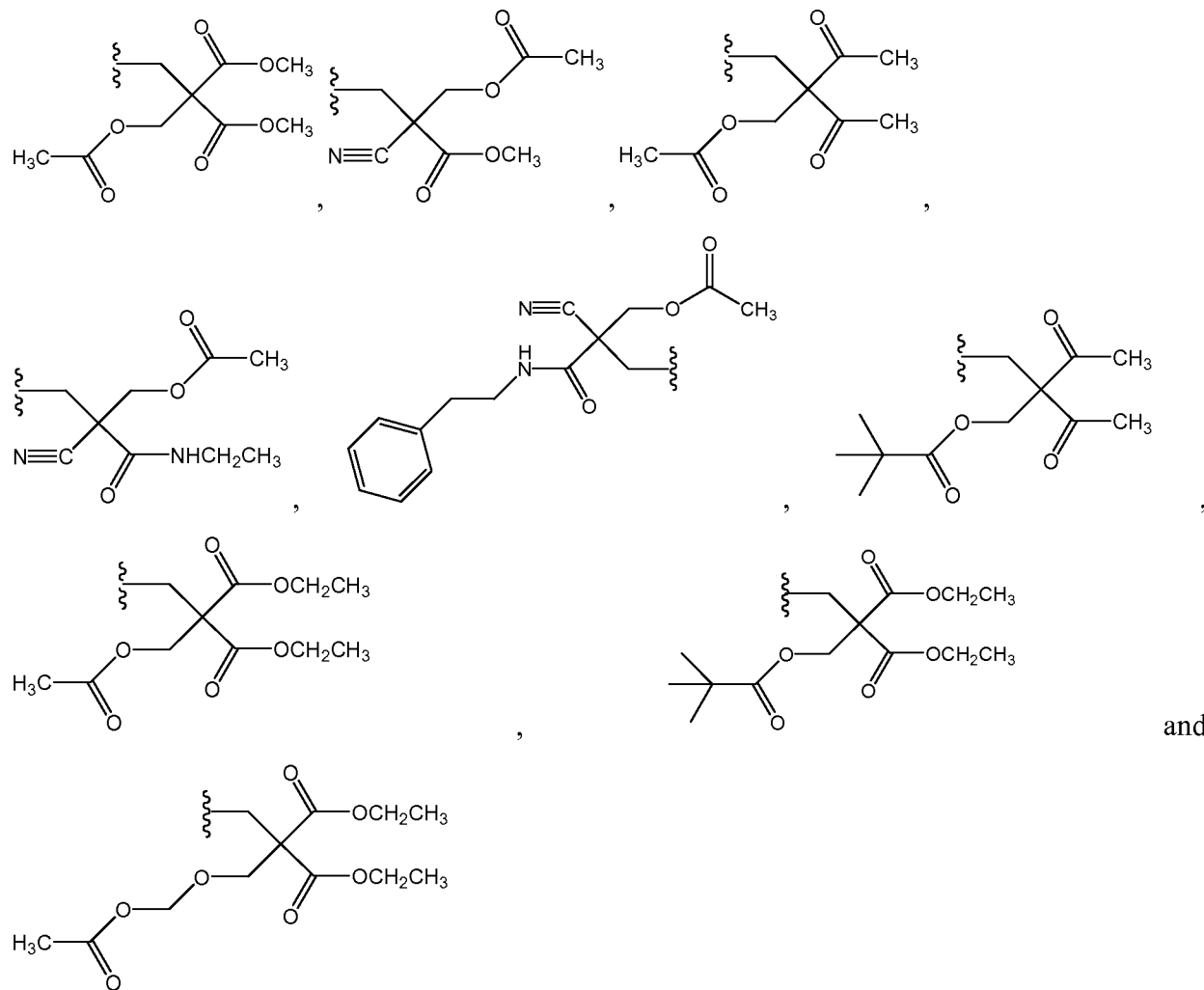
30. The use or method of Claim 28, wherein the optionally substituted C₁₋₈ alkoxycarbonyl is $-\text{C}(=\text{O})\text{OCH}_3$.

31. The use or method of any one of Claims 24-30, wherein R^{28A} is an optionally substituted C₁₋₄-alkyl

32. The use or method of any one of Claims 24-25, wherein



is selected from the group consisting of:



and

33. The use or method of Claim 17, wherein R^{6A} and R^{7A} are both an optionally substituted C₁₋₂₄ alkyl.

34. The use or method of Claim 17, wherein R^{6A} and R^{7A} are both an optionally substituted C₂₋₂₄ alkenyl.

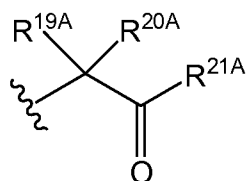
35. The use or method of Claim 17, wherein R^{6A} and R^{7A} are both $*(CR^{15A}R^{16A})_p-$ O-C₁₋₂₄ alkyl.

36. The use or method of Claim 17, wherein R^{6A} and R^{7A} are both $*(CR^{17A}R^{18A})_q-$ O-C₂₋₂₄ alkenyl.

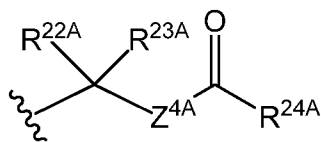
37. The use or method of Claim 17, wherein R^{6A} and R^{7A} are both an optionally substituted aryl.

38. The use or method of Claim 17, wherein R^{6A} and R^{7A} are both an optionally substituted aryl(C₁₋₆ alkyl).

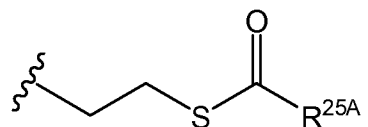
39. The use or method of Claim 17, wherein R^{6A} and R^{7A} are both



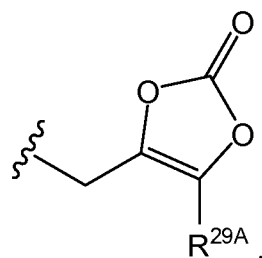
40. The use or method of Claim 17, wherein R^{6A} and R^{7A} are both



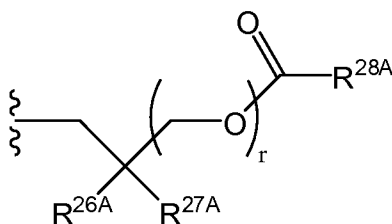
41. The use or method of Claim 17, wherein R^{6A} and R^{7A} are both



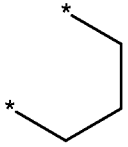
42. The use or method of Claim 17, wherein R^{6A} and R^{7A} are both

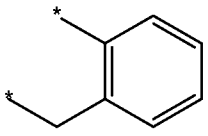


43. The use or method of Claim 17, wherein R^{6A} and R^{7A} are both

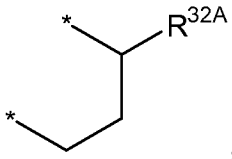
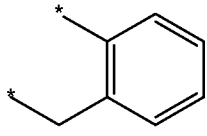


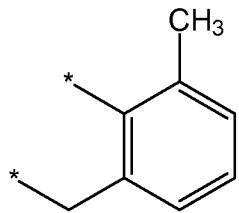
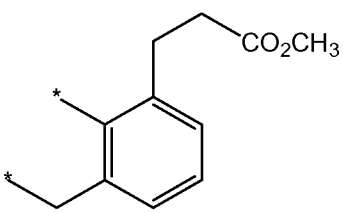
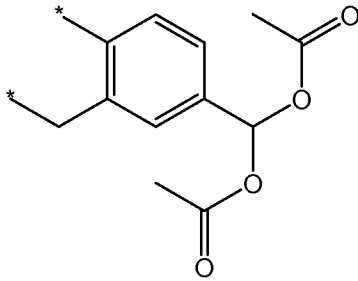
44. The use or method of Claim 17, wherein R^{6A} and R^{7A} can be taken together to

form a moiety selected from the group consisting of an optionally substituted  and an

optionally substituted , wherein the oxygens connected to R^{6A} and R^{7A} , the phosphorus and the moiety form a six-membered to ten-membered ring system.

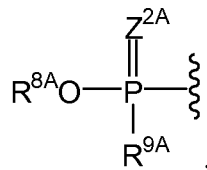
45. The use or method of Claim 44, wherein R^{6A} and R^{7A} can be taken together to

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.

46. The use or method of any one of Claims 17-45, wherein Z^{1A} is O.

47. The use or method of any one of Claims 17-45, wherein Z^{1A} is S.

48. The use or method of Claim 16, wherein R^{1A} is .

49. The use or method of Claim 48, 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.

50. The use or method of Claim 49, wherein R^{8A} is hydrogen, and R^{9A} is an optionally substituted C_{1-6} alkyl.

51. The use or method of Claim 48, 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.

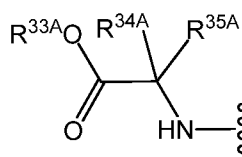
52. The use or method of Claim 48, wherein R^{8A} is absent or hydrogen; and R^{9A} is an optionally substituted N-linked amino acid or an optionally substituted N-linked amino acid ester derivative.

53. The use or method of Claim 48, 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.

54. The use or method of Claim 52 or 53, 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.

55. The use or method of Claim 54, 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.

56. The use or method of Claim 52 or 53, 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.

57. The use or method of Claim 56, wherein R^{34A} is an optionally substituted C_{1-6} -alkyl.

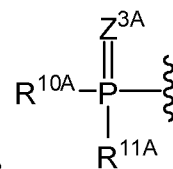
58. The use or method of Claim 57, wherein the optionally substituted C_{1-6} -alkyl is methyl.

59. The use or method of any one of Claims 56-58, wherein R^{35A} is hydrogen.

60. The use or method of any one of Claims 56-59, wherein R^{33A} is an optionally substituted C_{1-6} alkyl, an optionally substituted C_{3-6} cycloalkyl or an optionally substituted benzyl.

61. The use or method of any one of Claims 48-60, wherein Z^{2A} is O.

62. The use or method of any one of Claims 48-60, wherein Z^{2A} is S.



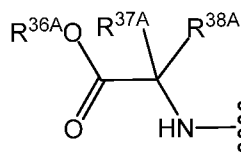
63. The use or method of Claim 16, wherein R^{1A} is

64. The use or method of Claim 63, 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.

65. The use or method of Claim 64, 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.

66. The use or method of Claim 65, 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.

67. The use or method of Claim 64, 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.

68. The use or method of Claim 67, wherein R^{42A} is an optionally substituted C_{1-6} -alkyl.

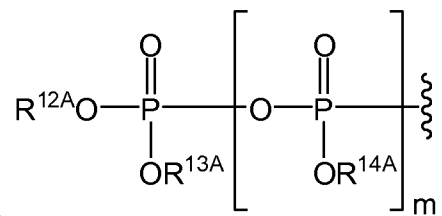
69. The use or method of Claim 68, wherein the optionally substituted C_{1-6} -alkyl is methyl.

70. The use or method of any one of Claims 67-69, wherein R^{43A} is hydrogen.

71. The use or method of any one of Claims 67-70, wherein R^{41A} is an optionally substituted C_{1-6} alkyl, an optionally substituted C_{3-6} cycloalkyl or an optionally substituted benzyl.

72. The use or method of any one of Claims 63-71, wherein Z^{3A} is O.

73. The use or method of any one of Claims 63-71, wherein Z^{3A} is S.



74. The use or method of Claim 16, wherein R^{1A} is

75. The use or method of Claim 74, wherein m is 0, and R^{12A} and R^{13A} are independently absent or hydrogen.

76. The use or method of Claim 74, wherein m is 1, and R^{12A} , R^{13A} and R^{14A} are independently absent or hydrogen.

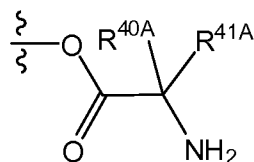
77. The use or method of Claim 16, wherein R^{1A} is H.

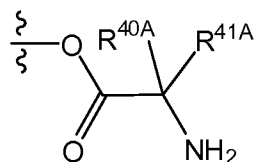
78. The use or method of Claim 16, wherein R^{1A} is an optionally substituted acyl.

79. The use or method of Claim 78, 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).

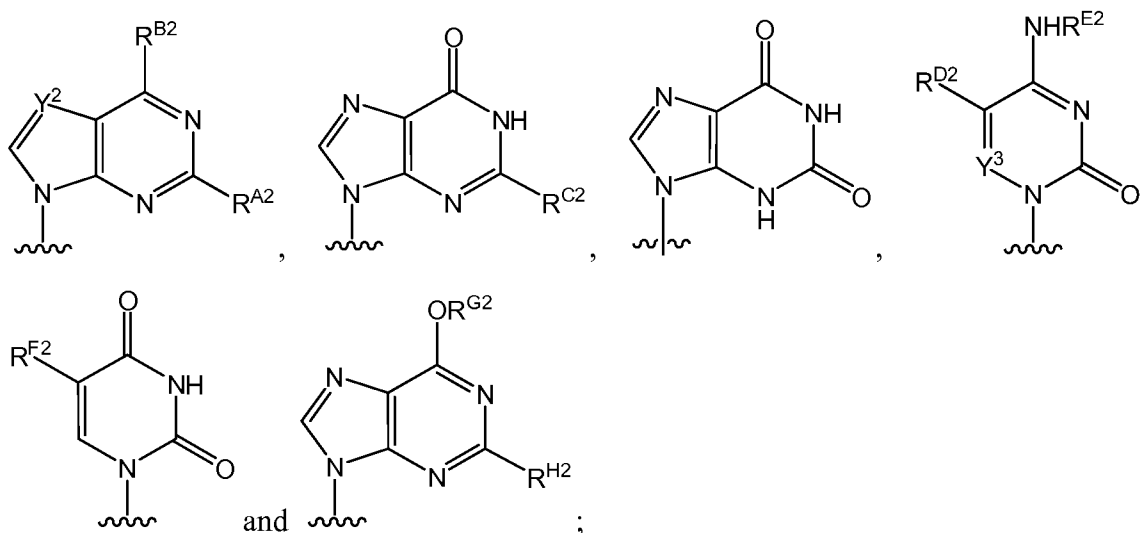
80. The use or method of Claim 79, wherein R^{39A} is substituted or unsubstituted C_{1-12} alkyl.

81. The use or method of Claim 16, wherein R^{1A} is an optionally substituted O-linked amino acid.



82. The use or method of Claim 16, 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.

83. The use or method of Claim 82, wherein R^{40A} is an optionally substituted C_{1-6} -alkyl.
84. The use or method of Claim 83, wherein the optionally substituted C_{1-6} -alkyl is methyl.
85. The use or method of any one of Claims 82-84, wherein R^{41A} is hydrogen.
86. The use or method of any one of Claims 16-85, wherein B^{1A} is selected from the group consisting of:



wherein:

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

R^{B2} is halogen or NHR^{W2} , wherein R^{W2} is selected from the group consisting of hydrogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl, an optionally substituted C_{3-8} cycloalkyl, $-C(=O)R^{M2}$ and $-C(=O)OR^{N2}$;

R^{C2} is hydrogen or NHR^{O2} , wherein R^{O2} is selected from the group consisting of hydrogen, $-C(=O)R^{P2}$ and $-C(=O)OR^{Q2}$;

R^{D2} is selected from the group consisting of hydrogen, halogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl and an optionally substituted C_{2-6} alkynyl;

R^{E2} is selected from the group consisting of hydrogen, 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;

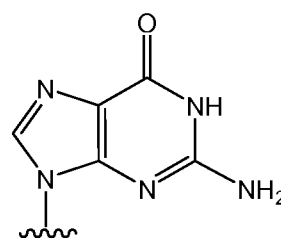
Y^2 and Y^3 are independently N or CR^{I2} , wherein R^{I2} is selected from the group consisting of hydrogen, halogen, an optionally substituted C_{1-6} -alkyl, an optionally substituted C_{2-6} -alkenyl and an optionally substituted C_{2-6} -alkynyl;

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

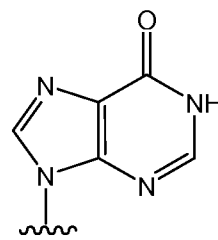
R^{H2} is hydrogen or NHR^{T2} , wherein R^{T2} is independently selected from the group consisting of hydrogen, $-C(=O)R^{U2}$ and $-C(=O)OR^{V2}$; and

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

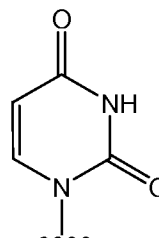
87. The use or method of Claim 86, wherein B^{1A} is



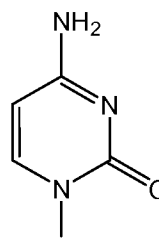
88. The use or method of Claim 86, wherein B^{1A} is



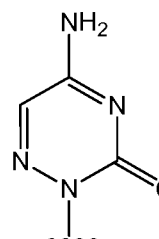
89. The use or method of Claim 86, wherein B^{1A} is

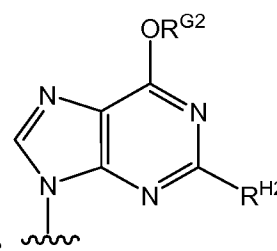


90. The use or method of Claim 86, wherein B^{1A} is



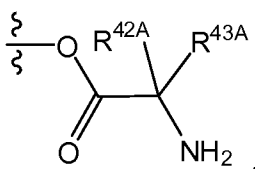
91. The use or method of Claim 86, wherein B^{1A} is



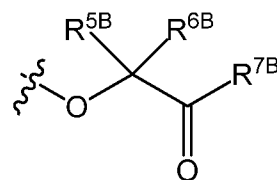


92. The use or method of Claim 86, wherein B^{1A} is .
93. The use or method of any one of Claims 16-92, wherein the dashed line (-----) is a single bond, R^{2A} is CH₂, and R^{3A} is O.
94. The use or method of any one of Claims 16-92, wherein the dashed line (-----) is absent, R^{2A} is selected from the group consisting of an optionally substituted C₁₋₆ alkyl, an optionally substituted C₂₋₆ alkenyl, an optionally substituted C₂₋₆ alkynyl, an optionally substituted -O-C₁₋₆ alkyl, an optionally substituted -O-C₃₋₆ alkenyl, an optionally substituted -O-C₃₋₆ alkynyl and cyano, and R^{3A} is selected from the group consisting of OH, -OC(=O)R^{3A} and an optionally substituted O-linked amino acid.
95. The use or method of Claim 94, wherein R^{2A} is an optionally substituted C₁₋₆ alkyl.
96. The use or method of Claim 95, wherein R^{2A} is unsubstituted C₁₋₆ alkyl.
97. The use or method of Claim 94, wherein R^{2A} is an optionally substituted C₂₋₆ alkenyl.
98. The use or method of Claim 97, wherein R^{2A} is unsubstituted C₂₋₆ alkenyl.
99. The use or method of Claim 94, wherein R^{2A} is an optionally substituted C₂₋₆ alkynyl.
100. The use or method of Claim 99, wherein R^{2A} is unsubstituted C₂₋₆ alkynyl.
101. The use or method of Claim 94, wherein R^{2A} is an optionally substituted C₃₋₆ cycloalkyl.
102. The use or method of Claim 94, wherein R^{2A} is an optionally substituted -O-C₁₋₆ alkyl.
103. The use or method of Claim 102, wherein R^{2A} is unsubstituted -O-C₁₋₆ alkyl.
104. The use or method of Claim 94, wherein R^{2A} is an optionally substituted -O-C₃₋₆ alkenyl.
105. The use or method of Claim 104, wherein R^{2A} is unsubstituted -O-C₃₋₆ alkenyl.
106. The use or method of Claim 94, wherein R^{2A} is an optionally substituted -O-C₃₋₆ alkynyl.
107. The use or method of Claim 106, wherein R^{2A} is unsubstituted -O-C₃₋₆ alkynyl.
108. The use or method of Claim 94, wherein R^{2A} is cyano.
109. The use or method of any one of Claims 16-108, wherein R^{3A} is OH.

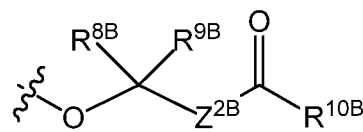
110. The use or method of any one of Claims 16-108, wherein R^{3A} is $-OC(=O)R^{7A}$.
111. The use or method of Claim 110, wherein R^{7A} is an optionally substituted C_{1-8} alkyl.
112. The use or method of any one of Claims 16-108, wherein R^{3A} is O-linked amino acid.
113. The use or method of Claim 112, 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 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.

114. The use or method of any one of Claims 16-108, 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.

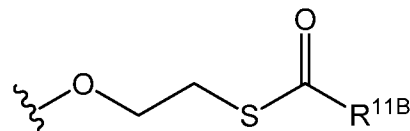
115. The use or method of Claim 114, wherein R^{42A} is an optionally substituted C_{1-6} -alkyl.
116. The use or method of Claim 115, wherein the optionally substituted C_{1-6} -alkyl is methyl.
117. The use or method of any one of Claims 114-116, wherein R^{43A} is hydrogen.
118. The use or method of any one of Claims 16- 117, wherein R^{5A} is hydrogen.
119. The use or method of any one of Claims 16-117, wherein R^{5A} is halogen.
120. The use or method of Claim 119, wherein R^{5A} is fluoro.
121. The use or method of any one of Claims 16-120, wherein R^{4A} is fluoro.
122. The use of any one of Claim 1 or 3-15 or the method of any one of Claims 2-15, wherein the compound is a compound of Formula (II).
123. The use or method of Claim 122, wherein R^{1B} is O^- or OH .



124. The use or method of Claim 122, wherein R^{1B} is



125. The use or method of Claim 122, wherein R^{1B} is



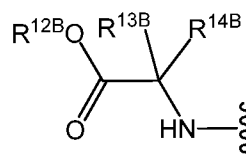
126. The use or method of Claim 122, wherein R^{1B} is

127. The use or method of Claim 122, wherein R^{1B} is an optionally substituted N-linked amino acid or an optionally substituted N-linked amino acid ester derivative.

128. The use or method of Claim 127, 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.

129. The use or method of Claim 128, 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.

130. The use or method of Claim 127, wherein R^{1B} has the structure



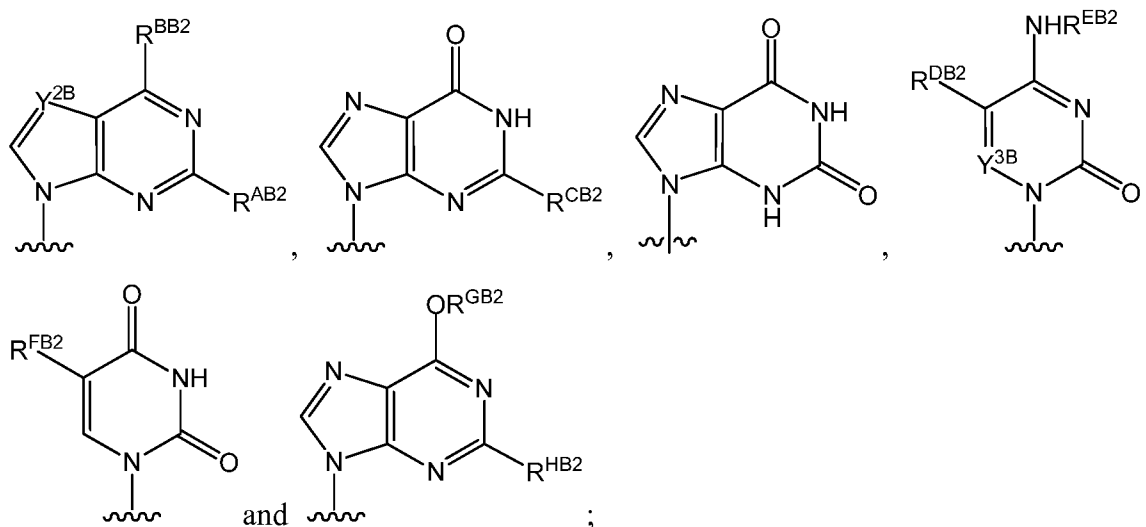
wherein R^{12B} is selected from the group consisting of hydrogen, an optionally substituted C₁₋₆-alkyl, an optionally substituted C₃₋₆ cycloalkyl, an optionally substituted aryl, an optionally substituted aryl(C₁₋₆ alkyl) and an optionally substituted haloalkyl; R^{13B} is selected from the group consisting of hydrogen, an optionally substituted C₁₋₆ alkyl, an optionally substituted C₁₋₆ haloalkyl, an optionally substituted C₃₋₆ cycloalkyl, an optionally substituted C₆ aryl, an optionally substituted C₁₀ aryl and an optionally substituted aryl(C₁₋₆ alkyl); and R^{14B} is hydrogen or an optionally substituted C₁₋₄-alkyl; or R^{13B} and R^{14B} are taken together to form an optionally substituted C₃₋₆ cycloalkyl.

131. The use or method of Claim 130, wherein R^{13B} is an optionally substituted C₁₋₆-alkyl.

132. The use or method of Claim 131, wherein the optionally substituted C₁₋₆-alkyl is methyl.

133. The use or method of any one of Claims 130-132, wherein R^{14B} is hydrogen.

134. The use or method of any one of Claims 130-133, wherein R^{12B} is an optionally substituted C_{1-6} alkyl, an optionally substituted C_{3-6} cycloalkyl or an optionally substituted benzyl.
135. The use or method of any one of Claims 122-134, wherein R^{2B} is an optionally substituted C_{1-6} alkyl.
136. The use or method of Claim 135, wherein R^{2B} is unsubstituted C_{1-6} alkyl.
137. The use or method of any one of Claims 122-134, wherein R^{2B} is an optionally substituted C_{2-6} alkenyl.
138. The use or method of Claim 137, wherein R^{2B} is unsubstituted C_{2-6} alkenyl.
139. The use or method of any one of Claims 122-134, wherein R^{2B} is an optionally substituted C_{2-6} alkynyl.
140. The use or method of Claim 139, wherein R^{2B} is unsubstituted C_{2-6} alkynyl.
141. The use or method of any one of Claims 122-134, wherein R^{2B} is an optionally substituted $-O-C_{1-6}$ alkyl.
142. The use or method of Claim 141, wherein R^{2B} is unsubstituted $-O-C_{1-6}$ alkyl.
143. The use or method of any one of Claims 122-134, wherein R^{2B} is an optionally substituted $-O-C_{3-6}$ alkenyl.
144. The use or method of Claim 143, wherein R^{2B} is unsubstituted $-O-C_{3-6}$ alkenyl.
145. The use or method of any one of Claims 122-134, wherein R^{2B} is an optionally substituted $-O-C_{3-6}$ alkynyl.
146. The use or method of Claim 145, wherein R^{2B} is unsubstituted $-O-C_{3-6}$ alkynyl.
147. The use or method of any one of Claims 122-134, wherein R^{2B} is an optionally substituted C_{3-6} cycloalkyl.
148. The use or method of any one of Claims 122-134, wherein R^{2B} is cyano.
149. The use or method of any one of Claims 122-148, wherein R^{4B} is hydrogen.
150. The use or method of any one of Claims 122-148, wherein R^{4B} is halogen.
151. The use or method of Claim 150, wherein R^{4B} is fluoro.
152. The use or method of any one of Claims 122-151, wherein R^{3B} is fluoro.
153. The use or method of any one of Claims 122-152, wherein Z^{1B} is O.
154. The use or method of any one of Claims 122-152, wherein Z^{1B} is S.
155. The use or method of any one of Claims 122-154, wherein B^{1B} is selected from the group consisting of:



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, 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 $-C(=O)OR^{SB2}$;

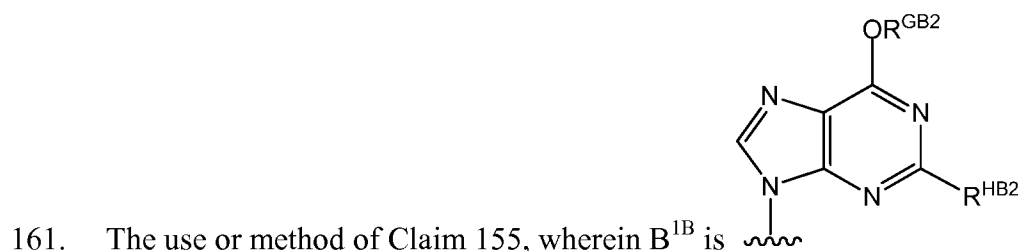
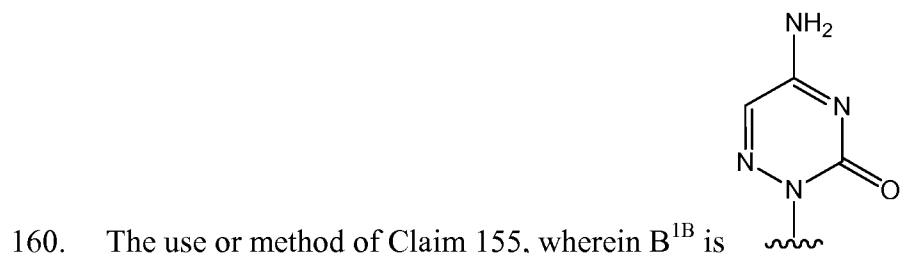
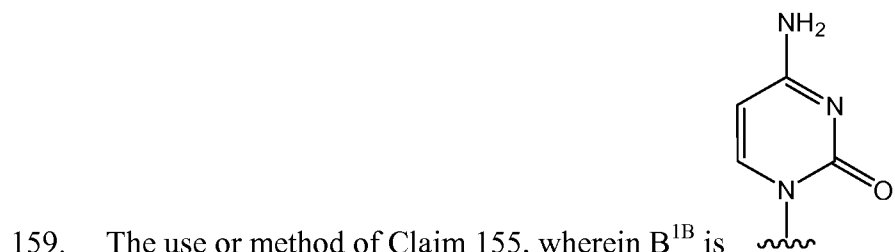
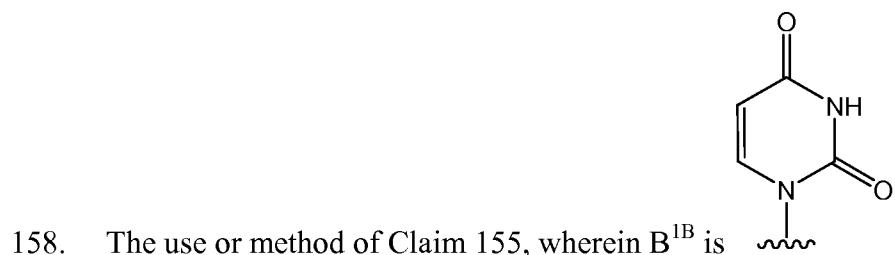
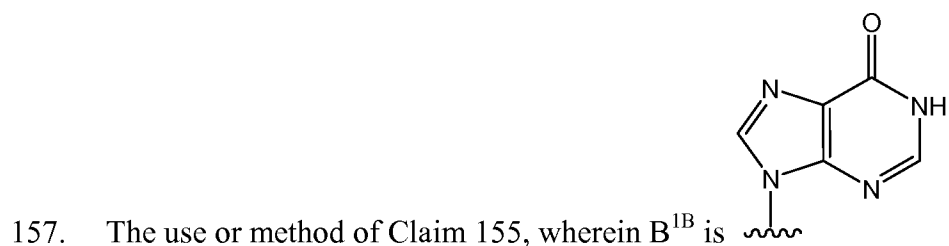
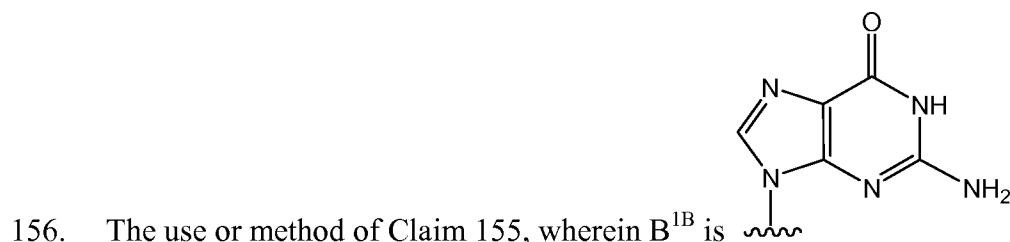
R^{FB2} is selected from the group consisting of hydrogen, halogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl and an optionally substituted C_{2-6} alkynyl;

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

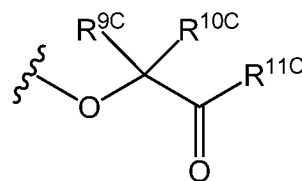
R^{KB2} , R^{LB2} , R^{MB2} , R^{NB2} , R^{PB2} , R^{QB2} , R^{RB2} , R^{SB2} , R^{UB2} and R^{VB2} are independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkenyl, C_{6-10} aryl, heteroaryl, heteroalicycyl, aryl(C_{1-6} alkyl), heteroaryl(C_{1-6} alkyl) and heteroalicycyl(C_{1-6} alkyl).



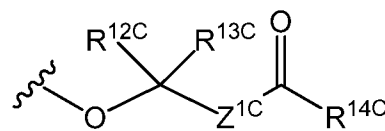
162. The use of any one of Claim 1 or 3-15 or the method of any one of Claims 2-15, wherein the compound is a compound of Formula (III).

163. The use or method of Claim 162, wherein R^{1C} is O^- or OH .

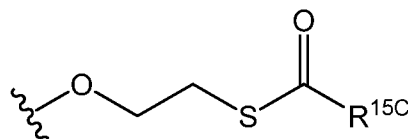
164. The use or method of Claim 162, wherein R^{1C} is an optionally substituted C_{1-6} alkoxy.



165. The use or method of Claim 162, wherein R^{1C} is



166. The use or method of Claim 162, wherein R^{1C} is



167. The use or method of Claim 162, wherein R^{1C} is

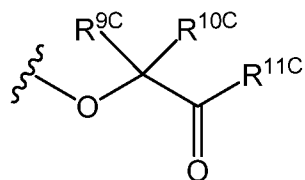
168. The use or method of Claim 162, wherein R^{1C} is an optionally substituted N-linked amino acid.

169. The use or method of Claim 162, wherein R^{1C} is an optionally substituted N-linked amino acid ester derivative.

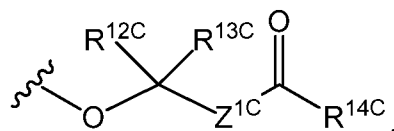
170. The use or method of any one of Claims 162-169, wherein R^{2C} is O^- or OH .

171. The use or method of any one of Claims 162-169, wherein R^{2C} is an optionally substituted C_{1-6} alkoxy.

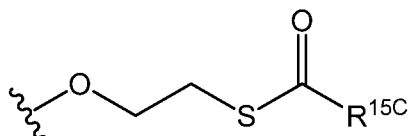
172. The use or method of any one of Claims 162-169, wherein R^{2C} is



173. The use or method of any one of Claims 162-169, wherein R^{2C} is



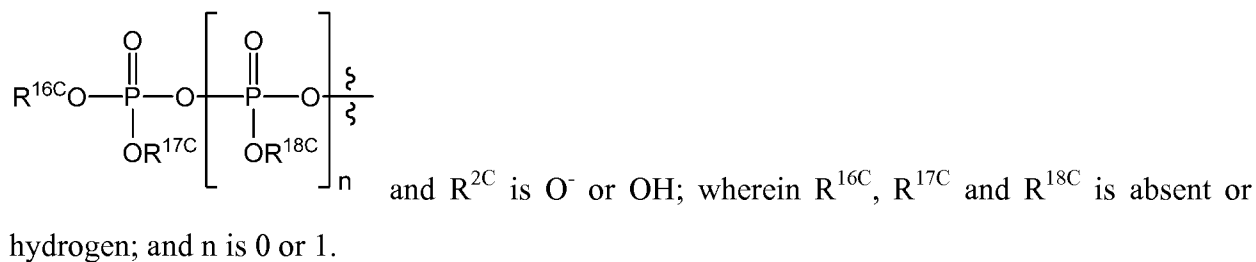
174. The use or method of any one of Claims 162-169, wherein R^{2C} is



175. The use or method of any one of Claims 162-169, wherein R^{2C} is an optionally substituted N-linked amino acid.

176. The use or method of any one of Claims 162-169, wherein R^{2C} is an optionally substituted N-linked amino acid ester derivative.

177. The use or method of any one of Claim 176, wherein R^{1C} is



178. The use or method of any one of Claims 162-177, wherein R^{3C} is an optionally substituted C_{1-6} alkyl.

179. The use or method of Claim 178, wherein R^{3C} is unsubstituted C_{1-6} alkyl.

180. The use or method of any one of Claims 162-177, wherein R^{3C} is an optionally substituted C_{2-6} alkenyl.

181. The use or method of Claim 180, wherein R^{3C} is unsubstituted C_{2-6} alkenyl.

182. The use or method of any one of Claims 162-177, wherein R^{3C} is an optionally substituted C_{2-6} alkynyl.

183. The use or method of Claim 182, wherein R^{3C} is unsubstituted C_{2-6} alkynyl.

184. The use or method of any one of Claims 162-177, wherein R^{3C} is an optionally substituted $-O-C_{1-6}$ alkyl.

185. The use or method of Claim 184, wherein R^{3C} is unsubstituted $-O-C_{1-6}$ alkyl.

186. The use or method of any one of Claims 162-177, wherein R^{3C} is an optionally substituted $-O-C_{3-6}$ alkenyl.

187. The use or method of Claim 186, wherein R^{3C} is unsubstituted $-O-C_{3-6}$ alkenyl.

188. The use or method of any one of Claims 162-177, wherein R^{3C} is an optionally substituted $-O-C_{3-6}$ alkynyl.

189. The use or method of Claim 188, wherein R^{3C} is unsubstituted $-O-C_{3-6}$ alkynyl.

190. The use or method of any one of Claims 162-177, wherein R^{3C} is an optionally substituted C_{3-6} cycloalkyl.

191. The use or method of any one of Claims 162-177, wherein R^{3C} is cyano.

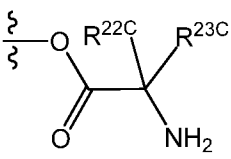
192. The use or method of any one of Claims 162-191, wherein R^{4C} is OH .

193. The use or method of any one of Claims 162-191, wherein R^{4C} is $-OC(=O)R^{nC}$.

194. The use or method of Claim 193, wherein R^{nC} is an optionally substituted C_{1-8} alkyl.

195. The use or method of any one of Claims 162-191, wherein R^{4C} is O-linked amino acid.

196. The use or method of Claim 195, 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 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.

197. The use or method of any one of Claims 162-191, 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.

198. The use or method of Claim 197, wherein R^{22C} is an optionally substituted C_{1-6} -alkyl.

199. The use or method of Claim 198, wherein the optionally substituted C_{1-6} -alkyl is methyl.

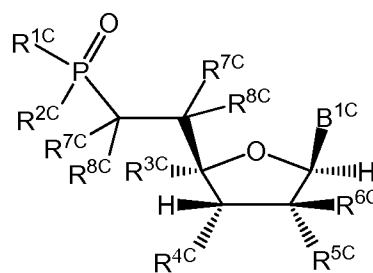
200. The use or method of any one of Claims 197-199, wherein R^{23C} is hydrogen.

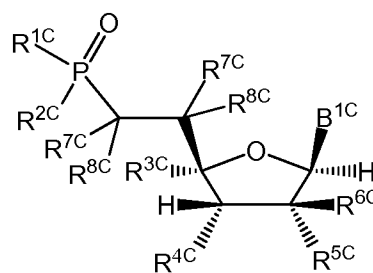
201. The use or method of any one of Claims 162-200, wherein R^{6C} is halogen.

202. The use or method of any one of Claims 162-200, wherein R^{6C} is hydrogen.

203. The use or method of any one of Claims 162-202, wherein R^{5C} is fluoro.

204. The use or method of any one of Claims 162-203, wherein ----- is a single bond



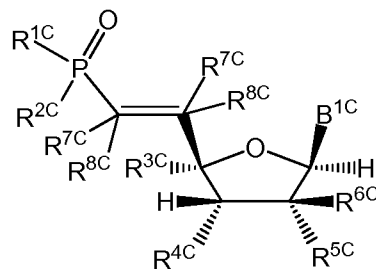
such that Formula (III) has the structure , wherein each R^{7C} and each R^{8C} is independently hydrogen or halogen.

205. The use or method of Claim 204, wherein the R^{7C} and the R^{8C} groups are all hydrogen.

206. The use or method of Claim 204, wherein one R^{7C} is halogen, one R^{7C} is hydrogen and both R^{8C} groups are all hydrogen.

207. The use or method of Claim 204, wherein one R^{7C} is halogen, one R^{7C} is hydrogen, one R^{8C} is halogen and one R^{8C} is hydrogen.

208. The use or method of any one of Claims 162-203, wherein ----- is a double



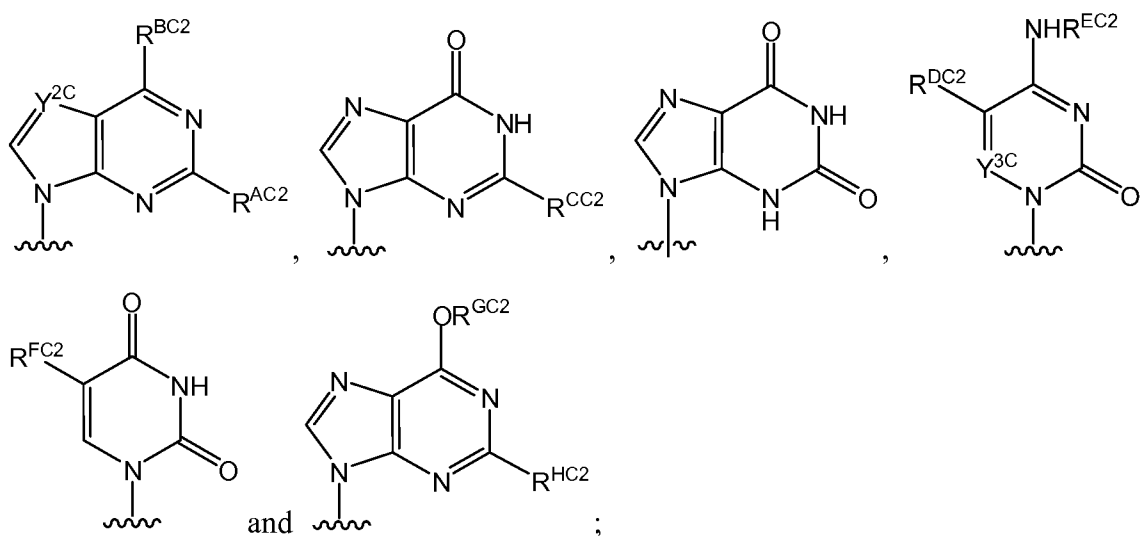
bond such that Formula (III) has the structure
absent and each R^{8C} is independently hydrogen or halogen.

209. The use or method of Claim 208, wherein both R^{8C} groups are hydrogen.

210. The use or method of Claim 208, wherein one R^{8C} is halogen and the other R^{8C} is hydrogen.

211. The use or method of Claim 208, wherein both R^{8C} groups are halogen.

212. The use or method of any one of Claims 162-211, wherein B^{1C} is selected from the group consisting of:



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 $-C(=O)OR^{SC2}$;

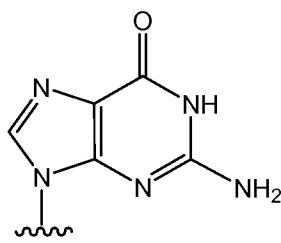
R^{FC2} is selected from the group consisting of hydrogen, halogen, an optionally substituted C_{1-6} alkyl, an optionally substituted C_{2-6} alkenyl and an optionally substituted C_{2-6} alkynyl;

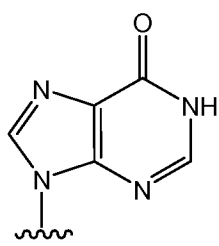
Y^{2C} and Y^{3C} are independently N or CR^{IC2} , wherein R^{IC2} is selected from the group consisting of hydrogen, halogen, an optionally substituted C_{1-6} -alkyl, an optionally substituted C_{2-6} -alkenyl and an optionally substituted C_{2-6} -alkynyl;

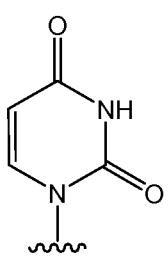
R^{GC2} is an optionally substituted C_{1-6} alkyl;

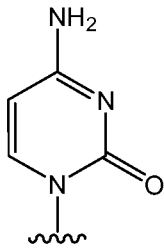
R^{HC2} is hydrogen or NHR^{TC2} , wherein R^{TC2} is independently selected from the group consisting of hydrogen, $-C(=O)R^{UC2}$ and $-C(=O)OR^{VC2}$; and

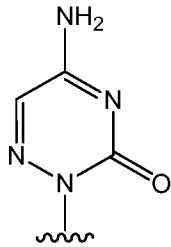
R^{KC2} , R^{LC2} , R^{MC2} , R^{NC2} , R^{PC2} , R^{QC2} , R^{RC2} , R^{SC2} , R^{UC2} and R^{VC2} are independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkenyl, C_{6-10} aryl, heteroaryl, heteroalicycyl, aryl(C_{1-6} alkyl), heteroaryl(C_{1-6} alkyl) and heteroalicycyl(C_{1-6} alkyl).

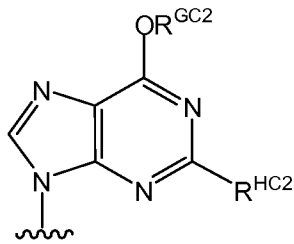
213. The use or method of Claim 212, wherein B^{1C} is  .

214. The use or method of Claim 212, wherein B^{1C} is  .

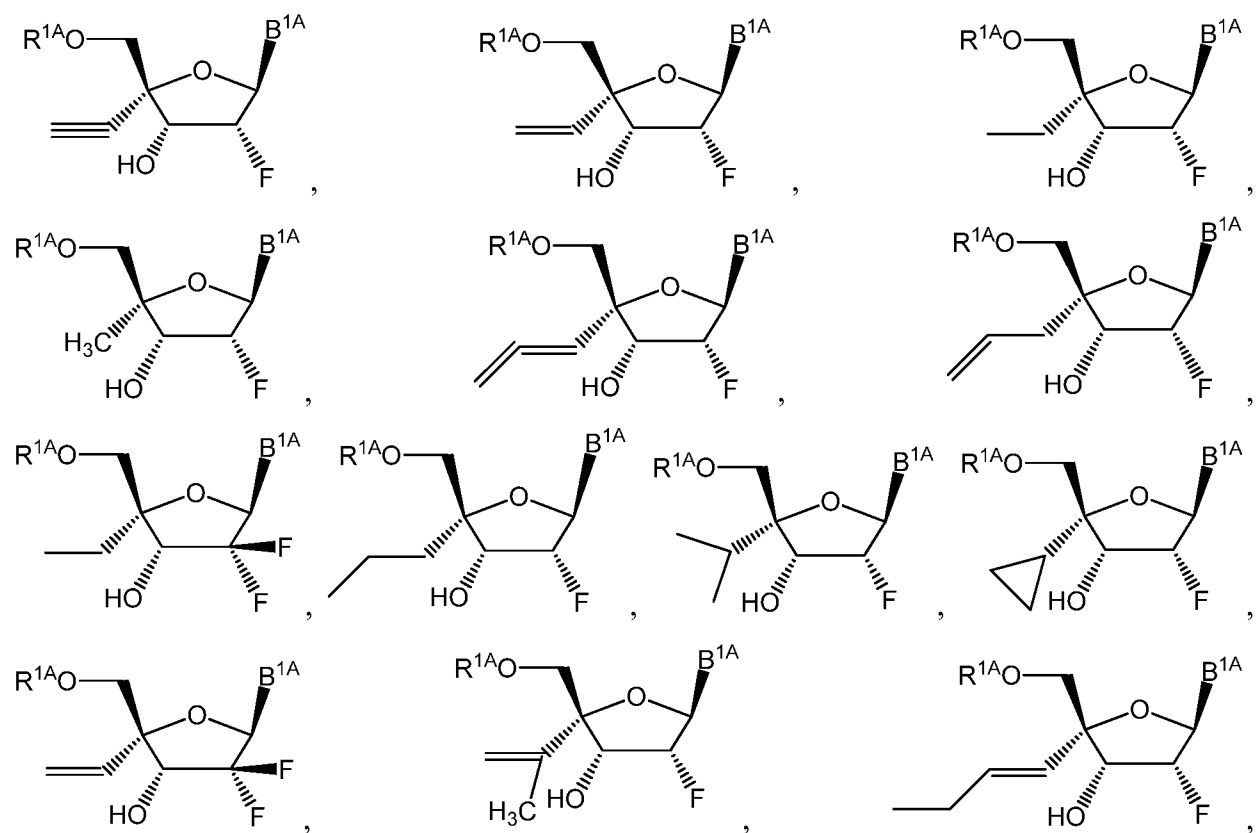
215. The use or method of Claim 212, wherein B^{1C} is  .

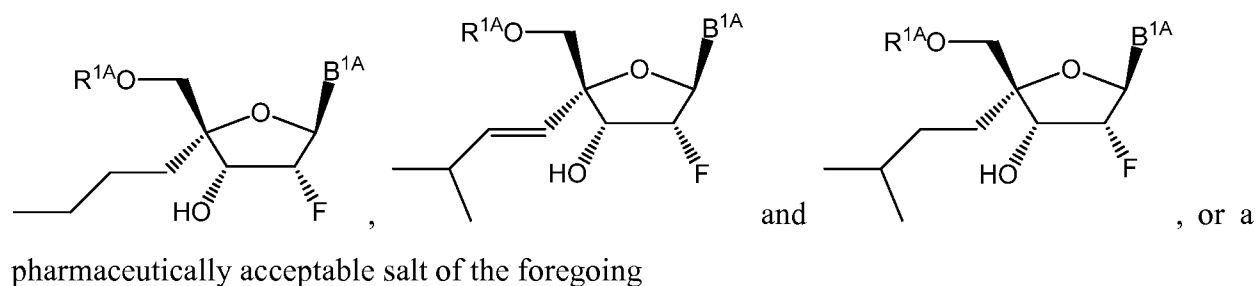
216. The use or method of Claim 212, wherein B^{1C} is  .

217. The use or method of Claim 212, wherein B^{1C} is  .

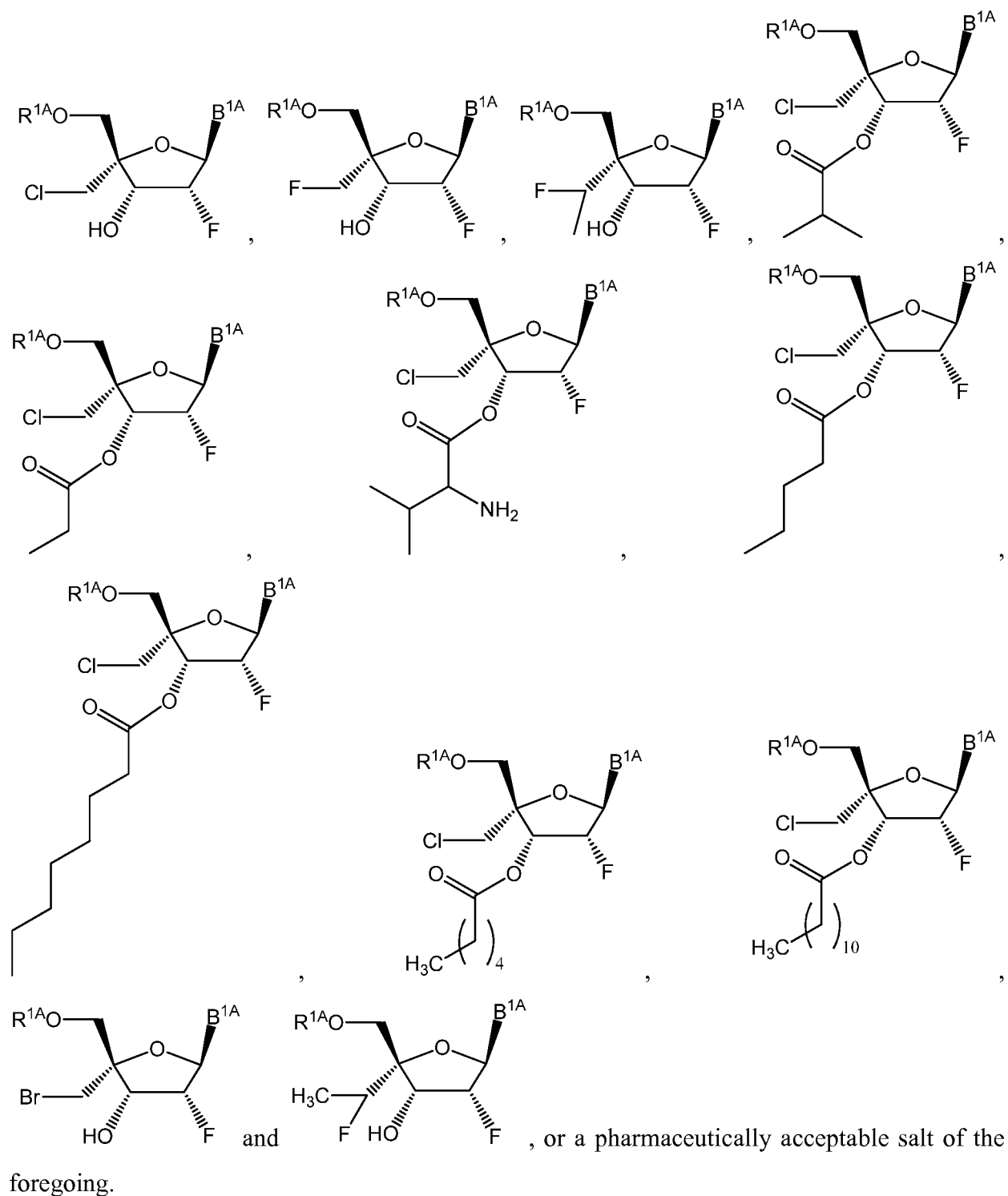
218. The use or method of Claim 212, wherein B^{1C} is  .

219. The use or method of Claim 16, wherein the compound of Formula (I) is selected from the group consisting of:

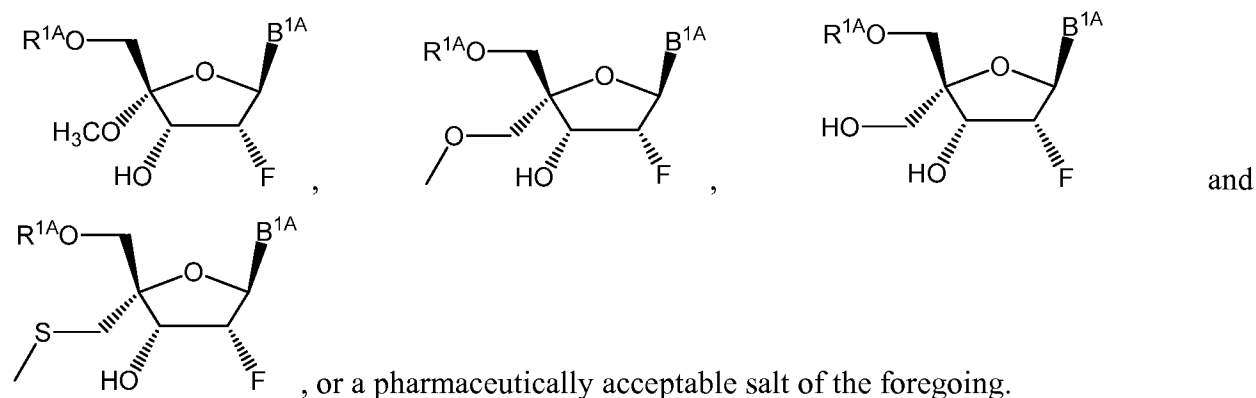




220. The use or method of Claim 16, wherein the compound of Formula (I) is selected from the group consisting of:



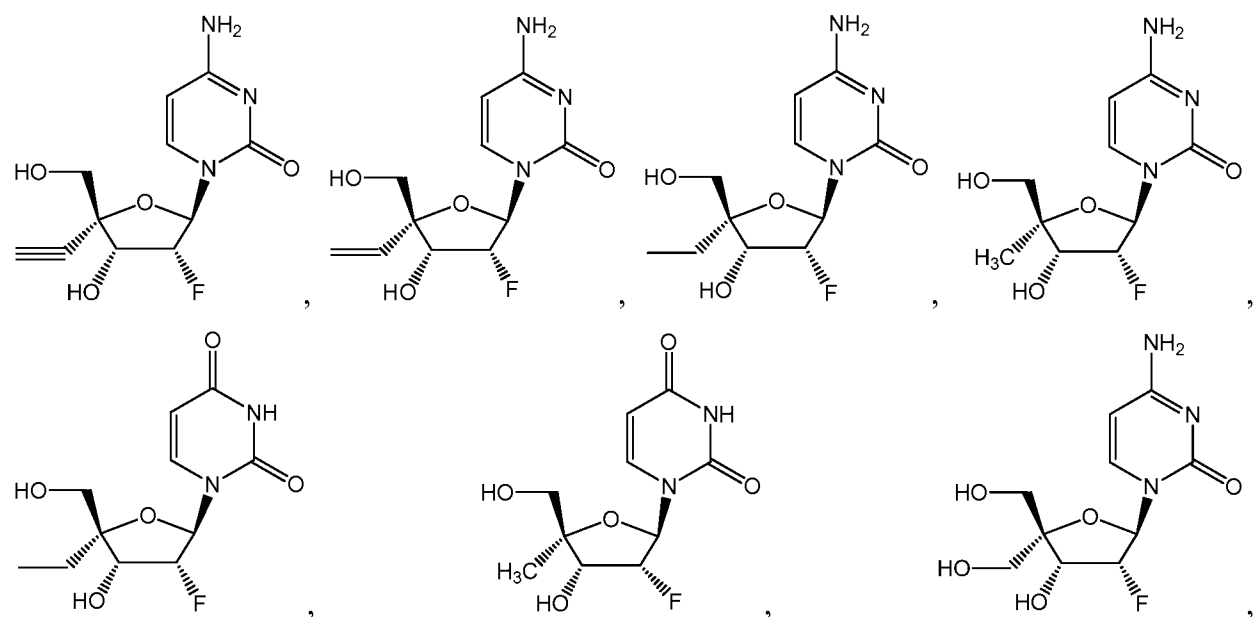
221. The use or method of Claim 16, wherein the compound of Formula (I) is selected from the group consisting of:



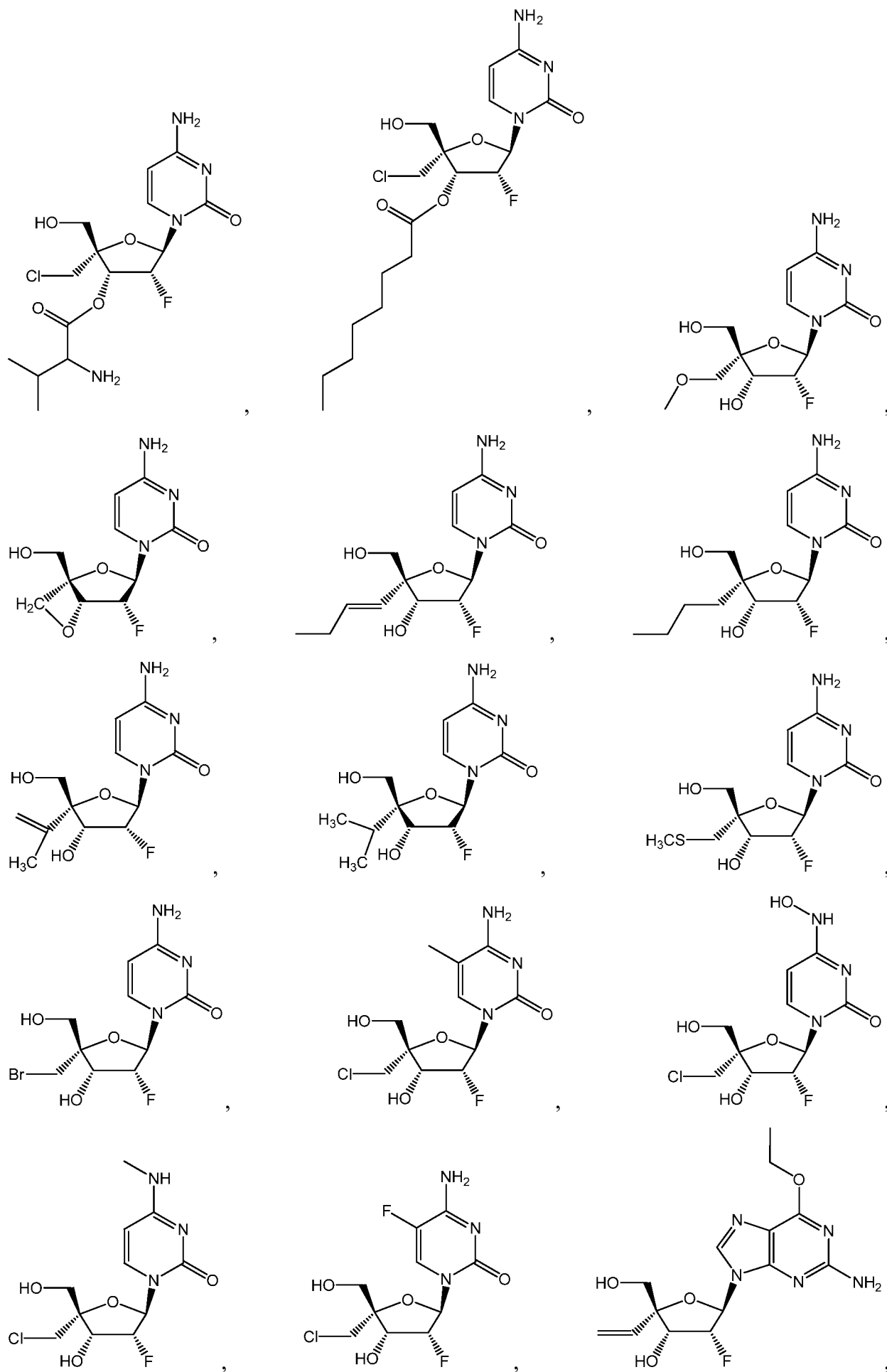
222. The use or method of Claim 16, wherein the compound of Formula (I) is , or a pharmaceutically acceptable salt thereof.

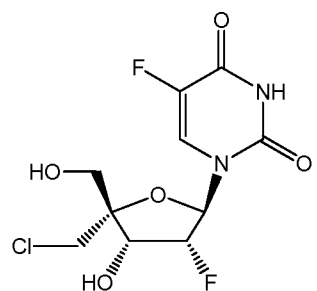
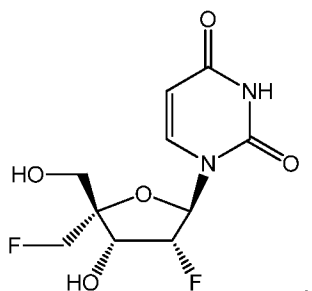
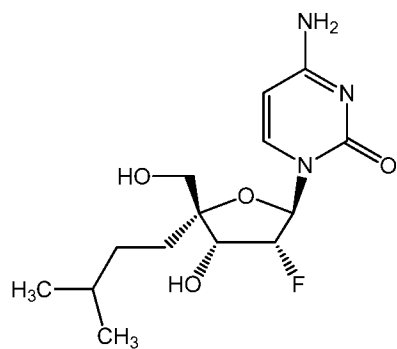
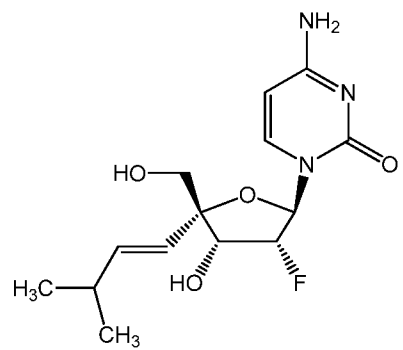
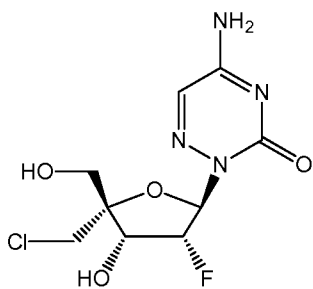
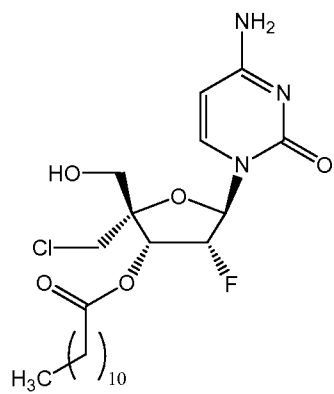
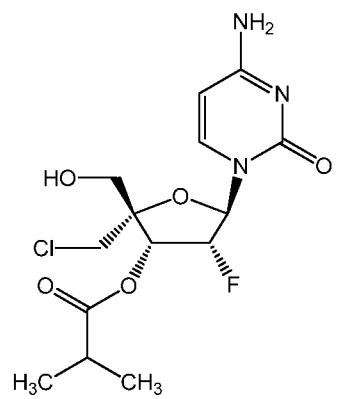
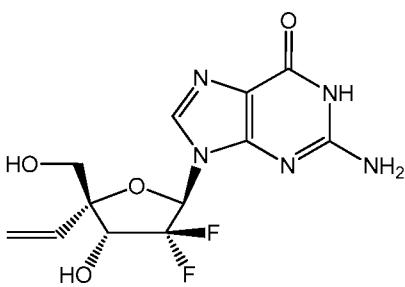
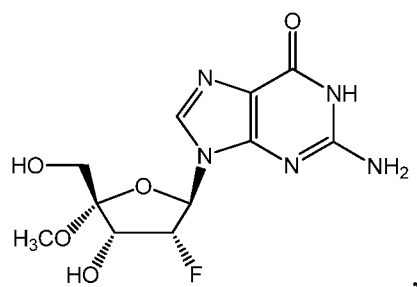
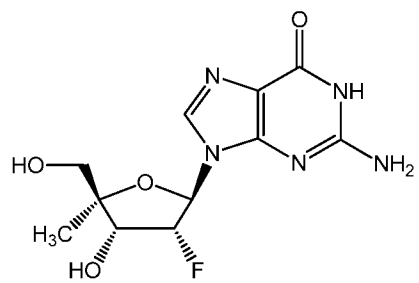
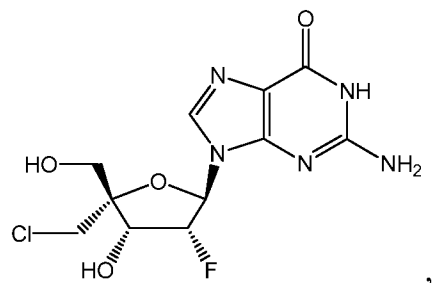
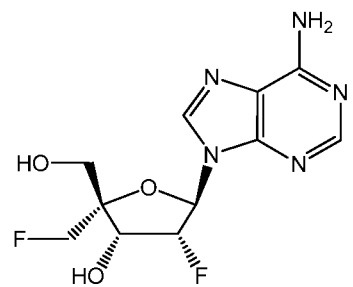
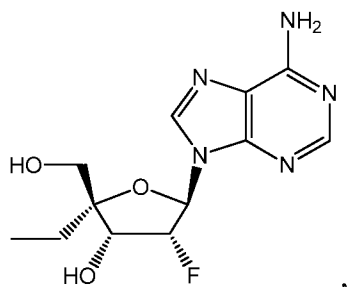
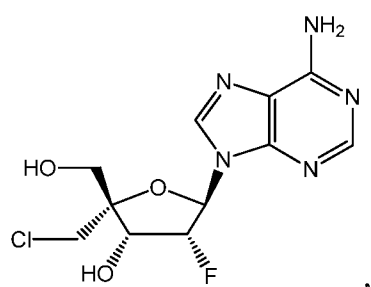
223. The use or method of Claim 16, wherein the compound of Formula (I) is , or a pharmaceutically acceptable salt thereof.

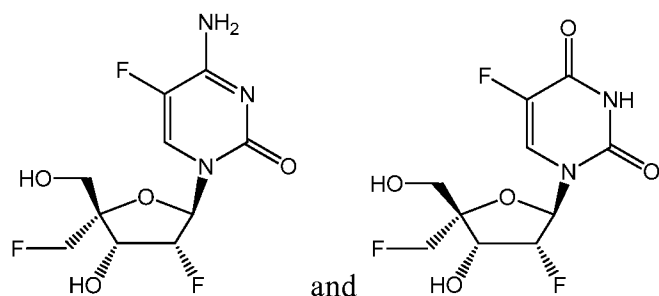
224. The use or method of Claim 16, wherein the compound of Formula (I) is selected from the group consisting of:





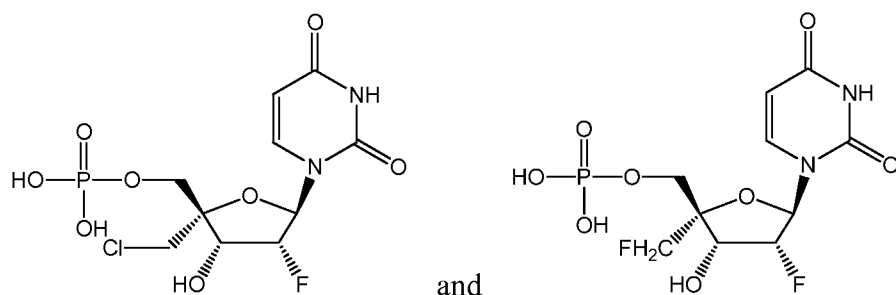






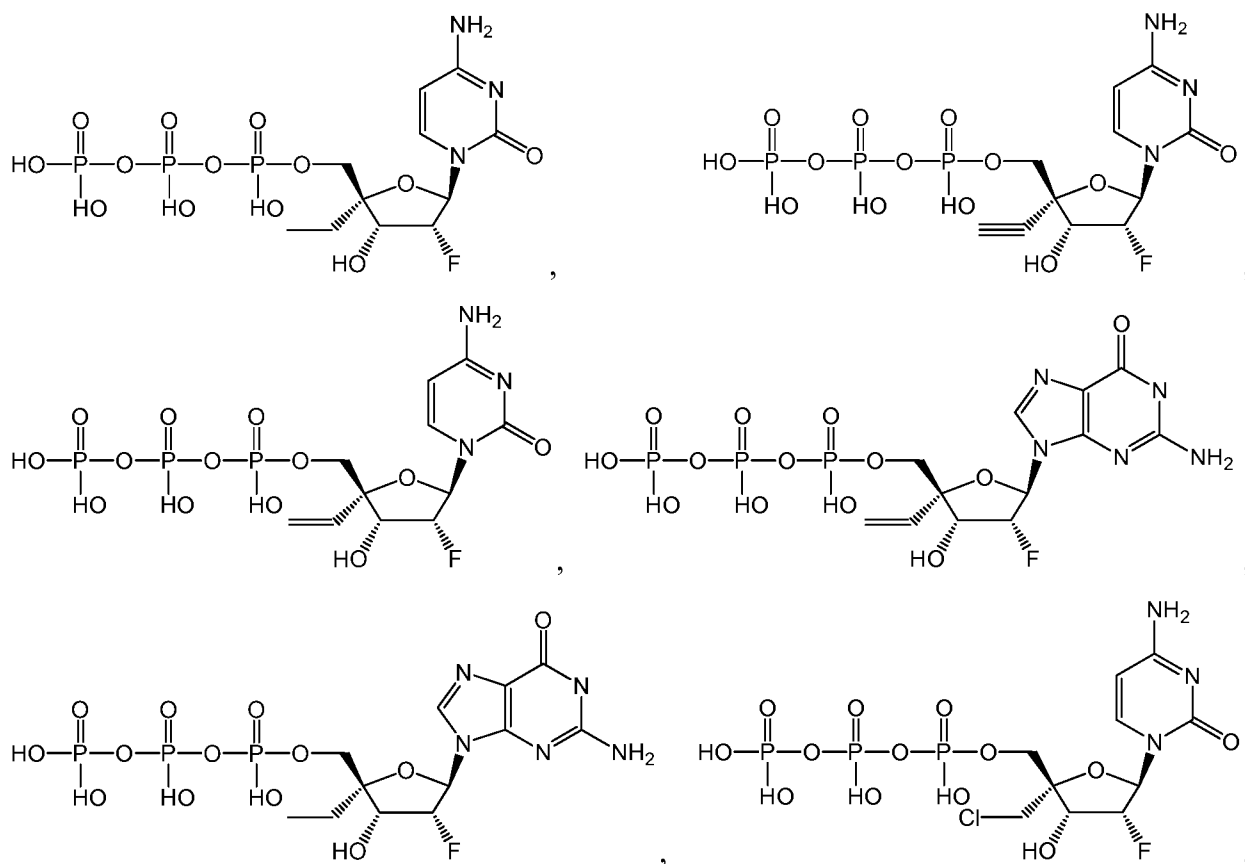
and , or a pharmaceutically acceptable salt of the foregoing.

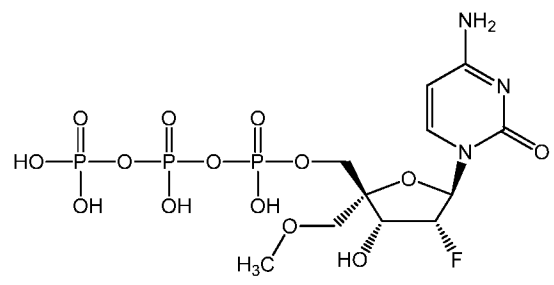
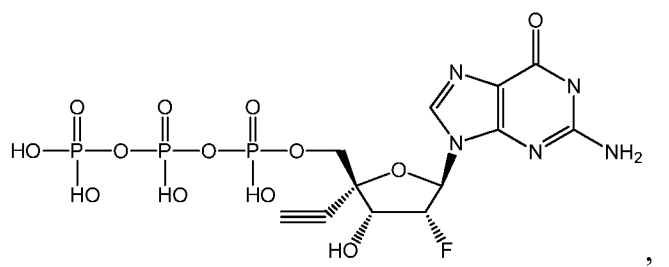
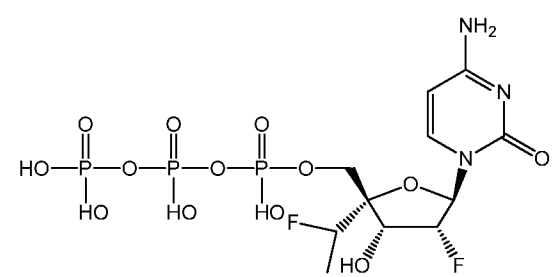
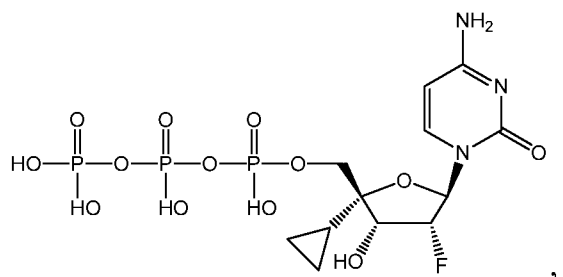
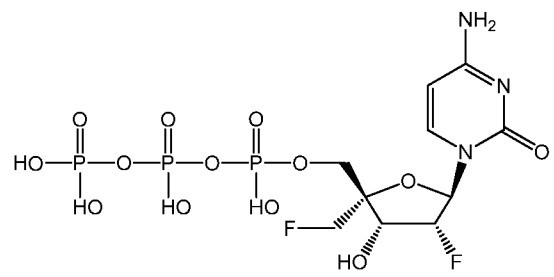
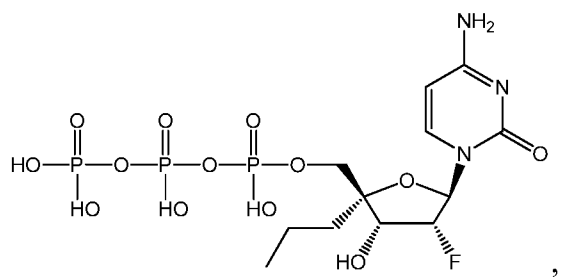
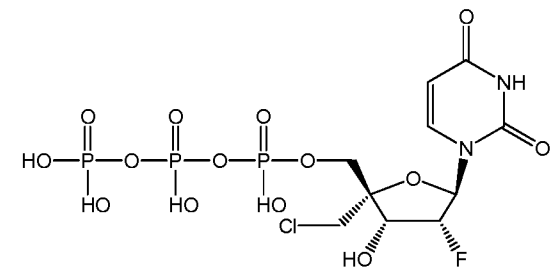
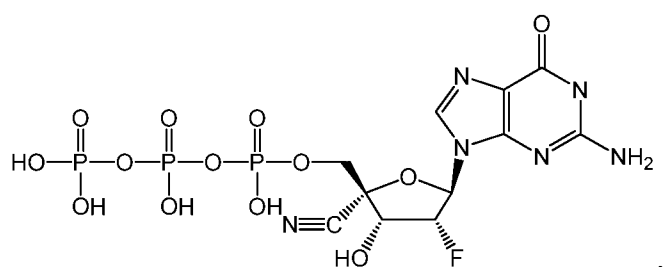
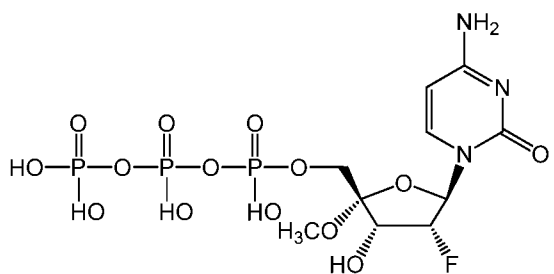
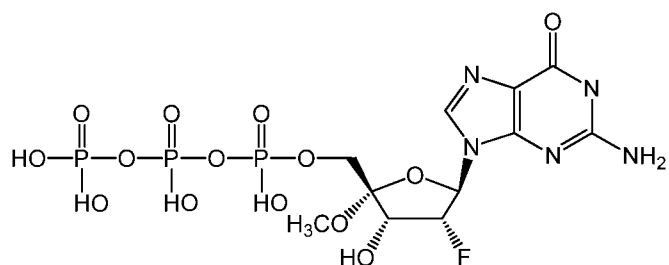
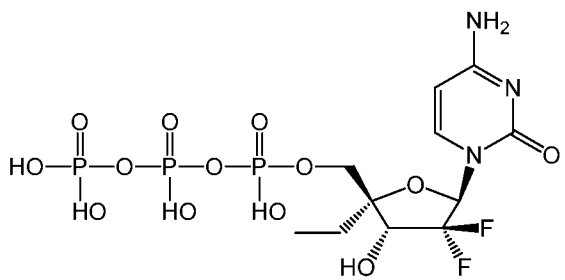
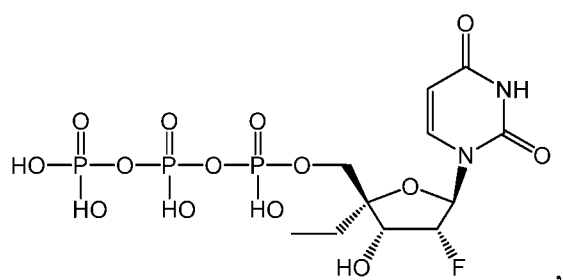
225. The use or method of Claim 16, wherein the compound of Formula (I) is selected from the group consisting of:

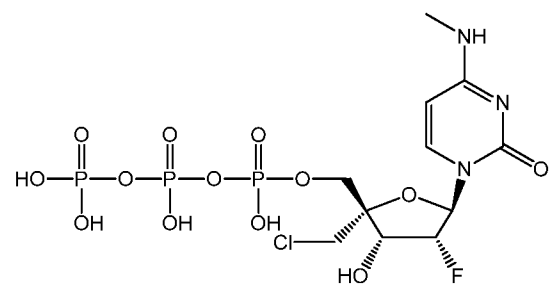
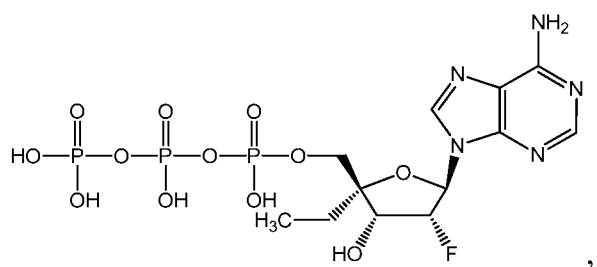
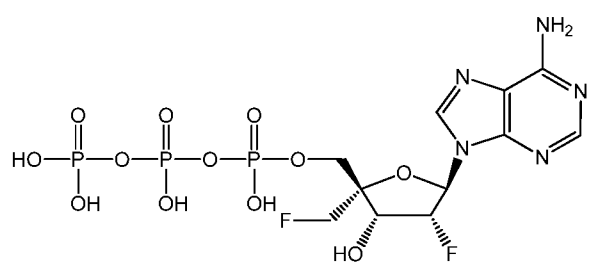
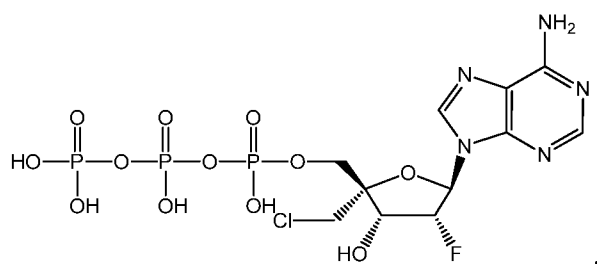
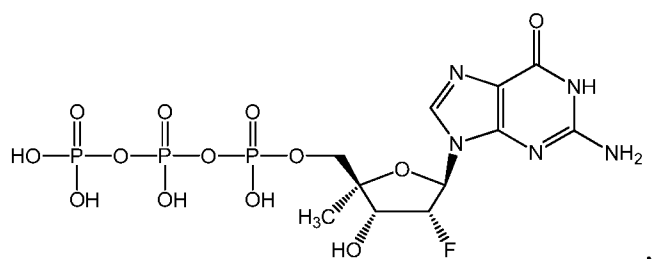
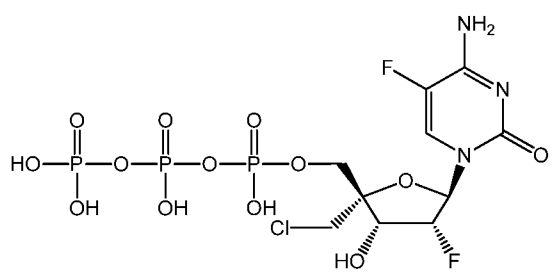
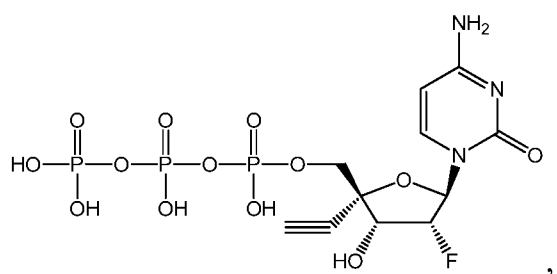
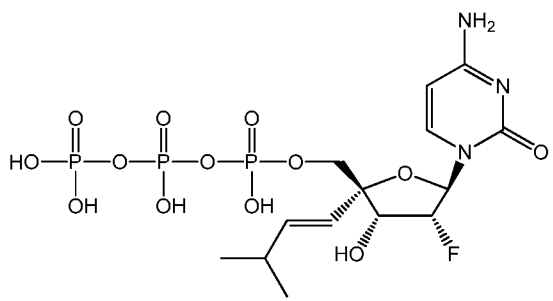
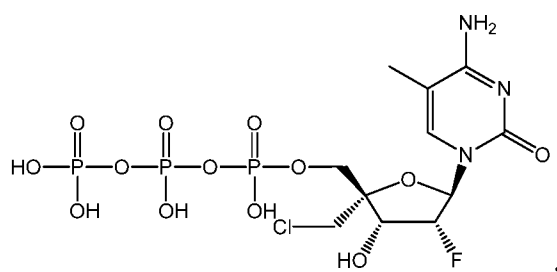
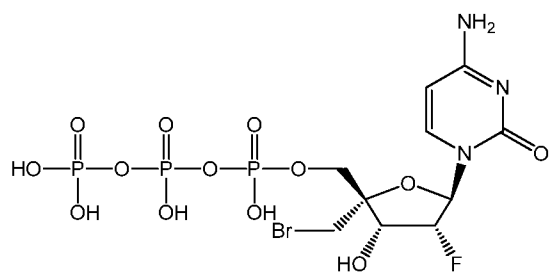
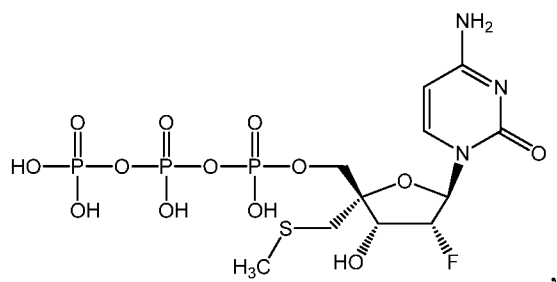


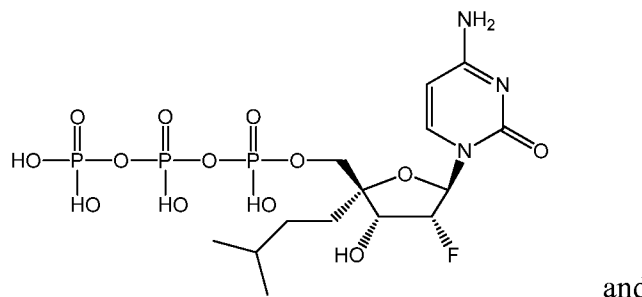
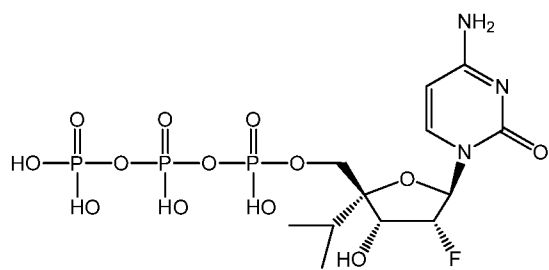
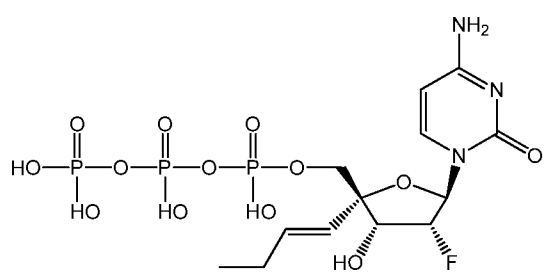
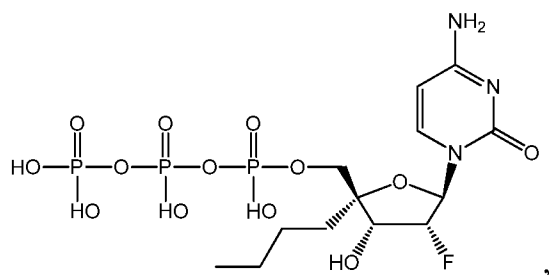
and , or a pharmaceutically acceptable salt of the foregoing.

226. The use or method of Claim 16, wherein the compound of Formula (I) is selected from the group consisting of:

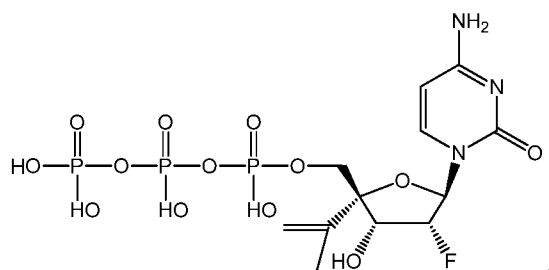








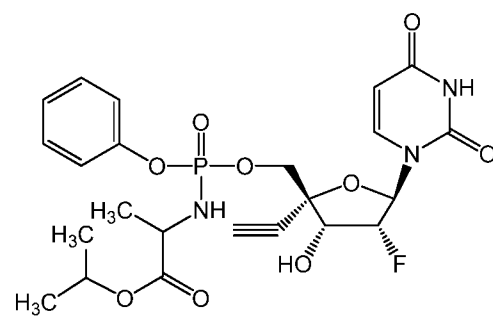
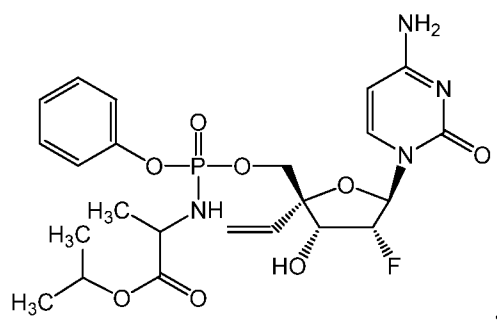
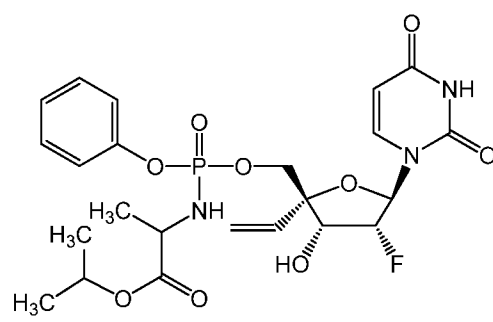
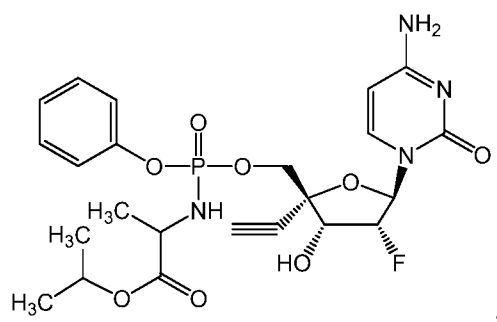
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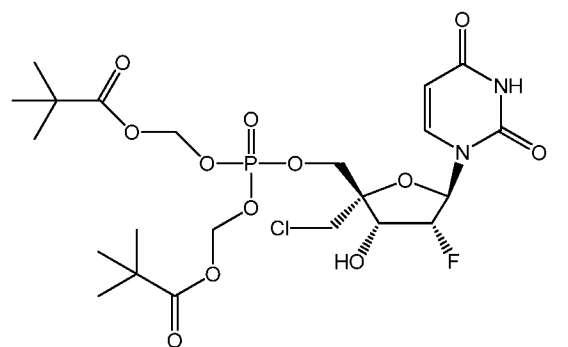
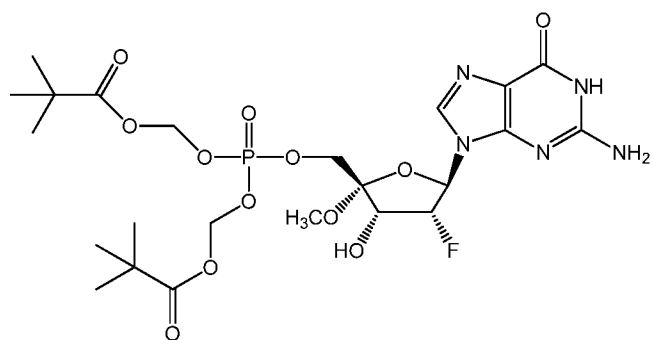
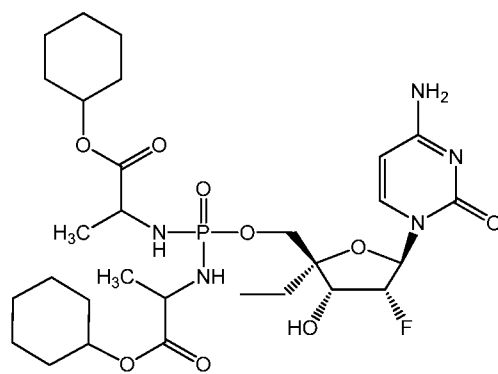
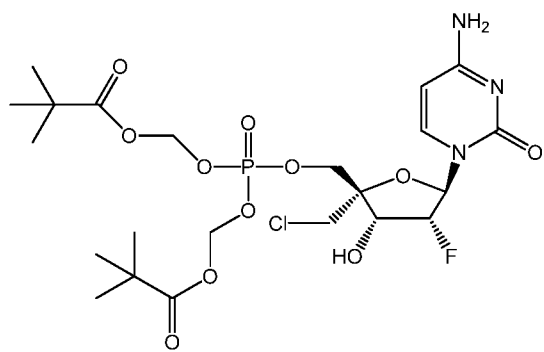
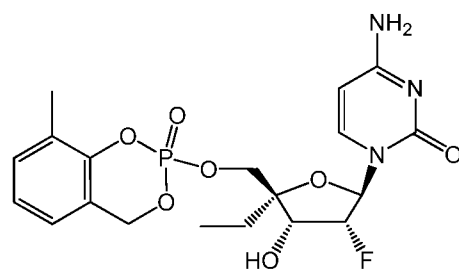
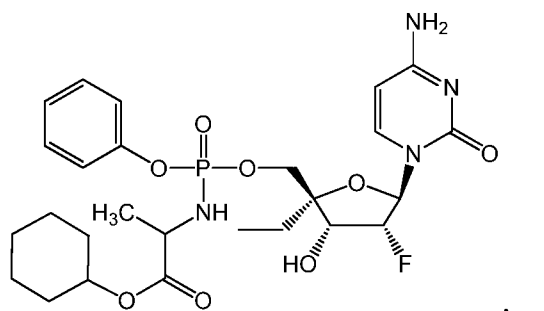
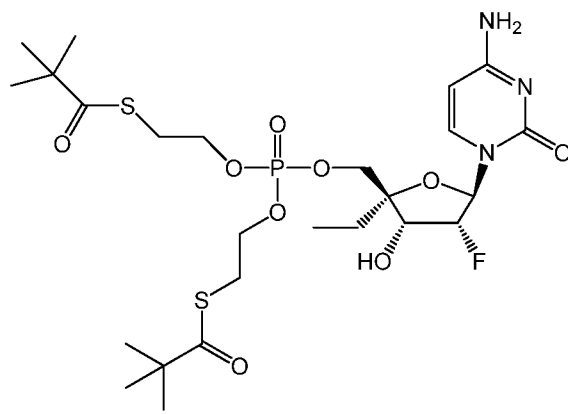
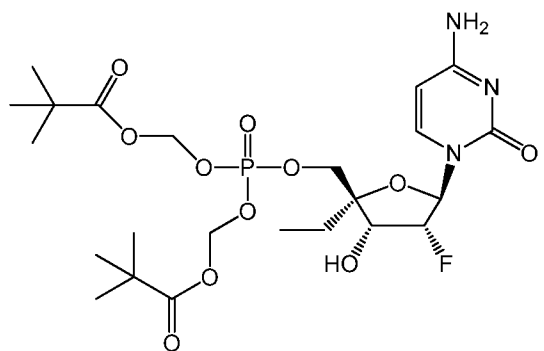
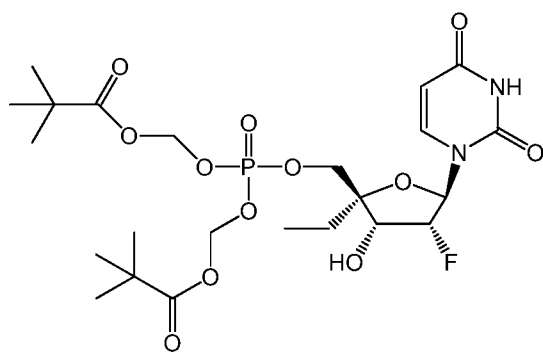
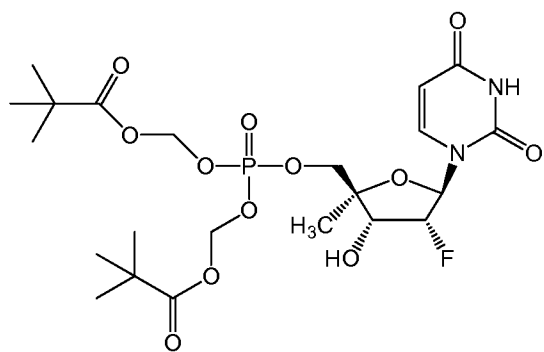


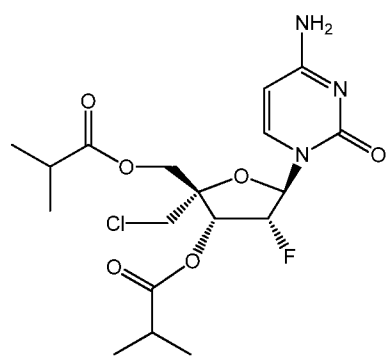
, or a pharmaceutically acceptable salt of the

foregoing.

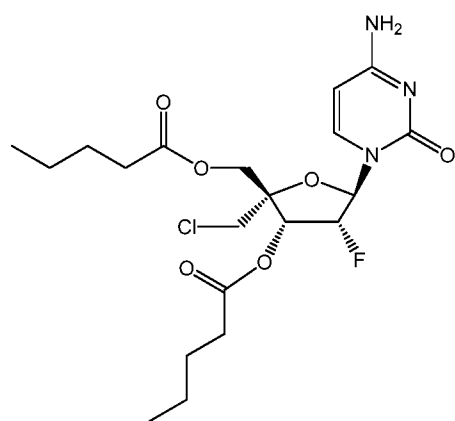
227. The use or method of Claim 16, wherein the compound of Formula (I) is selected from the group consisting of:





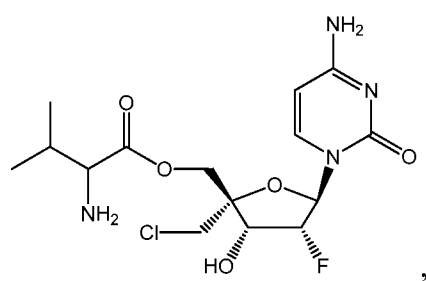


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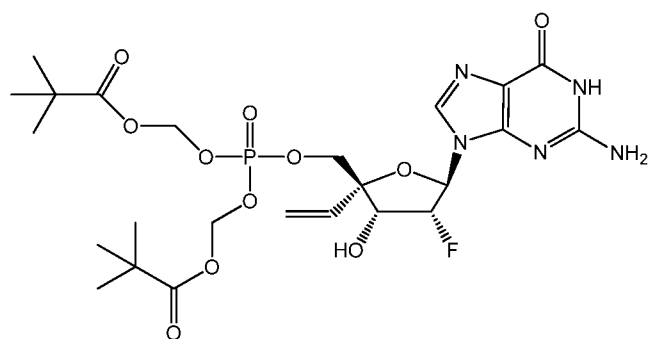


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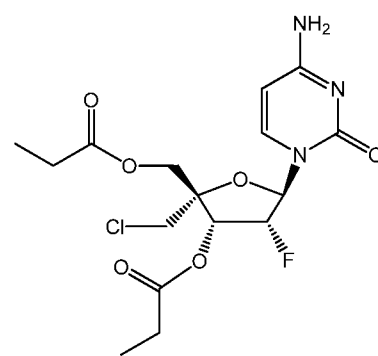
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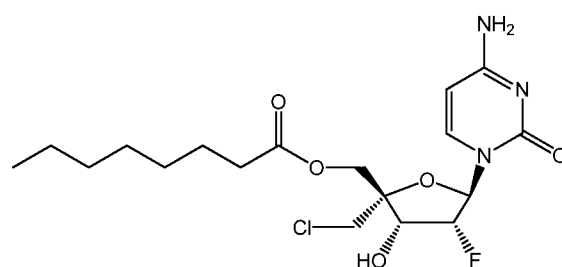
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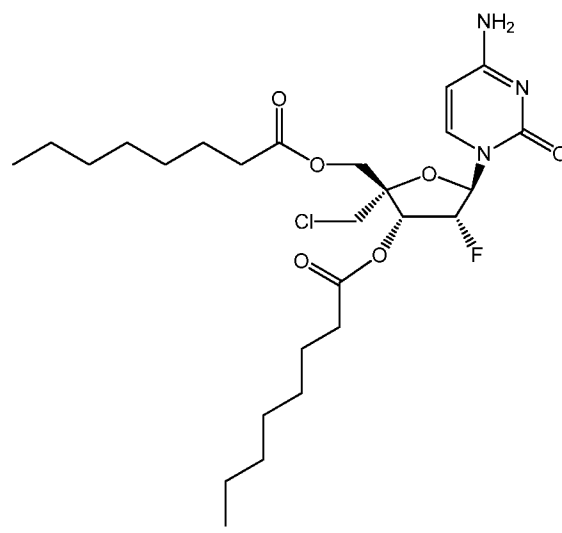
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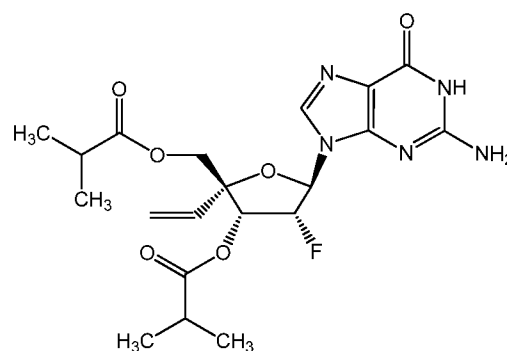
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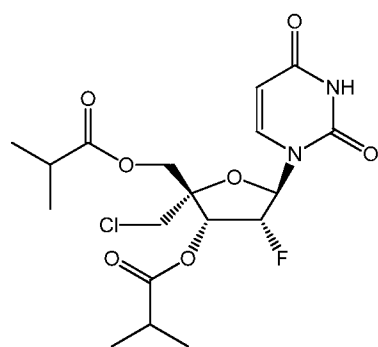
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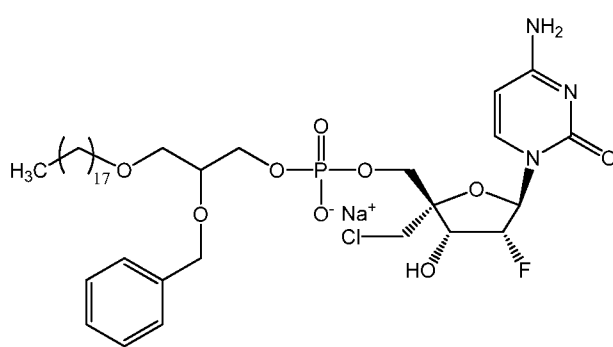
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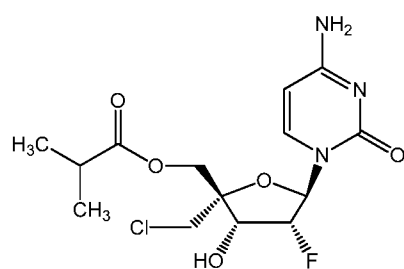
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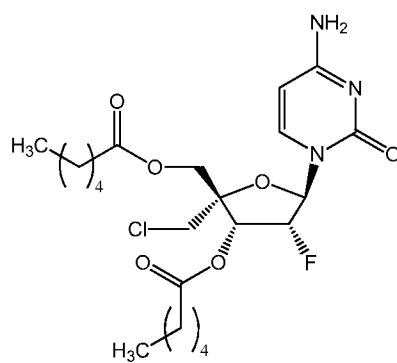
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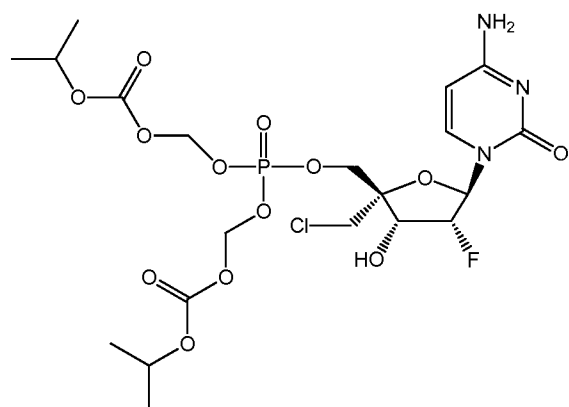
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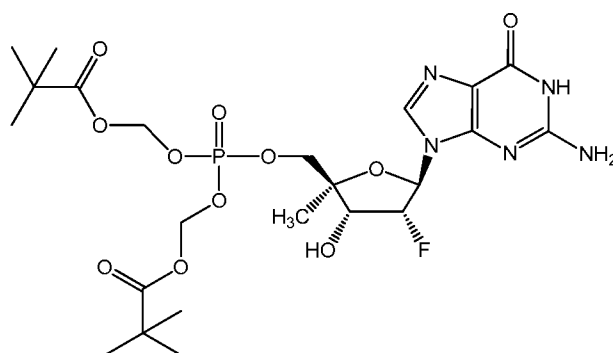
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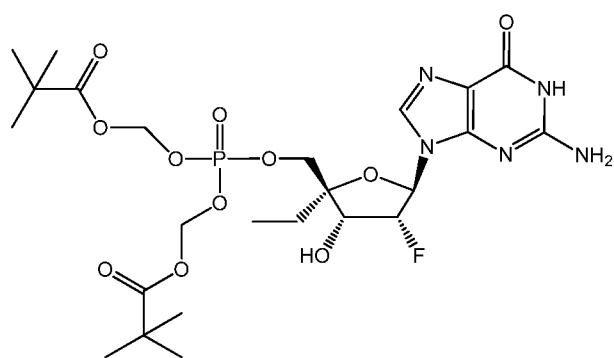
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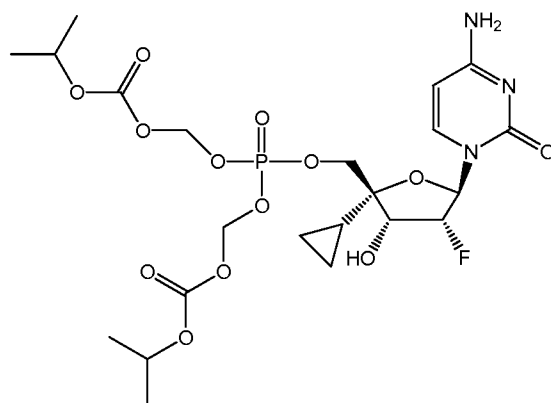
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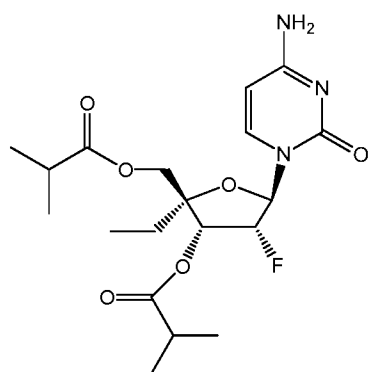
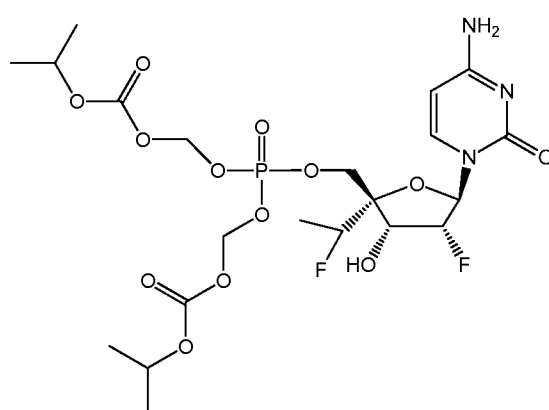
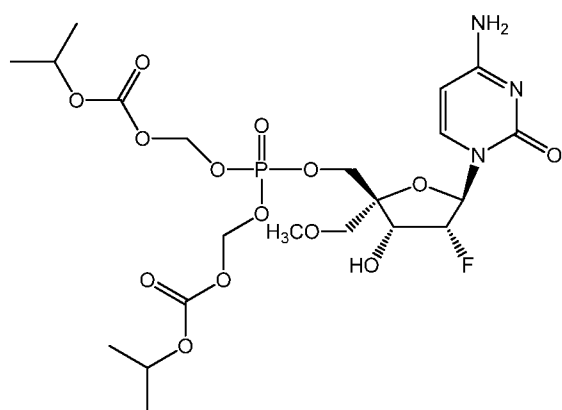
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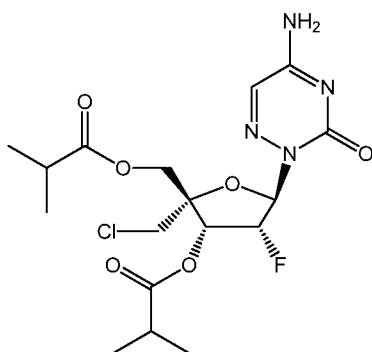
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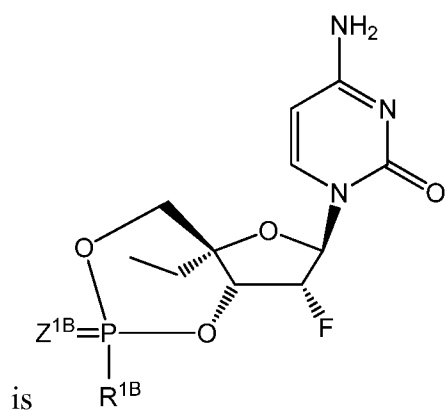
, and



, or a pharmaceutically acceptable

salt of the foregoing.

228. The use or method of Claim 122, wherein the compound of Formula (II)

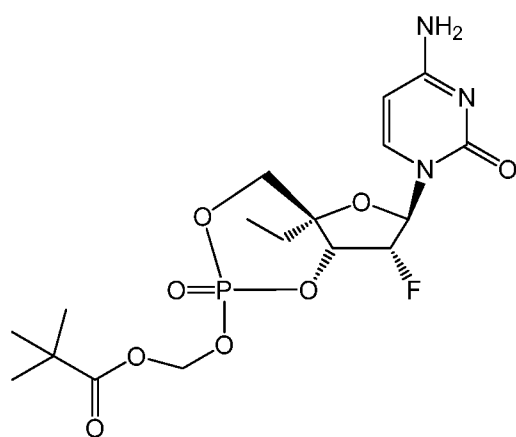


is

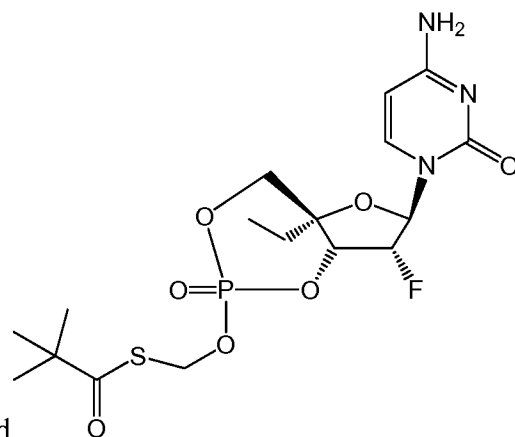
 R^{1B}

, or a pharmaceutically acceptable salt thereof.

229. The use or method of Claim 122, wherein the compound of Formula (II) is selected from the group consisting of:



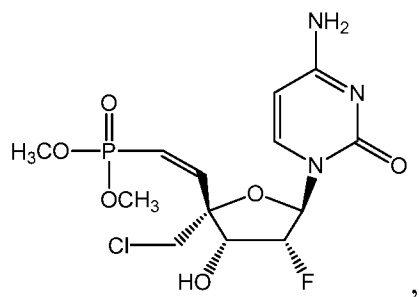
and



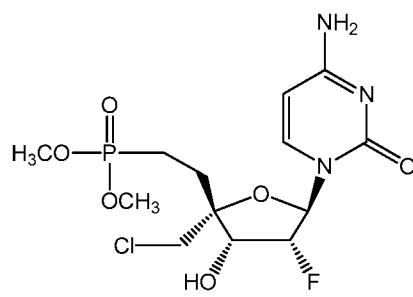
, or a

pharmaceutically acceptable salt of the foregoing.

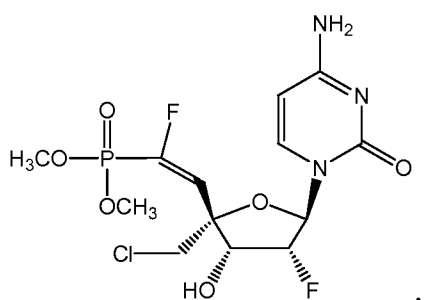
230. The use or method of Claim 162, wherein the compound of Formula (III) is selected from the group consisting of:



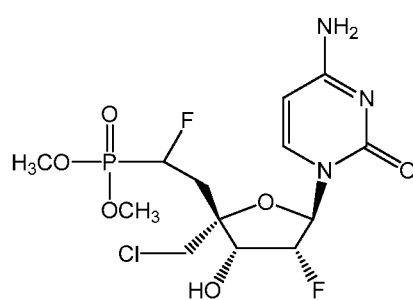
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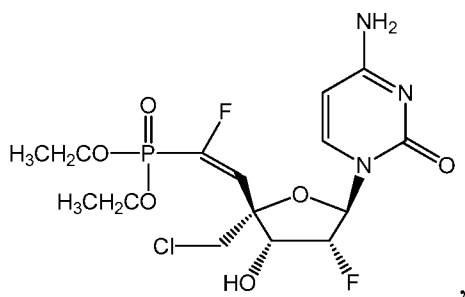
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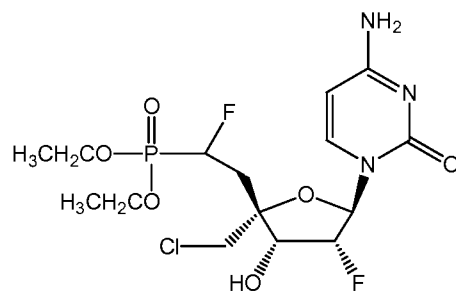
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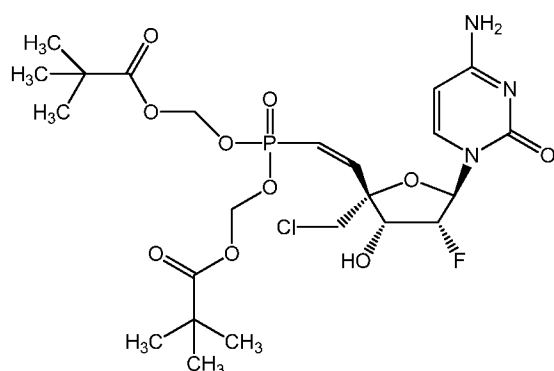
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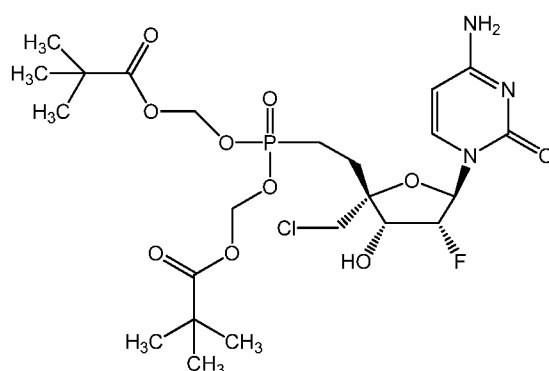
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,



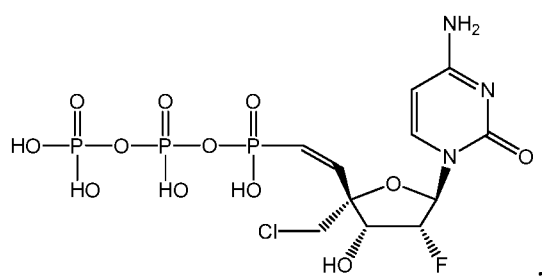
and



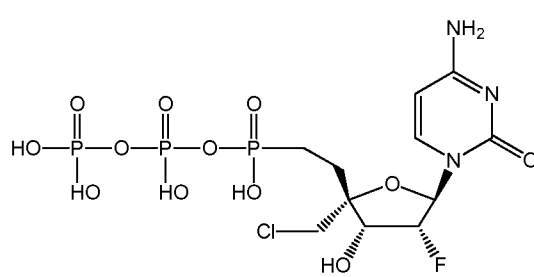
, or a

pharmaceutically acceptable salt of the foregoing.

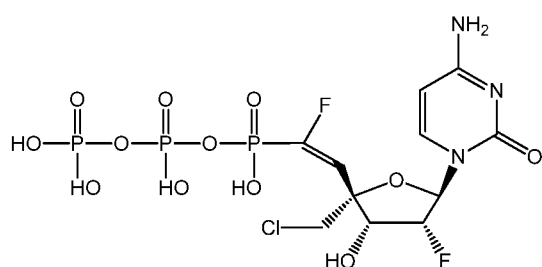
231. The use or method of Claim 162, wherein the compound of Formula (III) is selected from the group consisting of:



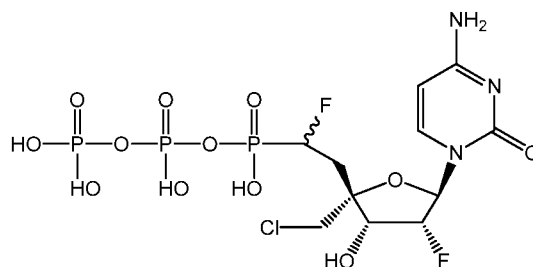
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,



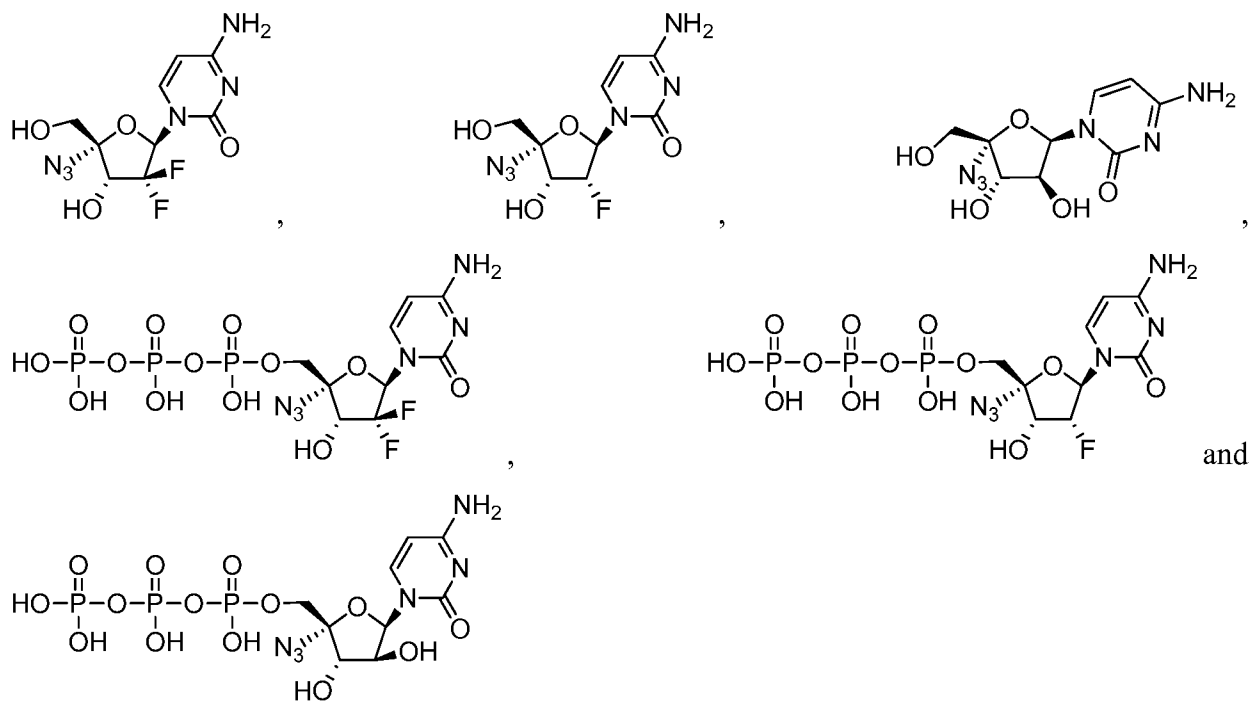
and



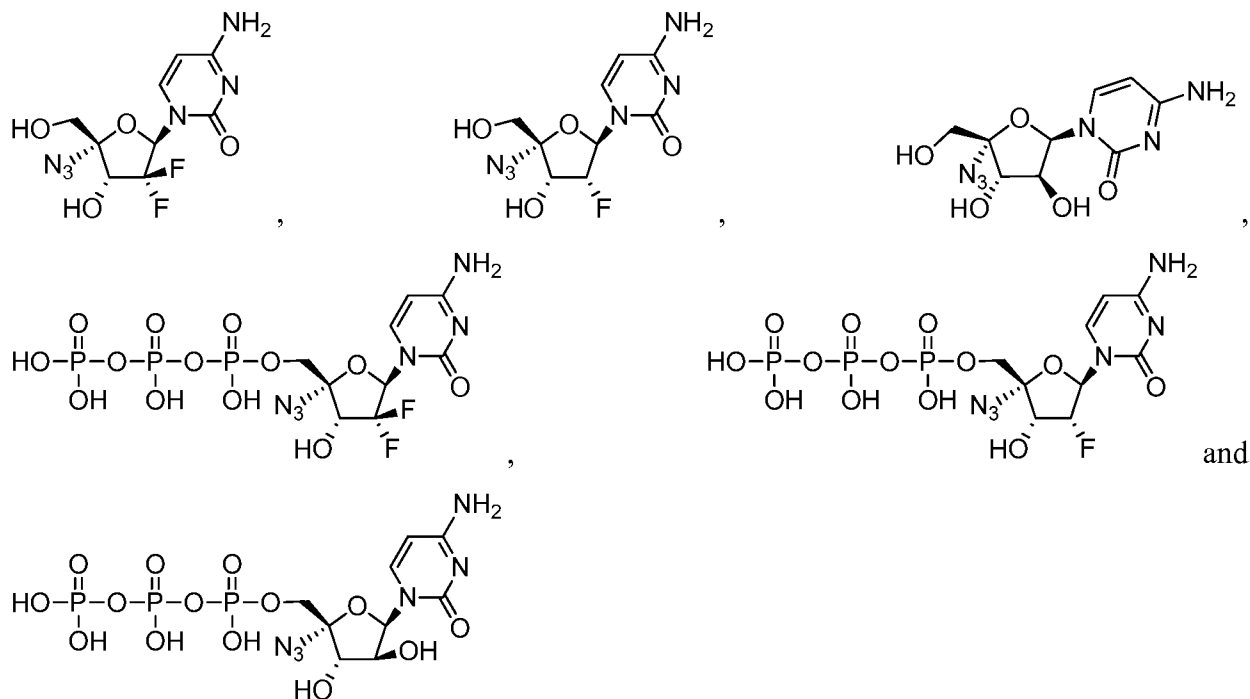
, or a

pharmaceutically acceptable salt of the foregoing.

232. Use of an effective amount of a compound, or a pharmaceutically acceptable salt thereof, for ameliorating or treating a viral infection caused by a virus selected from a henipavirus, a morbillivirus, a respirovirus, a rubulavirus and a metapneumovirus, wherein the compound is selected from:



233. A method for ameliorating or treating a viral infection caused by a virus comprising administering to or contacting a cell in a subject with an effective amount of a compound, or a pharmaceutically acceptable salt of thereof, wherein the virus is selected from a henipavirus, a morbillivirus, a respirovirus, a rubulavirus and a metapneumovirus, and wherein the compound is selected from:



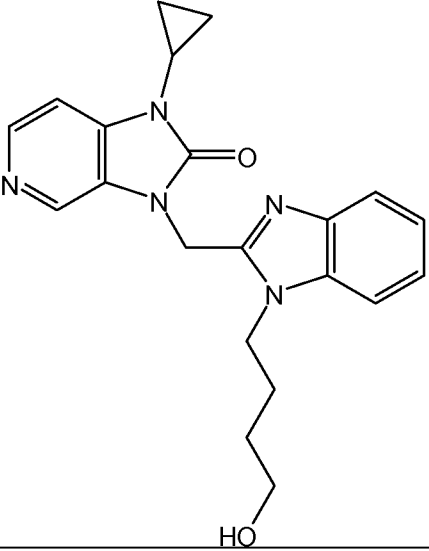
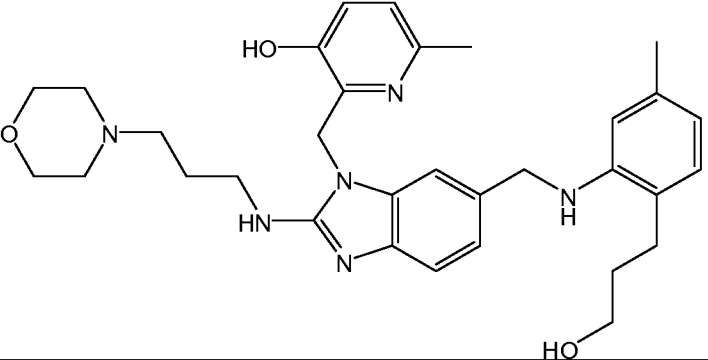
234. The use of Claim 232 or the method of Claim 233, wherein the virus is a henipavirus.

235. The use or method of Claim 234, wherein the henipavirus is a nipahvirus.

236. The use of Claim 232 or the method of Claim 233, wherein the virus is a morbillivirus.
237. The use or method of Claim 236, wherein the morbillivirus is the measles virus.
238. The use of Claim 232 or the method of Claim 233, wherein the virus is a respirovirus.
239. The use or method of Claim 238, wherein the respirovirus is human parainfluenza virus 1.
240. The use or method of Claim 238, wherein the respirovirus is human parainfluenza virus 3.
241. The use of Claim 232 or the method of Claim 233, wherein the virus is a rubulavirus.
242. The use or method of Claim 241, wherein the rubulavirus is the mumps virus.
243. The use or method of Claim 241, wherein the rubulavirus is human parainfluenza virus 2.
244. The use or method of Claim 241, wherein the rubulavirus is human parainfluenza virus 4.
245. The use of Claim 232 or the method of Claim 233, wherein the virus is a metapneumovirus.
246. The use or method of Claim 245, wherein the metaphenumovirus is human metapneumovirus.

1/1

Figure 1

Compound	Structure
BMS-433771	 The chemical structure of BMS-433771 features a central pyrazole ring. One nitrogen of the pyrazole is substituted with a 4-cyclopropyl-1H-imidazo[4,5-b]pyridin-2-yl group. The other nitrogen is substituted with a 4-(4-hydroxybutyl)-1H-benzimidazol-2-yl group.
TMC-353121	 The chemical structure of TMC-353121 features a central benzimidazole ring system. The 2-position of the benzimidazole is substituted with a 4-(4-hydroxybutyl)-1H-benzimidazol-2-yl group. The 4-position of the benzimidazole is substituted with a 4-(4-(4-methyl-2-hydroxyphenyl)butyl)piperazine group.

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/7068 (2006.01) A61K 31/7072 (2006.01) A61K 31/7076 (2006.01) A61K 31/708 (2006.01)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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

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

Registry, CAlplus: Substructure based on formulas (I), (II), (III) and the compounds defined in claims 232 and 233

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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



Further documents are listed in the continuation of Box C



See patent family annex

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

Date of the actual completion of the international search 9 July 2013	Date of mailing of the international search report 09 July 2013
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaustalia.gov.au Facsimile No.: +61 2 6283 7999	Authorised officer Andrew Bryce AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. +61 2 6283 3132

INTERNATIONAL SEARCH REPORT		International application No.
C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		PCT/US2013/033018
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2012/040124 A1 (ALIOS BIOPHARMA, INC.) 29 March 2012 Page 163, first row, left-hand column, page 163, fifth row, right-hand column, page 164, second row, left-hand column, abstract, paragraph [0002]	232-246
X	Smith D.B. et al. "The Design, Synthesis, and Antiviral Activity of Monofluoro and Difluoro Analogues of 4'-Azidocytidine against Hepatitis C Virus Replication: The Discovery of 4'-Azido-2'-deoxy-2'-fluorocytidine and 4'-Azido-2'-dideoxy-2',2'-difluorocytidine" The Journal of Medicinal Chemistry (2009) 52: 2971-2978 Compound 4 on page 2971, compound 10 in Scheme 1, compound 34 in Scheme 5, title, abstract	232-246
X	Chang W. et al. "Synthesis and anti-HCV activity of 3',4'-oxetane nucleosides" Bioorganic & Medicinal Chemistry Letters (2010) 20: 4539-4543 Title, abstract, compounds 4, 6 and 8 in Figure 3	1-17, 46, 77, 86, 90, 93, 118-121, 223, 224
X	WO 2010/030858 A1 (ENANTA PHARMACEUTICALS, INC.) 18 March 2010 Abstract, last compound of claim 12	1-17, 46, 77, 86, 90, 94, 97, 98, 109, 119-121, 219, 224
E	WO 2013/096679 A1 (ALIOS BIOPHARMA, INC.) 27 June 2013 claims 210-217, paragraph [0005]	1-231

Supplemental Box**Continuation of: Box III**

The specification does not comply with Section 40(4) because the claims do not relate to one invention only. I have found different inventions based on the following features that separate the claims into distinct groups:

- Claims 16-121 and 219-227 (in full) and claims 1-15 (in part) are directed to compounds of Formula (I). The generic structure of Formula (I) is specific to this group of claims.
- Claims 122-161, 228 and 229 (in full) and claims 1-15 (in part) are directed to compounds of Formula (II). The generic structure of Formula (II) is specific to this group of claims.
- Claims 162-218, 230 and 231 (in full) and claims 1-15 (in part) are directed to compounds of Formula (III). The generic structure of Formula (III) is specific to this group of claims.
- Claims 232-246 (in full) are directed to specific azide-containing compounds which do not fall within the scope of Formulas (I) to (III). The feature of 4'-azide substituted nucleoside analogues is specific to this group of claims.

Unity of invention is only fulfilled when there is at least one “special technical feature” present in the claims that both:

- provides a technical relationship among all the claims; and,
- makes a contribution over the prior art.

When there is no special technical feature common to all the claimed inventions there is no unity of invention. In the above groups of claims, the identified distinguishing features may have the potential to make a contribution over the prior art but are not common to all the claimed inventions and therefore cannot provide the required technical relationship. Therefore there is no special technical feature common to all the claimed inventions and the requirements for unity of invention are consequently not satisfied *a priori*.

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See Supplemental Box for Details

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT		International application No.	
Information on patent family members		PCT/US2013/033018	
This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.			
Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
WO 2012/040124 A1	29 Mar 2012	AU 2011305652 A1	02 May 2013
		CA 2812962 A1	29 Mar 2012
		TW 201216967 A	01 May 2012
		US 2012070415 A1	22 Mar 2012
		UY 33620 A	30 Apr 2012
		WO 2012040124 A1	29 Mar 2012
WO 2010/030858 A1	18 Mar 2010	US 8163707 B2	24 Apr 2012
		WO 2010030858 A1	18 Mar 2010
WO 2013/096679 A1	27 Jun 2013	WO 2013096679 A1	27 Jun 2013
End of Annex			



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(43) 申请公布日 2014. 12. 10

(21) 申请号 201380015428. 7

(51) Int. Cl.

(22) 申请日 2013. 03. 19

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(30) 优先权数据

A61K 31/7072 (2006. 01)

61/613, 836 2012. 03. 21 US

A61K 31/7076 (2006. 01)

13/721, 988 2012. 12. 20 US

A61K 31/708 (2006. 01)

(85) PCT国际申请进入国家阶段日

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PCT/US2013/033018 2013. 03. 19

(87) PCT国际申请的公布数据

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(71) 申请人 艾丽奥斯生物制药有限公司

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(72) 发明人 王广义 大卫·伯纳德·史密斯

莱昂尼德·贝格尔曼

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(74) 专利代理机构 北京英赛嘉华知识产权代理

有限责任公司 11204

代理人 王达佐 阴亮

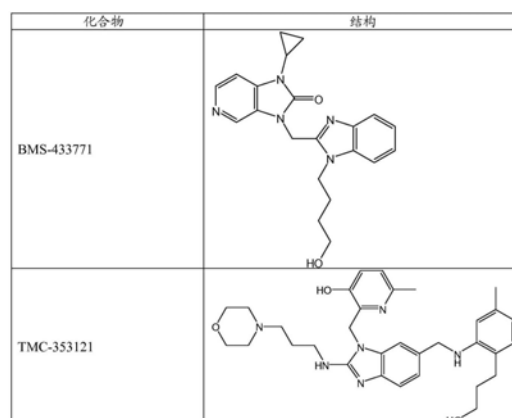
权利要求书42页 说明书202页 附图1页

(54) 发明名称

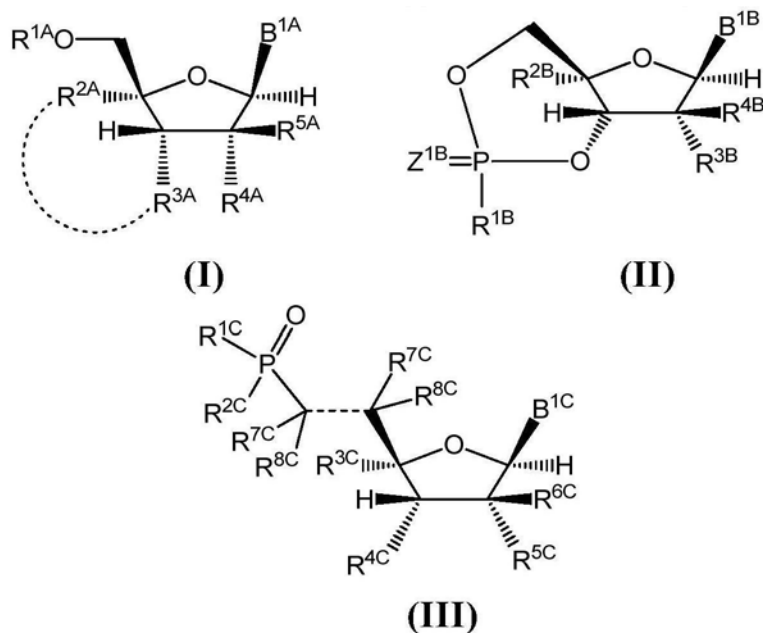
取代的核苷、核苷酸及其类似物

(57) 摘要

本文公开了核苷、核苷酸及其类似物、包含一种或多种核苷、核苷酸及其类似物的药物组合物以及合成上述的方法。本文还公开了使用核苷、核苷酸及其类似物减轻和 / 或治疗包括源自副粘病毒和 / 或正粘病毒的感染的疾病和 / 或疾病状态的方法。



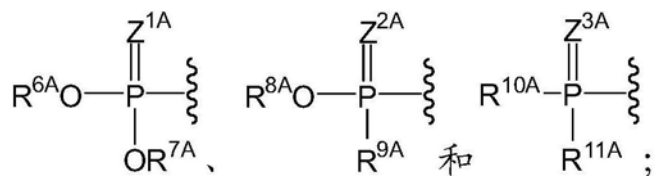
1. 有效量的选自式 (I)、式 (II) 和式 (III) 的化合物或前述的药物可接受的盐,用于减轻或治疗由选自亨尼帕病毒属、麻疹病毒属、呼吸道病毒属、腮腺炎病毒属和偏肺病毒属的病毒引起的病毒感染的用途,其中所述化合物选自具有以下结构之一的式 (I)、式 (II) 和式 (III) :



其中：

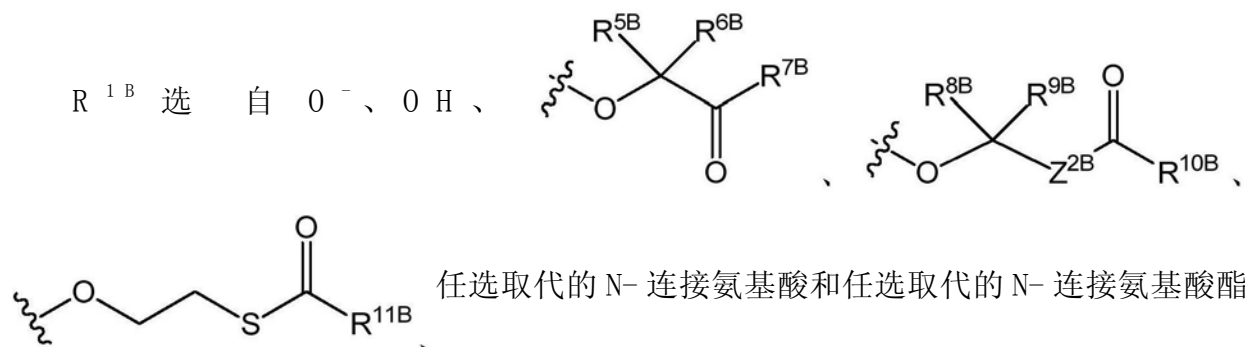
B^{1A}、B^{1B} 和 B^{1C} 独立地为任选取代的杂环碱或具有被护氨基的任选取代的杂环碱；

R^{1A}选自氢、任选取代的酰基、任选取代的O-连接氨基酸、



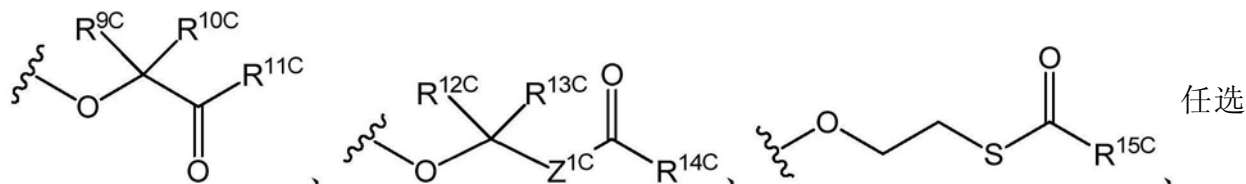
当所述式 (I) 的虚线 (-----) 为单键时, R^{2A} 为 CH_2 且 R^{3A} 为 O (氧);

当所述式 (I) 的虚线 (-----) 不存在时, R^{2A} 选自任选取代的 C_{1-6} 烷基、任选取代的 C_{2-6} 烯基、任选取代的 C_{2-6} 炔基、任选取代的 C_{3-6} 环烷基、任选取代的 $-O-C_{1-6}$ 烷基、任选取代的 $-O-C_{3-6}$ 烯基、任选取代的 $-O-C_{3-6}$ 炔基和氰基, 且 R^{3A} 选自 OH 、 $-OC(=O)R^A$ 和任选取代的 O -连接氨基酸;

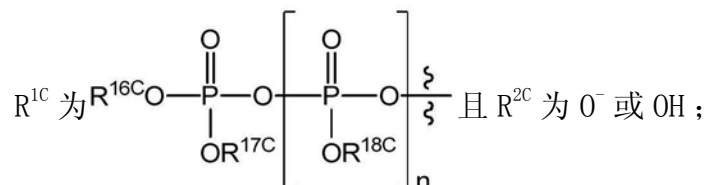


衍生物；

R^{1C} 和 R^{2C} 独立地选自 $O-$ 、 OH 、任选取代的 C_{1-6} 烃氧基、



取代的 N -连接氨基酸和任选取代的 N -连接氨基酸酯衍生物；或者



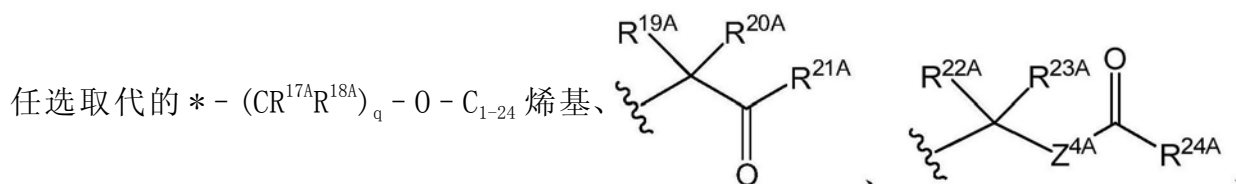
R^{2B} 和 R^{3C} 独立地选自任选取代的 C_{1-6} 烷基、任选取代的 C_{2-6} 烯基、任选取代的 C_{2-6} 炔基、任选取代的 C_{3-6} 环烷基、任选取代的 $-O-C_{1-6}$ 烷基、任选取代的 $-O-C_{3-6}$ 烯基、任选取代的 $-O-C_{3-6}$ 炔基和氰基；

R^{4C} 选自 OH 、 $-OC(=O)R^{5C}$ 和任选取代的 O -连接氨基酸；

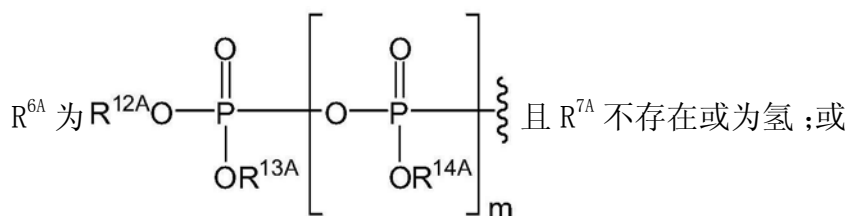
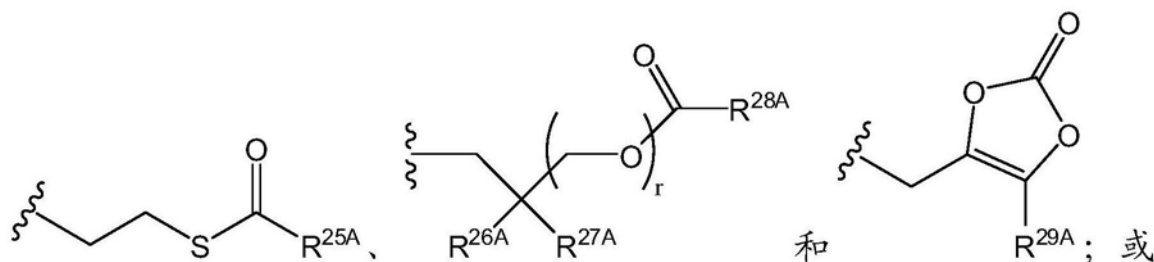
R^{4A} 、 R^{3B} 和 R^{5C} 独立地为卤素；

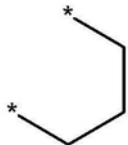
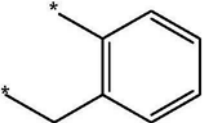
R^{5A} 、 R^{4B} 和 R^{6C} 独立地为氢或卤素；

R^{6A} 、 R^{7A} 和 R^{8A} 独立地选自不存在、氢、任选取代的 C_{1-24} 烷基、任选取代的 C_{2-24} 烯基、任选取代的 C_{2-24} 炔基、任选取代的 C_{3-6} 环烷基、任选取代的 C_{3-6} 环烯基、任选取代的芳基、任选取代的杂芳基、任选取代的芳基 (C_{1-6} 烷基)、任选取代的 $*(CR^{15A}R^{16A})_p-O-C_{1-24}$ 烷基、



任选取代的 $*(CR^{17A}R^{18A})_q-O-C_{1-24}$ 烯基、



R^{6A} 和 R^{7A} 在一起形成选自任选取代的  和任选取代的  的部分，

其中所述与 R^{6A} 和 R^{7A} 连接的氧、所述磷和所述部分形成六元至十元环体系；

R^{9A} 独立地选自任选取代的 C_{1-24} 烷基、任选取代的 C_{2-24} 烯基、任选取代的 C_{2-24} 炔基、任选取代的 C_{3-6} 环烷基、任选取代的 C_{3-6} 环烯基、 $NR^{30A}R^{31A}$ 、任选取代的 N-连接氨基酸和任选取代的 N-连接氨基酸酯衍生物；

R^{10A} 和 R^{11A} 独立地为任选取代的 N-连接氨基酸或任选取代的 N-连接氨基酸酯衍生物；

R^{12A} 、 R^{13A} 和 R^{14A} 独立地不存在或为氢；

各个 R^{15A} 、各个 R^{16A} 、各个 R^{17A} 和各个 R^{18A} 独立地为氢、任选取代的 C_{1-24} 烷基或 C_{1-24} 炔氧基；

R^{19A} 、 R^{20A} 、 R^{22A} 、 R^{23A} 、 R^{5B} 、 R^{6B} 、 R^{8B} 、 R^{9B} 、 R^{9C} 、 R^{10C} 、 R^{12C} 和 R^{13C} 独立地选自氢、任选取代的 C_{1-24} 烷基和任选取代的芳基；

R^{21A} 、 R^{24A} 、 R^{7B} 、 R^{10B} 、 R^{11C} 和 R^{14C} 独立地选自氢、任选取代的 C_{1-24} 烷基、任选取代的芳基、任选取代的 $-O-C_{1-24}$ 烷基和任选取代的 $-O-$ 芳基；

R^{25A} 、 R^{29A} 、 R^{11B} 和 R^{15C} 独立地选自氢、任选取代的 C_{1-24} 烷基和任选取代的芳基；

R^{16C} 、 R^{17C} 和 R^{18C} 独立地不存在或为氢；

R^{26A} 和 R^{27A} 独立地为 $-C \equiv N$ 或任选取代的选自 C_{2-8} 有机基羰基、 C_{2-8} 炔氧基羰基和 C_{2-8} 有机基氨基羰基的取代基炔氧基；

R^{28A} 选自氢、任选取代的 C_{1-24} 烷基、任选取代的 C_{2-24} 烯基、任选取代的 C_{2-24} 炔基、任选取代的 C_{3-6} 环烷基和任选取代的 C_{3-6} 环烯基；

R^{30A} 和 R^{31A} 独立地选自氢、任选取代的 C_{1-24} 烷基、任选取代的 C_{2-24} 烯基、任选取代的 C_{2-24} 炔基、任选取代的 C_{3-6} 环烷基和任选取代的 C_{3-6} 环烯基；

对于式 (III)，----- 为单键或双键；

当 ----- 为单键时，各个 R^{7C} 和各个 R^{8C} 独立地为氢或卤素；且

当 ----- 为双键时，各个 R^{7C} 不存在且各个 R^{8C} 独立地为氢或卤素；

R^{7A} 和 R^{7C} 独立地为任选取代的 C_{1-24} 烷基；

m 和 n 独立地为 0 或 1；

p 和 q 独立地选自 1、2 和 3；

r 为 1 或 2；

Z^{1A} 、 Z^{2A} 、 Z^{3A} 、 Z^{4A} 、 Z^{1B} 、 Z^{2B} 和 Z^{1C} 独立地为 0 或 S；且

条件是当所述式 (I) 的虚线 (-----) 不存在时： R^{1A} 为 $R^{8A}O-P(=Z^{2A})(R^{9A})$ 其中 R^{8A} 为未

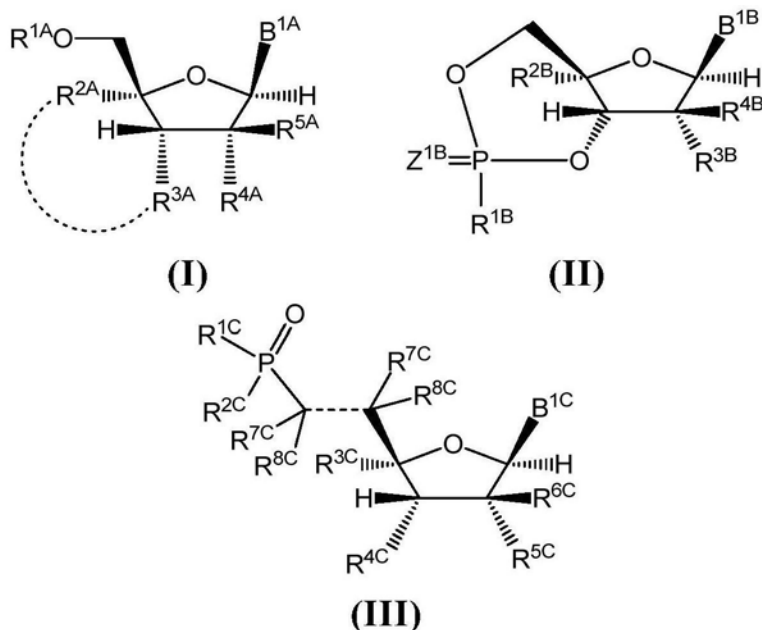
取代 C_{1-4} 烷基或任选被卤素或甲基对位取代的苯基且 R^{9A} 为氨基酸的甲基酯、乙基酯、异丙基酯、正丁基酯、苄基酯或苯基酯，所述氨基酸选自甘氨酸、丙氨酸、缬氨酸、亮氨酸、苯丙氨酸、色氨酸、蛋氨酸和脯氨酸； R^{3A} 为 OH； R^{4A} 为氟； R^{5A} 为氟或氢；且 B^{1A} 为未取代的尿嘧啶；则 R^{2A} 不为 $-OCH_3$ ；

条件是当所述式 (I) 的虚线 (-----) 不存在； R^{1A} 为 H； R^{3A} 为 OH； R^{4A} 为氟； R^{5A} 为氟；且 B^{1A} 为未取代的胞嘧啶；则 R^{2A} 不为烯基；

条件是当所述式 (I) 的虚线 (-----) 不存在； R^{1A} 为 H； R^{3A} 为 OH； R^{4A} 为氟； R^{5A} 为氢；且 B^{1A} 为未取代的胸腺嘧啶；则 R^{2A} 不为被 N-酰胺基取代的 C_1 烷基；且

条件是当所述式 (I) 的虚线 (-----) 不存在 ; R^{1A} 为 H ; R^{3A} 为 OH ; R^{4A} 为氟 ; R^{5A} 为氟 ;且 B^{1A} 为未取代的胞嘧啶 ;则 R^{2A} 不为乙炔基。

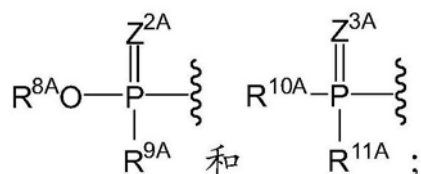
2. 减轻或治疗由病毒引起的病毒感染的方法,包括将有效量的选自式 (I)、式 (II) 和式 (III) 的化合物或前述的药物可接受的盐给予对象中的细胞或者使对象中的细胞与有效量的选自式 (I)、式 (II) 和式 (III) 的化合物或前述的药物可接受的盐接触,其中所述病毒选自亨尼帕病毒属、麻疹病毒属、呼吸道病毒属、腮腺炎病毒属和偏肺病毒属,并且其中所述化合物选自具有以下结构之一的式 (I)、式 (II) 和式 (III) :



其中 :

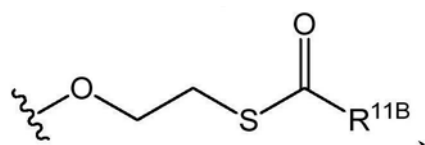
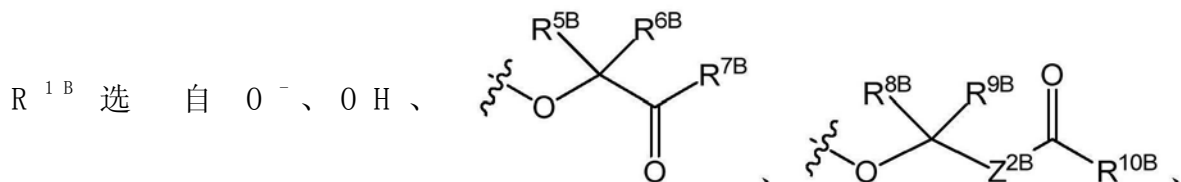
B^{1A} 、 B^{1B} 和 B^{1C} 独立地为任选取代的杂环碱基,或具有保护氨基的任选取代的杂环碱基 ;

R^{1A} 选自氢、任选取代的酰基、任选取代的 O-连接氨基、 $R^{6A}O-P(=Z^{1A})(OR^{7A})$ 、



当式 (I) 的虚线 (-----) 为单键时, R^{2A} 为 CH_2 , 且 R^{3A} 为 O (氧) ;

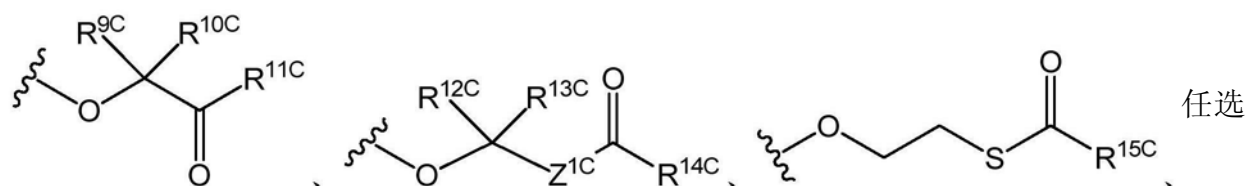
当式 (I) 的虚线 (-----) 为不存在时, R^{2A} 选自任选取代的 C_{1-6} 烷基、任选取代的 C_{2-6} 烯基、任选取代的 C_{2-6} 炔基、任选取代的 C_{3-6} 环烷基、任选取代的 $-O-C_{1-6}$ 烷基、任选取代的 $-O-C_{3-6}$ 烯基、任选取代的 $-O-C_{3-6}$ 炔基和氰基, 并且 R^{3A} 选自 OH、 $-OC(=O)R^{3A}$ 和任选取代的 O-连接氨基酸 ;



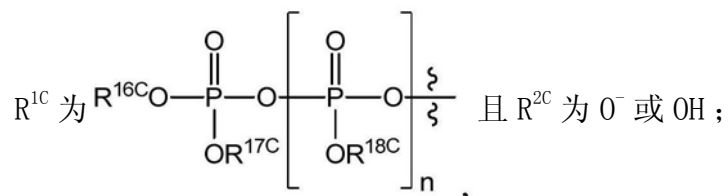
任选取代的 N-连接氨基酸和任选取代的 N 连接氨基酸酯衍

生物；

R^{1C} 和 R^{2C} 独立地选自 O^- 、 OH 、任选取代的 C_{1-6} 烷氧基、



取代的 N 连接氨基酸和任选取代的 N 连接氨基酸酯衍生物；或



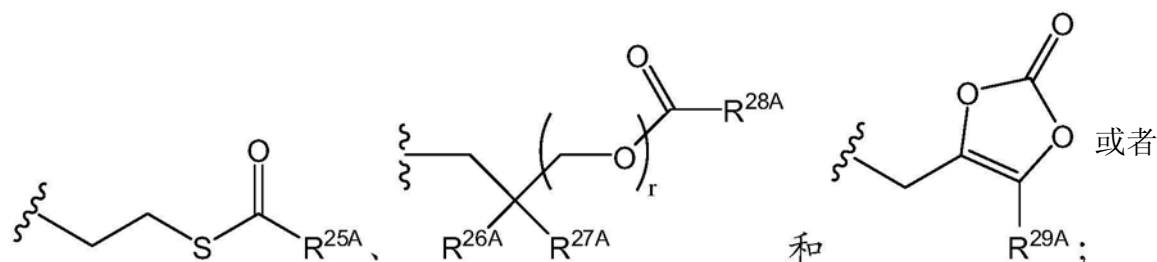
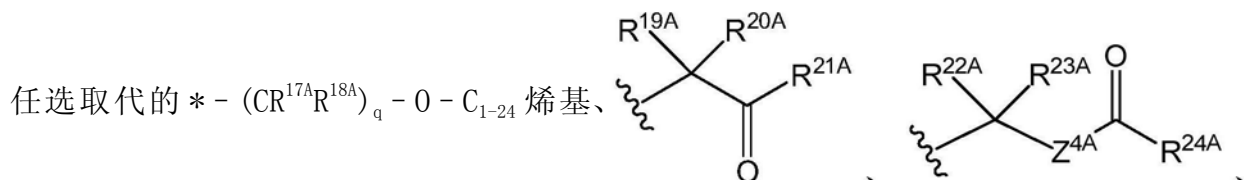
R^{2B} 和 R^{3C} 独立地选自任选取代的 C_{1-6} 烷基、任选取代的 C_{2-6} 烯基、任选取代的 C_{2-6} 炔基、任选取代的 C_{3-6} 环烷基、任选取代的 $-O-C_{1-6}$ 烷基、任选取代的 $-O-C_{3-6}$ 烯基、任选取代的 $-O-C_{3-6}$ 炔基和氰基；

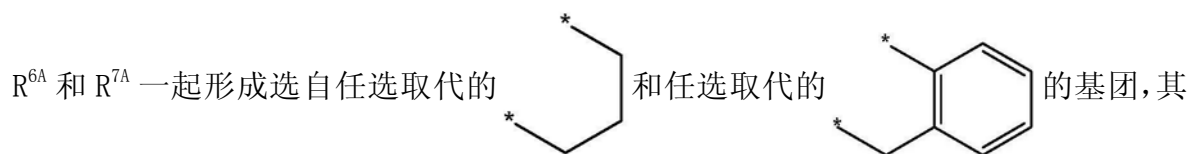
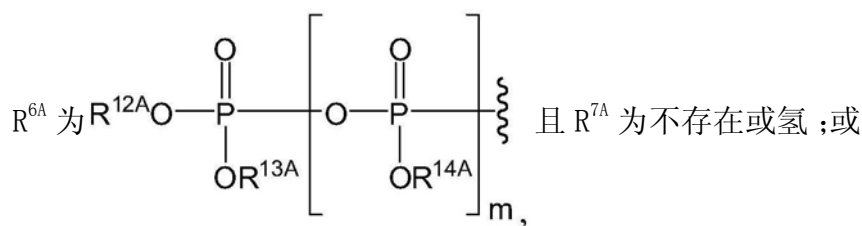
R^{4C} 选自 OH 、 $-OC(=O)R^{7C}$ 和任选取代的 O-连接氨基酸；

R^{4A} 、 R^{3B} 和 R^{5C} 独立地为卤素；

R^{5A} 、 R^{4B} 和 R^{6C} 独立地为氢或卤素；

R^{6A} 、 R^{7A} 和 R^{8A} 独立地选自不存在、氢、任选取代的 C_{1-24} 烷基、任选取代的 C_{2-24} 烯基、任选取代的 C_{2-24} 炔基、任选取代的 C_{3-6} 环烷基、任选取代的 C_{3-6} 环烯基、任选取代的芳基、任选取代的杂芳基、任选取代的芳基 (C_{1-6} 烷基)、任选取代的 $*(CR^{15A}R^{16A})_p-O-C_{1-24}$ 烷基、





中与 R^{6A} 和 R^{7A} 连接的氧、磷及所述基团形成六元至十元环系 ;

R^{9A} 独立地选自任选取代的 C_{1-24} 烷基、任选取代的 C_{2-24} 烯基、任选取代的 C_{2-24} 炔基、任选取代的 C_{3-6} 环烷基、任选取代的 C_{3-6} 环烯基、 $NR^{30A}R^{31A}$ 、任选取代的 N- 连接氨基酸和任选取代的 N- 连接氨基酸酯衍生物 ;

R^{10A} 和 R^{11A} 独立地为任选取代的 N- 连接氨基酸或任选取代的 N- 连接氨基酸酯衍生物 ;

R^{12A} 、 R^{13A} 和 R^{14A} 独立地为不存在或氢 ;

各个 R^{15A} 、各个 R^{16A} 、各个 R^{17A} 和各个 R^{18A} 独立地为氢、任选取代的 C_{1-24} 烷基或 C_{1-24} 烃氧基 ;

R^{19A} 、 R^{20A} 、 R^{22A} 、 R^{23A} 、 R^{5B} 、 R^{6B} 、 R^{8B} 、 R^{9B} 、 R^{9C} 、 R^{10C} 、 R^{12C} 和 R^{13C} 独立地选自氢、任选取代的 C_{1-24} 烷基和任选取代的芳基 ;

R^{21A} 、 R^{24A} 、 R^{7B} 、 R^{10B} 、 R^{11C} 和 R^{14C} 独立地选自氢、任选取代的 C_{1-24} 烷基、任选取代的芳基、任选取代的 $-O-C_{1-24}$ 烷基和任选取代的 $-O-$ 芳基 ;

R^{25A} 、 R^{29A} 、 R^{11B} 和 R^{15C} 独立地选自氢、任选取代的 C_{1-24} 烷基和任选取代的芳基 ;

R^{16C} 、 R^{17C} 和 R^{18C} 独立地为不存在或氢 ;

R^{26A} 和 R^{27A} 独立地为 $-C \equiv N$ 或任选取代的选自 C_{2-8} 有机基羰基、 C_{2-8} 烃氧基羰基和 C_{2-8} 有机基氨基羰基的取代基烃氧基 ;

R^{28A} 选自氢、任选取代的 C_{1-24} 烷基、任选取代的 C_{2-24} 烯基、任选取代的 C_{2-24} 炔基、任选取代的 C_{3-6} 环烷基和任选取代的 C_{3-6} 环烯基 ;

R^{30A} 和 R^{31A} 独立地选自氢、任选取代的 C_{1-24} 烷基、任选取代的 C_{2-24} 烯基、任选取代的 C_{2-24} 炔基、任选取代的 C_{3-6} 环烷基和任选取代的 C_{3-6} 环烯基 ;

对于式 (III), ----- 为单键或双键 ;

当 ----- 为单键时, 各个 R^{7C} 和各个 R^{8C} 独立地为氢或卤素 ; 且

当 ----- 为双键时, 各个 R^{7C} 不存在且各个 R^{8C} 独立地为氢或卤素 ;

R''^A 和 R'^C 独立地为任选取代的 C_{1-24} 烷基 ;

m 和 n 独立地为 0 或 1 ;

p 和 q 独立地选自 1、2 和 3 ;

r 为 1 或 2 ;

Z^{1A} 、 Z^{2A} 、 Z^{3A} 、 Z^{4A} 、 Z^{1B} 、 Z^{2B} 和 Z^{1C} 独立地为 0 或 S ; 且

条件是当式 (I) 的虚线 (-----) 为不存在时; R^{1A} 为 $R^{8A}O-P(=Z^{2A})(R^{9A})$ 其中 R^{8A} 为未取代 C_{1-4} 烷基或任选被卤素或甲基对位取代的苯基, 且 R^{9A} 为氨基酸的甲基酯、乙基酯、异丙基酯、正丁基酯、苄基酯或苯基酯, 所述氨基酸选自甘氨酸、丙氨酸、缬氨酸、亮氨酸、苯丙氨酸、色氨酸、蛋氨酸和脯氨酸; R^{3A} 为 OH; R^{4A} 为氟; R^{5A} 为氟或氢; 且 B^{1A} 为未取代的尿嘧啶; 则 R^{2A} 不为 $-OCH_3$;

条件是当式 (I) 的虚线 (-----) 为不存在时; R^{1A} 为 H; R^{3A} 为 OH; R^{4A} 为氟; R^{5A} 为氟; 且 B^{1A} 为未取代的胞嘧啶; 则 R^{2A} 不为烯基;

条件是当式 (I) 的虚线 (-----) 不存在; R^{1A} 为 H; R^{3A} 为 OH; R^{4A} 为氟; R^{5A} 为氢; 且 B^{1A} 为未取代的胸腺嘧啶; 则 R^{2A} 不能为被 N- 酰胺基取代的 C_1 烷基; 且

条件是当式 (I) 的虚线 (-----) 不存在; R^{1A} 为 H; R^{3A} 为 OH; R^{4A} 为氟; R^{5A} 为氟; 且 B^{1A} 为未取代的胞嘧啶; 则 R^{2A} 不能为乙炔基。

3. 如权利要求 1 所述的用途或权利要求 2 所述的方法, 其中所述病毒为亨尼帕病毒属。
4. 如权利要求 3 所述的用途和方法, 其中所述亨尼帕病毒属为尼帕病毒。
5. 如权利要求 1 所述的用途或权利要求 2 所述的方法, 其中所述病毒为麻疹病毒属。
6. 如权利要求 5 所述的用途或方法, 其中所述麻疹病毒属为麻疹病毒。
7. 如权利要求 1 所述的用途或权利要求 2 所述的方法, 其中所述病毒为呼吸道病毒属。
8. 如权利要求 7 所述的用途或方法, 其中所述呼吸道病毒属为人副流感病毒 1。
9. 如权利要求 7 所述的用途或方法, 其中所述呼吸道病毒属为人副流感病毒 3。
10. 如权利要求 1 所述的用途或权利要求 2 所述的方法, 其中所述病毒为腮腺炎病毒属。
11. 如权利要求 10 所述的用途或方法, 其中所述腮腺炎病毒属为腮腺炎病毒。
12. 如权利要求 10 所述的用途或方法, 其中所述腮腺炎病毒属为人副流感病毒 2。
13. 如权利要求 10 所述的用途或方法, 其中所述腮腺炎病毒属为人副流感病毒 4。
14. 如权利要求 1 所述的用途或权利要求 2 所述的方法, 其中所述病毒为偏肺病毒属。
15. 如权利要求 14 所述的用途或方法, 其中所述偏肺病毒属为人偏肺病毒。
16. 如权利要求 1 或 3-15 中任一权利要求所述的用途或权利要求 2-15 中任一权利要求所述的方法, 其中所述化合物为式 (I) 的化合物。

17. 如权利要求 16 所述的用途或方法, 其中 R^{1A} 为 $R^{6A}O-P(=Z^{1A})(OR^{7A})$ 。

18. 如权利要求 17 所述的用途或方法, 其中 R^{6A} 和 R^{7A} 均为氢。
19. 如权利要求 17 所述的用途或方法, 其中 R^{6A} 和 R^{7A} 均不存在。
20. 如权利要求 17 所述的用途或方法, 其中 R^{6A} 和 R^{7A} 之一为氢, 且 R^{6A} 和 R^{7A} 中的另一个选自任选取代的 C_{1-24} 烷基、任选取代的 C_{2-24} 烯基、任选取代的 C_{2-24} 炔基、任选取代的 C_{3-6} 环烷基、任选取代的 C_{3-6} 环烯基、任选取代的芳基、任选取代的杂芳基和任选取代的芳基 (C_{1-6}

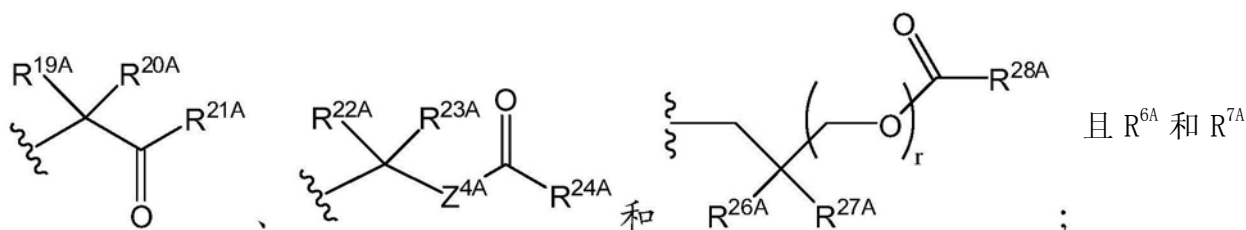
烷基)。

21. 如权利要求 20 所述的用途或方法, 其中 R^{6A} 和 R^{7A} 中的另一个为任选取代的 C_{1-24} 烷基。

22. 如权利要求 17 所述的用途或方法, 其中 R^{6A} 和 R^{7A} 二者独立地选自任选取代的 C_{1-24} 烷基、任选取代的 C_{2-24} 烯基、任选取代的 C_{2-24} 炔基、任选取代的 C_{3-6} 环烷基、任选取代的 C_{3-6} 环烯基、任选取代的芳基、任选取代的杂芳基和任选取代的芳基 (C_{1-6} 烷基)。

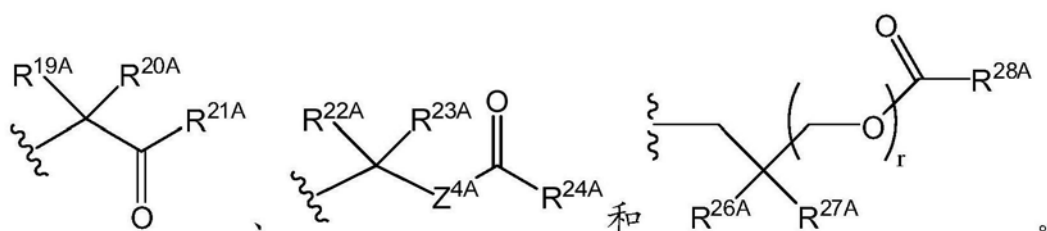
23. 如权利要求 22 所述的用途或方法, 其中 R^{6A} 和 R^{7A} 二者为任选取代的 C_{1-24} 烷基。

24. 如权利要求 17 所述的用途或方法, 其中至少一个 R^{6A} 和 R^{7A} 选自



中的另一个选自不存在、氢、任选取代的 C_{1-24} 烷基、任选取代的 C_{2-24} 烯基、任选取代的 C_{2-24} 炔基、任选取代的 C_{3-6} 环烷基、任选取代的 C_{3-6} 环烯基、任选取代的芳基、任选取代的杂芳基和任选取代的芳基 (C_{1-6} 烷基)。

25. 如权利要求 17 所述的用途或方法, 其中 R^{6A} 和 R^{7A} 二者独立地选自



26. 如权利要求 24-25 中任一权利要求所述的用途或方法, 其中 R^{26A} 和 R^{27A} 二者为任选取代的 C_{2-8} 有机基羰基。

27. 如权利要求 26 所述的用途或方法, 其中所述任选取代的 C_{1-8} 有机基羰基为 $-C(=O)CH_3$ 。

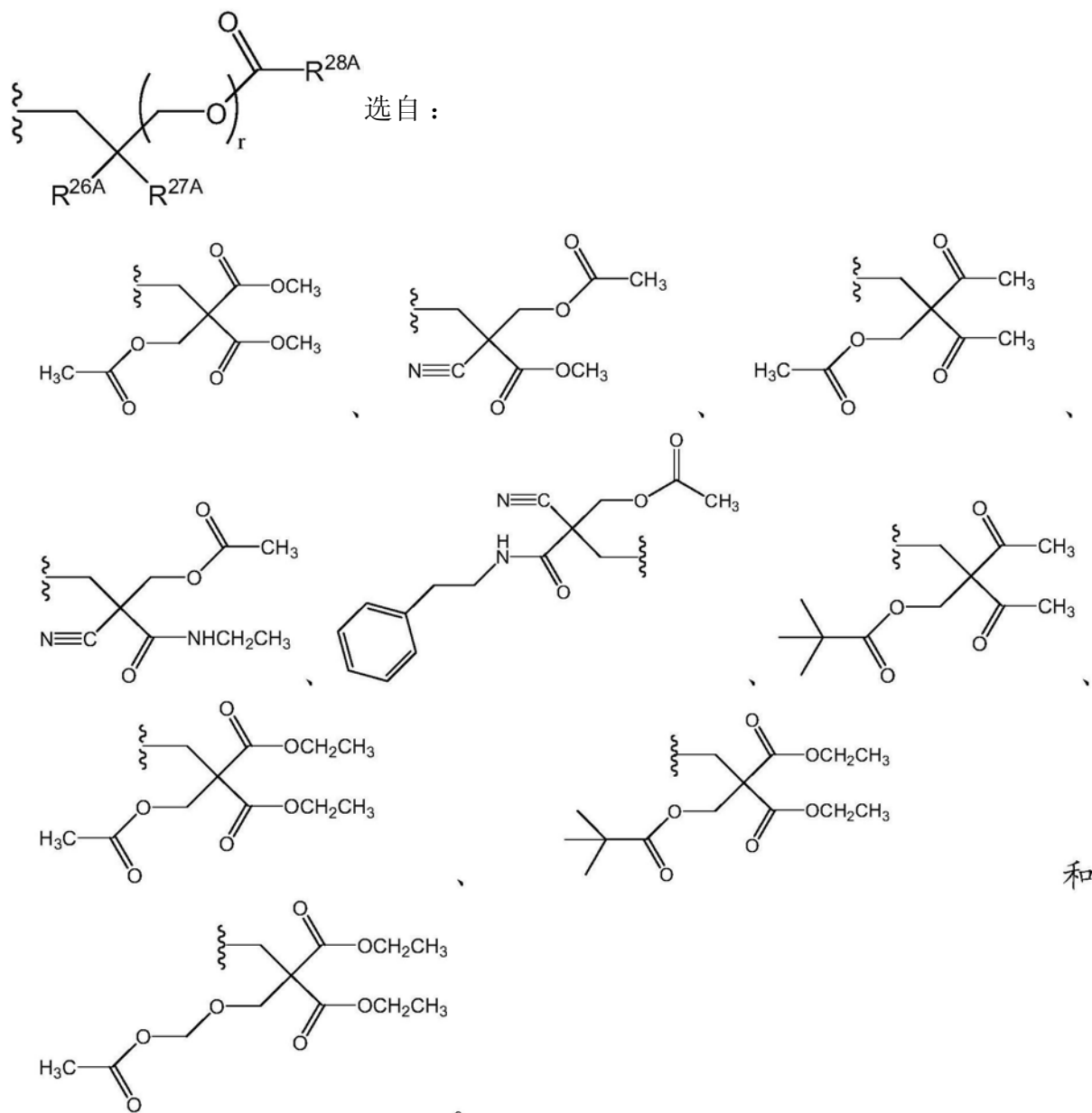
28. 如权利要求 24-25 中任一权利要求所述的用途或方法, 其中 R^{26A} 和 R^{27A} 二者为任选取代的 C_{2-8} 烃氧基羰基。

29. 如权利要求 28 所述的用途或方法, 其中所述任选取代的 C_{1-8} 烃氧基羰基为 $-C(=O)OCH_2CH_3$ 。

30. 如权利要求 28 所述的用途或方法, 其中所述任选取代的 C_{1-8} 烃氧基羰基为 $-C(=O)OCH_3$ 。

31. 如权利要求 24-30 中任一权利要求所述的用途或方法, 其中 R^{28A} 为任选取代的 C_{1-4} 烷基。

32. 如权利要求 24-25 中任一权利要求所述的用途或方法, 其中



33. 如权利要求 17 所述的用途或方法, 其中 R^{6A} 和 R^{7A} 均为任选取代的 C_{1-24} 烷基。

34. 如权利要求 17 所述的用途或方法, 其中 R^{6A} 和 R^{7A} 均为任选取代的 C_{2-24} 烯基。

35. 如权利要求 17 所述的用途或方法, 其中 R^{6A} 和 R^{7A} 均为 $*-(CR^{15A}R^{16A})_p-O-C_{1-24}$ 烷基。

36. 如权利要求 17 所述的用途或方法, 其中 R^{6A} 和 R^{7A} 均为 $*-(CR^{17A}R^{18A})_q-O-C_{2-24}$ 烯基。

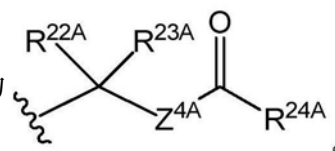
37. 如权利要求 17 所述的用途或方法, 其中 R^{6A} 和 R^{7A} 均为任选取代的芳基。

38. 如权利要求 17 所述的用途或方法, 其中 R^{6A} 和 R^{7A} 均为任选取代的芳基 (C_{1-6} 烷基)。

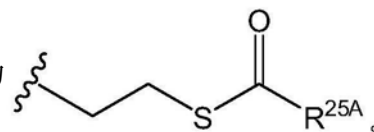
39. 如权利要求 17 所述的用途或方法, 其中 R^{6A} 和 R^{7A} 均为

*C(R19A)(R20A)C(=O)R21A

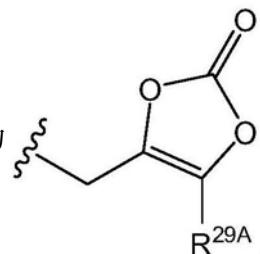
40. 如权利要求 17 所述的用途或方法, 其中 R^{6A} 和 R^{7A} 均为



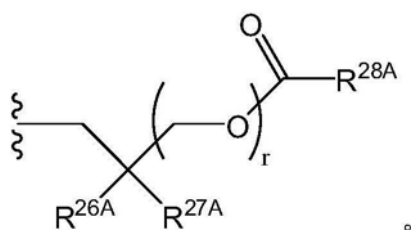
41. 如权利要求 17 所述的用途或方法, 其中 R^{6A} 和 R^{7A} 均为



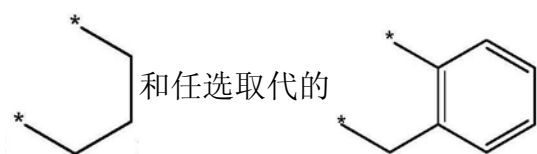
42. 如权利要求 17 所述的用途或方法, 其中 R^{6A} 和 R^{7A} 均为

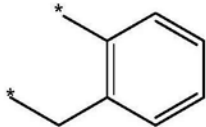


43. 如权利要求 17 所述的用途或方法, 其中 R^{6A} 和 R^{7A} 均为

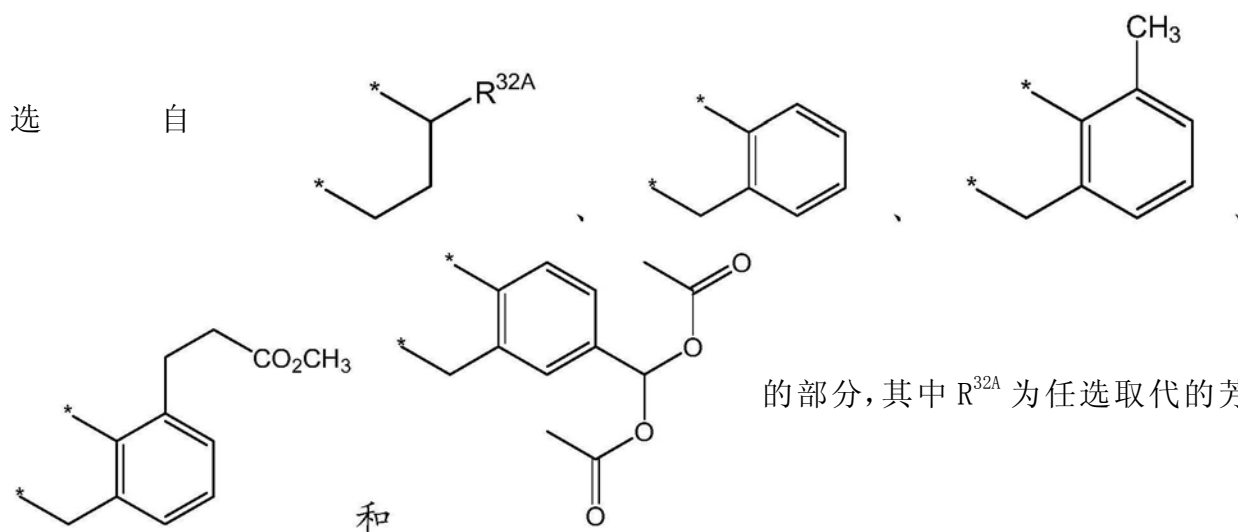


44. 如权利要求 17 所述的用途或方法, 其中 R^{6A} 和 R^{7A} 能在一起形成选自任选取代的



和任选取代的  的部分, 其中所述与 R^{6A} 和 R^{7A} 连接的氧、所述磷和所述部分形成六元至十元环体系。

45. 如权利要求 44 所述的用途或方法, 其中 R^{6A} 和 R^{7A} 能在一起形成



的部分, 其中 R^{32A} 为任选取代的芳

基、任选取代的杂芳基或任选取代的杂环基。

46. 如权利要求 17-45 中任一权利要求所述的用途或方法, 其中 Z^{1A} 为 0。

47. 如权利要求 17-45 中任一权利要求所述的用途或方法,其中 Z^{1A} 为 S。

48. 如权利要求 16 所述的用途或方法,其中 R^{1A} 为 $R^{8A}O-P(=Z^{2A})(R^{9A})$ 。

49. 如权利要求 48 所述的用途或方法,其中 R^{8A} 选自不存在、氢、任选取代的 C_{1-24} 烷基、任选取代的 C_{2-24} 烯基、任选取代的 C_{2-24} 炔基、任选取代的 C_{3-6} 环烷基和任选取代的 C_{3-6} 环烯基;且 R^{9A} 独立地选自任选取代的 C_{1-24} 烷基、任选取代的 C_{2-24} 烯基、任选取代的 C_{2-24} 炔基、任选取代的 C_{3-6} 环烷基和任选取代的 C_{3-6} 环烯基。

50. 如权利要求 49 所述的用途或方法,其中 R^{8A} 为氢,且 R^{9A} 为任选取代的 C_{1-6} 烷基。

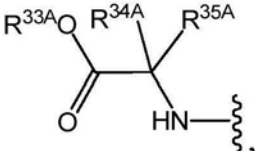
51. 如权利要求 48 所述的用途或方法,其中 R^{8A} 为氢,且 R^{9A} 为 $NR^{30A}R^{31A}$,其中 R^{30} 和 R^{31} 独立地选自氢、任选取代的 C_{1-24} 烷基、任选取代的 C_{2-24} 烯基、任选取代的 C_{2-24} 炔基、任选取代的 C_{3-6} 环烷基和任选取代的 C_{3-6} 环烯基。

52. 如权利要求 48 所述的用途或方法,其中 R^{8A} 不存在或为氢;且 R^{9A} 为任选取代的 N-连接氨基酸或任选取代的 N-连接氨基酸酯衍生物。

53. 如权利要求 48 所述的用途或方法,其中 R^{8A} 为任选取代的芳基;且 R^{9A} 为任选取代的 N-连接氨基酸或任选取代的 N-连接氨基酸酯衍生物。

54. 如权利要求 52 或 53 所述的用途或方法,其中 R^{9A} 选自丙氨酸、天冬酰胺、天冬氨酸、半胱氨酸、谷氨酸、谷氨酰胺、甘氨酸、脯氨酸、丝氨酸、酪氨酸、精氨酸、组氨酸、异亮氨酸、亮氨酸、赖氨酸、蛋氨酸、苯丙氨酸、苏氨酸、色氨酸、缬氨酸及其酯衍生物。

55. 如权利要求 54 所述的用途或方法,其中 R^{9A} 选自丙氨酸异丙基酯、丙氨酸环己基酯、丙氨酸新戊基酯、缬氨酸异丙基酯和亮氨酸异丙基酯。

56. 如权利要求 52 或 53 所述的用途或方法,其中 R^{9A} 具有结构  其

中 R^{33A} 选自氢、任选取代的 C_{1-6} 烷基、任选取代的 C_{3-6} 环烷基、任选取代的芳基、任选取代的芳基 (C_{1-6} 烷基) 和任选取代的卤代烷基; R^{34A} 选自氢、任选取代的 C_{1-6} 烷基、任选取代的 C_{1-6} 卤代烷基、任选取代的 C_{3-6} 环烷基、任选取代的 C_6 芳基、任选取代的 C_{10} 芳基和任选取代的芳基 (C_{1-6} 烷基);且 R^{35A} 为氢或任选取代的 C_{1-4} 烷基;或 R^{34A} 和 R^{35A} 在一起形成任选取代的 C_{3-6} 环烷基。

57. 如权利要求 56 所述的用途或方法,其中 R^{34A} 为任选取代的 C_{1-6} 烷基。

58. 如权利要求 57 所述的用途或方法,其中所述任选取代的 C_{1-6} 烷基为甲基。

59. 如权利要求 56-58 中任一权利要求所述的用途或方法,其中 R^{35A} 为氢。

60. 如权利要求 56-59 中任一权利要求所述的用途或方法,其中 R^{33A} 为任选取代的 C_{1-6} 烷基、任选取代的 C_{3-6} 环烷基或任选取代的苄基。

61. 如权利要求 48-60 中任一权利要求所述的用途或方法,其中 Z^{2A} 为 O。

62. 如权利要求 48-60 中任一权利要求所述的用途或方法,其中 Z^{2A} 为 S。

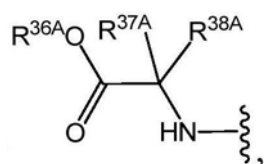
63. 如权利要求 16 所述的用途或方法, 其中 R^{1A} 为 $R^{10A}-P(=Z^{3A})(R^{11A})$ 。

64. 如权利要求 63 所述的用途或方法, 其中 R^{10A} 和 R^{11A} 均为任选取代的 N-连接氨基酸或任选取代的 N-连接氨基酸酯衍生物。

65. 如权利要求 64 所述的用途或方法, 其中 R^{10A} 和 R^{11A} 独立地选自丙氨酸、天冬酰胺、天冬氨酸、半胱氨酸、谷氨酸、谷氨酰胺、甘氨酸、脯氨酸、丝氨酸、酪氨酸、精氨酸、组氨酸、异亮氨酸、亮氨酸、赖氨酸、蛋氨酸、苯丙氨酸、苏氨酸、色氨酸、缬氨酸及其酯衍生物。

66. 如权利要求 65 所述的用途或方法, 其中 R^{10A} 和 R^{11A} 独立地选自丙氨酸异丙基酯、丙氨酸环己基酯、丙氨酸新戊基酯、缬氨酸异丙基酯和亮氨酸异丙基酯。

67. 如权利要求 64 所述的用途或方法, 其中 R^{10A} 和 R^{11A} 独立地具有结构



其中 R^{36A} 选自氢、任选取代的 C_{1-6} 烷基、任选取代的 C_{3-6} 环烷基、任选取

代的芳基、任选取代的芳基 (C_{1-6} 烷基) 和任选取代的卤代烷基; R^{37A} 选自氢、任选取代的 C_{1-6} 烷基、任选取代的 C_{1-6} 卤代烷基、任选取代的 C_{3-6} 环烷基、任选取代的 C_6 芳基、任选取代的 C_{10} 芳基和任选取代的芳基 (C_{1-6} 烷基); 且 R^{38A} 为氢或任选取代的 C_{1-4} 烷基; 或 R^{37A} 和 R^{38A} 在一起形成任选取代的 C_{3-6} 环烷基。

68. 如权利要求 67 所述的用途或方法, 其中 R^{42A} 为任选取代的 C_{1-6} 烷基。

69. 如权利要求 68 所述的用途或方法, 其中所述任选取代的 C_{1-6} 烷基为甲基。

70. 如权利要求 67-69 中任一权利要求所述的用途或方法, 其中 R^{43A} 为氢。

71. 如权利要求 67-70 中任一权利要求所述的用途或方法, 其中 R^{41A} 为任选取代的 C_{1-6} 烷基、任选取代的 C_{3-6} 环烷基或任选取代的苄基。

72. 如权利要求 63-71 中任一权利要求所述的用途或方法, 其中 Z^{3A} 为 O。

73. 如权利要求 63-71 中任一权利要求所述的用途或方法, 其中 Z^{3A} 为 S。

74. 如权利要求 16 所述的用途或方法, 其中 R^{1A} 为 $R^{12A}O-P(=O)(OR^{13A})-O-P(=O)(OR^{14A})_m$ 。

75. 如权利要求 74 所述的用途或方法, 其中 m 为 0, 且 R^{12A} 和 R^{13A} 独立地不存在或为氢。

76. 如权利要求 74 所述的用途或方法, 其中 m 为 1, 且 R^{12A} 、 R^{13A} 和 R^{14A} 独立地不存在或为氢。

77. 如权利要求 16 所述的用途或方法, 其中 R^{1A} 为 H。

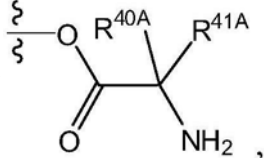
78. 如权利要求 16 所述的用途或方法, 其中 R^{1A} 为任选取代的酰基。

79. 如权利要求 78 所述的用途或方法, 其中所述任选取代的酰基为 $-C(=O)R^{39A}$, 其中 R^{39A} 选自任选取代的 C_{1-12} 烷基、任选取代的 C_{2-12} 烯基、任选取代的 C_{2-12} 炔基、任选取代的

C₃₋₈ 环烷基、任选取代的 C₅₋₈ 环烯基、任选取代的 C₆₋₁₀ 芳基、任选取代的杂芳基、任选取代的杂环基、任选取代的芳基 (C₁₋₆ 烷基)、任选取代的杂芳基 (C₁₋₆ 烷基) 和任选取代的杂环基 (C₁₋₆ 烷基)。

80. 如权利要求 79 所述的用途或方法, 其中 R^{39A} 为取代的或未取代 C₁₋₁₂ 烷基。

81. 如权利要求 16 所述的用途或方法, 其中 R^{1A} 为任选取代的 O- 连接氨基酸。

82. 如权利要求 16 所述的用途或方法, 其中 R^{1A} 为  其中 R^{40A} 选自氢、

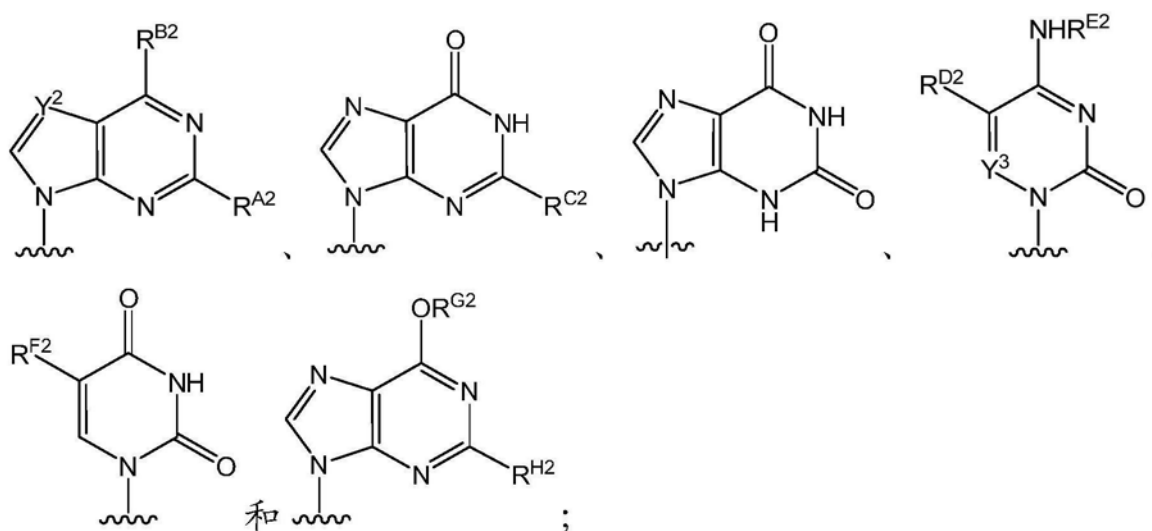
任选取代的 C₁₋₆ 烷基、任选取代的 C₁₋₆ 卤代烷基、任选取代的 C₃₋₆ 环烷基、任选取代的 C₆ 芳基、任选取代的 C₁₀ 芳基和任选取代的芳基 (C₁₋₆ 烷基); 且 R^{41A} 为氢或任选取代的 C₁₋₄ 烷基; 或 R^{40A} 和 R^{41A} 在一起形成任选取代的 C₃₋₆ 环烷基。

83. 如权利要求 82 所述的用途或方法, 其中 R^{40A} 为任选取代的 C₁₋₆ 烷基。

84. 如权利要求 83 所述的用途或方法, 其中所述任选取代的 C₁₋₆ 烷基为甲基。

85. 如权利要求 82-84 中任一权利要求所述的用途或方法, 其中 R^{41A} 为氢。

86. 如权利要求 16-85 中任一权利要求所述的用途或方法, 其中 B^{1A} 选自:



其中:

R^{A2} 选自氢、卤素和 NHR^{J2}, 其中 R^{J2} 选自氢、-C(=O)R^{K2} 和 -C(=O)OR^{L2};

R^{B2} 为卤素或 NHR^{W2}, 其中 R^{W2} 选自氢、任选取代的 C₁₋₆ 烷基、任选取代的 C₂₋₆ 烯基、任选取代的 C₃₋₈ 环烷基、-C(=O)R^{M2} 和 -C(=O)OR^{N2};

R^{C2} 为氢或 NHR^{O2}, 其中 R^{O2} 选自氢、-C(=O)R^{P2} 和 -C(=O)OR^{Q2};

R^{D2} 选自氢、卤素、任选取代的 C₁₋₆ 烷基、任选取代的 C₂₋₆ 烯基和任选取代的 C₂₋₆ 炔基;

R^{E2} 选自氢、羟基、任选取代的 C₁₋₆ 烷基、任选取代的 C₃₋₈ 环烷基、-C(=O)R^{R2} 和 -C(=O)OR^{S2};

R^{F2} 选自氢、卤素、任选取代的 C₁₋₆ 烷基、任选取代的 C₂₋₆ 烯基和任选取代的 C₂₋₆ 炔基;

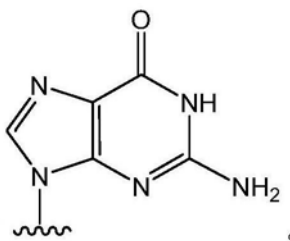
Y² 和 Y³ 独立地为 N 或 CR^{I2}, 其中 R^{I2} 选自氢、卤素、任选取代的 C₁₋₆ 烷基、任选取代的 C₂₋₆ 烯基和任选取代的 C₂₋₆ 炔基;

R^{G2} 为任选取代的 C₁₋₆ 烷基;

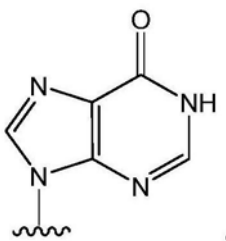
R^{H2} 为氢或 NHR^{T2} , 其中 R^{T2} 独立地选自氢、 $-C(=O)R^{U2}$ 和 $-C(=O)OR^{V2}$; 且

R^{K2} 、 R^{L2} 、 R^{M2} 、 R^{N2} 、 R^{P2} 、 R^{Q2} 、 R^{R2} 、 R^{S2} 、 R^{U2} 和 R^{V2} 独立地选自 C_{1-6} 烷基、 C_{2-6} 烯基、 C_{2-6} 炔基、 C_{3-6} 环烷基、 C_{3-6} 环烯基、 C_{6-10} 芳基、杂芳基、杂脂环基、芳基 (C_{1-6} 烷基)、杂芳基 (C_{1-6} 烷基) 和杂脂环基 (C_{1-6} 烷基)。

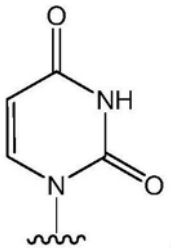
87. 如权利要求 86 所述的用途或方法, 其中 B^{1A} 为



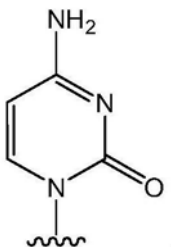
88. 如权利要求 86 所述的用途或方法, 其中 B^{1A} 为



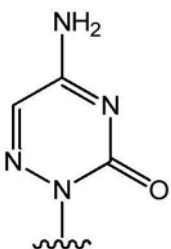
89. 如权利要求 86 所述的用途或方法, 其中 B^{1A} 为



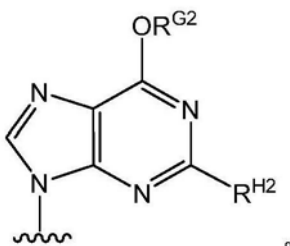
90. 如权利要求 86 所述的用途或方法, 其中 B^{1A} 为



91. 如权利要求 86 所述的用途或方法, 其中 B^{1A} 为



92. 如权利要求 86 所述的用途或方法, 其中 B^{1A} 为



93. 如权利要求 16-92 中任一权利要求所述的用途或方法, 其中所述虚线 (-----) 为

单键, R^{2A} 为 CH_2 且 R^{3A} 为 O。

94. 如权利要求 16-92 中任一权利要求所述的用途或方法, 其中所述虚线 (-----) 不存在, R^{2A} 选自任选取代的 C_{1-6} 烷基、任选取代的 C_{2-6} 烯基、任选取代的 C_{2-6} 炔基、任选取代的 $-O-C_{1-6}$ 烷基、任选取代的 $-O-C_{3-6}$ 烯基、任选取代的 $-O-C_{3-6}$ 炔基和氰基, 且 R^{3A} 选自 OH 、 $-OC(=O)R^{7A}$ 和任选取代的 O- 连接氨基酸。

95. 如权利要求 94 所述的用途或方法, 其中 R^{2A} 为任选取代的 C_{1-6} 烷基。

96. 如权利要求 95 所述的用途或方法, 其中 R^{2A} 为未取代 C_{1-6} 烷基。

97. 如权利要求 94 所述的用途或方法, 其中 R^{2A} 为任选取代的 C_{2-6} 烯基。

98. 如权利要求 97 所述的用途或方法, 其中 R^{2A} 为未取代 C_{2-6} 烯基。

99. 如权利要求 94 所述的用途或方法, 其中 R^{2A} 为任选取代的 C_{2-6} 炔基。

100. 如权利要求 99 所述的用途或方法, 其中 R^{2A} 为未取代 C_{2-6} 炔基。

101. 如权利要求 94 所述的用途或方法, 其中 R^{2A} 为任选取代的 C_{3-6} 环烷基。

102. 如权利要求 94 所述的用途或方法, 其中 R^{2A} 为任选取代的 $-O-C_{1-6}$ 烷基。

103. 如权利要求 102 所述的用途或方法, 其中 R^{2A} 为未取代 $-O-C_{1-6}$ 烷基。

104. 如权利要求 94 所述的用途或方法, 其中 R^{2A} 为任选取代的 $-O-C_{3-6}$ 烯基。

105. 如权利要求 104 所述的用途或方法, 其中 R^{2A} 为未取代的 $-O-C_{3-6}$ 烯基。

106. 如权利要求 94 所述的用途或方法, 其中 R^{2A} 为任选取代的 $-O-C_{3-6}$ 炔基。

107. 如权利要求 106 所述的用途或方法, 其中 R^{2A} 为未取代的 $-O-C_{3-6}$ 炔基。

108. 如权利要求 94 所述的用途或方法, 其中 R^{2A} 为氰基。

109. 如权利要求 16-108 中任一权利要求所述的用途或方法, 其中 R^{3A} 为 OH 。

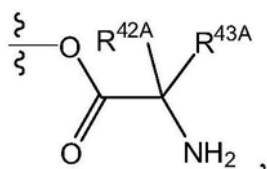
110. 如权利要求 16-108 中任一权利要求所述的用途或方法, 其中 R^{3A} 为 $-OC(=O)R^{7A}$ 。

111. 如权利要求 110 所述的用途或方法, 其中 R^{7A} 为任选取代的 C_{1-8} 烷基。

112. 如权利要求 16-108 中任一权利要求所述的用途或方法, 其中 R^{3A} 为 O- 连接氨基酸。

113. 如权利要求 112 所述的用途或方法, 其中所述 O- 连接氨基酸选自丙氨酸、天冬酰胺、天冬氨酸、半胱氨酸、谷氨酸、谷氨酰胺、甘氨酸、脯氨酸、丝氨酸、酪氨酸、精氨酸、组氨酸、异亮氨酸、亮氨酸、赖氨酸、蛋氨酸、苯丙氨酸、苏氨酸、色氨酸和缬氨酸, 适合的氨基酸的另外实例包括但不限于鸟氨酸、尾下素、2- 氨基异丁酸、脱氢丙氨酸、 γ - 氨基丁酸、瓜氨酸、 β - 丙氨酸、 α - 乙基 - 甘氨酸、 α - 丙基 - 甘氨酸和正亮氨酸。

114. 如权利要求 16-108 中任一权利要求所述的用途或方法, 其中 R^{3A} 为



其中 R^{42A} 选自氢、任选取代的 C_{1-6} 烷基、任选取代的 C_{1-6} 卤代烷基、任选取代的 C_{3-6} 环烷基、任选取代的 C_6 芳基、任选取代的 C_{10} 芳基和任选取代的芳基 (C_{1-6} 烷基); 且 R^{43A} 为氢或任选取代的 C_{1-4} 烷基; 或 R^{42A} 和 R^{43A} 在一起形成任选取代的 C_{3-6} 环烷基。

115. 如权利要求 114 所述的用途或方法, 其中 R^{42A} 为任选取代的 C_{1-6} 烷基。

116. 如权利要求 115 所述的用途或方法, 其中所述任选取代的 C_{1-6} 烷基为甲基。

117. 如权利要求 114-116 中任一权利要求所述的化合物,其中 R^{43A} 为氢。

118. 如权利要求 16-117 中任一权利要求所述的用途或方法,其中 R^{5A} 为氢。

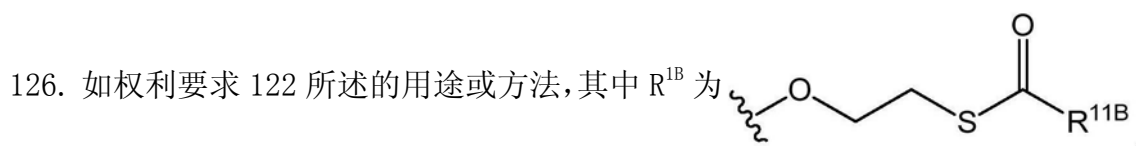
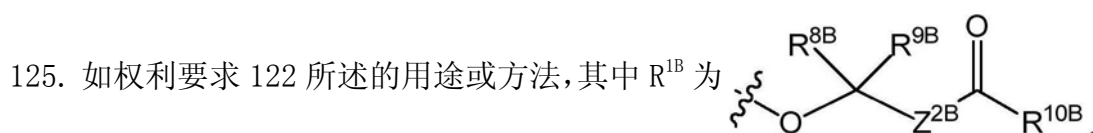
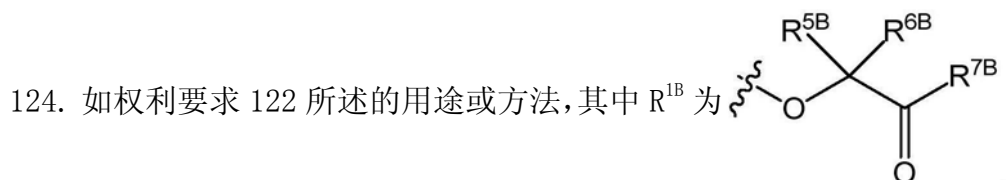
119. 如权利要求 16-117 中任一权利要求所述的用途或方法,其中 R^{5A} 为卤素。

120. 如权利要求 119 所述的用途或方法,其中 R^{5A} 为氟。

121. 如权利要求 16-120 中任一权利要求所述的用途或方法,其中 R^{4A} 为氟。

122. 如权利要求 1 或 3-15 中任一权利要求所述的用途或权利要求 2-15 中任一权利要求所述的方法,其中所述化合物为式 (II) 的化合物。

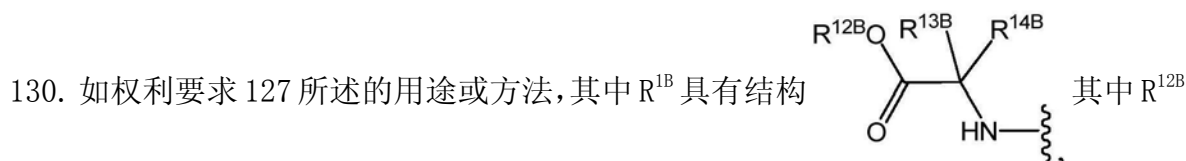
123. 如权利要求 122 所述的用途或方法,其中 R^{1B} 为 O^- 或 OH 。



127. 如权利要求 122 所述的用途或方法,其中 R^{1B} 为任选取代的 N-连接氨基酸或任选取代的 N-连接氨基酸酯衍生物。

128. 如权利要求 127 所述的用途或方法,其中 R^{1B} 选自丙氨酸、天冬酰胺、天冬氨酸、半胱氨酸、谷氨酸、谷氨酰胺、甘氨酸、脯氨酸、丝氨酸、酪氨酸、精氨酸、组氨酸、异亮氨酸、亮氨酸、赖氨酸、蛋氨酸、苯丙氨酸、苏氨酸、色氨酸、缬氨酸及其酯衍生物。

129. 如权利要求 128 所述的用途或方法,其中 R^{1B} 选自丙氨酸异丙基酯、丙氨酸环己基酯、丙氨酸新戊基酯、缬氨酸异丙基酯和亮氨酸异丙基酯。



选自氢、任选取代的 C_{1-6} 烷基、任选取代的 C_{3-6} 环烷基、任选取代的芳基、任选取代的芳基 (C_{1-6} 烷基) 和任选取代的卤代烷基; R^{13B} 选自氢、任选取代的 C_{1-6} 烷基、任选取代的 C_{1-6} 卤代烷基、任选取代的 C_{3-6} 环烷基、任选取代的 C_6 芳基、任选取代的 C_{10} 芳基和任选取代的芳基 (C_{1-6} 烷基); 且 R^{14B} 为氢或任选取代的 C_{1-4} 烷基; 或 R^{13B} 和 R^{14B} 在一起形成任选取代的 C_{3-6} 环烷基。

131. 如权利要求 130 所述的用途或方法,其中 R^{13B} 为任选取代的 C_{1-6} 烷基。

132. 如权利要求 131 所述的用途或方法,其中所述任选取代的 C_{1-6} 烷基为甲基。

133. 如权利要求 130-132 中任一权利要求所述的用途或方法,其中 R^{14B} 为氢。

134. 如权利要求 130-133 中任一权利要求所述的用途或方法,其中 R^{12B} 为任选取代的

C₁₋₆ 烷基、任选取代的 C₃₋₆ 环烷基或任选取代的苄基。

135. 如权利要求 122-134 中任一权利要求所述的用途或方法, 其中 R^{2B} 为任选取代的 C₁₋₆ 烷基。

136. 如权利要求 135 所述的用途或方法, 其中 R^{2B} 为未取代 C₁₋₆ 烷基。

137. 如权利要求 122-134 中任一权利要求所述的用途或方法, 其中 R^{2B} 为任选取代的 C₂₋₆ 烯基。

138. 如权利要求 137 所述的用途或方法, 其中 R^{2B} 为未取代 C₂₋₆ 烯基。

139. 如权利要求 122-134 中任一权利要求所述的用途或方法, 其中 R^{2B} 为任选取代的 C₂₋₆ 炔基。

140. 如权利要求 139 所述的用途或方法, 其中 R^{2B} 为未取代 C₂₋₆ 炔基。

141. 如权利要求 122-134 中任一权利要求所述的用途或方法, 其中 R^{2B} 为任选取代的 -O-C₁₋₆ 烷基。

142. 如权利要求 141 所述的用途或方法, 其中 R^{2B} 为未取代 -O-C₁₋₆ 烷基。

143. 如权利要求 122-134 中任一权利要求所述的用途或方法, 其中 R^{2B} 为任选取代的 -O-C₃₋₆ 烯基。

144. 如权利要求 143 所述的用途或方法, 其中 R^{2B} 为未取代的 -O-C₃₋₆ 烯基。

145. 如权利要求 122-134 中任一权利要求所述的用途或方法, 其中 R^{2B} 为任选取代的 -O-C₃₋₆ 炔基。

146. 如权利要求 145 所述的用途或方法, 其中 R^{2B} 为未取代的 -O-C₃₋₆ 炔基。

147. 如权利要求 122-134 中任一权利要求所述的用途或方法, 其中 R^{2B} 为任选取代的 C₃₋₆ 环烷基。

148. 如权利要求 122-134 中任一权利要求所述的用途或方法, 其中 R^{2B} 为氰基。

149. 如权利要求 122-148 中任一权利要求所述的用途或方法, 其中 R^{4B} 为氢。

150. 如权利要求 122-148 中任一权利要求所述的用途或方法, 其中 R^{4B} 为卤素。

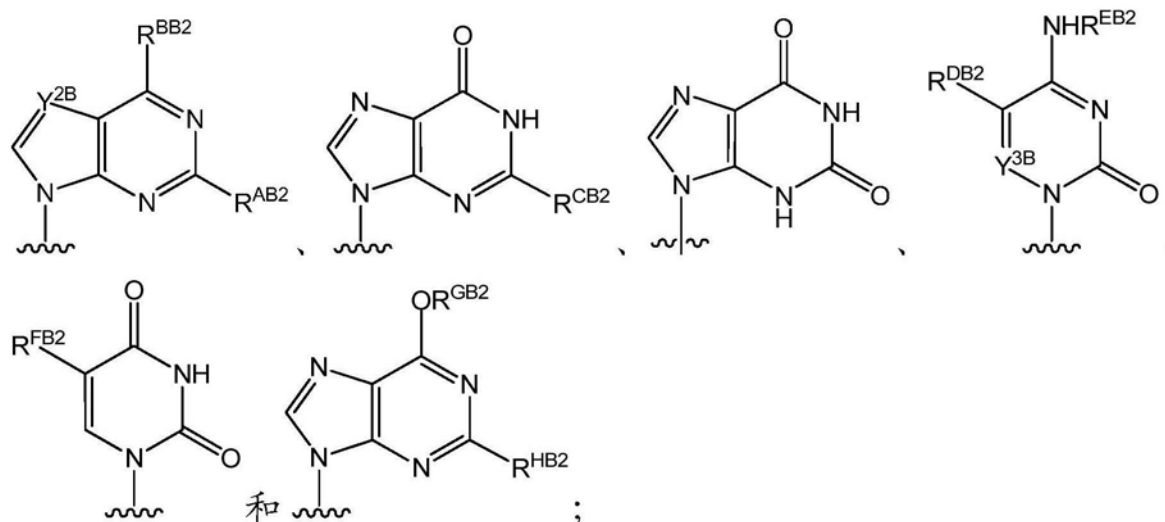
151. 如权利要求 150 所述的用途或方法, 其中 R^{4B} 为氟。

152. 如权利要求 122-151 中任一权利要求所述的用途或方法, 其中 R^{3B} 为氟。

153. 如权利要求 122-152 中任一权利要求所述的用途或方法, 其中 Z^{1B} 为 O。

154. 如权利要求 122-152 中任一权利要求所述的用途或方法, 其中 Z^{1B} 为 S。

155. 如权利要求 122-154 中任一权利要求所述的用途或方法, 其中 B^{1B} 选自:



其中：

R^{AB2} 选自氢、卤素和 NHR^{JB2} ，其中 R^{JB2} 选自氢、 $-C(=O)R^{KB2}$ 和 $-C(=O)OR^{LB2}$ ；

R^{BB2} 为卤素或 NHR^{WB2} ，其中 R^{WB2} 选自氢、任选取代的 C_{1-6} 烷基、任选取代的 C_{2-6} 烯基、任选取代的 C_{3-8} 环烷基、 $-C(=O)R^{MB2}$ 和 $-C(=O)OR^{NB2}$ ；

R^{CB2} 为氢或 NHR^{OB2} ，其中 R^{OB2} 选自氢、 $-C(=O)R^{PB2}$ 和 $-C(=O)OR^{QB2}$ ；

R^{DB2} 选自氢、卤素、任选取代的 C_{1-6} 烷基、任选取代的 C_{2-6} 烯基和任选取代的 C_{2-6} 炔基；

R^{EB2} 选自氢、羟基、任选取代的 C_{1-6} 烷基、任选取代的 C_{3-8} 环烷基、 $-C(=O)R^{RB2}$ 和 $-C(=O)OR^{SB2}$ ；

R^{FB2} 选自氢、卤素、任选取代的 C_{1-6} 烷基、任选取代的 C_{2-6} 烯基和任选取代的 C_{2-6} 炔基；

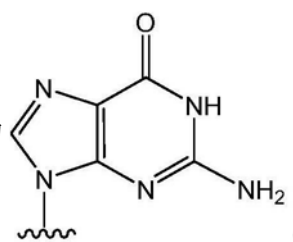
Y^{2B} 和 Y^{3B} 独立地为 N 或 CR^{IB2} ，其中 R^{IB2} 选自氢、卤素、任选取代的 C_{1-6} 烷基、任选取代的 C_{2-6} 烯基和任选取代的 C_{2-6} 炔基；

R^{GB2} 为任选取代的 C_{1-6} 烷基；

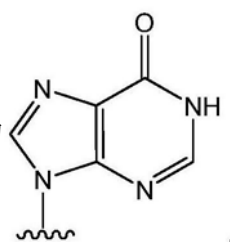
R^{HB2} 为氢或 NHR^{TB2} ，其中 R^{TB2} 独立地选自氢、 $-C(=O)R^{UB2}$ 和 $-C(=O)OR^{VB2}$ ；且

R^{KB2} 、 R^{LB2} 、 R^{MB2} 、 R^{NB2} 、 R^{PB2} 、 R^{QB2} 、 R^{RB2} 、 R^{SB2} 、 R^{UB2} 和 R^{VB2} 独立地选自 C_{1-6} 烷基、 C_{2-6} 烯基、 C_{2-6} 炔基、 C_{3-6} 环烷基、 C_{3-6} 环烯基、 C_{6-10} 芳基、杂芳基、杂脂环基、芳基 (C_{1-6} 烷基)、杂芳基 (C_{1-6} 烷基) 和杂脂环基 (C_{1-6} 烷基)。

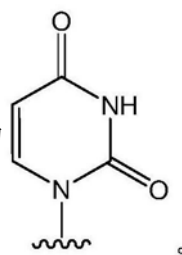
156. 如权利要求 155 所述的用途或方法，其中 B^{1B} 为



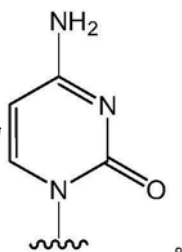
157. 如权利要求 155 所述的用途或方法，其中 B^{1B} 为



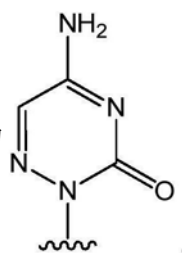
158. 如权利要求 155 所述的用途或方法, 其中 B^{1B} 为



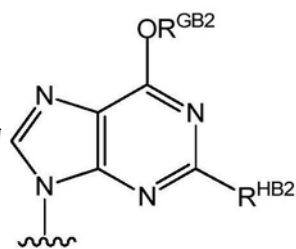
159. 如权利要求 155 所述的用途或方法, 其中 B^{1B} 为



160. 如权利要求 155 所述的用途或方法, 其中 B^{1B} 为



161. 如权利要求 155 所述的用途或方法, 其中 B^{1B} 为

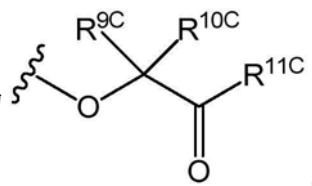


162. 如权利要求 1 或 3-15 中任一权利要求所述的用途或权利要求 2-15 中任一权利要求所述的方法, 其中所述化合物为式 (III) 的化合物。

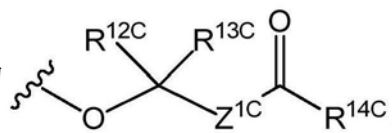
163. 如权利要求 162 所述的用途或方法, 其中 R^{1C} 为 O⁻ 或 OH。

164. 如权利要求 162 所述的用途或方法, 其中 R^{1C} 为任选取代的 C₁₋₆ 烃氧基。

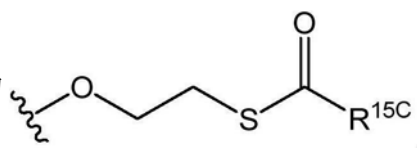
165. 如权利要求 162 所述的用途或方法, 其中 R^{1C} 为



166. 如权利要求 162 所述的化合物, 其中 R^{1C} 为



167. 如权利要求 162 所述的用途或方法, 其中 R^{1C} 为



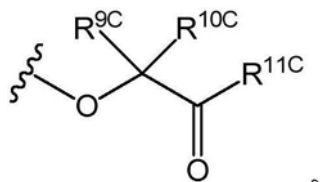
168. 如权利要求 162 所述的用途或方法, 其中 R^{1C} 为任选取代的 N- 连接氨基酸。

169. 如权利要求 162 所述的用途或方法, 其中 R^{1C} 为任选取代的 N- 连接氨基酸酯衍生物。

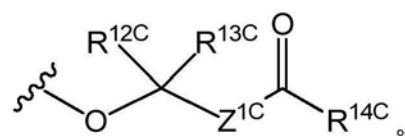
170. 如权利要求 162-169 中任一权利要求所述的用途或方法, 其中 R^{2C} 为 O^- 或 OH 。

171. 如权利要求 162-169 中任一权利要求所述的用途或方法, 其中 R^{2C} 为任选取代的 C_{1-6} 烃氧基。

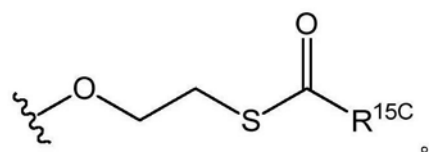
172. 如权利要求 162-169 中任一权利要求所述的用途或方法, 其中 R^{2C} 为



173. 如权利要求 162-169 中任一权利要求所述的用途或方法, 其中 R^{2C} 为



174. 如权利要求 162-169 中任一权利要求所述的用途或方法, 其中 R^{2C} 为



175. 如权利要求 162-169 中任一权利要求所述的用途或方法, 其中 R^{2C} 为任选取代的 N- 连接氨基酸。

176. 如权利要求 162-169 中任一权利要求所述的用途或方法, 其中 R^{2C} 为任选取代的 N- 连接氨基酸酯衍生物。

177. 如权利要求 176 所述的用途或方法, 其中 R^{1C} 为 $R^{16C}O-P(=O)(OR^{17C})-O-P(=O)(OR^{18C})-O$ 且 R^{2C}

为 O^- 或 OH ; 其中 R^{16C} 、 R^{17C} 和 R^{18C} 不存在或为氢; 且 n 为 0 或 1。

178. 如权利要求 162-177 中任一权利要求所述的用途或方法, 其中 R^{3C} 为任选取代的 C_{1-6} 烷基。

179. 如权利要求 178 所述的用途或方法, 其中 R^{3C} 为未取代 C_{1-6} 烷基。

180. 如权利要求 162-177 中任一权利要求所述的用途或方法, 其中 R^{3C} 为任选取代的 C_{2-6} 烯基。

181. 如权利要求 180 所述的用途或方法, 其中 R^{3C} 为未取代 C_{2-6} 烯基。

182. 如权利要求 162-177 中任一权利要求所述的用途或方法, 其中 R^{3C} 为任选取代的 C_{2-6} 炔基。

183. 如权利要求 182 所述的用途或方法, 其中 R^{3C} 为未取代 C_{2-6} 炔基。

184. 如权利要求 162-177 中任一权利要求所述的用途或方法, 其中 R^{3C} 为任选取代

的 $-O-C_{1-6}$ 烷基。

185. 如权利要求 184 所述的用途或方法, 其中 R^{3C} 为未取代 $-O-C_{1-6}$ 烷基。

186. 如权利要求 162-177 中任一权利要求所述的用途或方法, 其中 R^{3C} 为任选取代的 $-O-C_{3-6}$ 烯基。

187. 如权利要求 186 所述的用途或方法, 其中 R^{3C} 为未取代的 $-O-C_{3-6}$ 烯基。

188. 如权利要求 162-177 中任一权利要求所述的用途或方法, 其中 R^{3C} 为任选取代的 $-O-C_{3-6}$ 炔基。

189. 如权利要求 188 所述的用途或方法, 其中 R^{3C} 为未取代的 $-O-C_{3-6}$ 炔基。

190. 如权利要求 162-177 中任一权利要求所述的用途或方法, 其中 R^{3C} 为任选取代的 C_{3-6} 环烷基。

191. 如权利要求 162-177 中任一权利要求所述的用途或方法, 其中 R^{3C} 为氰基。

192. 如权利要求 162-191 中任一权利要求所述的用途或方法, 其中 R^{4C} 为 OH 。

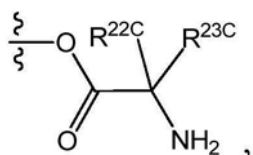
193. 如权利要求 162-191 中任一权利要求所述的用途或方法, 其中 R^{4C} 为 $-OC(=O)R^{5C}$ 。

194. 如权利要求 193 所述的用途或方法, 其中 R^{5C} 为任选取代的 C_{1-8} 烷基。

195. 如权利要求 162-191 中任一权利要求所述的用途或方法, 其中 R^{4C} 为 O -连接氨基酸。

196. 如权利要求 195 所述的用途或方法, 其中所述 O -连接氨基酸选自丙氨酸、天冬酰胺、天冬氨酸、半胱氨酸、谷氨酸、谷氨酰胺、甘氨酸、脯氨酸、丝氨酸、酪氨酸、精氨酸、组氨酸、异亮氨酸、亮氨酸、赖氨酸、蛋氨酸、苯丙氨酸、苏氨酸、色氨酸和缬氨酸, 适合的氨基酸的另外实例包括但不限于鸟氨酸、尾下素、2-氨基异丁酸、脱氢丙氨酸、 γ -氨基丁酸、瓜氨酸、 β -丙氨酸、 α -乙基-甘氨酸、 α -丙基-甘氨酸和正亮氨酸。

197. 如权利要求 162-191 中任一权利要求所述的用途或方法, 其中 R^{4C} 为



其中 R^{22C} 选自氢、任选取代的 C_{1-6} 烷基、任选取代的 C_{1-6} 卤代烷基、任选取

代的 C_{3-6} 环烷基、任选取代的 C_6 芳基、任选取代的 C_{10} 芳基和任选取代的芳基 (C_{1-6} 烷基); 且 R^{23C} 为氢或任选取代的 C_{1-4} 烷基; 或 R^{22C} 和 R^{23C} 在一起形成任选取代的 C_{3-6} 环烷基。

198. 如权利要求 197 所述的用途或方法, 其中 R^{22C} 为任选取代的 C_{1-6} 烷基。

199. 如权利要求 198 所述的用途或方法, 其中所述任选取代的 C_{1-6} 烷基为甲基。

200. 如权利要求 197-199 中任一权利要求所述的用途或方法, 其中 R^{23C} 为氢。

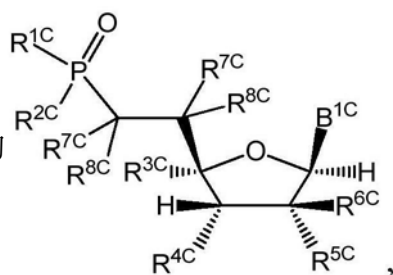
201. 如权利要求 162-200 中任一权利要求所述的用途或方法, 其中 R^{6C} 为卤素。

202. 如权利要求 162-200 中任一权利要求所述的用途或方法, 其中 R^{6C} 为氢。

203. 如权利要求 162-202 中任一权利要求所述的用途或方法, 其中 R^{5C} 为氟。

204. 如权利要求 162-203 中任一权利要求所述的用途或方法, 其中 ----- 为单键使

得式 (III) 具有结构



其中各个 R^{7C} 和各个 R^{8C} 独立地为氢或卤

素。

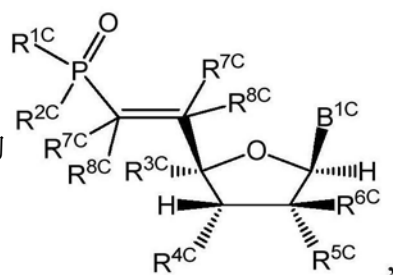
205. 如权利要求 204 所述的用途或方法, 其中 R^{7C} 和 R^{8C} 基团均为氢。

206. 如权利要求 204 所述的用途或方法, 其中一个 R^{7C} 为卤素, 一个 R^{7C} 为氢且两个 R^{8C} 均为氢。

207. 如权利要求 204 所述的用途或方法, 其中一个 R^{7C} 为卤素, 一个 R^{7C} 为氢, 一个 R^{8C} 为卤素且一个 R^{8C} 为氢。

208. 如权利要求 162-203 中任一权利要求所述的用途或方法, 其中 ----- 为双键使

得式 (III) 具有结构



其中各个 R^{7C} 不存在且各个 R^{8C} 独立地为

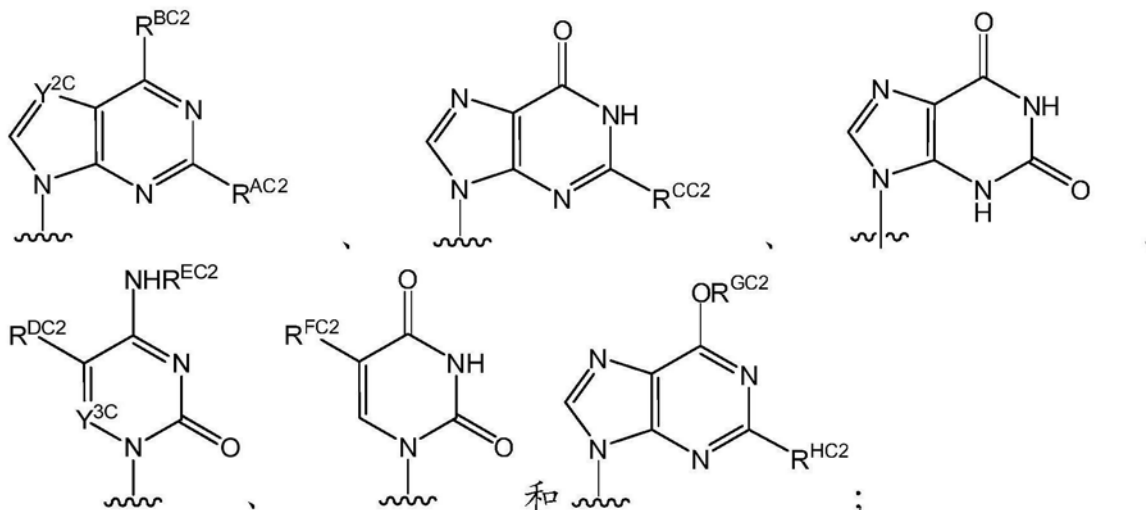
氢或卤素。

209. 如权利要求 208 所述的用途或方法, 其中两个 R^{8C} 基团为氢。

210. 如权利要求 208 所述的用途或方法, 其中一个 R^{8C} 为卤素且另一个 R^{8C} 为氢。

211. 如权利要求 208 所述的用途或方法, 其中两个 R^{8C} 基团为卤素。

212. 如权利要求 162-211 中任一权利要求所述的用途或方法, 其中 B^{1C} 选自:



其中:

R^{AC2} 选自氢、卤素和 NHR^{JC2} , 其中 R^{JC2} 选自氢、 $-C(=O)R^{KC2}$ 和 $-C(=O)OR^{LC2}$;

R^{BC2} 为卤素或 NHR^{WC2} , 其中 R^{WC2} 选自氢、任选取代的 C_{1-6} 烷基、任选取代的 C_{2-6} 烯基、任选取代的 C_{3-8} 环烷基、 $-C(=O)R^{MC2}$ 和 $-C(=O)OR^{NC2}$;

R^{CC2} 为氢或 NHR^{OC2} , 其中 R^{OC2} 选自氢、 $-C(=O)R^{PC2}$ 和 $-C(=O)OR^{QC2}$;

R^{DC2} 选自氢、卤素、任选取代的 C_{1-6} 烷基、任选取代的 C_{2-6} 烯基和任选取代的 C_{2-6} 炔基;

R^{EC2} 选自氢、羟基、任选取代的 C_{1-6} 烷基、任选取代的 C_{3-8} 环烷基、 $-C(=O)R^{RC2}$ 和 $-C(=O)OR^{SC2}$;

R^{FC2} 选自氢、卤素、任选取代的 C_{1-6} 烷基、任选取代的 C_{2-6} 烯基和任选取代的 C_{2-6} 炔基;

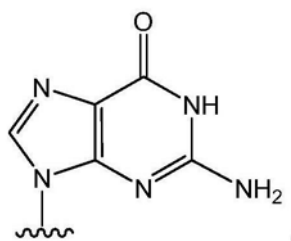
Y^{2C} 和 Y^{3C} 独立地为 N 或 CR^{IC2} , 其中 R^{IC2} 选自氢、卤素、任选取代的 C_{1-6} 烷基、任选取代的 C_{2-6} 烯基和任选取代的 C_{2-6} 炔基;

R^{GC2} 为任选取代的 C_{1-6} 烷基;

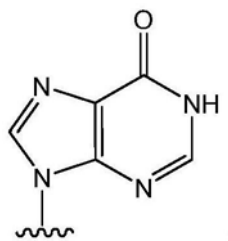
R^{HC2} 为氢或 NHR^{TC2} , 其中 R^{TC2} 独立地选自氢、 $-C(=O)R^{UC2}$ 和 $-C(=O)OR^{VC2}$; 且

R^{KC2} 、 R^{LC2} 、 R^{MC2} 、 R^{NC2} 、 R^{PC2} 、 R^{QC2} 、 R^{RC2} 、 R^{SC2} 、 R^{UC2} 和 R^{VC2} 独立地选自 C_{1-6} 烷基、 C_{2-6} 烯基、 C_{2-6} 炔基、 C_{3-6} 环烷基、 C_{3-6} 环烯基、 C_{6-10} 芳基、杂芳基、杂脂环基、芳基 (C_{1-6} 烷基)、杂芳基 (C_{1-6} 烷基) 和杂脂环基 (C_{1-6} 烷基)。

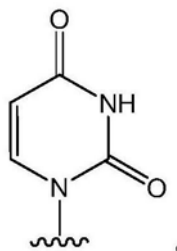
213. 如权利要求 212 所述的用途或方法, 其中 B^{1C} 为



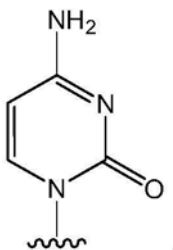
214. 如权利要求 212 所述的用途或方法, 其中 B^{1C} 为



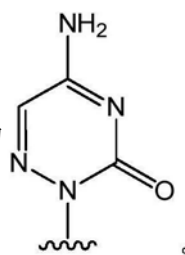
215. 如权利要求 212 所述的用途或方法, 其中 B^{1C} 为



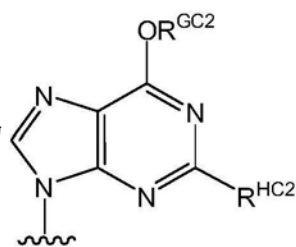
216. 如权利要求 212 所述的用途或方法, 其中 B^{1C} 为



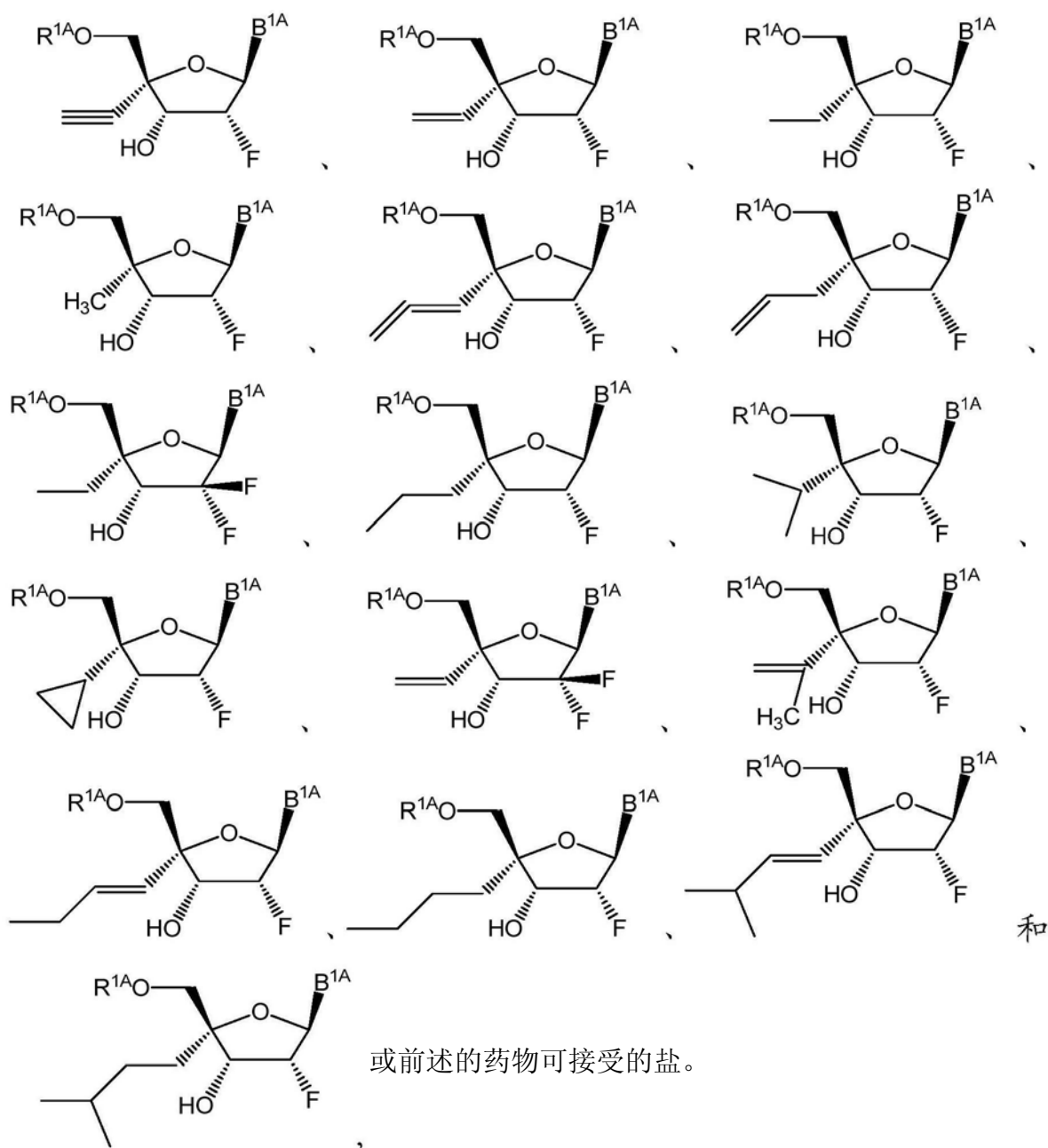
217. 如权利要求 212 所述的用途或方法, 其中 B^{1C} 为



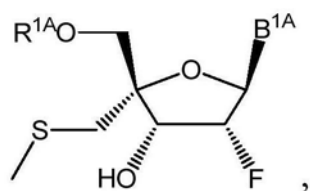
218. 如权利要求 212 所述的用途或方法, 其中 B^{1C} 为



219. 如权利要求 16 所述的用途或方法, 其中所述式 (I) 的化合物选自:

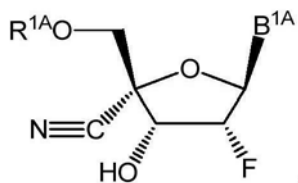


[illegible]



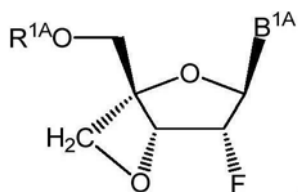
或前述的药物可接受的盐。

222. 如权利要求 16 所述的用途或方法, 其中所述式 (I) 的化合物为



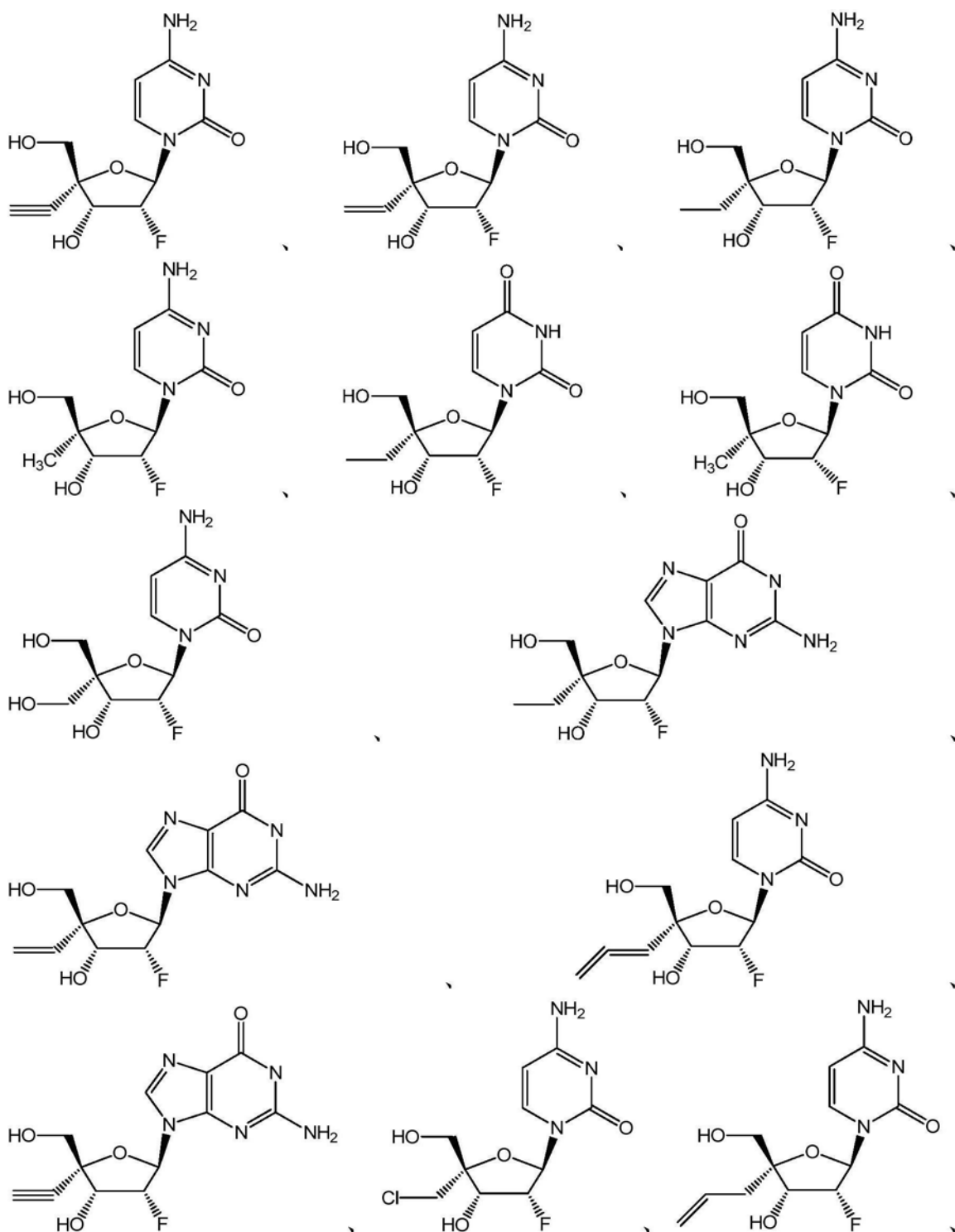
或其药物可接受的盐。

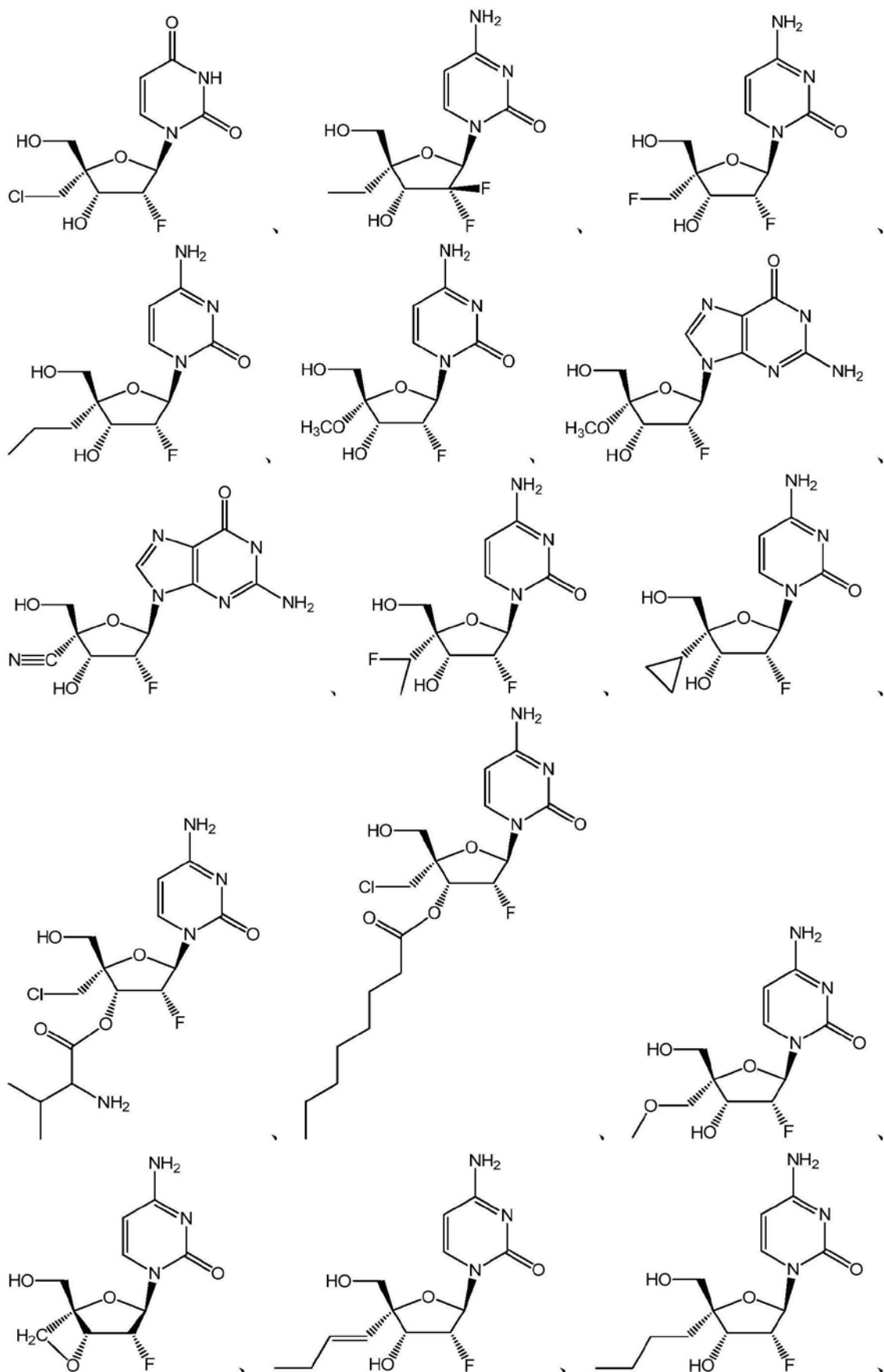
223. 如权利要求 16 所述的用途或方法, 其中所述式 (I) 的化合物为



或其药物可接受的盐。

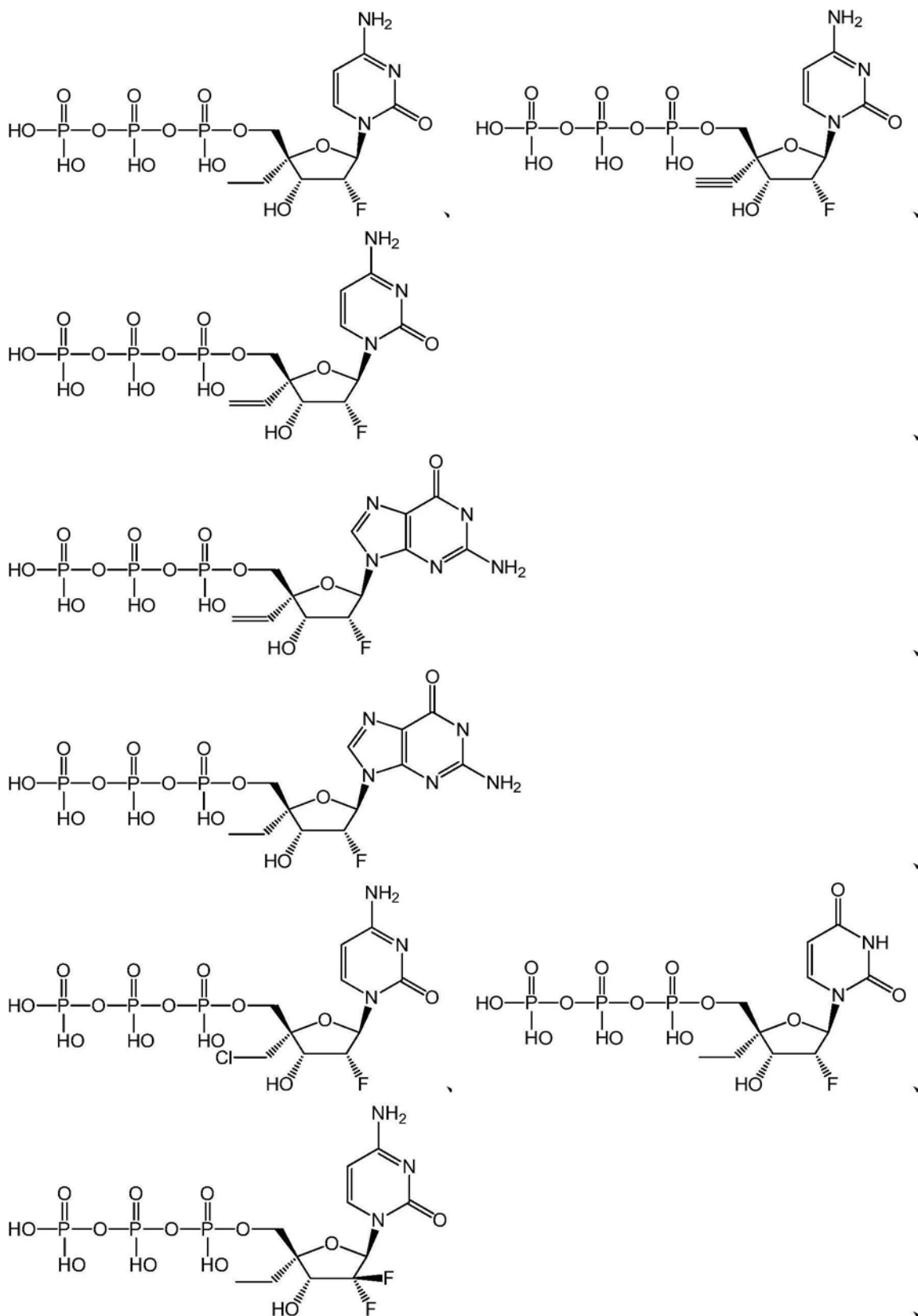
224. 如权利要求 16 所述的用途或方法, 其中所述式 (I) 的化合物选自:

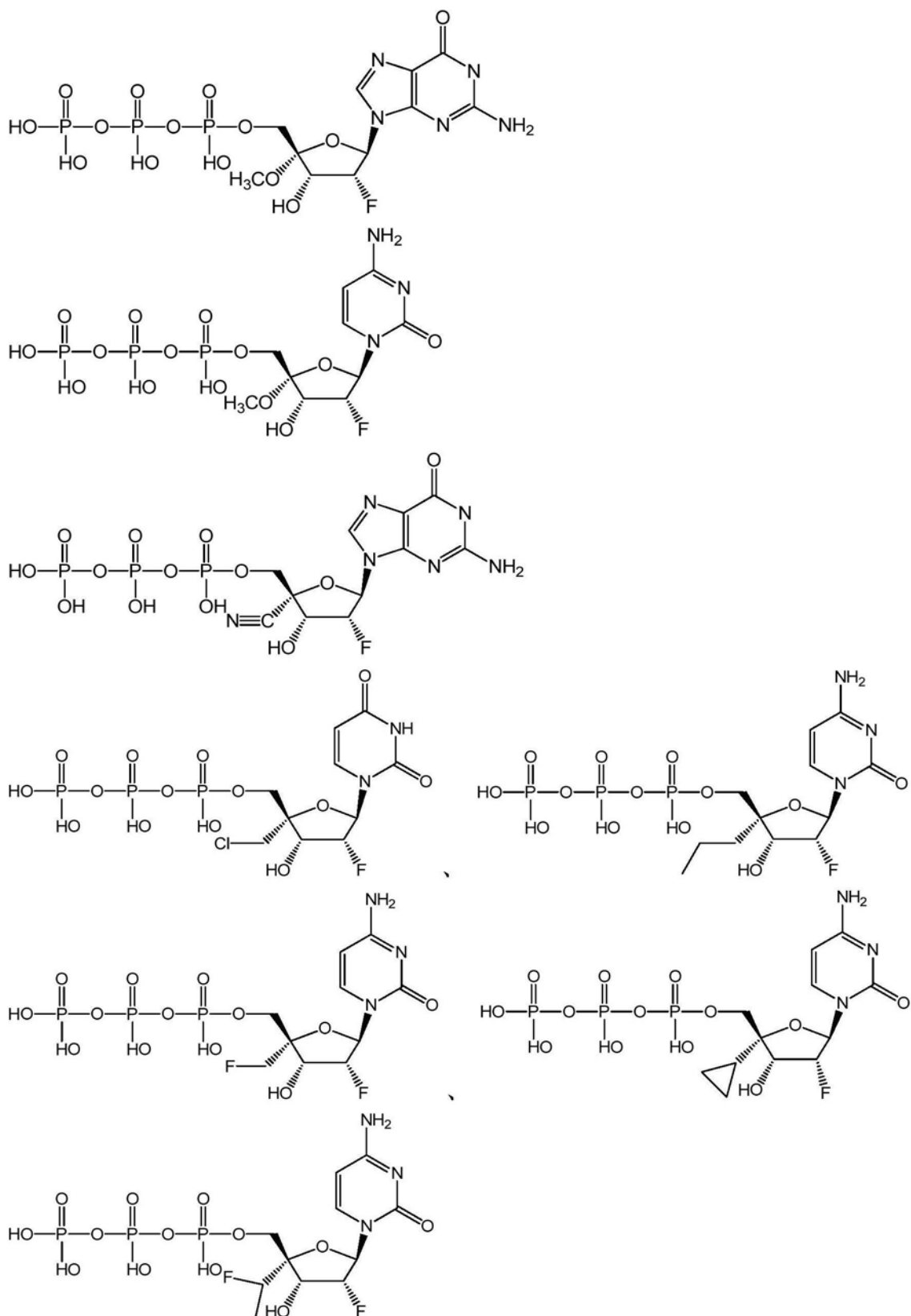


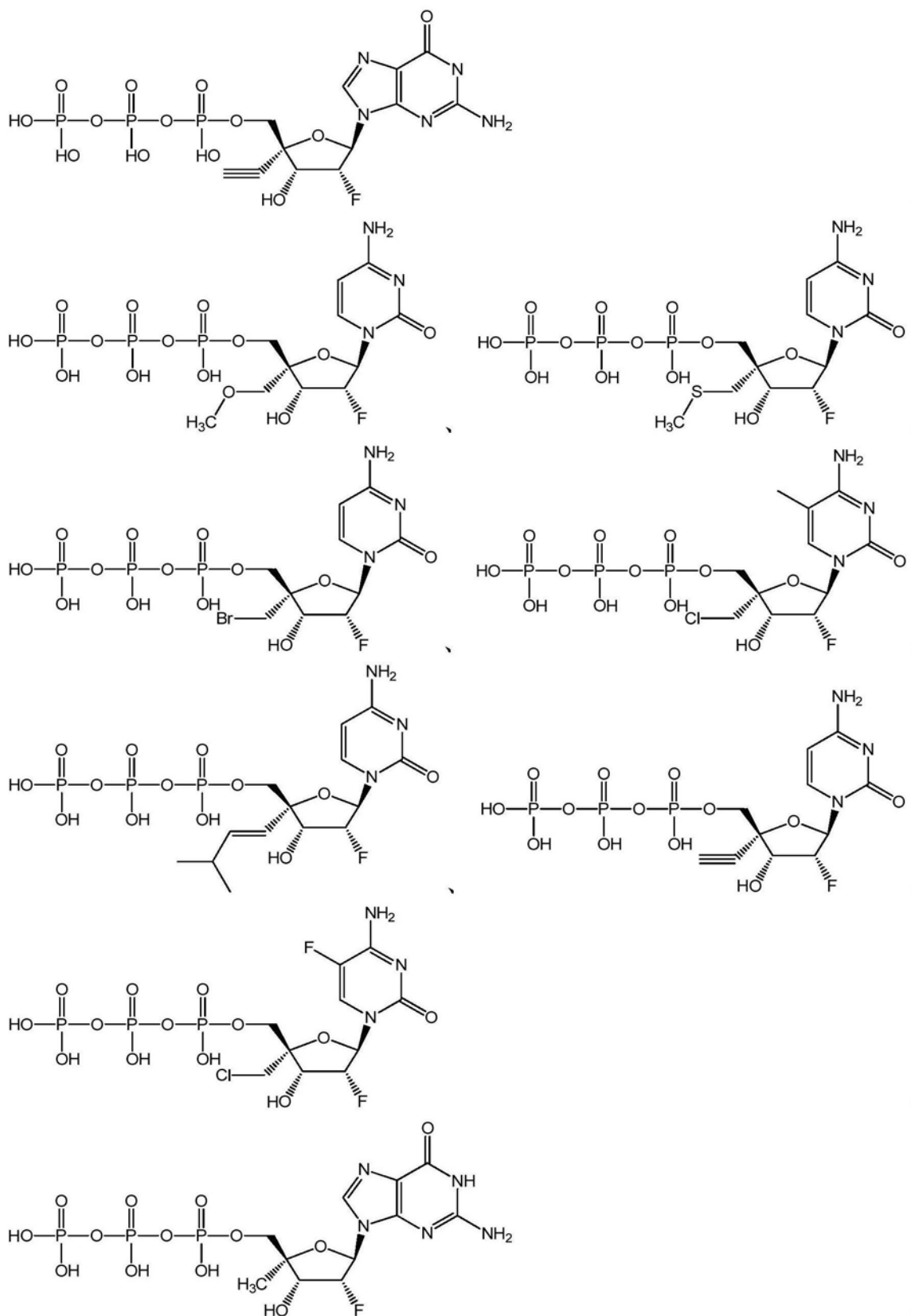


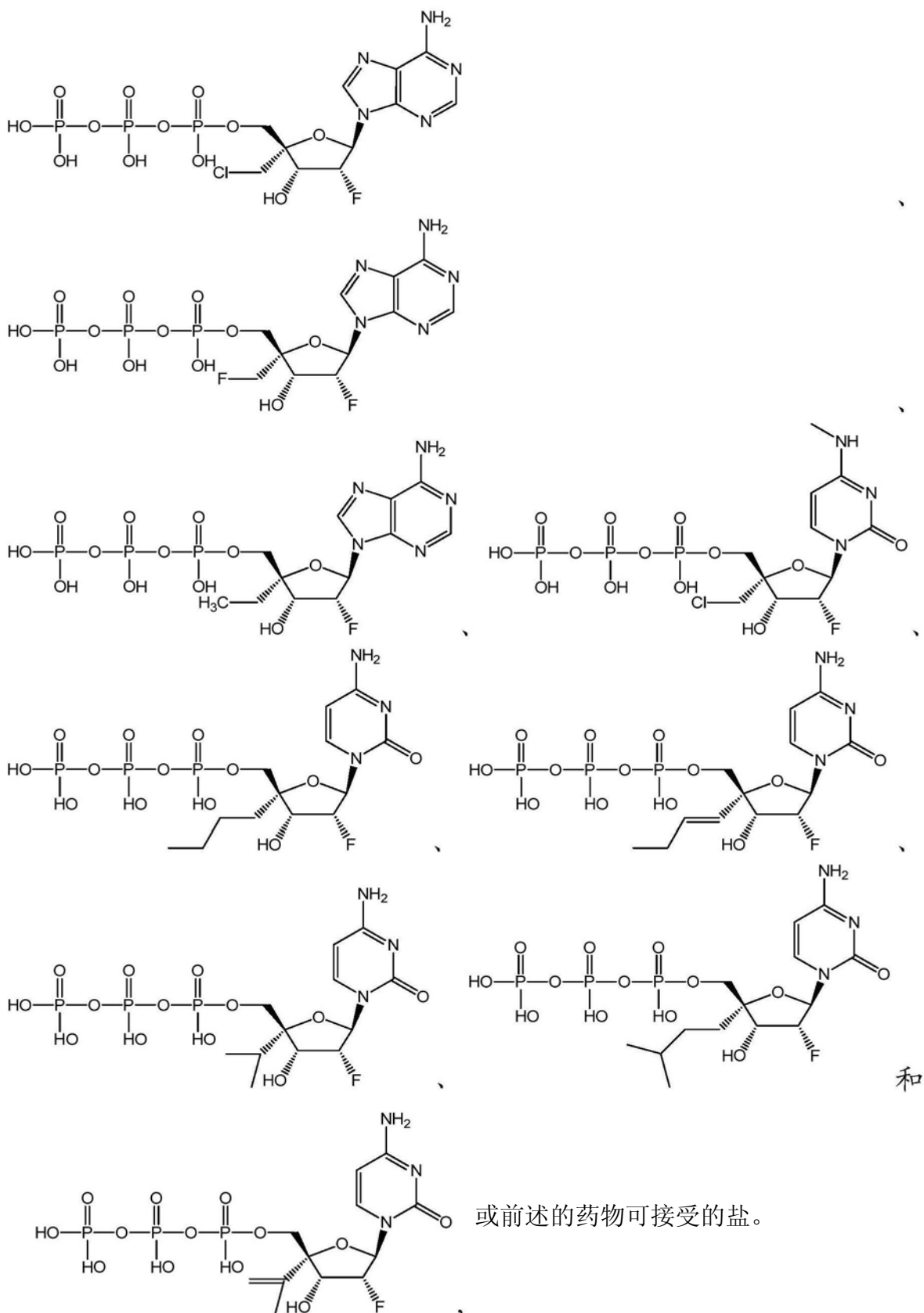




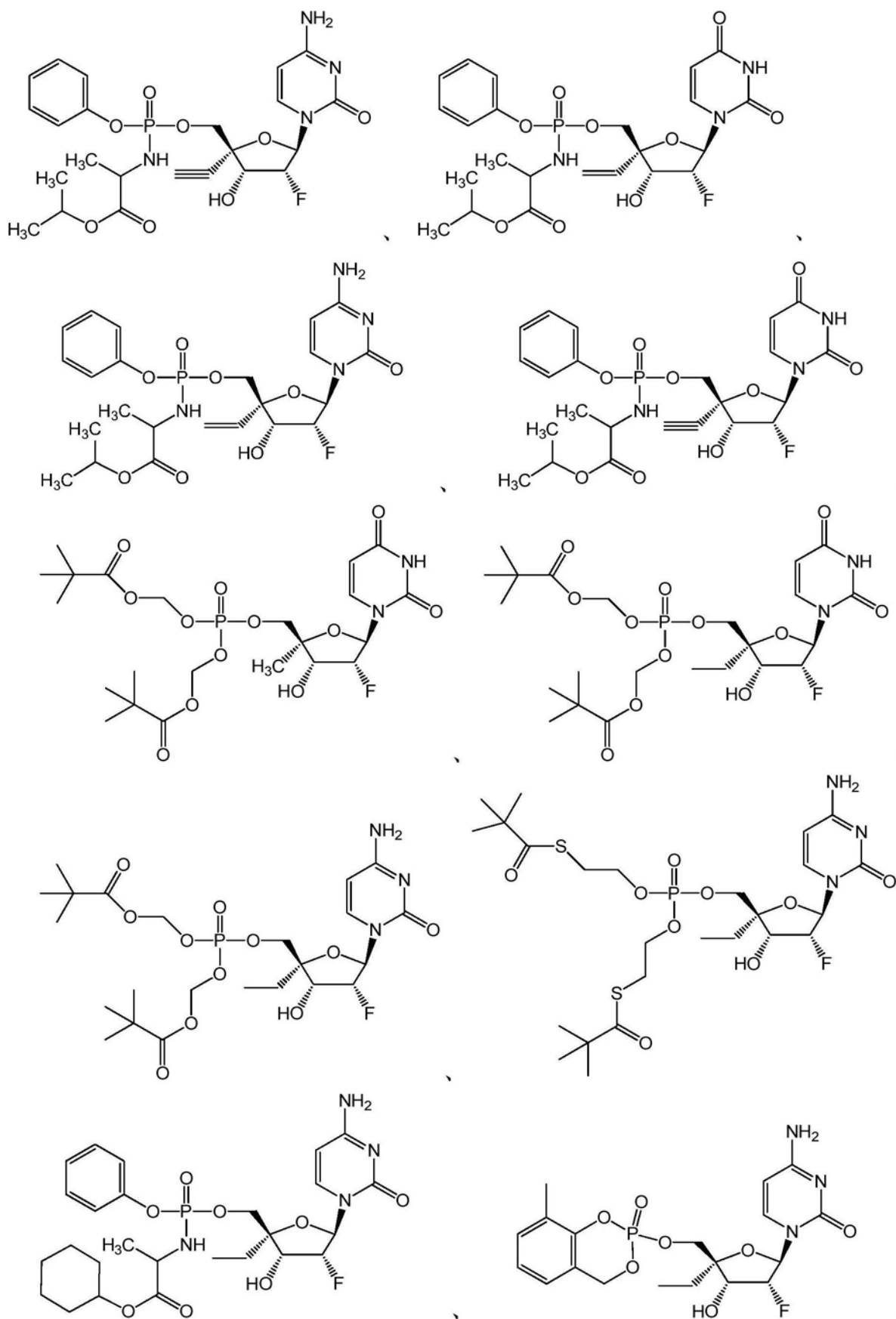


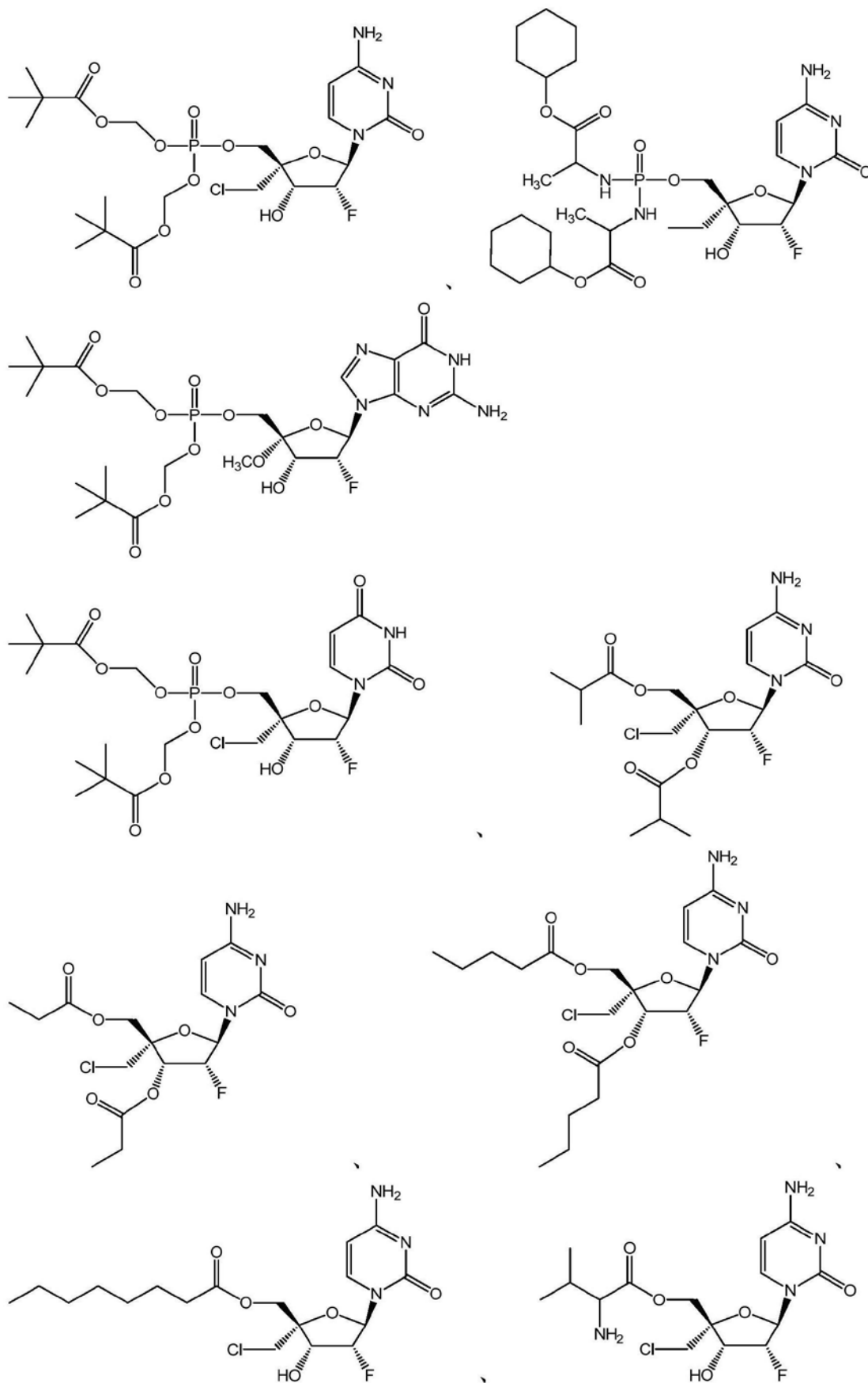


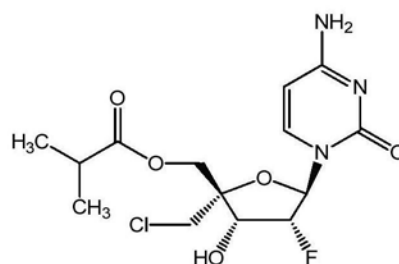
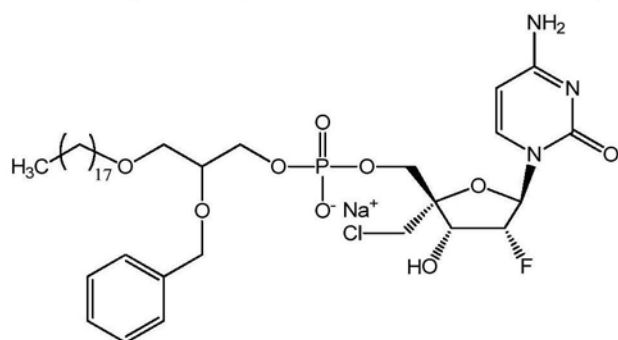
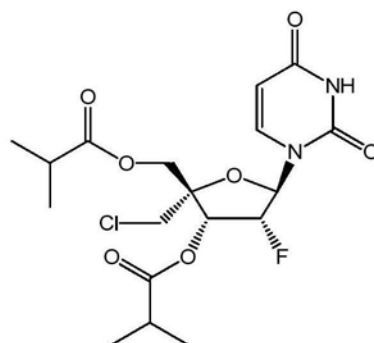
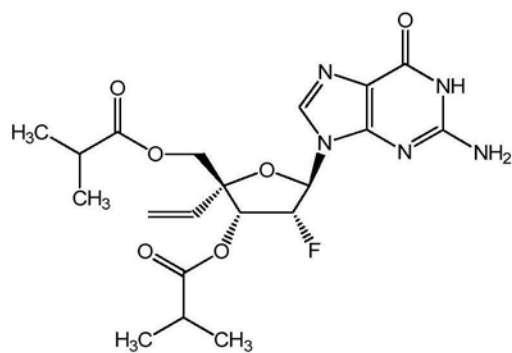
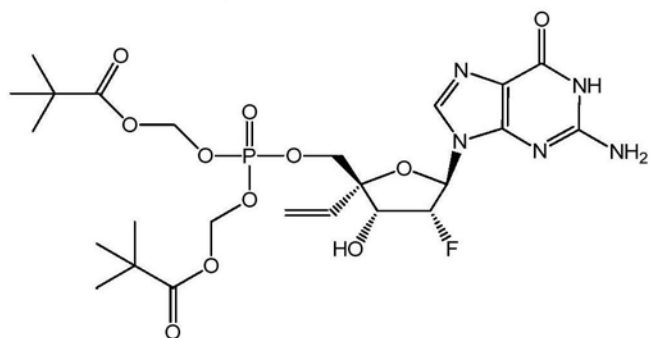
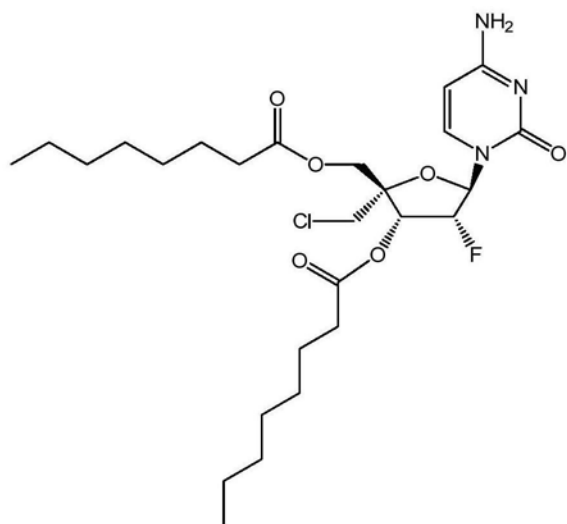


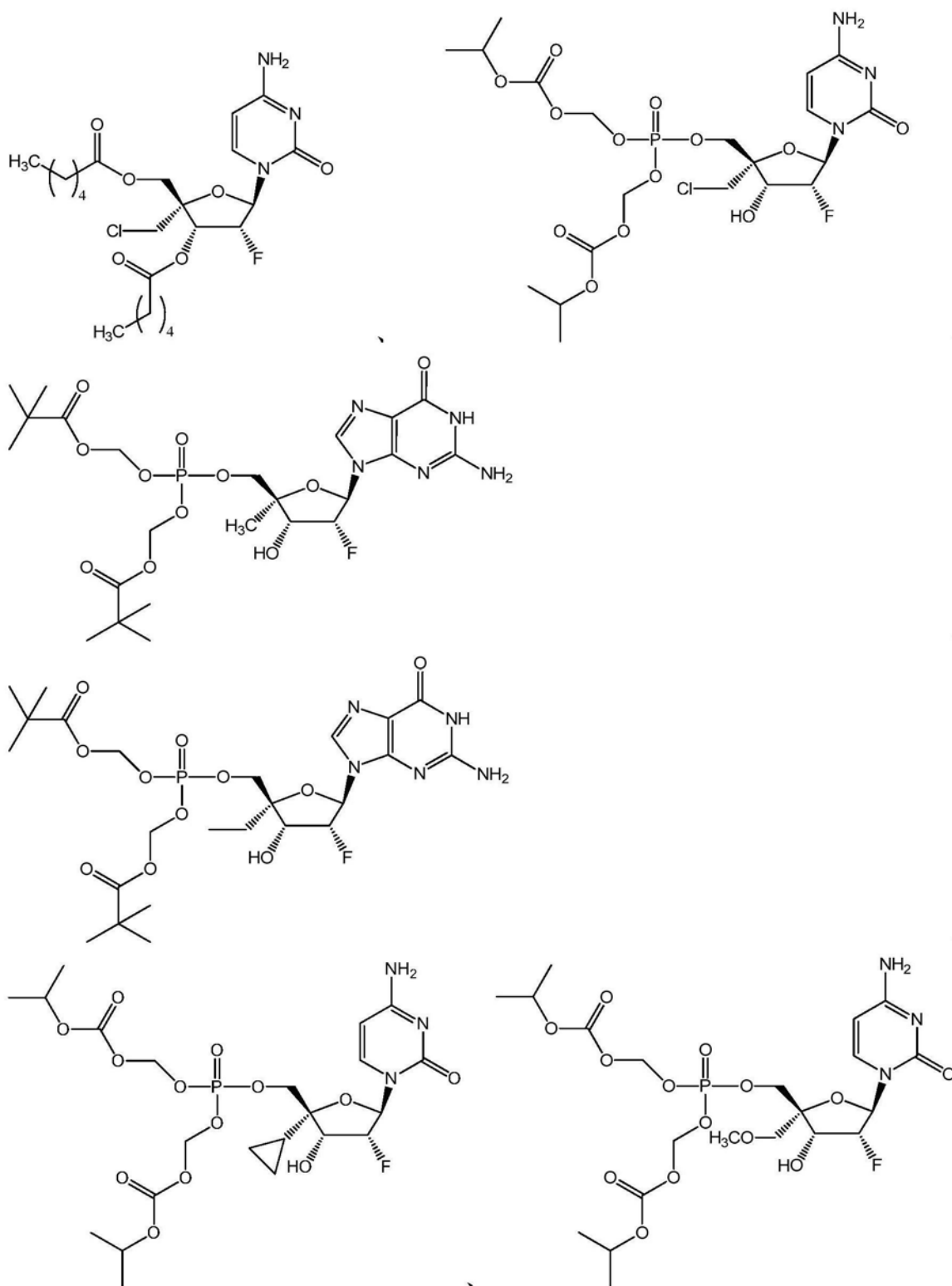


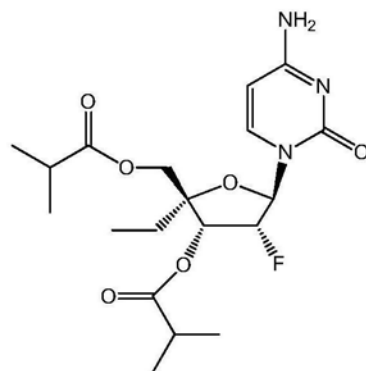
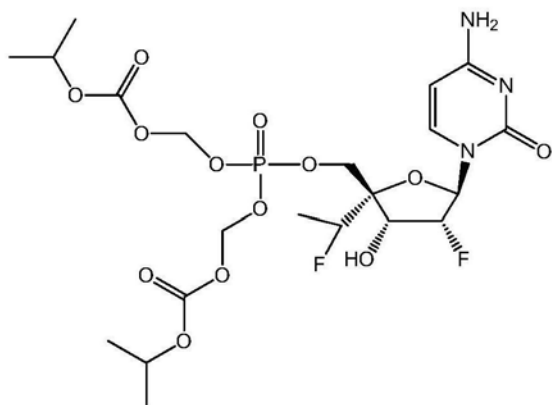
227. 如权利要求 16 所述的用途或方法, 其中所述式 (I) 的化合物选自:



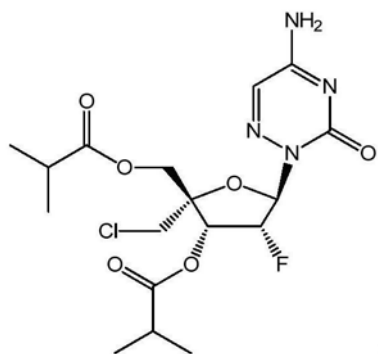






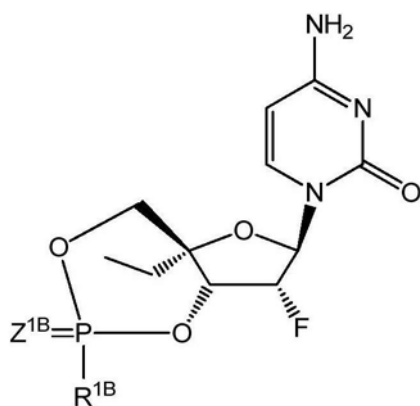


和



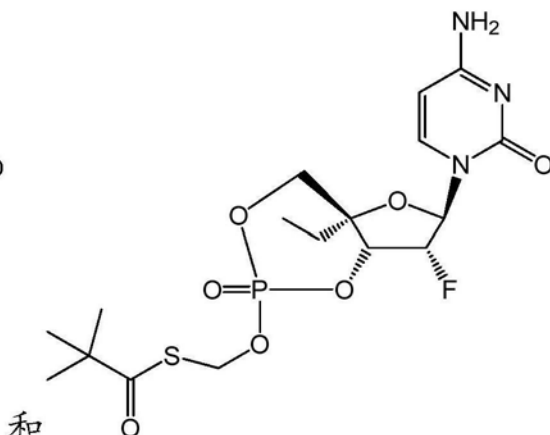
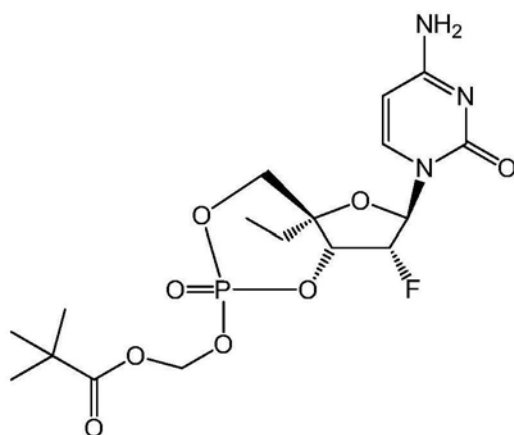
或前述的药物可接受的盐。

228. 如权利要求 122 所述的用途或方法, 其中所述式 (II) 的化合物为



或其药物可接受的盐。

229. 如权利要求 122 所述的用途或方法, 其中所述式 (II) 的化合物选自:

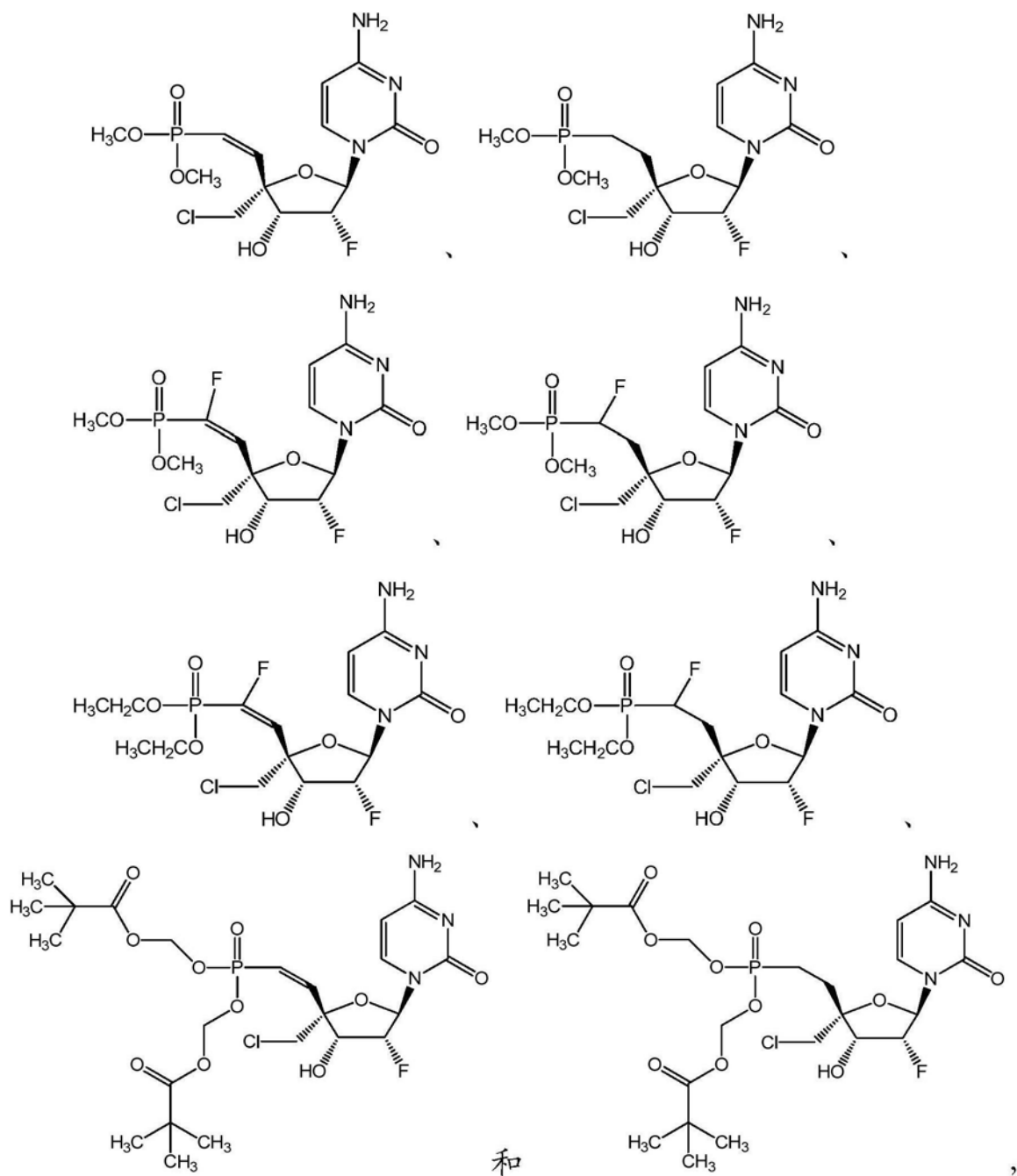


或前

和

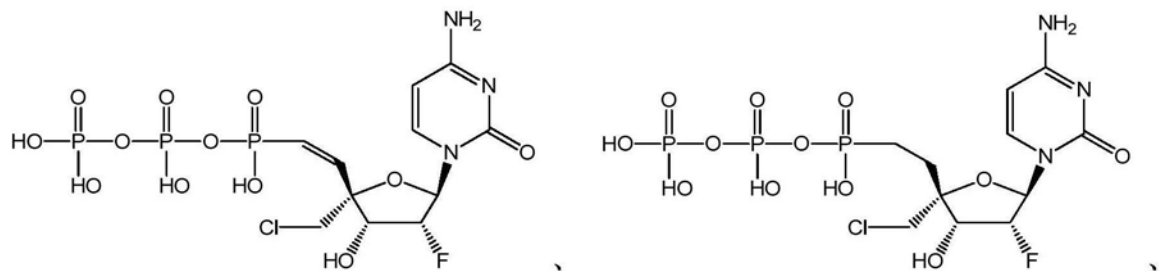
述的药物可接受的盐。

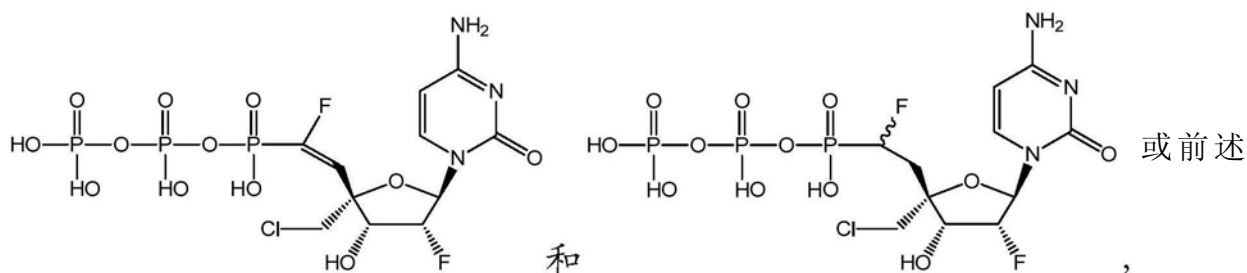
230. 如权利要求 162 所述的用途或方法, 其中所述式 (III) 的化合物选自:



或前述的药物可接受的盐。

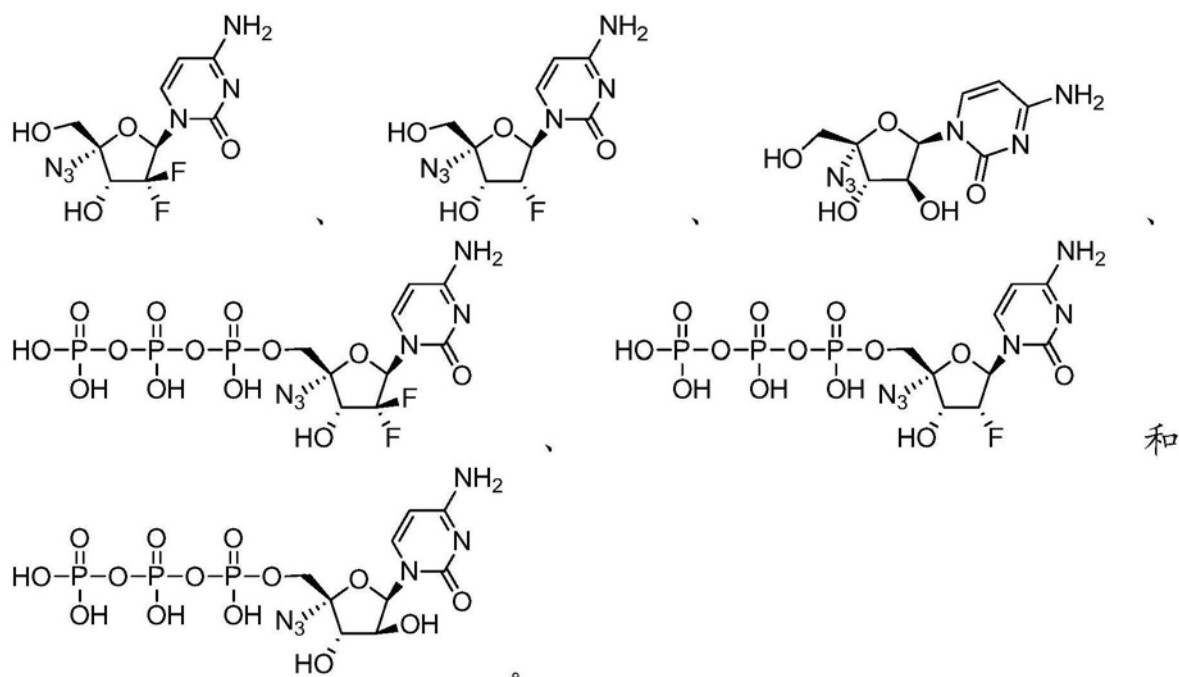
231. 如权利要求 162 所述的用途或方法,其中所述式 (III) 的化合物选自:



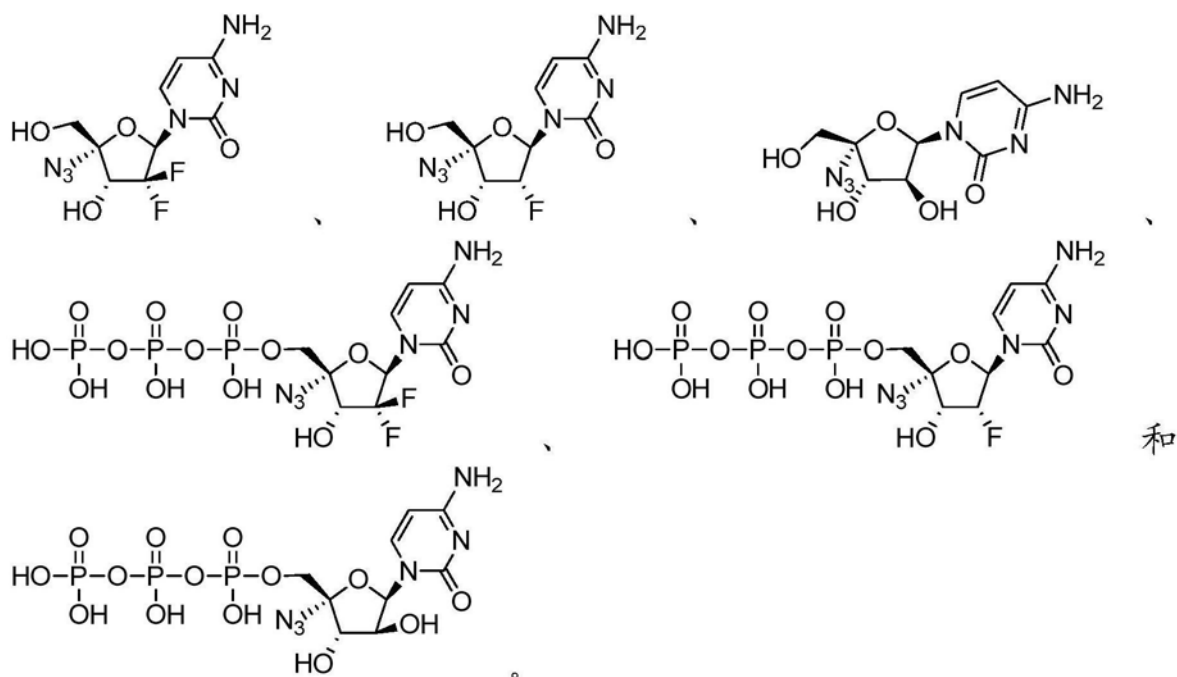


的药物可接受的盐。

232. 有效量的化合物或其药物可接受的盐用于减轻或治疗由病毒引起的病毒感染的用途,所述病毒选自亨尼帕病毒属、麻疹病毒属、呼吸道病毒属、腮腺炎病毒属和偏肺病毒属,其中所述化合物选自:



233. 减轻或治疗由病毒引起的病毒感染的方法,包括将有效量的化合物或其药物可接受的盐给予对象中的细胞或者使对象中的细胞与有效量的化合物或其药物可接受的盐接触,其中所述病毒选自亨尼帕病毒属、麻疹病毒属、呼吸道病毒属、腮腺炎病毒属和偏肺病毒属,并且其中所述化合物选自:



234. 如权利要求 232 所述的用途或权利要求 233 所述的方法,其中所述病毒为亨尼帕病毒属。

235. 如权利要求 234 所述的用途或方法,其中所述亨尼帕病毒属为尼帕病毒。

236. 如权利要求 232 所述的用途或权利要求 233 所述的方法,其中所述病毒为麻疹病毒属。

237. 如权利要求 236 所述的用途或方法,其中所述麻疹病毒属为麻疹病毒。

238. 如权利要求 232 所述的用途或权利要求 233 所述的方法,其中所述病毒为呼吸道病毒属。

239. 如权利要求 238 所述的用途或方法,其中所述呼吸道病毒属为人副流感病毒 1。

240. 如权利要求 238 所述的用途或方法,其中所述呼吸道病毒属为人副流感病毒 3。

241. 如权利要求 232 所述的用途或权利要求 233 所述的方法,其中所述病毒为腮腺炎病毒属。

242. 如权利要求 241 所述的用途或方法,其中所述腮腺炎病毒属为腮腺炎病毒。

243. 如权利要求 241 所述的用途或方法,其中所述腮腺炎病毒属为人副流感病毒 2。

244. 如权利要求 241 所述的用途或方法,其中所述腮腺炎病毒属为人副流感病毒 4。

245. 如权利要求 232 所述的用途或权利要求 233 所述的方法,其中所述病毒为偏肺病毒属。

246. 如权利要求 245 所述的用途或方法,其中所述偏肺病毒属为人偏肺病毒。

取代的核苷、核苷酸及其类似物

[0001] 背景

[0002] 领域

[0003] 本申请涉及化学、生物化学和医学领域。更具体地,本文公开了核苷、核苷酸及其类似物、包含一种或多种核苷、核苷酸及其类似物的药物组合物,以及合成上述的方法。还公开了使用一种或多种核苷、核苷酸及其类似物减轻和 / 或治疗副粘病毒和 / 或正粘病毒病毒感染的方法。

[0004] 描述

[0005] 呼吸道病毒感染包括上呼吸道和下呼吸道病毒感染传染并且是每年数百万人死亡的主要原因。上呼吸道病毒感染涉及鼻子、鼻窦、咽和 / 或喉。下呼吸道病毒感染涉及声带下面的呼吸系统,包括气管、主支气管和肺。

[0006] 核苷类似物是已被证实在体外和体内发挥抗病毒活性的一类化合物,因此已经成为用于治疗病毒感染的广泛研究的对象。核苷类似物通常是治疗非活性化合物,其被宿主或病毒酶转化为它们各自的活性抗代谢物,并且其反过来可抑制与病毒或细胞增殖有关的聚合酶。激活通过多种机制发生,例如一种或多种磷酸盐基团的添加,和 / 或结合其他代谢过程。

[0007] 概述

[0008] 本文公开的一些实施方案涉及式 (I)、式 (II) 和 / 或式 (III) 的化合物或前述的药物可接受的盐。

[0009] 本文公开的一些实施方案涉及减轻和 / 或治疗副粘病毒病毒感染的方法,其可包括给予患有副粘病毒病毒感染的对象有效量的一种或多种式 (I)、式 (II) 和 / 或式 (III) 的化合物或前述的药物可接受的盐,或包含一种或多种式 (I)、式 (II) 和 / 或式 (III) 的化合物或前述的药物可接受的盐的药物组合物。本文描述的其他实施方案涉及一种或多种式 (I)、式 (II) 和 / 或式 (III) 的化合物或前述的药物可接受的盐在制备用于减轻和 / 或治疗副粘病毒病毒感染的药物中的用途。本文描述的其他实施方案涉及用于减轻和 / 或治疗副粘病毒病毒感染的式 (I)、式 (II) 和 / 或式 (III) 的化合物或前述的药物可接受的盐。本文公开的其他实施方案涉及减轻和 / 或治疗副粘病毒病毒感染的方法,其可包括使感染副粘病毒的细胞与有效量的一种或多种式 (I)、式 (II) 和 / 或式 (III) 的化合物或前述的药物可接受的盐,或包含一种或多种式 (I)、式 (II) 和 / 或式 (III) 的化合物或前述的药物可接受的盐的药物组合物接触。本文公开的一些实施方案涉及抑制副粘病毒的复制的方法,其可包括使感染副粘病毒的细胞与有效量的一种或多种式 (I)、式 (II) 和 / 或式 (III) 的化合物或前述的药物可接受的盐,或包含一种或多种式 (I)、式 (II) 和 / 或式 (III) 的化合物或前述的药物可接受的盐的药物组合物接触。例如,副粘病毒病毒感染能由亨尼帕病毒属、麻疹病毒属、呼吸道病毒属、腮腺炎病毒属、肺病毒属 (包括呼吸道合胞体病毒感染)、偏肺病毒属、亨德拉病毒、尼帕病毒、麻疹病毒、仙台病毒、腮腺炎病毒、人副流感病毒 (HPIV-1、HPIV-2、HPIV-3 和 HPIV-4) 和 / 或人偏肺病毒引起。

[0010] 本文公开的一些实施方案涉及减轻和 / 或治疗正粘病毒病毒感染的方法,其可包

括给予患有正粘病毒病毒感染的对象有效量的一种或多种式 (I)、式 (II) 和 / 或式 (III) 的化合物或前述的药物可接受的盐,或包含一种或多种式 (I)、式 (II) 和 / 或式 (III) 的化合物或前述的药物可接受的盐的药物组合物。本文描述的其他实施方案涉及一种或多种式 (I)、式 (II) 和 / 或式 (III) 的化合物或前述的药物可接受的盐在制备用于减轻和 / 或治疗正粘病毒病毒感染的药物中的用途。本文描述的其他实施方案涉及能用于减轻和 / 或治疗正粘病毒病毒感染的式 (I)、式 (II) 和 / 或式 (III) 的化合物或前述的药物可接受的盐。本文公开的其他实施方案涉及减轻和 / 或治疗正粘病毒病毒感染的方法,其可包括使感染正粘病毒的细胞与有效量的一种或多种式 (I)、式 (II) 和 / 或式 (III) 的化合物或前述的药物可接受的盐,或包含一种或多种式 (I)、式 (II) 和 / 或式 (III) 的化合物或前述的药物可接受的盐的药物组合物接触。本文公开的一些实施方案涉及抑制正粘病毒的复制的方法,其可包括使感染正粘病毒的细胞与有效量的一种或多种式 (I)、式 (II) 和 / 或式 (III) 的化合物或前述的药物可接受的盐,或包含一种或多种式 (I)、式 (II) 和 / 或式 (III) 的化合物或前述的药物可接受的盐的药物组合物接触。例如,正粘病毒病毒感染可为流感病毒感染(例如,甲型流感、乙型流感和 / 或丙型流感)。

[0011] 本文公开的一些实施方案涉及减轻和 / 或治疗副粘病毒病毒感染和 / 或正粘病毒病毒感染的方法,其可包括给予患有病毒感染的对象有效量的本文描述的化合物或其药物可接受的盐(例如,一种或多种式 (I)、(II) 和 / 或 (III) 的化合物或前述的药物可接受的盐),或包含一种或多种本文描述的化合物结合一种或多种本文描述的试剂的药物组合物。本文公开的一些实施方案涉及减轻和 / 或治疗副粘病毒病毒感染和 / 或正粘病毒病毒感染的方法,其可包括使感染病毒的细胞与有效量的本文描述的化合物或其药物可接受的盐(例如,一种或多种式 (I)、(II) 和 / 或 (III) 的化合物或前述的药物可接受的盐)或包含一种或多种本文描述的化合物结合一种或多种本文描述的试剂的药物组合物接触。

[0012] 附图简述

[0013] 图 1 示出实施例 RSV 剂。

[0014] 详细描述

[0015] 副粘病毒 (Paramyxoviridae) 科是单链 RNA 病毒族。几种副粘病毒科的属包括亨尼帕病毒属、麻疹病毒属、呼吸道病毒属、腮腺炎病毒属、肺病毒属和偏肺病毒属。这些病毒能通过与被污染的呼吸道飞沫或污染物直接或紧密接触而在人与人之间传播。亨尼帕病毒属种包括亨德拉病毒和尼帕病毒。麻疹病毒属的种为麻疹。呼吸道病毒属的种包括仙台病毒和人副流感病毒 1 和 3;且腮腺炎病毒属的种包括腮腺炎病毒和人副流感病毒 2 和 4。偏肺病毒属的种为人偏肺病毒。

[0016] 肺病毒属的一种,人呼吸道合胞体病毒 (RSV) 能导致呼吸道感染,并且可能与细支气管炎和肺炎有关。RSV 感染的症状包括咳嗽、打喷嚏、流鼻涕、发烧、食欲下降和哮喘。RSV 是世界上一岁以下儿童的细支气管炎和肺炎的最常见原因,并且可能是幼儿和成人的气管支气管炎的原因。在美国,每年 75,000 至 125,000 的婴儿由于 RSV 而住院。在大于 65 岁的成人中,估计 14,000 死亡和 177,000 住院治疗是因为 RSV。

[0017] 目前,感染 RSV 的人的治疗方案是有限的。通常用来治疗细菌感染和非处方药物的抗生素对治疗 RSV 无效并且仅可帮助缓解一些症状。在严重情况下,例如沙丁胺醇的雾化支气管扩张剂可用来缓解一些症状,例如哮喘。RespiGram® (RSV-IGIV, MedImmune,

批准用于不满 24 个月的高危儿童)、**Synagis®** (帕利珠单抗, MedImmune, 批准用于不满 24 个月的高危儿童) 和 **Virzole®** (利巴韦林的气雾剂, ICN pharmaceuticals) 已被批准用于治疗 RSV。

[0018] 麻疹的症状包括发烧、咳嗽、流鼻涕、红眼和全身皮疹。一些患有麻疹的患者可能发展肺炎、耳感染和支气管炎。腮腺炎导致唾液腺的红肿。腮腺炎的症状包括发烧、食欲不振和疲乏。患者常通过接种三部分 MMR 疫苗 (麻疹、腮腺炎和风疹) 对抗麻疹和腮腺炎。人副流感病毒包括四种血清型, 并且能导致上呼吸道和下呼吸道感染。人副流感病毒 1 (HPIV-1) 能与喉头炎有关; 人副流感病毒 3 (HPIV-3) 能与细支气管炎和肺炎有关。根据疾病控制和预防中心 (CDC), 没有对抗人副流感病毒的疫苗。

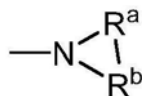
[0019] 流感是单链 RNA 病毒和正粘病毒科成员。目前有三种流感: 甲型流感、乙型流感和丙型流感。基于进入血凝素 (H 或 HA) 和神经氨酸苷酶 (N) 的病毒表面蛋白, 甲型流感被进一步分类。有大约 16H 抗原 (H1 至 H16) 和 9N 抗原 (N1 至 N9)。甲型流感包括几种亚型, 包括 H1N1、H1N2、H2N2、H3N1、H3N2、H3N8、H5N1、H5N2、H5N3、H5N8、H5N9、H7N1、H7N2、H7N3、H7N4、H7N7、H9N2、H10N7。正如 RSV, 流感病毒能与感染的分泌物和 / 或受污染的表面或物体直接接触而在人与人之间传播。来自流感病毒感染的并发症包括肺炎、支气管炎、脱水和鼻窦感染和耳感染。目前, FDA 批准对抗流感感染的药物包括金刚烷胺、金刚烷乙胺、**Relenza®** (扎那米韦, GlaxoSmithKline) 和 **Tamiflu®** (奥司他韦, Genentech)。

[0020] 定义

[0021] 除非另外规定, 本文所使用的所有技术和科学术语具有与本领域一般技术人员通常理解的相同含义。除非另外规定, 所有专利、申请、公开申请和本文引用的其他公开以其整体通过引用并入本文。除非另外规定, 在本文的术语有多个定义的情况下, 以本部分的定义为准。

[0022] 如本文使用的, 任何“R”基团, 例如但不限于 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^{25A} 、 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^{11B} 、 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^{15C} 、 R^{16C} 、 R^{17C} 、 R^{18C} 、 R^{19C} 、 R^{20C} 、 R^{21C} 、 R^{22C} 和 R^{23C} , 代表能与指出原子连接的取代基。R 基团可为取代的或未取代的。如果两个“R”基团被描述为“在一起”, 则 R 基团与其所连接的原子能形成环烷基、环烯基、环炔基、芳基、杂芳基或杂环。例如但不限于, 如果 NR^aR^b 基团的 R^a 和 R^b 被指明“在一起”, 则是指它们彼此共价连接以形成环:

[0023]



[0024] 此外, 如果两个“R”基团被描述为与其连接的原子“在一起”以形成环作为任选的技术方案, 则 R 基团不局限于前面定义的变量或取代基。

[0025] 每当基团被描述为“任选取代的”时, 则基团可为未取代的或被一个或多个所示的取代基取代。相似地, 当基团被描述为“未取代的或取代的”时, 如果是取代的, 则取代基可选自一种或多种所示的取代基。如果没有指出取代基, 则是所述的“任选取代的”或“取

代的”基团可单独和独立地被选自以下的一种或多种基团取代：烷基、烯基、炔基、环烷基、环烯基、环炔基、芳基、杂芳基、杂脂环基、芳烷基、杂芳烷基、（杂脂环基）烷基、羟基、被保护羟基、炔氧基、芳氧基、酰基、巯基、烷硫基、芳硫基、氰基、卤素、硫代羰基、O-氨基甲酰基、N-氨基甲酰基、O-硫代氨基甲酰基、N-硫代氨基甲酰基、C-酰胺基、N-酰胺基、S-磺酰胺基、N-磺酰胺基、C-羧基、被保护C-羧基、O-羧基、异氰酸基、硫氰酸基、异硫氰酸基、硝基、甲硅烷基、炔硫基、亚磺酰基、磺酰基、卤代烷基、卤代炔氧基、三卤代甲烷磺酰基、三卤代甲烷亚磺酰氨基、氨基、单取代氨基和双取代氨基及其被保护衍生物。

[0026] 如本文使用的，“ C_a 至 C_b ”是指烷基、烯基或炔基中的碳原子数，或环烷基、环烯基、环炔基、芳基、杂芳基或杂脂环基环中的碳原子数，其中“a”和“b”是整数。即，烷基、烯基、炔基、环烷基环、环烯基环、环炔基环、芳基环、杂芳基环或杂脂环基环可包含“a”至“b”个碳原子，包括“a”和“b”个碳原子。因此，例如，“ C_1 至 C_4 烷基”基团是指具有 1 至 4 个碳的所有烷基，即 CH_3- 、 CH_3CH_2- 、 $CH_3CH_2CH_2-$ 、 $(CH_3)_2CH-$ 、 $CH_3CH_2CH_2CH_2-$ 、 $CH_3CH_2CH(CH_3)-$ 和 $(CH_3)_3C-$ 。如果没有指定烷基、烯基、炔基、环烷基、环烯基、环炔基、芳基、杂芳基或杂脂环基的“a”和“b”，则假设这些定义中所描述的是最广泛的范围。

[0027] 如本文使用的，“烷基”是指包含完全饱和（没有双键或叁键）烃基团的直链烃链或支链烃链。烷基可具有 1 至 20 个碳原子（每当在本文出现时，诸如“1 至 20”的数值范围是指给定范围中的各个整数；例如，“1 至 20 个碳原子”是指可包含 1 个碳原子、2 个碳原子、3 个碳原子等直至并且包括 20 个碳原子的烷基，尽管本定义还涵盖其中没有指定数值范围的术语“烷基”的出现）。烷基还可为具有 1 至 10 个碳原子的中等大小烷基。烷基还可为具有 1 至 6 个碳原子的低级烷基。化合物的烷基可以指定为“ C_1 - C_4 烷基”或类似名称。仅通过实例，“ C_1 - C_4 烷基”表示烷基链中有一至四个碳原子，即，烷基链选自甲基、乙基、丙基、异丙基、正丁基、异丁基、仲丁基和叔丁基。典型的烷基包括但绝不限于甲基、乙基、丙基、异丙基、丁基、异丁基、叔丁基、戊基和己基。烷基可为取代的或未取代的。

[0028] 如本文使用的，“烯基”是指在直链或支链烃链中包含一个或多个双键的烃基。烯基可为未取代的或取代的。

[0029] 如本文使用的，“炔基”是指在直链或支链烃链中包含一个或多个叁键的烃基。炔基可为未取代的或取代的。

[0030] 如本文使用的，“环烷基”是指完全饱和的（无双键或叁键）单环或多环烃环体系。当由两个或多个环组成时，环可以稠合方式连接在一起。环烷基能在环中包含 3 至 10 个原子或在环中包含 3 至 8 个原子。环烷基可为未取代的或取代的。典型环烷基包括但绝不限于环丙基、环丁基、环戊基、环己基、环庚基和环辛基。

[0031] 如本文使用的，“环烯基”是指在至少一个环中包含一个或多个双键的单环或多环烃环体系；尽管，如果有多于一个，则双键不能形成遍及所有环的完全离域的 π -电子体系（否则，基团将为本文定义的“芳基”）。当包含两个或多个环时，环可以稠合方式连接在一起。环烯基可为未取代的或取代的。

[0032] 如本文使用的，“环炔基”是指在至少一个环中包含一个或多个叁键的单环或多环烃环体系。如果有多于一个叁键，则叁键不能形成遍及所有环的完全离域的 π -电子体系。当包含两个或多个环时，环可以稠合方式连接在一起。环炔基可为未取代的或取代的。

[0033] 如本文使用的，“芳基”是指具有遍及所有环的完全离域的 π -电子体系的碳环

(全部为碳)单环或多环芳香族环体系(包括其中两个碳环共享化学键的稠环体系)。芳基中的碳原子数可变化。例如,芳基可为 C_6 - C_{14} 芳基、 C_6 - C_{10} 芳基或 C_6 芳基。芳基的实例包括但不限于苯、萘和蒽。芳基可为取代的或未取代的。

[0034] 如本文使用的,“杂芳基”是指包含一个或多个杂原子,即除了碳之外的元素包括但不限于氮、氧和硫,的单环或多环芳香族环体系(具有完全离域的 π -电子体系的环体系)。杂芳基环中的原子数可变化。例如,杂芳基在环中可包含4至14个原子、在环中可包含5至10个原子或在环中可包含5至6个原子。此外,术语“杂芳基”包括其中两个环,例如至少一个芳基环和至少一个杂芳基环或至少两个杂芳基环,共享至少一个化学键的稠环体系。杂芳基环的实例包括但不限于呋喃、咪唑、噻吩、苯并噻吩、酞嗪、吡咯、噁唑、苯并噁唑、1,2,3-噁二唑、1,2,4-噁二唑、噻唑、1,2,3-噻二唑、1,2,4-噻二唑、苯并噻唑、咪唑、苯并咪唑、吡啶、吡唑、吡嗪、苯并吡唑、异噁唑、苯并异噁唑、异噻唑、三唑、苯并三唑、噻二唑、四唑、吡啶、哒嗪、嘧啶、吡嗪、嘌呤、蝶啶、喹啉、异喹啉、喹唑啉、喹喔啉、噌啉和三嗪。杂芳基可为取代的或未取代的。

[0035] 如本文使用的,“杂环基”或“杂脂环基”是指三元、四元、五元、六元、七元、八元、九元、十元、直至 18 元的单环、二环和三环环体系,其中碳原子与 1 至 5 个杂原子一起构成所述环体系。然而,杂环可任选包含一个或多个以在所有环中不发生完全离域的 π -电子体系的方式排列的不饱和键。杂原子是除了碳之外的元素,其包括但不限于氧、硫和氮。杂环还可包含一个或多个羰基或硫代羰基官能团以使所述定义包括氧代体系和硫代体系,例如内酰胺、内酯、环二酰亚胺(cyclic imide)、环硫代二酰亚胺和环氨基甲酸酯。当包含两个或多个环时,可以稠合方式将环连接在一起。此外,杂脂环中的任何氮可被季铵化。杂环基或杂脂环基团可为未取代的或取代的。这类“杂环基”或“杂脂环基”基团的实例包括但不限于 1,3-二氧杂环己烯、1,3-二氧杂环己烷、1,4-二氧杂环己烷、1,2-二氧杂环戊烷、1,3-二氧杂环戊烷、1,4-二氧杂环戊烷、1,3-氧硫杂环己烷、1,4-氧硫杂环己二烯、1,3-氧硫杂环戊烷、1,3-二硫杂环戊二烯、1,3-二硫戊环、1,4-氧硫杂环己烷、四氢-1,4-噻嗪、2H-1,2-噁嗪、马来酰亚胺、琥珀酰亚胺、巴比妥酸、硫代巴比妥酸、二氧化哌嗪、乙内酰脲、二氢尿嘧啶、三氧杂环己烷、六氢-1,3,5-三嗪、咪唑啉、咪唑烷、异噁唑啉、异噁唑烷、噁唑啉、噁唑烷、噁唑烷酮、噻唑啉、噻唑烷、吗啉、环氧乙烷、哌啶 N-氧化物、哌啶、哌嗪、吡咯烷、吡咯烷酮、四氢化吡咯(pyrrolidione)、4-哌啶酮、吡唑啉、吡唑烷、2-氧代吡咯烷、四氢吡喃、4H-吡喃、四氢噻喃、硫代吗啉、硫代吗啉亚砷、硫代吗啉砷和它们的苯并稠合类似物(例如,苯并咪唑烷酮、四氢喹啉和 3,4-亚甲基二氧苯基)。

[0036] 如本文使用的,“芳烷基”和“芳基(烷基)”是指通过低级亚烃基连接的作为取代基的芳基。芳烷基的低级亚烃基和芳基可为取代的或未取代的。实例包括但不限于苄基、2-苯基烷基、3-苯基烷基和萘基烷基。

[0037] 如本文使用的,“杂芳烷基”和“杂芳基(烷基)”是指通过低级亚烃基连接的作为取代基的杂芳基。杂芳烷基的低级亚烃基和杂芳基可为取代的或未取代的。实例包括但不限于 2-噻吩基烷基、3-噻吩基烷基、呋喃基烷基、噻吩基烷基、吡咯基烷基、吡啶基烷基、异噁唑基烷基、咪唑基烷基和它们的苯并稠合类似物。

[0038] “(杂脂环基)烷基”和“(杂环基)烷基”是指通过低级亚烃基连接的作为取代基的杂环或杂脂环基。(杂脂环基)烷基的低级亚烃基和杂环基可为取代的或未取代的。实

例包括但不限于四氢-2H-吡喃-4-基)甲基、(哌啶-4-基)乙基、(哌啶-4-基)丙基、(四氢-2H-硫代吡喃-4-基)甲基和(1,3-噻嗪烷-4-基)甲基。

[0039] “低级亚烃基”为通过其末端碳原子连接分子片段以形成键的直链-CH₂-共享基团。实例包括但不限于亚甲基(-CH₂-)、亚乙基(-CH₂CH₂-)、亚丙基(-CH₂CH₂CH₂-)和亚丁基(-CH₂CH₂CH₂CH₂-)。能通过在“取代的”定义下所列举的取代基来替换低级亚烃基的一个或多个氢从而将低级亚烃基取代。

[0040] 如本文使用的,“烃氧基”是指式-OR,其中R为本文定义的烷基、烯基、炔基、环烷基、环烯基、环炔基、芳基、杂芳基、杂脂环基、芳烷基、(杂芳基)烷基或(杂脂环基)烷基。烃氧基的非限制性列举为甲氧基、乙氧基、正丙氧基、1-甲基乙氧基(异丙氧基)、正丁氧基、异丁氧基、仲丁氧基、叔丁氧基、苯氧基和苄氧基(benzoxo)。烃氧基可为取代的或未取代的。

[0041] 如本文使用的,“酰基”是指通过羰基连接的作为取代基的氢、烷基、烯基、炔基或芳基。实例包括甲酰基、乙酰基、丙酰基、苯甲酰基和丙烯酰基。酰基可为取代的或未取代的。

[0042] 如本文使用的,“羟基烷基”是指其中一个或多个氢原子被羟基取代的烷基。示例性羟基烷基包括但不限于2-羟基乙基、3-羟基丙基、2-羟基丙基和2,2-二羟基乙基。羟基烷基可为取代的或未取代的。

[0043] 如本文使用的,“卤代烷基”是指其中一个或多个氢原子被卤素取代(例如,单卤代烷基、二卤代烷基和三卤代烷基)的烷基。这类基团包括但不限于氯甲基、氟甲基、二氟甲基、三氟甲基、1-氯-2-氟甲基和2-氟异丁基。卤代烷基可为取代的或未取代的。

[0044] 如本文使用的,“卤代烃氧基”是指其中一个或多个氢原子被卤素(例如,单卤代烃氧基、二卤代烃氧基和三卤代烃氧基)取代的烃氧基。这类基团包括但不限于氯甲氧基、氟甲氧基、二氟甲氧基、三氟甲氧基、1-氯-2-氟甲氧基和2-氟异丁氧基。卤代烃氧基可为取代的或未取代的。

[0045] 如本文使用的,“芳硫基”是指RS-,其中R为芳基,例如但不限于苯基。芳硫基可为取代的或未取代的。

[0046] “烃硫基”基团是指“-SR”基团,其中R可为氢、烷基、烯基、炔基、环烷基、环烯基、环炔基、芳基、杂芳基、杂脂环基、芳烷基、(杂芳基)烷基或(杂脂环基)烷基。烃硫基可为取代的或未取代的。

[0047] “亚磺酰基”基团是指“-S(=O)-R”基团,其中R可与相对于烃硫基的定义相同。亚磺酰基可为取代的或未取代的。

[0048] “磺酰基”基团是指“-SO₂R”基团,其中R可与相对于烃硫基的定义相同。磺酰基可为取代的或未取代的。

[0049] “O-羧基”基团是指“-RC(=O)O-”基团,其中R可为如本文定义的氢、烷基、烯基、炔基、环烷基、环烯基、环炔基、芳基、杂芳基、杂脂环基、芳烷基、(杂芳基)烷基或(杂脂环基)烷基。O-羧基可为取代的或未取代的。

[0050] 术语“酯”和“C-羧基”是指“-C(=O)OR”基团,其中R可与相对于O-羧基的定义相同。酯和C-羧基可为取代的或未取代的。

[0051] “硫代羰基”基团是指“-C(=S)R”基团,其中R能与相对于O-羧基的定义相同。

硫代羰基可为取代的或未取代的。

[0052] “三卤代甲烷磺酰基”基团是指“ X_3CSO_2- ”基团,其中各个 X 为卤素。

[0053] “三卤代甲烷亚磺酰氨基”基团是指“ $X_3CS(O)_2N(R_A)-$ ”基团,其中各个 X 为卤素,且 R_A 为氢、烷基、烯基、炔基、环烷基、环烯基、环炔基、芳基、杂芳基、杂脂环基、芳烷基、(杂芳基)烷基或(杂脂环基)烷基。

[0054] 如本文使用的,术语“氨基”是指 $-NH_2$ 基团。

[0055] 如本文使用的,术语“羟基”是指 $-OH$ 基团。

[0056] “氰基”基团是指“ $-CN$ ”基团。

[0057] 如本文使用的,术语“叠氮基”是指 $-N_3$ 基团。

[0058] “异氰酸基”基团是指“ $-NCO$ ”基团。

[0059] “硫氰酸基”基团是指“ $-CNS$ ”基团。

[0060] “异硫氰酸基”基团是指“ $-NCS$ ”基团。

[0061] “巯基”基团是指“ $-SH$ ”基团。

[0062] “羰基”基团是指 $C=O$ 基团。

[0063] “S-磺酰胺基”基团是指“ $-SO_2N(R_A R_B)$ ”基团,其中 R_A 和 R_B 可独立地为氢、烷基、烯基、炔基、环烷基、环烯基、环炔基、芳基、杂芳基、杂脂环基、芳烷基、(杂芳基)烷基或(杂脂环基)烷基。S-磺酰胺基可为取代的或未取代的。

[0064] “N-磺酰胺基”基团是指“ $RSO_2N(R_A)-$ ”基团,其中 R 和 R_A 可独立地为氢、烷基、烯基、炔基、环烷基、环烯基、环炔基、芳基、杂芳基、杂脂环基、芳烷基、(杂芳基)烷基或(杂脂环基)烷基。N-磺酰胺基可为取代的或未取代的。

[0065] “O-氨基甲酰基”基团是指“ $-OC(=O)N(R_A R_B)$ ”基团,其中 R_A 和 R_B 可独立地为氢、烷基、烯基、炔基、环烷基、环烯基、环炔基、芳基、杂芳基、杂脂环基、芳烷基、(杂芳基)烷基或(杂脂环基)烷基。O-氨基甲酰基可为取代的或未取代的。

[0066] “N-氨基甲酰基”基团是指“ $ROC(=O)N(R_A)-$ ”基团,其中 R 和 R_A 可独立地为氢、烷基、烯基、炔基、环烷基、环烯基、环炔基、芳基、杂芳基、杂脂环基、芳烷基、(杂芳基)烷基或(杂脂环基)烷基。N-氨基甲酰基可为取代的或未取代的。

[0067] “O-硫代氨基甲酰基”基团是指“ $-OC(=S)N(R_A R_B)$ ”基团,其中 R_A 和 R_B 可独立地为氢、烷基、烯基、炔基、环烷基、环烯基、环炔基、芳基、杂芳基、杂脂环基、芳烷基、(杂芳基)烷基或(杂脂环基)烷基。O-硫代氨基甲酰基可为取代的或未取代的。

[0068] “N-硫代氨基甲酰基”基团是指“ $ROC(=S)N(R_A)-$ ”基团,其中 R 和 R_A 可独立地为氢、烷基、烯基、炔基、环烷基、环烯基、环炔基、芳基、杂芳基、杂脂环基、芳烷基、(杂芳基)烷基或(杂脂环基)烷基。N-硫代氨基甲酰基可为取代的或未取代的。

[0069] “C-酰胺基”基团是指“ $-C(=O)N(R_A R_B)$ ”基团,其中 R_A 和 R_B 可独立地为氢、烷基、烯基、炔基、环烷基、环烯基、环炔基、芳基、杂芳基、杂脂环基、芳烷基、(杂芳基)烷基或(杂脂环基)烷基。C-酰胺基可为取代的或未取代的。

[0070] “N-酰胺基”基团是指“ $RC(=O)N(R_A)-$ ”基团,其中 R 和 R_A 可独立地为氢、烷基、烯基、炔基、环烷基、环烯基、环炔基、芳基、杂芳基、杂脂环基、芳烷基、(杂芳基)烷基或(杂脂环基)烷基。N-酰胺基可为取代的或未取代的。

[0071] 如本文使用的,术语“卤素原子”或“卤素”是指元素周期表第 7 列的放射稳定的

原子中的任一个,例如氟、氯、溴和碘。

[0072] 在未规定取代基(例如,卤代烷基)数量的情况下,可存在一个或多个取代基。例如,“卤代烷基”可包括一个或多个相同或不同卤素。作为另一实例,“C₁-C₃ 烃氧基苯基”可包括一个或多个相同或不同的包含一个、两个或三个原子的烃氧基。

[0073] 如本文使用的,除非另有说明,任何保护基团、氨基酸和其他化合物的缩写与它们的习惯用法、公认缩写或 IUPAC-IUB 生物化学委员会命名法(参见, Biochem. 11:942-944(1972))相一致。

[0074] 术语“核苷”以本领域技术人员理解的一般含义在本文使用,并且是指由通过 N-糖苷键与杂环碱或其互变异构体连接的任选取代的戊糖部分或改性戊糖部分,例如通过嘌呤碱基的 9-位或嘧啶碱基的 1-位连接的任选取代的戊糖部分或改性戊糖部分组成的化合物。实例包括但不限于包含核糖部分的核糖核苷和包含脱氧核糖部分的脱氧核糖核苷。改性戊糖部分为其中氧原子被碳取代和/或碳被硫或氧原子取代的戊糖部分。“核苷”是具有取代的碱基和/或糖部分的单体。此外,可将核苷并入较大的 DNA 和/或 RNA 聚合物和低聚物。在一些情况下,核苷可为核苷类似物药物。

[0075] 术语“核苷酸”以本领域技术人员理解的一般含义在本文使用并且是指具有与例如在 5'-位戊糖部分连接的磷酸酯。

[0076] 如本文使用的,术语“杂环碱”是指能与任选取代的戊糖部分或改性戊糖部分连接的任选取代的含氮杂环基。在一些实施方案中,杂环碱能选自任选取代的嘌呤-碱基、任选取代的嘧啶-碱基和任选取代的三唑-碱基(例如,1,2,4-三唑)。术语“嘌呤-碱基”以本领域技术人员理解的一般含义在本文使用,并且包括其互变异构体。类似地,术语“嘧啶-碱基”以本领域技术人员理解的一般含义在本文使用,并且包括其互变异构体。任选取代的嘌呤-碱基的非限制性列举包括嘌呤、腺嘌呤、鸟嘌呤、次黄嘌呤、黄嘌呤、别黄嘌呤、7-烷基鸟嘌呤(例如,7-甲基鸟嘌呤)、可可碱、咖啡因、尿酸和异鸟嘌呤。嘧啶-碱基的实例包括但不限于胞嘧啶、胸腺嘧啶、尿嘧啶、5,6-二氢尿嘧啶和 5-烷基胞嘧啶(例如,5-甲基胞嘧啶)。任选取代的三唑-碱基的实例为 1,2,4-三唑-3-甲酰胺。杂环碱的其他非限制性实例包括二氨基嘌呤、8-氧代-N⁶-烷基腺嘌呤(例如,8-氧代-N⁶-甲基腺嘌呤)、7-脱氮黄嘌呤、7-脱氮鸟嘌呤、7-脱氮腺嘌呤、N⁴,N⁴-乙醇胞嘧啶、N⁶,N⁶-乙醇-2,6-二氨基嘌呤、5-卤代尿嘧啶(例如,5-氟尿嘧啶和 5-溴尿嘧啶)、假异胞嘧啶、异胞嘧啶、异鸟嘌呤和第 5,432,272 号和第 7,125,855 号美国专利中描述的其他杂环碱,其通过引用并入本文并意于公开其他的杂环碱的限制性目的。在一些实施方案中,杂环碱能任选地被胺或烯醇保护基团取代。

[0077] 术语“-N-连接氨基酸”是指通过主链氨基或单取代的氨基与所示部分连接的氨基酸。当在-N-连接氨基酸中连接氨基酸时,作为主链氨基或单取代的氨基的一部分的氢原子之一不存在并且该氨基酸通过氮连接。N-连接氨基酸可为取代的或未取代的。

[0078] 术语“-N-连接氨基酸酯衍生物”是指其中主链羧酸基团已被转化为酯基团的氨基酸。在一些实施方案中,酯基团具有选自烷基-O-C(=O)-、环烷基-O-C(=O)-、芳基-O-C(=O)-和芳基(烷基)-O-C(=O)-的式。酯基团的非限制性列举包括下列取代的和未取代的形式:甲基-O-C(=O)-、乙基-O-C(=O)-、正丙基-O-C(=O)-、异丙基-O-C(=O)-、正丁基-O-C(=O)-、异丁基-O-C(=O)-、叔丁基-O-C(=O)-、新

戊基 $-O-C(=O)-$ 、环丙基 $-O-C(=O)-$ 、环丁基 $-O-C(=O)-$ 、环戊基 $-O-C(=O)-$ 、环己基 $-O-C(=O)-$ 、苯基 $-O-C(=O)-$ 、苄基 $-O-C(=O)-$ 和萘基 $-O-C(=O)-$ 。N-连接氨基酸酯衍生物可为取代的或未取代的。

[0079] 术语“ $-O-$ 连接氨基酸”是指通过来自其主链羧酸基团的羟基与所示部分连接的氨基酸。当在 $-O-$ 连接氨基酸中连接氨基酸时,作为其主链羧酸基团的羟基的一部分的氢不存在并且氨基酸通过氧连接。 $O-$ 连接氨基酸可为取代的或未取代的。

[0080] 如本文使用的,术语“氨基酸”是指任何氨基酸(标准和非标准氨基酸二者),包括但不限于 α -氨基酸、 β -氨基酸、 γ -氨基酸和 δ -氨基酸。适合的氨基酸的实例包括但不限于丙氨酸、天冬酰胺、天冬氨酸、半胱氨酸、谷氨酸、谷氨酰胺、甘氨酸、脯氨酸、丝氨酸、酪氨酸、精氨酸、组氨酸、异亮氨酸、亮氨酸、赖氨酸、蛋氨酸、苯基丙氨酸、苏氨酸、色氨酸和缬氨酸。适合的氨基酸的其他实例包括但不限于鸟氨酸、尾下素(hypusine)、2-氨基异丁酸、脱氢丙氨酸、 γ -氨基丁酸、瓜氨酸、 β -丙氨酸、 α -乙基-甘氨酸、 α -丙基-甘氨酸和正亮氨酸。

[0081] 术语“硫代磷酸酯”和“硫代磷酸酯(phosphothioate)”是指式 $S=P(O)(O^-)-O-$ 其

质子化形式(例如, $S=P(O)(OH)-O-$ 和 $S=P(O)(OH)_2$) 及其互变异构体(例如 $O=P(S)(OH)-O-$)

的化合物。

[0082] 如本文使用的,术语“磷酸酯”以本领域技术人员理解的一般含义使用,并且包括

其质子化形式(例如, $O=P(O)(OH)-O-$ 和 $O=P(O)(OH)_2$)。如本文使用的,术语“单磷酸酯”、

“二磷酸酯”和“三磷酸酯”以本领域技术人员理解的一般含义使用,并且包括质子化形式。

[0083] 本文使用的术语“保护基团”和“多个保护基团”是指加入至分子以防止分子中存在的基团发生不期望的化学反应的任何原子或原子基团。保护基团部分的实例在 T. W. Greene 和 P. G. M. Wuts, *Protective Groups in Organic Synthesis* (有机合成中的保护基), 第 3 版, John Wiley & Sons, 1999 并且在 J. F. W. McOmie, *Protective Groups in Organic Chemistry* (有机化学中的保护基团), Plenum Press, 1973 中进行描述, 其二者通过引用并入本文意于公开合适保护基团的限制性目的。保护基团部分可通过对某些反应条件稳定并且在方便阶段使用本领域已知方法容易去除的方式来进行选择。保护基团的非限制性列举包括苄基; 取代的苄基; 烷基羰基和烃氧基羰基(例如, 叔丁氧基羰基(BOC)、乙酰基或异丁酰基); 芳基烷基羰基和芳基烃氧基羰基(例如, 苄氧基羰基); 取代的甲基醚(例如, 甲氧基甲基醚); 取代的乙基醚; 取代的苄基醚; 四氢吡喃基醚; 甲硅烷基(例如, 三甲基甲硅烷基、三乙基甲硅烷基、三异丙基甲硅烷基、叔丁基二甲基甲硅烷基、三异丙基甲硅烷基氧基甲基、[2-(三甲基甲硅烷基)乙氧基]甲基或叔丁基二苯基甲硅烷基); 酯(例

如,苯甲酸酯);碳酸酯(例如,碳酸甲氧基甲酯);磺酸酯(例如,甲苯磺酸酯或甲磺酸酯);无环缩酮(例如,二甲基缩醛);环缩酮(例如,1,3-二氧杂环己烷、1,3-二氧杂环戊烷和本文描述的那些);无环缩醛;环缩醛(例如,本文描述的那些);无环半缩醛;环半缩醛;环二硫代缩酮(例如,1,3-二噻烷或1,3-二硫戊环(1,3-dithiolane));原酸酯(例如,本文描述的那些)和三芳基甲基(例如,三苯甲基;一甲氧基三苯甲基(MMTr);4,4'-二甲氧基三苯甲基(DMTr);4,4',4''-三甲氧基三苯甲基(TMTr);和本文描述的那些)。

[0084] 术语“药物可接受的盐”是指对所施用的生物体不产生显著刺激并且不破坏化合物的生物活性和性质的化合物的盐。在一些实施方案中,所述盐为化合物的酸加成盐。能通过使化合物与无机酸反应获得药物盐,所述无机酸例如氢卤酸(例如,氢氯酸或氢溴酸)、硫酸、硝酸和磷酸。能通过使化合物与有机酸反应获得药物盐,所述有机酸例如脂肪族或芳香族的羧酸或磺酸,例如甲酸、乙酸、琥珀酸、乳酸、苹果酸、酒石酸、柠檬酸、抗坏血酸、烟酸、甲烷磺酸、乙烷磺酸、对甲苯磺酸、水杨酸或萘磺酸。还能通过使化合物与碱反应以形成盐来获得药物盐,例如铵盐、诸如钠盐或钾盐的碱金属盐、诸如钙盐或镁盐的碱土金属盐、诸如二环己基胺、N-甲基-D-葡萄糖胺、三(羟基甲基)甲基胺、C₁-C₇烷基胺、环己基胺、三乙醇胺、乙二胺的有机碱盐和与诸如精氨酸和赖氨酸的氨基酸的盐。

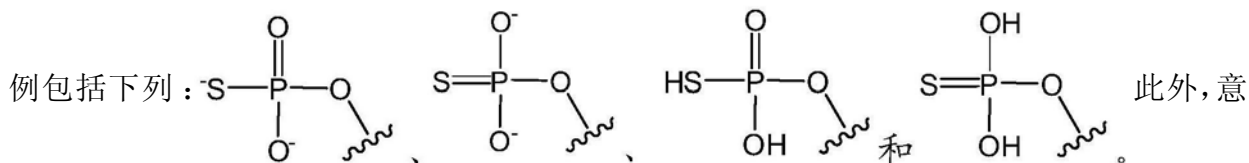
[0085] 除非另外规定,本申请中使用的术语和短语及其变型,特别是在所附的权利要求中应被解释为开放式的而非限定。作为前述的实例,术语“包括(including)”应被理解是指“包括而不限于(including, without limitation)”、“包括但不限于(including but not limited to)”等;本文使用的术语“包含(comprising)”与“包括(including)”、“含有(containing)”或“特征在于(characterized by)”同义并且为包括式或开放式,并且不排除附加、未列举的元素或方法步骤;术语“具有”应被解释为“具有至少”;术语“包括(includes)”应被解释为“包括但不限于”;术语“实例”用于提供所讨论项目的示例性实例,不是其详尽或限制性列举;并且术语如“优选地”、“优选的”、“期望的”或“所需的”和类似含义词语的使用不应被解释为暗示某些特征对于本发明的结构或功能是关键、必要的或甚至重要的,而相反应被解释为仅意图强调可或者不可用于特定实施方案的替代或附加的特征。此外,短语“具有至少”或“包括至少”与术语“包括”同义理解。当在方法的上下文中使用时,术语“包括”是指所述方法包括至少列举的步骤,但可包括附加步骤。当在化合物、组合物或设备的上下文中使用时,术语“包括”是指化合物、组合物或设备至少包括列举特征或组分,但还可包括附加特征或组分。类似地,除非另作明确说明,与连接词“和”连接的项目组不应被理解为存在于所述组中各个项目均是必须的,但相反应被理解为“和/或”。类似地,除非另作明确说明,与连接词“或”连接的项目组不应被理解为所述组之间需要相互排斥,但相反应被理解为“和/或”。

[0086] 关于本文基本上任何复数和/或单数术语的使用,本领域技术人员根据对上下文和/或申请的适用能从复数转化为单数和/或从单数转化为复数。为了清楚,可在本文明确阐述各个单数/复数排列。不定冠词“a”或“an”不排除复数。单个方法或其他装置可实现权利要求列举的几个项目的功能。以相互不同的从属权利要求形式列举的一些方案的单纯事实不表明这些方案的组合不具有优势。权利要求中的任何引用符号不应被解释为限制所述范围。

[0087] 应当理解,在本文描述的具有一个或多个手性中心的任何化合物中,如果未清楚

规定绝对立体化学,则各个中心可独立地为 R- 构型或 S- 构型或其混合物。因此,本文提供的化合物可为对映异构体纯的、对映异构体富集的、外消旋混合物、非对映异构体纯的、非对映异构体富集的或立体异构体混合物。此外,应当理解,在本文描述的产生可被定义为 E 或 Z 的几何异构体的具有一个或多个双键的任何化合物中,各个双键可独立地为 E 或 Z、其混合物。

[0088] 相似地,应当理解,在描述的任何化合物中,还意图包括所有互变异构体形式。例如,意图包括所有磷酸酯和硫代磷酸酯基团的互变异构体。硫代磷酸酯的互变异构体的实



图包括所有本领域已知的杂环碱的互变异构体,包括天然和非天然嘌呤-碱基和嘧啶-碱基的互变异构体。

[0089] 应当理解,在本文公开的化合物具有空化合价的情况下,则化合价被氢或其同位素填充,例如,氢-1(氕)和氢-2(氘)。

[0090] 应当理解,可将本文描述的化合物进行同位素标记。使用诸如氕的同位素取代可产生一些源于更大的代谢稳定性的治疗优势,例如,增加体内半衰期或减少剂量需求。化合物结构中代表的各个化学元素可包括所述元素的任何同位素。例如,在化合物结构中,可明确公开氢原子或者理解为存在于化合物中。在可存在氢原子的化合物的任何位置,氢原子可为任何氢的同位素,包括但不限于氢-1(氕)和氢-2(氘)。因此,除非上下文作出明确说明,本文对化合物的引用包括所有潜在同位素形式。

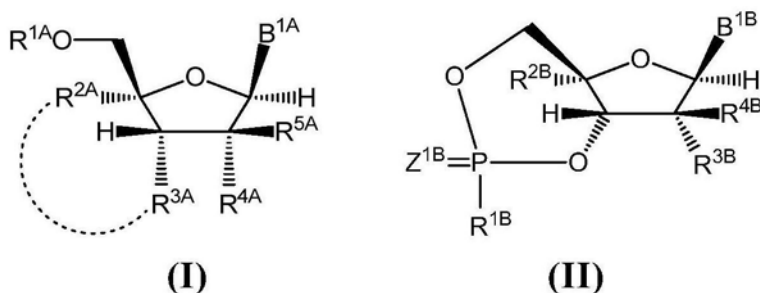
[0091] 应当理解,本文描述的方法和组合包括晶体形式(还称为多晶型,其包括化合物相同元素组合物的不同晶体堆积排列)、非晶相、盐、溶剂化物和水合物。在一些实施方案中,本文描述的化合物以具有诸如水、乙醇等的药物可接受的溶剂的溶剂化物形式存在。在其他实施方案中,本文描述的化合物以非溶剂化物形式存在。溶剂化物包含化学计量或非化学计量的溶剂,并且其可在结晶过程中与诸如水、乙醇等的药物可接受的溶剂形成。当溶剂为水时形成水合物,或者当溶剂为醇时形成醇化物。此外,本文提供的化合物能以非溶剂化物以及溶剂化物形式存在。通常,为了本文提供的化合物和方法的目的,溶剂化物形式被认为等价于非溶剂化物形式。

[0092] 在提供值的范围的情况下,应当理解,所述范围的上限和下限以及上限和下限之间的各个中间值包括在实施方案内。

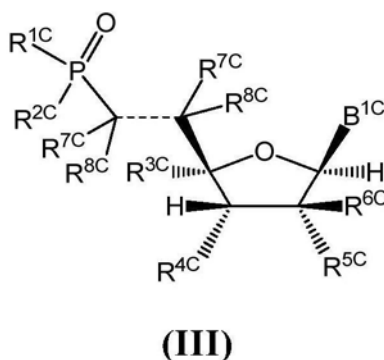
[0093] 化合物

[0094] 本文公开的一些实施方案涉及选自式(I)、式(II)和式(III)的化合物或前述的药物可接受的盐:

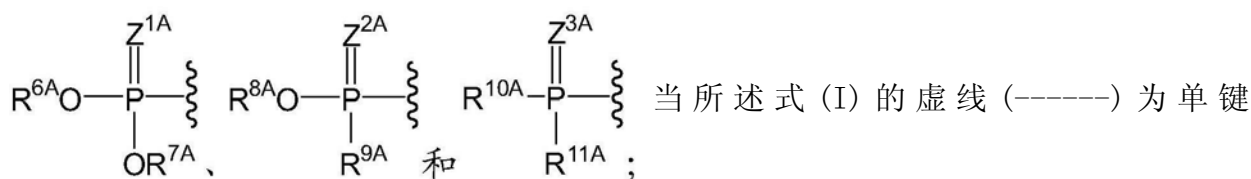
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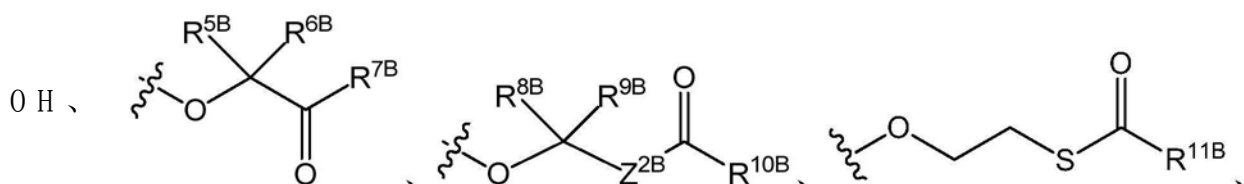
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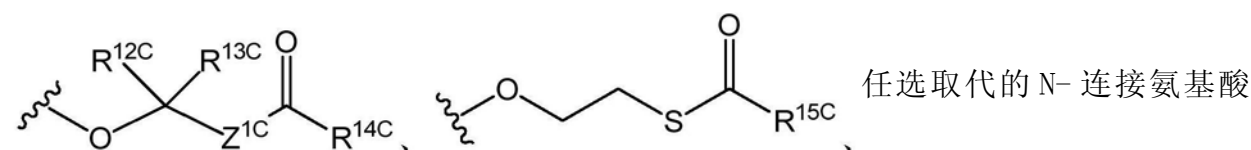
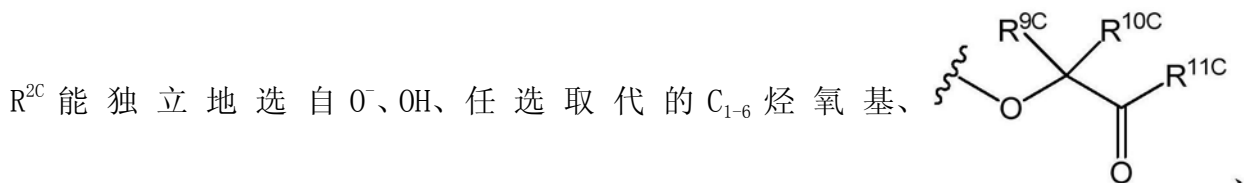
[0097] 其中: B^{1A} 、 B^{1B} 和 B^{1C} 可独立地为任选取代的杂环碱或具有被护氨基的任选取代的杂环碱; R^{1A} 能选自氢、任选取代的酰基、任选取代的 O- 连接氨基酸、



时, R^{2A} 可为 CH_2 且 R^{3A} 可为 O(氧); 当所述式 (I) 的虚线 (-----) 不存在时, R^{2A} 可选自任选取代的 C_{1-6} 烷基、任选取代的 C_{2-6} 烯基、任选取代的 C_{2-6} 炔基、任选取代的 C_{3-6} 环烷基、任选取代的 $-O-C_{1-6}$ 烷基、任选取代的 $-O-C_{3-6}$ 烯基、任选取代的 $-O-C_{3-6}$ 炔基和氰基, 且 R^{3A} 可选自 OH 、 $-OC(=O)R''^A$ 和任选取代的 O- 连接氨基酸; R^{1B} 可选自 O^- 、

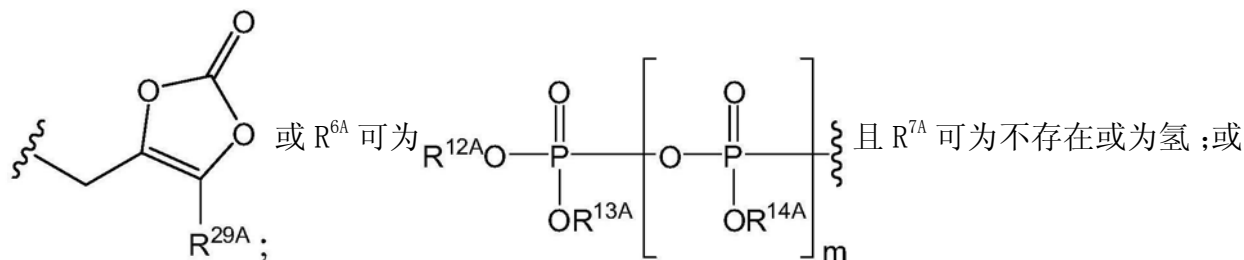
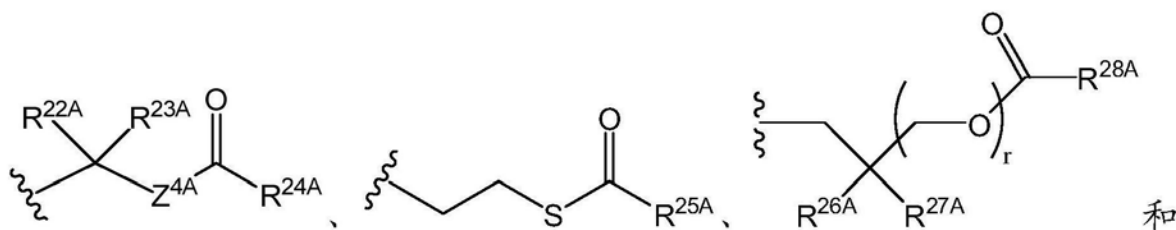
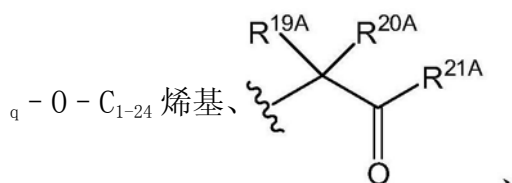


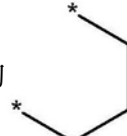
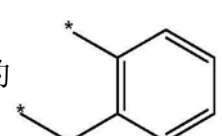
任选取代的 N- 连接氨基酸和任选取代的 N- 连接氨基酸酯衍生物; R^{1C} 和



和任选取代的 N- 连接氨基酸酯衍生物 ; 或者 R^{1C} 可为 $R^{16C}O-P(=O)(OR^{17C})-O-P(=O)(OR^{18C})_n$ 且 R^{2C} 可

为 O^- 或 OH ; R^{2B} 和 R^{3C} 可独立地选自任选取代的 C_{1-6} 烷基、任选取代的 C_{2-6} 烯基、任选取代的 C_{2-6} 炔基、任选取代的 $-O-C_{1-6}$ 烷基、任选取代的 $-O-C_{3-6}$ 烯基、任选取代的 $-O-C_{3-6}$ 炔基、任选取代的 C_{3-6} 环烷基和氰基 ; R^{4C} 可选自 OH 、 $-OC(=O)R^{4C}$ 和任选取代的 O- 连接氨基酸 ; R^{4A} 、 R^{3B} 和 R^{5C} 可独立地为卤素 ; R^{5A} 、 R^{4B} 和 R^{6C} 可独立地为氢或卤素 ; R^{6A} 、 R^{7A} 和 R^{8A} 可独立地选自不存在、氢、任选取代的 C_{1-24} 烷基、任选取代的 C_{2-24} 烯基、任选取代的 C_{2-24} 炔基、任选取代的 C_{3-6} 环烷基、任选取代的 C_{3-6} 环烯基、任选取代的芳基、任选取代的杂芳基、任选取代的芳基 (C_{1-6} 烷基)、任选取代的 $*(CR^{15A}R^{16A})_p-O-C_{1-24}$ 烷基、任选取代的 $*(CR^{17A}R^{18A})$



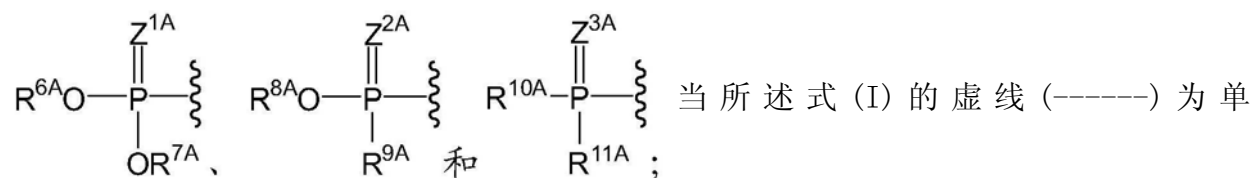
R^{6A} 和 R^{7A} 可在一起形成选自任选取代的  和任选取代的  的部分, 其中

所述与 R^{6A} 和 R^{7A} 连接的氧、所述磷和所述部分形成六元至十元环体系 ; R^{9A} 可独立地选自任选取代的 C_{1-24} 烷基、任选取代的 C_{2-24} 烯基、任选取代的 C_{2-24} 炔基、任选取代的 C_{3-6} 环烷基、任选取代的 C_{3-6} 环烯基、 $NR^{30A}R^{31A}$ 、任选取代的 N- 连接氨基酸和任选取代的 N- 连接氨基酸酯衍生物 ; R^{10A} 和 R^{11A} 可独立地为任选取代的 N- 连接氨基酸或任选取代的 N- 连接氨基酸酯衍生物 ; R^{12A} 、 R^{13A} 和 R^{14A} 可独立地为不存在或为氢 ; 各个 R^{15A} 、各个 R^{16A} 、各个 R^{17A} 和各个 R^{18A} 可独立地为氢、任选取代的 C_{1-24} 烷基或烃氧基 ; R^{19A} 、 R^{20A} 、 R^{22A} 、 R^{23A} 、 R^{5B} 、 R^{6B} 、 R^{8B} 、 R^{9B} 、 R^{9C} 、 R^{10C} 、 R^{12C} 和 R^{13C} 可独立地选自氢、任选取代的 C_{1-24} 烷基和任选取代的芳基 ; R^{21A} 、 R^{24A} 、 R^{7B} 、 R^{10B} 、 R^{11C} 和 R^{14C} 可独立地选自氢、任选取代的 C_{1-24} 烷基、任选取代的芳基、任选取代的 $-O-C_{1-24}$ 烷基和任选取代的 $-O-$ 芳基 ; R^{25A} 、 R^{29A} 、 R^{11B} 和 R^{15C} 可独立地选自氢、任选取代的 C_{1-24} 烷基和任选

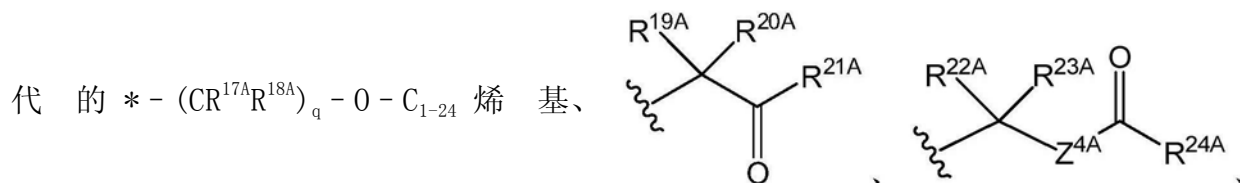
取代的芳基; R^{16C} 、 R^{17C} 和 R^{18C} 可独立地为不存在或为氢; R^{26A} 和 R^{27A} 可独立地为 $-C \equiv N$ 或任选取代的选自 C_{2-8} 有机基羰基、 C_{2-8} 炔氧基羰基和 C_{2-8} 有机基氨基羰基的取代基; R^{28A} 可选自氢、任选取代的 C_{1-24} 烷基、任选取代的 C_{2-24} 烯基、任选取代的 C_{2-24} 炔基、任选取代的 C_{3-6} 环烷基和任选取代的 C_{3-6} 环烯基; R^{30A} 和 R^{31A} 可独立地选自氢、任选取代的 C_{1-24} 烷基、任选取代的 C_{2-24} 烯基、任选取代的 C_{2-24} 炔基、任选取代的 C_{3-6} 环烷基和任选取代的 C_{3-6} 环烯基; 对于式 (III), ----- 可为单键或双键; 当 ----- 为单键时, 各个 R^{7C} 和各个 R^{8C} 可独立地为氢或卤素; 且当 ----- 为双键时, 各个 R^{7C} 不存在且各个 R^{8C} 可独立地为氢或卤素; R''^A 和 R'^C 可独立地为任选取代的 C_{1-24} 烷基; m 和 n 可独立地为 0 或 1; p 和 q 可独立地选自 1、2 和 3; r 可为 1 或 2; Z^{1A} 、 Z^{2A} 、 Z^{3A} 、 Z^{4A} 、 Z^{1B} 、 Z^{2B} 和 Z^{1C} 可独立地为 0 或 S; 且条件是当所述式 (I)

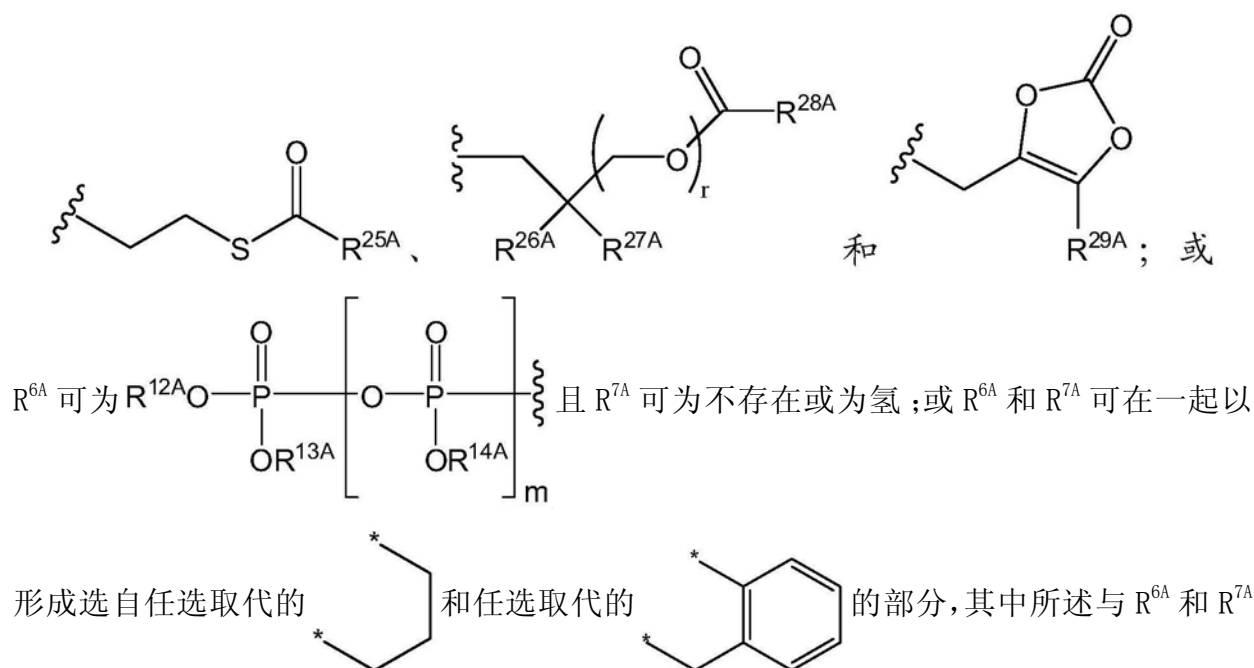
的虚线 (-----) 不存在时; R^{1A} 为 $R^{8A}O-P \begin{array}{c} \text{Z}^{2A} \\ \parallel \\ \text{---} \\ | \\ R^{9A} \end{array}$ 其中 R^{8A} 为未取代的 C_{1-4} 烷基或任选被卤素或甲基对位取代的苯基且 R^{9A} 为氨基酸的甲基酯、乙基酯、异丙基酯、正丁基酯、苄基酯或苯基酯, 所述氨基酸选自甘氨酸、丙氨酸、缬氨酸、亮氨酸、苯丙氨酸、色氨酸、蛋氨酸和脯氨酸; R^{3A} 为 OH; R^{4A} 为氟; R^{5A} 为氟或氢; 且 B^{1A} 为未取代的尿嘧啶; 则 R^{2A} 不可为 $-OCH_3$; 条件是当所述式 (I) 的虚线 (-----) 不存在时; R^{1A} 为 H; R^{3A} 为 OH; R^{4A} 为氟; R^{5A} 为氟; 且 B^{1A} 为未取代的胞嘧啶; 则 R^{2A} 不可为烯基; 条件是当所述式 (I) 的虚线 (-----) 不存在时; R^{1A} 为 H; R^{3A} 为 OH; R^{4A} 为氟; R^{5A} 为氢; 且 B^{1A} 为未取代的胸腺嘧啶; 则 R^{2A} 不可为被 N- 酰胺基 (例如, $-NC(=O)CF_3$) 任选取代的 C_1 烷基; 且条件是当所述式 (I) 的虚线 (-----) 不存在时; R^{1A} 为 H; R^{3A} 为 OH; R^{4A} 为氟; R^{5A} 为氟; 且 B^{1A} 为未取代的胞嘧啶; 则 R^{2A} 不可为乙炔基。

[0098] 在一些实施方案中, 化合物可为式 (I) 的化合物或其药物可接受的盐, 其中: B^{1A} 可为任选取代的杂环碱或具有被护氨基的任选取代的杂环碱; R^{1A} 可选自氢、

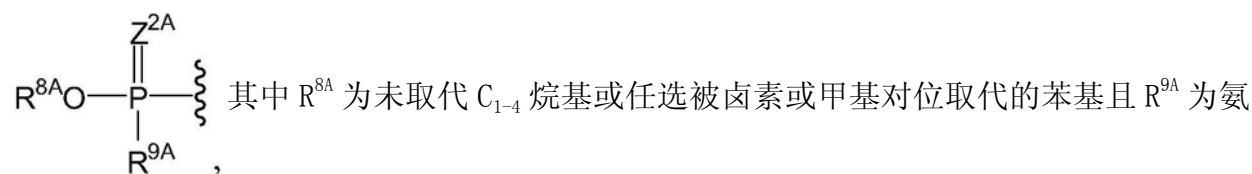


键时, R^{2A} 为 CH_2 且 R^{3A} 为 O (氧); 当所述式 (I) 的虚线 (-----) 不存在时, R^{2A} 可选自任选取代的 C_{1-6} 烷基、任选取代的 C_{2-6} 烯基、任选取代的 C_{2-6} 炔基、任选取代的 C_{3-6} 环烷基、任选取代的 $-O-C_{1-6}$ 烷基、任选取代的 $-O-C_{3-6}$ 烯基、任选取代的 $-O-C_{3-6}$ 炔基和氰基, 且 R^{3A} 为 OH; R^{4A} 可为卤素; R^{5A} 可为氢或卤素; R^{6A} 、 R^{7A} 和 R^{8A} 可独立地为选自不存在、氢、任选取代的 C_{1-24} 烷基、任选取代的 C_{2-24} 烯基、任选取代的 C_{2-24} 炔基、任选取代的 C_{3-6} 环烷基、任选取代的 C_{3-6} 环烯基、任选取代的芳基、任选取代的杂芳基、任选取代的芳基 (C_{1-6} 烷基)、任选取代的 $*(CR^{15A}R^{16A})_p-O-C_{1-24}$ 烷基、任选取





连接的氧、磷和该部分形成六元至十元环体系； R^{9A} 可独立地为选自任选取代的 C_{1-24} 烷基、任选取代的 C_{2-24} 烯基、任选取代的 C_{2-24} 炔基、任选取代的 C_{3-6} 环烷基、任选取代的 C_{3-6} 环烯基、 $\text{NR}^{30A}\text{R}^{31A}$ 、任选取代的 N-连接氨基酸和任选取代的 N-连接氨基酸酯衍生物； R^{10A} 和 R^{11A} 可独立地为任选取代的 N-连接氨基酸或任选取代的 N-连接氨基酸酯衍生物； R^{12A} 、 R^{13A} 和 R^{14A} 可独立地为不存在或为氢；各个 R^{15A} 、各个 R^{16A} 、各个 R^{17A} 和各个 R^{18A} 可独立地为氢、任选取代的 C_{1-24} 烷基或炔氧基； R^{19A} 、 R^{20A} 、 R^{22A} 和 R^{23A} 可独立地选自氢、任选取代的 C_{1-24} 烷基和任选取代的芳基； R^{21A} 和 R^{24A} 可独立地选自氢、任选取代的 C_{1-24} 烷基、任选取代的芳基、任选取代的 $-\text{O}-\text{C}_{1-24}$ 烷基和任选取代的 $-\text{O}-$ 芳基； R^{25A} 和 R^{29A} 可独立地选自氢、任选取代的 C_{1-24} 烷基和任选取代的芳基； R^{26A} 和 R^{27A} 可独立地为 $-\text{C}\equiv\text{N}$ 或选自 C_{2-8} 有机基羰基、 C_{2-8} 炔氧基羰基和 C_{2-8} 有机基氨基羰基的任选取代的取代基； R^{28A} 可独立地选自氢、任选取代的 C_{1-24} 烷基、任选取代的 C_{2-24} 烯基、任选取代的 C_{2-24} 炔基、任选取代的 C_{3-6} 环烷基和任选取代的 C_{3-6} 环烯基； R^{30A} 和 R^{31A} 可独立地选自氢、任选取代的 C_{1-24} 烷基、任选取代的 C_{2-24} 烯基、任选取代的 C_{2-24} 炔基、任选取代的 C_{3-6} 环烷基和任选取代的 C_{3-6} 环烯基； m 可为 0 或 1； p 和 q 可独立地选自 1、2 和 3； r 可为 1 或 2； Z^{1A} 、 Z^{2A} 、 Z^{3A} 和 Z^{4A} 可独立地为 0 或 S；在一些实施方案中，式 (I) 的化合物能具有本文显示的结构，条件是当所述式 (I) 的虚线 (-----) 不存在时； R^{1A} 为



基酸的甲基酯、乙基酯、异丙基酯、正丁基酯、苄基酯或苯基酯，所述氨基酸选自甘氨酸、丙氨酸、缬氨酸、亮氨酸、苯基丙氨酸、色氨酸、蛋氨酸和脯氨酸； R^{3A} 为 OH； R^{4A} 为氟； R^{5A} 为氟或氢；且 B^{1A} 为未取代的尿嘧啶；则 R^{2A} 不为 $-\text{OCH}_3$ ；条件是当所述式 (I) 的虚线 (-----) 不存在时； R^{1A} 为 H； R^{3A} 为 OH； R^{4A} 为氟； R^{5A} 为氟；且 B^{1A} 为未取代的胞嘧啶；则 R^{2A} 不为烯基；条件是当所述式 (I) 的虚线 (-----) 不存在时； R^{1A} 为 H； R^{3A} 为 OH； R^{4A} 为氟； R^{5A} 为氢；且 B^{1A} 为未取代的胸腺嘧啶；则 R^{2A} 不为被 N-酰胺基取代的 C_1 烷基；且条件是当所述式 (I) 的虚

线(-----)不存在时; R^{1A} 为H; R^{3A} 为OH; R^{4A} 为氟; R^{5A} 为氟;且 B^{1A} 为未取代的胞嘧啶;则 R^{2A} 不为乙炔基。

[0099] 在一些实施方案中, R^{1A} 可为 $R^{6A}O-P(=Z^{1A})(OR^{7A})_2$ 。在一些实施方案中, R^{6A} 和 R^{7A} 都可为

氢。在其他实施方案中, R^{6A} 和 R^{7A} 都可为不存在。在其他实施方案中,至少一个 R^{6A} 和 R^{7A} 可为不存在。在其他实施方案中,至少一个 R^{6A} 和 R^{7A} 可为氢。本领域技术人员理解当 R^{6A} 和/或 R^{7A} 不存在时,缔合的氧具有负电荷。例如,当 R^{6A} 不存在时,与 R^{6A} 缔合的氧具有负电荷。在一些实施方案中, Z^{1A} 可为O(氧)。在其他实施方案中, Z^{1A} 可为S(硫)。在一些实施方案中, R^{1A} 可为单磷酸酯。在其他实施方案中, R^{1A} 可为单硫代磷酸酯。

[0100] 在一些实施方案中,当 R^{1A} 为 $R^{6A}O-P(=Z^{1A})(OR^{7A})_2$ 时, R^{6A} 和 R^{7A} 中的一个可为氢,且 R^{6A} 和

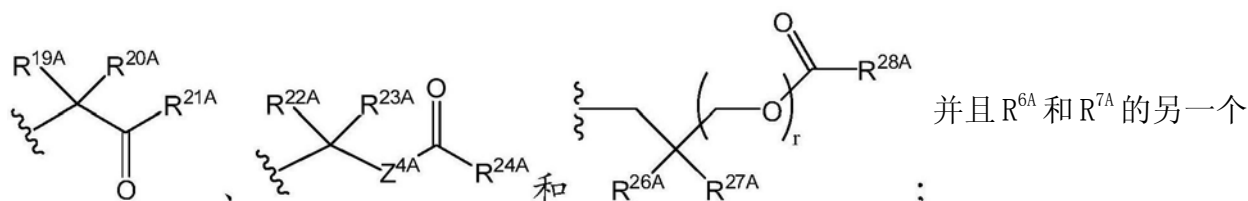
R^{7A} 中的另一个选自任选取代的 C_{1-24} 烷基、任选取代的 C_{2-24} 烯基、任选取代的 C_{2-24} 炔基、任选取代的 C_{3-6} 环烷基、任选取代的 C_{3-6} 环烯基、任选取代的芳基、任选取代的杂芳基和任选取代的芳基(C_{1-6} 烷基)。在一些实施方案中, R^{6A} 和 R^{7A} 中的一个可为氢,且 R^{6A} 和 R^{7A} 中的另一个可为任选取代的 C_{1-24} 烷基。在其他实施方案中, R^{6A} 和 R^{7A} 二者可独立地选自任选取代的 C_{1-24} 烷基、任选取代的 C_{2-24} 烯基、任选取代的 C_{2-24} 炔基、任选取代的 C_{3-6} 环烷基、任选取代的 C_{3-6} 环烯基、任选取代的芳基、任选取代的杂芳基和任选取代的芳基(C_{1-6} 烷基)。在一些实施方案中, R^{6A} 和 R^{7A} 二者可为任选取代的 C_{1-24} 烷基。在其他实施方案中, R^{6A} 和 R^{7A} 二者可为任选取代的 C_{2-24} 烯基。在一些实施方案中, R^{6A} 和 R^{7A} 可独立地为以下基团的任选取代的变型:十四碳烯基(myristoleyl)、肉豆蔻基、棕榈油酰基、十六烷醇基、十六碳烯基(sapienyl)、油烯基、9-反-十八烯基(elaidyl)、十八烯醇(vaccenyl)、亚油醇基(linoleyl)、 α -亚麻醇基(α -linolenyl)、花生酰基(arachidonyl)、二十碳五烯基(eicosapentaenyl)、二十二烯基(erucyl)、二十二碳六烯基(docosahexaenyl)、辛酰基(caprylyl)、癸酰基(capryl)、月桂酰基(lauryl)、硬脂酰基(stearyl)、二十烷醇基(arachidyl)、二十二烷醇基(beheryl)、二十四烷基(lignoceryl)和蜡基(cerotyl)。

[0101] 在一些实施方案中,至少一个 R^{6A} 和 R^{7A} 可为 $*(CR^{15A}R^{16A})_p-O-C_{1-24}$ 烷基。在其他实施方案中, R^{6A} 和 R^{7A} 都可为 $*(CR^{15A}R^{16A})_p-O-C_{1-24}$ 烷基。在一些实施方案中,各个 R^{15A} 和各个 R^{16A} 为氢。在其他实施方案中,至少一个 R^{15A} 和 R^{16A} 为任选取代的 C_{1-24} 烷基。在其他实施方案中,至少一个 R^{15A} 和 R^{16A} 为烃氧基(例如,苄氧基)。在一些实施方案中,p可为1。在其他实施方案中,p可为2。在其他实施方案中,p可为3。

[0102] 在一些实施方案中,至少一个 R^{6A} 和 R^{7A} 可为 $*(CR^{17A}R^{18A})_q-O-C_{2-24}$ 烯基。在其他实施方案中, R^{6A} 和 R^{7A} 都可为 $*(CR^{17A}R^{18A})_q-O-C_{2-24}$ 烯基。在一些实施方案中,各个 R^{17A} 和各个 R^{18A} 为氢。在其他实施方案中,至少一个 R^{17A} 和 R^{18A} 为任选取代的 C_{1-24} 烷基。在一些实施方案中,q可为1。在其他实施方案中,q可为2。在其他实施方案中,q可为3。当 R^{6A} 和 R^{7A} 的至少一个为 $*(CR^{15A}R^{16A})_p-O-C_{1-24}$ 烷基或 $*(CR^{17A}R^{18A})_q-O-C_{2-24}$ 烯基时, C_{1-24} 烷

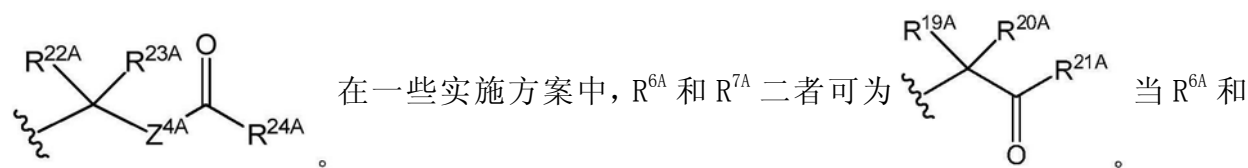
基可选自辛酰基、癸酰基、月桂酰基、肉豆蔻基、十六烷醇基、硬脂酰基、二十烷醇基、二十二烷醇基、二十四烷基和蜡基,且 C_{2-24} 烯基可选自十四碳烯基、棕榈油酰基、十六碳烯基、油烯基、9-反-十八烯基、十八烯醇、亚油醇基、 α -亚麻醇基、花生酰基、二十碳五烯基、二十二烯基、二十二碳六烯基。

[0103] 在一些实施方案中,当 R^{1A} 为 $R^{6A}O-P(Z^{1A})_2(OR^{7A})$ 时, R^{6A} 和 R^{7A} 的至少一个可选自



可选自不存在、氢、任选取代的 C_{1-24} 烷基、任选取代的 C_{2-24} 烯基、任选取代的 C_{2-24} 炔基、任选取代的 C_{3-6} 环烷基、任选取代的 C_{3-6} 环烯基、任选取代的芳基、任选取代的杂芳基和任选取代的芳基 (C_{1-6} 烷基)。

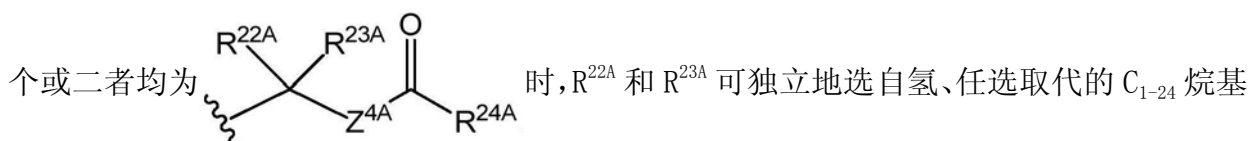
[0104] 在一些实施方案中, R^{6A} 和 R^{7A} 的至少一个可为



R^{7A} 中的一个或二者均为

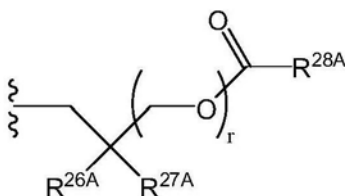
基和任选取代的芳基;且 R^{21A} 可选自氢、任选取代的 C_{1-24} 烷基、任选取代的芳基、任选取代的 $-O-C_{1-24}$ 烷基和任选取代的 $-O-$ 芳基。在一些实施方案中, R^{19A} 和 R^{20A} 可为氢。在其他实施方案中,至少一个 R^{19A} 和 R^{20A} 可为任选取代的 C_{1-24} 烷基或任选取代的芳基。在一些实施方案中, R^{21A} 可为任选取代的 C_{1-24} 烷基。在其他实施方案中, R^{21A} 可为任选取代的芳基。在其他实施方案中, R^{21A} 可为任选取代的 $-O-C_{1-24}$ 烷基或任选取代的 $-O-$ 芳基。

[0105] 在一些实施方案中, R^{6A} 和 R^{7A} 二者可为



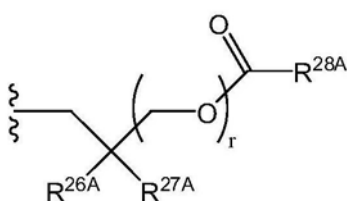
和任选取代的芳基； R^{24A} 可独立地选自氢、任选取代的 C_{1-24} 烷基、任选取代的芳基、任选取代的 $-O-C_{1-24}$ 烷基和任选取代的 $-O-$ 芳基；且 Z^{4A} 可独立地为O(氧)或S(硫)。在一些实施方案中， R^{22A} 和 R^{23A} 可为氢。在其他实施方案中，至少一个 R^{22A} 和 R^{23A} 可为任选取代的 C_{1-24} 烷基或任选取代的芳基。在一些实施方案中， R^{24A} 可为任选取代的 C_{1-24} 烷基。在其他实施方案中， R^{24A} 可为任选取代的芳基。在其他实施方案中， R^{24A} 可为任选取代的 $-O-C_{1-24}$ 烷基或任选取代的 $-O-$ 芳基。在一些实施方案中， Z^{4A} 可为O(氧)。在其他实施方案中， Z^{4A} 可为或S(硫)。在一些实施方案中， R^{6A} 和 R^{7A} 中的一个或二者可为异丙基羰基氧基甲基。在一些实施方案中， R^{6A} 和 R^{7A} 中的一个或二者可为特戊酰基氧基甲基。

[0106] 在一些实施方案中， R^{6A} 和 R^{7A} 二者均可作为



当 R^{6A} 和 R^{7A} 中

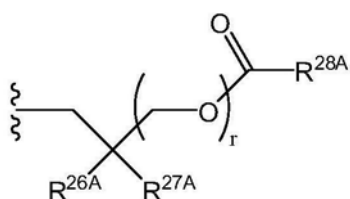
的一个或二者均为



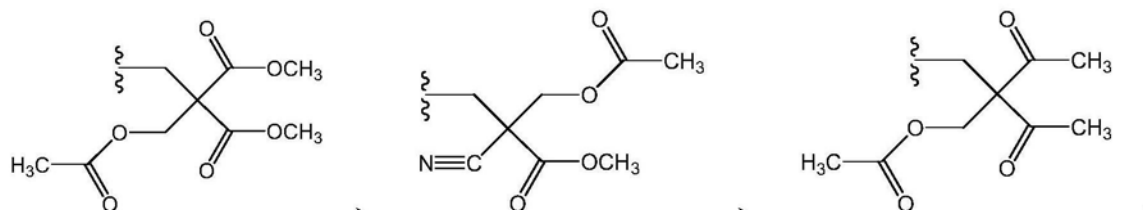
时， R^{26A} 和 R^{27A} 可独立地为 $-C \equiv N$ 或选自 C_{2-8} 有

机基羰基、 C_{2-8} 炔氧基羰基和 C_{2-8} 有机基氨基羰基的任选取代的取代基； R^{28A} 可选自氢、任选取代的 C_{1-24} 烷基、任选取代的 C_{2-24} 烯基、任选取代的 C_{2-24} 炔基、任选取代的 C_{3-6} 环烷基和任选取代的 C_{3-6} 环烯基；且 r 可为1或2。在一些实施方案中， R^{26A} 可为 $-C \equiv N$ 且 R^{27A} 可为任选取代的 C_{2-8} 炔氧基羰基、例如 $-C(=O)OCH_3$ 。在其他实施方案中， R^{26A} 可为 $-C \equiv N$ 且 R^{27A} 可为任选取代的 C_{2-8} 有机基氨基羰基，例如， $-C(=O)NHCH_2CH_3$ 和 $-C(=O)NHCH_2CH_2$ 苯基。在一些实施方案中， R^{26A} 和 R^{27A} 二者可为任选取代的 C_{2-8} 有机基羰基，例如 $-C(=O)CH_3$ 。在一些实施方案中， R^{26A} 和 R^{27A} 二者可为任选取代的 C_{1-8} 炔氧基羰基，例如， $-C(=O)OCH_2CH_3$ 和 $-C(=O)OCH_3$ 。在一些实施方案中，包括本段中描述的那些， R^{28A} 可为任选取代的 C_{1-4} 烷基。在一些实施方案中， R^{28A} 可为甲基或叔丁基。在一些实施方案中， R 可为1。在其他实施方案中， R 可为2。

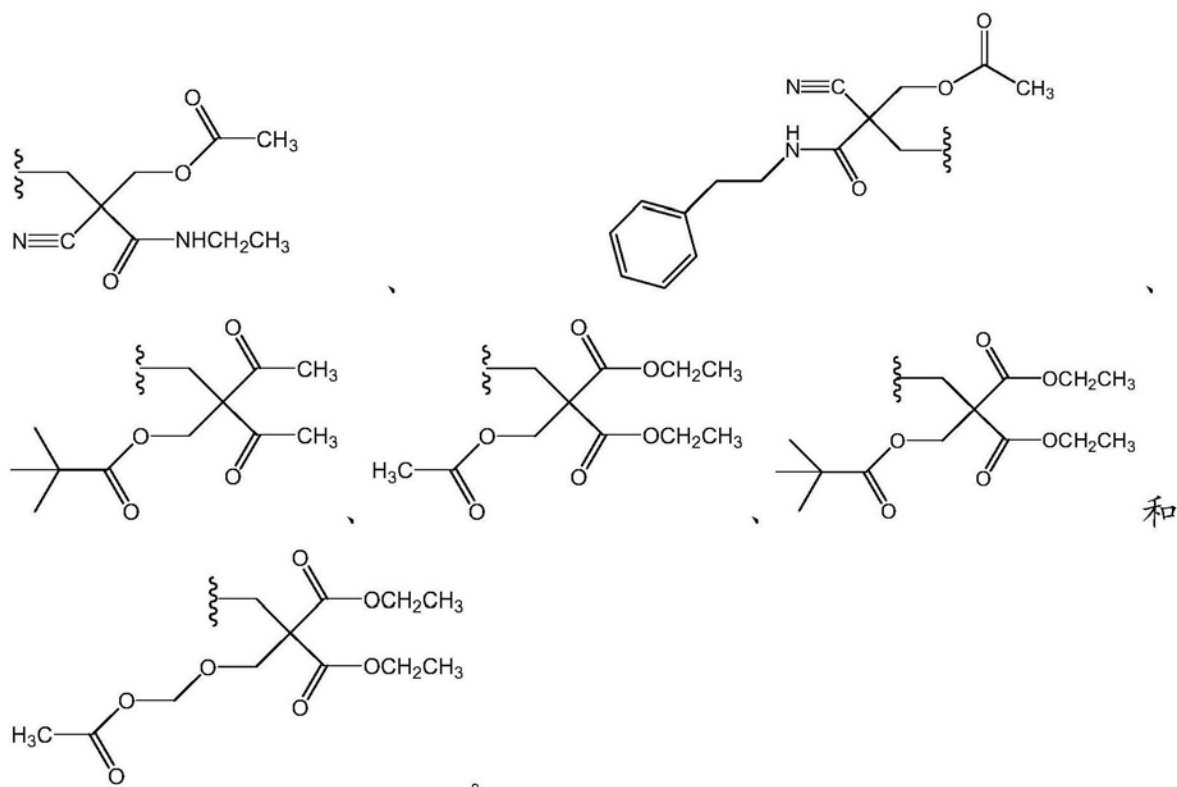
[0107] 的实例包括但不限于下列：



[0108]

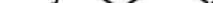


[0109]



[0110] 在一些实施方案中, R^{6A} 和 R^{7A} 都可为任选取代的芳基。在一些实施方案中, R^{6A} 和 R^{7A} 的至少一个可为任选取代的芳基。例如, R^{6A} 和 R^{7A} 二者均可可为任选取代的苯基或任选取代的萘基。当取代时, 取代的芳基能被 1、2、3 或多于 3 个取代基取代。当存在多于两个取代基时, 取代基可相同或不同。在一些实施方案中, 当至少一个 R^{6A} 和 R^{7A} 为取代的苯基时, 取代的苯基可为对 -、邻 - 或间 - 取代的苯基。

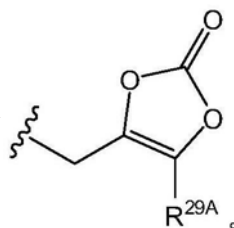
[0111] 在一些实施方案中, R^{6A} 和 R^{7A} 都可为任选取代的芳基 (C_{1-6} 烷基)。在一些实施方案中, 至少一个 R^{6A} 和 R^{7A} 可为任选取代的芳基 (C_{1-6} 烷基)。例如, R^{6A} 和 R^{7A} 二者可为任选取代的苄基。当取代时, 取代的苄基能被 1、2、3 或多于 3 个取代基取代。当存在多于两个取代基时, 取代基可相同或不同。在一些实施方案中, 芳基 (C_{1-6} 烷基) 的芳基可为对 -、邻 - 或间 - 取代的苯基。

[0112] 在一些实施方案中, R^{6A} 和 R^{7A} 都可为  在一些实施方案中,

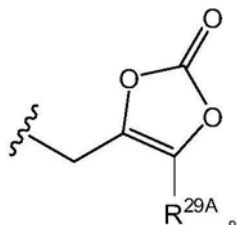
至少一个 R^{6A} 和 R^{7A} 可为  在一些实施方案中, R^{25A} 可为氢。在其他实

实施方案中, R^{25A} 可为任选取代的 C₁₋₂₄ 烷基。在其他实施方案中, R^{25A} 可为任选取代的芳基。在一些实施方案中, R^{25A} 可为 C₁₋₆ 烷基、例如, 甲基、乙基、正丙基、异丙基、正丁基、异丁基、叔丁基、戊基 (支链和直链) 和己基 (支链和直链)。

[0113] 在一些实施方案中, R^{6A} 和 R^{7A} 都可为

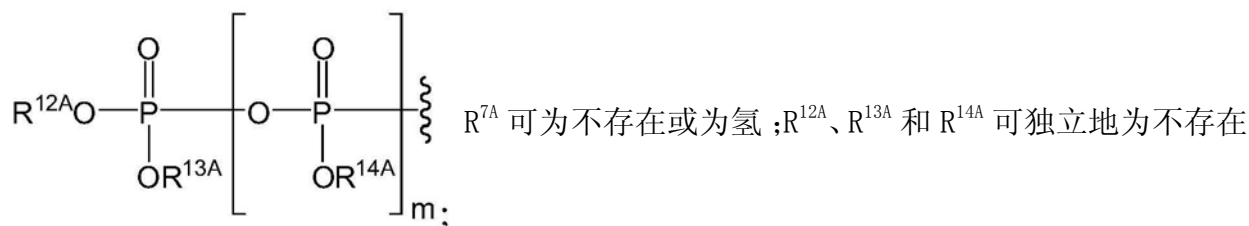
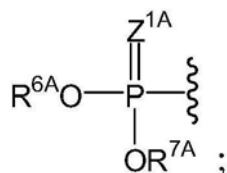


在一些实施方案中, R^{6A} 和 R^{7A} 的至少一个可为



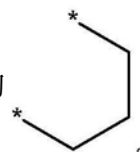
在一些实施方案中, R^{29A} 可为氢。在其他实施方案中, R^{29A} 可为任选取代的 C_{1-24} 烷基。在一些实施方案中, R^{29A} 可为 C_{1-4} 烷基, 例如甲基、乙基、正丙基、异丙基、正丁基、异丁基和叔丁基。在其他实施方案中, R^{29A} 可为任选取代的芳基, 例如任选取代的苯基或任选取代的萘基。

[0114] 在一些实施方案中, R^{1A} 可为

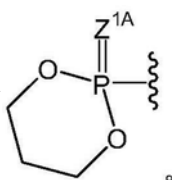


R^{7A} 可为不存在或为氢; R^{12A} 、 R^{13A} 和 R^{14A} 可独立地为不存在或为氢; 且 m 可为 0 或 1。在一些实施方案中, m 可为 0, 并且 R^{7A} 、 R^{12A} 和 R^{13A} 可独立地为不存在或为氢。在其他实施方案中, m 可为 1, 且 R^{7A} 、 R^{12A} 、 R^{13A} 和 R^{14A} 可独立地为不存在或为氢。本领域技术人员理解当 m 为 0 时, R^{6A} 可为二磷酸酯, 当 Z^{1A} 为氧时, 或 α -硫代二磷酸酯, 当 Z^{1A} 为硫时。同样地, 本领域技术人员理解当 m 为 1 时, R^{6A} 可为三磷酸酯, 当 Z^{1A} 为氧时, 或 α -硫代三磷酸酯, 当 Z^{1A} 为硫时。

[0115] 在一些实施方案中, R^{6A} 和 R^{7A} 可在一起以形成任选取代的

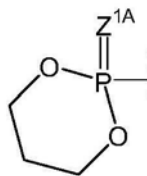


例如, R^{1A} 可为任选取代的



当取代时, 环能被取代 1、2、3 或 3 或多次。当被多个取代基取代时,

取代基可相同或不同。在一些实施方案中,当 R^{1A} 为

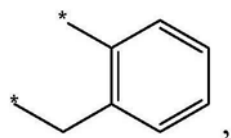


和 / 或任选取代的杂芳基取代。适合的杂芳基的实例为吡啶基。在一些实施方案中, R^{6A} 和

R^{7A} 可在一起以形成任选取代的 例如 其中 R^{32A} 可为任选取代的芳

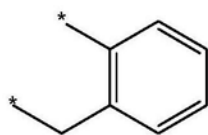
基、任选取代的杂芳基或任选取代的杂环基。

[0116] 在一些实施方案中, R^{6A} 和 R^{7A} 可在一起以形成任选取代的

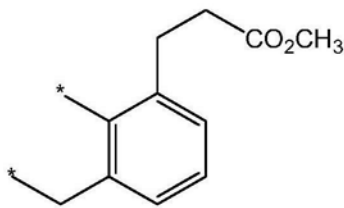
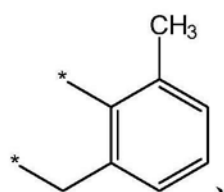
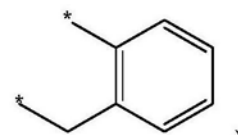


其中与 R^{6A} 和 R^{7A} 连接的氧、磷与该部分形成六元至十

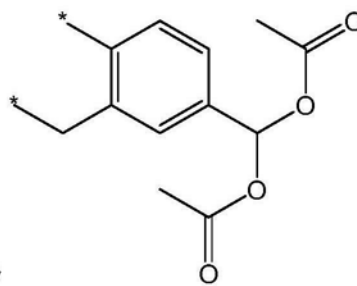
元环体系。任选取代的



的实例包括



和



[0117] 在一些实施方案中, R^{6A} 和 R^{7A} 可相同。在一些实施方案中, R^{6A} 和 R^{7A} 可不同。

[0118] 在一些实施方案中, Z^{1A} 可为氧。在其他实施方案中, Z^{1A} 可为硫。

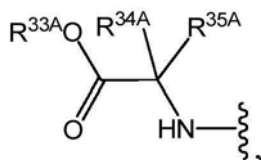
[0119] 在一些实施方案中, R^{1A} 可为 $R^{8A}O-P(=Z^{2A})(R^{9A})$ 在一些实施方案中, R^{8A} 可选自不存在、

氢、任选取代的 C_{1-24} 烷基、任选取代的 C_{2-24} 烯基、任选取代的 C_{2-24} 炔基、任选取代的 C_{3-6} 环烷基和任选取代的 C_{3-6} 环烯基;且 R^{9A} 可独立地选自任选取代的 C_{1-24} 烷基、任选取代的 C_{2-24} 烯基、任选取代的 C_{2-24} 炔基、任选取代的 C_{3-6} 环烷基和任选取代的 C_{3-6} 环烯基。

[0120] 在一些实施方案中, R^{8A} 可为氢,且 R^{9A} 可为任选取代的 C_{1-6} 烷基。适合的 C_{1-6} 烷基的实例包括甲基、乙基、正丙基、异丙基、正丁基、异丁基、叔丁基、戊基(支链和直链)和己基(支链和直链)。在其他实施方案中, R^{8A} 可为氢,且 R^{9A} 可为 $NR^{30A}R^{31A}$,其中 R^{30} 和 R^{31} 可独立地选自氢、任选取代的 C_{1-24} 烷基、任选取代的 C_{2-24} 烯基、任选取代的 C_{2-24} 炔基、任选取代的 C_{3-6} 环烷基和任选取代的 C_{3-6} 环烯基。

[0121] 在一些实施方案中, R^{8A} 可为不存在或为氢;且 R^{9A} 可为任选取代的 N-连接氨基酸

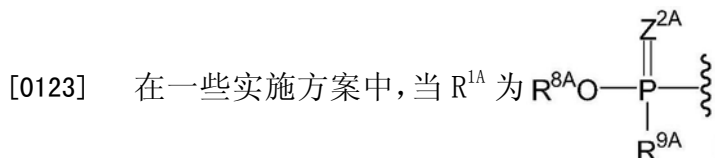
或任选取代的 N- 连接氨基酸酯衍生物。在其他实施方案中, R^{8A} 可为任选取代的芳基; 且 R^{9A} 可为任选取代的 N- 连接氨基酸或任选取代的 N- 连接氨基酸酯衍生物。在其他实施方案中, R^{8A} 可为任选取代的杂芳基; 且 R^{9A} 可为任选取代的 N- 连接氨基酸或任选取代的 N- 连接氨基酸酯衍生物。在一些实施方案中, R^{9A} 可选自丙氨酸、天冬酰胺、天冬氨酸、半胱氨酸、谷氨酸、谷氨酰胺、甘氨酸、脯氨酸、丝氨酸、酪氨酸、精氨酸、组氨酸、异亮氨酸、亮氨酸、赖氨酸、蛋氨酸、苯基丙氨酸、苏氨酸、色氨酸、缬氨酸及其酯衍生物。任选取代的 N- 连接氨基酸酯衍生物的实例包括以下基团的任选取代的变型: 丙氨酸异丙基酯、丙氨酸环己基酯、丙氨酸新戊基酯、缬氨酸异丙基酯和亮氨酸异丙基酯。在一些实施方案中, R^{9A} 能具有结构



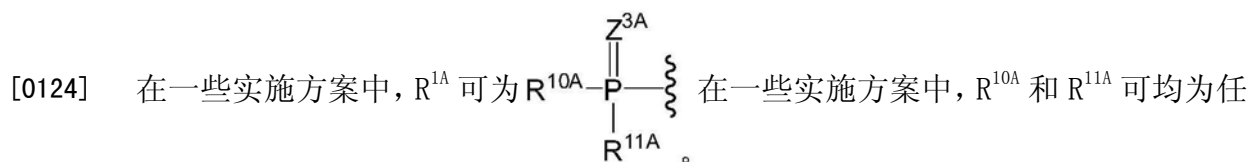
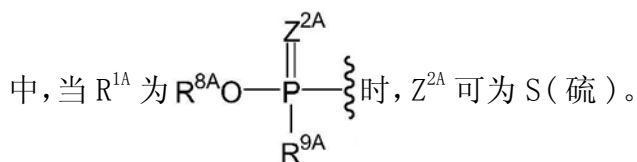
其中 R^{33A} 可选自氢、任选取代的 C_{1-6} - 烷基、任选取代的 C_{3-6} 环烷基、任选

取代的芳基、任选取代的芳基 (C_{1-6} 烷基) 和任选取代的卤代烷基; R^{34A} 可选自氢、任选取代的 C_{1-6} 烷基、任选取代的 C_{1-6} 卤代烷基、任选取代的 C_{3-6} 环烷基、任选取代的 C_6 芳基、任选取代的 C_{10} 芳基和任选取代的芳基 (C_{1-6} 烷基); 且 R^{35A} 可为氢或任选取代的 C_{1-4} - 烷基; 或 R^{34A} 和 R^{35A} 可在一起以形成任选取代的 C_{3-6} 环烷基。

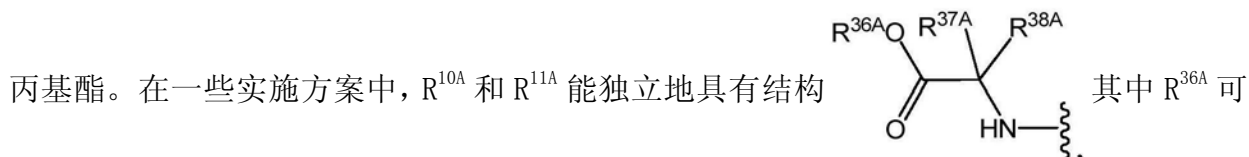
[0122] 当 R^{34A} 被取代时, R^{34A} 能被一个或多个取代基取代, 所述取代基选自 N- 酰胺基、巯基、烷硫基、任选取代的芳基、羟基、任选取代的杂芳基、O- 羧基和氨基。在一些实施方案中, R^{34A} 可为未取代的 C_{1-6} - 烷基、例如本文描述的那些。在一些实施方案中, R^{34A} 可为氢。在其他实施方案中, R^{34A} 可为甲基。在一些实施方案中, R^{33A} 可为任选取代的 C_{1-6} 烷基。任选取代的 C_{1-6} - 烷基的实例包括以下基团的任选取代的变型: 甲基、乙基、正丙基、异丙基、正丁基、异丁基、叔丁基、戊基 (支链和直链) 和己基 (支链和直链)。在一些实施方案中, R^{33A} 可为甲基或异丙基。在一些实施方案中, R^{33A} 可为乙基或新戊基。在其他实施方案中, R^{33A} 可为任选取代的 C_{3-6} 环烷基。任选取代的 C_{3-6} 环烷基的实例包括以下基团的任选取代的变型: 环丙基、环丁基、环戊基和环己基。在一个实施方案中, R^{33A} 可为任选取代的环己基。在其他实施方案中, R^{33A} 可为任选取代的芳基, 例如苯基和萘基。在其他实施方案中, R^{33A} 可为任选取代的芳基 (C_{1-6} 烷基)。在一些实施方案中, R^{33A} 可为任选取代的苄基。在一些实施方案中, R^{33A} 可为任选取代的 C_{1-6} 卤代烷基, 例如, CF_3 。在一些实施方案中, R^{35A} 可为氢。在其他实施方案中, R^{35A} 可为任选取代的 C_{1-4} - 烷基, 例如甲基、乙基、正丙基、异丙基、正丁基、异丁基和叔丁基。在一个实施方案中, R^{35A} 可为甲基。在一些实施方案中, R^{34A} 和 R^{35A} 可在一起以形成任选取代的 C_{3-6} 环烷基。任选取代的 C_{3-6} 环烷基的实例包括以下基团的任选取代的变型: 环丙基、环丁基、环戊基和环己基。根据对于 R^{34A} 和 R^{35A} 所选择的基团, R^{34A} 和 R^{35A} 连接的碳可为手性中心。在一些实施方案中, R^{34A} 和 R^{35A} 连接的碳可为 (R)- 手性中心。在其他实施方案中, R^{34A} 和 R^{35A} 连接的碳可为 (S)- 手性中心。



[0123] 在一些实施方案中, 当 R^{1A} 为 $R^{8A}O-P$ 时, Z^{2A} 可为 O (氧)。在其他实施方案

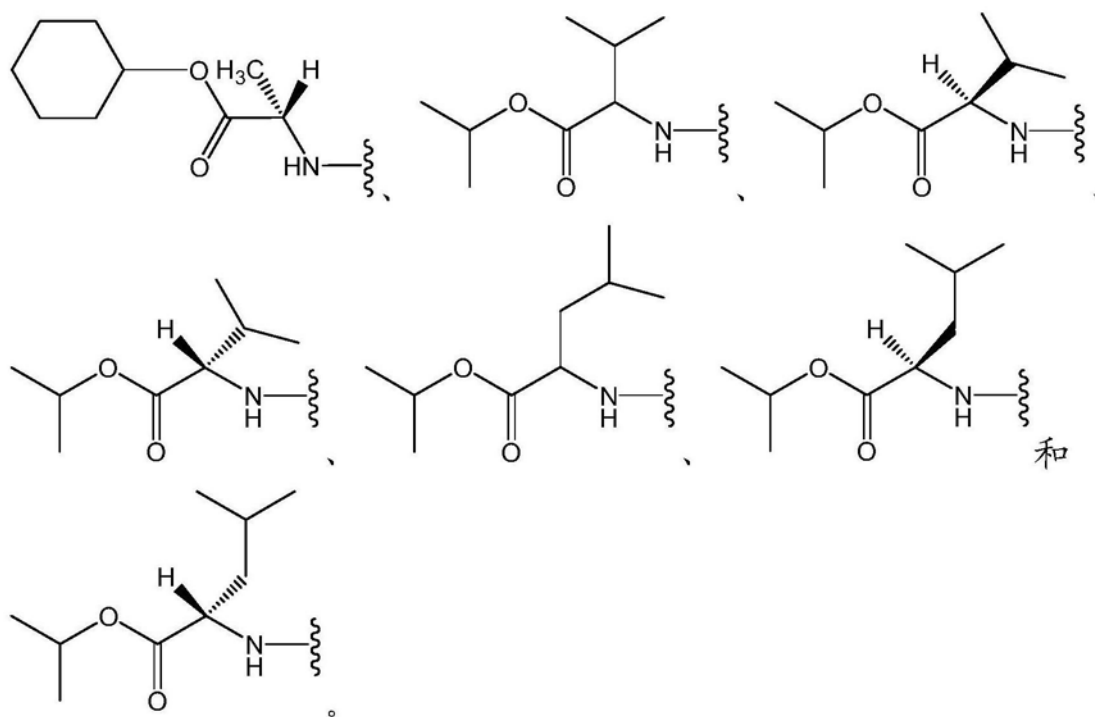


选取代的 N-连接氨基酸或任选取代的 N-连接氨基酸酯衍生物。在一些实施方案中, R^{10A} 和 R^{11A} 可独立地选自丙氨酸、天冬酰胺、天冬氨酸、半胱氨酸、谷氨酸、谷氨酰胺、甘氨酸、脯氨酸、丝氨酸、酪氨酸、精氨酸、组氨酸、异亮氨酸、亮氨酸、赖氨酸、蛋氨酸、苯基丙氨酸、苏氨酸、色氨酸、缬氨酸及其酯衍生物。在一些实施方案中, R^{10A} 和 R^{11A} 可为以下基团的任选取代的变型: 丙氨酸异丙基酯、丙氨酸环己基酯、丙氨酸新戊基酯、缬氨酸异丙基酯和亮氨酸异



选自氢、任选取代的 C_{1-6} -烷基、任选取代的 C_{3-6} 环烷基、任选取代的芳基、任选取代的芳基 (C_{1-6} 烷基) 和任选取代的卤代烷基; R^{37A} 可选自氢、任选取代的 C_{1-6} 烷基、任选取代的 C_{1-6} 卤代烷基、任选取代的 C_{3-6} 环烷基、任选取代的 C_6 芳基、任选取代的 C_{10} 芳基和任选取代的芳基 (C_{1-6} 烷基); 且 R^{38A} 可为氢或任选取代的 C_{1-4} -烷基; 或 R^{37A} 和 R^{38A} 可在一起以形成任选取代的 C_{3-6} 环烷基。

[0125] 当 R^{37A} 被取代时, R^{37A} 可被一个或多个取代基取代, 所述取代基选自 N-酰胺基、巯基、烷硫基、任选取代的芳基、羟基、任选取代的杂芳基、O-羧基和氨基。在一些实施方案中, R^{37A} 可为未取代的 C_{1-6} -烷基、例如本文描述的那些。在一些实施方案中, R^{37A} 可为氢。在其他实施方案中, R^{37A} 可为甲基。在一些实施方案中, R^{36A} 可为任选取代的 C_{1-6} 烷基。任选取代的 C_{1-6} -烷基的实例包括以下基团的任选取代的变型: 甲基、乙基、正丙基、异丙基、正丁基、异丁基、叔丁基、戊基 (支链和直链) 和己基 (支链和直链)。在一些实施方案中, R^{36A} 可为甲基或异丙基。在一些实施方案中, R^{36A} 可为乙基或新戊基。在其他实施方案中, R^{36A} 可为任选取代的 C_{3-6} 环烷基。任选取代的 C_{3-6} 环烷基的实例包括以下基团的任选取代的变型: 环丙基、环丁基、环戊基和环己基。在一个实施方案中, R^{36A} 可为任选取代的环己基。在其他实施方案中, R^{36A} 可为任选取代的芳基, 例如苯基和萘基。在其他实施方案中, R^{36A} 可为任选取代的芳基 (C_{1-6} 烷基)。在一些实施方案中, R^{36A} 可为任选取代的苄基。在一些实施方案中, R^{36A} 可为任选取代的 C_{1-6} 卤代烷基, 例如, CF_3 。在一些实施方案中, R^{38A} 可为氢。在其他实施方案中, R^{38A} 可为任选取代的 C_{1-4} -烷基, 例如甲基、乙基、正丙基、异丙基、正丁基、异丁基和叔丁基。在一个实施方案中, R^{38A} 可为甲基。在一些实施方案中, R^{37A} 和 R^{38A} 可在一起以形成任选取代的 C_{3-6} 环烷基。任选取代的 C_{3-6} 环烷基的实例包括以下基团的任选取代的变型: 环丙基、环丁基、环戊基和环己基。根据对于 R^{37A} 和 R^{38A} 选择的基团, R^{37A} 和 R^{38A} 连接的碳可为手性中心。在一些实施方案中, R^{37A} 和 R^{38A} 连接的碳可为 (R)-手性中心。在其他实施方案中, R^{37A} 和 R^{38A} 连接的碳可为 (S)-手性中心。



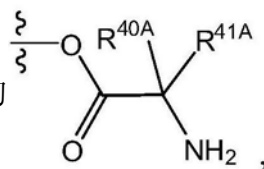
[0129] 在一些实施方案中, R^{10A} 和 R^{11A} 可相同。在一些实施方案中, R^{10A} 和 R^{11A} 可不同。

[0130] 在一些实施方案中, Z^{3A} 可为 O(氧)。在其他实施方案中, Z^{3A} 可为 S(硫)。

[0131] 在一些实施方案中, R^{1A} 可为氢。在一些实施方案中, R^{1A} 可为任选取代的酰基。在其他实施方案中, R^{1A} 可为 $-C(=O)R^{39A}$, 其中 R^{39A} 可选自任选取代的 C_{1-12} 烷基、任选取代的 C_{2-12} 烯基、任选取代的 C_{2-12} 炔基、任选取代的 C_{3-8} 环烷基、任选取代的 C_{5-8} 环烯基、任选取代的 C_{6-10} 芳基、任选取代的杂芳基、任选取代的杂环基、任选取代的芳基 (C_{1-6} 烷基)、任选取代的杂芳基 (C_{1-6} 烷基) 和任选取代的杂环基 (C_{1-6} 烷基)。在一些实施方案中, R^{39A} 可为取代的 C_{1-12} 烷基。在其他实施方案中, R^{39A} 可为未取代的 C_{1-12} 烷基。

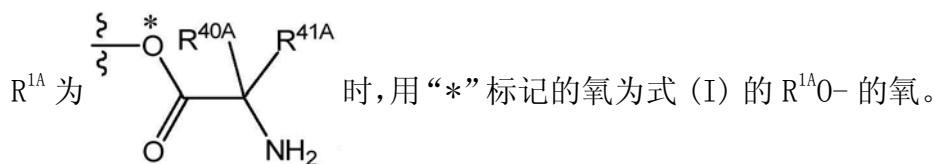
[0132] 在其他实施方案中, R^{1A} 可为任选取代的 O-连接氨基酸。适合的 O-连接氨基酸的实例包括丙氨酸、天冬酰胺、天冬氨酸、半胱氨酸、谷氨酸、谷氨酰胺、甘氨酸、脯氨酸、丝氨酸、酪氨酸、精氨酸、组氨酸、异亮氨酸、亮氨酸、赖氨酸、蛋氨酸、苯基丙氨酸、苏氨酸、色氨酸和缬氨酸。适合的氨基酸的另外实例包括但不限于鸟氨酸、尾下素、2-氨基异丁酸、脱氢丙氨酸、 γ -氨基丁酸、瓜氨酸、 β -丙氨酸、 α -乙基-甘氨酸、 α -丙基-甘氨酸和正亮氨酸。

在一些实施方案中, O-连接氨基酸能具有结构

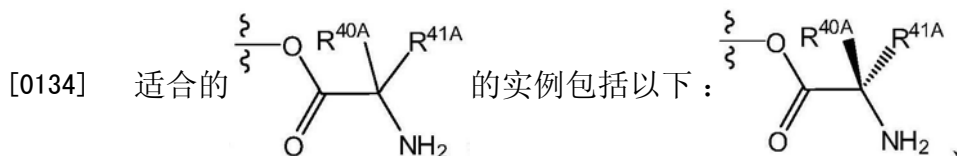


其中 R^{40A} 可选自氢、任选

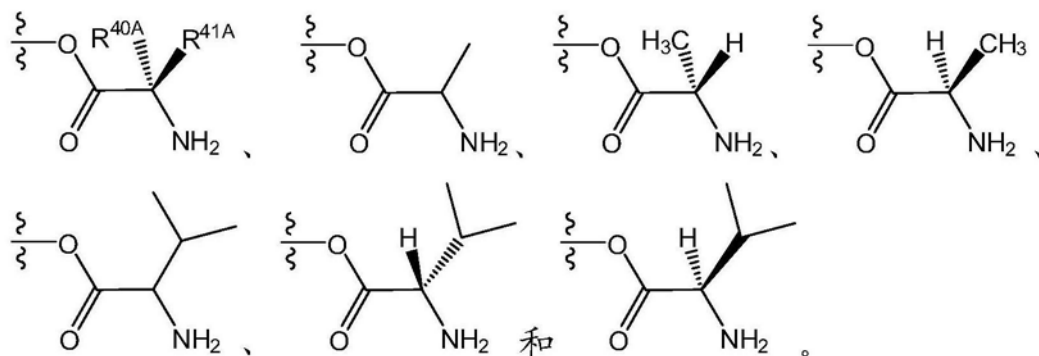
取代的 C_{1-6} 烷基、任选取代的 C_{1-6} 卤代烷基、任选取代的 C_{3-6} 环烷基、任选取代的 C_6 芳基、任选取代的 C_{10} 芳基和任选取代的芳基 (C_{1-6} 烷基); 且 R^{41A} 可为氢或任选取代的 C_{1-4} 烷基; 或 R^{40A} 和 R^{41A} 可在一起以形成任选取代的 C_{3-6} 环烷基。本领域技术人员理解当 R^{1A} 为任选取代的 O-连接氨基酸时, 式 (I) 的 $R^{1A}O-$ 的氧为任选取代的 O-连接氨基酸的一部分。例如, 当



[0133] 当 R^{40A} 被取代时, R^{40A} 可被一个或多个取代基取代,所述取代基选自 N- 酰胺基、巯基、烷硫基、任选取代的芳基、羟基、任选取代的杂芳基、O- 羧基和氨基。在一些实施方案中, R^{40A} 可为未取代的 C_{1-6} - 烷基、例如本文描述的那些。在一些实施方案中, R^{40A} 可为氢。在其他实施方案中, R^{40A} 可为甲基。在一些实施方案中, R^{41A} 可为氢。在其他实施方案中, R^{41A} 可为任选取代的 C_{1-4} - 烷基,例如甲基、乙基、正丙基、异丙基、正丁基、异丁基和叔丁基。在一个实施方案中, R^{41A} 可为甲基。根据对于 R^{40A} 和 R^{41A} 选择的基团, R^{40A} 和 R^{41A} 连接的碳可为手性中心。在一些实施方案中, R^{40A} 和 R^{41A} 连接的碳可为 (R)- 手性中心。在其他实施方案中, R^{40A} 和 R^{41A} 连接的碳可为 (S)- 手性中心。



[0135]

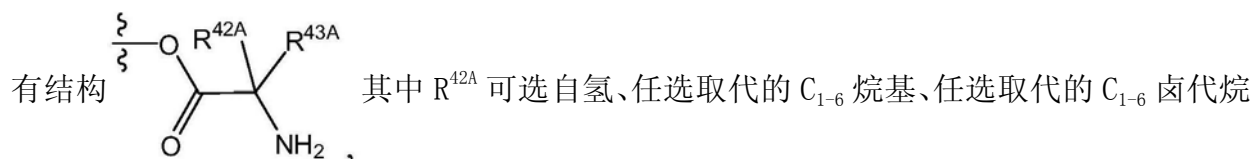


[0136] 在一些实施方案中,虚线 (-----) 可为单键, R^{2A} 可为 CH_2 且 R^{3A} 可为 O (氧)。当虚线 (-----) 为单键时, R^{2A} 为 CH_2 且 R^{3A} 为 O (氧),形成 4- 元环,包含戊糖环的 4'- 碳和 3'- 碳。在其他实施方案中,虚线 (-----) 可为不存在, R^{2A} 可选自任选取代的 C_{1-6} 烷基、任选取代的 C_{2-6} 烯基、任选取代的 C_{2-6} 炔基、任选取代的 -O- C_{1-6} 烷基、任选取代的 -O- C_{3-6} 烯基、任选取代的 -O- C_{3-6} 炔基和氰基,且 R^{3A} 可选自 OH、-OC(=O) R^{3A} 和任选取代的 O- 连接氨基酸。

[0137] 可将各个基团与戊糖环的 4'- 位连接。在一些实施方案中, R^{2A} 可为任选取代的 C_{1-6} 烷基。适合的 C_{1-6} 烷基的实例包括甲基、乙基、正丙基、异丙基、正丁基、异丁基、叔丁基、戊基 (支链和直链) 和己基 (支链和直链)。在一些实施方案中, R^{2A} 可为未取代的 C_{1-6} 烷基。在其他实施方案中, R^{2A} 可为取代的 C_{1-6} 烷基。例如, R^{2A} 可为卤素取代的 C_{1-6} 烷基、羟基取代的 C_{1-6} 烷基、炔氧基取代的 C_{1-6} 烷基或炔硫基取代的 C_{1-6} 烷基 (例如, - C_{1-6} 烷基 -S- C_{1-6} 烷基)。在其他实施方案中, R^{2A} 可为 C_{1-6} 卤代烷基。在其他实施方案中, R^{2A} 可为任选取代的 C_{2-6} 烯基。在一些实施方案中, R^{2A} 可为取代的 C_{2-6} 烯基。在其他实施方案中, R^{2A} 可为未取代的 C_{2-6} 烯基。例如, R^{2A} 可为乙烯基、丙烯基或丙二烯基。在其他实施方案中, R^{2A} 可为任选取代的 C_{2-6} 炔基。在一些实施方案中, R^{2A} 可为取代的 C_{2-6} 炔基。在其他实施方案中, R^{2A}

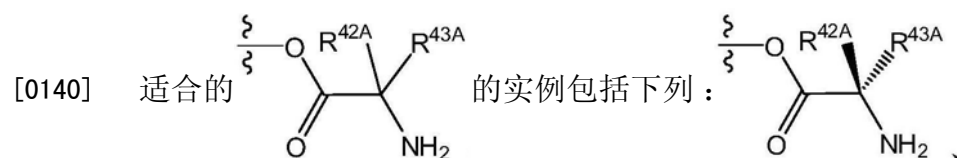
可为未取代的 C_{2-6} 炔基。适合的 C_{2-6} 炔基包括乙炔基和丙炔基。在其他实施方案中, R^{2A} 可为任选取代的 C_{3-6} 环烷基。在一些实施方案中, R^{2A} 可为取代的 C_{3-6} 环烷基。在其他实施方案中, R^{2A} 可为未取代的 C_{3-6} 环烷基。 C_{3-6} 环烷基的非限制性列举包括环丙基、环丁基、环戊基和环己基。在一些实施方案中, R^{2A} 可为任选取代的 $-O-C_{1-6}$ 烷基。在一些实施方案中, R^{2A} 可为取代的 $-O-C_{1-6}$ 烷基。在其他实施方案中, R^{2A} 可为未取代的 $-O-C_{1-6}$ 烷基。适合的 $O-C_{1-6}$ 烷基的实例包括甲氧基、乙氧基、正丙氧基、异丙氧基、正丁氧基、异丁氧基、叔丁氧基、戊氧基(支链和直链)、和己氧基(支链和直链)。在其他实施方案中, R^{2A} 可为任选取代的 $-O-C_{3-6}$ 烯基。在一些实施方案中, R^{2A} 可为取代的 $-O-C_{3-6}$ 烯基。在其他实施方案中, R^{2A} 可为未取代的 $-O-C_{3-6}$ 烯基。在其他实施方案中, R^{2A} 可为任选取代的 $-O-C_{3-6}$ 炔基。在一些实施方案中, R^{2A} 可为取代的 $-O-C_{3-6}$ 炔基。在其他实施方案中, R^{2A} 可为未取代的 $-O-C_{3-6}$ 炔基。在其他实施方案中, R^{2A} 可为氰基。

[0138] 与戊糖环的 3'-位连接的基团可变化。在一些实施方案中, 包括段落 [0119] 的那些, R^{3A} 可为 OH。在其他实施方案中, 包括段落 [0119] 的那些, R^{3A} 可为任选取代的 O-连接氨基酸。适合的 O-连接氨基酸的实例包括丙氨酸、天冬酰胺、天冬氨酸、半胱氨酸、谷氨酸、谷氨酰胺、甘氨酸、脯氨酸、丝氨酸、酪氨酸、精氨酸、组氨酸、异亮氨酸、亮氨酸、赖氨酸、蛋氨酸、苯基丙氨酸、苏氨酸、色氨酸和缬氨酸。适合的氨基酸的其他实例包括但不限于鸟氨酸、尾下素(hypusine)、2-氨基异丁酸、脱氢丙氨酸、 γ -氨基丁酸、瓜氨酸、 β -丙氨酸、 α -乙基-甘氨酸、 α -丙基-甘氨酸和正亮氨酸。在一些实施方案中, O-连接氨基酸能具有结构

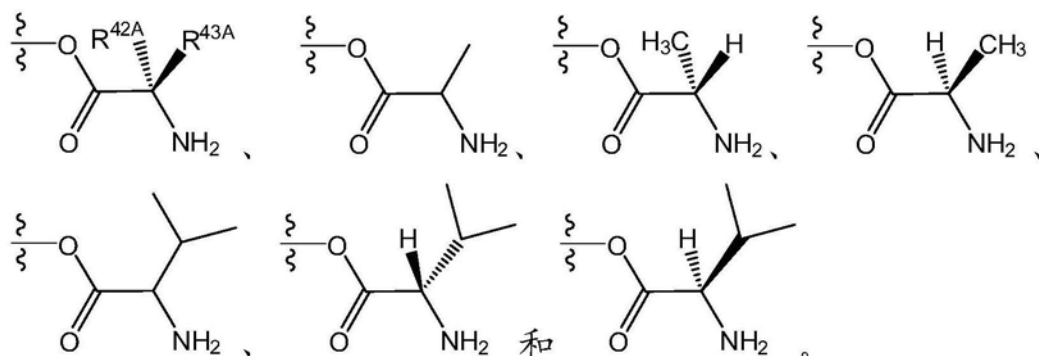


基、任选取代的 C_{3-6} 环烷基、任选取代的 C_6 芳基、任选取代的 C_{10} 芳基和任选取代的芳基 (C_{1-6} 烷基); 且 R^{43A} 可为氢或任选取代的 C_{1-4} -烷基; 或 R^{42A} 和 R^{43A} 可在一起以形成任选取代的 C_{3-6} 环烷基。

[0139] 当 R^{42A} 被取代时, R^{42A} 可被一个或多个取代基取代, 所述取代基选自 N-酰胺基、巯基、烷硫基、任选取代的芳基、羟基、任选取代的杂芳基、O-羧基和氨基。在一些实施方案中, R^{42A} 可为未取代的 C_{1-6} -烷基、例如本文描述的那些。在一些实施方案中, R^{42A} 可为氢。在其他实施方案中, R^{42A} 可为甲基。在一些实施方案中, R^{43A} 可为氢。在其他实施方案中, R^{43A} 可为任选取代的 C_{1-4} -烷基、例如甲基、乙基、正丙基、异丙基、正丁基、异丁基和叔丁基。在一个实施方案中, R^{43A} 可为甲基。根据对于 R^{42A} 和 R^{43A} 选择的基团, R^{42A} 和 R^{43A} 连接的碳可为手性中心。在一些实施方案中, R^{42A} 和 R^{43A} 连接的碳可为 (R)-手性中心。在其他实施方案中, R^{42A} 和 R^{43A} 连接的碳可为 (S)-手性中心。



[0141]



[0142] 在其他实施方案中,包括段落 [0119] 的那些, R^{3A} 可为 $-OC(=O)R^{7A}$, 其中 R^{7A} 可为任选取代的 C_{1-24} 烷基。在一些实施方案中, R^{7A} 可为取代的 C_{1-8} 烷基。在其他实施方案中, R^{7A} 可为未取代的 C_{1-8} 烷基。在其他实施方案中,包括段落 [0119] 的那些, R^{3A} 可为任选取代的 $-O-$ 酰基。在其他实施方案中,包括段落 [0119] 的那些, R^{3A} 可为 $-OC(=O)R^{44A}$, 其中 R^{44A} 可选自任选取代的 C_{1-12} 烷基、任选取代的 C_{2-12} 烯基、任选取代的 C_{2-12} 炔基、任选取代的 C_{3-8} 环烷基、任选取代的 C_{5-8} 环烯基、任选取代的 C_{6-10} 芳基、任选取代的杂芳基、任选取代的杂环基、任选取代的芳基 (C_{1-6} 烷基)、任选取代的杂芳基 (C_{1-6} 烷基) 和任选取代的杂环基 (C_{1-6} 烷基)。在一些实施方案中, R^{44A} 可为取代的 C_{1-12} 烷基。在其他实施方案中, R^{44A} 可为未取代的 C_{1-12} 烷基。

[0143] 各个取代基可存在于戊糖环的 2'-位。在一些实施方案中, R^{5A} 可为氢。在其他实施方案中, R^{5A} 可为卤素,例如,氟。在一些实施方案中, R^{4A} 可为卤素,例如氟。在一些实施方案中, R^{5A} 可为氢且 R^{4A} 可为卤素。在其他实施方案中, R^{4A} 和 R^{5A} 都可为卤素。

[0144] 在一些实施方案中,---- 可为单键、 R^{4A} 可为氟、 R^{5A} 可为氢且 R^{2A} 可为 C_{1-6} 卤代烷基。在一些实施方案中,---- 可为单键、 R^{4A} 可为氟、 R^{5A} 可为氢、 R^{2A} 可为 C_{1-6} 卤代烷基且 B^{1A} 可为胞嘧啶。

[0145] 在一些实施方案中, R^{2A} 不为甲氧基。在一些实施方案中, R^{2A} 不为甲氧基,当 B^{1A} 为取代的或未取代的尿嘧啶时。在一些实施方案中, B^{1A} 为取代的或未取代的胞嘧啶。在其他实施方案中, B^{1A} 为取代的或未取代的胸腺嘧啶。在其他实施方案中, B^{1A} 不为未取代的尿嘧啶。

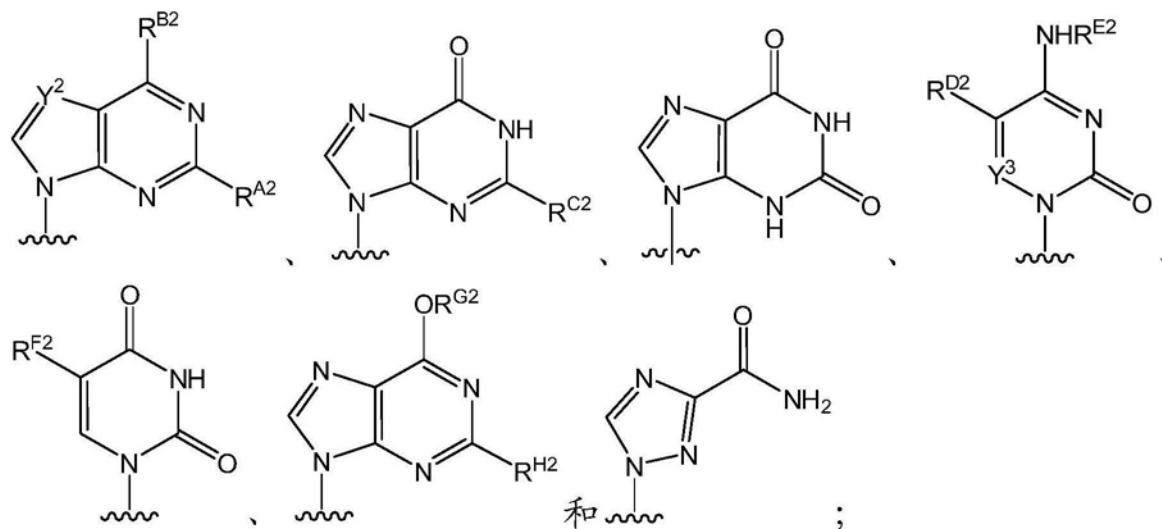
在一些实施方案中, R^{2A} 不为甲氧基,当 Z^{1A} 为 $R^{8A}O-P(=Z^{2A})(R^{9A})$ 时,其中 R^{8A} 为未取代的 C_{1-6} 烷基或对位取代的苯基;且 R^{9A} 为任选取代的 N-连接氨基酸或任选取代的 N-连接氨基酸酯衍生物。在一些实施方案中, R^{2A} 不为甲氧基,当 Z^{1A} 为 $R^{8A}O-P(=Z^{2A})(R^{9A})$ 时。在一些实施方案中,

中, R^{2A} 不为炔氧基(例如,当 Z^{1A} 为 $R^{8A}O-P(=Z^{2A})(R^{9A})$ 时)。在一些实施方案中, B^{1A} 不为胞嘧啶,当 R^{2A} 为未取代的烯基或未取代的炔基时。在一些实施方案中, B^{1A} 不为胸腺嘧啶,当 R^{2A} 为

任选取代的烷基时。在一些实施方案中, R^{2A} 不为未取代的烃氧基(例如甲氧基)、任选取代的烯基(例如丙二烯基)、未取代的炔基(例如乙炔基)或被非卤素取代基取代的 C_1 烷基。在一些实施方案中, R^{2A} 不为未取代的烃氧基(例如甲氧基)、任选取代的烯基(例如丙二烯基)、任选取代的取代的炔基(例如乙炔基)或被非卤素取代基取代的 C_{1-4} 烷基。在一些实施方案 R^{1A} 不为 H。在一些实施方案 R^{1A} 不为 H, 当 B^{1A} 为任选取代的胞嘧啶或任选取代的胸腺嘧啶时。

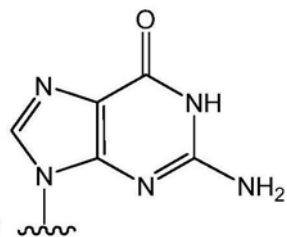
[0146] 各个任选取代的杂环碱可与戊糖环连接。在一些实施方案中, 可使用适合的保护基团保护一个或多个胺和/或氨基。例如, 可通过将胺和/或氨基转化为酰胺或氨基甲酸酯保护氨基。在一些实施方案中, 任选取代的杂环碱或具有一个或多个被护氨基的任选取代的杂环碱具有下列结构之一:

[0147]

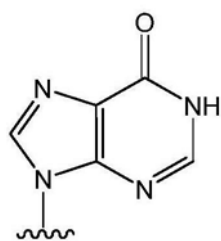


[0148] 其中: R^{A2} 可选自氢、卤素和 NHR^{J2} , 其中 R^{J2} 可选自氢、 $-C(=O)R^{K2}$ 和 $-C(=O)OR^{L2}$; R^{B2} 可为卤素或 NHR^{W2} , 其中 R^{W2} 可选自氢、任选取代的 C_{1-6} 烷基、任选取代的 C_{2-6} 烯基、任选取代的 C_{3-8} 环烷基、 $-C(=O)R^{M2}$ 和 $-C(=O)OR^{N2}$; R^{C2} 可为氢或 NHR^{O2} , 其中 R^{O2} 可选自氢、 $-C(=O)R^{P2}$ 和 $-C(=O)OR^{Q2}$; R^{D2} 可选自氢、卤素、任选取代的 C_{1-6} 烷基、任选取代的 C_{2-6} 烯基和任选取代的 C_{2-6} 炔基; R^{E2} 可选自氢、羟基、任选取代的 C_{1-6} 烷基、任选取代的 C_{3-8} 环烷基、 $-C(=O)R^{R2}$ 和 $-C(=O)OR^{S2}$; R^{F2} 可选自氢、卤素、任选取代的 C_{1-6} 烷基、任选取代的 C_{2-6} 烯基和任选取代的 C_{2-6} 炔基; Y^2 和 Y^3 可独立地为 N(氮)或 CR^{I2} , 其中 R^{I2} 可选自氢、卤素、任选取代的 C_{1-6} 烷基、任选取代的 C_{2-6} 烯基和任选取代的 C_{2-6} 炔基; R^{G2} 可为任选取代的 C_{1-6} 烷基; R^{H2} 可为氢或 NHR^{T2} , 其中 R^{T2} 可独立地选自氢、 $-C(=O)R^{U2}$ 和 $-C(=O)OR^{V2}$; 且 R^{K2} 、 R^{L2} 、 R^{M2} 、 R^{N2} 、 R^{P2} 、 R^{Q2} 、 R^{R2} 、 R^{S2} 、 R^{U2} 和 R^{V2} 可独立地选自 C_{1-6} 烷基、 C_{2-6} 烯基、 C_{2-6} 炔基、 C_{3-6} 环烷基、 C_{3-6} 环烯基、 C_{6-10} 芳基、杂芳基、杂脂环基、芳基 (C_{1-6} 烷基)、杂芳基 (C_{1-6} 烷基) 和杂脂环基 (C_{1-6} 烷基)。在一些实施方案中, 可通过使用选自“取代的”所定义提供的取代基的列举的取代基来取代一个或多个氢修饰上文显示的结构。

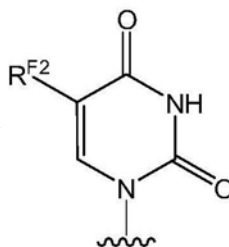
[0149] 在一些实施方案中, B^{1A} 可为



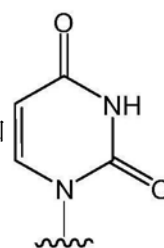
在其他实施方案中, B^{1A} 可为



在其他实施方案中, B^{1A} 可为

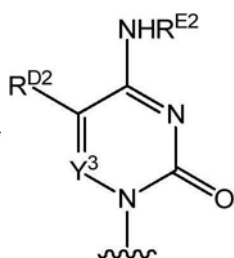


例如

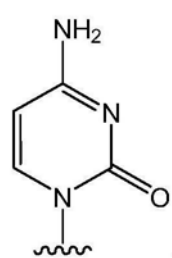


在其他

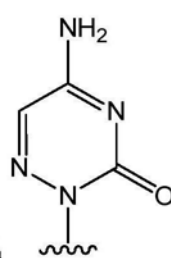
实施方案中, B^{1A} 可为



例如,

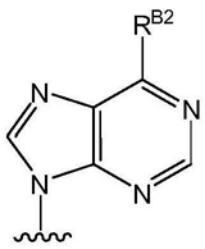


或



在一些实施方案

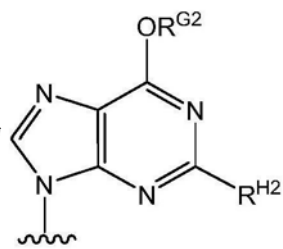
中, R^{D2} 可为氢。在其他实施方案中, B^{1A} 可为



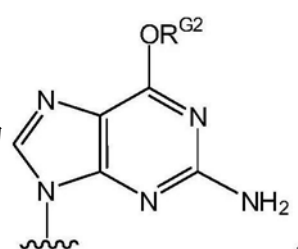
在一些实施方案中, R^{B2} 可为 NH_2 。

在其他实施方案中, R^{B2} 可为 NHR^{W2} , 其中 R^{W2} 可为 $-C(=O)R^{M2}$ 或 $-C(=O)OR^{N2}$ 。在其他实施

方案中, B^{1A} 可为

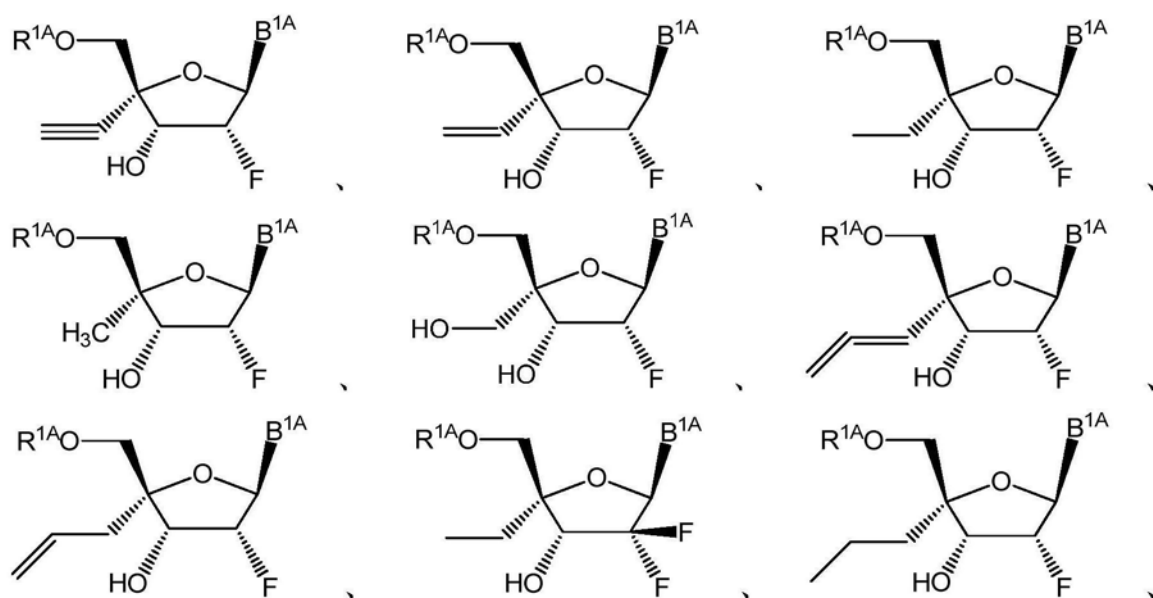


在一些实施方案中, B^{1A} 可为

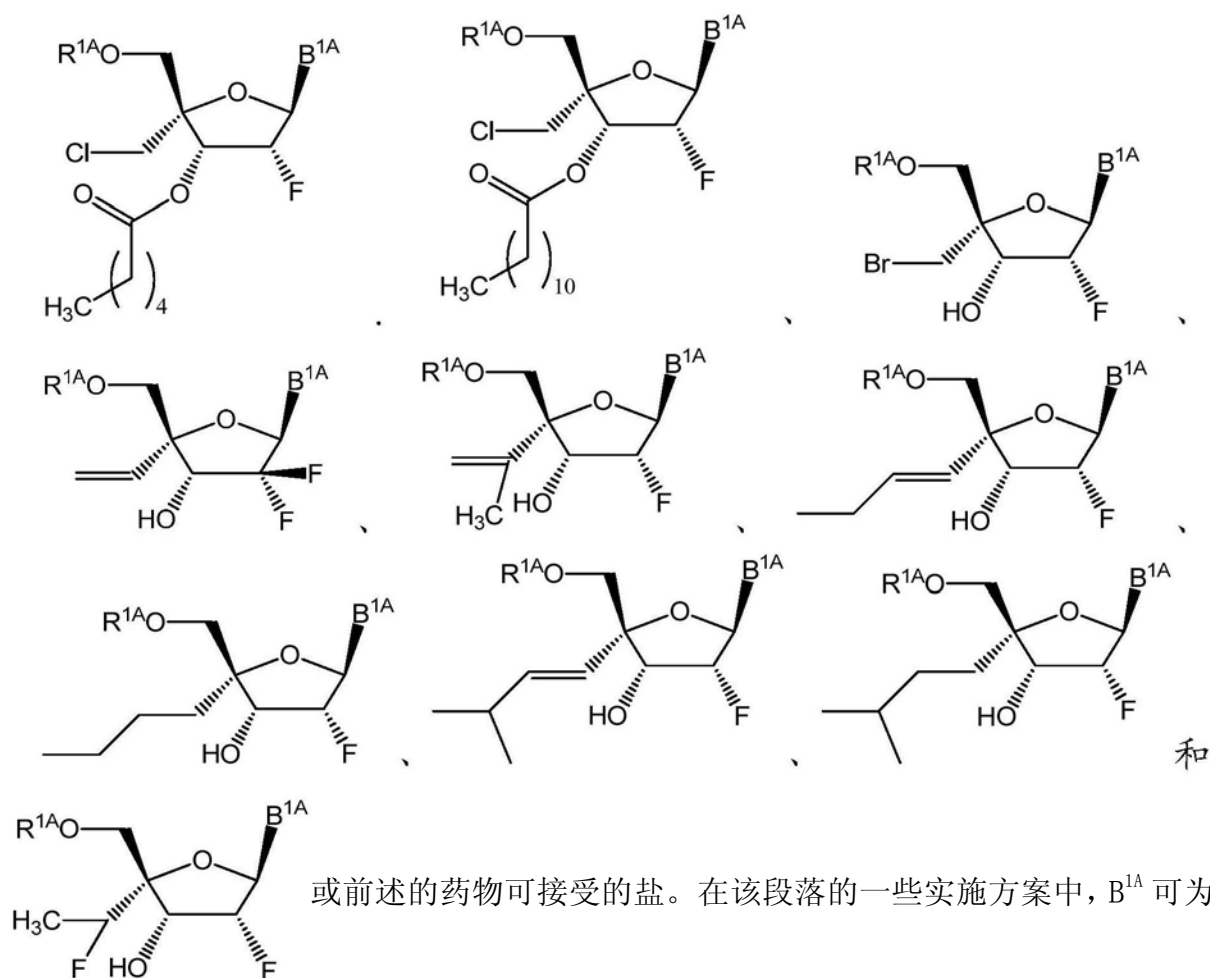


[0150] 在一些实施方案中, 式 (I) 的化合物可具有选自下列之一的结构:

[0151]

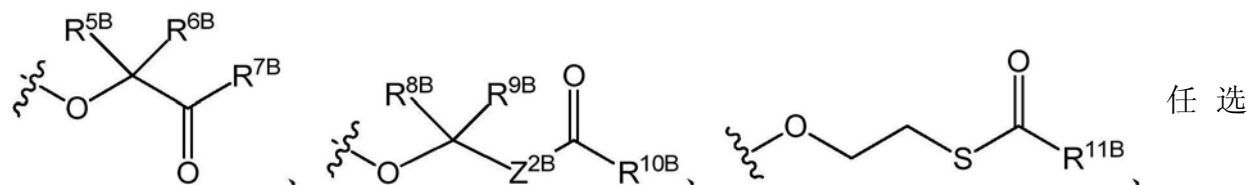


[0152]



选取代的嘌呤碱基。在该段落的其他实施方案中, B^{1A} 可为任选取代的嘧啶碱基。在该段落的一些实施方案中, B^{1A} 可为鸟嘌呤。在该段落的其他实施方案中, B^{1A} 可为胸腺嘧啶。在该段落的其他实施方案中, B^{1A} 可为胞嘧啶。在该段落的其他实施方案中, B^{1A} 可为尿嘧啶。在该段落的一些实施方案中, B^{1A} 可为腺嘌呤。在该段落的一些实施方案中, R^{1A} 可为氢。在该段落的其他实施方案中, R^{1A} 可为任选取代的酰基。在该段落的其他实施方案中, R^{1A} 可为单磷酸酯、二磷酸酯或三磷酸酯。在该段落的其他实施方案中, R^{1A} 可为氨基磷酸酯。在该段落的一些实施方案中, R^{1A} 可为酰氧基烷基酯磷酸酯前药。

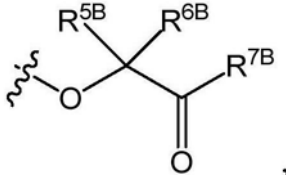
[0154] 在一些实施方案中, 化合物可为式 (II) 的化合物或其药物可接受的盐, 其中: B^{1B} 可为任选取代的杂环碱或具有被护氨基的任选取代的杂环碱; R^{1B} 可选自 O^- 、 OH 、



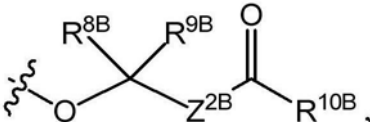
取代的 N-连接氨基酸和任选取代的 N-连接氨基酸酯衍生物; R^{2B} 可选自任选取代的 C_{1-6} 烷基、任选取代的 C_{2-6} 烯基、任选取代的 C_{2-6} 炔基、任选取代的 $-O-C_{1-6}$ 烷基、任选取代的 $-O-C_{3-6}$ 烯基、任选取代的 $-O-C_{3-6}$ 炔基和氰基; R^{3B} 可为卤素; R^{4B} 可为氢或卤素; R^{5B} 、 R^{6B} 、 R^{8B} 和 R^{9B} 可独立地选自氢、任选取代的 C_{1-24} 烷基和任选取代的芳基; R^{7B} 和 R^{10B} 可独立地选自氢、任选取代的 C_{1-24} 烷基、任选取代的芳基、任选取代的 $-O-C_{1-24}$ 烷基和任选取代

的 -O- 芳基 ; R^{11B} 可选自氢、任选取代的 C_{1-24} 烷基和任选取代的芳基 ; Z^{1B} 和 Z^{2B} 可独立地为 O 或 S。

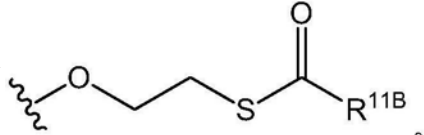
[0155] 在一些实施方案中, R^{1B} 可为 O^- 。在其他实施方案中, R^{1B} 可为 OH。

[0156] 在一些实施方案中, R^{1B} 可为  , 其中 R^{5B} 和 R^{6B} 可独立地选自氢、

任选取代的 C_{1-24} 烷基和任选取代的芳基 ;且 R^{7B} 可选自氢、任选取代的 C_{1-24} 烷基、任选取代的芳基、任选取代的 -O- C_{1-24} 烷基和任选取代的 -O- 芳基。在一些实施方案中, R^{5B} 和 R^{6B} 可为氢。在其他实施方案中,至少一个 R^{5B} 和 R^{6B} 可为任选取代的 C_{1-24} 烷基或任选取代的芳基。在一些实施方案中, R^{7B} 可为任选取代的 C_{1-24} 烷基。在其他实施方案中, R^{7B} 可为任选取代的芳基。在其他实施方案中, R^{7B} 可为任选取代的 -O- C_{1-24} 烷基或任选取代的 -O- 芳基。

[0157] 在一些实施方案中, R^{1B} 可为  , 其中 R^{8B} 和 R^{9B} 可独立地选

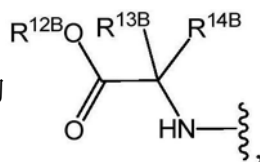
自氢、任选取代的 C_{1-24} 烷基和任选取代的芳基 ; R^{10B} 可独立地选自氢、任选取代的 C_{1-24} 烷基、任选取代的芳基、任选取代的 -O- C_{1-24} 烷基和任选取代的 -O- 芳基 ;且 Z^{2B} 可独立地为 O(氧) 或 S(硫)。在一些实施方案中, R^{8B} 和 R^{9B} 可为氢。在其他实施方案中,至少一个 R^{8B} 和 R^{9B} 可为任选取代的 C_{1-24} 烷基或任选取代的芳基。在一些实施方案中, R^{10B} 可为任选取代的 C_{1-24} 烷基。在其他实施方案中, R^{10B} 可为任选取代的芳基。在其他实施方案中, R^{10B} 可为任选取代的 -O- C_{1-24} 烷基或任选取代的 -O- 芳基。在一些实施方案中, Z^{2B} 可为 O(氧)。在其他实施方案中, Z^{2B} 可为 S(硫)。在一些实施方案中, R^{1B} 可为异丙基羰基氧基甲氧基。在一些实施方案中, R^{1B} 可为新戊酰基氧基甲氧基。

[0158] 在一些实施方案中, R^{1B} 可为  。 在一些实施方案中,

R^{11B} 可为氢。在其他实施方案中, R^{11B} 可为任选取代的 C_{1-24} 烷基。在其他实施方案中, R^{11B} 可为任选取代的芳基。在一些实施方案中, R^{11B} 可为 C_{1-6} 烷基,例如,甲基、乙基、正丙基、异丙基、正丁基、异丁基、叔丁基、戊基(支链和直链)和己基(支链和直链)。

[0159] 在一些实施方案中, R^{1B} 可为任选取代的 N-连接氨基酸或任选取代的 N-连接氨基酸酯衍生物。例如, R^{1B} 可为以下基团的任选取代的变型:丙氨酸、天冬酰胺、天冬氨酸、半胱氨酸、谷氨酸、谷氨酰胺、甘氨酸、脯氨酸、丝氨酸、酪氨酸、精氨酸、组氨酸、异亮氨酸、亮氨酸、赖氨酸、蛋氨酸、苯基丙氨酸、苏氨酸、色氨酸、缬氨酸及其酯衍生物。在一些实施方案中, R^{1B} 可选自丙氨酸异丙基酯、丙氨酸环己基酯、丙氨酸新戊基酯、缬氨酸异丙基酯和亮氨

酸异丙基酯。在一些实施方案中, R^{1B} 能具有结构

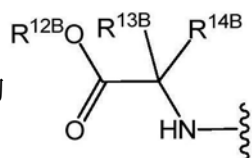


其中 R^{12B} 可选自氢、任

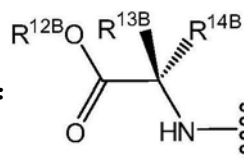
选取代的 C_{1-6} 烷基、任选取代的 C_{3-6} 环烷基、任选取代的芳基、任选取代的芳基 (C_{1-6} 烷基) 和任选取代的卤代烷基; R^{13B} 可选自氢、任选取代的 C_{1-6} 烷基、任选取代的 C_{1-6} 卤代烷基、任选取代的 C_{3-6} 环烷基、任选取代的 C_6 芳基、任选取代的 C_{10} 芳基和任选取代的芳基 (C_{1-6} 烷基); 且 R^{14B} 可为氢或任选取代的 C_{1-4} 烷基; 或 R^{13B} 和 R^{14B} 可在一起以形成任选取代的 C_{3-6} 环烷基。

[0160] 当 R^{13B} 被取代时, R^{13B} 可被一个或多个取代基取代, 所述取代基选自 N- 酰胺基、巯基、烷硫基、任选取代的芳基、羟基、任选取代的杂芳基、O- 羧基和氨基。在一些实施方案中, R^{13B} 可为未取代的 C_{1-6} 烷基、例如本文描述的那些。在一些实施方案中, R^{13B} 可为氢。在其他实施方案中, R^{13B} 可为甲基。在一些实施方案中, R^{12B} 可为任选取代的 C_{1-6} 烷基。任选取代的 C_{1-6} 烷基的实例包括以下基团的任选取代的变型: 甲基、乙基、正丙基、异丙基、正丁基、异丁基、叔丁基、戊基 (支链和直链) 和己基 (支链和直链)。在一些实施方案中, R^{12B} 可为甲基或异丙基。在一些实施方案中, R^{12B} 可为乙基或新戊基。在其他实施方案中, R^{12B} 可为任选取代的 C_{3-6} 环烷基。任选取代的 C_{3-6} 环烷基的实例包括以下基团的任选取代的变型: 环丙基、环丁基、环戊基和环己基。在一个实施方案中, R^{12B} 可为任选取代的环己基。在其他实施方案中, R^{12B} 可为任选取代的芳基, 例如苯基和萘基。在其他实施方案中, R^{12B} 可为任选取代的芳基 (C_{1-6} 烷基)。在一些实施方案中, R^{12B} 可为任选取代的苄基。在一些实施方案中, R^{12B} 可为任选取代的 C_{1-6} 卤代烷基, 例如, CF_3 。在一些实施方案中, R^{14B} 可为氢。在其他实施方案中, R^{14B} 可为任选取代的 C_{1-4} 烷基, 例如甲基、乙基、正丙基、异丙基、正丁基、异丁基和叔丁基。在一个实施方案中, R^{14B} 可为甲基。在一些实施方案中, R^{13B} 和 R^{14B} 可在一起以形成任选取代的 C_{3-6} 环烷基。任选取代的 C_{3-6} 环烷基的实例包括以下基团的任选取代的变型: 环丙基、环丁基、环戊基和环己基。根据对于 R^{13B} 和 R^{14B} 选择的基团, R^{13B} 和 R^{14B} 连接的碳可为手性中心。在一些实施方案中, R^{13B} 和 R^{14B} 连接的碳可为 (R)- 手性中心。在其他实施方案中, R^{13B} 和 R^{14B} 连接的碳可为 (S)- 手性中心。

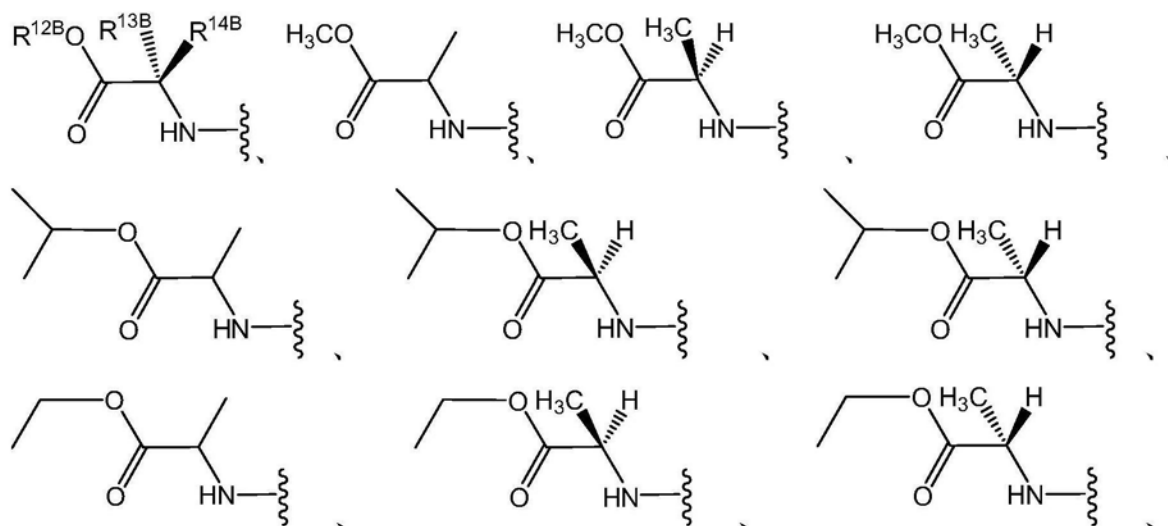
[0161] 适合的



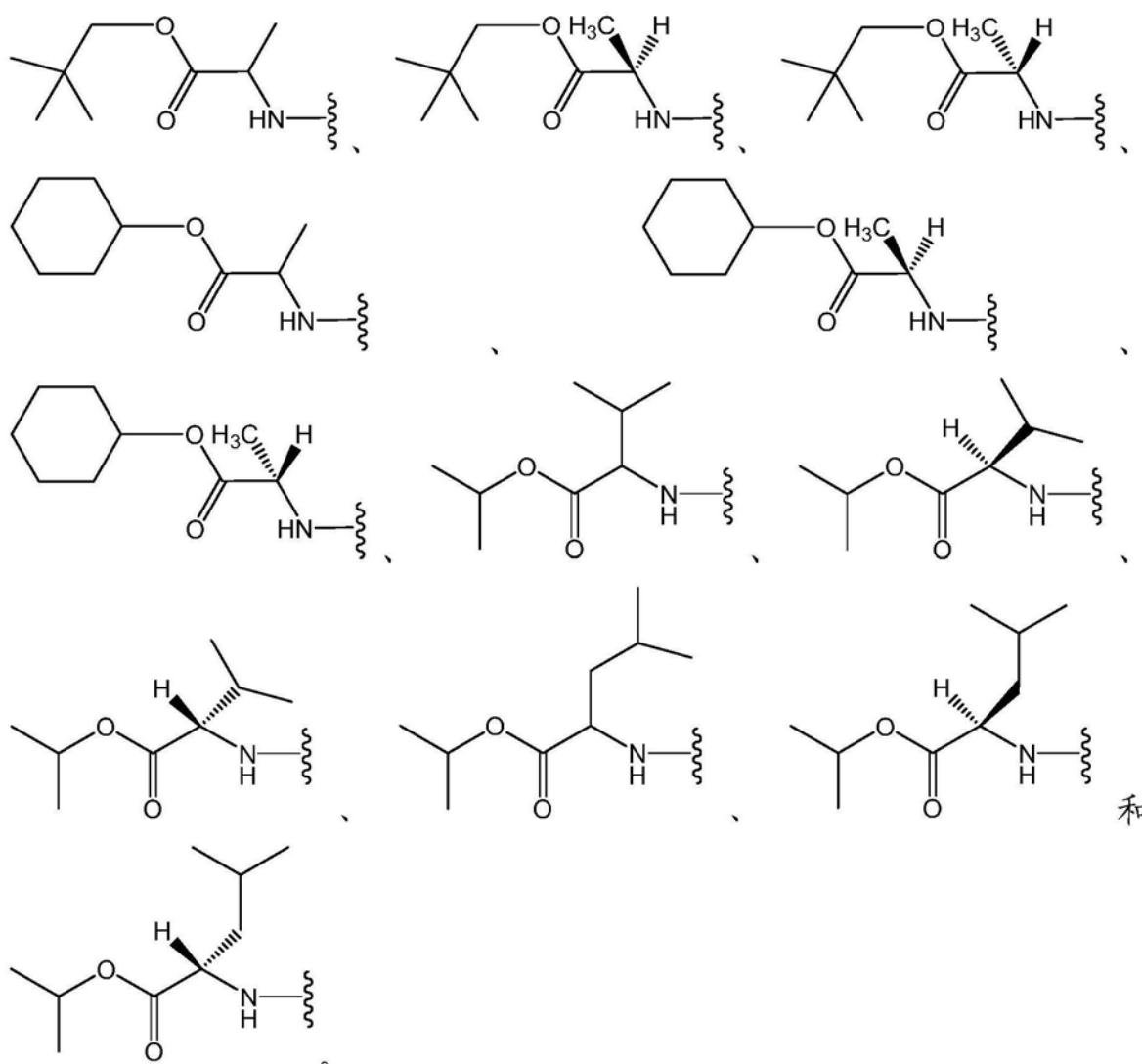
基团的实例包括下列:



[0162]



[0163]



[0164] 许多取代基可存在于戊糖环的 4' - 位。在一些实施方案中, R^{2B} 可为任选取代的 C_{1-6} 烷基。适合的 C_{1-6} 烷基的实例包括甲基、乙基、正丙基、异丙基、正丁基、异丁基、叔丁基、戊基 (支链和直链) 和己基 (支链和直链)。在一些实施方案中, R^{2B} 可为未取代的 C_{1-6} 烷基。在其他实施方案中, R^{2B} 可为取代的 C_{1-6} 烷基。例如, R^{2B} 可为卤素取代的 C_{1-6} 烷基、羟基

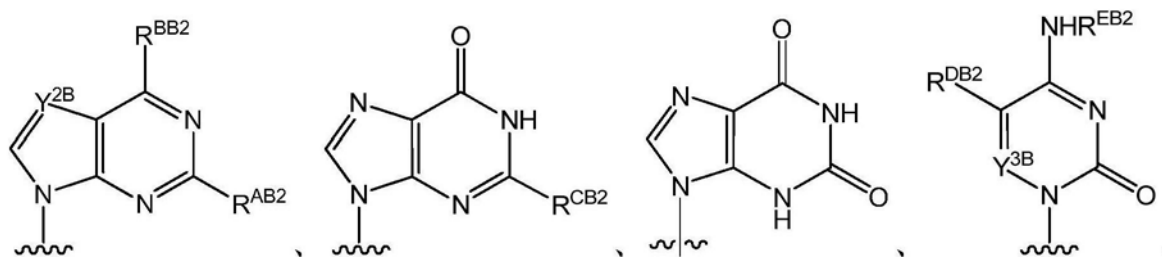
取代的 C_{1-6} 烷基、烃氧基取代的 C_{1-6} 烷基或烃硫基取代的 C_{1-6} 烷基（例如， $-C_{1-6}$ 烷基 $-S-C_{1-6}$ 烷基）。在其他实施方案中， R^{2B} 可为 C_{1-6} 卤代烷基。在其他实施方案中， R^{2B} 可为任选取代的 C_{2-6} 烯基。在一些实施方案中， R^{2B} 可为取代的 C_{2-6} 烯基。在其他实施方案中， R^{2B} 可为未取代的 C_{2-6} 烯基。例如， R^{2B} 可为乙烯基、丙烯基或丙二烯基。在其他实施方案中， R^{2B} 可为任选取代的 C_{2-6} 炔基。在一些实施方案中， R^{2B} 可为取代的 C_{2-6} 炔基。在其他实施方案中， R^{2B} 可为未取代的 C_{2-6} 炔基。适合的 C_{2-6} 炔基包括乙炔基和丙炔基。在其他实施方案中， R^{2B} 可为任选取代的 C_{3-6} 环烷基。在一些实施方案中， R^{2B} 可为取代的 C_{3-6} 环烷基。在其他实施方案中， R^{2B} 可为未取代的 C_{3-6} 环烷基。 C_{3-6} 环烷基的非限制性列举包括环丙基、环丁基、环戊基和环己基。在一些实施方案中， R^{2B} 可为任选取代的 $-O-C_{1-6}$ 烷基。在一些实施方案中， R^{2B} 可为取代的 $-O-C_{1-6}$ 烷基。在其他实施方案中， R^{2B} 可为未取代的 $-O-C_{1-6}$ 烷基。适合的 $O-C_{1-6}$ 烷基的实例包括甲氧基、乙氧基、正丙氧基、异丙氧基、正丁氧基、异丁氧基、叔丁氧基、戊氧基（支链和直链）和己氧基（支链和直链）。在其他实施方案中， R^{2B} 可为任选取代的 $-O-C_{3-6}$ 烯基。在一些实施方案中， R^{2B} 可为取代的 $-O-C_{3-6}$ 烯基。在其他实施方案中， R^{2B} 可为未取代的 $-O-C_{3-6}$ 烯基。在其他实施方案中， R^{2B} 可为任选取代的 $-O-C_{3-6}$ 炔基。在一些实施方案中， R^{2B} 可为取代的 $-O-C_{3-6}$ 炔基。在其他实施方案中， R^{2B} 可为未取代的 $-O-C_{3-6}$ 炔基。在其他实施方案中， R^{2B} 可为氰基。

[0165] 许多取代基可存在于戊糖环的 2' - 位。在一些实施方案中， R^{4B} 可为氢。在其他实施方案中， R^{4B} 可为卤素，例如氟。在一些实施方案中， R^{3B} 可为卤素，例如氟。在一些实施方案中， R^{4B} 可为氢且 R^{3B} 可为卤素。在其他实施方案中， R^{3B} 和 R^{4B} 都可为卤素。例如， R^{3B} 和 R^{4B} 都可为氟。

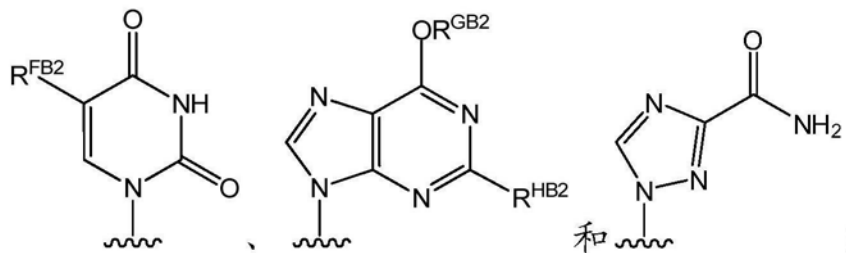
[0166] 在一些实施方案中， Z^{1B} 可为 O（氧）。在其他实施方案中， Z^{1B} 可为 S（硫）。

[0167] 各个任选取代的杂环碱可与戊糖环连接。在一些实施方案中，可使用适合的保护基团保护一个或多个胺和 / 或氨基。例如，可通过将胺和 / 或氨基转化为酰胺或氨基甲酸酯保护氨基。在一些实施方案中，任选取代的杂环碱或具有一个或多个被护氨基的任选取代的杂环碱具有下列结构之一：

[0168]

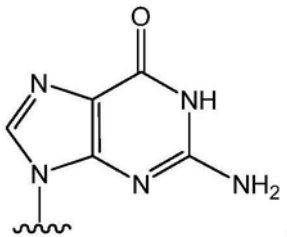


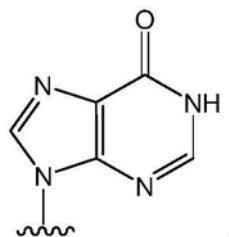
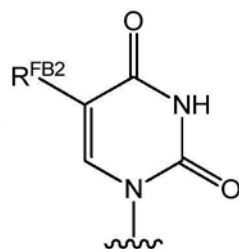
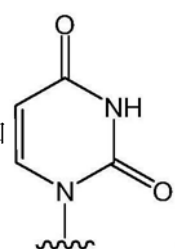
[0169]

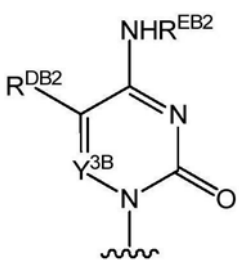
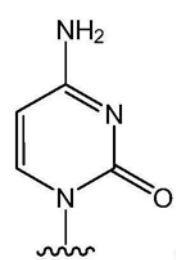
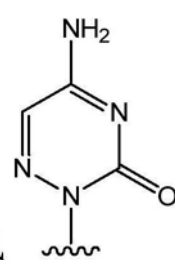


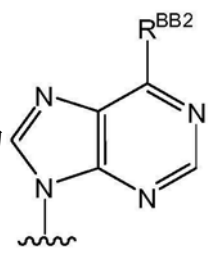
[0170] 其中： R^{AB2} 选自氢、卤素和 NHR^{JB2} ，其中 R^{JB2} 选自氢、 $-C(=O)R^{KB2}$ 和 $-C(=O)$

OR^{LB2} ; R^{BB2} 可为卤素或 NHR^{WB2} , 其中 R^{WB2} 可选自氢、任选取代的 C_{1-6} 烷基、任选取代的 C_{2-6} 烯基、任选取代的 C_{3-8} 环烷基、 $-C(=O)R^{MB2}$ 和 $-C(=O)OR^{QB2}$; R^{CB2} 可为氢或 NHR^{OB2} , 其中 R^{OB2} 可选自氢、 $-C(=O)R^{PB2}$ 和 $-C(=O)OR^{QB2}$; R^{DB2} 可选自氢、卤素、任选取代的 C_{1-6} 烷基、任选取代的 C_{2-6} 烯基和任选取代的 C_{2-6} 炔基; R^{EB2} 可选自氢、羟基、任选取代的 C_{1-6} 烷基、任选取代的 C_{3-8} 环烷基、 $-C(=O)R^{SB2}$ 和 $-C(=O)OR^{TB2}$; R^{FB2} 可选自氢、卤素、任选取代的 C_{1-6} 烷基、任选取代的 C_{2-6} 烯基和任选取代的 C_{2-6} 炔基; Y^{2B} 和 Y^{3B} 可独立地为 N (氮) 或 CR^{IB2} , 其中 R^{IB2} 可选自氢、卤素、任选取代的 C_{1-6} 烷基、任选取代的 C_{2-6} 烯基和任选取代的 C_{2-6} 炔基; R^{GB2} 可为任选取代的 C_{1-6} 烷基; R^{HB2} 可为氢或 NHR^{TB2} , 其中 R^{TB2} 可独立地选自氢、 $-C(=O)R^{VB2}$ 和 $-C(=O)OR^{VB2}$; 且 R^{KB2} 、 R^{LB2} 、 R^{MB2} 、 R^{NB2} 、 R^{PB2} 、 R^{QB2} 、 R^{RB2} 、 R^{SB2} 、 R^{UB2} 和 R^{VB2} 可独立地选自 C_{1-6} 烷基、 C_{2-6} 烯基、 C_{2-6} 炔基、 C_{3-6} 环烷基、 C_{3-6} 环烯基、 C_{6-10} 芳基、杂芳基、杂脂环基、芳基 (C_{1-6} 烷基)、杂芳基 (C_{1-6} 烷基) 和杂脂环基 (C_{1-6} 烷基)。在一些实施方案中, 能通过使用选自“取代的”所定义提供的取代基的列举的取代基来取代一个或多个氢而修饰上文显示的结构。

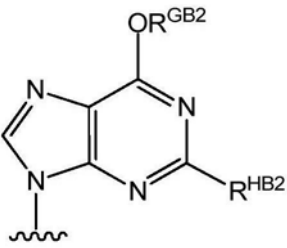
[0171] 在一些实施方案中, B^{1B} 可为  在其他实施方案中, B^{1B} 可为

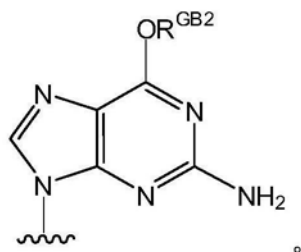
 在其他实施方案中, B^{1B} 可为 , 例如  在其

他实施方案中, B^{1B} 可为 , 例如,  或  在一些实

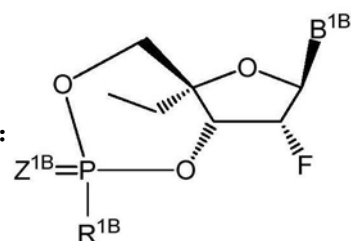
施方案中, R^{DB2} 可为氢。在其他实施方案中, B^{1B} 可为  在一些实施方案中,

R^{BB2} 可为 NH_2 。在其他实施方案中, R^{BB2} 可为 NHR^{WB2} , 其中 R^{WB2} 可为 $-C(=O)R^{MB2}$ 或 $-C(=$

0) OR^{NB2} 。在其他实施方案中, B^{1B} 可为  在一些实施方案中, B^{1B} 可为

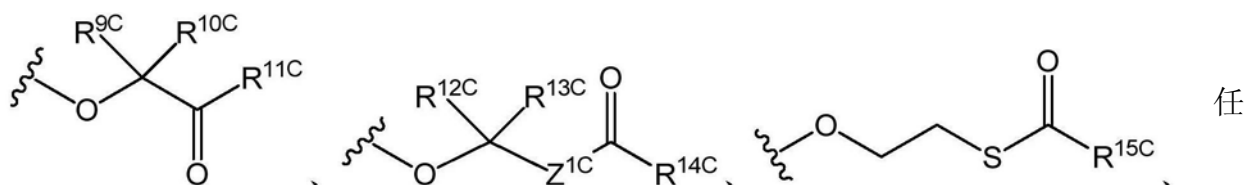


[0172] 在一些实施方案中, 式 (II) 的化合物能具有下列结构:



或前述的药物可接受的盐。在该段落的一些实施方案中, B^{1B} 可为任选取代的嘌呤碱基。在该段落的其他实施方案中, B^{1B} 可为任选取代的嘧啶碱基。在该段落的一些实施方案中, B^{1B} 可为鸟嘌呤。在该段落的其他实施方案中, B^{1B} 可为胸腺嘧啶。在该段落的其他实施方案中, B^{1B} 可为胞嘧啶。在该段落的其他实施方案中, B^{1B} 可为尿嘧啶。在该段落的一些实施方案中, B^{1B} 可为腺嘌呤。在该段落的一些实施方案中, Z^{1B} 可为氧。在该段落的一些实施方案中, Z^{1B} 可为硫。在该段落的其他实施方案中, R^{1B} 可为烷基羰基氧基烃氧基。

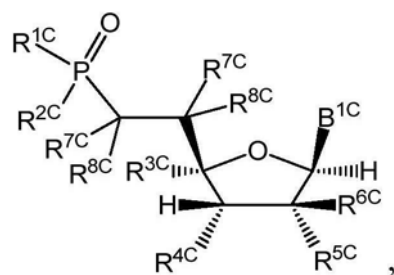
[0173] 在一些实施方案中, 化合物可为式 (III) 的化合物或其药物可接受的盐, 其中: B^{1C} 可为任选取代的杂环碱或具有被护氨基的任选取代的杂环碱; R^{1C} 和 R^{2C} 可独立地选自 O^- 、 OH 、任选取代的 C_{1-6} 烃氧基、



选取代的 N-连接氨基酸和任选取代的 N-连接氨基酸酯衍生物; R^{3C} 可选自任选取代的 C_{1-6} 烷基、任选取代的 C_{2-6} 烯基、任选取代的 C_{2-6} 炔基、任选取代的 $-O-C_{1-6}$ 烷基、任选取代的 $-O-C_{3-6}$ 烯基、任选取代的 $-O-C_{3-6}$ 炔基、任选取代的 C_{3-6} 环烷基和氰基; R^{4C} 可选自 OH 、 $-OC(=O)R^{7C}$ 和任选取代的 O-连接氨基酸; R^{5C} 可为卤素; R^{6C} 可为氢或卤素; R^{9C} 、 R^{10C} 、 R^{12C} 和 R^{13C} 可独立地选自氢、任选取代的 C_{1-24} 烷基和任选取代的芳基; R^{11C} 和 R^{14C} 可独立地选自氢、任选取代的 C_{1-24} 烷基、任选取代的芳基、任选取代的 $-O-C_{1-24}$ 烷基和任选取代的 $-O-$ 芳基; R^{15C} 可选自氢、任选取代的 C_{1-24} 烷基和任选取代的芳基; ———— 可为单键或双键; 当 ———— 为单键时, 各个 R^{7C} 和各个 R^{8C} 可独立地为氢或卤素; 且当 ———— 为双键时, 各个 R^{7C} 不存在且各个 R^{8C} 可独立地为氢或卤素; Z^{1C} 可为 O(氧) 或 S(硫); 且 R^{7C} 可为任选取

代的 C_{1-24} -烷基。

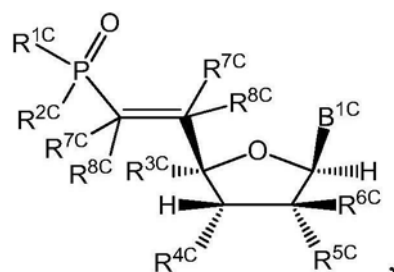
[0174] 在一些实施方案中,-----可为单键使得式(III)具有结构



其中各个 R^{7C} 和各个 R^{8C} 可独立地为氢或卤素。在一些实施方案中,

案中, R^{7C} 和 R^{8C} 基团都可为氢。在其他实施方案中,一个 R^{7C} 可为卤素,一个 R^{7C} 可为氢且两个 R^{8C} 基团都可为氢。在其他实施方案中,一个 R^{7C} 可为卤素,一个 R^{7C} 可为氢,一个 R^{8C} 可为卤素且一个 R^{8C} 可为氢。在一些实施方案中,与磷和所述 5'-碳连接的碳能各自独立地为 (S)-手性中心。在一些实施方案中,与磷和所述 5'-碳连接的碳能各自独立地为 (R)-手性中心。

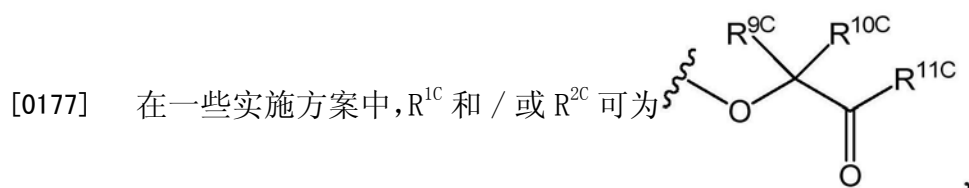
[0175] 在一些实施方案中,-----可为双键使得式(III)具有结构



其中各个 R^{7C} 不存在且各个 R^{8C} 可独立地为氢或卤素。在一些实施方案中,

实施方案中,两个 R^{8C} 基团可为氢。在其他实施方案中,一个 R^{8C} 可为卤素且其他 R^{8C} 可为氢。在一些实施方案中,两个 R^{8C} 基团可为卤素。在一些实施方案中,双键具有 (Z)-构型。在一些实施方案中,双键具有 (E)-构型。

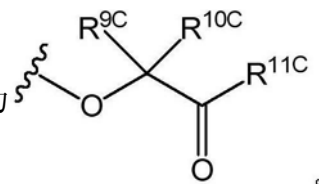
[0176] 在一些实施方案中, R^{1C} 和 / 或 R^{2C} 可为 O^- 。在其他实施方案中, R^{1C} 和 / 或 R^{2C} 可为 OH。在一些实施方案中, R^{1C} 和 R^{2C} 都可为 OH。

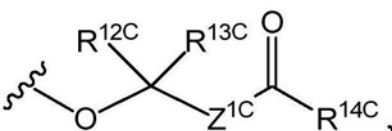


[0177] 在一些实施方案中, R^{1C} 和 / 或 R^{2C} 可为-----其中 R^{9C} 和 R^{10C} 可独

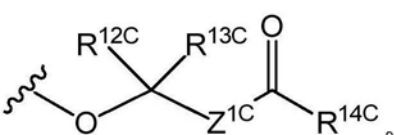
立地选自氢、任选取代的 C_{1-24} 烷基和任选取代的芳基;且 R^{11C} 可选自氢、任选取代的 C_{1-24} 烷基、任选取代的芳基、任选取代的 $-O-C_{1-24}$ 烷基和任选取代的 $-O-$ 芳基。在一些实施方案中, R^{9C} 和 R^{10C} 可为氢。在其他实施方案中,至少一个 R^{9C} 和 R^{10C} 可为任选取代的 C_{1-24} 烷基或任选取代的芳基。在一些实施方案中, R^{11C} 可为任选取代的 C_{1-24} 烷基。在其他实施方案中, R^{11C} 可为任选取代的芳基。在其他实施方案中, R^{11C} 可为任选取代的 $-O-C_{1-24}$ 烷基或任

选取代的 $-O-$ 芳基。在一些实施方案中, R^{1C} 和 R^{2C} 都可为-----。

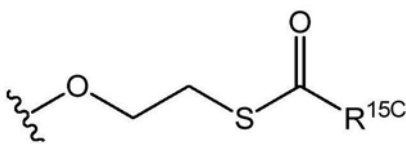


[0177] 在一些实施方案中, R^{1C} 和 / 或 R^{2C} 可为 , 其中 R^{12C} 和

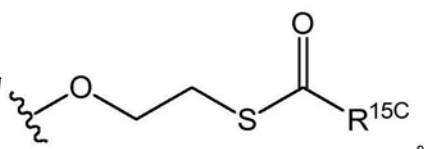
R^{13C} 可独立地选自氢、任选取代的 C_{1-24} 烷基和任选取代的芳基; R^{14C} 可独立地选自氢、任选取代的 C_{1-24} 烷基、任选取代的芳基、任选取代的 $-O-C_{1-24}$ 烷基和任选取代的 $-O-$ 芳基; 且 Z^{1C} 可独立地为 O(氧) 或 S(硫)。在一些实施方案中, R^{12C} 和 R^{13C} 可为氢。在其他实施方案中, R^{12C} 和 R^{13C} 的至少一个可为任选取代的 C_{1-24} 烷基或任选取代的芳基。在一些实施方案中, R^{14C} 可为任选取代的 C_{1-24} 烷基。在其他实施方案中, R^{14C} 可为任选取代的芳基。在其他实施方案中, R^{14C} 可为任选取代的 $-O-C_{1-24}$ 烷基或任选取代的 $-O-$ 芳基。在一些实施方案中, Z^{1C} 可为 O(氧)。在其他实施方案中, Z^{1C} 可为或 S(硫)。在一些实施方案中, R^{1C} 和 / 或 R^{2C} 可为异丙基羰基氧基甲氧基。在一些实施方案中, R^{1C} 和 / 或 R^{2C} 可为新戊酰基氧基

甲氧基。在一些实施方案中, R^{1C} 和 R^{2C} 都可为 。在一些实施方案

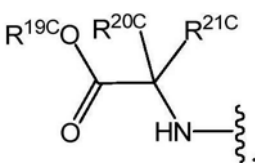
中, R^{1C} 和 R^{2C} 都可为异丙基羰基氧基甲氧基。在其他实施方案中, R^{1C} 和 R^{2C} 都可为新戊酰基氧基甲氧基。

[0179] 在一些实施方案中, R^{1C} 和 / 或 R^{2C} 可为 。在一些实施

方案中, R^{15C} 可为氢。在其他实施方案中, R^{15C} 可为任选取代的 C_{1-24} 烷基。在其他实施方案中, R^{15C} 可为任选取代的芳基。在一些实施方案中, R^{15C} 可为 C_{1-6} 烷基、例如, 甲基、乙基、正丙基、异丙基、正丁基、异丁基、叔丁基、戊基(支链和直链)和己基(支链和直链)。在一些

实施方案中, R^{1C} 和 R^{2C} 都可为 。

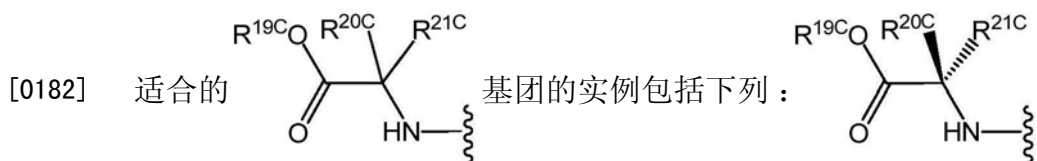
[0180] 在一些实施方案中, R^{1C} 和 / 或 R^{2C} 可为任选取代的 N-连接氨基酸或任选取代的 N-连接氨基酸酯衍生物。例如, R^{1C} 和 / 或 R^{2C} 可为以下基团的任选取代的变型: 丙氨酸、天冬酰胺、天冬氨酸、半胱氨酸、谷氨酸、谷氨酰胺、甘氨酸、脯氨酸、丝氨酸、酪氨酸、精氨酸、组氨酸、异亮氨酸、亮氨酸、赖氨酸、蛋氨酸、苯基丙氨酸、苏氨酸、色氨酸、缬氨酸及其酯衍生物。在一些实施方案中, R^{1C} 和 / 或 R^{2C} 可选自丙氨酸异丙基酯、丙氨酸环己基酯、丙氨酸新戊基酯、缬氨酸异丙基酯和亮氨酸异丙基酯。在一些实施方案中, R^{1C} 和 / 或 R^{2C} 能具有结

构  其中 R^{19C} 可选自氢、任选取代的 C_{1-6} 烷基、任选取代的 C_{3-6} 环烷基、任

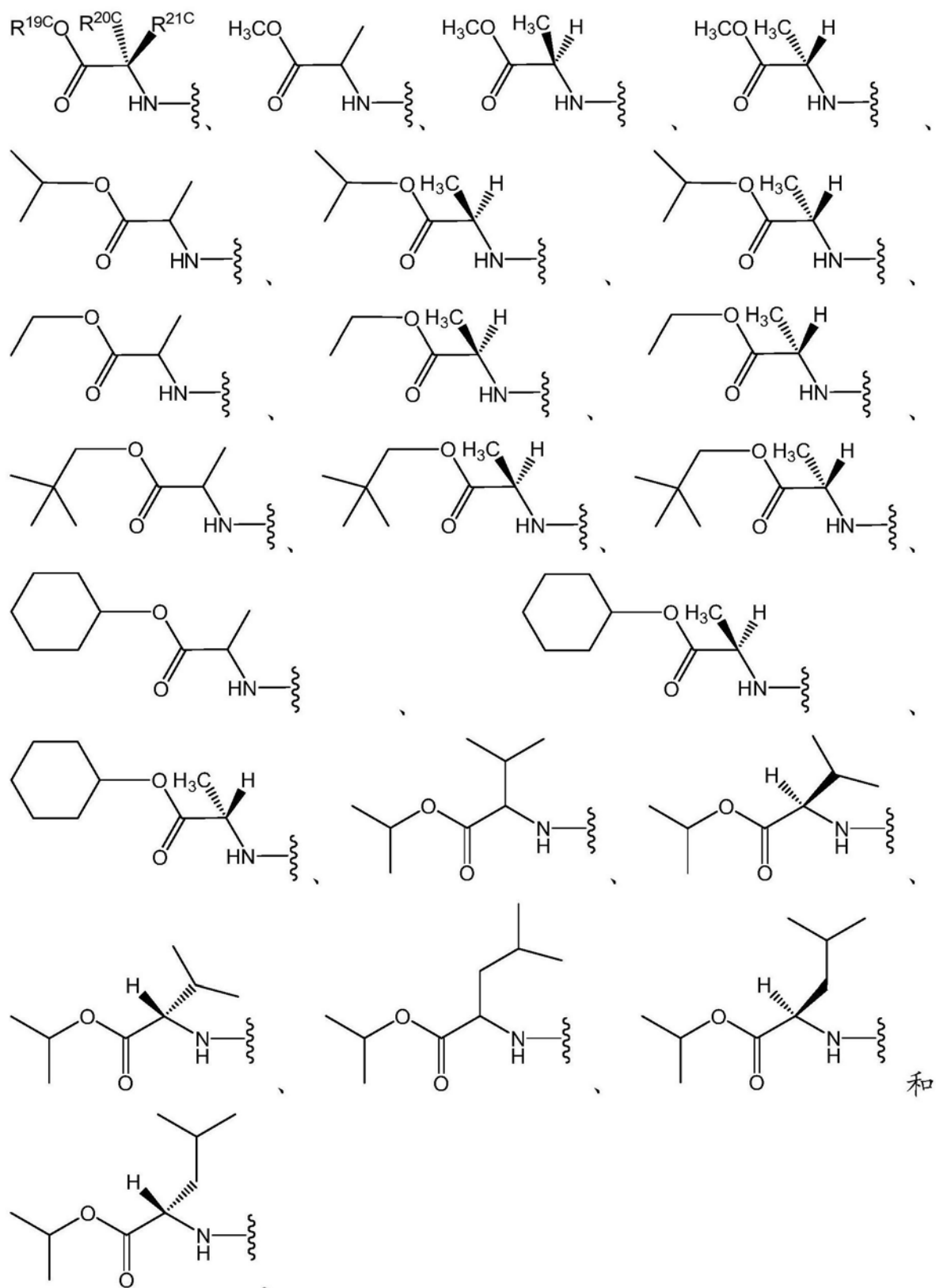
选取代的芳基、任选取代的芳基 (C_{1-6} 烷基) 和任选取代的卤代烷基; R^{20C} 可选自氢、任选取代的 C_{1-6} 烷基、任选取代的 C_{1-6} 卤代烷基、任选取代的 C_{3-6} 环烷基、任选取代的 C_6 芳基、任选取代的 C_{10} 芳基和任选取代的芳基 (C_{1-6} 烷基); 且 R^{21C} 可为氢或任选取代的 C_{1-4} 烷基; 或

R^{20C} 和 R^{21C} 可在一起以形成任选取代的 C_{3-6} 环烷基。

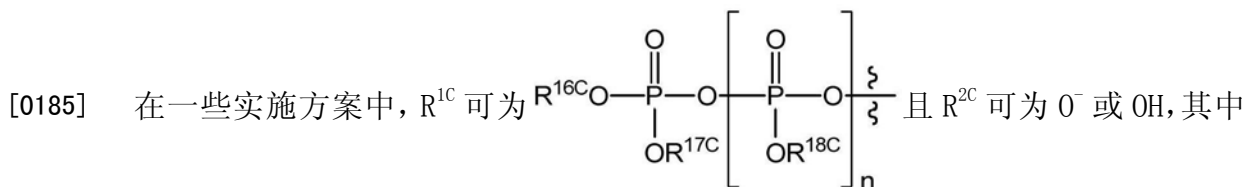
[0181] 当 R^{20C} 被取代时, R^{20C} 能被一个或多个取代基取代, 所述取代基选自 N- 酰胺基、巯基、烷硫基、任选取代的芳基、羟基、任选取代的杂芳基、O- 羧基和氨基。在一些实施方案中, R^{20C} 可为未取代的 C_{1-6} - 烷基, 例如本文描述的那些。在一些实施方案中, R^{20C} 可为氢。在其他实施方案中, R^{20C} 可为甲基。在一些实施方案中, R^{19C} 可为任选取代的 C_{1-6} 烷基。任选取代的 C_{1-6} - 烷基的实例包括以下基团的任选取代的变型: 甲基、乙基、正丙基、异丙基、正丁基、异丁基、叔丁基、戊基 (支链和直链) 和己基 (支链和直链)。在一些实施方案中, R^{19C} 可为甲基或异丙基。在一些实施方案中, R^{19C} 可为乙基或新戊基。在其他实施方案中, R^{19C} 可为任选取代的 C_{3-6} 环烷基。任选取代的 C_{3-6} 环烷基的实例包括以下基团的任选取代的变型: 环丙基、环丁基、环戊基和环己基。在一个实施方案中, R^{19C} 可为任选取代的环己基。在其他实施方案中, R^{19C} 可为任选取代的芳基, 例如苯基和萘基。在其他实施方案中, R^{19C} 可为任选取代的芳基 (C_{1-6} 烷基)。在一些实施方案中, R^{19C} 可为任选取代的苄基。在一些实施方案中, R^{19C} 可为任选取代的 C_{1-6} 卤代烷基, 例如, CF_3 。在一些实施方案中, R^{21C} 可为氢。在其他实施方案中, R^{21C} 可为任选取代的 C_{1-4} - 烷基, 例如甲基、乙基、正丙基、异丙基、正丁基、异丁基和叔丁基。在一个实施方案中, R^{21C} 可为甲基。在一些实施方案中, R^{20C} 和 R^{21C} 可在一起以形成任选取代的 C_{3-6} 环烷基。任选取代的 C_{3-6} 环烷基的实例包括以下基团的任选取代的变型: 环丙基、环丁基、环戊基和环己基。根据对于 R^{20C} 和 R^{21C} 选择的基团, R^{20C} 和 R^{21C} 连接的碳可为手性中心。在一些实施方案中, R^{20C} 和 R^{21C} 连接的碳可为 (R)- 手性中心。在其他实施方案中, R^{20C} 和 R^{21C} 连接的碳可为 (S)- 手性中心。



[0183]



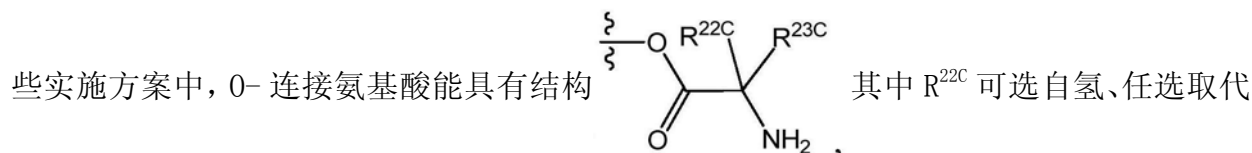
[0184] 在一些实施方案中, R^{1C} 和 R^{2C} 可相同。在其他实施方案中, R^{1C} 和 R^{2C} 可不同。



R^{16C} 、 R^{17C} 和 R^{18C} 可为不存在或为氢; 且 n 可为 0 或 1。本领域技术人员理解当 R^{16C} 、 R^{17C} 和 / 或 R^{18C} 不存在时, 缔合的氧将具有负电荷。在一些实施方案中, 当 n 为 0 时, 式 (III) 的化合物将为二磷酸酯。在其他实施方案中, 当 n 为 1 时, 式 (III) 的化合物将为三磷酸酯。

[0186] 许多取代基可存在于戊糖环的 4' - 位。在一些实施方案中, R^{3C} 可为任选取代的 C_{1-6} 烷基。适合的 C_{1-6} 烷基的实例包括甲基、乙基、正丙基、异丙基、正丁基、异丁基、叔丁基、戊基 (支链和直链) 和己基 (支链和直链)。在一些实施方案中, R^{3C} 可为未取代的 C_{1-6} 烷基。在其他实施方案中, R^{3C} 可为取代的 C_{1-6} 烷基。例如, R^{3C} 可为卤素取代的 C_{1-6} 烷基。在其他实施方案中, R^{3C} 可为任选取代的 C_{2-6} 烯基。在一些实施方案中, R^{3C} 可为取代的 C_{2-6} 烯基。在其他实施方案中, R^{3C} 可为未取代的 C_{2-6} 烯基。例如, R^{3C} 可为乙烯基、丙烯基或丙二烯基。在其他实施方案中, R^{3C} 可为任选取代的 C_{2-6} 炔基。在一些实施方案中, R^{3C} 可为取代的 C_{2-6} 炔基。在其他实施方案中, R^{3C} 可为未取代的 C_{2-6} 炔基。适合的 C_{2-6} 炔基包括乙炔基和丙炔基。在其他实施方案中, R^{3C} 可为任选取代的 C_{3-6} 环烷基。在一些实施方案中, R^{3C} 可为取代的 C_{3-6} 环烷基。在其他实施方案中, R^{3C} 可为未取代的 C_{3-6} 环烷基。 C_{3-6} 环烷基的非限制性列举包括环丙基、环丁基、环戊基和环己基。在一些实施方案中, R^{3C} 可为任选取代的 $-O-C_{1-6}$ 烷基。在一些实施方案中, R^{3C} 可为取代的 $-O-C_{1-6}$ 烷基。在其他实施方案中, R^{3C} 可为未取代的 $-O-C_{1-6}$ 烷基。适合的 $O-C_{1-6}$ 烷基的实例包括甲氧基、乙氧基、正丙氧基、异丙氧基、正丁氧基、异丁氧基、叔丁氧基、戊氧基 (支链和直链) 和己氧基 (支链和直链)。在其他实施方案中, R^{3C} 可为任选取代的 $-O-C_{3-6}$ 烯基。在一些实施方案中, R^{3C} 可为取代的 $-O-C_{3-6}$ 烯基。在其他实施方案中, R^{3C} 可为未取代的 $-O-C_{3-6}$ 烯基。在其他实施方案中, R^{3C} 可为任选取代的 $-O-C_{3-6}$ 炔基。在一些实施方案中, R^{3C} 可为取代的 $-O-C_{3-6}$ 炔基。在其他实施方案中, R^{3C} 可为未取代的 $-O-C_{3-6}$ 炔基。在其他实施方案中, R^{3C} 可为氰基。

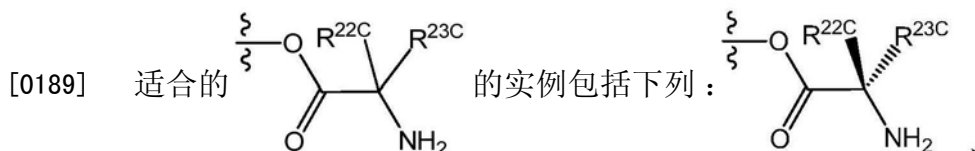
[0187] 可存在于戊糖环的 3' - 位上的取代基可变化。在一些实施方案中, R^{4C} 可为 OH 。在其他实施方案中, R^{4C} 可为任选取代的 O^- 连接氨基酸。适合的 O^- 连接氨基酸的实例包括丙氨酸、天冬酰胺、天冬氨酸、半胱氨酸、谷氨酸、谷氨酰胺、甘氨酸、脯氨酸、丝氨酸、酪氨酸、精氨酸、组氨酸、异亮氨酸、亮氨酸、赖氨酸、蛋氨酸、苯基丙氨酸、苏氨酸、色氨酸和缬氨酸。适合的氨基酸的其他实例包括但不限于鸟氨酸、尾下素、2- 氨基异丁酸、脱氢丙氨酸、 γ - 氨基丁酸、瓜氨酸、 β - 丙氨酸、 α - 乙基 - 甘氨酸、 α - 丙基 - 甘氨酸和正亮氨酸。在一



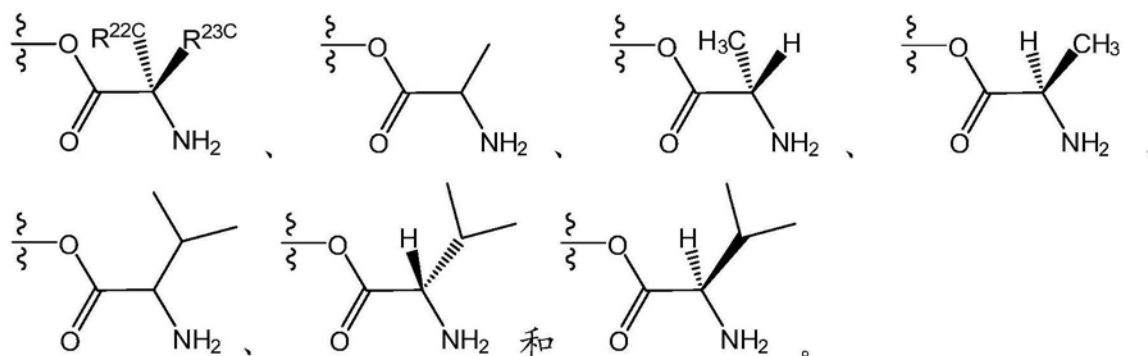
的 C_{1-6} 烷基、任选取代的 C_{1-6} 卤代烷基、任选取代的 C_{3-6} 环烷基、任选取代的 C_6 芳基、任选取代的 C_{10} 芳基和任选取代的芳基 (C_{1-6} 烷基); 且 R^{23C} 可为氢或任选取代的 C_{1-4} 烷基; 或 R^{22C} 和 R^{23C} 可在一起以形成任选取代的 C_{3-6} 环烷基。

[0188] 当 R^{22C} 被取代时, R^{22C} 可被一个或多个取代基取代, 所述取代基选自 N^- 酰胺基、硫

基、烷硫基、任选取代的芳基、羟基、任选取代的杂芳基、O-羧基和氨基。在一些实施方案中， R^{22C} 可为未取代的 C_{1-6} -烷基、例如本文描述的那些。在一些实施方案中， R^{22C} 可为氢。在其他实施方案中， R^{22C} 可为甲基。在一些实施方案中， R^{23C} 可为氢。在其他实施方案中， R^{23C} 可为任选取代的 C_{1-4} -烷基，例如甲基、乙基、正丙基、异丙基、正丁基、异丁基和叔丁基。在一个实施方案中， R^{23C} 可为甲基。根据对于 R^{22C} 和 R^{23C} 选择的基团， R^{22C} 和 R^{23C} 连接的碳可为手性中心。在一些实施方案中， R^{22C} 和 R^{23C} 连接的碳可为 (R)-手性中心。在其他实施方案中， R^{22C} 和 R^{23C} 连接的碳可为 (S)-手性中心。



[0190]

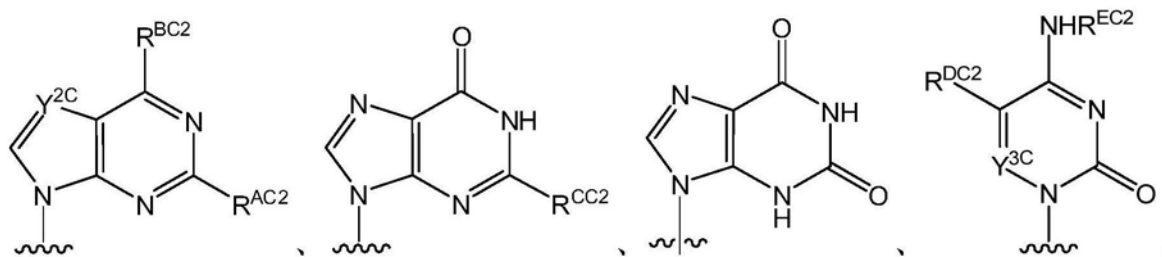


[0191] 在其他实施方案中， R^{4C} 可为 $-OC(=O)R^{nC}$ ，其中 R^{nC} 可为任选取代的 C_{1-24} 烷基。在一些实施方案中， R^{nC} 可为取代的 C_{1-12} 烷基。在其他实施方案中， R^{nC} 可为未取代的 C_{1-12} 烷基。在其他实施方案中， R^{nC} 可为取代的 C_{1-8} 烷基。在其他实施方案中， R^{nC} 可为未取代的 C_{1-8} 烷基。在一些实施方案中， R^{4C} 可为任选取代的酰基。在其他实施方案中， R^{4C} 可为 $-OC(=O)R^{nC}$ ，其中 R^{nC} 可选自任选取代的 C_{1-12} 烷基、任选取代的 C_{2-12} 烯基、任选取代的 C_{2-12} 炔基、任选取代的 C_{3-8} 环烷基、任选取代的 C_{5-8} 环烯基、任选取代的 C_{6-10} 芳基、任选取代的杂芳基、任选取代的杂环基、任选取代的芳基 (C_{1-6} 烷基)、任选取代的杂芳基 (C_{1-6} 烷基) 和任选取代的杂环基 (C_{1-6} 烷基)。在一些实施方案中， R^{nC} 可为取代的 C_{1-12} 烷基。在其他实施方案中， R^{nC} 可为未取代的 C_{1-12} 烷基。

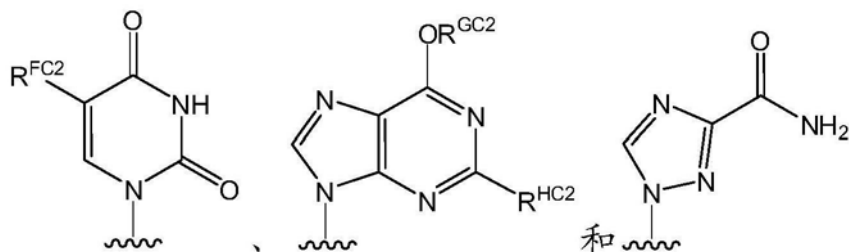
[0192] 许多取代基也可存在于戊糖环的 2'-位。在一些实施方案中， R^{6C} 可为氢。在其他实施方案中， R^{6C} 可为卤素，例如氟。在一些实施方案中， R^{5C} 可为卤素，例如氟。在一些实施方案中， R^{6C} 可为氢和 R^{5C} 可为卤素。在其他实施方案中， R^{5C} 和 R^{6C} 都可为卤素。例如， R^{5C} 和 R^{6C} 都可为氟。

[0193] 各个任选取代的杂环碱可与戊糖环连接。在一些实施方案中，可使用适合的保护基团保护一个或多个胺和 / 或氨基。例如，可通过将胺和 / 或氨基转化为酰胺或氨基甲酸酯保护氨基。在一些实施方案中，任选取代的杂环碱或具有一个或多个被护氨基的任选取代的杂环碱能具有下列结构之一：

[0194]

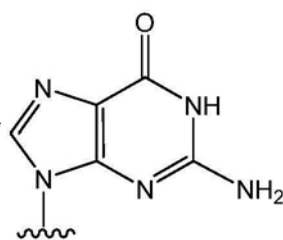


[0195]

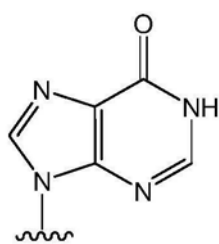


[0196] 其中： R^{AC2} 可选自氢、卤素和 NHR^{JC2} ，其中 R^{JC2} 可选自氢、 $-C(=O)R^{KC2}$ 和 $-C(=O)OR^{LC2}$ ； R^{BC2} 可为卤素或 NHR^{WC2} ，其中 R^{WC2} 可选自氢、任选取代的 C_{1-6} 烷基、任选取代的 C_{2-6} 烯基、任选取代的 C_{3-8} 环烷基、 $-C(=O)R^{MC2}$ 和 $-C(=O)OR^{NC2}$ ； R^{CC2} 可为氢或 NHR^{OC2} ，其中 R^{OC2} 可选自氢、 $-C(=O)R^{PC2}$ 和 $-C(=O)OR^{QC2}$ ； R^{DC2} 可选自氢、卤素、任选取代的 C_{1-6} 烷基、任选取代的 C_{2-6} 烯基和任选取代的 C_{2-6} 炔基； R^{EC2} 可选自氢、羟基、任选取代的 C_{1-6} 烷基、任选取代的 C_{3-8} 环烷基、 $-C(=O)R^{RC2}$ 和 $-C(=O)OR^{SC2}$ ； R^{FC2} 可选自氢、卤素、任选取代的 C_{1-6} 烷基、任选取代的 C_{2-6} 烯基和任选取代的 C_{2-6} 炔基； Y^{2C} 和 Y^{3C} 可独立地为 N(氮) 或 CR^{IC2} ，其中 R^{IC2} 可选自氢、卤素、任选取代的 C_{1-6} 烷基、任选取代的 C_{2-6} 烯基和任选取代的 C_{2-6} 炔基； R^{GC2} 可为任选取代的 C_{1-6} 烷基； R^{HC2} 可为氢或 NHR^{TC2} ，其中 R^{TC2} 可独立地选自氢、 $-C(=O)R^{UC2}$ 和 $-C(=O)OR^{VC2}$ ；且 R^{KC2} 、 R^{LC2} 、 R^{MC2} 、 R^{NC2} 、 R^{PC2} 、 R^{QC2} 、 R^{RC2} 、 R^{SC2} 、 R^{UC2} 和 R^{VC2} 可独立地选自 C_{1-6} 烷基、 C_{2-6} 烯基、 C_{2-6} 炔基、 C_{3-6} 环烷基、 C_{3-6} 环烯基、 C_{6-10} 芳基、杂芳基、杂脂环基、芳基 (C_{1-6} 烷基)、杂芳基 (C_{1-6} 烷基) 和杂脂环基 (C_{1-6} 烷基)。在一些实施方案中，能通过使用选自“取代的”定义提供的取代基的列举的取代基取代一个或多个氢修改上文显示的结构。

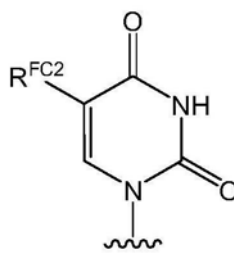
[0197] 在一些实施方案中， B^{1C} 可为



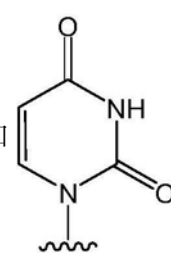
在其他实施方案中， B^{1C} 可为



在其他实施方案中， B^{1C} 可为

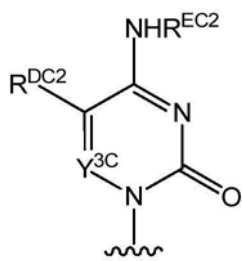


例如

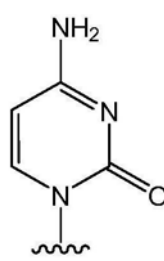


在其

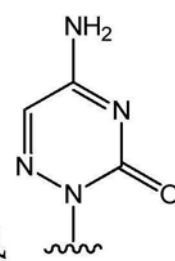
他实施方案中, B^{1C} 可为



例如,

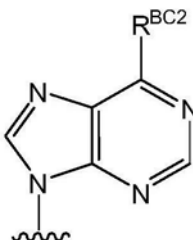


或



在一些实

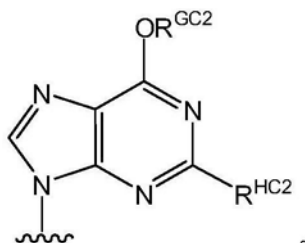
施方案中, R^{BC2} 可为氢。在其他实施方案中, B^{1C} 可为



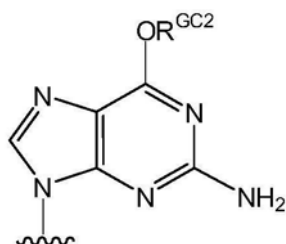
在一些实施方案中,

R^{BC2} 可为 NH_2 。在其他实施方案中, R^{BC2} 可为 NHR^{WC2} , 其中 R^{WC2} 可为 $-C(=O)R^{MC2}$ 或 $-C(=$

$O)OR^{NC2}$ 。在其他实施方案中, B^{1C} 可为

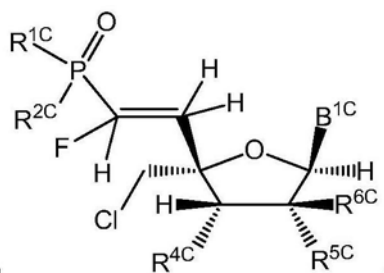
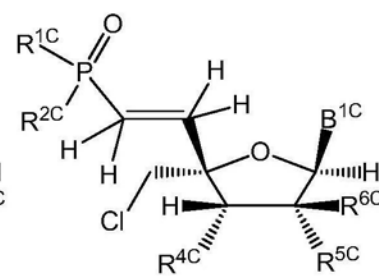
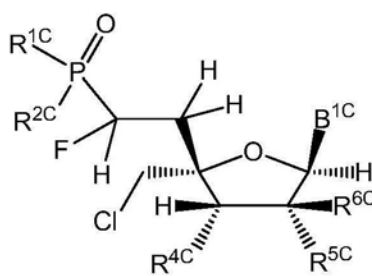
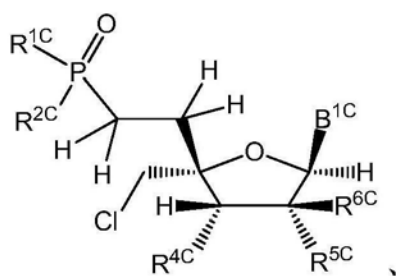


在一些实施方案中, B^{1C} 可为



[0198] 在一些实施方案中, 式 (III) 的化合物能具有下列结构:

[0199]



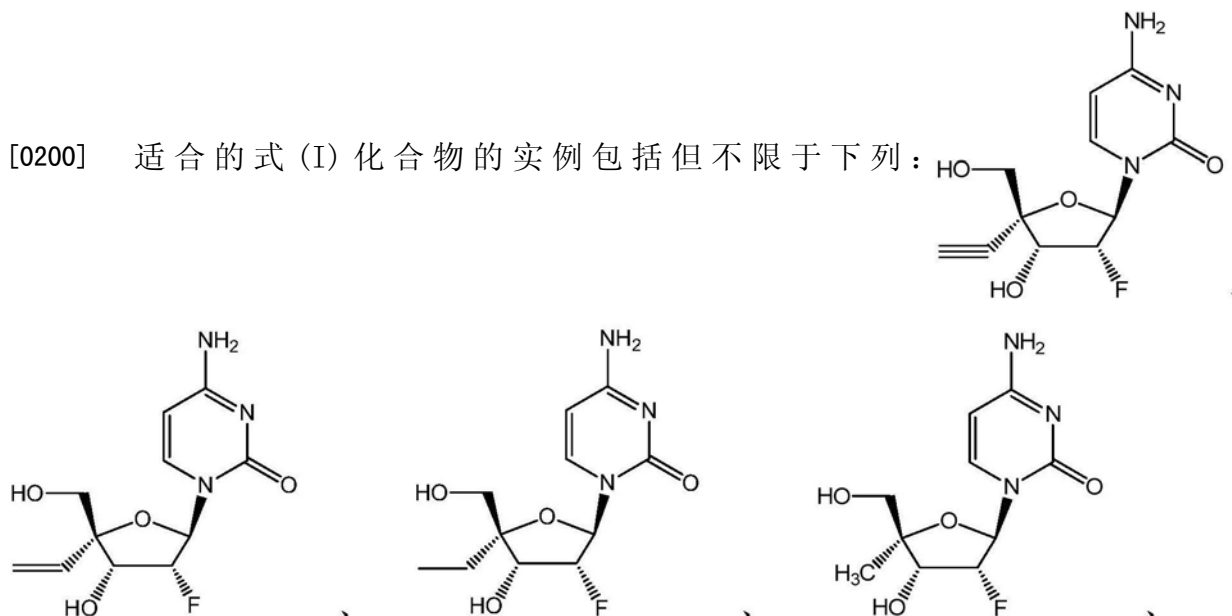
在该段落的一些实施方案中, B^{1C} 可为任选取代的嘌呤碱

或

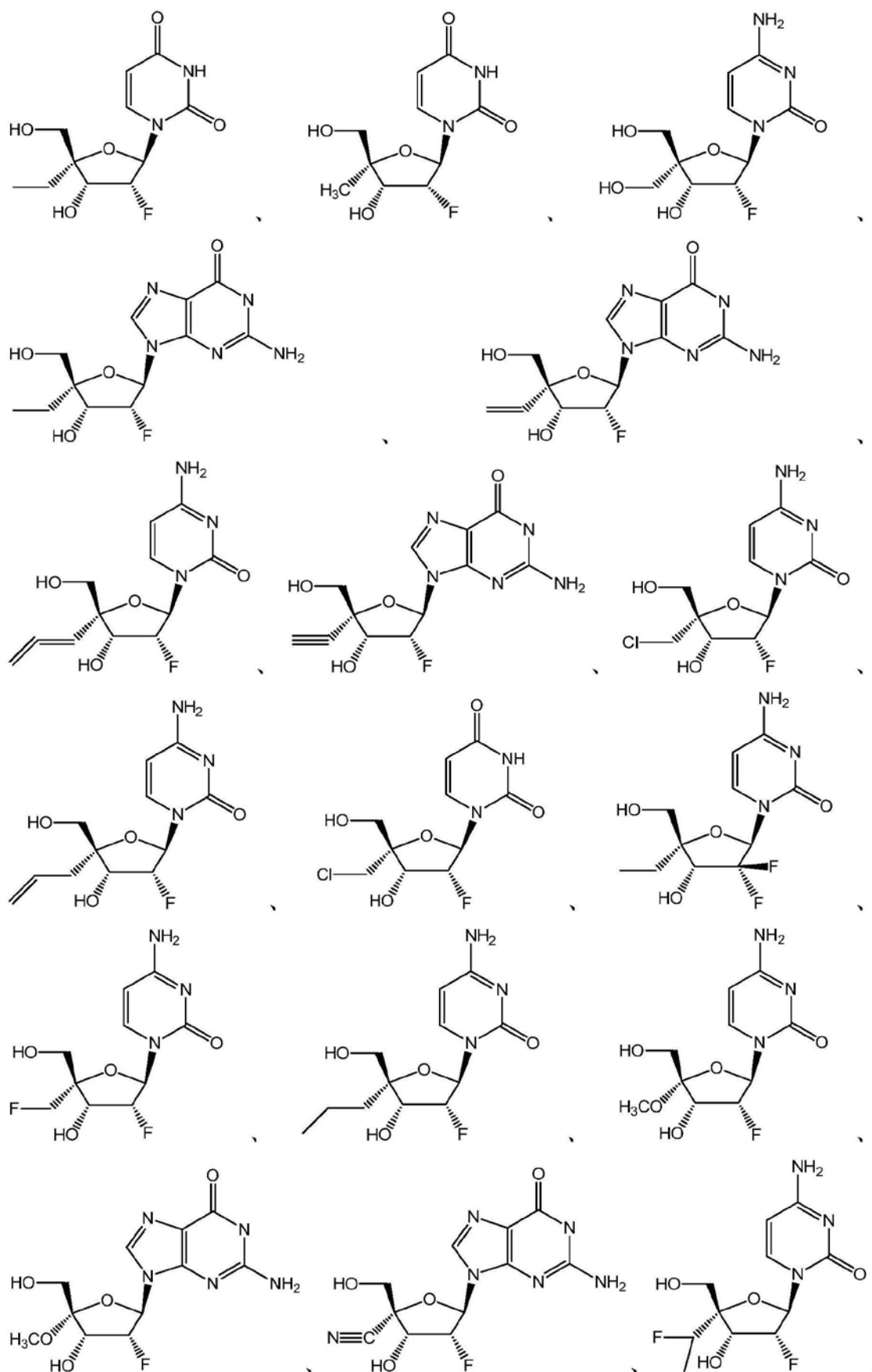
基。在该段落的其他实施方案中, B^{1C} 可为任选取代的嘧啶碱基。在该段落的一些实施方案

中, B^{1C} 可为鸟嘌呤。在该段落的其他实施方案中, B^{1C} 可为胸腺嘧啶。在该段落的其他实施方案中, B^{1C} 可为胞嘧啶。在该段落的其他实施方案中, B^{1C} 可为尿嘧啶。在该段落的一些实施方案中, B^{1C} 可为腺嘌呤。在该段落的一些实施方案中, R^{1C} 和 R^{2C} 能各自为任选取代的 C_{1-4} 烷基。在该段落的其他实施方案中, R^{1A} 可为任选取代的酰基。在该段落的其他实施方案中, R^{1C} 和 R^{2C} 能形成单磷酸酯、二磷酸酯或三磷酸酯。在该段落的其他实施方案中, R^{1C} 和 R^{2C} 能各自为烷基羰基氧基烃氧基。在该段落的一些实施方案中, R^{4C} 可为 OH。在该段落的一些实施方案中, R^{5C} 可为 F 且 R^{6C} 可为氢。

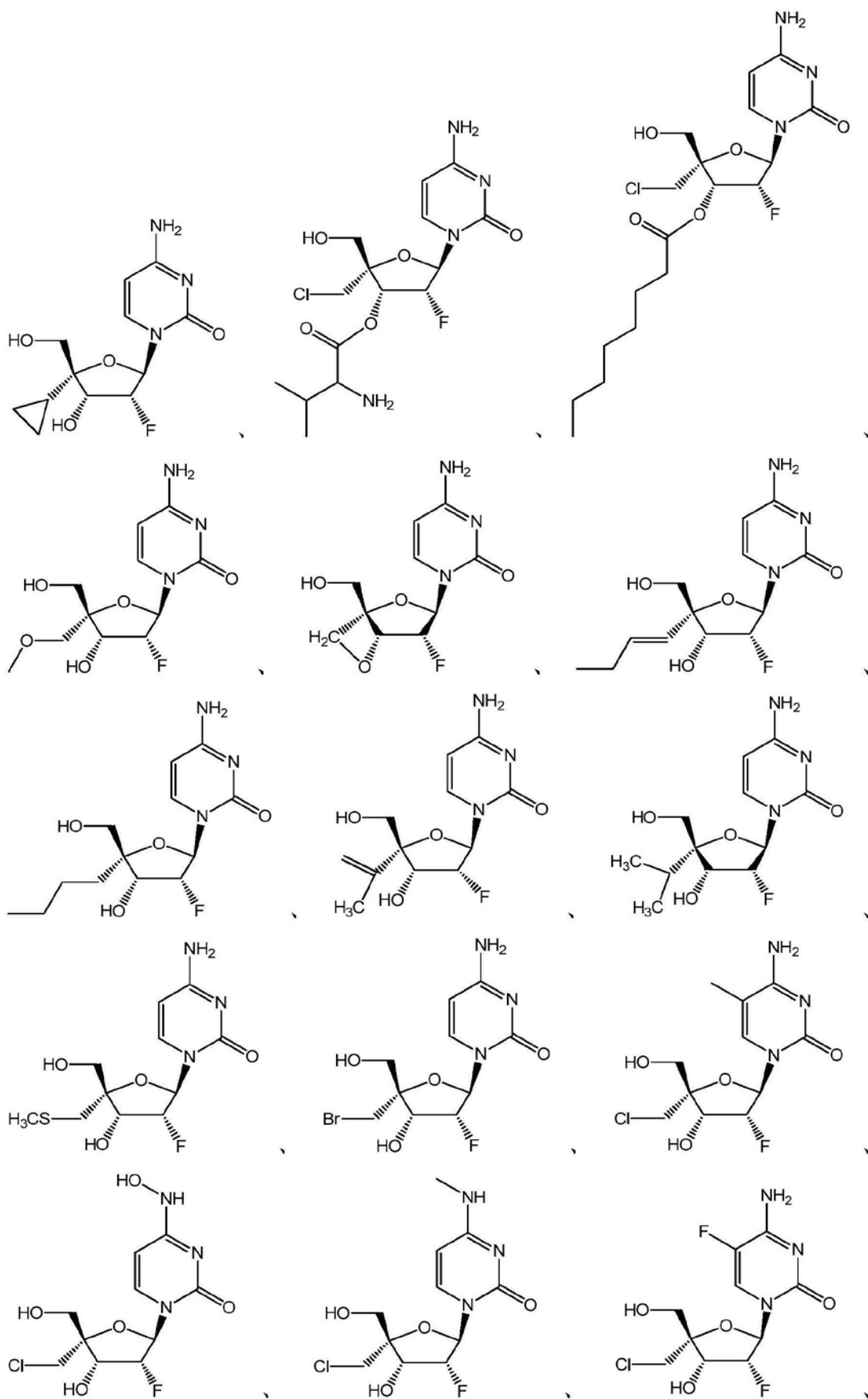
[0200] 适合的式 (I) 化合物的实例包括但不限于下列：



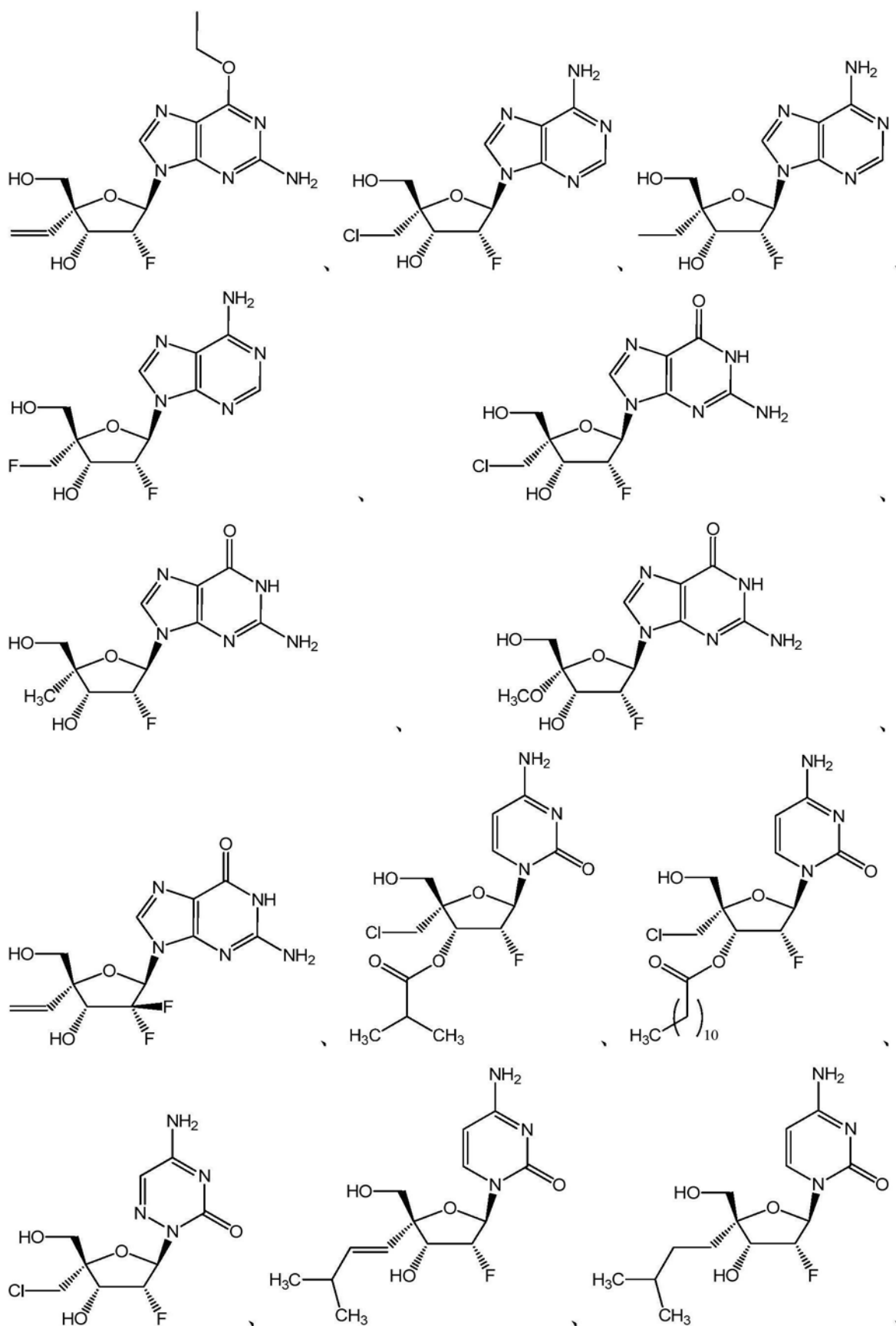
[0201]



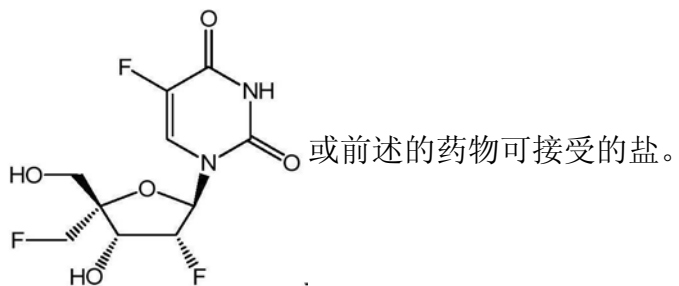
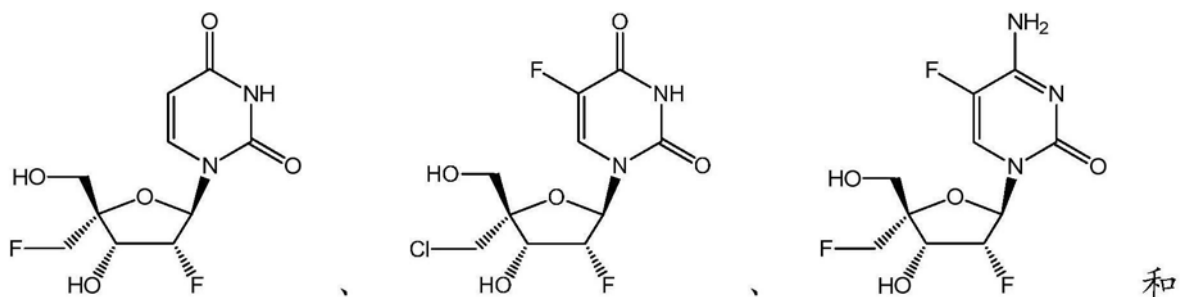
[0202]



[0203]

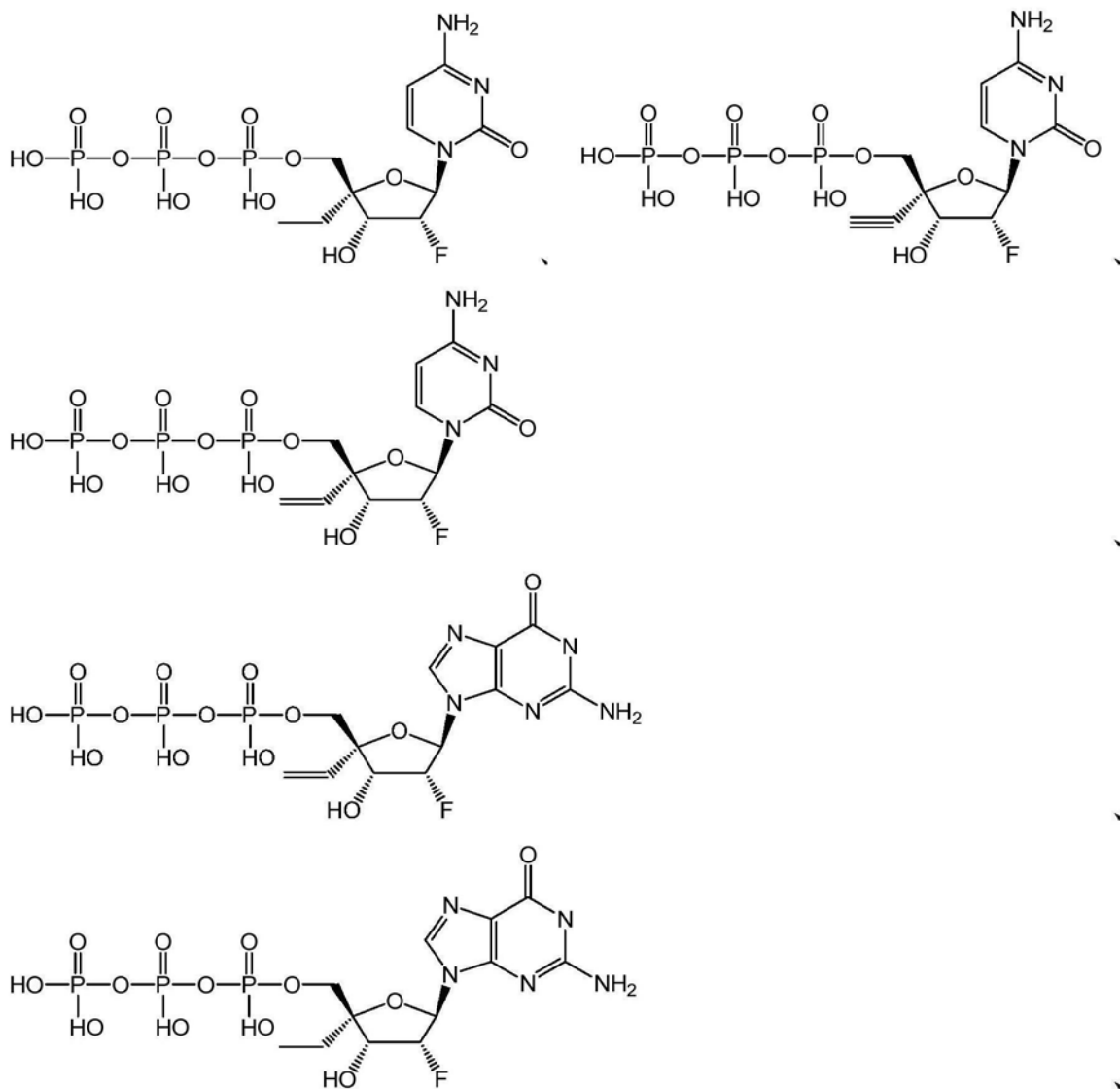


[0204]

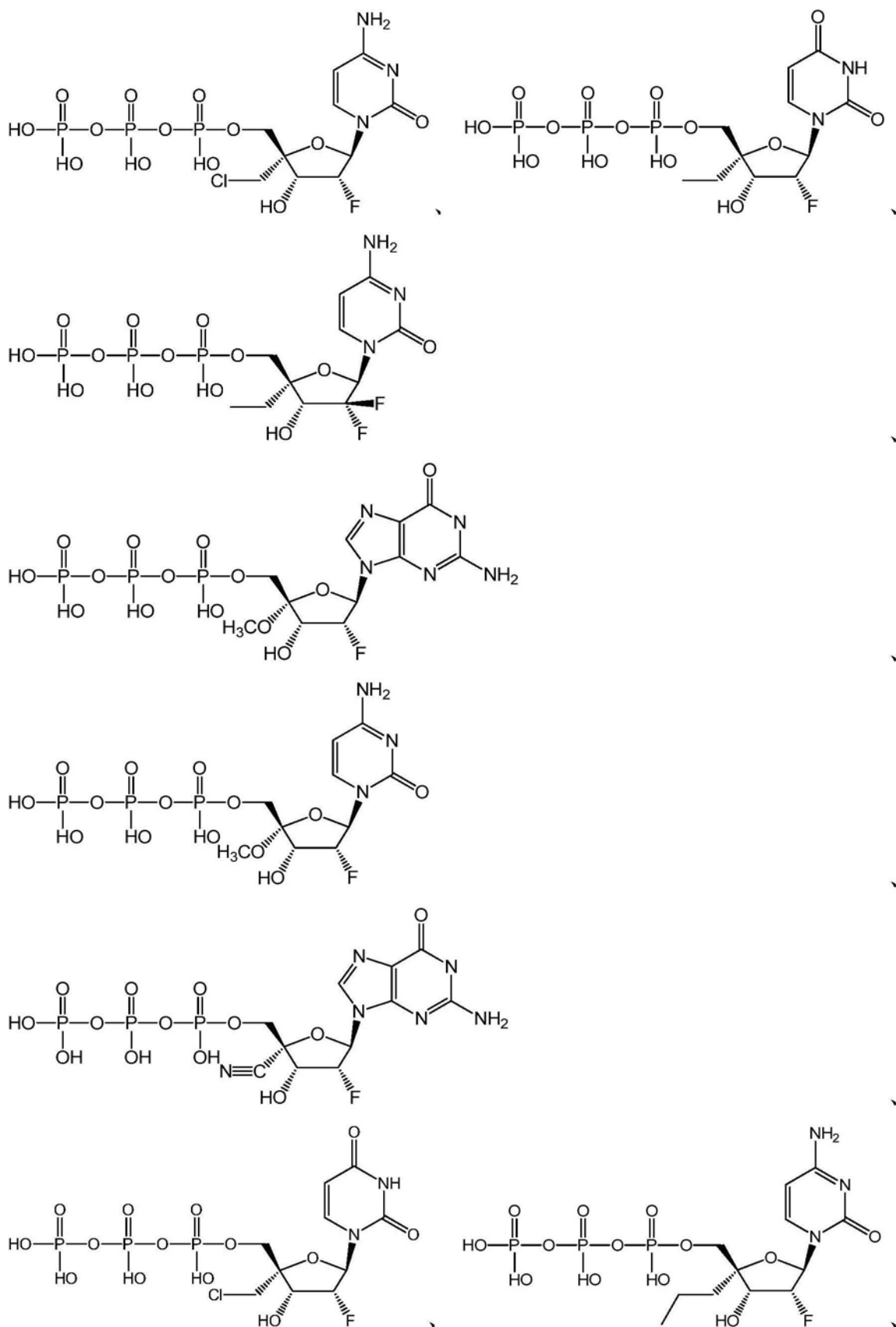


[0205] 式 (I) 化合物的其他实例包括下列：

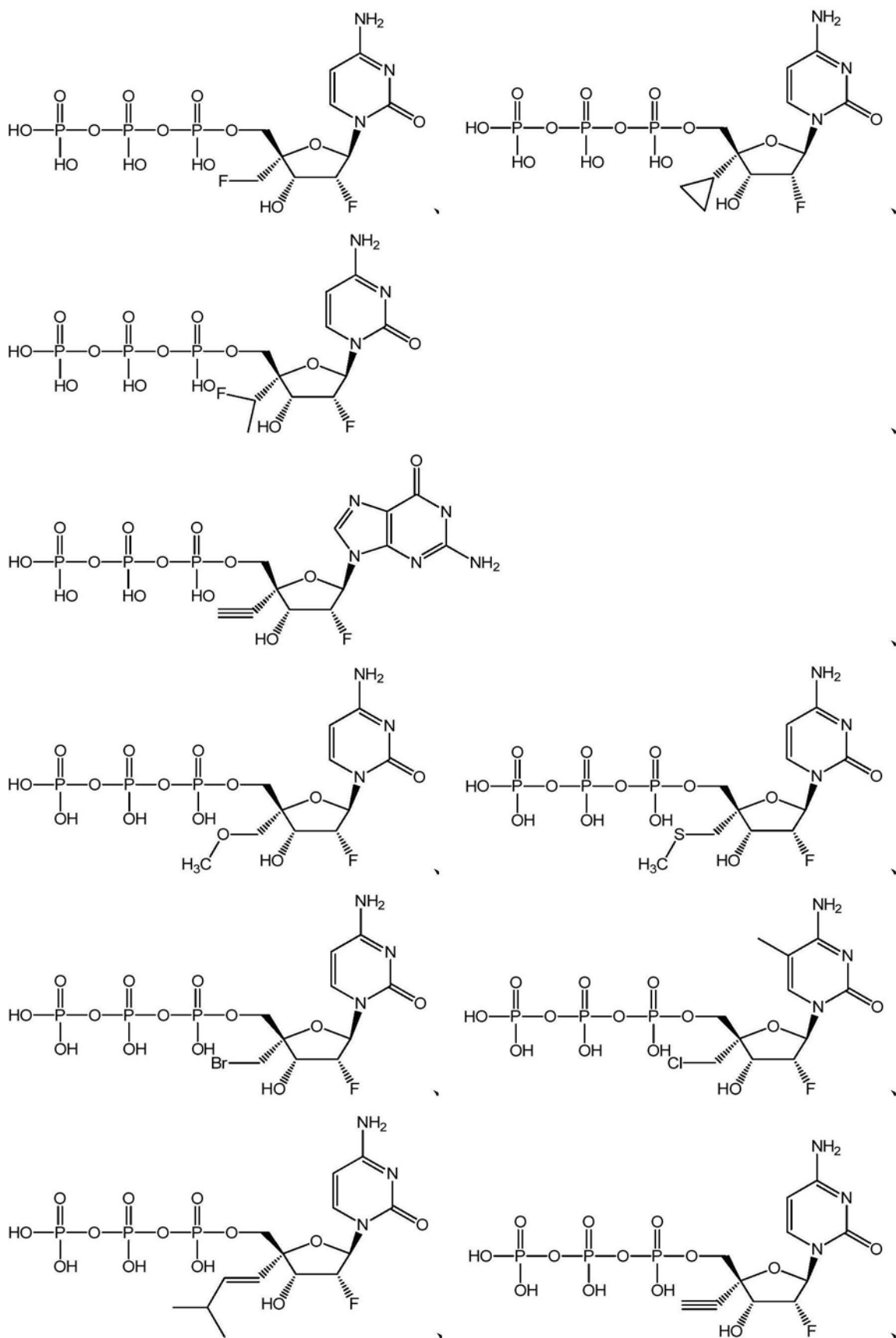
[0206]



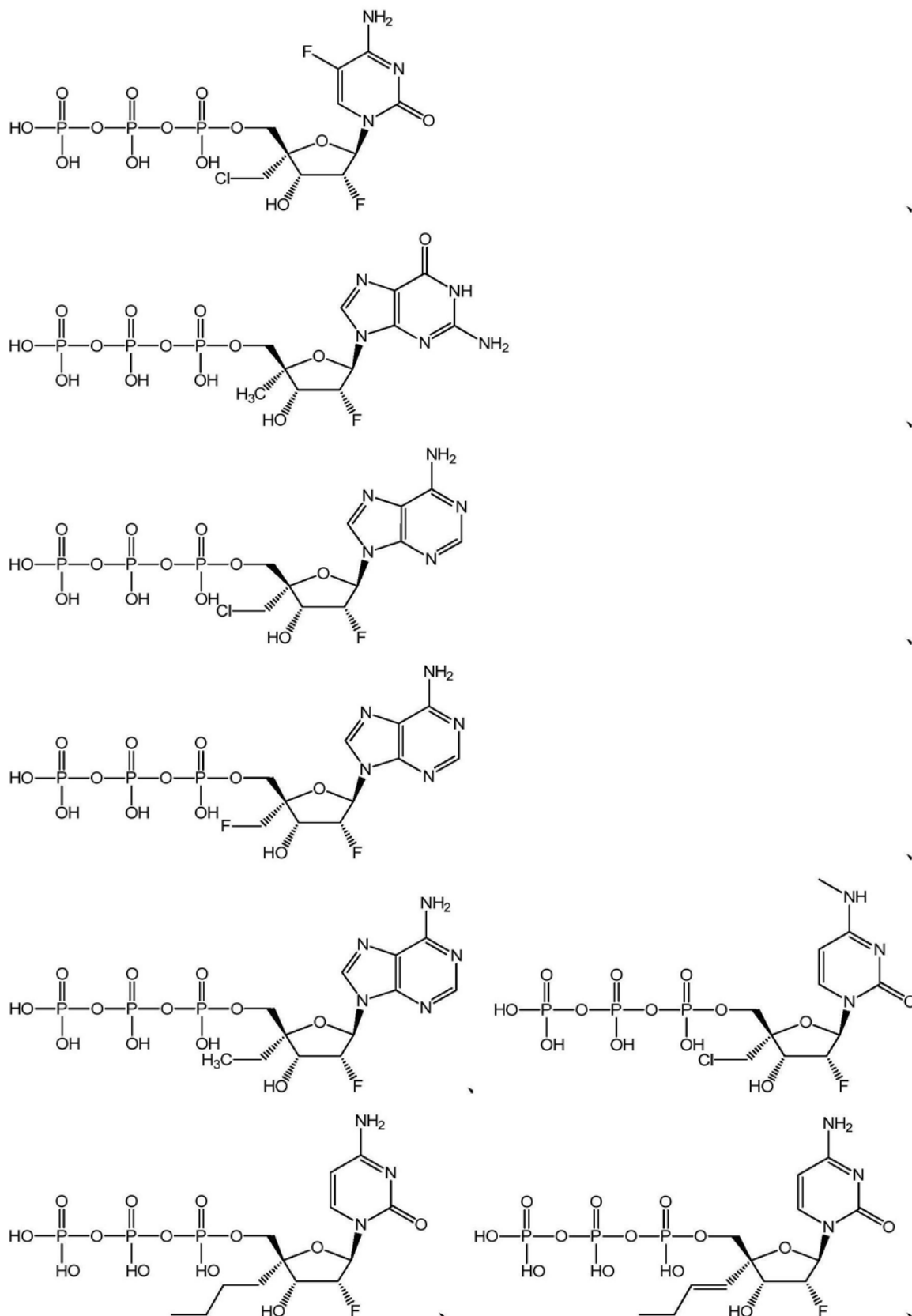
[0207]



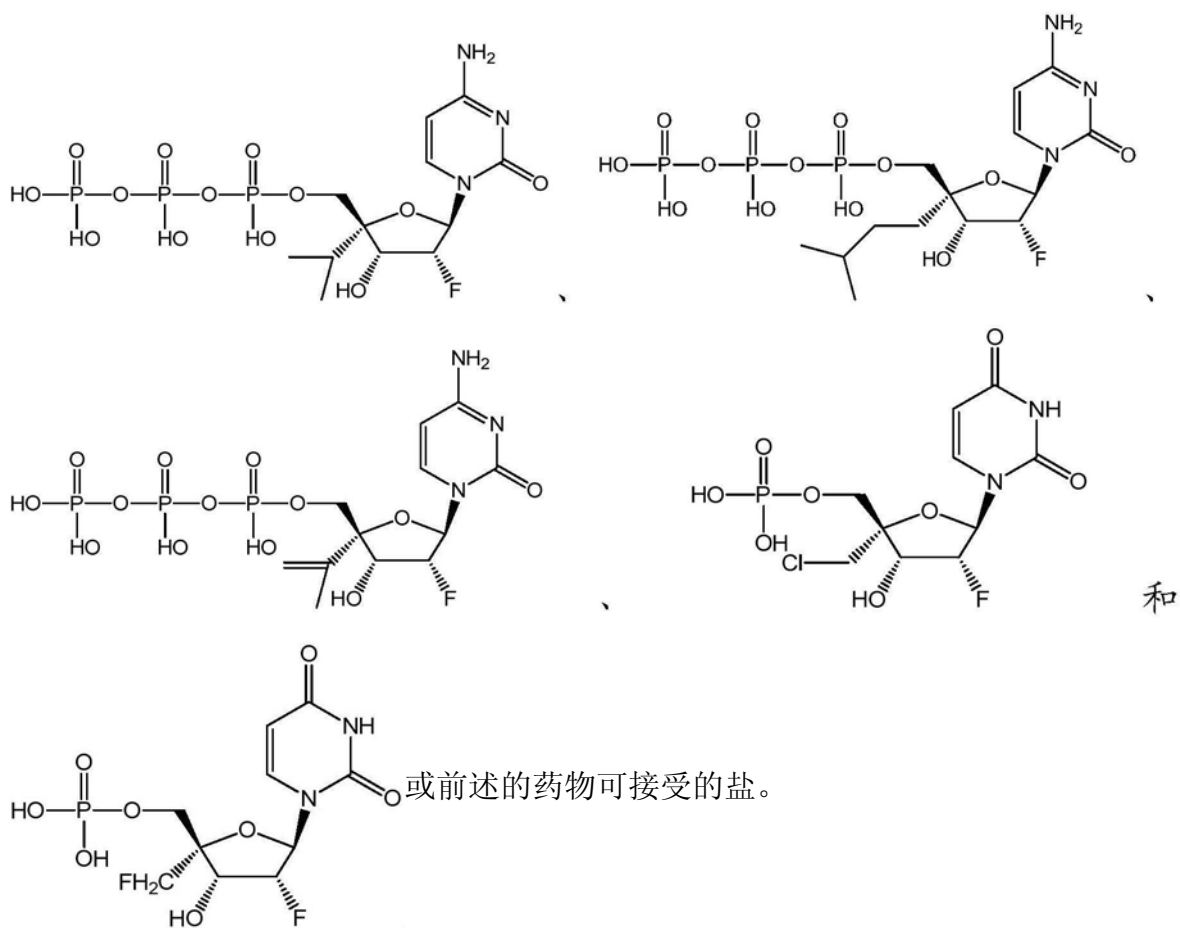
[0208]



[0209]

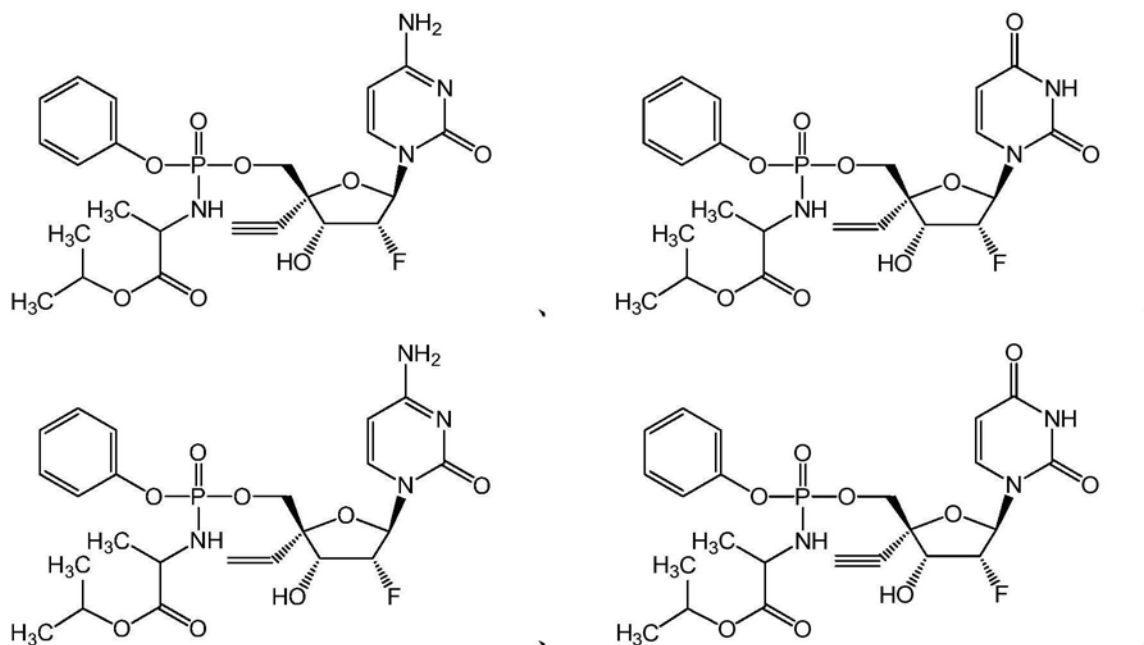


[0210]

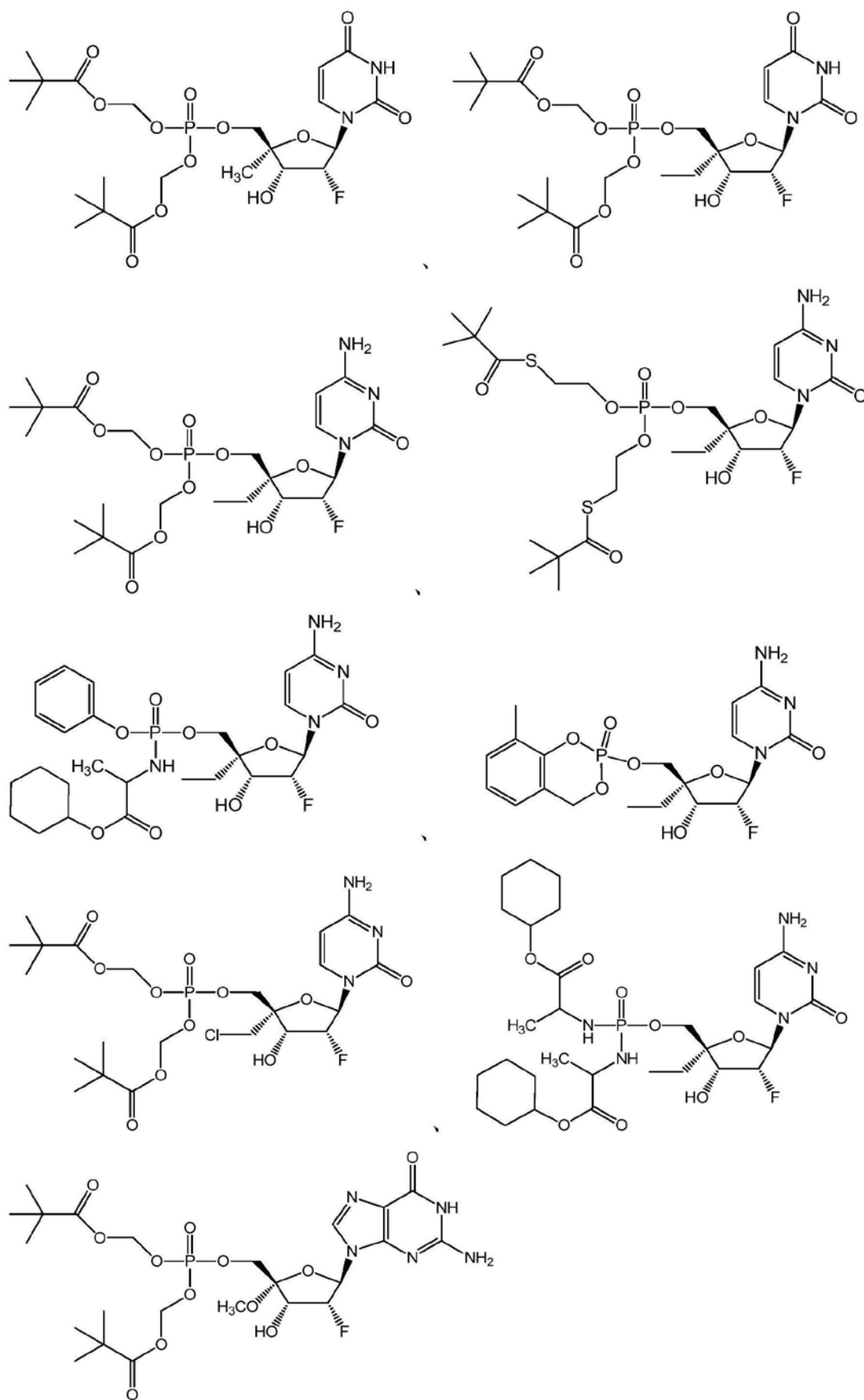


[0211] 式 (I) 化合物的其他实例包括但不限于下列：

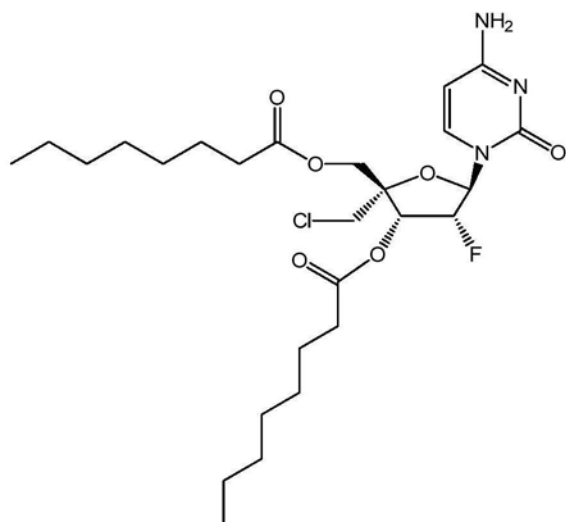
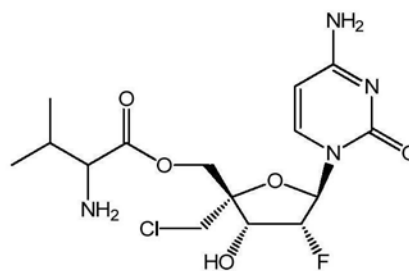
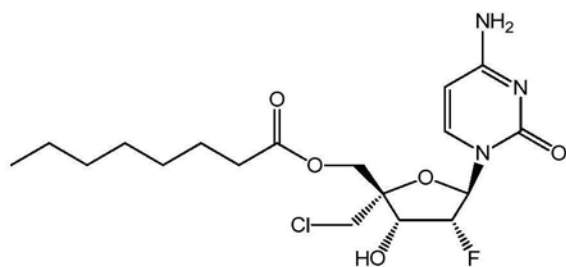
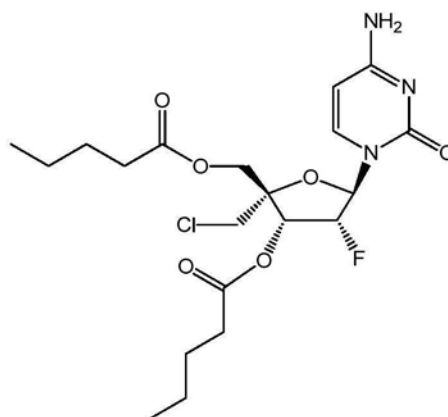
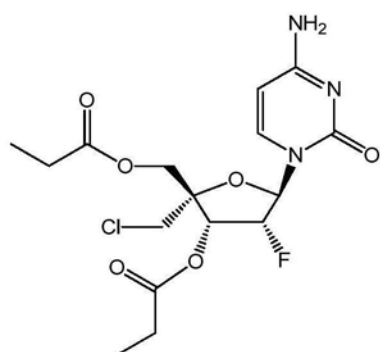
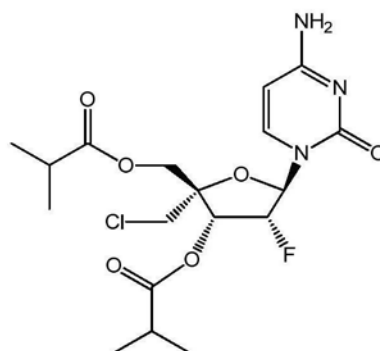
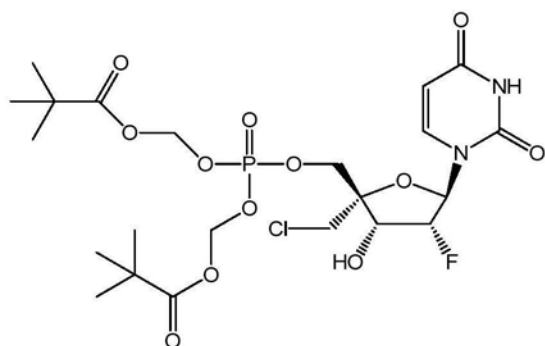
[0212]



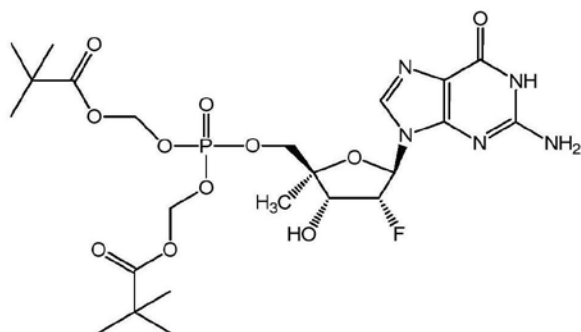
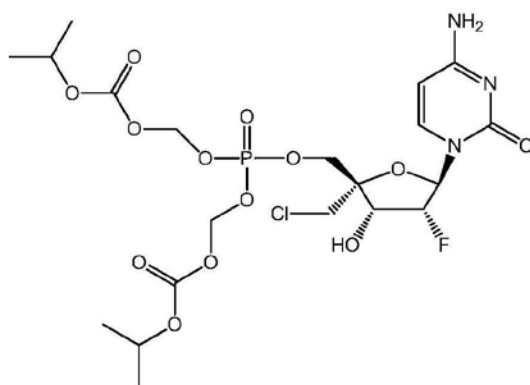
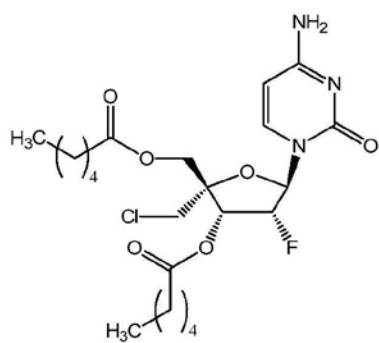
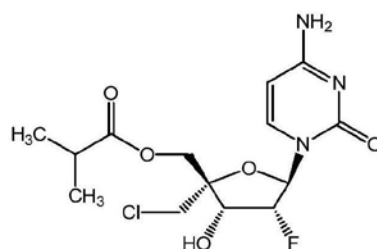
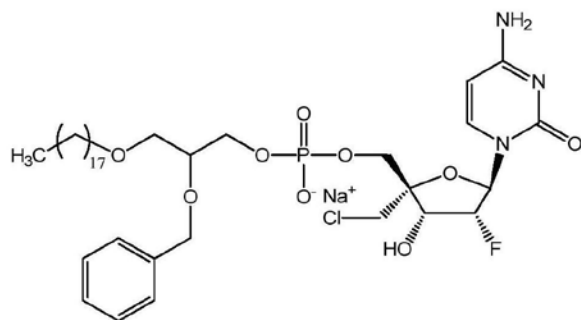
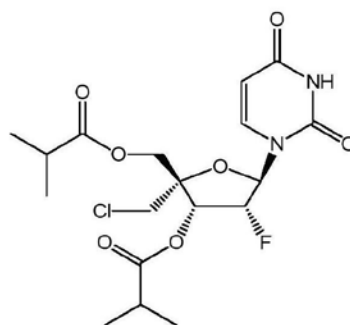
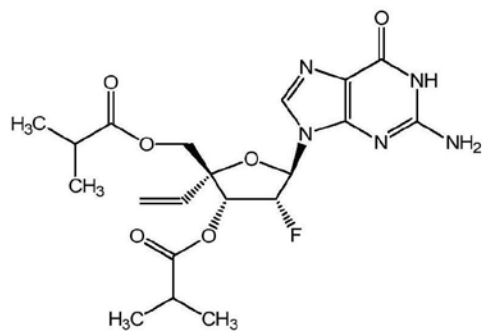
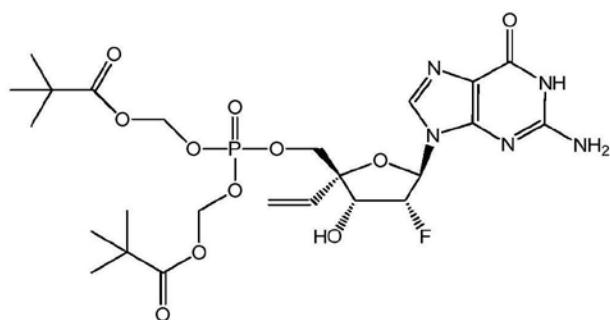
[0213]



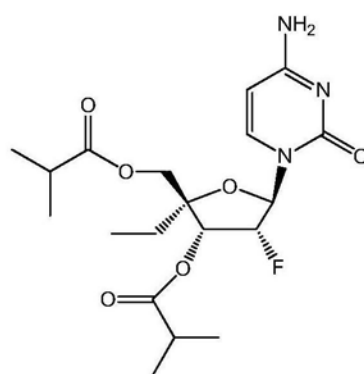
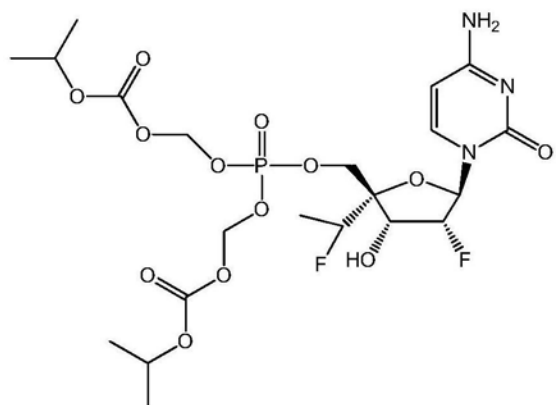
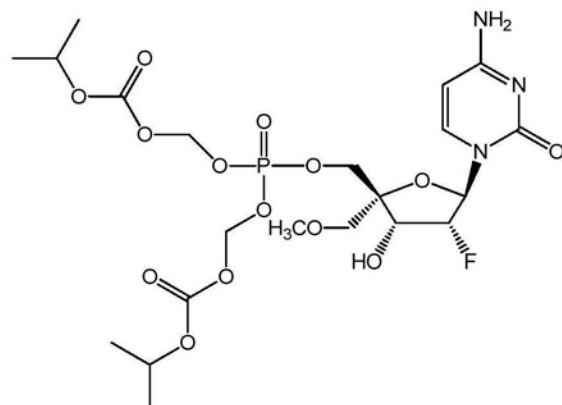
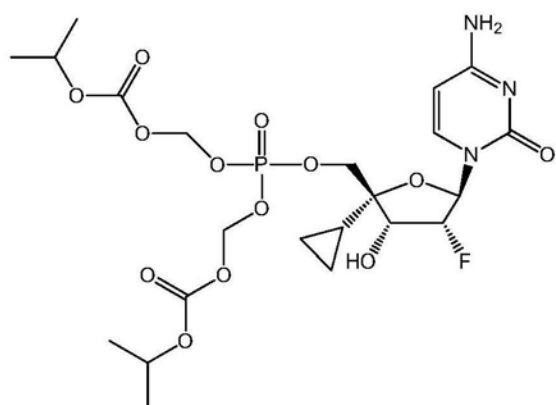
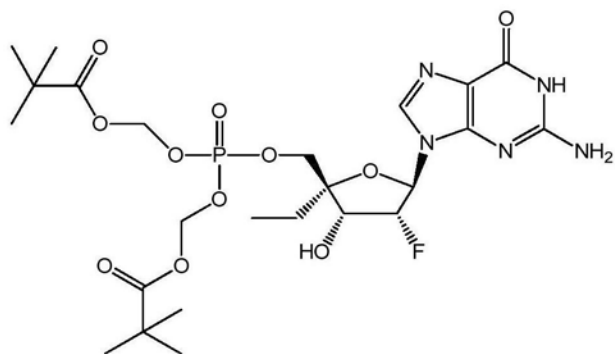
[0214]



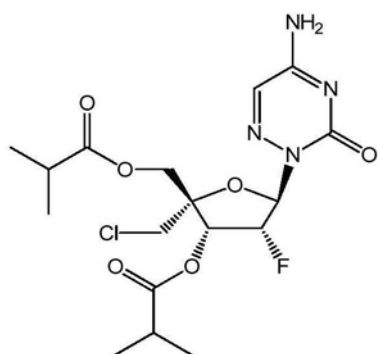
[0215]



[0216]



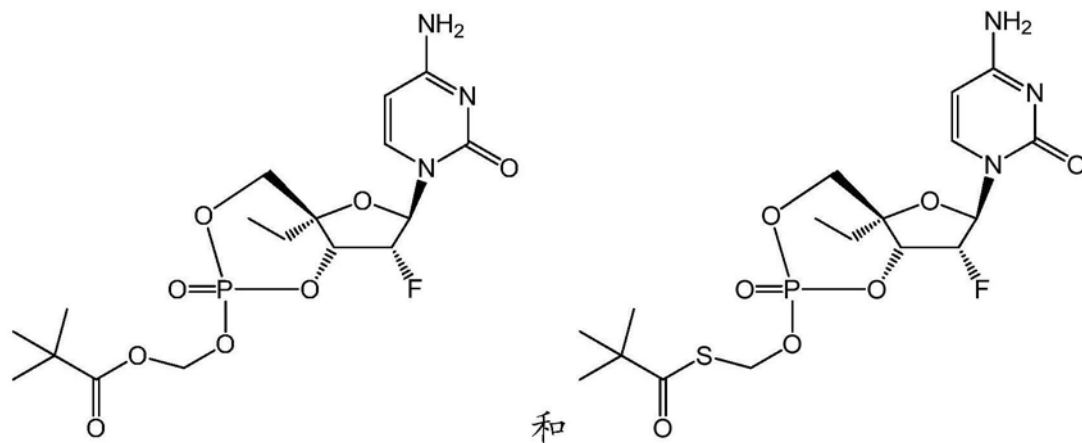
和



或前述的药物可接受的盐。

[0217] 式 (II) 化合物的实例包括但不限于下列：

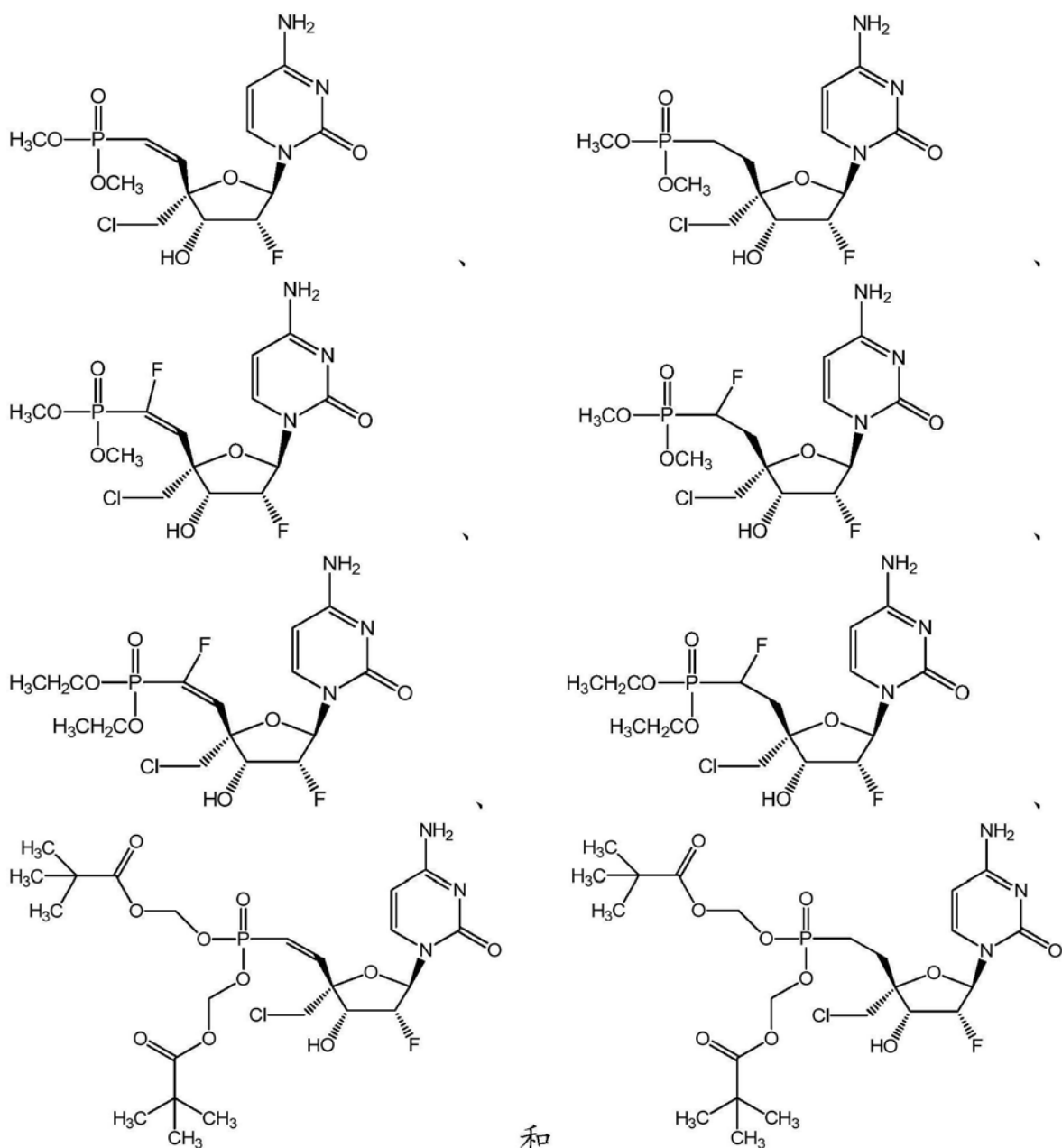
[0218]



或前述的药物可接受的盐。

[0219] 式 (III) 化合物的实例包括但不限于下列：

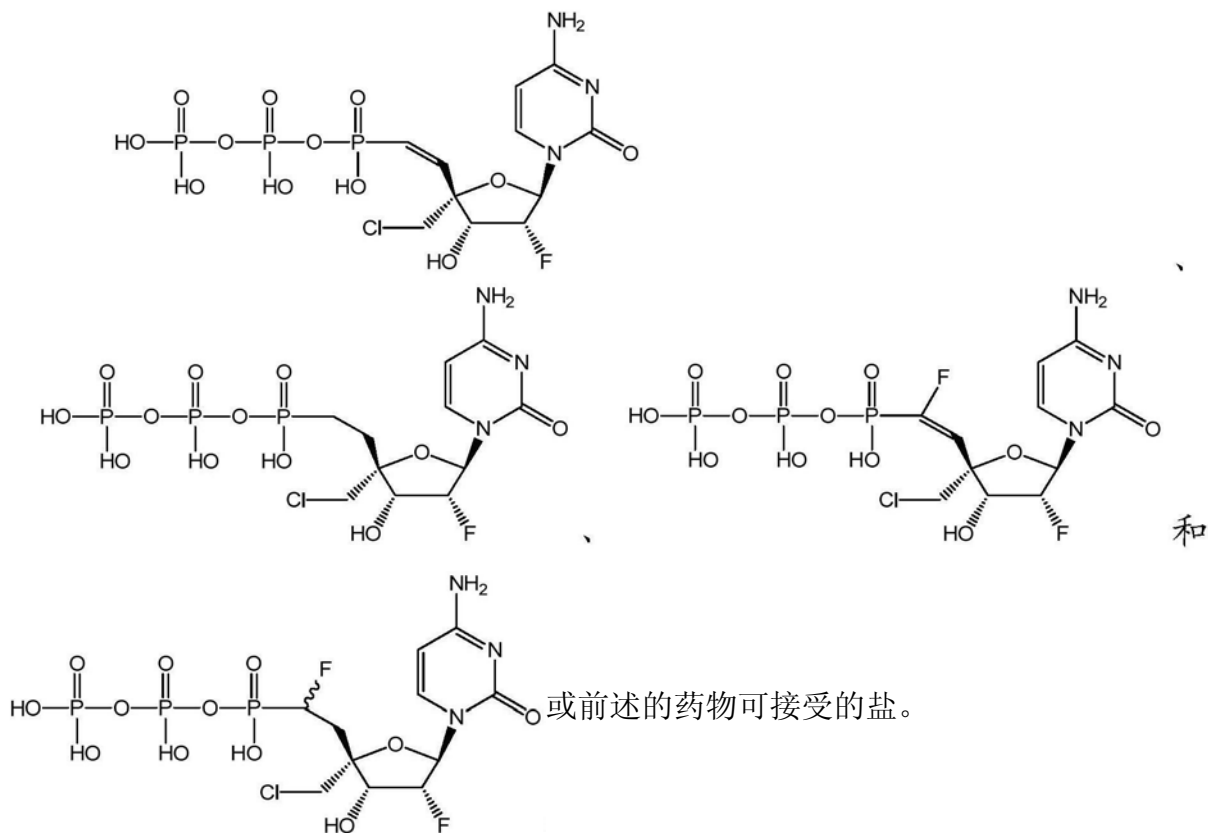
[0220]



[0221] 或前述的药物可接受的盐。

[0222] 式 (III) 化合物的其他实例包括但不限于下列：

[0223]

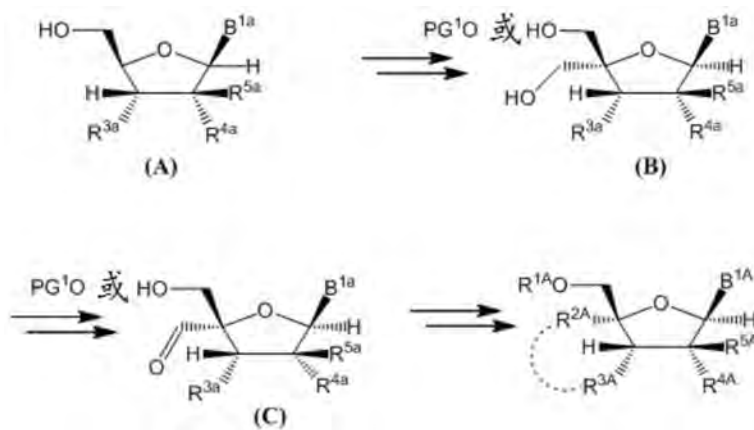


[0224] 合成

[0225] 可以多种方式制备式 (I)、式 (II) 和式 (III) 化合物和本文描述的那些化合物。能商业获得和 / 或使用已知合成步骤制备一些式 (I)、(II) 和 (III) 的化合物。式 (I)、(II) 和 (III) 化合物的一般合成路线和一些用于合成式 (I)、(II) 和 (III) 化合物的起始原料的实例在本文示出和描述。本文示出和描述的路线仅为例示性的并且不意图也不将它们解释为以任何方式限制权利要求的范围。本领域技术人员能够了解对所公开的合成的修改并且能够基于本文的公开内容设计替代的合成路线 ; 所有这样的修改和替代合成路线在权利要求范围内。

[0226] 反应方案 1

[0227]

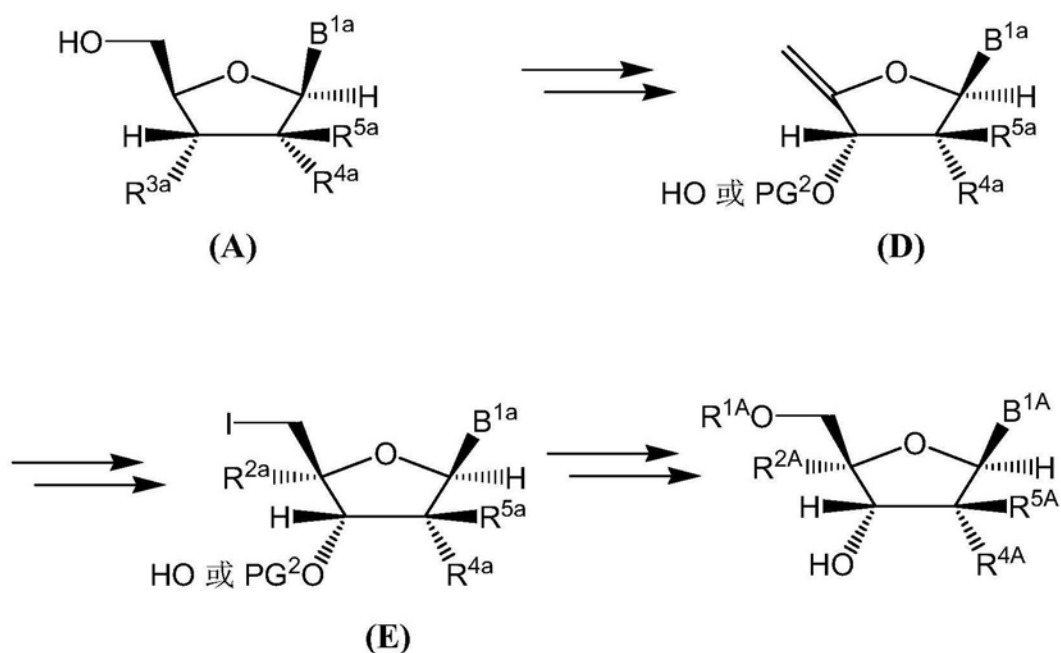


[0228] 如反应方案 1 所示,能从核苷,例如,式 (A) 的核苷制备式 (I) 的化合物。在反应方案 1 中, R^{3a} 、 R^{4a} 、 R^{5a} 和 B^{1a} 可与 R^{3A} 、 R^{4A} 、 R^{5A} 相同,并且 B^{1A} 与本文对式 (I) 的描述相同,并且 PG^1 为适合的保护基团。能使用本领域技术人员已知的合适条件在戊糖环的 4' - 位形成羟基烷基。用于形成羟基烷基的合适条件的实例包括使用 2- 碘酰基苯甲酸 (IBX) 甲醛水溶液和硼氢化钠。能使用适合的氧化剂将式 (B) 的化合物氧化为醛以形成式 (C) 的化合物。适合的氧化剂的实例为戴斯 - 马丁氧化剂 (Dess-Martin periodinane)。能使用本领域技术人员已知的方法在 4' - 位形成任选取代的 C_{2-6} 烯基或任选取代的 C_{2-6} 炔基,例如, Wittig 试剂和 $n\text{-BuLi}$ 、Wittig- 型反应、Peterson 烯化反应和 Corey Fuchs 反应。可通过将与 4' - 位连接的不饱和基团氢化 (例如,在钯 / 碳上使用氢气) 来获得任选取代的 C_{1-6} 烷基。

[0229] 或者,能使用适合的试剂将式 (B) 的化合物转化为卤代烷基,例如,使用咪唑、三苯基膦和碘转化为碘化物;使用二乙基氨基三氟化硫 (DAST) 转化为氟;或使用三苯基膦和四氯化碳的二氯乙烯 (DCE) 转化为氯。能使用本领域已知的方法将碘烷基转化为未取代的 C_{1-6} 烷基,例如,在钯 / 碳上的氢气。能使式 (C) 的化合物与羟胺反应以形成肟。能使用本领域已知的方法将肟转化为氰基,例如,使用甲烷磺酰氯。

[0230] 反应方案 2

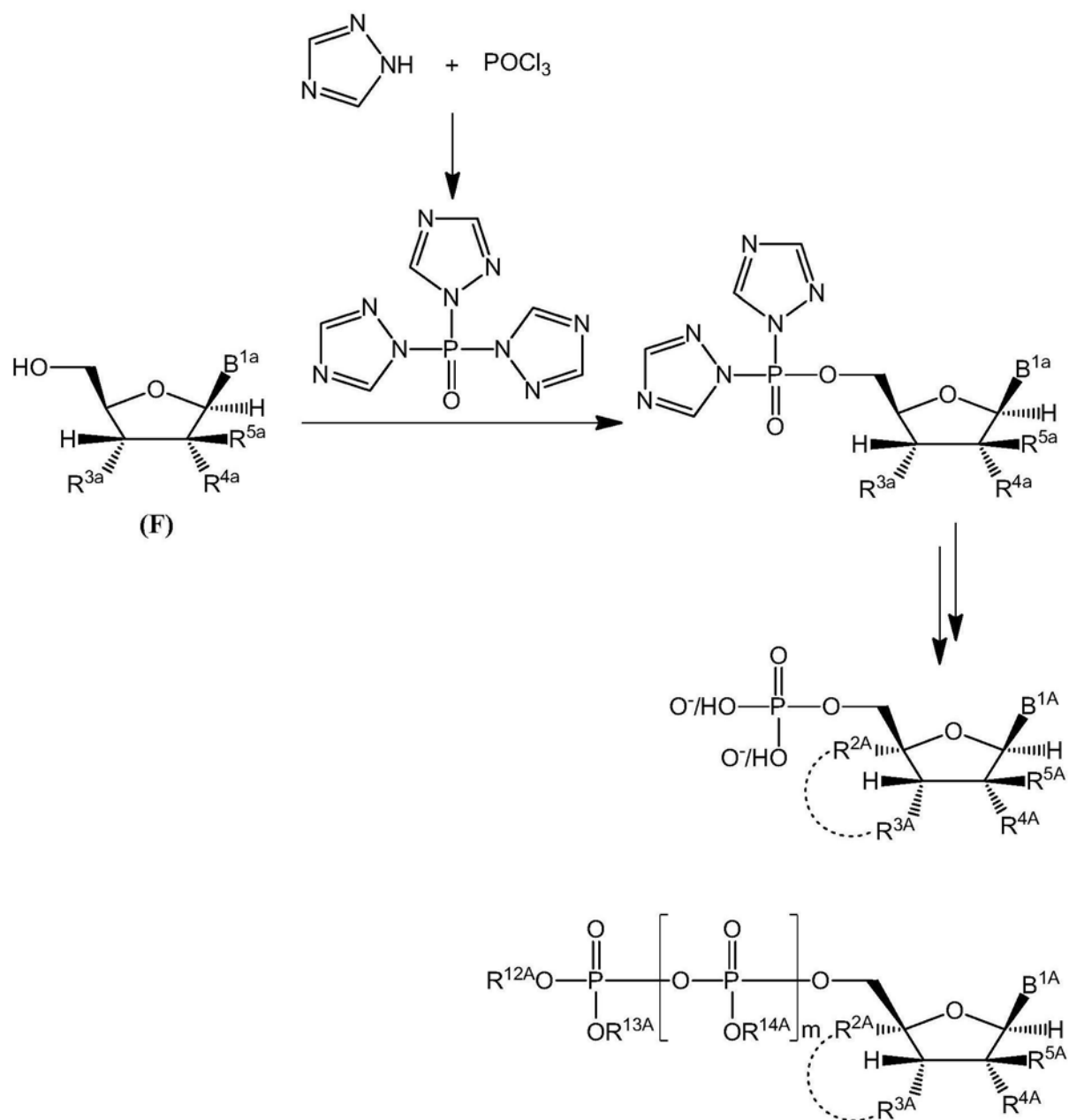
[0231]



[0232] 如反应方案 2 所示, 在 R^{2A} 为任选取代的 $-O-C_{1-6}$ 烷基、任选取代的 $-O-C_{3-6}$ 烯基或任选取代的 $-O-C_{3-6}$ 炔基的情况下, 能从核苷, 例如, 式 (A) 的核苷制备式 (I) 的化合物。在反应方案 2 中, R^{2a} 、 R^{3a} 、 R^{4a} 、 R^{5a} 和 B^{1a} 能可与 R^{2A} 、 R^{3A} 、 R^{4A} 、 R^{5A} 相同并且 B^{1A} 能与本文对式 (I) 的描述相同, 并且 PG^2 可为适合的保护基团。核苷能经历消除并且形成具有式 (D) 的一般式的烯烃。在碳酸铅和炔氧基源的存在下, 能使用碘化试剂处理式 (D) 的化合物以形成式 (E) 的化合物。然后, 能通过使用氧亲核试剂置换碘化物将式 (E) 的化合物转化为式 (I) 的化合物。

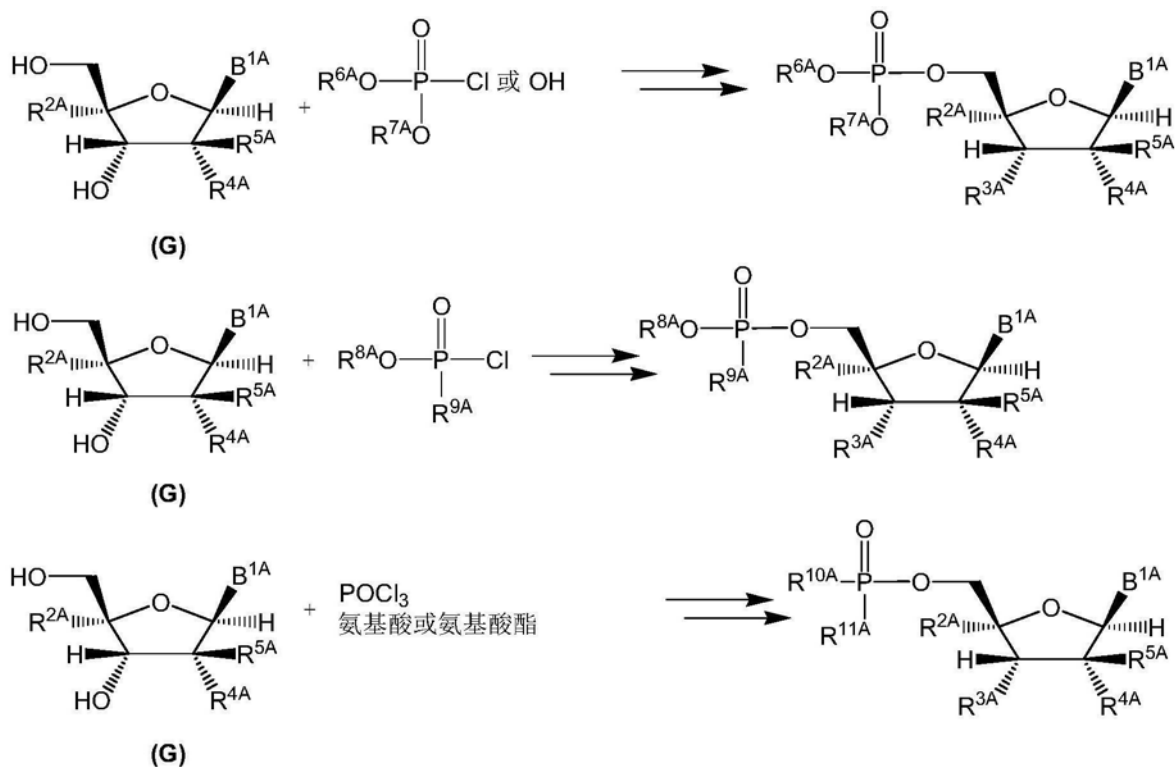
[0233] 反应方案 3

[0234]



[0235] 反应方案 4

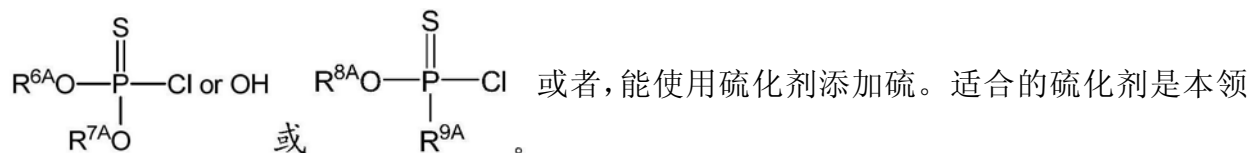
[0236]



[0237] 能使用本领域技术人员已知的多种方法制备具有与戊糖环的 5' - 位连接的含磷基团的式 (I) 化合物。方法的实例在反应方案 3 和 4 中示出。能将含磷前体与核苷偶联, 例如, 式 (F) 的化合物或式 (G) 的化合物。如反应方案 3 所示, 在含磷前体的偶联之后, 例如, 能在诸如水解的合适条件下断裂任何离去基团。能使用本领域技术人员已知的方法添加另外的含磷基团, 例如使用焦磷酸盐。

[0238] 在一些实施方案中, 能使用诸如 Grignard 试剂的有机金属试剂从式 (G) 的化合物产生醇盐。能将醇盐与含磷前体偶联。适合的 Grignard 试剂是本领域技术人员已知的并且包括但不限于烷基氯化镁和烷基溴化镁。在一些实施方案中, 能使用适合的碱基。适合的碱基的实例包括但不限于胺碱基、例如烷基胺 (包括一烷基胺、二烷基胺和三烷基胺 (例如, 三乙基胺))、任选取代的吡啶 (例如, 三甲吡啶) 和任选取代的咪唑 (例如, N- 甲基咪唑)。或者, 能将含磷前体加入至核苷并形成亚磷酸盐。能使用本领域技术人员已知的条件将亚磷酸盐氧化为磷酸盐。适合的条件包括但不限于间氯过氧苯甲酸 (MCPBA) 和碘作为氧化剂和水作为氧供体。

[0239] 当式 (I) 的化合物具有是硫的 Z^{1A} 、 Z^{2A} 或 Z^{3A} 时, 能以本领域技术人员已知的多种方式添加硫。在一些实施方案中, 硫可为含磷前体的一部分, 例如,

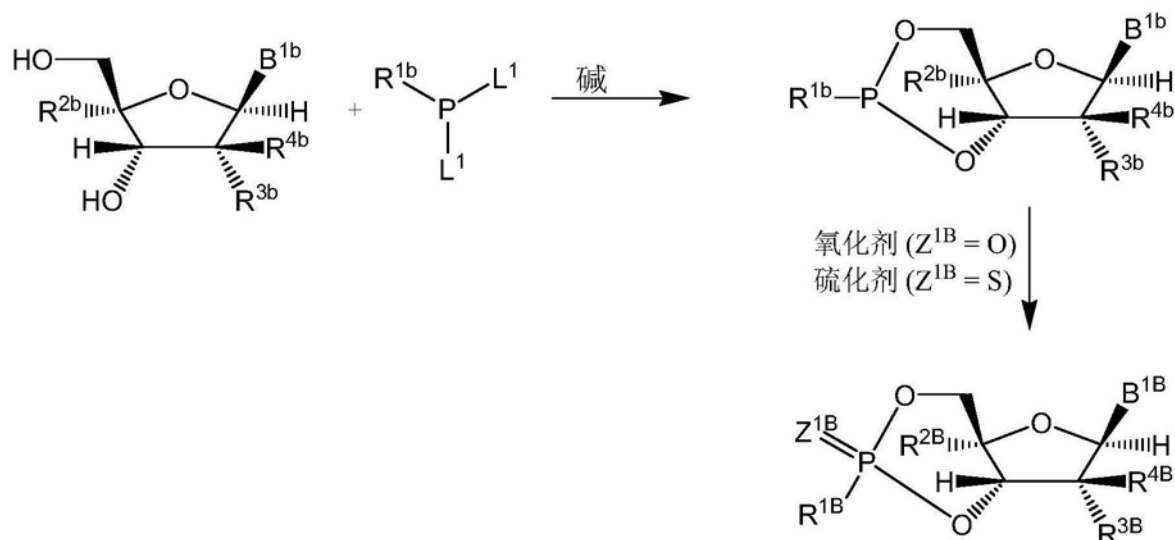


域技术人员已知, 并且包括但不限于, 元素硫、Lawesson 试剂、环八硫、3H-1, 2- 苯并二硫杂环戊二烯-3- 酮-1, 1- 二氧化物 (Beaucage 试剂)、3-((N, N- 二甲基氨基亚甲基) 氨基)-3H-1, 2, 4- 二噻唑-5- 硫酮 (DDTT) 和双 (3- 三乙氧基甲硅烷基) 丙基-四硫化物 (TEST)。

[0240] 适合的含磷前体能商购获得或通过本领域技术人员已知的合成方法制备。含磷前体的一般结构的实例在反应方案 3 和 4 中示出。

[0241] 反应方案 5：

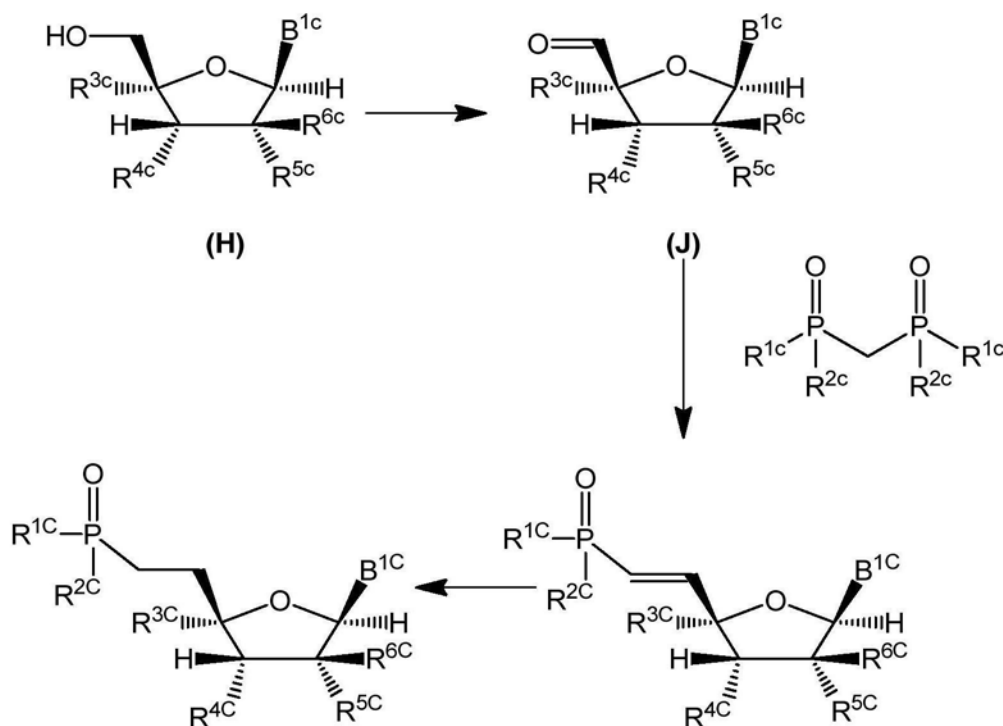
[0242]



[0243] 形成式 (II) 化合物的方法在反应方案 5 中示出。在反应方案 5 中, R^{1b} 、 R^{2b} 、 R^{3b} 、 R^{4b} 和 B^{1b} 可与 R^{1B} 、 R^{2B} 、 R^{3B} 、 R^{4B} 相同且和 B^{1B} 与本文对式 (II) 的描述相同, 各个 L^1 可为卤素、磺酸酯或胺 (一取代或二取代的), 且 X 可为氧或硫。如反应方案 5 所示, 在碱的存在下, 能使具有与 3'-碳连接的羟基和与 5'-碳连接的羟基的化合物与具有式 $(R^{1b})P(L^1)_2$ 的化合物反应, 以产生亚磷酸盐化合物。适合的碱是本领域技术人员已知的并且在本文描述。然后, 能使用适合的氧化剂将磷氧化为磷 (V) 以产生其中 X 为 O (氧) 的化合物。或者, 能使亚磷酸盐化合物与硫化剂反应以产生其中 X 为 S (硫) 的化合物。适合的氧化剂和硫化剂是本领域技术人员已知的。例如, 能使用碘作为氧化剂和水作为氧供体进行氧化。适合的硫化剂在本文描述。

[0244] 反应方案 6

[0245]



[0246] 用于形成式 (III) 化合物的方法在反应方案 6 中示出。在反应方案 6 中, R^{1c} 、 R^{2c} 、 R^{3c} 、 R^{4c} 、 R^{5c} 、 R^{6c} 和 B^{1c} 能与 R^{1c} 、 R^{2c} 、 R^{3c} 、 R^{4c} 、 R^{5c} 、 R^{6c} 相同并且 B^{1c} 与本文对式 (III) 的描述相同, 且 R^{7c} 和 R^{8c} 未示出。能使用本领域技术人员已知的方法和试剂将与式 (H) 化合物的 5'-碳连接的氧原子氧化为酮。例如, 能使用诸如戴斯-马丁氧化剂的氧化剂。然后, 在强碱 (例如, 氢化钠) 的存在下, 能将含磷试剂加入至式 (J) 的化合物。能例如, 使用氢气或 Pd/C 将双键氢化为单键。能使用诸如焦磷酸盐 (例如, 焦磷酸四丁基铵) 的适合的试剂, 通过磷酸化添加另外的磷酸盐以形成二磷酸盐或三磷酸盐。

[0247] 能使用本领域技术人员已知的方法在式 (I) 或 (III) 化合物的 5'-位和 / 或 3'-位添加酰基。一种适合的方法是使用酸酐的吡啶溶液。

[0248] 在合成任何本文描述的化合物过程中, 如果需要, 能使用一个或多个适合的保护基团保护任何与戊糖环连接的羟基、和任何 B^{1a} 、 B^{1b} 和 B^{1c} 上存在的 $-NH$ 和 / 或 NH_2 基团。适合的保护基团在本文描述。例如, 当 R^{3a} 和 / 或 R^{4c} 为羟基时, 能使用三芳基甲基或甲硅烷基保护 R^{3a} 和 / 或 R^{4c} 。同样地, 能使用例如三芳基甲基和甲硅烷基保护 B^{1a} 、 B^{1b} 和 B^{1c} 上存在的任何 $-NH$ 和 / 或 NH_2 基团。三芳基甲基的实例包括但不限于三苯甲基、一甲氧基三苯甲基 (MMTr)、4, 4'-二甲氧基三苯甲基 (DMTr)、4, 4', 4''-三甲氧基三苯甲基 (TMTr)、4, 4', 4''-三 (苯甲酰基氧基) 三苯甲基 (TBTr)、4, 4', 4''-三 (4, 5-二氯苯二甲酰亚氨基) 三苯甲基 (CPTTr)、4, 4', 4''-三 (乙酰丙基氧基 (levulinyloxy)) 三苯甲基 (TLTr)、对茴香基-1-萘基苯基甲基、二-邻茴香基-1-萘基甲基、对甲苯基二苯基甲基、3-(咪唑基甲基)-4, 4'-二甲氧基三苯甲基、9-苯基咕吨-9-基 (Pixyl)、9-(对甲氧基苯基) 咕吨-9-基 (Mox)、4-癸氧基三苯甲基、4-十六烷氧基三苯甲基、4, 4'-双十八烷基三苯甲基、9-(4-十八烷氧基苯基) 咕吨-9-基、1, 1'-双 (4-甲氧基苯基)-1'-苈基甲基、4, 4', 4''-三 (叔丁基苯基) 甲基 (TTTr) 和 4, 4'-二-3, 5-己二烯氧基三苯甲基。甲硅烷基的实例包括但不限于三甲基甲硅烷基 (TMS)、叔丁基二甲基甲硅烷基 (TBDMS)、三异丙基甲硅烷基 (TIPS)、叔丁基二苯基甲硅烷基 (TBDPS)、三异丙基甲硅烷基氧基甲基和 [2-(三甲基甲硅烷基) 乙氧基] 甲基。

或者,例如,通过形成原酸酯、环缩醛或环缩酮, R^{3a} 和 R^{4a} 和/或 R^{4c} 和 R^{5c} 可被单独的非手性或手性保护基团保护。适合的原酸酯包括甲氧基亚甲基缩醛、乙氧基亚甲基缩醛、2-氧代环亚戊基原酸酯、二甲氧基亚甲基原酸酯、1-甲氧基亚乙基原酸酯、1-乙氧基亚乙基原酸酯、亚甲基原酸酯、四氯苯酞原酸酯 1,2-二甲氧基亚乙基原酸酯和 α -甲氧基亚苄基原酸酯;适合的环缩醛包括亚甲基缩醛、亚乙基缩醛、叔丁基亚甲基缩醛、3-(苄氧基)丙基缩醛、亚苄基缩醛、3,4-二甲氧基亚苄基缩醛和对乙酰氧基亚苄基缩醛;且适合的环缩酮包括 1-叔丁基亚乙基缩酮、1-苄基亚乙基缩酮、异亚丙基缩酮、环亚戊基缩酮、环亚己基缩酮、环亚庚基缩酮和 1-(4-甲氧基苄基)亚乙基缩酮。本领域技术人员理解能使用各种保护基团保护与戊糖环连接的基团和任何 B^{1a} 、 B^{1b} 和 B^{1c} 上存在的 $-NH$ 和/或 NH_2 基团,并且能将任何存在的保护基团交换为其他保护基团。保护基团的选择和交换在本领域一般技术人员的技术范围内。能通过本领域已知的方法去除任何保护基团,例如,使用酸(例如,矿物酸或有机酸)、碱或氟化物源。

[0249] 药物组合物

[0250] 本文描述的一些实施方案涉及可包含有效量的一种或多种本文描述的化合物(例如,式(I)的化合物、式(II)的化合物和/或式(III)的化合物或前述的药物可接受的盐)和药物可接受的载体、稀释剂、赋形剂或其组合的药物组合物。

[0251] 术语“药物组合物”是指一种或多种本文公开的化合物与诸如稀释剂或载体的其他化学组分的混合物。药物组合物促进化合物向生物体的给药。还能通过使化合物与无机或有机酸反应获得药物组合物,所述酸例如氢氯酸、氢溴酸、硫酸、硝酸、磷酸、甲烷磺酸、乙烷磺酸、对甲苯磺酸和水杨酸。通常,调整药物组合物以适应特殊预期给药途径。

[0252] 术语“生理学可接受的”定义不破坏化合物的生物活性和性质的载体、稀释剂或赋形剂。

[0253] 如本文使用的,“载体”是指促进化合物进入细胞或组织的化合物。例如而不受限制,二甲基亚砜(DMSO)是促进许多有机化合物摄入个体的细胞或组织的通常使用的载体。

[0254] 如本文使用的,“稀释剂”是指缺乏药理学活性但可为药物必需或期望的药物组合物中的成分。例如,稀释剂可用于增加质量对于制备和/或给药太小的强效药的体积。它还可用于溶解药物以通过注射、摄食或吸入给药的液体。本领域稀释剂的常见形式为缓冲水溶液,例如但不限于模拟人血液组合物的磷酸盐缓冲盐水。

[0255] 如本文使用的,“赋形剂”是指加入至药物组合物以向组合物提供但不限于体积、一致性、稳定性、结合能力、润滑、崩解能力等的惰性物质。“稀释剂”为一种类型的赋形剂。

[0256] 能将本文描述的药物组合物本身、或者以将它们与其他活性成分混合的药物组合物形式、以组合疗法形式、或以载体、稀释剂、赋形剂或其组合形式给予人患者。适合的制剂依赖选择的给药途径。用于配制和给予本文描述的化合物的技术是本领域技术人员已知的。

[0257] 可以本身已知的方式制备本文公开的药物组合物,例如,通过常规混合、溶解、造粒、糖衣丸制备、粉碎、乳化、封装、包埋或制片方法。此外,以获得其预期目的有效的量包含活性成分。可以具有药物相容的抗衡离子的盐形式提供许多可用于本文公开的药物组合的化合物。

[0258] 本领域存在许多给予化合物的技术,其包括但不限于口服、直肠、局部、气雾剂、注

射和肠胃外递送,包括肌内注射、皮下注射、静脉内注射、髓内注射、鞘内注射、直接心室内注射、腹膜内注射、鼻内注射和眼内注射。

[0259] 还可以局部而非全身方式给予化合物,例如,通过将化合物直接注射至感染区域,常为持续释放或缓释制剂的形式。此外,可以标靶药物递送系统给予化合物,例如,为涂覆有组织特异性抗体的脂质体的形式。脂质体将以器官为靶向并且被器官有选择地吸收。

[0260] 如果需要,可以包含一个或多个包含活性成分的单位剂型的包装或分配器装置提供组合物。所述包装可例如包括金属或塑料箔,例如泡罩包装。包装或分配器装置可随附给药说明书。包装或分配器还可随附与由管理药物的制备、使用或销售的政府机构所规定的形式的容器有关的注意事项,所述注意事项反映人药或兽医管理机构形式的许可。例如,这种注意事项可为美国食品和药品管理局对方药批准的标签,或批准的产品插入物。还可制备在相容的药物载体中配制的包含本文描述的化合物的组合物,放置在适合的容器中并且用标签说明用于治疗所示疾病状态。

[0261] 使用方法:

[0262] 本文描述的一些实施方案涉及减轻、治疗和/或预防选自副粘病毒病毒感染和正粘病毒病毒感染的病毒感染的方法,其可包括给予对象有效量的一种或多种本文描述的化合物,或包含一种或多种本文描述的化合物(例如,式(I)的化合物、式(II)的化合物和/或式(III)的化合物或前述的药物可接受的盐)的药物组合物。在一些实施方案中,对象被确认为患有病毒感染(例如,副粘病毒病毒感染或正粘病毒病毒感染)。

[0263] 本文描述的其他实施方案涉及抑制选自副粘病毒和正粘病毒的病毒的病毒复制的方法,其可包括使感染病毒的细胞与有效量的式(I)的化合物或其药物可接受的盐、有效量的式(II)的化合物或其药物可接受的盐、有效量的式(III)的化合物或其药物可接受的盐、和/或包含一种或多种本文描述的化合物(例如,式(I)的化合物、式(II)的化合物和/或式(III)的化合物或前述的药物可接受的盐)的药物组合物接触。

[0264] 本文描述的其他实施方案涉及有效量的选自式(I)、式(II)和式(III)的化合物或前述的药物可接受的盐用于减轻或治疗由病毒引起的病毒感染的用途,所述病毒选自亨尼帕病毒属、麻疹病毒属、呼吸道病毒属、腮腺炎病毒属和偏肺病毒属。本文描述的其他实施方案还涉及减轻或治疗由病毒引起的病毒感染的方法,包括将有效量的选自式(I)、式(II)和式(III)的化合物或前述的药物可接受的盐给予对象中的细胞或者使对象中的细胞与有效量的选自式(I)、式(II)和式(III)的化合物或前述的药物可接受的盐接触,其中所述病毒可选自亨尼帕病毒属、麻疹病毒属、呼吸道病毒属、腮腺炎病毒属和偏肺病毒属。本文所述的其他实施方案还涉及有效量的选自式(I)、式(II)和式(III)的化合物或前述的药物可接受的盐,用于抑制选自亨尼帕病毒属、麻疹病毒属、呼吸道病毒属、腮腺炎病毒属和偏肺病毒属的病毒的复制(例如通过抑制所述病毒的聚合酶复合物)的用途。

[0265] 在一些实施方案中,有效量的一种或多种式(I)的化合物或其药物可接受的盐、一种或多种式(II)的化合物或其药物可接受的盐、有效量的一种或多种式(III)的化合物或其药物可接受的盐、和/或包含一种或多种本文描述的化合物(例如,式(I)的化合物、式(II)的化合物和/或式(III)的化合物或前述的药物可接受的盐)的药物组合物能用于治疗并/或减轻呼吸道合胞体病毒(RSV)感染。在一些实施方案中,有效量的一种或多种式(I)的化合物或其药物可接受的盐、一种或多种式(II)的化合物或其药物可接受的

盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物 (例如, 式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物或前述的药物可接受的盐) 的药物组合物能用于预防呼吸道合胞体病毒感染。在一些实施方案中, 有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物 (例如, 式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物或前述的药物可接受的盐) 的药物组合物能用于抑制呼吸道合胞体病毒的复制。在一些实施方案中, 有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物 (例如, 式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物或前述的药物可接受的盐) 的药物组合物能用于抑制 RSV 聚合酶复合物。

[0266] 在其他实施方案中, 有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物 (例如, 式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物或前述的药物可接受的盐) 的药物组合物能用于治疗 / 或减轻流感病毒感染。在其他实施方案中, 有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物 (例如, 式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物或前述的药物可接受的盐) 的药物组合物能用于预防流感病毒感染。在一些实施方案中, 有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物 (例如, 式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物或前述的药物可接受的盐) 的药物组合物能用于抑制流感病毒的复制。在一些实施方案中, 有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物 (例如, 式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物或前述的药物可接受的盐) 的药物组合物能用于抑制流感聚合酶复合物。

[0267] 在一些实施方案中, 有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐, 和 / 或包含一种或多种本文所述的化合物 (例如, 式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物, 或前述的药物可接受的盐) 的药物组合物, 可用于治疗和 / 或减轻亨尼帕病毒属感染。在一些实施方案中, 有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐, 和 / 或包含一种或多种本文所述的化合物 (例如, 式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物, 或前述的药物可接受的盐) 的药物组合物, 可用于防止亨尼帕病毒属感染和 / 或尼帕病毒 (nipahviral) 感染。在一些实施方案中, 有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种

或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐, 和 / 或包含一种或多种本文所述的化合物 (例如, 式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物, 或前述的药物可接受的盐) 的药物组合物, 可用于抑制亨尼帕病毒属复制。在一些实施方案中, 有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐, 和 / 或包含一种或多种本文所述的化合物 (例如, 式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物, 或前述的药物可接受的盐) 的药物组合物, 可用于抑制亨尼帕病毒属聚合酶复合物和 / 或尼帕病毒聚合酶复合物。

[0268] 在一些实施方案中, 有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物 (例如, 式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物或前述的药物可接受的盐) 的药物组合物能用于治疗 / 或减轻亨尼帕病毒属感染和 / 或尼帕病毒感染。在一些实施方案中, 有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物 (例如, 式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物或前述的药物可接受的盐) 的药物组合物能用于预防亨尼帕病毒属感染和 / 或尼帕病毒感染。在一些实施方案中, 有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物 (例如, 式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物或前述的药物可接受的盐) 的药物组合物能用于抑制亨尼帕病毒属病毒和 / 或尼帕病毒的复制。在一些实施方案中, 有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物 (例如, 式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物或前述的药物可接受的盐) 的药物组合物能用于抑制亨尼帕病毒属病毒聚合酶复合物和 / 或尼帕病毒聚合酶复合物。

[0269] 在一些实施方案中, 有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐, 和 / 或包含一种或多种本文所述的化合物 (例如, 式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物, 或前述的药物可接受的盐) 的药物组合物, 可用于治疗和 / 或减轻麻疹病毒属感染。在一些实施方案中, 有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐, 和 / 或包含一种或多种本文所述的化合物 (例如, 式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物, 或前述的药物可接受的盐) 的药物组合物, 可用于防止麻疹病毒属感染。在一些实施方案中, 有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐, 和 / 或包含一种或多种本文所述的化合物 (例如, 式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物, 或

前述的药物可接受的盐)的药物组合物,可用于抑制麻疹病毒属的复制。在一些实施方案中,有效量的一种或多种式(I)的化合物或其药物可接受的盐、一种或多种式(II)的化合物或其药物可接受的盐、有效量的一种或多种式(III)的化合物或其药物可接受的盐,和/或包含一种或多种本文所述的化合物(例如,式(I)的化合物、式(II)的化合物和/或式(III)的化合物,或前述的药物可接受的盐)的药物组合物,可用于抑制麻疹病毒属聚合酶复合物。

[0270] 在一些实施方案中,有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物 (例如,式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物或前述的药物可接受的盐) 的药物组合物能用于治疗 / 或减轻麻疹。在一些实施方案中,有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物 (例如,式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物或前述的药物可接受的盐) 的药物组合物能用于预防麻疹。在一些实施方案中,有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物 (例如,式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物或前述的药物可接受的盐) 的药物组合物能用于抑制麻疹病毒的复制。在一些实施方案中,有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物 (例如,式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物或前述的药物可接受的盐) 的药物组合物能用于抑制麻疹聚合酶复合物。

[0271] 在一些实施方案中,有效量的一种或多种式(I)的化合物或其药物可接受的盐、一种或多种式(II)的化合物或其药物可接受的盐、有效量的一种或多种式(III)的化合物或其药物可接受的盐,和/或包含一种或多种本文所述的化合物(例如,式(I)的化合物、式(II)的化合物和/或式(III)的化合物,或前述的药物可接受的盐)的药物组合物,可用于治疗和/或减轻腮腺炎病毒属感染。在一些实施方案中,有效量的一种或多种式(I)的化合物或其药物可接受的盐、一种或多种式(II)的化合物或其药物可接受的盐、有效量的一种或多种式(III)的化合物或其药物可接受的盐,和/或包含一种或多种本文所述的化合物(例如,式(I)的化合物、式(II)的化合物和/或式(III)的化合物,或前述的药物可接受的盐)的药物组合物,可用于防止腮腺炎病毒属感染。在一些实施方案中,有效量的一种或多种式(I)的化合物或其药物可接受的盐、一种或多种式(II)的化合物或其药物可接受的盐、有效量的一种或多种式(III)的化合物或其药物可接受的盐,和/或包含一种或多种本文所述的化合物(例如,式(I)的化合物、式(II)的化合物和/或式(III)的化合物,或前述的药物可接受的盐)的药物组合物,可用于抑制腮腺炎病毒属复制。在一些实施方案中,有效量的一种或多种式(I)的化合物或其药物可接受的盐、一种或多种式(II)的化合物或其药物可接受的盐、有效量的一种或多种式(III)的化合物或其药物可接受的盐,和/或包含一种或多种本文所述的化合物(例如,式(I)的化合物、式(II)的化合物和/或式

(III) 的化合物,或前述的药物可接受的盐) 的药物组合物,可用于抑制腮腺炎病毒属聚合酶复合物。

[0272] 在一些实施方案中,有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物 (例如,式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物或前述的药物可接受的盐) 的药物组合物能用于治疗 / 或减轻腮腺炎。在一些实施方案中,有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物 (例如,式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物或前述的药物可接受的盐) 的药物组合物能用于预防腮腺炎。在一些实施方案中,有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物 (例如,式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物或前述的药物可接受的盐) 的药物组合物能用于抑制腮腺炎病毒属的复制。在一些实施方案中,有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物 (例如,式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物或前述的药物可接受的盐) 的药物组合物能用于抑制腮腺炎聚合酶复合物。

[0273] 在一些实施方案中,有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物 (例如,式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物、或前述的药物可接受的盐) 的药物组合物能用于治疗 / 或减轻仙台病毒感染。在一些实施方案中,有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物 (例如,式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物、或前述的药物可接受的盐) 的药物组合物能用于预防仙台病毒感染。在一些实施方案中,有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物 (例如,式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物、或前述的药物可接受的盐) 的药物组合物能用于抑制仙台病毒的复制。在一些实施方案中,有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物 (例如,式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物、或前述的药物可接受的盐) 的药物组合物能用于抑制仙台病毒聚合酶复合物。

[0274] 在一些实施方案中,有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物 (例如,式 (I) 的化合物、

式 (II) 的化合物和 / 或式 (III) 的化合物、或前述的药物可接受的盐) 的药物组合物, 可用于治疗和 / 或减轻呼吸道病毒属感染。在一些实施方案中, 有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物 (例如, 式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物、或前述的药物可接受的盐) 的药物组合物, 可用于防止呼吸道病毒属感染。在一些实施方案中, 有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物 (例如, 式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物、或前述的药物可接受的盐) 的药物组合物, 可用于抑制呼吸道病毒属复制。在一些实施方案中, 有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物 (例如, 式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物、或前述的药物可接受的盐) 的药物组合物, 可用于抑制呼吸道病毒属聚合酶复合物。

[0275] 在一些实施方案中, 有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物 (例如, 式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物、或前述的药物可接受的盐) 的药物组合物能用于治疗 and / 或减轻 HPIV-1 感染和 / 或 HPIV-3 感染。在一些实施方案中, 有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物 (例如, 式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物、或前述的药物可接受的盐) 的药物组合物能用于预防 HPIV-1 感染和 / 或 HPIV-3 感染。在一些实施方案中, 有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物 (例如, 式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物、或前述的药物可接受的盐) 的药物组合物能用于抑制 HPIV-1 和 / 或 HPIV-3 的复制。在一些实施方案中, 有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物 (例如, 式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物、或前述的药物可接受的盐) 的药物组合物能用于抑制 HPIV-1 聚合酶复合物和 / 或 HPIV-3 聚合酶复合物。

[0276] 在一些实施方案中, 有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物 (例如, 式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物、或前述的药物可接受的盐) 的药物组合物能用于治疗 and / 或减轻 HPIV-2 感染和 / 或 HPIV-4 感染。在一些实施方案中, 有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的

盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物 (例如, 式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物、或前述的药物可接受的盐) 的药物组合物能用于预防 HPIV-2 感染和 / 或 HPIV-4 感染。在一些实施方案中, 有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物 (例如, 式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物、或前述的药物可接受的盐) 的药物组合物能用于抑制 HPIV-2 和 / 或 HPIV-4 的复制。在一些实施方案中, 有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物 (例如, 式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物、或前述的药物可接受的盐) 的药物组合物能用于抑制 HPIV-2 聚合酶复合物和 / 或 HPIV-4 聚合酶复合物。

[0277] 在一些实施方案中, 有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物 (例如, 式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物、或前述的药物可接受的盐) 的药物组合物能用于治疗 / 或减轻偏肺病毒属感染。在一些实施方案中, 有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物 (例如, 式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物、或前述的药物可接受的盐) 的药物组合物能用于预防偏肺病毒属感染。在一些实施方案中, 有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物 (例如, 式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物、或前述的药物可接受的盐) 的药物组合物能用于抑制偏肺病毒属的复制。在一些实施方案中, 有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物 (例如, 式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物、或前述的药物可接受的盐) 的药物组合物能用于抑制偏肺病毒属聚合酶复合物。在包括本段落的实施方案的一些实施方案中, 偏肺病毒属可为人偏肺病毒。

[0278] 在一些实施方案中, 有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物的药物组合物 (例如, 式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物、或前述的药物可接受的盐) 能用于治疗 / 或减轻由选自亨尼帕病毒属、麻疹病毒属、呼吸道病毒属、腮腺炎病毒属、肺病毒属、偏肺病毒属和流感病毒的病毒引起的上呼吸道感染。在一些实施方案中, 有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物的药物组合物 (例如, 式 (I) 的化合物、式 (II) 的化合物和 / 或

式 (III) 的化合物、或前述的药物可接受的盐) 能用于治疗 and / 或减轻由选自亨尼帕病毒属、麻疹病毒属、呼吸道病毒属、腮腺炎病毒属、肺病毒属、偏肺病毒属和流感病毒的病毒引起的下呼吸道病毒感染。在一些实施方案中, 有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物的药物组合物 (例如, 式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物、或前述的药物可接受的盐) 能用于治疗 and / 或减轻一种或多种由选自亨尼帕病毒属、麻疹病毒属、呼吸道病毒属、腮腺炎病毒属、肺病毒属、偏肺病毒属和流感病毒 (例如本文描述的那些) 的病毒引起的感染的症状。

[0279] 在一些实施方案中, 有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物的药物组合物 (例如, 式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物、或前述的药物可接受的盐) 能用于治疗 and / 或减轻由 RSV 感染、麻疹、腮腺炎、副流感病毒感染、偏肺病毒属和 / 或流感感染引起的上呼吸道病毒感染。在一些实施方案中, 有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物的药物组合物 (例如, 式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物、或前述的药物可接受的盐) 能用于治疗 and / 或减轻由 RSV 感染、麻疹、腮腺炎、副流感病毒感染、偏肺病毒属和 / 或流感感染引起的下呼吸道病毒感染。在一些实施方案中, 有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物的药物组合物 (例如, 式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物、或前述的药物可接受的盐) 能用于治疗 and / 或减轻一种或多种由 RSV 感染、麻疹、腮腺炎、副流感病毒感染、偏肺病毒属和 / 或流感感染 (例如, 本文描述的那些) 引起的感染的症状。

[0280] 在一些实施方案中, 有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物的药物组合物 (例如, 式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物、或前述的药物可接受的盐) 能用于治疗 and / 或减轻由于 RSV 感染、流感感染和 / 或人副流感病毒病毒 3 (HPIV-3) 感染产生的细支气管炎和 / 或气管支气管炎。在一些实施方案中, 有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物的药物组合物 (例如, 式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物、或前述的药物可接受的盐) 能用于治疗 and / 或减轻由于 RSV 感染、流感感染和 / 或人副流感病毒病毒 3 (HPIV-3) 感染产生的肺炎。在一些实施方案中, 有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合

物的药物组合物（例如，式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物、或前述的药物可接受的盐）能用于治疗 and / 或减轻由于 RSV 感染、流感感染和 / 或人副流感病毒病毒 1 (HPIV-1) 感染产生的喉头炎。

[0281] 在一些实施方案中，有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物的药物组合物（例如，式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物、或前述的药物可接受的盐）能用于治疗 and / 或减轻由于麻疹产生的发烧、咳嗽、流鼻涕、红眼、全身皮疹、肺炎、耳感染和 / 或支气管炎。在一些实施方案中，有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物的药物组合物（例如，式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物、或前述的药物可接受的盐）能用于治疗 and / 或减轻由于腮腺炎产生的唾液腺红肿、发烧、食欲不振和 / 或疲乏。

[0282] 在一些实施方案中，有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物的药物组合物（例如，式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物、或前述的药物可接受的盐）能用于预防流感病毒感染。在一些实施方案中，流感病毒感染可为甲型流感病毒感染。在其他实施方案中，流感病毒感染可为乙型流感病毒感染。在其他实施方案中，流感病毒感染可为丙型流感病毒感染。在一些实施方案中，一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、和 / 或一种或多种式 (III) 的化合物或其药物可接受的盐能用于治疗 and / 或减轻一种或多种流感亚型。例如，一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、和 / 或一种或多种式 (III) 的化合物或其药物可接受的盐可用于治疗 H1N1 和 / 或 H3N2。

[0283] 在一些实施方案中，有效量的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、有效量的一种或多种式 (III) 的化合物或其药物可接受的盐、和 / 或包含一种或多种本文描述的化合物的药物组合物（例如，式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物、或前述的药物可接受的盐）能用于预防人副流感病毒病毒感染。在一些实施方案中，人副流感病毒病毒感染可为人副流感病毒病毒 1 (HPIV-1)。在其他实施方案中，人副流感病毒病毒感染可为人副流感病毒病毒 2 (HPIV-2)。在其他实施方案中，人副流感病毒病毒感染可为人副流感病毒病毒 3 (HPIV-3)。在其他实施方案中，人副流感病毒病毒感染可为人副流感病毒病毒 4 (HPIV-4)。在一些实施方案中，一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、和 / 或一种或多种式 (III) 的化合物或其药物可接受的盐能用于治疗 and / 或减轻一种或多种人副流感病毒病毒亚型。例如，一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的化合物或其药物可接受的盐、和 / 或一种或多种式 (III) 的化合物或其药物可接受的盐能用于治疗 HPIV-1 和 / 或 HPIV-3。

[0284] 用于治疗、减轻和 / 或预防副粘病毒 (paramyxovirus) 和 / 或正粘病毒 (orthomyxovirus) 病毒感染的一种或多种式 (I) 的化合物或其药物可接受的盐、一种或多种式 (II) 的

化合物或其药物可接受的盐、和 / 或一种或多种式 (III) 的化合物或其药物可接受的盐可为在段落 [0084]–[0170] 中描述的任何实施方案中提供的式 (I) 的化合物或其药物可接受的盐、和 / 或式 (II) 的化合物或其药物可接受的盐、和 / 或式 (III) 的化合物或其药物可接受的盐。

[0285] 如本文使用的,术语“预防 (prevent)”和“预防 (preventing)”是指由于对象对所述感染具有免疫力对象未发展感染,或者如果对象被感染,与对象没有给予 / 接受所述化合物的对象的疾病的严重程度相比,疾病的严重程度较小。预防形式的实例包括向已经或可能暴露于诸如副粘病毒 (例如 RSV) 和 / 或正粘病毒 (例如,流感) 的传染剂的对象预防性给药。

[0286] 如本文使用的,术语“治疗 (treat)”、“治疗 (treating)”、“治疗 (treatment)”、“治疗 (therapeutic)”和“治疗 (therapy)”不一定是指完全治愈或废除疾病或疾病状态。疾病或疾病状态的任何不期望迹象或症状的任何程度的减轻可被认为是治疗 (treatment) 和 / 或治疗 (therapy)。此外,治疗可包括可能使对象的健康或外观的总体感觉恶化的行动。

[0287] 术语“治疗有效量”和“有效量”用于表示诱导指定的生物或药物反应的活性化合物或药物剂的量。例如,化合物的治疗有效量可为预防、减少或减轻疾病症状或延长受治疗对象的存活所需的量。该反应可在组织系统、动物或人中发生并且包括减轻受治疗疾病的迹象或症状。根据本文公开的内容,有效量的确定在本领域技术人员的技术范围内。以剂量形式需要的本文公开的化合物的治疗有效量依赖给药途径、受治疗的包括人的动物类型和研究中的特定动物的体貌特征。可调整剂量以达到期望效果,但根据诸如体重、饮食、并发药物和药学领域技术人员知道的其他因素。

[0288] 用于确定治疗诸如副粘病毒和 / 或正粘病毒感染的病毒感染的方法的有效性的各种指标是本领域技术人员已知的。合适指标的实例包括但不限于病毒载量的减少、病毒复制的减少、血清转化 (患者血清中不可检测的病毒) 时间的减少、临床结果中发病率或死亡率的减少和 / 或疾病反应的其他指标。

[0289] 在一些实施方案中,式 (I)、(II) 和 / 或 (III) 化合物或前述的药物可接受的盐的有效量是有效地将病毒滴度降低至不可检测水平的量,例如,至约 1000 至约 5000、至约 500 至约 1000、或至约 100 至约 500 基因组拷贝 /mL 血清。在一些实施方案中,式 (I)、(II) 和 / 或 (III) 化合物或前述的药物可接受的盐的有效量是与给予式 (I)、(II) 和 / 或 (III) 的化合物或前述的药物可接受的盐之前的病毒载量相比减少病毒载量有效的量。例如,其中病毒载量是给予式 (I)、(II) 和 / 或 (III) 化合物或前述的药物可接受的盐之前和在再次使用式 (I)、(II) 和 / 或 (III) 化合物或前述的药物可接受的盐完成治疗方案之后 (例如,完成后 1 周) 的量度。在一些实施方案中,式 (I)、(II) 和 / 或 (III) 化合物或前述的药物可接受的盐的有效量可为减少病毒载量至低于约 100 基因组拷贝 /mL 血清有效的量。在一些实施方案中,式 (I)、(II) 和 / 或 (III) 化合物或前述的药物可接受的盐的有效量是与给予式 (I)、(II) 和 / 或 (III) 化合物或前述的药物可接受的盐之前的病毒载量相比,有效实现对象血清中病毒滴度减少为约 1.5-log 至约 2.5-log 减少、约 3-log 至约 4-log 减少、或大于约 5-log 减少的量。例如,其中病毒载量是给予式 (I)、(II) 和 / 或 (III) 化合物或前述的药物可接受的盐之前和在再次使用式 (I)、(II) 和 / 或 (III) 化合物或前述的

药物可接受的盐完成治疗方案之后（例如，完成后 1 周）的量度。

[0290] 在一些实施方案中，式 (I)、(II) 和 / 或 (III) 化合物或前述的药物可接受的盐可导致相对于对象中治疗前水平的副粘病毒和 / 或正粘病毒复制至少 1、2、3、4、5、10、15、20、25、50、75、100- 倍或更多的减少，如在完成治疗方案之后（例如，完成后 1 周）测定的。在一些实施方案中，式 (I)、(II) 和 / 或 (III) 化合物或前述的药物可接受的盐可导致相对于约 2 至约 5 倍、约 10 至约 20 倍、约 15 至约 40 倍、或约 50 至约 100 倍的治疗前水平的副粘病毒和 / 或正粘病毒复制的减少。在一些实施方案中，与通过利巴韦林(**Virazole®**)获得的副粘病毒减少相比，式 (I)、(II) 和 / 或 (III) 化合物或前述的药物可接受的盐能导致副粘病毒复制减少 1 至 1.5log、1.5log 至 2log、2log 至 2.5log、2.5 至 3log、3log 至 3.5log 或 3.5 至 4log 更多减少，或者可在更短时间内获得与利巴韦林(**Virazole®**)治疗相同的减少，例如，在一周、两周、一个月、两个月或三个月内，与在利巴韦林(**Virazole®**) 治疗六个月后获得的减少相比。在一些实施方案中，与通过奥司他韦 (**Tamiflu®**) 获得的正粘病毒减少相比，式 (I)、(II) 和 / 或 (III) 化合物或前述的药物可接受的盐可导致正粘病毒复制减少 1 至 1.5log、1.5log 至 2log、2log 至 2.5log、2.5 至 3log、3log 至 3.5log 或 3.5 至 4log 更多减少，或者可在更短时间内获得与奥司他韦(**Tamiflu®**)治疗相同的减少，例如，在一周、两周、一个月、两个月或三个月内，与在奥司他韦(**Tamiflu®**) 治疗六个月后获得的减少相比。

[0291] 在一些实施方案中，有效量的式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物、或前述的药物可接受的盐是获得持续病毒反应有效的量，例如，在停止治疗后，在对象血清中发现不可检测或基本上不可检测的副粘病毒和 / 或正粘病毒 RNA（例如，少于约 500、少于约 400、少于约 200 或少于约 100 基因组拷贝每毫升血清），时间为至少约一周、两周、一个月、至少约两个月、至少约三个月、至少约四个月、至少约五个月或至少约六个月。

[0292] 一段时间后，传染剂能产生对一种或多种治疗剂的耐药性。如本文使用的，术语“耐药性”是指对治疗剂表现出延迟、减少和 / 或零反应的病毒菌株。例如，在使用抗病毒剂治疗后，与通过感染非耐药菌株量的对象显示的病毒载量减少相比，可将感染耐药病毒的对象病毒载量减少至更少程度。在一些实施方案中，可将式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物或前述的药物可接受的盐给予感染耐受一种或多种不同抗 RSV 剂（例如，利巴韦林）的 RSV 的对象。在一些实施方案中，与耐受其他 RSV 药物的 RSV 菌株的发展相比，当使用式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物或前述的药物可接受的盐的治疗对象时能延迟耐药 RSV 菌株的发展。在一些实施方案中，可将式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物或前述的药物可接受的盐给予感染耐受一种或多种不同抗流感剂（例如，金刚烷胺和金刚烷乙胺）的流感病毒的对象。在一些实施方案中，与耐受其他流感药物的流感菌株的发展相比，当使用式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物或前述的药物可接受的盐的治疗对象时能延迟耐药流感菌株的发展。

[0293] 在一些实施方案中，与经历使用利巴韦林治疗的并发症的对象的百分比相比，式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物或前述的药物可接受的盐可减少

经历来自 RSV 病毒感染的并发症的对象的百分比。在一些实施方案中,与经历使用奥司他韦治疗的并发症的对象的百分比相比,式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物或前述的药物可接受的盐可减少经历来自流感病毒感染的并发症的对象的百分比。例如,与使用利巴韦林或奥司他韦治疗的对象相比,经历并发症的使用式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物或前述的药物可接受的盐治疗的对象的比例可为 10%、25%、40%、50%、60%、70%、80% 和 90% 更少。

[0294] 在一些实施方案中,能结合一种或多种另外的试剂使用式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物或前述的药物可接受的盐,或包含本文描述的化合物的药物组合物。在一些实施方案中,能结合一种或多种目前用于治疗 RSV 的试剂使用式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物或前述的药物可接受的盐。例如,另外的试剂可为利巴韦林、帕利珠单抗和 RSV-IGIV。为了治疗 RSV,另外的试剂包括但不限于 ALN-RSV01 (Alnylam Pharmaceuticals)、BMS-433771 (1- 环丙基 -3-[[1-(4- 羟基丁基) 苯并咪唑 -2- 基] 甲基] 咪唑并 [4, 5-c] 吡啶 -2- 酮)、RFI-641 ((4, 4''- 双 {4, 6- 双 [3-(双氨基甲酰基甲基 - 氨磺酰基) - 苯基氨基] - (1, 3, 5) 三嗪 -2- 基氨基} - 联苯基 -2, 2''- 二磺酸))、RSV604 ((S)-1-(2- 氟苯基) -3-(2- 氧代 -5- 苯基 -2, 3- 二氢 -1H- 苯并 [e] [1, 4] 二 - 氮杂环庚烯 -3- 基) - 脲)、MDT-637 ((4Z)-2- 甲基磺酰基 -4-[(E)-3- 噻吩 -2- 基丙 -2- 亚烯基] -1, 3- 噻唑 -5- 酮)、BTA9881、TMC-353121 (Tibotec)、MBX-300、YM-53403 (N- 环丙基 -6-[4-[(2- 苯基苯甲酰基) 氨基] 苯甲酰基] -4, 5- 二氢噻吩并 [3, 2-d] [1] 苯并氮杂环庚烯基 -2- 甲酰胺)、莫维珠单抗 (Medi-524、MedImmune)、Medi-559、Medi-534、Medi-557、RV568 和 RSV-F 颗粒疫苗 (Novavax)。在一些实施方案中,能结合一种或多种目前用于治疗流感的试剂使用式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物、或前述的药物可接受的盐。例如,另外的试剂可为金刚烷胺、金刚烷乙胺、扎那米韦和奥司他韦。为了治疗流感,另外的试剂包括但不限于帕拉米韦 ((1S, 2S, 3S, 4R)-3-[(1S)-1- 乙酰胺基 -2- 乙基丁基] -4-(二氨基亚甲基氨基) -2- 羟基环戊烷 -1- 甲酸)、拉尼米韦 ((4S, 5R, 6R)-5- 乙酰胺基 -4- 甲脒基酰胺基 (carbamimidamido) -6-[(1R, 2R)-3- 羟基 -2- 甲氧基丙基] -5, 6- 二氢 -4H- 吡喃 -2- 甲酸)、法匹拉韦 (T-705、6- 氟 -3- 羟基 -2- 吡嗪甲酰胺)、流感酶 (DAS181、NexBio)、ADS-8902 (Adamas Pharmaceuticals)、IFN- β (Synairgen)、贝前列素 (4-[2- 羟基 -1-[(E)-3- 羟基 -4- 甲基八 -1- 烯 -6- 炔基] -2, 3, 3a, 8b- 四氢 -1H- 环戊二烯并 [b] [1] 苯并呋喃 -5- 基] 丁酸)、Neugene® 和 VGX-3400X (Inovio)。

[0295] 在一些实施方案中,能在单一药物组合物中与一种或多种另外的试剂一起给予式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物、或前述的药物可接受的盐。在一些实施方案中,能以两种或多种单独的药物组合物形式与一种或多种另外的试剂一起给予式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物或前述的药物可接受的盐。例如,能以一种药物组合物形式给予式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物或前述的药物可接受的盐,并且能以第二药物组合物形式给予至少一种另外的试剂。如果有至少两种另外的试剂,一种或多种另外的试剂能在包含式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物或前述的药物可接受的盐的第一药物组合物中,并且至少一种其他另外的试剂能在第二药物组合物中。

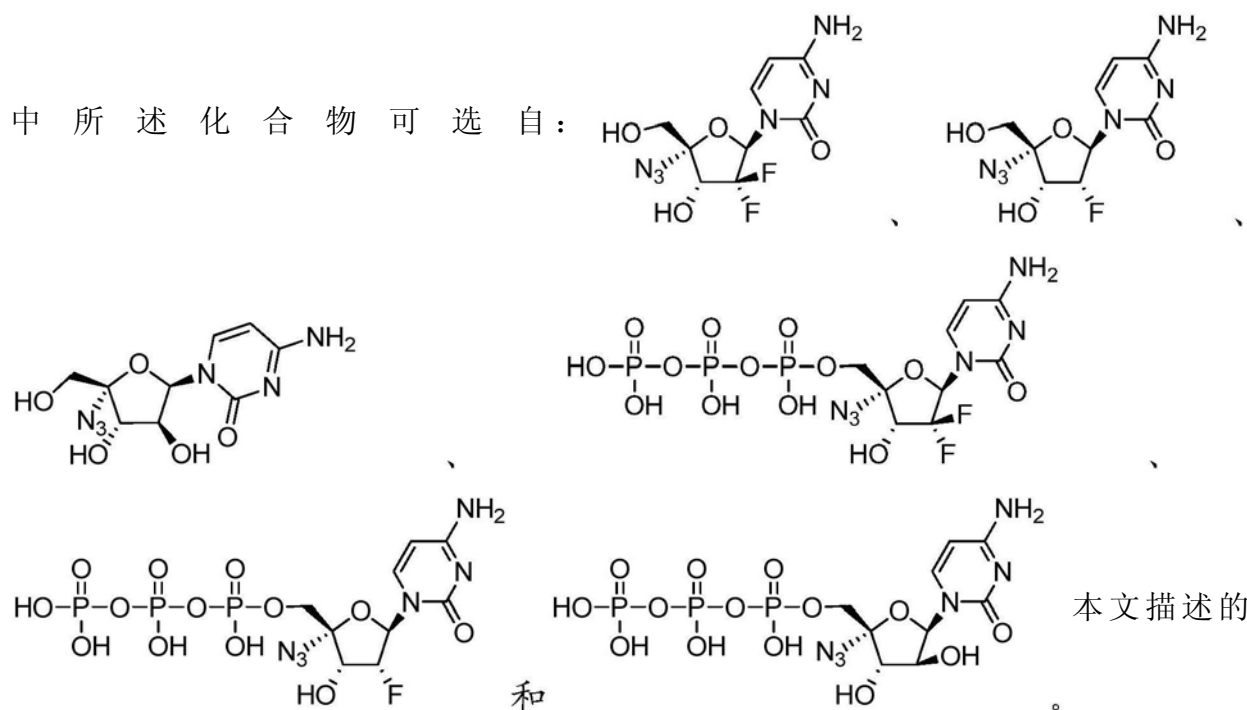
[0296] 式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物或前述的药物可接受的盐与一种或多种另外的试剂的给药顺序可变化。在一些实施方案中,能在所有另外的试剂之前给予式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物或前述的药物可接受的盐。在其他实施方案中,能在至少一种另外的试剂之前给予式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物或前述的药物可接受的盐。在其他实施方案中,能与一种或多种另外的试剂同时给予式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物或前述的药物可接受的盐。在其他实施方案中,能在至少一种另外的试剂给药之后给予式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物或前述的药物可接受的盐。在一些实施方案中,能在所有另外的试剂的给药之后给予式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物或前述的药物可接受的盐。

[0297] 使用式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物或前述的药物可接受的盐结合一种或多种段落 [0226] 中描述的另外的试剂包括其药物可接受的盐和前药的潜在优点可为减少一种或多种治疗本文公开的疾病疾病状态有效的段落 [0226] (包括其药物可接受的盐和前药) 的化合物的需要量 (例如, RSV 和 / 或流感), 与当给予一种或多种段落 [0226] 中描述的化合物, 包括其药物可接受的盐和前药而没有式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物或前述的药物可接受的盐时获得相同治疗结果需要的量相比。例如, 当以单一疗法给药时, 段落 [0226] 中描述的化合物包括其药物可接受的盐和前药的量能少于获得相同病毒载量减少需要的段落 [0226] 中描述的化合物包括其药物可接受的盐和前药的量。使用式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物或前述的药物可接受的盐结合一种或多种段落 [0226] 中描述的另外的试剂包括其药物可接受的盐和前药的另一潜在优点在于使用两种或多种具有不同作用机制的化合物能建立产生耐药病毒菌株更高的屏障, 当与以单一疗法形式给予化合物时的屏障相比。

[0298] 使用式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物或前述的药物可接受的盐结合一种或多种段落 [0226] 中描述的另外的试剂包括其药物可接受的盐和前药的其他优点可包括式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物或前述的药物可接受的盐和一种或多种段落 [0226] 中描述的另外的试剂 (包括其药物可接受的盐和前药) 之间的交叉耐药性较少甚至没有; 用于消除式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物或前述的药物可接受的盐和一种或多种段落 [0226] 中描述的另外的试剂 (包括其药物可接受的盐和前药) 的不同途径; 式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物或前述的药物可接受的盐和一种或多种段落 [0226] 中描述的另外的试剂 (包括其药物可接受的盐和前药) 之间的重叠毒性较少甚至没有; 对细胞色素 P450 的显著作用较少甚至没有; 和 / 或式 (I) 的化合物、式 (II) 的化合物和 / 或式 (III) 的化合物或前述的药物可接受的盐和一种或多种段落 [0226] 中描述的另外的试剂 (包括其药物可接受的盐和前药) 之间的药代动力学相互作用较少甚至没有。

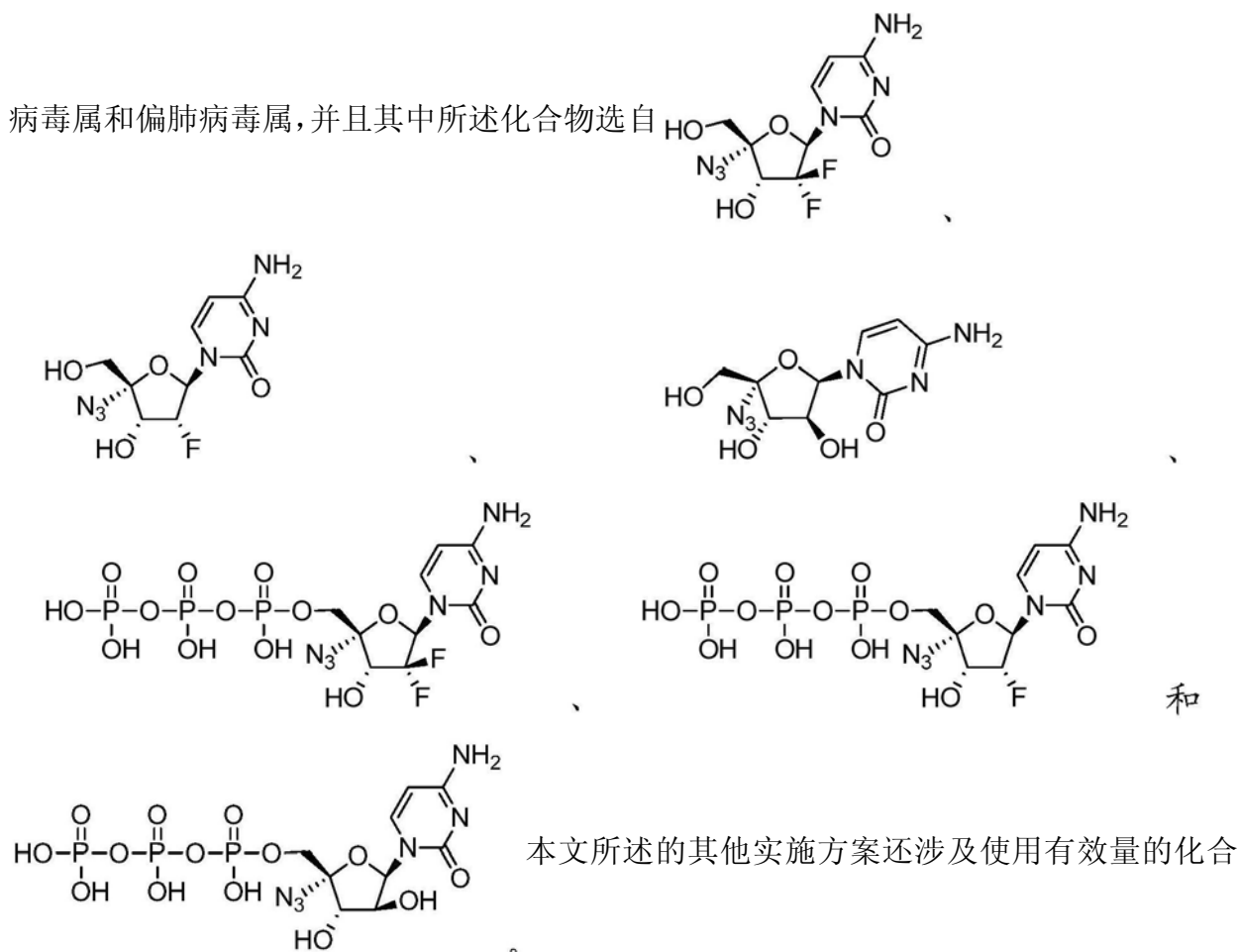
[0299] 本文描述的一些实施方案涉及有效量的化合物或其药物可接受的盐用于减轻或治疗由病毒引起的病毒感染的用途, 所述病毒选自亨尼帕病毒属、麻疹病毒属、呼吸道病毒属、腮腺炎病毒属和偏肺病毒属, 其

中所述化合物可选自：



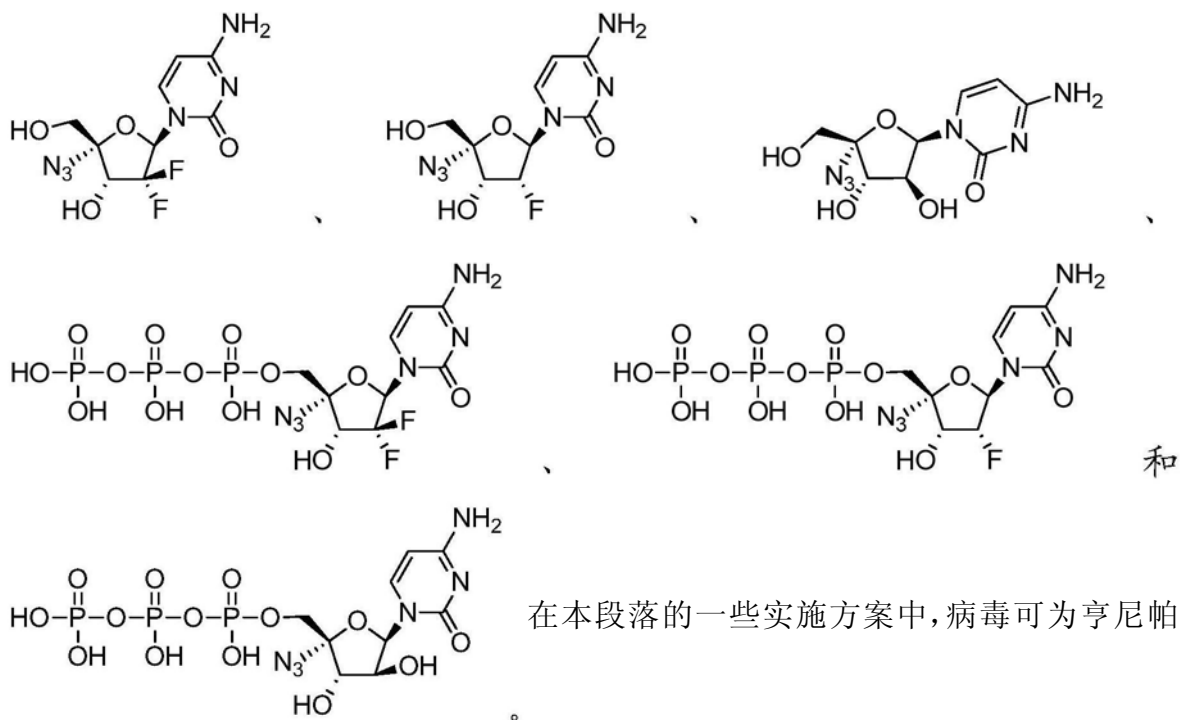
其他实施方案涉及减轻或治疗由病毒引起的病毒感染的方法,所述方法可包括将有效量的化合物或其药物可接受的盐给予对象中的细胞,或使对象中的细胞接触有效量的化合物或其药物可接受的盐,其中所述病毒选自亨尼帕病毒属、麻疹病毒属、呼吸道病毒属、腮腺炎

病毒属和偏肺病毒属,并且其中所述化合物选自



物或其药物可接受的盐抑制病毒复制,所述病毒选自亨尼帕病毒属、麻疹病毒属、呼吸道病毒属、腮腺炎病毒属和偏肺病毒属(例如,通过抑制所述病毒的聚合酶复合物),其中所述化合物可选自:

[0300]



在本段落的一些实施方案中,病毒可为亨尼帕病毒

属(例如,尼帕病毒)。在本段落的其他实施方案中,病毒可为麻疹病毒属,如麻疹病毒(measles virus)。在本段落的其他实施方案中,病毒可为呼吸道病毒属。在一些实施方案中,呼吸道病毒属可为人副流感病毒1。在其他实施方案中,呼吸道病毒属可为人副流感病毒3。在本段落的其他实施方案中,病毒可为腮腺炎病毒属。在一些实施方案中,腮腺炎病毒属可为人副流感病毒2。在其他实施方案中,腮腺炎病毒属可为人副流感病毒4。在其他实施方案中,腮腺炎病毒属可为腮腺炎病毒(mumps virus)。在本段落的一些实施方案中,病毒可为偏肺病毒属,如人偏肺病毒。

[0301] 如本领域技术人员容易理解的,待给予的有效体内剂量和特定的给药方式根据年龄、体重、痛苦的严重程度和受治疗的哺乳动物种类、使用的特殊化合物和这些化合物的特殊用途而变化。有效剂量水平的确定,即获得期望结果需要的剂量水平能由本领域技术人员使用常规方法,例如,人临床试验和体外研究来完成。

[0302] 剂量可能范围广泛,这取决于期望效果和治疗适应症。如本领域技术人员理解的,可基于或根据患者的表面积计算可选择剂量。尽管基于具体药物之间的情况来确定精确剂量,但在大多数情况下,能进行关于剂量的一些概括。成年人患者的每日剂量方案可为例如,0.01mg至3000mg的各个活性成分,优选1mg至700mg,例如5至200mg的口服剂量。剂量可为单独一种或在一天或多天期间给予的连续两种或多种,如对象需要的。在一些实施方案中,在连续治疗时间内给予化合物,例如一周或更多,或数月或数年。

[0303] 在其中针对至少一些疾病状态建立化合物的人剂量的实例中,可使用那些相同剂量,或约0.1%至500%、更优选约25%至250%的建立的人剂量的剂量。在没有建立人剂量的情况下,如新发现的药物组合物的情况,能从ED₅₀或ID₅₀值,或得自体外或体内研究的

其他合适值推测适合的人剂量,如通过动物中的毒性研究和功效研究限定的。

[0304] 在药物可接受的盐的给药的情况下,可以游离碱形式计算剂量。如本领域技术人员理解的,在一些情况下,可能需要以超过,或甚至远远超过上述规定的优选剂量范围的量给予本文公开的化合物以有效和积极地治疗治疗特殊的侵略性疾病或感染。

[0305] 可单独调整剂量和间隔以提供足以保持调节作用或最低有效浓度 (MEC) 的活性部分的血浆水平。MEC 针对各个化合物而变化但能从体外数据估算。获得 MEC 需要的剂量取决于对象特征和给药途径。然而,HPLC 检验或生物检验能用于测定血浆浓度。还能使用 MEC 值确定给药间隔。应使用保持血浆水平高于 MEC 时间为 10-90%,优选 30-90%且最优选 50-90%的方案给予组合物。在局部给药或有选择地吸收的情况下,药物的有效局部浓度可能不与血浆浓度相关。

[0306] 应当注意,主治医生知道由于毒性或器官功能障碍,如何及何时结束、中断或调整给药。相反地,主治医生还知道如果临床反应不充分(排除毒性)将调整治疗至较高水平。在相关病症的处理中给予的剂量的量级将随受治疗的疾病状态的严重程度和给药途径变化。可例如,部分地通过标准预后评价方法评价疾病状态的严重程度。此外,剂量和可能给药频率还根据各个患者的年龄、体重和反应而变化。与上述讨论相当的程序可用于兽医学。

[0307] 能使用已知方法评价本文公开化合物的功效和毒性。例如,可通过测定对例如哺乳动物并且优选人细胞系的细胞系的体外毒性来确定特定化合物或共享某些化学部分的化合物子集的毒理学。这些研究的结果常是动物(例如哺乳动物或更具体地人)中毒性的预测。或者,可使用已知方法测定动物模型(例如小鼠、大鼠、兔子或猴子)中特定化合物的毒性。可使用几种公认方法确定特定化合物的功效,例如体外方法、动物模型或人临床试验。当选择测定功效的模型时,技术人员可以当前的技术水平的指导来选择适合的模型、剂量、给药途径和/或方案。

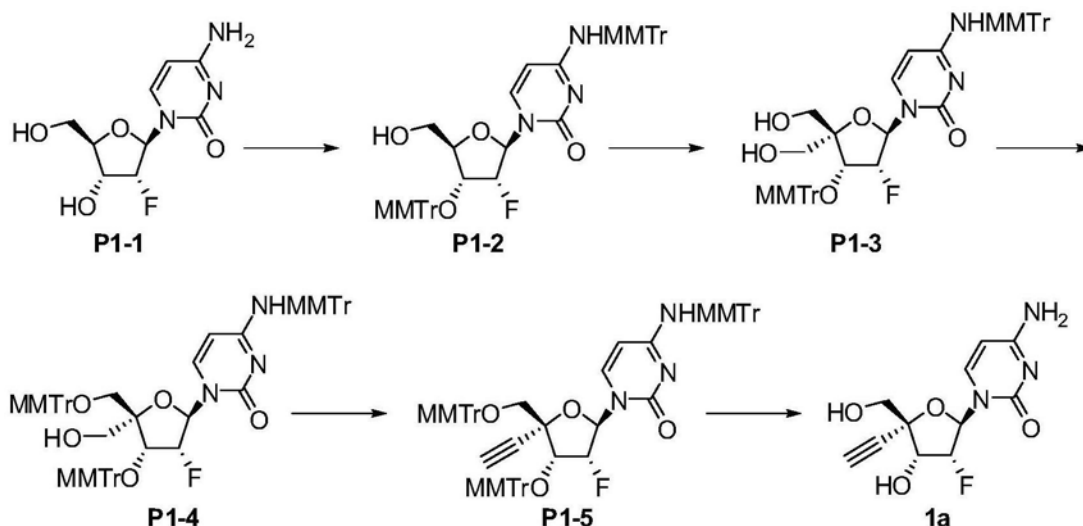
实施例

[0308] 在下列实施例中更详细地公开其他实施方案,所述实施例不意图以任何方式限制权利要求的范围。

[0309] 实施例 1

[0310] 化合物 (1a) 的制备

[0311]



[0312] (P1-2) 的制备: 在室温 (R. T.) 下, 向冰冷的 P1-1 (10. 0g, 40. 8mmol) 的干燥吡啶 (100mL) 溶液滴加 TBSCl 的吡啶 (1M, 53mL)。将反应混合物在 R. T. 下搅拌 16 小时。然后, 使用水淬灭反应混合物, 浓缩以产生剩余物。通过乙酸乙酯 (EA) 和饱和 NaHCO_3 水溶液分离剩余物。将有机相干燥并浓缩。在硅胶柱上 (5% MeOH 的 DCM 溶液) 纯化剩余物以产生白色固体形式的粗 5'-O-TBS 保护的中间体 (13. 4g, 91%)。将中间体溶于无水 DCM (100mL) 和对称三甲吡啶 (17. 9g, 149. 2mmol), 加入 AgNO_3 (25g, 149. 2mmol) 和 MMTrCl (45g, 149. 2mmol)。将混合物在 R. T. 下搅拌 16 小时。使用水淬灭混合物, 并将有机层分离并浓缩。在硅胶柱上 (30% PE 的 EA 溶液) 纯化剩余物以产生粗产物。将粗产物溶于 1M TBAF (50mL) 的 THF 溶液。将混合物在 R. T. 下搅拌 2 小时。去除溶剂, 并在硅胶柱上 (50% PE 的 EA 溶液) 纯化剩余物以产生白色固体形式的 P1-2 (21. 4g, 三步的产率为 66%)。

[0131] (P1-3) 的制备: 在氮气下, 在 10℃ 下向吡啶 (521mg, 6.59mmol) 的无水 DMSO (5mL) 溶液滴加 TFA (636mg, 5.58mmol)。将反应混合物搅拌直至溶液变澄清。然后, 在氮气下, 在 R. T. 下将溶液加入至 P1-2 (4.0g, 5.07mmol) 和 DCC (3.86g, 18.76mmol) 的无水 DMSO (18mL) 混合物。将反应混合物在 30℃ 下搅拌过夜。将水 (80mL) 加入至混合物, 使用 EtOAc (100mL) 稀释并过滤。使用 DCM (100mL × 6) 萃取滤液。The 使用饱和 NaHCO₃ 水溶液洗涤有机层, 干燥在 Na₂SO₄ 上并真空浓缩。在使用 1% MeOH 的 DCM 溶液洗脱的硅胶柱上纯化剩余物以产生黄色固体形式的中间体 (3.5g, 87.7%)。将中间体 (3.5g, 4.45mmol) 溶于二氧六环 (25mL) 并在 R. T. 下加入 HCHO 水溶液 (668mg, 22.25mmol), 然后加入 2N NaOH (4.5mL, 8.9mmol)。将反应混合物在 30℃ 下搅拌过夜。在 5℃ 下分批加入 NaBH₄ (593mg, 15.6mmol), 并将混合物在 R. T. 下搅拌 15min。使用水淬灭反应, 并使用 EtOAc (100mL × 3) 萃取混合物。在 Na₂SO₄ 上干燥有机层并真空浓缩。在使用 1% MeOH 的 DCM 溶液洗脱的硅胶柱上纯化剩余物以产生黄色固体形式的 P1-3 (2.5g, 67%)。¹H NMR (CDCl₃, 400MHz) δ 6.82-7.50 (m, 29H), 5.40 (d, J = 23.2Hz, 1H), 4.99 (d, J = 7.6Hz, 1H), 4.46 (dd, J₁ = 6.0Hz, J₂ = 54.4Hz, 1H), 3.94 (dd, J₁ = 4.4Hz, J₂ = 12.4Hz, 1H), 3.78 (s, 6H), 3.42-3.69 (m, 2H), 2.71-3.05 (m, 2H), 2.45 (m, 1H)。

[0314] (P1-4) 的制备: 向冰冷的 P1-3 (4.0g, 4.9mmol) 的干燥吡啶溶液 (20mL) 滴加 TBSCl 的吡啶溶液 (1M, 5.88mL)。将反应混合物在 R. T. 下搅拌 16 小时。然后, 使用水淬灭反应混合物, 浓缩以产生剩余物。在 EA 和饱和 NaHCO_3 水溶液中分离剩余物。将有机层分离并干燥, 然后浓缩。在硅胶柱上 (1% MeOH 的 DCM 溶液) 纯化剩余物以产生黄色固体

形式的中间体 (3.2g, 70%)。¹H NMR(CDCl₃, 400MHz) δ 7.53-6.83(m, 29H), 5.51(d, J = 21.2Hz, 1H), 4.98(d, J = 7.6Hz, 1H), 4.67(dd, J₁ = 5.6Hz, J₂ = 22.4Hz, 1H), 4.22(dd, J₁ = 5.6Hz, J₂ = 53.2Hz, 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)。

[0315] 将获得的中间体溶于无水 DCM(20mL) 和三甲吡啶 (360mg, 3mmol), 并加入 AgNO₃(500mg, 3mmol) 和 MMTTrCl(606mg, 2mmol)。将混合物在 R. T. 下搅拌 16 小时。使用水淬灭反应混合物, 并将有机层分离并浓缩。在硅胶柱上 (0.5% MeOH 的 DCM 溶液) 纯化剩余物以产生黄色固体形式的完全保护的中间体 (3.3g, 80%)。将中间体溶于 1M TBAF 的 THF(5mL) 并在 R. T. 下搅拌 2 小时。将溶液浓缩, 并在硅胶柱上 (1% MeOH 的 DCM 溶液) 纯化剩余物以产生 P1-3 和 P1-4 的混合物, 通过 HPLC(MeCN 和 0.1% HCOOH 的水) 分离将其分离以产生白色固体形式的 P1-4(1.5g, 25%)。

[0316] (P1-5) 的制备: 将 P1-4(1.5g, 1.22mmol) 悬浮在无水 DCM(50mL) 中, 并在 0℃ 下加入戴斯-马丁氧化剂 (1.2g, 2.73mmol)。将反应混合物在 R. T. 下搅拌 3 小时。然后, 使用饱和 Na₂S₂O₃ 和 Na₂CO₃ 水溶液淬灭反应混合物。将有机层分离并干燥, 然后浓缩以产生白色固体形式的醛中间体。

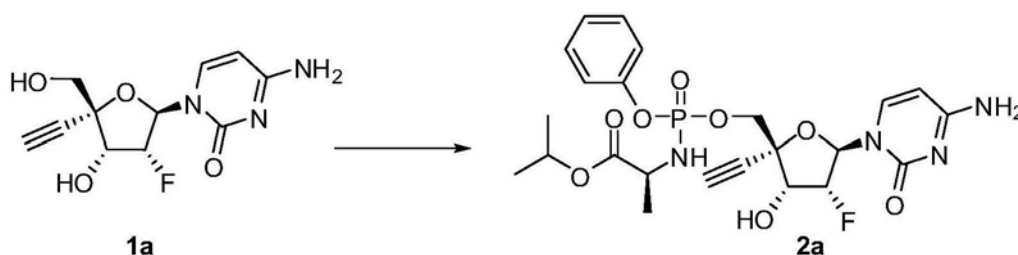
[0317] 将 ClCH₂PPh₃Br(2.19g, 5.6mmol) 的无水 THF(40mL) 溶液冷却至 -78℃。滴加 n-BuLi(2.5M, 2.3mL)。在加入之后, 将混合物在 0℃ 下搅拌 2 小时。然后, 加入醛的无水 THF(10mL) 溶液。将混合物在 R. T. 下搅拌 16 小时。使用饱和 NH₄Cl 水溶液淬灭反应并通过 EA 萃取。将有机层分离, 干燥并浓缩。在硅胶柱上 (1% MeOH 的 DCM 溶液) 纯化剩余物以产生黄色固体形式的中间体 (1.1g, 73%)。在 -78℃ 下, 向中间体 (1.1g, 0.98mmol) 的无水 THF(40mL) 溶液滴加 n-BuLi(2.5M, 6mL)。将混合物在 -78℃ 下搅拌 5 小时, 然后使用饱和 NH₄Cl 水溶液淬灭。使用 EA 萃取混合物。将有机层分离, 干燥并浓缩。在硅胶柱上 (2% MeOH 的 DCM 溶液) 纯化剩余物以产生黄色固体形式的 P1-5(910mg, 86%)。

[0318] (1a) 的制备: 将 P1-5(910mg, 0.84mmol) 悬浮在 80% CH₃COOH(50mL) 中, 并将反应混合物在 40℃ 下搅拌 15 小时。将溶剂蒸发, 并使用甲苯将剩余物共蒸发以去除痕量的酸和水。通过 HPLC 分离 (MeCN 和 0.1% HCOOH 的水) 纯化剩余物以产生白色固体形式的纯化合物 1a(101mg, 45%)。¹H NMR(MeOD, 400MHz) δ 7.90(d, J = 7.2Hz, 1H), 6.04(d, J = 19.6Hz, 1H), 5.87(d, J = 7.6Hz, 1H), 5.00(dd, J₁ = 5.2Hz, J₂ = 53.6Hz, 1H), 4.47(dd, J₁ = 5.2Hz, J₂ = 22.8Hz, 1H), 3.86(d, J = 12.4Hz, 1H), 3.73(d, J = 12.4Hz, 1H), 3.08(s, 1H); ESI-TOF-MS :m/z 270.09[M+H]⁺, 539.17[2M+H]⁺。

[0319] 实施例 2

[0320] 化合物 (2a) 的制备

[0321]



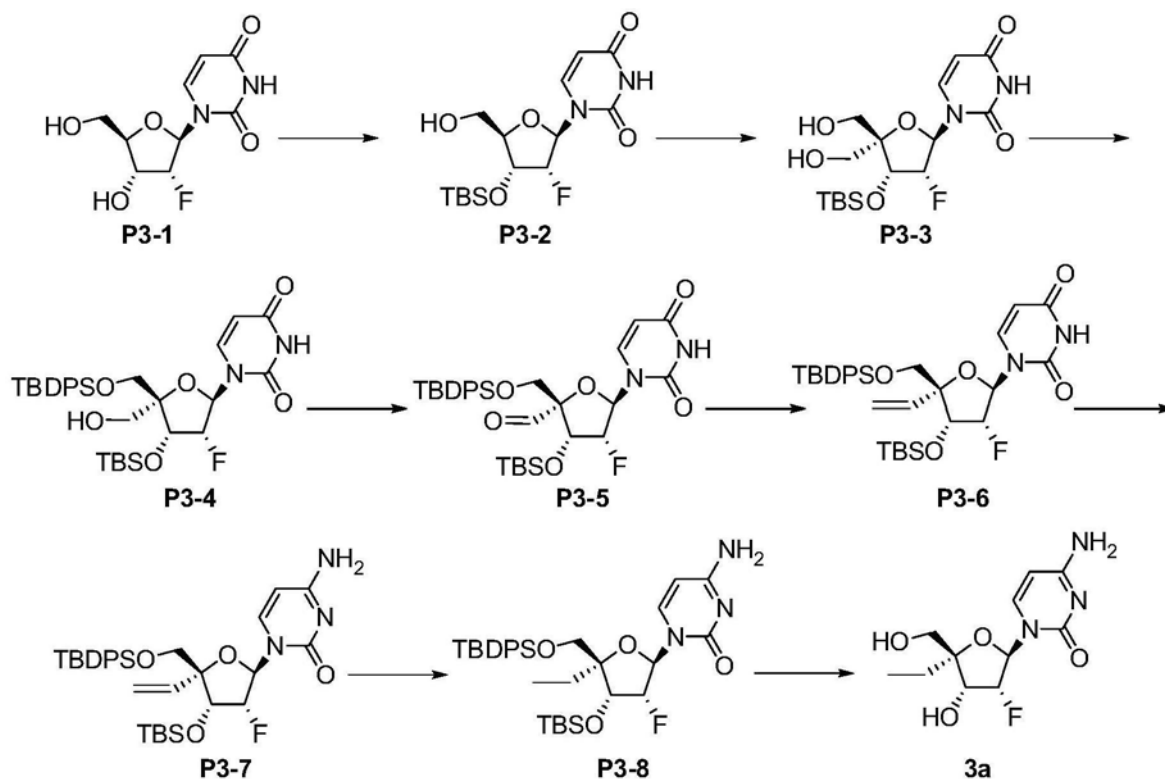
[0322] 在 -78℃ 下, 向搅拌的化合物 1a(50mg, 0.186mmol) 的无水 THF(3mL) 溶液滴

加 $t\text{-BuMgCl}$ (0.37mL, 1M 的 THF) 溶液。然后, 将混合物在 0°C 下搅拌 30min 并重新冷却至 -78°C 。滴加 (异丙氧基-L-丙氨酸基) 氯磷酸苯酯 (104mg, 0.4mmol) 的 THF (0.5mL) 溶液。在加入后, 将混合物在 25°C 下搅拌 16 小时。在 0°C 下, 使用 HCOOH (80% 水溶液) 淬灭反应。去除溶剂, 并在硅胶上 ($\text{DCM}:\text{MeOH} = 50:1$ 至 $10:1$) 纯化剩余物以产生白色固体形式的化合物 2a (两种 P 异构体的混合物, 8.0mg, 7.9%)。 ^1H NMR (MeOD , 400MHz) δ 7.71, 7.68 (2d, $J = 7.6\text{Hz}$, 1H), 7.17–7.37 (m, 5H), 6.02, 6.00 (2d, $J = 20.4\text{Hz}$, 1H), 5.90, 5.86 (2d, $J = 7.6\text{Hz}$, 1H), 5.03–5.18 (m, 1H), 4.91–4.99 (m, 1H), 4.45–4.55 (m, 1H), 4.34–4.43 (m, 1H), 4.26–4.33 (m, 1H), 3.87–3.95 (m, 1H), 3.25, 3.22 (2s, 1H), 1.29–1.34 (m, 3H), 1.20–1.22 (m, 6H)。 ^{31}P NMR (MeOD , 162MHz) δ 3.44, 3.27。ESI-LCMS : m/z 539.0 $[\text{M}+\text{H}]^+$ 。

[0323] 实施例 3

[0324] 化合物 (3a) 的制备

[0325]



[0326] (P3-2) 的制备: 向 P3-1 (100.0g, 406.5mmol) 的吡啶 (750mL) 溶液加入 DMTrCl (164.9g, 487.8mmol)。将溶液在 R.T. 下搅拌 15 小时。加入 MeOH (300mL), 并将混合物在减压下浓缩至干燥。将剩余物溶于 EtOAc 并使用水洗涤。在 Na_2SO_4 上干燥有机层并浓缩。将剩余物溶于 DCM (500mL)。加入咪唑 (44.3g, 650.4mmol) 和 TBSCl (91.9g, 609.8mmol)。将反应混合物在 R.T. 下搅拌 14 小时。使用 NaHCO_3 和盐水洗涤反应溶液。在 Na_2SO_4 上干燥有机层并浓缩以产生淡黄色固体形式的粗物质。将粗物质 (236.4g, 356.6mmol) 溶于 80% HOAc 水溶液 (500mL)。将混合物在 R.T. 下搅拌 15 小时。使用 EtOAc 稀释混合物并使用 NaHCO_3 溶液和盐水洗涤。在 Na_2SO_4 上干燥有机层并通过硅胶柱层析 (1–2% MeOH 的 DCM 溶液) 纯化以产生淡黄色固体形式的 P3-2 (131.2g, 89.6%)。 ^1H NMR ($\text{DMSO}-d_6$, 400MHz) δ 11.39 (s, 1H), 7.88 (d, $J = 7.2\text{Hz}$, 1H), 5.89 (dd, $J_1 = 18.0\text{Hz}$, $J_2 = 2.0\text{Hz}$, 1H), 5.64 (d, $J = 8.0\text{Hz}$, 1H), 5.21 (dd, $J_1 = J_2 = 7.2\text{Hz}$, 1H), 5.18 ~ 5.03 (m, 1H), 4.37 ~

4.29(m, 1H), 3.86(dd, $J_1 = J_2 = 3.2\text{Hz}$, 3H), 3.78 ~ 3.73(m, 1H), 3.51 ~ 3.56(m, 1H), 3.31(s, 1H), 0.89(s, 9H), 0.11(s, 6H); ESI-MS: m/z 802 $[M+H]^+$ 。

[0327] (P3-3) 的制备: 在 R.T. 下, 向溶液 P3-2(131.2g, 364.0mmol) 的无水 CH_3CN (1200mL) 加入 IBX(121.2g, 432.8mmol)。将反应混合物回流 3 小时, 然后冷却至 0°C 。将沉淀滤除, 并将滤液浓缩以产生黄色固体形式的粗醛(121.3g)。将醛溶于 1,4-二氧六环(1000mL)。加入 37% CH_2O (81.1mL, 1.3536mol) 和 2M NaOH 水溶液(253.8mL, 507.6mmol)。将混合物在 R.T. 下搅拌 2 小时, 然后使用 AcOH 中和至 $\text{pH} = 7$ 。向溶液加入 EtOH(400mL) 和 NaBH_4 (51.2g, 1.354mol)。将混合物在 R.T. 下搅拌 30 分钟。使用饱和 NH_4Cl 水溶液淬灭混合物并使用 EA 萃取。在 Na_2SO_4 上干燥有机层并浓缩。通过硅胶柱层析(1-3% MeOH 的 DCM 溶液) 纯化剩余物以产生白色固体形式的 P3-3(51.4g, 38.9%)。

[0328] (P3-4) 的制备: 在 0°C 下, 向 P3-3(51.4g, 131.6mmol) 的无水 DCM(400mL) 溶液加入吡啶(80mL) 和 DMTrCl(49.1g, 144.7mmol)。将反应在 R.T. 下搅拌 14 小时, 然后使用 MeOH(30mL) 处理。将溶剂去除, 并通过硅胶柱层析(1-3% MeOH 的 DCM 溶液) 纯化剩余物以产生黄色泡沫形式的单-DMTr 保护的中间体(57.4g, 62.9%)。向中间体(57.4g, 82.8mmol) 的 CH_2Cl_2 (400mL) 加入咪唑(8.4g, 124.2mmol) 和 TBDPSCl(34.1g, 124.2mmol)。将混合物在 R.T. 下搅拌 14 小时。将沉淀滤除, 并使用盐水洗涤滤液并在 Na_2SO_4 上干燥。将溶剂去除以产生白色固体形式的剩余物(72.45g)。将固体溶于 80% HOAc 水溶液(400mL)。将混合物在 R.T. 下搅拌 15 小时。使用 EtOAc 稀释混合物并使用 NaHCO_3 溶液和盐水洗涤。在 Na_2SO_4 上干燥有机层并通过硅胶柱层析纯化(1-2% MeOH 的 DCM 溶液) 以产生白色固体形式的 P3-4(37.6g, 84.2%)。 ^1H NMR(CD_3OD , 400MHz) δ 7.76(d, $J = 4.0\text{Hz}$, 1H), 7.70(dd, $J_1 = 1.6\text{Hz}$, $J_2 = 8.0\text{Hz}$, 2H), 7.66 ~ 7.64(m, 2H), 7.48 ~ 7.37(m, 6H), 6.12(dd, $J_1 = 2.8\text{Hz}$, $J_2 = 16.8\text{Hz}$, 1H), 5.22(d, $J = 8.0\text{Hz}$, 1H), 5.20 ~ 5.05(m, 1H), 4.74(dd, $J_1 = 5.6\text{Hz}$, $J_2 = 17.6\text{Hz}$, 1H), 4.16(d, $J = 12.0\text{Hz}$, 1H), 3.87 ~ 3.80(m, 2H), 3.56(d, $J = 12.0\text{Hz}$, 1H), 1.16(s, 9H), 0.92(s, 9H), 0.14(s, 6H)。

[0329] (P3-5) 的制备: 在氮气下, 在 0°C 下向 P3-4(11.8g, 18.8mmol) 的无水 DCM(100mL) 溶液加入戴斯-马丁氧化剂(16.3g, 37.6mmol)。将反应在 R.T. 下搅拌 2.5 小时。加入水(100mL), 然后将混合物过滤。使用饱和 NaHCO_3 水溶液洗涤滤液并浓缩。通过硅胶柱层析(20% EtOAc 的己烷溶液) 纯化粗剩余物以产生白色固体形式的 P3-5(10.1g, 86.0%)。

[0330] (P3-6) 的制备: 在氮气下, 在 -78°C 下向甲基三苯基溴化磷(15.7g, 48.5mmol) 的无水 THF(100mL) 混合物加入 $n\text{-BuLi}$ (19.4mL, 48.48mmol)。将反应在 0°C 下搅拌 30 分钟。在氮气下, 在 0°C 下滴加 P3-5(10.1g, 16.2mmol) 的无水 THF(70mL) 溶液。将反应在 R.T. 下搅拌 1.5 小时。通过 NH_4Cl 淬灭反应并使用 EtOAc 萃取。通过硅胶柱层析(20% EtOAc 的己烷溶液) 纯化粗产物以产生白色固体形式的 P3-6(8.3g, 82.2%)。 ^1H NMR(CDCl_3 , 400MHz) δ 8.16(s, 1H), 8.81(d, $J = 8.0\text{Hz}$, 1H), 7.58-7.67(m, 4H), 7.37-7.46(m, 6H), 6.17(d, $J = 16.0\text{Hz}$, 1H), 5.91(dd, $J_1 = 10.8\text{Hz}$, $J_2 = 17.6\text{Hz}$, 1H), 5.42(d, $J = 17.6\text{Hz}$, 1H), 5.22-5.30(m, 2H), 4.60-4.84(m, 2H), 3.69(dd, $J_1 = 11.6\text{Hz}$, $J_2 = 21.2\text{Hz}$, 2H), 1.10(s, 9H), 0.91(s, 1H), 0.12(d, $J = 8.0\text{Hz}$, 6H)。

[0331] (P3-7) 的制备: 在 R.T. 下, 向 P3-6(6.3g, 10.09mmol) 的无水 CH_3CN (50mL) 溶液加入 TPSCl(6.1g, 20.2mmol)、DMAP(2.5g, 20.2mmol) 和 NEt_3 (3mL)。将反应在 R.T. 下搅拌

2 小时。加入 NH_4OH (25mL), 并将反应搅拌 1 小时。使用 DCM (150mL) 稀释混合物并使用水、0.1M HCl 和饱和 NaHCO_3 水溶液洗涤。将溶剂去除, 并通过硅胶柱层析 (2% MeOH 的 DCM 溶液) 纯化粗产物以产生黄色固体形式的 P3-7 (5.9g, 93.6%)。

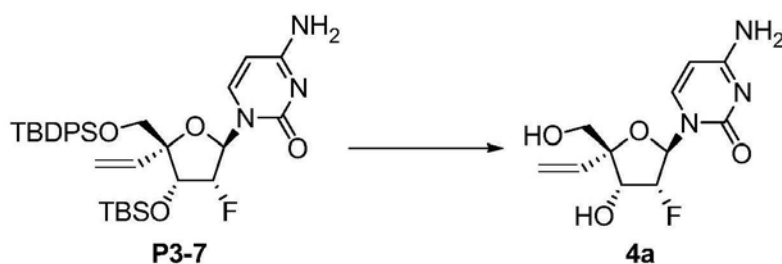
[0332] (P3-8) 的制备: 在 R. T. 下, 向 P3-7 (5.9g, 9.5mmol) 的 MeOH (10mL) 溶液加入 Pd/C (1.5g)。在 H_2 (气球) 下, 将反应在 R. T. 下搅拌 2 小时。将混合物过滤, 然后真空浓缩滤液以产生白色固体形式的 P3-8 (5.4g, 91.3%)。

[0333] (3a) 的制备: 向 P3-8 (5.4g, 8.6mmol) 的 MeOH (60mL) 溶液加入 NH_4F (10.0g), 并将反应混合物回流过夜。在冷却至 R. T. 后, 将混合物过滤, 并将滤液浓缩。通过硅胶柱层析 (10% MeOH 的 DCM 溶液) 纯化粗产物以产生白色固体形式的化合物 3a (1.6g, 67.8%)。 ^1H NMR (CD_3OD , 400M Hz) δ 8.08 (d, $J = 7.6\text{Hz}$, 1H), 6.07 (dd, $J_1 = 3.2\text{Hz}$, $J_2 = 15.6\text{Hz}$, 1H), 5.88 (d, $J = 7.2\text{Hz}$, 1H), 5.04 (ddd, $J_1 = 3.2\text{Hz}$, $J_2 = 5.2\text{Hz}$, $J_3 = 54.0\text{Hz}$, 1H), 4.45 (dd, $J_1 = 5.2\text{Hz}$, $J_2 = 17.2\text{Hz}$, 1H), 3.76 (d, $J = 12.0\text{Hz}$, 1H), 3.57 (d, $J = 12.0\text{Hz}$, 1H), 1.78–1.85 (m, 1H), 1.58–1.67 (m, 1H), 0.95 (t, $J = 7.6\text{Hz}$, 3H); ESI-MS: m/z 274 $[\text{M}+\text{H}]^+$, 547 $[2\text{M}+\text{H}]^+$ 。

[0334] 实施例 4

[0335] 化合物 (4a) 的制备

[0336]

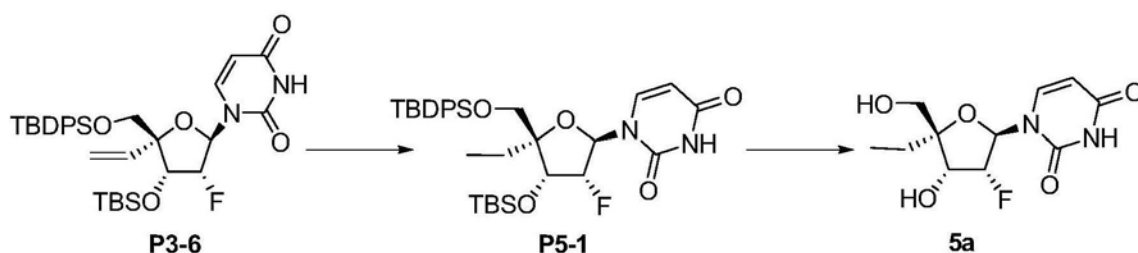


[0337] 在 R. T. 下, 向 P3-7 (280mg, 0.45mmol) 的 MeOH (10mL) 溶液加入 NH_4F (1.0g)。将反应混合物回流 5 小时。在冷却至 R. T. 后, 将混合物过滤, 并将滤液浓缩。通过硅胶柱层析 (10% MeOH 的 DCM 溶液) 纯化粗产物以产生白色固体形式的化合物 4a (82mg, 67.2%)。1.6g, 67.8%)。 ^1H NMR (CD_3OD , 400M Hz) δ 8.11 (d, $J = 7.6\text{Hz}$, 1H), 5.99–6.08 (m, 2H), 5.88 (d, $J = 7.6\text{Hz}$, 1H), 5.47 (dd, $J_1 = 1.2\text{Hz}$, $J_2 = 17.2\text{Hz}$, 1H), 5.26 (dd, $J_1 = 1.6\text{Hz}$, $J_2 = 11.2\text{Hz}$, 1H), 4.97 (d, $J = 5.2\text{Hz}$, 0.5H), 4.82 (d, $J = 7.6\text{Hz}$, 0.5H), 4.52 (dd, $J_1 = 5.2\text{Hz}$, $J_2 = 23.2\text{Hz}$, 1H), 3.65 (d, $J = 12.4\text{Hz}$, 1H), 3.54 (d, $J = 12.4\text{Hz}$, 1H); ESI-MS: m/z 272 $[\text{M}+\text{H}]^+$, 543 $[2\text{M}+\text{H}]^+$ 。

[0338] 实施例 5

[0339] 化合物 (5a) 的制备

[0340]



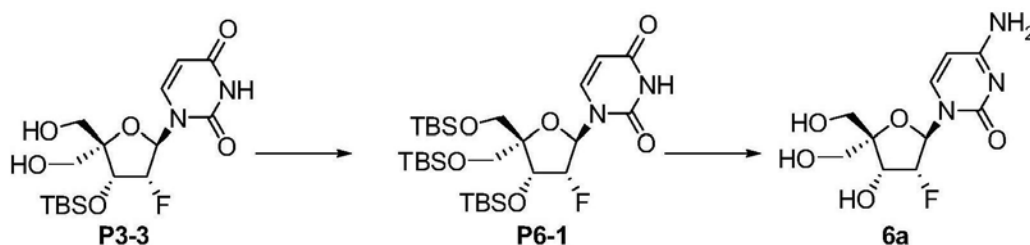
[0341] (P5-1) 的制备: 在 R. T. 下, 向 P3-6 (600mg, 0.96mmol) 的 MeOH (30mL) 溶液加入 10% Pd/C (320mg)。在 R. T. 下, 在 H₂ 气球下将混合物搅拌 3 小时。将反应混合物过滤, 并将滤液浓缩以产生无色固体形式的 P5-1 (540mg, 89.8%)。将粗产物直接用于下一步而不纯化。

[0342] (5a) 的制备: 在 R. T. 下, 向 P5-1 (540mg, 0.86mmol) 的 MeOH (8mL) 溶液加入 NH₄F (1.2g, 32.4mmol)。将混合物回流 30 小时。通过过滤去除固体, 并将滤液浓缩。通过硅胶柱层析 (2.5% -9% MeOH 的 DCM) 纯化剩余物以产生无色固体形式的化合物 5a (190mg, 80.6%)。¹H NMR (CD₃OD, 400MHz) δ 8.05 (d, J = 8.0Hz, 1H), 6.09 (dd, J₁ = 4.0Hz, J₂ = 14.8Hz, 1H), 5.04-5.20 (m, 1H), 4.42 (dd, J₁ = 5.2Hz, J₂ = 13.6Hz, 1H), 3.71 (d, J = 11.6Hz, 1H), 3.57 (d, J = 12.0Hz, 1H), 1.61-1.82 (m, 2H), 0.94 (t, J = 7.2Hz, 3H)。

[0343] 实施例 6

[0344] 化合物 (6a) 的制备

[0345]



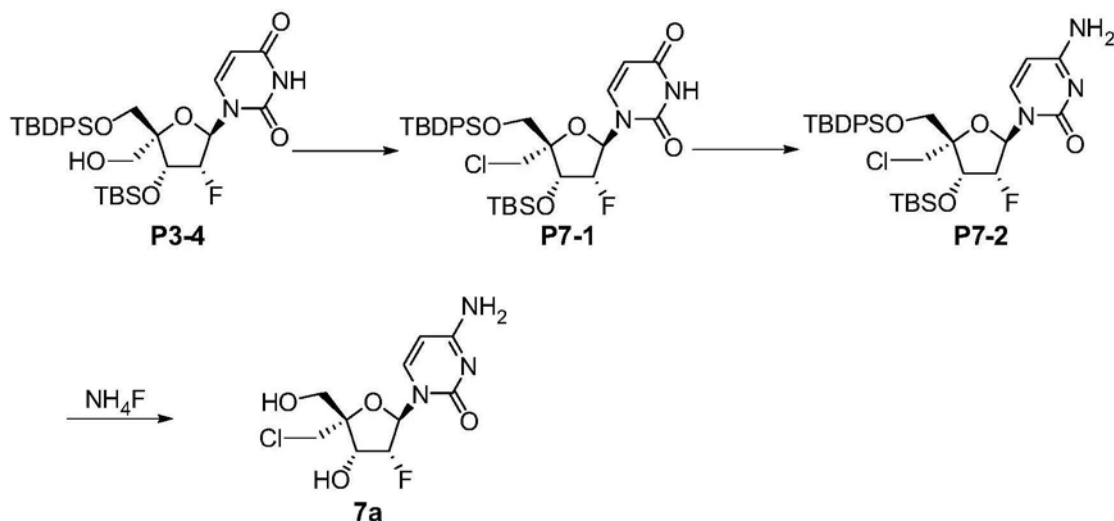
[0346] (P6-1) 的制备: 在 R. T. 下, 向 P3-3 (800mg, 2.05mmol) 的无水 DCM (15mL) 溶液加入咪唑 (558mg, 8.2mmol)、TBSCl (1.2g, 8.2mmol) 和 AgNO₃ (700mg, 4.1mmol)。将反应混合物在 R. T. 下搅拌过夜。将混合物过滤, 使用盐水洗涤滤液并真空浓缩。通过在硅胶上的柱层析纯化剩余物以产生白色固体形式的 P6-1 (950mg, 79.2%)。

[0347] (6a) 的制备: 在 R. T. 下, 向 P6-1 (600mg, 0.97mmol) 的无水 CH₃CN (18mL) 溶液加入 DMAP (239mg, 2.91mmol)、NEt₃ (294mg, 2.91mmol) 和 TPSCl (879mg, 2.91mmol)。将反应在 R. T. 下搅拌 1 小时。加入 NH₄OH (9mL), 并将反应搅拌 3 小时。使用 EtOAc (200mL) 稀释混合物并使用水、0.1M HCl 和饱和 NaHCO₃ 水溶液洗涤。将有机层分离, 干燥并浓缩以产生粗剩余物。通过在硅胶上的柱层析纯化粗剩余物以产生白色固体形式的产物 (500mg, 83.3%)。在回流温度下使用 NH₄F (1.0g) 的 MeOH (20mL) 溶液处理固体时间为 5 小时。将混合物过滤, 并将滤液真空浓缩。通过在硅胶上的柱层析 (15% MeOH 的 DCM 溶液) 纯化剩余物以产生白色固体形式的化合物 6a (132mg, 59.3%)。¹H NMR (DMSO-d₆, 400MHz) δ 7.89 (d, J = 7.6Hz, 1H), 7.22 (d, J = 18.8Hz, 2H), 6.09 (dd, J₁ = 4.4Hz, J₂ = 14.8Hz, 1H), 5.73 (d, J = 5.2Hz, 1H), 5.52 (d, J = 5.6Hz, 1H), 5.12 (t, J = 4.8Hz, 1H), 4.90-5.06 (m, 1H), 4.50 (t, J = 6.0Hz, 1H), 4.27-4.33 (m, 1H), 3.66 (dd, J₁ = 5.2Hz, J₂ = 12.0Hz, 1H), 3.47-3.58 (m, 3H); ESI-MS :m/z 276 [M+H]⁺, 551 [2M+H]⁺。

[0348] 实施例 7

[0349] 化合物 (7a) 的制备

[0350]



[0351] (P7-1) 的制备: 在 N_2 下, 在微波辐射下将 P3-4 (1.60g, 2.5mmol)、 PPh_3 (1.3g, 5.0mmol) 和 CCl_4 (0.76g, 5.0mmol) 的 DCE (20mL) 混合物加热至 $130^\circ C$ 时间为 40mins。在冷却至 R. T. 后, 将溶剂去除, 并在硅胶柱上 (PE/EA = 50/1 至 10/1) 纯化剩余物以产生白色固体形式的 P7-1 (1.1g, 68.8%)。

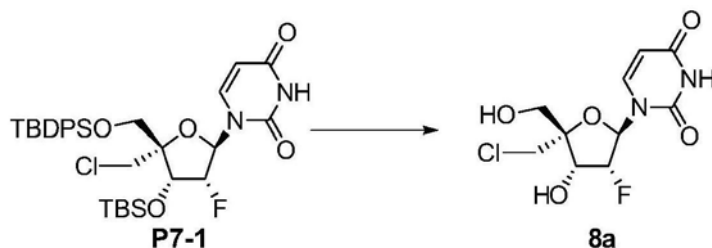
[0352] (P7-2) 的制备: 将 P7-1 (0.80g, 1.3mmol)、DMAP (0.3g, 2.6mmol)、TPSCl (0.8g, 2.6mmol) 和 Et_3N (0.3g, 2.6mmol) 溶于 MeCN (30mL)。将混合物在 R. T. 下搅拌 14 小时。将 NH_3 的 THF 溶液 (在 $0^\circ C$ 下饱和, 100mL) 加入至混合物, 并将混合物在 R. T. 下搅拌 2 小时。将溶剂去除, 并通过柱 (DCM/MeOH = 100:1 至 50:1) 纯化剩余物以产生白色固体形式的 P7-2 (0.63g, 78.8%)。

[0353] (7a) 的制备: 向 P7-2 (0.63g, 0.98mmol) 的 MeOH (10mL) 溶液加入 NH_4F (0.3g), 并将反应回流 12 小时。将反应冷却至 R. T., 并将沉淀滤除。真空浓缩滤液。通过硅胶柱层析 (10% MeOH 的 DCM 溶液) 纯化剩余物以产生白色固体形式的化合物 7a (153mg, 53.5%)。 ^1H NMR (CD_3OD , 400M Hz) δ 8.05 (d, $J = 7.2Hz$, 1H), 6.14 (dd, $J_1 = 3.6Hz$, $J_2 = 15.2Hz$, 1H), 5.92 (d, $J = 7.2Hz$, 1H), 5.15 (ddd, $J_1 = 4.0Hz$, $J_2 = 5.2Hz$, $J_3 = 53.6Hz$, 1H), 4.57 (dd, $J_1 = 4.8Hz$, $J_2 = 15.2Hz$, 1H), 3.93 (d, $J = 11.6Hz$, 1H), 3.75–3.84 (m, 3H); ESI-MS: m/z 294 $[M+H]^+$, 587 $[2M+H]^+$ 。

[0354] 实施例 8

[0355] 化合物 (8a) 的制备

[0356]



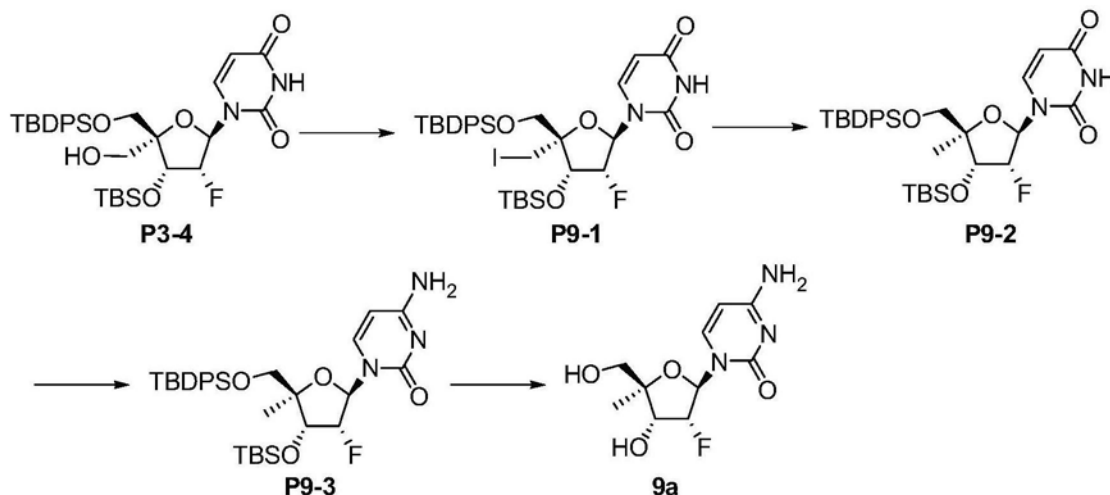
[0357] 向 P7-1 (630mg, 0.5mmol) 的 MeOH (10mL) 溶液加入 NH_4F (0.1g), 并将反应回流 12 小时。将混合物过滤, 并将滤液真空浓缩。通过硅胶柱层析 (10% MeOH 的 DCM 溶液) 纯化粗产物以产生白色固体形式的化合物 8a (153mg, 53.5%)。 ^1H NMR (CD_3OD , 400M Hz) δ 7.99 (d, J

= 8.0Hz, 1H), 6.17(dd, $J_1 = 4.4\text{Hz}$, $J_2 = 14.4\text{Hz}$, 1H), 5.70(d, $J = 8.0\text{Hz}$, 1H), 5.22(ddd, $J_1 = J_2 = 4.8\text{Hz}$, $J_3 = 53.2\text{Hz}$, 1H), 4.55(dd, $J_1 = 5.2\text{Hz}$, $J_2 = 12.4\text{Hz}$, 1H), 3.88(d, $J = 12.0\text{Hz}$, 1H), 3.76–3.79(m, 3H); 负-ESI-MS : m/z 293 $[M-H]^-$ 。

[0358] 实施例 9

[0359] 化合物 (9a) 的制备

[0360]



[0361] (P9-1) 的制备: 将 P3-4 (3.2g, 5.0mmol)、 Ph_3P (5.2g, 20mmol)、碘 (2.60g, 10.2mmol) 和咪唑 (1.4g, 20mmol) 的无水 THF (40mL) 混合物在 80°C 下搅拌 14 小时。将反应冷却至 R.T. 并使用饱和 $\text{Na}_2\text{S}_2\text{O}_3$ 水溶液淬灭。使用 EA 萃取溶液。在 Na_2SO_4 上干燥有机层并浓缩。通过硅胶柱层析 (20–50% EA 的 PE) 纯化剩余物以产生白色固体形式的 P9-1 (1.6g, 68.2%)。

[0362] (P9-2) 的制备: 在 H_2 (气球) 下, 将 P9-1 (1.4g, 0.2mmol)、 Et_3N (40mg, 0.4mmol) 和 Pd/C 的 EtOH (20mL) 混合物在 R.T. 下搅拌过夜。将沉淀滤除, 并将滤液浓缩。在硅胶柱上 (20%–50% EtOAc 的 PE) 纯化剩余物以产生白色固体形式的 P9-2 (1.1g, 78%)。 ^1H NMR (CDCl_3 , 400MHz) δ 8.11(br s, 1H), 7.76(d, $J = 8.0\text{Hz}$, 1H), 7.39–7.67(m, 10H), 6.18(dd, $J_1 = 3.2\text{Hz}$, $J_2 = 14.4\text{Hz}$, 1H), 5.26–5.30(m, 1H), 4.86(m, 1H), 4.42(dd, $J_1 = 5.2\text{Hz}$, $J_2 = 15.2\text{Hz}$, 1H), 3.81(d, $J = 11.2\text{Hz}$, 1H), 3.58(d, $J = 11.2\text{Hz}$, 1H), 1.16(s, 3H), 1.11(s, 9H), 0.91(s, 9H), 0.13(s, 3H), 0.08(s, 3H)。

[0363] (P9-3) 的制备: 将 P9-2 (650mg, 1.1mmol)、DMAP (270mg, 2.2mmol)、TPSCl (664mg, 2.2mol) 和 Et_3N (222mg, 2.2mmol) 溶于 MeCN (20mL)。将混合物在 R.T. 下搅拌 14 小时。将反应加入 NH_3 的 THF 溶液 (在 0°C 下饱和), 并将混合物在 R.T. 下搅拌 2 小时。将溶剂去除, 并在硅胶柱上 (1–10% MeOH 的 DCM 溶液) 纯化剩余物以产生淡黄色糖浆形式的 P9-3 (430mg, 粗物质)。

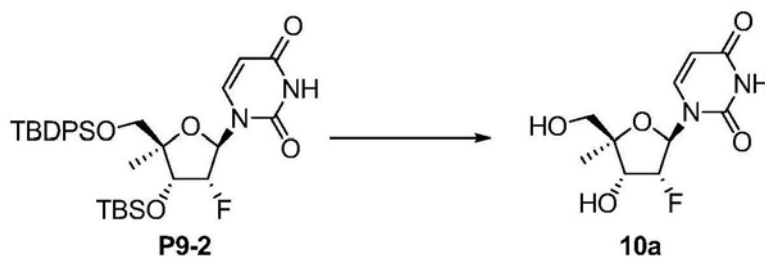
[0364] (9a) 的制备: 将 P9-3 (430mg, 0.7mmol) 和 NH_4F (97mg, 2.1mmol) 的 MeOH (10mL) 混合物回流 14 小时。将溶剂去除, 并在硅胶柱上 (5%–10% MeOH 的 DCM 溶液) 纯化剩余物以产生白色固体形式的化合物 9a (64.8mg, 35.4%)。 ^1H NMR (CD_3OD , 400MHz) δ 8.10(d, $J = 7.6\text{Hz}$, 1H), 6.03(dd, $J_1 = 2.0\text{Hz}$, $J_2 = 16.8\text{Hz}$, 1H), 5.87(d, $J = 7.6\text{Hz}$, 1H), 4.98(m, 1H), 4.37(dd, $J_1 = 5.2\text{Hz}$, $J_2 = 21.6\text{Hz}$, 1H), 3.59(dd, $J_1 = 12.0\text{Hz}$, $J_2 =$

28.4Hz, 2H), 1.23 (d, $J = 0.8$ Hz, 3H)。

[0365] 实施例 10

[0366] 化合物 (10a) 的制备

[0367]

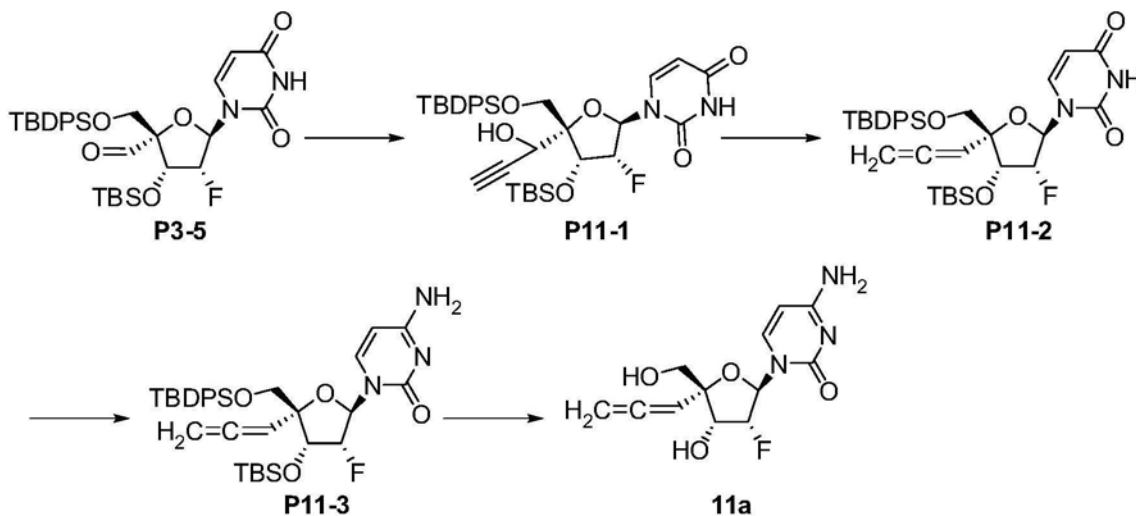


[0368] 向搅拌的 P9-2 (400mg, 0.65mmol) 的 MeOH (20mL) 溶液加入 NH_4F (52mg, 1.5mmol)。将混合物回流过夜。将溶剂去除,并在硅胶柱上 (5 ~ 10% MeOH 的 DCM 溶液) 纯化剩余物以产生白色固体形式的化合物 10a (140mg, 82.4%)。 ^1H NMR (CD_3OD , 400MHz) δ 8.05 (d, $J = 8.4$ Hz, 1H), 6.06 (dd, $J_1 = 2.8$ Hz, $J_2 = 16.4$ Hz, 1H), 5.67 (d, $J = 8.0$ Hz, 1H), 5.08 (m, 1H), 4.37 (d, $J_1 = 5.2$ Hz, $J_2 = 18.8$ Hz, 1H), 3.59 (dd, $J_1 = 12.0$ Hz, $J_2 = 26.4$ Hz, 2H), 1.23 (s, 3H)。ESI-TOF-MS : m/z 283 [$\text{M}+\text{Na}$] $^+$ 。

[0369] 实施例 11

[0370] 化合物 (11a) 的制备

[0371]



[0372] (P11-1) 的制备:在 -78°C 下,向 P3-5 (2.1g, 3.5mmol) 的无水 THF (25mL) 溶液加入乙炔基溴化镁 (5.1mmol)。将反应在 0°C 下搅拌 3 小时。使用饱和 NH_4Cl 水溶液 (10mL) 淬灭反应。使用 EtOAc (200mL) 稀释混合物并使用水和盐水洗涤。干燥有机层并浓缩以产生剩余物。通过在硅胶上的柱层析 (使用 DCM:MeOH = 60:1 洗脱) 纯化剩余物以产生白色固体形式的 P11-1 (870mg, 83.3%)。

[0373] (P11-2) 的制备:将 P11-1 (870mg, 1.34mmol) 溶于无水 DCM (12mL),并在 R. T. 下加入氯甲酸甲酯 (2.3mL) 和吡啶 (2.5mL)。将反应混合物在 R. T. 下搅拌 1 小时。使用 DCM 稀释混合物并使用饱和 NaHCO_3 水溶液洗涤。将有机层分离,干燥并浓缩以产生剩余物。通过在硅胶上的柱层析 (使用 PE:EtOAc = 8:1 洗脱) 纯化剩余物以产生白色固体形式的粗产物 (830mg, 88.4%)。在氮气下,在 R. T. 下,向 $\text{Pd}_2(\text{dba})_3$ (55mg, 0.06mmol) 的无

水 DMF (12mL) 混合物加入 $P(nBu)_3$ (35mg, 0.17mmol) 和 $HCOONH_4$ (108mg, 1.7mmol)。将反应混合物在 R. T. 下搅拌 30min。加入粗产物 (830mg, 1.16mmol) 的无水 DMF (16mL) 溶液, 并将反应混合物在 70℃ 下搅拌 3 小时。使用 EtOAc 稀释反应并使用盐水洗涤。将有机层分离, 干燥并浓缩以产生剩余物。通过在硅胶上的柱层析 (使用 PE:EtOAc = 9:1 洗脱) 纯化剩余物以产生白色固体形式的 P11-2 (510mg, 67.6%)。 ^1H NMR (CD_3OD , 400M Hz) δ 7.61-7.75 (m, 5H), 7.36-7.47 (m, 6H), 6.04 (d, J = 18.8Hz, 1H), 5.34 (t, J = 6.8Hz, 1H), 5.21 (dd, J_1 = 1.2Hz, J_2 = 7.2Hz, 1H), 5.10 (q, J_1 = 5.2Hz, J_2 = 53.6Hz, 1H), 4.80-4.92 (m, 1H), 4.59-4.79 (m, 2H), 3.86 (d, J = 12.0Hz, 1H), 3.75 (d, J = 12.0Hz, 1H), 1.09 (s, 9H), 0.92 (d, J = 4.4Hz, 9H), 0.15 (t, J = 4.0Hz, 6H)。

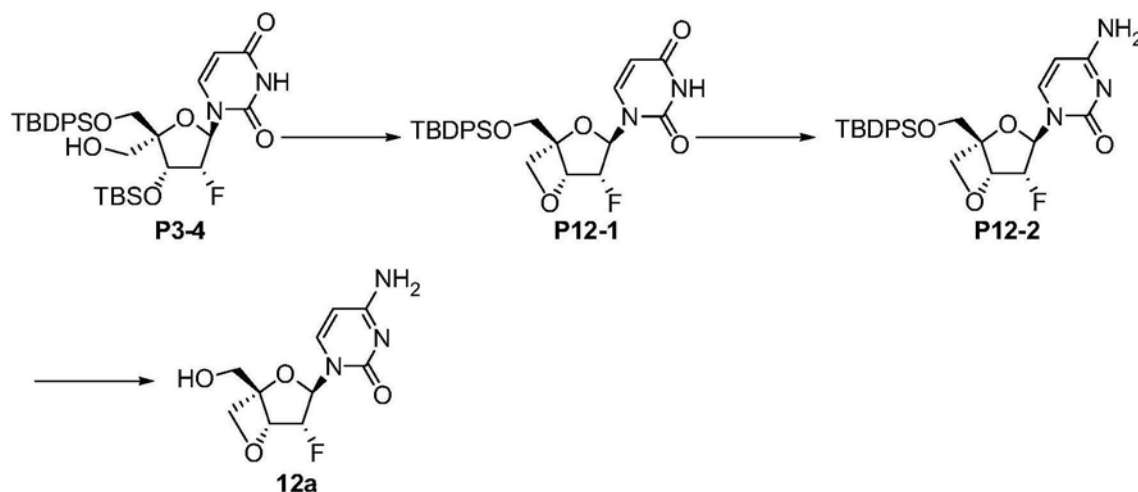
[0374] (P11-3) 的制备: 在 R. T. 下, 向 P11-2 (490mg, 0.77mmol) 的无水 MeCN (15mL) 溶液加入 TPSCl (700mg, 2.31mmol)、DMAP (282mg, 2.31mmol) 和 TEA (234mg, 2.31mmol)。将反应混合物在室温下搅拌 1 小时, 然后加入 NH_4OH (8mL) 并将反应混合物搅拌另外 4 小时。使用 EtOAc 稀释混合物并使用水、1.0M HCl 水溶液和饱和 $NaHCO_3$ 水溶液洗涤。将有机层分离并干燥, 浓缩以产生剩余物, 通过 HPLC 分离 (MeCN 和 0.1% $HCOOH$ 的水) 将其纯化以产生白色固体形式的 P11-3 (190mg, 38.8%)。 ^1H NMR (CD_3OD , 400MHz) δ 7.88 (d, J = 7.2Hz, 1H), 7.63-7.70 (m, 4H), 7.37-7.48 (m, 6H), 6.12 (d, J = 18.4Hz, 1H), 5.49 (d, J = 7.6Hz, 1H), 5.34 (t, J = 6.8Hz, 1H), 4.84-5.01 (m, 2H), 4.66-4.78 (m, 2H), 3.89 (d, J = 11.6Hz, 1H), 3.75 (d, J = 11.6Hz, 1H), 1.10 (s, 9H), 0.91 (d, J = 3.2Hz, 9H), 0.13 (t, J = 5.2Hz, 6H)。

[0375] (11a) 的制备: 向 P11-3 (130mg, 0.21mmol) 的 MeOH (8mL) 溶液加入 NH_4F (1g), 并将反应混合物回流 6 小时。将混合物过滤, 并将滤液真空浓缩。通过在硅胶上的柱层析 (使用 DCM:MeOH = 13:1 洗脱) 纯化剩余物以产生白色固体形式的化合物 11a (47mg, 79.1%)。 ^1H NMR (CD_3OD , 400MHz) δ 8.07 (d, J = 7.6Hz, 1H), 6.05 (dd, J_1 = 1.2Hz, J_2 = 16.8Hz, 1H), 5.86 (d, J = 7.6Hz, 1H), 5.40 (dd, J_1 = J_2 = 6.8Hz, 1H), 4.87-4.99 (m, 3H), 4.46-4.80 (m, 1H), 3.75 (d, J = 12.4Hz, 1H), 3.68 (d, J = 12.4Hz, 1H); ESI-MS: m/z 284.02 $[M+H]^+$, 567.08 $[2M+H]^+$ 。

[0376] 实施例 12

[0377] 化合物 (12a) 的制备

[0378]



[0379] (P12-1) 的制备: 在氮气下, 在 -65℃ 下向 P3-4 (500mg, 0.8mmol) 的无水甲

苯 (12mL) 溶液加入 DAST (0.3mL, 2mmol)。将反应混合物在 R.T. 下搅拌 2 小时。使用饱和 NaHCO_3 水溶液淬灭反应并使用 EtOAc 萃取。将有机层分离, 干燥并浓缩以产生剩余物。通过在硅胶上的柱层析 (使用 PE:EtOAc = 9:1 洗脱) 纯化剩余物以产生黄色固体形式的 P12-1 (170mg, 42.5%)。 ^1H NMR (CD_3OD , 400MHz) δ 7.66 (dd, $J_1 = 1.6\text{Hz}$, $J_2 = 18.0\text{Hz}$, 4H), 7.54 (d, $J = 7.6\text{Hz}$, 1H), 7.35–7.47 (m, 6H), 6.59 (dd, $J_1 = 5.6\text{Hz}$, $J_2 = 14.0\text{Hz}$, 1H), 5.78 (d, $J = 7.6\text{Hz}$, 1H), 5.05–5.24 (m, 2H), 4.93 (d, $J = 7.6\text{Hz}$, 1H), 4.57 (d, $J = 7.6\text{Hz}$, 1H), 3.93–4.00 (m, 2H), 1.07 (d, $J = 2.4\text{Hz}$, 9H)。

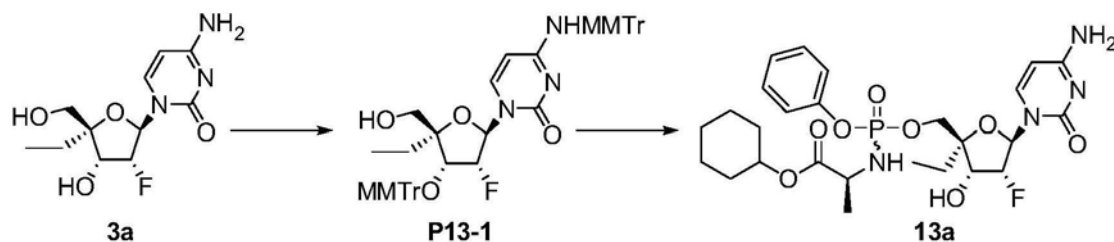
[0380] (P12-2) 的制备: 在氮气下, 在 R.T. 下向 P12-1 (100mg, 0.2mmol) 的无水 MeCN (5mL) 溶液加入 TPSCl (182mg, 0.6mmol)、DMAP (68mg, 0.6mmol) 和 TEA (61mg, 0.6mmol)。将反应混合物在 R.T. 下搅拌 1 小时。加入 NH_4OH (3mL), 并将反应搅拌 2 小时。使用 EtOAc 稀释混合物并使用水、1.0M HCl 和饱和 NaHCO_3 水溶液洗涤。将有机层分离, 干燥并浓缩以产生剩余物。通过在硅胶上的柱层析 (DCM:MeOH = 50:1) 纯化剩余物以产生黄色固体形式的 P12-2 (96mg, 96%)。

[0381] (12a) 的制备: 在 R.T. 下, 向 P12-2 (96mg, 0.2mmol) 的 MeOH (5mL) 溶液加入 NH_4F (500mg)。将反应回流 3 小时。将混合物过滤, 并通过 RP HPLC (MeCN 和 0.1% HCOOH 的水) 纯化剩余物以产生白色固体形式的化合物 12a (25mg, 48.7%)。 ^1H NMR (CD_3OD , 400MHz) δ 7.85 (d, $J = 7.6\text{Hz}$, 1H), 6.59 (dd, $J_1 = 5.2\text{Hz}$, $J_2 = 12.8\text{Hz}$, 1H), 6.04 (d, $J = 7.6\text{Hz}$, 1H), 5.10–5.26 (m, 2H), 4.79–4.90 (m, 1H), 4.57 (d, $J = 7.6\text{Hz}$, 1H), 3.82 (d, $J = 12.4\text{Hz}$, 1H), 3.76 (dd, $J_1 = 1.6\text{Hz}$, $J_2 = 12.4\text{Hz}$, 1H); ESI-MS: m/z 257.9 $[\text{M}+\text{H}]^+$ 、514.8 $[2\text{M}+\text{H}]^+$ 。

[0382] 实施例 13

[0383] 化合物 (13a) 的制备

[0384]



[0385] (P13-1) 的制备: 在 N_2 下, 在 R.T. 下向化合物 3a (700mg, 2.56mmol) 的无水吡啶 (5mL) 溶液加入 TBDPSCl (2.8g, 10.24mmol)、咪唑 (522mg, 7.68mmol) 和 AgNO_3 (870mg, 5.12mmol)。将反应混合物在 R.T. 下搅拌 3 小时。使用 MeOH 稀释混合物并过滤。将混合物浓缩, 并通过在硅胶上的柱层析 (使用 DCM:MeOH = 80:1 ~ 40:1 洗脱) 纯化剩余物以产生黄色固体形式的粗中间体 (1.05g, 80.8%)。 ^1H NMR ($\text{DMSO}-d_6$, 400MHz) δ 7.75 (d, $J = 7.6\text{Hz}$, 1H), 7.61–7.65 (m, 4H), 7.41–7.50 (m, 7H), 6.02 (dd, $J_1 = 2.8\text{Hz}$, $J_2 = 17.2\text{Hz}$, 1H), 5.69 (d, $J = 6.0\text{Hz}$, 1H), 5.56 (d, $J = 7.6\text{Hz}$, 1H), 4.96–5.11 (m, 1H), 4.37–4.46 (m, 1H), 3.82 (d, $J = 10.8\text{Hz}$, 1H), 3.62 (d, $J = 10.8\text{Hz}$, 1H), 1.70–1.78 (m, 1H), 1.53–1.59 (m, 1H), 1.02 (s, 9H), 0.79 (t, $J = 7.6\text{Hz}$, 3H)。在 N_2 下, 在 R.T. 下向粗中间体 (1.0g, 1.96mmol) 的无水 DCM (15mL) 溶液加入对称三甲吡啶 (1.4g, 11.76mmol)、 AgNO_3 (1.0g, 5.88mmol) 和 MMTrCl (4.8g, 15.6mmol)。将反应混合物在 R.T. 下搅拌过夜。将混合物过滤并浓缩。通过

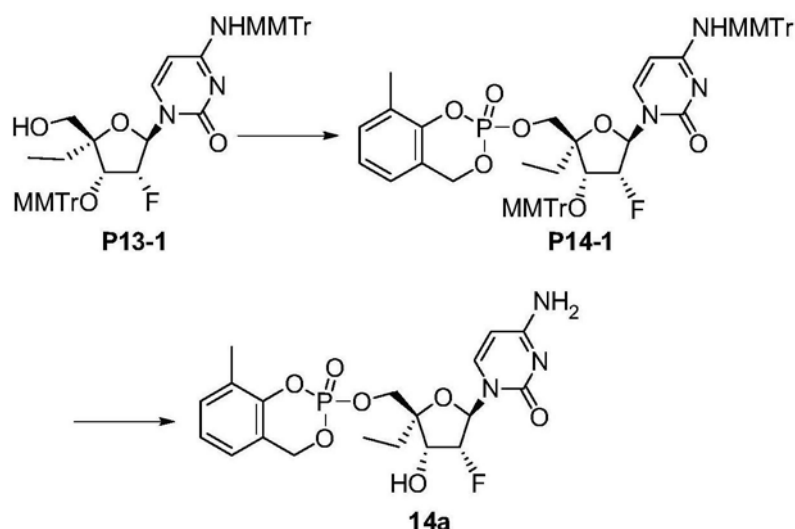
在硅胶上的柱层析(使用PE:EtOAc = 2:1洗脱)纯化剩余物以产生白色固体形式的粗完全保护的中间体(1.1g, 53.1%)。在R.T.下,向粗中间体(600mg, 0.57mmol)的THF(5mL)溶液加入TBAF(446mg, 1.71mmol)。将反应在40~50℃下搅拌过夜。通过使用PE:EtOAc = 3:2洗脱的硅胶上的柱层析纯化粗产物以产生黄色固体形式的粗P13-1(350mg, 75.1%)。

[0386] (13a)的制备:在N₂下,在R.T.下向P13-1(300mg, 0.37mmol)的CH₃CN(2.5mL)溶液加入NMI(2.5mL)和(异丙氧基-L-丙氨酸基)氯磷酸苯酯(2.55g, 7.4mmol)的CH₃CN(2.5mL)溶液。将反应混合物在R.T.下搅拌3小时。将混合物真空浓缩。通过在硅胶上的柱层析(PE:EtOAc = 1:1)纯化剩余物以产生黄色油状物形式的粗产物(500mg, 81%)。在R.T.下使用80% HCOOH(70mL)将粗产物进一步处理过夜。将混合物真空浓缩,并通过RP HPLC(MeCN和0.1% HCOOH的水)纯化粗产物以产生白色固体形式的化合物13a(两种P-异构体的混合物, 86mg, 两步的产率为40.3%)。¹H NMR(CD₃OD, 400MHz) δ 7.75, 7.71(2d, J = 7.6Hz, 1H), 7.33-7.38(m, 2H), 7.19-7.26(m, 3H), 6.02-6.10(m, 1H), 5.87, 5.82(2d, J = 7.6Hz, 1H), 4.99-5.02(m, 0.5H), 4.72-4.82(m, 1.5H), 4.14-4.43(m, 3H), 3.89-3.94(m, 1H), 1.68-1.81(m, 6H), 1.51-1.56(m, 1H), 1.30-1.43(m, 8H), 0.96-1.01(m, 3H); ESI-MS: m/z 582.93[M+H]⁺。

[0387] 实施例 14

[0388] 化合物(14a)的制备

[0389]



[0390] (P14-1)的制备:在N₂下,在0℃下向搅拌的P13-1(451mg, 0.55mmol)和NMI(1mL)的无水乙腈(2mL)溶液滴加2-氯-8-甲基-4H-苯并[d][1,3,2]二氧杂磷杂苯(phosphinine)(855mg, 4.2mmol)的乙腈(0.2mL)溶液。将混合物在R.T.下搅拌2小时。加入I₂(3.2g, 12.6mmol)、吡啶(9mL)、H₂O(3mL)和DCM(3mL)溶液。将反应混合物搅拌30mins。使用NaS₂O₃溶液淬灭反应并使用EA萃取。在Na₂SO₄上干燥有机层并浓缩。通过在硅胶上的柱(PE:EA = 1:1至1:2)纯化剩余物以产生白色固体形式的P14-1(205mg, 37%)。

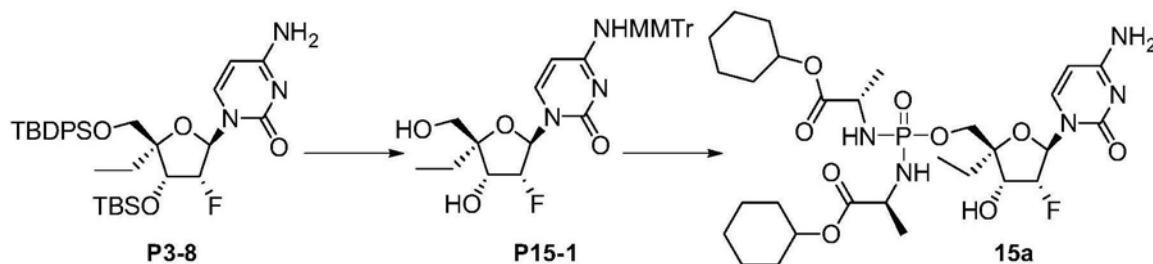
[0391] (14a)的制备:将P14-1(205mg, 0.21mmol)溶于80% HCOOH水溶液,并将混合物在R.T.下搅拌16小时。将溶剂去除,并通过RP HPLC(HCOOH体系)纯化剩余物以产生2种P-异构体混合物形式的化合物14a(24mg, 18%)。¹H NMR(CD₃OD, 400MHz) δ 7.60, 7.53(2d, J = 8.0Hz, 1H), 7.21-7.25(m, 1H), 7.02-7.12(m, 2H), 5.95-5.87(2dd, J₁ = 2.4Hz, J₂ =

18.0Hz, 1H), 5.71, 5.69 (2d, $J = 8.0$ Hz, 1H), 5.38–5.53 (m, 2H), 5.06, 5.04 (2ddd, $J_1 = 2.4$ Hz, $J_2 = 5.6$ Hz, $J_3 = 54.0$ Hz, 1H), 4.32–4.49 (m, 2H), 2.26 (d, $J = 3.6$ Hz, 3H), 1.83–1.92 (m, 1H), 1.64–1.72 (m, 1H), 0.96、0.93 (2t, $J = 7.6$ Hz, 3H)。 ^{31}P NMR (CD_3OD , 162MHz) δ -8.22、-8.50;ESI-LCMS :m/z 456 $[\text{M}+\text{H}]^+$ 。

[0392] 实施例 15

[0393] 化合物 (15a) 的制备

[0394]



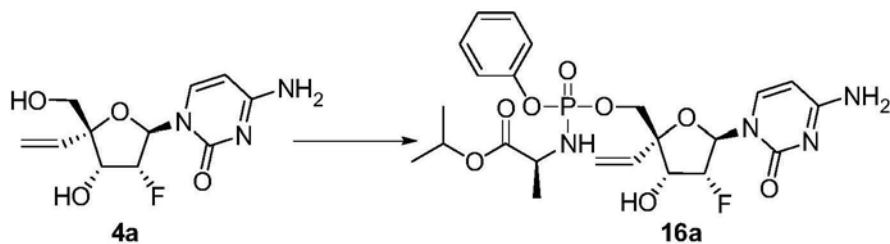
[0395] 步骤 1. (P15-1) 的制备:在 N_2 下,向 P3-8 (2.2g, 2.5mmol)、 AgNO_3 (844mg, 5.0mmol) 和三甲吡啶 (907mg, 7.5mmol) 的无水 DCM (10mL) 混合物加入 MMTrCl (1.54g, 5.0mmol)。将反应混合物在 R. T. 下搅拌过夜。通过 Buchner 漏斗过滤反应混合物。使用饱和 NaHCO_3 溶液和盐水洗涤滤液。将有机层分离,在无水 Na_2SO_4 上干燥并过滤。将滤液浓缩至干燥。通过硅胶上的柱 (PE:EA = 10:1 至 1:2) 纯化剩余物以产生中间体 (2.3g, 84%),在 N_2 下将其溶于 TBAF 的 THF (1M, 2.6mL) 溶液。将反应混合物在 R. T. 下搅拌过夜。将剩余物溶于 EA (200mL) 并使用水和盐水洗涤。将有机层分离,在无水 Na_2SO_4 上干燥并过滤。将滤液浓缩至干燥,并通过硅胶上的柱 (DCM/MeOH = 100:1 至 30:1) 纯化剩余物以产生白色泡沫形式的 P15-1 (1.3g, 94%)。

[0396] (15a) 的制备:在 0°C 下,通过注射器向搅拌的 P15-1 (300mg, 0.55mmol) 和质子海绵 (235mg, 1.1mmol) 的无水 MeCN (9mL) 溶液加入 POCl_3 (169mg, 1.1mmol) 的 MeCN (1mL) 溶液。将混合物在 R. T. 下搅拌 40mins。在 0°C 下加入 2-氨基丙酸 (S)-环己基酯盐酸盐 (525mg, 2.55mmol) 和 TEA (0.1mL) 的混合物。将混合物升温至 R. T. 并搅拌 3 小时。使用饱和 NaHCO_3 淬灭反应混合物,并使用 EA (100mL $\times$ 2) 萃取。在 Na_2SO_4 上干燥合并的有机层、浓缩并通过硅胶柱 (1 ~ 4% MeOH 的 DCM 溶液) 纯化以产生黄色固体形式的粗产物 (400mg, 78.15%)。在 R. T. 下使用 80% HCOOH (50mL) 将粗产物处理 16 小时。将溶剂去除,并通过 RP HPLC 纯化剩余物以产生白色固体形式的化合物 15a (40mg, 14%)。 ^1H NMR (MeOD, 400MHz) δ 7.82 (d, $J = 7.6$ Hz, 1H), 6.09 (dd, $J_1 = 2.8$ Hz, $J_2 = 14.0$ Hz, 1H), 5.98 (d, $J = 7.6$ Hz, 1H), 5.04 (ddd, $J_1 = 3.2$ Hz, $J_2 = 5.6$ Hz, $J_3 = 53.6$ Hz, 1H), 4.71–4.77 (m, 2H), 4.45 (dd, $J_1 = 5.6$ Hz, $J_2 = 12.4$ Hz, 1H), 4.14–4.18 (m, 1H), 3.97–4.01 (m, 1H), 3.84–3.92 (m, 2H), 1.31–1.87 (m, 28H), 0.99 (t, $J = 7.2$ Hz, 3H)。 ^{31}P NMR (CD_3OD , 162MHz) δ 13.94;ESI-LCMS :m/z 660 $[\text{M}+\text{H}]^+$ 。

[0397] 实施例 16

[0398] 化合物 (16a) 的制备

[0399]

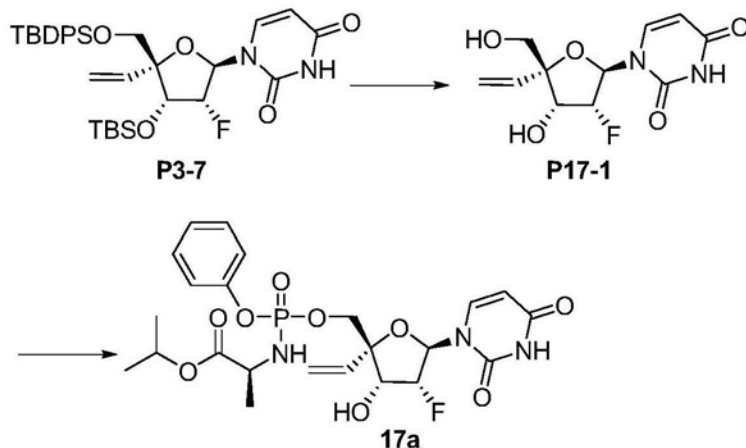


[0400] 在 -78°C 下, 向搅拌的化合物 4a(150mg, 0.56mmol) 的无水 THF(3mL) 溶液滴加 $t\text{-BuMgCl}$ (1.2mL, 1M 的 THF) 溶液。将混合物在 0°C 下搅拌 30min 并重新冷却至 -78°C 。滴加 (异丙氧基-L-丙氨酸基) 氯磷酸苯酯 (312mg, 1.2mmol) 的 THF(1.0mL) 溶液。在加入后, 将混合物在 25°C 下搅拌 16 小时。在 0°C 下使用 HCOOH (80% 水溶液) 淬灭反应。将溶剂去除, 并在硅胶上 ($\text{DCM}:\text{MeOH} = 50:1$ 至 $10:1$) 纯化剩余物以产生白色固体形式的化合物 16a (24.0mg, 15%)。 ^1H NMR (MeOD , 400MHz) δ 7.76(d, $J = 7.2\text{Hz}$, 1H), 7.17-7.38(m, 5H), 6.01-6.08(m, 2H), 5.81(d, $J = 7.6\text{Hz}$, 1H), 5.54-5.58(m, 1H), 5.35-5.38(m, 1H), 4.92-4.97(m, 2H), 4.45-4.52(m, 1H), 4.08-4.19(m, 2H), 3.88-3.92(m, 1H), 1.28-1.33(m, 3H), 1.20-1.22(m, 6H); ^{31}P NMR (CD_3OD , 162MHz) δ 7.36; ESI-LCMS m/z 541.0 $[\text{M}+\text{H}]^+$ 。

[0401] 实施例 17

[0402] 化合物 (17a) 的制备

[0403]



[0404] (P17-1) 的制备: 在 R. T. 下, 向 P3-7 (1.4g, 2.3mmol) 的 MeOH (50mL) 溶液加入 NH_4F (8.0g)。将反应混合物回流过夜。在冷却至 R. T. 后, 将混合物过滤, 并将滤液浓缩。通过硅胶柱层析 (10% MeOH 的 DCM 溶液) 纯化粗产物以产生白色固体形式的 P17-1 (410mg, 77.8%)。

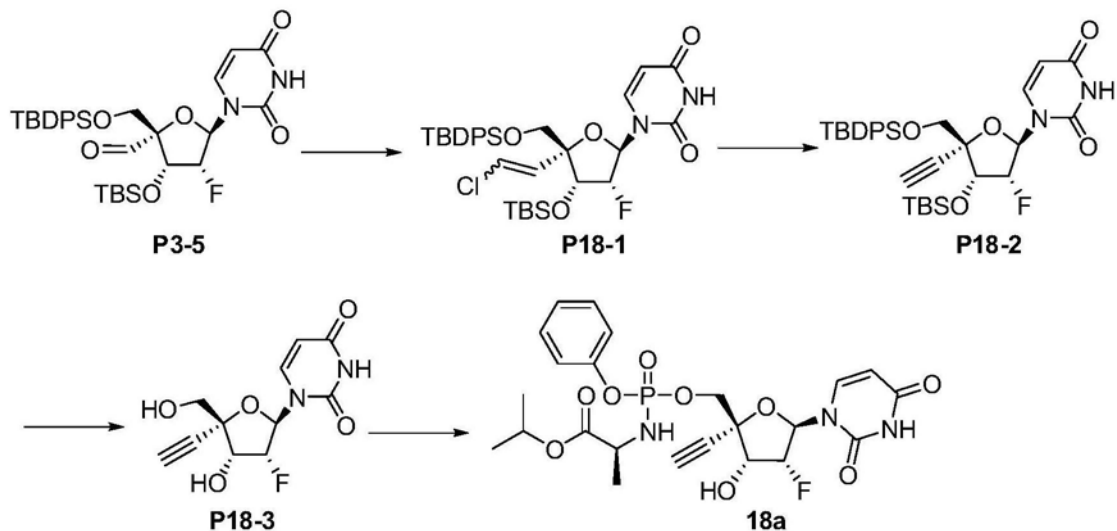
[0405] (P17) 的制备: 在 -78°C 下, 向搅拌的 P17-1 (60mg, 0.19mmol) 的无水 THF (3mL) 溶液滴加 $t\text{-BuMgCl}$ (0.38mL, 1M 的 THF) 溶液。将混合物在 0°C 下搅拌 30min 并重新冷却至 -78°C 。滴加 (异丙氧基-L-丙氨酸基) 氯磷酸苯酯 (104mg, 0.4mmol) 的 THF (0.5mL) 溶液。在加入后, 将混合物在 25°C 下搅拌 16 小时。在 0°C 下, 使用 HCOOH (80% 水溶液) 淬灭反应。将溶剂去除, 并在硅胶上 ($\text{DCM}:\text{MeOH} = 50:1$ 至 $10:1$) 纯化剩余物以产生白色固体形式的化合物 17a (两种 P 异构体的混合物, 11.0mg, 11%)。 ^1H NMR (MeOD , 400MHz) δ 7.71 (2d, $J = 8.0\text{Hz}$, 1H), 7.17-7.37 (m, 5H), 5.98-6.07 (m, 2H), 5.61, 5.68 (2d, $J = 8.0\text{Hz}$, 1H), 5.53-5.58 (m, 1H), 5.35-5.40 (m, 1H), 5.08-5.10 (m, 1H), 4.93-4.99 (m, 1H), 4.52-4.53 (m, 1H), 4.1

6-4.21 (m, 1H), 4.06-4.11 (m, 1H), 3.86-3.94 (m, 1H), 1.28-1.34 (m, 3H), 1.20-1.22 (m, 6H)。
³¹P NMR (MeOD, 162MHz) δ 3.72、3.45. ESI-LCMS :m/z 542.0 [M+H]⁺。

[0406] 实施例 18

[0407] 化合物 (18a) 的制备

[0408]



[0409] (P18-1) 的制备: 在氮气下, 在 -70 °C 下向 (氯甲基) 三苯基氯化膦 (2.1g, 6.0mmol) 的无水 THF (10mL) 溶液滴加 n-BuLi (4.6mL, 6.0mmol)。将反应在 -70 °C 下搅拌 50mins。在 -70 °C 下加入化合物 P3-9 (950mg, 1.5mmol) 的无水 THF (5mL) 溶液, 并将反应在 0 °C 下搅拌 3 小时。通过饱和 NH₄Cl 水溶液淬灭反应并使用 EtOAc 萃取。将有机层分离、干燥并浓缩以产生剩余物。通过在硅胶上的柱层析 (使用 PE:EtOAc = 6:1 洗脱) 纯化剩余物以产生黄色胶状物形式的 P18-1 (900mg, 91.2%)。

[0410] (P18-2) 的制备: 在氮气下, 在 -70 °C 下向化合物 P18-1 (600mg, 0.91mmol) 的无水 THF (18mL) 溶液滴加 n-BuLi (4.7mL, 10.9mmol)。将反应在 -70 °C 下搅拌 3 小时。通过饱和 NH₄Cl 水溶液淬灭反应并使用 EtOAc 萃取。将有机层分离、干燥并浓缩以产生剩余物。通过在硅胶上的柱层析 (使用 PE:EtOAc = 8:1 ~ 5:1 洗脱) 纯化剩余物以产生白色固体形式的 P18-2 (300mg, 53.0%)。

[0411] (P18-3) 的制备: 在 R. T. 下, 向 P18-2 (300mg, 0.44mmol) 的 MeOH (10mL) 溶液加入 NH₄F (1.0g)。将反应回流 3 小时。在冷却至 R. T. 后, 将混合物过滤, 并将滤液真空浓缩。通过在硅胶上的柱层析 (使用 DCM:MeOH = 50:1 ~ 30:1 洗脱) 纯化剩余物以产生白色固体形式的 P18-3 (135mg, 78.1%)。¹H NMR (CD₃OD, 400MHz) δ 7.84 (d, J = 8.0Hz, 1H), 6.06 (dd, J₁ = 1.6Hz, J₂ = 19.6Hz, 1H), 5.67 (d, J = 8.4Hz, 1H), 5.18-5.03 (m, 1H), 4.50 (dd, J₁ = 5.2Hz, J₂ = 21.6Hz, 1H), 3.85 (d, J = 12.4Hz, 1H), 3.72 (d, J = 12.4Hz, 1H), 3.09 (s, 1H)。

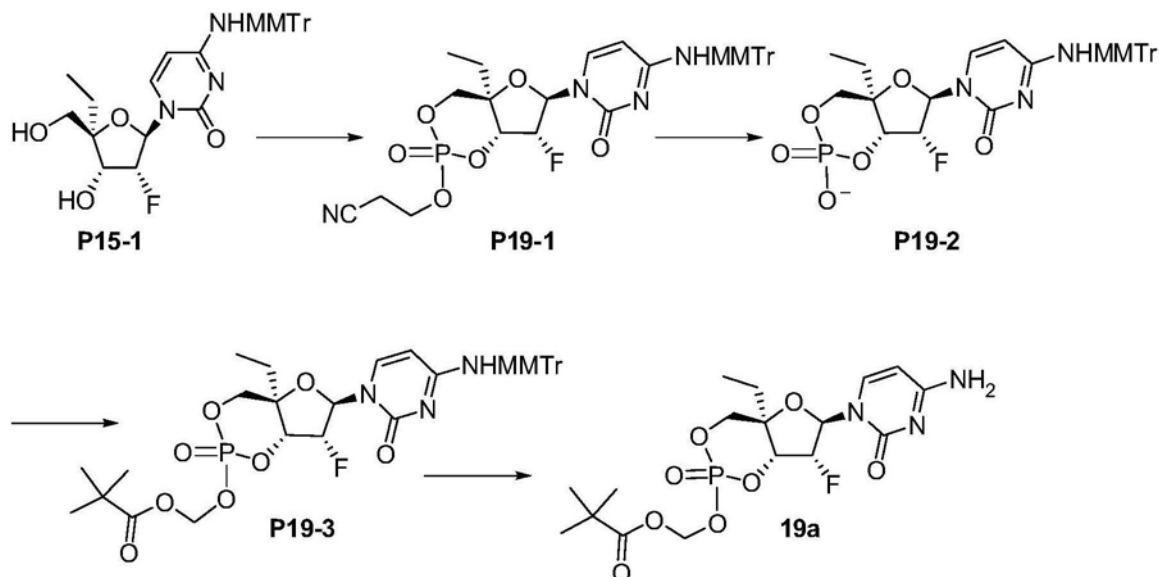
[0412] (18a) 的制备: 在氮气下, 在 -70 °C 下向 P18-3 (130mg, 0.5mmol) 的无水 THF (4mL) 溶液滴加 t-BuMgCl (1.0mL, 1.0mmol)。将反应在 R. T. 下搅拌 30mins。在 -70 °C 下, 加入 (异丙氧基-L-丙氨酸基) 氯磷酸苯酯的无水 THF (1M, 0.8mL, 0.78mmol) 溶液, 并将反应混合物在 R. T. 下搅拌 5 小时。通过 HCOOH 淬灭反应, 并将混合物真空浓缩。通过在硅胶上的柱层析 (DCM:MeOH = 60:1) 纯化剩余物以产生白色固体形式的化合物 18a (两种 P 异构体的混合物, 25mg, 7.7%)。¹H NMR (CD₃OD, 400MHz) δ 7.64, 7.60 (2d, J = 7.6Hz, 1H), 7.32-7.36 (m,

2H), 7.16–7.25 (m, 3H), 5.95–6.01 (m, 1H), 5.67, 5.62 (2d, $J = 8.0\text{Hz}$, 1H), 5.10–5.25 (m, 1H), 4.93–4.97 (m, 1H), 4.49–4.59 (m, 1H), 4.33–4.42 (m, 1H), 4.24–4.29 (m, 1H), 3.86–3.94 (m, 1H), 3.25, 3.22 (2s, 1H), 1.28–1.34 (m, 3H), 1.20–1.23 (m, 6H); ESI-MS : m/z 540.2 $[M+H]^+$ 。

[0413] 实施例 19

[0414] 化合物 (19a) 的制备

[0415]



[0416] (P19-1) 的制备: 将 P15-2 (1.2g, 2.2mmol) 溶于干燥的乙腈 (20mL), 并加入 0.45M 四唑 (24.0mL, 11.0mmol) 和 3-(双(二异丙基氨基)膦基氧基)丙腈 (1.13g, 3.74mmol)。在 R. T. 下, 在 N_2 下将反应混合物搅拌 1 小时。加入 TBDPH (2.7mL, 15mmol), 并将混合物搅拌 1 小时。通过 $Na_2S_2O_3$ 溶液淬灭反应并使用 EA 萃取。在 Na_2SO_4 上干燥有机层并浓缩。通过硅胶上的柱 (DCM:MeOH = 100:1 至 40:1) 纯化剩余物以产生白色固体形式的 P19-1 (759mg, 52%)。

[0417] (P19-2) 的制备: 将 P19-1 (750mg, 1.14mmol) 溶于饱和 NH_3 的 MeOH 溶液。将混合物在 R. T. 下搅拌 2 小时。将溶液浓缩至干燥以产生黄色固体形式的粗 P19-2 (662mg, 100%)。 ^1H NMR (DMSO- d_6 , 400MHz) δ 8.60 (s, 1H), 8.28 (s, 1H), 7.48 (d, $J = 7.6\text{Hz}$, 1H), 7.12–7.29 (m, 12H), 6.83 (d, $J = 8.8\text{Hz}$, 2H), 6.29 (d, $J = 7.6\text{Hz}$, 1H), 5.88 (d, $J = 8.8\text{Hz}$, 1H), 5.10 (d, $J = 4.8\text{Hz}$, 1H), 4.42–4.45 (m, 1H), 3.72 (s, 3H), 1.64–1.91 (m, 2H), 1.10–1.13 (m, 2H), 0.83–0.86 (m, 3H)。 ^{31}P NMR (CD_3OD , 400MHz) δ -4.48; 负-ESI-LCMS : m/z 606 $[M-H]^-$ 。

[0418] (P19-3) 的制备: 使用吡啶将 P19-2 (292mg, 0.47mmol) 共蒸发两次并溶于无水 DMF (0.5mL)。加入 DIPEA (1.2mL), 随后加入 2,2-二甲基-丙酸碘甲酯 (680mg, 2.8mmol)。在 N_2 下将反应混合物在 R. T. 下搅拌 16 小时。通过 $Na_2S_2O_3$ 溶液淬灭反应并使用 EA 萃取。在 Na_2SO_4 上干燥有机层并浓缩。通过硅胶上的柱 (DCM:MeOH = 100:1 至 30:1) 纯化剩余物以产生白色固体形式的 P19-3 (95mg, 30%)。

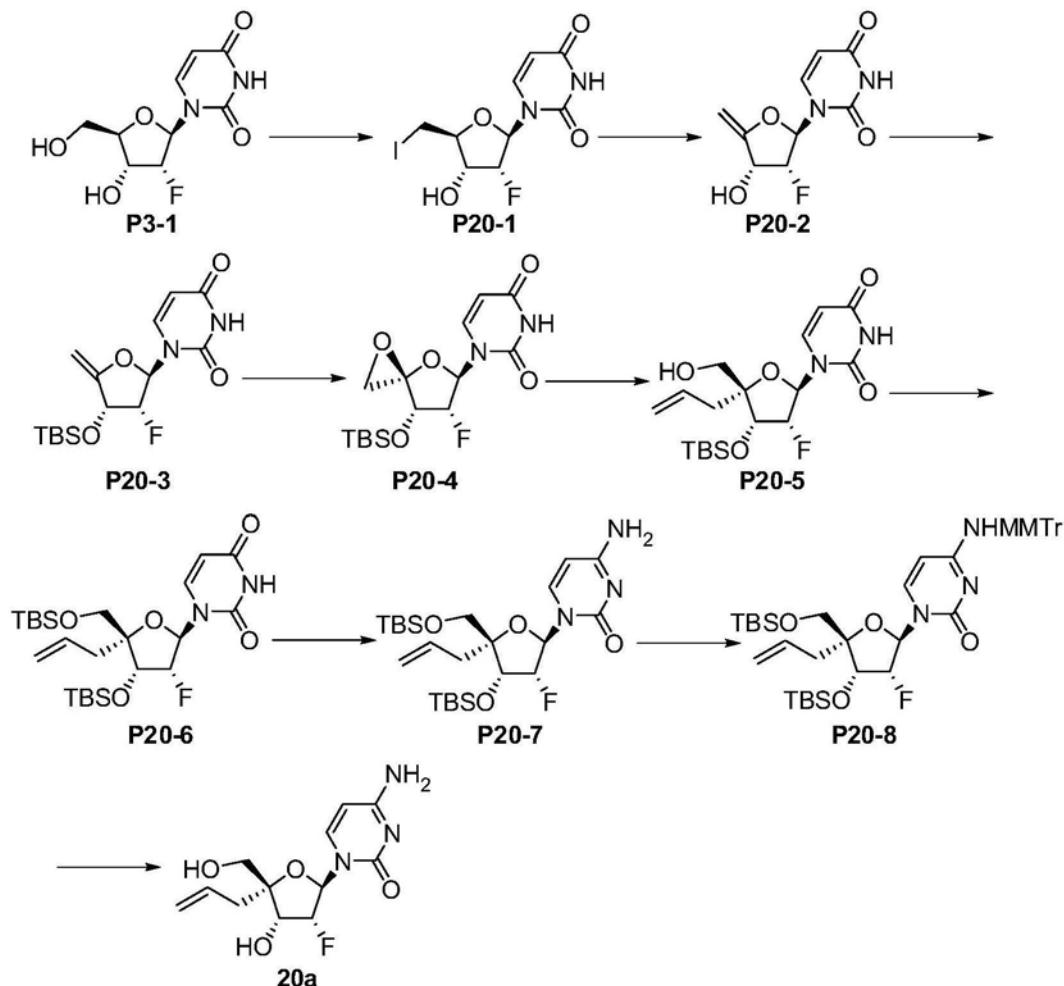
[0419] (19a) 的制备: 将 P19-3 (95mg, 0.13mmol) 溶于 80% $HCOOH$ 水溶液, 并将混合物在 R. T. 下搅拌 16 小时。将溶剂去除, 并通过 RP HPLC (MeCN 和 0.1% $HCOOH$ 的水) 纯化剩余物以产生白色固体形式的化合物 19a (10mg, 17%)。 ^1H NMR (CD_3OD , 400MHz) δ 7.69 (d, $J = 7.2\text{Hz}$, 1H), 5.91 (d, $J = 7.6\text{Hz}$, 1H), 5.84 (d, $J = 22.0\text{Hz}$, 1H), 5.73 (d, $J = 14.0\text{Hz}$, 2H), 5.52 (d, $J = 5.2\text{Hz}$, 1H), 5.13–5.22 (m, 1H), 4.53–4.61 (m, 1H), 4.31 (d, J

= 9.6Hz, 1H), 1.92–2.08 (m, 2H), 1.23 (s, 9H), 1.03–1.07 (m, 3H); ^{31}P NMR (CD_3OD , 162MHz) δ -7.93; ESI-LCMS: m/z 450 $[\text{M}+\text{H}]^+$.

[0420] 实施例 20

[0421] 化合物 (20a) 的制备

[0422]



[0423] (P20-1) 的制备: 在 0 °C 下, 向搅拌的 P3-1 (20.0g, 81.3mmol)、咪唑 (15.9g, 234.0mmol)、 PPh_3 (53.5g, 203.3mmol) 和吡啶 (90mL) 的无水 THF (360mL) 悬浮液滴加 I_2 (41.3g, 162.6mmol) 的 THF (350mL) 溶液。在加入后, 将混合物升温至 R. T. 并搅拌 14 小时。使用 $\text{Na}_2\text{S}_2\text{O}_3$ 水溶液 (150mL) 淬灭溶液并使用 EA 萃取。在 Na_2SO_4 上干燥有机层并浓缩。在硅胶柱上 (DCM:MeOH = 100:1 至 10:1) 纯化剩余物以产生白色固体形式的 P20-1 (22.1g, 76.4 %)。 ^1H NMR (CD_3OD , 400MHz) δ 7.70 (d, J = 8.0Hz, 1H), 5.88 (dd, J_1 = 1.6Hz, J_2 = 20.8Hz, 1H), 5.71 (d, J = 8.4Hz, 1H), 5.24 (dd, J_1 = 2.0Hz, J_2 = 5.2Hz, 1H), 5.10 (dd, J_1 = 2.0Hz, J_2 = 5.2Hz, 1H), 3.78–3.83 (m, 1H), 3.61–3.65 (m, 1H), 3.44 (dd, J_1 = J_2 = 6.0Hz, 1H)。

[0424] (P20-2) 的制备: 在 0 °C 下, 在 10mins 内向搅拌的 P20-1 (22.1g, 62.1mmol) 的无水 THF (200mL) 溶液滴加 DBU (14.2g, 93.1mmol) 的 THF (50mL)。将混合物在 60 °C 下搅拌 6 小时。使用 NaHCO_3 水溶液 (200mL) 淬灭反应并使用 EA 萃取。使用盐水洗涤有机层并在 Na_2SO_4 上干燥。将溶剂去除, 并在硅胶柱上 (MeOH:DCM = 1/100 至 1/30) 纯化剩余

物以产生白色固体形式的 P20-2 (8.7g, 61.5%)。¹H NMR (CD₃OD, 400MHz) δ 7.51 (d, J = 8.0Hz, 1H), 6.05 (dd, J₁ = 1.2Hz, J₂ = 17.2Hz, 1H), 5.73 (d, J = 8.0Hz, 1H), 5.26 (dd, J₁ = 1.2Hz, J₂ = 4.8Hz, 1H), 5.13 (dd, J₁ = 1.2Hz, J₂ = 4.8Hz, 1H), 4.63 (dd, J₁ = 2.0Hz, J₂ = 3.2Hz, 1H), 4.41 (dd, J₁ = J₂ = 2.0Hz, 1H)。

[0425] (P20-3) 的制备: 在 0℃ 下, 向搅拌的 P20-2 (3.2g, 14.0mmol) 的无水吡啶 (10mL) 和 DCM (100mL) 溶液滴加 TBSCl (4.2g, 28.0mmol) 溶液。在 R.T. 下, 将搅拌继续 18 小时。使用 DCM 稀释混合物。使用盐水洗涤有机层并在 Na₂SO₄ 上干燥。将溶剂去除, 并在硅胶柱上 (10% MeOH 的 DCM 溶液) 纯化剩余物以产生白色固体形式的 P20-3 (3.4g, 70.8%)。

[0426] (P20-4) 的制备: 在 0℃ 下, 向搅拌的 NaHCO₃ 的 H₂O (250mL) 和丙酮 (200mL) 溶液加入过硫酸氢钾 (30.0×4g)。将混合物升温至 R.T., 并在 -78℃ 下在稍微减压下收集蒸馏物 (120mL) 以产生 DMD0 的丙酮溶液。在 -40℃ 下, 向搅拌的 P20-3 (250.0mg, 0.7mmol) 的 DCM (20mL) 溶液加入 DMD0 (120mL) 溶液和 MgSO₄。将混合物升温至 R.T., 然后搅拌 2 小时。将溶液过滤, 并将滤液直接用于下一步。

[0427] (P20-5) 的制备: 在 -40℃ 下, 向搅拌的 P20-4 (500.0mg, 1.4mmol) 的无水 DCM (50mL) 溶液加入烯丙基-三甲基-硅烷 (760.0mg, 6.7mmol) 和 SnCl₄ (1.2g, 4.5mmol)。将混合物升温并在 0℃ 下搅拌 1 小时。使用饱和 NaHCO₃ 淬灭反应并使用 DCM 萃取。在 Na₂SO₄ 上干燥有机层并浓缩。在硅胶柱上 (20 ~ 50% EA 的 PE) 纯化剩余物以产生白色泡沫形式的 P20-5 (120mg, 41%)。¹H NMR (CD₃OD, 400MHz) δ 8.01 (d, J = 8.4Hz, 1H), 6.12 (dd, J₁ = 3.6Hz, J₂ = 15.2Hz, 1H), 5.87-5.96 (m, 1H), 5.71 (d, J = 8.4Hz, 1H), 5.06-5.22 (m, 3H), 4.60 (dd, J₁ = 5.6Hz, J₂ = 14.4Hz, 1H), 3.72 (d, J = 11.6Hz, 1H), 3.48 (d, J = 11.6Hz, 1H), 2.62-2.67 (m, 1H), 2.23-2.29 (m, 1H); ESI-LCMS :m/z = 422 [M+Na]⁺。

[0428] (P20-6) 的制备: 在 R.T. 下, 向搅拌的 P20-5 (270.0mg, 0.7mmol) 的干燥 DCM 溶液加入咪唑 (400.0mg, 5.9mmol) 和 TBSCl (390.0mg, 2.6mmol)。将混合物在 R.T. 下搅拌 18 小时。使用 EA 稀释溶液。使用盐水洗涤溶剂并在 Na₂SO₄ 上干燥。将溶剂去除, 并在硅胶柱上 (20 ~ 40% EA 的 PE) 纯化剩余物以产生白色泡沫形式的化合物 P20-6 (280mg, 80.7%)。ESI-LCMS :m/z 537 [M+Na]⁺。

[0429] (P20-7) 的制备: 在 R.T. 下, 向搅拌的 P20-6 (280.0mg, 0.5mmol) 的干燥 MeCN 溶液加入 TPSCl (350.0mg, 1.2mmol)、NEt₃ (400.0mg, 4.0mmol) 和 DMAP (270.0mg, 2.2mmol)。将混合物在 R.T. 下搅拌 18 小时。使用氨水淬灭溶液。使用盐水洗涤有机层并在 Na₂SO₄ 上干燥。将溶剂去除, 并通过 TLC (使用 EA) 纯化剩余物以产生化合物白色泡沫形式的 P20-7 (240.0mg, 85.7%)。ESI-LCMS :m/z 514 [M+H]⁺。

[0430] (P20-8) 的制备: 在 R.T. 下, 向搅拌的 P20-7 (270.0mg, 0.5mmol) 的干燥 DCM 溶液加入 AgNO₃ (1.5g, 8.8mmol)、MMTrCl (450.0mg, 1.5mmol) 和三甲吡啶 (500.0mg, 4.1mmol)。将混合物在 R.T. 下搅拌 18 小时。使用 DCM 稀释溶液。使用盐水洗涤有机层并在 Na₂SO₄ 上干燥。将溶剂去除, 并在硅胶柱上 (20 ~ 40% EA 的 PE) 纯化剩余物以产生白色泡沫形式的化合物 P20-8 (300mg, 81.6%)。ESI-LCMS :m/z 786 [M+H]⁺。

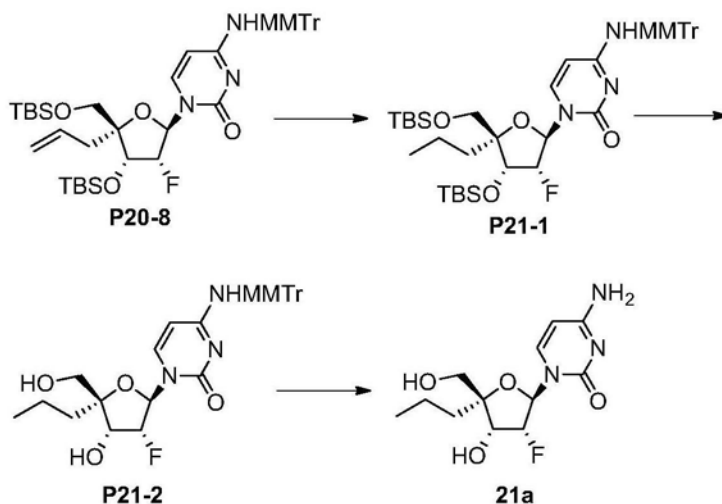
[0431] (20a) 的制备: 向搅拌的 P20-8 (170.0mg, 0.3mmol) 的干燥 MeOH 溶液加入 NH₄F (300.0mg, 8.1mmol), 并将混合物回流 24 小时。在减压下去除溶剂, 并在硅胶柱上 (2 ~ 5% MeOH 的 DCM 溶液) 纯化剩余物以产生粗产物。通过 RP HPLC (水和 0.1% HCOOH

的 MeCN) 进一步纯化粗产物以产生白色固体形式的化合物 20a (47.0mg, 49.8%)。¹H NMR (CD₃OD, 400MHz) δ 8.13 (d, J = 8.4Hz, 1H), 6.12 (dd, J_1 = 3.2Hz, J_2 = 12.0Hz, 1H), 5.87-5.97 (m, 2H), 4.98-5.14 (m, 3H), 4.45 (dd, J_1 = 5.2Hz, J_2 = 17.6Hz, 1H), 3.71 (d, J = 11.6Hz, 1H), 3.54 (d, J = 11.6Hz, 1H), 2.54-2.59 (m, 1H), 2.33-2.39 (m, 1H); ESI-LCMS :m/z 286 [M+H]⁺。

[0432] 实施例 21

[0433] 化合物 (21a) 的制备

[0434]



[0435] (P21-1) 的制备: 向搅拌的 P20-8 (250.0mg, 0.3mmol) 的 MeOH 溶液加入 Pd/C (500.0mg), 并在 R. T. 下, 在 H₂ (气球) 下将混合物搅拌 18 小时。将反应过滤, 并在减压下去除溶剂。通过制备 TLC (30% EtOAc 的 PE) 纯化剩余物以产生白色泡沫形式的 P21-1 (210.0mg, 84.0%)。

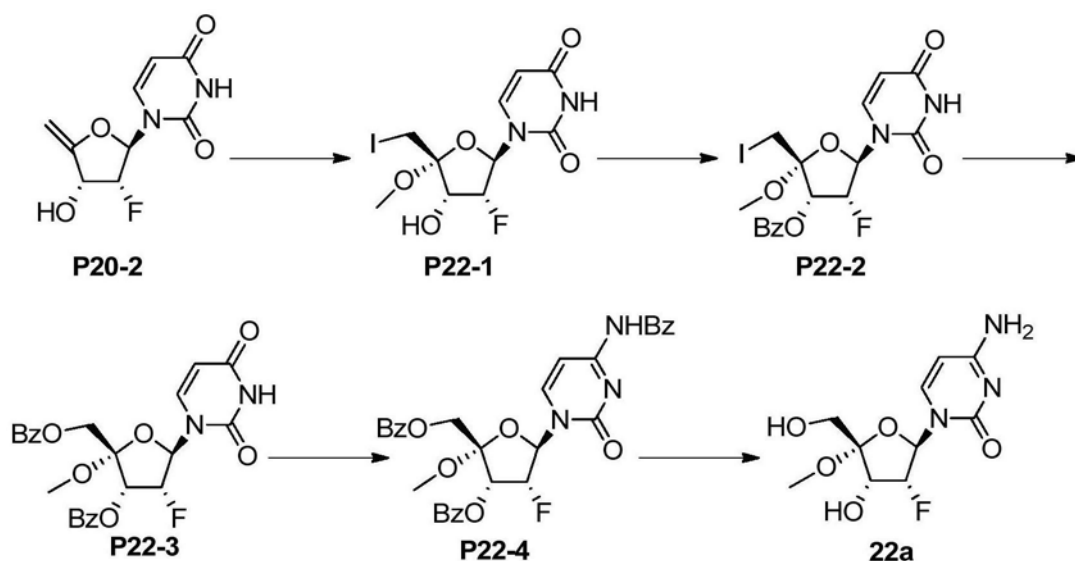
[0436] (P21-2) 的制备: 向搅拌的 P21-1 (210.0mg, 0.3mmol) 的干燥 THF 溶液加入 TBAF (1mL, 1mmol), 并将混合物在 R. T. 下搅拌 18 小时。在减压下去除溶剂, 并通过制备 TLC (30% EtOAc 的 PE) 纯化剩余物以产生白色泡沫形式的化合物 21a (111.2mg, 74.6%)。¹H NMR (DMSO-d₆, 400MHz) δ 8.49 (s, 1H), 7.75 (d, J = 6.8Hz, 1H), 6.83-7.32 (m, 14H), 6.25 (d, J = 7.6Hz, 1H), 5.95 (dd, J_1 = 4.8Hz, J_2 = 14.8Hz, 1H), 5.48 (d, J = 5.6Hz, 1H), 4.86-5.15 (m, 2H), 4.15-4.21 (m, 1H), 3.72 (s, 3H), 3.38-3.49 (m, 2H), 1.24-1.58 (m, 4H), 0.84 (t, J = 7.2Hz, 3H); ESI-MS :m/z 560 [M+H]⁺。

[0437] (P21) 的制备: 将化合物 P21-2 (81mg) 溶于甲酸 (80%) 和水 (20%) 的混合物 (5mL)。将生成的溶液在 R. T. 下搅拌 3 小时, 然后浓缩。使用甲醇 / 甲苯将剩余物共蒸发三次。使用 5-12% 甲醇的 DCM 溶液在硅胶上层析产生两种化合物的混合物, 使用一滴浓氨水将其溶于甲醇并浓缩。在使用 5-12% 甲醇的 DCM 溶液的硅胶上纯化剩余物以产生白色固体形式的化合物 21a (27mg); ¹H NMR (CD₃OD, 400MHz) δ 8.05 (d, J = 7.6Hz, 1H), 6.06 (dd, J_1 = 2.8Hz, J_2 = 16Hz, 1H), 5.87 (d, J = 7.6Hz, 1H), 5.10 (dd, J = 3.2, 5.2Hz, 0.5H), 4.96 (dd, J = 3.2, 5.2Hz, 0.5H), 4.42 (dd, J = 5.6, 17.2Hz, 1H), 3.67 (dd, J = 11.6, 76Hz, 2H), 1.70-1.79 (m, 1H), 1.31-1.61 (m, m, 3H), 0.94 (t, J = 6.8Hz, 3H)。MS :m/z 417 [M+2- 甲基庚胺]⁺。

[0438] 实施例 22

[0439] 化合物 (22a) 的制备

[0440]



[0441] (P22-1) 的制备: 在 R. T. 下, 向 P20-2 (5.23g, 23.1mmol) 的无水 MeOH (50mL) 溶液加入 PbCO_3 (12.7g, 46.3mmol)。然后, 在 0°C 下滴加 I_2 (11.7g, 46.3mmol) 的 MeOH (10mL) 溶液。将反应混合物在 R. T. 下搅拌过夜。使用 $\text{Na}_2\text{S}_2\text{O}_3$ 淬灭反应并溶于 EA。在 Na_2SO_4 上干燥有机层并浓缩。通过柱 (DCM/MeOH = 100/1 至 20/1) 纯化剩余物以产生白色固体形式的 P22-1 (5.6g, 71.8%)。 ^1H NMR (CD_3OD , 400MHz) δ 7.67 (d, $J = 8.0\text{Hz}$, 1H), 5.88 (dd, $J_1 = J_2 = 7.6\text{Hz}$, 1H), 5.73 (d, $J = 8.0\text{Hz}$, 1H), 5.24 (dd, $J_1 = 4.4\text{Hz}$, $J_2 = 6.4\text{Hz}$, 1H), 5.11 (dd, $J_1 = 6.4\text{Hz}$, $J_2 = 6.0\text{Hz}$, 1H); 4.65 (dd, $J_1 = 20.0\text{Hz}$, $J_2 = 20.4\text{Hz}$, 1H), 3.67 (d, $J = 11.6\text{Hz}$, 1H), 3.54 (d, $J = 11.6\text{Hz}$, 1H), 3.43 (s, 3H)。

[0442] (P22-2) 的制备: 在 0°C 下, 向搅拌的 P22-1 (5.6g, 14.5mmol) 的无水吡啶 (20mL) 溶液滴加 BzCl (2.9g, 20.9mmol)。将混合物在 R. T. 下搅拌 10 小时。使用 H_2O 淬灭反应, 并将溶液浓缩。将剩余物溶于 EA 并使用饱和 NaHCO_3 洗涤。在 Na_2SO_4 上干燥有机层并浓缩。在硅胶柱上 (20 ~ 40% EA 的 PE) 纯化剩余物以产生白色泡沫形式的 P22-2 (4.9g, 74.2%)。

[0443] (P22-3) 的制备: 将 P22-2 (4.9g, 10.0mmol)、 BzONa (14.4g, 100mmol) 和 15-冠-5 (22.0g, 100mmol) 溶于 DMF (200mL)。将混合物在 $60-70^\circ\text{C}$ 下搅拌 3 天。通过过滤去除沉淀, 并使用 EA 稀释滤液。使用盐水洗涤溶剂并在 Na_2SO_4 上干燥。将溶剂去除, 并在硅胶柱上 (20 ~ 60% EA 的 PE) 纯化剩余物以产生白色泡沫形式的 P22-3 (2.3g, 47.9%)。

[0444] (P22-4) 的制备: 将 P22-3 (2.3g, 4.8mmol)、DMAP (1.2g, 9.6mmol)、TPSCl (2.9g, 9.6mmol) 和 Et_3N (0.97g, 9.6mmol) 悬浮于 MeCN (10mL)。将混合物在 R. T. 下搅拌 14 小时。将 NH_3 的 THF (在 0°C 下饱和, 100mL) 加入至混合物, 并将混合物在 R. T. 下搅拌 2 小时。将溶剂去除, 并通过柱 (DCM/MeOH = 100:1 至 50:1) 纯化剩余物以产生粗产物 (1.2g)。将粗产物溶于吡啶, 并加入 BzCl (0.42g, 3.0mmol)。将混合物在 R. T. 下搅拌 16 小时并使用水淬灭。将溶剂去除, 并在硅胶柱上 (PE:EA = 2:1 至 1:1) 纯化剩余物以产生白色泡沫形式的 P22-4 (460mg, 31%)。

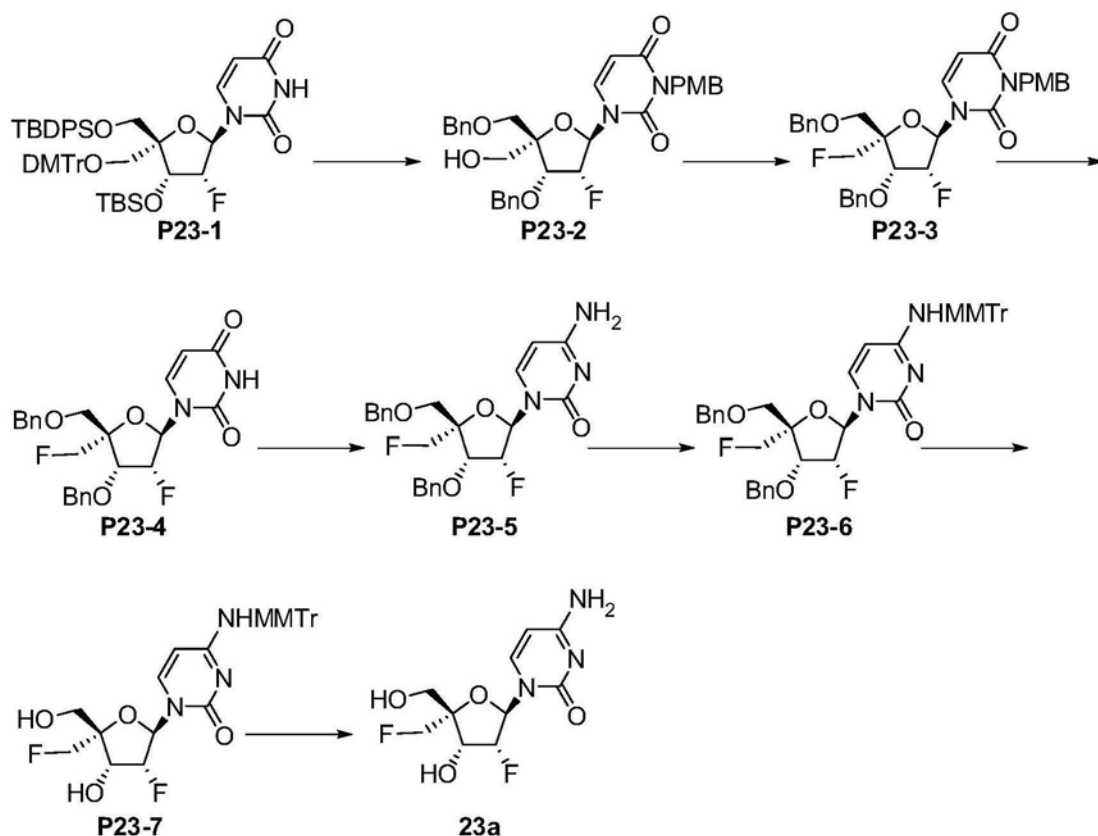
[0445] (22a) 的制备: 将 P22-4 (0.46g, 0.8mmol) 溶于饱和甲醇铵 (100mL), 并将混合物在 R. T. 下搅拌 14 小时。将溶剂去除, 并将剩余物溶于 H_2O 并使用 DCM 洗涤。将水

相冻干并通过制备 HPLC (0.1% 甲酸的水 / 乙腈) 进一步纯化以产生白色固体形式的化合物 22a (145mg, 78.9 %)。 ^1H NMR (CD_3OD , 400MHz) δ 7.88 (d, $J = 7.6\text{Hz}$, 1H), 6.03 (d, $J = 18.4\text{Hz}$, 1H), 5.87 (d, $J = 7.6\text{Hz}$, 1H), 4.86–5.00 (m, 1H), 4.49 (dd, $J_1 = 23.2\text{Hz}$, $J_2 = 22.8\text{Hz}$, 1H), 3.90 (d, $J = 12.0\text{Hz}$, 1H), 3.66 (d, $J = 12.0\text{Hz}$, 1H), 3.41 (s, 3H); ESI-MS : m/z 276 $[\text{M}+\text{H}]^+$ 。

[0446] 实施例 23

[0447] 化合物 (23a) 的制备

[0448]



[0449] (P23-2) 的制备: 向溶液 P23-1 (3.1g, 4.5mmol) 的 DMF (30mL) 加入无水 K_2CO_3 (1.24g, 9.03mmol) 和 PMBCl (1.40g, 9.03mmol)。将混合物在环境温度下搅拌过夜。使用水淬灭反应并使用 EA 萃取。将有机层浓缩, 并在硅胶柱上 (PE:EA = 10:1 至 4:1) 纯化剩余物以产生白色固体形式的中间体 (2.36g, 74.8 %)。 ^1H NMR (CDCl_3 , 400MHz) 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, $J = 11.2\text{Hz}$, 1H), 1.21 (s, 9H), 0.89 (m, 9H), 0.01–0.11 (m, 6H)。将中间体用于下一步。

[0450] 在 R. T. 下向搅拌的中间体 (11.0g, 10.47mmol) 的无水 THF (100mL) 溶液加入 TBAF (8.20g, 31.42mmol), 并将混合物在 R. T. 下搅拌 5 小时。将溶液去除, 并在硅胶柱上 (PE:EA = 5:1 至 1:1) 纯化剩余物以产生白色固体形式的第二中间体 (5.99g, 82 %)。

[0451] 在 0°C 下, 向搅拌的第二中间体 (500mg, 0.716mmol) 的无水 DMF (10mL) 溶液滴加 NaH (51.5mg, 2.14mmol) 和 BnBr (365mg, 2.14mmol)。将混合物在 R. T. 下搅拌过夜。使用水淬灭溶液并使用 EA 萃取。在硅胶柱上 (PE:EA = 10:1 至 4:1) 纯化浓缩的有机相以产生白

色固体形式的第三中间体 (496mg, 79%)。

[0452] 在 R. T. 下将第三中间体 (2.5g, 2.84mmol) 溶于 80% HOAc (25mL), 并将混合物在 R. T. 下搅拌过夜。使用 MeOH 淬灭反应, 并将溶剂去除。在硅胶柱上 (PE:EA = 5:1 至 1:1) 纯化粗物质以产生白色固体形式的 P23-2 (1.2g, 73%)。

[0453] (P23-3) 的制备: 在 -78 °C 下, 向搅拌的 DAST (1.39g, 8.68mmol) 的无水甲苯 (15mL) 溶液滴加 P23-2 (1.0g, 1.73mmol) 溶液。将混合物在 -78 °C 下搅拌 30mins。将溶液逐渐加热至 60 °C, 然后搅拌过夜。将混合物倾入饱和 Na₂CO₃ 溶液。在硅胶柱上 (PE:EA = 10:1 至 4:1) 纯化浓缩的有机相以产生白色固体形式的 P23-3 (449mg, 45%)。¹H NMR (CD₃OD, 400MHz) δ 7.87 (d, J = 8.4Hz, 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)。

[0454] (P23-4) 的制备: 将 P23-3 (1.20g, 2.07mmol) 和 CAN (3.41g, 6.23mmol) 混合物的 MeCN: 水 (3:1, 10mL) 溶液在 R. T. 下搅拌过夜。加入盐水 (10mL), 并使用 EA 萃取混合物。将合并的有机提取物干燥并在减压下蒸发。通过在硅胶上层析 (PE:EA = 10:1 至 2:1) 纯化剩余物以产生黄色固体形式的 P23-4 (475mg, 49.8%)。

[0455] (P23-5) 的制备: 在 R. T. 下向搅拌的 P23-4 (550mg, 210mmol) 的无水 MeCN (10mL) 溶液加入 TPSCl (725mg, 2.40mmol)、DMAP (293mg, 2.40mmol) 和 TEA (242mg, 2.40mmol), 并将混合物在 R. T. 下搅拌过夜。加入 NH₄OH (25mL), 并将混合物搅拌 2 小时。将溶剂去除, 并在硅胶柱上 (PE:EA = 8:1 至 2:1) 纯化剩余物以产生白色固体形式的 P23-5 (700mg 粗物质)。¹H NMR (CD₃OD, 400MHz) δ 7.86 (d, J = 8.4Hz, 1H), 7.27-7.36 (m, 10H), 6.13 (dd, J₁ = 17.2Hz, J₂ = 2.0Hz, 1H), 5.48-5.53 (m, 1H), 5.11-5.26 (m, 1H), 4.44-4.74 (m, 7H), 3.89 (dd, J₁ = 10.4Hz, J₂ = 2.0Hz, 1H), 3.69 (dd, J₁ = 10.8Hz, J₂ = 1.6Hz, 1H)。

[0456] (P23-6) 的制备: 在 R. T. 下向搅拌的 P23-5 (1.0g, 2.18mmol) 的无水 DCM (15mL) 溶液加入 MMTrCl (2.02g, 6.56mmol) 和 AgNO₃ (1.11g, 6.56mmol), 并将混合物在 R. T. 下搅拌过夜。将固体滤除并使用 DCM 洗涤。使用盐水洗涤滤液并在 Na₂SO₄ 上干燥。将有机相浓缩, 并在硅胶柱上 (PE:EA = 8:1 至 2:1) 纯化剩余物以产生白色固体形式的 P23-6 (520mg, 41%)。

[0457] (P23-7) 的制备: 向搅拌的 P23-6 (520mg, 0.713mmol) 的丙酮溶液加入甲酸铵 (2.0g, 31.7mmol, in portions) 和 10% 钯 / 碳 (1.0g)。将混合物回流 12 小时。将催化剂滤除并使用溶剂洗涤。将滤液加入 EA 并使用盐水洗涤。通过柱层析 (DCM:MeOH = 100:1 至 15:1) 和制备 TLC 纯化浓缩的有机相以产生白色固体形式的 P23-7 (270mg, 69.0%)。¹H NMR (CD₃OD, 400MHz) δ 8.54 (s, 1H), 7.73 (d, J = 7.6Hz, 1H), 7.13-7.32 (m, 12H), 6.83 (d, J = 8.4Hz, 2H), 6.29 (d, J = 7.6Hz, 1H), 5.99-6.04 (m, 1H), 5.82 (d, J = 5.6Hz, 1H), 5.39 (t, J = 5.2Hz, 1H), 5.09 (t, J = 5.2Hz, 1H), 4.32-4.58 (m, 3H), 3.54-3.72 (m, 5H)。ESI-MS :m/z 549.6 [M+H]⁺。

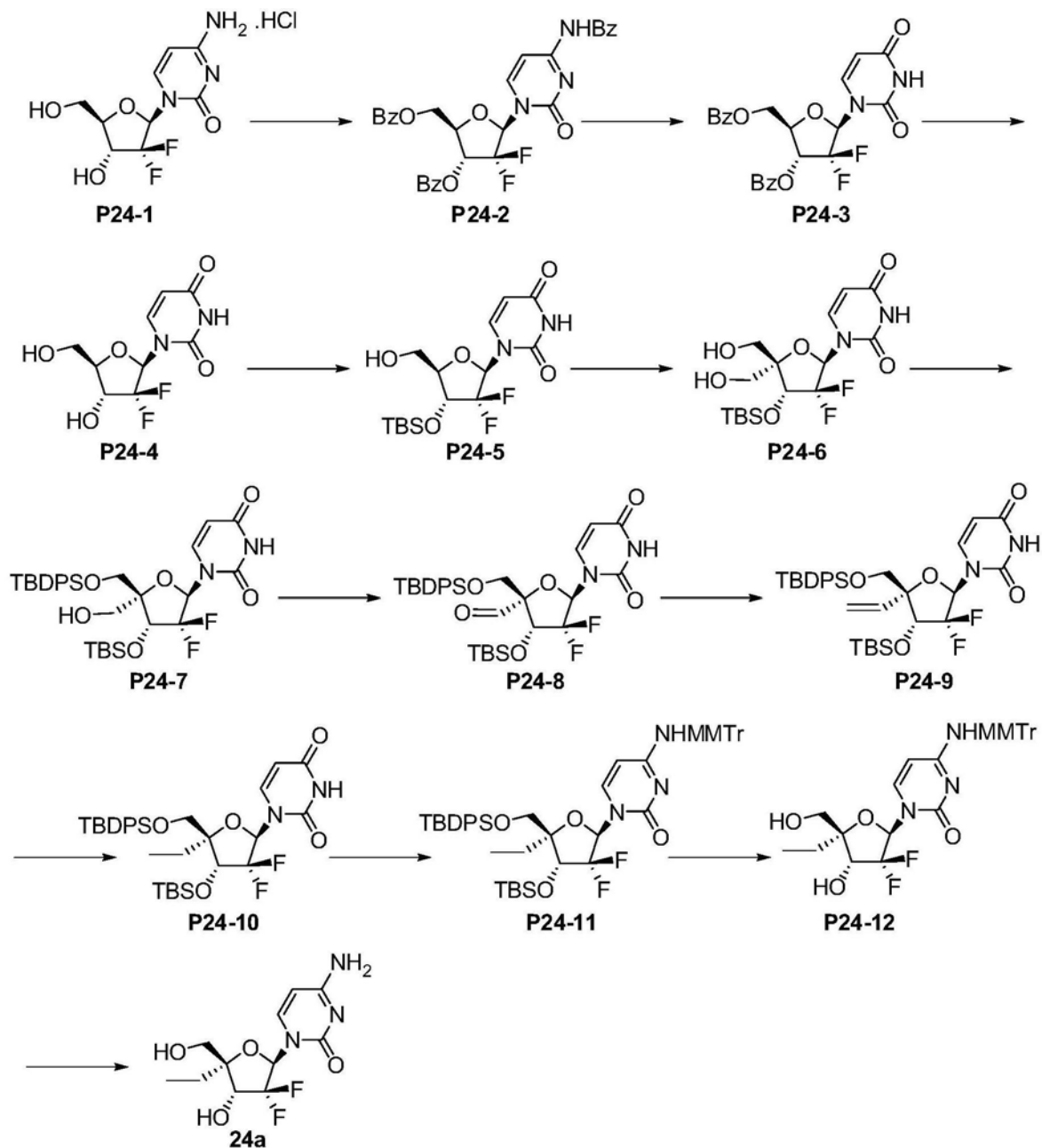
[0458] (23a) 的制备: 在 R. T. 下将 P23-7 (130mg, 0.236mmol) 溶于 80% HCOOH (20mL), 并将混合物在 50 °C 下搅拌 12 小时。将溶剂去除, 并使用甲苯将剩余物共蒸发两次。在 60 °C 下将剩余物重新溶于 MeOH (20mL) 并继续搅拌 48 小时。将溶剂去除, 并通过柱层析 (DCM:MeOH = 100:1 至 10:1) 纯化剩余物以产生白色固体形式的化合物 23a (45mg, 69.0%)。¹H NMR (CD₃OD, 400MHz) δ 8.00 (d, J = 7.6Hz, 1H), 6.13 (dd, J₁ =

16.0Hz, $J_2 = 4.0\text{Hz}$, 1H), 5.89(d, $J = 7.6\text{Hz}$, 1H), 5.18–5.21(m, 1H), 5.05–5.07(m, 1H), 4.60(s, 1H), 4.51–4.57(m, 2H), 3.84(dd, $J_1 = 12.0\text{Hz}$, $J_2 = 2.0\text{Hz}$, 1H), 3.75(dd, $J_1 = 12.0\text{Hz}$, $J_2 = 2.0\text{Hz}$, 1H)。ESI-MS :m/z 277.8[M+H]⁺, 554.8[2M+H]⁺。

[0459] 实施例 24

[0460] 化合物 (24a) 的制备

[0461]



[0462] (P24-2) 的制备: 在 25℃ 下向 P24-1 (30.0g, 100.0mmol) 的吡啶 (300mL) 溶液加入 BzCl (56.0g, 400mmol)。将混合物在 25℃ 下搅拌 15 小时。将混合物浓缩并通过柱层析 (PE:EA = 20:1 至 2:1) 纯化以产生粗 P24-2 (55.0g, 81%)。

[0463] (P24-3) 的制备: 将 P24-2 (55.0g, 92mmol) 溶于 80% HOAc 水溶液, 并将混合物回流 14 小时。在减压下去除溶剂, 并使用甲苯共蒸发剩余物。在硅胶柱上 (PE/EA = 4:1 至 2:1) 纯化剩余物以产生白色固体形式的 P24-3 (39.2g, 83%)。

[0464] (P24-4) 的制备:将 P24-3 (39.2g, 83mmol) 溶于饱和甲醇铵,并将生成的溶液在 R. T. 下搅拌 15 小时。将溶剂去除,并在硅胶柱上 (DCM/MeOH = 50:1 至 20:1) 纯化剩余物以产生 P24-4 (21.0g, 95.8%)。

[0465] (P24-5) 的制备:在 0℃ 下,向 P24-4 (21.0g, 79.5mmol) 的吡啶 (250mL) 溶液加入 DMTrCl (28.2g, 83.5mmol)。将溶液在 R. T. 下搅拌 15 小时。使用 MeOH 淬灭反应并在减压下浓缩至干燥。将剩余物溶于 EtOAc 并使用水洗涤。在 Na₂SO₄ 上干燥有机层并浓缩。将剩余物溶于 DCM (300mL)。加入咪唑 (13.6g, 200mmol) 和 TBSCl (30.0g, 200mmol)。将反应混合物在 R. T. 下搅拌 12 小时。使用 NaHCO₃ 和盐水洗涤反应混合物。在 Na₂SO₄ 上干燥有机层并浓缩。将剩余物 (48.5g, 79.5mmol) 溶于 80% HOAc 水溶液 (400mL)。将混合物在 R. T. 下搅拌 20 小时。使用 EtOAc 稀释混合物并使用 NaHCO₃ 溶液和盐水洗涤。在 Na₂SO₄ 上干燥有机层并通过硅胶柱层析 (1-2% MeOH 的 DCM 溶液) 纯化以产生白色固体形式的 P24-5 (21.0g, 70%)。¹H NMR (400MHz, MeOD) δ 7.83 (d, J = 8.0Hz, 1H), 6.14 (dd, J₁ = 6.0Hz, J₂ = 10.0Hz, 1H), 5.73 (d, J = 8.4Hz, 1H), 4.38-4.46 (m, 1H), 3.89-3.91 (m, 1H), 3.88 (dd, J₁ = 2.8Hz, J₂ = 5.2Hz, 1H), 3.72 (dd, J₁ = 2.8Hz, J₂ = 5.2Hz, 1H), 0.93 (s, 9H), 0.15 (m, 6H)。ESI-MS :m/z 379.1 [M+H]⁺。

[0466] (P24-6) 的制备:在 R. T. 下,向 P24-5 (21.0g, 55.6mmol) 的无水 CH₃CN (200mL) 溶液加入 IBX (17.1g, 61.1mmol)。将反应混合物回流 1 小时,然后冷却至 0℃。将沉淀滤除,并将滤液浓缩以产生黄色固体形式的醛 (21.0g, 55.6mmol)。向醛 (21.0g, 55.6mmol) 的二氧六环 (200mL) 溶液加入 37% CH₂O (22.2mL, 222.4mmol) 和 2N NaOH 水溶液 (55.6mL, 111.2mmol)。将混合物在 R. T. 下搅拌 2 小时,然后使用 AcOH 中和至 pH = 7。向反应加入 EtOH (50mL) 和 NaBH₄ (12.7g, 333.6mmol)。将混合物在 R. T. 下搅拌 30mins。使用饱和 NH₄Cl 水溶液淬灭反应。使用 EA 萃取。在 Na₂SO₄ 上干燥有机层并浓缩。通过硅胶柱层析 (1-3% MeOH 的 DCM 溶液) 纯化剩余物以产生白色固体形式的 P24-6 (13.5g, 59.5%)。

[0467] (P24-7) 的制备:在 0℃ 下,向 P24-6 (13.5g, 33.1mmol) 的 DCM (100mL) 溶液加入吡啶 (20mL) 和 DMTrCl (11.2g, 33.1mmol)。将溶液在 25℃ 下搅拌 3 小时,然后使用 MeOH (30mL) 处理。将溶剂去除,并通过硅胶柱层析 (DCM:MeOH = 300:1 至 100:1) 纯化剩余物以产生剩余物。将剩余物溶于无水吡啶 (150mL) 并加入 TBDPSCl (16.5g, 60mmol) 和 AgNO₃ (10.2g, 60mmol)。将混合物在 25℃ 下搅拌 15 小时,然后过滤并浓缩。将混合物溶于 EtOAc 并使用盐水洗涤。在 Na₂SO₄ 上干燥有机层。通过硅胶柱层析 (DCM:MeOH = 300:1 至 100:1) 纯化产生黄色固体形式的产物 (16.2g, 85.3%)。将固体溶于 80% HOAc 水溶液 (400mL)。将混合物在 R. T. 下搅拌 15 小时。使用 EtOAc 稀释混合物并使用 NaHCO₃ 溶液和盐水洗涤。在 Na₂SO₄ 上干燥有机层并通过硅胶柱层析 (DCM:MeOH = 200:1 至 50:1) 纯化以产生白色固体形式的 P24-7 (9.5g, 86.5%)。¹H NMR (CD₃OD, 400MHz) δ 7.39-7.70 (m, 11H), 6.34-6.38 (m, 1H), 5.12 (d, J = 8.0Hz, 1H), 4.79 (dd, J₁ = 10.0Hz, J₂ = 16.0Hz, 1H), 4.14 (dd, J₁ = 1.6Hz, J₂ = 11.6Hz, 1H), 3.48-3.84 (m, 2H), 3.49 (dd, J₁ = 1.6Hz, J₂ = 11.6Hz, 1H), 1.12 (s, 9H), 0.92 (s, 9H), 0.16 (s, 6H)。

[0468] (P24-8) 的制备:在氮气下,在 0℃ 下向 P24-7 (6.0g, 9.3mmol) 的无水 DCM (80mL) 溶液加入戴斯-马丁氧化剂 (7.9g, 18.6mmol)。将反应在 R. T. 下搅拌 1 小时。真空去除溶剂,并使用乙醚 (50mL) 研磨剩余物。通过 MgSO₄ 垫过滤混合物,并使用相等体积

的 $\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$ 的饱和 NaHCO_3 (50mL) 搅拌有机溶剂直至有机层变澄清 (约 10min)。将有机层分离, 使用盐水洗涤, 并在 MgSO_4 上干燥。在真空浓缩后, 获得红色固体形式的 P24-8 (5.8g, 98%)。

[0469] (P24-9) 的制备: 在氮气下, 在 -70°C 下, 向甲基三苯基溴化磷 (9.6g, 27.0mmol) 的无水 THF (60mL) 混合物加入 $n\text{-BuLi}$ (10.8mL, 27.0mmol)。将反应在 0°C 下搅拌 30mins。在氮气下, 在 0°C 下滴加 P24-8 (5.8g, 9.0mmol) 的无水 THF (20mL) 溶液。将反应在 R. T. 下搅拌 12 小时。使用 NH_4Cl 淬灭反应并使用 EtOAc 萃取。将有机层分离、干燥并浓缩, 并通过硅胶柱层析 (DCM:MeOH = 300:1 至 100:1) 纯化剩余物以产生白色固体形式的 P24-9 (3.0g, 51%)。

[0470] (P24-10) 的制备: 在氢气环境下, 在 25°C 下向 P24-9 (2.9g, 4.5mmol) 的无水 MeOH (20mL) 溶液加入 Pd/C (1.4g)。将混合物在 25°C 下搅拌 1 小时。将溶液过滤、蒸发至干燥并在硅胶柱上 (DCM:MeOH = 300:1 至 100:1) 纯化以产生白色固体形式的 P24-10 (2.3g, 79.3%)。

[0471] (P24-11) 的制备: 在 R. T. 下, 向 P24-10 (1.0g, 1.55mmol) 的无水 CH_3CN (20mL) 溶液加入 TPSCl (940mg, 3.1mmol)、DMAP (380mg, 3.1mmol) 和 NEt_3 (470mg, 4.6mmol)。将反应在 R. T. 下搅拌 5 小时。加入 NH_4OH (8mL), 并将反应搅拌 1 小时。使用 DCM (150mL) 稀释混合物并使用水、0.1M HCl 和饱和 NaHCO_3 水溶液洗涤。将溶剂去除, 并通过硅胶柱层析 (PE:EA = 10:1 至 1:1) 纯化剩余物以产生黄色固体形式的粗产物 (900mg, 90%)。在 R. T. 下, 向粗产物的 DCM (10mL) 溶液加入 MMTrCl (930mg, 3.0mmol)、 AgNO_3 (510mg, 3.0mmol) 和三甲吡啶 (colliding) (720mg, 6.0mmol)。将反应在 R. T. 下搅拌 12 小时。将反应过滤, 浓缩并通过硅胶柱层析 (DCM:MeOH = 200:1 至 50:1) 纯化以产生黄色固体形式的 P24-11 (1.1g, 77.6%)。

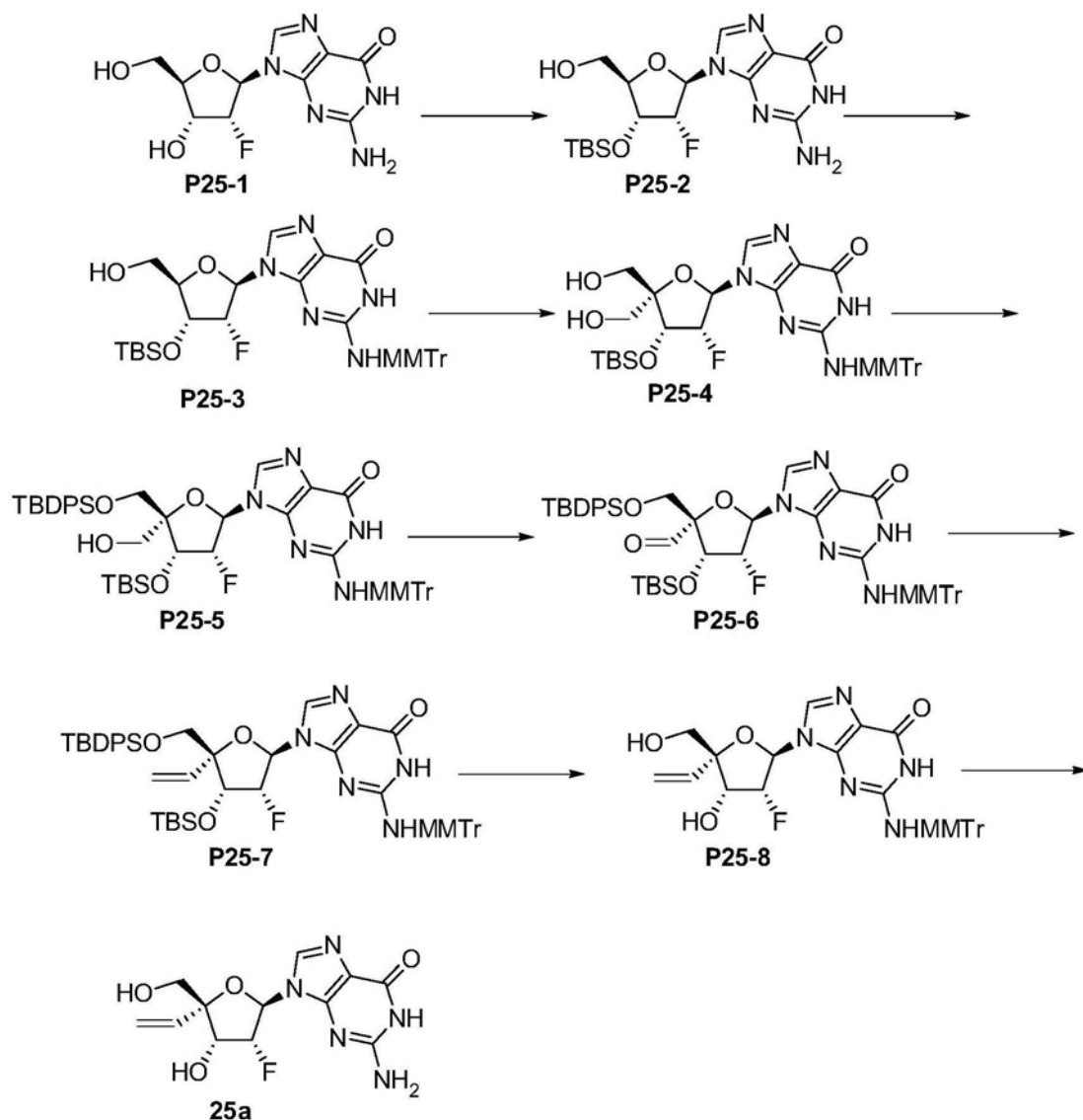
[0472] (P24-12) 的制备: 在 25°C 下, 向 P24-11 (1.1g, 1.2mmol) 的 MeOH (40mL) 溶液加入 NH_4F (1.0g, 30mmol) 并在 70°C 下搅拌 15 小时。将溶液过滤并蒸发至干燥, 并通过硅胶柱 (DCM:MeOH = 200:1 至 20:1) 纯化剩余物以产生白色固体形式的 P24-12 (450mg, 66.6%)。 ^1H NMR (400MHz, MeOD) δ 8.58 (s, 1H), 7.62 (d, J = 7.6Hz, 1H), 7.13–7.30 (m, 12H), 6.83–6.85 (m, 2H), 6.29 (d, J = 7.6Hz, 1H), 6.18 (d, J = 6.0Hz, 1H), 5.94 (t, J = 8.0Hz, 1H), 5.22 (t, J = 5.2Hz, 1H), 4.28–4.37 (m, 1H), 3.72 (s, 3H), 3.57–3.62 (m, 1H), 1.39–1.60 (m, 2H), 0.79–0.84 (m, 3H)。ESI-LCMS : m/z 563.6 $[\text{M}+\text{H}]^+$ 。

[0473] (24a) 的制备: 在 25°C 下, 将 P24-12 (250mg, 0.44mmol) 溶于 80% HCOOH 的 H_2O (6.0g)。将混合物在 35°C 下搅拌 15 小时。将溶液蒸发至干燥, 溶于 MeOH (30mL) 并在 60°C 下搅拌 12 小时。将溶液蒸发至干燥并通过硅胶柱层析 (DCM:MeOH = 100:1 至 100:1) 纯化以产生白色固体形式的化合物 24a (125.6mg, 97%)。 ^1H NMR (400MHz, MeOD) δ 7.91 (d, J = 7.6Hz, 1H), 6.19 (t, J = 7.6Hz, 1H), 5.90 (d, J = 7.2Hz, 1H), 4.47 (t, J = 13.6Hz, 1H), 3.67 (d, J = 12.0Hz, 1H), 3.52 (d, J = 12.0Hz, 1H), 1.73–1.82 (m, 1H), 1.53–1.63 (m, 1H), 0.95 (t, J = 7.6Hz, 3H)。ESI-LCMS : m/z 291.9 $[\text{M}+\text{H}]^+$ 。

[0474] 实施例 25

[0475] 化合物 (25a) 的制备

[0476]



[0477] (P25-2) 的制备: 在 25℃ 下, 向 P25-1 (20.0g, 70.16mmol) 的无水吡啶 (200mL) 溶液加入咪唑 (19.08g, 280.7mmol) 和 TBSCl (42.10g, 280.7mmol)。将溶液在 25℃ 下搅拌 15 小时, 然后在减压下浓缩至干燥。使用 EtOAc 洗涤剩余物以产生白色固体形式的粗产物 (36.4g)。将粗产物溶于 THF (150mL) 和 H₂O (100mL), 然后加入 HOAc (300mL)。将溶液在 80℃ 下搅拌 13 小时。将反应冷却至 R. T., 并在减压下将混合物浓缩至干燥。将剩余物溶解, 使用 EtOAc 洗涤并干燥以产生白色固体形式的 P25-2 (31.2g, 60.9%)。

[0478] (P25-3) 的制备: 向搅拌的 P25-2 (31.2g, 78.2mmol) 的无水吡啶 (300mL) 溶液加入 Ac₂O (11.96g, 117.3mmol)。将混合物在 25℃ 下搅拌 18 小时。然后, 加入 MMTTrCl (72.3g, 234.6mmol) 和 AgNO₃ (39.9g, 234.6mmol)。将溶液在 25℃ 下搅拌 15 小时。并加入 H₂O 以淬灭反应。在减压下将溶液浓缩至干燥。将剩余物溶于 EtOAc 并使用水洗涤。在 Na₂SO₄ 上干燥有机层并过滤。将滤液真空浓缩以产生剩余物。通过硅胶 (DCM:MeOH = 200:1 至 50:1) 纯化剩余物以产生产物。将产物溶于 NH₃/MeOH (300mL), 并将混合物在 25℃ 下搅拌 20 小时。将溶剂去除, 并在硅胶柱上 (DCM:MeOH = 100:1 至 50:1) 纯化剩余物以产生黄色固体形式的 P25-3 (28.6g, 86.5%)。¹H NMR (400MHz, MeOD) δ 8.01 (s, 1H), 7.23–7.35 (m, 12H), 6.85–6.87 (m, 2H), 5.60 (dd, J₁ = 11.2Hz, J₂ = 5.6Hz, 1H), 4.78–4.94 (m, 1H), 4.4

4 (dd, $J_1 = 8.0\text{Hz}$, $J_2 = 4.8\text{Hz}$, 1H), 3.78 (s, 3H), 3.60–3.63 (m, 1H), 3.50 (dd, $J_1 = 32.0\text{Hz}$, $J_2 = 12.0\text{Hz}$, 2H), 3.32 (s, 3H), 0.94 (s, 9H), 0.12–0.14 (m, 6H)。

[0479] (P25-4) 的制备: 在 20°C 下, 向 P25-3 (7.24g, 10.79mmol) 的无水 CH_3CN (100mL) 溶液加入 IBX (3.93g, 14.03mmol)。将反应混合物在 90°C 下回流 1 小时。将反应过滤, 并将滤液浓缩以产生黄色固体形式的醛 (7.1g)。向醛 (7.1g, 10.6mmol) 的二氧六环 (80mL) 溶液加入 37% CH_2O (4.2mL, 42.4mmol) 和 2N NaOH 水溶液 (8.0mL, 15.9mmol)。将混合物在 25°C 下搅拌 2 小时, 然后使用 AcOH 中和至 $\text{pH} = 7$ 。向反应加入 EtOH (30mL) 和 NaBH_4 (2.4g, 63.6mmol), 然后将反应搅拌 30mins。使用饱和 NH_4Cl 水溶液淬灭混合物。使用 EA 萃取混合物, 并在 Na_2SO_4 上干燥有机层。将溶剂去除, 并通过硅胶柱层析 ($\text{DCM}:\text{MeOH} = 200:1$ 至 $50:1$) 纯化剩余物以产生黄色固体形式的 P25-4 (4.86g, 65.4%)。

[0480] (P25-5) 的制备: 在 0°C 下, 向 P25-4 (3.8g, 5.4mmol) 的 DCM (40mL) 溶液加入吡啶 (10mL) 和 DMTrCl (1.8g, 5.4mmol)。将溶液在 25°C 下搅拌 1 小时。使用 MeOH (15mL) 处理反应混合物并浓缩。通过硅胶柱层析 ($\text{DCM}:\text{MeOH} = 200:1$ 至 $50:1$) 纯化剩余物以产生黄色固体形式的单- DMTr 保护的中间体 (3.6g, 66.4%)。向中间体的无水吡啶 (30mL) 溶液加入 TBDPSCl (2.96g, 10.8mmol) 和 AgNO_3 (1.84g, 10.8mmol)。将混合物在 25°C 下搅拌 15 小时。将混合物过滤并浓缩, 然后溶于 EtOAc 并使用盐水洗涤。在 Na_2SO_4 上干燥有机层, 然后浓缩。通过硅胶柱层析 ($\text{DCM}:\text{MeOH} = 200:1$ 至 $50:1$) 纯化剩余物以产生白色固体形式的纯中间体 (3.8g, 85.1%)。在 -78°C 下, 向中间体 (3.6g, 2.9mmol) 的无水 DCM (50mL) 溶液加入 Cl_2CHCOOH (1.8mL) 的无水 DCM (18mL)。将混合物在 -10°C 下搅拌 30mins。使用饱和 NaHCO_3 水溶液淬灭混合物并使用 DCM 萃取。在 Na_2SO_4 上干燥有机层, 然后通过硅胶柱层析 ($\text{DCM}:\text{MeOH} = 200:1$ 至 $50:1$) 纯化以产生白色固体形式的 P25-5 (2.2g, 80.7%)。

[0481] (P25-6) 的制备: 在 25°C 下, 将 P25-5 (2.2g, 2.3mol) 加入至戴斯-马丁氧化剂 (2.5g, 5.8mol) 的无水 CH_2Cl_2 (30mL) 悬浮液。将混合物在 25°C 下搅拌 4 小时。真空去除溶剂, 并使用乙醚 (30mL) 研磨剩余物。通过 MgSO_4 垫过滤混合物。使用相等体积的 $\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$ 的饱和 NaHCO_3 (30mL) 搅拌有机溶剂直至有机层变澄清 (约 10min)。将有机层分离, 使用盐水洗涤, 并在 MgSO_4 上干燥。真空去除溶剂以产生黄色固体形式的 P25-6 (2.1g, 95%)。

[0482] (P25-7) 的制备: 在 -78°C 下, 在 1 分钟内向搅拌的甲基-三苯基-溴化磷 (2.3g, 6.6mmol) 的无水 THF (30mL) 溶液滴加 $n\text{-BuLi}$ (2.6mL, 6.6mmol, 2.5M 的 THF)。将搅拌在 0°C 下继续 1 小时。将 P25-6 (2.1g, 2.2mmol) 加入至混合物, 然后在 25°C 下搅拌 15 小时。使用饱和 NH_4Cl (50mL) 淬灭反应。使用 EtOAc 萃取混合物。使用 Na_2SO_4 干燥合并的有机相、过滤并蒸发至干燥以产生淡黄色油状物。通过柱层析 ($\text{DCM}:\text{MeOH} = 200:1$ 至 $50:1$) 纯化油状物以产生白色固体形式的 P25-7 (1.6g, 76%)。

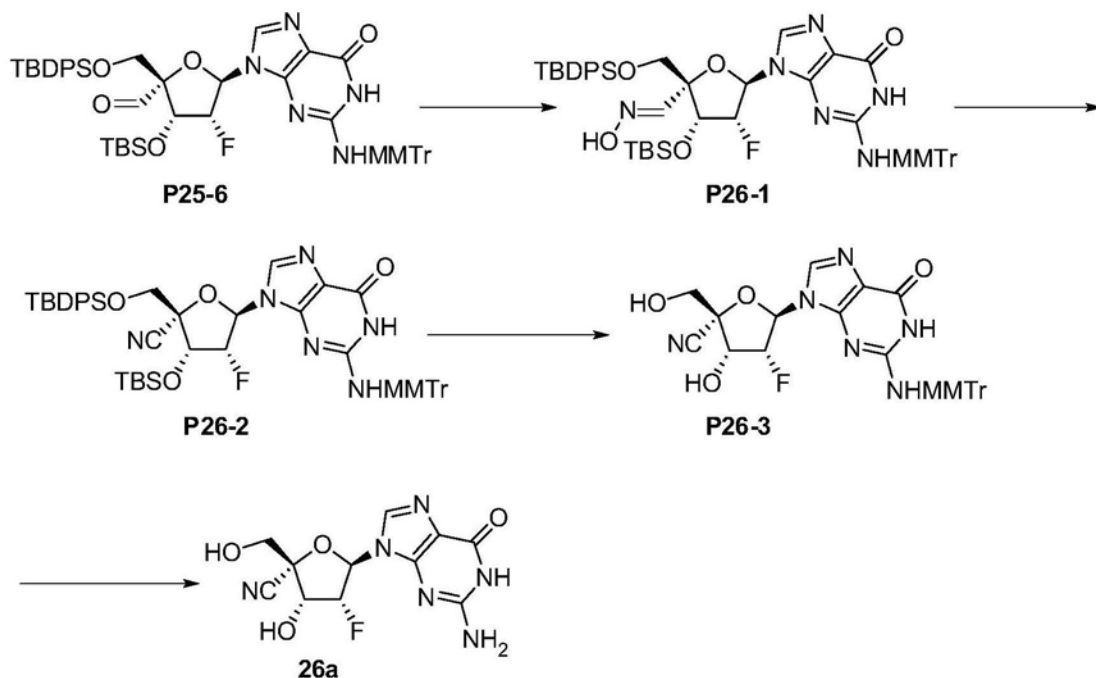
[0483] (P25-8) 的制备: 向 P25-7 (1.6g, 1.7mmol) 的 MeOH (50mL) 溶液加入 NH_4F (1.5g, 40mmol), 并将混合物在 70°C 下搅拌 15 小时。将溶液过滤并蒸发至干燥。通过硅胶柱 ($\text{DCM}:\text{MeOH} = 200:1$ 至 $20:1$) 纯化剩余物以产生白色固体形式的 P25-8 (450mg, 49%)。
 ^1H NMR (400MHz, MeOD) δ 7.95 (s, 1H), 7.21–7.33 (m, 12H), 6.82–6.84 (m, 2H), 5.92 (dd, $J_1 = 11.2\text{Hz}$, $J_2 = 17.6\text{Hz}$, 1H), 5.55–5.59 (m, 1H), 5.18–5.31 (m, 2H), 4.54–4.68 (m, 1H), 4.26–4.33 (m, 1H), 3.76 (s, 3H), 3.43 (dd, $J_1 = 12.4\text{Hz}$, $J_2 = 36.4\text{Hz}$, 2H)。ESI-LCMS: m/z 584.1 $[\text{M}+\text{H}]^+$ 。

[0484] (25a) 的制备: 将 P25-8 (130mg, 0.22mmol) 溶于 80% HCOOH 并将混合物在 25℃ 下搅拌 1 小时。然后将溶液蒸发至干燥。将剩余物溶于 MeOH (30mL) 并在 60℃ 下搅拌 12 小时。然后, 将溶液蒸发至干燥, 并通过 EtOAc 洗涤剩余物以产生白色固体形式的 P25 (52.3mg, 76%)。¹H NMR (400MHz, MeOD) δ 8.03 (s, 1H), 6.17 (dd, $J_1 = 3.2\text{Hz}$, $J_2 = 16.8\text{Hz}$, 1H), 6.03 (dd, $J_1 = 11.2\text{Hz}$, $J_2 = 17.2\text{Hz}$, 1H), 5.50 (dd, $J_1 = 1.6\text{Hz}$, $J_2 = 17.2\text{Hz}$, 1H), 5.23–5.38 (m, 2H), 4.76 (dd, $J_1 = 4.8\text{Hz}$, $J_2 = 18.0\text{Hz}$, 1H), 3.60 (dd, $J_1 = 12.0\text{Hz}$, $J_2 = 44.8\text{Hz}$, 2H)。ESI-MS :m/z 334.1 [M+Na]⁺。

[0485] 实施例 26

[0486] 化合物 (26a) 的制备

[0487]



[0488] (P26-1) 的制备: 在 25℃ 下, 向搅拌的 P25-6 (2.1g, 2.2mmol) 的吡啶溶液加入 HONH₂·HCl (0.61g, 8.8mmol)。将混合物在 25℃ 下搅拌 2 小时。将混合物浓缩, 并通过柱层析 (DCM:MeOH = 200:1 至 50:1) 纯化剩余物以产生白色固体形式的 P26-1 (1.8g, 83%)。

[0489] (P26-2) 的制备: 在 0℃ 下, 向搅拌的 P26-1 (1.4g, 1.47mmol) 的 DCM 溶液加入 TEA (0.44g, 4.4mmol) 和甲烷磺酰氯 (0.34g, 2.9mmol)。将混合物在 25℃ 下搅拌 1 小时。使用饱和 NaHCO₃ 水溶液淬灭混合物并使用 DCM 萃取。使用 Na₂SO₄ 干燥有机相、过滤并蒸发。通过柱层析 (DCM:MeOH = 200:1 至 50:1) 纯化剩余物以产生白色固体形式的 P26-2 (1.1g, 79%)。

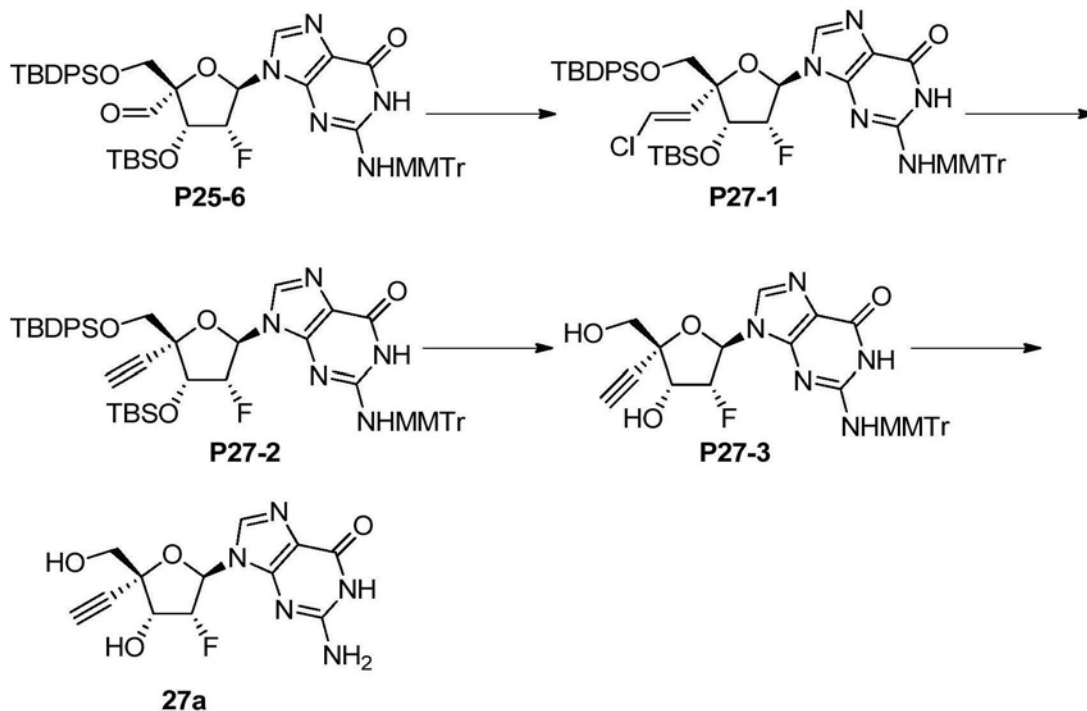
[0490] (P26-3) 的制备: 向 P26-2 (1.1g, 1.18mmol) 的 MeOH (50mL) 溶液加入 NH₄F (1.5g, 40mmol), 并将混合物在 70℃ 下搅拌 15 小时。将溶液过滤并蒸发至干燥。通过硅胶柱 (DCM:MeOH = 200:1 至 20:1) 纯化剩余物以产生白色固体形式的 P26-3 (400mg, 71%)。¹H NMR (400MHz, MeOD) δ 7.80 (s, 1H), 7.20–7.32 (m, 12H), 6.86–6.88 (m, 2H), 5.82 (dd, $J_1 = 2.0\text{Hz}$, $J_2 = 20.0\text{Hz}$, 1H), 4.51–4.66 (m, 1H), 3.94 (dd, $J_1 = 5.2\text{Hz}$, $J_2 = 20.8\text{Hz}$, 1H), 3.78 (s, 3H), 3.56 (dd, $J_1 = 12.4\text{Hz}$, $J_2 = 42.0\text{Hz}$, 2H)。ESI-LCMS :m/z 583.1 [M+H]⁺。

[0491] (26a) 的制备:将 P26-3(200mg, 0.34mmol) 溶于 80% HCOOH 水溶液。将混合物在 25℃下搅拌 1 小时。将溶液蒸发至干燥,溶于 MeOH(30mL) 并在 60℃下搅拌 12 小时。将溶剂去除,并通过 EtOAc 洗涤剩余物以产生白色固体形式的化合物 26a(100.4mg, 95%)。¹H NMR(400MHz, MeOD) δ 7.90(s, 1H), 6.34(dd, $J_1 = 2.0\text{Hz}$, $J_2 = 19.6\text{Hz}$, 1H), 5.49(ddd, $J_1 = 1.6\text{Hz}$, $J_2 = 4.4\text{Hz}$, $J_3 = 52.4\text{Hz}$, 1H), 5.01(dd, $J_1 = 4.8\text{Hz}$, $J_2 = 20.8\text{Hz}$, 1H), 3.93(dd, $J_1 = 12.4\text{Hz}$, $J_2 = 44.8\text{Hz}$, 2H)。ESI-MS :m/z 311.1[M+H]⁺。

[0492] 实施例 27

[0493] 化合物 (27a) 的制备

[0494]



[0495] (P27-1) 的制备:在 -78℃下,在 10mins 内向搅拌的氯甲基-三苯基-氯化磷(1.9g, 5.4mmol) 的无水 THF(30mL) 溶液滴加 n-BuLi(2.16mL, 5.4mmol, 2.5M 的 THF)。将搅拌在 -78℃下继续 2 小时。加入 P25-6(1.7g, 1.8mmol), 并将混合物在 25℃下搅拌 15 小时。使用饱和 NH₄Cl(50mL) 淬灭反应。使用 EtOAc 萃取混合物。使用 Na₂SO₄ 干燥合并的有机相、过滤并蒸发至干燥以产生淡黄色油状物。通过柱层析(DCM:MeOH = 200:1 至 50:1) 纯化油状物以产生白色固体形式的 P27-1(1.2g, 70%)。

[0496] (P27-2) 的制备:在 -78℃下,在 10mins 内向搅拌的 P27-1(1.2g, 1.3mmol) 的无水 THF(20mL) 溶液滴加 n-BuLi(8.0mL, 20mmol, 2.5M 的 THF)。将搅拌在 -78℃下继续 4 小时。使用饱和 NH₄Cl(50mL) 淬灭反应。使用 EtOAc(50×2mL) 萃取混合物。在 Na₂SO₄ 上干燥合并的有机相、过滤并蒸发至干燥。通过柱层析(DCM:MeOH = 200:1 至 50:1) 纯化剩余物以产生白色固体形式的 P27-2(1.0g, 83%)。

[0497] (P27-3) 的制备:向 P27-2(1.0g, 1.1mmol) 的 MeOH(40mL) 溶液加入 NH₄F(1.5g, 40mmol), 并将混合物在 70℃下搅拌 25 小时。将溶液过滤,并将滤液蒸发至干燥。在硅胶柱上(DCM:MeOH = 200:1 至 20:1) 纯化剩余物以产生白色固体形式的 P27-3(240mg, 38%)。¹H NMR(400MHz, MeOD) δ 7.85(s, 1H), 7.21-7.31(m, 12H), 6.84 ~

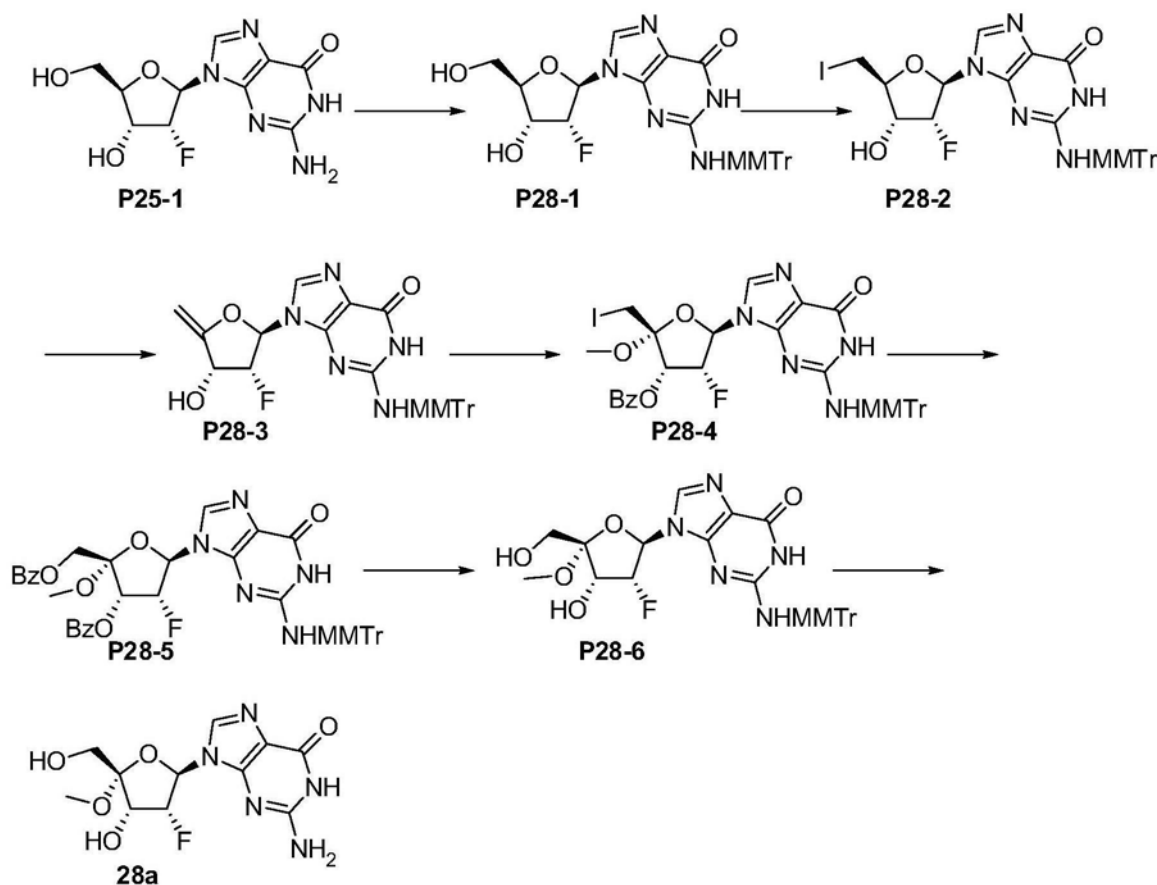
6.87 (m, 2H), 5.67 (dd, $J_1 = 1.6\text{Hz}$, $J_2 = 19.2\text{Hz}$, 1H), 4.47-4.62 (m, 1H), 3.94 (dd, $J_1 = 5.2\text{Hz}$, $J_2 = 22.4\text{Hz}$, 1H), 3.77 (s, 3H), 3.56 (dd, $J_1 = 12.4\text{Hz}$, $J_2 = 47.2\text{Hz}$, 2H), 3.04 (s, 1H)。ESI-LCMS :m/z 582.1 [M+H]⁺。

[0498] (27a) 的制备: 将 P27-3 (130mg, 0.22mmol) 溶于 80% HCOOH 水溶液。将混合物在 25℃ 下搅拌 1 小时。将溶液蒸发至干燥。将剩余物溶于 MeOH (30mL) 并在 60℃ 下搅拌 12 小时。将溶剂去除, 并使用 EtOAc 洗涤剩余物以产生白色固体形式的化合物 27a (43.0mg, 63%)。¹H NMR (400MHz, MeOD) δ 7.95 (s, 1H), 6.22 (dd, $J_1 = 2.4\text{Hz}$, $J_2 = 18.4\text{Hz}$, 1H), 5.49 (ddd, $J_1 = 2.0\text{Hz}$, $J_2 = 4.8\text{Hz}$, $J_3 = 53.2\text{Hz}$, 1H), 4.77 (dd, $J_1 = 5.2\text{Hz}$, $J_2 = 20.0\text{Hz}$, 1H), 3.79 (dd, $J_1 = 12.4\text{Hz}$, $J_2 = 46.8\text{Hz}$, 2H), 3.12 (s, 3H)。ESI-MS :m/z 310.1 [M+H]⁺。

[0499] 实施例 28

[0500] 化合物 (28a) 的制备

[0501]



[0502] (P28-1) 的制备: 在 0℃ 下, 向搅拌的 P25-1 (5.7g, 20mmol) 的无水吡啶 (20mL) 溶液滴加 Ac₂O (5.8mL, 60mmol)。将混合物在 R. T. 下搅拌 10 小时。加入 AgNO₃ (8.5g, 50mmol) 和 MMTrCl (15.5g, 50mmol)。将混合物在 R. T. 下搅拌 10 小时。使用饱和 NaHCO₃ 淬灭溶液并使用 EA 萃取。在 Na₂SO₄ 上干燥有机层并浓缩。在硅胶柱上 (DCM/MeOH = 100:1 至 50:1) 纯化剩余物以产生淡黄色固体形式的中间体 (12.1g, 93.4%)。在 R. T. 下使用饱和 NH₃ 的 MeOH 将固体处理 14 小时。将溶剂去除, 并通过硅胶柱层析 (DCM/MeOH = 80:1 至 30:1) 纯化剩余物以产生白色固体形式的 P28-1 (9.2g, 87.5%)。

[0503] (P28-2) 的制备:向搅拌的 P28-1 (9.2g, 16.5mmol) 的干燥 THF (300mL) 溶液加入咪唑 (9.0g, 132mmol) 和 PPh_3 (34.8g, 132mmol)。在 0℃ 下, 在 N_2 下滴加 I_2 (26.0g, 103mmol) 的 THF (100mL) 溶液。将混合物在 R.T. 下搅拌 18 小时。使用 $\text{Na}_2\text{S}_2\text{O}_3$ 溶液淬灭反应, 并使用 EtOAc 萃取混合物。在 Na_2SO_4 上干燥有机层并浓缩。通过硅胶柱层析 (DCM/MeOH = 80:1 至 30:1) 纯化剩余物以产生淡黄色固体形式的 P28-2 (10.3g, 93.4%)。

[0504] (P28-3) 的制备:向搅拌的 P28-2 (10.2g, 15.3mmol) 的干燥 THF (300mL) 溶液加入 DBU (4.7g, 30.1mmol)。将混合物在 60℃ 下搅拌 8 小时。使用 NaHCO_3 溶液稀释溶液并使用 EtOAc 萃取。在 Na_2SO_4 上干燥有机层并浓缩。通过硅胶柱层析 (PE/EtOAc = 3:1 至 1:3) 纯化剩余物以产生淡黄色泡沫形式的 P28-3 (6.2g, 75.6%)。 ^1H NMR (CD_3OD , 400MHz) δ 7.71 (s, 1H), 7.23-7.76 (m, 14H), 6.74 (d, $J = 0.8\text{Hz}$, 2H), 5.83-5.88 (dd, $J_1 = 2.8\text{Hz}$, $J_2 = 16.0\text{Hz}$, 2H), 4.57-4.89 (m, 2H), 4.30-4.35 (m, 1H), 4.79 (s, 3H)。ESI-MS :m/z 540 $[\text{M}+\text{H}]^+$ 。

[0505] (P28-4) 的制备:在 0℃ 下, 向搅拌的 P28-4 (5.42g, 10mmol) 的无水 CH_3OH (100mL) 溶液加入 PbCO_3 (13.7g, 53.1mmol), 随后是 I_2 (12.3g, 48.9mmol) 的 CH_3OH (300mL) 溶液。将混合物在 R.T. 下搅拌 10 小时。使用 $\text{Na}_2\text{S}_2\text{O}_3$ 溶液淬灭溶液并使用 DCM 萃取。使用 NaHCO_3 溶液洗涤有机层, 在 Na_2SO_4 上干燥并浓缩。通过制备 -HPLC (MeCN 和 0.1% HCOOH 的水) 纯化剩余物以产生白色泡沫形式的纯产物 (2.4g, 34%)。将产物溶于干燥吡啶 (20mL) 并在 0℃ 下滴加 BzCl (723mg, 5.2mmol)。将混合物在 0℃ 下搅拌 1 小时。使用 NaHCO_3 溶液淬灭溶液, 并使用 EtOAc 萃取。在 Na_2SO_4 上干燥有机层并浓缩。通过硅胶柱层析 (PE/EtOAc = 5:1 至 :1) 纯化剩余物以产生白色固体形式的 P28-4 (2.1g, 77.1%)。

[0506] (P28-5) 的制备: 将 P28-4 (2.0g, 2.5mmol)、 BzONa (3.6g, 25mmol) 和 15-冠-5 (5.5g, 25mmol) 悬浮于 DMF (50mL)。将混合物在 110-125℃ 下搅拌 5 天。通过过滤去除沉淀, 并使用 EA 稀释滤液。使用盐水洗涤溶液并在 Na_2SO_4 上干燥。将溶剂去除, 并在硅胶柱上 (PE/EA = 10/1 至 2/1) 纯化剩余物以产生淡黄色泡沫形式的粗 P28-5 (1.6g, 80%)。

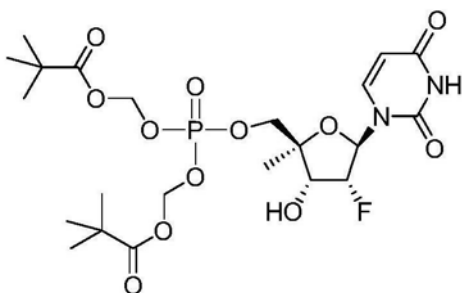
[0507] (P28-6) 的制备:将 P28-5 (1.6g, 2.0mmol) 溶于甲醇铵 (100mL, 饱和的), 并将混合物在 R.T. 下搅拌 20 小时。将溶剂去除, 并在硅胶柱上 (DCM/MeOH = 100:1 至 20:1) 纯化剩余物以产生白色固体形式的 P28-6 (410mg, 34.9%)。 ^1H NMR (400MHz, MeOD) δ 7.84 (s, 1H), 7.20-7.33 (m, 12H), 6.83-6.86 (m, 2H), 5.64 (dd, $J_1 = 1.6\text{Hz}$, $J_2 = 18.4\text{Hz}$, 1H), 4.46-4.62 (m, 1H), 4.08 (dd, $J_1 = 6.0\text{Hz}$, $J_2 = 22.0\text{Hz}$, 1H), 3.76 (s, 3H), 3.58 (dd, $J_1 = 12.4\text{Hz}$, $J_2 = 30.4\text{Hz}$, 2H), 3.31 (s, 3H)。ESI-LCMS :m/z 588.1 $[\text{M}+\text{H}]^+$ 。

[0508] (28a) 的制备:将 P28-8 (200mg, 0.34mmol) 溶于 80% HCOOH 并将混合物在 25℃ 下搅拌 1 小时。将溶液蒸发至干燥, 并将剩余物溶于 MeOH (30mL) 并在 60℃ 下搅拌 12 小时。将溶剂去除, 并使用 EtOAc 洗涤剩余物以产生白色固体形式的化合物 28a (46.1mg, 43%)。 ^1H NMR (400MHz, MeOD) δ 7.92 (s, 1H), 6.22 (dd, $J_1 = 1.6\text{Hz}$, $J_2 = 18.8\text{Hz}$, 1H), 5.25 (ddd, $J_1 = 1.6\text{Hz}$, $J_2 = 6.0\text{Hz}$, $J_3 = 54.0\text{Hz}$, 1H), 4.89-4.91 (m, 1H), 3.87 (d, $J = 11.6\text{Hz}$, 1H), 3.67 (d, $J = 12.0\text{Hz}$, 1H), 3.44 (s, 3H)。ESI-MS :m/z 316.1 $[\text{M}+\text{H}]^+$ 。

[0509] 实施例 29

[0510] 化合物 (29a) 的制备

[0511]

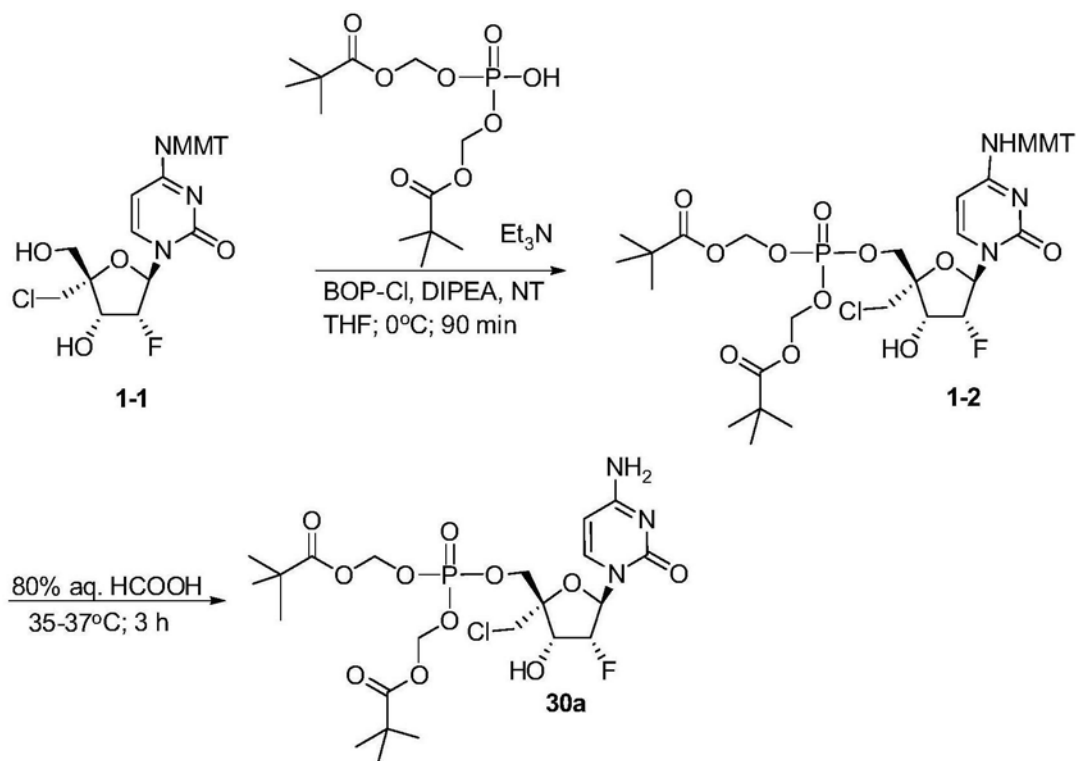


[0512] 在氩气下,在 0℃下将 DEAD(40%的甲苯、0.15mL, 0.33mmol) 加入至搅拌的三苯基膦(78mg, 0.3mmol) 的无水 1,4-二氧六环(0.5mL) 溶液。将混合物升温至 R.T. 并加入化合物 10a(26mg, 0.1mmol) 和双(新戊酰基氧基甲基)磷酸酯(98mg, 0.3mmol)。将生成的混合物在 65℃下搅拌 3 天。加入二异丙基乙胺(50 μL), 并将混合物在 70℃下搅拌 3 天。单独进行相同规模的另一反应。将两个反应混合物合并并浓缩。在使用 5-10% 甲醇的 DCM 的硅胶上层析产生具有少量杂质的目标产物(20mg)。在硅胶上第二次层析,随后使用乙腈/水的 RP HPLC 产生无色剩余物形式的化合物(2.8mg); ^1H NMR(CD_3OD , 400MHz) δ 7.65(d, $J = 8.0\text{Hz}$, 1H), 5.94(dd, $J_1 = 2.4\text{Hz}$, $J_2 = 18.8\text{Hz}$, 1H), 5.70(d, $J = 8.0\text{Hz}$, 1H), 5.69(d, $J = 0.8\text{Hz}$, 1H), 5.68(s, 1H), 5.654(d, $J = 1.2\text{Hz}$, 1H), 5.650(s, 1H), 5.21(dd, $J = 2.0, 5.2\text{Hz}$, 0.5H), 5.07(dd, 2.0, 5.2Hz, 0.5H), 4.42(dd, $J = 5.6, 20.8\text{Hz}$, 1H), 4.14(m, 2H), 1.223(s, 9H), 1.220(m, 9H); ^{31}P NMR(CD_3OD) 4.92(s); MS :m/z 698[M+2- 甲基庚胺] $^+$ 。

[0513] 实施例 30

[0514] 化合物 (30a) 的制备

[0515]



[0516] (1-2) 的制备:在 Ar 下向 1-1(313mg ;0.55mmol) 的 THF(8mL) 溶液加入双 (POM) 磷酸三乙基铵的 THF(从双 (POM) 磷酸盐(215mg ;1.2 当量) 制备的、THF(2mL) 和 Et_3N (0.1mL ;

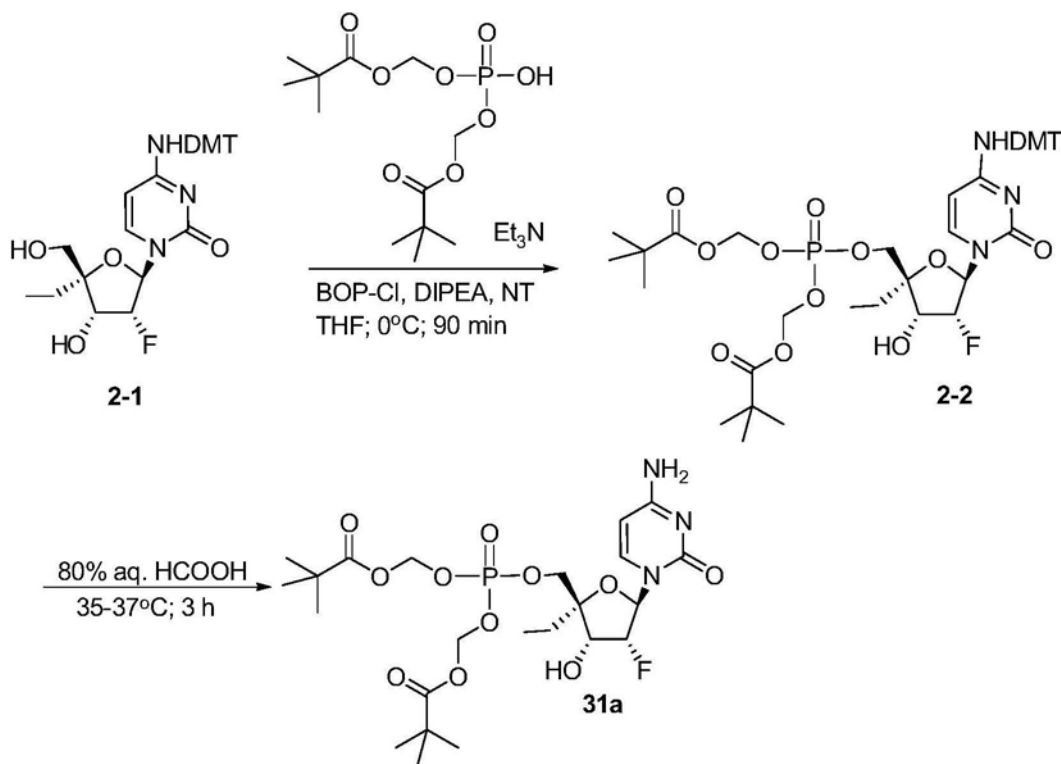
1.3 当量)) 溶液。将生成的混合物在冰浴中冷却。加入二异丙基乙胺 (0.38mL ;4 当量)。然后,加入 BOP-Cl (280mg ;2 当量) 和 3-硝基-1,2,4-三唑 (125mg ;2 当量)。将反应混合物在 0℃ 下搅拌 90mins。使用 CH₂Cl₂ (60mL) 稀释混合物并使用饱和 NaHCO₃ 水溶液 (2×10mL) 和盐水洗涤。使用 CH₂Cl₂ (约 20mL) 反萃合并的水层。干燥 (Na₂SO₄) 合并的有机萃取物并蒸发。在使用 CH₂Cl₂/i-PrOH 溶剂体系 (2-10%梯度) 的二氧化硅 (25g 柱) 上纯化剩余物。产率 :140mg (27%)。

[0517] (30a) 的制备:将 1-2 (110mg ;0.13mmol) 的 80% 甲酸水溶液在 35-37℃ 下加热 3 小时。将混合物蒸发以产生油状剩余物。使用甲苯将剩余物共蒸发 2 次。在使用 CH₂Cl₂/MeOH 溶剂体系 (4-10%梯度) 的硅胶柱上 (10g) 纯化以产生化合物 30a (46mg, 59%产率)。³¹P-NMR (DMSO-d₆) : δ -4.45。MS :m/z 646 (M+46-1)。

[0518] 实施例 31

[0519] 化合物 (31a) 的制备

[0520]



[0521] (2-2) 的制备:在 Ar 下向 2-1 (370mg ;0.64mmol) 的 THF (10mL) 溶液加入双 (POM) 磷酸三乙基铵 (330mg ;1.2 当量)。将混合物在冰浴中冷却,并加入二异丙基乙胺 (0.42mL ;4 当量)。然后,加入 BOP-Cl (305mg ;2 当量) 和 3-硝基-1,2,4-三唑 (137mg ;2 当量)。将反应混合物在 0℃ 下搅拌 90mins。使用 CH₂Cl₂ (50mL) 稀释混合物并使用饱和 NaHCO₃ 水溶液 (2×10mL) 和盐水洗涤。使用 CH₂Cl₂ (约 20mL) 反萃合并的水层。干燥 (Na₂SO₄) 合并的有机萃取物、蒸发,并在 使用 CH₂Cl₂/i-PrOH 溶剂体系 (2-10%梯度) 的二氧化硅 (25g 柱) 上纯化剩余物。产率 :154mg (27%)。

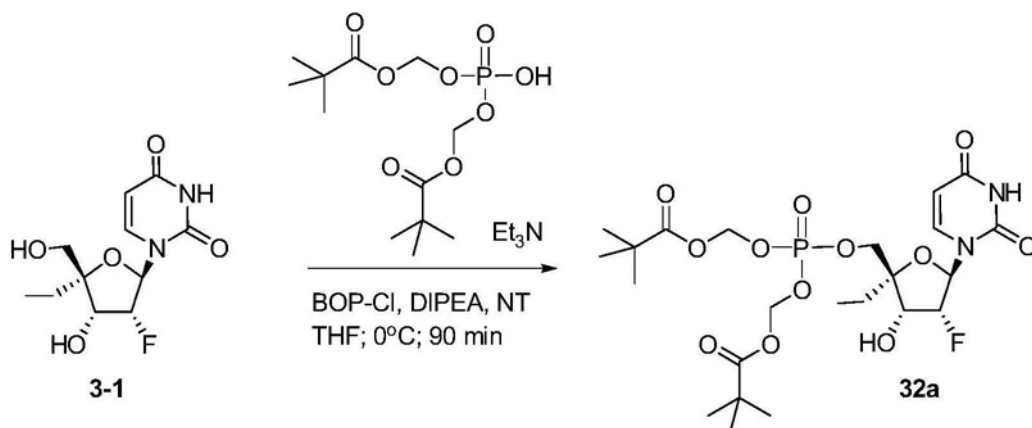
[0522] (31a) 的制备:将 2-2 (68mg ;0.08mmol) 的 80% 甲酸水溶液在 R. T. 下搅拌 3 小时。将混合物蒸发为油状剩余物。使用甲苯将剩余物共蒸发 2 次。在使用 CH₂Cl₂/MeOH 溶剂体系 (4-10%梯度 ;使用 8% MeOH 洗脱靶标化合物) 的硅胶柱上 (10g) 纯化产生 31a (35mg, 78%

产率)。 ^{31}P -NMR (DMSO-d_6) : δ -4.19。MS :m/z 580 (M-1), 646 (M+46-1), 550 (M-30-1)。

[0523] 实施例 32

[0524] 化合物 (32a) 的制备

[0525]

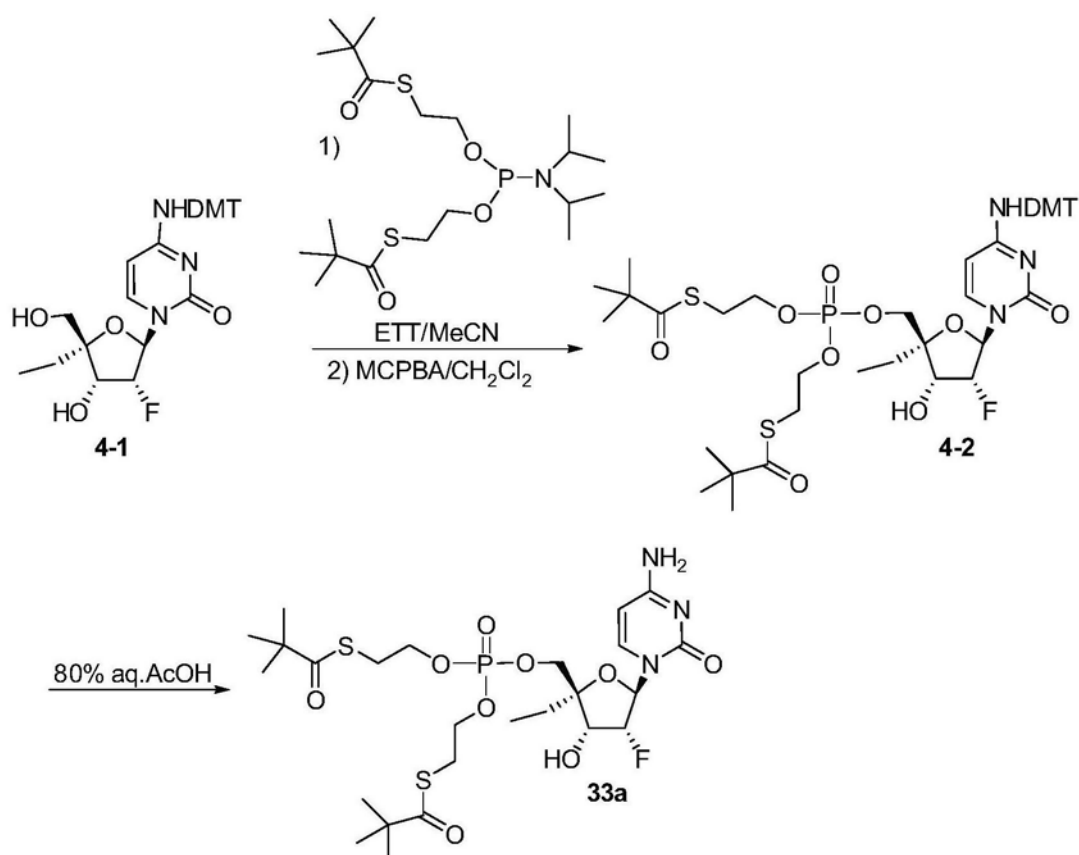


[0526] 在 Ar 下向 3-1 (71mg ;0.26mmol) 的 THF (4mL) 溶液加入双 (POM) 磷酸三乙基铵 (144mg ;1.2 当量), 并将生成的混合物在冰浴中冷却, 并加入二异丙基乙胺 (0.18mL ;4 当量)。然后, 加入 BOP-Cl (132mg ;2 当量) 和 3- 硝基 -1, 2, 4- 三唑 (59mg ;2 当量)。将反应混合物在 0°C 下搅拌 1 小时。使用 CH_2Cl_2 (50mL) 稀释混合物并使用饱和 NaHCO_3 水溶液 ($2 \times 10\text{mL}$) 和盐水洗涤。使用 CH_2Cl_2 (约 20mL) 反萃合并的水层。干燥 (Na_2SO_4) 合并的有机萃取物、蒸发, 并在使用 $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 溶剂体系 (4-10% 梯度) 的二氧化硅 (10g 柱) 上纯化剩余物。通过 RP-HPLC (35-90% B ;A :水, B :MeOH) 再纯化化合物 32a。产率 75mg (50%)。 ^{31}P -NMR (DMSO-d_6) : δ -4.14。MS :m/z 627 (M+46-1), 551 (M-30-1)。

[0527] 实施例 33

[0528] 化合物 (33a) 的制备

[0529]



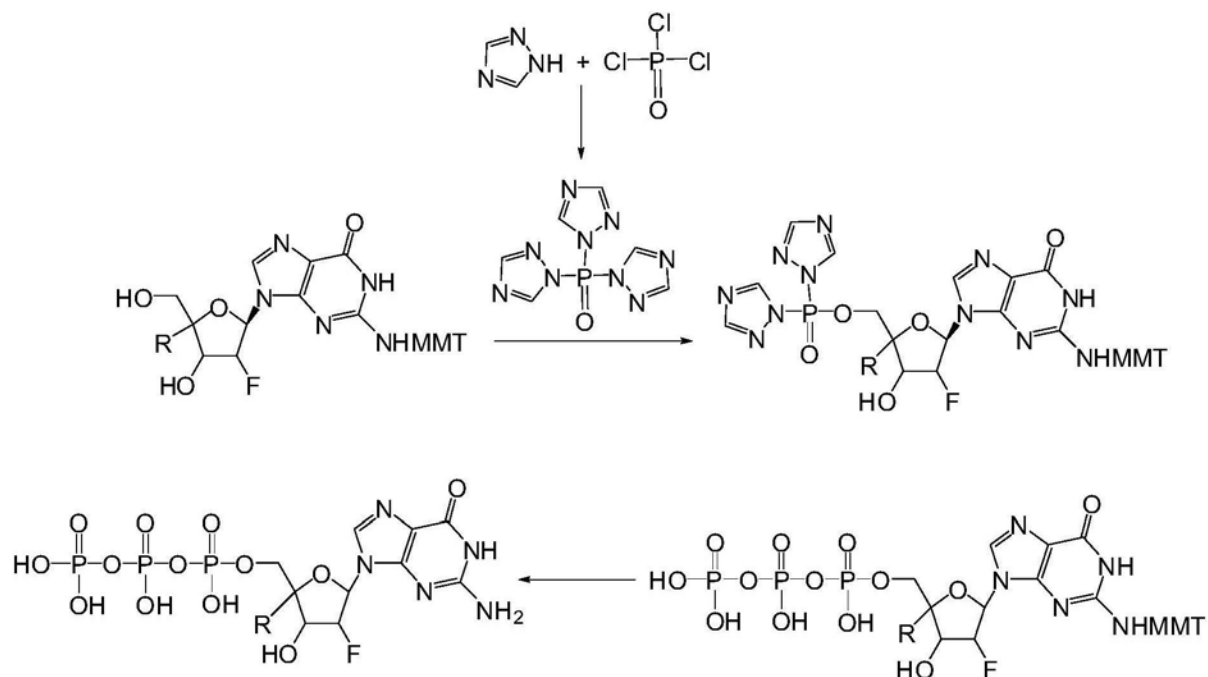
[0530] (4-2) 的制备: 向 4-1 (0.29g ; 0.5mmol) 的 MeCN (8mL) 溶液加入 5-乙基硫代-1H-四唑的 MeCN (0.25M ; 2.4mL ; 1.2 当量)。在 90mins 内加入双 SATE-氨基磷酸酯 (0.24g ; 1.05 当量) 的 MeCN (1.5mL)。将反应混合物在 R. T. 下搅拌 4 小时, 然后冷却至 -40°C 。加入 MCPBA (0.23g ; 2 当量) 的 CH_2Cl_2 (3mL)。将混合物升温至 R. T. 并使用 EtOAc (50mL) 稀释。使用 10% NaHSO_3 水溶液 ($2 \times 10\text{mL}$)、饱和 NaHCO_3 水溶液 ($2 \times 10\text{mL}$) 和盐水洗涤混合物。然后, 干燥 (Na_2SO_4) 混合物。在使用 $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 溶剂体系 (4-10% 梯度) 的二氧化硅 (10g 柱) 上纯化蒸发的剩余物以产生 4-2 (0.26g, 55% 产率)。

[0531] (33a) 的制备: 将 4-2 (0.21g ; 0.22mmol) 的 80% AcOH 水溶液 (15mL) 在 R. T. 下搅拌 4 小时。蒸发混合物并在使用 $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 溶剂体系 (4-10% 梯度) 的二氧化硅 (10g 柱) 上纯化。产率: 0.13g (90%)。 ^{31}P -NMR ($\text{DMSO}-d_6$) : δ -2.00。MS : m/z 686 ($M+46-1$)。

[0532] 实施例 34

[0533] 化合物 (34a)-(34e) 的制备

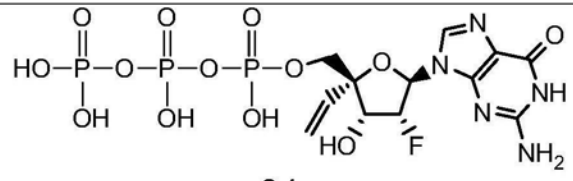
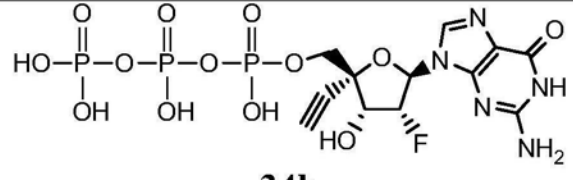
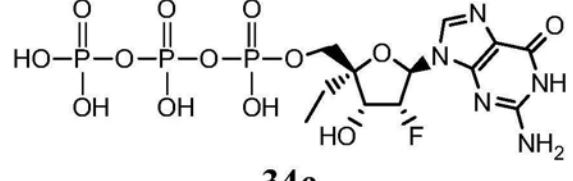
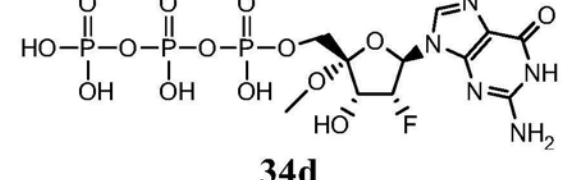
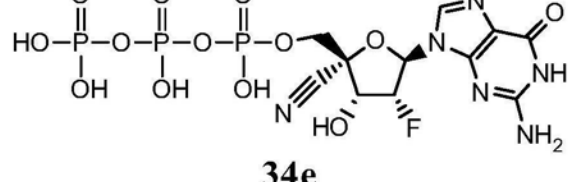
[0534]



[0535] 将 1,2,4-三唑 (42mg, 0.6mmol) 悬浮在干燥的 CH₃CN(1mL) 中。加入三乙胺 (0.088mL, 0.63mmol), 并将混合物涡流以获得澄清溶液。在加入 POCl₃(0.01mL, 0.1mmol) 后, 将混合物涡流并放置 20min。然后, 将混合物离心。将上清液加入至保护的核苷 (0.05mmol), 并将混合物在环境温度下保持 1 小时。加入三(四丁基铵)焦磷酸氢盐 (180mg, 0.2mmol), 并将混合物在 R. T. 下保持 2 小时。使用水淬灭反应、蒸发, 溶于 80% 甲酸并在 R. T. 下保持 2 小时。将甲酸蒸发, 并将剩余物溶于水 (5mL) 并使用 EA (2×2mL) 萃取。将水部分装载在具有 Q 琼脂糖高效 (线性梯度为 0 至 1N 的 50mM TRIS- 缓冲液 (pH = 7.5) 的 NaCl) 的柱 HiLoad 16/10 上。合并包含三磷酸盐的部分、浓缩并通过使用线性梯度为 0 至 20% 的甲醇的 50mM 醋酸三乙铵缓冲液 (pH 7.5) 用于洗脱的协同 4 微米 Hydro-RP 柱 (Phenomenex) 上的 RP HPLC 脱盐。根据该步骤合成下列表 1 显示的化合物:

[0536] 表 1 - 从实施例 34 获得的三磷酸盐

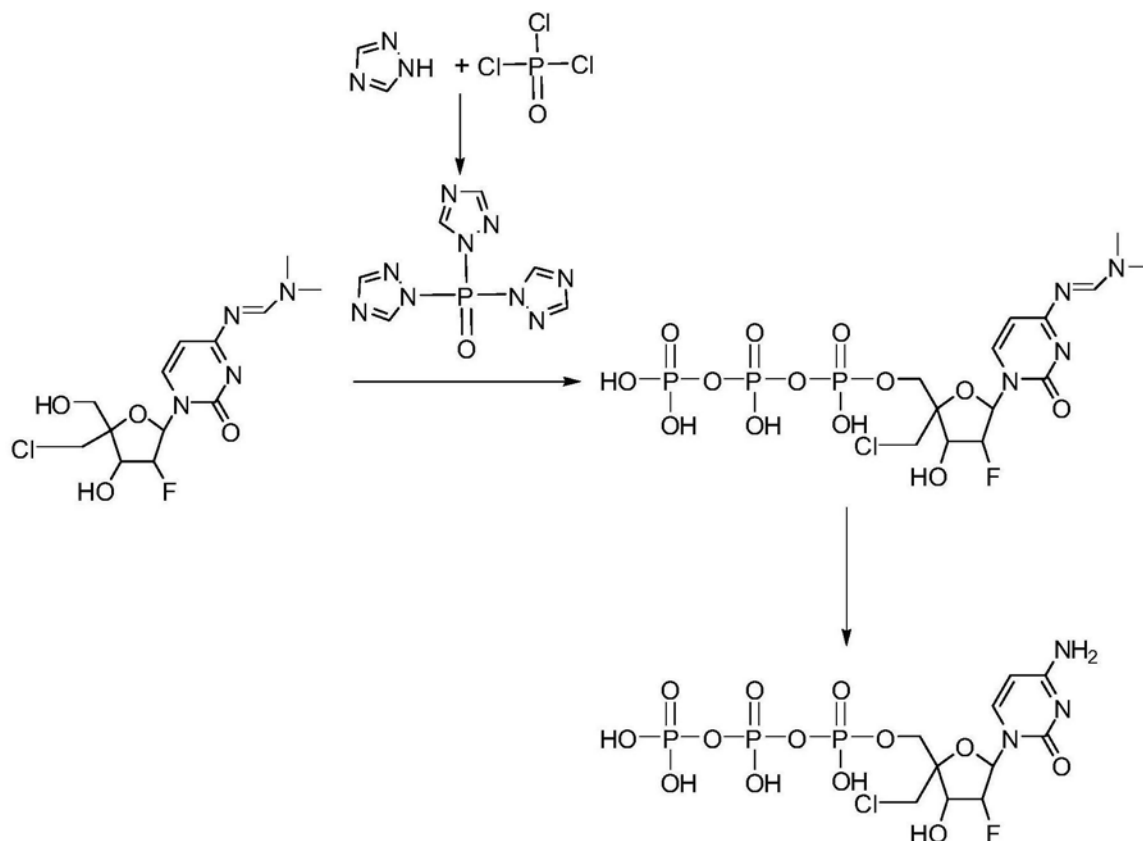
[0537]

化合物	^{31}P NMR P	^{31}P NMR P	^{31}P NMR P	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

[0538] 实施例 35

[0539] 化合物 (35a) 的制备

[0540]

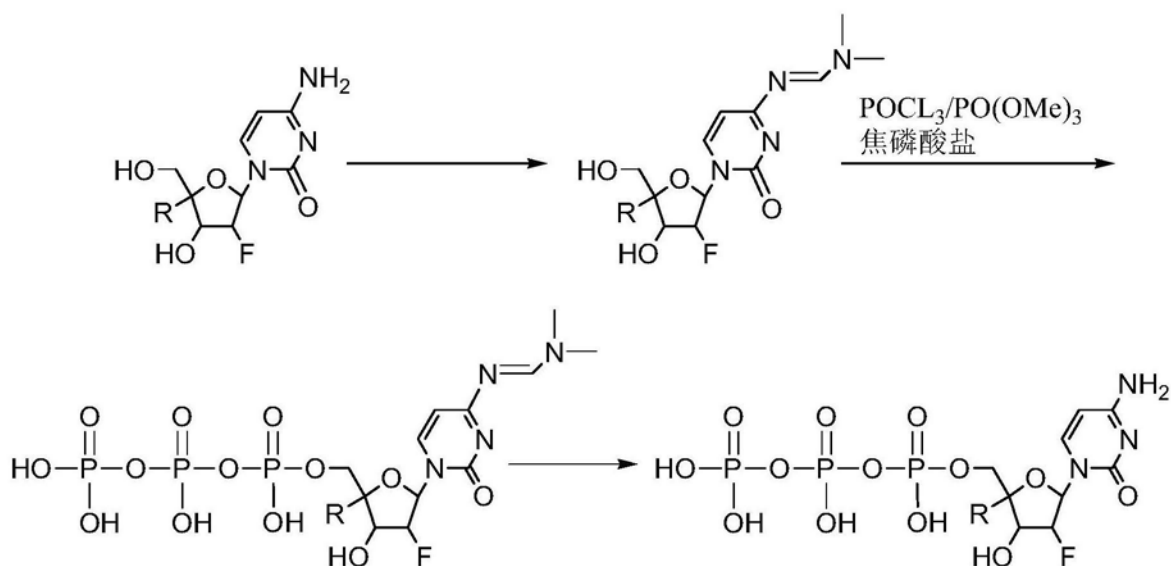


[0541] 将 1,2,4-三唑 (42mg, 0.6mmol) 悬浮在干燥的 CH₃CN(1mL) 中。加入三乙胺 (0.088mL, 0.63mmol), 并将混合物涡流以获得澄清溶液。在加入 POCl₃(0.01mL, 0.1mmol) 后, 将混合物涡流并放置 20min。然后, 将混合物离心, 并将上清液加入至保护的核苷 (0.05mmol)。将混合物在环境温度下保持 1 小时。加入三(四丁基铵)焦磷酸氢盐 (180mg, 0.2mmol), 并将混合物在 R. T. 下保持 2 小时。使用水淬灭反应、蒸发, 溶于氢氧化铵并在 R. T. 下保持 2 小时。将溶剂蒸发, 并将剩余物溶于水 (10mL)。将混合物装载在具有 Q 琼脂糖高效的柱 HiLoad 16/10 上。在线性梯度为 0 至 1N 的 50mM TRIS⁻ 缓冲液 (pH = 7.5) 的 NaCl 中进行分离。合并包含产物的部分, 浓缩并通过在协同 4 微米 Hydro-RP 柱 (Phenomenex) 上的 RPHPLC 脱盐。线性梯度为 0 至 20% 的甲醇的 50mM 醋酸三乙铵缓冲液 (pH 7.5) 用于洗脱。MS(M-1): 532.1。³¹P-NMR(δ ppm): -5.12(d), -11.31(d) 和 -20.43(t)。

[0542] 实施例 36

[0543] 化合物 (36a)-(36d) 的制备

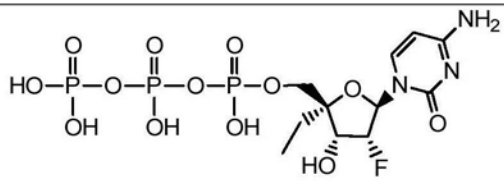
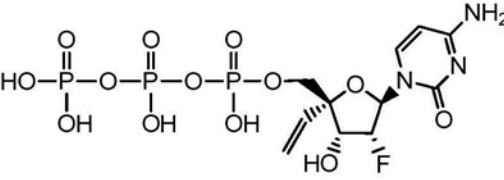
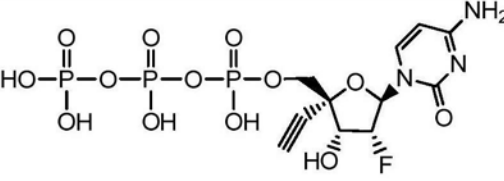
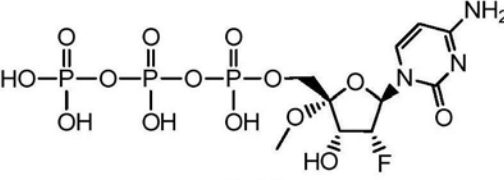
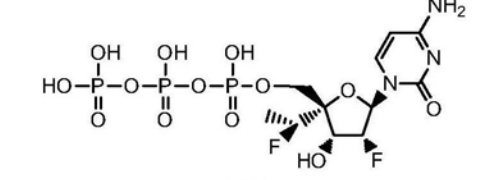
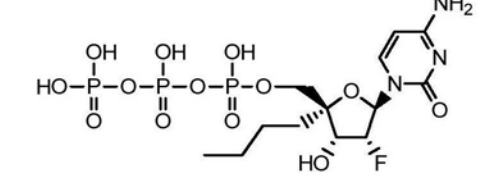
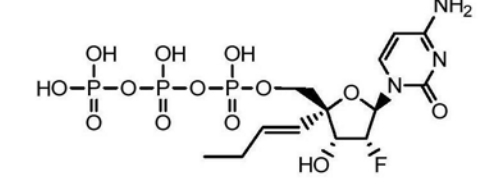
[0544]



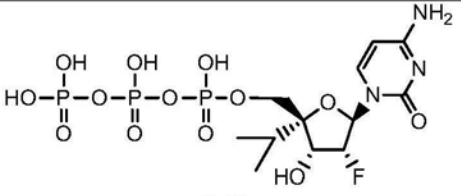
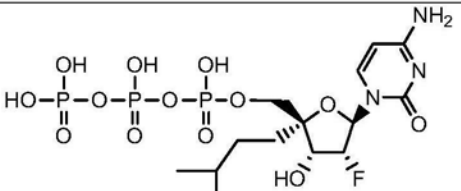
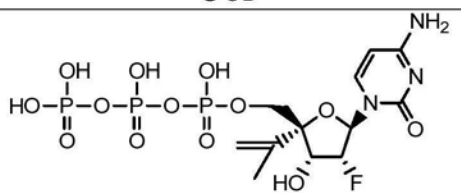
[0545] 将 2'-脱氧-2'-氟-4'-烷基-胞嘧啶核苷 (0.09mmol) 溶于 DMF (5mL) 和 N,N'-醋酸二甲基酯的 DMF (0.110mL, 0.9mmol) 混合物。将反应混合物在 R.T. 下放置过夜。将溶剂蒸发, 并通过梯度为 3% 至 20% 的甲醇的 DCM 的快速层析纯化剩余物。将 N-保护的核苷真空浓缩、干燥并溶于干燥的磷酸三甲酯 (0.7mL)。将溶液冷却至 4℃ 并加入 POCL₃ (0.017mL, 0.18mmol)。在 1 小时内, 在 R.T. 下加入三丁基胺 (0.102mL, 0.3mmol)。然后, 加入三丁基焦磷酸铵 (156mg, 0.34mmol)。加入干燥的 DMF (约 0.100mL) 以溶解焦磷酸盐。在 2 小时后, 使用 TEAB-缓冲液淬灭反应。通过实施例 35 中描述的 AKTA Explorer 上的离子交换层析分离产物。将包含产物的部分浓缩并在 R.T. 下使用 NH₄OH 处理 2 小时。通过实施例 35 描述的 RP HPLC 将产物脱盐。

[0546] 表 2 - 从实施例 36 获得的三磷酸盐

[0547]

化合物	^{31}P NMR P	^{31}P NMR P	^{31}P NMR P	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

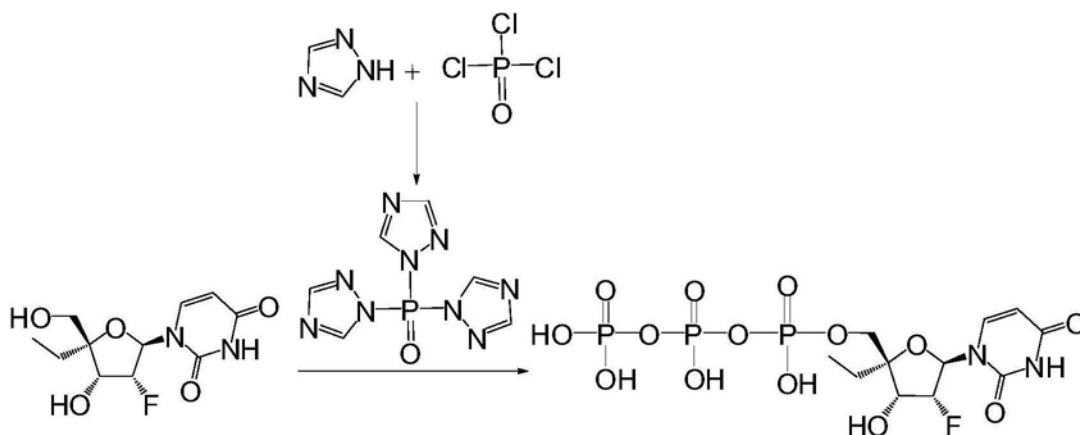
[0548]

 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

[0549] 实施例 37

[0550] 化合物 (37a) 的制备

[0551]

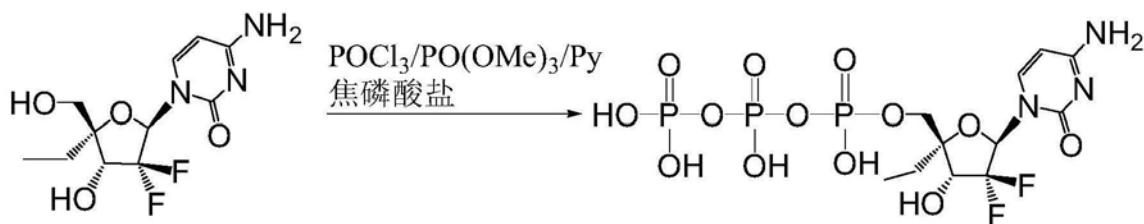


[0552] 通过如实施例 34 和 35 描述的磷(三-三唑化物)与 4'-乙基-2'-脱氧-2'-氟-尿苷的反应合成化合物 37a。MS(M-1): 513.1。³¹P-NMR(δ ppm): -9.43(bs), -11.68(d) 和 -23.09(bs)。

[0553] 实施例 38

[0554] 化合物 (38a) 的制备

[0555]

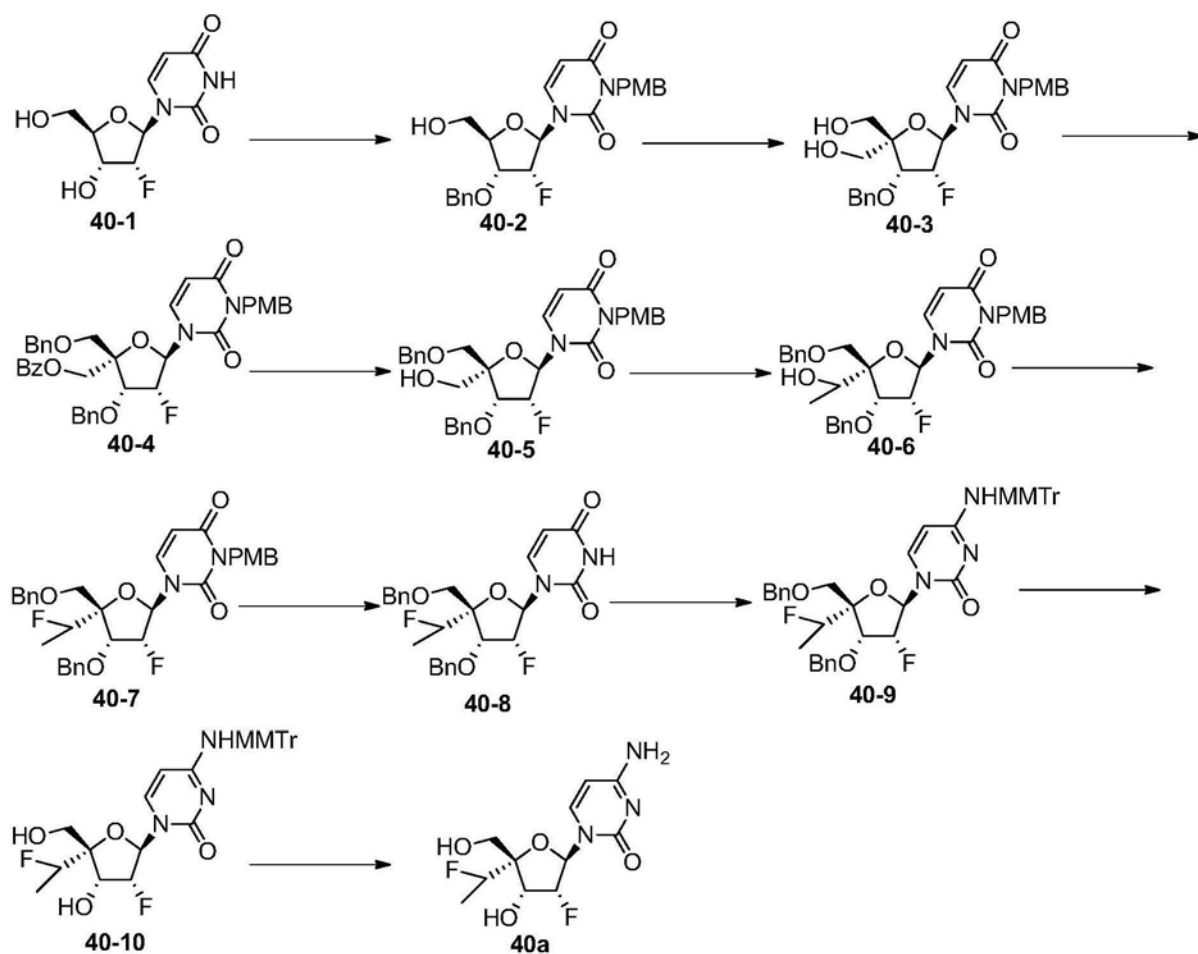


[0556] 将起始核苷 (15mg, 0.05mmol) 溶于干燥的磷酸三甲酯 (3mL)。将溶液冷却至 4℃。加入 POCl_3 (0.013mL, 0.125mmol), 随后加入吡啶 (0.01mL, 0.125mmol)。在 1 小时内, 在 R. T. 下加入三丁基胺 (0.035mL, 0.125mmol), 随后三丁基焦磷酸铵 (156mg, 0.34mmol)。加入干燥的 DMF (约 0.100mL) 以溶解焦磷酸盐。在 2 小时内, 使用 TEAB- 缓冲液淬灭反应。通过实施例 35 中描述的 AKTA Explorer 上的离子交换层析分离产物。将包含产物的部分浓缩并在 R. T. 下使用 NH_4OH 处理 2 小时。通过实施例 35 描述的 RP HPLC 将产物脱盐。MS (M-1) : 529.9。 ^{31}P -NMR (δ ppm) : -9.42(d), -11.59(d) and -23.03(t)。

[0557] 实施例 39

[0558] 化合物 (40a) 的制备

[0559]



[0560] (40-2) 的制备: 向 40-1 (50.0g, 205mmol) 的吡啶 (250mL) 溶液加入 DMTTrCl (75.0g, 225.0mmol)。将溶液在 R. T. 下搅拌 15 小时。加入 MeOH (120mL), 并在减压下将混合物浓缩至干燥。将剩余物溶于 EA 并使用水洗涤。在 Na_2SO_4 上干燥有机层并浓缩以产生淡黄色固体形式的粗 5'-O-DMTr 中间体 (80.52g)。将中间体溶于无水 DMF (300mL), 并加入 K_2CO_3 (80.52g, 583.2mmol), 随后加入 PMBCl (31.7g, 109.2mmol)。将混合物在 R. T. 下搅拌过夜。使用 EA 稀释反应并使用盐水洗涤。在 Na_2SO_4 上干燥有机相并浓缩以产生淡黄色固体形式的粗 5'-O-DMTr-N3-PMBFdu (98.8g)。将固体溶于 DMF (300mL), 并加入 NaH (10.42g, 260.5mmol), 随后加入 BnBr (73.8g, 434.2mmol)。将反应在 R. T. 下搅拌过夜, 然后使用水淬灭。使用 EA 稀释溶液并使用盐水洗涤。在 Na_2SO_4 上干燥有机相并浓缩以产

生粗完全封端 FdU 中间体,在硅胶柱上 (PE:EA = 10:1 至 3:1) 将其纯化为纯完全封端的 FdU(101.1g)。在 R. T. 下使用 80% H₂OAc(900mL) 将中间体处理过夜,并去除溶剂。在硅胶柱上纯化剩余物以产生白色泡沫形式的 40-2(42.1g, 4 步骤产率为 30.2%)。

[0561] (40-3) 的制备:在 R. T. 下,向 40-2(42.1g, 92.6mmol) 的无水 CH₃CN(300mL) 溶液加入 IBX(28.5g, 121.7mmol)。将反应混合物回流 1 小时,然后冷却至 0℃。将沉淀滤除,并将滤液浓缩以产生黄色固体形式的粗醛(39.22g)。向醛(39.22g)的 1,4-二氧六环(250mL)溶液加入 37% CH₂O(28.1mL, 345.6mmol) 和 2N NaOH 水溶液(86.4mL, 172.8mmol)。将混合物在 R. T. 下搅拌 2 小时,然后使用 AcOH 中和至 pH = 7。加入 EtOH(200mL) 和 NaBH₄(19.7g, 518.6mmol),在 R. T. 下搅拌 30mins。使用饱和 NH₄Cl 水溶液淬灭混合物,并使用 EA 萃取。在 Na₂SO₄ 上干燥有机层并浓缩。通过硅胶柱层析 (PE:EA = 4:1 至 2:1) 纯化剩余物以产生白色固体形式的 40-3(25.5g, 55.7%)。

[0562] (40-4) 的制备:在 0℃ 下,向搅拌的 40-3(25.5g, 52.5mmol) 的无水吡啶(150mL) 和无水 CH₃CN(150mL) 溶液滴加 BzCl(6.6g, 52.47mmol)。将混合物在 R. T. 下搅拌 14 小时。使用 H₂O 淬灭反应,并将溶液浓缩。将剩余物溶于 EA 并使用饱和 NaHCO₃ 洗涤。在 Na₂SO₄ 上干燥有机层并浓缩。在硅胶柱上 (PE/EA = 5:4) 纯化剩余物以产生白色泡沫形式的单-Bz 保护的中间体(18.1g, 60.0%)。向搅拌的该中间体(18.1g, 30.68mmol) 的 DMF(100mL) 溶液加入 Cs₂CO₃(30.0g, 92.03mmol) 和 BnBr(10.4g, 61.36mmol)。将混合物在 R. T. 下搅拌过夜。使用饱和 NH₄Cl 水溶液淬灭反应,使用 EA 萃取并使用盐水洗涤。去除溶剂以产生淡黄色固体形式的粗 40-4(19.3g, 95.1%)。

[0563] (40-5) 的制备:在 R. T. 下,向搅拌的 40-4(19.3g, 28.4mmol) 的无水 MeOH(230mL) 溶液加入 NaOMe(24.9g, 460mmol)。将混合物搅拌 1 小时。使用 AcOH(10mL) 淬灭反应并浓缩。在硅胶柱上 (PE/EA = 1/2) 纯化剩余物以产生白色固体形式的 40-5(11.2g, 54.0%)。

[0564] (40-6) 的制备:在 R. T. 下,向搅拌的化合物 40-5(200mg, 0.347mmol) 的无水 DCM(5mL) 溶液加入 DMP(168mg, 0.674mmol)。将混合物在 R. T. 下搅拌 2 小时。将溶剂去除,并在硅胶柱上 (PE:EA = 5:1 至 1:1) 纯化剩余物以产生淡黄色固体形式的醛粗(200mg)。在 -78℃ 下,向搅拌的醛(200mg) 的无水 THF(5mL) 溶液加入 MeMgBr(1.0mL, 1.01mmol)。将混合物在 -78℃ 下搅拌 1 小时。使用饱和 NH₄Cl 水溶液淬灭反应并使用 EA 萃取。通过柱层析 (PE:EA = 5:1 至 1:1) 纯化浓缩的有机相以产生白色固体形式的 40-6(立体异构体的混合物, 135mg, 65%)。

[0565] (40-7) 的制备:在 -78℃ 下,向搅拌的 DAST(1.64g, 10.17mmol) 的无水甲苯(40mL) 溶液滴加化合物 40-6(1.2g, 2.03mmol) 的溶液。将混合物在 -78℃ 下搅拌 30mins。将溶液缓慢升温至 60℃ 并继续搅拌过夜。将混合物倾入饱和 Na₂CO₃ 溶液。将浓缩的有机相浓缩并在硅胶柱上 (PE:EA = 10:1 至 3:1) 纯化以产生白色固体形式的 40-7(1.08g, 83.88%)。¹H NMR(CD₃OD, 400MHz) 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)。

[0566] (40-8) 的制备:将化合物 40-7(0.91g, 1.54mmol) 和 CAN(2.53g, 4.61mmol) 的 MeCN: 水(10m L) 的 3:1 溶液的混合物在 R. T. 下搅拌过夜。加入盐水(10mL), 并使用 EA 萃取混合物。将合并的有机提取物干燥并在减压下蒸发。通过使用 PE:EA = 10:1 至 2:1 的

硅胶柱上的层析纯化产生黄色固体形式的 40-8 (305mg, 41.96%)。

[0567] (40-9) 的制备: 在 R. T. 下, 向搅拌的 40-8 (350mg, 0.74mmol) 的无水 MeCN (8mL) 溶液加入 TPSCl (449mg, 1.48mmol)、DMAP (180mg, 1.48mmol) 和 TEA (374mg, 3.70mmol)。将混合物在 R. T. 下搅拌过夜。加入 NH_4OH (15mL), 并将混合物搅拌 2 小时。将溶剂去除, 并在使用 PE:EA = 8:1 至 1:1 的硅胶柱上纯化剩余物以产生粗物质 (380mg 粗物质), 将其溶于无水 DCM (10mL)。在 R. T. 下加入 MMTrCl (695mg, 2.25mmol) 和 AgNO_3 (380mg, 2.25mmol) 的混合物, 并将混合物在 R. T. 下搅拌过夜。将固体滤除并使用 DCM 洗涤。使用盐水洗涤滤液并在 Na_2SO_4 上干燥。在硅胶柱上 (PE:EA = 8:1 至 2:1) 纯化浓缩的有机相以产生黄色固体形式的 40-9 (460mg, 81.33%)。

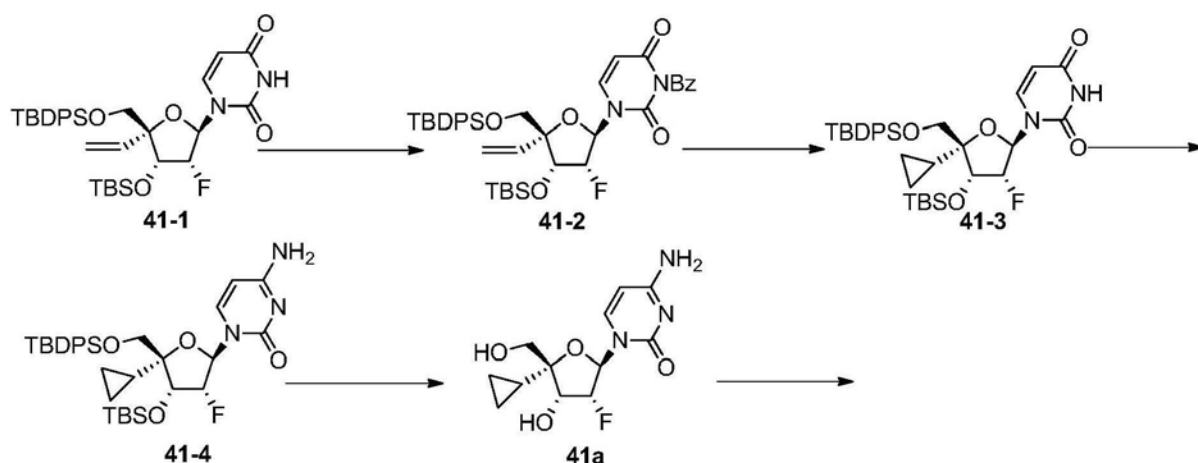
[0568] (40-10) 的制备: 向搅拌的化合物 40-9 (450mg, 0.61mmol) 的丙酮溶液加入甲酸铵 (1.29g, 20.6mmol, 分批) 和 10% 钨 / 碳 (1.0g)。将混合物回流 12h。将催化剂滤除并使用丙酮洗涤。使用 EA 稀释滤液并使用盐水洗涤。通过柱层析 (DCM:MeOH = 100:1 至 15:1) 纯化浓缩的有机相以产生白色固体形式的 40-10 (250mg, 72.8%)。 ^1H NMR (DMSO- d_6 , 400M Hz) δ 8.56 (s, 1H), 7.73 (d, J = 7.6Hz, 1H), 7.14-7.28 (m, 12H), 6.84 (d, J = 8.8Hz, 2H), 6.30 (d, J = 7.6Hz, 1H), 6.03-6.08 (m, 1H), 5.84 (d, J = 5.2Hz, 1H), 5.33-5.35 (m, 1H), 4.97-5.18 (m, 1H), 4.86-4.90 (m, 1H), 4.34 (d, J = 4.4Hz, 1H), 3.72 (s, 3H), 3.54-3.57 (m, 2H), 1.28 (dd, J_1 = 6.4Hz, J_2 = 25.6Hz, 3H)。ESI-MS : m/z 563.50 $[\text{M}+\text{H}]^+$ 。

[0569] (40a) 的制备: 在 R. T. 下, 将 40-10 (101mg, 0.179mmol) 溶于 80% HOAc (20mL)。将混合物在 50°C 下搅拌 5 小时。将溶剂去除, 并使用甲苯将剩余物共蒸发两次。通过柱层析 (DCM:MeOH = 100:1 至 10:1) 纯化剩余物以产生白色固体形式的 40a (36.6mg, 70.26%)。 ^1H NMR (CD_3OD , 400MHz) δ 7.98 (d, J = 7.6Hz, 1H), 6.20-6.24 (m, 1H), 5.92 (d, J = 7.2Hz, 1H), 5.17-5.30 (m, 1H), 4.99-5.14 (m, 1H), 4.51-4.86 (m, 1H), 3.78 (d, J = 1.6Hz, 2H), 1.35-1.43 (m, 3H)。ESI-MS : m/z 291.84 $[\text{M}+\text{H}]^+$, 582.81 $[2\text{M}+\text{H}]^+$ 。

[0570] 实施例 40

[0571] 化合物 (41a) 的制备

[0572]



[0573] (41-2) 的制备: 在 R. T. 下, 向 41-1 (3g, 4.8mmol) 的无水 DCM (50mL) 溶液加入 BzCl (1.3g, 9.6mmol)、DMAP (1.1g, 9.6mmol) 和 NEt_3 (4mL)。将反应在 R. T. 下搅拌 2 小时。加入水, 并将反应搅拌另外 1 小时。使用 DCM (150mL) 稀释混合物并使用水、0.1M HCl 和饱和

和 NaHCO_3 水溶液洗涤。将溶剂去除,并通过硅胶柱层析 (25% EtOAc 的 PE) 纯化粗产物以产生黄色固体形式的 41-2 (2.8g, 80.0%)。

[0574] (41-3) 的制备: 在 -78°C 下, 将 41-2 (2.6g, 3.6mmol) 和 $\text{Pd}(\text{OAc})_2$ (100mg) 的 DCM (50mL) 混合物悬浮在 CH_2N_2 的 Et_2O 溶液中 (通过标准步骤生成的, 350mL)。将反应搅拌至 R. T. 过夜。使用 HOAc 淬灭混合物, 并将反应搅拌另外 1 小时。使用 EtOAc (150mL) 稀释混合物并使用水和饱和 NaHCO_3 水溶液洗涤。将溶剂去除, 并将粗物质溶于 NH_3 , MeOH (饱和的, 100mL)。将反应搅拌至 R. T. 过夜。通过硅胶柱层析 (25% EtOAc 的 PE) 纯化粗产物以产生黄色固体形式的 41-3 (800mg, 35.2%)。

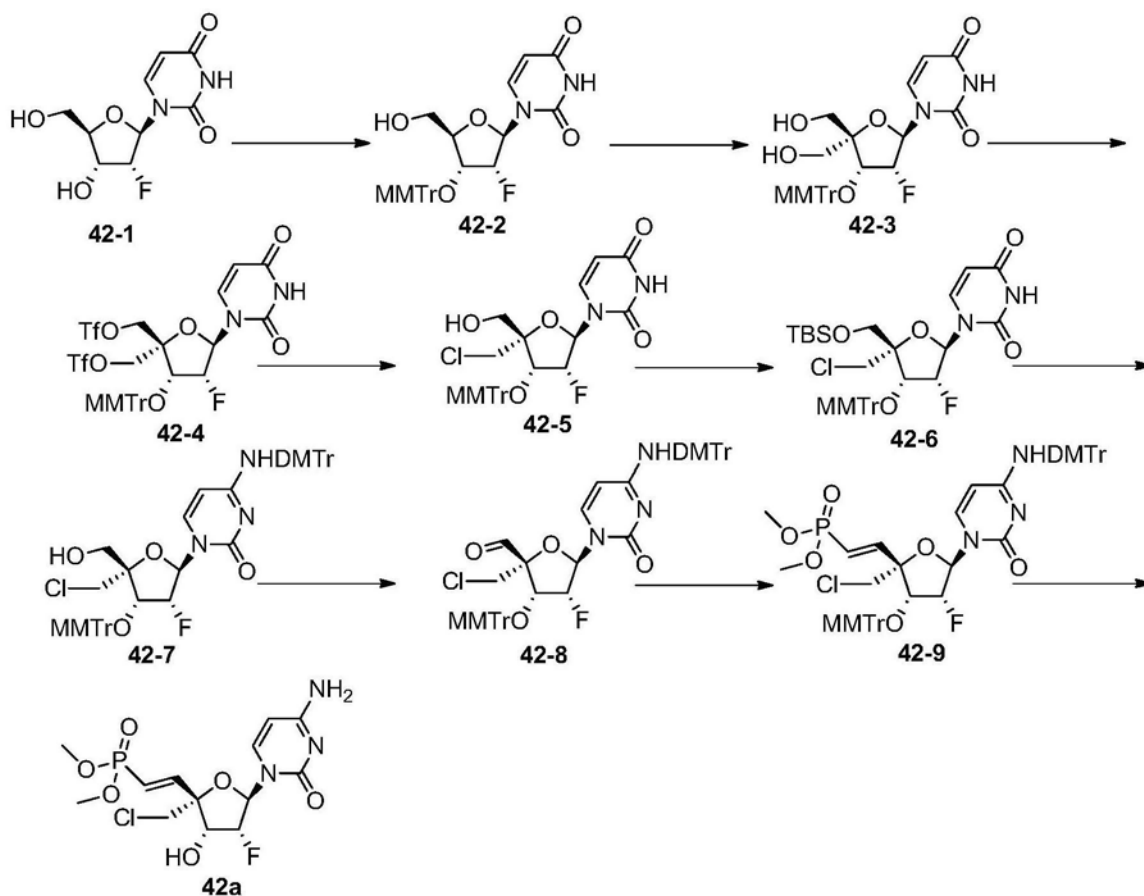
[0575] (41-4) 的制备: 在 R. T. 下, 向 41-3 (800mg, 1.3mmol) 的无水 CH_3CN (50mL) 溶液加入 TPSCl (755mg, 2.5mmol)、DMAP (305mg, 2.5mmol) 和 NEt_3 (400mg, 4mmol)。将反应在 R. T. 下搅拌 2 小时。加入 NH_4OH (25mL), 并将反应搅拌另外 1 小时。使用 DCM (150mL) 稀释混合物并使用水、0.1M HCl 和饱和 NaHCO_3 水溶液洗涤。将溶剂去除, 并通过硅胶柱层析 (25% EtOAc 的 PE) 纯化粗产物以产生黄色固体形式的 41-4 (340mg, 42.5%)。

[0576] (41a) 的制备: 向 41-4 (200.0mg) 的 MeOH (10mL) 溶液加入 NH_4F (600mg)。将反应回流 24 小时。将溶剂去除, 并通过在硅胶上的柱层析 ($\text{DCM}:\text{MeOH} = 15:1$) 纯化剩余物以产生白色固体形式的 41a (50.0mg, 55.9%)。 ^1H NMR (CD_3OD , 400M Hz) δ 8.13 (d, $J = 7.6\text{Hz}$, 1H), 6.01 (dd, $J_1 = 2.4\text{Hz}$, $J_2 = 15.6\text{Hz}$, 1H), 5.85 (d, $J = 7.6\text{Hz}$, 1H), 5.04-4.89 (m, 1H), 4.52 (dd, $J_1 = 5.2\text{Hz}$, $J_2 = 19.6\text{Hz}$, 1H), 3.66 (s, 2H), 1.00-0.94 (m, 1H), 0.54-0.30 (m, 4H); ESI-MS: m/z 285.82 $[\text{M}+\text{H}]^+$, 570.84 $[2\text{M}+\text{H}]^+$ 。

[0577] 实施例 41

[0578] 化合物 (42a) 的制备

[0579]



[0580] (42-2) 的制备：向 42-1 (50g, 203mmol) 的无水吡啶 (200mL) 溶液加入 TBDPSCl (83.7g, 304mmol, 1.5eq)。将反应在 R. T. 下搅拌过夜。将溶液在减压下浓缩以产生糖浆，将其在乙酸乙酯和水之间分层。分离有机层，使用盐水洗涤、在硫酸镁上干燥并浓缩以产生白色泡沫形式的 5'-OTBDPS 醚 (94g)。将粗醚溶于无水 DCM (300mL)，并加入硝酸银 (66.03g, 388.4mmol, 2.0eq) 和三甲吡啶 (235mL, 1.94mol, 10eq)。将混合物在 R. T. 下搅拌，并加入 MMTrCl (239.3g, 776.8mmol, 4eq)。在 R. T. 下搅拌过夜后，通过硅藻土过滤混合物并使用 MTBE 稀释滤液。相继使用 1M 柠檬酸、稀释的盐水和 5% 碳酸氢钠洗涤溶液。在硫酸钠上干燥有机溶液并真空浓缩以产生黄色泡沫形式的完全保护的中间体。将粗中间体溶于无水 THF (250mL) 并使用 TBAF (60g, 233mmol, 1.2eq) 处理。将混合物在 R. T. 下搅拌 2 小时，并在减压下去除溶剂。将剩余物放入乙酸乙酯并使用盐水洗涤。在硫酸镁上干燥后，真空去除溶剂。通过柱层析 (PE:EA = 5:1 至 1:1) 纯化剩余物以产生白色泡沫形式的 42-2 (91g, 86.4%)。

[0581] (42-3) 的制备：向 42-2 (13.5g, 26mmol) 的 DCM (100mL) 溶液加入吡啶 (6.17mL, 78mmol, 3eq)。将溶液冷却至 0°C 并加入戴斯-马丁氧化剂 (33.8g, 78mmol, 3eq)。将混合物在 R. T. 下搅拌 4 小时并通过加入 4% Na₂S₂O₃/4% 碳酸氢钠水溶液 (至 pH 6, 约 150mL) 淬灭。将混合物搅拌另外 15mins。分离有机层，使用稀释的盐水洗涤并在减压下浓缩。将剩余物溶于二氧六环 (100mL)，并使用 37% 甲醛水溶液 (21.2g, 10eq) 和 2N 氢氧化钠水溶液 (10eq) 处理溶液。将反应混合物在 R. T. 下搅拌过夜。使用饱和 NH₄Cl (约 150mL) 淬灭反应，并在减压下浓缩混合物。将剩余物在乙酸乙酯和 5% 碳酸氢钠之间分层。分离有机相，使用盐水洗涤，在硫酸镁上干燥并浓缩。通过柱层析 (MeOH:DCM = 100:1 至 50:1) 纯

化剩余物以产生白色泡沫形式的 42-3(9.2g, 83.6%)。

[0582] (42-4) 的制备: 使用甲苯将 42-3(23g, 42.0mmol) 共蒸发两次。将剩余物溶于无水 DCM(250mL) 和吡啶 (20mL)。将溶液冷却至 -35°C 。在 10mins 内滴加三氟甲磺酸酐 (24.9g, 88.1mmol, 2.1eq)。在该温度下, 将反应搅拌 40mins, 然后在 0°C 下使用水淬灭 (50mL)。将混合物搅拌 30mins, 并使用 EA(150mL $\times$ 2) 萃取。在 Na_2SO_4 上干燥有机相, 并通过硅胶垫过滤。在减压下浓缩滤液。通过柱层析 (PE:EA = 100:1 约 1:1) 纯化剩余物以产生褐色泡沫形式的 42-4(30.0g, 88.3%)。

[0583] (42-5) 的制备: 使用甲苯将 42-4(30g, 36.9mmol) 共蒸发两次并溶于无水 DMF(150mL)。将溶液冷却至 0°C , 并使用氢化钠 (60% 的矿物油; 1.5g, 40.6mmol) 处理。将反应在 R.T. 下搅拌 1h。加入氯化锂 (4.6g, 110.7mmol, 3eq)。当 LCMS 指示三氟甲磺酸酐中间体完全转化为酐-氯化物时, 将搅拌继续 2 小时。将混合物放入 100mL 的半饱和氯化铵和乙酸乙酯中。分离有机相, 使用稀释的盐水洗涤并在减压下浓缩。将剩余物溶于 THF(150mL), 并使用 1N 氢氧化钠水溶液 (约 41mL, 40.1mmol, 1.1eq) 处理溶液。将混合物在 R.T. 下搅拌 1h。使用半饱和碳酸氢钠 (约 60mL) 稀释反应并使用 EA 萃取。干燥 (硫酸镁) 有机相并在减压下浓缩。通过柱层析 (DCM:MeOH = 300:1 至 60:1) 纯化剩余物以产生黄色泡沫形式的 42-5(18.3g, 87.6%)。

[0584] (42-6) 的制备: 向 42-5(18.3g, 32.33mmol) 的无水 DCM(150mL) 溶液加入 TBSCl(17.7g, 64.6mmol) 和咪唑 (6.6g, 97mmol)。将反应在 R.T. 下搅拌过夜。使用水稀释反应并使用 DCM 萃取。分离有机层, 使用盐水洗涤、在 Na_2SO_4 上干燥并浓缩。通过柱层析 (DCM:MeOH = 300:1 至 80:1) 纯化剩余物以产生白色泡沫形式的 42-6(18.4g, 83.7%)。

[0585] (42-7) 的制备: 使用 2,4,6-三异丙基苯磺酰氯 (16.3g, 54.0mmol) 处理 42-6(18.4g, 27.1mmol)、DMAP(6.6g, 54.0mmol) 和 TEA(5.4g, 54.0mmol) 的 MeCN(450mL) 溶液。将混合物在 R.T. 下搅拌 3 小时。加入 NH_4OH (70mL), 并将混合物搅拌 2 小时。在减压下蒸发溶液, 并在硅胶柱上 (DCM/MeOH = 100:1 至 15:1) 纯化剩余物以产生粗物质 (18.0g)。将粗物质溶于无水 DCM(150mL)。加入三甲吡啶 (8.1g, 66.3mmol, 2.5eq)、硝酸银 (4.5g, 26.5mmol, 1.0eq) 和 DMTrCl (13.4g, 39.7mmol, 1.5eq)。将反应在 R.T. 下搅拌过夜。通过硅藻土过滤混合物。使用盐水洗涤滤液并使用 DCM 萃取。分离有机层, 在 Na_2SO_4 上干燥并浓缩。通过柱层析 (PE:EA = 60:1 ~ 3:1) 纯化剩余物为黄色泡沫形式。将泡沫溶于 THF(150mL) 并加入 TBAF(10.4g, 39.7mmol, 1.5eq)。在浓缩后将反应在 R.T. 下搅拌, 使用盐水洗涤混合物并使用 EA 萃取。分离有机层, 在 Na_2SO_4 上干燥并浓缩。通过柱层析 (PE:EA = 60:1 ~ EA) 纯化剩余物以产生黄色泡沫形式的 42-7(21.3g, 92.4%)。

[0586] (42-8) 的制备: 在氮气下, 在 0°C 下, 向 42-7(2.0g, 2.3mmol) 的无水 DCM(20mL) 溶液加入戴斯-马丁氧化剂 (1.95g, 4.6mmol)。将反应在 R.T. 下搅拌 5 小时。使用 EtOAc(100mL) 稀释混合物, 并使用饱和 $\text{Na}_2\text{S}_2\text{O}_3$ 水溶液和饱和 NaHCO_3 水溶液的混合物洗涤。通过在硅胶上的柱层析 (PE:EtOAc = 2:1) 纯化粗产物以产生黄色固体形式的 42-8(1.8g, 90%)。

[0587] (42-9) 的制备: 在氮气下, 在 0°C 下, 向亚甲基二磷酸四甲酯 (390mg, 1.68mmol) 的无水 THF(10mL) 溶液加入 NaH(84mg, 2.1mmol)。将反应在 0°C 下搅拌 30min。在 0°C 下滴加 42-8(1.2g, 1.4mmol) 的无水 THF(10mL) 溶液。将混合物在 R.T. 下搅拌 1h。使用饱和 NH_4Cl

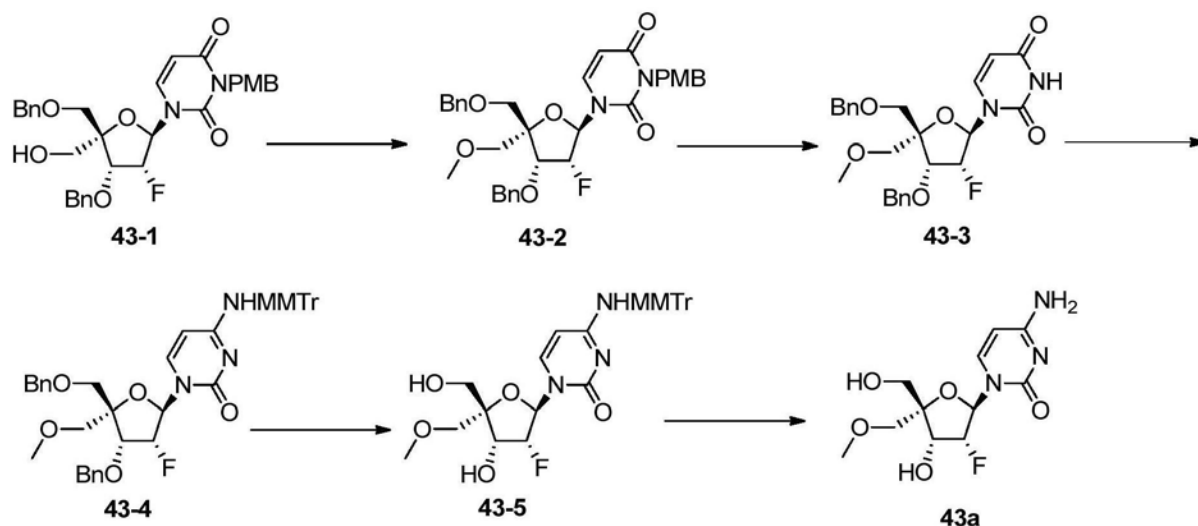
水溶液淬灭反应,并通过在硅胶上的柱层析(DCM:MeOH = 150:1)纯化粗产物以产生黄色固体形式的42-9(1.2g, 88.2%)。¹H NMR(DMSO-d₆, 400M Hz) δ 8.51(s, 1H), 7.46-7.09(m, 22H), 6.88-6.82(m, 6H), 6.62(q, $J_1 = 17.2\text{Hz}$, $J_2 = 22.4\text{Hz}$, 1H), 6.12(d, $J = 7.2\text{Hz}$, 1H), 5.86-5.75(m, 2H), 5.43(d, $J = 25.2\text{Hz}$, 1H), 4.63(dd, $J_1 = 4.8\text{Hz}$, $J_2 = 21.2\text{Hz}$, 1H), 4.45(d, $J = 12.0\text{Hz}$, 1H), 3.94(d, $J = 12.0\text{Hz}$, 1H), 3.72(s, 9H), 3.53(q, $J_1 = 11.2\text{Hz}$, $J_2 = 16.0\text{Hz}$, 6H); ESI-MS :m/z 971.59[M+H]⁺。

[0588] (42a) 的制备:将42-9(300mg)的80% HOAc(26mL)溶液在80-90℃下搅拌2h。将溶剂去除,并通过在硅胶上的柱层析(DCM:MeOH = 20:1)纯化粗产物以产生白色固体形式的42a(70mg, 57%)。¹H NMR(DMSO-d₆, 400M Hz) δ 7.61(d, $J = 7.6\text{Hz}$, 1H), 7.35(d, $J = 15.2\text{Hz}$, 2H), 6.72(q, $J_1 = 17.6\text{Hz}$, $J_2 = 24.4\text{Hz}$, 1H), 6.23(d, $J = 6.0\text{Hz}$, 1H), 5.99-5.85(m, 2H), 5.74(q, $J = 7.2\text{Hz}$, 1H), 5.37-5.21(m, 1H), 4.69-4.61(m, 1H), 3.96(d, $J = 12.4\text{Hz}$, 1H), 3.82(d, $J = 12.0\text{Hz}$, 1H), 6.72(q, $J_1 = 5.2\text{Hz}$, $J_2 = 10.8\text{Hz}$, 6H); ESI-MS :m/z 397.81[M+H]⁺。

[0589] 实施例 42

[0590] 化合物(43a)的制备

[0591]



[0592] (43-2) 的制备:在0℃下,向搅拌的43-1(3.8g, 6.6mmol)的无水DMF(100mL)溶液加入NaH(2.2g),随后加入CH₃I(9.3g, 66mmol)。在R.T.下继续搅拌过夜。使用饱和NH₄Cl水溶液淬灭反应。使用EA稀释混合物并使用盐水洗涤。在Na₂SO₄上干燥有机层并浓缩。通过硅胶柱层析(PE:EA = 2:1)纯化剩余物以产生白色固体形式的43-2(3.0g, 70%)。

[0593] (43-3) 的制备:将43-2(3.0g, 5.1mmol)和CAN(5.56g, 10.2mmol)的3:1的MeCN:水(16mL)溶液的混合物在R.T.下搅拌过夜。使用盐水(10mL)稀释溶液并使用EA萃取。干燥合并的有机提取物并在减压下蒸发。通过在二氧化硅(PE:EA = 1:1)上层析纯化产生黄色固体形式的43-3(1.71g, 72%)。

[0594] (43-4) 的制备:在R.T.下向搅拌的43-3(1.7g, 3.6mmol)的无水MeCN(50mL)溶液加入TPSCl(2.2g, 7.2mmol)、DMAP(880mg, 7.2mmol)和TEA(1.1g, 10.8mmol)。将混合物在R.T.下搅拌过夜。加入NH₄OH(25mL),并将混合物搅拌2小时。将溶剂去除,并在硅胶柱上(PE:EA = 8:1至2:1)纯化剩余物以产生中间体(1.4g)。将中间体溶于无水DCM(30mL),并

加入 MMTrCl (1.6g, 5.2mmol)、 AgNO_3 (1.4g, 7.8mmol) 和三甲吡啶 (1.57g, 13mmol)。将混合物在 R. T. 下搅拌过夜。滤除固体并使用 DCM 洗涤。使用盐水洗涤滤液并在 Na_2SO_4 上干燥。在硅胶柱上 (PE:EA = 3:2) 纯化浓缩的有机相以产生白色固体形式的 43-4 (1.1g, 57.9%)。

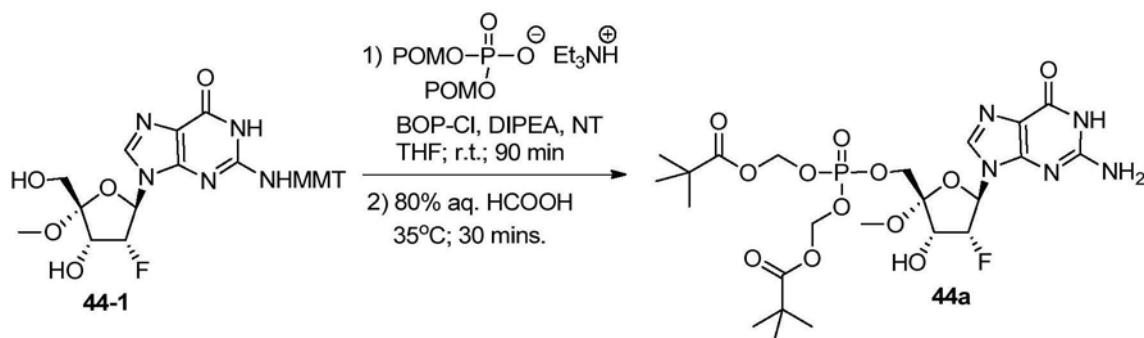
[0595] (43-5) 的制备: 向搅拌的 43-4 (550mg, 0.74mmol) 的丙酮溶液加入甲酸铵 (1.0g, 15.8mmol, 分批) 和 10% 钨 / 碳 (1.0g)。将混合物回流 48 小时。滤除催化剂并使用丙酮洗涤。使用 EA 稀释滤液, 使用盐水洗涤并干燥。通过柱层析 (DCM:MeOH = 50:1) 纯化浓缩的有机相以产生 43-5 (330mg, 72%)。

[0596] (43a) 的制备: 在 R. T. 下, 将 43-5 (200mg, 0.36mmol) 溶于 80% CH_3COOH (20mL)。将混合物在 60°C 下搅拌 12 小时。去除溶剂。通过柱层析 (DCM:MeOH = 10:1) 纯化剩余物, 并使用 DCM 洗涤生成的固体以产生白色固体形式的纯 43a (44mg, 42%)。 ^1H NMR (CD_3OD , 400MHz) δ 8.02 (d, $J = 7.2\text{Hz}$, 1H), 6.14 (dd, $J_1 = 3.6\text{Hz}$, $J_2 = 15.2\text{Hz}$, 1H), 5.88 (d, $J = 7.2\text{Hz}$, 1H), 5.10 (ddd, $J_1 = 4.0\text{Hz}$, $J_2 = 5.2\text{Hz}$, $J_3 = 53.6\text{Hz}$, 1H), 4.47 (dd, $J_1 = 5.2\text{Hz}$, $J_2 = 14.8\text{Hz}$, 1H), 3.84 (d, $J = 12.0\text{Hz}$, 1H), 3.70 (d, $J = 12.0\text{Hz}$, 1H), 3.58-3.64 (m, 2H), 3.36 (s, 3H)。ESI-MS : m/z 290 $[\text{M}+\text{H}]^+$ 。

[0597] 实施例 43

[0598] 化合物 (44a) 的制备

[0599]

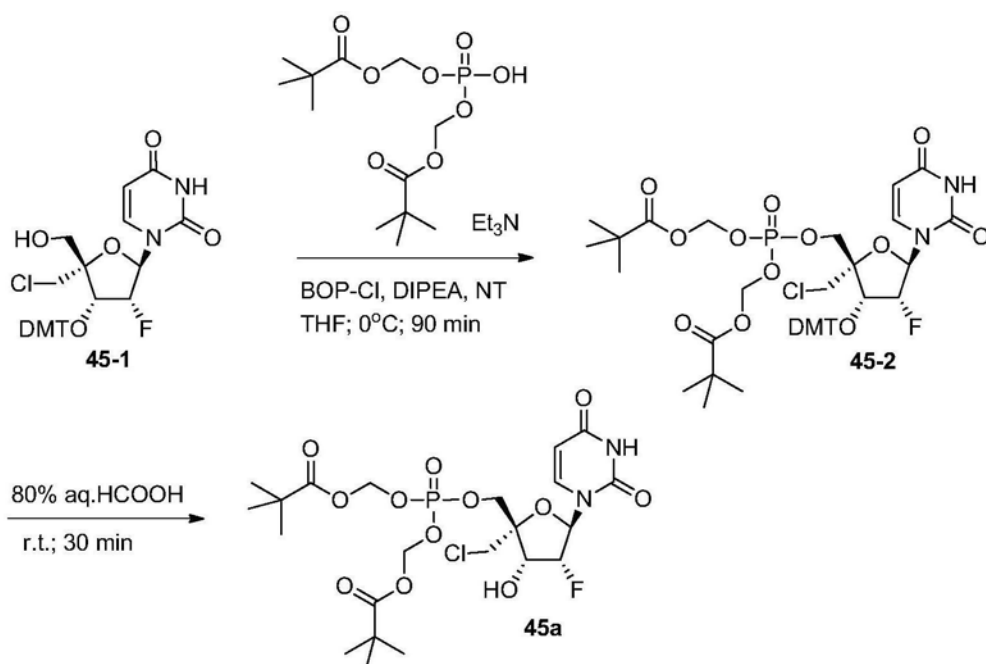


[0600] 向三乙基铵双 (POM) 磷酸盐 (0.3mmol, 从 100mg 的双 (POM) 磷酸盐和 50 μL 的 Et_3N 制备的) 的 THF (3mL) 溶液加入核苷 44-1 (150mg ; 0.26mmol)。将混合物在冰浴中冷却。然后, 加入二异丙基乙胺 (0.18mL ; 4 当量), 随后加入 BOP-Cl (132mg ; 2 当量) 和 3-硝基-1, 2, 4-三唑 (59mg ; 2 当量)。将反应混合物在 0°C 下搅拌 90mins, 然后使用 CH_2Cl_2 (30mL) 稀释并使用饱和 NaHCO_3 水溶液和盐水洗涤。使用 CH_2Cl_2 反萃合并的水层。干燥 (Na_2SO_4) 合并的有机萃取物、蒸发并在使用 CH_2Cl_2 /i-PrOH 溶剂体系 (3-10% 梯度) 的二氧化硅 (10g 柱) 上纯化剩余物。在 35°C 下使用 80% HCOOH 水溶液将获得的产物混合物处理 30mins, 然后蒸发并使用甲苯共蒸发。在使用 CH_2Cl_2 /MeOH 溶剂体系 (5-10% 梯度) 的二氧化硅 (10g 柱) 上蒸发纯化的剩余物以获得 44a (8mg, 5%)。 ^{31}P -NMR (DMSO-d_6) : δ -5.07。MS : m/z = 668 ($\text{M}+46-1$)。

[0601] 实施例 44

[0602] 化合物 (45a) 的制备

[0603]



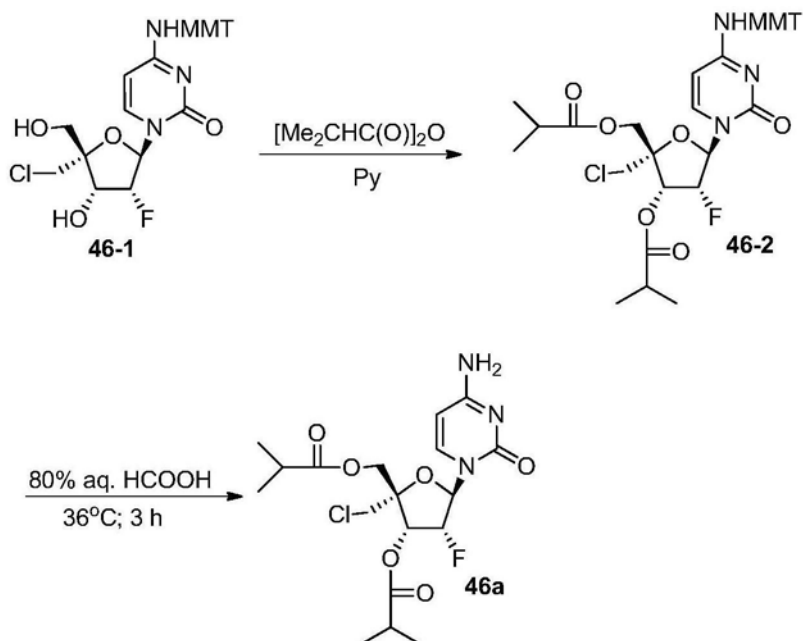
[0604] (45-2) 的制备:向三乙基铵双 (POM) 磷酸盐 (0.7mmol, 从 233mg 的双 (POM) 磷酸盐和 0.1mL 的 Et_3N 制备的) 的 THF (8mL) 溶液加入核苷 45-1 (253mg ;0.42mmol), 随后加入二异丙基乙胺 (0.36mL ;5 当量)、BOP-Cl (268mg ;2.5 当量) 和 3- 硝基 -1, 2, 4- 三唑 (120mg ;2.5 当量)。将反应混合物在 R. T. 下搅拌 2 小时。使用 CH_2Cl_2 (40mL) 稀释混合物并使用饱和 NaHCO_3 水溶液和盐水洗涤。使用 CH_2Cl_2 反萃合并的水层。干燥 (Na_2SO_4) 合并的有机萃取物、蒸发, 并在己烷 /EtOAc 溶剂体系 (40-100% 梯度) 的二氧化硅 (10g 柱) 上纯化剩余物以产生 45a (180mg, 47%)。

[0605] (45a) 的制备:在 R. T. 下, 将化合物 45-2 (0.12g ;0.13mmol) 的 80% HCOOH 水溶液 (8mL) 溶液搅拌 30mins。将混合物蒸发, 使用甲苯共蒸发并在使用 CH_2Cl_2 /MeOH 溶剂体系 (4-10% 梯度) 的二氧化硅 (10g 柱) 上纯化以产生 45a (55mg, 70%)。 ^{31}P -NMR ($\text{DMSO}-d_6$) : δ -4.36。MS :m/z = 647 (M+46-1)。

[0606] 实施例 45

[0607] 化合物 (46a) 的制备

[0608]



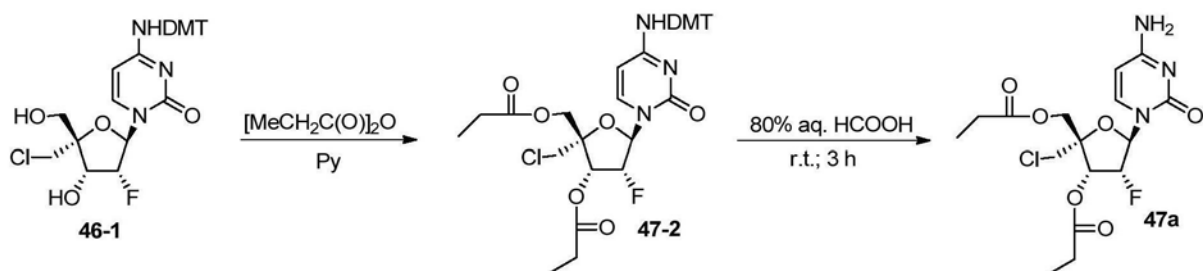
[0609] (46-2) 的制备: 在 R. T. 下, 将 46-1 (170mg ; 0.3mmol) 的吡啶 (3mL) 和异丁酸酐 (0.1mL ; 2 当量) 的混合物搅拌过夜 (o/n)。将混合物浓缩, 并在 EtOAc (30mL) 和饱和 NaHCO₃ 水溶液之间将剩余物分层。使用水、盐水洗涤有机层并干燥 (Na₂SO₄)。在使用己烷 / EtOAc 溶剂体系 (30 至 100% 梯度) 的二氧化硅 (10g 柱) 上纯化剩余物以产生 46-2 (180mg, 85%)。

[0610] (46a) 的制备: 将 46-2 (0.18g ; 0.25mmol) 的 80% HCOOH 水溶液 (5mL) 在 36℃ 下加热 3 小时。然后, 将混合物蒸发, 使用甲苯共蒸发并在使用 CH₂Cl₂/MeOH 溶剂体系 (4-10% 梯度) 的二氧化硅 (10g 柱) 上纯化以产生 46a (75mg, 70%)。MS : m/z = 434 (M+1)。

[0611] 实施例 46

[0612] 化合物 (47a) 的制备

[0613]



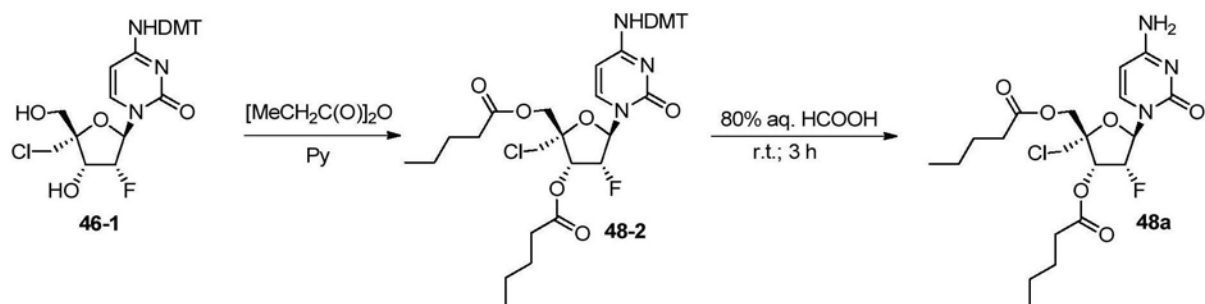
[0614] (47-2) 的制备: 以与 46-2 描述的相同方式从 46-1 (274mg, 0.46mmol) 和丙酸酐 (0.12mL, 2 当量) 的吡啶 (5mL) 制备 47-2 (260mg, 80%)。

[0615] (47a) 的制备: 在 R. T. 下, 使用 80% HCOOH 水溶液将 47-2 (120mg, 0.2mmol) 处理 3 小时。将混合物蒸发, 使用甲苯共蒸发并在使用 CH₂Cl₂/MeOH 溶剂体系 (4-10% 梯度) 的二氧化硅 (10g 柱) 上纯化以产生 47a (62mg, 75%)。MS : m/z = 404 (M-1)。

[0616] 实施例 47

[0617] 化合物 (48a) 的制备

[0618]



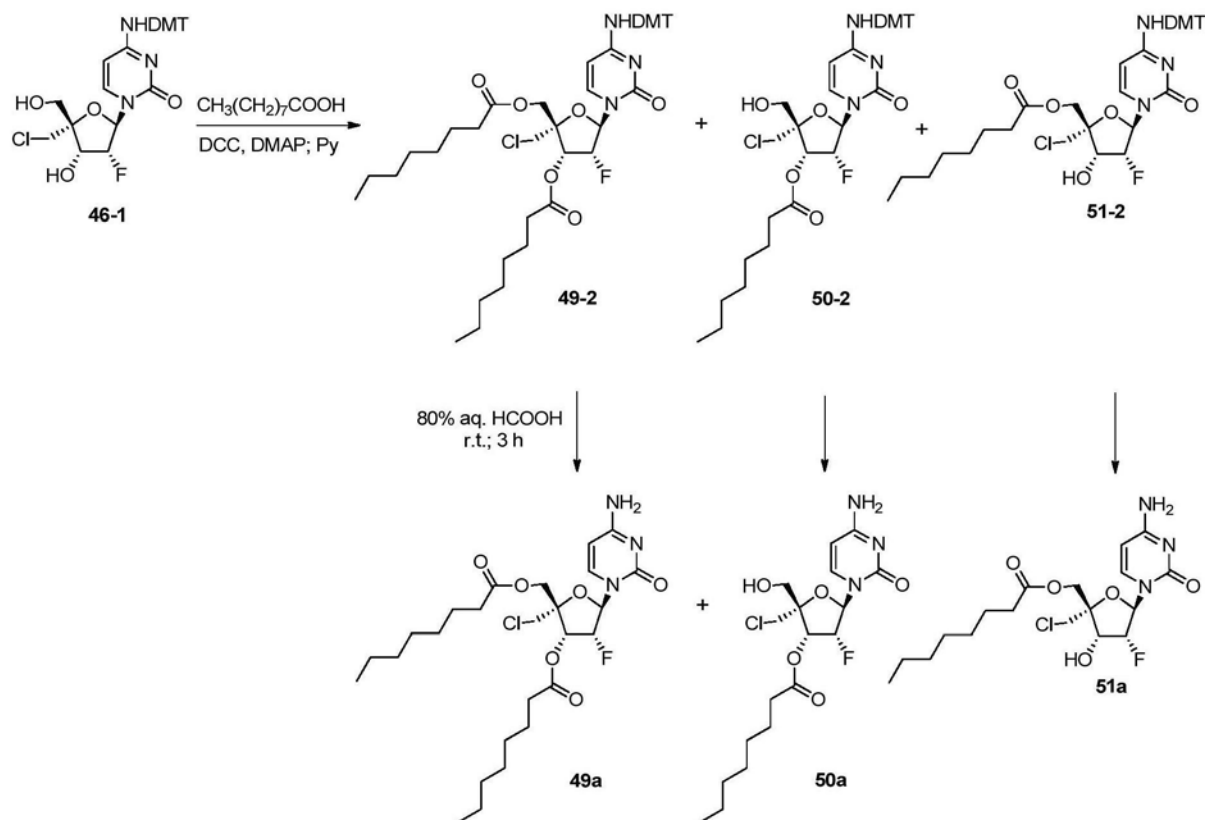
[0619] (48-2) 的制备: 以与 46-2 描述的相同方式从 46-1 (150mg, 0.27mmol) 和戊酸酐 (0.11mL, 2 当量) 的吡啶 (3mL) 制备 48-2 (150mg, 73%)。

[0620] (48a) 的制备: 在 R. T. 下, 使用 80% HCOOH 水溶液将 48-2 (140mg, 0.18mmol) 处理 3 小时。将混合物蒸发并在使用 CH₂Cl₂/MeOH 溶剂体系 (4-10% 梯度) 的二氧化硅 (10g 柱) 上纯化以产生 48a (70mg, 84%)。MS : m/z = 462 (M+1)。

[0621] 实施例 48

[0622] 化合物 (49a)、(50a) 和 (51a) 的制备

[0623]



[0624] (49-2)、(50-2) 和 (51-2) 的制备: 向 46-1 (1.26g, 2.12mmol) 的吡啶 (15mL) 溶液加入正辛酸 (0.34mL, 1.0 当量)、DCC (60% 的二甲苯 ; 0.81mL, 1 当量) 和 DMAP (52mg ; 0.2 当量)。将生成的混合物在 R. T. 下搅拌 6 小时。将混合物蒸发, 并在 CH₂Cl₂ (100mL) 和饱和 NaHCO₃ 水溶液 (25mL) 之间将剩余物分层。使用水、盐水洗涤有机层并干燥 (Na₂SO₄)。使用甲苯处理剩余物。滤除固体物质, 并在使用己烷 / EtOAc 溶剂体系 (30-100% 梯度) 的二氧化硅 (25g 柱) 上纯化滤液以产生 49-2 (0.57g, 32%)、50-2 (0.18g, 12%) 和 51-2 (0.2g, 13%)。

[0625] (49a) 的制备: 将 49-2 (114mg, 0.13mmol) 和 80% 甲酸水溶液的混合物在 R. T. 下

搅拌 3 小时。将混合物蒸发并使用甲苯共蒸发并在使用 $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 溶剂体系 (2-8% 梯度) 的二氧化硅 (10g 柱) 上纯化以产生 49a (53mg, 75%)。MS :m/z = 544 (M-1)。

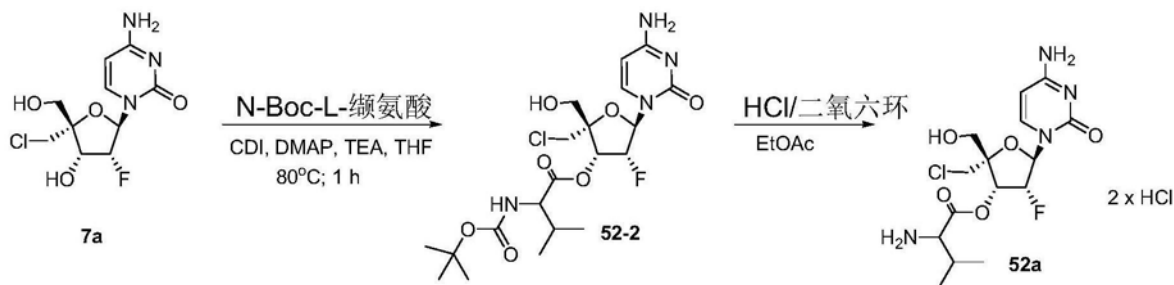
[0626] (50a) 的制备:通过使用 4-10% 梯度的 MeOH 的 CH_2Cl_2 用于纯化, 以与 49a 描述的相同方式从 50-2 (104mg, 0.14mmol) 制备 50a (44mg, 75% 产率)。MS :m/z = 418 (M-1)。

[0627] (51a) 的制备:通过使用 4-10% 梯度的 MeOH 的 CH_2Cl_2 用于纯化, 以与 49a 描述的相同方式从 50-2 (140mg, 0.2mmol) 制备 51a (60mg, 71% 产率)。MS :m/z = 418 (M-1)。

[0628] 实施例 49

[0629] 化合物 (52a) 的制备

[0630]



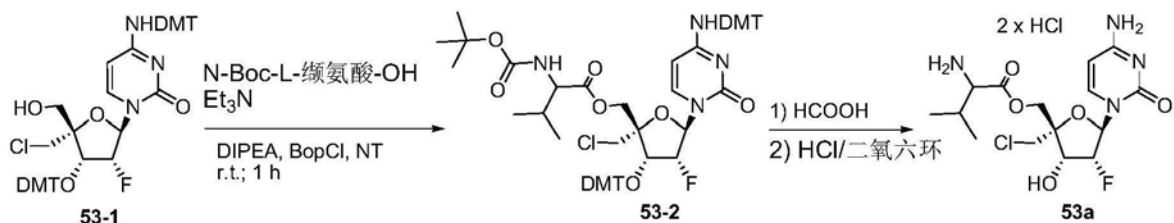
[0631] (52-2) 的制备:将 N-(叔丁氧基羰基)-L-缬氨酸 (0.41g, 1.9mmol) 和羰基二咪唑 (0.31g, 1.9mmol) 的 THF (9mL) 溶液在 R.T. 下搅拌 1.5 小时。然后, 将混合物在 40°C 下搅拌 20min。在 80°C 下, 将混合物加入至 7a (0.42g, 1.43mmol) 和 DMAP (25mg, 0.2mmol) 的 DMF (8mL) 和 TEA (4mL) 溶液。将反应混合物在 80°C 下搅拌 1h, 然后冷却并浓缩。将剩余物在叔丁基甲基醚 (100mL) 和水之间分层。使用水、盐水洗涤有机层并干燥 (Na_2SO_4)。在使用 $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 溶剂体系 (2-10% 梯度) 的二氧化硅 (25g 柱) 上纯化剩余物以产生 52-2 (0.32g, 90% 在具有 5'-异构体的混合物中), 通过 RP-HPLC (10-100% B; A: 水, B: MeOH) 将其再纯化。产率: 0.25g (35%)。

[0632] (52a) 的制备:伴随剧烈摇动, 使用 HCl/二氧六环 (4M; 0.6mL) 将 52-2 (0.12g; 0.24mmol) 的 EtOAc (0.6mL) 溶液处理 20min。将白色沉淀过滤, 使用乙醚洗涤并干燥以产生二盐酸盐形式的 52a (95mg; 85%)。MS :m/z = 391 (M-1)。

[0633] 实施例 50

[0634] 化合物 (53a) 的制备

[0635]



[0636] (53-2) 的制备:向 N-Boc-Val-OH (0.16g, 0.74mmol) 和 Et_3N (0.14mL, 1.0mmol) 的 THF 溶液加入 53-1。将生成的混合物蒸发, 使用吡啶和甲苯共蒸发并溶于 THF (4mL)。加入 DIPEA (0.38mL, 2.2mmol), 随后加入 BOP-Cl (0.28g, 1.1mmol) 和 3-硝基-1,2,4-三唑 (0.13g, 1.1mmol)。将反应混合物在 R.T. 下搅拌 1h。使用 CH_2Cl_2 (40mL) 稀释混合物并使用饱和 NaHCO_3 水溶液和盐水洗涤。使用 CH_2Cl_2 反萃合并的水层。干燥 (Na_2SO_4) 合并的有

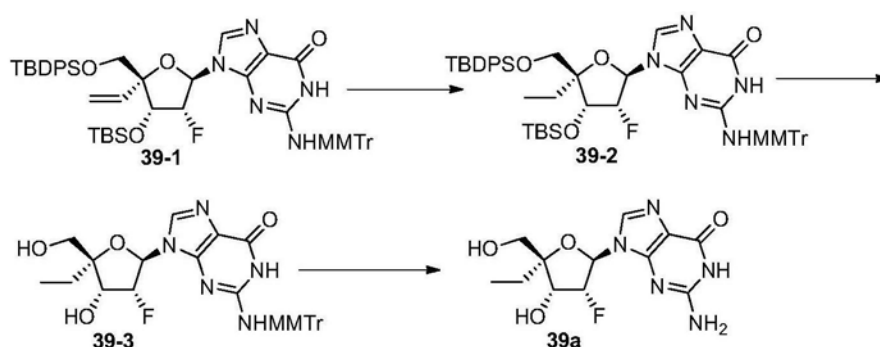
机萃取物、蒸发,并在使用己烷 /0.5% Et₃N/EtOAc 溶剂体系 (20-100% 梯度) 的二氧化硅 (10g 柱) 上纯化剩余物以产生 53-2 (0.39g, 81%)。

[0637] (53a) 的制备: 将 14-2 (0.37g, 0.33mmol) 和 80% HCOOH 水溶液 (10mL) 的混合物在 R. T. 下搅拌 3 小时。将混合物蒸发,并在水和 CH₂Cl₂ 之间将剩余物分层。使用 CH₂Cl₂ 洗涤水层并蒸发。将固体剩余物悬浮在 EtOAc (1.5mL) 中并伴随剧烈摇动使用 4N HCl 的二氧六环 (1.5mL) 处理。将固体过滤,使用乙醚洗涤并通过 RP-HPLC (A :0.5N HCOOH 的水, B :0.5N HCOOH 的乙腈) 纯化。通过悬浮在 EtOAc (2mL) 中并使用 4N HCl/ 二氧六环 (2mL) 处理将生成的 5'-O- 缬氨酰 (valyn) 酯的甲酸盐转化为 53a 二盐酸盐 (63mg, 40%)。MS :m/z = 391 (M-1)。

[0638] 实施例 51

[0639] 化合物 (39a) 的制备

[0640]



[0641] (39-2) 的制备: 使用 Pd/C (1.3g) 填充 39-1 (1.3g, 1.4mmol) 的无水 MeOH (20mL) 溶液并在 25℃ 下在氢气 (1atm) 环境下搅拌 1 小时。将溶液过滤,蒸发至干燥,并在硅胶柱上 (DCM:MeOH = 100:1 至 50:1) 纯化以产生白色固体形式的 39-2 (1.2g, 92.3%)。

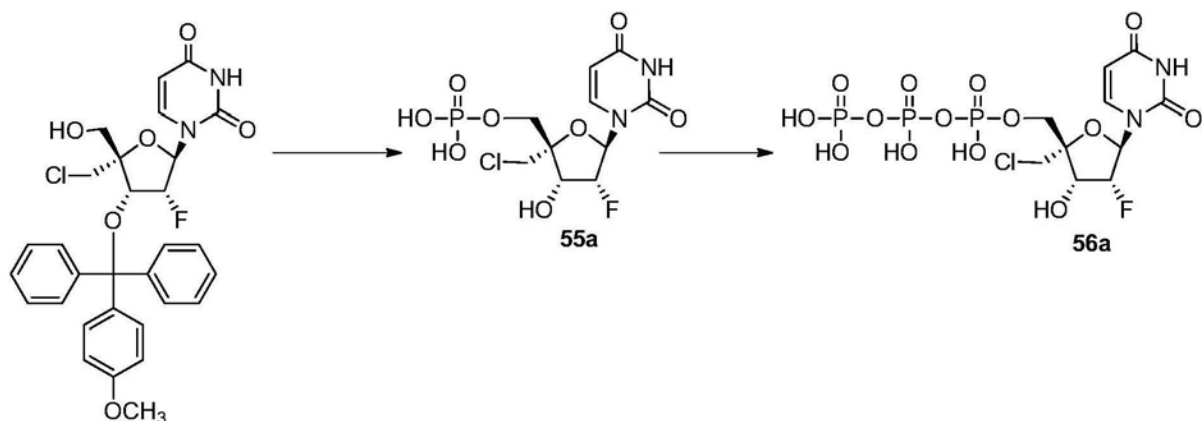
[0642] (39-3) 的制备: 在 25℃ 下向 39-2 (1.2g, 1.3mmol) 的 MeOH (40mL) 溶液加入 NH₄F (370mg, 10mmol) 并在 60℃ 下搅拌 6 小时。将溶液过滤,蒸发至干燥,并在硅胶柱上 (DCM:MeOH = 200:1 至 20:1) 纯化以产生白色固体形式的 39-3 (249mg, 30.7%)。
¹H NMR (MeOD, 400MHz) δ 7.92 (s, 1H), 7.19-7.33 (m, 12H), 6.83-6.85 (m, 2H), 5.50 (dd, J₁ = 4.0Hz, J₂ = 14.8Hz, 1H), 4.19-4.88 (m, 1H), 4.22 (dd, J₁ = 5.2Hz, J₂ = 16.0Hz, 1H), 3.76 (s, 3H), 3.41 (dd, J₁ = 12.0Hz, J₂ = 36.8Hz, 2H), 1.52-1.74 (m, 2H), 0.87 (t, J = 7.6Hz, 3H); ESI-LCMS :m/z 586.1 [M+H]⁺。

[0643] (39a) 的制备: 将 39-3 的 80% 甲酸 /20% 水 (3mL) 溶液在 RT 下放置 2 小时,然后浓缩至干燥。使用 MeOH/ 甲苯将剩余物共蒸发 (3 次),然后加入乙酸乙酯。将悬浮液的乙酸乙酯在 70℃ 下加热 5mins。使用移液管去除溶剂。将该洗涤重复 3 次。在使用乙腈 / 水作为流动相的反相 HPLC 上进一步纯化生成的产物 (44mg) 以产生淡白色固体形式的 39a (20mg)。
¹H NMR (DMSO, 400MHz) δ 7.92 (s, 1H), 10.82 (br, 1H), 7.96 (s, 1H), 6.56 (s, 2H), 5.99 (dd, J = 6.0, 12.8Hz, 1H), 5.65 (d, J = 4.8Hz, 1H), 5.58-5.45 (2t, J = 5.2Hz, 0.5H, 0.5H), 5.25 (br, 1H), 4.19-4.88 (m, 1H), 4.22 (dd, J₁ = 5.2Hz, J₂ = 16.0Hz, 1H), 3.76 (s, 3H), 3.41 (dd, J₁ = 12.0Hz, J₂ = 36.8Hz, 2H), 1.52-1.74 (m, 2H), 0.87 (t, J = 7.6Hz, 3H); ESI-LCMS :m/z 443.6 [M+6- 甲基 -2- 庚胺)]⁺。

[0644] 实施例 52

[0645] 化合物 (55a) 和 (56a) 的制备

[0646]

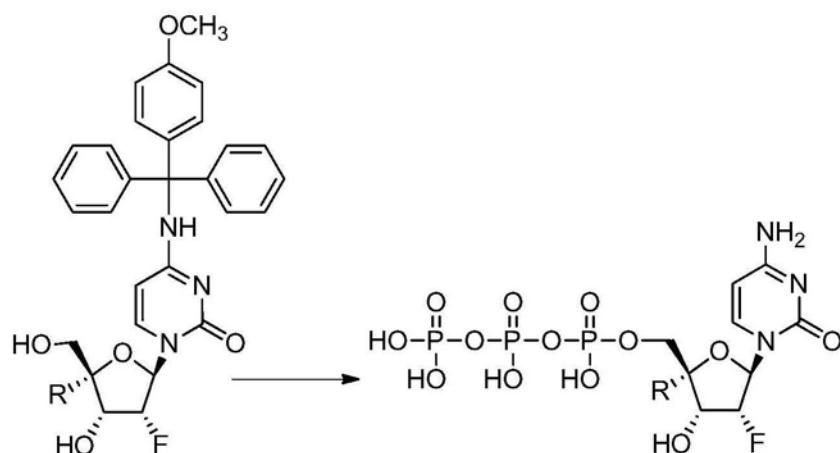


[0647] 将 1, 2, 4- 三唑 (21mg, 0.3mmol) 溶于 CH_3CN (0.7mL) 和 Et_3N (44 μL , 0.31mmol) 的混合物。加入 POCl_3 (9 μL , 0.1mmol), 并将混合物在 R. T. 下保持 20mins。将白色沉淀过滤, 并将滤液加入至干燥的核苷 (28mg, 0.05mmol)。通过 TLC 控制反应并通过起始核苷的消失监测。在反应完成后, 加入焦磷酸的四丁基铵盐 (150mg), 随后加入 DMF (0.5mL) 以获得均匀溶液。在环境温度下 1.5 小时后, 使用水 (4mL) 稀释反应并使用 DCM 萃取 (2 $\times$ 5mL)。将合并的有机提取物蒸发, 溶于 5mL 的 80% HCOOH 并在 R. T. 下放置 2 小时。将反应混合物浓缩并在水 (5mL) 和 DCM (5mL) 之间分层。将水部分装载在具有 Q 琼脂糖高效的柱 HiLoad 16/10 上。在线性梯度为 0 至 1N 的 NaCl 的 50mM TRIS- 缓冲液 (pH7.5) 中进行分离。获得两部分。在 70-75% B 下洗脱包含单磷酸盐 (55a) 的第一部分, 并在 75-80% B 下洗脱三磷酸盐 (56a)。通过 Synergy 4 微米 Hydro-RP 柱 (Phenomenex) 上的 RP HPLC 将两部分脱盐。线性梯度为 0 至 30% 的甲醇的 50mM 醋酸三乙基铵缓冲液 (pH 7.5) 用于洗脱。将相应部分合并、浓缩并冻干 3 次以去除过量的缓冲液。

[0648] 实施例 53

[0649] 化合物 (56b-e) 的制备

[0650]

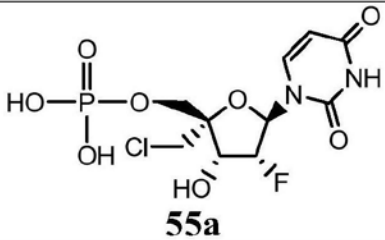


[0651] 将 1, 2, 4- 三唑 (21mg, 0.3mmol) 溶于 CH_3CN (0.7mL) 和 Et_3N (44 μL , 0.31mmol) 的混合物。加入 POCl_3 (9 μL , 0.1mmol), 并将混合物在 R. T. 下保持 20mins。将白色沉淀过滤, 并将滤液加入至干燥的核苷 (28mg, 0.05mmol)。通过 TLC 控制反应并通过起始核苷的消失监

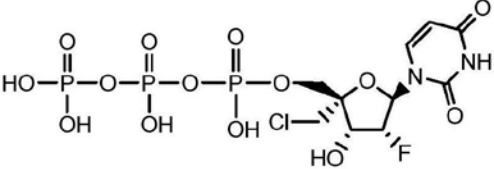
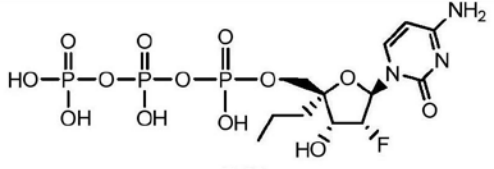
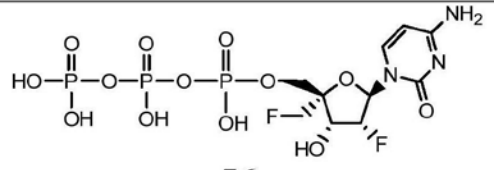
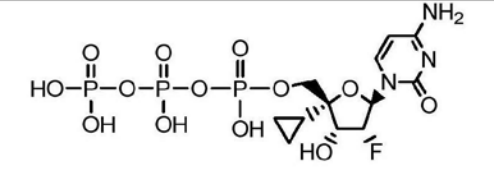
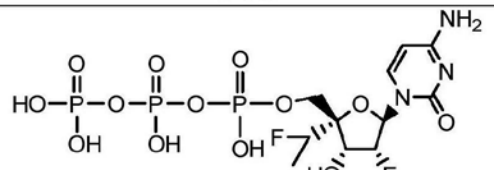
测。在反应完成后,加入焦磷酸的四丁基铵盐 (150mg),随后加入 DMF (0.5mL) 以获得均匀溶液。在环境温度下 1.5 小时后,使用水 (4mL) 稀释反应并使用 DCM 萃取 (2×5mL)。将合并的有机提取物蒸发,溶于 5mL 的 80% HCOOH 并在 38℃ 下放置 4 小时。将反应混合物浓缩并在水 (5mL) 和 DCM (5mL) 之间分层。将水部分装载在具有 Q 琼脂糖高效的柱 HiLoad 16/10 上。在线性梯度为 0 至 1N 的 NaCl 的 50mM TRIS- 缓冲液 (pH7.5) 中进行分离。获得两部分。在 75-80% B 下洗脱三磷酸盐 (56b-e)。通过 Synergy 4 微米 Hydro-RP 柱 (Phenomenex) 上的 RP HPLC 进行脱盐。线性梯度为 0 至 30% 的甲醇的 50mM 醋酸三乙基铵缓冲液 (pH 7.5) 用于洗脱。将相应部分合并、浓缩并冻干 3 次以去除过量的缓冲液。

[0652] 表 3 - 从实施例 53 获得的三磷酸盐

[0653]

化合物	MS (M-1)	³¹ P NMR P α	³¹ P NMR P β	³¹ P NMR P γ
 55a	373.00	+3.64 (s)	NA	NA

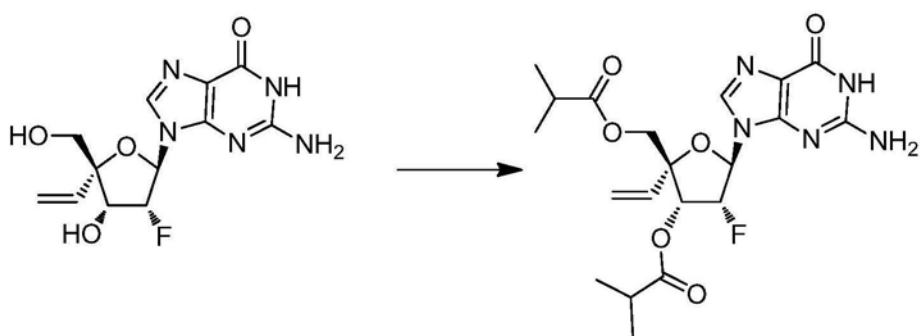
[0654]

 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)

[0655] 实施例 54

[0656] 化合物 (57a) 的制备

[0657]



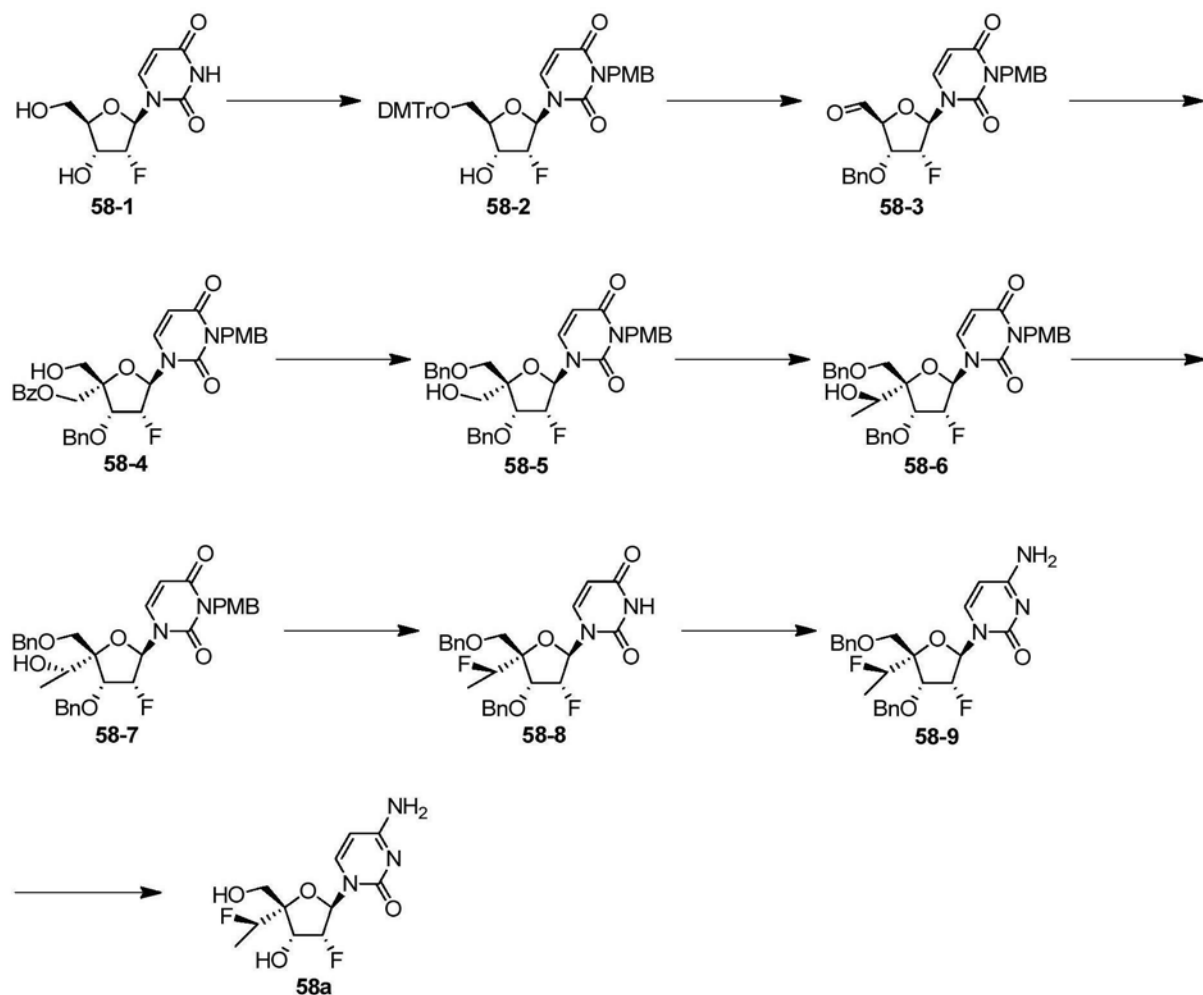
[0658] 将 2'-脱氧-2'-氟-4'-C-(乙烯基)鸟苷 (25a, 31mg, 0.1mmol) 溶于干燥吡啶 (3mL)。加入异丁酸酐 (50 μ L, 0.3mmol)。将反应混合物在环境温度下保持。在 40 小时后, 加入异丁酸酐 (100 μ L, 0.6mmol), 并将反应混合物放置过夜。将吡啶蒸发。通过使用梯度为 3% 至 10% 的甲醇的 DCM 的硅胶层析纯化剩余物以产生 57a (20mg, 50%)。¹H NMR (DMSO-d₆) δ : 10.72 (s, 1H), 7.88 (s, 1H), 6.47 (s, 2H), 6.18-6.13 (dd, 1H), 5.90-5.83 (dd, 1H), 5.79-5.62 (m, 2H), 5.49-5.44 (d, 1H), 5.35-5.32 (d, 1H), 4.28-4.25 (d, 1H), 4.12-4.10 (d, 1H), 2.6

0-2.45 (m, 2H), 1.12-1.09 (m, 6H), 1.02-0.96 (m, 6H); m/z 452 (M+1)。

[0659] 实施例 55

[0660] 化合物 (58a) 的制备

[0661]



[0662] (58-2) 的制备：向 58-1 (50.0g, 205mmol) 的吡啶 (250mL) 溶液加入 DMTrCl (75.0g, 225.0mmol)。将溶液在 R. T. 下搅拌 15 小时。加入 MeOH (120mL)，并在减压下将混合物浓缩至干燥。将剩余物溶于 EA 并使用水洗涤。在 Na_2SO_4 上干燥有机层并浓缩以产生淡黄色固体形式的粗 DMTr 保护的衍生物 (80.5g, 89%)。干燥 K_2CO_3 (80.52g, 583.2mmol)，然后将 PMBCl (31.7g, 109.2mmol) 加入至搅拌的 DMTr 保护的衍生物 (80g, 146mmol) 的无水 DMF (300mL) 溶液。将搅拌在环境温度下继续过夜。通过 TLC 监测反应。使用 EA 稀释混合物并使用水洗涤。在 Na_2SO_4 上干燥有机层并浓缩以产生淡黄色固体形式的 58-2 (98.8g, 90%)。

[0663] (58-3) 的制备：将 NaH (10.4g, 260.5mmol) 和 BnBr (73.8g, 434.2mmol) 加入至搅拌的 58-2 (98.8g, 147.9mmol) 的无水 DMF (300mL) 溶液，并将搅拌在 25°C 下过夜。通过 TLC 监测反应。使用水淬灭反应，使用 EA 萃取并使用盐水洗涤。将溶剂去除，并在硅胶上 (PE:EA = 10:1 至 3:1) 纯化剩余物以产生淡黄色固体形式的 Bn 保护的衍生物 (101.1g, 90%)。在 25°C 下，将 Bn 保护的衍生物 (101.1g, 133.4mmol) 溶于 80% HAc (900mL)。将混合物在 25°C 下搅拌过夜。使用 MeOH 淬灭反应，并将溶剂去除以产生白色泡沫形式的醇 (42.1g, 70%)。在 25°C 下，向醇 (42.1g, 92.6mmol) 的无水 CH_3CN (300mL) 溶液加入 IBX (28.5g, 121.7mmol)。

将反应混合物回流 1 小时,然后冷却至 0℃。将沉淀滤除,并将滤液浓缩以产生黄色固体形式的 58-3(39.2g, 93%)。

[0664] (58-4) 的制备:向 58-3(39.2g, 86.39mmol) 的 1,4-二氧六环(250mL) 溶液加入 37% CH_2O (28.1mL, 345.6mmol) 和 2N NaOH 水溶液(86.4mL, 172.8mmol)。将混合物在 25℃ 下搅拌 2h,然后使用 AcOH 中和至 $\text{pH} = 7$ 。向反应加入 EtOH (200mL) 和 NaBH_4 (19.7g, 518.6mmol)。将混合物在 25℃ 下搅拌 30mins。使用饱和 NH_4Cl 水溶液淬灭反应。使用 EA 萃取混合物,并在 Na_2SO_4 上干燥有机层并浓缩。通过硅胶柱层析($\text{PE}:\text{EA} = 4:1$ 至 $2:1$) 纯化剩余物以产生白色固体形式的二醇衍生物(25.5g, 55%)。在 0℃ 下,向搅拌的二醇衍生物(25.5g, 52.5mmol) 的无水吡啶(150mL) 和无水 CH_3CN (150mL) 溶液滴加 BzCl (6.6g, 52.47mmol)。然后,将混合物在 25℃ 下搅拌 14h。使用 H_2O 淬灭反应,并将溶液浓缩。将剩余物溶于 EA 并使用 NaHCO_3 洗涤。在 Na_2SO_4 上干燥有机层并浓缩。在硅胶柱上($\text{PE}:\text{EA} = 5:4$) 纯化剩余物以产生白色泡沫形式的 58-4(18.1g, 60%)。

[0665] (58-5) 的制备:将 Cs_2CO_3 (30.0g, 92.0mmol) 和 BnBr (10.4g, 61.3mmol) 加入至搅拌的化合物 58-4(18.1g, 30.6mmol) 的无水 DMF (300mL) 溶液,并将搅拌在 25℃ 下过夜。使用 NH_4Cl 淬灭反应,使用 EA 萃取并使用盐水洗涤。将溶剂去除以产生淡黄色固体形式的 Bz 保护的衍生物(19.3g, 95%)。在 25℃ 下,向搅拌的 Bz 保护的衍生物(19.3g, 28.4mmol) 的无水 MeOH (230mL) 溶液加入 NaOMe (24.9g, 460mmol),时间为 1h。使用 AcOH (10mL) 淬灭反应并浓缩。在硅胶柱上($\text{PE}:\text{EA} = 1/2$) 纯化剩余物以产生白色固体形式的 58-5(11.2g, 54%)。

[0666] (58-6) 的制备:在 25℃ 下,向搅拌的 58-5(200mg, 0.347mmol) 的无水 DCM (5mL) 溶液加入 DMP (168mg, 0.674mmol)。将混合物在 25℃ 下搅拌 2h。将溶剂去除,并在硅胶柱上($\text{PE}:\text{EA} = 5:1$ 至 $1:1$) 纯化剩余物以产生醛衍生物(161mg, 81%)。在 -78℃ 下,向搅拌的醛衍生物(200mg, 0.348mmol) 的无水 THF (5mL) 溶液加入 MeMgBr (1.0mL, 1.01mmol)。将混合物在 -78℃ 下搅拌 1h。使用 NH_4Cl 淬灭反应并使用 EA 萃取。通过柱层析($\text{PE}:\text{EA} = 5:1$ 至 $1:1$) 纯化浓缩的有机相以产生 58-6(135mg, 65%)。

[0667] (58-7) 的制备:在 0℃ 下,向 58-6(900mg, 1.5mmol) 的 DCM 溶液加入 DMP (2.5g, 6.0mmol)。在 0℃ 下搅拌 1h 后,使用 $\text{Na}_2\text{S}_2\text{O}_3$ 淬灭混合物。将溶剂去除,并在硅胶柱上($\text{PE}:\text{EA} = 5:1$ 至 $1:1$) 纯化剩余物以产生酮衍生物(700mg, 78%)。向酮衍生物(700mg, 1.52mmol) 的 MeOH 溶液分批加入 NaBH_4 。在相同温度下搅拌 1h 后,使用水淬灭混合物。将溶剂去除,并在硅胶柱上($\text{PE}:\text{EA} = 5:1$ 至 $1:1$) 纯化剩余物以产生 58-7(500mg, 71%)。

[0668] (58-8) 的制备:在 -78℃ 下,向搅拌的 DAST (1.39g, 8.68mmol) 的无水甲苯(15mL) 溶液滴加 58-6 的溶液(1.0g, 1.73mmol)。将混合物在 -78℃ 下搅拌 30min。将溶液缓慢升温至 25℃ 并继续搅拌过夜。将混合物倾入饱和 Na_2CO_3 溶液。在硅胶柱上($\text{PE}:\text{EA} = 10:1$ 至 $4:1$) 纯化浓缩的有机相以产生氟化物衍生物(449mg, 45%)。将氟化物衍生物(1.20g, 2.07mmol) 和 CAN (3.41g, 6.23mmol) 的 $3:1$ 的 MeCN 和水溶液(10mL) 的混合物在 25℃ 下搅拌过夜。加入盐水(10mL),并使用 EA 萃取混合物。将合并的有机提取物干燥并在减压下蒸发。通过在使用 $\text{PE}:\text{EA} = 10:1$ 至 $2:1$ 的二氧化硅上层析纯化产生黄色固体形式的 58-8(475mg, 50%)。

[0669] (58-9) 的制备:在 25℃ 下,向搅拌的 58-8(550mg, 210mmol) 的无水 MeCN (10mL)

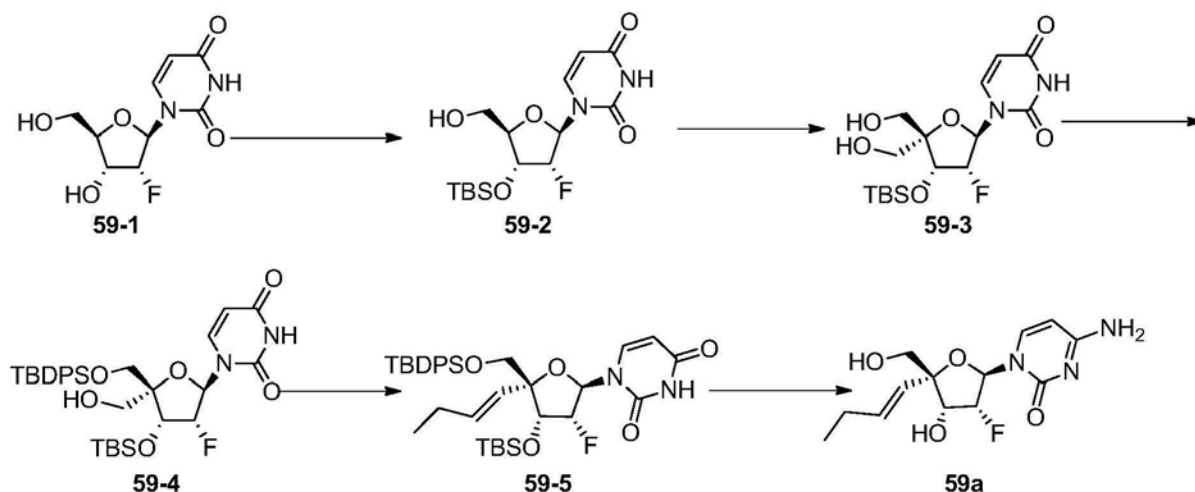
溶液加入 TPSCl (725mg, 2.40mmol)、DMAP (293mg, 2.40mmol) 和 TEA (242mg, 2.40mmol)。将混合物在 25℃ 下搅拌过夜。加入 NH_4OH (25mL) 并搅拌 2h。将溶剂去除,并在硅胶柱上 (DCM:MeOH = 10:1) 纯化剩余物以产生 58-9 (300mg)。 ^1H NMR (CD_3OD , 400MHz) δ 7.70 (d, J = 8.4Hz, 1H), 7.25-7.36 (m, 10H), 6.13 (dd, J = 2.8、16.8Hz, 1H), 5.40 (d, J = 7.6Hz, 1H), 5.15 (m, 1H), 4.81 (d, J = 11.6Hz, 1H), 4.40-4.52 (m, 4H), 3.82 (d, J = 8.8Hz, 7H), 3.62 (d, J = 9.6Hz, 7H), 1.35 (dd, J = 2.8, 14.4Hz, 3H)。ESI-MS : m/z 472.1 $[\text{M}+\text{H}]^+$ 。

[0670] (58a) 的制备:在 -78℃ 下,将 1M 三氯化硼的 CH_2Cl_2 (3.2mL; 3.2mmol) 溶液滴加至 58-9 (200mg, 0.42mmol) 的无水 CH_2Cl_2 (10mL) 溶液。将混合物缓慢 (在 4h 内) 升温至 -30℃ 并在 -30℃ 至 -20℃ 下搅拌 3h。加入醋酸铵 (1g) 和 MeOH (5mL),并使生成的混合物升温至环境温度。将溶剂去除,并通过 RP-HPLC (0-60% B; A:50mM TEAA 水溶液, B:50mM TEAA 的 MeOH) 纯化剩余物以产生 58a (75mg)。 ^1H NMR (CD_3OD) δ 7.97 (d, 1H), 6.20 (dd, 1H), 5.92 (d, 1H), 5.22 (dt, 1H), 4.98 (dq, 1H), 4.58 (dd, 1H), 3.73 (m, 2H), 1.40 (dd, 3H)。 ^{19}F NMR (CD_3OD) δ -205.80 (m, 1F), -188.54 (m, 1F)。ESI-MS : m/z 290.4 $[\text{M}-\text{H}]^-$ 。

[0671] 实施例 56

[0672] 化合物 (59a) 的制备

[0673]



[0674] (59-2) 的制备:向 59-1 (100.0g, 406.5mmol) 的吡啶 (750mL) 溶液加入 DMTrCl (164.9g, 487.8mmol)。将溶液在 R.T. 下搅拌 15h。加入 MeOH (300mL),并在减压下将混合物浓缩至干燥。将剩余物溶于 EtOAc 并使用水洗涤。在 Na_2SO_4 上干燥有机层并浓缩。将剩余物溶于 DCM (500mL)。向该溶液添加咪唑 (44.3g, 650.4mmol) 和 TBSCl (91.9g, 609.8mmol)。将生成的反应混合物在 R.T. 下搅拌 14h。使用 NaHCO_3 和盐水洗涤反应溶液。在 Na_2SO_4 上干燥有机层并浓缩以产生淡黄色固体形式的粗产物。将粗产物 (236.4g, 356.6mmol) 溶于 80% HOAc 水溶液 (500mL)。将混合物在 R.T. 下搅拌 15h。使用 EtOAc 稀释混合物,使用 NaHCO_3 溶液和盐水洗涤。在 Na_2SO_4 上干燥有机层并在硅胶柱上层析纯化 (1-2% MeOH 的 DCM 溶液) 以产生淡黄色固体形式的 59-2 (131.2g, 89.6%)。 ^1H NMR ($\text{DMSO}-d_6$, 400MHz) δ 11.39 (s, 1H), 7.88 (d, J = 7.2Hz, 1H), 5.89 (dd, J = 18.0Hz, J = 2.0Hz, 1H), 5.64 (d, J = 8.0Hz, 1H), 5.21 (dd, J_1 = J_2

= 7.2Hz, 1H), 5.18-5.03(m, 1H), 4.37 ~ 4.29(m, 1H), 3.86(dd, J = 3.2Hz, J = 3.2Hz, 3H), 3.78-3.73(m, 1H), 3.51-3.56(m, 1H), 3.31(s, 1H), 0.89(s, 9H), 0.11(s, 6H); ESI-MS :m/z 802 [M+H]⁺。

[0675] (59-3) 的制备: 在 R.T. 下, 向 59-2(131.2g, 364.0mmol) 的无水 CH₃CN(1200mL) 溶液加入 IBX(121.2g, 432.8mmol)。将反应混合物回流 3h, 然后冷却至 0℃。将沉淀滤除, 并将滤液浓缩以产生黄色固体形式的粗醛(121.3g)。将醛溶于 1,4-二氧六环(1000mL)。加入 37% CH₂O(81.1mL, 1.3536mol) 和 2M NaOH 水溶液(253.8mL, 507.6mmol)。将混合物在 R.T. 下搅拌 2h, 然后使用 AcOH 中和至 pH = 7。向溶液加入 EtOH(400mL) 和 NaBH₄(51.2g, 1.354mol)。将混合物在 R.T. 下搅拌 30mins 并使用饱和 NH₄Cl 水溶液淬灭。使用 EA 萃取混合物。在 Na₂SO₄ 上干燥有机层并浓缩。通过硅胶柱层析(1-3% MeOH 的 DCM 溶液) 纯化剩余物以产生白色固体形式的 59-3(51.4g, 38.9%)。

[0676] (59-4) 的制备: 在 0℃ 下, 向 59-3(51.4g, 131.6mmol) 的无水 DCM(400mL) 溶液加入吡啶(80mL) 和 DMTrCl(49.1g, 144.7mmol)。将反应在 R.T. 下搅拌 14h, 然后使用 MeOH(30mL) 处理。将溶剂去除, 并通过硅胶柱层析(1-3% MeOH 的 DCM 溶液) 纯化剩余物以产生黄色泡沫形式的单-DMTr 保护的中间体(57.4g, 62.9%)。向单-DMTr 保护的中间体(57.4g, 82.8mmol) 的 CH₂Cl₂(400mL) 加入咪唑(8.4g, 124.2mmol) 和 TBDPSCl(34.1g, 124.2mmol)。将混合物在 R.T. 下搅拌 14h。滤除沉淀, 并使用盐水洗涤滤液并在 Na₂SO₄ 上干燥。将溶剂去除以产生白色固体形式的剩余物(72.45g), 将其溶于 80% HOAc 水溶液(400mL)。将混合物在 R.T. 下搅拌 15h。使用 EtOAc 稀释混合物, 使用 NaHCO₃ 溶液和盐水洗涤。在 Na₂SO₄ 上干燥有机层并通过硅胶柱层析(1-2% MeOH 的 DCM 溶液) 纯化以产生白色固体形式的 59-4(37.6g, 84.2%)。 ¹H NMR(CD₃OD, 400MHz) δ 7.76(d, J = 4.0Hz, 1H), 7.70(dd, J = 1.6Hz, J = 8.0Hz, 2H), 7.66-7.64(m, 2H), 7.48-7.37(m, 6H), 6.12(dd, J = 2.8Hz, J = 16.8Hz, 1H), 5.22(d, J = 8.0Hz, 1H), 5.20-5.05(m, 1H), 4.74(dd, J = 5.6Hz, J = 17.6Hz, 1H), 4.16(d, J = 12.0Hz, 1H), 3.87-3.80(m, 2H), 3.56(d, J = 12.0Hz, 1H), 1.16(s, 9H), 0.92(s, 9H), 0.14(s, 6H)。

[0677] (59-5) 的制备: 在氮气下, 在 0℃ 下向 59-4(3.0g, 4.78mmol) 的无水 DCM(100mL) 溶液加入戴斯-马丁氧化剂(10.4g, 23.9mmol)。将反应混合物在 R.T. 下搅拌 5h。将混合物倾入 NaHCO₃ 和 Na₂S₂O₃(1:1) 水溶液。在无水 Na₂SO₄ 上干燥有机层并浓缩以产生剩余物。在硅胶柱上(20% EtOAc 的 PE) 纯化剩余物以产生白色固体形式的中间体(2.5g, 83.1%)。

[0678] 在氮气下, 在 0℃ 下, 向溴三苯基(丙基)磷(6.45g, 16.8mmol) 的无水 THF(3mL) 混合物加入 t-BuOK(16.8mL, 16.8mmol)。将反应混合物在 0℃ 下搅拌 50mins。在氮气下, 在 0℃ 下, 滴加上述中间体(1.5g, 2.4mmol) 的无水 THF(3mL) 溶液。将反应混合物在 R.T. 下搅拌 3h。通过 NH₄Cl 水溶液淬灭反应并使用 EtOAc 萃取。在无水 Na₂SO₄ 上干燥有机层并浓缩以产生剩余物。在硅胶柱上(20% EtOAc 的 PE) 纯化剩余物以产生白色固体形式的 59-5(1.3g, 83%)。

[0679] (59a) 的制备: 在 R.T. 下, 向 59-5(300mg, 0.45mmol) 的无水 CH₃CN(2mL) 溶液加入 TPSCl(341mg, 1.13mmol)、DMAP(138mg, 1.13mmol) 和 NEt₃(571mg, 5.65mmol)。将反应混合物在 R.T. 下搅拌 2h。加入 NH₄OH(1mL), 并将反应混合物搅拌 1h。使用 EA 稀释混合物并使用水洗涤。干燥有机层并浓缩以产生剩余物。在硅胶柱上(2% MeOH 的 DCM 溶液) 纯化剩

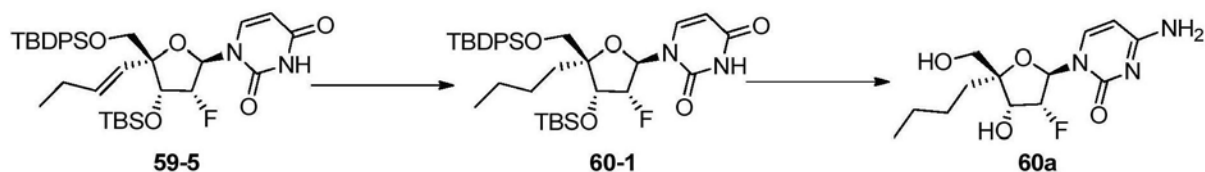
余物以产生白色固体形式的胞嘧啶核苷衍生物 (285mg, 95.0%)。

[0680] 在 R.T. 下向胞嘧啶核苷衍生物 (280mg, 0.43mmol) 的 MeOH(10mL) 溶液加入 NH_4F (1.0g)。将反应混合物回流 12h。将混合物过滤, 并将滤液浓缩。在硅胶柱上 (10% MeOH 的 DCM 溶液) 纯化剩余物以产生白色固体形式的 59a (81mg, 61%)。 ^1H NMR (CD_3OD , 400MHz) δ 8.11 (d, $J = 8.0\text{Hz}$, 1H), 5.91 (dd, $J = 1.2\text{Hz}$, $J = 17.6\text{Hz}$, 1H), 5.90 (d, $J = 7.6\text{Hz}$, 1H), 5.57-5.59 (m, 2H), 4.82-4.96 (m, 1H), 4.42 (dd, $J = 4.8\text{Hz}$, $J = 24.4\text{Hz}$, 1H), 3.72 (d, $J = 12.4\text{Hz}$, 1H) 3.58 (d, $J = 12.4\text{Hz}$, 1H), 2.31-2.41 (m, 2H), 0.99 (t, $J = 7.6\text{Hz}$, 3H)。ESI-TOF-MS :m/z 300.1 $[\text{M}+\text{H}]^+$ 。

[0681] 实施例 57

[0682] 化合物 (60a) 的制备

[0683]



[0684] (60-1) 的制备: 在 R.T. 下, 向 59-5 (450mg, 0.69mmol) 的 MeOH(10mL) 溶液加入 Pd/C (200mg)。在 H_2 (气球) 下, 将反应混合物在 R.T. 下搅拌 1h。将混合物过滤, 并将滤液浓缩以产生白色固体形式的粗 60-1 (440mg, 97.1%)。

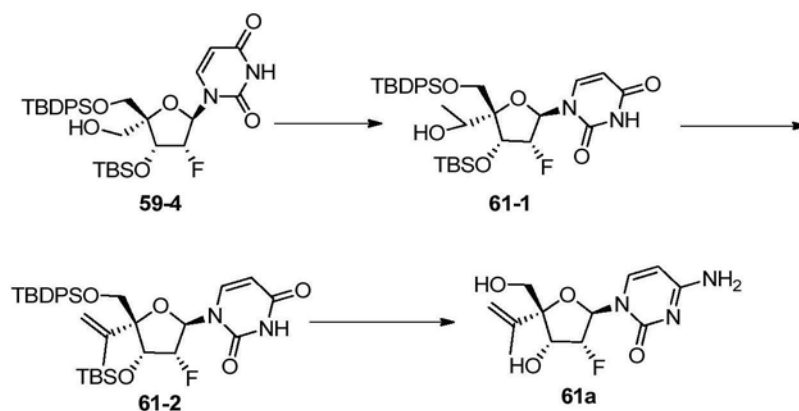
[0685] (60a) 的制备: 在 R.T. 下, 向 60-1 (440mg, 0.67mmol) 的无水 CH_3CN (2mL) 溶液加入 TPSCl (510mg, 1.68mmol)、DMAP (205mg, 1.68mmol) 和 NEt_3 (338mg, 3.35mmol)。将反应混合物在 R.T. 下搅拌 2h。加入 NH_4OH (1mL), 并将反应搅拌 1h。使用 EA 稀释混合物并使用水洗涤。将溶剂去除。在硅胶柱上 (2% MeOH 的 DCM 溶液) 纯化粗产物以产生白色固体形式的胞嘧啶核苷衍生物 (205mg, 46.5%)。

[0686] 在 R.T. 下, 向胞嘧啶核苷衍生物 (205mg, 0.31mmol) 的 MeOH(6mL) 溶液加入 NH_4F (0.6g)。将反应混合物回流过夜。在冷却至 R.T. 后, 将混合物过滤。将滤液浓缩, 并在硅胶柱上 (10% MeOH 的 DCM 溶液) 纯化剩余物以产生白色固体形式的 60a (59mg, 62.8%)。 ^1H NMR (CD_3OD , 400MHz) δ 8.09 (d, $J = 7.6\text{Hz}$, 1H), 6.01 (dd, $J = 3.2\text{Hz}$, $J = 15.6\text{Hz}$, 1H), 5.89 (d, $J = 7.2\text{Hz}$, 1H), 4.95-5.12 (m, 1H), 4.41 (dd, $J = 5.2\text{Hz}$, $J = 17.2\text{Hz}$, 1H), 3.75 (d, $J = 12.0\text{Hz}$, 1H) 3.56 (d, $J = 11.6\text{Hz}$, 1H), 1.73-1.80 (m, 1H), 1.55-1.63 (m, 1H), 1.40-1.46 (m, 4H), 0.92 (t, $J = 7.6\text{Hz}$, 3H)。ESI-MS :m/z 301.8 $[\text{M}+\text{H}]^+$ 。

[0687] 实施例 58

[0688] 化合物 (61a) 的制备

[0689]



[0690] (61-1) 的制备:在氮气下,在 0℃下向 59-4(1.5g, 2.39mmol) 的无水 DCM(100mL) 溶液加入戴斯-马丁氧化剂(5.2g, 11.95mmol)。将反应混合物在 R. T. 下搅拌 5h。将混合物倾入 NaHCO₃ 和 Na₂S₂O₃ 溶液并使用盐水洗涤。使用无水 Na₂SO₄ 干燥有机层并浓缩以产生白色固体形式的粗中间体(1.5g)。

[0691] 在 0℃下,向粗中间体(1.5g, 2.39mmol) 的 THF(12mL) 溶液滴加甲基溴化镁(2.4mL, 7.2mmol)。将生成的混合物在 0℃下搅拌 2h。在起始原料耗尽后,使用饱和 NH₄Cl 淬灭反应。使用 DCM 萃取反应混合物。使用盐水洗涤有机层,干燥并浓缩以产生粗 61-1(1.5g)。

[0692] (61-2) 的制备:向 61-1(1.5g, 2.39mmol) 的无水 DCM(50mL) 溶液加入戴斯-马丁氧化剂(4.5g, 10.6mmol)。将反应混合物在 R. T. 下搅拌过夜。将混合物倾入 NaHCO₃ 和 Na₂S₂O₃ 水溶液。将有机层分离,使用盐水洗涤、干燥并浓缩以产生剩余物。在硅胶柱上(10% EtOAc 的 PE) 纯化剩余物以产生白色固体形式的中间体(907mg, 58.6%)。

[0693] 在氮气下,在 0℃下向溴(甲基)三苯基磷(5.0g, 14mmol) 的无水 THF(8mL) 混合物加入 t-BuOK(12.6mL, 12.6mmol)。将混合物在 R. T. 下搅拌 50mins。在氮气下,在 0℃下滴加上述中间体(900mg, 1.4mmol) 的无水 THF(4mL) 溶液。将反应混合物在 R. T. 下搅拌 3h。使用 NH₄Cl 水溶液淬灭反应混合物并使用 DCM 萃取。将有机层分离,使用盐水洗涤,干燥并浓缩以产生剩余物。在硅胶柱上(5% EtOAc 的 PE) 纯化剩余物以产生白色固体形式的 61-2(700mg, 78.0%)。

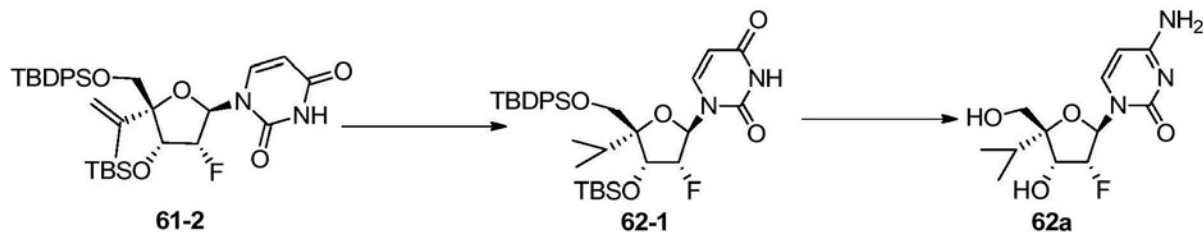
[0694] (61a) 的制备:在 R. T. 下,向 61-2(298mg, 0.46mmol) 的无水 CH₃CN(5.5mL) 溶液加入 TPSCl(346.5mg, 1.14mmol)、DMAP(139.6mg, 1.14mmol) 和 NEt₃(115.6mg, 1.14mmol)。将反应混合物在 R. T. 下搅拌 2h。加入 NH₄OH(1mL), 并将混合物搅拌另外 1h。使用 DCM 稀释混合物并使用水洗涤。将有机层分离,使用盐水洗涤,干燥并浓缩以产生剩余物。在硅胶柱上(2% MeOH 的 DCM 溶液) 纯化剩余物以产生白色固体形式的胞嘧啶核苷衍生物(250mg, 85.0%)。

[0695] 在 R. T. 下,向胞嘧啶核苷衍生物(250mg, 0.39mmol) 的 MeOH(10mL) 溶液加入 NH₄F(1.0g)。将反应回流 12h。将混合物过滤,并将滤液浓缩。在硅胶柱上(10% MeOH 的 DCM 溶液) 纯化剩余物以产生白色固体形式的 61a(55mg, 49%)。¹H NMR(CD₃OD, 400MHz) δ 8.11(d, J = 7.6Hz, 1H), 6.21(dd, J = 4.2Hz, J = 14.0Hz, 1H), 5.91(d, J = 7.6Hz, 1H), 5.10(dt, J = 4.8Hz, J = 53.6Hz, 1H), 5.13(brs, 1H), 5.00(brs, 1H), 4.46(dd, J = 4.8Hz, J = 11.6Hz, 1H), 3.83(d, J = 11.6Hz, 1H), 3.54(d, J = 11.6Hz, 1H), 1.84(s, 3H)。ESI-MS :m/z 285.9[M+H]⁺。

[0696] 实施例 59

[0697] 化合物 (62a) 的制备

[0698]



[0699] (62-1) 的制备: 在 R. T. 下, 向 61-2 (400mg, 0.63mmol) 的 MeOH (10mL) 溶液加入 Pd/C (400mg)。在 H₂ (气球) 下, 将反应在 R. T. 下搅拌 5h。将混合物过滤, 并将滤液浓缩以产生白色固体形式的粗 62-2 (350mg, 87%)。

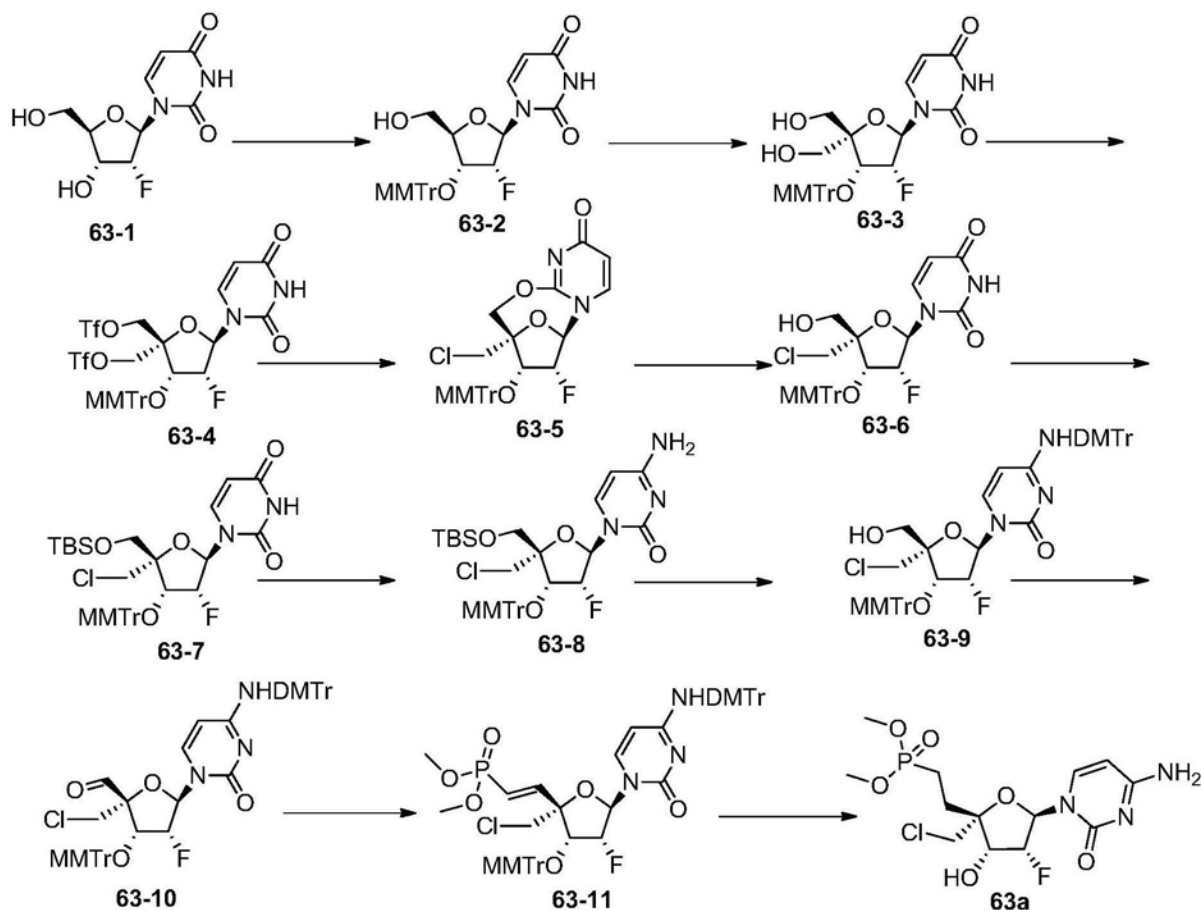
[0700] (62a) 的制备: 在 R. T. 下, 向 62-1 (350mg, 0.55mmol) 的无水 CH_3CN (6mL) 溶液加入 TPSCl (414mg, 1.4mmol)、DMAP (166.8mg, 1.4mmol) 和 NEt_3 (138.1mg, 1.4mmol)。将反应混合物在 R. T. 下搅拌 2h。加入 NH_4OH (1mL), 并将反应搅拌另外 1h。使用 EA 稀释混合物并使用水洗涤。将有机层分离, 干燥并浓缩以产生剩余物。在硅胶柱上 (2% MeOH 的 DCM 溶液) 纯化剩余物以产生白色固体形式的胞嘧啶核苷衍生物 (300mg, 85%)。

[0701] 在 R. T. 下, 向胞嘧啶核苷衍生物 (300mg, 0.47mmol) 的 MeOH(10mL) 溶液加入 NH_4F (1.5g)。将反应混合物回流过夜。在冷却至 R. T. 后, 将混合物过滤。将滤液浓缩。在硅胶柱上 (10 % MeOH 的 DCM 溶液) 纯化粗产物以产生白色固体形式的 62a (83mg, 61%)。 ^1H NMR (CD_3OD , 400MHz) δ 8.12 (d, $J = 7.6\text{Hz}$, 1H), 6.22 (dd, $J = 6.4\text{Hz}$, $J = 12.4\text{Hz}$, 1H), 5.94 (d, $J = 7.6\text{Hz}$, 1H), 5.25 (dt, $J = 5.6\text{Hz}$, $J = 54.0\text{Hz}$, 1H), 4.38 (t, $J = 4.8\text{Hz}$, 1H), 3.72 (d, $J = 11.6\text{Hz}$, 1H), 3.67 (d, $J = 11.6\text{Hz}$, 1H), 2.31-2.42 (m, 1H), 0.99 (2d, $J = 7.2\text{Hz}$, 6H)。ESI-MS :m/z 287.8 $[\text{M}+\text{H}]^+$ 。

[0702] 实施例 60

[0703] 化合物 (63a) 的制备

[0704]



[0705] (63-2) 的制备: 向 63-1 (50g, 203mmol) 的无水吡啶 (200mL) 溶液加入 TBDPS-Cl (83.7g, 304mmol)。使反应在 R. T. 下继续进行过夜。在减压下浓缩溶液以产生剩余物。在乙酸乙酯和水之间将剩余物分层。将有机层分离, 使用盐水洗涤, 在硫酸镁上干燥并在减压下浓缩以产生白色泡沫形式的 5'-OTBDPS 醚 (94g)。

[0706] 向 5'-OTBDPS 醚 (94.0g, 194.2mmol) 的无水 DCM (300mL) 溶液加入硝酸银 (66.03g, 388.4mmol) 和三甲吡啶 (235mL, 1.94mol)。在大多数硝酸银溶解 (约 15min) 后, 将混合物在 R. T. 下搅拌, 将混合物冷却至 0℃。一次性加入一甲氧基氯化三苯甲烷 (239.3g, 776.8mmol), 并将混合物在 R. T. 下搅拌过夜。通过硅藻土过滤混合物, 并使用 MTBE 稀释滤液。相继使用 1M 柠檬酸、稀释的盐水和 5% 碳酸氢钠洗涤溶液。在硫酸钠上干燥有机溶液并在真空下浓缩以产生黄色泡沫形式的完全保护的中间体。

[0707] 将完全保护的中间体溶于甲苯 (100mL), 并在减压下浓缩溶液。将剩余物溶于无水 THF (250mL) 并使用 TBAF (60g, 233mmol) 处理。将混合物在 R. T. 下搅拌 2 小时, 并在减压下去除溶剂。将剩余物放入乙酸乙酯, 并使用饱和碳酸氢钠和盐水洗涤溶液。在硫酸镁上干燥后, 真空去除溶剂。通过柱层析 (PE:EA = 5:1-1:1) 纯化剩余物以产生白色泡沫形式的 63-2 (91g, 86.4%)。

[0708] (63-3) 的制备: 向 63-2 (13.5g, 26mmol) 的 DCM (100mL) 溶液加入吡啶 (6.17mL, 78mmol)。将溶液冷却至 0℃ 并一次性加入戴斯-马丁氧化剂 (33.8g, 78mmol)。将反应混合物在 R. T. 下搅拌 4h。使用 Na₂S₂O₃ 溶液 (4%) 和碳酸氢钠水溶液 (4%) (将溶液调整至 pH 6, 约 150mL) 淬灭反应。将混合物搅拌 15min。将有机层分离, 使用稀释的盐水洗涤并在减压下浓缩。将剩余物溶于二氧六环 (100mL), 并使用 37% 甲醛水溶液 (21.2g, 10eq)

和 2N 氢氧化钠水溶液 (10eq) 处理溶液。将反应混合物在 R. T. 下搅拌过夜。在 R. T. 下搅拌 0.5h 后,使用饱和 NH_4Cl (约 150mL) 中和过量的氢氧化钠水溶液。在减压下浓缩混合物。在乙酸乙酯和 5% 碳酸氢钠之间将剩余物分层。将有机相分离,使用盐水洗涤,在硫酸镁上干燥并浓缩。通过柱层析 ($\text{MeOH}:\text{DCM} = 100:1-50:1$) 纯化剩余物以产生白色泡沫形式的 63-3 (9.2g, 83.6%)。

[0709] (63-4) 的制备:使用甲苯将 63-3 (23g, 42.0mmol) 共蒸发两次。将剩余物溶于无水 DCM (250mL) 和吡啶 (20mL)。将溶液冷却至 -35°C 。在 10mins 内滴加三氟甲磺酸酐 (24.9g, 88.1mmol)。将反应在 -35°C 下搅拌 40min。当 TLC ($\text{PE}:\text{EA} = 2:1$ 和 $\text{DCM}:\text{MeOH} = 15:1$) 显示反应完成时,在 0°C 下使用水淬灭 (50mL) 反应。将混合物搅拌 30mins,使用 EA 萃取。在 Na_2SO_4 上干燥有机相并通过硅胶垫过滤。在减压下浓缩滤液。通过柱层析 ($\text{PE}:\text{EA} = 100:1-1:1$) 纯化剩余物以产生褐色泡沫形式的 63-4 (30.0g, 88.3%)。

[0710] (63-5) 的制备:使用甲苯将 63-4 (30g, 36.9mmol) 共蒸发两次。将生成的双三氟甲磺酸酯溶于无水 DMF (150mL), 冷却至 0°C 并使用氢化钠 (60% 的矿物油; 1.5g, 40.6mmol, 1.1eq) 处理。将反应混合物在 R. T. 下搅拌 1h 直至 TLC ($\text{DCM}:\text{MeOH} = 15:1$) 显示双三氟甲磺酸酯消失和 2,5'- 酐中间体的形成。加入氯化锂 (4.6g, 110.7mmol, 3eq), 并将搅拌继续 2h。将混合物放入 100mL 的半饱和氯化铵和乙酸乙酯。将有机相分离,使用稀释的盐水洗涤并在减压下浓缩以产生 63-5。

[0711] (63-6) 的制备:将 63-5 溶于 THF (150mL), 并使用 1N 氢氧化钠水溶液 (约 41mL, 40.1mmol, 1.1eq) 处理溶液。将混合物在 R. T. 下搅拌 1h。通过 LCMS 监测反应。使用半饱和碳酸氢钠 (约 60mL) 稀释反应并使用乙酸乙酯萃取。干燥 (硫酸镁) 有机相并在减压下浓缩。通过柱层析 ($\text{DCM}:\text{MeOH} = 300:1-60:1$) 纯化剩余物产生黄色泡沫形式的 63-6 (18.3g, 87.6%)。

[0712] (63-7) 的制备:向 63-6 (18.3g, 32.33mmol) 的无水 DCM (150mL) 溶液加入 TBS-Cl (17.7g, 64.6mmol) 和咪唑 (6.6g, 97mmol)。使反应在 R. T. 下继续进行过夜。使用水稀释反应并使用 DCM 萃取。将有机层分离,使用盐水洗涤,在 Na_2SO_4 上干燥并浓缩。通过柱层析 ($\text{DCM}:\text{MeOH} = 300:1 \sim 80:1$) 纯化剩余物产生白色泡沫形式的 63-7 (18.4g, 83.7%)。

[0713] (63-8) 的制备:使用 2,4,6- 三异丙基苯磺酰氯 (TPSCl, 16.3g, 54.0mmol) 处理 63-7 (18.4g, 27.1mmol)、DMAP (6.6g, 54.0mmol) 和 TEA (5.4g, 54.0mmol) 的 MeCN (450mL) 溶液。将混合物在 R. T. 下搅拌 3h。加入 $\text{NH}_3\text{H}_2\text{O}$ (70mL), 并将混合物搅拌 2h。在减压下蒸发溶液,并在硅胶柱上 ($\text{DCM}:\text{MeOH} = 100:1$ 至 $15:1$) 纯化剩余物以产生淡黄色固体形式的 63-8 (18.0g)。

[0714] (63-9) 的制备:向 63-8 (18.0g, 26.5mmol) 的无水 DCM (150mL) 溶液加入三甲吡啶 (8.1g, 66.3mmol, 2.5eq)、硝酸银 (4.5g, 26.5mmol, 1.0eq) 和 DMTrCl (13.4g, 39.7mmol, 1.5eq)。使反应在 R. T. 下继续进行过夜。将混合物过滤。使用盐水洗涤滤液并使用 DCM 萃取。将有机层分离,在 Na_2SO_4 上干燥并浓缩。通过柱层析 ($\text{PE}:\text{EA} = 60:1 \sim 3:1$) 纯化黄色泡沫形式的剩余物。将泡沫溶于 THF (150mL), 并加入 TBAF (10.4g, 39.7mmol, 1.5eq)。使反应在 R. T. 下继续进行过夜。将混合物浓缩,使用盐水洗涤并使用 EA 萃取。将有机层分离,在 Na_2SO_4 上干燥并浓缩。通过柱层析 ($\text{PE}:\text{EA} = 60:1 \sim \text{EA}$) 纯化剩余物产生黄色泡沫形式的 63-9 (21.3g, 92.4%)。

[0715] (63-10) 的制备:在氮气下,在 0℃下向 63-9 (2.0g, 2.3mmol) 的无水 DCM(20mL) 溶液加入戴斯-马丁氧化剂 (1.95g, 4.6mmol)。将反应在 R. T. 下搅拌 5h。使用 EtOAc(100mL) 稀释混合物并使用饱和 $\text{Na}_2\text{S}_2\text{O}_3$ 水溶液和饱和 NaHCO_3 水溶液的混合物洗涤。通过在硅胶上的柱层析 (PE:EtOAc = 2:1) 纯化粗产物以产生黄色固体形式的 63-10 (1.8g, 90%)。

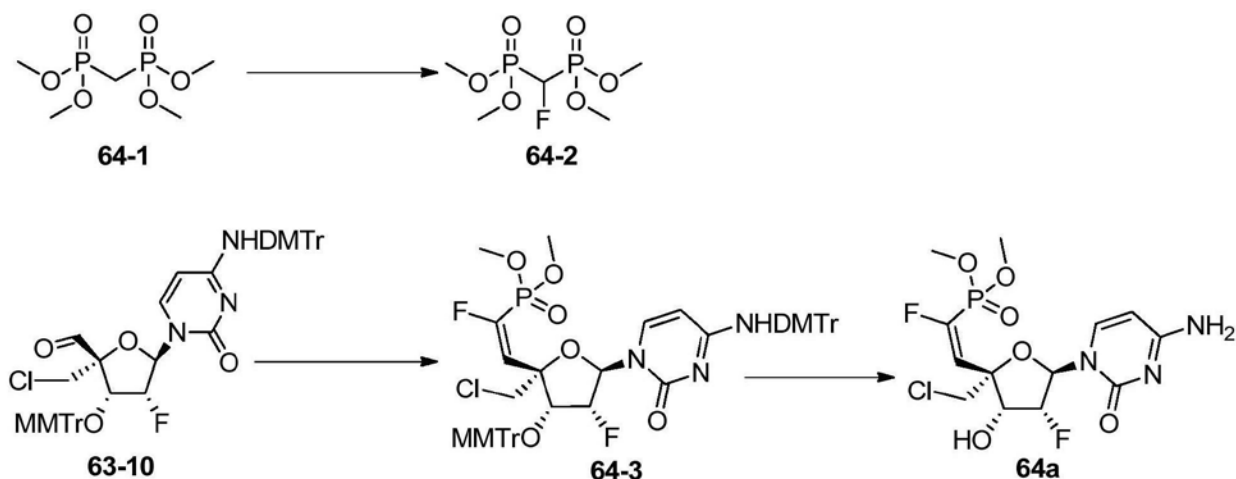
[0716] (63-11) 的制备:在氮气下,在 0℃下向亚甲基二磷酸四甲酯 (390mg, 1.68mmol) 的无水 THF(10mL) 溶液加入 NaH(84mg, 2.1mmol)。将反应在 0℃下搅拌 30min。在 0℃下滴加 63-10 (1.2g, 1.4mmol) 的无水 THF(10mL) 溶液。将反应混合物在 R. T. 下搅拌 1h。通过饱和 NH_4Cl 水溶液淬灭反应,并通过在硅胶上的柱层析 (DCM:MeOH = 150:1) 纯化粗产物以产生黄色固体形式的 63-11 (1.2g, 88.2%)。 ^1H NMR (DMSO- d_6 , 400M Hz) δ 8.51 (s, 1H), 7.46-7.09 (m, 22H), 6.88-6.82 (m, 6H), 6.62 (q, $J_1 = 17.2\text{Hz}$, $J_2 = 22.4\text{Hz}$, 1H), 6.12 (d, $J = 7.2\text{Hz}$, 1H), 5.86-5.75 (m, 2H), 5.43 (d, $J = 25.2\text{Hz}$, 1H), 4.63 (dd, $J = 4.8\text{Hz}$, $J = 21.2\text{Hz}$, 1H), 4.45 (d, $J = 12.0\text{Hz}$, 1H), 3.94 (d, $J = 12.0\text{Hz}$, 1H), 3.72 (s, 9H), 3.53 (q, $J = 11.2\text{Hz}$, $J = 16.0\text{Hz}$, 6H)。ESI-MS :m/z 971.59[M+H] $^+$ 。

[0717] (63a) 的制备:将 63-11 (1.0g, 1.03mmol) 的 80% HOAc (46mL) 溶液在 80-90℃下搅拌 2h。将溶剂去除,并通过在硅胶上的柱层析 (DCM:MeOH = 20:1) 纯化粗产物以产生白色固体形式的中间体 (337mg, 82.3%)。将中间体溶于 MeOH 并加入湿 Pd/C(300mg)。将反应混合物在 H_2 (1atm) 下搅拌 1h,然后过滤。将溶剂去除,并在硅胶柱上 (DCM:MeOH = 20:1) 纯化剩余物以产生白色固体形式的 63a (192mg, 63.9%)。 ^1H NMR (CD_3OD , 400MHz) δ 7.60 (d, $J = 7.6\text{Hz}$, 1H), 5.87 (d, $J = 7.2\text{Hz}$, 1H), 5.70 (dd, $J = 2.0\text{Hz}$, $J = 21.6\text{Hz}$, 1H), 5.31 (m, 1H), 4.67 (dd, $J = 5.6\text{Hz}$, $J = 19.6\text{Hz}$, 1H), 3.80 (m, 2H), 3.75 (2d, $J = 2.4\text{Hz}$, 6H), 1.92-2.20 (m, 4H)。 ^{31}P NMR (CD_3OD , 162MHz) δ 35.77。ESI-MS :m/z 400.0[M+H] $^+$ 。

[0718] 实施例 61

[0719] 化合物 (64a) 的制备

[0720]



[0721] (64-2) 的制备:向 64-1 (1.0g, 4.3mmol) 的 THF(20mL) 溶液加入 NaH(120mg, 3.0mmol),并将反应混合物在 0℃下搅拌 1h。将选择性氟 (1.2g, 3.4mmol) 加入反应混合物中。在硅胶柱上纯化粗产物并使用 EA 洗脱以产生白色固体形式的 64-2 (500mg, 57%)。 ^1H NMR (CD_3OD , 400MHz) δ 5.65 (dt, $J = 14.0\text{Hz}$, $J = 44.8\text{Hz}$, 1H), 3.90 (d, $J = 9.6\text{Hz}$, 12H)。

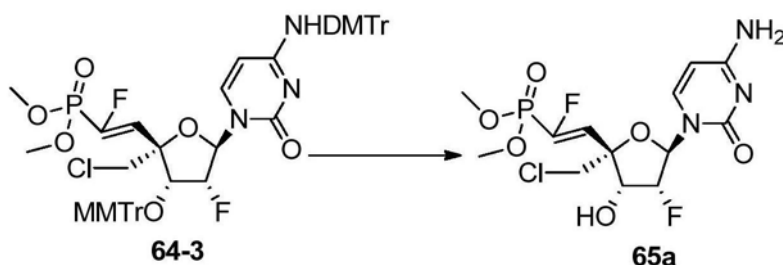
[0722] (64-3) 的制备: 在氮气下, 在 0℃ 下向化合物 64-2 (390mg, 1.68mmol) 的无水 THF (10mL) 溶液加入 NaH (84mg, 2.1mmol)。将反应混合物在 0℃ 下搅拌 30mins。在 0℃ 下滴加 63-10 (1.2g, 1.4mmol) 的无水 THF (10mL) 溶液。将反应混合物在 R. T. 下搅拌 1h。使用饱和 NH_4Cl 水溶液淬灭反应并浓缩以产生剩余物。在硅胶柱上 (DCM:MeOH = 150:1) 纯化剩余物以产生黄色固体形式的粗 64-3 (1.2g, 88.2%)。

[0723] (64a) 的制备: 将粗 64-3 (230mg, 0.23mmol) 的 80% HOAc (3mL) 溶液在 80-90℃ 下搅拌 2h。在硅胶柱上 (使用 DCM:MeOH = 20:1 洗脱) 纯化粗产物以产生白色固体形式的 64a (54mg, 53.7%)。 ^1H NMR (DMSO, 400MHz) δ 7.69 (d, J = 7.2Hz, 1H), 7.37 (d, J = 1.6Hz, 2H), 6.62-6.78 (m, 1H), 6.40 (d, J = 5.6Hz, 1H), 6.03-6.07 (m, 1H), 5.77 (d, J = 7.6Hz, 1H), 5.61-5.64 (m, 1H), 5.48-5.51 (m, 1H), 4.60-4.64 (m, 1H), 4.38 (d, J = 11.6Hz, 1H), 3.98 (d, J = 11.6Hz, 1H), 3.75 (2d, J = 11.6Hz, 6H)。ESI-MS : m/z 416.3 $[\text{M}+\text{H}]^+$ 。

[0724] 实施例 62

[0725] 化合物 (65a) 的制备

[0726]

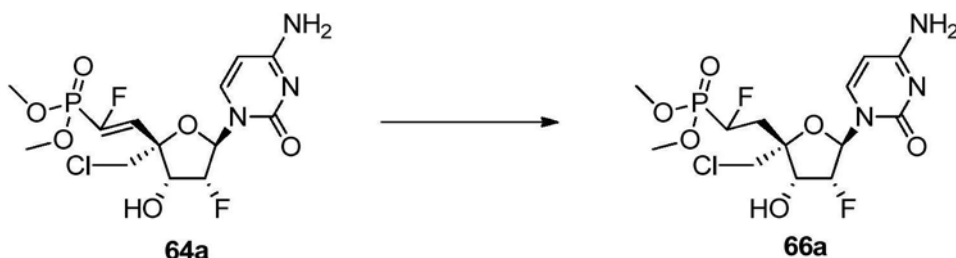


[0727] 将粗 64-3 (230mg, 0.23mmol) 的 80% HOAc (3mL) 溶液在 80-90℃ 下搅拌 2h。在硅胶柱上 (使用 DCM:MeOH = 20:1 洗脱) 纯化粗产物以产生白色固体形式的 64a (52mg, 33.7%)。 ^1H NMR (DMSO, 400MHz) δ 7.59 (d, J = 7.2Hz, 1H), 7.32 (s, 2H), 6.25-6.28 (m, 1H), 5.86-6.02 (m, 2H), 5.73 (s, 1H), 5.31 (d, J = 14.0Hz, 1H), 4.72 (d, J = 16.4Hz, 1H), 3.90 (d, J = 10.0Hz, 1H), 3.73 (2d, J = 11.6Hz, 6H)。

[0728] 实施例 63

[0729] 化合物 (66a) 的制备

[0730]

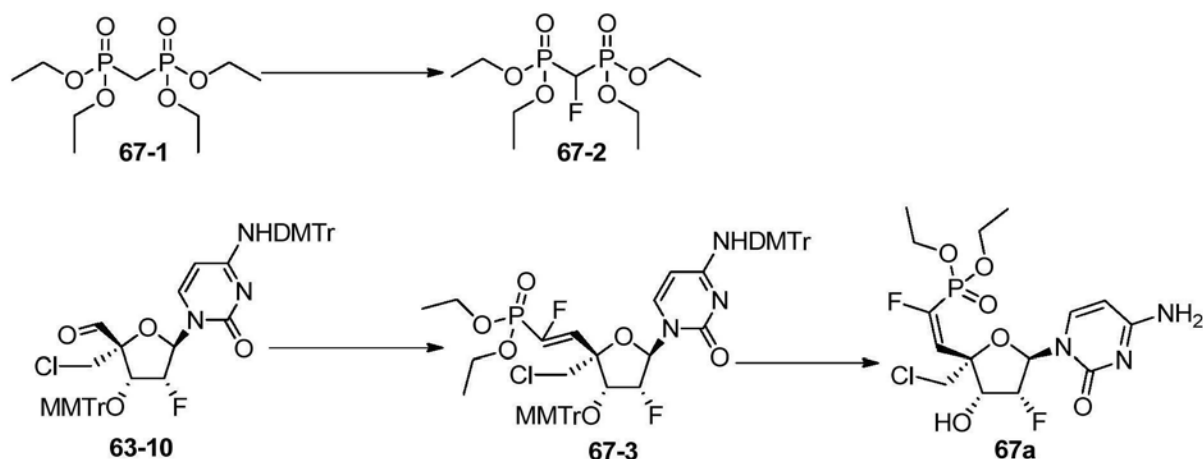


[0731] 在 H_2 (15Psi) 下, 将 64a (130mg, 0.3mmol) 的 EA:MeOH (5:1, 20mL) 溶液在 R. T. 下搅拌 2h。将反应混合物过滤并浓缩以产生剩余物。在硅胶柱上 (DCM:MeOH = 20:1) 纯化剩余物以产生白色固体形式的 66a (70mg, 54%)。 ^1H NMR (DMSO, 400MHz) δ 7.61 (d, J = 7.2Hz, 1H), 5.87 (d, J = 7.2Hz, 1H), 5.58-5.80 (m, 1H), 5.26-5.47 (m, 2H), 4.97-5.03 (m, 1H), 5.58-5.80 (m, 1H), 3.73-3.94 (m, 6H), 2.33-2.59 (m, 2H)。ESI-MS : m/z 418.3 $[\text{M}+\text{H}]^+$ 。

[0732] 实施例 64

[0733] 化合物 (67a) 的制备

[0734]



[0735] (67-2) 的制备: 向 67-1 (2.0g, 6.9mmol) 的 THF (20mL) 溶液加入 NaH (110mg, 2.8mmol), 并将反应混合物在 0℃ 下搅拌 1h。将选择性氟 (5.0g, 13.6mmol) 加入反应混合物中。使用饱和 NH_4Cl 淬灭反应并使用 EA 萃取。将有机层分离, 干燥并浓缩以产生粗产物。在硅胶柱上 (洗脱使用 EA) 纯化粗产物以产生白色固体形式的 67-2 (600mg, 28.3%)。 ^1H NMR (CD_3OD , 400MHz) δ 5.65 (dt, $J = 14.0\text{Hz}$, $J = 44.8\text{Hz}$, 1H), 4.24-4.46 (m, 8H), 1.35-1.39 (m, 12H)。

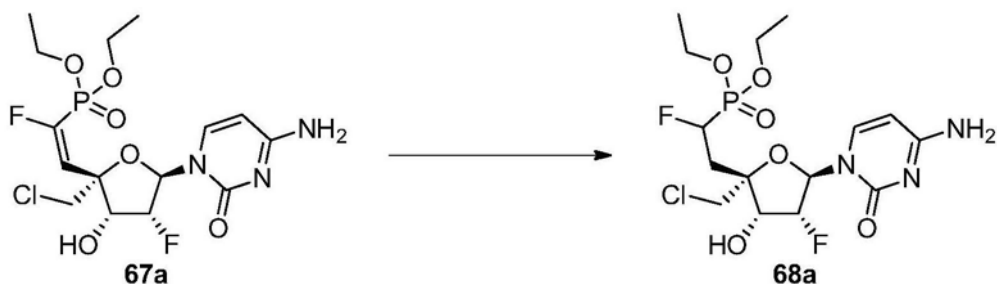
[0736] (67-3) 的制备: 在氮气下, 在 0℃ 下向 67-2 (2.14g, 7.0mmol) 的无水 THF (10mL) 溶液加入 NaH (84mg, 2.1mmol)。将反应混合物在 0℃ 下搅拌 30mins。在 0℃ 下滴加 63-10 (3.0g, 3.5mmol) 的无水 THF (10mL) 溶液。将反应混合物在 R.T. 下搅拌 1h。使用饱和 NH_4Cl 水溶液淬灭反应并浓缩以产生剩余物。在硅胶柱上 (DCM:MeOH = 150:1) 纯化剩余物以产生黄色固体形式的粗 67-3 (2.9g, 79.5%)。

[0737] (67a) 的制备: 将粗 67-3 (1.0g, 0.98mmol) 的 80% HAc (25mL) 溶液在 80-90℃ 下搅拌 2h。在硅胶柱上 (使用 DCM:MeOH = 20:1 洗脱) 纯化粗产物以产生白色固体形式的 67a (133mg, 32.5%)。 ^1H NMR (DMSO , 400MHz) δ 7.67 (d, $J = 7.2\text{Hz}$, 1H), 7.34 (d, $J = 12.8\text{Hz}$, 2H), 6.33-6.69 (m, 1H), 6.05 (d, $J = 6.8\text{Hz}$, 1H), 6.00-6.05 (m, 1H), 5.76 (d, $J = 7.6\text{Hz}$, 1H), 5.45-5.61 (m, 1H), 4.60-4.63 (m, 1H), 4.08-4.14 (m, 5H), 1.23-1.29 (m, 6H)。 ^{31}P NMR (DMSO , 162MHz) δ 1.93, 1.30。ESI-MS: m/z 466.1 $[\text{M}+\text{Na}]^+$ 。

[0738] 实施例 65

[0739] 化合物 (68a) 的制备

[0740]



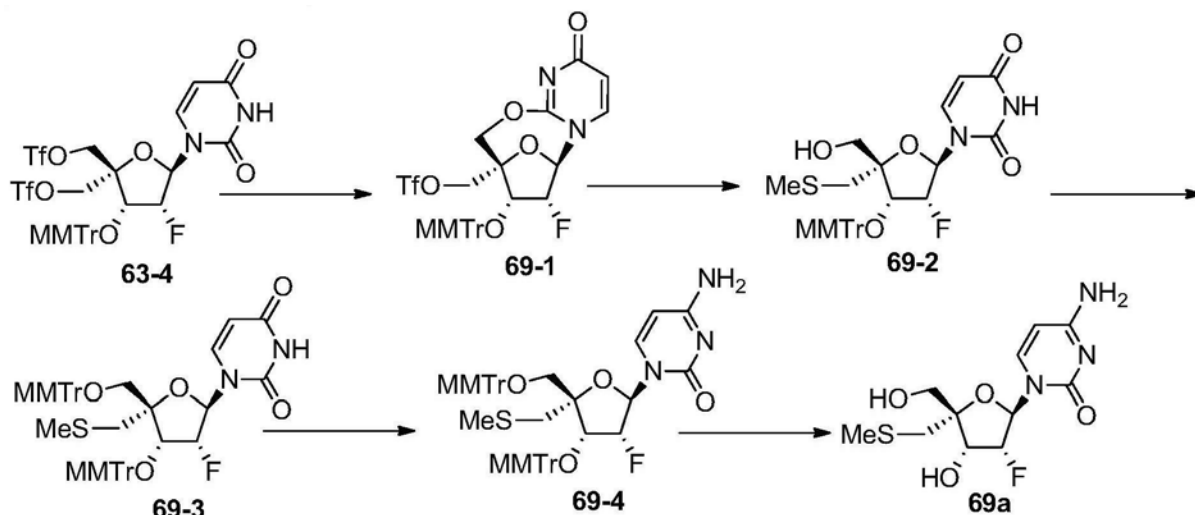
[0741] 在 H_2 (15Psi) 下, 将 67a (130mg, 0.29mmol) 的 MeOH (20mL) 溶液在 R.T. 下搅拌

2h。将反应混合物过滤并浓缩以产生剩余物。在硅胶柱上（洗脱使用 DCM:MeOH = 20:1）纯化剩余物以产生白色固体形式的 68a 的非对映异构体的混合物 (90mg, 69.2%)。¹H NMR(DMSO, 400MHz) δ 7.61–7.68 (m, 1H), 7.28–7.38 (m, 2H), 5.89–5.95 (m, 1H), 5.58–5.79 (m, 2H), 5.18–5.39 (m, 2H), 4.53–4.85 (m, 1H), 4.04–4.39 (m, 4H), 3.71–3.83 (m, 2H), 2.21–2.35 (m, 2H), 1.21–1.27 (m, 6H)。³¹P NMR(DMSO, 162MHz) δ 18.2, 18.02, 17.73, 17.56。ESI-MS: m/z 446.1 [M+H]⁺

[0742] 实施例 66

[0743] 化合物 (69a) 的制备

[0744]



[0745] (69-1) 的制备: 使用甲苯将 63-4 (3.0g, 3.69mmol) 共蒸发两次。将生成的双三氟甲磺酸酯溶于无水 DMF (20mL)。将溶液冷却至 0℃ 并使用氢化钠 (60% 的矿物油; 177mg, 0.43mmol) 处理。将反应在 R. T. 下搅拌 1h (TLC (PE:EA = 2:1) 显示双三氟甲磺酸酯完全消失和 2', 5'-酐中间体的干净形成)。将反应混合物用于下一步而不需任何进一步处理。

[0746] (69-2) 的制备: 在氮气下, 在 0℃ 下, 向上述搅拌的反应混合物加入 NaSMe (9.0g, 0.13mmol) 和 15-冠-5 (4.87g, 22.14mmol)。将溶液在 R. T. 下搅拌 2h (TLC (PE:EA = 1:1), 显示反应完成)。使用水淬灭反应。通过 EtOAc 萃取混合物, 使用盐水洗涤并在 MgSO₄ 上干燥。将混合物过滤并浓缩以产生剩余物。在硅胶柱上 (PE:EA = 5:2) 纯化剩余物以产生白色泡沫形式的 69-2 (1.23g, 59.0%)。

[0747] (69-3) 的制备: 在氮气下, 在 R. T. 下向搅拌的 69-2 (1.34g, 2.32mmol) 的无水 DCM (10mL) 溶液加入 MMTrCl (1.32g, 4.64mmol)、AgNO₃ (1.17g, 6.96mmol) 和三甲吡啶 (1.41g, 11.6mmol)。将反应混合物在 R. T. 下搅拌 1h (TLC (PE:EA = 1:1) 显示反应完成)。将混合物过滤并浓缩。在硅胶柱上 (PE:EA = 8:1) 纯化剩余物以产生白色泡沫形式的 69-3 (1.31g, 66.5%)。

[0748] (69-4) 的制备: 在氮气下, 在 R. T. 下向 69-3 (900mg, 1.06mmol) 的无水 MeCN (9mL) 溶液加入 DMAP (259mg, 2.12mmol)、TEA (214mg, 2.12mmol) 和 TPSCl (640mg, 2.12mmol)。将反应混合物在 R. T. 下搅拌 2h (TLC (DCM:MeOH = 10:1) 显示反应完成)。加入 NH₄OH (10mL), 并将反应混合物搅拌另外 1h (LCMS 显示反应完成)。使用水稀释溶液, 使用 EtOAc 萃

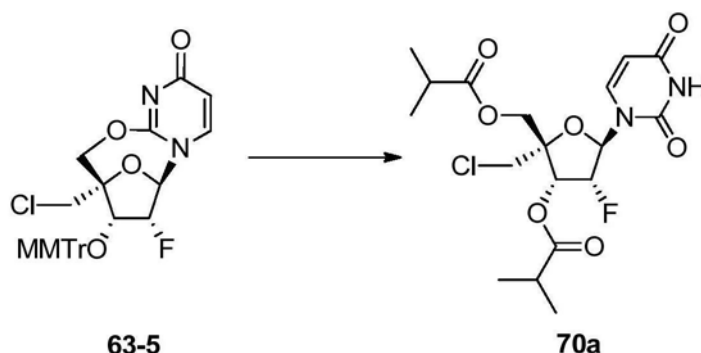
取。使用 1M HCl、饱和 NaHCO_3 和盐水洗涤有机层,并在 MgSO_4 上干燥。将混合物过滤并浓缩以产生剩余物。在硅胶柱上 ($\text{DCM}:\text{MeOH} = 70:1$) 纯化剩余物以产生白色固体形式的 69-4 (870mg, 68.5%)。

[0749] (69a) 的制备:将 69-4 (800mg, 0.95mmol) 溶于 80% HOAc 水溶液 (50mL)。将反应混合物加热至 75°C 过夜 (LCMS 显示反应完成)。将反应混合物浓缩并在硅胶柱上 ($\text{DCM}:\text{MeOH} = 15:1$) 纯化以产生白色固体形式的 69a (180mg, 62.5%)。 ^1H NMR (CD_3OD , 400MHz) δ 8.05 (d, $J = 7.2\text{Hz}$, 1H), 6.11 (dd, $J = 3.2\text{Hz}$ $J = 15.6\text{Hz}$, 1H), 5.87 (d, $J = 7.6\text{Hz}$, 1H), 5.05 (dt, $J = 4.8\text{Hz}$, $J = 53.6\text{Hz}$, 1H), 4.47 (dd, $J = 5.2\text{Hz}$ $J = 17.6\text{Hz}$, 1H), 3.83 (d, $J = 12.0\text{Hz}$, 2H), 2.84 (d, $J = 14.4\text{Hz}$, 2H), 2.15 (s, 3H)。ESI-MS : m/z 305.8 $[\text{M}+\text{H}]^+$ 。

[0750] 实施例 67

[0751] 化合物 (70a) 的制备

[0752]

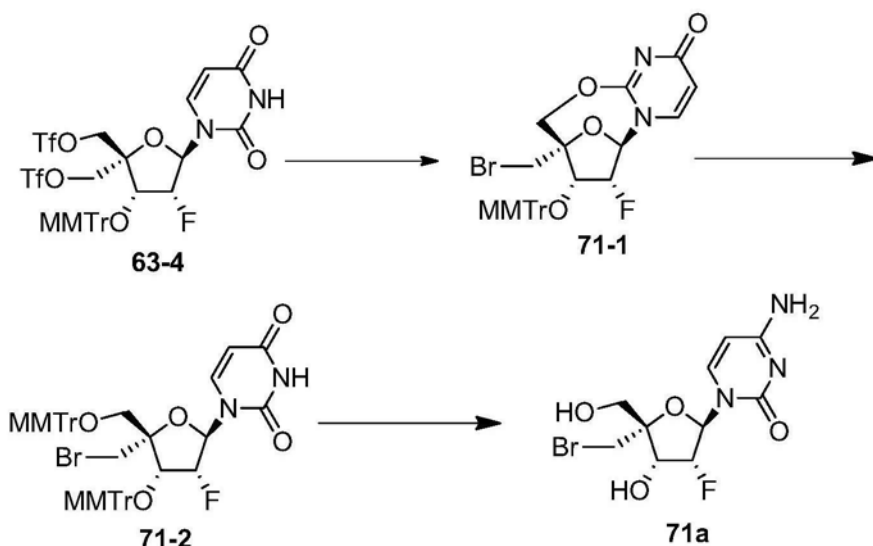


[0753] 向 63-5 (100g, 182.5mmol) 的 MeCN (2L) 溶液加入 6N HCl 水溶液 (15g)。将混合物在 40°C 下搅拌 7h, 然后使用 25% 氨溶液 (约 8g) 中和至 $\text{pH} = 5 \sim 6$ 。将混合物过滤以产生固体, 通过 PE 将其进一步洗涤以产生白色固体形式的中间体 (32.2g, 60%)。向中间体 (32.2g, 109.5mmol)、TEA (22.1g, 219mmol) 和 DMAP (1.34g, 11mmol) 的 MeCN (1L) 混合物加入无水异丁酸 (69.2g, 438mmol)。将混合物在 R. T. 下搅拌 3h。通过添加水 (200mL) 淬灭反应并使用 2-Me-THF (800mL) 萃取。使用饱和 NaHCO_3 和盐水洗涤有机层。干燥有机层并浓缩以产生剩余物, 通过硅胶柱 (10% 甲苯的庚烷) 将其纯化以产生白色固体形式的 70a (42.3g, 89%)。 ^1H NMR (CD_3OD , 400MHz) δ 7.65 (d, $J = 8.0\text{Hz}$, 1H), 5.95 (dd, $J = 2.8$ 、 20.4Hz , 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)。

[0754] 实施例 68

[0755] 化合物 (71a) 的制备

[0756]



[0757] (71-1) 的制备: 在 0℃ 下, 向 63-4 (4.2g, 5.17mmol) 的 DMF (50mL) 溶液加入 NaH (227mg 的 60% 分散体, 5.7mmol)。将混合物在 0℃ 下搅拌 2h, 然后加入 LiBr (1.34g, 15.5mmol)。将混合物在 R. T. 下搅拌过夜, 使用 EA (150mL) 稀释并相继使用水和盐水洗涤。在 Na₂SO₄ 上干燥有机层并浓缩。在使用 10% EA 的 PE 洗脱的硅胶柱上纯化剩余物以产生黄色固体形式的 71-1 (2g, 66%)。

[0758] (71-2) 的制备: 在 0℃ 下, 向 71-1 (1.74g, 2.9mmol) 的 THF (20mL) 溶液加入 1N NaOH (3.2mL, 3.2mmol), 并将混合物在 0℃ 下搅拌 2h。在 EA (100mL) 和水 (20mL) 之间将混合物分层, 并在 Na₂SO₄ 上干燥有机层并蒸发至干燥。在使用 20% EA 的 PE 洗脱的硅胶柱上纯化剩余物以产生黄色固体形式的 5'-OH 衍生物 (1.6g, 90%)。

[0759] 向 5'-OH 衍生物 (2.3g, 3.76mmol) 的无水 DCM (20mL) 溶液加入三甲吡啶 (0.8g, 6.7mol) 和 MMTTrCl (2.7g, 8.7mmol)。将反应混合物在 R. T. 下搅拌过夜。将混合物过滤并相继使用饱和 NaHCO₃ 水溶液和盐水洗涤, 在 Na₂SO₄ 上干燥并浓缩。在使用 10% EA 的 PE 洗脱的硅胶柱上纯化剩余物以产生黄色固体形式的 71-2 (2.4g, 73%)。

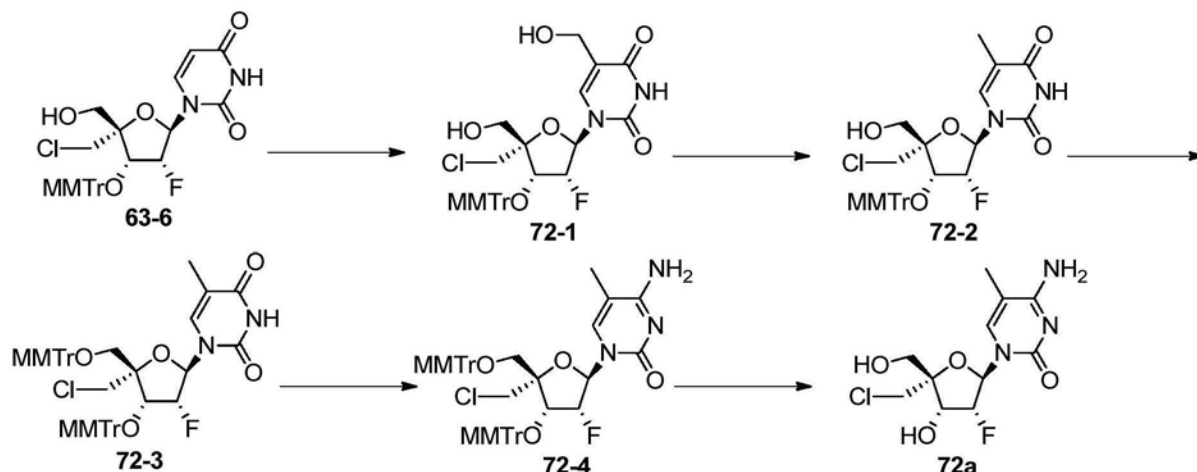
[0760] (71a) 的制备: 在 R. T. 下, 向 71-2 (2.4g, 2.72mmol) 的无水 CH₃CN (30mL) 溶液加入 TPSCl (1.65g, 5.44mmol)、DMAP (0.663g, 5.44mmol) 和 NEt₃ (1.5mL)。将混合物在 R. T. 下搅拌 3h, 并加入 28% 的氨水溶液 (30mL)。将混合物搅拌 1h。使用 EA (150mL) 稀释混合物并相继使用水、饱和 NaHCO₃ 水溶液和盐水洗涤。将溶剂去除, 并在 2% MeOH 的 DCM 溶液洗脱的硅胶柱上纯化剩余物以产生黄色固体形式的胞嘧啶核苷衍生物 (1.5g, 62%)。

[0761] 将胞嘧啶核苷衍生物 (1.35g, 1.5mmol) 溶于 80% AcOH (40mL), 并将混合物在 60℃ 下搅拌 2h。将混合物浓缩, 并在 5% MeOH 的 DCM 溶液作为洗脱液的硅胶柱上纯化剩余物以产生白色固体形式的 71a (180mg, 35%)。¹H NMR (MeOD, 400MHz) δ 8.00 (d, J = 7.2Hz, 1H), 6.12 (dd, J = 3.6Hz, J = 15.6Hz, 1H), 5.88 (d, J = 7.6Hz, 1H), 5.10 (dd, J = 4.8Hz, J = 53.2Hz, 1H), 4.59 (dd, J = 5.2Hz, J = 16.4Hz, 1H), 3.95 (d, J = 11.6Hz, 1H), 3.76 (d, J = 11.6Hz, 1H), 3.70 (d, J = 11.6Hz, 1H), 3.63 (d, J = 11.2Hz, 1H); ESI-TOF-MS :m/z 337.9[M+H]⁺。

[0762] 实施例 69

[0763] 化合物 (72a) 的制备

[0764]



[0765] (72-1) 的制备: 向 63-6 (1.0g, 1.8mmol) 的 1,4-二氧六环 (2mL) 溶液加入 TEA (3mL) 和 37% HCHO (3mL)。将反应混合物在 60℃ 下搅拌 10h。将反应在真空下浓缩至干燥, 并通过在硅胶柱上 (DCM:MeOH = 100:1-30:1) 的柱纯化剩余物以产生白色泡沫形式的 72-1 (470mg, 45%)。¹H NMR (DMSO-d₆, 400MHz) δ 11.4 (s, 1H), 7.27-7.49 (m, 13H), 6.89 (d, J = 8.8Hz, 2H), 4.90-4.95 (m, 1H), 4.58 (dd, J = 5.2Hz, J = 23.6Hz, 1H), 3.96-4.07 (m, 4H), 3.73 (s, 3H), 3.50-3.62 (m, 1H), 3.37-3.39 (m, 1H), ESI-TOF-MS :m/z 596.9 [M+H]⁺。

[0766] (72-2) 的制备: 向 72-1 (430mg, 0.72mmol) 的二氧六环 (2mL) 溶液加入 30% CH₃COOH (0.7mL) 和 PtO₂ (290mg)。在 H₂ (1atm) 下, 将反应混合物在 R.T. 下搅拌 2h。将混合物过滤, 并将滤液浓缩至干燥。在硅胶柱上 (DCM:MeOH = 100:1-30:1) 纯化剩余物以产生白色泡沫形式的 72-2 (268mg, 64%)。¹H NMR (DMSO-d₆, 400MHz) δ 11.3 (s, 1H), 7.27-7.46 (m, 13H), 6.88 (d, J = 8.8Hz, 2H), 5.78 (d, J = 20.8Hz, 1H), 5.06-5.08 (t, J = 20.8Hz, 1H), 4.49 (dd, J = 4.2Hz, J = 24.4Hz, 1H), 3.94-4.04 (m, 2H), 3.70 (s, 3H), 3.59-3.63 (m, 1H), 3.52-3.53 (m, 1H), 3.34-3.40 (m, 1H), 1.66 (s, 3H)。ESI-TOF-MS :m/z 580.9 [M+H]⁺。

[0767] (72-3) 的制备: 向 72-2 (260mg, 0.45mmol) 的无水 DCM (3mL) 溶液加入 AgNO₃ (228mg, 1.35mmol)、三甲吡啶 (223mg, 1.8mmol) 和 MMTTrCl (456mg, 1.35mmol)。将混合物在 R.T. 下搅拌 10h。将反应混合物过滤, 并将滤液浓缩至干燥。在硅胶柱上 (PE:EA = 50:1-3:1) 纯化剩余物以产生白色泡沫形式的 72-3 (303mg, 80%)。

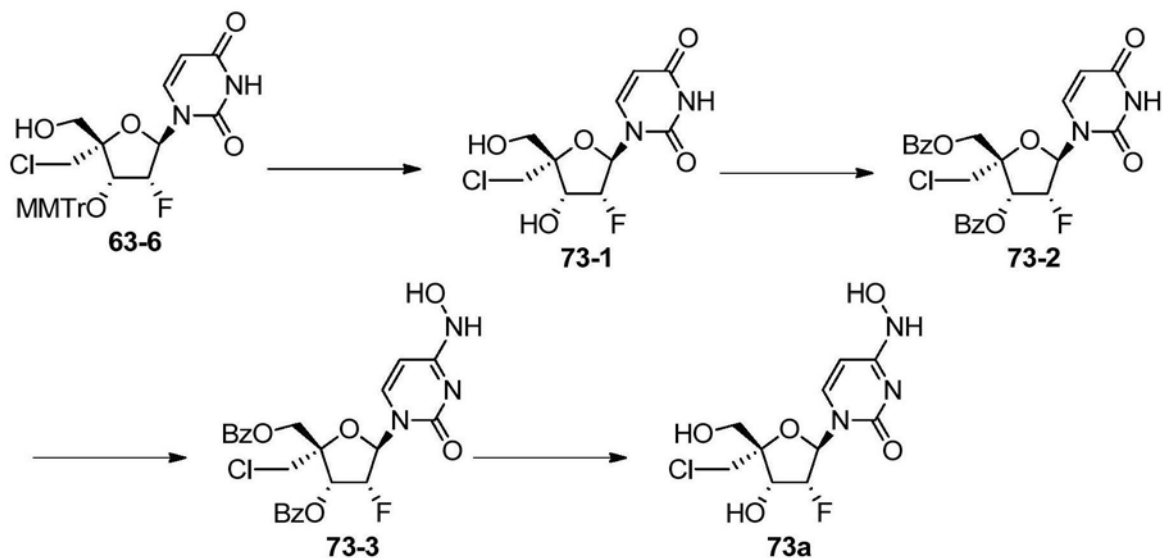
[0768] (72-4) 的制备: 在 R.T. 下, 向 72-3 (300mg, 0.35mmol) 的无水 CH₃CN (3mL) 溶液加入 DMAP (107mg, 0.88mmol)、TEA (141mg, 1.4mmol) 和 TPSCl (106mg, 0.35mmol)。将反应混合物在 R.T. 下搅拌 4h。加入 NH₄OH (1mL), 并将混合物在 R.T. 下搅拌另外 1h。将溶剂去除, 并通过 EA 和水将剩余物分层。通过盐水将有机层洗涤两次、干燥并浓缩以产生剩余物。在硅胶柱上 (PE:EA = 50:1-3:1) 纯化剩余物以产生白色泡沫形式的 72-4 (270mg, 90%)。

[0769] (72a) 的制备: 将 72-4 (260mg, 0.31mmol) 的 10mL 的 60% HCOOH 在 R.T. 下搅拌 2h。将溶剂去除, 并使用 EA 洗涤剩余物以产生白色粉末形式的 72a (31mg, 32%)。¹H NMR (MeOD, 400MHz) δ 7.85 (d, J = 0.8Hz, 1H), 6.12 (dd, J = 4.0Hz, J = 15.2Hz, 1H), 5.08-5.22 (m, 1H), 4.58 (dd, J = 4.8Hz, J = 14.8Hz, 1H), 3.92 (d, J = 15.6Hz, 1H), 3.74-3.84 (m, 3H), 1.94 (d, J = 0.8Hz, 1H)。ESI-TOF-MS :m/z 307.9 [M+H]⁺。

[0770] 实施例 70

[0771] 化合物 (73a) 的制备

[0772]



[0773] (73-1) 的制备: 将 63-6 (600mg, 1.06mmol) 的甲酸 (5mL, 80% 的水) 在 R. T. 下搅拌过夜。通过 TLC (DCM:MeOH = 10:1) 确定反应的完成。将溶剂去除以产生粗 73-1 (290mg, 93.2%)。

[0774] (73-2) 的制备: 向 73-1 (290mg, 0.98mmol) 的吡啶 (5mL) 和乙腈 (5mL) 溶液加入 BzCl (371mg, 2.65mmol)。将反应混合物在 0℃ 下搅拌 0.5h。将反应升温至 R. T. 并搅拌 2h。通过 LCMS 确定反应的完成。使用水淬灭反应并使用 EA 萃取。使用盐水洗涤有机层, 在 MgSO_4 上干燥, 过滤并浓缩。在硅胶柱上 (DCM:MeOH = 200:1) 纯化剩余物以产生白色固体形式的 73-2 (245mg, 49.8%)。

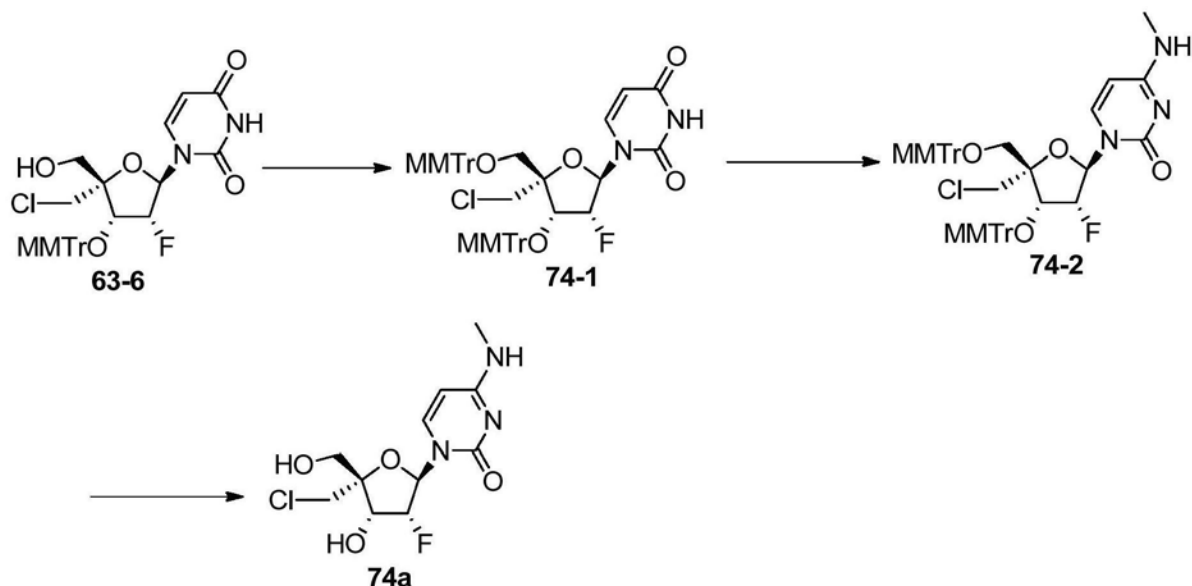
[0775] (73-3) 的制备: 向 73-2 (245mg, 0.49mmol) 的无水乙腈 (2.5mL) 溶液加入 TPSCl (394mg, 0.98mmol)、DMAP (119.5mg, 0.98mmol) 和 TEA (98mg, 0.98mmol)。将混合物在 R. T. 下搅拌 3h。加入 $\text{NH}_2\text{OH} \cdot \text{HCl}$ (68mg, 0.98mmol) 和 DBU (368mg, 1.47mmol), 并将反应混合物在 R. T. 下搅拌 2h。使用水稀释反应混合物并使用 EtOAc 萃取。使用 1M HCl、饱和 NaHCO_3 和盐水洗涤合并的有机层, 干燥并浓缩。在硅胶柱上 (DCM:MeOH = 20:1) 纯化剩余物以产生白色固体形式的 73-3 (49mg, 32.9%)。

[0776] (73a) 的制备: 将 73-3 (49mg, 0.1mmol) 的 NH_3/MeOH (30mL) 在 R. T. 下搅拌 2 天。将溶剂去除。在硅胶柱上 (DCM:MeOH = 30:1) 纯化剩余物以产生白色固体形式的 73a (12.9mg, 44.0%)。 ^1H NMR ($\text{DMSO}-d_6$, 400MHz) δ 10.07 (brs, 1H), 9.68 (brs, 1H), 7.02 (d, $J = 8.0\text{Hz}$, 1H), 6.06 (dd, $J = 6.4\text{Hz}$, $J = 13.6\text{Hz}$, 1H), 5.94 (d, $J = 5.6\text{Hz}$, 1H), 5.60 (d, $J = 8.4\text{Hz}$, 1H), 5.36 (t, $J = 5.2\text{Hz}$, 1H), 5.16 (dt, $J = 5.2\text{Hz}$, $J = 53.6\text{Hz}$, 1H), 4.31–4.35 (m, 1H), 3.58–3.76 (m, 2H), 3.57–3.58 (m, 2H)。ESI-TOF-MS: m/z 308.1 $[\text{M}-\text{H}]^+$ 。

[0777] 实施例 71

[0778] 化合物 (74a) 的制备

[0779]



[0780] (74-1) 的制备: 向 63-6 (1.2g, 2.12mmol) 的无水 DCM (20mL) 溶液加入三甲吡啶 (750mg, 6.51mmol) 和 MMTrCl (2.6g, 8.5mmol)。将反应混合物在 R. T. 下搅拌过夜。将反应过滤并相继使用饱和 NaHCO_3 水溶液和盐水洗涤、在 Na_2SO_4 上干燥并浓缩。在使用 10% EA 的 PE 洗脱的硅胶柱上纯化剩余物以产生黄色固体形式的 74-1 (1.4g, 72%)。

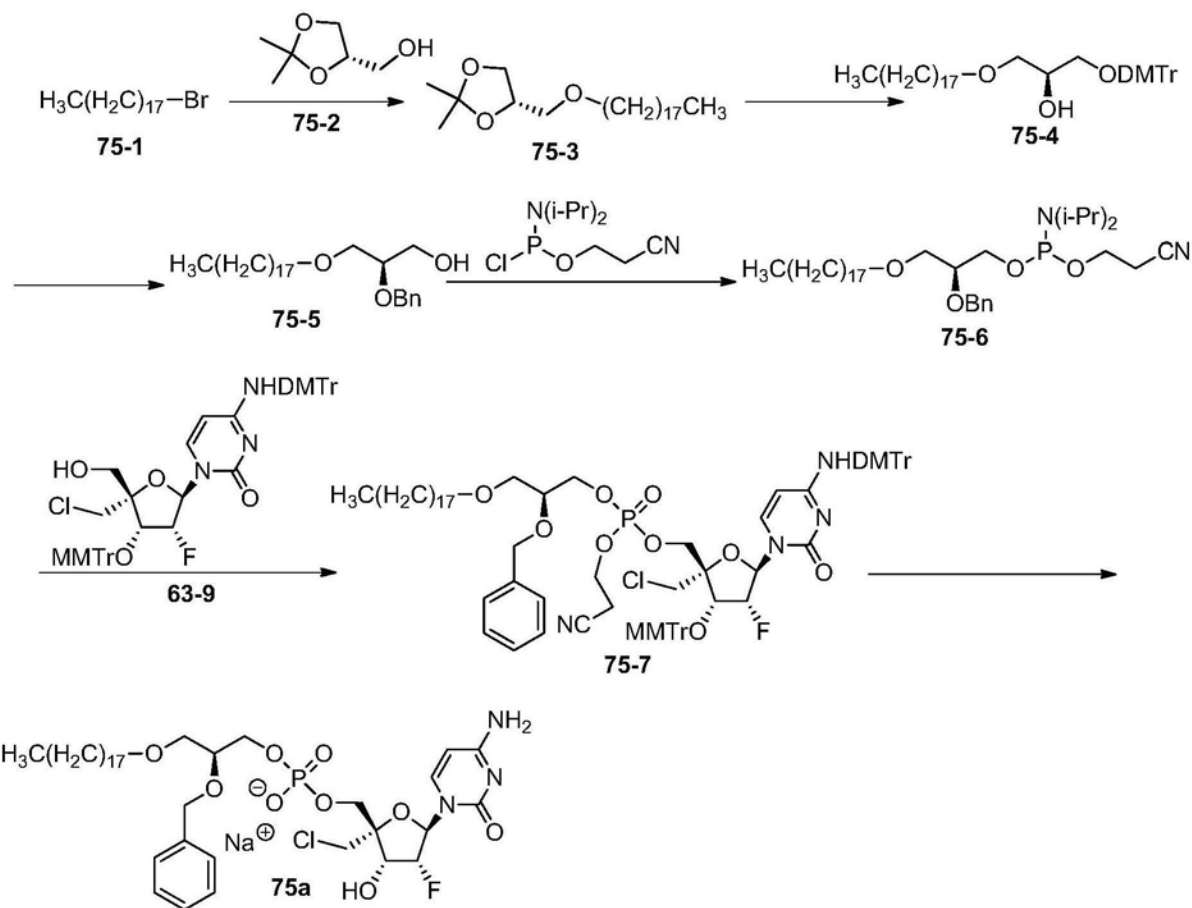
[0781] (74-2) 的制备: 向搅拌的 74-1 (600mg, 0.715mmol) 的无水乙腈 (6mL) 溶液加入 TPSCl (432mg, 1.43mmol)、DMAP (174mg, 1.43mmol) 和 TEA (144mg, 1.43mmol)。将混合物在 R. T. 下搅拌 2h。通过 TLC (DCM:MeOH = 10:1) 确定反应的完成。在 0℃ 下滴加 CH_3NH_2 (310mg, 10mmol)。将反应混合物在 R. T. 下搅拌 2h。使用水稀释混合物并使用 EtOAc 萃取。使用 1M HCl、饱和 NaHCO_3 和盐水洗涤合并的有机层。将溶剂去除, 并通过制备 -TLC (DCM:MeOH = 10:1) 纯化剩余物以产生白色固体形式的 74-2 (307mg, 50.45%)。

[0782] (74a) 的制备: 将 74-2 (300mg, 0.352mmol) 的甲酸 (10mL, 80% 的水) 在 R. T. 下搅拌过夜。通过 TLC (DCM:MeOH = 10:1) 确定反应的完成。将溶剂去除至干燥。将剩余物溶于 20mL 的甲醇。加入氨水 (0.5mL), 并将混合物在 R. T. 下搅拌 5mins。将溶剂去除, 并使用 PE (5×) 洗涤剩余物以产生白色固体形式的 74a (103mg, 95.3%)。 ^1H NMR (DMSO- d_6 , 400MHz) δ 7.79 (d, J = 4.8Hz, 1H), 7.72 (d, J = 5.2Hz, 1H), 6.10 (dd, J = 4.4Hz, J = 14.8Hz, 1H), 5.97 (brs, 1H), 5.73 (d, J = 7.6Hz, 1H), 5.39 (brs, 1H), 5.08 (dt, J = 4.2Hz, J = 53.2Hz, 1H), 4.37-4.40 (m, 1H), 3.73 (s, 2H), 3.54-3.70 (m, 2H), 2.73 (d, J = 4.4Hz, 3H)。ESI-TOF-MS: m/z 308.1 $[\text{M}+\text{H}]^+$ 。

[0783] 实施例 72

[0784] 化合物 (75a) 的制备

[0785]



[0786] (75-3) 的制备: 在 0℃ 下, 向搅拌的 75-1 (20.0g, 151mmol) 的无水 THF (200mL) 溶液分批加入 NaH (7.8g, 196mmol)。将混合物搅拌 1h, 并在 0℃ 下滴加 75-2 (65.0g, 196mmol)。将混合物在 R. T. 下搅拌 10h。使用水淬灭反应并使用 EA 萃取。使用盐水洗涤反应, 并将有机层浓缩以获得粗 75-3 (72g)。

[0787] (75-4) 的制备: 使用 80% CH₃COOH (300mL) 溶解粗 75-3 (72g, 151mmol) 并搅拌 10h。在减压下去除溶剂。将剩余物溶于 EA 并相继使用饱和 NaHCO₃ 和盐水洗涤。在 Na₂SO₄ 上干燥有机层并浓缩至干燥。在硅胶柱上纯化剩余物以产生粗中间体, 将其溶于无水吡啶 (80mL) 和 DCM (400mL)。在 0℃ 下滴加 DMTrCl (56.0g, 166mmol) 的 DCM (150mL) 溶液。将混合物在 R. T. 下搅拌 10h。将反应混合物浓缩至干燥, 并通过硅胶上的柱 (PE:EA = 2:1) 纯化剩余物以产生 75-4 (58.5g, 61%)。

[0788] (75-5) 的制备: 在 0℃ 下, 向搅拌的 75-4 (10.0g, 15.5mmol) 的无水 DMF (80mL) 溶液加入 NaH (0.8g, 20mmol)。将混合物在 R. T. 下搅拌 1h, 并加入 BnBr (33.8g, 20mmol)。将反应混合物在 R. T. 下搅拌 10h。使用水淬灭反应并使用 EA 萃取。使用盐水洗涤反应, 并将有机层浓缩以产生白色泡沫形式的粗中间体 (10.5g, 92%)。将粗中间体 (10.2g, 13.8mmol) 的 80% CH₃COOH (100mL) 在 R. T. 下搅拌 12h。将溶剂去除。并将剩余物溶于 EA, 相继使用饱和 NaHCO₃ 和盐水洗涤, 干燥并浓缩以产生剩余物。在硅胶柱上将剩余物纯化两次 (PE:EA = 3:1) 以产生白色泡沫形式的 75-5 (4.2g, 70%)。

[0789] (75-6) 的制备: 向 75-5 (4.0g, 9.2mmol) 的无水 CH₃CN (30mL) 溶液加入 DIPEA (6.1g, 47.6mmol) 和 2-氰基乙基 N,N-二异丙基氯亚磷酰胺 (2.8g, 11.9mmol)。将混合物在 R. T. 下搅拌 2h。将溶剂去除, 并通过 EA 和饱和 NaHCO₃ 将剩余物分层。在 MgSO₄ 上

干燥有机层并浓缩以产生剩余物。在硅胶柱上 (PE:EA = 3:1) 纯化剩余物以产生白色固体形式的 75-6 (5.1g, 88%)。

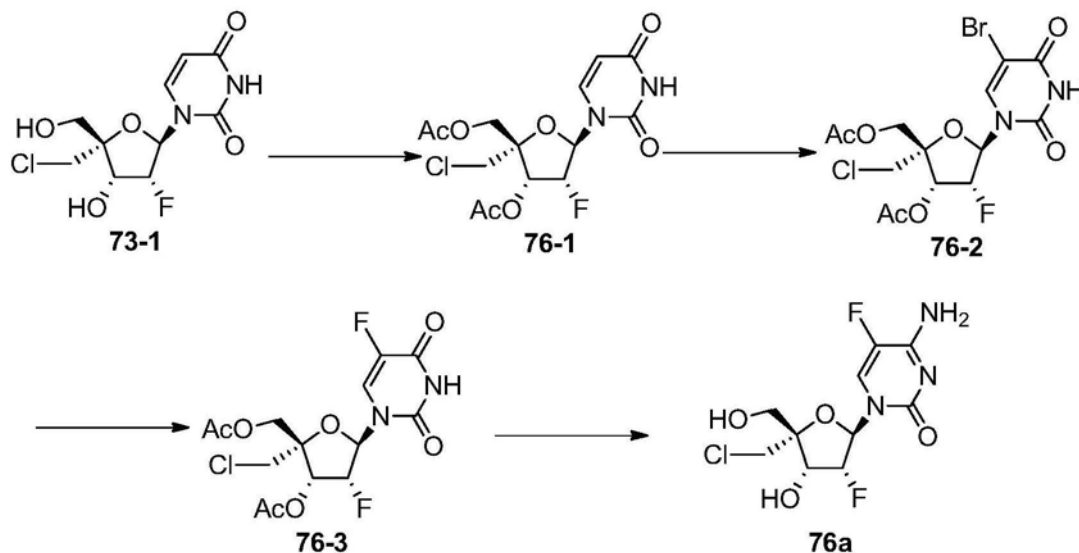
[0790] (75-7) 的制备: 在 R.T. 下, 向 75-6 (1.0g, 1.6mmol) 和 63-9 (925mg, 1.1mmol) 的无水 MeCN (1mL) 溶液滴加四唑 (12mL, 0.45M 的 MeCN、5.5mmol)。在搅拌 3h 后, 加入 TBDPH (0.96mL, 5M 4.8mmol)。并将反应混合物在 R.T. 下搅拌 1h。使用 EA 稀释混合物并使用饱和 Na_2SO_3 和盐水洗涤, 在无水 Na_2SO_4 上干燥并浓缩。通过硅胶层析 (PE/EA = 50:1 至 1:1) 纯化剩余物以产生白色固体形式的 75-7 (1.1g, 73.3%)。

[0791] (75a) 的制备: 将 75-7 (1.0g, 0.7mmol) 的 60% HCOOH (3mL) 在 R.T. 下搅拌 12h。将溶剂去除。将剩余物溶于 EA 并相继使用饱和 NaHCO_3 和盐水洗涤、干燥并浓缩以产生剩余物。在硅胶柱上 (DCM:MeOH = 30:1) 将剩余物纯化两次以产生白色泡沫形式的粗 75a (510mg, 86%)。向粗 75a (275mg, 0.33mmol) 的 $\text{C}_2\text{H}_5\text{OH}$ 溶液加入几滴 1N NaOH 直至 pH ~ 7.0。将混合物搅拌 0.5h。将混合物浓缩以产生剩余物。通过 HPLC (MeCN 和水, 中性体系) 纯化剩余物以产生白色固体形式的 75a (钠盐, 170mg, 64%)。 ^1H NMR (CD_3OD , 400MHz) δ 8.01 (d, J = 7.6Hz, 1H), 7.23-7.37 (m, 5H), 6.22 (dd, J = 3.6Hz, J = 14.4Hz, 1H), 6.01 (d, J = 7.6Hz, 1H), 5.01-5.16 (m, 1H), 4.63-4.72 (m, 2H), 4.52-4.11 (m, 1H), 4.23-4.29 (m, 1H), 3.91-4.09 (m, 3H), 3.69-3.81 (m, 3H), 3.51-3.60 (m, 2H), 3.41-3.45 (m, 2H), 1.48-1.55 (m, 2H), 1.21-1.35 (m, 32H), 0.87-0.91 (m, 3H)。 ^{31}P NMR (CD_3OD , 162MHz) δ -0.223. ESI-TOF-MS: m/z 788.3 $[\text{M}-\text{H}]^+$ 。

[0792] 实施例 73

[0793] 化合物 (76a) 的制备

[0794]



[0795] (76-1) 的制备: 在 R.T. 下, 向 73-1 (4.1g, 13.95mmol) 的吡啶 (40mL) 溶液加入 Ac_2O (3.13g, 30.68mmol), 并将混合物搅拌过夜。将混合物浓缩, 并在硅胶柱上 (PE:EA = 3:1) 纯化剩余物以产生 76-1 (4.0g, 75.9%)。

[0796] (76-2) 的制备: 在 R.T. 下, 向 76-1 (1.3g, 3.44mmol) 的吡啶 (20mL) 溶液加入 NBS (1.22g, 6.88mmol), 并将混合物搅拌过夜。将混合物浓缩, 并在硅胶柱上 (PE:EA = 4:1) 纯化剩余物以产生 76-2 (1.43g, 72.2%)。

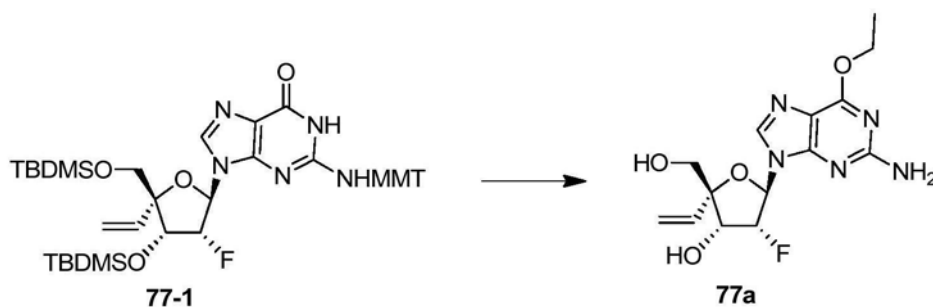
[0797] (76-3) 的制备: 在 N_2 环境下, 向 76-2 (770mg, 1.68mmol) 的二氧六环 (10mL) 溶液加入 Me_6Sn_2 (1.1g, 3.36mmol) 和 $(PPh_3)_2PdCl_2$ (100mg)。将混合物在 $80^\circ C$ 下加热 4h。将混合物浓缩, 并在硅胶柱上纯化剩余物以产生中间体 (400mg, 43.96%)。在 R. T. 下, 向中间体 (330mg, 0.61mmol) 的无水 MeCN (3mL) 溶液加入 **Selectflour®** (462mg, 1.34mmol)。将混合物在 R. T. 下搅拌 2 天。将混合物浓缩, 并在硅胶柱上 (PE:EA = 4:1) 纯化剩余物以产生 76-3 (100mg, 41.5%)。

[0798] (76a) 的制备: 向 76-3 (100mg, 0.25mmol) 的 MeCN (2mL) 溶液加入 DMAP (62mg, 0.51mmol)、TEA (51mg, 0.51mmol) 和 TPSCl (153mg, 0.51mmol)。将混合物在 R. T. 下搅拌 0.5h。加入 $NH_3 \cdot H_2O$ (0.75mL)。将混合物在 R. T. 下搅拌 0.5h。使用 EtOAc 萃取混合物并使用 1N HCl 和盐水洗涤。干燥有机层并浓缩。在硅胶柱上 (PE:EA = 1:1) 纯化剩余物以产生中间体 (60mg, 60.1%)。将中间体 (50mg, 0.13mmol) 的 $NH_3/MeOH$ (5mL) 在 R. T. 下搅拌 3h。将混合物浓缩, 并在硅胶柱上 (MeOH:DCM = 1:10) 纯化剩余物以产生 76a (30mg, 76.2%)。 ^1H NMR (CD_3OD , 400MHz) δ 8.25 (d, $J = 6.8Hz$, 1H), 6.09 (d, $J = 16.0Hz$, 1H), 5.00 (dt, $J = 4.0Hz$, $J = 53.2Hz$, 1H), 4.48-4.54 (m, 1H), 3.73-3.95 (m, 4H)。ESI-TOF-MS: m/z 312.1 $[M+H]^+$ 。

[0799] 实施例 74

[0800] 化合物 (77a) 的制备

[0801]

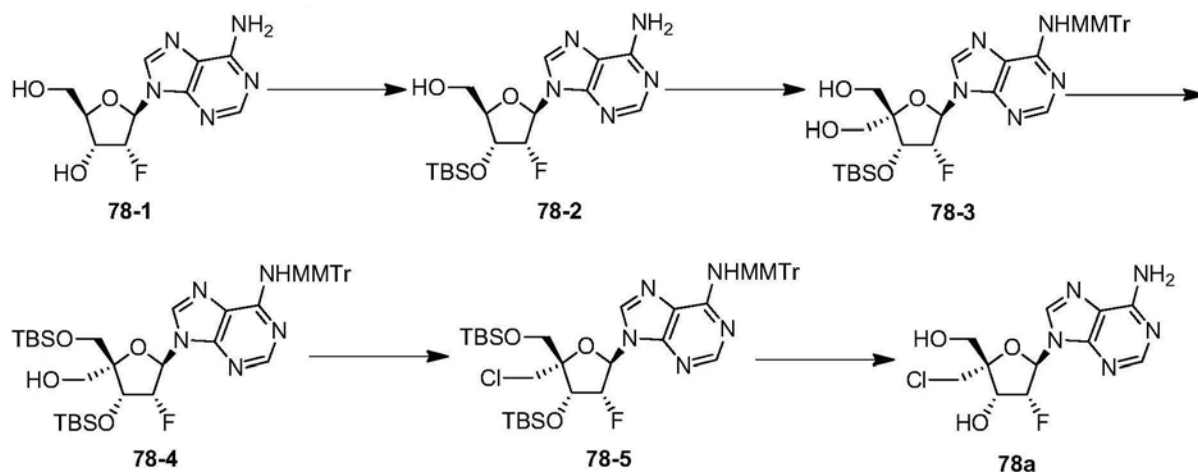


[0802] 将 77-1 (680mg, 0.8mmol) 和三苯基膦 (312mg, 1.2mmol) 溶于 5mL 的二氧六环和 0.25mL 的干燥的乙醇的混合物。加入偶氮二碳酸二异丙基酯 (40% w 溶液的甲苯、1.28mmol) 的 3mL 的二氧六环溶液, 并将混合物在 R. T. 下搅拌 2h。将混合物蒸发至干燥。将剩余物溶于 10mL 的 THF, 冷却至 $4^\circ C$ 并加入 2 当量的 TBAF 的 THF。将混合物升温至 R. T. 并将溶剂蒸发。在 R. T. 下使用 80% $HCOOH$ 将生成的核苷处理 3h, 然后将酸蒸发。使用 DCM (950mL)、MeOH (50mL) 和 NH_4OH (2.5mL) 的混合物用于洗脱的等度硅胶层析分离产生 77a (80mg, 30%)。 H^1 -NMR ($DMSO-D_6$) δ : 8.06 (s, 1H), 6.41 (s, 2H), 6.11-6.06 (dd, 1H), 5.98-5.89 (dd, 1H), 5.65-5.64 (d, 1H), 5.34-5.26 (m, 2H), 5.18-5.11 (m, 1H), 4.58-4.50 (dt, 1H), 4.42-4.36 (q, 2H), 3.50-3.28 (m, 2H), 1.30 (t, 3H)。MS: 384 ($M-1+HCOOH$)。

[0803] 实施例 75

[0804] 化合物 (78a) 的制备

[0805]



[0806] (78-2) 的制备: 在 25℃ 下, 向 78-1 (10.0g, 37.17mmol) 的无水吡啶 (100mL) 溶液加入咪唑 (9.54g, 140.4mmol) 和 TBSCl (21.1g, 140.4mmol)。将溶液在 25℃ 下搅拌 15h。在减压下将溶液浓缩至干燥。将剩余物溶于 EtOAc (200mL) 并使用水和盐水洗涤。将有机层分离, 在无水 Na₂SO₄ 上干燥并过滤。将滤液真空浓缩以产生剩余物。通过硅胶柱 (PE/EA = 10:1 至 2:1) 纯化剩余物以产生中间体 (11.8g, 64%)。在 N₂ 下, 以小部分向冰冷的中间体 (11.8g, 23.7mmol) 的 CH₂Cl₂ (150mL) 溶液加入对甲苯磺酸一水合物 (8.2g, 47.5mmol) 溶液。将混合物在 25℃ 下搅拌 30min, 然后使用饱和 NaHCO₃ 水溶液洗涤。将有机层分离, 在无水 Na₂SO₄ 上干燥并过滤。将滤液真空浓缩以产生剩余物, 通过硅胶 (PE/EA = 10:1 至 1:1) 将其纯化以产生固体形式的 78-2 (6.7g, 74%)。

[0807] (78-3) 的制备: 在 N₂ 下, 在 0℃ 下, 以小部分向 78-2 (6.7g, 17.5mmol) 的无水吡啶 (50mL) 溶液加入 TMSCl (2.8g, 26.2mmol)。将反应混合物在 25℃ 下搅拌过夜。在 N₂ 下, 以小部分加入 AgNO₃ (77.8g, 510mmol) 和 MMTTrCl (156.8g, 510mmol) 的无水吡啶 (50mL)。将反应混合物在 25℃ 下搅拌过夜。加入氨水 (30mL), 并将反应混合物搅拌 30min。通过 Buchner 漏斗过滤混合物, 并使用饱和 NaHCO₃ 溶液和盐水洗涤滤液。将有机层分离, 在无水 Na₂SO₄ 上干燥、过滤并浓缩。在硅胶上 (PE:EA = 10:1 至 2:1) 层析产生胺保护的衍生物 (6.1g, 53%)。在 0℃ 下, 向吡啶 (142mg, 1.8mmol) 的无水 DMSO (2mL) 溶液滴加 TFA (1.3mg, 0.9mmol)。将混合物在 25℃ 下搅拌直至形成澄清溶液。然后, 在 0℃ 下, 将溶液滴加至胺保护的衍生物 (1.0g, 1.5mmol) 和 DCC (0.95g, 4.6mmol) 的无水 DMSO 溶液。将搅拌在 25℃ 下继续 10h。加入水 (10mL), 并将混合物在 25℃ 下搅拌 1h。通过过滤去除沉淀, 并使用 EtOAc 萃取 (20mL) 滤液。使用盐水洗涤 (20mL) 有机层, 然后在 Na₂SO₄ 上干燥。将溶剂去除, 并在硅胶柱上 (EA:PE = 10:1 至 2:1) 纯化剩余物以产生醛衍生物 (850mg, 85%)。向醛衍生物 (2.6g, 4.0mmol) 的 1,4-二氧六环 (30mL) 溶液加入 37% CH₂O (1.3g, 16.0mmol) 和 2N NaOH 水溶液 (3.0mL, 6.0mmol)。将混合物在 25℃ 下搅拌 2h, 然后使用 AcOH 中和至 pH = 7。向反应加入 EtOH (10mL) 和 NaBH₄ (912mg, 24.0mmol)。将反应搅拌 30mins, 然后使用饱和 NH₄Cl 水溶液淬灭。使用 EA 萃取混合物, 并在 Na₂SO₄ 上干燥有机层。通过硅胶柱层析 (EA:PE = 10:1 至 2:1) 纯化产生黄色固体形式的 78-3 (1.1g, 40%)。

[0808] (78-4) 的制备: 将搅拌的 78-3 (685mg, 1.0mmol) 的无水 CH₃CN (5mL) 和无水吡啶 (5mL) 溶液冷却至 0℃。加入 BzCl (126mg, 0.9mmol), 并将反应混合物在 25℃ 下搅拌。在 1.5h 后。加入水 (5mL)。使用 DCM 萃取 (2×30mL) 生成的混合物。使用饱和 NaHCO₃

水溶液 (20mL) 洗涤合并的萃取物, 在 MgSO_4 上干燥并在减压下蒸发。通过硅胶柱层析 ($\text{DCM}:\text{MeOH} = 200:1$ 至 $50:1$) 纯化剩余物以产生 Bz- 保护的衍生物 (679mg, 86%)。向搅拌的 Bz- 保护的衍生物 (432mg, 0.55mmol) 的无水 DMF (5mL) 溶液加入咪唑 (258mg, 3.85mmol) 和 TBSCl (240.0mg, 1.65mmol)。将混合物搅拌 15h。加入水 (10mL), 并使用 EA 萃取混合物。使用 NaHCO_3 水溶液 (60mL) 和盐水 (60mL) 洗涤合并的萃取物, 在 MgSO_4 上干燥, 并在减压下蒸发以产生两种 -TBS 保护的衍生物 (680mg, 137%)。将两种 -TBS 保护的衍生物 (680mg, 0.75mmol) 溶于无水 CH_3OH (5mL), 并加入 NaOCH_3 (162mg, 3.0mmol)。将反应混合物在 35°C 下搅拌 2h。使用 80% AcOH (3mL) 淬灭反应并使用 DCM ($2 \times 50\text{mL}$) 萃取。使用 NaHCO_3 水溶液 (20mL) 洗涤合并的萃取物, 在 MgSO_4 上干燥, 并在减压下蒸发。通过硅胶柱层析 ($\text{EA}:\text{PE} = 20:1$ 至 $3:1$) 纯化剩余物以产生白色泡沫形式的 78-4 (239mg, 40%)。

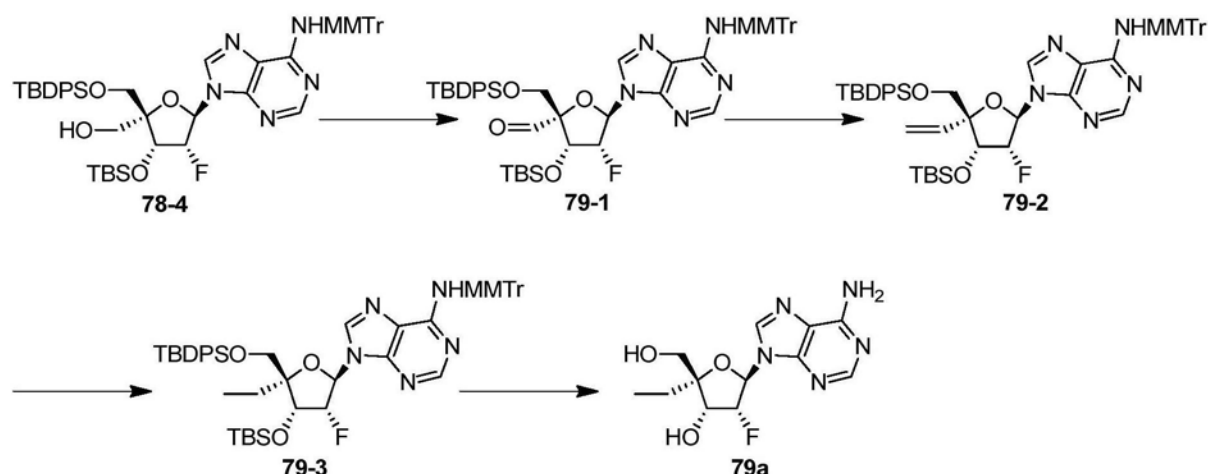
[0809] (78-5) 的制备: 使用甲苯将 78-4 (239mg, 0.30mmol) 共蒸发三次以去除 H_2O 。在 N_2 下, 在 0°C 下向 78-4 的 DCM (5mL) 溶液加入 DMAP (182mg, 1.50mmol) 和 TfCl (69mg, 0.45mmol)。将混合物在 0°C 下搅拌 40mins。通过 LCMS 确定反应的完成。将混合物浓缩以产生粗 Tf- 衍生物 (353mg)。在 N_2 下, 在 0°C 下向 Tf- 衍生物的 DMF (5mL) 溶液加入 LiCl (31mg, 0.76mmol)。将混合物在 25°C 下搅拌 40mins。使用 NaHCO_3 洗涤混合物并使用 EA 萃取。在 Na_2SO_4 上干燥合并的有机层并浓缩以产生淡黄色油状物形式的粗 78-5 (268mg)。

[0810] (78a) 的制备: 在 25°C 下, 向 78-5 (268mg, 0.328mmol) 的 MeOH (5mL) 溶液加入 NH_4F (37mg, 0.984mmol), 时间为 4h。将溶液过滤并蒸发至干燥。在 25°C 下, 将剩余物溶于 HCOOH (20mL) 和 H_2O (4mL)。将混合物在 25°C 下搅拌 1h 并浓缩。将混合物溶于 MeCN 并通过制备 -HPLC 纯化以产生白色固体形式的 78a (32mg)。 ^1H NMR (MeOD , 400MHz) δ 8.33 (s, 1H), 8.20 (s, 1H), 6.32 (dd, $J = 5.6, 12.4\text{Hz}$, 1H), 5.77 (m, 1H), 4.69 (m, 1H), 3.85 (m, 1H)。ESI-MS: m/z 317.9 $[\text{M}+\text{H}]^+$ 。

[0811] 实施例 76

[0812] 化合物 (79a) 的制备

[0813]



[0814] (79-1) 的制备: 在氮气下, 在 0°C 下, 向 78-4 (1.1g, 1.33mmol) 的无水 DCM (6.6mL) 溶液加入戴斯-马丁氧化剂 (1.45g, 3.33mmol)。将混合物在 25°C 下搅拌 4h。真空去除溶剂, 并使用甲基-叔丁基醚 (30mL) 研磨剩余物。通过 MgSO_4 垫过滤混合物。并使用等体积的 $\text{Na}_2\text{S}_2\text{O}_3$ 的 30mL 的饱和 NaHCO_3 搅拌有机溶剂直至有机层变澄清 (约 10min)。将有机层

分离,使用盐水洗涤,并在 MgSO_4 上干燥。在真空去除溶剂之前,在硅胶柱上 ($\text{PE}:\text{EA} = 7:1$) 纯化剩余物以产生白色固体形式的 79-1 (750mg, 75%)。

[0815] (79-2) 的制备:在 78°C 下,向搅拌的甲基-三苯基-溴化磷 (1.74g, 4.89mmol) 的无水 THF (8mL) 溶液滴加 $n\text{-BuLi}$ (1.91mL, 4.89mmol, 2.5M 的 THF)。将混合物在 0°C 下搅拌 1h。加入 79-1 (750mg, 0.81mmol), 并将混合物在 25°C 下搅拌过夜。使用饱和 NH_4Cl (30mL) 淬灭反应,并使用 EtOAc 萃取 ($2 \times 30\text{mL}$)。使用盐水洗涤合并的有机相,使用 MgSO_4 干燥、过滤并蒸发至干燥以产生淡白色固体。通过柱层析 ($\text{PE}:\text{EA} = 5:1$) 纯化固体以产生 79-2 (440mg, 60%)。

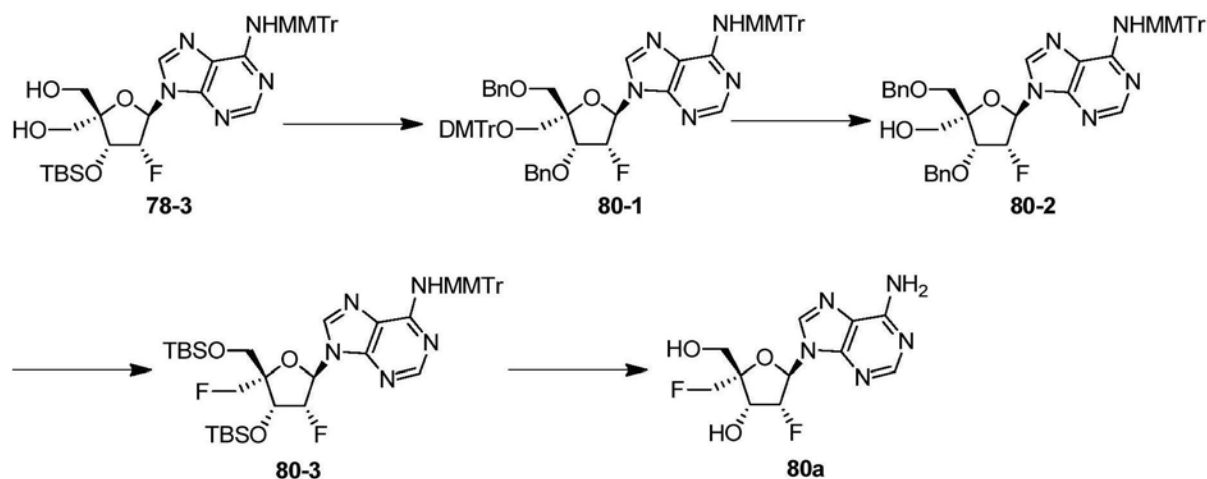
[0816] (79-3) 的制备:在氢气环境下,在 R. T. 下向 79-2 (440mg, 0.48mmol) 的 MeOH (8mL) 溶液加入 Pd/C (500mg, 10%)。将混合物在 R. T. 下搅拌 1.5h。将混合物过滤,并将滤液浓缩至干燥。将粗 79-3 (365mg, 83%) 用于下一步而不进一步纯化。

[0817] (79a) 的制备:将 79-3 (365mg, 0.40mmol) 的 MeOH (50mL) 加入 NH_4F (5.6g, 0.15mmol), 并将溶液加热至回流过夜。通过 LCMS 确定反应的完成。将混合物过滤,并将滤液浓缩至干燥。在硅胶柱上 ($\text{PE}:\text{EA} = 3:1$) 纯化剩余物以产生白色固体形式的胺保护的衍生物 (173mg, 77%)。将胺保护的衍生物 (100mg, 0.18mmol) 的甲酸 (4.4mL) 在 25°C 下搅拌过夜。将溶液浓缩至干燥,并在硅胶柱上 ($\text{PE}:\text{EA} = 1:3$) 纯化剩余物以产生白色固体形式的 79a (40mg, 90%)。 ^1H NMR (400MHz, CD_3OD) δ 8.25 (s, 1H), 8.09 (s, 1H), 6.14 (dd, $J = 6.0, 12.8\text{Hz}$, 1H), 5.58 (m, 1H), 4.45-4.48 (m, 1H), 3.60 (q, 2H), 1.66-1.74 (m, 2H), 0.88 (t, 3H); ESI-MS: m/z 297.9 $[\text{M}+\text{H}]^+$ 。

[0818] 实施例 77

[0819] 化合物 (80a) 的制备

[0820]



[0821] (80-1) 的制备:在氮气下,在 0°C 下,向 78-3 (4.4g, 6.4mmol) 的无水吡啶 (5mL) 和 DCM (25mL) 溶液滴加 DMTrCl (2.37g, 7.04mmol) 的 DCM (5mL) 溶液。在 2h 后,使用 CH_3OH 淬灭反应并浓缩至干燥。在硅胶柱上 ($\text{PE}:\text{EA} = 100:1$ 至 $2:1$) 纯化剩余物以获得 DMTr 保护的衍生物 (4.3g, 68%)。在 25°C 下,将 DMTr 保护的衍生物 (2.2g, 2.5mmol) 的 1M TBAF (2.5mL) 的 THF (2.5mL) 溶液搅拌 3h。真空去除溶剂,并通过柱层析 ($\text{PE}/\text{EA} = 50:1$ 至 $1:2$) 纯化剩余物以产生二醇衍生物 (1.86g, 96%)。在 0°C 下,向二醇衍生物 (1.3g, 1.5mmol) 的无水 THF (5mL) 溶液加入 NaH (132mg, 3.3mmol)。将混合物搅拌 1h, 并加入 TBI (276mg, 0.75mmol)

和 BnBr (558mg, 3.3mmol)。将混合物在 25℃ 下搅拌 10h。使用水淬灭反应, 并将溶剂蒸发。使用 EA 和盐水萃取混合物。在 Na₂SO₄ 上干燥有机层并蒸发以产生粗产物。通过硅胶 (PE/EA = 100:1 至 3:1) 纯化产物以产生白色泡沫形式的 80-1 (1.4g, 90%)。

[0822] (80-2) 的制备: 在 -78℃ 下, 向 80-1 (1.3g, 1.23mmol) 的无水 DCM (17mL) 溶液加入 Cl₂CHCOOH (1.57g, 12.3mmol)。将混合物在 -20-10℃ 下搅拌 40mins。使用饱和 NaHCO₃ 淬灭反应, 并使用 DCM (50mL) 稀释。使用盐水洗涤混合物, 并在 Na₂SO₄ 上干燥有机溶液并真空浓缩。在硅胶柱上 (PE/EA = 100:1 至 1:1) 纯化剩余物以产生白色泡沫形式的 80-2 (652mg, 70%)。

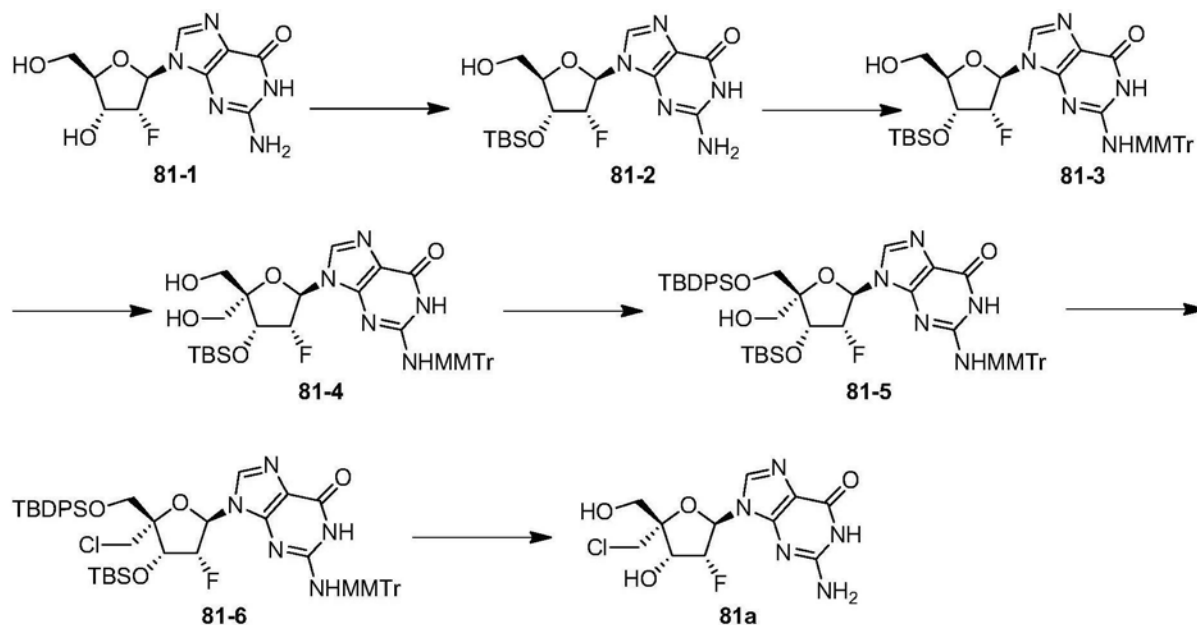
[0823] (80-3) 的制备: 在 -78℃ 下, 向 80-2 (630mg, 0.84mmol) 的无水 DCM (5mL) 溶液加入 DAST (1.35g, 8.4mmol)。将混合物逐渐升温至 0℃。使用饱和 NaHCO₃ 淬灭反应。使用 DCM (50mL) 稀释混合物并使用盐水洗涤。在 Na₂SO₄ 上干燥有机溶液并真空浓缩。在硅胶柱上 (PE/EA = 100:1 至 2:1) 纯化剩余物以产生白色固体形式的 80-3 (302mg, 48%)。

[0824] (80a) 的制备: 在 40psi H₂ 下, 将 80-3 (210mg, 0.28mmol) 和 Pd(OH)₂ (200mg) 的甲醇 (3mL) 混合物在 0℃ 下搅拌 20h。将 Pd(OH)₂ 滤除, 并将滤液浓缩至干燥。通过柱 (DCM/MeOH = 10:1) 纯化剩余物以产生 80a (12mg)。¹H NMR (400MHz, CD₃OD) δ 8.33 (s, 1H), 8.20 (s, 1H), 6.33 (dd, J = 6.0、13.2Hz, 1H), 5.79 (t, J = 5.6Hz, 1H), 5.66 (t, J = 5.2Hz, 1H), 4.52-4.80 (m, 3H), 3.80-3.82 (m, 2H)。ESI-MS :m/z 302.0 [M+H]⁺。

[0825] 实施例 78

[0826] 化合物 (81a) 的制备

[0827]



[0828] (81-2) 的制备: 在 25℃ 下, 向 81-1 (20.0g, 70.2mmol) 的无水吡啶 (200mL) 溶液加入咪唑 (19.1g, 280mmol) 和 TBSCl (42.1g, 281mmol)。将溶液在 25℃ 下搅拌 15h, 然后在减压下浓缩至干燥。将剩余物溶于 EtOAc 然后过滤。将滤液浓缩至干燥以产生 TBS 保护的衍生物 (36.4g, 99%)。将 TBS 保护的衍生物 (36.5g, 71.1mmol) 溶于 THF (150mL)。加入 H₂O (100mL), 然后加入 AcOH (300mL)。将溶液在 80℃ 下搅拌 13h。将反应冷却至 R. T., 然后

在减压下浓缩至干燥以产生白色固体形式的 81-2 (31.2g, 61%)。

[0829] (81-3) 的制备: 向 81-2 (31.2g, 78.2mmol) 的无水吡啶 (300mL) 溶液加入 Ac_2O (11.9g, 117.3mmol)。将混合物在 25°C 下搅拌 18h。加入 MMTrCl (72.3g, 234.6mmol) 和 AgNO_3 (39.9g, 234.6mmol), 并将溶液在 25°C 下搅拌 15h。加入 H_2O 以淬灭反应并在减压下将溶液浓缩至干燥。将剩余物溶于 EtOAc 并使用水洗涤。在 Na_2SO_4 上干燥有机层并过滤。真空浓缩滤液以产生剩余物, 通过硅胶 ($\text{DCM}:\text{MeOH} = 200:1$ 至 $50:1$) 将其纯化以产生 MMTr 保护的胺衍生物 (35.2g, 63%)。将 MMTr 保护的胺衍生物 (35.2g, 49.3mmol) 溶于 NH_3/MeOH (300mL)。将混合物在 25°C 下搅拌 20h。将溶液蒸发至干燥, 并通过硅胶柱 ($\text{DCM}:\text{MeOH} = 100:1$ 至 $50:1$) 纯化以产生黄色固体形式的 81-3 (28.6g, 87%)。

[0830] (81-4) 的制备: 在 0°C 下, 向 81-3 (12.0g, 17.9mmol) 的无水 DCM (200mL) 溶液加入戴斯-马丁氧化剂 (11.3g, 26.8mmol)。将混合物在 0°C 下搅拌 2h, 然后在 R.T. 下搅拌 2h。使用饱和 NaHCO_3 和 $\text{Na}_2\text{S}_2\text{O}_3$ 溶液淬灭混合物。使用盐水洗涤有机层 (2×) 并在无水 Na_2SO_4 上干燥。将溶剂蒸发以产生醛 (12.6g), 将其直接用于下一步。向醛 (12.6g, 18.0mmol) 的 1,4-二氧六环 (120mL) 溶液加入 37% HCHO (11.6g, 144mmol) 和 2N NaOH 水溶液 (13.5mL, 27mmol)。将混合物在 25°C 下搅拌过夜。加入 EtOH (60mL) 和 NaBH_4 (10.9g, 288mmol), 并将反应搅拌 30mins。使用饱和 NH_4Cl 水溶液淬灭混合物, 然后使用 EA 萃取。在 Na_2SO_4 上干燥有机层并通过硅胶柱层析 ($\text{DCM}:\text{MeOH} = 200:1$ 至 $50:1$) 纯化以产生黄色固体形式的 81-4 (7.5g, 59%)。

[0831] (81-5) 的制备: 在 0°C 下, 向 81-4 (3.8g, 5.4mmol) 的 DCM (40mL) 溶液加入吡啶 (10mL) 和 DMTrCl (1.8g, 5.4mmol)。将溶液在 25°C 下搅拌 1h。加入 MeOH (15mL), 并将溶液浓缩。通过硅胶柱层析 ($\text{DCM}:\text{MeOH} = 200:1$ 至 $50:1$) 纯化剩余物以产生黄色固体形式的 MMTr 保护的衍生物 (3.6g, 66%)。向 MMTr 保护的衍生物 (3.6g, 3.6mmol) 的无水吡啶 (30mL) 溶液加入 TBDPSCl (2.96g, 10.8mmol) 和 AgNO_3 (1.84g, 10.8mmol)。将混合物在 25°C 下搅拌 15h。将混合物过滤并浓缩。将混合物溶于 EtOAc 并使用盐水洗涤。在 Na_2SO_4 上干燥有机层, 然后通过硅胶柱层析 ($\text{DCM}:\text{MeOH} = 200:1$ 至 $50:1$) 纯化以产生固体形式的 TBDPS 保护的衍生物 (3.8g, 85.1%)。向 TBDPS 保护的衍生物 (3.6g, 2.9mmol) 的无水 DCM (50mL) 溶液加入 Cl_2CHCOOH (1.8mL) 的无水 DCM (18mL)。将混合物在 -78°C 下搅拌 1h。在 -78°C 下加入 Cl_2CHCOOH (3.6mL)。将混合物在 -10°C 下搅拌 30mins。使用饱和 NaHCO_3 水溶液淬灭混合物并使用 DCM 萃取。在 Na_2SO_4 上干燥有机层, 然后通过硅胶柱层析 ($\text{DCM}:\text{MeOH} = 200:1$ 至 $50:1$) 纯化以产生 81-5 (2.2g, 80%)。

[0832] (81-6) 的制备: 向冰冷的 81-5 (800mg, 0.85mmol) 的无水 DCM (20mL) 溶液滴加吡啶 (336mg, 4.25mmol) 和 Tf_2O (360mg, 1.28mmol)。将反应混合物在 0°C 下搅拌 15mins。通过冰水淬灭反应并搅拌 30mins。使用 EtOAc 萃取混合物, 使用盐水洗涤 (50mL) 并在 MgSO_4 上干燥。将溶剂蒸发以产生粗双(三氟甲磺酸酯)衍生物。向双(三氟甲磺酸酯)衍生物 (790mg, 0.73mmol) 的无水 DMF (35mL) 加入 LiCl (302mg, 7.19mmol)。将混合物加热至 40°C 并搅拌过夜。通过 LCMS 确定反应的完成。使用盐水洗涤溶液并使用 EtOAc 萃取。在 MgSO_4 上干燥合并的有机层, 并在硅胶柱上 ($\text{DCM}/\text{MeOH} = 100:1$) 纯化剩余物以产生 81-6 (430mg, 61%)。

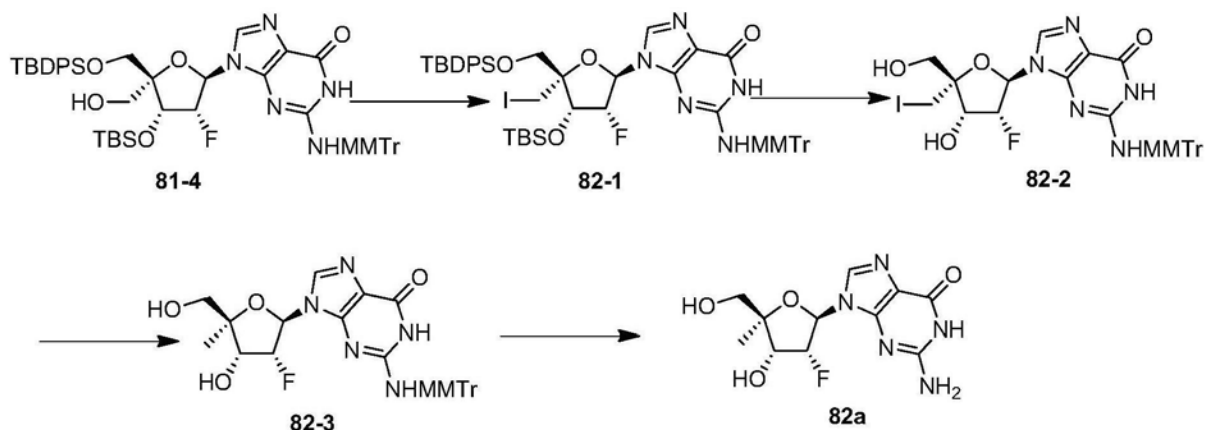
[0833] (81a) 的制备: 向 81-6 (470mg, 0.49mmol) 的 MeOH (85mL) 加入 NH_4F (8.1g, 5.92mmol), 并将溶液加热至回流过夜。将混合物过滤, 并将滤液浓缩至干燥。在

硅胶柱上 (DCM/MeOH = 20:1) 纯化剩余物以产生白色固体形式的二醇 (250mg, 84%)。将二醇 (130mg, 0.21mmol) 的甲酸 (5mL) 在 25℃ 下搅拌过夜。将溶液浓缩至干燥, 并将剩余物的 MeOH (30mL) 在 70℃ 下搅拌过夜。通过 LCMS 和 HPLC 确定反应的完成。将溶剂去除, 并使用 EtOAc 洗涤粗产物以产生白色固体形式的 81a (58mg, 81%)。¹H NMR (DMSO-d₆, 400MHz) δ 10.73 (br, 1H), 7.98 (s, 1H), 6.58 (br, 2H), 6.08 (q, J = 4.8, 9.2Hz, 2H), 5.64 (dt, J = 5.6, 52.8Hz, 1H), 5.40 (m, 1H), 4.52 (m, 1H), 3.80-3.82 (m, 2H), 3.64 (q, 2H)。ESI-MS :m/z 333.8 [M+H]⁺, 666.6 [2M+H]⁺。

[0834] 实施例 79

[0835] 化合物 (82a) 的制备

[0836]



[0837] (82-1) 的制备: 在 0℃ 下, 向 81-4 (310mg, 0.33mmol) 的无水 DCM (10mL) 溶液滴加吡啶 (130mg, 1.65mmol) 和通过 DCM 稀释的 Tf₂O (139mg, 0.49mmol)。将混合物在 0℃ 下搅拌 15mins。使用冰冷的水淬灭反应。将有机层分离并使用盐水洗涤。在 Na₂SO₄ 上干燥有机层并蒸发以产生三氟甲磺酸酯衍生物 (420mg 粗物质), 将其直接用于下一步。向三氟甲磺酸酯衍生物 (420mg 粗物质) 的无水戊-2-酮溶液加入 NaI (396mg, 2.64mmol)。将混合物在 40℃ 下搅拌 3H, 然后使用 EtOAc 溶解。使用 Na₂S₂O₃ 将有机层洗涤两次并使用盐水洗涤。在 Na₂SO₄ 上干燥有机层并蒸发以产生剩余物。通过柱 (DCM:MeOH = 300:1 至 100:1) 纯化剩余物以产生 82-1 (195mg, 两步的产率为 56%)。

[0838] (82-2) 的制备: 向 82-1 (650mg, 0.62mmol) 的 MeOH (10mL) 溶液加入 NH₄F (45.8g, 12.4mmol)。将混合物回流过夜。将混合物过滤并蒸发至干燥。在硅胶柱上 (DCM/MeOH = 200:1 至 20:1) 纯化剩余物以产生 82-2 (250mg, 58%)。

[0839] (82-3) 的制备: 向搅拌的 82-2 (300mg, 0.43mmol)、Et₃N (217mg, 2.15mmol) 的无水 MeOH (10mL) 溶液加入 10% Pd/C (50mg)。在 R.T. 下, 将混合物在氢化装置 (30psi 氢气) 中搅拌过夜。将催化剂滤除, 并将滤液蒸发以产生剩余物。在硅胶柱上 (DCM/MeOH = 200:1 至 20:1) 纯化剩余物以产生白色固体形式的 82-3 (180mg, 73%)。

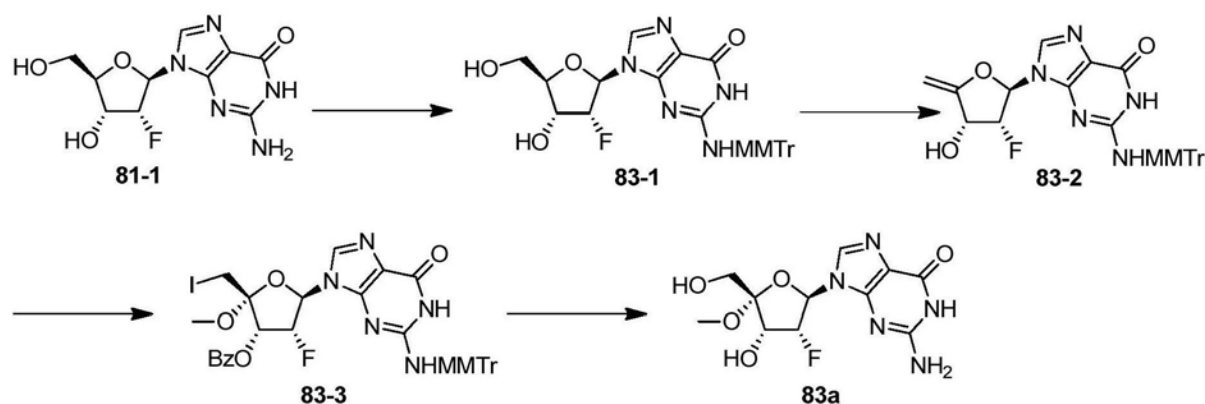
[0840] (82a) 的制备: 在 25℃ 下, 将 82-3 (110mg, 0.19mmol) 溶于 HCOOH (18g) 和 H₂O (6g), 并搅拌 1h。将溶液蒸发至干燥, 溶于 MeOH (30mL)。将混合物在 60℃ 下搅拌 12h。将溶液蒸发至干燥, 并溶于 EtOAc (50mL)。将混合物在 60℃ 下搅拌 1h。将混合物过滤并使用 EtOAc 洗涤以产生白色固体形式的 82a (45.3mg, 80%)。¹H NMR (400MHz, MeOD) δ 8.00 (s, 1H), 6.11-6.15 (m, 1H), 5.35-5.50 (m, 1H), 4.53-4.59 (m, 1H), 3.54-3.64 (m, 2H), 1.26 (s, 3H)。ESI-MS :

m/z 299.76 $[M+1]^+$, 598.66 $[2M+1]^+$ 。

[0841] 实施例 80

[0842] 化合物 (83a) 的制备

[0843]



[0844] (83-1) 的制备: 使用吡啶将 81-1 (5.7g, 20mmol) 共蒸发三次, 然后溶于吡啶 (20mL)。将混合物冷却至 0℃ 并滴加 Ac_2O (5.8mL, 60mmol)。将混合物在 25℃ 下搅拌 10h, 然后冷却至 0℃。分批加入 AgNO_3 (8.5g, 50mmol), 然后加入 MMTrCl (15.5g, 50mmol)。将混合物在 25℃ 下搅拌 10h。使用饱和 NaHCO_3 淬灭反应并使用 EA 萃取。在 Na_2SO_4 上干燥有机层并浓缩。通过硅胶柱层析 ($\text{DCM}/\text{MeOH} = 100:1$ 至 $50:1$) 纯化剩余物以产生淡黄色固体形式的 Ac 保护的衍生物 (12.1g, 93%)。将 Ac 保护的衍生物 (12.1g) 溶于甲醇 NH_3 (饱和的)。将混合物在 25℃ 下搅拌 14h。将溶剂去除, 并在硅胶柱上 ($\text{DCM}/\text{MeOH} = 80:1$ 至 $30:1$) 纯化剩余物以产生 83-1 (9.2g, 87%)。

[0845] (83-2) 的制备: 向搅拌的 83-1 (9.2g, 16.5mmol) 的干燥 THF (300mL) 溶液加入咪唑 (9.0g, 132mmol) 和 PPh_3 (34.8g, 132mmol)。在 0℃ 下, 在 N_2 下, 滴加 I_2 (26.0g, 103mmol) 的 THF (100mL) 溶液。将混合物在 25℃ 下搅拌 18h, 然后使用 $\text{Na}_2\text{S}_2\text{O}_3$ 溶液淬灭。使用 EtOAc 萃取混合物。在 Na_2SO_4 上干燥有机层并浓缩。在硅胶柱上 ($\text{DCM}/\text{MeOH} = 80:1$ 至 $30:1$) 纯化剩余物以产生淡黄色固体形式的碘化物衍生物 (10.3g, 93%)。向搅拌的碘化物衍生物 (10.2g, 15.3mmol) 的干燥 THF (300mL) 溶液加入 DBU (4.7g, 30.1mmol)。将混合物在 60℃ 下搅拌 8h。使用 NaHCO_3 溶液稀释溶液并使用 EtOAc 萃取。在 Na_2SO_4 上干燥有机层并浓缩。在硅胶柱上 ($\text{PE}/\text{EtOAc} = 3:1$ 至 $1:3$) 纯化剩余物以产生 83-2 (6.2g, 产率 76%)。

[0846] (83-3) 的制备: 向搅拌的 83-2 (5.42g, 10mmol) 的无水 CH_3OH (100mL) 溶液加入 PbCO_3 (13.7g, 53.1mmol)。在 0℃ 下, 滴加 I_2 (12.3g, 48.9mmol) 的 CH_3OH (300mL) 溶液。将混合物在 25℃ 下搅拌 10h。使用 $\text{Na}_2\text{S}_2\text{O}_3$ 溶液淬灭溶液并使用 DCM 萃取。使用 NaHCO_3 溶液洗涤有机层, 在 Na_2SO_4 上干燥并浓缩以产生剩余物。通过 HPLC (0.1% HCOOH 的水和 MeCN) 纯化剩余物以产生目标甲氧基衍生物 (2.4g, 34%)。在 0℃ 下, 向搅拌的甲氧基衍生物 (2.4g, 3.4mmol) 的干燥吡啶 (20mL) 溶液滴加 BzCl (723mg, 5.2mmol)。将混合物在 0℃ 下搅拌 1h。使用 NaHCO_3 溶液淬灭溶液并使用 EtOAc 萃取。在 Na_2SO_4 上干燥有机层并浓缩。通过硅胶柱 ($\text{PE}/\text{EtOAc} = 5:1$ 至 $1:1$) 纯化产生白色固体形式的 83-3 (2.1g, 77%)。

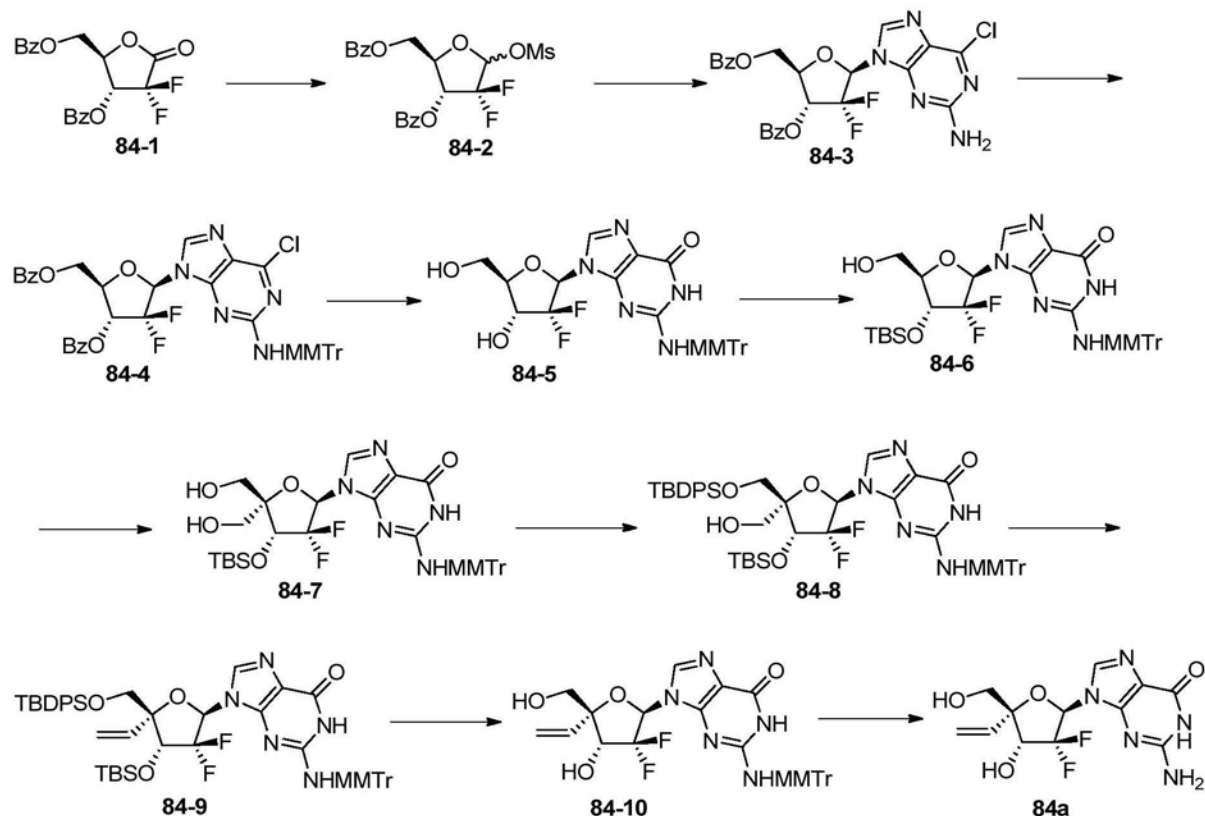
[0847] (83a) 的制备: 将 83-3 (2.0g, 2.5mmol)、 BzONa (3.6g, 25mmol) 和 15-冠-5 (5.5g, 25mmol) 悬浮于 DMF (50mL)。将混合物在 110-125℃ 下搅拌 5 天。通过过滤

去除沉淀,并使用 EA 稀释滤液。使用盐水洗涤溶液并在 Na_2SO_4 上干燥。将溶剂去除,并在硅胶柱上 ($\text{PE}/\text{EA} = 10/1$ 至 $2/1$) 纯化剩余物以产生粗 Bz 保护的衍生物 (1.6g, 80%)。将 Bz 保护的衍生物 (1.6g, 2.0mmol) 溶于甲醇铵 (100mL),并将混合物在 25°C 下搅拌 20h。将溶剂去除,并通过硅胶柱 ($\text{DCM}/\text{MeOH} = 100:1$ 至 $20:1$) 纯化剩余物以产生白色固体形式的二醇衍生物 (410mg, 35%)。在 25°C 下,将二醇衍生物 (200mg, 0.34mmol) 溶于 HCOOH (24g) 和 H_2O (6g),并将混合物在 25°C 下搅拌 1h。将溶液蒸发至干燥,并溶于 MeOH (30mL)。将混合物在 60°C 下搅拌 12h。将溶液蒸发至干燥并溶于 EtOAc (50mL)。将混合物在 60°C 下搅拌 1h。然后,将混合物过滤并使用 EtOAc 洗涤以产生白色固体形式的 83a (46.1mg, 43%)。 ^1H NMR (CD_3OD , 400MHz) δ 7.92 (s, 1H), 6.22 (dd, $J = 1.6, 18.8\text{Hz}$, 1H), 5.17–5.32 (m, 1H), 4.89–4.91 (m, 1H), 3.77 (m, 2H), 3.44 (s, 3H)。ESI-MS : m/z 316.1 $[\text{M}+\text{H}]^+$ 。

[0848] 实施例 81

[0849] 化合物 (84a) 的制备

[0850]



[0851] (84-2) 的制备:在 N_2 下,在 -78°C 下向搅拌的 84-1 (100.0g, 265.9mmol) 的干燥 THF (1000mL) 溶液加入 $\text{Li}(\text{O}-t\text{-Bu})_3\text{AlH}$ (318.9mL, 318.9mmol)。将混合物在 -78°C 下搅拌 1h,然后在 R.T 下搅拌 1h。将反应混合物冷却至 -50°C 并使用冰和饱和 NH_4Cl 溶液淬灭。使用 EtOAc 萃取混合物。在 Na_2SO_4 上干燥有机层并浓缩以产生白色固体形式的 1'-OH 衍生物 (100.5g)。在 0°C 下,向搅拌的 1'-OH 衍生物 (100.5g, 265.9mmol) 的干燥 DCM (600mL) 溶液滴加 NEt_3 (110mL) 和 MsCl (45.5g, 298.0mmol)。将混合物在 R.T. 下搅拌 2h。在 0°C 下使用冰水淬灭混合物并使用 DCM 萃取。在 Na_2SO_4 上干燥有机层,浓缩并在硅胶柱上 ($\text{PE}:\text{EA} = 50:1$ 至 $5:1$) 纯化以产生白色固体形式的 84-2 (113.4g, 产率:93.9%)。

[0852] (84-3) 的制备:向化合物 6-氯-9H-嘌呤-2-胺 (70.1g, 414.7mmol)、HMDS (480mL)

和 $(\text{NH}_4)_2\text{SO}_4$ (0.8g) 的悬浮液加入干燥的 DCE (400mL)。在 N_2 下将混合物回流 18h, 然后冷却至 R. T. 向甲硅烷基化 2-氨基-6-氯嘌呤溶液加入 84-2 (78.0g, 171.1mmol) 和 TMSOTf (60mL, 331.9mmol)。将混合物回流过夜, 浓缩并使用 NaHCO_3 溶液中和。将生成的沉淀过滤, 并使用 EtOAc 萃取滤液。在 Na_2SO_4 上干燥有机层并浓缩。在硅胶柱上 (PE:EA = 5:1 至 2:1) 层析产生淡黄色固体形式的 84-3 (10.8g, 产率: 11.9%)。

[0853] (84-4) 的制备: 向 84-3 (30.0g, 56.6mmol) 的 DCM (300mL) 悬浮液加入 MMTrCl (34.9g, 113.2mmol) 和 AgNO_3 (19.3g, 113.2mmol)。将反应混合物冷却至 0°C , 并加入三甲吡啶 (18.0g, 150mmol)。将生成的悬浮液在 R. T. 下搅拌 12h。将悬浮液过滤。使用 DCM 萃取滤液并使用 NaHCO_3 溶液洗涤。在 Na_2SO_4 上干燥有机层并浓缩。通过硅胶柱 (PE:EA = 20:1 至 3:1) 纯化以产生淡黄色固体形式的 84-4 (35.0g, 产率: 77.9%)。 ^1H NMR (CDCl_3 , 400MHz) δ 7.94–7.96 (m, 4H), 7.05–7.58 (m, 18H), 6.62–6.67 (m, 2H), 6.55 (dd, $J = 6.0\text{Hz}$, $J = 9.6\text{Hz}$, 1H), 5.60–5.66 (m, 1H), 4.69–4.76 (m, 2H), 4.55–4.58 (m, 1H), 3.64 (s, 1H)。ESI-MS: m/z 802 $[\text{M}+\text{H}]^+$ 。

[0854] (84-5) 的制备: 向搅拌的 84-4 (35.0g, 43.6mmol) 的干燥 MeOH (400mL) 溶液加入 NaOMe (23.5g, 436mmol) 和 2-巯基-乙醇 (30.6g, 392.4mmol)。将混合物回流过夜。使用 CO_2 将 pH 调整至 9–10。将沉淀过滤, 并将滤液浓缩。在硅胶柱上 (PE:EA = 10:1 至 1:1) 纯化产生淡黄色固体形式的纯 84-5 (24.0g, 产率 95.7%)。

[0855] (84-6) 的制备: 在 0°C 下, 向 84-5 (24.0g, 41.7mmol) 的吡啶 (250mL) 溶液加入 DMTrCl (28.2g, 83.5mmol)。将溶液在 R. T. 下搅拌 15h。加入 MeOH (50mL), 并在减压下将混合物浓缩至干燥。将剩余物溶于 EtOAc 并使用水洗涤。在 Na_2SO_4 上干燥有机层、过滤、浓缩并通过硅胶柱 (DCM:MeOH = 200:1 至 50:1) 纯化以产生黄色固体形式的第一中间体 (27.6g)。向第一中间体 (27.6g, 31.5mmol) 的 DCM (200mL) 溶液加入咪唑 (4.3g, 63mmol) 和 TBSCl (9.5g, 63mmol)。将混合物在 R. T. 下搅拌 12h。使用 NaHCO_3 和盐水洗涤溶液。在 Na_2SO_4 上干燥有机层, 过滤, 浓缩并通过硅胶柱 (DCM:MeOH = 200:1 至 100:1) 纯化以产生黄色固体形式的第二中间体 (30.2g)。向第二中间体 (30.2g, 30.4mmol) 的无水 DCM (50mL) 溶液加入 Cl_2CHCOOH (20ml) 的无水 DCM (500mL)。将混合物在 -78°C 下搅拌 1h。在 -78°C 下, 加入 Cl_2CHCOOH (30mL)。将混合物在 -20°C 下搅拌 2h。使用饱和 NaHCO_3 水溶液淬灭混合物并使用 DCM 萃取。在 Na_2SO_4 上干燥有机层, 然后通过硅胶柱 (DCM:MeOH = 200:1 至 30:1) 纯化以产生白色固体形式的 84-6 (18.0g, 62.5%)。 ^1H NMR (400MHz, MeOD) δ 8.27 (s, 1H), 7.16–7.38 (m, 12H), 6.79–6.83 (m, 2H), 6.42 (dd, $J = 4.4\text{Hz}$, $J = 10.0\text{Hz}$, 1H), 4.54–4.62 (m, 1H), 3.92 (d, $J = 8.8\text{Hz}$, 2H), 3.74 (s, 3H), 3.70–3.72 (m, 1H), 0.92 (s, 9H), 0.11–0.13 (m, 6H)。ESI-LCMS: m/z 690.0 $[\text{M}+\text{H}]^+$ 。

[0856] (84-7) 的制备: 在 0°C 下, 将 84-6 (7.0g, 10.0mmol) 加入至 DMP (10.6g, 25mmol) 的无水 CH_2Cl_2 (100mL) 悬浮液。将混合物在 25°C 下搅拌 2h。真空去除溶剂, 并使用乙醚 (100mL) 研磨剩余物。通过 MgSO_4 垫过滤混合物。使用等体积的 $\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$ 的 100mL 的饱和 NaHCO_3 搅拌有机溶剂直至有机层变澄清 (10min)。将有机层分离, 使用盐水洗涤, 并在 MgSO_4 上干燥。真空去除溶剂以产生红色固体形式的第三中间体 (6.5g, 95%)。向第三中间体 (6.5g, 9.5mmol) 的 1,4-二氧六环 (80mL) 溶液加入 37% CH_2O (6.0mL, 60mmol) 和 2N NaOH 水溶液 (9.5mL, 19mmol)。将混合物在 25°C 下搅拌 2h, 然后使用 AcOH 中和至 pH 7。加

入 EtOH(30mL) 和 NaBH₄(3.8g, 100mmol), 并将混合物搅拌 30mins。使用饱和 NH₄Cl 水溶液淬灭混合物, 然后使用 EA 萃取。在 Na₂SO₄ 上干燥有机层。通过硅胶柱 (DCM:MeOH = 200:1 至 30:1) 纯化产生黄色固体形式的 84-7(4.2g, 58.3%)。

[0857] (84-8) 的制备: 在 -20℃ 下, 向 84-7(4.2g, 5.8mmol) 的 DCM(50mL) 溶液加入吡啶 (5mL) 和 DMTrCl(1.9g, 5.8mmol)。将溶液在 0℃ 下搅拌 2h。使用 MeOH(15mL) 处理反应混合物, 然后浓缩。通过硅胶柱 (DCM:MeOH = 200:1 至 50:1) 纯化剩余物以产生黄色固体形式的第四中间体 (1.3g)。向第四中间体 (1.3g, 1.3mmol) 的无水吡啶 (15mL) 溶液加入 TBDPSCl(1.1g, 3.9mmol) 和 AgNO₃(0.68g, 4.0mmol)。将混合物在 25℃ 下搅拌 15h。将混合物过滤, 浓缩, 溶于 EtOAc 并使用盐水洗涤。在 Na₂SO₄ 上干燥有机层。通过硅胶柱 (DCM:MeOH = 200:1 至 100:1) 纯化产生固体形式的第五中间体 (1.4g)。向第五中间体 (1.4g, 1.1mmol) 的无水 DCM(50mL) 溶液加入 Cl₂CHCOOH(0.7mL) 的无水 DCM(18mL)。将混合物在 -78℃ 下搅拌 1h。在 -78℃ 下加入 Cl₂CHCOOH(1.5mL), 并将混合物在 -20℃ 下搅拌 1.5h。使用饱和 NaHCO₃ 水溶液淬灭混合物并使用 DCM 萃取。在 Na₂SO₄ 上干燥有机层。通过硅胶柱 (DCM:MeOH = 200:1 至 50:1) 纯化产生白色固体形式的 84-8(650mg, 11.6%)。

[0858] (84-9) 的制备: 在 N₂ 下, 在 10℃ 下向吡啶 (521mg, 6.59mmol) 的无水 DMSO(5mL) 溶液滴加 TFA(636mg, 5.58mmol)。将混合物搅拌直至形成澄清溶液。在 N₂ 下, 在 R.T. 下向该溶液 (0.8mL) 加入 84-8(650mg, 0.68mmol) 和 DCC(410mg, 2.0mmol) 的无水 DMSO(5mL) 混合物。将混合物在 20℃ 下搅拌过夜。加入水 (30mL)。使用 DCM(30mL) 稀释混合物并过滤。使用 DCM 萃取滤液。使用饱和 NaHCO₃ 水溶液洗涤有机层, 在 Na₂SO₄ 上干燥并真空浓缩。在硅胶柱上 (PE:EA = 10:1 至 1:1) 纯化粗产物以产生黄色固体形式的第六中间体 (600mg)。在 -78℃ 下, 在 1min 内向搅拌的甲基-三苯基-溴化磷 (714mg, 2.0mmol) 的无水 THF(5mL) 溶液滴加 n-BuLi (0.8mL, 2.0mmol, 2.5M 的 THF)。将搅拌在 0℃ 下继续 1h。将第六中间体 (600mg, 0.63mmol) 加入至混合物, 并将混合物在 25℃ 下搅拌 15h。使用饱和 NH₄Cl(20mL) 淬灭反应并使用 EtOAc 萃取。使用 Na₂SO₄ 干燥合并的有机相, 过滤并蒸发至干燥以产生淡黄色油状物。通过柱层析 (DCM:MeOH = 200:1 至 50:1) 纯化油状物以产生黄色固体形式的 84-9(250mg, 38.5%)。

[0859] (84-10) 的制备: 将 84-9(250mg, 0.26mmol) 溶于 THF(5.0mL)。在 20℃ 下加入 TBAF(131mg, 0.5mmol), 并将搅拌继续 2h。将溶液蒸发至干燥。将剩余物溶于 EA(50mL) 并使用水 (2×) 洗涤。将溶液蒸发至干燥, 并通过硅胶柱 (PE:EA = 10:1 至 1:2) 纯化以产生白色固体形式的 84-10(57.6mg, 36.9%)。¹H NMR(400MHz, MeOD) δ 8.34(s, 1H), 7.15-7.38(m, 12H), 6.79-6.82(m, 2H), 6.44(dd, J = 2.0Hz, J = 10.0Hz, 1H), 6.01(dd, J = 11.2Hz, J = 17.6Hz, 1H), 5.51(dd, J = 1.6Hz, J = 17.2Hz, 1H), 5.35(dd, J = 1.6Hz, J = 17.2Hz, 1H), 4.68-4.76(m, 1H), 3.74(s, 3H), 3.63(dd, J = 2.0Hz, J = 12.8Hz, 1H) 3.52(dd, J = 2.0Hz, J = 12.8Hz, 1H)。ESI-LCMS :m/z 602.0[M+H]⁺。

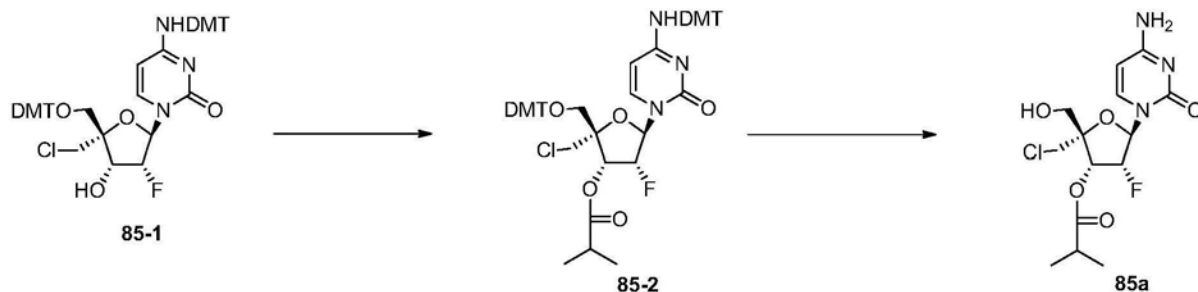
[0860] (84a) 的制备: 将 84-10(27mg) 的 1.5mL 的 80% 甲酸溶液在 R.T. 下放置 4.5h, 然后浓缩至干燥。将剩余物与水混合并冻干。加入 MeOH(1.5mL) 和 TEA(0.1mL), 并将混合物浓缩。将来自 MeOH 和 EtOAc 的沉淀过滤并使用 EtOAc 洗涤以产生轻微-琥珀色固体形式的 84(9.3mg)。¹H NMR(CD₃OD, 400MHz) δ 8.44(s, 1H), 6.57(d, J = 10.8Hz, 1H), 6.05(dd, J = 17.6Hz, 10.8Hz, 1H), 5.45(dd, J = 17.6Hz, J = 1.6Hz, 1H), 5.37(dd, J =

10. 8Hz, 1. 6Hz, 1H), 4. 78(dd, $J = 18. 4\text{Hz}, 17. 2\text{Hz}$, 1H), 3. 67(d, $J = 12. 4\text{Hz}$, 1H), 3. 56(dd, $J = 12. 4\text{Hz}, 2. 0\text{Hz}$, 1H); ESI-MS : m/z 328. 4 $[M-H]^+$ 。

[0861] 实施例 82

[0862] 化合物 (85a) 的制备

[0863]



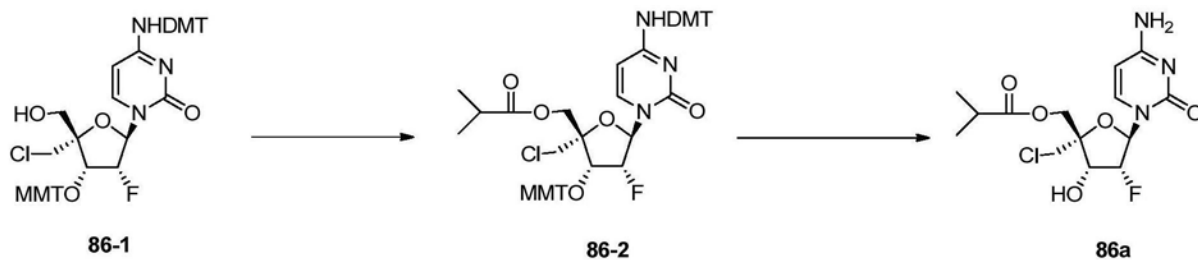
[0864] (85-2) 的制备: 将 85-1 (200mg ; 0. 22mmol) 的吡啶 (2. 5mL) 和异丁酸酐 (44 μ L ; 1. 2 当量) 混合物在 R. T. 下搅拌过夜。将混合物浓缩, 并在 EtOAc (50mL) 和水之间将剩余物分层。使用 1N 柠檬酸、水、饱和 NaHCO_3 水溶液和盐水洗涤有机层。使用 Na_2SO_4 干燥混合物。将溶剂蒸发并在使用己烷 /EtOAc (30 至 100% 梯度) 的二氧化硅柱 (10g 柱) 上纯化剩余物以产生 85-2 (0. 16g, 75%)。

[0865] (85a) 的制备: 将 85-2 (0. 16g ; 0. 16mmol) 的 80% HCOOH 水溶液 (5mL) 在 R. T. 下搅拌 3h。将溶剂蒸发, 然后使用甲苯共蒸发。在使用 $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (4-10% 梯度) 的二氧化硅柱 (10g 柱) 上纯化产生 85a (43mg, 74%)。 $^1\text{H-NMR}$ (DMSO-d_6) : δ 7. 75(d, 1H), 7. 33(d, 2H), 6. 07(dd, 1H), 5. 75(d, 1H), 5. 55(dd, 1H), 5. 43(dt, 1H), 5. 43(t, 1H), 3. 79(dd, 2H), 3. 63(ddd, 2H), 2. 64(单峰, 1H), 1. 12(d, 6H)。MS : $m/z = 362. 1[M+1]^+$ 。

[0866] 实施例 83

[0867] 化合物 (86a) 的制备

[0868]



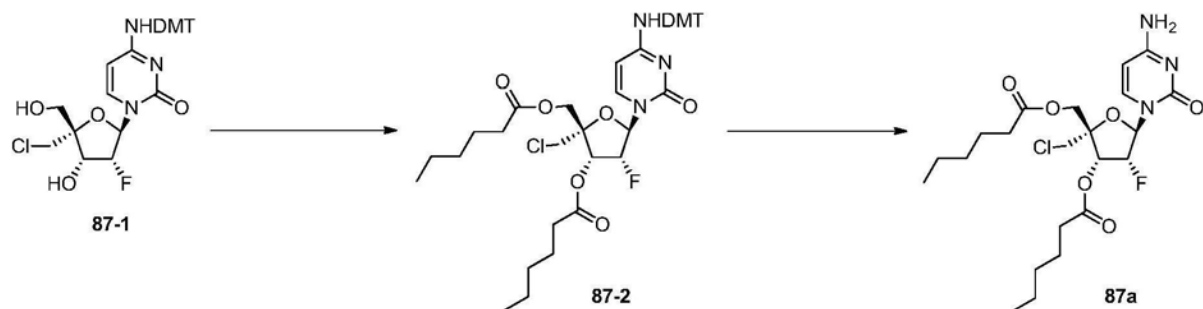
[0869] (86-2) 的制备: 使用下列用于制备 85-2 相似的步骤制备 86-2 : 86-1 (220mg ; 0. 22mmol)、(2. 5mL)、异丁酸酐 (0. 13mL ; 3. 6 当量)、EtOAc (30mL) 和己烷 /EtOAc (30 至 100% 梯度) 以产生 86-2 (175mg, 85%)。

[0870] (86a) 的制备: 使用下列用于制备 85a 相似的步骤制备 86a : 86-2 (117mg ; 0. 13mmol)、80% HCOOH 水溶液 (4mL) 和 $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (4-10% 梯度) 以产生 86a (36mg, 77%)。 $^1\text{H-NMR}$ (DMSO-d_6) : δ 7. 58(d, 1H), 7. 29(d, 2H), 6. 00(s, 1H), 5. 73(d, 1H), 5. 24(ddd, 1H), 4. 55(dd, 1H), 4. 22(dd, 2H), 3. 80(dd, 2H), 2. 58(单峰, 1H), 1. 08, 1. 07(2d, 6H)。MS : $m/z = 364[M+1]^+$ 。

[0871] 实施例 84

[0872] 化合物 (87a) 的制备

[0873]



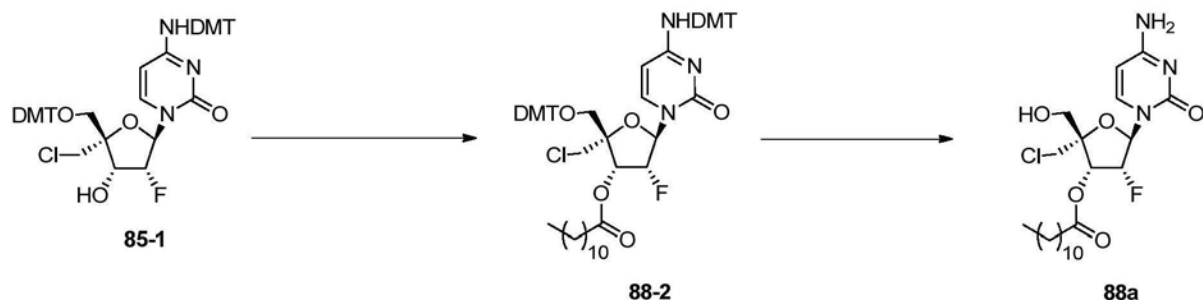
[0874] (87-2) 的制备: 使用下列用于制备 46-2 相似的步骤制备 87-2: 87-1 (178mg, 0.3mmol)、己酸酐 (0.14mL, 2 当量)、吡啶 (3mL) 以产生 87-2 (120mg, 50%)。

[0875] (87a) 的制备: 使用下列用于制备 85a 相似的步骤制备 87a: 87-2 (120mg, 0.15mmol)、80 % HCOOH 水溶液和 CH₂Cl₂/MeOH (4-10 % 梯度) 以产生 87a (62mg, 85%)。¹H-NMR (CDCl₃): δ 8.2 (br, 1H), 7.42 (d, 1H), 6.8 (br, 1H), 6.03 (d, 1H), 5.77 (dd, 1H), 5.64 (dd, 1H), 5.51 (ddd, 1H), 4.43 (dd, 2H), 3.82 (dd, 2H), 2.41 (m, 2H), 2.33 (m, 2H), 1.64 (m, 4H), 1.31 (m, 8H), 0.82 (m, 6H)。MS: m/z = 488 [M-1]。

[0876] 实施例 85

[0877] 化合物 (88a) 的制备

[0878]



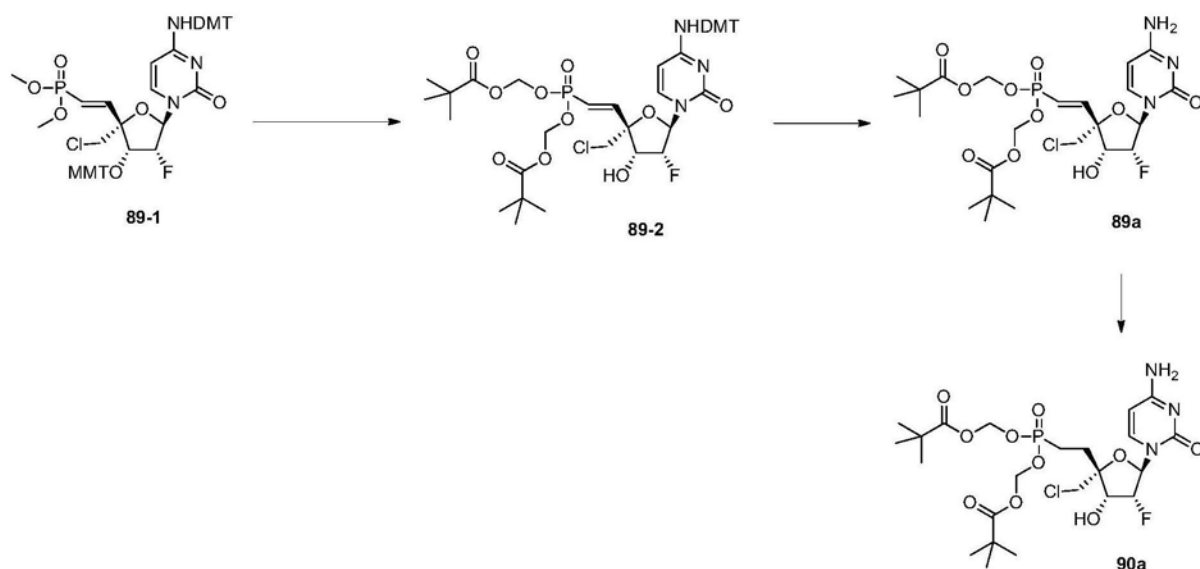
[0879] (88-2) 的制备: 使用下列用于制备 85-2 相似的步骤制备 88-2: 85-1 (220mg; 0.24mmol)、吡啶 (3mL)、十二烷酸酐 (0.12g; 1.3 当量)、EtOAc (50mL) 和己烷 /EtOAc (25% 至 -80% 梯度) 以产生 88-2 (0.22g, 85%)。

[0880] (88a) 的制备: 使用下列用于制备 85a 相似的步骤来制备 88a: 88-2 (0.19g; 0.17mmol)、80 % HCOOH 水溶液 (5mL) 和 CH₂Cl₂/MeOH (4-10 % 梯度), 以产生 88a (66mg, 82%)。¹H-NMR (DMSO-d₆): δ 7.77 (d, 1H), 7.35 (d, 2H), 6.07 (dd, 1H), 5.77 (d, 1H), 5.60 (dd, 1H), 5.55 (ddd, 1H), 5.43 (t, 1H), 3.78 (dd, 2H), 3.65 (ddd, 2H), 2.41 (m, 2H), 1.56 (m, 2H), 1.24 (m, 16H), 0.85 (m, 3H)。MS: m/z = 474 [M-1]。

[0881] 实施例 86

[0882] 化合物 (89a) 和 (90a) 的制备

[0883]



[0884] (89-2) 的制备: 在 0℃ 下, 向 89-1 (175mg; 0.18mmol) 的 MeCN (2.5mL) 溶液加入 TMSBr (0.28mL; 10 当量)。将混合物在 R. T. 下搅拌 1h, 蒸发并使用水处理。将获得的白色固体过滤, 干燥并使用 CH₂Cl₂ 洗涤。然后, 将白色固体溶于 NMP (2mL) 并使用 DIPEA (94 μL; 3 当量) 处理和新戊酰基氧基碘甲烷 (84 μL; 3 当量)。将混合物在 R. T. 下搅拌 1 天, 然后在水 (20mL) 和叔丁基甲基醚 (TBME; 60mL) 之间分层。使用饱和 NaHCO₃ 水溶液、水和盐水洗涤有机层。使用 TBME (2×20mL) 反萃合并的水溶液洗涤物。干燥合并的有机萃取物并在使用 CH₂Cl₂/i-PrOH (2-10% 梯度) 的二氧化硅柱 (10g 柱) 上纯化以产生 89-2 (42mg, 26%)。

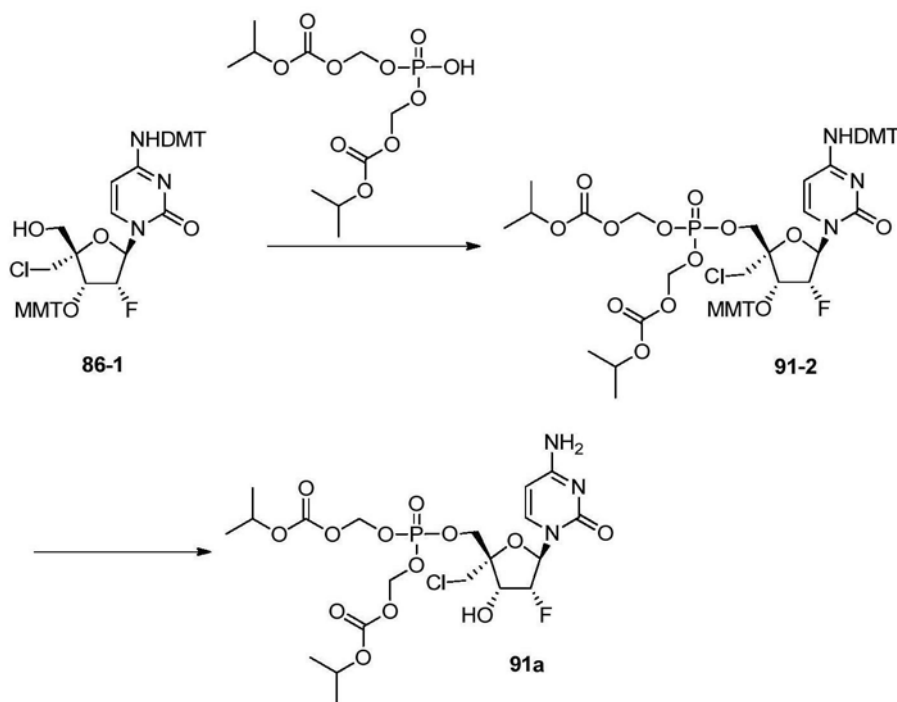
[0885] (89a) 的制备: 将 89-2 的 80% HCOOH 水溶液溶液在 R. T. 下搅拌 3h。将溶剂蒸发, 然后使用甲苯共蒸发。在使用 CH₂Cl₂/MeOH (4-15% 梯度) 的二氧化硅柱 (10g 柱) 上纯化产生 89a (17mg, 74%)。¹H-NMR (CD₃OD): δ 7.47 (d, 1H), 6.28 (dd, 1H), 6.04 (dd, 1H), 5.77-5.71 (m, 2H), 5.53 (m, 4H), 5.18 (ddd, 1H), 5.60 (dd, 1H), 3.77 (dd, 2H), 1.08 (m, 18H)。³¹P-NMR (CD₃OD): δ 17.64。MS: m/z = 598 [M+1]。

[0886] (90a) 的制备: 将 89a (12mg; 0.02mmol) 的 EtOH (1mL) 和 Pd/C (10%; 2.5mg) 混合物在大气压力的氢气下搅拌过夜。通过硅藻土垫过滤混合物。将溶剂蒸发并在 使用 CH₂Cl₂/MeOH (4-17% 梯度) 的二氧化硅柱 (10g 柱) 上纯化产物以产生 90a (6mg, 50%)。¹H-NMR (CD₃OD): δ 7.51 (d, 1H), 5.79 (d, 1H), 5.65-5.54 (m, 5H), 5.20 (ddd, 1H), 5.60 (dd, 1H), 3.70 (dd, 2H), 2.17-2.06 (m, 1H), 2.02-1.87 (m, 3H), 1.13 (m, 18H)。³¹P-NMR (CD₃OD): δ 33.16。MS: m/z = 600 [M+1]。

[0887] 实施例 87

[0888] 化合物 (91a) 的制备

[0889]



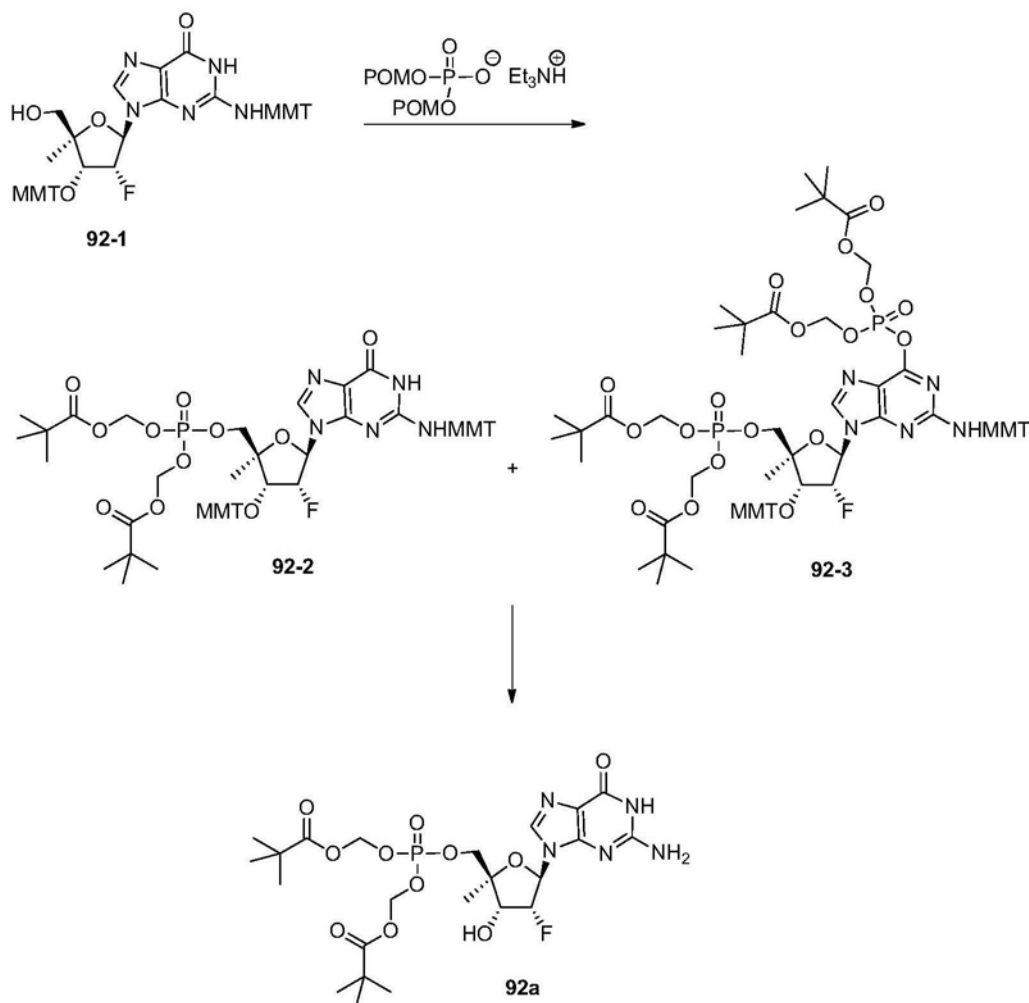
[0890] (91-2) 的制备: 向双(异丙氧基羰基氧基甲基)磷酸三乙基铵(0.33mmol, 从110mg 的双(POC)磷酸盐和0.1mL 的 Et_3N 制备的)的 THF(2mL) 溶液加入 86-1(100mg ; 0.11mmol)、随后加入二异丙基乙胺(0.19mL ;10 当量)、BOP-Cl(140mg ;5 当量) 和 3- 硝基-1, 2, 4- 三唑(63mg ;5 当量)。将混合物在 R. T. 下搅拌 90min., 然后使用 CH_2Cl_2 (30mL) 稀释。使用饱和 NaHCO_3 水溶液和盐水洗涤混合物。使用 Na_2SO_4 干燥混合物。将溶剂蒸发, 并在使用己烷 /EtOAc(40-100% 梯度) 的二氧化硅柱(10g 柱) 上纯化剩余物以产生 91-2(117mg, 90%)。

[0891] (91a) 的制备: 使用下列用于制备 85a 相似的步骤制备 91a :91-2(87mg ; 0.07mmol)、80% HCOOH 水溶液(5mL) 和 $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (4-15% 梯度) 以产生 91a(36mg, 85%)。
 $^1\text{H-NMR}$ (CD_3CN) : δ 7.67(dd, 1H), 6.35(dd, 1H), 6.1(br, 2H), 5.82(d, 1H), 5.62(m, 4H), 5.22(dm, 1H), 4.98(br, 1H), 4.89(m, 2H), 4.49(d, 1H), 4.34(m, 2H), 3.88(dd, 2H), 1.29(d, 6H), 1.28(d, 6H) ; $^{31}\text{P-NMR}$ (CD_3CN) : δ -4.49。MS :m/z = 606[M+1]。

[0892] 实施例 88

[0893] 化合物 (92a) 的制备

[0894]



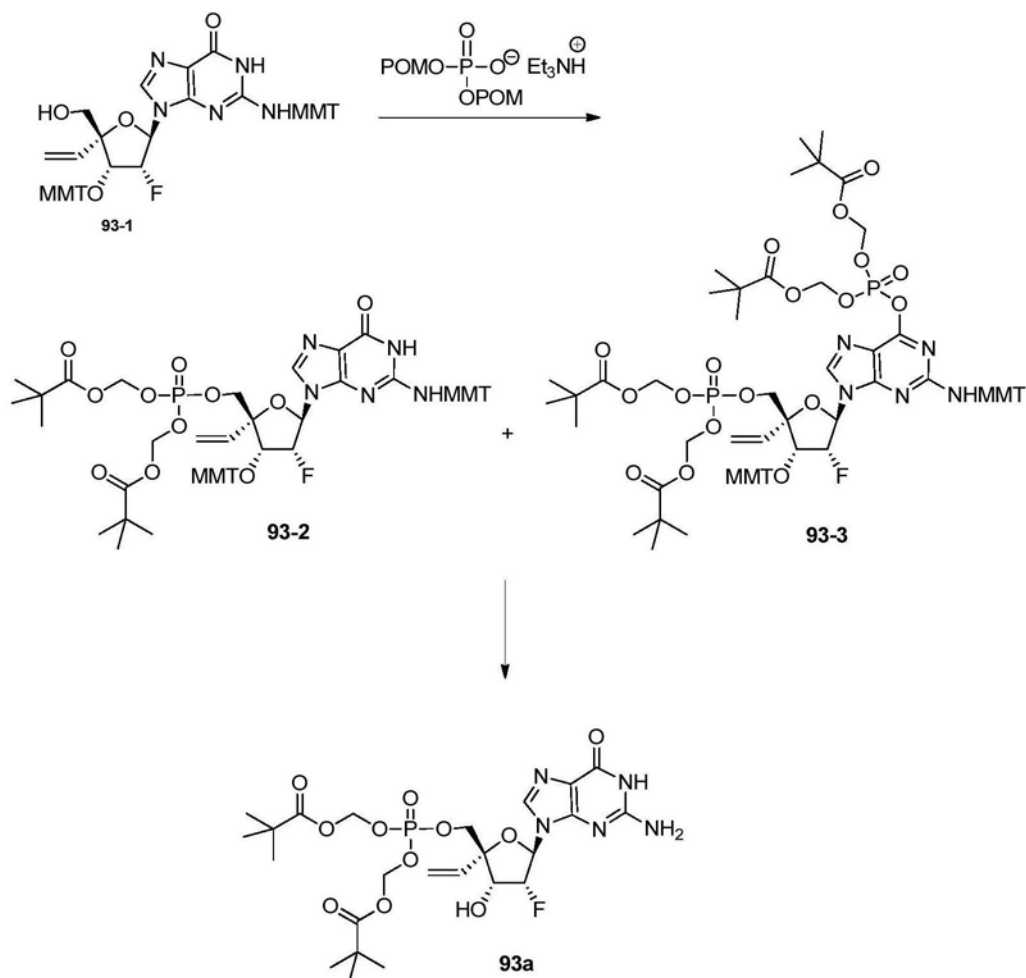
[0895] (92-2) 和 (92-3) 的制备: 向双 (POM) 磷酸三乙基铵 (0.48mmol, 从 176mg 的双 (POM) 磷酸盐和 0.15mL 的 Et_3N 制备的) 的 THF (2mL) 溶液加入 92-1 (150mg; 0.18mmol), 随后加入二异丙基乙胺 (0.31mL; 10 当量)、BOP-Cl (229mg; 5 当量) 和 3-硝基-1,2,4-三唑 (103mg; 5 当量)。将混合物在 R.T. 下搅拌 90mins., 然后使用 CH_2Cl_2 (30mL) 稀释。使用饱和 NaHCO_3 水溶液和盐水洗涤混合物。使用 Na_2SO_4 干燥混合物。将溶剂蒸发, 并在使用 CH_2Cl_2 /i-PrOH (2-10% 梯度) 的二氧化硅柱 (10g 柱) 上纯化剩余物以获得 92-2 (44mg, 21%) 和 92-3 (73mg, 28%)。

[0896] (92a) 的制备: 将 92-2 和 92-3 (73mg and 44mg) 和 80% HCOOH 水溶液 (3mL) 的混合物在 35°C 下加热 30mins。将溶剂蒸发, 然后使用甲苯共蒸发。将溶剂蒸发, 并在使用 CH_2Cl_2 /MeOH (4-10% 梯度) 的二氧化硅柱 (10g 柱) 上纯化剩余物以获得 92a (40mg, 75%)。
 $^1\text{H-NMR}$ (DMSO-d_6): δ 10.6 (br, 1H), 7.76 (s, 1H), 6.44 (br, 2H), 5.99 (dd, 1H), 5.83 (d, 1H), 5.53-5.27 (2m, 6H), 4.39 (dt, 1H), 4.04 (m, 2H), 1.17 (s, 3H), 1.06、1.08 (2s, 18H)。
 $^{31}\text{P-NMR}$ (DMSO-d_6): δ -4.09。MS: m/z = 608 $[\text{M}+1]$ 。

[0897] 实施例 89

[0898] 化合物 (93a) 的制备

[0899]



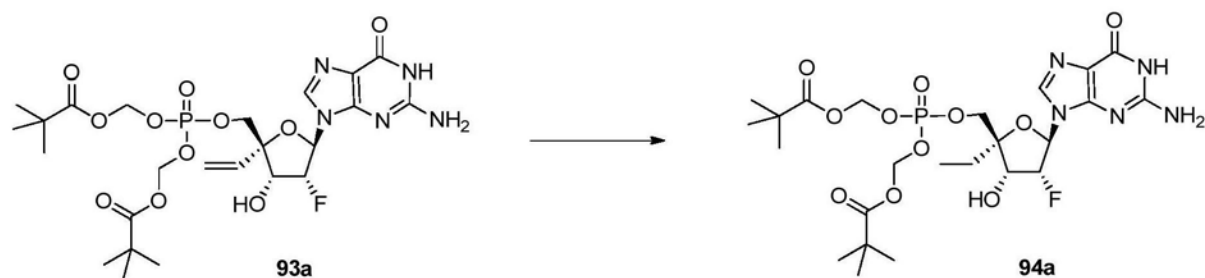
[0900] (93-2) 和 (93-3) 的制备: 以与 93-1 (200mg ; 0.23mmol) 和使用 DIPEA (0.4mL)、BopCl (290mg) 和 3-硝基-1,2,4-三唑 (130mg) 的 THF (3mL) 的双 (POM) 磷酸盐 (230mg) 作为 92-2 和来自 92-1 的 92-3 相同方式制备 93-2 和 93-3 (分别为 68mg 和 80mg)。

[0901] (93a) 的制备: 以与来自 92-2 和 92-3 的 92 相同的方式使用甲酸将 93-2 和 93-3 (分别为 68mg 和 80mg) 转化为 93 (42mg)。¹H-NMR (DMSO-d₆) : δ 7.73 (s, 1H), 6.46 (br, 2H), 6.04 (dd, 1H), 5.91 (dd, 1H), 5.87 (d, 1H), 5.48 (d, 4H), 5.33 (m, 1H), 5.24 (ddd, 1H), 4.60 (dt, 1H), 4.07 (m, 2H), 1.07, 1.06, 1.05 (4s, 18H)。³¹P-NMR (DMSO-d₆) : δ -4.37。MS : m/z = 620 [M+1]。

[0902] 实施例 90

[0903] 化合物 (94a) 的制备

[0904]



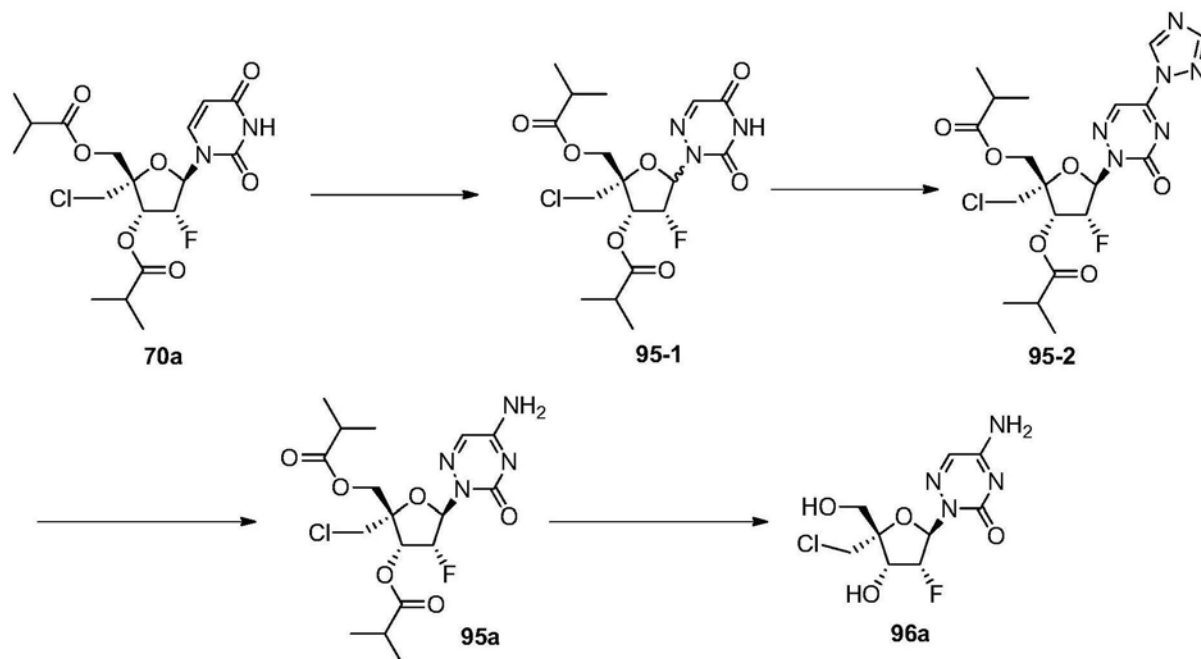
[0905] 向 93a (53mg ; 0.09mmol) 的 EtOH (2mL) 溶液加入 10 % Pd/C (10mg)。将混

合物在大气压力的氢气下搅拌 1h。通过硅藻土垫过滤混合物,并将滤液蒸发。在使用 $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (4-11 % 梯度) 的二氧化硅柱 (10g 柱) 上纯化产生 94a (45mg, 81 %)。
 $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) : δ 10.6 (br, 1H), 7.81 (s, 1H), 6.4 (br, 2H), 5.97 (dd, 1H), 5.85 (d, 1H), 5.60-5.44 (m, 5H), 4.37 (m, 1H), 4.11 (ddd, 2H), 1.66 (m, 2H), 1.09、1.06 (2s, 18H), 0.81 (7, 3H) ;
 $^{31}\text{P-NMR}$ ($\text{DMSO}-d_6$) : δ -4.10。MS : m/z = 622 [M+1]。

[0906] 实施例 91

[0907] 化合物 (95a) 和 (96a) 的制备

[0908]



[0909] (95-1) 的制备: 向 5-氨基-2H-[1,2,4]三嗪-3-酮 (180mg, 1.5mmol) 的 HMDS 溶液加入催化量的 $(\text{NH}_4)_4\text{SO}_4$ 。将混合物加热至回流 5h。将 HMDS 蒸发以产生粗产物。向粗产物的无水 CH_3CN 溶液加入 70a (220mg, 0.5mmol) 和 TMSOTf (0.45mL, 2.5mmol)。在密封管中将混合物加热至回流 24h。使用 NaHCO_3 淬灭反应并使用 EA 稀释。将有机溶剂去除,并首先通过制备-TLC 并通过 RP-HPLC (0.5 % HCOOH 的水和 MeCN) 纯化剩余物以产生纯 95-1 (100mg, 46 %)。

[0910] (95-2) 的制备: 向 95-1 (80mg, 0.18mmol) 的无水 CH_3CN 溶液加入 1,2,4-三唑 (911mg, 11.7mmol) 和 TEA (1.45g, 14.4mmol)。将混合物冷却至 0℃ 并加入 POCl_3 。将反应混合物在 25℃ 下搅拌 24h。将溶剂蒸发并使用 EA 和水分层。将有机层浓缩以产生粗 95-2 (80mg, 90 %)。

[0911] (95a) 的制备: 将 95-2 (90mg, 0.18mmol) 溶于 20mL 的饱和 THF 氨。将生成的溶液在 25℃ 下搅拌 2h。将溶剂去除,并在硅胶柱上 (EA:PE = 6:1) 纯化剩余物以产生白色固体形式的 95a (70mg, 70 %)。

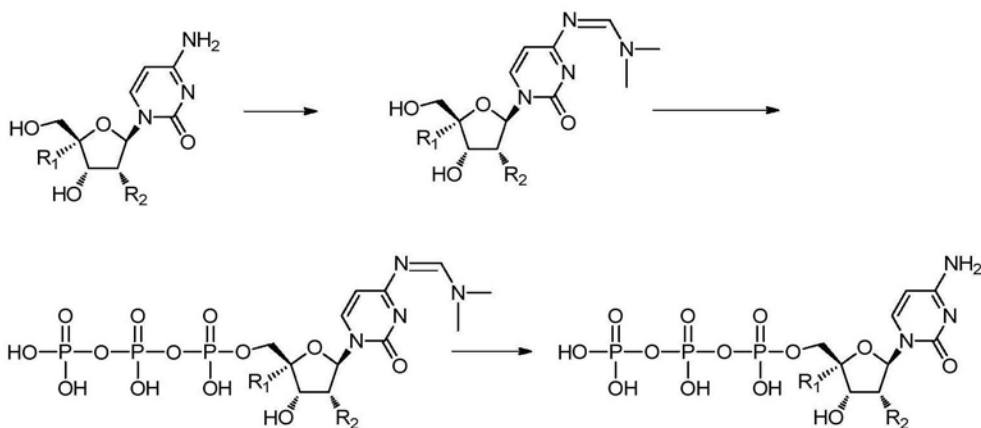
[0912] (96a) 的制备: 将 95a (70mg, 0.16mmol) 溶于 20mL 的饱和 MeOH 氨。将生成的溶液在 25℃ 下搅拌 2h。将溶剂去除,并通过 RP-HPLC (0.5 % HCOOH 的水和 MeCN) 纯化剩余物以产生白色固体形式的 96a (5mg, 11 %)。 $^1\text{H NMR}$ (CD_3OD , 400MHz) δ 7.57 (s, 1H), 6.35 (dd, J = 3.6Hz, J = 15.6Hz, 1H), 5.45-5.47 (m, 1H), 4.70 (dd, J = 4.8Hz, J =

16. 2Hz, 1H), 3. 83 (s, 2H), 3. 71 (d, $J = 1.6\text{Hz}$, 2H)。ESI-TOF-MS : m/z 295. 1 $[M+H]^+$ 。

[0913] 实施例 92

[0914] 化合物 (97a-g) 的制备

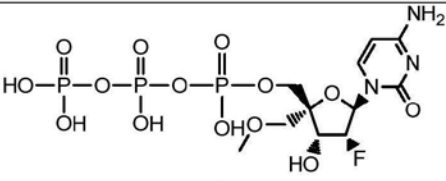
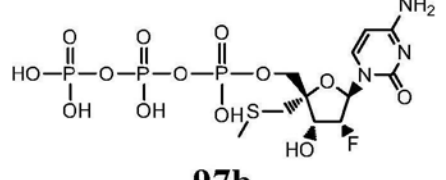
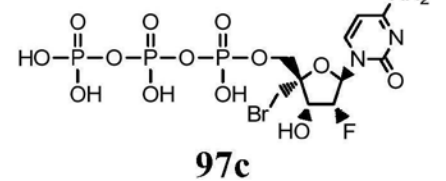
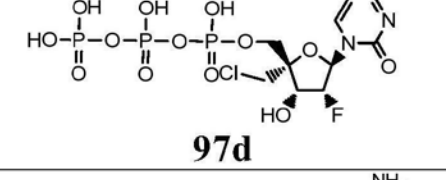
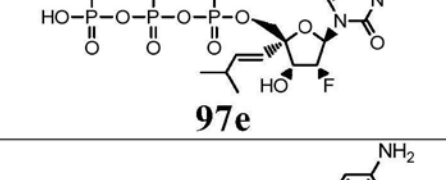
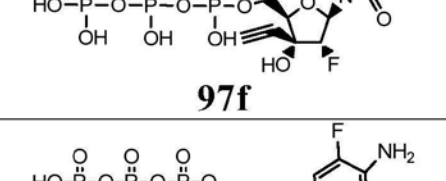
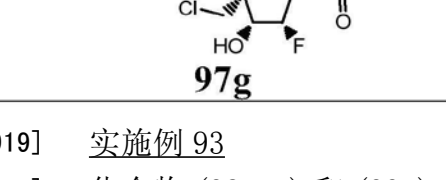
[0915]



[0916] 将干燥的核苷 (0.05mmol) 溶于 DMF (3mL) 和 DMA-DMF (0.04mL, 0.1mmol) 的混合物。将反应在环境温度下保持 4h, 然后蒸发至干燥。将剩余物溶于 $\text{PO}(\text{OMe})_3$ (0.7mL) 和吡啶 (0.3mL) 的混合物。将混合物在 42°C 下真空蒸发 15min., 然后冷却至 R.T. 加入 N-甲基咪唑 (0.009mL, 0.11mmol), 随后加入 POCl_3 ($9\mu\text{l}$, 0.11mmol)。将混合物在 R.T. 下保持 20-40mins。通过 LCMS 控制反应并通过相应核苷 5'-单磷酸盐的外观监测。在反应完成后, 加入焦磷酸的四丁基铵盐 (150mg), 随后加入 DMF (0.5mL) 以获得均匀溶液。在环境温度下 1.5h 后, 使用水 (10mL) 稀释反应。将混合物装载在具有 Q 琼脂糖高效的柱 HiLoad 16/10 上并在线性梯度为 0 至 1N 的 NaCl 的 50mM TRIS-缓冲液 (pH7.5) 中进行分离。在 75-80% B 下洗脱三磷酸盐 (97a-f)。将相应部分浓缩。将剩余物溶于 5% 氢氧化铵, 在 R.T. 下保持 15min 并浓缩。通过 Synergy 4 微米 Hydro-RP 柱上的 RPHPLC (Phenomenex) 完成脱盐。线性梯度为 0 至 30% 的甲醇的 50mM 醋酸三乙铵缓冲液 (pH 7.5) 用于洗脱。将相应部分合并, 浓缩并冻干 3 次以去除过量缓冲液。

[0917] 表 4 - 从实施例 92 获得的三磷酸盐

[0918]

化合物	MS (M-1)	³¹ P NMR P α	³¹ P NMR P β	³¹ P NMR 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)
 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)

[0919] 实施例 93

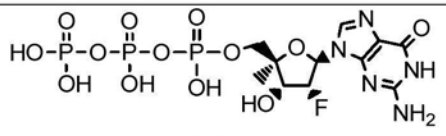
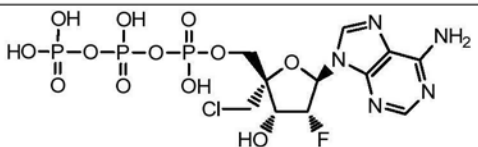
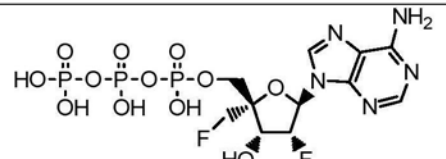
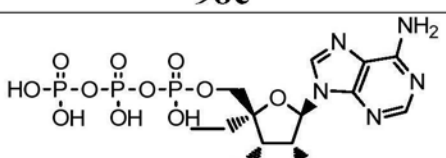
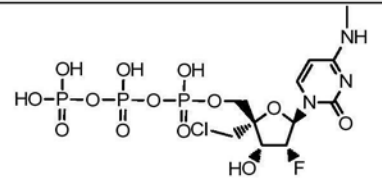
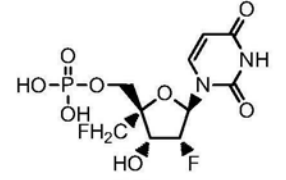
[0920] 化合物 (98a-e) 和 (99a) 的制备

[0921] 将干燥的核苷 (0.05mmol) 溶于 PO(OMe)₃ (0.7mL) 和吡啶 (0.3mL) 混合物。将混合物在 42℃ 下真空蒸发 15mins, 然后冷却至 R. T. 加入 N-甲基咪唑 (0.009mL, 0.11mmol), 随后加入 POCl₃ (9 μ l, 0.11mmol)。将混合物在 R. T. 下保持 20-40mins。通过 LCMS 控制反应并通过相应核苷 5'-单磷酸盐的外观监测。在反应完成后, 加入焦磷酸的四丁基铵盐

(150mg), 随后加入 DMF (0.5mL) 以获得均匀溶液。在环境温度下 1.5h 后, 使用水 (10mL) 稀释反应并装载在具有 Q 琼脂糖高效的柱 HiLoad 16/10 上。在线性梯度为 0 至 1N 的 NaCl 的 50mM TRIS- 缓冲液 (pH7.5) 中进行分离。在 75-80% B 下洗脱三磷酸盐 (98a-e)。将相应部分浓缩。通过 Synergy 4 微米 Hydro-RP 柱上的 RP HPLC (Phenomenex) 完成脱盐。线性梯度为 0 至 30% 的甲醇的 50mM 醋酸三乙铵缓冲液 (pH 7.5) 用于洗脱。将相应部分合并, 浓缩并冻干 3 次以去除过量缓冲液。

[0922] 表 5 - 从实施例 93 获得的化合物

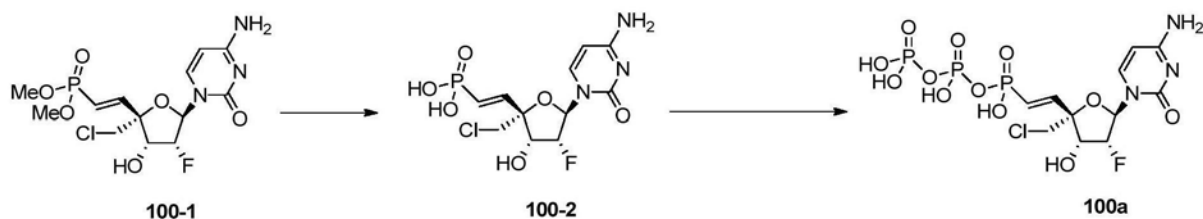
[0923]

化合物	MS (M-1)	³¹ P NMR P α	³¹ P NMR P β	³¹ P NMR 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

[0924] 实施例 94

[0925] 化合物 (100a) 的制备

[0926]



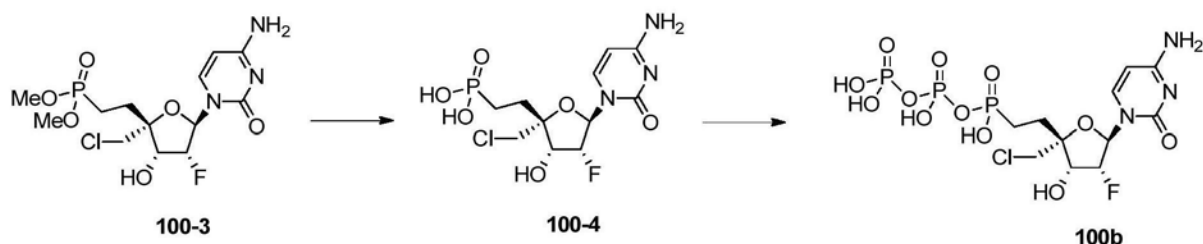
[0927] (100-2) 的制备: 向冰冷的 100-1 (22mg ; 0.055mmol) 的乙腈 (0.5mL) 溶液加入 TMSBr (80 μ L ; 10 当量)。将生成的混合物在 R. T. 下搅拌 1h。将混合物浓缩, 并在水和乙醚之间将剩余物分层。使用 Et₂O 洗涤水溶液层, 使用三乙基碳酸氢铵缓冲液中中和并冻干以产生 100-2 的三乙基铵盐。

[0928] (100a) 的制备: 通过与吡啶和甲苯共蒸发使 100-2 无水。将无水 100-2 溶于 HMPA (1mL) 并加入 1, 1- 羰基二咪唑 (32mg ; 0.2mmol)。将混合物在 R. T. 下搅拌 6h。加入焦磷酸四丁基铵 (0.22g ; 约 0.2mmol) 的 DMF (2mL) 溶液。将混合物在 R. T. 下搅拌过夜。使用三乙基醋酸铵缓冲液稀释混合物并通过使用梯度 0-60% B (A : 50mM 水溶液 TEAA, B : 50mM TEAA 的 MeOH) 的 RP-HPLC 纯化并通过使用梯度 0-30% B 的 RP-HPLC 再纯化以产生 100a。
³¹P-NMR (D₂O) : δ 3.22 (d, 1P), -8.21 (br, 1P), -22.91 (br, 1P)。MS : m/z = 528 (M-1)。

[0929] 实施例 95

[0930] 化合物 (100b) 的制备

[0931]



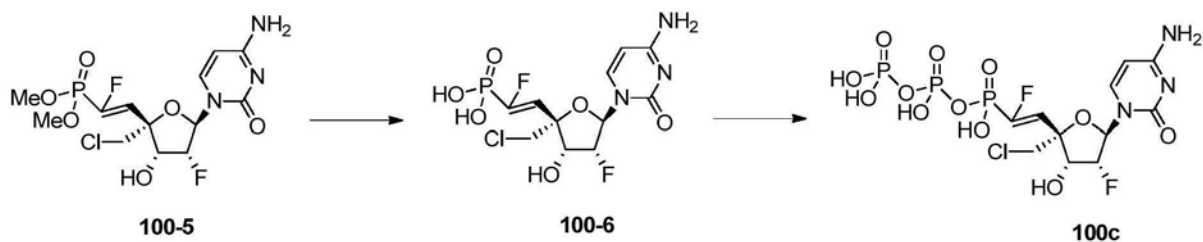
[0932] (100-4) 的制备: 使用与 100-2 的制备描述的相似步骤, 使用 TMSBr (0.18mL) 从 100-3 (54mg ; 0.13mmol) 的乙腈 (1.3mL) 制备 100-4。

[0933] (100b) 的制备: 使用与 100a 的制备描述的相似步骤, 使用 CDI (84mg) 和焦磷酸四丁基铵 (0.5g) 的 DMF (2mL) 从 100-4 的 HMPA (2mL) 制备 100b。
³¹P-NMR (D₂O) : δ 17.90 (d, 1P), -9.00 (d, 1P), -22.91 (t, 1P)。MS : m/z = 530 (M-1)。

[0934] 实施例 96

[0935] 化合物 (100c) 的制备

[0936]



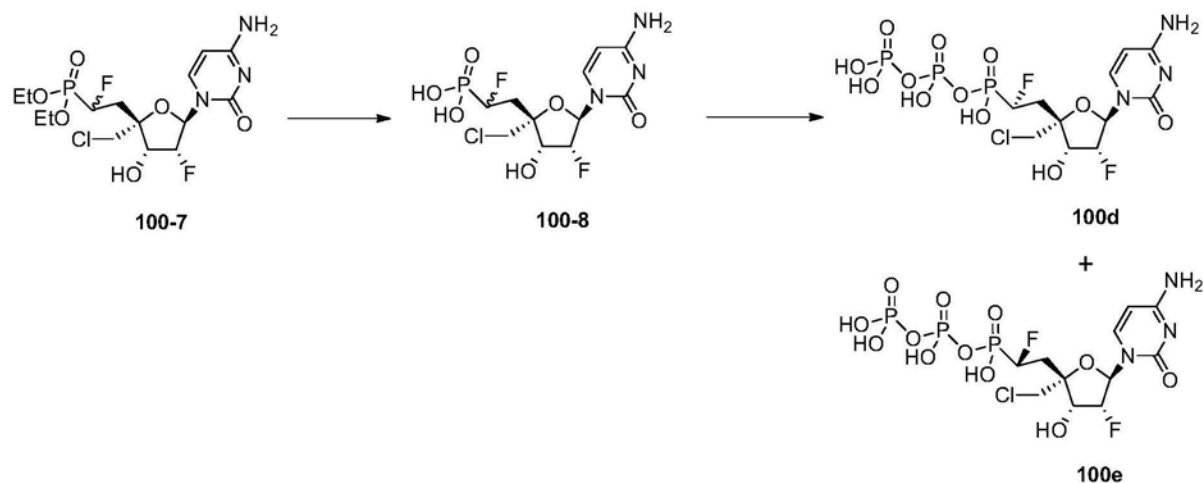
[0937] (100-6) 的制备: 使用与 100-2 的制备描述的相似步骤, 使用 TMSBr (0.1mL) 从 100-5 (40mg ; 0.09mmol) 的乙腈 (1mL) 制备 100-6。

[0938] (100c) 的制备:使用与 100a 的制备描述的相似步骤,使用 CDI (50mg) 和焦磷酸四丁基铵 (0.3g) 从 100-6 的 HMPA (1.5mL) 制备 100c。 ^{31}P -NMR(D_2O): δ -7.13(br, 1P), -10.14(d, 1P), -22.84(br, 1P)。 ^{19}F -NMR(D_2O): δ -117.53(dd, 1F), -197.8(m, 1F)。MS :m/z = 545.5(M-1)。

[0939] 实施例 97

[0940] 化合物 (100d) 和 (100e) 的制备

[0941]



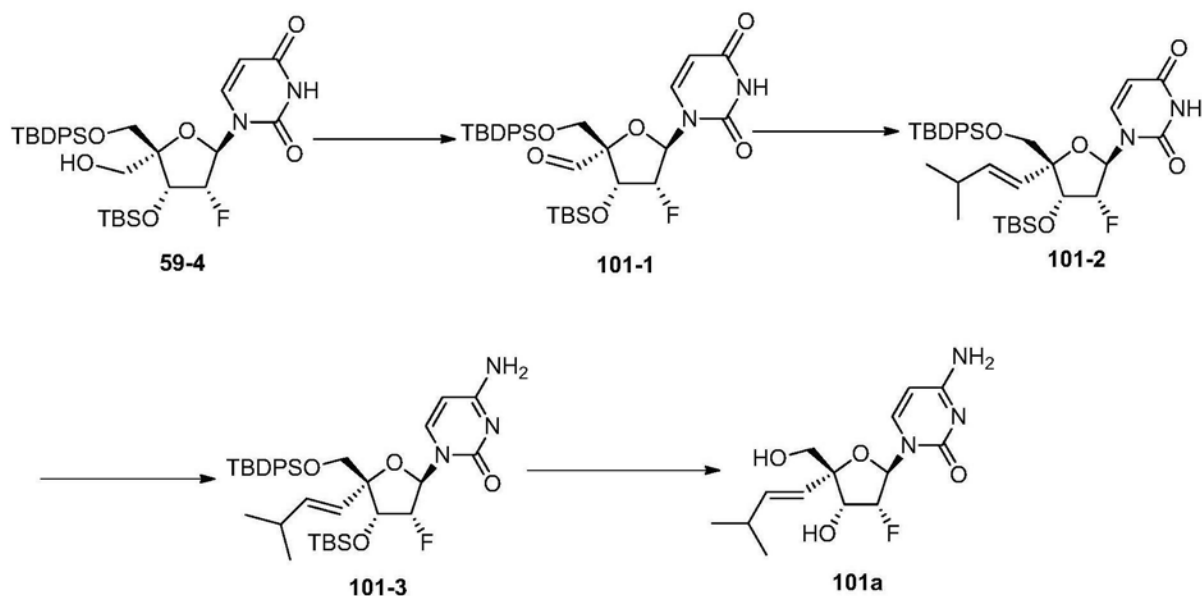
[0942] (100-8) 的制备:向冰冷的非对映异构体 100-7 (35mg ;0.08mmol) 的乙腈 (1mL) 溶液加入 TMSBr (0.1mL ;10 当量)。将生成的混合物在 R. T. 下搅拌过夜,然后浓缩。在水和 CH_2Cl_2 之间将剩余物分层。使用 CH_2Cl_2 洗涤水溶液层,使用三乙基碳酸氢铵缓冲液中和并冻干以产生 100-8 的三乙基铵盐。

[0943] (100d) 和 (100e) 的制备:通过与吡啶和甲苯共蒸发使 100-8 无水。将无水 100-8 溶于 DMF (1.5mL) 并 CDI (54mg ;0.3mmol)。将混合物在 R. T. 下搅拌 7h。加入焦磷酸四丁基铵 (0.3g ;约 0.3mmol) 的 DMF (4mL) 溶液。将混合物在 R. T. 下搅拌 3 天。使用三乙基醋酸铵缓冲液稀释混合物。使用梯度 0-60% B(A :50mM 水溶液 TEAA, B :50mM TEAA 的 MeOH) 和 0-40% B 的两个连续 RP-HPLC 纯化产生单一非对映异构体形式的 100d 和 100e。100d : ^{31}P -NMR(D_2O): δ 4.28(dd, 1P), -6.37(d, 1P), -22.36(t, 1P)。MS :m/z = 548.1(M-1)。100e : ^{31}P -NMR(D_2O): δ 4.13(dd, 1P), -6.38(d, 1P), -22.46(t, 1P)。MS :m/z = 548.1(M-1)。

[0944] 实施例 98

[0945] 化合物 (101a) 的制备

[0946]



[0947] (101-1) 的制备:在氮气下,在 0℃下向 59-4(1.5g, 2.39mmol) 的无水 DCM(100mL) 溶液加入戴斯-马丁氧化剂(5.2g, 11.95mmol)。将混合物在 R. T. 下搅拌 5h。将混合物倾入 NaHCO₃ 和 Na₂S₂O₃ 水溶液。使用盐水洗涤有机层,在无水 Na₂SO₄ 上干燥,并浓缩至干燥以产生白色固体形式的粗 101-1(1.5g),将其用于下一步而不进一步纯化。

[0948] (101-2) 的制备:在氮气下,在 0℃下向溴(异丁基)三苯基膦(4.8g, 12.03mmol) 的无水 THF(8mL) 混合物加入 t-BuOK(11.2mL, 11.2mmol)。将混合物在 R. T. 下搅拌 1h。在 0℃下滴加 101-1(1.0g, 1.6mmol) 的无水 THF(4mL) 溶液。将混合物在 R. T. 下搅拌 3h。使用 NH₄Cl 水溶液淬灭反应并使用 DCM 萃取。干燥有机层并浓缩以产生剩余物,通过硅胶柱层析(5% EtOAc 的 PE) 将其纯化以产生白色固体形式的 101-2(793mg, 74.4%)。

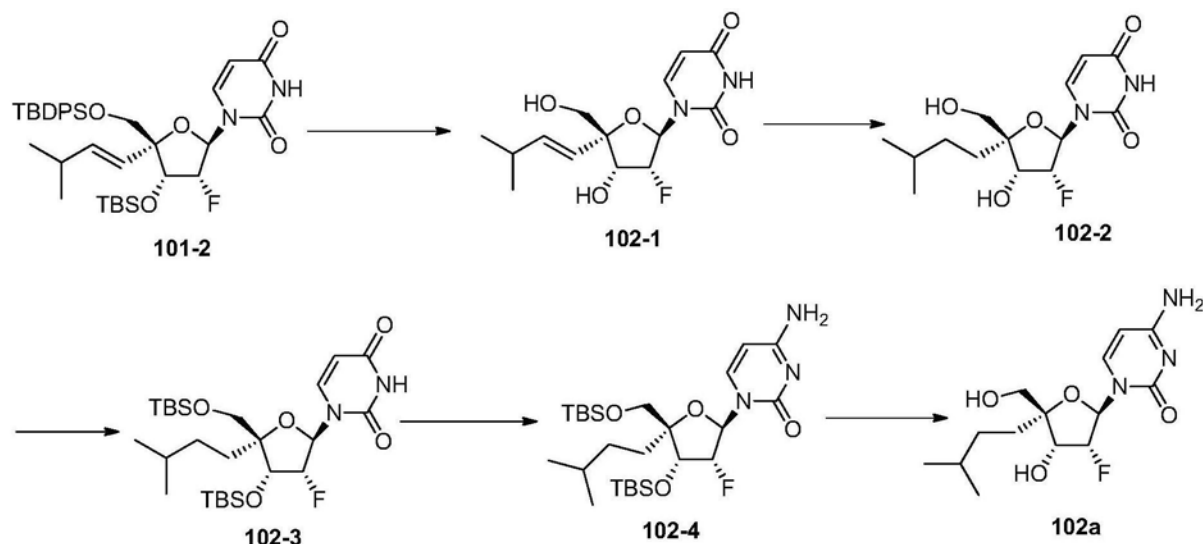
[0949] (101-3) 的制备:在 R. T. 下,向 101-2(364mg, 0.547mmol) 的无水 CH₃CN(6mL) 溶液加入 TPSCl(414mg, 1.37mmol)、DMAP(167mg, 1.37mmol) 和 NEt₃(138mg, 1.37mmol)。将混合物在 R. T. 下搅拌 2h。加入 NH₄OH(6mL),并将混合物搅拌另外 1h。使用 DCM 稀释混合物并使用 NaHCO₃ 水溶液洗涤。将有机层分离并浓缩以产生剩余物,通过硅胶柱层析(2% MeOH 的 DCM 溶液) 将其纯化以产生白色固体形式的 101-3(347mg, 95.0%)。

[0950] (101a) 的制备:在 R. T. 下,向 27-3(347mg, 0.52mmol) 的 MeOH(10mL) 溶液加入 NH₄F(1.5g)。将反应混合物回流 12h,然后过滤。真空浓缩滤液,并通过硅胶柱层析(10% MeOH 的 DCM 溶液) 纯化剩余物以产生白色固体形式的 101a(87mg, 53%)。¹H NMR(CD₃OD, 400MHz) δ 8.11(d, J = 7.6Hz, 1H), 6.03(dd, J = 1.2, 17.6Hz, 1H), 5.88(d, J = 7.2Hz, 1H), 6.03(dd, J = 1.6, 11.6Hz, 1H), 5.39(d, J = 10.8Hz, 1H), 4.88(dd, J = 3.2、60.0Hz, 1H), 4.41(dd, J = 4.8, 24.4Hz, 1H), 3.70(d, J = 12.4Hz, 1H), 3.57(d, J = 12.0Hz, 1H), 3.08-3.14(m, 1H), 0.94-0.98(m, 6H)。ESI-MS :m/z 626.9[2M+H]⁺。

[0951] 实施例 99

[0952] 化合物 (102a) 的制备

[0953]



[0954] (102-1) 的制备: 在 R. T. 下, 向 101-2 (1.0g, 1.5mmol) 的 MeOH (20mL) 溶液加入 NH_4F (6g), 并将混合物回流过夜。在冷却至 R. T. 后, 将混合物过滤, 并将滤液浓缩。通过硅胶柱层析 (8% MeOH 的 DCM 溶液) 纯化剩余物以产生白色固体形式的 102-1 (400mg, 85%)。

[0955] (102-2) 的制备: 在 R. T. 下, 向 102-1 (400mg, 1.27mmol) 的 MeOH (10mL) 溶液加入 Pd/C (400mg)。在 H_2 气球下, 将混合物在 R. T. 下搅拌 1.5h。将混合物过滤, 并真空浓缩滤液以产生白色固体形式的 102-2 (400mg, 99%)。

[0956] (102-3) 的制备: 在 R. T. 下, 向 102-2 (400mg, 1.26mmol) 的无水 DMF (5mL) 溶液加入咪唑 (968mg, 14.2mmol) 和 TBSCl (1.5g, 10.0mmol)。将混合物在 50℃ 下搅拌过夜。使用 DCM 稀释混合物并使用 NaHCO_3 水溶液洗涤。干燥有机层并浓缩。通过硅胶柱层析 (10% EA 的 PE) 纯化剩余物以产生白色固体形式的 102-3 (676mg, 98%)。

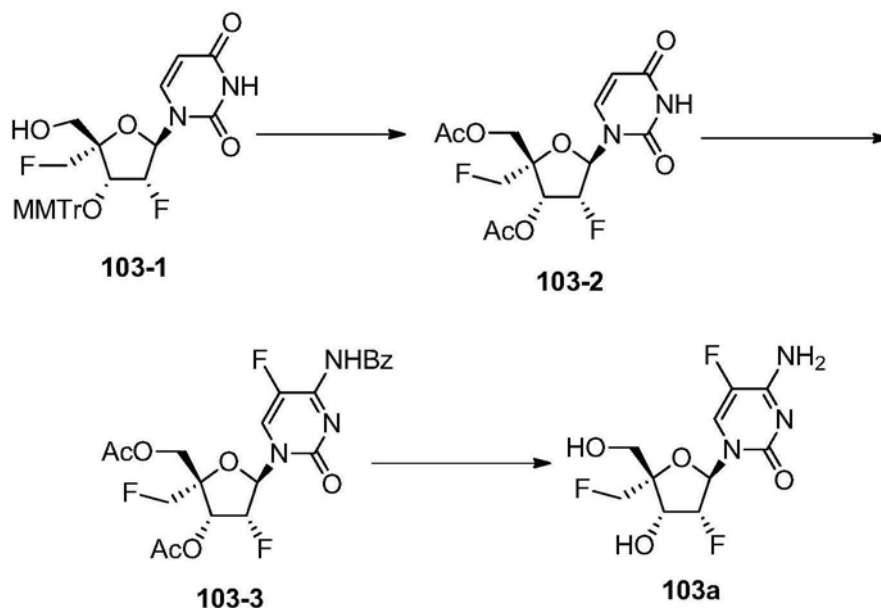
[0957] (102-4) 的制备: 在 R. T. 下, 向 102-3 (676mg, 1.24mmol) 的无水 CH_3CN (6mL) 溶液加入 TPSCl (941mg, 13.11mmol)、DMAP (379mg, 3.11mmol) 和 NEt_3 (314mg, 3.11mmol)。将反应在 R. T. 下搅拌 3h。加入 NH_4OH (1mL), 并将反应搅拌 4h。使用 DCM 稀释混合物并使用 NaHCO_3 溶液洗涤。干燥有机层并浓缩。通过硅胶柱层析 (2% MeOH 的 DCM 溶液) 纯化剩余物以产生白色固体形式的 102-4 (450mg, 67%)。

[0958] (102a) 的制备: 在 R. T. 下, 向 102-4 (450mg, 0.83mmol) 的 MeOH (10mL) 溶液加入 NH_4F (2g)。将反应混合物回流过夜。在冷却至 R. T. 后, 将混合物过滤, 并将滤液浓缩。通过硅胶柱层析 (8% MeOH 的 DCM 溶液) 纯化剩余物以产生白色固体形式的 102a (166.6mg, 64%)。
 ^1H NMR (CD_3OD , 400MHz) δ 8.09 (d, $J = 7.6\text{Hz}$, 1H), 6.07 (d, $J = 3.6\text{Hz}$, 1H), 6.05 (d, $J = 2.8\text{Hz}$, 1H), 5.89 (d, $J = 7.6\text{Hz}$, 1H), 5.03 (dd, $J = 5.2, 5.2\text{Hz}$, 1H), 4.41 (dd, $J = 4.2, 17.2\text{Hz}$, 1H), 3.74 (d, $J = 12.0\text{Hz}$, 1H), 3.54 (d, $J = 12.0\text{Hz}$, 1H), 1.23-1.78 (m, 5H), 0.90 (d, $J = 6.4\text{Hz}$, 6H)。ESI-MS: m/z 631.1 $[2\text{M}+\text{H}]^+$ 。

[0959] 实施例 100

[0960] 化合物 (103a) 的制备

[0961]



[0962] (103-2) 的制备: 将 103-1 (3.8g, 6.9mmol) 的 80% AcOH 水溶液在 50℃ 下搅拌 4h。将混合物浓缩以产生剩余物, 通过硅胶柱层析 (5% MeOH 的 DCM 溶液) 将其纯化以产生白色固体形式的尿苷衍生物 (1.5g, 78.2%)。在 R. T. 下, 向尿苷衍生物 (1.5g, 5.4mmol) 的 Py (10mL) 溶液加入 Ac₂O (1.38g, 13.5mmol)。将混合物在 R. T. 下搅拌 12h。将混合物浓缩以产生剩余物, 通过硅胶柱层析 (20% EA 的 PE) 将其纯化以产生白色固体形式的 103-2 (1.3g, 68%)。

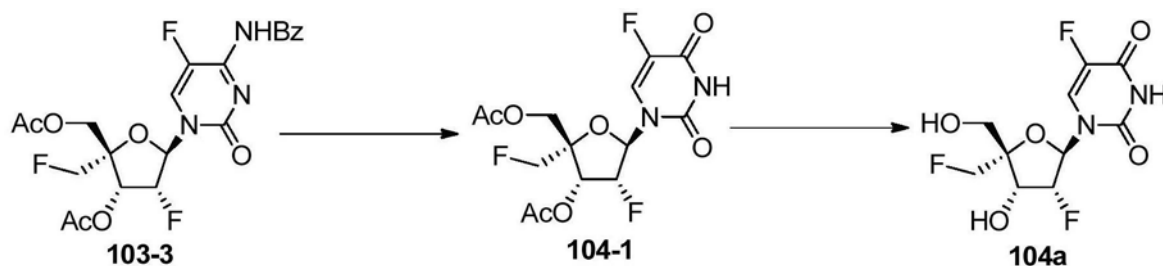
[0963] (103-3) 的制备: 向 N-(5-氟-2-羟基-1,2-二氢嘧啶-4-基) 苯甲酰胺 (0.5g, 2.1mmol) 的无水 PhCl (5mL) 溶液加入硫酸铵 (6mg, 0.043mmol), 随后加入 HMDS (0.7g, 4.3mmol)。将混合物加热至 130℃, 时间为 8h。将混合物在真空下浓缩至 2mL, 然后冷却至 0℃。然后加入 TMSOTf (310mg, 1.4mmol)。在 0℃ 下搅拌 10min 后, 加入 103-2 (150mg, 0.4mmol) 的 PhCl (5mL)。将混合物在 130℃ 下搅拌 10h。将混合物浓缩, 并将剩余物再溶于 DCM (10mL), 使用水 (5mL) 和饱和 NaHCO₃ 洗涤。在 Na₂SO₄ 上干燥有机层、蒸发至干燥并通过硅胶柱层析 (60% PE 的 EA 溶液) 纯化粗产物以产生白色固体形式的 103-3 (30mg, 16%)。

[0964] (103a) 的制备: 将 103-3 (150mg, 0.34mmol) 的 NH₃/MeOH (10mL) 溶液在 R. T. 下搅拌 3h。将混合物浓缩, 并通过 HPLC 分离 (0.1% HCOOH 的水和 MeCN) 纯化剩余物以产生白色固体形式的 103a (60mg, 60%)。¹HNMR (CD₃OD, 400MHz) δ 8.28 (d, J = 6.8Hz, 1H), 6.10 (dd, J = 2.0, 15.2Hz, 1H), 4.99-5.15 (m, 1H), 4.62-4.65 (m, 1H), 4.49-4.55 (m, 2H), 3.89 (dd, J = 1.6, 12.0Hz, 1H), 3.75 (dd, J = 1.2, 12.0Hz, 1H)。ESI-MS :m/z 613.1 [2M+Na]⁺。

[0965] 实施例 101

[0966] 化合物 (104a) 的制备

[0967]



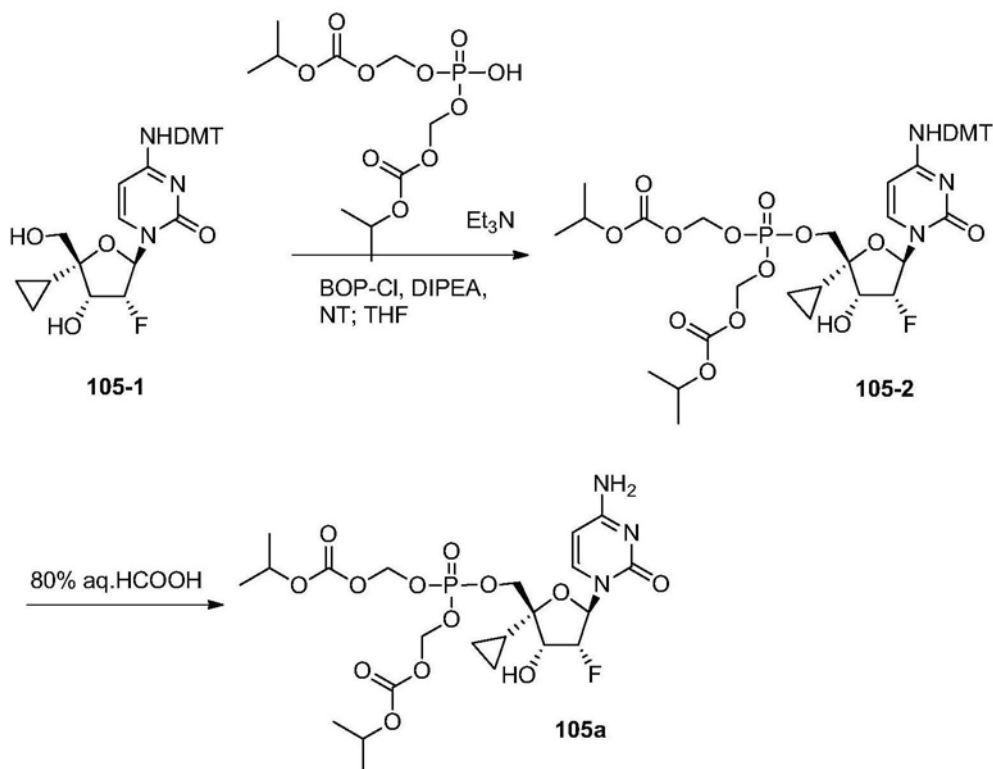
[0968] (104-1) 的制备: 将 103-3 (150mg, 0.31mmol) 溶于 80% 乙酸水溶液 (3mL)。将溶液加热至回流 2h。将混合物冷却至环境温度并使用水 (5mL) 稀释, 使用饱和 NaHCO_3 中和至 $\text{pH} > 7$ 并使用 EA 萃取。干燥有机层并蒸发至干燥。通过硅胶柱层析 (50% EA 的 PE) 纯化剩余物以产生白色固体形式的 104-1 (80mg, 70%)。

[0969] (104a) 的制备: 将 104-1 (80mg, 0.22mmol) 的饱和 NH_3/MeOH (10mL) 在 R. T. 下搅拌 3h。将混合物浓缩, 并通过硅胶柱层析 (5% MeOH 的 DCM 溶液) 纯化剩余物以产生白色固体形式的 104a (40mg, 60%)。 ^1H NMR (CD_3OD , 400MHz) δ 8.30 (d, $J = 6.8\text{Hz}$, 1H), 6.18 (dd, $J = 4.0, 14.0\text{Hz}$, 1H), 5.13–5.65 (m, 1H), 4.52–4.56 (m, 1H), 3.980–3.95 (m, 2H), 3.76 (s, 3H)。ESI-MS: m/z 319.1 $[\text{M}+\text{Na}]^+$ 。

[0970] 实施例 102

[0971] 化合物 (105a) 的制备

[0972]



[0973] (105-2) 的制备: 向双 (异丙氧基羰基氧基甲基) 磷酸三乙基铵 (0.065mmol, 从 22mg 的双 (POC) 磷酸盐和 Et_3N 制备的) 的 THF 溶液加入 105-1 (31mg; 0.05mmol)。将生成的混合物蒸发, 并通过与吡啶, 随后甲苯共蒸发使剩余物无水。将无水蒸发的剩余物溶于 THF (1mL) 并在冰浴中冷却。向溶液加入二异丙基乙胺 (35L; 4 当量), 随后加入 BOP-Cl (25mg; 2 当量) 和 3-硝基-1,2,4-三唑 (11mg; 2 当量)。将混合物在 0°C 下搅拌

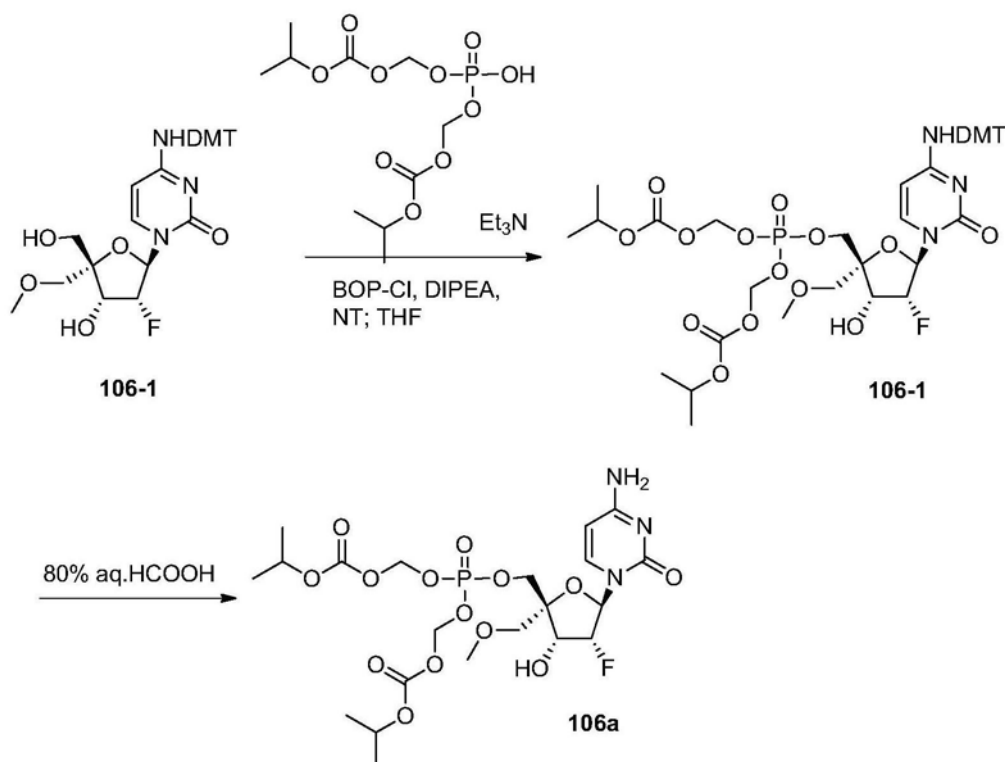
90min。使用 CH_2Cl_2 稀释混合物,使用饱和 NaHCO_3 水溶液和盐水洗涤,并使用 Na_2SO_4 干燥。在使用 $\text{CH}_2\text{Cl}_2/\text{i-PrOH}$ 溶剂体系(3-10%梯度)的二氧化硅(10g 柱)上纯化蒸发的剩余物以产生 105-2(13mg, 28%)。

[0974] (105a) 的制备:将 105-2(13mg ;0.014mmol) 的 80% HCOOH 水溶液(2mL) 在 R. T. 下搅拌 3h。将混合物蒸发,然后使用甲苯共蒸发。在使用 $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 溶剂体系(4-15%梯度)的二氧化硅(10g 柱)上纯化产物以产生 105a(7mg, 78%)。 $^1\text{H-NMR}$ (DMSO-d_6) : δ 7.52(d, 1H), 7.28、7.24(2brs, 2H) 5.92(dd, 1H), 5.74(d, 1H), 5.69(d, 1H), 5.62(d, 4H), 4.97(ddd, 1H), 4.82(m, 2H), 4.38(dt, 1H), 4.07(m, 2H), 1.23(m, 12H), 1.04(m, 1H), 0.37(m, 4H)。 $^{31}\text{P-NMR}$ (DMSO-d_6) : δ -4.51。 $^{19}\text{F-NMR}$ (DMSO-d_6) : δ -199.23(dt)。MS :m/z = 598.4(M+1)。

[0975] 实施例 103

[0976] 化合物 (106a) 的制备

[0977]



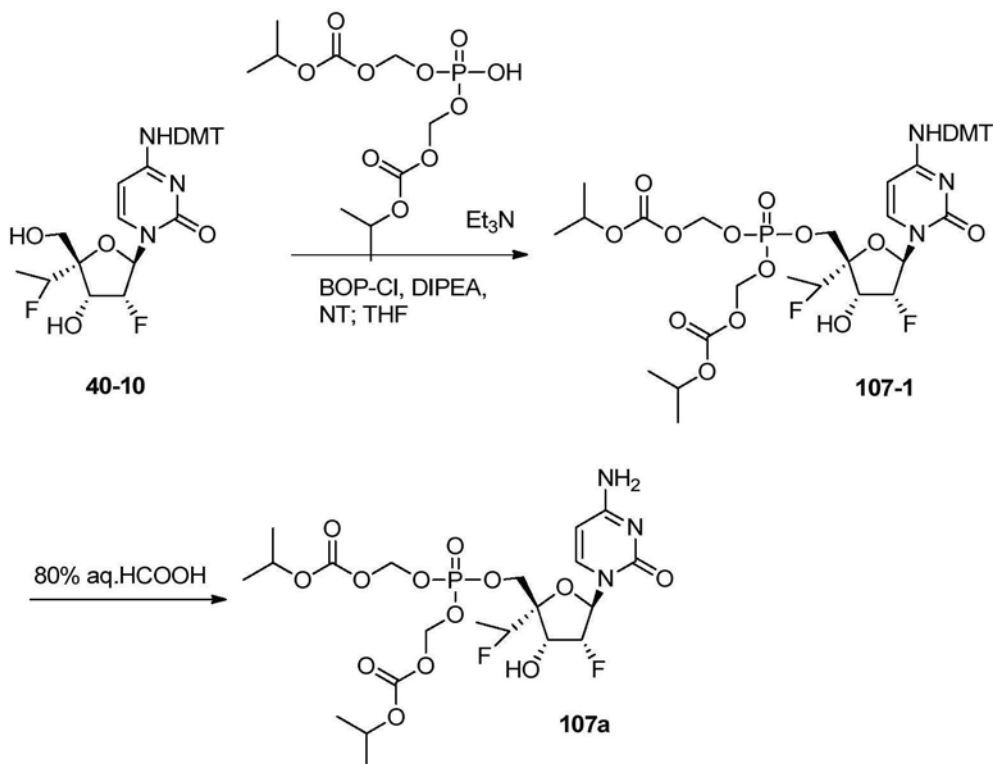
[0978] (106-1) 的制备:以使用 DIPEA(40 μL)、BopCl(29mg) 和 3- 硝基 -1, 2, 4- 三唑(13mg) 作为来自 105-1 的 105-2 的双 (POC) 磷酸盐 (24mg) 相同的方式从 43-5(32mg ; 0.057mmol) 制备 106-1(15mg ;30%产率)。

[0979] (106a) 的制备:以与 105-2 至 105a 相同的方式在甲酸中将 106-1(15mg) 转化为 106a(8mg ;78 % 产率)。 $^1\text{H-NMR}$ (DMSO-d_6) : δ 7.55(d, 1H), 7.32、7.27(2br s, 2H) 6.06(dd, 1H), 5.84(d, 1H), 5.73(d, 1H), 5.61(d, 4H), 5.08(ddd, 1H), 4.83(m, 2H), 4.36(m, 1H), 4.21(dd, H), 4.16(dd, 1H), 3.56(d, 1H), 3.49(d, 1H), 3.28(s, 3H), 1.25, 1.24(2d, 12H)。 $^{31}\text{P-NMR}$ (DMSO-d_6) : δ -4.45。MS :m/z = 602.4(M+1)。

[0980] 实施例 104

[0981] 化合物 (107a) 的制备

[0982]



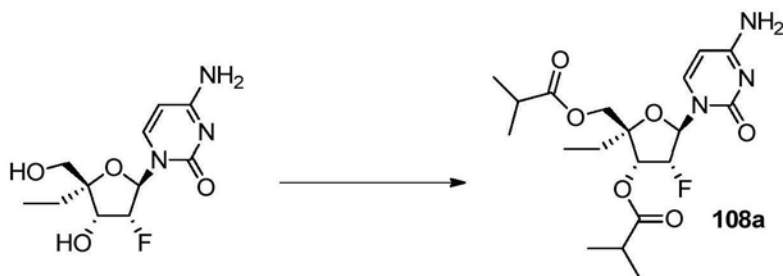
[0983] (107-1) 的制备: 以使用 DIPEA (80 μ L)、BopCl (58mg) 和 3-硝基-1,2,4-三唑 (26mg) 作为来自 105-1 的 105-2 的双 (POC) 磷酸盐 (49mg) 相同的方式从 40-10 (65mg; 0.115mmol) 制备 107-1 (30mg; 30% 产率)。

[0984] (106a) 的制备: 以与 105-2 至 105a 相同的方式在甲酸中将 107-1 (30mg) 转化为 107a (15mg; 73% 产率)。 $^1\text{H-NMR}$ (DMSO- d_6): δ 7.60 (d, 1H), 7.36, 7.32 (2br s, 2H), 6.02 (m, 2H), 5.74 (d, 1H), 5.62 (m, 4H), 5.17 (ddd, 1H), 4.99 (dq, 1H), 4.83 (m, 2H), 4.61 (m, 1H), 4.19 (m, 2H), 1.40 (dd, 3H), 1.24, 1.23 (2d, 12H)。 $^{31}\text{P-NMR}$ (DMSO- d_6): δ -4.52。 $^{19}\text{F-NMR}$ (DMSO- d_6): δ -185.92 (m, 1F), -200.48 (d, 1F)。 MS: m/z = 604.3 (M+1)。

[0985] 实施例 105

[0986] 化合物 (108a) 的制备

[0987]



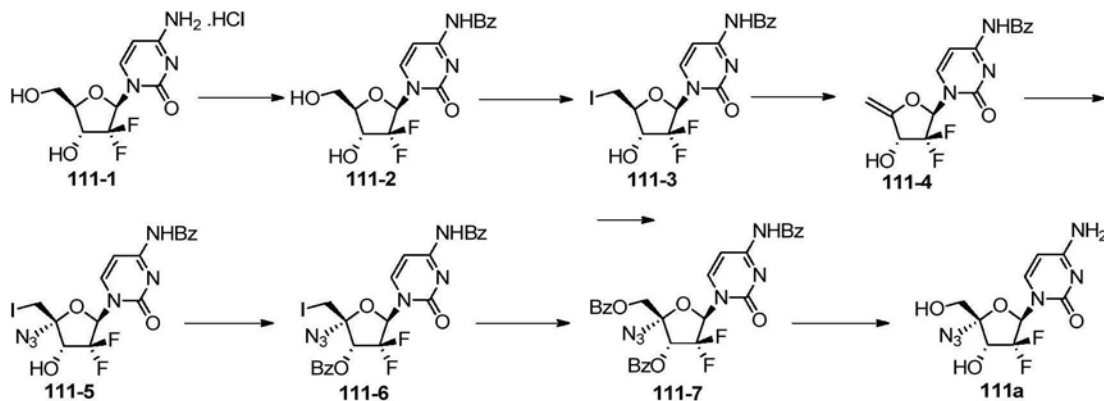
[0988] 向 4'-乙基-2'-氟胞嘧啶核苷 (50mg, 0.183mmol) 的 DMF (1mL) 溶液加入 DCC (113mg, 0.55mmol)、异丁酸 (48.5 μ L, 0.55mmol) 和 DMAP (22mg, 0.183mmol)。将混合物在 R.T. 下搅拌过夜。将混合物过滤, 并使用旋转蒸发器浓缩滤液直至达到其最初体积的一半。将 EA 加入至混合物。使用水, 随后盐水洗涤混合物。在无水 Na_2SO_4 上干燥混合物并真空浓缩以产生剩余物, 通过使用 DCM/MeOH = 95:5 的硅胶将其纯化以产生白色固体形式的 108a (40.8mg, 54%)。 $^1\text{H NMR}$ (DMSO- d_6 , 400MHz) δ 7.67 (d, J = 7.2Hz, 1H), 7.34 (br

的 110a (80mg, 60 %)。 ^1H NMR (CD_3OD , 400MHz) δ 8.31 (d, $J = 6.8\text{Hz}$, 1H), 6.17 (dd, $J = 4.0, 14.0\text{Hz}$, 1H), 5.13–5.27 (m, 1H), 4.52–4.56 (m, 1H), 3.92 (dd, $J = 12.0, 58.8\text{Hz}$, 2H)。ESI-TOF-MS: m/z 334.7 $[\text{M}+\text{Na}]^+$ 。

[0998] 实施例 108

[0999] 化合物 (111a) 的制备

[1000]



[1001] (111-2) 的制备: 将化合物 111-1 (30.0g, 0.1mol) 悬浮于无水吡啶 (300mL) 中, 并在室温下 (R. T.) 搅拌 1 小时。将悬液冷却至 0°C , 并逐滴加入 TMSCl (27.3g, 0.25mmol)。加入完成后, 使混合物升温至 R. T., 并搅拌 30min。然后将混合物再次冷却至 0°C , 并逐滴加入 BzCl (15.5g, 0.11mol)。使混合物升温至 R. T. 并搅拌过夜。将反应物冷却至 0°C , 并用 H_2O 淬灭。加入氨水, 并将反应物在 R. T. 下搅拌 2 小时。浓缩溶液, 并将残留物加入乙酸乙酯 (EA) 和 H_2O 中。用 EA 将水相抽提几次, 并将合并的有机层在 Na_2SO_4 上干燥, 并浓缩。在硅胶柱上纯化残留物以给出化合物 111-2, 其为白色固体 (28.2g, 76%)。ESI-LCMS: $m/z = 368 [\text{M}+\text{Na}]^+$ 。

[1002] (111-3) 的制备: 0°C 下, 向经搅拌的于无水 THF (300mL) 中的化合物 111-2 (18.4g, 50mmol)、 PPh_3 (22.3g, 85mmol) 和吡啶 (25mL) 的悬液中, 逐滴加入于 THF (80mL) 的 I_2 (19.05g, 75mmol) 溶液。添加后, 使混合物升温至 R. T., 并搅拌 60 小时。通过过滤去除沉淀物, 并浓缩滤液。将残留物溶于二氯甲烷 (DCM) 中, 并用饱和 $\text{Na}_2\text{S}_2\text{O}_3$ 水溶液洗涤, 然后用卤水洗涤。将有机层在 Na_2SO_4 上干燥并浓缩。在硅胶柱上纯化残留物, 以提供化合物 111-3 (16.4g, 69%)。ESI-LCMS: $m/z = 478 [\text{M}+\text{H}]^+$ 。

[1003] (111-4) 的制备: 0°C 下, 在 20min 内, 向搅拌的于无水二甲基甲酰胺 (DMF) (300mL) 中的化合物 111-3 (17.0g, 35.6mmol) 的溶液中, 逐滴加入于 DMF (120mL) 中的 $t\text{-BuOK}$ (10.0g, 89.1mmol) 溶液。 0°C 下继续搅拌 45min, 然后加入浓盐酸 (4.5mL)。通过加入饱和 NaHCO_3 溶液得到 8–9 的 pH 值。通过过滤去除沉淀物, 并用乙酸乙酯稀释滤液。用卤水洗涤溶液并在 Na_2SO_4 上干燥。去除溶剂, 并在硅胶柱上纯化残留物以提供化合物 111-4, 其为白色固体 (8.6g, 69%)。ESI-LCMS: $m/z = 350 [\text{M}+\text{H}]^+$ 。

[1004] (111-5) 的制备: 向搅拌的于 MeCN (600mL) 中的 $\text{Bn Et}_3\text{NCl}$ (37.4g, 0.16mol) 溶液中, 加入 NaN_3 (10.8g, 0.16mol)。对混合物声处理 20min, 然后在 R. T. 下搅拌 16 小时。将溶液过滤至于无水 THF (200mL) 中的化合物 111-4 (11.5g, 32.9mmol) 和 N-甲基吗啉 (3.5g) 的溶液中。将混合物冷却至 0°C , 并逐滴加入于 THF (100mL) 中的 I_2 (33.6g, 0.14mol) 溶液中。

在 0-10℃ 下继续搅拌 20 小时。加入 N-乙酰半胱氨酸直至无气体生成。加入饱和 $\text{Na}_2\text{S}_2\text{O}_3$ 溶液直至得到亮黄色溶液。浓缩溶液,然后用 EA 稀释。用卤水洗涤有机相并在 Na_2SO_4 上干燥。去除溶剂,并在硅胶柱上纯化残留物以给出化合物 111-5 (14.7g, 84%)。ESI-LCMS: $m/z = 519 [\text{M}+\text{H}]^+$ 。

[1005] (111-6) 的制备: 0℃ 下向经搅拌的于无水吡啶 (200mL) 中的化合物 111-5 (12.5g, 24.8mmol) 的溶液中,逐滴加入 BzCl (4.3g, 30mmol)。然后在 R.T. 下混合物搅拌 10 小时。用 H_2O 对反应物淬火,并浓缩溶液。将残留物溶于 EA 中,并用饱和 NaHCO_3 洗涤。在 Na_2SO_4 上干燥有机层并浓缩。在硅胶柱上纯化残留物,以给出化合物 111-6,其为白色泡沫 (11.2g)。ESI-LCMS: $m/z = 623 [\text{M}+\text{H}]^+$ 。

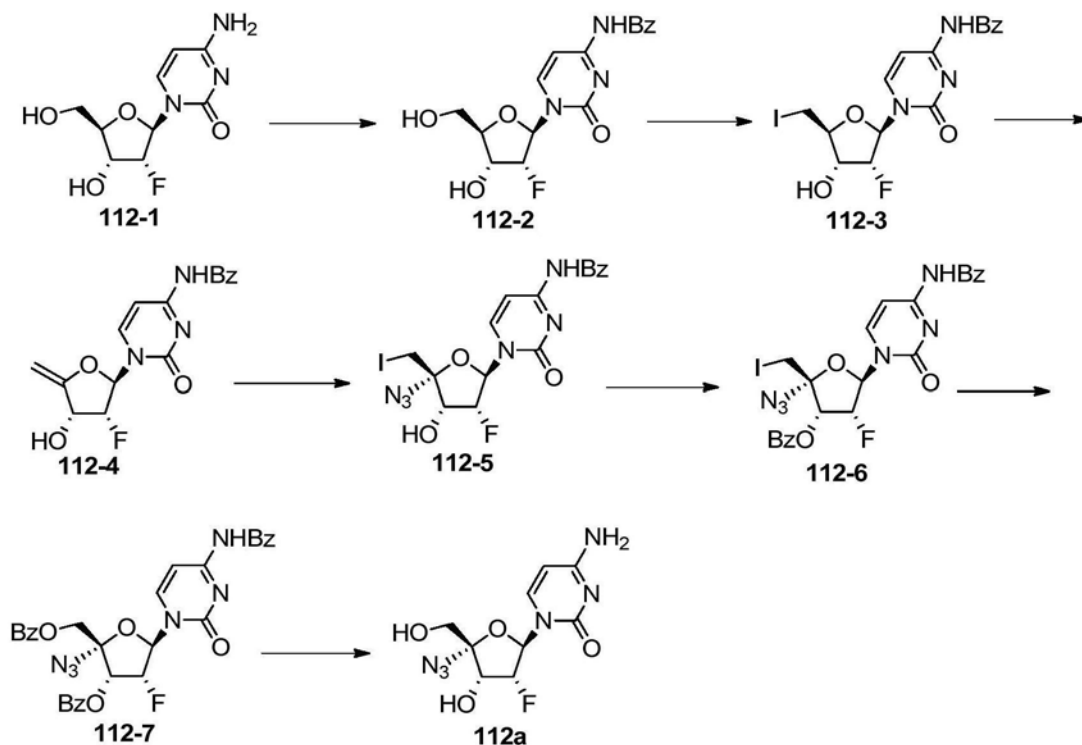
[1006] (111-7) 的制备: 将化合物 111-6 (9.43g, 15.2mmol)、 BzONa (21.9g, 152mmol) 和 15-冠-5 (33.4g, 152mmol) 悬浮于 200mL DMF 中。60-70℃ 下将混合物搅拌 3 天。通过过滤去除沉淀物,并用 EA 稀释滤液。用卤水洗涤溶剂并在 Na_2SO_4 上干燥。去除溶剂,并在硅胶柱上纯化残留物,以提供化合物 111-7,其为白色泡沫 (4.4g, 46%)。ESI-LCMS: $m/z = 617 [\text{M}+\text{H}]^+$ 。

[1007] (111a) 的制备: 将化合物 111-7 (4.4g, 7.13mmol) 溶于 100mL 的饱和甲醇氨中,并将产生的溶液在 R.T. 下搅拌 14 小时。去除溶剂,并在硅胶柱 (DCM/MeOH = 30:1-10:1) 上纯化残留物,以给出 111a,其为白色固体 (1.9g, 88%)。 ^1H NMR (CD_3OD , 400M Hz) δ 7.70 (d, $J = 7.6\text{Hz}$, 1H), 6.40 (t, $J = 7.2\text{Hz}$, 1H), 5.93 (d, $J = 7.6\text{Hz}$, 1H), 4.50 (t, $J = 13.2\text{Hz}$, 1H), 3.88 (dd, $J_1 = 12.0\text{Hz}$, $J_2 = 26.8\text{Hz}$, 2H); ESI-MS: $m/z = 305 [\text{M}+\text{H}]^+$, $609 [2\text{M}+\text{H}]^+$ 。

[1008] 实施例 109

[1009] 化合物 (112a) 的制备

[1010]



[1011] (112-2) 的制备:向经搅拌的于 DMF(100mL) 中的化合物 112-1(21.0g, 85.7mmol) 的溶液中,逐份加入苯甲酰酐(9.66g, 87mmol)。将混合物在 R. T. 下搅拌过夜。在减压下去除溶剂,并用 CH_2Cl_2 磨碎残留物,以给出化合物 112-2,其为白色固体(29.90g, 100%)。

[1012] (112-3) 的制备:0℃下向经搅拌的于无水 THF(100mL) 中的化合物 112-2(10.0g, 28.65mmol)、 PPh_3 (15.01g, 57.30mmol) 和吡啶(20mL) 的悬液中,逐滴加入于 THF(50mL) 中的 I_2 (14.55g, 57.30mmol) 溶液。加入后,使混合物升温至 R. T. 并搅拌 14 小时。用饱和 $\text{Na}_2\text{S}_2\text{O}_3$ (150mL) 水溶液对反应物淬火,并用 EA 抽提(100mL, 3 次)。在 Na_2SO_4 上干燥有机层并浓缩。在硅胶柱(DCM/MeOH = 100:1-50:1) 上纯化残留物以提供化合物 112-3(4.61g, 35.1%), 其为白色固体。

[1013] (112-4) 的制备:0℃下,在 10min 内,向经搅拌的于无水 DMF(100mL) 中的化合物 112-3(4.6g, 10.02mmol) 的溶液中,逐滴加入于 DMF(20mL) 中的 *t*-BuOK(3.36g, 30.06mmol) 溶液。R. T. 下将混合物搅拌 2 小时。然后用饱和 NH_4Cl (50mL) 水溶液对混合物淬火,并用 THF 和 EA 抽提。将有机层用卤水洗涤,并在 Na_2SO_4 上干燥。去除溶剂,并在硅胶柱(MeOH/DCM = 1/100-1/30) 上纯化残留物,以提供化合物 112-4,其为白色固体(3.30g, 99.6%)。

[1014] (112-5) 的制备:向经搅拌的于 MeCN(50mL) 中的 BnEt_3NCl (11.69g, 50.2mmol) 溶液中,加入 NaN_3 (3.26g, 50.2mmol)。将混合物超声处理 20min, 然后在 R. T. 下搅拌 16 小时。将溶液过滤至于无水 THF(80mL) 中的化合物 112-4(3.31g, 10.02mmol) 和 NMM(5.02g, 50.2mmol) 的溶液中。将混合物冷却至 0℃, 并逐滴加入于 THF(40mL) 中的 I_2 (12.5g, 50.2mmol) 溶液。0-10℃下继续搅拌 20 小时。加入 *N*-乙酰半胱氨酸直至无气体产生。加入饱和的 $\text{Na}_2\text{S}_2\text{O}_3$ 水溶液直至得到亮黄色溶液。将溶液浓缩,然后用 EA 稀释。用卤水洗涤有机相并在 Na_2SO_4 上干燥。去除溶剂,并在硅胶柱(PE:EA:DCM = 1:1:1) 上纯化残留物,以给出化合物 112-5(14.7g, 84%), 其为白色泡沫。 ^1H NMR(CD_3OD , 400MHz) δ 11.41(s, 1H), 8.19(d, J = 7.2Hz, 1H), 8.00(d, J = 7.2Hz, 1H), 7.62-7.66(m, 1H), 7.50-7.54(m, 2H), 7.39(d, J = 7.2Hz, 1H), 6.44(d, J = 6.8Hz, 1H), 6.13(d, J = 20.4Hz, 1H), 5.36-5.41(m, 1H), 4.70-4.76(m, 1H), 3.72(dd, J_1 = 17.6Hz, J_2 = 11.6Hz, 2H)。

[1015] (112-6) 的制备:0℃下向搅拌的于无水吡啶(80mL) 中的化合物 112-5(3.6g, 7.20mmol) 的溶液中,逐滴加入 BzCl (1.31g, 9.36mmol)。R. T. 下将混合物搅拌 10 小时。用 H_2O 对反应物淬火,并浓缩溶液。将残留物溶于 EA 中,并用饱和 NaHCO_3 水溶液洗涤。在 Na_2SO_4 上干燥有机层并浓缩。在硅胶柱(PE/EA = 10/1-1/1) 上纯化残留物,以给出化合物 112-6(3.2g, 73.7%), 其为淡黄色泡沫。

[1016] (112-7) 的制备:将化合物 112-6(2.0g, 3.31mmol)、 BzONa (4.76g, 33.1mmol) 和 15-冠-5(7.28g, 33.1mmol) 悬浮于 DMF(100mL) 中。60-70℃下将混合物搅拌 3 天。通过过滤去除沉淀,并用 EA 稀释滤液。用卤水洗涤溶液并在 Na_2SO_4 上干燥。去除溶剂,并在硅胶柱(PE/EA = 4/1-2/1) 上纯化残留物,以提供化合物 112-7,其为亮黄色泡沫(1.0g, 50.7%)。

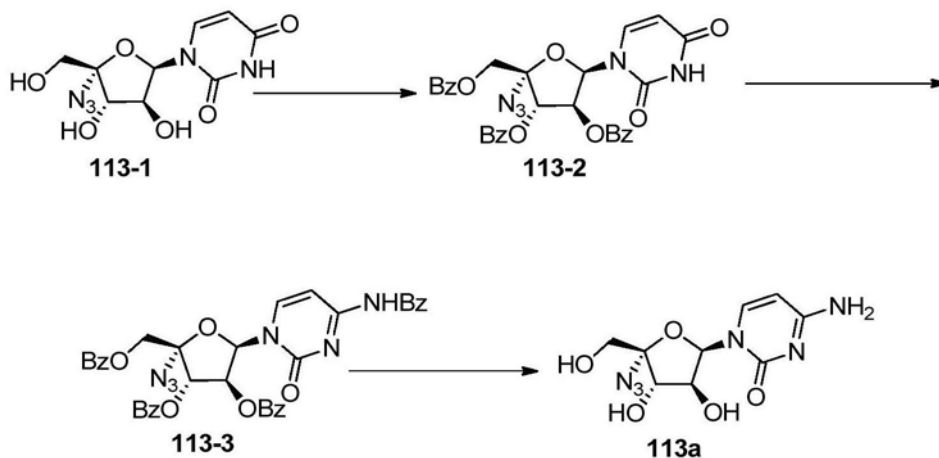
[1017] (112a) 的制备。将化合物 112-7(0.5g, 0.84mmol) 溶于甲醇氨(30mL) 中,并将混合物在 R. T. 下搅拌 14 小时。去除溶剂,并在硅胶柱(DCM/MeOH = 30:1-10:1) 上纯化残留物,以给出 112a,其为白色固体(0.11g, 41.8%)。 ^1H NMR(CD_3OD , 400MHz) δ 7.83(d, J = 7.6Hz, 1H), 6.10(dd, J_1 = 19.6Hz, J_2 = 1.6Hz, 1H), 5.94(d, J = 7.6Hz, 1H), 5.10(ddd, J_1 = 53.6Hz, J_2 = 5.2Hz, J_3 = 1.2Hz, 1H), 4.57(t, J = 5.2Hz, 1H), 3.82(dd, J_1 = 38.0Hz, J_2 =

12. 4Hz, 2H) ;ESI-MS: $m/z = 287 [M+H]^+$, $573 [2M+H]^+$ 。

[1018] 实施例 110

[1019] 化合物 (113a) 的制备

[1020]



[1021] (113-2) 的制备: 0°C 下向经搅拌的于无水吡啶 (40mL) 中的化合物 113-1 (4.6g, 16.2mmol) 的溶液中, 逐滴加入 BzCl (7.3g, 51.8mmol)。将混合物在 R. T. 下搅拌 14 小时。用 H_2O 对反应物淬灭, 并浓缩溶液。将残留物溶解于 EA 中, 并用饱和 NaHCO_3 洗涤。在 Na_2SO_4 上干燥有机层并浓缩。在硅胶柱 (PE/EA = 10/1-1/1) 上纯化残留物, 以给出化合物 113-2 (7.4g, 84.1%)。

[1022] (113-3) 的制备: 将化合物 113-2 (7.4g, 12.4mmol)、DMAP (3.1g, 24.8mmol)、TPSCl (7.5g, 24.8mmol) 和 Et_3N (2.5g, 24.8mmol) 悬浮在 MeCN (50mL) 中。将混合物于 R. T. 下搅拌 14 小时。去除溶剂, 并将残留物溶于 THF 中的 NH_3 (200mL) 中。将混合物在 R. T. 下搅拌 2 小时。去除溶剂, 并在硅胶柱 (DCM/MeOH = 100:1-50:1) 上纯化残留物, 以给出粗产物。 0°C 下将粗产物溶于无水吡啶 (50mL) 中, 并逐滴加入 BzCl (1.7g, 12.2mmol)。将混合物在 R. T. 下搅拌 14 小时。用 H_2O 对反应物淬灭, 并浓缩溶液。将残留物溶于 EA 中, 并用饱和 NaHCO_3 洗涤。在 Na_2SO_4 上干燥有机层并浓缩。在硅胶柱 (PE/EA = 10/1-1/1) 上纯化残留物, 以给出化合物 113-3, 其为白色泡沫 (4.2g, 48.4%)。

[1023] (113a) 的制备: 将化合物 113-3 (4.2g, 6.0mmol) 溶于 200mL 的饱和甲醇氨中, 并在 R. T. 下将混合物搅拌 14 小时。去除溶剂, 然后加入水。将含水混合物用 DCM 洗涤几次, 并冻干以给出 113a, 其为白色固体 (1.5g, 88%)。 ^1H NMR (CD_3OD , 400MHz) δ 7.74 (d, $J = 7.2\text{Hz}$, 1H), 6.43 (d, $J = 5.6\text{Hz}$, 1H), 5.87 (d, $J = 7.6\text{Hz}$, 1H), 4.39 (dd, $J_1 = 2.4\text{Hz}$, $J_2 = 5.6\text{Hz}$, 1H), 4.15 (d, $J = 5.6\text{Hz}$, 1H), 3.80 (s, 1H). ESI-MS: $m/z = 285 [M+H]^+$ 。

[1024] 实施例 111 RSV 抗病毒检验

[1025] 如对 Sidwell 和 Huffman 等人, Appl Microbiol. (1971) 22(5):797-801 描述的进行细微修改而进行 CPE 降低的检验。在 0.01 的多重感染 (m. o. i.) 下, 使浓度为 6000 细胞/孔的 HEP-2 细胞 (ATCC) 感染 RSV 长菌株 (ATCC), 并且提供各个试验化合物以使用 1/3 逐级稀释在从 $100\mu\text{M}$ 开始的最终浓度下复制孔。对于各个化合物, 将两个孔放置在一旁作为未感染的、未处理的细胞对照 (CC), 并且两个孔每个试验化合物仅接受病毒作为用于病毒复制的对照 (VC)。在病毒感染的未处理对照孔中的所有细胞显示病毒细胞病理学标志

(巨细胞形成、合胞体)之前,在6天后停止检验。在培养结束时,将20 μ l 的细胞计数试剂盒-8试剂(CCK-8, Dojindo Molecular Technologies, Inc.)加入至各个孔。在培养4小时后,根据制造商的说明检测各个孔中的吸光度,并基于各个浓度的化合物下的平均O.D.通过使用回归分析计算计算50%有效浓度(EC_{50})。

[1026] 以20000细胞/孔的浓度,在HEp-2细胞(ATCC:CCL-23)中进行基于RT-PCR的检验,并在96孔板中制板和培养过夜。各个试验化合物为1/3连续稀释的并且一式两份地给予HEp-2细胞。各个化合物的最高最终浓度为100 μ M。在24小时化合物预培养后,在0.1的MOI下加入RSV A2(ATCC:VR-1540)。将两个孔每个化合物放置在一旁作为未感染的、未处理的细胞对照(CC),并且四个孔每个试验化合物仅接受病毒作为用于病毒复制的对照(VC)。在病毒感染4天后停止检验并去除条件培养基用于病毒RNA分离。通过使用一组RSV特异性引物和探针的实时对RSV病毒的数量进行PCR检测。使用Prism软件分析数据,并将 EC_{50} 定义为从病毒对照(VC)减少病毒载量50%的药物浓度。

[1027] 在包含50mM醋酸tris pH 8、120mM醋酸K、4.5mM $MgCl_2$ 、5%甘油、2mM EDTA、50 μ g/mL BSA和3mM DTT的反应缓冲液中,在3 μ L RSV-感染细胞提取物的存在下进行标准RSV聚合酶检验。在30 $^{\circ}$ C下不同浓度的试验化合物用于开始RNA合成时间为120mins,并且放射性33P GTP(15uCi)用作示踪物。通过加入50mM EDTA停止反应,并通过G-50尺寸排阻旋转柱和苯酚-氯仿萃取纯化RNA样品。通过在6%聚丙烯酰胺TBE凝胶上的电泳法拆分放射标记的RNA产物,并在暴露于磷成像屏后显影和定量。在提高浓度的试验化合物的存在下以相同方式进行聚合酶抑制实验(IC_{50})。

[1028] 在表6和7所示检验中式(I)的化合物、式(II)和式(III)是具有活性的。在表6中,‘A’表示 $EC_{50} < 2 \mu$ M, ‘B’表示 $\geq 2 \mu$ M且 $< 10 \mu$ M的 EC_{50} 且‘C’表示 $EC_{50} \geq 10 \mu$ M且 $< 50 \mu$ M。在表7中,‘A’表示 $EC_{50} < 1 \mu$ M, ‘B’表示 $\geq 1 \mu$ M且 $< 10 \mu$ M的 EC_{50} 且‘C’表示 $EC_{50} \geq 10 \mu$ M且 $< 100 \mu$ M。

[1029] 表6 - 通过RSV聚合酶检验测定的化合物的活性

[1030]

编号	EC_{50}	编号	EC_{50}	编号	EC_{50}	编号	EC_{50}	编号	EC_{50}
35a	A	36i	B	56c	A	97b	A	97g	A
36a	A	36j	B	56da	A	97c	A	98b	A
36c	A	56a	B	56e	A	97d	A	98c	A
36e	A	56a	B	97a	A				

[1031] 表7- 通过RT-PCR检验测定的化合物的活性

[1032]

编号	EC_{50}	编号	EC_{50}	编号	EC_{50}	编号	EC_{50}	编号	EC_{50}	编号	EC_{50}
1a	C	14a	A	28a	B	48a	B	81a	B	106a	C

2a	C	20a	B	30a	A	50a	A	82a	A	108a	B
3a	A	21a	A	31a	B	52a	A	83a	B	—	—
4a	C	22a	C	33a	A	58a	C	85a	A	—	—
7a	A	23a	A	39a	B	69a	A	86a	A	—	—
9a	C	25a	C	41a	B	71a	A	87a	A	—	—
11a	B	26a	B	46a	B	73a	C	92a	C	—	—
13a	C	27a	B	45a	C	76a	A	105a	C	—	—

[1033] 实施例 112

[1034] 流感抗病毒检验

[1035] 在黑色 96-孔板中,在检验培养基(补充有 0.3% FBS、1% 盘尼西林/链霉素(全部 Mediatech, Manassas, VA) 和 1% DMSO(Sigma-Aldrich, St Louis, MO) 的 Ham 氏 F12 培养基)中以 5×10^4 细胞/mL (5×10^3 细胞/孔) 的密度将人肺癌 A549 细胞(ATCC, Manassas, VA) 制板。在 24 小时后,将连续稀释的试验化合物加入至细胞并培养另外 24 小时。使细胞感染 250IU/孔的流感菌株 A/WSN/33(H1N1) (Virapur, San Diego CA) 并在 37°C、5% CO₂ 下培养 20 小时。抽出细胞培养基上清液并将溶于 33mM MES, pH 6.5 的 50 μL 的 25 μM 2'-(4-甲基伞形基)-α-D-N-乙酰基神经氨酸(Sigma-Aldrich) (Emerald Biosystems, Bainbridge Island, WA) 加入至细胞。在 30°C 下培养 45mins 后,通过加入 150 μL 停止溶液(100mM 甘氨酸、pH 10.5、25% 乙醇、全部 Sigma-Aldrich) 将反应停止。在 Victor X3 多标记板读数仪(Perkin Elmer, Waltham, MA) 上分别使用 355 和 460nm 的激发和发射过滤器检测荧光性。通过加入 100 μL 的 **CellTiter-Glo®** reagent (Promega, Madison, WI) 测定未感染的平行培养基的细胞毒性,并在 R. T. 下培养 10mins。在 Victor X3 多标记板读数仪上检测发光。

[1036] 在表 8 所示检验中式 (I) 的化合物、式 (II) 和式 (III) 是具有活性的,其中 'A' 表示 $EC_{50} < 20 \mu M$, 'B' 表示 $\geq 20 \mu M$ 且 $< 100 \mu M$ 的 EC_{50} 且 'C' 表示 $EC_{50} \geq 100 \mu M$ 且 $< 250 \mu M$ 。

[1037] 表 8 - 化合物的活性

[1038]

编号	%抑制	编号	%抑制
1a	C	20a	C
2a	C	21a	C
3a	C	22a	C
4a	C	23a	C

6a	C	25a	A
7a	C	26a	C
9a	C	27a	B
12a	C	28a	C
16a	C	30a	C
17a	C	31a	C
18a	C	39a	B

[1039] 实施例 113

[1040] 流感 Pol 检验

[1041] 如 (Aggarwal S. 等人, PLoS ONE 2010) 描述的获得重组流感聚合酶三聚物。在 0.15uM 酶的存在下进行标准 RNA 聚合检验, 将 1.5uM 50-mer 寡核苷酸模板、400uM AG 引物和不同浓度的试验化合物在 30℃ 下在一起培养 40 分钟。放射性 ³³P GTP 用作示踪物并在 15% 聚丙烯酰胺 TBE 凝胶上通过电泳法拆分放射标记的 RNA 产物, 并在暴露于磷成像屏后显影和定量。在增加浓度的试验化合物的存在下以相同方式进行聚合酶抑制实验 (IC₅₀)。

[1042] 实施例 114

[1043] 副流感病毒 -3 (PIV-3) RT-PCR 检测

[1044] 在 A549 细胞 (ATCC:CCL-185) 中进行了基于 RT-PCR 的检测。将浓度为 20,000 细胞 / 孔的 A549 细胞接种于 96 孔板中, 并孵育过夜。将每种检测化合物进行 1/3 系列稀释, 并以一式两份给予 A549 细胞。每种化合物最高的终浓度为 100 μM。在 24 小时化合物预培养后, 加入 0.1 感染复数 (MOI) 的人副流感病毒 3 (hPIV3, ATCC:VR-93)。每种化合物留出两个孔作为未感染的、未处理的细胞对照 (CC), 并且每种检测化合物的 4 个孔仅接收病毒作为病毒复制对照 (VC)。在病毒感染后 7 天停止检测, 并移除条件培养基用于病毒 RNA 分离。通过实时 PCR, 使用一组 hPIV3 特异性引物和探针测量 hPIV3 病毒的量。用 Prism 软件分析数据, 其中 EC₅₀ 定义为从病毒对照 (VC) 减少 50% 病毒载量的药物浓度。结果在表 9 中给出, 并且表明式 (I)、式 (II) 和式 (III) 的化合物对 PIV-3 具有活性, 其中 ‘A’ 指 EC₅₀ < 20 μM, ‘B’ 指 EC₅₀ ≥ 20 μM 且 < 100 μM, 且 ‘C’ 指 EC₅₀ ≥ 100 μM。

[1045] 表 9

[1046]

编号	EC ₅₀ (μM)	编号	EC ₅₀ (μM)	编号	EC ₅₀ (μM)
3a	A	22a	C	71a	C
6a	C	23a	C	111a	A
7a	A	40a	C	112a	A

9a	C	43a	C	113a	C
20a	C	69a	A		

[1047] 实施例 115

[1048] 副流感病毒-3(PIV-3) 增强型绿色荧光蛋白 (eGFP) 检测

[1049] 在 A549 细胞 (ATCC:CCL-185) 中进行了基于 HPIV3-eGFP 的检测。将浓度为 20,000 细胞 / 孔的 A549 细胞接种于 96 孔板中, 并培养过夜。将每种检测化合物进行 1/3 系列稀释, 并以一式两份给予 A549 细胞。每种化合物的最高终浓度为 100 μ M。在 24 小时化合物预培养后, 加入 0.1MOI 的 hPIV3-eGFP, (Roth 等, Antiviral Res. (2009)82(1):12-21.)。每种化合物留出两个孔作为未感染的、未处理的细胞对照 (CC), 并且每种检测化合物的 4 个孔仅接收病毒作为病毒复制对照 (VC)。在病毒感染后 3 天, 通过移除条件培养基并加入 50 μ l / 孔的 RIPA 裂解缓冲液来终止检测。在 Victor 3 酶标仪中检测裂解缓冲液中的 eGFP 荧光信号。用 Prism 软件分析数据, 其中 EC_{50} 定义为从病毒对照 (VC) 减少 50% 病毒载量的药物浓度。结果在表 10 中给出, 且表明式 (I)、式 (II) 和式 (III) 的化合物对 PIV-3 具有活性, 其中 ‘A’ 指 $EC_{50} < 20 \mu$ M, ‘B’ 指 $EC_{50} \geq 20 \mu$ M 且 $< 100 \mu$ M, 且 ‘C’ 指 $EC_{50} \geq 100 \mu$ M。

[1050] 表 10

[1051]

编号	EC_{50} (μ M)	编号	EC_{50} (μ M)
3a	A	40a	C
4a	C	43a	C
6a	C	69a	B
7a	A	71a	C
9a	C	111a	A
20a	C	112a	A
22a	C	113a	C
23a	C		

[1052] 实施例 116

[1053] 副流感病毒-3(PIV-3) 噬斑检测

[1054] 在补充有 10% 胎牛血清和抗体 (C-EMEM) 的最小必需培养基 (MEM) 存在下, 将 MA-104 细胞在 24 孔板中培养至聚集度为 90%。然后将细胞用非完全最小必需培养基 (NC-EMEM) 洗涤两次。将检测物质溶解在 DMSO 中至 10mM 的储备浓度。

[1055] 然后将小份的不同浓度的 0.5mL 检测物质一式三份接种在孔中, 并于 37°C 用 5% CO_2 孵育 60 分钟, 以使检测物质扩散至 MA-104 细胞中。在孵育时间后, 将人 PIV 类型 3 的

储液解冻,并用 NC-EMEM 孵育以得到 10^4 pfu/mL 的病毒浓度。然后将小份的 0.1mL 接种至所有孔中,除了阴性和检测物质毒性对照孔。感染后,于 37°C ,在 5% CO_2 下将板孵育 72 小时。孵育后,在显微镜下检测板以记录细胞毒性。用 MA-104 细胞作为指示细胞,使用标准噬斑检测对收集的上清液进行病毒定量。

[1056] 为了进行噬斑检测,在 24 孔板中将 MA-104 细胞培养至聚集。用无血清培养基洗涤细胞,然后用 10 倍系列稀释的上清液样品培养一式双份的孔。 37°C 培养 1 小时后,吸出样品,并向每孔中加入 1.0mL 的甲基纤维素覆盖的培养基。培养 6 天后,固定细胞,并在 1% 戊二醛中用 0.06% 结晶紫染色,并计算病毒噬斑。用 Prism 软件分析数据,其中 EC_{50} 定义为从病毒对照 (VC) 减少 50% 病毒载量的药物浓度。表 11 提供了结果,且表明式 (I)、式 (II) 和式 (III) 的化合物对 PIV-3 具有活性,其中 ‘A’ 指 $\text{EC}_{50} < 20 \mu\text{M}$ 。

[1057] 表 11

[1058]

编号	$\text{EC}_{50} (\mu\text{M})$
3a	A
7a	A
111a	A

[1059] 实施例 117

[1060] 人偏肺病毒 (hMPV) TCID_{50} 检测

[1061] 在补充有 10% 胎牛血清和抗生素 (C-EMEM) 的最小必需培养基 (MEM) 存在下,将 LLC-MK2 细胞在 24 孔板中培养至聚集度为 90%。然后用非完全最小必需培养基 (NC-EMEM) 将细胞洗涤两次。将检测物质溶于 DMSO 中,至 10mM 的储备浓度。

[1062] 然后在孔中一式三份培养小份的不同浓度的 0.5mL 检测物质,并于 37°C 用 5% CO_2 培养 60 分钟,以使检测物质扩散至 LLC-MK2 细胞中。在培养期后,将人偏肺病毒的储液解冻,并用 NC-EMEM 稀释以获得 10^4 pfu/mL 的病毒浓度。然后将小份的 0.1mL 接种至所有孔中,除了阴性和检测物质毒性对照孔。感染后,于 37°C ,在 5% CO_2 下将板培养 7 天。培养后,在显微镜下检测板以记录细胞毒性。用 LLC-MK2 细胞作为指示细胞,使用标准 TCID_{50} 检测对收集的上清液进行病毒定量。用 Prism 软件分析数据,其中 EC_{50} 定义为从病毒对照 (VC) 减少 50% 病毒载量的药物浓度。检测结果在表 12 中给出,且表明式 (I)、式 (II) 和式 (III) 的化合物对人偏肺病毒具有活性,其中 ‘A’ 指 $\text{EC}_{50} < 20 \mu\text{M}$ 。

[1063] 表 12

[1064]

编号	$\text{EC}_{50} (\mu\text{M})$
3a	A
7a	A

111a	A

[1065] 尽管为了清楚和理解目的通过例示和实施例非常详细地描述上述内容,但本领域技术人员理解在不违背本公开实质下能进行许多和各种修改。因此,应当清楚地理解本文公开的形式仅为例示性的并且不意图限制本公开的范围,而相反还包括所有属于本发明真实范围和实质的所有修改和替代。

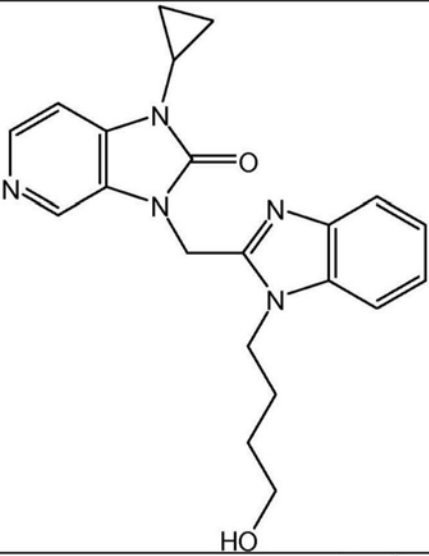
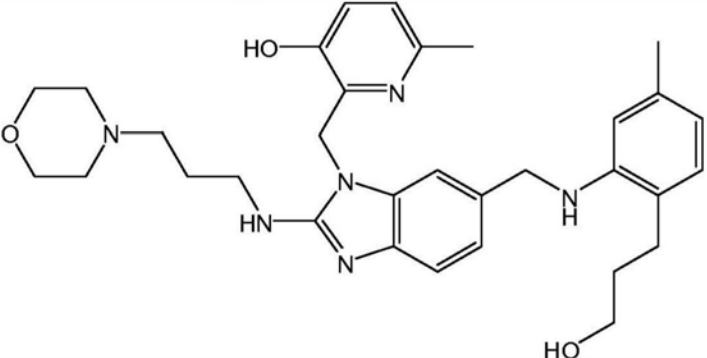
化合物	结构
BMS-433771	 The chemical structure of BMS-433771 is a complex molecule. It features a central benzimidazole core. One nitrogen of the benzimidazole is substituted with a cyclopropyl group. The other nitrogen is part of a five-membered ring containing a carbonyl group. This ring is further substituted with a pyridine ring. A side chain extends from the benzimidazole core, consisting of a methylene group, a nitrogen atom, and a butyl chain ending in a hydroxyl group.
TMC-353121	 The chemical structure of TMC-353121 is a complex molecule. It features a central benzimidazole core. One nitrogen of the benzimidazole is substituted with a morpholine ring. The other nitrogen is part of a five-membered ring containing a carbonyl group. This ring is further substituted with a pyridine ring. A side chain extends from the benzimidazole core, consisting of a methylene group, a nitrogen atom, and a butyl chain ending in a hydroxyl group.

图 1

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 paramyxovirus and/or an orthomyxovirus, with a nucleoside, a nucleotide and an analog thereof.